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Protocol

A Universal Mental Health–Promoting Mobile App for Adolescents: Protocol for a Cluster Randomized Controlled Trial

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Abstract

Background: In times of increasing mental health problems among young people, strengthening efforts to improve mental health through mental health promotion and prevention becomes increasingly important. Effective measures that support young people in coping with negative thoughts, feelings, and stress are essential, not just for the individual but also for society.

Objective: The aim of this paper is to provide a description of a cluster randomized controlled trial that will be conducted to examine the effectiveness of Opp, a universal mental health–promoting mobile app for adolescents aged 13 to 19 years that provides information and exercises to better cope with stress, negative thoughts, and negative feelings. The protocol was developed in accordance with the SPIRIT checklist.

Methods: An effectiveness study will be conducted with 3 measurement points: preintervention (T1), 2 weeks after the intervention (T2), and about 1 month after the intervention (T3). Adolescents will be recruited from middle and high schools in Norway and randomly assigned to the intervention or control groups. Randomization will be conducted on the school level. Opp can be downloaded from the Google Play or App Store but is password protected with a 4-digit code, which will be removed after study completion. Participants in the intervention group will receive a text message with the code to unlock the app. The participants in the intervention group can use Opp without limits on length or time of use. Objective data on how long or how often the participants use the app will not be collected. However, the second and third questionnaires for the intervention group contain app-specific questions on, for example, the use of the app.

Results: Recruitment and data collection started in August and September 2022. So far, 381 adolescents have answered the first questionnaire. Data collection was expected to end in December 2022 but has had to be prolonged to approximately June 2023. The results of the study will be available in 2023 at the earliest.

Conclusions: This project will contribute unique knowledge to the field, as there are few studies that have examined the effects of universal health-promoting mobile apps for adolescents. However, several limitations have to be taken into account when interpreting the results, such as randomization on the school level, the short time frame in which the study was conducted, and the lack of objective data to monitor the use of the app.

Trial Registration: ClinicalTrials.gov NCT05211713; https://www.clinicaltrials.gov/ct2/show/NCT05211713

International Registered Report Identifier (IRRID): PRR1-10.2196/42119

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KEYWORDS

mental health promotion; mobile app; mobile phone; adolescents; Opp; teens; application; effectiveness; intervention; effect; health; health promotion

Introduction

Background

The World Health Organization defines mental health as a "state of well-being in which the individual realizes his or her own abilities, can cope with the normal stresses of life, can work productively and fruitfully, and is able to make a contribution to his or her community" [1]. Good mental health is essential to good health in general and is strongly related to quality of life and participation in school and leisure activities. A scoping review that underlined how difficult it is to define and operationalize good mental health identified 14 core domains of good mental health in young people, including attitudes toward mental disorders, self-perceptions, emotions, behaviors, self-management strategies, social skills, family and significant relationships, and quality of life [2]. The authors wrote that mental health promotion "leads to increasing well-being, competence and resilience and makes individuals improve their mental health and increase their control over it" [2]. Mental health promotion focuses on promoting the positive factors associated with mental health. On the individual level, these factors are, for example, coping with negative thoughts, negative feelings, and stress, as well as increasing resilience and self-esteem [3]. The World Health Organization defines health promotion as "the process of enabling people to increase control over, and to improve their health" [4].

It is widely acknowledged that public health work should focus on universal health-promoting and preventive measures rather than on the treatment of disorders [5,6]. Preventing mental disorders and promoting good mental health is more cost-effective for society and has greater benefits for public health [7]. Working preventively and promoting good mental health is particularly important for young people. On the one hand, adolescence is a vulnerable period in which young people transition from being children to being adults; many mental disorders develop during this period [8]. On the other hand, adolescence is a time when young people can learn and adopt healthy habits and choices from which they can benefit throughout their lives.

In order to reach adolescents, mental health–promoting interventions should be conducted where adolescents actually spend their time. This can, for example, be at schools, at places where adolescents carry out their leisure activities, or online. In Norway, most adolescents have their own smartphones, which they use daily and often for multiple hours [9]. This may open new opportunities to implement mental health–promoting interventions through mobile apps. Despite potential barriers, apps can reach a large proportion of adolescents. This is especially important in countries like Norway that are geographically large and where health services are not always easily accessible. Furthermore, apps are also cost-effective and might be appealing to adolescents, who have a relatively high threshold for seeking help face-to-face [10]. Adolescents prefer to be anonymous, and app-based interventions may therefore be important for promoting good mental health [11]. Also, adolescents often look for health-related information online [9]. However, the quality of the information they find can vary. It is therefore important to offer information that is both high quality and easily accessible to adolescents, especially when it comes to mental health.

Reviews from 2013 and 2014 [12,13] concluded that digital self-management resources were promising, but that there was a need for more research. A recently conducted meta-review that synthesized the results of 14 meta-analyses concluded, on the other hand, that mobile phone–based interventions already have potential for mental health promotion, especially when it comes to reducing psychological symptoms (ie, stress, anxiety, and depression) and increasing quality of life [14]. Although the effects of apps are generally of small magnitude, they could have an important societal impact if they were made available to large groups.

Kenny et al [15] conducted the first and, to the best of our knowledge, only cluster randomized controlled trial to examine the effectiveness of a mental health mobile app–based intervention in a general population of adolescents. They recruited 560 subjects aged 15 to 18 years from 10 schools that were randomly assigned to an intervention or control condition. Participants in the intervention group used the app for about 4 weeks. However, no significant differences in well-being, emotional distress, emotional self-awareness, or coping strategies were found.

One of the largest cluster randomized controlled trials of the effectiveness of universal school-based mindfulness training on mental health and well-being in early adolescence, the MYRIAD (My Resilience in Adolescence) project, found no evidence that it was more effective than the provision of usual social-emotional learning [16]. A meta-analysis of the effectiveness of relaxation techniques to reduce distress, anxiety, and depression in adolescents, on the other hand, had promising results with small to moderate effect sizes [17].

Identifying effective interventions for improving mental health among adolescents is necessary, and studies that have no or negative results also play an important role in determining what helps to improve mental health and what does not [18]. Or as Kuyken et al [16] conclude, "There is need to ask what works, for whom and how, as well as considering key contextual and implementation factors."

The Current Paper

The aim of the current paper is to describe a cluster randomized controlled trial that will be conducted to evaluate the effectiveness of Opp. Opp is a universal mental health–promoting mobile app for adolescents that provides information about mental health, feelings, and help seeking, as well as exercises and techniques to better cope with negative thoughts, negative feelings, and stress.

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Opp is part of the research project UngRisk, which aims to develop and evaluate 2 mental health–promoting mobile apps that will be made available as free resources for easy access by young people. The other mobile app is called NettOpp and is aimed at young people aged 11 to 16 years who have experienced negative incidents online. A study similar to the one that is described here has already been conducted to examine NettOpp's effectiveness [19]. Data analysis is in progress.

Methods

Eligibility Criteria and Setting of the Effectiveness Study

Both the adolescents and participating schools are convenience samples. Adolescents aged 13 to 19 years are eligible for participation in the study and will be recruited through middle and high schools in Norway.

Inclusion and Exclusion Criteria

Adolescents aged 13 to 15 years need consent from their guardians, while adolescents that are 16 years or older can consent for themselves. Adolescents need a smartphone to use the app and need to be able to read Norwegian.

Intervention

Opp is a universal mental health–promoting mobile app that is aimed at adolescents aged 13 to 19 years. The Norwegian word *opp* means "up" in English. In Norwegian, *opp* also evokes the word *opplysning*, which means "enlightenment" or "information"; *opp* also evokes the word "uplifting," meaning to lift someone's spirit.

The overall goals of Opp are to (1) increase well-being and mental health, (2) increase knowledge about mental health, (3) increase coping skills to deal with stress, (4) increase help-seeking behavior, (5) increase self-esteem, (6) increase sleep quality, and (7) reduce mental health problems.

To achieve these goals, Opp is theoretically divided into psychoeducational and resource modules (modules 1 and 2, respectively). Module 1 contains information about mental health (eg, "What is mental health?" "How are thoughts, feelings, and behavior connected?" "Why is good mental health important?" "How to get and maintain good mental health?" "What are mental health problems?" and "When should one seek help for their challenges?"), about feelings (eg, "What are feelings?" "Why are feelings important?" "Can you control your feelings?" and "What do you do when feelings take over?"), and about help seeking (eg, "When should you seek help?" "How to tell somebody about problems?" "What should happen when you have told somebody about your problems?" and "Here you can get help").

Module 2 provides exercises and techniques on how to cope with difficult thoughts, feelings, and stress. For the latter, exercises include breathing and meditation exercises with animation and sound. Another exercise is inspired by cognitive behavioral therapy and aims at helping adolescents to recognize and challenge negative thoughts. Adolescents are guided through this exercise and can choose different statements (eg, "Nobody likes me"), how this thought makes them feel (eg, "sad"), and alternative thoughts (eg, "There are people who love and care about me"). In addition, there is an exercise in which the adolescents can choose different situations, choose what they might think and feel if they were in such situations, and choose how they would behave. This exercise also aims at raising awareness about the relationship between thoughts, feelings, and behavior. In addition, the app contains sleep hygiene advice, tips for maintaining good social relationships, and suggestions on how to increase self-esteem. The information is displayed through text, sound, and animation.

Opp can be downloaded from the Google Play and App Store, but the app is password protected. The password will be removed after study completion to make the app freely available to all users. Adolescents in the intervention group that have answered the first questionnaire can install Opp on their phone and will be provided with a 4-digit code via text message to unlock the app. It is up to the young people themselves to decide when they want to use the app and how much time they want to spend using it. It is not possible to monitor how much time the adolescents actually spend using Opp. However, there are app-specific questions in the second and third questionnaires, which the adolescents will be asked to fill in after approximately 2 and 4 weeks, respectively, that ask how often the adolescents have used the app. The participants are not provided with any training in using the app, but are instructed via text message on how to download the app. Also, the participants are given a phone number that they can call or send a text message to if they experience any problems with downloading or using the app.

User Involvement

Users, that is, adolescents aged 13 to 19 years, were involved in the project from the development of the content of the intervention to its evaluation. Approximately 15 adolescents were involved in 2 workshops to provide input on the content, design, and name of the app. Two adolescents critically read through a manuscript that described the content of Opp and provided feedback on wording and terminology. There was also an extended reference group consisting of teachers, school-health nurses, nurses from a health care center for adolescents, and a community psychologist who contributed to the development of Opp through a workshop.

In addition to this, 27 adolescents participated in a user survey. The study indicated that Opp had good usability, and the overall mean star ranking of the app was 3.78 (SD 0.42) on a 5-point scale. A large proportion of the adolescents thought that Opp was interesting to use (20/27, 74%), that the design was good (25/27, 93%), and that it was appropriate for the target group (24/27, 89%) [20].

Control

The waiting-list control group will receive the code to unlock the app after study completion.

Randomization

This study is a cluster randomized controlled trial with intervention and waiting-list control groups. Schools will be randomly assigned to one of the groups by a statistician after

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baseline assessment. SPSS (IBM Corp) will be used to generate a random number between 0 and 1 that will be assigned to each school. The half of the schools with lower values for the random number will be assigned to the control group and the half of the schools with higher values will be assigned to the intervention group.

Blinding

Neither schools, guardians, nor adolescent participants will know if they are assigned to the intervention or the control group prior to the baseline assessment.

Outcomes

Data will be collected at 3 measurement points: baseline (T1; preintervention); approximately 2 weeks after the intervention (T2; postintervention); and approximately 1 month after the intervention (T3; follow-up) through self-report measures that the adolescents fill in using the secure online tool Nettskjema (University of Oslo).

Primary Outcomes

Mental health will be assessed using the World Health Organization–5 Well-being Index (WHO-5) [21] and the Strengths and Difficulties Questionnaire (SDQ) [22]. Both the WHO-5 [23] and the SDQ [24] have been found to have adequate validity as outcome measures. The primary hypothesis is that there will be significant differences in changes in the mental health scores of the intervention and the control groups in favor of the intervention group.

Secondary Outcomes

Coping skills will be measured with the Norwegian version of the General Self-Efficacy Scale [25]. A Norwegian study found that this scale had satisfactory internal consistency, test-retest reliability, and factor structure [26]. Help-seeking behavior will be assessed with 3 items that measure if the adolescents sought help, who they sought help from, and if they received the help they needed. The Self-liking and Competence Scale [27,28] will be used to measure self-liking and self-competence; this scale has been found to have good internal consistency and factor structure in a Norwegian validation study [29]. Sleep quality will be measured with six questions from the Bergen Child Study [30].

In addition to these measures, there will be app-specific questions in the second and third questionnaires for the intervention group that ask about how often and for how long the adolescents used the app and what features of the app they liked best.

Power Calculations

Power calculations were conducted with PASS 16 (NCSS, LLC). Using multilevel analysis with a significance level of .05 will require a total sample of 1250 adolescents (625 in both the intervention and control groups, including 25 schools with 25 students per school) to achieve a power of .79 and to detect a small effect corresponding to Cohen d=0.20 when the expected interclass correlation at the school level is 0.02. Anticipating a drop-out rate of approximately 25%, a total of 1563 adolescents should be recruited [15].

Data Management

Data will be collected with the secure Nettskjema platform and will be directly sent to and stored on a secure server that only members of the research team have access to. Data collection, data cleaning, and statistical analyses will also only be performed by members of the research team. The statistical analyses will be conducted on anonymized data from the secure server.

Planned Statistical Analysis

Data analyses will be conducted using SPSS. Attrition analyses will be conducted to examine differences between those who complete the questionnaires and those who do not at different time points. A missing-values analysis will also be conducted. Variables for which there are a significantly greater number of missing values will be included as covariates in the analyses.

Correlations will be used to examine whether the different outcomes are related to each other at T1, and linear mixed models will be used to test the hypotheses. We will run 3-level mixed models with time nested within participants nested within schools, and model repeated measures using the *repeated* command in SPSS. We will assess the covariance structure of the repeated measurements by comparing models with different structures (ie, unstructured, compound symmetric, first-order auto-regressive, or others) using the Akaike information criterion.

Ethics Approval and Consent to Participate

The study, including the information letter sent to the guardians and study participants and the consent forms, has been approved by the regional Research Ethics Committee (279207) and by the Norwegian Center for Research Data (715456). The study has been registered on ClinicalTrials.gov (NCT05211713). Active parental consent from 2 guardians is required for adolescents that are younger than 16 years to participate in the effectiveness study. Adolescents that are aged 16 years or older can consent by themselves. Consent, as well as the answers adolescents provide, will be collected digitally using Nettskjema and stored using the services for sensitive data of the University of Oslo in Norway [31]. It is possible that there will be unintended adverse effects of using the app or answering the survey that adolescents might find distressing [18]. Therefore, we will provide information about where the adolescents can receive help if they need it in the app, in the information letter, and at the end of the survey. Participants that fill in the 3 questionnaires will be entered in a raffle for 1 of 100 gift cards with a value of NOK 300 (approximately US $29). The app itself does not collect personal or sensitive information about the users, nor does it need access to GPS, the camera, contact lists, or anything else on the mobile phone.

Results

Recruitment and data collection started in August and September 2022. However, teachers were on strike at that point for about 6 weeks, which made recruitment challenging as the schools were partly closed. Data collection was expected to end in December 2022 but had to be prolonged until approximately June 2023. So far, 381 adolescents have answered the first

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questionnaire. The results of the study will be available at the earliest at the end of 2023 or later, and will be published in international and national journals and presented at conferences.

Discussion

Principal Aims

The current paper describes a cluster randomized controlled trial that is being conducted to evaluate the effectiveness of a universal mental health–promoting mobile app (Opp) in Norway. Its evaluation will lead to new knowledge in the field, as there have been only a few studies published on the effectiveness of such universal interventions [15]. Fusar-Poli et al [2] wrote that "Promotion of good mental health in young people with and without mental disorders has received little empirical research attention and interventions for improving mental health in young people are not well established." Conducting well-designed effectiveness studies is challenging. However, they are necessary in order to identify interventions effective at improving child and adolescent mental health. Randomized controlled trials are considered the gold standard for evaluating the effectiveness of interventions [18].

After the effectiveness study is conducted, Opp will be made freely available in the Google Play and App Store. Results of the study will continue to be published as they are obtained.

Limitations

Several limitations will have to be considered when interpreting the results. Both the adolescents and schools are convenience samples, which could lead to selection bias and limit the conclusions that can be drawn from the study [32]. Another limitation is related to the randomization, which will be conducted on a school level and not an individual level [33].

Other limiting factors are related to adherence to the intervention and intervention fidelity. The app does not collect personal data from its users, and it is therefore not possible to objectively track if and how often the adolescents have used the app. However, the intervention group will answer app-related questions on the frequency of use. Both the intervention and control groups receive the same information letter, and participants that are randomized to the intervention group are informed that they can use the app whenever they want and as often as they want, without further instructions. In addition, the intervention group receives a text message with a code to unlock the app after the baseline assessment and randomization.

Another limitation is related to the length of follow-up, which should ideally be longer than 1 month. Kenny et al [15] wrote the following regarding this: "Findings suggest that a 4-week app-based intervention may not be enough to elicit intrapersonal changes in mental health outcomes in a general adolescent population." Furthermore, the study is based on self-report measures and not on more objective indicators or assessments from other informants, such as parents or teachers, which might be a limitation.

Conclusion

There are only a few studies that have examined the effects of universal health-promoting mobile apps for adolescents. Therefore, this project will contribute unique knowledge to the field. Opp can theoretically reach up to 420,000 adolescents aged 13 to 19 years in Norway (in 7 cohorts, each with 60,000 adolescents). However, a main challenge will be to implement Opp after its evaluation so that as many adolescents as possible know about the app and can use it if they need to. The findings of this effectiveness study will play an important part in informing decisions on how much effort should be put into implementing Opp in Norway.

Acknowledgments

The authors would like to thank the adolescents that participated in the workshop and that helped with the development of Opp for their valuable feedback and comments. We would also like to thank the adults that worked in child and adolescent mental health services who participated in workshops. We would like to thank Charlotte Elvedal at the Norwegian Council for Mental Health for her collaboration, as well as the team from Bouvet that designed and programmed Opp: Mari Søpstad Eggen, Ingrid Ødegaard, Jan Erik Kirkevold Nilsen, Hilde Stenvold, Eirik Aflekt Thommesen, Magnus Gaustad Eriksson, and Renate Kristiansen. The development of Opp was funded by a grant from Foundation Dam through the Norwegian Council of Mental Health (2020HE2-328433). The study was funded by the Norwegian Directorate of Health and UiT The Arctic University of Norway. The funding organizations were not involved in the design of the study, in the collection, analysis, or interpretation of the data, or in writing the manuscript.

Authors' Contributions

HK is the principal investigator of the study. HK, SK, MR, RJ, and MM developed the app. HK, SK, MR, RJ, HH, and MM provided substantial contributions to the study protocol in terms of conceptualization of the study, the study design, and the methods. SK wrote the first draft of the manuscript and MR, RJ, MM, HH, and HK read, edited, and approved the final version.

Conflicts of Interest

None declared.

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Abbreviations

SDQ: Strengths and Difficulties Questionnaire
WHO-5: World Health Organization–5 Well-being Index

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Protocol

The Evaluation of Web-Based Communication Interventions to Support Decisions About COVID-19 Vaccination Among Patients With Underlying Medical Conditions: Protocol for a Randomized Controlled Trial

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Abstract

Background: The timeliness of raising vaccine acceptance and uptake among the public is essential to overcoming COVID-19; however, the decision-making process among patients with underlying medical conditions is complex, leading individuals to vaccine hesitancy because of their health status. Although vaccine implementation is more effective when deployed as soon as possible, vaccine hesitancy is a significant threat to the success of vaccination programs.

Objective: This study aims to evaluate the effectiveness of a communication tool for patients with underlying medical conditions who should decide whether to receive a COVID-19 vaccine.

Methods: This 3-arm prospective randomized controlled trial will test the effect of the developed communication intervention, which is fully automated, patient decision aid (*SMART-DA*), and user-centered information (*SMART-DA*-α). The web-based intervention was developed to help decision-making regarding COVID-19 vaccination among patients with underlying medical conditions. Over 450 patients will be enrolled on the web from a closed panel access website and randomly assigned to 1 of 3 equal groups stratified by their underlying disease, sex, age, and willingness to receive a COVID-19 vaccine. *SMART-DA*-α provides additional information targeted at helping patients' decision-making regarding COVID-19 vaccination. Implementation outcomes are COVID-19 vaccination intention, vaccine knowledge, decisional conflict, stress related to decision-making, and attitudes toward vaccination, and was self-assessed through questionnaires.

Results: This study was funded in 2020 and approved by the Clinical Research Information Service, Republic of Korea. Data were collected from December 2021 to January 2022. This paper was initially submitted before data analysis. The results are expected to be published in the winter of 2023.

Conclusions: We believe that the outcomes of this study will provide valuable new insights into the potential of decision aids for supporting informed decision-making regarding COVID-19 vaccination and discovering the barriers to making informed decisions regarding COVID-19 vaccination, especially among patients with underlying medical conditions. This study will provide knowledge about the common needs, fears, and perceptions concerning vaccines among patients, which can help tailor information for individuals and develop policies to support them.

Trial Registration: Korea Clinical Information Service KCT0006945; https://cris.nih.go.kr/cris/search/detailSearch.do/20965

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International Registered Report Identifier (IRRID): DERR1-10.2196/42837

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KEYWORDS

COVID-19; vaccine; decision-making; randomized controlled trial; patient decision aid

Introduction

Background

Given the large-scale impact, timing, and unpredictability of the COVID-19 pandemic and the threat this has posed to the health care system's routine capabilities, the battle against COVID-19 is still ongoing. The development of effective vaccines was highly anticipated, and several are now available. The timeliness of raising vaccine acceptance and uptake among the public is essential to overcoming COVID-19. A sizable proportion of the population must be vaccinated to achieve herd immunity and prevent the continued spread of the virus. When COVID-19 vaccination was first implemented, the government of the Republic of Korea specified that herd immunity would be achieved by November 2021 and proposed the goal of vaccinating 70% of the population by the end of October 2021 [1]. Recent studies have shown that third shots (boosters) of COVID-19 vaccines effectively provide additional protection from infection, and some countries are now offering fourth doses [2].

The decision to receive a vaccine is complex and reflects one's values, attitudes, and experiences and the information one receives about vaccination. Although vaccine implementation is more effective when deployed as soon as possible, vaccine hesitancy is a substantial threat to the success of vaccination programs [3-5]. A well-known aspect of COVID-19 vaccination is that it may induce side effects. Data on the short-term and long-term side effects of vaccination have been reported [6,7], raising concerns regarding these side effects [8]. Although possible severe side effects are comparatively rare, the risk of their occurrence may considerably influence one's decision not to receive the vaccine, thereby leading to vaccine hesitancy [9,10].

For patients with underlying diseases, the decision process becomes even more complex, ultimately leading them to avoid vaccination owing to the risk of harming their health [10,11]. In Korea, individuals with underlying diseases are classified as high risk and selected as the priority demographic for vaccination [1]. Previous studies have shown inconsistent COVID-19 vaccination intentions among populations with medical conditions [12,13]. Korea Centers for Disease Control and Prevention data from 2021 show that patients with chronic diseases had a lower vaccination rate than the general population of Korea. More recent data from May 2022 show that although the vaccination rate among those aged 40 to 59 years in the general population is 96.7%, that among patients with chronic disease is approximately 2% to 7% lower (94.7% among patients with hypertension, 93.7% among patients with diabetes, and 90.3% among patients with solid organ malignancy) [14]. A study in Brazil showed that concurrent malignancy, fibromyalgia, hydroxychloroquine use, and recent corticosteroid pulse therapy were independently associated with higher odds of COVID-19 vaccine hesitancy [13]. Conversely, a Japanese study revealed that a higher COVID-19 vaccine rate was positively associated with underlying disease, as patients with underlying diseases perceived themselves as being more vulnerable to COVID-19 [12].

Communication interventions such as decision aids (DAs) may yield promising results in addressing this issue. The International Patient Decision Aid Standards (IPDAS) Collaboration defines DAs as "tools designed to help people participate in decision making about health care options" [15]. They provide information on different health care options and help patients by clarifying and communicating personal values while guiding them through the decision-making process [16]. DAs aim to include high-quality epidemiological evidence on the benefits, risks, and associated probabilities of outcomes [17]. Their most common forms are web-based tools, pamphlets, and videos, and they fall within the broader field of shared decision-making—a process by which patients and clinicians work together to (1) clarify treatment goals and (2) review information about the available options and their outcomes to reach a mutual agreement [18,19]. DAs have improved patients' perceptions of the decision-making process and increased their knowledge about the options that align with their values [20]. Although they effectively assist patients in making health treatment and screening decisions, less is known about the impact of DAs on vaccination uptake. A study that examined the impact of DAs on health care personnel's decisions regarding immunization against influenza [21] and hepatitis B [22] found that DAs could be good tools for addressing the phenomenon of vaccine hesitancy [19,23].

Goal of This Study

Several intervention studies attempting to increase the acceptance of COVID-19 vaccination via informational messages, behavioral nudges, web-based interventions, and videos appear in the academic literature [24-28]. However, interventions targeting patients with underlying medical conditions could not be uncovered in the literature. Therefore, the implementation of interventions with proven effectiveness targeting patients with underlying medical conditions are highly needed [29].

This study aims to evaluate the effectiveness of a communication tool for patients with underlying medical conditions for deciding on whether to receive a COVID-19 vaccine. This study develops a web-based communication intervention called "*SMART*," a COVID-19 vaccination DA, and a vaccine-related information program tailored to the target the population with underlying diseases.

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Methods

Study Design

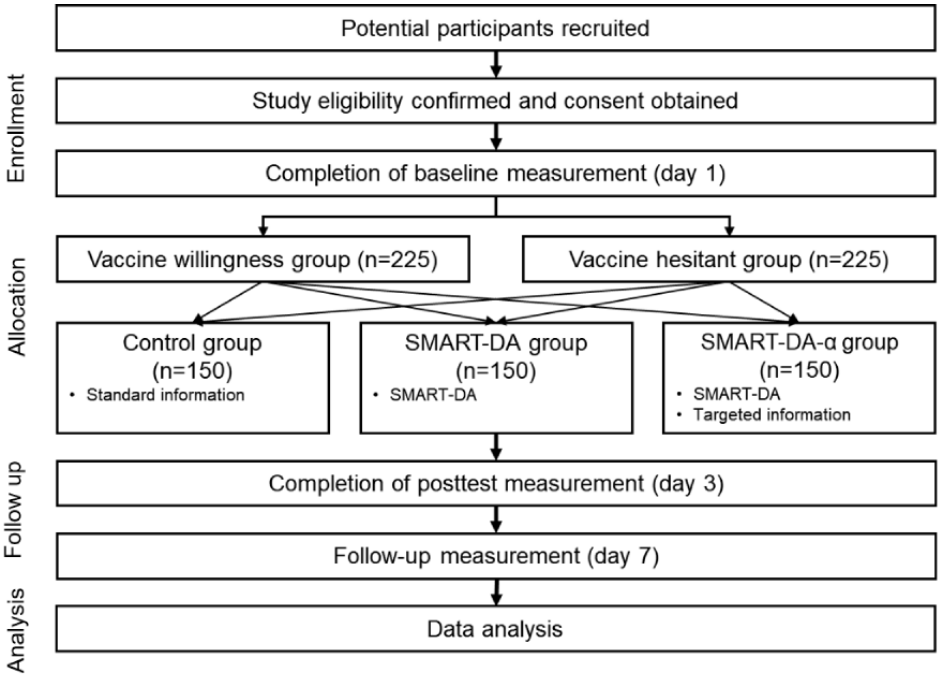
A randomized controlled trial (RCT) will be conducted and reported according to the CONSORT-EHEALTH (Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth) checklist, and the protocol timeline is shown in Table 1. This study is a 3-arm prospective RCT enrolling >450 participants with underlying medical conditions (Figure 1). The participants who complete their baseline web-based questionnaire will be recruited into the study and randomly assigned to 3 equal groups, stratified by their underlying disease, sex, age, and willingness to receive a COVID-19 vaccine (willingness and hesitation). The participants will be randomized to receive (1) standard information about COVID-19 vaccination (control group), (2) COVID-19 vaccination DA (intervention group *SMART-DA*), or (3) COVID-19 vaccination DA with targeted information provision (intervention group *SMART-DA*-α). Each group is described in detail in the following sections. After 1 week, we will follow-up with the participants and use an intention-to-treat (ITT) approach to determine the effects of their COVID-19 communication intervention on COVID-19 vaccination. There is no expected harms or unintended effects in each group.

Table 1. Spirit figure protocol timeline.

	Enrollment	Pretreatment assessment	Allocation	Postallocation assessment		Close out
Time point	$-t_1$	0	0	t_1	t_2	t_3
Enrollment						
Eligibility screen	✓					
Informed consent	✓					
Allocation			✓			
Interventions						
SMART-DA				✓		
SMART-DA-α				✓		
Assessments						
Sociodemographics		✓				
Health-related factors		✓				
Health literacy		✓				
COVID-19 vaccination intention		✓			✓	✓
Knowledge about COVID-19 vaccination		✓			✓	✓
Decisional conflict		✓			✓	✓
Stress related to COVID-19 vaccination		✓			✓	✓
Perceived benefits of COVID-19 vaccination		✓			✓	✓
Perceived barriers to COVID-19 vaccination		✓			✓	✓

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Figure 1. Overview of the stratified randomized controlled trial.



Participants and Setting

Recruitment will be conducted on the web to reflect the web-based nature of the intervention. The intervention study will be conducted via a web-based platform from a research company. The company will recruit participants by sending study invitations via emails or SMS text messages containing general information about the study (eg, the study aims and consent statement), and a URL to access the platform to survey panel members who meet the inclusion criteria. The inclusion criteria are as follows. First, the participants must have received a diagnosis of at least one of the following diseases: hypertension, diabetes, cancer, angina, myocardial infarction, or stroke. Second, the participants must be aged between 18 and 70 years. Third, the participants must have a fluent in the Korean language and be a resident of the Republic of Korea. Fourth, the participants must have access to the internet and the necessary internet literacy skills to use the interventions. Finally, those who have completed the COVID-19 vaccination (those who have received 2 or more doses and those who have been revaccinated regularly) will be excluded. Upon meeting all the inclusion criteria of the study, the participants will provide their informed consent electronically. The informed consent will appear on the study's first page, and the research company will ensure the confidentiality of all the participants. The participants will be informed that they may discontinue participation in the research study at any time without any penalty or loss of benefits. All the researchers in this project will be given access to the cleaned data sets, and all data sets will be password protected. To ensure confidentiality, the data dispersed to the project team members will be blinded of any identifying participant information.

Study Procedures and Implementation Strategies

Randomization

A representative sample of 450 individuals will be randomly selected through a proportional stratified sampling method based on sex and age from a list of candidates registered with the research company. The D-optimal blocking procedure proposed in a recent study [30] will be used for random assignment to reduce interference on the intervention effect by covariates such as the individual's underlying disease, sex, age, and intention to receive COVID-19 vaccination. D-optimality is based on the determinant of the information matrix for the design, which is the same as the reciprocal of the determinant of the variance-covariance matrix for the least squares estimates of the linear parameters of the model. The D-optimal blocking procedure uses a SAS/QC procedure OPTEX (version 9.4; SAS Institute) to randomly allocate the participants to 1 of the 3 arms by all the researchers. The assigned participants will be blinded so that they do not know whether they belong to the intervention group or control group. Both the assigned participants and data analysts will be blinded, and the data analysts will conduct effect analysis of the anonymized groups 1, 2, and 3 without being aware of whether the group is an experimental or control group. However, because the researcher providing the intervention is aware of which group the participants belong to, the study is single blind.

Intervention Group A: COVID-19 Vaccination DA (SMART-DA)

Initial Development of the COVID-19 Vaccination DA (SMART-DA)

The development process of the *SMART-DA* was based on the IPDAS guidelines for DA development. In line with these guidelines, the needs of end users and clinicians were assessed. In addition, we asked public health education experts for additional input. For the end users' needs assessment, 20

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interviews were used to determine end users' needs regarding COVID-19 vaccination decision-making that should be described in the DA. The input of these qualitative studies informed the design and content of the DA, supplemented by IPDAS background papers, other relevant literature in the field, and consultation with established experts.

Next, a prototype was developed and alpha tested with 30 potential end users and 5 public health experts. During the alpha test, the participants were asked to focus on the content of the DA. Before the beta test, the comprehensibility of the DA text for people with limited health literacy was evaluated by 3 coauthors. On the basis of this evaluation, some sections and sentences were rephrased or simplified.

Usability Testing of SMART-DA

After the alpha test, the DA was beta tested among 10 medical experts and 10 potential end users. The participants were given access to the DA to assess its usability using the heuristic evaluation method (medical experts) and think-aloud method (potential end users). Using the heuristic evaluation method, the medical experts were asked to evaluate the DA against a list of recognized usability principles: (1) uses simple and natural dialogue, (2) is in the user's language, (3) minimizes memory load, (4) is consistent, (5) provides feedback, (6) offers clearly marked exits, (7) includes shortcuts, (8) provides helpful error messages, (9) prevents errors, and (10) provides help and documentation. Using the think-aloud method, the end users used the DA while verbalizing their thoughts. The think-aloud method is particularly useful in understanding the processes of cognition and is of high value in evaluating an intervention's design for usability flaws [31]. The data gathered through these tests are compared and compiled into a summary describing the usability flaws of the DA.

Description of SMART-DA

The *SMART-DA* follows a stepwise approach and encourages decisions consistent with the participant's values and health condition. The *SMART-DA* consists of five steps: (1) clarify the decision; (2) explore the decision in terms of knowledge, values, and certainty; (3) clarify decisional support; (4) identify the decision-making needs; and (5) plan the next steps based on the needs.

Step 1 consisted of 4 questions that required the participants to consider the key decision. The following questions were addressed: (1) "What options are available when deciding to be vaccinated against COVID-19?" (2) "What is making your COVID-19 vaccination decisions difficult?" (3) "When do you think it is time to make a COVID-19 vaccination decision?" and (4) "How far have you reached the final decision on the COVID-19 vaccination?" Multiple options were provided to increase the participants' convenience. For question 1, we provided 3 options for COVID-19 vaccination decision-making: "Get vaccinated as soon as possible," "Delay vaccination as much as possible," and "Refuse vaccination." If necessary, they could write their responses in the "other" column.

In step 2, the participants explored their knowledge and values related to each option to clarify how certain they were in their decision-making. A list of reasons to choose and not to choose each option (eg, "Get vaccinated as soon as possible," "Delay vaccination as much as possible," and "Refuse vaccination") was provided, and the participants rated how much each reason mattered to them using a 6-point Likert-type scale. If necessary, they could write their reasons in the "other" column and rate how much they mattered. After the rating was completed, the total score for choosing each option and the reasons for not choosing it were calculated and shown. The participants were then asked what their preferred options were.

In step 3, the participants were asked to think about who supports their decision-making and how the support affects them. We asked them to identify whether other people supported their decision-making and, if so, who those individuals were. In addition, we asked them what role they preferred to play in decision-making and provided the response options "share the decision," "decide myself after hearing views," and "someone else decides."

In step 4, the participants identified their decision-making needs concerning knowledge, values, support, and certainty. The participants considered whether (1) they had adequate knowledge of the risks and benefits of each option (knowledge), (2) they identified their values related to the risks and benefits of each option (value), (3) they had sufficient support to make choices (support), and (4) they were certain of their choices (certainty). The responses were collected with a yes or no option; if the participants had ≥1 "no" responses, they were encouraged to start over from step 2.

In the final step, the participants received information about the actions they could perform based on their decision-making needs. For instance, if the value of each option was unclear, we recommended revising the scores given in step 2 after listening to others' experiences of COVID-19 vaccination or asking for advice from others.

As shown in Figure 1, the intervention group A is supplemented with *SMART-DA*. The participants were allowed to access and use *SMART-DA* whenever available, and as much as needed.

Intervention Group B: COVID-19 Vaccination DA With Targeted Information (SMART-DA-α)

As shown in Figure 1, the intervention group B is supplemented with targeted information in addition to the contents of intervention group A. The participants were allowed to access and use *SMART-DA*-α whenever available, and as much as needed. An educational program was planned to provide accurate and targeted information on COVID-19 vaccination to support decision-making among patients with underlying medical conditions. Educational material was developed with a tailored message to enhance the participants' intuitive understanding and provide information to those who hesitated to make decisions on vaccination. Tailored messages were developed based on the participants' interests in and perception of COVID-19 vaccination identified from the interview, such as their perception of COVID-19 vaccine safety, efficacy, and side effects. The findings revealed that the main messages in the educational material should be as follows:

1. COVID-19 vaccination: How effective is it?
2. COVID-19 vaccination: Is it safe?

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3. Refusal to be vaccinated: critical cases

Tailored messages targeting the information needs of patients with underlying medical conditions were developed and structured around actual cases in clinical settings.

Control Group

The participants in the control group will receive standard information about COVID-19 vaccination provided by the Korean Disease Control and Prevention Agency. This easy-to-understand information about COVID-19 vaccination is publicly available. The material is accessible on the Korean Disease Control and Prevention Agency web page or YouTube (Google LLC) [32].

Follow-up Measurements

After the intervention, the participants will complete follow-up surveys, 3 and 7 days after the intervention, amounting to a total of 3 surveys during the study period. The participants in all the study groups will receive automated text message notifications to complete their surveys to improve study retention.

Incentives

The participants will be able to earn up to KRW 15,000 (approximately US $13) in gift cards for completing the study's requirements. These incentives include a gift card worth KRW 5000 (US $4.01) for completing the initial baseline survey and engaging with the SMART-DA or SMART-DA-α intervention or control group material on the web; a gift card worth KRW 5000 for completing the 3-day survey; and a gift card worth KRW 5000 for completing the 7-day survey. All the incentives will be sent to the participants via their mobile phones.

Measures

Participant's Characteristics

Sociodemographic factors include sex (1=male and 2=female), age, family size (ie, living alone or with 1 or more person), the presence of children at home who attend school (more than one=1 and none=0), marital status (ie, married, single, divorced, or bereaved), and residence (urban=1 and rural=2). We will also assess educational level (1=middle school or below, 2=high school graduate, and 3=college and above) and monthly household income in KRW (1=<KRW 200 million, 2=KRW 200 million to 399 million, 3=KRW 400 million to 599 million, and 4=KRW ≥600 million).

Health-related factors include the respondent's seasonal influenza vaccination history, underlying diseases, and prior COVID-19 diagnosis. For seasonal influenza vaccination history, the participants will be asked, "Have you been vaccinated against the seasonal influenza flu in the last five years?" The responses include "every year," "more than once," "maybe once," "never," and "don't know." We will also investigate the presence of underlying diseases by asking the participants to indicate all diagnosed underlying diseases (eg, hypertension, dyslipidemia, diabetes, chronic cardiac disease, asthma, and cancer). The participants who have not been diagnosed with underlying diseases are excluded from further study.

To examine health literacy related to COVID-19, we adapt the HLS-COVID-Q22 that has been translated into Korean. The HLS-COVID-Q22 was developed in Germany in 2020 by Okan et al [33] based on the European Health Literacy Survey Questionnaire. Its validity and reliability were verified among the German population aged ≥16 years (α=.94; ρ=0.891) [33]. The HLS-COVID-Q22 contains 22 items organized into 4 subgroups: accessing (6 items), understanding (6 items), appraising (5 items), and applying (5 items) health-related information in terms of COVID-19. It is answered on a 4-point scale, ranging from "4=very easy" to "1=very difficult."

Primary and Secondary Outcomes

The primary and secondary outcomes and potential mediators are listed in Table 2. Our primary outcome is COVID-19 vaccination intention, which will be an important outcome during the 1-week follow-up period. The baseline, posttest (3-day), and follow-up (1-week) surveys will assess the participants' vaccination intention. A 5-point Likert scale questionnaire will measure the intention to be vaccinated against COVID-19. The participants will be asked, "If a vaccine for Coronavirus (COVID-19) becomes available, would you want to receive it?" and provided the response options "1=Definitely Would Not Want It, 2=Would Likely Not Want It, 3=Neutral or Unsure, 4=Would Likely Want It, and 5=Definitely Would Want It." The level of vaccine acceptance is defined as willing ("Definitely Would Not Want It," and "Definitely Would Want It") or hesitant ("Definitely Would Not Want It," "Would Likely Not Want It," and "Neutral or Unsure"). The secondary outcomes include knowledge level related to COVID-19, which will be assessed using a validated questionnaire that has been used in numerous studies [34,35], and decisional conflict, which will be assessed using the decisional conflict scale [36]. In addition, psychological stress owing to decision-making regarding COVID-19 vaccination will be measured.

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Table 2. Study outcome measures.

	Baseline measurement (day 1)	Posttest measurement (day 3)	Follow-up measurement (day 7)
Primary outcome			
COVID-19 vaccination intention	✓	✓	✓
Secondary outcomes			
Knowledge about COVID-19 vaccination	✓	✓	✓
Decisional conflict	✓	✓	✓
Stress related to COVID-19 vaccination	✓	✓	✓
Perceived benefits of COVID-19 vaccination	✓	✓	✓
Perceived barriers to COVID-19 vaccination	✓	✓	✓

Data Collection and Management

We collected quantitative data on the potential mediators of implementation effects, including attitudes toward COVID-19 vaccination (eg, perceived benefits and barriers). Questionnaires which were validated for web-based use and apply Checklist for Reporting Results of Internet E-Surveys items were designed to measure primary and secondary outcomes. Data collection is performed according to standard guidelines. To improve the reliability of data quality, real-time support through instant messages or phone calls regarding data collection were provided during the entire data collection period. The respondents entered a web-based data collection program, self-assessed through web-based questionnaires, which the research team reviews and rechecks for anomalous responses according to a defined monitoring strategy. If an error was found in the data, the research team asked the rater to correct or explain it, and all corrections were made after the research team confirms them. In addition, to facilitate retention, respondents reported any issues with the respondent. In the event of study discontinuation, a report was generated in a concise format. All available data were checked by the research team members. Every respondent was assigned a unique study ID, and the research team trained the researchers to protect the study data to ensure data safety. The data collection form does not contain any personally identifiable information. The password-protected electronic files were stored on a password-protected computer. Data managers and analysts independently conducted inspections for each evaluation.

Sample Size and Power

We sought to detect the main effects of the communication intervention within the 3 groups with at least 90% power using a 2-sided α of .05. We used G*Power (latest version 3.1.9.7; Heinrich-Heine-Universität Düsseldorf) to calculate the sample size for 3 repeated measurements (in-between interaction, small effect size of 0.2). Our target analytic sample size was 450 (150 per study group) participants. To achieve this analytic sample size, we randomized a projected 630 participants (210 per study group) and expected approximately 30% of the initial participants to drop out during the 7-day follow-up period.

Statistical Methods

Evaluation of Efficacy

We will also examine the descriptive statistics for the participants' baseline characteristics and compare them across the 3 study groups. The main analysis will be performed based on the ITT principle, involving all the randomized participants to investigate the effectiveness of the interventions. The ITT principle can minimize potential bias owing to dropouts and can be applied while performing further preprotocol analyses. The effects of the interventions on the primary outcome (eg, vaccination intention) and secondary outcomes (ie, knowledge related to COVID-19 vaccines, decisional conflict, psychological stress related to vaccination, perceived benefits of COVID-19 vaccines, and perceived barriers to COVID-19 vaccines) will be estimated using linear mixed-effects models for continuous outcome variables and generalized linear mixed-effects models for categorical outcome variables. The test statistic will be calculated to assess any significant intervention benefit; we will use 2-sided *P* values with α=.05 to calculate the level of significance.

Subanalyses

We will perform a path analysis to examine the theoretical constructs as potential mediators following the effect evaluation. For each outcome, a path analysis will be performed to describe the direct and indirect relationships, including the perceived benefits of and barriers to the COVID-19 vaccine. Path models are statistical methods that, compared with multiple regressions, allow for the simultaneous assessment of several regression paths occurring between multiple dependent and independent variables and for the computation of direct, indirect (mediated), and total effects. Standardized parameter estimates (standardized β) will be used to compare the magnitude of associations between media use and mediators. The model parameters and SE estimates are to be calculated. The participants with missing data will be excluded from analysis. Statistical analyses will be conducted using STATA (version 15; StataCorp LLC), SAS (version 9.4; SAS Institute), and R (version 4.2; R Foundation for Statistical Computing) software.

In addition, we will conduct subgroup analyses according to the preintervention intent for vaccination. We will observe how the degree of vaccination intention changes in the 2 groups. Among those who have already been willing to receive a

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COVID-19 vaccine, there are cases in which their decisions are passive or involuntary owing to social pressure or economic activity. Therefore, we seek to identify whether the nature of their decisions changes through the intervention.

The Data Monitoring Committee comprises the Principal Investigator, independent external data managers, and statisticians. The committee is responsible for data quality throughout the data collection, analysis, and reporting processes. The Data Monitoring Committee is independent of the research funding agency and has no competing interests.

Ethics Approval

Ethics approval for this study was obtained from the Korea National Open University's institutional review board on December 1, 2021 (IRB number ABN01-202111-21-13), and was registered with the Clinical Research Information Service Registry. The current protocol version is version 1.1, and there is no plan to change it. The risk of negative effects on participant outcomes is minimal. The possibility of SMART-DA not having a positive effect on the participants is present, but the risk of negative participant outcomes because of this is limited. The data will be analyzed at the completion of the trial, and the study findings will be published in major peer-reviewed journals. Upon meeting all the inclusion criteria of the study, all the study participants will provide their informed consent electronically.

Results

Data were collected from December 2021 to January 2022. This paper was initially submitted before data analysis began. The results are expected to be published in the winter of 2023.

The number of individuals who initially expressed their intention to participate was 1066. Of these 1066 individuals, 515 (48.31%) people participated in the first survey, excluding 551 (51.69%) people who did not meet the inclusion criteria. All dropouts were individuals without underlying diseases. Of the 515 participants in the first survey, 466 (90.5%) participated in all 3 rounds and 69 (13.4%) dropped out. No significant differences were observed in sex, age group, residence area, education level, marital status, or willingness to receive a COVID-19 vaccine between those who participated in all 3 surveys and those who dropped out based on the first survey (Table 3). The results of the chi-square test conducted to confirm the distribution bias of the participants assigned to the intervention groups (SMART-DA and SMART-DA-a) and those assigned to the control group, in terms of sex, age group, region of residence, education, marital status, and intention to receive a COVID-19 vaccine, showed that no significant differences were observed (Table 4). Among the 515 individuals who completed the first survey, 294 (57.1%) were male and 221 (42.9%) were female, and the age distribution was even (18-29 years, n=90, 17.5%; 30-39 years, n=98, 19%; 40-49 years, n=124, 24.1%; 50-59 years, n=123, 23.9%; 60-69 years, n=80, 15.5%). The rate of college education or higher (418/515, 81.2%) was higher than that of high school graduation (97/515, 18.8%), and the most common marital status was having a spouse (310/515, 60.2%). The proportion of those who responded that they had low or no intention of receiving a COVID-19 vaccine was 46% (237/515), and the proportion of those who responded that they had high intention of receiving a COVID-19 vaccine was 53.9% (278/515), indicated a rather high initial willingness among the participants to receive a COVID-19 vaccine.

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Table 3. Comparison of the participants who responded 3 times with those who responded <3 times (N=515).

	Incomplete response (<3 times; n=69), n (%)	Full response (3 times; n=446), n (%)	*P* value
Sex			.10
Male	33 (47.8)	261 (58.5)	
Female	36 (52.2)	185 (41.5)	
Age (years)			.37
18-29	10 (14.5)	80 (17.9)	
30-39	12 (17.4)	86 (19.3)	
40-49	16 (23.2)	108 (24.2)	
50-59	23 (33.3)	100 (22.42)	
≥60	8 (11.6)	72 (16.1)	
Residence			.53
Urban	66 (95.7)	418 (93.7)	
Rural	3 (4.3)	28 (6.3)	
Education			.81
High school graduation or lower	11 (15.9)	86 (19.3)	
College and above	58 (84.1)	360 (80.7)	
Marital status			.92
Other (unmarried, widowed, or divorced)	26 (37.7)	179 (40.1)	
With a spouse	43 (62.3)	267 (59.9)	
Willingness to receive a COVID-19 vaccine			.17
Low	37 (53.6)	200 (44.8)	
High	32 (46.4)	246 (55.2)	

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Table 4. Basic characteristics of the participants at baseline (N=515).

	Total, n (%)	SMART-DA group (n=172), n (%)	SMART-DA-α group (n=172), n (%)	Control group (n=171), n (%)	*P* value
Sex					.99
Male	294 (57.1)	99 (57.6)	98 (57)	97 (56.7)	
Female	221 (42.9)	73 (42.4)	74 (43)	74 (43.3)	
Age (years)					.93
18-29	90 (17.5)	26 (15.1)	32 (18.6)	32 (18.7)	
30-39	98 (19)	38 (22.1)	29 (16.9)	31 (18.1)	
40-49	124 (24.1)	42 (24.4)	41 (23.8)	41 (24)	
50-59	123 (23.9)	40 (23.3)	45 (26.2)	38 (22.2)	
≥60	80 (15.5)	26 (15.1)	25 (14.5)	29 (17)	
Residence					.29
Urban	484 (94)	162 (94.2)	158 (91.9)	164 (95.9)	
Rural	31 (6)	10 (5.8)	14 (8.1)	7 (4.1)	
Education					.73
High school graduation or lower	97 (18.8)	34 (19.8)	35 (20.3)	28 (16.4)	
College and above	418 (81.2)	138 (80.2)	137 (79.7)	143 (83.6)	
Marital status					.57
Other (unmarried, widowed, or divorced)	205 (39.8)	70 (40.7)	67 (39)	68 (39.8)	
With a spouse	310 (60.2)	102 (59.3)	105 (61)	103 (60.2)	
Willingness to receive a COVID-19 vaccine					.99
Low	237 (46)	79 (45.9)	80 (46.5)	78 (45.6)	
High	278 (54)	93 (54.1)	92 (53.5)	93 (54.4)	

Discussion

Principal Findings

This study is conducted to evaluate the effectiveness of a web-based communication intervention in assisting people with underlying diseases in making decisions about whether to receive a COVID-19 vaccine. This RCT will test the effectiveness of the developed communication intervention, patient DA, and user-centered information as implementation strategies to help patients with underlying medical conditions in making decisions regarding COVID-19 vaccination. This communication intervention aimed to shed light on how a DA for patients with underlying diseases with decision-making needs about COVID-19 vaccination should be designed to facilitate an informed decision-making process. Moreover, this intervention study aimed to contribute to a deeper understanding of individuals' preferences, attitudes, and values regarding COVID-19 vaccination and their impact on decisions.

A set of implications for interventions, communication strategies, and future research can be drawn from this study. First, the outcomes from this study provide valuable new insights into potential DAs for supporting informed decision-making regarding COVID-19 vaccination and discovering barriers to making informed decisions regarding COVID-19 vaccination, especially among patients with underlying medical conditions. Findings about what kind of information is especially misleading can help clinicians focus on these aspects in their consultations [37,38]. Moreover, knowledge about common needs, fears, and perceptions can help tailor information for individuals and develop policies to support them.

Second, this study is a critical step toward achieving the aim of increasing COVID-19 vaccination among patients with underlying diseases. It will comprehensively evaluate *SMART-DA* and *SMART-DA*-α. The results will explain the efficacy of the intervention and its potential mediators. If proven efficacious, *SMART-DA* could fill an important gap as a web-based intervention that allows patients to learn about COVID-19 vaccination and promotes vaccination by stimulating informed decision-making. Moreover, this intervention could be used not only to defeat the battle against COVID-19 but also to prepare for future epidemics. This tool could be potentially distributed on the web before and during the implementation of vaccination programs. As implementation planning is an important part of the process of implementing evidence-based practices [39], this study will enable public health authorities to use these tools as means of support for patients.

Limitations

This study has several limitations. First, we could not investigate the study participants' COVID-19 vaccination status as a

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primary outcome, as their medical records are not accessible. Therefore, we will investigate the participants' self-reported willingness to receive a COVID-19 vaccine. However, there is a risk of bias in self-reported willingness and actual vaccination behavior. Second, our study participants might have different underlying medical conditions; therefore, the findings will not be generalizable to all patients. Third, the sample of this study is limited to certain underlying conditions; for example, it did not include patients who receive immunosuppressive therapy, who have a high need for COVID-19 vaccination. However, the diseases targeted in this study are major chronic diseases with high prevalence in Korea, for which the Korean government or medical society recommends vaccination against COVID-19. In addition, because the vaccination rate among this population is generally lower than that among the general population, it can be considered a meaningful group to study. Finally, because the recruitment of participants and implementation of the intervention are conducted through the internet, it is limited to those who have no problems using the internet. Therefore, the participation of those with limited internet use, especially older adults, is restricted; therefore, caution is required in interpretation. Finally, as participants are recruited through the internet, we limit participation to individuals aged <70 years, as those aged >70 years tend to have poorer control over internet use in Korea. Nonetheless, we acknowledge that the older adult group is an important group with high rates of underlying conditions and decision-making needs for which the development of alternative in-person modes of DA may be required in future studies.

Conclusions

We initiated an intervention study to improve the situation in which people with underlying conditions requiring COVID-19 vaccination have lower vaccination rates compared with the general population. In this paper, we have outlined the study procedure and data management. This interventional study aimed to evaluate improvements in vaccination intention to control COVID-19. We plan to comprehensively analyze the data and continuously present new research to improve vaccination intentions.

Acknowledgments

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The authors are grateful for the support from the Patient-Centered Clinical Research Coordinating Center, Republic of Korea.

Data Availability

Data sharing does not apply to this study, as no data sets have been analyzed during this study. Data construction and analysis have been completed, and the data are available to the authors upon reasonable request and permission from the Korea National Open University's institutional review board.

Authors' Contributions

ML, BO, NHY, SK, and YIJ made substantial contributions to the design of the work; ML and drafted the manuscript, and YIJ substantively revised it. All the authors revised the manuscript critically for intellectual content, have read and approved the final manuscript, and have agreed both to be personally accountable for their own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even those in which they were not personally involved, are appropriately investigated and resolved, and the resolution will be documented in the literature.

Conflicts of Interest

The authors are owners of the web-based communication interventions.

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Abbreviations

CONSORT-EHEALTH: Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth
DA: decision aid
IPDAS: International Patient Decision Aid Standards
ITT: intention-to-treat
RCT: randomized controlled trial

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Protocol

Enhancing Self-care Among Oral Cancer Survivors: Protocol for the Empowered Survivor Trial

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Abstract

Background: Survivors of oral cavity and oropharyngeal cancer frequently experience difficulties in swallowing; tasting; speaking; chewing; and maintaining comfortable movements of the head, neck, and shoulder. Engagement in regular self-care can reduce further loss of function and mitigate late effects. Despite the substantial self-care requirements, there are no empirically based interventions to enhance the skills and confidence of these survivors in managing their ongoing care.

Objective: The aim of this study is to describe the rationale and methodology for a randomized controlled trial evaluating Empowered Survivor (ES) versus Springboard Beyond Cancer, a general web-based program for cancer survivors, on self-efficacy in managing care, preparedness for managing survivorship, and health-related quality of life (QOL).

Methods: This study will recruit a total of 600 individuals who were diagnosed with oral cavity or oropharyngeal cancer in the past 3 years and are currently cancer free primarily from state cancer registries; these individuals will be randomly assigned to either the ES or Springboard Beyond Cancer condition. The participants complete measures of self-efficacy in managing care, preparedness for survivorship, health-related QOL, and engagement in oral self-examination and head and neck strengthening and flexibility exercises at baseline and 2 and 6 months after baseline. The primary aim of this study is to evaluate the impact of ES versus Springboard Beyond Cancer on self-efficacy, preparedness, and health-related QOL. The secondary aim is to examine the mediators and moderators of ES's impact on self-efficacy in managing care, preparedness, and health-related QOL at 6 months. The exploratory aim is to conduct a process evaluation of ES to identify potential oncology or community settings for future implementation.

Results: Multilevel modeling will be used to examine whether there are significant differences between the ES and Springboard Beyond Cancer interventions over time. Mediational models will evaluate the indirect effects of ES on outcomes. Quantitative analyses will evaluate the predictors of ES use, and qualitative analyses will evaluate the preferred timing and settings for the implementation of ES.

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Conclusions: This randomized controlled trial evaluates a completely web-based intervention, ES, versus a general web-based program for cancer survivors, Springboard Beyond Cancer, on self-efficacy in managing care, preparedness for managing survivorship, and health-related QOL and identifies the putative mediators and moderators of the intervention's effects. If an effect on the primary outcomes is illustrated, the next step could be an implementation trial to evaluate the intervention's uptake in and impact on an oncology care setting or nonprofit organizations.

Trial Registration: ClincalTrials.gov NCT04713449; https://clinicaltrials.gov/ct2/show/NCT04713449

International Registered Report Identifier (IRRID): DERR1-10.2196/39996

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KEYWORDS

oral cancer; cancer survivorship; quality of life; digital interventions

Introduction

Background

In the United States, the American Cancer Society (ACS) estimates that there will be 54,000 new oral and oropharyngeal cancer cases, which will result in 11,230 deaths, in 2022 [1]. There are approximately 91,000 people living with oral cancer in the United States [1]; 50% of these are diagnosed with regional disease, and 17% are diagnosed with distant disease. Traditionally, the main risk factors for oral cancer have been tobacco and alcohol consumption [2]. The incidence also increases with age, with >90% of oral cancer cases occurring in individuals aged >45 years [3]. Gastroesophageal reflux disease has been associated with oral cancer [4]. Human papilloma virus (HPV) has been associated with oropharyngeal cancer and few other oral cancers [5]. This patient population differs from the population with non-HPV–associated oral cancers in that they are primarily White, nonsmoking, nondrinking males aged between 35 and 55 years who do not have other health issues [6,7]. The 5-year survival rate for all forms of oral cancer has increased from 52.5% to 66.3% over the past 30 years [8]. However, patients with HPV-associated oropharyngeal cancers have a much higher survival rate (80% at 5 years) and longer disease-free survival rate, largely because they are more responsive to therapy [9,10]. There are known disparities in oral cancers. Mortality from oral cancers is higher among Black men [11-15], among men in general [16], and increasing among individuals aged between 55 and 64 and those aged between 65 and 74 years [3,17,18]. In summary, there is a growing population of oral and oropharyngeal cancer survivors, particularly those with HPV-associated cancer [3].

Oral and oropharyngeal cancer survivors experience challenges in both the treatment regimen and long-term self-management and surveillance needs. Treatment can entail surgery, chemotherapy, or radiation. Because of the location of the structures involved, the disease, and the treatment, this cancer can result in debilitating and permanent disfigurement and functional changes that interfere with the ability to swallow, taste, speak, eat, and move the shoulders and neck [19-23]. Long-term medical maintenance needs are complex and can require a diverse care team that can include oncologists, reconstructive surgeons, dentists, physical rehabilitation specialists, speech and swallowing experts, and nutritionists to restore functions or prevent the deterioration of functions [24-27]. Current models of survivorship care place most of the day-to-day responsibility on self-management and care coordination. Even with rehabilitation, many survivors recover their precancer functioning. Thus, the primary goal is to prevent the deterioration of function and maintain comfort. These self-care needs persist throughout the survivor's lifetime.

Adding to these self-management needs are surveillance expectations. Because 20% of survivors develop a recurrence or metastatic disease within the first 2 years after treatment [28], the recommended follow-up regimen includes frequent surveillance by the oncology care team and survivors [1,29,30]. Regular self-examinations to locate suspicious areas in the mouth and neck are recommended [31], as lesions that are not evident on positron emission tomography scans can be detected earlier and checked by a professional. Early detection can reduce morbidity and mortality [32,33]. Adherence to this demanding care regimen is less than optimal: 30% to 50% do not adhere to follow-up appointments, and up to 80% do not adhere to oral care or swallowing recommendations [34-37]. More than half of the survivors continue to drink alcohol, which increases the risk of mortality [38].

This cancer can result in a deterioration in health-related quality of life (QOL). Both cross-sectional studies conducted over the survivorship trajectory [39] and longitudinal studies suggest that patients experience lower health-related QOL [40]. Cross-sectional studies have indicated that global QOL, oral function (chewing, swallowing, tasting, salivating, and speaking), dental issues, and appearance are low over the decade after diagnosis, and studies illustrated higher levels of depression and anxiety (Rogers et al [41]) [41-53]. Longitudinal studies have had variable findings depending on sample composition, time of assessments, and time since diagnosis. As a whole, results suggest that some domains of QOL improve over time (eg, depression, anxiety, appearance, speech, and pain), some return to baseline levels (leisure time activities and swallowing), but many deteriorate or continue to illustrate decrements (eg, dry mouth, shoulder mobility, taste, problems with teeth, sexuality, and role function for work and leisure activities) [54-56]. The literature consistently suggests that survivors report persistent support needs, which include the desire for more information and support regarding long-term effects, recommended follow-up, monitoring symptoms that prompt contacting a physician, maintaining nutrition, improving speech and swallowing, maintaining oral health, and addressing psychological concerns [57-63]. The fact that more than half of the survivors do not receive a survivorship care plan complicates

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matters and may reduce their ability to manage their posttreatment care [64-67]. Due to the ongoing care needs and compromised QOL, it is not surprising that survivors report low self-efficacy in managing their self-care regimen, particularly with regard to conducting oral self-examinations, maintaining proper nutrition, and managing dry mouth and swallowing issues [65,66,68].

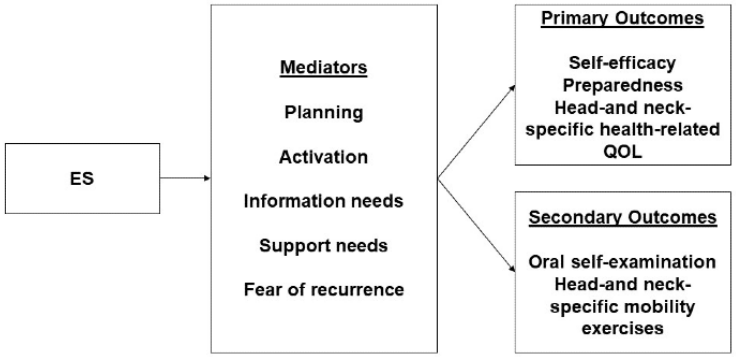
Effective self-management provides survivors with the ability to monitor their cancer-related symptoms and self-care and implement practices needed to maintain satisfactory functioning [69]. Despite the substantial care needs, low self-care self-efficacy, and low participation in self-care, there are only a few self-management interventions for this population. To date, the few published studies have focused on single-symptom pilot studies (eg, swallowing or couple communication) [65,70-72]. To address the need for improved self-management and bolster the self-efficacy in managing self-care, we developed and evaluated the feasibility and preliminary efficacy of a web-based self-management intervention for oral cancer survivors' care called Empowered Survivor (ES).

Theoretical Framework

The development of the ES intervention is guided by the theoretical construct of self-efficacy, which is drawn from social cognitive theory [73,74]. Social cognitive theory focuses on the development of competencies and self-regulation [73,74]. Self-efficacy is a competency defined as the belief in one's ability to execute actions to deal with a situation successfully and comprises 3 domains: knowledge and skills to accomplish the task, confidence in one's ability to motivate oneself and the resources available to accomplish the task, and confidence in one's ability to execute the task [75]. Self-efficacy is a task-specific expectation: people estimate their confidence in their ability to manage a task by evaluating the tasks involved in the successful completion of that task [73,74]. Individuals with high self-efficacy beliefs and abilities regarding a task call upon themselves to execute the task. Confidence in one's ability to execute a task is the most widely studied dimension of self-efficacy. Self-efficacy is linked to the initiation and maintenance of health behaviors [75-83], and greater efficacy is associated with better health behaviors among cancer survivors [84]. Efficacy also predicts psychosocial and functional outcomes among cancer survivors [85,86]. Social cognitive theory has formed the basis of effective intervention programs for improving health behaviors [87-89], disease management among chronically ill individuals, and [90] the health and well-being of cancer survivors [91].

Bolstering self-efficacy in survivorship care is a primary outcome and target of ES. To delineate the mediators of ES's impact, we propose a heuristic framework based on social cognitive theory. First, we use the work of Gollwitzer and Schwarzer, which proposes that planning is a key component of self-management and goal achievement [81,92-94]. In our pilot study, planning was associated with greater efficacy and survivorship preparedness [65]. Second, we integrate the construct of patient activation, defined as the willingness to take actions to manage care and understanding one's role in survivorship care [95]. Greater activation is associated with higher self-efficacy in our study [65] and is targeted by ES. Third, we include information needs, defined as the knowledge about treatment effects and care responsibilities. Knowledge of tasks improves self-efficacy, and lower information needs are associated with higher self-efficacy. Fourth, we include support needs, defined as the level of assistance required to accomplish self-care tasks. Unmet support needs are strongly linked to lower self-efficacy [65]. Finally, the fear of cancer recurrence is a common issue among oral cancer survivors and is associated with poorer QOL and lower self-efficacy [49,96,97]. Reducing the fear of recurrence by teaching coping strategies should increase self-efficacy. Our heuristic framework is illustrated in Figure 1. We have selected 3 long-term outcomes to reflect the key components of survivorship self-management: self-efficacy to manage care, preparedness for survivorship, and head- and neck-specific QOL. Finally, the role of self-management interventions in improving the engagement in self-management tasks among survivors has not been well studied. There is extensive literature suggesting that self-efficacy interventions have an impact on self-management among adults with chronic illness [98-101]. This study explores the impact of ES on self-management behaviors. We chose self-management behaviors that are commonly recommended for oral cancer survivors: oral self-examinations and head and neck mobility exercises. Self-examinations assist survivors in finding suspicious lesions early, and head and neck mobility exercises maintain the ability to easily eat, speak, and move. Engagement in both is low. There are other self-management behaviors (eg, not drinking alcohol and not smoking), but they are not issues for all survivors.

Figure 1. Heuristic framework for Empowered Survivor (ES). QOL: quality of life.



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Study Objectives

Overview

The purpose of this study is to evaluate the efficacy of a web-based intervention, ES, against a free, publicly available web-based self-management intervention developed for cancer survivors by the National Cancer Institute (NCI) and the ACS called Springboard Beyond Cancer [102]. A total of 600 patients diagnosed with a first primary oral or oropharyngeal cancer within the past 3 years are being recruited via the New Jersey State Cancer Registry (NJSCR), Cancer Registry of Greater California, and Pennsylvania State Registry and randomly assigned to ES or Springboard Beyond Cancer. The participants complete measures at baseline and at 2 and 6 months after baseline. A process evaluation of ES is completed. The study has 3 primary aims and 1 exploratory aim.

Primary Aim 1

The first primary aim is to evaluate the impact of ES versus Springboard Beyond Cancer on the primary outcomes of self-efficacy in managing care, preparedness for managing survivorship, and head- and neck-specific QOL. We hypothesize that the participants randomized to ES will report significantly greater improvements in self-efficacy for managing their care, preparedness for survivorship, and head- and neck-specific QOL at 6 months.

Primary Aim 2

The second primary aim is to evaluate the mediators (planning, information needs, support needs, activation, and fear of recurrence) and moderators (age, race and ethnicity, HPV status, baseline self-efficacy, and preparedness) of ES's impact on self-efficacy in managing care, preparedness, and health-related QOL. The primary outcomes are self-efficacy in managing self-care, preparedness for managing survivorship, and health-related QOL at 6 months. We hypothesize that the impact of ES on self-efficacy, preparedness, and health-related QOL will be mediated by improvements in survivorship care planning, reductions in information and support needs, and reductions in the fear of recurrence. Little is known about which survivor subgroups benefit the most from self-management interventions. In addition, we hypothesize that the survivors with fewer resources (survivors who belong to people of color, with lower education, who have not received a written survivorship care plan, with less baseline self-efficacy, and with less baseline preparedness) will benefit more from ES.

Primary Aim 3

The third primary aim is to evaluate the impact of ES versus Springboard Beyond Cancer on the secondary outcomes of engagement in oral self-examinations and head and neck mobility exercises.

We hypothesize that the participants randomized to ES will report more frequent engagement in and comprehensiveness of oral self-examinations and head and neck mobility exercises than the participants randomized to Springboard Beyond Cancer at 6 months.

Exploratory Aim

The exploratory aim is to conduct a process evaluation of ES to inform future implementations.

We hypothesize that the participants randomized to ES will use the intervention more, evaluate it more highly, have greater improvements in self-efficacy, preparedness, and QOL.

Methods

Ethics Approval

This study was reviewed and the protocol procedures were approved by the Rutgers University Institutional Review Board (protocol number Pro2020000768). All the participants had a discussion with a member of the research team and read and acknowledged electronic informed consent by clicking "agree to participate" before completing the baseline survey. The participants are assigned a study ID upon entry, and data are stored under the assigned ID. The participants are compensated for their participation in the form of e-gift cards worth US $150 after the completion of 3 surveys and up to US $120 after the completion of the web-based modules if randomly assigned to the ES intervention.

Design

This 5-year study comprises 2 phases. Phase 1 involves additional program development of 2 modules and a maintenance module. This phase of the work has been completed and will be described next. Phase 2 is a randomized clinical trial testing ES against Springboard Beyond Cancer on the web. In the last year, the team will complete the implementation planning to evaluate potential medical and community settings for implementing ES for future scale-up.

Phase 1: Enhancements to the Original Empowered Survivor Content

Original Content

The development of original web-based intervention ES was described in the study by Manne et al [65]. Briefly, it had 4 modules: Introduction, Oral Care, Swallowing and Muscle Strength, and Long-term Follow-up Care and Detecting Lesions. These modules are listed in Table 1. Module 1, Introduction, orients participants and reviews modules. Module 2, Oral Care, reviews the causes, contains a symptom self-assessment, and provides information on how to manage dry mouth. Module 3, Swallowing and Muscle Strength, provides information on the symptoms of swallowing difficulty, methods to reduce swallowing difficulty, and methods to improve flexibility and range of motion in the head and neck. Module 4, Long-term Follow-up Care and Detecting Lesions, describes the importance of head and neck self-examinations; provides information on how to conduct a head and neck self-examination, signs to pay attention to, goal setting, and managing barriers to self-examination; and provides a link to a survivorship care plan website that includes follow-up information, assesses alcohol and tobacco use, and reviews the participant's care team and recommendations. The original ES program had >20 interactive activities to engage participants and foster skill acquisition. An example is symptom assessment, which is followed by

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goal-setting feature. Participants rate symptom severity, frequency, concern about symptoms, and confidence in and importance of managing symptoms. Next, the participants select a goal related to the symptom; rate the importance of the goal; choose strategies to address the goal from a list of ideas; and rate benefits and barriers to achieving the goal, confidence in achieving the goal, and support needed to achieve the goal. This function is in modules 3 and 4.

Table 1. Empowered Survivor intervention modules.

Module	Goal	Activities
Original modules		
1: Introduction	• Orient participants and introduce team • Review program modules and navigation • Provide recommended modules • Enhance engagement with survivor stories • Introduce rationale, importance, and steps for self-management	• Narrated introduction by oral surgeon to introduce self-management • Discuss the importance of self-care and set expectations • Sample goal-setting exercise
2: Swallowing and Strength	• Understand the symptoms of swallowing difficulty • Optimize swallowing ability • Improve strength and mobility in head and shoulder • Improve lymphedema management • Facilitate personal goal setting	• Self-assessment of swallowing difficulty, lymphedema, and flexibility • Videos of swallowing and strengthening exercises • Videos of exercises for lymphedema • Goal setting, barriers, and strategies
3: Oral Care	• Understand causes of dry mouth and what exacerbates it • Assess dry mouth symptoms and severity • Understand strategies to keep one's mouth moist • Assess nutritional needs • Understand ways to improve nutrition • Facilitate goal setting for dry mouth and nutrition	• Videotaped introduction by surgeon • Patient experiences with dry mouth • Self-assessment of dry mouth symptoms • Tips for managing dry mouth • Food preparation for dry mouth • Choose high caloric foods (quiz) • Goal setting, barriers, and barriers
4: Long-term Follow-up Care	• Understand how to do a self-examination • Set goals and manage barriers for self-examination • Develop a survivorship care plan that includes follow-up recommendations • Create a personalized follow-up care plan • Identify your care team and unmet care team needs and create a list of health care resources • Learn strategies to communicate with oncology care team • Assess current smoking and alcohol use • Increase motivations to stop smoking and drinking • Understand and manage other medical issues	• Videotaped demonstrations of examinations • Self-management tool to plan oral examination • Get your survivorship care plan • Unmet need assessment for survivorship care • Who is your care team? Who does what? • Do you have any communication concerns? • Communicate with providers about survivorship • Create a plan for managing comorbid illnesses • Assess tobacco and alcohol use and treatment motivation • Education about the health impact of continued use of alcohol • Link to Drinkerscheckup and BetheMatch
New modules		
5: Calm and Connect	• Improve the understanding of psychological concerns • Enhance awareness about how feelings may affect self-care and that self-care of emotions is self-care • Devise strategies to manage emotions and worries • Assess and address special concerns for HPV[a]-associated oral cancer • Unique concerns for young adult survivors • Learn about survivors' emotional reactions and coping	• Rate worries and fears about cancer • Distress assessment • Rate confidence in the ability to manage worries and fears • Videotaped stories of how survivors coped • Link to meditation and mindfulness apps • Choose coping strategy and goals • Assessment of knowledge and worries about HPV-associated oral cancer
6: Maintaining	• Continue working on skills and goals • Learn new information about oral cancer • Communicate with other participants	• Select exercises and skills to move to "Favorites" • Goals are migrated to this module and can be updated and reworked • News posted regularly • Message board

[a]HPV: human papilloma virus.

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Enhancements to the Existing Modules

Enhancements were selected based on feedback from the pilot study participants as well as the team's experience with participants during the ES intervention. In module 1, a section containing information about self-care and goal setting to enhance self-care was added to familiarize the participants with the process. In module 2, the ability to set an email reminder to work on the oral care goal was included to optimize continued implementation. In module 3, because the participants liked the videotaped swallowing exercises and indicated that they would like to see more of them, additional exercises were developed with the team's speech pathologist. The strengthening exercises were originally presented as illustrations but were very highly rated. To foster engagement, the team's physical therapist developed videotaped demonstrations of exercises. Because lymphedema was mentioned as a survivorship concern in participant feedback from the pilot study, information about it and its management was added along with demonstrations of home exercises to manage lymphedema by the team's physical therapist. Finally, additional information on how to add caloric content to food was added. In module 4, to bolster the existing content and address common concerns that were not addressed previously, additional resources were added for tobacco cessation, alcohol use, comorbid medical issues, managing hearing loss, and survivorship care planning. More content on interest in quitting tobacco use and the risks of continued use was added. For current smokers, a link to Becomeanex [103] was provided. If the person indicated a desire to continue smoking, material on the increased risk for cancer recurrence and mortality and reduced treatment benefits for smokers and an assessment of the readiness to quit were added by the team member MBS. As for alcohol use, if the participant indicated a desire to continue drinking, a link to Drinkerscheckup [104], an empirically based, web-based treatment, was provided [105]. As comorbid medical issues are common in this survivor population, a section was added on "other medical issues." This section assesses comorbid medical problems, associated medications, and interest in improving the management of medical conditions and offers tailored input on the barriers to medication adherence based on an assessment of barriers. Finally, the team's audiologist added additional material to address the management of hearing loss and tinnitus.

New Modules

A total of 2 new modules, which were originally planned but not developed, were created: module 5, Calm and Connect, and module 6, Maintenance. The goals of Calm and Connect are to describe common psychological concerns patients experience after treatment, increase the awareness of how cancer has affected the participant's emotional well-being, assist the participant in developing useful methods to deal with emotions, provide free web-based resources on coping with stress, and discuss psychosocial aspects of having HPV-related oropharyngeal cancer. The introduction portion contains a video introduction by a psychologist portrayed by an actor and audiotaped narratives presenting patients' emotional experiences. In the next 3 sections, the following coping skills are addressed: (1) managing stress with relaxation, (2) increasing the tolerance for upsetting emotions using acceptance-based strategies, and (3) talking it out with others. A fourth section was developed to address the unique concerns experienced by the survivors of HPV-associated cancers, including common worries (eg, transmission to others), managing questions from friends and family about HPV, and feeling embarrassed about HPV, and the unique experiences of young cancer survivors**.** All sections include interactive activities. For example, the participants can select their key signs of stress, which activates a patient narrative about the signs of stress and narrated educational content. There are also audio relaxation exercises led by a psychologist portrayed by an actor, self-reflection exercises in which the participant types in responses, and links to outside resources such as web-based apps for meditation and mindfulness exercises (Headspace and Calm).

The goal of module 6, Maintenance, is to facilitate ongoing engagement in self-management, evaluate the progress on goals, provide opportunities for interaction with other study participants, and provide new information. This module has 4 features, namely (1) Favorites: the participants choose their favorite content and exercises from screens throughout the program. Across the ES program, 28 pages can be chosen as favorites. These pages are migrated to the Favorites section for future reference, and participants can log in directly to this content; (2) Goals: goals set by the participants in each module are automatically migrated to this section, where the participants can directly access, review, revise, and update them and set up email reminders about them to send to themselves; (3) News: articles of interest from science and medicine sources are posted by study staff on a regular basis; and (4) Message Board: the participants have access to the Message Board throughout their participation in this study. Every month or two, interesting news articles about oral cancer are placed on the board by the project team. When there is a post, the participants receive an email notification that a message has been posted. They can review the post and post messages at that time. They can also access the message board at any time.

Both enhancements to the existing content and new material were developed in collaboration with ITX, incorporated. ITX is a web-development company and the developer of the original ES intervention. Content was reviewed and implemented during a series of regular meetings between the study team and the ITX development team over a 6-month period. The videotaped and narrated content was created in collaboration with Mindful Designs.

Patient Advisory Board Feedback

The Patient Advisory Board consisted of 3 oral and oropharyngeal cancer survivors. The board members reviewed the Calm and Connect module after it was developed and provided feedback in a web-based meeting. Notes from the meeting were reviewed by the study team. No substantive content changes were made, other than those intended to fix grammatical and navigation issues.

After the new modules were finalized and enhancements were incorporated into the existing modules, the Patient Advisory Board reviewed ES. Board members were sent a link to ES and asked to review the content and note recommended changes and any feedback. Next, web-based 1:1 interviews were

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conducted to review content and collect feedback. The following key suggestions were given: several modules: correct navigation errors; module 1: provide more clarity with regard to navigating the menu bar, reduce expectations for goal setting by reminding participants that it may be easier to choose small goals, and add definitions of additional key terms; module 3: provide the ability to print the swallowing exercises; and module 5: add content to normalize the desire to get one's life back to normal. The study team reviewed the interviews to select modifications. All of the listed changes were made. There were several suggested changes that were evaluated as less relevant to most survivors and were not incorporated. Content changes were implemented using ITX. The final content is shown in Table 2. The sample content from modules 6 and 7 are shown in Figures 2-8. There are more than 75 interactive activities in ES, including in-session exercises, live links, self-assessments, and video and audio narratives. Multimedia Appendix 1 [106] outlines these activities.

Table 2. Study measurement schema.

Measure	Screening	Baseline	Time 2	Time 3
Covariates				
Date of birth	✓			
Sex		✓		
Marital status		✓		
Race and ethnicity		✓		
Education		✓		
Insurance status		✓		
Employment status				
Regular primary care		✓		
Financial hardship		✓		
Tobacco use and history		✓		
Alcohol use		✓		
Date of diagnosis		✓		
Treatment history		✓		
Survivorship care summary		✓		
Outcomes				
Self-efficacy	✓	✓	✓	✓
Preparedness	✓	✓	✓	✓
Head and neck QOL[a]	✓	✓	✓	✓
Oral self-examinations	✓	✓	✓	✓
Head and neck mobility exercises	✓	✓	✓	✓
Mediators				
Planning		✓	✓	✓
Activation		✓	✓	✓
Information needs		✓	✓	✓
Support needs		✓	✓	✓
Fear of recurrence		✓	✓	✓
Intervention evaluation (treatment evaluation)			✓	
Qualitative data (structured interviews)				✓
Adverse event assessment (depressive symptoms)		✓	✓	✓

[a]QOL: quality of life.

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Figure 2. Sample page from Calm and Connect Empowered Survivor (1).

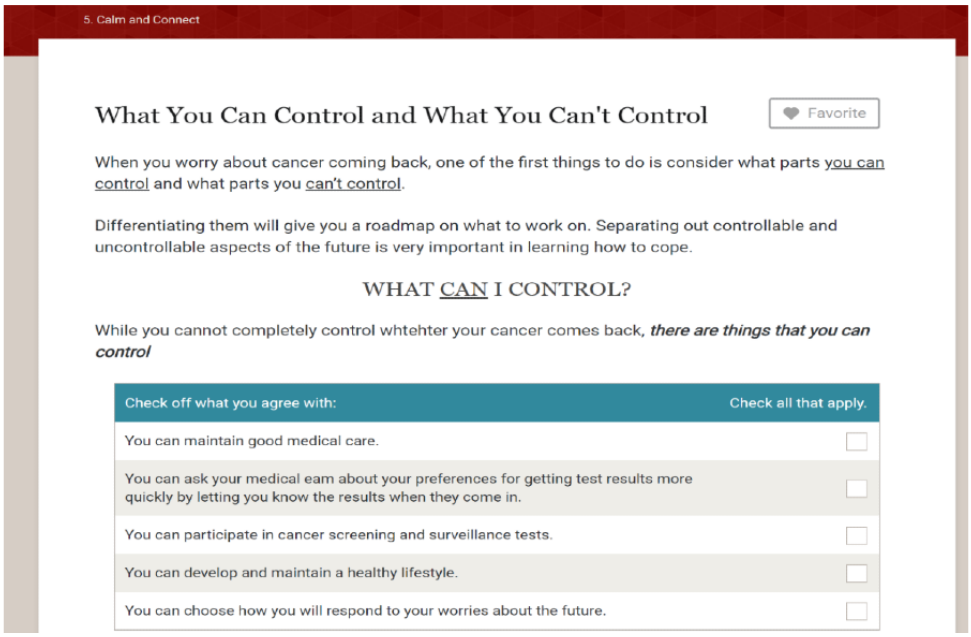
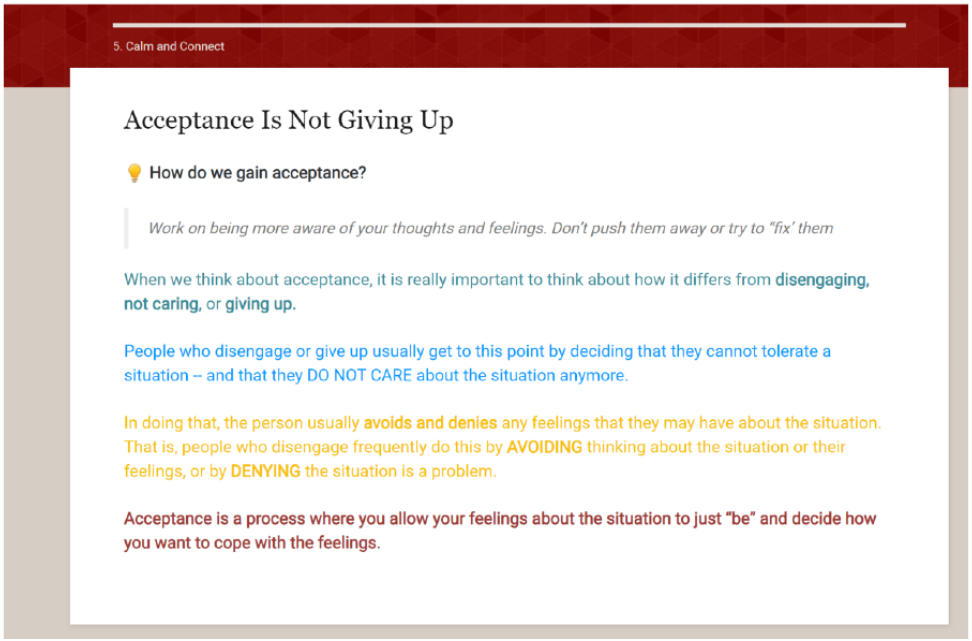


Figure 3. Sample page from Calm and Connect Empowered Survivor (2).



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Figure 4. Sample page from Calm and Connect Empowered Survivor (3).

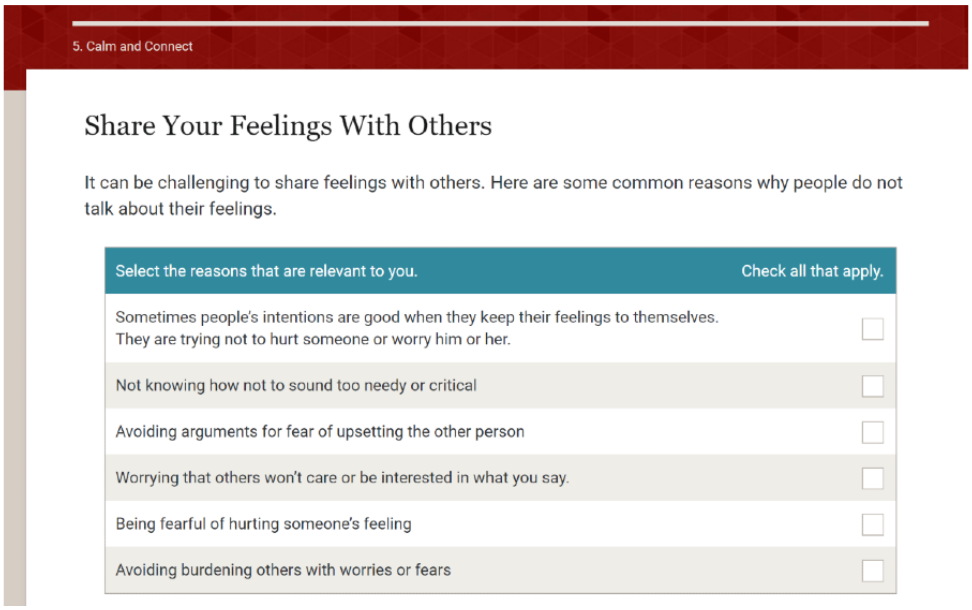
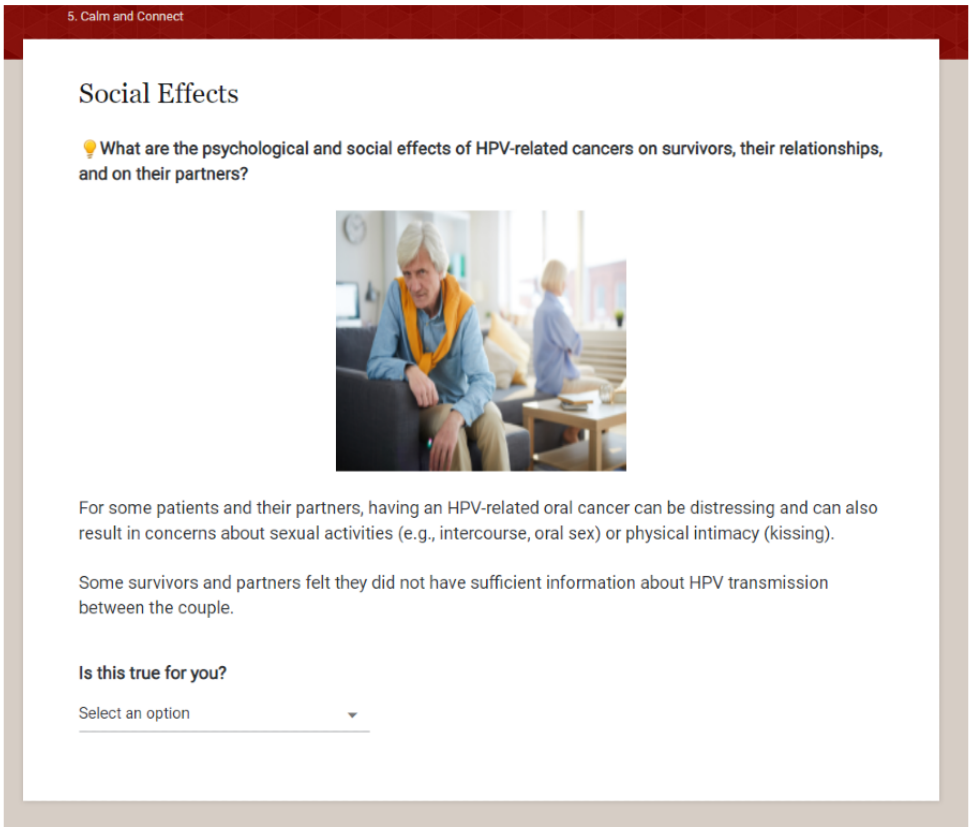


Figure 5. Sample page from Calm and Connect Empowered Survivor (4).



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Figure 6. Sample Maintenance module screenshot (1).

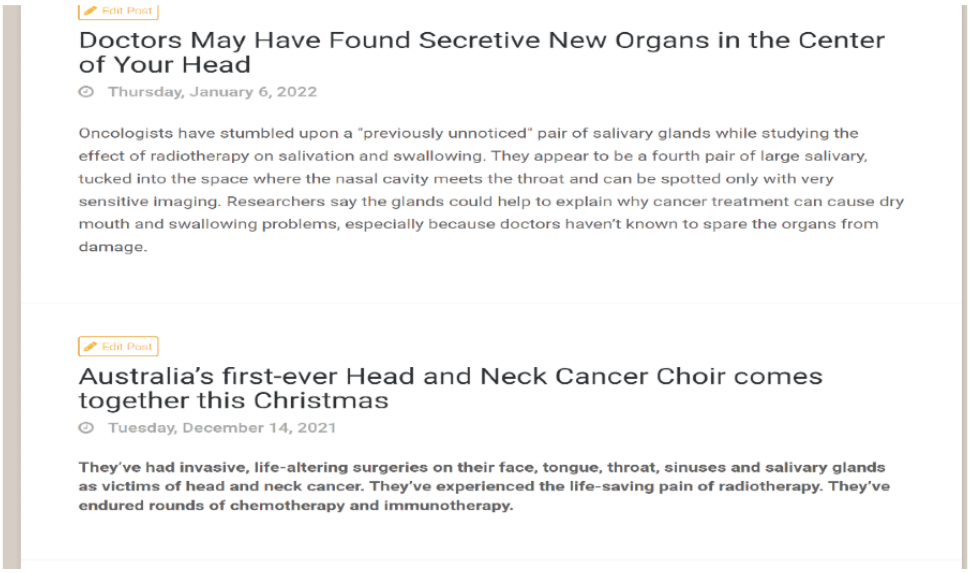
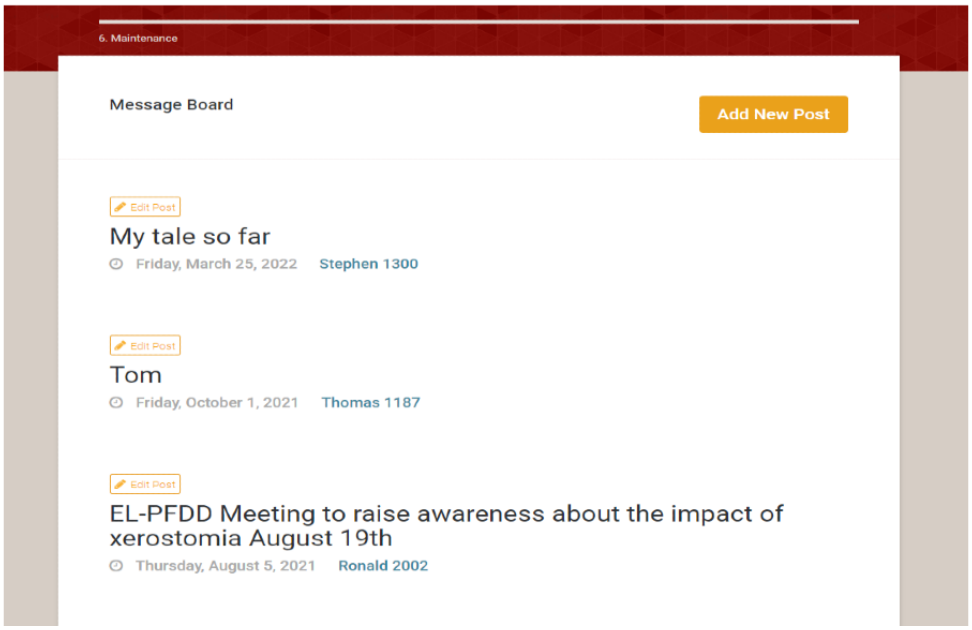
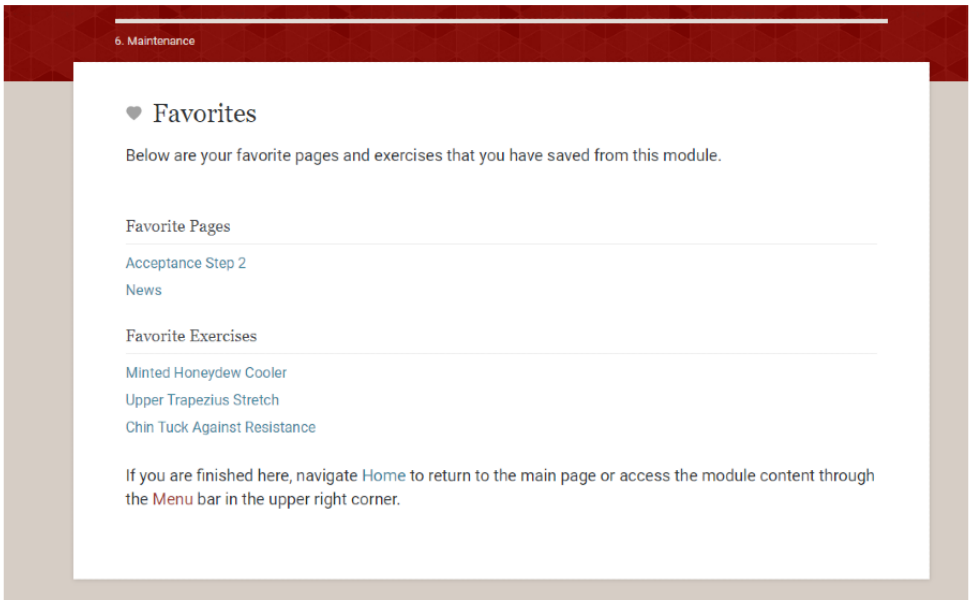


Figure 7. Sample Maintenance module screenshot (2).



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Figure 8. Sample Maintenance module screenshot (3).

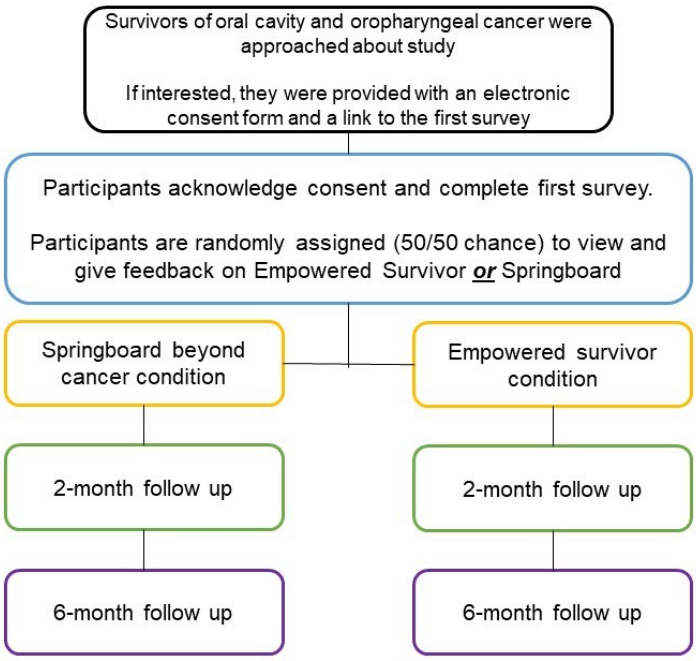


Phase 2: Randomized Controlled Trial

Design

This is a prospective, randomized controlled trial to evaluate the effect of ES on confidence in managing self-care, preparedness, and health-related QOL and on the secondary outcomes of oral self-examination and engagement in head and neck strengthening exercises. This is evaluated in 2 groups with a total of 600 survivors (ES vs Springboard Beyond Cancer) and by 3 assessments (baseline, 2 months, and 6 months). The participants complete surveys at baseline and 2 months and 6 months after baseline. Figure 9 illustrates the participant flow. A free, publicly available general survivorship-focused web-based program, called Springboard Beyond Cancer, was selected for comparison based on a review of the literature on the design of behavioral interventions [98,107,108]. This review suggested that there are pros and cons to all comparison conditions and that selection should be guided by the phase of the research. We selected a comparison condition that had the same method of delivery (web-based delivery), same frequency of delivery, and similar topics.

Figure 9. Study flowchart.



Participants

The participants are recruited from 2 state registries and through clinic recruitment. The eligibility criteria are as follows: participants should (1) be aged >18 years, (2) be diagnosed with a first primary oral cavity or oropharyngeal cancer in the last 3 years, (3) be currently cancer free (but could have experienced a recurrence), (4) have computer access, and (5) be able to read English. Children are not included because the incidence of

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these cancers in children is exceedingly rare (0.2 cases/100,000 children).

Among the cancer registries, approximately 1600 patients are diagnosed with a first primary oral or oropharyngeal cancer per year. Our pilot study suggested that 26% of eligible patients will consent and complete the baseline survey. This enrollment rate is consistent with or higher than that of other intervention trials recruiting from cancer registries (18%-30%) [99,100]. Recruitment will be conducted for approximately 27 months. The sample size is based on the power to detect the effects on our primary outcomes. With 1600 patients available each year and 3 years of data collection, we have a large pool: given the 4800 total participants available and 26% acceptance, we have about 1104 potential participants. The power analysis suggests that the study requires 600 participants.

To achieve this, we include pictures of minority patients on our recruitment materials and oversample Black males in our registry recruitment. We have set a goal to ensure that of the total number of participants enrolled, 8% (n=48) are Black men.

Recruitment

Recruitment was primarily conducted using state cancer registries. Recruitment procedures differ between state registries. For the NJSCR, the registry confirms patient eligibility and, if eligible, sends a letter to the patient's diagnosing physician, making the physician aware that their patient is eligible. If the NJSCR does not receive a disapproval from the physician within 2 weeks, the patient is sent a cover letter and an "agreement to contact" sheet. Potential participants are called by registry staff to discuss the study. The participants have the option of verbally consenting at that time. The participants who consent have their contact information and a copy of verbal consent forwarded to the members of the study staff, who call the patient. Patients deemed eligible are provided with a web-based consent and survey. The staff members contact patients weekly if they do not return the consent. Patients are considered passive refusers if they do not return a survey after repeated call attempts during days, nights, and weekends over a 3-week period after the consent is sent. For the Cancer Registry of Greater California and the Pennsylvania State Registry, the registry provides a list of patients and their contact information to the staff members. The staff members call patients, and those deemed eligible are provided with a web-based consent and survey, and the same procedures for enrollment as described above for the NJSCR are implemented. A maximum of 8 recruitment calls are allowed: 4 calls can be followed with a voicemail message, and 4 calls are counted as missed calls. Of these 8 contacts, 1 can consist of a text message. Once the electronic consent and survey are completed, the participants are automatically randomly assigned to the ES or Springboard condition using a data management system. Separate assignment schemas are set up for each registry by the study's statistician.

Participants who do not complete the consent and baseline are contacted by phone or email on a weekly basis for 1 month to facilitate survey completion. The participants are automatically linked to one of the web-based interventions (ES or Springboard) as soon as they are randomized upon the completion of the baseline survey.

Interventions

Empowered Survivor

The ES program is described in Table 1, and Figures 2-9 provide examples of the content. The content is accessible via any device that is connected to the internet such as a tablet, an iPad, a phone, or a computer. If the participants experience issues in viewing information, they are contacted by phone to troubleshoot. The ES program can be completed in 1 sitting however, the orientation encourages the participants to complete ES over a longer period and emphasizes setting and implementing self-care goals and building self-management skills. A week after randomization, a team member contacts the participants to conduct a brief motivational discussion, the goals of which are to go over the content and benefits of the intervention, ask the participant whether they were able to log into the program, ask whether the participant whether they have questions, and offer to log in with the participant to review the Introduction module. The participants who do not log in by day 3 are sent a reminder email to log in, and the participants who do not log in by day 5 are sent a second reminder email to log in. When "News" or "Message Board" content is added, an email alert is automatically generated for the participants. The participants are provided a small incentive for completing the modules (US $20). The participants who do not log into the program within a month are entered into a lottery for a gift card worth US $20. These methods are recommended in systematic reviews and meta-analyses of factors important for revisits and continued use of internet interventions [101].

Springboard Beyond Cancer

Springboard Beyond Cancer is a self-management program developed by the ACS and the NCI. The program covers 4 main topics: Symptoms, Stress and Mood, Wellness, and Get Support. Each topic has several pages describing the topic and providing information on signs and symptoms, tips on how to manage the issue, and links to resources. The participants can move the tips to their Action Deck for future reference. Unfortunately, at the end of 2020, the NCI ended its contract with the ACS, and no longer hosted the Springboard website. The website was moved to an archive status [102], and the dynamic features of the site (eg, videotaped content) were disabled. After discussions with the NCI and ACS, an archived version of Springboard Beyond Cancer was shared with the study staff, and the NCI confirmed that the link would remain active throughout the study period. The team was able to provide the disabled videotaped content as a Springboard YouTube playlist [102]. This playlist houses all videos embedded in the Springboard website that were deactivated. In addition, the participants are provided with the ACS Survivorship: Before and after treatment website [109], which includes information on coping with cancer, maintaining a healthy lifestyle after treatment, and managing cancer as a chronic illness and survivorship resources (ie, care plans). The participants receive the Springboard YouTube link in the welcome email once they are randomized to the Springboard arm. A week later, they receive a second welcome email, which contains live links to ACS and Cancers survivor network. Sample pages are shown in Figures 10-13.

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To facilitate engagement, within a week of sending the link to Springboard Beyond Cancer, the coordinator will reach out via phone to conduct a brief motivational discussion. The goals of this discussion are as follows: review program content and benefits, ask the participant whether they were able to log into the website, ask the participant whether they have questions, and offer to log in with the participant to review the Introduction. A week after the Springboard website is emailed to the participants, we will send another email with the ACS Survivorship website link. This email highlights sections of the website that the study team believes will be most useful for the participants. The coordinator manually sends an email or text to the participants 1 month after randomization, reminding them to return to the websites.

Figure 10. Sample page from Springboard Beyond Cancer (1).

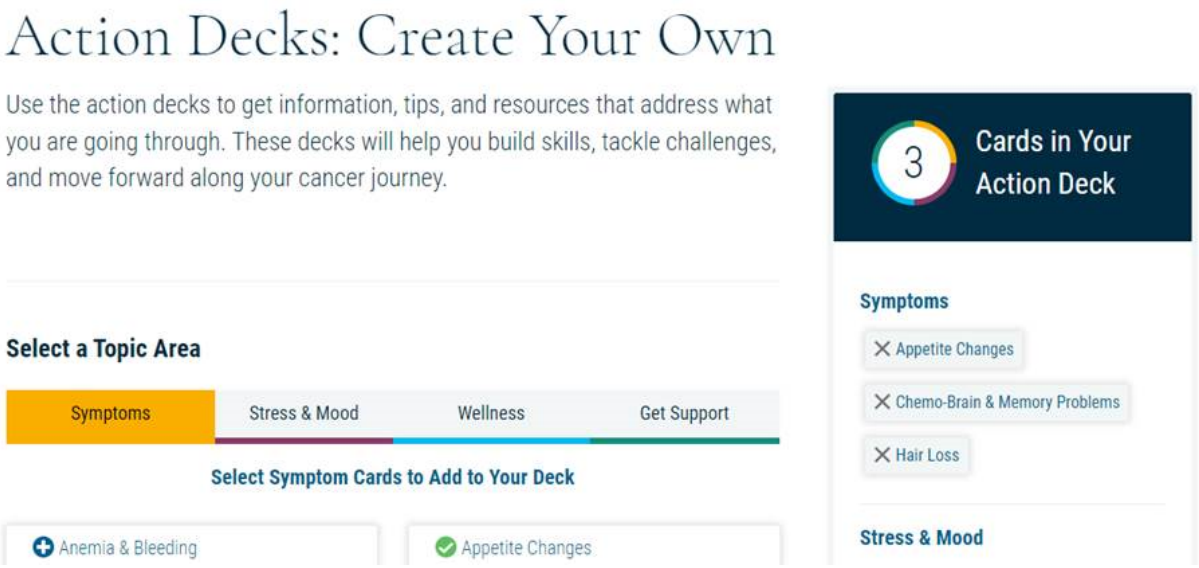
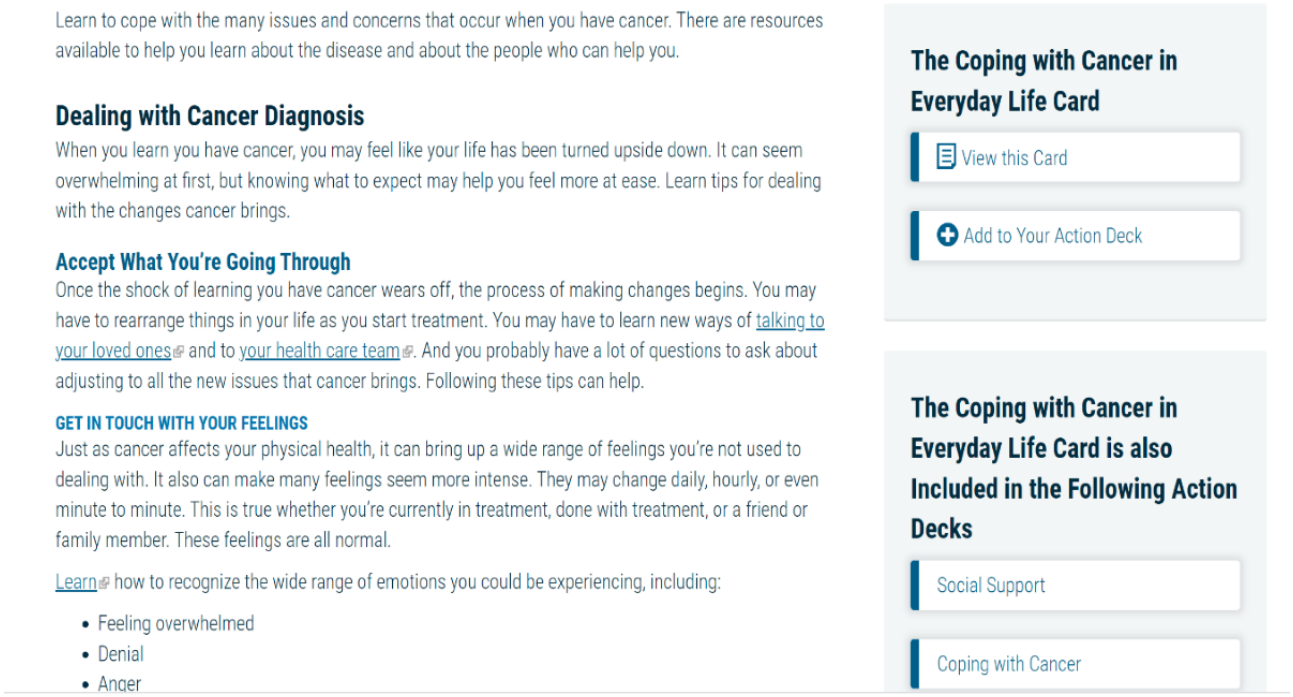


Figure 11. Sample page from Springboard Beyond Cancer (2).



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Figure 12. Sample page from Springboard Beyond Cancer (3).

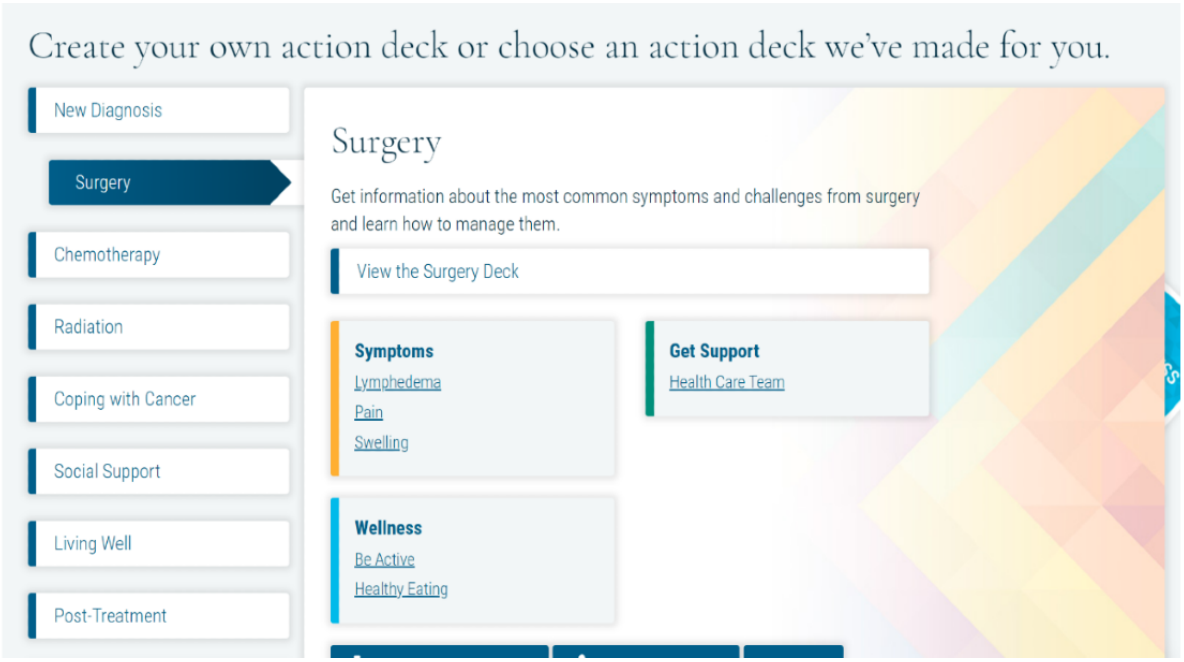
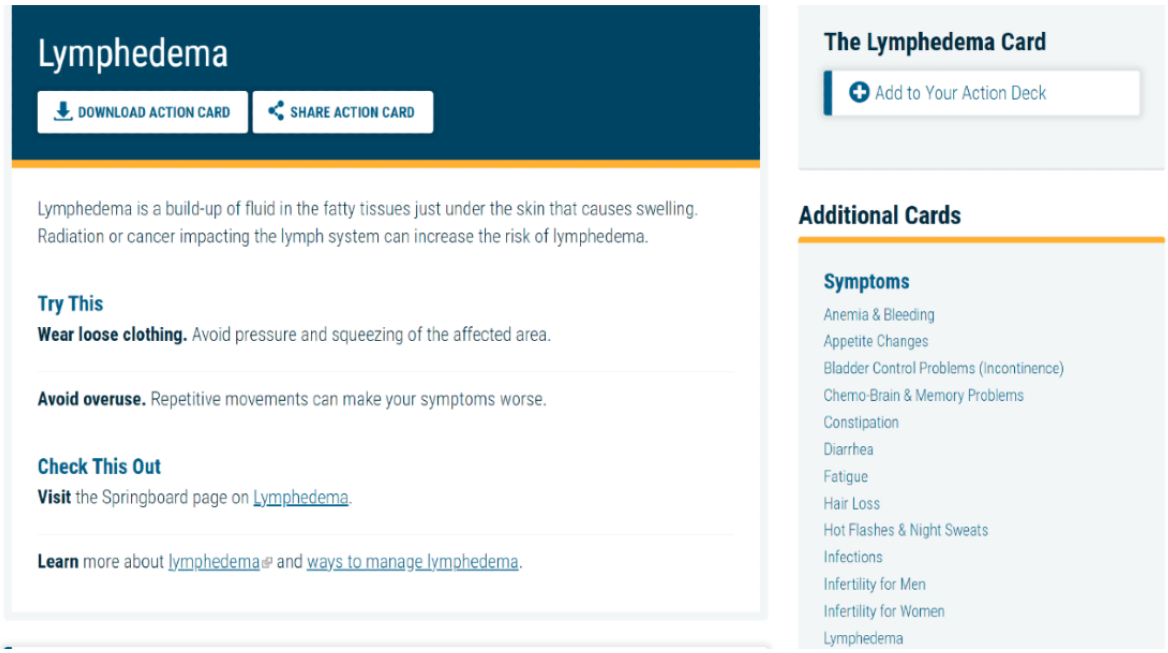


Figure 13. Sample page from Springboard Beyond Cancer (4).



Survey Procedures

The participants complete electronic surveys via a web-based data management system (DatStat) at 3 time points: baseline and 2 months and 6 months after baseline. Table 2 presents the timing of the measures. At the 2- and 6-month time points, regardless of the intervention progress, the participants are sent an email with a link to the follow-up survey. To the participants who do not complete the survey within a week, 3 weekly email and phone call reminders will be sent. After 4 weeks, the participants who do not complete the survey will be considered noncompleters for that survey but will be sent a link to the next follow-up survey. The participants will receive a web-based gift certificate worth US $50 for completing each survey. Each survey takes approximately 30 minutes to complete.

Primary Outcome Measures

Oral Cancer Self-management Self-efficacy

This scale was developed for the pilot study [65] and consists of 22 items assessing participants' confidence in dealing with 11 areas: management of dry mouth symptoms, dental care, proper nutrition, swallowing and speaking difficulties, neck and shoulder muscle flexibility and strength, follow-up care appointments, communication with providers, detecting lesions through self-examination, emotional responses, smoking, and alcohol use. One of the items assess the overall confidence in managing head and neck survivorship care. Ratings ranged from 1 (*not at all confident*) to 5 (*very confident*).

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Preparedness

This 10-item scale assesses whether the information received about survivorship care was sufficient, helpful, comprehensive, and covered self-care tasks (1=*strongly disagree*; 5=strongly *agree*) [65,110-112]. Of the 10 items, 2 items assess how satisfied the cancer survivors are with the quantity of the information provided and the way in which the information was provided (1=*not at all satisfied* and 4=*very satisfied*).

Head and Neck Health–Related QOL

The European Organization for Research and Treatment of Cancer-Quality of Life Questionnaire-Head and Neck-43 (EORTC-HN-43) is the updated version of the EORTC H&N 35. This measure has strong convergent validity with EORTC H&N 35 [113-115]. The EORTC-HN-43 is the most widely used measure of head and neck QOL and has been rigorously and systematically validated in 18 countries.

Secondary Outcome Measures

Performance of Oral Self-examinations

The participants are asked whether they conducted a comprehensive examination of the inside of their mouth, the outside of their mouth (the face), and their neck to look for signs of oral cancer in the last month. The participants who report conducting an examination are asked whether they checked 11 different areas (eg, face, neck, inside of cheek, floor, and roof of mouth) and asked the degree to which they know what to look for when conducting an examination (1=*not at all*; 5=*completely*).

Engagement in Swallowing and Jaw and Neck Strengthening Exercises

The participants are asked whether they engaged in exercises to improve swallowing (tongue, jaw, Masako maneuver, Mendelsohn maneuver, and effortful swallow) in the last month (*yes/no*) and whether they engaged in exercises to improve or maintain muscle strength in the jaw and neck (jaw relaxation, turtle, and neck flexion and extension) in the last month (*yes/no*).

Sociodemographic Measures

The participants report sex, age, education level, marital status, insurance status, race and ethnicity, income, and financial hardships in the last month ("Did you have adequate financial resources to meet the daily needs or you and your family?").

Medical and Clinical Measures

At baseline, the time since diagnosis, whether the survivor had been diagnosed with a second cancer, recurrence status, treatments received (radiation, chemotherapy, and surgery), and comorbidities (Charlson index [116]) are reported by the participants. At all time points, oncology-related service use is reported by the participants. Tumor location and cancer stage are extracted from the tumor registry data. Tumors are characterized as oral, oropharyngeal, or salivary cancers. The participants also report the receipt of a survivorship care plan, their HPV tumor status, their current tobacco and alcohol use, and their current insurance status.

Mediator Measures

Action Planning

This 8-item measure assesses the degree to which a detailed plan has been made for self-care tasks (related to dry mouth, swallowing, muscle strength, detecting lesions, and long-term follow-up care) and how to manage interference in these plans (1=*strongly disagree*; 5=*strongly agree*) [94,117].

Patient Activation

This measure consists of 13 items measuring attitudes toward adopting an active role in care [118]. These items were adapted to assess head and neck cancer care. The following are a couple of sample items: "When all is said and done, I am the person who is responsible for managing my head and neck cancer care" and "I am confident that I can take actions that will help prevent or minimize some symptoms or problems associated with my head and neck cancer care" (1=*disagree strongly*; 5=*agree strongly)*.

Information Needs

This 23-item scale, adapted from the Health-Related Topics section of the Follow-up Care Use Among Survivors [119] and prior work, assesses [67,119] the desire for more information about oral cancer topics (1=*yes* and 0=*no*).

Support Needs

The Supportive Care Needs Survey [120] is a 34-item scale assessing physical, psychological, and health care system needs (1=N/A [not applicable]; 5=*high need*).

Concerns About Recurrence

Five items assess the worry about the recurrence of oral cancer (eg, "How much does the possibility that your head and neck cancer could recur upset you?") [121]. An additional 27 items assess the degree to which worries about recurrence interfere with different life domains (eg, possibility of death, future treatment, femininity, sexuality, and body image).

Psychological Distress

The Patient Health Questionnaire-9 [122] is a self-report measure of depression that assesses key diagnostic criteria for depression based on the original PRIME-MD. It is a widely used measure and has demonstrated strong reliability and construct validity [123] in nonill populations as well as cancer populations [123]. Scores from 0 to 4 indicate no or mild depression, from 5 to 9 indicate mild depression, from 10 to 14 indicate moderate depression, from 15 to 19 indicate moderately severe depression, and from 20 to 27 indicate severe depression.

Treatment Evaluation

In both interventions, the following are assessed: (1) 17 items assess general features and content (use, helpfulness, learning something new, interesting, and valuable) and the degree to which the program improved confidence in managing symptoms and (2) 5 items assess website features (eg, for ES, survivor stories, goal setting, and discussion board and for Springboard, action card decks, symptoms page, stress and mood page, and wellness page). For ES, an additional 19 items assess the content of each module. Open-ended feedback is solicited.

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Semistructured Interviews With ES Participants and Providers

A total of 30 participants from the ES condition participate in a brief web-based or phone interview. The survivors will be contacted after they complete the 6-month follow-up. The questions ask the participants about the best timing for the intervention (during or after treatment or another time), delivery schedule (all at once or one module at a time), best setting to offer the intervention (eg, dental visits or oncology care), and whether the participant would be willing to pay for the intervention.

In year 5 of this project, the team will conduct key informant interviews with 30 oral cancer providers (eg, oncologists and physical therapists) who have contact with this population. Questions will focus on the timing (eg, right after treatment), duration (weekly vs all at once), and settings (eg, during dental visits) that they feel would make ES most useful.

Results

Approach to Missing Data

To account for missing values owing to loss to follow-up, we will adapt the sensitivity analysis method proposed by Scharfstein [124] to estimate effects over ranges of assumptions about the relationship between dropout and response. To evaluate bias, we will examine the predictors of dropout at follow-up. We will evaluate demographic and medical factors, baseline alcohol use and smoking, and baseline self-efficacy as predictors.

We will use an intent-to-treat approach to analyze primary and secondary outcomes. Our approach to recruitment and retention minimizes missing data by contacting participants who do not complete sections of the survey and by incentivizing participation. Initial analyses will examine the characteristics of noncompleters. As recommended by Lang and Little [125], multiple imputations (using 50 imputed samples) will be used to impute missing values.

The treatment of covariates also warrants attention. Possible covariates include the demographic variables, objective risk variables, and medical variables of the survivors. Finally, to determine which covariates should be included in the analyses, preliminary analyses in which each outcome is predicted by the full set of qualifying covariates will be conducted. Only those covariates that significantly predict at least 1 outcome will be included in the analyses. Once the set of covariates is determined in this manner, the same set of covariates will be included in all analyses.

Aim 1: Approach and Analysis Plan

Approach

The primary aim is to examine the relative impact of ES versus Springboard Beyond Cancer on our primary outcomes of self-efficacy in managing self-care, preparedness for managing survivorship, and health-related QOL at 6 months. We anticipate that 600 survivors will enroll (300 in each condition), and we conservatively estimate, based our ES pilot, that 80% (n=480) will complete the 1-month follow and 75% (n=450) will complete the 6-month follow-up. However, all available data will be included in the analyses.

Analysis

Multilevel modeling (MLM) will be used to examine whether there are significant differences between the ES and Springboard Beyond Cancer interventions over time. In our primary analysis, both time and treatment will be treated as categorical. This approach yields a main effect for treatment, a main effect for time, and an interaction between time and treatment. Covariates will include 3 effect-coded variables representing sex, race and ethnicity, marital status, education, age, tumor location, stage, time since diagnosis, whether the cancer recurred over the study period, whether the participant received a survivorship care plan, HPV status, and baseline tobacco and alcohol use. The MLM approach has the advantage that it does not exclude participants with missing data at some time points, as would be the case if a traditional ANOVA were used. Thus, this analysis used all available data.

Power and Sample Size

Power is calculated for the intent-to-treat effect sizes from the pilot study**,** assuming that 2-sided *z* tests are conducted at the $P<.05$ level. With an intent-to-treat analysis and a total sample of 600 participants, there is >99% power to detect significant differences between ES and Springboard Beyond Cancer in our primary outcomes of self-efficacy and preparedness for survivorship. There is 90% power to detect significant differences in health-related QOL at the 6-month follow-up.

Aim 2: Approach and Analysis Plan

Approach

This aim evaluates the hypothesized mediators of the expected association between the intervention and outcomes and hypothesized moderators of the intervention effects. Mediators include action planning, information needs, support needs, patient activation, and the fear of recurrence. Moderators include race and ethnicity, education, receipt of a survivorship care plan, baseline self-efficacy, and preparedness. Figure 2 depicts the proposed mediational model in which the intervention impacts the survivors' planning skills; reduces their information and support needs; and reduces their fear of recurrence, which ultimately impacts their self-efficacy, preparedness, and health-related QOL.

Analysis

Analyses will be conducted using 3 separate mediational models for the 3 primary outcomes. The indirect effects of ES on outcomes will be tested using changes in outcomes from baseline to 6 months as dependent variables, changes in the mediators from baseline to 2 months, and changes in mediators from baseline to 6 months. The SPSS macro (IBM Corp) will generate 5000 bootstrapped samples using random sampling with replacement to generate estimates and CIs around the indirect effects [126,127]. The mean of the 5000 indirect effect estimates based on the bootstrapped samples will be examined. Within a multiple mediator model, the indirect effect of each mediator is its unique effect on the outcome when controlling for the

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other mediators included in the model. We propose that ES will have stronger mediating effects than the Springboard Beyond Cancer intervention.

Treatment moderators will also be evaluated. Very little is known about which survivor subgroups benefit the most from self-management interventions. The available research suggests that survivors with fewer resources (eg, lower education) benefit more [128-132]. We will adopt a similar hypothesis and examine the role of low resources, people of color, lower education, not having received a written survivorship care plan, less baseline self-efficacy, and less baseline preparedness, in ES's effects. For moderation analyses with continuous or dichotomous (eg, care plan receipt; White race or people of color) moderators, we will simplify the analysis by using MLM with a regression approach in which condition will be effect-coded (ES=1 and generic=−1) and time will be treated as a quantitative variable that was coded in months (0, 2, and 6) and then grand-mean centered. Moderator variables will be grand-mean centered (eg, baseline self-efficacy) or effect-coded (eg, care plan receipt). Moderation analyses will include the same set of covariates used in the primary analyses described for the primary aims.

Power and Sample Size

On the basis of the simulations and corrected bootstrap method outlined in Fritz and Mackinnon [130], there is at least a power of 0.85 to detect small effects (Cohen *d*=0.26) from both the independent variable to the mediators and the mediators to the dependent variable.

Aim 3: Approach and Analysis Plan

Approach

This aim focuses on 3 recommended self-care tasks: oral self-examinations and the level of comprehensiveness of self-examinations, engagement in swallowing exercises, and engagement in head and neck mobility exercises.

Analysis

We will use the same approach as that outlined in the analysis of the primary aim.

Power and Sample Size

Assuming an intent-to-treat analysis and a total sample of 600 participants, we have 99% power to detect significant changes in oral self-examination and comprehensiveness of oral self-examination and 85% power to detect improvements in performance of swallowing exercises. Owing to low power, the performance of head and neck exercises is exploratory.

Exploratory Aim: Approach and Analysis Plan

Approach

The broad implementation of a survivorship-focused intervention involves a community-based implementation. It is premature to broadly implement ES before determining its efficacy. However, as a first step in this process, we will conduct a process evaluation. First, we will use participant treatment evaluations and use data from ES. Systematic reviews have found that the average adherence to web-based health interventions is 50% to 53% [132,133]. ES use was higher in the pilot study in that 75% of the participants viewed 3 to 4 modules [65]. Most web-based interventions are designed to be used at least weekly for several weeks, but many participants access the interventions only once [132-134]. We will examine the predictors of ES use and evaluate the association of ES use with the primary outcomes. This analysis assists in identifying subgroups for targeting to improve the use of the intervention. Second, we interview a randomly selected subset of 30 ES participants to provide feedback upon the completion of the last follow-up. Third, we conduct key informant interviews with 30 oral cancer providers (eg, oncologists and physical therapists) who have contact with this population to identify potential settings for implementation.

Analysis

As for the participants, we record whether, how frequently, and for how long the participants logged into ES and how many modules are completed. In the analyses, we (1) examine whether these variables are associated with the primary outcomes, (2) evaluate the association of demographic factors (race and ethnicity, alcohol use, and tobacco use) with ES use, and (3) use an evaluation survey and web-based use data from ES.

For the survivor and provider interviews, interview data are transcribed. The analysis explores feedback on barriers to ES use in clinical practice and the preferred timing of ES (eg, should ES be introduced at a follow-up visit, in the waiting room, and by a navigator or health coach?). Analysis of interview transcriptions follow the "constant comparison" analytic approach [135], a method of explanation building in which the findings of an initial case are compared with a provisional category and revised as needed with new cases. This process is continued until an area of interest is fully explicated, reaching theoretical saturation [135]. Central to this process is "thematic" coding. We will develop an initial set of codes. For each code, we will develop ≥1 "secondary codes" that represent more specific aspects of the phenomenon. The schema organizes and assimilates data. The transcripts will be coded by at least 2 coders. Discrepancies will be resolved, and the process will be repeated until an acceptable level of intercoder reliability is achieved (using chance-corrected statistics such as κ for nominal data) [136]. Coded transcripts will be analyzed using the ATLAS.ti qualitative software (ATLAS.ti Scientific Software Development GmbH) [137].

This information will be used to create a website that serves as a storage house for all the study materials. On this website, the team will publish a free manual that details how to access ES and the methods to enhance ES use and contains information on hard-to-reach survivors and our publications and presentations.

Data Safety and Monitoring

A serious adverse event (AE) is defined in this study in 2 ways. First, if the participant dies between baseline and follow-up, this is an AE. This situation will not be a study-related AE but will be reported to the Institutional Review Board. Second, if a participant endorses elevated depression at any of the 3 study survey time points, this is an AE. We monitor depression using the Patient Health Questionnaire-9 at each assessment time

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point. Scores in the moderate to severe range (defined as a score over 19) of depression indicate an AE. The procedure for handling AEs is that the study's principal investigator will reach out to these participants by phone to assess distress, immediate need for intervention, interest in psychosocial services, insurance needs, and financial needs to determine the appropriate type of service. After assessing distress and support resource needs, our procedures include (1) a mailed list of national cancer patient resources (eg, the Cancer Support Community toll free hotline, Cancer Care support line, and the ACS support line); 2) a mailed list of cancer support groups at hospitals located close to the participant's home, which will be prepared at the beginning of the study and updated regularly; and 3) a list of psychosocial providers within a 30-mile distance of the participant's home, which will be provided by mail and over the phone. We monitor the participants who have endured distress at one time point during the course of the study using the follow-up surveys.

Discussion

Overview

The diagnosis and treatment of oral cavity and oropharyngeal cancers can adversely impact oral functioning and QOL. The management of disease- and treatment-related effects can be complex and involve oncology and rehabilitation experts to restore and prevent further deterioration of function. Survivors carry the primary responsibility for managing their follow-up and self-care. Adherence to this regimen is less than optimal, and negotiating the return to normal life can be challenging. Survivors experience decrements in QOL and desire information and support regarding long-term effects, recommended follow-up, oral symptoms that prompt contacting a physician, maintenance of nutrition, improvement of speech and swallowing, maintenance of oral health, and psychological concerns. In addition, survivors report low self-efficacy in managing their self-care regimen. Despite the substantial self-care needs, compromised QOL, low self-care self-efficacy, and low participation in self-care, there are only a few self-management interventions for this population. In our prior work, we developed and evaluated a self-guided web-based intervention to assist in self-management, called ES, which illustrated a promising impact in formative studies [65]. The goal of this study is to bolster the ES intervention by enhancing the existing content and adding 2 new modules focused on managing psychological concerns and maintaining oral cancer self-care routines and to assess the impact of the intervention on self-efficacy, preparedness, and QOL.

This study will provide important information regarding the impact of this self-management intervention when compared with a less-intensive intervention as well as information on the levels of engagement and predictors of engagement in ES. Further impact of this study lies in the information that will be gathered on its potential dissemination in the last phase of the study, which will identify the settings in which it may be implemented and incorporated into survivorship care.

Limitations and Unanticipated Problems

The limitations of this study are the challenges related to recruitment into an intervention for cancer survivors, feasibility concerns associated with recruiting survivors via state cancer registries, reliance on self-report measures of oral self-examination and engagement in head and neck strengthening exercises, and well-described difficulties in engaging individuals in web-based interventions [138,139]. We leverage several strategies to enhance engagement, including lotteries for logging into the first module for those who do not log in after 2 weeks and incentives that will be provided after the completion of each module. In terms of feasibility, recruiting the participants via registries, although a way to increase diversity in a sample, can be challenging. Finally, although self-reported oral self-examinations and engagement in exercises are not the only self-care behaviors recommended for survivors, other self-care behaviors such as engagement in mouth care, changes in food intake to minimize swallowing difficulties, tobacco cessation, and alcohol use are less prevalent and less likely to apply to most survivors.

The findings of this study will provide important information on the efficacy of a web-based intervention on self-care among oral cancer survivors as well as initial information about the potential timing and settings for future scale-up. If efficacious, future research could evaluate potential implementation strategies to reach the survivors of oral cavity and oropharyngeal cancer.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Interactive components of Empowered Survivor.

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Abbreviations

ACS: American Cancer Society
AE: adverse event
EORTC-HN-43: European Organization for Research and Treatment of Cancer-Quality of Life Questionnaire-Head and Neck-43
ES: Empowered Survivor
HPV: human papilloma virus
MLM: multilevel modeling
NCI: National Cancer Institute
NJSCR: New Jersey State Cancer Registry
QOL: quality of life

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Protocol

Facebook Intervention for Young-Onset Melanoma Survivors and Families: Protocol for a Randomized Controlled Trial

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Abstract

Background: Individuals diagnosed with melanoma before the age of 40 years (young-onset melanoma survivors) and their first-degree relatives (FDRs) are a growing population at risk for developing recurrent melanoma or new melanomas. Regular surveillance using clinical skin examination (CSE) and skin self-examination (SSE) and engagement in preventive behaviors including sun protection are recommended. Given the growing population of survivors and their families who are at increased risk, it is surprising that no behavioral interventions have been developed and evaluated to improve risk-reduction behaviors.

Objective: We describe the rationale and methodology for a randomized controlled trial evaluating the efficacy of a Facebook intervention providing information, goal setting, and peer support to increase CSE, SSE, and sun protection for young-onset melanoma survivors and their FDRs.

Methods: Overall, 577 survivors and 577 FDRs will be randomly assigned to either the Young Melanoma Family Facebook Group or the Melanoma Family Healthy Lifestyle Facebook Group condition. Participants will complete measures of CSE, SSE, and sun protection, and mediator measures of attitudes and beliefs before and after the intervention. The primary aim is to evaluate the impact of the Young Melanoma Family Facebook intervention versus the Melanoma Family Healthy Lifestyle Facebook intervention on CSE, SSE frequency and comprehensiveness, and sun protection among FDRs. The secondary aims examine the efficacy of the Young Melanoma Family Facebook intervention on survivors' SSE frequency and comprehensiveness and sun

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protection behaviors and mechanisms of intervention efficacy for intervention impact on FDR and survivor outcomes. The exploratory aim is to evaluate the efficacy of the 2 interventions on perceived stress, physical activity, and healthy eating.

Results: This project was funded by the National Institutes of Health (R01CA221854). The project began in May 2018, and recruitment started in January 2019. We anticipate completing enrollment by November 2023. Power calculations recommended a sample size of 577 survivors and 577 FDRs. Multilevel modeling treating family as the upper-level sampling unit and individual as the lower-level sampling unit will be the primary data analytic approach. Fixed effect predictors in these models will include condition, role, sex, all 2- and 3-way interactions, and covariates.

Conclusions: The Young Melanoma Family Facebook intervention aims to improve primary and secondary skin cancer prevention for young-onset melanoma survivors and their family members. The intervention's delivery via a popular, freely available social media platform increases its impact because of the potential for dissemination in many contexts. If efficacious, this program could be disseminated by dermatologist practices, public health or nonprofit organizations focused on melanoma, and existing melanoma and skin cancer Facebook groups, thereby expanding its reach. This project will produce a content library of posts and a moderation guide for others.

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KEYWORDS

cancer survivors; melanoma survivors; skin self-examination; clinical skin examination; sun protection; behavioral intervention; social media

Introduction

Background

Young adults diagnosed with melanoma, defined as individuals diagnosed at or before the age of 39 years, have been identified by the National Cancer Institute as a growing population [1]. Melanoma risk is ≥6 times higher among young adults than it was 40 years ago [2] and is the most common malignancy for young adults aged between 25 and 29 years [3]. Young adult survivors are at a 9-fold risk for developing another melanoma and a higher relative risk for a second malignancy than adults diagnosed with cancer who are >39 years of age [4]. First-degree relatives (FDRs) of patients diagnosed with melanoma before the age of 40 years are also at an elevated risk of developing melanoma. Having an FDR with melanoma more than doubles the risk of melanoma [5].

The incidence of a second melanoma is increased in melanoma survivors, with cumulative risk ranging from 2% to 5% during the periods of 5 to 20 years after initial diagnosis [6-11]. Existing guidelines vary only slightly among specialty organizations. The National Comprehensive Cancer Network recommends lifelong clinical skin examination (CSE) at least annually for those with early-stage disease and more frequent follow-ups for the first 2 years for those with later stage disease (ie, every 3-6 months) [12]. The National Comprehensive Cancer Network guidelines and other professional agencies also recommend education in regular skin self-examination (SSE) and principles of sun safety exposure (avoidance of sun during peak hours or use of sun protective clothing, hat, or eyewear) [12-14]. Similarly, many professional societies suggest routine CSE and SSE and regular sun protection behaviors for FDRs [11,15].

Despite the growing population of young melanoma survivors and their FDRs, engagement in CSE, SSE, and sun protection behaviors in this population remains low. Bergenmar and Brandberg [16] evaluated young adults with a family history of melanoma and found that engagement in sun protection was low and levels of sun exposure were high. Zwemer et al [14] evaluated sun protection practices among melanoma survivors <30 years and reported low levels of sun protection in one-third of the sample. More than half of the participants reported sunbathing for >1 hour a week. Our preliminary data suggest that engagement in sun protection, SSE, and CSE is also relatively low among FDRs. Approximately 44% of FDRs never had a CSE, 73% had not conducted a comprehensive SSE in the past 2 months, and 33% had rarely or never used sunscreen or a wide-brimmed hat when outdoors during daytime hours (SL Manne, PhD, unpublished data, March 2019).

Given the growing population of young melanoma survivors and their family members who are at increased risk, it is surprising that no behavioral interventions have been developed and evaluated to improve risk-reduction behaviors in this population. Behavioral interventions have been evaluated to improve sun protection and skin surveillance among melanoma survivors and FDRs of patients of all ages [17-19], as well as SSEs among patients with melanoma of all ages [20-23]. However, no study has specifically targeted the growing population of young-onset patients and their FDRs. Furthermore, only 1 study has adopted a family-focused approach that delivers the intervention to both survivors and their FDRs [24]. This web-based intervention improved the comprehensiveness of SSE in hard-to-reach areas but did not affect CSE or sunscreen use [17].

The Young Melanoma Family Facebook Intervention

To address this gap, we developed the Young Melanoma Family Facebook intervention to increase the performance of risk-reducing behaviors for young melanoma survivors and their FDRs. We selected a social media delivery platform for this intervention. Other than the web-based intervention evaluated by Bowen et al [17], prior behavioral interventions for FDRs

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and patients have been delivered via individual print materials or telephone counseling [18,22,23,25-27]. Our intervention work extends prior research by using a social media platform, Facebook, as the intervention delivery method. Given the ubiquitous use of social media, its potential for reach and communication presents a unique opportunity for health-promotion interventions. To date, most health communication research has used social media as a tool to improve knowledge and awareness of cancer risks [28], such as human papillomavirus awareness [29] and awareness of breast cancer risk [30]. Social media has also shown promise as a platform for behavior change interventions, including promising results in weight loss [31], physical activity [32], and tobacco use [33].

Facebook was a particularly suitable way to deliver intervention content to a group of young melanoma survivors and their FDRs for 2 reasons. First, this demographic has high rates of Facebook use [34], and most Facebook users are already connected to family members via Facebook. Our multiple-family Facebook group intervention approach includes both young survivors and their family members, and thus addresses the unique needs of the young adult survivor population, who have higher needs for peer and family support [35-37], prefer to interact with other young adult survivors [34], and prefer to obtain support from peer survivors rather than from other sources [38]. Our use of Facebook as an intervention platform is also a good match for this population's preferences for information delivery, as they are frequent users of social media for health information [39]. Peer-to-peer and within- and between-family interactions have the potential to facilitate attitude and behavior change and set positive social norms for sun safety behavior.

The Young Melanoma Family Facebook intervention provides information, goal setting, and peer support to increase CSE, SSE, and sun protection behaviors for young-onset melanoma survivors and their FDRs. Content was guided by the Preventive Health Model [40-42] and the Theory of Normative Social Behavior [43,44]. The Preventive Health Model [41,42] is an integrative framework that includes the following constructs: risk, salience or coherence (benefits and barriers), and social and normative influences. The normative social influence construct is particularly important because of the family and group focus. The Theory of Normative Social Behavior proposes that normative influences are transmitted through interactions with family and peers about health behaviors, and these result in the internalization of norms. Facebook group participants may modify their own behavior and attitudes because of the norms about sun protection, CSE, and SSEs set by the intervention content and group members. If group members observe other members endorsing sun protection benefits and supporting regular self-examinations and CSE, normative changes may occur. Research on other group-based interventions supports this contention [45].

The Melanoma Family Healthy Lifestyle Facebook Intervention

The literature on Facebook interventions is emerging, and there is no clear guidance on comparison groups. To select an appropriate comparison group, we reviewed the literature on the design of behavioral interventions [46]. This review suggested that there are pros and cons to all comparison conditions and that selection should be guided by the phase of the research. We selected a comparison condition that had the same method of delivery, same frequency of postings and group duration, and the same group composition. The key differences in the comparison intervention are as follows: (1) content is focused on healthy lifestyle (eg, nutrition, physical activity, and smoking cessation) and cancer survivorship and (2) content does not contain any material relevant to skin cancer, sun protection, SSEs, CSE, or tanning. This comparison condition offers a similar level of interactivity to that offered by the Young Melanoma Family Facebook intervention.

Objectives

The purpose of this randomized clinical trial is to determine the efficacy of a Facebook intervention that provides information, goal setting, and peer support to increase CSE, SSE, and sun protection behaviors in young-onset melanoma survivors and their FDRs.

Primary Aim

The primary aim is to examine the efficacy of the Young Melanoma Family Facebook intervention versus a Melanoma Family Healthy Lifestyle Facebook intervention on CSE (primary outcome), SSE frequency and comprehensiveness, sun protection behaviors, and indoor tanning (secondary outcomes) of FDRs of young-onset melanoma survivors.

- Hypothesis: participants in the Young Melanoma Family Facebook intervention will report more CSE, more frequent and comprehensive SSEs, more sun protection behaviors, and less tanning at the 6-month follow-up compared with those in the Melanoma Family Healthy Lifestyle Facebook condition.

Secondary Aim 1

One secondary aim is to examine the efficacy of the Young Melanoma Family Facebook intervention on survivors' SSE frequency and comprehensiveness and sun protection behaviors. Survivors' behaviors are considered a secondary aim because the vast majority are compliant with CSEs. However, many survivors are not adherent to comprehensive SSE and sun protection behaviors; thus, we will focus on these outcomes.

- Hypothesis: survivor participants in the Young Melanoma Family Facebook intervention will report more frequent and comprehensive SSEs and higher sun protection at the 6-month follow-up compared with those in the Melanoma Family Healthy Lifestyle Facebook intervention condition.

Secondary Aim 2

Another secondary aim is to determine the mechanisms of intervention efficacy for both interventions' impact on FDR and survivor outcomes.

- Hypothesis: based on the Theory of Normative Social Behavior [43] as well as the Preventive Health Model [40-42], we propose that the effects of the Young Melanoma Family Facebook intervention on FDR's CSE, SSE, and sun protection behaviors and on survivors' SSE and sun

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protection will be mediated by increased normative influences, family support and discussion, risk, benefits, barriers, self-efficacy, and use of change strategies.

Exploratory Aim

The exploratory aim is to evaluate the efficacy of the Melanoma Family Healthy Lifestyle Facebook intervention versus Young Melanoma Family Facebook intervention on perceived stress, physical activity, and healthy eating patterns among FDRs and survivors.

- Hypothesis: participants in the Melanoma Family Healthy Lifestyle Facebook intervention will report less stress, more physical activity, and healthier eating patterns at the 6-month follow-up compared with those in the Young Melanoma Family Facebook condition.

Methods

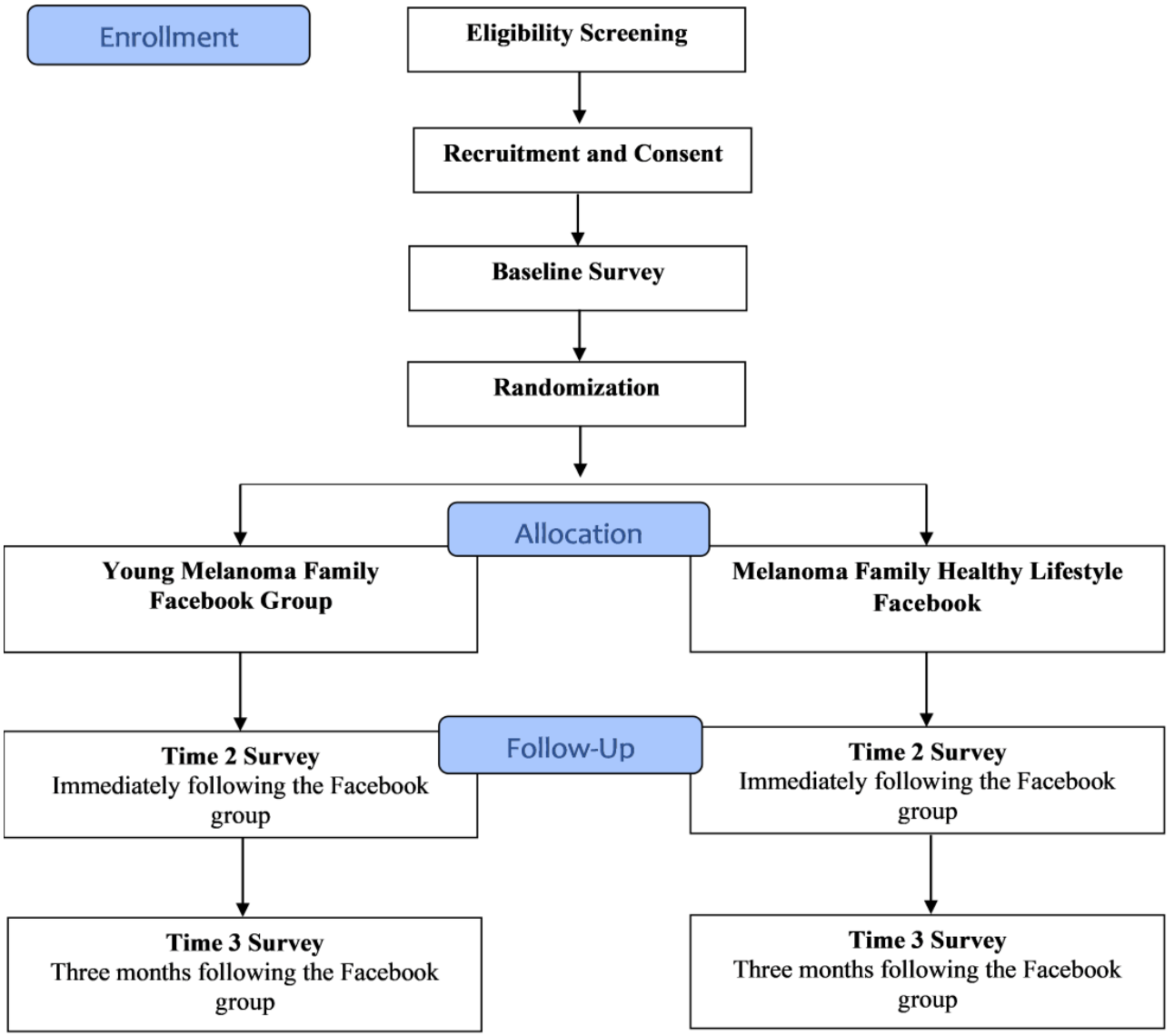
Ethics Approval

Study procedures were approved by the Rutgers University Institutional Review Board (IRB; Pro2019000158).

Design

This is a prospective, randomized controlled trial to evaluate the efficacy of the Young Melanoma Family Facebook intervention to increase engagement in CSE, SSE, and sun protection behaviors among young-onset melanoma survivors and their FDRs. Both the survivor and at least 1 FDR must consent and complete a baseline survey to be randomized. Eligible participants are randomly assigned to either the Young Melanoma Family Facebook intervention group or the Healthy Lifestyle Facebook intervention group and are asked to complete assessments at 3 time points: baseline, immediate postgroup intervention, and 3-month postgroup intervention. Members of the same family are assigned to the same condition. Figure 1 illustrates the overall design and participant flow of the study.

Figure 1. Participant flow.



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Participants

Participants include melanoma survivors who have completed treatment within the last 5 years and their FDRs. We define treatment completion as the date of the last cancer treatment (eg, surgery). Spouses of survivors are considered eligible for the trial if 1 FDR consented to the study and if the survivor nominated their spouse for the study. This accommodation is created because of the family nature of this study. Spousal data are not included in the analyses.

Recruitment

We use 2 different methods to recruit participants**:** state cancer registries and cancer centers. Survivors are recruited from the state cancer registries across the United States. Registry recruitment methods vary according to state laws. For some state registries, the registry confirms eligibility, approaches patients, and provides contact information to the main study site or sends contact information to the main study site. For other state registries, the registry identifies cases meeting the diagnosis time frame and current age and sends the list to the main site for recruitment. Eligible survivors are sent an electronic link to the informed consent. Once eligible, survivors provide the names, emails, and phone numbers of their parents, children aged >18 years, and full siblings. FDRs are contacted by telephone, and eligibility is confirmed. If eligible, FDRs are invited to participate. If interested, the electronic link to the consent and survey are provided by email. For both survivors and FDRs, calls are made 4 evenings per week and on weekends to ensure participants are reached. Up to 10 attempts are made to contact prospective participants by phone before they are deemed unable to locate.

To confirm eligibility before enrollment, the staff administer a series of screening questions to interested participants (Textbox 1). During eligibility screening, all survivors are asked to verify their date of birth, date of cancer diagnosis, internet access, and Facebook account status. All FDRs are asked to confirm their date of birth, internet access, and Facebook account status.

Textbox 1. Study eligibility.

- Survivor
  - Inclusion
    - Diagnosed with stage 0-3 melanoma in the last 5 years
    - Age at diagnosis 18-39 years
    - Completed treatment at least 3 months previously
    - At least 1 family member consents
  - Exclusion
    - Concurrent cancer diagnosis
    - Cannot speak and read English
    - Does not have access to computer, internet, and has a Facebook account
    - Physical Activity Readiness Questionnaire [47]: this is a 7-item scale that used as a disclaimer to identify individuals who should consult a physician for medical clearance (if they mark yes to any of the 7 items) before engaging in physical activity in the event they are in the control group.
- First-degree relative
  - Inclusion
    - Current age 18-80 years
    - First-degree relative of survivor
    - Survivor consents to the study
    - Has only 1 first-degree relative with melanoma (survivor)
    - Has not had a clinical skin exam in the past 3 years, has done SSE fewer than 3 times in the past year, OR has a sun protection habits average score ≤4 (“often”)
  - Exclusion
    - Does not have a personal history of melanoma
    - Cannot speak and read English
    - Does not have access to computer, internet, and has a Facebook account
    - Physical Activity Readiness Questionnaire [47]: this is a 7-item scale that used as a disclaimer to identify individuals who should consult a physician for medical clearance before engaging in physical activity in the event they are in the control group.

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Consent, Enrollment, Randomization, and Follow-up Survey Procedures

Once the prospective participant's eligibility is confirmed, informed consent is obtained using an electronic consent form hosted on DatStat. Participants are informed of the study requirements, the potential risks and benefits of study participation, and a breakdown of study compensation. After obtaining informed consent and baseline surveys, participants are assigned a study ID number. Both the survivor and at least 1 FDR must consent and complete a baseline survey to be randomized. Thus, randomization occurs only after both the survivor and 1 FDR complete these tasks. Participants are randomized to either the Young Melanoma Family Facebook Group or the Melanoma Family Healthy Lifestyle Facebook Group. The randomization scheme was developed by the study statistician. Clusters of participants (survivor + FDRs) are randomly assigned to conditions in blocks of 50 FDRs to achieve our target group size of approximately 25 survivors and 25 FDRs assigned to each group (Young Melanoma and Healthy Lifestyle). Members of the same family are assigned to the same condition. If additional FDRs join the study, they are assigned to the same condition. The team's project coordinator allocates participants to their randomized condition and notifies them of the study assignment via email.

Upon family randomization, participants are provided with the Facebook name of the intervention account that they have been randomly assigned to and asked to "friend" that respective account. Once participants "friend" the Facebook group account, the staff member posts a link into the intervention Facebook group account that participants use to authorize the Grytics software to capture their engagement data [48]. When a participant clicks the opt-in button, it redirects the participant to their own Facebook settings and provides more details about the information the app will be collecting (Facebook name, profile picture, posts, comments, and reactions). The participants have the option to indicate which of their Facebook groups the Grytics software can see by clicking "choose what you allow." When the participant accepts the invite, their request to join the group stays in "pending" status until the group administrator approves all members on day 1 of the group. The study staff contact those who do not "friend" the Facebook accounts.

After group completion, the participants are sent a link for the first follow-up survey and intervention evaluation, which is completed on the web. Three months after group completion, the participants are sent a link for the second follow-up survey, which is completed on the web.

Intervention Conditions

Young Melanoma Family Facebook Group

Participants are asked to join a secret Facebook group in which membership and content is only viewable by invited group members. The participants' group membership and activities are not publicly viewable to external Facebook users. The groups run for 12 weeks and contain up to 54 members (25 survivors and their FDRs). Posts are made twice a day for the first 8 weeks of the group, which is the frequency suggested by social media marketers to engage participants without overburdening them [49]. For weeks 9 to 12, a total of 4 to 6 posts are made each week. Each week is organized around one of the following topics: melanoma risk, physician skin examination, skin self-check, and sun protection habits. The first 4 weeks are organized according to the following topics: risk factors, CSE, skin self-check, and sun protection habits. Behavior change strategies such as goal setting and increasing support for CSE, SSE, or sun protection are woven into posts. During weeks 5 to 8, content is expanded for each topic, special topics are addressed, and news and stories about skin cancer are presented. Messages reinforce regular sun protection, CSE, SSE (eg, mole map pictures), and group discussions. The surgical oncologist and content expert on skin cancer (AB) will reply to the "Ask the Expert" postings in the Young Melanoma Family Group for questions that are not already included in the Question and Answer Library (Textbox 2).

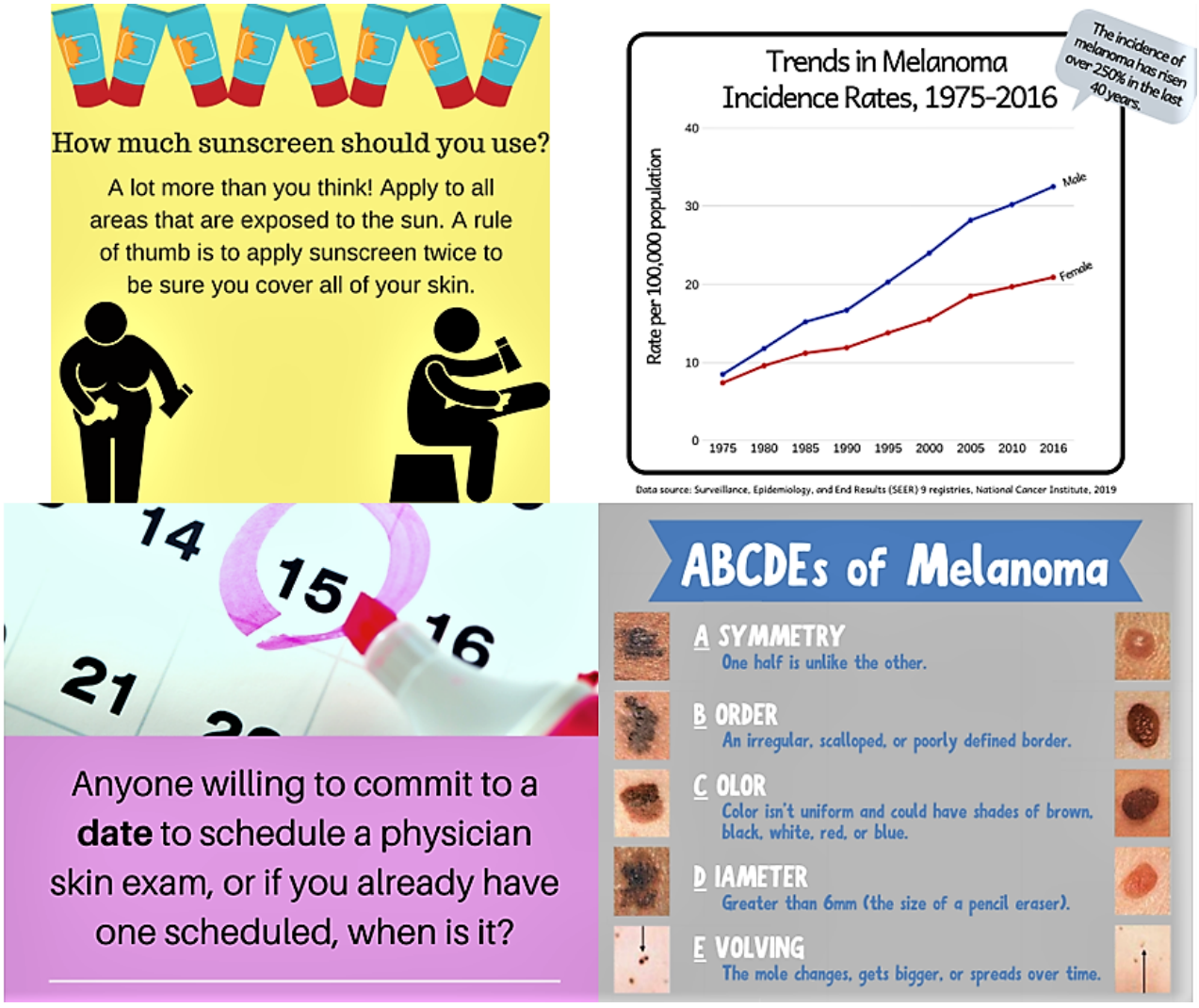
Sample posts are shown in Figure 2. Engagement is enhanced by engaging with humorous pictures, links to educational materials, polls, questions ("What is the ultraviolet light index in your town today?" "What is your favorite brand of sunscreen?"), memes, and holiday greetings. Each group ends at 12 weeks, at which time participants are no longer able to post. However, participants will be able to review the previous 12 weeks of postings.

Textbox 2. Young melanoma Facebook group content.

- Risk: information about elevated risk among relatives, information about skin cancer incidence among young adults, phenotypic risk factors, association between UV light exposure and skin cancer, Fitzpatrick skin type quiz.
- Clinical skin exams: information about clinical skin examination recommendations for persons at higher risk for melanoma, information about what is involved in a clinical skin examination, benefits of having an examination, barriers to having an examination, and opportunities to ask questions to a skin cancer expert.
- Skin self-check: professional recommendations regarding skin self-examination, how to prepare for and perform a skin self-check, how to recognize a suspicious growth, why skin self-examination is important in melanoma risk reduction, how to find a dermatologist, benefits of skin self-examination, barriers to skin self-examination, goal setting for skin self-examination, finding assistance in conducting a skin self-examination, what to do if something suspicious is found.
- Sun protection habits: sun safe behaviors, what sun protection factor means, importance of clothing that covers the body, why wide-brim hats are more protective, common barriers to sun safe behaviors and ways to address barriers.
- General engagement: fun and engaging posts such as holiday memes.

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Figure 2. Sample Facebook posts for the Young Melanoma Family Facebook Group.

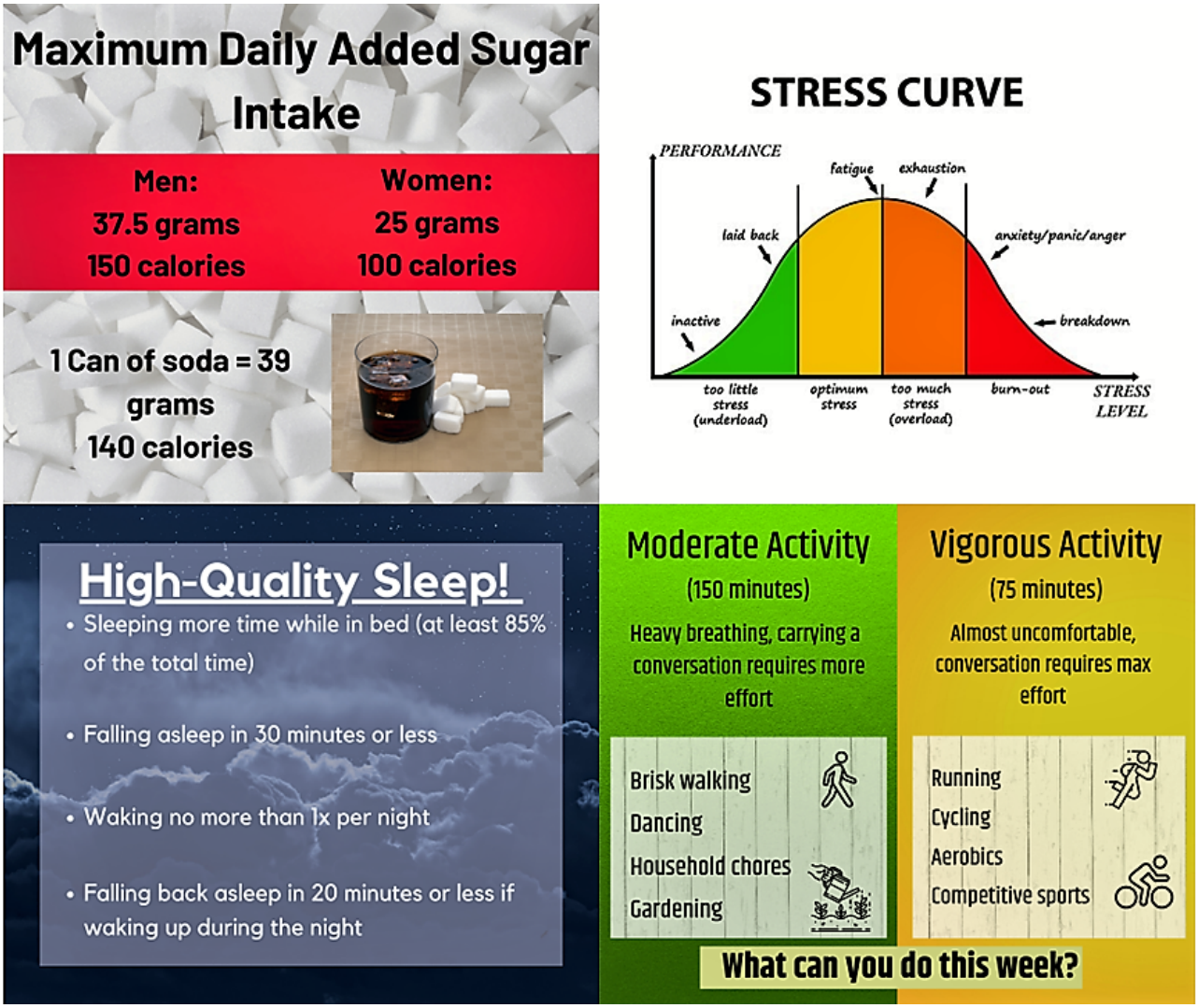


Melanoma Family Healthy Lifestyle Facebook Group

The procedures for joining the group, Facebook privacy settings, moderation guidelines, frequency of posts, group duration, and access after the group ends are the same as for the Young Melanoma Family Facebook Group. Each week is organized around one of the following topics: nutrition, physical activity, sleep, and stress. Sample posts are shown in Figure 3. Engagement is enhanced by including humorous memes, polls, conversation starters, and seasonal greetings (Textbox 3).

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Figure 3. Sample Facebook posts for the Melanoma Family Healthy Lifestyle Facebook Group.



Textbox 3. Melanoma Family Healthy Lifestyle Facebook Group content.

- Nutrition: content focuses on maintaining a healthy diet, benefits of a healthy diet, barriers to maintaining a healthy diet, and ways of improving dietary practices.
- Physical activity: content focuses on recommended levels of physical activity, types of physical activity, benefits of regular physical activity, barriers to achieving recommended levels of physical activity, and ways of improving physical activity levels.
- Sleep: content focuses on recommended number of hours of sleep, symptoms of sleep deficits, common reasons why people do not sleep well, benefits of getting a good night's rest, and strategies to improve sleep habits.
- Stress: content focuses on signs and symptoms of stress, benefits of reducing stress, reasons why people have problems managing stress, and strategies to reduce stress.
- General engagement: content includes fun and engaging posts, such as memes about exercise

Moderator Activities

The moderator logs in 2 to 3 times a day to review the activity and facilitate engagement by "liking" participants' comments and replying with supportive responses. Because Facebook norms are for brief and frequent interactions, moderator responses will be brief, but engage participants in discussions, reinforce engagement (eg, using a "like" reaction), and answer questions. The study collaborator, SP, reviews Facebook activity on a regular basis.

Facebook Group Privacy and Appropriate Behavior in Groups

To ensure the privacy and safety of participants in the Facebook groups, the study team takes the following measures. First, the study's informed consent documentation process includes a description of the privacy settings for Facebook groups. Second, during a phone contact with each participant before the group's initiation, the research staff describes what a "secret" Facebook group means in terms of privacy (eg, group and its contents are not visible to the public), the privacy limitations for a "secret"

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Facebook group (eg, cannot guarantee that other participants will not share content posted with others), and the confidentiality rules of the group. Third, if the study team learns that a participant has breached confidentiality in any way, we contact the participant to discuss confidentiality. Any breach in confidentiality is reported as a study adverse event and is reviewed by the study team on a bimonthly basis. In terms of appropriate posts by members, the moderator notifies the principal investigator (PI; SM) if unanticipated, distressing, or inappropriate comments are posted in the Facebook group. The study team will discuss the appropriate response to the issue and will provide guidance to the moderator on how best to proceed.

Enrollment Timeline

Enrollment began in January 2019. Recruitment is ongoing, and we anticipate completing recruitment in November 2023.

Measures and Assessment Periods

Participants complete electronic surveys via DatStat at 3 time points. Each self-report survey takes approximately 30 minutes to complete. The baseline survey is completed between 1 and 2 months before the initiation of a new Facebook group. The second survey is completed immediately after the group ends (approximately 3 months after group initiation). The third survey is completed 3 months after the group ends. To facilitate completion, research staff members reach out to participants who do not return a weekly survey. The data management program, DatStat, is programmed to send 3 reminder emails. Staff members complete a minimum of 1 phone call for incomplete surveys.

Primary and Secondary Outcome Measures

Clinical Skin Examination

The participants are asked about the last time a physician checked any part of their body for early signs of skin cancer (within the last month, 1-6 months ago, 7-12 months ago, >1 year ago, and never). CSE is defined as whether the participant had undergone such an examination in the previous year (yes or no). We expect that close to 100% of survivors will have had a CSE in the past year; thus, analyses of this outcome will focus on FDRs.

A randomly selected subset of 50% of the reported CSEs are confirmed by the physician or facility completing the CSE. The participants are asked to complete an electronic Health Insurance Portability and Accountability Act medical release form to provide the name and contact information of the provider or medical facility to verify the procedure and the date on which it was performed. The study staff member contacts the provider through either email or fax and requests verification of the procedure and the procedure date.

Skin Self-examination

Participants are asked whether they had checked any part of their body for early signs of skin cancer in the last 12 months. Participants who report that they checked their skin at least once indicate the number of times they checked their skin in the last 12 months, the last time they checked their body, and the specific areas that they thoroughly examined during their last skin check. Two outcomes are used: SSE performance in the past year (*yes or no*) and SSE comprehensiveness (the number of body parts [out of 15] checked in the last SSE). Note that because SSE (yes or no) overlaps with the number of body parts such that everyone with a "no" will have 0 body parts, we limit the analysis of the number of body parts to scores ranging from 1 to 15, omitting zeros from the analysis.

Sun Protection Behaviors

Participants rate how often they engaged in 6 behaviors in the last month: stay in the shade, wear a long sleeve shirt, wear long pants or cover legs, wear a wide-brimmed hat, wear sunglasses, and wear sunscreen with a sun protection factor ≥15 (1=*never* to 5=*always*) [50].

Indoor Tanning

Participants rate how many times they engaged in indoor tanning (tanning bed, sun lamp, and tanning booth) in the last 3 months.

Exploratory Outcome Measures

Perceived Stress

The Perceived Stress Scale-4 [51], designed for use in community populations, is a widely used psychological instrument for measuring the perception of stress. It is a measure of the degree to which situations in one's life are appraised as stressful in the previous month ("How often have you felt that difficulties were piling up so high than you could not overcome them?" 1=*never* to 5=*very often*).

Physical Activity

The Godin Leisure-Time Exercise Questionnaire [52] is a 4-item widely used self-report measure for describing patterns of vigorous and moderate physical activity during the last 7 days (eg, "How many days did you do vigorous physical activities like heavy lifting, aerobics, or fast bicycling?" *number of days/week with no vigorous activities*).

Healthy Dietary Practices

Four items assess how many days per week, over the last 7 days, that the participant has consumed fast food (*<1, 1-3, or ≥4*), daily servings of fruits and vegetables (*≥5, 3-4, or ≤2*), daily servings of nondietary soft drinks (*<1, 1-2, or ≥3*), and times per week desserts or other sweets are consumed (*≤1, 2-3, or ≥4*) [53].

Mediator Variables

Perceived Risk for Skin Cancer and Recurrent Melanoma

The perceived risk of melanoma is assessed using 4 items [54]. Sample items are "How would you rate your chances of developing melanoma as compared with other people with a similar family history of melanoma?" (1=*much higher than other people*, 5=*much lower than other people*) and "I may get a skin cancer if I don't protect my skin from the sun" (1=*strongly disagree*, 5=*strongly agree*).

Benefits

Six items assess benefits of engaging in sun protective behaviors (1=*strongly disagree* to 5=*strongly agree*) [55,56]. Nine items

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assess the benefits of engaging in CSE [55,57,58]. Ten items assess the benefits of engaging in SSE (1=*strongly disagree* to 5=*strongly agree*) [55,57,58]. An average is computed, and higher scores indicate more benefits.

Barriers

Fifteen items assess common barriers to using sunscreen and wearing sun protective clothing (1=*strongly disagree* to 5=*strongly agree)* [55,56]. Seven items assess common barriers to having a CSE, and 8 items measure common barriers to having an SSE [55,57,58]. The averages are computed for each scale, and higher scores indicate more barriers.

Self-efficacy

Eight items measure confidence in using sunscreen in various settings: 1=*not at all confident*, 5=*very confident* [55,56]. Eight items assess confidence in being able to conduct SSE [57,58].

Family Norms

Perceived attitudes and practices of other family members regarding tanning and sun protection are assessed using 9 items (1=*strongly disagree*, 5=*strongly agree*) [59], perceived attitudes and practices of other family members regarding CSE with 5 items [60], and perceived attitudes and practices of other family members regarding SSE with 6 items [60]. Higher scores indicate stronger norms.

Family Benefits for Engaging in Risk-Reduction Practices

Nine items measure perceived benefits to one's family if the individual engages in risk-reducing practices, as well as benefits for the individual if their family engages in risk-reducing practices. Items were adapted from our prior work on the relationship between the benefits of cancer screening [61] and sun protection [62]. Higher scores indicate more benefits for the family.

Family Discussion

The frequency of discussions regarding sun protection with the participant's sibling, parent, spouse, and children in the past month are reported in 4 items (eg, "How often did you discuss sun protection with your siblings, parents, children, or spouse?" *never*=0, *once*=1, *twice*=2, or *more than two times*=3) [59,61]. A sum of these items will be computed. However, because a participant may not have one or more of these family members (eg, they are not married or they do not have children), the family discussion variable will be computed by dividing the sum score by the number of available family member types. For example, a person with a parent, spouse, and child could have a maximum score of 9 on the sum measure. Therefore, the family discussion variable is computed by dividing the sum by 9 and multiplying by 100 to create a score that could range from 0 to 100. This approach was used in our prior work [63].

Three items assess the frequency of discussions about CSE and 3 items assess the frequency of discussions about SSE with the participant's siblings, parents, and spouses (ie, participants were not asked whether they discuss CSE or SSE with their child; *never*=0, *once*=1, *twice=2*, or *more than two times=3)*. As with sun protection, the family discussion variables for SSE and CSE will be computed by dividing the sum of the frequency of discussions by the number of available family member types to create a score that could range from 0 to 100. A score of 100 indicates that the person has discussed CSE (or SSE) at least 2 times with all available family members. Note that although we know that the person discussed CSE and SSE with at least 1 sibling, for example, we do not know if they discussed it with every sibling they have.

Action Planning

On the basis of prior work [59,64], 4 items were created to assess whether the participant made a detailed plan regarding when, where, and how to engage in sun protection behaviors and what to do if anything interferes. Using 4 items, we ask whether the participant made a detailed plan regarding when, where, and how to have a CSE and what to do if something interferes; 4 items assess whether the participant made a detailed plan regarding when, where, and how to do an SSE and what to do if something interferes (1=*strongly disagree*, 5=*strongly agree*). Higher scores indicate more planning.

Facebook Group Social Network Influence

Overview

Social network analysis (SNA) and content analysis of participant posts, comments, and reactions will be used to understand the mechanisms through which interactions in Facebook groups result in behavior and attitude change. This measures how much participants engaged with each other and whether these peer-to-peer engagements are predictive of the outcomes. Social influence is a function of three contextual factors: (1) traits of members of the reference group, (2) content of Facebook messages, and (3) social network exposure. We use SNA to derive individual, dyadic, and group-level measures to examine the role of the social structural context on normative influence [65-67]. Ties will be measured using the following Facebook data: (1) reactions (likes); (2) comments to member posts and comments; and (3) existing familial relationships. Tie measures will be combined to measure tie strength (0=*no tie*, minimum of 1=*tie*, strength=*sum of all ties across the weeks the group is running*; Textbox 4).

In addition, comments will be content analyzed using a codebook. The codebook will be developed through an iterative process that first started with a literature review to identify common themes that emerge in social media health intervention studies [72-77]. Examples of content-type themes from our review of the literature include "awareness," "support," "promotion," "information seeking," and "support seeking," among others. In addition to content-type themes, we will use themes that characterize content expression. This regards how comments are expressed and include "supportive," "humorous," "evaluative," and sentiment (positive, negative, and neutral affect). More themes will be identified through an initial reading of a randomly selected subset of 200 comments, across the 6 intervention waves. This open reading process will identify recurring themes [78] for an initial codebook. These codes will be applied to another randomly selected subset of 200 comments by a team of 2 trained coders, to establish an acceptable interrater reliability score (Cohen κ of at least 0.70). In

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discussions between coders and research team leads, the codebook will be refined by adding any additional emergent themes and merging similar themes into broader categories. This refined codebook will then be applied to a final subset of 200 comments to ensure improved interrater reliability among the team's coders. The coding team will then code the entire data set of comments. Comments could be coded for multiple themes. Each comment will include information on the number of "likes" and comments that it received [74]. The content analysis will be used in two ways: (1) determine theme frequency for each group and (2) codes (presence=1, absence=0) will be aggregated across all comments made by each group member (excluding project team). Thus, we will have summaries of each code for each participant, which will be used, along with network measures, to assess participants' levels of engagement, helpfulness (eg, number of informational comments), supportiveness (eg, number of supportive comments), and any other themes our team deems to be relevant for influence at the codebook development stage.

Textbox 4. Facebook-based social network context measures.

- Individual traits
  - Centrality: assess influence based on network position [68]
  - Survivor vs first-degree relative: as melanoma survivors, Facebook posts about risk or prevention are assumed to be influential
- Message content
  - Posts: information, stance, and sentiment communicating attitude about intervention and participant-posted content [69]
- Social Network exposure
  - Dyadic: ties between group members Feedback: likes and comments that communicate support, agreement, and encouragement [67] Reciprocity: likes and comments in response to feedback [70]
  - Group-level: group structure Subgroups: Subgroup formation based on high frequency interaction and consistent interests [71]

Facebook Engagement

General Use of and Connectedness With Facebook

Facebook use will be measured with 3 items (eg, log-ins per week, membership in private groups, or in public groups). Participants will complete the Facebook Intensity Scale [79], which consists of a 5-item experiential measure of Facebook use separate from behavioral measures of frequency and duration, incorporating emotional connectedness to the site and its integration into individuals' daily activities (eg, "I feel I am part of the Facebook community"). Ratings range from 1=*strongly disagree*, 5=*strongly agree*, and higher scores indicate more connections with Facebook.

Facebook Group Engagement

Facebook data will be extracted to assess behavioral engagement using Grytics extraction software to capture views, likes, and comments on posts. We will calculate descriptive information for each post, group cohort, and individual participant. Participant engagement (ie, reactions, replies, poll votes, and posts) will be analyzed as a predictor of response to treatment in the analyses.

Intervention Evaluation

Participants in both intervention conditions rate 18 items based on helpfulness, value, relevance, and accuracy of the materials posted, as well as aspects of group participation, such as comfort with participation, feeling connected with, actively involved with, enjoying expressing opinions, and reading posts (1=*not at all*, 7=*extremely*).

Covariate Measures

Demographic Information

Participants report their age, sex, race or ethnicity, education level, insurance status (*yes or no*), and whether they see a primary care provider at least once a year (*yes or no*).

Objective Risk Factors

Skin color, natural hair color (higher score: blonde or red hair), eye color (higher score: blue or green eyes), history of sunburns, skin reactivity to the sun (the degree to which the individual burns or tans when exposed to the sun, tanning ability, and depth of tan), freckling, and sensitivity to the sun (very sensitive to very resistant) are assessed.

Medical Factors (Survivor Only)

Data on months since melanoma surgery, stage of disease, and location of cancer are collected from medical charts.

Stakeholder Interviews

To inform future potential dissemination and implementation of the Young Melanoma Family Facebook Group intervention, we will conduct semistructured key informant interviews with three types of stakeholders: (1) 5 providers (cutaneous oncologists, dermatologists); (2) 5 cancer advocacy group leaders (eg, Stupid Cancer); and (3) 30 study participants (survivors and FDRs). Study participants will be purposively selected from the Young Melanoma Family Facebook Group condition, including approximately 15 survivors and 15 FDRs, and representing variation in participation in the intervention and scores on the 18 intervention evaluation items. Interviews (45-60 minutes in length) will be conducted using videoconferencing software and audio recorded with

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participant's permission. Interview participants will be compensated US $50.

Interview guides will be tailored to each of the 3 stakeholder types to assess multiple perspectives on the acceptability, feasibility, and appropriateness of the intervention. Providers and cancer advocacy group leaders will be introduced to the intervention at the beginning of their interviews. Interview questions and probes (as appropriate for each stakeholder group) will focus on (1) current approaches and practices to promote CSE, SSE, and sun protection; (2) perceived benefits and shortcomings of the Young Melanoma Family Facebook intervention; (3) actual and potential barriers to its use and delivery; (4) possible dissemination channels [80] to reach survivors and their families (eg, communication modes, provider recommendation, and social marketing); (5) pros and cons of suggested dissemination channels and strategies; (6) the "fit" of the intervention with the preferences of survivors and FDRs and the missions and objectives of providers and organizations [81]; and (7) resources, infrastructure, and other factors needed to implement and sustain the intervention outside of the research context.

Results

Approach to Missing Data

We will use an intent-to-treat approach to the analyses of primary and secondary outcomes. Our approach to recruitment and retention minimizes missing data by contacting participants who do not complete sections of the survey and by incentivizing participation. Initial analyses will examine the characteristics of noncompleters. As recommended by Lang and Little [82], multiple imputations (using 50 imputed samples) will be used to impute missing values (Table 1).

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Table 1. Study measures.

Measure	Screening	Baseline	Time 2	Time 3
Covariates				
Date of birth	✓			
Sex		✓		
Survivor date of diagnosis[a]		✓		
Race and ethnicity		✓		
Education		✓		
Insurance status		✓		
Regular primary care		✓		
Phenotypic risk		✓		
Outcomes				
Clinical skin examination	✓	✓	✓	✓
Skin self-examination	✓	✓	✓	✓
Sun protection behaviors	✓	✓	✓	✓
Perceived stress		✓	✓	✓
Physical activity		✓	✓	✓
Dietary patterns		✓	✓	✓
Indoor tanning		✓	✓	✓
Mediators				
Risk		✓	✓	✓
Benefits		✓	✓	✓
Barriers		✓	✓	✓
Self-efficacy		✓	✓	✓
Family norms		✓	✓	✓
Family benefits		✓	✓	✓
Family discussion		✓	✓	✓
Action planning		✓	✓	✓
Facebook intervention variables				
Facebook engagement				✓
Connectedness with Facebook	✓			
Facebook social influence				✓
Treatment evaluation			✓	
Qualitative data				
Stakeholder interviews				✓

Approach to Data Management

Although survivors are asked specifically to nominate parents or siblings as FDRs, experience indicates that some survivors will nominate spouses who are not FDRs. If this occurs, the spouse's data will be excluded from the analyses. A second complication in this area is when children are nominated. Although children are FDRs, our focus on young-onset melanoma survivors will likely result in a sample of survivors who rarely have children who are old enough to participate in the study. Given the distinct roles played by the different FDRs (ie, parental relationships and influence that likely differ from sibling relationships and influence), children will be included in analyses as FDRs only if they represent at least 5% of the FDRs in the study, so that the differences among parents, siblings, and children can be examined. Finally, after excluding spouses (and possibly children if the sample of children FDRs is small), there may be survivors with no valid FDRs in the study. Those survivors will be removed from analyses.

The treatment of covariates warrants further investigation. Possible covariates include demographic variables, objective

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risk variables, and medical variables for the survivor. To determine which covariates should be included in the analyses, preliminary analyses will be conducted in which each outcome is predicted by the full set of qualifying covariates. Only those covariates that significantly predict at least 1 outcome will be included in the analyses. Once the set of covariates is determined in this manner, the same set of covariates will be included in all analyses. Any covariates that are limited in their variation will be excluded from the analyses. Consider race or ethnicity as an example: rates of melanoma are strongly tied to race and ethnicity, with the highest rates for White, non-Hispanic individuals. If the distribution of race or ethnicity in the sample is limited (ie, 90% or more of the sample is White, non-Hispanic), race or ethnicity will not be included in the analyses. In addition to race or ethnicity, we anticipate that insurance status, visits to a primary care provider, and stage at diagnosis for the survivor may also show low variation; if so, they will be excluded from the analyses.

Survivors and FDR ages also present potential problems as covariates. The analysis described in subsequent sections systematically tests whether there are differences in outcomes as a function of role (survivor, parent, or sibling), sex, and their interaction. The interaction tests differences for mothers versus fathers, sisters versus brothers, and male survivors versus female survivors. Participant age will likely correlate strongly with the role variable (ie, parents will be relatively older than siblings and survivors) and, if so, age will not be included as a covariate in analyses to avoid multicollinearity.

Primary Aim, Secondary Aim 1, and Exploratory Aim Analysis Plan

The primary aim is to examine the efficacy of the Young Melanoma Family Facebook intervention on CSE, SSE frequency, comprehensiveness, and sun protection behaviors of FDRs after completion of the intervention, and the first secondary aim is to examine the efficacy of the intervention on *survivors'* SSE frequency and comprehensiveness and sun protection behaviors after completion of the intervention. These 2 aims (*primary aim and secondary aim 1*) will be addressed together using multilevel modeling (MLM) because the data from FDRs and survivors are assumed to be interdependent. The *exploratory aim* of testing whether the intervention is effective in reducing perceived stress and improving other outcomes such as physical activity will also use this approach. MLMs with the following attributes will be used to address the primary aim and secondary aim 1:

- Family is the upper-level sampling unit and individual (FDR or survivor) is the lower-level unit.
- Fixed effects variables include condition (Young Melanoma versus Melanoma Family Healthy Lifestyle Facebook), respondent role (parent, sibling, or survivor), respondent biological sex, all 2- and 3-way interactions, and the set of covariates, including the individual's baseline score on the outcome.
- Random intercepts will model interdependence within families.
- Models predicting dichotomous outcomes (CSE and SSE yes or no, any indoor tanning) will be estimated using binary logistic multilevel models.
- A standard multilevel analysis will be conducted to predict the SSE comprehensiveness of sun protection behavior, perceived stress, physical activity, etc, using the same fixed- and random-effect parameters.
- Exploratory analyses of moderators of intervention efficacy will be conducted using this MLM approach by including each moderator (eg, melanoma risk factors and month of the year enrolled) as an additional fixed effect factor in the model.

Power Calculations

Power analyses were computed assuming a total of 1154 participants (577 survivors and 577 FDRs). Outcomes were assumed to correlate within families with r=0.5. Given those values, the effective sample size taking clustering into account is a total of 773. Using a .05 significance level and 90% power, this sample size is sufficient to detect small effects for CSE (Cohen d>0.12). For SSE, the effect size was an overall increase in SSE in the Young Melanoma Family Facebook condition of 16.1% across FDRs and survivors. Using pretest-posttest pilot data, we found Cohen d=0.14 for sun protection behaviors across FDRs and survivors.

Secondary Aim 2: Analyses

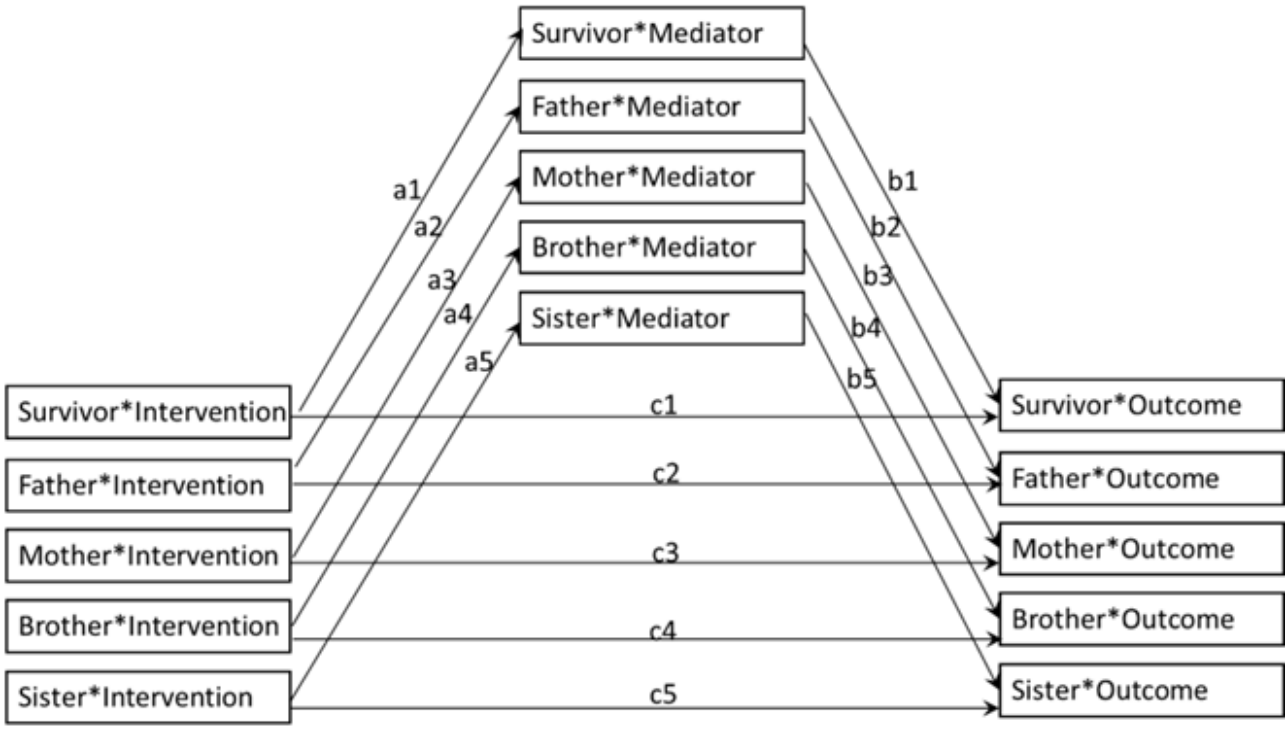
This aim evaluates hypothesized mediators of the expected association between the intervention and outcomes (FDR engagement in CSE, FDR, and survivor engagement in self-examinations and sun protection behaviors). Mediators that are outcome-specific (eg, benefits of engaging in CSE, SSE, and sun protection) include benefits, barriers, family norms, family discussions, and action planning. Mediators that are not outcome-specific include sunscreen self-efficacy and family benefits for risk reduction.

Mediation analyses will assess whether the effects of the intervention on outcomes are mediated by changes in family and normative factors (family discussion, family norms, and family benefits) and individual attitudes (eg, risk, benefits, barriers, self-efficacy, and action planning). MLM will be used to estimate the key mediation paths using 4-component steps [83]. These MLMs will include dummy-coded variables to denote the combination of biological sex and participant role (eg, mother or father). Each of these dummy variables will also interact with the treatment condition, and the overall intercept in this type of simple slope model is suppressed. To assess mediation (Figure 4), these predictors are included in a model that predicts the proposed mediator, and the coefficients from the interaction between the dummy variables and condition estimate the "a" path for each role. To assess the "b" paths, the interactions between the dummy variables and mediator are added to the model, and the outcome (CSE, SSE, or sun protection) is predicted. The contribution of the mediated effect will be assessed directly by using the approach recommended by Kenny et al [84] for multilevel models. Specifically, the product of the 2 pieces of the mediating path (ie, "a*b" from intervention group assignment to mediating variable and from mediating variable to outcome) will be calculated. Bootstrap

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procedures will be used to test the significance of the mediating pathway.

Figure 4. Mediation model.



To inform our interpretation of outcomes, we will examine social influence dynamics in both conditions. We conceptualize social influence as a function of three contextual factors: (1) traits of members of reference group; (2) content of messages; and (3) social network exposure. We will use SNA and content analysis of posts to understand the mechanisms through which interaction in Facebook groups results in behavior and attitude change. We use SNA to derive individual, dyadic, and group-level measures to examine the role of social structural context on normative influence. Ties will be measured as (1) reactions (likes); (2) comments to member posts; and (3) existing familial relationships. Tie measures will be combined to measure tie strength (0=no tie, minimum of 1=tie, strength=sum of all ties across the weeks the group is running). Once ties are established, SNA software Ucinet [85,86] will be used to compute network measures. We will derive variables from the content analysis of comments posted to the group that, along with network variables, will assess Facebook group members' influence—both individual members and in terms of broader group dynamics (eg, multiple members expressing consensus on a particular topic). Information, support, stance, and sentiment are some of the content-related characteristics that can drive influence. Other relevant variables may arise through the content analysis, as described earlier.

Secondary Aim 2: Sample Size and Power

Sample size calculations for mediated effects are based on simulation studies that model the 2 pieces of the mediating path (study arm to mediator; mediator to outcome) [87]. Assuming 583 survivors with 22% dropout, there is greater than 80% power to detect paths with regression coefficients of 0.33 (small-to-moderate effects) [88]. Assuming 577 FDRs with 22% dropout, there is 80% power to detect paths with regression coefficients between 0.20 and 0.23 (small effect sizes). With smaller intraclass coefficients, the effective size could be closer to 0.20.

Qualitative Analyses of Stakeholder Interviews

The audio recordings of key informant interviews will be transcribed verbatim. Transcript data and notes will be imported into ATLAS.ti software to facilitate analysis. Both deductive and inductive coding processes will be used [89]. Deductive directed content analysis will allow specification of constructs of interest a priori for coding (eg, acceptability, feasibility, appropriateness, and barriers), whereas an inductive coding process will allow development of additional codes identified through immersion in the transcripts. All qualitative coding procedures will follow rigorous procedures to ensure consistency and a close connection among the data and identified codes and categories [90] (eg, independent initial code development by multiple qualitatively trained research staff, iterative refinement of the codebook based on team meetings to review codes and resolve discrepancies, 6 randomly selected transcripts double-coded with the final codebook). Once coding is complete, the team will develop a summative grid of themes across and within stakeholder groups (providers, cancer advocacy group leaders, and survivors and FDRs), yielding multiperspective insights into multilevel dissemination and implementation strategies needed for future scale-up, dissemination, and implementation. Reporting of qualitative results will follow the Consolidated Criteria for Reporting Qualitative Research [91].

Data Safety and Monitoring

An adverse event in this study is defined as follows: (1) a participant dying between baseline and follow-up (not a

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study-related adverse event), (2) a participant reporting distress associated with study participation or (3) if the participant has breached confidentiality in the Facebook group (eg, sharing a group member's post that contains their name outside of the Facebook group). Participants reporting distress will be contacted by the site's PI. During this telephone contact, the causes and degree of distress will be discussed. If the site PI feels there is a need for referral of the participant for psychological intervention, they will identify providers near the participant and provide the referral information. Participants breaching confidentiality will be contacted to let them know that they cannot share posts outside of the group. All adverse events will be documented by the study staff and reviewed on a monthly basis by the study PI and the project coordinator and reported to the safety officer. The IRB and Rutgers Cancer Institute of New Jersey's Protocol Monitoring Committee reviews all adverse events. The National Institutes of Health and Rutgers IRB will be notified immediately in the event of serious adverse reactions or any unanticipated (not mentioned in the consent form) occurrence of physical or psychological harm or unexpected threat to privacy (eg, lost records) or safety of the participants.

Discussion

Principal Findings

Once the analyses are completed, we anticipate that FDR participants in the Young Melanoma Family Facebook intervention will report more CSE, more frequent and comprehensive SSEs, and more sun protection behaviors at the 6-month follow-up compared with those in the Melanoma Family Healthy Lifestyle Facebook condition. We also predict that survivor participants in the Young Melanoma Family Facebook intervention will report more frequent and comprehensive SSEs and higher sun protection at the 6-month follow-up compared with survivor participants in the Melanoma Family Healthy Lifestyle Facebook intervention condition. Indoor tanning is an exploratory outcome, and we propose that participants in the Young Melanoma Family Facebook intervention will report lower engagement in indoor tanning at the 6-month follow-up than participants in the Healthy Lifestyle Facebook intervention.

In terms of moderators and mediators, we expect that younger participants, those who engage more in the intervention and are heavier Facebook users will respond more favorably to the Young Melanoma Family Facebook condition. We expect that the effects of the Young Melanoma Family Facebook intervention on FDR's CSE, SSE, and sun protection behaviors and on survivors' SSE and sun protection will be mediated family support and discussion, risk, benefits, barriers, self-efficacy, use of change strategies, and by increased normative influences. The latter will be measured through variables derived from the SNA (eg, social network variables like centrality, reciprocity, and subgroup formation) and from the content analysis (eg, member comment informativeness, supportiveness, and sentiment). Finally, we expect that participants (FDRs and survivors) in the Melanoma Family Healthy Lifestyle Facebook intervention will report less stress, more physical activity, and more healthy eating patterns at the 6-month follow-up compared with those in the Young Melanoma Family Facebook condition.

Limitations

The results of this trial will be evaluated in the context of its limitations. For example, there are challenges with the Facebook delivery platform, recruitment of family members of survivors, and reliance on self-report measures of SSE and sun protection. First, Facebook posts tend to be brief, which may not be conducive for explaining complex concepts. Although videos can be used to explain complex concepts, many Facebook users may not be able to view lengthy videos. Furthermore, some group members may not engage in the group (eg, "lurk") or view all posts. Studies of Facebook interventions have shown that total group engagement tends to decline over time [65]. We leverage a number of strategies to enhance engagement, including use of polls, conversation starters, and Questions and Answers with experts in Facebook posts. Future studies may need to include only regular Facebook users. Second, recruiting a sufficiently large number of participants to populate multifamily groups of 50 to 60 family members within a relatively short period can be challenging. Timely enrollment is important when enrolling a cohort of 100 participants to randomize them into 2 groups. Finally, self-report sun protection measures show moderate correspondence with behavioral observations and diaries [92,93] and have moderate to high reproducibility and internal consistency [94-96].

Strengths and Significance

Despite these limitations, this is the first randomized controlled trial to evaluate a Facebook family group intervention to improve surveillance and prevention for young melanoma survivors and their family members, an understudied at-risk population who are not adherent to risk-reduction recommendations. The use of SNA will offer insights into the normative influences in Facebook family groups. SNA, which is the study of the pattern of ties between social actors, allows for more than a simple count of the number of individuals in a person's social network or the level of support that the individual receives from the network. SNA goes further to examine the social structures that emerge from the pattern of ties, and social network theory proposes that, through social influence processes, these network structures act as mechanisms that promote the adoption of health-related behaviors. We advance the science of social media–delivered interventions by examining the mechanisms by which the social networks that developed over the course of the Facebook intervention influence change. Although there is compelling evidence that behavior appears to "spread" through social networks, few studies (primarily in the laboratory setting) [97,98] have examined mechanisms by which this occurs. This knowledge will provide critical insights for improving the design of the next generation of web-based behavioral interventions. Finally, the use of key informant interviews with providers, cancer advocacy group leaders, and survivors and FDRs will elicit multiperspective, multilevel data regarding the acceptability, feasibility, appropriateness, and barriers to delivery and engagement in the Young Melanoma Family Facebook. From a "designing for dissemination"

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perspective [99], these qualitative findings will be essential in understanding the potential for and strategies needed to support widespread scale-up, dissemination, implementation, and maintenance of the intervention outside the research context, if it is found to be efficacious.

Future Directions

The impact of this trial lies in its implementation and dissemination potential in a variety of contexts given the use of a familiar, popular, freely available social media platform. We will produce a content library of posts and a user guide that can guide implementation by others. If efficacious, the intervention could be disseminated and delivered via dermatologist practices, public health organizations such as the American Cancer Society, nonprofit organizations focused on melanoma, or in partnership with existing melanoma and skin cancer Facebook groups. The ability to interact with a skin cancer expert and other families affected by melanoma synchronously and asynchronously on Facebook may not only be convenient, but it may also be interesting to participants and may lead to a more impactful intervention. Knowledge gained will provide important information about potentially cost-effective ways to reach survivors and their families. If efficacious, future research should evaluate potential implementation strategies to reach young survivors and their family members with social media interventions.

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Data Availability

The data sets generated during or analyzed during this study are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
CONSORT-eHEALTH checklist (V 1.6.1).
[PDF File (Adobe PDF File), 4278 KB - resprot_v12i1e39640_app1.pdf]

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Abbreviations

CSE: clinical skin examination
FDR: first-degree relative
IRB: Institutional Review Board
MLM: multilevel modeling
PI: principal investigator
SNA: social network analysis
SSE: skin self-examination

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Protocol

Comparing Smartphone Virtual Reality Exposure Preparation to Care as Usual in Children Aged 6 to 14 Years Undergoing Magnetic Resonance Imaging: Protocol for a Multicenter, Observer-Blinded, Randomized Controlled Trial

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Abstract

Background: A magnetic resonance imaging (MRI) procedure can cause preprocedural and periprocedural anxiety in children. Psychosocial interventions are used to prepare children for the procedure to alleviate anxiety, but these interventions are time-consuming and costly, limiting their clinical use. Virtual reality (VR) is a promising way to overcome these limitations in the preparation of children before an MRI scan.

Objective: The objective of this study is (1) to develop a VR smartphone intervention to prepare children at home for an MRI procedure; and (2) to examine the effect of the VR intervention in a randomized controlled trial, in which the VR intervention will be compared to care as usual (CAU). CAU involves an information letter about an MRI examination. The primary outcome is the child's procedural anxiety during the MRI procedure. Secondary outcomes include preprocedural anxiety and parental anxiety. We hypothesize that the VR preparation will result in a higher reduction of the periprocedural anxiety of both parents and children as compared to CAU.

Methods: The VR intervention provides a highly realistic and child-friendly representation of an MRI environment. In this randomized controlled trial, 128 children (aged 6 to 14 years) undergoing an MRI scan will be randomly allocated to the VR intervention or CAU. Children in the VR intervention will receive a log-in code for the VR app and are sent cardboard VR glasses.

Results: The VR smartphone preparation app was developed in 2020. The recruitment of participants is expected to be completed in December 2022. Data will be analyzed, and scientific papers will be submitted for publication in 2023.

Conclusions: The VR smartphone app is expected to significantly reduce pre- and periprocedural anxiety in pediatric patients undergoing an MRI scan. The VR app offers a realistic and child-friendly experience that can contribute to modern care. A smartphone version of the VR app has the advantage that children, and potentially their parents, can get habituated to the VR environment and noises in their own home environment and can do this VR MRI preparation as often and as long as needed.

Trial Registration: ISRCTN Registry ISRCTN20976625; https://www.isrctn.com/ISRCTN20976625

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KEYWORDS

virtual reality; VR; children; anxiety; magnetic resonance imaging; MRI; MRI scans; imaging; randomized controlled trial; MRI preparation; smartphone virtual reality; smartphone intervention; procedural anxiety; psychosocial intervention

Introduction

Magnetic Resonance Imaging (MRI) is a commonly used imaging technique that provides detailed images without the use of ionizing radiation. Research has shown that pediatric patients can experience a range of negative emotions during this procedure [1]. There are several components within an MRI procedure that can induce anxiety such as the loud noises generated during an MRI scan and the prolonged time spent in a confined space [2]. Although there is little research on how children experience an MRI scan, one study found that about 50% of children between aged 5 to 12 years with nonacute medical conditions experienced anxiety and discomfort during an MRI scan [3]. Younger children can be overwhelmed by the MRI environment with noises they have never heard before and by the MRI machine, whereas older children can experience claustrophobic feelings [4]. This can result in poor cooperation, eg, following breathing instructions or excessive movements, which has a negative effect on the scan quality since up to 90% of the MRI artifacts can be attributed to movement [5]. To combat MRI-related anxiety and discomfort, children are often sedated or completely anesthetized up to the age of 6 years [6,7]. The use of general anesthesia is not without risks. Pediatric patients can experience side effects such as emerging delirium, respiratory depression, nausea, vomiting, agitation, and cardiovascular bradycardia [8-11]. Different methods have been implemented to reduce the need for anesthesia and pre- and periprocedural anxiety, such as behavioral rehearsal using mock MRI scans [12], play therapy [13], and distraction during the procedure using MRI-compatible audiovisual tools [14]. The use of these interventions has been found to be effective but are time-consuming and often rely on the guidance by a professional [2].

To alleviate MRI-related anxiety, virtual reality (VR) offers a promising alternative to prepare children for the procedure. VR is a way to experience computer-generated scenarios that can be used to create experiences similar to or completely different from reality. With audiovisual stimulation, the user can interact with the virtual environment [15]. Research has shown that VR can positively affect self-reported pain and anxiety during several medical procedures [16]. Most VR studies focused on distracting patients during a medical procedure. Exposure, however, is one of the most effective interventions to reduce anxiety, and only a few studies investigated the impact of VR exposure before a medical procedure [17-20].

To our knowledge, there has been little research into the effectiveness of VR as preparation for an MRI in a clinical setting. In a cross-sectional study of 23 pediatric patients by Ashmore and colleagues [21], the VR preparation was highly rated on enjoyment, helpfulness, and ease of use. They also showed that for some pediatric patients, VR preparation helped them to undergo an MRI scan without general sedation. In an exploratory study, Nakarada-Kordic and colleagues [22] compared the feeling of being inside an MRI scanner in VR versus being in a mock MRI scanner in a sample of 20 adult participants. The authors did not find a significant difference between the experience of VR MRI and mock MRI scans, and 86% of the participants reported that the VR simulation could be a helpful way to prepare for a real MRI exam. Stunden and colleagues [19] studied VR exposure based on a 360-degree movie versus a standard preparatory manual and a hospital-based Child Life Program on anxiety in a simulated MRI scan in 92 children aged 4-13 years but could not demonstrate a difference between the 3 groups. While this study failed to find a significant effect of VR exposure on procedural anxiety, it did have several drawbacks. They used a simulated MRI scan instead of an actual clinical MRI scan to test intervention effectivity. This may have limited the emotional response generated. Finally, the use of 360-degree recorded images instead of rendered 3D graphics may have limited immersion, which could be an important mediator of intervention effectivity as shown in VR-based pain distraction [23].

VR preparation of pediatric patients for medical procedures is often done with a head-mounted displays tethered to a powerful computer within the hospital setting. A disadvantage of this approach is that it requires a trained professional to do the VR preparation and that the time a child can be prepared is often limited. An alternative is to deploy the VR preparation to a smartphone, head-mounted by means of a Google cardboard. With a smartphone VR app, children can get prepared in their own home environment under parental supervision at their own pace and as often and as long as they need. Another advantage of a smartphone VR app is that it can be employed on a large scale and requires limited involvement of health professionals, ultimately saving costs associated with the traditional VR goggles tethered to a powerful computer. Moreover, costs associated with a Google cardboard are negligible compared with computer-tethered or dedicated head-mounted VR displays.

The objective of this study is (1) to develop a realistic VR smartphone app to prepare children for an MRI scan, using an immersive, interactive VR approach with a fully rendered environment; and (2) to present a methodological approach to conduct a randomized controlled trial (RCT) that can test the effectiveness of the VR intervention in children who need to undergo an MRI scan. The clinical effect of the VR smartphone app will be compared with routine clinical care (care as usual [CAU]). The primary outcome is periprocedural anxiety. Secondary outcomes include preprocedural anxiety, user experience, child behavioral and emotional problems, and parental anxiety. We hypothesize that the VR preparation will result in a larger reduction of the periprocedural anxiety of both parents and children as compared to CAU. We further hypothesize that VR preparation will lead to a larger reduction in parental anxiety and preprocedural child anxiety as compared to CAU.

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Methods

VR Design

The VR tool encompasses a highly realistic virtual environment that replicates the MRI experience of the Erasmus University Medical Center (MC)–Sophia Children's Hospital, Rotterdam, the Netherlands. The designed virtual MRI environment does not significantly differ from that of the Amsterdam University Medical Centers (UMC).

A multidisciplinary team, consisting of child-life specialists, child psychologists, a child psychiatrist, anesthesiologists, a 3D-acting director, and a 3D project manager designed the script of the VR experience. Working together with specialized VR developers and animators, multiple 3D characters, asset, and environment artists created the scenery and character modeling. During the design and development phases, team meetings were held to review the process and make any necessary adjustments. Overall, the main goal was to create a dynamic and interactive environment that will prepare children for the MRI procedure in a realistic and child-friendly manner. Once the VR software was created, it was pilot-tested in healthy children (n=10). Based on the observations and responses of the pilot test, final adjustments were made.

Technical Specifications

Software and Hardware Details

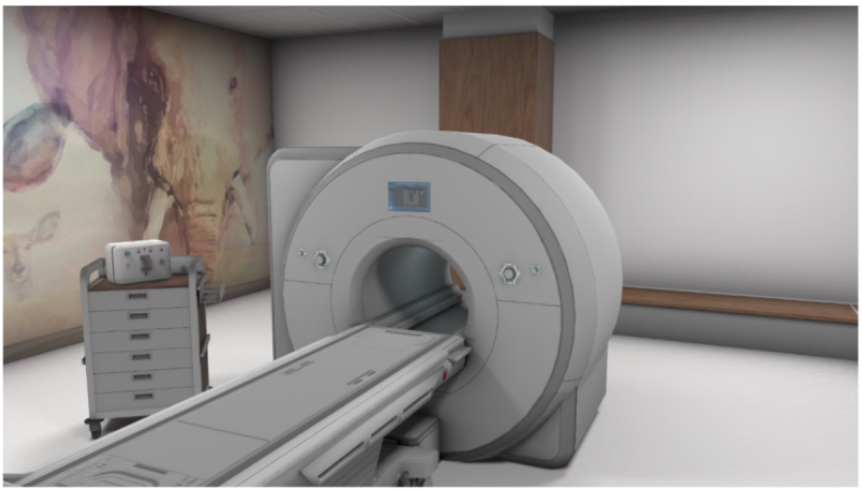
The 3D software in the VR smartphone app was developed using the Unity games engine, a cross-platform game engine developed by Unity Technologies. The app is designed to be used in a Google cardboard–like VR goggle, meaning a VR goggle relying on the use of a smartphone for its VR capabilities. The cardboard includes adjustable lenses and head straps—this makes the cardboard suitable for children. The software is usable on iPhone 5s or above or Android smartphones with operating system 4.4 or above. Participants can download the app in the Apple App Store or Google Play Store.

VR Storyline

The duration of the VR MRI smartphone intervention is approximately 5 minutes. The VR app takes place in a typical MRI room as seen in Figure 1 (and Multimedia Appendix 1), with an explanation given to a child by MRI technicians depicted on a monitor in the virtual MRI room. This design has been chosen to maximize the ease of program portability between different hospital settings and even between different languages by making it easy to switch out the supporting video with a localized alternative.

Participant can choose between 2 versions: one version for an upper body MRI and another version for a lower body MRI. The MRI experience starts with a technician that is visible on a screen on the wall of the MRI room. The technician introduces herself and explains that the participant is in the MRI room, what an MRI scan is, and that it makes a lot of noise but is not painful. She also explains that no metals are allowed in the MRI environment and that participants are not allowed to wear jewelry during the actual MRI examination. After this initial explanation, the participant is allowed to move around the virtual MRI room. The MRI room and machines are visible in 360 degrees and can be seen if the participant moves with his head. The participant can move around the MRI machine by looking at marked focus points (feet symbol) on the floor of the MRI room. When the participant is located behind the MRI machine, the technician explains that the MRI bore is open from the front to the back. When the participant is back at the starting position in the front of the MRI machine, the technician explains that some children like their parents to be present during the MRI, that they will get earplugs because of the MRI noise, and that it is important that they lie still within the MRI machine. After that, the participant can look at a focus point on the ceiling above the table of the MRI machine and is then transferred to this location. Subsequently, the participant is slowly transferred within the bore of the MRI machine. Depending on the version of the MRI machine, the participant is transferred within the bore of the MRI machine headfirst (upper body MRI) or feetfirst (lower body MRI). A scan with the duration of 1 minute is performed accompanied by varying MRI noises. When the scan is completed, the VR experience is finished, and the app returns to the home screen.

Figure 1. Image of the 3D environment in which the virtual reality experience takes place.



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Study Design

This multicenter, single-blinded, RCT is being performed at the Erasmus MC–Sophia by the Departments of Child and Adolescent Psychiatry/Psychology, Radiology, and Pediatric Anesthesiology and at the Amsterdam UMC–Emma Children's Hospital by the Department of Radiology. Children (N=128) will be randomly allocated to 2 parallel groups: VR smartphone application (n=64) or CAU (n=64). CAU involves an information letter given to the parents that consists of information about the MRI examination, the screening questionnaire that is used, and how to best explain the MRI exam to their child. Randomization will be performed as block randomization with a 1:1 allocation.

Ethics Approval

The study was approved by the medical ethical committees of the Erasmus MC (NL68075.078.19) and Amsterdam UMC (MEC-2019-0242).

Inclusion and Exclusion Criteria

Eligible participants are children aged between 6 and 14 years undergoing an MRI scan at the Erasmus MC–Sophia Children's Hospital or the Amsterdam UMC–Emma Children's Hospital (2 specialized children's university hospitals in the Netherlands) in the period between May 2021 and December 2022. Children that meet the following criteria will be excluded from participating: any intellectual disability, inability of parents to read or write in the Dutch language, epilepsy, visual impairments, and the need of general anesthesia during the scan.

Sample Size

To conduct analysis of covariance (ANCOVA) on the level of periprocedural anxiety at time point (T) 3 (primary outcome) with a Cohen *d* of 0.5, an α of .05 (2-tailed), and a power of .80, a sample size of 128 patients is needed (64 patients per group). Based on earlier studies, we anticipate finding a medium effect size [16].

Randomization

Participants will be randomly allocated to the intervention (VR) or control group (CAU) with a 1:1 allocation. A computer-generated randomization schedule will be used, stratified by age group (aged 6-10 vs 10-14 years) and the type of MRI (upper body vs lower body).

Patient Recruitment and Procedure

For the prospective recruitment of patients, in concert with the radiologist, the planned MRIs will be scanned a month ahead for eligible patients. They will be informed about the study by mail or phone. If needed, they will be reminded by phone in the following weeks. Besides the reminder, this will help to overcome doubts, because the staff can answer questions or motivate the patients to participate.

All participants will receive an invitation, information folders, and an informed consent form. Participation is not obligatory, and all data will be anonymized. Parents of all the patients will be asked to sign informed consent. Children aged 12-14 years will also be asked to provide informed assent themselves. Patients aged younger than 12 years will give their verbal permission.

After receiving signed informed consent, the participants will be stratified by the type of MRI scan (head or body scan). Then, they will be randomly assigned to the VR group (n=64) or the CAU group (n=64).

The children assigned to the VR group will receive Google cardboard–like VR glasses and instructions on how to download the VR app on their phone and use the VR intervention at home. They will receive a log-in code to use the smartphone VR app. Adherence will be promoted by giving the participants detailed information about the purpose of the study and how to use the VR preparation app and explaining how they can get help from the contact support staff if there are difficulties with the app or VR glasses.

The allocation sequence was executed by a researcher who is not involved in the assessment phase. The psychologist who assesses the child's anxiety state is blinded to the group assignment. This way, blinding for the treatment allocation will be guaranteed. Parents and children in both groups will be asked not to discuss their treatment allocation with the nurse, radiologist, or research psychologist.

Questionnaires will be assessed at the following time points: (1) T1, the weeks before the MRI scan (at home); (2) T2, the day of the MRI scan, before the procedure will start (in the waiting room); and (3) T3, right after the MRI scan (in the waiting room). The T3 questionnaires will retrospectively assess the child's experience during the MRI scan. In this way, we can measure the anxiety during the MRI scan without the interruption of the procedure.

The children assigned to the CAU group will receive an information letter in which child-friendly information is provided about the VR examination.

Participant Withdrawal

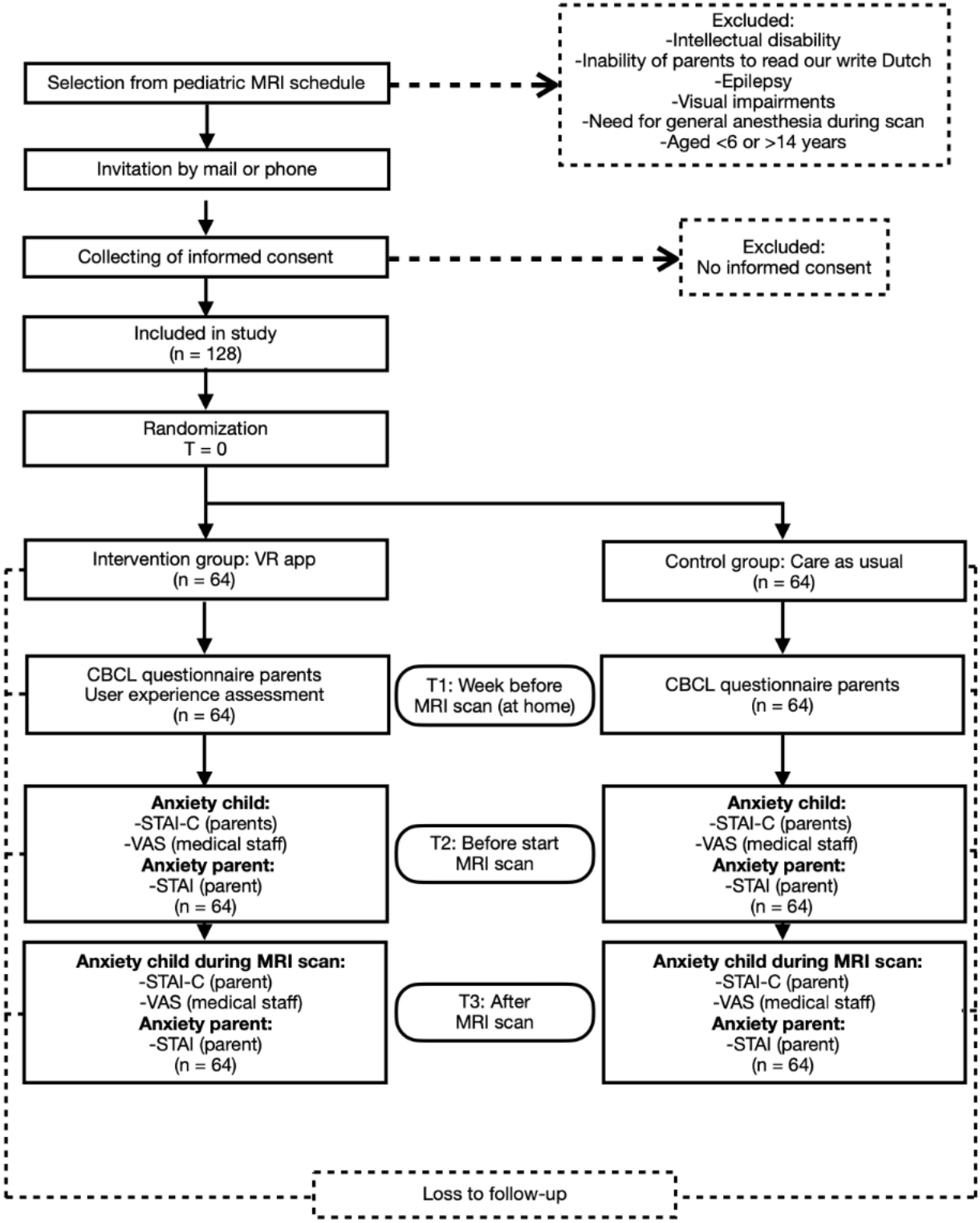
Participants can withdraw from the study for any reason at any time if they wish to do so, without any consequences. The investigator can decide to withdraw a participant from the study for urgent medical reasons.

Outcome Measures

The study design and variables at each time point are presented in Figure 2. The primary outcome is periprocedural anxiety at T3 (State-Trait Anxiety Inventory for Children [STAI-C] and Visual Analog Scale [VAS]). Secondary outcomes include preprocedural anxiety (VAS and STAI-C), user experience, child behavioral and emotional problems (Child Behavioral Checklist [CBCL]), and parental anxiety (State-Trait Anxiety Inventory [STAI]).

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Figure 2. Flow chart of the study design with the instruments at each time point. CBCL: Child Behavioral Checklist; MRI: magnetic resonance imaging; STAI: State-Trait Anxiety Inventory; STAI-C: State-Trait Anxiety Inventory for Children; T: time point; VAS: Visual Analog Scale; VR: virtual reality.



Background Variables

The following background variables will be collected: age, gender, and socioeconomic status (SES). Age and gender will be collected from the electronic record. SES will be based on a child's postal code.

Child Anxiety

The anxiety level of participants is measured before and after the MRI scan (T2 and T3) with the STAI-C, a questionnaire where parents and children evaluate statements on a scale from 0 (not at all) to 4 (completely true). The STAI-C is a widely used and validated self-report instrument for measuring state and trait anxiety [24]. The STAI-C has a good-to-excellent interobserver and intraobserver reliability and was validated in

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Dutch [25]. The VAS will be used to assess the child's anxiety level by the child himself, the parents, and the medical staff. The VAS shows 6 faces in order from not scared at all (most left face) to extremely scared (most right face; see Figure 3) [26]. The participants select the expression that fits their feeling before and after the MRI scan (T2 and T3). Because of the nonverbal character and the simplicity, this instrument offers a quick and reliable assessment that can be used in different settings [27,28]. The VAS is a widely used and studied instrument, has been shown to have a good reliability and validity, and is validated in Dutch [29]. The medical staff who accompanied the child were instructed to observe the anxiety of the child before the procedure in the MRI room and during the MRI scan (T2 and T3) by using the VAS [30].

Figure 3. The Visual Analogue Scale (VAS) with faces from not anxious (most left) to extremely anxious (most right).



Child Behavior Problems

In the weeks before the MRI scan (T1), the parents/guardians complete the CBCL to examine behavioral or emotional problems in the last 6 months. The version used for children between the age of 6-18 years consists of 113 items, has been proven valid and reliable, and is validated in Dutch [31]. The respondent evaluates each item as not true (0), a bit/sometimes (1), or obviously/often (2). An internalizing problem and externalizing problem scale can be calculated.

Parental Anxiety

Parents/guardians rate their own feelings of anxiety with the STAI at T2 and T3. This self-report instrument contains 2 separate scales for trait and anxiety, combined into 40 items that the respondent rates as not at all (0), somewhat (1), moderately (2), or very much (3). Earlier studies identified the STAI as a validated and reliable instrument to measure the anxiety state of the parents, and it is validated in Dutch [24,32].

User Experience

Children will provide subjective assessments of the VR MRI app using a 0-100 graphic rating scale at T1. They are asked (1) to rate the amount of "fun" they had during the VR preparation (no fun to most fun); (2) to what extent they felt nausea as a result of experiencing the virtual world (no nausea to severe nausea/vomiting [VR condition only]); (3) how real the objects in the virtual world seemed ("completely fake" to "indistinguishable from a real object" [VR condition only]); and (4) to what extent they felt like they went into the virtual world while experiencing VR ("I did not feel like I went into the virtual world at all" to "I went completely into the virtual world" [VR condition only]). Adherence will also be addressed in the user experience questionnaire by asking children and parents how often and how long they used the VR preparation app.

Monitoring and Harms

Monitoring of the study will be done by the Erasmus MC and will take place once a year. During the monitoring, the following will be monitored: (1) study documents and agreements; (2) patient inflow, consent, compliance, and source document verification; (3) patient safety; (4) the investigational intervention (VR); and (5) the study procedures.

The risk associated with the VR intervention is negligible and the burden should be considered minimal.

Protocol Amendments

Modification to the protocol, which may impact on the conduct of the study and potential benefit of the patient or may affect patient safety, will require a formal amendment to the medical ethical committee of the Erasmus MC.

Confidentiality

The handling of patient data will comply with the General Data Protection Regulation. All study data will be handled confidentially and coded with a unique study number. Only the research team involved in the study will be able to identify participants and have access to the data.

Statistical Analysis

Overview

The primary analysis will be conducted using an intention-to-treat basis. All patients recruited into the study will be included in this analysis. Patients will be analyzed within the group to which they were randomized, irrespective of what care they received. Regarding missing data, first, it will be analyzed if missing data/loss to follow-up reflects information bias or selection bias. Second, multiple imputation will be used to control for bias due to missing data.

Primary Study Parameter(s)

To test the efficacy of the VR intervention, we will compare the VR group to the CAU group with an ANCOVA. The primary outcome variable is the child's situational anxiety during MRI scan (T3; VAS child, continuous score), corrected for age, sex, baseline anxiety, and CBCL scores as well as type of MRI. In case of nonnormality, we will perform a Mann-Whitney *U* test.

Secondary Study Parameter(s)

The main secondary outcomes are child preprocedural anxiety at T2 and parental anxiety both before and during the procedure.

For the child's preprocedural anxiety, we will employ an identical analysis as for the primary end point. For parental anxiety, a repeated measures ANCOVA will be conducted with parental anxiety at T2 and T3 as within variable and group (VR vs CAU) as between variables. The analysis will be corrected

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for age, sex, baseline anxiety, and CBCL scores as well as type of MRI.

To identify medical or psychosocial moderators for treatment response to VR, we will perform exploratory linear regression analyses with child anxiety at T2 and T3. Predictor variables that will be examined are SES, age, sex, type of MRI, preprocedural child and preprocedural parental anxiety, and child emotional and behavioral problems. The user experience of children in the VR condition will be examined with descriptive analyses.

Results

The final version of the VR app has been approved. The recruitment of participants started in May 2021 and is currently ongoing and expected to be completed in December 2022. Data will be analyzed, and scientific papers will be submitted for publication in 2023.

Discussion

Expected Findings

Children often experience an MRI scan as an anxiety-provoking situation, and therefore, it is urgently needed that effective psychological preparations that are easy to use and cost-effective are developed and offered. VR has the potential to become a promising tool in the psychological preparation of pediatric patients for MRI. VR exposure has already been shown to be effective as a treatment for specific phobias in children. However, despite the fast-growing field of VR in medical care, there has been little research into the effectiveness of VR as preparation for an MRI scan in a clinical setting. Since VR is a promising tool for improvement in health outcomes, high-quality studies investigating innovative VR interventions are needed. Here, we describe the development of a smartphone-based VR intervention to prepare children for MRI scanning as well as an RCT to test its efficacy.

Strengths and Limitations

This study design has both strengths and limitations. A strength of this study is the RCT design and the multiple informant assessment of anxiety in children before and during the MRI scan. Most of the current preparation materials for children undergoing an MRI scan involve verbal explanation. The use of VR combines verbal explanation with visual information that can be beneficial for younger children or children who do not speak or understand the language. Additionally, the use of mobile phone–based VR creates the possibility to prepare children in their own time, at their own pace, and in the comfort of their own home. It also alleviates the personnel and space demands imposed by mock-scanner preparation. Due to the use of a smartphone-based VR experience that can be used at home, we can reduce the costs associated with using a tethered VR experience. The app presents a typical MRI room and thus can be used in any hospital without adjustments. Moreover, the app is designed to be easily localized to other languages. Furthermore, due to the use of 3D models instead of 360-degree video recordings, adjustments and adding or subtracting certain elements can be easily and cheaply done.

A limitation is that although we ask participants in the user experience questionnaire how often and for how long they have used the VR preparation app, we do not have more accurate measures of VR use. In addition, as the VR intervention is designed to be used at home in an environment that is comfortable for a child, we do not have information if the children used the VR MRI app with enough attention. The smartphone used by each child varies greatly in screen quality, size, and processing power. These differences might influence the VR experience, its image quality, and ultimately, the immersivity of the VR. Another limitation is that only children who do not need general anesthesia during the MRI scan are included, thereby potentially excluding the most highly anxious children. This may limit the generalizability of this study to children with less severe levels of anxiety. If this study shows that the VR MRI preparation app is efficacious, it would be important to study whether VR preparation can also reduce the need for anesthesia.

Conclusion

Most children experience anxiety before and during an MRI scan. To reduce this and reduce the need of anesthesia, there is a need to develop a more effective preparation method. VR offers a child-friendly and realistic environment where children can experience the procedure, without the use of real machines or medical staff. To examine the effect of this VR intervention, an RCT will be performed. If VR exposure is proven to be effective for preparation for an MRI scan, this easy-to-use tool can be implemented into standard medical care. We would like to emphasize though that even with the use of modern technology, education provided by health care professionals for both pediatric patients and their parents is still necessary, especially for older children.

Acknowledgments

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Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during the current study.

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Authors' Contributions

ZvS and KPL were responsible for writing this paper. BD and JSL were responsible for supervising the writing process of the paper and made important contributions to the development of the virtual reality app conceptualization. MD, JvS, and DS made an important intellectual contribution to this paper. MD, JvS, DS, BD, and JSL initiated the study design. BD and JSL are the lead investigators.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Images of the 3D environment in which the VR-experience takes place.
[PDF File (Adobe PDF File), 341 KB - resprot_v12i1e41080_app1.pdf]

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Abbreviations

ANCOVA: analysis of covariance
Amsterdam UMC: Amsterdam University Medical Centers
CAU: care as usual
CBCL: Child Behavioral Checklist
Erasmus MC: Erasmus University Medical Center
MRI: magnetic resonance imaging
RCT: randomized controlled trial
SES: socioeconomic status
STAI: State-Trait Anxiety Inventory
STAI-C: State-Trait Anxiety Inventory for Children
T: time point
VAS: Visual Analog Scale
VR: virtual reality

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Protocol

Digitally Delivered Dietary Interventions for Patients with Eating Disorders Undergoing Family-Based Treatment: Protocol for a Randomized Feasibility Trial

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Abstract

Background: Eating disorders (EDs) affect 9% of the United States population, and anorexia nervosa (AN), specifically, has the second highest mortality rate of all psychiatric disorders. Yet, only 20% are able to access treatment. Access to care issues include long waitlists, lack of trained specialists, financial, and geographic barriers, all of which highlight the need for effective telehealth interventions. Family-based therapy (FBT) is a first-line treatment for adolescents and young adults with EDs, and weight gain early in treatment is considered a primary predictor of success with FBT. However, nutrition requirements for patients with EDs are uniquely complex. A variety of dietary interventions for guiding the renourishment process are used in practice, but empirical data on the effectiveness and acceptability of the various interventions are sparse. The significance of nutritional restoration and issues with access to first-line treatments underscore the need for further research exploring virtually delivered dietary interventions.

Objective: Our objective is to compare the effectiveness and acceptability of 2 digitally delivered dietary interventions frequently used in eating disorder treatment settings: (1) calorie-based meal plans and (2) the Plate-by-Plate approach. Specifically, we will explore any potential differences in weight restoration achieved over 8 weeks of treatment as a primary measure of effectiveness, as well as additional treatment outcomes (ED symptoms, anxiety, depression, caregiver burden, and perceived effectiveness and acceptability for both caregivers and clinicians).

Methods: Patients (N=100) with either AN or avoidant restrictive food intake disorders (ARFID) aged 6-24 years seeking treatment at a nationwide virtual eating disorder treatment program, were enrolled between May and August 2022. Upon admission, patients were randomly assigned to receive either the calorie-based intervention or Plate-by-Plate approach from their registered dietitian, all of whom have received training as study interventionists. While we were primarily interested in responses during the first 8 weeks of treatment, patients will be followed for up to 12 months. Descriptive statistics were used to describe patient characteristics and demographics. Weight changes and other treatment outcomes between groups will be compared using generalized linear models. Semistructured caregiver and clinician interview transcripts will undergo qualitative analysis.

Results: Enrollment ran from March to August 2022, and we anticipate completion of data collection by November 2022. Analyses will be completed in January 2023.

Conclusions: This study contributes to existing FBT literature by thoroughly exploring the acceptability of dietary interventions and their influence on weight restoration, an area in which research is sparse.

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KEYWORDS

eating disorders; virtual treatment; dietary interventions; family-based treatment; anorexia; psychiatric disorder; digital health intervention; telehealth; virtual health

Introduction

Background

Eating disorders (EDs) are serious mental illnesses characterized by how one experiences a marked disturbance in weight and shape [1], afflicting people across all ages, genders, races, ethnicities, and body sizes. National prevalence estimates are 9%, and EDs have the second highest mortality rate (specifically anorexia nervosa [AN]) following opioid addiction [2]. The economic burden is also substantial, with an annual cost of US $64.7 billion [3]. Further, the COVID-19 pandemic has resulted in a staggering increase in new ED cases, as well as exacerbation of ED symptoms and decreased motivation for recovery for those with preexisting EDs [4,5]. The rise in demand and challenges with access to care were compounded by long waitlists, lack of trained specialists, financial and geographic barriers, and underscored need for improving access to effective ED treatments [6].

Telemedicine or digitally delivered ED treatment options offer an opportunity to meet the rising demand while addressing geographic barriers and providing patients with timely access to trained specialists and reduce barriers associated with accessing care. Telemedicine ED treatments have been on the rise primarily as a result of the COVID-19 pandemic, and recent research supports their effectiveness and comparability to in-person care [7-11]. Family-based treatment (FBT) is an approach through which caregivers are tasked with renourishing their child at home while given guidance by a team of specialists. FBT is a first-line treatment for adolescents and young adults with AN and shows promise as an effective modality for other ED subtypes as well [12,13]. Recent research supports the efficacy of digitally delivered FBT as outcomes rival those of in-person treatment options [14-16]. Nutritional restoration is a central treatment element across all ED subtypes, and weight gain in the first several weeks of FBT is considered a primary predictor of remission [17,18]. However, nutrition requirements for patients with EDs are uniquely complex and varied, with kilocalorie needs reaching 70-100 kcal per kg per day, and caregivers generally require ongoing support to successfully navigate home-based refeeding. The importance of nutritional restoration for remission highlights the need for a better understanding of the dietary interventions most commonly used in ED treatment settings. While the inclusion of the registered dietitian (RD) on multidisciplinary teams is standard in other ED treatment settings and modalities aside from FBT, historically, FBT was led by a family therapist who was also responsible for giving guidance around feeding. In recent years, the need for specialized nutrition support has become more apparent, and the presence of RD is more commonplace. The RD can skillfully address issues that arise in treatment (management of malnutrition, refeeding syndrome, weight plateaus, erroneous belief systems around food and weight, lack of diversity in food choices, and needs adjustments for patients return to sport) that may be unaddressed by therapists, but are vital for achieving remission [19,20]. Additionally, the RD assists by giving guidance on optimization of energy density, determination of goal weight range, alleviation or management of physical symptoms that arise secondary to refeeding, and identification of nutrients of concern, which is of particular importance for patients with avoidant restrictive food intake disorder (ARFID) [21]. However, a variety of dietary interventions are used in practice across the ED field, and the evidence comparing effectiveness of dietary approaches, in person or digitally delivered, is sparse.

Dietary Interventions

An overview of the interventions most commonly used in practice when treating ED patients are as follows: 1. Daily Calorie Target: caregivers or patients are provided a daily kilocalorie goal, and generally, the number of meals and snacks will also be prescribed, each with an associated kilocalorie goal. Provision of a daily calorie goal and discussions of calories in foods are generally discouraged in settings, where dietary interventions are patient-facing, as doing so may exacerbate ED thoughts and behaviors. Calorie targets may, however, be provided to caregivers as a means of guiding home-based refeeding efforts.

2. Plate-by-Plate approach: the Plate-by-Plate is a visual approach with primary intent for use in FBT, whereby caregivers are instructed to serve “normal” portions or plates versus using calories to guide meal or snack planning (Multimedia Appendix 1). This approach is regarded as a more flexible and intuitive, as calorie counting and measuring are discouraged. For patients requiring weight restoration, caregivers are instructed to create a plate consisting of 50% starch, 25% protein, and 25% vegetables and fruits, with dairy and fat servings specified by the RD for the meals. Key features of this approach include primary caregivers making the decision around what and how much to serve, with an emphasis on dietary variety and exposure to all foods. These features are thought to be important as they uphold parental empowerment, a core tenet of FBT [22].

3. Exchange system: this approach is most widely used in residential and partial hospitalization programs, where guidance is given directly to the patient [22]. The exchange system was developed by the American Diabetes Association as a way to categorize foods into 6 groups, and each “exchange” in a given food group is associated with a particular macronutrient range [23]. For example, 1 dairy exchange can be 1 oz of cheese or 8 oz milk. A number or range of exchanges are assigned to each meal and snack, thereby encouraging the patient to consider balance and dietary variety. The exchange system is seldom used in FBT given the different needs of caregivers versus patients.

This feasibility study will compare the acceptability of 2 digitally delivered dietary interventions and preliminary effectiveness in early stages of treatment: (1) calorie-based meal plans and (2) the Plate-by-Plate approach [24]. Our primary outcome of interest is weight restoration achieved after 8 weeks

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of treatment, as this is the best predictor of remission. We will also examine the following treatment outcomes by intervention: ED symptoms, anxiety, depression, caregiver burden and self-efficacy, and caregiver's acceptability and perception of effectiveness. Acceptability and perceived effectiveness will also be measured for clinicians once week 8 outcomes have been captured for all participants. While we are most interested in early treatment response, patients will be followed and clinical outcomes for patients and caregivers reported throughout the entirety of their treatment course as part of standard practice. We anticipate that the findings from this study will help us better understand the needs and experiences of caregivers undergoing FBT and ultimately, whether 1 approach is superior in terms of influence on treatment outcomes. We will also gain insight around commonly held assumptions, such as the running hypothesis that providing caregivers with a calorie target may undermine parental empowerment and self-efficacy. This study will add to existing FBT literature by exploring the impact of dietary interventions that guide caregivers' process for renourishing their child, for which there is currently no research.

Methods

Participants

We will examine the aspects of treatment outcome in patients aged 6-24 years self-selecting for web-based ED treatment at Equip Health. The inclusion criteria are as follows: (1) aged 6-24 years, (2) ED diagnosis of AN or ARFID, (3) consented to participate in treatment approach comparison research upon admission, (4) apparent need for weight restoration upon admission, (5) first time recipients of treatment at Equip Health, and (6) assigned to RD interventionist.

Setting

This single-site study takes place at Equip Health. Equip Health provides web-based ED treatment to children and adolescents ages 6-24 years across the United States using an FBT approach.

Ethical Considerations

This study was reviewed by the Biomedical Research Alliance of New York (BRANY) institutional review board (protocol number 22-016-1096), and it was determined that it does not meet the criteria for human subject's research as this is a quality improvement study of Equip Health treatment. Thus, institutional review board oversight was not required. Patients or caregivers consented to participate in treatment approach comparison studies upon admission and consented for treatment information to be evaluated and disseminated. Data will be stored in Equip's Health Insurance Portability and Accountability Act–compliant medical record platform and will be deidentified upon extraction by trained research personnel. Interviews with the RD interventionists will be conducted via a Health Insurance Portability and Accountability Act–compliant Zoom platform. The final study results will be reported in aggregate, and will not contain any personally identifiable information.

Recruitment

Patients seeking treatment at Equip inquire through Equip's web-based form through direct email or phone. We randomized 100 eligible patients who enrolled in ED treatment on a rolling basis from May through August 2022.

Group Assignment

As part of standard of care at Equip Health, all patients receiving FBT are assigned an RD as part of their multidisciplinary treatment team. Upon admission, patients eligible for this study and who consented to be a part of treatment comparison studies at Equip will be randomly assigned using a block design to receive either the calorie-based approach or the Plate-by-Plate approach during renourishment treatment with the RD. Participating patients were randomized for the purpose of having an equal number of participants in each treatment group. All other treatment procedures followed the standard of care for all Equip patients.

Assessments and Measures

Overview

Outcome measures are described below and summarized in Table 1. Additionally, the following demographic data will be extracted from the medical record: age, state of residence, biological sex, gender identity, ED diagnosis, and height. Patients will be followed for up to 12 months, and clinical assessment measures are taken throughout treatment as part of standard practice. However, our primary time point of interest is week 8 of treatment, as this will provide important information about the patient's response in the early phases of treatment, a critical time period for predicting remission.

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Table 1. Primary and secondary outcome measures.

Measure	Outcome	Frequency assessed and timepoints of interest
Primary outcome		
Weight	Weight change	Twice weekly (baseline, week 8)
Secondary outcomes		
Eating Disorder Examination Questionnaire Short Form	Global total score, Eating concern scale score, Weight concern scale score, and Shape concern scale score	Upon admission, weekly thereafter (baseline and week 8)
Burden Assessment Scale	Caregiver burnout	Every 40 days (baseline and week 8)
Parent versus Eating Disorders	Caregiver self-efficacy	Day 14, every 40 days thereafter (baseline and week 8)
Patient Health Questionnaire	Symptoms of depression	Upon admission, monthly thereafter (baseline and week 8)
Generalized Anxiety Disorder Scale	Symptoms of anxiety	Upon admission, monthly thereafter (baseline and week 8)
Clinician semistructured interview	Acceptability and perceived effectiveness of intervention	End of study
Caregiver semistructured interview	Acceptability and perceived effectiveness of intervention	Treatment week 8 (approximate)

Weight

Upon admission, caregivers receive instructions from their assigned Equip medical provider on proper procedure for checking weight. Weights are taken in the morning, after voiding, prior to any oral intake and patients are asked to wear light clothing. The patient's weight (in pounds) is taken twice weekly by caregivers and communicated via text message from caregivers to Equip's Health Insurance Portability and Accountability Act–compliant medical record platform. For each patient, the RD calculates a target weight for weight restoration. Target weight is calculated using expected weight data from each patient's CDC BMI-for-age Growth Charts. Our primary end point of interest is weight change during the first 8 weeks of treatment, which will include an average weekly rate of weight gain and total weight change from admission to treatment week 8.

Eating Disorder Examination Questionnaire Short Form

The Eating Disorder Examination Questionnaire Short Form is an abbreviated 12-item version of the 28-item Eating Disorder Examination Questionnaire survey. The Eating Disorder Examination Questionnaire Short Form is a well-validated and reliable measure, which assesses ED symptom severity. Scores range from 0 to 36, with higher scores suggesting increasing severity of ED behavior [25].

Patient Health Questionnaire

The Patient Health Questionnaire-9 is a brief, well-validated, and reliable diagnostic tool for depression. Patients are asked to rate 9 items pertaining to depression symptoms they have found bothersome over the last 2 weeks from "0" (not at all) to "3" (nearly every day). Higher scores indicate greater levels of depression [26].

Generalized Anxiety Disorder Scale

The Generalized Anxiety Disorder Scale is a widely used, validated, and reliable self-report tool for screening, diagnosing, and assessing the severity of an anxiety disorder. Patients are asked to rate 7 items pertaining to anxiety symptoms, which are scored from 0 to 3, and the score is totaled. Higher scores indicate increasing severity of anxiety [27].

Burden Assessment Scale

The Burden Assessment Scale is a 19-item validated questionnaire that focuses on specific objective and subjective caregiver consequences of individuals with mental illness. Ten items assess objective burden (eg, financial problems) and 9 items assess subjective aspects of burden (eg, feelings and attitudes). Caregivers were asked to indicate the extent to which they experienced the described problem on a 4-point scale, with higher scores indicating greater levels of caregiver burden [28,29].

Parent versus Eating Disorders

Parental self-efficacy will be assessed with the Parent versus Eating Disorders, which was adapted from the Parent Versus Anorexia scale. The Parent versus Eating Disorders was designed to capture caregivers' belief in their ability to overcome their loved one's eating disorder. Seven items are ranked on a 5-point scale with higher scores indicating greater self-efficacy [30].

Caregiver Semistructured Interviews

A semistructured interview (Multimedia Appendix 2) will be completed with caregivers to assess their experience with the assigned renourishment strategy. Caregivers will be contacted directly by a member of the research team via their preferred email address to schedule and the interviews will be conducted via phone. If the caregiver does not respond to contact efforts, a Health Insurance Portability and Accountability Act–compliant

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Google Forms link will be provided via preferred email through which the caregiver can answer the interview questions, after which efforts to reach the caregiver will be discontinued.

Clinician Semistructured Interviews

A semistructured interview (Multimedia Appendix 3) with the RD interventionist will also be completed to assess the interventionists' general experience with each approach. Interviews will be completed by a member of the Equip research team and completed remotely via Health Insurance Portability and Accountability Act–compliant Zoom platform.

Statistical Analysis

The treatment outcomes will be collected via our Health Insurance Portability and Accountability Act–compliant medical record platform and will be extracted by trained research personnel. Descriptive statistics will be used to describe patient characteristics and demographics of our patients and treatment outcomes defined in Table 1. To examine any differences in effectiveness between the 2 interventions, we will compare the rate of weight change between the groups using generalized linear models in R version 4.1.1 (R Core Team). We will also look at outcomes across ED subtypes.

Procedures

Upon beginning treatment at Equip Health, eligible patients will be randomly assigned to receive either the calorie-based approach or the Plate-by-Plate intervention within their first 1-2 sessions with their assigned RD. In the first phase of treatment, the RD meets exclusively with caregivers (eg, parents or guardians) at a weekly meeting cadence for the first month, and thereafter in accordance with the RD's judgment.

A high-level summary of each approach is as follows: (1) calorie-based nutrition prescription: following the completion of a nutrition assessment by the RD, caregivers will be prescribed a calorie goal and be instructed to aim to reach that goal daily as a primary focus of treatment. In collaboration with caregivers, a calorie goal will be assigned to 3 meals and 3 snacks daily. For example, the goal may be 3000 kcal per day, comprised of 700 kcal meals 3 times per day, and 300-kcal snacks 3 times per day. Additionally, caregivers are provided 7-day sample menus that align with their calorie prescription. If clinically indicated, they may also receive education on how to increase the caloric density of meals while maintaining low volume. Adjustments will be made throughout the treatment course to calorie prescriptions per RD's judgment to accommodate the weight restoration goal of 2 lbs per week. During the initial session, caregivers are instructed to send photos and density estimates of all foods consumed by the child to the RD, and feedback will be given speaking to the adequacy of calorie content of meals and snacks in the follow-up sessions. (2) Plate-by-Plate approach is summarized for caregivers in the following steps:

1. Choose 10-inch plate
2. Plate all food groups
3. Fill plate
4. Parent decides number of meals or snacks
5. Include variety
6. Does the meal make sense?
7. Final review: Does the plate make sense?

Caregivers are instructed to prompt the patient to complete the plate, and in the case of food refusal, oral supplements are provided to replace the remaining food.

Training and Fidelity

All Equip RDs have experience in treating EDs using a variety of dietary interventions within and outside of the FBT framework. Upon hiring, Equip RDs complete an in-depth video training on various interventions commonly used in ED treatment, including the Plate-by-Plate approach and calorie-based meal plans. RD interventionists undergo a live training session overviewing study protocols and each intervention, and a prerecorded training on the Plate-by-Plate intervention (led by authors of the Plate-by-Plate intervention). Interventionists will receive ongoing training as needed and supervision to ensure adherence to the respective approaches and will additionally be trained to notify research staff of any fidelity issues or protocol deviations by other providers on a treatment team.

Electronic records will be reviewed by study personnel on a weekly basis to ensure adherence to the assigned treatment approach. Specifically, session documentation, chat communications, and any document exchanges will be reviewed. Any fidelity issues (and the subsequent potential need for participant withdrawal) will be discussed by research personnel and interventionists. Further, should a patient discharge prior to week 8 of treatment, or if the RD determines that the assigned intervention is a poor fit for the patient, the patient may be withdrawn.

Results

Demographics

A total of 100 patients (with average age of 15 years) were enrolled on a rolling basis from March through August 2022. Fifty patients were assigned to the Plate-by-Plate group and 50 to the calorie target group. Overall, 83% of participants were cisgender females, 9% were cisgender males, 6% were nonbinary, and 2% were transgender. Furthermore, 66% of participants were diagnosed with AN restricting subtype, 18% with the AN binge-purge subtype, and 16% with ARFID. We anticipate completion of data collection by November 2022 and analysis by January 2023.

Significance

We anticipate that, following completion of this study, we will be able to (1) address common myths, assumptions, and misconceptions associated with each intervention; (2) identify differences in outcomes and emerging themes from interview data, and use findings to adapt interventions and the supporting digital resources; (3) identify a preferred, or "best practice" approach for improving outcomes in the early phase of FBT, as early response is predictive of remission; and (4) understand any potential differences or nuances that may exist by intervention across the 2 ED subtypes (AN and ARFID).

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Design Considerations

While a variety of interventions may be used in practice, we selected Plate-by-Plate and calorie-based approaches due to their common use in FBT. Discussions of calories and the use of calorie targets to guide renourishment are generally discouraged in ED treatment settings in an effort to decrease preoccupations with calorie counting. Building upon this hypothesis, Plate-by-Plate authors cite the following rationale for use of a visual approach: (1) informed by a study that found an association between calorie-tracking application use and either maintenance or worsening of ED symptoms [31], authors hypothesized that a visual and simplistic versus numbers-based approach may have a beneficial influence on eating disorder symptoms and would allow for a seamless transition to "normal," independent eating in later stages of treatment and beyond. Further, any calorie counting done by caregivers may "trickle down" to the patient and may thereby reinforce or exacerbate ED symptoms or thoughts. (2) A visual approach offers more flexibility by accommodating dietary restrictions, culturally appropriate food preferences, and easy adaptation for meals and snacks consumed outside of the home. (3) Given the lack of nutritional guidance due to exclusion of RDs in early FBT models, Plate-by-Plate was created to help parents with refeeding efforts using a more specialized approach, while still honoring the "parental empowerment" tenant central to FBT by allowing parents to select foods served.

With this study, we aim to test and challenge these assumptions through direct comparisons with a calorie-based approach. As part of standard practices at Equip Health, digital "food journals" (ie, photos and descriptions of foods) are provided by caregivers for assessment by RDs. In the absence of photos, the calorie-based approach allows parents to share calorie totals, which we suspect offer a more precise estimate of intake, and are less subject to parent interpretations and verbal description of portions or foods served and consumed. A calorie-based target may offer flexibility in "how" needs are met, and, like Plate-by-Plate, honors cultural preferences and dietary restrictions. We will further test the assumption that calorie targets trickle down to the patient, as caregivers are explicitly instructed not to share calorie information with patients, and ED patients have an existing general awareness of calorie content of foods and are able to quickly estimate upon provision of a meal or snack. Further, it is common practice in FBT to encourage parents to prepare and plate foods without the child present to minimize negotiations, resistance, and opportunity for patients to scrutinize components or portions.

Participant Selection

The decision was made to exclude ED subtypes other than AN and ARFID for the following reasons:

1. Need for weight restoration was an important part of the inclusion criteria as weight restoration is typically first priority and a core component of ED treatment. Given that we are less likely to encounter a need for weight restoration in other ED subtypes, and would thus yield a small sample size within those subtypes, we opted to include only patients with AN and those with ARFID, which are the primary presenting subtypes in our patient population. In addition, while caregiver feedback is important, various aspects of FBT can be challenging for caregivers. We felt it important to have an outcome measure (weight) that is most predictive of remission and success with FBT.
2. In addition to there being little research on dietary interventions in the ED space in general, research looking at dietary interventions for ARFID, and particularly for patients undergoing FBT, is especially sparse. Given the differences in symptoms and presentation between patients with ARFID and those with AN, we felt it is important to better understand the benefits and challenges associated with the use of a visual approach. For example, patients with ARFID may present with a very limited number of acceptable foods and the lack of variety may make it challenging for parents to present meals or snacks with multiple components from numerous food groups. It is our hope that the outcome data, coupled with rich insights from clinicians and caregivers, will help us understand which aspects of our interventions may be most appropriate for patients with ARFID, and the ways in which they differ from patients with AN.

Discussion

Strengths and Limitations

To our knowledge, this will be the first comparison of digitally delivered dietary interventions for the treatment of EDs. Given access issues faced by patients seeking ED treatment, and increasing acceptability and use of telehealth, it is of particular value to test interventions in the digital space. Testing assumptions upon which approaches are developed is also valuable as we were able to gain insights that help us tailor approaches that better resonate with caregivers and providers.

It should be noted that the majority of patients who present for ED treatment at Equip have engaged with numerous prior programs and providers, and as such, they may have encountered various dietary approaches. While it was not realistic nor warranted to exclude those with prior treatment histories, we addressed this by instructing RD interventionists to notify study personnel should it prohibitive to orient caregivers to the assigned approach. At that point, a determination will be made as to whether the patient should be withdrawn from the study. Further, although with FBT caregivers are tasked with renourishing their child between ages 6 and 24 years, it is possible that there may be differences in intervention across age ranges, particularly for patient-facing interventions. However, it should be noted that individual (patient) nutrition therapy is provided only in later stages of FBT (generally following several months of nutritional restoration).

Future Work

In this study, we compare 2 digitally delivered dietary interventions most commonly used by dietitians in eating disorder treatment settings and subsequent outcomes. Future research is needed to examine the effectiveness of interventions delivered directly to patients and across the broad range of ED subtypes.

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Data Availability

The data that will support the findings of this study will be derived from patient medical record data. The data are not publicly available and individual data cannot be shared due to privacy and institutional restrictions.

Conflicts of Interest

MH, JHB, and DS have equity in Equip Health.

Multimedia Appendix 1
Semistructured registered dietitian interventionist interview script.
[DOCX File , 16 KB - resprot_v12i1e41837_app1.docx]

Multimedia Appendix 2
Semistructured caregiver interview script.
[DOCX File , 14 KB - resprot_v12i1e41837_app2.docx]

Multimedia Appendix 3
Overview of Plate-by-Plate approach.
[PDF File (Adobe PDF File), 7199 KB - resprot_v12i1e41837_app3.pdf]

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Abbreviations

AN: anorexia nervosa
ARFID: avoidant restrictive food intake disorder
ED: eating disorder
FBT: family-based treatment
RD: registered dietitian

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Protocol

The Effects of a Web-Based Intervention to Reduce Alcohol Consumption Among Middle-Aged Women: Protocol for a Randomized Controlled Trial

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Abstract

Background: In the last decade, alcohol consumption among middle-aged women (40-65 years old) in Australia increased, despite declines in overall population consumption. Web-based, brief interventions are promising for reducing alcohol consumption, with efficacy shown in a wide range of populations. However, no published interventions have been designed specifically for and tested with middle-aged women.

Objective: This study aims to design and implement a web-based intervention intended to reduce alcohol consumption among middle-aged women.

Methods: The study is a 3-arm randomized controlled trial with a web-based intervention plus ecological momentary assessment (EMA) group compared to an EMA-only and a pre-post only control group. The study is aimed at middle-aged women, defined as women aged between 40 and 65 years, who consume alcohol at least weekly or who have consumed 4 or more drinks on 1 occasion in the last month. The intervention aims to reduce alcohol consumption through 4 modules that provide information on the health impacts of alcohol, mindfulness, social influences, and alcohol marketing. Intervention participants will also fill out biweekly EMA assessments. The comparators are EMA-only and pre-post control only. The primary outcome is alcohol consumption at 8 weeks compared between groups. Secondary outcomes are awareness of alcohol-related harms, readiness to change alcohol consumption, health status, mental health, and social support.

Results: Ethics approval for this project was received on September 11, 2019. The trial was registered on August 14, 2020. Recruitment has commenced, and the expected results will be available in 2022.

Conclusions: This web-based intervention aims to reduce alcohol consumption among middle-aged women, a currently understudied cohort in alcohol research.

Trial Registration: Australia New Zealand Clinical Trials Registry (ANZCTR) ACTRN12620000814976; https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?ACTRN=12620000814976

International Registered Report Identifier (IRRID): DERR1-10.2196/34842

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KEYWORDS

alcohol consumption; web-based; online intervention; middle-aged women; Australia; intervention; alcohol research; alcohol; ecological momentary assessment; EMA

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Introduction

Background

Historically, men have been larger consumers of alcohol than women, but recent evidence has shown a gender convergence in rates of alcohol consumption [1]. In Australia, this is particularly notable among middle-aged women; rates of long-term risky drinking (measured as 2 or more standard drinks a day) have increased significantly among women aged 40-65 years from 8.8% in 2001 to 11.7% in 2019 [2]. Similarly, rates of risky single-occasion drinking (measured as 5 or more standard drinks on 1 occasion) rose from 13.5% to 19.8% over this same period [2]. This increase is of concern as women are more susceptible to the long-term negative health effects of alcohol including cardiovascular disease, cancer, and diabetes [3]. Women are also more likely to develop alcohol-use disorders from lower levels of consumption than men and are more vulnerable to the neurotoxic effects of alcohol [3].

Several systematic reviews have been carried out to determine the overall efficacy of web-based interventions aimed at reducing alcohol consumption. The most recent, a review of systematic reviews [4], found that web-based interventions were effective in reducing alcohol consumption, albeit effect sizes were mostly small, reflecting a weekly reduction of between 2 and 3 UK units (1 unit=8 grams of ethanol) or between 1 and 2.5 European units (1 unit=10 grams). Studies of interventions that have included women in the sample have often found that higher proportions of women than men take up the intervention [5], suggesting web-based interventions are an appropriate medium for female drinkers. Of studies demonstrating the efficacy of web-based interventions with women, the majority have only included college students [6,7].

There is a specific need for interventions designed by, and targeted at, middle-aged women for several reasons. Firstly, men and women have different patterns of alcohol use and different motives for consumption [3,8,9]. For example, women are lighter drinkers than men, and use alcohol to experience respite from their traditional female domestic and caring responsibilities. Further, most web-based interventions that are female-centric have been aimed at pregnant women or those of childbearing age, with the content heavily tailored to these specific groups and a particular focus on the harms of alcohol to unborn babies [10,11]. Lastly, it has been shown that tailoring interventions using co-design with a target population is particularly efficacious in ensuring the effectiveness of an intervention or program [12,13]; thus, an intervention designed by and for middle-aged women is likely to have amplified effectiveness.

To our knowledge, there are no web-based interventions targeted specifically at middle-aged women that have been documented in the literature. Our study aims to fill this gap by developing and testing the effectiveness of a web-based intervention in reducing alcohol consumption among women aged 40-65 years. The primary aim of this study is to test the effectiveness of a 3-arm web-based intervention in reducing both the frequency of alcohol consumption as well as the alcohol intake per occasion among middle-aged women. Secondary aims include testing the effectiveness of the intervention in increasing awareness of the long- and short-term harms associated with alcohol consumption, increasing motivation to reduce alcohol consumption, reducing alcohol-related harm, improving reported health status and mental health, and increasing social support. We will also test reactivity to the ecological momentary assessment (EMA) by comparing a control group with weekly assessment to a pre-post control group.

Hypothesis 1

We hypothesize that by the end of the intervention period, participants in the web-based intervention group will report significantly lower alcohol consumption compared with participants in the pre-post control group (H1).

Hypothesis 2

We hypothesize that by the end of the intervention period, participants in the web-based intervention group will display significant increases in their awareness of harms associated with alcohol consumption (H2a), their motivation to reduce their alcohol consumption (H2b), social support (H2c), and current health status (H2d); they will also display significant decreases in alcohol-related harm (H2e) when compared to the pre-post control only group.

Hypothesis 3

We hypothesize that by the end of the intervention period, participants in the control group with weekly assessment will have greater reductions in alcohol consumption compared with participants in the pre-post control group (H3a). We further hypothesize that participants in the intervention group will report a greater reduction in alcohol consumption compared with participants in the control group with weekly assessment.

Methods

Study Design

This study is a 3-arm randomized controlled trial including 1 intervention group, 1 pre-post control group and 1 control group with weekly assessment. The trial was registered with Australia New Zealand Clinical Trials Registry (ACTRN12620000814976) on August 14, 2020.

Ethics Approval and Consent to Participate

This study has received ethics approval from the La Trobe University Human Research Ethics Committee (HEC19938). Participants who are eligible for the intervention will be emailed a consent form with brief information about the study, prior to completing the baseline survey. Upon randomization, participants will complete a second short written consent form which will contain information specific to their intervention arm.

Participants

For this study, participants will be eligible if they are aged between 40 and 65 years, identify as female, reside in the Australian Capital Territory or a surrounding postcode that covers the Australian Capital Territory, are able to understand written English, are able to provide informed consent, own a mobile phone with SMS text messaging capabilities, have access

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to the internet, and consume alcohol at least weekly or consume 4 or more standard drinks at least once a month.

Women will be ineligible for the study if they are currently receiving treatment for a substance use disorder or are not in Australia for the duration of the study.

Sample Size Calculation

The effect sizes obtained in brief interventions, that is, change in the intervention group compared to the control group, are usually relatively small [4]. Power analyses in the statistical software G*Power 3.1.9.4 [14] were conducted to determine the power (probability) to successfully find differences between the intervention group and the 2 control groups. In this study, we aim to recruit 3000 participants. However, we may be short on this aim by one-third and have one-third attrition leaving us with a sample of 1333. Using repeated measures ANOVA with within-between interactions (ie, 2 measurements over time [pre-post assessments; note that in any case the EMA assessments will have a higher test power] interacting with the membership in 1 of 3 groups), this reduced sample will still have a power (probability) of more than 99% to detect even small effect sizes (P=.99; [15]) with an α-error threshold of .001. In other words, the intended sample size is sufficient to test all hypotheses successfully.

Recruitment

Recruitment will be carried out through a multipronged approach using both "online" and "offline" access points. Online recruitment will occur through media outlets such as Facebook, Twitter, websites, web-based newsletters, and magazines. Offline recruitment will include advertisements in school newsletters, local community group newsletters, general practitioner clinics, libraries, and gyms. Advertisements will include a link and QR code for a brief web-based screening questionnaire to assess participant eligibility.

We will undertake rolling recruitment, such that participants will be recruited continuously until 3000 individuals are participating in the study. Each participant will undertake the baseline assessment immediately after recruitment to ensure retention.

Procedures

This study is a 3-arm randomized controlled trial of a web-based intervention to reduce alcohol consumption in middle-aged women.

Potential participants responding to an advertisement will be linked to the study website, which will provide them with a brief description of the study and an eligibility screener. Participants who are eligible will be electronically sent an initial consent form with brief information about the study and will be asked to complete the baseline survey. Participants who do not respond to the initial prompt to complete the baseline survey will be sent 3 reminders over 2 weeks. Upon completion of the baseline survey, participants will be randomized into 1 of 3 groups through the back-end platform specifically designed for the intervention, using a computer-generated number allocated to each participant. Participants will then complete a second short consent form that contains information specific to their intervention arm. As with most behavioral interventions, although it is not possible to blind participants to the procedures relating to their own group, they will not be aware of the procedures relating to the other groups. The researchers responsible for analysis will also be blinded. Only 1 member of the research team, who will be the contact point for any participants experiencing technical difficulties or presenting with queries, will be aware of participant allocation, if required to provide support.

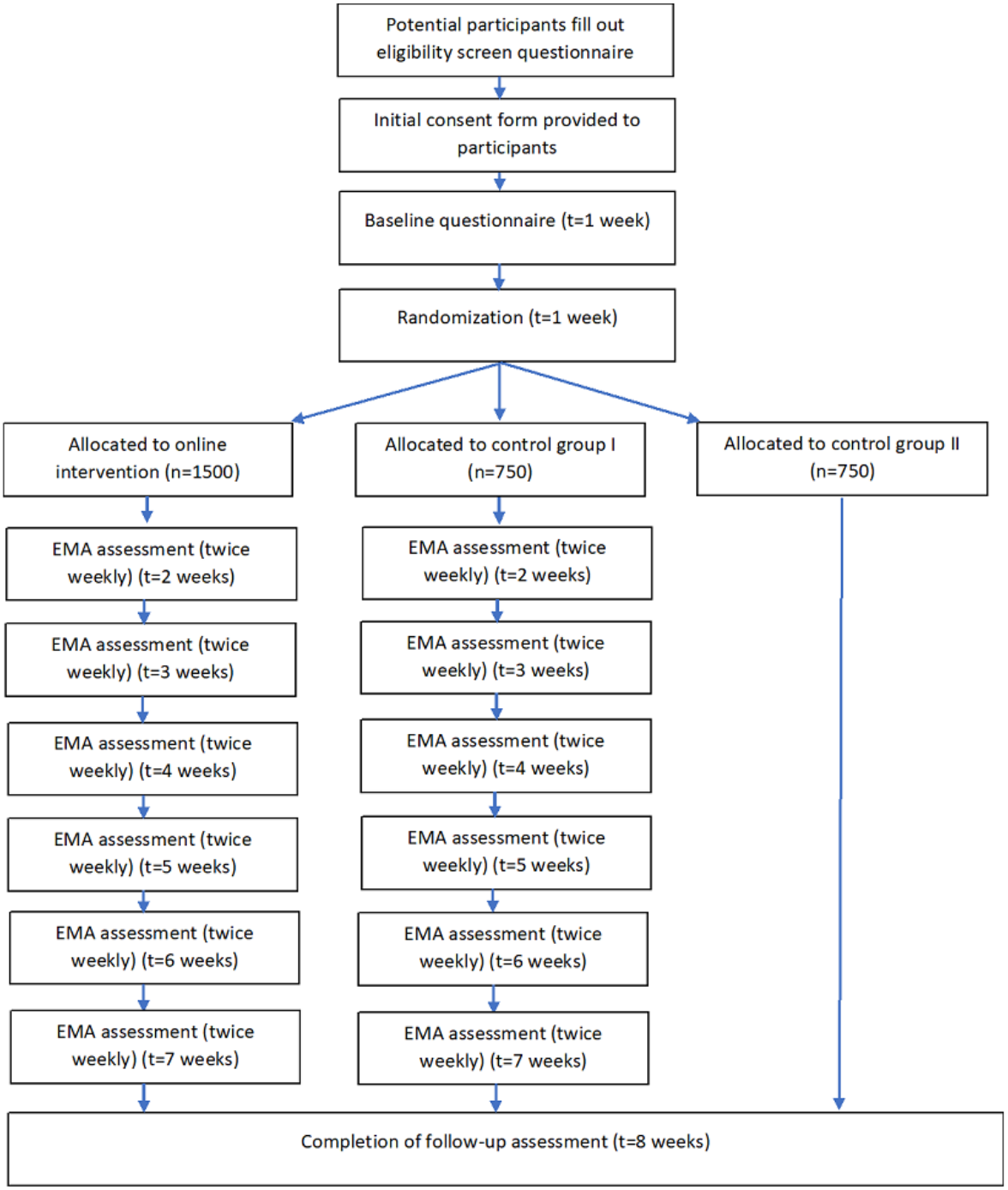
The study will include 3 parallel conditions, of which all 3 will complete a baseline and follow-up questionnaire. The intervention design is shown in Figure 1. Beyond that, the 3 conditions will include the experimental condition (web-based intervention and EMA), and 2 control groups (control group 1: baseline and follow-up assessment only, and control group 2: baseline and follow-up assessment plus EMA). They will undertake assessments of their alcohol consumption over an 8-week period, providing EMA measurements of their alcohol consumption on a twice-weekly basis (measuring their daily alcohol consumption retrospectively). Screenshots of the intervention are shown in Multimedia Appendix 1.

Participants will be able to withdraw from the intervention at their request. If a participant reports an adverse event or complaint, they will be unblinded by matching their participant ID with the contact details database to enable us to establish contact and respond to any issues accordingly. A risk management database will be maintained where records of any issues will be logged.

To promote retention, all participants who complete the study (ie, complete the final assessment measures) will be entered into a draw to win 1 of 24 vouchers. There will be 12 AUD $50 vouchers, 9 AUD $100 vouchers, and 3 AUD $250 vouchers available (AUD $1=US $0.67). The large number of vouchers available reflects the repeated engagement required of participants as well as the intended large number of participants.

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Figure 1. Intervention design. EMA: ecological momentary assessment; t: time point.



Intervention

The underlying theory for this web-based intervention is based on the assumptions of the Integrated Behavioral Model. This model posits that the most important determinant of behavior is the intention to perform the behavior, informed by individuals' attitudes, perceived norms, and personal agency [16]. Within this model, intention to perform a behavior is modified by four key factors: knowledge and skills, environmental constraints, the salience of the behavior to the individual, and the role of habits [16]. The Transtheoretical Model of Change [17] will also be used to determine each participant's readiness to change their alcohol use to understand how the intervention impacts motivation to change. The intervention also follows the principles of brief interventions for substance use [18]. Additionally, the intervention is based on the outcomes of interactive focus group workshops that were run by the research team with women aged 40-65 years.

The Integrated Behavioral Model

Initially, participants will be surveyed on their alcohol use and provided with feedback on their current consumption, in line with brief intervention practice. Following this, participants will *set goals* around their intentions to reduce their alcohol use over the period of the intervention in order to promote personal agency or self-efficacy. Participants will also be able to *track their alcohol use* throughout the intervention period to become more aware of their habits and behaviors. Participants will work

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through four *modules of content*, which will provide information aimed at changing participants' attitudes and perceived norms. This will include the following: (1) the Low-Risk Drinking module, which will provide evidence on the harms of alcohol use and information on what a standard drink is; (2) the Mindful Drinking module, which will provide information about drinking motives and provide participants with skills to both learn to consume alcohol mindfully and to apply the broader techniques of mindfulness to their lives to reduce the common antecedents of alcohol use (such as stress); (3) the Social Drinker module, which will explore the social influences of drinking, including facts about how people influence each other both consciously and unconsciously, encourage participants to reflect on where alcohol currently fits into their social lives, and help build participant's skills to talk about their alcohol consumption with others; and (4) the Alcohol is Everywhere module, which will look at the broader factors that influence alcohol consumption, including information about the normativity of alcohol in Australian society and how alcohol availability and outlet density impact consumption, the ways in which the alcohol industry specifically targets women, how alcohol advertising impacts children, and the broader alcohol industry tactics used to promote their products. The overall aim of the content is to make participants more aware of their alcohol use and the impacts it has on their lives and on the lives of others, in order to produce attitudinal and normative changes, while building skills to cope with stress and increase self-efficacy for reducing consumption in social situations.

To improve participants' knowledge and skills to reduce their alcohol use, and to remove environmental constraints, each module will have between 1 and 3 associated *challenges*. The challenges include, for example, an opportunity for participants to write a script for a conversation with a friend or family member on how to say no when offered alcohol, information on alternate activities participants can do to relax, and an opportunity to track how they engage in these activities over a 1-week period.

Participants will be sent reminders to complete their assessments, and upon completion of the assessment, will be redirected back to the intervention content. Participants can complete the intervention content in any order and will have the entire intervention period to access and work through all of the content.

At the conclusion of the trial, participant summaries will be developed and distributed to those participants who request one.

Comparator

Participants in control group 1 will not be contacted again until the 8-week follow-up questionnaire. Participants in control group 2 (baseline and follow-up assessment plus EMA) will undertake the web-based repeated measures assessment of their alcohol consumption retrospectively twice a week. After they are recruited and randomized, these participants will be sent a link via text message to a web-based EMA. The assessment on Sunday at 12 PM will ask them about their drinking patterns over the weekend (ie, Thursday afternoon until Sunday morning), and the assessment on Thursday at 12 PM will ask about their drinking patterns during the week (ie, Sunday afternoon until Thursday morning). All participants in the control groups will be given access to the web-based intervention at the completion of the study.

Outcomes

The primary outcomes include frequency of alcohol consumption, as well as alcohol intake per drinking occasion. The secondary outcomes are awareness of alcohol-related harms, willingness to change alcohol consumption, alcohol-related harm, current health status, mental health, and social support or loneliness.

Measures

The following measures will be used, administered at baseline, EMA, and follow-up.

Baseline Survey: Demographic Questions

The baseline survey will assess a series of demographic characteristics, including educational level, country of birth, marital status, income, whether the participating women have children, the number of dependent children living in the household, employment status, as well as smoking status and frequency.

Alcohol-Related Measures

Typical Drinking (Baseline and Follow-up)

Participants will also be asked to report on how much they typically drink each day of the week (eg, "How many drinks containing alcohol do you consume on a typical Monday?")

Frequency of Risky Single-Occasion Drinking (Baseline and Follow-up)

Frequency of binge drinking will be assessed by asking participants how often they have had 4 or more standard drinks (containing 10 grams of pure ethanol) on 1 drinking occasion over the last 12 months.

Daily Alcohol Consumption (Baseline, EMA, and Follow-up)

Participants' daily alcohol consumption will be measured using a drinking diary, where twice a week they will retrospectively report on the number of beverages they consumed each day (eg, "Thinking back over the last three days, how many standard drinks containing alcohol did you have on each day of the week?")

Alcohol-Related Harm (Baseline and Follow-up)

A total of 15 items from the Rutgers Alcohol Problem Index [19] and the Young Adult Alcohol Consequences Questionnaire [20] were selected based on their age-appropriateness to our target group. Participants will be asked the following: "How many times has this happened to you while you were drinking or because of your drinking during the last year?": "Got into fights with other people," "Went to work drunk," "Missed out on other things because you spent too much money on alcohol," "Caused shame or embarrassment to someone," "Neglected your responsibilities," "Friends or relatives avoided you," "Felt that you needed more alcohol than you used to in order to get the same effect," "Tried to control your drinking (tried to drink only at certain times of the day or in certain places, that is, tried to change your pattern of drinking)," "Had withdrawal

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symptoms, that is, felt sick because you stopped or cut down on drinking," "Noticed a change in your personality," "Felt that you had a problem with alcohol," "Missed a day (or part of a day) of work," and "Kept drinking when you promised yourself not to," with four possible answer categories ranging from 0 (none) to 3 (more than 5 times).

Pressures From Different Sources to Drink More and to Drink Less (Baseline and Follow-up)

Two questions on pressures to drink have been adapted from the core questionnaire from the GenACIS project [21], which are as follows: "During the last 12 months, have any of the following persons attempted to influence your drinking so that you would drink less or cut down?" and "During the last 12 months, have you felt influenced to drink or drink more by someone who drinks more than you do?" with each question having the following response options: "Your spouse/partner/romantic partner?" "Your child or children?" "Some other female member of your family?" "Some other male member of your family?" "Someone at your work?" "A female friend or acquaintance?" "A male friend or acquaintance?" and "A doctor or health worker?" with yes or no answer categories for each option.

Awareness of Alcohol Harms (Baseline and Follow-up)

As no validated scale currently exists to measure awareness of alcohol harms, 2 questions will be taken from the scale used in the 2017 study by Coomber et al [22]: (1) "Which of the following do you think are likely consequences of a single occasion of heavy drinking (ie, short-term consequences)?" with participants asked to rank the accuracy (ranging from definitely untrue to definitely true) of the following consequences: "Lack of coordination and slower reflexes," "Reduced concentration," "Motor vehicle, bicycle and pedestrian accidents," "Injuries associated with falls, accidents, violence and intentional self-harm," "Alcohol poisoning," "Drownings," "Coma and death," and (2) "Which of the following do you think are likely consequences of consuming alcohol over many years (ie, long-term consequences)?" with participants asked to rank the accuracy of the following consequences: "Harm to unborn babies," "Cirrhosis of the liver," "Brain damage," "Stomach problems," "Heart and blood disease," "Pancreatitis," "Bowel cancer," "Pharyngeal cancer," "Oesophageal cancer," "Mouth cancer," "Larynx cancer," and "Breast cancer."

Drinking Motives Questionnaire (Baseline and Follow-up)

Drinking motives will be assessed using the Drinking Motives Questionnaire-Revised [23].

Baseline and Follow-up Survey: Other Measures

Readiness to Change (Baseline and Follow-up)

Readiness to change will be measured using the 12-item Readiness to Change Questionnaire [24].

Current Level of Stress (Baseline, EMA, and Follow-up)

Current level of stress will be measured using the 4-item Perceived Stress Scale [25].

Self-efficacy (Baseline, EMA, and Follow-up)

Self-efficacy will be measured using the 10-item General Self-Efficacy Scale [26].

Relationship Quality (Baseline and Follow-up)

Relationship quality will be measured using the second item of the Relationship Assessment Scale [27], "In general, how satisfied are you with your relationship?" with five possible answer categories ranging from 1 (not satisfied) to 5 (very satisfied).

Current Health Status (Baseline and Follow-up)

Current health status will be measured using the first item of the General Health Questionnaire [28]— "In general, would you say your health is," with five possible answer categories ranging from 1 (poor) to 5 (excellent).

Mental Health (Baseline and Follow-up)

Mental health will be measured using the 5-item Mental Health Inventory [29].

Social Support or Loneliness (Baseline, EMA, and Follow-up)

Social support or loneliness will be measured using the 8-item UCLA Loneliness Scale-8 [30].

Current Use of Technology (Baseline)

Five items from the Media and Technology Usage and Attitudes Scale [31] will be used to capture attitudes toward technology. Participants will be asked how strongly they agree with the following questions: "I feel it is important to be able to access the Internet anytime I want," "I think it is important to keep up with the latest trends in technology," "I get anxious when I don't have my cell phone," "I get anxious when I don't have the internet available to me," and "New technology makes people waste too much time." Participants will also be asked to report how many hours per week on average they spend on their computer (for leisure and for work), on their mobile phone, on a tablet, searching the internet on any device, and using apps on any device.

Client Satisfaction Survey (Follow-up)

The 8-item Client Satisfaction Questionnaire Adapted for Online Interventions [32] will be used.

Participant's Use of Intervention (Follow-up)

The intervention's back-end system will record the number of times participants log in to view the intervention content, and the time they spend on the website each time they log in. It will also record whether participants complete the requested number of follow-up EMAs. These data (number of visits, time spent on website, and number of EMAs completed) will be extracted from the system to assist in assessing the fidelity of the implementation of the intervention.

Data Management

Participants will complete all assessments and access the intervention online; data will be stored on a secure server based in Australia. Access to the data will be password protected and limited to the members of the research team.

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Data Analysis

The reporting and presentation of this trial will be in accordance with the CONSORT (Consolidated Standards of Reporting Trials) guidelines for randomized controlled trials, and data on screening, refusals, and dropout will be coded and reported on per the guidelines [33]. The comparative analysis will be analyzed in accordance with the intention-to-treat principle and the completers-only framework. Participants will have to sign up to the intervention and complete approximately 30% of the EMA surveys to be considered for inclusion in the analysis; missing data will be handled accordingly. The intention-to-treat analyses' multiple imputation methods will be used, while completers-only analyses will be conducted on participants providing scores for all measurements.

All data that are collected will be analyzed using statistical software packages such as STATA (StataCorp) and Mplus (Muthén & Muthén). ANOVAs, contrasting the intervention groups against both control groups, will be run, and logistic and linear regression models will be used to determine potential influencing variables. Longitudinal analyses will be conducted to test group differences in EMA assessments over time.

Besides testing the main effects of the intervention, moderating effects of age, drinking status (whether participants are "risky" drinkers according to the Australian Alcohol Guidelines [34]), educational status, and presence of dependent children in the household will be investigated to establish whether specific subgroups are more likely to benefit from the intervention.

Results

Ethics approval for this project was received on September 11, 2019. The trial was registered on August 14, 2020. Recruitment has commenced, and the expected results will be available in 2022.

Discussion

Expected Outcomes

This paper describes the study protocol of a randomized controlled trial to assess the benefit of a targeted web-based intervention to reduce alcohol consumption among middle-aged women. Intervention with this group is imperative because their alcohol consumption has increased at a time when that of other groups has remained stable or declined [35]. The primary aim of the study is to test whether a web-based intervention can reduce alcohol consumption, increase awareness of alcohol-related harms, increase motivation to reduce alcohol consumption, increase social support and reported health status, and decrease alcohol-related harms, when compared to a no-intervention control group.

Strengths and Limitations

Most web-based interventions aimed at reducing alcohol consumption have been designed for the general adult population, youth, or pregnant women. This study will be, to our knowledge, the first web-based intervention designed by and tested on middle-aged women. Additionally, the use of repeated-measured assessment (EMA) will allow us to gain rich data on participants' alcohol consumption over an 8-week period, which is a strength. Further, the use of 2 control groups (1 with EMA and 1 without) will enable us to assess the true effect of the intervention, as well as determine whether EMAs alone may result in reduced alcohol consumption. As with most alcohol research, the reliance on self-report data can lead to reporting bias; however, it is not anticipated that this bias will differ among the 3 groups. The intervention will only be tested initially on women residing in 1 Australian state, so generalizability may be limited in the first instance.

Acknowledgments

We acknowledge the contribution of the Foundation for Alcohol Research and Education (FARE) and greatly thank the women who participated in our focus groups.

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Availability of Data and Materials

The data generated and analyzed during the study are not publicly available due to privacy issues but are available from the corresponding author on reasonable request.

Authors' Contributions

EK and SK conceived the original concept of the study. All authors contributed to the design of the intervention and trial. MM drafted the manuscript. All authors provided comments on the draft and read and approved the final manuscript.

Conflicts of Interest

None declared.

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Multimedia Appendix 1
Screenshots of intervention.
[PDF File (Adobe PDF File), 98 KB - resprot_v12i1e34842_app1.pdf]

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Abbreviations

CONSORT: Consolidated Standards of Reporting Trials
EMA: ecological momentary assessment

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Protocol

Assessing the Feasibility of a Text-Based Conversational Agent for Asthma Support: Protocol for a Mixed Methods Observational Study

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Abstract

Background: Despite efforts, the UK death rate from asthma is the highest in Europe, and 65% of people with asthma in the United Kingdom do not receive the professional care they are entitled to. Experts have recommended the use of digital innovations to help address the issues of poor outcomes and lack of care access. An automated SMS text messaging–based conversational agent (ie, chatbot) created to provide access to asthma support in a familiar format via a mobile phone has the potential to help people with asthma across demographics and at scale. Such a chatbot could help improve the accuracy of self-assessed risk, improve asthma self-management, increase access to professional care, and ultimately reduce asthma attacks and emergencies.

Objective: The aims of this study are to determine the feasibility and usability of a text-based conversational agent that processes a patient's text responses and short sample voice recordings to calculate an estimate of their risk for an asthma exacerbation and then offers follow-up information for lowering risk and improving asthma control; assess the levels of engagement for different groups of users, particularly those who do not access professional services and those with poor asthma control; and assess the extent to which users of the chatbot perceive it as helpful for improving their understanding and self-management of their condition.

Methods: We will recruit 300 adults through four channels for broad reach: Facebook, YouGov, Asthma + Lung UK social media, and the website Healthily (a health self-management app). Participants will be screened, and those who meet inclusion criteria (adults diagnosed with asthma and who use WhatsApp) will be provided with a link to access the conversational agent through WhatsApp on their mobile phones. Participants will be sent scheduled and randomly timed messages to invite them to engage in dialogue about their asthma risk during the period of study. After a data collection period (28 days), participants will respond to questionnaire items related to the quality of the interaction. A pre- and postquestionnaire will measure asthma control before and after the intervention.

Results: This study was funded in March 2021 and started in January 2022. We developed a prototype conversational agent, which was iteratively improved with feedback from people with asthma, asthma nurses, and specialist doctors. Fortnightly reviews of iterations by the clinical team began in September 2022 and are ongoing. This feasibility study will start recruitment in January 2023. The anticipated completion of the study is July 2023. A future randomized controlled trial will depend on the outcomes of this study and funding.

Conclusions: This feasibility study will inform a follow-up pilot and larger randomized controlled trial to assess the impact of a conversational agent on asthma outcomes, self-management, behavior change, and access to care.

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KEYWORDS

conversational agent; chatbot; health; well-being; artificial intelligence; health education; behavior change; asthma

Introduction

Asthma and Digital Health Interventions

It is estimated that 334 million people worldwide have asthma, which, in some countries, is 15%-20% of the population [1]. Despite effective treatments and extensive efforts, the UK death rate from asthma is the highest in Europe. Moreover, 65% of people with asthma in the United Kingdom do not receive the professional care they are entitled to (including a yearly review, feedback on how to use their inhaler correctly, or an asthma action plan). One of the reasons for this is believed to be poor self-assessment of risk by those with asthma. According to the charity Asthma + Lung UK, the illness is often not taken seriously enough. For example, 1 in 6 people in the United Kingdom do not know or are unsure if the condition can be fatal [2].

Mobile health interventions can help address these gaps in knowledge, self-assessment, and basic care. Mobile technologies can provide just-in-time, anywhere approaches to self-care or mixed mode care. They have been shown to be cost-effective in a number of health domains, and according to a recent systematic review, 87% improved adherence and 53% demosnstrated improved health outcomes [3]. Most often they are used to deliver clinical information, but efficacy has also been shown for providing elements of basic care and health risk feedback as well as supporting behavior change through personalized dialogue with conversational agents (CAs; as reviewed in [4-6]). For example, in the asthma domain specifically, Rhee et al [7] described an automated SMS text messaging system able to interpret conversational English SMS text messages, particularly around asthma symptoms. The system was tested by 15 adolescent-parent dyads, the results of which indicated that the messaging system was well received, easy to use, and convenient. More recently, Kadariya et al [8] tested kBot, a chatbot supporting pediatric asthmatic patients, integrated as part of an Android app. kBot was tested by clinicians and researchers (but not patients). Another study [9] described MAX, a CA focused on helping children learn about asthma and better use of their inhalers. MAX interacted with patients through SMS text messages and did not require a dedicated app. This single-arm feasibility study recruited patients' family members in primary and secondary care (again patients were not included) and showed that using a CA can lead to improved cognitive and behavioral skills. These studies show the promise of this new digital health care approach and ways that it can complement primary and secondary care. What they do not contribute is a better understanding of what drives users to engage with such tools.

The Collaborative Design Process

The larger project surrounding the study described in this protocol aims to develop a text-based automated CA to provide asthma risk assessment and follow-up support for improving asthma self-management. The design process entails development of the conversational scripts (conversational design) for the chatbot and technical development of the CA. The design process has involved patients, asthma nurses, and doctors (including 2 respiratory specialists) from the earliest stages. Stakeholder input was gathered in a variety of ways, including a stakeholder design workshop at the launch of the project, sample dialogue sessions with patients and doctors, a large patient survey (n=1257), and regular reviews of the chatbot and its conversational texts by 3 asthma nurses and 3 doctors.

Regular stakeholder involvement has shaped the content, format, and conversational style of the chatbot. A first critical design decision arising from stakeholder consultations was the choice to provide the chatbot through the popular WhatsApp platform rather than through a new dedicated app. The advisory team based the decision on WhatsApp's lower barrier of entry for users. For example, because WhatsApp is used by a majority of people with asthma (85% in our survey) and does not require computer expertise or high-end hardware, it is more easily accessible for users than downloading and using a new app. Easier access is especially important for helping harder-to-reach populations.

Design and development of the chatbot was informed by a user research survey (N=1257) with adults with asthma. The survey explored prospective user preferences with respect to an asthma chatbot and perceptions around chatbots and technologies for health more broadly. Survey results indicated that 53% of respondents were very or somewhat interested in an asthma chatbot, yet only 7% had used an asthma app. The survey complemented previous surveys commissioned by Asthma + Lung UK, which also provide evidence for user interest in digital technologies for self-care [10].

Design of the conversational dialogues for the chatbot were also informed by qualitative research activities including analysis of a series of asthma conversations held between patients and clinicians. The complete results of the survey and qualitative studies have not yet been published. The conversational design was also informed by existing literature, input from our steering committee, and survey results.

Privacy is of utmost importance in health conversations. While a chatbot using WhatsApp may not be Health Insurance Portability and Accountability Act compliant, conversations are encrypted "end-to-end," meaning that the messages are not readable by WhatsApp. Asthma + Lung UK and many other organizations already provide support, for example, by asthma nurses communicating through this channel.

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Exacerbation Risk Models

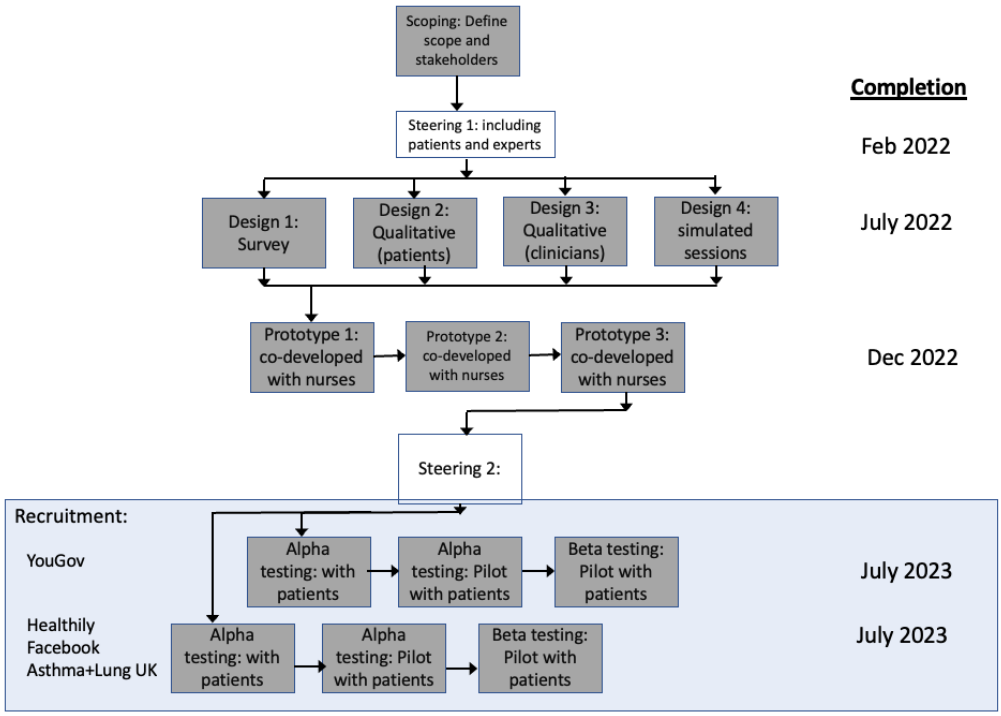
Machine learning experts and epidemiologists within the project have so far developed two risk models. One is based on the Clinical Practice Research Datalink (CPRD) data sets, while the other implements a machine learning model trained on voice recordings of individuals with or without a self-reported asthma diagnosis.

For the first model, we used the unique medical records of 1,277,745 patients and logistic regression. These were divided into three parts to implement temporal validation: 948,934 (74.3%) in the training sample; 244,588 (19.1%) in the testing sample; and 84,223 (6.6%) in the validation sample.

The voice-based risk model is intended to detect the level of asthma control and is based on the sound of their voice. It is based on a similar approach used successfully for COVID-19 diagnosis. The asthma risk model has been initially trained with a database available to researchers upon request and after signing a use agreement [11]. The database contains multilingual voice recordings and other metadata, including age, smoking status, and health information such as COVID-19 or other pulmonary diseases. Voice recording data submitted by participants will help to improve the voice risk model.

The findings from developing these models will be reported when completed and are out of scope for this feasibility protocol. Overall, the design engineering process, described in Figure 1 is similar to the systematic development process for patient decision aids described by Coulter et al [12].

Figure 1. Design engineering process. The highlighted area describes the scope of this feasibility study. The rest shows the iterative and multistakeholder design process so far.



Engagement With Health Care and Technology

Self-determination theory (SDT) has been used as a theoretical framework for assessing efficacy of both health care environments and technologies. For example, it has been shown that a health care environment can improve health outcomes by supporting the basic psychological needs of patients [13]. Likewise, SDT can be used to predict the conditions for motivation to engage with a technology [14] as well as user satisfaction with that technology [14] (D Peters and R Calvo, unpublished data, 2023). As such, the conditions for need-supportive design of technology and health care environments from the SDT literature [15,16] will be incorporated into the design of the chatbot. Accordingly, we will include a set of SDT measures [14] in the postquestionnaire.

Of the different categories of clinical communication identified by Street Jr and Epstein [17], *information exchange* is the most readily used with CAs. In other words, CAs are typically used for collecting data from users by asking questions (eg, gathering a clinical history) and for disseminating information to them (eg, general information about an illness or how it can be managed). Other functions described in the Street Jr and Epstein [17] model, such as helping clients with managing uncertainty or decision-making, are less common because they rely more on open-ended exchanges. As such, exploring the feasibility of supporting such decision-making, including through a mix of closed- and open-ended dialogues, is among the aims of our project.

Person-centered care focuses on "understanding the patient as a unique human being" [18]. As such, our CA will focus on customizing conversation as much as possible, for example, by asking questions to understand the user's unique asthma triggers, lifestyle factors, and risk of exacerbation, and then tailoring advice accordingly. Critically, this information gathering and sharing will be delivered as part of a natural dialogue that can

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adapt to user responses and convey information in gradual conversational chunks, where the user can control the pacing and focus. These features differentiate it from a more traditional questionnaire and results approach.

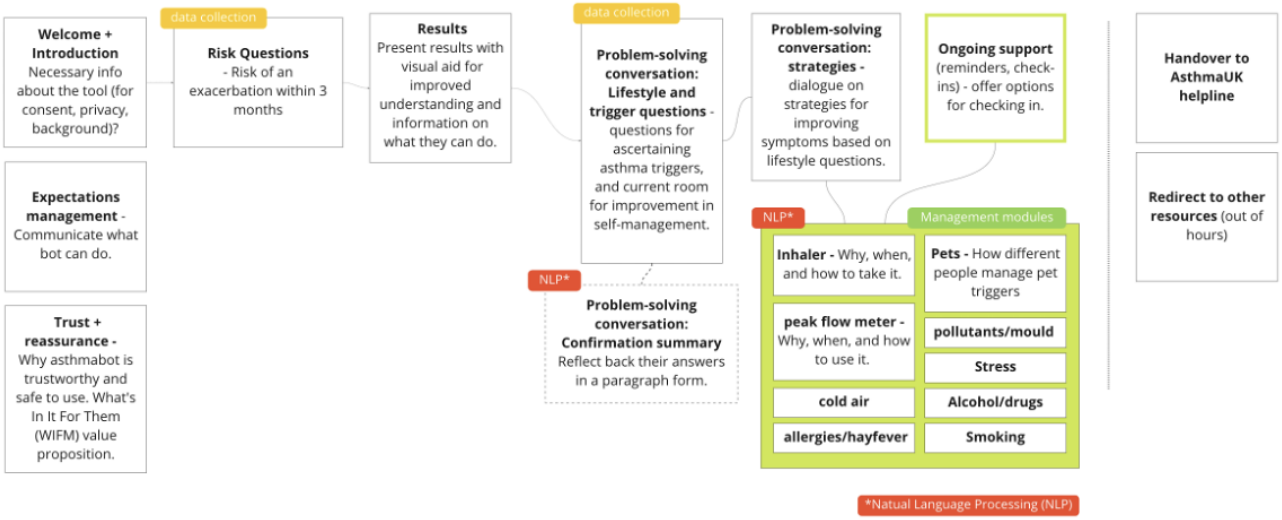
For example, the risk assessment form on the Asthma + Lung UK website presents the user with a series of form questions and then presents a collection of information based on their results. The form is easy to fill out and the results are personalized and carefully presented to make the information as useful as possible. However, the result is still similar to an information sheet. This relies on the user reading all the information and being able to absorb a large amount of mixed information at once. In contrast, we anticipate that the added adaptive agility, familiarity, and progressive disclosure of information that occurs as part of a conversation may provide benefits to understanding, retention, and behavior change, at least for some groups. In this initial feasibility study, we will include a number of self-report measures with respect to understanding and behavior change to begin to test this possibility. However, to compare the two approaches rigorously in a future study, we hope to arrange a controlled experiment comparing the chatbot with an online questionnaire to determine the advantages of each.

Chatbot Content and Features

Following best practices for person-centered care technologies [19], the chatbot system described herein has been designed collaboratively with asthma patients, asthma nurses, and specialist doctors. Based on this approach, the chatbot was designed with a number of dialogue components each representing a topic about which the chatbot can engage in a conversation with the user (Figure 2). In short, the bot assesses a user's risk of having an asthma exacerbation and then provides guidance on how to reduce this risk. The risk reduction guidance process proceeds by first supporting the user to identify their triggers and presenting strategies for managing their specific triggers based on their specific situation (see the example dialogue excerpt in Figure 3). The strategy dialogues will include referrals to Asthma + Lung UK or National Health Service content (eg, inhaler technique videos, smoking cessation clinic sites) with direct links to these resources. We will track click-throughs on these links as an indicator of engagement and impact.

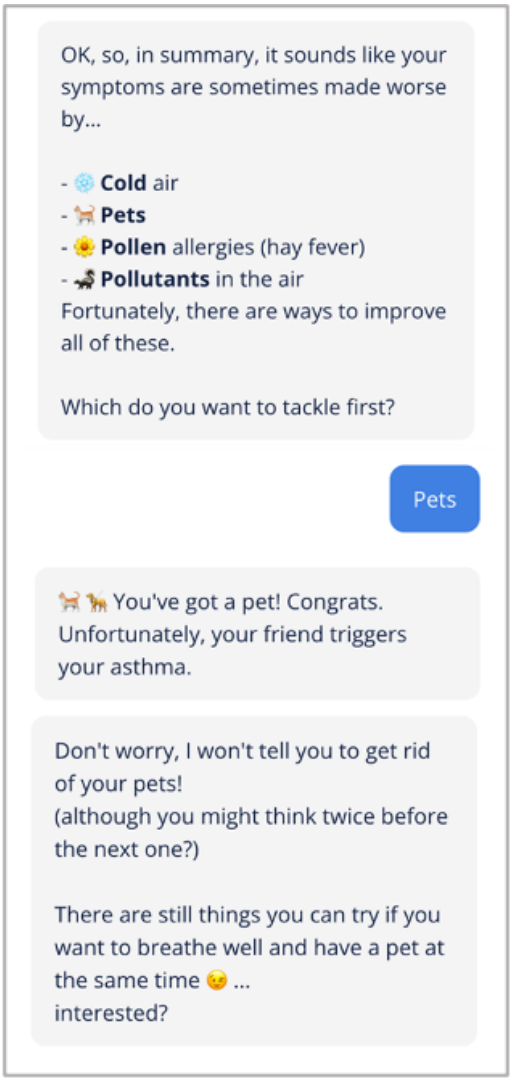
The various dialogues can be triggered either by arriving at them naturally at the end of another dialogue (eg, the risk assessment component leads users to the problem-solving conversation component), selecting them from a list of options (like a menu, users can choose to skip the risk assessment and jump to a conversation about their asthma triggers), or through open-text input (a user can type "what about my dog?" and the system will respond with the dialogue on strategies for managing pet triggers). Free text is processed by a dedicated natural language processing server. For example, the chatbot asks for a description of the perceived triggers and maps it to specific categories. If none are automatically identified, a multiple-choice menu is offered.

Figure 2. Diagram of conversational components. Boxes marked "NLP" include dialogues that may be generated based on a synthesis of user text input or that may be triggered by open-text input.



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Figure 3. Example dialogue excerpt from the problem-solving component.



Methods

Recruitment

Participants for the alpha and beta phases will be patients with an asthma diagnosis, as described above. Participants should be 18 years or older, able to communicate fluently in English, and willing to use WhatsApp on their mobile phones.

Participants will be compensated for their time (which involves trying the chatbot at least once and filling out a pre- and postquestionnaire on day 1 and 28, respectively) with a £10 (approximately US $12) voucher. The research study questionnaires will be provided in Qualtrics, separate from the chatbot so as not to interfere with the experience of the chatbot itself.

A total of 300 individuals will be recruited in three waves. Only approved phone numbers (of people who have consented to the study) will be able to interact with the chatbot.

Recruitment will be done over four channels:

1. YouGov: 120 adults with diagnosed asthma will be recruited through YouGov. We expect roughly 10% of the cohort who participated in the survey or 20% of those who expressed interest in the chatbot.
2. Facebook: 60 participants with self-reported asthma will be recruited through Facebook's advertising engine.
3. Healthily: 60 participants with self-reported asthma will be recruited through Healthily (a medically approved self-care platform). Healthily will advertise the study in the "Asthma Hub" accessed by people with, or interested in, asthma. The timeline will be as the one above. People using Healthily are interested in self-care and pay £29.99 (approximately US $36.70) per year to access it.
4. Asthma + Lung UK social media: 60 participants with self-reported asthma will be recruited through social media channels managed by our partner organization.

The social media channels will direct people to a web page that will screen for inclusion criteria. Those who meet the criteria will be invited to participate, asked for informed consent, and directed to the prequestionnaire and then to the chatbot in WhatsApp on their mobile phones.

Recruitment and chatbot use will be phased to allow for iterative improvements. We will start recruitment through YouGov. The first batch of 20 individuals will use it for 1 week, and their feedback and engagement measures will be used to inform a

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new iteration of improvements. The same will be done with a second batch of 20 people. We refer to these groups as alpha testing in Figure 1. The third and final batch of 260 people will be drawn from the remaining recruitment channels and will use the system for 28 days. We refer to this group as beta testing in Figure 1.

Procedure

We estimate that the average conversation will take less than 15 minutes. Participants will be sent randomly timed messages once a week to invite them to track their asthma risk during the period of the study. After the data collection period (28 days), participants will respond to survey items related to the quality of the interaction. At day 28, they will be sent a final reminder inviting them to complete the exit questionnaire with a link to a Qualtrics form. A follow-up WhatsApp message sent 3 months later will ask users to report if they had an asthma exacerbation within the last 3 months (since they used the bot), and they will have one additional month (which means 4 months from using the bot) to provide this information on exacerbations.

For clarity, if the project were to start on January 1, the first group would finish on January 7. Feedback would take a week to address, and the second group would start on January 14, finishing on January 21. The third batch would start on February 1 and finish on March 1; a follow-up message asking about any asthma exacerbations would be sent on June 1 (allowing them to respond until July 1).

The outcome variables and associated measures are presented in Table 1.

Table 1. Outcome variables and associated measures.

Variable	Measure
Acceptability, usability, and satisfaction of the chatbot, including the risk assessment dialogue and follow-up dialogues on asthma triggers and management strategies for improvement of asthma control	We will combine the following standard technology satisfaction measures: • Task completion (% complete risk assessment process vs drop-out rate) • Net Promoter Score question: "how likely are you to recommend the chatbot to someone else with asthma on a scale from 0 to 10" • User satisfaction questions for each dialogue topic (eg, "Did you measure your risk using the chatbot? How useful did you find this feature?") • Open-ended questions on what worked well and what did not, and how the chatbot could be improved
Motivational quality, engagement, and user experience in relation to basic psychological needs	• Motivation, Engagement, and Thriving in User Experience questionnaire [14]
Alignment between expected and calculated risk, and whether the calculated result changes risk self-assessment	• Self-report questions on risk score expectation vs result and trust in result
Changes to asthma understanding, attitudes, and behaviors following use of the app	• Self-report questions on changes to understanding, attitudes, and behaviors related with asthma self-management
Self-reported level of asthma control and symptoms, including changes over time	• The Asthma Control Questionnaire [20] will be asked at the beginning and end of the study
Patterns of engagement and satisfaction for different types of users, particularly those who do not access professional services and those with poor asthma control	• Analysis of pre- and postquestionnaires and additional self-report questions on use of professional services (eg, "when was the last time you spoke to a GP about asthma")

Ethics Approval

The study protocol will be submitted to the Imperial College London research ethics committee. The user research survey informing the chatbot development was approved by the Imperial College London Ethics committee 21IC7403.

Data Management and Plan

Transcripts (and data extracted from them) will be stored in a secure database. Responses to the pre- and postquestionnaires will be stored on Qualtrics' servers.

Each user's WhatsApp number will be recorded by the system to ensure that the user has provided consent to take part in the research study, track engagement by the same participant over time as well as link engagement patterns to questionnaire data, and improve the user experience (eg, the bot can then store the answers users gave in a previous session and does not start from scratch each time the conversation is returned to). Emails will be stored to send the £10 (approximately US $12) electronic voucher rewards.

Quantitative analysis of dialogue transcripts, use statistics, and questionnaire data will explore patterns and seek findings in relation to the variables and measures in Table 1.

Analysis Plan

We seek to answer the following questions:

- Are there differences among the dialogue topics with regards to engagement? If so, which topic is most engaging? Do participants engage more, less, or equally with the artificial intelligence–enhanced motivational interviewing informed dialogues versus the health education branching

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dialogues? Does engagement with any topic correlate with better health or technology satisfaction outcomes?
- Although the goal of the study is not assessing the efficacy of the intervention, will the group's asthma control improve at the end of the 4 weeks? A future randomized controlled trial will explore the efficacy with appropriate power and rigor, but this study might give initial indications of effect sizes.
- Did the iterative development approach improve outcomes? To test if the alpha and beta predict different effects, and assuming they have nonnormal distributions, we will use the nonparametric Kruskal-Wallis test.

Results

This study was funded in March 2021 and started in January 2022. We plan to publish the results from the user research survey and qualitative studies in the near term and results from the feasibility study in the following term. We have already developed the CA and several risk assessment algorithms. The conversational design and algorithms will be improved and validated with the data collected during phase 1, started in September 2022.

Phase 2 of this feasibility evaluation will start recruitment in January 2023. The anticipated completion of the study is July 2023.

We hope the results will identify the extent to which the chatbot is a viable product that users find valuable, in particular for those who do not access professional services and whose asthma is poorly controlled. We expect that the level of engagement of all users will be positively related to how well the system supports their psychological needs.

Discussion

People living with asthma need support to improve the accuracy of their risk self-assessment and asthma self-management, increase their access to professional care, and ultimately reduce asthma attacks and emergencies. Digital health technologies like apps offer new ways to address these but are often not used. In our survey, only 7% of people with asthma had used an asthma app. On the other hand, most use messaging platforms; in particular, 85% use WhatsApp. This has led us to develop a chatbot intervention to be delivered through WhatsApp that estimates the risk of an asthma exacerbation and provides recommendations on how to manage it better.

Our proposed study will evaluate the feasibility of this WhatsApp chatbot, with a particular focus on improving our understanding of the drivers and obstacles of engagement. While the chatbot has been designed and developed using the best practices available, such understanding will allow for better health chatbots in the future.

With respect to study limitations, since this is only a feasibility study, we are recruiting a relatively low number of participants (N=300). As such, we do not expect to find sex or age differences within the current sampling, and we do not expect to measure statistically significant improvements in asthma control over the 28 days. Furthermore, as we rely on self-report of diagnosed asthma (including having been prescribed a blue reliever inhaler that is only available through prescription), we could get some responses from someone who incorrectly answered the screening questionnaire.

In the future, findings from this study will be validated as part of a randomized controlled trial to determine whether the chatbot can measurably improve health outcomes. All these results will inform the development process of future chatbots in the health domain.

Acknowledgments

This research was made possible by grant EP/W002477/1 from the UK Engineering and Physical Sciences Research Council and Asthma + Lung UK.

Data Availability

Risk models were created with Clinical Practice Research Datalink data and are available from the UK's Medicines and Healthcare products Regulatory Agency, as described at [21]. Pending ethics approval and to support scientific transparency, dialogue data will be made available upon request to the corresponding author.

Conflicts of Interest

EW received honorarium from Chiesi Limited for lectures, received conference sponsorship from Chiesi Limited and has a joint working agreement for a project between Imperial College Healthcare NHS Trust and AstraZeneca UK. JQ has received grants from MRC, Health Data Research UK, GSK, Bayer, Boehringer Ingelheim, Asthma + Lung, Chiesi, and AstraZeneca, and personal fees for advisory board participation or speaking fees from GlaxoSmithKline, Boehringer Ingelheim, AstraZeneca, Chiesi, Teva, Insmed, and Bayer.

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Abbreviations

CA: conversational agent
CPRD: Clinical Practice Research Datalink
SDT: self-determination theory

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Protocol

Mobile Mental Health in Women's Community-Based Organizations: Protocol for a Pilot Randomized Controlled Trial

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Abstract

Background: Of every 10 women in rural India, 1 suffers from a common mental disorder such as depression, and untreated depression is associated with significant morbidity and mortality. Several factors lead to a large treatment gap, specifically for women in rural India, including stigma, lack of provider mental health workforce, and travel times. There is an urgent need to improve the rates of detection and treatment of depression among women in rural India without overburdening the scarce mental health resources.

Objective: We propose to develop, test, and deploy a mental health app, MITHRA (Multiuser Interactive Health Response Application), for depression screening and brief intervention, designed for use in women's self-help groups (SHGs) in rural India.

Methods: We will use focus groups with SHG members and community health workers to guide the initial development of the app, followed by iterative modification based on input from a participatory design group consisting of proposed end users of the app (SHG members). The final version of the app will then be deployed for testing in a pilot cluster randomized trial, with 3 SHGs randomized to receive the app and 3 to receive enhanced care as usual.

Results: This study was funded in June 2021. As of September 2022, we have completed both focus groups, 1 participatory design group, and app development.

Conclusions: Delivering app-based depression screening and treatment in community settings such as SHGs can address stigma and transportation-related barriers to access to depression care and overcome cultural and contextual barriers to mobile health use. It can also address the mental health workforce shortage. If we find that the MITHRA approach is feasible, we will test the implementation and effectiveness of MITHRA in multiple SHGs across India in a larger randomized controlled trial. This approach of leveraging community-based organizations to improve the reach of depression screening and treatment is applicable in rural and underserved areas across the globe.

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KEYWORDS

mobile mental health; women; community-based; depression; rural; stepped care

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Introduction

Background

Treatment rates for major depression range from 23% in high-income countries to 3% in low- and lower-middle–income countries [1]. The treatment gap is higher in rural populations, especially among women [2], despite the fact that 1 in 10 women in rural India has a common mental disorder (CMD) such as depression [3]. Untreated depression is associated with significant morbidity and mortality [4,5]. Risk factors that are more prevalent in rural areas, such as low levels of education, financial difficulties, intimate partner violence, and alcohol use in the husband [6], directly influence the outcomes of CMD and help seeking, creating barriers to care [7]. Factors contributing to the treatment gap include the dearth of psychiatrists and other mental health professionals [8,9], poor transportation infrastructure, and stigma, leading to patients not accessing care [10]. Integrating a mental health program into rural primary health centers can improve access but cannot fully address concerns about high rates of medication nonadherence and treatment dropouts [11]. In previous studies [12] and in our recent qualitative analysis [13], women cite travel times and inability to take time off from work as a significant barrier to seeking mental health care in the primary health center (PHC), and as a reason for treatment discontinuation. This barrier is relevant throughout the country, as although India's District Mental Health Program aims to provide community-based accessible mental health care, 40% of patients still travel more than 10 km to access mental health services [14].

Partnering with community-based organizations (CBOs) is one way to address barriers to accessing mental health treatments [15]. CBOs for women (called "mahila mandals" or "sthree shakthi"–women power or self-help groups [SHG]) are instrumental in increasing women's empowerment and participation in microfinancing systems in rural India. Each group consists of about 15 to 20 women members from a defined geographic area who meet regularly (weekly, biweekly, or monthly) [16]. SHG activities include pooling of resources and extending microcredit, discussion of social issues, and supporting skill development and education [17]. Rates of positive depression screens among SHG attendees range from 10% to 13% [18].

Even mild depression is associated with decreased work productivity and presenteeism (working while sick) [19], and costs associated with presenteeism tend to be 5-10 times higher than those associated with absenteeism across different countries [20]. Identifying and treating mild depressive symptoms adequately can prevent major depression [21]. There is therefore an urgent need and opportunity to identify and treat mild-to-moderate depression without increasing burden on the strained health care system. Self-administered treatments are effective in reducing mild-to-moderate depressive symptoms [22]. Self-administered treatments include bibliotherapy and online or app-based online psychotherapy modules, and when combined with regular monitoring of symptoms, can be an effective treatment for mild-to-moderate depression. There is a strong evidence base for the stepped care approach to mental health treatment in which treatment begins with low-intensity interventions, which are then stepped up if symptoms persist [23] or if the patient declines the first-line treatment. Patients with high-level symptomatology are triaged to more intense interventions at the outset. This approach is especially useful in leveraging the available workforce in resource-constrained settings [24,25]. App-based depression interventions can improve access to treatment for CMD due to ease of access and availability even in resource-poor settings [26,27]. India has the second largest wireless communication subscriber base in the world [28], and most people have access to a mobile phone and network coverage [29]. However, there are differences in usage patterns that prompted us to develop a multiuser app on a tablet rather than an app designed to be used on a personal cell phone. For example, in rural India, while 87% of people own a cell phone, only 14% of them use text messaging [26], perhaps because of the high rate of illiteracy [30]. In addition, although women in rural India do report owning a mobile phone, this is often a shared family phone that is with the husband for most of the day [13].

We propose, in this funded grant, to develop, with end user feedback, a multiuser mobile app (MITHRA [Multiuser Interactive Health Response Application]="friend" in Kannada, the regional language) for use in CBOs in rural India, to support the identification, initial treatment, and referral of women with depression. Our app will account for barriers such as illiteracy and lack of access to a personal mobile device. Our participatory approach will ensure that the app is responsive to local perceived needs by obtaining end user or consumer feedback at every stage of development [13]. The app will deliver education about depression and activity scheduling, based on the Healthy Activity Program (HAP), which is an evidence-based intervention delivered from 6 to 9 sessions; is acceptable, efficacious, and cost-effective in the treatment of depression; and has been tested in rural India [31]. Moreover, it is effective in the treatment of moderate-to-severe depression [32] and can benefit mildly depressed individuals who may not require the involvement of a mental health professional. Mild-to-moderate symptoms will be addressed by delivering the HAP via multimedia modules. This ensures that most women with mild-to-moderate depression receive initial treatment without having to overcome transportation barriers. Those with severe or nonresponsive symptoms will be directed to the PHC for assessment and treatment.

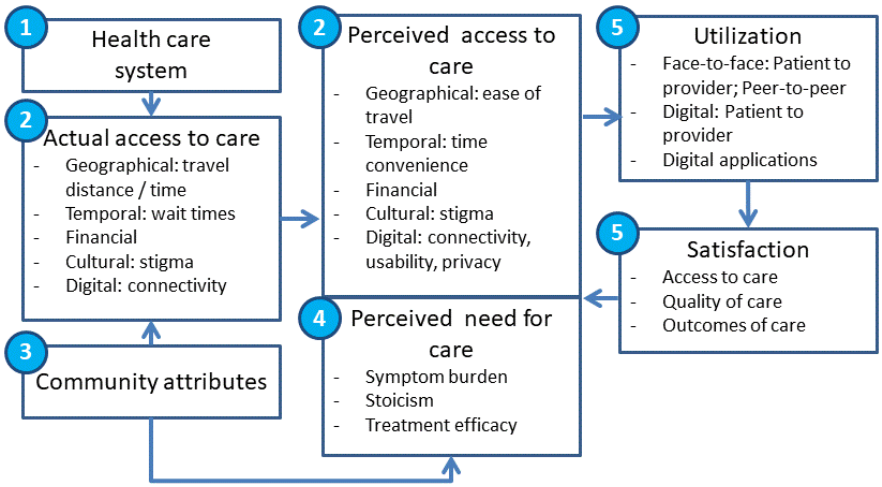
Conceptual Model

Our conceptual model is based on the access to care model by Fortney et al [33] (Figure 1). MITHRA targets each of the barriers to access to care (actual and perceived) commonly identified by patients and integrates them into both the health care system and the community. By using non–encounter-based screening, tracking, and low-intensity interventions, MITHRA improves access among women for whom stigma and travel times are a barrier. By providing education about depression, it addresses the perceived need for care among women who may not be proactive in seeking mental health care and supports adherence among those who initiate care. By integrating into existing social systems such as SHGs and using existing health care systems such as community health workers (CHWs) and

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the PHC, MITHRA will efficiently increase the scalability and reach of mental health treatments.

Figure 1. MITHRA conceptual model. 1. MITHRA will refer to Primary Health Center women with severe symptoms or nonresponse. 2. MITHRA provides depression screening and tracking in the community. 3. MITHRA leverages scheduled gatherings of women from the same community. 4. Education delivered through MITHRA will influence perceived need for care 5. MITHRA will potentially improve utilization rates and satisfaction with care.



Methods

Overview

This study will be conducted in two phases—user-centered app development in Phase 1 and a pilot cluster randomized controlled trial (RCT) in Phase 2. The study site will be within the Anekal taluk, including 10 villages with functional SHGs with a total population of 9724 [34]. Focus groups and individual interviews, usability testing, and deployment of the tablet-based apps for the pilot RCT will all be conducted in these SHGs.

Study Population

In Phase 1, during app development, we will recruit women SHG participants aged 18 to 59 years and residents of the village (ie, not a guest attendee at the SHG) for focus groups. We will also recruit community health workers and administrators of the SHGs who have their current role for at least 6 months. Those who are unable to participate in the informed consent discussion will be excluded. In Phase 2, for the pilot RCT, we will recruit women aged 18 to 59 years, who are residents of the village (ie, not a guest attendee) and are planning to attend SHG meetings regularly. Women who have been diagnosed with a severe mental illness such as bipolar disorder or schizophrenia, those who have had a suicide attempt or severe alcohol or substance use in the past 6 months, and those who are unable to participate in the informed consent discussion will be excluded from the pilot RCT.

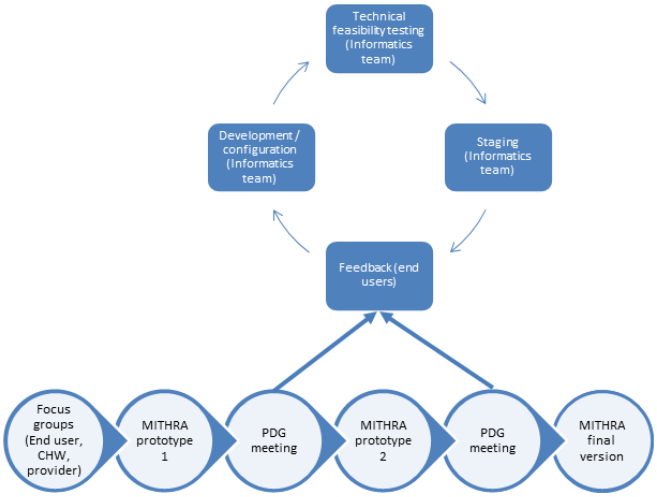
Focus Groups for App Development

App development will follow a user-centered iterative design approach (Figure 2). The process of administering the assessment questions and HAP modules will be based on the inputs provided by the SHG participants through the focus groups. One focus group will include community health workers (CHWs) and SHG administrators, and 1 will include SHG participants. We will develop interview guides [35,36] based on the acceptability on the interventions framework [37]. We will include questions on specifications such as simplified touchscreen, length of modules to be viewed, and women's preferences regarding viewing HAP modules at home or at the SHG. We will record and transcribe focus group content and analyze it using Dedoose (SocioCultural Research Consultants), a qualitative analysis software. Using a thematic content analysis approach, we will identify common themes to help guide app development.

Next, we will enroll 5 to 6 members (including CHWs and SHG participants, representing the end users of the proposed app) from the focus groups into a participatory design group (PDG). During Phase 1, the team will build a prototype for the app, which includes video content based on the HAP modules, iteratively modifying the content and interface based on discussions with the PDG. We will complete the standard life cycle of software development, which includes development and configuration. We will then deploy the working prototype on the staging environment and complete further configurative iterations based on technical feasibility testing conducted with the PDG. Once iterative modifications are complete, the final version of the app will be deployed on the production environment for the RCT.

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Figure 2. Stages of development of the MITHRA (Multiuser Interactive Health Response Application) app. CHW = Community Health Worker; PDG = Participatory Design Group (CHWs and women who attend CBO meetings).



Data Analysis

We will record, transcribe, and translate the focus group content and analyze it using Dedoose. Using thematic content analysis, we will identify common themes to help guide app development. For the PDGs, we will collect end-user feedback on app prototypes until saturation of issues raised in PDG meetings is reached.

Description of MITHRA

The MITHRA app will be available on tablets placed in SHGs in an assigned private place. Each SHG will be provided with 2-3 tablets. Women can log in to MITHRA with a fingerprint-secure, single-user sign-on to complete the depression screening using the Patient Health Questionnaire-9 (PHQ-9). On completion of the PHQ-9, each woman will receive a prompt based on her total score. Those who score <5 will receive a prompt to watch general information on depression; those who score 5 or higher will watch select HAP modules, which will be short interactive multimedia-based modules, each 10 to 15 minutes long (or of other duration, based on findings from the focus group). They will also receive information on how to seek mental health care. Users can unlock virtual reward points or badges upon completion of the required questionnaires, modules, and activities. Any woman who scores anything other than 0 on question 9 of the PHQ-9 (suicidal ideation item) will be asked to call the CHW associated with that SHG. For these women, the app will also trigger an alert to the CHW, who will immediately contact the SHG administrator on site and call the patient to complete a risk assessment based on the suicidal ideation protocol [38].

The app will include a dashboard for the study team to access participant summary data and provide necessary alerts. Offline capabilities will ensure seamless use in areas with low to no internet connectivity. Data synchronization will occur at times of network connectivity, and the study team will ensure periodic synchronization of data between the study devices and servers hosted at the study team headquarters in India to ensure data security and to align with the institutional review board guidelines.

Pilot RCT

Once app development is complete, we will randomize 3 SHGs to use MITHRA and 3 SHGs to enhanced usual care (EUC). Randomization will be clustered to account for distance from the PHC. In SHGs randomized to the intervention (MITHRA), a CHW will encourage women to use the MITHRA app. At each app use, women will complete the PHQ-9 screening and modules based on their individual depression score. Women typically attend SHG meetings 2-3 times a month, and the use of MITHRA at every attendance will be encouraged.

In the EUC SHGs, CHWs will offer monthly 45-minute group education regarding the symptoms of depression. The CHWs will in turn be trained in depression, screening and common treatments, resources, and referrals by study investigators to help support group education. In both MITHRA and EUC SHGs, CHWs will conduct community outreach to encourage women to attend meetings, as depression can lead to amotivation, and women with depression may be less likely to attend SHG meetings. CHWs will maintain rosters of SHG attendees at MITHRA SHGs and EUC SHGs. In monthly review sessions with the study investigators, the CHWs will review questionnaire completion and scores and directly contact the woman (by phone or home visit or at a SHG meeting) if there is a need to step up care beyond that advised by the app. We will aim to recruit approximately 60 women across 3 SHGs. The total number of participants will depend on the number of members in each enrolled SHG, which varies. We estimate an average of 10 in each SHG, or approximately 30 each in the intervention and control arms.

At recruitment, 3 months, and 6 months, a research assistant blinded to randomization status will administer outcome assessments in person or over the telephone. To avoid unblinding of SHG randomization status (eg, the presence of tablets in the SHGs), research assessments will be carried out by phone or in the PHC.

Outcome Measures

The outcomes measures can be listed as follows: (1) app usage rates—we will obtain data on women's rates of use of the MITHRA app; (2) depression measured by Quick Inventory of

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Depressive Symptoms [39] at baseline, 3 months, and 6 months. Quick Inventory of Depressive Symptoms is a measure of depression symptoms severity that is sensitive to change; (3) behavioral activation—Behavioural Activation Depression Scale [40]. We will administer the Behavioural Activation Depression Scale to all women to calculate adherence to behavioral activation recommendations (for women enrolled in the intervention arm) and to measure degree of behavioral activation (for women enrolled in the EUC arm); (4) mental health services use—we will obtain information on rates of utilization of mental health services, including number of contacts with mental health providers and details of medications taken; and (5) System Usability Scale (SUS) [41], which is a widely used validated 10-item Likert scale that can be used to determine the usability of a wide variety of products and services, including hardware, software, mobile devices, websites, and applications, and it will be measured at the end of app usage from each woman enrolled in the intervention arm. Scores are "normalized" to produce a percentile ranking. Based on research, a SUS score of above 68 would be considered above average, and anything below 68 is below average.

Data Analysis

We will descriptively summarize rates of initiation and continued use of the app in MITHRA sites. Usage rate calculations will be enabled by the single-user sign-on. We will also collect data on the usability of the app by administering the SUS to users of the app at 3 months and 6 months. For our primary outcome measures, we will perform intent-to-treat analyses. Although we expect that randomization will be successful and the 2 groups will be similar, we will compare baseline variables for differences, and in our analyses, control for variables were found to be significantly different between the 2 groups. We will use these preliminary data to examine the feasibility of randomization and measurement, as well as a methodological approach for a future larger trial, and initial signals regarding efficacy of the intervention.

Ethical Considerations

This study has been reviewed and approved by the University of Washington Institutional Review Board and the Institutional Ethics Committee at St. John's Medical College (approval number STUDY 00010415). All participants will be given adequate opportunity to ask for clarifications on study participation and procedures and will be recruited only after they provide informed consent; for those who cannot read, we will explain the study details and obtain consent by thumbprint and by recording verbal consent. A unique identifying code for each participant's data will maintain confidentiality. Any forms with identifying information, such as the informed consent forms and participant list with assigned identification numbers, will be kept separate from study data in locked cabinets or on password-protected computers. Encryption will be used wherever data are transferred. At the end of the data retention period, all patient identifiers will be deleted in compliance with Health Insurance Portability and Accountability Act regulations. The app will be available on a tablet in the CBO, in a private location with headsets to maintain privacy. Each participant will be given a unique secure single-user sign on (which can be signed in using fingerprint for illiterate participants), thereby ensuring privacy of their information on this multiple-user app. All participants will receive Rs 200 (approximately $3) for participation. This amount represents a payment for the time and potential stress associated with the study procedures, which is comparable with other similar studies at this location and commensurate with the average income in the region, ensuring that consent is not unduly influenced by financial consideration.

Results

This study was funded in June 2021. As of September 2022, we have completed both focus groups, 1 PDG, and the development of app wire frames.

Discussion

Principal Findings

The use of app-based screening in an SHG on a tablet that can be used by multiple women is in line with the description of mobile instruments as a "collectivist machine" rather than an individuality-enhancing device in rural areas of India [42]. Leveraging SHG meetings helps address the stigma and transportation-related barriers to access to depression care and overcomes the cultural and contextual barriers to mobile health use. MITHRA will support population-level symptom surveillance and tracking, monitoring adherence to recommendations, health education, and communication between patient and health worker. In addition, it can help promote awareness in the community about mental illness and help reduce stigma [43]. App-based delivery of brief psychotherapeutic interventions can address the mental health workforce shortage. In this study, we propose to iteratively develop an app to screen for depression and deliver brief psychological interventions in women's CBO. We have successfully completed focus groups with women and administrators to inform the development of the app.

Limitations

It is possible that we will encounter difficulties in developing an app that is audio enabled. However, the informatics team has substantial experience developing similar health care apps and will be able to troubleshoot accordingly. Participating women may not be enthusiastic about the use of the app. As we include input from potential users from the initial stages of app development, we hope to incorporate in our design specific features that women identify as desirable. EUC CBOs will only receive depression education from CHWs; however, this is still an enhancement compared to usual care, which is that these CBOs do not typically have depression-screening or health-education sessions.

Impact and Future Directions

If we find that the MITHRA approach is feasible, we plan to further test the implementation and effectiveness of MITHRA in multiple CBOs across India. In India, women's mental health is especially relevant to the health of the entire family as they play a multidimensional role in the family. The benefits of adequately treating depression in women will therefore accrue

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in their family as well. In the future, similar apps can be deployed in men's CBOs. This approach of leveraging CBOs to improve the reach of depression screening and treatment is also applicable in rural and underserved areas across the globe. For example, in the United States, many low-income women receive support from CBOs such as Women's Infant and Children [44] and other nutritional programs and peer-support groups, and these might be appropriate platforms for app-based screening and stepped care treatment.

The next steps could include examining the feasibility of making telepsychiatry available for women with severe depressive symptoms or those who do not respond to the first-line app-based treatment. Since the onset of the COVID-19 pandemic, telemedicine is being used in many settings and is acceptable to patients. There is emerging evidence for the feasibility of telepsychiatric consultations to district hospitals from academic centers [45], and this approach could be extended to examine the feasibility and effectiveness of telepsychiatry to SHGs. If the delivery of app-based screening and brief psychological interventions is found to be feasible in this study, we will test the effectiveness of this approach in a large RCT.

Acknowledgments

We would like to thank all focus group participants and CBO (community-based organization) members and administrators for their support. This project is funded by the National Institutes of Health (NIH 1R21MH124073).

Data Availability

The data sets generated during and/or analyzed during the current study will be available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

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Abbreviations

CBO: community-based organization
CHW: community health worker
CMD: common mental disorder
EUC: enhanced usual care
HAP: Healthy Activity Program
MITHRA: Multiuser Interactive Health Response Application
PDG: participatory design group
PHC: primary health center
PHQ: Patient Health Questionnaire
RCT: randomized controlled trial
SHG: self-help group
SUS: System Usability Scale

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Protocol

Tough Talks COVID-19 Digital Health Intervention for Vaccine Hesitancy Among Black Young Adults: Protocol for a Hybrid Type 1 Effectiveness Implementation Randomized Controlled Trial

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Abstract

Background: Interventions for increasing the uptake of COVID-19 vaccination among Black young adults are central to ending the pandemic. Black young adults experience harms from structural forces, such as racism and stigma, that reduce receptivity to traditional public health messaging due to skepticism and distrust. As such, Black young adults continue to represent a priority population on which to focus efforts for promoting COVID-19 vaccine uptake.

Objective: In aims 1 and 2, the Tough Talks digital health intervention for HIV disclosure will be adapted to address COVID-19 vaccine hesitancy and tailored to the experiences of Black young adults in the southern United States (Tough Talks for COVID-19). In aim 3, the newly adapted Tough Talks for COVID-19 digital health intervention will be tested across the following three southern states: Alabama, Georgia, and North Carolina.

Methods: Our innovative digital health intervention study will include qualitative and quantitative assessments. A unique combination of methodological techniques, including web-based surveys, choose-your-own-adventures, digital storytelling, user acceptability testing, and community-based participatory approaches, will culminate in a 2-arm hybrid type 1 effectiveness implementation randomized controlled trial, wherein participants will be randomized to the Tough Talks for COVID-19 intervention arm or a standard-of-care control condition (N=360). Logistic regression will be used to determine the effect of the treatment arm on the probability of vaccination uptake (primary COVID-19 vaccine series or recommended boosters). Concurrently, the inner and outer contexts of implementation will be ascertained and catalogued to inform future scale-up. Florida State University's institutional review board approved the study (STUDY00003617).

Results: Our study was funded at the end of April 2021. Aim 1 data collection concluded in early 2022. The entire study is expected to conclude in January 2025.

Conclusions: If effective, our digital health intervention will be poised for broad, rapid dissemination to reduce COVID-19 mortality among unvaccinated Black young adults in the southern United States. Our findings will have the potential to inform

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efforts that seek to address medical mistrust through participatory approaches. The lessons learned from the conduct of our study could be instrumental in improving health care engagement among Black young adults for several critical areas that disproportionately harm this community, such as tobacco control and diabetes prevention.

Trial Registration: ClinicalTrials.gov NCT05490329; https://clinicaltrials.gov/ct2/show/NCT05490329

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KEYWORDS

COVID-19; COVID; vaccine hesitancy framework; African American; young adults; implementation science; digital health; mHealth; behavioral intervention; vaccination; intervention; mortality; USA

Introduction

Background

Interventions for increasing the uptake of COVID-19 vaccination among young adults are central to ending the pandemic [1]. Given their high rate of asymptomatic infection [2], young adults represent a priority population on which to focus efforts for promoting COVID-19 vaccine uptake [1]. The acceptance of COVID-19 vaccination is lower among African American or Black (henceforth referred to as *Black*) young adults aged 18 to 29 years. In 2020, a population-based study indicated that only 42% of Black Americans reported being likely to accept vaccination against COVID-19, whereas 63% of White and Hispanic or Latinx adults were likely to accept COVID-19 vaccination [3]. In a nationally representative survey on the same topic, lower vaccine acceptance was associated with younger age [4]. Although the vaccination gap between the Black and White adult populations has narrowed, the disparity between Black and White young adults aged 18 to 29 years persists, with Black young adults being at about a 14% disadvantage when compared to their White peers [5]. COVID-19 has exacerbated the disparities experienced by Black young adults, particularly those residing in the southern United States, where health care access continues to be a barrier, and the vaccination gap between White and Black southern US adults is about 7.2% [5,6]. From May to August 2020, Black individuals accounted for 18.7% of COVID-19 deaths despite making up just 12.5% of the US population [7]. Stigma, discrimination, and distress are highest among those with intersectional identities (eg, Black, young, rural, etc) [8], reinforcing health inequities [9,10]. Recent studies found that respondents who reported experiences of racial discrimination had increased odds of higher vaccine hesitancy when compared to those who did not report such experiences and that vaccine hesitancy was intertwined with institutional distrust [11,12].

Over the past year, there have been notable changes in the epidemiology, public health recommendations, and pandemic-related mitigation strategies surrounding COVID-19. The rates of COVID-19 vaccination are currently at 61.8% in Alabama, 64.3% in Georgia, and 82.2% in North Carolina, and these rates continue to be lower among Black populations in these southern states [13]; yet, only 34.1%, 34.9%, and 25.1% of Alabama, Georgia, and North Carolina residents, respectively, have accepted a booster. Those who remain unvaccinated may be highly resistant toward accepting vaccination or overwhelmingly apathetic due to the numerous, fast-paced changes in COVID-19 knowledge and messaging that occurred during the course of the past year.

Digital health interventions (DHIs) can reach young adults regardless of geographic location and stigmatizing experiences with health care institutions [14]. DHIs can enable young adults to make informed decisions about their health, using a familiar modality that young adults value and trust. DHIs are well suited for young adults, given the ubiquity of technology use. A recent report found that 96% of 18- to 29-year-old adults in the United States owned a smartphone [15]. As such, smartphones are suitable for delivering content that is tailored to each user's unique needs. Further, DHIs have been shown to increase knowledge, self-efficacy, and motivation for change while also ameliorating distrust, fear, and stigma across a variety of health conditions [16-21]. Young adults already rely on digital technologies to build their social networks, receive social support, and obtain health information [18,22,23]. Access to credible web-based resources is critical, given that the majority of young adults access COVID-19 information from web-based news and social media sites [24].

Considering these factors, we developed this protocol to adapt a previously developed DHI in the domain of HIV status disclosure (Tough Talks) to a COVID-19 vaccine decision-making context (Tough Talks for COVID-19 [TT-C]) [25]. The TT-C intervention aims to enable Black young adults in the southern United States to make informed, autonomous decisions about COVID-19 vaccine receipt via nonstigmatizing and tailored messaging. Through engaging activities and narrative communication, TT-C will address the structural contexts (eg, issues of confidence, distrust in medicine, and stigma), misinformation (eg, vaccination knowledge), environmental barriers (eg, access to care and health insurance), and potential consequences (eg, outcomes related to accepting or refusing vaccination) [26] related to vaccine decisions. Using community-based participatory research (CBPR) methods to cocreate TT-C with Black young adults will promote personal agency, bolster resilience in the face of the pandemic, strengthen intervention quality, and increase intervention relevance and engagement [27-29].

The CBPR Approach

CBPR is a collaborative approach to science that involves authentic partnerships between researchers and the community being supported [30]. The goals of CBPR are to collaboratively create solutions, such as an intervention (as is the case in our study), that are meaningful and helpful to the community and

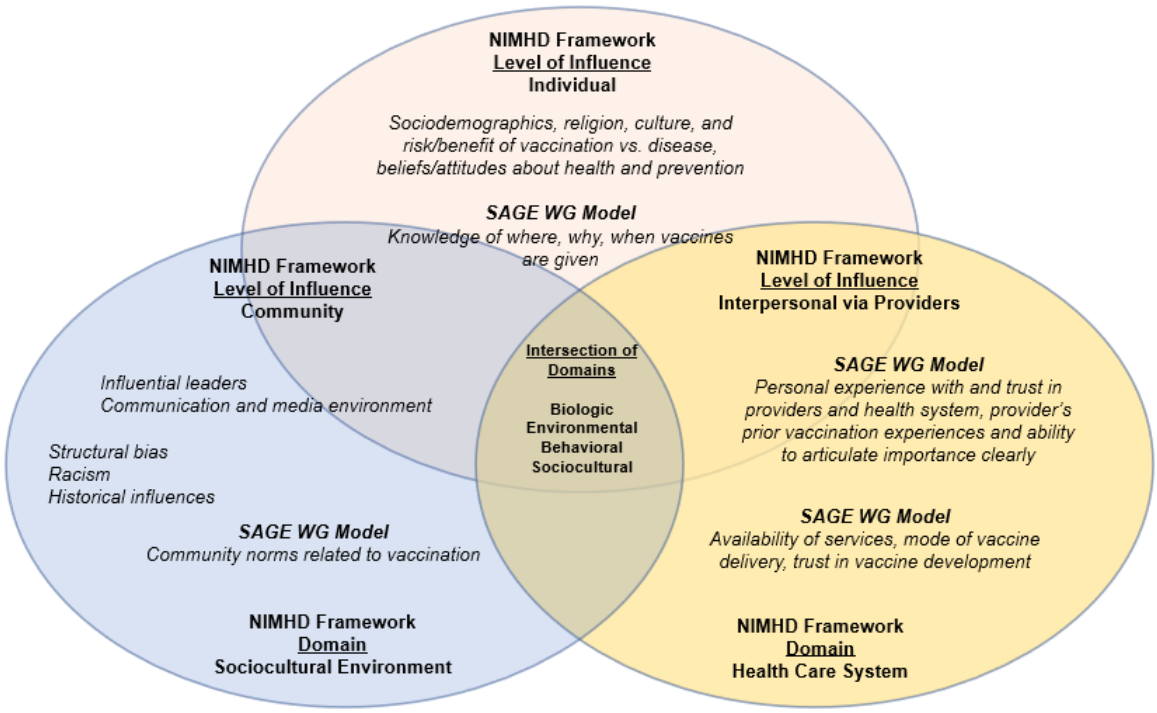
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to partner with the community to address potential concerns or barriers. CBPR acknowledges that the community has expertise and that active participation and community feedback are essential to project success [30,31]. Considering the persistent mistreatment of Black communities within health care institutions that has resulted in skepticism and distrust toward new health interventions and research studies, the study team felt that it was imperative to adopt CBPR within the TT-C DHI research project.

Framework

Vaccine hesitancy is influenced by factors at the individual, community, provider, health care system, and societal levels [32]. As espoused by the World Health Organization Strategic Advisory Group of Experts, individual and social group influences, contextual influences, and vaccine-specific issues must be identified and targeted through multicomponent and tailored interventions to increase vaccine uptake within key populations [33]. We will therefore utilize the National Institutes of Health/National Institute of Minority Health Disparities research framework to assess multilevel factors at the individual (knowledge, attitudes, and normative beliefs), interpersonal (peer and family influences), institutional (provider communication and health care system), and structural levels (stigma and discrimination) that influence COVID-19 vaccine hesitancy and refusal. We have created a model (informed by the Strategic Advisory Group of Experts Working Group; Figure 1) that depicts the determinants that are relevant to understanding and addressing vaccine hesitancy among Black young adults [34]. This model will be used to guide the development of our intervention.

Figure 1. Vaccine hesitancy model for US-based minoritized populations. The model is informed by the NIMHD research framework and the World Health Organization Strategic Advisory Group of Experts. NIMHD: National Institute of Minority Health Disparities. SAGE WG: Strategic Advisory Group of Experts Working Group.



Objectives

Our protocol includes 3 objectives (ie, specific aims). For aim 1, we conducted multimethod formative research to elicit the behavioral, cognitive, and environmental determinants influencing COVID-19 vaccine hesitancy among Black young adults. For aim 2, in collaboration with expert advisors, community partners, and Black young adult end users, we will leverage the ADAPT-ITT (assessment, decision, administration, production, topical experts, integration, training, and testing) framework [35] to develop and refine TT-C. For aim 3, we will conduct a hybrid type 1 effectiveness implementation randomized controlled trial (RCT) with 360 Black young adults from Alabama, Georgia, and North Carolina to assess the effectiveness of TT-C in increasing COVID-19 vaccine uptake while concurrently evaluating the implementation contexts that affect intervention delivery.

Timeline

Ours is a 4-year (48-month) study, and regulatory activities will be conducted between months 1 and 6 of the study. The development team will work to adapt the Tough Talks platform to create TT-C during months 6 to 18, which will include the internal testing of the platform's features and usability (aims 1 and 2). Following feedback from the full investigative team, our expert advisors, the community, and youth advisory members, the intervention will be tested for feasibility and acceptability with youth through a technical pilot during months 18 to 24 (aim 2). We plan to launch the RCT by month 24, which will conclude at month 48 (ie, at the end of 4 years; aim 3).

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Methods

Ethics Approval

All study materials and procedures were reviewed and approved by the University of North Carolina, Chapel Hill Institutional Review Board (approval number: 21-1746) and by the Florida State University Institutional Review Board (STUDY00003617). Informed consent will be collected digitally from all study participants prior to data collection and randomization. Study data will be deidentified and stored on a secure server. Study participants will receive an incentive of a US $50 gift card payment for each data collection.

Young Adult Advisory Board

Young adults from 3 states will be recruited for the TT-C young adult advisory board (YAB) through our community and academic partners, and we will pay special attention to ensuring diversity in age, gender, and vaccine-related perceptions. The TT-C YAB will be formed in the first quarter of the study and will meet monthly for the entire project period. The TT-C YAB will provide guidance on (1) young adults' knowledge, beliefs, and attitudes toward COVID-19 vaccination; (2) sources of vaccine misinformation and disinformation, support, and resource needs; and (3) strategies for communicating with Black young adults to address vaccine hesitancy. The health inequities laid bare by the pandemic and the calls for social justice for racial minorities will be the center of this approach. We will ensure that TT-C YAB members are supported to share their lived experiences and advise the investigator team on addressing racism and discrimination in TT-C.

Community Advisory Group

We include respected experts in health disparities, social justice and equity, CBPR, community activism and advocacy, and stigma. Our advisory board includes scientists of color, leadership from historically Black colleges and universities, and community advocates. Members will provide guidance on all aspects of the study. The full board will meet biannually; individual board members will meet with the study team as needed to provide feedback.

Recruitment

For all aims, our recruitment strategy includes (1) free and paid advertising and posting on social media sites; (2) information distribution through national organizations working with Black young adults, including historically Black colleges and universities; and (3) information distribution through our community partners and other network collaborations. We will use methods that were successfully deployed in our prior studies to recruit participants through social media sites that are frequented by Black young adults and rely on our network of community and academic partners for additional dissemination [36,37]. The recruitment procedures may vary slightly depending on the community organization and study phase, but all recruitment materials will use consistent messaging that frames the study as a mechanism for learning more about COVID-19 vaccines.

Eligibility Criteria

The aim 1 eligibility criteria include being aged 18 to 29 years; identifying as Black; being proficient in English; having access to a personal smartphone; and being a current resident of Alabama, Georgia, or North Carolina. The aim 2 eligibility criteria include being aged 18 to 29 years; identifying as Black; being proficient in English; having access to a personal smartphone; being a current resident of Alabama, Georgia, or North Carolina; and being hesitant toward COVID-19 vaccines. The aim 3 eligibility criteria include being aged 18 to 29 years; identifying as Black; being proficient in English; having access to a personal smartphone; being a current resident of Alabama, Georgia, or North Carolina; and being out of compliance with vaccination guidelines [38]. Participants who do not comply with vaccination guidelines include both individuals who have never received a COVID-19 vaccine and those who have not received any booster.

Screening for Eligibility

All potential participants (whether recruited via the internet or in person) will complete a web-based screening survey via Qualtrics (Qualtrics International Inc) to provide consent for screening and verify all inclusion criteria. For those who met the eligibility criteria for aim 1, the screening survey directed participants to an informed consent video with accompanying text. Those who meet eligibility criteria for aims 2 and 3 will be asked to record their first name, email address, and phone number if they are interested in participating in the study. Those who are disinterested in participating can decline by exiting the website. Potential participants who do not meet the eligibility criteria will be asked if they would like to be contacted about other research studies and, if so, to provide contact information.

Aim 1

Overview

At the time of publication, data collection for aim 1 has already been completed. Aim 1 included the following two distinct phases: a web-based survey and digital storytelling workshops. A total of 150 Black young adults were recruited from Alabama, Georgia, and North Carolina to participate in a web-based survey. A subsample was invited to participate in a web-based digital storytelling workshop to produce digital stories that will become part of the TT-C intervention.

Aim 1 Survey

Participants completed a one-time web-based survey through the Qualtrics survey platform, which included both validated survey constructs and choose-your-own-adventure formats [39,40]. Within the choose-your-own-adventure portion, participants were presented with culturally and contextually realistic scenarios, and we asked them to make decisions and reflect on the outcomes of these decision. Each story path included multiple branch points where participants made a behavioral choice. Each choice impacted the subsequent information presented and later scenario branches. Short multiple-choice questions and open-ended questions were included within each path to assess how participants made their choices and to capture their reflections on these decisions. This survey took about 30 to 45 minutes to complete. Participants

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who reported high levels of vaccine confidence were invited to participate in the digital storytelling workshop.

Aim 1 Digital Storytelling Workshop

Interested and eligible survey respondents were directed to informational text that described the digital storytelling workshop and its purpose [41]. Once the participants consented, they were invited to participate in 1 of 2 web-based digital storytelling workshops; each consisted of 3 sessions. Each workshop session lasted about 3 hours, and sessions were conducted 1 week apart. Participants were informed that the goal was to develop a video that would be included in an intervention that aims to help peers learn from their COVID-19 pandemic–related lived experiences. During the workshops, participants created digital stories (1- to 3-minute videos) that included still and moving images, voice-over recordings of the participants telling their stories, and background music or text to document their experiences related to the COVID-19 pandemic and why they chose to be vaccinated. Select digital stories will be incorporated into a TT-C module entitled "Hear from you peers." This module will be available to aim 3 participants who are randomized to the intervention condition.

Aim 2

Overview

Up to 16 young adults who have expressed COVID-19 vaccine hesitancy will participate in web-based focus groups. The focus groups will consist of 2 rounds of usability testing activities that will be conducted 1 to 2 months apart. During round 1, participants will review TT-C content, generate additional ideas, and identify assets on which to build, guided by the ADAPT-ITT framework (Table 1) [35]. Young adults will provide recommendations and context-relevant insights regarding any requested additions or changes. The study team will collectively review the recommendations and prioritize and address the actionable ideas to be presented for further feedback and testing with YAB members. Beta testing will (1) allow for a full assessment of intervention content (eg, identification of any remaining spelling, text, or graphical errors) and technical functionality, (2) ensure that the back-end collection of app analytics data is being performed appropriately, and (3) help finalize pilot test procedures. All errors and technical bugs will be addressed or optimized prior to the RCT.

Table 1. ADAPT-ITT[a] model: Phases and methodology.

ADAPT-ITT phase	Aim	Study method
Assessment	1	Formative research with Black young adults via a web-based survey, digital storytelling, and focus groups
Decision	2	Adapt Tough Talks based on established feasibility, acceptability, and early effectiveness data
Administration	2	Usability testing with Black young adults in Alabama, Georgia, and North Carolina
Production	2	Produce initial intervention prototype
Topical Experts	2	Review TT-C[b] with identified scientific and community experts and young adult advisors
Integration	2	Integrate content from topical experts, young adult advisors, and Black young adult participants of the technical pilot
Training	2	Train staff on TT-C app functionality
Testing	3	Conduct hybrid type 1 effectiveness implementation randomized controlled trial

[a]ADAPT-ITT: assessment, decision, administration, production, topical experts, integration, training, and testing.

[b]TT-C: Tough Talks for COVID-19.

TT-C Intervention and Control Condition

The TT-C intervention will be finalized to be self-directed and fully asynchronous, so that there will be no need for the participants to engage with an interventionist. The initial assessments suggest that to complete all activities and review all content, the study participants will need to dedicate about 2 to 4 hours of time (spread across 1 month). Our standard-of-care control will be the provision of COVID-19 vaccine materials, which will be adapted from the Centers for Disease Control and Prevention and shared via email. Standard-of-care materials will be hosted via the internet and will be accessible to the general public. In the final phase of aim 2, the YAB and community partners will participate in an assessment of the TT-C intervention to assess intervention feasibility and acceptability and finalize RCT study procedures.

Aim 3

Overview

In aim 3, we will conduct a hybrid type 1 effectiveness implementation RCT. We will enroll 360 Black young adults from Alabama, Georgia, and North Carolina who are unvaccinated, have only received 1 dose of a 2-dose series, or have not received boosters against COVID-19 in accordance with current Centers for Disease Control and Prevention booster eligibility criteria [42]. After collecting informed consent, using block randomization by state, we will allocate 180 participants to each arm. The web-based screener will automatically randomize participants (N=360) to the control condition (n=180) or the TT-C intervention arm (n=180). Self-report data, including vaccination status, will be collected at baseline and at 1 and 3 months after baseline.

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Statistical Power

Power calculations were conducted based on the assumptions that dropout would be equivalent across arms and approximately 15% of participants would be lost to follow-up; therefore, we assume that 306 participants will complete the primary end point assessment. If the rate of COVID-19 vaccination in the control arm is between 10% and 20%, we will have 80% power to detect an odds ratio of 1.92 to 3.21 when comparing vaccination uptake between arms, assuming a sample size of 306 and a 2-sided α of .05. We anticipate that the vaccination rate in the control arm will be low, given that COVID-19 vaccines have been available for some time. Therefore, we expect that a total sample size of 360 will provide sufficient power to detect a clinically meaningful difference in vaccine uptake.

Aim 3 Effectiveness Measures and Analysis

The aim 3 primary effectiveness outcome is COVID-19 vaccine uptake, which will be defined as the receipt of any COVID-19 vaccine (primary series or boosters). The secondary effectiveness outcomes are vaccine hesitancy and confidence [43], as well as vaccine knowledge, attitudes, and beliefs [44]. We will also collect quantitative data on implementation outcomes, the social cognitive theory constructs targeted by TT-C, COVID-19–specific risks and behaviors, and pertinent constructs that have been validated in the extant literature on Black young adults (Table 2).

Table 2. Effectiveness measures.

	Baseline	Follow-up
Number and percentage of participants who receive any new vaccine during the study period (eg, participants who accept the first dose of a COVID-19 vaccine, complete the vaccine series, or receive a booster shot)		✓
Vaccine hesitancy [32], confidence [43], knowledge [45], attitudes, and beliefs [32]	✓	✓
Usability (including acceptability; ie, TT-C[a] satisfaction and completion), demand (including the number of youths screened, enrolled, and retained), and practicality (based on the TT-C intervention's cultural appropriateness and fit) [46]		✓
Physical environmental factors (access, utilization, and vaccine misinformation), social environmental factors (discrimination, as measured via the Adapted Everyday Discrimination Scale for Medical Settings [47]; stigma; social support, as measured via the MOS[b] social support survey [48]; social norms; and medical mistrust, as measured via the Group-Based Medical Mistrust Scale [49]), outcome expectations (COVID-19–specific knowledge, attitudes, and beliefs), observational learning (vaccination [eg, flu or HPV[c]] experiences of self or others), and perceived self-efficacy (vaccination barriers and facilitators)	✓	✓
Sociodemographic characteristics (age, race, ethnicity, gender identity, income, employment, and education [eg, current student])	✓	✓
Pre-existing conditions (eg, diabetes, cardiovascular conditions, etc)	✓	✓

[a]TT-C: Tough Talks for COVID-19.

[b]MOS: Medical Outcomes Study.

[c]HPV: human papillomavirus.

We will use logistic regression to determine the effect of the treatment arm on the probability of vaccination uptake ("yes" or "no") at month 3. We will focus on the odds ratios for comparing the probability of vaccination in the treatment group with the probability of vaccination in the control group. As an exploratory analysis, we will examine primary and secondary outcomes by enrollment vaccination status (not vaccinated vs vaccinated with 1 or 2 doses and no booster shot). The secondary outcomes—vaccine hesitancy [4]; vaccine confidence [43]; and vaccine knowledge, attitudes, and beliefs [44]—will all be assessed by using previously validated scale scores, of which each will consist of the continuous sum of responses to a series of questions with Likert scale responses. We will use linear regression models with treatment group as the exposure to determine whether continuous secondary outcomes vary among treatment groups. Lastly, we will use the causal mediation framework proposed by Valeri and Vanderweele [50] to understand the mechanisms for any intervention effects through each of our hypothesized mediators [50-53]. We will use the *g-formula* command in Stata (StataCorp LLC), which uses the mediational g-formula, to estimate the controlled direct effects, natural direct effects, and natural mediated (indirect) effects [54].

In sensitivity analyses, we will also use inverse probability of treatment weights to account for missing data and potential differential retention between study arms over the study period. We will weight outcome models by using stabilized inverse probability of censoring weights that include the treatment arm as a predictor to account for differential loss to follow-up.

Aim 3 Implementation Outcomes and Analysis

We will conduct qualitative interviews with a group of purposively selected participants (we estimate 18-24 participants) to assess how the intervention was internalized and experienced. We will conduct in-depth exit interviews on a rolling basis after participants have concluded the 3-month study cycle. All interviews will be audio-recorded and transcribed verbatim. Qualitative analyses will be conducted in the NVivo (QSR International) coding program. Study participants will be asked questions on how sociocultural nonintervention contexts affected the likelihood of vaccine acceptance, vaccine series completion, and vaccine hesitancy.

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Interviews will last about 1 hour. We will perform a rapid content analysis, which is routinely used in implementation science to assess and disseminate results quickly and accurately [55]. The findings will be explored as a function of participant age, sex, and state. Qualitative findings will provide direct insight into real-world implementation considerations.

Results

Our study was funded at the end of April 2021. Approval from the University of North Carolina, Chapel Hill Institutional Review Board was obtained shortly thereafter. Aim 1 data collection concluded in early 2022. The entire study is expected to be complete at the end of January 2025.

Discussion

Overview

The TT-C intervention will address COVID-19–related vaccine hesitancy among Black young adults in Alabama, Georgia, and North Carolina by including tailored content to engage Black young adults and promote agency and autonomy in decision-making related to vaccination, while also addressing the persistent effects of historic contexts and structural stigma and racism against Black populations in the United States. The TT-C DHI will address issues that not only impact COVID-19 vaccine uptake but also influence the acceptance of other vaccines and health services, such as addressing medical distrust, highlighting the role of Black scientists in vaccine development and medicine, and providing tailored content on how to assess misinformation. The TT-C app will be developed to retain relevance as the pandemic shifts, and it can be adapted to address other conditions that disproportionately affect Black young adults.

Limitations

In assessing trial designs, we considered stepped wedge and waitlist formats. However, since our aim is to reach Black young adults who are often not engaged in care, particularly those in the southern United States, we determined that multipronged recruitment and individual-level randomization would be the best approaches. Because the landscape of COVID-19 prevention and related science are quickly changing (eg, masking, the definition of *fully vaccinated*, etc), ideally, the app should be flexible and responsive. Although the content delivered through the TT-C app is adaptable, not all components can be adjusted once they are developed.

Conclusion

If the TT-C DHI is effective in increasing COVID-19 vaccination uptake among Black young adults in the southern United States, we will be poised for rapid dissemination and broad implementation to reduce COVID-19 morbidity and mortality among unvaccinated or partially vaccinated Black young adults in the southern United States.

Acknowledgments

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Data Availability

The data sets generated during aim 3 of our study will be shared in compliance with National Institutes of Health data sharing policies and will be made available from the senior author on reasonable request.

Authors' Contributions

LBHW (contact principal investigator) and HB are co–principal investigators of the study. HB is the first and lead author. LBHW is the last and senior author on this protocol manuscript. MAL is the mobile app development lead. EET, ACMB, and MLGC provided leadership on digital storytelling and community engagement. MCDS and DB are statistical and quantitative experts. KEM and AP are epidemiology and intervention scholars who are contributing their expertise to the study. CT and CLB are part of research operations. All authors contributed to the writing and editing of this protocol.

Conflicts of Interest

None declared.

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Abbreviations

ADAPT-ITT: assessment, decision, administration, production, topical experts, integration, training, and testing
CBPR: community-based participatory research
DHI: digital health intervention
RCT: randomized controlled trial
TT-C: Tough Talks for COVID-19
YAB: Young Adult Advisory Board

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Protocol

Layperson-Facilitated Internet-Delivered Cognitive Behavioral Therapy for Homebound Older Adults With Depression: Protocol for a Randomized Controlled Trial

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Abstract

Background: Depression in older adults has serious biological, psychological, and social consequences. Homebound older adults experience a high burden of depression and significant barriers to accessing mental health treatments. Few interventions to address their specific needs have been developed. Existing treatment modalities can be challenging to scale up, are not tailored to unique population concerns, and require significant staffing support. Technology-assisted, layperson-facilitated psychotherapy has the potential to overcome these challenges.

Objective: The aim of this study is to assess the efficacy of a layperson-facilitated internet-delivered cognitive behavioral therapy program tailored for homebound older adults. The novel intervention, Empower@Home, was developed based on user-centered design principles and partnerships between researchers, social service agencies, care recipients, and other stakeholders serving low-income homebound older adults.

Methods: This 2-arm, 20-week pilot randomized controlled trial (RCT) with a waitlist control crossover design aims to enroll 70 community-dwelling older adults with elevated depressive symptoms. The treatment group will receive the 10-week intervention immediately, whereas the waitlist control group will cross over and receive the intervention after 10 weeks. This pilot is part of a multiphase project involving a single-group feasibility study (completed in December 2022). This project consists of a pilot RCT (described in this protocol) and an implementation feasibility study running in parallel with the pilot RCT. The primary clinical outcome of the pilot is the change in depressive symptoms after the intervention and at the 20-week postrandomization follow-up. Additional outcomes include acceptability, adherence, and changes in anxiety, social isolation, and quality of life.

Results: Institutional review board approval was obtained for the proposed trial in April 2022. Recruitment for the pilot RCT began in January 2023 and is anticipated to end in September 2023. On completion of the pilot trial, we will examine the preliminary efficacy of the intervention on depression symptoms and other secondary clinical outcomes in an intention-to-treat analysis.

Conclusions: Although web-based cognitive behavioral therapy programs are available, most programs have low adherence and very few are tailored for older adults. Our intervention addresses this gap. Older adults, particularly those with mobility difficulties and multiple chronic health conditions, could benefit from internet-based psychotherapy. This approach can serve a pressing need in society while being cost-effective, scalable, and convenient. This pilot RCT builds on a completed single-group feasibility study by determining the preliminary effects of the intervention compared with a control condition. The findings will provide a foundation for a future fully-powered randomized controlled efficacy trial. If our intervention is found to be effective, implications extend to other digital mental health interventions and populations with physical disabilities and access restrictions who face persistent disparities in mental health.

Trial Registration: ClinicalTrials.gov NCT05593276; https://clinicaltrials.gov/ct2/show/NCT05593276

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International Registered Report Identifier (IRRID): PRR1-10.2196/44210

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KEYWORDS

depression; depressive; gerontology; gerontological; geriatric; psychotherapy; older adult; elder; home based; community based; community living; homebound; low-income; eHealth; mHealth; digital mental health; internet intervention; iCBT; CBT; mental health; cognitive behavioral therapy; internet based; internet delivered

Introduction

Background

Depression in older adults has serious consequences, including worsened physical health and chronic disease progression [1-3], increased functional limitations and disabilities [4,5], institutionalization [6], and premature mortality due to comorbid conditions and suicide [7,8]. Low-income and homebound older adults are especially at high risk for experiencing depression. In one US representative sample, estimates for rates of depression in homebound older adults were approximately 40% [9]. Further complicating this burden of depression is a recent steep increase in the number of homebound older adults, likely in part driven by COVID-19 [10].

Although evidence-based pharmacological and nonpharmacological treatments exist, not all options are readily accessible to all populations of older adults [11]. Low-income and homebound older adults face significant access barriers to mental health treatments due to mobility, transportation, and financial difficulties. In addition, few providers have specialized training in working with older populations [12,13]. Given the lack of service providers, high rates of depression in specific subpopulations of older adults, and demographic trends toward a higher number of homebound older adults, interventions that are both accessible and scalable are urgently needed.

Digital mental health interventions have the potential to address the gaps in mental health treatment faced by low-income and homebound older adults. Affirming this, a recent national panel of expert stakeholders recommended that digital mental health interventions be broadly adopted and that insurers expand their coverage and reimbursement [14]. Cognitive behavioral therapy (CBT) is an evidence-based form of psychological treatment and has been adapted to multiple age groups [15-17] as well as medical and social contexts [18,19]. CBT is well suited for digital-based delivery, given its highly structured format and skill-based learning [20]. Hundreds of clinical trials have taken place in the last decade to test internet-delivered CBT (iCBT) and presented robust findings supporting the acceptability and effectiveness of this treatment modality [21-25]. iCBT is convenient and self-paced, less expensive than traditional psychotherapy, and scalable due to content delivery automation.

Research has consistently shown that tailoring treatment to specific populations, contexts, and settings is associated with increased uptake, acceptability, and sustainability [26,27]. In the case of older adults, procedural and content modifications to CBT have been discussed that incorporate differences in thinking styles in older adults and age-related adjustments [28]. However, when packaged for internet delivery, empirically supported iCBT programs often employ a one-size-fits-all approach, and very few have been designed to consider the needs of older adults [29-31]. In general, older adults are underrepresented in iCBT trials. A review found that only 3% of iCBT trial participants were older adults [32]. Since then, older adults' participation has increased. However, a recent systematic review found that older adults are still largely under-represented as participants in rigorously designed studies [25].

Recent studies involving homebound older adults have shown that modifications to both contents (eg, adding aging-related themes) and web interface (website or app) are needed to improve adherence and engagement with iCBT [33,34]. These studies suggest that older adults had difficulty applying lessons when presented with content that failed to address aging-related topics and were less tolerant to poor usability issues, possibly due to a combination of age-related changes (eg, cognitive, vision, motor control, speech, and hearing), physical disabilities, and their lack of familiarity with modern technology. Most well-established iCBT programs contain a large amount of text, are highly didactic, and are hosted on interfaces that are not age-friendly (eg, small text and buttons). Usability issues and technical challenges are frequently reported, which can lower adherence and ultimately reduce treatment effects. The lack of tailored solutions may be more problematic for homebound older adults, who tend to be older, less tech-savvy, have more cognitive and functional limitations, and are more likely to experience usability issues [35].

Objective

The primary aim of this study is to evaluate the efficacy of a 9-session iCBT program in treating depression in low-income homebound older adults. Additional outcomes and potential covariates will be captured, including anxiety, loneliness, and health-related quality of life.

A lack of iCBT products suitable for homebound older adults reflects and contributes to the digital divide experienced by them. Barring treatment innovation, older adults will continue to be left behind and face persistent mental health disparities related to access. This study aims to fill this void by testing the preliminary effects of a novel iCBT program designed for homebound older adults.

Intervention Model

Empower@Home is an iCBT program designed to treat the core symptoms of depression in older adults. It consists of 9 web-based sessions grounded in CBT principles and homework assignments (ie, weekly practices) made available over 10 weeks. Each lesson is presented as a series of short videos with

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voice-overs that include didactic text, images of diverse older adults, inspirational quotes, and interactive exercises. Sessions are written at an eighth-grade reading level, and all spoken content is captioned. The weekly home practice tasks are modest and typically require 20 minutes or less of commitment from the user. A workbook with summarized session content and home practices is also provided to participants.

The sessions are enhanced with an animated case story series featuring a 74-year-old homebound woman named Jackie. The animated story is embedded within each session, like an episode of a television show. This content serves to reinforce core skills and techniques taught. Prior research has found that including short multimedia entertainment is a useful approach for communicating learning objectives in psychoeducational materials [36].

The session scripts of Empower@Home were developed by a team of researchers, clinicians, older adults, and social service providers via a co-design process. The web platform that delivers Empower@Home is a custom learning management system built using state-of-the-art, agile development processes. All interface features are compatible with accessibility standards and current best practices for making an age-friendly user interface and experience design [37]. For example, the main user interface features large buttons, text, icons with text descriptions, high-contrast color schemes, and intuitive navigation.

Informed by the Efficiency Model of Support [38], support from trained laypersons called Empower Coaches supplements the core web-based sessions of Empower@Home. Human support aims at increasing a participant's ability to use the technology to obtain the intended treatment outcome [38]. Previous studies have shown that supported iCBT is more effective and associated with better adherence than unsupported interventions [39-41]. However, support mechanisms are generally underspecified and understudied, and it is not entirely clear what type and intensity of support are needed for homebound older adults to engage in iCBT successfully.

Informed by our previous research and the Efficiency Model of Support, we provide weekly check-ins with a supportive guide (ie, Empower Coach). The weekly check-ins are Coach-initiated contacts designed to prevent and address potential failure points, including engagement, working knowledge of the iCBT platform, and implementation of iCBT. All weekly check-ins are telephone-based. The Empower Coaches are laypersons without specialized mental health training or independent clinical licensure. The support content includes simple feedback, encouragement, homework review, and assistance with self-help tools without additional traditional therapy. Coaching sessions are highly individualized to meet the particular needs of the participants. On the basis of participants' preferences, they may use the weekly check-in sessions to go over the web-based program with their coaches, whereas others complete the web-based portion on their own before the phone-based check-in sessions. Coaching sessions can range from 5 minutes to an hour per week, depending on the participants' needs and preferences.

Coach training involves reviewing all web-based sessions of Empower@Home (takes approximately 4-5 hours to complete), a self-directed asynchronous web-based training (approximately 1.5 hours), and a synchronous training workshop (approximately 3 hours). The total training burden is approximately 9-10 hours per coach.

Methods

Preliminary Study

The procedures described in this protocol, including recruitment, assessments, coaching calls, and device shipments and returns, have been tested in a completed single-group uncontrolled feasibility study. Findings from the single-group study have not yet been published, but preliminary analysis shows that the intervention is feasible and acceptable, with high satisfaction ratings, and is associated with significant within-group reductions in depressive symptoms and several secondary clinical outcomes. Study procedures for the pilot randomized controlled trial (RCT) are refined based on lessons learned from the feasibility pilot.

Study Setting and Aims

The study will be managed from the University of Michigan in collaboration with community agencies serving older adults. Participants will reside throughout Michigan in both rural and urban areas. All participants will be 60 years or older and are expected to be predominantly low income. Participants will complete the intervention in their own homes, with all assessments and technological support provided remotely by phone.

Eligibility Criteria

To be eligible for the trial, participants must be at 60 years or older and have at least mild depression (score of ≥8 on the Patient Health Questionnaire-9 [PHQ-9]). Participants will be excluded if they (1) have probable cognitive impairment based on the Blessed Orientation-Memory-Concentration Test (score ≥10), (2) do not speak English, (3) have moderate to high risk of suicide based on the Columbia-Suicide Severity Rating Scale, (4) have a terminal illness or are in unstable physical health with a high risk of repeated hospitalizations within the next 3 months, (5) have a visual impairment based on self-reported inability to use a screen with correction, (6) have a current or recent history of substance use based on a score of ≥2 on the CAGE-AID Substance Abuse Screening Tool, (7) have a psychotic disorder based on self-report, or (8) are currently receiving psychotherapy. The study will not exclude participants based on racial or gender identification. Completing the intervention will require a tablet and internet accessibility. Participants are not required to have a computer or internet access; those who lack 1 or both resources will be provided a tablet and access to the internet at no cost during the active intervention period.

Recruitment and Compensation

Participants will be recruited into the study on a rolling basis and will be drawn from multiple community agencies as well as other public places, including social media and local news

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outlets. The social service agencies that participated in this study's intervention development and implementation feasibility phase were predominantly Area Agencies on Aging based throughout Michigan. These agencies serve older adults by offering services to enable their clients to maintain independence. These services may involve case management, caregiver services, and meals on wheels. These agencies will refer participants to the study based on their judgment of the appropriateness of the intervention for their clients.

After receiving referrals, study personnel will contact potential participants via phone to screen for eligibility. The initial screening is expected to take 20 minutes to complete. Participants will provide recorded verbal consent. Those who decline to participate will be referred back to their case managers or agency when possible. Advertisements placed via social media (eg, Facebook and Nextdoor) and through research registries will also allow participants to self-refer and be screened for eligibility.

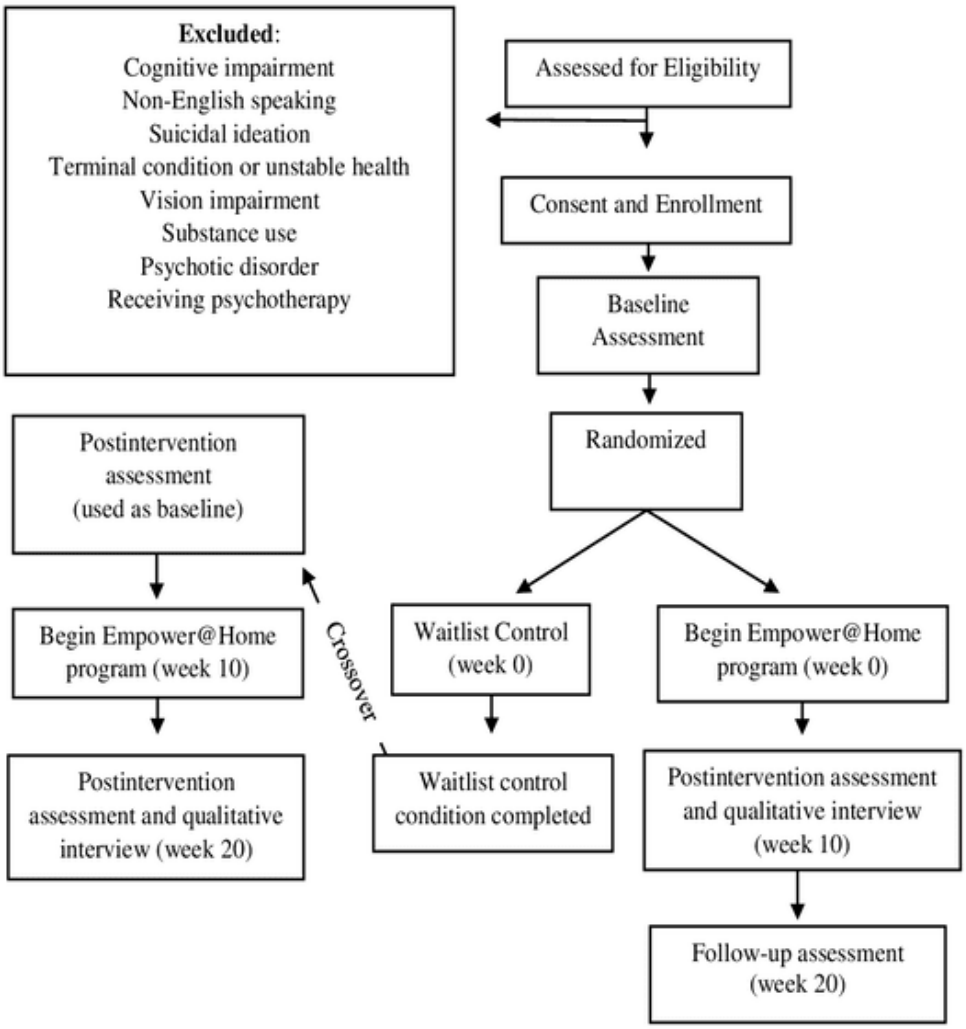
Those who qualify for the trial will be paid up to US $100. Compensation is determined based on the number of assessments completed. Partial compensation is available (eg, participants who complete only the baseline assessment will receive US $30).

Study Design

Eligible and consented participants will be assigned either to an active treatment or a waitlist condition group that will cross over to the intervention at 10 weeks. A computer-generated random sequence will be used for assignment into either condition at a ratio of 1:1. Given the content of the intervention and study design, blinding the participant and evaluator to the condition will not be feasible.

All participants will be assessed using the same schedule. All will be invited to complete the comprehensive baseline assessment, postintervention or control assessment at week 10, and a follow-up assessment at week 20. Participants on the waitlist control will receive the intervention after their post-test at week 10 (Figure 1).

Figure 1. Study design.



Waitlist Condition

The attention control waitlist condition involves a comparable amount of phone contact to the intervention condition, with roughly 20 minutes of companionship calls per week. However, in the attention control, participants will not be exposed to CBT-related content. The purpose of companionship calls is to

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provide socialization and contact with supportive individuals without introducing structured therapeutic content.

Discontinuation

Consented participants may still be deemed ineligible during study participation if they develop significant clinical worsening of depression, suicidal ideation, or other circumstances (eg, terminal illness or prolonged hospitalization) that preclude their ongoing involvement with the trial. Participants will be consulted regarding potential removal. Should a participant report suicidal ideation, a protocol will be in place that involves the participation of the study principal investigator and a clinical social worker. Should a participant's circumstance interfere with their ongoing participation in the trial, the study team will discuss the risks and benefits of the participant's ongoing involvement with the trial until a consensus is reached. If there is a clinically significant worsening of depressive symptoms, considerable effort will be made to expedite entry into the best available treatment outside the research protocol.

Clinical Management and Storage

All data related to the study (screening, pretest, coaching sessions, posttest, and follow-up) will be entered directly by project staff into REDCap [42]. During the active intervention, participants will be asked to fill out the PHQ-9 every other week, administered as a part of the web-based therapy lesson. These assessment data are stored in a HIPAA (Health Insurance Portability and Accountability Act)–compliant database hosted by the University of Michigan.

Measures

All measures are presented in Table 1. The primary clinical outcome in the study will be depressive symptoms as measured by the PHQ-9. The PHQ-9 is widely used in clinical research and has been used to evaluate older adults with medical and psychiatric illnesses in and outside of health care settings [43,44]. The PHQ-9 has been found to perform comparably to the Geriatric Depression Scale in identifying depression in older adults [45]. Scores on the PHQ-9 can range from 0 to 27 and indicate minimal, mild, moderate, moderately severe, or severe depression symptom severity. Sample items include "In the last week, have you had little interest or pleasure in doing things?" and "In the last two weeks, have you been feeling down, depressed, or hopeless?" Respondents indicate answers on a 4-point Likert scale ranging from "not at all" to "nearly every day." In primary care patients, the measure has a sensitivity of 88% and a specificity of 88% [43]. The PHQ-9 will be administered at initial screening, baseline, after intervention, and 20-week follow-up. In addition, participants will complete a PHQ-9 self-assessment built into the web-based sessions every other week. To mimic the additional assessment patterns in the treatment group, participants in the control condition will also be administered the PHQ-9 every other week via phone during the 10-week waiting period.

Table 1. Study measures and time points.

Variable	Assessment or activity	Screening	Baseline	Postrandomization		Follow-up
				Biweekly	Post	
Depression	PHQ-9[a]	✓	✓	✓	✓	✓
Anxiety	GAD-7[b]		✓		✓	✓
Social isolation	PROMIS-SI 8a[c]		✓		✓	✓
Health self-assessment	PROMIS-GH[d]		✓		✓	✓
Well-being and quality of life	EQ-5D-5L		✓		✓	✓
Skill acquisition	CBTSQ[e]		✓		✓	✓
Acceptability	Modified TEI[f]				✓	
Adherence	Session completion				✓	
Participant background	Sociodemographic, health status, and physical functioning	✓	✓			

[a]PHQ-9: Patient Health Questionnaire-9.

[b]GAD-7: Generalized Anxiety Disorder-7.

[c]PROMIS-SI 8a: Patient-Reported Outcomes Measurement Information System–Social Isolation 8a.

[d]PROMIS-GH: Patient-Reported Outcomes Measurement Information System–General Health.

[e]CBTSQ: Cognitive-Behavioral Therapy Skills Questionnaire.

[f]TEI: Treatment Evaluation Inventory.

Anxiety will be assessed with the General Anxiety Disorder-7, which has been validated in populations of older adults [46]. Sample items include "How often have you been bothered by feeling nervous, anxious, or on edge in the last two weeks?" and "How often have you been bothered by worrying too much about different things in the last two weeks?" Like the PHQ-9, respondents answer on a 4-point Likert scale ranging from "not at all" to "nearly every day." In primary care patients, the measure has a sensitivity of 89% and a specificity of 82% [47].

Social isolation will be measured using the Patient-Reported Outcomes and Measures Information System–Social Isolation

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(PROMIS-SI 8a). This measure has been used extensively in older adults with chronic health conditions and depression [48-50]. This 8-item measure uses a 5-point Likert scale with responses ranging from "always" to "never." Sample items include "I feel isolated from others" and "I feel that people avoid talking to me." The PROMIS-SI has high internal consistency (Cronbach α=.91) [51].

The PROMIS–General Health (PROMIS-GH) will be used as a global measure of health and health-related quality of life. This 10-item measure uses a 5-point Likert scale ranging from "excellent" to "poor." It contains items such as "In general, would you say your health is...?" and "In general, how would you rate your satisfaction with your social activities and relationships…?" The PROMIS-GH has been validated in older adults with chronic health conditions, demonstrating moderate internal reliability (ordinal α=.82-.88) [52].

Quality of life will be measured using the EQ-5D-5L. Respondents answer on a 5-point Likert scale ranging from "I have no problems with…" to "I am unable to…/I have extreme…" They rate their experience in 5 life areas (mobility, self-care, usual activities, pain, and anxiety or depression). It also includes an overall health ranking on a scale of 0-100. In a systematic review including 99 studies that included a diverse range of medical conditions, the EQ-5D-5L exhibited overall excellent psychometric properties [53].

To explore the role of CBT skill acquisition, participants will complete the Cognitive-Behavioral Therapy Skills Questionnaire. This validated 16-item questionnaire assesses a respondent's ability to apply cognitive restructuring, behavioral activation, and other CBT-related skills [54]. Participants are asked how often they currently do sample activities, such as making plans over the weekend, motivating themselves to do things, and socializing even though they do not want to. Items are answered on a 5-point Likert scale ranging from "I don't do this" to "I always do this."

Acceptability will be assessed by the number of sessions participants completed (ie, adherence) and the modified Treatment Evaluation Inventory. This 11-item inventory has been previously used to evaluate the acceptability of cognitive therapy for depression interventions among older adults and has good convergent validity and internal consistency (α=.92) [55]. The measure will be administered after the intervention. The measure is answered on a 5-point Likert scale ranging from "never" to "always."

Qualitative Interviews

After completing the intervention, participants will complete a semistructured qualitative interview lasting roughly 30 minutes. The interview probes several domains, including their experience with the program, likes and dislikes, and experience with specific program components (eg, storyline, home practice, materials, and ease of use). Additional questions will relate to participants' relationship with their Empower Coach.

Sample Size

A sample size of 70 (n=35 per group) should provide at least 80% power, allowing for a 20% attrition rate for both arms. Specifically, we considered the case where the 2 arms are compared in terms of weekly changes in the mean PHQ-9 survey responses between the baseline, 5 interim in-app PHQ-9 assessments (roughly at weeks 1, 3, 5, 7, and 9), and the 10-week follow-up PHQ-9 survey. We assume that the changes in the mean response can be expressed in terms of a linear trend, and the treatment effect can be expressed in terms of the difference in slopes or rate of change ($\delta = -0.8 \times 5$ in the total PHQ-9 score over 10 weeks; 5 is the SD in the change scores in our feasibility study). Sample size estimates used the following inputs: (1) type I error rate (α)=.05; (2) the smallest meaningful difference to be detected (δ) over the 10 weeks; (3) power (γ)=.80; (4) we assumed that outcome within-subject variance ($\sigma^2=6^2$; estimated from our feasibility study data) is constant over time; (5) the number of repeated measurements per person (n): 1 baseline, 5 in-app assessments, 1 final postbaseline for a total of 7 repeated assessments; and (6) regarding between-subject variation of the slopes, we assumed a variance of random slopes $\tau^2=0.2$ (estimated from our feasibility study data). The sample size is 52 for both arms with equal randomization probabilities; with an attrition rate of 20% for both arms, the total required sample size is 65. We set the final target sample size to 70 to allow room for higher attrition and lower adherence.

Analytic Plan

To reduce bias, analyses will involve an intention-to-treat design. Linear mixed models will be used to test within-group changes over time and to compare changes between the treatment and control groups in outcomes of interest. The LASSO (least absolute shrinkage and selection operator [56,57]) variable selection technique will be used to find the optional selection of covariates for the final model. Exploration of mechanisms of change variables involves a procedure described by Hayes [58] that uses bootstrapping to test indirect effects. Statistical analysis will be conducted using Stata 15 SE. Although this trial is not fully powered for mediation analysis, findings from these analyses will inform future research to identify mechanisms of change.

We will use a pragmatic approach involving inductive and deductive coding for qualitative data. Qualitative analysis of the interview data collected from the completed single-group feasibility study is underway, and a codebook will be created during the process. The codebook from the single group study will serve as a framework for us to code the qualitative data collected from the pilot RCT. The codebook will be iteratively refined by reviewing the data and themes several times. Qualitative analysis will be conducted using Dedoose, a web app for mixed methods research.

Ethics Approval

This study was reviewed and approved by the Health Sciences and Behavioral Sciences institutional review board (IRB) at the University of Michigan. Approval was granted on April 19, 2022 (HUM00212950).

A waiver of documentation for written consent was approved by the IRB. Consent to participate in the study will be obtained orally from participants. Consent will be obtained at 2 points. At first contact, participants will provide consent to be screened.

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Second, after screening and before the baseline interview, study-eligible participants will be asked to provide oral consent to participate in the study. This will be recorded via a tape recorder after a verbal review of an informed consent document. To ensure the quality of consent, all participants will reconsent at the beginning of the first web-based session of the intervention. This will be accomplished by providing a brief written consent document on the first page of the web-based session. Participants must confirm their understanding of the document to proceed to the first web-based session.

The privacy of participants will be protected in several ways. All participants will complete web-based therapy sessions by themselves in their private homes. Direct identifiers are not stored in the web-based program. Mental health assessment data collected as part of the web-based sessions are stored in a HIPAA-compliant database. Other study data (eg, baseline and posttest assessments) are entered and managed on REDCap. Only the study team members directly authorized by the principal investigator will have access to study data with identifiers. Access is typically restricted to the principal investigator and project coordinators. As the study involves follow-up, direct identifiers will be retained for this purpose. After completion of the study and data cleaning, all direct identifiers will be removed from the database, rendering the final data set anonymous.

Those who qualify for the trial will be paid up to US $100 for participation. Compensation is determined based on the number of assessments completed. Partial compensation is available (eg, participants who complete only the baseline assessment will receive US $30). Participants will be provided US $30 for the baseline, US $50 for the posttest, and US $20 for the follow-up. Payment will be provided directly to the participant via mailed check or Visa gift card, whichever is preferred by the participant.

Results

Funding for this multiphase project was awarded in November 2020. IRB approval for the single-group feasibility study and the proposed RCT was attained in April 2022. Enrollment for the single-group study began in May 2022, and all subjects completed the intervention by December 2022. Recruitment for the RCT began in January 2023, and the study completion is anticipated by December 2023. The trial is registered at ClinicalTrials.gov (NCT05593276).

Discussion

Principal Findings

To our knowledge, this is the first RCT of layperson-facilitated iCBT for low-income homebound older adults with depression. We hypothesize that the Empower@Home intervention will be feasible and acceptable, reduce depressive symptoms, and improve psychosocial functioning and health-related quality of life. Existing evidence-based mental health treatments are often inaccessible to homebound older adults, who have been largely excluded from digital mental health interventions. This trial addresses that gap by testing an intervention specifically designed to the needs of this population.

iCBT participants are exposed to the same components as conventional CBT, though they receive psychoeducational materials through a self-directed internet platform. A meta-analysis of iCBT trials with older adults found a large pooled within-group effect size, although most studies adopted weak designs [24]. In a recent iCBT pilot trial led by the last author, homebound older adults with low computer literacy found that iCBT was an acceptable way of treating depression and resulted in significant reductions in depressive symptoms at the posttest [33]. A recent RCT showed that iCBT also effectively prevented depression among older adults with multiple chronic conditions [29].

As a result of the COVID-19 pandemic, virtual care is gaining rapid traction, which provides unprecedented opportunities for integrating digital mental health interventions into community aging services. The COVID-19 pandemic has accelerated the adoption of technology and virtual care in community settings, which is likely to stay after the pandemic. Although notable age differences in technology use remain, the adoption of key technologies by older adults has grown markedly, and the age-related digital divide continues to narrow. For example, smartphone ownership increased from 46% in 2018 to 61% in 2021 among those 65 years and older [59]. Given the increased focus on digital inclusion, there is likely to be continued growth in access to broadband internet. The Affordable Connectivity Program (formerly Emergency Broadband Benefit), a long-term, US $14 billion program authorized by the 2021 Infrastructure Investment and Jobs Act, provides up to US $30 per month toward internet service and up to US $100 to purchase a computer or tablet device for eligible households. With providers and clients more willing to use technology, increased funding, regulatory changes, and improved technology infrastructure, digital mental health interventions are ripe for implementation in community aging services, where many homebound older adults receive services.

The pilot RCT will provide crucial data for a fully-powered effectiveness trial in the future. If confirmed effective, several probable funding mechanisms can facilitate long-term sustainability. These funding sources include Medicaid, federal grants, private pay, and commercial insurance. For example, community agencies can apply for federal grants authorized by the Older Americans Act that support community-based health-promotion programs. Many commercial insurance providers are already reimbursing for iCBT services [60,61]. Agencies could also charge a sliding scale fee to cover operating costs and raise revenues. In terms of training, most of the provider training materials are web-based, making it relatively easy to scale up.

Strengths and Limitations

The strengths of this study include an iteratively developed intervention incorporating patient and provider feedback, randomized design, use of laypersons as interventionists, and recruitment of an underserved, hard-to-reach population with high unmet mental health needs. For limitations, this study uses a small sample size and a waitlist control design, which may

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lead to an overestimation of treatment effects [62]. Though this intervention is intended to address depression in older adults, it may also address related conditions not measured in this study, such as demoralization [63,64].

Conclusions

The planned study addresses the shortage of iCBT products suitable for homebound older adults. Our treatment innovation, if found effective, will contribute to closing the digital divide and mental health disparities in homebound older adults. Study implications extend to other digital mental health interventions and populations with physical disabilities and access restrictions who face persistent disparities in mental health.

Acknowledgments

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Data Availability

The data sets generated or analyzed in this study will not be publicly available. Consent and ethical approval for this study does not include a provision for the sharing of data from this study.

Conflicts of Interest

None declared.

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Abbreviations

CBT: cognitive behavioral therapy
HIPAA: Health Insurance Portability and Accountability Act
iCBT: internet-delivered cognitive behavioral therapy
IRB: institutional review board
PHQ-9: Patient Health Questionnaire-9
PROMIS-GH: Patient-Reported Outcomes Measurement Information System–General Health
PROMIS-SI: Patient-Reported Outcomes Measurement Information System–Social Isolation
RCT: randomized controlled trial

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Protocol

The Design, Development, and Implementation of a Web-Enabled Informatics Platform to Enhance the Well-being of Individuals Aged 18-24 Years: Protocol for an Experimental Study

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Abstract

Background: Well-being is multidimensional, complex, and dynamic in nature. It is an amalgam of physical and mental health, essential for disease prevention and the promotion of a healthy life.

Objective: This study aims to explore the features that impact the well-being of individuals between 18 and 24 years of age in an Indian setting. It further aims to design, develop, and evaluate the usefulness and effectiveness of a web-based informatics platform or stand-alone intervention to enhance the well-being of individuals aged 18-24 years in an Indian setting.

Methods: This study follows a mixed method approach to identify factors influencing the well-being of individuals in the age group of 18-24 years in an Indian setting. The college-going students in this age group from the states of Uttarakhand (urban settings of Dehradun) and Uttar Pradesh (urban settings of Meerut) will be enrolled. They will be randomly allocated to the control and intervention groups. The participants in the intervention group will have access to the web-based well-being platform.

Results: This study will examine the factors that influence the well-being of individuals aged 18-24 years. It will also facilitate the design and development of the web-based platform or stand-alone intervention, which will enhance the well-being of individuals in the age group of 18-24 years in an Indian setting. Furthermore, the results of this study will help generate a well-being index for individuals to plan tailored interventions. The 60 in-depth interviews have been conducted as of September 30, 2022.

Conclusions: The study will help understand the factors that influence the well-being of individuals. The findings of this study will help in the design and development of the web-based platform or stand-alone intervention to enhance the well-being of individuals in the age group of 18-24 years in an Indian setting.

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KEYWORDS

well-being; mental health; nutrition; youth; digital health; interventions; India; health; lifestyle

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Introduction

Background and Rationale

Well-being combines physical and mental health, essential for disease prevention and the promotion of a healthy life. It is complex and multidimensional in nature. Well-being consists of objective and subjective measures. The objective measures indicate the quality of life, whereas the subjective measures comprise spiritual, social, psychological, affective, and cognitive judgments [1].

Psychological well-being refers to the psychological aspect. It consists of hedonic well-being (eg, the feeling of happiness), evaluative well-being (eg, contentment from life), eudaimonic well-being (eg, self-actualization, to know the meaning of life), and the other aspects of feeling well (eg, optimism) [1].

Mental health is described as a condition of well-being in which the person understands his or her ability to manage the usual pressures of life, can work effectively and productively, and can also contribute to the community [2]. As per Global Health Estimates 2016, the leading cause of nonfatal disease is mental and substance use disorders [3]. In the United States in 2017, more than 46.6 million adults were reported to have mental illness in the previous year [4]. In the entire world, in 2017, mental health was the second leading cause of the burden of disease in terms of years lived with disability and the sixth main factor of disability-adjusted life-years, which is a substantial threat to health systems, especially in low- and middle-income countries. Mental health is considered a crucial factor around the world; therefore, it is included in health policies and Sustainable Development Goals [5].

One-fourth of the entire world population is between 10 and 24 years of age, and in South Asia and Africa, 1 in 3 people are young. Mental health problems range from 10% to 20% worldwide among children and young people [6]. A study in 27 countries assessed the pooled prevalence of global mental health problems to be 13.4% among children and young people [7]. Disruptive behavior was commonly observed among children and young people. It is estimated that, in young people aged 16-24 years, 1 in 4 has experienced a minimum of 1 mental health issue in the previous year. The literature has shown that young people worldwide are less aware of mental health. To promote the mental well-being of young individuals, there is a need to educate them, raise awareness, and develop interventions [8].

As per the Registrar General of India, 34.8% of India's population is between 15 and 34 years of age, and it is projected to be 34.1% by 2021. In India, in 2017, the prevalence of mental disorders was 197.3 million, which comprised 45.7 million people with depressive disorders and 44.9 million with anxiety disorders [9]. This was due to an increase in issues like nutritional disorders, phubbing, sedentary lifestyles, social media addiction, and substance abuse in lower-income countries. A study has been carried out in rural India to find the effectiveness of delivering evidence-based psychological treatment for depression by training community health workers [10]. One of the prior studies has shown an association between unhealthy eating and anxiety, stress, and depression in university students [11].

Research has demonstrated the usefulness and effectiveness of web-based interventions in youth with mental health issues [8]. It has been seen that young people feel more comfortable gathering mental health information through the internet for sensitive and personal matters. Therefore, studies recommend that there be a need to promote personalized digital health interventions (DHIs). The intervention should have the ability to engage individuals by sending personalized messages, reminders, or alerts to increase motivation. Research has also shown that technology acceptance and user engagement can be increased by using pictures and interactive content [12].

The findings of one study depicted that, to promote well-being to a significant population level, there is a need for intervention and educational programs in all segments of society [13].

However, there is limited literature on DHIs to improve the well-being of youth in India [14,15].

Study Objectives

The following are the proposed study objectives:

1. To examine factors that influence the well-being of individuals aged 18-24 years in an Indian setting
2. To design and develop the web-based platform or stand-alone intervention to enhance the well-being of individuals in the age group of 18-24 years in an Indian setting
3. To evaluate the usefulness and effectiveness of the proposed informatics-enabled decision aid platform to enhance the well-being of individuals aged 18-24 years in an Indian setting

Methods

Study Design and Population

A mixed methods approach will be adopted that uses both qualitative and quantitative data to identify factors influencing the well-being of individuals in the age group of 18-24 years in an Indian setting. In this study, 100 individuals will be enrolled each in the intervention and control group at Uttarakhand and Uttar Pradesh colleges.

We will design and develop the proposed platform using human-centered design principles. Individuals will be randomly allocated to an intervention group (access to the proposed well-being platform) and a control group (standard education). The standard educational material will be mailed to the participants in pdf format on the following topics:

- Importance of physical activity
- Role of a balanced diet
- How to cope with depression, anxiety, and stress
- Steps to lead a healthy life

Study Setting

We will recruit college-going students aged 18-24 years from the states of Uttarakhand (urban Dehradun) and Uttar Pradesh (urban Meerut).

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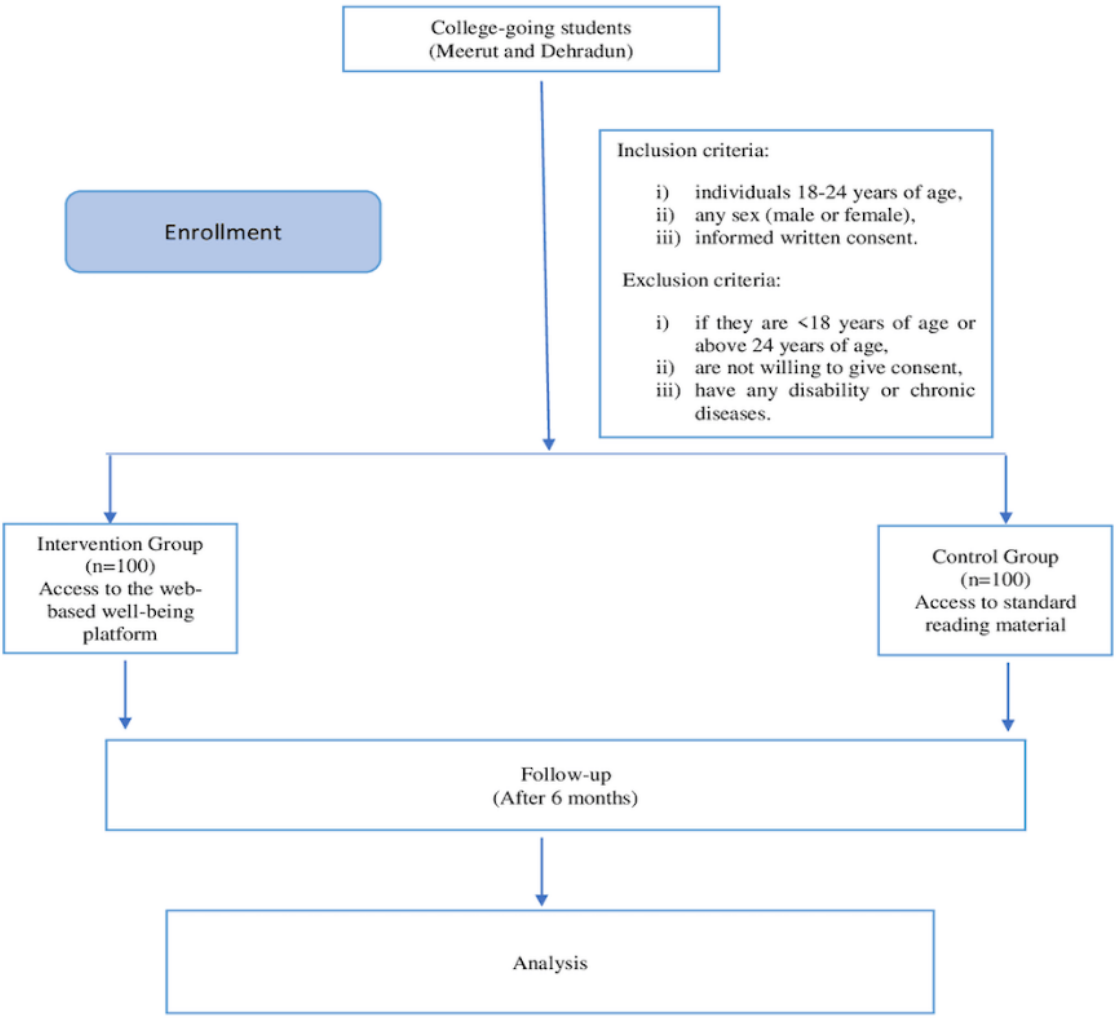
Study Eligibility

The inclusion criteria are as follows: (1) individuals 18-24 years of age, (2) of any sex (male or female), and (3) willing to give informed written consent.

Participants will be excluded if they are younger than 18 years or older than 24 years, are not willing to give consent, or have any disability or chronic diseases. Figure 1 shows a schematic illustration of the methodology.

This study will follow a mixed methods pre- and postapproach for data collection using electronic data collection tools for qualitative and quantitative data from the study participants.

Figure 1. Schematic illustration of the methodology.



Achieving Objective 1

We will conduct 60 in-depth interviews by enrolling participants from Dehradun and Meerut. These interviews will be conducted through Zoom meetings, and the sessions will be recorded after having consent from the participants. Both quantitative and qualitative data will be gathered from the participants. In the interview, the participants will be asked questions to assess their awareness of well-being, the challenges they come across, how they deal with them, and the impact of COVID-19 on their well-being. Each interview will take around 15-45 minutes.

The data collected will help us examine the factors that influence the well-being of students in the age group of 18-24 years. Emphasis will also be placed on understanding individuals' prior knowledge and attitude related to stress, unhealthy diet, and physical inactivity.

The data will be gathered on the following variables: sociodemographic profile, medical history, and anthropometric status; familiarity with technology; health behavior; Depression, Anxiety, and Stress Scale (DASS-21); General Self-Efficacy Scale; psychological well-being scales; global physical activity; and dietary diversity.

In addition, content analysis of the qualitative data will help generate critical themes on the well-being of students in the age group of 18-24 years in an Indian setting.

Achieving Objective 2

We will use principles of a human-centered approach to design and develop a web-based informatics platform to improve the well-being of individuals in the age group of 18-24 years in an Indian setting.

The usability of the web-based informatics platform will be evaluated by individuals who will use it and will provide

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feedback. The literature has shown that a 10-item Likert scale questionnaire called System Usability Scale calculates the usability of websites, mobile devices, hardware, software, and other technological applications. Based on the feedback on usability evaluation, system modification can be done. Finally, the proposed web-based well-being platform will be implemented in a randomized controlled trial to evaluate its usefulness and effectiveness.

Achieving Objective 3

We will perform a randomized controlled trial with 100 college-going students from Dehradun and Meerut each in the intervention and control group. So the total number of students enrolled will be 200. The students will be randomly allocated to either a control group or an intervention group. The students in the intervention group will have access to the web-based well-being platform. A study was carried out to evaluate the efficacy of a web- and mobile-based intervention on college-going students (n=150) [16].

The data will be collected on the following variables: sociodemographics, health behavior, health literacy, depression, stress, anxiety assessments, general efficacy, physical activity, and dietary pattern at baseline and a follow-up at 6 months.

Study Groups

The study participants will be randomly allocated either to the intervention group or the control group.

Intervention Group

The participants in the intervention group will have access to the web-based well-being platform. It can be accessed from an Android smartphone or web-based platform. The proposed platform will have the following components: (1) screening component, (2) learning component, and (3) evaluation component.

- Screening component: Variables recorded in the screening component include sociodemographics; health behavior (eg, physical activity levels and anthropometric assessments); health literacy; family history; familiarity with the use of technology; well-being scale; depression, stress, and anxiety assessments; and self-efficacy levels. In the screening component of the intervention, we will evaluate the health literacy level according to the education that will be given to the individual. Based on the data collected, a well-being index will be constructed to reflect on the variables attributing to the well-being of the youth. As the literature shows, well-being is dependent on various factors and is affected by the physical, social, and economic environment, life experience in every stage, family, poverty, and activity pattern [17,18].
- Learning component: Based on the well-being index generated for each individual, tailored messaging will be done using a series of culturally and contextually relevant messages. In this component, the individuals will get personalized feedback after interpreting the information gathered on all the parameters asked. In addition, they will receive weekly reminder messages to follow healthy behavior for their excellent well-being.
- Evaluation component: We will assess the usefulness and acceptance of the system using the system usability scale and monitor the usage. In addition, we will determine youth well-being using the well-being scale at baseline and a follow-up at 6 months.

Informed Consent

The ethics committee of the university has approved the informed consent form. The research team will obtain the consent from all the individuals participating in the study. The research team will also explain them the analysis, duration, and need of the study. Individuals who are willing to participate will be asked to sign the consent form, and a copy of the consent form with study details will be given to them. The study is on college-going students, so everyone will be able to read and write. The research team is aware of both English and Hindi language, so they will be able to understand the response. The data captured will be stored safely and protected. The confidentiality of data will be maintained. The participants will be allowed to withdraw from the ongoing study anytime by giving reasons to withdraw. All the data gathered, including those from the participants who will withdraw, will be reported for the final analysis. No monetary compensation will be given to the participants enrolled in the study. The voluntary participation and time of the participants will be respected.

Data Collection, Data Entry, and Quality Assurance

The data will be collected and entered by following standard techniques and protocols. Complete confidentiality of the information obtained from the study participants will be ensured. Frequent backups will retain all the data gathered, and all computers and specific data files will be password protected and kept in a locked file cabinet.

Variable Assessment

Sociodemographic and Family History

The questionnaire included questions regarding the demographic factors of the respondents, like age, sex, family history, educational status, occupation, and income levels.

Health Behavior

Four crucial behavioral risk factors will be collected: tobacco consumption, alcohol consumption, impact of COVID-19, and sleep duration.

Familiarity With Technology

Individual assessment will include access to the type of smartphone, familiarity with the use of the internet, and knowledge of texting.

Anthropometric Measurements

Variables assessed include duration of diabetes, recent blood sugar report, type of medication, and height and weight measures that would help calculate BMI.

The measures in Textbox 1 will be administered.

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Textbox 1. Measures to be used.

Sociodemographic and family history
Age; sex; educational status; religion; income, if any; parents' occupation
Health literacy
Rapid Estimate of Adult Literacy in Medicine scale
Familiarity with technology
Access to the smartphone and internet and knowledge of texting
Health behavior
Information on smoking, alcohol, physical activity, and substance abuse disorders
Well-being scale
Ryff scale
Depression, stress, and anxiety assessments
Depression, Anxiety, and Stress Scale
Self-efficacy
General Self-Efficacy Scale
Dietary diversity
Food and Nutrition Technical Assistance Diet Diversity
Anthropometric measurements
Height, weight, BMI
Physical activity
Global Physical Activity Questionnaire
System usability
System Usability Scale

Data Security and Privacy

The data security will be done through regular backups, and all computers and specific data files will be password protected and kept in a locked file cabinet. In addition, the computers in which data is stored will be password protected and safely stored for 3 years after the completion of the study.

Outcomes

The well-being index generated from this study can be used in other geographic regions for a similar population. If the youth of a nation is healthy, it will lead to the country's growth.

The primary outcome of the study will be development of the student well-being index among urban settings. This will also facilitate the understanding of the various factors that affect the student well-being.

The secondary outcome of this study will further help us to understand the relationship between sociodemographic factors with dietary diversity, physical activity, depression, stress, and anxiety among college-going students.

A cross-sectional study was conducted, and the results showed significant associations between physical activity levels and sleep quality with mental health. The mental health issues are the same in both male and female college students [19].

The outcomes will be assessed by using the following tools.

Health Literacy

Health literacy is defined as the cognitive and social skills that determine the motivation and ability of individuals to gain access to, understand, and use information in ways that promote and maintain good health [20]. Conversely, low literacy can create misunderstanding of the environment and impact health outcomes [21].

Health literacy requires acquiring information, processing it, and then understanding the data to develop the reasoning required to make the decision. Many studies have shown that literacy level is related to cost and health characteristics like knowledge, health status, and health facilities. However, little work has been done on the health literacy of adolescents and young adults. The literature also shows the association between poor health literacy and adverse health outcomes such as smoking and obesity [22].

The Rapid Estimate of Adult Literacy in Medicine is one of the most accepted tests to assess health literacy. This test is performed by seeing the patient's potential to pronounce 66 words, including lay terms for parts of the body, illnesses, and common medical words. It is a quick tool that can be administered in less than 2 minutes. As a result, it is one of the most popular tools for assessing health literacy levels. The scoring is divided into 2 groups: 0-44=low health literacy and 45-66=higher health literacy.

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Well-being Scale

The Ryff scale is a 42-item scale that measures 6 dimensions of well-being and happiness: environmental mastery, self-acceptance, purpose in life, positive relations with others, autonomy, and personal growth [20].

Depression, Anxiety, and Stress Scale

A randomized control trial was conducted on young adults to reduce the symptoms of depression with a brief diet intervention. In this study, the DASS-21 tool will be used to assess the symptoms of depression [23].

This scale evaluates depression, anxiety, and stress associated with a negative emotional situation. It is a 42-item self-report questionnaire that has been concise to a scale of 21. It measures on a 0-3 pointing scale, where 0 is for "did not apply to me" and 3 stands for "applicable to me or majority of the time."

Dietary Diversity

In lower-income countries, dietary diversity tools are used to study dietary adequacy. Dietary diversity is a significant problem among poor people as they usually consume starchy staples with or without limited consumption of animal products, fruits, and vegetables [24].

The Food and Nutrition Technical Assistance Diet Diversity score will be computed based on the information obtained regarding consuming several food items within each food group.

General Self-Efficacy Scale

It is a 10-item tool validated in Asia [7]. It can also be applied to diverse cultural backgrounds and positively correlated with depression, anxiety, and optimism. To calculate the total score, the total of all items is considered. The total score ranges between 10 and 40, with a higher score indicating more self-efficacy. It is universally accepted and considered an adequate scale to measure self-reported self-efficacy. A relation has been seen in general self-efficacy and social cognitive variables, health behavior, and well-being [25,26].

International Physical Activity Questionnaire

The International Physical Activity Questionnaire is considered a validated tool to monitor physical activity among youth and older adults in diverse settings [27].

The participants will complete the questionnaire so that their physical activity can be assessed. The total time spent in physical activity for recreation, occupation, household work, and transportation in the past 7 days will be calculated. The total weekly physical activity (metabolic equivalents of task [MET-hour/week]) will be calculated as the weighted sum of the reported time spent at each intensity using an MET value specific to each category.

Data Analysis Plan

The data gathered at baseline will include sociodemographics, KAP (knowledge, attitude, and practice), diet assessment, physical activity, health literacy, social media, and familiarity with technology. Baseline and follow-up data collected will be statistically analyzed.

For continuous and categorical variables, means and SDs and frequencies, respectively, will be calculated. Finally, cross-tabulation of the data from the intervention group against outcome variables will be done to calculate the direction and degree of association in this initial stage. The analysis will be done using SAS v9.3 (SAS Institute), and the results will be reported at 95% CIs and P=.049.

Project Timeline and Milestone

A detailed timeline is presented in Table 1.

Table 1. Scheduled timeline of the tasks in the study.

Tasks involved	Timeline (months)							
	1-3	3-5	5-7	7-9	9-15	15-17	17-20	20-22
Focus group discussion and analysis	✓	—[a]	—	—	—	—	—	—
Content creation for the web-based platform	—	✓	—	—	—	—	—	—
Design and development of the web-based platform	—	—	✓	—	—	—	—	—
Heuristic and usability evaluation	—	—	—	✓	—	—	—	—
Data collection	—	—	—	—	✓	—	—	—
Analysis of data	—	—	—	—	—	✓	—	—
Thesis writing and manuscript preparation	—	—	—	—	—	—	✓	—
Dissemination	—	—	—	—	—	—	—	✓

[a]Not applicable.

Ethics Approval

This study has received ethical approval from the University Research Ethics Committee of Dehradun Institute of Technology University, Dehradun, India (Protocol DITU/UREC/2021/07/9, dated July 21, 2021). The study results will be presented at conferences and webinars to disseminate information to researchers. The results will also be published in national and international scientific journals.

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Results

This study will bring forward the factors that influence the well-being of individuals aged 18-24 years. The 60 in-depth interviews had been conducted by September 30, 2022. Thematic analysis of the qualitative data gathered through the in-depth interviews will be performed. The evidence-based well-being index will be generated for the youth.

Discussion

Principal Findings

This research will help understand the factors that influence the well-being of individuals aged 18-24 years. It will also provide in-depth information on the barriers and challenges among youth for well-being. As this is the most critical period of their development, these barriers and challenges will affect their productivity and will indirectly affect their families and community if left unresolved. The findings of this study will help in the design and development of a web-based platform or stand-alone intervention to enhance the well-being of individuals and evaluate the usefulness and effectiveness of the proposed informatics-enabled decision aid platform to improve well-being in the age group of 18-24 years in an Indian setting.

Well-being is the fundamental human goal, which includes feeling good and functioning well [28]. Considering all the variables on which data have been collected, we will develop the well-being index. The World Health Organization-5 Well-Being Index is a simple, short measure of subjective well-being. This scale is used for screening for depression [29] and will also consider other aspects of well-being.

The well-being index generated from this study can be used in other geographic regions for similar populations. If the youth of a nation is healthy, it will lead to the country's growth.

Limitations

The first limitation of this study will be the recalling bias as the participants have to fill out the questionnaires on their own. Second, the small sample size will make it difficult to generalize the results on a large number of students.

The study results will be presented at conferences and webinars to disseminate information to researchers. The results will also be published in national and international scientific journals.

Conclusions

This study will be able to bridge the gap of well-being in college-going students. It is seen that mental health issues are prevalent in low- and middle-income countries due to lack of mental health care. It has a negative impact on the academic performance of university students [30]. As digital health technologies are getting popular and will play a key role in future, it is important that a multidisciplinary approach should be undertaken; only this can bring a change from digital health to digital well-being [31].

The evidence-based digital mental interventions that can be implemented using smartphones or web-based platforms are required for college-going students as they can reduce the existing barriers to getting traditional mental health services that include time and sigma as well [32].

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Conflicts of Interest

None declared.

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Abbreviations

DASS: Depression Anxiety Stress Scale
DHI: digital health intervention
MET: metabolic equivalents of task

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Protocol

A Relational Agent Intervention for Adolescents Seeking Mental Health Treatment: Protocol for a Randomized Controlled Trial

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Abstract

Background: Unmet pediatric mental health (MH) needs are growing as rates of pediatric depression and anxiety dramatically increase. Access to care is limited by multiple factors, including a shortage of clinicians trained in developmentally specific, evidence-based services. Novel approaches to MH care delivery, including technology-leveraged and readily accessible options, need to be evaluated in service of expanding evidence-based services to youths and their families. Preliminary evidence supports the use of Woebot, a relational agent that digitally delivers guided cognitive behavioral therapy (CBT) through a mobile app, for adults with MH concerns. However, no studies have evaluated the feasibility and acceptability of such app-delivered relational agents specifically for adolescents with depression and/or anxiety within an outpatient MH clinic, nor compared them to other MH support services.

Objective: This paper describes the protocol for a randomized controlled trial evaluating the feasibility and acceptability of an investigational device, Woebot for Adolescents (W-GenZD), within an outpatient MH clinic for youths presenting with depression and/or anxiety. The study's secondary aim will compare the clinical outcomes of self-reported depressive symptoms with W-GenZD and a telehealth-delivered CBT-based skills group (CBT-group). Tertiary aims will evaluate additional clinical outcomes and therapeutic alliance between adolescents in W-GenZD and the CBT-group.

Methods: Participants include youths aged 13-17 years with depression and/or anxiety seeking care from an outpatient MH clinic at a children's hospital. Eligible youths will have no recent safety concerns or complex comorbid clinical diagnoses; have no concurrent individual therapy; and, if on medications, are on stable doses, based on clinical screening and as well as study-specific criteria.

Results: Recruitment began in May 2022. As of December 8, 2022, we have randomized 133 participants.

Conclusions: Establishing the feasibility and acceptability of W-GenZD within an outpatient MH clinical setting will add to the field's current understanding of the utility and implementation considerations of this MH care service modality. The study will also evaluate the noninferiority of W-GenZD against the CBT-group. Findings may also have implications for patients, families, and providers looking for additional MH support options for adolescents seeking help for their depression and/or anxiety. Such options expand the menu of supports for youths with lower-intensity needs as well as possibly reduce waitlists and optimize clinician deployment toward more severe cases.

Trial Registration: ClinicalTrials.gov NCT05372913; https://clinicaltrials.gov/ct2/show/NCT05372913

International Registered Report Identifier (IRRID): DERR1-10.2196/44940

(JMIR Res Protoc 2023;12:e44940) doi:10.2196/44940

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KEYWORDS

adolescent; digital health; cognitive behavioral therapy; CBT; chatbot; feasibility; therapeutic alliance; depression; anxiety; relational agent; mental health care; intervention; agent; youth; teenager; mental health; treatment; protocol; feasibility; randomized controlled trial; acceptability; telehealth; outcome; utility

Introduction

Background

In 2021, leading child-focused organizations declared a national emergency in child and adolescent mental health (MH) [1], echoed by the Surgeon General's advisory on youth MH [2]. The prevalence of MH concerns among youths has increased exponentially since the onset of the COVID-19 pandemic [1], with recent estimates indicating a doubling of clinically elevated depression and anxiety symptoms [3]. Depression onset in adolescence confers risk for long-term depression as well as other psychiatric sequelae [4,5]. Similarly, persistent untreated anxiety in adolescence can interfere with typical development, potentially affecting the foundation for longer-term well-being, resilience, and functioning [6]. The World Health Organization states that depression and anxiety are the leading cause of illness and disability among adolescents [7], but only 41.6% of adolescents with a major depressive episode were treated in the past year [8]. Lack of access to child MH clinicians skilled in high-quality, evidence-based psychotherapy is an unfortunately common and familiar treatment barrier for many adolescents [9]. The rising incidence of MH concerns coupled with unmet needs for care underscores that innovative alternative approaches for adolescent MH care are urgently needed.

"Stepped care," a MH service delivery approach recommended by the National Institute for Health and Care Excellence, suggests that individuals (including youths) with lower-acuity symptoms initially receive low-intensity services, such as guided self-help, bibliotherapy, or brief therapeutic or supportive interventions, as the first "step" in their care [10]. Those with initial higher-acuity or persistent symptoms after low-intensity intervention receive more intensive services. Stepped care models attempt to distribute limited clinical intervention resources optimally [10]. Early low-intensity intervention options may include technology modalities such as smartphone app-delivered interventions. Integrating such technology-leveraged treatment options within a health care ecosystem increases the total continuum of service offerings and may reduce waitlists as well optimize clinician deployment toward more severe cases.

Technology-Leveraged MH Care Interventions

Decades of research and treatment guidelines suggest that cognitive behavioral therapy (CBT) is the treatment of choice for adolescents with depression and/or anxiety [11,12]. Indeed, CBT is efficacious when delivered in guided self-help and group-based formats [13,14] or via telehealth [15]. Computer-delivered, rather than clinician-delivered, CBT programs are also effective among an adolescent population [16]. However, these programs suffer from poor adherence, as well as limited tailoring and interactional styles typical in CBT treatment [17,18]. Recently, the availability of MH applications for youths, including video games, mood trackers, journals, and text-based solutions [16], has grown exponentially, yet data on their clinical efficacy remain limited. More meaningful interactions may be possible through the use of interactive technology, such as conversational agents. This may be particularly advantageous in adolescent MH interventions, as this group is well-versed in conversational agent and texting interactions [19]. Such interactions may improve users' treatment responsiveness to interventions [20,21].

Woebot for Adolescents (W-GenZD) is an investigational mobile app with a relational agent, "Woebot," that offers a CBT-guided self-help program designed to reduce symptoms of depression and/or anxiety. Although primarily based in CBT, W-GenZD also includes elements of other well-researched and scientifically validated psychotherapeutic interventions including interpersonal psychotherapy for adolescents and dialectical behavior therapy [22,23]. Previous research on other Woebot programs have demonstrated feasibility, acceptability, and preliminary efficacy among various populations including young adults with depression [18], adults with substance abuse concerns [24], and adult women with postpartum mood concerns [25]. A retrospective analysis with over 35,000 adults found that users reported forming a therapeutic alliance with Woebot [20]. Therapeutic alliance, a construct familiar in psychotherapeutic treatment outcomes research, refers to the therapeutic relationship and affective bond between provider and patient and is associated with the efficacy of psychotherapy [26,27]. A randomized controlled pilot among adolescents aged 13-17 years (n=17) demonstrated W-GenZD's preliminary feasibility and utility in an outpatient primary care pediatric setting [28], but further evaluation of its feasibility and acceptability as well as clinical efficacy is warranted.

The proposed study (trial registration: ClinicalTrials.gov NCT05486611) seeks to understand the feasibility and acceptability of W-GenZD among adolescents seeking treatment for depression and anxiety. The study will also compare 2 forms of technology-leveraged interventions, W-GenZD and brief telehealth-delivered CBT-based skills group (CBT-group), among adolescents presenting with depression and/or anxiety. Both interventions are conceptualized as potential "first-step" interventions within a stepped care model. The setting for the study is an outpatient children's hospital that currently deploys a brief telehealth-delivered CBT-group as a first step for youths screened and triaged into low-intensity intervention.

Methods

Objectives

The primary aim of this randomized controlled study will be to evaluate the feasibility and acceptability of W-GenZD for adolescents with depression and/or anxiety in an outpatient children's hospital system. Feasibility and acceptability will be assessed through self-report measures rating intervention feasibility, acceptability, and satisfaction, as well as study

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enrollment, app engagement, and group attendance. The secondary aim will be to compare the clinical impact of both the W-GenZD and skills group to reduce depression symptoms at 4 weeks end of treatment (EOT) relative to baseline (BL), with a corresponding hypothesis that W-GenZD will be noninferior to the skills group. As tertiary aims, therapeutic working alliance, mood, and anxiety levels in both groups will be assessed. Exploratory aims will include the observation of the utilization and performance of the safety procedures utilized within this study (please see below for a description of the safety net protocol and adverse event and serious adverse event assessment).

Study Design

This study will randomize adolescents aged 13-17 years seeking treatment for depression and/or anxiety to the W-GenZD or CBT-group. The study will include 3 core assessments at screening/BL, EOT at week 4, and end of study (EOS) at week 8, plus 2 brief surveys to be completed 5 days and 2 weeks after randomization. The primary outcomes for feasibility and acceptability will be assessed at EOT; app engagement and group attendance metrics will be collected throughout the intervention period. Self-reported depression symptoms (secondary aim) will be collected via the 8-item Patient Health Questionnaire (PHQ-8) [29] at BL, week 2, EOT, and EOS. Therapeutic working alliance (tertiary aim) will be assessed at day 5 as well as at EOT. Mood and anxiety levels (tertiary aims) will be assessed via the Mood and Feelings Questionnaire (MFQ) [30] and Generalized Anxiety Disorder questionnaire (GAD-7) [31], respectively, at BL, EOT, and EOS. Exploratory outcomes, specifically the utilization of safety procedures will be collected throughout the study.

Ethics Approval

This study was reviewed and approved by WIRB-Copernicus Group institutional review board on March 31, 2022 (#20221397). Subsequent modifications were implemented to refine eligibility criteria, enhance recruitment language, and provide further clarification within the informed consent forms.

Study Population

Study Setting

The study site is a 206-bed, freestanding not-for-profit children's hospital and the heart of an integrated pediatric health care system. Situated in the southeastern United States, the hospital serves a racially and economically diverse region that is home to approximately 500,000 youths younger than the age of 21 years. The outpatient practice's stepped care model begins with a semistructured brief clinical needs assessment, which identifies unmet basic needs and the level of care needed. Youths who meet 1 or more of the following criteria indicate a higher level of needs and are fast-tracked to comprehensive assessment and individual treatment: have had suicidal ideation within the last 2 weeks or is a current risk to self/others, present symptoms of psychosis, meet criteria for an active eating disorder, have a history of mania, have a substance use disorder as the primary clinical problem, are at an imminent risk of expulsion, or are currently prescribed 4 or more psychotropic medications. Most patients with routine level of needs are offered low-intensity, telehealth skill-based group interventions while waiting for individual treatment. Patients who decline or are not appropriate for the specific groups are placed on a waitlist for individual treatment. The proposed study did not influence or change these prescreening criteria.

Recruitment

Youths with low-intensity needs who are not currently in therapy and who have not had recent medication changes are invited to learn more about the proposed study. Families receive information about the study through a flyer in a practice registration packet, the elevators, and waiting room. Caregivers of all children seen in the practice are invited to provide verbal or written consent for contact from the research team for more information about the study. Clinicians are encouraged to provide information about the study after the initial clinical needs assessment for youths who may be eligible. Study staff will reintroduce the study over the phone and assess the family's (adolescent and parent/guardian) interest in participating.

In terms of waiting list management, participants in need of additional care are able to access individual treatment after the study concludes. If a waiting list opening becomes available during the study, participants are informed of this and can choose to accept it. If accepted, they are withdrawn from the study. If participants access treatment from another provider during the study, they are withdrawn from the study.

Inclusion and Exclusion Criteria

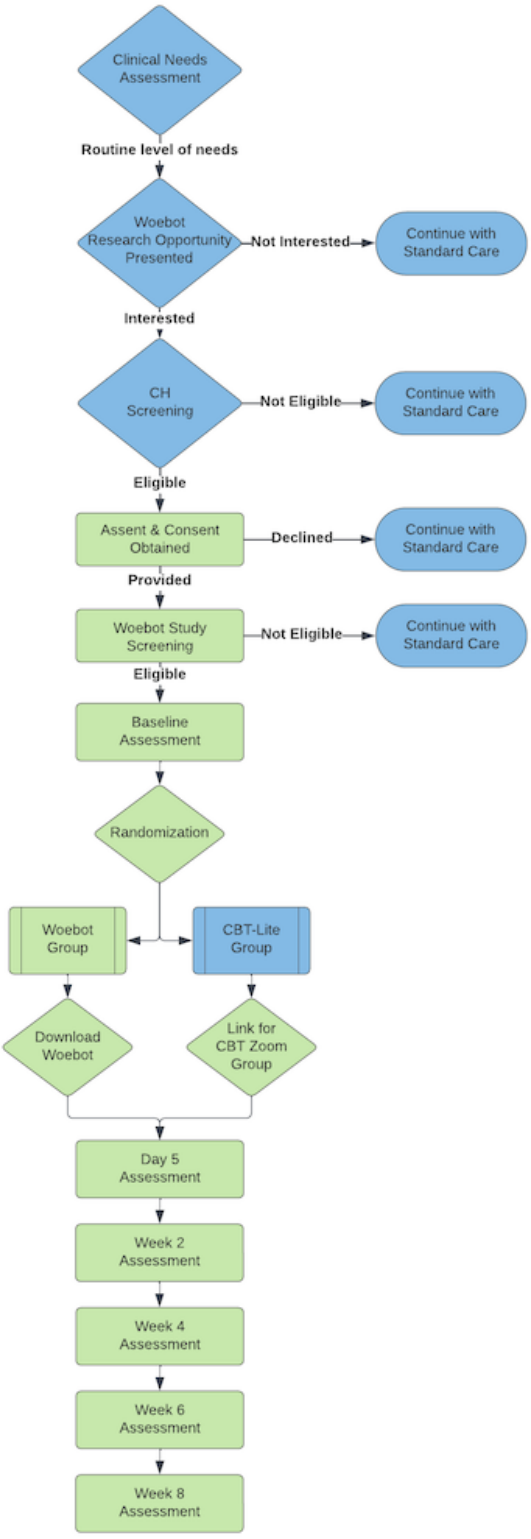
Youths eligible for participation in the proposed study must also meet all of the following study-specific inclusion criteria: (1) have a routine level of need based on a brief clinical needs assessment; (2) have a diagnosis of depression and/or anxiety; (3) be 13-17 years of age, inclusive; (4) be a US resident; (5) be able to read and write in English (adolescent and parent/guardian); (6) own or have reliable access to a smartphone and reliable Wi-Fi access or sufficient data to engage with assigned treatment condition for the duration of the study; (7) be on a stable dose of any psychiatric medications for at least 60 days; (8) not be currently engaged in psychotherapy; (9) be available and committed to engaging with the program and complete assessments for an 8-week duration; and (10) have a family member who can engage in the discussion of safety planning in the event of suicidal ideation.

Youths who meet any of the following exclusion criteria will not be eligible for participation: (1) lifetime diagnosis of a psychotic disorder (including schizophrenia or schizoaffective disorder), bipolar disorder, autism spectrum disorder, or pervasive developmental disorder; (2) current diagnosis of developmental delay or intellectual disability; (3) reported suicidal ideation with a plan or intent or a suicide attempt within the past 12 months; (4) history of diagnosis of substance abuse within the past 12 months; (5) current use of benzodiazepines or certain sleep aids (zolpidem, eszopiclone, and zaleplon); (6) previous Woebot application use; and (7) enrollment of more than 1 member of the same household. Participants who meet all inclusion criteria and none of the exclusion criteria will complete BL assessments and be randomly assigned to a study

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treatment condition. Figure 1 shows the participant flow through the study.

Figure 1. Participant flow through the study. CBT: cognitive behavioral therapy; CH: children's hospital.



Sample Size

The noninferiority analysis for comparing the 2 study conditions will be based on self-reported depressive symptom (PHQ-8) outcomes. In contrast, an exploratory analysis will be conducted on self-reported anxiety symptom (GAD-7) outcomes. In order to perform the noninferiority analysis, 260 participants (130 participants/arm) will be enrolled. Group sample sizes of 86 and 86 will achieve 81% power to detect noninferiority using a 1-sided, 2-sample *t* test. The margin of noninferiority is 2.0 [32]. The actual difference between the means is assumed to be –0.5. The significance level (α) of the test is .025. The data are drawn from samples with SDs of 5.3 and 4.3. Based on a sample size estimate of 172, the final sample size was set to 260 to

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account for 33% attrition (current recruitment status is provided in the *Results* section).

Randomization and Masking

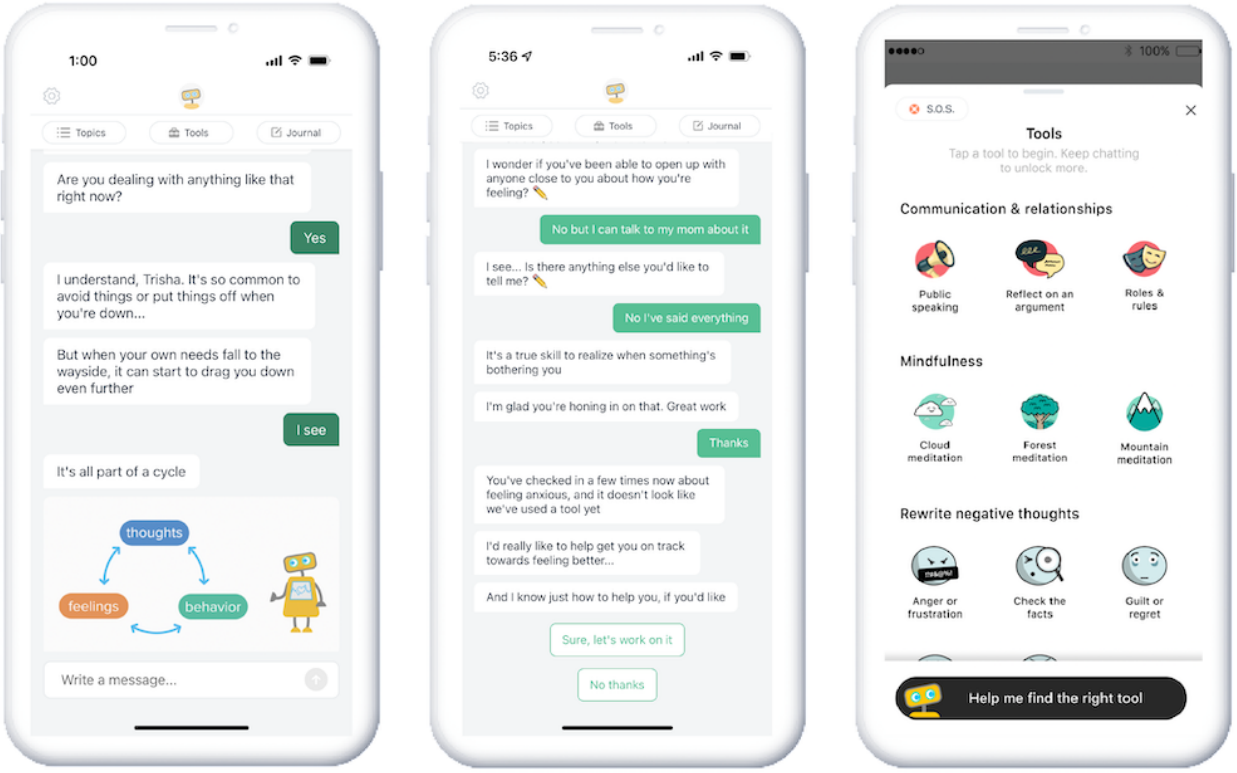
Adolescents who meet inclusion criteria will be randomized 1:1 to the treatment groups. All clinical outcome measures are completed directly by participants accessing links to the measures in an electronic data capture platform. Neither participants nor staff are blinded to group assignment.

Interventions

W-GenZD App

W-GenZD is accessible as an iOS or Android app and is a relational agent–guided self-help program. It is only available to study participants using an access code for the investigational device. Using proprietary natural language processing and artificial intelligence, Woebot, the relational agent embedded in W-GenZD, guides users through a program that is personalized each day, in real time, to the user's needs. Push notifications will prompt users to check in, and the cadence is based on the level of user activity (higher activity=higher cadence). The W-GenZD user experience is centered around mood and symptom tracking and goal-oriented conversations with Woebot. These conversations are tailored to the adolescent's real-time report of the presenting situation, to help the adolescent develop emotion regulation skills in the context of their everyday life for the problem at hand, in their moment of need (see Figure 2). Users become familiar with Woebot as a friendly, helpful character that is explicitly not a human nor a therapist. Participants in the W-GenZD arm of the study will have access to W-GenZD for 4 weeks after randomization and are encouraged to use the app for a minimum of 5-10 minutes per day during the treatment period.

Figure 2. Screenshots of Woebot for Adolescents (W-GenZD), including examples of tools available to users.



Safety Considerations

W-GenZD follows safety recommendations from the American Psychiatric Association [33] and American Medical Association [34]. W-GenZD's safety features include providing the app's privacy policy and terms of service, informing the user that they are talking to a robot and not a real person, stating that the app is not a crisis intervention for suicidal ideation, encouraging them to seek additional support if they are feeling unwell, and providing helplines for assistance. In addition, W-GenZD's "safety net protocol" is based on a natural language processing algorithm that is designed to detect concerning language. The algorithm detects if a user inputs, via free-response text entry, concerning phrases or words that match an a priori identified and thorough list that may be used in crisis situations. When this occurs, the user is reminded that the app is not a crisis intervention service and helplines for additional support are offered.

For the purposes of this study, we have developed an escalation procedure that combines W-GenZD's language detection capabilities with follow-up by trained clinicians. After the algorithm detects concerning language and if the adolescent confirms this, Woebot will let the adolescent know that someone on the hospital's care team will be notified. W-GenZD will then send a Health Insurance Portability and Accountability Act (HIPAA)–compliant alert to designated clinical staff who will be on call to provide 24/7 follow-up of these messages. The licensed clinician on the study team will contact the adolescent, assess their safety and well-being, and refer to emergency services as necessary. Triage decisions resulting from the

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follow-up assessment will be logged separately, in accordance with the hospital's standard procedures. Participants will continue in the study if they continue to meet the study inclusion criteria and do not require a higher level of care.

Study personnel may also learn of participant safety concerns in CBT-groups or by family or participant reports to the study team. In these instances, the follow-up procedure will be the same; the licensed clinician will contact the adolescent to assess their safety and well-being, with triage as needed and corresponding documentation.

Brief Telehealth-Delivered CBT-Group

The open CBT-groups are a rotating, 4-week intervention held once weekly for an hour. At least 2 groups are offered per week to allow the participants to attend the one that best fits their schedule. A licensed clinician facilitates each teletherapy group with up to 10 adolescents in each session. Group sessions begin with orientation and reviewing group rules, individual check-ins with each participant (rating stress level and hopefulness), followed by a guided mindfulness moment. Group attendees may choose to have their cameras on or off during group sessions but will be asked to have their cameras turned on for introductions and again at the very end of the session before they leave.

Groups are conducted on an open enrollment, rolling topic basis, allowing participants to join the next available session following randomization and complete all 4 sessions during their study treatment period. The 4 topics include: (1) building a coping toolbox, (2) accepting your feelings, (3) challenging negative thoughts, and (4) problem-solving.

The decision to use a 4-week CBT intervention was made to ensure that the duration of intervention of W-GenZD and CBT-group were equivalent. Both interventions are considered brief in duration.

Measures

There will be 5 categories of measures that will be collected in this study: participant demographics and psychiatric history, feasibility and acceptability, clinical outcomes, safety data and engagement. Table 1 describes each category and its included measures, the source and content of data for each measure, and corresponding administration points. Participants complete assessments at BL, day 5, week 2, week 4 (EOT), and week 8 follow-up (EOS). After EOT, participants will no longer participate in the CBT-group nor have access to W-GenZD. Parents participate in telephonic check-ins at weeks 2, 4, 6, and 8 to identify changes in their child's medications or logistical or safety concerns; if the latter is identified, the aforementioned safety follow-up protocol is initiated. Participants will receive reminders via email and SMS text messages for assessments with corresponding links to the surveys. Participants can be compensated up to US $125 in Amazon gift cards for the completion of all assessments.

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Table 1. Assessment measures and administration schedule.

Assessment type and measure	Description	Administration
Participant demographics and psychiatric history		
Survey questions	• Demographic: gender and sexual identity, racial and ethnic background, highest level of education completed, etc • Psychiatric history: psychiatric diagnoses and any prior or concomitant medications and prior therapy	BL[a]
Feasibility and acceptance		
Client Satisfaction Questionnaire [35]	• 8-item measure used to assess client's satisfaction with treatment on a 4-point scale (1="very dissatisfied" to 4="very satisfied") [35]	EOT[b]
Satisfaction Questionnaire	• 3 open-ended questions about what they found most helpful about their treatment, what would make it better, and if there is any other feedback they would like to share	EOT
URPI[c]-Feasibility and URPI-Acceptability (from the URPI-Revised scale [36])	• 6-item subscales inquire about factors that impact treatment usage (ie, intervention quality)	BL and EOT
Clinical outcomes		
PHQ[d] [29]	• Abbreviated version of the PHQ-9, the PHQ-8, will be used to assess mood and anxiety symptoms	BL, week 2, EOT, and EOS[e]
GAD[f] [31]	• Self-report tool to assess the frequency and severity of anxious thoughts and behaviors over the past 2 weeks; it is a widely utilized, reliable, and valid measure of anxiety	BL, EOT, and EOS
MFQ[g] [30]	• Short version is a child self-report assessment consisting of a series of 13 descriptive phrases related to the participant's recent feelings and behaviors	BL, EOT, and EOS
WAI-SR[h] [37]	• 12-item Working Alliance Inventory–Short Revised version with minor changes to language, replacing "therapist" with the name of the assigned treatment group measure of therapeutic bond; consists of a composite score and 3 subscales: Bond, Goal, and Task	Day 5 and EOT
Safety data		
Incident reports	• Utilization data, including frequency, type, and outcomes to report on incidents of "safety net protocol" triggers and the occurrence and relatedness of adverse events or serious adverse events	Throughout study
Engagement		
W-GenZD[i] use and CBT-group[j] attendance	• W-GenZD: days in app and content engagement • CBT-group attendance	Throughout treatment until EOT

[a]BL: baseline.

[b]EOT: end of treatment.

[c]URPI: Usage Rating Profile–Intervention.

[d]PHQ: Patient Health Questionnaire.

[e]EOS: end of study.

[f]GAD: Generalized Anxiety Disorder.

[g]MFQ: Mood and Feelings Questionnaire.

[h]WAI-SR: Working Alliance Inventory.

[i]W-GenZD: Woebot for Adolescents.

[j]CBT-group: cognitive behavioral therapy–based skills group.

Data Collection

All study data, from participant self-report and on-site study personnel, are gathered through a HIPAA-compliant survey and electronic data capture platform. All data obtained via the mobile app will be encrypted and stored on Amazon Web Services and/or Google Cloud Platform; Woebot Health data-gathering and storage procedures are compliant with both HIPAA and the

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European Union's General Data Protection Regulation. Only members of the research team will have access to identifiable study data. Deidentified data will be accessible to the product development team (designers, user researchers, and product managers) as well as the research team.

Statistical Analysis

Data will be reported per treatment arm and overall, for all time points in the study. For continuous variables, means and SDs will be reported if the data are normally distributed; for nonnormal data, medians and IQRs will be reported. For categorical variables, frequencies and percentages will be reported.

To assess the primary aim (feasibility and acceptability of W-GenZD), the descriptive statistics to be reported include the Usage Rating Profile–Intervention (URPI), Client Satisfaction Questionnaire, Satisfaction Questionnaire, and URPI-Feasibility and URPI-Acceptability scales, as well as app engagement and group attendance metrics. For the secondary aim (comparison of the clinical impact of W-GenZD and the skills group to reduce depression symptoms), a test of noninferiority (1-sided) will be used to determine if EOT PHQ-8 change scores for W-GenZD are noninferior to the CBT-group. α will be set to .025. CIs will be reported for the EOT clinical outcomes. The main analyses will be conducted within the intent-to-treat group and with a sensitivity analysis in the per-protocol group. If the data are nonnormally distributed, a suitable nonparametric model will be used. For the tertiary aim (assessment of therapeutic working alliance, mood, and anxiety levels in both groups), descriptive statistics will be reported for the Working Alliance Inventory–Short Revised version, GAD-7, and MFQ at all time points.

Additional sensitivity analysis will be performed. Although randomization should ensure the equality of the 2 groups at BL, tests of potential between-group differences will be conducted. If differences are found, a regression-based approach will be used for the noninferiority test-based CIs. Any BL covariate where a significant difference between the 2 treatment groups was achieved would be input into the model. If the model is a poor fit, a suitable nonparametric alternative will be selected. All statistical analyses will be performed using R statistical software (R Foundation for Statistical Computing).

Results

Recruitment began in May 2022. At the time of submitting this paper for review (December 8, 2022), we have randomized 133 participants. The study's a priori planned end of recruitment date was November 30, 2022, which has been extended to December 16, 2022, to allow for those presently in the queue in the children's hospital screening process to be assented/consented and screened for study eligibility. Final enrollment numbers will be reported in the outcome's manuscript.

Discussion

Significance of Study

This paper describes the rationale, design, and corresponding methodology for testing the feasibility and acceptability of W-GenZD, which includes Woebot, a relational agent that offers a CBT-guided self-help program delivered through a smartphone app. Embedding the study within a MH treatment environment, a children's hospital's outpatient MH clinic, allows for learnings specific to real-world clinical practice settings. In this study, adolescents diagnosed with depression and/or anxiety and who are treatment seeking will be randomized to 1 of 2 technology-leveraged treatments, W-GenZD or CBT-group, both of which are potential "first step" interventions within a stepped care treatment paradigm. Participants in the study must meet both existing criteria for participation in a low-intensity treatment as well as the study-specific inclusion and exclusion criteria. Thus, enrolled youths randomized in the study are representative of treatment-seeking youths with depression and anxiety within this hospital's community. This study will also evaluate if the outcomes yielded by the W-GenZD and brief telehealth-delivered CBT-group are analogous. We anticipate that W-GenZD will be noninferior to the CBT-group in reducing adolescent depression (PHQ-8) at 4 weeks. We will also explore self-reported mood (MFQ) and anxiety symptom levels (GAD-7) in both treatment groups as a tertiary aim.

Working alliance has been long identified and studied as an important construct in the psychotherapeutic literature, including across treatment modalities and theoretical foundations. Not only has it been associated with positive treatment outcomes, but it also holds face validity as a meaningful manifestation of a productive and aligned therapeutic relationship. Previous data demonstrated Woebot's ability to establish and sustain working alliance at levels analogous to human-delivered CBT interventions [20]. The inclusion of working alliance in this study allows for further exploration of this construct as it applies to a sample of treatment-seeking adolescents diagnosed with depression and/or anxiety engaged in a technology-supported MH intervention. By evaluating therapeutic alliance levels in both study conditions, we can gain a greater understanding of therapeutic bonding in both a relational agent and a telehealth-delivered brief CBT-group, with the latter being a more relatively familiar group treatment modality. In future work, the potential relationship of therapeutic alliance to improvement in symptoms among adolescents can be explored.

This protocol integrates a real-world safety assessment into the use of W-GenZD as well as the CBT-group to ensure a safety net is available to adolescents who may express ideation of self-harm. This allows the study of responses to safety concerns with a vulnerable research population receiving either a relational agent (W-GenZD) intervention or a telehealth-delivered group CBT intervention. The application and refinement of this protocol may provide an opportunity for the expansion of real-world digital MH intervention to other adolescent clinical populations.

This study goes beyond self-report measures alone and will invite perspectives from both caregivers and adolescents. This

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multireporter approach is critical in providing multiple perspectives about the adolescent's functioning. It is consistent with real-world clinical practice, in which the youth's voice is a primary source of clinical information and family perspectives are integrated into the formulation [38].

Limitations

Study participants include treatment-seeking youths who present alongside their parent/guardian's request for MH care and therefore may not be representative of non–treatment-seeking symptomatic youths in the community. For safety reasons, our study excluded youths with high-acuity symptoms such as active suicidal ideation and bipolar disorder. As a result, findings may not be generalizable to youths with more acute symptoms and treatment needs. In addition, in a study of depression and anxiety, group therapy as a treatment arm may limit the representativeness of the sample due to the potential discomfort of some young people with a group modality. Finally, to ensure equal durations of intervention, the group therapy intervention was designed as a brief course of treatment, which may be less representative of typical longer courses of group CBT treatment.

Conclusion

We have described a randomized controlled trial that seeks to establish the feasibility and acceptability of a relational agent digitally delivering CBT within a pediatric outpatient MH hospital setting. Demonstrating W-GenZD as noninferior to a CBT-group may have implications for the expansion of options for adolescents seeking MH treatment for depression and/or anxiety. Providing technology-leveraged effective treatment options for those at lower-acuity levels may help reserve limited resources for those with more severe MH needs.

Acknowledgments

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Authors' Contributions

EC, KM, AR, and MMG contributed to the conceptualization, study design, implementation, and manuscript preparation of this study. AW reviewed the study design and provided the statistical analysis plan. CP and NW provided input on on-site procedures and reviewed the manuscript.

Conflicts of Interest

EC, KM, AR, and AW are employees of Woebot Health. This study was funded by Woebot Health, which included support for the percent effort dedicated to the project by the Children's Hospital of The King's Daughters (CHKD) on-site team including CP, NW, and MMG.

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Abbreviations

BL: baseline
EOS: end of study
EOT: end of treatment
GAD-7: Generalized Anxiety Disorder
HIPAA: Health Insurance Portability and Accountability Act
MFQ: Mood and Feelings Questionnaire
MH: mental health
PHQ-8: Patient Health Questionnaire
URPI: Usage Rating Profile-Intervention
W-GenZD: Woebot for Adolescents

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Protocol

Attitudes of Physicians and Individuals Toward Digital Mental Health Tools: Protocol for a Web-Based Survey Research Project

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Abstract

Background: Digital transformation is impacting health care delivery. Great market dynamism is bringing opportunities and concerns alike into public discussion. Digital health apps are a vibrant segment where regulation is emerging, with Germany paving the way with its DiGA (Digitale Gesundheitsanwendungen, in German, meaning digital health apps) program. Simultaneously, mental ill-health constitutes a global health concern, and prevalence is expected to worsen due to the COVID-19 pandemic and its containment measures. Portugal and its National Health System may be a useful testbed for digital health interventions.

Objective: The paper outlines the protocol for a research project on the attitudes of physicians and potential users toward digital mental health apps to improve access to care, patient outcomes, and reduce the burden of disease of mental ill-health.

Methods: Web surveys will be conducted to acquire data from the main stakeholders (physicians and the academic community). Data analysis will replicate the statistical analysis performed in the studies from Dahlhausen and Borghouts to derive conclusions regarding the relative acceptance and likelihood of successful implementation of digital mental health apps in Portugal.

Results: The findings of the proposed studies will elicit important information on how physicians and individuals perceive digital mental health app interventions to improve access to care, patient outcomes, and reduce the burden of disease of mental ill-health. Data collection ran between September 26 and November 6, 2022, for the first study and September 20 and October 20, 2022, for the second study. We obtained 160 responses to the first study's survey and 539 answers to the second study's survey. Data analysis is concluded, and both studies' results are expected to be published in 2023.

Conclusions: The results of the studies projected in this research protocol will have implications for researchers and academia, industry, and policy makers concerning the adoption and implementation of digital health mental apps and associated interventions.

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KEYWORDS

mental health; mobile apps; digital technology; government regulation

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Introduction

Digital Transformation in Health

Digital transformation and its impact on health [1] is evermore present [2]. Investment inflow into the digital transformation in the health care market registered a 10.4% compounded annual growth rate from 2016 to 2020, with a further 14% compounded annual growth rate expected in 2021-2031, denoting strong market dynamics [3]. According to IQVIA Institute for Human Data Science's Digital Health Trends 2021 report [4], mobile apps in the business-to-consumer market registered at "(…) top app stores worldwide are now over 350,000 in number, with more than 90,000 digital health apps added in 2020—an average of more than 250 apps per day."

The growth of digital tools applied to health has, however, been largely achieved without regulatory scrutiny appropriate to the needs of a digital society and due consideration for the quality, safety, and effectiveness of tools. There is rising concern that mobile apps, for one, do not meet enough clinical or technical validation standards or even register any type of empirical support [5-8]. Further, following a rush of optimism as the COVID-19 pandemic became a global challenge and research organizations tried to leverage technological tools, the evidence showed that, for instance, artificial intelligence–based mechanisms often failed to deliver on their promise [9], thus making the discussion more relevant. If COVID-19 brought concerns about the tools used for digital health delivery, it is also true that it provided a very significant impulse to their adoption, laying the ground for their widespread use in a postpandemic world [10], including in fields such as digital mental health (MH) [11].

Physicians and prospective patients alike have several concerns regarding digital health, and there are myriad challenges and risks ahead. These include lack of digital literacy, barriers to health care access that stem from the digital divide, and worries about losing touch with a familiar model such as face-to-face consultation [12-16]. Further questions arise around legal and ethical questions around topics such as confidentiality, privacy, patient autonomy, or the trustworthiness and accountability of care delivery [17-20].

The scope of our research protocol encompasses 2 different concepts that need clarification: digital health and, more particularly, digital mental health apps (DMHAs). This clarification is important as none of these constructs has a stabilized definition due both to the evolving nature of their underlying fields and to the heterogeneity of stakeholders that work with them, ranging from academia to governmental institutions and industry.

For this research protocol and its papers, digital health will be defined as technologies that connect and empower people and populations to manage their health and wellness by augmenting workforce capacity while leveraging digital tools and technologies to shape care delivery [21]. It uses information and communication technologies to facilitate the understanding of health problems and challenges faced by people receiving medical treatment and social prescribing in more personalized and precise ways [22-25].

Within digital health, we will be focusing on DMHAs—a type of digital MH [26] tool that uses the format of a mobile app to aid MH assessment, support, prevention, and treatment [27,28].

The Rise of Digital Health Apps—Regulatory Concerns

Digital health apps promise to empower users and provide a unique opportunity for access to health (eg, by expanding remote care) while increasing the volume and variety of information available to physicians. More than 350,000 health apps are available from various app stores, with 110 downloaded over 10 million times and accounting for almost 50% of all downloads [4]. According to the same source, COVID-19 increased app use, and MH, cardiovascular, and diabetes condition management apps accounted for nearly 50% of disease-focused apps. However, considering the difficulty in assessing the impact of digital health apps [29] on health, policy makers have recently taken measures to reduce the uncertainty surrounding digital health apps by introducing standardized processes for evaluation akin to medicines or medical devices [30].

The identification of digital health apps that are safe and effective presents a significant challenge for health systems across the globe, making proper regulation essential to minimize risks and magnify benefits. Apps that tackle high-risk or chronic conditions, or that attempt to perform diagnosis or treatment, are especially relevant in this scenario given the time one is expected to use them or the sensitivity of associated information. Regulation constitutes an aprioristic need to produce payment and reimbursement pathways that balance costs and benefits while ensuring access and defining clear use policies aside from those that are market based (eg, star ratings in app stores) [31].

When it comes to implementing a regulatory framework aimed at digital health apps and their market access and reimbursement, Germany assumed a pioneering role. Its DiGA (Digitale Gesundheitsanwendungen, in German, meaning digital health apps) [32] program was inaugurated in October 2020, and, on December 20, 2022, 34 apps had qualified for statutory insurance reimbursement (of these, 14, or 41%, were classified as being DiGA for mental disorders) [33]. An app is accepted into the DiGA program after the German Federal Agency for Medicines and Health Products evaluates it in terms of general requisites (concerning technical safety and user-friendliness) and positive clinical effects. If an app has not yet proven the latter, it has 12 months to do so and is included in a provisory listing; if it fails to comply, it is withdrawn. If the app can prove both compliances with general requisites and positive clinical effects, German Federal Agency for Medicines and Health Products approves it, and price and reimbursement negotiations follow with the association of statutory insurers (GKV-SV), after which it is included in the DiGA Directory [33]. France is studying a replication of the DiGA approach and is expected to implement it until the end of 2022 [34].

Belgium ranks second in implementation—even though the mHealthBelgium [35] initiative was launched in 2018, it officially started conducting appraisal and reimbursement

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processes in January 2021. Its selection process is based on a 3-level validation pyramid [36] consisting of criteria related to legal and regulatory issues (level 1), safe communication and privacy (level 2), and financing and reimbursement (level 3, subdivided into 3^-, if it has provisional reimbursement while proving socioeconomic benefits, and 3^+, if it already has proven those same benefits). On June 2, 2022, 23 apps had level 1 clearance, and 12 apps had level 2 clearance. Moreover, 1 app received 3^- clearance, and none had been cleared for level 3^+.

Other European countries have so far opted for softer, more decentralized approaches, with legal obligations and compliance rules based on the General Data Protection Regulation [37] or the Medical Devices Regulation [38]. Singapore and the United States, on the other hand, resort to their own medical devices regulations, with the Food and Drug Administration issuing guidance in 2021 [39] regarding a pilot project at the federal level and, thus far, assessing software as a medical device [40].

Mental Health, Anxiety and Depression, and Pandemic: A Troublesome Cocktail

Mental disorders are globally responsible for 4.92% of total disability-adjusted life years (DALYs) and 13.04% of all disease prevalence cases. Depressive disorders are accountable for 1.84% of global DALYs and 3.76% of total disease prevalence, while anxiety answers for 1.13% of global DALYs and 4.05% of disease prevalence in the globe [41]. The 2 conditions accounted for more than half of the impact MH disorders had on global health in 2019 according to the GBD Compare tool developed by the Institute for Health Metrics and Evaluation.

Table 1 presents a breakdown of the impact mental disorders as a category, alongside anxiety and depression, had not only in global health but also on the health status of some geographies of concern for us in this protocol—the United States, the European Union, and Germany—in 2019, measured in DALY and disease prevalence cases. Data were gathered using the previously mentioned GBD Compare tool [41].

Table 1. Share of DALY[a] and disease prevalence (in percentage points) per condition and geography.[b]

	World		United States		European Union		Germany	
	DALY (%)	Prevalence (%)	DALY (%)	Prevalence (%)	DALY (%)	Prevalence (%)	DALY (%)	Prevalence (%)
Mental disorders	4.92	13.04	6.56	17.03	6.65	15.34	6.43	15.59
Depression	1.84	3.76	2.38	4.92	2.42	4.6	2.16	4.32
Anxiety	1.13	4.05	1.68	6.51	1.69	5.82	1.95	7.07

[a]DALY: disability-adjusted life year.

[b]Institute for Health Metrics and Evaluation [41].

In all geographies considered in the paradigm, depression and anxiety account for over half of the burden of disease generated by mental disorders. Furthermore, these conditions are always a relevant public health issue in any of the mentioned contexts due to their prevalence, thus making the importance of addressing them undisputable.

These data are with regard to 2019, and consequently do not factor in the consequences of the COVID-19 pandemic and its containment measures in MH deterioration. Many experts have alerted to the deleterious impact [42-44] of this pandemic, especially for children and adolescents [45], and have issued calls to action on the need to tackle this issue heads on [46,47]. It has been suggested that digital MH tools could help manage the burden of the disease brought about by mental disorders, in particular anxiety and depression [48]. Rapid and affordable mechanisms of population screening and follow-up are necessary in a postpandemic world; otherwise, the burden of the disease will be unbearable for any health system [49-51].

Portugal and Its Mental Health Landscape

The Portuguese National Health Service (NHS) is a publicly owned, tax-financed health system that aims at ensuring wide, universal, and mostly free-of-charge care [52]. Regarding total health care activity in Portugal in 2019 (the most recent and pandemic-free full-year available), the NHS delivered 59.8% of 21.1 million outpatient consultations, 76.5% of 8.2 million emergency room episodes, and performed 66.2% of 1.21 million surgeries. The NHS was also responsible for 82.1% of 180.3 million uses of complementary means of medical diagnosis and therapy, as well as for 71.5% of 1.1 million hospitalizations and 84.7% of 86.4 thousand births [53]. The Portuguese NHS was therefore accountable for 79.5% of the health care delivered in Portugal. Regarding funding, the government financed 63.8% of total health care expenditure, with out-of-pocket family spending representing 30.5% and private insurance companies accounting for 3.8% of the total [54].

The data point to an eminently public health system both in funding and activity, with significant household financial strain and a modest contribution of private insurers. It also means that most of the Portuguese population relies on the care provided by the publicly financed and managed NHS. This is a significant difference from health systems such as those of Germany [55] or the United States [56], where health and care are largely privately owned, financed, and managed. In these countries, the government only intervenes in specific cases, mostly related to income deprivation or market failures. Such differences entail different economic, managerial, and organizational incentives, reflecting different cultures and preferences [57].

Several studies draw attention to a lack of MH and care resources within the scope of the Portuguese NHS, chief among them is the first (and so far, sole) national epidemiological questionnaire on MH [58]. This constitutes an alarming background considering the Portuguese population's particularly

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worrisome MH status: 51.4% of the population is expected to have a MH issue at some point in their lives. This datum reports to 2013; the Order of Portuguese Psychologists reported, in its factsheet on depression dated December 2021, that depression alone affected 10% of the population [59].

Evidence on the quasiepidemic nature of MH issues grows; the prevalence of MH disorders in 2019 was estimated at 8.27% of DALYs and 19.27% of disease cases. The statistics for anxiety and depressive disorders were, respectively, expected to be 2.58% and 3.16% of total DALYs and prevalence valued at 9.08% and 5.88% [60].

These data add to the public health relevance of these conditions, and several experts point out that, due to socioeconomic constraints ranging from stigma to lack of accessibility or affordability, these figures might be altogether underestimated [61-64]. At the same time, the World Health Organization expects the COVID-19 pandemic to have a detrimental effect on these statistics, further exacerbating the issue [65]. Children and adolescents at risk due to both family context and the COVID-19 pandemic [66-68] constitute further cause for worry.

Primary care services and digital health tools for self-management have been singled out as an opportunity to tackle this and other issues concerning health and care [69-72], namely chronic illness and quality of life, rising health costs, or significant burden of disease [73,74]. Portugal has registered a very significant uptake of telemedicine consultations [75] in its NHS, and the pandemic has arguably played a role in catalyzing this change. In context, the country ranks 16th (ie, slightly below average) in the European Commission's 2021 Digital Economy and Society Index [76], which assesses the digital maturity of each Member State.

Unleashing the eventual potential of digital health to help manage health conditions overall and MH issues (such as anxiety and depression) in the Portuguese context implies understanding the agents, their incentives, and interconnections. The problem at its core has 2 main primary actors: physicians (defined as psychiatrists or psychologists) and patients.

Doctors are important since patients usually delegate medical decisions to doctors [77,78]; therefore, MH professionals' attitudes toward digital health apps are a key success factor likely to steer not only adherence but also outcomes as well [79]. By the same token, we can expect doctors to be more willing to use digital tools if patients demand them. Consequently, patient buy-in is needed to make this system work, and that will only be possible if digital health developers and companies consider their expectations and concerns [80]. These can range from user interface and user experience [81] considerations to confidentiality and privacy issues [82-84].

Portugal has no direct equivalent to prescription apps or the German Ministry of Health's DiGA program. The Portuguese reimbursement scheme for pharmaceuticals is centrally negotiated and decided by the Regulatory Authority for Medicines and Medical Devices (INFARMED). Medical devices in the European Union market are subject to a conformity assessment [38], being the definition of medical devices already extended, in law, to software and software apps. INFARMED is the authority responsible for notified bodies and has a coordinating role in verifying conformity assessments and selecting third parties to become notified bodies responsible for conformity assessments in high-risk cases.

In turn, the Shared Services of the Portuguese Ministry of Health (SPMS), largely responsible for the development of the country's eHealth strategy, make adhesion to their health app store (MySNS Seleção [85]) conditional on an assessment system that evaluates apps concerning performance, safety, public utility, and information quality and security according to European Union Law [86]. Even though these 2 regulatory players display some level of scrutiny in European Union terms, ample room remains for economic, social, and regulatory development, showing a lag vis-à-vis German, Belgian, or French ambitions [87].

This research project is an opportunity to assess whether DMHA would be welcomed in Portugal and in a health care system with its political economy. By comparing Portugal with Germany (from the physicians' point of view) and the United States (from the individual's point of view) in similar settings, we hope to enrich the comparison between health systems with a very significant private sector role and systems where government plays a key function in ensuring access to and funding of health care, particularly concerning MH and the use of electronic or digital tools.

This constitutes a relevant contribution to the scientific literature not only of life sciences and their digital potential but also in terms of the industrial characterization of health economics for these subtopics and the mapping of expectations and perceptions from both supply and demand sides of MH and care.

Aim and Objectives

The research project we refer to is composed of 2 papers, both aimed at publication in the context of a doctoral research project being pursued by the first author of this paper under the supervision of its second author.

In this research project, we aim to understand how physicians and individuals might perceive digital MH tools. These constitute, respectively, the supply and demand sides of this market. Furthermore, we seek to provide a more precise landscape of the digital health setting in Portugal and provide grounds for academic, policy, and business development. Finally, we speculate on the potential use of digital health interventions for quantifying and providing tools to tackle the increasingly unmanageable burden of mild to moderate anxiety disorder and depression.

We will try to answer the following research questions: (1) How do physicians perceive digital health apps? (2) How digitally literate do physicians perceive themselves and their patients to be? (3) How do physicians see their own role in digitalizing health care provision? (4) What are the largest benefits, risks, barriers, and opportunities in digital health apps? (5) How do individuals perceive MH apps? Which factors determine the decision of using MH apps, and how do individuals feel about doing it? (6) What are individuals' preferences concerning resources and strategies for getting MH care? (7) How do

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individuals rate their MH and what impacts it? and (8) What perceptions do individuals have regarding MH and its treatment?

Methods

First Paper (Physicians)

The first paper will replicate the study performed by Dahlhausen et al [88] with adaptations. It will seek to understand the attitudes of physicians (both psychiatrists and psychologists) toward DMHA. The paper will allow us to characterize the implications of the supply side (ie, physicians who constitute the labor for the provision of MH services) for the adoption of DMHA in Portugal.

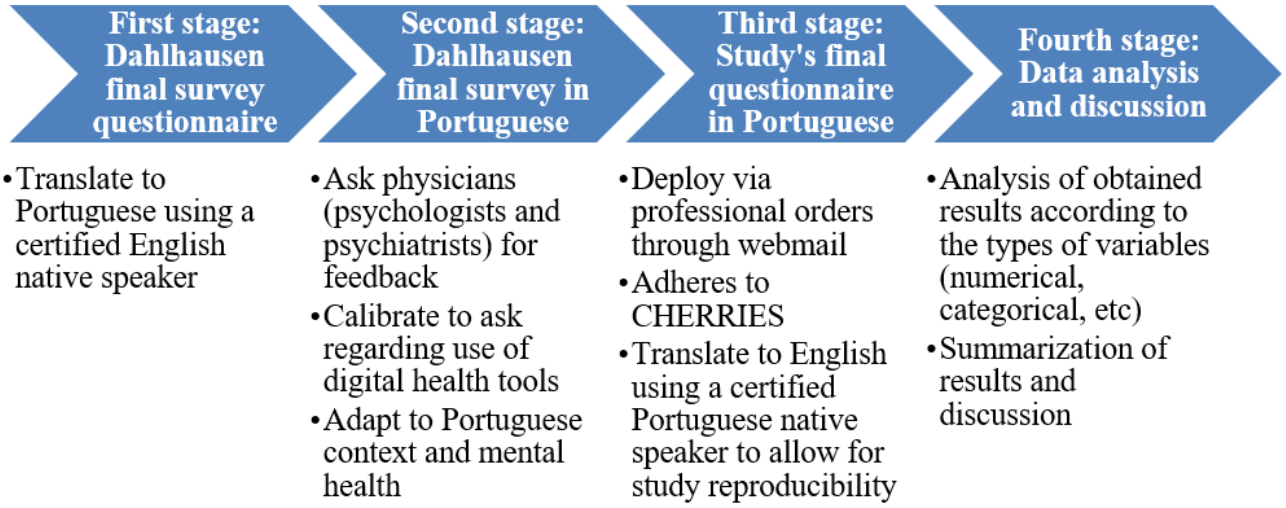
The study will be based on a cross-sectional, web-based survey. We will not include the qualitative part of Dahlhausen study as it was destined to complement the literature's findings to develop a survey. Instead, we will take the final survey questionnaire made available on Dahlhausen's study as given.

We will first translate it to Portuguese using a licensed translator and deliver it to physicians (both psychologists and psychiatrists, 5 each) for input. Physicians' feedback will be focused on how to calibrate it to (1) reflect important questions to ask regarding the usage of digital health tools by doctors and (2) adapt to a Portuguese MH care context.

The feedback obtained from physicians will be incorporated to produce a final web-based survey questionnaire for this study. This survey will be deployed via Inqueritos@UP (the University of Porto's internal survey manager, powered by LimeSurvey) as widely as possible and with the support of the Portuguese Order of Psychologists and the Psychiatry Specialty College of the Portuguese Order of Medical Doctors.

The survey will adhere to and be reported following the CHERRIES (Checklist for Reporting Results of Internet E-Surveys) guidelines. For the certified translation of the Dahlhausen et al [88] questionnaire to Portuguese, as well as our final survey questionnaire in both Portuguese and English (the latter produced by a certified native Portuguese speaker translator from Portuguese to English), refer to Multimedia Appendix 1. Figure 1 summarizes the study's stages.

Figure 1. First study workflow. CHERRIES: Checklist for Reporting Results of Internet E-Survey.



There is no public information concerning the number of psychologists registered with the Order of Portuguese Psychologists. Registered psychiatrists (summing the stand-alone specialty with the subspecialty of children and adolescents) are a total of 1528. All will be invited to participate in this web-based survey via their respective professional orders.

To preserve privacy, respondents will not be asked to provide any identifiable information for completion of the survey. Additionally, invited participants will not be tracked for having started or completed the survey, increasing privacy but limiting the possibility of reminders. To establish a basis for comparison with a reimbursable apps system, we will ask physicians who answer the survey to bear in mind a scenario where these apps fulfill regulatory requirements and address safety, quality, and efficacy concerns. This establishes an equivalency between the definition of DiGA apps as outlined in the "Introduction" section and the definition of DMHA used in our study.

To maximize response, the only inclusion criterion will be that of being registered and of good standing (ie, not responsible for any infractions) with the physician's respective professional order. No exclusion criteria will be introduced. There will be no financial incentives for filling the survey.

Gathered data will be assessed according to the same model as in the Dahlhausen et al [88] paper to allow for maximum comparability between results. This entails the breakdown between the sociodemographic characteristics of the sample and the answers to the questions in the survey concerning the 4 main topics at hand: perceived benefits, potential barriers to, measures to support adherence to, and prescription intentions for DMHA. All variables that allow for it will be characterized by descriptive statistical analysis. Estimates of association for the variables that correspond to the Dahlhausen et al [88] "Perceived Benefits From and Attitudes Toward DiGA" and "Prescription Intentions" subsections will also be computed.

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Only data excluded due to different health system organizations and their consequences for citizens or physicians (eg, statutory health insurance in Germany vs little to no point-of-care payments in Portugal) or to reasonable suggestion during the foreseen feedback period will be treated differently, being subjected to either descriptive statistical analysis or association estimation according to the nature of the variable at hand.

Second Paper (Individuals)

The second study produced in the context of this doctoral research project will replicate the paper by Borghouts et al [89]. The paper's aim is to ascertain which factors determine public acceptance and usage of MH apps. The definition of MH apps in Borghouts study encompasses generic apps that can fall, for example, into the category of wellness, and our survey instrument will not impose any restrictions, thereby considering DMHA as an equivalent of MH apps in a broad sense.

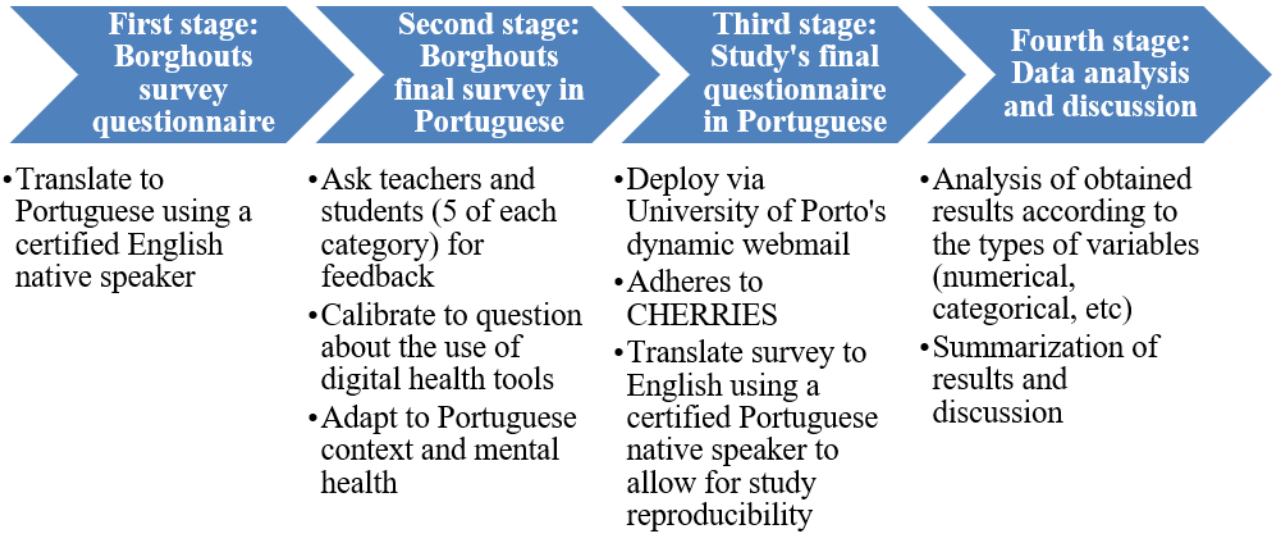
The described study will simultaneously allow us to illustrate the demand side (ie, people who may potentially request MH services and care) for the adoption of MH apps in Portugal. Even though it is limited to an academic community, it is expected that it will have a reasonable mix of population characteristics. Limitations, both ex-ante and ex-post data collection, will be documented in the paper.

The study will start with a cross-sectional, web-based survey delivered through the University of Porto's dynamic email function. The web-based survey will be based on the survey questionnaire made available in Borghouts paper. This questionnaire will be translated into Portuguese using a licensed translator. Afterward, it will be circulated between an equal number of students and teachers (estimated to be 5 each) affiliated with the Faculty of Medicine of the University of Porto for input. Received input will concentrate on how to adjust it to (1) include important questions to ask regarding the usage of digital health tools with a focus on MH and (2) adapt to a Portuguese MH context.

Obtained feedback will be incorporated to produce a final web-based survey questionnaire for this study. This survey will be deployed via Inqueritos@UP (the University of Porto's internal survey manager, powered by LimeSurvey) as widely as possible and with the support of the University of Porto's services.

The survey will abide by and be reported following CHERRIES guidelines. For the certified translation of the Borghouts et al [89] questionnaire from English to Portuguese, as well as our final survey questionnaire in both Portuguese and English (the latter produced by a certified native Portuguese speaker translator from Portuguese to English), refer to Multimedia Appendix 2. Figure 2 summarizes the study's stages.

Figure 2. Second study workflow. CHERRIES: Checklist for Reporting Results of Internet E-Survey.



It is estimated that the dynamic email function of the University of Porto will allow us to reach approximately 36,700 members of the University's community and invite them to take part in this anonymous web-based survey. We will also ask the University of Porto's website management team to divulge the survey, providing a link to access it and following all privacy-related issues.

To preserve privacy, respondents will not be asked to provide any identifiable information. Additionally, invited participants will not be tracked for having started or completed the survey, increasing privacy but limiting the possibility of reminders.

High comparability with the Borghouts et al [89] study is expected due to the nature of the questions in the Borghouts et al [89] survey instrument and their relevance in a Portuguese population, leading us to believe that few questions will be dropped or significantly altered. Gathered data will be assessed according to the same pattern as that offered in the Borghouts et al [89] paper to allow for maximum comparability between results. This means that, aside from a sociodemographic depiction of the sample, we will measure the same constructs as the Borghouts et al [89] paper: barriers to MH resources, important aspects of MH apps, activities people wish for in MH apps, the presence of MH issues, past use of professional MH services, perceived stress, perceived need to seek help, MH

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concerns, perceived stigma, the impact of other people's expectations, and privacy concerns. Factor analysis and multicollinearity checking will be performed to limit the analysis to relevant constructs. Direct effect and full mediation models will be built.

All variables will be characterized by descriptive statistical analysis except when not possible. Only data that are excluded due to reasonable suggestion during pretest interviews will be treated differently, being subjected to either descriptive statistical analysis or association estimation according to the nature of the variable at hand.

To maximize response, the only inclusion criterion will be active registration with the University of Porto, defined as the ability to receive the email containing the invitation to answer the questionnaire. No exclusion criteria will be introduced. There will be no financial incentives for filling out the survey.

Ethical Considerations

Ethical considerations and safeguards for the 2 manuscripts to be produced and their supporting documents include the following and incorporate advice received from the Data Protection Officer of the University of Porto:

- To preserve the privacy of participants, they will not be asked to provide any personally identifiable information. In addition, participants will not be tracked for having started or completed the survey, increasing privacy but limiting the possibility of reminders.
- Informed consent and consenting capacity: All potential participants (physicians and academic community members) will be given web-based written information on the study and its objectives and will be asked to provide consent (click-to-agree) that they are happy to participate, and that nonparticipation will not compromise their current roles. Participation in the study will be voluntary, and no inducements or incentives to participate will be offered.
- Confidentiality: Any data or personal details that could potentially reveal the identity of individuals will be removed. Only anonymized, deidentified information will leave the place of origin. A database with responses will be maintained on a password-protected database. All research data will be stored on a password-protected desktop computer at the host organization. Study participants will be invited, through a link provided on the last page of the survey, to provide their name and electronic address to allow the research team to facilitate their receiving a synopsis of the study findings on publication. This list will be kept separately on a password-protected database and a password-protected desktop computer at the host organization. All data will be stored securely at the host institution and destroyed 3 years after the PhD defense date.
- General Data Protection Regulation compliance will be adhered to in terms of the following:
  - Data privacy rights: Participants will have the right to request information about their data throughout the research process.
  - Transfer of data: Participants will be informed about the circumstances under which their data may be transferred and safety measures that will be taken to protect the data (eg, data are encoded).
  - Retention of data: Participants will be informed how long their data will be stored.

By using Inqueritos@UP, survey data will be stored at the University of Porto's servers, and thus not shared with external entities, constituting another layer of privacy protection.

The Ethics Committee of the Faculty of Medicine of the University of Porto has pronounced itself favorable to the research project on June 30, 2022.

Ethics Approval

The research protocol was approved by the Doctoral Program in Health Data Science Director and the Ethics Committee of the Faculty of Medicine of the University of Porto (Rapport 52/CEFMUP/2022 of June 30, 2022). Data collection ran from September 26 and November 6, 2022, for the first study, and between September 20 and October 20, 2022, for the second study.

Results

The findings of the proposed studies will elicit important information on how physicians and potential users perceive and respond to the usage of DMHAs to improve access to care and patient outcomes, along with the reduction of the burden of disease.

Discussion

Principal Findings

This will be the first research project known to the authors with the specific aim of assessing whether DMHA would be welcomed in Portugal and in a health care system with its political economy. It will do so by mapping the expectations of agents that determine the demand and supply sides for DMHA.

As such, the research project will provide valuable inputs on what would be the key success factors for any market- or government-based actors who decide to enter the market by collecting key information to advise health policy and service development in Portugal and in international settings by providing a key benchmarking tool by comparing Portugal with Germany (from the physicians' point of view) and Portugal with the United States (from the individual's point of view) in similar contexts.

It is also the first research project establishing a comparison between health systems with a very significant private sector component and systems where government plays a key role in ensuring access to and funding health and care, particularly concerning MH and the use of digital tools. Finally, in characterizing the market's industrial organization by mapping the expectations of demand and supply sides, it adds to the literature on digital health economics.

Strengths and Limitations

Potential limitations of the research project include bias associated with the method chosen to select the sample in the

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second paper, as it considers that the academic community replicates the country's population distribution. Bias may impact external validity as this community may not necessarily replicate the Portuguese population's digital literacy or access to information and communication technology tools, and therefore the implicit digital divide.

In addition, the sample's average age may be younger than the country's average due to the teacher-student ratio and the respective average ages of these groups. Lack of generalizability may also derive from participant self-selection; those more interested in research or in using digital health tools will more likely fill the survey. Question-order, interviewer, and acquiescence biases may have a minor influence on conducted surveys. Notwithstanding these limitations, our research project is expected to provide important information on physicians' and individuals' attitudes toward digital MH tools.

To counter the previously identified limitations and enhance the comparability of results, the authors have produced a "Checklist for a future researcher" (Multimedia Appendix 3). Its aim is to facilitate further research both in Portugal and abroad by listing the main points requiring adaptation to reproduce this protocol in different settings.

Conclusions

The results of the studies projected in this research protocol will have implications for researchers and academia, industry, and policy makers concerning the adoption and implementation of digital health mental apps and associated interventions. Rapid and accessible screening, diagnostic, and treatment care strategies are needed to provide postpandemic access to MH care, and this project will inform key factors in designing and implementing successful digital health interventions based on DMHA both in Portugal and abroad.

Acknowledgments

This work has been done under the scope of, and funded by, the Health Data Science PhD Program of the Faculty of Medicine of the University of Porto, Portugal [90].

Data Availability

The data sets generated and analyzed during this study are not publicly available but are available from the corresponding author upon reasonable request.

Conflicts of Interest

This study was conducted as part of the doctoral research project at the Health Data Science PhD Program, Faculty of Medicine of the University of Porto, Portugal. All authors participated in these projects while employed by the Faculty of Medicine of the University of Porto. Both are working on a project co-funded by the European Union concerning the digitalization of clinical trials in the North of Portugal (CR—Digital: Digitize clinical research in the North of Portugal: NORTE-01-0145-FEDER-083448). This research protocol was executed during the authors' personal time. The European-funded project or the Faculty of Medicine of the University of Porto was at no point involved in the research aside from required administrative approvals. There was also no funding, pay, or other commercial interest provided by the Faculty of Medicine of the University of Porto aside from the costs related to the publication of this paper.

Multimedia Appendix 1
First study's final questionnaire in Portuguese and English.
[DOC File , 1518 KB - resprot_v12i1e41040_app1.doc]

Multimedia Appendix 2
Second study's final questionnaire in Portuguese and English.
[DOCX File , 3001 KB - resprot_v12i1e41040_app2.docx]

Multimedia Appendix 3
Checklist for a future researcher.
[DOCX File , 17 KB - resprot_v12i1e41040_app3.docx]

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Abbreviations

CHERRIES: Checklist for Reporting Results of Internet E-Surveys
DALY: disability-adjusted life year
DiGA: Digitale Gesundheitsanwendungen, in German, meaning digital health apps
DMHA: digital mental health app
INFARMED: Regulatory Authority for Medicines and Medical Devices (Autoridade Nacional do Medicamento e Produtos de Saúde, I.P.)
MH: mental health
NHS: National Health Service (Serviço Nacional de Saúde, or SNS, in Portuguese)
SPMS: Shared Services of the Portuguese Ministry of Health (Serviços Partilhados do Ministério da Saúde, in Portuguese)

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Protocol

Evaluation of Two Web-Based Interventions (Res-Up! and REMOTION) in Routine Outpatient Psychotherapy (Therapy Online Plus—TOP): Protocol for a Randomized Controlled Trial

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Abstract

Background: Only 11%-40% of those with a mental disorder in Germany receive treatment. In many cases, face-to-face psychotherapy is not available because of limited resources, such as an insufficient number of therapists in the area. New approaches to improve the German health care system are needed to counter chronification. Web-based interventions have been shown to be effective as stand-alone and add-on treatments to routine practice. Interventions designed for a wide range of mental disorders such as transdiagnostic interventions are needed to make treatment for mental disorders more accessible and thus shorten waiting times and mitigate the chronification of mental health problems. In general, interventions can be differentiated as having either a capitalization (CAP) focus—thus drawing on already existing strengths—or a compensation (COMP) focus—trying to compensate for deficits. Up to now, the effectiveness of transdiagnostic web-based interventions with either a CAP or a COMP focus has not yet been evaluated.

Objective: This study is the first to examine the effectiveness of two transdiagnostic web-based interventions: (1) the activation of resilience and drawing on existing strengths (CAP: Res-Up!) and (2) the improvement of emotion regulation (COMP: REMOTION), compared with care as usual (CAU) in routine outpatient psychotherapy.

Methods: Adults with at least 1 mental health disorder will be recruited at 4 outpatient centers in Germany. Participants will then be randomized equally into 1 of the 2 intervention groups Res-Up! (CAP) and REMOTION (COMP) or into the control group (CAU). Assessments will be made at baseline (T0), at 6 weeks after treatment start (T1), and at 12 weeks after treatment start (T2). A primary outcome will be symptom severity (Brief Symptom Inventory-18). Secondary outcomes will focus on emotion regulation and resilience.

Results: Participant recruitment and data collection started in April 2020 and were ongoing as of July 2022. We expect participants to benefit more from the interventions than from the CAU control on the dimensions of symptom severity, resilience, and emotion regulation. Furthermore, we expect to find possible differences between CAP and COMP. The results of the study are expected in 2023.

Conclusions: This randomized controlled trial will compare CAU with the transdiagnostic web-based interventions Res-Up! and REMOTION, and will thus inform future studies concerning the effectiveness of transdiagnostic web-based interventions in routine outpatient psychotherapy.

Trial Registration: ClinicalTrials.gov NCT04352010; https://clinicaltrials.gov/ct2/show/NCT04352010

International Registered Report Identifier (IRRID): DERR1-10.2196/41413

(JMIR Res Protoc 2023;12:e41413) doi:10.2196/41413

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KEYWORDS

online therapy; randomized controlled trial; transdiagnostic; resilience; emotion regulation; capitalization; compensation; intervention; psychotherapy; Germany; treatment; mental disorder; effectiveness

Introduction

Overview

Approximately 1 in 6 people worldwide have met the criteria for a mental disorder in the last 12 months (17.6%); 29.2% have been identified as having experienced a mental disorder at some time in their life [1]. Mental health problems and disorders have a profound impact on individuals affected by symptoms and society as a whole. Still, in Germany, only 11%-40% of patients receive treatment [2], often due to the long waiting times for psychotherapy (20.1 weeks in 2019) [3]. Therefore, the German mental health care system needs innovative intervention concepts, using approaches beyond standard face-to-face therapy and serving a wide range of mental disorders. Transdiagnostic web-based interventions can provide such an approach [4-6].

Web-Based Interventions

Recent global developments have fast-forwarded digitalization, and thus the use of web-based tools to support mental health care has rapidly increased all over the world. Research on web-based interventions in psychotherapy supports the effectiveness of different intervention programs for a variety of mental disorders [5,7,8]. With limited access to psychotherapy, web-based interventions are an economical, flexible, and practical alternative or addition to conventional treatment [5]. Particularly when face-to-face psychotherapy is not available because of limited resources (like insufficient availability of therapists), web-based interventions can help to avoid long waiting times for treatment and thus mitigate the chronification of mental health problems [4].

Among web-based interventions, stand-alone web-based programs can be differentiated from blended treatment (BT)—the combination of face-to-face psychotherapy and a web-based intervention [9]. Although BT can take on many different forms [10], a differentiation can be made between integrated blends (eg, conceptual coordination between web-based intervention elements and face-to-face psychotherapy sessions via a specified protocol) and add-on blends (eg, a web-based intervention provided in parallel before or after face-to-face psychotherapy without conceptual coordination or integration between the two). BT, where a web-based intervention was provided as an add-on to face-to-face psychotherapy, has been shown to be more effective than psychotherapy alone [11]. A transdiagnostic approach might be particularly relevant for add-on conceptualizations as coordination with a potential face-to-face therapy focusing on a specific disorder is less relevant.

Although even unguided web-based interventions (without any contact between the patient and the provider of the intervention) seem to be effective, therapist-supported web-based interventions are most likely more effective than self-guided treatments [5,12,13]. Although the exact mechanism behind the benefit of guidance remains unclear, this may be due to higher adherence and lower dropout rates resulting from the positive effect of the accompanying support on motivation and on engagement with the intervention [5,11].

Capitalization or Compensation: Basic Orientations in Psychotherapy

Overall, a differentiation has been made in psychotherapy research between capitalization (CAP)–oriented versus compensation (COMP)–oriented *interventions*. CAPs aim to draw on the person's already existing strengths (in a wide sense: action repertoire, resilience strategies, and external and internal resources), and COMPs identify dysfunctional maintenance factors of psychopathology and teach (respectively train) the person to use new strategies or build new behavior against relative deficits [14-18]. In an early study, Wingate et al [18] compared the outcomes of compensation versus capitalization in the treatment of suicidality in young adults, finding results favoring COMPs, whereas other studies find results favoring CAPs [14,17]. According to the current sparse research, there is no agreement on which of these 2 strategies should be pursued in psychotherapy [14,17,19-22].

Certain interventions in psychotherapy are inherently more focused on capitalization (eg, focusing on action repertoire, resilience strategies, and external and internal resources) or on compensation (eg, focusing on the building of new strategies for deficit compensation). Although outcome differences between CAPs and COMPs in face-to-face psychotherapy seem to be small [14], there are no studies comparing the 2 approaches for web-based therapy. Web-based therapy involves less therapeutic guidance and thus relies more strongly on the person's self-management capacities. Thus, the possible effects of therapists' support in face-to-face therapy compensating deficits in both CAP and COMP cease in a web setting. Thus, this randomized controlled trial explores, for the first time, the effect of 2 transdiagnostic web-based interventions inherently capitalization or compensation oriented: activation of resilience (CAP) (respectively improvement of emotion regulation [COMP]) compared with a care-as-usual (CAU) group.

As discussed above, capitalization and compensation can be conceptualized as features of interventions. Another possible conceptualization is via the interaction of intervention focus with patient variables. If particularly patients with a high level of adaptive emotion-regulation strategies profit from an intervention focusing on the improvement of emotion-regulation strategies, this would point toward a capitalization change process. If patients with a low level of adaptive emotion-regulation strategies profit particularly from an intervention focusing on the improvement of emotion-regulation strategies, this points to a compensation change process. Thus, in this trial, differential effects of patients' initial resilience (respectively emotion-regulation competencies) on the outcome of a resilience and emotion-regulation intervention will also be explored.

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Resilience

Resilience as psychological resistance to adversity was originally conceptualized in the context of developmental psychology [23,24]. Today, resilience and resources are often discussed in the field of positive psychology [25], which focuses on factors that make and keep people healthy rather than ill. Although most research on resilience and resources has a compensation focus, aiming to create new resources and building up new strengths [26], the personal model of resilience (PMR) is a CAP intervention that was developed by Padesky and Mooney [27] from a cognitive perspective.

The PMR focuses on individuals' pre-existing resources and resilient strategies to increase awareness and implementation of these strengths. The basic assumptions of the PMR are as follows: every person is resilient and has resilience strategies that are already part of their action repertoire and have the potential to also be used in challenging situations. The model is based on evidence-based standards for cognitive behavioral therapy [28].

The model was evaluated in a pilot study with students [29], a randomized study with a waiting control group [30], and in a web version with active plus waiting control groups (web-based intervention program vs face-to-face vs ABC [activating events, belief systems, emotional and behavioral consequences] model vs waiting control group) [31]. Medium effect sizes for the face-to-face model and small effect sizes for the web version were observed. Based on the feedback of participants, the web version was redesigned and is being re-evaluated [32]. The redesigned version of the program (Res-Up!: Resilience program of the University of Witten/Herdecke) showed medium effect sizes in preliminary results for resilience (d=0.51-0.55) and emotional competence (d=0.51), greater effect sizes for self-compassion (d=0.70), and small effect sizes for self-esteem (d=0.41) [32].

Emotion Regulation

Emotion regulation refers to the way individuals attempt to influence emotions and includes the upregulation and downregulation of positive and negative emotions in accordance with regulatory goals [33]. Emotion regulation and specifically the fostering of flexible use of different emotion-regulation strategies are important topics in the treatment of mental health disorders and more specifically in psychotherapy research. This is made evident by the large number of publications that focus on the topic of emotion regulation [34-37]. Interestingly, emotion regulation has been discussed as a transdiagnostic factor related to psychopathology and the treatment of mental health disorders [34,38-40]. More recently, several mental health interventions that address or target emotion regulation have been developed as web- or mobile-based programs. For example, Böhme and Berking [41] describe the application of an emotion regulation app based on Affect Regulation Training.

By using the extended process model of emotion regulation as a theoretical framework to structure an emotion-regulation intervention [42], Bielinski et al [43] developed REMOTION. The web-based program aims to reduce the symptom severity of patients with a range of different diagnoses while improving their emotion regulation [43]. REMOTION is currently being examined as a blended intervention in an outpatient psychotherapy setting in a pilot randomized controlled trial [43]. It is also currently being examined as an add-on to acute inpatient psychiatric care in another pilot randomized controlled trial (ClinicalTrials.gov NCT04990674). Results for both trials are expected in 2023.

Aims

Web-based interventions have been efficient and helpful in considering different mental disorders and in self-selected samples in many controlled studies [7]. Nevertheless, little is known about the efficacy of web-based interventions in routine psychotherapeutic practice and their usefulness as an add-on to conventional psychotherapy (BT).

The *first goal* of this study is to assess the effectiveness of 2 web-based interventions (Res-Up! and REMOTION) in an outpatient psychotherapeutic routine setting in comparison with CAU.

The *second goal* of this study is to explore, in a web-based therapy context, the implementation of interventions with either a CAP or COMP focus by using 2 transdiagnostic web-based intervention programs, centered either on activating resilience (CAP; "Res-Up!") or on emotion regulation (COMP; "REMOTION").

Further subanalyses considering differences in patients' benefits depending on their diagnoses will be conducted. In addition, the differential effects of initial resilience and emotion-regulation competencies on the effectiveness of Res-Up! and REMOTION will be explored. To accomplish this, the initial status of resilience and emotion-regulation competencies will be assessed and related to intervention effects in the intervention groups.

Methods

Study Design

The study is a multicenter 3-arm randomized controlled trial in which a CAU approach will be compared with 2 different web-based intervention programs (CAP: Res-Up! and COMP: REMOTION), which will be administered as an add-on to CAU.

Participants in the intervention groups will be given access to Res-Up! and REMOTION immediately, whereas participants in the CAU group will receive access to one of the interventions after 12 weeks (participants in the CAU group can choose which intervention they want to access). Assessments will be made at baseline, 6 weeks (post), and 12 weeks (follow-up) for all participants. Assessments at 6 and 12 weeks will be made irrespective of whether the participant is in face-to-face treatment.

The multicenter trial will take place at the outpatient clinics of the Training Center for Psychological Psychotherapy OWL (Bielefeld, Germany), the Centers for Psychotherapy Dortmund and Muenster (all German Association of Behavioral Therapy—Deutsche Gesellschaft für Verhaltenstherapie [DGVT]), and the Center for Mental Health and Psychotherapy

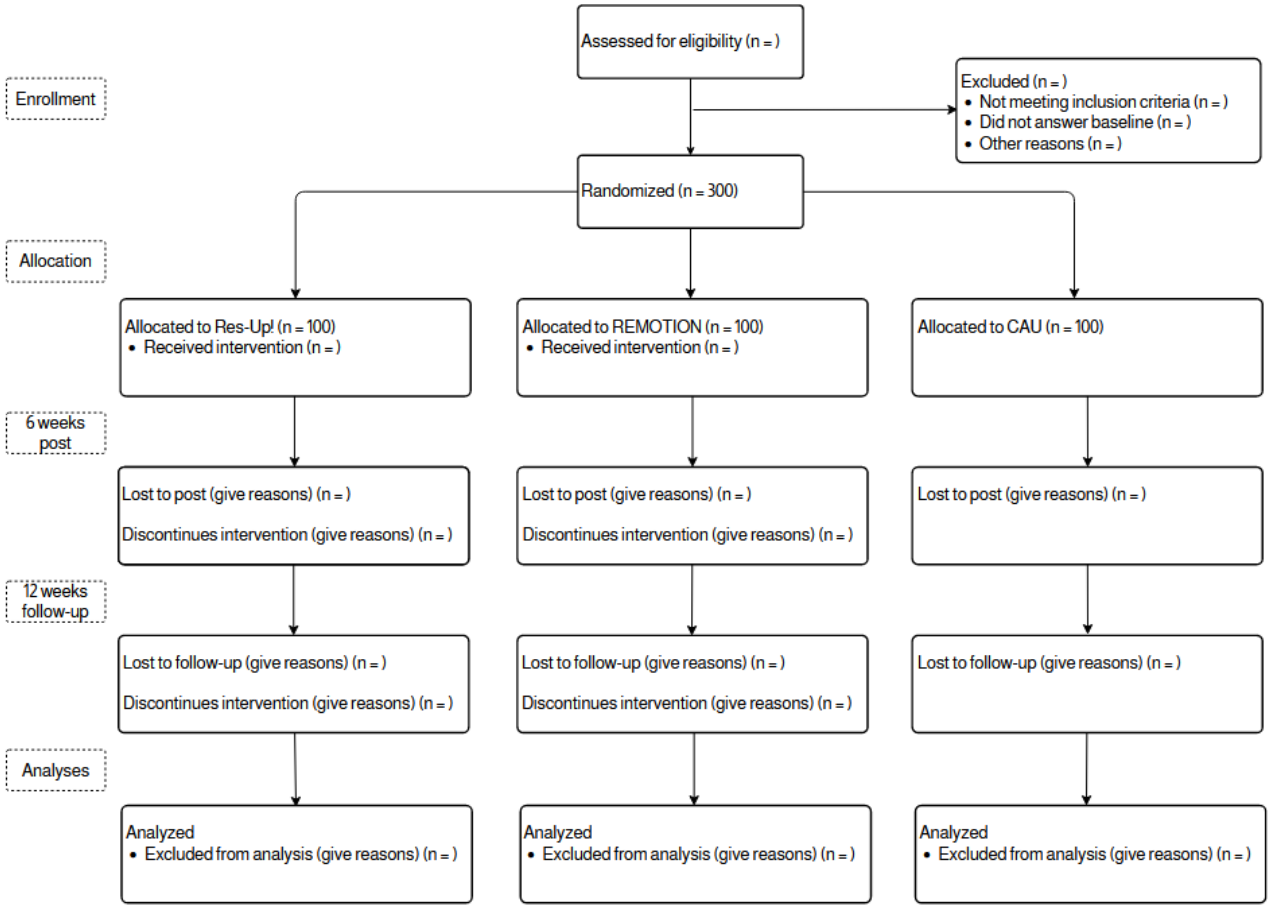
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(Department of Psychology and Psychotherapy, University Witten/Herdecke).

Primary and secondary outcomes will be gathered via link to web-based self-report questionnaires based on Qualtrics software [44] at baseline and 6 and 12 weeks after baseline.

All participants will be required to give their informed consent before enrollment in the study. The written consent will be obtained by trained psychotherapists at the outpatient centers. Furthermore, all participants are given the option to contact a study member during the intervention ("guidance on demand") either via email (REMOTION) or chat (Res-Up!) but are not actively contacted by the team (except for reminders to complete the interventions or questionnaires and a welcome message). Figure 1 displays the flow of patients through the study.

Figure 1. Flow of participants. CAU: care as usual.



Sample Size Calculation

Sample size was calculated with the software G*Power [45]. We aim to detect small effect sizes of Cohen *d*=0.20 regarding the Time×Group interaction for the 2 active conditions at an error level of .05. A power analysis revealed that a sample size of 80 participants in each of the active study arms is required to detect a statistically significant difference with a power ($1 - \beta$) of .80. The sample size was further estimated based on a dropout rate of approximately 25%. We finally decided to randomize 100 participants to each of the conditions (3 arms, 100 per arm; CAU, Res-Up!, and REMOTION). The second goal of the study is exploratory, and thus no assumptions about differential effects can be made.

Eligibility Criteria

The inclusion criteria are as follows: (1) current diagnosis of a mental disorder according to *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* or *International Classification of Diseases, 10th Revision*; (2) recruitment at one of the participating outpatient clinics listed above; (3) interest to receive psychotherapy at one of the centers but not currently enrolled; (4) at least 18 years of age; and (5) reliable web access. The exclusion criteria are as follows: (1) current severe episode of major depression, (2) current psychotic disorder, (3) acute suicidal tendency, (4) other severe mental disorders (eg, bipolar disorder), and (5) insufficient German language skills. These diagnoses were ruled out because of their severity, as they impair the ability to concentrate on web-based interventions and stay committed for several weeks of programs and measurements. Access to face-to-face psychotherapy after enrollment is not restricted while participants are working with the web-based programs in order to approximate naturalistic conditions.

Recruitment and Randomization

Recruiting training centers for psychological psychotherapists in Germany are located in Bielefeld, Dortmund, Muenster (training centers of DGVT) and in Witten, Germany (Center of Mental Health and Psychotherapy, Witten/Herdecke University). Trained psychotherapists at all centers will inform interested individuals coming to the institution for a face-to-face consultation session. As waiting lists for psychotherapy are

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quite long in Germany, the consultation generally does not mark the beginning of psychotherapy but is scheduled to evaluate whether the person has a clinically relevant psychiatric disorder with a structured clinical interview. Interviewers gather written consent to participate in the study, which is forwarded to the study team members. After study eligibility is proven, participants receive an email with a personalized code to the baseline questionnaires. Once participants have filled out the baseline questionnaires, they are randomized via Qualtrics software [44].

Ethics Approval

The study will be conducted according to local regulations and the Declaration of Helsinki. The study was approved by the ethics committee of the University Witten/Herdecke (221/2019). Written informed consent regarding the gathered data and following analyses as well as scientific publications in an anonymous form will be obtained from all patients by the recruiting therapists in outpatient centers. The trial is registered with ClinicalTrials.gov (NCT04352010). Data will only be analyzed in an anonymous form and will be deidentified by a specific member of the research team.

Interventions

Res-Up!

Res-Up! is a web-based intervention focusing on patients' strengths and positive experiences developed at the University Witten/Herdecke. The intervention is based on the PMR [27], which is a positive cognitive intervention that uses patients' strengths to overcome problems. The PMR activates resilient emotions, thoughts, metaphors, images, and behaviors in 4 steps structured into 5 modules. A variety of psychotherapy elements (cognitive behavioral therapy, emotion-focused therapy, positive therapy, etc) are integrated in the program. Participants are asked to work on 1 of 5 consecutive modules per week; completing a module takes about 1-2 hours. Res-Up! is conducted on the web platform Minddistrict [46], which has been approved by the privacy policy office of Witten/Herdecke University before the start of the study. The intervention can be administered as a stand-alone or add-on treatment to psychotherapy. The basic assumption of the PMR is that every individual has a repertoire of resilience strategies that can be used in everyday life or in situations of crisis. Res-Up! aims to identify these strategies and improve, support, and implement them in problematic situations where they were not used before. In the first module, participants are educated on the concept of resilience. In the second session, individual resilience areas of the participant are elaborated. The goal of the third module is to construct the individual's current PMR. The PMR is further developed in the fourth module in which resilient strategies from the model are used and adapted for still problematic areas. At the end of this module, a behavioral experiment is planned. The experiment is evaluated in the last module. To further increase participants' motivation to use their model and resilience strategies, the individual's experiences with the PMR are summarized.

Training and intervention elements are presented as informational texts as well as interactive modules, individualized questions, videos, and audio files. Throughout the whole intervention, participants can ask for guidance (via chat or email) by a member of the study team who is trained in the program and has at least a master's degree in psychology. To increase adherence, reminder messages to complete the modules in time are sent via chat. With continuous participation, participants should complete the intervention within 6 weeks.

REMOTION

The web-based intervention REMOTION is aimed at reducing symptom severity and improving emotion regulation of individuals with different mental health disorders [43]. The theoretical background and exact structure of REMOTION have been described in detail elsewhere [43]. REMOTION includes an introduction and 5 further modules, and individuals are asked to work on 1 module per week, ideally for around 1-2 hours per week. Intervention elements are presented in different formats including video, text, and audio along with different types of exercises throughout the program. The intervention is accessed via a platform provided by the University of Berne, and the access is password protected. Textbox 1 shows the content of the intervention.

For this study described in this protocol, and to allow comparability with the Res-Up! intervention, REMOTION is administered as a stand-alone or an add-on treatment to psychotherapy. If individuals do not work with the program for an entire week, they are then reminded to work with the program, but no other active guidance components (like weekly emails) are added. Individuals are, however, able to contact the study team via email if they have any questions. Like Res-Up!, completion of the REMOTION program should take around 6 weeks.

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Textbox 1. The content of REMOTION shown in detail.

Introduction

- Information about the structure of the intervention and about the theoretical background, and a user guide are provided in this module

Psychoeducation

- Information is provided as to what emotions are, what their functions are, and what types of emotional experiences there are
- The concept of emotion regulation is introduced and the relationship between emotion regulation and mental illness is explored

Identification

- Emotional awareness, which is identified as key to the perception substep of the identification stage of emotion regulation [42], is explored in this module
- If and when to regulate emotions, along with information on the value of emotion regulation, is introduced in this module

Selection

- This module shows patients what types of emotion-regulation strategies are available
- The focus is on the selection of an emotion-regulation strategy [42]
- The strategies situation selection or modification, attentional deployment, cognitive change, and response modulation are introduced in this module [47]
- Furthermore, strategies specific to over- and under-regulated states are also introduced [48-50]

Implementation

- This module shows patients how the previously introduced strategies can be implemented, for example, translated to different tactics [42]
- Exercises are introduced for every emotion-regulation strategy, and advice is provided as to how these exercises can be implemented into daily life

Modification and flexibility

- The importance of the flexible use of strategies (being able to modify strategies and being able to apply them flexibly) [42,51] is discussed in this module
- Patients are encouraged to flexibly use strategies, to apply them to different contexts, to practice, and to also attempt sequences or blends of strategies that work for them as individuals

Note: The textbox is adapted from Bielinski et al [43] which is published under Creative Commons Attribution 4.0 International License [52].

CAU Group

Participants in the CAU group will not get access to the web-based interventions for 12 weeks after baseline. They will answer the questionnaires before randomization as well as 6 (respectively 12) weeks later. They get access to the web-based interventions of their choice after completing the follow-up assessment. During the waiting time, participants are allowed to stay on the wait list or start psychotherapy as they would usually.

Trial Organization

Participants are being recruited during their registration to regular psychotherapy in the outpatient centers in Germany mentioned above. Recruiting outpatient centers received information about the study from a member of the study team via a short instruction manual, an instruction video, and a personal introduction for psychotherapists in associated centers. Information on the study and the interventions (Res-Up! and REMOTION) is given to interested patients face to face with additional written information by trained psychotherapists. Written consent to participate is solicited by the respective practitioner. Written consent and necessary information (name, birth date, diagnoses, date of recruitment, and email) is given to a member of the study team. Participants then receive an email from the study team with an individualized code to the baseline measure via Qualtrics [44]. Answering individual questionnaires will take approximately 30 minutes at every assessment point. After completing the baseline, participants are randomly assigned by a randomized computer generator (in Qualtrics [44]) to 1 of the 3 treatment arms. As the interventions are planned for 6 weeks, posttreatment measures are provided 6 weeks after baseline. Twelve weeks after baseline, participants are invited to fill out the follow-up measures in order to reach participants with minimal overlap with face-to-face psychotherapy.

Participants in the CAU group are informed that they will have to complete the following two assessments and will get access to the program of their choice after completing the follow-up. In the experimental conditions, participants receive an email with their web access to either (1) Res-Up! (focusing on resilience) or (2) REMOTION (focusing on emotion regulation).

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Measures

Overview

Items recording demographic information of patients will be presented at baseline and a reduced battery at 6 and 12 weeks. Patient diagnostic status will be obtained during the initial interview by conducting a Structured Clinical Interview I (German version) for Diagnostic and Statistical Manual of Mental Disorders (respectively a clinical assessment) by an experienced psychotherapist [53,54]. A full description of all outcomes in the study is provided in Table 1. All measures will be provided via a web platform. Data collection will be supported by email reminders.

Table 1. Assessments listed by time points.

Variable and outcome	Instrument	Time point		
		Baseline	6 weeks	12 weeks
Demographics		✓	✓	✓
Structured clinical interview or clinical assessment		✓		
Primary outcome				
Symptom severity	BSI-18[a]	✓	✓	✓
Secondary outcomes				
Resilience	WIRF[b]; CD-RISC-10[c]	✓	✓	✓
Emotion regulation	SEK-27[d]; FrAGe[e]	✓	✓	✓
Other outcomes				
Depressive symptoms	PHQ-9[f]	✓	✓	✓
Self-esteem	RSES[g]	✓	✓	✓
Self-compassion	SCS-D[h]	✓	✓	✓
Working alliance	WAI-I[i]		✓	✓

[a]BSI-18: Brief Symptom Inventory [55,56].

[b]WIRF: Witten Resource Questionnaire [57].

[c]CD-RISC-10: Connor-Davidson Resilience Scale [58].

[d]SEK-27: Self-assessment of Emotion Regulation Skills [59].

[e]FrAGe: Questionnaire Assessing the Acceptance of Unpleasant and Pleasant Emotions [60].

[f]PHQ-9: Patient Health Questionnaire-9 [61].

[g]RSES: Rosenberg-Self-Esteem Scale [62].

[h]SCS-D: Self-Compassion Scale—German [63].

[i]WAI-I: Working Alliance Inventory I (adapted for web-based interventions) [64].

Primary Outcome Measure

The primary outcome measure in this study is general symptom severity measured with the Brief Symptom Inventory—a short form (BSI-18; German version) [55] of the Symptom-Checklist-90-Revised (SCL-90R) [65]. The BSI-18 has 18 items and is a frequently used questionnaire to measure general symptom severity (Cronbach α=.85-.89) with good psychometric properties [56], comparable to those of the SCL-90R [65].

Secondary Outcome Measures

Resilience will be assessed by two instruments: (1) the Witten Resource Questionnaire [57], a 37-item self-report of personal and external resources with high reliability (Cronbach α=.72-.85), and (2) the Connor-Davidson Resilience Scale-10 [58], an internationally used 10-item self-report of individual resilience with high reliability (Cronbach α=.81-.90).

Emotion regulation will be assessed via the following two instruments: (1) Self-assessment of Emotion Regulation Skills-27 (Selbsteinschätzung emotionaler Kompetenzen) [59], a 27-item self-report measure of emotion-regulation skills with high reliability and validity (Cronbach α=.90), and (2) the Questionnaire Assessing the Acceptance of Unpleasant and Pleasant Emotions (Fragebogen zur Akzeptanz von Gefühlen) [60], a 32-item self-report of the acceptance and suppression of pleasant and unpleasant emotions with good reliability and validity.

Other Outcome Measures

Severity of depression will be assessed with the German version of the Patient Health Questionnaire-9 (PHQ-9) [61]. The PHQ-9 is an internationally used 9-item self-report for screening, diagnosing, monitoring, and measuring the severity of depression with a high retest reliability and validity (Cronbach α>.86).

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Self-esteem will be assessed with the Rosenberg-Self-Esteem Scale [62], an internationally used 10-item self-report of general self-esteem with high reliability and validity (Cronbach α=.72-.85).

Self-compassion will be assessed with the Self-Compassion Scale [63], an internationally used 26-item self-report of self-compassion with high reliability and validity (Cronbach α>.90).

In accordance with meta-analytic results [66], the *therapeutic alliance* between participants and the web-based intervention or study team will be measured with an adapted version of the Working Alliance Inventory for guided Internet Interventions (WAI-I) at the end of the intervention [64]. The WAI-I showed good internal consistency at total and subscale level (Cronbach α between .92 and .94). For the purpose of this study, the term "psychologist" was substituted with the term "study team" in the questionnaire.

Information about whether patients started psychotherapy while working with the web-based interventions will be gathered at 6 weeks and 12 weeks. An overview of the assessments and the measures is provided in Textbox 1. Participants receive up to a maximum of 3 weekly reminders via email if they do not answer the questionnaires in time.

Planned Analysis

Data will be analyzed using an intention-to-treat (ITT) approach, including all randomized patients in the outcome analyses, and handling missing data accordingly. Participants will be defined as dropouts if no baseline measurement is given. The primary outcome measure, general symptom severity, will initially be analyzed descriptively. The effects of the interventions on the primary and secondary outcome measures will be analyzed with linear mixed-effect models (LMMs). LMMs are recommended for ITT analyses with missing data because of the possibility to accommodate for missing data without having to exclude or impute data and do not depend on limited assumptions about the variance-covariance matrix. Sensitivity analysis will be conducted to analyze the impact of dropouts, psychotherapy, and medication on results. The effect sizes of all within groups for pre- to follow-up changes will be computed as Cohen *d*. In addition, clinical significance of changes will be analyzed (reliable change index) [67].

For categorical data, amount, or percentage will be reported. Significance testing of dichotomous data will be conducted with chi-square tests. Results will be reported in accordance with CONSORT (Consolidated Standards of Reporting Trials) [68] and CONSORT-EHEALTH (Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth) checklists [69].

Results

Participant recruitment and data collection started in April 2020 and completed in July 2022. Results for the study are expected in 2023. Regarding our research questions, we expect participants of our study to benefit more from the interventions than participants in the CAU control on the dimensions of resilience and emotion regulation, respectively. To accomplish the initial status of resilience and emotion-regulation competencies, they will be assessed and related to intervention effects in the intervention groups. Furthermore, we expect to find possible differences between CAP and COMP when the intervention is delivered via a web platform.

Discussion

Principal Findings

This study aims to compare a CAU control with 2 transdiagnostic web-based intervention programs, focusing either on resilience (as an example of capitalization strategies) or on emotion regulation (as an example of compensation strategies).

In accordance with previous research [11], we hypothesize that both interventions will be more efficacious than no additional treatment (CAU). According to Fuhr et al [12], web-based interventions that focus on individual parts of psychotherapy—preferably in a blended approach—might be more effective than all elements of a disorder-specific therapy when implemented in a routine setting. Because of the dearth of studies comparing CAP versus COMP interventions directly, no directed hypothesis can be formulated in this context. While the primary outcome targets symptom severity, secondary outcomes assess resilience and emotion regulation as the specific target areas of the individual interventions.

The study will be conducted in Germany in 4 outpatient centers in a clinical sample of approximately 300 participants, 100 in each of the 3 study arms. Matching the transdiagnostic approach of the interventions, participants in the sample will have a variety of different mental disorders and varying symptom severity.

Results from this study will be valuable for practitioners, patients, and mental health services in all fields, due to the transdiagnostic approach. Furthermore, it will contribute to the knowledge and efficacy of evidence-based web-based intervention programs and possibilities of implementation in outpatient routine care. In particular, it will create new knowledge for web-based interventions focusing on resilience and emotion regulation and thus shine light on possible differences of capitalization- and compensation-oriented interventions in web settings.

Limitations

There could be several *limitations* that can be considered. First, our results might not be generalizable to the general population of outpatient psychotherapy patients because we will apply exclusion and inclusion criteria and recruit a self-selected sample. Clinical practitioners in outpatient clinics recruit participants and inform in advance to ensure a clinical sample. Second, dropout rates from web assessments due to nonadherence to the interventions are a frequently known problem of web-based interventions [11]. Third, there might be an influence on the results due to Res-Up! and REMOTION being distributed through 2 different platforms, as usability rates might vary. Furthermore, participants have the possibility to contact the study team via email or chat throughout the whole

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intervention, which should increase adherence to the web-based programs and support motivation [13]. However, it must be taken into consideration that participants were able to reach out to the study team via 2 different methods (chat and email), which might influence adherence. Starting a psychotherapy during participation will be controlled in the study and the analyses. Whether such a combination of web-based interventions and psychotherapy not coordinated with the web-based interventions is regarded as BT or not is a matter of debate in the field [9]. This debate will be addressed in the study publications.

Conclusions

Therapy Online Plus is a multicenter randomized controlled trial, comparing for the first time in a clinical sample a CAU group with 2 transdiagnostic interventions: Res-Up! and REMOTION. To explore the comparison of the 2 transdiagnostic web-based intervention programs, it will assess the transdiagnostic effectiveness of the above interventions, considering different mental disorders. Furthermore, results will extend existing knowledge about the possibilities of implementing web-based interventions in routine psychotherapy settings.

Acknowledgments

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Data Availability

The data sets generated or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

LFT wrote the initial version of the manuscript. All authors contributed to further drafts of the manuscript. UW and TB are the principal investigators of the study.

Conflicts of Interest

None declared.

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Abbreviations

BSI-18: Brief Symptom Inventory-18
BT: blended treatment
CAP: capitalization
CAU: care as usual
COMP: compensation
CONSORT: Consolidated Standards of Reporting Trials
CONSORT-EHEALTH: Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth
DGVT: Deutsche Gesellschaft für Verhaltenstherapie
LMM: linear mixed-effect model
PHQ-9: Patient Health Questionnaire-9
PMR: personal model of resilience
WAI-I: Working Alliance Inventory I (adapted for web-based interventions)

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Protocol

Shoulder Rehabilitation Exercises With Kinematic Biofeedback After Arthroscopic Rotator Cuff Repair: Protocol for a New Integrated Rehabilitation Program

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Abstract

Background: The recovery of scapular and humeral physiological kinematic parameters, as well as the sensorimotor control of movement, plays a primary role in the rehabilitation process after arthroscopic rotator cuff repair. A highly customized rehabilitation approach is required to achieve this aim. Biofeedback can be a useful tool, but there is poor evidence of its application in the rehabilitation after arthroscopic rotator cuff tear repair.

Objective: The aim of this paper is to outline an innovative exercise-based rehabilitation program exploiting visual biofeedback for the recovery of patients arthroscopically treated for rotator cuff repair.

Methods: For establishment of the innovative program, a multidisciplinary team involving experts in shoulder surgery, rehabilitation medicine, physical therapy, and biomedical and clinical engineering was formed. Starting from a conventional rehabilitation program, the team selected a set of exercises to be integrated with a biofeedback tool, named the INAIL (National Institute for Insurance against Accidents at Work) Shoulder and Elbow Outpatient program (ISEO program). ISEO is a motion analysis system based on inertial wearable sensors positioned over the thorax, scapula, humerus, and forearm. ISEO can return a visual biofeedback of humerus and scapula angles over time or of the scapula-humeral coordination, with possible overlap of patient-specific or asymptomatic reference values. A set of 12 progressive exercises was defined, divided into four groups based on humerus and scapula movements. Each group comprises 2-4 of the 12 exercises with an increasing level of complexity. Exercises can require the use of a ball, stick, rubber band, and/or towel. For each exercise, we present the starting position of the patient, the modality of execution, and the target position, together with notes about the critical factors to observe. The type of visual biofeedback to adopt is specified, such as the coordination between angles or the variation of a single angle over time. To guide the therapist in customizing the patient's rehabilitation program, a list of operative guidelines is provided.

Results: We describe various applications of the ISEO exercise program in terms of frequency and intensity.

Conclusions: An innovative rehabilitation program to restore scapular and humeral kinematics after rotator cuff repair based on kinematic biofeedback is presented. Biofeedback is expected to increase patient awareness and self-correction under therapist supervision. Randomized controlled trials are needed to investigate the potential effect of the exercise-based biofeedback in comparison with conventional rehabilitation programs.

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KEYWORDS

rotator cuff tear repair; wearable sensor; biomechanic; eHealth; rehabilitation; scapula; biofeedback; kinematic; exercise; shoulder

Introduction

Scapular dyskinesis is a common condition in a variety of shoulder disorders, including rotator cuff tears [1-5], with the medio-lateral and anterior-posterior scapular rotations most commonly affected [6]. The evaluation and treatment of scapular dyskinesis are challenging; in particular, finding accurate and repeatable measures to define "how much" scapular movement is dyskinetic and if it is a cause or effect of the rotator cuff tear is objectively difficult [7,8].

An exercise-based, manual, and proprioceptive treatment of scapular dyskinesis should be included in an individualized rehabilitation program following arthroscopic rotator cuff tear repair, with the purpose to restore pain-free physiological function of the shoulder [9]. Current rehabilitation programs should always refer to the time of tendon healing, surgical technique, evidence-based guidelines, literature, biomechanics, and kinesiology foundations, and should avoid a generic approach or a too-strict protocol [10-12]. However, the current literature lacks tools to specifically support therapists in the difficult challenge to tackle shoulder dyskinesis.

To address this aim, biofeedback systems might support patients in improving their own body function by receiving additional information about its status. This is typically achieved by sensing the target function though a wearable technology and returning this information to the patient through an alternative intrinsic sensory feedback (eg, audio, tactile, visual) [13].

Evidence about the use of biofeedback in rehabilitation of shoulder disorders remains limited in terms of both quantity and quality [14,15]. Some preliminary evidence suggests that biofeedback can improve scapular control in patients with adhesive capsulitis [16] and subacromial impingement syndrome, either based on electromyography (EMG) or simple video qualitative biofeedback [17-19]. However, there is poor evidence about the impacts of biofeedback based on quantitative kinematic data. In 2018, Hotta et al [20] reported a study on 26 subjects with impingement syndrome who were assessed during arm elevation before and after completion of a scapula training protocol based on kinematic biofeedback. No substantial differences were found for the range of motion (ROM) of the three scapular rotations, whereas the segmental coordination between the scapula and humerus showed significant differences with respect to scapular tilt in the lowering of the arm and with respect to internal rotation in the elevation and lowering of the arm. Opposite conclusions can be gathered from the study of Antunes et al [21], who completed a randomized controlled trial involving 30 healthy subjects divided into two groups. They tested the effectiveness of kinematic biofeedback on motor relearning transfer during shoulder flexion and a daily activity (drinking from a glass). All subjects were tested before and after the training. The training comprised scapular-focused exercises, performed with a real-time kinematic biofeedback tool consisting of 2D visual information of the scapulo-thoracic orientation. The results demonstrated that real-time kinematic biofeedback introduced relevant differences on scapula control and performance. These studies [20,21] refer to the immediate effect of a single-session biofeedback protocol based on few exercises. However, to our knowledge, there are no studies about the application of kinematic biofeedback for the recovery from rotator cuff tear surgical repair.

To fill this gap, we here propose a newly developed innovative exercise-based program, named the INAIL (National Institute for Insurance against Accidents at Work) Shoulder and Elbow Outpatient program (ISEO program), for the recovery of patients arthroscopically treated for rotator cuff repair. This program integrates the conventional rehabilitation program developed at the Service of Functional Recovery and Rehabilitation of the Azienda Unità Sanitaria Locale (AUSL) Romagna (Ceccarini Hospital, Riccione, Italy), with use of a kinematic visual biofeedback tool that provides a real-time objective and accurate evaluation of the upper arm kinematics [22].

Methods

Conventional Rehabilitation Program

The conventional rehabilitation program is based on a biomechanical foundation, the literature, clinical experience, time of tendon healing, and surgical instructions [10,23-25], providing therapists a timeline scheme with restrictions and objectives for each phase.

In phase 1 (day 1 to day 21), immobilization is established with use of an antirotation sling for 21 days. The sling can be removed for personal care or for active mobilization of the elbow, hand, and only sliding movements in elevation/depression and protraction/retraction of the scapula, keeping the gleno-humeral joint in resting position. Patients are instructed about how to wear and correctly remove the sling and about movement restrictions. Individual outpatient rehabilitation sessions start from day 15 and occur twice per week.

In phase 2 (day 21 to day 35), passive gleno-humeral mobilization on the scapular plane under a 90° angle is allowed (no rotational movements), as well as mobilization of the scapula. The sling is gradually removed from day 21 and passive ROM can be gradually increased over 90°. In this phase, basic exercises to activate scapular stabilizers and humeral head depressors are recommended, as well as improving postural alignment. It is crucial to avoid overstress of the repaired tendon. Two individual outpatient sessions per week are performed.

In phase 3 (day 35 to day 60), the aim is to restore full passive ROM, achieve good control of the kinematics, and correct the timing of muscles activation. From day 35, the patient can start performing gleno-humeral extra rotations and active humerus elevation exercises. Restoration of full passive ROM continues.

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In this phase, water exercises are integrated in the recovery program [26]. Four sessions per week are performed: two individual outpatient sessions and two sessions of aquatic therapy in a small group.

The final phase, phase 4 (from day 60 until return to work), occurs 2 months after surgery, in which dynamic strengthening exercises gradually advance using weights and rubber bands, with an increasing load on the repaired tendon. Functional exercises are integrated in the recovery program. In this phase, two individual outpatient sessions and, if still needed, two aquatic sessions per week are performed.

ISEO Program

Overview

The ISEO program integrates use of instrumental kinematic biofeedback in the conventional rehabilitation program, focusing on the improvement of scapular control of patients recovering from arthroscopic rotator cuff tear repair. The ISEO program is based on recent literature about rotator cuff diseases [27,28], EMG and kinematic studies [29-34], shoulder biomechanical foundations [35], exercises described in other randomized controlled trials without biofeedback [36-40], and clinical experience. The ISEO program was developed following Consensus on Exercise Reporting Template (CERT) guidelines [41].

Device

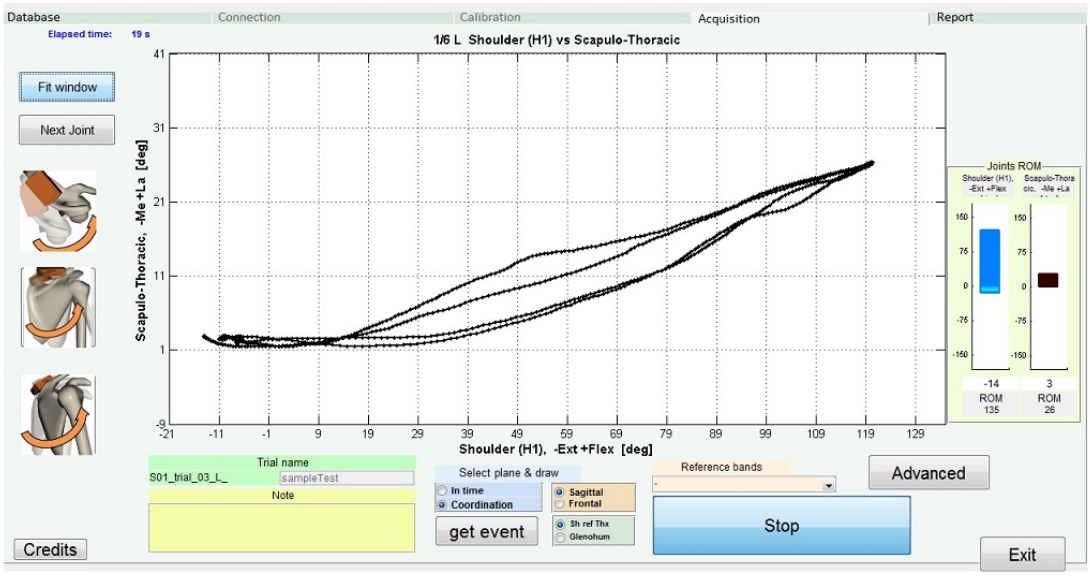
The ISEO program is based on the previously described ISEO protocol application [22]. ISEO was validated against an optoelectronic system [22], and the agreement with respect to the "Scapula-Tracker" method was tested [42]. The reliability of ISEO was assessed, investigating the agreement both within and between testers [43], and age-dependent prediction bands of asymptomatic subjects were estimated [44]. To collect kinematic data, ISEO exploits an inertial and magnetic measurement system (Xsens Technologies, NL). This system is portable, small, easy to use, and comprises four wireless sensors that are placed over the thorax, scapula, humerus, and forearm.

Owing to a dedicated sensor-to-segment calibration and biomechanical model, ISEO provides a quantitative real-time evaluation of humerus and scapula rotations over time with respect to the thorax, as well as the scapulo-humeral coordination by measuring the three scapular rotations with respect to humerus elevation. Specifically, the scapulo-thoracic joint is described by means of three rotations: protraction-retraction, medio-lateral rotation, and posterior-anterior tilting [45]. The humerus orientation is described in terms of elevation with respect to the thorax in the sagittal (flexion-extension) and scapular (abduction-adduction) planes and in the axial rotation (external rotation [ER]/internal rotation [IR]). The scapular plane is intended to be 30°-40° anterior to the frontal plane.

The system provides two types of real-time kinematic data plots, which are reported on a computer screen visible to both the therapist and the patient. The first is the scapulo-humeral coordination plot (Figure 1), which is an angle-angle plot representing humeral elevation on the X-axis (flexion-extension or abduction-adduction) and scapula rotations on the Y-axis (one plot for each scapula rotation). The patient can see how the scapula is moving while performing humerus flexion-extension or abduction-adduction. Preset reference bands [44], based on values obtained from asymptomatic subjects, can be used as targets during the exercises. Furthermore, a custom reference target can be created: the patient performs a reference movement with the help of the therapist, which can serve as the target for all subsequent exercises.

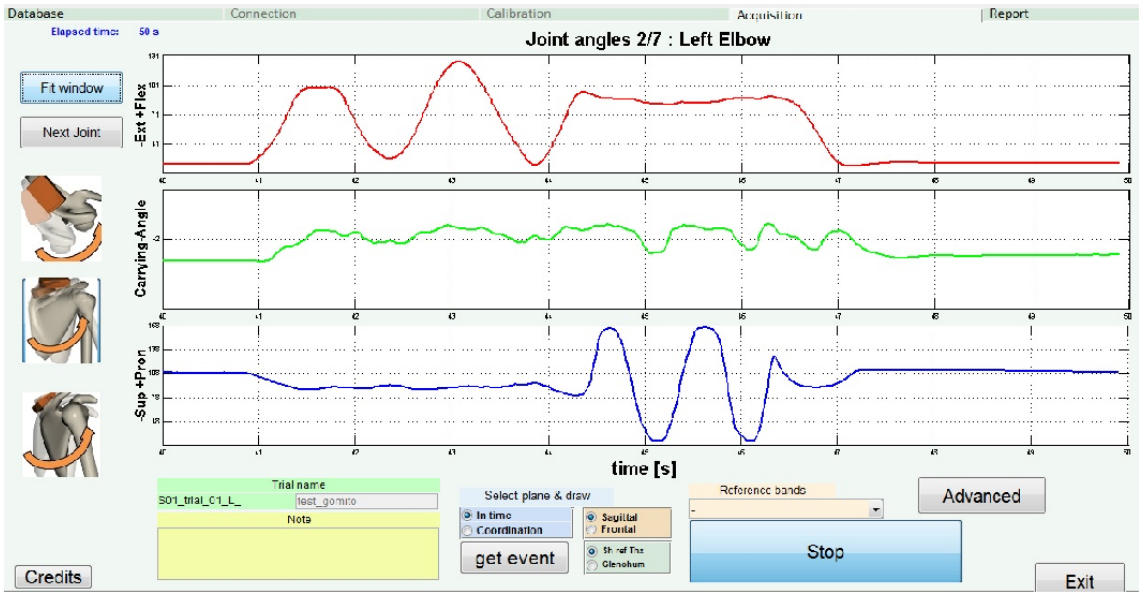
The second is the time plot in which kinematic data are plotted with respect to time (Figure 2), representing humerus-thoracic and scapulo-thoracic rotations changes over time. The relative ROM is also updated in real time.

Figure 1. Scapulo-humeral coordination plot. Example of an angle-angle plot representing humeral flexion on the X-axis and scapula medio-lateral rotation on the Y-axis. L: left; H1: humerus [22]; Me-La: Medio-Lateral rotation; deg: degree; ROM: Range of Motion; Ext: extension; Flex: flexion; Sh ref Thx: shoulder referred to the thorax [22].



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Figure 2. Time plot. Example of elbow kinematic data plotted with respect to time. Sup: supination; Pron: pronation.



Biofeedback Program Development

A multidisciplinary team was established for development of the ISEO program with the professionals typically involved in postoperative rehabilitation, patient assessment, and technology management. Specifically, the team comprised three experts in shoulder surgery and specific experience in shoulder rotator cuff arthroscopy (687 cumulative cases per year), two in rehabilitation medicine, two in physical therapy, and three in biomedical and clinical engineering (two with a PhD in shoulder biomechanics), each with more than 15 years of experience in the field.

After learning the ISEO motion analysis protocol, the team selected exercises from the conventional rehabilitation program as a starting point for integrating the biofeedback technology. In selecting and adapting the exercises, the team assumed the following constraints: (1) ISEO sensors shall not interfere with exercise execution and vice versa (eg, avoiding supine position or sensor contact with any physiotherapy equipment); (2) the therapist must not touch ISEO sensors during a possible manual interaction with the patient (eg, touching the shoulder); (3) the use of aids such as a ball, stick, and elastic band shall be preserved; (4) the visual biofeedback shall be clearly defined to facilitate the patient's engagement and therapist interpretation; (5) exercises shall be performed while watching the visual interface on a screen in a comfortable position for both the patient and the therapist; (6) every exercise shall be monitored and directed by manual and/or verbal inputs by the therapist [46]; (7) to facilitate instructions to the patients, exercises shall only consider humerus movements in one of the main motion planes (sagittal, frontal, and transverse); and (8) exercises shall span all levels of skills, from early to end-phase rehabilitation.

Specifically, the multidisciplinary team selected 12 exercises. The two physical therapists and the two engineers then met during four 3-hour sessions to practice with the ISEO systems while performing the exercises. The two physical therapists, in turns, served as the test subject and therapist. This allowed them to have direct experience in exploiting the system from both the clinician and the patient perspective. Each exercise was checked in terms of respecting the selection constraints. During the practical sessions, engineers supported the physical therapists in identifying the best visual biofeedback to exploit, following the principles reported in the next section. At the end of the four practical sessions, the multidisciplinary team reconvened for a conclusive internal consensus meeting, to (1) review and confirm that all constraints were met, (2) group exercises based on the plane of moment, (3) define their progression, (4) define the physical therapy equipment, and (5) agree on the modality of visual biofeedback. Moreover, the modality of the intervention was set, together with a set of guidelines for therapists.

Biofeedback Graphical Interface and Interpretation

The choice of the graphical interface to be used during the execution of a specific exercise is determined by the objective of the exercise itself.

If the main objective of an exercise is to work on a single joint angle (eg, ER/IR of the humerus with the scapula in a fixed position or scapular protraction/retraction with the humerus in a fixed position), a time plot of the angle of interest should be used. In this case, the main objective of an exercise is usually to obtain variation of the ROM (ie, ROM maximization for physiologic movements or ROM minimization for compensatory movements). The patient and therapist can monitor the trend and the ROM of the specific angle in real time.

If the main objective of an exercise is to work on a multisegmental coordination (eg, scapula medial rotation vs humerus sagittal elevation), then a scapulo-humeral plot should be used. This type of graph is particularly relevant for modulation of the scapulo-humeral coordination, which is usually altered in dyskinetic shoulders. The therapist can ask the patient to minimize or maximize the specific scapula movement during elevation of the humerus. Reference bands [44] can be used as the target (if indicated), and both the patient and the therapist can monitor the performance of the coordination in real time.

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It should be considered that use of a time plot graph during an assessment and correction of a coordinated movement can lead to substantial loss of information, and therefore to a partial and potentially misleading feedback. By contrast, the use of a scapulo-humeral plot graph during a single joint movement can unnecessarily complicate the biofeedback graph and may not clearly highlight the kinematic trend of interest.

Figures 1 and 2 are examples of the graphs provided to both the therapist and the patient during execution of the exercises. During the first session, the therapist should instruct the patient with an extensive description of the graphs, and then a brief refresh session should be provided at the beginning of each exercise. Even if the patient is not capable of appreciating the biomechanical details of the graphs, they will be able to associate their movement variations to the curves plotted, and, with therapist assistance, understand the association between segmental movements and graph variations.

Exercises

Overview

The ISEO program includes four groups of exercises (Table 1). The grouping is based on the plane of movement of the humerus (Groups 1 to 3) or of the scapula (Group 4). Each group includes a set of exercises, with a progression in difficulty and/or in load.

Table 1. List of the exercises included in the ISEO program.[a]

Exercise[b]	Physiotherapy equipment	Biofeedback
Group 1		
A: Active assisted flexion/extension with a Bobath ball	Bobath ball	Coordination plots for the humerus elevation in the sagittal plane; time plot for ER/IR[c] of the humerus with respect to the thorax
B: Active assisted flexion/extension with a stick	Stick	Coordination plots for the humerus elevation in the sagittal plane; time plot for ER/IR of the humerus with respect to the thorax
C: Active flexion/extension by stretching a rubber band	Rubber band	Coordination plots for the humerus elevation in the sagittal plane; time plot for ER/IR of the humerus with respect to the thorax
D: Active flexion/extension open chain	Optional: weight and/or rubber band	Coordination plots for the humerus elevation in the sagittal plane; time plot for ER/IR of the humerus with respect to the thorax
Group 2		
A: Active assisted abduction/adduction with a Bobath ball	Bobath ball	Coordination plots for the humerus elevation in the scapular plane; time plot for ER/IR of the humerus with respect to the thorax
B: Active abduction/adduction by stretching a rubber band	Rubber band	Coordination plots for the humerus elevation in the scapular plane; time plot for ER/IR of the humerus with respect to the thorax
C: Active abduction/adduction open chain without/with load	Optional: weight and/or rubber band	Coordination plots for the humerus elevation in the scapular plane; time plot for ER/IR of the humerus with respect to the thorax
Group 3		
A: Active ER/IR arm in adduction	Soft ball, towel, or pillow	Time plots for the three scapula rotations; time plot for ER/IR of the humerus with respect to the thorax
B: Active ER/IR at 90° flexion	Optional: weight and/or rubber band	Time plots for the three scapula rotations; time plot for ER/IR of the humerus with respect to the thorax
C: Active ER/IR at 90° abduction	Optional: weight and/or rubber band	Time plots for the three scapula rotations; time plot for ER/IR of the humerus with respect to the thorax
Group 4		
A: Push-up	None	Time plots for the three scapula rotations
B: Protraction-retraction at 90° and 120° of shoulder flexion	Optional: weight	Time plots for the three scapula rotations

[a] INAIL (National Institute for Insurance against Accidents at Work) Shoulder and Elbow Outpatient program.

[b]Grouping is based on the plane of movement of the humerus or of the scapula: Group 1=sagittal plane; Group 2=scapular plane; Group 3=external-internal rotation; Group 4=scapulo-thoracic.

[c]ER/IR: external rotation/internal rotation.

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Group 1: Sagittal Plane

This group comprises four exercises characterized by movements of the humerus in the sagittal plane. The principal aim of the motor tasks is to achieve good scapular kinematic control while performing flexion and return. Coordination plots for the humerus elevation in the sagittal plane are used as visual biofeedback for monitoring the three scapula rotations.

The secondary aim is to check the associated ER of the humerus during elevation. For this purpose, the therapist selects the time plot as visual biofeedback to show the patient the active ROM in the ER/IR of the humerus with respect to the thorax.

The focus is on dynamic scapula stabilizer, infraspinatus, teres minor, and core stability (Textbox 1).

In this group, to ease trunk symmetry and stability, and avoid mistakes in scapulo-thoracic movement due to lateral tilt and/or rotation of the spine, all exercises are performed bilaterally, except exercise D that can be performed with one arm only. The progression from exercise C and D can be switched according to patient skills.

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Textbox 1. Description of the exercises in Group 1 (sagittal plane).

- **Exercise A: Active assisted flexion/extension with a Bobath ball**

Starting position: standing with the Bobath ball on a bench, both hands over the ball at shoulder level, and the elbow flexed (Figure 3a).

Figure 3. Group 1 (sagittal plane), exercise A: active assisted flexion/extension with a Bobath ball. (a) Initial position; (b) arrival position at maximum humerus flexion.



Execution: to push the ball ahead using both arms.

Target position: standing position, humerus 90° flexed or more, elbows extended (Figure 3b).

Notes: as soon as the patient gains a wider gleno-humeral range of motion (ROM), they add flexion of the hips and lower back, with a stabilized trunk, to reach a humeral elevation of 120° or more. This exercise allows unloading the supraspinatus and deltoid. For this reason, it is the first to be performed.

- **Exercise B: Active assisted flexion/extension with a stick**

Starting position: standing or sitting position, hands hold the stick (the distance between the hands corresponds to the distance between the shoulders) (Figure 4a).

Figure 4. Group 1 (sagittal plane), exercise B: active assisted flexion/extension with a stick. (a) Initial position; (b) arrival position at maximum humerus flexion.



Execution: with the help of the other arm, the patient performs humerus elevation with the elbow extended.

Target position: standing or sitting position, humerus at 90° of flexion or more, elbows extended (Figure 4b).

Notes: it is important to check the trunk alignment and avoid hyperextension of the spine. If this happens, the exercise must be performed in sitting position and/or the target ROM must be reduced. If pain or inability to perform effective correction of scapular pattern occurs, the exercise can be performed with more distance between the hands, more assistance by the other arm, and/or changing the starting position of the hands (supinated, pronated, neutral).

- **Exercise C: Active flexion/extension by stretching a rubber band**

Starting position: standing or sitting position, elbow extended or at 90° of flexion, with a rubber band slightly stretched by both hands (Figure 5a).

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Figure 5. Group 1 (sagittal plane), exercise C: active flexion/extension by stretching a rubber band. (a) Initial position; (b) arrival position at maximum humerus flexion.



Execution: the patient performs a small external rotation (reaching neutral position, with thumbs up) by stretching the rubber band, lifting up the arms with extended elbows while keeping the rubber band stretched and the humerus extra-rotated.

Target position: standing or sitting position, humerus at 90° flexion or more, elbows extended (Figure 5b). *Notes*: it is important to check trunk alignment and avoid hyperextension of the spine. The use of a rubber band provides greater activation of the infraspinatus and teres minor in comparison to the exercise performed without resistance.

- **Exercise D: Active flexion/extension open chain without/with load**

Starting position: standing or sitting position, extended elbow (Figure 6a).

Figure 6. Group 1 (sagittal plane), exercise D: active flexion/elevation open chain without/with load. (a) Initial position; (b) arrival position at maximum humerus flexion.



Execution: the patient lifts up the arms keeping both elbows extended.

Target position: standing or sitting position, humerus at 90° flexion or more, elbows extended (Figure 6b).

Notes: it is important to check the trunk alignment and avoid hyperextension of the spine; if performing with one arm, lateral flexion or rotation of the spine should be avoided. The exercise can be performed starting with 90° elbow flexion. Starting without a load is recommended as a first step; a weight or a rubber band can be progressively added later.

Group 2: Scapular Plane

This group comprises three exercises characterized by movements of the humerus in the scapular plane. The principal aim of the motor tasks is to achieve good scapular kinematic control during gleno-humeral abduction/adduction. Coordination plots in the scapular plane are used as visual biofeedback for monitoring the three scapula rotations during humeral elevation. The secondary aim is to check the associated ER of the humerus during elevation. For this purpose, the therapist selects the time plot as visual biofeedback to show the patient the active ROM in the ER/IR of the humerus with respect to the thorax.

The focus is on dynamic scapula stabilizer, infraspinatus, teres minor, and core stability (Textbox 2).

It is important to note that elevation on the sagittal and scapular plane is a functional motion (eg, reaching), and therefore needs to be trained as soon as possible and with accuracy. There is high activation of the serratus anterior and lower trapezius, resulting in lateral rotation of the scapula [32]. The lower trapezius maintains the instantaneous center of rotation of the scapula and helps the serratus anterior maintain the scapula close to the thorax, even if each muscle inserted in the scapula contributes to dynamic stabilization [3].

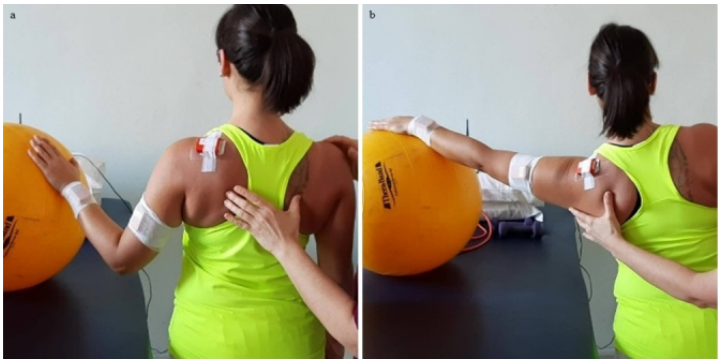
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Textbox 2. Description of the exercises in Group 2 (scapular plane).

- **Exercise A: Active assisted abduction/adduction with a Bobath ball**

Starting position: standing position, Bobath ball on a bench or on the physiotherapy bed, hand over the ball at shoulder level, elbow in flexion (Figure 7a).

Figure 7. Group 2 (scapular plane), exercise A: active assisted abduction/adduction with a Bobath ball. (a) Initial position; (b) arrival position at maximum humerus abduction.



Execution: the patient pushes the ball sideways on the scapular plane.

Target position: standing position, shoulders at 90° flexion, elbow extended (Figure 7b).

Notes: as soon as the patient gains a wider gleno-humeral range of motion (ROM), they add low back lateral flexion to reach a humerus abduction of 120° or more.

- **Exercise B: Active abduction/adduction by stretching a rubber band**

Starting position: standing or sitting position with extended elbows and a rubber band slightly stretched by both hands (Figure 8a).

Figure 8. Group 2 (scapular plane), exercise B: active abduction/adduction by stretching a rubber band. (a) Initial position; (b) arrival position at maximum humerus abduction.



Execution: the patient performs a small external rotation by stretching the rubber band, keeping both thumbs up, and then lifts up the arms on the scapular plane while keeping the rubber band stretched, the elbows extended, and the thumbs up.

Target position: standing or sitting position, humerus at 90° abduction on the scapular plane or more, elbows extended (Figure 8b).

Notes: it is important to check the trunk alignment and avoid hyperextension of the spine. The use of a rubber band provides greater activation of the infraspinatus and teres minor in comparison to the exercise performed without resistance.

- **Exercise C: Active abduction/adduction open chain without/with load**

Starting position: standing or sitting position with extended elbows (Figure 9a).

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Figure 9. Group 2 (scapular plane), exercise C: active abduction/adduction open chain without/with load band. (a) Initial position; (b) arrival position at maximum humerus abduction.



Execution: the patient lifts both arms upward.

Target position: standing or sitting position, humerus at 90° abduction on the scapular plane or more, elbows extended (Figure 9b).

Notes: it is important to check the trunk alignment and avoid hyperextension of the spine; if performing with one arm, the lateral flexion or rotation of the spine should be avoided. Starting without a load is recommended as the first step; a weight or a rubber band can be progressively introduced.

Group 3: External-Internal Rotation

This group comprises three exercises characterized by axial rotational movements of the humerus. The principal aim of this session is to achieve good scapular kinematic control during gleno-humeral ER and IR considering different humeral elevation positions. Time plots of the scapula are used as visual biofeedback to monitor the variation of the three scapula rotations during the execution of the exercise (eg, the patient must keep the line as flat as possible). The secondary aim is to achieve good active rotational ROM of the humerus and restore the strength of the rotator cuff muscles; time plots of the humerus with respect to the thorax are used as visual biofeedback for this purpose.

The focus is on dynamic scapula stabilizers, rotator cuff muscles, and core stability (Textbox 3).

Note that the progression for every exercise starts without a load, which can then be increased by using a rubber band or weights. Exercises B and C start with the arm laying on a horizontal support and progress without support (the patient keeps their arm lifted on their own). All exercises can be performed with both arms at the same time. The execution of the exercises in standing position requires higher core stability. In the case of poor postural core stability, the exercises can be performed with the back against the wall.

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Textbox 3. Description of the exercises in Group 3 (external/internal rotation).

- **Exercise A: Active external/internal rotation arm in adduction**

Starting position: standing or sitting position, arm adducted, hand on the belly, thumbs up, elbow 90° flexed, a small soft ball (or a towel or small pillow) between the elbow and trunk (Figure 10a).

Figure 10. Group 3 (external-internal rotation), exercise A: active external/internal rotation arm in adduction. (a) Initial position; (b) arrival position at maximum humerus external rotation.



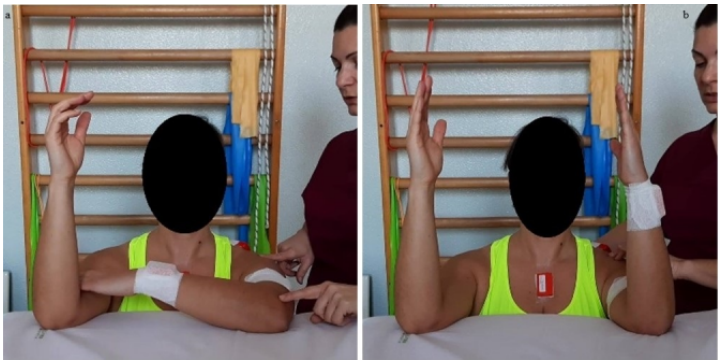
Execution: the patient performs an external rotation of the humerus, keeping the ball fixed.

Target position: standing or sitting position, arm adducted, humerus externally rotated, elbow 90° flexed, thumbs up (Figure 10b).

- **Exercise B: Active external/internal rotation at 90° flexion**

Starting position: sitting or standing position, with the humerus at 90° flexion and internally rotated, elbow at 90° flexion, and forearm in horizontal position (Figure 11a).

Figure 11. Group 3 (external-internal rotation), exercise B: active external/internal rotation at 90° flexion. (a) Initial position; (b) arrival position at maximum humerus external rotation.



Execution: the patient performs an external rotation of the humerus.

Target position: humerus at 90° flexion and externally rotated, elbow at 90° flexion, and forearm in vertical position (Figure 11b).

- **Exercise C: Active external/internal rotation at 90° abduction**

Starting position: sitting or standing position, with the humerus at 90° abduction in the scapular plane and internally rotated, elbow at 90° flexion, and forearm in horizontal position (Figure 12a).

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Figure 12. Group 3 (external-internal rotation), exercise C: active external/internal rotation at 90° abduction. (a) Initial position; (b) arrival position at maximum humerus external rotation.



Execution: the patient performs an external rotation of the humerus.

Target position: humerus at 90° abduction and externally rotated, elbow at 90° flexion, and forearm in vertical position (Figure 12b).

Group 4: Scapulo-Thoracic

This group comprises two exercises characterized by movements of the scapula with respect to the thorax, while keeping the humerus in a predefined fixed elevation position. The principal aim of this session is to achieve strengthening of the serratus anterior together with the lower and medium trapezius and rhomboids. Scapula time plots are used as visual biofeedback to monitor the variation of the three scapula rotations during the execution of the exercises.

The focus is on the serratus anterior, trapezius, rhomboids, and core stability (Textbox 4).

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Textbox 4. Description of the exercises in Group 4 (scapulo-thoracic).

- **Exercise A: Push-up**

Starting position: feet on the ground, hands on a bench or on a physiotherapy bed (more height means less load), and humerus at 90° flexion (Figure 13a).

Figure 13. Group 4 (scapulo-thoracic), exercise A: push-up. (a) Initial position; (b) arrival position.



Execution: while keeping core stability, the patient performs elbow flexion/extension, nearing the body to the bench and back.

Target position: during the nearing, the elbows must stop before passing the line of the trunk (Figure 13b).

Notes: the therapist guides the patient to obtain good postural alignment and to stabilize the scapula. In this exercise, the scapula time plots have to be as flat as possible.

Weight-bearing exercises in a close kinetic chain show significantly greater muscle activation (mainly on the serratus anterior and infraspinatus) while increasing the load on the shoulder [29,34]. The progression of the exercise is from a standing, weight-bearing position to full weight-bearing (if possible).

- **Exercise B: Protraction-retraction at 90° and 120° shoulder flexion**

Starting position: sitting position, humerus in flexion (between 90° and 120°), and elbows extended (Figure 14a).

Figure 14. Group 4 (scapulo-thoracic), exercise B: protraction-retraction at 90° and 120° shoulder flexion. (a) Initial position; (b) arrival position.



Execution: while keeping core stability, the patient performs protraction and retraction of the shoulder girdle.

Target position: sitting position, humerus in flexion (between 90° and 120°), elbows extended, and shoulder girdle in maximum protraction (Figure 14b).

Notes: the exercise should be performed with both arms at the same time. In this exercise, the scapula time plots are used to check the variation of protraction-retraction and medio-lateral rotations. Progression starts with support of the elbow and forearm and then free (with or without holding a weight).

This exercise is specific for the serratus anterior and can be performed in standing position, but this requires higher core stability. In case of poor postural core stability, the exercises can be performed with the back against the wall.

Guidelines for the Therapist

Textbox 5 provides operative guidelines to guide the therapist in customizing the patient's rehabilitation program.

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Textbox 5. Operative guidelines for therapists during execution of the program.

- **Assessment**

To choose the appropriate exercise and its starting level, the therapist first assesses the patient's passive and active range of motion (ROM), the presence of pain at rest and during active movements, and the capability to maintain good postural control during active elevation.

- **Exercise presentation**

The therapist must provide a description and demonstration of the exercise to the patient, explaining what is shown on the screen and the visual goal to achieve.

- **Performance evaluation**

For every exercise, the aim is to achieve satisfactory neuromuscular control, without pain or compensatory strategies, with good postural alignment and core stability.

- **Intervention**

If an exercise is performed incorrectly and/or with compensation or pain, the therapist intervenes, giving physical and/or verbal guidance. The exercise can be modified (eg, decreasing the load, changing the starting position) or changed to an easier one.

- **Progression and load**

Any increase in difficulty and load must be gradual, individually adjusted, and with respect of the patient's pain. Exercise progression can be achieved by increasing the ROM, the load, and changing the dosage and the starting position. All active exercises start with no weight other than the arm weight, and progress in 0.5-kg increments. Exercises with a rubber band (Rep band) start with light resistance (Level 1, yellow band) and progress with greater resistance (Level 2, orange band; Level 3, green band; Level 4, blue band). The progression of load occurs when the patient is able to perform a series of 10 repetitions for the specific exercise with no pain and any compensate. The assessment of scapula compensations can be performed using reference bands [44] provided for the scapulo-humeral coordination movements (while executing the specific movement, patient kinematic values should be within bands). If the time plot graph is used, the ROM of the specific angles should be observed and assessed: ROM maximization for physiologic movements and ROM minimization for compensatory movements.

Results

We foresee the application of the exercise program twice a week, during individual physiotherapeutic sessions. Each session shall include 10 minutes for system preparation and calibration on the subject: sensors can be fixed over body segments (thorax, scapula, humerus, and forearm) by means of elastic bands and tape, following the previously detailed protocol [43]. The screen displaying the biofeedback graphs should be positioned to ensure a comfortable view for the patient and then 30 minutes of effective treatment will be conducted. Application of the ISEO program should start from the 45th day after surgery (or the timeline specified by surgeons) until the end of the rehabilitative treatment (ie, time of return to work).

Discussion

Strengths of the ISEO Program

We developed an innovative exercise-based program (ISEO program) for the recovery of patients arthroscopically treated for rotator cuff repair, which incorporates a kinematic visual biofeedback tool providing a real-time objective and accurate evaluation of the upper arm. We expect the biofeedback tool to support therapists and patients in the difficult challenge to tackle shoulder dyskinesis.

Specifically, with a multidisciplinary team of shoulder surgeons, physiatrists, physical therapists, and engineers, we defined a set of 12 progressive exercises divided in four groups based on the plane of movement of the humerus (Groups 1 to 3) or of the scapula (Group 4). Exercises can require the use of balls, sticks, rubber bands, and towels. For each exercise, the neuromotor goal and type of visual biofeedback is specified. Lastly, a detailed description of the method of administration of the protocol and a complete list of guidelines for therapists are provided for correct application and patient-specific customization (eg, administration of the progression and load for a single patient). To our knowledge, this is the first presentation of such a comprehensive rehabilitation program incorporating kinematics biofeedback; therefore, no direct comparisons to the literature are possible.

The ISEO rehabilitation program exploits quantitative motion analysis measures collected in real time by ISEO, owing to the use of wearable inertial and magnetic sensors. The ISEO protocol is extensively documented in the literature, with full details provided allowing its implementation on a wide range of possible hardware platforms. The documentation includes the availability of quantitative prediction bands for patient classification based on bootstrap statistical parameters. Reference bands were provided in Excel files as annexes of the main publication [44] for prompt availability. Commercial solutions are available by companies unrelated to the authors.

The description of the ISEO rehabilitation program is the first step toward randomized controlled trials investigating its potential efficacy and effectiveness in improving patients' functional outcomes, activity level, and quality of life in comparison with conventional programs not incorporating kinematics biofeedback. In particular, it can be hypothesized that the ISEO program can be more effective than a conventional, nonvisual biofeedback protocol in increasing patient function in the short-term (90 days) and mid-term (1 year).

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In this context, we believe that among many possible outcome measures, the following three would allow forming a global picture of the patients and might serve as primary outcome measures depending on the study aims.

Outcome Measures

Functional Outcomes

The Scapula-Weighted Constant-Murley score [47], which is a modified version of the well-established Constant-Murley score for shoulder disorders, incorporating a specific assessment of scapula dyskinesis, was applied for the assessment of 32 patients arthroscopically treated for rotator cuff tear undergoing postoperative rehabilitation. The study showed that when scapula dyskinesis is accounted for, the number of patients with "good results" at 90 days postsurgery decreased from 31% to 9.5%, and at follow-up (after at least 6 months), the percentage dropped from 87.5% to 50%. This highlights the impact of scapula dyskinesis on the overall shoulder function and reinforces the common agreement that rehabilitation protocols should specifically address scapula dyskinesis [1,48].

Activities

The Disabilities of the Arm, Shoulder and Hand (DASH) score [49], exploring the impact of impairment on activities of the daily living, including work and recreational tasks, can be used as an outcome measure of activity. Psychometric properties specific for rotator cuff disease have been established supporting its use [50].

Health-Related Quality of Life

the EuroQuol-5D (EQ-5D) [51] instrument is an established measure of quality of life, which is recommended in cost economics and heath technology assessment studies, including interventions at the shoulder such as rotator cuff repair [52].

Limitations

The ISEO program has limitations. A complete description of shoulder kinematics would also comprise sternoclavicular and acromioclavicular motion. Due to the size of the wearable sensors and the impossibility to reliably track segment position, the direct measure of sternoclavicular and acromioclavicular motion is not part of the current ISEO protocol. Therefore, their contribution to shoulder movement was not considered. The ISEO program does not have an age-range limitation, but requires patients to construct an intuitive understanding of the graphs and plots used for the visual feedback and link them to their own body motion. In the initial phase of the program, this requires some extra communication effort by the therapist to introduce the visual biofeedback to the patient. We might hypothesize that patients with a higher degree of confidence with digital systems can benefit the most or more quickly from the biofeedback system. In addition, the ISEO program was developed primarily for patients who underwent an anatomical rotator cuff repair and reconstruction. Finally, the ISEO program requires additional time for therapists to set up the system, and to troubleshoot hardware and software warnings, which can potentially slow down the active part of the therapy.

Conclusions

We believe that the major strength of the ISEO program is providing a comprehensive tool that might effectively and quantitatively support rehabilitation professionals in tackling scapula dyskinesis, as recommended in the literature, by enhancing patient body awareness. Furthermore, the ISEO program can provide the opportunity to undertake a more engaging rehabilitation process, leveraging on the ludic aspect of the "digital feedback" and its novelty. The ISEO protocol provides quantitative parameters that can improve therapist-patient communication (as well as intra- and interprofessional communication), who can refer to objective enhancement or worsening of the kinematics over several sessions.

Acknowledgments

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Conflicts of Interest

None declared.

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Abbreviations

AUSL: Azienda Unità Sanitaria Locale
CERT: Consensus on Exercise Reporting Template
DASH: Disabilities of the Arm, Shoulder and Hand
EMG: electromyography
EQ-5D: EuroQuol-5D
ER: external rotation
INAIL: National Institute for Insurance against Accidents at Work
IR: internal rotation
ISEO: INAIL shoulder and elbow outpatient protocol
ROM: range of motion

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Protocol

An Evidence-Based Serious Game App for Public Education on Antibiotic Use and Antimicrobial Resistance: Protocol of a Randomized Controlled Trial

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Abstract

Background: The misuse and overuse of antibiotics contribute to the acceleration of antimicrobial resistance (AMR), but public knowledge on appropriate antibiotic use and AMR remained low despite ongoing health promotion efforts. App gamification has gained traction in recent years for health promotion and to affect change in health behaviors. Hence, we developed an evidence-based serious game app "SteWARdS Antibiotic Defence" to educate the public on appropriate antibiotic use and AMR and address knowledge gaps.

Objective: We aim to evaluate the effectiveness of the "SteWARdS Antibiotic Defence" app in improving the knowledge of, attitude toward, and perception (KAP) of appropriate antibiotic use and AMR among the public. The primary objective is to assess the changes in KAP of antibiotic use and AMR in our participants, while the secondary objectives are to assess the extent of user engagement with the app and the level of user satisfaction in using the app.

Methods: Our study is a parallel 2-armed randomized controlled trial with a 1:1 allocation. We plan to recruit 400 participants (patients or their caregivers) aged 18-65 years from government-funded primary care clinics in Singapore. Participants are randomized in blocks of 4 and into the intervention or control group. Participants in the intervention group are required to download the "SteWARdS Antibiotic Defence" app on their smartphones and complete a game quest within 2 weeks. Users will learn about appropriate antibiotic use and effective methods to recover from uncomplicated upper respiratory tract infections by interacting with the nonplayer characters and playing 3 minigames in the app. The control group will not receive any intervention.

Results: The primary study outcome is the change in participants' KAP toward antibiotic use and AMR 6-10 weeks post intervention or 6-10 weeks from baseline for the control group (web-based survey). We will also assess the knowledge level of participants immediately after the participant completes the game quest (in the app). The secondary study outcomes are the user engagement level (tracked by the app) and satisfaction level of playing the game (via the immediate postgame survey). The satisfaction survey will also collect participants' feedback on the game app.

Conclusions: Our proposed study provides a unique opportunity to assess the effectiveness of a serious game app in public health education. We anticipate possible ceiling effects and selection bias in our study and have planned to perform subgroup

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analyses to adjust for confounding factors. The app intervention will benefit a larger population if it is proven to be effective and acceptable to users.

Trial Registration: ClinicalTrials.gov NCT05445414; https://clinicaltrials.gov/ct2/show/NCT05445414

International Registered Report Identifier (IRRID): DERR1-10.2196/45833

(JMIR Res Protoc 2023;12:e45833) doi:10.2196/45833

KEYWORDS

antibiotic resistance; antibiotic use; app development; development; educational intervention; health education; public education; randomized controlled trial; serious games; user engagement; user satisfaction

Introduction

Background

Antimicrobial resistance (AMR) has been a long-standing public health threat since the 1940s [1]. The widespread use of antibiotics has accelerated the growth of antibiotic-resistant bacteria, which can cause infections that are fatal and resistant to treatment [1]. In 2019, 4.95 million and 1.29 million global deaths were associated with and attributable to bacterial AMR [2]. It is estimated that 10 million global deaths will be attributable to AMR annually if no action is taken to tackle the problem [3].

AMR infections are often costly to health systems due to the excess length of hospital stays, more outpatient visits, and increased use of intensive care and isolation units [4]. For example, a methicillin-resistant *Staphylococcus aureus* infection could result in an additional US $31,338 (~SGD $42,620) hospitalization cost per patient [5]. AMR infections can also incur societal costs in terms of loss in work productivity and the risk of further infections [6,7].

The misuse and overuse of antibiotics are major drivers of AMR [8]. One pertinent factor contributing to the misuse of antibiotics is the public's knowledge deficit of the indication for and proper use of antibiotics [9]. This knowledge deficit often leads to unnecessary patient demand for antibiotics and subsequent misuse of antibiotics [10,11]. Knowledge deficit in antibiotic use and AMR was consistently present among populations worldwide [12]. A nationally representative survey conducted in 2021 on adult Singaporeans demonstrated the association between poor knowledge of antibiotics and inappropriate use [9]. The study also showed that younger adults with poor knowledge had a higher likelihood of misusing antibiotics when compared with older adults, highlighting the need to address knowledge deficits on antibiotic use among the younger population in Singapore to mitigate the problem of AMR in the community [9].

Rationale for the Study

Traditional mass public educational efforts using brochures, posters, and advertisements are extensive in outreach but questionable in improving the general public's knowledge on appropriate antibiotic use and AMR [13,14]. In recent years, gamification—the use of game-playing elements to encourage the use of services—has gained attention as a novel strategy to affect change in health behaviors [15,16]. Increased user engagement can potentially lead to higher knowledge gains and retention for sustained behavioral change. Gamification was found to improve the knowledge of AMR. For example, a study found that the E-bug student website significantly increased the knowledge of appropriate antibiotic use among schoolchildren in the United Kingdom [17]. Another study using an web-based board game also found significant improvement in medical students' knowledge of AMR immediately and 1 month post intervention [16]. These proof-of-concept studies support the effectiveness of gamification in increasing knowledge on appropriate antibiotic use among young people, which should be strengthened with randomized controlled trials along with other segments of the population and age groups.

Hypothesis and Objectives

The public has low awareness of the gravity of AMR as many people perceive AMR as a nonimminent life-threatening problem for themselves [18]. We expect serious games to increase user engagement in learning, which leads to short- and long-term improvements in knowledge of, attitude toward, and perception (KAP) of the appropriate use of antibiotics. Leveraging digital technology to increase the awareness of AMR and the knowledge of appropriate antibiotic use is timely as Singapore develops into a digitalized nation. Hence, we have developed an evidence-based serious game app, "SteWARdS Antibiotic Defence," to educate the public on appropriate antibiotic use and AMR. Users will learn about antibiotic use and AMR through the minigames and the bite-sized information released from the app.

We aim to evaluate the effectiveness of the "SteWARdS Antibiotic Defence" app in improving the KAP of appropriate antibiotic use and AMR among the public in Singapore. The primary objective is to compare the changes in KAP of antibiotic use and AMR among the app users with the control group. The secondary objectives are to assess (1) the extent of user engagement with the app by evaluating the users' average screen time per day and (2) the level of user satisfaction in using the app for learning through a user satisfaction survey.

Methods

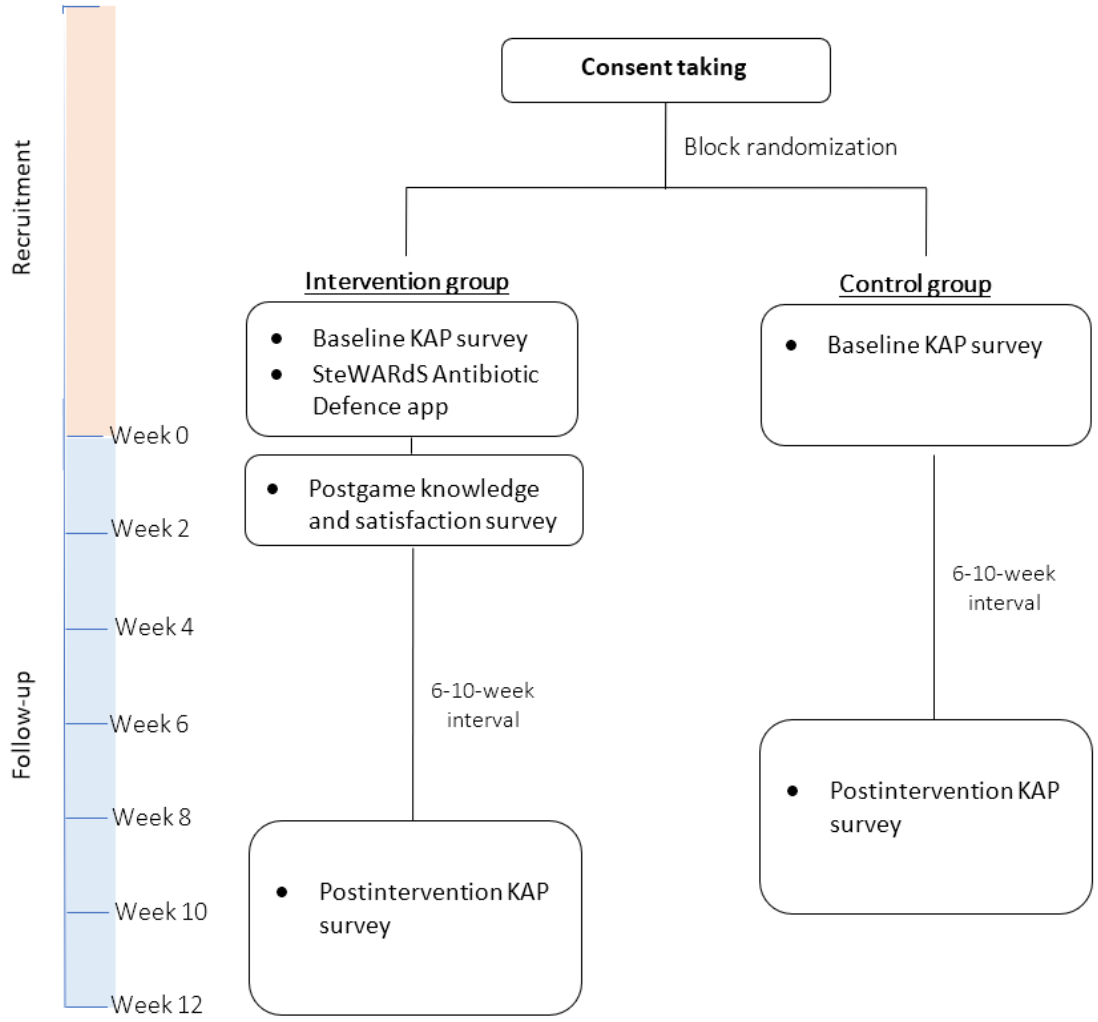
Study Design

Our study is a parallel 2-armed randomized controlled trial (RCT) assessing the effectiveness of a serious game app in increasing the knowledge and changing the attitudes and perceptions about appropriate antibiotic use and AMR among the public. Participants randomized to the intervention group will be asked to download and complete the quest in the

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"SteWARdS Antibiotic Defence" app within 2 weeks on their smartphones. "SteWARdS Antibiotic Defence" is an evidence-based serious game app developed by the study team. The app will deliver bite-sized information on (1) the management of upper respiratory tract infections (URTIs), (2) appropriate antibiotic use, and (3) development of AMR to users as they complete the game quest (refer to the section on "Serious Game App Intervention"). Participants randomized to the control group will not be required to download the app. All participants will be followed up for 6-10 weeks to assess the effects of short-term knowledge retention. The design of the trial is presented in Figure 1.

Figure 1. Trial schedule. KAP: knowledge of, attitude toward, and perception.



Recruitment

Study Setting

We will recruit patients or their caregivers from government-funded primary care clinics (ie, polyclinics) in Singapore. These polyclinics manage 20% of Singapore's primary health care needs by providing subsidized services such as medical treatment for acute and chronic conditions, vaccinations, and health education [19]. The conditions seen at the polyclinics are acute and are managed outside the health care setting (eg, at home) after consultation with a health care provider. Hence, the intervention will occur outside the health care setting.

Inclusion and Exclusion Criteria

Participants must be older than 18 years, be a visitor of National Healthcare Group (NHG) polyclinic, have access to an Android smartphone, and be able to comprehend the English language to be eligible for the study. Those who are unable to install Android app, not proficient with smartphone apps, and have visual or cognitive impairment will be excluded from the study.

Randomization and Blinding

Participants will be block randomized into the intervention or control group (4 participants per block) by drawing lots from a box. They will not be blinded from the randomization as the study team has to explain the study to them. Only participants assigned to the intervention group have access to the serious game app.

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Serious Game App Intervention

App Development

The "SteWARdS Antibiotic Defence" app was developed in collaboration with Temasek Polytechnic, a public tertiary institution in Singapore. The study intervention involves the completion of a quest in the "SteWARdS Antibiotic Defence" app. Participants are required to respond to 11 baseline knowledge items before they can begin the game quest. The game quest involves passing all levels of 2 minigames (ie, Tower Defence and Match3), while the third game (ie, Endless Runner) allows participants unfamiliar with the game mechanics to earn extra coins to complete the intervention within the stipulated time frame.

Completing the baseline knowledge items is a prerequisite to proceed to the minigames, while completing the postgame knowledge items will fulfill the app intervention. The app will release bite-sized messages to reinforce concepts on the prevention and management of URTI and the appropriate use of antibiotics and AMR through gameplay and interaction with the nonplayer characters in the app. Participants are given only 3 "lives" daily to complete the Tower Defence and Match3 levels. Hence, the game completion may take slightly longer if the participant fails the levels more than 3 times in a day.

Evidence-Based Content

Many serious game apps intended for improving user knowledge failed to consider the cognitive process of learning, which limited the effectiveness of the intended outcome of the app. Therefore, we used Bloom's revised taxonomy [20] as a guide to design the game mechanics. Concepts such as "antibiotics are effective for bacteria and not viruses" are reinforced repeatedly in the minigames to enhance memory. Users have to apply the concepts they learn to advance the game levels. For example, users must eliminate bacteria with the antibiotic turret and viruses with the symptomatic relief medication turret in the Tower Defence game and use the correct weapon to shoot the correct organism in the Endless Runner game. Users will also experience the "cost" of AMR by realizing that "misusing" antibiotic turrets in the earlier levels will drain their resources for tackling the superbug in the final level. Feedback (whether users respond to the items correctly or not) will be provided for the postgame knowledge survey to help users evaluate the concepts they learn from the game quest.

We derived the educational content in the app from a rigorous review of knowledge gaps [9,12,21], antibiotic guidance [22], and inputs from health care professionals. The in-app messages were also adapted to the local context to ensure their relevance to users.

Game Components

Overview

The app was designed with gamification elements to enhance user engagement and the learning process [23]. Gamification was achieved through clear rules, goal-oriented challenges, and rapid feedback. Users learn about appropriate antibiotic use and effective methods to recover from uncomplicated URTIs by interacting with the nonplayer characters and playing the minigames in the app. The 3 minigames are as follows.

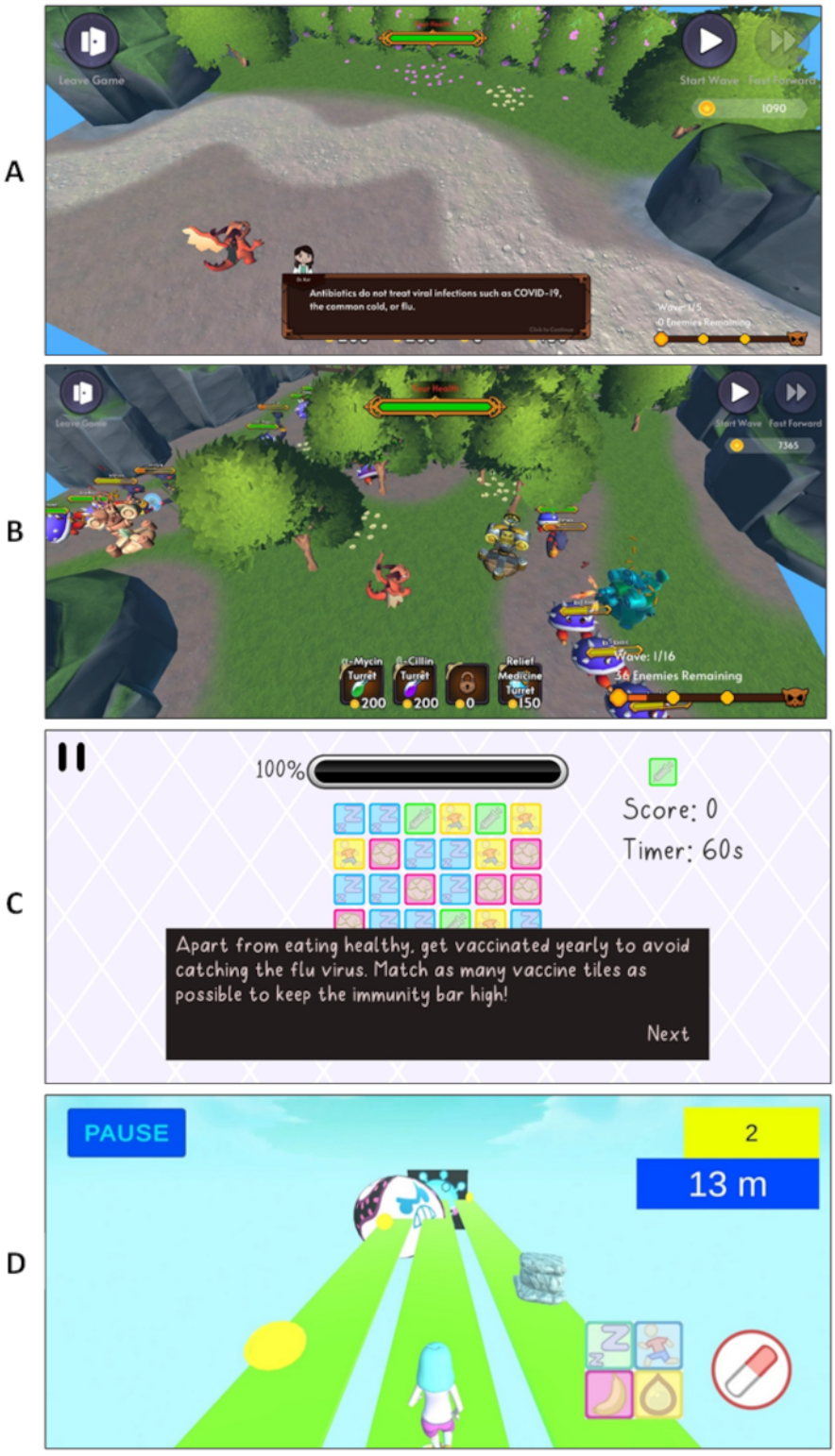
Tower Defence

Players are required to build turrets (types of medication) to defend their fort (immunity bar) against enemies (bacteria or viruses) and have to cross 9 levels to complete this game. Players have to choose the appropriate turrets and strategically place them at appropriate locations to effectively target their enemies.

The first 2 levels teach players that antibiotics are effective against bacteria. Players are encouraged to buy and build antibiotic turrets to survive the onslaught of bacteria enemies (Figure 2A). The next 2 levels build on this knowledge by introducing the concept that antibiotics are bacteria specific. There will be 2 different types of bacteria (α-bac and β-bac), and players must build antibiotic turrets (α-mycin and β-cillin) specific to each bacteria enemy to clear the level (Figure 2B).

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Figure 2. (A) Scene in the Tower Defence game with bite-sized educational messages. (B) Scene in the Tower Defence game with α-bac, β-bac, and viruses. (C) Scene in the Match3 game with messages for healthy living. (D) Scene in the Endless Runner game. The round icon represents a bacterium.



Levels 5 and 6 educate users that antibiotics are not effective against viruses. New enemies (viruses) are introduced, and players must buy immunity turrets to attack the viruses. To further instill this concept within players, bacteria and virus enemies attack simultaneously in levels 7 and 8, and players need to select the appropriate antibiotic and immunity turrets to complete the levels.

The last level educates players on antibiotic resistance by introducing multidrug-resistant organisms. Players have to invest in an expensive antibiotic turret effective against the multidrug-resistant organisms to complete this level.

The game difficulty increases with the levels, while players must be mindful of the coins they spend when purchasing and upgrading the necessary turrets. The immunity levels of the

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players are affected when too many enemies reach the end point. Players lose the level when their immunity bar falls to 0.

Match3

Match3 attempts to educate players on good health habits. Level 1 encourages participants to get a healthy amount of sleep. Level 2 focuses on the importance of a nutritious diet. The third level emphasizes on immunization, and the last level urges participants to care for their health in a holistic manner. Users are required to match 3 or more tiles within a specific time limit to successfully clear each level (Figure 2C).

Endless Runner

This game aims to reinforce the message that antibiotics are only effective against bacteria and not viruses. The player has to dodge obstacles and collect coins while running. An antibiotic gun is effective in shooting away bacteria obstacles, while an immunity gun can be used to shoot virus obstacles. This game also allows players to collect coins for use in the Tower Defence game in an engaging manner (Figure 2D).

Study Procedures

We will randomize participants who are eligible for the study into the control or intervention group and collect their personal details in a password-protected file. Their demographic information will be collected on FormSG, a trusted web-based form manager developed by the Singapore government to collect survey data securely. We will require all participants to complete a 10-minute baseline KAP survey. For participants randomized into the intervention group, a study team member will assist participants in installing the "SteWARdS Antibiotic Defence" app on their mobile phones and provide further instructions regarding the game quest. Participants will need to complete the game quest in the app within 2 weeks, after which they will need to complete the postgame knowledge and an app satisfaction survey to complete the intervention. Participants will be contacted 6-10 weeks after completing the game quest and be asked to complete a 10-minute postintervention KAP survey.

Control group participants will complete a 10-minute baseline KAP survey and be contacted 6-10 weeks after recruitment to complete another 10-minute KAP survey. Participants will receive personalized messages via WhatsApp with a FormSG survey link and instructions to complete the postintervention survey during the study follow-up. We will provide reimbursement to all participants for their participation in the study. Reimbursement is structured according to behavioral economics principles to motivate participants to complete the intervention [24]. For example, reimbursement is divided over smaller amounts and is tiered to a higher value as the participant completes tasks toward the completion of the study. If the participant withdraws from the study, he or she will be asked to uninstall the app and will not be further contacted other than for reimbursement. The data collected prior to study withdrawal will be used for intention-to-treat analysis.

Outcome Measures

Primary Outcomes

The primary outcome is the change in participants' KAP toward antibiotics use and AMR 6-10 weeks post intervention from the baseline, measured by the KAP survey. We developed the KAP survey by assessing the literature [9,21,25] and adapting questions from the World Health Organization's multicountry public awareness survey on antibiotic resistance [12]. Our KAP survey comprises 11 knowledge items with binary responses and 14 three-point Likert-scale items assessing participants' attitudes and perceptions on antibiotics use and AMR (Table 1). We reverse-scored a few knowledge items in the postgame and postintervention surveys to reduce memory effects on knowledge gains.

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Table 1. Knowledge, attitudes, and perception survey items.

Item number	Items	Response options
Knowledge items		True and false
1	If bacteria are resistant to antibiotics, it can be very difficult or impossible to treat the infections they cause.	
2	It is okay to buy the same antibiotics or request for them from a doctor, if they had helped you get better previously when you had the same symptoms.	
3	It is okay to use antibiotics that were given to a friend or family member, as long as they were used to treat the same illness.	
4	I can stop my antibiotics course when I start feeling better.	
5	Antibiotic resistance is an issue that could affect me or my family.	
6	Antibiotic resistance is only a problem for people who take antibiotics regularly.	
7	Many infections are becoming increasingly resistant to antibiotics treatment.	
8	Antibiotic resistance is an issue in other countries and in Singapore.	
9	Antibiotic resistance occurs when your body becomes resistant to antibiotics and antibiotics no longer work as well.	
10	Bacteria which are resistant to antibiotics can spread from person to person.	
11	Antibiotic-resistant infections could make medical procedures like surgery, organ transplant, and cancer treatment much more dangerous.	
Statements on attitudes and perceptions		Agree, disagree, and unsure
12	I feel that there is no harm in taking antibiotics.	
13	I need antibiotics to help me to recover faster from the common cold and flu.	
14	I need antibiotics to help me to recover from serious symptoms of the common cold and flu.	
15	I need antibiotics if I continue to have flu symptoms after 2 weeks.	
16	I will keep leftover antibiotics for future use if I have similar symptoms.	
17	I would stop my course of antibiotics if I am concurrently using alternative remedy (eg, Traditional Chinese Medicine, Ayurveda medicine, Jamu).	
18	I am scared of getting antibiotic resistance infections.	
19	I will see another doctor if my doctor does not give me antibiotics.	
20	How I use antibiotics does not affect my chances of getting antibiotic resistance infections.	
21	How I use antibiotics does not affect other people's chance of getting antibiotic resistance infections.	
22	I normally keep antibiotic stocks at home in case of emergency.	
23	If my family member is sick, I will usually give my antibiotics to them.	
24	I normally stop taking antibiotics when I start feeling better.	
25	I will take leftover antibiotics when I think I need them.	

Secondary Outcomes

The secondary outcomes are the assessment of the user engagement level (tracked by time spent on the app) and satisfaction level of playing the game (via the immediate postintervention survey). The satisfaction survey will also collect participants' feedback on the game app.

Sample Size

Based on 2 meta-analyses, the effect size of serious games on improving the knowledge of chronic disease management among young people is 0.361 (95% CI 0.098-0.624) [26] and healthy lifestyle promotion in general is 0.334 (95% CI 0.260-0.407) [27]. Using the smaller 2-tailed effect size of 0.334 with a 1:1 allocation ratio, a minimum sample size of 142 per group is required to detect significant changes in knowledge at a power of 80% and an α level of .05. Assuming an attrition rate of 30%, we will require a sample size of 200 participants per group for the study.

Statistical Analysis

We will analyze the changes in the KAP scores with multivariable linear regression models and app satisfaction levels among intervention group participants with descriptive analyses. We will also conduct a post hoc power analysis to

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ensure that the sample size used in our study is adequately powered to detect a significant change.

Ethical Considerations

This study was approved by the NHG Domain Specific Review Board in Singapore (National Healthcare Group Domain Specific Review Board Ref: 2022/00479).

Results

We plan to recruit 400 participants for the study by April 2023. Results are expected to be achieved by June 2023. The data analysis and manuscript are expected to be completed by September 2023.

Discussion

Overview

Our protocol describes an upcoming RCT to evaluate the effectiveness of an evidence-based serious game app in changing the KAP of antibiotic use and AMR among the public. There is currently a paucity of RCTs on the effect of serious game apps on health promotion and health behavior change due to the complexity of evaluating such studies in the population. Many clinical teams have developed stand-alone apps to solve clinical problems, but these apps are often not evidence-based or validated with population-based studies. The myriad of stand-alone apps causes app fatigue and is often unsustainable and limited in its outreach.

The few serious game app studies are targeted at improving physicians' antibiotic prescribing habits [28]. These studies had limited success in changing physicians' prescribing habits and antibiotic use in the community, as patients can influence physicians' prescribing decisions. Since antibiotic prescribing is multifactorial [29,30], it is imperative to concurrently target public awareness of appropriate antibiotic use to slow the progression of AMR. To our knowledge, this is the first RCT that assesses the effect of a serious game app for public education on antibiotic use and AMR. We developed the app with a rigorous review of evidence from the literature and inputs from clinicians, game design specialists, allied health professionals, academics, computer engineers, and members of the public. Therefore, this study will provide us with a rare opportunity to assess the effectiveness of serious game apps in public education to address the threats of AMR.

Potential Limitations

Health promotion efforts to improve the public's knowledge of antibiotics use are ongoing in Singapore via traditional mass media such as posters, advertisements, and billboards. These advertisements may contaminate and dilute the effects of our intervention but should not have a measurable impact on our study as the study period falls outside the national "antibiotic awareness week" campaign. Participants with good baseline knowledge may not see knowledge improvement due to the ceiling effect. We anticipate this problem to be minor, as a recent national study found that knowledge of good antibiotic use and AMR is poor among the population.

We will also ensure that only 1 adult from each household can participate in the study to minimize the possibility of contamination due to randomization (ie, 1 member is randomized into the control group and another into the intervention group). However, we would not be able to ensure that the recruited participant is the person completing the quest in the app, as family members (ie, children) may help to complete the game quest.

Older adults who are not technologically astute may also be excluded from our study or face difficulty in completing the game quest even if they meet the inclusion criteria. We will report problems with recruitment and follow-up and conduct subgroup analyses to assess outcomes between older and younger participants.

Conclusions

Our proposed study provides a unique opportunity to assess the effectiveness of a serious game app in public health education. We may incorporate the "SteWARdS Antibiotic Defence" app as a minigame in an institutional health app platform to provide a sustainable learning resource for a larger population if the intervention is effective and acceptable to users. The findings of this study will also provide a reference for funders, researchers, policymakers, and organizations considering app-based educational interventions for the general population.

Acknowledgments

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Invention disclosure number for the Antibiotic SteWardS Defence app: NHG/ID/202206/03

Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed for this protocol.

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Authors' Contributions

ZH codeveloped the app, conceived the manuscript, obtained the catalyst grant, and drafted the manuscript. WET provided inputs to the study design and support for running the trial. HG codeveloped the app. KN supported the study set up and assisted in drafting the manuscript. AC codeveloped the app, obtained the ALIVE (gAmes for heaLthInnoVationscEntre) grant, and provided inputs to the study design of the trial. TWY obtained the ALIVE grant. All authors critically reviewed the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

AMR: antimicrobial resistance
KAP: knowledge of, attitude toward, and perception
NHG: National Healthcare Group
RCT: randomized controlled trial
URTI: upper respiratory tract infection

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Protocol

Evaluation of the Effectiveness of Therapy for Anxiety in Williams Beuren Syndrome Using a Smartphone App: Protocol for a Single-Case Experiment

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Abstract

Background: Williams syndrome (WS-OMIM 194050, orphaned number: Orpha 904) is a rare condition mostly associated with intellectual disability. People with Williams syndrome are 8 times more likely to have anxiety disorders than the general population. Therapeutic solutions to treat the anxiety remain limited, particularly nonpharmacological therapy. However, cognitive behavioral therapy (CBT) has been found efficacious in managing anxiety disorders and can be used for people with intellectual disability.

Objective: This paper describes a protocol to assess the efficiency of a CBT program based on digital support for people with Williams syndrome and anxiety based on a research methodology designed for rare diseases.

Methods: We will recruit 5 individuals with Williams syndrome and anxiety. They will participate in 9 CBT sessions. Participants will perform daily self-assessments of anxiety using a digital app, which will allow for ecological and repeated evaluation of their anxiety. This digital app will provide support for each therapy session. Anxiety and quality of life will be externally assessed before and after the program and at a 3-month follow-up. This is a single-case intervention research design with multiple baselines implying repeated measures of judgment criteria. The present protocol ensures high internal validity and will help identify encouraging contributions for later clinical trials.

Results: Participant recruitment and data collection began in September 2019, and we project that the study findings will be available for dissemination by spring 2023.

Conclusions: This study will allow the assessment of the efficiency of a CBT program based on digital support to treat anxiety in people with Williams syndrome. Finally, the program could be used as an example of nonpharmacological therapy for rare diseases.

Trial Registration: ClinicalTrials.gov ID: NCT03827525; https://clinicaltrials.gov/ct2/show/NCT03827525

International Registered Report Identifier (IRRID): DERR1-10.2196/44393

(JMIR Res Protoc 2023;12:e44393) doi:10.2196/44393

KEYWORDS

single case experimental design; cognitive behavioral therapy; intellectual disability; rare disease; Williams syndrome; smartphone application; ecological momentary assessment

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Introduction

Williams syndrome (WS) is a rare neurodevelopmental disorder caused by a 7q11.23 deletion encompassing about 25 genes on chromosome 7 [1]. The estimated prevalence is 1 in 7500 live births [2]. Most individuals present with intellectual disability and peculiarities in neuropsychological functioning. The cognitive profile is heterogeneous in terms of strengths and weaknesses and in global functioning [3]. Language skills are generally good, often with deficits in certain executive functions (especially inhibition) [4].

The prevalence of anxiety disorders in WS is high, varying from 16% to 82% [5]. With an anxiety rate 8 times higher than in the general population and 4 times higher than in other individuals with intellectual disability [6], it is the most prevalent mental health problem for individuals with WS. The available drug treatments have been found effective in reducing the level of anxiety in individuals with WS. However, they have side effects [7]. Despite the consequences on quality of life (QoL), there is a lack of research on therapeutic protocols for anxiety for people with WS.

Cognitive behavioral therapy (CBT) belongs to a class of scientifically validated therapeutic interventions. It aims to modify dysfunctional ways of thinking, as well as behavioral patterns, to reduce psychological problems. CBT interventions for anxiety share a focus of changing dysfunctional beliefs and anxious anticipation by using different cognitive, behavioral, and emotional techniques [8]. A meta-analysis [9] showed that CBT provided greater clinical benefit than other forms of psychotherapy in treating several psychological disorders in individuals with intellectual disability. However, in the context of intellectual disability, the number of participants recruited in these studies remains low, and the methodologies used have numerous limitations (eg, no controlled manipulation of the treatment delivered, studies with only 1 patient [10-12], studies evaluating the impact of therapy during 1 week of hospitalization, studies do not allow for patient empowerment [13]). Many of the results tend to show that CBT is a promising therapy for treating the anxiety of patients with intellectual disability [14], but the few studies available and their methodological limitations make further research necessary [15].

A pilot study carried out in 2013 highlighted a mindfulness-based intervention for individuals with WS [13]. The practice of mindfulness is frequently used in CBT interventions. It teaches one to pay attention and to have moment-to-moment awareness [16]. This CBT treatment approach has been found efficacious in treating emotional disorders in individuals with WS. This pilot research took place in a 5-day institutional setting, and the long-term effects of the treatment were not evaluated. In addition, the application of treatment in a context of institutionalization raises the question of the generalization of the results and the autonomy of individuals with WS.

Another study was conducted in 2022, in which a group of 4 adults with WS were virtually delivered an adapted CBT intervention [17]. In this study, a CBT program was adapted for people with intellectual disability. Participants and caregivers in this study reported a high level of satisfaction and a reduction in their anxiety. This study provided support for the acceptability and feasibility of group-based CBT treatment for anxiety in WS. However, the sample size was small, and the methodology used did not have strong scientific reliability.

The objective of our study is to propose and discuss clinical interest in CBT with digital support for anxiety in people with WS, taking into account intellectual disability. Because of the rarity of WS, the single-case methodology seems appropriate. In addition, this methodology allows for analyzing the effects of the intervention at an individual level. The development of digital support will allow participants to perform the therapy exercises at home. This could be particularly interesting for people with intellectual disabilities who need to be assisted with the realization of a number of daily tasks. The objective of the digital support is to empower them. Furthermore, this application makes it possible for the patient to evaluate himself or herself from home on a daily basis, allowing an ecological repeated assessment. We hypothesize that patients with WS will be able to engage in an adapted CBT protocol. We hypothesize that individuals' anxiety will decrease over the course of therapy. We also hypothesize that other factors such as QoL will be improved with this therapy protocol.

Methods

Study Design

We will use a multiple baseline AB single-case experimental design across participants to evaluate the efficacy of the intervention. This method allows for manipulating the intervention in an experimentally controlled manner and testing causal relations among variables of interest in a small group of participants. The multiple baseline design is well-suited for interventions that are irreversible due to learning effects, and it enables testing of whether the improvement in mental health is due to therapy or random factors changing with time [18]. For this purpose, we will use a multiple baseline across subjects and across behaviors design, as our patients will complete a daily self-assessment of 6 items related to their emotions. We will recruit only 5 patients because WS is a rare disease and a minimum of 3 replications of the effect is recommended to increase the reliability of our findings [19]. For each participant, we will first obtain repeated measures during the baseline phase (A) when no treatment is provided. Patients will be assigned to different lengths of the baseline phase to ensure at least 3 replications of the treatment effect [20]. The possible duration of the baseline phase ranges from 14 days to 30 days before treatment onset, as a minimum of 5 measurement points is required [21]. These repeated measures during the baseline phase serve as control conditions to evaluate what changes can be expected without the treatment [9,22]. The duration of the baseline will be randomly assigned by the experimenter. Following that, repeated measures are obtained during a 9-week treatment phase (B) and during 3 months after the treatment to ensure that our measures did not return to the baseline level after the treatment has been withdrawn. Patients will also

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complete a range of nomothetic outcome measures 3 times: (1) baseline, (2) intervention, and (3) follow-up termination.

Participants

We will recruit 5 participants for this study. The inclusion criteria are age >18 years, molecular confirmation of WS, sufficient level of language assessed by a score >7 on the Clinical Evaluation of Language Fundamentals 4 test [23], and complaints of anxiety. The complaints of anxiety can be expressed by the individual or the individual's representative. For the inclusion criteria in this study, we chose to evaluate this complaint with the following Likert scale completed by the participant: "This week I have been anxious" or "This week the individual has been anxious." To be included in the protocol, the participant will need to score at least 1 on this self-rated Likert scale. We chose to include people with low anxiety as well as high anxiety, even if an anxiety disorder is not characterized, because anxiety is generally underestimated in WS, with one longitudinal study finding co-occurring anxiety in approximately 82% of patients with WS [24].

Exclusion criteria are uncorrected visual disturbance, uncorrected deafness, or being already treated for anxiety. Because of the intellectual disability, individuals with WS will be accompanied by a caregiver during visits requiring signing consent or a hetero-evaluation.

Individuals will be recruited from patient associations and among individuals followed in the medical genetics department of Montpellier University Hospital. Interested individuals will receive information about the study, first with a letter; then, they will be in contact with a doctor involved in the study to ask questions. Because of the rarity of WS, individuals recruited could live far from the hospital where the study is taking place. Financial support for travel costs will be offered to each individual taking part in this study. Individuals with WS who wish to be involved and a legal representative will sign written informed consent; then, the individual will be prescreened for inclusion and exclusion criteria.

Ethical Approval

The study has been registered with the committee of protection of people (CPP) Sud-Ouest et Outre-Mer 1 (approval number CPP 1-18-86/SI:1752 (2° HPS)).

Procedures

Baseline

We will recruit 5 individuals with WS. Each participant will have a different length of the baseline period (A). The participants will be allocated to a baseline lasting from 2 weeks to 5 weeks. The baseline phase will begin at the same time for each participant. This multiple baseline design allows for the multiple assessments to serve as control conditions to evaluate what changes can be expected without the treatment [22]. During this baseline period, no therapeutic intervention will take place. The participants will continue their daily life without changing their habits. They will complete a daily self-assessment of 6 items related to their emotions.

Intervention

After the baseline period, each individual will undergo a psychotherapeutic intervention with digital support. This intervention will extend over 9 sessions, spaced 1 week to 2 weeks apart depending on the individual's availability. Each session will last from 45 minutes to 90 minutes and will be carried out with the same clinical psychologist. Participants will use a smartphone app daily as support for the therapy. The app will include relaxation exercises and mindfulness audio. Individuals will continue their daily self-assessment during this intervention period.

Follow-up

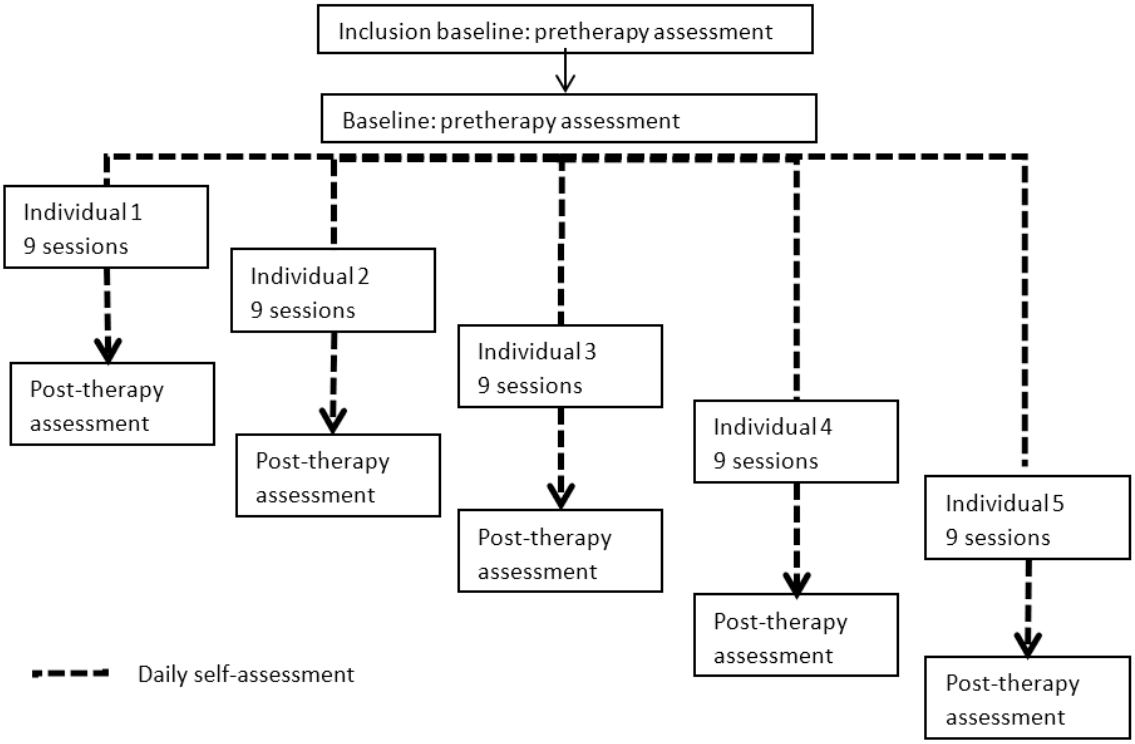
After the 9 intervention sessions, individuals will be invited to continue to apply tools delivered during the intervention in their daily life. They will continue their daily self-assessment for 3 months after the intervention.

During the research (baseline, intervention, follow-up), the individual's representative will complete daily evaluations.

Hetero-evaluations will be carried out during the inclusion visit (baseline), the visit at the start of the intervention (T1), the visit at the end of the intervention (T9), and the follow-up visit 3 months after the end of intervention (Figure 1).

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Figure 1. Protocol flow.



Measures

Repeated Measures: Real-Time Monitoring Technology

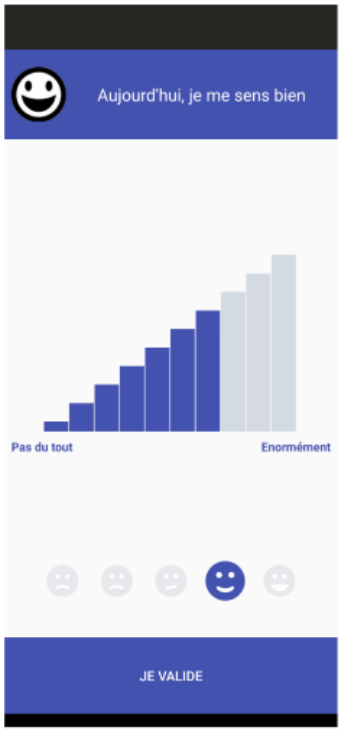
There is no validated tool to assess anxiety repeatedly in our target population, to our knowledge [25]. To take into account the specificity of a population with intellectual disability, a smartphone tool has been developed to allow for repeated self-assessment. It is an app named WillCope. Screenshots of this app are presented in Figures 2 and 3. This app includes 6 questions, each related to anxiety manifestations that are usually used to assess anxiety. The items evaluated were initially chosen by a working committee of 10 people including doctors, psychologists, patients, and caregivers. The choice of these items was based on the Hamilton Rating Scale for Anxiety (HAM-A) [26-28]. Items and questions were tested in a study of >300 persons with intellectual disability.

Figure 2. Screenshot of the WillCope app.



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Figure 3. Screenshot of the WillCope app.



We will use a single item to measure each targeted behavior because it can be more easily included in an experiment in which patients have to perform daily self-assessments for several months. In addition, single items have been shown to be as reliable as assessments using longer scales [29]. In this study, 6 questions will be presented to the 5 individuals, who will evaluate the intensity of each of the items on a daily basis using a Likert scale from 1 to 10. These 6 questions make it possible to evaluate the principal components encountered in anxiety disorders in people with intellectual disability, taking into account the somatic dimension. The wording of the questions is in easy-to-understand language and is associated with a pictogram as well as an audio reading. The questions are formulated in French and are related to anxiety, pain, sleep, motor agitation, well-being, and motivation.

Regarding anxiety, Williams et al [30] demonstrated the scientific validity of a single-item scale for assessing anxiety: “Today, I am anxious.”

Pain is included because of the importance of somatic symptoms associated with anxiety: “Today, I have pain in my body.”

Sleep is included because of the impact of anxiety on sleep: “Today, I slept well.”

Motor agitation is part of the manifestations of anxiety, especially with intellectual disability: “Today, I need to move around.”

Well-being is directly affected by anxiety: “Today, I am happy.”

Motivation can also be affected by anxiety: “Today, I feel like doing things.”

The primary outcome will be the score obtained for the first question related to anxiety.

The neuropsychologist will check that the questions are correctly understood during the first evaluation. A support person may also accompany the individual in the daily evaluation for guidance, without answering for the individual.

A repeated assessment questionnaire will also be provided to the support person or the caregiver accompanying the individual, to obtain a repeated hetero-assessment of the individual's anxiety. The questions will be the same as in the self-evaluation but will be formulated in the third person.

The smartphone support allows for real-time monitoring of the emotional state of individuals in an ecological environment in their daily life. Patients with intellectual disability might have difficulties self-assessing using classical CBT tools like charts to complete or notebook-based assessments completed with paper and pencil. The app was developed in easy-to-read and understand language, with pictograms and audio support, which makes it accessible to people who cannot read or write. An alarm is integrated into the app to remind the participants to complete the exercises. A backup of each of the patient’s self-assessment is encrypted and stored in the app. It can then be shared by email but requires decryption software to be opened. This backup allows visibility on the frequency of use of the app for self-assessment.

Nomothetic Quantitative Measures

Nomothetic quantitative measures will be completed at the assessment, termination, and follow-up visits.

A hetero-assessment of anxiety will be performed by a clinical psychologist using the HAM-A [26,27]. This scale is the most widely used test to assess the intensity of anxiety symptoms. It is applicable to all adults and consists of 14 questions rated according to the severity of symptoms: anxious mood (worry, apprehension, irritability); feelings of tension, fatigability,

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inability to relax, startled reactions, crying, tremors, fears; sleeping troubles; difficulty concentrating and memory problems; depressed mood; somatic symptoms; and behavior during the interview. Symptoms are rated using 5 degrees of severity, from absence to disabling intensity. The overall score ranges from 0 to 56: the higher the score, the more severe the anxiety. This scale will be administered by a clinical psychologist.

This scale does not constitute our main criterion of analysis and will be used in addition to the single-item repeated measures of anxiety-related behaviors and manifestations. It seems to us interesting to allow a descriptive analysis of the evolution of anxiety before and after treatment, and this scale presents several advantages for evaluating anxiety in a population with intellectual disability. Indeed, it allows a hetero-evaluation of anxiety by a psychologist. It also allows the somatic dimension of anxiety, as well as the patient's behavior with its anxious manifestations, to be taken into account. QoL will be assessed with the Abbreviated World Health Organization Quality of Life (WHOQOL-BREF) questionnaire [31]. This scale consists of 26 items, each rated from 0 to 5. The scale will be completed by the representative and by the individual with WS assisted by a clinical psychologist who can explain the items that would be difficult to understand.

Ideographic Qualitative Measures

Individuals will undergo a semidirected interview with a psychologist at each session to identify any significant events in the patient's life. This interview can last from 5 minutes to 30 minutes. The objective will be to observe the presence of factors that cannot be measured by quantitative analyses. The main themes addressed will be the following: the occurrence of a significant event in the participant's life, daily activities, relationships and social situation, autonomy. We will also observe the perception of the impact of the therapy on daily life and elements of daily life modified thanks to the therapy.

In addition, a questionnaire will be completed by the patient at the end of the research and at 3 months after the therapy to evaluate the benefit of and satisfaction with the therapy. The semistructured interviews will be transcribed verbatim. We will determine the presence or absence of the aforementioned factors. The data will be extracted and combined with the data from the questionnaire completed at the end of the therapy and at the follow-up, to evaluate the effectiveness of the intervention.

Intervention

In our study, the intervention will consist of a CBT program based on a process-based approach targeting the processes underlying emotional disorders [32]. This protocol has the advantage of targeting cognitive processes common to different forms of anxiety disorders. Anxiety disorders can have different manifestations in WS, and the rarity of this disease does not allow us to recruit a sufficient number of patients with the same clinical picture. Thus, this protocol is particularly suitable to target the cognitive anxiety processes common to all our patients despite their differences in expression. We will build on the unified protocol designed for children and first developed in 2011 [33]. This protocol has been adapted for WS based on existent literature [30]. It has been found that people with intellectual disability can perform better when linking situations directly to emotions than they do when attempting to link the triad of beliefs, emotions, and situation [34]. It has been shown that the identification of behavior and feelings is associated with verbal ability and the identification of thoughts is linked to IQ [35]. Language ability is very developed in people with WS, but their ability to understand some abstract situations is more limited. It has been shown that the behavioral elements are more consistently effective than the cognitive elements and the behavioral elements are more amenable to short-term intervention [36], which is the case in our study. For these reasons, we decided to not emphasize cognitive restructuration in our protocol but to focus on emotion identification, exposure, and meaningful actions.

During the entire protocol, the psychologist will speak slowly and repeat information. He will give the participant time. He will only emphasize the essential points and give concrete examples. The content of each module is simplified and adapted in easy-to-read and understand language in a way that empowers individuals with WS. Nonverbal communication is emphasized.

People with intellectual disability often have poor self-image, so the following points, which are important in any psychotherapy work, are particularly so with this population. The therapeutic alliance is very important. The patient must be involved in the choice of exercises to be done at home. The objectives must be simple and achievable. Throughout the work, positive reinforcement and appreciation of the participant are essential.

A clinical psychologist specializing in CBT will perform the intervention during the 9-session therapy protocol. Each session will last about 1.5 hours and will be organized as described in Table 1.

First, mindfulness, which has been found effective in individuals with WS, will be integrated into each session [37]. Mindfulness is our innate capacity to pay conscious and full attention to something in the moment. It is often defined as "the awareness that emerges through paying attention on purpose, in the present moment, and nonjudgmentally to the unfolding of experience" [16]. Usually, anxiety therapy is based on mindfulness-based stress reduction. In this protocol, we adapted mindfulness exercises with some exercises used with children [38-40]. The main exercises are mindfulness of the body, of the breath, and of the senses. Mindfulness exercises are integrated into the app so that the participant can repeat them from home on a daily basis. The protocol will target increasing awareness of the emotions present as well as tolerance to emotional sensations. It will also aim to increase cognitive flexibility and will identify and prevent emotional avoidance behaviors as well as exposure.

The intervention will require the daily use of the WillCope app. In addition to allowing daily assessment by the patient, the WillCope app will provide therapy support through relaxation and mindfulness tools. The presence of a single support to allow self-assessments, as well as the realization of mindfulness and relaxation exercises, is facilitating for patients.

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Table 1. Main stages of therapy.

Stage of therapy	Description
Retrospective	Each session begins with a look back at the past week and a return to the exercises performed at home.
Mindfulness and relaxation	
Overall	In every session, individuals with WS[a] will be taught how to perceive their body, thoughts, and emotions objectively, in the present moment, without judging them. Mindfulness helps to stay with difficult feelings without analyzing, suppressing, or encouraging them. Individuals with WS often report that their emotions are out of their control, suddenly invading them in a confusing, disturbing way. This module will help individuals recognize the interaction between thoughts, feelings, and behaviors during the emotional experience. The therapist will help identify primary reactions, or early emotional responses to a situation or memory, and reactions to these primary emotions, which tend to be negative and not focused on the present moment. These concepts are taught during the sessions using concrete emotional situations, activating experiences adapted to each individual. Specifically, reactions to emotions tend to be subjective, judgmental, and negative. An example is a concern that anxiety could hinder the smooth running of an activity in the future. To the extent that these reactions are not based on actual information in the present moment, they may block positive information about the nature of emotional responses.
Unit 1: functional analysis (3 sessions)	
Problem identification	What are the triggers, in what context, what are the associated behaviors and thoughts; intensity of emotions; duration of emotions; consequences of associated behaviors
Identification of motivational elements	What are the individual's values, what are the things that make him happy, and what does he want to develop in his life?
Realization	A schematic illustrating the preceding points is reviewed with the individual.
Unit 2: psychoeducation (3 sessions)	This module consists of a psychoeducation session on emotions in general and anxiety in particular. Emotions such as anger, sadness, and fear are described. During this module, the therapist explains the cognitive, physiological, and behavioral components of emotions and their interactions. Individuals should then begin to understand that their emotions have an adaptive and functional role, providing information about the environment and motivating certain actions. The therapist can describe how avoidance during the emotional event (consequence) leads to maintenance of the anxiety and distress associated with the emotional experience. Schematics are built to illustrate the components of the different emotions of the individual, based on experience in daily life
Unit 3: exposure and engagement in meaningful actions (3 sessions)	Previous sessions allowed the individual to become familiar with feelings related to emotions. One of the difficulties with anxiety is a limitation of the individual's activities and autonomy due to avoidance. Therefore, the last sessions of the therapy are devoted to setting up exposure and actions that allow the individual to maintain autonomy and engage in actions that count, even if unpleasant emotions are present. In each session, examples are applied to the individual's daily life. Tools are provided to deal with some difficult emotions. For example, squeezing a frozen lemon in the hands can defocus the attention of anxiety or anger and defer an impulsive response.
Representative	At the end of each session, the tools presented during the session are described to the individual’s representative.
At home	Exercises to be carried out daily in connection with the current module. Every day, the individual with WS must continue to perform self-evaluation as well as a relaxation or mindfulness exercise available on the WillCope app.

[a]WS: Williams syndrome.

Data Analysis

Our primary outcome will be the changes in the level of anxiety evaluated with a repeated scale. We will graph and analyze data for each participant and each target behavior. We will first visually inspect the analyses as per the guidelines for visual analysis in single-case studies [23]. Within-condition analysis (baseline and intervention phases) will include the evaluation of the stability of the level of data by condition by calculating means, medians, ranges, and stability envelopes. The absolute level of change will be evaluated by calculating the difference between the first and last values in each condition. Between-condition analysis of data will allow for comparisons of adjacent data in the study. The change in the trend direction between phases A and B will be evaluated by identifying the trend as accelerating, decelerating, or zero-celerating. The therapeutic or contra-therapeutic direction will also be reported. The level of change between conditions will be evaluated by calculating the median level of change.

A comparative table of data will be edited for each repeated measure, patient, and step of the protocol. The means, medians, range, stability envelope, and absolute level of change will be presented in this table.

We will use the Tau-*U* to examine the within-phase trend and between-phase difference to estimate the treatment effect both within and between phases. We prefer the Tau-*U* to alternative statistics (ie, proportion of nonoverlapping data) because it provides a baseline trend–corrected estimation of trends in treatment and follow-up phases by combining nonoverlap between phases and trends within phases. The following 3 Tau-*U* indices will be calculated: (1) Tau-*U* A-to-A compares

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a phase-A score with another phase-A score, (2) Tau-*U* B-to-B compares a phase-B score with another phase-B score, and (3) Tau-*U* A-to-B compares a phase-A score with a phase-B score. The Tau-*U* A-to-B is similar to the Mann-Whitney *U* test for group independence, and a *P* value is produced in addition to an estimate of effect size. These Tau-*U* indices estimate the effect of the treatment on both within phase trends and between-phase differences. We will use the following 2 forms of the Tau-*U* indices: the uncorrected and corrected Tau-*U*. The corrected Tau-*U* estimates the degree of the baseline trend and adjusts baseline and treatment phase observations to remove the effect of the baseline trend. We will use the corrected Tau-*U* to estimate an effect size from the corrected data when the Tau-*U* A-to-A is significant [41]. We will use the Tau-*U* calculator web-based application [42].

We will estimate the reliability of change for our nomothetic outcomes using the reliable change index (RCI) [43]. The RCI measures in which direction an individual has changed and estimates whether this change is reliable and clinically significant. We will calculate the RCI statistic for the 3 dimensions of the French WHOQOL-BREF (physical health, psychological health, and social relationships) for which reliability coefficients are available [31]. For each of these 3 WHOQOL-BREF dimensions, we will calculate the value of the standard using our patients' scores at baseline. A reliable change in both treatment and follow-up compared with baseline measures will be achieved with values ≥1.96.

Concerning the HAM-A, there is no fidelity index validated in French, which does not allow the calculation of an RCI value. The results obtained from this evaluation will therefore be used in a descriptive manner, in order to relate them to the repeated evaluations of anxiety that constitute our main evaluation criterion.

A comparative table data will also be edited with the nomothetic outcome measures.

Results

As of spring 2019, the app was fully developed. Participant recruitment and data collection began in September 2019. Due to the COVID-19 crisis, data processing was postponed in 2022-2023, and it is projected that the study findings will be available for dissemination by summer 2023.

Discussion

In this manuscript, we describe the research protocol for evaluating an anxiety therapy program for individuals with WS. WS is a rare genetic disease in which individuals present with intellectual disability of variable intensity but, in general, have good language skills. Most individuals with WS present with anxiety. Because of the rarity of WS, there is a lack of validated studies on the psychotherapy of anxiety in these individuals. Therefore, their anxiety is usually treated with medication, and the side effects are more severe than in the general population. However, some therapies have been found effective in individuals with intellectual disability. Because of their good language skills, such individuals could particularly benefit from psychotherapy.

This manuscript describes the research protocol to test the effectiveness of CBT for anxiety in individuals with WS. This protocol is based on the single-case and multiple baseline research methodology. This methodology is particularly interesting for 2 aspects. First, it is a scientific research method that applies to small samples (as few as 3 people), so it is a particularly interesting methodology for rare diseases. Second, this methodology enables consideration of interindividual variations by observing the results of each individual individually. It enables evaluation of the fluctuations of anxiety in the daily life of individuals. For this protocol, a smartphone app was developed. This app allows daily self-assessment of anxiety by the patients and can be a support mechanism for the therapy protocol. This app can be particularly helpful for a population with an intellectual disability, for whom the appropriation of certain CBT tools may be difficult.

However, this work has some limitations. First, regarding the app, some improvements might be possible. The developed app has not yet been validated from a psychometric point of view. It can only be used to assess the evolution of anxiety for each patient but cannot be used as a diagnostic tool.

In addition, this app makes it possible to store the participant's evaluation data and thus to know when the patient evaluated his or her anxiety, but there are no data to know how the participant used the other tools in the app (the therapy support tools). It would be interesting to integrate a module to know how often the participant uses the app for therapeutic purposes.

Finally, this protocol only includes a small sample of patients with WS. Depending on the results, it would be interesting to evaluate this protocol with patients with other pathologies.

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Authors' Contributions

NL conceptualized the study, designed the protocol, designed the methodology, performed the investigation, wrote the original manuscript draft, and acquired the funding. RT designed the methodology, performed the validation, performed the formal

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analysis, reviewed the manuscript, and supervised the study. DG provides resources, designed the methodology, reviewed the manuscript, supervised the study, and acquired the funding.

Conflicts of Interest

None declared.

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Abbreviations

CBT: cognitive behavioral therapy
CPP: committee of protection of people
HAM-A: Hamilton Anxiety Rating Scale
QoL: quality of life
RCI: reliable change index
WHOQOL-BREF: Abbreviated World Health Organization Quality of Life
WS: Williams syndrome

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Protocol

A Probiotic Intervention With Bifidobacterium longum NCC3001 on Perinatal Mood Outcomes (PROMOTE Study): Protocol for a Decentralized Randomized Controlled Trial

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Abstract

Background: Perinatal mood disorders such as depression and anxiety are common, with subclinical symptomology manifesting as perinatal mood disturbances being even more prevalent. These could potentially affect breastfeeding practices and infant development. Pregnant and lactating women usually limit their exposure to medications, including those for psychological symptoms. Interestingly, the naturally occurring probiotic *Bifidobacterium longum* (BL) NCC3001 has been shown to reduce anxious behavior in preclinical models and feelings of low mood in nonpregnant human adults. During the COVID-19 pandemic, mental health issues increased, and conventionally conducted clinical trials were restricted by social distancing regulations.

Objective: This study, Probiotics on Mothers' Mood and Stress (PROMOTE), aimed to use a decentralized clinical trial design to test whether BL NCC3001 can reduce symptoms of depression, anxiety, and stress over the perinatal period.

Methods: This double-blind, placebo-controlled, randomized, and 3-parallel-arm study aimed to recruit 180 women to evaluate the efficacy of the probiotic taken either during pregnancy and post partum (from 28-32 weeks' gestation until 12 weeks after delivery; n=60, 33.3%) or post partum only (from birth until 12 weeks after delivery; n=60, 33.3%) in comparison with a placebo control group (n=60, 33.3%). Participants consumed the probiotic or matched placebo in a drink once daily. Mood outcomes were measured using the State-Trait Anxiety Inventory and Edinburgh Postnatal Depression Scale questionnaires, captured electronically at baseline (28-32 weeks' gestation) and during e-study sessions over 5 further time points (36 weeks' gestation; 9 days post partum; and 4, 8, and 12 weeks post partum). Saliva and stool samples were collected longitudinally at home to provide mechanistic insights.

Results: In total, 520 women registered their interest on our website, of whom 184 (35.4%) were eligible and randomized. Of these 184 participants, 5 (2.7%) withdrew after randomization, leaving 179 (97.3%) who completed the study. Recruitment occurred between November 7, 2020, and August 20, 2021. Advertising on social media brought in 46.9% (244/520) of the prospective participants, followed by parenting-specific websites (116/520, 22.3%). Nationwide recruitment was achieved. Data processing is ongoing, and there are no outcomes to report yet.

Conclusions: Multiple converging factors contributed to speedy recruitment and retention of participants despite COVID-19–related restrictions. This decentralized trial design sets a precedent for similar studies, in addition to potentially

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providing novel evidence on the impact of BL NCC3001 on symptoms of perinatal mood disturbances. This study was ideal for remote conduct: because of the high digital literacy and public trust in digital security in Singapore, the intervention could be self-administered without regular clinical monitoring, and the eligibility criteria and outcomes were measured using electronic questionnaires and self-collected biological samples. This design was particularly suited for a group considered vulnerable—pregnant women—during the challenging times of COVID-19–related social restrictions.

Trial Registration: ClinicalTrials.gov NCT04685252; https://clinicaltrials.gov/ct2/show/NCT04685252

International Registered Report Identifier (IRRID): DERR1-10.2196/41751

(JMIR Res Protoc 2023;12:e41751) doi:10.2196/41751

KEYWORDS

perinatal mood disturbances; pregnancy; randomized clinical trial; low mood; stress; anxiety; depression; probiotics; mobile phone

Introduction

Background

Anxiety and depression during pregnancy and post partum are referred to as perinatal mood disorders [1-3]. Subclinical symptomatology, including low mood and stress, that does not reach thresholds for clinically diagnosable pre- and postpartum depression and anxiety is also becoming an area of concern. Collectively, such symptoms of varying severity in the perinatal period will be referred to as perinatal mood disturbances (PMD) in this paper. Depressive symptoms are relatively common in the perinatal period, and many women experience mild forms of such negative feelings, typically called *baby blues*, owing to many factors, including physiological hormonal changes [1-5]. It is estimated that as many as 70% of women experience “baby blues” during the postpartum period [4], and approximately 24% of women in their third trimester of pregnancy and 15% of postpartum women experience anxiety [6-8]. Furthermore, low mood and stress often coexist in the postpartum period [4]. The consequences of PMD, even within normal variation of mood and stress, can also have a downstream impact on the infant’s development and behavior owing to alterations in the in utero environment [1-3,8] and in postnatal mother-infant interactions [9,10]. In addition, postpartum mood disorders are reported to be negatively associated with the initiation and duration of breastfeeding [1-4,10,11], which are known to have multiple short- and long-term consequences on maternal and infant health [11,12].

Many women opt to avoid taking pharmacological treatments to address feelings of low mood and stress during the perinatal period [1,13], often to prevent the potential risk of drugs being transferred to the baby through the placenta or breast milk. Thus, there is a specific need for alternative solutions for pregnant and breastfeeding mothers [14]. Currently, many pregnant women are open to consuming naturally occurring probiotics, which are emerging as a potential solution to modulate mood. The concept of a gut-brain axis linking differences in gut microbiome with central nervous system function via endocrine factors, inflammatory mediators, neurotransmitters, and autonomic nervous signaling is becoming more compelling and could explain how probiotics may affect emotions and mood [15].

A randomized controlled trial of the probiotic *Lactobacillus rhamnosus* HN001, whose primary outcome was infant eczema, showed its potential role in reducing PMD as a secondary outcome [16]. However, the strength of the conclusions was limited by the lack of baseline mood scores, mood evaluation at a single time point, and the retrospective collection of mood data 4 to 11 months post partum potentially contributing to recall bias. A more recent study, which assessed the effect of a multiple probiotic strain combination of *Lactobacillus rhamnosus* GG and *Bifidobacterium lactis* BB12 administered to pregnant women with obesity between 12 and 36 weeks of pregnancy, showed no difference between the intervention and placebo groups in improving prenatal depression or anxiety [17]. Other probiotic trials in pregnancy also found no statistically significant effects on PMD [18,19]. Such mixed findings suggest variation in the impact of different probiotics on PMD, consistent with findings of strain-specific effects of probiotics on other health outcomes [20].

Outside of the perinatal setting, the naturally occurring probiotic *Bifidobacterium longum* (BL) NCC3001 normalized anxiety-like behavior in different preclinical models [21,22] and reduced feelings of low mood and emotional reactions to fearful stimuli in human adults with irritable bowel syndrome [23]. However, a possible effect of this probiotic during the perinatal period has not yet been tested.

This study was designed to test the efficacy of the probiotic BL NCC3001 as a nonpharmacological intervention in reducing PMD. In addition, we are investigating the optimal time window for commencement of probiotic intake to obtain a protective effect: whether there is a need to start the intervention prenatally or whether there would still be a beneficial effect if it is started only after delivery. We hypothesize that daily ingestion of the probiotic BL NCC3001 in the perinatal period will lower time-trend scores of mood and stress as measured by the validated State-Trait Anxiety Inventory (STAI) [24] and Edinburgh Postnatal Depression Scale (EPDS) [25] questionnaires.

Decentralized Study

With the unprecedented advent of the COVID-19 pandemic at the start of 2020, the conduct of many clinical trials was hampered by government-imposed restrictions on face-to-face contact. It was particularly challenging to set up new trials to evaluate interventions unrelated to COVID-19 infections,

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especially in populations considered vulnerable, such as pregnant women. Clinical trials that could be designed for remote conduct using digital tools were at an advantage [26]. Given that our intervention could be self-administered without clinical monitoring and that the primary outcome was measurable using electronic questionnaires, the design allowed for decentralized remote conduct. This approach was thought to be also well suited to the advanced, high-resource setting of Singapore where participants have easy access to the technology needed for remote contact with study teams. Here, we present the protocol of an entirely decentralized study in Singapore, the Probiotics on Mothers' Mood and Stress (PROMOTE) study, which could serve as a basis for the design of similar studies in the future.

Methods

Design

Study aspects as well as the technical means used for each aspect are presented in Textbox 1.

Textbox 1. Study aspect and technical means used for each aspect of this decentralized study.

Recruitment

- Digital advertising (social media, parenting websites, and workplace website)
- Physical posters in public places (public transport and stores)
- Paper brochure dissemination in mailboxes and partner locations
- Word of mouth

Registration of interest

- Secured online form; participant-initiated self-referral

Screening and study sessions

- Video call with screen-sharing capabilities

Signing of the informed consent form

- REDCap (Research Electronic Data Capture; Vanderbilt University) electronic database

Delivery of intervention product and study materials, as well as biological sample collection

- Trained and licensed courier service

Self-reported questionnaires

- Medidata Patient Cloud (Medidata Solutions Inc) mobile app in which participants can complete questionnaires (automatically syncs to iMedidata; Medidata Solutions Inc)

Product compliance and all non–self-reported data

- iMedidata electronic patient-reported outcome database entry completed by study team

Recruitment and Remote Study Conduct

This trial was set up and conducted in Singapore, where the smartphone penetration rate in the population is 98% and where 42.5% of the population, including 34.3% of women of reproductive age, use social media predominantly to research brands [27]. There is also a high level of trust in digital security systems associated with governmental organizations such as the Agency for Science, Technology and Research (A*STAR).

Recruitment in the community at large in Singapore was carried out via self-referral by interested women who heard about the study through the following channels: (1) social media advertising; (2) parenting websites as well as internet forums, platforms, and group chats; (3) physical posters on public transport; (4) brochures in mailboxes and partner locations; and (5) word of mouth. Relevant groups were approached through strategies such as targeted advertising to female users of reproductive age and specific estimated due date groups on various social media and messaging platforms, sending out electronic direct mail messages to members of the parenting websites engaged for the study, and placing physical posters in maternity stores or electronic posters on relevant websites such as the A*STAR Singapore Institute for Clinical Sciences web page.

All advertisements included the distinctive, easily recognizable PROMOTE logo. Electronic advertisements contained a convenient web link, and public posters incorporated a QR code to allow potential participants to scan and be directly taken to the website of an official government organization with a secure address to view the eligibility criteria and register their interest. Once they had submitted the forms on the website, the research coordinators would call them to confirm their interest, explain the study, and arrange a screening session via video chat to confirm their eligibility.

The study was designed to be conducted completely remotely, with all interaction between study team members and

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participants taking place via video chat sessions and with collection of biological samples by a licensed courier service.

Online Screening Session

The screening session involved 3 parties (the potential participant, the study coordinator, and a witness who may be another member of the study team or a participant's spouse, relative, or friend) engaged in a video call when the participant was at approximately 27 (range 24-30) weeks' gestation. If the woman was agreeable to taking part after a detailed explanation of the study, a remote electronic signing of the informed consent form was then undertaken by all 3 parties within the same sitting. The eligibility of the potential participant was confirmed according to the inclusion and exclusion criteria (Textbox 2) and immediately recorded on the electronic research database with each participant assigned a unique participant identification code.

Textbox 2. Inclusion and exclusion criteria.

Inclusion criteria

- Pregnant women aged ≥21 years at recruitment
- Willing and able to provide written informed consent
- Gestation of 28 to 32 weeks at randomization
- Singleton pregnancy at recruitment
- Able to complete questionnaires in English
- Hospital Anxiety and Depression Scale [28] score of ≥5 (out of 21) for either depression or anxiety subscale to indicate some general feelings of low mood or stress; each participant to fill out the questionnaire using a secured app with the scores programmed to be computed instantly and automatically upon submission
- Intention to breastfeed

Exclusion criteria

- Not willing or unable to comply with the study procedures and requirements
- Diagnosed food allergy
- Has taken probiotic supplements in the 4 weeks before screening
- Has received pharmacological treatment for anxiety or depression in the 12 weeks before recruitment
- Major complications during pregnancy (eg, pre-eclampsia, gestational diabetes requiring insulin intervention, severe intrauterine growth restriction, and fetal anomalies)
- Preexisting medical conditions (eg, hypertension, diabetes mellitus, thyroid diseases, autoimmune diseases such as systemic lupus erythematosus, antiphospholipid syndrome, and other major chronic illness)
- Active participation in another clinical trial or ongoing observational study

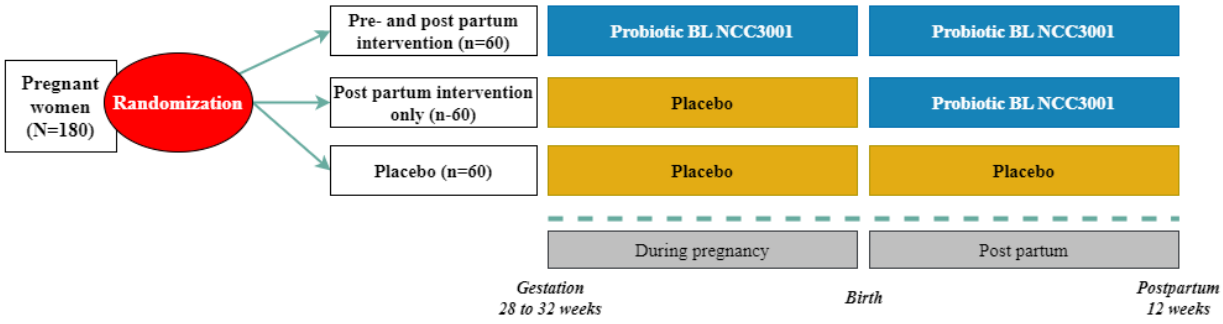
Randomization Procedure and Study Arms

This is a double-blind, placebo-controlled, randomized, and 3-parallel-arm study aimed at assessing time trends in perinatal mood and stress with ingestion of the probiotic BL NCC3001, starting from either the third trimester (28-32 weeks' gestation) or immediately after birth until 12 weeks post partum, compared with placebo. The 3 arms are (1) prepartum + postpartum probiotic, (2) prepartum placebo + postpartum probiotic, or (3) prepartum + postpartum placebo in a 1:1:1 ratio (Figure 1). Participants were randomly allocated via an electronic database to 1 of these 3 arms at the first virtual study session when the participant was at 30 (allowed window 28-32) weeks' gestation.

Until the database lock of the primary outcome, neither the investigator nor the participant nor the site team nor the independent monitor managing the study will know to which investigational product each participant was allocated, with the exception of specified delegated regulatory staff within Nestlé, the product manufacturing site, and the supply and quality managers at the sponsor's clinical research unit.

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Figure 1. Graphical representation of the 3-parallel-arm study design. Participants are randomly allocated to 1 of the 3 different arms of the trial in a 1:1:1 ratio, with the probiotic intervention taken either (1) during pregnancy and post partum (n=60) or (2) post partum only (n=60) compared with (3) a placebo control group (n=60). BL: Bifidobacterium longum.



Intervention

The daily intervention comprised a dry powder stick pack containing 1.0×10^{10} colony-forming units of the probiotic strain BL NCC3001 (8.25%) premixed with a maltodextrin (91.75%) carrier. It is being compared against a placebo of similar sensory characteristics, packaged in a dry powder stick pack containing maltodextrin (84%), yeast extract (12%), pea flour (2%), and cysteine (2%). Both products need to be stored refrigerated and were couriered to participants by designated services trained to maintain the cold chain. The participants were instructed to first dissolve the probiotic in an approved liquid medium (eg, plain water or milk) at room temperature or cooler, then consume it within an hour, in the evening with a meal on a daily basis.

The dosage and schedule were identical to those of a previous study [23], and this approach has been shown to induce an immunologic or microbiota host response to the probiotic in healthy human adults [29]. BL NCC3001 has also been administered at a similar dose to pregnant and lactating women [30,31] as well as infants [32] in studies unrelated to PMD, with no major adverse effects reported.

Adherence was assessed by participant recall at each study session. Good adherence was predefined as at least 80% over the study period. Upon the resupply or return of unused products, product consumption was additionally verified.

Usual consumption of foods containing probiotics was recorded at baseline (screening session) and again at the end of the study. Participants were requested not to increase the intake of probiotic foods across the duration of the study. In any case, the intake of particular diets, treatments, medications, or concomitant therapies such as probiotic supplements and antibiotics that may interfere with the intervention, as well as medications known to affect mood and stress, during the trial period were captured.

Study Outcomes and Other Assessments

The primary outcome is change in time trends of mood and stress scores as measured by the STAI [24] and EPDS [25] evaluated across 6 study sessions between baseline at 28 to 32 weeks' gestation and 12 weeks post partum.

The secondary outcomes will be derived from validated self-reported questionnaires, including probable depression requiring follow-up (defined as an EPDS score of ≥13) at each time point; change in Hospital Anxiety and Depression Scale score [28] (anxiety and depression subscales) from baseline to post partum; Parenting Stress Index [33] score at 12 weeks post partum; Pittsburgh Sleep Quality Index [34] at 36 weeks' gestation and 12 weeks post partum; a longitudinal assessment of the Gastrointestinal Symptom Rating Scale score (explores any experience of bloating, rumbling, flatulence, and abdominal pain, as well as stool frequency and consistency) [35]; and a longitudinal assessment of the duration, initiation, and exclusivity of breastfeeding as well as breastfeeding practices using the Early Feeding Questionnaire. Other secondary outcomes will be derived from digital measures and biological sample analyses, including longitudinal changes in stress biomarkers (assessed using a digital app linked to the central electronic database and morning salivary cortisol measures) and in maternal gut microbiota (composition and probiotic strain colonization to generate mechanistic insights). The digital stress app is designed to use transdermal optical imaging of the face to measure heart rate variability and blood flow, which is then extracted and used to generate a *stress index* score on a scale ranging from 1 to 5, where higher scores reflect greater stress levels [36]. Interviewer-administered questionnaires specifically designed for this study were used to (1) capture sociodemographic and medical history, (2) record probiotic food and medication intake, and (3) record pregnancy complications and birth outcomes. Scores from a validated self-administered Childbirth Experience Questionnaire [37] were also captured because this could potentially influence postnatal mood. The timing and activities at each of the 6 study sessions are listed in Table 1.

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Table 1. Study sessions and procedures.

Procedure	Screening session during pregnancy: gestation 27 weeks (+3 or −3 weeks)	Treatment period					
		During pregnancy		Post partum			
		Session 1: gestation 30 weeks (+2 or −2 weeks)	Session 2: gestation 36 weeks (+2 or −2 weeks)	Session 3: post partum 9 days (+5 or −5 days)	Session 4: post partum 4 weeks (+7 or −7 days)	Session 5: post partum 8 weeks (+7 or −7 days)	Session 6: post partum 12 weeks (+7 or −7 days)
Informed consent	✓						
Inclusion and exclusion criteria	✓						
HADS[a]	✓			✓			✓
Demographics	✓						
Obstetric history	✓						
Medical history	✓						
Randomization		✓					
Biological sampling							
Salivary cortisol sampling		✓	✓	✓	✓	✓	✓
Maternal fecal sampling		✓	✓		✓		✓
Stress index via digital app		✓	✓	✓	✓	✓	✓
Questionnaires							
EPDS[b]		✓	✓	✓	✓	✓	✓
STAI[c]		✓	✓	✓	✓	✓	✓
Probiotic food intake		✓					✓
PSI[d]							✓
PSQI[e]			✓				✓
EFQ[f]		✓		✓	✓	✓	✓
CEQ[g]				✓			
Birth events				✓			
GSRS[h]		✓	✓	✓	✓	✓	✓
Investigational product							
Intervention dispensing and return		✓		✓			✓
Intervention intake		✓	✓	✓	✓	✓	✓
Adverse event collection		✓	✓	✓	✓	✓	✓
Concomitant therapies		✓	✓	✓	✓	✓	✓
Adherence			✓	✓	✓	✓	✓

[a]HADS: Hospital Anxiety and Depression Scale.

[b]EPDS: Edinburgh Postnatal Depression Scale.

[c]STAI: State-Trait Anxiety Inventory.

[d]PSI: Parenting Stress Index.

[e]PSQI: Pittsburgh Sleep Quality Index.

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[f]EFQ: Early Feeding Questionnaire.

[g]CEQ: Childbirth Experience Questionnaire.

[h]GSRS: Gastrointestinal Symptom Rating Scale.

All sessions were conducted virtually (e-sessions) using video or voice calls accessed via a secure link that maintains data privacy. Participants filled out self-administered questionnaires on their own devices through Medidata Patient Cloud (Medidata Solutions Inc), an electronic patient-reported outcome app that was automatically integrated with the web-based research database (iMedidata; Medidata Solutions Inc). Each study participant was provided with a deidentified personal username and password to access the electronic patient-reported outcome system. For interviewer-administered questionnaires, the study team entered the answers directly into iMedidata. Each participant was assigned a clinical research coordinator for the entire duration of her participation to help build rapport and increase participant retention; regular contact included reminders for upcoming study sessions and the accompanying activities. If a participant became noncommunicative, attempted follow-up was carried out via SMS text messaging or email, and the case was only classed as lost to follow-up or withdrawn after the window period for her final study session had passed.

Ethics Approval, Study Conduct and Registration, and Participation

Ethics approval was granted by the A*STAR institutional research board (2020-065), and all women provided signed informed consent. This study is being conducted in line with Good Clinical Practice [38] and the Declaration of Helsinki [39]. The study has been registered on ClinicalTrials.gov (NCT04685252). The clinical data management systems developed for this study complied with Good Clinical Practice [38], predicate rule requirements, and laws and regulations (personal data protection), and they allow an audit of actions by users. Participants were reimbursed for their participation in the form of electronic vouchers that could be redeemed at a local chain of malls. Reimbursement was prorated based on the number of study sessions and tasks completed, with a maximum possible value of SGD $330 (approximately US $240) for the entire trial duration for participants who completed all activities.

Biological Sample Collection

Saliva and stool samples were self-collected at participants' residences and couriered back to the study site by a designated, reliable, and licensed courier trained to respect the *cold chain* to maintain sample integrity. Biological samples are being stored at –80 °C at an appropriately regulated tissue repository until the planned batch analyses at the end of the study. This strategy required comprehensive collection kits to be sent to participants, which included a clear, illustrated, and concise manual, as well as items to alleviate any concerns about needing to store the biological samples in their freezer between the time of collection and courier pickup. These items included laboratory-grade biohazard bags and additional containers to contain the biohazard bags to have multiple degrees of separation between the collected biological sample and the food items in the freezer.

Monitoring and Safety Reporting

Monitoring was carried out periodically by an external, independent monitor. This allowed the evaluation of the trial progress, verification of the accuracy and completeness of electronic case report forms, and resolution of any inconsistencies in the trial records, as well as ensured that all protocol requirements, applicable local laws, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use [38] guidelines, and investigator obligations were fulfilled.

Safety reporting was conducted in accordance with a preagreed study safety monitoring plan. All adverse and serious adverse events were recorded in the study database.

Statistics

This is an exploratory study of the effect of BL NCC3001 on mood in pregnant and postpartum women; therefore, effect sizes are unknown. However, illustrative power calculations are shown in Table 2. Once completed, this trial will allow a potential follow-up trial to be designed and powered properly, where observations could be confirmed.

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Table 2. Illustration of error rates and statistical power for the Edinburgh Postnatal Depression Scale (EPDS) and State-Trait Anxiety Inventory (STAI) over 1000 simulations.

Outcome and hypothesis	Comparison	Max-*t* test[a], %
EPDS		
Null	Prepartum + postpartum probiotic vs placebo control	1.70
Null	Postpartum-only probiotic vs placebo control	1.60
25% difference	Prepartum + postpartum probiotic vs placebo control	72.00
25% difference	Postpartum-only probiotic vs placebo control	48.10
STAI		
Null	Prepartum + postpartum probiotic vs placebo control	2.20
Null	Postpartum-only probiotic vs placebo control	1.30
25% difference	Prepartum + postpartum probiotic vs placebo control	69.20
25% difference	Postpartum-only probiotic vs placebo control	50.30

[a]Rows where the hypothesis is null display the error rate, whereas the ones where the hypothesis is 25% difference in time trends display the power of the test. For the control group, the means and SDs of mood scores were based on previous perinatal studies of longitudinal Edinburgh Postnatal Depression Scale scores [40] and assumed to be normally distributed. For the prepartum + postpartum intervention group, the test scores are assumed to be gradually decreasing over time with a maximal difference of 25% with respect to the controls. For the postpartum probiotic intervention group, the effect was assumed to have the same kinetics but with onset at birth. The correlation between study sessions was assumed to be 0.5.

The trial has 2 primary outcome variables (EPDS and STAI scores) and 2 primary group comparisons (prepartum + postpartum intervention vs placebo control and postpartum-only intervention vs placebo control). Thus, the false positive rate controlled at 5% level is as follows: $\alpha / 4 = 0.0125$ (for each combination of a primary outcome variable and a group comparison). The time trends for comparing prepartum + postpartum intervention versus control (session 2-session 6; Table 1) and for comparing postpartum-only intervention versus control (session 3-session 6; Table 1) are modeled by 2 separate mixed models where baseline scores (session 1; Table 1), time point (considered a categorical variable), treatment, and the interactions between the time point and treatment were fixed effects, and participant was included as a random effect (random intercept). A history of previous pregnancy complications will be added as a binary covariate to the model. The global test for time-trend differences between groups is a max-*t* test. For each group comparison, the multiplicity coming from comparison at multiple time points is dealt with by performing inference based on the joint distribution of the test statistics from the appropriate set of linear contrasts of the linear mixed model parameters (using the R library *multcomp*).

A simulation using R statistical software (version 3.6.1; R Foundation for Statistical Computing) showed a power of 50% to 70% for observing statistically different time trends when considering recruiting 60 individuals per group, after accounting for an expected dropout rate of 20%, representing 48 participants per group completing the study (Table 2).

With the substantially lower observed dropout rate of 2.7% compared with the initially anticipated 20%, more participants than expected have completed the study, and the power therefore is increased from this initial illustration. Although every effort has been made to obtain complete data sets, the mixed model used for analysis is robust against missing values and valid under missing at random. Outliers will be detected before unblinding, with appropriate action taken considering the medical context. The primary analysis will be an intention-to-treat analysis (considering all randomized participants who took at least 1 dose of the assigned product and provided postrandomization data) with a secondary per-protocol analysis planned. No interim analysis was performed for this trial.

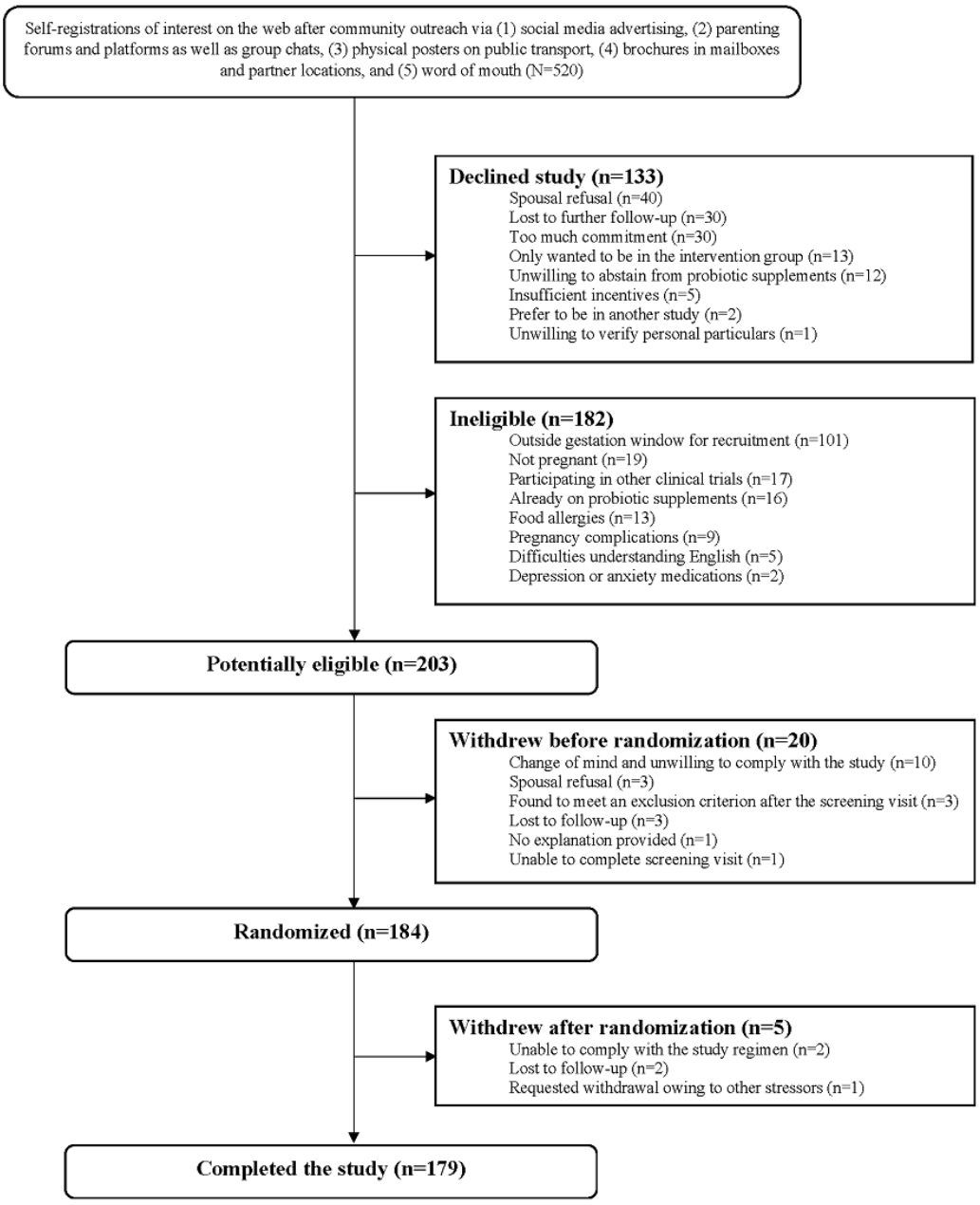
Results

Recruitment and Retention

Recruitment for the trial commenced on November 7, 2020, and was completed in the following 10 months, with the last participant recruited on August 20, 2021. A total of 520 women expressed interest in the trial through online registration, of whom 205 (39.4%) were agreeable and potentially eligible to participate. Of these 205 participants, 21 (10.2%) withdrew or were found to be ineligible after the screening session, leaving 184 (89.8%) women who were randomized. Of these 184 women, 5 (2.7%) withdrew after randomization, and 179 (97.3%) completed the study (Figure 2). Therefore, we exceeded our target of at least 48 participants per group completing the study (the original target for the 3 groups was $48 \times 3 = 144$ in total) because the final attrition rate was 2.7% instead of the anticipated 20%.

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Figure 2. CONSORT (Consolidated Standards of Reporting Trials) diagram showing participant flow through the different phases of the trial, from expressions of interest and randomization to expected trial completion.



Recruitment Strategies

Of all the recruitment strategies used (Table 3), advertisements on major general social media platforms were the avenues that most women expressing interest claimed were their first knowledge of the trial (244/520, 46.9%), followed by other parenting-specific web-based platforms (116/520, 22.3%). None of them claimed to have been attracted via advertisements on the main popular search engines despite efforts to target female users of reproductive age. The recruitment avenue with the next highest success rate was via physical posters on public transport (64/520, 12.3%). The local metro train system, known as Mass Rapid Transit (MRT), is used daily by 2.2 million passengers [41], which is equivalent to approximately 41% of the population of Singapore [42].

The geodemographic data of Singapore were considered so that resources could be focused on the MRT routes most used by our target population. We first targeted the North-East Line, which services District 19, a catchment area that includes an area with the highest number of residents aged <5 years, an indicator of young families. Almost a quarter (122/520, 23.5%) of the prospective participants reported residing in District 19 [43,44]. The strategy was then extended to other major lines, including the Downtown Line, North-South Line, and East-West Line, that serve other districts with young families [43]. Of the 28 Singapore districts, 7 (25%) are known to have the highest proportions of residents aged <5 years; of these 7 districts, 5 (71%) contributed nearly half (233/520, 44.9%) of the potentially eligible participants, whereas the other 2 (29%; Districts 17 and 24) did not contribute any participants and were incidentally not covered by an MRT line (Figure 3).

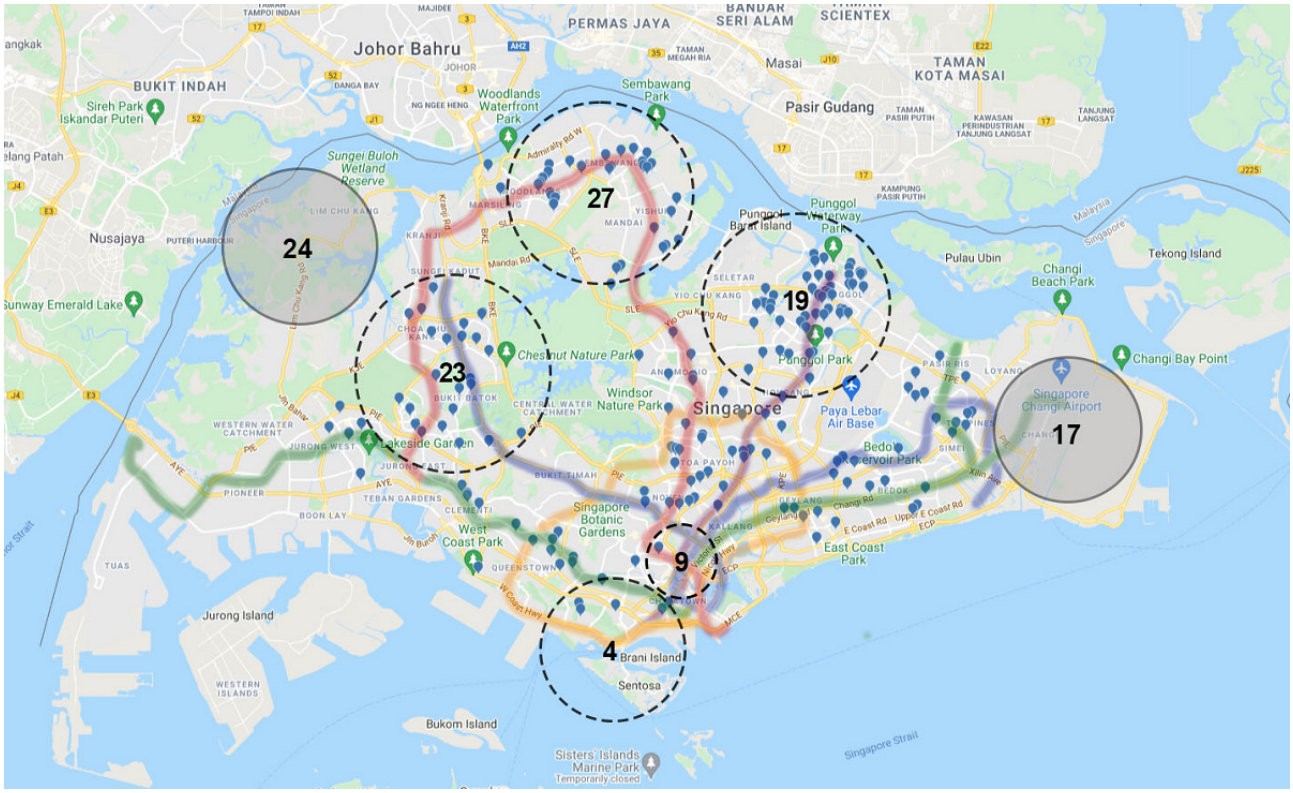
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Table 3. Source of recruitment advertisement reported by potential participants during self-registrations of interest on the web (N=520).

Source of recruitment advertisement or study recruitment strategy	Potential participants, n (%)
Social media	244 (46.9)
Parenting-specific online platforms	116 (22.3)
Public transport (Mass Rapid Transit trains)	64 (12.3)
Word of mouth	42 (8.1)
Physical poster or brochure	26 (5)
Internal A*STAR[a] electronic outreach and email blast	28 (5.4)
Advertisements on search engines	0 (0)

[a]A*STAR: Agency for Science, Technology and Research.

Figure 3. Distribution of participants' area of residence with Mass Rapid Transit (MRT) route map of Singapore (map data: Google, 2022). Each blue drop represents 1 potentially eligible participant. Participants were recruited from across the country, particularly from districts with the highest density of residents aged <5 years (dotted circles: districts 4, 9, 19, 23, and 27) and along targeted MRT lines (purple: North-East Line, blue: Downtown Line, red: North-South Line, and green: East-West Line). Two of the 7 districts with the highest number of residents aged <5 years (districts 17 and 24) contributed no participants; in addition, they were not served by an MRT line.



Discussion

Overview

This double-blind, placebo-controlled, and randomized controlled trial will be the first to examine the efficacy of the naturally occurring probiotic BL NCC3001 in alleviating or suppressing symptoms of PMD when taken either from the third trimester or immediately after birth until 12 weeks post partum. It was designed to be conducted entirely remotely in Singapore and was successfully carried out during the height of the COVID-19–related restrictions, using digital technology in all aspects of the conduct of the study while complying fully with research governance and regulations.

Although other probiotic interventions have been tested in pregnant women for their impact on PMD with inconsistent results [16-19], it is important to note that these studies differed in one or more methodological aspects from our study. Aside from different probiotic strains or multiple probiotic strain combinations used, there were variations in probiotic concentrations; combinations with other nutritional supplements; study populations with specific comorbidities in addition to being pregnant or post partum; and different timelines for intervention intake, such as commencement in the first half of the pregnancy [17-19].

The COVID-19 era has posed many challenges globally. The first challenge concerned the need for social distancing and the associated unpredictable restrictions on in-person activities,

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including participation in conventional clinical trials. The second challenge concerned the fact that pregnant women are considered a vulnerable group with compromised immunity—in the early stages of the pandemic, very little was known about the detrimental effects of the virus on pregnant women and their unborn child; hence, more precautionary steps were taken to promote their isolation. Therefore, designing a research study that could overcome these hurdles and decrease barriers to participation was crucial to ensure feasibility, continuity, and the eventual successful completion of the study in the face of unpredictable governmental regulations. This study was designed to maintain robust operating procedures that would be resilient to the constant changes in COVID-19–related mandates in Singapore. This was possible because of several reasons, many novel to the local research arena. The remote approach contributed to minimizing inconvenience, reducing exposure risk to COVID-19 infection, and complying with local social distancing regulations. This included all study sessions being conducted virtually (e-visits), which comprised using digital apps to answer self-reported questionnaires and web-based databases that securely synced with these apps, and the intervention products being delivered by courier services, with self-collection of biological samples by participants conducted at their own residences and trained couriers engaged to transport the samples back, with a contactless pickup provided as an option for the participants as well. Despite the apparent success in the recruitment phase, there were some initial challenges before the study could begin. In particular, the ethics board had to be convinced of the reliability and feasibility of remote consenting procedures and approve of the entirely remote conduct of the trial, especially for a population considered vulnerable, such as pregnant women. We also had to design a new secure, acceptable, and legally valid remote e-consenting process to allow consecutive instantaneous signing by a participant, researcher, and witness located at different places, which could be completed rapidly.

The widespread ownership and use of personal mobile phone and computerized devices, high availability of internet (both cellular and home internet), trust in digital security systems associated with established local institutions, and greater IT savviness among the target age group [27], coupled with high health and research literacy, likely increased participant comfort with engaging digitally for research purposes. The established consumer trend of women of reproductive age using social media as a main avenue to research new brands, obtain information, and establish connections is another aspect that may have made the use of online channels for recruitment and conducting research in the study plausible and successful. The study team was able to achieve a much wider community reach, passively capturing a more diverse pool of participants attending different institutions for maternity care and including those mostly confined to their own home owing to COVID-19–related restrictions. The strategy of using social media proved the most effective recruitment tool because it resulted in the highest traffic of potential participants, especially during the recruitment phase that occurred from late 2020 to mid-2021 at the height of the COVID-19 pandemic when restrictions were at their most stringent in Singapore and before widespread vaccination of the pregnant population. This is in contrast to recruitment from particular health facilities (eg, a university hospital's maternity department), which is often restrained by a geographical catchment area and the need for physical accessibility to the location to view a poster, receive a brochure, or be approached by staff to introduce the study. The same reasons that explain the success of an entirely remotely conducted clinical trial could also be used to explain the particular success of our social media recruitment strategy, despite the various other recruitment strategies being afforded similar resources in terms of time, finances, and workforce hours.

Although most of the participants (244/520, 46.9%) claimed that social media platforms gave them their first knowledge of the trial, recruitment efforts were strengthened when different avenues of recruitment were used simultaneously. Most notably, when we were targeting recruitment from a geographical perspective, interest from a particular district with a high density of young families peaked when brochures were dropped into residential letter boxes at a similar time to a physical poster advertisement campaign running on the main MRT line servicing that area. We speculate that these different forms of advertisements provided multiple reminders that increased the likelihood of expression of interest. The effectiveness of our nationwide community recruitment strategies is reflected by our data indicating that participants come from all parts of the country.

Another aspect integral to the success of the study was the at-point-of-residence self-collection of biological samples. Extensive thought and planning were required to design a biological sample collection workflow that was easy to follow, convenient, and acceptable to participants. Good coordination among the study team, participants, and the licensed courier tasked for pickup was essential. The courier had to follow a robust workflow, maintain the cold chain in tropical Singaporean weather, and demonstrate flexibility in response to constant changes in local COVID-19–related restrictions. Additional benefits that likely attracted participation include increased convenience, attributable in part to no traveling time required to attend sessions. Similarly, this also increased overall time and cost saved for the study team.

The actual subject matter of mood disorders also likely resonated more with pregnant women during the COVID-19 pandemic, which helped with study recruitment. Generally increased stress levels across the population have been widely reported worldwide during the pandemic, with pregnant women highlighted as a particularly affected group [45,46]. We aimed to recruit women who already had some symptoms of low mood or anxiety, as determined by the Hospital Anxiety and Depression Scale, to allow for the possibility of improvement with intake of the intervention product. Our data showed that none of the women who consented to join the study were excluded specifically because they did not fulfill this criterion; this means that all who were interested in participating already had some PMD symptoms. These women may have been motivated to reduce their PMD to avoid negative impacts on the health of both mother and baby and were open to exploring probiotics as a solution that is thought to have few or no unwanted effects.

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As many women try to avoid taking pharmacological treatments during pregnancy and lactation [4,13], there is a potential opportunity for natural and nutrition-based solutions to provide mood benefits in this population [47]. However, a systematic review of nutritional interventions concluded that current evidence is inconsistent and inconclusive on whether nutritional factors influence the risk of PMD [48,49]. As there is some evidence suggesting that probiotics could help fill this gap [50], this study of the probiotic BL NCC3001 was designed to help inform that possibility. As the intervention had been classed by the Health Sciences Authority of Singapore as a nutrition product and not a pharmaceutical drug, it meant that the study design did not need to include the usually extensive in-person monitoring that drug trials would normally require. This, therefore, decreased the barriers to participation and study retention.

Conclusions

Multiple converging factors contributed to the study being able to recruit at speed and retain the required number of participants despite COVID-19–related restrictions. In addition to providing novel evidence for the potential benefit of the probiotic BL NCC3001 in reducing the symptoms of PMD, this entirely remote research study design sets a precedent for similar studies. Such studies could be highly suitable if (1) the intended study population has a high rate of digital device penetration and internet access, (2) systems allow secure data exchange and capture, (3) the intervention can be self-administered without clinical monitoring, and (4) eligibility criteria and outcome measures can be reliably assessed remotely either by digital capture or self-collected biological samples. We have described here such a study that has been successfully conducted in a group considered vulnerable, pregnant women, despite the presence of challenges and barriers presented by the COVID-19 pandemic.

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Conflicts of Interest

At the time of writing, all authors were employees of Singapore Institute for Clinical Sciences, an institute within the Agency for Science, Technology and Research (A*STAR), a governmental body of Singapore, and Société des Produits Nestlé, Switzerland.

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Abbreviations

A*STAR: Agency for Science, Technology and Research
BL: Bifidobacterium longum
EPDS: Edinburgh Postnatal Depression Scale
MRT: Mass Rapid Transit
PMD: perinatal mood disturbances

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PROMOTE: Probiotics on Mothers' Mood and Stress
STAI: State-Trait Anxiety Inventory

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Protocol

Personalized, Naturalistic Virtual Reality Scenarios Coupled With Web-Based Progressive Muscle Relaxation Training for the General Population: Protocol for a Proof-of-Principle Randomized Controlled Trial

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Abstract

Background: Virtual reality (VR) is an innovative tool that can facilitate exposure to either stressful or relaxing stimuli and enables individuals who have difficulties visualizing scenes to be involved in a more realistic sensorimotor experience. It also facilitates multisensory stimulation, a sense of presence, and achievement of relaxation. VR scenarios representing visual and auditory elements of natural relaxing environments can facilitate the learning of relaxation techniques such as the progressive muscle relaxation technique (PMRT). A complementary standardized technique deployed to reduce anxiety symptoms is the integration of PMRT and guided imagery (GI). Exposure to a pleasant imaginary environment helps the establishment of an association between a relaxing scenario and the relaxation technique, consequently promoting relaxation. Empirical evidence has shown that VR scenarios can increase the effects of relaxation techniques by enabling people to experience emotional conditions in more vivid settings.

Objective: The main aim of this pilot study protocol is to investigate the impact on state anxiety of PMRT, associated with a personalized relaxing scenario in VR, and the role of VR scenarios in facilitating the recall of relaxing images and a sense of presence. A secondary aim is to understand if relaxing sessions administered via Zoom are more effective for managing anxiety and stress than a procedural setting based on audio-track guidance.

Methods: Based on a longitudinal, between-subject design, 108 university students will be randomly exposed to one of three experimental conditions: (1) PMRT via Zoom and GI exposure, (2) PMRT via Zoom and personalized VR exposure, and (3) PMRT based on audio-track guidance and personalized VR exposure. Individuals are assessed before and after 7 training sessions based on self-report questionnaires investigating anxiety, depression, quality of life, coping strategies, sense of presence, engagement, and side effects related to VR exposure. Heart rate data are also detected by an Mi Band 2 sensor.

Results: The experimental procedure is ongoing. In this paper, preliminary data from a sample of 40 participants will be illustrated. The experimental phase is expected to conclude in May 2023, and the final results of the research will be presented in June 2023.

Conclusions: The results of this study will help shape the experimental design to apply it on a subsequent randomized controlled trial, also considering clinical samples. This work is expected to measure whether VR is a more engaging and helpful technique in promoting relaxation and decreasing anxiety levels than GI, by making the visualization process easier and by helping people to face more realistic sensory experiences. Assessing the efficacy of the PMRT in alternative delivery modes may extend its

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applications, especially in situations where the standard procedure is more challenging to be administered. To our knowledge, no equivalent study has been published so far on this matter.

Trial Registration: ClinicalTrials.gov NCT05478941; https://clinicaltrials.gov/ct2/show/NCT05478941

International Registered Report Identifier (IRRID): DERR1-10.2196/44183

(JMIR Res Protoc 2023;12:e44183) doi:10.2196/44183

KEYWORDS

digital health; progressive muscular relaxation technique; mental well-being; virtual reality therapy; anxiety; relaxation; e-therapy; e-Health; virtual reality; tool; symptoms; depression; quality of life; coping

Introduction

Background

Virtual reality (VR) is widely used to treat various mental diseases [1], also in association with different types of relaxation training (eg, progressive muscle relaxation training), and it facilitates multisensory stimulation, sense of presence, and achievement of relaxation [2,3]. VR can facilitate the learning of relaxation techniques through exposure to scenarios in which natural environments, which are commonly considered relaxing, are shown [2]. VR also has several advantages such as follows: easy to use, user-friendly, promotes engagement, and allows a full multisensory immersion in the virtual experience facilitating the control of external disturbing stimuli [4,5].

It was also highlighted that the customization of VR environments is an element that promotes relaxation. This latter type of user-centered approach [6] allows individuals to experience more realistic emotional conditions, like those experienced in everyday life, and it enhances relaxation, sense of presence, and perception of security in the virtual context (eg, [7]).

Standard relaxation programs usually include more directive techniques that imply larger involvement of the cognitive functioning system (eg, hypnosis) or the physiological response system (eg, progressive muscle relaxation technique [PMRT]), as well as fewer directive procedures that may be based on the cognitive functioning control (eg, meditation) or the physiological feedback (eg, autogenic training), respectively [8]. All these protocols are effective in promoting relaxation.

Jacobson [9] developed the PMRT protocol in 1938, suggesting that the overactivation of the sympathetic nervous system is primarily responsible for excessive skeletal muscle activity. Thus, interference in the skeletal muscle activity based on progressive relaxation reduces the activation. This process also positively affects other physiological parameters (eg, heart rate frequency) [10,11].

On these grounds, the training consists in learning how to tense and release several muscle groups.

Evidence suggests that stress-competing relaxation techniques are among the most effective training programs for enhancing psychological resources and reducing psychological distress [12].

PMRT is based on “top-down” and “bottom-up” neuronal processing. The “top-down” pathway is turned on by higher cognitive activities, such as focused attention, related to the cerebral cortex and the cerebellum, which send commands to peripheral areas by controlling muscle tension and gradual release. The holding and releasing activities allow proprioceptive stimulation from peripheral sensory afferents to the higher nervous system regions via the spinal cord and the brainstem as a “bottom-up” pathway [13-15]. Also, based on these processes, PMRT is considered one of the most effective and adaptable techniques for relaxation, anxiety management, stress, and depression reduction considering different kinds of target populations (eg, nonclinical individuals, patients with cancer, chronic pain, osteoarthritis, heart disease, chronic headache, anxiety, and depression) [16-20].

Still, the administration of combined methods appears very useful in reducing anxiety and the perception of pain in patients with medical conditions or during pregnancy [19-21]. Indeed, complementary methods that imply the administration of integrated cognitive and behavioral procedures are studied to manage anxiety, stress, depression, and pain, particularly in populations such as patients with cancer. Notably, the integration of PMRT and guided imagery (GI) enhances and facilitates the effect of relaxation, reducing anxiety and depression symptoms [19,22].

The application of GI, or VR, and PMRT is based on classical conditioning theory that involves learning relaxation techniques and exposure to relaxing mental images as conditioned stimuli useful for overcoming stress and specific fear [23,24].

The integration of PMRT and GI has been highlighted in the literature as an effective complementary method for reducing pain and anxiety symptoms (eg, [19,21]). GI is useful in creating mental imagery and refocusing attention on positive and relaxing imagined visual, auditory, tactile, or olfactory sensations, resulting in specific psychological and physiological responses, such as relaxation [25]. GI may also increase the reduction of the autonomic nervous system responses [19,25,26]. This combination can promote a higher sense of relaxation during training sessions, but it should also play a role in recalling a state of relaxation during everyday activities.

The combined methods introduced by Baird and Sands [19] implement eight steps [27-31]:

1. Setting a comfortable and protected real environment in which to relax
2. Recreating an imagined scene involving different senses
3. Guiding the user in focusing on breathing
4. Using passive progressive relaxation techniques

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5. Recalling the imagined scene to direct the attention to pleasant stimuli
6. Feeling a release from pain and activation (eg, imagining a decrease in painful sensations)
7. Imagining moving into the scene by continuing to use focused breathing and relaxation
8. Ending the session ("Breathe deeply. When you are ready, allow the image to fade. Stretch and open your eyes" [19]).

Considering the positive impact on relaxation of GI associated with PMRT, exposure to a more vivid, closer-to-reality virtual experience should be a useful technique in further improving the relaxation learning promoted by the PMRT.

Furthermore, it is well known that before delivering PMRT with GI, some sessions of PMRTs, focused on learning to recognize and relax the muscle areas of our body, are needed. Usually, these training sessions are administered face-to-face in the therapist's presence. Finally, to investigate the effectiveness of web-based psychotherapy interventions, there are controversial results regarding a PMRT procedure administered in vivo or via audio-tracks [32-34]. To our knowledge, no recent study exists addressing the comparison among training sessions administered in vivo, in a remote modality, or via audio-tracks. In light of the pandemic due to SARS-CoV-2, we intend to explore PMRT's efficacy in a remote situation via both Zoom and audio-tracks.

In general, it is essential to point out that remote treatments have been increased. They promote users' independence in managing some psychotherapy techniques, leaving time for other face-to-face psychotherapy activities that require the active involvement of both the patient and the therapist. Assessing the efficacy of PMRT in alternative settings may facilitate the administration of treatment where it is impossible to implement the standard procedure. It may also increase the positive impact of abbreviated relaxation session and combining relaxation methods with patients who have chronic pain or must be exposed to invasive medical treatments (eg, chemotherapy) [35,36].

Study Overview and Objectives

The purposes of the present research project are as follows:

1. Investigating if PMRT associated with a personalized relaxing scenario in VR can facilitate relaxation and lower state anxiety
2. Understanding if the VR scenario helps recall the relaxing image assessed during the follow-up session
3. Investigating if VR is more effective in promoting the association between the relaxing scenario and PMRT than the standard procedure, consisting of PMRT associated with the imagery-induced exposure to a subjective relaxing environment
4. Analyzing if the relaxing sessions administered via Zoom are more effective in managing anxiety and stress than a procedure administered via audio-tracks.

We hypothesize that VR would be more effective than GI in promoting relaxation and decreasing state anxiety because it would facilitate the visualization process, allowing individuals to have more realistic sensory experiences than imagery-induced exposure.

Methods

Ethics Approval

This study protocol involving human participants was General Data Protection Regulation compliant and developed following the Declaration of Helsinki (Italian law 196/2003, European Union General Data Protection Regulation 679/2016). The institutional review board of the Interdepartmental Ethical Committee of Psychology (17 Area) of the University of Padova (Italy) approved the study protocol on May 28, 2021 (approval number 4213). In February 2022, the trial was tested based on a convenience sample of 5 individual volunteers from the general population. Then, it was decided to introduce the following questionnaires: the Coping Orientation to the Problems Experienced-New Italian Version (COPE-NVI), the ITC-Sense of Presence Inventory (ITC-SOPI), the Vividness of Visual Imagery Questionnaire [37,38], and the Test of Visual Imagery Control [37,38]. The amendments and supplementations have been accepted, and the protocol received the final approval of the institutional review board of the Interdepartmental Ethical Committee of Psychology (17 Area) of the University of Padova, Italy (approval number 4701; April 29, 2022). Before their study enrollment, the participants signed a written informed consent form based on a paper-and-pencil form, agreeing to participate in all the study sessions.

They were informed that (1) their data would be confidential, (2) they could omit any information they did not wish to give, and (3) they could withdraw from the study without providing any explanation.

Eligibility, Recruitment of Study Participants, and Randomization

The recruitment phase started in May 2022. Study participants were recruited in Northeast Italy via social networking websites (eg, Facebook groups) and by providing information on the research during university lectures. Those interested in participating were asked to make an appointment with the investigators to participate in the first assessment phase (T0) in which the inclusion and exclusion criteria were evaluated, written informed consent was obtained, and a baseline evaluation was made.

Eligible participants were adults from the general population (18 years or older), native Italian speakers, owning a PC, and able to use a PC and smartphone.

Participants were excluded from the study if they had been diagnosed with a severe mental disorder or medical conditions that could hinder their participation in the study (eg, neuromuscular disorders, severe psychiatric or neurological disorders, and assumption of drugs that could interfere with heart rate assessment and the subjective relaxation state), or if a psychotherapeutic treatment was ongoing.

Eligible participants were randomly allocated to 1 of 3 experimental conditions based on a simple blinded randomization via an Excel (Microsoft Inc) file.

Two experimenters, trained in cognitive and behavioral psychotherapy, conducted the relaxation sessions, each

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administering to 50% of the sample of each group to control for possible biases related to the therapist's personality and competence. The 2 therapists who administered the experimental procedure received the same PMRT training and were supervised by a senior researcher and psychotherapist supervisors.

The Integrated PMRT and Virtual Environment Design

The virtual environment design and the hardware and software equipment are described in the paper by Pardini et al [39], in which the aim was to investigate the user experience, preferences, and engagement of the exposure to personalized, natural, and realistic VR scenarios.

Specifically, we adapted the procedure that Baird and Sands [19] introduced to propose an integrated intervention using different new technologies.

The protocol concerns the learning of the adapted abbreviated PMRT [33] in 5 sessions 2 times a week, as follows:

- Four sessions of active progressive muscle relaxation, in which participants are required perceptively learn the differences between the tension and relaxation of different muscle sections of the body. Each session has a duration of approximately 25 minutes. The first session is dedicated to the hands, forearms, arms, neck, shoulders, and back; the second to the facial muscles; the third to the diaphragmatic breathing; and the fourth to the abdomen, buttocks, and lower limbs. These sessions take place via the Zoom platform and are conducted by a cognitive-behavioral psychotherapist. Each Zoom session consisted of filling out 2 measures for the state anxiety and relaxation state based on the Moodle e-learning platform, sharing general standardized instructions for conducting relaxation and the rationale of the PMRT, guided relaxation aimed at relaxation of a dedicated body site, and filling out the same measures administered at the beginning of the session. A profile was created for each participant to access the Moodle platform. For the participants in condition "intervention B" (described in the following section) who participated in the first 4 PMRT sessions through the audio-track, all sessions were self-managed within the Moodle platform. Various activities have been scheduled based on the beginning of the training and the end of the activities planned in previous sessions.
- The fifth VR session is administered at the University of Padova Laboratory. All participants are asked to wear a smartwatch for heart rate detection. A total of 5 measurements (1 per minute) are made before the VR experience, 12 during the entire exposure in the virtual environment, and 5 after the experience in the virtual context. A duration of approximately 12 minutes has been established to avoid potential cybersickness symptoms during the virtual experience. This brief relaxation session is practiced by inexperienced individuals allowing for a decrease in anxiety and negative mood [40,41].

Study Design

The present protocol of the proof-of-concept study is a longitudinal, between-subjects, 3-armed randomized controlled trial aiming to compare three treatment conditions (Figure 1):

1. Active Comparator condition, consisting of the deployment of the PMRT training via Zoom and GI exposure. It consists of a standard behavioral intervention based on 4 individual PMRT sessions via Zoom (t1-t4), an in vivo PMRT relaxing session and GI conducted by a psychotherapist (T1) after a week from the baseline assessment (T0), and a follow-up phase (T2) after 2 weeks consisting in recovering the GI relaxing scenario and PMRT session (see Multimedia Appendix 1 and Figure 2).
2. Intervention A is an experimental condition in which the complementary intervention is composed of the PMRT administered via Zoom integrated with a personalized VR exposure deployed by a head-mounted display (Oculus Quest 2). It comprises 4 individual PMRT sessions via Zoom (t1-t4), an in vivo PMRT relaxing session and VR exposure (T1) after a week from T0, and a follow-up phase that consists of the same activities as the Active Comparator condition (see Multimedia Appendix 1 and Figure 3).
3. Intervention B is an experimental condition in which the complementary intervention is composed of progressive muscle relaxation training administered through an audio-track integrated with the same personalized VR exposure setup in Intervention A. It is composed of 4 individual PMRT sessions via an audio-track delivered on the Moodle platform (t1-t4), an in vivo PMRT relaxing session and VR exposure (T1) after a week from T0, and a follow-up phase that consists of the same activities as the Active Comparator and the Intervention A conditions (see Multimedia Appendix 1 and Figure 4).

The assessment phases take place at baseline (T0), before and after the 4 PMRT sessions (via Zoom or audio-track), at the fifth in-presence session (T1), and a week later (T2).

The T0 (baseline) assessment phase has a duration of approximately 37 minutes, is the same for all participants, and is administered at the Virtual Reality Laboratory (A10-A11), Department of General Psychology, University of Padova (Italy). In this phase, the following measures are administered: (1) a demographic schedule (addressing age, gender, nationality, mother tongue, marital status, years of school attendance, employment status, psychological problems or disorders, ongoing psychological treatment, drug use, medical conditions, neuromuscular issues, previous injures, previous experiences in relaxation practice or anxiety management training, or with Oculus), and also, refraining from smoking, intense physical exercise, consuming caffeine for at least 1 hour before testing, and consuming alcohol for at least 6 hours before testing [42]; (2) a series of self-report questionnaires investigating depression, anxiety, stress, quality of life, and distress coping strategies (State Trait Anxiety Inventory-Y [STAI-Y], Depression Anxiety Stress Scales-21 [DASS-21], Psychological General Well-Being Index [PGWBI], and COPE-NVI); and (3) resting heart rate detection with an Mi Band 2 sensor.

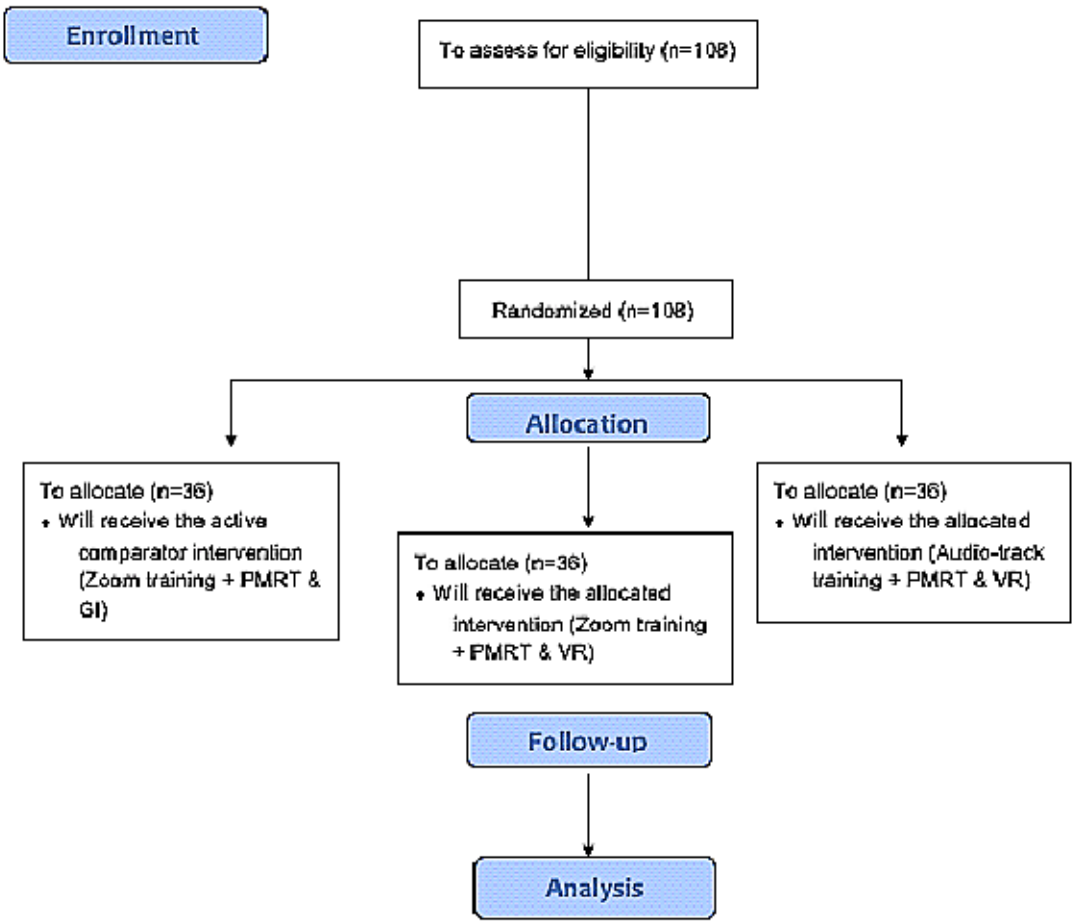
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Before and after each relaxation session (t1-t4), in approximately 20 minutes, the personal level of tension is assessed by using a visual analog scale from 0 (no tension) to 10 (extreme tension level). The state-anxiety level is evaluated based on the STAI-Y1. The 4 relaxation sessions are administered 2 to 3 days apart from each other for all 3 groups. The assessment phase is administered through Moodle, an e-learning platform used for data collection.

The T1 phase (day 7) required approximately 60 minutes. Before and after the relaxation session, states of tension and anxiety are assessed by using a 0 (no tension) to 10 (extreme tension level) scale, and the state-anxiety level is evaluated based on the STAI-Y1. Then, participants are exposed to a PMRT session merged with a VR or a GI procedure. Before the GI or the VR experience, all the participants fill out the Vividness of Visual Imagery Questionnaire and the Test of Visual Imagery Control. After the PMRT session, users compile a series of self-report questionnaires investigating depression, anxiety, stress, and quality of life (STAI-Y, DASS-21, PGWBI), and the VR group only fill out the Virtual Reality Sickness Questionnaire to monitor VR-related side effects (eg, sickness) and the ITC-SOPI to assess the sense of presence at the end of the T1 phase. The Mi Band 2 sensor is used during the entire T1 phase administration to detect resting heart rate activity. This assessment phase is administered through the Moodle e-learning platform.

The T2 phase (follow-up) is deployed for approximately 45 minutes. Before and after the relaxation session, states of tension and anxiety are assessed using a visual analog scale from 0 (no tension) to 10 (extreme tension level). The state-anxiety level is evaluated based on the STAI-Y1. All the users are exposed to a self-GI experience in which those who were part of the VR group are asked to recall the personalized VR scenario experienced during the T1 phase (day 7). Instead, the GI group retrieve the image participants had used in association with the PMRT during the T1 phase (day 7). After the session, participants fill out a series of self-report questionnaires investigating depression, anxiety, stress, quality of life (STAI-Y, DASS-21, PGWBI), and an ad hoc version based on the ITC-SOPI to assess the sense of presence experienced during the imagery experience. This assessment phase is administered based on the Moodle e-learning platform. The Mi Band 2 sensor is used during the entire T1 phase administration (day 7) to detect resting heart rate activity.

Figure 1. Consolidated Standards Of Reporting Trials 2010 flowchart. GI: guided imagery; PMRT: progressive muscle relaxation technique; VR: virtual reality.



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Figure 2. Graphic description of the activities carried out during the Active Comparator condition: progressive muscle relaxation technique (PMRT) training via Zoom and guided imagery (GI) exposure.

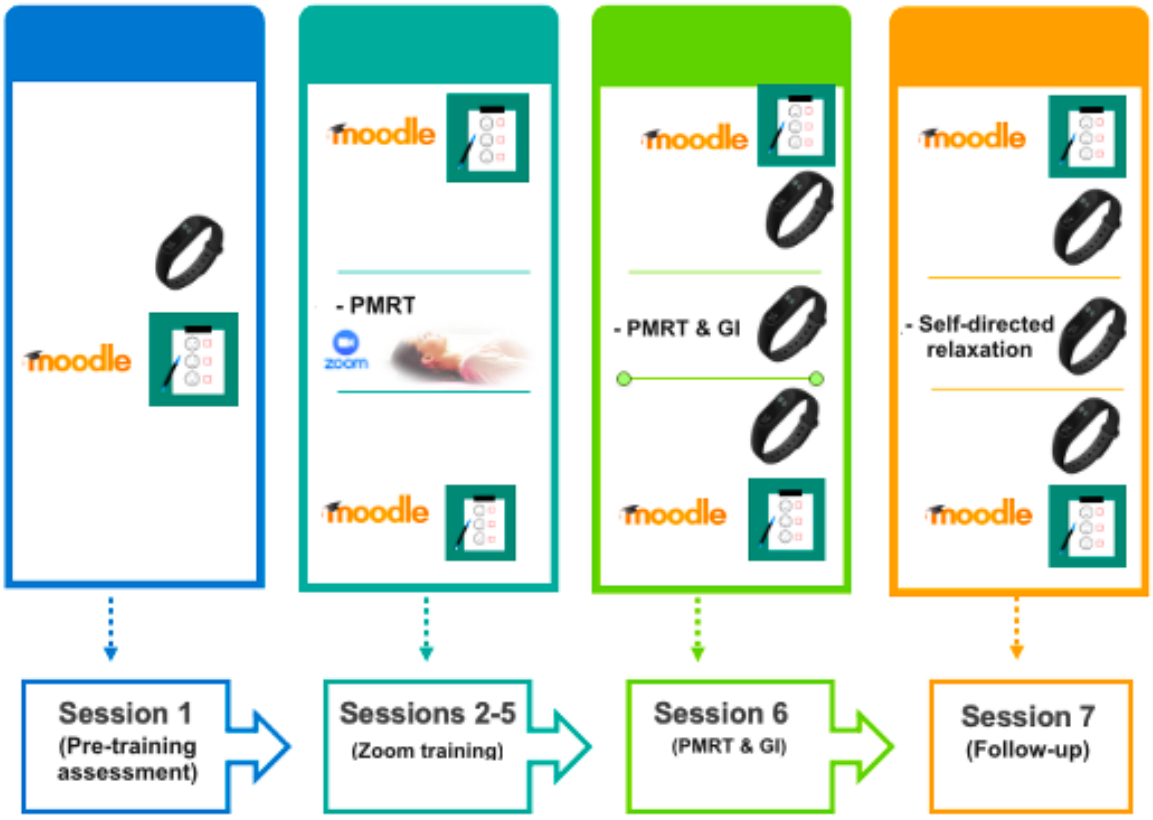
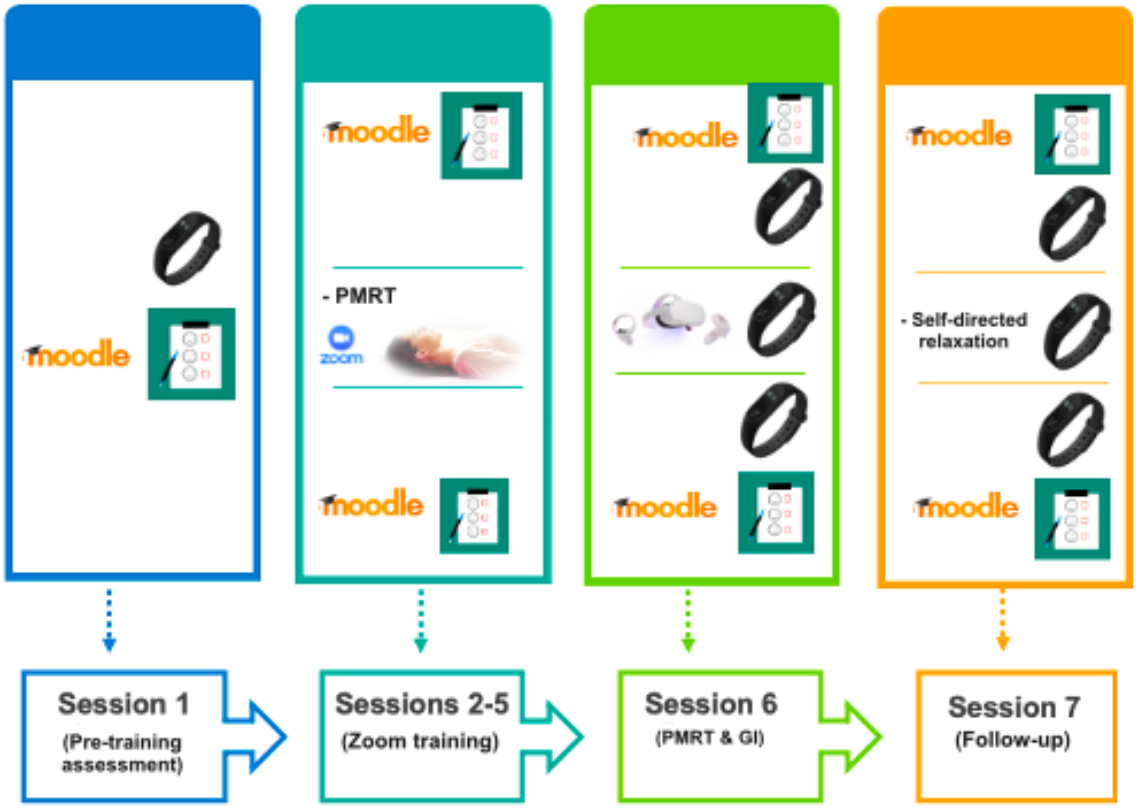
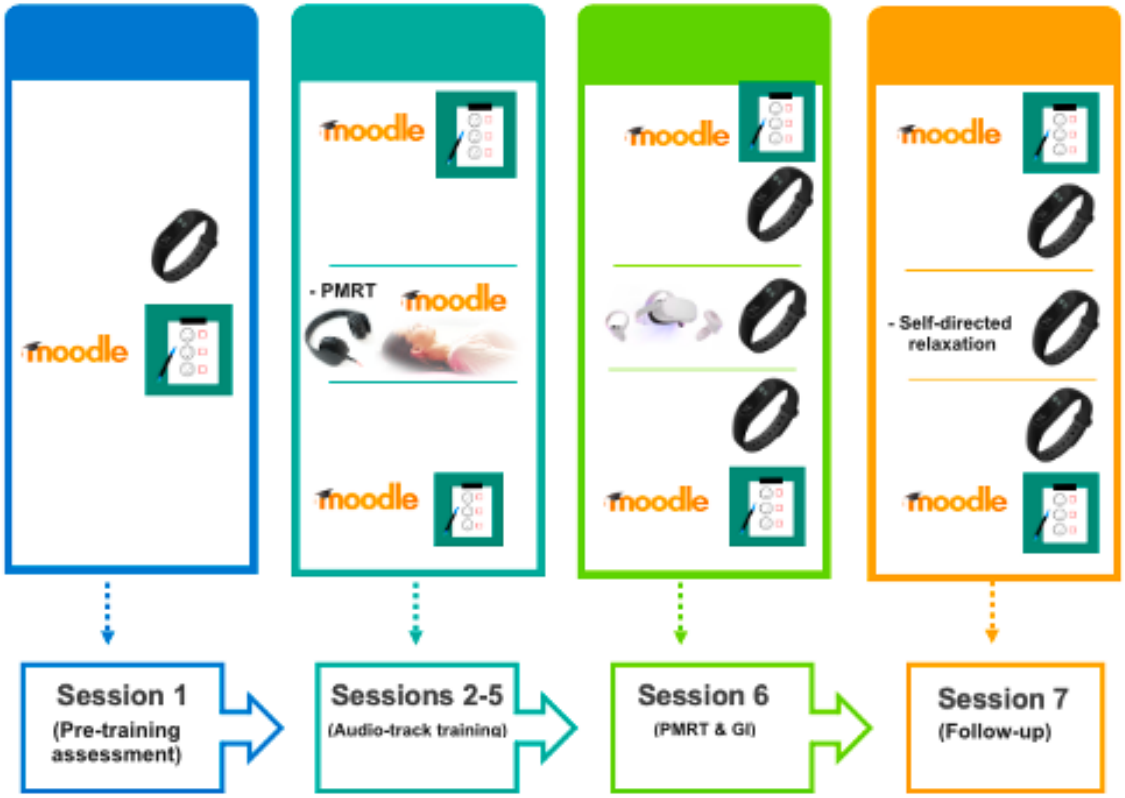


Figure 3. Graphic description of the activities carried out during the Intervention A: PMRT training administered via Zoom integrated with a personalized virtual reality exposure deployed by a head-mounted display (Oculus Quest 2). GI: guided imagery; PMRT: progressive muscle relaxation technique.



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Figure 4. Graphic description of the activities carried out during the Intervention B: PMRT training administered based on the Moodle platform via an audio-track integrated with a personalized virtual reality exposure deployed by a head-mounted display (Oculus Quest 2). GI: guided imagery; PMRT: progressive muscle relaxation technique.



Power Calculation

Sample size estimation was computed with G*Power 3.1 software (Heinrich Heine Universität Düsseldorf) [43]. As a statistical test, the repeated-measures ANOVAs between factors have been considered. The effect size was set as 0.25, the α as .05, and the Power (1β error probability) as 0.80. We have 3 separate groups and 3 measurements. On the basis of these parameters, we estimated having to recruit at least 36 participants for each of the 3 groups.

Data Collection, Storage, and Security

Based on informed consent, participants are informed about the experimental procedure; how data are collected, transmitted, and stored; and who has access to the data. Any digital data, such as responses to web-based questionnaires, are uploaded and saved to a secure server. Any hard copy documents are stored in a locked cabinet. Both digital data and hard copy documents are retained for 10 years after the end of the study and then securely destroyed.

Measures-Screening and Primary Outcomes

In Table 1, all the assessment and primary outcome measures are described.

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Table 1. Evaluation tools and methods by outcome of interest.

Primary objective	Description	Evaluation tool
1. Number of participants with virtual reality (VR)–related side effects as assessed by the Virtual Reality Sickness Questionnaire (VRSQ) and the investigators' observations[a]	Participants in the 2 VR experimental arms (Interventions A and B) are asked to refer to whether the VR head-mounted display was painful, too heavy, or uncomfortable. Participants are asked if they have experienced negative side effects during the VR exposure based on the VRSQ, administered at the end of the VR exposure. This questionnaire is based on a dichotomous answer (Yes/No). During the VR experience, the investigator observes participant reactions and records the behaviors and signs that suggest an unpleasant experience.	VRSQ [44,45]
2. Changes between and within subjects in depression scores[b]	Differences between groups and change from baseline to the T1 and T2 phases in depression scores are assessed based on the Depressive Anxiety Stress Scale-21 (DASS-21-Depression Subscale). Items are answered using a 4-point Likert scale (0-3). Scores range from 0 to 42 (the scores will need to be multiplied by 2 to calculate the final score). Higher scores indicate more severe depression.	DASS-21-Depression Subscale [46-48]
3. Change is being assessed between and within subjects in trait-anxiety scores[b]	Differences between groups and change from baseline to the T1 and T2 phases in trait-anxiety scores are assessed based on the State-Trait Anxiety Inventory-Y2 (STAI-Y2, Trait Anxiety). The measure is a self-report questionnaire investigating trait anxiety based on a 4-point Likert scale (1-4). Scores range from 20 to 80. Higher scores indicate higher trait-anxiety severity.	STAI-Y2 [49-51]
4. Changes between and within subjects in state-anxiety scores[b]	Differences between groups and change from baseline to the T1 and T2 phases in state-anxiety scores are assessed based on the State-Trait Anxiety Inventory-Y1 (STAI-Y1, State Anxiety) before and after each session. The STAI-Y1 is a self-report questionnaire investigating the state anxiety based on a 4-point Likert scale (1-4). Scores range from 20 to 80. Higher scores indicate greater state-anxiety severity.	STAI-Y1 [49-51]
5. Change is being assessed between and within subjects in autonomic arousal, skeletal muscle effects, situational anxiety, and subjective experience of anxious affect[b]	Differences between groups and change from baseline to the T1 and T2 phases in anxiety scores are assessed by the "DASS-21-Anxiety Subscale" based on a 4-point Likert scale (0-3). Scores range from 0 to 42 (the scores will need to be multiplied by 2 to calculate the final score). Higher scores indicate more anxiety severity.	DASS-21-Anxiety Subscale [46-48]
6. Change is being assessed between and within subjects in bodily anxiety sensations[b]	Differences between groups and change from baseline to the T1 and T2 phases in bodily anxiety sensations scores are assessed based on the Self-Assessment Manikin (SAM). The SAM is a nonverbal imagery-based assessment technique used to assess bodily anxiety sensations that directly measure the pleasure, arousal, and dominance associated with a person's affective reaction to a wide variety of stimuli. Each sensation is assessed on 5 different images distributed in order of size. Participants can tick either of the 5 pictures or 4 spaces in between, making it a 9-point Likert scale. The SAM varies from a minimum score of 3 to a maximum score of 27.	SAM [52]
7. Change is being assessed between and within subjects in levels of chronic nonspecific arousal (stress)[b]	Differences between groups and change from baseline to the T1 and T2 phases in levels of chronic nonspecific arousal (stress) scores are assessed by the "DASS-21-Stress Subscale" based on a 4-point Likert scale (0-3). Scores range from 0 to 42 (the score will need to be multiplied by 2 to calculate the final score). Higher scores indicate a higher level of stress.	DASS-21-Stress Subscale [46-48]
8. Change is being assessed between and within subjects in relaxation levels[b]	Differences between groups and change from baseline to the T1 and T2 phases in relaxation levels are assessed based on the visual analog scale administered before and after each session. This measure assesses relaxation levels before and after each VR experience. Participants had to express how relaxed they felt (0 =not at all relaxed; 10=completely relaxed; 0 =absent; 10=complete). Higher scores indicate higher relaxation levels.	Visual analog scale-relaxation level

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Primary objective	Description	Evaluation tool
9. Change is being assessed between and within subjects in quality-of-life scores[c]	Change from baseline to the T1 and T2 phases in quality-of-life scores on the Psychological General Well-Being Index (PGWBI) is assessed at 3 different assessment times. The measure consists of 22 self-administered items, rated on a 6-point scale (0-5), which assesses psychological and general well-being. Scores range from 0 to 110. Higher scores indicate greater well-being.	PGWBI [53-55]
10. Change is being assessed between and within subjects in coping strategies scores[b]	Change from baseline to the T1 and T2 phases in coping strategies is assessed at 3 different assessment times. The Coping Orientation to the Problems Experienced-New Italian Version (COPE-NVI) is a self-report questionnaire developed to assess the different coping strategies people use in response to stress; it is based on 60 items rated on a 4-point scale (1-4). Total scores range from 60 to 240. Higher scores indicate that a certain coping strategy is frequently used by the person.	COPE-NVI [56]
11. Change is being assessed between and within subjects in sense of presence scores related to the VR and guided imagery experiences[c]	Differences between groups and change from the T1 and T2 phases in sense of presence related to the VR or guided imagery experience are assessed at 2 different assessment times based on a visual analog scale and the ITC-Sense of Presence Inventory (ITC-SOPI). The ITC-SOPI is a self-report questionnaire assessing the sense of presence. Items are rated on a 5-point Likert scale (1-5). Scores range from 36 to 180. To obtain the scores for each of the scales, the average of the items is calculated. Higher scores indicate a higher sense of presence.	ITC-SOPI [57]; Visual analog scale-sense of presence
12. Change is being assessed between and within subjects in heart rate[b]	Differences between groups and change from baseline to the T1 and T2 phases in heart rate are assessed based on the Xiaomi Mi Band 2 sensor. It is used in 3 different assessment times (T0, T1, T2). During T1 and T2 heart rate is measured before, during, and after the in-presence relaxation session.	Xiaomi Mi Band 2 tool [58,59]

[a]T1 (day 7) phase.

[b]T0 (baseline), T1 (day 7), and T2 (day 14) phases.

[c]T1 (day 7) and T2 (day 14) phases.

Statistical Procedure and Data Analysis

Quantitative statistical analyses will be performed using SPSS (versions 27.0 and 28.0; IBM Corp) [60,61] and R package [62]. To investigate the normal data distributions of the dependent variables, ranges of skewness and kurtosis will be determined. The Kolmogorov-Smirnov and the Shapiro-Wilk tests will also be performed to evaluate the statistical significance (mean, 95% CI) and normality of the distributions. In addition, Cronbach α will be assessed for each self-report questionnaire's subscales. To explore sociodemographic features, frequencies, means, and SDs will be measured.

To examine differences between and within subjects, the 3 groups will be evaluated by a repeated-measures ANOVA for mixed designs, where individuals will be the random effect, while the type of intervention and time (T0/T1/T2/before and after each session) will be the fixed effects. The Akaike information criterion and binary logistic regression will be performed to explore significant influence factors.

Spearman rank correlation coefficient will be used to investigate the relationship between the self-reported measures and heart rate.

Results

As of July 2022, a total of 45 individuals have been assessed as eligible for study enrollment (Multimedia Appendix 2).

Preliminary data showed adequate Cronbach α for all the T0 self-report questionnaire scores (ranging from .66 to .83). No differences emerged between the GI and VR groups at the baseline (T0) for all the sociodemographics and psychological features investigated (gender, marital status, school attendance, employment, participation in relaxation training in the past, use of VR in the past, anxiety, depressive and stress symptomatology, and the ability to imagine in a vividness way mental images) except for age ($F_{1,39}$=12.32; P<.001) and years of education ($F_{1,39}$=4.81; P=.04), factors that have been controlled for in the following group comparisons. To preliminarily investigate the differences between the VR and GI groups in experiencing state anxiety before and after the relaxation session (T1) and at T2, repeated-measures multivariate ANOVAs have been computed. At T1, our preliminary analysis showed a significant difference of the state-anxiety symptoms ($F_{1,39}$=22.48;P<.001) between groups with lower scores in state anxiety (VR group: mean 30.10, SD 4.35; GI group: mean 39.35, SD 4.71; $t_{1,39}$=5.92;P<.001) for the VR group after the relaxation session. Moreover, the VR group perceived a higher sense of physical presence ($F_{1,39}$=7.38;P<.01). The study's experimental phase is expected to conclude in May 2023, and the results of the research will be presented in June 2023. The results obtained from this work will be published in an open-access scientific paper and in the form of posters and conference papers to be presented at national and international conferences.

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Discussion

This study aims to evaluate the impact of exposure to customized natural and realistic VR-based scenarios as a factor that may enhance relaxation when administered with PMRT. To our knowledge, few studies have addressed this topic [63].

Furthermore, in light of the COVID-19 pandemic, innovative VR treatment protocols are increasingly requested and helpful in managing relaxation, also due to the possibility to be administered with larger flexibility in several different contexts and partially independent from the presence of the therapist [64].

Moreover, delivering an entire PMRT protocol with a psychotherapist present may require a considerable amount of time and higher costs. The introduction of VR may positively reduce intervention costs, as it allows partial self-management of the treatment. Furthermore, in the case of patients with medical problems (eg, cancer), the integration of VR may facilitate the administration of the relaxation intervention during specific invasive treatments (eg, chemotherapy sessions).

Assessing the efficacy of PMRT in alternative ways could extend the treatment administration, especially in situations where the standard delivery procedure is more difficult to implement.

With the aim to preliminarily investigate this study's main objective, initial analyses showed that VR with PMRT facilitates a greater decrease of state anxiety than GI. Based on our knowledge, no studies have investigated VR with PMRT as an alternative complementary technique instead of GI. The current findings are promising and will be extensively investigated at the end of the recruitment phase.

This study is characterized by a series of limitations that should be considered and solved in the implementation of future studies. First of all, it is essential to consider the prominent role that psychophysiological parameters have in measuring relaxation, defined as the ability of the human body to reduce physiological arousal, and which can be assessed by measuring a decrease in muscular tension, heart rate, respiration rate, and sweating rate [3,65]. Although our project is targeted at investigating a self-reported sense of presence, engagement, and relaxation feeling, it should be important to also investigate psychophysiological measures other than heart rate, such as breathing rate, heart rate variability, galvanic skin response, cortical levels, and changes in brain wave activities. Research conducted so far investigated these parameters to understand the impact of distinct VR-based relaxation techniques different from progressive muscle relaxation, showing promising results [3]. Moreover, it would be important to thoroughly investigate psychophysiological activity also when VR is merged with PMRT both with clinical and nonclinical samples.

Data Availability

The data set generated and analyzed during the current study is available from the corresponding author on reasonable request.

Authors' Contributions

SP, CN, SG, and SF contributed to the conceptualization of the protocol; SP, CN, and SG contributed to the methodology; MD worked on the hardware and software components; SP and SO contributed to the curation and formal analysis, and wrote the original manuscript; CN and SG revised the analysis and the original manuscript; and SP, FF, SG, CN, SO, and CL contributed to the manuscript's editing and revision. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) diagram. Overview of the enrollment, interventions, and assessment phases.
[PNG File , 38 KB - resprot_v12i1e44183_app1.png]

Multimedia Appendix 2
CONSORT 2010 flowchart.
[PDF File (Adobe PDF File), 67 KB - resprot_v12i1e44183_app2.pdf]

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Abbreviations

COPE-NVI: Coping Orientation to the Problems Experienced-Nuova Versione Italiana
DASS-21: Depression Anxiety Stress Scales-21
GI: guided imagery
ITC-SOPI: ITC-Sense of Presence Inventory
PGWBI: Psychological General Well-Being Index
PMRT: progressive muscle relaxation technique
STAI-Y: State-Trait Anxiety Inventory-Y
T0: baseline
T1: the fifth in-presence session
T2: the last session
VR: virtual reality

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Protocol

Action Observation Treatment for Upper Limb Rehabilitation in Patients With Stroke: Protocol for a Multicenter Randomized Controlled Trial

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Abstract

Background: In the last few years, new noninvasive strategies have emerged as rehabilitative treatments for patients with stroke. Action observation treatment (AOT) is a rehabilitation approach based on the properties of the mirror neuron system with a positive impact on modifying cortical activation patterns and improving the upper limb kinematics. AOT involves the dynamic process of observing purposeful actions with the intention of imitating and then practicing those actions. In recent years, several clinical studies suggested the effectiveness of AOT in patients with stroke to improve motor recovery and autonomy in activities of daily living. However, a deeper knowledge of the behavior of the sensorimotor cortex during AOT seems to be essential.

Objective: The aim of this clinical trial, conducted in 2 neurorehabilitation centers and in patients' homes, is to investigate the effectiveness of AOT in patients with stroke, confirming the translational power of a tailored treatment. Particular emphasis will be placed on the predictive value of neurophysiological biomarkers. In addition, the feasibility and impact of a home-based AOT program will be investigated.

Methods: A 3-arm, assessor-blinded, randomized controlled trial will be performed by enrolling patients with stroke in the chronic stage. A total of 60 participants will be randomly allocated to receive 15 sessions of AOT with different protocols (AOT at the hospital, AOT at home, and sham AOT), 3 sessions per week. The primary outcome will be assessed using the Fugl-Meyer Assessment-Upper Extremity scores. Secondary outcomes will be clinical, biomechanical, and neurophysiological assessment.

Results: The study protocol is part of a project (project code GR-2016–02361678) approved and funded by the Italian Ministry of Health. The study began with the recruitment phase in January 2022, and enrollment was expected to end in October 2022. Recruitment is now closed (December 2022). The results of this study are expected to be published in spring 2023. Upon completion of the analyses, we will examine the preliminary effectiveness of the intervention and neurophysiological outcomes.

Conclusions: This study will be used to evaluate the effectiveness of 2 different AOT scenarios (ie, AOT at the hospital and AOT at home) in patients with chronic stroke and to assess the predictive value of neurophysiological biomarkers. Specifically, we will attempt to induce the functional modification of the cortical components by exploiting the features of the mirror neuron system, demonstrating relevant clinical, kinematic, and neurophysiological changes after AOT. With our study, we also want to provide, for the first time in Italy, the AOT home-based program while assessing its feasibility and impact.

Trial Registration: ClinicalTrials.gov NCT04047134; https://clinicaltrials.gov/ct2/show/NCT04047134

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KEYWORDS

action observation treatment; stroke rehabilitation; upper limb kinematics; EEG; electroencephalography; qEEG; quantitative electroencephalography

Introduction

Background

Stroke is a leading cause of death and one of the most common causes of long-term disability that interferes with good quality of life [1]. Currently, one of the major components of rehabilitation interventions is focused on disability reduction to achieve the functional motor goal [2]. In the last few years, to improve activities of daily living (ADL), new noninvasive strategies that have emerged as rehabilitative treatments have been added to conventional motor rehabilitation programs [3,4].

One such noninvasive strategy is the action observation treatment (AOT), supported by results collected through randomized controlled trials [5-10]. This new rehabilitation approach is based on the network properties of the mirror neuron system (MNS) [11-13]. AOT involves the dynamic process of observing purposeful actions with the intention of imitating and then practicing those actions.

Extensive research over the last 20 years on human MNS [14-16] showed its importance not only in action recognition [17] but also in understanding action intentions and other important social cognitive aspects [14,16]. Moreover, higher activation of temporoparietal networks was found when a goal-directed action was observed [18]. Enabling the patients to acquire new skills and potentially relearn movement patterns, AOT is involved in the motor learning process and could be a helpful adjunctive treatment to conventional therapy in upper limb motor rehabilitation. Indeed, AOT seems to be a useful rehabilitation strategy in addition to physical therapy for improving upper limb functions, especially in daily activities after stroke [19,20], alone or in association with motor imagery [21]. Finally, because it is also recruited in the damaged brain [22,23], the MNS is demonstrated to provide remarkable rehabilitative outcomes [7,24-27].

On the basis of the MNS properties able to activate the sensory-motor system through the observation of actions as well as the execution of the same actions, the AOT is proving to be an innovative rehabilitative approach for recovery of patients with stroke in chronic stage with upper limb impairment; several findings are present in scientific literature [5,23,27-31].

On the basis of these results, several clinical studies have been published in recent years, suggesting the effectiveness of AOT in improving motor recovery and autonomy in ADL [19,20,24,32]. However, a deeper knowledge of the behavior of the sensorimotor cortex during AOT seems to be essential. Recent studies have investigated cortical responses during the visualization of standardized actions by using 4 biomarkers primarily: related desynchronization and synchronization of alpha and beta rhythms (event-related desynchronization [ERD] and event-related synchronization [ERS]), beta brain coherence, and mu rhythm suppression [33-36].

In our previous work, we administered AOT treatment to a group of patients with stroke and observed the predictive value of ERD of electroencephalography (EEG) alpha rhythm (ie, 8-13 Hz) during rehabilitation tasks and at the end of the treatment, as a sign of neural plasticity. In addition, increased functional dexterity was found in patients with stroke in the subacute stage that had AOT compared with their peers who underwent a control treatment [8].

Recently, our research group conducted a pilot study to assess which type of ADL visual stimulus was the most effective in inducing motor excitability during action observation. EEG signals were recorded in 20 patients with stroke in chronic stage during the observation of task-oriented upper limb tasks (including self-care and feeding actions) and nonfinalized actions. The comparison of EEG rhythms between the 2 groups of motor actions (ie, task-oriented and non–task-oriented) revealed that an increased suppression of mu and beta bands occurred during the observation of the former category [37].

The procedures described in this protocol, including recruitment, assessments, and visual stimuli for motor action, have been tested in a single-group uncontrolled feasibility study. Preliminary analysis from a qualitative observation of a few collected data by using the proposed protocol showed desynchronization effects of all cerebral rhythms (especially of the beta rhythm) after the AOT treatment (ie, pretest vs posttest assessment). In addition, a few patients had alpha and beta rhythm desynchronization compared with a group of healthy participants.

The encouraging results obtained from clinical outcomes were confirmed by studies that included instrumental assessments, among others: AOT has an additional positive impact on modifying cortical activation patterns [9,26,38] and in improving upper limb kinematics [39].

Furthermore, in Italy, to the best of our knowledge, no evidence has been found related to the effectiveness of home-based AOT programs compared with the same AOT performed in the hospital.

According to the inspiring results reported in the literature, AOT rehabilitative treatment exemplifies a translational step from neuroscience to clinical rehabilitation applications.

Aims

The project aims to achieve the following objectives: (1) induce functional modification of the cortical components underpinning the action organization, exploiting the peculiar features of the

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MNS and demonstrating the relevant clinical, kinematic, and neurophysiological changes after AOT—in particular, the analysis of the AOT effectiveness will also consider the predictive value of neurophysiological biomarkers; and (2) provide the home-based AOT program, to the best of our knowledge, for the first time in Italy, thereby rendering evidence-based considerations regarding the feasibility and impact of our home-based AOT program for future systematic application of the approach.

Methods

Overview

A randomized, parallel-arm, controlled, outcome measurer–blinded, and multicenter clinical trial conducted in 2 neurorehabilitation centers in Italy aims to investigate the effectiveness of AOT in patients with chronic stroke (ie, >6 months from the first event) using quantitative EEG biomarkers, confirming the translational power of a tailored treatment.

A total of 60 individuals who have been enrolled will be randomized to the experimental group in hospital (EG@Hosp), experimental group at home (EG@Home), or control group (CG) in a 1:1:1 ratio.

The EG@Hosp will observe and execute ADL that are task-oriented actions (AOT protocol); the EG@Home will observe and perform the same ADL at home (AOT protocol at home); and the CG will not observe any motor task videos (but will watch video only on landscapes and historical issues), and after verbal instructions, they will perform the same actions observed by the other 2 groups.

After completing the patient screening, randomization will be performed before the first treatment session (T0). At baseline (T0), midintervention (after the 7th session; T1), and after the intervention (15th session or 5th week; T2), outcomes (ie, clinical scales, EEG and electromyography [EMG] signals, and kinematic parameters) will be assessed to evaluate impairment and functional abilities.

For each group, the total duration of the intervention will be 5 weeks (3 times a week) for a total of 15 sessions. After the end of the intervention, a 2-month follow-up assessment period (T3) will be scheduled to assess the maintenance and long-term effects.

The primary outcome assessed at T2 will be assessed by the Fugl-Meyer Assessment-Upper Extremity (FMA-UE) scores.

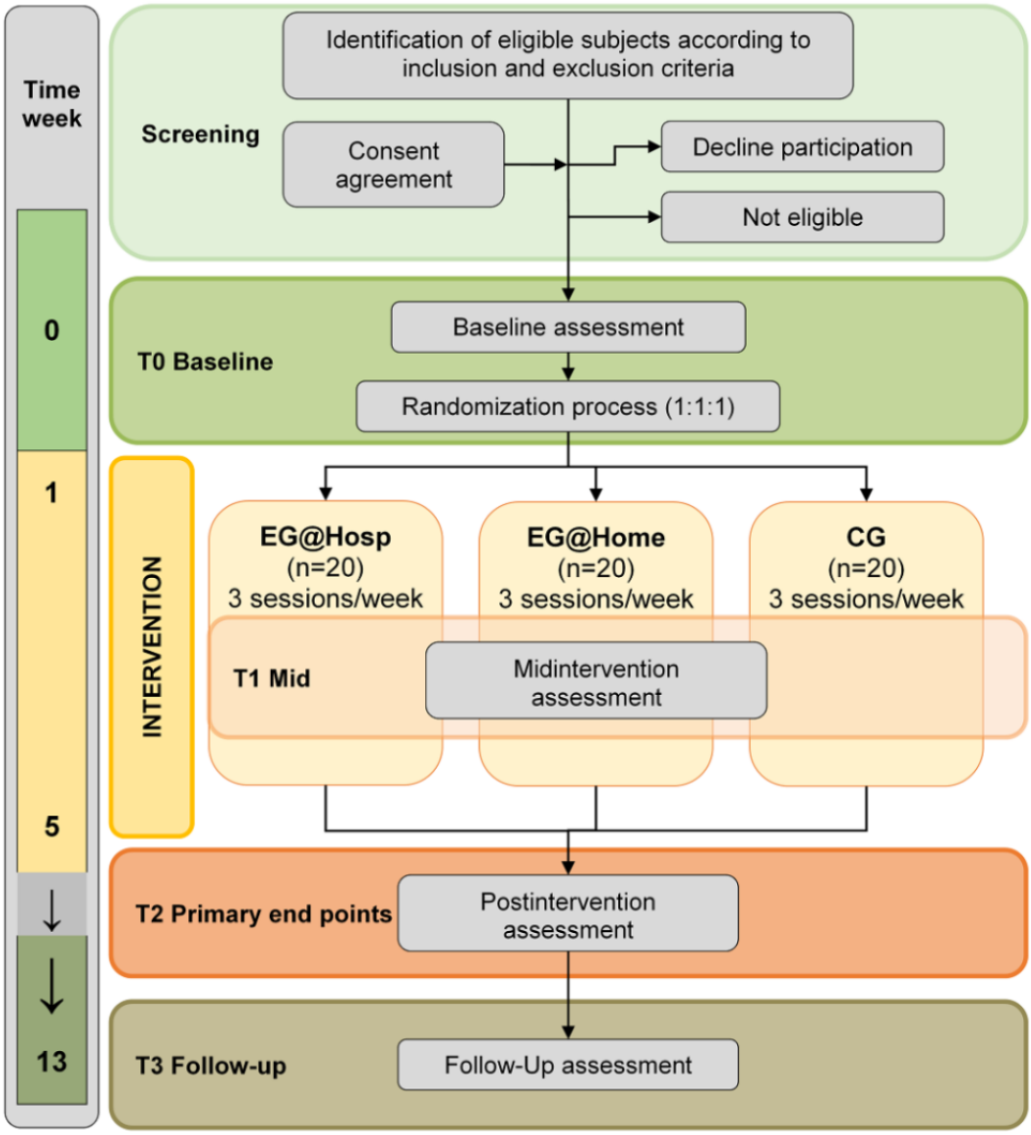
The trials will be performed at 2 neurorehabilitation centers in Italy: IRCCS San Raffaele Roma Hospital in Rome and at Casa di Cura del Policlinico Hospital in Milan.

All the data will be recorded in electronic case report forms through the REDCap (Research Electronic Data Capture; Vanderbilt University) system, accessed on the web via the internet for data collection and management.

A specific route diagram is presented in Figure 1. The protocol for this study was developed in accordance with the Standard Protocol Items: Interventional Trial Recommendations guidelines (SPIRIT) [40].

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Figure 1. Flowchart of the proposed randomized controlled trial according to the Consolidated Standards of Reporting Trials. CG: control group; EG@Home: experimental group at home; EG@Hosp: experimental group in hospital.



Study Population, Setting, and Recruitment

This study will be conducted in patients with chronic stroke. Between January 2022 and October 2022, a total of 60 outpatients or inpatients were recruited from the 2 centers mentioned earlier. The intervention will be provided in 2 different settings: rehabilitation centers (EG@Hosp and CG) and the patient's home (EG@Home).

Patients will be included after signing a written informed consent form, provided the inclusion and exclusion criteria are met.

The schedule of enrollment, interventions, and assessments are presented in Figure 2.

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Figure 2. Standard Protocol Items: Interventional Trial Recommendations (SPIRIT) diagram describing schedule of enrollment, interventions, and assessments. *Only for experimental group at home intervention group. BBT: Box and Block Test; CG: control group; EEG: electroencephalography; EG@Home: experimental group at home; EG@Hosp: experimental group in hospital; EMG: electromyography; FAT: Frenchay arm test; FMA-UE: Fugl-Meyer Assessment-Upper Extremity; MAS: Modified Ashworth Scale; mBI: Modified Barthel Index; TAM: Technology Acceptance Model.

Time point / Action	-T1 (Screening)	T0 (Baseline)	T1 (Mid treatment)	T2 (Post treatment)	T3 (Follow-up)
ENROLLMENT					
Recruitment	X				
Eligibility screen	X				
Informed consent	X				
Randomization (1:1:1)		X			
INTERVENTIONS					
EG@Hosp		◆—	—	—◆	
EG@Home		◆—	—	—◆	
CG		◆—	—	—◆	
ASSESSMENTS					
FMA-UE		X	X	X	X
FAT		X	X	X	X
BBT		X	X	X	X
MAS		X	X	X	X
mBI		X	X	X	X
Motor activity log		X	X	X	X
Nine hole peg test		X	X	X	X
EEG		X	X	X	X
Surface EMG		X	X	X	X
Kinematic parameters		X	X	X	X
TAM*				X	
Non structured interview*				X	

Selection Criteria

The inclusion and exclusion criteria of participants is shown in Textbox 1.

Patients with intellectual disability or other serious pathological conditions (eg, aphasia and hemianopsia) that affect their ability to watch or understand the proposed video were excluded.

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Textbox 1. Participant inclusion and exclusion criteria.

Inclusion criteria

- First ever unilateral ischemic stroke in the chronic stage (ie, the time elapsed from the event>6 months) provoked a clinically evident upper limb or hand deficit that affects the daily activities
- Diagnosis verified by brain imaging (magnetic resonance imaging)
- Aged 18-85 years
- Cognitive function sufficient to understand the experimental instructions (Mini-Mental State Examination Score of≥24)
- Chedoke-McMaster Stroke Assessment Scale—arm-hand section score of>1

Exclusion criteria

- Bilateral impairment
- Severe sensory deficits in the paretic upper limb
- Cognitive impairment or behavioral dysfunction
- Any other neurological or orthopedic deficit that affects arm function
- Any severe cardiovascular disease that can preclude intervention
- Any other current severe medical problems
- Refusal or inability to provide informed consent

Randomization

On the enrollment day, by using the electronic data capture system software (ie, REDCap) and the method of central stratified regional group randomization, the enrolled patients will be randomly allotted to one of the 3 groups (ie, EG@Hosp, EG@Home, and CG).

Blinding

Participants and intervention delivery facilitators cannot be blinded to group allocation. Evaluators conducting the clinical, neurophysiological (EEG and EMG), and physical (kinematics) assessments will be blinded to group allocation.

Interventions

Overview

For all groups of participants (ie, EG@Hosp, EG@Home, and CG), the intervention will include 15 sessions spanning 5 weeks (3 sessions per week) in addition to the conventional motor rehabilitation program expected for each patient's condition. Motor rehabilitation will be based on the relevant ADL that include at least one of the following: feeding, self-care, or external actions on the affected side. A total of 5 different videos (with the same motor task) will be presented in each session, beginning with the easiest action and ending with the most complex action. Each session will last approximately 15 minutes and will be repeated twice a day, at least 60 minutes apart.

AOT Protocol for EG@Hosp

Participants will be asked to carefully observe the videos showing different daily actions. Each motor act will be presented for 2 minutes. At the end of each motor act presentation, participants will execute the observed motor sequence for 1 minute (without any verbal instructions) with the affected upper limb.

Participants enrolled in EG@Hosp will perform rehabilitation treatment in the hospitals' premises.

The video will be played on a 15-inch monitor at a distance from the participant such that there will be sufficient space to perform the required movements. During the repetition of the motor action, a black screen will appear on the monitor.

AOT Protocol for EG@Home

After appropriate training of patients and caregivers, the use of tablets will allow home-based treatment. In particular, a tablet will be enabled with a web-based program that will be used to train the patients (and receive feedback on their progress).

Participants enrolled in EG@Home will be asked to carefully observe the videos showing different daily actions on the tablet. The web-based program will present each motor act for 2 minutes. At the end of each motor act presentation, the web-based program will ask the participants to execute the observed motor sequence for 1 minute (by audio or video message) with the affected upper limb.

Participants enrolled in EG@Home will perform rehabilitation treatment at their homes.

A 7-inch tablet with Android software 11.0 will be used for the experimentation. Before handing the tablet to the patient, the researcher will schedule the AOT program via the web, defining the days when the patients should perform the treatment independently at home. Patients can check the days on which treatment will be performed by consulting the web-based application, specifically the section where the scheduling of sessions is provided, on the tablet. The research teams will be remotely monitoring the progress of the EG@Home sessions using a dedicated web platform.

The web-based application was developed by a specialist following the researchers' specification.

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CG Protocol

The participants will be asked to observe video clips with no content on human motor activities. Videos will concern scientific, geographical, and historical issues.

For EG@Hosp and EG@Home, 5 different video clips (each 2 minute long) will be presented during each session. At the end of each video, and after the therapist's verbal instructions, participants will execute the motor task actions for 1 minute with the affected upper limb.

In this way, both the groups and controls will undergo the same amount of motor practice and receive the same amount of visual stimulation, with the only difference being the visual stimulus content.

Participants enrolled in the CG will perform rehabilitation treatment in the hospitals' premises.

The video will be played on a 15-inch monitor at a distance from the participant such that there will be sufficient space to perform the required movements. During the repetition of the motor action, a black screen will appear on the monitor.

Assessment: Instrumental Setup

The assessment setup and protocol will be the same as those used in similar studies [33,41] for the evaluation of impaired upper extremity functionality. The participant will sit in front of a target panel (eg, a 24-inch touch screen monitor) to perform the pointing task evaluation test.

The panel will have 9 targets; 8 of these, arranged in a circle, will be positioned 20 cm from its center, that is, the ninth target. The center of the target panel will be aligned with the shoulder acromion of the impaired upper limb. The distance between the participant and the center of the panel will be set according to each participant's arm length measured with the fist closed. During the pointing task trials, the participants will be instructed to reach, at their self-selected speed, one of the 9 targets on the board.

All the participants enrolled in this study will perform assessment tasks in the hospitals' premises.

Assessment: Primary and Secondary End Points

Overview

A thorough assessment of the clinical improvement in the functionality of the affected upper extremity will be performed using the FMA-UE (primary outcome), which will be combined with other clinical scales (secondary clinical outcomes).

In addition, the secondary instrumental outcomes (ie, EEG, EMG, and kinematics) will be included to verify neural plasticity and motor recovery using neurophysiological and kinematic parameters.

In addition, only for home-based treatment (EG@Home) group, the usability of the platform and the participants' satisfaction with the services will be evaluated using a specific questionnaire (Technology Acceptance Model [TAM]) and a nonstructured interview.

The variables related to the secondary instrumental outcomes (ie, EEG, EMG, and kinematics) will be evaluated during the standardized pointing task described earlier.

All the data will be analyzed using MATLAB software (MathWorks Inc). Specifically, the EEG recordings will be preprocessed offline using the MATLAB's toolbox called *EEGLAB* for artifact removal.

The Functionality of the Affected Upper Extremity

To perform a thorough assessment, different motor components of the affected upper extremity will be evaluated using the FMA-UE combined with 6 other scales.

1. The FMA-UE [34,35] (primary outcome) is a stroke-specific, performance-based impairment index. It is designed to assess motor function, balance, sensation, and joint function in patients with poststroke hemiplegia.
2. The Frenchay Arm Test [36] is a measure of upper extremity proximal motor control and dexterity during ADL performance in patients with impairments resulting from neurological conditions. The Frenchay arm test is an upper extremity–specific measure of activity limitation.
3. The Box and Block Test [42] assesses the unilateral gross dexterity of the hand. It requires participants to move as many blocks as possible from one side to the other in 1 minute.
4. The Modified Ashworth Scale [43] measures resistance during passive soft tissue stretching and is used as a simple measure of spasticity of all movements of the different joints of the upper extremity.
5. The Modified Barthel Index [44] is an ordinal scale used to measure ADL performance. Each performance item is rated on this scale, with a given number of points assigned to each level or ranking. It uses 10 variables to describe ADL and mobility.
6. The Motor Activity Log [45] assesses the quantity (*amount* subscale) and quality (*how well* subscale) of the use of the upper limb during ADL performance.
7. The Nine Hole Peg Test [46] measures hand dexterity. This requires participants to repeatedly place and then remove 9 pegs into 9 holes, one at a time, as quickly as possible.

Neurophysiological Biomarkers

The following biomarkers will be used in the study:

1. The EEG signal will be recorded (0.01-100 Hz band pass; sampling frequency: 1024 Hz) using 64 to 128 electrodes (high-density EEG, system 10-10 increased) during the pointing task (described earlier). Alpha (8-13 Hz), beta (14-30 Hz), and mu (8-13 Hz) bandwidths will be registered. EEG biomarkers will be ERD and ERS of alpha and beta rhythms, beta brain coherence, and mu rhythm suppression [47-50].
2. Surface EMG signals from the activation of 2 pairs of agonist and antagonist muscles from 4 upper arm and shoulder muscles (brachial biceps, brachial triceps, anterior deltoid, and posterior deltoid) will be recorded. Dual Ag-AgCl snap electrodes with an interelectrode spacing of 2 cm will be used during the acquisitions. A standard procedure, in accordance with Surface ElectroMyoGraphy

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for the Noninvasive Assessment of Muscles recommendations [51], will be used for skin preparation and electrode placement. The reference electrode will be placed over the electrically neutral lateral wrist epicondyle. The outcome of this analysis will be the cocontraction index calculated during the initial portion (epoch) of the single pointing movement (forward and return movement will be analyzed separately), which is identified as the acceleration phase of the hand kinematics.

Kinematics

Kinematic parameters of the pointing motor task will be acquired at 100 Hz by using a 7-camera motion capture system (Vicon, Oxford Metrics Ltd). Spherical reflective markers for motion tracking will be placed on specific body landmarks. In addition, an inertial measurement unit will be placed over the metacarpophalangeal joint of the middle finger.

The data acquired during the assessment trial with respect to the hand trajectory (ie, metacarpophalangeal joint of the middle finger) will be evaluated using the following metrics, related to the entire turn [52]:

1. Number of peaks of the speed profile: If a point-to-point reaching movement has a low number of peaks, it means that few acceleration and deceleration periods are present [53].
2. The smoothness described by Teulings's index is the rate of change of the acceleration in a movement [54]; a lower value of Teulings's index indicates a smoother movement.
3. Movement accuracy will be evaluated using the normalized path length parameter, as described by Colombo et al [55]; essentially, it is the line obtained by normalizing the effective length path with the ideal path; when this parameter approximates 1, the movement accuracy is very high.
4. The absolute hand path error, as computed by Franklin et al [56], is the area between the actual movement path and the straight line; this is considered an index of learning, and a reduction of this metric indicates a better adaptation to the required task.

Usability of the Platform (Only for Home-Based Treatment)

The feasibility of the home-based treatment and the usability of the platform, as well as the participants' satisfaction with the services, will be assessed by patients at the end of the intervention (T2) with the following scales:

1. TAM [57] includes 3 criteria (perceived ease of use, perceived usefulness, and behavioral intention to use). A Likert scale has been developed in which the user will rate from 1 to 7 whether they agree with a series of statements.
2. Nonstructured interviews (adapted from the TAM) to investigate patients' feelings.

Sample Size

As the changes in the effects of upper limb AOT in patients with stroke on EEG biomarkers have not been previously investigated, we have estimated the sample size based on previously published studies [58,59], comparing AOT and conventional therapy. We estimated the sample size required to detect differences in the effects of "group"×"time" interactions on primary clinical outcome (FMA-UE).

For this outcome, an effect size of 0.495 [60,61] is expected based on previous studies. Given the expected effect size, a total sample size of 54 will be required for repeated ANOVA with a power of 0.8 and a 2-sided type-I error of 0.05 (number of groups=3 [ie, EG@Hosp, EG@Home, and CG]; number of measurements=3 [ie, T1, T2, and T3]). Therefore, when considering a dropout rate of 10%, we plan to recruit 20 participants for each group (a total of 60 participants) for this study.

Statistical Analysis

Baseline Comparability Analysis

The baseline characteristics of the participants will be summarized and compared. These include the descriptions of demographic data, symptoms, and general conditions. The 2-tailed *t* test or nonparametric statistical method will be used for quantitative data. Categorical data will be analyzed using chi-square or Fisher exact tests and the Wilcoxon test.

Analysis of the Effectiveness

Analysis of the primary outcome (ie, functionality of the affected upper extremity) will be performed using the per-protocol principle. Treatment effects will be compared using a 2-way repeated ANOVA for clinical measurements, considering "time" (3 levels: T0, T1, and T2) as a within-subject factor and "group" (3 levels: EG@Hosp, EG@Home, and CG) as a between-subject factor.

In addition, the percentage of participants who passed the minimal clinically important differences of the FMA-UE will be compared using chi-square tests between the 3 groups.

The mean power across the assessment "time" (ie, T0 and T2) related to the action observation condition will be implemented in a mixed-design ANOVA to evaluate significant changes. A separate ANOVA will be performed to assess power changes in the stimuli selection data, using "treatment" (ie, EG@Hosp vs EG@Home vs CG) as the between-subjects factor and action as the within-subjects factor. To assess the predictive value of biomarkers for AOT effectiveness, an analysis of covariance (ANCOVA) will be performed considering the clinical data as the dependent variable, the "group" as a fixed factor, and the biomarkers as covariates.

Subsequently, to evaluate kinematic parameters recovery, a mixed design ANOVA will be implemented with "time" and "treatment" as within- and between-subjects factors, respectively.

The level of significance will be set at $P<.05$. For post hoc comparisons, the level of significance will be set at $P<.017$ after Bonferroni adjustment (.05/n; the number of comparisons, n=3) for the comparison of interaction effects. Cohen *d* will be calculated to determine the effect size of the change in scores for the behavioral motor outcomes between the groups. Immediate training effects (data from T0-T2) and the durability

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of training effects (data from T2-T3) will be separately investigated using mixed effect models.

Clinical-neurophysiological correlations will also be analyzed: the correlation between the ERD and factors such as the clinical scale score will be studied. To evaluate the differences in trends related to the clinical evolution of the patients, we will define a new variable to group the participants according to the presence or absence of relevant clinical improvements. The relevant clinical improvement will be defined by a clinical specialist for this purpose.

Data Collection and Management

The study data will be collected and managed using REDCap electronic data capture tools hosted at the IRCCS San Raffaele Roma Hospital and Casa di Cura del Policlinico Hospital [62,63]. REDCap is a secure web-based software platform designed to support data capture for research studies, providing (1) an intuitive interface for validated data capture, (2) audit trails for tracking data manipulation and export procedures, (3) automated export procedures for seamless data downloads to common statistical packages, and (4) procedures for data integration and interoperability with external sources.

Ethics Approval

The ethics committees of both involved centers (ie, IRCCS San Raffaele Roma Hospital and Casa di Cura del Policlinico Hospital) reviewed and approved the study protocol (Ethics Committee IRCCS San Raffaele Roma: protocol code RP05/2018; Ethics Committee Milano Area 2: protocol 705_2018bis).

The institutional review boards of both centers approved the study and will receive study reports at the middle and end of the study and monitor the study implementation and data collection.

Any deviations from the protocol will be promptly notified to the ethics committees and will be applied only after approval.

This study will be conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent forms will be obtained from each participant before the start of the study. Only those participants who provided informed written consent before starting will be included. During the study, written data will be stored in a closed cabinet; all data, after anonymization, will be entered into a REDCap electronic data capture repository. The input data will be double-checked by another research assistant. Personal data will be discarded after 5 years.

The results of this study will be disseminated through peer-reviewed journals and national and international academic conferences only by the professionals directly involved in the clinical trial.

Patient Withdrawal Criteria

Patients will be informed of the possibility of interrupting the study at any time they deem appropriate. Any interruption will be fully documented in the case report form by the investigators. The investigators shall make all reasonable efforts to maintain the patients who express a willingness to interrupt the participation in the study protocol.

Patients may prematurely discontinue the study if any of the following conditions occur:

1. Request from the patient, even if not motivated
2. Withdrawal of consent by the patient to participate in the study
3. Modification of the psychophysical state of the patient, significantly altering at least one of the variables considered in the inclusion or exclusion criteria
4. The occurrence of serious adverse reactions, which in the opinion of the investigator, make the continuation of the study impossible
5. Absence from >3 consecutive experimental session
6. Inability of the patient to continue the study for organizational and personal reasons

Results

Participants will be identified from hospital records or among those who show interest in participating by seeing the initiative through the communication channels of the hospitals, posters, and networks; all of them will be contacted by phone. After obtaining permission, the physicians will visit and explain the study. If they agree, the research assistants will manage their recruitment. This will be performed every week to identify participants.

The results of the evaluations will be released to the participants upon request. The results of this study will be presented at national and international patient organizations and to the general public.

The study protocol is part of a project (project code GR-2016–02361678) approved and funded by the Italian Ministry of Health.

Discussion

Rationale

The rationale of this study protocol is based on the AOT in patients with chronic stroke for upper limb rehabilitation. AOT relies on the MNS network to boost motor functions in patients affected by motor impairments, engaging the brain networks active during action execution. The imitation of observed gestures may increase the reorganization of the primary motor cortex, contributing to the formation of motor memories of the observed action, thus improving the physiological processes underlying motor learning [28,30].

It is well known that the MNS plays an essential role in considering the actions of others and in our ability to learn by imitation [64]. Furthermore, the activation of motor areas by AOT seems to be reinforced by the subsequent active execution of observed actions [9]. Indeed, as a motor representation technique, AOT has become an emerging motor learning training strategy to improve motor recovery in different healthy and pathological populations. Moreover, AOT preactivates specific areas of the brain, reinforcing intact cortical networks and facilitating the activation of the damaged ones [65]. Recently,

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a systematic review on this topic highlighted how AOT is an effective method for improving upper limb motor functions after stroke and that task-based AOT (based on goal-oriented activities, eg, a reaching task) might be superior to movement-based AOT (eg, a pure movement of elbow extension without any functional goals), as mirror neurons are more receptive to object-related actions [24]. The authors concluded that the optimal dosage, substantiality of effects, and underlying neural mechanisms of AOT in improving upper limb motor functions in patients with stroke should be considered in further investigations [24]. According to previous findings, we believe that increasing evidence supporting the effectiveness of observation-based inventions to assist traditional therapeutic practice in the rehabilitation of motor disorders [66] must be explored.

On the basis of these findings, the proposed study protocol aims to identify the effects of AOT and motor rehabilitative treatment on the clinical and functional status of patients with stroke through an advanced multidomain assessment and to infer the effects on brain plasticity.

This study will be a starting point for the evaluation of the effectiveness of the 2 AOT scenarios proposed (ie, AOT in the hospital and AOT at home) in patients with chronic stroke (ie, the time elapsed from the event is >6 months), as well as for the assessment of the predictive value of neurophysiological biomarkers.

Specifically, we will attempt to induce functional modification of the cortical components by exploiting the features of the MNS, demonstrating relevant clinical, kinematic, and neurophysiological changes after AOT.

The added value of a multidomain assessment that includes test and clinical scales and kinematic and neurophysiological (ie, EEG and EMG) outcomes aims to identify neurophysiological biomarkers capable of evaluating the effectiveness of AOT and confirming the translational power of a tailored rehabilitation treatment for chronic stroke.

Moreover, as AOT is involved in the motor learning process and could be a useful addition to conventional therapy, an innovative home-based AOT program will be implemented in the framework of this protocol study. Indeed, the continuity of care and personalized rehabilitation for people who are affected by chronic diseases is often interrupted after transitioning from the hospital to the home environment [67].

Future Implications

As a result of the COVID-19 pandemic, telerehabilitation and home care are growing rapidly, offering opportunities for integrating digital health interventions into community-based aging services. The COVID-19 pandemic has accelerated the adoption of technology and virtual care in patients' homes, and this trend likely to stay after the pandemic. Although notable age differences in technology use remain, the adoption of key technologies by older adults is the new challenge. With this purpose, this study protocol will permit the investigation of whether a home-based program could be effective, especially in terms of exercise capacity and perceived ease of use, offering comparable benefits to hospital-based programs.

The translational research results will ensure advances in the optimization and personalization of the rehabilitative process, both in hospitals and at home, thus improving upper limb motor functions and the quality of life of patients with chronic stroke.

Acknowledgments

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Data Availability

The data sets generated and analyzed during this study will be available from the corresponding author upon reasonable request.

Authors' Contributions

FI, IS, and PT conceived the study design. PT wrote the drafts of the protocol with significant contributions from MC, MP, and AS at all stages. MO, PA, PR, MP, MG, RR, and SP participated in the conception and design of the trial, planned the data analysis, and drafted the manuscript. Neurological review was performed by MF and MC.
All authors contributed, read, and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

ADL: activities of daily living
ANCOVA: analysis of covariance
AOT: action observation treatment
CG: control group
EEG: electroencephalography

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EG@Home: experimental group at home
EG@Hosp: experimental group in hospital
EMG: electromyography
ERD: event-related desynchronization
ERS: event-related synchronization
FMA-UE: Fugl-Meyer Assessment-Upper Extremity
MNS: mirror neuron system
REDCap: Research Electronic Data Capture
SPIRIT: Standard Protocol Items: Interventional Trial Recommendations guidelines
TAM: Technology Acceptance Model

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Protocol

Breaking Down Barriers to a Suicide Prevention Helpline: Protocol for a Web-Based Randomized Controlled Trial

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Abstract

Background: Globally, suicide is among the leading causes of death, with men being more at risk to die from suicide than women. Research suggests that people with suicidal ideation often struggle to find adequate help. Every month, around 4000 people fill in the anonymous self-test for suicidal thoughts on the website of the Dutch suicide prevention helpline. This self-test includes the Suicidal Ideation Attributes Scale (SIDAS), which educates users about the severity of their suicidal thoughts. The vast majority (70%) of people who complete the self-test score higher than the cutoff point (≥21) for severe suicidal thoughts. Unfortunately, despite this, less than 10% of test-takers navigate to the web page about contacting the helpline.

Objective: This protocol presents the design of a web-based randomized controlled trial that aims to reduce barriers to contacting the suicide prevention helpline. The aim of this study is 2-fold: (1) to measure the effectiveness of a brief barrier reduction intervention (BRI) provided in the self-test motivating people with severe suicidal thoughts to contact the Dutch suicide prevention helpline and (2) to specifically evaluate the effectiveness of the BRI in increasing service use by high-risk groups for suicide such as men and middle-aged people.

Methods: People visiting the self-test for suicidal thoughts on the website of the suicide prevention helpline will be asked to participate in a study to improve the self-test. Individuals with severe suicidal thoughts and little motivation to contact the helpline will be randomly allocated either to a brief BRI, in which they will receive a short tailored message based on their self-reported barrier to the helpline (n=388) or care as usual (general advisory text, n=388). The primary outcome measure is the use of a direct link to contact the helpline after receiving the intervention or control condition. Secondary outcomes are the self-reported likelihood of contacting the helpline (on a 5-point scale) and satisfaction with the self-test. In the BRI, participants receive tailored information to address underlying concerns and misconceptions of barriers to the helpline. A pilot study was conducted among current test-takers to identify these specific barriers.

Results: The pilot study (N=1083) revealed multiple barriers to contacting the helpline. The most prominent were the belief that a conversation with a counselor would not be effective, fear of the conversation itself, and emotional concerns about talking about suicidal thoughts.

Conclusions: Our study will provide insight into the effectiveness of a brief BRI designed to increase the use of a suicide prevention helpline provided in a self-test on suicidal thoughts. If successful, this intervention has the potential to be a low-cost, easily scalable, and feasible method to increase service use for helplines across the world.

Trial Registration: ClinicalTrials.gov NCT05458830; https://clinicaltrials.gov/ct2/show/NCT05458830

International Registered Report Identifier (IRRID): PRR1-10.2196/41078

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KEYWORDS

barrier reduction intervention; suicidal ideation; self-help; suicide prevention helpline; randomized controlled trial; help-seeking

Introduction

According to the World Health Organization, suicide is among the leading causes of death worldwide, with more lives taken by suicide than by malaria, HIV/AIDS, breast cancer, or war and homicide. Globally, men are more likely to die from suicide than women, with a 2.3 times higher age-standardized suicide rate among males than females [1]. Unfortunately, research suggests that people with suicidal thoughts often do not seek help, making them invisible for preventive measures and targeted support [2-4]. Connecting individuals with suicidal ideation to appropriate mental health care services is, therefore, a key preventive effort.

A recently conducted systematic review by Tang et al [5] examined the factors associated with not using formal mental health services among individuals who died by suicide. They found the following key factors: male sex, both younger and older age, and living in a rural location. A subsequent systematic review by the same authors identified predictors of not receiving formal mental health services among people at risk of suicide. The findings of this review indicated that among people experiencing suicidality, minority ethnicity, better perceived general health, lower psychological distress, lower severity of suicidality, no mental health diagnosis, a lower perceived need for treatment, and lower use of medical services are all associated with nonreceipt of formal mental health services [6].

It is also assumed that a considerable percentage of people with suicidal ideation do not disclose their ideation. Studies among the general public in France and the Netherlands indicate that almost half of the adults with suicidal ideation do not disclose their thoughts about suicide to others [7,8]. And even when people are engaged in mental health care, disclosure of suicidality is not self-evident. A recent study among young Australians (aged 16-25 years) who had experienced suicidal ideation and were engaged with a mental health professional, revealed that 39% had never disclosed their suicidality to their clinician, with concerns about confidentiality as the most common reason [9].

In order to increase help-seeking behavior, it is important to have insight into the barriers that people experience when seeking help for suicidal thoughts. Known barriers to care are a lack of perceived need for services, the preference for self-management, fear of hospitalization, structural factors like time and finances, and stigmatizing attitudes toward suicide, mental health problems, and toward seeking professional treatment [3,10]. Another important issue is that of unmet mental health needs. Individuals may not receive the help they need because there are insufficient services available, they are unable to afford the cost of care, or they feel their treatment is not meeting their needs [11,12].

Previous studies that compared web-based and offline help-seeking among people with suicidal ideation found that people who sought help on the internet reported higher levels of suicidal ideation, indicating that individuals may choose to go on the internet when their suicidality becomes more severe [13,14]. Anonymous digital help can be a low-threshold first step toward professional face-to-face help. In their innovative study, Jaroszewski et al [15] provide evidence that a brief, risk assessment and intervention platform increased crisis service use among those on the internet and in current mental health crisis. Due to their accessible, affordable, and often anonymous nature, digital innovations have the potential to reduce structural barriers to help-seeking. But as Jaroszweski et al [15] state, attitudinal barriers like the preference for informal help remain. It is, therefore, important to develop and evaluate interventions that address those barriers, particularly on digital platforms. However, robust research on reducing barriers to help-seeking in a web-based environment is scarce.

In the Netherlands, the suicide prevention organization “113 Suicide Prevention” provides around-the-clock anonymous support by phone and chat, as well as a web-based self-help course, self-assessment tests, and brief web-based coaching and therapy. Since its opening in 2009, the organization has seen an annual increase in brand awareness and service users, with almost 140,000 chat and phone call conversations and 1.3 million website visits in 2021 [16]. Apart from the homepage, the “test yourself” page is the most visited section of the helpline’s website. Every month, around 4000 people fill in the anonymous self-test for suicidal thoughts. This self-test includes the Suicidal Ideation Attributes Scale (SIDAS) and informs the test-taker of the severity of their suicidal thoughts [17]. Although the vast majority (70%) of people who complete the test score higher than the cutoff point (≥21) for severe suicidal thoughts, only approximately 10% of test-takers go on to navigate to the web page about contacting the helpline. And although due to the anonymity of the helpline’s services, it is not possible to know if people follow up on the advice of contacting the helpline, the difference in demographic distributions between the users of the self-test and the crisis helpline confirms the assumption that a substantial group does not continue using helpline service. While the percentage of men among the self-test users is 40%, it is only around 25% among the users of the helpline [18].

This paper presents the design of a web-based randomized controlled trial (RCT) that aims to reduce barriers to a suicide prevention helpline. The trial is inspired by Jaroszewski et al’s [15] study in which they evaluated a brief, automated barrier reduction intervention (BRI) designed to increase the use of crisis service referrals provided in the mental health app, Koko [19]. Although help-seeking behavior and barriers have been studied in traditional mental health care, guiding reluctant high-risk individuals in web-based environments toward professional help is still relatively uncharted territory. To the best of our knowledge, this study will be the first web-based RCT among people with severe suicidal ideation aimed to reduce

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the barriers to a helpline. The aim of this study is 2-fold: (1) to measure the effectiveness of a brief barrier reduction intervention (BRI) provided in the self-test motivating people with severe suicidal thoughts to contact the Dutch suicide prevention helpline and (2) to specifically evaluate the effectiveness of the BRI in increasing service use by high-risk groups for suicide such as men and middle-aged people [20].

Methods

Study Design

The study is designed as a web-based randomized controlled trial for the anonymous users of a web-based self-test for suicidal thoughts in which individuals with severe suicidal thoughts and no interest in contacting the helpline will be randomly allocated either to a short BRI or receive a general advisory text (care as usual). To minimize the burden on our high-risk and sensitive study population, we aim that it is feasible to complete the intervention within 10 minutes.

Participants

The participants of the trial will be recruited among the anonymous visitors to the helpline's website. People who would like to participate will be directed to a web-based information letter and consent form. If they give their consent to the processing of their data for research purposes, the participants will be transferred to the web-based RCT on the survey platform Qualtrics. To assure strict anonymity, no identifying information or IP addresses will be collected.

Exclusion Criteria

Participants will be excluded from the study if (1) they are younger than 16 years old, (2) they score below the cutoff point for severe suicidal thoughts (SIDAS score <21), (3) they score above the cutoff point for severe suicidal thoughts (SIDAS score ≥21) and report being likely to contact the suicide prevention helpline. They will be directly transferred to the contact details of the helpline.

People who do not meet the inclusion criteria will be directed to a web page thanking them for their time and encouraging them to contact the helpline if they feel distressed.

Sample Size

When assuming probabilities of 0.49 and 0.39 for contacting the helpline for the intervention group and the control group, respectively (based on Jaroszweski et al [15]), a power of .8 and alpha of .05, a sample size calculation for logistical regression analysis (2-tailed) indicates a total sample size of 775 participants [21]. We estimate that about 10% of participants drop out during the intervention; therefore, at least 853 participants have to be included. Furthermore, we estimate that approximately 30% of respondents score below the cutoff point for high risk of suicidal behavior, and based on Jaroszewski et al [15], we expect that 20% of respondents will indicate a high probability of contacting the helpline [15]. We, therefore, estimate that a minimum of 1706 respondents need to be recruited. We will continue to recruit participants until there are enough participants per condition.

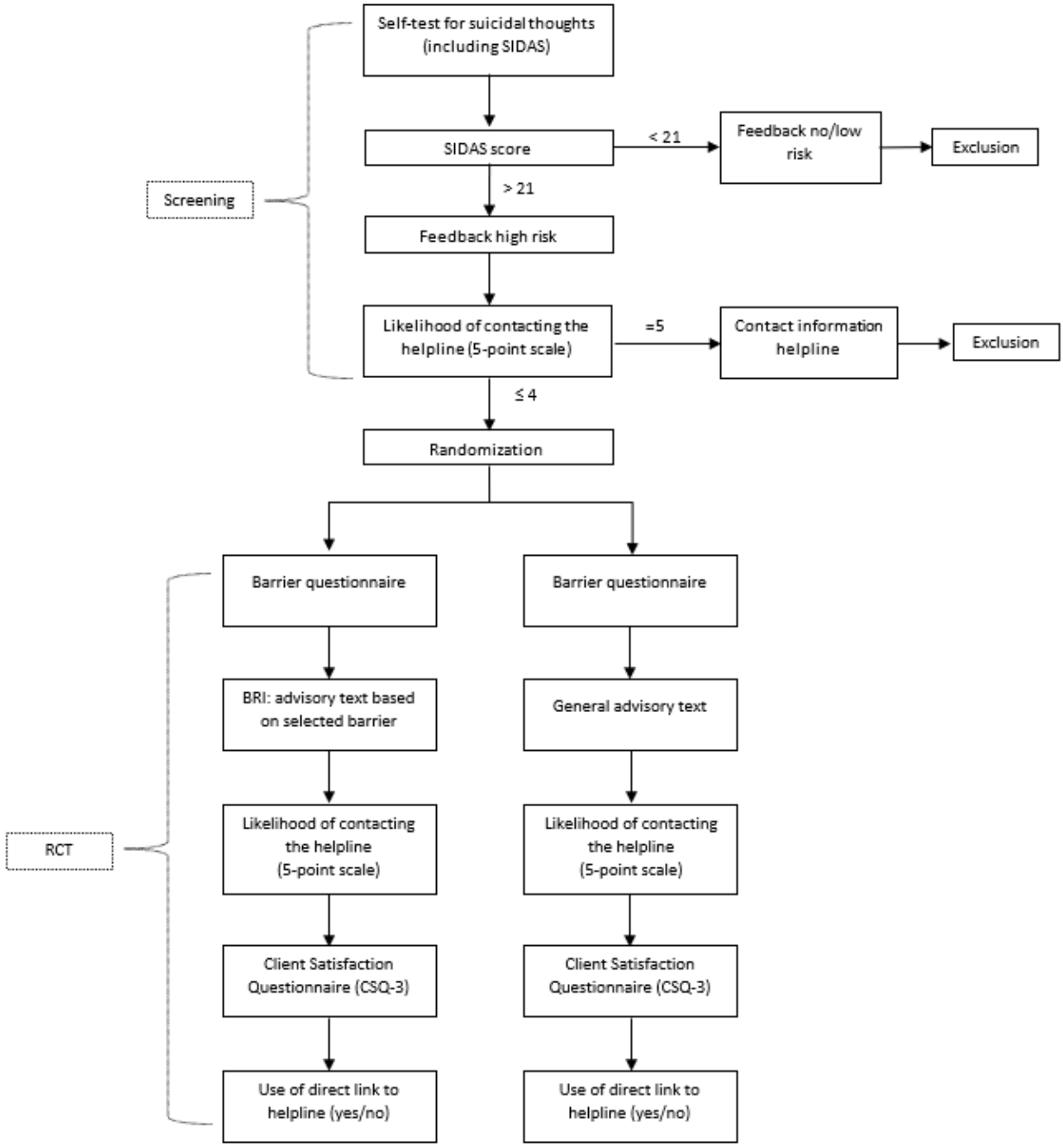
Procedure

After giving their informed consent and stating that they are 16 years or older, participants will be transferred from the helpline's website to the Qualtrics platform. Figure 1 displays the study's flowchart. During the screening phase, respondents start with the self-test. The self-test includes the SIDAS, which consists of 5 items on a 10-point scale measuring the frequency of suicidal thoughts, controllability, closeness to an attempt, distress, and interference with daily activities [17]. The self-test also contains questions regarding gender, age, and if the test-taker is currently in treatment for mental health problems. As mentioned in the exclusion criteria, if respondents score below the cutoff point for severe suicidal thoughts or score above the cutoff point but report that they are likely to contact the helpline, they will be excluded from the RCT.

After inclusion, participants will be randomly assigned to either the intervention or control condition. In both conditions, participants receive a barrier questionnaire to identify the reason why their self-reported likelihood of contacting the helpline in the screening phase was not very likely. After the barrier questionnaire, they receive a general advisory text (control) or an advisory text based on their selected barrier.

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Figure 1. Flowchart. BRI: barrier reduction intervention; RCT: randomized controlled trial; SIDAS: Suicidal Ideation Attributes Scale.



Measures

The primary outcome measure is the use of a direct link to the helpline after completing the intervention or the control condition. Due to the anonymous nature of the helpline, it is not possible to measure if people who do not directly use the link to the helpline, contact the helpline at a later point in time. Therefore, the self-reported likelihood of contacting the helpline will be included as a proxy measurement. This will be measured by the question “How likely are you to contact 113's helpline via chat or phone?” with answering options ranging from “not likely” to “very likely” on a 5-point scale. Other measures include gender, age group, SIDAS score, being in treatment for mental health problems (yes, no, and on a waiting list), and satisfaction with the self-test (Dutch CSQ-3) [22].

Persuasive System Design Model

Preceding research and literature on the design of persuasive eHealth technologies often cover software or applications intended for continuous use, whereas our study entails a single-session intervention. With this in mind, the BRI has been designed with the use of the persuasive system design (PSD) model [23,24]. The PSD model is a framework for the development and evaluation of persuasive behavior change technologies and offers 28 design principles [23]. Table 1 gives an overview of the applicable and relevant principles for our intervention, the corresponding requirements, and the implementation goals for the BRI.

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Table 1. Design principles originating from the persuasive system design model applied to the intervention.

Principle [24]	Requirement	Implementation goals
Primary task support		
Reduction ("A system that reduces complex behavior into simple tasks")	The system should lower the barrier toward help-seeking; breaking it down into small steps.	• Guiding toward the first small step in the help-seeking process: emphasis on different low-threshold methods of contact (24/7 chat and telephone) and the anonymous nature of the helpline
Tunneling ("Using the system to guide users through a process or experience provides opportunities to persuade along the way")	The system should guide users in the attitude change process by providing means for action.	• Self-test offers the test-taker information about the severity of their suicidal thoughts.
Tailoring ("Information provided by the system will be more persuasive if it is tailored to the potential needs, interests, personality, usage context, or other factors relevant to a user group")	The system should provide tailored information based on the user's level of suicidality and barriers toward the helpline.	• User receives feedback on their level of suicidality. BRI[a] provides different information based on the selected barrier.
Simulation ("Systems that provide simulations can persuade by enabling users to observe immediately the link between cause and effect")	The system should persuade users to contact the helpline with experiences from others.	• BRI provides statements of people with lived experiences of suicidality.
Dialogue support		
Similarity ("People are more readily persuaded through systems that remind them of themselves in some meaningful way")	The system should be designed in such a way that users can identify with the stories.	• BRI includes photos from people with lived experience and counselors of the helpline of different ages and gender.
Liking ("A system that is visually attractive for its users is likely more persuasive")	The system should appeal to the target group.	• Self-test and BRI use the same design and tone of voice as the helpline's website.
System credibility support		
Trustworthiness ("A system that is viewed as trustworthy will have increased powers of persuasion")	The system should provide information that is truthful, genuine, and unbiased.	• Feedback after the self-test score and information offered in BRI are written in a noncoercive style and leave all autonomy to the user, for example, "We respect your decision, of course, but would encourage you to talk about your feelings, either with us or with someone close to you."
Expertise ("A system that is viewed as incorporating expertise will have increased powers of persuasion")	The system should provide information that conveys knowledge, experience, and competence.	• The BRI was built on the results of a pilot study conducted among the users of the current self-test. • The information or feedback provided has been developed by the professionals of 113 (psychologists, communication advisors, and researchers).
Real-world feel ("A system that highlights people or organizations behind its content or services will have more credibility")	The system should provide information about the organization and the people behind it.	• BRI includes photos and experiences from counselors telling about their work in the helpline.
Authority ("A system that leverages roles of authority will have enhanced powers of persuasion")	The system should convey authority.	• Self-test and BRI are in the same style and tone of voice as the helpline's website and include the helpline's logo. • BRI includes persuasive messages about the many help seekers that contact the helpline. • BRI includes persuasive messages about the expertise of the helpline and its counselors.

[a]BRI: barrier reduction intervention.

Tailored Information

After selecting a barrier in the barrier survey, participants receive tailored information with the purpose of addressing common concerns and misconceptions about the helpline. Tailored information is useful for giving people the right information and suitable feedback and helps with selecting the most effective persuasive strategies. To persuade people to overcome their barriers to the helpline, the principles of the PSD model as well as the principles of consistency, social proof, likability, and authority derived from Cialdini's [24] principles of influence will be used [23].

Statistical Analysis

The analyses will be carried out with an intention-to-treat analysis. Missing values will be imputed using the MICE package in R (v4.2.2; R Core Team 2022) [25]. In order to verify the randomization process and inspect drop-outs, independent

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t tests and chi-square tests will be used to determine whether the control group and the intervention group, as well as the completers and noncompleters, are comparable on baseline factors (ie, gender, age, SIDAS score, and in treatment or not). Chi-square analysis will also be used to test the hypothesis that participants who receive the brief BRI are more motivated to contact the suicide prevention helpline (using the direct link yes/no) than participants in the control condition. To evaluate the effectivity of the BRI in increasing service use by men and middle-aged people, and to examine potential moderators, logistic regression analysis will be used.

Ethics Approval

This study protocol is designed in accordance with the relevant guidelines. This research is not subject to the Research Involving Human Subjects Act (Wet medisch-wetenschappelijk onderzoek met mensen) because participants are not subject to procedures and are not required to follow rules of behavior. All participants of the trial will be directed to a web-based information letter and consent form. After giving consent and stating to be 16 years or older, respondents will be transferred to the web-based RCT. No identifying information or IP addresses will be gathered to ensure strict anonymity. This study was reviewed and approved by the Medical Ethics Committee of the Vrije Universiteit Medical Centre (registration number 2021.0443) and is registered at ClinicalTrials.gov (NCT05458830).

Results

Overview

The BRI has been designed with the use of the PSD model, the expertise of the professionals at the helpline, and relevant literature. For the design of the barrier questionnaire, a pilot study was carried out among the users of the current self-test.

Pilot Study

To gain insight into the specific barriers to the helpline of people who fill in the self-test, a pilot study has been carried out. Between August 5 and October 14, 2021, people who took the self-test were asked the following additional questions; “What is the likelihood of you contacting the helpline to talk to our counsellors about your thoughts about suicide?” (5-point scale) and “If this likelihood is small, would you please indicate the main reason why you do not want to talk to one of our counsellors at the moment?” (open text field). During the pilot study, 7252 people filled in the self-test, of which 72% (n=5200) scored higher than the cutoff point (≥21) for severe suicidal thoughts. Almost 20% (n=1441) of all test-takers completed the open question, with 82% (n=1175) of them scoring above the cutoff point for severe suicidal thoughts. Cleaning the data led to a data set containing the answers of 1083 people in the high-risk category. Their answers revealed multiple barriers to contacting the helpline. The most prominent of them was mentioned 259 times and was the belief that a conversation with a counselor would not be effective (eg, “nobody can help me,” “it has no point anyway,” “I don’t see any possibility that my situation will change for the better,” “I already had professional help before and nothing helps,” “they would not believe me and think I exaggerate”). The second most mentioned barrier (151 times) concerned the fear of the conversation itself (eg, “I’m afraid to call,” “I’m too nervous and scared,” “I’m afraid to talk to people I don’t know,” “I don’t know what to expect”). The third most mentioned barrier (148 times) can be described as emotional concerns regarding talking about suicidal ideation (eg, “I’m not ready to talk about it yet,” “I’m afraid to talk about those feelings,” “I’m afraid that when I talk about it out loud it will get worse,” “I would not know what to say,” “I cannot articulate my feelings”). The fourth most frequently observed barrier concerned shame, stigma, and the fear that someone finds out about their contact with the helpline (eg, “I’m ashamed of my feelings,” “I’m afraid my parents will find out,” “I don’t want my spouse to know”). Other barriers concerned the topics of not wanting to be helped, being afraid to be a burden to someone, believing their problems were not bad enough, precious negative experiences with the helpline, wanting to solve their problem themselves, being already in treatment, having no energy or motivation, being afraid of the consequences (eg, having to go to a facility/crisis help or police involvement), or practical reasons such as not being in the right environment or having time restrictions.

Assessment of Barrier

To be able to provide customized information and advice, a barrier survey is included in the BRI. To not overwhelm the test-takers or expose them to more barriers than they have thought of themselves, the barrier questionnaire lists a limited number of options. As described earlier, previous studies identified the following key barriers to care: lack of perceived need for services; the preference for self-management; the fear of hospitalization; structural factors (eg, time and finances); and stigmatizing attitudes toward suicide, mental health problems, and seeking professional treatment [3,10]. Although these barriers were reflected among the users of the self-test, the pilot study revealed other, more frequently mentioned, barriers among our target population. We, therefore, chose to include the following barriers in the BRI: (1) “I don’t think that 113 can help me,” (2) “I’m scared to talk about my feelings,” (3) “I don’t think that my problems are serious enough for 113,” (4) “I’m scared that people will find out,” (5) “I would rather solve it myself,” and the remaining option (6) “I have other reasons.”

Testing of Prototypes

During the testing phase of the prototype, which included the names and photos of some counselors, the staff raised concerns regarding the anonymity and privacy of the counselors. We, therefore, decided to design the brief BRI with text-based feedback only and to anonymize the participating counselors (see Figure 2).

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Figure 2. Screenshots of barrier reduction intervention. Note: translated from Dutch to English.



Discussion

Principal Findings

This paper describes the study protocol for a web-based RCT of a brief barrier reduction intervention. The aim of the trial is 2-fold: (1) to measure the effectiveness of a brief BRI provided in the self-test motivating people with severe suicidal thoughts to contact the Dutch suicide prevention helpline and (2) to specifically evaluate the effectivity of the BRI in increasing service use by high-risk groups such as men and middle-aged people. The goal of the intervention is to reduce self-stigma, provide information, and clear up misconceptions on which barriers to the helpline are based. To identify these barriers specific to self-test users, a pilot study was conducted. The open-ended answers of 1083 current self-test users in the high-risk category revealed multiple barriers to the helpline, of which the most common were the belief that a conversation with a counselor would not be effective, fear of the conversation itself, and emotional concerns about talking about suicidal thoughts. These identified barriers were used to design the barrier questionnaire.

Limitations

To our best knowledge, our study will be the first web-based RCT among people with severe suicidal ideation aimed to reduce the barriers to a suicide prevention helpline. One of the strengths of the study that should not be underestimated is the fact that it will take place among the actual service users of 113 Suicide Prevention, a difficult-to-reach and high-risk population. Moreover, by measuring the intended outcome measure, contacting the helpline, behavioral as well as attitudinal, we increase the measure's reliability and validity. Furthermore, we expect to achieve a substantial sample size and will, therefore, be able to provide a reliable estimate of the intervention's effectiveness. However, our study is not without limitations. First, although the study takes place among the target population, it is still possible that some form of selection bias will occur as it is less likely that users in severe distress will participate in the study. Second, as mentioned before, due to the helpline's anonymous nature it is not possible to have a follow-up measurement to determine if those who will not use the link directly after the intervention will contact the helpline at a later moment in time. For that reason, a respondent's self-reported likelihood of contacting the helpline will be measured as well as the use of a direct link to the helpline. Third, the BRI is only text-based, it would also be valuable to examine the effects of different components (eg, video material) in a BRI.

Conclusions

The short barrier reduction intervention built in a self-test for suicidal thoughts aims to motivate people with severe suicidal thoughts to contact the Dutch suicide prevention helpline. Guiding people with suicidal ideation to appropriate resources is a key aspect of suicide prevention. Our study will add to a growing body of research on web-based mental health interventions and provide a better understanding of the effect of tailored information and dispelling misconceptions in a high-risk group. Furthermore, if it proves to be effective, this intervention has the potential to be a low-cost, highly scalable, and easily implementable method to increase service use for mental health and crisis helplines worldwide.

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Acknowledgments

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Data Availability

The data set generated and analyzed during this study will not be publicly available due to company policies regarding help-seekers' data but are available from the corresponding author upon reasonable request.

Conflicts of Interest

None declared.

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Abbreviations

BRI: barrier reduction intervention
PSD: persuasive system design
RCT: randomized controlled trial
SIDAS: Suicidal Ideation Attributes Scale

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Protocol

A Medicoeconomic Evaluation of a Telehealth Platform for Elective Outpatient Surgeries: Protocol for a Randomized Controlled Trial

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Abstract

Background: The number of elective outpatient surgeries in Canada has increased markedly in the last 10 years. However, unanticipated cancellations on the day of surgery and adverse postoperative events are frequent. Modern technologies have been shown to be of great help in the medical field in improving patient care. Thus, it is likely that dedicated technologies could also significantly improve surgical outpatients' pathways. Therefore, the department of anesthesiology at the University of Montreal Medical Center, in collaboration with LeoMed, a telemedicine platform, has developed a telehealth solution to offer more efficient perioperative support and follow-up for patients undergoing ambulatory surgery.

Objective: The objective is to evaluate the medicoeconomic benefit of a dedicated perioperative telehealth platform for patients undergoing day surgery. Our hypothesis is that this dedicated telecare solution will allow more efficient patient care, which will reduce all types of medical costs related to day surgery pathways.

Methods: This study is a single-center, single-blinded, 2-group randomized controlled trial. One thousand patients aged over 18 years with internet access who are scheduled to undergo ambulatory surgery will be enrolled and randomized either to follow a perioperative path that includes a patient-tailored perioperative digital app via the LeoMed telecare platform for 1 month or to follow the standard of care, which does not offer personalized digital support. The primary outcome will be to evaluate the cost-effectiveness of the telecare platform, assessing direct costs from factors such as unanticipated cancellations on the day of surgery due to preoperative instructions not being followed, calls to the local health information line, calls to the provincial health information line, emergency department consultations, unplanned readmissions, or medical visits for problems related to the surgical procedure within the first 30 days after the intervention. The secondary outcome will be to evaluate cost utility using a questionnaire assessing quality-adjusted life years. A blinded independent research team will analyze outcomes. All data will be analyzed according to the intention-to-treat principle. A sample size of 500 subjects in each group was calculated to detect a 21% reduction in postoperative complications with a power of 90%. This study has been approved by the ethics board of Centre hospitalier de l'Université de Montréal (University of Montreal Health Centre). No employee of LeoMed was involved in the study conception, and none will be involved in either data collection or analysis.

Results: Results of this trial will be useful to determine the economic benefit of a telecare platform specifically developed for surgical outpatient pathways.

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Conclusions: We believe that the deployment of a dedicated perioperative telehealth app will lead to better patient care and fewer postoperative complications, which will lower all types of costs related to surgical outpatient care.

Trial Registration: ClinicalTrials.gov NCT04948632; https://ClinicalTrials.gov/ct2/show/NCT04948632

International Registered Report Identifier (IRRID): DERR1-10.2196/44006

(JMIR Res Protoc 2023;12:e44006) doi:10.2196/44006

KEYWORDS

outpatient surgery; cost-effectiveness; telehealth solution; surgery; technologies; quality; safety; support; patient; cost; telecare; telehealth; platform; development

Introduction

Outpatient surgeries have increased significantly in the last 3 decades [1]. In Canada, there was an overall 30% increase in outpatient surgeries between the fiscal years 1995-1996 and 2005-2006 [2]. In some countries, day surgeries account for more than 70% of all elective procedures [3]. Nowadays, it is common to perform day surgeries for both higher-risk patients and procedures [4]. However, postoperative measures currently in place to support and follow patients undergoing day surgeries are suboptimal. Indeed, a recent Canadian study has shown that the same-day cancellation rate for outpatient surgeries ranges from 8% to 10% [5,6]. The authors of that study also mentioned that 60% of these cancellations could have been avoided with better preoperative support [7]. Despite current recommendations, adverse postoperative events are very rarely searched for or detected by health care institutions [8-10]. The most common reasons for readmission, emergency department consultation, or unplanned medical visits are postoperative pain, nausea, and vomiting [10]. In addition, the prevalence of moderate-to-severe postoperative pain after ambulatory surgery ranges from 21% to 30% at 24 hours, and as much as 24% to 43% at 7 days [11,12]. This could lead to inappropriate postoperative use of opioids [13]. Inadequate pain relief is also one of the main risk factors for impairment of patients' overall quality of life after surgery [14]. A recent report by the Canadian Institute for Health Information showed that patients scheduled for day surgery in Canadian teaching hospitals return to the emergency department or are readmitted within 30 days postoperatively at incidence rates of 9.4% and 7.3%, respectively [15]. The additional costs associated with these cancellations and unplanned readmissions amount to several billion dollars every year [15].

In efforts to ensure better perioperative support and follow-up for patients undergoing day surgeries, many tools have been developed [16]. With recent technological advances and with the widespread use of smartphones and tablets, digital solutions have been suggested to guide and follow these patients [17].

The department of anesthesiology at the Centre hospitalier de l'Université de Montréal (CHUM; University of Montreal Medical Center in English), in collaboration with LeoMed, has developed a dedicated digital smart solution specifically designed to offer personalized perioperative support and follow-up via a telecare platform that can easily be installed on any smartphone. We hypothesize that the implementation of this telehealth platform at CHUM will (1) reduce the rate of unanticipated cancellations of elective surgeries through better preoperative information and communication, (2) improve quality of life 30 days after surgery due to faster and better recognition of postoperative complications, and (3) reduce the rate of emergency department or unplanned medical visits and unnecessary calls to the health information line, as well as reduce unplanned hospital readmissions, through more personalized health support. Our overall conjecture is that including the LeoMed patient-tailored telecare platform in the perioperative day-surgery pathways of patients will improve the medicoeconomic impact of care services compared with standard care. The main objective of this study is to assess the cost-effectiveness of the LeoMed platform, and our secondary objective is to perform a cost-utility analysis.

Methods

Design

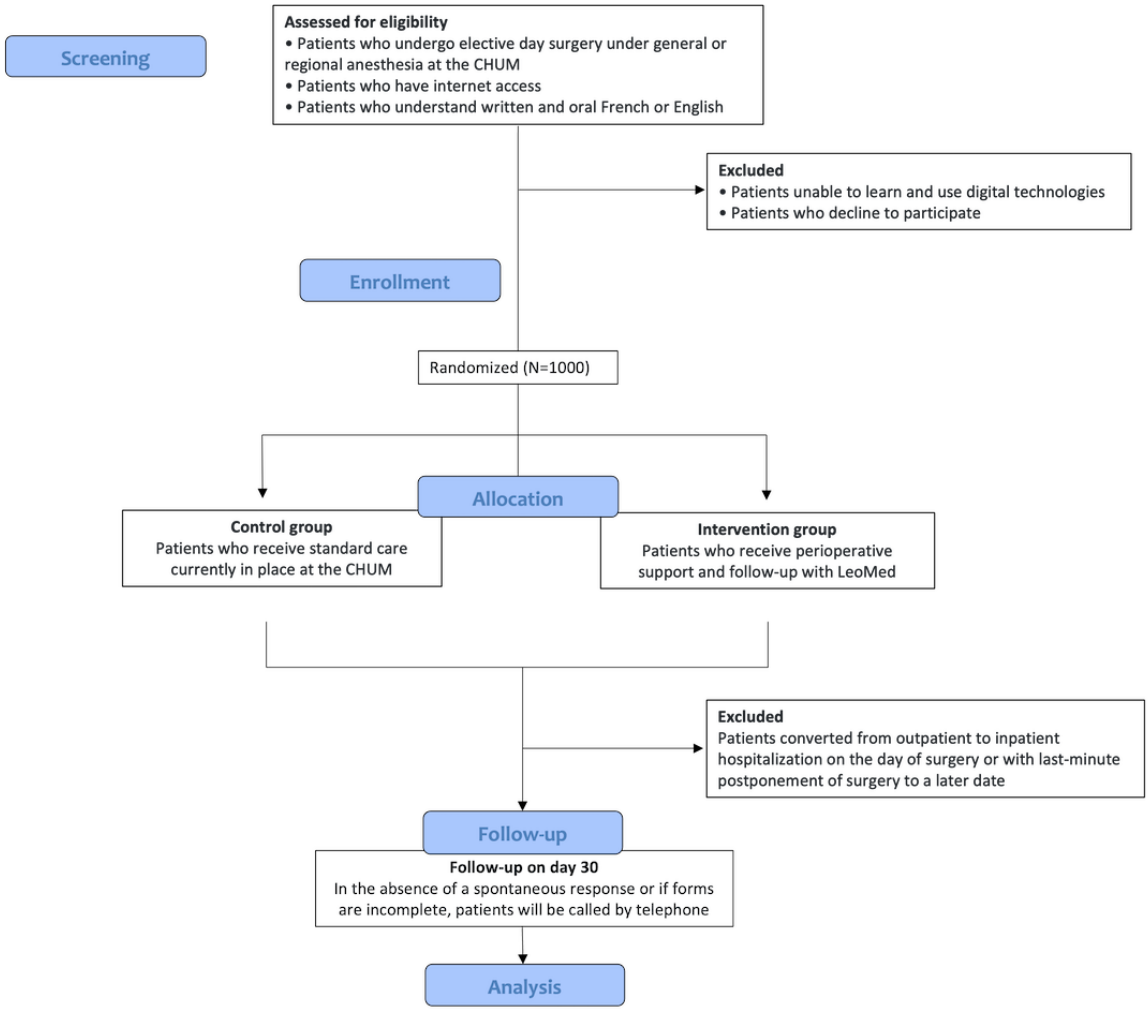
In order to achieve the abovementioned objectives, we propose to conduct a single-center, single-blinded, 2-group randomized controlled trial. A group of patients who use the LeoMed patient-tailored telecare platform will be compared to a group of patients who have access to usual care. As mentioned earlier, the study will be conducted at CHUM.

Population

All patients aged over 18 years who undergo elective day surgery under general or regional anesthesia at CHUM will be eligible. All included patients must (1) have internet access and (2) understand written and oral French or English. Patients were possibly excluded at two stages: (1) before randomization, if they were unable to learn and use the digital technologies or if they refused to participate, and (2) after randomization, in cases of conversions from outpatient to inpatient hospitalization on the day of surgery or in cases of last-minute postponement of the surgery to a later date. Figure 1 shows the trial flowchart.

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Figure 1. Flowchart of study participation. CHUM: Centre hospitalier de l'Université de Montréal.



Blinding and Allocation Concealment

Eligible patients will first be approached by telephone by a member of the research team when the preoperative clinical appointment is booked. During the preoperative clinical assessment, patients will receive both oral and written information on the study by a research nurse not involved in patient care. Patients will be included in the trial only after a research nurse has obtained written informed consent.

All included patients will be electronically randomized into the intervention group or the control group. Randomization will be performed by one of the investigators using the MedSharing Randomizer for Clinical Trial web application. The 2 groups will be balanced at a 1:1 ratio. Patients who are recruited but do not receive surgery within the study time frame will be secondarily excluded.

The study will be single-blinded. Statisticians will assess the primary and secondary outcomes, blinded to the randomization group. However, due to the nature of the intervention, neither the patients nor the care providers will be blinded to the randomization.

Recruitment and Intervention

During the recruited patients' visits to the preoperative clinic, they will benefit from safe and restricted web access to the LeoMed telehealth platform. After confirmation of the date of surgery, patients will be allocated according to the randomization list to the intervention group or the control group.

Intervention Group

The day before their surgery, patients will receive an email or SMS notification encouraging them to access the LeoMed platform. The platform prompts patients to click on links that direct them to the digital portal of the CHUM website, where all health sheets describing the perioperative pathway are published and grouped together, and preoperative psychological empowerment video resources are available that have been specifically created with the help of the CHUM communications service.

Postoperatively, notifications will be sent to the participants every day during the first 4 days. These notifications will direct patients to online forms assessing their medical condition. The questionnaires used are derived from the Brief Pain Inventory [18] and the Institut national de santé publique du Québec (INSPQ; Quebec Public Health Expertise and Reference Center in English) [19], which suggests using a simple questionnaire with 4 items for identification of surgical site infections. The items include redness at the surgical site, presence of pus at the surgical site, fever, and wound pain.

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The LeoMed platform will automatically classify patients' responses using an artificial intelligence algorithm and generate alerts on the home page. The home page is displayed on a giant screen on CHUM's telehealth service, which will offer tailored support according to patients' clinical need.

Health support will be provided by CHUM's telehealth service, which comprises a team of 50 nurses. This department is a 24/7 call center that manages many telecare platforms dedicated to remote patient support for various medical specialties. All the staff of this service are trained in new technologies. Their mission is to provide health care remotely and to coordinate the interventions of different medical and paramedical personnel within the hospital. Specifically for this project, patient responses appear on a giant screen in the main open space where the CHUM telehealth service nurses work. In the event of an alert, a nurse will contact the patient within a maximum of 8 hours and provide appropriate care.

On postoperative day (POD) 15 and 30, the LeoMed platform will send a follow-up form that aims to evaluate all indicators considered in the medicoeconomic analysis. All the indicators are detailed in Table 1.

Table 1. Schedule of enrollment, interventions, and assessments.

Timepoint	Preoperative consultation	At the confirmation of the date of surgery	Preoperative day 1	POD[a] 1	POD 4	POD 7	POD 15 and POD 30
Enrollment							
Eligibility screening	✓						
Informed consent	✓						
Allocation		✓					
Intervention							
Intervention group	✓		✓	✓	✓	✓	✓
Control group	✓						✓
Assessments on the LeoMed platform							
Quality of life (EQ-5D-5L visual analogue scale)	✓						✓
Unplanned readmissions							✓
Unplanned visits (eg, family doctor, walk-in clinic)							✓
Emergency department visits							✓
Calls to CHUM[b] online support							✓
Calls to the Quebec health information line							✓
Assessments from the electronic medical record system							
Same-day cancellations				✓			
Calls to CHUM online support							✓

[a]POD: postoperative day.

[b]CHUM: Centre hospitalier de l'Université de Montréal.

Control Group

Participants assigned to the control group will be followed up according to usual care, which consists of a telephone call the day before the procedure as a reminder of safety instructions. Postoperative follow-up is not standardized and remains specific to each surgical specialty. Access to a limited version of the LeoMed platform will also be given to these participants during the preoperative clinic visit. This version includes a preoperative questionnaire and follow-up forms at POD 15 and POD 30 that are identical to those received by the intervention group and collect the indicators considered in the primary analysis (Table 1). Like the patients in the intervention group, the control patients will have 24/7 access to the provincial or CHUM health information lines, if needed.

Primary Outcome

The primary outcome will be the cost-effectiveness of the LeoMed telecare platform deployment assessed by its direct costs, including unanticipated cancellations on the day of surgery due to preoperative instructions not being followed, calls to the local CHUM health information line, calls to the Quebec health information line (ie, 811), visits to the emergency department, and unplanned readmissions or medical visits (to family doctors or outpatient clinics) for problems related to the procedure within the first 30 days after the procedure.

Secondary Outcome

The secondary outcome considered for the cost-utility analysis will be quality-adjusted life years (QALYs). According to a recent update of the guide for economic evaluation published

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by the French National Authority for Health [20], the EQ-5D-5L visual analog scale (VAS) is the preferred measure used to assess quality of life and to derive utility values for use in health technology appraisals. It will be assessed at POD 30 and compared with the preoperative baseline [21]. The EQ-5D-5L VAS is a questionnaire that is well validated. It includes 5 dimensions, each describing a different aspect of health: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Patient satisfaction with care services will also be assessed.

Data Collection

Data for primary and some secondary outcome measures will be collected from the LeoMed platform until POD 30, with the exception of same-day cancellations. These data will be collected on POD 1 from the electronic medical record (EMR) system by 1 member of the research team (Table 1). In the absence of spontaneous responses from patients at POD 30 or if the forms are incomplete, patients will be called by one of the research assistants to assess the indicators included in the cost-effectiveness and cost-utility analyses. If a postoperative event is reported via the form, the patient will also be contacted personally by telephone.

For each patient, data will be systematically registered and archived on a local secure server. Patients will be identified using a unique numeric code, and all patient data will be anonymized to ensure confidentiality. All data will be extracted and cross-referenced with Oacis (Telus Health), the EMR system used at CHUM.

Data Analysis

Data analysis will be performed by a team of researchers at the École des Hautes Études Commerciales in Montreal, Quebec, using SPSS (version 28; IBM Corp). All data will be analyzed according to the intention-to-treat principle. Descriptive statistics will be reported as frequencies and proportions for categorical data and means and standard deviations for continuous variables. Demographic data for the 2 groups of patients will be compared using the Mann-Whitney *U* test (for ordinal data), the chi-square test (for nominal data), and a 2-tailed *t* test (for continuous data).

Considering the Canadian guidelines for the economic evaluation of health technologies [22], the perspective of the health care system will be privileged in this study. Specifically, 2 main types of analyses will be carried out. First, all interventions in both groups related to surgery (calls to the provincial or CHUM information lines, visits to the ambulatory unit, hospital readmissions, and visits to the emergency department) will be recorded during the study to perform the cost-effectiveness analysis. Second, a cost-utility analysis will be conducted to quality-weight each effectiveness outcome measured in QALYs. QALYs will be calculated as life with the health state under study multiplied by the utility associated with that health state. CHUM's internal data will be used to determine the cost of health care staff and the average cost of an emergency room visit for the clientele concerned in fiscal year 2019-2020. For hospitalizations, we will use the average costs calculated according to the American diagnosis-related groups method, which was applied at CHUM in 2019-2020. Technology costs will be estimated based on license prices in effect at the time of the study and amortized on a straight-line basis over a 5-year period. All calculations will be in Canadian dollars. Last, patient satisfaction with care services will be measured in both groups at the end of the trial using Likert scales adapted from Sicotte et al [23]. This protocol follows the SPIRIT (Standard Protocol Items: Recommendation for Interventional Trials) 2013 Statement for trial protocols [24].

Sample Size

There are very few studies that have examined the effects of digital solutions for personalized support and follow-up for patients undergoing day surgery. We based our sample size calculations on Jaensson et al [25], assuming that a better postoperative recovery (ie, decreased symptoms and complications) should reduce the number of postoperative calls to the health information line, visits to the emergency department, unplanned readmissions and medical visits, and the associated costs (our primary outcome). Jaensson et al [25] reported better recovery (based on the global Swedish Web Version of the Quality of Recovery [SwQoR] score) in an intervention group (ie, day surgery patients using a recovery assessment mobile phone app) compared with a control group (standard care) on POD 7 (effect size 0.21; $P<.001$). With a significance level of .05 and a statistical power of .90, G*Power (Heinrich Heine University) generated a group size of 357. To allow for a 20% rate of loss to follow-up and protocol deviations, we thus aim to recruit 500 patients per arm. In the third quarter of 2019, CHUM provided nearly 630 outpatient surgical stays per month on average. Considering 70% of patients should be eligible for the study [26], it will take about 12 months to recruit 1000 patients.

Ethics Approval

The study conforms to the principles outlined in the Helsinki Declaration. The project has been approved by the institutional review board and research ethics committee at CHUM (21.110). The trial was registered at the ClinicalTrials.gov (NCT04948632). If any protocol amendments are needed, research committees and the institutional review board at CHUM will be asked to approve them. Participant recruitment began in August 2022.

Results

The platform was launched in January 2022. A patient-as-partner approach was chosen in the initial phase, where 12 patients who had undergone day surgery in the last 6 months were recruited to test the platform. Another 12 patients scheduled for outpatient surgery tested the optimized support and follow-up platform. Their feedback helped to correct and improve the platform before beginning study recruitment. The inclusion of the first patients began in August 2022. As of October 31, 2022, we enrolled 142 patients.

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Discussion

Principal Findings

Outpatient surgeries have been significantly increasing in the last decade in Canada, with more than 1.8 million interventions being performed annually [2]. These surgeries were historically restricted to low-risk interventions, but recent improvements in anesthesia care and the development of minimally invasive surgical techniques have resulted in moving some higher-risk interventions to day-surgery pathways. Limitations in the number of hospital beds due to the COVID-19 pandemic have probably accelerated the transition toward outpatient surgery. Nowadays, major procedures, including intra-abdominal, intrathoracic, orthopedic, and endovascular surgeries, are commonly performed as ambulatory surgeries [27-29].

In addition, the number of elderly patients undergoing same-day surgery is set to increase. In 2010, the American Ambulatory Surgery survey showed that among patients who underwent day surgery, 35% and 15% were aged 65 years or older and 75 years or older, respectively [30]. The burden of comorbidities in patients undergoing day surgery also has changed. Nowadays, patients with American Society of Anesthesiologists Physical Status III and IV are commonly eligible. These older patients with more comorbidities are sent home on the day of surgery, raising questions about quality of recovery and prognosis.

To resolve these issues, digital health solutions represent an attractive option. They have been highlighted by the World Health Organization as a potential lever to increase quality of health, enhance equality of care, and reach more patients, including those in rural areas [31]. As mentioned earlier, LeoMed's telehealth platform is specifically designed to offer perioperative support and follow-up for outpatient care. The platform was developed by the LeoMed company in partnership with members of the anesthesia department at CHUM to meet the challenges of patients' perioperative day-surgery pathways.

One challenge is ensuring optimal communication of the measures that should be followed preoperatively to promote rapid postoperative recovery. In our institution, patients are informed of these preoperative measures during their visit at the preoperative clinic. The average time between this preoperative visit and the surgery is often one to several weeks. In the intervention group, we again provide all the documents containing the useful preoperative information in a text message sent the day before the intervention. Ideally, we would have liked to provide this information 48 to 72 hours in advance to give patients more time to read and assimilate it. Unfortunately, the operating program is confirmed only on the day before surgery due to institutional COVID-19 policy.

In the postoperative context, several studies have shown that telehealth reduces the use of opioids and improves quality of recovery [25,32,33]. We previously showed that the prevalence of moderate to severe postoperative pain after ambulatory surgery ranges from 21% to 30% at 24 hours, and as much as 24% to 43% at 7 days [12]. Inadequate pain relief is one of the main risk factors for impairment of patients' overall quality of life after surgery [14] and can lead to inappropriate postoperative use of opioids [13]. Yet, to our knowledge, no study has demonstrated solid economic effects at the health-system level [34,35]. Hence, the lack of medicoeconomic data does not encourage government institutions and public medical insurance to recognize and promote the use of mobile technologies for outpatient surgeries. This trial aims to fill this gap.

Limitations

We propose to conduct a randomized controlled trial that is single-center, which represents the main limitation of our study protocol. Indeed, we will not be able to generalize our findings to ambulatory centers that perform other types of surgical procedures, specifically minor procedures. This limitation must be balanced with the difficulty of developing and implementing the same telehealth solution in many hospitals. Moreover, technical challenges, costs, and data security issues might represent barriers to the successful implementation of similar telehealth solutions in other settings.

Conclusions

This trial will help determine the cost-effectiveness of telehealth when used in the perioperative context. The trial is also necessary because it will improve knowledge about postoperative pain and adverse effects after day surgery. Outpatient surgery will not remain at low risk of complications for long. Nowadays, many procedures previously requiring hospitalization are evolving toward day-surgery pathways, and monitoring of potential adverse events is mandatory to control associated costs. This study will provide a clearer view of patient-reported outcome measures after outpatient surgery.

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Data Availability

The data sets generated during and/or analyzed during this study will be made available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

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Abbreviations

CHUM: Centre hospitalier de l'Université de Montréal
EMR: electronic medical record
INSPQ: Institut national de santé publique du Québec
POD: postoperative day
QALY: quality-adjusted life years
VAS: visual analogue scale

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Protocol

Combining Behavioral Economics–Based Incentives With the Anchoring Strategy: Protocol for a Randomized Controlled Trial

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Abstract

Background: Chronic (ie, long-term) elevated stress is associated with a number of mental and physical health conditions. Mindfulness meditation mobile apps are a promising tool for stress self-management that can overcome several barriers associated with in-person interventions; however, to date, poor app-based intervention adherence has limited the efficacy of these mobile health tools. Anchoring, or pairing, a new behavior with an existing routine has been shown to effectively establish habits that are maintained over time, but this strategy typically only works for those with high initial motivation and has yet to be tested for maintaining meditation with a mobile app.

Objective: This study will test novel combinations of behavioral economics–based incentives with the anchoring strategy for establishing and maintaining adherence to an effective dose of meditation with a mobile app.

Methods: This 16-week study will use a 5-arm, parallel, partially blinded (participants only), randomized controlled design. We will implement a fractional factorial study design that varies the use of self-monitoring messages and financial incentives to support participants' use of their personalized anchoring strategy for maintaining adherence to a ≥10 minute-per-day meditation prescription during an 8-week intervention period, followed by an 8-week postintervention observation period. Specifically, we will vary the use of self-monitoring messages of either the target behavior (ie, meditation tracking) or the outcome associated with the target behavior (ie, mood symptom tracking). We will also vary the use of financial incentives conditional on either meditation at any time of day or meditation performed at approximately the same time of day as participants' personalized anchors.

Results: Continuous meditation app use data will be used to measure weekly meditation adherence over the 16-week study period as a binary variable equal to 1 if participants complete ≥10 minutes of meditation for ≥4 days per week and 0 otherwise. We will measure weekly anchoring plan adherence as a binary variable equal to 1 if participants complete ≥10 minutes of meditation within +1 or −1 hour of the timing of their chosen anchor on ≥4 days per week and 0 otherwise. In addition to these primary measures of meditation and anchoring plan adherence, we will also assess the secondary measures of stress, anxiety, posttraumatic stress disorder, sleep disturbance, and meditation app habit strength at baseline, week 8, and week 16.

Conclusions: This study will fill an important gap in the mobile health literature by testing novel intervention approaches for establishing and maintaining adherence to app-based mindfulness meditation. If successful, this study will identify an accessible and scalable stress self-management intervention that can help combat stress in the United States.

Trial Registration: ClinicalTrials.gov NCT05217602; https://clinicaltrials.gov/ct2/show/NCT05217602

International Registered Report Identifier (IRRID): DERR1-10.2196/39930

(JMIR Res Protoc 2023;12:e39930) doi:10.2196/39930

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KEYWORDS

habits; mindfulness meditation; mobile apps; mobile health; mHealth; adherence; meditation; mindfulness; intervention; apps; smartphone apps; stress; management; mobile phone

Introduction

Problem Statement

The prevalence of stress in the United States is at an all-time high, with >75% of US adults reporting elevated levels of stress in 2021 [1,2]. Chronic (ie, long-term) elevated stress is associated with a number of mental and physical health conditions, such as depression, anxiety, cardiovascular disease, and reduced cognitive functioning [3-5]. The COVID-19 pandemic exacerbated stress levels, with 78% of Americans reporting that the pandemic was a significant stressor in their lives and 67% of Americans experiencing significantly increased stress over the course of the pandemic [6]. Recent reports by the American Psychological Association have documented the cumulative negative effects of increased stress during the pandemic on mental and physical health, where 84% of Americans in 2021 reported feeling at least 1 emotion associated with prolonged stress, such as anxiety, sadness, or anger [2,7]. In addition, the reported physical health consequences of chronic elevated stress during the pandemic include undesired weight changes, sleep problems, and increased alcohol consumption [2,7].

These findings demonstrate the significant consequences that chronic elevated stress can have on health outcomes, and existing research has shown that these negative health effects also impose a large economic burden. Recent reports suggest that stress is associated with annual costs of >US $300 billion owing to workplace absenteeism, accidents, reduced productivity, and employee turnover, in addition to direct medical, legal, and insurance costs [8]. Despite the clear need for stress management resources, only 54% of Americans reported seeking help for their mental health in 2020 [9], and nearly half of Americans delayed or canceled health care service appointments after the beginning of the pandemic [7]. Thus, there is an urgent need for novel stress self-management solutions that are more accessible and that can provide alternative approaches for stress reduction than those currently offered by conventional mental health care in the United States.

The rapid development and widespread availability of mobile health (mHealth) apps for treating mental health conditions may be a key self-care solution to address the ongoing stress epidemic. Mindfulness meditation apps are a particularly promising tool for stress self-management, as they can overcome several barriers associated with in-person interventions, such as cost, stigma, and accessibility [10]. Importantly, previous research has demonstrated the efficacy of app-based mindfulness meditation interventions for improving mental health outcomes, such as depression, anxiety, and sadness, compared with both control groups and traditional in-person interventions [10]. In addition, our own work with the Calm meditation app, one of the most popular commercially available mindfulness meditation apps [11], has shown that meditation with Calm can improve a wide range of mental health outcomes and reduce stress [12-14].

Despite these promising findings, many mHealth app–based studies have reported significant dropout rates and poor intervention adherence (intervention adherence rates ranging from 39% to 92%), which ultimately limit the efficacy of app-based meditation interventions for stress management [15,16]. In general, user retention rates for mHealth apps are low, with one systematic review finding median 15- and 30-day mental health app retention rates of 4.9% and 4.7%, respectively [17]. This pattern of declining user engagement with apps has been frequently observed in the mHealth literature [18-20] and mirrors the decline in treatment adherence documented in other behavioral interventions and clinical settings [21-23]. Although a growing field of research has started to examine the issue of maintaining adherence to app-based interventions and other behavioral and medical treatments [19,24], little is known about the strategies that can successfully maintain adherence in these settings. Thus, there exists a critical need for researchers to identify and implement novel, effective, and accessible strategies for maintaining adherence to health apps, particularly meditation apps, that can help combat the alarming rates of elevated stress in the United States.

Study Aims

This study will test novel combinations of behavioral economics–based incentives with a habit formation intervention from the psychology literature for establishing and maintaining adherence to an effective dose of meditation with a mobile app. In a 5-arm randomized controlled trial, we will implement a fractional factorial study design that varies the use of self-monitoring messages and financial rewards to support participants' use of the anchoring strategy for maintaining adherence to a ≥10 minute-per-day meditation prescription during an 8-week intervention period, followed by an 8-week postintervention observation period. The study is designed to examine 3 specific study aims. First, we will assess the study group differences in adherence to daily meditation prescriptions during the 8-week intervention. Second, we will estimate the study group differences in meditation adherence maintenance over the 8-week postintervention observation period. Third, we will investigate the role of anchoring performance during the intervention on participants' ability to maintain their meditation app adherence during the postintervention observation period. In this paper, we will outline previous research on mobile meditation apps, the background and rationale behind the adherence strategies we developed, our research methodology, and our hypotheses.

App-Based Mindfulness Meditation: Strengths and Weaknesses

Previous research has demonstrated the effectiveness of mindfulness meditation interventions in improving a wide range of health outcomes in both clinical and nonclinical populations, including stress, anxiety and depressive symptoms, well-being, and sleep [15,16,25]. While traditional mindfulness meditation interventions have been delivered via in-person sessions,

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app-based interventions have become increasingly popular in recent years because they are less costly and more accessible than face-to-face interventions [15,16]. In addition, a growing body of research has established the feasibility and acceptability of app-based mindfulness meditation interventions [26,27], suggesting that they are scalable and acceptable alternatives to traditional in-person interventions [12,13,16,28]. Several randomized controlled trials and meta-analyses have also documented the efficacy of app-based interventions on various mental health outcomes, including stress reduction, finding similar effects when compared with in-person interventions and when compared with control groups [12,16,29]. Many of these effects have also been observed during the COVID-19 pandemic [29], suggesting that meditation apps may be a useful self-management tool for reducing stress during a prolonged period of stress, such as the pandemic.

Despite these promising findings, the efficacy and generalizability of app-based interventions are limited by their substantial attrition and poor adherence. Previous meta-analyses have estimated app-based intervention study attrition rates to range from 31% to 42% and intervention adherence rates (ie, the number of sessions actually completed compared with the prescribed amount) to range from 39% to 92% [15,16,30]. Baumel et al [17] examined objective user adherence with various mental health Android apps, including those specifically for mindfulness meditation, and found that only a small portion of users actually used the apps for an extended period, with open rates declining >80% between days 1 and 30 across all mental health apps. For mindfulness meditation apps specifically, median 15- and 30-day retention rates were 4.9% and 4.7%, respectively [17], greatly limiting the efficacy of these mHealth tools. Similar patterns of declining adherence have been observed in our research with the Calm meditation app, in which adherence rates to the daily prescription of ≥10 minutes of meditation with Calm fell by approximately 68% over the course of a 16-week study period [31]. This pattern of rapidly declining meditation app use limits the impact of these mental health solutions. The next step in the mHealth research is therefore to find effective interventions to keep mobile app users engaged, that is, to maintain meditation app adherence.

In general, study attrition and adherence are critical issues in mHealth interventions that must be addressed to improve the efficacy of these therapeutic tools. Health behavior models such as the transtheoretical model [32,33] outline several key stages of behavior adoption that should be considered when developing interventions: precontemplation, contemplation, preparation, action, and maintenance stages. Individuals who download a health app and purchase a subscription are likely to be in the preparation or action stage because they have taken steps to initiate behavior change. However, common app-based mHealth issues, such as poor adherence, suggest that significant barriers exist when moving from the preparation and action stages to the maintenance stage. The proposed socio-cognitive intervention strategies have focused on bolstering self-efficacy for dealing with obstacles, increasing motivation, and reiterating the long-term benefits of performing a behavior; however, to date, these strategies have largely been unsuccessful in maintaining health behavior changes [34-38]. Thus, in this study, we synthesized theory- and evidence-based intervention approaches from psychology and behavioral economics to test novel combined strategies for maintaining adherence to meditation using the accessible and scalable Calm app.

Habits as a Key Strategy to Maintain Adherence

Psychological research suggests that developing a habit may be a successful behavioral strategy for maintaining behaviors over time [39]. Habits have been shown to underlie many long-term healthy behaviors [40] and may be a key strategy for maintaining adherence to a mindfulness meditation app [31,41]. Existing research has shown that habits are formed gradually over time as an individual repeatedly and consistently performs a behavior in response to the same stimulus or contextual cue, to the point where it can be performed automatically with little or no cognitive effort [23,41,42]. Through such "context-dependent repetition," [43] exposure to the cue reflexively, or nonconsciously, triggers the initiation of the behavior [44]. In this way, behavioral control is delegated to external cues, thereby reducing the demand on an individual's attention and memory processes [42,45,46]. Importantly, habits have been shown to persist long term despite declining motivation or willpower [47-49] and even when participants were distracted [50]. In addition, habit formation strategies have been used to successfully maintain various health behaviors, such as dietary habits [51,52], physical activity [53-56], medication adherence [57-60], and dental hygiene [61,62], among others [63,64].

One common intervention strategy for promoting habit formation is anchoring, which is when a new behavior is paired, or "anchored," to an existing routine (ie, the contextual cue) [23]. Anchoring has successfully established health habits, such as increased physical activity [65], improved diet [51,66-68], smoking cessation [69], and medication adherence [70,71]. However, it takes approximately 3 months of adherence to an anchoring plan to form a habit [43,72-74], and many participants fail to adhere to their anchoring plan for this entire habit formation period [23,75,76]. Common barriers to anchoring plan adherence include lack of motivation [77,78] and self-efficacy [79,80] and forgetfulness [81]; on average, only 55% of anchoring intervention participants stick with anchoring long enough to form a habit. In a recent study, using the anchoring plan alone did not lead to meditating for more days per week over a 3-month intervention [82], which further suggests that additional strategies may be needed to increase anchoring plan adherence for establishing a new meditation habit.

Other common behavioral intervention strategies include reminder messages, personalization, and self-monitoring. Text message reminders are increasingly being used in health promotion interventions as a simple and cost-effective way to enhance healthy behaviors [83]. Several meta-analyses have demonstrated the efficacy of text message reminders across a wide range of populations and behaviors, with personalized messages being the most efficacious compared with generic messages or no messages at all [83,84]. Our previous work also suggests that using anchoring plan text message reminders in addition to the anchoring plan can lead to small, but significant,

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increases in meditation practice over an 8-week period [31]. Although the evidence to support the long-term effectiveness of text message reminders has been inconsistent [85], using personalized anchoring plan text message reminders may be a feasible, acceptable, and effective way to increase anchoring plan adherence [31,84].

Different types of self-monitoring messages may also influence anchoring plan adherence [86-88]. Self-monitoring has been cited as an important facilitator of behavior change and habit formation [74], and many existing mHealth apps have incorporated self-monitoring features to improve and sustain user engagement [89-91]. In addition, existing interventions have successfully used prompts either alone or in combination with other strategies to support health behavior change [92,93]. According to Michie et al [94], there are 2 types of self-monitoring: self-monitoring of behavior and self-monitoring of behavior outcomes. Messages that focus on self-monitoring of a target behavior (eg, number of completed meditation sessions during the past week and changes in the number of completed meditation sessions over time) may increase self-efficacy for a behavior by helping individuals visualize their effort investment and compliance with their behavioral goals [74]. Self-monitoring of behavior also helps individuals build self-regulatory skills [95], which may be particularly useful during the "learning phase" of the habit formation process [46]. Alternatively, messages that focus on self-monitoring of the outcomes associated with the meditation practice may increase the salience of both the immediate and long-term benefits of meditation practice, which may not be as clear from meditation practice alone [96,97]. In fact, our previous work on the Calm app's self-monitoring mood check-in feature (ie, assessing and documenting mood before or after meditation practice) found that using mood check-ins was associated with increased meditation engagement, particularly among inactive subscribers [96]. As the mental health benefits of meditation are not immediately observable, messages that focus on the self-monitoring of outcomes of behaviors (ie, mood check-ins) may be a more effective way to reinforce participants' adherence to the ≥10 minute-per-day meditation prescription than messages that focus on self-monitoring of behavior, which can only provide an indirect signal of participants' mental health benefits. By varying the type of self-monitoring messages (ie, behavior or outcomes of behavior) between intervention study groups, we will be able to test the following hypothesis:

- *Hypothesis 1*: the study groups receiving messages that focus on self-monitoring of outcomes of meditation behavior will have greater adherence to the ≥10 minute-per-day meditation prescription during the 8-week intervention and during the 8-week postintervention observation periods than the study groups receiving messages that focus on self-monitoring of meditation behavior.

In addition to self-monitoring messages, offering financial or in-kind incentives may be a successful strategy to further increase anchoring plan adherence [98]. Research from the behavioral economics literature suggests that traditional external rewards are often successful in *initiating* a wide range of health behaviors [99-101]. While the effects of these behavioral economics–based incentives often disappear once the incentives are withdrawn [21,23], it is possible that combining incentives with the anchoring strategy may leverage the short-term effectiveness of incentives to increase anchoring plan adherence and establish long-term habits [24]. One way in which this combined approach could be implemented is by using "time-contingent" incentives that are conditional on performing the target behavior at approximately the same time that the planned anchor (ie, existing routine) is expected to occur. Such time-contingent incentives (TCIs) may direct participants' focus and attention to the use of their anchors, which may help to better maintain meditation after the incentives are withdrawn. To test this approach and compare these strategies with the previous behavioral economics literature, the intervention study groups will receive either TCIs or non-TCIs (NTCIs) during the 8-week intervention period. This variation in intervention approaches will allow us to evaluate the following hypothesis:

- *Hypothesis 2*: The study groups receiving TCIs will have greater adherence to their anchoring plans and to the ≥10 minute-per-day meditation prescription during the 8-week intervention and during the 8-week postintervention observation periods than the study groups receiving NTCIs.

Combining anchoring, a well-studied habit formation strategy, with additional intervention strategies (ie, self-monitoring messages and incentives) is a novel behavioral intervention that may overcome adherence barriers and develop strong meditation habits. Therefore, our study will test anchoring in combination with varying forms of these 2 additional strategies to determine the optimal combined approach for establishing and maintaining meditation with a mindfulness meditation app. Importantly, our findings will test the following hypothesis regarding the success of the anchoring plan for maintaining the behavior change:

- *Hypothesis 3*: The study groups that display the greatest anchoring plan adherence during the 8-week intervention will be the most successful in maintaining meditation adherence during the 8-week postintervention observation period.

Methods

Study Setting

This study will be conducted using a nationwide sample of new, self-initiated Calm subscribers who purchased 1-year-long membership. There is no specified location for this study, as all study procedures can be completed remotely through our web-based surveys and the meditation app, and participants will not be required to complete any in-person laboratory procedures.

Study Design

This study will use a 5-arm, parallel, partially blinded (participants only) randomized controlled design. After completing a web-based eligibility survey, the participants will be randomized into 1 of the 5 study groups. Stratified randomization methods will be used to ensure that race and ethnicity (ie, Hispanic) are equally represented across study groups. The 5 study groups include a control group that will use the anchoring plan to form a meditation habit with Calm and then receive no additional intervention supports, while the

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4 intervention groups will also use the anchoring plan in combination with 1 of the 2 different types of self-monitoring messages and 1 of the 2 different forms of incentives. Participants in the 4 intervention groups will also be eligible for an in-kind reward (eg, Calm t-shirt, Calm tote bag, or Calm water bottle; all gifts have a retail value of roughly US $25 but a wholesale cost of US $5) conditional on either completing ≥10 minutes of meditation at any time of day on at least 8 days over a 2-week period (NTCIs) or completing ≥10 minutes of meditation within a 2-hour window around the time their chosen anchor typically occurs during the day (ie, anchor time1 hour) on at least 8 days over a 2-week period (TCIs). All additional interventions to support adherence to the anchoring plan will be delivered for 8 weeks; thus, participants are eligible to win up to 4 in-kind incentives during the intervention period. Participants within the intervention groups will also be randomly assigned to receive either messages that focus on self-monitoring of behavior (eg, "You completed a meditation session using your Calm app on at least 8 days during the past 2 weeks") or messages that focus on self-monitoring of outcomes of behavior (eg, "We encourage you to continue using the 'How Are You Feeling?' check-in feature after completing your meditation sessions"). The "How Are You Feeling?" check-in feature is an existing feature available to all users of the Calm app that allows users to record their current mood state (eg, happy, sad, or anxious). The fractional factorial study design is shown in Table 1.

After randomization, all participants will complete a baseline survey that includes self-report questionnaires, a study introduction video (described below under *Introductory Video*), a comprehension quiz, and a web-based worksheet that will guide the participants on how to develop their meditation anchoring plan. At weeks 8 and 16, participants will complete a follow-up survey to assess changes in our secondary outcome measures as well as satisfaction with the Calm app, their anchoring plan, and the intervention. Figure 1 outlines the timeline of all study activities.

Table 1. Fractional factorial study design[a].

Study group	AP[b]	BM[c]	OM[d]	NTCI[e]	TCI[f]
Control	1	0	0	0	0
Treatment 1	1	1	0	1	0
Treatment 2	1	0	1	1	0
Treatment 3	1	1	0	0	1
Treatment 4	1	0	1	0	1

[a]This table shows which of the intervention strategies are received by each of the 5 study groups, where the column headers list each strategy and 1 indicates that the strategy is received by the study group listed in the row label.

[b]AP: anchoring plan.

[c]BM: self-monitoring of behavior messages.

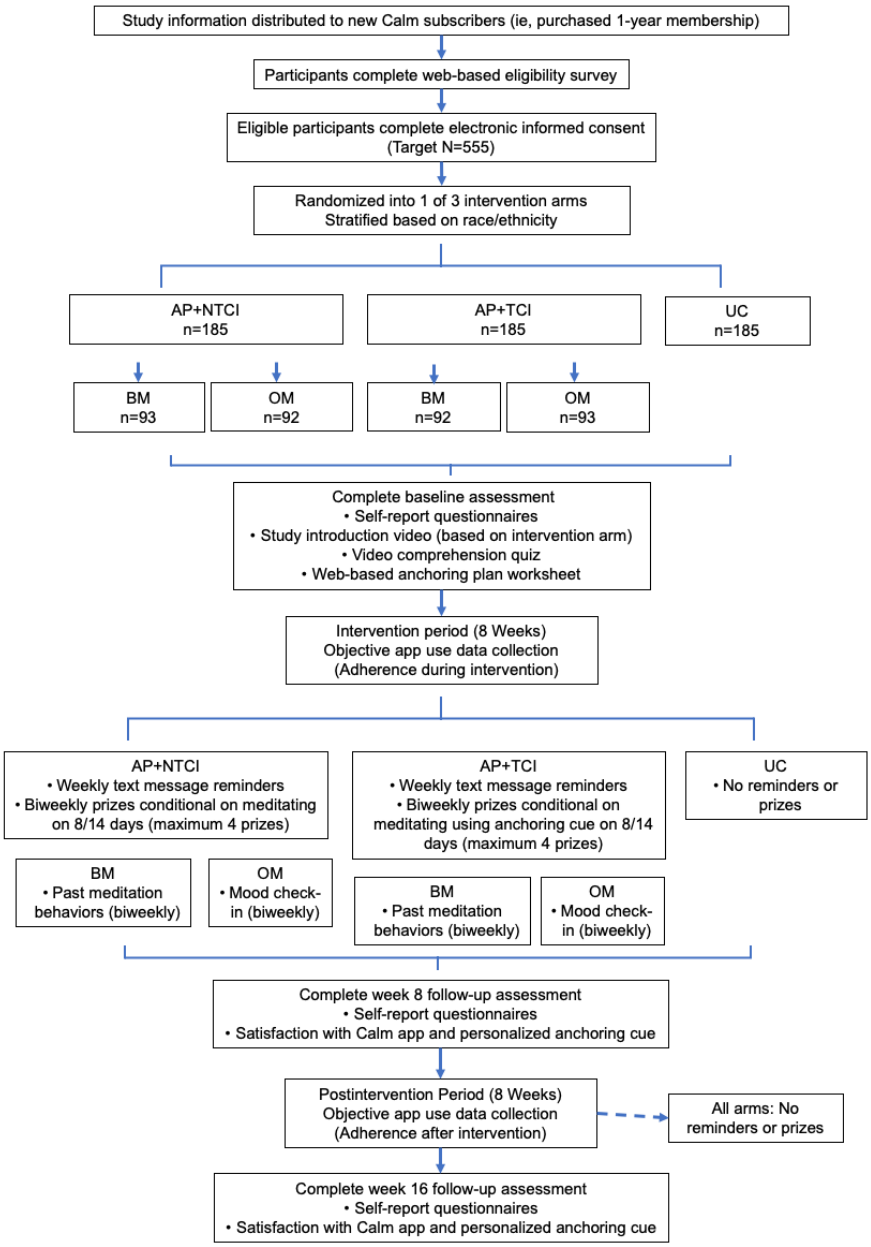
[d]OM: self-monitoring of outcomes of behavior messages.

[e]NTCI: non–time-contingent incentive.

[f]TCI: time-contingent incentive (conditional on meditation within a 2-hour window around anchor timing).

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Figure 1. Timeline of study activities. AP: anchoring plan; BM: self-monitoring behavior; NTCI: non–time-contingent incentive; OM: self-monitoring outcomes; TCI: time-contingent incentive; UC: usual Calm.



Sample Size

The target recruitment sample size for this study is 555 participants, with 111 participants per study group. On the basis of our existing studies using the Calm app, we anticipate a 20% study attrition, which will yield an effective study group sample size of 88. Our primary measure of meditation app adherence is a binary indicator variable for performing ≥10 minutes of meditation on at least 4 days of the week. This measure of adherence is based on the concept of behavioral regularity, which was proposed by Cheung et al [102] as a standardized measure of treatment adherence. In addition, researchers have recommended that practicing mindfulness for 3 to 4 days per week is the sufficient level of adherence (or regularity) for attaining the mental health benefits associated with meditation, such as stress reductions [103], and this recommendation is theoretically consistent with the notion that a mindful mind is the product of frequent, effortful, and persistent training [104,105]. Thus, we determined our sample size to detect study group differences in meditation regularity at the end of the study (week 16). Using data from our previous studies with Calm, we know that approximately 15% of new Calm users regularly meditate (ie, complete ≥10 minutes of meditation for at least 4 days of the week) 8 weeks after first subscribing to the app and fewer than 10% regularly meditate with Calm 16 weeks after subscribing. An effective study group sample size of 88 provides adequate statistical power (1–β=.82) for detecting study group differences of 18 percentage points in the likelihood of regular mediation in week 16 (Cohen h=0.43, which is a small to medium effect size).

Eligibility

Participants will be eligible and included in our sample if they are aged at least 18 years, are new Calm subscribers (ie, have purchased at least 1-year of membership within the past week), are able to read and understand English, have access to a

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smartphone daily, reside in the United States or a US territory, and have a Perceived Stress Scale (PSS; PSS-4) score ≥6. Participants will be excluded if they are new Calm subscribers but have used Calm for ≥2 days in the last week, have practiced meditation (including meditative movement, ie, yoga or tai chi) for >60 minutes a month in the past 6 months, or are unable to provide consent or understand study procedures owing to mental illness or cognitive limitations.

Recruitment and Enrollment Procedures

Potential participants will be invited to participate in the study via weekly recruitment emails sent by Calm to all new subscribers. The recruitment email will contain a link to complete an eligibility survey using the survey software Qualtrics (Qualtrics International Inc). Recruitment emails will be sent every week for 6 consecutive weeks or until the target sample size has been met. Participation will be voluntary, and participants may withdraw from the study at any time.

The eligibility survey will contain a brief overview of the study along with a series of questions based on the eligibility criteria listed in the previous section. If eligible, the participants will be asked to read an electronic consent form and provide their consent via electronic signatures. The electronic consent form also contains 2 comprehension questions to ensure that participants understand the study procedures. Once consented and enrolled, participants will be told that they will receive additional study instructions (ie, the baseline survey) via email in the coming weeks. During this time, eligible participants will be randomized based on the stratification dimensions described in the *Study Design* section.

Data Collection Tools and Procedures

Overview

Data will be collected at 3 time points: baseline, week 8 (following completion of the intervention), and week 16 (following the 8-week postintervention observation period). Objective app use data will be collected via the Calm app, which will record the day and time of every app session; the duration of sessions; the type of session (eg, meditation, sleep story, and breathing exercise); and title of sessions (eg, Daily Calm and Daily Move) performed during the study period. Table 2 shows the primary and secondary outcome measures collected at each administration time point.

Table 2. Primary and secondary outcome measures at each administration time point.

Measure	Assessment	Baseline	8-week follow-up	16-week follow-up	Continuous data collection
Primary outcomes					
Meditation adherence	Objective app use data	N/A[a]	N/A	N/A	Yes
Anchoring plan adherence	Objective app use data	N/A	N/A	N/A	Yes
Secondary outcomes					
Stress	Perceived Stress Scale	Yes	Yes	Yes	N/A
Anxiety	Hospital Anxiety and Depression Scale	Yes	Yes	Yes	N/A
PTSD[b]	Impact of Events Scale—Revised	Yes	Yes	Yes	N/A
Sleep disturbances	Insomnia Severity Index	Yes	Yes	Yes	N/A
Habit strength	Self-report Behavioral Automaticity Index	Yes	Yes	Yes	N/A

[a]N/A: not applicable.

[b]PTSD: posttraumatic stress disorder.

Primary Outcomes: Adherence Maintenance (Objective App Use Data)

The primary outcomes for this study measure participants' ability to maintain adherence to the ≥10 minute-per-day meditation prescription over the 16-week study period. Specifically, we will measure meditation adherence as a binary variable equal to 1 if participants complete ≥10 minutes of meditation for ≥4 days per week and 0 otherwise. This meditation adherence outcome will be defined weekly during both the 8-week intervention and the 8-week postintervention observation periods. We will also measure objective meditation app use using the number of days with ≥10 minutes of meditation per week and the total number of meditation minutes per week, both of which will allow us to investigate the behavioral frequency of app-based meditation and improve the statistical power of our analyses. We will also augment these objective app-based meditation measures with a self-reported measure of days with any meditation (ie, either using the app or meditation outside the app) over the past week that is assessed at baseline, week 8, and week 16 time points. We will measure anchoring plan adherence as a binary variable equal to 1 if participants complete ≥10 minutes of meditation within 1 hour of the timing of their chosen anchor for ≥4 days per week and 0 otherwise. Similar to overall meditation, we will also measure anchoring plan adherence as the number of days completing ≥10 minutes of meditation within 1 hour of the timing of their chosen anchor per week.

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Secondary Outcomes: Stress, Anxiety, and Posttraumatic Stress Disorder

We will assess stress at baseline, week 8, and week 16 using the PSS-10. The PSS is a 10-item self-report inventory that assesses the degree to which individuals have felt stressed during the past month [106]. The PSS is a widely used measure of self-reported stress that has demonstrated acceptable validity and reliability in previous research [107]. We will also assess anxiety symptoms at baseline, week 8, and week 16 using the Hospital Anxiety and Depression Scale. The Hospital Anxiety and Depression Scale is a 14-item self-report inventory that assesses the severity of anxiety and depressive symptoms during the past week [108]. For our purposes, we will only be focusing on the anxiety subscale. Finally, we will assess posttraumatic stress disorder (PTSD) symptoms at baseline, week 8, and week 16 using the Impact of Events Scale—Revised. The Impact of Events Scale—Revised is a 22-item self-report inventory that assesses the severity of PTSD symptoms (eg, trouble sleeping, irritability, and jumpiness) over the past 7 days [109]. The instructions were modified to include PTSD symptoms resulting from specific trauma or from the ongoing COVID-19 pandemic.

Secondary Outcome: Sleep Disturbances

We will assess sleep disturbances at baseline, week 8, and week 16 using the Insomnia Severity Index (ISI). The ISI is a 7-item self-report inventory that assesses the severity of sleep problems, noticeability of sleep problems, stress resulting from sleep problems, and the perceived impact of these problems on daily functioning and quality of life [110]. The ISI is a valid and reliable measure that has demonstrated excellent internal consistency in previous research [111].

Secondary Outcome: Habit Strength

We will assess habit strength at baseline, week 8, and week 16 using the Self-Report Habit Index (SRHI). The SRHI is a brief self-report inventory that assesses the perceived habit strength (ie, automaticity) of a specific behavior, such as meditation [112]. The SRHI has been used to assess habit strength in a wide range of behaviors and has demonstrated adequate reliability in previous research [112].

Demographic Information

The following demographic information will also be collected from participants at baseline assessment: age; gender; race; Hispanic status; employment information (ie, status, hours, and work from home); annual household income; number of adults and children in the household (if any); marital status; education level; past mental health diagnosis (ie, PTSD and depression); current mental health medications (if any); self-rated physical health (5-point Likert scale); and any current chronic medical condition diagnosis (eg, high blood pressure, diabetes, and asthma).

Satisfaction

Participant satisfaction will be assessed at weeks 8 and 16. All participants will be asked to rate their overall enjoyment and satisfaction with the Calm app and the study itself, as well as their intent to continue using the app along with the app features (eg, mood tracking and session tracking) and app content (eg, daily meditations, sleep meditations, and soundscapes) that they found most helpful for maintaining their daily meditation practice. Then, participants will be asked specific questions regarding their chosen meditation anchor, such as how easy it was to select and use their chosen anchor during the intervention, their intent to continue using their meditation anchor, and the helpfulness of the anchoring plan in maintaining their meditation practice. Participants in the intervention groups will also be asked questions related to the incentives, including how easy it was to understand the incentive process; how easy it was to earn incentives; if they liked the incentive options, how motivated they were by the incentives; and if there was anything that would have motivated them more. This information will provide helpful qualitative data that can be used to improve future adherence studies, including the types of anchoring strategies that are most successful in establishing a meditation habit and what motivates people to establish and maintain an app-based meditation habit.

Attrition will be assessed at all stages of the study: (1) enrolled but did not complete the baseline assessment, (2) completed baseline assessment but lost to follow-up during the 8-week intervention period (ie, did not complete week 8 assessment), and (3) completed the 8-week assessment but lost to follow-up during the 8-week postintervention observation period (ie, did not complete the week 16 assessment).

Intervention

Randomization and Baseline

This randomized controlled trial aims to test the effectiveness of different strategies on adherence to the daily ≥10-minute meditation prescription via a mindfulness meditation app. Note that the meditation prescription and the anchoring plan are not interventions; rather, the interventions are the additional supports that are provided for the anchoring plan to establish an app-based meditation habit. After randomization, all participants will complete a web-based baseline survey to collect additional demographic information and to assess the baseline levels of the secondary outcome measures listed in the previous sections.

Introductory Video

Immediately following the web-based surveys, participants will then watch 1 of 3 brief 5-minute introductory videos that will vary slightly based on their experimental conditions. All 3 videos will contain background information on the benefits of mindfulness meditation and habit formation (eg, previous research and theory); a sample anchoring plan (eg, “After [insert behavior here], I will meditate for 10 minutes”); a study timeline (ie, baseline assessment, 8-week intervention period, follow-up assessment, 8-week postintervention period, and second follow-up assessment); and compensation information for completing the 3 web-based surveys (US $20 gift card). In addition to these foundation elements, participants in the NTCI and TCI groups will be told in the video that they are eligible for incentives every 2 weeks during the 8-week intervention period conditional on either meditating at any time (NTCIs) or meditating using their anchoring plan (TCIs). The video for the usual Calm condition will only include the foundation elements mentioned previously, with no mention of incentives or personalized feedback messages. Information in all 3 videos

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will be presented by a member of the study team using both written and spoken texts. Participants in the NTCI and TCI groups will also receive instructions regarding prize eligibility as detailed in the *Study Design* section.

Anchoring Plan Worksheet

After watching the introductory video, participants will complete a video comprehension quiz to ensure that they understand the study timeline and requirements. Participants must score 100% on the quiz to move on with the study. Then, all participants will be asked to complete a web-based worksheet to help them develop a meditation anchoring plan. This worksheet will first ask participants to fill out a basic implementation intention plan (ie, "After _____, I will meditate for 10 minutes") based around a routine behavior (ie, their anchor) they perform in the morning, given that previous research suggests the morning habits are easiest to form [31]. Next, participants will be instructed to add additional details to their anchoring plan to make it more specific (eg, anchor timing and anchor location), as generic plans may not be as effective as plans that specifically outline when and where this behavior will occur. After finalizing their anchoring plan, the participants will be emailed a copy of their anchoring plan for their records.

Intervention, Postintervention, and Follow-up Surveys

The 8-week intervention period will begin once the participants complete the baseline assessment and anchoring plan worksheet. All the participants will be asked to meditate for ≥10 minutes every day during the intervention period. Every 2 weeks, participant use data will be checked to determine incentive eligibility for participants in the NTCI and TCI groups. Every week, all the participants will also receive a text message from the study team as a reminder to continue meditating using their chosen anchor. In addition, participants in the BM group will receive a message focused on self-monitoring of their meditation behavior every 2 weeks that informs participants of the number of ≥10-minute meditations they completed during the past 2 weeks. Participants in the self-monitoring of outcomes of behavior messages groups will receive a message focused on self-monitoring of outcomes of their meditation behavior (ie, mood tracking) every 2 weeks that encourages the participants to keep track of their mood using the "How Are You Feeling?" feature in the Calm app. After 8 weeks, participants will be emailed a link to complete the first of the 2 follow-up surveys. These surveys will assess any improvements in the secondary outcome measures assessed at baseline, as well as their satisfaction with both the Calm app itself and the interventions. Following the completion of the 8-week intervention period and the week-8 follow-up survey, participants will be asked to continue using their anchors to strengthen their meditation habits during the 8-week postintervention observation period. However, unlike in the intervention period, participants in all intervention groups will no longer receive weekly reminders, biweekly self-monitoring messages, or incentives during the postintervention period. Participants will then be contacted at week 16 to complete the second follow-up survey to assess changes in the secondary outcome measures at week 16.

Data Analysis Plan

To examine our specific aims, statistical analyses comparing group-level differences in the primary and secondary outcome measures will be performed. First, an analysis of covariance framework will be used to test for group-level differences in each primary and secondary outcome, controlling for participant characteristics that are found to significantly differ between study groups at baseline. For analyses of dichotomous outcomes, such as meditation regularity at weeks 8 and 16, a nonparametric McNemar test and multiple logistic regression that controls for additional participant-level covariates will be used to assess study group differences. In addition to static comparisons of group means for each outcome, the longitudinal nature of the app use data will be leveraged by using repeated measures and time-series techniques. Specifically, a linear mixed model with repeated observations will be fitted using maximum likelihood through "xtmixed" in the software package Stata (StataCorp) to study group-level temporal dynamics in the primary and secondary outcomes.

To estimate the impact of our intervention on our static primary outcomes of meditation regularity and anchoring plan regularity at weeks 8 and 16, we will use logistic regressions with the following specifications.

Our main unadjusted model will have the following form:

$$\Pr(y_i) = \exp(\beta_0 + \beta_1 T + \beta_2 T2 + \beta_3 T3 + \beta_4 T4 + \varepsilon_i) \quad \textbf{(1)}$$

Our main adjusted model has the following form:

$$\Pr(y_i) = \exp(\beta_0 + \beta_1 T + \beta_2 T2 + \beta_3 T3 + \beta_4 T4 + X_i\beta_5 + \varepsilon_i) \quad \textbf{(2)}$$

where y_i is a binary variable equal to 1 if individual i completed ≥10 minutes of meditation for ≥4 days during week 8 of the study; T1 is an indicator for treatment group 1 (that receives self-monitoring behavior messages and NTCIs); T2 is an indicator for treatment group 2 (that receives self-monitoring outcome messages and NTCIs); T3 is an indicator for treatment group 3 (that receives self-monitoring behavior messages and TCIs); T4 is an indicator for treatment group 4 (that receives self-monitoring outcome messages and TCIs); and $_i$ is the idiosyncratic error. The coefficients of interest are β_1 through β_2. Equation 2 has the term $X_i\beta_5$, which includes a vector of the following observable participant characteristics (X_i): age, education, sex, race, ethnicity, household income, self-reported mental and physical health, baseline meditation habit strength, intrinsic motivation for meditation, and measures of time and risk preferences and the respective coefficients (β_5). For more information on our data analysis plan, please see Multimedia Appendix 1.

In addition, we will investigate potential intervention moderators and mediators. Specifically, we will use the same regression models specified earlier in this section and include additional interaction terms between each study group indicator variable and a single moderating variable measured at baseline. Significant coefficients estimated for these interaction terms will be used to identify the moderating effects of participants' baseline characteristics, such as age, gender, race, and

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employment information. In addition, we will separately examine the mediating effects of anchoring plan adherence and habit strength at the end of the intervention on the maintenance of mediation following the procedures outlined by Judd and Kenny [113]. We will first regress meditation measured in week 16 on indicator variables for each study group and then regress meditation in week 16 on indicator variables for each study group as well as anchoring plan adherence measured over the first 8 weeks (ie, during the intervention). The mediating effect of anchoring plan adherence (our third hypothesis) will be calculated by subtracting the coefficients estimated in the first regression from those in the second regression. We will also use these procedures to investigate the mediating effect of habit strength measured at week 8 (ie, immediately after the intervention). We will also use a modern mediation analysis technique that allows for additional covariates when estimating the direct and indirect treatment effects in the equations described earlier [114].

Ethics Approval

This research was reviewed and approved by the Arizona State University Institutional Review Board (STUDY00014710) on 11/9/2021. This study has also been registered at ClinicalTrials.gov NCT05217602. Participants will provide consent electronically and will be emailed a copy of the consent form for their records. Participants can withdraw from the study at any time without penalty and request that their data be removed from the analysis. The data collected by the research team will be stored on a password-protected cloud-based secure server. All data retrieved from the questionnaires will be deidentified (kept separate from any personal identifying information, including consent forms). The questionnaire data will only be linked to individual participants via the assigned study ID numbers. Only anonymous aggregated data regarding app use during the 8-week study and an additional 8-week postintervention observation period will be retrieved from the Calm informatics team. All the participants will be compensated US $20 in electronic gift cards for completing the 3 web-based surveys (ie, baseline, postintervention, and follow-up surveys). Participants in either the NTCI or TCI groups will also be eligible to win up to 4 incentives during the intervention period, in addition to a US $20 gift card as compensation for completing all 3 web-based surveys.

Results

Recruitment for this study was expected to occur between March 2022 and May 2022. Data collection is expected to be completed by October 2022. The results from this study will be available within 12 months of the final data collection date, which will be sometime between late 2022 and early 2023. The findings of this research will be disseminated using various methods, including peer-reviewed journals, academic conferences, and other verbal and digital communication platforms.

Discussion

Overview

Mobile meditation apps can be an effective and feasible way to deliver mindfulness meditation interventions. However, low intervention adherence over time limits the long-term potential of these apps. This study aims to address this critical issue by testing a combination of behavioral intervention strategies to determine the optimal combined strategy for establishing and maintaining meditation habits with a mobile app. To accomplish this, we have three specific aims: (1) assess study group differences in adherence to the daily meditation prescription during the 8-week intervention, (2) estimate study group differences in adherence maintenance over the 8-week postintervention observation period, and (3) investigate the role of anchoring performance during the intervention on the participants' ability to maintain their meditation app adherence during the postintervention observation period.

This study will make important contributions to mHealth and behavior change research. First, the results of this study will improve future app-based interventions by identifying the most effective strategies for establishing and maintaining adherence to a mobile app, adding to the sparse body of literature on adherence to app-based interventions, particularly those for mindfulness meditation. Current research on app-based interventions is limited by poor adherence, and improving adherence is necessary to understand the full potential of app-based interventions for promoting health behavior change as well as the associated benefits from these health apps. This is particularly important for health behaviors such as mindfulness meditation, which requires maintaining a long-term practice to experience the maximum physical and mental health benefits. Second, this study will assess adherence by using objective app use data. Previous studies examining adherence in app-based interventions have found significant discrepancies between self-reported (eg, retrospective, daily diaries) and objective measures of adherence, as self-report measures are subject to more biases such as recall or response bias [115]. Testing strategies for maintaining objective measures of app-based intervention adherence will provide more rigorous evidence that will help to better understand the habit formation process in this setting. Finally, this research will make important contributions to the behavior change literature, in which existing interventions in the psychology and behavioral economics literature have largely been unsuccessful in maintaining behavior changes after interventions. By combining the anchoring habit formation strategy from psychology with behavioral economics–based incentives (ie, in-kind prizes awarded for short-term behaviors), this study will provide important evidence for a novel combined approach that may be more successful in maintaining behavior changes and will help improve our understanding of the habit formation process.

Several potential limitations of this study must also be addressed. First, the 8-week intervention period may not be sufficient to develop a strong and long-lasting meditation habit. Similarly, the 8-week intervention and 8-week postintervention periods may not be long enough to adequately assess our

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primary and secondary outcomes. Future research should plan to assess adherence and our secondary outcomes over longer periods to better understand the long-term effectiveness of these strategies. Another limitation to consider is the likely demographic characteristics of the recruited sample. Previous studies using Calm have reported samples that consisted of predominantly individuals who are White, female, and have bachelor's degrees or higher qualification [116,117]. As a result, we anticipate having difficulty recruiting a diverse sample, which will limit the generalizability of our findings. In addition, studying the meditation app behavior of paid subscribers to a meditation app may not be generalizable to the general population. We plan to address this limitation by using a stratified randomization method to ensure that each study group has equal representation across racial and ethnic groups. Finally, it is possible that the incentives (ie, Calm prizes) provided to the NTCI and TCI groups during the intervention period may not be incentivizing to participants. We will test this by comparing the NTCI and TCI groups with the control group and by examining which items were most commonly chosen by eligible participants, and we will publish the results of these analyses to help determine the magnitude of incentives in future incentive-based meditation studies.

Conclusions

This study will contribute to an important gap in the literature by testing novel intervention approaches for establishing and maintaining adherence to app-based mindfulness meditation. We are using unique combinations of previously established intervention strategies from the psychology and behavioral economics literature to help participants better maintain adherence to an effective dose of meditation that can reduce stress. If successful, this study will identify an accessible and scalable stress self-management intervention to combat the ongoing stress epidemic in the United States.

Conflicts of Interest

CS was a member of the Scientific Advisory Board at Calm during the implementation of the survey but no longer receives any financial or nonfinancial compensation from Calm. At the time this research was completed, JH conducted investigator-initiated research and used the Calm app to deliver mindfulness meditation interventions. Calm financially supported her research with a postdoctoral scholar and 2 research coordinators (contractors). The roles of these persons were to help JH with her investigator-initiated research using the Calm app. JH consulted for Calm as the Director of Science and Director of the Scientific Advisory Board at Calm. Her role was to ensure the quality of Calm's science and she had no specific obligations to the company. JH is no longer working with Calm.

Multimedia Appendix 1
Data analysis plan.
[DOCX File , 14 KB - resprot_v12i1e39930_app1.docx]

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Abbreviations

ISI: Insomnia Severity Index
mHealth: mobile health
NTCI: non–time-contingent incentive
PSS: Perceived Stress Scale
PTSD: posttraumatic stress disorder
SRHI: Self-report Habit Index
TCI: time-contingent incentive

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Protocol

Effect of the Red Bull Energy Drink on Perfusion-Related Variables in Women Undergoing Microsurgical Breast Reconstruction: Protocol and Analysis Plan for a Prospective, Multicenter Randomized Controlled Trial

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Abstract

Background: Maintaining a sufficiently high systolic blood pressure is essential for free flap perfusion after microsurgical breast reconstruction. Yet, many women undergoing these procedures have low postoperative systolic blood pressure. Intravenous volume administration or vasopressors may be needed to maintain systolic blood pressure above a predefined threshold. However, excessive volume administration may lead to volume overload and flap stasis, and the postoperative use of vasopressors may be limited depending on institutional standards. Additional nonpharmacological measures to raise blood pressure might be beneficial. Evidence suggests that the Red Bull energy drink could raise blood pressure. It has been shown to increase systolic and diastolic blood pressure in healthy volunteers and athletes.

Objective: The primary objective of this study is to determine the difference in systolic blood pressure between an intervention group receiving Red Bull and a control group receiving still water after microsurgical breast reconstruction. Secondary objectives include postoperative heart rate, 24-hour fluid balance, pain level, or necessity for revision surgery due to flap complications.

Methods: The Red Bull study is a prospective, multicenter randomized controlled trial comparing the effect of postoperative ingestion of Red Bull energy drink against still water in female patients undergoing unilateral microsurgical breast reconstruction. A total of 250 mL of Red Bull (intervention group) or 250 mL of still water (control group) will be administered to the study participants 2 hours postoperatively as well as for breakfast and lunch on postoperative day 1, amounting to a total volume of 750 mL per 24 hours. Female patients between 18 and 70 years of age undergoing unilateral microsurgical breast reconstruction will be included. Exclusion criteria are a history of arterial hypertension, cardiac rhythm disorder, diabetes mellitus, gastric or duodenal ulcer, thyroid disease, and current use of antihypertensive or antiarrhythmic drugs or thyroid hormones, as well as intolerance to Red Bull.

Results: Recruitment for the study started in June 2020 and was completed in December 2022. There is evidence that the Red Bull energy drink increases blood pressure in healthy volunteers and athletes. We hypothesize that postoperative ingestion of Red Bull will increase systolic blood pressure in women after microsurgical breast reconstruction. Red Bull could hence be used as a nonpharmacological adjunct to vasopressors or volume administration in women with hypotensive blood pressure after microsurgical breast reconstruction.

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Conclusions: This paper describes the Red Bull study trial protocol and analysis plan. The information will increase the transparency of the data analysis for the Red Bull study.

Trial Registration: ClinicalTrials.gov NCT04397419; https://clinicaltrials.gov/ct2/show/NCT04397419

International Registered Report Identifier (IRRID): DERR1-10.2196/38487

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KEYWORDS

analysis; blood pressure; breast; energy drinks; heart rate; mammaplasty; microsurgery; pain; patient; perfusion; postoperative; prospective studies; reconstruction; surgery; systolic; taurine

Introduction

Overview

Maintaining a sufficiently high systolic blood pressure is vital for free flap perfusion after microsurgical breast reconstruction. However, many women undergoing microsurgical breast reconstruction have low systolic blood pressure postoperatively. Often, intravenous volume administration or vasopressors are needed to maintain systolic blood pressure above 100 mm Hg. Yet, intravenous volume administration may lead to volume overload and flap stasis, and the use of vasopressors in the postoperative setting may be limited depending on institutional policies. Additional nonpharmacological measures to guarantee adequate postoperative perfusion pressure would be beneficial.

Clinical Evidence for Red Bull Energy Drink

Red Bull energy drink has shown varying effects on the hemodynamic profile and pain perception in clinical studies performed on healthy participants and athletes [1-3]. A randomized crossover study showed a negative hemodynamic profile in response to Red Bull [2]. Participants who ingested 355 mL of Red Bull showed increased systolic and diastolic blood pressure, increased heart rate, and cardiac output without significantly reduced endothelial function compared with a control group who received 355 mL of tap water. This was reproduced in another randomized crossover study that further explored the combined effect of Red Bull and mental stress on cardiovascular parameters [1]. The combination of Red Bull and mental stress leads to an additional increase in systolic and diastolic blood pressure and heart rate, suggesting a cumulative effect.

Energy drinks have shown varying effects on endothelial function [4,5]. In a case report, a reduced reactive hyperemia index was observed after ingestion of Monster energy drink, suggesting worsened endothelial function [4]. In contrast, Red Bull improved endothelial function in a prospective study involving 6 volunteers [5]. Ingestion of 250 mL of Red Bull significantly increased endothelial function as measured by the reactive hyperemia index. In the same study, coffee containing comparable amounts of caffeine did not affect endothelial function. These results suggest that ingredients other than caffeine account for the vasodilatory effect.

Considering the mild diuretic effect of caffeine, Red Bull energy drink may increase urine formation rate and decrease urine specific gravity. Although urinary output increased with caffeine and Red Bull energy drink in 1 study [6], this trend could not be observed elsewhere [7].

Red Bull energy drink may furthermore increase pain tolerance [7]. Levels of pain after a cold pressor test were measured in participants before and after consumption of 250 mL of Red Bull. All participants reported a decreased perception of pain directly following Red Bull consumption.

Interventional Product

Red Bull energy drink was first introduced in Austria in 1987 and launched in Switzerland in 1994. It is among the most popular energy drinks with over 6 billion cans being sold annually worldwide [8]. A can of 250 mL Red Bull energy drink contains 80 mg caffeine, 1 g taurine, 240 mg glucuronolactone, 27 g carbohydrates as well as water, sodium citrate, vitamins (B3, B5, B6, and B12), flavoring, and coloring agents [9]. This corresponds to total calorie content of 194 kJ (46 kcal) per 100 mL [8].

Despite anecdotal reports that linked Red Bull consumption with ventricular tachycardia and symptoms of cardiovascular disease, limited daily consumption of 500 mL of Red Bull appears safe [7,9]. When investigated in clinical studies no deleterious effects of Red Bull energy drink on cardiovascular function have been found [10]. Any adverse effects after excessive consumption are most likely due to the accumulation of caffeine, which is known to cause nervousness, anxiety, tremor, insomnia, tachycardia, arrhythmia, and nausea with ingestion exceeding 200 mg/day [11,12]. The amounts of taurine contained in Red Bull are far below the threshold to cause adverse effects [11].

Caffeine is an adenosine receptor antagonist with stimulating properties on the central nervous system It is known to increase blood pressure and peripheral vascular resistance through sympathetic stimulation [13]. Taurine is a sulfur-containing amino acid that constitutes the most abundant intracellular amino acid in humans [14]. Taurine seems to modulate skeletal muscle contractile function and possesses antiarrhythmic, inotropic, and chronotropic properties [15]. Glucuronolactone occurs naturally in small amounts within the body. Little data exists on its function in humans [9]. The amount of sugar provided in a can of 250 mL Red Bull energy drink is 27 g, which corresponds to 6.5 teaspoons of sugar [9]. Consuming moderately concentrated carbohydrate solutions (5%-8%) has been shown to promote prolonged exercise performance without causing adverse effects [15].

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Dose Rationale

The authors selected a daily administration of 250-500 mL of Red Bull in the study. Most investigators studied the effect of Red Bull after ingestion of 250, 355, or 500 mL. When ingested in standard amounts, Red Bull energy drink is a safe beverage without notable side effects [7,9].

Risks

Daily oral administration of 500 mL of Red Bull has proven safe, and any side effects after consumption exceeding 500 mL daily have been linked to caffeine [9]. These include nervousness, anxiety, tremor, insomnia, tachycardia, arrhythmia, and nausea. To minimize adverse events, participants with allergies or intolerance to any component of Red Bull will be excluded from the study.

Study Aim

The authors prospectively study the effect of postoperative ingestion of Red Bull energy drink on perfusion-related variables and patient recovery after microsurgical breast reconstruction. To our knowledge, there are no competing trials.

Objectives

This study aims to assess perfusion-related variables, postoperative levels of pain, type of postoperative complications, operative reexploration rate due to complications, and total duration of hospital stay in patients undergoing autologous microsurgical breast reconstruction with postoperative ingestion of Red Bull Energy drink.

Primary Objective

The primary objective is to assess the difference in systolic blood pressure (mm Hg) between the intervention group and the control group at 15, 30, 45, 60, 75, 90, 105, and 120 minutes after each of 3 Red Bull (intervention group) or water (control group) applications.

Secondary Objective

The secondary objective is to document and assess the following variables in the intervention group and the control group:

1. Diastolic and mean arterial blood pressure (mm Hg) at 15, 30, 45, 60, 75, 90, 105, and 120 minutes after each of 3 Red Bull (intervention group) or water (control group) applications.
2. Postoperative heart rate (1/min) at 15, 30, 45, 60, 75, 90, 105, and 120 minutes after each of 3 Red Bull (intervention group) or water (control group) applications.
3. Postoperative urinary output (mL) during the first postoperative 24 hours.
4. Intraoperative and postoperative fluid administration (mL) until 24 hours after surgery.
5. Intraoperative and postoperative administration of vasoactive drugs (mg) until 24 hours after surgery.
6. Postoperative pain (numeric rating scale [NRS]) during the first postoperative 24 hours.
7. Postoperative administration of opioid analgesics (analgesic in mg).
8. Postoperative administration of nonopioid analgesics (analgesic in mg).
9. Postoperative administration of benzodiazepines (mg).
10. Rate of operative reexplorations during the first hospitalization (%).
11. Flap loss (%).
12. Duration of hospital stay (number of nights spent at hospital).
13. Wound healing 4 weeks after surgery (photo documentation).

Safety Objective

Notable adverse events of Red Bull energy drink in this population are as follows: nervousness, nausea, anxiety, tremor, insomnia, arrhythmia, need for revision surgery, and flap loss.

Methods

Overview

This is an open-label, multicenter, prospective, and randomized controlled trial comprising a cohort of 100 patients. Patient selection and inclusion as well as the anesthetic visit will occur preoperatively in an outpatient clinic. During hospitalization, microsurgical breast reconstruction will be performed under general anesthesia by JF, AML, or DB. Additionally, oral ingestion of Red Bull energy drink (intervention group) or still water (control group) will occur 2 hours after surgery and on a postoperative day 1 for breakfast and for lunch. Finally, wound healing and scarring will be assessed at the 4-week follow-up in our clinic using photo documentation.

Participants are expected to participate from the signing of the informed consent form until the 4-week follow-up visit. All patients enrolled prospectively in the trial will receive a Red Bull energy drink or still water. Blinding or masking is not feasible.

Study Population

The study population will be women between 18 and 70 years of age undergoing unilateral microsurgical breast reconstruction by JF, AML, or DB at 2 institutions.

Inclusion and Exclusion Criteria

Textbox 1 shows the inclusion and exclusion criteria.

As a standard of care, all patients are asked to perform a check-up by their general practitioner (GP) within 2-4 weeks before the microsurgical procedure. Their GP fills in a standardized form provided by the Institute of Anesthesiology, from which all inclusion and exclusion criteria can be drawn. Additionally, the GP performs an electrocardiogram and a blood test (complete blood count, electrolytes, creatinine, and international normalized ratio or Quick) for the patient and sends the result to the institute of anesthesiology at the respective clinic.

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Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Female patients between 18 and 70 years of age.
- Ability to give written informed consent before participation in the study.
- Ability to comply with the requirements and restrictions listed in the consent form.

Exclusion criteria

- History of arterial hypertension.
- History of cardiac rhythm disorder.
- History of diabetes mellitus.
- History of gastric or duodenal ulcer.
- History of hyperthyroidism or hypothyroidism.
- Current use of antihypertensive drugs, antiarrhythmic drugs, and thyroid hormones.
- Allergy or intolerance to the component of Red Bull energy drink.
- Not fulfilling inclusion criteria.

Intervention

All consecutive female patients receiving unilateral autologous microsurgical breast reconstruction will be administered a total of either 750 mL Red Bull energy drink (intervention group) or 750 mL of still water (control group) at predefined intervals. The first dose of 250 mL of Red Bull energy drink or still water will be given 2 hours after surgery in the postanesthesia care unit. The following doses will be given on postoperative day 1 at 8 AM for breakfast (250 mL) and at 12 PM for lunch (250 mL). Full consumption of the study drink will be verified by a nurse. The study will be carried out at the 2 centers where JF, AML, and DB have been accredited: Klinik Pyramide am See, Zurich, Switzerland and Klinik Hirslanden, Zurich, Switzerland. The perioperative protocols have been standardized at both institutions and standard operating procedures have been implemented.

The systolic and diastolic blood pressure as well as pulse will be measured noninvasively using a 24-hour ambulatory blood pressure monitor (Tonoport VI, Anandic Medical Systems AG) during the first postoperative 24 hours. The device will be applied to the participant's arm upon their arrival in the postanesthesia care unit and remain in place for 24 hours. Upon completion of these 24 hours, the readings will be downloaded on the study computer by the study personnel, using the software provided by Anandic Medical Systems AG.

Total fluid administered intraoperatively and postoperatively as well as intraoperative and postoperative administration of vasoactive drugs will be recorded. The daily urinary output will be measured 24 hours after surgery. Pain levels will be measured on NRS with values ranging from 0 to 10. The rate of operative reexplorations, flap loss, and total length of primary hospital stay will be recorded. Wound healing and scarring will be assessed 1 month after surgery in our clinic and documented photographically.

The variables obtained from the intervention group receiving Red Bull energy drink postoperatively will be compared with the corresponding variables of patients in the control group receiving the same amount of still water.

Randomization and Blinding

Randomization is undertaken with equal allocation to each study group (Red Bull:still water=1:1) using a computed code. Blinding or masking is not feasible.

Other Measures of Minimizing Bias

We will measure the systolic and diastolic blood pressure using ambulatory 24-hour blood pressure monitors (Tonoport VI, Anandic Medical Systems AG) to ensure comparable measurements (same side of arm and same cuff) and reduce intermeasurer variability. All patients will remain in bed during the first 12 hours postoperatively and will have a urinary catheter during this period. This further reduces changes in blood pressure not related to the study intervention. Additionally, all patients entering hospital preoperatively will have fasted for 6 hours (solids) and 2 hours (liquids). Also, oral fluid and food intake during the first 24 hours after a microsurgical procedure is typically low among all patients to ensure that patients could be taken back to theater in a timely manner should flap complications occur. The preoperative regular consumption of caffeinated products and the consumption of additional caffeinated products during the hospital stay will be recorded and incorporated in the final analysis. If a patient requires additional vasopressors postoperatively, this will be documented and incorporated in the final analysis.

Outcomes

Primary Outcome

Difference in systolic blood pressure between the intervention group and control group at 15, 30, 45, 60, 75, 90, 105, and 120 minutes after each of 3 Red Bull (intervention group) or water (control group) ingestions as measured by the ambulatory blood pressure monitoring device.

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Secondary Outcomes

Difference in the following postoperative variables between participants with or without postoperative intake of Red Bull energy drink:

- Diastolic and mean arterial blood pressure at 15, 30, 45, 60, 75, 90, 105, and 120 minutes after each of 3 Red Bull (intervention group) or water (control group) ingestions as measured by the ambulatory blood pressure monitoring device.
- Postoperative heart rate (1/min) at 15, 30, 45, 60, 75, 90, 105, and 120 minutes after each of 3 Red Bull (intervention group) or water (control group) applications.
- Postoperative urinary output (mL) during the first postoperative 24 hours.
- Intraoperative and postoperative fluid administration (mL) until 24 hours after surgery.
- Intraoperative and postoperative administration of vasoactive drugs (mL) until 24 hours after surgery.
- Postoperative pain (NRS) during the first postoperative 24 hours.
- Rate of operative reexplorations during the first hospitalization (%): flap complications (%) and flap loss (%); total duration of hospital stay (number of nights spent at hospital); wound healing 4 weeks after surgery (photo documentation).

Other Outcomes of Interest

Patient- and tumor-related data, such as age, BMI (size and weight), tobacco use; diabetes mellitus, indication for surgery (oncologic or prophylactic), neoadjuvant chemotherapy, previous irradiation, side and type of flap, flap weight, and ischemia time will be assessed perioperatively or collected from the medical history.

Harm Outcomes

Differences in the incidence of notable adverse events between both groups. Adverse events include nervousness, nausea, anxiety, tremor, insomnia, arrhythmia, need for revision surgery, and flap loss.

Frequency and Duration of Follow-up

The schedule of trial enrolment, interventions, and assessments are presented in Table 1. Following surgery, the study intervention will take place in the recovery room and on the ward of the 2 study sites. The follow-up ends 4 weeks post operation in clinic.

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Table 1. Schedule of enrolment, interventions, and assessments for the Red Bull study.

	First clinic appointment with the reconstructive team (preoperative)	Preoperative appointment with an anesthesiologist (up to 4 weeks before surgery)	Perioperative (treatment) period			Follow-up (4 weeks post surgery)
			Day of surgery	POD1[a]	Discharge from hospital	
Visit	1 (start)	2	3	3	3	4 (end)
Patient information and signed informed consent[b]	✓					
Demographic data	✓					
Medical history and letter from GP[c]	✓	✓				
Inclusion and exclusion criteria	✓					
Physical examination	✓					
Vital signs		✓ (provided by GP)	✓	✓		
Laboratory tests		✓ (provided by GP)				
Surgery (unilateral microsurgical breast reconstruction)			✓			
Administer Red Bull (intervention) or still water (control)			✓	✓		
Record blood pressure and heart rate			✓	✓		
Record urinary output			✓	✓		
Record volume of intravenous fluid administered			✓	✓		
Record volume of vasoactive drugs administered			✓	✓		
Record volume of oral fluid administered			✓	✓		
Record flap complications			✓	✓	✓	
Record operative reexploration			✓	✓	✓	
Record pain levels (NRS[d] 0-10)			✓	✓	✓	
Record duration of hospital stay					✓	
Record adverse events of Red Bull ingestion			✓	✓	✓	
Assess wound healing and document photographically						✓

[a]POD1: postoperative day.

[b]Informed consent form to be signed within 30 days of planned surgical procedure.

[c]GP: general practitioner.

[d]NRS: numeric rating scale.

Recruitment

Participants are recruited for the study in outpatient clinic. All patients undergoing elective microsurgical breast reconstruction will be screened. Patients who consent to participate in the study are randomized at the moment of surgery planning. No compensation or payment is given to the study participants.

Data Collection

Data are collected from clinical proformas, clinical notes, and study-specific forms and then entered onto a Excel (Microsoft Corp) file. The data collection form is provided in the Multimedia Appendix 1. The database has been programed by NES and MM. No identifiable data will be entered into the database. Participants will be identified using a unique code and initials. To avoid unauthorized people accidentally or deliberately perform changes, copies, or deletions of the analyzed data in Microsoft Excel, the following precautions are planned: after each relevant processing step, the new data version is saved and is not allowed to be changed. Such a new

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data version will be converted into a secured document (PDF file).

Sample Size

The following assumptions estimated from literature and clinical experience:

- Mean systolic blood pressure (mm Hg): We assume the same SDs (ie, 15) for both groups and the correlation coefficient among repeated measures to be 0.7. If we assume no differences in time in the control group (mean 115 mm Hg) and assume the difference between the intervention group and the control group to be about 10 mm Hg, the required sample size would be 27 per group.
- Heart rate (1/min): We assume the same SDs (10) for both groups and the correlation among repeated measures to be 0.7. If we assume no differences in time in the control group (mean 80/min) and assume the difference between the intervention group and the control group to be 5/min, the required sample size would be 46 per group.
- Vasoactive drug Ephedrine (mg): We assume the mean drug dose in the control group to be 63 and the mean drug dose in the intervention group to be 48. Assuming equal SDs (ie, 25) we get 45 per group.

The predefined parameters include a significance level (α level) of .05 and power (1-β) of 0.8.

We calculated the patients needed to be included using the application STATA (version 15.1; StataCorp, 2017; Stata Statistical Software: Release 15) and G*Power (version 3.1.9.4—a program written by Franz Faul, Universität Kiel). Considering the different calculations and accounting for potential missing data or dropouts, 50 patients per group will be included, leading to a total of 100 patients.

Statistical Methods

We are planning to measure mean systolic blood pressure at 8 time points. For this, the right statistical model is a mixed ANOVA where the group is an independent (unpaired) factor, and the time is a dependent (paired) factor. The comparison of drug intake between the Red Bull group and the control group will be performed by student *t* test for independent data (assuming data will follow a normal distribution). In case data will not follow a normal distribution, an alternative nonparametric test will be used (Mann-Whitney *U* test).

Analysis Plan

As the null hypothesis (H0), we assume that mean systolic blood pressure from baseline to 120 minutes post drinking does not differ between the 2 groups. The analysis will be conducted by a senior statistician (MM) in accordance with the above mentioned statistical methods.

Analysis of Harm Outcomes

The frequency of adverse events and the number of patients experiencing events will be tabulated by relation to the study intervention (ie, as adverse reaction, serious adverse event, or serious adverse reaction) and by study group. Nonserious adverse events unrelated to the intervention are recorded in the medical notes only.

Handling of Missing Data and Dropouts

If vital data relevant for the calculation of the primary and secondary end point are missing (ie, blood pressure recordings) patients will be excluded from the participant list. Dropouts will be replaced by consecutive patients.

Ethics Approval

Ethics approval was granted from the Cantonal Research Committee, Switzerland (KEK-ZH 2020-00493). Patients receive an information sheet and provide informed consent before screening to participate in study-specific procedures. The study will be carried out in accordance with the protocol and with principles enunciated in the current version of the Declaration of Helsinki, the guidelines of Good Clinical Practice issued by ICH, the Swiss Law and Swiss regulatory authority's requirements.

Compensation

Participants will not be compensated for their participation in this scientific research project.

Publication and Dissemination Policy

After the statistical analysis of this trial, the principal investigator will make every endeavor to publish the data in a medical journal. Participants will be informed about the outcome of the study once the trial results have been published.

Results

Recruitment of the study participants started in June 2020 and was completed in December 2022. As described previously, there is evidence that Red Bull energy drink increases blood pressure in healthy volunteers and athletes [1,2]. We hypothesize that systolic blood pressure will be higher after each drink ingestion in the intervention group receiving Red Bull compared with the control group receiving still water. Red Bull could hence be used as a nonpharmacological adjunct to vasopressors or volume administration after microsurgical breast reconstruction. It could be particularly useful in settings where the postoperative use of vasopressors is limited.

Discussion

The Red Bull study is a multicenter randomized controlled trial that will explore the effect of Red Bull energy drink intake on perfusion-related variables and flap outcome after microsurgical breast reconstruction. This paper describes the study protocol and statistical analysis plan. The trial sponsor is Plastic Surgery Group. Recruitment started on June 1, 2020, and completed in December 2022. Database lock and data extraction for analysis were carried out in February 2023 when all randomized patients completed the surgical procedure and follow-up period.

There is evidence that the Red Bull energy drink increases blood pressure in healthy volunteers and athletes [1,2]. We hypothesize that Red Bull will increase systolic blood pressure in women after microsurgical breast reconstruction. Red Bull could hence be used as a nonpharmacological adjunct to vasopressors or volume administration in women with hypotension after microsurgical breast reconstruction.

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Strengths and Limitations

This trial has some strengths. This is the first trial assessing the influence of Red Bull on perfusion-related variables after surgery. To minimize adverse events and limit premature dropout from the study, participants with allergies or intolerance to any component of Red Bull will be excluded from the study. Also, diabetes mellitus is considered an exclusion criterion. Red Bull contains 27.5 g of sugar per 250 mL. Patients with diabetes mellitus might require the intake of sugar-free Red Bull, which could, however, be associated with a different hemodynamic pathway [16]. Furthermore, patients with thyroid disease or patients requiring the intake of thyroid hormones will be excluded from this study as the intake of Red Bull was associated with an increased heart rate in a previous study [2]. This trial also has some limitations. Blood pressure is measured noninvasively, which might not be as precise as arterial blood pressure monitoring.

After the statistical analysis of this trial, the principal investigator will make every endeavor to publish the data in a medical journal. Participants will be informed about the outcome of the study once the trial results have been published. The reporting of results from the outlined statistical analysis will comply with the consolidated standards of reporting trials protocol.

Acknowledgments

The authors would like to thank Noël M Speck, BSc for designing the randomization code. This study will be entirely financed by Plastic Surgery Group.

Data Availability

The protocol and statistical analysis plan can be obtained by contacting the corresponding author. The data will be the property of the principal investigator. The study team will retain the exclusive use of the trial data until publication of major outputs has been completed.

Authors' Contributions

NES contributed to the study design, is responsible for acquisition of the data and drafted the manuscript. MM developed the statistical analysis plan. KD contributed to the study design and designed the perioperative anesthetic regimen. DB assists with the acquisition of data. AML contributed to the study design and assists with the acquisition of data. JF is the principal investigator; he conceived the study and contributed to the study design. All authors contributed to the writeup of the protocol and statistical analysis plan for publication, approved the final version to be published and agreed to be accountable for all aspects of the work.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Data Collection Form.
[DOCX File , 53 KB - resprot_v12i1e38487_app1.docx]

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Abbreviations

GP: general practitioner
NRS: numeric rating scale

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Protocol

Acceptability and Feasibility of a Patient-Oriented Music Intervention to Reduce Pain in the Intensive Care Unit: Protocol for a Crossover Pilot Randomized Controlled Trial

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Abstract

Background: Many patients experience pain in the intensive care unit (ICU) despite receiving pain medication. Research has shown that music can help reduce pain. Music interventions studied so far have not used music streaming to generate playlists based on patient preferences while incorporating recommended tempo and duration. Previous research has focused on postoperative ICU patients able to self-report, which is underrepresentative of the ICU population that might benefit from a music intervention for pain management. We developed a new patient-oriented music intervention (POMI) that incorporates features based on theoretical, empirical, and experiential data intended to be used in the ICU. Such a music intervention should consider the expertise of ICU patients, family members, and nursing staff, as well as the practicality of the intervention when used in practice.

Objective: The primary objectives of this study are to (1) evaluate the acceptability and feasibility of the POMI to reduce pain in ICU patients and (2) evaluate the feasibility of conducting a crossover pilot randomized controlled trial (RCT) for intervention testing in the ICU. A secondary objective is to examine the preliminary efficacy of the POMI to reduce pain in ICU patients.

Methods: A single-blind 2×2 crossover pilot RCT will be conducted. Patients will undergo 1 sequence of 2 interventions: the POMI which delivers music based on patients' preferences via headphones or music pillow for 20-30 minutes and the control intervention (headphones or pillow without music). The sequence of the interventions will be inverted with a 4-hour washout period. Timing of the interventions will be before a planned bed turning procedure. Each patient will undergo 1 session of music. Twenty-four patients will be recruited. Patients able to self-report (n=12), family members of patients unable to self-report (n=12), and nursing staff (n=12) involved in the bed turning procedure will be invited to complete a short questionnaire on the POMI acceptability. Data will be collected on the feasibility of the intervention delivery (ie, time spent creating a playlist, any issue related to headphones/pillow or music delivery, environmental noises, and intervention interruptions) and research methods (ie, number of patients screened, recruited, randomized, and included in the analysis). Pain scores will be obtained before and after intervention delivery.

Results: Recruitment and data collection began in March 2022. As of July 5, 2022, in total, 22 patients, 12 family members, and 11 nurses were recruited.

Conclusions: Methodological limitations and strengths are discussed. Study limitations include the lack of blinding for patients able to self-report. Strengths include collecting data from various sources, getting a comprehensive evaluation of the intervention, and using a crossover pilot RCT design, where participants act as their own control, thus reducing confounding factors.

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Trial Registration: ClinicalTrials.gov NCT05320224; https://clinicaltrials.gov/ct2/show/NCT05320224
International Registered Report Identifier (IRRID): DERR1-10.2196/40760

(JMIR Res Protoc 2023;12:e40760) doi:10.2196/40760

KEYWORDS

music; pain; intensive care unit; pilot; feasibility; acceptability

Introduction

Background and Rationale

Pain is a common symptom in critically ill adults, both in patients able and unable to self-report [1]. Guidelines recommend the use of a multimodal approach to pain management to reduce opioid use and optimize pain relief [1]. Music has been suggested as a nonpharmacologic intervention in acute and chronic care settings, but little is known about its efficacy and feasibility in the intensive care unit (ICU) [2-8]. We conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) to establish the efficacy of music in the adult ICU. Music interventions of 20 to 30 minutes were effective to reduce pain by almost 2 points on a 0-10 numeric rating scale (NRS) in ICU patients able to self-report [9]. However, the effect of music on pain in ICU patients unable to self-report remains unknown. In a previous review, some studies reported that family members of ICU patients expressed their interest in participating in the music selection process and in the pain management of their loved ones [10]. Therefore, music interventions for patients unable to self-report could involve the participation of family members based on their intimate knowledge of the patient and their music preferences.

Current recommendations for music interventions in postoperative patients are to provide music in the range of 60-80 beats per minute (bpm) [11]. However, most ICUs do not have access to music therapists, who have the expertise to provide personalized music within this range. Thus, there is a need to develop an easy-to-use music intervention that produces individualized music playlists with a tempo of 60-80 bpm for ICU patients. Music streaming services allow for the music selection of specific tempo ranges and should be explored as a simple means to provide a more accessible music intervention in the adult ICU.

Studies conducted thus far have mainly focused on postsurgical patients, mechanically ventilated, and able to communicate despite the fact that many patients are likely to be unable to communicate during their ICU stay [9,12,13]. Therefore, RCTs conducted until now on the effect of music to reduce pain in critically ill adults have limited generalizability to the entirety of the ICU population, despite the knowledge that all patients can experience pain and could benefit from this nonpharmacological pain management intervention.

Another limitation in previous RCTs analyzed in the systematic review relates to sample size [9]. In 4 RCTs, no sample size calculation was reported [14-17]. In 3 RCTs, the sample size was calculated based on outcomes other than pain [18-20]. In another 3 studies, the calculated sample size required was not attained for various feasibility issues attributed to “slow” or “difficult” recruitment (due to time limit, refusal rate due to randomization or family visits, and narrow inclusion criteria), or withdrawal of ICU adult patient participants who did not like the music chosen for them [21-23]. In 1 study, it was unclear whether the sample size represented the number of ICU adult patient participants or the number of observations [24]. Inadequate power may explain why 11 of the 18 RCTs found a significant pain reduction while 7 did not. Therefore, there is a need to evaluate the feasibility of research methods by conducting a pilot RCT prior to evaluating the efficacy of any new music intervention in the adult ICU.

Objectives

This study aims to (1) evaluate the acceptability and feasibility of a new patient-oriented music intervention (POMI) to reduce pain in ICU patients (primary objective); (2) evaluate the feasibility of conducting a crossover pilot RCT for intervention testing in the adult ICU (primary objective); and (3) examine the preliminary efficacy of the POMI (secondary objective).

Trial Design

A single-blind 2×2 crossover pilot RCT was selected for this study protocol, where patients undergo a sequence of 2 intervention periods: the POMI and the control intervention (CTL: headphones or pillow without music), with an allocation ratio of 1:1.

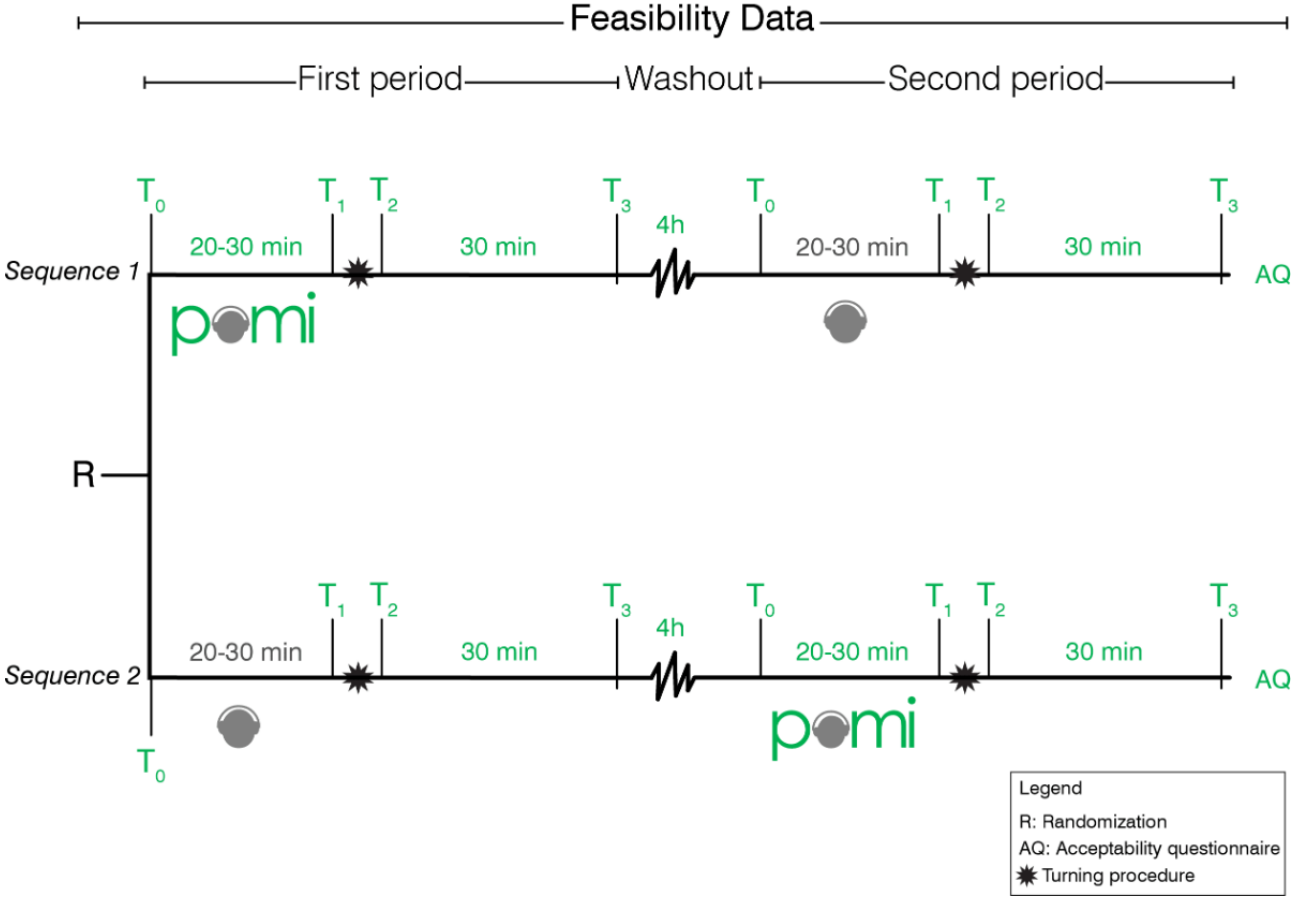
Methods

Design

A single-blind 2×2 crossover pilot RCT is being conducted to evaluate the acceptability, feasibility, and preliminary efficacy of the POMI. Recruitment is planned to occur over a period of 6 months during which we aim to enroll a total of 24 patient participants. As shown in Figure 1, each participating patient is randomly assigned to 1 sequence (sequence 1 or 2) of 2 intervention periods: the POMI and the CTL (headphones or pillow without music). Patients in sequence 1 receive the POMI during the first intervention period, followed by the CTL in the second intervention period; and patients in sequence 2 receive the CTL first, followed by the POMI. Each 20-30–minute intervention period is provided before a bed turning procedure that is planned as part of the participating patient’s usual care by the nursing staff. There is a 4-hour minimum washout period between both intervention periods, with data collected during the day and evening. Data collection begins as soon as possible following recruitment, always in coordination with patient care. Therefore, the first period of data collection may occur in the daytime or in the evening.

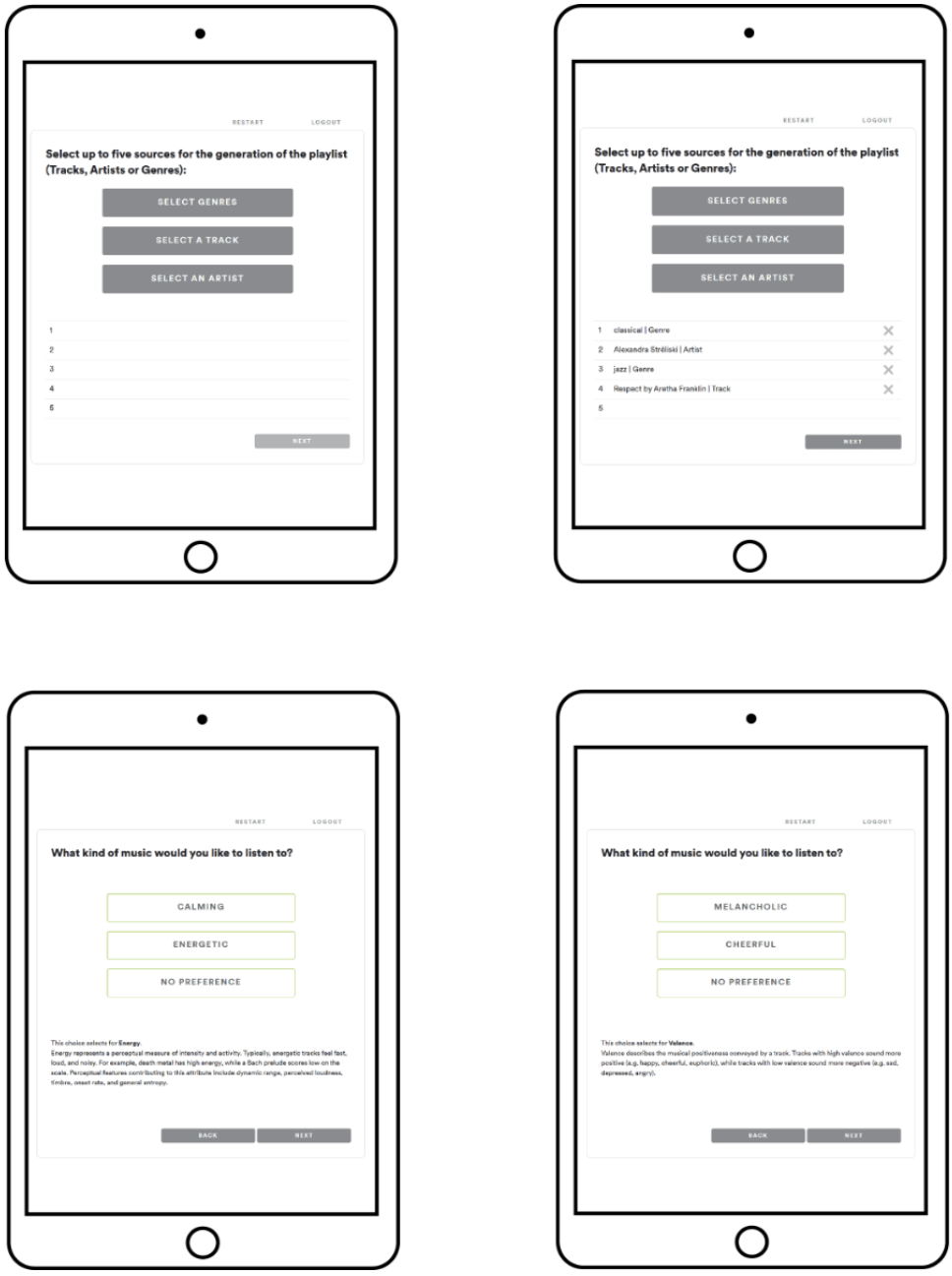
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Figure 1. Study design for the 2×2 crossover pilot randomized control trial.



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Figure 2. Example of web-based tool screenshots for the patient-oriented music intervention.



Recruitment

Recruitment is conducted by the first author (MRL), who is introduced to the eligible patient and family member by the nurse caring for the eligible patient. If the eligible candidate is interested in hearing about the study, the student researcher meets with them at the ICU bedside to present the study, provides a copy of the informed consent form, and answers any question. The eligible candidate is then given time to think about whether they are interested in the study. ICU nursing staff (ie, nurses and orderlies) involved in the turning procedure during the study are invited individually prior to the scheduled bed turning procedure. Eligible nursing staff are given the informed consent form and can choose to participate at their convenience. Eligible criteria are detailed in Table 1.

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Table 1. Eligibility criteria.

	Type of participant			
	Patient able to self-report	Patient unable to self-report	Family member	Nursing staff
Inclusion criteria				
Is ≥18 years old	✓	✓	✓	✓
Is admitted to ICU[a]	✓	✓		
Has a loved one admitted to the ICU			✓	
Works in the ICU				✓
Is able to self-report	✓		✓	✓
Is able to listen to music as per patient or a family member for patients unable to self-report	✓	✓		
A family member is present at the bedside		✓		
Considers self to have knowledge of the patient's music preferences			✓	
Is qualified to consent to any care required by the state of health for the incapable ICU adult patient			✓	
Is present during the turning procedure at the time of the POMI[b] project data collection				✓
Exclusion criteria				
Cannot be turned	✓	✓		
Does not speak or understand French or English	✓	✓	✓	✓
Is unarousable, as defined by a score of −5 on the Richmond Agitation Sedation Scale (RASS)	✓	✓		
Is under the effects of neuromuscular blocking agent	✓	✓		

[a]ICU: intensive care unit.

[b]POMI: patient-oriented music intervention.

Participants

Sample Size

A minimal sample size of 10 participants per group is recommended in pilot studies [25,26]. Because studies with repeated measures (such as crossover designs) require more time commitment from participants (ie, multiple measurements over time), an attrition rate of approximately 15% (n=2 per group) can be anticipated, which is consistent with what has been reported in previous studies conducted in the targeted population [27,28]. To account for this, the recruited sample size was estimated to be 12 participants per group.

Patients

A sample size of 24 patients is targeted, with 12 being able to self-report and 12 unable to self-report. Patients able to self-report will be asked about their music preferences, levels of pain intensity, distress, and acceptability of the POMI.

Family Members

Family members are defined by the patient or, in the case of those unable to self-report, by their surrogates. In such cases, the family may be related or unrelated to the patient. Family members are the individuals who provide support and with whom the patient has a significant relationship [29]. A sample size of 12 family members is targeted: 1 for each patient unable to self-report. Family members will be responsible for providing information on the music preferences of their loved one unable to self-report, as well as answering questions on the POMI acceptability.

Nursing Staff

A total of 12 members of nursing staff involved in a participating patient's bed turning procedure will be recruited to answer questions on the acceptability of the POMI from their perspective.

Randomization

For the equal allocation of both groups, 24 opaque envelopes were prepared in advance by an independent member of the research team, with the use of a digitally generated list [30]. Once patients or their representatives consent to participate and agree to randomization, patient participants are categorized as either able to self-report or unable to self-report, producing 2 strata. Within each stratum, patients are randomized to either sequence 1 or sequence 2, following a permuted block randomization to ensure balance within each stratum. A block size of 4 was used (3 blocks per stratum) for a sample size of 24 ICU adult patient participants (in each block, 2 patient participants will be assigned to sequence 1 and 2 patient participants will be assigned to sequence 2, and the ordering will be random).

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Patient-Oriented Music Intervention

Overview

The brief name given to this intervention is POMI (patient-oriented music intervention). In POMI, music is delivered to adult patients either via headphones (Bose, QuietComfort 35) or by a music pillow (MusiCure, hospital grade). Adult patients admitted to the ICU and able to self-report can choose the mode of delivery based on their personal preference. Adult patients admitted to the ICU and unable to self-report are given the music pillow. For patients able to self-report, individualized music playlists are created based on the patient's music preferences. For patients unable to self-report, a family member is asked about the patient's music preferences. Questions about music preferences include music genre, track title, artist name, instrumentalness, acousticness, energy, and valence, as defined by the streaming service Spotify.

Playlist Creation

The personalized music playlist is generated prior to the POMI period for each patient participant. To determine the participant's music preferences, the following questions are asked, based on possible recommendations through the Spotify Application Programming Interface [31]:

1. Is there any music genre that you would like to listen to?
2. Is there any specific song title that you would like to listen to?
3. Is there any music artist that you would like to listen to?
4. Would you like to hear music that is more instrumental, more vocal, or do you have no preference?
5. Would you like to hear music that is more acoustic, more electric, or do you have no preference?
6. Would you like to hear music that is more calming, more energetic, or do you have no preference?
7. Would you like to hear music that is more cheerful, more melancholic, or do you have no preference?
8. Would you like to hear music that is more popular, less popular, or do you have no preference?
9. Would you like to hear music that is recorded in studio, do you prefer live recordings of music, or do you have no preference?

Any or all the questions can be skipped as preferred if at least 1 answer is given to questions 1, 2, or 3. Definitions of any of the music attributes (eg, electric and energetic) are provided if necessary and are available on the web-based tool.

The reported preferences are entered into a POMI web-based tool (Figure 2) to generate a personalized music playlist on Spotify, with a tempo restriction of 60-80 bpm as recommended [11]. Music is then played for 20 to 30 minutes via a smart device (iPad, 8th generation).

At all times, patients can control the music (eg, skip a song or stop the music, either briefly or permanently) by accessing the iPad themselves or communicating with the student researcher. Patients unable to self-report are continually monitored by the student researcher while the music is playing so that any nonverbal reaction to the music, indicating such dislike of the music, would lead the student researcher to stop the music immediately.

Control Intervention

The CTL consists of providing a 20-30–minute period without music either while wearing headphones (Bose, QuietComfort 35) or with the head resting on a music pillow (MusiCure, hospital-grade), which is consistent with the mode of delivery for the POMI. Adult patients admitted to the ICU and able to self-report can choose 1 of the 2 modes of delivery. Patients unable to self-report are given the music pillow.

Washout Period

To allow for any pain-reducing effect of the POMI to dissipate before the CTL, a washout period of at least 4 hours is scheduled between both intervention periods, based on previous data on the duration of the analgesic effect of music on pain [32].

Video Recordings

Video will be recorded for the duration of the intervention period and at each pain assessment time point. These video recordings will be used to have an independent member of the research team evaluate: (1) the Critical-Care Pain Observation Tool (CPOT) scores for each patient participant (to ensure blinding of the research team member interrater to sequence allocation) and (2) the intervention fidelity.

Outcomes

Acceptability

The acceptability questionnaire is adapted from the treatment acceptability and preferences (TAP) validated measure [33]. The TAP is comprised of 4 items: suitability, appropriateness, effectiveness, and willingness to comply, each of which is rated on a 5-point scale ranging from 0 (not at all) to 4 (very much) with higher scores indicating greater acceptability [33]. The total scale score is then obtained by calculating the mean of all the items' scores. The TAP was shown to have a Cronbach α coefficient greater than .75, supporting good internal consistency [34], and it has been used to evaluate a variety of interventions in different acute and postsurgical care settings [35-37]. The TAP can capture "the complex nature of [participants'] preferences" and yet being simple enough for use in the ICU setting [33]. As recommended [38], 1 item has been added to the questionnaire to determine the risks of side effects of the POMI, an additional important aspect in assessing the acceptability of the intervention.

Feasibility of Intervention

The items for the assessment of intervention feasibility include (1) time spent (in minutes) creating the individualized playlist; (2) the presence or absence of any issue with headphone or pillow use; (3) the presence or absence of any issue with music delivery; (4) the presence or absence of skipping one or more songs from the generated playlist; (5) the presence or absence of any environmental noise (eg, alarms and voices) during intervention delivery; (6) the presence or absence of any POMI interruptions; (7) whether the patient participant received the full duration of the POMI; (8) the dose (duration in minutes) of

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the music delivered; (9) the characteristics of the music delivered (eg, music genres).

Additionally, as part of the feasibility of the intervention, the fidelity of the intervention will be assessed based on specific criteria [39] and will include meeting with participants to discuss music preferences, producing a personalized playlist, and playing music once at least for 20 minutes. Any issues with the delivery of the POMI will also be recorded.

Feasibility of Research Methods

The items for the assessment of the feasibility of research methods, based on the CONSORT guidelines for pilot and feasibility RCTs [40,41], include the number of patients screened, number of eligible patients, number of participants recruited, number of participants randomized, and number of participants included in the analysis.

Preliminary Efficacy of POMI on Acute Pain

Pain will be assessed at 4 different timepoints for each intervention period: before the intervention, immediately after the intervention, during the bed turning procedure, and 30 minutes after the bed turning procedure (Figure 1, T_0-T_3). Pain assessments will be performed using validated tools as recommended in ICU clinical practice guidelines [1]. For all patient participants, the CPOT will be used because it is one of the most valid behavioral scales for assessing pain in critically ill adults [42]. In addition to the CPOT, patient participants able to self-report will be asked to rate their pain intensity using the 0-10 Faces Pain Thermometer [43] and their pain distress on a 0-10 NRS [44,45].

Data Analysis

Overview

A data bank will be created with the SPSS software (version 27.0; IBM Corp) [46], where the collected data on acceptability, feasibility, and preliminary efficacy will be entered. All the statistical analyses described below will be performed using SPSS.

Acceptability of the Intervention

The acceptability of the POMI will be determined using the TAP questionnaire. The frequencies, medians, and IQRs will be calculated for each item as well as for the total score, which will be calculated by taking the median, out of 4, of all items. The first 4 items (suitability, appropriateness, perceived effectiveness, and willingness to comply) will be scored in sequence (with 0 being the least favorable and 4 being the most favorable), whereas the last item (risks or side effects) will be scored in reverse (with 4 being the least favorable and 0 being the most favorable), as it is a negatively worded question. Any notes or comments added to the ratings will be compiled by category and presented descriptively to accompany the numerical ratings. A median above 2 out of 4 for the total score will be considered as an acceptable intervention, overall. An item median score above 2 out of 4 will be considered an acceptable attribute of the POMI. A median below 2 out of 4 will indicate the need to look more closely at the comments accompanying the ratings and modify the intervention to improve the acceptability of the POMI (eg, mode of delivery and dose). The acceptability of the POMI will be established via data triangulation from all study participants: patients, family members, and nursing staff [47].

Feasibility and Fidelity of Intervention

Descriptive statistics will be obtained to compute the frequencies for each of the intervention feasibility items. The POMI will be considered a feasible intervention if there are no issues in over 50% of the items for the assessment of the intervention feasibility (as listed above) for at least 80% of the patient participants in each group [48]. Regarding the fidelity of the intervention, descriptive data will be computed on the amount of time spent creating the music playlists (≤10 minutes), delivery of the overall POMI (use of headphones or pillow), as well as the amount of time the music will be listened to (once, for at least 20 minutes). The percentage of items completed on the fidelity checklist will also be computed in order to ensure that at least 80% of the intervention fidelity items will be delivered as planned, yet to allow for a certain amount of flexibility, if needed [48,49].

Feasibility of Research Methods

Descriptive statistics will be generated for each of the feasibility of research methods items. The screening and recruitment procedures will be described and include the number of patients screened, the proportion of eligible patients as well as the number of enrolled participants. If less than 50% of the potential patient participants are found to be eligible, considerations will be made to broaden the inclusion criteria in an eventual full-scale RCT [39]. Time to recruit will be considered adequate if 24 patient participants are enrolled within 6 months. All issues related to recruitment will be described and grouped into categories by the student researcher.

The retention rates will be calculated and expected to be above 80%. Reasons for participant withdrawal will be described, when known, and if retention rates are below 80%, strategies will be recommended to reduce attrition, based on the reasons for study withdrawal. If more than 10% of the participants (in each group) are found to have missing data, reasons for missing data will be described to inform how to reduce the amount of missing data in future research.

Preliminary Efficacy

Descriptive statistics will be computed for all outcomes (CPOT, pain intensity, and pain distress scores). The 95% CIs will be computed for each dependent variable at each time point.

Considering the small sample size for a pilot study, the potential efficacy of the POMI will be analyzed using nonparametric tests. For the dependent variables (CPOT, pain intensity, and pain distress scores), the Friedman test will be used to compare the scores at individual time points in each group separately. If the Friedman test is found to tend toward significant (P<.10), the Wilcoxon signed rank test will be used to compare 2 timepoints in pairs with a Bonferroni correction (.05 per number of tests) to locate the differences.

The preliminary efficacy findings will not be used to inform the decision to pursue a full-scale RCT. However, any tendency

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toward statistical significance (P<.10) or significant lower pain scores in the music period versus the control period will support that the intervention group might decrease pain over time, compared to the control group. A formal hypothesis of efficacy will need to be tested in a full-scale RCT, which will only be recommended if the POMI is deemed acceptable and feasible.

Ethics Approval

Ethics approval was submitted in July 2021 and approved in December 2021 (Project #2022-3005). Participation in this research project is voluntary and ongoing for all participants. Participants are free to refuse to participate and may withdraw from this research study at any time, without having to give a reason, and without any consequence to them now or in the future. The participant's decision not to participate in the study, or to withdraw from it, will have no impact on the quality of care and services to which they are otherwise entitled. Participants are free to refuse to answer any question and remain in the study. Participants are free to refuse to be video recorded.

For a patient who is unable to consent to participate in the study, a family member representative will provide the written consent on behalf of the patient. From this time and until the patient participant is discharged from the ICU, the student researcher will follow up on the ICU adult patients who were unable to consent to determine if they regain the ability to consent for themselves. In the case where a patient participant who was previously unable to consent regains the ability to consent at any time, before or after the intervention, the student researcher will present the research project and the information and consent form to allow the ICU adult patient to make an informed decision regarding their participation in the study.

The data collected from a participant as part of this study, excluding the video recordings, could be used for future research projects related to this study only with the participant's explicit permission. The results of the research study, excluding video recordings, may be presented at conferences, published in specialized journals or be the subject of scientific discussions, or be used for teaching purposes. No identifying information will be published in any way.

At any time, participants have the right to consult their study file in order to verify the information gathered and to have it corrected if necessary. All study data will be stored safely for 10 years, after which time they will be permanently destroyed by being either shredded or permanently deleted from the server.

Patients and families will be offered the hyperlink to their playlist as well as a paper version of the list of songs played as part of the study. Nursing staff participants will be offered a US $20 gift certificate to compensate for their time spent participating in the study.

Results

This study was registered to ClinicalTrials.gov (NCT05320224) in March 2022. Recruitment and data collection began in March 2022.

Discussion

Methodological Strengths

One strength of this study is the evaluation of the intervention acceptability from multiple sources: ICU patients, families, and nursing staff. This will allow us to gain access to the different perspectives of the various stakeholders and acquire a more comprehensive understanding of the overall acceptability of the intervention. The crossover design is another strength as it allows each patient participant to be their own control, thus reducing confounding factors that are usually present in between-subject designs [50,51]. Moreover, the crossover design will allow for patient participants able to self-report to share their preference between the POMI and the CTL because they will experience both interventions. Information about participant preference will add rich qualitative data beyond the quantitative comparison of preliminary efficacy [41,51]. The crossover design is relevant to use during procedures that are planned within a short period of time (eg, molar extractions at 2 different times) [50]. In addition to intervention comparisons and patient participant preferences, we will be able to determine the pain and distress differences individually (numerically) and compute the proportion of patient participants for whom the treatment was effective in reducing pain by more than 1 point on a 0-10 NRS, for example [51]. The crossover design will also enable us to describe whether any reduction in pain or distress was qualified as meaningful by the patient participant (for those able to self-report). These data could later contribute to the understanding of the minimally clinically significant difference in procedural pain in the adult ICU population [51]. Knowing that patient participants will receive both interventions as part of the crossover design may allow them to think more objectively about pain levels in each intervention period (thus minimizing the placebo effect) compared to if they participated in a parallel-group trial, in which the patient participants' hope to receive the intervention may influence their pain rating [50]. Finally, blinding patient participants unable to self-report will reduce the risk of bias based on these participants' expectations of music efficacy to reduce pain.

Methodological Limitations and Mitigation Strategies

The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials recommendations state that the use of a crossover trial at an earlier stage study, followed by confirmation of the results in a larger parallel-group study, is an efficient approach, as long as a washout period is carefully planned to minimize or avoid carryover effects [50]. To allow for any pain-reducing effect of the POMI to dissipate before the CTL, there will be a washout period of at least 4 hours between both intervention periods, based on previous data on the duration of the analgesic effect of music on pain [32]. Due to the sample size and to evaluate the time effect, the Friedman and Wilcoxon rank sum tests will be used when analyzing pain-related data for each subgroup [51]. To avoid response shifts due to the crossover design, baseline pain intensity will be measured for each intervention period (T_0 in Figure 1). Because blinding will be difficult with patient participants receiving both the POMI and the CTL, there is a risk of ascertainment bias for patient

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participants. To address this, patient participants able to self-report will be asked about their perception of how effective they think the music is compared to the CTL. To minimize possible interruptions and noise during intervention periods, the nurse responsible for the patient will be met to discuss and plan for the best time to start the intervention period, prior to a scheduled bed turn.

Due to the current context of the pandemic and this study being conducted in an ICU setting, it is possible that limited family visits and nursing staff shortages will impact recruitment from these populations. To mitigate these possible limitations, meeting families at the bedside will be coordinated with the nursing staff.

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Data Availability

The data sets generated during and analyzed during the current study are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

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Abbreviations

bpm: beats per minute
CPOT: Critical-Care Pain Observation Tool
CTL: control intervention
ICU: intensive care unit
NRS: numeric rating scale
POMI: patient-oriented music intervention
RCT: randomized controlled trial
TAP: treatment acceptability and preferences

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Protocol

Clinical Assessment of Eye Movement Desensitization and Reprocessing in Memory Distress: Protocol for a Double-Blinded Randomized Controlled Trial

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Abstract

Background: Exposures to “traumatic” events are widespread and can cause posttraumatic stress disorder (PTSD). Cognitive behavioral therapy and eye movement desensitization and reprocessing (EMDR) are frequently used and validated behavioral PTSD treatments. Despite demonstrated effectiveness, highly upsetting memory reactions can be evoked, resulting in extensive distress and, sometimes, treatment dropout. In recent years, multiple treatment approaches have aimed at reducing such upsetting memory reactions to traumatic memories while therapeutic progress proceeds. One of these methods, the flash technique (FT), a modification of standard EMDR (S-EMDR), appears effective in distressing memory reduction. This study will examine FT-EMDR and S-EMDR efficacies when both methods are delivered via web-based video.

Objective: This study aims to assess the relative efficacy of (web-based) FT-EMDR versus S-EMDR in reducing the PTSD symptoms, anxieties, and depression associated with traumatic memories at postintervention and 1-month follow-up.

Methods: This double-blinded, web-based, 2-arm randomized controlled trial will employ self-report outcomes. A total of 90 participants will be identified from the web-based CloudResearch platform and randomly allocated to the experimental or comparison group. Inclusion criteria are as follows: (1) approved for engagement by the CloudResearch platform; (2) 25-60 years of age; (3) residing in Canada or the United States; (4) a recalled disturbing memory of an event >2 years ago that has not repeated and was moderately or more upsetting during occurrence; (5) memory moderately or more upsetting at baseline and not linked to an earlier memory that is equally or more than equally disturbing. Exclusion criteria are bipolar disorder, borderline personality disorder, obsessive-compulsive disorder, schizophrenia, substance abuse or addiction in the past 3 months, suicidal ideation, and suicide attempt in the past 6 months. Interventions include guided video instruction of full FT or guided video of EMDR. Outcome measures are as follows: Primary outcome is PTSD symptoms that are measured by the PTSD Checklist for DSM-5 (Diagnostic and Statistical Manual of Mental Disorders-5) at 1-month follow-up. Secondary outcomes are State Anxiety subscale of State-Trait Anxiety Inventory at baseline, postintervention, and 1-month follow-up; Trait Anxiety subscale of State-Trait Anxiety Inventory; depression (Patient Health Questionnaire-9); and Positive and Negative Affect Schedule measured at 1-month follow-up.

Results: If, at 1-month follow-up, the web-based FT-EMDR intervention is more effective in reducing PTSD symptoms (as measured by the PTSD Checklist for DSM-5) than EMDR, it may help reduce traumatic memory distress in multiple contexts.

Conclusions: This randomized controlled trial will advance current understandings of PTSD symptoms and interventions that target traumatic memory–related distress.

Trial Registration: ClinicalTrials.gov NCT05262127; https://clinicaltrials.gov/ct2/show/NCT05262127

(JMIR Res Protoc 2023;12:e38552) doi:10.2196/38552

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KEYWORDS

EMDR variants; eye movement desensitization reprocessing; flash technique-EMDR; posttraumatic stress disorder

Introduction

Posttraumatic stress disorder (PTSD) can occur after direct or indirect exposure to traumatic events with frequent symptoms of reexperiencing, avoidance, cognitive-mood alterations, and heightened arousal or reactivity [1]. Traumatic exposures are widespread [2-4], and a study of 2991 Canadian adults indicated that 76% of participants reported one or more traumatic exposures of the type that can lead to diagnosed PTSD [5]. The prevalence of diagnosed PTSD is ~3.9% worldwide and 10% in Canada (~3.7 million people) [5-7]. Disturbing memory retention can lead to diagnosable PTSD, while adversely impacting psychological and physiological well-being [8-10]. Innovative interventions that reduce memory-based disturbance can prevent PTSD diagnoses and improve current status.

Pharmacological PTSD treatments include antidepressants, sympatholytic drugs, antipsychotics, anticonvulsants, and benzodiazepines [11-13]. Despite the availability of these agents, their limited efficacy has motivated adjunctive behavioral interventions [14,15]. A meta-analysis of PTSD treatment indicated that psychological therapies were generally more effective than drug therapies in symptom reduction [14].

Several of the most prominent methods addressing "traumatic" memories are trauma-focused cognitive behavioral therapy, cognitive processing therapy, prolonged exposure, and eye movement desensitization and reprocessing (EMDR) [16-18]. Other exposure-based treatments designed for PTSD are narrative exposure therapy and written exposure therapy [19]. In traditional EMDR, patients follow the horizontal movement of the therapist's index finger while recalling details of the traumatic memory [20]. The attention devoted to finger movement during recall has been proposed to reduce the intensity and intrusiveness of memory disturbance [20-24]. EMDR is now widely supported as a treatment for PTSD and is being tested for other mental health conditions (eg, generalized anxiety disorders, addiction, and depression) [25,26].

The mechanisms by which EMDR delivers benefits are controversial [27-29] and differ substantially from those proposed for other psychological therapies [30-32]. The divergence maps onto a frequent limitation acknowledged in exposure approaches, namely, traumatic memory confrontation, can generate high arousal levels, emotional distress, dissociation, and treatment dropout [33,34]. The novel variant of EMDR for PTSD investigated in the proposed study, the flash technique-EMDR (FT-EMDR) [35,36], emphasizes, in combination with standard EMDR (S-EMDR) procedures, the use of a positive engaging focus (PEF), which is recalled and imagined while a right-hand-left-hand alternate knee tapping proceeds [35-38]. Although several explanations for the mechanisms mobilized by this method are proposed, their identification is secondary to our goal of assessing efficacy within a double-blinded randomized controlled trial (RCT) that compares S-EMDR with FT-EMDR. If the FT variant demonstrates greater efficacy, mechanism identification and measurement may proceed more clearly.

As FT is a novel EMDR variant, the related research is in its early stages. Nonetheless, our study will follow prior findings that suggest FT efficacy in reducing the distress associated with disturbing memories [35-38]. If efficacy is indicated, one or both approaches could be used in geographic areas that require more immediate treatment needs, such as when warfare or natural disasters evoke traumatic reactions that are more prevalent.

This study has following three objectives: (1) to evaluate whether web-based delivery of FT is more effective in reducing PTSD symptoms than web-based S-EMDR at 1-month follow-up measured by the PTSD Checklist for DSM-5 (Diagnostic and Statistical Manual of Mental Disorders-5) (PCL-5); (2) to assess whether web-based delivery of FT-EMDR is more effective in reducing state anxiety symptoms than S-EMDR at postintervention and 1-month follow-up; and (3) to evaluate whether web-based delivery of FT-EMDR is more effective in reducing depressive symptoms than S-EMDR at postintervention and 1-month follow-up.

Methods

Overview

Previous studies of FT-EMDR have indicated that guided in-person FT effectively reduces subjective units of distress caused by distressing memories. These studies were limited due to a lack of randomization and adequate control comparison. This study will be an assessor-blinded, 2-arm (experimental and control) randomized controlled trial, which minimizes placebo effects and implements an adequate sample size and psychometric measurement. This study is expected to have an overall duration of 3 months. The length of study for each participant will be 4 weeks. The recruitment period is estimated to last for 2 months.

Ethical Considerations

The study was approved by the Research and Ethics Board at York University (087/2020) and is registered with ClinicalTrials.gov (NCT05262127).

Informed Consent

After eligibility is confirmed by the investigator, web-based informed consent will be obtained from participants. Each participant will review approved informed consent documents where guaranteed privacy and confidentiality protections are specified, along with assurances that all study data will be anonymized and deidentified. Each participant is compensated US $17 for participation. Participants will be informed about the scientific benefits of the study; however, they are informed that their participation is voluntary, and they have the right to terminate their participation at any time. The signed form will be retained as part of the study records.

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Sample Size

Overview

With the assistance of the Institute for Social Research at York University, the sample size was calculated for a 3-way repeated measures ANOVA. Sample size calculation was conducted using G*Power 3.1.9.4. The options in G*Power 3.1.9.2 were as follows: (1) test family: "*F* test"; (2) statistical test: "ANOVA: Repeated measures, between factor interaction"; and (3) type of power analysis: "A priori: Compute required sample size–given α, power, and effect size." An a priori power analysis was completed using a moderate effect size (F=0.25), 0.8 power (1β error probability), and an α error probability at P<.05. G*Power 3.1.9.4 determined that a minimum sample size of 37 participants per group provides ample testing power. Considering a 20% (n=7.4) oversampling to account for potential participant dropout and experimental error, a proposed minimum sample size of 44 per group is deemed adequate to detect within-group and between-group differences based on a repeated measures design.

Inclusion Criteria

Participants must pass the CloudResearch platform's standardized assessment of *attention*, *engagement*, and *language comprehension* for study participation [39]. Language comprehension and engagement are assessed by identifying synonyms, reading articles, and answering comprehension questions. Additional attentional competencies are assessed by evaluating factual correctness in answers to demographic questions (eg, "I work 28 hours in a typical workday"). In addition, the CloudResearch platform screening is based on a recorded history of providing high-quality data in prior study participation.

In the investigator-based criteria, participants must (1) be between 25 and 60 years of age and maintain residence in the United States or Canada; (2) be able to identify a memory regarding an event that occurred more than 2 years ago and has not been since repeated; (3) identify the memory as moderately upsetting, or more than moderately upsetting, when it occurred; (4) clearly recall the identified memory; (5) find the memory to be still moderately upsetting, or more than moderately upsetting, when recalled; and (6) identify the memory as not tied to an earlier memory that is equally or more disturbing.

Since participants are exposed to only 1 brief session, processing a series of upsetting memories is unreasonable and potentially harmful. Hence, the inclusion of only a single distressing memory, which should be distant from the participation date, was carefully implemented to minimize emotional arousal.

Exclusion Criteria

Exclusion criteria are as follows: (1) individuals who disclose a past or present self-reported diagnosis of bipolar disorder, borderline personality disorder, obsessive-compulsive disorder, schizophrenia, or a substance abuse or addiction in the past 3 months; and (2) individuals who disclose having suicidal ideation or who have attempted suicide in the past 6 months prior to the study.

Recruitment Plan

Participants will be recruited from a web-based platform (CloudResearch) [40]. Potentially eligible participants will be prescreened and eligibility assessed. After eligibility screening, they will be invited to a Zoom meeting where the study investigator further explains the study procedures. If the participant is interested, written consent will be obtained prior to randomization. The investigator will perform electronic randomization, with study IDs blindly assigned to experimental and control group participants. Study ID information will be recorded on an excel sheet as well as on the SurveyMonkey platform. After a participant completes baseline questionnaires, blinded research assistants will play a taped version of the video assigned to the participant in accordance with the randomization plan.

The randomly assigned participants will proceed to watch a 15-minute guided video of either FT-EMDR (experimental condition) or S-EMDR (comparison condition) in a quiet environment. Assessments will take place at pre- and postintervention and 1-month follow-up.

A streaming recruitment method will be employed where the study description is made available on the internet (CloudResearch platform) for a duration of 15 minutes prior to a participation-designated interview time slot. This will enable potential participants to enter the study description link, read a description of the study format, and pass the eligibility criteria before proceeding further if interested in study participation.

The additional steps to "streaming recruitment" require specifying how many participants can access the experiment's Zoom link at a given time, up to a maximum of 15. When more than one subject uses the link to enter the Zoom waiting room, the researcher will allow the first participant to enter the Zoom study meeting, while the remaining waiting room occupants are thanked for their interest and prompted to sign off. Once 1 eligible participant enters the video interview, the Zoom meeting will be locked, and no additional participants can access or join.

Procedure

This study will require 2 contact commitments from participants during a 4-week period. The first interaction will include gaining consent, completing preintervention psychometric questionnaires, and then watching and engaging in the 15-minute either intervention or control video. Subsequently, participants will complete postintervention measures and are provided with a debriefing statement.

The second interaction will be a follow-up of intervention outcomes 1 month after the initial interaction. A SurveyMonkey link will be sent out to participants via the CloudResearch platform, which will include all primary and secondary outcome measures. Both participants and research assistants will be blinded to experimental and control conditions throughout the trial.

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Interventions

Experimental Group

After a participant consents and completes demographic and baseline psychometric questionnaires, a "blinded" research assistant will share the computer screen and play a taped video of FT-EMDR containing vocalized and viewable instructions by licensed EMDR practitioners. Participants will be asked to follow the instructions with their full attention in a distraction-free environment. Participants assigned to the experimental condition will be invited by the video instructor to perform the following additional tasks: (1) identify a traumatic memory and rate its disturbance on a numerical scale that extends from 0 (no disturbance at all) to 10 (most disturbing)—This is often referred to as the Subjective Units of Distress Scale (SUDS) [41]; (2) identify a PEF, which can include a person, vacation, pet, favorite activity, or favorite music that is immediately gratifying when recalled or is a reminder of a past gratifying experience; (3) rhythmically tap knees while thinking of the selected PEF; periodically, the video instructor will say the word "flash," prompting 4-6 rapid blinks of the eyes, simultaneously establishing the blink rhythm and duration; (4) continuously envision the proposed PEF after blinking; and (5) respond to periodic check-ins concerning changes in the memory experience.

At the end of the video, the instructor will ask participants to rate their target memory once again on the SUDS. The assigned research assistant will collect SUDS reports at baseline and postintervention.

The PEF is considered essential to the FT-EMDR approach component. Participants will be instructed to immerse themselves into their PEF while rhythmically tapping their knees; however, they will not be instructed to avoid and suppress their target memory. Conversely, participants will be encouraged to bring their attention back to their PEF once distracted by the target memory.

Comparison Group

Members of the comparison group will be exposed to a pretaped video following similar instructions by the same licensed EMDR practitioners as the experimental group. In a procedure that is identical to the experimental group, participants will be instructed to identify a traumatic event as a target memory. The concept of PEF, however, will not be mentioned, precluding any engagement with or use of it. Instructions will specify that participants should only focus on their traumatic memory and recall as many details as possible. The duration and rhythm of tapping and blinking are identical to what is done with the experimental group, and SUDS measurements are taken in a similar manner. The comparison group protocol will closely follow the S-EMDR format, where clients generate back-and-forth eye movements while focusing on vivid recalls of the traumatic event.

Outcome Measures

Primary Outcome

The primary outcome measure will be the PCL-5 [42]. It is a 20-item self-report instrument measuring the presence and severity of PTSD symptoms. Each item is rated on a 5-point Likert scale ranging from 0 (not at all) to 4 (extremely), indicating how much each symptom has bothered the respondent in the past month. Higher scores indicate more severe PTSD-like symptoms, and a score higher than 31-33 alerts to a possible PTSD diagnosis.

Secondary Outcomes

Four self-reported secondary outcome measures will be employed only at baseline and 1-month follow-up. All outcome measures will be carried out on the internet via SurveyMonkey links.

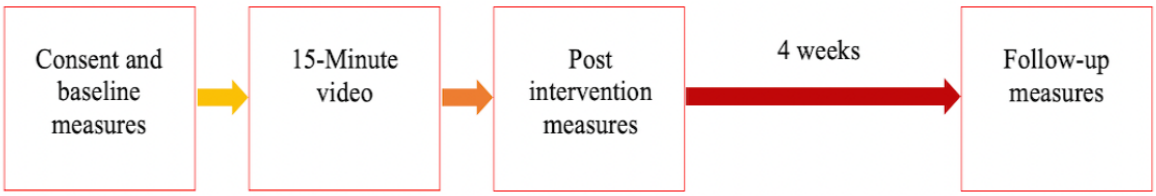
The State-Trait Anxiety Inventory (STAI) Form Y-1 (S-STAI, where S is state subscale) [43] is a 20-item self-report scale that measures subjective tensions, apprehension, nervousness, worries, and physiological arousal. The customary cutoff score for probable clinical levels of anxiety is 40 and above. Trait anxiety is measured by STAI Form Y-2 (T-STAI; trait subscale) [43], which is a 20-item self-report scale. The trait scale measures how people generally feel and it is the most widely used measures for assessing anxiety in clinical and experimental settings [44].

Patient Health Questionnaire-9 (PHQ-9) [45] is used to assess depression levels. This questionnaire has 9 items rated on a 5-point Likert scale from 0 (not at all) to 4 (nearly every day). Similarly, expected ranges for nonminimal, mild, moderate, moderately severe, and severe depression are 0-4, 5-9, 10-14, 15-19, and 20-27.

Positive and Negative Affect Schedule (PANAS) [46] is a 20-item questionnaire that measures positive (10 items) and negative (10 items) affects. Each item is scored with a 5-point Likert scale ranging from 1 (not at all) to 5 (very much). Higher scores on a positive scale translate to higher levels of positive affect, whereas lower scores on negative affect suggest low levels of negative affect. This reliable and valid self-report scale is brief, easily administered, highly internally consistent, and stable at appropriate levels over about as long as a 2-month time period [46]. Visual representation of the study procedures is shown in Figure 1.

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Figure 1. Visual representation of study procedure. Baseline measures: State Subscale-State-Trait Anxiety Inventory (S-STAI), Trait Subscale-STAI (T-STAI), Subjective Units of Distress Scale (SUDS), Posttraumatic Stress Disorder Checklist for DSM-5 (PCL-5), Patient Health Questionnaire-9 (PHQ-9), and Positive and Negative Affect Schedule (PANAS). Postintervention measures: S-STAI and SUDS. Follow-up outcome measures: S-STAI, T-STAI, PCL-5, PHQ-9, and PANAS.



Hypotheses

FT-EMDR (the experimental condition) will be significantly more effective than S-EMDR in reducing self-report scores on the PCL-5 at 1-month follow-up to the intervention than traditional EMDR.

FT-EMDR (the experimental condition) will be significantly more effective than S-EMDR in reducing self-report scores on the S-STAI at postintervention and 4-week follow-up than traditional EMDR.

FT-EMDR will be significantly more effective than S-EMDR in decreasing self-report scores on the PHQ-9 at 1-month follow-up.

Statistical Analyses

Statistical analysis will include the calculation of descriptive statistics for demographic and psychological characteristics at baseline, postintervention, and the follow-up period. Study outcomes will be presented as means and SDs for numeric variables and frequencies and percentages for categorical variables. In addition, potential between-group differences at baseline will be evaluated using *t* tests for numeric variables and chi-square tests of independence for categorical variables. Significance will be set at $P \leq .05$ and will be presented with *r* values for each questionnaire.

To evaluate the effects of the intervention on primary study outcome (PCL-5) and secondary outcomes (PHQ-9, S-STAI, Trait Subscale-State-Trait Anxiety Inventory, PANAS-Positive, and PANAS-Negative), linear mixed models (LMM) will be employed with an AR (1) covariance structure and random intercepts for each study participant to allow for both fixed and random effects. The LMM assumes that the outcome measure is normally distributed. All models will include adjustments for age and sex (among other psychological characteristics). Statistically significant group×time interactions, indicating between-group changes in outcomes, will be followed by simple main effect evaluation. Cohen d effect sizes for between-group and within-group comparisons will also be calculated according to procedures outlined in Lakens [47]. All analyses will be conducted using RStudio [48] and associated statistical packages, including nlme [49], psych [50], and ggplot2 [51].

Missing Data

Missing data in the context of this study occurs if study participants miss an assessment at the immediate postintervention or drop out prematurely before the 1-month follow-up assessment. Missing observations, in addition to specific reasons for dropout, will be monitored and presented as part of the associated study flow diagram. The LMM does not require imputations and uses a restricted maximum likelihood strategy to estimate study parameters. Restricted maximum likelihood produces unbiased estimates of variance and covariance variables.

Results

Our findings are scheduled for a full analysis, with expectations that analyses will be completed by July, 2023. Our intention is to publish results in peer-reviewed journals.

Discussion

In this study, 2 videotaped EMDR variants are compared for efficacy within a double-blinded RCT. They are conveyed by registered EMDR therapists in a web-based format and compared for efficacy using standard psychometric scales at postintervention and 1-month follow-up. The innovations addressed are (1) use of videotaped approaches conveyed through web-based contacts; and (2) different EMDR approaches, varying by insertion of a PEF (in FT-EMDR) and its absence (in S-EMDR). Aside from the inclusion or omission of the PEF, the approaches to EMDR employed in this study are nearly identical. It is important to note that a qualified clinical psychologist will be available while participants undergo either one of these interventions in case of psychological disturbance.

If study findings reveal the efficacy of these interventions, one or both innovations could be potentially useful when individuals with disturbing memories are distant geographically from areas where face-to-face encounters with EMDR therapists can be arranged. Some individuals may also find the typical professional fees too expensive. The web-based alternative is likely to be considerably less expensive. Given the divergences from routine EMDR services, these interventions might be considered stop-gap measures. Nonetheless, this trial provides an initial evaluation of these alternative (web-based) treatments.

Other investigators interested in PTSD treatment have been experimenting with web-based and video-based tools [52,53]. For example, an actuator- and web-based system based on EMDR principles was tested to reduce anxiety, distress, and negative cognitions [52]. This autonomous system used video, tactile, and audio *actuators* and an artificial intelligence "chatbot." In a pilot single-arm study of 31 subjects selected for moderate baseline scores on the Impact of Events Scale-Revised [54] and the STAI [43], subjects demonstrated significant reductions on the Impact of Events Scale-Revised

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and STAI following a single session of intervention. The system directed by the investigators recruited 24 participants and exposed them to a 1-session intervention, using a "Blind 2 Therapist" EMDR protocol as a videoconference psychotherapy format that included nondisclosure of the traumatic target memory [53]. This group also reported significant reductions on several self-report scales, notably a SUDS and Validity of Cognition Scale [21], designed to evaluate cognitive structure on emotional and somatic levels. Significant reductions in several self-report instruments were found at postintervention, 1-month, and 6-month follow-up.

The limitations of both studies are the nonblinded, posttreatment assessments that are invariably susceptible to placebo responding. In our study, the double-blinded RCT design aims to limit the placebo response. The data we derive must be regarded as preliminary and preparatory to follow-up studies that, optimally, would include several additional components: (1) a larger group of EMDR-trained therapists to convey interventions (so as to compare results across varying backgrounds, training, and gender); (2) comparisons between participants recruited using the internet (in a similar manner) versus participants recruited through clinics (to compare results regarding initial contact mode). Other acknowledged study limitations include the sole employment of self-report measures and the use of only postintervention and 1-month follow-up, rather than a more extensive series of longitudinal measures.

In conclusion, the study represents a step forward in evaluating web-based, video-taped interventions, which may prove useful where large populations are traumatically exposed (ie, through environmental disasters and warfare) and routine psychological therapy is difficult to deliver. Once widely available, a combination of EMDR variants with other technological tools could possibly broaden the opportunity for more accessible therapy.

Acknowledgments

This study will be a part of a master's thesis in Kinesiology and Health Sciences at York University. No specific funding was obtained for this investigation.

Data Availability

Following analysis, an anonymized data set will be made available to interested fellow investigators by the corresponding author upon reasonable request.

Conflicts of Interest

None declared.

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Abbreviations

DSM-5: Diagnostic and Statistical Manual of Mental Disorders-5
EMDR: eye movement desensitization and reprocessing
FT: flash technique
FT-EMDR: flash technique-eye movement desensitization and reprocessing
LMM: linear mixed models
PANAS: Positive and Negative Affect Schedule
PCL-5: PTSD Checklist for DSM-5
PEF: positive engaging focus
PHQ-9: Patient Health Questionnaire-9
PTSD: posttraumatic stress disorder
RCT: randomized controlled trial
S-EMDR: standard eye movement desensitization and reprocessing
S-STAI: State Subscale-State-Trait Anxiety Inventory
STAI: State-Trait Anxiety Inventory
SUDS: Subjective Units of Distress Scale

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Protocol

Feasibility, Usability, and Safety of ParaGym, an Intelligent Mobile Exercise App for Individuals With Paraplegia: Protocol for a Pilot Block-Randomized Controlled Trial

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Abstract

Background: Exercise is crucial for individuals with paraplegia to reduce the risk of secondary diseases and improve independence and quality of life. However, numerous barriers such as inadequate accessibility restrict their participation in exercise programs. Digital exercise apps can help overcome these barriers. Personalization is considered a crucial feature of mobile exercise apps, as people with paraplegia have individual requirements regarding exercise programs depending on their level of impairment. Despite the increasing popularity of mobile exercise apps, there are none available that target the individual needs of this cohort. The ParaGym mobile exercise app prototype was designed to automatically tailor exercise sessions to the individual needs of users with paraplegia.

Objective: This study aims to evaluate the feasibility, usability, safety, and preliminary effectiveness of the ParaGym mobile exercise app prototype.

Methods: This pilot block-randomized controlled feasibility trial will include 45 adult participants with paraplegia. Eligible participants will be block randomized to either the intervention or waitlist control group. The intervention group will perform a 6-week exercise program using the ParaGym mobile exercise app, comprising three 35-minute exercise sessions per week. The waitlist control group will continue their usual care and receive access to the app after study completion. Participants will record all exercise sessions conducted with the app as well as additional exercise sessions conducted during the study period using exercise diaries. The primary outcomes include feasibility, usability, and safety. Feasibility will be assessed through semistructured interviews, study adherence, and retention rates. Usability will be measured using the System Usability Scale. Safety will be determined by the occurrence of adverse events. Secondary outcomes include the effects of the intervention on peak exercise capacity (VO_2 peak); handgrip strength; independence, which will be measured using the Spinal Cord Independence Measure III (SCIM III); and health-related quality of life, which will be measured using the Short Form–36 Health Survey (SF-36).

Results: Recruitment commenced in November 2022. Overall, 12 participants were enrolled at the time of submission. Data collection commenced in January 2023, with completion expected in April 2023.

Conclusions: To the best of our knowledge, this is the first study to assess the feasibility, usability, and safety of an intelligent mobile exercise app for individuals with paraplegia. Thereafter, the app should be adapted according to the findings of this trial. Future trials with an updated version of the app should aim for a larger sample size, longer intervention duration, and more diverse target group. In the long term, a fully marketable version of the ParaGym app should be implemented. This would increase the

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access to personalized, independent, and evidence-based exercise training for this cohort and, in the future, other people who use wheelchairs.

Trial Registration: German Clinical Trials Register DRKS00030370; https://drks.de/search/de/trial/DRKS00030370

International Registered Report Identifier (IRRID): DERR1-10.2196/45652

(JMIR Res Protoc 2023;12:e45652) doi:10.2196/45652

KEYWORDS

spinal cord injury; mixed methods; exercise; fitness; home-based; algorithm; personalization; prototype; telemedicine; digital; mobile app; mobile phone

Introduction

Background

A high level of sedentary behavior is associated with an increased risk of noncommunicable diseases, such as type 2 diabetes, cardiovascular diseases, and cancer [1]. This especially affects people who depend on a wheelchair for mobility, such as those with a spinal cord injury (SCI) [2,3]. Individuals with SCI show lower physical activity levels than able-bodied individuals and individuals with other chronic diseases [3,4]. This results in a 2- to 4-fold increased risk of obesity, diabetes, and cardiovascular diseases [5]. To prevent comorbidities and secondary diseases resulting from a sedentary lifestyle, exercise is of fundamental importance for this cohort [2,6,7]. Regular exercise increases muscle strength and cardiovascular fitness [8-13], leading to greater independence [10,14], improved mobility [8,14], and higher quality of life [11,15]. Furthermore, individuals with SCI who are engaged in sports show substantially higher social integration [15-17] and fewer depressive symptoms [10,17] than those in the inactive comparison group.

For individuals with SCI, engaging in sports is complicated by multiple infrastructural (eg, inadequate accessibility to buildings), internal (eg, not knowing how to exercise), and monetary barriers [18-20]. Digital exercise platforms have the potential to overcome these barriers and promote exercise participation because they do not require transportation, offer a guided program addressing the needs of individuals with SCI, and may be cheaper than a gym membership or personal training [21]. Using a digital exercise platform has been shown to promote adherence to exercise guidelines in able-bodied individuals during the COVID-19 pandemic, when access to sports facilities was restricted [22]. It can be assumed that this is also applicable to individuals with SCI. However, despite the wide variety [23] and recent increasing popularity of mobile fitness apps [24-26], a mobile exercise app targeting the needs of people with paraplegia does not exist.

Only 2 studies have assessed the feasibility of exercise apps for individuals with SCI, the WHEELS mobile health app [27] and the Fisiofriend app [28], although neither of these is available on the mobile app market. People with SCI have individual requirements regarding exercise programs depending on the level of impairment of their trunk stability and leg function [2,29]. Therefore, the exercise programs provided by apps must be personalized [30]. The exercise programs delivered by these 2 apps can be individualized by the users themselves [27] or by a clinician [28], but untrained individuals may not have the expertise to create and tailor their own exercise programs. In addition, the requirement of support from a health care professional further restricts the user's independence.

To our knowledge, there is no mobile fitness app available that provides an exercise program for individuals with paraplegia that is automatically tailored to the user's requirements while the user is completely independent of health care professionals. A prototype of the ParaGym mobile exercise app was developed to enable people with paraplegia to have their own virtual personal fitness coach in addition to their usual care. The app uses an intelligent algorithm that automatically personalizes its exercise program to the user's needs, considering their physical capacity, fitness level, and exercise equipment.

Bizzarini et al [28] and Hoevenaars et al [27] showed that using a mobile app to promote physical activity in this cohort was feasible. However, there are no instances of conducting an exercise program tailored by an algorithm in this cohort. Therefore, a pilot study is needed to assess whether exercise using the new ParaGym mobile exercise app is feasible and safe for people with thoracic or lumbar SCI.

Aims of the Study

The primary aims of this trial are as follows:

- To qualitatively assess the feasibility of an app-based exercise program (ParaGym) tailored by an algorithm to the needs of people with paraplegia
- To investigate the usability of the ParaGym app prototype in terms of the app's design, information provided by the app, app's ease of use, satisfaction with the app, and app's functionality using the System Usability Scale (SUS)
- To assess the safety of this program by considering adverse events (AEs) and serious AEs (SAEs)

The secondary aim is to analyze the effects of a 6-week training intervention using the ParaGym mobile exercise app on peak exercise capacity, handgrip strength, independence, and health-related quality of life.

Methods

Study Schedule

The SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2013 statement was used to develop the content, quality, and completeness of this protocol [31]. A SPIRIT study schedule (Table 1) and checklist (Multimedia Appendix 1) are provided.

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Table 1. SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2013 study schedule.

	Study period			
	Enrollment (t_0)	Allocation (t_0)	Postallocation period	Postintervention measure (t_1)
Enrollment				
Eligibility	✓			
Informed consent	✓			
Medical screening	✓			
Allocation		✓		
Intervention				
App			✓	
Usual care			✓	
Assessment				
Participant characteristics				
Demographics		✓		
Lesion level		✓		
Lesion completeness		✓		
Time since injury		✓		
Anthropometrics		✓		
Feasibility				
Exercise diary			✓	
Adherence			✓	
Retention			✓	✓
Interview				✓
Usability				
System Usability Scale				✓
Safety				
Adverse events			✓	
Serious adverse events			✓	
Effectiveness				
VO_2 peak[a]		✓		✓
Maximal heart rate		✓		✓
Resting blood pressure		✓		✓
PO peak[b]		✓		✓
Borg RPE[c]		✓		✓
Handgrip strength		✓		✓
SCIM III[d]		✓		✓
SF-36[e]		✓		✓

[a]VO_2 peak: peak oxygen uptake.

[b]PO peak: peak power output.

[c]Borg RPE: Ratings of Perceived Exertion Scale.

[d]SCIM III: Spinal Cord Independence Measure III.

[e]SF-36: Short Form–36 Health Survey.

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Development of the ParaGym Mobile Exercise App Prototype

The development of the ParaGym mobile exercise app prototype is based on the Kernwerk mobile exercise app (Kernwerk GmbH), which was designed to improve general fitness in able-bodied individuals. The Kernwerk app offers daily functional training sessions created by exercise scientists and uses an intelligent algorithm to individualize these sessions to the user's needs. The goal of the ParaGym project is to develop a prototype of an intelligent mobile exercise app for individuals with paraplegia.

The ParaGym mobile exercise app uses the same algorithm to provide an automatically individualized training program for people with paraplegia. The steps taken to develop the app are as follows. A user-centered approach was adopted to create the ParaGym exercise app for people with paraplegia. This included a survey among the target group and an extensive review of the literature [32] to identify both health-related and disability-related demands for an exercise program and a mobile fitness app. The results of the survey and the literature review revealed the following: (1) there is an urgent need for accessible and personalized exercise programs; (2) exercises with free weights are preferred over exercises with machines; (3) the exercise pool should contain stretching exercises and exercises to improve scapula coordination; (4) workouts should focus on the dorsal rather than the ventral shoulder musculature to avoid overuse injuries; and (5) users should be provided with comprehensive information about the potential risks of exercising (eg, increased risk of autonomic dysreflexia) and, if required, be cleared by a physician.

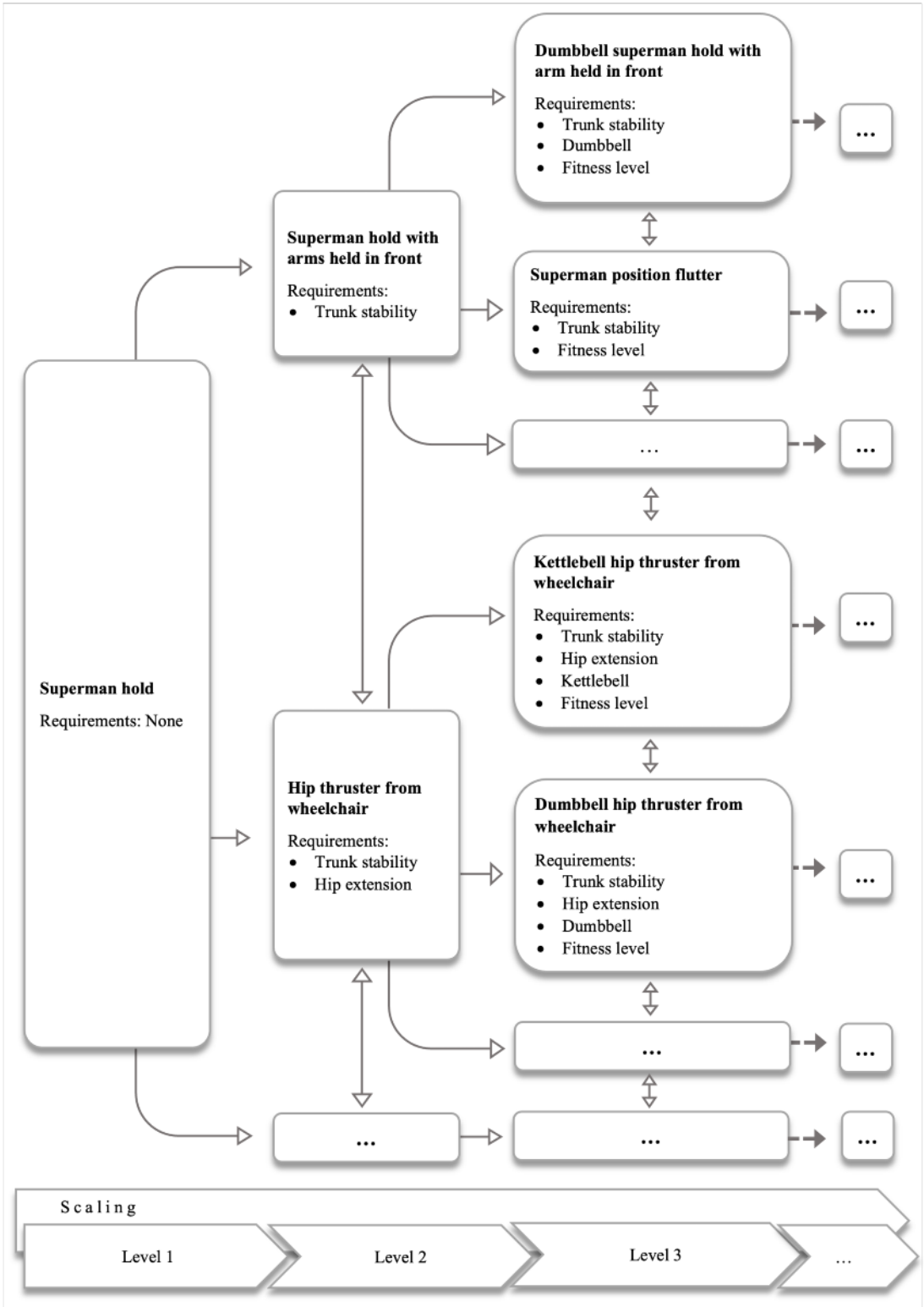
On the basis of the results of the survey and literature review, in cooperation with physiotherapists and sports scientists from different spinal cord centers, we developed a pool of 56 exercises to strengthen the core, upper, and lower body musculature; increase aerobic capacity; and improve wheelchair mobility and flexibility. Exercise videos and step-by-step descriptions were added for each exercise. Before integrating the exercises into the app, all exercises, including exercise videos and descriptions, were tested and evaluated in terms of feasibility, usability, and comprehensibility by 10 workshop participants with paraplegia [33]. Adjustments to all 3 components were made based on the feedback of the workshop participants and 3 physiotherapists. This resulted in a total of 67 exercises.

In the next step, further attributes were added for each exercise, specifying the required equipment (eg, dumbbells), required environmental conditions (eg, sufficient space for wheeling), difficulty level ranging from 1 (very easy, no specific requirements) to 150 (very difficult), and required physical capacity (eg, the extent of core stability and articular movements, such as "hip flexion" or knee extension). In addition, similar exercises were linked to each other. The linkage of the exercises and attributes results in an exercise scaling tree (Figure 1). All these factors are considered by the algorithm so that if 1 attribute does not apply, a similar but more appropriate exercise will be suggested automatically. Whereas information on available training equipment and environmental conditions is provided by the users, the appropriate difficulty level is assessed by rating each exercise on a scale from 1 (too easy) to 7 (too hard) after each training session (Figure 2D). If an exercise is rated "too easy," a more advanced version of this exercise will be suggested to the user in the following training sessions. Thus, the intelligent algorithm can adjust the exercise level to the current fitness level of the user.

Training sessions focusing on different training goals (eg, improvement of wheelchair mobility or increase in strength) were created based on the exercise pool. The exercises and training sessions were then integrated into the mobile app.

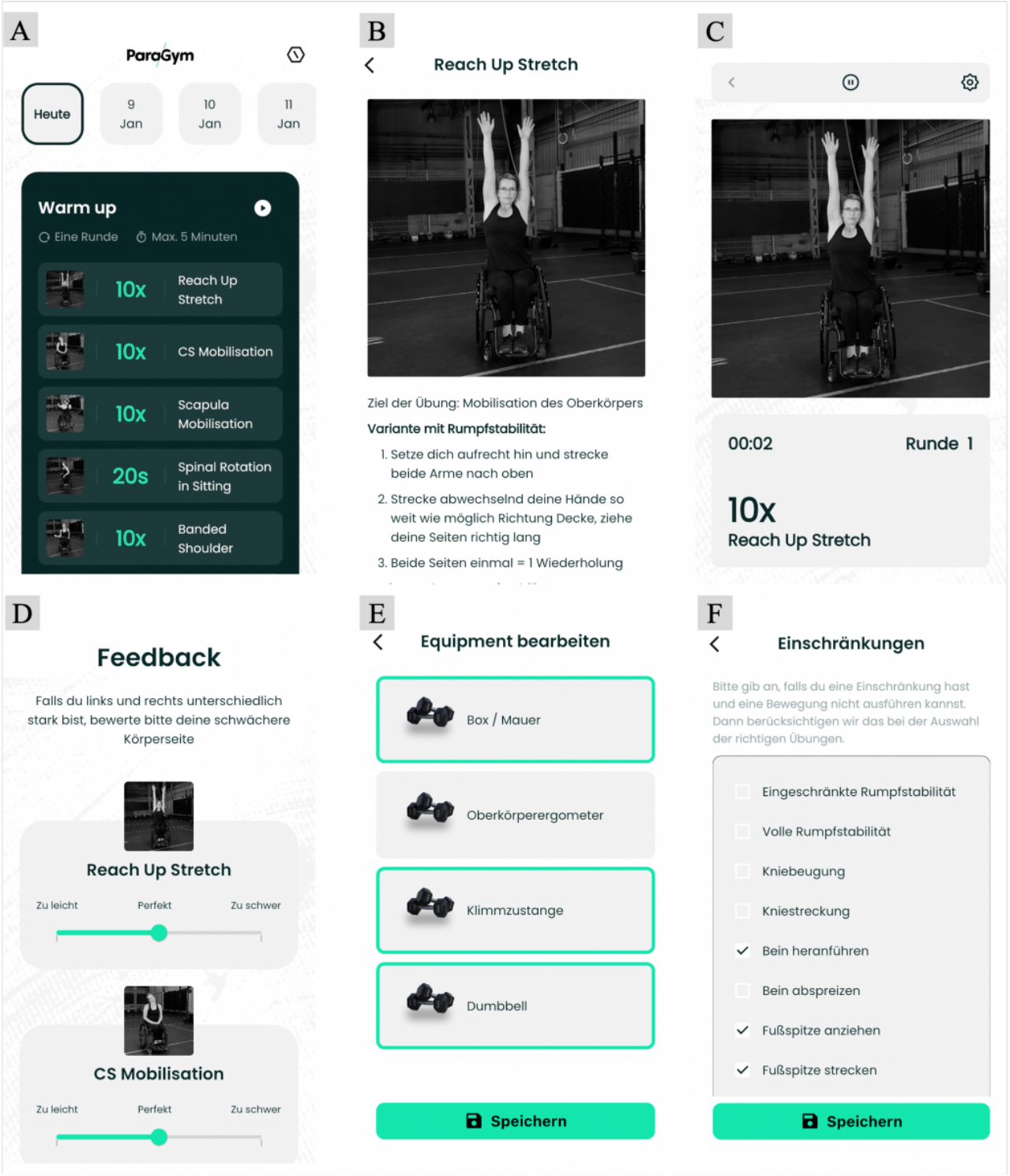
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Figure 1. Example of an exercise scaling tree for the exercise “Superman hold.”



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Figure 2. Overview of the ParaGym mobile exercise app prototype. (A) Summary of the daily training session and home screen. (B) Exercise video and description. (C) Screen during workout mode showing the first exercise. (D) Difficulty level rating. (E) Exercise equipment settings. (F) Physical capacity settings.



Description and Content of the ParaGym Mobile Exercise App Prototype

The ParaGym mobile exercise app prototype offers a daily training session that is automatically tailored to the individual requirements of people with paraplegia. Users must input information on their height, weight, age, gender, available exercise equipment (eg, dumbbells), and physical capacity (eg, impaired trunk stability and ability to extend the knee) when registering. The home screen of the app summarizes the daily training session (Figure 2A). Users can choose between different workouts by selecting another date on the timeline above the workout summary. Upon selecting one of the exercises within this summary, the exercise video and description will be displayed (Figure 2B). If one of the exercises selected for the workout is not appropriate, it can be excluded through the settings as described in the subsequent paragraph. To start a workout, users press “play.” Before starting the first exercise,

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users must confirm that they have read the general safety advice (eg, regarding bowel and bladder management) and specific advice regarding the execution of the exercise (eg, "sit up straight"). When starting the workout, a 10-second countdown will be shown before the first exercise appears on the display (Figure 2C). Users can skip to the next exercise by touching the screen. They can pause or discontinue the workout at any time.

On the home screen, users can tap on the hexagon symbol in the upper right corner to navigate to settings, where they can find a list of all exercises included. Upon selecting one of the exercises within the list, the users are given the option to block the exercise from being included in the workouts or view the exercise video and description. In addition, they can find a link to the project website, receive comprehensive safety information for exercising, and obtain contact information.

Users can make changes to their personal profile by selecting their name in the top row to access the profile settings. Within the section "Sportliches" (English: sporty), users can edit the information on their available exercise equipment (Figure 2E) and physical capacity (Figure 2F). Changes made to this information influence the exercise selection within the workouts.

Study Design

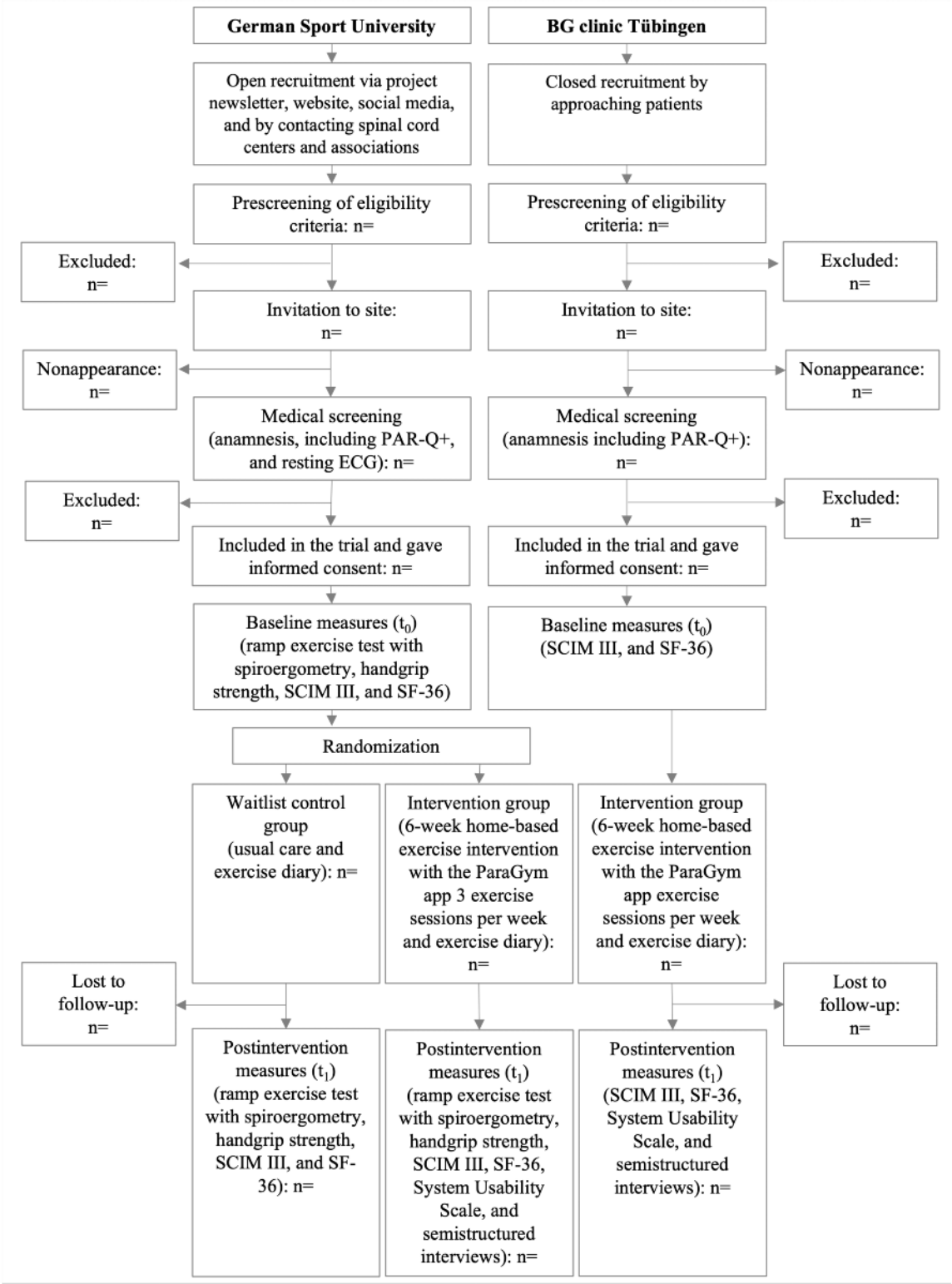
This pilot mixed methods block-randomized controlled feasibility trial with an allocation ratio of 1:1 for the intervention and waitlist control groups is conducted at the German Sport University Cologne (GSU), Germany. The trial was registered with the German Clinical Trials Register (DRKS00030370).

Participants will be recruited at the GSU and the SCI center at the BG (*Berufsgenossenschaft*; English: occupational insurance association) clinic Tübingen, Germany. Participants will be recruited at the GSU via the project newsletter, the project website, social media, and by contacting rehabilitation centers and spinal cord associations. The BG clinic in Tübingen will recruit among their patients.

Measurements will be conducted at baseline (t_0) and after the intervention (t_1; Table 1). The primary outcomes (feasibility, usability, and safety) will be assessed during the intervention and at t_1. The secondary outcomes (peak exercise capacity, handgrip strength, independence, and quality of life) will be assessed at t_0 and t_1. As data collection at the BG clinic Tübingen will focus on the primary outcomes and owing to limited capacity, the ramp exercise test for evaluating peak exercise capacity and handgrip strength test will be conducted only at the GSU and not at the BG clinic Tübingen. After randomization and group allocation, participants in the intervention group will be provided with the ParaGym mobile exercise app and uptake a 6-week home-based training intervention. The participants will be instructed to complete 3 training sessions per week. For this cohort, resistance training for at least 2 days a week is recommended [2,6]. As the training sessions delivered by the app comprise not only strength but also aerobic and flexibility exercises, we decided to provide training sessions for 3 days instead of 2. Eitivipart et al [34] recommend 3 sessions for a minimum duration of 20 minutes per week over at least 6 weeks to achieve substantial outcomes. The waitlist control group will proceed with their usual care and receive access to the mobile app once they have completed the trial. After the 6-week intervention, participants in the intervention group will be interviewed over the phone to assess feasibility and usability. Subsequently, both groups will return to the study site (t_1) for the SUS questionnaire and secondary outcome measures. The study design and planned participant flow are presented in Figure 3.

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Figure 3. Study design and planned participant flowchart. BG: Berufsgenossenschaft; ECG: electrocardiogram; PAR-Q+: The Physical Activity Readiness Questionnaire for Everyone; SCIM III: Spinal Cord Independence Measure III; SF-36: Short Form–36 Health Survey.



Participants

Eligibility Criteria

Participants are eligible for the study if they meet the following inclusion criteria: (1) chronic paraplegia (time since injury >1 year), (2) age between 18 and 67 years, (3) sufficient German language skills, (4) ability to provide informed consent, and (5) access to a smartphone. Participants will be excluded from the trial if they have any of the following conditions or diseases: (1) acute infection or inflammation (eg, urinary tract infection or pressure ulcers), (2) uncontrolled hypertension or diabetes, (3) manifest cardiovascular diseases, (4) psychiatric or mental conditions that compromise informed consent or may interfere with the study results (eg, major depression and psychotic disorders), (5) ongoing alcohol or substance abuse, and (6) other

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medical contraindications. In addition, they will be excluded if they are high-performance athletes (in the national team).

Potential participants will be enrolled based on the results of the medical screening using their medical records, a resting electrocardiogram, and the Physical Activity Readiness Questionnaire for Everyone (PAR-Q+) [35]. Because participants recruited by the BG clinic Tübingen will not perform exercise tests, a resting electrocardiogram is not required.

Randomization

Only the 30 participants recruited at the GSU will be block randomized, stratified by the level (high vs low paraplegia) and completeness (complete vs incomplete paraplegia) of the SCI with a block size of 4. This will be done using Excel (Microsoft Corp). The randomization code will be released after the participant has completed all baseline measures. The randomization list will be password protected. Only JB and AL, who conduct the randomization and allocation, will have access to the list. No randomization is required at the BG clinic Tübingen, as data collection at that site focuses on the primary outcomes.

Intervention

Following baseline measures, the intervention group will receive an introduction to the downloading process and a demonstration of the app [28,36-39]. They will also be provided with a user's manual and 2 resistance bands with a resistance of their choice (TheraBand, The Hygenic Corporation), one of which is for backup. The intervention group will perform a 6-week home-based exercise program delivered by the ParaGym mobile exercise app, comprising three 35-minute exercise sessions per week. The app offers a different workout every day, and participants get to choose the days on which they want to exercise. An exercise session consists of 4 parts: warm-up, 2 exercise parts, and cooldown. The first exercise part focuses on the correct execution of the exercises at a moderate intensity and prepares the musculature for the high-intensity second part. Exercise sessions aim at various training goals, such as stabilization of the shoulder girdle and improvement of wheelchair mobility. The waitlist control group will only maintain usual care and receive access to the mobile app after postintervention measurements.

Measures

Primary Outcomes

Overview

The primary outcomes are feasibility, usability, and safety. Six weeks after commencing the intervention, semistructured interviews will be conducted via phone to investigate feasibility and usability. An interview guide was conceptualized based on interview domains and topics in similar studies [27,36,39-43]. The following topics will be addressed: (1) overall experience, (2) ease of use, (3) app functionality, (4) perceived safety, (5) technical functionality, (6) communication, (7) perceived effects and usefulness, (8) adherence and motivation, and (9) recommendation. The interviews will be audio recorded with the consent of the participants.

Feasibility

During their first site visit, participants in both the intervention and waitlist control groups will be provided with an exercise diary (Multimedia Appendix 2). They will be asked to record the following: (1) any physical activities, including app exercise sessions, additional exercise sessions (eg, hand biking), and physical therapy; (2) the time spent performing the exercise; (3) the intensity of the exercise; and (4) any annotations concerning the exercise sessions as needed (eg, whether the session adapted by the algorithm was appropriate in terms of the choice of exercise and intensity). This will help obtain more information about the feasibility of the app in addition to the information provided in the retrospective interviews and help assess adherence to the program. Adherence rates in terms of completed sessions will also be measured based on app use data. Furthermore, retention rates will be measured by assessing dropout rates and reasons. As both adherence and retention are study outcomes, they should not be influenced by the investigators. Therefore, no measures will be taken to promote either of them. All outcome measures will be obtained regardless of adherence.

Usability

The SUS [44] is a 10-item Likert scale ranging from 1 ("strongly disagree") to 5 ("strongly agree") and is a common tool for investigating the usability of health-related mobile apps [27,36,38,39,41-43,45,46]. The score will be converted according to Brooke [44], so the total score will range from 0 to 100. The app will be considered usable if the overall SUS score is at least 70 [47].

Safety

The safety of the app-based exercise program will be determined based on the occurrence of intervention-related AEs and SAEs. Participants will be instructed to report any AEs or health-related interruption of the intervention within 24 hours. AEs and SAEs will be classified by the grade of severity based on the Spinal Adverse Events Severity System version 2 (SAVES-V2) scale [48] (Table 2) and expectance. The following AEs and SAEs can occur because of physical strain or are common complications after SCI and are, therefore, classified as expected AEs or SAEs: (1) autonomic dysreflexia, (2) pressure ulcers, and (3) shoulder pain [49].

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Table 2. Classification of adverse events (AEs) and serious adverse events (SAEs) based on the Spinal Adverse Events Severity System version 2 scale.

Severity of AE or SAE	Clinical impact
1	AE—no treatment
2	AE—outpatient treatment
3	SAE—inpatient treatment
4	SAE—life-threatening injury
5	SAE—death

Secondary Outcomes

Overview

The secondary outcome is the effect of the intervention on peak exercise capacity, handgrip strength, independence, and quality of life. Peak exercise capacity and strength parameters were chosen because they are important factors for improving quality of life [11,15] and independence [10,14]. Quality of life and independence were chosen because these parameters are integral to the overall rehabilitation goal of people with SCI [50]. Furthermore, the guidelines for the conduct of clinical trials for SCI [51] suggest using the Spinal Cord Independence Measure III (SCIM III) for functional assessments and the Short Form–36 Health Survey (SF-36) for quality-of-life assessments.

Ramp Exercise Test

Participants will perform a ramp exercise test on an arm crank ergometer (ergo-metrics 800s, Ergoline). The rotational axis of the ergometer will be set at shoulder level. The distance between the wheelchair and ergometer will be set such that there is a slight flexion in the elbow joint when the participant extends their arm. A 3-minute warm-up will be conducted at a cadence of 60 to 70 revolutions per minute and a resistance of 0 W. After the warm-up, the workload will be increased by 10 W per minute (1 W every 6 seconds) until volitional exertion is reached [52]. Volitional exertion is reached when the cadence drops below 50 revolutions per minute [52] or rate of perceived exertion exceeds 18 on the Borg scale ranging from 6 to 20 [53]. Heart rate (Polar H7 chest belt, Polar Electro Oy), workload, and respiratory gas exchange parameters (MetaMax 3B, Cortex) will be monitored throughout the exercise test [52]. Participants will be asked to rate their level of perceived exertion on the Borg Rate of Perceived Exertion scale upon the termination of the exercise test.

Handgrip Strength

The determination of handgrip strength using a handgrip dynamometer is a widely applied, simple, and reliable method for evaluating the efficacy of a treatment [54] and predicts functional independence [55]. An electronic hand dynamometer (Trailite TL-LSC1000, LiteXpress GmbH) will be used to determine maximal handgrip strength. Participants will be asked to grip the handle with maximal effort [56]. As warm-up trials decrease the variability of strength measurements [54], participants will be given 1 warm-up trial for each hand. A total of 3 attempts will be made for each hand for a duration of 3 seconds each at a 90-degrees elbow flexion and neutral wrist position [54,55,57]. A rest period of 60 seconds will be provided in between. The sum of the highest values for the right and left hands will be used to determine handgrip strength [55].

Independence

The SCIM III was developed to sensitively detect changes in function (eg, concerning respiration) in individuals with SCI [58] and changes in various activities of daily living (eg, bed-wheelchair transfers) [59]. It shows a very high interrater reliability (r=0.98; P<.001). The SCIM III is subdivided into 3 categories: (1) self-care, (2) respiration and sphincter management, and (3) mobility. The score ranges from 0 to 100. A higher score indicates greater independence. In this study, the German version of the SCIM III will be used [60].

Quality of Life

The SF-36 is the most commonly used questionnaire to assess quality of life in people with SCI and has been shown to be valid and reliable for this population [61]. The survey comprises 36 items across 8 domains. The score ranges from 0 to 100, with a higher score indicating a better quality of life [62]. As previously recommended [11,63,64], 2 items referring to "climbing stairs" were replaced with "going up stairs" (German: *Stufen überwinden*), and 3 items referring to "walking" were replaced with "going" (German: *fortbewegen*).

Data Management and Analyses

Data Management

Data will be entered into Microsoft Excel (version 2018) by one researcher and double-checked by another researcher before being analyzed using SPSS Statistics (version 29, IBM Corp). To ensure confidentiality, data will be recorded using the participants' study ID instead of their names. All data forms will be stored electronically and protected by a password in addition to being stored in paper form and secured in a locker in a room with restricted access. Only the authors of this manuscript will have access to the full data set. The principal investigator (JB) will monitor AEs. The data will be deleted upon participants' request.

Sample Size

The aim is to recruit a total of 45 participants between November 2022 and January 2023: 30 participants at the GSU and 15 participants at the BG clinic Tübingen. As this is a pilot trial, the sample size was based on previous studies with similar aims and methods [27,28] and recommendations for usability testing [65].

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Qualitative Analysis

The interview audio recordings will be transcribed verbatim and analyzed using a qualitative content analysis approach according to Mayring [66] using MAXQDA (version 22, VERBI). Categories arising from the interview guide will be determined a priori. Two researchers will identify codes for the first 3 interviews and assign them to a category deductively. An inductive approach will be used to create additional categories and subcategories. Disagreements between researchers during the categorization process will be discussed until a consensus is reached. The interviews will be revised upon considering possible changes in the category system. More interviews will be analyzed until data saturation is achieved [40,45].

Quantitative Analysis

Quantitative data analysis will be performed using SPSS. All data will be tested for normal distribution using the Shapiro-Wilk test. Study participant characteristics will be presented descriptively by calculating means and SDs for normally distributed variables. Median values and IQR will be calculated for skewed continuous variables, and absolute and relative frequencies will be calculated for nominal variables. Group differences at baseline will be calculated for independent samples using a 2-tailed *t* test, Mann-Whitney *U* test, or chi-square test depending on the distribution and level of measurement. At t_1, normally distributed continuous variables will be analyzed using a mixed analysis of variance model to test for significant effects for group and time. For skewed continuous variables, Wilcoxon and Mann-Whitney *U* tests will be conducted to test the differences between the groups and between t_0 and t_1. The significance level will be set at $P<.05$. Absolute and relative frequencies will be reported for adherence and retention.

Feasibility will be assumed if (1) at least 66% of the training sessions (equivalent to 2 out of 3 sessions per week) are completed [43] and (2) the retention rate is at least 75% [67]. Exercise diaries will be analyzed in terms of the frequency, duration, and intensity of the training sessions. Safety will be assessed by comparing the number of study-related AEs or SAEs in the intervention group with that in the waitlist control group [68].

Spearman correlations will be used to assess the association between performance and strength outcomes and SCIM III and SF-36 outcomes. Subgroup analyses might be conducted for lesion level (high vs low paraplegia) and age. Missing data will not be imputed.

Ethics Approval

The conduct of the trial was approved by the ethics committee of the GSU (ethics committee number 180/2021). Comprehensive study information is sent to potential study participants before their first site visit to allow sufficient time to fully read and understand all the information. Study information includes details on the following: (1) general information and background; (2) eligibility criteria; (3) study aims and procedures; (4) participants' rights, duties, and benefits; (5) potential risks; (6) data protection and management; (7) insurance; (8) funding; and (9) contact persons.

Participants will confirm that they have read, understood, and agreed to the terms of study participation by providing written informed consent before inclusion in the trial.

Precautions that will be taken to minimize the risk of cardiovascular events and AEs include the application of exclusion criteria, the conduct of a medical screening before enrollment, the distribution of a safety advice sheet, and integration of safety advice into the app.

To ensure confidentiality, we pseudonymized all participants' data (refer to the *Data Management* section). Participants will receive compensation for travel expenses and the interpretation of their test results upon study completion. Any amendments to the protocol will be documented, and substantial changes will need to be approved by the ethics committee.

Results

This trial is part of the FIT-IN^3 (ParaGym) project, which is funded by the German Federal Ministry of Education and Research in September 2020 (funding number 16SV8572). The project started in September 2020 and is expected to be completed by August 2023. Recruitment for the trial began on November 1, 2022. A total of 12 participants were enrolled in the trial at the time of the submission of this manuscript (Table 3). Data collection will begin in January 2023 and is expected to be completed by April 2023. The results will be published in accordance with the CONSORT (Consolidated Standards of Reporting Trials) 2010 statement for randomized pilot and feasibility trials [69] as well as the CONSORT-EHEALTH (Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth) statement [70].

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Table 3. Characteristics of the participants (n=12) enrolled in the study at the time of submission.

Characteristics	Intervention group (n=8)	Control group (n=4)
Gender, n (%)		
Women	4 (50)	2 (50)
Men	4 (50)	2 (50)
Age (years), median (IQR)	55 (37-62.5)	34 (18.5-56)
Lesion level, n (%)		
T1-T6[a]	3 (38)	0 (0)
T7-S5[b]	5 (62)	4 (100)
Lesion completeness, n (%)		
Motor complete (AIS[c] A-B)	6 (75)	2 (50)
Motor incomplete (AIS C-D)	2 (25)	2 (50)
Time since injury (years), median (IQR)	11 (4.5-26.5)	17 (8-24.5)
Experience with exercise apps, n (%)		
Yes	4 (50)	0 (0)
No	4 (50)	4 (100)

[a]T: thoracic vertebra.

[b]S: sacral vertebra.

[c]AIS: American Spinal Injury Association Impairment Scale.

Discussion

Principal Findings

To the best of our knowledge, this is the first trial to investigate the feasibility, usability, and safety of a 6-week exercise program delivered by an intelligent mobile exercise app for individuals with paraplegia using qualitative and quantitative measures. As secondary outcomes, the preliminary effects of this program on peak exercise capacity, handgrip strength, independence, and quality of life will be assessed. As the app is currently at a prototype stage, technical issues compromising feasibility and usability might occur. Both the semistructured interviews and exercise diaries will provide detailed insights into the users' experience with the app. This will help identify various aspects regarding the feasibility and usability of the exercise sessions, app's interface, and app's technical functionality, including intelligent personalization. Furthermore, users' practical suggestions for improvement will contribute to drawing practical implications. These could include the following: (1) further adapting the app to meet the needs of the target group; (2) fixing technical issues; (3) improving the ease of use, (4) improving the design, intensity, and duration of the exercise sessions; and (5) improving the overall satisfaction with the app. Before integrating the exercises into the app, all exercises, including the exercise videos and descriptions, were tested and evaluated in terms of feasibility, usability, and comprehensibility by 10 workshop participants with paraplegia. Therefore, we expect these exercises to be feasible and usable. The program is expected to be safe, as a very low incidence of AEs has been reported during exercise trials with this cohort [49,71].

Similar mobile apps for promoting a healthy lifestyle in people with SCI have been shown to be feasible [27,28]. However, these apps were not declared to be at a prototype stage. In contrast to these already existing mobile apps, the ParaGym mobile exercise app delivers individualized training sessions without the need for exercise selection by the users or health care professionals. Thus, training sessions can be performed independently by people without specific knowledge of training and exercise. In fact, the most frequently mentioned suggestion for improvement of the WHEELS app [27] was related to personalization and better tailoring to the user's needs and functional capabilities.

This trial will provide preliminary insights into the potential effects of the intervention on peak exercise capacity, handgrip strength, independence, and quality of life. Integrated exercises were designed to be appropriate for a beginner's fitness level, so they will be feasible for most participants.

Strengths and Limitations

Using the SPIRIT 13 Guidelines [31,72] for reporting the planned trial and the SCI trial guidelines [51,73] for designing as well as randomizing and controlling the trial improves its strength. In addition, the GSU cooperates with the BG clinic Tübingen to reach a larger sample size. Another strength is the compatibility of the app with various operating systems such as iOS (Apple Inc) and Android. However, smartphones should not be older than approximately 5 years to guarantee absolute functionality.

The ParaGym mobile app is currently at a prototype stage. Therefore, only basic functions and features are currently included. This could impact the variety of exercises, especially for users with severe impairments, which may decrease their motivation to use the app. The conclusiveness and generalizability of the results will be limited owing to the small

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sample size. In addition, only healthy adults with paraplegia were included in the study. Therefore, many individuals will be excluded from the study. Generalizability is also limited because the prevalence of cardiovascular diseases is high in individuals with SCI [74,75]. In addition, not restricting additional sports activities may have a major impact on the postintervention measurement results. Moreover, selecting exercises that are mainly suitable for beginners may compromise the effectiveness for intermediate users. Finally, all exercises will be performed using body weight or a resistance band, which will limit the user's opportunity to increase intensity compared with using additional weights.

Conclusions and Implications

By using both qualitative and quantitative measures, the results of this trial will generate a comprehensive understanding of the limitations and strengths of the ParaGym mobile exercise app as well as possible solutions to address the limitations. In the next step, in addition to fixing technical issues, the app should be adapted according to the findings of this study. This could include the expansion of the exercise pool and the addition of more equipment to increase variability and meet the needs of more advanced users. Hence, this could lead to an increased intensity of exercise sessions, which might result in greater effectiveness. Furthermore, the app interface might need to be adjusted to improve the ease of use. Finally, users may desire more features, such as the opportunity to design individual workouts or the integration of gamification to visualize the training process and promote adherence.

This pilot study will provide important results that need to be considered in the planning of future trials with an updated version of the app, which would aim for a larger sample size, longer intervention duration, and more diverse target group. As other individuals who use wheelchairs may also benefit from using the app, a requirement analysis addressing a broader target group should be conducted. Subsequently, a full-scale multicenter trial [73] including a broader target group, for example, people with acute SCI, tetraplegia, or other impairments, should be undertaken. In addition, by solely including healthy adults with SCI, a large proportion of the population was excluded. The prevalence of secondary diseases, such as cardiovascular diseases, is higher in individuals with SCI than in able-bodied people [74,75]. Therefore, investigators of future trials should consider including individuals with secondary diseases to assess the safety of the intervention for this group as well. Finally, future trials should include follow-up measures to investigate long-term motivation and adherence. In the long term, a fully marketable version of the ParaGym app should be implemented to make it publicly accessible.

An additional application of the ParaGym app could be its incorporation into workplace health programs, offering an exercise program for individuals who use wheelchairs and individuals with high levels of sedentary time at work.

A feasible, usable, and safe intelligent exercise app would increase access to personalized, independent, and evidence-based exercise training for this cohort and, in the future, for other individuals who use wheelchairs.

Acknowledgments

This trial is part of the FIT-IN^3 (ParaGym) project, which is funded by the German Federal Ministry of Education and Research in September 2020 (funding number 16SV8572). The trial design and conduct are entirely independent of the funding party.

Data Availability

The results of the trial will be published with open access in international journals after study completion. Additional anonymized information is available from the corresponding author upon request.

Authors' Contributions

JB is acting as a trial sponsor, taking responsibility for the conception and implementation of the trial; data management, analysis, interpretation; and reporting of results. The sponsor's contact information is consistent with that of the corresponding author. JB, AL, HGP, and CP conceived the study design and methodology. JB, AL, RM, and AB are responsible for recruitment and will implement the study. Data will be collected and assembled by JB, AL, and RM. Statistical analysis and data interpretation will be conducted by JB and AL with support from CP. JB drafted the first manuscript. All authors contributed to editing and critically revising the study protocol and approved the final version. All authors agree to be accountable for all aspects of this work.

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2013 checklist.
[PDF File (Adobe PDF File), 131 KB - resprot_v12i1e45652_app1.pdf]

Multimedia Appendix 2
Exercise diary.

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[PDF File (Adobe PDF File), 170 KB - resprot_v12i1e45652_app2.pdf]

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Abbreviations

AE: adverse event
BG: Berufsgenossenschaft
CONSORT: Consolidated Standards of Reporting Trials
CONSORT-EHEALTH: Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth
GSU: German Sport University Cologne
PAR-Q+: Physical Activity Readiness Questionnaire for Everyone
SAE: serious adverse event
SAVES-V2: Spinal Adverse Events Severity System version 2
SCI: spinal cord injury
SCIM III: Spinal Cord Independence Measure III
SF-36: Short Form–36 Health Survey
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
SUS: System Usability Scale

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Protocol

Coping After Breast Cancer: Protocol for a Randomized Controlled Trial of Stress Management eHealth Interventions

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Abstract

Background: One-third or more of breast cancer survivors report stress and other psychological and physical complaints that can negatively impact their quality of life. Psychosocial stress management interventions, shown to mitigate the negative impact of these complaints, can now be delivered as accessible and convenient (for the patient and provider) eHealth interventions. In this randomized controlled trial (RCT), Coping After Breast Cancer (CABC), 2 modified versions of the stress management eHealth intervention program StressProffen were created: one with predominantly cognitive behavioral stress management content (StressProffen-cognitive behavioral therapy intervention [StressProffen-CBI]) and another with predominantly mindfulness-based stress management content (StressProffen-mindfulness-based intervention [StressProffen-MBI]).

Objective: This study aims to investigate the effects in breast cancer survivors of using StressProffen-CBI and StressProffen-MBI compared with a control group (treatment as usual).

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Methods: Women diagnosed with breast cancer (stage I-III, unequivocally human epidermal growth factor receptor 2–positive or estrogen receptor-negative tumors) or ductal carcinoma in situ (DCIS) aged 21-69 years who completed the Cancer Registry of Norway–initiated health survey on quality of life are invited to the CABC trial about 7 months after diagnosis. Women who give consent to participate are randomized (1:1:1) to either the StressProffen-CBI, StressProffen-MBI, or control group. Both StressProffen interventions consist of 10 modules of stress management content delivered through text, sound, video, and images. The primary outcome is between-group changes in perceived stress at 6 months, assessed with Cohen 10-item Perceived Stress Scale. The secondary outcomes comprise changes in quality of life, anxiety, depression, fatigue, sleep, neuropathy, coping, mindfulness, and work-related outcomes approximately 1, 2, and 3 years after diagnosis. Long-term effects of the interventions on work participation, comorbidities, relapse or new cancers, and mortality will be assessed using data from national health registries.

Results: Recruitment is scheduled from January 2021 to May 2023. The goal is to recruit 430 participants (100 in each group). As of April 14 2023, 428 participants have been enrolled.

Conclusions: The CABC trial is possibly the largest ongoing psychosocial eHealth RCT in patients with breast cancer. If 1 or both interventions prove to be effective in reducing stress and improving psychosocial and physical complains, the StressProffen eHealth interventions could be beneficial, inexpensive, and easily implementable tools for breast cancer survivors when coping with late effects after cancer and cancer treatments.

Trial Registration: Clinicaltrials.gov NCT04480203; https://clinicaltrials.gov/ct2/show/NCT04480203

International Registered Report Identifier (IRRID): DERR1-10.2196/47195

(JMIR Res Protoc 2023;12:e47195) doi:10.2196/47195

KEYWORDS

breast cancer; stress management; mindfulness; cognitive behavioral therapy; psychosocial; StressProffen; RCT; eHealth; digital; intervention

Introduction

Breast Cancer Treatment and Long-Term Complaints

Breast cancer survival rates largely depend on cancer subtype, stage, treatment, and age. The 5-year relative survival rate for individuals with early breast cancer is firmly increasing and has exceeded 90% in most Western countries due to advances in diagnostics and treatment [1,2]. In Norway, nationwide mammography screening programs combined with high breast cancer awareness have contributed to most patients being diagnosed with stage I with 100% 5-year survival rate [2].

Supportive therapies have improved and thus reduced the immediate side effects of adjuvant systemic therapies. Nonetheless, breast cancer diagnosis and treatment may still cause substantial psychosocial complaints (stress, distress, anxiety and depression), pain, fatigue [3,4], and several physical complaints that usually emerge during treatment and often persist over a longer term [5,6].

These complaints can affect the ability to manage thoughts, feelings, and behavior [7,8] and negatively impact the individual's perceived physical, mental, and social well-being, often assessed through measures of health-related quality of life [9-11]. A breast cancer diagnosis and therapy may also have persistent negative effects on work and increase the risk of both short-term sick leave [12-14] and long-term disability pension [15-24], thus resulting in a lower workforce participation years following the diagnosis [25]. With an increasing prevalence of cancer worldwide [26], interventions to improve quality of life for cancer survivors are therefore important [27].

Psychosocial Stress Management Interventions

Psychosocial stress management interventions have been shown to mitigate short- and long-term complaints following a cancer diagnosis and treatment [9,28,29]. This includes improvement of negative psychosocial impacts of breast cancer [30-32], reduction of stress and stress-related symptoms [31,33,34], anxiety [31], depression [10,31,35], fatigue [31,35-37], insomnia [37-39], and pain [34], as well as improvement in quality of life [9,37,40,41]. The prevalence of distress and the potential negative impact of unrecognized and untreated distress in patients with cancer are widely recognized [42], and so is the potential effectiveness of psychosocial interventions for stress and distress management [43].

Psychosocial stress management interventions typically include components of cognitive behavioral therapy (CBT) and mindfulness techniques, designed to teach patients strategies for managing stress [27,44]. The basis of CBT is understanding that cognitions mediate the relationship between life events and emotional reactions [45]. CBT strategies target unhelpful or maladaptive cognitions with various techniques and behavioral strategies to moderate emotional responses and unhelpful coping behavior [45]. CBT-based interventions (CBIs) often combine aspects such as cognitive restructuring, coping effectiveness training, assertiveness, and anger management skills with relaxation (eg, muscle relaxation and imagery) [46].

Mindfulness-based interventions (MBIs) aim to cultivate present-moment awareness coupled with attitudes of acceptance, nonjudging, and nonattachment, through both formal (eg, awareness of breathing, sitting, walking, body scan) and informal (eg, mindfulness in everyday life) mindfulness practices. MBIs are typically adapted from the Mindfulness-Based Stress Reduction program of Kabat-Zinn

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[31,47]. One such adaptation, mindfulness-based cancer recovery [29], is specifically designed for patients and survivors of cancer [48].

Although often used in combination, there are distinct theoretical and methodological differences between CBIs and MBIs for stress management. Although one of the core components in CBIs is to help modify "unhelpful" ways of thinking, MBIs fall within a group of "acceptance-based therapies" and focus on adopting a state of nonjudgmental awareness and acceptance of the present moment, without a specific intent to modify thoughts or behavior [49]. CBIs such as cognitive behavioral stress management interventions have been used extensively in studies with breast cancer survivors [9,10] with positive effects in both short and long term [9,10]. This includes a reduction in psychosocial and physical complaints and improvement of physical and mental quality of life [9], up to 15 years after the intervention [50]. MBIs have shown positive short-term effects on psychosocial and physical complaints and improvement in measures of quality of life [51-54], but the long-term effects are either inconclusive or have not been studied [37]. Furthermore, whether the effects of CBIs and MBIs on stress management are comparable is unknown, as no known direct comparison between the intervention types has been conducted.

The optimal window for when to deliver stress management interventions has not been established [55]. Many psychosocial interventions have been conducted short term following a breast cancer diagnosis as this represents an acute period of stress that may influence treatment response and relevant clinical outcomes. There have also been successful psychological interventions implemented after surgery, although not as frequently as after other types of treatment for breast cancer survivors [55].

e-Health Interventions

Although in-person face-to-face delivery of psychosocial stress management interventions has been the most common, technical innovations that have accelerated due to the COVID-19 pandemic have resulted in increased use of eHealth interventions in clinical practice [55]. There are advantages to developing eHealth versions of established stress management interventions that extend beyond an adaptation to the restrictions imposed by the pandemic. eHealth interventions are often less expensive to implement after the initial production costs, and are more accessible for people living in remote areas. These can also be more convenient for persons with movement restrictions or other reasons for not being able to see health care providers face-to-face [56]. Studies testing eHealth psychosocial stress management interventions have been considered acceptable and feasible for breast cancer survivors [56,57], with positive effects on quality of life in patients with cancer following diagnosis [58]. However, more research is needed [55], as the effects of psychosocial eHealth interventions, in general in cancer survivors, have been mixed and inconclusive [59-63]. Furthermore, there is a need for studies testing stress management eHealth interventions in larger samples, after the initial phase of medical treatment, and with longer follow-up than previous research [64].

The Coping After Breast Cancer (CABC) trial was designed to test the effect of 2 eHealth-based stress management interventions (CBI and MBI groups), in comparison to a treatment as usual (TAU) control condition, on improving psychosocial factors, physical complaints, and work-related outcomes in breast cancer survivors. With long-term follow-up on work participation, comorbidities, relapse or new cancers, and mortality, the trial addresses the overall aim of validating eHealth stress management interventions to facilitate future implementation.

Methods

Objective and Hypotheses

The overall objective of the CABC trial is to investigate the effects of using eHealth interventions with cognitive behavioral stress management content (CBI group) or mindfulness-based stress management content (MBI group) in breast cancer survivors compared with a TAU control group (TAU group).

Specific Hypotheses

- The CBI and MBI groups will achieve a statistically significant larger reduction in perceived stress after 6 months of access to the interventions (13 months after diagnosis) compared with the TAU control group (*primary outcome*).
- The CBI and MBI groups will achieve a significantly larger reduction in perceived stress, distress, fatigue, peripheral neuropathy, vaginal symptoms, and arthralgia and a significantly larger improvement in quality of life, mindfulness, sleep, coping, and work-related outcomes 13, 24, 35, and 36 months after diagnosis compared with the TAU control group (*secondary outcomes*).
- Additionally, exploratory analyses will be conducted to investigate the following:
  - characteristics of study responders and intervention completers versus nonresponders and noncompleters;
  - predictors of intervention effects;
  - potential differences in intervention effects between the CBI and MBI groups;
  - long-term consequences of the interventions related to work participation; and
  - long-term effects of the interventions on comorbidities, relapse or new cancers, and mortality.

Study Design and Setting

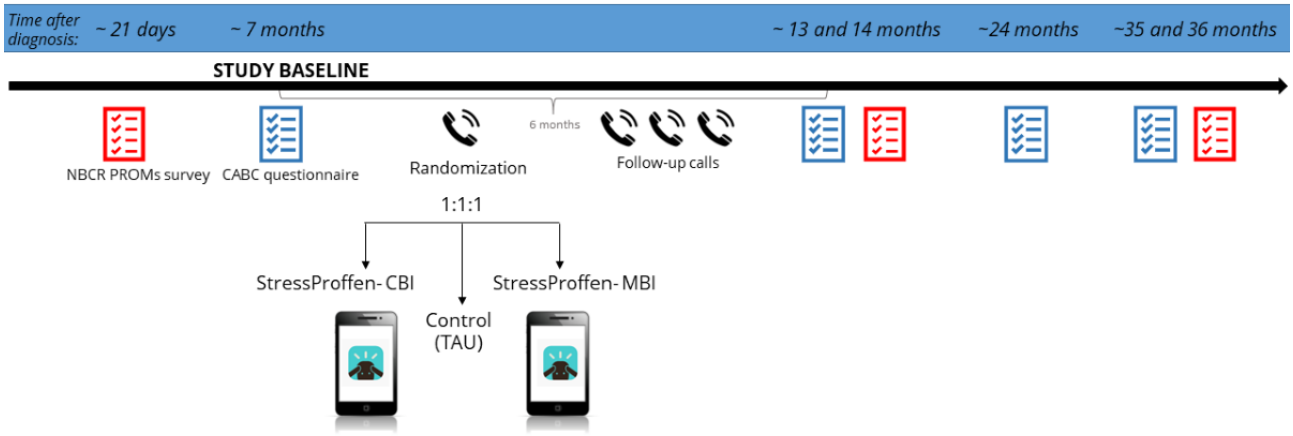
The CABC trial is a randomized controlled trial (RCT; ClinicalTrials.gov identifier NCT04480203) assessing the effects of 2 stress management eHealth interventions compared with TAU in breast cancer survivors. The trial is conducted at the Cancer Registry of Norway (CRN) at Oslo University Hospital. The eHealth interventions are delivered through the mobile app StressProffen [65], which was developed, and is managed, by a team led by 2 of the coauthors (LSN and EB) at the Department of Digital Health Research at Oslo University Hospital.

The study protocol of the CABC trial is presented according to the SPIRIT (Standard Protocol Items: Recommendations for

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Interventional Trials) initiative [66] (Multimedia Appendix 1). The study outline is shown in Figure 1 and described in further detail in the following sections.

Figure 1. Overview of milestones in the CABC RCT. Study baseline is approximately 7 months after breast cancer diagnosis. Eligible participants who have completed the CRN PROMs survey, consented to the CABC study, and completed baseline questionnaires are randomized to either the StressProffen-CBI, StressProffen-MBI or a control group (TAU). Recruitment is scheduled from January 2020 to May 2023. Pictures from colourbox.com and StressProffen. CRN PROMs survey: The Cancer Registry of Norway Patient Reported Outcome Measures; CABC: Coping After Breast Cancer; CBI: cognitive behavioral intervention; MBI: mindfulness-based intervention; NBCR: Norwegian Breast Cancer Registry; RCT: randomized controlled trial; TAU: treatment as usual.



Participants and Eligibility

The Cancer Registry of Norway

Study participants with incident breast cancer are identified and included from the CRN. The CRN has recorded incident cancer cases in Norway since 1952 with accurate and almost complete ascertainment of cases (99% complete on a minimum of diagnostic information on solid tumors [2]). The CRN hosts the Norwegian Breast Cancer Registry that has detailed information on breast cancer diagnoses extracted from pathology reports, and details on treatment including the type of breast and axillary surgery, radiotherapy, and systemic therapy. Nonetheless, as of 2020, the CRN also collects and stores data on patient-reported outcome measures (PROMs). The CRN PROMs survey is an ongoing, digital survey sent through the official Norwegian health portal Helsenorge [67] or an official digital mailbox (Digipost/eBox) to patients with breast cancer and age-matched controls approximately 21 days, 14 months, and 36 months following diagnosis. Currently, 88% of eligible patients with breast cancer are invited to this survey, and the response rates were 52% in 2020 and 49% in 2021 [68]. Specific data from the CRN PROMs survey will be included as outcomes in this study, and the survey content is therefore described further below.

CABC Trial Eligibility

Women who are aged between 21 and 69 years when diagnosed with subtypes of invasive breast cancer, International Classification of Diseases, 10th revision (ICD-10) code C50, or ductal carcinoma in situ (DCIS), ICD-10 code D05.9, in the period from 2020 to 2023, and who have completed the initial CRN PROMs survey are eligible for inclusion in the CABC trial, at about 7 months (6-9 months) after diagnosis. The timing was chosen to ensure that most patients have completed the first part of their treatment, and that details about the breast cancer subtype have been coded in the CRN.

See Textbox 1 for an overview of the inclusion criteria. Participants in the intervention groups must also have access to, and be able to use, a smartphone or a tablet. There are no restrictions regarding types of treatment, nor any geographical restrictions, given the digital nature of the intervention.

The upper age limit of 69 years was chosen to correspond with the upper age limit of the participants in the Norwegian breast screening program. To avoid overlap with 2 ongoing clinical trials in Norwegian patients with breast cancer (EMIT, ClinicalTrials.gov Identifier: NCT03904173 and OPTIMA [no registration number]), recruitment of the invasive cases in the CABC trial is restricted to those with stage I-III estrogen receptor (ER)–negative or human epidermal growth factor receptor 2 (HER2)–positive tumors, or a combination of ER+ and HER2–. This is typically about 15% of all breast cancer cases (unpublished data from the CRN during 2020-2021).

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Textbox 1. Inclusion and exclusion criteria for the Coping after Breast Cancer trial.

Inclusion criteria

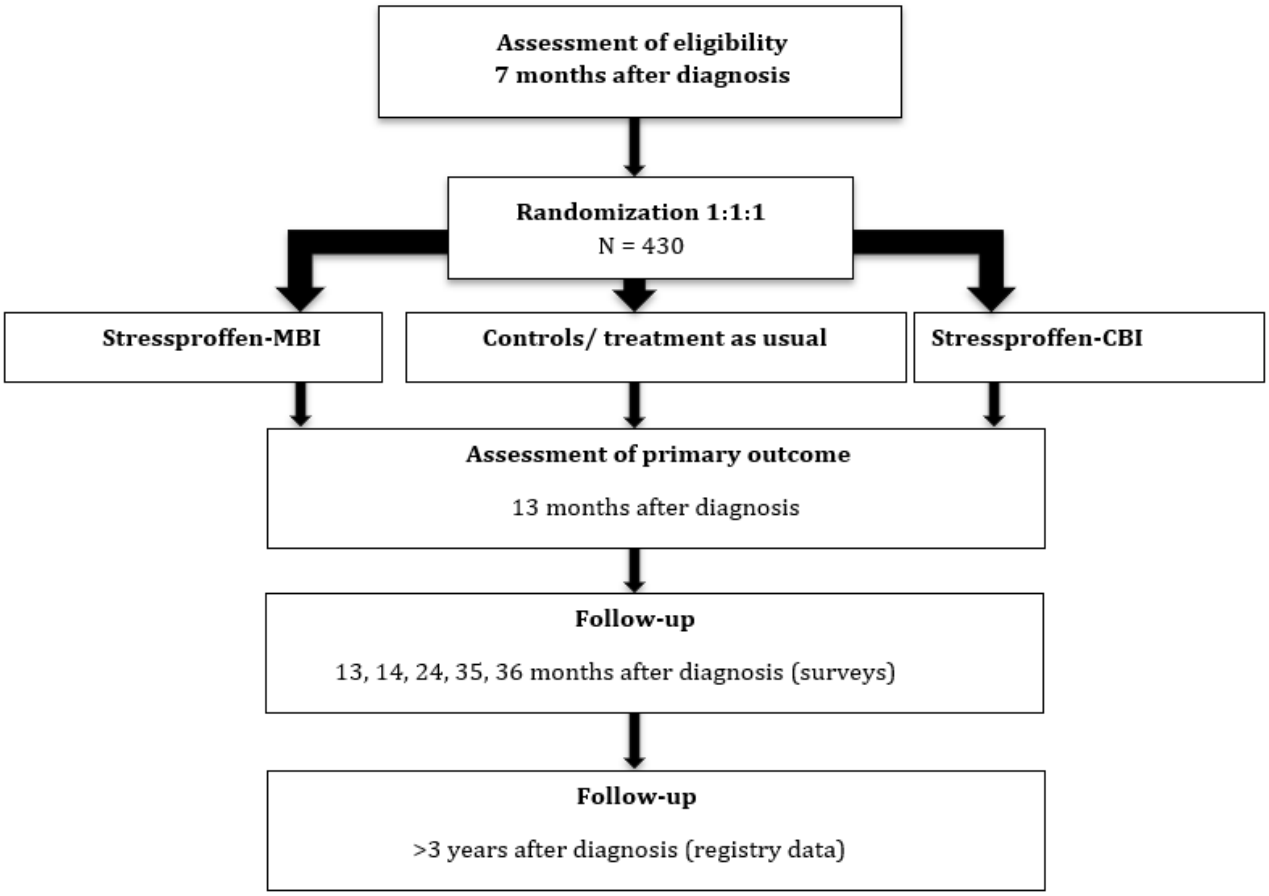
- Women;
- Incident: ductal carcinoma in situ or breast cancer stage I-III, unequivocally human epidermal growth factor receptor 2–positive or estrogen receptor–negative tumor(s);
- Age 21-69 years;
- Residing in Norway;
- Submitted the initial Cancer Registry of Norway patient-reported outcome measures (CRN PROMs) survey, which is sent 21 days after diagnosis. This also implies that they are fluent in Norwegian and are active users of the digital portal: Helsenorge [67] or have a digital mailbox.
- Submitted the initial Coping after Breast Cancer (CABC) survey, which is also sent 21 days after diagnosis. This also implies that they are fluent in Norwegian and are active users of the digital portal: Helsenorge or have a digital mailbox (that imply consent to participation).

CABC Trial Enrollment

Study recruitment is scheduled from January 2021 to May 2023 with patients diagnosed over the previous year. Participants are continually recruited at approximately 7 months after their breast cancer diagnosis.

Invitations are sent every week (except during holiday periods) along with the study-specific CABC survey. In total, 430 participants will be enrolled in the trial (Figure 2).

Figure 2. Flowchart of inclusion of study participants invited ≈7 months after diagnosis. CBI: cognitive behavioral intervention. MBI: mindfulness-based intervention.



Randomization

Once an eligible participant has submitted the CABC survey at baseline (that also implies consent to participate), the participant is allocated to 1 of the intervention groups or the control group in the ratio 1:1:1 (Figure 1). The randomization algorithm uses a variant of block randomization, with no stratification, where block sizes vary between 12, 18, 21, and 27. The output of the randomization algorithm for each participant is a string representing an access code to 1 of the 2 interventions (each intervention has a unique access code), or a string indicating that the participant was randomized to the control group. The access code is used to download the StressProffen program (an

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app). The randomization is performed in R studio version 1.2.1335 (The R Foundation for Statistical Computing).

Intervention identification is not possible from the access code, and participants in the 2 intervention groups are not informed to which of the intervention they have been assigned to. However, an informed participant may detect which group they are in by identifying content when using the assigned app. Hence the trial is single blinded.

After randomization, participants randomized to 1 of the intervention groups receive a letter containing information about the scheduled time for the first phone call. For participants randomized to the control group, the letter contains information about the timing of further follow-up surveys.

StressProffen Interventions

The interventions used in this trial are 2 modified versions of an evidence-based stress management eHealth intervention program (StressProffen) developed for cancer survivors [65,69-71]. For privacy reasons, there is, however, no mention of the word "cancer" in either intervention.

The original StressProffen program includes both CBT and mindfulness. It contains psychoeducational materials (eg, about stress, coping, social support, anger management, assertiveness, and health behaviors) and a variety of exercises, including exercises related to how to cope with challenging thoughts, feelings, and bodily states (eg, positive self-talk, diaphragmatic breathing, progressive muscle relaxation, guided imagery, mindfulness, and meditation) [65].

For the CABC trial, the project team modified the StressProffen program and developed 2 distinct stress management interventions: a CBI (StressProffen-CBI) and an MBI (StressProffen-MBI) (E. Børøsund et al, unpublished data, 2022).

Both interventions contain 10 modules of stress management education material and exercises delivered through text, sound, video, and images/pictures [65]. After 1 module is completed, there is a 3-day delay before the next module is available. The purpose of this delay is to encourage the participant to spend time reflecting and practicing previous content and exercises. The program has several features that make it easy to use, such as the ability to mark exercises as favorites, offline mode, and the possibility to set reminders [65].

Modification of the content/content development was conducted by 4 subject matter experts (AM, HRE, LSN, and EB), an epidemiologist (GU), and a content editor (CMR). As in the original StressProffen intervention program, the StressProffen app was used for both interventions. General information (ie, text unrelated to CBI and MBI) was retained from the original StressProffen program and reused for both interventions, and the team strived to balance the number and length of the other modules and subsections, exercises, figures, and models between the 2 interventions.

The content of the final interventions relied on the original StressProffen program, with most of the original content being retained in the CBI version, but with some adjustments, including minor therapeutic language adjustments. More content adjustments and revisions were made for the MBI version, with new developed content from the project team experts, as well as inclusion of adapted content (ie, translation and modifications to fit the language and structure) from the Mindfulness-Based Cancer recovery manual [29]. The adaptation included translation and modifications to fit the language and structure used in the current intervention (E. Børøsund et al, unpublished data, 2022).

All participants in the intervention groups have access to the assigned StressProffen interventions for the entire study period and in the future for as long as Oslo University Hospital manages the app. The control group receives access to StressProffen upon request when their participation in the trial is finished.

Potential Intervention Harms

The CBI and MBI interventions have no known harms. A feeling of disappointment might arise if the participant does not feel that their stress level has been reduced during the study period. Although the vast majority of literature says otherwise, it cannot be completely ruled out that meditation-based therapies may lead to distress [72].

As the participants do not have access to individual therapy through the study, participants in both intervention groups are encouraged to seek professional help from their primary caregiver, should they wish/feel a need to do so.

Follow-up

The initial phone call to participants in the intervention groups is scheduled shortly after randomization and consists of a structured introduction to the StressProffen program lasting 15-20 minutes (Figure 1). During this phone call, participants download the StressProffen app, obtain, and enter their access code, and consequently receive access to download 1 of the 2 interventions. Participants are encouraged to start using the app immediately after the phone call.

After the initial phone call, there are 3 additional follow-up phone calls (approximately 1, 3, and 6 weeks following the initial phone call) to increase adherence to the protocol, especially to support motivation and prevent dropouts by checking how participants are doing with the intervention and resolving any technical issues. For the follow-up phone calls, 3 weekly attempts to reach the participants are undertaken. During the final phone call at 6 weeks, participants are informed that further follow-up in the CABC trial will consist of annual surveys over the next 3 years (Figure 1).

Communication

In addition to the scheduled follow-up calls, participants are encouraged to call the study telephone number with any questions they may have. The cancer advisory unit at the patient advocate organization, the Norwegian Cancer Society [73], and the Breast Cancer Oncology Group (Norwegian Breast Cancer Group) [74] also have basic information about the CABC trial, in case the participants call them for support. Furthermore, the CRN and the Norwegian Breast Cancer Society share information about the trial occasionally through their social media platforms and newsletters. These channels will also be

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used to inform people about published results. In addition to scientific publications and presentations of results at scientific conferences, results will be communicated to the public through various media outlets after the study end. Any changes to the protocol will be recorded simultaneously at the ClinicalTrials.gov registry [75].

Outcome Measures

Surveys

Outcomes are assessed with 2 digital surveys: the ongoing CRN PROMs survey and the study-specific CABC survey (Table 1).

Table 1. Detailed information on outcome measures that will be obtained from the CABC[a] survey and the CRN PROMs[b] survey.

Outcome(s)	Assessed with	Number of items, n
CABC survey: ≥7, 13, 24, and 35 months after diagnosis		
Primary outcome (from 7 to 13 months after diagnosis)		
Perceived stress	Cohen 10-item Perceived Stress Scale [76]	10
Secondary outcomes (all time points)		
Perceived stress	Cohen 10-item Perceived Stress Scale [76]	10
Health and health-related quality of life	RAND Corporation 36-Item Short Form Health Survey [11]	36
Coping	Theoretically Originated Measure of the Cognitive Activation Theory of Stress [77]	7
Fatigue[c]	Chalder's Fatigue Scale [78]	11+2[d]
Awareness/mindfulness	Baer's Mindfulness Questionnaire [49,79]	15
Distress	Patient Health Questionnaire [80]	4
Sleep	The Survey of Shift Work, Sleep and Health [81]	10
Work and use of social services[e]	Work, use of social services, and Ability Index [82] and single-item question [83]	3
CRN PROMs survey: ≥21 days and 14 and 36 months after diagnosis		
Secondary outcomes (all time points)		
Cancer-related quality of life	European Organization of Research and Treatment of Cancer-Core Quality of Life Questionnaire [84]	30
Breast cancer–related quality of life	European Organization of Research and Treatment of Cancer-Core Quality of Life Questionnaire: Breast Cancer–Specific Module [85]	23
Neuropathy/neuropathic pain, vaginal symptoms, arthralgia	Functional Assessment of Cancer Therapy: Gynecologic Oncology Group—Neurotoxicity and Endocrine Symptoms [86]	8
Fatigue	Chalder's Fatigue Scale [78]	11+2[d]
Workability and use of social services	Work Ability Index [82] and single-item question [83]	3
Stress[f]	Stress Experience Scale [87]	1
Background questions	Educational level, living with children <18 years (yes/no), household income, living situation, income, physical activity level (light and high intensity), smoking and alcohol habits, and height and weight	11

[a]CABC: Coping After Breast Cancer.

[b]CRN PROMs survey: Cancer Registry of Norway patient-reported outcome measures survey.

[c]Chalder's Fatigue Scale is only included at baseline and at month 24 by the CABC survey because it is assessed with the CRN PROMs survey at 13 and 36 months after diagnosis.

[d]The survey sent to participants diagnosed in 2020 included the 11-item Chalder's Fatigue Scale, whereas questions on duration and extent of fatigue symptoms [88,89] were added to the survey sent to participants enrolled and followed up after 2021.

[e]Only included at 24 months of follow-up in the CABC survey.

[f]Stress assessed as 1 item is not defined as a secondary outcome but can be used in exploratory analysis.

The CRN PROMs Survey

The CRN PROMs survey is sent to all patients with breast cancer 21 days and 14 and 36 months following diagnosis. Several measures from the CRN PROMs survey are included as secondary outcomes in this study as outlined in Table 1.

Fatigue is assessed using variants of Chalder's Fatigue Scale rating subjective physical and mental features of fatigue [78,88,89]. Peripheral neuropathy, vaginal symptoms, and arthralgia are measured by the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group—Neurotoxicity and Endocrine Symptoms questionnaire [86] (only available for

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patients diagnosed from 2021). Quality of life is assessed by the 30-item European Organization of Research and Treatment of Cancer-Core Quality of Life Questionnaire (EORTC QLQ-C30) [84] and its Breast Cancer–Specific Module (EORTC QLQ-BR23) [85]. Report on work-related outcomes including use of social services is assessed with the Work Ability Index [82] and single-item question [83].

The CRN PROMs survey also contains self-reported information on background data including educational level, living situation, number of children less than 18 years, income, physical activity level, smoking and alcohol habits, height, and weight (Table 1).

Coping After Breast Cancer Questionnaire

Participants receive the baseline CABC survey at approximately 7 months after diagnosis and the follow-up CABC surveys 13, 24, and 35 months after diagnosis (Figure 1). The follow-up surveys were sent about 1 month after the CRN PROMs surveys, in order for participants not to confuse the 2 data collections.

The Cohen 10-item Perceived Stress Scale [76] in the CABC survey will be used to assess the primary outcome: 6-month change in perceived stress (from 7 to 13 months following diagnosis) between each of the intervention groups and TAU (Table 1).

The following secondary outcomes are also obtained from the CABC survey: distress ranging from sadness and worry to anxiety and depression, as measured by the Brief Version of the Patient Health Questionnaire for Depression and Anxiety [80]. (Health-related) quality of life is measured by the RAND Corporation 36-Item Short Form Health Survey (RAND-36). RAND-36 assesses 8 health concepts: physical functioning, role limitations caused by physical health problems, role limitations caused by emotional problems, social functioning, emotional well-being, energy/fatigue, pain, and general health perceptions [11]. Mindfulness is assessed using the 15 items from Baer's 5 Facet Mindfulness Questionnaire [49]. Sleep (duration and quality) is measured by items from the Norwegian Shift Work, Sleep and Health survey [81]. Coping, defined as 3 dimensions of response outcome expectancies related to an individual's ability to handle stressors and challenges in everyday life related to coping, hopelessness, and helplessness, is measured by the Theoretically Originated Measure of the Cognitive Activation Theory of Stress [77].

As there is no CRN PROMs survey 24 months after diagnosis, the work-related outcomes are included in the CABC survey after 24 months, whereas Chalder's Fatigue Scale is included at baseline and at month 24 (Table 1).

Other Outcomes

The study will further explore characteristics of those who respond to the CABC trial (responders versus nonresponders) and those who complete the interventions (at least 7 out of 10 modules of StressProffen-CBI or StressProffen-MBI) and their counterparts. Data from the CRN PROMs survey 21 days prior to diagnosis will be used to assess differences in CABC trial invitation responders and nonresponders. Differences in intervention effects (primary and secondary outcomes) between StressProffen-CBI and StressProffen-MBI will also be explored.

Participant data will be linked to the Norwegian Labor and Welfare Administration database, Statistics Norway, the CRN, the Norwegian Patient Registry, the Norwegian Prescription database, and the Norwegian Cause of Death Registry. In addition to data from the surveys, data from the registries will be used for exploratory analysis, including predictors of intervention effects and long-term effects of study participation on comorbidities, relapse and new cancers, and mortality. Detailed and objective information on work participation including sick leave, disability pension, and use of social services will also be obtained. These linkages will enable long-term follow-up of participants in the CABC trial until study end (currently 2035).

Monitoring Compliance

Those who have not completed the CRN PROMs survey and the CABC survey automatically receive 1-2 reminders (unless they have opted out of receiving reminders) during a 30-day period. To ensure as high participation rate as possible, the CABC survey sent 13 months after diagnosis is available for 45 days and includes 2 additional reminders: 1 by phone and 1 by a standard motivational letter. There is no manual review or monitoring of survey responses during the trial. Survey data and participant data (ie, name, phone number, randomization string, scheduled and actual phone calls, and participant dropouts) are stored in CRN databases protected with 2-factor authentication. Access to survey data is limited to selected employees from the CRN, while participant data are further restricted to employees involved in the CABC study.

In addition to using survey data for monitoring compliance, system usage data (eg, the number of modules completed and time spent on each module and between modules) are logged and stored at the Services for Sensitive Data at the University of Oslo. Only approved study personnel have access to this information prior to study end.

Pilot Study

Before study implementation in 2021, a pilot study with 23 women (of 59 invited) was conducted to inform the need for adjustments prior to the RCT. Adjustments included minor rewordings of the informed consent, scheduling additional follow-up calls, and reducing the number of items in the CABC survey (eg, the 24-item version of Baer's Mindfulness Questionnaire [90] was replaced with the 15-item version [49,79]).

Ethical Considerations

Data collection in the CRN PROMs survey is based on informed consent—Article 6 (1) (a) and Article 9 (2) (a) of the European Union's General Data Protection Regulation. The Regulations on Population-Based Health Surveys give additional conditions for data collection and processing and what data can be accessed in this study.

All participants are asked to provide informed consent by responding to the CABC survey. Participants are informed that consent also implies consent to have their data linked to several

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national registries. This includes the CRN; the Norwegian Breast Cancer Registry, where cancer subtypes are recorded; the Norwegian Patient Registry; the Norwegian Cause of Death Registry; and the Norwegian Prescription Database (for comorbidity, morbidity, mortality, and prescription data). Data are also linked with the Norwegian Labor and Welfare Administration Database and Statistics Norway to obtain information on work participation including sick leave and disability. Registry linkages can currently be performed until the end of the study (ie, up to December 31, 2035).

As the intervention is digital, including digitally completed outcome measures, no methods to identify adverse effects have been identified. Further, there is no monitoring committee and hence no stopping guidelines have been implemented. Participants can withdraw from the study at any time and without stating their reasons for doing so. This will not have any consequences for their further treatment. Participants are also free to stop using the app whenever they wish to do so.

The study is approved by Regional Committee for Medical Research Ethics Southeast Norway (reference number 32637 "Stressmestring etter brystkreft" [CABC] and registered at ClinicalTrials.gov, NCT04480203 [CABC]).

Sample Size Calculations

Power calculation in the CABC trial was conducted on the primary outcome (ie, 6-month between-group difference in perceived stress) using independent sample *t* tests. The α level was adjusted for multiple comparisons (comparing 2 intervention groups with 1 control group for each outcome) by setting the significance level to 2.5%. Estimates of effect sizes and SDs were retrieved from previous StressProffen interventions on multiple groups of patients with cancer, which found a mean difference in perceived stress of 2.8 and SDs of 6.6 and 8.3 in the case and control groups, respectively [70]. As the CABC trial includes a more homogenous population (only female patients with breast cancer), the effect size was set to 3 and the SD to 6.

With an estimated 80% power to detect a difference between 1 of the intervention groups and the control group, a sample size of 235 participants is needed. With an assumed completion rate of 70%, a total of 335 participants will need to be enrolled, 70 in each group.

Statistical Analysis

Between-group differences in primary and secondary outcomes will be analyzed using intention-to-treat and per-protocol analyses. Continuous outcomes will be analyzed using standard *t* tests (2-tailed and unpaired) and multivariable linear and mixed regression models to adjust for potential differences between groups occurring by chance. Categorical outcomes will be analyzed with chi-square tests and multivariate logistic regression analyses. When analyzing longitudinal data, multivariate regressions with clustered standard errors, multilevel models, or generalized estimating equations may be used to account for the correlation between repeated measurements.

Potential interaction effects between the interventions and relevant covariates such as age at diagnosis, disease characteristics (triple negative, HER2+, or DCIS), and primary treatment will also be explored, either by stratification or by estimating multivariate models including interaction effects.

Missing data will be handled using multiple imputation techniques, primarily if the proportion of participants with missing information exceeds 15%. A detailed description of statistical analysis will be developed. All statistical analyses will be performed using STATA statistical software version 15 or later (StataCorp LLC).

Results

During inclusion there were signs that the completion rate among participants was lower than expected. By contrast, during the pandemic, a higher than expected percentage of newly diagnosed patients with breast cancer were digitally active (88% in 2022), which resulted in an increase in the percentage of eligible patients with breast cancer that were invited to the CRN PROMs survey in 2022. This provided an opportunity to account for the lower completion rate by recruiting more participants. The target number was therefore increased from 335 to 430 participants (about 100 in each group; enrollment end date May 31, 2023). As of April 14, the total number recruited is 428.

The project has received funding from the Norwegian Breast Cancer Society's "Pink Ribbon" charity funding (principal investigator: GU).

Discussion

Impact of Stress Management

Psychosocial and physical long-term complaints after breast cancer treatment remain a major public health challenge with substantial social and personal costs [9]. Psychosocial stress can be associated with inflammation, tumor progression, and disease prognosis [55,91,92], as well as increased risk and prognosis of other chronic diseases [93,94]. Stress management interventions have been effective in reducing stress and other long-term complaints following a cancer diagnosis [64]. Cancer survivors using the original StressProffen intervention (ie, with a combination of CBT and MBI) over a 12-month study period reported significantly greater reduction in perceived stress, depression, and anxiety compared with controls (ie, TAU). The intervention also showed significantly improved health-related quality of life for cancer survivors receiving StressProffen compared with controls [71].

The CABC trial will study similar outcomes as in the original StressProffen intervention, but solely in breast cancer survivors and with additional long-term follow-up. If any or both of the current interventions have effects that are superior to findings from the TAU control group, implementation of the convenient eHealth intervention StressProffen should be considered in clinical practice, perhaps as a future extension to precision oncology care [55].

The original StressProffen program (ie, the app) targeting cancer survivors is in the process of being made commercially available

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in English and Norwegian versions, whereas the StressProffen-CBI and MBI versions are only available for study participants. Future distribution will depend on study findings.

Strengths

The CABC trial is, to our knowledge, currently the largest psychosocial eHealth intervention (RCT) in patients with breast cancer. The trial has a long-term follow-up with an assessment of intervention effects 1, 2, and 3 years after a breast cancer diagnosis, corresponding to up to 29 months after baseline. Furthermore, study participants can be prospectively followed up with respect to comorbidity, relapse and new cancers, and mortality until the end of the study (ie, currently, December 31, 2035) through linkage with national health registries using personal identification numbers (mandatory for all Norwegians). The feasibility of the StressProffen app was assessed initially by Børøsund and colleagues [71] and the CABC trial has further extended the StressProffen research line through developing the StressProffen-CBI and StressProffen-MBI interventions, pilot tested these, and implemented necessary adjustments. Another strength of the trial is the ongoing systematic collection of CRN PROMs survey data. This enables us to compare study participants with all CRN PROMs survey data.

Development of the 2 interventions strived to balance design and content presentation to enhance the chance of any effect differences arising due to theoretical content (ie, CBI/MBI). However, due to statistical power limitations, direct comparisons of the 2 interventions will solely be conducted on an exploratory basis. The flexibility of the intervention can be beneficial for patients with cancer undergoing treatment while coping with everyday activities [64]. Given the high percentage of the population that has access to digital platforms within Norway [68], the study has a unique possibility to recruit participants across different socioeconomic statuses and geographical locations. Digital intervention delivery also demands less resources than face-to-face interventions [56]. Thus, if found to be effective, the StressProffen eHealth intervention may have a better chance of being integrated as part of clinical practice than costly face-to-face interventions.

Limitations

The CABC trial has some limitations. First, outcome measures are primarily self-reported. Second, data related to outcomes prior to breast cancer diagnosis are not available. Third, the study only includes a subsample of patients with breast cancer with either noninvasive disease (DCIS) or severe (triple-negative or HER2 positive) breast cancer. Participants are therefore likely to be a heterogenous group of patients with breast cancer with varying treatment according to stage and subtype (eg, in addition to surgery, patients with DCIS may only receive radiation therapy, whereas patients with triple-negative or HER2-positive cancer are advised chemotherapy for several months) [95]. Selection bias may be present as participation depends on the use or access to the digital mailbox and willingness to participate in the CRN PROMs survey (ie, about 50%) [68]. These factors could also limit the generalizability of the study results. However, an eHealth intervention requires the use of digital resources and access to digital tools as requirements.

Conclusions

The CABC trial is possibly the largest ongoing psychosocial eHealth RCT in patients with breast cancer. If 1 or both interventions prove to be effective in reducing stress and improving psychosocial and physical complains, the StressProffen eHealth interventions could be beneficial, inexpensive, and easily implementable tools for breast cancer survivors when coping with late effects after cancer and cancer treatments.

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Availability of Data and Materials

The informed consent as well as the General Data Protection Regulation will limit the extent to which individual-level data can be shared with other researchers.

Authors' Contributions

AM, HRE, and GU conceptualized the study and design. KS, LSN, AM, IML, YMG, EB, CMR, TÅM, CEK, HS, KVR, MHA, TC, IM, LEC, HRE, and GU contributed to the planning or implementation of the study. KS, LSN, AM, IML, EB, CMR, YMG, HRE, and GU handle the ongoing data collection and management of the Coping After Breast Cancer (CABC) trial. KS, EB, LSN, AM, TÅM, HRE, and GU will have the overall responsibility of data analysis and all authors will contribute to interpretation of the data. KS, GU, and HRE wrote the initial draft of the protocol. All authors contributed by editing the manuscript for content. All authors consent to publication and have read and approved the final manuscript and agreed both to be personally accountable for their own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in

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which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

Conflicts of Interest

KS, AM, IML, EB, CMR, YMG, TÅM, HS, KVR, IM, CEK, and GU declare no conflicts of interest. LSN is an unpaid board member of dHealth AS, a company aiming to commercialize the original StressProffen program. TC is Co-chief investigator on a National Institute for Health and Care Research (NIHR) program grant in the UK testing a modified acceptance and commitment therapy intervention to improve quality of life for people with a range of cancers in the posttreatment phase. MHA is a consultant for Blue Note Therapeutics and Atlantis Healthcare, both digital health software companies. LEC receives royalties for 2 mindfulness book titles, and from eMindful for an online mindfulness-based cancer recovery program. HRE is a co-founder and a shareholder of a company offering lectures, education, and supervision about stress and coping (Stressprofessorene AS). HRE has no commercial interest in the StressProffen program.

Multimedia Appendix 1
Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist.
[PDF File (Adobe PDF File), 122 KB - resprot_v12i1e47195_app1.pdf]

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Abbreviations

CABC: Coping After Breast Cancer
CBI: cognitive behavioral intervention
CBT: cognitive behavioral therapy
CRN: Cancer Registry of Norway
DCIS: ductal carcinoma in situ
EORTC QLQ: European Organization of Research and Treatment of Cancer-Core Quality of Life Questionnaire
EORTC QLQ-BR23: European Organization of Research and Treatment of Cancer-Core Quality of Life (Breast Cancer–Specific Module) Questionnaire
EORTC QLQ-C30: European Organization of Research and Treatment of Cancer-Core Quality of Life Questionnaire
ER: estrogen receptor
HER2: human epidermal growth factor receptor 2
ICD-10: International Classification of Diseases, 10th revision
MBI: mindfulness-based intervention
PROM: patient-reported outcome measure
RAND-36: RAND Corporation 36-Item Short Form Health Survey
RCT: randomized controlled trial
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
TAU: treatment as usual

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Protocol

Internet-Delivered Dialectical Behavioral Therapy Skills Training for Chronic Pain: Protocol for a Randomized Controlled Trial

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Abstract

Background: Emotion dysregulation is key to the development and maintenance of chronic pain, feeding into a cycle of worsening pain and disability. Dialectical behavioral therapy (DBT), an evidence-based treatment for complex transdiagnostic conditions presenting with high emotion dysregulation, may be beneficial to manage and mitigate the emotional and sensory aspects of chronic pain. Increasingly, DBT skills training as a key component of standard DBT is being delivered as a stand-alone intervention without concurrent therapy to help develop skills for effective emotion regulation. A previous repeated-measure single-case trial investigating a novel technologically driven DBT skills training, internet-delivered DBT skills training for chronic pain (iDBT-Pain), revealed promising findings to improve both emotion dysregulation and pain intensity.

Objective: This randomized controlled trial aims to examine the efficacy of iDBT-Pain in comparison with treatment as usual to reduce emotion dysregulation (primary outcome) for individuals with chronic pain after 9 weeks and at the 21-week follow-up. The secondary outcomes include pain intensity, pain interference, anxiety symptoms, depressive symptoms, perceived stress, posttraumatic stress, harm avoidance, social cognition, sleep quality, life satisfaction, and well-being. The trial also examines the acceptability of the iDBT-Pain intervention for future development and testing.

Methods: A total of 48 people with chronic pain will be randomly assigned to 1 of 2 conditions: treatment and treatment as usual. Participants in the treatment condition will receive iDBT-Pain, consisting of 6 live web-based group sessions led by a DBT skills trainer and supervised by a registered psychologist and the iDBT-Pain app. Participants in the treatment-as-usual condition will not receive iDBT-Pain but will still access their usual medication and health interventions. We predict that iDBT-Pain will improve the primary outcome of emotion dysregulation and the secondary outcomes of pain intensity, pain interference, anxiety symptoms, depressive symptoms, perceived stress, harm avoidance, social cognition, sleep quality, life satisfaction, and well-being. A linear mixed model with random effects of individuals will be conducted to investigate the differences between the baseline, 9-week (primary end point), and 21-week (follow-up) assessments as a function of experimental condition.

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Results: Recruitment started in February 2023, and the clinical trial started in March 2023. Data collection for the final assessment is planned to be completed by July 2024.

Conclusions: If our hypothesis is confirmed, our findings will contribute to the evidence for the efficacy and acceptability of a viable intervention that may be used by health care professionals for people with chronic pain. The results will add to the chronic pain literature to inform about the potential benefits of DBT skills training for chronic pain and will contribute evidence about technologically driven interventions.

Trial Registration: Australian New Zealand Clinical Trials Registry ACTRN12622000113752; https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=383208&isReview=true

International Registered Report Identifier (IRRID): PRR1-10.2196/41890

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KEYWORDS

internet-delivered; dialectical behavioral therapy; chronic pain; emotion dysregulation; emotion-centric intervention; mobile phone

Introduction

Background and Rationale

Chronic pain, defined as any pain condition that persists continuously or intermittently beyond 3 months [1], is a substantial and costly burden on individuals and society [2,3]. Regardless of the condition (eg, arthritis, musculoskeletal pain, back pain, and fibromyalgia), chronic pain is a multidimensional construct incorporating both unpleasant sensory (eg, pain intensity) and psychological (eg, emotional) components [1]. Evidence corroborates the detrimental effect of chronic pain on emotions [4-7], demonstrating a cyclical association between negative emotional states, such as fear, anger, worry, and low mood, and worsening pain intensity and disability [8-10]. Beyond negative emotional states, co-occurring anxiety and depressive disorders present in up to 80% of people with chronic pain [11-14]. Other related issues include reduced sleep quality (up to 70%) and lower quality of life and well-being [15].

Increasingly, emotion dysregulation is regarded as a mechanism that underpins negative emotional states in people with chronic pain [16-18]. Emotion dysregulation is defined as an extreme sensitivity to emotional events and a reduced capacity to identify and moderate emotions [19]. The modal model of emotions helps make sense of the association between chronic pain and emotion dysregulation. According to this model, when a stimulus is experienced, it gives rise to an emotion that is then cognitively appraised before determining physiological arousal and a behavioral response [10,20]. For people with chronic pain, this process may be disrupted because emotion regulation capabilities are fatigued by persistent negative emotions that are likely a result of the debilitating and distressing symptoms of chronic pain and the experience of missing out because of episodes of escalating pain (eg, on career, social, and educational opportunities) [8-10]. Over time, emotion dysregulation appears to lead to a greater focus on pain, reports of heightened levels of pain intensity, and increasing negative emotions [21].

The development of emotion dysregulation may be further explained by previous experiences and neurobiological changes in people with chronic pain. The persistent presence of pain has been related to neurotransmitter dysregulation—specifically, a reduction in key neurochemicals (γ-aminobutyric acid and glutamate) in the medial prefrontal cortex—which is thought to affect social cognition, including the integration of emotions for decision-making, culminating in emotion dysregulation [22]. In addition, a recent mini review connects hyperactivity in emotion-regulating brain pathways with trauma, posttraumatic stress disorder (PTSD), and the presence and severity of chronic pain [23]. Trauma has been extensively reported as a risk factor for the development of chronic pain [21]. Emotion dysregulation may also be an antecedent to chronic pain, whereby certain personality traits manifest in emotion dysregulation, thereby increasing the risk of developing chronic pain [24,25]. Notably, chronic pain is a condition that is unpredictable in how it transpires over time, but regardless, psychological factors, specifically emotion dysregulation, appear to be a key factor in its development and maintenance [21].

Although a definitive explanation of how and why people with chronic pain present with emotion dysregulation remains elusive, the role of effective emotion regulation in reducing pain intensity and emotional distress is increasingly evident [26,27]. Successful emotion regulation includes emotional awareness, understanding and accepting emotions, and an ability to modify emotions or emotional expression consistent with social norms [19]. Existing psychological interventions for chronic pain, such as cognitive behavioral therapy, mindfulness-based stress reduction, and acceptance and commitment therapy, include few strategies for effective emotion regulation and have shown at best minimal improvement in mood and pain severity [28-30]. Including specific strategies to develop effective emotion regulation skills may mean that psychological interventions for chronic pain are more beneficial [16].

Owing to this promising evidence, psychological interventions for chronic pain that focus on improving emotion regulation are increasingly being investigated. Examples include interventions that incorporate emotion regulation training into cognitive behavioral therapy [31] and emotion awareness and expression therapy [32] and the integration of emotion regulation methods from dialectical behavioral therapy (DBT) [33]. A recent systematic review of randomized controlled trials (RCTs) summarized that emotion-regulation focused interventions, defined as studies that target emotion regulation as a mechanism of chronic pain, have a substantial clinical benefit in reducing

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pain; however, findings about psychological outcomes (eg, emotion dysregulation, depression, and anxiety) are uncertain owing to a lack of data [34]. Several pilot studies have begun to explore the effect of DBT on psychological outcomes, finding that DBT may improve anxiety and depression (in a study of 6 patients with chronic gastrointestinal pain [35]); depressive symptoms and emotion dysregulation (in a case study with a patient with chronic pain [36]); and negative emotion, fear, depression, and anxiety (seen in 5 out of 6 study participants with chronic lower back pain [37]). However, as these are all small pilot trials, further evidence is needed to understand the effects of psychological factors related to chronic pain in addition to pain intensity. Understanding how these types of interventions affect emotion dysregulation may be particularly important considering its potential role in the development and maintenance of chronic pain (as discussed previously).

Building on previous evidence of DBT for chronic pain, our group used one mode of DBT, DBT skills training, to develop a 6-session internet-delivered intervention focused on improving emotion dysregulation in people with chronic pain. Standard DBT is an evidence-based treatment for clients with multiple diagnoses presenting with high emotion dysregulation [38]. Standard DBT encompasses a comprehensive treatment plan using 4 modes delivered over 12 months: group skills training, individual therapy, phone coaching, and a therapist consultation team. However, increasingly, DBT skills training as a key mode of standard DBT is delivered as a stand-alone intervention without the 3 other modes [39]. An advantage of stand-alone DBT skills training is that the resources and time to deliver it are substantially reduced, whereas a real-world study found that improvements in emotion dysregulation are comparable with those of standard DBT (ie, all modes) [40]. In addition, DBT skills training does not necessarily require a psychologist; it can be delivered by DBT trainers, who can be anyone well trained on the principles of the training and skills (eg, teachers, professional trainers, volunteers, therapists, physiotherapists, and nurse practitioners) [39,41].

The DBT skills training developed for this trial is the internet-delivered DBT skills training for chronic pain (iDBT-Pain), a guided intervention designed to enhance emotion regulation through learning key skills from DBT in mindfulness, emotion regulation, and distress tolerance. These modules are first taught by a DBT skills trainer and a supervising psychologist in weekly sessions and then reinforced and practiced by accessing an app. As an intervention that is optimized for mobile use (eg, on a smartphone or tablet), iDBT-Pain is functional for anyone with a mobile device and an internet connection. To our knowledge, iDBT-Pain is the first guided internet-delivered DBT intervention for people with chronic pain even though technologically supported interventions have been encouraged since a Cochrane report in 2014 [42]. Importantly, internet-delivered psychological interventions increase accessibility for remote communities, where it can be difficult to access mental health services, and enable access for people with restricted mobility because of chronic pain [42].

A previous trial using a repeated single-case experimental design (SCED) explored the efficacy of iDBT-Pain, showing promising findings to improve both emotion dysregulation and pain intensity with effect sizes of −0.88 and −0.81, respectively [43]. However, although the findings of this previous trial are encouraging, further evidence is necessary to compare iDBT-Pain to usual modes of treatment in a larger sample to generalize the findings more broadly. This protocol details the methods to be used in an RCT to investigate the efficacy of iDBT-Pain. This trial will test a group-based version of iDBT-Pain that builds on the individualized treatment previously investigated in the SCED trial. Group treatment has advantages over individualized treatment, including enabling individuals to interact with others like themselves, resulting in validation that can in itself be therapeutic [39].

Overall, this trial builds on the literature on interventions that focus on improving emotion regulation as a key mechanism related to chronic pain. This trial will add evidence to the current literature on the efficacy and acceptability of a potentially viable emotionally focused intervention that may be administered by health care professionals for people with chronic pain.

Choice of Comparators

To investigate the efficacy of iDBT-Pain, we chose treatment as usual (TAU) as a comparator, with the open-ended definition of TAU as any treatment received for chronic pain that an individual accesses from their usual health care provider. The rationale for this comparator is that we consider it necessary to compare the efficacy of iDBT-Pain with those treatment options that would be available in the absence of the intervention. In addition, TAU as a comparator assists with the feasibility of the study as there is no need to recruit expert clinicians on a specific comparator therapy method. Therefore, the chosen trial design enables a feasible comparison of the efficacy of iDBT-Pain with the general practice in chronic pain treatment and enables the investigation of whether iDBT-Pain can come close to the effects of the multifaceted, individually adjusted chronic pain treatment currently delivered by health care services in the community.

Objectives

Primary Objective

Our primary objective is to evaluate the efficacy of iDBT-Pain in reducing emotion dysregulation (primary outcome) in individuals with chronic pain. The 9-week iDBT-Pain intervention is hypothesized to improve emotion dysregulation compared with TAU.

Secondary Objectives

First, we will investigate the efficacy of iDBT-Pain in improving the secondary outcomes of pain intensity, pain interference, anxiety symptoms, depressive symptoms, perceived stress, posttraumatic stress, social cognition, sleep quality, life satisfaction, and well-being. It is hypothesized that the group administered the 9-week iDBT-Pain intervention will improve in the secondary outcomes compared with the TAU control group.

Second, we will investigate the efficacy of the iDBT-Pain intervention at the 21-week follow-up on the primary and secondary outcomes. It is hypothesized that the iDBT-Pain

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intervention group will significantly improve in both the primary and secondary outcomes compared with the TAU control group.

Finally, we will investigate the acceptability of the iDBT-Pain intervention at the 9- and 21-week follow-ups. It is anticipated that these findings will help determine participants' affective and cognitive responses to the intervention as well as indicate the most useful aspects of the intervention for future development and testing.

Trial Design

In a 2-arm randomized controlled superiority trial, participants with chronic pain will be allocated at a ratio of 1:1 to either receive iDBT-Pain (in addition to TAU) or continue with TAU only. Assessments will take place at baseline and the 9-week (primary end point) and 21-week follow-ups. The efficacy of iDBT-Pain will be determined by comparing treatment with TAU for the primary and secondary outcomes. The acceptability of iDBT-Pain will be investigated using a mixed methods approach whereby quantitative and qualitative data (semistructured interviews) will be collected, separately analyzed, and then collectively interpreted [44]. Reporting of this protocol is in accordance with the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines [45] (Multimedia Appendix 1).

Methods

Study Setting

This study will be conducted by researchers in Australia at the University of New South Wales (UNSW). The iDBT-Pain intervention will be administered by researchers using videoconferencing and an app, meaning that it will be accessed entirely on the web by participants in their everyday life. Assessments, including participant screening for eligibility, will be conducted remotely via telephone and links to web-based questionnaires.

Eligibility Criteria

Participants will be eligible for this trial if they fulfill the inclusion and exclusion criteria outlined in Table 1.

Table 1. Inclusion and exclusion criteria.

	Inclusion criteria	Exclusion criteria
Age	Adults aged >18 years	Individuals aged <18 years
Chronic pain	Average pain rating of ≥3 for the past 7 days (Numeric Rating Scale)	Average pain rating of <3 for the past 7 days (Numeric Rating Scale)
Technology	Access and capability to use the internet to participate in the iDBT-Pain[a] sessions and access to a smartphone or tablet device capable of running the iDBT-Pain app	No access or capability to use the internet or no access to an internet-enabled device (eg, smartphone or tablet)
Commitment	Ability to commit to the expectations of the trial (eg, weekly sessions lasting 90 minutes and daily practice)	Inability to commit to the expectations of the trial
Psychiatric disorders	No diagnosed psychotic or personality disorders	Diagnosed psychotic (eg, schizophrenia) or personality (eg, borderline personality disorder or bipolar disorder) disorders; uncontrolled mental health disorder
Dementia or Alzheimer disease	No presence of dementia or Alzheimer disease	Diagnosis of dementia or Alzheimer disease
Language	Reasonable level of written and spoken English	Poor level of written and spoken English
Country of residence	Located in Australia	Located outside Australia

[a]iDBT-Pain: internet-delivered dialectical behavioral therapy skills training for chronic pain.

Informed Consent Process

Informed consent will be obtained after potential participants have been screened as eligible (see the *Recruitment* section) and stated their interest in participating in the trial and before they complete the baseline questionnaires. A trained research assistant or a member of the research team will contact the potential participant by email to arrange a time for a call to discuss informed consent. Before the call, the potential participant will be sent a link to the participant information statement and consent form to ensure that they have the full details about the trial and consent process ahead of the call. During the call, the opportunity to ask questions about the trial and consent will be emphasized, and the procedure and opportunity to withdraw from the trial will be fully explained. To ensure understanding and that the questions have been addressed adequately, a teach-back method of informed consent will be used whereby the researcher will ask the potential participant to restate information back in their own words. Consent will be obtained only from individuals with the capacity to make an informed decision regarding their participation. Potential participants who wish to consent to participate will be sent a link to sign the consent form in a secure web-based application (Qualtrics [Qualtrics International Inc]). This form will then be countersigned by the principal investigator, and a copy will be emailed to the participant for their records.

Additional Consent Provisions

On the consent form, participants can optionally consent to (1) their anonymized data being used in future research, (2) being contacted about future research studies for which they might be suitable, (3) being contacted about potential participation in media events, (4) allowing video recording of the iDBT-Pain Zoom (Zoom Video Communications) sessions, (5) being

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entered into a prize draw if they complete the study, and (6) using the iDBT-Pain app after the study. For more details, copies of the participant information statement and consent form are available upon request from the corresponding author. This trial does not involve collecting biological specimens.

Interventions

Treatment Group

Participants in the treatment group will receive the iDBT-Pain intervention (Table 2), consisting of two key elements: (1) the iDBT-Pain sessions, involving six 60- to 90-minute iDBT-Pain sessions delivered via Zoom to groups of 8 to 12 participants, and (2) the iDBT-Pain app, accessed by participants on their own smart devices (eg, smartphone) to watch videos and complete tasks (Figure 1). In addition to the iDBT-Pain sessions and app, there will be an introductory session to explain the trial and a concluding session. To develop iDBT-Pain [46], evidence-based protocols for DBT skills training according to the DBT Skills Training Manual [39] were used. Participants in the treatment group may continue to receive their usual care (eg, medication and physiotherapy) while in the trial; any such treatment will be monitored (see the *Medication and Health Intervention Measures* section).

The intervention will be delivered by a DBT skills trainer who is a psychology graduate, PhD candidate, and qualified in DBT skills from the Linehan Institute [41]. An Australian Health Practitioner Regulation Agency–registered psychologist will supervise the DBT trainer. Both the trainer and supervisor are familiar with the iDBT-Pain intervention, having delivered it in the previous trial [43], and will adhere to the intervention manual. To ensure treatment fidelity and manual adherence, with the participants' permission, Zoom sessions will be recorded.

Table 2. Internet-delivered dialectical behavioral therapy skills training for chronic pain (iDBT-Pain) intervention protocol.

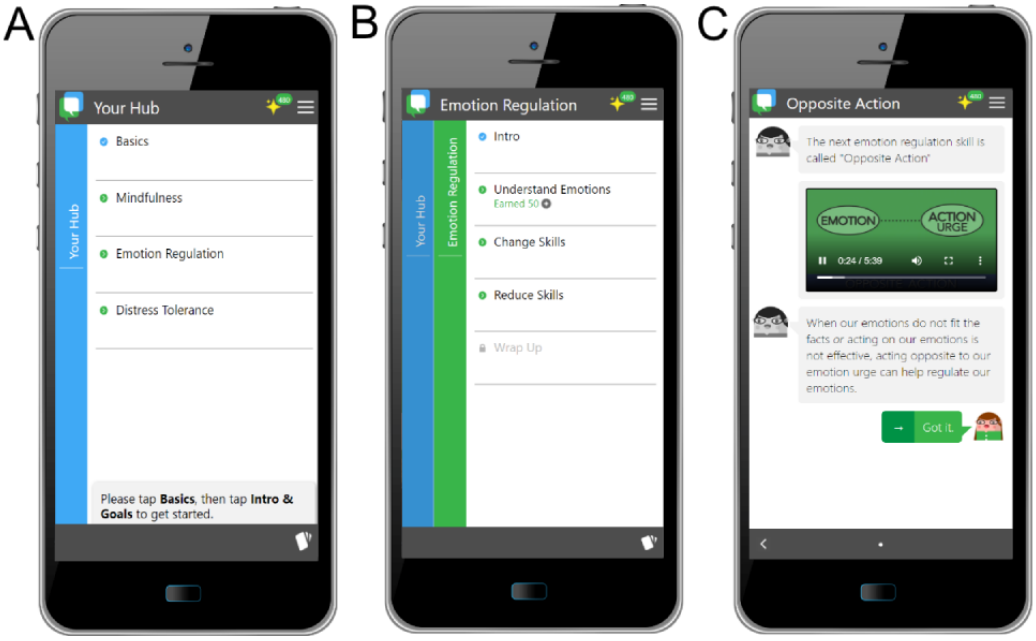
Week	iDBT-Pain session content (via Zoom [Zoom Video Communications])	iDBT-Pain app content
1	Introductory session: meet the skills trainers and the group; intervention overview; and association between chronic pain, the brain, and emotions	N/A[a]
2	Session 1—mindfulness 1: rationale for mindfulness for chronic pain and skills of *wise mind* and mindfulness *whats*	Introduction to mindfulness; *Wise mind*; 3 mindfulness *whats* skills (observe, describe, and participate); and watching the video about the association between chronic pain, emotions, and the brain
3	Session 2—mindfulness 2: mindfulness *how* skills to practice mindfulness with skillful effectiveness	Mindfulness *how* skills (nonjudgmentally, one mindfully and effectively)
4	Session 3—emotion regulation 1: how to identify and label emotions as a function for emotion regulation	Introduction to emotion regulation and understanding and naming emotions
5	Session 4—emotion regulation 2: skills to reduce the frequency and quantity of unwanted emotions	Handling unwanted emotions
6	Session 5—emotion regulation 3: skills to build future resilience against intense emotion	Building mastery and coping ahead
7	Session 6—distress tolerance: skills that help weather crises and intense negative emotions	Distress tolerance skills: TIP[b] and distract
8	Concluding session: recap the skills learned and the association between chronic pain and difficulties with emotions	Train daily in all skills for mindfulness, emotion regulation, and distress tolerance
9	No session	Train daily in all skills for mindfulness, emotion regulation, and distress tolerance

[a]N/A: not applicable.

[b]TIP: temperature of face, intense exercise, and paced breathing.

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Figure 1. Screenshots of the key sections within the internet-delivered dialectical behavioral therapy skills training for chronic pain (iDBT-Pain) app. (A) iDBT-Pain app home page; (B) the 3 emotion regulation modules; and (C) learning the skill of opposite action.



Control Group

Participants in the control group will receive TAU, meaning that they may receive treatment options offered by their usual health care provider (eg, general practitioner). Treatment received outside the trial will be monitored and described [47].

Criteria for Discontinuing or Modifying the Allocated Interventions

Dropout from the study will be recorded, including the reasons. Participants will be free to withdraw at any point. Withdrawn participants will not be replaced. If a participant chooses to withdraw, the research team will only contact them to ascertain reasons for not wishing to take part or continue and ask if they would still be willing to take part in the assessments to enable the intention-to-treat (ITT) analysis.

In the case of an adverse event, an evaluation form will be completed by the research team for the principal investigator in accordance with the UNSW Safety Monitoring Register Template. The form will include a description of the event; a classification of seriousness; an assessment of the potential relationship to the intervention; and, if considered serious, an assessment of the need for change in the consent or the study activities, a summary of known previous health issues, and the event outcome. This process will inform whether the adverse event warrants a trial or treatment modification or discontinuation by a participant.

Strategies to Improve Adherence

To improve adherence to the intervention, at the outset of the trial, all participants in the treatment group will be emailed a calendar invite to book the time for the weekly Zoom sessions in their diary and provide them with the Zoom link. Participants will then be contacted (eg, by email) with a reminder the day before the weekly Zoom session. Participants will be asked to attend all Zoom sessions live unless there are circumstances where they are unable to do so (eg, they have an urgent appointment to attend). On occasions in which a participant cannot attend the live session, after the Zoom session has finished, they will be contacted by the DBT skills trainer, emailed a link to a secure password-protected web page that will contain a recording of the Zoom session, and asked to watch the video before the next weekly Zoom session. To ensure adherence to using the app daily, all participants will be sent detailed instructions to set up the app on their smartphone at the outset of the trial and will be reminded in each of the weekly Zoom sessions to continue to practice in the app for homework. Participants allocated to TAU will receive access to the app after completing the questionnaires in the study. Participants in the TAU group will also be reminded of the importance of their contribution to the research to try to avoid resentment.

Relevant Concomitant Care Permitted or Prohibited During the Trial

Participants who are currently taking medication (eg, pain-relieving analgesics) and receiving therapeutic interventions (eg, physiotherapy) will be eligible for the trial. Medication and intervention use will be documented (see the *Secondary Outcome Measures* section) at the 3 assessment time points (baseline, 9-week follow-up, and 21-week follow-up). All patients will be encouraged to continue their usual treatments that they access for their pain.

Ancillary Provisions and Posttrial Care

The clinical trial insurance held by the trial sponsor (UNSW) provides indemnity against personal injury claims from trial participants arising from their involvement in a UNSW-sponsored human clinical trial.

Outcome Measures

Overview

In addition to clinical and demographic data assessed at baseline (eg, age, sex, education, marital status, pain condition, and pain location), outcomes, measures, and their assessment time points

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are presented in Table 3. All measures used for the primary and secondary outcomes have demonstrated validity and reliability. Measures to monitor participants' ongoing medication and health interventions accessed during the trial are also listed. All measures, including demographic data, will be self-reported by the participants on the web. Links to the questionnaires will be emailed to participants at 3 time points: baseline, 9-week follow-up, and 21 week follow-up.

Table 3. Measures and time points of administration to participants.

Domain	Measure	Time point		
		Baseline	9-week follow-up	21-week follow-up
Emotion dysregulation[a]	Difficulties in Emotion Regulation Scale–18	✓	✓	✓
Pain intensity[b]	Numeric Rating Scale	✓	✓	✓
Pain interference[b]	PROMIS[c] Pain Interference instrument	✓	✓	✓
Anxiety[b]	State-Trait Anxiety Inventory	✓	✓	✓
Depression[b]	Beck Depression Inventory	✓	✓	✓
Perceived stress[b]	NIH[d] Toolbox Perceived Stress Scale	✓	✓	✓
Posttraumatic stress[b]	PTSD[e] Checklist–Civilian Version	✓	✓	✓
Social cognition[b]	The Awareness of Social Inference Test	✓	✓	✓
Sleep quality[b]	Medical Outcomes Study Sleep Scale	✓	✓	✓
Harm avoidance[b]	Temperament and Character Inventory	✓	✓	✓
Quality of life[b]	Satisfaction with Life Scale	✓	✓	✓
Well-being[b]	COMPAS-W[f] scale	✓	✓	✓
Medication and health interventions	Health Utilization Questionnaire	✓	✓	✓
Medication and health interventions	Medication and health interventions	✓	✓	✓
Acceptability[b,g]	DBT[h] Ways of Coping Checklist (DBT skills)	✓	✓	✓
Acceptability	Usefulness, Satisfaction, and Ease of Use Questionnaire		✓	✓
Acceptability	Patient Global Impression of Change		✓	✓
Acceptability	Semistructured interviews		✓	
Acceptability	Treatment adherence		✓	✓

[a]Primary outcome.

[b]Secondary outcome.

[c]PROMIS: Patient-Reported Outcomes Measurement Information System.

[d]NIH: National Institutes of Health.

[e]PTSD: posttraumatic stress disorder.

[f]COMPAS-W: Composure, Own-worth, Mastery, Positivity, Achievement, Satisfaction with Life–Well-being.

[g]Using the listed quantitative and qualitative measures, seven domains of acceptability will be assessed according to the theoretical framework of acceptability [48]: (1) affective attitude, (2) burden, (3) ethicality, (4) intervention coherence, (5) opportunity costs, (6) perceived effectiveness, and (7) self-efficacy.

[h]DBT: dialectical behavioral therapy.

Primary Outcome Measure

The primary outcome of emotion dysregulation will be measured using the Difficulties in Emotion Regulation Scale [49], an 18-item Likert-type scale ranging from 1 (*almost never*) to 5 (*almost always*) with some reverse-coded items. Total scores will be used for this study, with higher scores indicating a higher level of emotion dysregulation.

Secondary Outcome Measures

Numeric Rating Scale

Pain intensity will be measured using the Numeric Rating Scale [50], a rating scale ranging from 0 to 10, with 0 representing one extreme (*no pain*) and 10 representing the other extreme (*pain as bad as it could be*) over the last 7 days.

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Patient-Reported Outcomes Measurement Information System Pain Interference Instrument

Pain interference will be measured with the Patient-Reported Outcomes Measurement Information System Pain Interference instrument [51], an 8-item Likert-type scale ranging from 1 (*not at all*) to 5 (*very much*), to assess how much pain has interfered with life in the last 7 days. Total raw scores will be converted to a standardized score, with higher scores representing higher pain interference.

State-Trait Anxiety Inventory

State anxiety will be measured using the state anxiety subscale of the State-Trait Anxiety Inventory [52], a 20-item Likert-type scale ranging from 1 (*not at all*) to 4 ("very much so"), to measure current anxiety. Higher scores denote higher anxiety.

Beck Depression Inventory

Depressive symptoms will be measured using the Beck Depression Inventory [53], a scale where participants select the best-fitting statement from 4 options ranging from 0 to 3 to measure depressive symptoms experienced in the last 7 days. Higher scores reflect greater depressive symptoms.

National Institutes of Health Toolbox Perceived Stress Scale

Perceived stress will be measured using the National Institutes of Health Toolbox Perceived Stress Scale [54], a 10-item Likert-type scale with scores ranging from 1 (*never*) to 5 (*very often*), to assess the levels of stress experienced in the past month. Total raw scores will be converted to a standardized score, with higher scores representing higher stress.

PTSD Checklist–Civilian Version

Posttraumatic stress symptoms will be measured using the PTSD Checklist–Civilian Version [55], a 17-item Likert-type scale with scores ranging from 1 (*not at all*) to 5 (*extremely*), to assess how much participants have been bothered by problems regarding past traumatic events over the last month. Total scores will be used, with higher scores indicating a higher level of posttraumatic stress symptoms (re-experiencing, avoidance, and hyperarousal).

The Awareness of Social Inference Test–Short

Social cognition will be measured using a web-based version of the Awareness of Social Inference Test–Short [56]. The Awareness of Social Inference Test–Short uses audiovisual vignettes separated into three parts: (1) The Emotion Evaluation Test, in which participants identify emotions (happy, neutral, sad, anxious, angry, and disgusted); (2) the Social Inference–Minimal; and (3) the Social Inference–Enriched. For parts 2 and 3, participants are asked to answer *Yes*, *No* or *Don't Know* to 4 probe questions about thoughts, intentions, and feelings. The 3 parts are scored, and there is an overall score (sum of the 3 parts), with higher scores indicating higher social cognition.

Medical Outcomes Study Sleep Scale

Sleep quality will be measured using the Sleep Problems Index II from the Medical Outcomes Study Sleep Scale [57], a 9-item Likert-type scale ranging from 1 (*all of the time*) to 6 (*none of the time*), to measure sleep quality over the last 4 weeks. Higher scores indicate greater sleep problems over the last 4 weeks.

Temperament and Character Inventory–Harm Avoidance Scale

The personality trait of harm avoidance will be measured using the Temperament and Character Inventory–Harm Avoidance Scale [58], a 35-item scale that uses alternate-response questions (true or false) to measure how individuals usually feel. Total scores are converted to percentile scores (84%-100%=very high; 67%-83.3%=high; 34%-66.7%=average; 17%-33%=low; 0%-16.7%=very low).

Satisfaction With Life Scale

Overall life satisfaction will be measured using the Satisfaction with Life Scale [59], a 5-item Likert-type scale ranging from 1 (*strongly disagree*) to 7 (*strongly agree*). Scores are summed to obtain a total, with higher scores indicating higher life satisfaction.

The Composure, Own-Worth, Mastery, Positivity, Achievement, Satisfaction With Life–Well-being Scale

Well-being will be measured using the Composure, Own-worth, Mastery, Positivity, Achievement, Satisfaction with Life–Well-being Scale [60], a 26-item Likert-type scale ranging from 1 ("strongly disagree") to 5 (*strongly agree*) with 5 items reverse-coded (items 5, 7, 14, 21, and 26). Participants' scores are summed and compared with standardized cutoffs: languishing (<88), moderate (89-108), and flourishing (>109).

Acceptability Measures

A mixed methods (qualitative and quantitative) approach will be used to measure acceptability in accordance with the theoretical framework for acceptability (TFA) [48]. The TFA encompasses seven domains to measure cognitive and emotional responses to a health care intervention: (1) affective attitude, (2) burden, (3) ethicality, (4) intervention coherence, (5) opportunity costs, (6) perceived effectiveness, and (7) self-efficacy [48].

Semistructured Interview

A semistructured interview will be administered via video conference at 9 weeks to participants one-on-one in the treatment group. The question topics in the semistructured interview will be guided by the TFA [48]. Specifically, questions will provide insights into affective attitude (eg, "what are your thoughts about the program?"), burden (eg, "Has the effort required to participate in the intervention outweighed the burden of participating?"), ethicality (eg, "How likely would you be to recommend the program?"), intervention coherence (eg, "What's been your experience of using the web app?"), self-efficacy (eg, "How confident are you in your abilities to use the intervention?"), opportunity costs (eg, Have you had to give up anything that is of benefit to you to do the intervention?), and perceived effectiveness (eg, "How does this approach compare to other treatments? Has it had more effect/less?").

Usefulness, Satisfaction, and Ease of Use Questionnaire

The Usefulness, Satisfaction, and Ease of Use Questionnaire [61] is a 30-item Likert-type scale ranging from 1 (*strongly*

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disagree) to 7 (*strongly agree*) whereby average scores are calculated for 4 dimensions of usability (usefulness, ease of use, ease of learning, and satisfaction). A higher mean reflects a greater presence of the dimension, with a suggested threshold score of 5 denoting a positive rating [62]. The TFA constructs of burden, self-efficacy, intervention coherence, and ethicality will be assessed using the Usefulness, Satisfaction, and Ease of Use Questionnaire subscales of usefulness, ease of use, ease of learning, and satisfaction, respectively.

DBT Ways of Coping Checklist–DBT Skills Subscale

The DBT skills subscale of the DBT Ways of Coping Checklist [63], which evaluates DBT skills use, will be used to help evaluate intervention coherence. An average score across the subscale items will be calculated, with higher average scores indicating greater intervention compliance.

Patient Global Impression of Change Scale

Perceived effectiveness will be measured using the Patient Global Impression of Change Scale [64], a 7-point scale depicting overall improvement related to activity limitations, symptoms, emotions, and overall quality of life, and a scale of 0 (*much better*) to 10 (*much worse*) points to identify the degree of change since the start of treatment.

Treatment Adherence

The burden of the intervention will be evaluated according to session attendance (eg, iDBT-Pain sessions attended) and time spent using the app, recorded by the DBT skills trainer and on the app server. A higher attendance and greater amount of time spent on the app will indicate a lower burden.

Medication and Health Intervention Measures

Although participants will be asked to refrain from making changes to their current medication (eg, pain analgesics) and health care treatment (eg, physiotherapy) during the trial, it is realistic that the treatment that participants access from their regular health care providers may change. To capture information about medication and health care changes, participants will be asked to complete two measures: (1) the Chronic Pain Medication and Health Intervention Questionnaire and (2) the Healthcare Utilization Questionnaire.

Participant Timeline

Interested participants will undergo a structured screening process that includes a web-based screening survey and, for those eligible after their survey responses, a phone call with a study investigator. Phone screening will be conducted as soon as possible after the web-based screening. After obtaining informed consent, baseline questionnaires will be administered within a window of 3 weeks before randomization. Participants will be randomly allocated and will learn about group assignment at least 1 week before the first Zoom session. After the 9-week intervention delivery period, participants will be assessed again at 9 and 21 weeks after randomization. Participants will be asked to complete the assessment within 1 week and will be prompted by phone, SMS text message, and email a maximum of 3 times for up to 4 weeks if they are not responsive. See Table 4 for a schematic showing the schedule of enrollment, interventions, and assessments.

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Table 4. Participant timeline (SPIRIT [Standard Protocol Items: Recommendations for Interventional Trials]) showing the schedule of enrollment, interventions, and assessments.

	Study period				
	Enrollment	Baseline and allocation	Postallocation		
Time point	−12 to −1 week	−2 to −1 week	0-9 weeks (intervention)	9-week follow-up	21-week follow-up
Enrollment					
Eligibility screening (online and phone)	✓				
Informed consent	✓				
Allocation		✓			
Interventions					
iDBT-Pain[a]			✓		
Treatment as usual			✓		
Assessments					
Primary outcome measure					
Difficulties in Emotion Regulation Scale-18		✓		✓	✓
Secondary outcome measures					
Numeric Rating Scale		✓		✓	✓
PROMIS[b] Pain Interference Instrument		✓		✓	✓
State-Trait Anxiety Inventory		✓		✓	✓
Beck Depression Inventory		✓		✓	✓
NIH[c] Toolbox Perceived Stress		✓		✓	✓
PTSD[d] Checklist–Civilian Version		✓		✓	✓
The Awareness of Social Inference Test		✓		✓	✓
Medical Outcomes Study Sleep Scale		✓		✓	✓
Temperament & Character Inventory		✓		✓	✓
Satisfaction with Life Scale		✓		✓	✓
COMPAS-W[e] Scale of Wellbeing		✓		✓	✓
Health Utilization Questionnaire		✓		✓	✓
Medication & Health Interventions		✓		✓	✓
Acceptability measures					
DBT[f] Ways of Coping Checklist		✓		✓	✓
Usefulness, Satisfaction & Ease of Use				✓	✓
Patient Global Impression of Change				✓	✓

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	Study period				
	Enrollment	Baseline and allocation	Postallocation		
Time point	−12 to −1 week	−2 to −1 week	0-9 weeks (intervention)	9-week follow-up	21-week follow-up
Semistructured interview				✓	
Treatment adherence			✓	✓	✓

[a]iDBT-Pain: internet-delivered DBT skills training for chronic pain.

[b]PROMIS: Patient-Reported Outcomes Measurement Information System.

[c]NIH: National Institutes of Health.

[d]PTSD: posttraumatic stress disorder.

[e]COMPAS-W: Composure, Own-worth, Mastery, Positivity, Achievement, Satisfaction with Life–Well-being.

[f]DBT: dialectical behavioral therapy.

Sample Size

The sample size for this trial was calculated using the SAS software (version 9.4; SAS Institute) of the SAS system (SAS and all other SAS Institute Inc product or service names are registered trademarks or trademarks of SAS Institute Inc in the United States and other countries) and is based on the large effect size (pain intensity; effect size=0.81) obtained from our previous trial [46]. The power analysis is based on the effect size of the secondary outcome from the previous trial rather than the primary outcome effect size of 0.88 for emotion dysregulation to obtain a more cautious sample size estimate given that the previous trial was conducted with a small population using a single-case design. To detect a large mean difference (η^2=0.14) between the treatment groups in this trial, a total of 40 people (20 in each group) will be required. This assumes 80% power, a Cronbach α of .05, and a within-subject correlation of 0.5. Attrition rates for studies investigating cognitive behavioral treatments for chronic pain vary between 0% and 30%, with a mean attrition of 13% (SD 10%); thus, we have set expectations for attrition at 20%, resulting in a total sample size of 48 [65]. We expect this estimate to be transferable to the web-based delivery of psychological interventions as research suggests that trials using remote delivery generally show comparable or even lower rates of attrition [66]. Rates of attrition will be monitored by the research team at regular milestones during the trial (eg, at the point where 50% of the participants have reached their scheduled 21-week follow-up time), and we will consider taking steps to increase sample size if this is required.

Recruitment

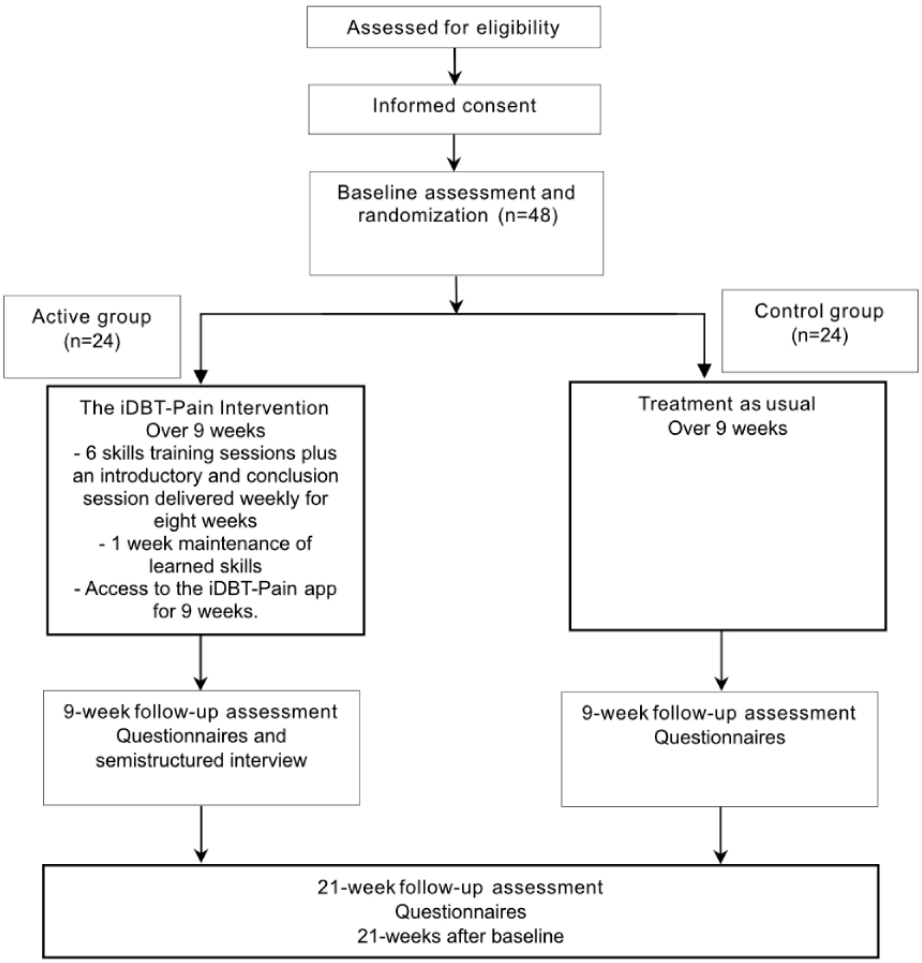
Individuals with chronic pain who had previously contacted our group (n=300) and requested information about participating in studies on chronic pain will receive by email the study details, including the participant information statement, and a link to the study web page. Recruitment will also use ethically approved web-based community advertising on Facebook. There is growing evidence that Facebook is a useful recruitment tool for research, particularly to access hard-to-reach populations [67] such as the chronic pain population. The Facebook advertisement will include a link to the study web page.

From the study web page, interested participants can click through to a web-based screening survey that will ask questions about age and demographics, chronic pain condition, existing and previous psychological and neurological diagnoses, internet accessibility, fluency in reading and speaking English, contact details, and location. Potential participants who are positive on their web-based screening will be contacted to arrange a phone call with a study investigator. The purpose of the phone call is to ask further questions to determine eligibility. Questions will ascertain chronic pain diagnosis, injury, current medications, therapy, and interventions being received, along with plans for any upcoming medication or treatment changes or surgery. An important part of the screening phone call is to determine whether there is a previous or current diagnosis of any psychological or neurological disorder that may exclude the participant from the study. The researcher will ask the potential participant if there is any current or previous diagnosis of schizophrenia, borderline personality disorder, or bipolar disorder and whether there is a current diagnosis of a psychological disorder that is uncontrolled (eg, depression that is not being treated with psychotherapy or antidepressants). Those who do not meet the eligibility criteria will be informed of this sensitively and asked if they wish to remain on our secure database to be contacted about future trials.

Participants that are eligible will be emailed after the phone call to complete the informed consent process, whereby they will have the opportunity to discuss the Participant Information Statement and consent process with a researcher before electronically signing the consent form. Eligible, fully informed, and consenting participants will then be entered into the study for baseline assessment and randomization (Figure 2).

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Figure 2. Flowchart of the study design. iDBT-Pain: internet-delivered dialectical behavioral therapy skills training for chronic pain.



Allocation

Sequence Generation

Following informed consent, participants will be randomly allocated to groups (treatment or TAU) at a ratio of 1:1. A block randomization schedule will be used with a block size of 2 generated by a statistician blinded to study recruitment, treatment, and data collection. Opaque sealed envelopes will ensure concealment from the DBT trainer and psychologist administering the intervention until the interventions are assigned. An independent research assistant will prepare the envelopes. Once the participant has consented to the trial and completed the baseline assessment, the independent research assistant will open the envelope to assign the participant. Owing to the nature of this intervention, the participants and DBT skills trainer delivering the intervention will not be blinded to group allocation. The skills trainer will be made aware of the group allocation by the research assistant and will then advise the participants of their group after completion of the baseline assessment. The statistician conducting the primary data analysis will be blinded to group allocation.

Concealment Mechanism

Opaque sealed envelopes will ensure concealment until interventions are assigned.

Implementation

A statistician blinded to study recruitment, treatment, and data collection will generate the allocation sequence. Participants will be enrolled in the study by the researchers, who will be blinded until after intervention assignment. An independent research assistant will assign participants to the interventions.

Blinding

Owing to the nature of this intervention, the participants and those delivering the intervention (DBT skills trainer and psychologist) will not be blinded to group allocation after the baseline assessment. However, the baseline assessment is conducted before randomization, meaning that there is no risk of disclosure of treatment allocation to the assessor or participant at the time. All assessments will be distributed remotely via automated email with a web link to complete the assessment on the web, thereby ruling out any potential effects of assessors on assessments of outcomes at the 9- and 21-week follow-ups. The statistician analyzing the outcome data will remain blind to treatment allocation throughout the analysis.

Data Collection and Management

Plans for Assessment and Collection of Outcomes

Data will be collected sequentially using web-based questionnaires administered through the Qualtrics survey platform at 3 time points: baseline and 9- and 21-week follow-ups. The measures for the primary and secondary

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outcomes are validated and commonly used instruments (see the *Outcome Measures* section). Web-based data collection is an appropriate way of collecting data for our study as questionnaires can be answered and delivered remotely, consistent with the web-based nature of the trial. Participants will self-report data about their pain, emotions, and psychological states and traits.

Plans to Promote Participant Retention and Complete Follow-up

To aid retention, participants in both groups who complete the trial may enter a prize draw to receive 1 of 2 Aus $200 (US $133.72) gift cards. To further aid retention, participants (treatment and TAU) who complete the study (ie, following the 21-week follow-up assessment) will be asked if they would like to retain or obtain access to the iDBT-Pain app. In addition, the use of web-based assessments will reduce the burden on participants to promote retention. Dropout from the study will be recorded, including the reasons. Participants will be free to withdraw at any point. Withdrawn participants will not be replaced. Upon conclusion of the study (ie, following the 21-week follow-up assessment), all participants (treatment and TAU) will be asked if they would like to retain or obtain access to the iDBT-Pain app.

Data Management

The research team will treat all participant information ethically and with confidentiality in accordance with the UNSW data governance policy. Data will be anonymized and stored on a secure data platform at UNSW protected via username and password. Personal and identifiable information will be stored separately from the anonymized trial data, and data will be anonymized wherever possible. For analysis, the qualitative and statistical data will be downloaded onto password-protected computers accessible by the trial investigators. Data from the web-based questionnaires will be quality checked by the research team before analysis.

Confidentiality

Information collected as part of the trial will be kept strictly confidential within the research team. Participants' names and contact details will be stored in password-protected files on secure servers and separately to linked anonymized data. To ensure skills trainer adherence and competency, the sessions will be recorded with the consent of all participants appearing in the recording. With the consent of the participants, recordings will be made available to participants who need to catch up on missed content on a password-protected web link to view the video on the web. Participants will have the option to keep their camera off during the session. Access to these recordings is restricted to those with the link and password.

Access to Data

All investigators will be able to access the full trial data set. To ensure confidentiality, data dispersed to the project team members and the statistician conducting the analysis will not contain any identifying participant information.

Data Analysis Methods

Statistical Methods

Overview

For all primary and secondary outcomes that are normally distributed and measured over time, a linear mixed model with random effects of individuals will be specified. The fixed effects of time, treatment group, and their interaction will be included. Treatment differences at 9 and 21 weeks and change from baseline to 9 and 21 weeks within each group will be estimated. If the distributional assumption of normality is not tenable, an appropriate transformation of the outcome will be conducted. Alternatively, a generalized linear mixed model with appropriate distribution will be used.

The data will be analyzed on an ITT basis. Unadjusted and adjusted analyses will be conducted. The adjusted analyses will include age at baseline and sex. P values of $<.05$ will be considered significant. Effect sizes will be expressed in terms of pooled baseline SD units, as described by Feingold [68].

Qualitative Methods

Qualitative data from the semistructured interviews will be transcribed, coded, and then summarized according to the TFA framework [48]. Specifically, under the headings of the TFA constructs (affective attitude, burden, perceived effectiveness, ethicality, intervention coherence, opportunity costs, and self-efficacy), a thematic analysis will be used to code responses according to key emerging themes [69]. Quantitative data from measures that assess domains of acceptability along with treatment adherence data will be descriptively summarized according to the individual measures. A collective summary of both quantitative and qualitative data will be reported to provide a comprehensive understanding of the acceptability of the iDBT-Pain intervention.

Methods for Additional Analyses

There is no a priori plan to conduct subgroup analyses.

Methods in Analysis to Handle Protocol Nonadherence and Any Statistical Methods to Handle Missing Data

Although linear mixed models do allow for unbiased estimates of the treatment effect with missing data assuming data that are missing at random [70], we will also use multiple imputation to estimate the treatment effect in the primary outcome as a sensitivity analysis. Supposing that the missing-at-random assumption is tenable, we will use multiple imputation using chained equations, include variables of baseline pain intensity and psychological factors in the imputation model, and then estimate the treatment effect in the imputed data.

As a sensitivity analysis, a modified ITT analysis will be performed. As detailed in the *Allocation* section, participants are randomized into a treatment group, but they will be included in the final data set only if they have completed the 6 iDBT-Pain skills training sessions delivered via Zoom in weeks 2 through 7 either by attending the session or by watching a video of the session.

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Data Monitoring

An independent data monitoring committee has not been arranged as the intervention occurs over a short period, the protocol will not be modified irrespective of data collected during the intervention, and there are minimal risks to participants. No interim analyses are planned.

Trial Management Group

The Trial Management Group (TMG) will oversee the day-to-day conduct of the trial and will be responsible for reviewing the safety information to identify any serious emerging safety concerns. Any major amendments required to the study or changes to the protocol will first be agreed upon by the TMG and then communicated to participants as soon as possible by one of the researchers. The TMG will be responsible for seeking the advice of the ethics committee and the trial sponsor. The TMG is a board of elected individuals comprising the principal investigator, researchers, DBT skills trainers, trial managers, and research assistants.

Adverse Event Reporting and Harms

DBT skills training is an evidence-based protocol for emotion dysregulation [39,71] and a standardized approach with no known side effects [35,36]. Thus, although we will measure safety, we do not anticipate any intervention- or study-related adverse events or reactions and consider the potential risks to be mild and of minimal likelihood to occur. Potential risks include experiencing temporary and transient increases in distress during the skills training, discomfort in terms of fatigue from attending up to 9 hours of Zoom sessions over the course of the intervention, and upset or discomfort when answering the questionnaires. To identify risk issues, participants will have the ability to communicate with the research staff throughout the study via email and phone, with concerns then raised to the TMG. Where necessary, participants will be provided with details of support services or advised to contact their regular health care professional (eg, general practitioner). To mitigate fatigue during the Zoom sessions, the sessions will be spaced evenly throughout the intervention period, 1 per week over 8 weeks, with sufficient time between sessions and breaks as necessary. Participants will also be asked to have a glass or bottle of water during the Zoom sessions to stay hydrated. If participants find the questionnaires distressing, they will be advised that they can skip to the next question or stop immediately.

Safety will be measured according to adverse events (untoward medical occurrence) or reactions (unintended response to treatment) related to iDBT-Pain, with data collected about the incidents by the research team in trial-related Safety Monitoring and Adverse Events forms.

Frequency and Plans for Auditing Trial Conduct

The TMG will be responsible for periodic auditing to evaluate trial conduct and compliance with the protocol, good clinical practice, standard operating procedures, and UNSW sponsor and ethics requirements.

Protocol Amendments

In the instance that amendments to the protocol are needed, the TMG will seek sponsor approval, after which trial registrations and the published protocol will be amended accordingly. A member of the TMG will communicate any resulting changes in the protocol to the participants.

Dissemination Plans

To enable effective dissemination, the results will be considered for submission to appropriately selected peer-reviewed journals, summarized in a press release for the media, and included in presentations at conferences. This will ensure the dissemination of this research and data to other researchers and interested parties. Anonymized data sets and associated material may be available upon reasonable request from the corresponding author. Participants will be sent a summary of the research findings if they consent to this.

Ethics Approval and Consent to Participate

Ethics approval was obtained from the University of New South Wales Human Ethics Committee (HC220078). Written informed consent to participate will be obtained from all participants.

Results

Recruitment started in February 2023, and the clinical trial started in March 2023. Data collection for the final assessment is planned to be completed by July 2024.

Discussion

Potential Clinical Implications

Emotion dysregulation is key to the development and maintenance of chronic pain, leading to a cycle of worsening pain intensity, disability, and emotional difficulties [16-18]. Evidence is arising that DBT may be a viable intervention to target emotion dysregulation in people with chronic pain, helping reverse this cycle of pain and emotional distress and leading to improved physical and psychological function [35-37]. Specifically, iDBT-Pain, a guided internet-delivered approach encompassing live web-based sessions and access to an app, has been found in a previous SCED trial to reduce symptoms of emotion dysregulation and pain intensity [46].

In this protocol, we described an RCT to test iDBT-Pain compared with a control group. We plan to investigate the efficacy of iDBT-Pain in improving the primary outcome of emotion dysregulation and the secondary outcomes of pain intensity, pain interference, anxiety symptoms, depressive symptoms, perceived stress, posttraumatic stress, harm avoidance, social cognition, sleep quality, life satisfaction, and well-being. The RCT will test the acceptability of a group-based version of iDBT-Pain that builds on the individualized treatment previously investigated in the SCED trial.

To our knowledge, iDBT-Pain is the first guided internet-delivered DBT intervention for people with chronic pain. As an internet-delivered approach, iDBT-Pain offers an accessible option for those with restricted mobility and remote communities where there are often limited psychological

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services for people with chronic pain. If our hypotheses are confirmed, our findings will contribute to the evidence for the efficacy and acceptability of a viable intervention that may be used by health care professionals for people with chronic pain. Similarly, the results will add to the chronic pain literature to inform about the potential benefits of DBT and technologically driven interventions. More broadly, the findings will contribute to the evidence on whether interventions that target emotion dysregulation in people with chronic pain can lead to improved emotions and less pain.

Limitations

The limitations of this study include the potential for participants to access other interventions and pain analgesics while in the trial. However, we will ask participants to disclose their pain medication and treatments and advise us of any changes in their dosages that occur during the trial period. Thus, the results can be considered in the context of any confounding factors related to treatment outside the trial. A further limitation is that therapist blinding is not possible because of the nature of the intervention. In addition, the sample size may limit the ability to generalize the findings to a larger population and detect more subtle effects.

Acknowledgments

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Data Availability

Anonymized data sets and associated material will be available upon reasonable request from the corresponding author.

Authors' Contributions

NNN and SMG conceptualized the idea for this trial. CRW, J Schroeder, and J Suh were responsible for the original development of the app, with updates by NNN and SMG. The trial and analysis plan were developed by NNN, SMG, CRW, NEB, YQ, NHS, and JHM. NNN prepared the first draft of the manuscript. Successive drafts received substantial contributions from all authors to revise and critically review all content and plans for the analysis. The final version of the manuscript was approved by all authors.

Conflicts of Interest

CRW receives consulting fees from Mindstrong Health, Behavioral Tech, and Lyra Health. All other authors declare no conflicts of interest.

Multimedia Appendix 1
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist.
[PDF File (Adobe PDF File), 129 KB - resprot_v12i1e41890_app1.pdf]

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Abbreviations

DBT: dialectical behavioral therapy
iDBT-Pain: internet-delivered dialectical behavioral therapy skills training for chronic pain
ITT: intention-to-treat
PTSD: posttraumatic stress disorder
RCT: randomized controlled trial
SCED: single-case experimental design
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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TAU: treatment as usual
TFA: theoretical framework for acceptability
TMG: Trial Management Group
UNSW: University of New South Wales

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Protocol

Adaptation of a Mobile Interactive Obesity Treatment Approach for Early Severe Mental Illness: Protocol for a Mixed Methods Implementation and Pilot Randomized Controlled Trial

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Abstract

Background: Obesity is common in individuals with severe mental illness (SMI), contributing to a significantly shortened lifespan when compared to the general population. Available weight loss treatments have attenuated efficacy in this population, underscoring the importance of prevention and early intervention.

Objective: Here, we describe a type 1 hybrid study design for adapting and pilot-testing an existing mobile health intervention for obesity prevention in individuals with early SMI and Class I or early-stage obesity, defined as a BMI of 30-35.

Methods: An existing, evidence-based interactive obesity treatment approach using low-cost, semiautomated SMS text messaging was selected for adaptation. Community mental health clinics and Clubhouse settings in Eastern Missouri and South Florida were identified to participate. This study has the following 3 aims. First, using the Enhanced Framework for Reporting Adaptations and Modifications to Evidence-based interventions, contextual aspects of the clinical and digital treatment environments are identified for adaptation, considering 5 main stakeholder groups (clinical administrators, prescribing clinicians, case managers, nurses, and patients). Following a 2-week trial of unadapted SMS text messaging, Innovation Corps methods are used to discover needed intervention adaptations by stakeholder group and clinical setting. Second, adaptations to digital functionality and intervention content will be made based on themes identified in aim 1, followed by rapid usability testing with key stakeholders. A process for iterative treatment adaptation will be developed for making unplanned modifications during the aim 3 implementation pilot study. Individuals working in partner community mental health clinics and Clubhouse settings will be trained in intervention delivery. Third, in a randomized pilot and feasibility trial, adults with 5 years or less of treatment for an SMI diagnosis will be randomized 2:1 to 6 months of an adapted interactive obesity treatment approach or to an attentional control condition, followed by a 3-month extension phase of SMS text messages only. Changes in weight, BMI, and behavioral outcomes, as well as implementation challenges, will be evaluated at 6 and 9 months.

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Results: Institutional review board approval for aims 1 and 2 was granted on August 12, 2018, with 72 focus group participants enrolled; institutional review board approval for aim 3 was granted on May 6, 2020. To date, 52 participants have been enrolled in the study protocol.

Conclusions: In this type 1 hybrid study design, we apply an evidence-based treatment adaptation framework to plan, adapt, and feasibility test a mobile health intervention in real-world treatment settings. Resting at the intersection of community mental health treatment and physical health promotion, this study aims to advance the use of simple technology for obesity prevention in individuals with early-stage mental illness.

Trial Registration: ClinicalTrials.gov NCT03980743; https://clinicaltrials.gov/ct2/show/NCT03980743

International Registered Report Identifier (IRRID): DERR1-10.2196/42114

(JMIR Res Protoc 2023;12:e42114) doi:10.2196/42114

KEYWORDS

community mental health services; implementation science; mental disorders; obesity; primary prevention

Introduction

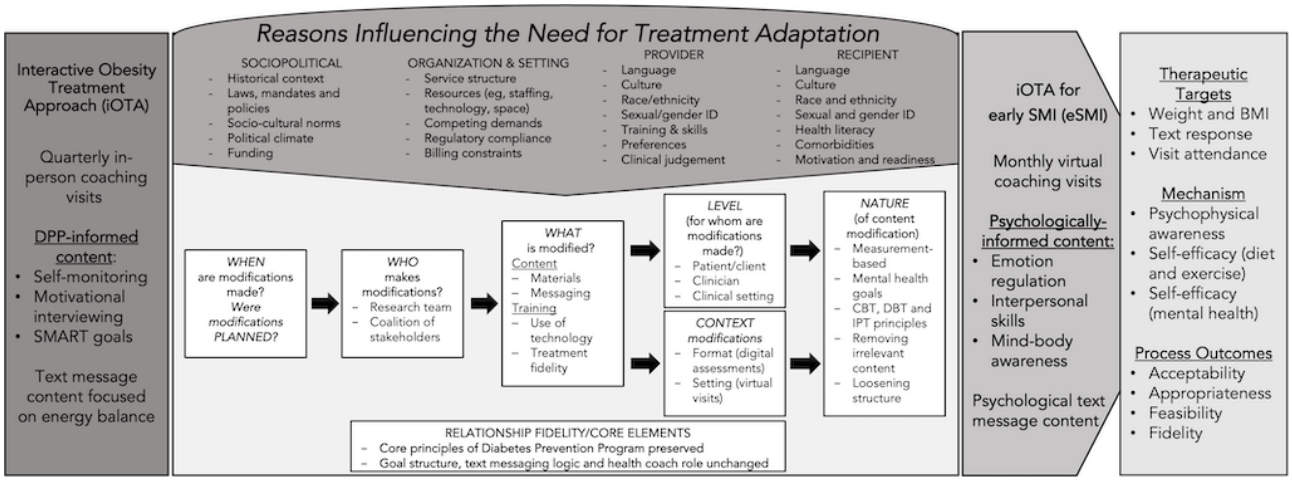
Background and Rationale

Younger and treatment-naïve individuals with early severe mental illness (eSMI) experience adverse health effects associated with medications, including significant weight gain, metabolic dysregulation, and early onset cardiovascular disease [1,2]. eSMI patients are at high risk for treatment nonadherence, and benefit from behavioral programming that recognizes their unique engagement needs, which include psychological support to shore up healthy coping strategies and reduce cognitive load [3-5]. Successful health behavior change requires promotion of self-determination and cognitive control [6,7] as well as development of psychophysical self-knowledge through accurate interpretation of interoceptive cues (eg, hunger and satiety) [8,9]. These target mechanisms map onto the National Institute of Mental Health Research Domain Criteria [10] constructs for cognitive systems, cognitive control, and social processes (social awareness, self-awareness), offering a constructive pathway to achieve self-determination for health behaviors [11], cognitive control, and interoceptive awareness.

Digital or mobile health (mHealth) interventions show promise for enhancing engagement in lifestyle interventions among adolescents and young adults with chronic medical conditions [12-14]. Nonetheless, digital interventions to prevent or attenuate weight gain occurring early in the course of treatment remain understudied [15,16]. We have modified an existing interactive obesity treatment approach (iOTA) [17,18] involving collaborative goal setting with a health coach and interactive SMS text messaging to provide ongoing support and self-monitoring of behavior change goals in adults with severe mental illness (SMI) (iOTA-SMI) [19,20]. Adaptation of iOTA-SMI for a prevention focus in eSMI, however, requires unique target mechanism engagement, due to the cognitive and functional characteristics of patients with eSMI, who are still coming to terms with the brain system dysfunction caused by their illness.

Adaptation of effective interventions for new populations and settings (eg, eSMI and prevention) necessitates a formal evaluation process and implementation science framework. Stirman's Framework for Reporting Adaptation and Modifications-Enhanced (FRAME, Figure 1) [21], offers an evidence-based approach for identifying adaptation needs based on contextual information that will inform adaptations specific to underrepresented racial, ethnic, socioeconomic and gender groups. Using FRAME, this study will further adapt the existing iOTA for obesity prevention in people with eSMI, hypothesizing treatment-related change in body weight will be inversely related to psychophysical awareness and self-efficacy for managing physical and mental health.

Figure 1. Framework for Reporting Adaptation and Modifications-Enhanced. CBT: Cognitive Behavior Therapy; DBT: Dialectic Behavior Therapy; DPP: Diabetes Prevention Program; eSMI: early severe mental illness; iOTA: interactive obesity treatment approach; IPT: Interpersonal Therapy.



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The mixed methods approach for this project involves the following three research aims to be conducted over 3 years: (1) identify adaptation targets to optimize iOTA for use by younger patients with eSMI treated in community mental health clinics (CMHCs) settings, incorporating perspectives from underrepresented groups; (2) adapt the existing iOTA, including modifications to key messaging to facilitate engagement and understanding in racial, ethnic socioeconomic, and gender-diverse groups in addition to adaptations relevant to eSMI in younger adults; and (3) conduct a randomized pilot test of the adapted iOTA in eSMI patients, evaluating both treatment effectiveness (change in body weight) and implementation effectiveness (feasibility, acceptability, and appropriateness) over 24 weeks.

Trial Design

Employing the FRAME model, we will apply Innovation Corps (I-Corps) methods [22,23] to identify perceived barriers and challenges to implementing an iOTA in CMHC settings. Attention will be given to challenges related to the patient population (eg, early illness, cognitive impairment, and negative symptom effects on the ability to engage), care setting, case manager burden, lack of time and human resources, limited training, and supervision or accountability) and to the collection of multilevel (eg, patient, family, clinical staff, and administrator) and multimethod (eg, focus groups, semistructured interviews) data that can inform adaptations to increase the likelihood of success. Finally, key process outcomes will be measured (eg, acceptability, feasibility, fidelity, and appropriateness) during adaptation and pilot testing [24].

Methods

Aim 1: Identify iOTA Adaptation Needs for eSMI Using I-Corps Methods

This aim will determine how to best facilitate health behavior change in eSMI patients through interventions at the level of the individual, the health care provider, and the broader health care organization.

Study Settings

To achieve diversity in the participant samples, treatment settings, and social determinants, the proposed project will be conducted in CMHC and community Clubhouse settings in Missouri and Florida. Locations were chosen for the long-term collaboration between research teams and the representative racial and ethnic diversity of client and clinician populations and marked diversity of health care environments.

Study Procedures

I-Corps Methods

Starting with a list of hypotheses about barriers or challenges to implementation in CMHC settings, the study team identifies individuals who represent consumers or customers at multiple levels within the organization. Interviews and focus groups are conducted to test the hypotheses. Once facts have been obtained, the team reviews data looking for emergent themes that inform an overall “value proposition” for the customer or key stakeholder, identifying potential “pain” and “gain” areas. The team can then determine actions needed to change or adapt iOTA to best fit the CMHC environment. Purposive sampling methods will be applied to avoid bias in focus group responses, working with community partners to ensure group composition represents a broad range of perspectives from underrepresented populations.

Focus Groups

Once the focus group participants are identified, they will be asked to participate in one in-person or phone visit to set up health goals and related SMS text messages. They will then participate in 1-2 weeks of iOTA SMS text messaging to facilitate optimal feedback on intervention adaptations. Focus groups will be scheduled within 1 week of completing the 2-week iOTA trial. Groups will be conducted at the CMHC site during a time that is convenient for participants and will be facilitated by a research assistant facilitator and CMHC staff member taking additional notes.

Eligibility Criteria

We will conduct 8 focus groups of 5 participants each at each CMHC site, for a total of 16 focus groups (Table 1). Focus group composition will be monitored to balance groups with respect to age, race, and gender, taking care to include outlier perspectives on mHealth technology and obesity treatment. Participants will include administrators, prescribers, nursing staff, case workers, clients, and client social support.

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Table 1. Focus group composition and questions.

Group type	Participant type	Areas of interest
Directors and Supervisors	Medical director, clinical supervisor	• What should the qualifications and characteristics of the health coach be? • Is it reasonable for the health coach to be an existing staff member?
Prescribing clinicians	Psychiatrists, advanced practice nurses	• What type of training should health coaches receive? • How often should face-to-face health coaching meetings be?
Nursing staff	Nursing staff, nurse care managers	• What should the content of health coaching meetings be? • How frequent should text messages be?
Community support workers	Community and peer support specialists	• What should the content of the messages be? • Is it helpful to have secure, 2-way texting capability?
Administrative staff	Supervisors and clinic managers	• How much time could existing staff devote to intervention delivery? • What would the optimal amount of time be for intervention effectiveness?
Members or clients	Adult clients (18-45 years of age)	• What would make the intervention acceptable to younger adults? • Are there modifications needed to address social determinants of health?

Data Management and Analytic Plan

Recorded groups will be transcribed, and text data will be entered into NVivo, coded by 2 independent raters. We will use inductive coding methods based on pragmatic-variant grounded theory to develop a coding tree based on the focus group question framework and new themes identified in the focus group transcripts. Precoding data exploration will identify the most used words and phrases by focus group, which are then explored for meaning and context to establish content themes.

Aim 2: Adapt the Parent iOTA for Use in Younger Adults With eSMI

Contextual, content, and training aspects of the treatment will be adapted based on qualitative data collected using the I-Corps methods within the FRAME treatment adaptation model in aim 1. Adaptations will be tested for feasibility by members of the focus groups queried in aim 1.

Eligibility Criteria

Individuals who participated in aim 1 focus groups will be queried with individual semistructured interviews to obtain feedback on treatment adaptations.

Study Procedures

iOTA Adaptation

Existing libraries of SMS text messages will be tested for usability and cultural appropriateness among members of our target population of eSMI patients. We will conduct key informant interviews using the I-Corps methodology following this testing and adapt the messages and risk assessment platform as needed based on this information.

Key Informant Interviews

Using a standardized interview guide developed using I-Corps methods, we will conduct semistructured, in-person key informant interviews with 1-2 members from each focus group at each study site to obtain impressions about adaptations made based on focus group results. Interviewing will be curtailed when saturation occurs (ie, when the same themes repeatedly emerge) [25,26].

Data Management and Analytic Plan

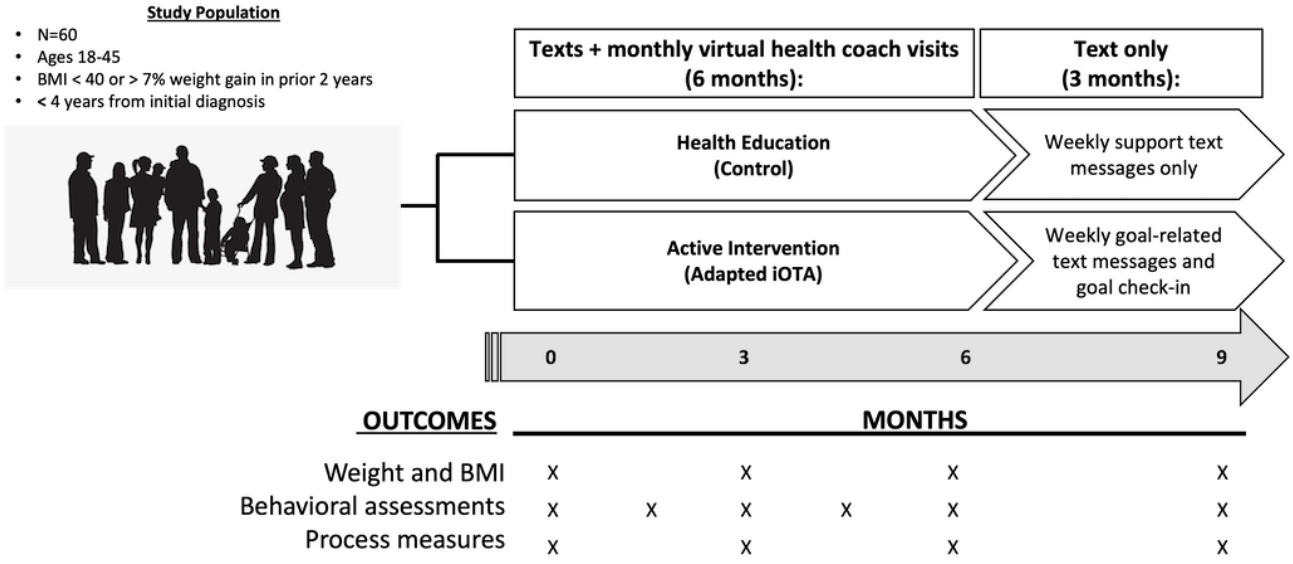
Interviews will be digitally recorded and transcribed verbatim. Data will be analyzed using standard content analysis strategies listed in aim 1.

Aim 3: Randomized Controlled Pilot Test of the Adapted Intervention

In this aim, we will conduct a randomized 24-week pilot study of the adapted iOTA-eSMI intervention, followed by 12 weeks of SMS text messaging intervention alone in 60 participants (30 at each study site), evaluating both intervention and implementation effectiveness (Figure 2).

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Figure 2. Study overview. iOTA: interactive obesity treatment approach.



Eligibility Criteria

To capture "early" phase mental illness, we will use the length of illness requirement commonly used in Food and Drug Administration Phase III clinical trials testing treatment efficacy in early mental illness (eg, less than 5 years from diagnosis). "At risk" weight is categorized using the Food and Drug Administration definition of clinically significant weight gain (eg, more than 7%) or overweight or early Class 1 obesity by BMI.

Study Procedures

Screening Assessments

To ensure minimal cognitive capacity to understand treatment materials and engage in SMS text messaging, we will use the Rapid Estimate of Adult Literacy in Medicine-Short Form (REALM-SF) minimal score of 5 (consistent with 7th grade reading level) and the University of California San Diego Brief Assessment of Capacity to Consent score of 15 or higher (consistent with the capacity to consent). To ensure minimal psychiatric symptom stability, we will use the Clinical Global Impression-Severity scale minimal score of 4 (consistent with moderate illness severity) or lower. The schedule of study visits and assessments is presented in Table 2.

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Table 2. Schedule of assessments.

	Enrollment	Allocation	Postallocation							Closeout
	Screen and startup	Baseline	T1	T2	T3	T4	T5	T6	T7	T8
Study week	−2	0	1	4	8	12	16	20	24	36
Screening and baseline assessments										
Informed consent[a]	✓									
CEI[b]	✓									
CGI[c]	✓									✓
Medication reconciliation	✓	*[d]	*	*	*	*	*	*	*	✓
Health status questionnaire	✓									✓
Height, weight, BMI	✓									
PASS[e]		✓								✓
Self-efficacy[f]		✓								✓
1-week Fitbit activity	✓	✓								✓
Treatment allocation		✓								
Time spent (hours)	1	1.5	0.15	0.15	0.15	0.15	0.15	0.15	0.15	1
Study visit assessments										
Adherence (visit attendance)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Height, weight and BMI	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Feasibility and acceptability							✓			✓
Treatment satisfaction							✓			✓
Time spent (hours)	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15	1.5
mHealth assessments										
Adherence (% SMS text message response)			✓	✓	✓	✓	✓	✓	✓	✓
Weekly body weight (lbs)			✓	✓	✓	✓	✓	✓	✓	✓
Weekly goal progress			✓	✓	✓	✓	✓	✓	✓	✓
Time spent (hours)	0	0	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15
Health coach self-assessments										
Response to intervention			✓	✓	✓	✓	✓	✓	✓	✓
Treatment fidelity			✓	✓	✓	✓	✓	✓	✓	✓
Time spent (hours)	0	0	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15

[a]Ability to provide Informed Consent assessed via the Rapid Evaluation of Adult Literacy in Medicine-Short Form and University of California, San Diego Brief Assessment of Capacity to Consent.

[b]CEI: credibility and expectations for improvement.

[c]CGI: clinical global impression scale.

[d]Assessments done as needed based on clinician judgment.

[e]PASS: psychophysical awareness and skills scale.

[f]Self-efficacy: self-efficacy for mental health, diet and physical activity.

Primary and Secondary Outcomes

The overall goals of this study are to establish the feasibility and acceptability of iOTA-eSMI as well as to inform sample size calculations for future randomized studies. Thus, the primary outcome will be a change in body weight (lbs) during 24 weeks of randomized treatment. Secondary outcomes will include changes in BMI, psychophysical awareness and skills, and self-efficacy for mental and physical health [27-29]. An increase in self-efficacy and psychophysical awareness are the proposed mechanisms of action for active iOTA intervention.

Psychophysical Awareness and Skills Scale

This composite measure draws from research domain criteria domains of cognitive systems and social processes, including cognitive control, perception, and understanding of self,

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self-awareness, self-monitoring, and self-knowledge. The composite measure includes 10 items that assess cognitive control [30], self-determination [31,32], and interoceptive awareness [33].

Self-Efficacy for Eating and Exercise Habits

For this study, we will use abbreviated surveys developed by Sallis et al [11] to measure self-efficacy in health behaviors involving eating and physical activity. Self-efficacy for diet and exercise will be measured at each study visit.

Mental Health Self-Efficacy Scale

The Mental Health Self-Efficacy Scale assesses belief in one's capability to perform behaviors related to mental health self-care and has been shown to predict response to mHealth interventions for mental health [27]. The Mental Health Self-Efficacy Scale will be completed at each in-person health coaching visit [28].

Exploratory Outcomes

We will characterize intervention feasibility, engagement, and implementation challenges as measured by enrollment, retention, and visit adherence; intervention acceptability [5,34]; engagement as measured by visit attendance and SMS text messaging response rates; health coach self-assessment of competence and fidelity to the intervention [5,35]; and intervention appropriateness and acceptability [36,37] as rated by clients and staff. Finally, participants will be provided a Fitbit Flex to be worn for 1 week before study visits 1 (baseline) and 7 (24 weeks) to assess for change in physical activity through step counts. Data will be downloaded upon return of the device.

Study Interventions

Parent iOTA

The individual-level iOTA intervention for adults with an SMI [20,38] is based on assessment of individual behavior risks, collaborative goal setting with a health coach, and use of an interactive SMS text messaging system that prompts participants to report their weight and their progress on achieving their goals with a "check-in" day each week, and sends immediate, tailored feedback about their progress. Weekly and monthly health tip messages are customized to the participant's selected health goals. If a participant is making progress on their goal, the SMS text messaging system provides an opportunity to increase goal difficulty between health coaching sessions.

iOTA-eSMI Active Intervention

Monthly in-person visits consist of assessing current health behaviors, working collaboratively with the client to identify desired behavior changes, then using a list of existing goals with a stepped level of difficulty based on the participant's current behaviors, the client and health coach collaboratively select up to 3 goals for the next month. These goals have prescribed SMS text messaging tailored to the level of difficulty to support the participant daily with health behavior change [20].

Health Education

The Health Education attentional control condition matches iOTA in time and number of sessions. Participants randomized to the control conditions will receive monthly in-person health coaching visits and a weekly SMS general "Health Tip" text message. Visits will be structured according to the current US Preventive Services Task Force recommendations to counsel participants on energy balance, physical activity, and nutrition [39,40], but will not involve formal goal setting.

Ensuring Rigor and Reproducibility

Treatment Fidelity

Health coach adherence to the intervention protocol is determined by structured, direct observation of individuals carrying out the behavioral intervention, evaluating for evidence of (1) adherence to the treatment protocol and (2) competence in the treatment delivery. Health coaches will self-monitor treatment fidelity as noted above, and implementation challenges will be discussed during weekly study teleconferences.

Outcomes

Both clinical and implementation-related outcomes will be measured, with the primary endpoint being 24 weeks. Clinical outcomes of interest are related to obesity either directly (weight, BMI), or indirectly (self-efficacy, psychophysical awareness). Implementation outcomes include engagement, acceptability, appropriateness, and fidelity.

Recruitment

Targeted educational and recruitment in-services will be conducted at clinical sites in Missouri and Florida. The goal of the in-service will be to make clinicians and clinical administrators aware of this project and to assist in identifying eligible participants. Recruitment and retention tracking across sites will be reviewed on weekly study team conference calls between the sites to identify recruitment shortfalls and broaden recruitment efforts.

Randomization Strategy

As it is anticipated that participants in the health education group will either continue to gain weight or at least maintain their current weight, participants will be randomized 2:1 to either the iOTA-eSMI intervention or to the health education control condition. Groups will be balanced to reflect the age, gender, racial, and ethnic distribution of the client base at each site.

Data Collection, Management, and Analysis

Data Collection Methods

All data will be entered into the Research Electronic Database Capture (REDCap) database through a secure web portal and stored on secure servers. Databases are built with multiple layers of security, following best practices and institutional requirements for securing sensitive data. All automatic system-generated messages in the iOTA program will be sent directly to participants' mobile phones through a web-based app developed and supported by a Health Insurance Portability and Accountability Act–compliant digital platform that has been approved by the institutional review board (IRB) [19].

Planned Primary and Secondary Analyses

The primary outcome for this study will be mean change in body weight (lbs) after 24 weeks of iOTA-eSMI or Health

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Education. Secondary outcomes include a change in BMI, psychophysical awareness and skills, and health-related self-efficacy. We will use a repeated measure mixed model to look at trajectory over the study course with a time × treatment interaction estimating treatment effect. Structural equation growth models will be used to estimate the correlation between the trajectory of psychophysical skills and related self-efficacy and that of weight or BMI.

Exploratory Analyses

Additional analyses will focus on characterizing feasibility, engagement, and implementation challenges as measured by enrollment and retention; visit adherence and text response rates; client expectations for improvement [41]; fidelity of treatment delivery; client and staff-rated feasibility, appropriateness, and acceptability. Exploratory analyses will also evaluate the relationship between mental health self-efficacy and psychotropic medication compliance and iOTA treatment compliance or engagement.

Monitoring

Data Monitoring

All electronic files (eg, database, spreadsheet, etc) containing identifiable participant information are password protected. Databases that contain private health and identifiable information are behind firewalls and require a password or username for access. All data will be entered into the REDCap [42] through a secure web portal. Databases are built with multiple layers of security, following best practice requirements for securing sensitive data. Conditional mean imputation will be used to account for missing data.

Harms

Potential Risks

All participants will be informed of potential risks before enrollment. Participation is voluntary, and the participant may choose not to participate in the research study or to withdraw at any time.

Prevention of Risk

All data collected from participants participating in the intervention will only be used for research purposes. Only members of the research team will have access to the data collected as part of this proposed study. No individual's data will be shared outside of the research team. Participants will be advised that their participation in the research study is completely voluntary, that they may choose not to participate in the study, and that they may withdraw their participation in the research study at any time without impacting their ongoing psychiatric or medical care.

Auditing

Before study enrollment, all current and ongoing health issues and medications will be identified and documented. Over the course of the study, participants will be asked to report any health events, changes in medication, and hospitalizations, and a determination will be made as to whether these may be related to their participation in the study protocol and/or intervention. Follow-up surveys will contain questions on potential adverse events (AEs), and interactions with the health coach will include specific inquiries about potential AEs. We will track the dates of each event, intervention needed (if applicable), severity, and the likelihood that the event is related to the study.

AE Definitions

An AE is defined as any untoward medical occurrence in a participant that is temporally associated with participation in the clinical study, whether it is attributed to the study. Unanticipated AEs are those occurrences not noted in the study consent form. A severe adverse event (SAE) will be defined as an AE that is life-threatening, requires inpatient hospitalization, and/or results in death or severe disability.

AE Reporting

All AEs and SAEs will be reviewed within 72 and 24 hours, respectively. Reports will be generated for each event and will include a description of the event, when and how it was reported, as well as any official chart records or documentation to corroborate the event, and determination of attribution. AE and SAE reports will then be sent to the IRB and the National Institutes of Health (NIH) program official.

Reporting Timeframes

Any "related" or "possibly related" deaths will be reported within 1 day of when we become aware of the event. Unanticipated AEs will be reported to the IRB within 10 working days. Any study-related SAE will be reported to the NIH within 2 weeks; all others will be included in the annual report to NIH. Anticipated AEs will be reported to the IRB at the time of continuing review. Any action resulting in temporary or permanent suspension of study conduct will be immediately reported to the appropriate NIH program official.

Safety and Study Progress Reviews

Oversight of data collection, management and intervention development, and delivery will be provided during weekly supervisory teleconferences with the study team delivering the intervention during the pilot study.

Ethics Approval

Research Ethics Approval

The Washington University Institutional Review Board (IRB) approved the focus groups (IRB ID: 201907136) and the randomized pilot study (IRB ID: 201911123).

Protocol Amendments

Protocol versions and related changes are listed in Table 3.

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Table 3. Protocol version, date, and description of amendment content.

Version	Approval date	Protocol modifications
1.0	December 9, 2019	Initial protocol approval
1.1	December 16, 2019	Updated recruitment materials, modification of total planned enrollment
1.2	May 6, 2020	Added and removed research staff; added a clinical site in Missouri; added option for doing "in-person" study visits virtually or by phone; added verbal consent by phone and waiver of written consent if no access to a computer; rationale for no power calculation (pilot and feasibility study) added to the analysis plan
1.3	June 5, 2020	Updated consent language
1.4	December 16, 2020	Added and removed research staff; updated inclusion and exclusion criteria–increased upper age limit to 60 years from 45 years; removed the REALM-SF[a] from consent process; removed exclusion for stable or well-managed type 2 diabetes; added recruitment from EPIC
1.5	March 17, 2021	Added research staff
1.6	November 5, 2021	Added and removed research staff; added a clinical site in Florida
1.7	November 27, 2021	Added research staff
1.8	March 4, 2022	Added research staff; added methods for sending test and secure, encrypted emails as well as option for participants to opt out of encrypted email communication with study staff (eg, can authorize emails to be sent without encryption)
1.9	June 9, 2022	Added research staff

[a]REALM-SF: Rapid Estimate of Adult Literacy in Medicine-Short Form.

Consent and Assent

Each participant will be administered the REALM-SF to estimate literacy and the University of California, San Diego Brief Assessment of Capacity to Consent to establish understanding of the study and active treatment. Prior to randomization, all participants will undergo 1 week of SMS text messaging to ensure that they are able to receive and appropriately respond to SMS text messages.

Confidentiality

The potential risk to privacy and/or confidentiality is that protected health information may be accidentally disclosed outside of the study. To avoid sending messages to the wrong number, the research team will first send a test message to ensure that messages are being sent to correct number. Participants will also be encouraged to use passcode protection to keep information on their phones private.

Access to Data

All data collected as part of the study will be coded with a unique study identification number. Only research study staff trained in the Health Insurance Portability and Accountability Act, Collaborative Institutional Training Initiative, and Good Clinical Practice training will have access to the data collected. At each site, data collected for this study will be stored in locked files in locked offices and only designated members of the research team will have access to the files.

Ancillary and Posttrial Care

Participants will continue to receive primary medical and psychiatric care as usual from their existing treatment teams during study participation, and health coaches will communicate any relevant information on their medical and psychiatric progress to treatment teams as authorized by the participant to coordinate care. At the conclusion of the study, participants will remain in the care of their existing treatment teams.

Dissemination Policy

The sharing of information created by this project will follow the NIH's requirement for sharing raw, descriptive, and analyzed data (positive and negative) with the National Institute of Mental Health (NIMH) Data Archive via the National Database for Clinical Trials Related to Mental Illness. The data generated by NIH funding and other support will be presented at national or international scientific conferences and published in peer-reviewed journals. All publications will abide by the NIH Public Access policy, and any unique research resources or tools resulting from the project will be made readily available for research purposes to qualified individuals within the scientific community after publication and upon request.

Results

The characteristics of focus group participants from aim 1 are outlined in Table 4. The Community Support Specialist group included Peer Specialists (6/16, 38% of the overall support specialist group). The "Prescriber" group included psychiatrists (7/9, 78% of the prescriber group) and psychiatric nurse practitioners (2/9, 22%).

At the time of publication, a total of 52 participants have been enrolled in aim 3. The baseline characteristics are reported in Table 5.

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Table 4. Baseline participant.

Characteristic	Participants (N=72)
Participant demographics	
Located in Eastern Missouri, n (%)	45 (62.5)
Located in South Florida, n (%)	27 (37.5)
Age (years), mean (SD)	41.9 (12.0)
Male, n (%)	22 (30.6)
Female, n (%)	46 (63.9)
Preferred not to answer (sex), n (%)	4 (5.6)
White, non-Hispanic, n (%)	30 (41.7)
White, Hispanic, n (%)	9 (12.5)
Black, non-Hispanic, n (%)	22 (30.6)
Asian, non-Hispanic, n (%)	2 (2.8)
American Indian or Alaskan Native, n (%)	1 (1.4)
Preferred not to answer (race), n (%)	3 (4.2)
More than 1 Race, non-Hispanic, n (%)	1 (1.4)
More than 1 Race, Hispanic or Latino, n (%)	3 (4.2)
Clinic role, n (%)	
Clinical supervisor or director	26 (36.1)
Prescribing clinicians	9 (12.5)
Community support specialist	16 (22.2)
Administrative staff	8 (11.1)
Nursing Staff	1 (1.4)
Client or member	12 (16.7)

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Table 5. Baseline participant characteristics, aim 3.

Variable	Total (N=52)	iOTA[a] (n=33)	Education (n=17)
Demographics			
Age (years), mean (SD)	38.2 (11.2)	39.8 (11.3)	37.4 (11.2)
Male, n (%)	21 (42)	16 (48)	5 (29)
Female, n (%)	29 (58)	17 (52)	12 (71)
Caucasian (White), n (%)	17 (34)	12 (36)	5 (29)
African American (Black), n (%)	24 (48)	15 (45)	9 (53)
Other (Mexican American), n (%)	1 (2)	1 (3)	0 (0)
Other (multirace), n (%)	2 (4)	1 (3)	1 (6)
Other (not specified), n (%)	2 (10)	2 (6)	0 (0)
Prefer not to answer (race), n (%)	4 (8)	2 (6)	2 (12)
Hispanic, n (%)	12 (24)	9 (27)	3 (18)
Non-Hispanic, n (%)	33 (66)	21 (64)	12 (71)
Prefer not to answer (ethnicity), n (%)	5 (10)	3 (9)	2 (12)
Primary diagnosis, n (%)			
Schizophrenia spectrum disorder	25 (52)	18 (55)	7 (41)
Bipolar disorder	16 (33)	11 (33)	5 (29)
Major depressive disorder	14 (29)	7 (21)	7 (41)
Anxiety disorder	8 (16)	3 (9)	5 (29)
Posttraumatic stress disorder	7 (15)	4 (12)	3 (18)
Autism spectrum disorder	2 (4)	2 (6)	0 (0)
Baseline values of key outcome measures, mean (SD)			
Weight (lbs)	254.5 (75.4)	252.4 (75.8)	257.7 (77)
BMI	40.8 (11.8)	39.8 (11.7)	42.3 (12.2)
Clinical global impression severity scale	3.7 (0.7)	3.7 (0.6)	3.6 (0.8)
Self-efficacy for diet and exercise	120.2 (28.6)	116.5 (31.3)	129.0 (19.3)
Self-efficacy for mental health	40.4 (13.1)	41.3 (13)	38.7 (13.9)
Psychophysical awareness and skills scale	34.5 (4.8)	34.2 (4)	34.9 (6)
Device type, n (%)			
Smartphone	48 (94)	32 (97)	16 (94)
Cell phone with SMS text messaging capability	3 (6)	1 (3)	1 (6)
Health insurance, n (%)			
Medicaid	31 (62)	22 (67)	9 (53)
Medicare	6 (12)	3 (9)	3 (18)
Commercial	8 (15)	3 (9)	4 (24)
Other (both Medicaid and Medicare)	1 (2)	1 (3)	0 (0)
Prefer not to answer	4 (8)	3 (9)	1 (6)

[a]iOTA: interactive obesity treatment approach.

Discussion

Early-onset obesity and premature mortality due to cardiovascular disease are more prevalent in mentally ill persons, who experience many barriers to engaging in healthy lifestyle behaviors. Furthermore, communities of color, and those who live with chronic medical conditions like SMI and obesity are disproportionately affected, and particularly those living in underserved areas, may not have access to high-quality health promotion programs. Here, we describe the design of a hybrid pilot and feasibility study evaluating both the effects of a

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mHealth obesity prevention program on body weight and the implementation of an intervention in real-world clinical settings.

The study design and baseline characteristics of the enrolled participant population for aims 1 and 3 largely reflect what has been reported in other studies of individuals with SMI. Participants who reported ethnicity as Hispanic or Latino (12/72, 17%) is similar to the 19% reporting any mental illness in the 2020 Census Bureau but lower than the number of individuals of Hispanic or Latino ethnicity reporting any mental health disorder in 2020 (27%) [43]. The proportion of focus group participants who reported race as Black or African American (22/72, 31%) was higher than in the overall US population (12%) [44] but is similar to the proportion of Black Americans reporting any mental health disorder (28%) in the 2020 National Survey on Drug Use and Health [43]. The proportion of individuals enrolled and randomized in aim 3 who were assigned as female at birth (29/52, 58%) and those of Hispanic ancestry (24/52, 24%) are consistent with what has been reported in large population-based studies [43,45,46]. However, the proportion of African American participants represented in the overall study sample (24/52, 48%) is higher than what has been reported in larger studies of both the prevalence of SMI [43,47] and the prevalence of obesity in the general population [48]. Finally, the mean age of 38.2 (SD 11.2) years and BMI of 40.8 (SD 11.8) at baseline were both on the higher end of the range allowable by inclusion criteria.

This study is subject to important limitations. First, although not completed, the sample size for the study is small, and therefore, subgroup analyses are unlikely to yield interpretable results. Second, the results may not be generally applicable in all contexts. That the enrolled population in this study is predominantly Black and, in general, physically and psychiatrically more symptomatic at baseline than expected could be explained in part by timing. Enrollment began at the height of the COVID-19 pandemic when community clinics across the country were shut down to new admissions and in-person visits [49]. Thus, the higher than expected physical and psychiatric comorbidities at baseline, a greater proportion of Black participants, and higher mean age than expected likely reflect the now well-described disproportionate impact the pandemic had on individuals with SMI from underrepresented communities [49].

Obesity prevention programs that use technology as the primary intervention delivery method may increase patient engagement with health promotion programs in general, in addition to reducing care delivery costs and increasing accessibility. This is especially relevant in the era of COVID-19 infection control precautions, which favor remote health care delivery. By pilot-testing this intervention in real-world clinical settings, we aim to adapt the intervention in real-time based on the prominent challenges and barriers that arise in the CMHC context. The results of this study will inform not only how such interventions may need to be modified for optimal effectiveness in eSMI, but also help us to understand how digital and mHealth interventions can be adapted for use in the unique ecosystems of clinical care delivery in community mental health settings, where implementation of digital interventions has been limited.

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Data Availability

Dissemination (ie, sharing) of all data created by this study is an explicit goal of the overall project. Thus, raw, descriptive, and analyzed data (positive and negative) will be uploaded to the National Institute of Mental Health Data Archive via the National Database for Clinical Trials Related to Mental Illness. This process is part of our data safety and management plan for the study. All publications will abide by the National Institutes of Health Public Access policy, and any unique research resources and tools will be made readily available for research purposes to qualified individuals within the scientific community after publication and upon request.

Authors' Contributions

GEN contributed in conceptualization, funding acquisition, project administration, investigation, supervision, data curation, writing (original draft, review, and editing), and visualization. MJ was involved in writing (original draft, review, and editing). AR was responsible for conceptualization, funding acquisition, investigation, and writing (review and editing). JAS was involved in project administration, supervision, investigation, and writing (review and editing). MDY was responsible for data curation, formal analysis, and writing (review and editing). KK was responsible for software, validation, resources, project administration, and writing (review and editing). ZG contributed in data management and primary analysis. BE was involved in software, resources, investigation, and writing (review and editing). JWN was responsible for conceptualization, funding acquisition, investigation, supervision, data curation, and writing (original draft, review and editing).

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Conflicts of Interest

GEN has received grant support from the National Institutes of Health, the Health Resources and Services Administration, the Barnes Jewish Hospital Foundation, the McDonnell Center for Systems Neuroscience, LB Pharmaceuticals, Alkermes, Inc., and Usona Institute (drug only), and has served as a consultant for Alkermes, Inc., Novartis, Otsuka America, Inc., and Sunovion. BE has received funding from the National Institutes of Health and the Centers for Disease Control and Prevention. JJP has participated in advisory panels or consulted with Merck, Boehringer-Ingelheim, Lundbeck, Otsuka, and Janssen. JWN has received grant support from the National Institutes of Health and the Substance Abuse and Mental Health Services Administration; has served as a consultant for Alkermes, Inc., Intra-cellular Therapies, Inc., Sunovion and Merck; and served on a data safety monitoring board for Amgen. EHM has provided consulting services to Eli Lilly, Reata Pharmaceuticals, Syneos Health, and United Healthcare Services. MJ, AR, JAS, and KK have no disclosures.

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Abbreviations

AE: adverse event
CMHC: community mental health clinics
eSMI: early severe mental illness
FRAME: Framework for Reporting Adaptation and Modifications-Enhanced
I-Corps: Innovation Corps
iOTA: interactive obesity treatment approach
IRB: institutional review board
mHealth: mobile health
NIH: National Institutes of Health
NIMH: National Institute of Mental Health
REALM-SF: Rapid Estimate of Adult Literacy in Medicine-Short Form
REDCap: research electronic database capture
SAE: severe adverse event
SMI: severe mental illness

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Protocol

Coach-Supported Versus Self-guided Digital Training Course for a Problem-solving Psychological Intervention for Nonspecialists: Protocol for a Pre-Post Nested Randomized Controlled Trial

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Abstract

Background: Psychosocial interventions delivered by nonspecialists can be effective at reducing common adolescent mental health problems in low-resource settings. However, there is a lack of evidence on resource-efficient methods for building capacity to deliver these interventions.

Objective: The objective of this study is to evaluate the effects of a digital training (DT) course, delivered in a self-guided format or with coaching, on nonspecialists' competency to deliver a problem-solving intervention intended for adolescents with common mental health problems in India.

Methods: We will conduct a pre-post study with a nested parallel, 2-arm, individually randomized controlled trial. The study aims to recruit 262 participants, randomized 1:1 to receive either a self-guided DT course or a DT course with weekly individualized coaching provided remotely by telephone. In both arms, the DT will be accessed over 4 to 6 weeks. Participants will be nonspecialists (ie, without prior practice-based training in psychological therapies) recruited from among university students and affiliates of nongovernmental organizations in Delhi and Mumbai, India.

Results: Outcomes will be assessed at baseline and 6 weeks post randomization using a knowledge-based competency measure that incorporates a multiple-choice quiz format. The primary hypothesis is that self-guided DT will lead to increased competency scores among novices with no prior experience of delivering psychotherapies. The secondary hypothesis is that digital training with coaching will have an incremental effect on competency scores compared with DT alone. The first participant was enrolled on April 4, 2022.

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Conclusions: The study will address an evidence gap on the effectiveness of training methods for nonspecialist providers of adolescent mental health interventions in low-resource settings. The findings from this study will be used to support wider efforts to scale up evidence-based mental health interventions for young people.

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KEYWORDS

adolescent mental health; capacity building; digital training; India; problem-solving intervention; randomized controlled trial

Introduction

Task-sharing is increasingly used to address unmet mental health needs in low-resource settings. Task-sharing approaches deploy trained community and voluntary sector workers in service delivery roles that are traditionally held by specialized professionals [1]. Trials have demonstrated the effectiveness of resource-efficient "low-intensity" psychological interventions delivered by nonspecialists [2,3], but there is a lack of evidence on how to make these solutions work sustainably.

Training capacity has been a major supply-side barrier, with traditional face-to-face methods requiring a critical mass of expert trainers and physical infrastructure [4]. The growing use of web-based educational materials, which accelerated during the COVID-19 pandemic, presents significant opportunities for building workforce capacity at scale [5,6]. The supporting evidence from the global mental health literature suggests benefits of digital training (DT) in terms of time, efficiency, flexibility, and reduced economic costs [7]. However, differences in training approaches and evaluation measures limit comparability of findings across studies. Moreover, key engagement challenges identified for digital learning from the wider pedagogical literature leading to relatively high rates of dropout [8-10] have not been systematically addressed or studied in relation to nonspecialist providers of mental health care.

This study addresses the lack of evidence on workforce development strategies for scaling up evidence-based adolescent mental health interventions in low-resource settings. The aim is to evaluate 2 versions of DT for nonspecialists, recruited from a variety of contexts in India, and compare their effects on knowledge-based competency needed to deliver a brief evidence-based problem-solving intervention for common adolescent mental health problems. The effects of the problem-solving intervention on adolescent mental health have been previously evaluated in a randomized controlled trial in Indian secondary schools where lay counselors were trained using face-to-face methods [3]. In this study, we are interested in assessing the effects of DT on competency in a nonspecialist workforce that could deliver the problem-solving intervention more widely.

We are particularly interested in the potential incremental effects of providing personalized coaching for learners on a DT course. A recent pilot study involving nonspecialist primary care workers in Madhya Pradesh, India, demonstrated that the addition of remote telephone coaching improved training completion rates for a digital program [11], for training frontline community health workers on a brief psychological treatment for adults with depression [12]. We wished to test whether a similar coaching approach may enhance engagement with, and competencies attained, with a DT package related to an adolescent mental health intervention.

Our specific objectives are to (1) evaluate the effects of DT on knowledge-based competency of trained nonspecialists to deliver an evidence-based problem-solving intervention for common adolescent mental health problems; (2) evaluate the incremental effect of digital training with coaching (DT-C) in comparison with self-guided DT on nonspecialists' competency to deliver the problem-solving intervention; and (3) investigate the implementation of the training intervention in both arms.

Methods

Design

This protocol adheres to the Standard Protocol Items: Recommendations for Interventional Trials guidelines [13,14]. A parallel, 2-arm, individually randomized controlled trial design will be nested within a pre-post intervention study. Outcomes will be assessed at baseline and 6 weeks post randomization.

Setting

This study will be conducted in partnership with 4 universities (2 coeducational colleges in the National Capital Territory of Delhi, 1 coeducational college in Bangalore, Karnataka, and 1 girls-only college in Mumbai, Maharashtra), and 5 nongovernmental organizations (NGOs) working in the fields of adolescent health and education. The sampling frame comprises approximately 2500 university students and 2500 staff and volunteers associated with NGOs.

Participants

Participants will be sampled from two broad groups: (1) university students currently enrolled in a bachelor's-level degree program in psychology, education, or allied fields; and (2) NGO employees who are working as teachers, social workers, or mental health advocates. Eligible participants in both groups will be aged 18 years or older; be fluent in written and spoken Hindi or English; and have regular access to a web-enabled smartphone or computer that can be used to participate in the digital course. Potential participants will be excluded from the study if they have prior practice-based training in psychological therapies.

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Interventions

Self-guided DT Arm: Digital Content

The DT course comprises 16 modules organized into 2 sections: nonspecific counseling skills and skills that are specific to problem-solving counseling. The course content is based on an existing manual for the Premium for Adolescents (PRIDE) problem-solving intervention [2], which was designed in India as a first-line treatment within a transdiagnostic stepped care architecture for adolescents with elevated mental health concerns of varying types. A previous randomized controlled trial in India showed that the problem-solving intervention effectively reduces adolescents' self-rated psychosocial problems and mental health symptoms when implemented by relatively inexperienced lay counselors in four or five 20- to 30-minute sessions held across 3 weeks [3,15]. The manual was translated into a DT course in 5 steps as described in Textbox 1, following a structured process established in previous research [16].

Textbox 1. Intervention development process.

Create curriculum outline

- A course outline was developed to ensure alignment between the learning objectives and the core content of the Premium for Adolescents (PRIDE) problem-solving intervention manual
- Three members of the current study team (SM, TS, and RM) drafted the course blueprint, which was reviewed by 3 of the original PRIDE manual developers (DM, CF, and VP) to ensure that all key competencies were represented

Develop training content

- Written content from the PRIDE manual was adapted into multimodal content including videos, text, and PowerPoint for the training course
- Draft materials were reviewed again by the original PRIDE manual developers to ensure faithful translation of concepts and procedures

Digitize training content

- Materials were produced in digital formats that could be accessed from both a smartphone app and website
- These included video-based lectures, role plays, animated summary slide shows, and quizzes
- Materials were checked for accuracy and visual appeal by members of the study team

Adding content to a learning management system (LMS)

- Digital content was published on an open-source web-based LMS
- The platform included learner performance tracking and metrics, a customizable interface available in multiple languages, and a user-friendly dashboard

Conduct user testing

- User testing was carried out in a group format with 20 undergraduate psychology students
- On the basis of feedback received, the app was further optimized for viewing video content, a message repository was prepared to send automated notifications to motivate learners
- The numbering of videos was made simpler, the glossary was expanded, and a recruitment video was prepared

The course will be hosted on a learning management system (LMS) hosted by Sangath, the implementing organization in India, which can be accessed through a smartphone app and website in either Hindi or English, based on the user's preference. The content will be delivered through a variety of instructional methods including video-based lectures, role-play videos, animated summary slide shows, quizzes, and brief readings adapted from the source problem-solving manual. The training requires approximately 20 hours to complete, accounting for the time needed to engage with the various content areas. This can be spaced out over 4 weeks, with 4 modules being unlocked every week to facilitate sequential learning. Participants who are unable to complete the course within 4 weeks will be offered an extension for up to 2 weeks during the trial, after which their access to the course will be locked for the duration of endline assessment.

Automated support features include weekly emails and text notifications on the LMS platform that serve as reminders and motivators to engage with the digital content. In addition, participants will be able to send technical queries (eg, related to accessing and navigating the digital platform) to a dedicated WhatsApp number. This account will be monitored during regular working hours by a research assistant who will provide support accordingly, while declining to answer any course content-related queries.

DT-C Arm

Coaching

In addition to the DT program, participants in the DT-C arm will receive personalized remote coaching for the duration of the course. The main functions of the coach are to (1) review core concepts from the course content, (2) respond to specific content-related queries, and (3) reinforce progress toward completing the course in the allocated time frame. There will be 4 coaches, each of whom will be bilingual and possess an undergraduate degree. Coaches will have completed training in

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the PRIDE problem-solving intervention, as well as receiving 5 days of office-based training in the coaching protocol that was designed specifically for the current study. The coaching protocol (see the outline in Table 1) has been adapted from 2 existing psychotherapy coaching protocols intended for nonspecialists [11,17].

Table 1. Outline of the coaching protocol.

Content sections (activities done by the coach)	Description
Build rapport	Engage the learner and create a collaborative space for coaching
Orient learner	Introduce learner to the course and coaching and set expectations
Plan for course completion	Discuss timetable over the intended 4-week course duration, including time required for each module and schedule for weekly coaching calls
Review progress	Assess progress on a weekly basis and troubleshoot challenges to completion
Resolve queries	Answer any queries from the learner about course content
Provide motivation	Encourage the learner by verbally reinforcing progress
Set learning goals	Collaboratively set learning goals for week ahead
Wrapping up	Recap material and discuss potential for skills practice and application

Coaching will be delivered through voice-based telephone calls and SMS text messages. The coach will call participants once per week over the 4-week duration, which may be extended by up to 2 weeks. Each coaching call is intended to last for approximately 30 minutes and follow a structured agenda. Prior to the call, the coach will review key performance metrics (modules completed and scores on formative quizzes) collected from the LMS dashboard. During each call, the coach will check if the participant has experienced progress-related challenges, clarify any difficulties with course concepts, reinforce continued participation, and collaboratively set learning goals for the week ahead. Participants will also have the option to ask queries via SMS text messages to their coach between calls. Depending upon the nature of the query, a coach may respond over text or address the query during the next scheduled phone-based coaching session. Additionally, coaches will send a reminder message to learners 1 day prior to scheduled coaching calls.

Throughout the trial, coaches will participate in weekly peer group supervision meetings lasting 2 to 3 hours. Group supervision will include quality ratings of audio-recorded coaching sessions and trouble-shooting around logistical/technical issues, which will be moderated by a supervising masters- or doctoral-level clinical or counseling psychologist. The coaches will be able to make ad hoc calls to a supervising psychologist in case of any pressing concerns outside the group supervision sessions.

Coaches will not supervise learners in the applied use of the problem-solving intervention for treating adolescent mental health problems. The study recruitment materials will emphasize that a suitably experienced and qualified clinician should be engaged in supervising any such clinical activity with appropriate quality assurance and safeguarding arrangements in place. An outline of the coaching components is given in Table 1.

Procedure

The study schedule is summarized in Table 2 and set out in further detail below.

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Table 2. Schedule for enrolment, interventions, and assessments.

Time point	Baseline (week 0)	Intervention (weeks 0-24, with a 2-week allowance)	Follow-up (week 6, with a 2-week allowance)
Procedures			
Eligibility screening	✓	N/A[a]	N/A
Informed consent	✓	N/A	N/A
Baseline assessment and allocation	✓	N/A	N/A
Intervention		✓	
Follow-up assessment			✓
Data collection			
Demographic information	✓	N/A	N/A
KOPS[b]	✓	N/A	✓
MUSIC[c]			✓
LMS[d] process data		✓	
Coaching process data		✓	

[a]N/A: not applicable.

[b]KOPS: knowledge of problem solving scale.

[c]MUSIC: eMpowerment, usefulness, success, interest, and caring scale.

[d]LMS: learning management system.

Recruitment and Consent

Participants will be recruited through sensitization webinars that will raise awareness about the study and opportunities to participate in the DT course. The webinars will be coordinated with the 9 partner organizations (NGOs and universities) using existing communication channels such as email lists and WhatsApp groups. Sessions will be conducted throughout the recruitment period to maintain a consistent flow of referrals until our target sample is achieved. Webinars will be facilitated by a member of the intervention team using a PowerPoint presentation, video demonstration, and Q&A. A telephone number and REDCap platform URL [18] will be provided to individuals who wish to begin the enrollment process. Where possible, physical posters, with information about the study and associated training opportunities, will also be displayed in preselected locations on the premises of the collaborating organizations.

Following sensitization activities, interested individuals will be able to initiate a referral by directly visiting the study website, or by contacting a dedicated centralized number (via call or SMS text message) to request further information and leave their preferred contact details. A research assistant will respond by emailing and, if required, by texting a link to the study website (hosted on the REDCap platform). When accessing the REDCap platform, they will be able to read information about the study before completing a series of eligibility questions on the web. The questions will ask about age, current occupation, device access, preferred language for training, and prior training or other experience in delivering psychological therapies. Individuals who require assistance to complete the eligibility form will be able to contact the study helpline and speak to a research assistant. Details of the helpline contact will be shared through the recruitment posters and messages shared via WhatsApp and email. If an individual leaves the eligibility screening form incomplete for 2 days, a research assistant will contact the participant to identify and clarify any difficulties they are facing. If the participant is ineligible for the study, then they will not be followed up by the research team and instead redirected to the Sangath website to view other information about alternative courses. Once eligibility is confirmed, a prospective participant will be emailed a weblink to the study information sheet and consent form. Each consenting participant will be asked to complete a demographic proforma (see "measures" below).

Baseline Assessment

Consenting individuals will be directed to complete the baseline assessment measure (see "measures" below) via a weblink contained within a further email. Each participant will also have the option to contact the study helpline if they face technical difficulties during the assessment. If the baseline assessment has not been completed within 2 days after enrollment, a research assistant will make contact by telephone to remind the participant. If needed, research assistants will make up to 4 more attempts to contact the individual over the subsequent 2 weeks.

Randomization and Allocation Concealment

Participants will be randomized in a 1:1 allocation ratio to 1 of the 2 trial arms. Randomization will be stratified by the type of organization, using randomly sized blocks of 4 or 6. The randomization sequence for each stratum will be generated by an independent statistician and deployed on REDCap by the data manager on site. The trial principal investigator, trial

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coordinator, trial statisticians, and members of the Trial Steering Committee will remain blinded to allocation arms throughout the trial and until the final analysis is complete. It will not be possible to blind the participants or coaches to the allocation because of the nature of the intervention. The data manager will also not be blinded. A separate Data Monitoring Committee was not established, since this is not clinical trial and there is no risk to the safety or participants.

An onboarding email will be sent to the participant informing them of their allocation status within 24 hours of randomization. This email will also contain details of the course and study structure, login details to access the DT platform, and a link to a tutorial video explaining participants how to access and navigate the training platform. Participants in the DT-C arm will additionally receive an introductory onboarding call from their coach to orient them toward coaching within 24 hours of randomization. A daily check will be performed by the data manager to evaluate if allocations are consistent with the allocation code.

Follow-Up Assessment

A link to the follow-up assessment materials will be shared with participants using their registered email address at 42 days (ie, 6 weeks) post randomization. The course has been structured in such a way that each week, 4 modules are unlocked for the learners. This would ensure that the learners can comfortably complete the course within 4 weeks. However, we have given the provision of additional 2 weeks for the learners to complete the course. Research assistants will make up to 4 more attempts to contact the participant over the subsequent 2 weeks or until the follow-up assessment is completed on the study website. Participants will be given a maximum allowance of 2 weeks to complete the follow-up assessment.

Measures

Participant Characteristics

Sociodemographic data will be collected at baseline on age, gender, education level, occupation, years of experience (if employed), year and course of study (if currently a student), and preferred language for receiving the course (English or Hindi).

Primary Outcome

Self-completed outcome data will be collected remotely through the REDCap platform at baseline and 6 weeks after randomization into the study. The primary outcome will be a knowledge-based competency measure, the knowledge of problem-solving (KOPS) scale. This was developed specifically for the current study and contains 17 multiple-choice questions organized around 5 session vignettes. The measure produces a score ranging from 0 to 17, where higher scores indicate higher levels of competency. The vignette-based format was informed by previous research on competency assessments for nonspecialists [19-21]. Twelve questions assess knowledge of specific problem-solving competencies (eg, problem identification) and 5 questions assess nonspecific competencies of relevance to psychotherapies generally (eg, rapport building). To enhance external validity, question domains were cross-referenced with problem-solving items from an established CBT competency framework implemented widely in the United Kingdom [22] and nonspecific counseling items from 2 existing competency measures used in previous studies with nonspecialist providers in South Asia [23-25]. The wording of questions and details of the case vignettes were refined through piloting with a reference sample that included both experienced counselors and novices. The process of developing the KOPS measure is described in detail elsewhere (S Mathur et al., unpublished data).

Parallel forms of the case vignette and quiz will be used at baseline and end line assessments (ie, respondents will be assessed on the same domains but with different cases and alternative question formulations at each time point). In each form, participants will be presented with a written case description followed by 5 session vignettes in a logical sequence. The participant will be required to respond sequentially to a set of multiple-choice questions after each of these vignettes (3 to 4 questions per set). The sequencing of the 2 forms will be determined at random. Participants will have up to 90 minutes to complete the quiz once they begin answering, after which the assessment link will expire. The remaining time available will be visible as a countdown clock on the assessment screen.

Secondary Outcomes

User satisfaction data will be obtained from participants in both trial arms using the MUSIC (eMpowerment, Usefulness, Success, Interest, and Caring) questionnaire. We will use a version of the MUSIC scale that has been adapted in previous DT trials in India [11,26]. The scale will include 26 items, each rated on a 6-point scale, covering domains of feasibility, acceptability, adoption, and appropriateness. The questionnaire provides a score on each of the 5 scales (empowerment, usefulness, success, interest, and caring), each based on 4 to 6 items. Two supplementary free-text items will be used to obtain written qualitative feedback from participants about what they enjoyed the most in the course, as well as suggestions for improvement.

Process Evaluation

Data on enrolment, randomization, and completion of assessment procedures will be obtained from the REDCap platform. This will include numbers and proportions of study referrals that are assessed, eligible, consented, and randomized (by host organization, age, and gender); and reasons for missed assessments, ineligibility, declined consent, and missed randomization. Session record forms and automated data captured from the LMS will be used to assess frequency of log-ins, number of modules completed, and time spent logged into the LMS. Additional process variables in the DT-C arm will include number and duration of attended coaching sessions (and number of missed coaching sessions and reasons for nonattendance). Fidelity of coaching will be assessed using independent ratings of audio-recorded coaching calls (based on 10% of recorded calls). Coaches will also document the frequency and duration of calls (and reasons for missed calls), as well as frequency of SMS text messages received and sent in response.

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Study Size

For the primary hypothesis that the DT intervention improves competency score, a sample size of 262 participants will provide 80% power to detect an effect size of 0.19 (ie, a standardized mean difference [SMD] of post vs pretraining scores), assuming 20% loss-to-follow-up, and a 5% 2-sided significance level. This indicative effect size (SMD=0.19) was informed by a systematic review and meta-analysis of web-based learning evaluations which compared analogous learning conditions [27]. For the second hypothesis that the DT-C intervention is superior to the DT intervention, this sample size will provide 80% power to detect an effect size (standardized mean difference) of 0.39 between the DT and DT-C arms with a 1:1 allocation ratio between randomized arms. With the 20% loss-to-follow-up, we anticipate that 210 (80%) participants will complete follow-up and contribute to the endline analysis (105 per arm).

Data Security and Management

The principal investigator (VP) will act as custodian of the data in accordance with regulations of the research sponsor (Harvard Medical School) and funder (Wellcome Trust, United Kingdom). Each participant will be assigned a unique ID and password to access both the DT course and secure REDCap platform for outcome assessments. Data will be stored on a secure and backed-up server operated by a trusted third party (Sangath) in a managed environment that protects against data loss and corruption, unauthorized access, and modification. To mitigate the risk of identifying participants from the data collected in the study, we will not record direct identifiers on study data. Data in its original form will be retained on the server and will be accessible only to core research team members who are directly involved in the study.

Participant information sheets (and instructions for completing the outcome measures) will clearly explain that scores will remain confidential and will not be shared with university authorities, employers, or any other third parties. Participants will be informed through the information sheet that they can withdraw from the study at any time and their data will be removed up to the point when the primary analysis is completed. Anonymized participant data and a data dictionary will be made available 12 months after study completion. Data will be shared after approval by the PRIDE principal investigator, following a reasonable submitted request.

Statistical Analysis

General Principles

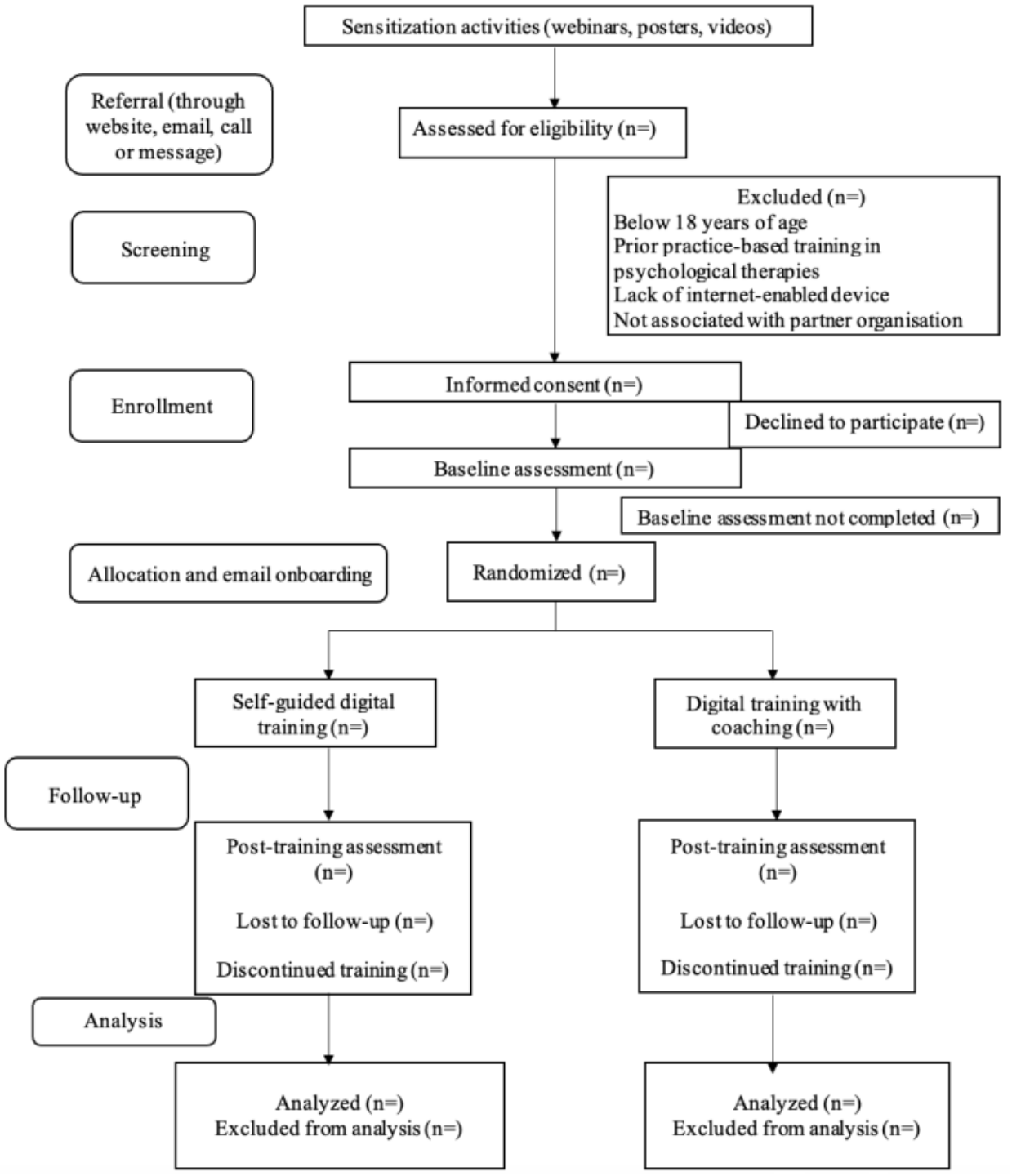
Except otherwise specified, analysis will be conducted according to the arm participants were randomized to, regardless of intervention effectively received (“intention to treat” principle), CIs will be reported at the 95% level, and significance considered at a 2-sided 5% α.

Descriptive Statistics

We will describe participants’ baseline characteristics overall and by arm. A CONSORT flow diagram (Figure 1) will be used to summarize trial processes. Adherence to the intervention will be reported descriptively, including the number of modules and number of coaching calls completed.

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Figure 1. Consolidated standards of reporting trials (CONSORT) flow diagram.



Psychometric Analysis

We will use the baseline data of outcome scores obtained from all participants to establish the psychometric properties of the multiple-choice KOPS competency measure. Prior to unblinding the trial data set, a 2-parameter Rasch model will be fitted to estimate the item characteristic curves, discrimination, and difficulty parameter for each item on both forms of the competency measure. In addition, the test information function will be estimated to look at the overall characteristics of the forms. Based on this analysis, items may be removed, and the primary outcome analysis will be conducted using retained items. Items that have poor discrimination or are at the very extremes of difficulty may be removed in the interests of a test information function that suggests that the scale as a whole provides information across a range of abilities. If any items are removed, a sensitivity analysis will be conducted in which the original 17-item version is used as the outcome for the model that tests the main trial hypothesis.

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Missing Data

We will compare baseline characteristics of study completers versus noncompleters. The main analyses (hypotheses 1 and 2) will use multiple imputation under the missing at random assumption, by chained equations, and including the main predictors of missing data in the imputation model. Sensitivity analysis will include complete case analysis, adjusting for factors associated with missing data, and under missing not-at-random assumptions.

Analysis of Pre-Post Differences

The analysis of pre-post differences will be conducted by doing a linear regression of the change in competency score between baseline and 6 weeks. The null hypothesis will be that there is no change in score.

Randomized Controlled Trial Analysis

The second hypothesis will be analyzed by a linear regression of the change in competency score between baseline and 6 weeks, testing for a difference between the 2 arms. The analysis will be adjusted for strata, and baseline competency score.

Analysis of Effect Modification

To assess on whom the DT and additional coaching may work best, we will assess effect-modification on the primary and secondary outcomes by *a priori* defined modifier (age, gender, language, and type of organization [NGO vs university]), by including these factors as predictors (pre-post analysis), or as interaction terms (trial analysis) testing for heterogeneity of treatment effects in the regression models specified above.

Secondary Outcomes Analysis

The effect of coaching on the secondary outcomes (MUSIC 5 subscales and DT course completion) will be conducted similarly to the trial analysis model described above, but without adjusting for baseline score. The MUSIC subscales will be analyzed as continuous variables using linear regression (or a suitable transformation). Course completion as a binary variable will be analyzed using logistic regression.

Compliance Analysis

We will report descriptively adherence to the intervention (number of training modules and coach sessions completed). Change in competency score will be reported descriptively by level of intervention received, in a dose-response type analysis.

Process Evaluation

Process data will be used to facilitate interpretation of the main trial results. Findings from the various data sources will be triangulated and used to develop explanatory hypotheses about potential differences in training delivery and participation across arms, subgroups of participants and coaches. We may conduct further analyses to test hypotheses generated from the integration of the process evaluation and trial outcome data (eg, on whether the duration of time taken to complete the training influences outcomes).

Ethics Approval

Institutional review board approvals have been obtained from Sangath (the implementing organization in India; VP_2015_017); Harvard Medical School (IRB21-1197), United States (the sponsor; IRB21-1197); and the London School of Hygiene and Tropical Medicine, United Kingdom (a collaborating organization; 26565).

Dissemination Plan

A multimodal dissemination strategy will share findings with diverse stakeholders. Strategies will include scientific publications, training manuals and videos, and web-based dissemination. All publications will be in an open access format and authorship will be determined according to the International Committee of Medical Journal Editors' guidelines [28]. Targeted stakeholders will include practitioners, academics, NGOs, authorities involved in education and health, policy makers, and donors at state and national levels.

Results

Participant sensitization sessions began on March 31, 2022. The first participant was enrolled on April 4, 2022, and their 6-week assessment was completed on May 18, 2022.

Discussion

Although India has been an incubator for some of the most widely cited task-sharing innovations in mental health care, the lack of implementation of these interventions at scale is a major challenge. The current trial will address this critical implementation gap by evaluating DT for nonspecialists, recruited from a range of contexts in India. This research expands on prior workforce development studies by evaluating 2 approaches to implementing DT, 1 self-guided and the other supported by remote individualized coaching, with a specific focus on competencies needed to treat adolescent mental health problems [8,17,29]. The evaluation design will enable a primary analysis of the effects of DT on knowledge required to deliver a brief evidence-based problem-solving intervention. A secondary analysis will compare outcomes for the DT package when delivered with and without coaching.

The coaching protocol has been designed in part to address motivational challenges highlighted in previous research on DT [30,31]. Research has recommended blended methods that combine e-learning with face-to-face or remote human support to increase engagement [11,31,32]. We have also included provision for a technical helpline, distinct from coaching, which can be used by participants in both arms of the trial.

The strengths of this trial are including participants from varied contexts across India and assessing their competency through counseling vignettes that approximate real-life situations, thus adding to their ecological validity. However, we recognize the limitation that the study does not directly assess the applicability of the acquired knowledge in counseling settings. The latter is a future research priority.

The results from the study will provide important insights into how competencies in youth-focused psychotherapies can be developed at scale outside specialist mental health settings. Related evidence will also be produced about how to motivate and support nonspecialists in settings where expert trainers and supervisors are scarce. Such evidence can be used to shape the

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wider dissemination of the PRIDE problem-solving intervention, and similar low-intensity psychotherapies, to address the mental health treatment gap for adolescents in India and globally.

Acknowledgments

The authors offer particular thanks to members of the PRIDE Scientific Advisory Group and colleagues who contributed to intervention and research activities across the various phases of the study, including Shreyas Kamat, Abhija Teli, Keshav Shakya, Niket Agarwal, Rukhsar Akram, Sai Priya Kumar Chodankar, Mamta, Aarohi Sharma, Manogya Sahay, Meenakshi Pandey, Sarita Rao, Shouaib Ahmed, and Himanshu Gupta. The authors also gratefully acknowledge the contributions made by the Population Foundation of India in designing the digital training course. This study was supported by a Principal Research Fellowship awarded to VP by the Wellcome Trust (grant 106919/A/15/Z). The funders had no role in the design of the study, data collection, or the writing of the manuscript. For open access, the author has applied a CC BY public copyright license to any author accepted manuscript version arising from this submission.

Data Availability

The data sets that will be generated during this study will be available from the corresponding author on reasonable request.

Authors' Contributions

SM, DM, and VP conceptualized the study. SM led on drafting the protocol, with critical inputs from DM and VP. HAW, MN, BL, and APF contributed to the statistical analysis plan. SM, TS, JEJ, PN, and RM contributed to the coordination and implementation of the trial. KM contributed to the refinement of the protocol. All authors read and approved the final manuscript. DM and VP contributed equally as senior authors.

Conflicts of Interest

None declared.

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Abbreviations

DT: digital training
DT-C: digital training with coaching
KOPS: knowledge of problem-solving
LMS: learning management system
MUSIC: eMpowerment, usefulness, success, interest, and caring
NGO: nongovernmental organization
PRIDE: Premium for Adolescents
SMD: standardized mean difference

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Protocol

Audit, Feedback, and Education to Improve Quality and Outcomes in Transurethral Resection and Single-Instillation Intravesical Chemotherapy for Nonmuscle Invasive Bladder Cancer Treatment: Protocol for a Multicenter International Observational Study With an Embedded Cluster Randomized Trial

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Abstract

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Background: Nonmuscle invasive bladder cancer (NMIBC) accounts for 75% of bladder cancers. It is common and costly. Cost and detriment to patient outcomes and quality of life are driven by high recurrence rates and the need for regular invasive surveillance and repeat treatments. There is evidence that the quality of the initial surgical procedure (transurethral resection of bladder tumor [TURBT]) and administration of postoperative bladder chemotherapy significantly reduce cancer recurrence rates and improve outcomes (cancer progression and mortality). There is surgeon-reported evidence that TURBT practice varies significantly across surgeons and sites. There is limited evidence from clinical trials of intravesical chemotherapy that NMIBC recurrence rate varies significantly between sites and that this cannot be accounted for by differences in patient, tumor, or adjuvant treatment factors, suggesting that how the surgery is performed may be a reason for the variation.

Objective: This study primarily aims to determine if feedback on and education about surgical quality indicators can improve performance and secondarily if this can reduce cancer recurrence rates. Planned secondary analyses aim to determine what surgeon, operative, perioperative, institutional, and patient factors are associated with better achievement of TURBT quality indicators and NMIBC recurrence rates.

Methods: This is an observational, international, multicenter study with an embedded cluster randomized trial of audit, feedback, and education. Sites will be included if they perform TURBT for NMIBC. The study has four phases: (1) site registration and usual practice survey; (2) retrospective audit; (3) randomization to audit, feedback, and education intervention or to no intervention; and (4) prospective audit. Local and national ethical and institutional approvals or exemptions will be obtained at each participating site.

Results: The study has 4 coprimary outcomes, which are 4 evidence-based TURBT quality indicators: a surgical performance factor (detrusor muscle resection); an adjuvant treatment factor (intravesical chemotherapy administration); and 2 documentation factors (resection completeness and tumor features). A key secondary outcome is the early cancer recurrence rate. The intervention is a web-based surgical performance feedback dashboard with educational and practical resources for TURBT quality improvement. It will include anonymous site and surgeon-level peer comparison, a performance summary, and targets. The coprimary outcomes will be analyzed at the site level while recurrence rate will be analyzed at the patient level. The study was funded in October 2020 and began data collection in April 2021. As of January 2023, there were 220 hospitals participating and over 15,000 patient records. Projected data collection end date is June 30, 2023.

Conclusions: This study aims to use a distributed collaborative model to deliver a site-level web-based performance feedback intervention to improve the quality of endoscopic bladder cancer surgery. The study is funded and projects to complete data collection in June 2023.

Trial Registration: ClinicalTrials.org NCT05154084; https://clinicaltrials.gov/ct2/show/NCT05154084

International Registered Report Identifier (IRRID): DERR1-10.2196/42254

(JMIR Res Protoc 2023;12:e42254) doi:10.2196/42254

KEYWORDS

TURBT; bladder cancer; quality improvement; performance feedback; transurethral resection; urology; oncology; recurrence; surgery; surgical; quality indicator; performance; feedback; evaluation

Introduction

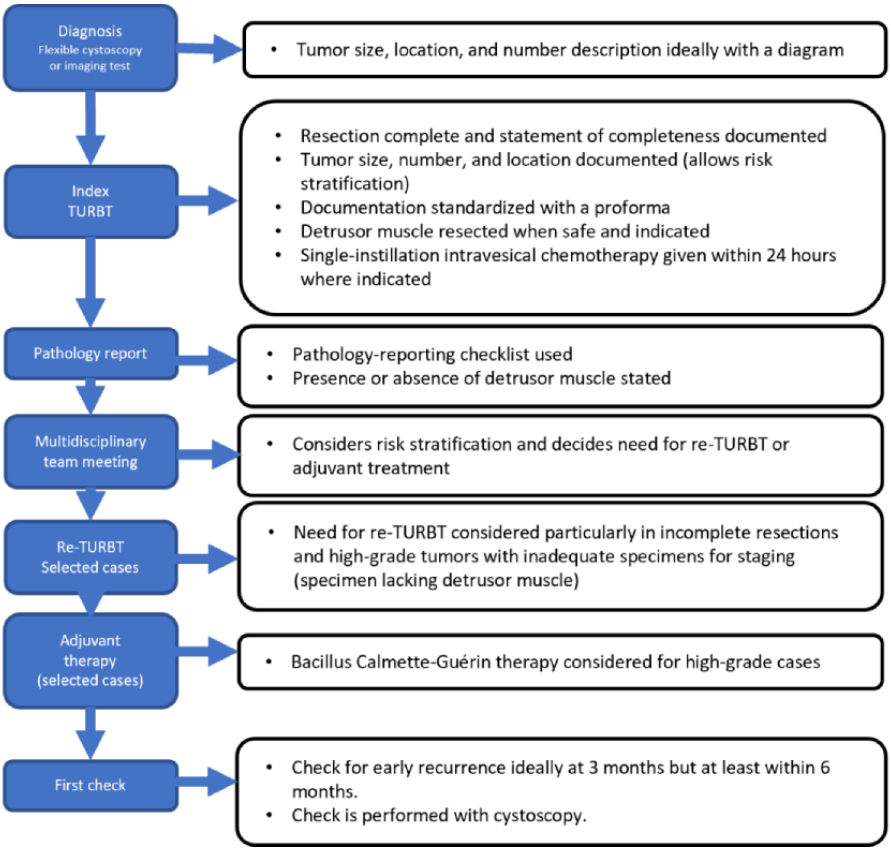
Background

Nonmuscle invasive bladder cancer (NMIBC) is a common disease with an incidence of 19.1 and 4.0 cases (men and women, respectively) per 100,000 person-years in the European Union [1]. Three-quarters of all new bladder cancer diagnoses are that of NMIBC [2]. This disease is the most expensive to manage, per patient, from diagnosis to death [3,4].

The standard of care management for all suspected NMIBC is surgical transurethral resection of bladder tumor (TURBT). Evidence guides how the initial TURBT should be performed and perioperative practice, including the use of single-instillation intravesical chemotherapy (SI-IVC) to reduce recurrence rates of cancer [5]. It has been proposed that achieving “good-quality” NMIBC surgery and perioperative practice results in reduced recurrence rates [6]. This evidence forms the basis for the recommendations made in guidelines including those by the European Association of Urology (EAU) [5], the American Urological Association (AUA) [7], and the National Institute for Health and Care Excellence (NICE) [8] in England and Wales. The usual NMIBC diagnosis and treatment pathway is shown in Figure 1.

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Figure 1. Nonmuscle invasive bladder cancer diagnosis and treatment pathway. TURBT: transurethral resection of bladder tumor.



The Problem

Compliance with best practice for TURBT surgery and perioperative guidelines varies widely [9], which may impact oncological outcomes [10-12]. There is a significant variation in early tumor recurrence rates between different sites that cannot be accounted for by patient, tumor, or adjuvant treatment factors [10], suggesting surgical factors may be the cause. In a survey of practice in 9 European countries published in 2019, significant deviation from guidelines was identified even for interventions with high certainty of evidence, such as SI-IVC administration [9]. There has recently been a proposed set of "quality indicators" for TURBT but the published review acknowledged that there was a lack of evidence that implementing these quality indicators resulted in improved outcomes [13]. A long-running study on quality standards in TURBT surgery in Scotland demonstrated that being involved in a national audit and feedback program of TURBT quality performance indicators did lead to a trend in improvement of quality indicator achievement over time, but a critical limitation was that there was no control group or comparison to baseline performance [14,15]. This work also established the utility and measurability of certain TURBT quality indicators in the real world.

The Intervention: Electronic Audit, Feedback, and Education

Audit and feedback have the potential to improve professional practice and impact patient outcomes. Meta-analyses of the effects of audit and feedback in health care demonstrate wide variation in effect size [16]. The median baseline performance–adjusted improvement in compliance with desired practice was 4.3% but varied from 0.5% to 16%. Further, there is theory and evidence that education on addressing deficiencies highlighted by audit may enhance the effectiveness of audit and feedback [17,18].

A systematic review concluded that feedback can improve surgical performance, but the strength of the conclusions was tempered by the heterogeneity, the lack of randomization, and the lack of controls in the included studies [15,19,20]. A systematic review of electronic audit and feedback interventions concluded that effects were variable and only 2 of 7 identified studies used theory to guide interventions [21].

For bladder cancer surgery, there are professional practice behaviors under the control of the surgeon that have proven to be associated with patient outcomes after TURBT surgery [6,22-25]. Given that audit, feedback, and education is a cost-effective and simple intervention and has demonstrated efficacy in other settings, we would hypothesize that this intervention also improves perioperative indicators of surgical quality. Furthermore, there is evidence that targeting "process measures" as the unit for change is more effective than targeting patient outcomes [26]. Therefore, we chose to target professional practice behaviors (or quality indicators) as the primary outcomes rather than a disease outcome such as recurrence rates.

Objectives

Main Objective

The primary objective is to determine whether "audit, feedback, and education" improves achievement of TURBT quality indicators.

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Other Objectives

The other objectives are to determine (1) if audit, feedback, and education improves the early recurrence rate of NMIBC after first TURBT; (2) if achievement of TURBT quality indicators is associated with early recurrence rate of NMIBC after the first TURBT; (3) the average and variation in achievement of TURBT surgery quality indicators and early recurrence rate across surgeons, sites, countries, and health care settings (site type and operating list type); and (4) associations among site, surgeon, and surgical factors and achievement of TURBT quality indicators and early recurrence rate.

Methods

Study Design

This is an international, observational, multicenter study with an embedded prospective cluster–cluster randomized, parallel-arm, superiority trial of audit, feedback, and education. A cluster randomized trial was chosen because intrasite contamination would be expected if randomization was at the clinician level. A cluster is defined as one or more hospitals within the same health care organization where the same surgeons perform TURBT surgery. Sites will be informed of any updates to the protocol or standard operating procedures with the latest trial documents available on the BURST RESECT study website (protocol version 4.0 November 11, 2020).

Data Collection, Management, and Privacy

Data will be entered into a web-based secure database hosted at University College London (Research Electronic Data Capture [REDCap]). Collected data are anonymous. Case report forms were developed with peer review and national and international testing (tested in the United Kingdom, France, and the United States). Data range checks, data sense rules, and essential required variable alerts will be programed at outset to improve accuracy and completeness. In total, 10% of all records will be manually checked for sense and completeness. Manually identified errors will be coded as automated rules, and the whole database scanned or audited for errors. Identified errors will be alerted to sites for correction before database lock. Data errors and incomplete or missing follow-up data will be queried with sites on a patient-by-patient basis through a web-based data auditing app. The resection and single-instillation intravesical chemotherapy for nonmuscle invasive bladder cancer treatment study data analysis group comprising statisticians based at the University of Aberdeen will have access to the final data set.

Ethical Considerations

Local and national ethical and institutional approval or exemption will be obtained at each participating site. In the United Kingdom, the University of Aberdeen deemed this study exempt from research ethical approval in line with health research authority guidelines. There is no compensation to sites associated with this study. The study will be published in peer-reviewed journals and presented at national and international scientific congresses. Individual sites or surgeons will not be identified in study reports or performance feedback.

Inclusion and Exclusion Criteria

Site Inclusion and Exclusion Criteria

Sites anywhere in the world will be included if they perform TURBT for NMIBC and could include at least 20 consecutive eligible cases in a period of 12 months. Sites will be excluded if they fail to include 20 cases with a minimum required data set to determine baseline performance. Where a site requests removal from the study, data collected to date will be maintained for reporting purposes unless the site requests deletion.

TURBT Case Inclusion and Exclusion Criteria

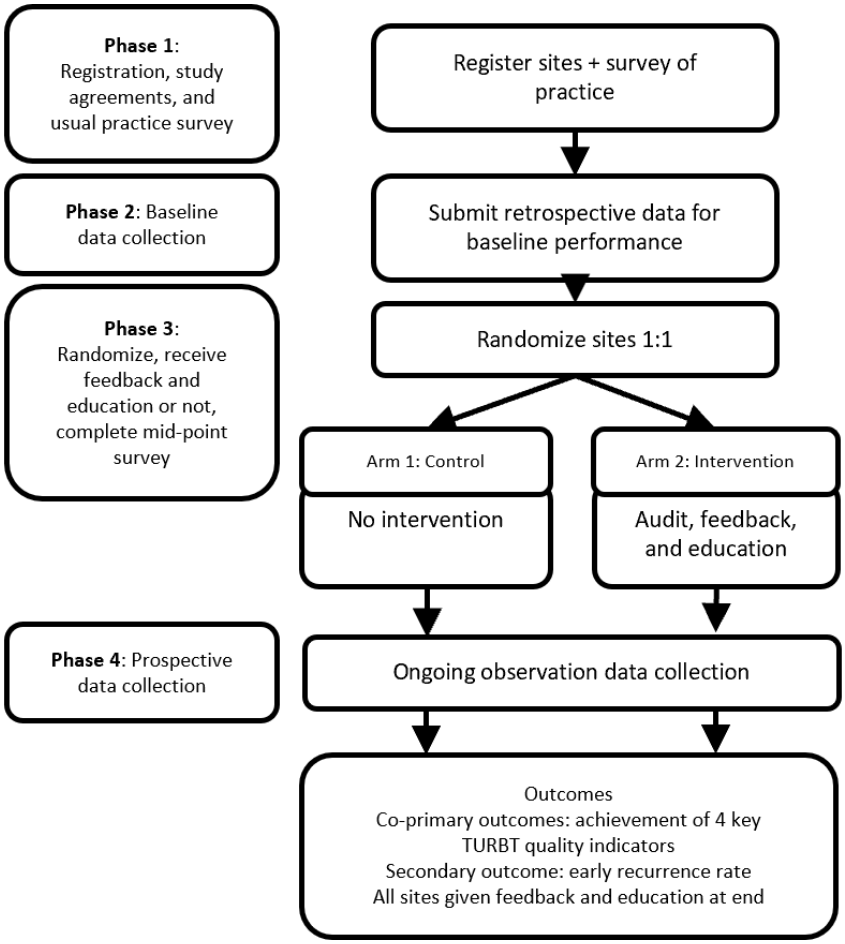
Sites will include consecutive cases of first, curative intent, elective transurethral surgery for a new diagnosis of urothelial carcinoma, thought to be nonmuscle invasive at the time of surgery, across all surgeons at their site. Cases with known concurrent upper tract urothelial carcinoma will be excluded.

Study Design

The study will have four phases, which are summarized in Figure 2: (1) phase 1: site registration, study agreements, and usual practice surveys; (2) phase 2: retrospective baseline data collection; (3) phase 3: randomization to either arm of “no intervention,” or “audit, feedback, and education”; and (4) phase 4: prospective data collection.

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Figure 2. Study phases and design. TURBT: transurethral resection of bladder tumor.



Site Registration, Study Agreements, Surgeon Registration, and Usual Practice Surveys

Sites will complete a survey about their location, hospital type, and their usual practice. An agreement will be signed by the site principal investigator including consent to randomization. Each surgeon performing TURBT at the site will be registered along with details about their surgical experience including their grade, number of TURBTs performed per month, and years of experience.

Baseline Data Collection

Sites will be asked to enter data about consecutive eligible TURBT cases performed at their site counting backward from the date of site registration. The rationale is to sample cases from before a site had awareness of the study to obtain a cohort free from the Hawthorne effect [27].

Randomization

Sites will be randomized 1:1 in parallel arms when the submission of the minimum required retrospective data is complete. Sites will be randomized to either (1) no intervention (the site continues to submit data on consecutive eligible cases but without performance feedback and education during the study). Once the study is complete, these sites will be provided with performance and education feedback or (2) audit, feedback, and education (performance feedback and education provided before beginning further prospective phase of study).

Sites will be randomized using the randomization app at the Centre for Healthcare Randomised Trials (CHaRT), University of Aberdeen, which developed the randomization sequence. This randomization app is available 24 hours a day, 7 days a week as a web-based app. Randomization will be minimized for site-level variables that are thought to significantly impact achievement of TURBT quality indicators. There is no blocking. These are baseline performance from the baseline audit, geographical region (continent, except that the United Kingdom is considered alone, Australia will be combined with mainland Europe), and the presence of an existing TURBT audit at that site before the study. In addition, a random component is used in the minimization algorithm to ensure concealment of the allocation.

The study administrator will access the web-based system. They will enter the minimization variables into the web-based system, which returns the allocation status. The chief investigator of the site will be informed of their allocation following randomization. There is no blinding. To prevent contamination following randomization, sites randomized to no intervention will not be granted access to the dedicated personalized feedback and education resources, which are username and password protected.

Data Management

Local data will be routinely collected health care data accessed by members of the clinical team. Nonidentifiable data will be manually entered into the secure, password-protected study

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database (hosted at University College London) after appropriate local approvals have been obtained. Only the study management and statistical team will have access to the full data set.

Results

Audit, Feedback, and Education Design

The audit, feedback, and education intervention was designed using evidence-based theories about interventions that cause behavior change. These theories were both general [16,18,28-31] and specific to TURBT surgery based on our previous work [12,32].

The intervention is delivered at the site level with recommendations about how to engage with, disseminate, and use the feedback and education. There is no mandated change to clinician behavior or patient care, all patient treatment and professional practice decisions are at the discretion of the clinician. Sites can request to leave the study at any time, and all withdrawals will be reported. It will not be permitted for a site allocated to "no intervention" to receive the intervention during the study period.

Our group previously used qualitative methods to assess barriers and facilitators to a coprimary outcome for this study: SI-IVC administration [32]. The data from this qualitative study and a systematic review of barriers to NMIBC guideline compliance [12] were used to identify intervention functions and behavior change techniques (BCTs) using the theoretical domains framework, as suggested in the implementation science literature [29,30,33].

Conclusions from systematic reviews and expert groups about improving effectiveness of audit and feedback were used to inform the design of the feedback and education. For example: "feedback may be more effective when baseline performance is low [16]"; "if the source is a supervisor or colleague [16]"; "it is delivered in both verbal and written formats [16]"; "it includes both explicit targets and an action plan [16]"; and "process of care measures are more positively influenced by feedback than outcome of care [26]." In addition, adding education to feedback may enhance the effectiveness of audit and feedback and so this strategy will be adopted [17]: "audit and feedback interventions will be more effective when recommendations related to the audit and feedback are based on good quality evidence" [18] and if it "creates opportunity to learn [18]."

The design of the feedback is further informed by Brehaut et al's [34] "15 suggestions for optimising effectiveness" of practice feedback interventions, the Clinical Performance Feedback Intervention Theory [31], and Colquhoun et al's [18] "Theory Informed Hypotheses" for improving effectiveness of audit and feedback.

Finally, the study steering group applied the APEASE (Affordability, Practicability, Effectiveness and Cost-effectiveness, Affordability, Side-effects, Equity) [29] criteria to the possible BCTs. This process highlighted suitable BCTs and feedback and education components detailed in Table 1.

The performance feedback will take the form of a web-based feedback dashboard that will be freely available at any time to those given access as well as a report of the individual cases that make up their performance outcomes and other components. The components of the feedback dashboard are described in Table 1 and Figure 3 and displayed in Figure 4.

The study team or lead investigator will receive an email detailing the feedback and education intervention. They will be asked to forward the email and feedback and education dashboard access to all the surgeons at their site and present and discuss the feedback at a departmental meeting. The lead investigator must then complete a survey about how the feedback and education were used and disseminated at their site and any specific changes they have made (Figure 3).

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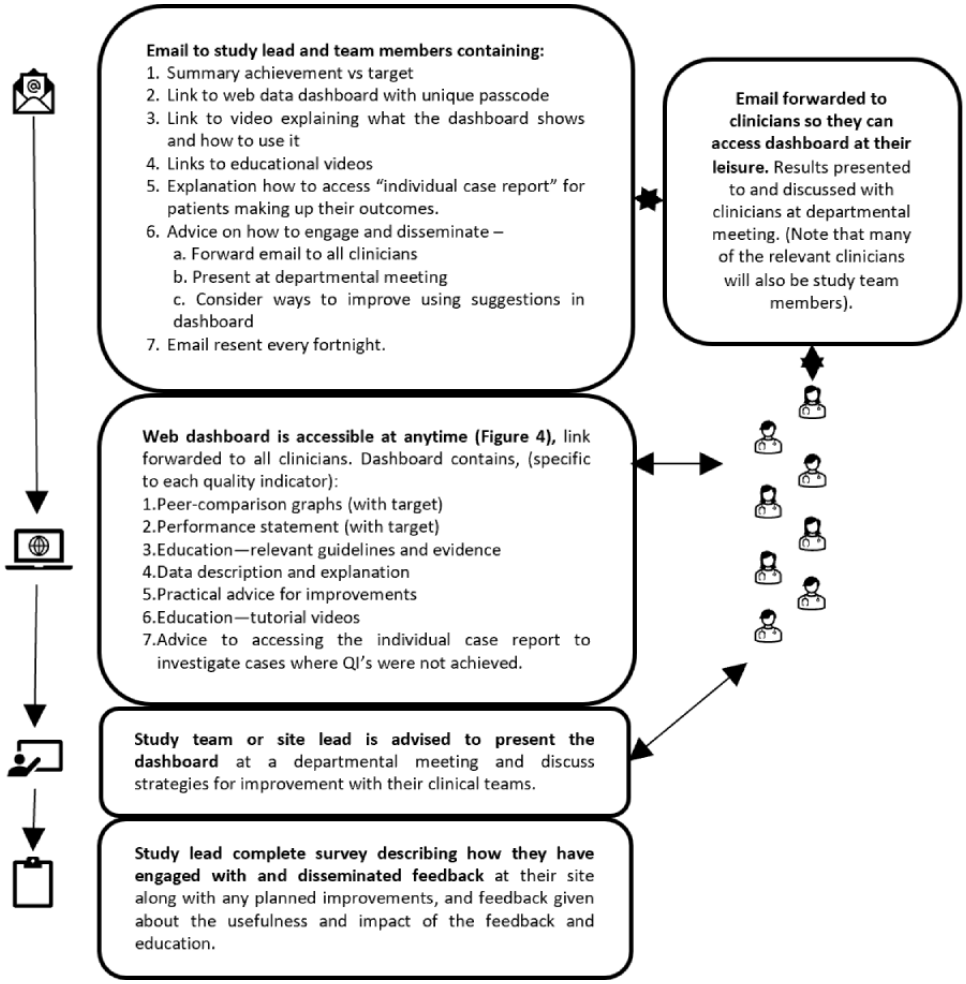
Table 1. Feedback and education intervention components, behavioral change techniques, theories, and mode of delivery.

Component	Description	Behavior change technique [30] or audit and feedback effectiveness theories or evidence	Mode of delivery
Performance feedback			
1. Peer-comparison graphs	• "Rate of achievement" scatter graphs displayed at both the site and surgeon level. All sites and surgeons are displayed but are anonymous, only current site data points are labeled with anonymous unique ID. Filterable by tumor grade.	Social comparison (6.2), "for those with a mastery goal orientation" feedback will be more effective if it involves comparison to others [18].	Web-based data dashboard, accessed via link in feedback email with site-specific passcode.
2. Performance statement	• The site's level of achievement, the average level of achievement, the target, and whether they are considered above or below an explicit target. This is based on the experience of the Scottish Quality Performance Indicator programme [15].	Social comparison (6.2), Explicit target given [16].	In feedback email and displayed alongside peer-comparison graphs on web dashboard.
3. Data description	• An optional pop-up box described how the graphs were generated including the description of numerator and denominator, advice on interpretation, justification of quality indicator selection, target and case selection.	Theory of trust or credibility and nature of the data [18].	An optional pop-up box alongside each peer-comparison graph in the web dashboard.
4. Action plan	• Actions specific to each behavior provided, for example, an operative recording proforma to improve documentation outcomes.	Instruction on how to perform the behavior (4.1), restructuring the physical environment (12.1), adding objects to the environment (12.5), prompts or cues (7.1).	Displayed beneath the peer-comparison graph of each quality indicator with links to either written resources or to download the operative proforma.
5. Individual case report	• The cases analyzed for each quality indicator, along with selected clinically relevant variables (eg, tumor details and operating surgeon code) can be reviewed in a filterable report, and individual database records easily entered for case review and discussion.	Theory of feedback specificity, user-guided experience, and social engagement [18].	The site-specific reports are available in the study REDCap[a] database environment, instructions about how to use are included in the feedback email and dashboard.
6. Provide feedback more than once	• The feedback dashboard is available throughout and displays live performance. Sites will be encouraged to engage with this at a departmental level regularly. Feedback email is resent encouraging ongoing feedback engagement every 2 weeks.	Provide multiple instances of feedback [34].	Same delivery method.
Education			
7. Evidence and guideline education	• Key evidence and related guidelines about why the behavior is important are summarized and links are provided to published evidence.	Information about health (5.1) and social and environmental consequences (5.2).	Provided beneath the peer-comparison graph for each of the quality indicators. Links to web-hosted publicly available resources. Accessible at any time after dashboard access is given.
8. Tutorial videos	• Evidence reviewed and practice from a center of excellence presented by an expert in the field. Operative video tutorials for practical skills provided. • The videos can be accessed at any time, and access is unsupervised. Collaborators are encouraged to review them together at departmental meeting but they may also be accessed individually.	Instruction on how to perform the behavior (4.1) and demonstration on how to perform the behavior (6.1) by a credible source (9.1).	Links to web-hosted videos provided beneath the peer-comparison graphs on the dashboard and in the feedback email. Accessible at any time after dashboard access is given.

[a]REDCap: Research Electronic Data Capture.

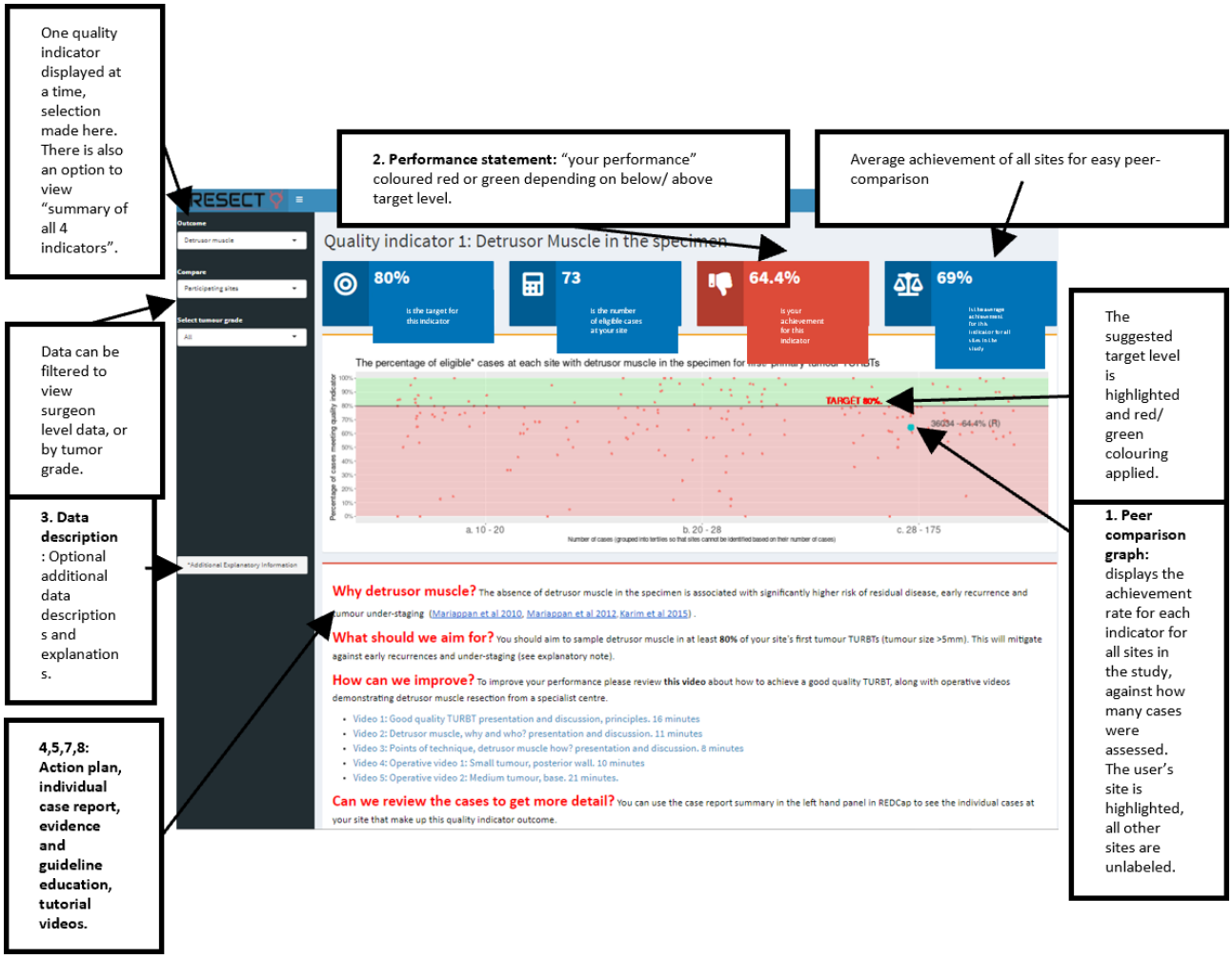
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Figure 3. Intervention and mode of delivery. QI: quality indicator.



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Figure 4. Intervention and design. Web-based performance feedback and education dashboard—accessible to only sites in the intervention arm during the study. Numbers in the boxes relate to the components in Table 1.



Prospective Data Collection After Randomization

Sites will be asked to submit observational data about all consecutive eligible TURBT cases performed after they have been randomized. Sites in the feedback and education arm will only be permitted to submit cases in the prospective phase once the mid-point survey has been received. The purpose of the midpoint survey was to determine if any unprompted changes to practice or performance had been made since the site registration survey was completed and confirm that sites had disseminated the education and feedback at their site (if relevant) and assess how this had been done.

Primary Outcomes

Principles

The study will use 4 coprimary outcomes. The primary outcomes are key "surgical quality indicators" or "process measures." The outcomes were chosen through a combination of evidence, guidelines associating their performance with improved bladder cancer outcomes, expert steering group consensus, and independent external peer review. Primary outcomes were chosen to meet the following criteria: (1) They are behaviors or practices associated with the primary operation or occurring at the time of the primary operation. (2) It is possible for the surgeon to directly influence these practices. (3) They are practices recommended by professional guidelines or evidence associating them with improved outcomes. (4) They can be objectively measured through review of the standard patient record.

Coprimary outcomes were chosen because not all behaviors are applicable to all patients and no single behavior may indicate overall quality. The 4 outcomes chosen draw on experience and the outcomes used in the Scottish Quality Performance Indicator programme and work by Mariappan et al [14,15].

The intervention will be considered effective if any one of the 4 coprimary outcomes is significantly improved. "Eligible cases" and excluded cases were determined for each coprimary outcome. Eligible cases (after exclusions) make up the denominator for calculation of the proportion of cases achieving the outcome.

Quality Performance Indicator 1: The Proportion of Eligible Cases Where Detrusor Muscle Is Present in the Surgical Specimen

Rationale

International evidence-based guidelines include clear recommendations related to TURBT [5,7]. There is evidence that resection of detrusor muscle at the index TURBT is associated with reduced early recurrence rate [6,22] and

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long-term mortality [25] and is more likely to be resected by experienced than inexperienced surgeons [6,22]. If detrusor muscle is not obtained, it is not possible to accurately determine the tumor stage and all of the tumor may not have been removed, which may lead to recurrence. It is accepted that detrusor muscle resection is not appropriate in all patients and is a clinical judgment. Therefore, the average rate of detrusor muscle will be used as a performance indicator.

Eligibility

All cases where the tumor maximal diameter is estimated at >5 mm by the operating surgeon.

Assessment

The outcome will be determined from the surgical pathology report.

Exclusions

Where the data for the presence or absence of detrusor muscle in the specimen are investigator-missing, the case will be excluded.

Quality Performance Indicator 2: The Proportion of Eligible Cases Where SI-IVC Is Administered Within 24 Hours of TURBT

Rationale

There is high-certainty evidence supporting the use of SI-IVC, such as Mitomycin C following TURBT. It is known that SI-IVC administration can significantly reduce the rate of NMIBC recurrence [23,35-39]. EAU and AUA guidelines recommend administration of SI-IVC within 24 hours of surgery in patients most likely to benefit [5,7].

Eligibility

All cases at sites where it is possible to give SI-IVC.

Assessment

The outcome will be determined from review of the patient record.

Exclusions

It is anticipated that a small number of sites will be unable to provide SI-IVC due to local or national service, supply, or economic restraints. These sites will be identified from the study registration survey and excluded from this indicator a priori. Cases where a patient has a documented allergy to SI-IVC will be excluded. Where this data field is investigator-missing, the case will be excluded from this outcome.

Quality Performance Indicator 3: The Proportion of Eligible Cases Where Resection Completeness Is Documented in the Operation Record

Rationale

Guidelines strongly recommend documenting the completeness of resection [5]. Using a TURBT proforma to document the surgical procedure and findings at surgery in a standardized way is associated with improved patient outcomes [15,24,40]. Completely removing all visible tumors is a core surgical principle in cancer surgery. Documentation of this is essential for subsequent multidisciplinary team meeting decisions on the management of individual patients as it determines the need for repeat resection, which can improve oncological outcomes in selected patients [41].

Eligibility

All cases included in the study.

Assessment

The outcome will be determined from review of the operation note. To achieve the indicator, a statement that the resection was either complete, incomplete, or uncertain is required. Where there is no statement of resection completeness in the operation record the indicator will be failed.

Exclusions

Where this data field is investigator-missing, the case will be excluded from this outcome.

Quality Performance Indicator 4: The Proportion of Eligible Cases Where All of the Tumor Number, Size, and Location Are Documented in the Operation Record

Rationale

Guidelines strongly recommend documenting the tumor location, appearance, size, and multifocality [5]. Tumor size and number are associated with recurrence risk and are required to risk-stratify patients according to European Organisation for Research and Treatment of Cancer (EORTC) risk categories as recommended by both AUA and EAU guidelines [5,7]. Documentation of these factors and subsequent risk stratification allows multidisciplinary team meeting decisions for individual patients, determining the need for adjuvant treatments, which determine long-term oncological outcomes. Documenting tumor location also allows appropriate assessment of recurrence and resection completeness at reresection surgeries and during cystoscopic surveillance.

Eligibility

All cases included in the study.

Assessment

The outcome will be determined from review of the official operation note. To achieve the indicator, a statement of the tumor number, size (an assessment of tumor maximal diameter and at least to a resolution of <3 cm or ≥ 3 cm [a risk category cut-off in the EAU guidelines]), and location is required. Where record of any of these 3 features is missing from the operation record, the outcome will be failed.

Exclusions

Where this data field is investigator-missing, the case will be excluded from this outcome.

Secondary Outcomes

Key Secondary Outcome: Early Recurrence Rate

Rationale

International guidelines recommend that a “check” cystoscopy be performed approximately 3 months after complete TURBT [5,7]. The rationale is that recurrence detected at this early stage

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is due to surgical failure rather than disease process [6]. Therefore, the early recurrence rate represents an outcome of surgical quality.

Eligibility

All cases where a cystoscopy has been performed within 6 months of complete index TURBT or planned completion re-TURBT, or, in cases where an adjuvant treatment course is given prior to check cystoscopy, at a check cystoscopy performed within 12 months.

Assessment

The outcome will be determined from review of the patient record. Recurrence will be defined as either (1) a clinical assessment of "highly likely" recurrence where fulguration is applied, and no surgical specimen is obtained or (2) when a surgical specimen is obtained, and then histological confirmation of cancer will be required.

Exclusions

Where this data field is investigator-missing. Where muscle-invasive bladder cancer is identified in either the primary or re-TURBT pathology. Where the patient is deemed not fit or appropriate for further surveillance.

Other Secondary Outcomes

Other secondary outcomes include (1) the proportion of eligible patients in whom all applicable primary quality indicators are achieved (not all quality indicators are applicable in every patient) and the association of this composite outcome with early recurrence rate and (2) the rate of complications of grade 3 or greater, within 30 days of surgery according to the Clavien-Dindo [42] classification.

Sample Size

The intervention will be delivered to centers, and so the primary outcomes will also be measured at the center level. The only published data about intersite achievement of the listed coprimary outcomes are the Scottish Quality Performance Indicator programme covering 11 sites in Scotland. The outcome with the largest SD (SI-IVC) was used to determine the overall sample size. With mean 0.651 (SD 0.2) for SI-IVC, recruiting 172 sites (86 per arm) would give 90% power to detect a difference of 0.1 between the intervention and control groups at the 5% significance level. Where a smaller SD of 0.1 (detrusor muscle in specimen) or 0.15 (resection documenting) can be assumed, this would provide 90% power at the 5% significance level to detect differences of 0.05 and 0.075, respectively. It is possible that some sites may have missing data for 1 or more of the coprimary outcomes. Missing data will not be imputed for the primary outcomes. In that case, the site will be excluded from the analysis for that outcome. A sensitivity analysis will be performed to determine the effect of missing data in that outcome. An extensive international marketing campaign will be undertaken to ensure sample size is reached, along with endorsement of the study by the British Association of Urological Surgeons to all urology centers in the United Kingdom.

Analysis

The average rate of achievement of each of the 4 co-primary outcomes per site will be compared between sites that received education and feedback and those that did not. The primary outcomes will be analyzed using mixed effects linear regression to compare the outcome between the group that received audit, feedback, and education and the control group. The primary outcomes are the proportion of cases where the relevant outcome is obtained and measured at the site level (a continuous variable). The regression model will have fixed effects for the study arm (intervention group); audit already in place at the site before the study; and the baseline achievement of the relevant outcome. A random effect will be included for the region. Outcomes will be assessed in subgroups of low- and high-grade tumors, tumors with estimated maximum diameter of ≤3 cm or >3 cm and in single vs multiple tumors for the detrusor muscle, and intravesical chemotherapy outcomes.

The early recurrence rate is a secondary outcome. This is measured at the patient level. In this instance, the outcome is binary. A mixed effect logistic regression will be used including random effects for site and surgeon to incorporate the 2 levels of clustering. Fixed effects will be included for intervention arm and tumor variables known to be associated with early recurrence (tumor size, tumor number, grade, and stage). Patient age will also be included as a fixed effect. A second analysis will be undertaken for the early recurrence outcome at the patient level to determine if the quality indicators are associated with reduced recurrence rate regardless of performance feedback.

Secondary Analyses

This study is an observational audit with an embedded cluster randomized design and was planned so that the following factors could be analyzed for association with TURBT quality indicator achievement and early recurrence rate: (1) surgeon factors: (a) the experience of the operating surgeon in years, (b) total number of cases performed by the surgeon to date, (c) number of cases performed per month on average in the last year, and (d) a self-declared specialist interest in bladder cancer; (2) TURBT surgery performed on a dedicated TURBT list; (3) the estimated annual TURBT case volume of the site; (4) the use of en-bloc resection; (5) the use of diagnostic visual aids including: (a) photodynamic diagnosis–assisted resection, (b) narrow band imaging, and (c) Storz Professional Image Enhancement System; (6) the length of inpatient stay; (7) geographical region—continent; (8) World Health Organization health care quality and access index for the country; (9) the preexistence of a TURBT audit at the site; (10) the use of re-TURBT; (11) the use of primary adjuvant BCG or Mitomycin C; and (12) patient factors: age and sex.

Discussion

This study aims to use a distributed collaborative model to deliver a site-level web-based performance feedback intervention to improve the quality of endoscopic bladder cancer surgery. The goal is to gain incremental benefit across vast numbers of patients using a simple and cheap intervention that will amount to large absolute benefits across the population of

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patients with NMIBC. We have considered previous advice from systematic reviews of previous audit and feedback interventions and used the theoretical domains framework to design the feedback intervention. We have worked closely with expert international clinical, methodological, and statistical professionals to ensure quality of study design.

The effectiveness of audit and feedback in improving professional practice varies depending on "baseline performance and how feedback is provided" as well as setting [16]. We have determined that a clinically relevant relative difference between intervention and control arms is 10% and powered this study accordingly. Electronic audit and feedback have also been found to have variable effectiveness, and a systematic review recommended closer attention to theoretical domains targeted [21]. We have done this as part of the study design. This study is unique because of its global multicenter reach and therefore aspires to power a cluster-cluster randomized controlled study design to confidently determine the effect of the intervention. The Hawthorne effect will be accounted for since we measure performance retrospectively (when the study was not known about) and then compare 2 parallel arms in the randomized study. There have been previous time-series studies of audit and feedback in TURBT surgery, which suffer from the lack of a contemporaneous control group [15,40]. To our knowledge, this will be the first randomized study of audit and feedback in TURBT surgery. Limitations of the study design include the pragmatic intervention—clinicians can choose to engage or not, and implementation at the site level is left up to local teams. The site-level intervention and analysis will limit the ability to make conclusions about the behavior of individuals. In conclusion, this study will determine if audit, feedback, and education is effective in improving professional practice in the quality of TURBT surgery and if this reduces NMIBC early recurrence rates.

Acknowledgments

We would like to acknowledge the input and expertise of our protocol external peer reviewers: Christopher Blick, Ashish Kamat, Jim Catto, Hugh Mostafid, Richard Sylvester, and John McGrath. This study was supported by the Rosetrees Trust grant CF1\100002, the Urology Foundation, Action Bladder Cancer UK, Karl Storz agreement, Photocure agreement, Medac Pharma agreement, and the British Journal of Urology International Charity. None of the study funders had any academic input to the study design analysis or reporting. This study was sponsored by British Urology Researchers in Surgical Training.

Data Availability

The data sets generated and analyzed during this study are not publicly available due to a need to maintain anonymity of the included sites as set out in the study agreement but are available from the corresponding author on reasonable request. All statistical code will be made available upon request.

Authors' Contributions

VK, KG, SML, and NB conceptualized the study. VK, KG, NB, PM, SML, LA, DC, SK, KC, MK, ED, BG, PH, GM, and JY-CT designed the study. VK, KG, NB, PM, SML, LA, DC, SK, KC, MK, ED, BG, TOB, and MN were part of study steering and endpoint adjudication committee. KG, NB, VK, and KC managed the data. KG wrote the manuscript. VK, KG, NB, PM, SML, LA, DC, SK, KC, MK, TOB, MN, ED, BG, AA, AL, TA, FG, PH, GM, and JY-CT reviewed the manuscript.

Conflicts of Interest

This study has received funding from 3 industry sources—Karl Storz, Photocure, and Medac Pharma. Funds were provided as unrestricted grants with no influence on the design, analysis, or reporting of the study. PM is a designer and chief investigator for the Scot BC Quality OPS clinical project.

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Abbreviations

APEASE: Affordability, Practicability, Effectiveness and Cost-effectiveness, Affordability, Side-effects, Equity
AUA: American Urological Association
BCT: behavior change technique
CHaRT: Centre for Healthcare Randomised Trials
EAU: European Association of Urology
EORTC: European Organisation for Research and Treatment of Cancer
NICE: National Institute for Health and Care Excellence
NMIBC: nonmuscle invasive bladder cancer
REDCap: Research Electronic Data Capture
SI-IVC: single-instillation intravesical chemotherapy
TURBT: transurethral resection of bladder tumor

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Protocol

Positive Psychological Intervention Delivered Using Virtual Reality in Patients on Hemodialysis With Comorbid Depression: Protocol and Design for the Joviality Randomized Controlled Trial

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Abstract

Background: Depression is highly prevalent in individuals on hemodialysis, but it is infrequently identified and remains undertreated. In this paper, we present details of the methodology of a randomized controlled trial (RCT) aimed at testing the feasibility and preliminary efficacy of a 5-week positive psychological intervention in individuals on hemodialysis with comorbid depression delivered using immersive virtual reality (VR) technology.

Objective: We aim to describe the protocol and design of the *Joviality* trial whose main objectives are 2-fold: determine the feasibility of the *Joviality* VR software through metrics capturing rates of recruitment, refusal, retention, noncompliance, and adherence, as well as end-user feedback; and assess preliminary efficacy for outcomes measures of depressive symptoms, psychological well-being and distress, quality of life, treatment adherence, clinical biomarkers, and all-cause hospitalizations.

Methods: This 2-arm RCT is scheduled to enroll 84 individuals on hemodialysis with comorbid depression from multiple outpatient centers in Chicago, Illinois, United States. Enrollees will be randomized to the following groups: VR-based *Joviality* positive psychological intervention or sham VR (2D wildlife footage and nature-based settings with inert music presented using a head-mounted display). To be eligible, individuals must be on hemodialysis for at least 3 months, have Beck Depression Inventory-II scores of ≥11 (ie, indicative of mild-to-severe depressive symptoms), be aged ≥21 years, and be fluent in English or Spanish. The *Joviality* VR software was built using agile design principles and incorporates fully immersive content, digital avatars, and multiplex features of interactability. Targeted skills of the intervention include noticing positive events, positive reappraisal, gratitude, acts of kindness, and mindful or nonjudgmental awareness. The primary outcomes include metrics of feasibility and acceptability, along with preliminary efficacy focused on decreasing symptoms of depression. The secondary and tertiary outcomes include quality of life, treatment adherence, clinical biomarkers, and all-cause hospitalization rates. There are 4 assessment time points: baseline, immediately after the intervention, 3 months after the intervention, and 6 months after the

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intervention. We hypothesize that depressive symptoms and hemodialysis-related markers of disease will substantially improve in participants randomized to the VR-based *Joviality* positive psychology treatment arm compared with those in the attention control condition.

Results: This RCT is funded by the National Institute of Diabetes and Digestive and Kidney Diseases and is scheduled to commence participant recruitment in June 2023.

Conclusions: This trial will be the first to test custom-built VR software to deliver a positive psychological intervention, chairside, in individuals on hemodialysis to reduce symptoms of depression. Within the context of an RCT using an active control arm, if proven effective, VR technology may become a potent tool to deliver mental health programming in clinical populations during their outpatient treatment sessions.

Trial Registration: ClinicalTrials.gov NCT05642364; https://clinicaltrials.gov/ct2/show/NCT05642364

International Registered Report Identifier (IRRID): PRR1-10.2196/45100

(JMIR Res Protoc 2023;12:e45100) doi:10.2196/45100

KEYWORDS

virtual reality; hemodialysis; positive psychology; emotional well-being; mindfulness; depression; comorbid depression

Introduction

Background

End-stage kidney disease (ESKD) requiring hemodialysis is a taxing condition that requires difficult self-care practices (eg, multiple weekly treatment center visits) [1]. Depression is the most pervasive psychological issue in this patient population and presents a substantial added burden: one-third of individuals on hemodialysis in the United States report compromised emotional well-being [2]. Comorbid depression exacerbates disease progression and is associated with increased markers of systemic inflammation; compromised cellular immunity [3]; and adverse clinical outcomes, including lower rates of treatment adherence [4], greater hospitalization risk, and shorter survival [5]. Possible mechanisms by which depression heightens morbidity and mortality in individuals on hemodialysis include negative effects on treatment adherence, impairment of the immune system, and hampering of healthy dietary practices [6].

Few individuals on hemodialysis experiencing psychological distress are currently being diagnosed and treated [7]. Pharmacotherapy has seen limited application, given the substantial pill burden among individuals on hemodialysis and reluctance by physicians given the possibility for drug-drug interaction and low medication adherence [8]. Health care providers and patients are reluctant to add another drug to the existing regimen unless severe psychopathology (eg, suicide ideation) is evident [8]. Despite the limited uptake of antidepressant medication in people on hemodialysis, nonpharmacologic strategies to boost psychological well-being continue to be underused and understudied [9,10].

The few published trials on efficacy of psychosocial strategies to improve depressive symptoms in individuals on hemodialysis overwhelmingly focus on face-to-face delivery of cognitive behavioral therapy [10]. Although cognitive behavioral therapy shows promise in reducing symptoms of depression and improved compliance of fluid intake [11,12], this approach presents significant challenges given the complexity and intensiveness needed for deployment, which requires highly trained and skilled clinicians for appropriate delivery and multiple in-person communications.

Rationale for the Study

There is a critical need to identify practical, well-accepted, sustainable, and cost-effective strategies to reduce depressive symptoms and increase levels of psychological well-being in individuals on hemodialysis considered at risk. Fittingly, there has been a proliferation of programs that promote psychological assets and resilience, with the recognition of the importance of focusing on individual-level strengths and human flourishing—instead of solely focusing on negative psychological indicators, deficits, and emotional pathology [13,14]. Evidence shows that positive psychological assets (eg, optimism, positive affect, life meaning, and purpose) are uniquely related to better emotional and physical well-being, independent of the effects of negative emotion [15-21]. A meta-analysis of 25 positive strengths-based interventions targeting constructs such as gratitude, happiness, and optimism found a medium effect size for relief of depressive symptoms (median r=0.26), with stronger effects seen for phenotypes of participants with current depressive symptoms [22,23]. Published studies comparing positive psychology interventions with treatment as usual show effectiveness and durability similar to those of traditional psychotherapy or pharmacotherapy [22].

Accompanying expanded focus on strengths-based approaches is an increase in the use of technology to deliver these interventions that explicitly target boosting of positive emotions and factors of resilience. Testing remote distribution options (eg, mobile phone apps) for strengths-based interventions provides evidence of their efficacy and cost-effectiveness. Advantages of web-based delivery options include generally lower cost, easier dissemination, more consistent fidelity to the intervention protocol through automation that counteracts going off script, and greater accessibility in settings with Wi-Fi availability [24,25]. Comparative effectiveness trials document similar effect sizes for internet-based psychotherapy compared with traditional face-to-face approaches, with high patient satisfaction when rating these high-technology platforms [26,27]. Barriers to entry associated with traditional in-person forms of therapy may be bridged using web-based platforms that offer low-threshold and convenient at-home alternatives.

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A participative technology that has rarely been used in individuals on hemodialysis is fully immersive 3D virtual reality (VR), although recent evidence in other clinical populations hints at its promise as an effective therapeutic tool [28]. VR is an evolving technology that presents an immersive experience to transport users to fictitious yet realistic and lifelike environments. Users wear a head-mounted display (HMD) or headset that recognizes physical motion (eg, head movement and remote control) to navigate VR (3D) worlds, which can replicate realistic settings or complex science fiction environments [29]. A meta-analysis confirms the utility of VR for pain reduction when pooling 11 trials that included individuals experiencing varied pain-inducing therapies or complaints (ie, burn injuries and wound redressing, postsurgical pain, and complex dental procedures, among others) [30]. This is the question that remains: "How might VR technology be used in individuals on hemodialysis to decrease procedural pain and discomfort and simultaneously deliver strengths-based programming to address the pervasive psychological distress experienced in this patient population?"

Hypothesis and Objectives

To answer the question of the utility of VR in individuals on hemodialysis, we describe the design for a randomized controlled trial (RCT) that tests whether VR is a viable interface to deliver an evidence-based positive psychological intervention as a means to boost emotional well-being and reduce symptoms of depression in individuals on hemodialysis. VR has the benefit of allowing individuals on hemodialysis to digitally travel to multiple settings across the globe and briefly leave the confines of the clinic, which may offer further salutary benefits.

Specifically, we describe the design and protocol for testing our VR-based *Joviality* software, intended to decrease depressive symptoms and boost psychological well-being in individuals on hemodialysis. This study details the methodology of a prospective, 2-arm, parallel RCT that is set to launch in the June of 2023 and that has the following aims: to (1) evaluate the acceptability and feasibility of a 5-week positive psychological intervention, delivered using a VR platform, through the consideration of rates of recruitment, refusal, retention, noncompliance, and adherence, as well as end-user feedback; and (2) test the preliminary efficacy of our VR-based positive psychological intervention in comparison with that of an active control arm on outcomes of depressive symptoms, psychological well-being and distress, quality of life, treatment adherence, clinical biomarkers, and all-cause hospitalizations in individuals on hemodialysis at 3 and 6 months after the intervention. At trial conclusion, we expect that our software will have high system usability with superior performance, offering an enjoyable and positive end-user experience, and that participants in the *Joviality* treatment arm will show significant improvements in psychological well-being, treatment adherence, and hospitalization rates.

Methods

Overview and Study Design

This study describes the design and protocol of a 2-arm RCT, inclusive of both groups requiring use of an HMD: (1) VR-based *Joviality* positive psychological intervention, an immersive program that teaches 8 different skills to boost positive emotion with focused lessons on noticing of positive events, positive reappraisal, gratitude, acts of kindness, and mindful or nonjudgmental awareness, among others; and (2) sham VR [31], which consists of 2D wildlife and nature-based videos with inert background music. This prospective trial plans to recruit and enroll study participants from the University of Illinois Hospital Outpatient Dialysis Center, DaVita Kidney Care, and Nephrology Associates of Northern Illinois and Indiana. Both arms will be exposed to the virtual environments intraprocedurally during regular hemodialysis treatment sessions (ie, 3 times per week for 25- to 30-minute immersive sessions on each occasion). After the 6-month assessment period, participants in the control arm will be given access to the *Joviality* software.

Randomization procedures will use the web-based REDCap (Research Electronic Data Capture; Vanderbilt University) system, with 1:1 allocation across trial arms. Block randomization will occur among varying block sizes of 4, 6, and 8, with stratification by sex, depressive symptom severity, and recruitment site. The randomization procedure will be generated by our lead statistician (RD) and implemented by the project director (GM), who will actively participate in intervention delivery. However, the project director will not be involved in survey assessments to ensure safeguards against the risk of bias. Research staff conducting survey assessments will be blinded on assignment across intervention arms. Enrolled participants will also be blinded to randomization assignment, with a generic description of the VR content as *VR travel* and identification as either *groupA* or *groupB*.

Ethics Approval

This VR-based trial has been approved by the institutional review board of the University of Illinois Urbana-Champaign and the University of Illinois Chicago (19190). Following requirements for an ethics approval process, all study-related documents (eg, recruitment flyers and consent forms) conform to specific language approved by the lead institutional review board, inclusive of its content, elements, and wording.

Trial Registration and Guidelines

The trial has been registered a priori at ClinicalTrials.gov (NCT05642364). The clinical trial will follow published CONSORT (Consolidated Standards of Reporting Trials) guidelines, along with auxiliary standards of the CONSORT 2010 statement for social and psychological interventions (CONSORT-SPI 2018) [32].

Staff Training, Data Collection, and Participation

Research staff and coinvestigators will be required to undergo human participants research training by completing the National Institutes of Health Human Research Protection Training module or the Collaborative Institutional Training Initiative program. Survey data will be collected using Health Insurance Portability and Accountability Act (HIPAA)–compliant server software, with each enrollee assigned a unique identifier to ensure privacy and confidentiality. All enrollees will provide written informed consent. Enrollees of both trial arms will be compensated for

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their time and participation. They will receive US $120 for participation in trial activities, specifically, for the completion of all survey assessments (US $30 for baseline assessment and US $30 for each follow-up measure).

Sample Size

We estimated sample size requirements of a 2-arm RCT to evaluate whether our VR-based positive psychological intervention will result in clinically meaningful improvements in depressive symptoms compared with an active control. The following operational characteristics were assumed: (1) medium Cohen effect size of d=0.35, (2) a within-participant correlation of depressive symptoms over time (P=.60), (3) a 1-sided type I error probability of 0.10 [33], and (4) a statistical power of 85% [34]. This approach yields an estimated sample size requirement of 34 participants per study arm under equal allocation. Assuming an attrition rate of 20%, an updated estimation produces a sample size of 34 / 0.8 = 42 participants per study arm.

Study Setting, Participants, and Eligibility

Trial participants must meet the following inclusion criteria: (1) on hemodialysis for at least 3 months before trial enrollment, (2) a Beck Depression Inventory-II (BDI-II) score of ≥11 [35], (3) age ≥21 years, (4) sufficient visual and audio acuity to enable immersion in the VR world, and (5) fluent in English or Spanish. Participation is restricted to individuals with a BDI-II score of ≥11 because this indicates elevated depressive affect and represents a group that may procure most benefit from the intervention (ie, greatest possible effect size) through targeting of psychological well-being and resilience. Women are eligible independent of pregnancy status. The exclusion criteria include (1) unavailable for study period; (2) cognitive impairment denoting dementia [36]; (3) diagnosis severely limiting life expectancy (eg, metastatic cancer); (4) physical limitations restricting use of an HMD (eg, facial injury); and (5) a history of epilepsy, seizures, or vertigo.

Recruitment and Enrollment

Potentially eligible patients will be recruited in person by approaching them in the waiting room of the clinic before or during regularly scheduled hemodialysis sessions and at other suitable times during the patient consult or treatment period. Patients will also be remotely recruited through telephone calls made by research staff through contact information extracted from electronic medical records (EMRs). Research staff will also distribute flyers and brochures (chairside) to individuals on hemodialysis during regular clinic visits. Once full eligibility is determined and the patient expresses willingness to enroll in the trial, they will be provided a copy of the informed consent form for their signature. After submitting the signed informed consent form and before randomization, enrollees will complete the baseline assessment consisting of REDCap interviewer-led surveys.

Intervention Arm: VR-Based Joviality Positive Psychological Intervention

The VR *Joviality* software architecture and content were built by the University of Illinois Urbana-Champaign Center for Innovation in Teaching & Learning, as led by the digital art director (KS) and principal investigator (RH). Adapted from the web-based course developed by Cohn et al [25], that is, *Developing Affective Health to Improve Adherence*, the original text-based curricula were transposed into a VR software system (ie, Unity [Unity Technologies]) using agile design principles, including brainstorming, storyboarding, designing, testing, and refining, thus transforming textual content into an interactive 3D environment. Finally, software design features have integrated an interface to easily modify the language in which content is presented (ie, English vs Spanish).

The 3D VR software, called *Joviality*, is a strengths-based positive psychological intervention that consists of a skills-based curricula to boost positive emotion and foster individual-level characteristics of resilience and grit. Our multicomponent 5-session intervention teaches the following eight skills: (1) noticing positive events, (2) amplifying positive events, (3) gratitude, (4) behavioral activation, (5) mindfulness, (6) positive reappraisal, (7) personal strengths, and (8) acts of kindness (Table 1). The skills are presented sequentially, starting with noticing of positive events in daily life and ending with the benefits of volunteerism and carrying out of acts of kindness. Only 1 new lesson is made available each week. Successive curricular content is unlocked only after all assigned weekly activities have been completed. Once the lessons are unlocked, participants can revisit prior lessons as a refresher or if they enjoyed a particular previous module.

Each skill is taught in a distinctive virtual environment using the Meta Quest Pro (October 2022 release date). The delivery of intervention content will require VR use for no more than 30 minutes during each hemodialysis session (ie, 30-minute sessions thrice weekly)—this will deter social isolation because patients will have ≥3 hours remaining to interact with neighboring patients and staff. VR immersion will only occur chairside when patients are already sedentary and in a seated position during regularly scheduled hemodialysis treatment. Table 1 details the weekly curricular content and the VR setting in which each lesson is delivered. As noted previously, end users on hemodialysis will be able to select whether the curricular VR content is presented in English or Spanish based on their preference and fluency.

As part of *Joviality*, end users begin each lesson in a virtual lobby outfitted with lounge furniture, flatscreen television, and an instructional green wall where they sequentially select curricular lessons (Figure 1). Skill 1 takes place in a Japanese garden with lush greenery, wildlife, and a waterfall, where end users learn about positive events while snapping virtual photographs using head gaze movement. During skill 2, end users are transported to an art gallery where they participatively display the photographs they took while at the Japanese garden. The lesson on gratitude takes place in an outdoor patio where end users receive didactic instructions, view 2D videos augmenting curricular content, and visit 3D environments to appreciate nature and wildlife. Skills 4 and 5 are situated in a greenhouse, garden, or beach environment where end users play interactive games reinforcing lessons on behavioral activation, mindfulness, and meditation. The remaining lessons take place in the main lobby space. Across all lessons, VR environments

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present didactic instructions and interactive games and quizzes, along with 2D videos throughout.

Table 1. Joviality positive psychology curricular content and lessons.

Week and title	Description	Virtual reality environment
Week 1		
Noticing positive events	Recognizing and focusing on positive events in life	Japanese garden
Amplifying positive events	Capitalizing on positive events and making the events more vivid and longer lasting	Museum gallery
Gratitude	Practicing thankfulness and appreciation of life, positive circumstances, and family or friends	Outdoor patio
Week 2		
Activation	Breaking out of the harmful spirals that worsen emotions	Greenhouse
Week 3		
Mindfulness and meditation	Paying attention and developing nonjudgmental awareness of one's thoughts, feelings, and physical sensations in the present moment	Meditation garden and private beach
Week 4		
Positive reappraisal	Understanding positive reappraisal and that reappraisal can substantially increase positive emotions in the face of stress, particularly when the silver lining is identified	Lobby and neighborhood bus stop
Personal strengths	Recognizing and enhancing a unique set of personal strengths, talents, skills, and positive qualities	Lobby
Week 5		
Acts of kindness	Understanding the positive effects on mental and physical health when engaging in kind acts, volunteerism, and helping others	Lobby

Figure 1. Scenes across Joviality modular lessons.



Control Arm: Nonimmersive Sham VR

Participants randomized to the control arm will receive a rigorous placebo, based on the clinical trial guidelines of the VR Clinical Outcomes Research Experts panel [37], that consists of 2D nonimmersive visual content displayed on the HMD [28,38]. Footage of wildlife and nature-based settings are visually displayed as part of the sham VR with inert music that is unlikely to promote high levels of relaxation or distraction. The sham VR experience has very passive features such that it mimics viewing content on a large flatscreen television. Passive viewing during the sham VR experience rotates content using 20 different videos and has a duration time that is matched to that of *Joviality* over the 5-week intervention period. The delivery of the sham VR content will use the same VR hardware (ie, Meta Quest Pro) as that of the intervention arm to further promote the blinding of end users and research staff.

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Study Outcome Measures

The VR-based randomized trial has 4 assessment time points: baseline (T0), immediately after the intervention (T1; five weeks after baseline), follow-up 1 (T2; three months after the intervention), and follow-up 2 (T3; six months after the intervention). Figure 2 provides a visual of the design and timeline of survey measures. Staff collecting baseline and follow-up data (interview assessors), will be blinded to intervention assignment of enrollees and will not be involved in randomization procedures or any aspects of intervention delivery.

Figure 2. Joviality trial timeline and flowchart. VR: virtual reality.

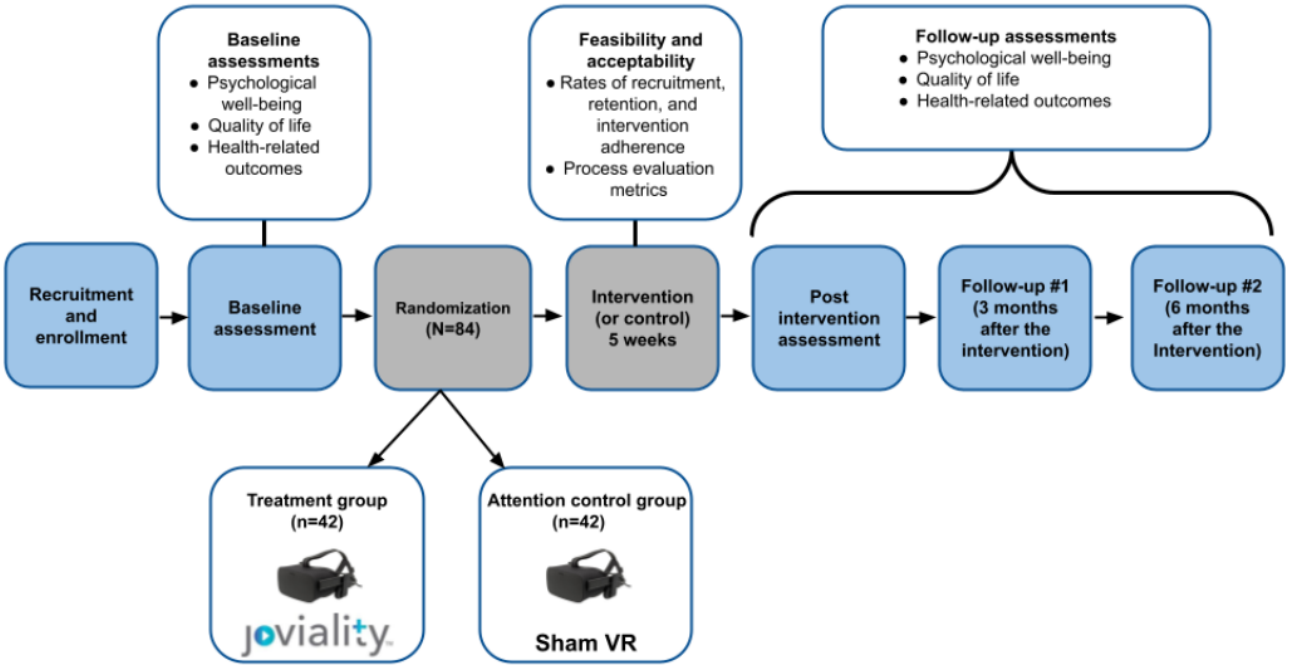


Table 2 details the primary, secondary, and tertiary outcomes of the RCT, along with process evaluation metrics. The primary outcome testing efficacy targets depressive symptoms, as measured by the BDI-II [35]. The PROMIS (Patient-Reported Outcomes Measurement Information System) [39,40] computer adaptive test for depressive symptoms will serve as an additional measure to triangulate the findings of the BDI-II. The central construct serving as our main secondary outcome is psychological well-being, inclusive of its hedonic, evaluative, and eudaimonic domains. Specific domains of psychological well-being will be assessed using PROMIS adaptive measures, including life satisfaction, positive affect, life meaning and purpose, and self-efficacy for managing emotions in the context of a chronic condition [39,40]. PROMIS measures have undergone psychometric testing and show high levels of reliability and validity [41]. Additional measures of psychological well-being include optimism using the 7-item State Optimism Measure [42]; emotional vitality, as measured using select items of the General Well-Being Schedule [43,44]; and the 10-item Flourishing Index, which broadly captures "a state in which all aspects [health and well-being] of a person's life are good" [45]. PROMIS measures will also be used to assess anxiety levels [39,40], along with use of the Perceived Stress Scale [46].

The tertiary measures focus on quality of life, treatment adherence, and disease-related outcomes. First, we will assess self-reported quality of life using the 24-item Kidney Disease Quality of Life-Short Form [47]. Data extracted from the EMR, triangulated through interviews with enrollees or proxies, will be used to document the number of dialysis sessions missed and the total number of hospitalizations, with details on cause and length of stay. EMR data will also be used to capture the following biomarkers: urea reduction ratio, serum albumin concentration, blood urea nitrogen concentration, creatinine concentration, calcium phosphate product, and interdialytic weight gain (% Δ kg per day). We will also capture the etiology of chronic kidney disease via EMR data and self-reported information from enrollees.

Data on relevant covariates will be collected. These will include demographic factors, medical comorbidities [48], and medication use. The EMRs will be used to collect data on age, date of birth, sex, height, and weight. Surveys will be used to collect information on annual household income, educational attainment, marital status, health insurance status, employment, nativity status and number of years in the United States, and country of origin. The Charlson Comorbidity Index [48] will be used to extract codes of the International Classification of Diseases, Tenth Revision (ICD-10), from EMRs, inclusive of the following 18 conditions: myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatic disease, peptic ulcer, mild liver disease, diabetes without chronic complications, diabetes with chronic complications, hypertension, hypercholesterolemia, hemiplegia or paraplegia, any malignancy (including lymphoma and leukemia, except malignant neoplasm of the skin), moderate-to-severe liver disease, metastatic solid tumor, and AIDS or HIV. Medication use will be extracted by research staff through the review of

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medication lists using EMR data. Interview assessors will review the medication list with study participants to verify its accuracy and note any errors or inconsistencies.

We will also collect feasibility and process evaluation metrics (Table 3). Finally, we will extract information from the Meta Quest Pro across patient end users, inclusive of accelerometer data, eye tracking, and visual scanning of pupils, along with facial expressions.

Table 2. Joviality measures of feasibility and metrics testing efficacy.

Measure	Time frame	Type	Source
Psychological well-being			
Beck Depression Inventory-II	In the past 2 weeks	Primary outcome	REDCap[a]
PROMIS[b] computer adaptive tests			
Depression	In the past 7 days	Secondary outcome	REDCap
Anxiety	In the past 7 days	Secondary outcome	REDCap
General life satisfaction	N/A[c]	Secondary outcome	REDCap
Positive affect	In the past 7 days	Secondary outcome	REDCap
Life meaning and purpose	N/A	Secondary outcome	REDCap
Self-efficacy for managing chronic conditions—managing emotions	Right now	Secondary outcome	REDCap
Perceived Stress Scale	In the last month	Secondary outcome	REDCap
State Optimism Measure	Right now or present moment	Secondary outcome	REDCap
Emotional vitality (via General Well-Being Schedule)	In the last month	Secondary outcome	REDCap
Flourishing Index	In the past days	Secondary outcome	REDCap
Quality of life: 24-item Kidney Disease Quality of Life-Short Form	N/A	Tertiary outcome	REDCap
Health-related outcomes			
Interdialytic weight gain (% Δ kg per day)	N/A	Tertiary outcome	EMR[d] or MyChart (EPIC Systems Corporation)[e]
Dialysis sessions missed	N/A	Tertiary outcome	EMR or MyChart (EPIC Systems Corporation)
All-cause hospitalizations	N/A	Tertiary outcome	EMR or MyChart (EPIC Systems Corporation)
Kidney-related biomarkers: urea reduction ratio, serum albumin concentration, blood urea nitrogen concentration, creatinine concentration, calcium phosphate product, and hemodialysis etiology	N/A	Tertiary outcome	EMR or MyChart (EPIC Systems Corporation)
Feasibility and process evaluation: VR[f] utility and usability			
Simulator Sickness Questionnaire	N/A	Feasibility	REDCap
Igroup Presence Questionnaire	N/A	Feasibility	REDCap
System Usability Scale	N/A	Utility	REDCap

[a]REDCap: Research Electronic Data Capture (Vanderbilt University).

[b]PROMIS: Patient-Reported Outcomes Measurement Information System.

[c]N/A: not applicable.

[d]EMR: electronic medical record.

[e]EPIC: Electronic Health Record for the Integrated Care Team.

[f]VR: virtual reality.

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Table 3. Joviality trial metrics of feasibility and acceptability.

Measure	Description	Target
Recruitment and refusal	Measured by the proportion of potential enrollees who were approached for recruitment but decided not to enroll	N/A[a]
Retention	Defined as completing all postintervention assessments, categorized as a binary outcome (yes or no), %	≥75
Adherence	Measured by the proportion of the intervention completed (eg, number of virtual reality environments viewed out of the total possible available across skill lessons in the intervention), %	≥75
Acceptability	Measured by whether a participant would recommend Joviality to other individuals on hemodialysis (ranging from 0=definitely not to 10=definitely yes)	≥8.0

[a]N/A: not applicable.

Planned Analyses

Aim 1: Software Testing and Quality Assurance

Before deploying the *Joviality* VR software among patient end users, the software will be tested by the digital art director (KS) and visual media designer (DF) to ensure that the experience aligns with the original intentions of the research team and to ferret out accessibility or usability concerns. The software will also be tested for performance to ensure that the equipment can run the software without dropping frames or lagging, which can lead to motion or simulation sickness in participants on hemodialysis. User testing will also inform software editing. End users will have the option to experience the final content and audio of the VR environment in English or Spanish.

Aim 2: Acceptability and Feasibility

Key metrics to assess acceptability and feasibility are as follows: (1) recruitment rates, (2) refusal rates, (3) retention rates, and (4) noncompliance and adherence rates (Table 3). A mixed methods approach will be used to assess acceptability through consideration of participants' subjective ratings of the intervention content and modality of delivery and whether it was deemed enjoyable, understandable or clear, and beneficial, along with the measurement of motion sickness, system usability, and end-user perspectives on being fully present in the 3D virtual space. This will be accompanied by open-ended qualitative inquiry on overall thoughts across VR environments and associated content.

Aim 3: Testing of Intervention Effects

Participants will complete survey measures at 4 time points: baseline, immediately after the intervention (5 weeks after baseline), 3 months after the intervention, and 6 months after the intervention. Our exploratory aim will test intervention effects on depressive symptoms, positive psychological well-being (eg, optimism and positive affect) and distress, quality of life, disease-related biomarkers, missed hemodialysis treatment time (in minutes), and rates of hemodialysis sessions missed and hospitalizations.

Central Hypothesis

Our central hypothesis is that our VR-based intervention will lead to postintervention improvements in depressive symptoms, emotional well-being, quality of life, and treatment adherence, along with reduced hospitalization rates and improvements across multiple clinical biomarkers. We will use repeated measures analysis of covariance to compare mean differences in depressive symptoms between the control and intervention arms as measured at baseline and follow-up, that is, immediately after the intervention at 5 weeks, and at 3 months and 6 months after the intervention. Analyses will be adjusted for baseline outcome values to account for the regression to the mean effect and to improve statistical power. To be precise, the average postrandomization effect in the VR-based intervention will be compared with the average postrandomization effect in the active control group. We will also implement an intention-to-treat approach. Multiple imputation procedures will be used across missing values to ensure inclusion of all observations, particularly those resulting from participants who withdraw, are lost to follow-up, or do not complete all assessments. Furthermore, sensitivity analyses will be implemented via the application of mixed effects models, assuming that data are missing at random. The independent variables include a time variable t (t=T0, baseline; T1, immediately after the intervention at 5 weeks; T2, six months after the intervention; and T3, six months after the intervention), a dummy variable k (k=1 if VR-based intervention condition and k=0 if active control arm), and baseline score of dependent variables. Unbalanced variables (mean differences across treatment arms) will be adjusted for, if necessary. Similar analyses will be repeated when examining outcomes of psychological well-being, quality of life, disease-related biomarkers, dialysis treatment adherence, and hospitalization rates.

At the individual level, we will calculate reliable change indices (RCIs) for each participant, as per Jacobson and Truax [49]. The RCI addresses whether the changes that participants experience are statistically reliable by comparing pre-post change with the reliability of the measurement instrument. RCI scores are calculated as follows:

$$RCI = x_2 - x_1 / SE_{diff} \quad \textbf{(1)}$$

where x_1 represents a participant's baseline score and x_2 represents a participant's postintervention score, and SE_{diff} represents the SE of the difference between the 2 scores. RCI scores of >1.96 (approximately 2 SDs from the mean difference) are considered to be reliable [49]. We will present the percentage of participants who experienced reliable change for scores across the measures of interest. RCIs will also be expressed as percentage change from baseline by dividing the RCI score by the baseline score and multiplying by 100. At the sample level, we will conduct 1-tailed paired sample t tests to determine the magnitude of pre-post changes across the main outcomes of interest at each time point. In addition to reporting nominal P

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values, we will implement a false discovery rate approach to accommodate potential inflation of type I error rate owing to multiple comparisons. Furthermore, 95% CIs will be constructed to report meaningful differences between the groups, even if statistical difference is not achieved.

Sex as a biological variable will be addressed in exploratory analyses by tabulating disaggregated data by sex and via sex-stratified analyses of the main outcomes.

Results

This RCT testing our *Joviality* software is funded by the National Institute of Diabetes and Digestive and Kidney Diseases through the funding period lasting from September 1, 2021, to July 31, 2024. The first 18 months of the funding period were dedicated to software development and the final build of the 3D immersive experience. The recruitment of patients on hemodialysis is scheduled to commence in June 2023. Participant recruitment is projected to end in December 2023, with the commencement of data analysis and submission of results for peer review in 2024.

Discussion

Overview

A dialysis treatment session is an ideal time for the delivery of strength-based interventions to boost psychological well-being because it constitutes a 3- to 4-hour window where patients are a captive audience [50], particularly because the lengthy treatment session is often described by patients as a wasteful and monotonous experience in a sterile environment. VR not only offers interactive technology to deliver much needed strengths-based interventions, but it also has the added advantage of allowing individuals on hemodialysis to digitally travel outside the clinical walls and into more relaxing and enjoyable settings. It has become evident that large-scale dissemination and scalability of face-to-face delivery of psychosocial interventions by trained clinicians are difficult, given the limited resources, unequitable health care access, and lack of bilingual practitioners, which makes the use of technology a particularly viable and attractive modality.

Our protocol provides the description of an RCT that adapts and tailors VR technology for use in a clinical population that encounters special needs and challenges. Our team of engineers has designed an intuitive system that requires simple head movement for interactability and that incorporates user-friendly features and an interface for adults with limited technology-based experience [51]. The trial sets the stage for fully immersive technologies in individuals with ESKD aimed at promoting positive emotional and physical health outcomes. Our trial is a preliminary step toward the design of patient-centered interactive VR technologies where patients are given autonomy to select their avatar, language, setting of choice, and much more. This, of course, would be accompanied by future integration of artificial intelligence to autonomously modify and predict end-user preferences for aesthetics, VR content, and travel locations.

VR technology has largely been exploited in video gaming and simulation training with clinicians and military personnel [52]. More recently, VR technology has been used in clinical settings with patients experiencing high-level pain and psychological phobias with favorable results [30,53]. In a randomized trial with patients with burn injuries aged 5 to 18 years, significantly lower pain scores were reported among those engaged in VR gaming while their wounds were being redressed [29]. In individuals with severe phobias, a systematic review found VR exposure therapy to be just as effective as in vivo therapies, particularly for cases of acrophobia (the fear of heights), claustrophobia, and blood injection phobia (the fear of injection exposure), with significant reductions in levels of fear, anxiety, and avoidance [54]. Other successful use cases with meta-analytic evidence include VR in palliative care [55], physical therapy and rehabilitation [56], and cognitive functioning (eg, memory and attention) [57].

In the context of hemodialysis, gamification techniques have focused primarily on nonimmersive gaming devices (eg, *Nintendo Wii*), which overlooks the advantages of fully immersive technologies where end users are teleported to artificial environments to interact with 3D virtual content. As VR technologies continue gaining traction in health care, it is important to decipher the mechanism involved and identify the active ingredients. Theorized pathways on the impacts of VR on health may include (1) cognitive distraction through appealing stimuli, (2) decreased autonomic parameters and healthful physiological responses, (3) targeted induction of body movement and physical activity, and (4) the delivery of evidence-based programming. Much research remains to be conducted to fully understand the role of VR in health care and the mechanisms at play. However, certain considerations should be kept at the forefront, including accessibility across the spectrum of socioeconomic backgrounds, so that immersive technology does not further widen the chasm of health disparities in the United States and abroad.

Our previous work, using the largest cohort of Hispanic or Latino adults, that is, the Hispanic Community Health Study/Study of Latinos, found a positive association between psychological well-being and ideal cardiovascular health in adults with early-stage chronic kidney disease [58]. Each unit increase in positive affect was associated with higher odds of ideal cardiovascular health across multiple indicators. There is no doubt that accumulating evidence documents the merit and healthful benefits of positive emotions and psychological assets in the context of disease-related stress and trauma. As such, this VR-based trial is also a call for greater focus on the strengths and factors of resilience that individuals with ESKD possess, with a focus on programming that will further amplify these positive attributes.

Potential Limitations and Conclusions

Despite the innovativeness and strengths of this RCT, a few limitations should be noted. First, the inclusion criteria capturing elevated symptoms of depression will use the self-report BDI-II survey measure and will not rely on a more precise clinical diagnosis. Nonetheless, the BDI-II has been widely tested in individuals on hemodialysis and has documented satisfactory

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psychometric properties to suggest a higher likelihood of clinical depression. Generalizability of the results may be restricted if recruitment fails to enroll individuals on hemodialysis who are averse to the use of technology or if those with severe depression are reluctant to engage with research staff, thus selectively reducing enrollment rates. It is also possible that the VR content may lead to relaxation that induces sleep, a possibility that our engineering team has contemplated. Thus, triggering design features have been incorporated to alert research staff and end users if prolonged inactivity in the VR space is detected. Finally, given the small targeted enrollment goal, we may not have the power to explore mechanisms through which VR exerts protective effects (if any), nor will it be possible to fully test important effect modifiers of the intervention (eg, race, ethnicity, and socioeconomic status).

In conclusion, we seek to examine whether VR is an effective platform to deliver a positive psychological intervention in individuals on hemodialysis with comorbid depression to improve emotional well-being and clinical health outcomes. If successful, VR headsets could be salient clinical tools in hemodialysis clinics in the United States and abroad. Our VR-based approach could become the new evidence-based tool that clinics house and adopt to improve mental health outcomes in individuals on hemodialysis, with the added potential benefit of improving treatment adherence and healthy longevity.

Acknowledgments

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Data Availability

This paper presents details of the protocol and design for a randomized controlled trial testing virtual reality in the context of hemodialysis; as such, this study does not generate or analyze an associated data set, making data sharing nonapplicable. Once the protocol is implemented and data are made available, we will use a National Institutes of Health–approved data repository to share derived data in a deidentified format and follow rigorous procedures to ensure protection of the privacy, rights, and confidentiality of human research participants. Finally, the public will have access to the detailed protocol and general findings of the trial (when available) at ClinicalTrials.gov (NCT05642364).

Conflicts of Interest

None declared.

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Abbreviations

BDI-II: Beck Depression Inventory-II
CONSORT: Consolidated Standards of Reporting Trials
CONSORT-SPI 2018: Consolidated Standards of Reporting Trials 2010 statement for social and psychological interventions
EMR: electronic medical record
ESKD: end-stage kidney disease
HIPAA: Health Insurance Portability and Accountability Act
HMD: head-mounted display
ICD-10: International Classification of Diseases, Tenth Revision
PROMIS: Patient-Reported Outcomes Measurement Information System
RCI: reliable change index
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
VR: virtual reality

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Protocol

Prevention and Treatment of Social Anxiety Disorder in Adolescents: Protocol for a Randomized Controlled Trial of the Online Guided Self-Help Intervention SOPHIE

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Abstract

Background: Social anxiety symptoms are highly prevalent among adolescents and are associated with poor quality of life and low psychosocial functioning. If untreated, social anxiety often persists into adulthood and increases the risk for comorbid disorders. Therefore, early interventions for social anxiety to prevent negative long-term consequences are critical. However, adolescents rarely seek help and often avoid face-to-face psychotherapeutic interventions due to the perceived lack of autonomy and anonymity. Thus, online interventions represent a promising opportunity to reach adolescents who have social anxiety but do not seek help yet.

Objective: This study aims to evaluate the efficacy, moderators, and mediators of an online intervention developed to reduce social anxiety in adolescents.

Methods: A total of 222 adolescents aged 11-17 years with subclinical social anxiety (N=166) or with a diagnosis of social anxiety disorder (N=56) are randomly assigned to the online intervention or a care-as-usual control group. The 8-week guided online intervention is based on the Cognitive Model of Social Phobia and evidence-based online interventions for social anxiety adapted to the specific needs of adolescents. The care-as-usual group will be given access to the online intervention after the follow-up assessment. Participants are assessed at baseline, at 4 and 8 weeks post intervention, and at 3-month follow-up assessment on the primary outcome, that is, social anxiety, on secondary outcomes (eg, level of functioning, fear and avoidance, general anxiety, depression, quality of life, self-esteem, and negative effects of the intervention), on potential moderators (eg, therapy motivation, therapy expectancy, and satisfaction with the intervention), and potential mediators (eg, therapeutic alliance and adherence to the intervention). Data will be analyzed based on an intention-to-treat approach and both groups (intervention and care-as-usual) will be compared at each assessment time point. Furthermore, potential mechanisms of change and generalization of intervention effects on daily life are assessed using an ecological momentary assessment procedure that includes items on maintaining mechanisms of social anxiety, social context, and affect. Participants are prompted 3 times a day during the first 8 weeks of the study and again for 2 weeks following the follow-up assessment.

Results: Recruitment is ongoing; initial results are expected in 2024.

Conclusions: Results are discussed considering the potential of online interventions as a low-threshold prevention and treatment option for adolescents with social anxiety and in light of current advances in dynamic modeling of change processes and mechanisms in early intervention and psychotherapy in adolescents.

Trial Registration: ClinicalTrials.gov NCT04782102; https://clinicaltrials.gov/ct2/show/NCT04782102

International Registered Report Identifier (IRRID): DERR1-10.2196/44346

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KEYWORDS

prevention; treatment; social anxiety disorder; internet-based; adolescent; online intervention; anxiety; psychotherapy; youth; child; comorbid; mental health; social phobia; mobile phone

Introduction

Adolescence marks a crucial timespan for the development of social anxiety disorder (SAD) with the peak of onset between 13 and 15 years. Prevalence rates in adolescents meeting SAD criteria range from 12% to 36%. Additionally, 16% of adolescents report subclinical levels of social anxiety [1-5]. The burden of disease on adolescents with SAD or subclinical social anxiety is considerable, including poor quality of life, low psychosocial functioning [6-8], and high risk of persistence into adulthood and of developing comorbid mental disorders [9-12]. Promising strategies to prevent or diminish these detrimental effects of SAD include low-threshold early interventions that are delivered online.

Online interventions might be especially appealing to adolescents as [3,13-15] they experience higher stigma regarding seeking and accepting help than adults [16,17], particularly those with social anxiety [13]. Low help-seeking behavior results in few adolescents receiving adequate treatment. This is exacerbated by the lack of available psychotherapeutic services for adolescents worldwide [14,15]. Thereby, online interventions bear the promise to offer adolescents help at a low threshold and with high confidentiality [16].

Meta-analyses have generally supported the efficacy of online interventions in adolescents [17]. These online interventions primarily targeted anxiety and depressive symptoms based on cognitive behavioral therapy (CBT). They have been demonstrated to be superior to passive control conditions (eg, waitlist) and equally efficacious to active control conditions (eg, face-to-face CBT) [18]. Notably, face-to-face interventions targeting several anxiety disorders simultaneously are less efficacious in patients with SAD than other anxiety disorders [19-22]. This emphasizes the need for interventions specifically targeting symptoms of social anxiety such as those proposed in the Clark and Wells or Heimberg model [22,23]. Face-to-face trials imply that the Cognitive Model of social anxiety by Clark and Wells [24] also applies to adolescent samples [25-27]. Online interventions targeting social anxiety in adolescents showed large effects compared to passive (ie, waitlist [28,29]) and active control conditions (ie, online support [30]) but, unlike the face-to-face trials, was equally efficacious compared to a generic CBT program for anxiety [29]. These results are promising but need to be interpreted cautiously as some studies primarily focused on a small sample size with older adolescents with speech anxiety [28] or reported high dropout rates in the study and low adherence rates to the online intervention [29]. Poor engagement with online interventions is a known issue [17]. Human support in the form of guidance (eg, sending summaries and reminders and answering questions) can enhance adherence to and effects of online interventions in adult samples [31,32]. So far, there is no conclusive evidence about adolescents; nevertheless, initial studies suggest that guidance is generally accepted and beneficial for adherence and efficacy [33-36].

Since levels of social anxiety and the incidence of SAD increase during adolescence [37], it is important to detect and treat first signs of SAD as early as possible to prevent the development of a full-blown disorder and address associated high rates of psychosocial impairments early on [8]. Most prevention efforts for anxiety disorders have been delivered as universal programs [38]. Indicated prevention offered to individuals already experiencing elevated, subclinical levels of social anxiety below the diagnostic threshold is still relatively scarce, although may be experienced as more satisfying and less resource-intensive than universal programs [38]. Accordingly, studies suggest that indicated prevention carried out in schools [39] or online [40] can produce small but beneficial effects in adolescent samples. As for interventions addressing social anxiety specifically, an online game to improve social skills [41] and an online cognitive bias modification training [42] were shown to be efficacious in adolescents.

Based on these findings, online interventions may be helpful for adolescents with subclinical social anxiety and with SAD, but our understanding of the mechanisms of change underlying these interventions in adolescent samples is still limited [43].

One method of identifying mechanisms of change is to derive them theory-based and examine them as mediators [43]. Possible mechanisms of change for social anxiety may be the hypothesized maintaining factors of SAD derived from the Cognitive Model (eg, automatic thoughts, self-focused attention, safety behavior, pre-, and postevent processing [24]). In correlational and experimental studies, these factors were positively associated with a higher level of social anxiety [44-47]. However, mediation analysis inherently implies a temporal order of the relationship between the intervention, mediators, and the outcome. Therefore, these variables must be assessed longitudinally ideally at multiple times such as in ecological momentary assessment (EMA) [43,48-50]. Previous intervention studies in adolescents including EMA have mostly assessed global social anxiety, momentary social context, and affect but missed to assess individual maintaining factors [51,52]. As EMA captures events as they occur at the moment, this method thereby minimizes memory bias, incorporates contextual information from participants' natural environment, and accounts for variability in answering behavior [43,48]. This allows to assess mediators of change and the efficacy in participants' daily lives and extends the knowledge about intervention benefits to their natural and variable contexts [53]. Eventually, this information may add valuable input to improve interventions in the future.

Further efforts to optimize treatments and outcomes involve the modeling of mental disorders as a network of symptoms to identify central treatment targets [54]. According to the network

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perspective, a mental disorder is best understood as a complex system of dynamically interacting symptoms [55]. Central symptoms (eg, fear of humiliation) of such a network are supposed to spread quickly by activating other strongly interrelated symptoms, while bridging symptoms (eg, low self-esteem) may link clusters of symptoms. Both central and bridging symptoms may represent important intervention targets as they are supposed to be causally linked to other symptoms of an individual's network [55-57]. To this point, studies of cross-sectional networks have demonstrated that dysfunctional cognitions function as central symptoms and influence multiple other social anxiety symptoms, especially behavioral components such as avoidance and safety behavior in adolescents [58,59]. Examining social anxiety as networks at symptom level over the course of the intervention could add to this knowledge by exploring whether participants' network structures change from beginning to end of the intervention, in particular, by identifying relevant core and bridging symptoms as drivers of clinical change, by investigating differences in symptom networks between intervention and control group, and by studying the influence of possible moderators (eg, age, gender, and diagnostic status) on networks.

Overall, first studies suggest that online interventions have positive effects on adolescents with SAD; however, much uncertainty still exists about the efficacy of indicated prevention trials including adolescents with subclinical social anxiety. Moreover, previous research has focused mainly on the efficacy of interventions while neglecting both the mechanisms of change and the symptom-level network structure of SAD.

The primary objective of this study is to examine the efficacy of an online intervention called SOPHIE for adolescents with subclinical social anxiety or SAD compared to a care-as-usual (CAU) control group. Thereby, the name SOPHIE is derived from the German term "SOziale PHobIE" (social phobia). It is hypothesized that SOPHIE will be superior to CAU in reducing social anxiety symptoms post assessment and that the intervention effect will be maintained until follow-up assessment 3 months after intervention completion. Furthermore, it is hypothesized that SOPHIE will also have beneficial effects on secondary outcomes, such as depressive as well as general anxiety symptoms, level of functioning, self-esteem, and quality of life at post assessment and follow-up. It is further hypothesized that intervention effects will be moderated by therapeutic alliance, adherence, treatment motivation, and treatment expectation of the online intervention. Moreover, by measuring social anxiety symptoms in their natural context longitudinally, we will examine if intervention effects translate into everyday life and if the postulated maintaining factors of SAD function as mediators of change. Additionally, we intend to model the network structure of social anxiety symptoms at each time point and observe differences in networks of adolescents (eg, regarding age, gender, and severity of social anxiety).

Methods

Study Design

This randomized controlled trial (RCT) investigates the efficacy of the online intervention SOPHIE for adolescents with subclinical social anxiety or a diagnosis of SAD. SOPHIE is compared to a CAU control condition in a 2×2×4 design with a 2-level between-subjects factor (2 experimental conditions: SOPHIE vs CAU), a 2-level between-subjects factor (2 diagnostic conditions: SAD vs subclinical social anxiety), and a 4-level within-subjects factor (repeated measures: baseline, midintervention at week 4, post intervention at week 8, and follow-up 5 months after randomization, ie, 3-months follow-up). All participants are additionally assessed in EMA surveys during the first 8 weeks (from baseline to postassessment) and for 2 weeks after follow-up assessment. Participants in the intervention group have additional process assessments at weeks 2 and 6 during the intervention.

Ethical Considerations

The trial was registered in ClinicalTrials.gov (NCT04782102) and was approved by the Ethics Committee of the Canton Bern in Switzerland (CEC Bern, Project ID 2020-02501). Any changes to the protocol will be submitted to the Ethics Committee. Adolescents and, if younger than 14 years, their guardians must sign the informed consent form prior to the first assessment. Adolescents and their guardians can withdraw from the study at any time. Withdrawal from the study will not be associated with any disadvantages and is fully documented and explained in the informed consent form. Data collected up to withdrawal will still be used for the planned data analyses. All details about privacy and confidentiality protection are given in *Data Management and Monitoring* subsection. Participants were not compensated for their participation in the study. However, they have the opportunity to participate in a lottery and win Netflix, BookBeat, Spotify, or Apple Music vouchers worth CHF 30 (~US $33).

Procedures

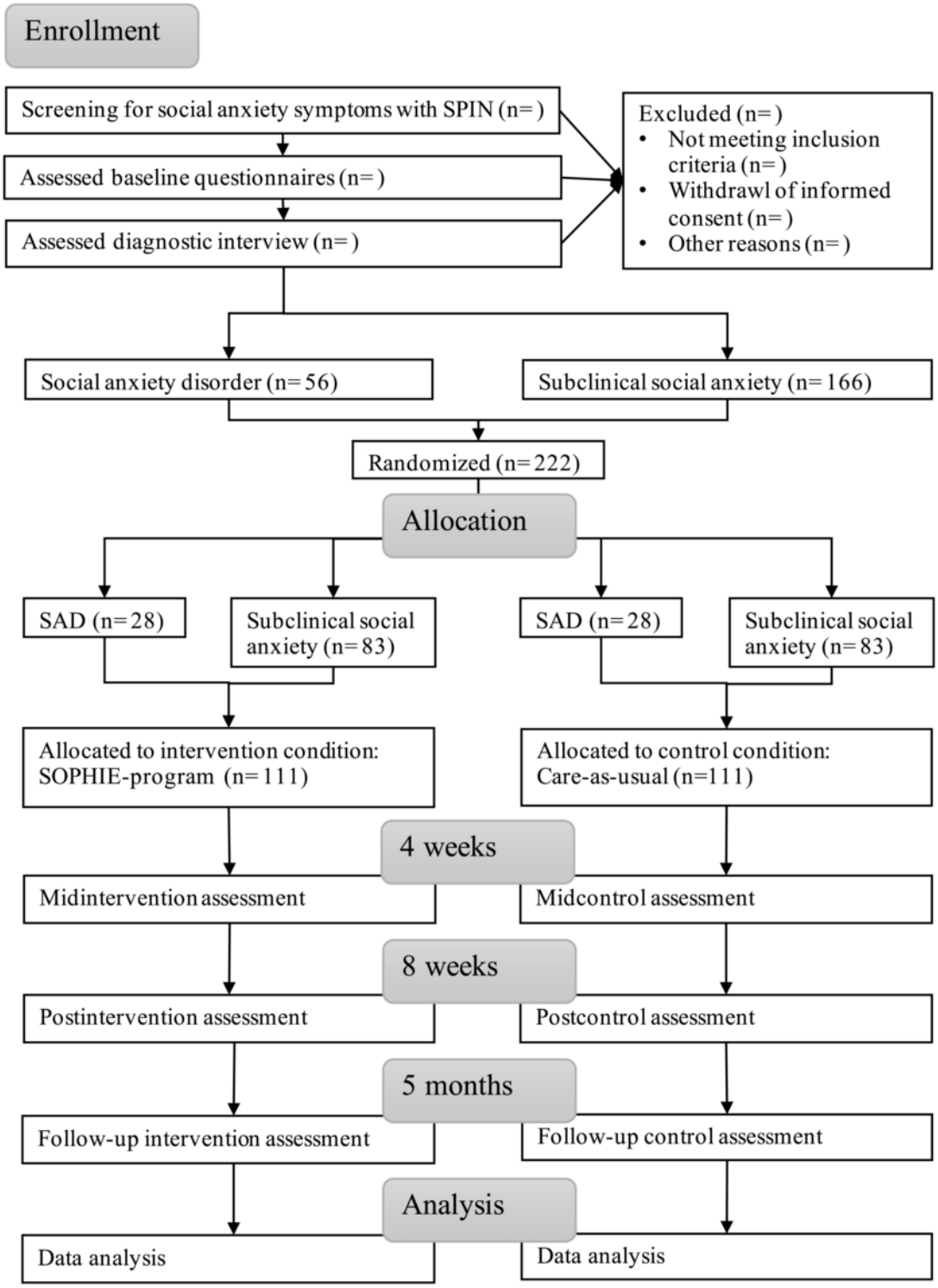
Adolescents interested to take part in the study leave their email addresses on the study website [60]. They receive the participant study information by email and are asked to provide informed consent or assent (see Figure 1 for study flow). Participants younger than 14 years provide written assent, and their parent or guardian provides written consent. Participants 14 years or older provide consent on their own. Informed consents are accepted both on paper by mail and electronically as scans via email. Once the consent forms have been received, they are printed out and stored in analog form. Afterward, potential participants are screened for eligibility. Those with a score lower than 16 on the Social Phobia Inventory (SPIN) [61,62] are not included in the study but receive immediate access to the online intervention. The cutoff of 16 was chosen in reference to a previous study that showed good discrimination between healthy and subclinical adolescents [63]. Adolescents with a SPIN score of 16 or higher receive the remaining baseline questionnaires. Subsequently, they are interviewed by trained psychology graduate students via phone to ascertain whether they fulfill the diagnostic criteria for SAD or not. Those with a current

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diagnosis of SAD are assigned to the SAD group, while those with no current and no past SAD diagnosis are assigned to the subclinical social anxiety group. Training and weekly supervision of the graduate students are carried out by the first and last authors.

Participants are assigned to the intervention group or the control group by stratified block randomization to ensure that both groups are balanced regarding the diagnostic status: SAD or subclinical social anxiety. The randomization is carried out after all data collected by the diagnostic interview including diagnoses are entered into the electronic protocol form hosted on Qualtrics (Qualtrics XM) [64]. Randomization was set up before the start of the study by the first author (ie, number of groups, allocation ratio [1:1], and size of blocks). During the study, the allocation list was produced using an automated computer-generated random numbers table and was concealed from the investigators and the participants. After randomization, the intervention group receives immediate access to the online intervention.

Figure 1. SOPHIE trial flowchart. SAD: social anxiety disorder; SPIN: Social Phobia Inventory.



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During study participation, all participants are reminded twice for each noncompleted questionnaire. For post- and follow-up assessments, an additional reminder is sent out. For EMA surveys, participants are prompted 3 times a day: in the morning before school or work, in the afternoon after school or work, and in the evening with the Smartphone Ecological Momentary Assessment application (SEMA^3 app) [65].

At post- and follow-up assessment, all participants are contacted again for a telephone interview. Assessors are blinded to the diagnostic status diagnosed at baseline and study condition of the participant, and participants are asked not to mention either of those. CAU group members receive access to the online intervention after they completed all follow-up assessments and the interview.

Participants, Recruitment, and Eligibility

Participants are recruited in German-speaking countries using advertisements on social media platforms (ie, TikTok and Instagram), self-help forums, and websites (eg, Google ads). Additionally, we share information through partner organizations (eg, school social work, open youth work, and parent counseling), and during school visits. To be included in the study, participants must be between 11 and 17 years of age, understand German, and have access to both a device connected to the internet and a smartphone. In Switzerland, more than 99% of adolescents have their own smartphone and access to the internet [66]. Exclusion criteria are a known diagnosis of autism spectrum disorder, acute suicidality at baseline, and a past diagnosis of SAD for the subclinical group. In case of acute suicidality, we follow a predefined suicidality protocol described in the section “Project and Risk Management.”

Outcome Measures

Primary and Secondary Outcomes

The primary outcome is the severity of social anxiety assessed by the SPIN [67]. The National Institute of Health and Care Excellence guidelines recommend the SPIN as a screening and assessment instrument suited for adolescents [23]. Please see Table 1 for a detailed description and assessment points of the primary and secondary outcomes: social anxiety, social and role functioning, utilization of help, anxiety, depression, quality of life, self-esteem, therapy expectation, therapy motivation, negative effects of the intervention, satisfaction with the intervention, therapeutic alliance, and adherence to the intervention.

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Table 1. Overview of assessments and assessment points during the SOPHIE study.

Construct	Description of assessment	Timeline of assessment					
		Baseline	Week 2	Midintervention or control at week 4	Week 6	Postintervention or control at week 8	Follow-up at week 20
Sociodemographic variables							
Demographic information	During the first telephone interview, participants are asked about their gender, age, nationality, native language, and living as well as family situation.	✓					
Socioeconomic status	During the first telephone interview, the *Family Affluence Scale* with 6 items is assessed as an indicator for socioeconomic status and demonstrates good psychometric properties to detect socioeconomic differences in Western European countries [68,69].	✓					
Primary outcome							
Social anxiety	The *Social Phobia Inventory* (SPIN) is a self-report questionnaire assessing 3 dimensions of social anxiety: fear, avoidance, and physiological symptoms. In 17 items, adolescents rate the frequency of each symptom on a 5-point Likert scale from *not at all* (0) to *extremely* (4) ([61], German version by [62]). The SPIN is a reliable self-report measure with good psychometric properties in adolescents [70,71]. Cut-off for subclinical social anxiety symptoms is set at 16 [63].	✓		✓		✓	✓
Secondary outcomes							
Mental disorders	The *structured clinical interview for mental disorders across the life span* is a structured clinical interview to assess the presence of SAD[a] and comorbid past and present mental disorders according to the Diagnostic and Statistical Manual of Mental Disorders-5 ([72], German Version of Kinder-DIPS; [73]). In this study, the full interview is conducted by phone at baseline. At post- and follow-up assessment, only the section for SAD and sections of previously met diagnoses are assessed.	✓				✓	✓
Global functioning	The *Global Functioning Social and Role Scale* is a structured interview that is also carried out via phone in this study [74]. Two subscales (social and role) allow for an assessment of the level of functioning (concurrently and in the past year) on a scale ranging from 1 to 10 with 10 representing the highest level.	✓				✓	✓

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Construct	Description of assessment	Timeline of assessment					
		Baseline	Week 2	Midintervention or control at week 4	Week 6	Postintervention or control at week 8	Follow-up at week 20
Utilization of help	The *Client Socio-Demographic and Service Receipt Inventory* [75,76] is a standardized interview to assess the utilization of help and help seeking behavior. The applied version has already been tested in adolescents [76] and is administered during the postintervention and follow-up telephone interview.					✓	✓
Fear and avoidance	The *Social Anxiety Scale for Adolescents* measures fear of negative evaluation and social avoidance in adolescents with 18 items answered on a 5-point Likert scale from *not at all* (1) to *all the time* (5) [77]. Validity and reliability were tested in both clinical and nonclinical samples [77,78].	✓		✓		✓	✓
Anxiety	The *Generalized Anxiety Disorder 7* [79] questionnaire measures self-reported frequency of anxiety symptoms with 7 items answered on a 4-point Likert scale from *not at all* (0) to *nearly every day* (3). The German questionnaire produced good psychometric properties in adolescents [79,80].	✓		✓		✓	✓
Depression	The *Patient Health Questionnaire-9 for Adolescents* [81] assesses depressive symptomatology with 9 items asking about the frequency of symptoms over the last 2 weeks on a 4-point Likert scale from *not at all* (0) to *nearly every day* (3). The self-report questionnaire has good psychometric properties for depression detection in adolescents [82].	✓		✓		✓	✓
Quality of life	The KIDSCREEN-10 is used to measure health-related quality of life with 10 items answered on a 5-point Likert scale and has good psychometric properties [83].	✓		✓		✓	✓
Self-esteem	The *Rosenberg Self-Esteem Scale* [84] assesses self-esteem in 10 items on a Guttman scale. This questionnaire is applicable to different age groups; in this study, the adolescent version is applied.	✓		✓		✓	✓
Therapy expectancy	The *Credibility or Expectancy Questionnaire* [85] assesses treatment expectancy and credibility with 6 items. There are 2 rating scales, 1 from *not at all* (1) to *very* (9) and another from 0 to 100%. For this study, the wording of the items was adapted to the target group of adolescents.	✓					

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Construct	Description of assessment	Timeline of assessment					
		Baseline	Week 2	Midintervention or control at week 4	Week 6	Postintervention or control at week 8	Follow-up at week 20
Therapy motivation	The *Motivation for Youth's Treatment Scale* (MYTS) [86] measures adolescent's motivation for therapy through a self-report questionnaire. Eight items are rated on a 5-point Likert scale from strongly disagree (1) to strongly agree (5). All adolescents complete this assessment at baseline, only adolescents randomized to the intervention group complete the MYTS at week 2, 4, 6, and 8.	✓	(✓)[b]	(✓)	(✓)	(✓)	
Negative effects of intervention	The *Inventory for assessment of negative effects in psychotherapy* (German: Inventar zur Erfassung Negativer Effekte in der Psychotherapy, Kinder-INEP; [87,88]) has been adjusted to the online format of the intervention, reducing the questionnaire by 6 items to 15 items. This questionnaire is only answered by adolescents in the intervention group.					(✓)	
Satisfaction with the intervention	The *ZUF-8* is an 8-item questionnaire for global, unidimensional assessment of patient satisfaction [89]. The questionnaire was adapted accordingly to measure satisfaction with the online intervention. Adolescents randomized to the intervention answer questions on a 4-point Likert scale from 1 to 4.					(✓)	
Therapeutic alliance	The *Working Alliance Inventory for guided Internet Interventions* (WAI-I; [90]) is a self-report questionnaire that measures therapeutic alliance in online interventions with therapeutic support. The 12 items rated on a 5-point Likert scale from *rarely* (1) to *always* (5) were adapted to adolescents. Only adolescents in the intervention group are assessed with the WAI-I.		✓	✓	✓	✓	
Adherence to the online intervention	Adherence is operationalized through the extent to which the online intervention is used. The number of finished modules, the number of completed exercises, and the time spent in the online intervention are recorded automatically. As in other studies of online interventions, adherence is calculated with respect to each of these variables and with respect to a composite measure [91].					(✓)	

[a]SAD: social anxiety disorder.

[b]Indicated time points in parentheses reflect assessments only administered in the intervention group.

Ecological Momentary Assessment

The same set of EMA questions is provided at all prompts: (1) 10 questions of the *Positive and Negative Affect Schedule for Children* [92] measure positive affect (happy, cheerful, proud, joyful, and lively) and negative affect (sad, scared, miserable, afraid, and mad). The Positive and Negative Affect Schedule for Children has been used in a diary study and showed good psychometric properties in intensive longitudinal designs [93]. (2) The *Social Phobia Weekly Summary Scale* [94] assesses maintaining factors of social anxiety. Six items rated on a 9-point Likert scale from 0 to 8 evaluate the extent of social anxiety, social avoidance, self-focused versus external attention, pre-event, and postevent processing. All items were adapted to

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reflect the time frame of the EMA measurement (ie, "Since the last prompt") and the language of the target group. To assess all maintaining mechanisms of social anxiety suggested in the Cognitive Model by Clark and Wells [24] and based on similar existing items [95], we formulated 2 additional items to evaluate automatic thought processing and level of self-confidence in social situations: "In social situations, I have had many negative automatic thoughts running through my head" and "Since the last prompt, I have had little confidence in myself." Both items are rated on a 9-point Likert scale accordingly. (3) *Momentary social context* is assessed by 4 questions based on similar EMA items from a repository [95]; initially, participants indicate in which social situation they currently are: alone, family, close friends, boyfriend or girlfriend, colleagues, known persons, or strangers. Depending on their answer, they are asked if they would prefer to be alone or with someone (yes or no). Additionally, they indicate if they are currently in contact with others online (yes or no). Finally, they rate their experienced pleasantness in the current situation on a visual analog scale from not at all (0) to extremely (100).

Guardian Assessment

Guardians who provide their email addresses on the consent form voluntarily are assessed at baseline, midintervention, postintervention, and follow-up. In all assessments, they rate their child's social anxiety using the *Parents' Questionnaire on Social Anxieties in Childhood and Adolescence* (German: Elternfragebogen zu sozialen Ängsten im Kindes und Jugendalter) [96]. In 18 items, statements about the adolescent's behaviors and fears are rated on a 4-point Likert scale from not at all (0) to very much (3). Furthermore, guardians provide demographic data and answer questions about their child's treatment motivation and expectations during the baseline assessment. The *Motivation for Youth's Treatment Scale* [86] assesses guardians' motivation for treatment with 8 items rated on a 5-point Likert scale from do not agree at all (–2) to agree completely (2). The *Credibility or Expectancy Questionnaire—Parent Version* [97] measures guardians' expectations of the online intervention using 6 items. In total, 4 items are rated on a scale from not at all (1) to very (9), and 2 items on a scale from 0 to 100%.

Study Group Condition

SOPHIE Intervention

The internet-delivered self-help intervention SOPHIE (see Table 2) has a duration of 8 weeks and is based on the Cognitive Model by Clark and Wells [24] adapted to specific needs of adolescents [47] and existing evidence-based online interventions for adults with SAD [98-104]. The first version of the SOPHIE intervention was tested on 46 healthy adolescents. Based on their feedback, we improved the usability and understandability. An introductory module familiarizes adolescents with the intervention. Successively, 6 modules cover the maintaining mechanisms of the Cognitive Model and instruct adolescents to apply the learned strategies in exposure exercises in everyday life. The last module contains a short repetition and summary. The structure of each module includes a review of the previous module, an introduction to the current module's content, a summary at the end, and a quiz. Content is provided by animated video inputs, short text explanations, and exercises.

To enhance adherence and motivation throughout the intervention, adolescents receive guidance from e-coaches who provide weekly personalized support via a secured text-based messaging system. They summarize completed exercises, provide a preview of upcoming modules, send reminders to use the intervention, answer questions, and motivate participants by relating exercises to their personal goals. e-Coaches are psychology graduate students who were trained by the first or last author in offering guidance. Before sending, each guidance message is additionally peer-reviewed by another e-coach.

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Table 2. Description of all modules of the SOPHIE program[a].

Module	Image	Content
(1) Introduction		A user guide explains the structure and different elements of the online intervention. Participants are introduced to the 2 protagonists, Sophie and Leon, and can choose their avatar. They learn what social anxiety is, in which situations they may arise, and *set their personal goals* for the online intervention. Additionally, they are introduced to a progressive muscle relaxation exercise and are instructed to do this exercise daily.
(2) Emergence and maintenance of social anxiety		Participants learn about *etiological and maintaining factors of social anxiety*. In an exercise, they write down their personal anxiety cycle. For the following week, they are instructed to observe their social anxiety symptoms and enter their observations in their logbook.
(3) Automatic thoughts		Participants are introduced to *automatic thoughts* and their importance in maintaining social anxiety. In 2 exercises, they are instructed on how to recognize and modify their negative automatic thoughts. An additional relaxation exercise “safe place” is introduced to support their daily relaxation practice.
(4) Self-image		Participants learn about *self and other perspective* of a person, reasons for a positive self-image as well as possible consequences of a negative self-image. During an exercise, they are instructed to reflect on their assumptions of themselves, to recognize both negative and positive sides thereof, and to find a good balance. Participants learn 3 strategies to positively improve their self-image.
(5) Self-focused attention		Participants discover *self-focused attention* and the reinforcing impact it has on social anxiety. In an exercise, they train to shift their attention. In front of a virtual audience, they must tell a story and are instructed to focus their attention on the situation instead of themselves. They are introduced to a new relaxation exercise “relaxing world” to complement their relaxation practice.
(6) Reality tests I		Participants are introduced to reality tests (*exposure exercises*). To prepare for their own reality tests, participants establish their fear hierarchy. In the upcoming week, they conduct their reality tests and record the level of anxiety before and after.
(7) Reality tests II		Participants learn about strategies to deal with possible difficulties in reality tasks. Further, they are introduced to *socially competent behavior*. Thereby, examples of competent behavior are contrasted with examples of insecure behavior in social situations. Participants are instructed to continue with their reality tests.
(8) Repetition		The last module summarizes the content of the online intervention and participants reflect on their personal goals. They record a video of themselves in which they explain what social anxiety is, how they experience it, and how they learnt to cope with it. Later, they can replay this video to remind themselves of their progress.

[a]Displayed pictures were generated with the video program Vyond [105].

Care-as-Usual Group

Participants randomized to the CAU group are only contacted for assessments and receive access to the online intervention after follow-up. They are free to take advantage of any other health service. To account for additional help, the use of assistance is assessed post intervention and follow-up (details in Table 1).

Project and Risk Management

In weekly monitoring procedures, project implementation, clinical (eg, study withdrawals and adverse events), and research integrity (eg, blindness, data safety, important harms, or unintended effects) are ensured. Potential risks to participants are minimal. However, there is a potential inconvenience as filling out the questionnaires and the online intervention requires time.

In the case of suicidality (assessed at every assessment point by item 9 of the Patient Health Questionnaire [81]), a predefined suicidality protocol is applied; participants immediately receive an email with numbers for psychiatric services. Additionally, a member of the study team contacts the participant on the following working day to clarify acute suicidality. If acute suicidality is present, we offer additional help for instance by providing contact details on mental health services near to the adolescent’s home, if necessary, we support the referral to an appropriate service and decide on the continuation in the study. All participants must provide a safety contact in case that we cannot reach the adolescent who triggered the suicidality protocol.

Adverse events, all untoward events in a participant, including events not necessarily caused by or related to the online intervention, are monitored from randomization to follow-up 5 months after randomization. All adverse events are reported to the principal investigator, the ethics committee, and are documented in the participant’s case report form.

Data Management and Monitoring

All data are collected electronically except for informed consent and case report forms. Electronic data from all servers are extracted monthly and saved on a secure server of the University of Bern. All data are deidentified by removing names, email addresses, and location information, and are only accessible to the core study team as well as the head of research management for auditing purposes. Personal information is password-protected and stored in a secure electronic vault,

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separately from outcome data. All data will be stored for 15 years after the termination of the study. The research management of the Faculty of Human Sciences of the University of Bern supervises data collection and storage in quarterly meetings.

All participants create password-protected accounts for the online intervention and are allocated a unique identification number. The online intervention is hosted on a secure platform of the University of Bern. All questionnaire and interview data are recorded via Qualtrics [64]. Qualtrics uses the same unique identification number. Thus, no personal data are entered in Qualtrics. EMA data are assessed with the SEMA^3 app and saved on a server of the University of Melbourne [65]. SEMA^3 requires personal data only to send out invitations and deletes them immediately afterward. For identification, participants are allocated a SEMA^3 numeric identification code.

Plan of Analysis

All analyses will follow the intention-to-treat approach. Patterns of missing data in the Growth Mixture Models will be analyzed, and in case of "missing at random" or "missing completely at random," multiple imputation will be applied.

Main Analyses

The primary outcome, that is, change in social anxiety, will be tested using Linear Mixed Effects Models. Time (baseline, midintervention, post intervention, and follow-up), intervention condition (SOPHIE and CAU), diagnostic status (SAD and subclinical social anxiety), and interactions (time*intervention condition; time*diagnostic status; intervention condition*diagnostic status; time*intervention condition*diagnostic status) will be specified as fixed effects, baseline SPIN value will be added as a fixed covariate and participant as a random effect to allow for between-person variation.

Further Analyses

Secondary outcomes (ie, global functioning, general anxiety symptoms, depressive symptoms, quality of life, self-esteem, and guardians' rating of their child's social anxiety) will be analyzed using Linear Mixed Effects Model as described earlier. In further analyses, therapy expectancy, therapy motivation (both adolescents' and guardians'), and satisfaction with the intervention will be added as moderators. Categorical outcomes (eg, diagnostic status) will be analyzed using General Linear Mixed Effect Models with intervention condition, diagnostic status, and time course as fixed effects and participants as random effect. Additionally, Growth Mixture Modeling will be used to identify subpopulations with comparable growth trajectories of social anxiety and secondary outcomes over time (latent classes) and to identify predictors of these classes.

Mediation Analyses

Mediation effects of therapeutic alliance and adherence to the intervention will be analyzed in a 1-1-1 multilevel mediation model with all variables measured at assessment time points (ie, baseline, midintervention, and post intervention), and all causal paths allowed to vary between participants.

Mediation effects of mechanisms of change in social anxiety will be explored in 2 different lower-level mediation analyses using multilevel modeling. In a 2-1-1 mediation analysis, time will be included as a fixed effect, baseline social anxiety as a level-2 fixed effect predictor, mechanisms of change (ie, automatic thoughts, avoidance, self-focused attention, pre-event, and postevent processing) as a level-1 random effect mediator, and momentary social anxiety as a level-1 random effect outcome. In a 1-1-1 mediation analysis, all constructs will be assessed at level-1. Thereby, social anxiety as a random effect predictor will be assessed concurrent with the random effect mediator, mechanisms of change in social anxiety, and the random effect outcome social anxiety will be assessed 1 prompt later (lead analysis).

Network Analyses

Baseline, mid-, post-, and follow-up data of current levels of symptoms and functioning will be modeled by network analysis to explore how networks differ by age, gender, diagnostic status, intervention condition, and assessment point in terms of centrality, closeness, betweenness, and clustering.

Sample Size

The sample size of 222 was determined in 2 a priori power analyses for the primary research question using G*Power [106] based on an intention-to-treat approach to account for possible dropouts and repeated measures ANOVA. In the SAD group, we expected a small to moderate effect size (Cohen d=0.35) [18,107], and for the group with subclinical anxiety, a small effect size (Cohen d=0.20) [38,108-110]. For both groups, we assumed an α level of 5%, power of 80%, and a correlation between measurements of r=0.4. Consequently, the SAD group should consist of 56 participants, and the subclinical social anxiety group of 166 participants.

Results

Data collection started in August 2021, and as of April 2023, a total of 106 participants are enrolled in the study. First results are expected in 2024.

Discussion

Due to the limited availability of mental health services for adolescents, online interventions offer the opportunity to provide early, low-threshold, and low-cost help. In this protocol, we describe an RCT that aims to test the efficacy of an online intervention for adolescents with subclinical social anxiety or a diagnosis of SAD compared to a CAU control group. A positive evaluation of this intervention holds several implications for the future: first, it may offer an efficacious intervention for both clinical as well as subclinical levels of social anxiety; second, the delivery format provides a high level of confidentiality as well as autonomy and may reach more adolescents in need than face-to-face psychotherapy interventions, in particular, those who need care but have not sought help yet; and third, it could also precede or complement more resource-intensive face-to-face interventions in terms of a stepped care approach [111-113].

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Previous studies have provided initial evidence for the efficacy of online interventions for adolescents with social anxiety [28-30]. The study described in this protocol may extend them in several ways. So far, a comprehensive understanding on empirical evidence of age-adapted treatments to meet the needs of developing adolescents has yet to be fully established [47]. In this regard, findings based on moderator analyses of intervention effects and network analysis may provide more profound insights into which subgroups of adolescents an online intervention are especially beneficial and for which a different delivery format might be indicated [16]. Next, the empirical investigation of conceptually derived mechanisms of change may complement the efficacy and moderator analyses by highlighting which factors are particularly important for clinical change [114,115]. Lastly, to the best of our knowledge, this would be the first study to provide information on whether the same online intervention can be used as both indicated prevention and therapy for adolescents with social anxiety.

Despite these promises, this study will have some limitations. The self-selected sample will limit the generalizability of the study. Although the first version of the SOPHIE program was well accepted by adolescents, it is unlikely that 1 intervention is suitable for all participants spanning a large age range associated with heterogeneous needs and capacities. In this aspect, results on efficacy among subgroups that benefit most from the intervention, for example, based on their age, gender, or symptom severity, or based on idiographic analyses of the data, will be beneficial to better personalize interventions in the future [116]. Finally, there is some evidence that even answering EMA questions may lead to a change in behavior [117]. Since both the intervention and control group receive EMA prompts, this may have an impact on between-group comparisons.

Notwithstanding these limitations, the findings of this RCT may lead to a better understanding of SAD in adolescents, may provide important insights into the subgroups of adolescents for whom an online intervention may be an important complementary mental health service, and may help to optimize the effects of current interventions for SAD and subclinical social anxiety in adolescents by targeting the identified mechanism of change more directly. Overall, this online intervention may thereby offer a low-threshold prevention and treatment option to reduce the treatment gap and improve mental health care in adolescents.

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Data Availability

Data sharing is not applicable to this paper as no data sets were generated or analyzed for this protocol.

Authors' Contributions

NW wrote the initial version of the manuscript. All authors contributed to further drafts and approved the final manuscript. SJS is the principal investigator of the study.

Conflicts of Interest

None declared.

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Abbreviations

CAU: care-as-usual
CBT: cognitive behavioral therapy
EMA: ecological momentary assessments
RCT: randomized controlled trial
SAD: social anxiety disorder
SEMA3: Smartphone Ecological Momentary Assessment
SPIN: Social Phobia Inventory

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Protocol

Evaluating the Feasibility of a Multiplayer Role-Playing Game as a Behavioral Health Intervention in Adolescent Patients With Chronic Physical or Mental Conditions: Protocol for a Cohort Study

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Abstract

Background: Numerous studies have revealed that adolescents with chronic physical or mental conditions (CPMCs) are at an increased risk for depression and anxiety, with serious direct and indirect negative effects on treatment adherence, family functioning, and health-related quality of life. As game-based approaches are effective interventions in treating anxiety and depression, we propose to explore the use of a multiplayer role-playing game (RPG) as a potential intervention for social isolation, anxiety, and depression.

Objective: The objectives of this study were to (1) determine the feasibility of using Masks, a multiplayer RPG, as an intervention for social isolation, anxiety, and depression in adolescents with CPMCs; (2) evaluate the viability of the research process; and (3) gauge participation in and engagement with RPG-based interventions.

Methods: This study is a remote synchronous game-based intervention for adolescents with CPMCs aged 14-19 years. Eligible participants completed a web-based baseline survey to assess anxiety, depression, and social isolation and to identify their gaming habits. After completing the baseline survey, they participated in 5 moderated Masks game sessions. In Masks, players assume the roles of young superheroes; select their character types, superpowers; and perform actions determined by the game's rule system and dice rolls. All game sessions were played using Discord, a communication platform commonly used by gaming communities. Games were led and moderated by game masters (GMs). After each game session, participants completed surveys to assess changes in anxiety, depression, and social isolation, and their attitude toward the game and the user experience. The participants also completed an exit survey after all 5 game sessions (modified version of the Patient Health Questionnaire and the Generalized Anxiety Disorder Questionnaire, and 17 open-ended questions). The GMs rated each game session and reported on gameplay, player behavior, comfort, and engagement levels of the players.

Results: As of March 2020, six participants were recruited for the pilot study to participate in moderated web-based game sessions of Masks; 3 completed all game sessions and all required assessments. Although the number of participants was too low to draw generalizable conclusions, self-reported clinical outcomes did seem to indicate a positive change in depression, anxiety, and social isolation symptoms. Qualitative analysis of postgame survey data from participants and GMs indicated high levels of engagement and enjoyment. Furthermore, the participants provided feedback about improved mood and engagement related to weekly participation in Masks. Lastly, responses to the exit survey showed interest in future RPG-related studies.

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Conclusions: We established a workflow for gameplay and evaluated a research protocol for evaluating the impact of RPG participation on isolation, anxiety, and depression symptoms in adolescents with CPMCs. Preliminary data collected from the pilot study support the validity of the research protocol and the use of RPG-based interventions in larger clinical studies.

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KEYWORDS

role-playing games; social isolation; depression; game-based interventions; development; intervention; game; teen; patient; chronic; mental condition; quality of life; engagement; symptoms; data; clinical

Introduction

Numerous studies have revealed that adolescents with chronic physical or mental conditions (CPMCs) are at an increased risk for depression and anxiety, with serious direct and indirect negative effects on treatment adherence, family functioning, and health-related quality of life [1-3]. Regular participation in social activities with peers is particularly crucial in adolescence where it can provide a critical key component for developing healthy psychological development and identity formation [4,5]. Moreover, support from peers can also play a significant role in helping young people with CPMCs cope with illness and with its "inherent psychosocial and lifestyle changes" [6].

A number of studies have shown advantages of web-based socialization and web-based peer support for patients with disorders such as autism [7,8], social anxiety disorder [9], and chronic conditions such as cystic fibrosis (CF), where the danger of cross-infection of respiratory tract bacteria [10-12] prevents patients with CF from socializing in person.

With the outbreak of the COVID-19 pandemic, social isolation has become an even more critical problem, preventing adolescents with CPMCs from socializing not only with their peers but also with family members and other members of their support networks [13-15]. A number of mobile apps and web-based interventions have emerged to help patients with CPMCs to deal with stress [16], social isolation [17,18], anxiety [19], depression [19,20], symptom burden [16], and disease management [21,22]. Although numerous studies have shown a positive impact of these apps [16-18,20-22], none of the app-based interventions that we reviewed had social elements that would allow patients to interact with their peers or members of their support networks. Moreover, we were unable to find the majority of the apps described in the reviewed studies on publicly available app stores such as Apple App Store, Google Play Store, or Steam, suggesting that the apps used as part of research studies either were not available to the general public or did not have long-term support from the developers. Another shortcoming of many app-based interventions is that they target a specific mental or physical health condition (eg, autism [23] and diabetes [21,22]) but do not generalize to broader populations of adolescents with CPMCs.

Several attempts have been made to develop or study game-based interventions for social isolation. The use of video games as mental health interventions has been well explored in recent years [24-26], but, surprisingly, little work has been done to research the use and impact of video games on social isolation. Pearce et al [27], Zhu [28], and Martinez et al [29] explored how individual players as well as entire families leveraged the *Animal Crossing: New Horizons* game to battle pandemic-related social isolation. Udapola [30,31] proposes the use of social virtual reality (VR) platforms as an intervention for socially isolated adolescents with significant illness. Although many studies have found VR interventions to be effective tools for cognitive behavioral therapy [32-34], the availability and cost of VR devices may prove to be a significant barrier to scaling VR-based interventions to large populations of socially isolated adolescents.

However, to the best of our knowledge, there are no studies that explore the use of role-playing games (RPGs) in facilitating adolescents with CPMCs to escape their real world by creating an in-game character that may allow for identity exploration without the limitations of their CPMCs. Furthermore, as of the time of this writing, we were unable to find studies that evaluate the impact of RPG participation on self-reported isolation, anxiety, and depression symptoms in adolescents with CPMCs.

According to the Adventure Game Industry Market Research Summary [35], an estimated 5.5 million people in the United States regularly play RPGs. There is more to RPGs than the sheer number of players—there is strong evidence to suggest that RPGs facilitate the creation and sustainability of game enthusiasts' communities [36,37].

We hypothesize that participation in RPG communities of their peers (other adolescents with CPMCs) may decrease social isolation, increase feelings of acceptance, and enhance peer support for adolescents with CPMCs. The gameplay itself and the community around the game may provide peer support around some of the struggles and difficulties that adolescents with CPMCs have, including physical and mental health maintenance, adherence to complex medication regimens, self-advocacy, reduction in depression and anxiety symptoms, and transition from pediatric to adult health care.

Before studying whether participation in RPG communities provides this benefit in adolescents with CPMCs, it is important to understand whether it is feasible to engage adolescents with CPMCs through RPG communities.

The goals of this pilot work are to (1) understand the feasibility of recruiting adolescents with CPMCs to participate in an RPG game; (2) assess the feasibility of using Masks, a multiplayer tabletop RPG game, to engage adolescents with CPMCs; and (3) develop a research protocol for using and evaluating RPG

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games as potential clinical interventions for anxiety and depression associated with social isolation.

Methods

Initial Recruitment Challenges

We conducted a series of semistructured interviews with 12 patients with pediatric CF (aged 13-18 years) to understand their gaming habits and preferences and gauge their interest in a research study involving RPGs. For this first iteration, we considered setting up a private World of Warcraft (WoW) [38,39] server to allow us to create custom in-game quests for the participating patients with CF. However, 7 of the interviewed patients reported that they did not like WoW or did not want to spend multihour sessions going on quests with strangers. Three of the patients stated that they already spend between 1 and 3 hours per day playing video games and that their parents would object to their participation in a study that requires hours of computer-based gameplay. Lastly, 3 patients indicated that their parents perceived WoW as a violent RPG and would not allow them to participate in such a study.

In a second iteration, we conducted a round of semistructured interviews with a different group of 5 patients with pediatric CF (aged 14-17 years, no overlap with the first group). We asked the participants to describe elements of an RPG that they would be interested in playing. A word frequency analysis of the collected data showed the following words being present in every response: adventure, action, puzzle, superhero. After discussing interview results with several University of Pittsburgh game design instructors, a lead game designer from a Pittsburgh-based game design studio, and with members of 2 student-based RPG clubs, we selected the Masks RPG as a potential intervention for this study.

Our original Masks RPG-based study design called for weekly 3-hour game sessions. Once we began the recruitment phase, we focused on the population with pediatric CF. A total of 11 patients with CF expressed interest in participating in the study. However, during the informed consent process, once they understood the required time investment, 7 participants withdrew before being consented. Either the participants or their parents expressed concerns over the required time commitment. The remaining 4 participants were not able to find a common weekly 3-hour slot that would work for the entire group.

In our next recruitment iteration, we expanded the participant inclusion criteria to any pediatric onset chronic disease that requires rigid medication or treatment adherence, including CF, type 1 diabetes, sickle cell anemia, and pediatric cancers that require maintenance chemotherapy. From this population, we recruited and consented 8 participants and scheduled weekly Masks game sessions. A total of 6 of the 8 participants left the study after the first 2 game sessions, stating scheduling difficulties and interference with school activities as primary reasons for leaving the study.

On the basis of the recruitment and retention difficulties described above and the feedback received from participants who left the study, we redesigned the study workflow, shortened gameplay to approximately 1.5 hours per game session, and expanded participant inclusion criteria to all adolescents with CPMCs aged 14-19 years. It is important to note that shortening the gameplay sessions did not alter the game scenarios—we split scenarios between multiple game sessions, with each subsequent session's scenario, activities, and storylines picking up where the previous session left off.

Study Design

After the initial screening, participants completed an onboarding questionnaire to collect basic demographic information, as well as baseline data related to depression, social isolation, social support, and symptom burden. Questions included a modified version of the Patient Health Questionnaire omitting the last suicidality question due to anonymity and difficulty reaching participants who express risk (PHQ-8) [40], the Generalized Anxiety Disorder Questionnaire (GAD-7) [41], Social/Informational Support section of the RAND Social Support Survey Instrument (SSSI) [42], and the modified 4-question version of the revised UCLA Loneliness Scale (LS) [43-45]. PHQ-8, GAD-7, SSSI, and LS are extensively validated instruments that have shown good reliability, validity, and adaptability for patients across multiple research studies (Figure 1).

After completing the onboarding questionnaires, participants played a series of 5 weekly games, with the average game session duration of 1.5 to 2 hours.

Each game session was guided by 2 game masters (GMs). The role of a GM is to guide the narrative, environments, and the non-player aspects of the game, as well as provide guidance to players and address any player disputes. In the context of this study, the GMs also played an additional role of field researchers, recording their perceptions of how the players interacted with each other and with the game, whether players were engaged, and whether players discussed their CPMC symptoms or their personal lives with each other.

All GMs who helped facilitate this study were University of Pittsburgh students. At the time of the study, 2 of the GMs were second-year students at the School of Medicine, one was a second-year student at the School of Pharmacy and one a third-year student at the School of Engineering. All 4 GMs were selected based on 2 criteria: prior GM experience with tabletop RPGs such as Dungeons & Dragons (D&D) and prior academic research experience in a university setting. As part of the screening, all GMs had to learn how to plan and execute a Masks game session with this project's investigators as players. Once the GMs demonstrated their ability to plan, organize, and run game sessions, they were required to complete the Responsible Conduct of Research, Conflict of Interest, and Human Subjects Research (both biomedical and social/behavioral/educational) web-based training modules required by the University of Pittsburgh Human Research Protection Office.

Throughout the study, the GMs were responsible for planning, scheduling, and running game sessions, as well as for ensuring that participants complete postgame surveys.

The GMs rated each game session on the scale of 1 to 10 (1=worst and 10=best), provided their opinion on what could have made the session better, described any issues with

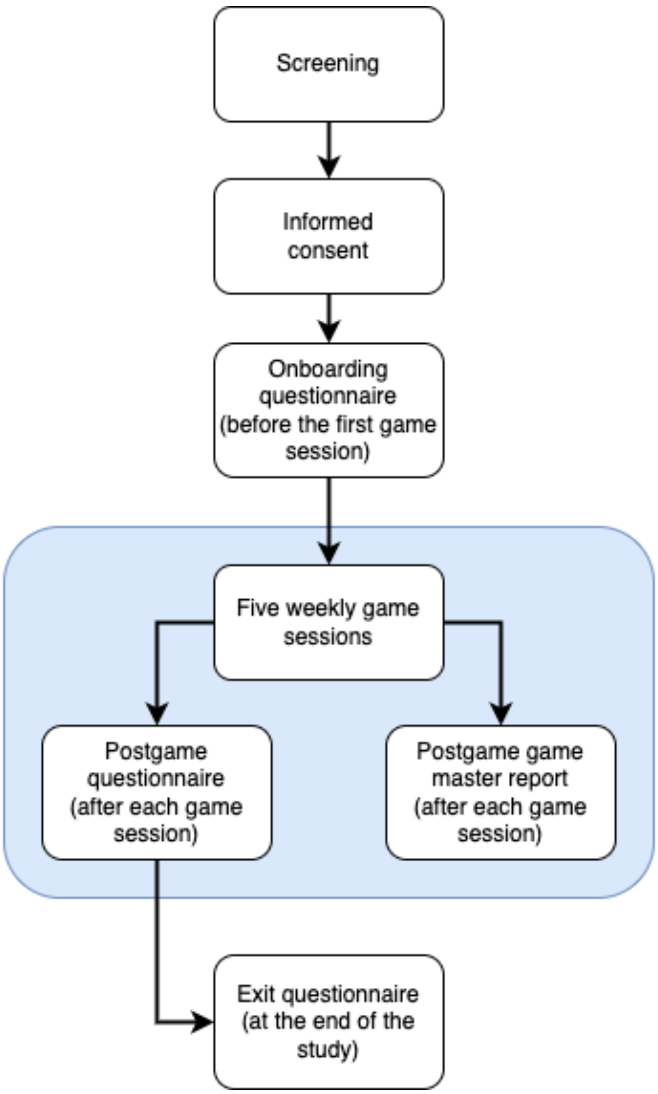
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gameplay or with player behavior, and provided comments on comfort and engagement levels of the players.

At the end of each game, participants completed a 27-question Likert questionnaire (Textbox 1) to collect feedback on the game session. Questions focused on participants' interactions with other players and with the GM, as well as their opinions of the storyline, how the game was handled, and whether the game was engaging or entertaining.

Lastly, the participants completed an exit questionnaire after they concluded all 5 game sessions. The exit questionnaire contained a modified version of the PHQ-9 and GAD-7 questionnaires. Additionally, the exit questionnaire also contained 17 open-ended questions (Textbox 2), such as "What was the most frustrating moment or aspect of the game experience?" and "If you had a magic wand to wave, and you could change, add, or remove anything from the game experience, what would it be?"

Figure 1. Study design flow diagram.



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Textbox 1. Postgame questionnaire (responses for the questions are on the scale of 1 to 5: 1=strongly disagree, 2=somewhat disagree, 3=neither agree nor disagree, 4=somewhat agree, 5=strongly agree).

1. I enjoyed playing the game tonight
2. I would like to play the game again
3. I felt emotionally safe playing the game
4. I felt the other players treated me with respect
5. I felt the other players treated each other with respect
6. I felt the other players were kind to me
7. I felt the other players were kind to each other
8. I felt comfortable talking to the other players
9. I was interested in what the other players had to say
10. I would like to get to know the other players more
11. Playing this game made me feel happy
12. Playing this game made me feel less anxious
13. Playing this game made me feel less depressed
14. Playing this game made me feel less alone
15. I felt comfortable talking about my experience with chronic physical or mental conditions (CPMCs)
16. I liked talking about my experience with CPMCs
17. I liked that I was able to play with other people with CPMCs
18. I liked that I was able to talk with other people with CPMCs
19. I am looking forward to the next gaming session
20. The game master was helpful
21. The game master made me feel safe
22. The game master talked too much
23. The game master talked just right
24. The game master talked too little
25. I liked having the game master present
26. I like the game Masks
27. I like role-playing games

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Textbox 2. Masks research study exit questionnaire, open-ended questions.

1. What was the most frustrating moment or aspect of the game experience?
2. What was your favorite moment or aspect of the game experience?
3. Was there anything you wanted to do that you couldn't?
4. If you had a magic wand to wave, and you could change, add, or remove anything from the experience, what would it be?
5. What were you doing in the experience?
6. What was your role?
7. Why did you choose this particular role?
8. How would you describe this game to your friends and family?
9. Did you talk to your parents about playing this game?
10. Did your participation in this game interfere with other activities?
11. Did your parents mind that game sessions took 3 hours to complete?
12. Why did you agree to participate in this study?
13. Was it because of the pay, or were there any other reasons?
14. Did you ever feel uncomfortable during any of the game sessions? If so, why?
15. During the games, did you discuss your symptoms with any other players?
    - What were these discussions like?
    - What specifically did you discuss?
16. How did participating in these games make you feel?
17. Would you be interested in continuing playing this game or other games like it in the future, outside of this study?

Study Population

For the purposes of this study, we defined CPMC as any physical or mental condition where the symptoms have persisted for at least 1 year and where the participant has been receiving treatments from health care professionals for a period of at least 1 year. We required that each participant have consistent access to a computer and could demonstrate native-like fluency in the English language. Participants with impairments that prevent them from using a computer were excluded from the study because it would not have been possible for them to interface with the study materials.

Ethics Approval

Ethics Review

This study was reviewed and approved by the University of Pittsburgh Human Research Protection Office (protocol number STUDY19090313, “Multiplayer RPG as depression/isolation intervention”).

Informed Consent

After the initial screening phone call with the participant and parent dyad, the research team emailed the consent form to the parent and the participant for review and to have as a reference at the time of the consent form review. A research team member met with both the parent and the participant via a Zoom conference call to review the consent form and to answer any questions. The consent form included general explanations of what research is, specific information describing the study, explanation of inclusion criteria and how they relate to the specific participant being consented, detailed explanation of the game, participation requirements, potential benefits, and possible risks and discomforts. After the consent form review and after the parents and the participants confirmed that they understand the information and do not have additional questions, we asked the parents and the participants to digitally sign the consent form via the DocuSign electronic signature service. The final signed copy was automatically emailed to all parties and stored on the University of Pittsburgh DocuSign service cloud.

Privacy Protection

This study did not collect any identifiable data from the parents or the participants except for the data required for the consent forms. Signed consent forms were automatically stored on the University of Pittsburgh DocuSign service cloud, accessible only to the study’s principal investigator. After the consent process, participants were identified only by their chosen game character names, with no links to their names or their Health Insurance Portability and Accountability Act–protected information. Transcripts from game sessions (ie, Discord chat transcripts) and all raw survey data were reviewed after each game session by at least 3 investigators to ensure that no identifiable data were entered. Coded data from interviews, game transcripts, and survey responses were stored in a secure University of Pittsburgh–approved Microsoft OneDrive folder accessible only by the investigators.

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Compensation

Participants were compensated US $20.00 per each completed game session and an additional US $20.00 for completing all the questionnaires associated with the study.

Intervention

Masks [46] is a tabletop role-playing system produced by Magpie Games. In Masks, players assume the roles of young superheroes in a team (such as the Teen Titans or the X-Men) as they come of age in the face of superheroic trials and tribulations.

A tabletop RPG is an RPG in which the players "describe their characters' actions through speech" and determine the actions of their characters based on their character sheets. The outcomes of the characters' actions are determined by a formal system of rules and guidelines. "Within the rules, players have the freedom to improvise; their choices shape the direction and outcome of the game" [47].

The players select playbooks [48], which are based around the type of superhero they want to be and create their own characters to play as. They are similar to other tabletop RPGs like D&D, because the key element of gameplay is acting as a character in scenarios designed and led by a GM. By acting as their characters in response to these scenarios, the group creates a narrative that they experience together. Dice and other tools to decide outcomes are used to add an element of unpredictability to the narrative and aid in the improvisation process.

Unlike most other RPGs, Masks' mechanics are more focused around a character's emotional state and personal development. For example, the Label system explains mechanically how the characters grow into their powers based on the realizations they make about themselves and the influence of others around them. Instead of taking damage in ways that could lead to their characters dying, the system focuses more on the feelings that challenges and enemies can impose on the characters. A character who fails to use his or her powers against a formidable opponent in a stressful situation could feel insecure or, potentially, angry. By focusing on emotional states rather than physical health, players are free to invest in their characters without fear of them dying, while being given opportunities to create dramatic and narrative tension.

To ensure that players are kept comfortable enough to take creative risks and better tell the story they want to tell, it is very important that practices such as the "Blackcard" be used to ensure that every player is having fun. The "Blackcard" is a sign that can be raised if anybody in the party is feeling uncomfortable out of character about something in the game. If it is raised, the game will stop, and the situation will be resolved out of character before play resumes.

Game Sessions

At the beginning of the study, we conducted game session 0 (zero), where the GMs explained the game mechanics to the players and the players selected their in-game characters. We used the *MASKS: A New Generation* core book (purchased directly from Magpie Games) for the world, scenario, rule descriptions, and character sheets [48]. Players selected their in-game characters from the list of predefined characters described in the core book (Table 1).

Table 1. Character types selected by the participants.[a]

Participant (in-game alias)	Character type	Abilities
Kichi Ito	The Delinquent	(1) Teleportation; (2) tricks illusions; (3) gadgetry and hacking; and (4) psychic weapons, emotion control, and power negation
Rio	The Bull	Someone or something changed you, made you into a perfect weapon: superhumanly tough, incredibly strong, and uniquely skilled at fighting. Decide how each of those abilities manifests
Ryder	The Janus	(1) Rodent or insect control; (2) one generation, venom, or webs; (3) energy absorption; (4) supernatural senses; (5) impossible mobility; and (6) substance mimicry

[a]PHQ-9: Patient Health Questionnaire.

Every subsequent game session began with a recap of the events from the previous session. According to participants' and GMs' feedback, this was helpful for the group as it kept everyone on the same page and ensured that no one had forgotten anything major from the previous sessions' storylines or activities.

After the recap, the GM described the setting for the current scene, and the players responded by describing their characters' actions and reactions, causing the scene to evolve and to change. If a character performed an action where the outcome was uncertain, the player had to roll the dice to find out what the character's action (or reaction) would be.

At the end of every session, the GMs debriefed the players by asking them to describe how the events of the session changed each character's opinion of themselves or of the team they are a part of. Afterward, the GMs asked for comments, questions, and concerns and asked the players if there was anything that they wanted to see more of or less of in the game.

Remote Play Tools

Despite "tabletop" being in the name, physical proximity is not required to play Masks. Games can easily be conducted using chat with tools such as Discord [49], allowing for play anywhere with reliable internet access.

Discord is a free voice, video, and text chat application with both mobile and desktop clients. Discord allows its users to create private, invite-only virtual servers, a feature that helps ensure participants' privacy and provides researchers with full control over the conversations and the interactions. We chose Discord over comparable communication tools such as Slack or Microsoft Teams because of its popularity in web-based gaming communities [50], availability of clients for all major

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operating systems (ie, MacOS, Microsoft Windows, iOS, and Android), and its documented use in multiple research studies [51-54].

For this study, we created a private server accessible only to the research team members and the participants (players). We used the text chat function in this server to coordinate scheduling and the voice chat functionality to conduct game. Although Discord can also display video during voice calls, we disabled that functionality to protect participants' privacy.

Because Masks requires each player to roll a pair of 6-sided dice, we used M.A.D.D.I.E. ("Masks Automated Discord Dice Interpreter & Explainer!"), a user-created Discord chatbot to simulate dice rolls and facilitate game mechanics. In a dedicated text channel accessible within Discord, M.A.D.D.I.E responds to a concise syntax with both the requested dice rolls and relevant portions of the playbook describing its consequence, reducing the need for manual referencing, and allowing for smoother gameplay.

Lastly, in lieu of having each participant maintain a physical character playbook, we used a Google Drive–hosted common player sheet for character creation and tracking [55].

Data Analysis Methods

It is important to note that this pilot feasibility study had only 3 participants and that the statistical methods described in this section were initially chosen with a larger study in mind.

To determine how the participants' perceptions of the game and self-reported anxiety and depression scores changed over time, we calculated the change in per-question response score from session to session, as well as the overall mean response change per participant. When more data are collected from future studies, we will use the Wilcoxon signed rank test to compare both before and after changes in assessment measures.

Because of the small number of participants who participated in this study, we decided to report the participants' and the GMs' paraphrased or directly quoted responses. In future iterations of this study, we plan for analyzing participants' open-ended text responses using inductive theme analysis.

Results

Overview

As of March 2020, we recruited 6 adolescents with CPMCs aged 14-19 years through the UPMC Children's Hospital of Pittsburgh and the ETUDES Center (the Center for Enhancing Triage and Utilization for Depression and Emergent Suicidality in Pediatric Primary Care) [56].

Of the 6 consented participants, 4 participated in the initial game sessions and 3 completed all game sessions and all required surveys.

The 3 participants who participated in all game sessions had the mean and median age of 17 years. Participants identified their gender as cisgender male, transgender female, and nonbinary assigned female at birth. Two of the participants were White, and one was African American. Two of the participants completed 11 grades of high school, and one participant recently graduated from high school (completed 12 grades).

The participants' self-reported CPMCs included sensory processing disorder and diabetes, and all 3 participants indicated that they need or use more medical care, mental health, or educational services than is usual for most children their age. All participants reported that they have at least 5 people in their immediate support network who provide emotional support "most of the time" to "all of the time." PHQ-8, GAD-7, SSSI, and LS scores at the time of onboarding are reported in Table 2.

All participants indicated that they prefer to play with other people rather than alone, on average playing between 10 and 20 hours per week, with game genre preferences leaning toward action, adventure, and strategy or puzzles. All participants had prior experience with video game or tabletop RPGs, including games such as D&D, Minecraft [57], Stardew Valley [58], and Undertale [59].

Even though we did not have enough participants in this pilot study to measure the impact of participation in Masks on the participants' quality of life and mental health with any statistical significance, it is worth mentioning that PHQ-9 and GAD-7 scores we did collect indicated a reduction of depression and anxiety symptoms. Moreover, the postgame questionnaire results showed a consistent positive change in the participants' opinion of the game from one game session to the next.

Responses to the postgame questionnaire (Textbox 1) indicated a positive trend in participants' opinions of and engagement with Masks, individual game sessions, and their comfort levels with other players and with the GMs. Figure 2 shows the trend in the mean response change to the postgame questionnaire over the course of 5 sessions.

In the exit questionnaire, all 3 participants reported that they talked to their parents and friends about the game and the study, that their participation in game sessions did not interfere with other activities, and that their parents did not mind that each game session took several hours to complete.

One participant reported that initially they had difficulties following the story. Another participant reported that at first, they "had a really hard time talking [...] and wanted to stay quiet."

Favorite aspects of the game included creative environments, unpredictable situations, and doing "something stupid as a team and [working it out together]."

All 3 participants indicated that there was never a situation in the game where they wanted to do something but could not either because of the game environment constraints or due to any issues with other players or the GMs.

To the question of "Why did you choose your particular role?" one participant responded, "I've always enjoyed playing the 'bad boy' type characters," while another indicated that "[the role] is similar to how I see myself."

All 3 participants indicated that the game was fun to play and that the characters and other players were "comfortable" and

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"relatable," and only 1 participant reported being initially too nervous to talk. None of the participants discussed their physical or mental health during game sessions.

All 3 participants reported that they initially agreed to join the study because of the compensation but "ended up having a really good time."

It is also worth noting that to the question "Would you be interested in continuing playing this game or other games like it in the future, outside of this study?" all 3 participants answered "Yes."

Lastly, all participants indicated that playing the game made them "happy" and "excited." To quote one of the participants, "It made me very happy. I felt safe and it was a lot of fun. It was one of my favorite parts of the week. I looked forward to it every week."

Table 2. Participants' PHQ-9[a], GAD-7[b], LS[c], and SSSI[d] scores from the onboarding questionnaire.

Participant (in-game alias)	PHQ-8 score	GAD-7 score	LS score	SSSI score
Kichi Ito	10	2	40	9
Rio	18	5	30	10
Ryder	11	3	23	8

[a]PHQ-9: Patient Health Questionnaire.

[b]GAD-7: Generalized Anxiety Disorder Questionnaire.

[c]LS: UCLA Loneliness Scale.

[d]SSSI: RAND Social Support Survey Instrument.

Figure 2. Overall mean change in participants' engagement and comfort with the game over the course of 5 sessions.



GM Postgame Reports

The GMs reported minor technical problems, the most common being connection issues to Discord servers. The GMs did not report any behavior issues (such as toxic behavior or negative language) among the players. The only reported minor issues included lateness to a game session from one player. After the first session, the GMs reported that one player did not feel comfortable and was shy throughout the gameplay. The players did not discuss their personal lives or any topics related to their physical or mental health in any of the game sessions.

Discussion

In this paper, we presented our pilot work on (1) determining the feasibility of using Masks, a multiplayer RPG, as an intervention for social isolation, anxiety, and depression in adolescents with chronic physical or mental health conditions; (2) evaluating the viability of the research process; and (3) gauging participation in and engagement with RPG-based interventions.

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We found that recruiting adolescents to participate from clinical settings was difficult despite study design changes. These recruitment difficulties were mainly due to scheduling difficulties and dedicated time requirements.

For those participants who did participate, we were able to establish a workflow for gameplay and successfully conducted 5 sessions. Participants overall reported satisfaction and enjoyment with gameplay but did not engage in discussing their CPMCs during play as hypothesized. Of particular interest were participants' preferences to play with other people rather than alone and participants' prior experience with multiplayer games. These findings correspond to findings in other studies related to game-based interventions [60-63], suggesting that participants with prior multiplayer game experience are more likely to participate in game-related studies. These findings also suggest that in future iterations of this study we will attempt to recruit adolescents with CPMCs from multiplayer game communities rather than from clinical settings.

Although the number of participants was too low to draw generalizable conclusions, self-reported clinical outcomes did seem to indicate a positive change in depression, anxiety, and social isolation symptoms. Furthermore, the participants provided feedback about improved mood and engagement related to weekly participation in Masks.

It is also important to note that all participants reported that they talked to their parents and friends about the game and the study. Several studies suggest that parents or caregivers of children with CPMCs perceive children's distress symptoms (anxiety, depression, and physical symptom burden) differently, with parents or caregivers consistently rating the children's symptoms lower than the children [64-68]. In future iterations of this study, we will explore gameplay design features that could facilitate and promote communications between children and parents or caregivers.

In discussing this work, it is important to acknowledge its limitations. One of the main limitations of this study was recruitment and retention. In the initial phases, we attempted to recruit from clinical practices and hospital settings, but because of scheduling difficulties, dedicated time requirements, and school and family obligations, most participants dropped out of the study. Because of time requirements and scheduling constraints, participants participated in only 5 consecutive game sessions of the planned 10. Another limitation was that one participant did not complete all the questionnaires despite multiple reminders from the GMs and the research team. It is also worth noting that we do not know how the fact that the GMs and the players are all strangers to one another affects interaction and gameplay dynamics compared with a typical game of Masks where the players have had prior social interaction. Although our limited data show that the participants reported being comfortable with the GMs and each other, it would be important to empirically compare a game dynamics and comfort levels of players who are strangers to each other versus players who know each other outside of the gameplay world. Lastly, we planned to compare pre- and post-LS and SSSI scores to determine if the scores have improved over time with each game session. However, we were unable to compare these scales with poststudy values because of accidental omission of including them in the exit questionnaire.

Although the small number of participants (n=3) does not allow us to make generalizable conclusions about the efficacy of RPG-based interventions, we did establish a workflow for gameplay and evaluated a research protocol for evaluating the impact of RPG participation on isolation, anxiety, and depression symptoms in adolescents with CPMCs. It is also worth noting that many recent and past research studies focused on developing custom interventions for a specific health or mental condition. From our own experience [69-72], we know how expensive and time-consuming it is to develop game-based interventions and how difficult and costly they are to maintain and support. This work strongly suggests that it is possible to take a widely available and relatively inexpensive multiplayer tabletop RPG, one that already has an established support network and gamer community, and use it as a possible intervention for social isolation.

Many support groups, community centers, and even entire neighborhoods already have established community game events (eg, game nights and game jams), with a positive impact on player engagement, mental health, and community building [73-76]. If future studies with larger patient samples show significant short- and long-term improvement in social isolation, depression, and anxiety symptoms, clinical practices that provide health care services to adolescents with CPMCs should consider either partnering with existing gamer communities or establishing their own consistently recurring multiplayer RPG events for their patients. Such "game nights" could potentially be used as a supplement to existing group therapies.

Lastly, we believe that the preliminary data collected from the pilot study support the validity of the research protocol and the use of RPG-based interventions in larger clinical studies.

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Data Availability

The data sets generated or analyzed during this study are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

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Abbreviations

CF: cystic fibrosis
CPMC: chronic physical or mental condition
D&D: Dungeons & Dragons
ETUDES: Center for Enhancing Triage and Utilization for Depression and Emergent Suicidality in Pediatric Primary Care
GAD-7: Generalized Anxiety Disorder Questionnaire.
GM: game master
LS: UCLA Loneliness Scale.
M.A.D.D.I.E.: Masks Automated Discord Dice Interpreter & Explainer!
PHQ-8: eight-item Patient Health Questionnaire depression scale
RPG: role-playing game
SSSI: RAND Social Support Survey Instrument.
VR: virtual reality
WoW: World of Warcraft

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Protocol

Improvement in Quality of Life With the Use of a Technological System Among Patients With Chronic Disease Followed Up in Primary Care (TeNDER Project): Protocol for a Randomized Controlled Trial

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Abstract

Background: Among chronic diseases, cognitive, neurological, and cardiovascular impairments are becoming increasingly prevalent, generating a shift in health and social needs. Technology can create an ecosystem of care integrated with microtools based on biosensors for motion, location, voice, and expression detection that can help people with chronic diseases. A technological system capable of identifying symptoms, signs, or behavioral patterns could provide notification of the development of complications of disease. This would help the self-care of patients with chronic disease and save health care costs, promoting the autonomy and empowerment of patients and their caregivers, improving their quality of life (QoL), and providing health professionals with monitoring tools.

Objective: The main objective of this study is to evaluate the effectiveness of a technological system (the TeNDER system) to improve quality of life in patients with chronic diseases: Alzheimer disease, Parkinson disease, and cardiovascular disease.

Methods: A multicenter, randomized, parallel-group clinical trial will be conducted with a follow-up of 2 months. The scope of the study will be the primary care health centers of the Community of Madrid belonging to the Spanish public health system. The study population will be patients diagnosed with Parkinson disease, Alzheimer disease, and cardiovascular disease; their caregivers; and health professionals. The sample size will be 534 patients (380 in the intervention group). The intervention will consist of the use of the TeNDER system. The system will monitor the patients by means of biosensors, and their data will be

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integrated into the TeNDER app. With the information provided, the TeNDER system will generate health reports that can be consulted by patients, caregivers, and health professionals. Sociodemographic variables and technological affinity will be measured, as will views on the usability of and satisfaction with the TeNDER system. The dependent variable will be the mean difference in QoL score between the intervention and control groups at 2 months. To study the effectiveness of the TeNDER system in improving QoL in patients, an explanatory linear regression model will be constructed. All analyses will be performed with the 95% CI and robust estimators.

Results: Ethics approval for this project was received on September 11, 2019. The trial was registered on August 14, 2020. Recruitment commenced in April 2021, and the expected results will be available during 2023 or 2024.

Conclusions: This clinical trial among patients with highly prevalent chronic illnesses and the people most involved in their care will provide a more realistic view of the situation experienced by people with long-term illness and their support networks. The TeNDER system is in continuous development based on a study of the needs of the target population and on feedback during its use from the users: patients, caregivers, and primary care health professionals.

Trial Registration: ClinicalTrials.gov NCT05681065; https://clinicaltrials.gov/ct2/show/NCT05681065

International Registered Report Identifier (IRRID): DERR1-10.2196/47331

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KEYWORDS

chronic disease; environmental monitoring; technological development; quality of life; caregivers; health professionals; primary care; public health; monitoring; cognitive impairment; TeNDER

Introduction

Background

With the increase in population aging in Europe, chronic diseases are becoming more prevalent [1]. This reality represents a major challenge to health care systems due to comorbidities and outcomes such as increased dependency [2-4]. It is a priority to promote the autonomy and empowerment of patients and their caregivers, improve their quality of life (QoL), and provide tools enabling better monitoring by health professionals [5-7].

Among chronic diseases, cognitive, neurological, and cardiovascular impairments are becoming increasingly prevalent, generating a shift in health and social needs [8]. According to the World Health Organization (WHO) in a 2018 report, cognitive impairment and dementias, including Alzheimer disease (AD), remain one of the greatest global public health challenges facing our society [9]. The number of people worldwide living with a cognitive impairment such as dementia, is estimated at 44 million; this is expected to double by 2030 and is likely to increase to around 152 million by 2050. Among neurological disorders, Parkinson disease (PD) affects 1.2 million people in Europe [10]. Patients with PD, in addition to symptoms related to movement disorders, also develop cognitive impairment and emotional and behavioral disturbances that are important to follow closely [10]. Cardiovascular disease (CVD) accounted for 31% of all global deaths in 2016, and it is considered the leading cause of premature death (37% of all deaths under the age of 70) and disability in Europe and worldwide [11]. Early detection of disease progression and early treatment is essential [12].

Technology can create an ecosystem of care integrated with microtools based on biosensors for motion, location, voice, and expression detection that can help people with chronic diseases [13]. Today, these data streams, including sensor measurements, activity logs, and user-generated content, are used to measure or provide robust proxies for human behavior and function in both health and disease. This is called digital phenotyping [14].

Digital phenotyping is the in situ, moment-to-moment quantification of the human phenotype at the individual level using data from personal digital devices [15]. These microtools are able to recognize changes in a person's habitual behaviors, movements, and mood through a multisensory system composed of smartphones, wearables, and other connected devices [16]. In addition, digital phenotyping allows the integration of an interactive communication service between health and social services, which can bring advantages in patient care and help detect risk situations, improving the autonomy of patients and the care they receive from caregivers and health professionals [17].

The development of a technological system capable of identifying symptoms, signs, or behavioral patterns that could provide alerts for the development of complications of these diseases would help the self-care of people with chronic diseases, their caregivers, and health professionals, as well as save costs for the health care system [18,19]. Some studies on digital phenotyping in patients with chronic disease have demonstrated its usefulness in treatment for mental health problems, diabetes, asthma, and CVD, showing positive effects on self-care and adherence to treatment [20,21]. This has been achieved by detecting clinical phenomena through digital tools that have enabled health professionals to adapt their assistance to the environment and characteristics of patients [21].

Until now, research on digital phenotyping has been led and developed by teams specialized in the technological field. As suggested by Huckvale et al [20], these challenges must be addressed under a multifaceted and multidisciplinary perspective involving health professionals and users in the development of such technological systems.

Needs such as the detection of behavioral changes in patients with dementia, gait changes and fall prevention in patients with

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PD, and the close monitoring of risk factors for CVD could be covered by intelligent monitoring system [19]. This would help the self-care of patients with chronic diseases, promoting the autonomy and empowerment of patients and their caregivers and improving their QoL.

Objectives

The main objective of this study is to evaluate the effectiveness of a technological system (the TeNDER system) to improve QoL in patients with chronic diseases, including AD, PD, and CVD.

The secondary objectives are (1) to describe the satisfaction of patients, caregivers, and health professionals with the TeNDER system; (2) to describe the characteristics of the usability of the TeNDER system from the perspective of its potential users; and (3) to explore whether the use of the TeNDER system increases caregivers' perceived satisfaction with the care provided and, in relation to this, improves their QoL.

Methods

Design

A multicenter, randomized, parallel-group clinical trial will be conducted with a follow-up of 2 months. The unit of randomization will be the patient.

This study protocol is part of a proposal with European funding under the European Union's Horizon 2020 Research and Innovation Programme (grant 875325). The European consortium that developed the proposal is composed of different countries: Spain, Portugal, Italy, Slovenia, Greece, Germany, and Belgium [22].

The TeNDER project is developed in 4 European countries (Spain, Germany, Italy, and Slovenia). To account for the differences in the health systems of the participating countries and organizations, this research protocol refers to the primary care health centers (PCHCs) of the Madrid Health Service, which belongs to the Spanish public health system.

The TeNDER project brings together experts in technological development and users, including chronic patients, their caregivers, and primary care health professionals (PCHPs). Therefore, it will have an initial phase of cocreation in which the needs of the users will be explored. Based on the results, the technical team will work on improving and adapting the TeNDER system.

Study Population

The TeNDER project will include patients diagnosed with at least one of the following chronic conditions: PD, AD, other dementias, and CVD. Along with the patients, their caregivers, and their health professionals from the PCHCs will also be included as participants.

All participants must accept and sign the informed consent form. If a patient does not have the capacity to do so, a family member will sign the form on their behalf.

General Inclusion Criteria for Patients

Patients will be included if they are older than 60 years at follow-up, are referred by a PCHP at the PCHC, and are able to understand the local language. If a patient is dependent on others, they must have a caregiver or other responsible party.

General Exclusion Criteria for Patients

Patient who according to the judgment of their caregiver or PCHP are unable to follow the requirements of the study (eg, patients with inability to move or move around at home) or who have a life expectancy of less than 6 months will be excluded.

Specific Criteria for Patients With Each Chronic Illness

Patients with PD must have a confirmed diagnosis. Patients with AD must have a Mini Mental State Examination score between 19 and 28 points. Patients with a Global Deterioration Scale over 6 or 7 will be excluded. Patients with CVD will include those with the following conditions: heart failure with NYHA (New York Heart Association) Scale grade II to III heart function, and stable coronary artery disease or artery coronary disease with or without ST-elevation, atrial fibrillation, pacemaker, and stroke. Patients with arterial coronary disease that occurred less than 4 weeks ago or with severe aortic stenosis will be excluded.

Inclusion Criteria for Caregivers

Caregivers of the selected patients who are aware of the patient's health and social situation and who provide direct care or support for daily activities will be included. In addition, caregivers must be able to use a smartphone.

Exclusion Criteria for Caregivers

Caregivers will be excluded if they do not understand the local language.

Inclusion Criteria for PCHPs

Medical doctors and nurses attending the adult population of the participating PCHC will be included. They must carry out their professional activity in a PCHC that participates in the study and have at least one year of professional experience. They should be able to provide continuity of care for the patient during the intervention.

No exclusion criteria were applied for the PCHPs.

Sample Size

The European consortium that developed the proposal called for a sample size of 1766 patients (1031 in the control group and 735 in the intervention group) with the aim of using the TeNDER system to achieve an improvement in QoL, as measured by the Short Form–36 Health Survey (SF36) [23], of 6 points in the intervention group as compared to the control group.

According to previous studies, the SD for QoL score in the population with the chronic diseases under study (PD, AD, and CVD) ranges between 16 and 27 [23-25]. For the power calculation, we used the highest value of this SD. Therefore, the sample size will allow a power of 98.8% to detect ≥6

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differences in the overall score of the SF36 questionnaire, if they exist. Calculations were performed with Epidat (version 4.2; Xunta de Galicia).

In the PCHC of the Madrid Health Service, as part of the European consortium, 534 patients will be included (380 in the intervention group and 254 in the control group). No differentiation by pathology will be established.

Recruitment

Five PCHCs in Madrid will be recruited. A total of 187 PCHPs will be invited to participate in the study. Based on experiences in previous studies, we expect a participation rate of 45%, which means 84 participating professionals. If necessary, the number of participating PCHCs will be expanded to reach the required sample size. PCHPs will participate in the study on a voluntary basis after signing the informed consent form.

Each participating PCHP will recruit 8 patients with a quota for each disease (5 with CVD, 1 with PD, and 2 with AD) consecutively as they attend the office. After the recruitment of patients, their caregivers will be invited to participate. For independent patients, it will not be necessary to recruit a caregiver.

During the recruitment interview, the PCHP will provide all information about the study as a detailed verbal explanation accompanied by a patient information sheet, making sure that the patient understands it.

Randomization

Once the participants have been selected, after the initial visit, the patients will be randomized by pathology. Patients included in the intervention group will be included together with their caregiver and PCHP, creating a participant unit (patient-caregiver-PCHP or patient-PCHP). There will be no masking in any phase of the study. Assignment will be performed centrally by the Research Support Unit of the Primary Care Management of Madrid.

Patients in the intervention group will be fitted with the TeNDER system device best suited to their needs and will be treated according to standard clinical practice. Patients in the control group will be treated according to standard clinical practice.

Subsequently, each PCHP will be informed of which patients have been assigned to each group; based on this, they will have a different role in each case (ie, using the TeNDER system with the intervention group and usual practice with the control group).

Intervention

The intervention is described in Figure 1 as recommended by Perera et al [26]. The intervention includes the use of the TeNDER system, a tool created by the consortium of the TeNDER group under the coordination of the Visual Telecommunications Applications Group (Grupo de Aplicación de Telecomunicaciones Visuales; GATV) of the Polytechnic University of Madrid.

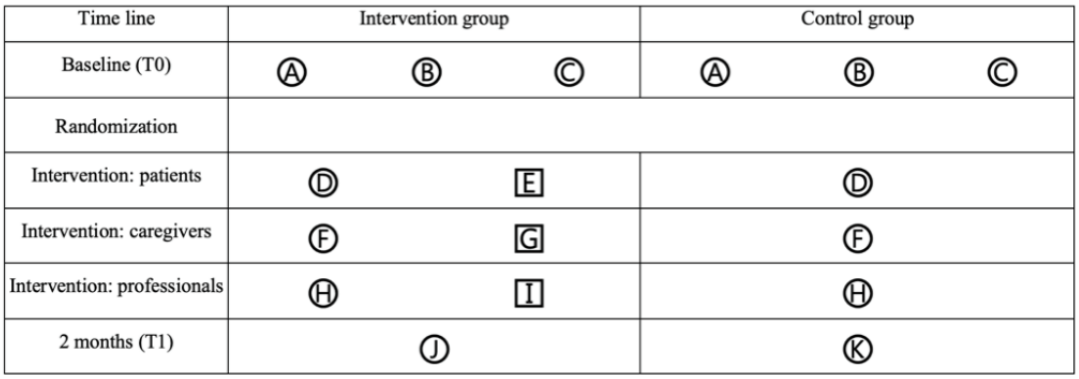
The TeNDER system integrates multiple monitoring sensors that provide data to build an integrated technological ecosystem. The patient is monitored on a daily basis through one or more devices that offer different monitoring records (Table 1). The type of device will be chosen by the participant unit according to the patient's health status and their needs as expressed by the patient and their caregiver.

With the registered information, the TeNDER system will generate different functionalities (Textbox 1) that can be used through a mobile app and a web app. The functionalities for each participant will be activated according to their profile. Patients will have access to all functionalities, while caregivers and professionals will only be able to access functionalities that the patient authorizes.

Each participant unit will receive assistance in downloading and installing the app, creating an account, and creating a user profile. The use of the TeNDER system does not require advanced knowledge, only a basic user level. However, technical support will be provided by the GATV of the Polytechnic University of Madrid.

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Figure 1. Details of patient flow, the intervention, and data collection.



Ⓐ	Recruitment and informed consent
Ⓑ	Cocreation of the TeNDER system. Questionnaires and interviews to explore the needs of patients, caregivers, and professionals. The information collected will be used to adapt the system to the needs of users.
Ⓒ	Baseline visit (T0): collection of baseline variable, including sociodemographics, clinical information, quality of life, degree of autonomy, and technology affinity (patients); sociodemographics, quality of life related to the care provided, and perceived satisfaction and technology affinity (caregivers); and sociodemographics and technology affinity (primary care health professionals).
Ⓓ	Standard practice based on assessment, transmission of information, advice, and usual treatments, as well as review according to the clinical practice guidelines of the various chronic diseases presented by the patient.
[E]	TeNDER system for patients: smartphone, one or more selected devices, and TeNDER system with patient profile (this allows use of all the functionalities of the TeNDER system and management of the data query permission for users who are linked to caregivers or primary care health professionals).
Ⓕ	Standard practice based on assessment, transmission of information, advice, and treatment according to the clinical practice guidelines and recommendations.
[G]	TeNDER system for caregivers: smartphone and TeNDER system with caregiver profile, including functionalities for record consultation and instant messaging. If authorized by the patient or for dependent patients, the caregiver is allowed to access all the functionalities of the system.
Ⓗ	Standard practice; primary care health professionals will see and receive information from their patients in face-to-face visits or during telephone consultations following standard practice.
[I]	TeNDER system for primary care health professionals: smartphone and TeNDER system with primary care health professional profile, including functionalities for record consultation, instant messaging, and a recommender.
Ⓙ	Final visit (T1): collection of T0 variables and measurement of satisfaction and usability among all participants.
Ⓚ	Final visit (T1): collection of T0 variables.

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Table 1. Devices and monitoring record.

Devices	Sleep quality detection	Emotional state detection	Physical activity[a]	Fall detection	Skeleton motion data[b]	Safety and security at home[c]
App for smartphones and tablets	✓	✓	✓	✓	✓	✓
Smartphone/tablet	✓	✓	✓	✓	✓	✓
Mini PC (low-end)	✓		✓	✓		
Mini PC (high-end)		✓			✓	✓
Speaker						
Smartband Fitbit			✓	✓	✓	✓
Environmental sensors (temperature and humidity)						✓
Microphone		✓				
Withings sleep analyzer (Withings France SA)	✓					
Localization sensor						✓
Open-close window and door sensors						✓
RGB camera (Intel RealSense)				✓	✓	

[a]Steps and heart rate.

[b]Balance, freezing, or both.

[c]Environmental status, door and window status, location, and activity at home.

Textbox 1. Functionalities of the TeNDER system.

Functionalities

- Monitoring of variables collected by devices and biosensors
- Consultation of records and reports generated from the data collected by the biosensors
- Use of a smart calendar in which to schedule important events, medical appointment reminders, and medication reminders
- Possibility to generate notifications, including reminders and alerts
- Instant messaging channel for the exchange of messages between patient, caregiver, and primary care health professional
- Recommender function to explore a certain topic with the patient and, based on their answers, provide useful recommendations

Data Collection

Two types of data will be collected based on the nature of the data: direct data (through questionnaires) and indirect data (through devices and biosensors).

Direct Data Collection

Once participants have agreed to participate in the study, they will be scheduled for the baseline visit (T0). At this visit, baseline and tool cocreation data will be collected. The final visit (T1) will take place 2 months after the intervention. Data collection during both visits will take place at the PCHC or at the patient's home and will be carried out as face-to-face hetero-administered interviews by 2 project nurses. Data will be collected through questionnaires, and interviews will be indexed in an electronic data collection record (eDCR).

The primary outcome variable will be the QoL of patients measured using the SF36 questionnaire [23]. This is a 36-item questionnaire that includes 8 domains: physical functioning, role limitations due to physical problems, bodily pain, general health perceptions, mental health, role limitations due to emotional problems, social functioning, and vitality. Eight domain scores and a summary score (range 0-100) can be obtained; higher scores indicate better health-related QoL (HRQoL). In addition, six Likert-type questions are used to collect proxy indicators of QoL related to the TeNDER system. These questions are related to the perception of improved autonomy, support, improved self-care, and safety. In addition, we will collect sociodemographic variables such as sex, age, and nationality from patients, caregivers, and PCHPs. Also, technology affinity among the 3 types of users will be collected through a single ad hoc question. Clinical information collected from patients will include their main disease and other chronic diseases. The degree of autonomy and the need for help will be studied through ad hoc questionnaires at T0 and T1.

For a description of the usability of and satisfaction with TeNDER system after the intervention, the validated System Usability Scale questionnaire [24,25] will be administered to patients, caregivers, and PCHPs.

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Caregivers' QoL related to the care provided and the perceived satisfaction with the care provided will be studied through an ad hoc questionnaire.

The questionnaires (at T0 and T1) are included in Multimedia Appendix 1.

Indirect Data Collection

Indirect data collection will be performed through devices and biosensors. These data are transmitted to the TeNDER cloud platform using an intermediary broker messaging service (RabbitMQ). A mini PC, on which the local health tracking tool server is installed, serves as a gateway for the biosensors to communicate with the cloud.

To ensure seamless data collection, most sensors are connected to the local area network wirelessly. The biosensors collect a wide range of data, including the following:

- The Withings sleep analyzer captures sleep data, monitors heart rate and breathing rate, and is able to detect apnea states.
- The Smartwatch Fitbit Versa 2 detects heart rate and number of steps taken. In addition, raw accelerometer measurements extracted by the device help track fall incidents and patient location.
- A location sensor measures the signal strength of the smartwatch (via the Bluetooth connection) to determine position and presence at room level.
- A microphone and speaker provides real-time audio recording and is able to identify screams or cries through the collection of recordings and tone of voice.
- The Aqara Hub integrates several secondary devices, such as a room temperature and humidity sensor and binary door, window opening, and window closing sensors.
- The RealSense device captures the patient's skeleton motion data in the form of coordinates in space. When combined with the Fitbit Versa 2 smartwatch, the system is able to identify the skeleton, and with the additional use of a microphone, can detect falls.

Storage and Security of Collected Data

All the direct data will be stored in an eDCR on the EUSurvey platform. This platform is developed by the Commission of the European Union and complies with the European Union Regulation No 2018/1725 of the European Parliament and of the Council of 23 October 2018, by which it guarantees data privacy through its policy on the protection of natural persons with regard to the processing of personal data. Only project researchers will have access to the data stored in EUSurvey by means of a username and password. The data collected will be pseudoanonymized using an alphanumeric code, and only the researcher administering the questionnaire to the participant will be able to link these data to the participant. The data stored will remain in the database for up to 25 years after the end of data collection in accordance with current regulations.

As for indirect data, the TeNDER System platform is hosted on domains recommended and endorsed by the European Union, which guarantees the highest standards of security and privacy protection. Once collected, the data are temporarily stored on the device itself for a few days if there is no connection to the TeNDER system. After connection, the data are stored in an anonymized form in the secure infrastructure of the TeNDER system and can be accessed by project researchers using credentials and tokens.

Data Analysis and Statistical Plan

A descriptive analysis of the characteristics of the participants will be performed with frequencies and percentages for qualitative variables and the mean (SD) or median (IQR) for the quantitative variables, according to their distribution. The mean difference in QoL score between the intervention and control groups will be studied with the corresponding 95% CIs at T1 (2 months). Differences in qualitative variables will be analyzed with the Pearson chi-squared test, and differences in normally distributed quantitative variables will be analyzed with the Student *t* test (2-tailed).

To study the effectiveness of the TeNDER System in improving QoL in patients, an explanatory linear regression model will be constructed. The dependent variable will be the mean difference in QoL score between the intervention and control groups at T1 (2 months). As patients will be recruited grouped by cluster (ie, PCHC), all the estimations will be performed with robust estimators. The analyses will be performed with Stata (version 14; StataCorp).

Ethical Considerations

This study protocol was approved by the Ethics Committee for Research Involving Medicinal Products of the Hospital 12 de Octubre (20/450) and obtained permission from the Central Research Commission of the Primary Care Healthcare Management of Madrid (PC:39/20) to carry it out in the primary care setting of the Community of Madrid. The processing, communication, and transfer of data will be carried out in accordance with the provisions of the General Data Protection Regulation of the European Union (RGPD 2016/679) of the European Parliament and of the Council of 27 April 2016 and the Organic Law on Data Protection and Guarantee of Digital Rights in the Spanish territory (LOPDGDD 3/2018 of 5 December).

Results

Ethics approval for this project was received on September 11, 2019. The trial was registered on August 14, 2020 (ClinicalTrials.gov NCT05681065). Recruitment commenced in April 2021 and the expected results will be available during 2023 or 2024.

Discussion

Previous studies on the use of technological tools by people with chronic disease have shown an improvement in their self-management, self-care, and adherence to therapy. However, few studies have examined all users involved in the care of chronic patients in their use of these tools.

The strength of this work is to investigate the use of a technological tool focused on health and self-care by, on one hand, patients with chronic disease older than 65 years, and on

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the other hand, their caregivers or family supporters, as well as, finally, the health professionals who are responsible for monitoring their health status, in particular the PCHPs. This clinical trial among patients with highly prevalent chronic diseases and the people most involved in their care will provide a more realistic view of how technology can be integrated into their lives as an aid to care.

Another strong point is the involvement of users in the development and improvement of the TeNDER system. To this end, this work includes a cocreation phase in which the needs of the users are explored in order to develop a system that is adapted to them.

The main objective of this study is to improve the QoL of chronically ill patients older than 60 years. Despite the difficulties of achieving this with a 2-month intervention, there are certain proxy indicators of QoL that are sensitive to improvement, and this can be reflected in the HRQoL. Therefore, ad hoc questions have been included as variables that aim to detect elements that have an impact on QoL, such as safety and autonomy.

Among the main limitations are that due to the nature of the intervention, the trial cannot be masked. This may result in participants who are in the intervention group perceiving an improvement in their health follow-up; therefore, the difference in score with respect to the control group will increase. Thus, we propose to look for an increase of at least 6 points in the main improvement variable (QoL). In the same sense, the use of the TeNDER system can also lead to an improvement in patients' adherence to treatment, as they feel observed and monitored by the system (ie, the Hawthorne effect).

Another limitation is selection bias in the sample of participants. In many cases, older people and people with low digital literacy have the greatest need for health support. However, since the intervention requires the use of technology, it may be those with the greatest interest in its use who agree to participate in the study. This may result in a missed opportunity to address the digital divide. Studying the effectiveness of a technological system in an older population (ie, patients aged >60 years) may imply an initial reluctance toward technology. The digital age gap can be a barrier to use, and as a consequence, this can affect satisfaction and usability.

In order to reduce this effect and to be able to achieve good satisfaction and adapt the system to the participating population, the TeNDER system is developed based on a study of the needs of the target population (patients, caregivers, and PCHPs) and is constantly improved based on feedback from them.

In addition, in order to reduce the frustration that may arise with the use of technology, continuous telephone support will be provided to address any doubts or problems that may arise for participants.

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Data Availability

Data sharing is not applicable to this paper as no data sets were generated or analyzed during this study.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Questionnaires administered at T0 and T1 for patients, caregivers, and primary care health professionals.
[DOCX File , 36 KB - resprot_v12i1e47331_app1.docx]

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Abbreviations

AD: Alzheimer disease
CVD: cardiovascular disease
eDCR: electronic data collection record
EU: European Union
GATV: Grupo de Aplicación de Telecomunicaciones Visuales
HRQoL: health-related QoL
NYHA: New York Heart Association
PCHC: primary care health center
PCHP: primary care health professional
PD: Parkinson disease
QoL: quality of life
SF36: Short Form–36
WHO: World Health Organization

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Protocol

Remote Patient Monitoring and Teleconsultation to Improve Health Outcomes and Reduce Health Care Utilization of Pediatric Asthma (ALPACA Study): Protocol for a Randomized Controlled Effectiveness Trial

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Abstract

Background: Childhood asthma is imposing a great financial burden on the pediatric health care system. Asthma costs are directly related to the level of asthma control. A substantial part of these costs may be preventable by the timely and adequate assessment of asthma deterioration in daily life and proper asthma management. The use of eHealth technology may assist such timely and targeted medical anticipation.

Objective: This paper describes the Ambulatory Pediatric Asthma Care (ALPACA) study protocol to investigate the effectiveness of an eHealth intervention consisting of remote patient monitoring and teleconsultation integrated into the daily clinical care of pediatric patients with asthma. This intervention aims to reduce health care utilization and costs and improve health outcomes compared to a control group that receives standard care. In addition, this study aims to improve future eHealth pediatric asthma care by gaining insights from home-monitoring data.

Methods: This study is a prospective randomized controlled effectiveness trial. A total of 40 participants will be randomized to either 3 months of eHealth care (intervention group) or standard care (control group). The eHealth intervention consists of remote patient monitoring (spirometry, pulse oximetry, electronic medication adherence tracking, and asthma control questionnaire) and web-based teleconsultation (video sharing, messages). All participants will have a 3-month follow-up with standard care to evaluate whether the possible effects of eHealth care are longer lasting. During the entire study and follow-up period, all participants will use blinded observational home monitoring (sleep, cough/wheeze sounds, air quality in bedroom) as well.

Results: This study was approved by the Medical Research Ethics Committees United. Enrollment began in February 2023, and the results of this study are expected to be submitted for publication in July 2024.

Conclusions: This study will contribute to the existing knowledge on the effectiveness of eHealth interventions that combine remote patient monitoring and teleconsultation for health care utilization, costs, and health outcomes. Furthermore, the observational home-monitoring data can contribute to improved identification of early signs of asthma deterioration in pediatric patients. Researchers and technology developers could use this study to guide and improve eHealth development, while health care professionals, health care institutions, and policy makers may employ our results to make informed decisions to steer toward high-quality, efficient pediatric asthma care.

Trial Registration: ClinicalTrials.gov NCT05517096; https://clinicaltrials.gov/ct2/show/NCT05517096

International Registered Report Identifier (IRRID): PRR1-10.2196/45585

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(JMIR Res Protoc 2023;12:e45585) doi:10.2196/45585

KEYWORDS

asthma; children; telemedicine; home monitoring; randomized controlled trial; health care utilization; health care costs; protocol; spirometry; adherence; nebulizer; pediatric care; utilization; remote monitoring; asthma care

Introduction

Background

Asthma is one of the most common pediatric chronic diseases with a prevalence between 7% and 10% [1,2]. Childhood asthma imposes a significant physical and social burden on the affected child and their family. It may prevent children from participating in play and recreational activities, hamper social contacts, and lead to school absence and reduced school performance [2-4]. As a result, children with asthma have a reduced quality of life (QoL) in comparison to their healthy peers [5-7].

Asthma is also imposing a great financial burden on the pediatric health care system [8]. High-income countries spend between 1% and 2% of their health care budget on asthma [1,9]. For example, in the Netherlands, direct pediatric asthma health care costs have doubled over the last 2 decades and amounted to €90.8 million (US $92 million) in 2017 [10], compared to US $5.92 billion in the United States in 2013 [11]. Hospital and pharmacy costs occupy an increasing share and are the primary contributors to the total health care costs [10,11]. Additionally, pediatric asthma also exerts a large indirect economic burden due to missed school and workdays [12]. The economic burden of asthma is disproportional along with the severity of the disease [13]. Moreover, asthma costs are directly related to the level of asthma control, as poor control is associated with more hospitalizations, emergency visits, and other health care contacts [14].

A substantial part of these costs may be preventable and asthma outcomes can be improved if we are able to overcome existing challenges in pediatric asthma care. These challenges include (1) a limited opportunity for health care professionals (HCPs) to retrieve objective insight into the severity and dynamics of asthma symptoms in daily life [15], (2) the difficulty of attuning an optimal treatment that not only treats the intermittent symptoms but also the underlying inflammation sufficiently [16], (3) low adherence and poor inhaler technique of asthma therapy in children with asthma [17,18], and (4) inadequate assessment of severity or failure of the family to call for help when required [19].

The use of eHealth technology, like remote patient monitoring and teleconsultation, may help overcome these challenges [20]. In recent years, the development and validation of these types of eHealth technologies for pediatric asthma have skyrocketed [21-23]. Studies cautiously show evidence that eHealth can improve health outcomes and QoL and that it can be cost-effective [22,24,25]. However, the generalizability of these results is hindered by high heterogeneity in study end points and designs and poor quality of evidence [26-28]. Moreover, these results are often limited to a single disease management or monitoring domain (eg, medication adherence [29]), but asthma is a multifaceted disease with variable manifestations influenced by asthma severity, the level of adequate disease management, and the influence of (environmental) triggers [2,30]. There is limited scientific evidence that provides insights into the combination of monitoring parameters and interventional tools to predict early signs of asthma deterioration in a timely manner [31,32]. A recent study showed that remote patient monitoring may identify cues and causes of asthma control deterioration at home and help provide insights into patterns of asthma [33]. Furthermore, another study showed that teleconsultation and remote patient monitoring allows patients and caregivers to rapidly regain asthma control through timely and targeted medical anticipation, thereby progressing from reactive to proactive therapy and preventing asthma exacerbation [34].

The research gap, therefore, lies in the evaluation of pediatric asthma eHealth strategies consisting of a multidomain remote patient monitoring and teleconsultation approach while using a high-quality research design with relevant clinical end points on health care utilization, asthma outcomes, and QoL [26].

Objectives

In this study, called Ambulatory Pediatric Asthma Care (ALPACA), we will investigate an eHealth intervention for pediatric asthma care, in which multidomain, objective remote patient monitoring (ie, lung function, therapy adherence, and oxygen saturation) and teleconsultation (ie, web-based app to chat with HCPs, symptom questionnaires, and share videos) are integrated into clinical care and the patients' daily lives for 3 months.

The main study objective is to investigate whether children with asthma who use this eHealth intervention have reduced asthma health care utilization and costs compared to a control group that receives standard care for 3 months.

We will investigate the effects of this eHealth intervention on asthma outcomes (ie, asthma control, lung function, and the number of exacerbations), therapy adherence, self-management, and QoL after the intervention period of 3 months and at the 3-month follow-up. Overall use, acceptance, and satisfaction will be evaluated as well.

To enable further improvement of pediatric eHealth asthma care, we will exploratively investigate possible relations between objective home-monitoring parameters and asthma outcomes, the relation between self-reported dyspnea and home-measured lung function, and possible early signals in the preluding period before an asthma exacerbation. Moreover, we will explore the contribution of different eHealth intervention elements to asthma outcomes, patient-reported outcomes, and decision-making and identify patient characteristics of participants with successful eHealth care outcomes, such as health care utilization and adherence.

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Hypothesis

Based on the recent literature [22] and results from previous studies [33-35], we hypothesize that over 3 months, compared to standard care, the ALPACA eHealth intervention will lead to a significant reduction in health care utilization and costs with at least equal asthma outcomes and QoL.

Methods

Study Design

The ALPACA study is a prospective 2-arm randomized controlled effectiveness trial of an eHealth intervention in pediatric patients with asthma, which builds on a previous eHealth feasibility trial [34]. Participants will be randomized to either eHealth care (ie, intervention group) or standard care (ie, control group). During the 3-month follow-up, all patients will receive standard care and blinded observational home monitoring to evaluate the sustained effects of eHealth compared to the control group. The study protocol was designed in accordance with the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines (Table 1) [36].

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Table 1. Schematic SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) schedule of enrollment, interventions, and assessments.

Time point	Study period					
	Enrollment	Allocation/first visit	Postallocation			Closeout/end visit
	$-t_1$	t_0	t_1 Intervention period: 3 months	t_2 middle visit	t_3 follow-up period: 3 months	t_e
Enrollment						
Eligibility screen	✓					
Informed consent	✓					
Instruction and installment eHealth		✓				
Allocation		✓				
Interventions						
eHealth care (the Engage web portal, spirometry, pulse oximetry, smart inhaler)			✓(A[a])			
Standard care + observational monitoring (spirometry, pulse oximetry, smart inhaler)			✓(B[a])		✓	
Observational monitoring (cough sensor, air sensor, sleep monitor)			✓		✓	
Assessments						
Baseline variables (age, gender, BMI, *z* score, GINA[b] medication step, allergic rhinitis, asthma-related medical history, and baseline spirometry, such as FEV1[c] and FVC[d]	✓	✓				
Medical utilization data Number of visits (planned/ emergency/hospital admissions), diagnostic tests, telephonic/internet consultations, total health care costs			✓		✓	
Questionnaire evaluations: health literacy (HLS[e]), asthma control (C-ACT[f]), quality of life (PAQLQ[g] and EQ-5D-Y), self-management (PAM-13[h])		✓		✓		✓
Quality of care (CSQ[i])				✓		✓
Monitoring data: medication use, sleep, nocturnal heart/respiratory rate, nocturnal coughing/ wheezing, air quality, lung function, and oxygen saturation			✓		✓	
Intervention data: intervention use logs, and nebulizer use			✓(A[a])			
eHealth–specific evaluations: system usability (SUS[j]), technology acceptance (TAM[k]), and interview				✓(A[a])		

[a]Depending on the randomization. Group A receives eHealth care, and group B receives standard care within the intervention period (t_1).

[b]GINA: Global Initiative for Asthma.

[c]FEV1: forced expiratory volume.

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[d]FVC: forced vital capacity.
[e]HLS: Health Literacy Survey.
[f]C-ACT: Childhood Asthma Control Test.
[g]PAQLQ: Pediatric Asthma Quality of Life Questionnaire.
[h]PAM-13: 13- Item Patient Activation Measure.
[i]CSQ: Client Satisfaction Questionnaire.
[j]SUS: System Usability Scale.
[k]TAM: Technology Acceptance Model.

Ethics Approval

This study protocol was approved by the Medical Research Ethics Committees United (NL74559.100.21) and registered in ClinicalTrials.gov (NCT05517096). The data handling and storage will comply with the European Union (EU) General Data Protection Regulation (GDPR).

Study Setting and Eligibility Criteria

A total of 40 children with moderate-to-severe pediatrician-diagnosed asthma between 4 and 11 years of age will be recruited from the Medisch Spectrum Twente (MST) hospital in Enschede, the Netherlands. Pediatrician-diagnosed asthma includes confirmation of asthma diagnosis with a positive reversibility or challenge test [2]. Children are classified as having moderate or severe asthma if they meet one of the criteria shown in Table 2. Children with comorbid chronic diseases, previous asthma eHealth care intervention trial experiences [34], or children/parents with an inability to understand or speak Dutch are not eligible to participate. Additionally, children that do not live for more than 80% at the same address or those who do not have a stable Wi-Fi connection at home are excluded from participation.

Participants will be recruited from the pediatric department of MST using consecutive sampling, which is expected to take 40 weeks. A study flyer will be displayed in the pediatric ward and distributed among pediatric patients with asthma after an outpatient visit. Patients who indicate that they may be contacted will be contacted after 1 week, but patients may also contact the researchers themselves for further verbal and written study information. Offline written informed consent from parents will be obtained prior to participation in this study.

Table 2. Criteria for classification as moderate or severe asthma.

Condition	Moderate asthma	Severe asthma
Medication	GINA[a] step 3/4 or uncontrolled (C-ACT[b]<20) in GINA step 2 [2]	Step 5 or uncontrolled (C-ACT<20) despite medium to high-dose ICS[c]-LABA[d] in step 4
Recent exacerbation (<3 months) despite controller medication	Needing a salbutamol regimen of oral cortical steroid therapy	Leading to a hospital admission
Bronchial hyperreactivity assessed with an exercise challenge test in cold air [37,38]	Between 25% and 50% decrease in FEV1[e] [39]	>50% decrease in FEV1 [39]

[a]GINA: Global Initiative for Asthma.
[b]C-ACT: Childhood Asthma Control Test.
[c]ICS: inhaled corticosteroid.
[d]LABA: long-acting beta2-agonist.
[e]FEV1: forced expiratory volume.

Randomization and Blinding

Patients will be randomized to either eHealth care (intervention group) or standard care (control group) during the intervention period (t_1) by independent block randomization at the first home visit. The electronic data capture (EDC) software Castor (Castor) will allocate the participants using stratified block randomization with multiple block sizes (2, 4, and 6) into either group A or group B with an allocation ratio of 1:1 [40]. Castor randomly mixes these block sizes and hides the block size from the executor, which guarantees concealed allocation [40]. Randomization will be stratified on the number of hospital visits concerning asthma in the past 6 months (using 4 strata: 0-1 visit, 2-3 visits, 4-5 visits, or 6 or more visits), as it is known that previous exacerbations and health care utilization are risk factors for future exacerbations [2,41]. From this point, the blinding will be broken as the researchers, HCPs, and patients will need to know whether they should prepare for, provide, or receive eHealth care, respectively.

Intervention

The eHealth care intervention, consisting of remote patient monitoring and teleconsultation, was designed to detect loss of asthma control timely and accurately in daily life, increase awareness about the severity of asthma symptoms, and improve the safety of care for both physicians and patients by using objective measurements as the basis for shared decision-making. The technologies that are used for this eHealth care are a web-based patient portal, remote monitoring devices, and home-nebulizer therapy. This intervention was designed based on previous work on multidomain monitoring [33] and clinically implemented eHealth care [34].

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eHealth Technologies

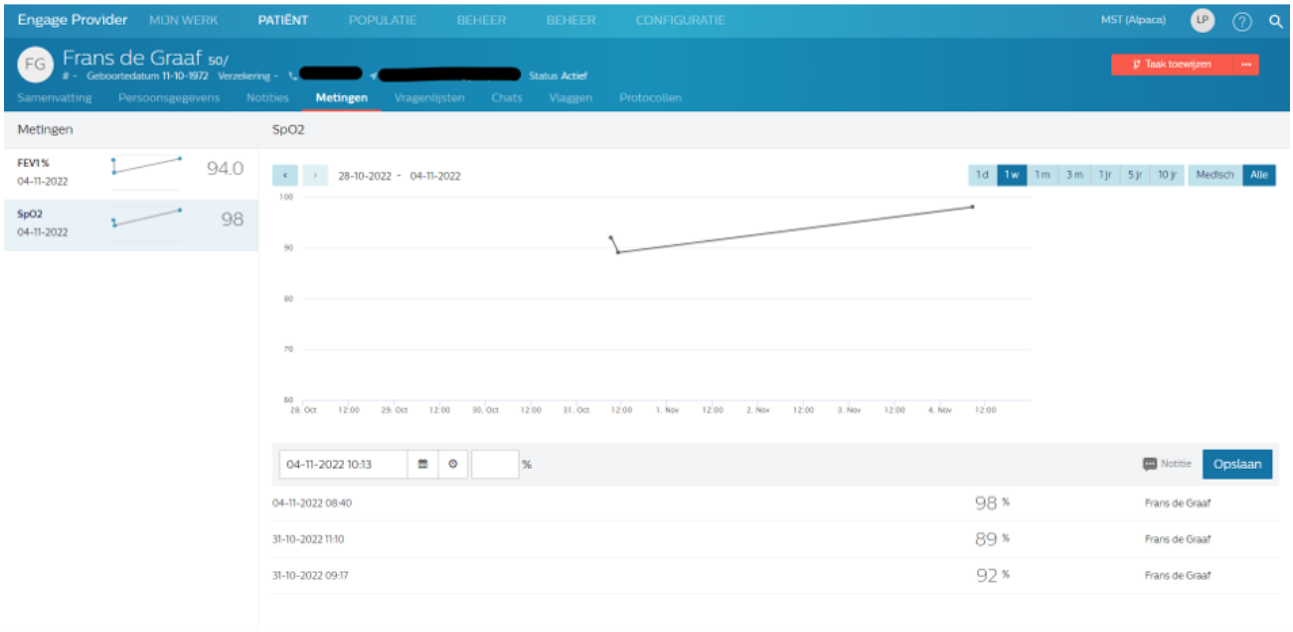
Web-Based Patient Platform

For the eHealth care, component a digital platform called Engage will be used that allows HCPs and patients to collaborate by facilitating web-based communication, displaying home measurements and questionnaire data, and allowing HCPs to share educational content. The configuration of the patient platform was specifically developed for this study in collaboration with the HCPs using the elements of the customizable Philips VitalHealth Engage platform (Royal Philips). This is a certified platform according to the European Medical Device Regulation; it is Conformité Européenne (CE) certified, classified as a class IIa medical device, and has been used in several clinical trials.

For patients, the Engage platform involves a personal page designed to provide children/parents the opportunity to unobtrusively share a request for help and integrate time- and event-based repeated measures or diary entries [42]. The page includes a chat function to allow the children/parents and HCPs to communicate in real time or according to their availability and wishes. The participants also have the option to share photos, sound recordings, or video files with the HCP (eg, to aid in the clarification of symptoms). Participants can enter their spirometry and oxygen saturation (SpO_2) measurements into the platform. Additionally, participants will be requested to fill in the Childhood Asthma Control (C-ACT) questionnaire on their page weekly.

For HCPs, the platform provides access to a dashboard for each patient, which displays trends of the measurements and allows access to details of measurements and questionnaires (Figure 1).

Figure 1. Example of health care professional (HCP) dashboard for lung function and oxygen saturation measurement of a specific patient.

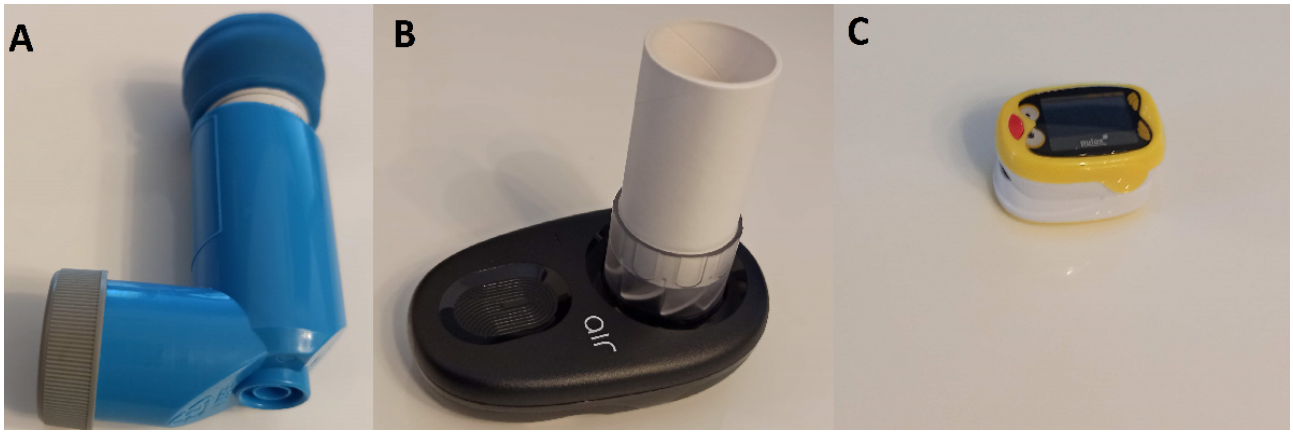


Remote Monitoring Devices

Our study combines several remote monitoring devices to actively monitor the participants in the intervention group during the eHealth care component. A total of 3 interventional monitoring devices, FindAir ONE smart inhaler (FindAir Sp), NuvoAir Air Next spirometer (NuvoAir AB), and Pulox PO-210B pulse oximeter (Novidion Gmbh; Figure 2), as well as a smartphone, will be provided to the children and their parents. Data reports will be shared by the participant through the Engage platform and automatically stored and accessible for HCPs through web-based cloud storage.

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Figure 2. Interventional monitoring devices: from left to right: A) FindAir ONE smart inhaler to track rescue use and controller adherence. B) NuvoAir Air Next spirometer to track lung function. C) Pulox PO-210B pulse oximeter to monitor oxygen saturation during exacerbation.



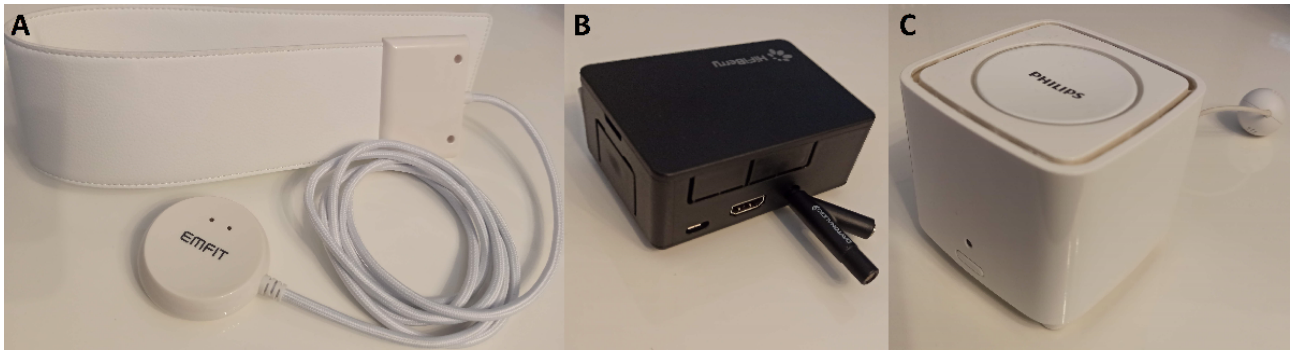
The FindAir ONE is a smart inhaler cap that will be placed on top of metered dose inhalers of the participants. It will always be used in combination with valved holding chambers. The sensor continuously collects data on the date and timestamps of inhalation, which is automatically synced and can be assessed in real time by both the patient and HCP on the FindAir platform.

NuvoAir Air Next is a handheld spirometer designed for home monitoring of lung function, with a built-in temperature sensor to compensate for the flow and volume for the body temperature pressure saturated correction [43]. This measurement will be performed twice per week or upon indication of the HCPs or the participants themselves during symptoms.

The Pulox PO-210B is a children's edition of SpO_2 pulse oximeter. It will be used offline as needed within the intended use for clinical reasons, in case of asthma exacerbations to monitor SpO_2, and if the lung function measurement quality is poor.

In addition, and not part of the intervention, 3 investigational devices, namely, an Emfit QS+ACTIVE sleep monitor (Emfit Ltd), a Philips cough monitor, and a Philips Snifferbee air sensor (Figure 3), will exclusively be used for observational research purposes in both the intervention and standard care group and follow-up of this study. The observational data of the investigational devices will therefore be stored in the cloud (Emfit QS platform and Philips platform). The data will not be shown to the HCPs and patients and only be used to investigate possible relations between objective home monitoring parameters and asthma outcomes.

Figure 3. Investigational observational monitoring devices: from left to right: A) Emfit QS+ACTIVE ballistography sleep sensor to track sleep. B) Philips cough and wheeze monitor to track respiratory sounds during sleep. C) Philips Snifferbee air sensor to track air quality in participants' bedrooms.



The Emfit QS+ACTIVE is a commercially available contactless sleep monitor that can provide a detailed description of sleep quality using ballistography [9]. The sensor is installed under the mattress to monitor activity, heart rate, and respiration rate at night and has been validated and previously used for sleep studies in both adults and children [44-46]. The device is CE marked and will be used for its intended use.

The Philips cough monitor is a device intended to store and transmit respiratory sound features and snippets (1 second), which are measured by the microphone in the device. The device will be placed next to the bedside to monitor nocturnal coughing and wheezing.

Snifferbee is Philips' air quality monitor prototype. It consists of multiple sensors to detect air quality and identify triggers for asthmatic reactions. Snifferbee can measure particles in the room air of 2.5 µm (optical scattering sensor), along with temperature, humidity, and carbon dioxide levels (with a nondispersive infrared sensor). The SnifferBee will be used within its intended use to measure air quality in the participants' bedrooms.

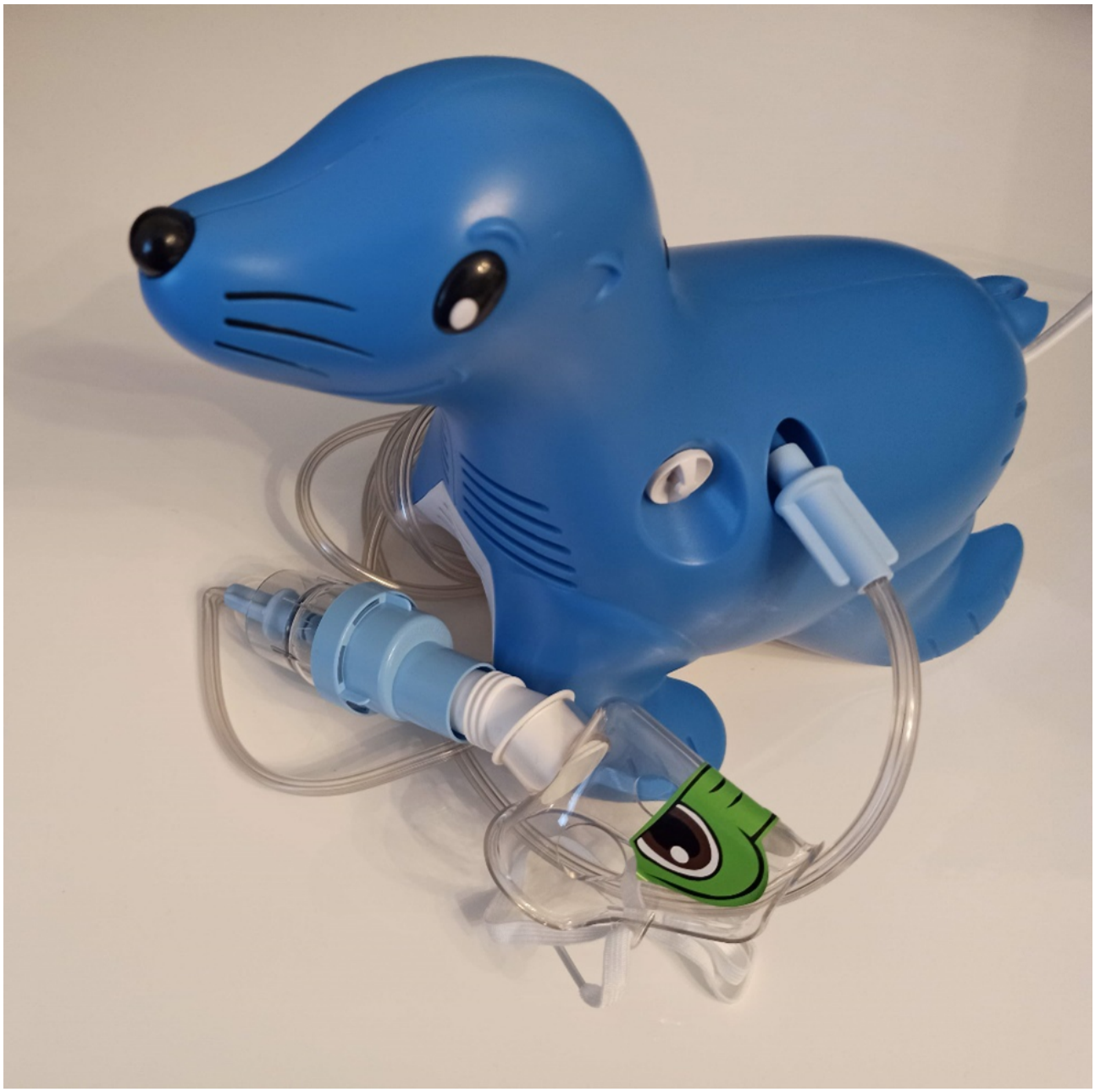
Home Nebulizer Therapy

All participants will receive a Philips Sami the Seal nebulizer for the intervention phase and will be trained and supervised for correct use and nebulizer hygiene (Figure 4) [47]. Nebulizing

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therapy is often started when bronchodilator inhalers do not have the expected effect anymore or in the hospital during an acute exacerbation. During the intervention phase of this study, nebulizing therapy may be started at home under the supervision of an experienced HCP (via video call). Criteria for starting nebulizing therapy under supervision at home during the intervention period are (1) SpO_2 ≤94% without significant effect of the reliever inhaler medication (as recommended by the Dutch Pediatricians Association) [48]; (2) reproducible lung functions <50% predicted, without significant effect of the reliever inhaler medication (defined as an increase of at least 10% and increase to lung function above 50% predicted); or (3) on the advice of the pulmonary pediatrician.

Figure 4. Philips Sami the Seal home nebulizer.



eHealth Care Intervention

Intervention Group

Participants will be in contact with the HCPs via the web-based Philips Engage platform (Figure 1). HCPs will provide care according to current care standards [2,48] while applying a state-of-the-art web-based care pathway [34]. Within this care pathway, HCPs aim to build up the confidence of the participants and their parents by enhancing their understanding and self-management of the disease via feedback on the web-based communication platform substantiated with monitoring data during real-life events. The key focus will be on important asthma management issues, such as symptom perception, therapy adherence, inhalation techniques, trigger control, and acute asthma management [2]. Participants will be repeatedly and pragmatically supported and coached using elements from behavioral theories (eg, self-monitoring, goal setting, immediate feedback, contingency management) and be involved in shared

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management to progress on an individual pace toward self-assessment and self-management [49].

During the eHealth intervention, HCPs (ie, nurse practitioners, a technical physician, and a pediatric pulmonologist) will be notified in real time of new communications on the Engage platform by push notifications and will respond at least within 1 workday to allow for timely anticipation. Participants will be instructed to not wait for communications in the case of an emergency and to proceed to emergency care. Moreover, once a week, the HCPs will have a multidisciplinary meeting to discuss data trends and patient communications to adjust the individual treatment strategies as necessary. HCPs will always have the option to invite patients for a hospital visit if this is needed to fulfill the current care standards [2,48].

Standard Care Control Group

Participants in the control group will receive standard care and therefore will not receive the home nebulizer. The spirometer, pulse oximeter, and smart inhalers will be provided but only used for observational monitoring in the control group, similar to the investigational devices (cough monitor, air quality sensor, and sleep monitor). The control group will be able to use the Engage portal to share measurements and questionnaire data, but they will not receive any feedback or data interpretation. This same protocol holds for the 3-month follow-up period to be able to assess differences in the primary and secondary outcome parameters after cessation of the intervention.

Outcome Measures

Demographic characteristics (age, gender, medication use, other medication use, allergy due to aeroallergens, eczema, doing sports, and smoking behavior at home) will be retrieved from electronic patient records.

The primary outcome variables are health care utilization and costs. All health care activities (ie, hospital admissions, outpatient visits, emergency visits, diagnostic activities, etc) will be labeled using the Dutch health care registration system of the Dutch Healthcare Authority. The accompanying health care costs will be calculated using activity-based costing [50]. Furthermore, the specific eHealth care costs will be calculated using bottom-up gross costing, consisting, for example, of the working hours of the HCPs and the depreciation costs of the monitoring devices [50].

Multimedia Appendix 1 contains the description and analysis of other outcome variables to investigate the effects of the eHealth intervention, which will enable research that can further improve pediatric eHealth asthma care.

All data will be handled according to the EU GDPR and the Dutch Act on the Implementation of the GDPR and securely stored in the Castor EDC system.

Sample Size

Previous data from an eHealth clinical feasibility study (N=30) using a comparable intervention within the same patient population revealed a reduction in health care utilization of 80% [34]. This data showed an average reduction in the number of outpatient consultations from 3.9 to 0.7 (SD 1.8) per patient per half year.

A power simulation was performed for a Mann-Whitney-Wilcoxon 2-sided test. The health care utilization was assumed to be Poisson distributed with means according to the clinical feasibility study. For the control group, the Poisson rate was equated to the historical data of the pilot divided by 2 to account for the study durations. The intervention group's rate was taken to be the postdata of the feasibility study divided by 2. As the ALPACA study makes use of the intention-to-treat principle, noncompliance to the intervention was included in the simulation. The number of nonadherent participants was random in the simulation according to a binomial distribution (similar to the clinical feasibility study data, with 3 out of 33 participants). This was used to calculate the control group rate, which is a conservative estimate of no benefit from the intervention. Together with the assumption of an Alpha Type 1 error of 0.05, the sample size calculation results in 36 (18 intervention and 18 controls), with a power of 97.1% for the primary outcome and 80% for secondary follow-up effects (assuming a lasting effect of 80%). Accounting for dropouts (n=4), we would need to include 40 children.

Study Procedures

After enrollment ($-t_1$), an HCP will perform a home visit (t_0) to allocate the participant to the intervention or control group, install the monitoring devices, and carefully instruct participants about the use of the eHealth platform and monitoring devices. All oral instructions will be complemented with written and digital instruction flyers to ensure that all the instructed information can be retrieved afterward. A second home visit (t_2) is planned after the intervention period to check all devices. Moreover, an in-person semistructured interview will be held to evaluate the user experience of the interventional and investigational technology together with filling in the feasibility and acceptance questionnaires (Multimedia Appendix 1). A third, final home visit (t_e) will be held at the end of the study after follow-up (t_3) to retrieve all monitoring devices and evaluate this period via the evaluation questionnaires (Multimedia Appendix 1).

Data and Statistical Analyses

Descriptive statistics will be used to examine all continuous outcome measures expressed in mean and SD for normally distributed variables and with median and IQR for nonnormal distributed variables. Univariate analyses will be performed with SPSS software (version 22.0; IBM Corp). The homogeneity of variances will be verified with the Levene test. Histogram plots and the Shapiro-Wilk test will be used to determine whether the variables are normally distributed among the groups. A *t* test (or nonparametric Mann-Whitney U test) will be used to compare the primary outcomes between eHealth care and standard care, and $P \leq .05$ will be considered significant. The analysis will be performed according to the intention-to-treat principle [51], and missing data will be handled with pairwise deletion. An interim analysis will be conducted after half the participants are done with the intervention. In case the interim

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analysis reveals a significant increase in health care utilization in the intervention group, this study will be prematurely ended.

Results

This study was approved by the Medical Research Ethics Committees United on August 11, 2022, and by the institutional review boards of Philips on August 8, 2022, and MST on January 11, 2023.

The expected timeline of the ALPACA study is 15 months, including an enrollment period of 9 months and a study duration of 6 months. As of August 2023, we expect to start enrollment, which will make data collection compete in May 2024. The results are expected shortly afterward in July 2024.

Discussion

Expected Knowledge Contribution

Childhood asthma is imposing a great financial burden on the pediatric health care system, but a substantial part of the costs may be preventable by timely and adequate medical anticipation using eHealth. Therefore, In the ALPACA study, we will investigate whether children with asthma who use an eHealth intervention have reduced asthma health care utilization and costs compared to the control group. This study protocol applies a combination of relevant monitoring domains of pediatric asthma based on the recent literature [22,33,34] and guidelines [2]. Primary validated monitoring devices will be combined with web-based communication between HCPs and patients to enable pediatricians to make well-informed and substantiated treatment decisions and allow targeted support for optimal disease management. This randomized controlled effectiveness trial design captures an extensive prospective longitudinal home monitoring data set, which allows the evaluation of the effect of eHealth pediatric asthma care on health care utilization, asthma outcomes, and QoL, including additional information about longer-lasting effects after cessation of eHealth care. Moreover, the holistic eHealth monitoring of physiological, environmental, and disease management data allows a comprehensive set of secondary analyses for insight into pediatric asthma. This study may therefore contribute to the existing knowledge of eHealth applications in secondary health care and to a better understanding of the value of home-monitoring diagnostics for pediatric asthma.

Strengths and Limitations

This study is a follow-up of a quasi-experimental eHealth evaluation study [34]. Therefore, the involved HCPs of the hospital are experienced with using eHealth technology, and the care pathway is already aligned to deliver remote care in a safe and efficient way, which are commonly the most important barriers to successful eHealth evaluation trials [52]. Moreover, improvements based on prior eHealth trials within our hospital are integrated into this protocol to maximize its feasibility.

Another strength of the ALPACA study is the fact that it uses a set of home-monitoring devices chosen to be as unobtrusive as possible to minimize the daily living burden of the participating children and their parents. The current literature shows an increase in the development and evaluation of these unobtrusive sensing systems, enabling adherent long-term use for monitoring chronic disease course and management [53]. Additionally, this study uses a communication platform to provide children and their parents the opportunity to unobtrusively share a request for help or advice and integrate time- and event-based repeated home monitoring measurements or diary entries to obtain valid, real-life self-reports [42].

Objectified feedback to participants in eHealth care about inhalation technique (via videos) and therapy adherence (via smart inhaler data) could be a great addition to the current asthma care for children [54], as inhalation technique and therapy adherence appear to be poor but often remain “the elephant in the room” and stay unaddressed [55-58]. Automated synchronization of the mobile device and the inhaler add-ons provides a burden-free way to increase awareness of therapy adherence among children with asthma and their parents and provides HCPs with the necessary information to make informed medication adjustments [34,59].

Since a critical evaluation of financial cost-effectiveness is lacking in the literature for electronic health tools in pediatric asthma [60], the design of the ALPACA study is favored, as all direct hospital health care utilization is registered in combination with asthma outcomes. This gives us the opportunity to perform a thorough cost analysis of the care transformation to eHealth care. Moreover, the follow-up period of this study allows us to investigate whether the effect may endure when eHealth is ceased, providing interesting information on the possible long-term benefits of eHealth care.

A limiting factor in eHealth studies may be the timing of inclusion, as the asthma outcomes are subject to the episodic variation of asthma (viral infection, weather conditions, and pollen seasons) and COVID-19 regulations (lockdowns versus free contact) [2,61]. This effect is canceled to a great extent by the randomized design of this study. However, this study may be limited in the secondary pre-post evaluation of the different eHealth intervention elements. In addition, the worldwide generalizability of this study may be limited based on the eligibility criteria (children who live >80% of the time at the same home and have a stable WiFi connection).

Previous research has shown that the circadian rhythm influences the severity of asthma symptoms [62,63]. Symptoms tend to be worse during the night and gradually improve during the day. To avoid any bias of this circadian rhythm on the spirometry measurements, we will instruct all participants to perform the standard monitoring measurements at approximately equal times prior to dinner.

Implications for Pediatric Asthma Health Care

The results of the ALPACA study may benefit future pediatric asthma health care in several ways. Researchers and the technology industry will be able to tease out relevant intervention elements that can act as digital markers for composing effective interventions, which can guide them in appropriate eHealth development [35]. Moreover, hypothesized health care utilization reductions provide positive incentives and increase the sense of urgency among stakeholders to take

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joint action toward scalable eHealth solutions [64]. Additionally, HCPs, health care institutions, and policy makers may use the ALPACA results to make informed decisions to steer toward a new, high-quality efficient pediatric asthma care pathway that goes beyond current traditional planned follow-up care and evolves toward proactive and targeted care, wherein the patient is actively involved via shared decision-making and self-management while being safeguarded by home-monitoring technology.

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Conflicts of Interest

NW is an employee of Phillips Research.

Multimedia Appendix 1
Outcome measures and statistical analysis of the secondary parameters.
[DOCX File , 277 KB - resprot_v12i1e45585_app1.docx]

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Abbreviations

ALPACA: Ambulatory Pediatric Asthma Care
C-ACT: Childhood Asthma Control Test
CE: Conformité Européenne
EU: European Union
GDPR: General Data Protection Regulation
HCP: health care professional
MST: Medisch Spectrum Twente
QoL: quality of life
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
SpO2: oxygen saturation

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Protocol

Adaptive P300-Based Brain-Computer Interface for Attention Training: Protocol for a Randomized Controlled Trial

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Abstract

Background: The number of people with cognitive deficits and diseases, such as stroke, dementia, or attention-deficit/hyperactivity disorder, is rising due to an aging, or in the case of attention-deficit/hyperactivity disorder, a growing population. Neurofeedback training using brain-computer interfaces is emerging as a means of easy-to-use and noninvasive cognitive training and rehabilitation. A novel application of neurofeedback training using a P300-based brain-computer interface has previously shown potential to improve attention in healthy adults.

Objective: This study aims to accelerate attention training using iterative learning control to optimize the task difficulty in an adaptive P300 speller task. Furthermore, we hope to replicate the results of a previous study using a P300 speller for attention training, as a benchmark comparison. In addition, the effectiveness of personalizing the task difficulty during training will be compared to a nonpersonalized task difficulty adaptation.

Methods: In this single-blind, parallel, 3-arm randomized controlled trial, 45 healthy adults will be recruited and randomly assigned to the experimental group or 1 of 2 control groups. This study involves a single training session, where participants receive neurofeedback training through a P300 speller task. During this training, the task's difficulty is progressively increased, which makes it more difficult for the participants to maintain their performance. This encourages the participants to improve their focus. Task difficulty is either adapted based on the participants' performance (in the experimental group and control group 1) or chosen randomly (in control group 2). Changes in brain patterns before and after training will be analyzed to study the effectiveness of the different approaches. Participants will complete a random dot motion task before and after the training so that any transfer effects of the training to other cognitive tasks can be evaluated. Questionnaires will be used to estimate the participants' fatigue and compare the perceived workload of the training between groups.

Results: This study has been approved by the Maynooth University Ethics Committee (BSRESC-2022-2474456) and is registered on ClinicalTrials.gov (NCT05576649). Participant recruitment and data collection began in October 2022, and we expect to publish the results in 2023.

Conclusions: This study aims to accelerate attention training using iterative learning control in an adaptive P300 speller task, making it a more attractive training option for individuals with cognitive deficits due to its ease of use and speed. The successful replication of the results from the previous study, which used a P300 speller for attention training, would provide further evidence to support the effectiveness of this training tool.

Trial Registration: ClinicalTrials.gov NCT05576649; https://clinicaltrials.gov/ct2/show/NCT05576649

International Registered Report Identifier (IRRID): DERR1-10.2196/46135

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KEYWORDS

ADHD; attention; BCI; brain-computer interface; cognitive deficit; cognitive disease; cognitive training; dementia; EEG; electroencephalography; ERP; event-related potential; neurodegeneration; neurofeedback training; P300 speller; stroke

Introduction

Background

Cognition includes many facets of complex processing functions, such as, and not limited to, attention, the acquirement of knowledge, memory, decision-making, and comprehension [1]. Cognitive deficits often present as symptoms in many underlying neurological disorders.

In the aging population, cognitive decline is common, however, can be accelerated by neurodegenerative diseases, such as dementia, or through brain trauma and stroke. Furthermore, the increased prevalence of cognitive deficits is apparent in every age demographic. As a result of the COVID-19 pandemic, many long-term neurological effects have been identified in patients who have experienced COVID-19 infection. In a study published by Hartung et al [2], it was identified that of a sample group of 969 patients, approximately 26% of patients experience mild cognitive impairment in the aftermath of the infection. Other cognitive diseases, such as attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorder, are common neurocognitive disorders that are identified in children. All these diseases feature a profound effect on the quality of life of the individual because of impairments in cognition [3-5].

The common treatments for these conditions are pharmacological interventions or therapeutic interventions. However, these disorders have no known cure, and rather, treatments are created to alleviate the symptoms of the disorder.

Pharmacological interventions, such as the use of psychostimulant medicines, have been rendered highly effective in treating symptoms of cognitive deficits. However, they have been criticized for the adverse effects which can occur due to their use [6]. Methylphenidate and lisdexamfetamine are 2 common psychostimulants used in the treatment of a variety of cognitive disorders, including ADHD. Both stimulants have shown to be efficacious in the treatment of the symptoms associated with the disorder but can result in insomnia, decreased appetite, headaches, and abdominal pain [7].

Cognitive disorders and their interventions, both pharmacological and nonpharmacological, can be highly costly, not only for the individual but also for health care systems globally [8,9]. This can cause great distress for individuals, as diagnosis and treatment for cognitive disorders can become inaccessible, as well as immense pressure on health care systems due to the increasing burden of these diseases. For these reasons, there is a clear need for low-cost and effective treatments for neurocognitive disorders.

Neurofeedback Training

Electroencephalographic neurofeedback (EEG-NFB) is a type of brain-computer interface (BCI), which provides real-time feedback to the individual based on neural signals of interest as measured by electroencephalography (EEG), thus training the individual to self-regulate their brain activity [10]. EEG-NFB was introduced in the 1960s independently by Nowlis and Kamiya [11], and Sterman et al [12], and was commonly referred to as EEG biofeedback. Nowlis and Kamiya [11] presented data to confirm that patients could control their brain activity as a result of engaging with rewards using an EEG measuring device. Sterman et al [12] discovered through training cats that they too could modulate brain wave activity. As a result of these discoveries, a variety of treatments have been developed to alleviate symptoms of many cognitive disorders, including ADHD, schizophrenia, and many others [13-15].

Due to criticism relating to the efficacy of EEG-NFB in the 1970s, there was a decline in research on the use of EEG-NFB [16]. However, in recent years there has been a reemergence of the use of EEG-NFB globally in many research and clinical settings [10].

One example of a novel EEG-NFB is the adaptive P300 speller for attention training by Arvaneh et al [17]. The P300 speller was first introduced by Farwell and Donchin [18] in 1988 as a tool for patients who could not communicate, such as in the case of patients who have “locked-in” syndrome. In the speller, a matrix of symbols (eg, letters and numbers) is presented to the user. Each row and column in the matrix of symbols is highlighted or flashed in random order. When the user only focuses on the flashes of a target symbol and ignores the other flashes, the BCI can select this target symbol by identifying the row and column that elicited a P300 wave, thus allowing the user to spell words with their mind. In this process, each row and column are flashed several times, so that the signal-to-noise ratio (SNR) of the EEG signals can be increased by averaging. Usually, this number of flashes per row and column is fixed to allow the user to spell words sufficiently well in an acceptable amount of time. However, Arvaneh et al [17] progressively reduced the number of flashes in a training session based on the user’s performance to intentionally decrease the SNR. This makes it more difficult for the user to spell words correctly, thus encouraging them to improve their focus in order to maintain their performance. The researchers demonstrated that a single training session on healthy adults resulted in an increase in performance in a cognitive task, as well as an enhancement of event-related potentials (ERPs) [17].

This study intends to replicate the experiment by Arvaneh et al [17], comparing their adaptation of the number of flashes to a novel adaptation approach based on iterative learning control (ILC).

Framework of ILC

ILC is a type of control engineering that was introduced by Ukiyama [19] in the late 1970s and Arimoto et al [20] in the 1980s. ILC is applied to repetitive processes, where the same tracking task is repeated several times. Examples of traditional application areas of ILC are the control of pick-and-place industrial robots or semiconductor manufacturing [21]. ILC exploits the repetitiveness of processes such as these by learning

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from past experiences, thus reducing the tracking error over time, as well as adapting to small changes in the processes. An iterative learning controller is able to learn from past experiences by taking the control input and error of previous iterations into account when determining the control input for the next iteration. The typical framework for ILC is

$$u_{k+1}(\cdot)=f(e_{k+1}(\cdot),\ldots,e_{k-s}(\cdot),u_k(\cdot),\ldots,u_{k-r}(\cdot)), \textbf{(1)}$$

where k is the iteration index, u is the control input, and e is the tracking error. There are different ways to determine the function f in (1). The simplest ILC algorithm is Arimoto et al's [20] algorithm, where the next control input is equal to the control input plus the scaled error of the previous iteration, that is,

$$u_{k+1}(t)=u_k(t)+\gamma e_k(t+1), \textbf{(2)}$$

where t is discrete time, and γ is a scalar controller parameter. ILC algorithms generally take the form

$$u_{k+1}(t)=u_k(t)+Ke_k(t+1), \textbf{(3)}$$

where K is the so-called learning-gain operator, which is often based on a model of the system, such as the inverse-model ILC algorithm [22] or the Adjoint algorithm [23]. The algorithms described in (2) and (3) are so-called P-type ILC algorithms as they use the error from previous iterations. Algorithms that use the derivative of the error instead are known as D-type ILC [24].

While ILC was mostly used in industrial and manufacturing processes in its early days, it has found popularity in other application areas, such as stroke rehabilitation [23] or the control of exoskeletons [25] in more recent years.

Since rehabilitation and training, whether physical or cognitive, are inherently repetitive processes, where the task difficulty needs to change progressively, this application area lends itself nicely to the use of ILC.

Objectives

The primary objective of this study is to accelerate P300-based attention training by progressively and optimally adjusting the task difficulty in a training session to each individual using ILC. The proposed iterative learning controller, which determines the task difficulty based on previous performance and task difficulty level, will be compared to the adaptation algorithm used in a previous study by Arvaneh et al [17]. Thus, we will be able to analyze the replicability of Arvaneh et al's [17] study. A random task difficulty control group will also be used in this study to compare the training effects of personalized approaches with the training effects due to exposure to a range of nonpersonalized task difficulty levels.

While we expect the cognitive enhancements achieved during the training session to be similar among the groups, we expect the experimental group, where the task difficulty is determined by an iterative learning controller, to complete the training session more quickly than the other groups.

Methods

Study Design

In this single-blind, 3-arm randomized controlled trial with parallel-arm design, the effectiveness of different task difficulty adaptation approaches in a P300 speller task will be evaluated and compared. The study involves a single experimental session that lasts no longer than 2 hours (including setup). The experiments will be conducted in an electrically shielded, dark, and quiet room on the Maynooth University campus.

Recruitment

The participants for this study will be recruited from the staff and student community of Maynooth University through an open enrollment process. Study participants will be alerted to the study through advertisement flyers distributed throughout the Maynooth University campus and through email advertisements sent to staff and students.

Participants

The participants will be healthy individuals aged 18 years or older with no self-reported history of neurological or cognitive illness, and normal or corrected-to-normal vision. Interested participants who do not meet these criteria, have a negative reaction to the electroconductive gel, or who are illiterate will be excluded from the study.

Based on previous work using a P300-based BCI for attention training [17,26], a sample size of 45 participants (15 per group) was determined. Participant recruitment will continue until the sample size is reached. It is expected that around 50 participants will be recruited due to a 10% dropout rate.

Ethical Considerations

This study was approved by the Maynooth University Ethics Committee (BSRESC-2022-2474456) and is registered on ClinicalTrials (NCT05576649). Interested participants who meet the eligibility criteria and give informed consent to study participation, allowing the recording of their performance in the training session and their brain signals, as well as the use of the collected data for this study and future research, will be invited to conduct a patch test to mitigate the risk of allergic reactions to the electroconductive gel. Participants will be advised that they have the freedom to withdraw from the experiment at their discretion at any time throughout the course of the experiment and will not be compensated for their participation in the study. The data from this study will be irreversibly anonymized immediately upon collection.

Procedure

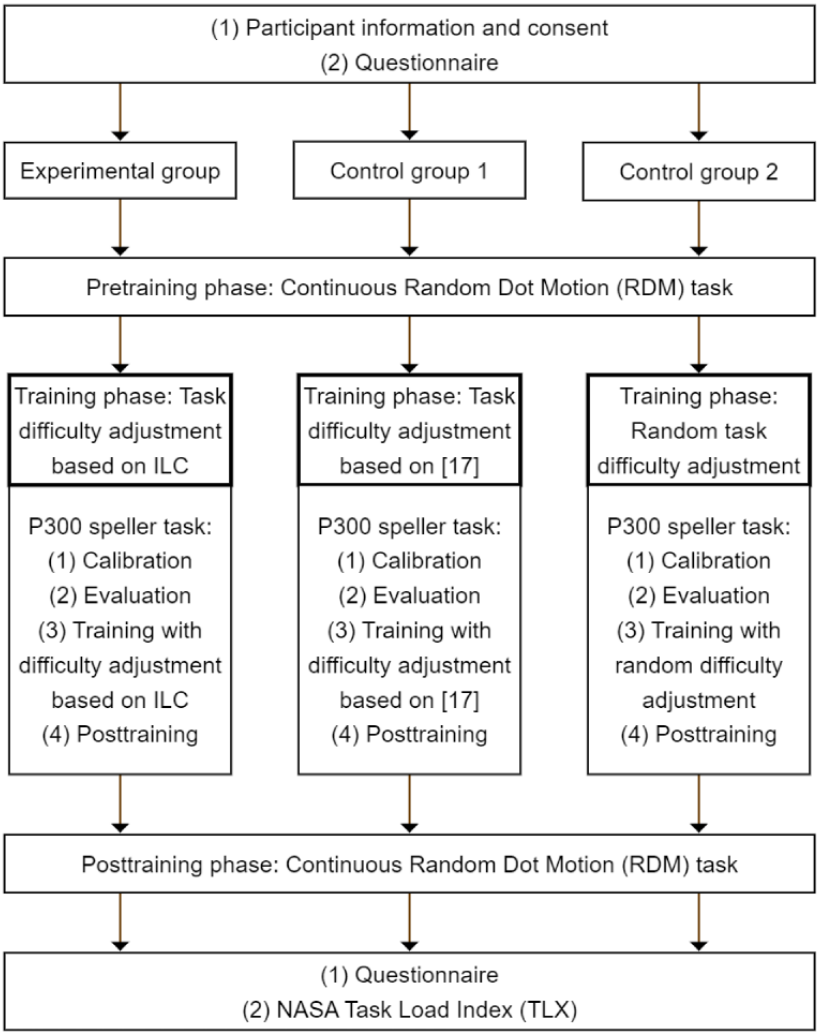
The experimental procedure of this study is based on previous work by Arvaneh et al [17]. An overview of the procedure can be found in Figure 1.

Participants will be asked to fill in a questionnaire at the beginning and end of the experiment. They will then complete a continuous random dot motion (RDM) task, which will serve as a baseline for their cognitive abilities. Afterward, participants will receive attention training using a P300 speller task, where the task difficulty in each run of the speller is either chosen

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randomly (control group 2) or adjusted to the participant's performance (control group 1 and experimental group). To analyze improvements in cognitive abilities, participants are asked to complete the RDM task again after the training.

Figure 1. Study procedure based on Arvaneh et al [17]. ILC: iterative learning control.



EEG Data Acquisition

Participants' EEG data will be recorded during the P300 speller training phase of the experiment. EEG data will be collected using the battery-operated ANT Neuro eego rt [27] with a 32-channel waveguard cap [28]. The sintered silver–silver chloride electrodes are located in standard 10-20 positions. Impedances will be maintained below 5 kΩ during recording.

The EEG signals will be acquired in the OpenViBE software [29] at a sampling rate of 500 Hz. All channels will be band-pass filtered (1-20 Hz) and down-sampled by a factor of 4 before further processing.

Offline analysis of the EEG data will be carried out in MATLAB [30] using the EEGLAB toolbox [31]. Since this study is a replication of Arvaneh et al's [17] study, the following offline analysis steps closely follow the steps described in the study. The continuous EEG signals will be rereferenced to Fz, band-pass filtered between 0.5 and 35 Hz and separated into baseline-corrected epochs of 150 milliseconds before the stimulus to 550 milliseconds post stimulus, where the 150 milliseconds prestimulus period is used as the baseline. Epochs with an amplitude of more than 75 µV or those with a voltage step of more than 150 µV within a 200-millisecond window will be excluded from analysis.

Tasks and Stimuli

Questionnaire

Participants will be asked to complete the same 10-point Likert scale questionnaire as in Arvaneh et al [17]. It consists of the four questions: (1) How tired are you now? (2) How alert do you feel? (3) How bored do you feel? (4) Do your eyes feel tired?

This questionnaire will be completed at the beginning and end of the experiment so that responses before and after training can be compared.

In addition, the NASA Task Load Index will be used at the end of the experiment to assess participants' perceived workload of the training [32].

RDM Task

The continuous RDM task is based on Arvaneh et al [17] and Kelly and O'Connell [33]. In this task, the participants will

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focus on moving dots on the screen, which transition from incoherent motion to coherent motion. During incoherent motion, all dots will continuously move in random directions, whereas in coherent motion, a significant fraction of the dots will move in one direction, either left or right. The participants will be asked to indicate the direction of the coherent motion by pressing the left or right arrow key once they are sure of the motion direction. In both the pre- and posttraining phases, the main task consists of 40 trials, where the coherence level, that is, the fraction of coherently moving dots, and the motion direction vary in each trial.

An average of 118 dots, with a size of 6×6 pixels each, are displayed in a circular aperture of 5° at a viewing distance of 70 cm, resulting in a dot density of approximately 10.8%. Each dot is black against a grey background. The dots are moving at a speed of 3.33°/second. The incoherent motion lasts for either 3.1, 4.2, or 5.7 seconds, and the coherent motion always lasts for 1.9 seconds. The coherence level is either 19% or 25%.

To allow participants to understand the task, a practice session will be carried out before the pretraining phase. The practice session consists of 3 blocks of 6 trials each. In the first block, the coherence levels are either 60% or 80%, reducing to 30% or 40% in the second block, and finally reaching 20% or 25% in the last block of the practice session. All other parameters of the task are the same as above. During the practice session, participants will receive verbal feedback on hits, misses, and false alarms.

The code for this task was developed in-house using PsychoPy [34] and the stimuli are presented on a 52.7-cm-wide LED monitor with a refresh rate of 60 Hz and a resolution of 1920×1080 pixels.

P300 Speller Task

Overview

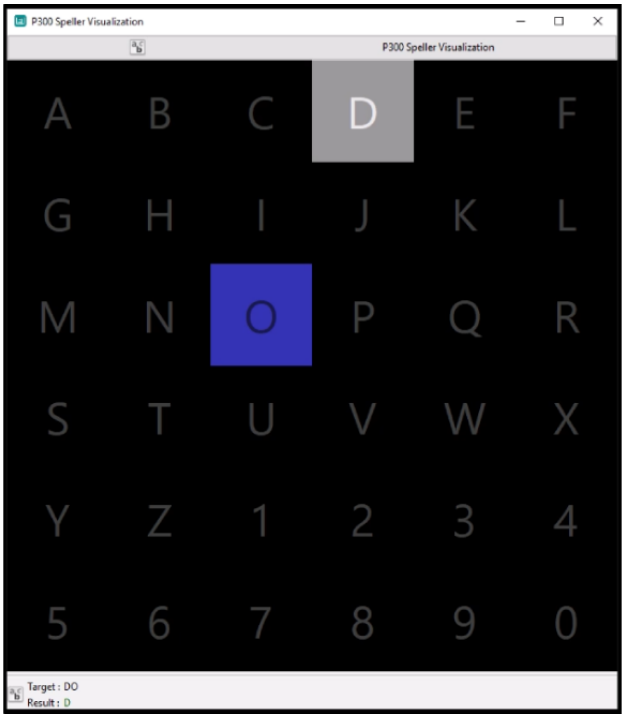
In this study, the P300 speller implementation in OpenViBE [29] is used. This P300 speller uses the xDAWN algorithm [35] to train a spatial filter that enhances the SNR of the P300 ERPs. This reduces the 32 EEG channels to 3 components, which are weighted combinations of all channels. A linear discriminant analysis classifier is used to distinguish target and nontarget trials. It should be noted that the row and column with the highest probability of belonging to the target class are chosen, even if that is below 50%. Both the spatial filter and classifier are trained for each participant using calibration data.

Figure 2 shows the 6 by 6 grid of letters and numbers that is displayed on the screen. The word to be copy-spelled and the identified symbols can be seen below the grid. If the identified symbol is the same as the target symbol, it will be displayed in green. If the identified symbol is in the same row or column as the target symbol, it will be displayed in orange and if it is wrong, it will be displayed in red.

Outside of the training phase, 12 flashes per row and column are used. Each flash lasts 55 milliseconds with an interflash interval of 117 milliseconds. Each target symbol is highlighted in blue for 6 seconds before the flashing begins.

In each run after the calibration phase, the spelling accuracy, that is, the fraction of symbols that were identified correctly, is calculated for all numbers of flashes between 1 and the actual number of flashes used.

Figure 2. OpenViBE [29] implementation of the P300 speller. The next target letter in the word “dog,” “o,” is currently highlighted in blue. The previous letter, “d,” was correctly identified by the speller and is therefore highlighted in grey. The target symbols are displayed below the grid of letters and numbers (“Target:”), and the previously identified symbols can be seen below the target (“Result:”).



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Calibration Phase

The calibration phase is used to collect training data for the spatial filter and classifier. The participants will complete 2 runs, where the words “the” and “quick” are copy-spelled without feedback. The recorded EEG signals from both runs are concatenated and then used to first train the xDAWN spatial filter before the linear discriminant analysis classifier is trained. Both target and nontarget trials are separated into epochs ranging from stimulus onset to 600 milliseconds poststimulus. The spatial filter is trained using the continuous EEG signals as well as the target epochs, whereas the classifier uses target and nontarget epochs for training.

Evaluation Phase

Once the spatial filter and classifier are trained, the participants will copy-spell the word “dog.” If at least 2 of the 3 letters are correctly identified by the P300 speller, the participant will move on to the training phase. Otherwise, the spatial filter and classifier will be retrained with the added EEG signals from the latest run. They will then copy-spell the word “fox.” If only 1 of the 3 letters is identified correctly, the participant will be removed from the study.

Training Phase

During the training phase, all participants will copy-spell the word “beautiful” for 5 runs. Ten flashes per row and column are used for the first run of the training phase, for all groups. The number of flashes in all subsequent runs is adapted randomly (control group 2) or based on the participants’ performance in the previous run (control group 1 and experimental group). The participants in all groups will receive feedback but will not be told why the number of flashes varies in each run.

The details of the task difficulty adaptation for each group are described below:

Control group 1: The adaptation algorithm in control group 1 is a replication of the work described in [17]. The number of flashes in each run, N_i, is the average of the minimum number of flashes needed to reach more than 66% spelling accuracy in the previous run, referred to as $N_{(i-1)66}$, and the actual number of flashes used in the previous run, N_{i-1}, that is,



where N_i is rounded to the nearest integer. If the spelling accuracy in the previous run was below 66%, then the number of flashes in the next run is increased by 1, that is,

$$N_i=N_{i-1}+1. \quad \textbf{(5)}$$

Control group 2: The task difficulty adaptation of control group 2 is not based on the participants’ performance. Instead, the number of flashes in each run is chosen at random between 1 and 10 flashes. Choosing the number of flashes in this way will expose the participants in control group 2 to varying task difficulties in an unpredictable way. This allows the authors to compare the personalized adaptation approaches of the other 2 groups to a nonadaptive difficulty adjustment approach under similar conditions. Using a constant task difficulty in this group would potentially lead to differences due to an easier average task difficulty [36] and reducing the number of flashes by the same amount each run would introduce predictability, which the other groups do not have.

Experimental group: In the experimental group, a P-type ILC controller is used to adapt the number of flashes in the next run, N_i, based on the number of flashes and error in the previous run, N_{i-1} and $e_{i-1}=1-J_{1(\,i-1)}$ (where J_1 is the spelling accuracy). The update law of the controller is

$$N_i=N_{i-1}+f(e_{i-1}), \quad \textbf{(6)}$$

where ε is a controller parameter and

$$f(e_{i-1})=2e_{i-1}-1. \quad \textbf{(7)}$$

Figure 3 shows $f(e_{i-1})$ against e_{i-1}. As can be seen, if only half of all symbols in the previous run were identified correctly, that is, 50% error, $f(e_{i-1})$ will be 0, which means that the number of flashes in the next run will remain the same as that in the previous run. $f(e_{i-1})$ will be –1, if all symbols were identified correctly, and1 if no symbols were identified correctly. This means that the controller parameter is the maximum update step of the number of flashes from one run to the next. ε was tuned in simulation and pilot experiments to the following:



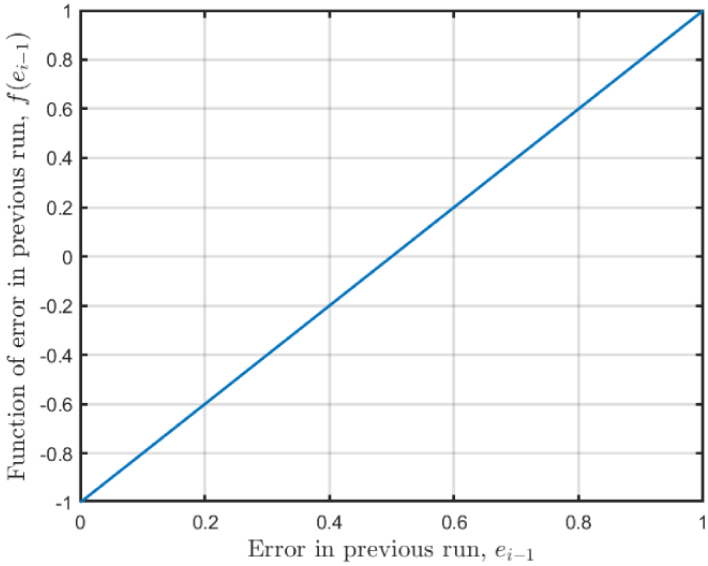
The update law described in (6), (7), and (8) can therefore be simplified to

$$N_i=N_{i-1}(e_{i-1}+0.5). \quad \textbf{(9)}$$

The new number of flashes, N_i, is then rounded up to the next highest integer.

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Figure 3. The function of the error in the previous run, f(e_{i-1}), used in the P-type ILC update law, plotted against the error in the previous run, e_{i-1}.



Posttraining Phase

After the training phase, which differs for each group and individual, the participants in all groups will copy-spell the word "dance" with 12 flashes per row and column. This is done to compare any posttraining differences between the groups.

Data Analysis

The offline data analysis steps closely follow the steps described by Arvaneh et al [17] to allow for comparability of results.

Questionnaire

The answers to Arvaneh et al's [17] questionnaire will be analyzed for between-group and within-group differences, using statistical tests, such as repeated measures ANOVA and paired *t* tests.

Similarly, between-group differences in responses to the NASA Task Load Index questionnaire [32] will be analyzed, for example, using a 1-way ANOVA. The raw score of each question will be used for the data analysis.

RDM Task

The change in performance in the RDM task between pre- and posttraining phases will be analyzed in terms of accuracy and response time. The accuracy is the number of correct trials over the total number of trials, and the response time is the elapsed time between onset of the coherent motion until the correct button is pressed before the end of the coherent motion. The response time of incorrect trials will not be considered. The mean response time will be calculated for each participant individually. Statistical tests, such as ANOVA and paired *t* tests, will be conducted to analyze between-group and within-group differences for both the accuracies and mean response times.

P300 Speller Task

Spelling Accuracy

The between-group differences in performance in the P300 speller in terms of spelling accuracy will be analyzed for all participants. Only the evaluation run, the first run of the training phase, and the posttraining run will be considered, as these 3 runs use the same number of flashes per row and column for all participants. Training runs 2-5 are different for each individual as the number of flashes is either determined by their previous performance (control group 1 and experimental group) or chosen randomly (control group 2). This means that the performance during these runs cannot be compared directly.

Length of Training

Since 1 of the objectives of this study is to accelerate attention training, the length of the training will be compared in terms of the total number of flashes used in runs 2-5 of the training phase. A statistical test, such as the 1-way ANOVA, will be carried out to compare between-group differences.

ERP Components

The changes in the ERP components throughout the training will be analyzed. For this purpose, epochs from 150 milliseconds to 550 milliseconds poststimulus onset will be extracted from the EEG data for both target and nontarget trials. Subsequently, the total power across the same centroparietal electrodes as used in [17] (ie, C3, Cz, C4, P3, Pz, and P4) will be calculated for each epoch.

The average total power for all epochs of the calibration and evaluation phases, the training phase, and the after-training phase, respectively, will be calculated. A training-to-calibration ratio of the average power for both target and nontarget trials will be obtained by dividing the average total power during the training phase by the average total power during the calibration and evaluation phases. The same will be done with the average total power during the after-training phase to obtain an after-training-to-calibration ratio.

A ratio of greater than unity indicates an increase in average total power, whereas a ratio of less than unity indicates a decrease in average total power compared to the calibration and evaluation phase. For target trials, an increase in power means that the participant improved their attention, and a decrease in power of nontarget trials can be interpreted as the participant being less distracted by nontarget flashes [17].

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Appropriate statistical tests, such as ANOVA, will be conducted to analyze within-group and between-group differences in the aforementioned ratios.

Time-Frequency Analysis

Similarly, to the training-to-calibration and after-training-to-calibration ratios of the average total power, these ratios will be calculated for the power of the alpha rhythm (7-12 Hz) of nontarget trials that are not presented immediately after a target trial. The alpha power will be calculated for the same centroparietal electrodes as before, for a period of 150 milliseconds poststimulus.

The training-to-calibration alpha ratio is the average alpha power during the training phase divided by the average alpha power during the calibration and evaluation stages, and the after-training-to-calibration alpha ratio is the average alpha power during the after-training phase divided by the average alpha power during the calibration and evaluation stages. A ratio of less than unity means that a participant is less distracted by nontarget stimuli compared to the calibration and evaluation phases [17].

Between-group differences of the training-to-calibration and after-training-to-calibration alpha ratios will be analyzed using statistical tests, such as 1-way ANOVA.

Correlation Between EEG and RDM Performance

The potential correlation between the brain activity during the P300 speller phase of the training session and the performance in the RDM task will be investigated with tests, such as the Pearson correlation coefficient or the nonparametric Spearman correlation test. The training-to-calibration and after-training-to-calibration ratios of total power and alpha power will be used as performance metrics during the P300 speller task. Similar ratios will be obtained for the response times and accuracies of the RDM task by dividing the posttraining phase response times and accuracies by the pretraining phase response times and accuracies, respectively.

Results

This study was approved by the Maynooth University Ethics Committee (BSRESC-2022-2474456) and is registered on ClinicalTrials.gov (NCT05576649). Participant recruitment and data collection began in October 2022. We expect to publish the results in 2023. This study is replicating the experimental protocol of Arvaneh et al [17], comparing their task difficulty adaptation approach to a novel approach using an iterative learning controller, as well as random task difficulty levels in each run.

Arvaneh et al [17] showed a significant enhancement of ERP components and performance in the RDM task after the P300 speller training, suggesting that participants' attention improved. We expect such an improvement for all groups in this study, with changes in the length of the training between groups due to the different adaptation approaches.

Discussion

Overview

This study aims to evaluate the use of an adaptive P300 speller as a neurofeedback training tool for attention training. We aim to accelerate the training process using ILC and compare personalized and nonpersonalized task difficulty adaptation approaches. By replicating the experimental protocol of Arvaneh et al [17], who demonstrated the adaptive P300 speller's potential as an easy-to-use and effective neurofeedback training tool, we seek to gather further evidence supporting this application for attention training.

The findings of this study will contribute to the understanding of how different adaptation approaches, both personalized and nonpersonalized, can impact the efficacy of neurofeedback training tools. These insights can guide the design of future BCI-based cognitive training and rehabilitation interventions. Accelerating the training with the P300 speller, without affecting its effectiveness or the users' frustration levels, will make it a more attractive training option for people with cognitive deficits.

Limitations

There are limitations to this protocol. The participants will only receive a single session of the neurofeedback training and therefore the long-term impacts of the neurofeedback training will not be obtained. Due to the short length of the training session, participants may not experience significant cognitive enhancements. The participants for this study will be healthy, and most likely young (due to recruitment in the university community) adults. It can be assumed that these individuals possess close to maximal cognitive abilities, which further limits the significance of the cognitive enhancements of the training.

Conclusions

Due to an aging and growing population, the number of people with cognitive deficits and illnesses is rising. It is therefore important to develop cognitive training and rehabilitation tools that are affordable, easy to use, and effective. The adaptive P300 speller that will be evaluated in this study might have the potential to be an efficient training tool. Positive findings of this study may demonstrate that the adaptive P300 speller, and more broadly BCIs, can be effective tools in cognitive training and rehabilitation.

Acknowledgments

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Data Availability

The data sets that will be generated during this study will be available in the Zenodo repository once work on this study has been completed.

Authors' Contributions

S-CN contributed to methodology, software, validation, formal analysis, investigation, writing of original draft, and funding acquisition. EW is responsible for validation, formal analysis, investigation, and writing the original draft. TW performed conceptualization, methodology, resources, writing, review, editing, and supervision. JVR contributed to conceptualization, methodology, resources, writing, review, editing, and supervision.

Conflicts of Interest

None declared.

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Abbreviations

ADHD: attention-deficit/hyperactivity disorder
BCI: brain-computer interface
EEG: electroencephalography
EEG-NFB: electroencephalographic neurofeedback
ERP: event-related potential
ILC: iterative learning control
RDM: random dot motion
SNR: signal-to-noise ratio

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Protocol

Leveraging Electronic Health Record Technology and Team Care to Address Medication Adherence: Protocol for a Cluster Randomized Controlled Trial

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Abstract

Background: Low medication adherence is a common cause of high blood pressure but is often unrecognized in clinical practice. Electronic data linkages between electronic health records (EHRs) and pharmacies offer the opportunity to identify low medication adherence, which can be used for interventions at the point of care. We developed a multicomponent intervention that uses linked EHR and pharmacy data to automatically identify patients with elevated blood pressure and low medication adherence. The intervention then combines team-based care with EHR-based workflows to address medication nonadherence.

Objective: This study aims to describe the design of the Leveraging EHR Technology and Team Care to Address Medication Adherence (TEAMLET) trial, which tests the effectiveness of a multicomponent intervention that leverages EHR-based data and team-based care on medication adherence among patients with hypertension.

Methods: TEAMLET is a pragmatic, cluster randomized controlled trial in which 10 primary care practices will be randomized 1:1 to the multicomponent intervention or usual care. We will include all patients with hypertension and low medication adherence who are seen at enrolled practices. The primary outcome is medication adherence, as measured by the proportion of days covered, and the secondary outcome is clinic systolic blood pressure. We will also assess intervention implementation, including adoption, acceptability, fidelity, cost, and sustainability.

Results: As of May 2023, we have randomized 10 primary care practices into the study, with 5 practices assigned to each arm of the trial. The enrollment for the study commenced on October 5, 2022, and the trial is currently ongoing. We anticipate patient recruitment to go through the fall of 2023 and the primary outcomes to be assessed in the fall of 2024.

Conclusions: The TEAMLET trial will evaluate the effectiveness of a multicomponent intervention that leverages EHR-based data and team-based care on medication adherence. If successful, the intervention could offer a scalable approach to address inadequate blood pressure control among millions of patients with hypertension.

Trial Registration: ClinicalTrials.gov NCT05349422; https://clinicaltrials.gov/ct2/show/NCT05349422

International Registered Report Identifier (IRRID): DERR1-10.2196/47930

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KEYWORDS

medication adherence; hypertension; clinical decision support; proportion of days covered; EHR; electronic health record; technology; adherence; primary care

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Introduction

Low medication adherence, frequently defined as a proportion of days covered (PDC) of less than 80% [1,2], is associated with increased cardiovascular morbidity and mortality and has a prevalence as high as 30%-50% among patients with hypertension [3-5]. Assessment of adherence in clinical practice is challenging; however, as most objective measures of adherence are of limited use, electronic monitoring is expensive and challenging to scale, while pharmacy claims data are limited to certain insured patients and only available to primary care providers (PCPs) with delays [4,6-8]. However, recent uptake of electronic prescribing from the electronic health record (EHR) to pharmacies offers the opportunity for scalable, real-time measurement of medication adherence that can be used for interventions at the point of care [9]. Despite the recent integration of pharmacy medication fill data into many EHRs, their use in addressing medication adherence at the point of care has not been thoroughly evaluated [10,11].

These limitations in the assessment of medication adherence in combination with the limited PCP time due to competing demands have led to insufficient attention to medication adherence in primary care practice [12]. Prior studies have demonstrated that clinical teamlets comprising PCPs paired with medical assistants (MAs) might be able to improve screening for adherence as well as medication-taking behavior [13-15]. Furthermore, the ability of teamlets to communicate and effectively change behavior can be enhanced through tight integration into the workflow using EHRs. However, the benefits of an intervention that combines teamlets with scalable, EHR-based adherence data and integrated workflows have not been studied.

The purpose of this study is to describe the design and protocol of the Leveraging EHR Technology and Team Care to Address Medication Adherence (TEAMLET) study. This cluster randomized controlled trial will evaluate the effectiveness of a multicomponent intervention on medication adherence and blood pressure control among patients with hypertension who are seen in primary care. The intervention combines a data-driven approach to automatically identify patients with elevated blood pressure and low medication adherence, team-based care to address low medication adherence, and user-centered EHR workflows. We will also evaluate the implementation of the intervention into primary care clinical sites.

Methods

Study Design

A 2-arm hybrid type I effectiveness-implementation pragmatic, cluster randomized controlled trial will be performed to assess the effectiveness of a multicomponent intervention on medication adherence (primary outcome) and systolic blood pressure (secondary outcome) for patients with hypertension. The clusters for randomization are primary care practices in a large health care network. The intervention is guided by the Capability-Opportunity-Motivation Model of Behavior (COM-B) framework, a parsimonious amalgamation of existing theories of behavior change, which has been proven effective for designing programs that help patients improve medication adherence [16]. Our evaluation is based on Proctor Implementation Outcomes Framework, a conceptual framework that guides the evaluation of distinct outcomes that serve as indicators of implementation success [17].

Setting and Eligibility

This study is being conducted at primary care practices in the NYU Langone Health network. NYU Langone Health includes a diverse network of hospital-based practices, community-based practices, and community health centers in New York City and the surrounding areas. The health system includes over 60 distinct primary care practices that all use the same EHR, Epic (Epic Systems). From these practices, we will recruit 10 to participate in the study.

This study will include all adult patients seen at one of the recruited practices who have hypertension, uncontrolled blood pressure, and poor medication adherence. Specifically, we will include patients aged ≥18 years who were seen for a visit at one of the included practices in the study during the first 6 months of the commencement of the trial at that site. Patients with an active order for at least 1 antihypertensive medication will be included. To ensure patients have inadequately controlled hypertension (and mitigate variability associated with clinic blood pressure readings), we will include those with a measured clinic blood pressure ≥140/90 mm Hg on the day of the visit plus a blood pressure reading greater than or equal to 140/90 mm Hg on the previously recorded blood pressure measurement. Low medication adherence will be defined by a PDC <80% during the prior 6 months, where PDC is defined as the proportion of days that a patient had a medication from pharmacy fills while the medication had an active prescription [1,9]; for example, if a medication is initially prescribed at the start of the 6-month period, is not discontinued, and is only filled once for 90 days, the PDC would be 90/180=50%. PDC will be calculated using the algorithm in our EHR, which is based on the Pharmacy Quality Alliance measure [18]. This calculation will include adherence to all antihypertensive medications used in the prior 6 months, even if the medication was no longer active on the day of assessment. For patients on multiple antihypertensive medications, the algorithm considers a patient to be adherent on a given day only if medication fills are available for all medications on that day.

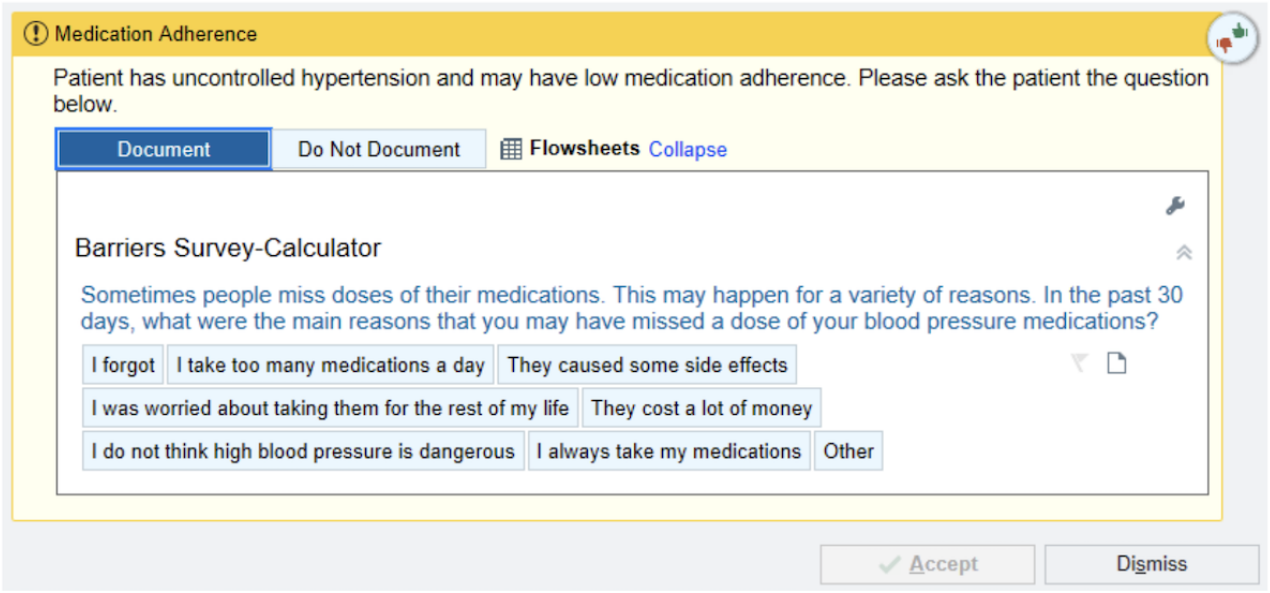
Intervention

The intervention is an EHR-based workflow that consists of four components: (1) identification of patients with poorly controlled hypertension and low medication adherence at the point of care; (2) prompts for the MA to screen for important barriers to medication nonadherence; (3) alerting the PCP of low medication adherence and important barriers, with the intent of facilitating a conversation with the patient regarding medication adherence; (4) clinical decision support (CDS) to assist PCPs in addressing the barriers to medication adherence. These components have been informed through interviews and usability sessions with PCPs and MAs as well as a patient survey [19]. The process for intervention begins when the MA records the blood pressure of a given patient presenting to see their PCP.

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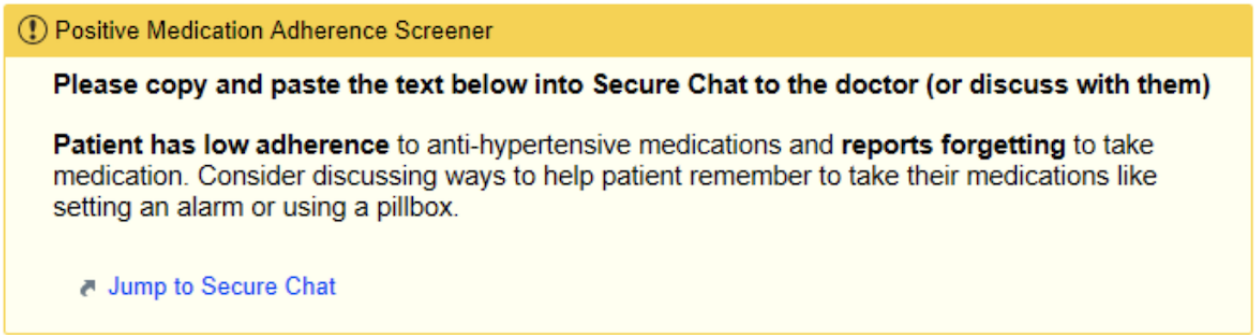
If the blood pressure is recorded as ≥140/90 mm Hg, the algorithm within the EHR will automatically screen the patient for the other inclusion criteria. If the patient meets all the criteria, that is, if their age is ≥18 years, the prior blood pressure is ≥140/90 mm Hg, they are taking an antihypertensive medication, and their PDC <80%, the MA will then receive a CDS alert to ask the patient about whether 1 of the 6 barriers contributed to missing medications (Figure 1). These 6 barriers are based on a validated questionnaire and survey of the patient population in our health system [19-21]. After responding to the question, the MA will receive an alert to communicate this result to the PCP, either through secure chat or through another method (Figure 2). The PCP then will receive the secure chat message, which will include a prompt to review the CDS related to medication adherence (Figure 3). Even if the message is not communicated from the MA to the PCP, the passive CDS will still be available to the PCP. The CDS will convey the barrier to medication adherence and provide suggestions to address the barrier (Figure 4). Additionally, the CDS will link to an order set, which will include auto documentation related to medication adherence and barriers, appropriate patient instructions, and an International Classification of Diseases, Tenth Revision (ICD-10) diagnostic code to add to the visit (Figure 5). Ultimately, our goal is for these tools to facilitate a discussion between the PCP and the patient to address barriers to medication adherence.

Figure 1. Electronic health record–based workflows for the intervention: medical assistant alerts to ask medication adherence barrier questionnaire.



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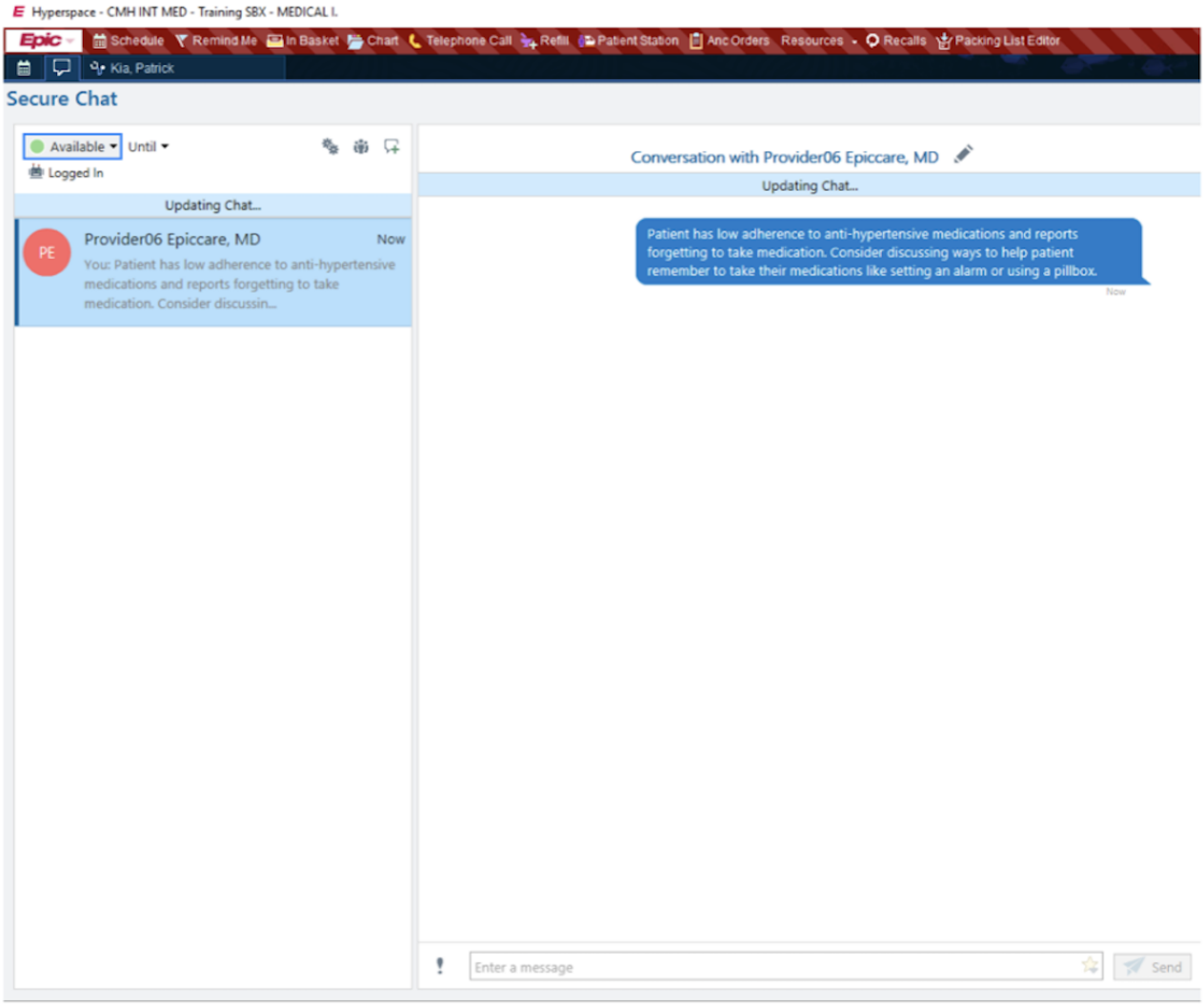
Figure 2. Electronic health record–based workflows for the intervention: follow-up medical assistant alert advising communication of the result to the primary care provider.



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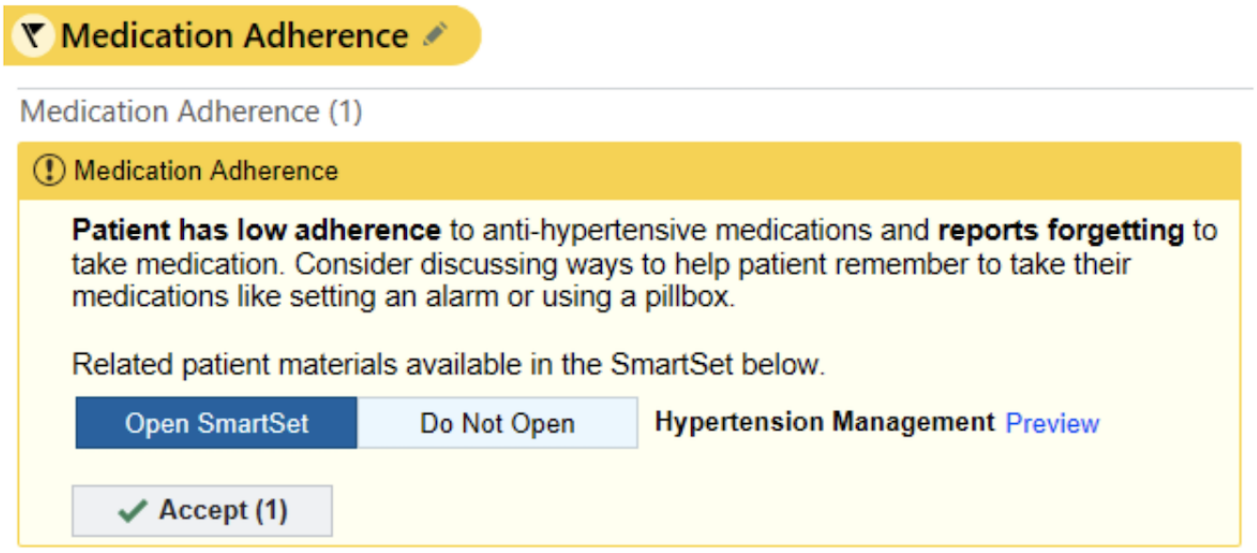
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Figure 3. Electronic health record–based workflows for the intervention: example of secure chat to the primary care provider.



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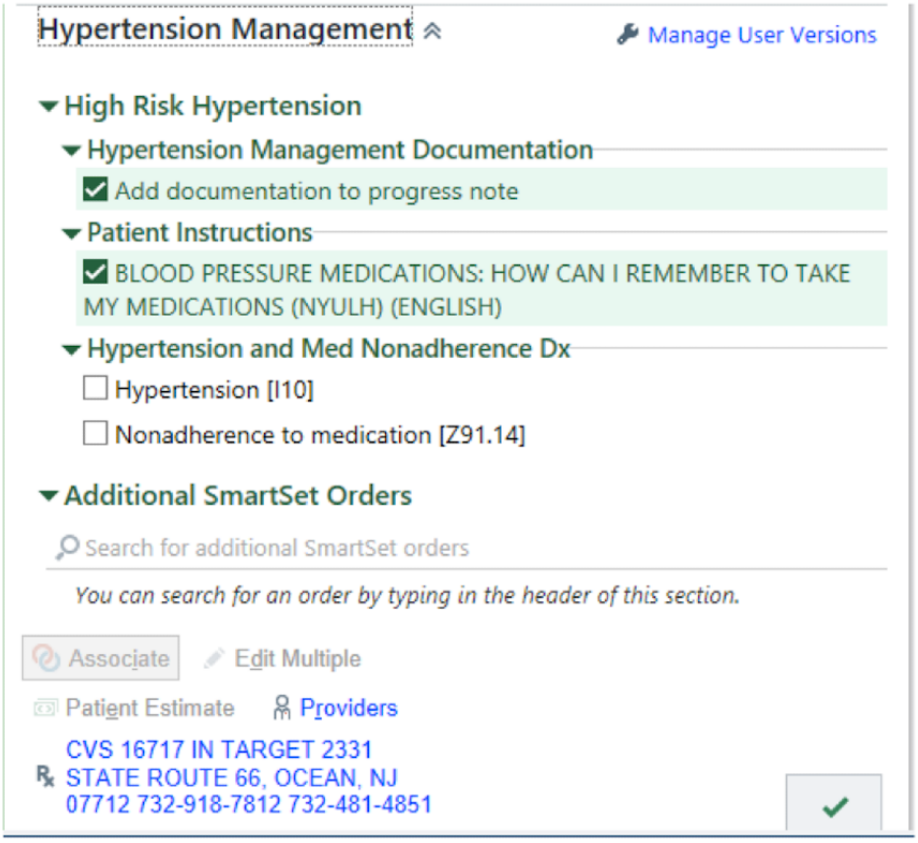
Figure 4. Electronic health record–based workflows for the intervention: primary care provider alert notifying of results.



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Figure 5. Electronic health record–based workflows for the intervention: order set available to primary care provider through the alert.



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MA and PCP Training

We will use a multipronged approach to train MAs and PCPs about the intervention. First, individual emails will be sent out to each MA and PCP group alerting them to the study. Included in the email will be an attachment of a tip sheet about the intervention and its components. Second, an in-person or web-based practice site meetings will be presented to include an overview of medication adherence, a walk-through of the intervention components, and suggestions for communication with patients. Third, 3 training videos that contain similar content will be built: the first containing general information about medication adherence, the second describing patient communication, and the third detailing the intervention. These supplemental videos will be accessible to intervention MAs and PCPs at any time if questions arise, although they are not required for the success of the CDS, which stands on its own. Fourth, study staff will be on-site for the first week of intervention to provide support and answer any questions during the implementation period.

Ongoing Support

In addition to the availability of training videos that can be used at any time, site administration, PCPs, and MAs will be provided with study staff's contact information to discuss any questions or concerns, as needed. Study team members will make monthly site visits to offer additional support. Additionally, study team members will be in regular contact with site leadership to learn of any staffing changes and encourage the training of newly hired MAs and PCPs.

Control

MAs and PCPs in the control group will receive individual emails informing them of inclusion in the study. The email will include an overview of medication adherence and will describe current tools available related to medication adherence that are available within the EHR. The first and second training videos available for the intervention group will also be accessible to control group PCPs; these videos contain general information about medication adherence and a description about communication with patients.

Recruitment and Randomization

This study will use a practice-level cluster randomized design, with 1:1 randomization of 10 practices, resulting in 5 per study arm. We will use block randomization of 4 to 6 practices at a time with go-lives occurring approximately monthly to stagger the intervention rollout across the network.

Recruitment will be performed through email outreach to medical directors and practice managers at individual practice sites. The email will contain a brief description of the project, expectations of the practice for participation, and an offer to have a virtual meeting to present the project and answer additional questions.

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Enrollment and Follow-up Period

Patients who meet inclusion criteria will be included in the analysis if seen in one of the interventions or control primary care sites in the first 6 months after site enrollment into the trial. The patients will be evaluated for the outcome 12 months after the index clinic visit. The research support staff will support intervention implementation at each site for a total of 18 months to ensure complete 12-month follow-up for all included patients. After this time, we will observe outcomes for an additional 6 months without direct support from the research staff to assess the sustainability of the intervention.

Clinical Outcomes

Clinical outcomes will be based on the data extracted from the EHR. Our primary outcome will be medication adherence assessed at 12 months. Adherence will be measured by PDC as a continuous variable using a lookback period of 6 months. The secondary clinical outcomes will be medication adherence as measured as a binary variable of PDC ≥80% [1,2] and clinic systolic blood pressure assessed continuously. When available, we will use the mean of the last 2 clinic blood pressure measurements within 1 year of the initial clinic visit, in order to increase reliability with multiple blood pressure measurements [22].

Implementation Outcomes

Our implementation measures are guided by Proctor Implementation Outcomes Framework and will include adoption, acceptability, fidelity, cost, and sustainability of the intervention (Table 1). Data for our implementation measures will be obtained from both EHR data and semistructured interviews of PCPs and MAs.

Table 1. Description of implementation outcomes.

Outcome and measure	Data source
Adoption	

• For MAs[a], we will assess:
  • If the MAs completed the survey (yes or no)
  • The percentage of times the MA sent a secure chat to the PCP[c] (yes or no)
  • Assessment of MA participation
• For PCPs, we will assess:
  • If the PCP interacted with the CDS[d] (yes or no)
  • If the orders were placed from the order set (yes or no)
  • If the PCP documented discussion of medication adherence with the patients. (yes or no)
  • Assessment of PCP participation
	• EHR[b]
	• Semistructured interviews

Acceptability	
• We will ask MA and PCP about the acceptability of the intervention	• In-person and email survey • Semistructured interviews
Fidelity	

• Chart review for documentation of discussions MA and PCP self-reported adherence
• For MAs, we will assess:
  • The percentage of times that MAs completed the survey
  • The percentage of times the MA sent a secure chat to the PCP
• For PCPs, we will assess:
  • The number of times PCP interacted with the CDS
  • The number of orders placed from the order set
  • The percentage who documented discussion of medication adherence with the patients.
	• Chart review
	• Semistructured interviews
	• EHR

Cost	
• Time spent by MAs and PCPs on intervention, multiplied by average salary	• EHR • Public salary data
Sustainability	
• Evaluate outcomes at 18 months • Identify factors that influence sustainability and integration	• EHR data • Semistructured interviews

[a]MA: medical assistant.

[b]EHR: electronic health record.

[c]PCP: primary care provider.

[d]CDS: clinical decision support.

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Adoption

EHR data will be used to measure the adoption of the intervention by MAs and PCPs. For MAs, we will evaluate the number of MAs that completed the barriers questionnaires and the number that sent secure chat messages (measured as a yes or no dichotomous variable). For PCPs, we will assess if the order set was opened from the CDS and if the autodocumentation and patient handouts were added from the order set (measured as a yes or no variable). A qualitative assessment to understand MA and PCP participation will also be performed.

Acceptability

We will ask the PCPs and MAs about the acceptability of the intervention during interviews and will administer a validated survey, the Acceptability of Intervention Measure at the end of the intervention [23].

Fidelity

To assess fidelity (a metric of implementation success and quality), we will perform a chart review for a sample of eligible patients to determine the frequency of documentation of provider actions to address medication adherence, including discussions with patients and switching to alternative medications for cost or side effect issues. A weekly review will be performed at each site for the first month, then monthly throughout the study period, and provide feedback to sites if medication adherence does not appear to be addressed. The EHR data will also be used to measure the fidelity to the intervention protocol, as intended. For MAs, the percentage of barriers questionnaires completed and the percentage of secure chats sent will be measured. For PCPs, the percentage of times the order set was opened from the CDS and the number of times that auto documentation and patient handouts were added from the order set will be assessed.

Cost

We will evaluate the cost of the intervention by estimating the additional time spent by MAs and PCPs on the intervention and then multiplying this by their average national salaries with fringe. Both self-report and data to estimate the time spent will be used. We will survey MAs and PCPs from the intervention group on how much additional time they spend with each patient for whom they receive the intervention. This value will be compared to the time the MAs spent between receiving the CDS and completion of the survey. For the PCPs, the average time spent in the EHR for intervention patients will be measured and compared to the average time on control patients. We will measure average salaries using publicly available data from the US Bureau of Labor Statistics [24].

Sustainability

During semistructured interviews, we will ask PCPs and MAs about the opportunities to maximize the sustainability of the intervention, and the strategies to optimize continued integration of the intervention into the routine workflow. In addition, to assess the sustainability of the intervention over time, PDC will be measured longitudinally at the following time intervals: baseline, 6 months, 12 months, and 18 months (6 months post completion of intervention). Similarly, if available, blood pressure at these time points will be assessed.

Covariate Measures

The baseline patient characteristics at the time of the initial visit with the PCP in which inclusion criteria are met will be assessed. Demographic characteristics to be collected will include patient age, sex, race, ethnicity, and insurance. Baseline clinical characteristics to be collected will include clinic blood pressure, number of medications, and comorbidities. Additionally, we will assess the number of clinic visits during the follow-up period.

Statistical Methods

Sample Size

Our sample size estimate is based on the clinical outcome of medication adherence after 12 months, which is measured as a continuous variable. We plan on a 6-month enrollment period. Based on the preliminary data from primary care practices in our health system, we estimate a median of 182 eligible patients per practice during this period. Based on our prior work of having MAs perform counseling related to adherence, we anticipate a group difference of at least 20% between the intervention and the control groups [15]. Applying this effect size to our study, and assuming 80% power, 5% type I error rate (α), 30% attrition over the 18-month study period, and an intraclass correlation coefficient of 0.15 to account for clustering of patients within sites, we estimate a necessary sample size of 10 practices in the study. Calculations of sample size were estimated using a standard approach (eg, design effect) for cluster randomized trials [25].

Descriptive Analyses

We will summarize baseline characteristics, clinical outcomes, and quantitative implementation outcomes. Frequencies and percentages will be used to describe categorical variables, and means and SDs will be used to characterize continuous outcomes. Medians and IQRs will be reported for continuous variables that exhibit skewness.

Analyses of Primary and Secondary Outcomes

The analysis of all outcomes will follow the intention-to-treat principle. For the intention-to-treat approach, all participants randomly assigned to one of the 2 arms will be included in the analysis under their assigned group, regardless of compliance. The primary study outcome will be PDC, which can take on values ranging from 0% to 100%. We will develop a generalized linear mixed model with PDC as the dependent variable. The model will include a categorical indicator variable for the randomized study arm (control as reference), a variable corresponding to time (baseline as reference), and the interaction of the 2, representing the primary independent variable. The primary study end point will be at 12 months, with secondary end points measured at 6 and 18 months; these secondary end points will be used to assess sustainability. We will also adjust for any sociodemographic or clinical covariates imbalanced at baseline, as well as the number of clinic visits per patient to assess the frequency of exposure to intervention. The model will include practice-level random effects to account for

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clustering of patients within clinics during randomization. Prior to analyzing the data, we will compare dropout and missing data across the 2 arms and examine whether any patient characteristics were associated with the missing data. If necessary, additional analyses utilizing multiple imputation methods will be conducted.

The secondary study outcome will be blood pressure, also measured as a continuous variable using a similar generalized linear mixed model approach. Exploratory outcomes will include subgroup analyses to identify individual components of the intervention that may be influential on the clinical outcomes and other EHR-based measures.

Qualitative Collection and Analyses

Semistructured interviews of PCPs and MAs will be conducted toward the end of the trial to identify emerging themes related to Proctor implementation outcomes. The interview guide, informed by the implementation outcomes, will consist of 10-15 questions regarding acceptability, adoption, fidelity, and sustainability, with an emphasis on barriers and facilitators to implementing the intervention. This qualitative data collection will be complemented by quantitative data collected in the study.

Qualitative analysis will include both semistructured interviews with PCPs and MAs as well as narrative reports to assess adherence. Interviews will be audio-recorded and transcribed verbatim by an outside vendor. Qualitative data will be analyzed using thematic analysis [26]. We will begin with open codes and progressively group and refine codes into categories. In addition to identifying key a priori codes based on our framework, coders will initially review a selection of interviews and develop codes to describe the content for the initial code list. The codebook will be updated and revised throughout the review process. Once all interviews are coded, the investigative team will meet to discuss and identify code clusters, relationships between codes, and common themes.

In addition, we will follow the National Institutes of Health's best practices for mixed-methods research [27] in synthesizing quantitative results and qualitative themes by constructing a joint display for statistics-by-theme and side-by-side interpretation of the qualitative data [28]. The mixed methods approach will allow us to integrate the qualitative findings with quantitative results, providing a comprehensive understanding of the impact of the intervention, and identify the best practices for implementation.

Ethics Approval

This study was approved by the institutional review board at NYU Langone Health (#21-00133). Verbal consent was obtained at the practice level from the medical director in addition to the ambulatory system and enterprise EHR leadership at each primary care practice. We have obtained a waiver of consent from the institutional review board at NYU Langone Health for patients included in the trial.

The Data and Safety Monitoring Board will be responsible for monitoring the study. The Data and Safety Monitoring Board will receive information specific to the intervention and control arms to evaluate the progress of the trial, including periodic assessments of data quality and timeliness; participant recruitment, accrual; and retention; participant risk versus benefit; the performance of trial sites; and other factors that can affect the study outcome.

Results

As of May 2023, we have randomized 10 primary care practices into the study, with 5 practices assigned to each arm of the trial. Enrollment for the study commenced on October 5, 2022, and the trial is currently ongoing. We anticipate patient recruitment to go through the fall of 2023 and the primary outcomes to be assessed in the fall of 2024.

Discussion

Medication nonadherence is a major contributor to inadequate blood pressure control [29]. However, health care providers underestimate the frequency of patient nonadherence to antihypertensive medications [30]. Relatedly, medication nonadherence is not well addressed in clinical practice: 40% of primary care visits do not include discussions about medication adherence among patients with elevated cardiovascular risk [31]. Even when these conversations do occur, they amount to a very brief discussion [32]. Lack of resources, inadequate skills, and insufficient system-level supports are the most common barriers expressed by PCPs for the lack of integration of adherence counseling into routine practice [12].

The TEAMLET intervention was developed to provide system-level support and resources to address medication nonadherence. In this study, we will conduct a cluster randomized controlled trial of this multicomponent intervention on medication adherence and blood pressure control among patients with hypertension. The intervention draws on 2 innovations to address the gaps in screening for and addressing medication nonadherence. First, the intervention uses a data-driven approach to automatically identify patients with low medication adherence and high blood pressure. Our medication adherence measure will use EHR-based pharmacy fill data, which is a scalable and reliable measure of adherence that is available in real-time clinical care [4]. To date, few studies have used these data for real-time adherence measurement and most used cases have been limited to a closed health system that includes a pharmacy [10,11]. Conversely, our study is within a health system that includes patients with various insurance providers or who are uninsured and that interfaces with hundreds of pharmacies. The second innovation of the intervention is that it relies on teamlets in primary care to address medication adherence [33]. Specifically, we will give MAs the tools to assess barriers to medication adherence and then relay this information to providers during regular clinical practice. This will allow PCPs to focus their limited time on the patient's specific issue related to adherence and deliver tailored health coaching.

Our study has potential limitations. First, medication adherence is based on PDC from pharmacy fills; as such, it is not a direct measure of medication adherence. While PDC is commonly used in the literature to assess medication adherence, it is subject

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to misclassification. Nonetheless, PDC from pharmacy fill data has been shown to be well correlated with medication continuity, biomarkers, and clinical outcomes, and there is evidence that improvement in PDC leads to improvement in clinical outcomes [4,34-36]. We are also examining a clinically meaningful secondary outcome of blood pressure. Second, patient-level inclusion in the intervention and our secondary clinical outcome are based on clinic-based blood pressure measurement, which may be subject to misclassification due to issues including white coat hypertension [37]. As a result, we use a conservative definition for patients with hypertension that includes multiple high readings and a cutoff of 140/90, which is endorsed by some guidelines [38,39] but considered conservative by others [40]. Third, the study will be conducted in 1 health care system that uses 1 EHR platform. Nonetheless, Epic is the most commonly used EHR platform in the United States [41] and the intervention workflows can be generalized to most health systems and EHRs.

In this protocol, we describe a clinic-based, cluster randomized controlled trial of the TEAMLET intervention. We hypothesize that the intervention will lead to improved medication adherence among patients with hypertension being seen in primary care clinics. If shown to be true, we believe that this intervention, which is centered on data available in many EHRs and teamlets typically available in primary care settings, can be easily scaled to help address inadequate blood pressure control.

Data Availability

In order to prioritize participant privacy and confidentiality, we will not be sharing any electronic health record data or qualitative data from this study due to ethical concerns regarding the sensitivity and potential reidentification risks associated with these data. However, any high-level aggregate data sets generated and analyzed in the randomized controlled trial will be made available upon reasonable request from the corresponding author.

Conflicts of Interest

None declared.

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Abbreviations

CDS: clinical decision support
COM-B: Capability-Opportunity-Motivation Model of Behavior
EHR: electronic health record
ICD-10: International Classification of Diseases, Tenth Revision
MA: medical assistant
PCP: primary care provider
PDC: proportion of days covered
TEAMLET: Leveraging Electronic Health Record Technology and Team Care to Address Medication Adherence

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Protocol

The Effect of Catgut Embedding at Acupoints Versus Nonacupoints in Abdominal Obesity: Protocol for a Multicenter, Double-Blind, 16-Week Randomized Controlled Trial

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Abstract

Background: Obesity is an increasing problem worldwide. The effective treatments for obesity mainly include diet, physical activity, behavioral intervention, pharmacotherapy, and bariatric surgery, which all have certain limitations. As a specific type of acupuncture therapy, acupoint catgut embedding (ACE) has gained substantial attention in the management of obesity in recent years. Previous studies suggested that ACE may be an effective obesity treatment. However, the evidence for the efficacy of ACE in abdominal obesity (AO) remains inadequate due to the paucity of high-quality studies.

Objective: This study aims to investigate the difference in the effectiveness of catgut embedding at acupoints and catgut embedding at nonacupoints in patients with AO and to further validate the efficacy and safety of ACE for AO.

Methods: This is a multicenter, double-blind, 16-week randomized controlled trial. A total of 92 eligible participants with AO will be randomly divided into 2 groups (1:1 allocation ratio). The ACE group will receive catgut embedding at acupoints and the control group will receive catgut embedding at nonacupoints. The intervention will be performed every 2 weeks for a total of 6 sessions. Follow-up will be performed every 2 weeks for a total of 2 visits. The primary outcome is waist circumference. Secondary outcomes include body weight, BMI, hip circumference, and the visual analog scale of appetite. Upon the completion of the trial, we will evaluate the effect of catgut embedding at acupoints or nonacupoints on obesity indicators in patients with AO. For treatment outcomes, an intention-to-treat analysis will be performed.

Results: The start of recruitment began in August 2019 and is expected to end in September 2023.

Conclusions: Although studies have been conducted to demonstrate the effectiveness of ACE in the treatment of obesity, the evidence for the efficacy of ACE in AO remains insufficient due to the quality of the studies. This rigorous normative randomized controlled trial will verify the effect of catgut embedding at acupoints or nonacupoints in patients with AO. The findings will provide credible evidence as to whether ACE is an effective and safe treatment for AO.

Trial Registration: Chinese Clinical Trial Registry ChiCTR1800016947; https://tinyurl.com/2p82257p

International Registered Report Identifier (IRRID): DERR1-10.2196/46863

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KEYWORDS

acupoint catgut embedding; nonacupoints; abdominal obesity; randomized controlled trial; protocol; waist circumference

Introduction

Obesity has become a global health issue regardless of race, region, and age [1]. Globally, the prevalence of obesity in adults was approximately 13% (603.7 million). There were approximately 107.7 million children and adolescents who were obese [2,3]. The prevalence of obesity was about 20% or more in the United States, the Middle East and North Africa, the Caribbean, Polynesia, and Micronesia [4]. The increase of adults who are obese has leveled off in several high-income countries, but the incidence is dramatically on the rise in most low- and middle-income countries, particularly in urban regions [1,5]. As a major type of obesity, the prevalence of abdominal obesity (AO) in adults was 29.1% (28.6% in men and 29.6% in women) in China [6]. Obesity is a worldwide problem and a burden in many diseases [2,7,8]. Studies have demonstrated that obesity may lead to diabetes, subfertility, chronic spontaneous urticaria, nonalcoholic fatty liver disease, Alzheimer disease, cardiovascular diseases, and even cancer [2,9-18]. In addition to diseases, obesity can also affect disability-adjustment life-years and generate a large economic burden [4,19-21]. Obesity is also a persistent problem, where most children who are obese will remain obese in adolescence [22].

The effective treatments for obesity mainly include diet, physical activity, behavioral intervention, pharmacotherapy, and bariatric surgery [23-29]. Diet and physical activity require great self-discipline and enough time, which are difficult to adhere to. The effect of behavioral intervention for obesity is typically limited [30]. Side effects such as abdominal pain, vomiting, nervousness, insomnia, headache, dizziness, dysgeusia, and insomnia may accompany pharmacotherapy [31]. Pharmacotherapy could not be used for patients who are obese with complicated active cardiovascular disease, glaucoma, uncontrolled hypertension, anorexia, thyroid, and many other diseases [32,33]. For pregnant individuals and children, the safety of pharmacotherapy is still not guaranteed currently [34]. Bariatric surgery requires a high level of medical technology and may increase the risk of fractures [35-37]. Alternative therapies such as acupuncture, moxibustion, acupoint catgut embedding (ACE), and massage are increasingly used for the treatment of obesity [38-42].

ACE is a special acupuncture therapy that combined the absorbable surgical suture and acupoint, and the effective stimulation of every ACE treatment could persist for 2 weeks. Previous studies indicated that ACE was an efficient treatment for obesity, but the risk of bias was significantly high [43]. Therefore, this rigorous and normative randomized controlled trial (RCT) study is designed to verify the efficiency of catgut embedding at acupoints and nonacupoints in participants with AO. The findings will provide credible evidence as to whether ACE is an effective and safe treatment for AO.

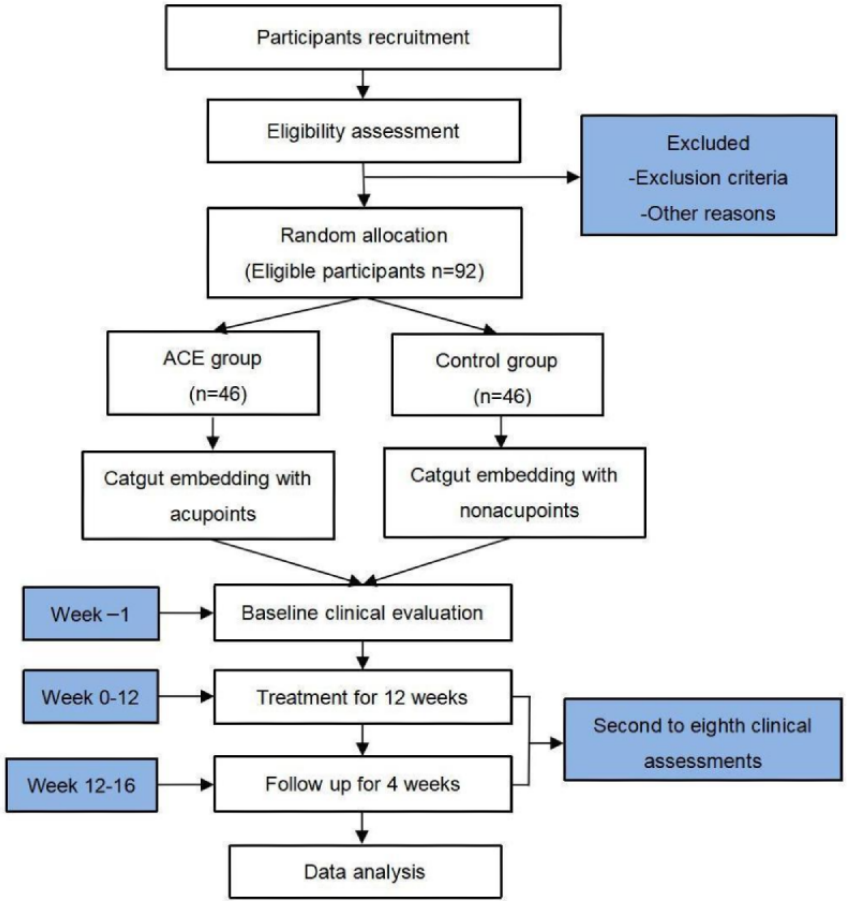
Methods

Study Design and Setting

This multicenter, double-blind, 16-week RCT will be conducted from August 2019 to September 2023 in 4 clinical centers: The Second Affiliated Hospital of Yunnan University of Chinese Medicine, The Sports Trauma Specialist Hospital of Yunnan Province, Kunming Hospital of Traditional Chinese Medicine, and ShengAi Hospital of Traditional Chinese Medicine. A total of 92 eligible participants with AO will be assigned to 1 of 2 groups (catgut embedding at acupoints or nonacupoints) using central randomization (1:1 allocation ratio). Every participant will receive a 12-week intervention period and a 4-week follow-up. The flowchart of this study is shown in Figure 1.

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Figure 1. Flowchart of the trial. ACE: acupoint catgut embedding.



Ethics Approval

This protocol is in line with the Declaration of Helsinki and has been approved by the Hospital Ethics Committee of The Sports Trauma Specialist Hospital of Yunnan Province (2018CK-001) in June 2018. The study has been registered in the Chinese Clinical Trial Registry (ChiCTR1800016947). This protocol is compliant with the principles of the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials; see Multimedia Appendix 1) and CONSORT (Consolidated Standards for Reporting Trials) guidelines [44]. The SPIRIT checklist is presented in Multimedia Appendix 1 and the schedule is shown in Table 1.

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Table 1. Study schedule for data measurements.

	Study period and time point (week)									
	Enrollment	Allocation	Treatment phase						Follow-up	
	–1	0	2	4	6	8	10	12	14	16
Enrollment										
Eligibility screen	✓									
Informed consent	✓									
Physical examination	✓									
Randomization		✓								
Interventions										
ACE[a] group (n=46)			✓	✓	✓	✓	✓	✓	✓	✓
Control group (n=46)			✓	✓	✓	✓	✓	✓	✓	✓
Assessments										
BW[b]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
BMI	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
WC[c]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
HC[d]		✓	✓	✓	✓	✓	✓	✓	✓	✓
VAS[e] of appetite		✓	✓	✓	✓	✓	✓	✓	✓	✓
Safety										
AE[f]			✓	✓	✓	✓	✓	✓		

[a]ACE: acupoint catgut embedding.

[b]BW: body weight.

[c]WC: waist circumference.

[d]HC: hip circumference.

[e]VAS: visual analogue scale.

[f]AE: adverse event.

Participants

Participants who meet all the following criteria will be included: (1) aged between 18 and 60 years with simple obesity; (2) BMI ≥28 kg/m^2 and waist circumference (WC) ≥90 cm for male participants and ≥85 cm for female participants; (3) agreed to participate in this study and signed written informed consent for this trial and catgut embedding therapy; and (4) did not participate in other trials within past 3 months. Participants will be excluded if they meet any one of the following criteria: (1) secondary obesity, such as obesity caused by endocrine disease (Cushing syndrome, thyroid disease, hypothalamic disease, pituitary disease, gonadal disease, etc) and medication (glucocorticoid or antipsychotics); (2) pregnancy, lactation, and childbirth within the past 6 months; (3) heart disease; hematopoietic system, liver, kidney, and other important organ diseases; and hypertension that is not effectively controlled; (4) severe mental and neurological diseases where the patient is unable or unwilling to cooperate; (5) allergy to alcohol and animal protein or immune diseases; and (6) received other weight loss treatment within the past 3 months.

Criteria for Elimination From the Study

Those who meet the following criteria should be eliminated from the study: (1) misdiagnosis and misrepresentation; (2) poor treatment tendency; (3) involvement with other treatments after being selected; and (4) participants' withdrawal before the first test recording.

Recruitment and Randomization

All participants with eligible AO will be recruited from the 4 hospitals and the community. Recruitment methods mainly include posters, public notice boards, and WeChat public numbers in hospitals and communities. The randomization sequence will be generated by the Clinical Research Center of Yunnan University of Chinese Medicine using a computerized random number generator and placed in opaque envelopes. Stratified randomization will be performed for the 4 clinical centers. To ensure allocation concealment, randomization will be performed by an independent researcher. The research assistant will open the envelope when the participant begins treatment to determine the assigned group and will not disclose grouping information under any circumstances. The acupuncture therapist will be responsible for manipulation only.

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Blinding and Informed Consent

Participants will be informed that they have a 1 in 2 chance of being assigned to 1 of 2 treatments: catgut embedding at acupoints or nonacupoints. The procedure and stimulation of the catgut embedding at acupoints are identical to catgut embedding at nonacupoints. Therefore, participants will be blinded to their treatment assignment. Both groups of participants will be assigned to different treatment rooms to prevent intercommunication. In addition, the acupuncturist, outcome assessor, and those involved in data collection and statistics will be blinded to treatment assignment throughout the trial. Research assistants with knowledge of grouping information will be asked not to communicate with participants or outcome assessors regarding treatment procedures and responses. All patients will be fully informed about the study (including the purpose of the trial and possible risks, etc) prior to participation in the trial, and they have the right to withdraw from the trial at any time without giving a reason. They will sign a written informed consent for voluntary participation prior to enrollment.

Sample Size Calculation

According to the existing literature [45], the mean BMI of simple obesity was 32.30 kg/m^2, whereas after 12 weeks and 6 treatment of acupuncture combined with a low-energy diet, the mean BMI was 30.98 kg/m^2, and the improvement value was 1.32 kg/m^2. In contrast, the improvement value was 1.02 kg/m^2 in a control group with a variation from 32.74 kg/m^2 to 31.73 kg/m^2 when treated by sham acupuncture combined with a low-energy diet, and the SD of the 2 groups was 0.31 kg/m^2. In this project, the expected improvement value of the mean BMI of the Shu-Mu acupoints embedding group after treatment is 1.14 kg/m^2 and that of the nonacupoints embedding group is 0.9 kg/m^2, with the SD of each group being 0.31 kg/m^2. The significant level is α=.05, and the power of a test is $1 - \beta = 0.95$. The sample size is 84 as calculated by German G*power software 3.1 [46]. According to the 10% dropout, the total sample is 92 cases, and 46 cases will be assigned to each group.

Interventions

All catgut embedding manipulations will be performed by an acupuncturist with national medical qualifications. The participants will receive treatment every 2 weeks for a total of 6 sessions.

ACE Group

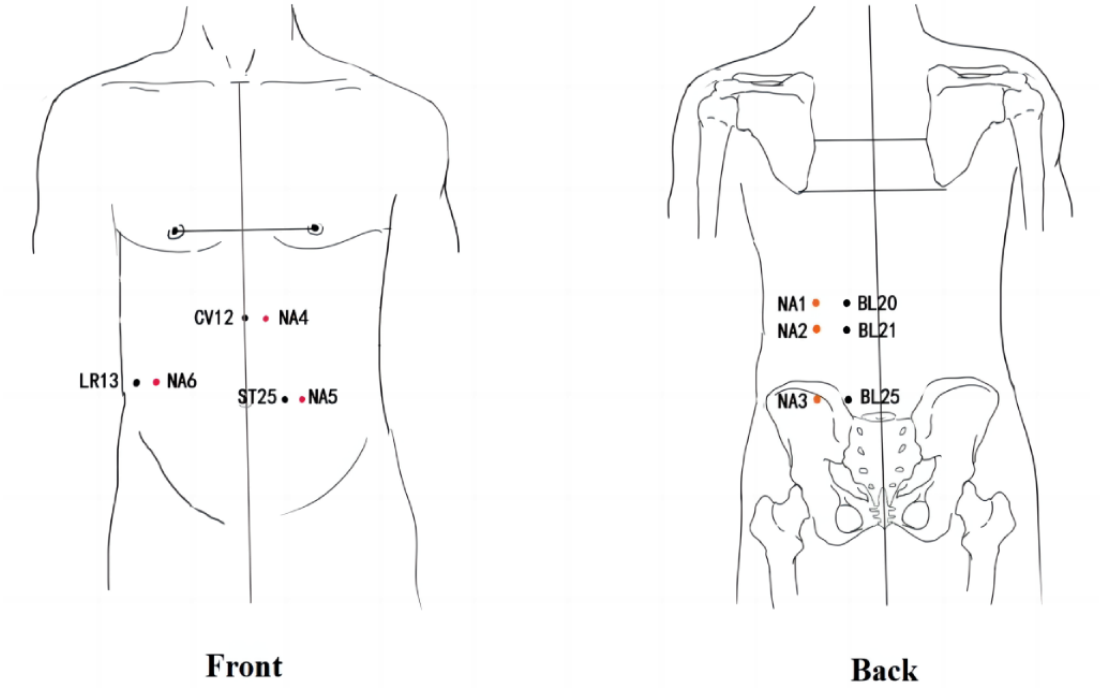
The selection of acupoints for treatment in the ACE group will be based on the theory that obesity is closely related to the spleen, stomach, and large intestine in traditional Chinese medicine and the Shu-Mu acupoints allocation method commonly used in the current clinical treatment of obesity. The acupoint prescription includes BL20 (Pishu), BL21 (Weishu), BL25 (Dachangshu), RN12 (Zhongwan), ST25 (Tianshu), and LR13 (Zhangmen). All acupoints except Zhongwan are selected bilaterally, for a total of 11 acupoints. The locations of these acupoints are shown in Table 2 and Figure 2.

Table 2. The locations of acupoints.

Acupoints	Location
BL20 (Pishu)	In the upper back region, at the same level as the inferior border of the spinous process of the 11th thoracic vertebra (T11), 1.5 B-cun lateral to the posterior median line
BL21 (Weishu)	In the upper back region, at the same level as the inferior border of the spinous process of the 12th thoracic vertebra (T12), 1.5 B-cun lateral to the posterior median line
BL25 (Dachangshu)	In the lumbar region, at the same level as the inferior border of the spinous process of the fourth lumbar vertebra (L4), 1.5 B-cun lateral to the posterior median line
CV12 (Zhongwan)	On the upper abdomen, 4 B-cun superior to the center of the umbilicus, on the anterior median line
ST25 (Tianshu)	On the upper abdomen, 2 B-cun lateral to the center of the umbilicus
LR13 (Zhangmen)	On the lateral abdomen, inferior to the free extremity of the 11th rib

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Figure 2. Locations of acupoints and nonacupoints (NAs). Acupoints: BL20: Pishu, BL21: Weishu, BL25: Dachangshu, CV12: Zhongwan, LR13: Zhangmen, and ST25: Tianshu.



Control Group

The acupoints in the control group will be selected based on the acupoints in the ACE group by moving each acupoint 2-3 cm outward horizontally in the median line (CV12 to the left side only) as a nonacupoints (not located on or overlapping with other meridians). They are labeled NA1, NA2, NA3, NA4, NA5, and NA6, respectively, for a total of 11 acupoints. The locations of these acupoints are shown in Table 3 and Figure 2, marked as red points.

Table 3. The location of nonacupoints (NAs).

Nonacupoint	Location
NA1	The sitting position of the patient, in alignment with BL20 and the midpoint of the first and second lateral line of the bladder channel
NA2	The sitting position of the patient, in alignment with BL21 and the midpoint of the first and second lateral line of the bladder channel
NA3	The sitting position of the patient, in alignment with BL25 and the midpoint of the first and second lateral line of the bladder channel
NA4	The supine position of the patient, in alignment with RN12 and the midpoint of the left kidney and stomach channel
NA5	The supine position of the patient, in alignment with ST25 and the midpoint of the stomach and spleen channel
NA6	The sitting position of the patient, in alignment with LR13; a vertical line is made from Zhangmen to the spleen channel and the midpoint of the vertical line

Operation Instruments

The thread-embedding needle used in this study is an 8# disposable needle (Jiangxi Glance Medical Equipment Co Ltd Production), and the medical protein string is an absorbable collagen line with the specification of 2-0, 2 cm × 20 length (Jiangxi Longteng Biotechnology Co, Ltd).

Manipulation

The specific manipulation is as follows: participants are instructed to be placed in an appropriate position; the separate research assistant marks the acupoints or nonacupoints and routinely disinfects the skin around them; and a sterile sheet is spread, leaving only the buried area. Then, acupuncturists, who are unaware of the group allocation, take a sterile protein cord 1-2 cm long (the length depends on the location of the acupoints), place it on the front end of the trocar, connect the needle core, lift the partial skin with the thumb and forefinger of one hand, and pierce the needle with the other hand. When the piercing reaches the desired depth, apply appropriate push-and-twist techniques, push the needle core and remove the needle tube, and implant the sterile protein string in the subcutaneous tissue or muscle layer of the acupoints. After removing the needle, press the needle hole with a dry cotton ball for half a minute to stop the bleeding. Meanwhile, check that there is no thread residue exposure and no bleeding and then paste a bandage to protect the needle hole. It will be

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recommended that patients do not take a bath for 24 hours and keep the embedding place dry.

Outcomes and Assessment

Primary Outcome

The primary outcome is the change of WC every 2 weeks, from baseline to end points. To collect the measurements, participants will stand their body upright, feet at shoulder width. An inelastic, 1-mm minimal tapeline will be used, set on the midpoint between the upper border hipbone and lower border 12th rib of the right midaxillary line. At the end of normal exhalation, they will be measured around the abdomen in the horizontal direction and without pressing the skin. The WC will be measured in millimeters (mm) and accurate to 1 mm.

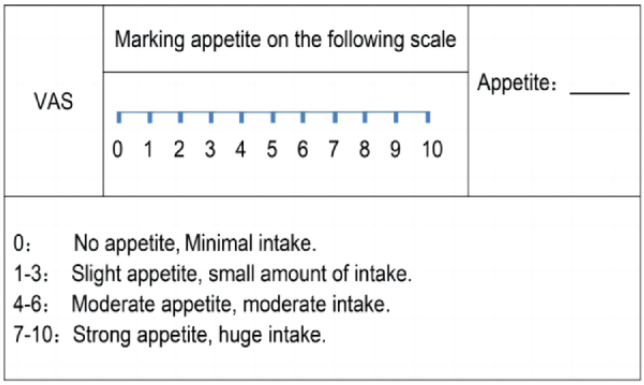
Secondary Outcomes

The following secondary outcomes will be assessed:

1. The change of body weight (BW) will be measured every 2 weeks, from baseline to end points. Participants will be fasting 2 hours before the assessment. Shoes will be taken off, and only light clothing should be worn in a warm room while standing upright in the middle of the calibrated scale. BW will be measured in kilograms (kg) and accurate to 10 g.
2. The change of BMI will be measured every 2 weeks, from baseline to end points: *BMI = BW (kg) ÷ height2 (m2)*. Height will be measured after the weight measurement, with the participants standing upright and close to the measuring stick. Height will be measured from the top of the head to the bottom of the feet in meters (m) and accurate to 1 mm.
3. The change of hip circumference (HC) will be measured every 2 weeks, from baseline to end points. HC is the circumference of the most prominent point of the pelvis. Participants will stand upright, feet at shoulder width. The circumference at the end of the normal exhalation will be measured in millimeters (mm) and accurate to 1 mm.
4. The visual analog scale (VAS) of appetite will be scored every 2 weeks, from baseline to end points. Appetite will be assessed by VAS as reported in Doucet et al [47] (see Figure 3): no appetite and minimal intake (score of 0), slight appetite and a small amount of intake (score of 1-3), moderate appetite and moderate intake (score of 4-6), and strong appetite and huge intake (7-10 score of 7-10).

All of the above measurements and evaluations will be performed by a separate researcher in the morning, with the patient coming to the hospital without eating breakfast.

Figure 3. The visual analogue scale (VAS) of appetite.



Safety Evaluation

Due to puncture injury and protein wire stimulation, participants may experience local sterile inflammatory reactions such as redness, swelling, fever, pain, or small amounts of exudate within 1-5 days, which are normal, generally do not require treatment, and are kept under close observation. If there is more exudate from the acupoints; localized redness; swelling; increased pain; increased temperature; or even protein line spillage, wound fat liquefaction, or nerve damage, treatment will be suspended when these adverse reactions occur. Participants will be treated aggressively until they have fully recovered and reported to the study center for evaluation by a medical professional to see if the trial can continue. Serious or unexpected adverse events will be verbally reported within 24 to 48 hours. All information will be classified as a safety event.

Data Management and Quality Control

The outcome evaluator will complete the initial data in the case report form and enter it into a Microsoft Excel spreadsheet. The protocol will be reviewed several times by an acupuncturist with the title of director and a statistical expert. To ensure the smooth conduct of the study, the study leader shall provide uniform training to all study personnel before the start of the study and provide detailed operational training on the project implementation protocol and observation indicators to familiarize them with the study process and specific implementation details to ensure the reliability of the study results. The project leader shall supervise and check the entire study process to confirm that all study data and case report forms are recorded and reported truthfully, accurately, completely, and consistently with the original data. Any deviation from the protocol will be reported to the ethics committee of The Sports Trauma Specialist Hospital of Yunnan Province, which will ultimately decide whether we must change the protocol or terminate the trial. To ensure participant compliance, all treatments and tests will be provided free of charge.

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Statistical Analysis

All data will be analyzed by SPSS statistical software (version 19.0; IBM Corp). The clinical outcomes and baseline characteristics are based on the intention-to-treat population, which will include participants who have received at least one treatment. Continuous variables will be shown as the mean and SD, whereas the nonnormally distributed variables will be presented as the median and IQR. Categorical variables will be described as numbers and percentages. The normality of continuous variables will be determined using the Shapiro-Wilk test, Kolmogorov-Smirnov test, skewness, and kurtosis. The homogeneity of continuous variables will be determined by *F*-test, Brown-Forsythe, and Bartlett tests. Comparisons between groups will be made using independent samples 2-tailed *t* tests or nonparametric tests (Mann-Whitney *U* test). Repeated measures within groups (≥3) will be analyzed using one-way ANOVA or nonparametric (Friedman) tests. Paired 2-tailed *t* tests or nonparametric tests (Wilcoxon test) will be used for within-group pre-post comparisons. For categorical data, the chi-square test will be used to assess the significance of differences. Values of $P<.05$ will be considered significant using a 2-sided test.

Results

The start of recruitment began in August 2019 and is expected to end in September 2023.

Discussion

Expected Findings

In the past, obesity was considered a problem in high-income countries. However, recent studies reported that the prevalence of obesity is rapidly increasing in low- and middle-income countries [4,48-50]. As a type of obesity, AO is also related to cardiovascular diseases, cancer, and many other diseases [51-54].

ACE is a traditional Chinese medical practice that has been used in clinical practice since the mid-1960s. Compared with other treatments, ACE has the advantages of a short single-treatment time, long effective stimulation time, low impact on daily life, as well as being time-saving and low cost and having few side effects, which are well suited for the fast-paced modern society and become gradually favorable to patients who are obese. As a specific type of acupuncture therapy, ACE has gained substantial attention in the management of obesity in recent years. Research has demonstrated that ACE has a certain impact on obesity. First, it can reduce BW by regulating appetite and food intake. ACE stimulates specific acupoints, promoting the release of neurotransmitters and hormones to regulate feelings of hunger and satiety and ultimately reducing food intake [55]. Second, ACE can improve metabolic function. Studies have shown that acupoint stimulation can affect various physiological processes, including the endocrine, nervous, and immune systems, thus regulating energy and fat metabolism, improving insulin sensitivity, and enhancing blood lipid levels [41]. Additionally, ACE may also have positive effects on obesity by improving psychological well-being and sleep quality, among other factors [56]. However, current research has some limitations, including small sample sizes and inconsistent study designs [57]. Therefore, to better assess the effectiveness and safety of ACE treatment, further high-quality studies with larger sample sizes are needed.

The decrease of several indicators such as BW, WC, BMI, HC, and appetite is not only beneficial to personal health but also helps people who are obese to reshape their bodies [58]. Among them, BMI is the most commonly used indicator in obesity research, but it mainly reflects total body fat and cannot distinguish between fatty obesity and muscular obesity. HC is affected by both sex and age, and changes in abdominal fat cannot be accurately reflected promptly [59]. WC can directly reflect abdominal fat, so we use WC as the main outcome indicator and other related indicators as secondary outcome indicators. According to the classification adopted by the Chinese Medical Association of China in 2019, the inclusion criteria was set as WC ≥90 cm for male individuals and ≥85 cm for female individuals, rather than those of other Asian countries (WC ≥102 cm for male individuals and WC ≥88 cm for female individuals or WC ≥ 90cm for both male and female individuals) [6,60].

The combination of Shu and Mu acupoints is one of the classical methods of acupuncture and is mainly used in clinical practice to treat metabolic diseases of the viscera. According to the identification theory of traditional Chinese medicine, obesity is mainly caused by the dysfunction of the spleen, stomach, and large intestine, so we chose the Shu and Mu acupoints of these 3 internal organs as the treatment prescription. Our preliminary analysis of 175 obesity ACEs in the early stage also found that the existing high-frequency acupoints for obesity ACEs were mainly Shu and Mu acupoints of the spleen, stomach, and large intestine [61].

Strengths and Limitations

First, this study is a multicenter RCT designed to investigate the efficacy and safety of ACE in AO with a relatively long study period, and the results will provide powerful evidence for the clinical application of ACE in the treatment of obesity. Second, participants' diet and exercise will not be intervened, which will allow participants to maintain their original lifestyle habits throughout and maximize the efficacy of ACE. Finally, to maintain the success of the double-blind method, contact between participants from different groups will be avoided. The acupuncturist, data evaluator, and statistician will also be hidden from the group assignment, which will minimize possible bias in the results.

Limitations of this study are as follows. First, the relatively short follow-up period of this study may not be comprehensive enough to assess the durability of ACE efficacy. Second, the selection of nonacupuncture acupoints as an intervention in the control group in this study may inevitably produce some efficacy as well [62,63]. Third, only patients with AO are selected as the study population in this study, and further studies on different types of obesity will be conducted at a later stage.

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Conclusions

In summary, our trial aims to investigate the difference in the effectiveness of catgut embedding at acupoints and catgut embedding at nonacupoints in patients with AO. This finding will provide reliable evidence to support whether ACE is an effective and safe treatment for AO.

Acknowledgments

All authors are grateful for the support of all participants or participants who will join the trial, as well as the support of other institutions.

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TG and XZ (doczhangxh@163.com) are cocorresponding authors for this manuscript.

Data Availability

The data sets generated or analyzed in this study will not be publicly available. Consent and ethical approval for this study do not include a provision for the sharing of data from this study.

Authors' Contributions

TG and XZ are the principal investigators and were primarily responsible for the conception and design of this study; QL and GH wrote the original manuscript; RY, ZL, XP, XT, RZ, and YH participated in the implementation of the study and acquisition of data; XZ was primarily responsible for the analysis of the data; and CX provided ethical approval. All authors contributed to the revision and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist.
[PDF File (Adobe PDF File), 109 KB - resprot_v12i1e46863_app1.pdf]

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Abbreviations

ACE: acupoint catgut embedding
AO: abdominal obesity
BW: body weight
CONSORT: Consolidated Standards for Reporting Trials
HC: hip circumference
RCT: randomized controlled trial
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
VAS: visual analogue scale
WC: waist circumference

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Protocol

Does an Internet-Based Emotion Regulation Intervention Provide Added Value for Acute Psychiatric Inpatient Care? Protocol for a Randomized Controlled Pilot Trial

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Abstract

Background: There is a lack of studies on internet-based interventions in inpatient settings. This is especially true for studies of internet-based interventions in acute psychiatric inpatient care. Internet-based interventions in this specific setting may provide benefits such as patient empowerment and overall improved treatment outcomes. However, there may also be specific barriers to their implementation that are unique due to the complexity of acute psychiatric inpatient care.

Objective: The aim of this study is to examine the feasibility and preliminary evidence for effectiveness of a web-based emotion regulation intervention provided as an add-on to acute psychiatric inpatient care.

Methods: The goal is to randomly allocate 60 patients with a range of different diagnoses in a 1:1 ratio to either treatment as usual (TAU), which consists of acute psychiatric inpatient treatment, or to the intervention group, which will receive TAU plus access to a web-based intervention that focuses on reduction of emotion regulation difficulties and improvement of emotion regulation skills. The primary outcome is symptom severity, assessed with the short form of the Brief Symptom Inventory at baseline, after 4 weeks, after 8 weeks, and at hospital discharge. Secondary outcomes include 2 emotion regulation parameters, intervention use, usability, patient satisfaction, and reasons for patient loss to follow-up.

Results: Participant recruitment started in August 2021 and as of March 2023 was ongoing. First publication of study results is expected in 2024.

Conclusions: This study protocol describes a study that intends to examine a web-based emotion regulation intervention in acute psychiatric inpatient care. The study will provide information on the feasibility of the intervention and possible effects on symptom severity and emotion regulation. The results will provide new insights on blended treatment, in this case the combination of a web-based intervention and face-to-face psychiatric treatment, in an understudied patient group and setting.

Trial Registration: ClinicalTrials.gov NCT04990674; https://clinicaltrials.gov/ct2/show/NCT04990674

International Registered Report Identifier (IRRID): DERR1-10.2196/47656

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KEYWORDS

blended treatment; inpatient; emotion regulation; internet intervention; acute psychiatric setting; randomized controlled pilot trial; randomized controlled trial; RCT; transdiagnostic; feasibility; emotion; mental health; psychiatric; psychiatry; randomized; internet based; digital health

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Introduction

Internet interventions are efficacious and effective for treating various mental health disorders [1-3]. In recent years, the combination of internet intervention and face-to-face treatment (blended treatment [4,5]) has been examined. Several studies point to the efficacy and effectiveness of blended treatment approaches in the outpatient setting for patients with depression [6-9]. Studies have also been conducted on outpatient blended treatment for anxiety disorders [10] and substance dependence [11,12]. Moreover, blended treatments with a more explicit transdiagnostic focus have also been examined in the outpatient setting. Examples include a treatment for emotional disorders [13] and transdiagnostic treatments with an emotion regulation focus [14]. However, only a few studies on blended treatment have been conducted with adult inpatients.

Several studies have focused on web-based and mobile-based interventions as aftercare after an inpatient stay [15-20]. For example, 2 studies evaluated aftercare interventions for eating disorders [16,17]. The first found a therapist-guided smartphone-based intervention showed high acceptance rates but nonsignificant effects on BMI and eating disorder symptoms [16]. The second found that a web-based program for women with bulimia nervosa applied as aftercare led to a significantly lower frequency of vomiting episodes but no significant differences in abstinence rates compared to treatment as usual (TAU) [17]. Another study investigated the effect of a self-help smartphone app on self-esteem among inpatients with depression after discharge from a psychiatric hospital [15]. While there was no significant improvement in the primary outcome (self-esteem) or secondary outcomes (depressive symptoms and quality of life), there was a small positive effect on self-competence in favor of the intervention group. Schlicker et al [18] examined a text message–based maintenance intervention for depression and determined whether individualized messages would lead to better outcomes than standardized messages that target emotion regulation. The results of the study suggested that standardized messages with an emotion regulation focus led to a significantly smaller increase in depressive symptoms than a waitlist condition. This was not the case for the condition with the individualized messages.

Regarding transdiagnostic interventions applied as aftercare in samples with mixed diagnoses, a study by Ebert et al [19] examined an internet-based maintenance intervention after inpatient treatment and found the intervention to be more effective than TAU with regard to the long-term outcomes of inpatient psychotherapy. Furthermore, a study by Zwerenz et al [20] was able to show that a group that received a psychodynamic web-based intervention provided after inpatient psychotherapy had improved depressive symptoms, quality of life, and emotional competence compared to a waitlist control group. However, completion rates for the program were low.

Regarding internet interventions applied during an inpatient stay, a few studies have focused on the feasibility of these types of interventions. Dorow and colleagues [21] examined an internet-based self-management program for depression, focusing on user acceptance and chances and barriers from both the patient and medical expert perspectives. User acceptance was reported to be moderate to high. Experts mentioned some aspects to be relevant barriers, such as technical problems, the severity of the course of depression, and the ability of patients to concentrate. Patients mentioned positive aspects of the intervention, such as ease of use and flexible availability, but also negative aspects, such as the design and structure of the program. Schwarz and colleagues [22] examined the feasibility of a tool for depressive disorders in inpatient care. They reported feasibility of the intervention but also low use rates. Moreover, general attitudes toward and acceptance of internet interventions by mental health professionals working in psychiatric hospitals have also been examined [23,24]. For example, a study by Sander and colleagues [23] showed that participants had little experience or knowledge about internet-delivered interventions. Their attitudes toward these types of interventions in inpatient care were indifferent. Participants mentioned benefits, such as optimized treatment structure and patient empowerment. They also mentioned anticipated barriers, such as patient symptom severity and insufficient technical equipment.

Even fewer studies have focused on the effectiveness of internet interventions during inpatient treatment. Zwerenz and colleagues [25,26] examined an internet intervention in an inpatient setting where patients with depression received the self-guided program as an addition to psychodynamic psychotherapy. The study showed a positive effect of the intervention (inpatient stay plus access to the internet intervention) on depressive symptoms with small to medium effect size at the end of the intervention (d=0.44) [25] and a medium effect size (d=0.58) at a follow-up assessment compared to an active control group [26]. Richter and colleagues [27] examined the same program that was investigated by Zwerenz and colleagues [25,26] but in a routine psychiatric inpatient setting with guidance added for the program. They found a medium-sized effect (d=–0.73) in favor of the intervention group, which received TAU plus access to the guided internet intervention, compared to the TAU group at the 12-week assessment timepoint and earlier discharge for patients who received access to the internet intervention compared to patients in the TAU condition. Finally, Bendig and colleagues [28] examined the feasibility of blended group training for social skills in inpatient acute psychiatric care. The blended treatment lasted 4 weeks and consisted of 4 face-to-face group sessions and 3 online modules. In the 1-group trial without a control group, the effect on social skills was not statistically significant, but the blended group training was deemed feasible for use in an acute inpatient setting.

Implementing an internet intervention in an acute psychiatric inpatient setting may offer benefits. On the one hand, the addition of an internet intervention to standard care or TAU may improve overall treatment effects, as has been demonstrated previously in outpatients and in studies focusing on inpatient treatment [6,25-27]. An internet intervention may thus provide a useful complement to treatment, one that is easily accessible during the inpatient stay, where patients may have idle timeslots during the treatment program. The few studies on an internet intervention in acute or routine psychiatric inpatient settings point toward the feasibility of such interventions [27,28].

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However, implementing an internet intervention in acute psychiatric care may also come with specific barriers and complexities. Individuals in acute psychiatric inpatient care often enter treatment in acute crisis with severe disorders and with one or more comorbidities. A recent study by Becker and colleagues [29] showed that the number of diagnoses and symptom severity were associated with active or inactive participation in an online intervention during and after inpatient and day-clinic psychotherapeutic treatment. A lack of motivation due to symptom severity was also a reason for patients to decline participation in an inpatient study on e–mental health implementation by Van Assche et al [30]. According to Wentzel and colleagues [31], crisis risk and psychosocial problems are important factors to consider for a fit for blended treatment. Moreover, stays in acute wards are nowadays often short [28], and during this time, inpatients may already be saturated with other treatment components (eg, medication, psychotherapy, ergotherapy, and physiotherapy), making it difficult for patients to focus on an additional internet intervention. Wentzel and colleagues [31] also mention that having a private place to work is an important condition for blended treatment. This may not be available in an acute inpatient ward. Finally, all the different stakeholders involved in acute inpatient treatment may also make the implementation of such an intervention more complex [28].

The aim of this randomized controlled pilot trial is to investigate an internet-based intervention in acute psychiatric inpatient care. To this end, a web-based emotion regulation intervention (REMOTION; an acronym for “Regulate Emotion”) will be provided as an add-on to acute inpatient treatment in public psychiatric care at a university hospital. Different feasibility parameters will be recorded, including specific intervention parameters, such as use of the program and adherence, usability, satisfaction with the intervention, and reasons for patient loss to follow-up. Effects of the intervention will be assessed by comparing patients that receive access to REMOTION in addition to TAU to patients who receive TAU only on general symptom severity and emotion regulation difficulties and skills.

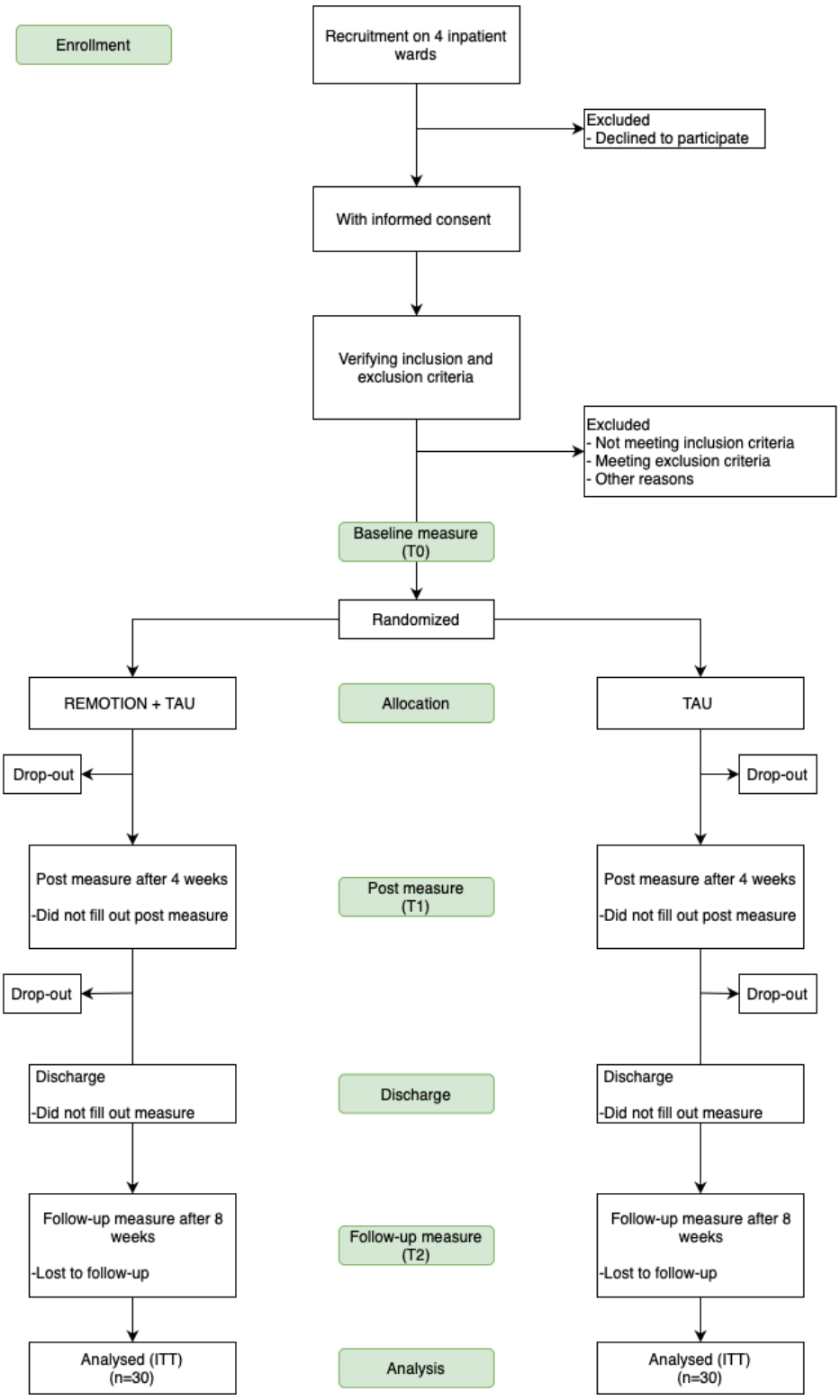
Methods

Study Design

Sixty patients will be randomized in a 1:1 ratio to 2 trial arms: REMOTION plus TAU and TAU alone. Assessments will take place at baseline, after 4 weeks, after 8 weeks, and after discharge from inpatient stay (Figure 1). Assessments will take place irrespective of inpatient stay duration. The planned duration of the study is approximately 2 years, to reach 60 individuals. Since external validity and the generalizability of the results to acute inpatient care settings play an important role, the inclusion and exclusion criteria are broadly defined.

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Figure 1. Planned study flow. Discharge can take place at any time after randomization. ITT: intention to treat; TAU: treatment as usual.



Setting

The setting for the study is the acute inpatient psychiatric wards at the University Hospital of Psychiatry and Psychotherapy, Bern, Switzerland. The University Hospital of Psychiatry and Psychotherapy is part of the Universitäre Psychiatrische Dienste (UPD), Bern. The UPD guarantees psychiatric care in the Bern region, including adult and geriatric psychiatry, as well as child and adolescent psychiatry for the entire canton [32]. The University Hospital of Psychiatry and Psychotherapy treats patients with a variety of mental health diagnoses. For the study, patients are recruited from 4 different acute inpatient wards at the University Hospital of Psychiatry and Psychotherapy.

Sample Size

Based on recommendations in the literature [33], the aim is to recruit a minimum of 30 participants per group during the trial.

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No power analysis is performed, as is commonly the case with randomized controlled pilot trials.

Eligibility Criteria

To take part in the study, patients should fulfill the following criteria: (1) be older than 18 years, (2) be in acute inpatient treatment, (3) have access to the internet, and (4) provide written informed consent. The exclusion criteria include (1) participation in another specific intervention for emotion regulation; (2) a current episode or a history of psychotic disorders or bipolar disorder, intellectual disability, or organic mental disorders; (3) acute suicidality; and (4) not being fluent in German.

Procedure

After consultation with the individual ward team at the weekly interdisciplinary ward meeting, individual patients are asked about study participation. Information on the study is provided and patients are asked if they would like to participate. Once written informed consent is provided, the inclusion and exclusion criteria are checked. Eligible patients are asked to complete the baseline questionnaires online. This takes approximately 15 to 20 minutes. Randomization occurs after baseline assessment. A computerized randomization procedure concealed from the study team is used to randomize patients. Patients randomized to the intervention group receive immediate access to REMOTION. Patients in TAU are informed that they can have access after the 8-week assessment, per request. There is no blinding implemented in the study. During the study period, the ward staff is informed about a patient's designated trial arm. Patients receive a reminder to work on the program, either face-to-face from the study team if still on the ward or by telephone or email if discharge has already occurred, once a week for 4 weeks. For individuals who fail to complete follow-up assessments, interviews on reasons for loss to follow-up will be performed via telephone. Prior to study initiation, all 4 acute ward teams are informed in detail about the study, including the provision of a 1-hour workshop on the REMOTION intervention for each ward.

Interventions

Control Group (TAU)

The active control group in this study receives TAU, comprising acute psychiatric inpatient treatment at the University Hospital of Psychiatry and Psychotherapy. This treatment consists of integrative, psychiatric-psychotherapeutic treatment. Depending on the individual conditions, it includes pharmacotherapy informed by current guidelines and adapted to individual needs, psychotherapy, contact with psychiatric nursing, specialist therapies such as occupational therapy or music therapy, and contact with social workers. The ward teams are informed not to talk about REMOTION content with patients in the control group. Individuals in the control group receive access to the intervention on request after the 8-week mark.

Intervention Group (REMOTION and TAU)

Patients in the intervention arm are given access to REMOTION in addition to TAU on the acute inpatient ward. The web-based intervention REMOTION was developed at the University of Bern by authors LLB and TB with input from author FM. It is structurally based on the extended process model (EPM) of emotion regulation [34]. It is currently also being examined as an add-on to outpatient psychotherapy in a different study [35] and is being examined in a large, randomized, controlled, 3-armed outpatient trial in Germany that focuses on effectiveness [36]. It has never been examined in an inpatient setting up to this point. The intervention contains an introduction module and 5 further modules: psychoeducation, identification, selection, implementation, and monitoring/flexibility [35]. The intervention's aim is to reduce symptom severity and improve patient emotion regulation. As such, it does not target specific mental health disorders but is meant to be applied transdiagnostically, across disorders. Such an intervention may be of particular interest for inpatient populations, where comorbidity is likely highly prevalent [37]. A full overview of the intervention content for each module can be found in Table 1 and has also been published in 2 previous publications [35,36]. REMOTION is only available in German. The intervention runs on a server from the University of Bern and access is strictly password protected. Individuals in the intervention group immediately receive access to REMOTION and are asked to work on content for 4 weeks (1 to 2 modules a week). The study team reminds patients to work on the content once a week face-to-face if patients are still on the ward or by telephone or email if already discharged. Patients on the 4 wards have access to their smartphones, laptops, and tablets during their inpatient stay. Moreover, each ward is equipped with a ward computer that patients can use to engage with the program throughout their stay, if desired.

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Table 1. REMOTION modules and content. Note that this entire textbox is adapted from tables already published in previous publications by Bielinski et al [35] and Trimpop et al [36], which are published under Creative Commons Attribution 4.0 International License [38].

Module	Content of module
Introduction	This module provides information on the content of the intervention and instructs patients on how to use the intervention.
Psychoeducation	This module provides psychoeducational content on emotions, their function, and types of emotional experience. It also introduces the concept of emotion regulation and its relationship to mental illness.
Identification	Emotional awareness (the perception substep of the identification stage of emotion regulation [34]) is explored in this module. The value of emotion regulation and information on if and when to regulate emotions is provided in this module.
Selection	In the selection module, patients learn about the types of emotion regulation strategies that are available. Situation selection or modification, attentional deployment, change of cognition, and response modulation are introduced to patients [39]. Furthermore, strategies specific to over- and underregulated states [40-42] are described.
Implementation	In the implementation module, patients learn how the strategies from the previous module can be implemented. Exercises are introduced for every emotion regulation strategy, and application of strategies in daily life is discussed.
Monitoring/flexibility	In the monitoring/flexibility module, patients are motivated to flexibly use emotion regulation strategies. Modifying strategies, maintaining, switching, and stopping [34,43] are discussed. Patients are encouraged to apply strategies to different contexts, to practice, and to try sequences or blends of strategies.

Measures

Overview

All measures will be assessed via the internet, except for patient diagnoses at intake and medication at discharge, which will be retrieved from the hospital's patient records. Interviews with patients will be conducted via telephone, and interviews with ward teams will be conducted face-to-face or via telephone. At baseline assessment, several demographic and other items will be assessed. These include questions on age, gender, nationality, mother tongue, highest degree of education, employment status, civil status, household size and composition, income, previous inpatient stays, previous experience with emotion regulation interventions, current involvement in an emotion regulation intervention, current involvement in other online therapy interventions, and frequency of use of online media. Study feasibility parameters, such as number of individuals approached for written informed consent, number of individuals with written informed consent, number randomized, and number of patients who completed all questionnaires, will be recorded for the study flow and presented in the main outcome paper to inform other institutions on the feasibility of the study design.

Primary Outcome Measure

The short version of the Brief Symptom Inventory (BSI-18) [44-46] is used to assess the primary outcome: general symptom severity. The BSI-18 contains the Global Severity Index (GSI), including all 18 items, as well as the three 6-item scales Somatization, Depression, and Anxiety [45]. The internal consistency is considered good for all 4 scales: Somatization (α=.82), Depression (α=.87), Anxiety (α=.84), and GSI (α=.93) [45]. The items are assessed on a 5-point Likert scale ranging from 0="not at all" to 4="very strong." The BSI-18 is presented to patients at baseline assessment, after 4 weeks, at discharge, and after 8 weeks.

Secondary Outcome Measures

Emotion Regulation

Emotion regulation is assessed with 2 different questionnaires at baseline, after 4 weeks, after 8 weeks, and at discharge. One of the two questionnaires is the Emotion Regulation Skills Questionnaire (Fragebogen zur standardisierten Selbsteinschätzung emotionaler Kompetenzen; SEK-27) [47]. The questionnaire assesses emotional skills and includes a total of 27 items. The items are assessed on a 5-point Likert scale ranging from 0="not at all" to 4="almost always." Studies have found good reliability and validity for the German and English versions of the questionnaire [48,49]. The Cronbach α is between .68 and .81 for the subscales and .90 for the total scale [47].

The second questionnaire is the Difficulties in Emotion Regulation Questionnaire (DERS) [50]; the study uses the German version by Ehring et al [51]. The DERS was developed to assess emotion regulation difficulties. It includes 6 subscales: lack of emotional awareness (Awareness), lack of emotional clarity (Clarity), nonacceptance of emotional responses (Nonacceptance), limited access to emotion regulation strategies (Strategies), difficulties engaging in goal-directed behaviors (Goals), and impulse control difficulties (Impulse) [50]. These subscales and the overall DERS score have high internal consistency (α=.93) [50].

System Usability

The System Usability Scale (SUS) is a 10-item scale giving a global view of subjective assessments of system usability [52]. The questionnaire asks users to rate their level of agreement with statements covering a range of usability characteristics, such as the complexity of the system and any support or training participants feel they need to use the system effectively. The evaluation of the questionnaire results in a usability score in the range of 0 to 100. Values greater than 68 typically indicate good usability [53]. The questionnaire will be provided to individuals in the intervention group after 4 weeks, after 8 weeks, and at discharge.

Patient Satisfaction

Patient satisfaction will be assessed with the Client Satisfaction Questionnaire (CSQ-8 [54]; the German version is the Fragebogen zur Patientenzufriedenheit; ZUF-8 [55]). Eight items are used to measure general satisfaction with aspects of the treatment received. The CSQ-8 is suitable for economic

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screening of patient satisfaction The CSQ-8 consists of 8 items that are formulated as questions; each has 4 predefined answer options without a neutral position (eg, excellent, good, less good, and poor) [55]. The CSQ-8 proves to be a reliable (Cronbach α=.90) 1-dimensional scale [56] and has validity regarding detailed quality assessment of the service and treatment outcome [56]. For this study, the CSQ-8 was adapted for an internet intervention (as has been done in previous studies [57,58]). The questionnaire will be provided to individuals in the intervention group after 4 weeks, after 8 weeks, and at discharge.

Program Use

Program use will be assessed by number of modules completed at 4 weeks and 8 weeks, number of exercises completed at 4 weeks and 8 weeks, and time spent in the program at 4 weeks and 8 weeks. These use parameters will be assessed for the intervention arm only.

Interviews With Patients Lost to Follow-Up

Telephone interviews are conducted with patients who are lost to follow-up. The purpose is to explore reasons why patients have not continued with the intervention and have not completed the questionnaires. The authors designed questions specific to the study. Interviews with patients lost to follow-up will be conducted by phone and audio recorded.

Other Measures

Interviews With Acute Inpatient Ward Staff

During the study, interviews with staff members from 3 of the 4 acute ward teams will be conducted. These interviews will occur at the earliest a few months after study commencement for teams to have sufficient experience with the intervention. Purposive sampling will be applied. A minimum of 1 member of the following stakeholder groups per ward will be interviewed: physicians, psychologists, and nurses, and if applicable, social workers and other stakeholder groups. Ward staff will provide written informed consent, fill out a short demographic data questionnaire, and be interviewed using a semistructured interview developed specifically for the study. Interview questions focus on expectations and attitudes toward blended treatment in acute inpatient care, specific experiences with the web-based intervention examined in this study, and the implementation of internet-based interventions in acute inpatient care. The analyses of these interviews will be published in a separate publication to the main outcome publication.

Planned Analysis

Feasibility parameters (use, usability, and patient satisfaction) will be analyzed descriptively. Means, SD, and CIs will be reported for continuous data and counts or percentages will be reported for nominal data. The recorded interviews of patients lost to follow-up will be transcribed according to rules specified by Dresing and Pehl [59]. Patient interviews will then be analyzed with a content analysis approach [60]. The focus will be on the coding process to build categories where similarities and differences between patients will be explored [60]. MAXQDA (2022 version; VERBI Software) will be used for the analysis.

To examine the effects of the intervention, means and SDs for the primary and secondary outcomes will be reported at baseline (T0), at the end of the intervention (4 weeks; T1), at inpatient discharge, and at follow-up after 8 weeks (T2). Within- and between-groups effect sizes will be calculated using guidelines specified by Cohen [61].

Data will also be examined using inferential statistics. An intention-to-treat approach will be used. All patients who were initially assigned after randomization will be included. In a first step, baseline differences between the intervention group and the control group will be examined for all relevant variables. For metric variables, this is done using a 2-tailed *t* test for independent samples. For nominally scaled data, the chi-square test is used. In case of meaningful differences, those variables will be included in further analyses and controlled accordingly. In a second step, mixed models with “group” as the between-group factor and “time” as the within-group factor will be used to examine differences between groups. In a first analysis, a model including the study timepoints (eg, baseline, after 4 weeks, and after 8 weeks) will be calculated. In addition, an analysis including the discharge timepoint in the model will also be calculated. Specifically, the interaction between time and group will be of interest. The significance level is set at 5%.

Interviews with ward staff members will be audio-recorded and then transcribed using the guidelines specified by Dresing and Pehl [59]. Transcripts will be analyzed using thematic analysis [62] to examine ward staff experiences with the REMOTION intervention. MAXQDA software will be used for the analysis.

All quantitative analyses will be performed with the most current versions of R (R Core Team) and SPSS (IBM Corp).

Ethical Considerations

The study has been approved by the Ethics Committee of the Canton of Bern, Switzerland (2020-01139). Informed consent is obtained from all participants. The trial is registered with clinicaltrials.gov (NCT04990674). The study will be conducted according to local regulations and the Declaration of Helsinki. The CONSORT-EHEALTH (Consolidated Standards of Reporting Trials for e-Health) [63] checklist will be followed in reporting the trial. Participants receive no compensation for taking part in the trial.

Results

Recruitment for the study started in August 2021. As of March 2023, it was still ongoing. Results for the study are expected in 2024.

Discussion

Expected Findings

While a few trials on blended treatment in inpatient care exist, patients in the acute psychiatric inpatient setting are understudied, and there is a need for the examination and evaluation of internet-based interventions in this specific setting. This randomized controlled pilot trial explores a web-based emotion regulation intervention in this treatment setting. The

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study is designed to obtain information on the feasibility of the intervention. It is also designed to provide estimates of the effectiveness concerning reduction of symptom severity and improvement of emotion regulation. The study will inform future trials on blended treatment (ie, the combination of internet-based interventions with face-to-face treatment) in acute psychiatric inpatient care and thus provide evidence on the potential added value of a web-based intervention in this specific setting.

Limitations

This is a randomized controlled pilot trial, and the targeted sample size is small. All estimations of possible effects on symptom severity and emotion regulation are thus preliminary only. The focus of the study lies with feasibility. As there are only a few studies on internet interventions in acute psychiatric care, the study is inherently exploratory. Several components of the specific acute psychiatric inpatient care setting may be challenging for study feasibility: recruitment of more severely impaired patients, fast turnaround on wards, the possibility of conversations between patients from different trial conditions on one ward, and multiple stakeholders being involved in treatment. We have tried to consider these factors by providing an adequate study duration; informing ward staff in detail about the study prior to commencement, including the fact that the TAU group should not receive information on REMOTION content; and by incorporating weekly reminders to work on the intervention, even if patients have been discharged.

Conclusion

This randomized controlled pilot study is the first to examine a web-based emotion regulation intervention, REMOTION, in acute psychiatric inpatient care at a public university hospital. This type of blended treatment is grossly understudied. The results of the study will provide information on the potential added value of such an intervention for patients with severe mental health disorders in acute psychiatric care.

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Data Availability

The data sets generated and analyzed during the study described in this protocol will be available from the corresponding author on reasonable request.

Authors' Contributions

LLB and GW drafted the first version of the manuscript. FM, TB and CN provided critical revision of further drafts of the manuscript. LLB, FM, TB and CN contributed to conceptualization of the study. FM is the principal investigator of the study.

Conflicts of Interest

CN is a member of the advisory boards of Idorsia and Lundbeck. The other authors have no conflicts of interest to declare.

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Abbreviations

BSI: Brief Symptom Inventory
CSQ: Client Satisfaction Questionnaire
DERS: Difficulties in Emotion Regulation Questionnaire
EPM: extended process model
GSI: Global Severity Index
REMOTION: Regulate Emotion
SEK: Fragebogen zur standardisierten Selbsteinschätzung emotionaler Kompetenzen
SUS: System Usability Scale
TAU: treatment as usual
UPD: Universitäre Psychiatrische Dienste
ZUF: Fragebogen zur Patientenzufriedenheit

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Protocol

Creating an Innovative Artificial Intelligence–Based Technology (TCRact) for Designing and Optimizing T Cell Receptors for Use in Cancer Immunotherapies: Protocol for an Observational Trial

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Abstract

Background: Cancer continues to be the leading cause of mortality in high-income countries, necessitating the development of more precise and effective treatment modalities. Immunotherapy, specifically adoptive cell transfer of T cell receptor (TCR)-engineered T cells (TCR-T therapy), has shown promise in engaging the immune system for cancer treatment. One of the biggest challenges in the development of TCR-T therapies is the proper prediction of the pairing between TCRs and peptide-human leukocyte antigen (pHLAs). Modern computational immunology, using artificial intelligence (AI)-based platforms, provides the means to optimize the speed and accuracy of TCR screening and discovery.

Objective: This study proposes an observational clinical trial protocol to collect patient samples and generate a database of pHLA:TCR sequences to aid the development of an AI-based platform for efficient selection of specific TCRs.

Methods: The multicenter observational study, involving 8 participating hospitals, aims to enroll patients diagnosed with stage II, III, or IV colorectal cancer adenocarcinoma.

Results: Patient recruitment has recently been completed, with 100 participants enrolled. Primary tumor tissue and peripheral blood samples have been obtained, and peripheral blood mononuclear cells have been isolated and cryopreserved. Nucleic acid

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extraction (DNA and RNA) has been performed in 86 cases. Additionally, 57 samples underwent whole exome sequencing to determine the presence of somatic mutations and RNA sequencing for gene expression profiling.

Conclusions: The results of this study may have a significant impact on the treatment of patients with colorectal cancer. The comprehensive database of pHLA:TCR sequences generated through this observational clinical trial will facilitate the development of the AI-based platform for TCR selection. The results obtained thus far demonstrate successful patient recruitment and sample collection, laying the foundation for further analysis and the development of an innovative tool to expedite and enhance TCR selection for precision cancer treatments.

Trial Registration: ClinicalTrials.gov NCT04994093; https://clinicaltrials.gov/ct2/show/NCT04994093

International Registered Report Identifier (IRRID): DERR1-10.2196/45872

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KEYWORDS

AI; artificial intelligence; colorectal cancer; HLA; human leukocyte antigen; immunotherapy; neoantigen; T cell receptors; TCR

Introduction

Overview

Cancer has been recognized as a leading cause of death in high-income countries [1]. Currently, cancer treatment is based on 1 of the 3 available modalities: surgery, radiotherapy, and/or chemotherapy. However, recent research advancements in the field of cancer molecular biology have contributed to the development of novel tumor treatment approaches, such as targeted therapies and immunotherapies [2].

Immunotherapy uses the immune system against cancer cells by using monoclonal antibodies, tumor vaccines, or adoptive cell transfer (ACT). In 2013, immunotherapy was announced as the breakthrough technology of the year by the prestigious journal *Science*, while in 2018, two immunologists, James P Allison and Tasuku Honjo, were awarded the Nobel Prize in Medicine and Physiology for the discovery of the so-called immune checkpoints: programmed death receptor 1 and cytotoxic T cell antigen 4 [3,4]. They have shown that antibodies blocking these receptors, known as immune checkpoint inhibitors, cause reactivation of T cells, thus allowing them to attack and eradicate cancer cells. The first immune checkpoint inhibitor (ipilimumab) was approved by the US Food and Drug Administration (FDA) in 2011 to treat metastatic melanoma [5]. Recognition of immunotherapy as a cancer treatment modality paved the way for further studies and the development of other immunotherapeutic strategies.

Advancements in ACT for Cancer Treatment

ACT is a type of immunotherapy where tumor-reactive immunocytes are infused into a patient with cancer to eradicate tumor cells and maintain durable immune responses. To date, T lymphocytes are the most commonly used immune cells in ACT. T cells are responsible for a specific recognition of tumor neoantigens and subsequent destruction of malignant cells. The idea that tumor-reactive T cells can be used for cancer treatment evolved from early studies in 1991 by van der Bruggen et al [6] who showed that melanoma cells express antigens presented by the human leukocyte antigen (HLA)-A1 molecule and are specifically recognized by cytotoxic T cells. Importantly, the authors underlined that the presented antigen was not found in the panel of healthy tissues, which raised the possibility of the development of a targeted immunotherapy for patients with melanoma. Further studies and the subsequent discovery of tumor antigens, such as melanoma antigen recognized by T-cells 1 (MART-1), glycoprotein 100, or New York esophageal squamous cell carcinoma 1 (NY-ESO-1), proved that T cells are able to specifically recognize tumor antigens [7].

Initially, ACT treatment was based on tumor-infiltrating lymphocytes (TILs) that were isolated from the tumor lesion and expanded in vitro. However, one of the major limitations of this approach was associated with the fact that it only applied to resectable tumors and to tumors that were infiltrated by T cells. Furthermore, ex vivo expansion of TILs was proven to be problematic and time-consuming [8,9]. To bypass these limitations, an approach using blood-derived T cells, engineered ex vivo to recognize tumor antigens and then infused back into the patient, was introduced as an alternative.

Chimeric Antigen Receptor and T Cell Receptor T Cells

Currently, there are 2 main approaches to retarget T cells: chimeric antigen receptor (CAR)- and T cell receptor (TCR)-based. Despite the fact that both approaches involve redirecting T cell specificity, their mechanisms of action are different.

CAR-T cells use a single-chain fragment variable from monoclonal antibodies to specifically recognize tumor antigens that are expressed on the cell surface [10]. Spectacular results were achieved when CAR-T cells were used against the cluster of differentiation (CD) 19 molecule, leading to a complete remission in many patients with B-cell acute lymphoblastic lymphoma (B-ALL). This resulted in the first FDA-approved genetically engineered cell therapy in 2017 [11].

On the other hand, TCR-based technology uses heterodimers of α and β chains that recognize peptides in the context of HLA. The major advantage of this technology over CAR-T cells is that TCRs recognize intracellular antigens that are presented by major histocompatibility complex molecules [10,12]. In 2006, Morgan et al [13] demonstrated that ACT treatment using autologous TCR-engineered T cells (TCR-T) to specifically recognize the MART-1 antigen mediated a durable regression of metastatic melanoma lesions. Similarly, phase I and II clinical trials with TCR-engineered autologous lymphocytes

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reprogramed to express high-affinity TCR against NY-ESO-1 and L-antigen 1, cancer-testis antigens, showed clinical response in 80% of patients with advanced myeloma with 70% demonstrating a complete response to the treatment [14]. These results not only showed that autologous T cells can be redirected by introducing TCR with defined specificity and affinity against tumor antigens, but also provided hope for the treatment of incurable metastatic disease. Despite the promising results, TCR-based technology faces several drawbacks associated with (1) finding a good antigenic peptide presented by HLA, (2) screening for a TCR that binds a given peptide-human leukocyte antigen (pHLA), (3) optimizing affinity and avidity of the pHLA:TCR complex, and (4) performing safety evaluations, all of which require extensive laboratory work. This is why a search for artificial intelligence (AI) models to address these issues has been gaining substantial interest in the past few years.

TCR-T Therapy With a pHLA:TCR Database

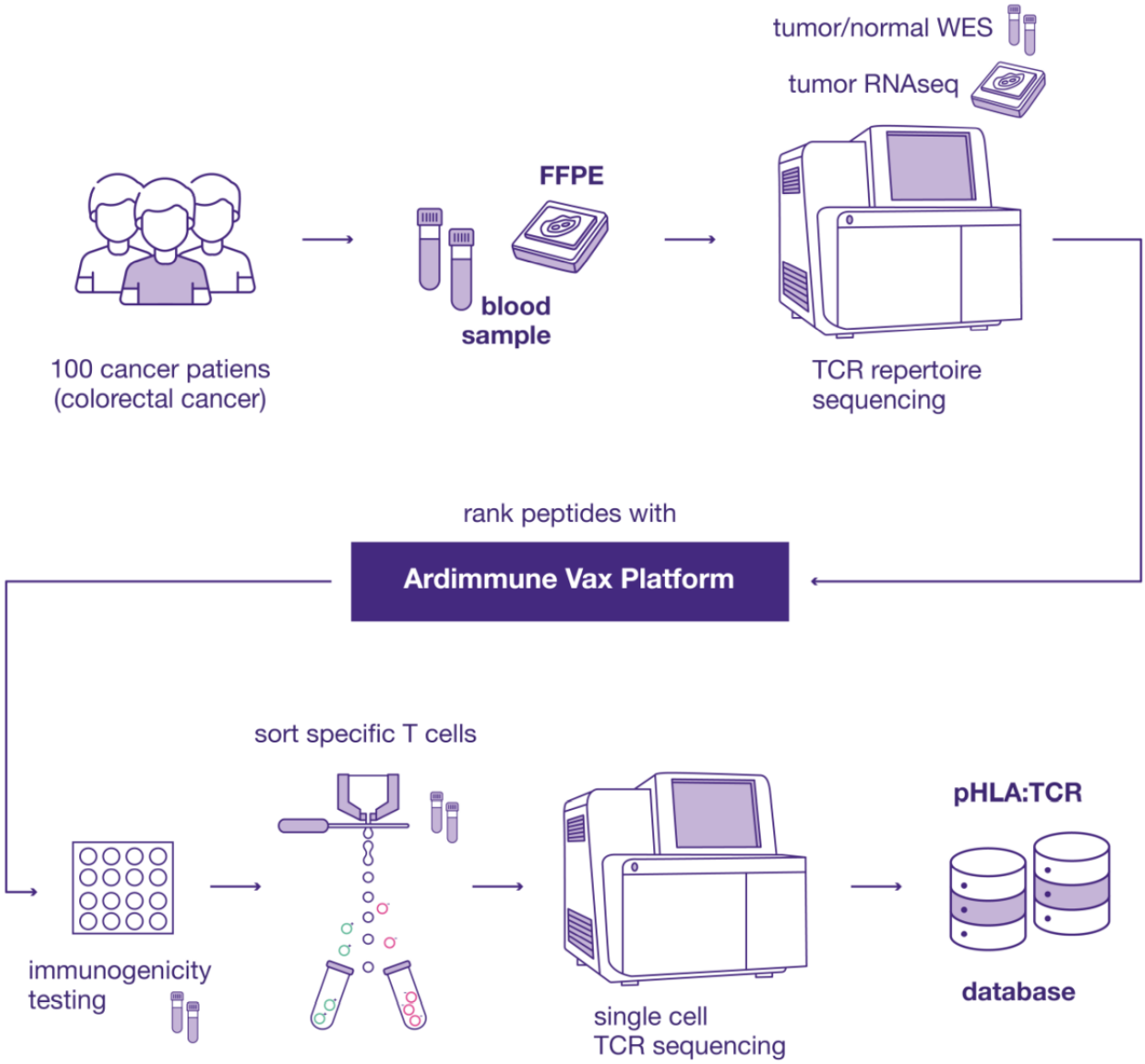
The use of AI in medicine has been gaining momentum in recent years. There have been successful attempts at applying AI in clinical histopathology [15,16], mammogram analysis [17], and immuno-oncological studies involving checkpoint inhibitors [18]. Furthermore, recent studies have shown that deep learning can be successfully applied for the prediction of TCR-peptide binding specificity [19-21] at least for some of the possible validation scenarios (eg, the scenarios single peptide binding, TCR peptide pairing-I to TCR peptide pairing-III [20]), with the general problem (predictions for pHLA complexes and TCRs unseen by the AI models during training) being still challenging for the current methods [21].

In TCR-T cell therapies, a reliable approach for predicting pHLA:TCR binding is of great importance although it presents challenges, which should be properly addressed. One of the major obstacles concerns the data available in the public domain to train such models, which is often limited or incomplete. In many cases, these data describe only 1 chain, mainly the β chain of TCR, while data on the α chain are missing. This is a major drawback to screening for antigen-binding TCRs, since the complementarity determining region 3 loops sequences of both α and β chains determine the TCR binding specificity [20]. It is important to emphasize that currently, there are no available solutions that allow for in silico predictions of TCR sequences binding a specific, novel peptide in the context of HLA. The algorithms that are used for TCR sequencing data analysis do not provide data regarding matched pHLA complexes. Similarly, bioinformatics tools for the prediction of TCR antigen binding for human TCRs offer results for a limited number of known epitopes. Additionally, the evaluation of possible toxicities associated with TCRs requires extensive and expansive in vitro experiments.

Herein, we present the study protocol for collecting patient material necessary to build a pHLA:TCR database for training and validating AI technology that can be used for screening and optimizing TCRs for TCR-T cell therapies (Figure 1). As highlighted above, the current lack of proper data training for AI-based pHLA:TCR interaction prediction models poses a major limitation in the discovery of specific TCRs. Therefore, in our opinion, creating a comprehensive database is the first and most fundamental step in building an efficient AI model for TCR discovery. We believe that the incorporation of AI technology will not only accelerate and advance the entire process relating to the identification of specific TCRs but will also provide a new approach to personalized cancer treatment using therapeutic T cells.

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Figure 1. Schematic overview of the workflow required for the generation of the proposed pHLA:TCR (peptide-human leukocyte antigen: T cell receptor) database. FFPE: formalin-fixed paraffin-embedded; RNAseq: RNA sequencing; WES: whole exome sequencing.



Methods

Study Design and Objectives

This is a multicenter observational study performed by the surgical oncology departments in Poland: the Maria Sklodowska-Curie National Research Institute of Oncology in Cracow, Brothers Hospitallers of Saint John of God Hospital in Cracow, Ludwik Rydygier Memorial Hospital in Cracow, St Raphael Hospital in Cracow, Voivodeship Multi-Specialist Center for Oncology and Traumatology in Lodz, Holy Cross Cancer Center in Kielce, J Struś Multispecialist Municipal Hospital, and Heliodor Swiecicki Clinical Hospital in Poznan. The overall objective of this study is to create a pHLA:TCR database to aid the development of an AI-based platform for the selection of specific TCRs used in cancer immunotherapy. This aim will be achieved by collecting high-quality blood and tissue samples from patients with colorectal cancer (CRC) that can be used for next generation sequencing, single-cell, and bulk TCR repertoire sequencing. The sequencing data will be processed with Ardigen (Ardigen SA)-developed platforms to generate a pHLA:TCR database.

Ethical Considerations and Regulatory Approvals

This study has been approved by the Maria Sklodowska-Curie National Research Institute of Oncology, Gliwice branch (KB/430-87/21). It was carried out in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines issued by the International Conference on Harmonization (ICH-E6, 17/07/1996). The enrolled participants were evaluated based on the inclusion and exclusion criteria. The selected participants provided written informed consent before the start of all experimental procedures. All the participants were provided with a thorough explanation of the proceedings planned in the study with an emphasis on the type and quantity of biological samples that will be collected from them. Furthermore, the participants were informed on the type of experiments that will be performed and how the samples will be stored. Generated data reports will be confidential and stored safely at a repository at Ardigen.

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Patient Selection

All the patients with CRC admitted to the surgical oncology wards of the participating hospitals were evaluated for their study eligibility. All the participants were required to be older than 18 years with a diagnosed and histopathologically confirmed advanced resectional CRC adenocarcinoma in active stage II, III, or IV. Participants were excluded from the study if they were unwilling to sign the informed consent form; had a history of inflammatory bowel disease, mucinous adenocarcinoma of the colon, cancer of the anal canal and verge, or adenocarcinoma of the appendix; had a histopathological diagnosis other than adenocarcinoma; were undergoing neoadjuvant and radiotherapies; were pregnant; had HIV infection or active hepatitis B or C infections; or had a leukocyte (white blood cell) levels <4000/mm^3. Qualified participants agreed to make the formalin-fixed paraffin-embedded (FFPE) tissue from the primary tumor available for research as well as to have their blood drawn.

Study Procedure

After the selection process, the enrolled participants underwent medical history review and physical examination by a medical doctor of the research team. Once completed, tissue samples of the primary tumor and blood were obtained from the participants. The tissue samples were provided in the form of FFPE blocks with a total area of embedded tissue of at least 100 mm^2 or alternatively as a minimum of 10 histopathological slides, the quality of which was confirmed by a pathologist. Blood sample collection was performed twice by qualified medical personnel (ie, a nurse or medical doctor) after which the sample was secured for further processing.

Study participants had the option of terminating their participation in the study at any given time. The participants could have also been withdrawn from the study at the discretion of the investigational team.

Sample Processing

Sample Collection

Biological samples that were obtained from the study participants included FFPE blocks of the primary tumor tissue or histopathological slides derived from it and their peripheral blood samples. The FFPE blocks and histopathological slides were provided by the hospital laboratory or department of pathomorphology of the participating institution. Peripheral blood samples were collected into heparin-containing tubes in 2 blood draws, 40 mL each. Additionally, at the first venipuncture, 2.5 mL of peripheral blood was collected per 1 PAXgene Blood DNA and 1 PAXgene Blood RNA tube (Thermofisher) for DNA and RNA isolation, respectively. If an insufficient number of peripheral blood mononuclear cells (PBMCs; <50 million) was obtained after the first 2 draws, an additional 40 mL of blood was collected from eligible participants (eg, those who had not yet started chemotherapy) after receiving their consent. Samples were transported to the Biobank Lab at the Head Department of Oncobiology and Epigenetics, Faculty of Biology and Environmental Protection, University of Lodz, according to the standard operating procedures. For long-term storage, the samples in PAXgene Blood DNA and PAXgene Blood RNA tubes are stored at –80 °C, and FFPE blocks and histopathological slides are stored at 2-8 °C.

PBMC Isolation

Blood collected into heparin-containing tubes was used for PBMC isolation. The isolation procedure for all samples started within 3 hours after venipuncture and was performed under sterile conditions according to standard density gradient centrifugation protocol. Briefly, blood samples were diluted with a phosphate-buffered solution in a 1:1 ratio at room temperature (RT) and layered onto Histopaque-1077 reagent (Sigma-Aldrich) in 50 mL test tubes. Next, the samples were centrifuged according to the manufacturer's instructions (at 400*g* at RT for 30 minutes without braking or acceleration). After centrifugation, the leukocyte phase was transferred into new tubes and washed with phosphate-buffered saline followed by centrifugation at 300*g* at RT for 10 minutes. To remove erythrocytes, the cell pellet was treated with a red blood cell lysis buffer according to the manufacturer's instructions. The viability of the isolated PBMCs was assessed using trypan blue staining. If applicable, the PBMCs were resuspended in fetal bovine serum with 10% of dimethyl sulfoxide and cryopreserved in liquid nitrogen for long-term storage.

DNA and RNA Isolation

DNA and RNA were isolated from tumor FFPE block samples after macrodissection and evaluation of corresponding hematoxylin and eosin (H&E)-stained slides with tumor area distinctly labeled by a pathomorphologist.

For DNA and RNA extraction from blood samples collected in the PAXgene Blood DNA and PAXgene Blood RNA tubes, the PAXgene Blood DNA and PAXgene Blood RNA kits (Qiagen) were used, respectively, according to the manufacturer's protocol.

Next Generation Sequencing

Isolated DNA from both FFPE blocks and peripheral blood was prepared for whole exome sequencing (WES) sequencing with commercial kits for 100 bp paired-end read lengths. The RNA isolated from FFPE blocks was used for RNA library preparation for paired-end sequencing with read lengths of 100 bp. The quality of prepared libraries was checked with Fragment Analyzer and sequenced on an Illumina sequencer with expected depth for DNA of 150x and 300x for PBMC and FFPE samples, respectively. RNA sequencing was set to obtain at least 100 million reads for each sample.

Identification of Immunogenic Peptides and Sequencing TCRs That Bind Them

ARDesign (previously called ArdimmuneVax) is an Ardigen-developed platform that uses in-house created AI models to design off-the-shelf and personalized peptide-based cancer vaccines and target identification for TCR-based therapies [22,23]. ARDesign platform includes ARDitox, the ARDisplay—presentation model, Ardimmune—immunogenicity model, and Meta-model, which considers the output of these models and other metrics. DNA sequences will be aligned to

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the reference genome and both somatic and germline mutation will be called, which will constitute one of the inputs for the ARDesign platform. Expression profiles derived from RNA sequences will comprise the other input for the platform.

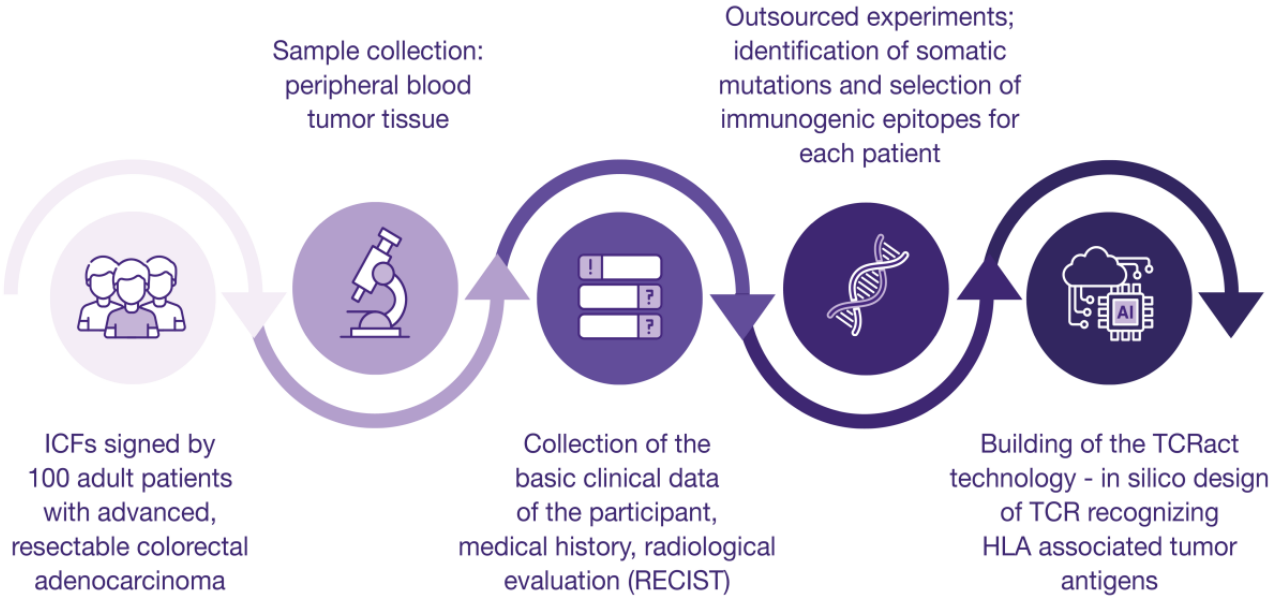
Next, based on ARDesign results, peptide immunogenicity can be validated by in vitro functional assays (ie, ELISpot), and fluorescently labeled pHLA multimers can be synthesized and applied for the isolation of reactive T cells with a flow cytometry cell sorting methodology. For that purpose, the isolated, biobanked PBMCs will be stained with fluorescent pHLA multimers and a panel of antibodies allowing the gating of pHLA-specific $CD8^+$ T cells.

Sorted $CD8^+$ T cells will be analyzed using the 10x Genomics (10x Genomics, Inc) single-cell technology to obtain paired α and β sequences of the TCRs with information about the pHLA that they bind.

Additionally, RNA isolated from the peripheral blood collected into PAXgene Blood RNA tubes will be used for bulk TCR repertoire sequencing to enable profiling of TCR repertoire diversity and clonality and to help to prepare negative training data sets for the pHLA:TCR database.

Altogether, the gathered results can serve as the basis to generate a reliable pHLA:TCR database that includes validated TCRαβ-paired sequences of a known peptide specificity. The overall process of the proposed pHLA:TCR database generation is presented in Figure 2.

Figure 2. Overview of creating an artificial intelligence–based technology (TCRact) for T cell receptors (TCRs) design and optimization. HLA: human leukocyte antigen; ICF: informed consent form; RECIST: response evaluation criteria for solid tumors.



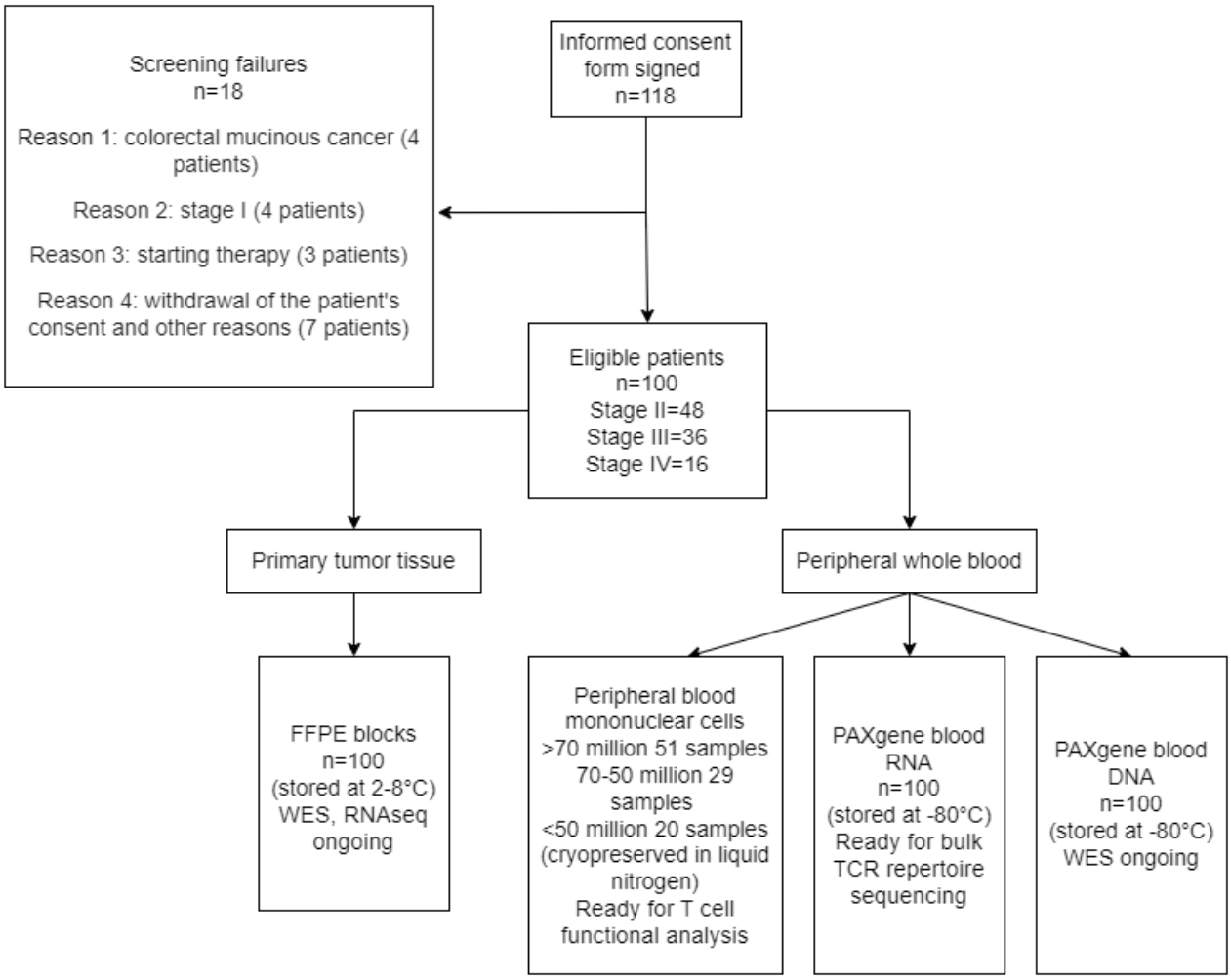
Results

Participant recruitment and sample collection started in October 2021 and was completed at the end of 2022. To date, primary tumor (FFPE blocks) and peripheral blood samples have been obtained from 100 participants. Isolation of PBMCs from peripheral blood has been performed for all 100 patients. On average, 74 million PBMCs were isolated from 80 mL of blood with average cell viability of 93%. All the isolated PBMCs were cryopreserved and are being stored at the Biobank Lab, University of Lodz.

To date, 85 participants have had their DNA and RNA extracted from both FFPE and peripheral blood samples. In 57 cases, WES was performed to analyze the occurrence of somatic mutations. Altered gene expression analysis was done for 57 participants using the RNA sequencing method. Additionally, RNA samples (isolated from blood) will be undergoing bulk TCR repertoire sequencing to enable profiling of TCR repertoire diversity and clonality. In all of the cases mentioned above, the obtained sequencing data (DNA and RNA) were incorporated into the ARDesign platform to rank the immunogenic potential of tumor peptides. Final study results are expected to be analyzed by September 2023. For further information regarding the progress of the study refer to the study flowchart presented in Figure 3.

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Figure 3. Flowchart of participants, specimens, and samples through the study. FFPE: formalin-fixed paraffin-embedded; RNAseq: RNA sequencing; TCR: T cell receptor; WES: whole exome sequencing.



Discussion

Overview

This study describes a protocol of a trial for creating a comprehensive database containing pHLA-TCR sequences with paired α and β chains of TCRs. The generated database will be used for the development and testing of an AI-based platform designed for the prediction and optimization of TCR sequences that specifically recognize tumor antigens. These types of platforms are of great interest, especially for the development of antitumor immunotherapies using TCR-T cells. ACT trials using TCR-T cells or CAR-T cells have shown that complete and durable eradication of tumor cells in the primary tumor is possible [24]; however, there are also reports suggesting that this type of immunotherapy might be effective in the treatment of metastatic disease [25,26], which is a major challenge for current treatment modalities. A great example of ACT efficacy against neoplastic disease is a therapy involving CD19 CAR-T cells in the treatment of relapsed or refractory B-ALL and relapsed or refractory diffuse large B-cell lymphoma in adult patients. This therapy was approved by FDA in 2017, and in 2018 it was authorized by the European Medicines Agency, which underlines that these technologies are highly promising for the treatment of neoplastic diseases [27]. Nevertheless, despite the spectacular effect of CAR-T cells in the treatment of some blood cancers, these types of cells are not as effective in the treatment of solid tumors [28]. TCR-T cell therapy appears to be a better approach for the treatment of solid tumors [29], which make up the majority of all cancer cases. Furthermore, unlike CAR-T technology, TCR-T cells are able to recognize mutated intracellular proteins, which make up a much larger part of cellular proteins than surface antigens by themselves [30,31]. In other words, the range of potential antigen targets is larger in the case of TCRs than CARs. Thus, the development of TCR-T technology might offer hope for “universal” cancer treatment. For this reason, many pharma and biotech companies are involved in the development of TCR-based therapies and clinical trials involving patients with cancer. Nevertheless, the advancement of TCR-T technologies had been slowed down by several drawbacks. The main obstacle with TCR-engineered ACT is associated with finding the appropriate TCRs that specifically recognize tumor antigens and do not show “on-target, off-tumor” toxicities at the same time. Another challenge is finding a TCR with proper avidity for the target. Currently, the development of TCR-T cells for therapeutic purposes is based on extensive lab work, which is time-consuming, labor-intensive, and very expensive.

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For this reason, our study aims to develop a platform for faster TCR selection and simultaneous prediction of potential toxicities. Our platform is intended not only to accelerate TCR identification but also to reduce the cost of the entire process. One of the main stages of TCRact platform development is to create a unique pHLA:TCR database. Currently, high-throughput TCR sequencing enables deep analysis of the TCR repertoire, which allows for comparison between different tissues and individuals. Currently, several databases of TCR sequences are available, such as VDJdb, McPAS-TCR, and IEDB, and subsequently, algorithms that allow for TCR specificity prediction have also been developed (ie, TCRdist and TCRex) [32-36]. It has to be stressed that the available databases are often incomplete and, in many cases, provide a sequence of only one of the TCR chains, or both α and β chains that are not paired. Furthermore, in many cases, they lack information about the cognate peptides and HLA types involved in peptide presentation. Hence, the function of only a minor fraction of TCRs is known, especially in the context of TCR-peptide-HLA interactions. Recently, Zvyagin et al [37] pointed out this problem by concluding that there is a lack of studies and protocols that allow for good prediction of TCRs and epitopes based on their sequences.

To build the database with a size that is comparable to the publicly available data set, we are aiming to use samples from approximately 100 patients [38]. Notably, our database will be based on the data obtained from the primary tumor and blood samples of patients with cancer. This approach is more specific (as tumor neoantigens are highly similar to self-antigens, unlike viral or bacterial antigens) for the identification of the TCR-peptide-HLA complex in the context of neoplastic disease in comparison to TCR data obtained from infectious diseases or vaccine monitoring studies [15,34,39,40]. Our approach helps to populate the database with a unique set of sequences that may be invaluable in the context of immuno-oncological therapies using TCR-T cells. For this reason, close cooperation with clinical sites guaranteeing the highest quality of the collected biological specimens together with complete clinical data is essential for the completion of this project's goals.

In this study, an AI-based platform is being developed as a tool for designing a precise and safe immunotherapeutic approach in tumor treatment. Adopting this type of approach would allow oncogenic, personalized immunotherapy to be widely accessible to the general public.

Limitations

Although we strongly believe that TCR-T therapies developed with the aid of AI-based platforms, such as the one discussed in this study, will become more accessible for cancer treatment with time, there are still a number of limitations that need to be addressed. The first major obstacle concerns the sharedness of the target (ie, neoantigen and tumor-specific antigen) for such therapies. There is a limited number of defined shared peptide targets. Furthermore, the method for creating the pHLA:TCR database described in this study will mainly provide data for personal neoantigens (specific to a given patient) and the TCRs that bind them. However, we believe that including neoantigens in the database might address the key limitation in pHLA:TCR binding prediction with AI models and the limited diversity of pHLAs in the training set. Another limitation to consider involves the number of patients in the study cohort itself and the number of pHLA:TCR pairs that it can potentially generate. Our cohort is composed of 100 patients, and we plan to choose 1 pHLA per patient. However, it is difficult to predict what number of different T cell clones per pHLA will be identified in our experimental approach, as the number can differ greatly depending on epitope sequence, clonal diversity, and clone size. In summary, the pHLA:TCR database that we plan to build using the approach described in this study may turn out to be of modest size. However, we believe that it will make a significant contribution to the field because our data set will provide information about specific cancer antigens that are currently underrepresented in public databases.

Conclusions

The results of this study provide the basic information for the development of an innovative platform that allows for fast and safe in silico prediction of TCRs to be used in cancer immunotherapy.

Acknowledgments

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Data Availability

The data sets generated and analyzed in this study are available from the corresponding author on reasonable request.

Authors' Contributions

SK supervised the recruitment of patients and the course of clinical study and consulted the study protocol. JB and KW drafted the manuscript. ASD, AB, and M Balawejder conceived, designed, and wrote the study protocol and manuscript. RS and A Kociniak reviewed and corrected the manuscript. AB and M Balawejder conceived and designed the study and patients' recruitment, coordinated clinical study, and reviewed the manuscript. ZO, JW, GT, MJ, T Kucharczyk, LW, M Borys, HS, MW, M Kayser,

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MES, A Kosmowska, KH, TG, BM, T Kowalczyk, JK, M Karczewski, and MS recruited patients. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

ACT: adoptive cell transfer

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AI: artificial intelligence
B-ALL: B-cell acute lymphoblastic lymphoma
CAR: chimeric antigen receptor
CD: cluster of differentiation
CRC: colorectal cancer
FDA: Food and Drug Administration
FFPE: formalin-fixed paraffin-embedded
H&E: hematoxylin and eosin
HLA: human leukocyte antigen
MART-1: melanoma antigen recognized by T-cells 1
NY-ESO-1: New York esophageal squamous cell carcinoma 1
PBMC: peripheral blood mononuclear cell
pHLA: peptide-human leukocyte antigen
RT: room temperature
TCR: T cell receptor
TCR-T: TCR-engineered T cell
TIL: tumor-infiltrating lymphocyte
WES: whole exome sequencing

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Protocol

Personalized Integrated Care Promoting Quality of Life for Older People: Protocol for a Multicenter Randomized Controlled Trial

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Abstract

Background: Alzheimer disease (AD) and Parkinson disease (PD) are the 2 most common neurodegenerative diseases affecting millions of people worldwide. The *Personalized Integrated Care Promoting Quality of Life for Older People* (PC4L) project proposes an integrated, scalable, and interactive care ecosystem that can be easily adapted to the needs of several neurodegenerative and chronic diseases, care institutions, and end user requirements.

Objective: The study protocol developed within the framework of the PC4L project aims to iteratively test the integrated platform and its modules, and focuses primarily on assessing the impact of the proposed solution (ie, the PC4L platform) on patients' quality of life, as well as its usability and feasibility on a large-scale sample size in 3 different scenarios (home, neurorehabilitation, and day care centers).

Methods: A prospective multicenter clinical study is conducted in 5 European countries (Germany, Italy, Portugal, Romania, and Spain) at 6 different pilot centers, for 3 months, in patients with PD, Parkinsonism, AD, and other dementias (ODs). Patients were randomized in a ratio of 1:1 to the intervention group (use of the PC4L system) or the control group (no intervention). The PC4L system consists mainly of a wristband for monitoring parameters such as steps and levels of physical activity, and the PC4L app, which includes different engaging functionalities. Both groups are assessed through baseline and end-of-study clinical evaluations, including assessment of quality of life through the EQ-5D-3L scale.

Results: The study protocol is part of a project approved and funded by the European Commission Horizon 2020 (grant agreement number 875221). The ethics committees of all involved centers reviewed and approved the study protocol. The study began with the recruitment phase in September 2022, and enrollment ended in February 2023. Recruitment is now closed (April 2023). The results of this study are expected to be published in summer 2023. A total of 558 patients, 279 per study group, were recruited. The results will allow to clarify the impact of PC4L on quality of life, will assess the empowerment of patients and the medical resources use, as well as the usability of the final version of the PC4L system. It will also provide information on the support of the system as a tool to facilitate the decision-making process.

Conclusions: The PC4L project intends to test a technology-based, integrated, scalable, and interactive care platform on patients with neurodegenerative diseases and proposes a good coordinated care model between all involved actors. Future developments

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of the PC4L solution may involve caregivers and socio-health professionals in the decision-making process in order to facilitate efficient communication between all stakeholders and ensure reliable and protected access to data within Europe.

Trial Registration: ClinicalTrials.gov NCT05538455; https://clinicaltrials.gov/study/NCT05538455

International Registered Report Identifier (IRRID): DERR1-10.2196/47916

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KEYWORDS

Parkinson disease; dementia; neurodegenerative; chronic diseases; health care technologies; integrated care

Introduction

Background

There is an urgent need to increase the efficiency and sustainability of health and social care systems across Europe, as there is a growing trend in public spending, which is expected to reach 14% of gross domestic product by 2030 [1]. The aging of the population, accompanied by an increase in chronic diseases, including cardiovascular diseases, diabetes, asthma, mental and physical disorders, and neurodegenerative conditions, represents the main cause of this situation [2,3]. In fact, the existence of comorbidities and the confluence of several chronic diseases are progressively more frequent in older adults, which increases the need to develop models and tools to improve integrated health care systems.

The aging of the population has also led to major reforms in long-term care policy and systems in many European Union (EU) countries, raising the necessity for alternatives. This implies the need for help with household tasks or other practical errands, transport to hospital/clinic visits or social visits, social companionship, emotional guidance, or organizing professional care. In most European countries, much of the care for people older than 60 years is based on informal care [4].

Among the most common chronic diseases in older adults, neurocognitive disorders, such as dementia, Alzheimer disease (AD), and Parkinson disease (PD), are the most disabling. Today, more than 10 million Europeans live with neurocognitive impairment disorders at different stages of dementia.

In recent years in Europe, digitalization is recognized as a powerful tool to achieve many potential benefits such as improving quality of life and putting patients at the center of the care process [5].

Therefore, the current situation can be improved by the creation of an integrated care platform, capable of establishing correlations between comorbidities, investigating the use of polypharmacy, mitigating potential health risks, studying the social variables involved, and promoting unified treatment procedures or social services. This solution could help patients, caregivers, and social health professionals to better monitor several diseases, while also considering the social context [6-8]. Besides, according to a recent work [9], the inclusion of a web platform for monitoring signs and symptoms of older persons by health care professionals over time has proved to be an important resource.

In addition, people with chronic diseases experience difficulties in their daily lives and require specialized care services as well as treatments, imposing high burdens on the public budget: this requires special attention to adequately address the sustainability of the social health system in Europe.

Personalized Integrated Care Promoting Quality of Life for Older People (PC4L) is a European Commission Horizon 2020 project (grant agreement number 875221) that proposes an integrated, scalable, and interactive care ecosystem, and can be easily adapted to the reality of several chronic diseases, care institutions, and end user requirements, benefiting all the involved actors, from patients to caregivers and health professionals. Its main contributions consist of the following:

- Building an integrated, scalable, and interactive care ecosystem for neurodegenerative diseases and adaptable to other chronic conditions
- Finding the best actions and measures from a medical and social point of view that can facilitate an improved quality of life, awareness, and care management for senior users with neurodegenerative and other chronic diseases
- Providing a personalized recommendation and interaction model, which can support the user through gamification techniques, with the final goal of adopting healthy habits, maintaining a good daily routine, and following the prescribed actions by the professionals
- Enabling multidisciplinary communication between all involved stakeholders, facilitating better time management for social and health professionals, and contributing to a cost-efficient, flexible, and highly adaptable solution for senior users with short- or long-term conditions

By adopting a user-centered design approach starting from the early stages of the project [10], the inclusion of the needs and requirements of the end users has been crucial toward the PC4L platform development and implementation [11] and the current outline of the protocol presented here. In fact, through the work performed during the first part of the project, we identified the more important factors from the personal, social, and health points of view that are able to influence the daily lives of the end users and reflect on their expectations regarding the PC4L solution.

Aims

This study represents the third, and last, phase (pilot 3) of large-scale pilots aiming to gradually co-design and iteratively test the PC4L integrated platform and modules.

While pilot phases 1 and 2 focused on technical feasibility and patients' satisfaction, this protocol focuses on the following objectives:

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- To assess the impact of using the PC4L platform on patients' quality of life
- To compare the metrics generated by the PC4L platform in real-life conditions with the clinical outcome measures
- To evaluate the feasibility and safety of measuring disease progression and patient health status through the global functioning of the PC4L system
- To assess and compare the feasibility and usability of 2 different versions of the PC4L system (fully equipped version vs cloud-based solution)
- To increase patients' safety and empowerment

As the primary outcome, the study will provide:

- The difference in quality of life between groups (experimental vs control group), measured by the EQ-5D-3L scale at the end of the study

The following secondary outcomes will also be acquired:

- The correlation coefficient of the PC4L platform metrics (eg, steps and physical activity levels, sleep, number of falls, cognitive scores) with the clinical outcome measures (eg, motor clinical evaluation, sleep questionnaire, Falls Efficacy Scale-International [FES-I], cognitive evaluations) measured at baseline, end of the study, and the values of change from baseline
- System usability assessment, measured through the System Usability Scale (SUS), at the end of the study
- Users' satisfaction with the PC4L system, measured through a 5-point Likert Scale, the mHealth User Satisfaction Questionnaire, and the participants' answers to open questions, at the end of the study
- Changes in patients' satisfaction and empowerment, measured by the Patient Assessment of Chronic Illness Care (PACIC) and the Short Assessment of Patient Satisfaction (SAPS) scales, respectively, at baseline and at the end of the study
- Change in patients' use of medical resources (number of admissions and number of days spent in health institutions) in the last month, measured at baseline and at the end of the study

Methods

PC4L Platform

Instrumental Setup

The PC4L ecosystem consists of the following:

- Wearable sensors that are used by the patient for monitoring disease-related parameters in passive and interactive paradigms (eg, simple biomeasurements such as heart rate or complex biomeasurements such as motor behavior; passive measurement if initiated automatically, and interactive measurement if initiated by the patient). The wearable sensor used is the smartwatch Fitbit Versa 2 (Google LLC). Patients will wear the sensor in the dominant arm
- The PC4L app for processing data directly from the smartphone (Samsung A20 or another similar model) inertial measurement unit sensors and GPS and directly from users. In particular, the data collected will be anthropometric data and symptoms, as well as data related to medication uptake, which are to be provided directly by the patient or the caregiver, via short questionnaires and annotations. Data related to motor behaviors through GPS and inertial sensors
- Depth camera that will be deployed in the clinical centers (rehabilitation) for monitoring motor parameters of the patients. In principle, cameras will collect both 2D and 3D images to facilitate the extraction of events (eg, falls, loss of balance, wandering episodes), point trajectories, and "skeleton" data from patients for extraction of different motor behaviors and movements (eg, freezing, festination). The selected camera is the Intel RealSense depth camera (model D435)
- Tablet or computer to collect data related to cognitive abilities of the patients: the cognitive games app includes 6 different games about short-term memory, visual recognition, understanding, semantic memory, vocabulary, and mathematics. This app collects not only the results of the games, but also information related to the user interaction with it
- A local computer collects data from the patients via the sensorial ecosystem, which includes several fixed and dynamic sensors such as wearables, sensors, and cameras

In addition, the PC4L integrated care platform (accessible via internet browsers) provides an electronic health record or personal information sheet (fed with data provided by the PC4L ecosystem) and complex interface for personalized interaction and communication between patients and health care professionals.

PC4L Mobile App

The PC4L app includes a prescription dashboard, which monitors drug compliance; questionnaires on health status and physical activity, to be filled periodically; a symptom diary, which registers the symptoms experienced by the patient (ie, falls, freezing, loss of balance); physical activity recommendations; and daily personalized notifications on physical activity, hydration, and nutrition.

Decision Support System

As part of the decision support system, the PC4L platform includes a recommendation component. This component collects information from different sources available (directly from sensors, from the cognitive games, from the patients' and users' questionnaires, and from the multimodal fusion engine), and under clinical and health care professional guidance, after the assessment of the potential improvement or worsening of the patients' conditions, issues personalized recommendations to address the problems identified. Recommendations are related to the following major areas: physical activity, sleep, cognitive, nutrition, social support, and stress management (for informal caregivers).

These recommendations are sent generally to the PC4L app installed on the patients' mobile, where they appear as pop-up notifications when received. In most cases, the content of the

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notifications is readily available in the app in case the patient wants to check it again at a later time.

Under clinical supervision, the decision support system will indicate scores' impacts and the contributions to either the improvement or the worsening of the patients' health conditions. Finally, these decisions lead the recommender engine to provide personalized recommendations such as physical activity, nutrition, social support, and stress management. Additionally, reminders for therapy adherence to improve patients' quality of life can be integrated.

Multimodal fusion aims to predict deviations from patients' daily/normal routines, taking into consideration the input modalities (ie, cognitive state, medication intake, motor symptoms, sleep, physical activities, comorbidities, and patient's profile). It focuses on detecting deviations in motor functions, cognitive abilities, sleep routines, and physical activities. The fusion approach benefits from domain knowledge and uses it in a computational framework to fuse the input modalities and detect the probability of deviations in the patient's condition to support them. The multimodal fusion brings together the input modalities to enhance decision-making and gives stronger inferences using dynamic and personalized fusion through Bayesian networks. In the fusion approach, health care professionals use the patients' profile information and the static scores to incorporate their knowledge regarding a patient into the fusion algorithm. In other words, the multimodal fusion algorithm utilizes the long-term analysis of the behavioral analysis modalities to gather broader insights into the deviations in patients' health conditions and routines.

Metrics

During the monitoring period, specific metrics (Table 1) are collected, continuously and passively, through the PC4L system.

Table 1. Metrics and related devices used during patients' monitoring.

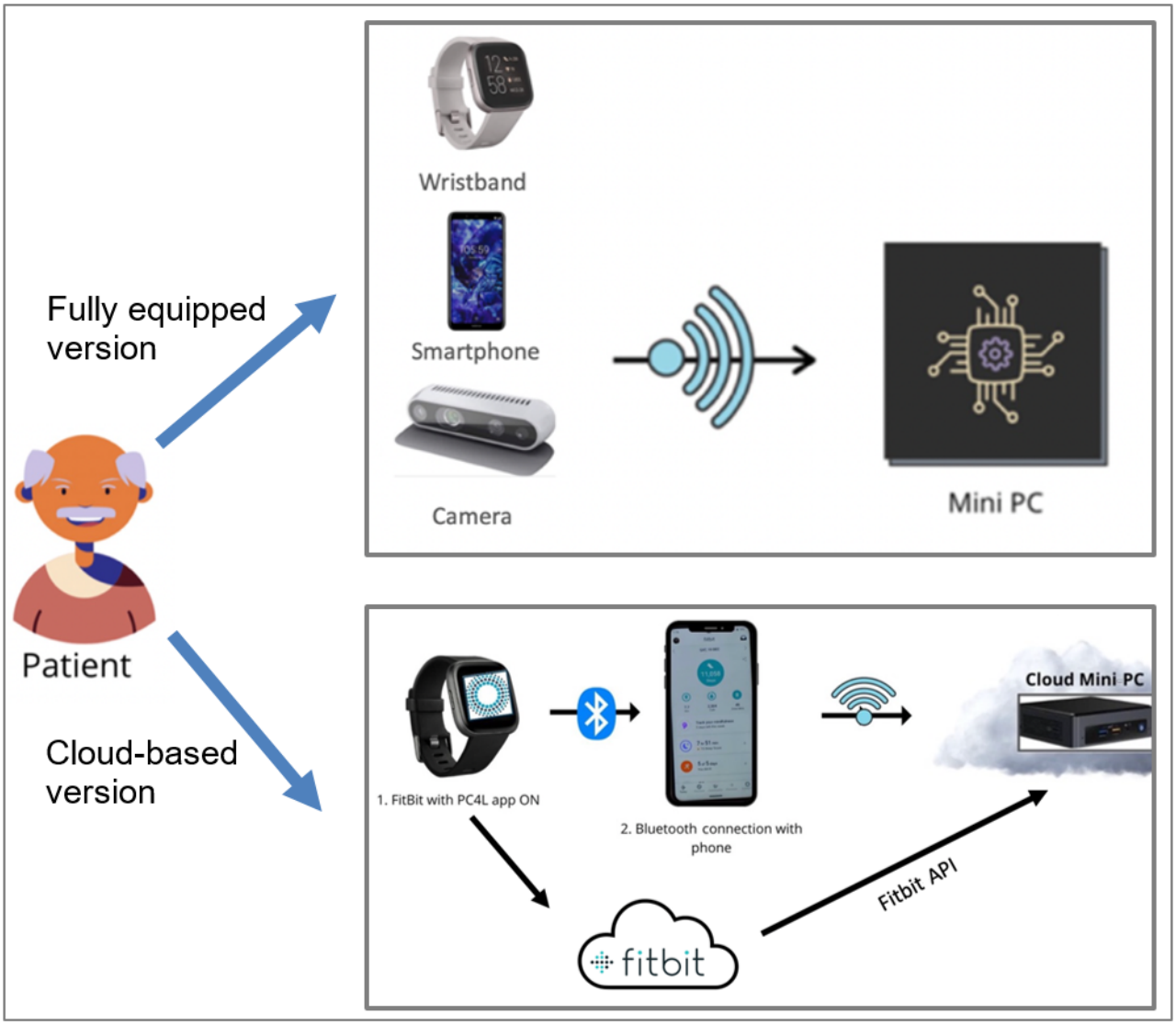
Metrics	Devices
Walking parameters	Wristband and phone
Bradykinesia	Wristband and phone
Loss of balance	Cameras
Falls	Cameras and wristband
Festination	Wristband and phone and camera
Physical activity	Wristband
Freezing	Wristband and phone and camera
Inactivity	Wristband
Compliance with medication	App
Sleeping pattern	Wristband
Interaction patterns with the devices	Platform or app
Usage of the physical activity recommendation services	Number of clicks per week of the different services

PC4L System Versions

Two different versions of the PC4L system were used (Figure 1): a fully equipped version, with all the devices enumerated above provided to the patients, and a cloud-based system that only requires a smartphone and a wearable sensor. Of those patients using the PC4L system, 25.1% (70/279) used the fully equipped version, whereas the remaining ones (209/279, 74.9%) used the cloud-based system.

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Figure 1. Illustrations of the PC4L solutions. API: application programming interface; PC4L: Personalized Integrated Care Promoting Quality of Life for Older People.



Study Design

A prospective multicenter clinical study is conducted in 5 European countries: Germany, Italy, Portugal, Romania, and Spain (also including 6 pilot centers).

The pilot sites are (1) Asociacion Parkinson Madrid (APM), Madrid (Spain); (2) Casa di Cura del Policlinico (CCP), Milano (Italy); (3) Campus Neurológico Sénior (CNS), Lisbon (Portugal); (4) University and Emergency Hospital of Bucharest (UHB), Bucharest (Romania); (5) University of Medicine and Pharmacy (UMF), Bucharest (Romania); and (6) Wohlfahrtswerk für Baden-Württemberg (WBW), Stuttgart (Germany).

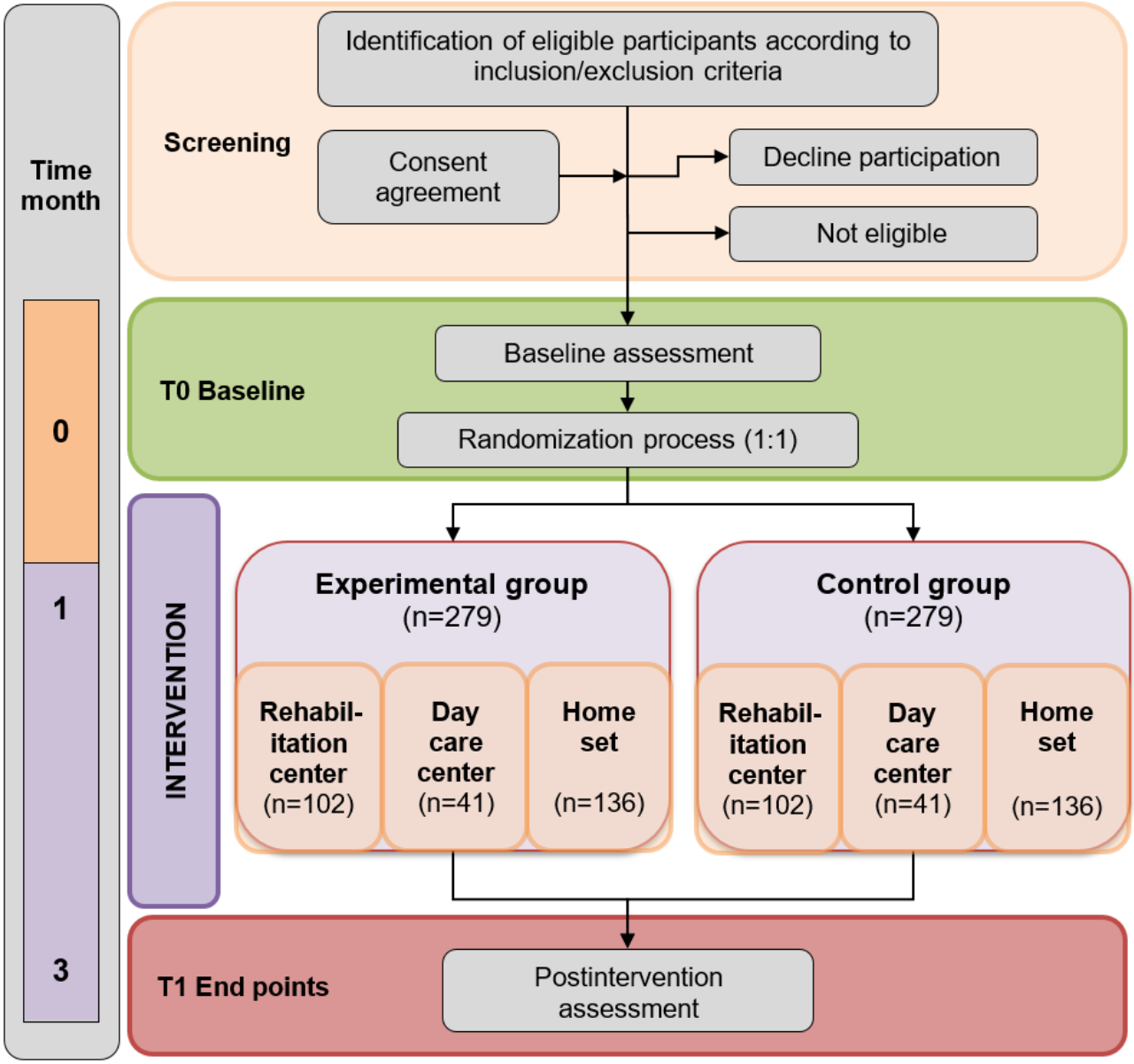
There are also 3 different scenarios: (1) rehabilitation center (inpatients and outpatients); (2) day care centers; and (3) home set (ie, patients' home).

The duration per patient, at home and in the day care center, will be up to 3 months. Participants in the rehabilitation center participated during the period of their stay in the center (not exceeding the 3 months).

A specific route diagram is presented in Figure 2 in accordance with the CONSORT (Consolidated Standards of Reporting Trials) guidelines. The protocol of this study was developed in accordance with the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines (Figure 3) [12]. The schedule of enrollment, interventions, and assessments is presented in Figure 3.

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Figure 2. Flowchart of the proposed randomized controlled trial according to the CONSORT (Consolidated Standards of Reporting Trials) guidelines.



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Figure 3. SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) diagram describing the schedule of enrollment, interventions, and assessments. *only for the EG intervention branch. AD: Alzheimer disease; BI: Barthel Index; CDRS: Clinical Dementia Rating Scale; CIRS-G: Cumulative Illness Rating Scale-Geriatric; FES-I: Falls Efficacy Scale International; MDS-UPDRS: Movement Disorder Society -Unified Parkinson's Disease Rating Scale; mHealth: mobile health; OD: other dementia; PACIC: Patient Assessment of Chronic Illness Care electromyography; PD: Parkinson disease; PSQI: Pittsburgh Sleep Quality Index; SAPS: Short Assessment of Patient Satisfaction; STAI: State-Trait-Anxiety-Inventory; SUS: System Usability Scale.

Action \ Time point	-T1 Screening	T0 Baseline	T1 Post
ENROLLEMENT			
Recruitment	X		
Eligibility screen	X		
Informed consent	X		
Randomization (1:1)		X	
INTERVENTIONS			
Experimental group		◆——	——◆
Control group		◆——	——◆
ASSESSMENTS			
Demographic data (age, gender, level of education, professional activity, social support)		X	
MDS-UPDRS Total (PD) CDRS (AD and OD)		X	X
FES-I		X	X
PSQI		X	X
STAI		X	X
Presence of festination, dysphasia, wandering episodes		X	X
BI		X	X
PACIC		X	X
SAPS		X	X
CIRS-G		X	X
EQ-5D-3L		X	X
*SUS			X
*mHealth User Satisfaction Questionnaire			X
Adverse events reporting Global Satisfaction End-of-study open questions			X

Selection Criteria

The inclusion and exclusion criteria of participants are shown in Textbox 1.

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Textbox 1. Participant inclusion and exclusion criteria.

Inclusion criteria

- For patients with Parkinson disease (PD) and Parkinsonism:
  - Patients diagnosed with PD according to the Movement Disorder Society (MDS) criteria
  - Hoehn and Yahr stages between II and IV assessed in the "on" state
- For patients with Alzheimer disease (AD) or other dementia (OD):
  - Clinical diagnosis of AD or OD
  - General inclusion criteria
  - Willing to participate
  - Aged 65 years or older
  - Willing to interact with technology devices
  - Willing and able to provide written informed consent to participate in the study or having a legal representative responsible for signing

General exclusion criteria

- Clinically significant and severe cognitive decline or intellectual disability that may compromise their ability to use a mobile phone or other electronic devices
- Fever or acute infection such as COVID-19 or influenza
- Life-threatening coexisting disease with life expectancy

Additional criteria regarding the different scenarios

- Home set scenario: Living at home with or without caregiver
- Rehabilitation center scenario: Enrolled in a rehabilitation program with or without caregiver
- Day care center scenario: Being in the day care center program with a caregiver

Recruitment

Patients with PD and other parkinsonian syndromes, AD, or ODs were invited to participate from the clinical centers involved in the study. Each participant organization was assigned to recruit a number of participants related to their skills, experience, number of researchers involved, and access to users (Table 2).

Table 2. Distribution of participants per clinical center and scenario.

Scenario/clinical center	Rehabilitation (n=204), n	Day care (n=82), n	Home (n=272), n	Total (N=558), n
APM[a]	80	N/A[b]	26	106
CCP[c]	63	N/A	62	125
CNS[d]	46	N/A	86	132
UHB[e]	15	N/A	15	30
UMF[f]	N/A	30	30	60
WBW[g]	N/A	52	53	105

[a]APM: Asociacion Parkinson Madrid.

[b]N/A: not applicable.

[c]CCP: Casa di Cura del Policlinico.

[d]CNS: Campus Neurológico Sénior.

[e]UHB: University and Emergency Hospital of Bucharest.

[f]UMF: University of Medicine and Pharmacy.

[g]WBW: Wohlfahrtswerk für Baden-Württemberg.

To reach the planned number of recruits, many strategies were implemented: participants were contacted through online webinars; through brochures placed in specific centers such as pharmacies, leisure centers, and medical offices; and through patients' associations. Further, regular updates were posted via online newsletters on different websites, such as the PC4L

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website and end users organizations' websites. In addition, information about the PC4L pilot 3 study was shared during national and international conferences. Recruitment was also promoted in a collaborative way thanks to partners from other European projects. Finally, participants were recruited in person when accessing the medical facilities and via phone contact or emails after searching local databases.

Patients who discontinue the study participation because of medical conditions (ie, infections, falls, medical emergencies) or unwilling to participate any longer for other reasons (ie, difficulty with technology, loss of interest) will be considered dropouts.

Randomization

Patients were randomized in a ratio of 1:1 to the intervention group (use the PC4L system) or the control group (no intervention) by an independent, nonclinical partner of the project consortium.

Patients allocated in the intervention group were randomized in a ratio of 3:1 to the "cloud-based solution" and the "fully equipped" PC4L system version.

Blinding

Participants and intervention delivery facilitators could not be blinded to group allocation. Evaluators conducting the clinical assessments were blinded to group allocation.

Interventions

Overview

All participants that fulfil inclusion criteria were invited to participate. Information about objectives, duration, procedures, and voluntariness was given to patients and informed consent was obtained. None of the procedures of the study started before the informed consent had been signed by the participants.

Control Group

The patients allocated in the control group, after the baseline assessment, received general written recommendations on the aforementioned major areas (physical activities, sleep, cognitive, and nutrition; social support and stress management for caregivers). At the end of the study period, patients performed end-of-study evaluations.

Intervention Group

The patients recruited and assigned to the experimental group received specific instruction in using the project platform, but without any specific program concerning the activities.

Specifically, patients, after the baseline assessment, received the instrumental setup and indications on its functionalities. Patients were instructed about the use of the Fitbit, the PC4L app, and the cognitive games on a tablet or computer. Patients were also provided with manuals.

Specifically, according to the study approach detailed by Biehl et al [9], the patients were instructed to complete the following questionnaires in the app during the first week and during the last week of the study period: the 10-item Eating Assessment Tool (EAT10) [13] for evaluation of dysphagia; the Edmonton Symptom Assessment System (ESAS) [14] and the Patient Global Impression (PGI)—Severity [15] for evaluation of symptoms; and the International Physical Activity Questionnaire (IPAQ) [16] for evaluation of physical activity. In addition, during the last week of using the app, patients were requested to complete the SUS [17], via the app, for evaluation of usability.

The platform was installed in each scenario with the assistance of the project research staff (ie, bioengineers).

A total of 2 versions of PC4L systems were installed: while the cloud-based system (which only required a smartphone and a wearable sensor) was used in all scenarios, a fully equipped version was implemented only in the rehabilitation scenario.

The patients received the same directions in all 3 scenarios.

At the end of the study period, patients performed end-of-study evaluations and returned the instrumental setup.

Study Assessments

In-person assessments took place at baseline and at the end of the study (3 months follow-up or at discharge from the rehabilitation program).

Specifically, the sample characterization and clinical evaluation of the participants (both experimental and control group patients) were performed at baseline. The clinical evaluation with specific tests and scales was repeated at the end of the study.

At the beginning and at the end of the study, all patients were assessed on quality of life through a specific scale (EQ-5D-3L).

Only for patients assigned to the intervention group, their experience with the PC4L platform was assessed in terms of usability at the end of the experimental period.

Figure 3 and the "Data Collection and Analysis" section report specific outcomes that will be used.

Data Collection and Analysis

Clinical Assessment

Evaluators (ie, medical doctor, physical therapist, and neuropsychologist), at the beginning and at the end of the study, conducted the following clinical evaluation scales and tests:

- The Movement Disorder Society-Unified Parkinson Disease Rating Scale (MDS-UPDRS) [18] will be used to objectively quantify the motor and nonmotor aspects of PD. Changes in the MDS-UPDRS score will be investigated, with higher scores meaning worse outcome
- The Clinical Dementia Rating Scale (CDRS) [19] will be used to assess the cognitive status of AD and OD. It yields a single score on a scale of 0-5, with higher scores indicating worse outcome. Change in the CDRS score will be measured at baseline and at the end of the study
- The FES-I will be used to evaluate the subjective fear of falling of the patients. It yields a single score on a scale of 16-64, with higher scores indicating worse outcome
- The Pittsburgh Sleep Quality Index (PSQI) [20] will be used to evaluate the quality of sleep. Change in the PSQI score will be measured at baseline and at the end of the

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study. It yields a single score on a scale of 0-21, where higher scores mean worse outcome
- The State-Trait-Anxiety-Inventory (STAI) [21] will be used to assess the anxiety status (trait and state). Change in the STAI score will be measured at baseline and at the end of the study. It yields a single score on a scale of 20-80, where higher scores mean worse outcome
- Presence of festination, dysphasia, wandering episodes, and nonprogrammed medical resources use in the last month will be assessed (eg, access to emergency room)
- The Barthel Index (BI) is an ordinal scale used to measure performance in activities of daily living (ADLs) [22]. Each performance item is rated with a given number of points assigned to each level or ranking. It uses 10 variables describing ADL and mobility and yields a single score on a scale of 0-100, where higher scores mean better outcome
- The PACIC will be used to determine the involvement of the patient in his/her care plan. Change in the PACIC score will be measured at baseline and at the end of the study. It yields a single score on a scale of 0-5, where higher scores mean better outcome
- Similarly, the SAPS was used to evaluate the user's satisfaction with respect to the medical treatment received. Change in the SAPS score will be measured at baseline and at the end of the study. It yields a single score on a scale of 0-28, where higher scores mean better outcome
- The Cumulative Illness Rating Scale-Geriatric (CIRS-G) [23] is used to include the presence of comorbidities in the clinical profile. Change in the CIRS-G score will be measured at baseline and at the end of the study. It yields a single score on a scale of 0-56, where higher scores mean worse outcome

In addition, patients' characterization in terms of demographic and clinical data (age, gender, level of education, professional activity, social support, and previous use of technology) was performed.

Demographic and clinical data were aggregated, extracted, and analyzed using dedicated spreadsheet files (Microsoft Corporation).

Quality of Life Assessment

The primary outcome of the study will be the difference in quality of life between groups, measured by the EQ-5D-3L scale [24], before and after the experimentation.

The EQ-5D-3L descriptive system comprises 5 dimensions, namely, mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each domain was scored by patients through 3 levels: no problems (1), some problems (2), and extreme problems (3) in the execution of the specific item.

Quality of life data were analyzed using dedicated spreadsheet files.

Usability and Satisfaction Assessment

At the end of the experimental period, patients allocated to the experimental group performed the usability evaluation of the PC4L platform solution by means of the SUS [17], Global Satisfaction and mHealth User Satisfaction questionnaires, adverse events reporting, and end-of-study open questions.

The SUS is used to measure how easy or difficult the proposed system is to use. We will compare the usability of 2 different versions of the PC4L system (fully equipped and cloud-based solutions). The overall SUS score will be calculated and assessed consistently with the literature: a score of 100 corresponds to the best imaginable usability, while acceptable usability is defined by an SUS score above 68 points [17,25].

The Global Satisfaction Questionnaire is used to assess the overall level of satisfaction or dissatisfaction with the platform experience.

The mHealth User Satisfaction questionnaire is used to measure user satisfaction and usability of the recommendation component of the solution [26].

As a completion of end-of-study assessment, an adverse events report and end-of-study open questions of preferred and less preferred aspects of the platform, as well as suggestions for improvements, will be collected for each user.

Sample Size

According to published evidence [27], the minimal clinically important difference using the EQ-5D-3L in patients with PD is 5.23 points. The sample size calculation was based on these values and on the data provided in a previous study [28] in the PD field that compared the quality of life of 2 groups of patients, resulting in 10% of difference between groups, corresponding to 6 points. It was estimated that 558 patients, 279 per study group, are necessary to improve 10% in the EQ-5D-3L score, with 95% power. Dropouts were not considered in the calculation. Based on this result, the number of participants was distributed among clinical centers, according to their recruitment capacity (Table 2).

Statistical Analysis

Descriptive analysis will be performed for all variables to characterize the sample. For continuous variables, mean, SD, median, and range values will be calculated. For categorical variables, absolute and relative frequencies will be used to describe the data [29-31].

Normality will be studied using the Kolmogorov-Smirnov and Shapiro-Wilk tests. The effect of using the PC4L system will be analyzed by applying the paired-sample *t* test (2-tailed) and the Wilcoxon signed rank test to each variable (statistical significance will be set at $P<.05$).

The Pearson and Spearman correlation tests will be used to validate the PC4L systems metrics (statistical significance will be set at $P<.05$).

Data Collection and Management

The information will be handled confidentially to prevent participant names or other directly identifiable information from appearing in any report, publication, or other disclosure of results. Data (eg, name, age, length of illness) are collected and stored in separate folders. The investigator will enter the pseudonymous data into a database for statistical analysis.

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Essential documents shall be archived in such a way as to ensure that they are readily available, on request, to the competent authorities.

The collected data of the PC4L components are only made available in a pseudonymized form in the secure cloud "Amazon Web Services," which is located within Europe [32]. The patient will therefore be assigned a code to ensure the pseudonymity of his/her data. The data on the cloud are only accessible to the project partners, with whom a data processing agreement was made.

The data processing agreement was stipulated as an agreement between the data controller (partner 1, ie, clinical partners collecting the data) and a data processor (partner 2, ie, partner responsible for data analysis) within the consortium, with the purpose of regulating the processing of any personal data collected. In the context of joint controllers, partner 1 is responsible for the processing of personal data in a conventional form from participants (health data and medical data set derived from patients involved in the user requirements phase and in the pilots, data from caregivers, professionals, and other stakeholders). Partner 2 is—within the framework of joint controllers—responsible for the processing of personal data in device data and annotations (social and medical data set/audiovisual).

The data obtained will be used only for the purposes of the research and not for other purposes. The results of the research will be shared more widely, for example, through publications and conferences, but no personal information will be displayed. The processing, communication, and transfer of personal data will be carried out in accordance with the provisions of Regulation (EU) 2016/679 [33] and Law 3/2018 [34], of 5 December, on the Protection of Personal Data and the Guarantee of Digital Rights. In accordance with the legislation, the participant may exercise his/her rights of cancellation, opposition, portability, limitation, access, and rectification by contacting the professional who informed the participant about the project. Likewise, the consortium adheres to the principles of the General Data Protection Regulation (GDPR; legality, equity and transparency; purpose limitation; minimization of data; accuracy; storage limitation; integrity and confidentiality; and responsibility).

Any inaccuracy regarding the functioning of the system will be promptly reported to the technical partners of the project who will intervene in correcting them. The interruption of operation of 1 or more components of the PC4L system will not have any kind of feedback/effect on the participant.

Ethics Approvals

Study Approval

The study protocol was reviewed and approved by the local ethical committees in Germany [number 2022-29-MB-FA4, Ethical committee of Westfälische Wilhelms-Universität (WWU), Münster], Italy (number 734-2022bis, Comitato Etico Milano Area 2), Portugal (number 6-2022 R, CNS Ethic Committee), Romania (numbers 7/19.07.2022, Comisia de Etică a Cercetării din Spitalul Colentina and 36432, Comitetul local de etică SUUB/ Spitalul Universitar de Urgen ă Bucure ti), and Spain (number 22/392-E, Ethical committee of Hospital Clinico San Carlos – Salud Madrid). The institutional review board of all centers approved the study and will receive study reports during mid-study and at the end of the study, and will monitor the study implementation and data collection. Any deviations from the protocol will be promptly notified to the ethics committees and applied only after its approval.

The randomized controlled trial has been registered at ClinicalTrials.gov (identifier NCT05538455).

The study is conducted in accordance with the principles of the Declaration of Helsinki.

The results of this study will be disseminated through peer-reviewed journals and national and international academic conferences only by the professionals directly involved in the clinical trial.

Patient's Informed Consent

After the study had been fully explained to the patient, written informed consent was obtained prior to any study-related proceedings. The method of obtaining and documenting the informed consent and the contents of the consent comply with ICH-GCP (International Conference on Harmonisation good clinical practice), all applicable regulatory requirements, and legal requirements.

In case the patient is unable to read or sign, a legal guardian is allowed to sign the informed consent, only after confirming that the study has been comprehensively explained to the patient by the research team.

Security and Adverse Event Reporting

Any adverse event (serious or nonserious) and any other abnormal clinical, personal, social finding will be recorded in the patient's case report form. For all adverse events, sufficient information will be pursued to permit the following:

- a determination of a temporal relationship;
- an adequate determination of the outcome of the event (ie, whether the event should be classified as a serious adverse event); and
- an assessment of the casual relationship between the adverse event and the study requirements.

An abnormal result finding will be classified as an adverse event if 1 or more of the following criteria are met:

- the result finding leads to a discontinuation of patient participation in the research study and
- the result finding is considered an adverse event by the researcher.

Withdrawal of Participants

Participation in this study is voluntary. Patients may withdraw from the study at any time, without giving reasons and without disadvantage in terms of the quality of care they would receive if they did not participate. After the withdrawal, no further data will be collected or taken into consideration for statistical purposes.

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Results

The recruitment began in September 2022, and enrollment ended in February 2023. Recruitment is now closed (April 2023). The results of this study are expected to be published during the summer 2023.

The results of this study will be presented at national and international patients' organizations and to the public.

The study protocol is part of a project (grant agreement number 875221) approved and funded by the European Commission in the framework of Horizon 2020 action.

The results of pilot 3 will allow clarification of the usability of the final version of the PC4L system, its impact on patients' and caregivers' quality of life, empowerment, and use of medical resources. It would also provide information on the support of the system as a tool to facilitate the decision-making process.

At the time of the deployment of this study, as for the previous protocols, issues due to the COVID-19 pandemic in European countries were managed to avoid safety-related risks.

Discussion

PC4L recognizes that today in health care an integrated care process should be adopted for harmonizing health models with social services from a holistic perspective [35]. Therefore, the project intends to develop and test a technology-based, integrated, scalable, and interactive care platform by involving patients with neurodegenerative diseases, such as PD and dementias. The principal aims of this project are to improve the quality of life of patients and to enable active living and better disease management. These aims will be achieved through large-scale assessments across Europe (in 5 countries and 6 end user organizations), with the final scope to validate the reliability of the overall system in a real-life context.

Eventually, the main advantage of the PC4L project is to propose a system that can be easily adapted to the reality of various chronic diseases, care institutions, and end user needs, thus benefiting all actors involved.

To assess the impact on quality of life and usability, we decided to adopt a randomized controlled trial model because it minimizes selection bias and allows reaching an adequate sample size to achieve power.

In the context of improved technologies and digitalization strategies, the use of wearable sensors and smartphone apps has the advantage of providing objective, longitudinal, and precise information about the status of the patients in their own home environment, as highlighted by Klucken et al [36], especially in cases of neurodegenerative diseases.

Based on the extensive literature on the benefit of physical activity in neurodegenerative diseases [37-46], we expect an improvement in quality of life. This is also facilitated by the early detection of signs and symptoms (eg, falls) through proactive monitoring.

Moreover, in terms of digital health, the inclusion of participants is a crucial part [47]. Based on our recent work, we considered that the ICT-integrated care platform should not promise functionalities that are too complex for too many users [11]. Instead, we focused on selection and restriction to fewer but essential aspects. Users and other stakeholders have in fact been involved in these decisions by being considered active actors from the early stages of the project. Notably, the clinical study here described is conducted in 3 different real-life scenarios, providing relevant information on the everyday life of the patients.

Regarding the home scenario, the primary advantage of implementing this scenario is the ability to monitor patients at home, measuring their general health condition, asking about their perceived state, and detecting their symptoms (eg, gait disturbances or falls). The acquisition of these data will enrich patients' perception of their own condition and will allow the comparison between their insight and the clinical and instrumental data. Health professionals, from their perspective, can take advantage of all these data by adapting the prescribed therapy in a highly personalized manner. Thus, patient-doctor communication will be improved, facilitating patients' engagement with their own health care process.

Central to the study is also the implementation of the PC4L solution in the rehabilitation centers, as such controlled environments involve patients in different kinds of activities, under the supervision of a multidisciplinary team. Here, patients perform personalized treatments in dedicated rooms, such as motor training and exercises connected to ADL, as well as cognitive exercises to improve memory and attention. The main advantages of PC4L in this scenario are (1) the possibility to provide objective information to professionals to study the evolution, treatment personalization, and rehabilitation suggestions; (2) to check the communication between professionals, patients, and caregivers, especially exercise recommendations based on the evolution of patient's movement skills; and (3) to design a decision support tool taking into account the patient's personal and health condition.

Finally, in the third scenario of day care centers, patients perform activities connected to ADL like at home, but under the supervision of professionals (day care center workers). Additionally, the participation of caregivers in this scenario can support the patients. The benefits are to check the communication between professionals and the caregiver, who does not live in the same house with the patient, and to monitor the patient's evolution.

In this pilot study, as already reported by Espay et al [48], low digital skills could be a limitation to the appropriate use of the PC4L solution and, therefore, the correct monitoring of the participants. The consortium mitigated this risk by adopting simplified age-appropriate questionnaires and tools.

Another risk could be the completion of the recruitment of the patients: for this purpose, the consortium of PC4L has adopted several mitigation measures (described earlier).

Trying to provide a balance between an acceptable benefit-to-burden ratio and the delivery of reliable, clinically

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relevant insights, through mobile health (mHealth) technologies, as suggested by Espay et al [49], the main solution of PC4L includes the continuous use of the wristband for monitoring parameters such as steps and levels of physical activity, and the PC4L app, which includes easy but engaging functionalities.

The final goal of the PC4L project is to obtain a good coordinated care model between all involved actors. Future developments of such projects might dwell into the active involvement of caregivers and socio-health professionals and into the support of professionals in the decision-making process, to facilitate efficient communication between all stakeholders and ensure reliable and protected access to data within Europe [8].

Acknowledgments

The authors thank the patients, caregivers, and professionals who agreed to participate in this study; the researchers from the study sites; and all the consortium members of the Personalized Integrated Care Promoting Quality of Life for Older People (PC4L) project. PC4L is funded by the European Commission via the Horizon 2020 program (grant agreement number 875221).

Data Availability

The data sets generated during or analyzed during this study will be available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

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Abbreviations

AD: Alzheimer disease
ADL: activity of daily living
APM: Asociacion Parkinson Madrid
BI: Barthel Index
CCP: Casa di Cura del Policlinico
CDRS: Clinical Dementia Rating Scale
CIRS-G: Cumulative Illness Rating Scale-Geriatric
CNS: Campus Neurológico Sénior
CONSORT: Consolidated Standards of Reporting Trials
EAT10: 10-item Eating Assessment Tool
ESAS: Edmonton Symptom Assessment System
FES-I: Falls Efficacy Scale-International
GDPR: General Data Protection Regulation
ICH-GCP: International Conference on Harmonisation good clinical practice
IPAQ: International Physical Activity Questionnaire
MDS: Movement Disorder Society
MDS-UPDRS: Movement Disorder Society-Unified Parkinson Disease Rating Scale
OD: other dementia
PACIC: Patient Assessment of Chronic Illness Care
PC4L: Personalized Integrated Care Promoting Quality of Life for Older People
PD: Parkinson disease
PGI: Patient Global Impression
PSQI: Pittsburgh Sleep Quality Index
SAPS: Short Assessment of Patient Satisfaction
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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STAI: State-Trait-Anxiety-Inventory
SUS: System Usability Scale
UHB: University and Emergency Hospital of Bucharest
UMF: University of Medicine and Pharmacy
WBW: Wohlfahrtswerk für Baden-Württemberg

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Protocol

Evaluation of 2 Artificial Intelligence Software for Chest X-Ray Screening and Pulmonary Tuberculosis Diagnosis: Protocol for a Retrospective Case-Control Study

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Abstract

Background: According to the World Bank, Malaysia reported an estimated 97 tuberculosis cases per 100,000 people in 2021. Chest x-ray (CXR) remains the best conventional method for the early detection of pulmonary tuberculosis (PTB) infection. The intervention of artificial intelligence (AI) in PTB diagnosis could efficiently aid human interpreters and reduce health professionals' work burden. To date, no AI studies have been evaluated in Malaysia.

Objective: This study aims to evaluate the performance of Putralytica and Qure.ai software for CXR screening and PTB diagnosis among the Malaysian population.

Methods: We will conduct a retrospective case-control study at the Respiratory Medicine Institute, National Cancer Institute, and Sungai Buloh Health Clinic. A total of 1500 CXR images of patients who completed treatments or check-ups will be selected and categorized into three groups: (1) abnormal PTB cases, (2) abnormal non-PTB cases, and (3) normal cases. These CXR images, along with their clinical findings, will be the reference standard in this study. All patient data, including sociodemographic characteristics and clinical history, will be collected prior to screening via Putralytica and Qure.ai software and readers' interpretation, which are the index tests for this study. Interpretation from all 3 index tests will be compared with the reference standard, and significant statistical analysis will be computed.

Results: Data collection is expected to commence in August 2023. It is anticipated that 1 year will be needed to conduct the study.

Conclusions: This study will measure the accuracy of Putralytica and Qure.ai software and whether their findings will concur with readers' interpretation and the reference standard, thus providing evidence toward the effectiveness of implementing AI in the medical setting.

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KEYWORDS

artificial intelligence; AI; evaluation; pulmonary tuberculosis; PTB; chest x-ray; CXR; screening

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Introduction

Tuberculosis is a contagious disease that leads to substantial morbidity and mortality worldwide. It is caused by the *Mycobacterium tuberculosis* bacteria (MTB). Tuberculosis is spread from infected people to others through the air. Even though tuberculosis is curable and preventable, the World Health Organization (WHO) estimated that 10 million people contracted tuberculosis and 1.6 million people died from it worldwide in 2021 [1]. In Malaysia, the incidence of tuberculosis is alarming, where 21,186 cases were reported in 2021 with an estimated 97 cases per 100,000 people, which is growing at an average annual rate of 1.96% [2].

The diagnosis of active tuberculosis is made either by skin test, blood test, chest x-ray (CXR), sputum acid-fast bacilli (AFB) smear and culture, polymerase chain reaction, or a combination of these tests. CXR remains the best conventional method for early detection of pulmonary tuberculosis (PTB) infection and the most recommended method for tuberculosis prevalence survey due to its high sensitivity [3]. The specificity of CXR for PTB could be more significant than evaluating symptoms alone, depending on how the CXR is read. Triage using CXR will also help to minimize the number of individuals undergoing bacteriological tuberculosis testing without reducing the detection of true tuberculosis cases [4]. Despite numerous advantages, the lack of qualified radiologists who can interpret CXR images, especially in high–tuberculosis burden countries, and the high inter- and intrareader variability are among the substantial drawbacks of implementing CXR as one of the diagnostic tools [4]. This leads to the impairment of screening efficacy and scale-up efforts [4,5]. Thus, the introduction of artificial intelligence (AI) in medical imaging with multiple technological approaches aided in reducing those obstacles [6,7].

AI is the ability of a digital computer or machine to perform tasks commonly associated with intelligent beings [8]. The rapid development of information technology worldwide and its use in multidiscipline practice make AI a new area of interest, especially in the medical profession [9]. Recently, approaches to using innovation in the health care system to support patient care are highly sought-after comorbidities. Thus, with AI technology, medical imaging (digital x-ray) can reduce the period of tuberculosis management, and patients with tuberculosis can receive early treatment. At present, various AI methodologies for the diagnosis of tuberculosis are being developed, that is, general regression neural network, multilayer neural network, convolutional neural network (CNN), artificial immune system, fuzzy logic controller, and real-world tournament selection, all of which have yielded promising accuracy for tuberculosis detection [10]. The capability of AI to recognize tuberculosis-related abnormalities via CXR, especially in mass screening with minimal time, has substantially improved and outperformed the human interpreter, thus reducing the work burden of health professionals [11]. Several studies have evaluated the efficacy and accuracy of using AI worldwide [12], but no such study has been carried out in Malaysia.

Therefore, this study aims to evaluate the performance of Putralytica and Qure.ai software for CXR screening and PTB diagnosis among the Malaysian population.

Methods

Sampling Design

This is a retrospective case-control AI software evaluation study that will take place at 3 different health facilities: the Respiratory Medicine Institute, National Cancer Institute, and Sungai Buloh Health Clinic. The study is expected to take 1 year to complete. We will collect CXR images from all adults (≥15 years) who meet the inclusion criteria for this study (Textbox 1). A total of 1500 CXR images will be retrieved; 500 of which will be abnormal PTB cases, 500 of which will be abnormal non-PTB cases, and 500 of which will be normal cases (healthy control). In this study, these images will serve as the reference standard. Primary demographic data from the CXR reports (patient's age, gender, and race), patients' clinical investigations and medical history (symptoms, CXR interpretation, and comorbidity), and laboratory results (AFB smear, MTB culture, and GeneXpert assay) will be collected by assessing electronic or hard-copy medical records.

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Textbox 1. Inclusion criteria.

Inclusion criteria for abnormal pulmonary tuberculosis (PTB) cases

- Aged 15 years and older
- One chest x-ray (CXR) per PTB case or mix case with other lung pathology who completed treatment for tuberculosis
- One CXR per patient upon diagnosis
- Spectrum of severity is reflective of real clinical setting

Inclusion criteria for abnormal non-PTB cases

- Aged 15 years and older
- One CXR per abnormal case (non-PTB case)
- One CXR per patient upon diagnosis
- Spectrum of disease(s) is reflective of real clinical setting

Inclusion criteria for normal cases (healthy control)

- Aged 15 years and older
- One CXR per healthy control
- Latest CXR image is used

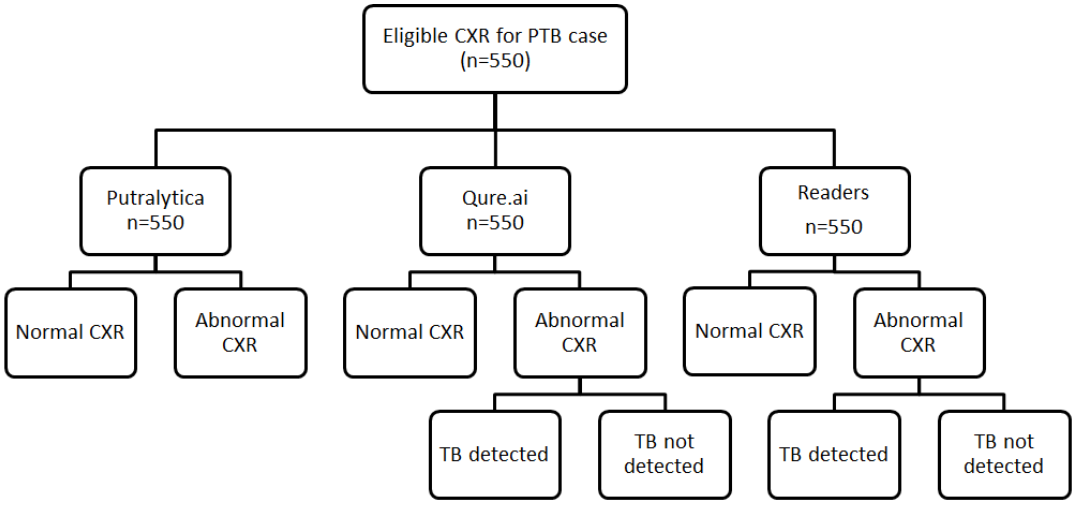
Sample Size Calculation

According to a sample size estimation when comparing sensitivities (Sn) or specificities (Sp) in a matched-groups diagnostic study in radiology research, a total of 1500 CXR images are needed in this study. It was calculated with the assumption that the probability of disagreement between both AI software is 0.131, with the highest Sp/Sn being 0.95 and the lowest Sp/Sn being 0.91, a power of 80%, and significant level of 5%:

Work Flowchart

The reporting of this study will adhere to the Standard for the Reporting of Diagnostic Accuracy Studies (STARD) guidelines. The work flowchart for CXR images of each case is shown in Figures 1-3.

Figure 1. Work flowchart for chest x-ray (CXR) images of abnormal pulmonary tuberculosis (PTB) cases. TB: tuberculosis.



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Figure 2. Work flowchart for chest x-ray (CXR) images of abnormal non-PTB cases. PTB: pulmonary tuberculosis.

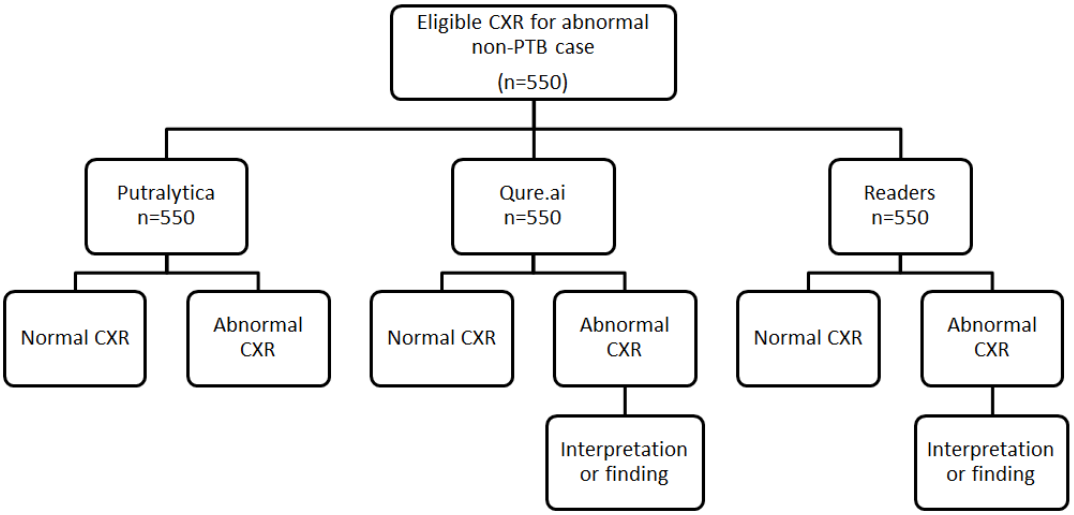
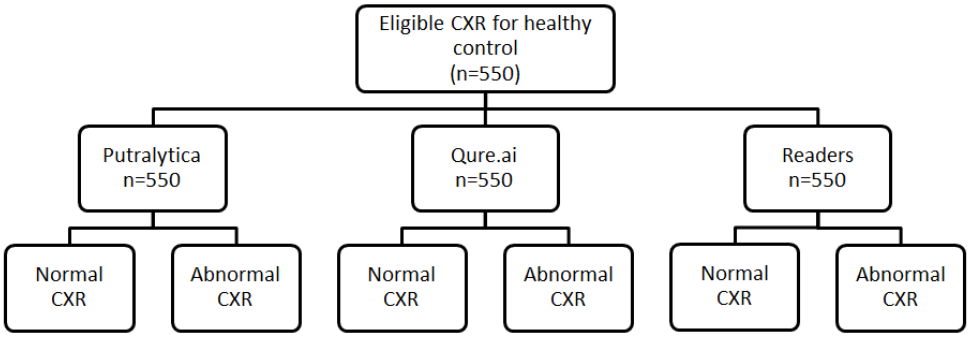


Figure 3. Work flowchart for chest x-ray (CXR) images of normal cases (healthy control).



Reference Standard

The reference standard in this study is the interpretation of the preselected CXR images according to the 3 aforementioned categories. First, an abnormal PTB case is defined as a patient with PTB who had been prescribed and completed PTB treatment based on the following criteria: formal diagnosis; symptom status; CXR interpretation; and results from laboratory investigation, including AFB smear, MTB culture, and GeneXpert assay. Second, an abnormal non-PTB case is defined as any patient with lung abnormalities that are not PTB, based on the following criteria: formal diagnosis, symptom status, and CXR interpretation. Third, a healthy control is defined as any healthy person with normal CXR, including health screening and contact with a person with PTB who completed follow-up, based on the following criteria: formal diagnosis and CXR interpretation.

Index Test

Qure.ai (India)

Qure.ai is a CXR screening tool that detects signs of pulmonary, hilar, and pleural tuberculosis. The AI algorithm underlying Qure.ai is trained to detect normal and abnormal CXR images, classical primary PTB, and atypical manifestations. The software is trained and validated using a data set of over 2.5 million CXR images worldwide. Qure.ai classifies findings from the CXR into 3 categories: active tuberculosis, nonactive tuberculosis and other lung or chest abnormalities, and normal. The final interpretation generated by this software is either PTB or not PTB, together with a conclusive radiological finding for abnormalities other than PTB. The AI algorithms produce a continuous abnormality for threshold scoring (from 0 to 1), representing the probability of the presence of tuberculosis. It claims to yield an accuracy of >90%, with the established threshold of 0.5 by the AI developer. The software can be accessed with or without an internet connection.

Putralytica (Malaysia)

Putralytica is a web-based platform that uses machine learning and automatic detection of pathology. This AI software is a type of CNN that can interpret normal and abnormal CXR only. The CNN was trained and internally validated using an open-access public CXR data set from the National Institutes of Health containing 112,120 frontal view CXR images. The software was developed using the Python 3 language with the KERAS and Tensorflow 2.0 application programming interface framework. The AI algorithms produce a continuous abnormality for threshold scoring (from 0 to 100), representing the probability of the CXR abnormality. It claims to yield an accuracy of >85%, with the established threshold of 60% by the AI developer. The software can be accessed with or without an internet connection.

Readers' Interpretation

The readers consist of 3 professionals with varying levels of experience in the radiology field: a clinical radiologist with >10 years of service, a clinical radiologist with <10 years of service,

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and a medical officer who works in the radiology department. These readers will be oblivious to clinical and sociodemographic information about patients, and they will analyze the CXR images independently. They will fill out a structured form to provide their interpretation based on the given variables.

Case Definition

Clinically Diagnosed Tuberculosis

A clinically diagnosed tuberculosis case is a patient who does not fulfil the criteria for bacteriological confirmation but has been diagnosed with active tuberculosis by a clinician or other medical practitioner, who has decided to give the patient an entire course of tuberculosis treatment. This definition includes cases diagnosed with x-ray abnormalities or suggestive histology and extrapulmonary cases without laboratory confirmation. Clinically diagnosed cases subsequently found to be bacteriologically positive (before or after starting treatment) should be reclassified as bacteriologically confirmed [13].

Bacteriologically Confirmed Tuberculosis

A bacteriologically confirmed tuberculosis case is a patient from which a biological specimen is positive by smear microscopy, culture, or WHO-recommended rapid diagnostic tool such as the GeneXpert MTB/RIF assay. All such cases should be notified, regardless of whether tuberculosis treatment has started [13].

Working Definition

In this study, a PTB case is defined as an abnormal CXR (suggestive of PTB), clinical finding with a formal diagnosis suggestive of PTB, a laboratory investigation suggestive of the presence of tuberculosis, or any combination of these. An abnormal non-PTB case is defined as any abnormal CXR excluding the PTB cases, and a normal case for healthy control is defined as any normal CXR finding.

Data Collection and Data Handling

A structured form will be designed to retrieve and collate data from the existing reports of CXR examination and laboratory investigation with AI software–interpreted results and the readers' interpretation. The information will be kept in an assigned documented file where it can only be accessed by the investigators. Considering the duration of this research project and to allow the process of publishing the findings, the research data will be stored and archived for 18 months. Afterward, the research data will be destroyed by permanently deleting the file from the storage hard disk.

Ethics Approval

Ethics approval had been granted by National Medical Research Register and Medical Research and Ethics Committee. Permission to conduct the study is upon approval by the State Health Director.

Privacy and Confidentiality

For all data, privacy and confidentiality will be maintained. The result of the study will be anonymized. The information revealed will not allow the identification of any individual participants. The result will also be in an aggregated form and will not identify any individual or address. Only those involved with this study and data analysis will have access to the data.

Dissemination

The analysis results will be presented in technical or scientific meetings at the state or Ministry of Health level and published as technical reports or journal articles. Details of individuals will not be disclosed but will only be reported in an aggregated form.

Statistical Analysis

All retrieved data will be downloaded and exported to the SPSS software (IBM Corp) for analysis. Data will be grouped based on the variable, description, and data type to facilitate analysis (Table 1). The results of CXR interpretation from both software and the readers will be specified solely based on the description provided (Table 2). This is done to avoid lengthy reader responses and ensure interpretation consistency and uniformity. Descriptive analysis will be used to describe the sociodemographic and clinical characteristics of the patients. Data analysis will be performed for both AI software against the reference standard by constructing 2×2 tables to determine true positive, false positive, false negative, and true negative results. The overall diagnostic accuracy parameters and their 95% CIs will be computed: sensitivity and specificity, positive likelihood ratio, negative likelihood ratio, Youden index, and area under the curve. Cohen κ statistic will be applied to determine interrater agreement among the readers and between the readers' and the AI software's interpretations.

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Table 1. Patients' medical history and laboratory investigation.

Variable and definition	Description	Data type
1. Sociodemographic information		
Research ID	Unique coding	String
Ethnicity among Malaysian patients	1=Malay 2=Chinese 3=Indian 4=Bumiputera Sabah 5=Bumiputera Sarawak 6=Others (specify)	Categorical
Date of birth (≥15 years)	Exact date of birth (dd/mm/yyyy)	String
Sex	1=Male 2=Female	Categorical
2. Clinical background		
Date of admission	N/A[a]	String
Date of CXR[b] taken	N/A	String
Formal diagnosis	N/A	String
Comorbidities	1=Diabetes 2=Hypertension 3=Hypercholesterolemia 4=History of tuberculosis 5=HIV 6=Smoking 7=Asthma 8=COPD[c] 9=Bronchiectasis 10=Chronic bronchitis 11=Heart failure 12=Pulmonary fibrosis 13=Others (specify)	Categorical
Tuberculosis-like symptoms status	1=Coughing for >2 weeks (prolonged cough) 2=Coughing up mucus 3=Coughing up blood 4=Fever (prolonged fever) 5=Weight loss 6=Night sweat	Categorical
3. Laboratory investigation		
Sample type	1=Sputum 2=Aspirate 3=BAL[d] 4=BW[e] 5=PF[f] 6=Others (specify)	Categorical
Date of direct smear	N/A	String
Direct smear	1=Positive (3+) 2=Positive (2+) 3=Positive (1+) 4=Negative 5=Not done	Categorical

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Variable and definition	Description	Data type
Date of MTB[g] culture	N/A	String
MTB culture	1=Growth (MTB) 2=No growth 3=Non-MTB (specify) 4=Not done	Categorical
Date of GeneXpert assay	N/A	String
GeneXpert assay	1=Detected (High, RIF[h] resistance) 2=Detected (High) 3=Detected (Med, RIF resistance) 4=Detected (Med) 5=Detected (Low, RIF resistance) 6=Detected (Low) 7=Not detected 8=Not done	Categorical

[a]N/A: not applicable.
[b]CXR: chest x-ray.
[c]COPD: chronic obstructive pulmonary disease.
[d]BAL: bronchoalveolar lavage.
[e]BW: bronchial wash.
[f]PF: pleural fluid.
[g]MTB: *Mycobacterium tuberculosis* bacteria.
[h]RIF: rifampin.

Table 2. Chest x-ray (CXR) interpretation.

Variable name	Definition	Description	Data type
1. CXR interpretation for abnormalities (PTB[a] and non-PTB related)	Results for: 1. Qure.ai 2. Radiologist	1=Consolidation 2=Cavity lesion 3=Nodule (tuberculoma) 4=Pleural effusion 5=Hilar 6=Miliary tuberculosis 7=Discrete nodule (without calcification) 8=Discrete nodules with retraction 9=Discrete fibrotic scar, line opacity, or reticular densities 10=Discrete fibrotic scar with retraction 11=Cardiac enlargement or anomalies 12=Pulmonary abnormality (mass) 13=Pleural thickening irregularities 14=Blunting 15=Granuloma 16=Other	Categorical
2. CXR interpretation (basic)	Results for: 1. Putralytica 2. Qure.ai 3. Radiologist	1=Abnormal (active tuberculosis) 2=Abnormal (nonactive tuberculosis) 3=Abnormal (not tuberculosis) 3=Abnormal 4=Normal	Categorical

[a]PTB: pulmonary tuberculosis.

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Results

Data collection on sites is expected to commence in August 2023, once the funding has been granted. It is anticipated that 1 year will be needed to conduct the study. Data collection will commence in phase 1 of the project (3-5 months), whereas CXR image distribution for readers' interpretation will take place in phase 2 of the project (3-6 months). All results will be collated and presented at the state and ministry levels. Reports and manuscripts will be produced throughout 2024 after obtaining approval and resolution from all parties involved.

Discussion

This study considers biases commonly overlooked by researchers, particularly in diagnostic accuracy studies. To reduce the spectrum of bias (disease and nondisease), this study will include a variety of CXR abnormalities, not only to detect the presence of PTB but also other abnormalities, with CXR images chosen based on severity level. All CXR images will be in the form of digitalized images to standardize the methodology and reduce measurement bias. Most studies only focused on software performance or the agreement between radiological interpretations of CXR image results independently. Some studies do not use MTB culture and GeneXpert assay as bacteriological evidence in their reference standard, and some do not even compare the performance of the AI with human readers. This study, indeed, will incorporate all variables and analyses into a single comprehensive assessment. The difficulty we encountered while conducting this study was the need to visit several sites to collect CXR images for use as the standard reference. We had to adjust various processes and workflow to get the patients' information without interfering with the staff's primary responsibilities at the study sites. In the future, this study will be instrumental in proving that AI is appropriate when there are various obstacles, whether in clinical settings or fieldwork. In clinical settings, AI can alleviate the burden on medical personnel, particularly in areas where imaging technology is widely used with large workloads. In fieldwork, AI is very beneficial for prevalence studies involving data collection in remote areas and studies that require interpreting numerous results quickly and accurately.

Acknowledgments

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Authors' Contributions

MFMH conceived the idea and study methods, was involved in data extraction, and contributed to the drafting and editing of the manuscript. NAL, ENM, and FNA aided data extraction and contributed to the drafting and editing of the manuscript. MIM and ZAB supervised the preparation of the protocol and reviewed the manuscripts. All authors have approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

AFB: acid-fast bacilli
AI: artificial intelligence
CNN: convolutional neural network
CXR: chest X-ray
MTB: Mycobacterium tuberculosis bacteria
PTB: pulmonary tuberculosis
STARD: Standard for the Reporting of Diagnostic Accuracy Studies
WHO: World Health Organization

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Protocol

Evaluation of a Web-Based Self-Help Intervention for Patients With Generalized Anxiety Disorder: Protocol for a Randomized Controlled Trial

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Abstract

Background: Generalized anxiety disorder (GAD) is a highly prevalent and severely distressing condition that can lead to functional impairments and is considered one of the most difficult anxiety disorders to treat. Following new technological developments, a highly structured cognitive behavioral therapy (CBT) approach that has already shown success in face-to-face psychotherapy can be implemented: internet-delivered CBT (iCBT). There is now evidence for the efficacy of both guided and unguided iCBT interventions for GAD regarding symptom reduction.

Objective: To establish the usefulness of such interventions, we plan to evaluate the efficacy of a web-based self-help program (Selfapy) for GAD in a relatively large sample. We aim to assess effects beyond symptom reduction, including effects on well-being, functioning, and mental health literacy, as well as the effect on health care burden, while testing the intervention in conditions comparable to routine care.

Methods: Patients (n=156) who have been diagnosed with GAD, are aged between 18 and 65 years, have internet access, and have sufficient German language skills will be recruited for this study. The intervention group (n=78) will receive access to the 12-week self-help web-based program Selfapy. The waitlist control group (n=78) will receive no intervention in the context of the study. However, both groups will be allowed to access further health care services (eg, psychotherapy, medication), reflecting current routine care in Germany. Outcome measures will be assessed at baseline (T1) and 6 weeks (T2) and 12 weeks (T3) after the start of the intervention. The primary outcome will be generalized anxiety symptoms and quality of life at T3. Additional outcomes include depression, work capacity, therapy-related expenses and burdens, health literacy, and negative effects.

Results: By May 2023, all participants had finished the trial and the report was being prepared for publication.

Conclusions: Web-based interventions may be an important addition to the German health care system to reduce barriers to treatment access. Further, they may prove cost-effective for the treatment of GAD.

Trial Registration: Deutsches Register Klinischer Studien DRKS00023799; https://tinyurl.com/22bds38x

International Registered Report Identifier (IRRID): DERR1-10.2196/41440

(JMIR Res Protoc 2023;12:e41440) doi:10.2196/41440

KEYWORDS

generalized anxiety disorder; GAD; online self-help; randomized controlled trial; RCT; self-help; guided; anxiety; online intervention; mental health; mental illness; mental disorder; psychotherapy; internet-based; internet intervention; web-based

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Introduction

Background

Generalized anxiety disorder (GAD) is characterized by generalized and persistent excessive worry about various aspects of the past, present, or future without being confined to specific environmental conditions [1]. GAD can lead to severe distress and limitations in the daily lives of those affected [2] and is often associated with comorbid depressive disorders [3]. Subsequently, GAD poses an economic challenge to the health care system [4,5]. Lifetime prevalence is estimated at 6.2% [6].

GAD can be successfully treated by pharmacotherapy or psychotherapy [7]. Still, as individuals affected by GAD show lower response rates to therapies than other anxiety disorders, it is considered one of the most challenging anxiety disorders to treat [8]. One reason may be that individuals with GAD wait on average about a decade until they begin treatment [9]. Therefore, many cases remain undiagnosed and untreated, especially in the context of long waiting times and limited resources [9]. Following technological advancements, technology-based treatment alternatives have been increasingly developed over the past years to address the aforementioned problems [10]. Cognitive behavioral therapy (CBT) is especially suited for the transfer to web-based interventions due to its highly structured, directive, and standardized nature, as well as its emphasis on psychoeducation and homework [11]. In addition to being independent of limited resources, internet-delivered CBT (iCBT) also provides easier access for those who reject traditional forms of therapy due to stigma or other reasons [12].

Systematic reviews and meta-analyses [13] suggest that the use of iCBT programs for GAD compared to inactive control groups was significantly more effective and had moderate to large effect sizes (Hedges g=0.79) in reducing GAD symptoms. Further, iCBT programs for GAD achieved comparable effects to face-to-face CBT while the time required for each patient was 7.8 to 13 times less [14-17]. Of particular note is the benefit of iCBT to the health care system, as it may be a more cost-effective treatment alternative for GAD [18] since it can help reduce the waiting time for outpatient therapy, which averages 5 months in Germany [19] and has increased since the beginning of the COVID-19 pandemic [20].

While most of the literature focuses on guided forms of iCBT with therapeutic support, minimally guided, self-directed iCBT programs also show large effect sizes in the treatment of GAD (eg, Cohen d=2.43 [21]). Dear et al [22] found no significant differences between guided and unguided iCBT in terms of symptom reduction, completion rates, and satisfaction in the treatment of GAD. Moreover, first evidence suggests that characteristics of the guidance, such as the frequency of supportive monitoring [23], type of reminder (eg, phone, email), and the experience or training of the support person [24], do not have a significant influence on GAD symptom reduction. Nevertheless, it is important to take steps to promote adherence and minimize the typically high dropout rates of web-based, particularly self-directed, interventions [25] (eg, motivational content).

Objective

Taken together, minimally guided web-based interventions provide a low-threshold method of access to mental health care and may be particularly helpful for GAD patients who often do not seek help [9]. We aim to establish further evidence for a web-based self-help program in a setting comparable to routine care. For this purpose, a comparison is made with a wait-list control group within a randomized controlled trial framework. Further, we want to address outcomes beyond symptom reduction, such as functioning in both daily life and the workplace, as well as mental health literacy and the health care burden.

Methods

Participants

Recruitment is carried out through newsletters and social media advertising drawing attention to Selfapy. Interested individuals can register for participation on the web, and after a successful video call–based screening procedure they will be contacted by the study center to schedule a diagnostic appointment.

Video calls will be conducted with all subjects, during which eligibility will be evaluated based on a diagnostic interview, the Diagnostic Interview for Mental Disorders–Open Access (DIPS-OA) [26]. Trained interviewers with at least a master's degree (or equivalent) in psychology focusing on clinical psychology will conduct all interviews. The interviewers are trained at the Justus Liebig University in Giessen, Germany. Furthermore, there is close supervision on questions of diagnostics, as well as the inclusion and exclusion criteria, by a psychotherapist licensed in CBT.

Eligible subjects (1) are aged between 18 and 65 years, (2) have sufficient knowledge of the German language, (3) have uninterrupted internet access, (4) provide electronic informed consent to participate in the study, and (5) currently meet the diagnostic criteria according to the Diagnostic and Statistical Manual of Mental Disorders [1] for a diagnosis of GAD (International Classification of Diseases, 10th Revision code F41.1).

Subjects will be excluded if they do not fulfill any of the inclusion criteria or meet any of the following exclusion criteria: (1) past or current diagnosis of bipolar disorder, (2) past or current diagnosis of psychotic disorder, (3) current diagnosis of substance dependence, (4) current diagnosis of a severe major depressive episode, and (5) acute suicidality. A primary diagnosis of a disorder other than GAD is not an exclusion criterion, as we want to represent routine care. However, substance dependence, bipolar disorder, or psychotic illness are exclusion criteria because they conflict with the implementation of the program. Subjects who do not meet our inclusion criteria due to severity of illness are encouraged to seek professional help. Adequate language skills will be determined during the initial interview.

Study Design

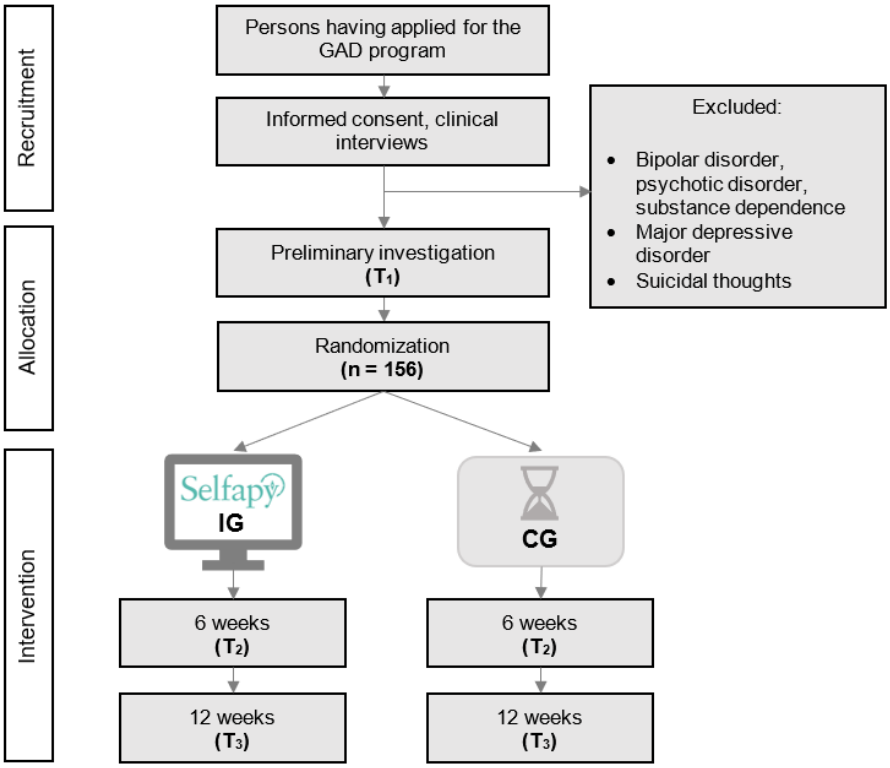
A 2-arm randomized controlled trial is being conducted to test the efficacy of the minimally guided web-based program Selfapy

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for GAD. The web-based course is defined as minimally guided as it is completed independently by the participant. However, as part of the patient safety concept, a psychologist monitors the participant's progress to support the patient and respond to adverse events, such as suicidality. The participants can ask a psychologist questions about the program via an integrated messaging function. Figure 1 shows the schematic study design for patients in the intervention group and control group. After a structured diagnostic interview (DIPS-OA [26]) to clarify the inclusion and exclusion criteria, eligible patients will receive the first questionnaire and subsequently will be randomly assigned to the intervention group or control group. Patients in the intervention group will be able to use Selfapy immediately after randomization, while the control group will only have access to Selfapy after a waiting period of 12 weeks. Interim and final evaluations will occur 6 weeks (T2) and 12 weeks (T3) after the entry survey.

Subjects in the intervention group will have free access to the 12-week internet-based self-help treatment. Participants are advised to spend at least 15 to 20 minutes per day on the program. If no module is finished over 4 weeks, this will be counted as a dropout for an additional sensitivity analysis. Patients in the control group will not receive any treatment or support from the researchers during the first 12 weeks after the initial survey. However, they are free to seek any other assistance they desire, including pharmacological and psychological treatments. All concurrent therapies will be repeat-measured using self-reports.

Figure 1. Flowchart of the study design for intervention and control groups. GAD: generalized anxiety disorder; CG: control group; IG: intervention group.



Measures

Table 1 provides an overview of survey instruments at each time point, and more detailed descriptions are also provided below.

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Table 1. Survey instruments at each time point.

Time point	Survey instrument

Pretreatment measurement (T1)	• Video interview: Diagnostic Interview in Mental Disorders–Open Access (DIPS-OA).
	• Primary outcomes (self-assessed via web-based questionnaire)
	  • Generalized anxiety disorder symptomatology (Generalized Anxiety Disorder–7; GAD-7)
	  • Quality of life (World Health Organization–Five Well-Being Test; WHO-5)
	• Secondary outcomes (self-assessed via web-based questionnaire)
	  • Coping with difficulties in everyday life due to illness (Work and Social Adjustment Scale; WSAS)
	  • Work Capability (Institute for Medical Technology Assessment Productivity Cost Questionnaire; iPCQ)
	  • Health Literacy (Mental Health Literacy Scale; MHLS).
	  • Reduction of therapy-related expenses and burdens for patients and their relatives (Client Sociodemographic and Service Receipt Inventory; CSSRI)
	• Secondary outcomes
	  • Demographic questionnaire
	  • Anxiety symptomatology (Beck Anxiety Inventory; BAI)
	  • Depressive symptoms (Patient Health Questionnaire–9; PHQ-9)

Intermediate measurement 6 weeks after T1 (T2)	• Same as T1, except that there is no video interview
	• Further surveys
	  • Negative effects (Negative Effects Questionnaire; NEQ)
	  • Short demographic questionnaire

Posttreatment measurement 12 weeks after T1 (T3)	• Same as T2

Video Interview

The DIPS-OA [26] is used to classify mental disorders and record inclusion and exclusion criteria. The person conducting the interview is part of the evaluation team (ie, part of the Faculty of Psychology and Sport Science, Giessen University) and independent of Selfapy.

Primary Outcomes

Generalized anxiety disorder symptoms will be assessed with the Generalized Anxiety Disorder Scale–7 (GAD-7 [27]). The GAD-7 consists of 7 statements rated on a 4-point scale and has an internal consistency of α=.92.

The measurement used to assess well-being is the World Health Organization–Five Well-Being Test (WHO-5 [28]). The WHO-5 consists of 5 items rated on a 6-point Likert scale and has an internal consistency of α=.92.

Secondary Outcomes

Coping with functional impairments will be assessed with the Work and Social Adjustment Scale (WSAS [29,30]), which consists of 5 items for which the true score is given as a number between 0 and 8. The WSAS is used to assess the degree of functional impairment in various domains. The WSAS has been used in comparable studies, such as a study by Gräfe et al [31]. The internal consistency of the WSAS ranges from α=.70 to α=.94 [30].

Work ability and productivity are assessed via the Institute for Medical Technology Assessment Productivity Cost Questionnaire (iPCQ [32]). The iPCQ asks about long-term (>2 weeks) and short-term (<2 weeks) absences from work. In addition, the iPCQ includes three questions on productivity losses as a result of illness-related work efficiency limitations. The iPCQ was validated by Friedli et al [33].

The Mental Health Literacy Scale (MHLS [34]) will be used to measure mental health literacy. The MHLS consists of 20 items, of which the first 15 items are rated on a 4-point Likert scale and the remaining items are rated on a 5-point Likert scale. The internal consistency of the overall scale is α=.87. The MHLS has previously only been validated in English and was translated into German for this study with the involvement of a natively bilingual collaborator in a translation-backtranslation process.

Therapy-related expenses and burdens for patients and their relatives are captured using the Client Sociodemographic and Services Receipt Interview (CSSRI [35]). The CSSRI asks participants to report the actual service utilization (eg, contact with health care providers, number of therapy sessions, amount of contact with psychotherapists and psychiatrists).

Additional Outcomes

The Penn State Worry Questionnaire (PSWQ [36]) is used to assess worry as an accompanying syndrome of GAD; it consists of 16 items rated on a 5-point Likert scale. The PSWQ shows internal consistencies approximately in the range between α=.84 [37] and α=.86 [38] in GAD patients.

The Beck Anxiety Inventory (BAI [39]) is used to assess the severity of anxiety in adults and adolescents. It consists of 21 descriptive statements rated on a 4-point scale. The internal consistency of the BAI is α=.90 in clinical samples. The German version was validated by Margraf and Ehlers [40].

The Patient Health Questionnaire-9 (PHQ-9 [41]) is used to assess the presence and severity of depressive disorders. The PHQ-9 consists of 9 items rated on a 4-point Likert scale and has an internal consistency of α=.89.

To capture possible negative effects of the intervention, the Negative Effects Questionnaire (NEQ [42]) is used, which

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consists of 32 items rated on a 4-point Likert scale. The NEQ has an internal consistency of α=.95.

The adherence of the intervention group is recorded via the log files of the web-based platform Selfapy. The number of modules that have been worked on is recorded.

Hypotheses

The main objective of this trial is to determine the efficacy of the 12-week Selfapy course for patients with GAD compared to a wait-list control group. Additional outcome data will be collected at 6 weeks. However, our confirmatory hypotheses, which will evaluate a positive health care effect, will focus on the 12-week outcomes. The following 2 hypotheses refer to our primary outcomes:

- GAD symptomatology (measured with the GAD-7 [27]) will significantly decrease with the use of the Selfapy course for GAD after 12 weeks compared to a wait-list control group.
- Perceived quality of life (measured with the WHO-5 [28]) will significantly increase after 12 weeks of the Selfapy course for GAD compared to a wait-list control group.

The following secondary outcomes will only be analyzed if the hypotheses for the primary outcomes are confirmed. They will also be tested using Bonferroni-Holm adjustment:

- Difficulties in daily life (measured with the WSAS [30]) will significantly decrease after using the Selfapy course for GAD after 12 weeks compared to a wait-list control group.
- Using the Selfapy course for GAD will lead to significantly better recovery of working ability (measured with the iPCQ [32]) after 12 weeks compared to a wait-list control group.
- Health literacy (measured with the MHLS [34]) will significantly improve with the use of the Selfapy course for GAD after 12 weeks compared to a wait-list control group.
- The extent of therapy-related efforts and burdens of patients and their relatives (measured with the CSSRI [35]) will be significantly reduced after using the Selfapy course for GAD compared to a wait-list control group after 12 weeks.

Our exploratory hypotheses do not address the target symptoms and are therefore not adjusted for α accumulation:

- Worry symptoms (measured with the PSWQ [36]) will significantly decrease with the use of the Selfapy course for GAD after 12 weeks compared to a wait-list control group.
- Self-rated anxiety symptoms (measured with the BAI [39]) will significantly decrease with the use of the Selfapy course for GAD after 12 weeks compared to a wait-list control group.
- Self-rated depressive symptoms (measured with the PHQ-9 [41]) will significantly decrease with the use of the Selfapy course for GAD after 12 weeks compared to a wait-list control group.
- The Selfapy course for GAD will not lead to any side effects compared to a wait-list control group after 12 weeks (measured with the NEQ [42]).

Intervention

Selfapy is a program for the treatment of GAD [43]. The program uses evidence-based methods and exercises based on CBT and elements of mindfulness-based therapy (see, eg, Hoyer et al [44] and Volz and Stieglitz [45]). The web-based course consists of a core course, which includes mandatory and optional exercise content, and a subsequent set of modular specialization areas that are individually selectable (Table 2). The program can be used via desktop browsers and mobile devices. The web-based course is divided into different lessons, each covering a specific topic, such as exposure, mindfulness, or problem-solving training, and consists of informative texts, videos, audio, and interactive exercises. Table 2 provides an overview of the core course with examples and possible in-depth areas and gives a brief overview of their content.

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Table 2. Overview of modules with example content of the generalized anxiety disorder program.

Module	Content
Your start	In the first module, users can describe their problems and set personal goals.
First findings	This module focuses on psychoeducation. Users learn to recognize and understand the background of their problems. In addition, users begin keeping a worry log to identify triggers and patterns regarding their worries and fears.
The mental level	This module deals with the thoughts behind the users' anxiety disorder. With the help of various exercises, users learn to question their worries and replace them with more realistic thoughts.
The physical level	In this module, users learn about the fear response and the physical symptoms of generalized anxiety disorder.
The behavioral level	In this module, users learn about how avoidance and reassurance contribute to maintaining their anxiety disorder and how the 3 levels of anxiety interact.
The first exposure	In this module, users are introduced to exposure-based methods. They learn how exposure works and why it is helpful in the treatment of anxiety disorders. Users will also receive information on how to perform an in sensu exposure and consider when to do so.
The second exposure	This lesson is dedicated to in vivo exposure. Users are informed about what it looks like and what to consider when performing it.
Optional areas of specialization	
Self-efficacy	In this module, users learn about self-efficacy. Through various exercises, they are trained in self-efficacy so as to believe more in themselves and their abilities.
Mindfulness	A mindful approach to life can have a supportive effect to better deal with one's problems. With the help of formal and informal mindfulness exercises, users learn how to integrate a mindful approach to themselves into everyday life.
Social environment	This module deals with the impact of the social environment on one's own life. Through social networks and communication exercises, users can optimize their social support and strengthen their social skills.
Problem solving training	This module provides training in problem-solving skills. Users learn to perceive a concrete problem, grasp reaction possibilities, and implement an action to change the situation.
Your anti-anxiety package	In the final module, users take stock of the completed course. They summarize which content was particularly helpful and where they can still improve their anxiety disorder. At the end of the program, the user gains an antianxiety package to use when problems arise again or a relapse has already set in.

Randomization and Blinding

Subjects meeting the inclusion criteria will be randomly assigned to 1 of 2 groups and will receive either (1) immediate access to the minimally-guided Selfapy GAD course (the intervention group) or (2) access to the Selfapy GAD course after a waiting period of 12 weeks (the control group).

Randomization takes place after the participant has finished the entry questionnaire, which is conducted by a member of the psychology department who is not involved in the project, using a computer-assisted procedure. Random assignment is done only if participants fulfill the inclusion criteria for the study. Until this time, which group the person will be assigned to if included is unknown (allocation sequence concealment). Participants will be assigned to 1 of the 2 groups in a nonstratified 1:1 ratio. Subjects will be informed of the outcome of the random assignment via email. Participants are told that the waiting time will randomly vary between 0 and 12 weeks. Thus, patients in the control group will not know that the sample is divided into 2 groups. One group will start the intervention immediately while the other group will wait 12 weeks before receiving access to the therapy. The diagnostic interviewers will be blind to the group membership of the participants. After completing data collection, statistical analysis of the outcomes will also be performed in a blinded manner.

Power and Sample Size

The between-group effect size estimate is based on recent meta-analytic evidence for effect sizes in unguided web-based psychological interventions for anxiety disorders (Cohen *d*=0.45; see, for example, McCall et al [46]). Even though Selfapy is minimally guided, we chose this meta-analysis since the degree of guidance is not associated with the effect size [16,17]. This effect size will be used as the basis for sample size design. For the planned mixed model with 2 measurement time points with a general correlation structure [47], a directed hypothesis, a group allocation of 1:1, a power of 0.80, and an α level of .025 after Bonferroni-Holm correction, a total of 156 patients (n=78 per group) are needed. The number of cases was calculated using the R tool *longpower* [48]. For the secondary outcomes, this sample size yields a power of $1-\beta=.67$.

Statistical Analyses

For the psychometric outcome analyses, all patients who were randomly assigned to the 2 conditions and completed the initial survey (T1) will be included in an intention-to-treat (ITT) analysis. All available data will be used for this purpose. Missing values in the data will be replaced by multiple imputations (multivariate imputation by chained equations with n=5 imputations) based on the control arm, using the variables "age" and "gender" as predictors in addition to the measurement-repeated stress indicators. In addition,

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last-observation-carried-forward, baseline-observation-carried-forward, reference-based-multiple imputation (jump-to-reference approach [49]), and completer sensitivity analyses will be performed.

The confirmatory analysis of the primary outcomes consists of calculating a mixed model with 2 measurement time points and a general correlation structure [47]. A random effect for the subjects is calculated (random intercept) and 3 fixed effects (group assignment, time, and the interaction of the 2 predictors). The 2 measurement time points are nested within subjects. The primary outcomes will be evaluated using a Bonferroni-Holm correction for α error inflation. Secondary confirmatory outcomes will only be analyzed if the results of the primary analysis confirm the hypotheses, and the same mixed model with a random intercept for the subject will be applied. Again, a Bonferroni-Holm correction will be used.

Independent 2-tailed *t* tests and chi-squared tests will be used to estimate differences between groups in pretreatment sample characteristics. In addition to the ITT sample, a "per-protocol" sample sensitivity analysis is defined for exploratory analyses, including all patients in the intervention group who completed at least 4 of the modules.

There are different approaches to calculating effect sizes for mixed modeling data in the literature [50]. Hedges [50] and Westfall et al [51] propose an effect size based on the Cohen *d*, which is also used for power analysis [47]:



To assess the magnitude of the treatment effects, the fixed interaction effect of time and group assignment is divided by the root of the summed variances of the random effects. Effect sizes can be roughly interpreted according to the Cohen *d*: effect sizes of 0.2 are considered small, 0.5 moderate, and 0.8 large [52]. Differences in response rates and additional health care service utilization rates are examined with 2-tailed *t* tests and chi-squared tests.

All data analyses are performed without knowing group membership (blinded data analysis). The evaluator does not know which expression of the group variable indicates membership in the intervention group and which indicates membership in the control group. Multimedia Appendix 1 shows example code for the R analysis of the outcomes.

Ethical Considerations

Participants are asked about suicidality at all measurement time points (T1, T2, and T3). For safety reasons, subjects will be contacted if they report suicidal thoughts and an emergency plan is drawn up with them. Nevertheless, the subject's data will not be passed on to the police or other authorities. If participants endorse suicidality, they will be excluded from further data analyses, and only the assessments up to the occurrence of suicidality will be used.

The study center at the University of Giessen is responsible for storing and analyzing patient data. Besides the initial interview, all data are collected via a web-based platform (SoSci Survey; SoSci Survey GmbH) that uses SSL encoding to protect the data and stores them on servers located in Germany. Participant data are stored pseudonymously in order to access contact data in cases of suicidality. However, after the study is finished, the data will be immediately deidentified. Written informed consent is obtained from all participants before participation, and the ethics committee of the Faculty of Behavioral and Empirical Cultural Science at the study center at Heidelberg University approved the clinical protocol (AZ Prüß 2021 1/1). The trial is registered at the German Clinical Trials Register (DRKS00023800) and follows the ethical principles of the Declaration of Helsinki. All patients receive an allowance of €30 (US $33) after completing the study.

Results

By May 2023, all participants completed the study, and a paper reporting the results is being prepared. The report will be submitted for publication in the coming months.

Discussion

This study tests the efficacy of a minimally guided web-based intervention (Selfapy) for the treatment of GAD in routine clinical care. The study has several strengths. First, the study was designed to strike a balance between a high degree of internal validity (eg, randomization, a standardized diagnostic procedure), allowing us to attribute observed group differences to the intervention with sufficient certainty and a high external validity (eg, allowing participants to use additional health care services) to evaluate the effects in an ecologically valid context. In particular, we did not prepare artificial measures to increase adherence to gain a representative impression of routine care patient adherence. Second, to the best of our knowledge, this study is one of the most highly powered studies on iCBT for GAD [13]. Third, we will investigate outcomes beyond symptom reduction, such as functioning and health care use. Limitations of this study include the lack of an active control group instead of a wait-list control group, even though this design allows only limited conclusions regarding the specificity of the effects found. We chose this design in an attempt to assess the incremental effect of Selfapy for GAD patients compared to the current situation in the German health care system. Patients who want to undergo outpatient psychotherapy in Germany have to wait for an average of 20 weeks to start treatment [19]. One of the main advantages of an internet intervention like the one investigated in this study is its availability. If implemented in routine clinical care, patients can make use of these interventions without delay and can expect results comparable to traditional face-to-face therapy [14]. One could argue that the waiting period in the control group (12 weeks) is too short, given the average waiting time in the health care system of 20 weeks. Still, we decided to restrict the waiting time in the control group to 12 weeks for several reasons. First, for ethical reasons, we wanted to limit the waiting time as much as possible. Withholding a likely helpful intervention should only be done as long as necessary. Again, we want to highlight that patients in the control group, as well as those in the intervention group, were allowed to seek additional treatment and help if they thought it necessary. No patients were asked to refrain from any

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other mental health services. Second, 12 weeks is the time the intervention takes when completed on the recommended schedule. Therefore, fixing the control group to the same measurement schedule as the intervention allows us to evaluate the effects of having access to Selfapy for GAD compared to not having access to this intervention. Another limitation lies in the use of deception in telling the patients that the intervention will start some time between 0 and 12 weeks later. This is done to attenuate dissatisfaction with being in the control group. However, patients in the control group may still feel dissatisfied and unlucky when they have to wait what they think is the maximum amount of time for the intervention. Also, we do not assess the frequency of personality disorders, which may be reasonable because GAD is associated with higher rates of personality disorders [53]. Further limitations include the lack of follow-up measurement, the lack of a power calculation for the secondary outcomes, and the lack of a mindfulness measure despite the intervention including a mindfulness-based approach.

Due to current technological progress, the implementation of web-based interventions may be an important addition to the German health care system. This may reduce barriers to treatment provision and complement current clinical care. Therefore, we aim to assess a routine-care web-based intervention for its impact on symptom reduction, well-being, work capability, and other measures of disease burden.

Acknowledgments

This study was funded by a European Regional Development Fund awarded to Selfapy. The Professorship for Psychotherapy Research at the University of Giessen was asked by Selfapy to independently evaluate its product to the best of our knowledge and following the standards of good scientific practice. Selfapy made suggestions for the selection of survey instruments in the study's design but had no influence on the data collection, analysis, and interpretation or production of the resulting publication.

Data Availability

The data sets generated during the upcoming study will be available in the OSF repository [54].

Authors' Contributions

JR, JQ, LR, and CL wrote the manuscript. LP, CT, SH, SB, and DR read the manuscript and provided critical feedback. All authors were included in the planning phase of the study.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Example code for the analysis in R.
[DOCX File , 16 KB - resprot_v12i1e41440_app1.docx]

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Abbreviations

BAI: Beck Anxiety Inventory
CBT: cognitive behavioral therapy
CSSRI: Client Sociodemographic and Service Receipt Inventory
DIPS-OA: Diagnostic Interview in Mental Disorders-Open Access
GAD-7: Generalized Anxiety Disorder 7
iCBT: internet-delivered cognitive behavioral therapy
iPCQ: Institute for Medical Technology Assessment Productivity Cost Questionnaire
ITT: intention-to-treat
MHLS: Mental Health Literacy Scale
NEQ: Negative Effects Questionnaire
PHQ-9: Patient Health Questionnaire 9
WHO-5: World Health Organization–Five Well-Being Test
WSAS: Work and Social Adjustment Scale

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Protocol

Effects of the Pregnancy and Newborn Diagnostic Assessment (PANDA) App on Antenatal Care Quality in Burkina Faso: Protocol for a Cluster Randomized Controlled Trial

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Abstract

Background: The Pregnancy and Newborn Diagnostic Assessment (PANDA) system is a digital clinical decision support tool that can facilitate diagnosis and decision-making by health care personnel in antenatal care (ANC). Studies conducted in Madagascar and Burkina Faso showed that PANDA is a feasible system acceptable to various stakeholders.

Objective: This study primarily aims to evaluate the effects of the PANDA system on ANC quality at rural health facilities in Burkina Faso. The secondary objectives of this study are to test the effects of the PANDA system on women's satisfaction, women's knowledge on birth preparedness and complication readiness, maternal and child health service use, men's involvement in maternal health service utilization, and women's contraception use at 6 weeks postpartum. Further, we will identify the factors that hinder or promote such an app and contribute to cost-effectiveness analysis.

Methods: This is a randomized controlled trial implementing the PANDA system in 2 groups of health facilities (intervention and comparison groups) randomized using a matched-pair method. We included pregnant women who were <20 weeks pregnant during their first antenatal consultation in health facilities, and we followed up with them until their sixth week postpartum. Thirteen health centers were included, and 423 and 272 women were enrolled in the intervention and comparison groups, respectively. The primary outcome is a binary variable derived from the quality score, coded 1 (yes) for women with at least 75% of the total score and 0 if not. Data were collected electronically using tablets by directly interviewing the women and by extracting data from ANC registers, delivery registers, ANC cards, and health care records. The study procedures were standardized across all sites. We will compare unadjusted and adjusted primary outcome results (ANC quality scores) between the 2 study arms. We added a qualitative evaluation of the implementation of the PANDA system to identify barriers and catalysts. We also included an economic evaluation to determine whether the PANDA strategy is more cost-effective than the usual ANC strategy.

Results: The enrollment ran from July 2020 to January 2021 due to the COVID-19 pandemic. Data collection ended in September 2022. Data analyses started in January 2023, ended in June 2023, and the results are expected to be published in February 2024.

Conclusions: The PANDA system is one of the most comprehensive apps for ANC because it has many features. However, the use of computerized systems for ANC is limited. Therefore, our trial will be beneficial for evaluating the intrinsic capacity of the PANDA system to improve the quality of care. By including qualitative research and economic evaluation, our findings will be significant because electronic consultation registries are expected to be used for maternal health care in the future in Burkina Faso.

Trial Registration: Pan-African Clinical Trials Registry (PACTR) PACTR202009861550402; https://pactr.samrc.ac.za/TrialDisplay.aspx?TrialID=12374

International Registered Report Identifier (IRRID): DERR1-10.2196/37136

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KEYWORDS

telemedicine; PANDA; pregnancy and newborn diagnostic assessment; quality; antenatal care; Burkina Faso; trial; pregnancy; pregnant; newborn; diagnostic; mobile app; prenatal care; randomized trial; first trimester; postpartum; qualitative research; maternity; prenatal; antenatal; mobile phone

Introduction

Background

Antenatal care (ANC) is one of the strategies that contributes to reducing maternal and neonatal mortality. In the early 2000s, the concept of ANC was introduced and refocused to be more efficacious [1-3]. Essential activities such as the prevention of anemia and malaria in pregnant women, preparation for delivery and obstetric emergencies, and advice on good nutrition for women and newborns have found their place in the new vision of ANC [4]. In addition, the World Health Organization (WHO) guidelines recommend 8 antenatal visits to the clinic so that each point of contact will ensure a smooth and safe pregnancy [5]. According to the WHO, increasing the frequency of ANC visits for women and adolescents is associated with a reduced risk of stillbirths. These visits provide additional opportunities to detect and manage potential problems [5]. Additionally, regular antenatal visits to the clinic increase the chance of delivering at a health facility [6].

Despite the importance of ANC, data on the use of services by pregnant women remain scarce in sub-Saharan Africa [7-9]. Several reasons could explain this situation, including the quality of care and satisfaction of pregnant women with health services. Nikiema et al [10] showed that the different steps of ANC are not carefully adhered to, ignored, or misunderstood by health care providers in Burkina Faso. Tiembré et al [11] who evaluated the quality of ANC in Grand-Bassam (Ivory Coast) reported that the interpersonal communication skills of the health care providers with patients were poor. It is essential to systematically follow the different stages of ANC to provide quality care to pregnant women. One solution to improving the quality of ANC is the standardization of care, obliging health workers to systematically follow all the steps of ANC consultation [12-14]. Therefore, the use of mobile apps and telemedicine seems appropriate. The WHO insists on using mobile apps to provide maternal and child health care because these apps play an essential role in improving the quality of health care services [15]. In 2013, the World Health Assembly passed numerous resolutions on information and communication technologies in the health care sector. The use of apps in health care has been noted to be related to reduced health care costs, improved quality, and equitable access to health services [15]. The application of information and communication technologies in the health sector includes client education and behavior change, medical record management, electronic decision support, quality care in health services, human resource management, and supply chain management [16].

Concerning decision support and quality of care, ANC has been a particular focus of mobile app interventions. However, different studies [12-17] show contrasting results. In 2018, Chen et al [18] conducted a systematic review of 245 studies, including 51 randomized controlled trials, on the effectiveness and appropriateness of mobile apps for maternal and child health care between 2011 and 2016. Their results showed that mobile apps had no effect on the quality of health care in approximately half (43%) of the randomized controlled trials.

The Pregnancy and Newborn Diagnostic Assessment (PANDA) system [19,20] is a digital clinical decision support tool that facilitates diagnosis and decision-making by health care personnel in ANC. Feasibility and acceptability studies of the PANDA system have been conducted in Madagascar and Burkina Faso [14,21]. The study [21] conducted in the Koupéla district of Burkina Faso in 2016 with the nongovernmental organization, Enfants du Monde, Switzerland, showed that the PANDA system is a feasible tool for improving the quality of care for pregnant women and for collecting detailed information in the electronic form. The women in that study [21] expressed high satisfaction with the antenatal visits using this telemedicine system except for the average duration of ANC (women found that the average duration of ANC is high with the PANDA app), which would increase with the app use. The health care workers expressed their satisfaction with the service improvements and noted the different steps of ANC according to the recommendations of Burkina Faso. In the PANDA app, the different steps of ANC are presented in an imposed chronology to the health care provider. The completeness of the data for all fields conditions the passage from one stage to the next. Therefore, it is impossible to omit information. Following these encouraging results, the Ministry of Health of Burkina Faso expressed interest in using the PANDA telemedicine system for maternal and neonatal health care to improve the quality of care. Hence, we plan to implement a randomized controlled trial to evaluate the effectiveness of PANDA in improving the quality of ANC.

Study Objectives and Hypothesis

The objective of this study was to evaluate the effects of the PANDA system on the quality of ANC in Burkina Faso. We hypothesize that the PANDA telemedicine system improves (1) the quality of ANC provided to pregnant women, (2) women's satisfaction, (3) women's knowledge on birth preparedness and complication readiness, (4) maternal and child health service use, (5) men's involvement in maternal health service utilization, and therefore (6) postpartum contraception use.

Study Setting

This study was conducted in Burkina Faso, where the ANC rate varies according to the area of residence. The 2010 Demographic and Health Survey and Multiple Indicator Cluster Survey (Burkina Faso Enquête Démographique et de Santé et à Indicateurs Multiples [EDSBF-MICS IV]) showed that 1.5% and 5.7% of the pregnant women did not attend antenatal visits in the urban and rural areas, respectively [22]. Moreover,

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according to the EDSBF-MICS IV, only 33.7% of the pregnant women have received at least 4 ANC consultations as recommended by the WHO. Only 41.2% of the women had their first ANC visit in the first trimester of pregnancy, and the median number of months of pregnancy at the first ANC visit was 4.4 months at the national level [22]. Among the women who received ANC for the most recent birth 5 years before 2010, only slightly more than half (53%) had been informed about the signs of pregnancy complications. In ANC, it is crucial for pregnant women to know the pregnancy danger signs. The EDSBF-MICS IV also showed that almost all women (95%) received ANC from a trained provider, and the majority (61%) of these trained providers were auxiliary birth attendants. Midwives provided ANC for 17% of the women, and nurses examined almost the same proportion of women (16%). Approximately one-third of the women (34%) had at least 4 antenatal visits, which aligns with the Burkina Faso Ministry of Health's recommendations. There were significant differences between the areas of residence in Burkina Faso: in Ouagadougou (Burkina Faso's capital), 54% of the women attended the 4 recommended visits compared with 38% in other cities and only 31% in rural areas [22]. The consequences of this low access to maternal, newborn, and child health services are high maternal and infant mortality rates. One in 8 children die before 5 years, and the maternal mortality ratio was 341 deaths per 100,000 live births in 2010 [22]. We chose the health district of Koupéla (Centre-East Region of Burkina Faso) because of its proximity to Ouagadougou. At that time, there were no ongoing ANC interventions in this district. The other reason for choosing this district is that the PANDA feasibility test was conducted in this district in 2016.

Methods

Conceptual Framework of This Study

Our research project consists of implementing an intervention called the PANDA telemedicine system. This study phase, which we call the interventional phase (as it follows the design and feasibility phases of the intervention), involves 2 groups of health facilities in the same district (an intervention group and a comparison group). We compared the effects of the intervention with those of the usual ANC offered in the comparison group through a cluster randomized trial. The interventional phase also employs qualitative research and a cost-effectiveness study at the end of the trial. The qualitative research identifies the barriers and catalysts of using the PANDA system for ANC in the intervention group. The cost-effectiveness analysis provides information on the costs of implementing the PANDA system in Burkina Faso. The expected effects of the app are improvement in (1) the quality of ANC provided to pregnant women, (2) women's satisfaction, (3) women's knowledge of birth preparedness and complication readiness, (4) use of maternal and child health services, (5) men's involvement in maternal health service utilization, and (6) contraception use at 6 weeks postpartum. The long-term impact of this app is the reduction of maternal and neonatal mortality.

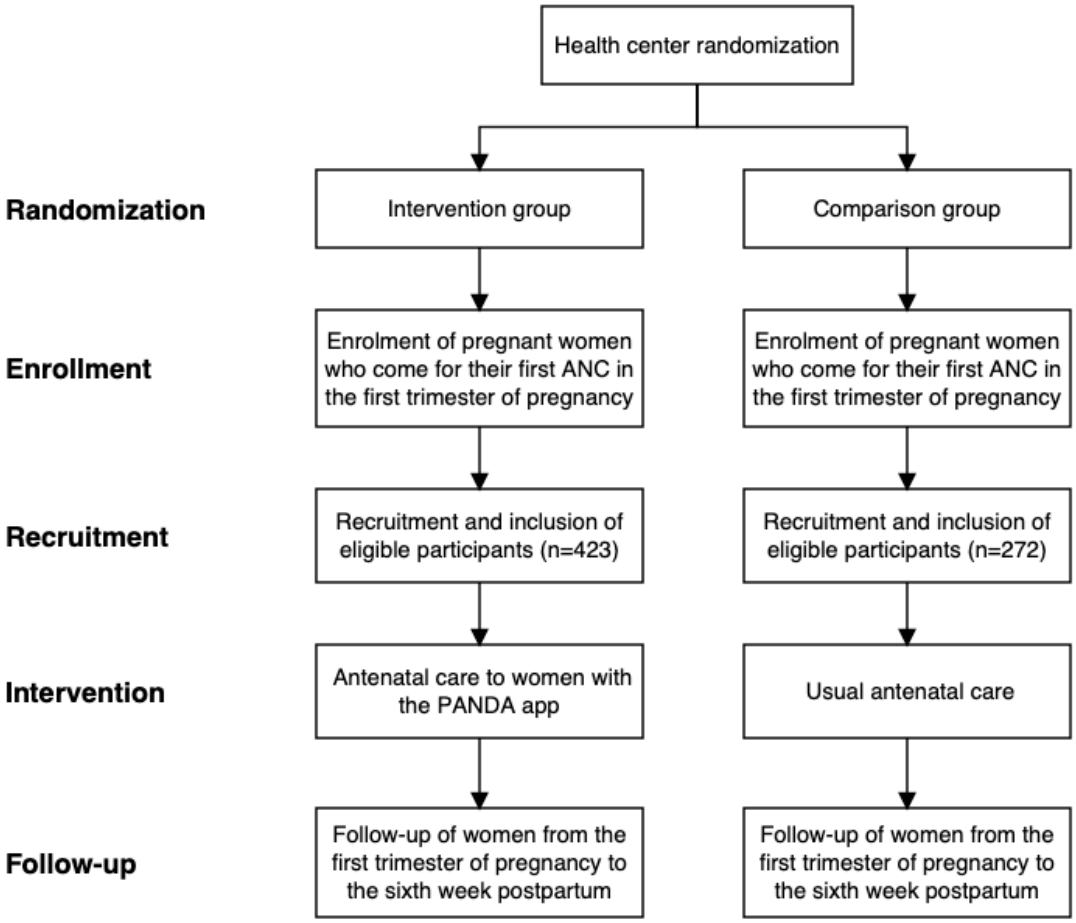
Cluster Randomized Controlled Trial

Study Design

In this study, the intervention is the PANDA telemedicine system. It involves 2 groups of health facilities in the same district (an intervention group and a comparison group). The intervention group offered ANC using the PANDA app installed on tablets. Each health facility in this group had at least one tablet. The health centers in the comparison group offered ANC as usual (the PANDA app was not used in these health facilities). The rationale for implementing a cluster randomized trial is that the intervention (training and use of the PANDA system) cannot be implemented at the individual (pregnant woman) level but only at the health center level. The study design is shown in Figure 1.

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Figure 1. Study design. ANC: antenatal care; PANDA: Pregnancy and Newborn Diagnostic Assessment.



Participant Eligibility Criteria

The participants were pregnant women with gestational age between 14 and 20 weeks of amenorrhea, regardless of age, residence, and socioeconomic level. They were screened for eligibility for this study: first by health care workers on arrival and second by the data collectors of this study. Any pregnant woman who met the following criteria was eligible for this study: (1) <20 weeks of gestation, (2) belonging to the health facility area, (3) no plan to travel in the next 9 months (from inclusion in this study to 6 weeks postpartum), (4) not taking part in any other ongoing research, (5) volunteering to participate, (6) being in a clinical and obstetrical condition that allows delivery at the health center (no need to refer to the next level), and (7) has the intention to deliver in that health center.

Interventions

PANDA is a telemedicine system developed through a private-public partnership in Italy, with funding from the European Union, in collaboration with the WHO. The PANDA system was designed to meet the health care needs of women during pregnancy in resource-scarce settings by expanding and standardizing ANC according to the WHO guidelines. The PANDA system, designed for use by low-skilled health care workers such as community health care workers, supported remotely by skilled personnel, aims to standardize and improve the quality of ANC visits. In addition, the system can automatically generate and provide the data necessary to measure its performance. The original PANDA system, as designed for use by community health care workers, consists of 3 integrated components (see Figure 2).

1. The PANDA phone: This smartphone with an Android app allows for a standardized and quality antenatal visit by using pictograms according to the national and WHO guidelines. The health care workers enter the women's data and obstetrical and medical-surgical history into the system. The system also includes pages for medical tests to ensure that health care workers perform these tests. At the end of the visit, the PANDA phone sends the data and test results to the medical unit.
2. The PANDA point of care: A series of medical tests are performed to screen for anemia, syphilis, HIV, malaria, eclampsia, diabetes, and malnutrition. The test results are entered manually or via Bluetooth into the PANDA phone.
3. PANDA medical unit: A database system receives data from the PANDA phone, establishes diagnoses and the management of pregnant women, and maps pregnancies in the region. The PANDA medical unit in the maternity ward typically consults this database.

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Figure 2. The Pregnancy and Newborn Diagnostic Assessment system. PANDA: Pregnancy and Newborn Diagnostic Assessment.



The PANDA system used in our proposed study is like the system used in the pilot feasibility and acceptability study in 2016 [21]. It has already been adapted to the Burkinabè context. The PANDA system will be integrated into the Burkinabè health system and used by the Ministry of Health's care providers in the health center under the supervision of the district management team. The PANDA app and the PANDA medical unit will be readapted to the new national norms and standards for ANC, which are currently under revision based on the new "WHO Recommendations on Antenatal Care for a Positive Pregnancy Experience" [4]. To adapt the tool to other telemedicine systems in practice in Burkina Faso, tablets have replaced smartphones. A user's manual for the PANDA app was made available to the stakeholders for the judicious use of the app. We organized several forms of training to explain better the use of the PANDA app (user training at the health center and medical unit levels).

Outcomes

The primary outcome is a binary variable derived from the quality score. It will be coded 1 (yes) for women with at least 75% of the total score and 0 if not (Table 1). The quality score considers all the components of good ANC according to the gestational age of the pregnancy. The different components are grouped into 7 main dimensions with items. These items are derived from Burkina's guidelines on ANC [23]. The categorization is that each woman has a total score for each ANC (from the first consultation to the last).

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Table 1. Summary of the components of quality antenatal care.

Item (1 if yes, 0 if no)	Data source
Antenatal consultation performed	Woman's health card reports
Partner's presence at the consultation	Item asked to the woman
Possession of a verified health record	Woman's health card reports
Pregnancy test performed	Woman's health card reports
Date of last period requested	Item asked to the woman
Probable date of delivery given to the pregnant woman	Item asked to the woman
Hypertension was investigated	Item asked to the woman
Asthma was investigated	Item asked to the woman
Testing for sickle cell disease	Item asked to the woman
Diabetes was investigated	Item asked to the woman
Surgical history was obtained	Item asked to the woman
Number of pregnancies was queried	Woman's health card reports
Number of deliveries was queried	Woman's health card reports
Number of abortions or miscarriages was queried	Woman's health card reports
Number of caesarean deliveries was queried	Woman's health card reports
Number of living children was queried	Woman's health card reports
Alcohol consumption queried	Woman's health card reports
Tobacco use queried	Woman's health card reports
Sugar and albumin levels in the urine measured	Woman's health card reports
Syphilis test performed	Woman's health card reports
An HIV test was offered to the woman	Woman's health card reports
HIV test was performed	Woman's health card reports
Blood pressure measurement	Woman's health card reports
Fetal heart sounds recorded	Woman's health card reports
Search for edema of the feet and face	Woman's health card reports
Weight gain	Woman's health card reports
Temperature checks	Item asked to the woman
Physical examination: uterine height measured	Woman's health card reports
Physical examination: vaginal touch performed	Woman's health card reports
Physical examination: decision on obstetrical prognosis (normal pelvis, borderline pelvis, etc)	Woman's health card reports
Tetanus vaccination verified and performed	Woman's health card reports
Hepatitis B vaccination verified and performed	Woman's health card reports
Antianemia prophylaxis (iron–folic acid) prescribed	Woman's health card reports
Antianemia prophylaxis: woman explains dosage correctly	Item asked to the woman
Prescribed antimalarial prophylaxis	Woman's health card reports
Malarial prophylaxis: woman explains dosage correctly	Item asked to the woman
Danger signs of pregnancy explained to the woman	Item asked to the woman
Place of delivery discussed	Item asked to the woman
Importance of exclusive breastfeeding explained	Item asked to the woman
Early breastfeeding of the baby has been advised	Item asked to the woman
Maternal nutrition: good feeding practices discussed	Item asked to the woman

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Item (1 if yes, 0 if no)	Data source
Postpartum contraception was discussed	Item asked to the woman
Use of an impregnated net was explained	Item asked to the woman
Newborn care was explained	Item asked to the woman
The childbirth preparation plan was discussed	Item asked to the woman
The woman was asked to raise concerns where appropriate	Item asked to the woman
The next meeting was negotiated	Item asked to the woman
Summary of the antenatal care written in the woman's health record	Woman's health card reports

The secondary outcomes to measure include the satisfaction of pregnant women (measured at each ANC), women's knowledge on birth preparedness and complication readiness (measured in the first trimester and just before delivery), use of maternal health services, men's involvement in health service use (defined as the proportion of men who accompany their wives to the health centers for ANC sessions and delivery and the proportion of men who attended an ANC session or delivery), and finally, the women's use of postpartum family planning (measured at the sixth week postpartum).

Other Variables

We collected women's sociodemographic characteristics such as women's age, education, marital status, residence, and occupation. We also collected data on women's autonomy (Multimedia Appendix 1). We asked the women, in some situations, regarding who makes the final decision: herself, her husband, mother-in-law, father-in-law, or any other person. She could name more than one person if the decision was made collectively. These autonomous situations or items could be small household expenses, major household expenses, women's expenses, women's job, buying children's clothes, where to go for advice if her child is ill, where to go to see a doctor if she is ill, buying medicines, visiting her parents (when or where), number of children in her household, and using the family planning method. The woman's autonomy variable will be derived from these variables (composite index) and will have 3 modalities (low autonomy, moderate autonomy, and high autonomy).

Sample Size

In addition to the desired statistical power and percentage of potential lost to follow-up, the calculation of the required size considered several statistical features inherent to the design of the study, such as the number of participants per cluster, the intraclass correlation coefficient (ICC), and the inflation factor [24-27]:

1. Number of participants: To be practical and comfortable with data collection, we considered 40 women per health center, excluding those lost to follow-up.
2. ICC: This measures the extent of the cluster effect and assesses the degree of similarity between the individuals within a cluster. It is based on the relationship between the intercluster variance and the intracluster variance. For this reason, the sample sizes must be increased to account for the clustering effect. In particular, the value of ICC depends on the unit of randomization and the type of outcome. In our case, we have women likely to come from the rural areas of several health zones. Given the composition of health care workers in rural health centers (midwives and birth attendants), it is reasonable to assume that there will be slight variations between women moving from one health center to another. For this, we propose an ICC of 0.015.
3. Inflation factor: The increase required to account for the cluster effect is influenced by ICC and cluster size. The standard sample size was increased by an inflation factor equal to $[1 + (n – 1) \rho]$, where n is the average cluster size and ρ is the estimated ICC. By numerical application, inflation factor = 1.585.
4. The desired statistical power was 80%.
5. The margin of error was 5%.
6. The estimated proportion of those lost to follow-up was set to 10%.

Using Stata 15.1 software [28], health centers needed to detect a difference of at least 15% (80% in the intervention group vs 65% in the control group) in the proportion of women with an excellent ANC quality score in 6 health centers in each group. Considering the loss to follow-up proportion at 10%, the minimum final size required is 264 women in each group with 12 health centers, except the urban health facility. The hypothetical proportion of 65% in the comparison group was derived from a study conducted in Ghana in 2019 by Baafi et al [29].

Participant Recruitment

The health care providers recruited the participants during the ANC sessions after history taking and physical examination. After screening a potentially eligible woman, her consent (free and informed decision) to participate in this study was obtained after she received all the necessary information from the data collector.

Randomization

Facilities were randomized using a matched-pair method. Health centers were selected by identifying 6 pairs of comparable health centers. The matching criteria were (1) number of total ANC visits in the year before the trial, (2) number of total deliveries in the year before the trial, (3) number of total postnatal care visits in the year before the trial, (4) number of women of childbearing age in the health center area, (5) total number of health care workers in the health center as well as the distribution by profile (midwives, nurses, and auxiliary birth attendants), and (6) size of the population served. These matching variables allow us to obtain facilities within each pair

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that are similar to each other regarding these matching factors. Within each pair, the center that received the PANDA app was chosen randomly using the draw of 1 health center from each pair; the names of the health centers were previously arranged in individual envelopes and sealed. The drawer was different from the one who prepared the envelopes and did not attend the sealing. The draw, therefore, was carried out 6 times. All consecutive and eligible participants were included in the clusters.

To assess women in the semiurban environment (city of Koupéla), we included the health center in Koupéla, which unfortunately could not be matched to another city, given its size and characteristics. To minimize the likelihood of cross-group contamination, facilities are chosen to ensure they are far enough apart. Moreover, women generally did not move from one center to another due to the distance between the health centers. They usually visit the same health center for ANC during their pregnancy. We included only the women who were sure they would realize all their ANC visits in the health center where they were included in this study. Lastly, no staff move was noted during the study between the 2 arms. The health centers selected as the study sites are shown in Table 2.

Table 2. Study sites.

	Health center
Pair 1	Baskouré and Kalwêga
Pair 2	Boangtenga and Zaogo
Pair 3	Dialgaye and Yargo
Pair 4	Baadtenga and Sampongho
Pair 5	Gounghin and Ligdi-Malguem
Pair 6	Kabéga and Zéguédéga
One semiurban center	Koupéla health center

Implementation

After the health care workers were trained in the intervention group's health centers, supervisions were organized throughout the data collection period to verify the implementation of the intervention.

Blinding

Given our intervention's nature, blinding the participants and the research team was impossible.

Data Collection Methods

Data collectors were trained before the inclusion of participants on all the procedures of inclusion, follow-up, and how data must be collected (data sources). They were not health care workers. Therefore, the study procedures were standardized across all sites. Data were collected from women on the day of inclusion and at each successive ANC, up to the sixth week after delivery. One data collector was assigned to 2 neighboring health centers for the duration of the study (1 intervention group health center and 1 comparison group health center). The questionnaires were administered to the participants immediately after the antenatal visit, after the delivery, and after each postpartum visit. The interviewer visited the health center according to the ANC schedule. A field coordinator was recruited and responsible for checking all the data collection steps, including the recruitment of participants.

The participant's knowledge was measured at the study inclusion and at the end of pregnancy. This knowledge covered topics such as the danger signs of pregnancy, signs of labor starting, danger signs after childbirth for the woman, and newborn's danger signs. All these signs are normally discussed with the woman at each ANC visit to improve her knowledge to stimulate early consultation if any one of the following signs occur:

1. Danger signs of pregnancy: vaginal bleeding, fever, intense intractable headache, difficulty breathing, convulsions and loss of consciousness, intense abdominal pain, non–bloody vaginal discharge, lack of fetal movement, and feet and hands edema.
2. Signs of the onset of labor: loss of water, painful and regular contractions, and discharge of red and viscous mucus.
3. Newborn danger signs: fever, hypothermia, convulsions, inability to breastfeed, vomiting, pus or bleeding from the cord, purulent discharge from the eyes, jaundice, hypotonia, unexplained crying, abdominal pain, bloating, diarrhea, and difficulty breathing.
4. Danger signs after childbirth for the woman: convulsions, heavy vaginal bleeding, intense abdominal pain, intense headaches, dizziness, rapid or difficult breathing, fever, bad odor discharge from the vulva, and paleness of the mucous membranes.

For each group of signs, there was a proportion of women who knew no signs and a proportion of women who knew at least 3 signs. Furthermore, we measured women's birth preparedness by asking the woman if she had identified a health facility for her delivery or in case of emergency, if she had identified a companion of choice for labor and childbirth, or in case of emergency, if she had planned the financing of the main expenses related to her delivery and if she had identified one means of transport to reach the health facility for the delivery. Those who took precautions for each of the 4 questions scored 1 for each question and 0 if the woman took no precautions. The use of maternal and child health services was measured by the number of ANC visits attended by the woman, place of delivery, postnatal consultation on days 6-10, and postnatal consultation in 6-8 weeks. The different variables with their measurement periods are presented in Figure 3.

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Figure 3. Schedule of participants' enrollment, allocation, interventions, and assessments in the randomized controlled trial. ANC: antenatal care; PANDA: Pregnancy and Newborn Diagnostic Assessment.

			Study period							
	Enrollment	Allocation	Postallocation							Closeout
Timepoint			t_1	t_2	t_3	t_4	t_5	t_6	t_7	t_8
	ANC1 (1st trimester of pregnancy)		ANC2	ANC3	ANC4	ANC5	ANC6	ANC7	Delivery	6th week postpartum
Enrollment										
Eligibility screen (estimate)	2000									
Informed consent (estimate)	750									
Allocation		695								
Interventions and controls										
PANDA system (7 health centers)		423	←	—	—	—	—	—	—	→
Routine ANC (6 health centers)		272	←	—	—	—	—	—	—	→
Assessments										
Baseline variables										
Sociodemographic factors (women's age, education, marital status, residence, occupation)	✓									
Women's medical history	✓									
Women's autonomy	✓									
Main outcome: score of antenatal care quality	✓		✓	✓	✓	✓	✓	✓		
Secondary outcomes										
Pregnant women's satisfaction	✓		✓	✓	✓	✓	✓	✓		
Women's knowledge on birth preparedness and complication readiness	✓							✓		
Use of maternal health services	✓		✓	✓	✓	✓	✓	✓	✓	✓
Men's involvement in maternal health	✓		✓	✓	✓	✓	✓	✓	✓	✓
Use of postpartum family planning										✓

For this study, data were collected using a closed questionnaire by directly interviewing the women and extracting data from ANC registers, delivery registers, ANC cards, and health care records. To understand the satisfaction of pregnant women, we use a satisfaction scale consisting of very satisfied, satisfied, neutral, not very satisfied, and not at all satisfied, which will be rated as 4, 3, 2, 1, and 0, respectively. The data collector explained to the woman that she is free to give the number of green stars corresponding to her satisfaction level for each subitem listed in Textbox 1 below. The image is shown and explained to the woman in order to rate her satisfaction. The number of green stars chosen correspond to her level of satisfaction with that subitem. The maximum score for each subitem is 4 and the minimum is 0. This satisfaction was measured at each antenatal visit for each woman enrolled in the research. It should be recalled that the data collectors were women without health care training who were recruited and assigned to each health center. Data collectors did not interfere in the care relationship with the women.

Textbox 1. Items and subitems for measuring the satisfaction of pregnant women.

Women's satisfaction with interpersonal relations with staff (5 subitems)

- Welcoming
- Respecting the confidentiality of consultation with the health care provider
- Respecting privacy during consultation
- Respect and courtesy of the health care providers during antenatal care
- Goodbye from staff

Quality of service (9 subitems)

- Waiting time
- Overall time spent in the health center
- Other times to wait for test results
- Health care provider skills
- Explanation of iron–folic acid dosing
- Explanation of malarial prophylaxis
- Explanation of preventive measures against malaria
- Explanation of women's diet
- Explanation of different complementary examinations

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Data Management

Data collection was performed electronically by using tablets. Only the identifying information of the participants was collected on paper to maintain the anonymity of the women in the different databases. In both groups, registers, health records, ANC cards, and women's self-report were used for data collection. We developed a data quality assurance plan for the duration of the trial. Implementation was under the supervision of the research team. Confidentiality of the data was ensured by protecting devices with passwords kept in a secure location. A data entry program was developed using the CSEntry Android app of Census and Survey Processing System software [30]. The data manager exported the data to Stata 15.1 for correction and use. We implemented the following measures to ensure effective data management:

1. The information collected during the various contacts with women was verified several times at different levels. Data collectors were responsible for ensuring that all data collected were accurate. They reviewed all the completed forms before uploading them to the server to guarantee completeness and resolve inconsistencies.
2. All data were stored on a server compatible with good clinical practice, and data transmission will be encrypted to ensure data integrity and patient confidentiality. The access to data management was password protected, and only authorized users had access.

Statistical Methods

Quantitative data were extracted and transferred to Stata 15.1 for analysis. We will perform an intention-to-treat and per-protocol analysis of the cluster randomized trial. The unit of analysis will be women. The analysis will compare the intervention and comparison groups' unadjusted and adjusted primary outcomes results. Unbalanced factors between the 2 study groups will be used to adjust the intervention effects on the study outcomes. These factors will be women's sociodemographic factors and women's autonomy. The means and proportion comparison tests for independent samples will be used at the 5% threshold. In case of nonnormality of a quantitative variable (satisfaction scores, knowledge scores, etc), robust or Poisson regression will be used.

Data Monitoring

Since the participants were not given an experimental drug, we did not conduct an interim analysis to determine whether to stop. The team was supervised every month. The management focused on aspects such as the quality of the collected data, careful adherence to every step of the protocol and validated methods, and using the PANDA app. In addition, monthly meetings were held online with all technical and financial partners to resolve difficulties. The supervision and meeting reports were produced and archived systematically.

Ethics Approval

This trial was retrospectively registered with the Pan-African Clinical Trials Registry under PACTR202009861550402 on September 21, 2020. The Burkina Faso Health Research ethics committee approved the research protocol for this trial under approval 2020-3-051. This study does not introduce any new drug treatments. The PANDA system was designed by the standards and protocols in force in Burkina Faso. Any problems identified will be managed according to the procedures and practices in the health system. Adult participants (at least 18 years old) were included after obtaining their informed consent. Minor participants were included by obtaining their assent and parental consent. In the case of minor participants, informed consent of the parent or the respective legal guardian was obtained in conjunction with informed permission of the underage participant (younger than 18 years). The interviewers assigned to the various health centers were responsible for obtaining consent. This process was carefully checked during the field supervision of the research team. All questionnaires in the database did not contain any information that could be used to identify a woman formally. The participants' phone numbers and identities were recorded in a physical document, allowing the interviewer to locate the woman, if necessary, to administer a questionnaire.

Qualitative Analysis of Factors Hindering or Facilitating Implementation

We conducted a qualitative evaluation of the implementation of the PANDA system to identify the interactions (positive or negative) between the intervention and the implementation environment. The target population comprised the intervention group and the resource personnel. The intervention group included women who had recently given birth, providers of the health centers where the PANDA system was used, and resource persons. With women, we measured mainly their perceptions of the quality of care and interactions with health providers. The health care providers were interviewed to give their opinion about the PANDA system's technical aspects, interactions with women, and perceptions of the quality of the medical procedures provided. Given their positions in this research, the resource persons were the key informants. They were the district management team, managers of the medical unit, Directorate of Health Information Systems, Directorate of Family Health, and members of 2 nongovernmental organizations, namely, Enfants du Monde, Switzerland, and the Private and Community Initiative for Health and the Response to HIV/AIDS in Burkina Faso.

Following the reasoned approach, we performed 4 focus groups with women who had recently given birth (1 focus group per center in 4 health centers), 22 in-depth individual interviews, and again with women who had recently given birth in the 7 health centers (3 interviews per center); 18 in-depth individual interviews were conducted with the health workers of the 7 health centers (2 per center, including the medical unit). However, given the size of the CSPS Urbain (the only semiurban center), the number of health workers interviewed was 4. We also conducted 4 in-depth individual interviews with the technical and financial partners. In total, 44 individual interviews and 4 focus groups were performed.

The qualitative component used the semistructured interview [31]. The women were recruited in a reasoned manner from among those included in the study—mainly the last women enrolled in this study to give birth to guarantee the freshness of memory. In addition to the primary data, secondary data were

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collected through activity reports (training missions since the beginning, supervision missions conducted by the research team, etc), budgets allocated to program activities, national health policy documents, PANDA app user guide, etc. The explored themes were as follows: the satisfaction of the participants in the intervention group, the acceptability of the intervention to health care workers, and the barriers and catalysts for an efficient and effective implementation of the PANDA system.

Content analysis [32] was used as the data processing and analysis technique. The digitally collected data were transcribed into French and entered into Microsoft Word. The transcribed data were analyzed thematically using a manual approach with the help of analysis tables. The analysis model used was the strengths-weaknesses-opportunities-threats model. It enabled us to identify the interactions (positive or negative) between the intervention on the one hand and the implementation environment on the other. These diversions will allow us to consider the necessary readjustments for greater efficiency and effectiveness of the intervention.

Economic Evaluation

An economic evaluation was added to this research to determine whether the PANDA strategy is more cost-effective than the usual ANC strategy in Burkina Faso's context. The economic assessment collected data from pregnant women (expenses related to antenatal visits), health agents, and financial partners (costs of designing the app, training costs, acquiring equipment, etc). The direct prices included drugs and consumables for health centers. For women, the costs included direct costs such as transport costs for the health center visit and indirect costs, especially the monetary value of the time spent visiting the antenatal service. As ANC is currently free for women, no expenses of ANC-related care are paid by women in principle.

The economic evaluation data were analyzed using Stata software (version 17.1; StataCorp LLC) for the descriptive analyses and R software (version 4.0.2; R Foundation for Statistical Computing) for the Monte Carlo simulations. We also adapted the WHO CostIt tool [33] to calculate the costs according to the ingredients approach [34] for each cost category. Incremental cost-effectiveness was examined based on comparisons of costs and effects between the study groups. We conducted a probabilistic sensitivity analysis by testing the effect of simultaneous variations in several parameters by using Monte Carlo simulations to generate plausible values from the baseline parameter distributions. A total of 10,000 iterations were generated by R programming. A cost-effectiveness acceptability curve was developed based on the willingness to pay to gain a percentage of ANC quality and compared to the gross domestic product per capita of Burkina Faso in 2020.

Results

Participant recruitment in this study was influenced by the COVID-19 pandemic. Although recruitment was planned to start in May 2020, the inclusion finally began only on July 12, 2020, and was done progressively in different health centers included in this study. Participant selection continued until the end of January 2021. The inclusion period extended more than expected because only women at <20 weeks of gestational age were included. There were only few such cases in the study health centers because women usually start their antenatal visits late in Burkina Faso. As women were to be followed up until 6 weeks postpartum, the last data collection interview ended in September 2022. Data analysis was completed in June 2023, and the results are expected to be published in February 2024.

Discussion

Study Overview

With the rise of information and communication technologies and the WHO's recommendations for the use of mobile technology in antenatal health care, several clinical trials using mobile health apps have been conducted with varied results. Most of these clinical trials [12-17] used a mobile text messaging system for sending awareness and information messages to pregnant women. Those studies proposed to measure pregnant women's knowledge and the quality of ANC. Apart from mobile apps, some computerized clinical decision support systems have been implemented. Haddad et al [35] conducted a systematic review of these computerized systems in 2019 and found 9 systems that met their eligibility criteria, including the PANDA system. The PANDA system was found to be one of the most comprehensive apps with several features. However, those authors concluded that the use of these systems for ANC was limited [35]. Adepoju et al [36] conducted a systematic review of clinical decision support systems in sub-Saharan Africa in 2017 and reached the same conclusion. However, they noted that clinical decision support systems could improve patient-provider relationships by building trust in the provision of health services. They also noted that although health care workers are generally enthusiastic about using these types of systems, there are concerns about the effects of increased workload, workflow changes, and technical challenges. These different barriers to implementing health apps were also found by Zakane et al [37] in Burkina Faso. Thus, the added value of these systems remains to be proven. Although studies on the PANDA system have shown that it can provide standardized ANC as per the WHO's guidelines [14], it is still essential to evaluate its intrinsic capacity to improve the quality of care by conducting a high-level evidence study. In this sense, the randomized trial that will be conducted in our research will be of crucial importance because it will help to demonstrate whether, in addition to offering standardized care, the PANDA system allows for an improvement in the quality of care provided to pregnant women, their satisfaction, and their knowledge on birth preparedness and complication readiness. Moreover, considering that Burkina Faso is a country with limited resources, such health policies could be cost-effective; hence, the economic evaluation carried out throughout the implementation is pertinent and essential. In addition, the results of this trial will be significant because computerized clinical decision support systems are anticipated to be implemented in Burkina Faso in the future in several fields, including reproductive health (through the electronic consultation register for maternal care) and child health (through the electronic consultation register for the management of child diseases).

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Strengths and Limitations of This Study

The limitations and challenges of this complex intervention include difficulties in coordinating with study sites and challenges related to the COVID-19 pandemic in implementing the intervention, maintaining its fidelity, and keeping the trial on schedule. Although we have designed a cluster randomized controlled trial, neither the study sites nor the participants are blinded to the study conditions because of the nature of the intervention. Moreover, the participating sites are limited to 1 rural district of Burkina Faso; thus, the results may not be generalizable at the national level (no urban facilities are included in this study). However, our results could guide countrywide policies for improving maternal and newborn health, highlighting the benefits of such an electronic decision support system for similar rural African areas where maternal and newborn morbidity and mortality rates are high.

Conclusion

This study will help to determine the proportion of women who receive quality ANC as recommended in clinical standards and protocols and whether electronic registries can help improve ANC in a context of low-quality human resources, like in Burkina Faso. This study's qualitative research and economic evaluation will identify the barriers and facilitators of such an app in resource-limited countries such as Burkina Faso and contribute to the cost-effectiveness analysis of 2 strategies (PANDA vs usual care). In a randomized study design, the results will likely provide a high level of evidence compared to the results already available in the literature, which are from pilot or feasibility studies with smaller sample sizes.

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Data Availability

The data sets generated and analyzed during this study will be available from the corresponding author upon reasonable request following the completion of the trial and publication of the primary outcome paper.

Authors' Contributions

AC wrote the first draft with important contributions from SK. AC and SK are members of the research team. SK is the principal investigator and AC is the coinvestigator. The authors agree to be accountable for all aspects of this work.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Data collection instrument.
[PDF File (Adobe PDF File), 107 KB - resprot_v12i1e37136_app1.pdf]

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Abbreviations

ANC: antenatal care
EDSBF-MICS: Burkina Faso Enquête Démographique et de Santé et à Indicateurs Multiples
ICC: intraclass correlation coefficient
PANDA: Pregnancy and Newborn Diagnostic Assessment
WHO: World Health Organization

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Protocol

Identifying the Most Effective Recruitment Strategy Using Financial Reimbursements for a Web-Based Peer Network Study With Young People Aged 16-18 Years: Protocol for a Randomized Controlled Trial

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Abstract

Background: Peers are an important determinant of health and well-being during late adolescence; however, there is limited quantitative research examining peer influence. Previous peer network research with adolescents faced methodological limitations and difficulties recruiting young people.

Objective: This study aims to determine whether a web-based peer network survey is effective at recruiting adolescent peer networks by comparing 2 strategies for reimbursement.

Methods: This study will use a 2-group randomized trial design to test the effectiveness of reimbursements for peer referral in a web-based cross-sectional peer network survey. Young people aged 16-18 years recruited through Instagram, Snapchat, and a survey panel will be randomized to receive either scaled group reimbursement (the experimental group) or fixed individual reimbursement (the control group). All participants will receive a reimbursement of Aus $5 (US $3.70) for their own survey completion. In the experimental group (scaled group reimbursement), all participants within a peer network will receive an additional Aus $5 (US $3.70) voucher for each referred participant who completes the study, up to a maximum total value of Aus $30 (US $22.20) per participant. In the control group (fixed individual reimbursement), participants will only be reimbursed for their own survey completion. Participants' peer networks are assessed during the survey by asking about their close friends. A unique survey link will be generated to share with the participant's nominated friends for the recruitment of secondary participants. Outcomes are the proportion of a participant's peer network and the number of referred peers who complete the survey. The required sample size is 306 primary participants. Using a multilevel logistic regression model, we will assess the effect of the reimbursement intervention on the proportion of primary participants' close friends who complete the survey. The secondary aim is to determine participant characteristics that are associated with successfully recruiting close friends. Young people aged 16-18 years were involved in the development of the study design through focus groups and interviews (n=26).

Results: Participant recruitment commenced in 2022.

Conclusions: A longitudinal web-based social network study could provide important data on how social networks and their influence change over time. This trial aims to determine whether scaled group reimbursement can increase the number of peers

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referred. The outcomes of this trial will improve the recruitment of young people to web-based network studies of sensitive health issues.

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KEYWORDS

young adult; incentive reimbursement; research subject; study participant; financial; research subject recruitment; social network; peer network; web-based network; randomized; friend; recruit; incentive; reimburse; reward; incentivized; youth; adolescent; teenage; recruitment; reinforcing factor; enabling factor; disambiguation; intrinsic incentive; extrinsic incentive; motivation; reward system; positive reinforcement; compensation; monetary; remuneration; remunerative incentive; financial incentive; bonus; stipend; donation

Introduction

Background

Late adolescence is an important time in health and social development when many potentially modifiable health risks arise. This period often includes the exploration and initiation of behaviors including sexual activity, alcohol and other drug use, and the emergence of mental health problems [1]. Peer relationships are one of many interrelated determinants of health during adolescence [1]. For instance, adolescents with peers who engage in tobacco, alcohol, and cannabis use are more likely to initiate these behaviors themselves [2,3]. Despite the acceptance of peers as an important determinant of health, there is little recent quantitative research examining the influence of adolescents' peer networks compared to research focused on the individual. Furthermore, the social environment that adolescents live in is constantly evolving, with more interactions taking place on the internet than in previous generations [4]. There is therefore a need for updated research about the influence of peers in the current context that leverages these new interactions and social connections.

Social network theory is an approach used to understand the influence of adolescents' peers, among other things [5]. In the context of adolescent health behaviors, social network research involves the collection and analysis of information about relationships between individuals and their health behaviors [6]. Research seeks to understand the influence of a peer network and the mechanisms of this influence (eg, social pressure, communication of attitudes and norms, and social support) [6]. Understanding peer influence and its mechanisms can be used to design health interventions that leverage the strengths of adolescents' social networks [7]. The majority of prior social network studies on adolescents have recruited participants from schools, with the "network" cast as entire classes or schools [3]. This recruitment setting produces high response rates and high ascertainment of contacts and links. It also has the potential for demographic diversity within the sample (particularly if several different schools were selected for the study). However, many longitudinal studies of this type were designed with relatively short follow-up periods (eg, 1-2 years) due to students changing classes and leaving school [8-10]. Studying a whole network (eg, an entire school or class) also limits the generalizability of findings to the wider adolescent population. As the network boundary is restricted, respondents are commonly limited to nominating friends from a directory within their class or their school year [11,12]. Alternative recruitment settings in social network research are community or health organizations. These settings were used by studies that sought specific subgroups (eg, youth experiencing homelessness or those with a specific health condition) and where recruitment staff had pre-established relationships with the participants [13,14]. However, studies recruiting from these settings reported difficulties reaching the desired sample sizes at sufficient speed [15,16]. Moreover, analyses of peer influence and sociometry in these studies were limited to egocentric data, meaning that primary participants report on the characteristics and behaviors of their friends, which limits the accuracy and reliability of behavioral reports [14].

Conducting social network research on peer groups using web-based techniques could overcome some of these disadvantages and has the potential to be used in longitudinal studies for the ongoing collection of information about people's social networks beyond school. More broadly, web-based mechanisms are increasingly being used to recruit young people, as researchers have found web-based studies can effectively reach many young people, including those in more marginalized groups such as young people who identify as lesbian, gay, bisexual, transgender, queer, asexual, or other (LGBTQA+) [17,18]. Web-based questionnaires also provide greater privacy during completion than in person- or school-administered questionnaires, which is particularly important for sensitive topics such as sexual health and substance use [19]. To our knowledge, there are no social network studies with adolescents conducted entirely on the internet, but web-based cross-sectional, individual-level surveys have used social media recruitment, specifically Facebook, to recruit young people [17,20,21]. Social media platforms rapidly emerge, update, and outdate, resulting in frequent changes to their popularity and hence their usefulness as recruitment sites.

Web-based respondent-driven sampling (webRDS) offers a model for how we could recruit adolescents' peer networks. Like traditional respondent-driven sampling (RDS), webRDS involves primary participants who are incentivized to recruit a specific number of peers into the study by offering a monetary reimbursement per recruited peer [22]. Studies using webRDS have either recruited the primary participants in person through study administrators [22,23] or used targeted Facebook advertising and phone screening to enroll primary participants [24]. Referral of secondary participants has been facilitated using emails [22,24] or private messages primarily via Facebook [23,24]. Reported benefits of using webRDS were that it was

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quicker, cheaper, and overcame barriers related to participants distributing physical coupons compared to RDS [23]. Potential limitations and considerations of webRDS include differences in participant demographics and risk profiles between recruitment using RDS and webRDS [23]. Fraudulent or duplicate cases were identified as a problem due to some participants trying to increase their reimbursement by creating false email addresses to artificially increase their number of referrals [24]. The reimbursements offered for survey completion and friend referral varied between each study, and the impact of the reimbursement was not tested. Therefore, the extent to which a reimbursement affects the recruitment of peers remains an important practical question that impacts the cost and feasibility of conducting a web-based social network study.

Rationale

Our study will address gaps identified in previous research by determining whether a web-based approach is effective in recruiting adolescent peer networks. We will also address how different reimbursement models impact recruitment. In group 1 (experimental group: scaled group reimbursement), all participants within a peer network will receive an additional Aus $5 (US $3.70) voucher for each referred participant who completes the study, up to a maximum total value of Aus $30 (US $22.20) per participant. In group 2 (control group: fixed individual reimbursement), participants will only be reimbursed for their own survey completion.

If a web-based social network study proves feasible, this method has the potential to overcome barriers related to conducting longitudinal network research and use this web-based approach to better examine how social networks and their influence change over time. Identifying the characteristics associated with successful peer network recruitment would enable us to determine whether adolescents with certain key demographics or at-risk groups are more or less likely to refer their peers. By identifying these groups, we can gather further feedback and tailor the study methods in the future so that these social networks may be better captured.

Aims and Research Questions

The primary aim of this study is to compare the effectiveness of 2 different financial reimbursement strategies for recruiting young people into a web-based peer network study. This will be explored through the following research questions:

1. Does a scaled group financial reimbursement for peer referral increase the proportion of an individual's close friend network that completes the survey compared to having no peer referral reimbursement?
2. Does a scaled group financial reimbursement for peer referral increase the number of close friends per participant who complete the survey compared to having no peer referral reimbursement?

We hypothesize that a scaled group financial reimbursement for peer referral will result in a significantly higher proportion of participants' close friend networks and a significantly higher number of close friends per participant who complete the survey, compared to a fixed reimbursement rate for individuals.

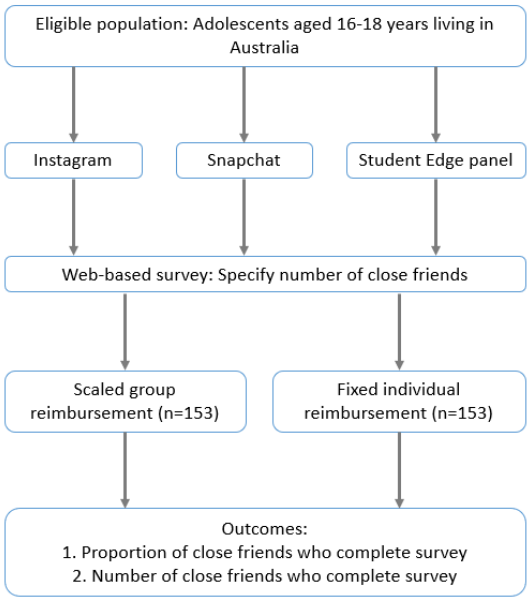
The secondary aim is to determine what demographic and behavioral factors are associated with successfully recruiting close friends.

Methods

Study Design

This study uses a 2-group randomized trial design to test the effectiveness of reimbursements for peer referral in a web-based cross-sectional peer network survey. Participants will either be randomized to scaled group reimbursement (the experimental group) or fixed individual reimbursement groups (the control group). The trial will be of 60 days duration. Figure 1 illustrates the study design.

Figure 1. Study design.



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Participants and Eligibility

This trial involves both primary participants and secondary participants. Primary participants are defined as individuals recruited through the recruitment platforms (Instagram, Snapchat, and the Student Edge panel) and are able to refer their close friends. Secondary participants are individuals nominated by a close friend and referred to the study by a primary participant.

Primary participants will be eligible if they are aged between16 and 18 years and are currently living in Australia. Secondary participants will be eligible if they are aged 16 years or older and currently living in Australia.

Intervention

All primary and secondary participants will receive Aus $5 (US $3.70) as reimbursement for their own survey completion. Primary participants will be randomized to either (1) scaled group reimbursement (experimental) or (2) fixed individual reimbursement (control). In the scaled group reimbursement, all participants within a peer network (ie, the primary participant and all secondary participants) will receive an additional Aus $5 (US $3.70) voucher for each added secondary participant that the primary participant recruits to the study, up to a maximum total value of Aus $30 (US $22.20) per participant. The reimbursement per participant stops increasing at 6 per peer group, but up to 11 people in a peer group can be referred and reimbursed up to Aus $30 (US $22.20) each (1 primary and 10 secondary). In the fixed individual reimbursement, all participants will only be reimbursed Aus $5 (US $3.70) for their own survey completion. Table 1 describes the reimbursement amounts for participants in each group depending on the number of secondary participants who complete the survey within their friendship group.

Table 1. Reimbursements for each intervention group.

Number of participants in friend group who complete survey	Reimbursement value per participant	
	Scaled group reimbursement (experimental)	Fixed individual reimbursement (control)
1 primary; 0 secondary	Aus $5 (US $3.70)	Aus $5 (US $3.70)
1 primary; 1 secondary	Aus $10 (US $7.40)	Aus $5 (US $3.70)
1 primary; 2 secondary	Aus $15 (US $11.10)	Aus $5 (US $3.70)
1 primary; 3 secondary	Aus $20 (US $14.80)	Aus $5 (US $3.70)
1 primary; 4 secondary	Aus $25 (US $18.50)	Aus $5 (US $3.70)
1 primary; 5-10 secondary	Aus $30 (US $22.20)	Aus $5 (US $3.70)

Reimbursements are in the form of a gift voucher sent by SMS to participants' mobile numbers using a third-party service provider at the end of the trial period. However, due to the procedures of Student Edge, primary participants recruited through this setting will receive the initial Aus $5 (US $3.70) reimbursement on survey completion through Student Edge and further reimbursements via SMS at the end of the study, if applicable.

Outcomes

The primary outcome is defined as the proportion of primary participants' close friends who complete the survey. Survey completion is recorded if the secondary participant clicks the final survey submission button. This outcome measure indicates the level of complete data about each primary participant's close friend network.

The secondary outcome is the number of close friends who complete the survey per primary participant. This outcome measure assesses whether the reimbursement model results in an overall higher number of participants.

Sample Size

We calculated the required sample size to test the difference in proportion of an individual's close friend network that completes the survey between the intervention and control groups. Based on previous literature, we estimated that the average number of close friends listed in the survey (nominations) is expected to be 3 [9,11,25], and that approximately half of the primary participants in the scaled reimbursement group would successfully recruit at least one friend into the study [22,23]. Based on these data and assuming that the probability of recruiting each friend is binomial, with the probability of recruiting no friends being $(1–p)^n$, where n is the total number of friends and p is the probability of each friend being recruited, we estimated that the probability of any one nomination being recruited would be 0.2. We assessed the sample size required for 80% power to detect a 2-fold difference in proportion between the scaled group reimbursement and fixed individual reimbursement groups. We assumed some variation between friendship groups and considered each friendship group as a cluster, with an assumed intracluster correlation (ICC) of 0.5 and a mean cluster size of 3, with a coefficient of variation for cluster size of 0.83. Based on these assumptions, 153 primary participants must be randomized to each group, and a total sample of 306 primary participants is required. Based on this sample size, we will also be able to detect a difference in the number of close friends per participant who complete the survey of 1.4 and 80% power. In total, across both groups, we estimate that at least 92 secondary participants will be recruited based on conservative assumptions.

Since we plan to recruit through 3 primary participant recruitment settings, we intend to recruit 102 primary participants from each setting (Instagram, Snapchat, and the Student Edge panel). Recruitment in each setting will continue until 102 primary participants are reached, or 6 weeks have passed. If fewer than 102 participants are recruited from any

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setting, further recruitment will be conducted from successful settings.

Recruitment

Primary participants will be recruited from 3 web-based platforms: Instagram advertising, Snapchat advertising, and the Student Edge panel. Specific details about each recruitment platform and how participants will be recruited are outlined below:

- Instagram is a free-to-use photo and video sharing social network service predominantly used through smart phone apps. Instagram allows users to engage with a range of advertisements outside of their immediate social network. Instagram is currently owned by Meta, which administers Instagram's advertising manager function. Using the advertising manager, businesses and users can manage paid advertisements on Instagram. The study will use the advertising manager to select target ages 16-18 years and limit the geographic area to Australia. The advertisement will feature images relating to the survey topics and text outlining the study. Tapping or swiping on the Instagram advertisement will direct prospective participants to the study information page.
- Snapchat is an instant messaging app that allows users to share pictures and videos (called "snaps"). Messages are usually only available to recipients for a short period before they can no longer be viewed. The study will use Snapchat's paid advertising feature to select the target audience of people aged 16-18 years, within the geographic area of Australia. Paid advertisements in the form of a short video appear between viewing friends' snaps, and people can swipe up to interact with the ad. The advertisement will feature a short, animated video with text outlining the study. By tapping on the advertisement, prospective participants will be redirected to the study information page.
- Student Edge [26] is a web-based organization targeted toward people in high school, technical and further education (TAFE), and university in Australia. The website provides students with study tips, news, promotions, competitions, job listings, and surveys. People can voluntarily sign up for the Student Edge Surveys panel to earn rewards. Student Edge will send an email invitation to prospective participants aged 16-18 years, who have signed up for their panel. Participants then click on the link in the email and are redirected to the study survey page.

Secondary participants are recruited by primary participants. When primary participants reach the end of the survey, a default message and URL unique to them and their friendship group will be generated. The primary participant is asked to discuss the project with their friends and share the message and URL. Secondary participants can click on the link to take them to the study information page and then proceed to the survey. One reminder email is sent to the primary participant 72 hours after they complete the survey. Secondary participants are not given the option to refer additional friends (ie, there is only 1 wave of secondary recruitment).

All participants will be required to provide their email address and mobile phone number. To prevent multiple responses from the same individual, repeat email addresses and mobile phone numbers will be detected by Research Electronic Data Capture (REDCap; Vanderbilt University), which is used to collect data (see below), and these participants will not be able to proceed with the survey.

Allocation of Intervention

Primary participants are randomized upon opening the study webpage. Randomization is managed through a REDCap survey form to enable automatic allocation independent of the researchers. The timestamp when a participant opens the webpage determines their allocated group, with those opening at an even number of seconds assigned to the scaled group (intervention) and at an odd number of seconds to the fixed group (control). Primary participants are informed about their intervention group after they answer how many close friends they have. Secondary participants are assigned to the same intervention group as the primary participant who recruited them. Researchers will not be blinded to the intervention group as they have no direct contact with the participants.

Data Collection

Participants will complete a web-based survey using the REDCap data collection tool [27]. The survey will capture information about peer networks, mental health, alcohol and other drug use, COVID-19 vaccination, sexual health, social media, and media related to sexual health, including pornography, sexting, and dating apps. The survey begins with a study information webpage containing a brief video accompanied by written information explaining the purpose of the research, what is involved, and how to participate. After the study information, participants proceed to a sign-up or consent page. Participants provide their contact details (email and mobile number) and will be asked to complete a checkbox list indicating their informed consent to confirm they understand and agree to provide their information and the use of that information for the purpose of the study. Participants complete a 2-step authentication by entering a code sent to their nominated mobile number. Participants will then be directed to complete the survey. If the individual is a primary participant, a unique URL will be generated at the end of the survey to share with their friends.

The target peer networks for recruitment are assessed by asking primary participants about their close friends. Participants are asked how many people they consider to be their close friends and to give their initials or a codename for each. Participants proceed to answer questions about each friend's age, gender, and perceived closeness. If participants have more than 10 close friends, they are asked to answer the questions for their 10 closest friends. Therefore, the possible range of nominated close friends who may be referred to as secondary participants is 0 to 10. A network size of up to 10 was deemed sufficient, as in other studies, most young people nominate only 2-3 close friends [9,27]. A limit was necessary to minimize the burden on participants to answer too many questions and manage the study's budget for participant reimbursements.

Potential factors associated with close friends completing the survey are collected through the web-based survey. Primary

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participant-level factors include primary participant demographic characteristics, recruitment settings (Instagram, Snapchat, and the Student Edge panel), and health outcomes and behaviors. Health domains include mental health and well-being, sexual health, social media use, technology use related to sex, alcohol, tobacco smoking, other drugs, and COVID-19 vaccination. Friend-level predictors include network size and close friends' gender, age, perceived closeness, and frequency of discussing various health-related topics.

Data Management

Survey data for participants within the same peer network group will be linked using the unique auto-generated survey URL. Secondary participants' survey data will be linked to the primary participants' reported data using codenames and initials.

Statistical Analysis

All analysis will be conducted in Stata (version 15; StataCorp). We will first compare the 2 baseline groups to determine whether they are comparable on key demographic factors. If not, further analysis will be adjusted for any differences.

Our primary analysis will assess the effect of the reimbursement intervention on the proportion of primary participants' close friends who complete the survey using a multilevel logistic regression model. In this model, close friend nominees are the lowest level of data and are grouped by primary participant. Each close friend nominee can either be successfully recruited or not recruited (a binary outcome).

For aim 2, to determine the effect of the intervention on the number of close friends per primary participant who complete the survey, we will use a regression model with a count distribution appropriate for the data.

In secondary analysis, we will identify factors associated with successfully recruiting each close friend by including friend-, relationship-, and primary participant–level variables. We will use a logistic regression model where the outcome is whether a primary participant successfully recruited at least one friend or recruited zero friends, and the potential predictors include recruitment setting, demographics, health variables, and network size.

Data Monitoring

This study is the first time we have tested this referral approach. The number of reimbursements needed depends on the number of secondary participants. Therefore, we plan to monitor the secondary participant referral rate during data collection to ensure we do not exceed the budget for reimbursements (Aus $20,000; US $14,800). If the referral rate indicates we will exceed this budget, we will stop advertising the project and close the survey early to new primary participants. We will monitor the secondary participant referral rate at recruitment of 50, 100, 150, and 200 primary participants.

Community Engagement

Young people were involved in the development of the study design through previous focus groups and interviews [28]. Twenty-six participants aged between 16 and 18 years living in Victoria were recruited through paid advertisements on Facebook and Instagram. In these interviews, young people were asked about their perspectives on acceptable and engaging ways to conduct peer network research. Young people identified recruitment settings and strategies to communicate the study to participants. For the recruitment of social networks, young people endorsed having the autonomy to ask their friends if they would like to participate and using a referral link. Young people recommended using reimbursements to overcome barriers to participation and to show them that the researchers value their participation and experience. Young people suggested including video, more information about the researchers conducting the project, and a visually appealing design for research materials to improve how research participation is communicated to them, build trust with the research organization and increase their engagement in the research project. The researchers developed the research questions and outcomes for this study. Young people then gave their feedback on the acceptability of the survey topics and suggestions to improve their comfort with answering sensitive questions. This study is informed by this previous work and will test the strategies identified by young people. Young people who participated in formative development will not be involved in the conduct of this trial.

Ethics Approval

This study has been approved by the Monash University Human Research Ethics Committee (23132). Our study involves primary participants aged 16-17 years, and some secondary participants will also be aged 16-17 years. Individuals aged 16-17 years can have the competence and capacity to give informed consent without parental knowledge or permission [29]. As this study takes place on the internet and aims to ask participants about sensitive topics such as pornography and sexual health, it would be inappropriate and uncomfortable to require parental consent for participation in the study. If participants wish, they are encouraged to discuss the study with their parents or guardians. Despite being a randomized controlled trial, the study was not registered, as the primary outcome (recruitment of friends) was not a direct health or medical outcome.

Some primary participants may be concerned about their friends' privacy, as they are sharing information about their friends. We will only collect the minimal required information about friends to enable linking data within peer networks. We are not collecting identifiable information from primary participants about their friends (such as friends' email addresses or mobile numbers). Friends choose to voluntarily participate and provide their own contact information directly.

To further protect friends' right to freely choose to participate, primary participants will not be informed about whether their friend has signed up for the study. A reminder email contains a generic message and disclaimer to ignore it if they have already discussed the project with their friend.

We will disseminate our findings through peer-reviewed publications, conference presentations, and a PhD thesis. A summary of results will be sent to participants and posted on the research organization's website.

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Results

Participant recruitment commenced in March 2022 and was completed in May 2023. Data analysis has not yet commenced.

Discussion

Principal Findings

This new social network research study about young people's peer networks uses web-based methods (ie, recruitment, peer referral, and survey). If feasible and effective, our study design could be used to overcome previous barriers to conducting longitudinal social network research with young people and take advantage of the benefits of using web-based methods (eg, reach marginalized groups and improve privacy). The randomized controlled trial design will enable us to determine the effect of 2 different reimbursement models on the recruitment of young people's peer networks. The limitations of this study are convenience sampling and cross-sectional design, which limit the extent to which the findings would apply to a longitudinal study.

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Conflicts of Interest

None declared.

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Abbreviations

ICC: intracluster correlation
LGBTQA+: lesbian, gay, bisexual, transgender, queer, asexual, or other
TAFE: technical and further education
RDS: respondent-driven sampling
webRDS: web-based respondent-driven sampling

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Protocol

Effects of Increased Standing and Light-Intensity Physical Activity to Improve Postprandial Glucose in Sedentary Office Workers: Protocol for a Randomized Crossover Trial

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Abstract

Background: Prolonged bouts of sedentary time, independent from the time spent in engaging in physical activity, significantly increases cardiometabolic risk. Nonetheless, the modern workforce spends large, uninterrupted portions of the day seated at a desk. Previous research suggests—via improved cardiometabolic biomarkers—that this risk might be attenuated by simply disrupting sedentary time with brief breaks of standing or moving. However, this evidence is derived from acute, highly controlled laboratory experiments and thus has low external validity.

Objective: This study aims to investigate if similar or prolonged cardiometabolic changes are observed after a prolonged (2-week) practice of increased brief standing and moving behaviors in real-world office settings.

Methods: This randomized crossover trial, called the WorkWell Study, will compare the efficacy of two 2-week pilot intervention conditions designed to interrupt sitting time in sedentary office workers (N=15) to a control condition. The intervention conditions use a novel smartphone app to deliver real-time prompts to increase standing (STAND) or moving (MOVE) by an additional 6 minutes each hour during work. Our primary aim is to assess intervention-associated improvements to daily postprandial glucose using continuous glucose monitors. Our secondary aim is to determine whether the interventions successfully evoke substantive positional changes and light-intensity physical activity (LPA). Other outcomes include the feasibility and acceptability of the intervention conditions, fasting blood glucose concentration, femoral artery flow-mediated dilation (f-FMD), and systolic and diastolic blood pressure.

Results: The trial is ongoing at the time of submission.

Conclusions: This study is a novel, randomized crossover trial designed to extend a laboratory-based controlled study design into the free-living environment. By using digital health technologies to monitor and prompt participants in real time, we will be able to rigorously test the effects of breaking up sedentary behavior over a longer period of time than is seen in traditional laboratory-based studies. Our innovative approach will leverage the strengths of highly controlled laboratory and free-living experiments to achieve maximal internal and external validity. The research team's multidisciplinary expertise allows for a broad range of biological measures to be sampled, providing robust results that will extend knowledge of both the acute and chronic real-life effects of increased standing and LPA in sedentary office workers. The WorkWell Study uses a rigorous transdisciplinary protocol that will contribute to a more comprehensive picture of the beneficial effects of breaking up sitting behavior.

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KEYWORDS

sitting bouts; digital health intervention; standing desk; endothelial function; glycemic control; sleep; blood pressure; insulin; mHealth

Introduction

Society is rapidly evolving to embrace the technological advances in communication, entertainment, and transportation that have benefited nearly every sector of daily life. These advances have also contributed to the accumulation of time spent engaging in sedentary behaviors, with approximately 60% of waking hours spent sedentary [1]. Sedentary behavior (defined by the Sedentary Behavior Research Network as <1.5 metabolic equivalents in a seated posture) [2] is a growing public health concern due to its well-established links to cardiometabolic disease development and premature mortality, independently from time spent in moderate to vigorous physical activity (MVPA) [3-7]. Meeting the recommended 150 minutes per week of MVPA is associated with beneficial cardiometabolic health outcomes [8-11]. However, MVPA alone does not offset the numerous negative health outcomes associated with prolonged bouts of inactivity. Research suggests that for each additional hour spent sedentary, the likelihood of developing metabolic syndrome and type 2 diabetes increases by 39% and 22%, respectively [12]. Therefore, reducing time spent in prolonged bouts of inactivity may lead to favorable long-term health outcomes [13].

Breaking up prolonged bouts of sitting attenuates the negative health outcomes associated with sedentary behavior [14-20], likely due to postural change and contraction of large skeletal muscle groups [13]. These actions result in increased vascular blood flow and shear stress via gravitational pull and the skeletal muscle pump, thus increasing venous return, decreasing blood pooling in the lower limbs, and activating contraction- and insulin-mediated glucose uptake pathways [21]. Taking a break to stand, walk, or exercise—in some cases, for as little as 2 minutes for every 20 minutes spent sitting [14,17]—improves glycemic control [14-19,22], insulin sensitivity [16,17], vascular response [14,23], and cardiometabolic health outcomes [16,19].

Adults spend 7.7 to 11.5 hours per day engaging in sedentary time [4,24,25], with modern office-based employees spending more than 89% of their workday seated [20]. This sedentary time, however, might be reduced through various intervention techniques. A meta-analysis reported that environmental (eg, sit-stand workstation at work) and multicomponent (eg, sit-stand workstation, education, and mobile app) intervention approaches resulted in sedentary time reductions of 40.6 and 35.5 minutes per day, whereas behavioral interventions (eg, education) resulted in a modest reduction of 23.87 minutes of sedentary time [26]. Studies using isotemporal modeling indicate that replacing sitting bouts of 30-60 minutes with either light-intensity physical activity (LPA) or MVPA is associated with reduced risk for all-cause and cardiovascular mortality, and improved cardiometabolic risk biomarkers, particularly in adults who are less active [27,28]. These findings support the feasibility and efficacy of interventions targeting sedentary time reduction and resulting health benefits [26-31].

Intervention-based research aimed at reducing sitting time and improving health outcomes has typically been conducted in tightly controlled laboratory environments, and the few studies conducted in real-world settings lack the intensive clinical and behavioral measures of a laboratory-based study. Thus, workplace-based efficacy and feasibility studies incorporating rigorous procedures with high internal validity are needed to better evaluate interventions aimed at reducing sitting time. The protocol described is a workplace study using evidence-based intervention components along with mobile and wearable technologies. A randomized crossover design will be used to explore cardiometabolic outcomes resulting from the addition of brief periods of standing or LPA during work hours while also assessing the efficacy and feasibility of the intervention in the real-world office setting.

Methods

Study Aims

The primary aim of this study is to examine the impact of 2 different intervention conditions (STAND and MOVE) on 3-hour postlunch postprandial glucose compared to the baseline control condition. Interventions entail adding 6 minutes per hour to baseline standing and LPA minutes during the workday. We hypothesize that both intervention conditions will improve postprandial glucose regulation. The secondary aim is to assess intervention adherence and changes in standing and LPA. Exploratory aims include (1) assessing participant acceptability and satisfaction during the intervention; and assessing intervention-induced changes in (2) sleep, (3) anthropometrics and body composition, (4) endothelial function, (5) central and peripheral blood pressure, (6) fasting blood glucose concentration, (7) fasting insulin concentration, (8) fasting high-density lipoprotein (HDL) concentration, (9) low-density lipoprotein (LDL) oxidation, (10) fasting triglycerides, (11) total antioxidant capacity (TAC), (12) hemoglobin A_{1c} (HbA_{1c}), (13) microbial diversity of the gut, (14) metabolomics from stool and plasma, and (15) DNA variants that may explain differences in response to the intervention.

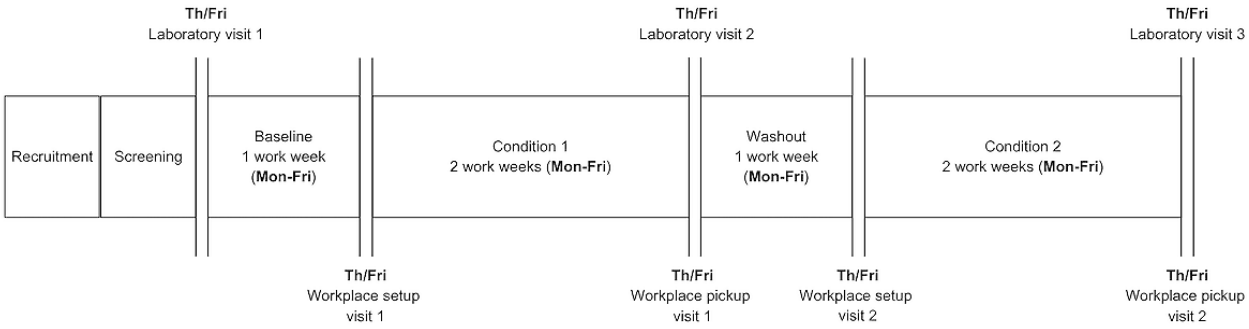
Study Design

The WorkWell Study is a pilot 6-week randomized crossover design with 2 balanced arms. Across 2 intervention periods, all participants (N=15) will experience both workplace interventions following a baseline control condition: (1) MOVE,

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an intervention targeting 6-minute increase in baseline LPA each work hour and (2) STAND, an intervention targeting 6-minute increase in baseline standing each work hour via a sit-stand workstation. Participants will wear a Bluetooth accelerometer and will be prompted with a mobile app during each intervention period. The intervention sequence is randomized and a washout period of at least 1 week will occur between interventions to reduce any potential carryover effect. Clinic-based assessments will occur at baseline and after each intervention period is completed (Figure 1).

Figure 1. WorkWell Study timeline.



Study Eligibility

Potential participants will go through a biphasic screening process to determine eligibility, see full eligibility criteria in Textbox 1. Participants will complete the web-based screening questionnaire, which will be reviewed by staff to determine initial eligibility; individuals who are conditionally eligible will be asked to consent to continue the screening process and to complete a medical history review. Next, an in-laboratory visit will confirm BMI eligibility. Those with qualifying BMIs are considered eligible to participate in the WorkWell Study and will have the opportunity to undergo full informed consent.

Textbox 1. Eligibility criteria

Inclusion criteria

- Age of ≥18 years
- Primary work activities performed seated
- Ability to use sit-stand workstation
- Works ≥4 days per week (in-office or remote)
- BMI of ≥25 (≥23 for Asian descent)

Exclusion criteria

- Taking certain medications and supplements, which includes glucose control, blood pressure, and blood thinner medications; hormone replacement therapy; corticosteroids; high-dose statins; second-generation antipsychotics; and prebiotics, probiotics, or antibiotics (in previous 3 months)
- Inability to stand or move for prolonged periods due to lower limb injury, disability, preexisting medical condition, or doctor's orders
- Serious medical conditions including, neuromuscular, cardiovascular, and respiratory disorders, as well as inflammatory bowel or intestinal malabsorption conditions, or food allergies
- Actively using a sit-stand workstation
- Work travel of ≥3 days per week
- Smoking

Procedures

Study Recruitment

Participants will be recruited on a rolling basis from the Arizona State University community via email listserves, slack channels, e-newsletters, staff website advertisements, and word-of-mouth. Preexisting partner businesses and organizations throughout the Phoenix Metropolitan area will be contacted by email. Employee-facing flyers containing study information and a link to the screening questionnaire will be disseminated electronically through the aforementioned channels.

Baseline Period

Once enrolled and initial baseline measures taken, participants will go through a 1-week baseline period in which they are outfitted with multiple devices that they will wear during each intervention period: a continuous glucose monitor (FreeStyle Libre, Abbott Diabetes Care), activPAL micro (PAL Technologies), and GENEActiv accelerometer (ActivInsights). These devices will be worn continuously (ie, 24 hours per day) for 7 consecutive days to assess baseline glycemic response, activities (including sitting, standing, and lying behaviors), and sleep, respectively. Participants will engage in their normal behaviors during the week-long baseline period.

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Lunch will be delivered on workdays during the baseline period and both intervention periods. Participants will select options from a standardized menu (approximately 33% of daily caloric needs is equal to 660 kcals, with macronutrient composition of 55% carbohydrate is equal to approximately 90.75 g, 30% fat carbohydrate is equal to approximately 22 g, 15% protein [±10%] is equal to 24.75 g) created from a list of local vendors. The standardized meal choices will be consistently repeated each week during the trial, with the same meals provided Monday to Friday during baseline and both intervention periods. Participants will be asked to avoid eating or drinking (with the exception of water and black coffee or tea) 3 hours before and post lunchtime. Food logs will be used to report when they started and finished eating their lunch, how much food they ate, and the exact food consumed during the trial.

Randomization

After completion of the baseline period, each participant will be randomized to an intervention sequence (MOVE-STAND or STAND-MOVE). Randomization is completed using the REDCap (Research Electronic Data Capture; Vanderbilt University) randomization tool and a preloaded table with treatment sequences [32,33].

Interventions

The MOVE and STAND interventions will be delivered across 2 work weeks (approximately 10 days). Both use the WorkWell mobile app and Bluetooth Activator micro (PAL Technologies) device as intervention tools in conjunction with the equipment worn during the baseline period (Figure 2). The primary behavioral target of the MOVE intervention will be to increase baseline LPA time by an additional 6 minutes per hour during work. Similarly, the primary behavioral target of the STAND intervention will be to increase baseline standing time by an additional 6 minutes per hour during work. This target of adding 6 minutes per working hour of standing and LPA was selected as an achievable goal with evidence for cardiometabolic health improvements [14-19,22].

After the baseline period is completed, the self-reported work hours and corresponding activPAL micro data will be used to identify the average minutes of standing and moving for each hour of the participant's workday. The intervention goals will be identified for each participant by adding 6 minutes to these hourly averages. For example, if a participant stands for an average of 10 minutes per work hour during the baseline period, their STAND intervention goal will be 16 minutes of standing per work hour. The same approach will be used to identify MOVE intervention goals. The WorkWell app will use live feedback from the Bluetooth Activator micro to prompt participants in the STAND intervention to meet their hourly standing goals using a sit-stand workstation, while the MOVE intervention will prompt participants to engage in light-intensity movements (eg, walking) to meet their hourly goals.

Prior to the start of the intervention, staff will meet with participants to provide the devices, equipment, and logs needed during the intervention period. Participants will undergo an introductory tour before each intervention and are reminded of their intervention goal for that period. During the intervention, participants will wear the Bluetooth Activator micro device on the mid-thigh and use the WorkWell mobile app during their workday in conjunction with the continuously-worn continuous glucose monitoring (CGM), activPAL, and GENEActiv. When the workday begins, participants will wear the Bluetooth Activator micro and log their work start time in the app, signaling the "start" of the intervention for that day. The Activator micro device will send real time accelerometer data to the WorkWell app via a Bluetooth signal, providing live participant-facing feedback on hourly goal progress as well as day-level summary information. Summary data will also be sent to a secure server, allowing study staff to monitor participant compliance and to facilitate support when needed. Participants will additionally receive a variety of prompts, including hourly reminders to work toward their hourly goal, encouraging messages, or messages that acknowledge that they achieved their hourly goal. Participants will be instructed to log the end of their workday in the app before removing the Bluetooth Activator micro, thus signaling the "end" of that day's intervention.

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Figure 2. WorkWell intervention tools—WorkWell mobile app and Activator micro device.



Measures

All measurements will be completed at the baseline visit and after each intervention period, for a total of 3 laboratory visits. Table 1 shows the measures collected and the associated measurement period. Demographic and health history information will be assessed at baseline. During the baseline period, as well as during each intervention period, participants will complete 3 paper-form daily logs for sleep, work, and food recall. All other study data and questionnaires will be collected and managed using REDCap hosted at Arizona State University [32,33]. REDCap is a secure, web-based software platform designed to support data capture for research studies, providing (1) an intuitive interface for validated data capture, (2) audit trails for tracking data manipulation and export procedures, (3) automated export procedures for seamless data download to common statistical packages, and (4) procedures for data integration and interoperability with external sources.

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Table 1. WorkWell measurement schedule.

Measures	Baseline	Intervention 1	Intervention 2
Screening			
Demographics and health history	✓[a]	—[b]	—
BMI (kg/m^2)	✓[c]	—	—
Primary outcomes			
Postprandial blood glucose (incremental area under the curve)	✓[d]	✓[d]	✓[d]
Secondary outcomes			
Intervention adherence (% goal met)	✓[d]	✓[d]	✓[d]
Posture/activity (minutes/day)	✓[d]	✓[d]	✓[d]
Exploratory outcomes			
Sleep	✓[d]	✓[d]	✓[d]
Intervention feasibility	✓[a]	✓[a]	✓[a]
Anthropometrics			
Body weight (kg)	✓[c]	✓[c]	✓[c]
Body fat percentage (%)	✓[c]	✓[c]	✓[c]
Waist circumference (cm)	✓[c]	✓[c]	✓[c]
Endothelial function (% flow-mediated dilation)	✓[c]	✓[c]	✓[c]
Blood pressure (mm Hg)	✓[c]	✓[c]	✓[c]
Fasted blood measures			
Glucose (mg/dL)	✓[c]	✓[c]	✓[c]
Insulin (µlU/mL)	✓[c]	✓[c]	✓[c]
HDL-cholesterol (mg/dL)	✓[c]	✓[c]	✓[c]
LDL oxidation (U/L)	✓[c]	✓[c]	✓[c]
Triglycerides (mg/dL)	✓[c]	✓[c]	✓[c]
Total antioxidant capacity (µmol/L)	✓[c]	✓[c]	✓[c]
Microbial diversity	✓[c]	✓[c]	✓[c]
Hemoglobin A_{1c} (mg/dL)	✓[c]	N/A[e]	N/A
Metabolomics (stool and plasma)	—	—	—
DNA variants	✓[c]	—	—

[a]Self-administered survey via REDCap (Research Electronic Data Capture).

[b]Not measured.

[c]Measured at each laboratory visit.

[d]Measured continuously (device-based).

[e]N/A: not applicable.

Primary Outcomes

Our primary outcome, the change in 3-hour postlunch postprandial glucose excursion, will be assessed using a CGM device. This small, single-use sensor is placed on the back of the arm and samples glucose levels approximately once every 15 minutes for up to 14 days [34]. This device provides a valid and reliable measure of glucose using flash glucose monitoring [35,36]. Research staff will facilitate the insertion of the CGM for baseline and both intervention periods. If the device falls off or is accidentally removed, staff will replace the device as needed. Participants will be provided a macronutrient-controlled meal (approximately 33% of daily caloric needs, with macronutrient composition of 55% carbohydrate, 30% fat, 15%

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protein [±10%]) delivered daily for lunch during the work week to control for dietary variability. The 3-hour postlunch postprandial incremental area under the curve (iAUC) and mean blood glucose concentration in response to the lunchtime meal will be calculated from these data.

Secondary Outcomes

The secondary outcomes of the interventions will assess intervention adherence and changes in sitting, standing, and LPA during work hours. Intervention adherence is defined as meeting the hourly intervention goal of ≥80% of the workday (eg, meeting the hourly goal for ≥8 hours during a 10-hour workday). The Activator micro device will be taped midthigh during work hours and will communicate with the WorkWell smartphone app via Bluetooth technology. The app's user-friendly interface will provide real time feedback, allowing participants to monitor their progress as 8 bubbles gradually turn green to signify the hourly goals that were met. The WorkWell app will sync to a secure server, providing real time stand-and-move data for study staff to monitor adherence to intervention protocols; data will be stored for broader analysis upon trial conclusion.

The activPAL micro will also assess sitting, standing, and moving behaviors. Work logs will be used to differentiate between work and nonwork hours. Device attachment procedures are based on several large-scale intervention studies [5,6,37]. Devices will be waterproofed using a medical grade adhesive covering and placed on the midline of the thigh with breathable, hypoallergenic tape, to allow for 24 hours per day of continuous wear during measurement periods without removing for bathing or other water-based activities. Data will be processed into bouts of sitting or lying, standing, stepping, or time in bed (ie, primary lying bout) and expressed as minutes per day, assessing posture and intensity using activPAL software version 8.10. Waking time assessed as lying or seated will be categorized as sedentary behavior. Stepping time will be split into periods of LPA (<100 steps per minute) and MVPA (≥100 steps per minute) [38]. Total physical activity will be a cumulative daily value of LPA and MVPA. The following periods of wear will be excluded: (1) continuous sitting or standing behavior >6 hours (considered nonwear), (2) days with ≤10 hours of valid wear time during the wake period, and (3) participants with only 1 valid day of activPAL wear.

Exploratory Outcomes

Additional exploratory outcomes will include sleep, intervention acceptability and satisfaction, body anthropometrics, femoral artery flow-mediated dilation (f-FMD), central aortic blood pressure, fasting glucose, fasting insulin, HDL, LDL, LDL oxidation, triglycerides, TAC, gut microbial diversity, HbA_{1c}, metabolomics of the blood and stool, and genetic variants assessed during 1 or more measurement periods.

Sleep will be assessed using the wrist-worn GENEActiv accelerometer (ActivInsights) (initialized to collect at 40 Hz); participants will wear the device 24 hours per day during the measurement periods while also completing a validated sleep diary each night to identify sleep from wake periods. The GENEActiv device has been validated for sleep [39-42] and will be used in conjunction with a sleep log that differentiates sleep or wake periods in data [43]. An open-source and validated algorithm (GGIR package, R-software) [42] will be used to process device-based sleep measures, including sleep duration, sleep efficiency, sleep onset latency, and wakefulness after sleep onset [44-47]. Sleep will be considered the total sleep time accumulated within the sleep window; wake time, daytime sleep, and the time of sleep onset will not be counted. GGIR signal processing includes autocalibration using local gravity as a reference [45], detection of prolonged abnormal high values, nonwear detection and average magnitude of dynamic acceleration calculation, corrected for average gravity over 5-second epochs and reported in milligravitational units (mg). Data files will be excluded if a postcalibration error of >0.01 g (10 mg), <3 days of valid wear (defined as >16 hours per day [44,48]), or wear data are not present for each 15 minutes period of the 24-hour cycle. Nonwear detection is described elsewhere [44]. The default nonwear setting will be used, which includes invalid data that will be imputed by the average at similar time points on different days during the assessment week. Sleep duration will be calculated using automated sleep detection (HDCZA sleep detection algorithm) [47]. The average of all valid days will be used.

Intervention acceptability and satisfaction will be assessed using the Treatment Evaluation Questionnaire (TEQ) to measure the adherence and feasibility outcomes of the study. Prior to starting each intervention, participants will be provided an introductory tour to explain the intervention and describe how to use the WorkWell app and device. Research staff will actively discuss strategies to assist participants in engaging with the intervention. After this session and prior to the start of the intervention, participants will be sent a pre-study survey with the TEQ; once each intervention is completed, a postsurvey is sent also containing the TEQ.

Body anthropometrics, including height, weight, body fat percentage, and waist circumference, will be measured at each laboratory visit. Height and weight will be measured using the Seca scale and stadiometer (Seca 286 EMR Ready Ultrasonic Measuring Station). Waist circumference (taken at the level of the iliac crest) will be measured twice using a Gulick tape measure. Body fat percentage will be measured twice using the Tanita TBF-400 digital scale device (Tanita), which calculates percent body fat using bioimpedance. If there is a difference of ≥0.2% for body fat, an additional measurement will be taken. Values will be averaged to arrive at a final measure.

f-FMD will be used to measure the endothelium-dependent, flow-mediated dilation of the superficial femoral artery using B-mode ultrasound (Terason uSmart 3300+TM) via guidelines set forth by the Brachial Artery Reactivity Task Force [49]. Participants will be asked to lie quietly for 15 minutes on the ultrasound table before baseline images are obtained from their left upper thigh. Simultaneous ultrasound images (B-mode) and Doppler waveforms will be recorded for 30 seconds. An appropriately sized cuff will be selected based on manufacturer guidelines (Hokanson Instruments) and subsequently wrapped around the participant's upper thigh, 3-4 cm below the bifurcation of the common femoral artery. After baseline images of the superficial femoral artery are acquired, the blood pressure

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cuff on the participant's upper thigh will be inflated using a rapid-cuff inflator (Hokanson instruments) to a suprasystolic pressure of 250 mm Hg for 5 minutes. The recording of the image will begin 30 seconds prior to the cuff release. At 5 minutes following cuff inflation, the cuff will be rapidly deflated and arterial images are recorded for 6 minutes. Images obtained will be analyzed by a trained, blinded researcher using previously validated edge-detection software [50]. In our laboratory, intraclass correlation coefficients for baseline and peak diameter are 0.994 and 0.995, respectively (Cronbach α=.976).

Central aortic blood pressure that includes both central and peripheral blood pressure, and aortic stiffness (via applanation tonometry) will be measured using the SphygmoCor XCEL (CvMS; ATCOR Medical). This device has been found to reflect measures of central pressures and stiffness reliably and accurately [51,52]. All measurements will be taken after the participant rests in a supine position for approximately 15 minutes, prior to f-FMD initiation, to ensure hemodynamic stability. Triplicate measures will be collected, and the 2 closest values averaged and reported.

Fasting blood samples will be collected at each laboratory visit via venipuncture. The 15-mL samples will be immediately processed and aliquoted for storage at –80 °C for subsequent analysis. Fasting blood glucose will be examined in multiple batches, pairing samples from the same participant's previously aliquoted plasma. Plasma glucose concentration will be analyzed using the AU480 Chemistry Analyzer (Beckman Coulter, Inc) in accordance with manufacturer's instructions. Exploratory cardiometabolic disease risk analysis will be performed on plasma and serum glucose, insulin, triglycerides, total cholesterol, HDL cholesterol, LDL cholesterol, LDL oxidation, and TAC. Exploratory, targeted metabolomics analyses will also be performed with plasma samples using mass spectrometry (MS).

Participants will be provided with a stool sample collection kit and instructions at each laboratory visit. All participants will be given the option to schedule sample pick-up at their home or workplace; alternatively, samples can be dropped off at the Translational Research Center. Participants will be instructed to collect this sample within 4 days of each laboratory visit for a total of 3 collections. Once collected, samples will be frozen at –80 °C within 24 hours of the sample leaving the body. Participants will be instructed to contact staff to retrieve the sample when ready. The stool samples will later be thawed at 4 °C and microbial DNA extracted for microbiome sequencing and characterization of intervention-specific bacterial community differences. Microbial DNA sequencing will be carried out in batches of paired samples from the same participant. Bacterial DNA will be extracted from the stool samples using DNeasy PowerSoil Pro DNA Isolation Kit (47014, Qiagen) as per manufacturer recommendations. DNA quality and concentration will be quantified (QIAxpert System Qiagen) before being sent out for sequencing (Illumina MiSeq instrument, Illumina, Inc.) at ASU's DNASU Genomics Core Facility. Raw Illumina microbial data will be cleaned and analyzed using the Quantitative Insights into Microbial Ecology 2 software, as previously described [53]. Exploratory, targeted metabolomics analyses will be performed with the stool samples using MS. Short-chain fatty acids, bile acids, pathway-specific targeted liquid chromatography tandem MS, liquid chromatography–MS, gas chromatography–MS aqueous metabolite profiling, and liquid chromatography–MS global lipidomic profiling will be carried out.

HbA_{1c} will be collected at baseline only using the DCA Vantage analyzer (Siemens Munich) with 1 µL of blood obtained using a finger stick. After collection, the results are obtained within 6 minutes and data will be used for descriptive purposes.

Saliva samples will be collected at baseline using Oragene Discover collection kits (OGR-600 Ottawa), and will be archived for future exploration of genetic variants.

Data Analysis

Statistical Analysis Plan

Participant characteristics will be reported as frequencies or means with SDs. Outcome variables with nonnormal distributions will be log-transformed to assume normal distribution. All data processing and statistical analyses will be performed in SAS (version 9.4; SAS Institute) with an α criterion of .05. To address our specific aims and hypotheses, we will use linear mixed model analyses [54,55] for intervention (ie, MOVE and STAND), sequence (ie, MS and SM), and time period (ie, 1 or 2) as fixed factors and an unstructured covariance structure for the 3 repeated measurements per person. The primary outcome will be postprandial glucose iAUC, and secondary outcome will be change in posture and LPA. All data from randomized participants will be included in the analyses in accordance with intent-to-treat principles.

Sample Size Calculation

To determine the sample size needed, we based our effect size estimates on previous studies [17,56] that have similarly evaluated the impact of interrupting prolonged sitting on glucose iAUC. These studies reported a 20%-30% decrease in iAUC level for the intervention groups. Therefore, for the WorkWell Study, we used a conservative estimate of 15% difference between baseline and the 2 intervention measurements (with a 1% population estimate of SD). Using G*Power software (version 3.1.9.2) [57], we estimated that we will have to recruit 15 individuals (allowing for 80% retention) to obtain a final sample size of 12 participants (α=.05, power=80%).

Ethics Approval

This study has been reviewed and approved by the institutional review board at Arizona State University (STUDY00010172) as well as registered on ClinicalTrials.gov (NCT04269070). Screening consent will be obtained prior to in-person screening visit and subsequent full-informed consent will be obtained from all qualifying participants prior to enrollment. All participant information and data will be deidentified and assigned an identification number in which all subsequent data, samples, and surveys will be labeled to ensure confidentiality. As a part of the study intervention, participants will be provided lunchtime meals during the work week as well as up to US $65 in a web-based gift card of their choice for completion of the study.

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Results

Recruitment is ongoing as of January 2023. To date, 10 participants have been enrolled, with 2 withdrawing from the study for personal reasons. Enrollment was completed in March 2023.

Discussion

Comparison to Prior Work

While low levels of physical activity have been a public health concern, there is evidence that sedentary behavior duration may also confer health risks [13]. Observational studies suggest that breaking up sedentary time is associated with improved cardiometabolic health [58]. These free-living, mainly observational studies have demonstrated the theoretical feasibility of workplace interventions, yet cannot control for potentially confounding factors, obscuring the meaningful analysis of the relationship. Laboratory studies, however, suggest a causal relationship between decreased sedentary time and cardiometabolic health [59]. While these studies are tightly controlled in both the environment and intervention, they lack important context regarding the translation of these findings into real-world settings.

The WorkWell Study is a novel randomized controlled crossover trial that has been designed to extend laboratory-based, controlled study designs into the natural environment of the workplace. To accomplish this, we have used digital health technologies to monitor and prompt participants in real time while maintaining rigorous adherence to increased standing and moving regimes. This innovation will allow us to test the effects of breaking up sitting with standing and LPA over a longer period of intervention than has been used in traditional laboratory-based studies. Additionally, we have included a broad set of concomitant biological measures, including dynamic changes in postprandial and 24-hour glucose, as well as outcomes in the emerging areas of metabolome and gut microbiome composition. We will use two 2-week interventions targeting behavior change to decrease sitting time in the workplace as well as to improve cardiometabolic health and to assess behavior change. This study was carefully designed to extend laboratory-based studies—both in duration, as well as translation into more ecological settings—thus providing more evidence on the causal role of interrupted sitting time (with standing and moving) on cardiometabolic health. As a result, we will be able to address (1) statistical association via baseline and washout weeks that allow participants to serve as their own controls, (2) temporality via continuous accelerometer tracking and prescheduled laboratory visits, and (3) nonspuriousness via randomized assignment and controlled treatment dosage.

Strengths and Limitations

Our project attempts to achieve levels of internal validity previously found only in laboratory-based studies while simultaneously maximizing external validity. While others have demonstrated the benefit of breaking up sedentary behavior in either highly controlled laboratory environments or ecological environments, we will use emerging technologies (ie, wearable sensors and smartphone apps) to deliver a rigorous clinical trial within an employee's real-life workspace. Despite this important strength, some potential challenges warrant discussion. Recruitment and retention of participants in longitudinal research is challenging. We hope to overcome this challenge by allowing participants to engage in the study in their typical work setting, rather than having participants carry out the intervention in a laboratory setting. If successful, this approach will add important information to our current understanding of how best to intervene and engage participants in reducing sedentary time in workplace settings. Participants may also feel uneasy about collecting fecal samples. To ensure this is not a barrier for successful completion of the trial, the study team will provide participants with a discrete collection kit that can be used mostly anywhere that is comfortable for the participant. Delivery of samples to the research facility can then be initiated by the participant or the study staff can retrieve the sample at a place of convenience for the participant. This method has been used by our investigative team in previous studies and has proven beneficial for ensuring receipt of quality samples within the required time frame.

With a wide range of expertise represented on our research team, we are able to consider outcomes in the behavioral, physiological, and microbial realms and are able to examine our outcomes in an integrated and transdisciplinary fashion. While previous research has broadly examined some of these factors, our design and transdisciplinary approach will allow for a more global viewpoint of the influence of breaking up sedentary time during the workday on cardiometabolic health. Currently, the biological and metabolic underpinnings of sedentary behavior-linked disease are grossly understudied. Previous observational work has highlighted potential microbial and metabolic derangements [60-63], but these findings have not been extended to longitudinal interventions, leaving the previous work highly correlational. Our team is well-positioned to advance this area of study toward better mechanistic understandings of sedentary behavior and how intervention in real-world settings can improve health.

Conclusions

The WorkWell Study is a randomized controlled crossover trial examining the feasibility and impact of breaking up sedentary behavior on cardiometabolic health using the scientific rigor of a laboratory-based study with the context and translatability of a free-living setting. We will explore the effects that standing or moving 6 additional minutes per hour has on postprandial glucose and other physiological measures in the real-world workplace and assess intervention feasibility. Using a rigorous transdisciplinary approach, we seek to fill gaps in previous research and contribute to a more comprehensive picture of the beneficial effects of breaking up sitting behavior.

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Data Availability

The data generated are not publicly available due to the fact that this trial is ongoing. Data will be available from the corresponding author upon reasonable request.

Conflicts of Interest

None declared.

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Abbreviations

CGM: continuous glucose monitoring
f-FMD: femoral artery flow-mediated dilation
HbA_{1c}: hemoglobin A_{1c}
HDL: high-density lipoprotein
iAUC: incremental area under the curve
LDL: low-density lipoprotein
LPA: light-intensity physical activity
MS: mass spectrometry
MVPA: moderate to vigorous physical activity
REDCap: Research Electronic Data Capture
TAC: total antioxidant capacity
TEQ: Treatment Evaluation Questionnaire

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Protocol

Evaluating the Effectiveness of a Codeveloped e-Mental Health Intervention for University Students: Protocol for a Randomized Controlled Trial

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Abstract

Background: University life typically occurs during a period of life transition, where the incidence of mental health and substance use problems and disorders peaks. However, relatively few students obtain effective treatment and support. e-Interventions have proven effective in improving the psychological outcomes of university students and have the potential to provide scalable services that can easily integrate into existing models of care. *Minder* is a mobile app codeveloped with university students that offers users a collection of evidence-based interventions tailored to help university students maintain their mental health and well-being and manage their substance use.

Objective: This paper describes the protocol for a randomized controlled trial (RCT) that aims to assess the effectiveness of the *Minder* app in improving the mental health and substance use outcomes of university students.

Methods: This study is a 2-arm, parallel assignment, single-blinded, 30-day RCT with 1 intervention group and 1 waitlist control group. Overall, 1496 (748 per trial arm) university students from the University of British Columbia Vancouver Campus (N=54,000) who are aged ≥17 years, have a smartphone with Wi-Fi or cellular data, and speak English will be recruited via a variety of web-based and offline strategies. Participants will be randomized into the intervention or control group after completing a baseline survey. Those randomized into the intervention group will gain immediate access to the *Minder* app and will be assessed at 2 weeks and 30 days. Those randomized into the control group will be given access to the app content after their follow-up assessment at 30 days. The primary outcomes are measured from baseline to follow-up at 30 days and include changes in general anxiety symptomology, depressive symptomology, and alcohol consumption risk measured by the General Anxiety Disorder 7-Item scale, Patient Health Questionnaire 9-Item scale, and US Alcohol Use Disorders Identification Test-Consumption Scale, respectively. Secondary outcomes include measures related to changes in the frequency of substance use, mental well-being, self-efficacy in managing mental health and substance use, readiness to change, and self-reported use of mental health services and supports (including referral) from baseline to follow-up at 30 days.

Results: Trial recruitment and data collection began in September 2022, and the completion of data collection for the trial is anticipated by June 2023. As of May 10, 2023, a total of 1425 participants have been enrolled.

Conclusions: The RCT described in this protocol paper will assess whether the *Minder* app is effective in improving the mental health and substance use outcomes of a general population of Canadian university students. Additional secondary outcome research

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aims to explore additional outcomes of interest for further research and better understand how to support students' general mental well-being.

Trial Registration: ClinicalTrials.gov NCT05606601; https://clinicaltrials.gov/ct2/show/NCT05606601

International Registered Report Identifier (IRRID): DERR1-10.2196/49364

(JMIR Res Protoc 2023;12:e49364) doi:10.2196/49364

KEYWORDS

mental health; substance use; college students; digital interventions; randomized controlled trial; mobile phone

Introduction

Background

University represents a period of transition where many students move away from home for the first time, requiring them to navigate the newfound independence and overcome unanticipated challenges when trying to make new friends and preserve existing relationships [1-3]. Students may find themselves suddenly dealing with new stressors without their previously relied upon support systems [4]. These stressors related to university life are combined with a period of development where the onset of many mental health and substance use disorders peaks [5,6]. Certain individuals may also be more likely to experience mental health problems in university based on various factors such as age, sexual orientation, ethnicity, and adverse childhood experiences [7]. Overall, this results in a population with a relatively high prevalence of mental health and substance use disorders [8,9]. For example, a study of college students across multiple countries found the 12-month prevalence of major depressive disorder, generalized anxiety disorder, and alcohol use disorder to be 18.5%, 16.7%, and 6.3%, respectively [9]. Despite the high prevalence of emerging mental health and substance use concerns, many university students do not seek help for these issues [10,11].

e-Interventions that promote self-management and link students to in-person services represent a promising means of addressing needs related to substance use and mental health issues. The potential of digital mental health interventions (eg, web-based programs and mobile apps) has been widely promoted, as they are often easily scalable and as beneficial as in-person therapies in promoting university students' mental health [12-14]. Considering the high co-occurrence between mental health and substance use concerns [15], e-interventions are well positioned to offer low-barrier access to content supporting transdiagnostic approaches to interventions that acknowledge not only each individual concern but also their intersectionality. Existing digital interventions also address a range of challenges, including depression and anxiety [16], substance use [17], safety and risk management [18,19], and levels of severity (eg, subclinical mild to moderate symptom management and treatment for clinical conditions), and can be easily integrated into existing systems of care as a form of low-intensity, self-directed support [20].

Objective

To address these needs, a mental health and substance use mobile app called *Minder* was codeveloped with and for Canadian university students. This codevelopment process involved significant input from students through the creation of a Student Advisory Committee (SAC), usability testing via a virtual bootcamp (ie, individual user testing combined with a web-based survey), focus groups, and a pilot feasibility study [14]. By combining the prevention and early intervention components, the *Minder* app has been designed to target the general population of university students. This paper describes the protocol for a pragmatic 2-arm randomized controlled trial (RCT) to assess the effectiveness of the *Minder* mobile app in improving university students' mental health and substance use outcomes.

Methods

Study Objectives and Hypotheses

Our primary objective is to test whether the *Minder* intervention improves mental health and substance use outcomes in a general population of university students. Our null hypothesis is that there is no difference between the intervention group, who are given access to a full version of the *Minder* mobile app, and the control group, who are given access to a restricted version of the app that sends reminder notifications about baseline and follow-up surveys but prevents access to all intervention components. We hypothesize that assignment to the intervention group will result in greater effects on the primary mental health and substance use outcomes. As such, we expect that participants assigned to the intervention group will be more likely to experience improvements in their mental health and substance use outcomes than those in the control condition.

Study Design and Setting

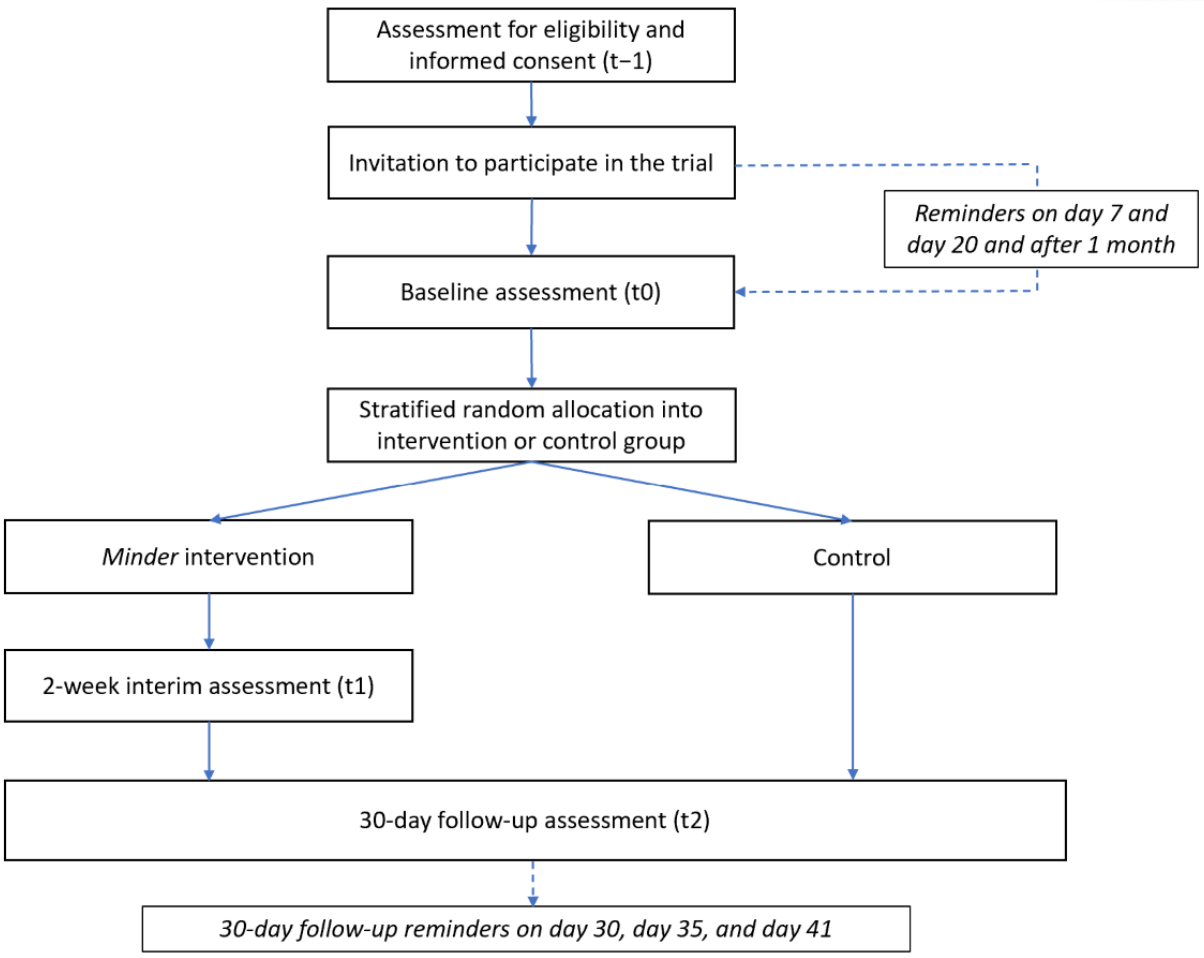
The study is a single-blinded, 2-arm parallel assignment RCT with 1 intervention group and 1 control group (Figure 1). In the pretrial period (t−1), all students are screened for eligibility and invited to enroll in the study; enrolled participants then complete the baseline assessment survey (t0). After randomization, all participants enter into the trial (with full access or restricted access to the *Minder* app, depending on group assignment), concluding with a follow-up assessment survey at 30 days (t2; see Table 1 for participant flow through the study). In addition to the baseline and follow-up surveys, the intervention group will also complete an assessment at 2 weeks. The baseline and follow-up assessments contain all primary and secondary outcomes, whereas the 2-week survey contains only 2 primary outcome measures (Patient Health Questionnaire 9-Item [PHQ-9] and General Anxiety Disorder 7-Item [GAD-7]). All assessments are delivered through the app and typically require approximately 15 minutes to complete but may be completed at the participant's own pace. The 30-day follow-up assessment

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may be completed for up to 14 days after the 30-day study period end point.

Upon the completion of the randomized controlled trial, participants in the control group will be offered access to the intervention for ethical reasons and will be followed (with those already in the intervention group) for up to 6 additional months as part of a separate period of natural observation not included in the formal RCT analyses. This trial was registered with ClinicalTrials.gov (NCT05606601) on November 4, 2022. The study will be conducted at the University of British Columbia (UBC), Vancouver Campus. All data will be collected in Canada.

Figure 1. Outline of the trial process, including eligibility assessment, consent, baseline, randomization, and follow-up.



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Table 1. Participant flow through the trial.

	Enrollment (t−1)	Study period		
		Baseline assessment and allocation (t0)	Interim assessment (t1; 2 weeks)	Follow-up assessment (t2; 30 days)
Enrollment				
Eligibility screen	✓			
Informed consent	✓			
Group allocation and assessment				
Minder intervention		✓	✓	✓
Control		✓		✓
Assessment measures				
Anxiety symptoms (GAD-7[a])		✓	✓	✓
Depressive symptoms (PHQ-9[b])		✓	✓	✓
Alcohol consumption risk (USAUDIT-C[c])		✓		✓
Opioid use frequency		✓[d]		✓
Stimulant use frequency		✓[d]		✓
Cannabis use frequency		✓		✓
Alcohol binge frequency (question 3, US-AUDIT-C)		✓		✓
Alcohol use frequency (questions 1 and 2, USAUDIT-C)		✓		✓
Mental well-being (SWEMWS[e])		✓		✓
Readiness to change		✓		✓
Self-efficacy: mental health		✓		✓
Self-efficacy: substance use		✓		✓
Connection to services and supports		✓		✓

[a]GAD-7: General Anxiety Disorder 7-Item.

[b]PHQ-9: Patient Health Questionnaire 9-Item.

[c]USAUDIT-C: US Alcohol Use Disorders Identification Test-Consumption Scale.

[d]Baseline measure used for study group allocation.

[e]SWEMWS: Short Warwick-Edinburgh Mental Wellbeing Scale.

Eligibility Criteria and Assessment

Participant eligibility will be determined through an eligibility screener delivered on Qualtrics, a web-based survey platform, before registering for the study.

Participants must meet all the following inclusion criteria: student currently enrolled at the UBC Vancouver campus, aged ≥17 years, have access to and be able to use a smartphone with Wi-Fi or cellular data, and speak English. Students will be excluded based on an eligibility screening item assessing suicidality risk (“We want to make sure that this app is appropriate for you at this time. Do you have a current suicidal plan [i.e., a plan to end your life]?”). Anyone endorsing a current suicidal plan (ie, answering “yes”) will not proceed with the registration form and will instead be provided with a list of crisis resources.

Intervention

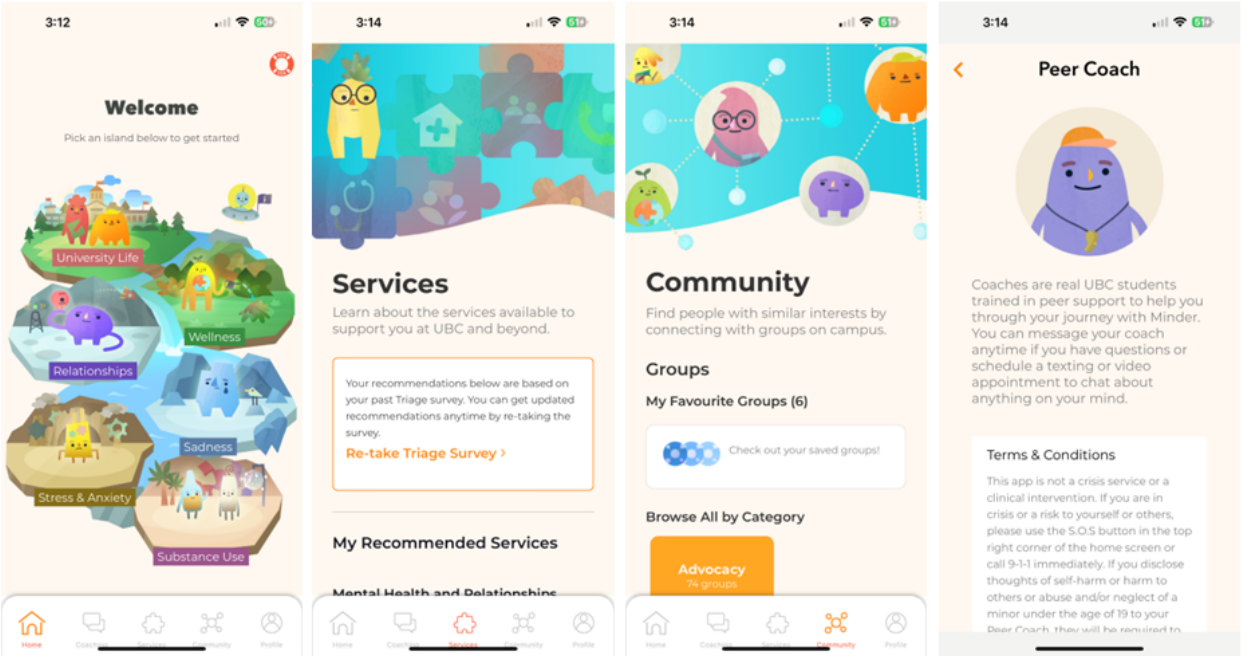
Minder was codeveloped with input from 225 university students, including 44 student project team members. Codevelopment occurred through engaging students and volunteers on the project team, a SAC, and quantitative and qualitative studies (web-based survey, pilot feasibility RCT, and focus groups). Feedback was used to guide the app revisions following each of these processes, resulting in a final app that differed considerably from the initial prototype. Details of each component of these adaptation processes can be found in the study by Vereschagin et al [14].

Minder delivers a suite of evidence-based interventions that have been tailored to help university students improve their well-being and manage their substance use through 4 main components: Chatbot Activities, Services, Community, and Peer Coaching (Figure 2). The Chatbot Activities consist of an automated preprogrammed chatbot text and videos that draw

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primarily from cognitive behavioral therapy (CBT), given its demonstrated transdiagnostic efficacy in web-based intervention programs [21-24]. The Chatbot Activities also incorporate evidence-based content derived from metacognitive therapy, dialectical behavioral therapy, and motivational interviewing. These activities have been developed through collaboration with mental health professionals and university students so that the information can be presented in a way that is consistent with evidence-based practices and appropriate for this demographic. The Chatbot Activities were designed to support students on a range of topics and include content to manage mild to moderate distress and emotions and to help navigate general student life (eg, relationships, time management, and sleep hygiene). In addition, the content of the Chatbot Activities relates to the use of alcohol, cannabis, opioids, and stimulants, including general psychoeducation and motivational interviewing. These topics encapsulate many general skills included in CBT for managing emotions (eg, recognizing automatic thoughts) as well as additional topics highlighted by students through our codevelopment process as being more relevant to student well-being, such as transitioning to university. To increase the accessibility of the app, all activities that include video content have been closed-captioned in both English and French. Users have access to this entire range of content in the app and can choose to engage with any activities, regardless of their current mental health or substance use status. The Services component of *Minder* includes a validated psychosocial screening tool that provides users with tailored recommendations and resources based on their current needs and preferences [25]. It consists of a short survey with several categories (mental health, safety, substance use, abuse, housing, education, and sexual wellness) and an individually tailored list of relevant services that can be filtered by factors such as cost, availability, and delivery method. The Community component of *Minder* contains a searchable inventory of student groups or clubs at the university, which can be filtered according to the student's interest. Finally, to support the use of the app, Peer Coaches (university student volunteers that have been trained by the research team's clinicians) are available to help users navigate through different app components and provide nonclinical peer support. Once a Peer Coach is assigned, users can communicate with their coach through secure in-app texting or video calls in a synchronous or asynchronous manner. In this study, users in the intervention group will be offered Peer Coaches who will reach out to their assigned users twice during the study period (ie, at the beginning of the trial upon assignment and around the midpoint of the trial). Additional information on the development of *Minder* and its components can be found in the study by Vereschagin et al [14].

Figure 2. Minder main app components. The Minder app home page has 6 islands (University life, Relationships, Stress and Anxiety, Wellness, Sadness, and Substance Use) that deliver a variety of activities through an interactive chatbot. The Services component includes a short survey that assesses needs and preferences and matches users with resources. The Community component provides users with a directory of student groups and clubs they can filter through by interest. The Peer Coaching component matches users with a trained peer that provides psychosocial and app support.



Outcomes

Primary Outcomes

The primary outcomes are changes in general anxiety symptomology, depressive symptomology, and alcohol consumption risk from baseline to follow-up at 30 days.

Anxiety Symptoms

The GAD-7 scale is a commonly used self-report scale to assess symptoms of generalized anxiety. Questions on the scale draw from the Diagnostic and Statistical Manual of Mental Disorders, 4th edition [26], criteria for anxiety disorders and were formally validated against diagnostic psychiatric interviews [27]. Each question is scored from 0 (not at all) to 3 (nearly every day),

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with total scores ranging from 0 to 21 and higher scores indicating a worse outcome (ie, greater frequency of anxiety symptoms). In this study, changes in anxiety symptomology from baseline to follow-up at 30 days will be based on the GAD-7 total scores in both the intervention and control groups.

Depression Symptoms

The PHQ-9 scale is a self-report scale used to assess symptoms of depression and has been validated against diagnostic interviews administered by mental health professionals [28]. The 9 questions are based on the Diagnostic and Statistical Manual of Mental Disorders, 4th edition [26], diagnostic criteria for depressive disorders and scored on a scale of 0 (not at all) to 3 (nearly every day). The total scores range from 0 to 29, with higher scores indicating a worse outcome (ie, greater frequency of depression symptoms). In this study, changes in depressive symptomology from baseline to follow-up at 30 days will be based on the PHQ-9 total scores in both the intervention and control groups.

Alcohol Consumption Risk

The US Alcohol Use Disorders Identification Test-Consumption Scale (USAUDIT-C) is a 3-item self-report scale adapted from the consumption questions in the widely used Alcohol Use Disorders Identification Test (AUDIT). Compared with the AUDIT, the USAUDIT-C includes expanded response options for the first 3 AUDIT questions—from 5 to 7 categories—to allow for more precise measurements in accounting for differences in standard drink sizes and cut-off limits [29]. Although the USAUDIT-C was primarily adapted for US contexts, we believe the expanded response options will also allow for a more precise assessment of adherence to guidelines in drinking frequency (question 1), drinking quantity (question 2), and binge drinking (question 3) within Canadian contexts. For questions 1 and 3, scoring ranges from 0 to 6, where 0 represents “Never” and 6 represents “Daily” frequency. For question 2, scoring ranges from 0 to 6, where 0 represents “1 drink” and 6 represents “10 or more drinks” on a typical day when drinking. The total scores summed from all 3 questions range from 0 to 18, with higher scores indicating a worse outcome (ie, higher-risk level of excessive or harmful alcohol consumption). In this study, changes in alcohol consumption risk from baseline to follow-up at 30 days will be based on the USAUDIT-C total scores in both the intervention and control groups.

Secondary Outcomes

Overview

To provide further information on the underlying mechanisms and areas in which *Minder* is affecting participants’ overall well-being, a variety of secondary outcomes will be examined. Secondary outcomes include measures related to changes from baseline to follow-up at 30 days in the frequency of substance use (cannabis consumption, binge drinking, alcohol use, opioid use, and nonmedical stimulant use), mental well-being, self-efficacy managing mental health and substance use, readiness to change, and self-reported use (including referral) of mental health services and supports. An example of the questions used to assess secondary outcomes is provided in Multimedia Appendix 1.

Substance Use: Opioid Use Frequency

Changes will be based on the self-reported frequency of *both medical and nonmedical* opioid use in both the intervention and control groups.

Substance Use: Stimulant Use Frequency

Changes from baseline to follow-up at 30 days will be based on the self-reported frequency of nonmedical stimulant use in both the intervention and control groups.

Substance Use: Cannabis Use Frequency

Changes from baseline to follow-up at 30 days will be based on the self-reported frequency of cannabis consumption in both the intervention and control groups.

Substance Use: Alcohol Binge Frequency

Changes from baseline to follow-up at 30 days will be based on the responses to question 3 of the USAUDIT-C in both the intervention and control groups.

Substance Use: Alcohol Use Frequency

Changes from baseline to follow-up at 30 days will be based on the responses to questions 1 and 2 of the USAUDIT-C in both the intervention and control groups.

Mental Well-Being

Changes from baseline to follow-up at 30 days will be based on the total scores from the Short Warwick-Edinburgh Mental Wellbeing Scale in both the intervention and control groups. The Short Warwick-Edinburgh Mental Wellbeing Scale is a 7-item scale that has been widely validated, has strict unidimensionality, and is free from item bias [30]. The total scores range from 7 to 35, with higher scores indicating better outcome (ie, higher positive mental well-being).

Readiness to Change

Changes from baseline to follow-up at 30 days for the use of individual substances (alcohol, cannabis, opioids, and stimulants) will be based on self-reported readiness to change ladder assessments in both the intervention and control groups. The ladder assessments consist of a single item for each substance that asks participants to rate their readiness to change their use on a Likert-type response scale ranging from 0 (no thought of changing) to 10 (taking action to change). The response range parallels stages in the behavior change process from precontemplative to action stages, with higher scores indicating higher readiness to change and, therefore, a higher likelihood of changing their current substance use behavior. These questions were adapted from a readiness to change measure used by Merrill et al [31] to assess anticipated changes in alcohol use (adapted from The Contemplation Ladder, originally validated by Biener and Abrams [32]).

Self-Efficacy

Changes in mental health self-efficacy from baseline to 30-day follow-up are based on 5 survey questions in the intervention and control groups. Each question is scored separately using a Likert-type response ranging from 1 (not at all confident or

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likely) to 5 (totally confident or likely), with higher scores indicating a better outcome (ie, greater self-efficacy). Similarly, in both the intervention and control groups, changes in substance use self-efficacy from baseline to follow-up at 30 days will be based on 4 self-report survey questions assessing different aspects of self-efficacy related to substance use management. Each question is scored separately using a response ranging from 1 (not at all confident) to 5 (totally confident), with higher scores indicating a better outcome (ie, greater self-efficacy). Both the mental health and substance use self-efficacy survey questions were developed by the research team based on the theory of self-efficacy by Bandura [33].

Connection to Services and Supports

Changes in the use of mental health services and supports in both groups will be assessed by comparing responses to 2 yes-or-no survey questions from baseline to 30-day follow-up. The questions ask if participants have been diagnosed or treated by a professional for a list of mental health conditions and whether they have used any mental health treatments (medication, psychotherapy, mindfulness, and web-based tools) in the past 30 days or currently. Two additional survey questions are only asked at the 30-day follow-up: accessing types of support services and joining any university clubs or participating in any club-related events.

Supplementary Feedback on User Experience

In addition to questions on the primary and secondary outcomes associated with the randomized controlled trial, participants in the intervention group will be asked a set of 12 additional questions on their experience using the *Minder* app at the end of the 30-day follow-up assessment. These questions will be used to inform the ongoing development of the app and use a combination of Likert-type and open text box responses to collect information on experiences using specific app components, reasons for using (or not using) features such as the Peer Coach, and any suggestions for improving key features such as the *Minder* chatbot.

Sample Size and Power

The sample size calculation for a small effect assessed by the PHQ-9, GAD-7, and USAUDIT-C was calculated using an effect size defined by Cohen $d=\Delta/\sigma$, where Δ is the group mean difference at the completion of the study and σ is the (pooled) within-group SD. For a small effect size (Cohen $d=0.2$), the sample size required to have 80% power at the level of significance $P=.02$ (0.05/3 primary outcomes) is 524 in each group. Assuming a 30% attrition rate, we require 748 participants in each group. To account for a conservative estimate of a small effect size and a 30% attrition rate, we estimate that a minimum of 748 randomized participants will be needed for each study group, totaling at least 1496 participants.

Sample Recruitment

Sample recruitment will use a widespread, multifaceted approach that includes web-based and offline interactions with students as well as university faculty and administrators.

Web-based recruitment will occur through social media engagement via Facebook, Instagram, Twitter, and Reddit research laboratory or project pages or through recruitment material reposted by organizations represented on the SAC or UBC-affiliated groups (eg, student clubs and student government representatives). Web-based recruitment will also occur through the linked Student e-Mental Health survey, a version of the World Mental Health International College Student survey adapted for Canadian contexts and administered at UBC (approved by the UBC Behavioral Research Ethics Board under ethics ID #H19-02538 [34]). At the end of the linked survey, prospective participants will receive a message offering an opportunity to test a mental health and substance use app, and interested students will be redirected to a registration form for this study where they can consent and register to participate if qualified.

Offline recruitment will include in-person booths of student team members in frequented communal areas with high student traffic (eg, student union and main campus lawn or pathway) around the UBC Vancouver campus; placing recruitment posters in public places on campus; and distributing mini posters with QR codes to classes, students, and student groups on campus.

Student engagement will also occur through collaboration with select UBC faculty members and administrators. Specifically, members of the research team will attend in-person and web-based courses at the university to provide students with a short presentation about the study and will request that recruitment materials be included on course web pages and emails. In addition, student groups at the university will be contacted to share recruitment information with their members through emails and newsletters or to coordinate with study team members attending group meetings or events to directly share information about the study. Invitations to participate in this study will also be sent to students who have previously expressed interest in participating in research studies and asked to be contacted if study opportunities with the research laboratory became available.

Widespread signage will also be implemented through posters at on-campus bus stops and digital screens in on-campus buildings, as well as printed posters within buses designated for routes with direct connections to the university.

Randomization and Study Arms

A study participant is defined as an individual who has completed the baseline survey and has been randomly assigned into either the control or intervention group. Participants are randomized using a stratified block randomization function built into the app. The randomization list for the built-in function was created using the web-based stratified block randomization list creator in the clinical trial software Sealed Envelope (Clerkenwell Workshop) [35]. To ensure that each arm of the randomized trial contains an equal number of participants endorsing a history of substance use, participants will be assigned to either group A (substance use: any medical opioid use, nonmedical opioid use, or nonmedical stimulant use) or group B (nonsubstance use), based on their answers to the opioid and stimulant use questions in the baseline survey. After being stratified into group A or group B, individuals are then

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automatically randomly assigned (via the randomization list embedded into the app) to either the control or intervention arm of the trial using a 1:1 ratio in blocks of 10.

Those randomized into the control group will receive a message saying that they will be asked to complete an additional survey at 30 days and will only receive full access to the app after that. During the 30-day study period, the control group participants will receive a restricted version of the app that only permits access to the following: an introduction video with several students providing a broad overview of the different aspects of the app and its potential value, several onboarding slides with a short summary of the main app components, and baseline and follow-up assessment surveys plus reminder notifications to complete those surveys. Participants randomized into the intervention group will receive immediate access to the full *Minder* app.

Strategies to Improve Adherence to Intervention Protocols

All participants will receive both email reminders and in-app push notifications to complete the assessment surveys. More specifically, after the initial email to prospective participants with instructions to download the app and complete the baseline survey (to be randomized), an email reminder to complete the baseline survey will be sent on day 7 and again on day 20 to those who have not yet completed it. Participants who have not completed the baseline after 1 month may receive an additional email reminder. Participants assigned to the intervention group will then receive an email and push notification to complete the 2-week survey. Participants in both the intervention and control groups will receive an email and push notification 30 days after baseline completion and a group assignment to notify them to complete the follow-up survey, along with a reminder email 5 days and 11 days later if the survey has still not been completed.

Participants in the intervention group will also receive general in-app push notifications on days 4, 18, and 24 to highlight the different features of the app. The intervention group also receives a push notification when they have a new in-app message from their assigned Peer Coach, either a scheduled message (at assignment and around the study midpoint) or a reply to an ongoing text conversation with the participant.

Data Management and Withdrawal

All data are collected in the app and stored on secure servers located in Canada. The research team will download all study data regularly (business days excluding statutory holidays) and monitor for any issues with data collection. Access to the data will be limited to the members of the research team. To ensure that participant information and privacy are protected, the *Minder* app backend will abide by the UBC Research Ethics Board guidelines and British Columbia's Freedom of Information and Protection of Privacy Act. Participant data are collected using a unique study ID value within the system to ensure that survey response data and app use data remain separate from identifying information contained in the participant registration and remuneration documentation. The only exception will be if a participant elects to withdraw from the study and indicates their decision to have their data deleted; in this case, the data manager will use the unique study ID value to link their registration information with their survey response data and app use data and delete all their data from the system and all saved files.

Data Analysis Plan

Statistical Analysis

The primary analysis will be intention to treat (ITT) to estimate the causal effects of the assignment to treatment on the trial outcomes for all participants. A participant within the study is defined as an individual who has completed the baseline assessment survey and has been randomized into either the control or intervention group. The analysis will consider the following 2 features of the trial design: 3 primary end points and the method of randomization. The effects of some of these design features (ie, randomized blocks) are expected to be small and statistically nonsignificant. Nonetheless, we will use multilevel regression and SAS (version 9.4; SAS Institute Inc) and R (version 4.3.1; R Foundation for Statistical Computing) software in our analyses to control for these effects.

Before any testing, we will compare the baseline differences between the randomization groups on demographic (eg, sex, gender, and ethnicity), socioeconomic (eg, year of study), and personal risk variables (eg, mental health diagnoses and use of mental health treatments). Any baseline prognostic variable with a standardized difference between the groups of Cohen $d>.05$ will be considered a candidate variable to control for in the analysis. The selection of Cohen $d>.05$ is arbitrary: there is no accepted threshold to determine a meaningful difference between the 2 groups. However, this is a very small effect and indicates approximately a 4% nonoverlap between the 2 populations.

For the 3 primary end points (PHQ-9, GAD-7, and USAUDIT-C), a global test with the null hypothesis of no treatment difference in all primary end points between the control and treatment groups will be conducted using a marginal multivariate regression model for correlated data on PHQ-9, GAD-7, and USAUDIT-C. Compared with testing each outcome separately, the advantages of the global test from joint modeling include more parsimonious hypothesis tests and mitigated concern of multiple testing issues [36-38] as well as pooling of the information over the correlated outcomes to increase study power, especially with missing outcomes [39]. When the global test rejects the null hypothesis and we conclude that there is an intervention effect on at least 1 of the 3 end points, we will then analyze each end point separately to identify which of the 3 study end points are affected by the intervention. We will use the sequential Hochberg correction method [40] to control the overall family-wise error rate at $\alpha=.05$ when testing the hypothesis for each individual primary end point.

The general approach for analyzing all the types of study outcomes separately (including the 3 primary end points and the secondary end points) will be the generalized linear mixed-effect models (GLMMs) for clustered measures, with the randomization block as the clustering variable. These models can handle a wide range of outcome types, including continuous, binary, ordinal, and count, and can account for the correlations

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among observations within the same cluster. Specifically, we will analyze each primary end point using a linear mixed-effect model, a special case of the GLMM. For secondary outcomes, we will use linear mixed-effect models to analyze mental well-being measures and readiness to change measures, mixed logit models to analyze the connection to services and support-related measures (binary: yes or no), mixed-effects quasi-Poisson regression models with the log link (a special case of GLMMs) for substance use frequency measures, and mixed-effects proportional odds ordinal logistic regression (another special case of GLMMs) for self-efficacy measures. The treatment effect on an outcome at 30 days will be assessed using a GLMM with the treatment allocation as the main explanatory variable and with adjustment for baseline outcome assessment value and other baseline prognostic factors as fixed effects and the randomization block as a random effect. By properly specifying the GLMM, a wide range of scientific hypotheses can be tested, including the primary ones regarding treatment effect estimation. The quality of statistical inferences will be substantiated through rigorous model checking and validation techniques. When statistical models assume that residuals at certain levels follow normal distributions, this assumption will be checked using a normal probability plot, in which the ranked residuals are plotted against corresponding points on a normal distribution curve. When substantial departures from the normal residual assumption are found, robust empirical SE estimates that are valid with nonnormal residuals will be used for statistical inference. We will use SAS software (version 9.4; SAS Institute Inc) and R (version 4.3.1; R Foundation for Statistical Computing) for the statistical analyses of our primary and secondary outcomes. Subgroup analysis will be performed using the GLMM on the subsets of data formed by the subgroup.

Missing data will take two forms: (1) missed questions or items and (2) unit nonresponse or attrition (withdrawals and lost to follow-up). We anticipate that most missing data are owing to attrition, which leads to unit nonresponse at the 30-day assessment. To reduce bias and avoid the loss of statistical power in our analysis of primary and secondary outcomes, we will use likelihood-based direct estimation, which is equivalent to performing multiple imputations under the model to predict values for missing data. One advantage of using the abovementioned multilevel GLMMs for analyzing primary and secondary outcomes is that it uses all the available data by including those study units with missing outcome values and it produces valid inference under the assumption of missing at random, which is a more relaxed assumption of missing data mechanism than missing completely at random. The missing values will be regarded as missing at random when the nonresponse behavior is believed to be a function of observed data, particularly common when assessing mental health and substance use behaviors and using a digital self-report format. The potential bias of these inferences will be quantified if these missing data were suspected to be nonrandom even after conditioning on the observed data, using the methods [41,42] developed by our team member and implemented in R package *isni* [43]. In summary, state-of-the-art statistical methods will be used to address these missing data issues.

In addition to the primary analysis using ITT, we will conduct a secondary analysis to evaluate the Complier Average Causal Effect (CACE) of the intervention. The primary analysis using ITT estimates the causal effects of treatment assignment on the trial outcomes for all participants, regardless of whether those assigned to the intervention actually use the *Minder* app (ie, complying with the treatment assignment). The results from the ITT analysis will be useful to policy makers and inform the effects of applying the treatment program to the population. Although ITT analysis is informative and valid, one limitation of the ITT analysis is that it estimates the program effectiveness rather than method efficacy. The program effectiveness depends on the proportion of compliers, which can change (eg, students change their willingness to use the intervention after they learn that the intervention works). Thus, to complement this approach, we will also conduct a CACE analysis that will focus on the intervention efficacy of those who actually use the e-intervention. The CACE analysis in conjunction with the abovementioned ITT analysis will provide a more complete picture of the intervention effect. By identifying who uses and benefits from the intervention, the trial can yield findings of direct interest to the scientific community and individual students. To overcome the challenge that the study participants' compliance and app use behaviors are self-selected in nature and not randomized, we will use the principal stratification approach to estimate the CACE effects on multiple end points in RCTs with treatment noncompliance [36] and the dose-response relationship between the extent of app use (eg, completed Chatbot Activities and number of contacts with Peer Coach) and intervention effect [44]. Given the diverse nature of the target population combined with the self-guided use of intervention components, we also plan to examine heterogeneity in treatment effects using a series of exploratory analyses that use sociodemographic (eg, gender and year of study) and assessment data (eg, symptom level on PHQ-9 and GAD-7) collected at baseline to examine the impact of the *Minder* app on key subgroups.

Masking

The study will use a single-blinded approach where only the investigators (including the statistician) will be blinded to the treatment group assignment when examining the primary hypotheses.

Continued Monitoring

There will be no stopping rules in this study—the anticipated benefits and unanticipated adverse effects are not life threatening and too small to merit such an approach. In addition, there will be no sequential analyses of the data: the analyses will commence at the end of the trial when the data manager provides the statistician with a blinded database for the analyses. Of note, data from the 2-week assessment completed by the intervention group will be removed from the data set used for the primary outcome analysis to maintain the blinding of the statistician.

Ethics Approval

This study was approved by the UBC Behavioral Research Ethics Board on January 6, 2022 (ethics ID: H21-03248). Any

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changes to the protocol will be submitted for approval to the UBC Research Ethics Board.

Consent

Consent will be obtained using a web-based UBC Qualtrics form before the email validation process (ensuring current student enrollment and only 1 study registration per student), which provides access to the app and baseline assessment survey.

Results

The trial was registered on ClinicalTrials.gov (NCT05606601) on November 4, 2022. Recruitment and data collection began in September 2022. As of May 10, 2022, a total of 1425 participants have been enrolled. The results of the study will be available at the end of 2023 and will be published in international and national journals and presented at conferences.

Discussion

Expected Findings

Postsecondary students have been found to have high rates of mental health and substance use problems but many of these students do not access mental health or other professional supports [10]. e-Interventions have been shown to be effective among university students and may help address barriers to seeking support by providing tools that are easily accessible and can be scaled up for university campuses [16]. This manuscript describes the study protocol for a RCT to assess whether the *Minder* app is effective in improving mental health and substance use outcomes in a general population of Canadian university students. We hypothesize that individuals assigned to the intervention group will be more likely to experience improvements in mental health and substance use outcomes compared with individuals in the control condition. Additional secondary outcomes and analyses seek to inform potential mechanisms through which future studies can be conducted to better understand how to support the mental well-being of students and support the ongoing improvement of the *Minder* app as an effective digital mental health tool.

Limitations

Although many similar e-interventions have experienced large loss to follow-up and poor participant engagement, the incorporation of Peer Coaches for each participant in addition to well-spaced reminders to return to the app and complete baseline and follow-up surveys are expected to improve app engagement and reduce loss to follow-up. It is also important to note that this intervention was designed for use in the general population with mild symptomology so recruitment may be challenging as these students may be less interested than a clinical population in participating in a mental health study. We have addressed this challenge by using a comprehensive set of recruitment methods to engage potential participants in the broader university population. The intervention also includes components relevant to all students, including content addressing general well-being and more clinically relevant content. Students who choose to participate in this study may also be more motivated than the general population to seek help or to improve their mental health or substance use concerns. This may impact their willingness to participate and responses to self-report surveys, which may lead to reporting bias; however, we believe that these biases will not differ across the surveys or between intervention and control groups. Moreover, mental health and substance use concerns are high among university populations, with a large fraction experiencing psychological distress; therefore, a study sample reporting a range—including elevated levels—of mental health or substance use concerns is representative of students' functioning, which supports the generalizability of the results to the broader student population. In addition, participants in the intervention group will be unblinded, which could lead to biased self-reports of mental health symptomology related to placebo effects and social desirability. Although our use of standardized assessments completed via nonidentifiable web-based surveys should help mitigate some of these risks, it will be important to address this limitation in future studies on the *Minder* app by incorporating a sham or placebo control in future trials and examining the cognitive mechanisms associated with targeted outcomes.

Conclusions

Despite these limitations, the findings from this trial will inform the ongoing refinement of the *Minder* app. One key aspect of the *Minder* app that separates it from other similar tools is its extensive codevelopment process with students, especially in the development of content that is presented in a chatbot manner that is more interactive than other modular, web-based CBT interventions. It is designed to support a general population of students across many potential topics, whereas many existing tools target specific issues (eg, depression or anxiety). Thus, by designing a tool that can be used by all students, we hope to provide a suite of interventions (eg, from time management to managing emotions) that builds resilience across a range of conditions and improves the well-being of students as they face the many challenges associated with postsecondary education and young adulthood. This includes the tailoring and ongoing improvement of content using focus groups and continued engagement with specific groups of university students who may have more unique university experiences, including international students; lesbian, gay, bisexual, transgender, queer, 2-spirit, intersex, asexual, and similar minority (LGBTQ2IA+) students; and Indigenous and other racialized students. Through further analyses of app use data and subgroup analyses, we hope to identify areas of particular interest and need to help us better understand how to improve and scale up the delivery of the app to other student populations.

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Acknowledgments

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Data Availability

The data sets generated during this study are not publicly available in accordance with our ethics approval. Interested researchers are advised to contact the corresponding author for further information on gaining access to anonymous data as further approval by the relevant research ethics boards may be needed.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Secondary outcome questions.
[DOCX File , 51 KB - resprot_v12i1e49364_app1.docx]

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Abbreviations

AUDIT: Alcohol Use Disorders Identification Test
CACE: Complier Average Causal Effect
CBT: cognitive behavioral therapy
GAD-7: General Anxiety Disorder 7-Item
GLMM: generalized linear mixed-effect model
ITT: intention to treat
LGBTQ2IA+: lesbian, gay, bisexual, transgender, queer, 2-spirit, intersex, asexual, and similar minority
PHQ-9: Patient Health Questionnaire 9-Item
RCT: randomized controlled trial
SAC: Student Advisory Committee
UBC: University of British Columbia
USAUDIT-C: US Alcohol Use Disorders Identification Test-Consumption Scale

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Protocol

Just-In-Time Adaptive Intervention to Sit Less and Move More in People With Type 2 Diabetes: Protocol for a Microrandomized Trial

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Abstract

Background: Reducing sedentary behavior and increasing physical activity in people with type 2 diabetes (T2D) are associated with various positive health benefits. Just-in-time adaptive interventions offer the potential to target both of these behaviors through more contextually aware, tailored, and personalized support. We have developed a just-in-time adaptive intervention to promote sitting less and moving more in people with T2D.

Objective: This paper presents the study protocol for a microrandomized trial to investigate whether motivational messages are effective in reducing time spent sitting in people with T2D and to determine what behavior change techniques are effective and in which context (eg, location, etc).

Methods: We will use a 6-week microrandomized trial design. A total of 22 adults with T2D will be recruited. The intervention aims to reduce sitting time and increase time spent standing and walking and comprises a mobile app (iMove), a bespoke activity sensor called Sedentary Behavior Detector (SORD), a messaging system, and a secured database. Depending on the randomization sequence, participants will potentially receive motivational messages 5 times a day.

Results: Recruitment was initiated in October 2022. As of now, 6 participants (2 female and 4 male) have consented and enrolled in the study. Their baseline measurements have been completed, and they have started using iMove. The mean age of 6 participants is 56.8 years, and they were diagnosed with T2D for 9.4 years on average.

Conclusions: This study will inform the optimization of digital behavior change interventions to support people with T2D Sit Less and Move More to increase daily physical activity. This study will generate new evidence about the immediate effectiveness of sedentary behavior interventions, their active ingredients, and associated factors.

Trial Registration: Australian New Zealand Clinical Trial Registry ACTRN12622000426785; https://anzctr.org.au/Trial/Registration/TrialReview.aspx?id=383664

International Registered Report Identifier (IRRID): DERR1-10.2196/41502

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KEYWORDS

diabetes; just-in-time adaptive intervention; JITAI; micro-randomized trial; MRT; physical activity; sedentary behavior

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Introduction

Overview

People with type 2 diabetes (T2D) have higher levels of sedentary behavior (SB) and lower levels of moderate to vigorous intensity physical activity (PA) compared with those without T2D [1]. Device-based measurement of SB has shown that people with T2D spend >64% of their daily waking time sedentary [1], which has subsequently sparked calls for targeted behavior change programs to reduce SB in this population, in addition to the promotion of regular PA [2].

SB has become a distinct target for individuals who are susceptible to or have been diagnosed with T2D [3]. It is suggested that people with T2D break up their sitting time by light PA, which can serve as a means for gradually adopting a more active lifestyle [4]. Reducing sitting time by either standing or light ambulation has been shown to improve glucose homeostasis among people at risk of or diagnosed with T2D [3].

Ubiquitous mobile health (mHealth) technologies such as smartphones and wearable sensors offer considerable potential to improve access to and delivery of behavior change support for reducing SB and promoting PA [5,6]. Progress in mHealth technology has enabled the design of just-in-time adaptive interventions (JITAIs), which aim to deliver behavior change support in real or near time, matched to when users need or want the support [7,8]. JITAIs harness information captured through mHealth technologies (smartphone sensors, GPS, and internet access) to determine which behavior change support component should be delivered and tailor it to an individual's changing context (where) or status (when) [9]. The delivery of more contextually aware intervention support at more salient times to end users is hypothesized to enhance behavior change compared with other delivery approaches (eg, face-to-face and websites) [9].

It has been argued that conventional experimental designs are not sufficient to support the development of JITAIs because they do not enable researchers to determine empirically when a particular intervention component should be delivered and whether a JITAI that was delivered exerted the intended effect [10]. Traditional randomized controlled trial designs evaluate the overall effect of an intervention on a specific behavior or health outcome, not specific components of that intervention. Moreover, randomized controlled trials do not provide information on the particular time when the intervention had an effect and the moderators that affected the behavior change [11].

Other study designs, such as factorial designs, enable researchers to determine the effects of each intervention component, the interactions between components, and the dosing of the intervention. However, they are unable to delineate the time when the intervention was most receptive and what moderators influenced the intervention [11]. To address these limitations, Klasnja et al [11] proposed the microrandomized trial (MRT), which, they argued, could supplement the use of behavioral theory to guide the development of JITAIs. The MRT design provides data on the effects of specific intervention components, changes in effects over time, and potential moderators, including contextual and psychological factors [11]. Due to the dynamic nature of SB and PA that change throughout the day and in various contexts, adaptive designs such as MRT align well with interventions targeting SB and PA behavior change [12]. The MRT design has been suggested as necessary to leverage the potential of smartphones as a tool to improve PA and reduce SB [13]. MRT enables assessing the immediate effects of antisedentary and walking interventions [14] and therefore contributes to the optimization of SB and PA interventions.

Microrandomization refers to randomly allocating an intervention option at relevant times when a person would be most responsive to an intervention (based on theory, the person's past behavior, and the current context), thereby enhancing the effectiveness of the intervention [11]. MRTs explain the causal relationship between each randomized intervention component (eg, Sit Less or Move More notifications) and the proximal effects (ie, what happens in a limited time window, eg, within 1 hour, following the randomized intervention component) [11]. The distal outcome results from an aggregation of proximal effects obtained through repeated exposure to intervention components over time [11]. For example, a distal outcome would be people achieving recommended levels of PA and longer-term clinical outcomes such as improved glycemic control or improved fasting or postprandial glucose [15].

Aims

The primary aim of this study is to assess the effectiveness of theory-based motivational messages for reducing proximal sitting time and increasing proximal standing or walking time (ie, nonsitting time). The secondary aims involve (1) assessing what type of behavioral components (ie, behavior change techniques) are most effective in reducing sitting time and increasing standing and walking time, measured proximally, and (2) determining relevant contextual moderators for reducing sitting time and increasing standing and walking time.

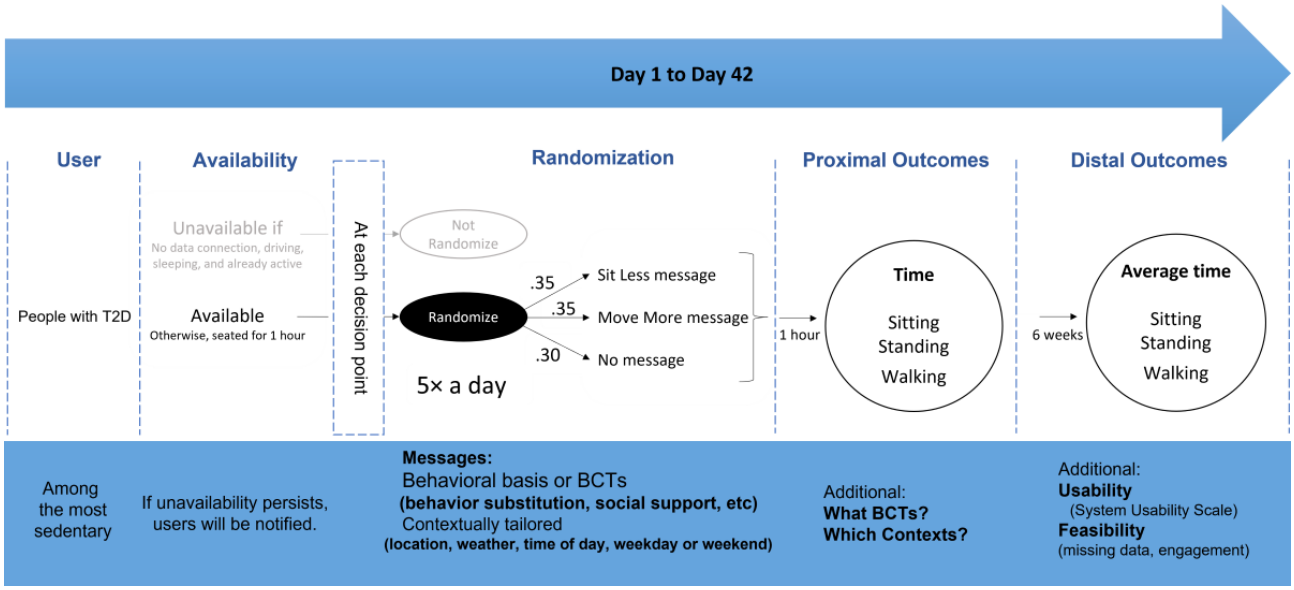
Methods

Design

A 6-week MRT will be conducted (see Figure 1). Using this design, participants will be randomly assigned an intervention option (Sit Less message, Move More message, or no intervention) at each relevant decision point.

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Figure 1. A summary of the microrandomized trial (MRT) design. Target group, availability conditions, study duration and arms, randomization probability, and outcomes are presented. BCT: behavior change technique; T2D: type 2 diabetes.



Participants and Recruitment

Overview

Participants will be recruited digitally through social media advertisements (eg, Facebook and Instagram). Moreover, posters will be placed on noticeboards of general practitioner and specialist clinics, and emails will be sent to potential participants who have indicated their willingness to participate in research studies. The plain "language statement and consent form" will be sent to eligible participants who express their interest in participating before any data collection.

Sample Size

A total of 22 participants are estimated to detect a small proximal treatment effect size of 0.13 for increasing nonsitting time with 80% power at the level of 5% statistical significance. This was based on the assumptions of 5 decision points per day, a constant randomization probability of 0.7, and an expected participant availability of 70% [16].

Eligibility Criteria

Eligible participants will be adults with T2D, aged between 35 and 65 years, who own an Android smartphone (version 7.0 or higher) and currently interact or engage with apps, have no limitations (including physical problems and medical complications) to engage in low- and moderate-intensity PA, are able to communicate in English, and can provide informed consent.

Volunteers who use other activity trackers and mobile apps that target PA, highly active people, those diagnosed with T2D less than 3 months ago, and people with psychiatric problems, attention, or memory issues will be excluded. We assume highly active people as those who meet World Health Organization (WHO) recommendation of 10,000 steps per day or 150 minutes of moderate to vigorous PA per week. The International Physical Activity Questionnaire—Short Form will be used to assess activity levels [17]. A 1-week run-in period will assess nonadherence with the activity tracker. Individuals with more than 50% incomplete data will be excluded.

Intervention Platform

The intervention comprises a bespoke mobile app (iMove app) [18] and a Bluetooth-enabled wearable sensor (SORD) developed and validated by our research group [19]. iMove is a JITAI that aims to support people to decrease sedentary time (Sit Less) and increase PA (Move More) [20]. It consists of a home tab that illustrates sitting, standing, and walking activities, an activity tab to select activities manually in situations where technical issues exist with the app, a goal setting tab to set sitting and walking goals, a notification history tab to compile previous notification messages, and a profile tab (see Figures 2 and 3). SORD is a bespoke thigh-worn device that connects to the iMove app and measures sitting, standing, lying, and PA (eg, walking) [19].

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Figure 2. iMove app images.

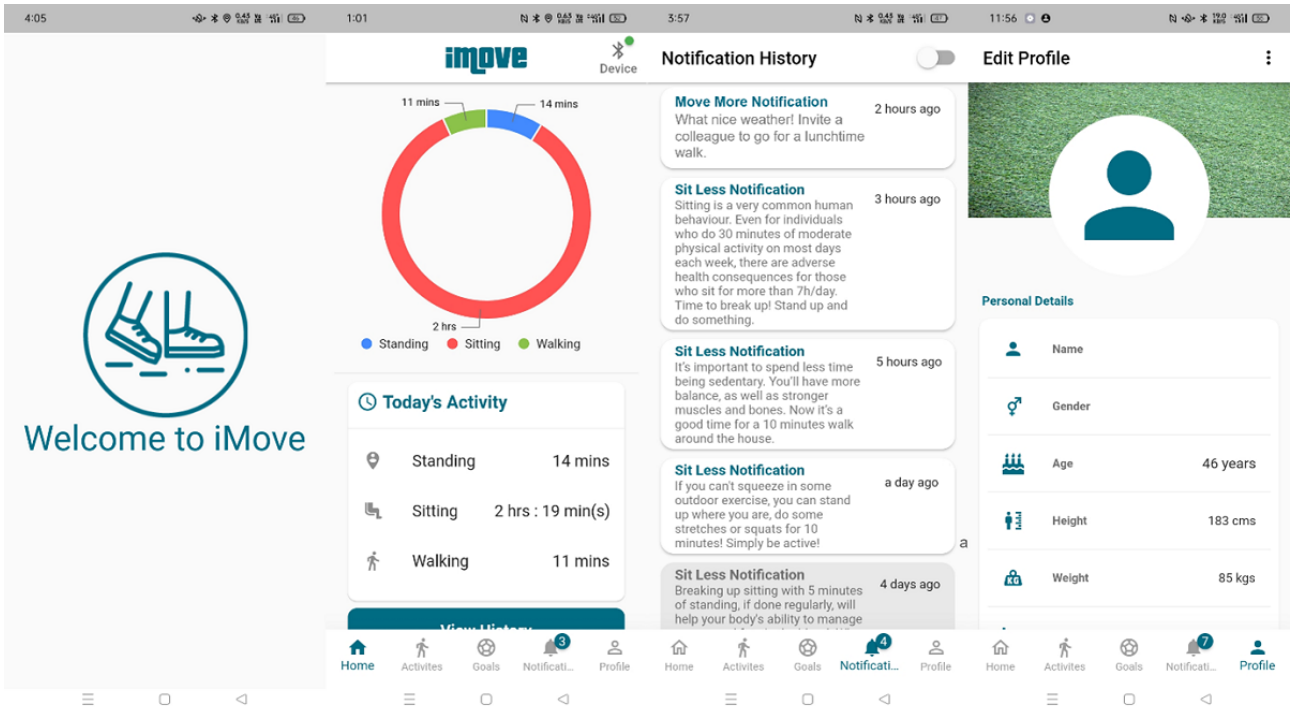


Figure 3. Sedentary Behavior Detector (SORD) device.



Intervention

Overview

Through the iMove app, participants will receive a series of Sit Less and Move More intervention messages (notifications) to serve as cues to action [21] and increase readiness to engage in activity. A pop-up message will appear on the phone screen with a sound effect when a notification is received. There will be 2 intervention options, which include Sit Less (sedentary interruption and transition to standing) and Move More (walking) for 1.5-3 minutes, approximately equivalent to 500-1000 steps, and a control option (no messages). Participants can switch off the push notification for a certain amount of time on any given day.

A list of messages is provided in Multimedia Appendix 1.

Notifications are adapted to 4 different context dimensions, including time of day, day of the week (weekend vs weekdays), location (home vs workplace), and weather conditions (good or suitable for PA, rainy and cold or not suitable for PA). Notifications are delivered on 5 occasions (decision points) throughout the day and include morning, lunchtime, afternoon 1, afternoon 2, and evening (details are presented in the "Decision Points" section below).

At each decision point, participants are randomized only if they are available (ie, they are not driving, not sleeping, not active already, and are connected to the internet). The following probabilities are used for randomization: 70% in the intervention (35% SB, 35% PA) and 30% as active control at each particular decision point. GPS will assist with the recognition of driving if the user is on the move. A preset time (9 PM to 8 AM) will be considered for rest and sleeping. In addition, both driving and sleeping can be manually modified by users.

Decision Points

A total of 5 decision points, from 8 AM to 8:30 PM, will be selected as shown in Table 1.

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Table 1. Occasions (decision points) when notifications are delivered.

Decision point	Time
Morning	8 AM to 10:30 AM
Lunchtime	10:30 AM to 1 PM
Afternoon 1	1 PM to 3:30 PM
Afternoon 2	3:30 PM to 6 PM
Evening	6 PM to 8:30 PM

Intervention Messages

Notifications were developed by the research team and incorporate effective behavior change techniques to Sit Less and Move More. Behavior change techniques including behavior substitution [22], social support [23], problem-solving or barrier identification [23], instruction on how to perform the behavior [22,24], providing information on the consequences of PA specific to the individual [23], prompts or cues [24], prompting generalization of a target behavior [23], goal setting [23], self-monitoring [22], and feedback on behavior [22] were used to create messages. Table 2 presents examples of intervention messages and their associated behavior change techniques.

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Table 2. Examples of Sit Less and Move More messages and their respective behavior change techniques.

Message type and behavior change technique	Example message
Sit Less	
Behavior substitution	You have been sitting for about 1 hour this morning. Why not stand up and do some stretches for 2-3 minutes.
Social support	Ask your partner to do some house chores with you (e.g., sweeping, mopping, vacuuming, etc.). It is more fun when you do this together while talking as well!
Problem-solving or barrier identification	You might not notice your long periods of sitting time, but it adds up to a lot of hours (e.g. we may sit during meals, travelling to/from work, in front of the computer, watching TV,…). Now it's the right time to take a break and stand up and do some stretches or warm-up exercise.
Instructions on how to perform the behavior	Time to stand up: you may want to grab a drink of water, talk on the phone while walking around or go and talk to your colleagues instead of emailing them.
Providing information on the consequences of physical activity (PA) specific to the individual	It's important to spend less time being sedentary. You'll have more balance, as well as stronger muscles and bones. Now it's a good time for a 10 minutes walk around the house.
Prompts or cues	Why not go take one of your favorite books and enjoy reading! This way you break up your sitting.
Prompting generalization of a target behavior	It looks like you are doing well reducing your sitting time during the mornings. Try to break your sitting time in the evenings as well. It's the time!
Goal setting	Your daily sedentary behaviour goal is *[<VALUE hours]*. While working, you can stand up and do some stretches. This helps you achieve your daily goal.
Self-monitoring	Check how much time you spent in sedentary (sitting) state yesterday.
Feedback on behavior	Congratulations! You achieved your daily sedentary behaviour goal *[<VALUE hours]* today. Keep it up!
Move More	
Behavior substitution	It's a beautiful day today, instead of sitting why not grab your lunch, go out and find a place to enjoy your food.
Social support	Invite a colleague to join you for lunch today! You can find a nice place outside to sit and enjoy!
Problem-solving or barrier identification	If most of your colleagues are inactive people and you think you have no company, you can encourage them or make new friends who are usually active. Invite someone to an afternoon walk now.
Instructions on how to perform the behavior	Getting out to walk in the rain is still a great way to connect and enjoy the outdoors. It's time to take an umbrella and go out!
Providing information on the consequences of PA specific to the individual	If you have an active lifestyle it helps you manage your blood sugar. It's time to do some outdoor light exercises in your neighbourhood.
Prompts or cues	Try now if you like: Walk around your building for a break during lunchtime.
Prompting generalization of a target behavior	Can you try to increase your activity time (while you do at work) also when you are at home? It's the right time to be active now!
Goal setting	You can achieve your daily physical activity goal (*[>=VALUE minutes]*) by engaging in short walks in your backyard or nearby park, etc. Try it now!
Self-monitoring	Check how much time you spent in physical activities yesterday.
Feedback on behavior	Congratulations! You achieved your daily physical activity goal *[>=VALUE minutes]* today. Keep up the good work!

Overview of Procedures

Eligible participants who provide their consent will be provided with the iMove app installer and invited to a web-based individual orientation session through the Zoom videoconferencing platform. During the web-based meeting, participants will be assisted in installing the app and informed about how to use the iMove app and SORD device. Weight, height, and other demographic measures (age, gender, marital status, job status, and education level) will be assessed at baseline as well as after intervention.

Data Collection and Storage

Activity sensor data (sitting, standing, and walking time) and other mobile data (location, weather, and calendar information) will be collected automatically through SORD and iMove and sent to a Deakin University secured server. Participant questionnaire data, including demographics questionnaire and system usability, will be captured digitally using Deakin secured Qualtrics surveys.

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Proximal Outcome

Time spent sitting (T_{sit}), standing (T_s), and walking (T_w) within 1 hour after sending the push notification are the proximal outcomes.

Distal Outcome

The distal outcomes of interest are the "average weekly time spent sanding and walking altogether, that is, nonsitting time" and the "average time spent being in the sitting state." Moreover, we will also assess total sitting, standing, walking, and exercising time.

Contextual Measures

Contextual factors, including weather and location, will be assessed using embedded smartphone sensors (GPS) and weather application programming interfaces (APIs; eg, OpenWeatherMap).

Other Outcome Measures

Other outcome measures include feasibility and acceptability. Feasibility will be assessed with descriptive statistics, including the proportion of missing data and engagement with the app (the average time the app was opened every day). Usability is assessed using the System Usability Scale through a web-based survey at the end of the intervention [25,26].

Noncompliance with the intervention platform (ie, SORD and iMove) will be evaluated by sending reminders and phone calls. In case no data have been gathered at one decision point, an automated text message reminder will be sent to the user. This reminder will be triggered once a day. If the data remain uncollected for the second day, the system will notify the research team, and a human investigator will contact the user to encourage them to use the platform and offer assistance in resolving any problems. Each user will be expected to continue the study until they provide data for the corresponding number of days × decision times (42 days × 5 = 210).

Data Analysis

Primary Analysis

Data from the 22 participants who generated 42 days of expected data, totaling 4620 decision points, will be analyzed. The study days will be continued until we reach the required number of days of data for each individual. Moreover, to deal with missing data at various decision points that could result from Bluetooth issues with the transfer of data or any other reasons (eg, activity states not being recorded), we will impute 0 for all missing minutes of sitting, standing, and walking.

MRT data will be analyzed using the weighted and centered least-squares estimator as previously described [27]. Using this analytical method, time-varying covariates can be handled, and the causal effect can be consistently estimated. Statistical analyses will be performed using R software (R Foundation for Statistical Computing) using the geepack R package.

Primary outcome measures include decision point, day, availability, interventions, and proximal change in activity states (ie, within 1 hour after the intervention is delivered). Overall effects of delivering a suggestion compared with not providing a suggestion on the subsequent 1-hour sitting, standing, and walking behaviors will be assessed. Moreover, linear treatment effects for Sit Less and Move More suggestions will evaluate the interaction between suggestion effects (ie, Sit Less or Move More) and decision points.

Statistics including β estimate, 95% CI, and *P* values will be reported for the average proximal effect as well as the multivariate effect (main effect). Sit less, Move More, and no suggestion (ie, control) conditions will be compared.

Secondary Analysis

Applying control systems principles [28], matchable-observable linear identification algorithms will be used to estimate linear time-invariant models from iMove intervention data [28]. Behavioral changes, including standing and walking time, will be assessed as a function of the onset, and offset of individual intervention components (ie, messages) and time-variant determinants (eg, contextual factors). Changes to the input variable (eg, behavior change technique) enable estimation and validation of computational models, therefore allowing exploration of personalized models. An individualized mathematical model of standing and walking time (outputs) will be created for Sit Less and Move More messages considering different contextual factors in different models. Also, further analysis will reveal unique intervention messages that generate the most effective behavior change (ie, either increasing standing or walking time) across various contexts.

Ethics Approval

The study received ethical approval from the Deakin University Human Research Ethics Committee (2021-258).

Results

The iMove app and integration with SORD were finalized in August 2022. Recruitment was initiated in October 2022. So far, 6 participants (2 female and 4 male) have provided their consent and enrolled in the study. They have completed baseline measurements and started using iMove. The mean age of 6 participants is 56.8 years, and they were diagnosed with T2D for 9.4 years on average.

Discussion

Overview

We present an MRT to evaluate the development of a Sit Less and Move More JITAI intervention in people with T2D [20]. The proximal and distal main effects of the sedentary and PA interventions on reducing sitting time and increasing standing or walking time (ie, nonsitting time), along with their univariate effects, will be evaluated. Moreover, the most effective behavior change technique will be recognized. Furthermore, the most critical contexts (eg, location: home or workplace) in which users are most responsive to interventions will be identified.

Too much sitting is a distinct behavior consideration from too little exercise for increasing the risk of cardiovascular disease [20]. Practical and integrated approaches involving both Sit Less and Move More have been introduced for risk reduction

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[20]. It is expected that interventions delivering a combination of Sit Less and Move More would add to the overall daily activity of an individual rather than focusing on at least 150 minutes of weekly exercise [20].

To our knowledge, there are no previous MRT studies targeting SB and PA among people with T2D. Other studies have focused on the general public including healthy sedentary adults [14] and university students [29]. The study by Klasnja et al [14] showed that the 6-week MRT intervention (antisedentary or walking vs no suggestion) among healthy sedentary adults (n=44) was effective to increase the average 30-minute step counts (ie, within 30 minutes after the intervention) by 14%. The study by Figueroa et al [29] conducted a 6-week MRT with university students (n=99) to improve their PA level. They showed that receiving the intervention (motivational messages and feedback on step counts vs no suggestion) increased daily steps by 729 steps, but this effect was diminished over time to –33 steps a day. They recommend that future studies need to take into account both user context and preferences [29].

These theory-based MRT studies were mainly focused on walking [14] rather than standing. Incorporating standing into the intervention package could make the Sit Less and Move More concept more practical. Replacing sitting time with standing could be considered a medium in which the most sedentary populations (eg, T2D) may make the initial transition from an inactive lifestyle to a more active lifestyle [30].

Limitations and Strengths

Due to the data-intensive nature of this study and the reliance on mobile apps for data transfer, heavy data loads may complicate data transfer to the backend server and generate missing instances. Even though multiple troubleshooting steps have been taken to develop iMove, such issues could still occur on certain smartphones with restricted manufacturers' system mandates. A key strength of this study is the incorporation of standing as a measured outcome. Because the focus of this MRT is on supporting people with T2D transition from sedentary to more overall physical activities, assessing transitional states, that is, standing, seems relevant. Assessing standing time, distinct from sitting and moving time, is expected to provide more robust evidence on how such Sit Less and Move More MRT performs.

Conclusions

Overall, the results of this study will inform the optimization of digital behavior change interventions to reduce SB and increase PA among people with T2D. Moreover, the findings will provide practical implications to clinicians concerned about recommending high-intensity exercise to older people with T2D. Finally, policy makers will be informed about simple smartphone-based interventions to reduce the burden of sedentariness among people with chronic diseases (eg, diabetes).

Conflicts of Interest

None declared.

Multimedia Appendix 1
An example list of iMove notification.
[PDF File (Adobe PDF File), 306 KB - resprot_v12i1e41502_app1.pdf]

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Abbreviations

API: application programming interface
JITAI: just-in-time adaptive intervention
mHealth: mobile health
MRT: microrandomized trial
PA: physical activity
SB: sedentary behavior
SORD: Sedentary Behavior Detector
T2D: type 2 diabetes
WHO: World Health Organization

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Protocol

An eHealth Program for Insomnia in Children With Neurodevelopmental Disorders (Better Nights, Better Days): Protocol for an Economic Evaluation of a Randomized Controlled Trial

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Abstract

Background: Children with neurodevelopmental disorders have a high risk of sleep disturbances, with insomnia being the most common sleep disorder (ie, chronic and frequent difficulties with going and staying asleep). Insomnia adversely affects the well-being of these children and their caregivers. Pediatric sleep experts recommend behavioral interventions as the first-line treatment option for children. Better Nights, Better Days for Children with Neurodevelopmental Disorders (BNBD-NDD) is a 5-session eHealth behavioral intervention delivered to parents to improve outcomes (eg, Pediatric Quality of Life Inventory [PedsQL]) for their children (ages 4-12 years) with insomnia and who have a diagnosis of mild to moderate attention-deficit/hyperactivity disorder, autism spectrum disorder, cerebral palsy, or fetal alcohol spectrum disorder. If cost-effective, BNBD-NDD can be a scalable intervention that provides value to an underserved population.

Objective: This protocol outlines an economic evaluation conducted alongside the BNBD-NDD randomized controlled trial (RCT) that aims to assess its costs, efficacy, and cost-effectiveness compared to usual care.

Methods: The BNBD-NDD RCT evaluates the impacts of the intervention on children's sleep and quality of life, as well as parents' daytime functioning and psychosocial health. Parent participants were randomized to the BNBD-NDD treatment or to

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usual care. The economic evaluation assesses outcomes at baseline and 8 months later, which include the PedsQL as the primary measure. Quality of life outcomes facilitate the comparison of competing interventions across different populations and medical conditions. Cost items include the BNBD-NDD intervention and parent-reported usage of private and publicly funded resources for their children's insomnia. The economic evaluation involves a reference case cost-effectiveness analysis to examine the incremental cost of BNBD-NDD per units gained in the PedsQL from the family payer perspective and a cost-consequence analysis from a societal perspective. These analyses will be conducted over an 8-month time horizon.

Results: Research funding was obtained from the Kids Brain Health Network in 2015. Ethics were approved by the IWK Health Research Ethics Board and the University of Calgary Conjoint Health Research Ethics Board in January 2019 and June 2022, respectively. The BNBD-NDD RCT data collection commenced in June 2019 and ended in April 2022. The RCT data are currently being analyzed, and data relevant to the economic analysis will be analyzed concurrently.

Conclusions: To our knowledge, this will be the first economic evaluation of an eHealth intervention for insomnia in children with neurodevelopmental disorders. This evaluation's findings can inform users and stakeholders regarding the costs and benefits of BNBD-NDD.

Trial Registration: ClinicalTrial.gov NCT02694003; https://clinicaltrials.gov/study/NCT02694003

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KEYWORDS

eHealth intervention; pediatric insomnia; neurodevelopmental disorders; attention-deficit/hyperactivity disorder; autism spectrum disorder; cerebral palsy; fetal alcohol spectrum disorder; economic evaluation; cost-effectiveness

Introduction

Background

Neurodevelopmental disorders (NDDs), estimated to affect 5%-9% of children [1,2], are a heterogeneous group of chronic conditions that affect the central nervous system. Children with NDDs are a vulnerable population that experiences significant health disparities compared to typically developing (TD) children, including high rates of sleep difficulties. In children with NDDs, sleep difficulties contribute to morbidity and impair cognition, emotional regulation, and neurobehavioral functioning [3]. Prevalence rates of sleep disturbances have exceeded 90% in children with certain NDDs, with insomnia being the most frequently cited sleep disorder [4]. Sleep disturbances can have a negative impact on children's quality of life (QoL) and exacerbate stress in their caregivers [3].

Despite limited safety and efficacy data in children, pharmacotherapies, both over-the-counter and prescription, are often given to treat insomnia in this population [5]. However, pediatric sleep experts recommend that psychosocial interventions be implemented first [6]. Specifically, the intervention would start with psychoeducation and healthy sleep practices, and be followed by psychological interventions such as bedtime fading or modified extinction [7-9]. Then, if psychosocial interventions are ineffective or unfeasible, medications become an option [7-9].

The existing literature has demonstrated the efficacy of treating insomnia in TD children with psychosocial interventions [10,11]. While there is less research on children with NDDs, the available evidence also demonstrates the effectiveness of these interventions. A review of nonpharmacological interventions for sleep problems in youths with chronic health conditions concluded that the effectiveness of psychosocial interventions was not exclusive to specific health conditions but had comparable effects across children with a variety of mental and physical health conditions, including NDDs [12]. Psychosocial interventions for pediatric insomnia have also been shown to improve parents' sleep and increase their feelings of competence and control [13,14].

Existing psychosocial interventions are typically delivered in conventional settings (eg, hospital clinics, outpatient professionals' offices), consisting of weekly training sessions for parents [15-18] and several visits with health care providers [19,20]. Hence, time constraints and required travel expenses to health facilities may be access barriers for families. Reaching families in rural or remote communities and those who are financially constrained or lack insurance coverage for private psychological and other necessary clinical services are significant challenges in the delivery of behavioral interventions [21].

Economic Evaluation

Economic evaluations can help guide policy making and resource allocation decisions. Little is known about the cost-effectiveness of eHealth (internet-based in this case) behavioral interventions for sleep problems in children. Many parents are interested in internet-based interventions for their children's sleep problems [22]. An internet-delivered treatment program may be an effective tool to address and overcome barriers to accessing pediatric insomnia care [22,23]. The cost-effectiveness of internet-based sleep interventions for children in comparison to usual care has not been determined for children with NDDs [22].

The value for money of internet-based interventions can be assessed using cost-effectiveness analysis (CEA) and cost-consequence analysis (CCA) [24]. A CEA incorporates cost and a single measure of effectiveness into a metric represented by an incremental cost-effectiveness ratio (ICER) [25]. An ICER is calculated by dividing the difference in cost by the difference in outcome measure between 2 interventions,

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often treatment and control conditions in randomized controlled trials (RCTs). A CCA reports various costs and outcomes to enable decision makers to decide which are most relevant to their context and perspective [24]. It can capture costs to the user, system, and society and portray health, nonhealth, and nonpatient impacts [24].

An economic evaluation will be performed alongside the Better Nights, Better Days for Children with Neurodevelopmental Disorders (BNBD-NDD) RCT (ClinicalTrial.gov ID NCT02694003), which seeks to determine the efficacy of the eHealth behavioral intervention compared to usual care. BNBD-NDD is a parent-implemented eHealth behavioral program delivered to parents to enable accessible and effective care for insomnia in children with NDDs. The web-based nature of BNBD-NDD allows it to be readily scalable to reach many users. BNBD-NDD is transdiagnostic because it targets children ages 4 to 12 years with diagnoses of mildly to moderately severe attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD), cerebral palsy (CP), and fetal alcohol spectrum disorder (FASD). Although these 4 conditions present a broad range of cognitive, physical, and social characteristics, they are all associated with higher than normal rates of insomnia [26,27].

This protocol describes the BNBD-NDD economic evaluation, consisting of a CEA to evaluate the cost-effectiveness of BNBD-NDD in children with NDD compared with usual care and a CCA to examine outcomes beyond QoL. A CEA will be undertaken using the parent-reported Pediatric Quality of Life Inventory (PedsQL) questionnaire total scores, which will assess the children's QoL. The QoL measure is used in economic evaluation because it allows comparison of the health outcomes of competing alternative interventions over time and across populations [28]. In addition, to illustrate a more comprehensive picture of BNBD-NDD's impacts, a CCA will also be conducted to examine outcomes beyond the children's health-related quality of life (HRQoL), including children's sleep, parents' daytime functioning, and psychosocial health.

Understanding the added value of BNBD-NDD is essential to informing the intervention's scale and spread. Thus, this protocol aims to complement the BNBD-NDD RCT and describe the economic evaluation from both family and societal perspectives.

Methods

Recruitment

Participants were recruited for the BNBD-NDD trial nationwide in Canada and stratified based on the parent-reported primary NDD diagnosis of their child. Potential parent participants were targeted via three groups: (1) parents of children with NDDs, (2) external stakeholders and organizations, and (3) the media. Internet-based tools were primarily used for recruitment, notably this study's website and social media, as well as print materials and presentations to health care professionals.

Inclusion Criteria

Participants must (1) reside in Canada and (2) be caregivers of children (3) ages 4 to 12 years who have been diagnosed with (4) ADHD, ASD, CP, or FASD by a health care provider and (5) meet the research criteria for insomnia. Insomnia criteria (ie, sleep onset disturbance) were characterized by at least 2 of 3 symptoms (>20 minutes to fall asleep, parent remaining in room for sleep onset, and more than 2 reunions) occurring 2 to 4 times per week for at least a month [29]. Additionally, these caregivers must have (6) regular access to a high-speed internet connection, (7) an email account, and (8) be proficient in English for everyday tasks.

Sample Size Calculation

The BNBD-NDD RCT was powered to detect a group by time interaction across the 3 data collection time points (baseline, 4-month, and 8-month) and between the BNBD-NDD and usual care groups. The primary sleep outcome was the Disorders of Initiating and Maintaining Sleep (DIMS) [22] variable. To achieve a power of 0.80 with an α of .05, 39 participants per group would have to complete the DIMS measure at 8 months. Based on this analysis and the anticipated postenrollment dropout rate of 50% from a previous BNBD RCT, an estimated 160 participants were targeted for enrollment at baseline.

Randomization and Blinding

Participants were randomized using a block stratified approach with 1:1 allocation to either the intervention (BNBD-NDD) or the usual care group and were not blinded to their assigned group. Stratification was by parent-reported primary NDD diagnosis.

Study Groups

Participants were randomized to either the intervention group or the usual care group. Both groups may use alternative resources and other programs or services during this study. The intervention group was provided access to the BNBD-NDD program for 8 months after randomization (the duration of this study). As such, participants in the intervention group were regarded as receiving BNBD-NDD plus usual care. The usual care group could access BNBD-NDD after completing all follow-up assessments at 8 months.

BNBD-NDD Intervention

BNBD-NDD is an eHealth program for parents or caregivers of children with NDDs and insomnia. The program is parent-implemented, incorporating transdiagnostic, evidence-based behavioral approaches, such as sleep education, stimulus fading, and scheduled awakenings, and presents NDD-specific strategies. The intervention is accessible via desktops, laptops, tablets, and mobile devices.

BNBD-NDD includes 5 sessions for participants to work through sequentially, with the recommended completion time ranging from 5 to 10 weeks. The sessions cover the following topics: (1) about BNBD-NDD; (2) healthy sleep practices; (3) settling to sleep independently; (4) night waking, napping, and early morning awakenings; and (5) looking back and ahead. Participants may access and complete the program at times that are convenient for them. Treatment fidelity and adherence were evaluated through process measurements and user statistics gathered by the intervention platform software. Participants may withdraw from the program at any time and are invited to provide reasons for withdrawal through open-ended questions.

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Perspective

Costs and outcomes are weighed differently by various decision makers. A way to determine the most pertinent perspective is by asking whom the analysis is intended to inform [30]. As BNBD-NDD is designed as a direct-to-user product, with the program's users and beneficiaries being the parents and their children with NDDs and insomnia, this economic evaluation aims to inform them of the costs and effects of the program. The reference case costing will be completed from the perspective of the family payer (in this case, the parents). In accordance with recommendations from the Canadian Agency for Drugs and Technologies in Health, the reference case analysis will evaluate the QoL outcome for children, the primary target beneficiaries of the program [25]. In the nonreference case analysis from a societal perspective, the outcomes for caregivers (ie, daytime fatigue, psychosocial health), specific measures of children's sleep (ie, DIMS score), and societal costs (ie, treatment utilization [TU]) will also be examined.

Time Horizon

In the BNBD-NDD RCT, data collection occurred at baseline, 4 months, and 8 months. The reference case CEA and secondary CCA will use an 8-month time horizon, focusing on baseline and 8-month data; 8-month data are used to best capture the longer term costs and effects.

Outcomes for Economic Evaluation

PedsQL is an instrument that measures generic (rather than disease-specific) HRQoL and has been shown to have appropriate psychometric properties when used with children with NDDs [31]. It can be used to evaluate HRQoL in healthy children, youths, and those with medical conditions [32]. PedsQL uses a modular approach with 4 multidimensional scales on physical, emotional, social, and school functioning [33]. Parents rate each item using a 5-point Likert scale from 0 (never) to 4 (always) [31]. A Total Scale Score is calculated by adding all of the items and dividing the total by the number of items answered in all scales [33]. Mean Scale Scores are computed by dividing the sum of the items by the number of items answered in the scale [33]. Depending on the age of the participant's child, 3 parent-report versions were used (for ages 2-4 years, 5-7 years, and 8-12 years) to accommodate the age range of this study sample. The difference between the intervention and usual care groups' average Total Scale Score in parent-proxy reports of their children's PedsQL at baseline and 8 months will be evaluated in the reference case CEA. Secondary analyses will examine each of the 4 modules and age group trends; it is noted that inconsistent reporting of the school functioning section may occur due to age and the time of year of data collection (off-school period). The scoring and missing data (where applicable) will be completed in accordance with the PedsQL user manual [34].

In the CCA, the children's sleep and parental outcomes are analyzed by comparing baseline and 8-month data and looking at changes in sample averages. Based on parent-reported questionnaire data, the DIMS score quantifies the severity of children's sleeping problems. The Single Item Fatigue Impact Scale [35] and the Depression, Anxiety, and Stress Scales [36] are used to evaluate the daytime fatigue and psychosocial health, respectively, of parents. Single Item Fatigue Impact Scale is adapted from the 40-item Fatigue Impact Scale [35]. The Depression, Anxiety, and Stress Scales have demonstrated adequate construct validity and high reliability [36].

Resource Use and Costing

BNBD-NDD Cost

The direct cost of BNBD-NDD to the families is primarily the retail cost of the intervention. As the program was offered free of charge for our RCT, we used the average of parents' (proxy payers for their children) reported willingness to pay. The participating families were expected to have internet access, which was not assessed or included in the direct costs. Retail pricing will be explored further from the willingness to pay data, which obtained a hypothetical willingness to pay (HWTP) by directly asking for the maximum cost participants would pay for the program. The HWTP responses may contain hypothetical bias influenced by factors such as the absence of a budget constraint effect and strategic answering, as some may perceive their input to potentially affect future pricing [37].

Treatment Utilization

The TU questionnaire [38] estimated the health care services families sought to address their children's sleep problems, including publicly and privately funded ones. Care may be provided by family physicians, physician specialists (eg, pediatricians), and other health professionals (eg, psychologists). The mean frequency and costs of these services at baseline and at 8 months for the BNBD-NDD and usual care groups will be compared to see if BNBD-NDD impacted the usage rate. Out-of-pocket expenses reported for a health professional's or provider's help will also be assessed. Unit costs will be estimated using publicly available resources, such as the Canadian Agency for Drugs and Technologies in Health [39].

Data Analysis

Overview

For the reference case CEA analysis, the mean sample PedsQL at baseline and 8 months will be compared. Regression analyses will examine the impacts of baseline characteristics (geographical region, age groups, sex, household income, and NDD diagnosis) on the efficacy measures. For all regression analyses, the mean difference between groups will be reported, as well as the variance, *P* value, and goodness of fit using R^2.

Reference Case CEA

In the reference case analysis using the family payer perspective, the ratio of the difference in mean cost between groups to the difference in mean PedsQL total score per group will be used to estimate the ICER. An ICER will be calculated from the family's perspective.

$$\text{ICER} = \text{Costs}_{(\text{BNBD-NDD + usual care})} - \text{Costs}_{(\text{usual care})} / \text{Effect}_{(\text{BNBD-NDD + usual care})} - \text{Effect}_{(\text{usual care})}$$

Secondary CCA

The CCA will assess the impacts on children's sleep disturbance severity, parents' daytime functioning, and psychosocial health.

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It adopts a broader perspective, providing a wider range of relevant costs and outcomes [24]. This allows various decision makers to focus on aspects and contexts specific to them [24]. The costs examined will extend beyond the family and include the costs of reported publicly and privately funded services sought.

Subgroup Analysis

Subgroup analyses will be performed to determine if there are any trends, similarities, or differences in the mean outcomes of the 4 NDD diagnostic groups (ADHD, ASD, CP, and FASD); the CP and FASD groups are likely to have relatively fewer participants than the ADHD and ASD groups due to their lower prevalence.

Sensitivity Analysis

Sensitivity analysis will test variations in assumptions regarding estimated costs and reported health care usage. With the retail cost of the intervention under discussion, a range of prices will be explored based on the HWTP data, and the corresponding ICERs will be calculated. Parameter uncertainties associated with TU will be explored through scenario analyses, incorporating the 95% CI of mean estimates.

Missing Data

Multiple imputation techniques are used to address missing data. This method works well for longitudinal data and is robust to violations of the nonnormality of the variables analyzed. Participants who do not complete both the baseline and the 8-month follow-up will not be included in the analysis. Where applicable, the measures' user guides on missing data will be followed. For the PedsQL, the means of completed items in the scale will be imputed when 50% or more of the items are completed [34].

Discount Rate

As all costs and outcomes assessed are within 1 year, a discount rate will not be applied [25].

Ethics Approval

All study participants provided informed consent to participate in the BNBD-NDD RCT. Ethical approval for the BNBD-NDD trial (REB-1020681) was granted by the IWK Health Centre Research Ethics Board and the associated economic evaluation by the IWK REB and the University of Calgary Conjoint Health Research Ethics Board (REB22-0694). This study complies with all applicable standards and procedures of the IWK REB, the Personal Health Information Act, the Personal Information International Disclosure Protection Act, and the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans.

Results

The BNBD-NDD RCT data collection started in June 2019 and ended in April 2022. Research funding was obtained from the Kids Brain Health Network in 2015. Ethics were approved by the IWK Ethics Board and Conjoint Health Research Ethics Board in January 2019 and June 2022, respectively. The data examining the primary outcomes of this RCT are currently being analyzed. The relevant data for the economic evaluation have been cleaned and are being prepared for analysis.

Discussion

In this paper, we have described an economic evaluation protocol for the BNBD-NDD eHealth intervention, which aims to improve insomnia in children with NDDs. The economic evaluation will identify, measure, and value the costs and outcomes of BNBD-NDD compared to usual care. The reference case CEA will assess the costs and QoL of the children, and the CCA will examine measures beyond QoL for the children and their caregivers.

The prevalence of sleep disorders has been observed to be higher in children with NDDs relative to TD children [40]. BNBD-NDD has the potential to deliver an evidence-based and cost-effective insomnia intervention to children with NDDs, which is critically important given the lack of available treatments. The eHealth delivery system may also overcome some existing barriers to treatment access. If cost-effective, this program can improve sleep outcomes and positively affect the well-being of children with NDDs and their caregivers. To our knowledge, BNBD-NDD is the first eHealth insomnia intervention for children with NDD. No published reports have evaluated internet-based interventions for insomnia in preschool- and school-aged children; 1 study has reported an effective internet intervention for sleep disturbances in infants and toddlers [41].

Some limitations of this study are the uncertainties with cost estimates, the parental-reported measures on behalf of the children, the recall bias of their children's 12-month service usage, and the lack of objective outcome data. With family and societal payer perspectives, the breadth of the costing analysis is limited by the collected cost data in the RCT and thus likely to be an underestimation of real-world costs. While the CCA provides a wider scope of relevant outcomes and costs for decision makers, the interpretation of the results may be prone to subjective bias [24]. The BNBD intervention would benefit from real-world evidence to evaluate its effectiveness and also explore its applicability to children with other medical conditions.

Despite a direct-to-user approach for the intervention, the economic evaluation can stimulate conversations with relevant stakeholders, better understand the efficacy of web-based alternatives, and provide evidence to support potential public payer funding initiatives. Dialogue on the integration of eHealth interventions in the delivery of care in the health system is another area for future examination. The findings of this study will provide users and other stakeholders with a holistic picture of the costs and impacts of BNBD-NDD and play a role in informed decision-making for resource allocation.

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Data Availability

The data sets generated and analyzed during this study are not publicly available as the participants of this study did not give written consent for their data to be shared publicly. Due to the sensitive nature of the research, supporting data are not available.

Authors' Contributions

XYJ led the writing of this paper. JZ and XYJ designed the economic analysis. PC is the principal investigator of the Better Nights, Better Days for Children with Neurodevelopmental Disorders (BNBD-NDD) randomized controlled trial (RCT) grant and was involved in the formulation and writing of this paper. AHD, CB, EC, GR, IS, OI, PA, RG, SS, and SKW were all involved in the design of the BNBD-NDD RCT protocol and reviewed the draft version of this paper. This paper has been approved by all the authors.

Conflicts of Interest

While there are no current conflicts of interest, it is possible that the Better Nights, Better Days program will be commercialized in the future.

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Abbreviations

ADHD: attention-deficit/hyperactivity disorder
ASD: autism spectrum disorder
BNBD: Better Nights Better Days
BNBD-NDD: Better Nights, Better Days for Children with Neurodevelopmental Disorders
CCA: cost-consequence analysis
CEA: cost-effectiveness analysis
CP: cerebral palsy
DIMS: Disorders of Initiating and Maintaining Sleep
FASD: fetal alcohol spectrum disorder
HRQoL: health-related quality of life
HWTP: hypothetical willingness to pay
ICER: incremental cost-effectiveness ratio
NDD: neurodevelopmental disorder
PedsQL: Pediatric Quality of Life Inventory
QoL: quality of life
RCT: randomized controlled trial
TD: typically developing
TU: treatment utilization

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Protocol

Evaluating a WeChat-Based Health Behavioral Digital Intervention for Patients With Hypertension: Protocol for a Randomized Controlled Trial

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Abstract

Background: Hypertension is the most prevalent chronic condition and a significant risk factor for cardiovascular and kidney diseases. The efficacy of health behavioral interventions in blood pressure (BP) control has been demonstrated by a large and expanding body of literature, with “adherence” playing a crucial role. WeChat is the most common social communication mobile app in China, and it has been shown to be an acceptable delivery platform for delivering health interventions. The WeChat-based health behavioral digital intervention program (WHBDIP) showed high feasibility and efficacy. However, the results regarding BP improvement between the WHBDIP and control groups were inconsistent.

Objective: The objective of this study is to develop a WHBDIP and assess its efficacy in controlling BP and improving adherence among patients with hypertension.

Methods: A 2-arm, parallel-group, and randomized trial design was used. Patients older than 60 years and with hypertension were randomly assigned to either the control group or the experimental group, which received a 12-week intervention. The program, primarily developed based on the Behavior Change Wheel (BCW) theory, offers health education on exercise, diet, BP monitoring, and medicine adherence (MA). It also includes other behavior interventions guided by an intervention manual, incorporating behavior change techniques (BCTs). The primary outcomes encompass BP and adherence indicators, while the secondary outcomes encompass cardiovascular function indicators, body composition indicators, learning performance, satisfaction, and acceptability. The exercise and blood pressure monitoring adherence (BPMA) indicators for the WHBDIP group were assessed weekly via WeChat during the initial 3 months, while other outcome data for both groups will be collected at the baseline assessment phase, 3 months after the intervention, and 1 year after the program.

Results: The trial will assess the efficacy of WHBDIP for patients with hypertension (N=68). The WHBDIP seeks to enhance participants' knowledge of healthy behaviors and assist patients in developing positive health behaviors to improve their health outcomes. Patient recruitment for individuals with hypertension commenced on September 5, 2022, and concluded on September 19, 2022. The 3-month intervention and phased data collection were finalized in January 2023. Data analysis will commence in August 2023, and the final 1-year health outcome results will be collected in September 2023.

Conclusions: A successful WHBDIP will establish the management mode as a feasible approach for hypertension management in the community. Additionally, it will pave the way for the development of related mobile health programs.

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KEYWORDS

adherence; community health; hypertension; health behavior; mobile phone

Introduction

Hypertension, the most prevalent chronic condition and a significant risk factor for stroke, ischemic heart disease, and kidney disease, has become a primary contributor to the global disease burden [1,2]. It is directly responsible for more than 8.5 million deaths worldwide annually [3]. Furthermore, it imposes a substantial economic burden. In China, hypertension accounts for 6.6% of the total national health expenditure [4]. Over the past 30 years, the number of adults with hypertension has risen from 650 million to 1.28 billion [1]. In China, the prevalence of hypertension in adults was 25.2% [5] with awareness, treatment, and control rates at 51.5%, 45.8%, and 16.8%, respectively [6].

Less than half of young patients with hypertension and two-thirds of eligible older patients with hypertension achieve blood pressure (BP) control goals [6]. The low control rate may be attributed to lifestyle-related risk factors, such as poor eating habits and low levels of physical activity [2]. Researchers have found that encouraging patients to follow the recommended health behaviors significantly reduces BP. For example, patients under the supervision of medication taking experienced a 5-mm Hg decrease in daily systolic blood pressure (SBP) compared to unsupervised individuals [7]. Adhering to the Dietary Approaches to Stop Hypertension (DASH) resulted in a 26% reduction in developing high BP [8], and in those already diagnosed with hypertension, SBP and diastolic blood pressure (DBP) decreased by 1.5 and 1.1 mm Hg, respectively [9]. Following various types of recommended exercise led to an SBP reduction of 7.23-8.69 mm Hg [10]. Improving BP monitoring adherence behavior resulted in SBP and DBP reductions of 2.53-4.2 and 1.45-2.4 mm Hg, respectively [11]. High medication adherence, combined with comprehensive interventions such as diet and exercise management, can achieve better BP control effects [12,13]. The results showed a reduction of 12.1 and 26.1 mm Hg in SBP and DBP, respectively, before and after comprehensive health behavior intervention [14], and a decline of 7.5 and 3.9 mm Hg for SBP and DBP, when compared with nonintegrated intervention group [15]. Considering all of this evidence, it appears that comprehensive health behavior intervention can achieve better BP control effects, with adherence being the key.

Digital health (such as mobile health [mHealth] or telehealth) intervention strategies have been used to improve hypertension management outside the hospital. These strategies enhance patient adherence behaviors and increase the feasibility of delivering convenient, continued health interventions in primary health care settings with unequal resource distribution and understaffing. Several recent meta-analyses have demonstrated that using an internet-based interactive intervention mode combining health information with decision support via a computer or mobile phone could lead to a reduction of mean SBP by 2.23-3.74 mm Hg and mean DBP by 1.14-2.99 mm Hg [16-18]. Most of the interventions conducted by the investigators aimed to influence “self-management” or “adherence behaviors” in patients with hypertension [16-18]. Another systematic review of the literature showed the improvement of patient adherence after mHealth intervention [12,17,19-21].

WeChat, a mobile app, is the most prevalent social communication tool in China, with over 1 billion monthly active users of all ages. Approximately 902 million users log into WeChat every day [22]. A substantial amount of prior research in health promotion has focused on WeChat-based programs, which have demonstrated high acceptability, feasibility, and efficacy [23]. WeChat-based health interventions have been found to increase adherence and willingness to seek treatment, improve follow-up rates, enhance health outcomes, quality of life, and self-care ability, and also promote patient satisfaction [23-28]. For hypertension management, WeChat-based programs showed improvements in BP monitoring, diet, self-efficacy, and self-management scores [29,30]. However, the effect of lowering BP is inconsistent. One study reported a significant improvement in BP (SBP: –6.9 and DBP: –3.1 mm Hg) between the intervention and control groups [30], while another study showed no statistical differences between the 2 groups [31]. Therefore, we aim to assess the effectiveness of the WeChat-based health behavioral digital intervention program (WHBDIP) in 2 groups after 3 months of intervention and at the end of an extended additional 7 months. This program involves exercise, diet, BP monitoring, and medication adherence intervention strategies. Our plan is to investigate whether this approach is accessible and effective in improving outcomes for older individuals with hypertension.

Methods

Trial Design and Setting

This is a 2-arm, parallel-group, randomized trial that includes a WeChat-based health behavioral digital intervention lasting for 12 weeks. The trial has been conducted at 2 community health centers, both located in Anhui province—1 in Hefei and the other in Bengbu. The primary data collection and evaluation will take place at 3 time points: the beginning of the project, after 3 months of intervention, and 1 year after the project starts.

Patients

In this trial, patients with hypertension were recruited through phone or verbal invitations from community health centers. Interested individuals were asked for further information by contact staff members. To promote recruitment, relevant

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physical health assessments were offered for free to candidates, and unqualified candidates were excluded at this stage. Written informed consents were obtained from eligible patients before randomization. The inclusion criteria for the participants were as follows: (1) previous diagnosis of essential hypertension by medical institutions or initiation of antihypertensive drug treatment, (2) older than 60 years of age, and (3) proficiency in using smartphones and the WeChat app. Patients with the following conditions were excluded: (1) prehypertension or not taking antihypertensive drugs; (2) contraindications to exercise, such as serious cardiovascular and cerebrovascular diseases, muscle and joint pain, or inability to participate in exercise as recommended by a doctor; (3) diabetes or nephrosis; (4) participation in other health intervention programs; and (5) not having a sphygmomanometer.

Sample Size

The sample size was calculated based on the primary outcome of BP. The effect size, widely used to measure treatment effects of continuous outcomes, is calculated as the difference between groups divided by the pooled SD. A previous meta-analysis, comparing mHealth intervention treatments with other traditional treatments, with the primary outcome being BP, reported an effect size of 0.7 [17]. Assuming α=.05, β=.2, and accounting for up to 20% attrition, a sample size of 68 is needed for this study.

Intervention

WHBDIP Development

WHBDIP is a web-based individual telehealth intervention program for patients with hypertension on WeChat, which includes nondrug intervention health education and behavior change strategies. WHBDIP consists of 4 sections: exercise, diet, BP monitoring, and medication adherence behavior interventions, which together constitute a comprehensive health behavior intervention program.

The exercise intervention was based on an intelligent personalized exercise prescription. This prescription has been verified by experts and has been proved by a 1-year real-world clinical research [32]. Before prescribing, health data are collected by an intelligent health promotion system (including networked equipment and a questionnaire system) installed in the community health service center. The intelligent decision-making module of this system generates safe, reliable, and personalized prescriptions according to the complex health conditions of the residents, especially older patients with 1 or more chronic diseases. In WHBDIP, the health education content matching the exercise prescription was compiled into text and then transformed into animation or video to be included in the electronic knowledge base.

The dietary intervention was designed based on the principles of the DASH. After revising the simplified DASH grading diet index score (SDGDIS), videos related to DASH health education were produced and delivered to subjects through WeChat. Subjects were required to upload photos of their 3 meals per day (including a fist for size comparison) within 7 days. The scores (based on the SDGDIS) and qualitative evaluation text were provided to subjects during this period. After 7 days, the subjects and interveners were required to provide their respective scores.

For BP monitoring and medicine adherence (MA) intervention, we have created health education videos and used WeChat to send reminders and supervise the health behavior of the subjects. The content of health education related to WHBDIP is displayed in Table 1, and the video screenshots are shown in Figure 1.

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Figure 1. Video screenshots.



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Table 1. Topics and forms of health education content.

Topic	Form
Exercise intervention	
Intelligent personalized exercise prescription	Pictures and text
The benefits of exercise	Video
The difference between aerobic and anaerobic exercise	Video
The choice of exercise intensity	Pictures and text
Seated strength training for the older	Video
Running breath	Video
Running posture	Video
When should stop exercising	Video
Aerobics for middle-aged and older	Video
Stretching	Video
Dietary intervention	
What is the "DASH"[a]	Video
"DASH" teaches you how to eat	Video
How to rate your "DASH"?	Video
BP[b] monitoring	
How to choose a sphygmomanometer	Video
How often should BP be measured?	Video
How much does BP drop to reach the target?	Video
The use of mercury sphygmomanometer	Video
The use of upper arm electronic sphygmomanometer	Video
The use of wrist electronic sphygmomanometer	Video
MA[c] intervention	
Why can't stop taking the medicine on my own?	Video

[a]DASH: Dietary Approaches to Stop Hypertension.

[b]BP: Blood pressure.

[c]MA: Medicine adherence.

To promote adherence behavior change, we adopted the behavior change wheel (BCW), which is a systematic framework for selecting 25 behavior change techniques (BCTs) from Michie et al's [33] taxonomy that correspond to the 9 intervention functions (shown in Table 2). The use of BCTs was documented in the intervention manual.

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Table 2. Implementation of BCTs[a] following Michie et al's [33] BCW[b] and taxonomy.

Intervention functions and BCTs	Examples
Education: increasing knowledge or understanding	
4.1 Instruction on how to perform the behavior	Provide healthy educational content on how to exercise and eat
5.1 Information about health consequences	Tell the intervention the benefits of exercising
4.3 Reattribution	If the subjects attributed their lack of exercise to frequent bad weather, intervenor indicated that the "real" reason might be the person's lack of motivation
Persuasion: using communication to induce positive or negative feelings or stimulate action	
15.3 Focus on past success: advise to think about or list previous successes in performing the behavior	Suggest the subjects to think about or list the successful experience of a certain behavior (quit smoking and drinking) before to convince him that he can also develop the habit of scientific exercise or diet
15.1 Verbal persuasion about capability	Tell the subjects that they can successfully increase their physical activity
13.5 Identity associated with changed behavior	Ask the subjects to articulate their new identity as "ex-inactive person"
Incentivization: creating an expectation of reward	
10.2 Material reward (behavior)	Arrange for the subjects to receive WeChat red packet (money)
10.6 Nonspecific incentive	Indicates a happy mood for completing the task, such as instructing the subjects to imagine that he has successfully completed today's exercise task, sweating profusely, and feeling happy
Coercion: creating an expectation of punishment or cost	
—[c]	—
Training: imparting skills	
8.1 Behavioral practice or rehearsal	Ask subjects to continue to rate their diet for 7 days
15.4 Self-talk	Encourage the subjects to use talk to themselves (aloud or silently) before and during exercise to encourage, support and maintain action, like "I Can!"
Restriction: using rules to reduce the opportunity to engage in the target behavior (or to increase the target behavior by reducing the opportunity to engage in competing behaviors)	
—	—
Environmental restructuring: changing the physical or social context	
12.6 Body changes	Remind the subjects to stretch before and after exercise (except health care type) to prepare their bodies
12.2 Restructuring the social environment 3.1 Social support	Encourage the subject to invite family members or friends to exercise together
Modeling: providing an example for people to aspire to or imitate	
—	—
Enablement: increasing means or reducing barriers to increase capability (beyond education and training) or opportunity (beyond environmental restructuring)	
1.1. Goal setting (behavior)	Determine the weekly exercise time based on exercise prescriptions
2.7 Feedback on outcomes of behavior	Feedback on diet score and comprehensive evaluation
2.4 Self-monitoring of behavior	Provides a subjective method to assess exercise intensity and allows subjects to self-monitor
1.9 Commitment	Sign a contract with subjects that they can do healthy behavior
1.4 Action planning	Prompt planning of a particular physical activity (running) at a particular time (before work) on certain days of the week

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Intervention functions and BCTs	Examples
1.5 Review behavior goals	Examine how well subjects' performance corresponds to agreed goals such as exercise 30 minutes at a time
1.6 Discrepancy between current behavior and goal	Compare the difference between the real exercise volume and the target volume
7.1 Prompts or cues	Send medication reminder to subject
8.3 Habit formation	Ask the subjects to check in on sports and upload photos of their diets every day
7.3 Reduce prompts or cues	Reduce medication reminders
1.2 Barrier identification or problem solving	Analyze the reasons (information are collected by questionnaire) for impeding movement and provide solutions (according to intervention manual)
4.2 Information about antecedents: advise to keep a record of situations or events occurring prior not to exercise	Record the reasons for not exercising
11.2 Reduce negative emotions	Instruct the subject to perform relaxation exercises in situations when exercise brings about negative emotions

[a]BCTs: behavior change techniques.

[b]BCW: behavior change wheel.

[c]Not available.

Validation of WHBDIP

The WHBDIP (health education content and intervention plan) has been validated through a 2-round Delphi survey by a panel of experts. The panelists consisted of 15 experts, including 4 nutritionists and 1 professor of nutriology, 2 clinical cardiologists, 3 clinical nurses or nursing teachers, and 5 exercise-related experts. All of them held a bachelor's degree or higher and had at least 5 years of work experience in their respective fields. The panelists were divided into 3 groups to evaluate the content's appropriateness and relevance for exercise, diet, and BP monitoring or MA management. The content validity index (CVI) was calculated using item-level content validity index (ICVI) and rated on a 4-level scale. In the first round, the ICVI ranged from 0.6 to 0.8. Based on the experts' comments, the content was modified. In the second round, the ICVI reached 1.

Intervention Procedure and Monitoring

Prior to the experiment, we conducted a physical examination on the subjects at the intelligent health hut and used the system to generate intelligent exercise prescriptions. Health behavioral digital intervention was provided to the experimental group by 5 trained interventionists through WeChat. The interventionists sent health education materials, specific text (such as reminders to take medicine or exercise), or electronic questionnaires according to the intervention manual's procedures. They collected data or pictures about exercise, diet, self-measured BP, and medication every day during the initial 3 months. The control group received routine health interventions, including oral health education about printed exercise prescriptions, dietary guidance, BP monitoring, and the importance of regular medication. After the program, they will have free access to health education electronic materials.

Randomization, Allocation, and Blinding

This study followed a process of randomization. Before randomization, an individual not involved in subject recruitment and data collection used the SPSS software (version 23; IBM Corp) to generate 68 random numbers and assigned them to either 1 (experimental group) or 2 (control group) using visual binning. These 68 sets of random numbers were printed separately and sealed in individual envelopes. After recruiting a participant, the facilitator opened the envelopes sequentially, and the number found inside each envelope determined the group to which the particular participant belonged. In this study, we blinded data collectors both before and after the trial.

Ethics Approval

This study received approval from the Ethics Committee of Bengbu Medical College (2022-103) in June 2022. Informed written consent forms were obtained from parents with hypertension prior to the start of the study. All the participants agreed to the anonymous use of their data. Upon completing the intervention and data collection at the community health center, the participants were provided with 50 RMB (based on the current exchange rate of US $1=7.29￥, here it is about US $6.86) worth of daily necessities.

Outcomes

Primary Outcomes

BP will be measured using a cardiovascular function monitor (BX-CFTI-100, Institute of Intelligent Machines) at 3 time points: the first baseline assessment phase (T0), the 12-week end point assessments phase (T1), and the end of the 1-year program (T2). The assessment details have been published elsewhere [32].

Exercise adherence (EA), DA, MA, and BPMA indicators were collected once a week through WeChat for the intervention group until T1. The BPMA will also be collected at T0, T1, and

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T2 for the control group. The exercise adherence indicator was calculated as the ratio of actual exercise time that meets the prescription's recommended intensity to the total time of the prescription-recommended intensity. PAT will be measured as an indicator by questioning subjects in both groups at T0, T1, and T2 about the type, duration (in minutes), and frequency (per week). It will be measured using the minutes or metabolic equivalent per week. The MA indicator will be measured at T0, T1, and T2 for both groups using the Modified Morisky Scale (Chinese version-MMS-8, Certificate Number: 8538-1877-1559-6025-5310) [34-36], which includes 8 simple questions. The rating is “poor medication adherence” for a final total score of <6 points, “moderate medication adherence” for a score of 6-7, and “good medication adherence” for a score of 8. Dietary adherence (DA) will be assessed at T1 and T2 for both groups based on their compliance with the “types of diet” and the “recommended amount of diet” (3 response levels for each question).

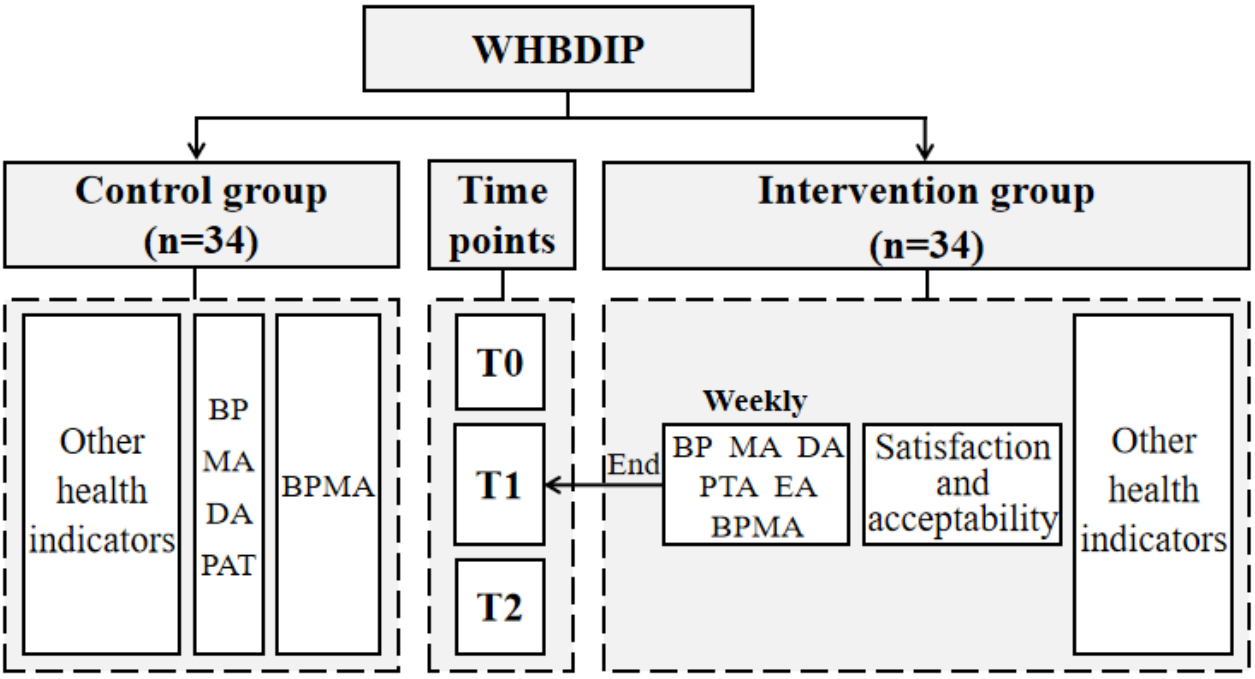
Secondary Outcomes

Cardiovascular function indicators and body composition indicators will be assessed at T0, T1, and T2 in the community health center. Specific details have been published elsewhere [32]. Learning performance of health education knowledge will be evaluated using a comprehensive self-made questionnaire about the material at T0 and T1. Satisfaction and acceptability of this program were assessed at T1 for the intervention group through face-to-face interviews using 3-5 semistructured questions. The questions included: (1) “Do you find the program useful?” (2) “Is it worth your time?” and (3) “Would you feel confident recommending this program?” These questions were used in previous studies [37].

Data Collection and Management

Health-related data will be collected and entered into the intelligent health promotion system at T0, T1, and T2. During the intervention, data for the intervention group were collected using WeChat (as shown in Figure 2). An independent data manager checked the database every week to ensure its integrity. Data lockup is being implemented to prevent any postmodification.

Figure 2. Figure 2. Study flowchart. BP: blood pressure; BPMA: blood pressure monitoring adherence; DA: dietary adherence; EA: exercise adherence; MA: medicine adherence; PAT: physical activity time; WHBDIP: WeChat-based health behavioral digital intervention program.



Statistical Analysis

All analyses will be performed using SPSS. Continuous variables will be presented as mean and SD values. Categorical variables will be expressed as numbers and percentages. Independent samples *t* tests and chi-square tests will be conducted to assess the significance of differences in baseline characteristics or outcomes between the control group and intervention group at 3 time points: before the start of the intervention, 12 weeks after the intervention, and 1 year after the program. Paired *t* tests and McNemar's test will be used to compare the differences in some outcomes before and after the 3-month intervention, as well as before the trial and after the end of the program. A *P* value of less than .05 will be considered statistically significant.

Results

The study was funded in December 2021. The WHBDIP trial was approved by the Ethics Committee of Bengbu Medical College in June 2022 (2022-103) and registered in August 2022 (ChiCTR2200062643). Patient recruitment for those with hypertension started on September 5, 2022, and was completed on September 19, 2022. The 3-month intervention and phased

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data collection were completed in January 2023. Data analysis will commence in August 2023, and the final 1-year health outcome results will be collected in September 2023. We expect the primary outcomes to show changes in adherence indicators during the 3-month intervention, and health outcomes, including BP and other cardiovascular indicators, to change after the intervention and 1 year later. Furthermore, we will report on dropout rates and reasons for dropout during the trial.

Discussion

The WHBDIP is a WeChat-based digital health program that aims to improve the self-management of BP and promote adherence behavior change among patients with hypertension. If the effectiveness of WHBDIP can be verified, it may be attributed to several key characteristics. First, all interventions were developed based on robust evidence, and we further optimized them. Similar to DASH, a proven effective diet for patients with hypertension, we have created a map of food portions tailored to the dietary characteristics of Chinese people and included beverage options in the scoring table. Second, WHBDIP is a theory-based intervention tailored to patients with hypertension. We specified the target behavior (adherence) and conducted a scientific and systematic procedure to identify the appropriate functions from the 9 behavior functions. We then selected the corresponding BCTs from Michie et al's [33] taxonomy based on the BCW. These BCTs were compiled into the intervention manual, which will serve as the foundation for the development of the mHealth intervention program. Third, we provided tailored interventions, including intelligent personalized exercise prescriptions and different intervention contents for adherence. For example, people with different movement barriers require different persuasion techniques. Fourth, we provided one-to-one web-based health services, which could increase participant satisfaction. Fifth, this trial involved health-related professionals and followed a community-based telehealth intervention approach. Finally, we designed this trial to meet methodological demands, including adequate power, allocation concealment, and necessary blinding.

If the WHBDIP is proven to be effective, it could be integrated into the upcoming eHealth promotion program. We will develop community-based apps to promote the management of patients with hypertension, including patient terminals and health service provider terminals. The app will deliver personalized e-interventions, such as reminders, videos, and other content, to patients through specific logic that incorporates behavioral change techniques. This will enable the manual intervention to be automated. It may serve as an alternative, convenient, and cost-effective approach, deserving further experimental verification, for doctors and nurses in primary health care institutions to provide tailored and consistent health services for patients with hypertension.

The study has some limitations. First, due to the nature of the intervention, interventionists in this trial cannot be blinded. To reduce the impact, we provide detailed training and an intervention manual to minimize the subjective influence of interventionists. This way, interventions can be standardized as much as possible. Second, some outcome measures rely on patient self-report scales, which may somewhat affect the reliability of the results.

Acknowledgments

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Data Availability

Data sharing is not applicable to this paper, as the trial is not finished. The data that will be collected at the end of the trial will be described in the next paper, which will be published in a future paper when the data become available.

Conflicts of Interest

None declared.

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Abbreviations

BCT: behavior change technique
BCW: behavior change wheel
BP: blood pressure
BPMA: blood pressure monitoring adherence
CVI: content validity index
DA: dietary adherence
DASH: Dietary Approaches to Stop Hypertension
DBP: diastolic blood pressure
EA: exercise adherence
ICVI: item-level content validity index
MA: medicine adherence

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mHealth: mobile health
PAT: physical activity time
SBP: systolic blood pressure
SDGDIS: simplified DASH grading diet index score
WHBDIP: WeChat-based health behavioral digital intervention program

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Protocol

Internet-Based Cognitive Behavioral Therapy and Virtual Reality Exposure Therapy for Social Anxiety Disorder: Protocol for a Randomized Controlled Trial in Hong Kong

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Abstract

Background: Social anxiety disorder (SAD), also known as social phobia, is one of the most common mental disorders worldwide. In Hong Kong, the prevalence of SAD is high, but its treatment rate is low. SAD has immense impact on academic or work performance, social life, career development, and quality of life. One of the most effective treatments for SAD is cognitive behavioral therapy (CBT), with internet-based CBT (iCBT) and virtual reality exposure therapy (VRET) showing promise in treating SAD. However, internet interventions are underdeveloped in Chinese communities including Hong Kong.

Objective: This study aims to develop an iCBT program that includes VRET, called "Ease Anxiety in Social Event Online" (Ease Online), for Hong Kong adults with SAD in a randomized controlled trial.

Methods: The 14-week Ease Online program is a guided self-help iCBT program with a blended mode of service delivery. The program comprises 9 web-based modules and 5 individual counseling sessions (including 2 VRET sessions) conducted remotely or face-to-face with a therapist to provide therapist support, as guided iCBT shows superior effects than unguided iCBT. Other program components include therapist feedback on assignments, internal messages, forums, client portfolios, web-based questionnaires, reminders, and web-based bookings. The program can be accessed either through a mobile app or program website through a PC with an internet connection. The participants are openly recruited and screened using a questionnaire and through an intake interview. Eligible participants are randomized by placing them into a web-based iCBT group, app-based iCBT group, or a waitlist control (WLC) group. Participants in the WLC group are assigned to the app-based program upon completion of the service of the 2 experimental groups. Measurements of social anxiety, depression and anxiety symptoms, psychological distress, automatic thoughts, and quality of life are administered at pretest, posttest, and 3- and 6-month follow-ups. Multivariate ANOVA with repeated measures will be performed to determine the intervention effectiveness on the continuous variables over time.

Results: Participant recruitment commenced in January 2021. As of February 2023, a total of 1811 individuals applied for the Ease Online program. In total, 401 intake interviews have been completed, and 329 eligible participants have joined the program, among whom 166 have completed the service. Data collection is still ongoing, which is expected to be completed in March 2024.

Conclusions: This study is the first of its kind in combining iCBT and VRET for the treatment of SAD in Hong Kong. At a theoretical level, this study contributes to the development and evaluation of internet-based psychological interventions in Hong Kong. At a practical level, the Ease Online program may serve as an alternative service option for SAD clients in Hong Kong if proven effective.

Trial Registration: ClinicalTrials.gov NCT04995913; https://clinicaltrials.gov/study/NCT04995913

International Registered Report Identifier (IRRID): DERR1-10.2196/48437

(JMIR Res Protoc 2023;12:e48437) doi:10.2196/48437

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KEYWORDS

internet-based cognitive behavioral therapy; virtual reality exposure therapy; social anxiety disorder; Chinese; CBT; iCBT; internet; virtual reality; anxiety; social phobia; mental disorder; mental health; quality of life; treatment; cognitive behavioral therapy; psychological intervention

Introduction

Background

Social anxiety symptoms have increased significantly during the COVID-19 pandemic [1]. Social anxiety disorder (SAD) is one of the most common mental health problems, yet few seek treatment [2]. Individuals with SAD experience excessive fear and anxiety during social interactions, which is disproportionate to the social situation itself. SAD often involves negative evaluation and rejection by others and a constant fear of embarrassment or humiliation [3]. Therefore, individuals with SAD often avoid social interactions, which may have detrimental impacts on most areas of life, including their career, education, social relationships, and mental health [4]. Social anxiety usually emerges during performance situations (such as job interviews, public presentations, or attending a meeting) and interpersonal situations (such as greeting someone, drinking and eating in public, taking part in social gatherings, or shopping). In Hong Kong, the 12-month prevalence rate of SAD is reported to be 3.2% [5], which translates into an estimated 230,000 cases. However, only 8.7% of people with SAD in Hong Kong had previously sought treatment [5].

People with SAD face certain treatment barriers that prevent them from seeking mental health services, including fear of judgement, uncertainty of the resources for receiving help, and skepticism regarding anxiety disorders [6]. In Hong Kong, the barriers also include the social and self-stigmas of mental illnesses, long waiting lists for public health care, and exorbitant costs of private treatment. However, people with SAD consider the internet as a good social outlet, which not only helps them to alleviate their fear during general social interactions but also meets their social needs [7].

Cognitive behavioral therapy (CBT) is the first-line treatment for SAD [8]. Clark and Wells [9] proposed a cognitive model of social anxiety that considers social cognition, safety behaviors, self-focused attention, and somatic symptoms as the maintaining factors of social anxiety. Thus, the effective treatment components of CBT for SAD primarily include exposure to fearful conditions, cognitive restructuring, attentional bias modification, and relaxation and social skills training [10]. Telemental health services, including internet-based CBT (iCBT) and virtual reality exposure therapy (VRET), have become a worldwide trend for the treatment of mental health problems, particularly SAD, which can reduce the therapist's time required for each client [11]. For example, the average time spent in VRET is 8 minutes per session [12], and the therapist's time in iCBT can be saved by more than half for the same level of reduction in social anxiety [13].

iCBT for SAD

iCBT is used to deliver CBT on the web or through a mobile app. In a recent meta-analysis study, Andrews et al [14] showed that there are no significant differences between iCBT and face-to-face CBT in their efficacy for treating anxiety and depressive disorders, thus indicating equivalent overall effects elicited by both types of treatments. Their study also lends support to the effectiveness, acceptability, and practicality of iCBT for treating anxiety disorders. A number of randomized controlled trials (RCTs) have demonstrated the effectiveness of guided iCBT in reducing general and social anxieties, avoidance, depression, and dysfunctional thinking, as well as improving the quality of life and functioning of people with SAD [15-19]. Guided iCBT programs for SAD have shown promising diagnostic response rates [20] with complete and partial recovery rates of 34.2% and 36.8%, respectively, upon completion of the treatment [19]. The positive treatment effects are maintained at the 6-month [19], 1-year [15], 2-year [21], and 4-year [22] follow-ups. Therapist contact is reportedly a significant predictor of intervention outcomes in guided iCBT programs for SAD [23]. Therapist support is usually provided via telephone, email, videoconferences, SMS text messages, and web-based discussion forums [17,24].

The intervention skills in the various iCBT programs for SAD generally include psychoeducation, cognitive restructuring, behavioral experiments, exposure and reality testing, modifying attention bias, social skills training, developing healthy lifestyles, problem-solving, and preventing relapses [15,20,21]. The presentation formats of the iCBT program involve text, images, audio, video, text entry fields, animation, comic slides, e-books, etc [24]. Interventions include monitoring moods, performing exposure exercises and homework assignments, writing a web-based diary, answering essay questions, participating in user forums, and receiving emails or text message reminders, and awards [17,18].

VRET for SAD

One of the central components of CBT for SAD is exposure therapy in which clients are exposed to social stimuli that cause anxiety while eliminating safety behaviors so that they learn and understand that the anticipated negative consequences are ill-founded [3]. Exposure therapy can activate and modify anxious responses by having individuals confront the fear stimuli and via habituation and extinction learning, respectively, in which the fear stimuli then cease to provoke anxious responses or render them less threatening. Given that in vivo exposure therapy in real life is not frequently offered, VRET has become an important alternative for reproducing social situations [3]. Computer graphics, body tracking devices, visual displays, and other sensory input devices are integrated to immerse clients in a computer-generated virtual environment [25]. As virtual reality (VR) can elicit moderate levels of sense of presence and anxiety during virtual social interactions [26], VRET has become a promising application for treating SAD.

Meta-analyses have consistently found a significantly large effect size for VRET compared to a waitlist or psychological

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placebo conditions for SAD treatment, and no significant difference in effect size between VRET and in vivo or imaginal exposure therapy [27,28], thus indicating that VRET is effective for SAD treatment with effects comparable to those of traditional exposure therapy. Specifically, VRET is effective in reducing social anxiety symptoms, such as fear and avoidance, fear of negative evaluation, self-reported public speaking anxiety, catastrophic belief expectancy, probability and cost biases, distress, perceived stress, and depressive symptoms, and increasing the length of speech time, perceived performance quality, and confidence [2,16,29,30]. The positive effects are maintained at the 3-month, 6-month, 12-month, 5.5-year, and 6-year follow-ups [29,31,32]. More than half of treated individuals no longer meet the diagnostic criteria for SAD (54%) and self-reported to be "very much" or "much" improved (68%) 6 years after treatment [31]. Thus, VRET is considered an efficacious alternative to in vivo exposure therapy [27].

Both psychological and physiological indicators are measured in VRET studies. The commonly used psychological indicators include self-reported anxiety and fear, distress, and self-confidence [33,34]. As anxiety often emerges in the form of physical symptoms, VRET studies have measured physiological responses, such as blood oxygen level [35] and heart rate [36].

This Study

Technology-assisted CBT programs have great potential to extend mental health services to people with social anxiety who are unwilling or unable to seek face-to-face therapy [23]. However, these programs are underdeveloped in Chinese societies, such as Hong Kong. This study has, therefore, developed an iCBT program with VRET, called "Ease Anxiety in Social Event Online" (Ease Online), for Hong Kong adults with SAD in an RCT.

Methods

Participants

To be included in the study, participants should be Hong Kong residents who (1) are fluent in Cantonese, (2) are aged between the 18 and 70 years, (3) obtained a score of 24 or higher on the Chinese version of the Social Phobia Inventory (SPIN) [37], (4) have a social anxiety disorder as assessed by the Structured Clinical Interview for disorders listed in the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition [38], (5) have not received any psychological treatment at the time of registration for participation in this study, (6) have access to a computer or smartphone with an internet connection, and (7) have a valid email address. We will exclude individuals who have (1) severe depression, with a score above 30 on the Beck Depression Inventory-II (BDI-II) [39]; (2) suicidal risk in the past 3 months (score of item 9 on the BDI-II is "2" or "3" and assessed to have suicidal risk in the intake interview); and (3) a severe psychiatric condition (eg, bipolar disorder, schizophrenia, or personality disorder) diagnosed by a psychiatrist or clinical psychologist.

Sample Size

The sample size was calculated by using a computer program called G*Power (version 3.1.5; Universität Düsseldorf). The statistical method used was a multivariate ANOVA with repeated measures (within-between interactions). The effect size was assumed to be 0.40 (large) [40]. The number of groups was 3 (2 experimental groups and 1 control group) and 7 measures applied (please see the *Outcome Measures* section). The α value was set at .01. The calculations resulted in a minimum sample size of 139. This study aims at recruiting 330 eligible participants, with 110 in each experimental group and the waitlist control (WLC) group, respectively.

Participant Recruitment and Screening

Participants were recruited from the general population on an ongoing basis through various means, such as advertisements on social media (Facebook and Instagram) and Google, press conferences, posters, and referrals from local nongovernmental organizations. Interested participants were asked to complete a screening questionnaire that includes the Chinese version of the Beck Anxiety Inventory (C-BAI), BDI-II, and Chinese version of the SPIN on the program website [41]. Initially qualified participants were invited for a 1.5-hour intake interview in person or via Zoom with a psychological counselor or an experienced social worker for further assessment of suitability for participation (including assessment of suicidal risk and social anxiety disorder based on the diagnostic criteria of the Structured Clinical Interview for disorders listed in the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition [38]). Marginal cases were discussed in a case meeting (which involved author J-YP, an intake worker, and a program therapist) for participation eligibility. A project assistant contacted the eligible participants to reconfirm their desire to participate before randomization took place. High-risk individuals with severe depression or suicidal risk (or both) identified at the screening stage were referred to the local mental health service sectors for further diagnosis and treatment with their consent.

Research Design

Although deterioration in a control condition can take place [42], Steinert et al [43] conducted a meta-analysis and found only small changes in the WLC groups during short-term wait periods for clients with SAD in RCTs. Thus, this study adopts a WLC group design to conduct a 3-arm RCT as shown in Table 1.

There were 2 experimental groups that joined either the web-based or app-based iCBT program (Ease Online). The WLC group received the app-based treatment immediately after the 2 experimental groups completed the program. All 3 groups completed the same web-based questionnaire at pretest, posttest, and 3- and 6-month follow-ups. The WLC group completed the questionnaire one more time at posttest after the 2 experimental groups completed the program. To increase the submission rate of questionnaire, participants were given 2 more weeks to submit an email questionnaire after the submission deadline in the program system. The RCT was conducted in cohorts for implementation feasibility. Specifically, in each cohort, around 30 qualified participants were randomized into one of the 3

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groups through computer-generated random numbers, with approximately 10 in each group. The program evaluators were blinded to the allocation of the participants. The participant recruitment flowchart is shown in Figure 1.

Table 1. Participant group design.

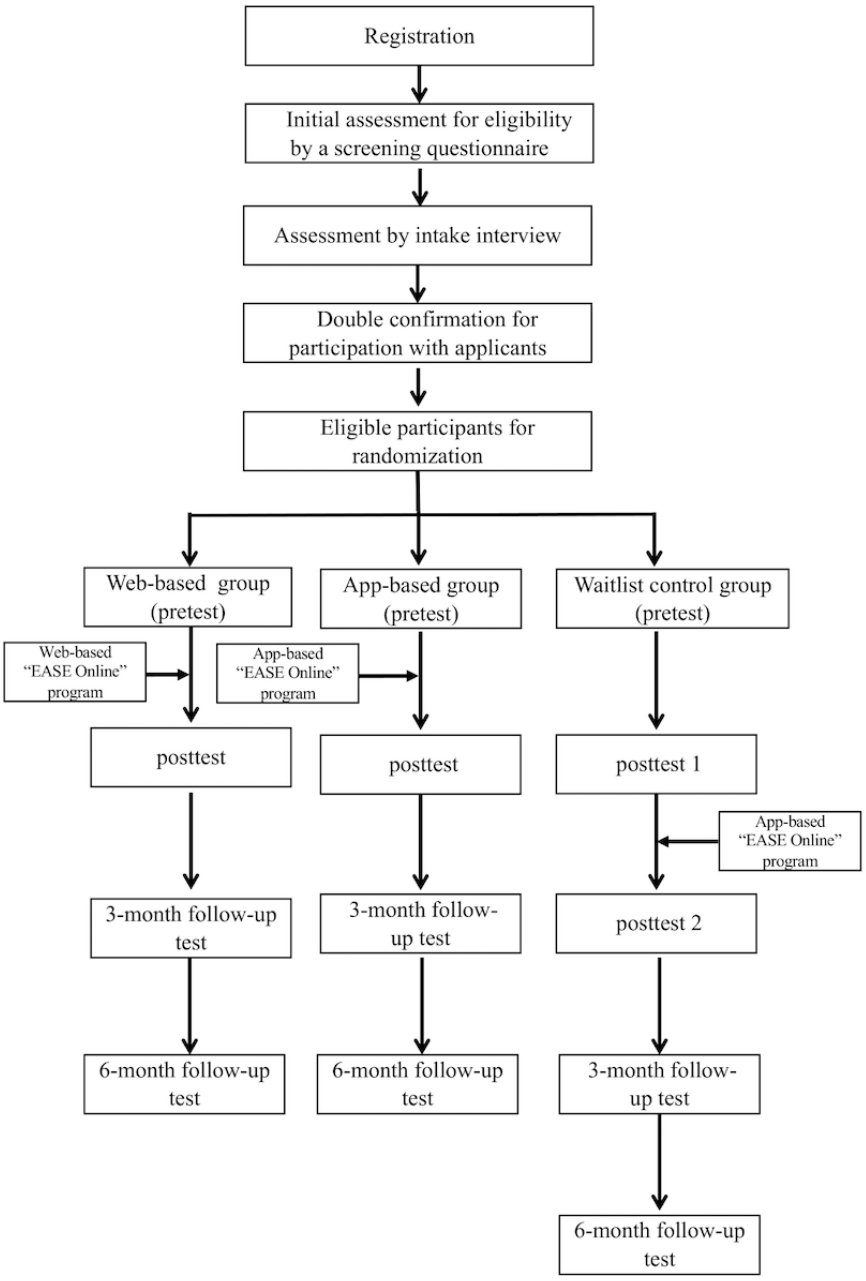
Groups	Research design						
Web-based	O[a]	X[b]	O		O	O	N/A[c]
App-based	O	X	O		O	O	N/A
Waitlist control	O		O	X	O	O	O

[a]O: test.

[b]X: intervention.

[c]N/A: not applicable.

Figure 1. Flowchart for participant recruitment in this study. Ease Online: Ease Anxiety in Social Event Online.



Intervention: the Ease Online Program

The Ease Online program is 14 weeks in duration. The program adopts a blended mode of service delivery as guided self-help iCBT has demonstrated lower attrition than nonguided self-help iCBT [18], and therapist contact has been found to be a significant predictor of retention and outcomes [23]. The

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program consists of 9 web-based modules and 5 individual counseling sessions (including 2 VRET sessions). The program contents were developed on the basis of the CBT model developed by Beck [44] and CBT delivered to Chinese clients by Wong [45] and Pan and Zhuang [46]. Specifically, a variety of cognitive behavioral skills for coping with social anxiety are introduced in the 9 web-based modules, each with a specific theme. The themes of the nine web-based modules are (1) recognizing your social anxiety responses, (2) identifying automatic thoughts and cognitive distortions, (3) self-talk and positive statements, (4) behavioral experiment, (5) fear hierarchy, (6) exposure therapy, (7) identifying cognitive rules, (8) relaxing dysfunctional cognitive rules, and (9) saying bye-bye to social anxiety. The CBT skills are briefed and debriefed by using an animation video and demonstrated through 4 case videos. Each web-based module starts with a mood check for social anxiety in the past week and ends with a session review and an assignment that helps clients to apply the learned skills to cope with their own social anxiety. Other components of the program include therapist feedback on assignments, internal messages, forums, client portfolios, web-based questionnaires, reminders, and web-based bookings. An introduction video of the program provides a navigation on all of the program components after the clients log into the system. The client platform has a web-based version in which clients can log into the program website or a mobile app that can be downloaded through Google Play or Apple Store. After being randomized into the program, clients were provided an account to log into the system. Clients who are assigned a PC web account cannot log in through the app and vice versa. All clients were assigned to a therapist who not only provided web-based feedback on their assignments and responded to their private messages, but also offered 5 individual counseling sessions that monitored the progress of the clients and addressed any challenges that the clients encountered when working on the web-based modules. There is also a backstage management platform for the therapist, which offers different functions including creating cohorts, managing bookings and forums, providing feedback on client exercises, monitoring client progress, etc. The therapist helped the clients understand and review the module contents and apply the CBT skills into their own situations in 5 individual counseling sessions that were conducted either in person or on Zoom or WhatsApp.

A VR system for exposure therapy has also been developed for this program, which includes 5 virtual scenarios: (1) interviewing for a job, (2) delivering a presentation, (3) participating in work performance evaluation, (4) expressing disagreement, and (5) drinking in public. The VR system uses an 180° video of real humans. There is a storyline for each VR scenario and a couple of interactions between the client and the VR environment, which are guided by a prerecorded voice-over. The clients wear a head-mounted display and respond by moving their head. The voice responses of the clients are recorded in the VR system for replay. The technologies used for the development of the VR system include voice recording, VR180 stitching, VR game engine development, VR motion tracking on the target point, and an auto-trigger based on the user's headset direction. An administration control panel has been developed for the therapist to control the VR interaction. In the beginning of each VRET session, the therapist provides a short briefing and asks the client to choose one VR scenario. Then, the client participates in the VRET for no longer than 15 minutes. The therapist then proceeds to debrief the client upon completion of each VRET session and submits a session report on the Ease Online system. Examples of VRET photographs are shown in Figure 2.

The program sessions outlined in Table 2 are released to the client on a weekly basis. The treatment schedule is programmed into the Ease Online system. Progress is recorded as a score when the client completes a task, and a total score is calculated as the total progress. All of the program videos are tailored for Hong Kong people and developed from local cases. The Cantonese language is used in the program. To ensure data security and privacy, 2-factor authentication is adopted when logging in with a password that is preset by the user and a one-time password sent to his/her email address. All of the collected electronic data are encrypted. The program is hosted on the server of the Information and Technology Office of the university where the author is employed. Before the program launched, a user acceptance test was conducted by the author and project staff, and bugs were fixed accordingly by the programmer of this project.

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Figure 2. Examples of images in virtual reality exposure therapy. (A) Client wearing a head mounted display. (B) Control panel of the VR system. (C) Virtual scenario of work performance appraisal. (D) Virtual scenario of expressing disagreement. VR: virtual reality.



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Table 2. Structure and content of the Ease Anxiety in Social Event Online program.

Week	Session	Mode	Theme
0	F0	F2F[a]	Intake interview
1	1	Web– or app–based	Recognizing your social anxiety responses
2	2	Web– or app–based	Identifying automatic thoughts and cognitive distortions
3	3	Web– or app–based	Self-talk and positive statements
4	F1	F2F	Counseling session (1)
5	4	Web– or app–based	Behavioral experiment
6	5	Web– or app–based	Fear hierarchy
7	6	Web– or app–based	Exposure therapy
8	F2	F2F	Counseling session (2)
9	F3	F2F	VR[b] exposure therapy (1)
10	F4	F2F	VR exposure therapy (2)
11	7	Web– or app–based	Identifying cognitive rules
12	8	Web– or app–based	Relaxing dysfunctional cognitive rules
13	9	Web– or app–based	Saying bye-bye to social anxiety
14	F5	F2F	Counseling session (3)

[a]F2F: face-to-face session (in-person or on Zoom/WhatsApp).

[b]VR: virtual reality.

Therapist Credibility

The therapist for the Ease Online program has a master's degree in counseling (clinical mental health) and is registered as a certified counselor in both the United States and Canada. She has 9 years of counseling experience in Hong Kong. The intake worker is a registered social worker in Hong Kong who has a bachelor's and a master's degree in social work and counseling experience that spans more than 30 years in a variety of settings. The intake interviews were conducted by both the therapist and the intake worker, and all the service and initial screenings were delivered and conducted by the therapist—both are native Cantonese speakers.

Compliance With the Intervention

Several strategies were adopted to ensure compliance with the intervention: (1) progress reports were completed and submitted by the therapist after each individual counseling session to record the understanding of the clients of the web-based modules and their difficulties in learning them, and applying CBT skills to cope with their own social anxiety; (2) the therapist completed and submitted a progress report in the system after each VRET session to record the session contents, including the VRET experience of the client, skills that the clients have learned to cope with social anxiety, and client feedback; the VRET process was recorded for debriefing in each VRET session; and (3) all the tasks completed by the clients were recorded in the system. A reward score was assigned to clients when they completed a task. Clients were provided a program workbook as an incentive if they completed 80% of the intervention contents.

Outcome Measures

Primary Outcome Measures

The Chinese version of the SPIN [37,47] was used to assess the severity of social phobia symptoms. The measure consists of 17 items with 3 subscales: fear, avoidance, and physiological response. Participants were asked to rate their distress for each symptom during the past week on a 5-point Likert scale that ranges from "0" (not at all) to "4" (very much so). All of the item scores were summed up into a total score that ranged from 0 to 68, with a higher score indicating a higher level of anxiety. Sample items included "fear of others watching," "avoid talking to others," and "feeling bothered by blushing." The α coefficient is .89 for the Chinese version of the SPIN [37].

Secondary Outcome Measures

The C-BAI [48,49] was used to measure the cognitive and somatic symptoms of anxiety. Participants were asked to rate 21 items on a 4-point Likert scale. Item scores were summed, with a higher total score indicating a higher level of anxiety. Sample items included "unable to relax" and "heart pounding or racing." The α coefficient is .95 for the C-BAI [49].

The Chinese version of the BDI-II [39,50] was used to measure depressive symptoms. Participants were asked to rate 21 items on a 4-point Likert scale. The item scores were summed, with a higher total score indicating a higher level of depression. Sample items included "sadness" and "loss of pleasure." The α coefficient is .86 for the Chinese version of the BDI-II [50].

The Chinese version of the General Health Questionnaire-12 [51] was adopted to evaluate psychological distress. The 0-0-1-1 scoring method was used to calculate the scale score (which ranged from 0 to 12), with higher scores indicating higher levels

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of psychological distress. The Cronbach α is .87 in a Hong Kong Chinese sample [52].

The Chinese Automatic Thoughts Questionnaire [53] contains 14 items for assessing positive and negative automatic thoughts. Participants were asked to rate the frequency of each thought in the past week on a 5-point Likert scale (which ranged from 1="not at all" to 5="all the time"). Item scores were summed up as the 2 subscale scores, with higher scores indicating more positive and negative automatic thoughts, respectively. Sample items included "I am worthless" and "No matter what happens, I know I'll make it." The Cronbach α is .83 in a Hong Kong Chinese sample [53].

The Chinese adaptation of the abbreviated version of the World Health Organization Quality of life Scale [54] was used to assess quality of life. This measure consists of 28 items, including 2 items that measure the overall quality of life and 26 items that measure physical and psychological health, social relationships, and the environment. Each item was rated on a 5-point Likert scale that ranged from 1="very dissatisfied" to 5="very satisfied," with a higher score indicating better quality of life. The Cronbach α ranges from .59 to .78 and test-retest reliability ranges from 0.72 to 0.83 for this scale [54].

The Chinese version of the Internalized Stigma of Mental Illness scale [55,56] was used to evaluate the subjective experiences of self-stigma on mental illness. The measure consists of 24 items and 4 subscales: shame or alienation, stereotype endorsement, perceived discrimination, and social withdrawal. Participants were asked to rate items on a 4-point Likert scale that ranged from 1="strongly disagree" to 4="strongly agree." All items were averaged as a scale score, with a higher score indicating a higher level of self-stigma. The Cronbach α is .93 in a Hong Kong Chinese sample [56].

In addition, before and after each VRET session, physical arousal through heart rate and blood oxygen levels were measured with a smart watch that the clients wore on their wrist.

Ethical Considerations

Ethics approval was granted by the Human Research Ethics Committee (REC/18-19/0241) of the Hong Kong Baptist University. Participation in this study is voluntary and free of charge. Participants could withdraw at any time without any repercussions. High-risk cases identified at the screening stage were referred to local nongovernmental organizations or governmental social service sectors upon the consent of the applicant. Each participant was assigned a code number for identification in the program database to protect their privacy and anonymity.

Data Analysis

Intent-to-treat analysis, which is the least biased way to estimate an intervention's effects [57], was used for data analysis. Missing data will be managed using multiple imputation [58]. Multivariate ANOVA with repeated measures will be performed to test the intervention's effectiveness on continuous variables over time. Time (pretest, posttest, and 3- and 6-month follow-ups), condition (web-based iCBT, app-based iCBT, and WLC), and the interaction of time-by-condition will be specified as the categorical fixed factors. Medication and demographic factors (eg, gender, age, and marital status) will be specified as fixed covariates to control the potential confounding effects. Cohen *d* will be calculated as the index of the effect size both within and between groups.

Results

The Ease Online program was developed between July 2019 and December 2020 and officially launched in a press conference on January 18, 2021. The principal investigator and project staff have since been involved in promoting the program and recruiting, screening, and referring participants, taking part in intake interviews and case meetings, conducting service delivery and monitoring duties, collecting data, modifying and enhancing the system, providing technical support, responding to enquiries, and other tasks. As of February 2023, a total of 1811 individuals were enrolled in the Ease Online program. A total of 401 intake interviews have been completed, and 329 participants have joined the program, among whom 166 have completed the intervention. A total of 1924 written comments have been provided for client assignments, 604 individual counseling sessions have taken place, and 392 VRET sessions have been conducted. Data collection is still ongoing, which is expected to be completed in March 2024.

Discussion

Overview

SAD often has a high prevalence and low treatment rate. People with SAD often underperform and underachieve. Treatment of SAD can not only improve their achievement and quality of life, but also increase productivity in the society as a whole. This study is the first of its kind in combining iCBT and VRET for the treatment of social anxiety in Hong Kong. At a theoretical level, this study will contribute to the development and evaluation of internet-based psychological interventions in Chinese communities. At a practical level, if proven to be effective, this study will provide an alternative e–mental health service option for people in Hong Kong with easy access. In addition, if adopted by local social service sectors, the Ease Online program will fill in a large service gap between the overwhelming service demand by mental health clients and the insufficiency of mental health professionals in Hong Kong.

Lessons Learnt

In the process of developing the Ease Online program, several lessons have been learnt: (1) considering the extremely low treatment rate of SAD in Hong Kong (8.7%) [5], iCBT serves as a more preferred and accessible treatment option for Hong Kong clients with SAD; flexibility in time and space as well as the web-based format might encourage people with SAD to seek treatment in a way that is less threatening to them. (2) Culturally relevant intervention contents are important. All of the case demonstration videos were tailored for Hong Kong clients with SAD based on local cases, which increases their relevance and resonates with the real-life situations of the clients. The program focuses on working with culturally relevant beliefs related to social anxiety by choosing CBT skills that

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have been suitable for Chinese clients in previous studies; for example, the "pie chart" technique is used to relax the cognitive rule of "I have to make no mistakes to be a good offspring." (3) Compared with cartoons or 3D characters, the use of real humans in VR videos may increase the sense of reality and presence in VR situations. (4) Guided self-help iCBT in service delivery, including therapist support in the form of exercise feedback and counseling sessions, is important to help clients to apply the CBT skills learned from the web-based modules to deal with their social anxiety. (5) Compared to text-based iCBT, Hong Kong people prefer video-based iCBT. As Hong Kong people are generally very busy, they may not have time to read long passages of text. Watching short videos that present the key CBT skills with case demonstration is more acceptable to Hong Kong clients. (6) Participant screening using a screening questionnaire and through intake interviews and case meetings ensures eligibility and screening out of high-risk cases and referring other resources to them. (7) Both the web-based platform and the mobile app are developed as computers and smartphones are widely used in Hong Kong. (8) Aside from psychological assessment, the use of physiological assessments, such as heart rate and blood oxygen levels, in VRET can provide more objective evaluations.

Limitations

There are several limitations of this study that should be considered. First, only completed tasks are recorded in the system, but there are no records of therapist time and use time of the client in the system. User time can be recorded in the system in future research to calculate the average therapist time spent and the amount of time for which the clients use the system. Second, the number of missing data at posttest and follow-up is quite high—this may be related to the busy lifestyle in Hong Kong and nature of free services provided in this study, although various means including email and phone calls have been used to remind clients to complete the web-based questionnaires after the intervention. Different approaches need to be used in future research to increase the response rate of postintervention assessments. Third, although several strategies are adopted ensuring compliance with the intervention, future research may include independent ratings by certified cognitive behavioral therapists of a random selection of the progress reports of the individual counseling and VRET sessions as well as assignment feedback. Fourth, participants are mainly recruited via open recruitment, which may cause recruitment difficulties and a high nonresponse rate after enrollment. Collaboration with local social service sectors is suggested in future research for participant recruitment and follow-up with service delivery and data collection. Fifth, in the VR system, 180° videos are produced, which may limit the view of clients in the VR environment. Future research may aim to develop 360° videos for the VRET system. Finally, 5 VR scenarios are developed in this study; future research may aim to develop more VR scenarios to allow clients to choose social situations that are more relevant to them.

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Conflicts of Interest

None declared.

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Abbreviations

BDI-II: Beck Depression Inventory-II
C-BAI: Chinese version of the Beck Anxiety Inventory
CBT: cognitive behavioral therapy
Ease Online: Ease Anxiety in Social Event Online
iCBT: internet-based cognitive behavioral therapy
RCT: randomized controlled trial
SAD: social anxiety disorder
SPIN: Social Phobia Inventory
VR: virtual reality
VRET: virtual reality exposure therapy
WLC: waitlist control

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Protocol

Effectiveness, Acceptability, and Feasibility of a Telehealth HIV Pre-Exposure Prophylaxis Care Intervention Among Young Cisgender Men and Transgender Women Who Have Sex With Men: Protocol for a Randomized Controlled Trial

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Abstract

Background: Despite its promise for HIV prevention, the uptake of pre-exposure prophylaxis (PrEP) has been slow, and there have been substantial inequities in PrEP access. Young men who have sex with men and transgender women of color are most in need of PrEP and least likely to have that need fulfilled. PrEP telehealth care, which provides remote PrEP care via electronic communication, seems well suited to address several of the challenges of PrEP provision, including discomfort with stigmatizing and difficult-to-access health care systems, transportation challenges, and privacy concerns, and address disparities in PrEP access. Research suggests that PrEP telehealth care has promise and is a favored option for many prospective recipients of PrEP. However, despite growing attention to telehealth approaches as an avenue for increasing access to PrEP amidst the COVID-19 pandemic, there have been no published randomized controlled trials (RCTs) on PrEP telehealth care to date, making it difficult to draw strong conclusions about the advantages or disadvantages of telehealth compared with usual PrEP care. We developed PrEPTECH, a telehealth intervention that focuses specifically on alleviating issues of stigma, access, cost, and confidentiality for young people with risk factors for HIV infection who are seeking PrEP care. Leveraging data from the 2017 observational pilot study, we redesigned and enhanced PrEPTECH.

Objective: This study aims to assess the effectiveness, acceptability, and feasibility of a telehealth HIV PrEP care intervention, PrEPTECH, in increasing PrEP uptake.

Methods: This is the protocol for an RCT of young cisgender men and transgender women who have sex with men in 4 regions within the United States: the San Francisco Bay Area, California; Los Angeles County, California; Miami-Dade County, Florida; and Broward County, Florida. Participants in the intervention arm received access to a web-based telehealth program, PrEPTECH, which offers a fully web-based pathway to PrEP, whereas those in the control arm received access to a dynamic web page containing publicly available informational resources about PrEP. Follow-up data collection occurred at 3 and 6 months. An analysis will be conducted on outcomes, including PrEP initiation, persistence, adherence, coverage, and medication prescription, as well as PrEPTECH acceptability and feasibility.

Results: The study was funded in 2019 and received institutional review board approval in 2020. The PrEPTECH intervention was developed over the next 1.5 years. Study recruitment was launched in February 2022 and completed in September 2022, with 229 participants recruited in total. Data collection was completed in April 2023.

Conclusions: The results of this RCT will offer valuable evidence regarding the effectiveness, acceptability, and feasibility of telehealth HIV PrEP care interventions among young cisgender men and transgender women who have sex with men.

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International Registered Report Identifier (IRRID): PRR1-10.2196/47932

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KEYWORDS

youth; young people; men who have sex with men; transgender women; HIV; pre-exposure prophylaxis; PrEP; effectiveness; acceptability; feasibility; telehealth; web-based intervention; digital intervention; randomized controlled trial; RCT

Introduction

Background

The use of antiretroviral medications as pre-exposure prophylaxis (PrEP) is an effective biomedical HIV prevention approach first approved by the US Food and Drug Administration in 2012 [1]. Copious research has established that HIV PrEP presents few significant safety risks and substantially reduces the likelihood of contracting an HIV infection in individuals at risk when taken consistently. Research has confirmed the effectiveness of PrEP for adolescent men who have sex with men [2] and transgender women [3] when it is taken consistently.

Despite its promise for HIV prevention [4,5], the uptake of PrEP has been slow, although it has improved recently, and there have been substantial inequities in PrEP access. PrEP is indicated for an estimated 1.2 million people in the United States according to the Centers for Disease Control and Prevention, but in 2020, only 24.7% of those for whom PrEP was recommended were prescribed it (compared with approximately 3% in 2015) [6]. There are substantial racial and gender disparities in PrEP uptake. Specifically, 4 in 10 Black/African American men who have sex with men and 2 in 10 Hispanic/Latino men who have sex with men will be diagnosed with HIV infection in their lifetime, compared with only 1 in 10 White men who have sex with men [7]. However, PrEP coverage (the percentage of those with an indication for PrEP who received a PrEP prescription) ranges from 65.4% among White people to 15.7% among Hispanic/Latino people to 9.1% among Black/African American people [6]. The prevalence of HIV among transgender women in the United States is 14%, over 30 times higher than that in the US population overall [8], but a nationally representative study of transgender people found that 3% of transgender respondents who were having sex with cisgender men or transgender women were taking PrEP [9]. People aged 16 to 24 years have the lowest rates of PrEP uptake of any age group, with only 15.6% of those with an indication for PrEP receiving a prescription for PrEP in 2020 (Centers for Disease Control and Prevention) [6]. Adherence to and persistence in the use of PrEP are also less favorable among Black/African American men who have sex with men and youth [10,11]. There is a dearth of research on the rates of adherence to and continuation of PrEP among transgender women [12]. In sum, young people of color, particularly young men who have sex with men and transgender women of color, are most in need of PrEP access and least likely to have that need fulfilled.

Researchers have identified a range of factors that may interfere with initiating and adhering to PrEP, including a lack of awareness or knowledge of PrEP, poverty, health system inaccessibility, stigma, concerns about side effects, competing stressors, and low HIV risk perception [13-17]. Health system factors that impede PrEP access include primary care providers' lack of familiarity or comfort with dispensing PrEP care, racial and ethnic bias, homophobia, and transphobia among health care providers, and distrust in the medical system among potential PrEP recipients [18]. Logistical difficulties, such as the lack of transportation, prevent people seeking PrEP from reaching PrEP clinics, which are sparser in areas with higher poverty, larger Black/African American and Hispanic/Latino populations, and lower rates of insurance coverage [19]. Concerns about insurance and the ability to pay can also present obstacles. Obstacles to the continuation of PrEP include health system barriers, acute medication side effects, decreased sexual risk-taking and perceived HIV risk, and health system factors such as cost and difficulty attending appointments [20-22].

Telehealth or telemedicine, the use of electronic communication to improve patient health [23], seems well suited to addressing many of the challenges of PrEP dissemination and has become increasingly relevant during the COVID-19 pandemic [24]. Telehealth interventions may remove obstacles within the health care system that complicate beginning and remaining on PrEP. Telehealth may simplify the process of obtaining PrEP and lessen the impact of stigma by allowing participants to access PrEP more privately [25]. A survey of a nationwide cohort of men who have sex with men who were HIV negative and had not initiated PrEP found that the vast majority said that they would prefer to undergo follow-up home testing and receive mail-delivered PrEP after an initial in-person appointment to start PrEP care (termed "home-based care" in the study) over regular follow-up at a clinic [26]. Men who were younger or reported being distant from the nearest lesbian, gay, bisexual, transgender, and queer (LGBTQ+)–friendly health care provider were more likely to prefer home-based PrEP care, as were those who had more potential exposure to HIV infection and a stronger intention to start PrEP. A meta-ethnography reviewing data from 11 unique qualitative studies of men who have sex with men in the United States concluded that structural interventions, including telehealth for PrEP, may help circumvent barriers to PrEP for some men who have sex with men, such as difficulty obtaining transportation and maintaining engagement with treatment [14].

Many PrEP care providers, such as health care providers, have generally turned to telehealth approaches because of the evident need for alternatives to in-person care since the beginning of the COVID-19 pandemic [27,28]. A small study of patient

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satisfaction following a clinic's transition to telehealth-delivered PrEP care midpandemic found a preference for telehealth PrEP visits over traditional in-clinic PrEP visits [29]. The ranks of commercial and nonprofit providers of PrEP telehealth care have grown in the past few years, with multiple nationwide companies providing telehealth care, alongside numerous local efforts, in the United States [22].

PrEP Telehealth Delivery

Despite growing attention to telehealth approaches as an avenue for dispensing PrEP, research on PrEP telehealth delivery has been mostly limited to general reports on implementation [30]. PrEP telehealth projects that researchers have reported on include Iowa TelePrEP, a public health–partnered regional PrEP telehealth project; a telehealth extension of a Seattle PrEP clinic; a San Francisco clinic transitioning to a telehealth-focused model in the midst of the COVID-19 pandemic; and PlushCare and Nurx, 2 commercial providers of telehealth PrEP care. Research on user experience and preferences has largely found that patients are receptive to PrEP telehealth and largely report positive experiences. A qualitative report on user experience with the Nurx telehealth PrEP service found strongly favorable responses and appreciation for the service's achievement of a balance between efficiency (simplicity, speed, and convenience) and humanity (feeling of personalized service, connection, and care) [31]. Research on the San Francisco clinic transitioning to telehealth found that telehealth-based care was preferred by many prospective PrEP users because of the convenience and perceived safety of telehealth, whereas technical barriers and unfamiliarity of the platform were considered disadvantages of PrEP telehealth [32]. In addition, in a PrEP telehealth pilot that enrolled 40 participants and provided PrEP to 20 participants, only 13% (n=5) of the participants said that they would have preferred in-person–only PrEP care to exclusive telehealth care or a blend of telehealth and in-person care [33].

The limited research on the rates of PrEP uptake in the PrEP telehealth setting suggests that PrEP telehealth can be effective. Most Iowa TelePrEP clients who completed video-based telehealth visits (91%) started PrEP, and the intervention had a 61% retention rate at 6 months, indicating that widely available technology can be a viable tool for delivering PrEP in small urban and rural settings [25]. In the mixed methods evaluation of their laboratory testing site versus home testing options for routine monitoring, home kit use was associated with higher completion of some tests (extragenital swabs) and lower completion of others (blood tests); self-efficacy in using kits, time, convenience, privacy, and confidentiality were the primary factors influencing the use of home test kits [26]. In addition, a report on the telehealth extension of a Seattle PrEP clinic, which described implementation and compared 10 patients who opted to receive telehealth care with 38 patients who did not opt to receive telehealth care, found no significant differences between the groups in the proportion of participants prescribed PrEP, attendance at their first follow-up visit, and adherence at 1 month but found low rates of attendance at the 3-month visit among patients who opted to receive telehealth PrEP who had not yet been referred to another health care provider for PrEP.

We developed PrEPTECH, a telehealth intervention that focuses specifically on alleviating issues of stigma, access, cost, adherence, and confidentiality in young people with risk factors for HIV infection who are seeking PrEP care. A 2017 observational pilot study of PrEPTECH found that the intervention helped users bypass some of the documented barriers to PrEP access, uptake, and adherence [34]. The 25 men who have sex with men who were HIV negative, were aged 18 to 25 years, were from the San Francisco Bay Area, and enrolled in the pilot study reported high satisfaction with PrEPTECH, and over 85% expressed preference for telehealth-delivered PrEP care over clinic-delivered PrEP care. Leveraging the data from the pilot study, we redesigned and enhanced PrEPTECH and are now testing whether the updated platform enhances PrEP uptake among young cisgender men and transgender women who have sex with men through a randomized controlled trial (RCT). Ultimately, this study will add to the growing evidence base about the effectiveness, feasibility, and acceptability of telehealth HIV PrEP care.

Methods

Study Design

This study is an RCT for assessing the effectiveness, acceptability, and feasibility of a telehealth HIV PrEP care intervention, PrEPTECH, in increasing PrEP uptake over 6 months among young cisgender men and transgender women who have sex with men in 4 regions within the United States, namely the San Francisco Bay Area, California; Los Angeles County, California; Miami-Dade County, Florida; and Broward County, Florida, when compared with those of standardized web-based PrEP information resources.

Study Objectives

The study has two primary objectives: (1) to test the effectiveness of a telehealth intervention, PrEPTECH, in enhancing PrEP uptake in comparison with that of a condition in which only standardized web-based PrEP information resources are provided and (2) to assess the acceptability and feasibility of PrEPTECH as a telehealth HIV PrEP care intervention for young cisgender men and transgender women who have sex with men.

In addition, the study has two secondary objectives: (1) to test the effectiveness of a telehealth intervention, PrEPTECH, in improving adherence to PrEP in comparison with that of a condition in which only web-based standardized PrEP information resources are provided and (2) to examine the moderators of PrEP use, including HIV risk perception, PrEP attitudes, sexual behaviors associated with HIV risk, and insurance status.

Study Hypotheses

We hypothesize that participants in the intervention arm will show higher rates of PrEP initiation at both 3 and 6 months than those in the control arm. We also hypothesize that PrEPTECH is an acceptable and feasible telehealth HIV PrEP care intervention for young cisgender men and transgender women who have sex with men.

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Study Setting

The study will be completed digitally among self-referred participants living in the San Francisco Bay Area, California (the 9 counties of Alameda, Contra Costa, Marin, Napa, San Mateo, Santa Clara, Solano, Sonoma, and San Francisco); Los Angeles County, California; Miami-Dade County, Florida; or Broward County, Florida.

Sample Size

We calculated the sample size to provide adequate statistical power for our first objective, which is to test the effectiveness of a telehealth intervention, PrEPTECH, in enhancing PrEP uptake. Data suggest that PrEP uptake among relevant populations is low. Only 16% of young people aged 16 to 24 years use PrEP [6]. We also reviewed recent RCTs aimed at increasing PrEP uptake in comparable study populations. A pilot study of linkage to PrEP care among men who have sex with men and transgender women identified as partners of people diagnosed with a sexually transmitted infection (STI) found an uptake rate of PrEP of 11% among controls receiving standard HIV prevention programming, including PrEP care [31]. In a pilot trial of a 2-session motivational interviewing–based behavioral intervention, 28% of controls receiving treatment as usual at an urban STI clinic received a PrEP prescription [35]. Furthermore, 2 RCTs of web-based interventions for increasing PrEP uptake among sexual minorities with published protocols estimated anticipated control arm uptake ranging from 2% to 15% for the purpose of their power analyses [36,37].

Using this recent research on PrEP uptake in relevant populations and comparable research projects, including ongoing RCTs of digital interventions, we assumed 20% PrEP uptake in the control population. We proposed a minimum sample size target of 192 participants. Retaining 83.3% (160/192) of these participants at the 90-day and 180-day follow-up was our benchmark, as a loss to follow-up of greater than 20% in RCTs is seen as potentially introducing a source of bias [38]. We calculated statistical power using the following assumptions: power $(1 - \beta)=.80$, significance level $(\alpha)=.05$, PrEP uptake in the control group of 20%, and PrEP uptake in the intervention group of ≥40%. The power analysis results indicate a required sample size target of 96 per group or 80 per group after anticipated attrition.

Eligibility Criteria

To be eligible, participants must live in the San Francisco Bay Area, California (the 9 counties of Alameda, Contra Costa, Marin, Napa, San Mateo, Santa Clara, Solano, Sonoma, and San Francisco); Los Angeles County, California; Miami-Dade County, Florida; or Broward County, Florida. Participants must self-report having sex with men and identify as a cisgender male and be aged 15 to 17 years (in California only; minors in Broward or Miami-Dade County will not be eligible), identify as a cisgender male and be aged 18 to 27 years, or identify as a transgender female (or assigned male at birth and identify as a woman) and be aged 18 to 27 years (transgender females outside this age range will not be not eligible). In addition, participants, in keeping with guidelines for the provision of PrEP for sexual risk factors, must qualify for PrEP by self-reporting being diagnosed with an STI (including chlamydia, genital herpes, gonorrhea, syphilis, genital warts, human papilloma virus infection, and trichomoniasis) in the past 6 months or self-reporting condomless anal intercourse in the past 90 days [39]. Having a current known HIV-positive sexual partner and an indication for PrEP based on injection drug use were not included as eligibility criteria because of their expected rarity in our young study population. Among individuals aged 21 to 30 years, 1.5% reported ever injecting a drug not under a physician's orders and only 0.5% reported sharing needles in this way in their lifetime [40], and in a study of youths aged 12 to 24 years at high risk for HIV infection, only 7.7% reported ever having sex with a person living with HIV [41]. Only participants who attested to feeling comfortable reading and speaking in English were included, as, owing to development costs, creating a version of the website in Spanish was not feasible and other services associated with the intervention, including laboratory and pharmacy services, were in the English language only. Participants are not eligible if they have taken PrEP in the past 30 days; have ever been diagnosed with HIV infection, hepatitis B infection, chronic kidney, liver, or bone disease; or do not meet the eligibility criteria.

Recruitment and Randomization

To recruit potential participants, we contracted with an LGBTQ+ marketing and communications company to run paid advertising campaigns on social media platforms (eg, Facebook [Meta Platforms, Inc] and Instagram [Meta Platforms, Inc]) and LGBTQ+ dating apps (eg, Grindr [Kunlun Tech Co Ltd], Scruff [Perry Street Software Inc], Jack'd [Perry Street Software Inc], and Adam4Adam [A4A Network Inc]). The advertisements were targeted to the age and geographic eligibility criteria of the study and included a diverse array of men who have sex with men and transgender people, prominently featuring Black/African American and Hispanic/Latino individuals.

In addition to web-based recruitment, we identified community-based organization partners in each geographic location of the study and paid them to conduct web-based and in-person outreach. Community partners received printed assets (eg, palm cards and flyers) with the link to the study website and a QR code linked to the study website, as well as social media assets, including graphics sized for multiple social media platforms (eg, Instagram, Facebook, and Twitter [Twitter, Inc]), suggested captions, and potential hashtags.

Upon recruitment, prospective participants were directed to the study website and asked to complete an eligibility screener. Participants who were eligible completed an informed consent process.

To ensure that participants understood the risks that PrEP and participation in this study entail, the informed consent text outlined the risks in a detailed plain language summary. Taking advantage of the functionality available in a web-based setting, comprehension questions were incorporated into the informed consent text; prospective participants could not advance through the document until each question was correctly answered. We received a waiver of parental permission and, therefore, did not require or seek parental consent for minor participants.

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Participants who correctly answered the comprehension questions and consented to participate were brought to a baseline survey; upon completion, they were randomized into one of the two study arms. Only those who met the eligibility criteria and consented to participate were included in the study.

Eligible participants were randomized equally between the intervention arm, a web-based telehealth program offering a fully web-based pathway to PrEP, and the control arm, a dynamic web page containing publicly available informational resources about PrEP. We intended to ensure equal allocation of participants across the 4 study areas and equal numbers of adolescent cisgender males and adult transgender females in each study arm (approximately 20 individuals belonging to each subgroup in each study condition).

Community Advisory Board

During the development of the PrEPTECH intervention, we convened a 6-member community advisory board (CAB), composed of individuals who met the age and geographic eligibility criteria for the study and identified as a cisgender male or transgender female. Over the course of 5 web-based meetings, CAB members provided critical input and feedback on visual design, user experience, survey tools, recruitment approaches, and marketing and communication efforts. CAB members provided general guidance on how to appeal to prospective participants, suggesting that we highlight the incentive, potential to help the community through participation in this research, and benefits of PrEP. They offered the tagline used in the study's marketing materials, "PrEP on your own terms," following their discussion of the value of emphasizing PrEP as a personal exercise of autonomy, and, over several sessions, provided feedback on and later selected images and designs proposed by an in-house graphic designer for use on the PrEPTECH website and marketing materials. Each CAB member also took a draft survey and submitted feedback on any questions that they felt confused by or uncomfortable with; we also solicited input from the CAB about important topics that might be missing from the survey and on potential barriers to PrEP access that should be asked about.

Intervention

Participants allocated to the intervention arm of the study gained access to a web-based telehealth platform called PrEPTECH, which provides PrEP education via self-guided reading material, access to laboratory testing for PrEP eligibility delivered to a participant's home, and optional SMS text messages or email reminders to aid in medication adherence. PrEPTECH also provides access to telehealth care and PrEP prescriptions for eligible patients asynchronously through a web-based form or synchronously through telephone appointments with the study clinician, an infectious disease physician with expertise in PrEP care licensed in California and Florida. The PrEPTECH intervention tested here is an extension of the piloted PrEPTECH intervention. A brief report on the results of the pilot also discusses the development of the initial intervention by a multidisciplinary team in concert with a previous CAB [42]. It was adjusted to serve a larger group and to be completely web-based. In the second version of PrEPTECH, we incorporated a home laboratory testing kit service, built a platform for offering web-based health evaluations, and developed back-end systems for PrEPTECH to enable the clinical team to review submitted information and communicate with participants. The site was also redesigned for mobile platform compatibility.

All participants who completed at-home laboratory testing and an asynchronous or telephone appointment with the study clinician for whom PrEP was indicated received a prescription for Truvada (emtricitabine, 200 mg or tenofovir disoproxil fumarate, 300 mg). Adult cisgender male participants aged 18 to 27 years received a free 30-day supply of PrEP and subsequently had to pay for PrEP medication through insurance, through patient assistance programs, or out of pocket, should they choose to continue taking PrEP. Adolescent cisgender male participants aged 15 to 17 years and adult transgender female participants aged 18 to 27 years received free PrEP medication for the duration of their 6-month participation in the study because these subgroups were not included in the pilot study of PrEPTECH. Knowing less about the suitability of this intervention for these susceptible populations, the study team opted to provide free medication to them for the duration of the study. PrEPTECH also provides support for signing up for PrEP access programs, prescription transfer, and coordination with community partners.

After randomization to the PrEPTECH group, participants entered the PrEP education section, which included information about use, side effects, and effectiveness, and completed quiz questions to ensure comprehension. Next, a myLAB Box home testing kit for HIV, hepatitis B, syphilis, creatinine, gonorrhea, and chlamydia was sent to an address of their choice (typically, their home) [43]. Participants collected the specimens required through swab and finger prick and sent them via a postage paid mailer. If the participant tested negative for HIV antibodies or another STI, the web-based results were made available to the participants, and they were prompted to complete a medical intake questionnaire. This questionnaire was reviewed by the study clinician to confirm that there were no contraindications to PrEP medication for the participant. Synchronous telehealth appointments (telephone or video calls) were provided to all adolescent participants because it was anticipated that they might have a greater need for explanation and guidance that could best be offered in this format. For all other participants, synchronous telehealth appointments were offered as needed or requested.

If the study clinician was satisfied that the participant was eligible, he would issue a 6-month prescription for PrEP. A free initial supply of PrEP would be filled by Ridgeway Pharmacy, a mail order pharmacy serving both California and Florida, and mailed to a location of the participant's choice (typically, their home) [42]. For adult cisgender male participants, this initial shipment would be a 30-day supply of PrEP, but for adolescent cisgender male or adult transgender female participants, a 90-day free supply was sent. If a participant tested positive for HIV antibodies or another STI or any significant laboratory abnormalities were found, rather than reporting the results directly to the participant, a synchronous telehealth appointment would immediately be scheduled, and the study clinician would share the laboratory results, provide any necessary counseling,

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and refer the participant to a community provider for care. These participants would remain included in the study and would still be prompted to take the 90- and 180-day surveys. Then, 30 days after the prescription was sent, participants completed a second medical intake questionnaire, which was reviewed by the study clinician to assess any side effects or challenges encountered in taking PrEP. Participants could also request a synchronous appointment with the study clinician at any time during the study. Furthermore, 3 months (90 days) after enrollment, participants completed a second myLAB Box home testing kit for HIV, syphilis, gonorrhea, and chlamydia, as well as a third medical intake questionnaire, which was reviewed by the study clinician, with similar follow-up procedures as before. Follow-up laboratory tests did not include PrEP adherence measures such as hair sample or blood spot test, as they cannot be performed in the commercial laboratory with which we are working. Communication about steps toward accessing treatment is made through emails and texts, depending on the preferences expressed by the user, which can be indicated on the website itself.

Following their completion of the PrEP knowledge module, participants were queried about their insurance coverage and preferences with regard to paying for PrEP beyond their free supply. Using this information, the study staff worked with each participant to identify a means of payment, should the participant choose to continue taking PrEP. Participants could opt to use their existing insurance or pay out of pocket, in which case they would contact a pharmacy of their choice and request a transfer of the prescription. If they did not have insurance, they could seek coverage through Ready, Set, PrEP, a nationwide program that covers the cost of PrEP [44]. Ready, Set, PrEP allows care providers and patient navigators to sign up prospective participants. Participants would be given the option of signing up for Ready, Set, PrEP themselves, in which case the PrEPTECH platform provided detailed instructions for correctly completing their application, or they may authorize the study team staff to sign up on their behalf. Alternatively, if a participant opted for a community partner referral, they would be connected to an organization offering PrEP navigation in their geographic area. Near the end of a participant's time in the study, additional information and offers of support for transitioning to community care were provided again, including referrals to community partners.

Sample images from the PrEPTECH intervention can be found in Multimedia Appendix 1.

Control

Participants allocated to the control arm of the study gained access to a dynamic web page containing publicly available standardized informational resources about PrEP, including information on eligibility, use, side effects, effectiveness, access, and payment, as well as specific PrEP resources for transgender females. This web page also provides a list of alternative telehealth-based PrEP providers and contact information for community partners offering PrEP navigation in each geographic area.

The personal landing page for each participant was customized based on their study arm and subgroup (adolescent, adult transgender woman, or adult cisgender man who has sex with men). Participants allocated to the control condition could not access any of the PrEPTECH features, which were not displayed to them. A second panel on the control arm participants' landing page shows what surveys they have taken and are currently eligible to take.

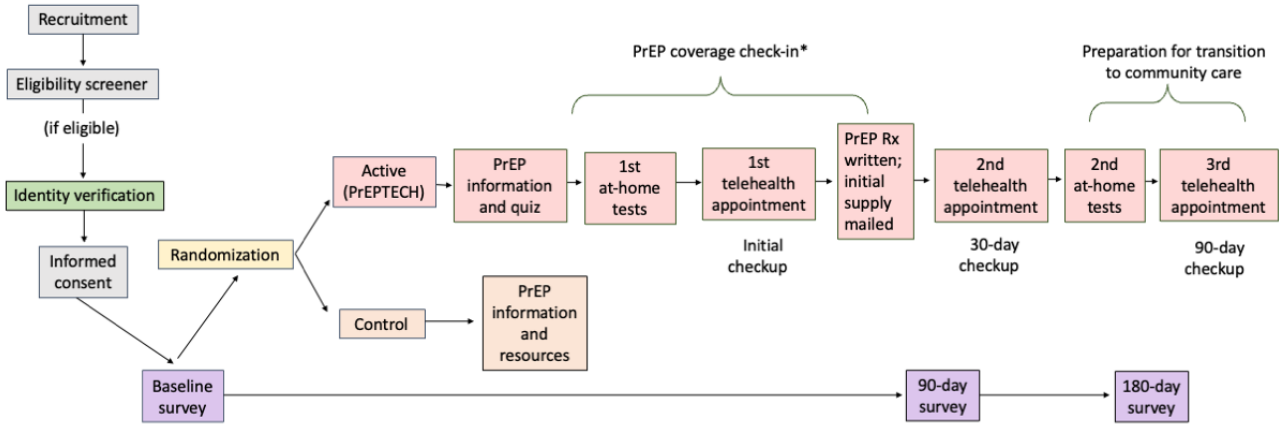
Participant Timeline

The entire 6-month web-based study is completed on the PrEPTECH website. A sequential illustration of participants' experiences is shown in Figure 1.

1. Recruited prospective participants review web-based materials on the PrEPTECH website and elect whether to create a web account, which requires them to verify their email address and phone number and provide their name.
2. After creating an account, prospective participants are screened for eligibility via a web-based survey. Those meeting the inclusion criteria proceed to step 3.
3. Each participant then verifies their identity by providing a photo of themselves with a photo ID card or a link to a public social media profile that shows their name with a visible photo of themselves.
4. Participants who provide identity verification are invited to complete the baseline web-based survey.
5. Each participant is randomized after baseline completion, informed of their assignment, and provided with standardized web-based resources on PrEP access or brought to the first step of the PrEPTECH intervention.
6. All participants are invited to take the midpoint survey 90 days after the baseline survey.
7. All participants are invited to take the final survey 180 days after the baseline survey.

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Figure 1. PrEPTECH study and intervention participant experience. *For adult men who have sex with men who are initially provided with a 30-day supply of free pre-exposure prophylaxis (PrEP), information and guidance on paying for PrEP (through insurance, patient access programs or self-pay) is provided concurrently with the provision of at-home laboratories and the initial telehealth appointment. Rx: prescription.



Data Collection and Management

Study data come from surveys completed by participants at three time points, namely (1) before randomization (baseline); (2) 3 months (90 days) after enrollment; and (3) 6 months (180 days) after enrollment, as well as study implementation records that document participant follow-up activities and participant progress through the intervention. Additional study data come from the laboratory tests and medical intake forms collected before the provision of the first PrEP prescription and approximately 90 days later, completed by participants in the intervention arm.

All survey data are collected digitally and entered directly by participants via embedded surveys hosted by Qualtrics (Qualtrics International, Inc) into the PrEPTECH study website. For participants in the intervention arm, laboratory test and medical intake information is collected via myLAB Box (laboratory test) and an embedded survey hosted by Qualtrics (medical intake). Medication prescription information is transferred electronically, using DrChrono (EverCommerce), to Ridgeway Pharmacy.

Participants receive automated email and SMS text message reminders to complete all surveys, with additional customized follow-up via email and SMS text message from the study team. To maximize the response rate and study retention, participants are compensated with web-based gift cards for the completion of each survey: US $40 at baseline, US $50 at 3 months, and US $60 at 6 months.

Upon randomization, each participant was assigned a unique identifier used throughout the study. However, data will be associated with personal identifiers while the study is ongoing, as this is necessary for participant follow-up. Electronic data will be stored for 3 years after the conclusion of the study. All data relevant to the study will ultimately reside in ETR Associates' Amazon Web Services system (Amazon Web Services, Inc) using Aptible (Aptible Inc) to ensure Health Insurance Portability and Accountability Act compliance.

Outcomes

Primary Outcomes

PrEP initiation at 3 months after enrollment will be assessed using participant self-report of having taken at least one dose of PrEP medication between study enrollment and midpoint survey administration.

Secondary Outcomes

PrEP Initiation

PrEP initiation at 6 months after enrollment will be assessed using participant self-report of having taken at least one dose of PrEP medication at any point during the intervention period.

PrEP Persistence

PrEP persistence at 3 and 6 months after enrollment will be assessed using participant self-report of having taken at least one dose of PrEP medication during both the first and second 90-day periods of the intervention.

PrEP Adherence

PrEP adherence at 3 and 6 months after enrollment will be assessed through multiple measures. Continuous adherence will be assessed using participant self-report of the number of doses of PrEP taken in the past 30 days, excluding participants taking event-based PrEP, as adherence would need to be conceptualized differently for this approach to PrEP administration. Categorical adherence will be assessed using participant self-report of taking a dose of PrEP medication for at least four days per week, "all of the last 4 weeks (4 out of 4 weeks)" or "most of the last 4 weeks (3 out of 4 weeks)," excluding participants taking event-based PrEP.

PrEP Coverage

PrEP coverage at 3 and 6 months after enrollment will be assessed using participant self-report of the number of instances in the past 30 days of vaginal or anal sex in which there was no protection from event-driven PrEP (defined as taking PrEP between 2 and 24 hours ahead of the sex act and ≥2 doses 24 and 48 hours after the first dose), continuous PrEP (defined as taking a minimum of 4 doses of PrEP within a week of the sex

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act), or long-acting PrEP (defined as taking injectable PrEP within 2 months before the sex act).

PrEP Medication Prescription

PrEP medication prescription at 3 and 6 months after enrollment will be assessed through multiple measures, including self-report of having received a PrEP prescription at any point during the intervention, as well as documented medication prescription through study electronic health records (among eligible intervention arm participants only).

PrEPTECH Acceptability and Feasibility

The acceptability and feasibility of PrEPTECH as a telehealth HIV PrEP care intervention for young cisgender men and transgender women who have sex with men will be assessed through multiple measures, including the likelihood of recommending PrEPTECH; preference for continuing PrEPTECH beyond the study; and other variables assessing the perceived trustworthiness, privacy, helpfulness, and convenience of and comfort with PrEPTECH. We will also calculate a mean System Usability Scale score, which is a standard scale for evaluating web apps [45], and conduct a thematic analysis of responses to 4 free-text questions about participants' perception of and experience with the PrEPTECH intervention and barriers to PrEP access encountered during the study. We will also examine clinical data, data on study attrition and completion, and other data from study implementation records.

Demographics

Participants' age, sex, gender, gender identity, sex partners' gender, sexual orientation, race, ethnicity, educational attainment, and living situation (living alone or with housemates or family) and whether languages other than English are spoken at participants' home will be assessed.

Moderators and Mediators

The following parameters will be assessed at baseline as potential moderators of PrEP uptake: history of PrEP use, HIV risk perception (assessed using the Perceived Risk of HIV Scale) [46], PrEP attitudes (assessed using a PrEP attitude and stigma scale with scores ranging from 10 to 50) [47], behaviors associated with HIV risk (eg, instances of anal intercourse without a condom in the past 90 days), health insurance status, and reasons for enrolling in the study (using a predefined list of possible reasons formulated by the study staff with input from the CAB). A series of questions assess the barriers to PrEP access participants may have encountered during the study period as a potential mediator of differences in PrEP uptake. Participants are asked to attest to whether they have encountered specific PrEP access barriers compiled in consultation with the CAB and with reference to the literature falling into the categories of financial or insurance coverage, health care access, medical concerns, privacy, PrEP stigma, and practical considerations (including loss, theft or selling of medication). A single item on the 2 follow-up surveys will also ask all participants to rate whether they have a source of PrEP that meets their needs.

Data Analysis

Overview

We will report the participant flow through the trial and the results in line with the CONSORT (Consolidated Standards of Reporting Trials) guidelines [48]. All analyses will be carried out following intention-to-treat principles. Data from participants will be allocated to the arm they were initially assigned to, regardless of whether they complete the intervention.

Data analysis will be conducted in SPSS (version 29 or higher; IBM Corp). Descriptive statistics will be calculated to describe the sample at baseline. Binary and categorical variables will be assessed through counts and percentages, and continuous variables will be assessed through means and SDs (medians will be computed for highly skewed variables). To assess baseline equivalence between the intervention and control arms of the study, regression analyses will be performed using age, race, ethnicity, gender, and educational attainment as dependent variables, with intervention condition as the independent variable. The groups will be considered not equivalent at baseline if a given variable differs significantly ($P<.05$) between the intervention arms. Differential and overall attrition will also be assessed using the What Works Clearinghouse recommended approach [49]. We expect ≤5% of the data to be missing; therefore, a complete case analysis is planned with no outcome or baseline imputation. However, if missing data go beyond 5%, then multiple imputation will be explored and run using the *mice package* in R (R Foundation for Statistical Computing) [50].

Primary and Secondary Outcome Analyses

Objective 1

To assess the effectiveness of PrEPTECH in enhancing PrEP uptake in comparison with the control condition, multiple logistic regression will be applied with the primary outcome (taking at least one dose of PrEP in the last 90 days, a dichotomous variable) as the dependent variable. The model will also include indicator variables denoting (1) the intervention group, (2) the number of days between the baseline and follow-up surveys (if there is a large range, which we do not expect), (3) the standard demographics of age at baseline and race and ethnicity at baseline, and (4) a set of a priori demographics and outcome-related covariates that screened positively as candidates for inclusion. A priori covariates that will be screened as candidates for inclusion into the model include gender, educational attainment, health insurance status, state, location, language spoken at home, sexual orientation, gender of sex partners, sexual risk factors, and the participants' relationships with the persons they are living with. If there is high correlation ($r>0.50$) between some of these indicators, they will be excluded from the model. Bivariate analyses will be used to test for relationships between the outcome variable and potential covariates, with a threshold of $P<.15$. The standardized effect size of the intervention on PrEP uptake will also be calculated to determine the magnitude of the effect of the intervention.

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Objective 2

To evaluate the acceptability of PrEPTECH as a telehealth HIV PrEP care intervention for young cisgender men and transgender women who have sex with men, we will assess participants' likelihood of recommending PrEPTECH; participants' preference for continuing PrEPTECH beyond the study; and other variables assessing the perceived trustworthiness, privacy, helpfulness, and convenience of and comfort with PrEPTECH among those in the intervention group. The percentage of participants expressing agreement or strong agreement with each item will be calculated. The System Usability Scale score will be calculated according to published guidelines to obtain a score out of 100 [45]. In addition, free-text answers to 3 questions about the benefits and drawbacks of PrEPTECH and how participants would characterize the intervention to a friend will be analyzed using a thematic approach.

The feasibility of PrEPTECH as a telehealth HIV PrEP care intervention for young cisgender men and transgender women who have sex with men will be assessed through a review of the study records. Clinical data will be used to assess loss to follow-up at various intermediate points in the intervention (eg, failure to return at-home laboratory kits or complete asynchronous medical intake forms). Records of clinical communications, written prescriptions, and efforts to assist intervention arm participants and to remind them to complete intervention steps will also be reviewed, with the number of contacts required at various stages calculated.

Objective 3

To examine the effects of PrEPTECH on adherence to PrEP, we will examine continuous measures. In each case, a multiple linear regression model will be applied. As described under *Objective 1*, the model will include (1) the intervention group, (2) the number of days between the baseline and follow-up surveys (if applicable), (3) the standard demographics of age at baseline and race and ethnicity at baseline, and (4) a priori demographics and outcome-related covariates that screened positively as candidates for inclusion. Variables will be screened in as described earlier.

The standardized effect size of the intervention on PrEP adherence will also be calculated to determine the magnitude of the effect of the intervention.

Objective 4

To examine the moderators of PrEP use, including HIV risk perception, PrEP attitudes, indications of sexual risk, insurance status, and reason for enrolling in the study, we will create multiple logistic regression models with PrEP uptake at 3 and 6 months as the outcome variable, intervention group as the predictor, and the potential moderator as an interaction term. The moderator will be considered statistically significant if $P<.05$.

A more detailed statistical analysis plan will be agreed upon before final analysis.

Ethical Considerations

This study has been approved by the institutional review board (number 0000283) of ETR Associates and is registered on ClinicalTrials.gov (NCT04902820) [51].

Results

This study was funded in 2019 with institutional review board approval in 2020. The PrEPTECH intervention was built over the next 1.5 years. Study recruitment was launched in February 2022 and completed in September 2022, with 229 participants recruited in total. Data collection was completed in April 2023, and analysis will be complete in September 2023. We expect to publish the results by the end of 2023.

Discussion

Overview

Despite the rapid expansion of telehealth services for PrEP in recent years, formal and rigorous evidence of their effectiveness is sparse. We describe the protocol for an RCT to assess the effectiveness, acceptability, and feasibility of a telehealth HIV PrEP care intervention, PrEPTECH, in increasing PrEP uptake among young cisgender men and transgender women who have sex with men. We hypothesize that participants in the intervention arm will show higher rates of PrEP uptake at both 3 and 6 months than those in the control arm and that PrEPTECH is a feasible and acceptable telehealth HIV PrEP care intervention for young cisgender men and transgender women who have sex with men.

Limitations

One key limitation of this study is that it will rely on self-report data for PrEP uptake and adherence. In self-report, study participants may tend to overestimate their PrEP use. The use of electronic monitoring (such as medication event monitoring systems) and measurement of plasma or blood concentration yield more reliable measures of true PrEP use [52,53]; however, these were cost prohibitive for this study. Because we are using the same measurement approaches across both randomized groups, we do not anticipate differential bias across the study arms.

It is also worth noting that based on previous research from the PrEPTECH pilot study [36], in our original study proposal, we assumed 50% PrEP uptake in the control population and, therefore, calculated a sample size target of 400 participants, anticipating retaining 80% (n=320) of these participants at 180-day follow-up. However, 6 months into data collection, we revised our sample size calculations using the latest data on PrEP uptake in relevant populations and comparable research projects, including ongoing RCTs of digital interventions, to ensure that the participant sample size was adequate yet feasible given the resources required to enroll and retain participants.

Conclusions

The study findings will be disseminated through open-access journals and academic conferences. A summary of the results will also be shared with all community partners, CAB members,

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and study participants and published via our agency's website, newsletter, and social media channels. We anticipate that the study results will offer valuable evidence about the effectiveness, acceptability, and feasibility of telehealth HIV PrEP care interventions in this population.

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Data Availability

The data sets generated and analyzed during this study are not publicly available because of participant consent restrictions. However, the data sets are available from the corresponding author upon reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Sample screenshots of the PrEPTECH intervention.
[PDF File (Adobe PDF File), 63861 KB - resprot_v12i1e47932_app1.pdf]

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Abbreviations

CAB: community advisory board
CONSORT: Consolidated Standards of Reporting Trials
LGBTQ+: lesbian, gay, bisexual, transgender, and queer
PrEP: pre-exposure prophylaxis
RCT: randomized controlled trial
STI: sexually transmitted infection

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Protocol

Obstructive Sleep Apnea and a Comprehensive Remotely Supervised Rehabilitation Program: Protocol for a Randomized Controlled Trial

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Abstract

Background: Obstructive sleep apnea (OSA) is characterized by recurrent, intermittent partial or complete obstruction of the upper respiratory tract during sleep, which negatively affects the patient's daily quality of life (QoL). Middle-aged and older men who smoke and have obesity are most at risk. Even though the use of continuous positive airway pressure (CPAP) during sleep remains the gold standard treatment, various rehabilitation methods, such as exercise, respiratory therapy, myofunctional therapy, and nutritional lifestyle interventions, also appear to be effective. Moreover, it is increasingly recommended to use alternative or additional therapy options in combination with CPAP therapy.

Objective: This study aims to evaluate if a comprehensive home-based, remotely supervised rehabilitation program (tele-RHB), in combination with standard therapy, can improve OSA severity by decreasing the apnea-hypopnea index (AHI); improve objective parameters of polysomnographic, spirometric, anthropometric, and body composition examinations; improve lipid profile, maximal mouth pressure, and functional capacity tests; and enhance the subjective perception of QoL, as well as daytime sleepiness in male participants with moderate to severe OSA. Our hypothesis is that a combination of the tele-RHB program and CPAP therapy will be more effective by improving OSA severity and the abovementioned parameters.

Methods: This randomized controlled trial aims to recruit 50 male participants between the ages of 30 and 60 years with newly diagnosed moderate to severe OSA. Participants will be randomized 1:1, either to a 12-week tele-RHB program along with CPAP therapy or to CPAP therapy alone. After the completion of the intervention, the participants will be invited to complete a 1-year follow-up. The primary outcomes will be the polysomnographic value of AHI, Epworth Sleepiness Scale score, 36-Item Short Form Health Survey (SF-36) score, percentage of body fat, 6-minute walk test distance covered, as well as maximal inspiratory and expiratory mouth pressure values. Secondary outcomes will include polysomnographic values of oxygen desaturation index, supine AHI, total sleep time, average heart rate, mean oxygen saturation, and the percentage of time with oxygen saturation below 90%; anthropometric measurements of neck, waist, and hip circumference; BMI values; forced vital capacity; forced expiratory volume in 1 second; World Health Organization's tool to measure QoL (WHOQOL-BREF) score; and lipid profile values.

Results: Study recruitment began on October 25, 2021, and the estimated study completion date is December 2024. Analyses will be performed to examine whether the combination of the tele-RHB program and CPAP therapy will be more effective in the reduction of OSA severity and improvement of QoL, body composition and circumferences, exercise tolerance, lipid profile, as well as respiratory muscle and lung function, compared to CPAP therapy alone.

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Conclusions: The study will evaluate the effect of a comprehensive tele-RHB program on selected parameters mentioned above in male participants. The results of this intervention could help the further development of novel additional therapeutic home-based options for OSA.

Trial Registration: ClinicalTrials.gov NCT04759456; https://clinicaltrials.gov/ct2/show/NCT04759456

International Registered Report Identifier (IRRID): DERR1-10.2196/47460

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KEYWORDS

obstructive sleep apnea; telerehabilitation; telemonitoring; CPAP; apnea-hypopnea index; telehealth; telemedicine; sleep; respiratory; home based; rehabilitation; RCT; randomized controlled trial

Introduction

Background

Obstructive sleep apnea (OSA), the most common type of sleep-related breathing disorder [1], is characterized by recurrent, intermittent partial or complete collapse or obstruction of the upper respiratory tract during sleep [2]. Risk factors for its development include male gender, middle and older age, tobacco use, and obesity [3,4]. The high worldwide prevalence and increased risk of morbidity and mortality, especially due to cardiovascular diseases, make OSA a serious health-related global problem [5-7]. In addition, OSA can negatively affect the patient's quality of daily life (QoL) [8]. For instance, excessive daytime sleepiness; impaired cognitive functions; work performance; ability to concentrate; or the occurrence of depression, headaches, snoring, and nocturnal urination; or disharmony in social interactions are particularly limiting [9,10]. The gold-standard treatment for OSA is continuous positive airway pressure (CPAP). The aim of CPAP therapy is to reduce the frequency of apneic and hypopneic pauses during sleep [11,12]. It is increasingly recommended to use alternative or additional therapy options in combination with CPAP [13]. These options include lifestyle and nutrition interventions, physical activity, pharmacotherapy, and behavioral therapy [13]. A recent meta-analysis has shown that a positive effect of exercise therapy, together with a reduction-diet intervention, leads to a significant reduction in the severity of OSA [14]. Based on several meta-analyses, the severity of the disease could be improved either by adjusting to a more nutritional lifestyle [14-16] or by implementing a physical intervention [17,18]. A significant reduction in the apnea-hypopnea index (AHI) was also achieved by training orofacial muscles with oropharyngeal exercises (ie, myofunctional therapy) [19]. According to Camacho et al [19], myofunctional therapy could represent an additional part of OSA therapy. Even the standard treatment representing CPAP therapy or mandibular advancement devices should also include exercise training [20]. A recent meta-analysis also showed a positive effect of respiratory therapy and respiratory muscle training elements in influencing OSA [21]. However, the authors stated that further research is needed to confirm the effect of additional therapeutic options already mentioned [12,15,17-19,21].

Aerobic and respiratory muscles training, oropharyngeal exercises, and regimen recommendations concerning lifestyle, nutrition, and behavior changes are individual components of the comprehensive home-based remotely supervised rehabilitation (tele-RHB) program conceived in this study. No recent literature has been found that deals with the effects of a similar and thus complex remotely supervised intervention. The absence of such an intervention in the context of OSA, as a possible therapeutic option for additional at-home training in combination with CPAP therapy, was the reason for conducting our research.

Objective

This study protocol describes the first-ever randomized controlled trial to solely evaluate the effectiveness of the tele-RHB program among male adults with moderate to severe OSA. This study aims to assess whether completing a comprehensive telerehabilitation program and CPAP therapy positively affects the severity of OSA, QoL, body composition and circumferences, exercise tolerance, lipid profile, and respiratory muscle and lung function. Our hypothesis is that a combination of tele-RHB program and CPAP therapy will be more effective in the reduction of OSA severity and improvement of QoL, body composition, exercise tolerance, lipid profile, as well as respiratory muscle and lung function, compared to CPAP therapy alone.

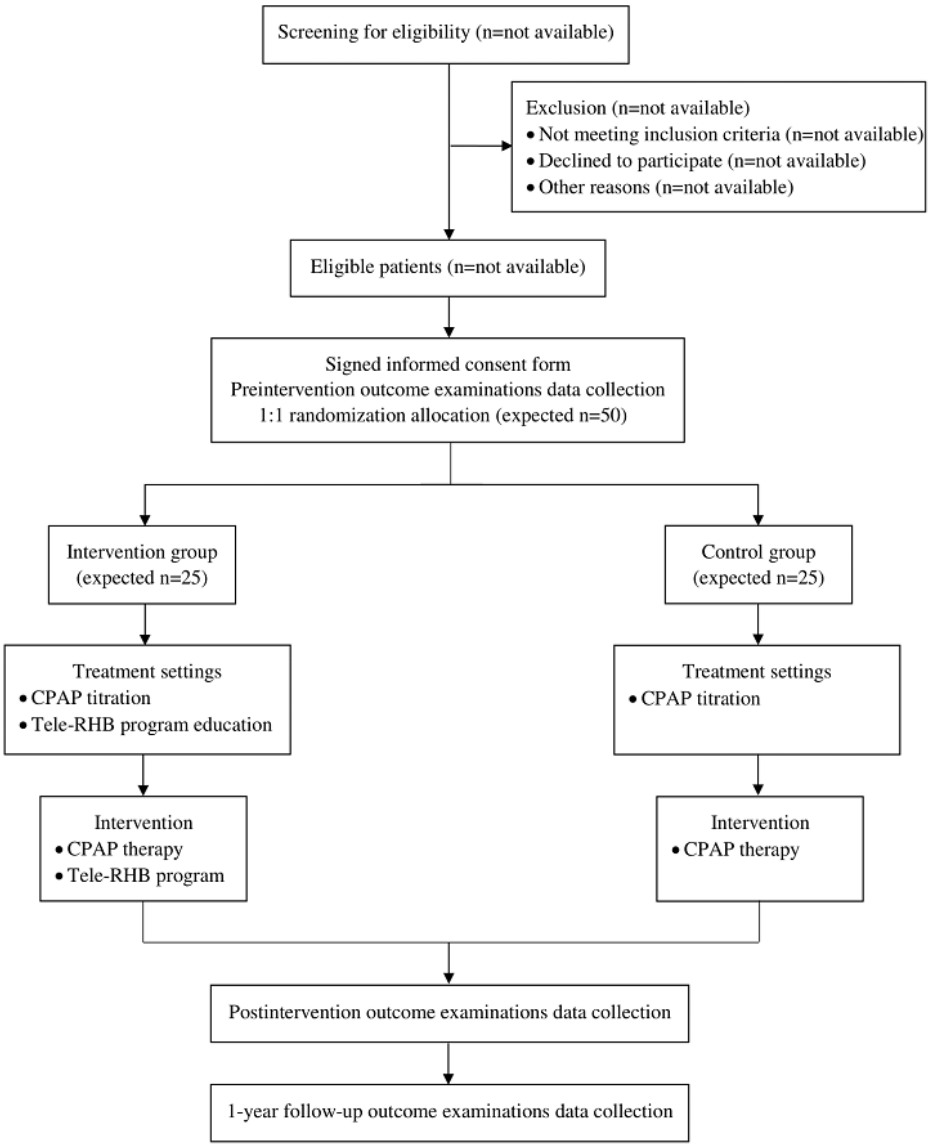
Methods

Study Design

This study is a 2-arm parallel single-blind randomized controlled trial (registered on ClinicalTrials.gov: NCT04759456), with the per-protocol analysis investigating the effect of the tele-RHB program among 50 male patients with newly diagnosed OSA indicated to CPAP therapy. Patients were recruited from the Sleep Centre of the International Clinical Research Center of St Anne's University Hospital in Brno (FNUSA-ICRC). After providing informed consent, the patients will be randomized to the 12-week tele-RHB program along with CPAP therapy; 25 patients will be randomized to the intervention arm, and 25 will be in the control arm (CPAP therapy alone) in a 1:1 ratio, following the methods described below (Figure 1).

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Figure 1. Flow diagram of the study protocol. CPAP: continuous positive airway pressure; tele-RHB: comprehensive home-based remotely supervised rehabilitation.



Ethical Considerations

The study protocol follows the Declaration of Helsinki and received approval from the Ethics Committee of the University Hospital Brno in the Czech Republic (06-090920/EK). Participation in the study will be voluntary, without any compensation or remuneration, and participants will be allowed to withdraw from the study at any moment without providing a reason.

All participants will provide written informed consent. This informed consent form provides details about the purpose of the study, requirements for study participation, randomization process, personal data processing, storage and protection process, and contact information for research team staff. The original informed consent allows the secondary analysis of obtained data without additional consent.

All participants' obtained data will be pseudonymized and deidentified; only an authorized person of the study research team will be able to identify the participants on the basis of personal data. The obtained data will be published anonymously, and no report or publication will contain any data that could lead to the participants' identification.

Inclusion Criteria

Participants will be eligible if they are male patients, aged 30-60 years, have newly diagnosed OSA with an AHI ≥15 episodes per hour, are indicated to CPAP therapy, and are interested in our adjunct tele-RHB program.

Exclusion Criteria

Participants are excluded if they have another type of OSA treatment, chronic corticosteroid therapy or long-term oxygen therapy; they are also excluded if they have at least one of the following health problems: central sleep apnea, chronic obstructive pulmonary disease III or IV, severe pulmonary hypertension, New York Heart Association III or IV, acute coronary syndrome, heart failure, ejection fraction <40%, electrocardiographic-documented heart arrhythmia, severe heart valve disease, cerebrovascular disease, psychiatric disease, and physical disability; in addition, they will be excluded if they do

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not cooperate during the intervention or do not follow the tele-RHB program and CPAP therapy protocol.

Recruitment, Enrollment, and Procedure

The patients who meet the inclusion criteria will be recruited from the Sleep Centre of the FNUSA-ICRC. The details of the study overview are shown in Table 1. On the first visit, patients will undergo polysomnography (PSG), blood sampling for lipid profile, and completion of the Epworth Sleepiness Scale (ESS) with a known score. Those who are found to have moderate to severe OSA will be contacted for further intervention alongside the standard CPAP therapy. These patients will be verbally informed and will receive an information leaflet about the ongoing study of the 12-week tele-RHB program. Then, they will complete anthropometric and spirometric examinations, measurements of maximal inspiratory mouth pressure (MIP) and maximal expiratory mouth pressure (MEP) as well as body composition, 6-minute walk test (6MWT), and QoL questionnaires in the Cardiovascular Rehabilitation Clinic at the University Hospital Brno (CRC-UHB). After that, during the interview with a physiotherapist, participants will receive detailed and comprehensive information regarding their possible participation in the study. Then, potential participants will be given at least 24 hours to decide before signing the informed consent.

On the second visit, patients who agreed to participate in the study will sign the informed consent form and will be then randomized 1:1 to the intervention or control group.

On the third visit, participants of both groups will undergo individual titration of CPAP therapy at the Sleep Centre of the FNUSA-ICRC. The intervention group will subsequently receive education about the tele-RHB program, along with theoretical and practical instruction on its individual components in the CRC-UHB. Participants of the intervention group will also receive a training brochure containing information needed for the tele-RHB program with remote supervision by a physiotherapist.

After the completion of the 12-week tele-RHB program, on the fourth visit, participants of both groups will undergo the same examinations and measurements as those conducted at the baseline, at the Sleep Centre of the FNUSA-ICRC and in the CRC-UHB.

After 1 year from the 12-week tele-RHB program's completion, on the fifth visit, participants of both groups will undergo the same examinations and measurements as they did at the baseline in both health facilities.

Table 1. An overview of the study flow.

Timeline	Preintervention outcome examination (0-7 days)		Treatment settings (8-28 days)	Intervention (12 weeks)	Postintervention outcome examination (1-5 days after)	Follow-up (1 year after)
	First visit	Second visit	Third visit	N/A[a]	Fourth visit	Fifth visit
Screening	✓					
Signed informed consent form		✓				
Interview	✓					
Randomization		✓				
Polysomnography	✓				✓	✓
Epworth Sleepiness Scale	✓				✓	✓
Lipid profile	✓				✓	✓
Anthropometry	✓				✓	✓
Spirometry	✓				✓	✓
Maximal mouth pressures	✓				✓	✓
6-minute walk test	✓				✓	✓
Body composition	✓				✓	✓
Questionnaires	✓				✓	✓
CPAP[b] titration			✓			
Education			✓			
Teleconsultations				✓		

[a]N/A: not applicable.

[b]CPAP: continuous positive airway pressure.

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Randomization

Participants will be randomized 1:1 to the intervention and control group by a noninvestigating member of the research group in the CRC-UHB with the help of the website "randomization.com" [22] into 6 blocks of 8 and 1 block of 2 participants. Participants and caregivers will be instructed not to comment on their ongoing therapy. The outcome assessor will be blinded. Physiotherapists who educate the intervention group participants about the tele-RHB program and who carry out regular teleconsultations during this program are the only unblinded members of the research group.

Measures

Measurements and Examinations

All participants will take part in baseline, postintervention, and follow-up examinations. PSG will be performed by trained medical staff in accordance with recent guidelines [23]. The variables extracted from PSG will be AHI, oxygen desaturation index, supine AHI, total sleep time, average heart rate, mean oxygen saturation (SpO_2), and the percentage of time with SpO_2 saturation below 90%. PSG will be performed with Grael 4K PSG:EEG (Compumedics Limited). All of the above-mentioned data will be collected without the CPAP device in use.

Standardized questionnaires, including the 36-item Short Form Health Survey (SF-36), the World Health Organization's tool to assess QoL (WHOQOL-BREF) [24], and ESS, will be filled in by all participants under the supervision of a medical specialist. The ESS questionnaire will be a tool for the participant's subjective daytime sleepiness, and the SF-36 and WHOQOL-BREF questionnaires will assess the subjective perception of QoL.

Participants will undergo a bioelectrical impedance examination with InBody 370S (BridgePower Corp) to evaluate changes in body composition performed by trained medical personnel. Data on the participant's sex, age, height, weight, and BMI will also be recorded. The monitored parameter will be the value of the percentage of body fat.

Participants will undergo a standardized 6MWT in accordance with American Thoracic Society guidelines to objectively assess their functional capacity by trained medical personnel [25]. The monitored parameter will be the distance in meters, which the participants will be able to walk in 6 minutes.

MIP and MEP will be measured with MicroRPM Respiratory Pressure Meter (Micro Direct Inc) and will be performed by a medical specialist based on recent recommendations for testing respiratory muscles [26,27].

Anthropometric parameters of the neck, waist, and hip circumference will be measured with a tape measure by trained medical staff. The current BMI value will also be calculated from actual body height and weight.

All participants undergo a standardized spirometric examination performed by a medical specialist with Spirobank II Basic (Medical International Research) in accordance with recommended procedures to objectively evaluate their lung function [28]. The parameters of forced vital capacity and forced expiratory volume in 1 second will be monitored.

All participants' CPAP devices will be regularly remotely monitored by a Sleep Centre medical doctor to track CPAP compliance and adherence to treatment during their sleep-at-home conditions. Participants will use one of the following devices: AirSense 10 AutoSet (ResMed Inc) or Prisma 20A Auto CPAP (Löwenstein Medical Technology GmbH + Co. KG).

Participants will have laboratory blood tests with the intention of finding out the current values of their lipid profile. Values of the total cholesterol, triacylglycerols, high-density lipoprotein (HDL) cholesterol, low-density lipoproteins (LDL) cholesterol, and non-HDL cholesterol will be detected.

Primary Outcomes

Primary outcomes include changes from baseline in AHI, obtained from PSG; ESS score; SF-36 score; percentage of body fat; 6MWT distance; as well as MIP and MEP values.

Secondary Outcomes

Secondary outcomes include changes from baseline in oxygen desaturation index, supine AHI, total sleep time, average heart rate, mean SpO_2, the percentage of time with oxygen saturation below 90%, obtained from PSG; neck, waist, and hip circumference; BMI values; forced vital capacity and forced expiratory volume in 1 second values; WHOQOL-BREF score; CPAP adherence; as well as total cholesterol, triacylglycerols, HDL cholesterol, LDL cholesterol, and non-HDL cholesterol values.

Intervention Group

Participants of the intervention group will undergo home-based 12-week tele-RHB program with regular teleconsultations via phone calls and emails at least 1-2 times a week with a physiotherapist. Teleconsultations will include telemonitoring and analysis of previously completed training sessions and the current course of the program; additionally, telecoaching for upcoming training sessions and motivation to continue the program will also be provided. Participants will also record the details of their completed training sessions during the intervention in a training diary and will regularly send it to the physiotherapist for evaluation. As previously stated, participants will receive a training brochure with a detailed description of the tele-RHB program and its components (Multimedia Appendix 1). Tele-RHB program will include nutrition, health-related lifestyle and behavior change recommendations, and a minimum of 5 times a week—each lasting 30 minutes—of moderate-intensity aerobic training; in addition, there will be 10 minutes of inspiratory and 10 minutes of expiratory muscle training with breathing devices (Threshold IMT and Threshold PEP) and 10 minutes of oropharyngeal exercise along with individually titrated CPAP therapy. After the completion of the 12-week tele-RHB program, participants should be motivated to continue performing this comprehensive rehabilitation program in home conditions during the 1-year follow-up, but without the regular remote supervision by a physiotherapist. This tele-RHB program was developed based on previous

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research or guideline recommendations for patients with OSA or cardiovascular diseases [6,29-36].

Control Group

Participants of the control group will undergo individually titrated CPAP therapy alone, throughout 12 weeks.

Data Analysis

Statistical Analysis

TIBCO Statistica (TIBCO Software Inc) will be used for statistical analysis of the obtained data. Statistical analysis will be performed by a person blinded to the experimental conditions. The Shapiro-Wilk test will be used to assess the normality of the data obtained. To compare participants' baseline and postintervention obtained data within the same group, a paired 2-tailed *t* test will be used for statistical analysis. When comparing the baseline and postintervention data of the participants between both groups, an unpaired *t* test will be used. The level of statistical significance will be set as $P<.05$. The acquired data will be securely collected on an encrypted external hard drive.

Sample Size

A power analysis was performed based on a previous study by Hupin et al [37], and the expected improvement in AHI was estimated to be approximately 8 (SD 10) episodes per hour at the end of the program versus the baseline. The number of participants in each of the two groups (n=25), necessary to achieve such an effect size, was calculated by statistical analysis at 80% statistical power with $\alpha=.05$.

Results

Study recruitment began on October 25, 2021, and the estimated study completion date is December 2024. Analyses will be performed to examine whether the combination of the tele-RHB program and CPAP therapy will be more effective in the reduction of OSA severity and improvement of QoL, body composition and circumferences, exercise tolerance, lipid profile, as well as respiratory muscle and lung function, compared to CPAP therapy alone.

Discussion

OSA is a severe global problem [6,7,38], negatively affecting the QoL and its various aspects [8,38]. Furthermore, although CPAP therapy is currently considered the gold standard of treatment [38], adherence to its long-term use is low [39]. According to Aardoom et al [40], about 30% to 80% of patients with OSA are nonadherent to their CPAP therapy. However, CPAP adherence and therapy compliance can be improved by a telemedicine-based approach (ie, eHealth) containing regular teleconsultations via video calls [41]. According to Hnatiak et al's [42] opinion, an additional therapy consisting of the implementation of the tele-RHB program could also improve the severity of OSA or even help with adherence to CPAP therapy. In addition, our comprehensive program, consisting of effective elements of rehabilitation, includes aerobic exercise training [17,18], oropharyngeal training [19], and respiratory muscle training [21], along with recommendations focusing on nutrition, lifestyle, and behavior changes [14-16].

The development of this tele-RHB program for the examined population was based on currently available knowledge. The comprehensive tele-RHB program was designed according to information about effective additional treatment options for OSA mentioned earlier. The study included only middle-aged and older male adults due to the risk of more frequent OSA occurrences in these individuals [3,4]. Thus, significant risk factors for the development of OSA also include middle [4] or older age, smoking [3], and obesity [3,4].

A possible limitation may be the lack of direct physiotherapist supervision during the remotely monitored intervention in a home-based setting. According to Hnatiak et al [42], regular communication of participants with physiotherapists during the intervention should help the standard course of the intervention. Thus, we assume that the completion of this intervention will produce interesting results that will help the further development of additional therapeutic options for OSA.

Our study intends to determine whether the completion of a tele-RHB program positively affects OSA in middle-aged and older men, and therefore, provide evidence for a possible recommendation of this tele-RHB program as an effective adjunctive treatment to CPAP therapy in male patients. The study will focus on the expected improvement in OSA severity, QoL, body composition, exercise tolerance, lipid profile, as well as respiratory muscles and lung function, resulting from the completed intervention.

Acknowledgments

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Data Availability

The data sets generated and analyzed during this study are available from the corresponding author upon reasonable request.

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Authors' Contributions

JH, OL, and LZG contributed to the conceptualization of the research. JH, PW, and LZG conceived and implemented the study. LB and FD contributed to data curation and statistical analyses. OL supervised the study. JH prepared and wrote the original draft; all authors reviewed, edited, and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Training brochure—detailed description of the Tele-RHB (comprehensive home-based remotely supervised rehabilitation) program.
[PDF File (Adobe PDF File), 339 KB - resprot_v12i1e47460_app1.pdf]

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Abbreviations

6MWT: 6-minute walk test
AHI: apnea-hypopnea index
CPAP: continuous positive airway pressure
CRC-UHB: Cardiovascular Rehabilitation Clinic at the University Hospital Brno
ESS: Epworth Sleepiness Scale
FNUSA-ICRC: International Clinical Research Center of St Anne's University Hospital in Brno
HDL: high-density lipoproteins
LDL: low-density lipoproteins
MEP: maximal expiratory mouth pressure
MIP: maximal inspiratory mouth pressure
OSA: obstructive sleep apnea
PSG: polysomnography
QoL: quality of life
SF-36: Short Form Health Survey-36
SpO_2: oxygen saturation
Tele-RHB: comprehensive home-based remotely supervised rehabilitation
WHOQOL-BREF: World Health Organization Quality of Life-BREF

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Protocol

Working Memory Training for Children Using the Adaptive, Self-Select, and Stepwise Approaches to Setting the Difficulty Level of Training Activities: Protocol for a Randomized Controlled Trial

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Abstract

Background: A common yet untested assumption of cognitive training in children is that activities should be adaptive, with difficulty adjusted to the individual's performance in order to maximize improvements on untrained tasks (known as transfer). Working memory training provides the ideal testbed to systematically examine this assumption as it is one of the most widely studied domains in the cognitive training literature, and is critical for children's learning, including following instructions and reasoning.

Objective: This trial aimed to examine children's outcomes of working memory training using adaptive, self-select (child selects difficulty level), and stepwise (difficulty level increases incrementally) approaches to setting the difficulty of training activities compared to an active control condition immediately and 6-month postintervention. While the aim is exploratory, we hypothesized that children allocated to a working memory training condition would show greater improvements: (1) on near transfer measures compared to intermediate and far transfer measures and (2) immediately postintervention compared to 6-month postintervention.

Methods: This double-blinded, active-controlled, parallel-group randomized trial aimed to recruit 128 children aged 7 to 11 years from 1 metropolitan primary school in Melbourne, Australia. Following baseline testing, children were randomized into 1 of 4 conditions: adaptive, self-select, or stepwise working memory training, or active control. An experimental intervention embedded in Minecraft was developed for teachers to deliver in class over 2 consecutive weeks (10 × 20-minute sessions). The working memory training comprised 2 training activities with processing demands similar to daily activities: backward span and following instructions. The control comprised creative activities. Pre- and postintervention, children completed a set of working memory tests (near and intermediate transfer) and the Raven's Standard Progressive Matrices (far transfer) to determine training outcomes, as well as motivation questionnaires to determine if motivations toward learning and the intervention were similar across conditions. Caregivers completed the ADHD-Rating Scale-5 to measure their child's attention (far transfer). Statistical analysis will include traditional null hypothesis significance testing and Bayesian methods to quantify evidence for both the null and alternative hypotheses.

Results: Data collection concluded in December 2022. Data are currently being processed and analyzed.

Conclusions: This trial will determine whether the adaptive approach to setting the difficulty of training activities maximizes cognitive training outcomes for children. This trial has several strengths: it adopts best practices for cognitive training studies

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(design, methods, and analysis plan); uses a range of measures to detect discrete levels of transfer; has a 6-month postintervention assessment; is appropriately powered; and uses an experimental working memory training intervention based on our current understanding of the cognitive mechanisms of training. Findings will inform future research and design of cognitive training interventions and highlight the value of the evidence-based principles of cognitive training.

Trial Registration: Australian New Zealand Clinical Trials Registry, ACTRN12621000990820; https://www.anzctr.org.au/ACTRN12621000990820.aspx

International Registered Report Identifier (IRRID): DERR1-10.2196/47496

(JMIR Res Protoc 2023;12:e47496) doi:10.2196/47496

KEYWORDS

children; working memory; memory training; adaptive training; cognitive training; transfer effects; training effects; cognitive outcomes; randomized controlled trial

Introduction

Background

Cognitive training interventions targeting core cognitive abilities such as working memory, attention, and problem-solving are in demand. Supporters of cognitive training explain that repeated practice on an activity will lead to performance gains that can transfer to improved performance on untrained tasks, an outcome known as transfer [1-4]. Transfer is the ultimate goal of cognitive training, and this intervention method is therefore of considerable interest to practitioners in health and education sectors seeking to prevent and ameliorate the disadvantage associated with low cognitive abilities, including inattention and learning related challenges (eg, psychologists, psychiatrists, and other mental health professionals; speech and language therapists; pediatricians; and teachers, special education needs coordinators, and specialist teachers). Transfer has been described on a continuum, ranging from near transfer to far transfer. *Near transfer* refers to improvement on measures structurally similar to the training activity, for example, performance on a measure using the same paradigm as the training activity but different stimulus, mode of presentation, or response modality. *Far transfer* focuses on performances on measures beyond the trained cognitive domain that rely on the trained skill. More recently, researchers have also been examining *intermediate transfer*, which describes improvement on measures that assess the same cognitive domain but use a different paradigm to the training activity. Working memory training benefits typically diminish with time, and with decreasing similarities between the training activity and outcome measure, providing consistent evidence for near transfer, less evidence for intermediate transfer, and little convincing evidence for far transfer [5-8].

A key design feature of cognitive training that is assumed to maximize training outcomes is *adaptivity* of the training activities. In this approach, the difficulty of the training activity is adjusted to the trainee's performance, thought to sufficiently challenge the trainee's cognitive limits to induce plasticity [9-12]. Indeed, most commercially available cognitive training programs are adaptive. Initial support for adaptive cognitive training in children came from studies demonstrating greater training effects and transfer following adaptive training, in which training difficulty varied, compared to a nonadaptive control, in which training difficulty was fixed at a low level [11,13-16]. This design is problematic for evaluating the adaptive method, with adaptivity and difficulty of the training activities confounded: children in the adaptive condition were exposed to varying difficulty levels, but those in the nonadaptive condition only experienced a single difficulty level. To address this important limitation, von Bastian and Eschen [7] systematically examined in adults the outcomes of working memory training with difficulty of the training activities being adaptive, self-selected, or randomized compared to an active control. The adults in the adaptive condition outperformed those in the active control condition on the training activity, but this was also the finding for the self-selected and randomized conditions. While near transfer effects were not examined, none of the training conditions showed improvements on intermediate or far transfer tests. The authors postulated that varying the difficulty level of the training activities may be sufficient to induce training effects, and that training and transfer effects may not be modulated by a specific approach to setting the difficulty of a training activity. These findings question the common assumption that an adaptive approach is superior for maximizing cognitive training outcomes.

Working memory training provides the ideal testbed to systematically examine the assumption that the adaptive approach maximizes cognitive training outcomes. It is one of the most widely studied domains in the cognitive training literature [17,18]. Working memory is a mental workspace capable of holding and processing information for brief periods in the course of ongoing cognitive activity [19]. This ability is critical for children's learning as it facilitates a host of complex cognitive activities such as comprehension, reasoning, and problem-solving [20]. Indeed, low working memory is commonly associated with poor scholastic attainments [20,21]. Meta-analyses examining near transfer effects following cognitive training reveal the highest effect sizes for training targeting working memory (g=0.50) than either inhibitory control (g=0.24) or cognitive flexibility (g=0.37) [6,17]. Evidence from high-quality trials also demonstrates near transfer effects of working memory training programs in children, such as Cogmed [15,22] and Braintwister [16,23]. However, there is less support for intermediate transfer, and the evidence for far transfer is negligible when methodological issues, such as the lack of an active control group, are taken into account [6,8,17,22,24-26].

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Aims and Hypotheses

This randomized controlled trial assessed the common assumption that cognitive training in children should be adaptive. The trial aimed to examine children's outcomes of working memory training using adaptive, self-select, and stepwise approaches to setting the the difficulty of training activities compared to an active control condition immediately and 6-month postintervention. Although the aim is exploratory, we hypothesized that children allocated to the working memory training conditions would show greater improvements: (1) on near transfer compared to intermediate and far transfer measures and (2) immediately postintervention compared to 6-month postintervention.

Methods

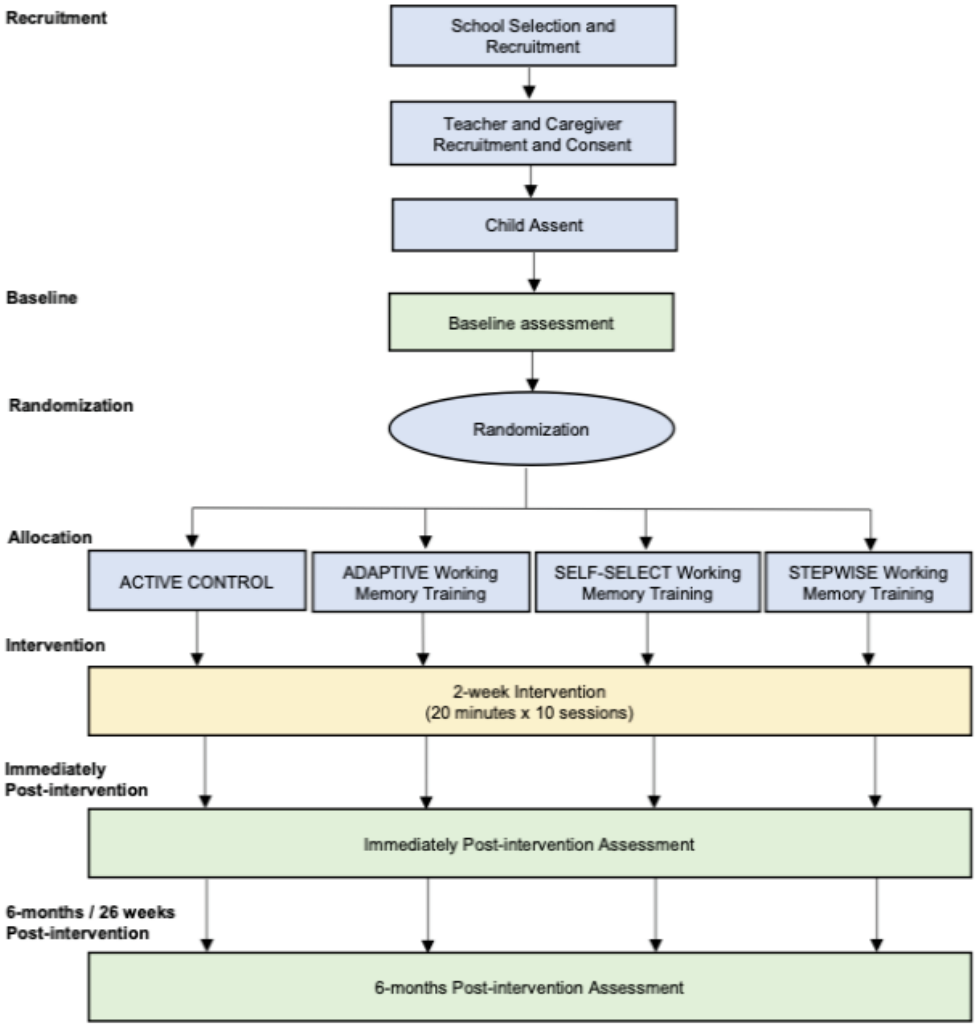
Ethics Approval

This trial was approved by the Monash University Human Research Ethics Committee (24305) in January 2021 and Melbourne Archdiocese Catholic Schools (1066) in February 2021. It was registered with the Australian New Zealand Clinical Trials Registry (ACTRN12621000990820) on July 28, 2021. We note that due to time constraints associated with COVID-19 lockdowns in Melbourne, Australia, the first participant was enrolled in the trial on July 13, 2021, when approval from the Australian New Zealand Clinical Trials Registry was pending, resulting in the trial's retrospective registration status.

Design and Blinding

This double-blinded, active-controlled, parallel-group, randomized superiority trial is part of the larger Common Assumptions of Cognitive Training (COMET) study. Researchers involved in child assessments were blinded to the child's intervention allocation and past assessment results. Teachers, caregivers, and children were informed that the study was examining children's thinking skills, and they were unaware of the different conditions. Thus, participants were unaware that this was a randomized controlled trial with different conditions, thereby preserving blinding. This trial was conducted and will be reported according to CONSORT (Consolidated Standards of Reporting Trials) guidelines. Figure 1 summarizes the trial design. This trial was expected to run for 15 months, with school selection and recruitment taking 3 months, and consent, data collection, and intervention carried out over 12 months.

Figure 1. Trial design.



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Setting

The research was conducted in a primary school in metropolitan Melbourne in the state of Victoria (population of 6.6 million in 2022), Australia [27].

School Recruitment

Eligible primary schools were within 20 km of the Monash University Clayton campus (for practical reasons) and had at least 197 children in grades 2 to 5 (to achieve the required sample size based on power calculations). Schools were randomly invited until one agreed to participate.

Participant Recruitment

All children in grades 2 to 5 (7 to 11 years) at the participating school were invited to participate in this trial. The grade 2 to 5 teachers distributed the caregiver explanatory statement and caregiver consent form for the children to take home to their caregivers. Caregivers were asked to provide consent for completing questionnaires about themselves and their child, and for their child to participate in cognitive testing. The children returned the completed consent forms to their teachers to pass on to the research team. Child assent was obtained during the baseline child testing session. Consent was sought from the teachers for their involvement in obtaining caregiver consent.

Eligibility Criteria

Children were included if they had caregiver consent, and provided written assent to participate. They were excluded if they had caregiver-reported vision impairment that cannot be corrected by glasses, including color vision deficiency, hearing impairment that cannot be corrected by a hearing aid, fine motor impairment, or intellectual disability that would prevent participation in the intervention.

Randomization

Following baseline testing, children were randomized to 1 of the 4 number-coded conditions (adaptive, self-select, stepwise working memory training, or active control) using a randomization scheme generated in advance and set up in Research Electronic Data Capture (REDCap) hosted at Monash University by the trial statistician (JFW) who was not involved in data collection. Specifically, block sizes of variable size (4 or 8) were used to assure allocation concealment and preguessing of the allocation sequence at the end of each block. Randomization was stratified by age at baseline: 7 to 8 years, 9 to 10 years, and 11 years.

Intervention

Overview

The Brain Space Program intervention was designed and developed by our team in Minecraft Education (Mojang Studios and Xbox Game Studios) for the COMET project (not an official Minecraft product, not approved by or associated with Mojang), and in this trial includes 3 working memory training conditions (adaptive, self-select, and stepwise) and an active control condition. All conditions were in the same Minecraft environment and had the same motivating features, including a “space mission” narrative for each session and the acquisition of experience points that could be used at the end of each training session for creative activities.

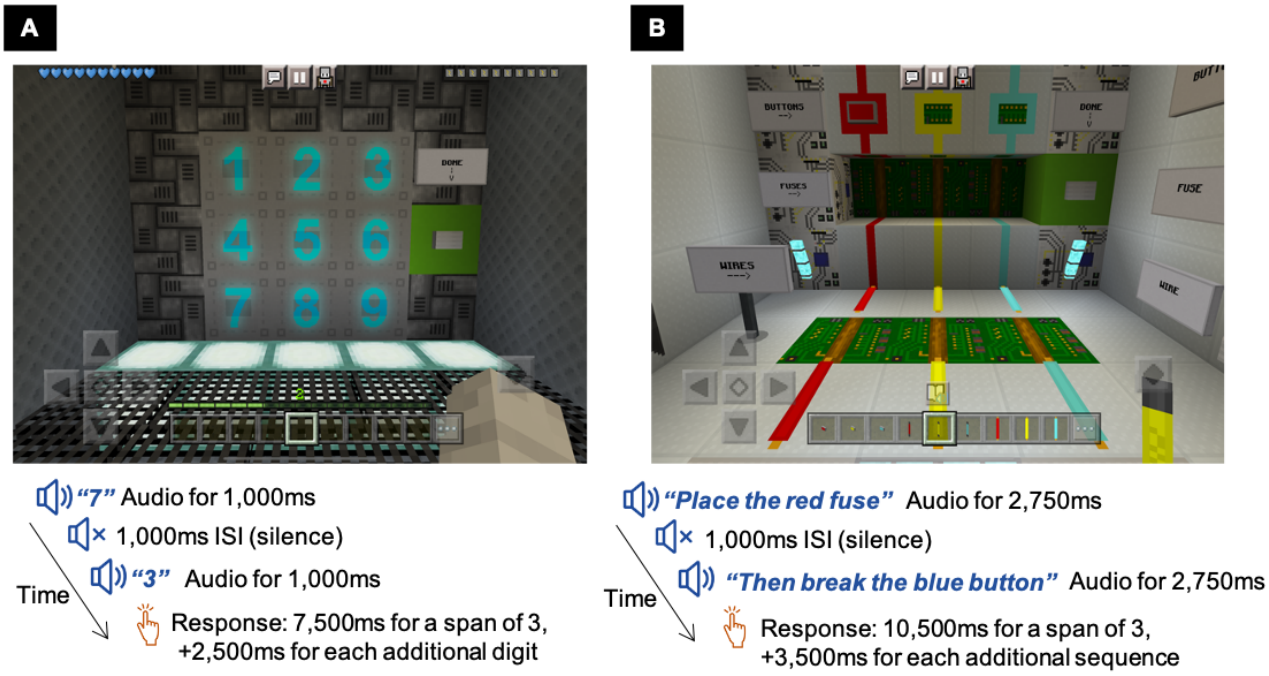
The teacher delivered the intervention in class. Children completed a session lasting 20 minutes on each school day for 2 consecutive weeks (total 10 sessions, total dose 200 minutes). Children individually performed the intervention on an iPad with headphones (provided by the researchers) to reduce distraction. To account for missed sessions (eg, child absences, school events, and public holidays), children were allowed to complete up to 3 training sessions per day during the intervention period. Researchers were in the classroom during the intervention period to ensure protocol adherence and compliance.

Working Memory Training Conditions

The working memory training consisted of 2 activities that required the child to temporarily store and manipulate verbally presented information: a backward span activity and a following instructions activity (see Figure 2). These paradigms were selected based on the current understanding of the cognitive mechanisms of training. Importantly, first, processing demands are sufficiently unfamiliar so the child is required to generate novel cognitive routines (strategies) that improve efficiency in performance and can be applied to new activities with sufficient overlap in task structure [5,6]. Second, processing demands overlap with daily activities, such as following teacher directions, leading to potential practical benefits [2,28].

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Figure 2. The working memory training activities: (A) backward span and (B) following instructions. ms = milliseconds, ISI = Interstimulus Interval.



In the backward span training activity, a series of digits were presented auditorily, and the child had to remember and immediately recall in reverse order the sequence of items by tapping the digits on the iPad screen. The difficulty level was manipulated by increasing the number of digits to be recalled. The following instructions training activity is based on a classroom analog test of working memory developed by Gathercole et al [29]. In this training activity, the child was introduced to 3 objects, each object comes in 3 colors, and 2 actions that require different tapping responses on the iPad screen. The child had to remember and immediately implement an action-color-object sequence (eg, break the red wire, then place the blue button, reflecting a span of 2) by using the relevant tapping response on the screen of the iPad with the corresponding color-objects. Difficulty level was manipulated by increasing the number of action-color-objects in the sequence the child has to perform. Each activity comprised 5 blocks of trials per session, and each block had 4 trials of a span level (per session: total 20 backward span trials, then 20 following instructions trials).

In this trial, there were three different working memory training conditions, each with a different approach to adjusting the difficulty level of the training activities: (1) *adaptive* condition, the difficulty level adapted to the child's performance during each training session on a block-by-block basis for the first 4 blocks (adapted between block 1 to 2, block 2 to 3, and block 3 to 4, and block 5 retained the same difficulty as block 4) within the training sessions for each activity; (2) *self-select* condition, the child decided at the end of each session if they would like a training activity to be easier, the same, or more difficult in the next session; and (3) *stepwise* condition, the difficulty level increased incrementally across sessions and this progression was predetermined and stratified by age based on current understanding of the development of children's working memory: 7 years, 8 to 9 years, and 10 to 11 years [30].

Active Control Condition

The active control involved the child completing a series of creative building and discovery activities each session. The activities were embedded in the same environment as the working memory training activities, and therefore the condition can be considered a placebo [1]. The activities were selected based on a review of activities available on the Minecraft Education website for school teachers to use with children aged 7 to 11 years in the classroom that do not require working memory [31].

Measures

Overview

Table 1 summarizes the measures, respondents, administration time points, as well as the primary outcomes of this trial.

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Table 1. Trial measures.

Domain or measure	Respondent	Baseline	Immediately postintervention	6 months postintervention
Child characteristics				
Participant information questionnaire	Caregiver	✓	N/A[a]	N/A
Near transfer				
Backward span digits	Child	✓	Primary outcome	✓
Following instructions objects	Child	✓	Primary outcome	✓
Backward span letters	Child	✓	✓	✓
Following instructions letters	Child	✓	✓	✓
Intermediate transfer				
2-back objects	Child	✓	✓	✓
Far transfer				
Raven's SPM[b] sets A to E	Child	✓	N/A	N/A
Raven's SPM sets A and B	Child	N/A	✓	✓
ADHD-5-RS[c]	Caregiver	✓	✓	✓
Child motivation				
Intrinsic Motivation Scale	Child	✓	N/A	N/A
Intrinsic Motivation Inventory	Child	N/A	✓	N/A

[a]N/A: Not applicable, test not performed at this time point.

[b]SPM: Standard Progressive Matrices.

[c]ADHD-5-RS: ADHD-Rating Scale-5, home version.

Child Characteristics

Caregivers completed a participant information questionnaire that collected demographic information about their child, including their child's sex, developmental and medical history, and family socioeconomic risk factors [32].

Training Outcomes

Near Transfer

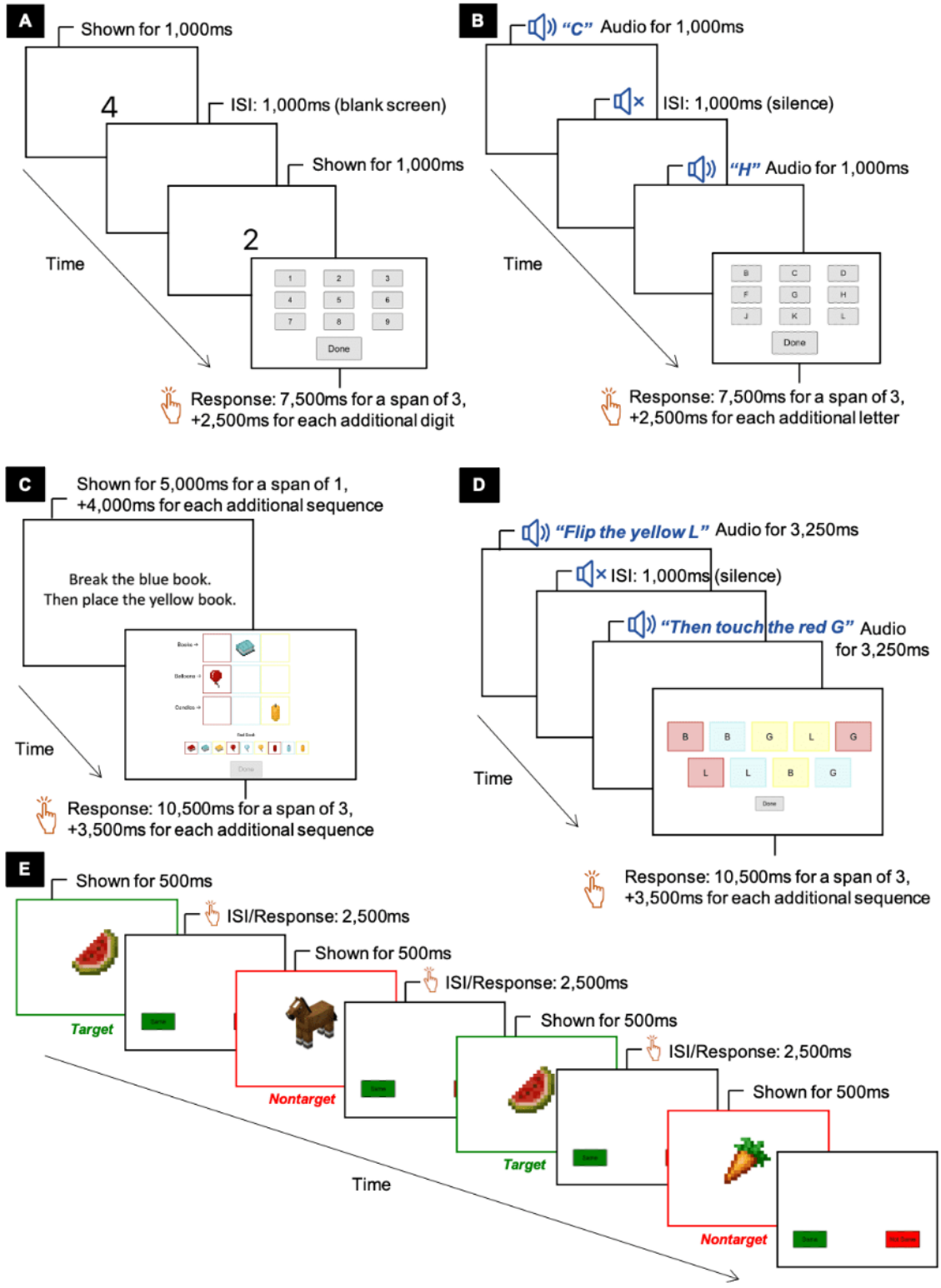
A set of four experimental working memory tests that have the same paradigms as the training activities, but different stimulus features, provided measures of near transfer (Table 2, Figures 3A to 3D): (1) *backward span* tests, digits and letters versions, and (2) *following instructions* tests, objects and letters versions [6]. For each test, there were 4 trials per block of a span level. Responses were self-paced with a cut-off duration for response time adjusted per span level. The span level increased by 1 if the child scored 3 or more out of the 4 trials in that block (≥75% accuracy); otherwise, the test ended. The tests, including instructions, practice items, and corrective feedback, were delivered via an iPad-based web app developed for this research. These multiple near transfer tests provide the opportunity to detect discrete levels of transfer by minimizing confounders associated with training effects [4].

Table 2. Comparison of the working memory training activities and near transfer tests. Responses provided on an iPad by tapping on-screen buttons.

Activity or test	Stimulus type	Stimulus, presentation	Response modality (response layout)
Backward span			
Training activity	Digits	Auditory	Motor (3×3 keypad)
Near transfer test	Digits	Visual	Motor (3×3 keypad)
Near transfer test	Letters	Auditory	Motor (3×3 keypad)
Following instructions			
Training activity	Items: space objects; actions: place, break	Auditory	Motor (3×3 grid)
Near transfer test	Items: common everyday objects and animals; actions: place, break	Visual	Motor (3×3 grid)
Near transfer test	Items: letter cards; actions: touch, flip	Auditory	Motor (2-row keyboard)

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Figure 3. The experimental working memory transfer tests delivered on an iPad: (A) backward span digits, (B) backward span letters, (C) following instructions objects, (D) following instructions letters, (E) 2-back objects. (A) to (D) depict each test at a span level of 2. ms = milliseconds, ISI = Interstimulus Interval.



Intermediate Transfer

An experimental n-back test measured intermediate transfer (Figure 3E). In this *2-back* test, the child was presented with a continuous stream of 22 common objects and animals (eg, carrot, flower, and cat; 6 targets and 16 nontargets), and the child had to decide for each object if it matched the object that was presented 2 items ago [5,33,34]. The child responded by tapping the "same" or "not same" on-screen button within the time limit. This test was delivered via the same iPad-based web app as the near transfer tests.

Far Transfer

Far transfer measures assessed children's reasoning and attention. Children's reasoning ability was measured using the Raven's Standard Progressive Matrices (SPM), standardized

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for individuals aged 6.5 to 80 years [35,36]. The Raven's SPM contains 5 sets (A to E) of 12 items. Each item has a geometric design with a missing piece on the bottom right. The child had to select the correct figure that would complete the overall geometric design vertically and horizontally from 6 or 8 possible options. The items increased in difficulty within sets and across sets. Children were allowed as much time as they needed to complete the task. The Raven's SPM has excellent split half-reliability and test-retest reliability (>0.80), and its concurrent validity is well established [37]. There is a moderately strong correlation (0.50 to 0.70) between SPM and conventional intelligence tests such as Stanford-Binet and Wechsler's tests [38].

Children's inattention and hyperactivity-impulsivity behaviors were assessed using the caregiver-rated ADHD-Rating Scale-5 (ADHD-RS-5, home version), standardized for children and adolescents aged 5 to 17 years [39]. The ADHD-RS-5 has an inattention subscale (9 items) and a hyperactivity-impulsivity subscale (9 items) that closely follow the Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition) criteria for attention-deficit/hyperactivity disorder. Caregivers rated their child's behaviors at home based on the previous 6 months, and at the immediate postintervention time point based on the past 2 weeks to assess any changes observed during the intervention period. Internal consistency of the symptom subscales (0.61 to 0.83) and concurrent validity were established by high correlations (>0.78) with respective subscales from the Connors Parent Rating Scale [39].

Child Motivation

Overview

Intrinsic motivation, an internal drive to seek out new and challenging experiences to learn and expand one's abilities [40], has been associated with performances on cognitive training activities and outcomes in children [41-43] and adults [44]. We measured aspects of children's motivation to rule out the potential influence of differences in expectations between the working memory training conditions and the active control [1,45].

Motivation Toward Classroom Activities

Children's motivation toward typical classroom activities was measured using the Intrinsic Motivation Scale (IMS) [46]. The IMS consists of 3 subscales: challenge (6 items; eg, I like hard work because it's difficult), curiosity (6 items; eg, I ask questions in class because I want to learn new things), and independent mastery (5 items; eg, I like to try to figure things out at school on my own). The child responded using a 3-point Likert scale (yes: 3 points; sometimes: 2 points; no: 1 point). The IMS has very high internal consistency (0.90) and high test-retest reliability with a 6-week interval (0.74) [46].

Motivation Toward the Intervention

Children's motivations toward the intervention were measured using a modified Intrinsic Motivation Inventory (IMI) [47], which has been used in child cognitive training studies [41-43]. This modified IMI consists of 4 subscales: interest or enjoyment (7 items; eg, it was fun to do), perceived competence (6 items; eg, I think I am pretty good at the training), effort or importance (5 items; eg, I put a lot of effort into it), and value or usefulness (4 items; eg, I think the training could help me). Identical to the IMS, the child responded on a 3-point Likert scale. This modified IMI has been used in a previous randomized control trial of working memory training with similar-aged children and has high internal consistency (≥0.74) [41].

Data Management and Confidentiality

Personal and trial data were collected and managed using REDCap electronic data capture tools hosted and managed by Helix (Monash University) [48,49]. Personal data required to disseminate the caregiver questionnaires were held securely and will not be used for any other purpose. Given the sample size, the trial's timeframe, and the minimal risks associated with participation, there is no data monitoring committee.

Procedures

Children participated in testing sessions, and caregivers completed behavioral questionnaires at baseline, immediately, and 6 months postintervention. The baseline and immediately postintervention measures were completed 1 week before and after the intervention, respectively. The 6-month postintervention measures were completed approximately 26 weeks postintervention (±8 weeks due to school term breaks).

Children were tested in small groups of 6 to 8. The group child testing sessions were led by a doctoral provisional psychologist and conducted in a quiet room on the primary school campus. The test order and administration protocol was the same at each time point. Children first completed the working memory measures on an iPad with headphones to reduce distraction, the Raven's SPM, and then motivation questionnaires. General task instructions were delivered to the children as a group. Children were encouraged to ask clarifying questions, and the researcher responded with standardized additional instructions and ensured the child understood how to complete the task before proceeding with testing.

Power Calculations and Sample Size

Calculations in G*Power (effect size f^2=0.07; 80% power; α=.05) [50,51] indicated a sample size of 29 children per condition would be required to detect a small to moderate effect of each working memory training condition (adaptive, self-select, and stepwise) compared to the active control on the near transfer measures immediately postintervention (primary outcome). This effect size was based on previous research, which indicates working memory training programs produce a small to moderate effect compared to a control condition on near transfer measures [6,17]. The target sample size was increased to 32 children per condition to account for 10% attrition [22]. Our previous school-based trial of a working memory training program had a 65% child recruitment rate [22]. Thus, to achieve our target sample size, the participating primary school had to have at least 197 children enrolled in grades 2 to 5.

Statistical Analysis

Primary analyses will be intention to treat (ITT) with sensitivity analyses only with children who completed the allocated intervention. Primary analyses will be separate linear regressions

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for each primary outcome at the primary end point (immediately postintervention) as the dependent variable, the outcome at baseline and the stratification factor (age) as covariates, and conditions (dummy coded with the active control as the reference) as the independent variables. Statistical significance will be set at α=.05 (2-tailed). If outcomes do not meet the normality assumption, a nonparametric bootstrap will be used. Effect sizes and 95% CI will be reported to demonstrate the magnitude of differences in outcomes between each training condition relative to the active control. Bayesian methods will be used to quantify the strength of evidence in favor of the null hypothesis and the alternative hypothesis. Interpretation of results will consider the strength of effects and *P* values. The same analytic approach will be applied to secondary outcomes and to both primary and secondary outcomes at the 6-month postintervention time point.

Results

This trial was supported by internal research funding from the School of Psychological Sciences and the Turner Institute for Brain and Mental Health at Monash University, awarded in December 2019. Data collection was attempted in July 2021 but was ceased shortly after due to COVID-19 lockdowns in Melbourne. Data collection occurred from February 2022 to December 2022. Data are currently being processed and analyzed. It is anticipated that the results of this trial will be published by 2024.

Discussion

The potential transfer of skills learned from a cognitive training intervention to other untrained activities is of interest to practitioners in health and education sectors, and families. Cognitive training interventions are intensive and typically comprise adaptive training activities, yet whether this approach to setting the difficulty of training activities maximizes transfer effects has only been systematically evaluated once in adults [7]. This trial aims to examine outcomes of working memory training using adaptive, self-select, and stepwise approaches to setting the difficulty level of training activities compared to an active control condition. This will be the first trial to systematically examine methods of setting the difficulty of working memory training activities in children. Our design includes evaluation of nonadaptive approaches (self-select and stepwise) and thereby eliminates task difficulty as a confounder, which was an important limitation of initial studies in the field.

This trial has important strengths. The trial design, methods, and analysis plan are in line with best-practice standards for cognitive training trials [1]. The trial was randomized, participants and assessors were blinded, and an active control condition was used. The active control condition (instead of a passive or no-contact control) was designed to be believable as an intervention, indistinguishable from the working memory training conditions in terms of the environment and motivating features, and thus was designed to ensure children experience a similar level of engagement, and experimenter and teacher attention to children allocated to the working memory training conditions. The set of outcome measures was designed to detect discrete levels of near transfer by minimizing confounders associated with training effects [4], and intermediate and far transfer effects are measured too. Training outcomes were assessed immediately postintervention and again at 6-month postintervention to determine any persisting training benefits. The trial is sufficiently powered to detect differences between the working memory training conditions and the active control condition. Importantly, our novel experimental working memory training interventions are designed specifically for this research and reflect the current understanding of the cognitive mechanisms of training: the processing demands of the training activities are (1) sufficiently unfamiliar such that the child needs to generate novel cognitive routines to do well, and the routines can then be applied to new activities that are similar but untrained; and (2) overlap with daily activities, such as following teacher directions, which overlap with daily activities. This is the first time the following instructions paradigm has been used as a working memory training activity. The nonadaptive approaches used in this trial reflect a similar approach to learning that children experience in daily activities, such as having autonomy over their learning (self-select), and mastering simpler concepts before complex concepts (stepwise). Motivation questionnaires will be used in analyses to determine if children in the training and active control conditions have similar motivation toward learning in the classroom and expectations of the intervention.

It is acknowledged that this trial was not powered to detect potential differences between the adaptive, self-select, and stepwise working memory training conditions. The lack of research and effect sizes from nonadaptive approaches makes calculating appropriate power challenging. We anticipate the differences in effect sizes between the 3 conditions will be small, and therefore a particularly large sample size would be required and this may not be practical or feasible.

This trial will determine whether the adaptive approach to setting the difficulty of working memory training activities is superior for maximizing training outcomes. It is our intention to present findings at national and international conferences and publish findings in peer-reviewed journal papers. Families and staff of the participating school will receive a summary of the findings. Findings will contribute to our understanding of the design of effective working memory training interventions, discrete levels of transfer of working memory training, and the malleability of cognitive functions in children. Knowledge gained could have implications for other types of cognitive training that target core domains such as attention and inhibitory control, and for other populations, including aging and dementia [3]. This work could help highlight the value of evidence-based principles of cognitive training and shift the focus from studying the effectiveness of different programs to more rigorous evaluations of the foundational principles of cognitive training. In summary, the results have the potential to influence the future direction and application of cognitive training.

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Data Availability

The data sets generated and analyzed during this study are not publicly available due to the restricted consent from participants but may be available from the corresponding author on reasonable request.

Authors' Contributions

MSS, PJA, and SG conceived of the trial and initiated the trial design. RCL, PJA, SG, JFW, and MSS made substantial contributions to the conception and design of the trial. RCL, PJA, SG, and MSS designed the intervention. RCL, PJA, and MSS designed the near and intermediate outcome measures. PM, FS, and DH developed the intervention and outcome measures. JFW provided statistical expertise in clinical trial design. RCL and MSS drafted this paper. All authors have reviewed and contributed to the final version of this paper. All authors have read and approved the final paper.

Conflicts of Interest

None declared.

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Abbreviations

ADHD-RS-5: ADHD-Rating Scale-5, home version
COMET: Common Assumptions of Cognitive Training
CONSORT: Consolidated Standards of Reporting Trials
IMI: Intrinsic Motivation Inventory
IMS: Intrinsic Motivation Scale
ITT: intention to treat
REDCap: Research Electronic Data Capture
SPM: Standard Progressive Matrices

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Protocol

Guided Internet-Based Cognitive Behavioral Therapy for Women With Bulimia Nervosa: Protocol for a Multicenter Randomized Controlled Trial

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Abstract

Background: Individual face-to-face cognitive behavioral therapy is known to be effective for bulimia nervosa (BN). Since foods vary considerably between regions and cultures in which patients live, cultural adaptation of the treatment program is particularly important in cognitive behavioral therapy for BN. Recently, an internet-based cognitive behavioral therapy (ICBT) program was developed for Japanese women with BN, adapted to the Japanese food culture. However, no previous randomized controlled trial has examined the effectiveness of ICBT.

Objective: This paper presents a research protocol for strategies to examine the effects of guided ICBT.

Methods: This study is designed as a multicenter, prospective, assessor-blinded randomized controlled trial. The treatment groups will be divided into treatment as usual (TAU) alone as the control group and ICBT combined with TAU as the intervention group. The primary outcome is the total of binge eating and purging behaviors assessed before and after treatment by an independent assessor. Secondary outcomes will include measures of eating disorder severity, depression, anxiety, quality of life, treatment satisfaction, and working alliances. Treatment satisfaction and working alliances will be measured post assessment only. Other measures will be assessed at baseline, post intervention, and follow-up, and the outcomes will be analyzed on an intention-to-treat basis.

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Results: This study will be conducted at 7 different medical institutions in Japan from August 2022 to October 2026. Recruitment of participants began on August 19, 2022, and recruitment is scheduled to continue until July 2024. The first participants were registered on September 8, 2022.

Conclusions: This is the first multicenter randomized controlled trial in Japan comparing the effectiveness of ICBT and TAU in patients with BN.

Trial Registration: University Hospital Medical Information Network UMIN000048732; https://center6.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000055522

International Registered Report Identifier (IRRID): DERR1-10.2196/49828

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KEYWORDS

bulimia nervosa; internet-based cognitive behavioral therapy; ICBT; randomized controlled trial; RCT; protocol; randomized; controlled trial; bulimia; eating; cognitive behavioral therapy; CBT; binge eating; purging; mobile phone

Introduction

Background

Bulimia nervosa (BN) is an eating disorder characterized by binge eating, purging or fasting, and concerns associated with body shape and weight [1]. Patients with BN often have a distorted body image despite being at standard levels with regard to shape and weight [2]. Consequently, they perform frequent purging or fasting or excessive exercise on the basis of a subjectively abnormal perception of their body shape and weight [3]. Body image distortion involves perceptual disturbances and body dissatisfaction [4]. Repeated episodes of binge eating and inappropriate compensatory behaviors can cause serious physical and mental health concerns. Vomiting after overeating may result in thickened skin on the knuckles, broken teeth, and thyroid dysfunction due to problems with metabolic rate and caloric intake [5,6]. In terms of mental health, patients with BN frequently show low self-esteem, self-harming behaviors, suicidal tendencies, depression, anxiety disorders, sleep disorders, and fatigue or exhaustion [7-12].

Prevalence of BN and Accessibility to the Treatment

Epidemiological studies confirm that eating disorders are highly prevalent, particularly among women: 2.58% of women in Western countries [13]. The overall observed prevalence of eating disorders was 3.5% between 2000 and 2006 and increased to 7.8% between 2013 and 2018 [14]. A recent meta-analysis estimated that the lifetime and 12-month prevalence of eating disorders was 0.91% and 0.43%, respectively, while the lifetime prevalence of BN was 0.63% [13]. Face-to-face cognitive behavioral therapy (CBT) has been shown to be effective for eating disorders [15], but poor access to treatment remains a problem [16]. In fact, only 19%-36% of people with eating disorders have access to treatment within 1 year [17-19], and 35%-40% of these patients receive standard treatment for eating disorders [20,21]. Furthermore, treatment for eating disorders is sought an average of 5-15 years after the onset of the disorder [16,22]. Access to these appropriate treatments is often hampered by physical barriers, lack of practitioners, and stigma. These problems are particularly associated with face-to-face delivery. Web-mediated interventions may be effective in initiating appropriate early treatment [23,24]. CBT via the internet can dramatically improve access to treatment, especially in developed countries, in which the internet infrastructure is well-developed and information communication devices are widely used.

A New CBT Model for BN

Enhanced CBT has been shown to be effective in treating eating disorders, including BN. Enhanced CBT encourages the early establishment of healthy and safe eating habits and facilitates behavioral changes and cognitive modification through psychoeducation and self-monitoring. In addition, accumulating evidence from many clinical studies is being integrated to establish CBT techniques that have shown promise for the treatment of eating disorders. In a network analysis, fear of weight gain was suggested to be central to the psychopathology of BN, and hypersensitivity to physical sensations was shown to bridge BN with anxiety or depression [25]. Based on the evidence, this network meta-analysis argued that focusing on the fear of weight gain during exposure therapy and interventions focused on interoceptive exposure is effective in treating BN. However, several other CBTs may also be effective in treating BN, including attentional bias correction training to correct the direction of excessive attention to the body, weight, and food [26], relaxation, and mindfulness to reduce physiological responses such as anxiety and tension [27], traumatic memory care for experiences of being criticized for one's body type and appearance [28], and impulse control, such as cue exposure [29]. A therapist's manual for CBT of BN that systematically summarizes these CBT components has been published by Hamatani and Matsumoto [30]. Our research group recently developed a web-based program based on this CBT therapist's manual by checking the cultural adaptability in Japan [31].

Objectives

As mentioned earlier, we developed an internet-based cognitive behavioral therapy (ICBT) program for BN that is adapted to Japanese culture and based on Japanese food culture [30,31]. This paper describes the study protocol for a randomized controlled trial (RCT) involving female patients with BN and is designed to evaluate its clinical effects. We will include an intervention group receiving ICBT in addition to treatment as usual (TAU) and a control group receiving TAU alone.

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Methods

Study Design

This study is designed as a multicenter, prospective, randomized, assessor-blinded clinical trial. The RCT and follow-up study are planned from August 2022 to October 2026 (UMIN000048732). It will be conducted at the following 7 institutions (6 university hospitals and a national medical center) in Japan: University of Fukui Hospital, Kagoshima University Hospital, Chiba University Hospital, Tokushima University Hospital, Dokkyo Medical University, Tohoku University Hospital, and National Center for Neurology and Psychiatry.

Participants and Eligibility Criteria

Eligible participants will be women aged 13-65 years (1) diagnosed with BN according to the Diagnostic and Statistical Manual of Mental Disorders criteria during a clinical interview [1]; (2) having a BMI over 17.5 kg/m^2; (3) using computers, tablets, smartphones, etc, on a daily basis, with access to the internet and the minimum necessary information and communications technology skills; and (4) with no history of CBT in the last 2 years. Exclusion criteria include (1) serious mental disorders such as organic brain disorders, psychotic disorders, and drug dependence; (2) imminent risk of suicide; (3) repeated engagement in antisocial behavior; (4) serious progressive physical disease; and (5) difficulty in exposure to feared objects due to severe stress reactions or dissociation symptoms due to acute stress disorder or posttraumatic stress disorder. The purpose of the study is to investigate the effects of an ICBT program that has been adapted based on the culture of Japanese women. Men and women differ in their caloric needs, and most studies regarding eating disorders include female patients. This intervention program is based on the findings of previous studies; therefore, only women will be recruited. In addition, information and communication technology literacy varies considerably by patient age in Japan, with older adults having lower information and communication technology literacy. The intervention in this study is mainly self-help CBT using a web-based platform. Therefore, patients aged 65 years and older will be excluded from the study.

Recruitment

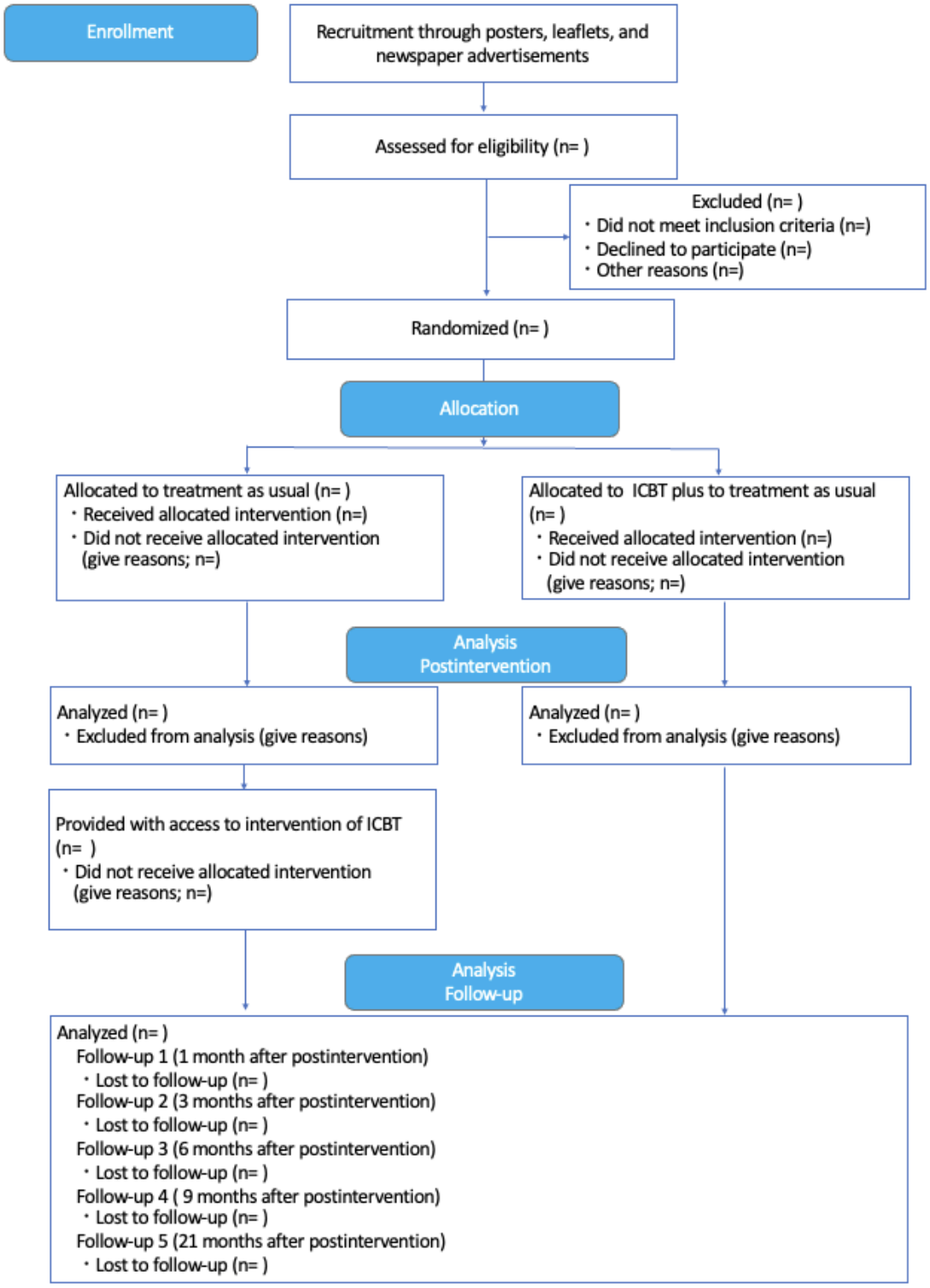
From August 2022 to July 2024, we will recruit 60 out-participants with female BN through posters, flyers, web or app advertisements (Google Ads, Twitter, and Facebook), newspaper advertisements, etc, posted at medical institutions throughout Japan. Since all participants will continue to be treated, they will be required to obtain clearance from their primary care physician prior to their study enrollment. The participants pay for TAU, but guided ICBT is free. Participants will be rewarded US $82.51 after intervention or waiting completion, regardless of group allocation. These include the amount of time patients spent on the trial and the difficulty of recruiting patients. To participate in this study, some hospitals will require referrals, which may cost the participant money.

Procedure

Participants will be directed to a website for this study by the various media mentioned earlier. There they will access the study website to apply for enrollment in the study. The clinical trial office at the University of Fukui that receives this application will coordinate the informed consent and eligibility test. Written informed consent will be solicited after the participants are provided research briefing either face-to-face or in a video call. Similarly, in the case of a minor, written informed consent from a legal representative is required. Next, they will complete a screening survey and a structured interview using Mini International Neuropsychiatric Interview version 5 [32,33]. Finally, they will be asked to complete a baseline data questionnaire on the web. The decision regarding the participant's exclusion or inclusion in the study will be made after they have completed the questionnaire. See Figure 1 for the flow of participants in this RCT.

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Figure 1. Flowchart of the recruitment and assessments during this study. ICBT: internet-based cognitive behavioral therapy.



Interventions

Guided ICBT Program

This ICBT program is based on the treatment manual for BN in Japanese [30]. The ICBT program consists of 1 assessment module and 12 treatment modules, each dedicated to one theme, along with reporting of the development process [31]. Each module includes psychoeducation and practice exercises on CBTs. Each module begins with a video containing complex supporting explanations and messages of encouragement (see Table 1 for details). A secure web-based platform [34] will be used for communication between therapists and participants, distribution of program materials, and collection of assessments. At the start of the intervention, participants will receive an email containing their username and a link to create their own password so that they can log into the platform. Participants will be provided access to 1 new module each week for the duration of the 12-week intervention, starting with module 1.

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For the first week, an assessment module (module 0) will be provided together with module 1. Once accessible, the modules will be available throughout the treatment duration. Participants who have not viewed the material or practiced it for a particular week will be sent a reminder once a week. If they have any questions, they can contact their therapists via the secure messaging feature on the platform. The therapist is a well-trained and experienced cognitive behavioral therapist (SH). The therapist will receive supervision from KM on the treatment of BN.

Table 1. The internet-based cognitive behavioral therapy modules in the randomized controlled trial.

	Module	Explanation
0	Assessment and goal-setting	First, a description of how to use the program and how the program is structured. Data on the user's basic clinical background, family composition, and chief complaint are collected. Then, treatment goals are set at the end.
1	Psychoeducation and cognitive behavioral model	An overview of the DSM-5[a] diagnostic classification [1] is provided and the epidemiological features of BN[b] [35]. Psychoeducation about CBT[c] for BN is introduced. Perceptions, attention, images, emotions, memories, thoughts, and the vicious circles of habitual behaviors are created graphically [30].
2	Relaxation and mindfulness medication	An introduction to the autonomic nervous system and training in breathing techniques, progressive muscle relaxation, and mindfulness meditation are provided [27,29].
3	Metacognitive training	Metacognition, one of the cognitive functions, is vulnerable in eating disorders [36], and there is evidence that cognitive weakness affects QOL[d] [37]. Metacognitive interventions may improve eating disorder severity, depression, and QOL [24,38]. This involves dichotomous thinking, emotional judgment, jumping to conclusions, and perfectionism, among others [30,31].
4	Attention bias modification and modification of interpretation for appearance	People with eating disorders tend to focus on body shape, weight, and food overload [39,40]. Exercises are provided that shift attention from food stimuli to neutral stimuli [41,42]. People with eating disorders frequently rate their body shape and weight negatively [43]. When recognizing the threatening bias of one's natural body shape and weight, the client can use techniques of relaxation and metacognition to handle concerns about perceived body shape and weight.
5	Behavioral experiment for binge eating	Behavioral experiments will be used to see that eating does not lead to uncontrolled weight gain [44].
6	Management of healthy food contents and eating habits	Self-monitoring using food diaries reduces the frequency of binge eating in web-based programs [45]. We propose a Japanese food menu to achieve a well-balanced diet [31]. This approach was developed based on a nutritional rehabilitation called "mechanical diet" by Garner et al [46].
7	Creating an anxiety hierarchy chart and stepwise exposure	Addressing fears associated with overeating can reduce overeating in BN [47,48].
8	Exposure to cues preceding binge eating and purging	Triggers for overeating and purging vary from person to person; however, exposure to such cues can reduce overeating and purging [29].
9	Cognitive restructuring	Negative self-statements associated with eating disorders are frequently observed in BN [49]. Such self-assertions shape the person's own identity and values [50]. Cognitive restructuring fosters alternative ways of thinking about these self-statements (adaptive thinking).
10	Rewriting of traumatic memory for image of the body	There are often individuals with BN who have negative childhood experiences [51]. If the interpretation of a traumatic memory is tormenting the patient, it should be rewritten to make it safer.
11	Schema work	Rescripting dysfunctional beliefs (schemas) may reduce the frequency of binge eating and purging as well as body shape concerns [52]. Dysfunctional beliefs are organized and alternative beliefs are written down.
12	Prevention of relapse	A summary of what participants have learned from the treatment will be solicited and used to plan future efforts to further reduce symptoms and prevent relapse.

[a]DSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.

[b]BN: bulimia nervosa.

[c]CBT: cognitive behavioral therapy.

[d]QOL: quality of life.

TAU (Control Group)

Participants will be allowed to continue receiving counseling, psychotropics, and other medications for the duration of the study. No new drug therapy or additional changes will be recommended during the study period by the study staff. However, the participant's primary care physician will not be prevented from modifying medications and refer participants to counseling or second-line therapy if deemed clinically appropriate. All changes in TAU will be documented along with the reasons for these changes. Participants in the control group (TAU) will be offered ICBT after a waiting period as well.

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Measures

Demographic Data

Participants will be asked about age, educational level, marital status, employment status, BMI, age at BN onset, duration of BN, comorbidities, and the presence or absence of psychotropic or antidepressant drug use.

Primary Outcome

The primary outcome will be the weekly combined frequency of binge eating and purging behaviors. These will be measured by an independent assessor whose allocations are masked.

Secondary Outcomes

Secondary self-reported outcomes will be the Eating Disorders Examination Questionnaire [53,54], Patient Health Questionnaire-9 [55,56], Generalized Anxiety Disorder Scale-7 [56,57], EQ-5D [58,59], Brunnsviken Brief Quality of Life Scale [60] at baseline, postintervention, and follow-up (1-, 3-, 6-, 9-, and 21-month follow-ups). Assessments based on the Working Alliance Inventory-Short Form [61] and Client Satisfaction Questionnaire [62,63] will be performed only after the treatment.

Sample Size

The required sample size was calculated using statistical analysis software (G*Power, version 3.1; Heinrich-Heine-Universitaet Duesseldorf). An effect size of Cohen *d*=0.90 from a previous study was used as a reference [64]. The significance level was set at *P* values <.05 for 2-sided tests. The power was set to 80%. The required sample size (assigned number of participants) will be 60 when considering a 30% noncompletion rate based on a previous study [65]. Completers in this study are defined as those who complete at least 80% of the module [65]. In addition, dropouts in this study are defined as those who drop out by not providing postevaluation data or those who discontinue their participation due to adverse events.

Randomization

Participants confirmed to be eligible and enrolled will be randomized in a 1:1 ratio to either the intervention (TAU added guided ICBT) or TAU alone groups by the truncated binomial design using UMIN's (University Hospital Medical Information Network) computer program (UMIN Center). The truncated binomial design is that complete randomization will be performed until the number of randomizations to any group reaches n/2, after which all subjects are allocated to the other group to prevent an imbalance in the number of people.

Statistical Analysis Plan

Statistical analysis will be performed using SPSS Statistics software (version 29; IBM Corp). Statistical analysis will be performed in accordance with the CONSORT (Consolidated Standards of Reporting Trials) guidelines and based on the intention-to-treat principle (Multimedia Appendix 1). Missing data will be handled by multiple imputations. Unpaired *t* test and Fisher exact test will be used to investigate the difference between the 2 groups at baseline. To compare treatment effects, we will use analysis of covariance for primary and all secondary outcomes. As a covariate, we plan to include a scale that is significantly different between the 2 groups at baseline. We also will perform a per-protocol analysis by excluding patients who deviate from the protocol. Analysis of covariance will also be performed on the follow-up data. However, if there are many missing values, we would consider generalized linear mixed models. All *P* values are 2-tailed, and *P* values <.05 will be considered statistically significant.

Ethical Considerations

The clinical trial protocol was approved by the Research Ethics Committee of the University of Fukui on August 15, 2022 (20220054), and was registered in the UMIN Domestic Clinical Trial Database (UMIN000048732). Each participant will then be informed that all participants will receive TAU from the general practitioner and that half of the participants will receive ICBT in addition to TAU. All adverse events will be reported, and serious adverse events will be reported immediately to the institutional review board. An adverse event is defined as any symptom or illness occurring during a clinical trial, whether related to the ICBT program or not. The results of the trial will be published in the appropriate journal, regardless of the outcomes. The trial will be implemented and reported in accordance with the CONSORT recommendations.

Results

Recruitment began on August 19, 2022, following the attainment of ethics approval on August 15, 2022, and the granting of permission to conduct the study on August 18, 2022. The first participant was enrolled on September 8, 2022, and recruitment is scheduled until July 2024. First, we plan to report the results using pre-post data from the RCT design. Subsequently, we will also report the 2-year long-term effects of those who received ICBT.

Discussion

Anticipated Findings

This paper presents the research protocol for the first RCT designed to investigate the effectiveness of therapist-guided ICBT for female Japanese patients with BN. Notably, a recent RCT demonstrated the efficacy of ICBT for binge eating disorder and other specified feeding or eating disorders [66]. However, although that study, conducted in the Netherlands, showed promising results for guided ICBT in these eating disorders, it involved participants with varying BMI of 19.5 or 40.0 kg/m^2 and did not include patients specifically diagnosed with BN. In contrast, this study protocol uses specific eligibility criteria, focusing solely on individuals with BN as the primary diagnosis while excluding other eating disorders, such as binge eating disorder. Consequently, the patient cohort to be included in our RCT is anticipated to be homogenous, thereby bolstering confidence in the treatment's effectiveness. Meanwhile, a systematic review and meta-analysis examining e-therapy's impact on eating disorders reported inconclusive evidence regarding the effect on overeating frequency in patients with BN [67]. Although this meta-analysis found improvements in various aspects, such as binge eating, vomiting, and laxative misuse, and in the discontinuation rate of overeating symptoms

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at the intervention's conclusion, the estimates were imprecise due to the heterogeneity in the quality of studies included in the analysis. Therefore, the authors concluded that e-therapy, including guided ICBT, could be effective for the management of eating disorders; however, further research is needed. A recent single-arm ICBT study targeting patients with eating disorders, including BN, reported positive outcomes [65]. In evidence-based medicine, individual RCT holds the highest level of evidence among single clinical trials [68]. Nevertheless, the outcomes of single-arm clinical trials lacking a control group should be interpreted with caution. In this context, our RCT may expand the understanding of the efficacy of guided ICBT for BN. To our knowledge, even recent RCTs have not provided effect estimates for patients with BN alone, as they also included other eating disorders [69,70]. Therefore, this study, by adhering closely to the RCT protocol described herein, will be well-positioned to offer valuable insights into the efficacy of guided ICBT on the frequency of overeating and purging along with any secondary symptoms in patients with BN. Furthermore, to the best of our knowledge, this is the first study designed to examine the effects of ICBT on behavioral changes related to eating styles in Japan. This is especially significant given Japan's distinct food culture and medical system that sets it apart from Western countries. The investigation into the effects of ICBT for BN within the context of Japan carries particular importance, as it navigates cultural nuances and differences in the medical system. Therefore, a multicenter study design is more likely to reduce bias and yield findings with broader generalizability.

Limitation

One limitation of the study is that it would not allow elucidation of the specific effects of the ICBT program because it does not use a psychological placebo group to control for nonspecific factors.

Conclusions

This RCT aims to validate and prove evidence for the efficacy of a Japanese culture–adapted ICBT program for female patients with BN. This will allow discussion of efficacy beyond the preliminary results obtained to date. The low availability of CBT is an international problem, and the implementation rate of CBT in Japanese psychiatric clinics is extremely low at 6.2% [71]. If positive results are obtained from this RCT, more patients with BN could receive early treatment, which could lead to early improvement in eating disorders that tend to be prolonged and chronic.

Acknowledgments

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Data Availability

Data sharing is not applicable to this paper as no data sets were generated or analyzed during this study.

Authors' Contributions

SH initiated the project, planned the research, obtained funding, and wrote the paper. KM, YH, HK, and YM are funded research collaborators who contributed significantly to the study conception or design. GA participated in data management and write-up of the report. YT, SN, RK, AS, YS, SF, NS, MN, RO, and RS contributed significantly at the various stages of research and development toward practical implementation. YM oversaw the overall conduct of the study. All authors read, critically revised, and approved the final paper.

Conflicts of Interest

None declared.

Multimedia Appendix 1
CONSORT-eHEALTH checklist.
[DOCX File , 23 KB - resprot_v12i1e49828_app1.docx]

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Abbreviations

BN: bulimia nervosa
CBT: cognitive behavioral therapy
CONSORT: Consolidated Standards of Reporting Trials
ICBT: internet-based cognitive behavioral therapy
RCT: randomized controlled trial
TAU: treatment as usual
UMIN: University Hospital Medical Information Network

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Protocol

Comparing the Efficacy of an Electronically Delivered Cognitive Behavioral Therapy Program to a Mental Health Check-In Program for Generalized Anxiety Disorder: Protocol for a Randomized Trial

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Abstract

Background: Generalized anxiety disorder (GAD) is a prevalent anxiety disorder, with cognitive behavioral therapy (CBT) being the gold standard treatment. However, it is inaccessible and costly to many, as the mental health industry is overwhelmed by the demand for treatment. This means effective, accessible, and time-saving strategies must be developed to combat these problems. Web-based interventions for mental health disorders are an innovative and promising way to address these barriers. While electronically delivered CBT (e-CBT) has already proved productive and scalable for treating anxiety, other less resource-intensive interventions can be innovated. Checking up on mental health face-to-face has been shown to provide similar benefits to patients with anxiety disorders previously, but more research is needed to evaluate the efficacy of web-based delivery of this intervention.

Objective: This study will compare the efficacy of e-CBT and a web-based mental health check-in program to treat GAD. These programs will both be delivered through a secure, web-based care delivery platform.

Methods: We will randomly allocate participants (N=100) who are 18 years or older with a confirmed diagnosis of GAD to either an e-CBT program or a mental health check-in program over 12 weeks to address their anxiety symptoms. Participants in the e-CBT arm will complete predesigned modules and homework assignments while receiving personalized feedback and asynchronous interaction with a therapist through the platform. Participants in the mental health check-in arm will be contacted weekly through the web-based platform's written chat feature (messaging system). Therapists will ask the participants a series of predesigned questions that revolve around a different theme each week to prompt conversation. Using clinically validated questionnaires, the efficacy of the e-CBT arm will be compared to the mental health check-in arm. These questionnaires will be completed at baseline, week 6, and week 12.

Results: The study received ethics approval in April 2021, and participant recruitment began in May 2021. Participant recruitment has been conducted through targeted advertisements and physician referrals. Complete data collection and analysis are expected to conclude by August 2023. Linear and binomial regression (continuous and categorical outcomes, respectively) will be conducted.

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Conclusions: To the research team's knowledge, this will be the first study to date comparing the efficacy of e-CBT with a web-based mental health check-in program to treat GAD. The findings from this study can help progress the development of more scalable, accessible, and efficacious mental health treatments.

Trial Registration: ClinicalTrials.gov NCT04754438; https://classic.clinicaltrials.gov/ct2/show/NCT04754438

International Registered Report Identifier (IRRID): DERR1-10.2196/48899

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KEYWORDS

anxiety; cognitive behavioral therapy; eHealth; electronic care; generalized anxiety disorder; internet; mental health; psychotherapy; treatment; web-based

Introduction

Overview

Generalized anxiety disorder (GAD) is a prevalent and debilitating mental health disorder. More than 450 million people are living with mental and behavioral disorders, with many being unable to receive adequate treatment [1-3]. Cognitive behavioral therapy (CBT) is considered one of the first-line treatments for GAD; however, it is not without its drawbacks [4-7]. CBT is often inaccessible to patients because it requires in-person time commitment during work hours, travel to appointments, high costs, and potential exposure to social stigma [8]. CBT is extremely resource-intensive, requiring a large time commitment from a trained mental health professional. With the prevalence of mental health disorders as high as they are, the demand for this first-line therapy is not being met by North American health care systems, leaving them overwhelmed and patients unable to receive treatment [8,9]. Innovative interventions that optimize resources without sacrificing the quality of care are required to meet this demand.

Fortunately, web-based interventions for mental health disorders are growing in prevalence and are a promising way to address the barriers associated with in-person treatment, such as accessibility and convenience [10-15]. The structured nature of CBT has allowed it to be effectively adapted into a web-based format (electronically delivered CBT; e-CBT) where patients can access standard concepts remotely and in their own time. While e-CBT has already proven productive and scalable for treating anxiety disorders [10,16-19], developing less-intensive interventions that still benefit patients could allow for even more scalability. Not all patients may require the full structure of e-CBT and could still benefit from a less-intensive option, such as structured mental health conversations with a care provider. Checking in on individual mental health has previously shown benefits to patients with anxiety disorders, but much of this research has investigated in-person approaches and synchronous web-based deliveries [20-22]. Transferring this to a web-based asynchronous messaging format could allow for increased privacy, accessibility, temporal flexibility, and decreased cost and geographical barriers. Understanding how the delivery of e-CBT compares to a web-based delivery of mental health check-in conversations with a care provider can provide insight into the application of this as a viable intervention in the future.

Objectives

The primary objective will be to compare the efficacy of an e-CBT program to a web-based mental health check-in program. Additionally, the individual effects of each treatment will be evaluated using clinically validated symptomology questionnaires.

Methods

Study Design

This study will use an open-label randomized controlled trial design to investigate the effects of e-CBT versus a web-based check-in program for GAD. Participants will be randomly assigned, in a ratio of 1:1, to either a 12-week e-CBT program tailored to GAD or a 12-week mental health check-in program to address their symptoms. In addition to these interventions, participants will continue with treatment as usual (ie, lifestyle, family physician appointments, and medications).

Participants

Participants (total=100; e-CBT=50; and check-in=50) will be recruited in Kingston, Ontario, from outpatient psychiatry clinics at both Kingston Health Sciences Centre sites (Hotel Dieu Hospital and Kingston General Hospital). Additional recruitment from Providence Care Hospital, family doctors, physicians, clinicians, and self-referrals will occur. Once informed consent is obtained, participants will be evaluated by a psychiatrist on the research team through secure video appointments to make or confirm a diagnosis of GAD using the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) [23].

Inclusion criteria include being aged 18 years or older at the start of the study, having a diagnosis of GAD according to the DSM-5 criteria by an attending psychiatrist on the research team, having the competence to consent to participate, having the ability to speak and read English, and having consistent and reliable access to the internet. Exclusion criteria include active psychosis, acute mania, severe alcohol or substance use disorders, and active suicidal or homicidal ideation. To avoid any confounding effect on the efficacy of this e-CBT program, participants currently receiving or having received CBT in the past year will also be excluded from this study to avoid confounding effects of treatment. If eligible for the study, participants will be randomly assigned to either the e-CBT program (n=50) or the mental health check-in program (n=50). Following the completion of the study, participants who were

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randomly assigned to the mental health check-in arm will be offered the e-CBT program if they are interested. During the informed consent process, it will be explained to all participants that this program is not a crisis resource and that they will not always have access to their therapist. In the case of an emergency, participants will be directed to the proper resources (ie, emergency department and crisis lines), and this event will be reported to the principal investigator.

Procedures

CBT Arm

The e-CBT modules are designed to instill balanced and constructive coping strategies in participants. During the e-CBT program, the focus will be on essential thinking and behavioral skills to assist participants in becoming more engaged in day-to-day activities (Table 1). Additional focus will be placed on the connection between thoughts, behaviors, emotions, physical reactions, and the environment. All care providers are research assistants hired by the principal investigator. They all undergo training in psychotherapy delivery and additional training by the principal investigator on the research team, who is also a licensed therapist and an expert in web-based delivery, before interacting with participants. During this training, therapists complete feedback on practice homework, which is reviewed to ensure adequate quality of work. All care providers are supervised by a licensed therapist [10-12,16,24-26] who will review feedback before submission.

Table 1. Overview of the 12-week electronically delivered CBT[a] program content.

Week	Session	Description
1	What is generalized anxiety disorder?	Provides expectations for the course and introduces anxiety and CBT.
2	The 5-part model	Introduces the concept of the 5-part model and how a situation, thoughts, feelings, physical reactions, and behaviors are connected and how they interact.
3	Strategies for stressful situations	Provides an overview of helpful strategies that can be used in stressful situations, including pleasurable activities and helpful breathing techniques.
4	Situation, thoughts, feelings, physical reactions, and behaviors	Provides a further detailed exploration of the 5-part model and how changes in one area can affect the other 4 parts.
5	The thought record	Highlights the first 3 columns of the thought record; a tool used to help understand the connection between feelings, behaviors, and thoughts. The first 3 columns include the situation, followed by the feelings and automatic thoughts associated with it.
6	Automatic thoughts	This delves into the role of automatic thoughts and how they influence feelings. The focus of this session is to understand how to identify automatic thoughts and specifically identify the most dominant idea, or "hot thought," when presented with a stressful situation. Common thinking errors are also discussed in this session.
7	Activity scheduling	Provides a break from learning about the thought record and instead explains how to use an activity record; a tool designed to record and plan weekly activities. This session focuses on how tracking activities can inform mood changes and reinforce the scheduling of pleasurable activities.
8	Evidence	Focuses on the fourth and fifth columns of the thought record, which are designed to help gather the information that supports or does not support the identified hot thought.
9	Alternative and balanced thinking	Focuses on the final 2 columns of the thought record, which reflect on the evidence columns to help find an alternative or balanced view of the situation. The last column invites the viewer to rerate their feelings based on the completion of the thought record.
10	Experiments	Explain the importance of conducting experiments to start believing alternative or balanced thoughts from the thought record and initiating changes in ineffective thinking patterns.
11	Action plans	Centered around identifying a problem that needs to be solved and provides a framework for creating a plan for solving the problem.
12	Review	The final session is a review of the course and summarizes the main CBT concepts and tools that have been taught throughout the program.

[a]CBT: cognitive behavioral therapy.

The e-CBT care plan consists of 12 weekly sessions of approximately 30 slides and interactive content, delivered through the Online Psychotherapy Tool (OPTT), a secure, web-based, cloud-based mental health care delivery platform. The e-CBT module content will mirror in-person standard CBT content, including different weekly topics, general information, skill overviews, and homework. Participants will be instructed to go through the content and complete homework at the end of the session, which will help them practice the skills they learned during that session. Homework will be submitted directly through OPTT and reviewed by the care provider assigned to the participant, who will provide personalized feedback within 3 days of submission. Care providers will have access to predesigned session-specific feedback templates to use as a basic structure to write their feedback. Doing so reduces the time needed to respond to each patient; therefore, the number of patients each care provider can handle increases. On average, developing this feedback will take a care provider 15-20 minutes per patient. In addition to the weekly feedback, participants have the option to message their care provider through the

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platform throughout the week regarding any questions or concerns they may have.

Mental Health Check-In Arm

Participants in the mental health check-in arm will have weekly interactions with a care provider through the chat feature in OPTT. The care provider will reach out weekly using structured question prompts to initiate interaction with the patient (Table 2).

Table 2. Mental health check-in weekly procedures and question prompts.

Week	Topic	Question prompts
1	Mood	Tell me about yourself. How have you been feeling lately? How has the pandemic affected your mood? What differences have you noticed in your mood compared to the past?
2	Sleep	How have you been? Tell me about your week. I want to ask about your sleep. How many hours do you get? Do you feel rested? Do you think you need to make any changes to your sleep hygiene?
3	Activity	How was your week? How has your anxiety level been? What do you usually do to stay active during the day? Are there any indoor activities you can do at your place? Have you been using any online exercise programs?
4	Hobbies	What did you do in the past week? Do you have any hobbies? How long have you been doing them? Have you found any new activities that you enjoy recently?
5	Friendship	How was your week? How has the pandemic affected your relationship with your friends? Have you stayed in touch with your close friends during the pandemic? How often do you interact with your friends?
6	New events	How have you been? Have there been any new events in the past weeks? Are you planning to do anything new this week? Are you planning to do anything new this week? Are you expecting to hear any news from your family/friends?
7	Job and study	How have you been? Tell me about your week. How are you managing your day-to-day responsibilities (eg, job, school, personal, etc)?
8	Diet and food	How was your week? Let's talk about your eating habits. How does your anxiety affect your appetite? Are you satisfied with your diet? How often do you cook? Do you prefer homemade food or take-out?
9	Books, movies, and television	How was your week? Has your anxiety affected your concentration? Do you like reading books? What is the last book you read? Are there any books you would recommend to your friends? What shows do you enjoy watching? What are some shows you would recommend to your friends?
10	Phone, apps, and games	Tell me about your week. How many hours a day do you usually spend on your phone? What is your favourite app? Do you play any games? What kinds of games do you like to play (eg, board games, cards, video games, etc)?
11	Habits	How have you been? How was your week? What do you think are some of your healthy habits? What are some habits you would like to change?
12	Accomplishments	How was your week? How did you find this program? Were the weekly check-ins helpful? Overall, was this program helpful for you? Why or why not? Are you interested in an online cognitive behavioural therapy program? Why or why not?

Outcome Evaluation and Analysis

Participants in both arms will complete the following clinically validated questionnaires at baseline: State-Trait Anxiety Inventory (STAI) [27], Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form (Q-LES-Q-SF) [28], Generalized Anxiety Disorder-7 item (GAD-7) [29], Depression Anxiety Stress Scale-42 item (DASS-42) [30], and a demographic questionnaire. All questionnaires will be completed through OPTT. The STAI, Q-LES-Q-SF, GAD-7, and DASS-42 will be completed again during week 6 and week 12. Using data from previous research incorporating this e-CBT program, a sample of 50 participants in each group was determined to be sufficient for an effect size of 0.5, a power of 0.8, and an α of .05 [31].

Before analysis, the data will be examined for missing, nonsensical, and outlying variables. Missing data will be removed on a per-protocol basis, with a statistical analysis significance level set at .05. Demographic information (ie, age, gender, and race) will be assessed between groups and program noncompleters using independent sample *t* tests. A 2×3 repeated measures ANOVA will be completed for each questionnaire score at the time points to investigate the differences between the 2 groups. An intention-to-treat analysis will be completed to assess whether the outcome of treatment impacts participants' likelihood of not completing the program. Data will also be assessed with linear mixed-effects models with random effects as patient identification and fixed effects as treatment, time, and their interaction. SPSS (version 24; IBM Corp) will be used for all statistical analyses.

Data Privacy

Participants will only be identifiable by an anonymous identification number, and all files are stored securely on a server with password encryption. Participant data will only be accessible by the care providers directly assigned to the participant, and anonymized data will be provided to the analysis team members. Participants can withdraw from the study at any point and request that their data be removed from the analysis.

OPTT is compliant with the Health Insurance Portability and Accountability Act, the Personal Information Protection and Electronic Documents Act, and Service Organization Control-2.

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Additionally, all servers and databases are hosted in the Amazon Web Service cloud infrastructure, which is managed by MedStack to assure all privacy and security regulations are met. OPTT does not collect any identifiable personal information or IP addresses for privacy purposes. OPTT only collects anonymized metadata to improve its service quality and provide advanced analytics to the clinician team. OPTT encrypts all data, and no employee has direct access to participant data. All encrypted backups will be kept in the S3 storage that is dedicated to Queen's University.

Ethic Approval

The study was approved (File 6032033) by the Queen's University Health Science and Affiliated Teaching Hospitals Research Ethics Board in April 2021.

Results

The recruitment of participants for this study began in May 2021. Participant recruitment has been conducted through social media advertisements, physical advertisements, and physician referrals. To date, 50 participants have been recruited. Data collection is expected to conclude by August 2023, and data analyses are expected to be completed by September 2024, with linear regression analysis (for continuous outcomes) and binomial regression analysis (for categorical outcomes) being conducted.

Discussion

This study protocol outlines the methods to compare a 12-week e-CBT program and a 12-week check-in program for the management of GAD symptoms. Additionally, the individual effects of each treatment will be evaluated using clinically validated symptomology questionnaires.

GAD is a prevalent mental health disorder that demands resource-intensive interventions to properly address symptoms. CBT is currently one of the first-line treatments for GAD, but it tends to be inaccessible to patients and requires a high level of time commitment from mental health care professionals. Using the internet to deliver mental health treatments has become a promising solution in recent years, with e-CBT being scalable, accessible, and effective in treating GAD [16-18,32-34]. Now that e-CBT is an effective treatment option for patients with GAD, understanding ways to tailor the care to each patient, with varying intensity levels, is crucial for the future of scalability [11,12,16,24-26]. Checking in on patients' mental health is another form of mental health care that can be less resource-intensive while still offering benefits to patients with GAD. Delivering this electronically and asynchronously would allow for more accessible access to treatment while also providing decreased time commitment, allowing more patients to be helped. There is less research on the impact of a check-in intervention over messaging services, identifying a knowledge gap. By directly comparing this check-in intervention to e-CBT, the efficacy and feasibility of implementing this as a treatment option in a web-based mental health clinic can be investigated. This comparison is original to previous literature, providing a direct comparison between e-CBT and mental health check-ins to investigate whether this is a viable resource to implement in a real-world setting. Most previous literature has investigated the comparison of e-CBT to in-person interventions, treatment groups, medications, or control groups, but none of the sort in this protocol, to the author's knowledge.

The limitations of this protocol include the lack of a control group. However, the e-CBT program used in this protocol has been previously clinically validated [11], and the main objective of this study is to uncover the differences between these 2 treatment arms. Furthermore, this protocol does not currently include a long-term follow-up, which is something that could be explored in the future.

These findings can provide valuable insight into the effectiveness of a weekly mental health check-in from a care provider versus a validated 12-week e-CBT intervention. If the check-in intervention proves to be a viable and effective option, it could be used as a less resource-intensive option, used in conjunction with e-CBT, or as an option for patients presenting with less severe symptoms. By providing a framework for future research to use these forms of check-in interventions, more work can be done investigating the effects in conjunction with other treatments as well. Electronically delivered mental health interventions are an ever-expanding area with a focus needed on how to continue growing the reach to more patients without sacrificing accessibility and quality of care.

Data Availability

The data sets generated during and/or analyzed during this study will be made available from the corresponding author on reasonable request.

Conflicts of Interest

NA and MO have cofounded the care delivery platform in use (ie, Online Psychotherapy Tool) and have ownership stakes in OPTT Inc.

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Abbreviations

CBT: cognitive behavioral therapy
DASS-42: Depression and Anxiety Stress Scale-42 item
DSM-5: Diagnostic and Statistical Manual of Mental Disorders, 5th edition
e-CBT: electronically delivered cognitive behavioral therapy
GAD-7: Generalized Anxiety Disorder-7 item
OPTT: Online Psychotherapy Tool
Q-LES-Q-SF: Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form
STAI: State-Trait Anxiety Inventory

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Protocol

A Suicide Prevention Intervention for Emerging Adult Sexual and Gender Minority Groups: Protocol for a Pilot Hybrid Effectiveness Randomized Controlled Trial

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Abstract

Background: Suicide attempts and suicide death disproportionately affect sexual and gender minority emerging adults (age 18-24 years). However, suicide prevention strategies tailored for emerging adult sexual and gender minority (EA-SGM) groups are not widely available. The Safety Planning Intervention (SPI) has strong evidence for reducing the risk for suicide in the general population, but it is unclear how best to support EA-SGM groups in their use of a safety plan. Our intervention (Supporting Transitions to Adulthood and Reducing Suicide [STARS]) builds on content from an existing life skills mobile app for adolescent men who have sex with men (iREACH) and seeks to target core risk factors for suicide among EA-SGM groups, namely, positive affect, discrimination, and social disconnection. The mobile app is delivered to participants randomized to STARS alongside 6 peer mentoring sessions to support the use of the safety plan and other life skills from the app to ultimately reduce suicide risk.

Objective: We will pilot-test the combination of peer mentoring alongside an app-based intervention (STARS) designed to reduce suicidal ideation and behaviors. STARS will include suicide prevention content and will target positive affect, discrimination, and social support. After an in-person SPI with a clinician, STARS users can access content and activities to increase their intention to use SPI and overcome obstacles to its use. EA-SGM groups will be randomized to receive either SPI alone or STARS and will be assessed for 6 months.

Methods: Guided by the RE-AIM (reach, efficacy, adoption, implementation, and maintenance) framework, we will recruit and enroll a racially and ethnically diverse sample of 60 EA-SGM individuals reporting past-month suicidal ideation. Using a type-1 effectiveness-implementation hybrid design, participants will be randomized to receive SPI (control arm) or to receive SPI alongside STARS (intervention arm). We will follow the participants for 6 months, with evaluations at 2, 4, and 6 months. Preliminary effectiveness outcomes (suicidal ideation and behavior) and hypothesized mechanisms of change (positive affect, coping with discrimination, and social support) will serve as our primary outcomes. Secondary outcomes include key implementation indicators, including participants' willingness and adoption of SPI and STARS and staff's experiences with delivering the program.

Results: Study activities began in September 2021 and are ongoing. The study was approved by the institutional review board of the University of Pennsylvania (protocol number 849500). Study recruitment began on October 14, 2022.

Conclusions: This project will be among the first tailored, mobile-based interventions for EA-SGM groups at risk for suicide. This project is responsive to the documented gaps for this population: approaches that address chosen family, focus on a life-course

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perspective, web approaches, and focus on health equity and provision of additional services relevant to sexual and gender minority youth.

Trial Registration: ClinicalTrials.gov NCT05018143; https://classic.clinicaltrials.gov/ct2/show/NCT05018143

International Registered Report Identifier (IRRID): DERR1-10.2196/48177

(JMIR Res Protoc 2023;12:e48177) doi:10.2196/48177

KEYWORDS

lesbian, gay, bisexual, transgender, queer, plus; LGBTQ+ health; suicide; peer navigator; emerging adults; life skills; mobile phone

Introduction

Background

Suicidal behavior disproportionately affects sexual and gender minority youth [1] who are also at high risk for risk factors for suicide including harassment and trauma [2-4], yet few interventions address the specific needs of this population. In the United States, suicide rates increased for emerging adults (aged 18-24 years) in the past decade; suicide is now the second leading cause of death [5,6]. Youth who identify as sexual and gender minorities are >3 times more likely to have made a suicide attempt than those identifying as heterosexual [7]. Although sexual and gender minority individuals constitute only 4.5% of the general population (rates vary widely across studies), 10% of emerging adult (aged 18-24 years) suicide deaths occur among people who identify as sexual and gender minorities, representing a significant disparity [8]. Evidence-based suicide prevention programs tailored for emerging adult sexual and gender minority (EA-SGM) groups are not widely available.

Interventions to reduce suicidal ideation and behavior must address the unique risk factors that predict suicidal ideation and attempts in EA-SGM groups, including discrimination [9-11], family or friend rejection [9,12-16], and low positive affect [17]. Moreover, interventions promoting protective behaviors and social support may provide a complementary approach to traditional interventions to reduce risk in EA-SGM groups [18,19]. Developing youth's assets (eg, coping strategies and activity scheduling to promote positive affect) and linkage to health-promoting resources (eg, social support and access to safe spaces) may reduce suicidal ideation. EA-SGM people who can envision a healthy future in which they achieve their long-term goals have, on average, great psychological well-being [20], few risk behaviors [21,22], and improved use of health services [23]. These findings are consistent with the suicide prevention literature, in which goal-action consistency is targeted to reduce suicide risk [24-26] and improve mood regulation [27,28], and social connection is viewed as a factor that reduces the likelihood of developing suicidal ideation [29,30] or the intensity of suicidal ideation [31]. Studies are yet to evaluate the extent to which improving coping with discrimination, promoting positive affect, and improving social support are associated with reduced risk for suicide among EA-SGM groups.

Individuals at risk for suicide and clinicians alike perceive Safety Planning Intervention (SPI) as acceptable and useful [32,33]. SPI is a brief intervention that combines evidence-based strategies to reduce suicidal behavior by providing prioritized coping strategies, identifying sources of social and professional support, and providing lethal means counseling to reduce access to potential suicide methods. Several studies have demonstrated that SPI can be successfully implemented in a variety of contexts, including university counseling centers [34] and crises call centers [35]. However, this intervention has not been explicitly evaluated among sexual and gender minority youth. This is important because there are many unique circumstances in some sexual and gender minority youths' lives that may require adaptation of SPI, including reduced family support [36], experiences of discrimination [37], and low positive affect in general [38], each of which is a unique risk factor for suicide.

SPI and follow-up contact is associated with a significantly reduced risk of suicide attempts [39]; however, some studies indicate that individuals struggle to use the safety plan in suicidal crises. Patients reported barriers to using their safety plan after they generate it, which include the following: difficulty in finding the paper form; not thinking about or being motivated to use the plan during crises; and struggling with social isolation, which reduces the ability to enact safety plan steps to connect with one's support network [40]. Recent studies have found that mobile apps, such as BeyondNow, Safety Net, and MYPLAN, show promise for implementing safety plans [41]. However, patients tend to discontinue using mobile apps in general, and among sexual and gender minority communities, a common sentiment is that apps are initially engaging but not necessarily effective [42]. To address this issue, we propose to bolster app engagement by providing users with weekly peer mentor sessions. The potential of this peer mentor care navigator approach in reducing suicide risk among lesbian, gay, bisexual, transgender, queer, plus (LGBTQ+) youth has not been evaluated.

EA-SGM people are early adopters of technology and rely heavily on e-delivered information [43,44], often ranking the web as their top resource to explore their sexuality and to access social support [45-49]. Our proposed intervention takes advantage of this phenomenon by examining whether a web intervention, Supporting Transitions to Adulthood and Reducing Suicide (STARS), reduces suicidal ideation among EA-SGM groups. We propose to examine a mobile app, STARS, which leverages peer mentoring and support to ensure that EA-SGM groups can implement their safety plan in times of suicidal crises. STARS will provide users with web opportunities to receive goal-related feedback and social support from clinically supervised peer mentors, who will function as care navigators.

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This peer-to-peer approach offers a confidential and user-controlled opportunity to support EA-SGM groups. We will assess whether the peer mentor model to provide social support reduces the impact of discrimination, promotes positive affect, overcomes barriers to SPI use, and decreases suicidal ideation.

Objectives

STARS was developed based on the Integrated Behavior Model [50] and will include both the app and peer mentor access. Consistent with type-1 hybrid effectiveness randomized controlled trial design, our pilot study examines preliminary efficacy end points alongside implementation targets. We use the RE-AIM (reach, efficacy, adoption, implementation, and maintenance) framework [51] to guide the assessment of these concurrent end points. If successful, this pilot study will identify the potential clinical utility of STARS for suicide prevention in a vulnerable, often marginalized population based on key parameters needed to inform a future clinical trial.

Our study goals are (1) to develop STARS through a systematic adaptation of an existing web intervention (iREACH [52]) using the assessment, decision, administration, production, topical experts–integration, training, and testing (ADAPT-ITT) [53] framework; (2) to examine the preliminary efficacy (suicidal ideation and behaviors) and mechanisms of action of STARS, relative to our control condition (SPI only); and (3) to examine STARS' implementation outcomes when compared with the control arm using RE-AIM [51,54] metrics. This exploratory project will identify the potential clinical utility of STARS for suicide prevention in a vulnerable, often marginalized population based on key parameters needed to inform a future efficacy trial.

Methods

Study Design

We will use the RE-AIM implementation science framework [51] to guide the assessment of the program's RE-AIM. We will pilot-test STARS using a type-1 effectiveness-implementation hybrid design in a racially and ethnically diverse sample of 60 EA-SGM individuals living in Philadelphia, PA, who report past-month suicidal ideation. Participants will be randomized to receive an in-person SPI (control arm) or to receive in-person SPI alongside STARS (intervention arm). After the baseline evaluation, we will follow participants for 6 months, evaluating them at 2, 4, and 6 months.

Consistent with our type-1 design, we will prioritize the preliminary effectiveness outcomes (suicidal ideation and behavior) and hypothesized mechanisms of change (coping with discrimination, social support, and positive affect). These measures will help us estimate critical parameters for a future trial as our *primary outcomes*. We will also monitor implementation targets related to reach, adoption, implementation, and maintenance as *secondary outcomes*.

This study is registered on ClinicalTrials.gov (NCT03678181).

Participants and Enrollment Procedures

Eligibility Criteria

Participants will (1) be aged between 18 and 24 years, (2) live in the Philadelphia Metropolitan Area (given that we are most familiar with those emergency service options) and plan to live in the area for the next 6 months, (3) report past-month suicidal ideation, (4) identify as a sexual minority (ie, identify with a sexual identity other than heterosexual) or gender minority (ie, sex assigned at birth is different from gender identity), and (5) report owning and having regular access to a smartphone that they can use to participate in study activities. Those with symptoms of psychosis that are not adequately treated will be excluded.

Recruitment, Screening, and Enrollment

With increasing use of the internet, there exists a great opportunity for reaching traditionally hard-to-reach and vulnerable populations, including EA-SGM groups and racially diverse groups. We will reach the population using recruitment advertisements on social media platforms (eg, Facebook, Instagram, Reddit, and Twitter). We developed advertisements that promote our target population's interest by including diverse images of youth (ie, images of different ages and portraying diverse races and ethnicities) and using advertisement-targeting specific to sociodemographic characteristics (eg, youth living in our region and who meet our age range) and interests (eg, youth following media with LGBTQ+ themes). Materials avoid identifying candidates as EA-SGM groups in the recruitment text to prevent unintended disclosure. Advertisements will link interested individuals to the study survey in REDCap (Vanderbilt University), where they may verify their eligibility, email the team, or locate a toll-free number if they want to learn about the study. We have recruited through these platforms for more than a decade with a significant track record of demonstrated success [55] and plan to use lessons learned from these efforts to guide the implementation of our proposed recruitment strategy.

We anticipate reaching our recruitment goal within 9 months of beginning enrollment. In previous trials in Philadelphia with sexual and gender minorities in this age group, we have found that >40% of individuals who clicked on our web advertisements through social media screen were eligible. Of those, 80% provided full contact information, and approximately 40% scheduled and attended an in-person enrollment visit. We expect that most (approximately 85%) will consent and enroll in the trial. Thus, for the proposed study, we expect to screen approximately 550 individuals, conduct full eligibility evaluations with approximately 70 (12.7%) EA-SGM individuals in person over the 9-month period, and obtain consent from and randomize 60 (10.9%) for our study. On the basis of these estimates, we will randomize 5 to 7 participants per month over the course of 9 months. As an enrollment strategy, we will provide complimentary rideshare to and from the baseline visit site as needed.

The web screener survey (through REDCap) will include initial consent to be screened, followed by questions that relate to eligibility based on our inclusion and exclusion criteria.

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Participants will be screened for self-reported psychosis using 2 questions taken from the Diagnostic Interview for Anxiety, Mood, and OCD and Related Neuropsychiatric Disorders screener [56]. Participants who report no active psychosis and meet all other criteria for eligibility will be asked the final eligibility question of whether they have had suicidal ideation in the past month. Participants who meet all the preliminary eligibility requirements will be asked to provide contact information and preferred mode of contact.

Phone Screening

Participants who are found to be preliminarily eligible via the web screening process will be contacted via phone. During phone screening, information about the potential participants' physical location will be collected (if emergency services are needed) and a brief safety check will be conducted. Then, potential participants will be scheduled for their baseline evaluation.

Baseline Evaluation

If preliminarily eligible, participants will be scheduled for an in-person visit where they will complete the informed consent process and be evaluated by a licensed clinician for suicidal ideation and attempts using the Columbia–Suicide Severity Rating Scale (C-SSRS) [57]. Ineligible participants will be provided with referrals to mental health services based on their insurance. Enrolled participants will receive SPI, complete the baseline survey, and then be randomized. EA-SGM participants randomized to STARS will have immediate access to the app, be scheduled for their 6 peer mentor check-ins, and learn how they can reschedule future peer mentor sessions.

Randomization

Enrolled participants will be randomized during the baseline visit through REDCap's randomization module. A statistician created a block randomized list to ensure that there is an equal number of control and STARS participants, with a total of 102 assignments in blocks of size 4 or 6. Participants randomized to the control condition will complete follow-up assessments over 6 months. Although providing the gold-standard SPI to participants in the control condition may result in a floor effect, withholding this protocol would be unethical, given the participants' vulnerability to suicide. This design will allow for a preliminary evaluation of whether the incorporation of STARS improves the use of SPI among EA-SGM groups.

Control Arm

SPI [58] involves a collaborative and personalized conversation between the intervention facilitator and a person who is at high risk for suicide. SPI reduces the likelihood of future suicide attempts by collaboratively developing a written safety plan that consists of six steps (Table 1): (1) identifying warning signs, (2) implementing internal coping strategies, (3) using social interactions for distraction, (4) using one's social network (family and friends) for help, (5) using professional resources for help, and (6) making the environment safe by reducing access to lethal means.

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Table 1. Core components, scientific rationale, and measurement metrics.

Features	Description	Scientific rationale (measurement metrics)
Safety plan	• Readable and editable digital version of the six-step Safety Planning Intervention, which includes: (1) warning signs, (2) internal coping strategies, (3) using social people and situations for distraction, (4) using one's social network (family and friends) for help, (5) using professional resources for help, and (6) making the environment safe • Phone numbers are tappable to facilitate calling • Call 911 button	• Increase the use of the Safety Planning Intervention [58] during times of crises by pairing the safety plan app content with peer mentor care navigator support (number of times accessed, number of times edited, and total time spent)
Resources and activities	• Multimedia resources and information about relationships, support, identity, stress, emotional well-being, safety planning and suicide, discrimination, drugs and alcohol, and life skills—tailored for emerging adult sexual and gender minorities, inclusive learning styles and health literacy • Robust management system to create new content and activities • Activity types include quizzes, self-assessments, goal setting, choose-your-own-adventure, sorting (eg, sort activities into healthy or unhealthy coping), and matching formatted to promote skills acquisition (eg, match the emotion to a typical behavior)	• Content corresponds to and aligns with the Integrated Behavior Model [50] (number of articles read and total time spent) • Interactive activities to address suicide prevention and reinforce emerging adult sexual and gender minorities' social support, coping with discrimination, and positive affect (number of activities completed and total time spent)
Peer mentor appointments	• Schedule of upcoming peer mentor appointments with links to web-based meeting room • List of completed peer mentor appointments	• Provide social support, reduce the impact of discrimination, promote positive affect, and reduce barriers for emerging adult sexual and gender minorities to enact their Safety Plans (number of sessions attended)
Profile	• Personalized username, customizable avatar, brief bio, badges earned, list of forum posts, and comments	• Personalization, gamification, and cues to incentivize engagement (number of times visited)
Goals	• Select from researcher-created goals or create new goals with milestones, tasks, and a journal feature	• Goals feature builds on self-management skills (number of goals set and milestones and tasks completed)
Forum	• Start or add to existing discussions; upload images, videos, memes; and so on • Favorite posts and follow others • Staff monitor and add to forum posts and include polls to encourage dialogue	• Peer support for resilience and behavior change (number of posts, comments, and likes; total time; and content of posts)
Gamification	• Sophisticated tracking of app use to trigger behavior-specific rewards • Badges awarded for tracked events	• Gamification [59] features incentivize continued engagement (number of log-ins and badges earned)

Intervention Arm

In the STARS intervention, our transdisciplinary team will develop and pilot-test an intervention to reduce suicidal ideation and behaviors among EA-SGM groups. STARS will include content about suicide prevention, including safety planning and targeting positive affect, and discrimination and social support. STARS will consider the unique cultural factors that may influence the efficacy of safety planning for EA-SGM groups (eg, access to LGBTQ+ resources) and include supports that promote the use of a suicide safety plan constructed with a licensed clinician.

Theoretical Foundation

The Integrated Behavior Model informs STARS in that the intervention acknowledges that EA-SGM groups' attitudes, norms, self-efficacy, and intentions are key constructs to target to effect behavior change (Figure 1). For STARS, we will adapt the Integrated Behavior Model–informed intervention messaging to promote EA-SGM groups' use of the safety plan during times of crisis by improving participants' attitudes toward, intention to use, and self-efficacy in using their safety plan (Multimedia Appendix 1). By enlisting peer mentor support, STARS will also target perceived norms about the frequency of safety plan use among their peer group. In addition, STARS will include a copy of the participant's safety plan and have topics to facilitate using the plan, with special attention dedicated to differences in social networks and previous negative experiences with health care to improve the impact of SPI among EA-SGM groups [11,60]. STARS provides life skills training (eg, building affirming relationships, applying to schools, study skills,

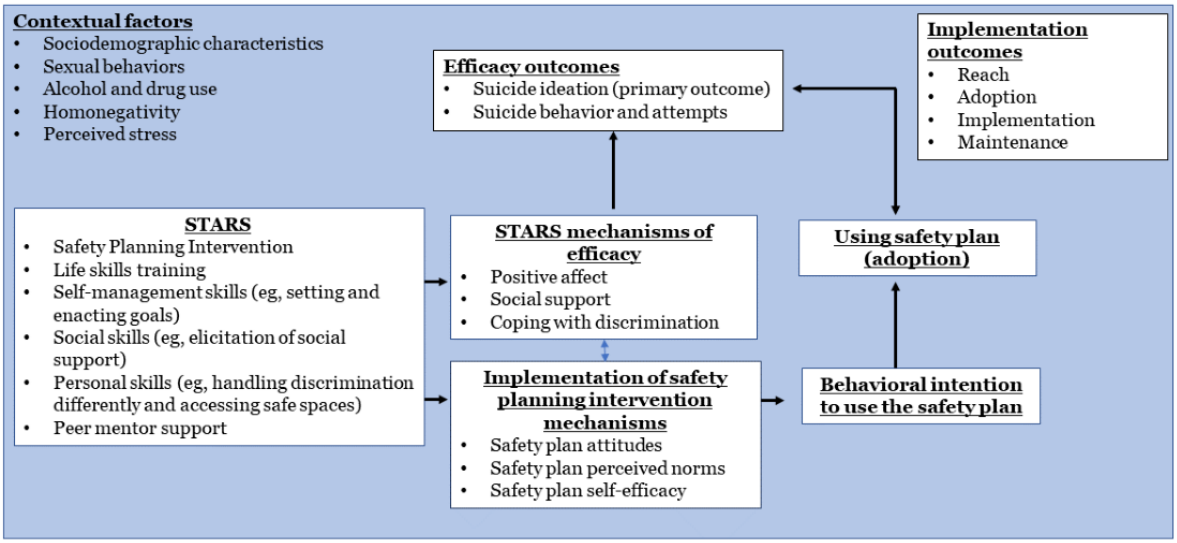
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resume-writing skills, and emotion management skills; Table 1) and peer-delivered motivational interviewing (to support the use of the safety plan), through which, EA-SGM groups will learn about suicide prevention, set goals to shift their attitudes toward their safety plan, increase their intention to use their safety plan, and engage with a community that understands their needs and norms. This will help participants to manage their suicidal thoughts without engaging in suicidal behavior.

Consistent with the Integrated Behavioral Model, we recognize the importance of bolstering the linkage between intention and behavior to use their safety plan. To support this linkage, STARS will focus on three major skill sets: (1) self-management skills (eg, setting and enacting goals to promote positive affect), (2) social skills (eg, elicitation of social support), and (3) personal skills (eg, coping with discrimination more effectively and seeking safe spaces). With the support of peer mentors, EA-SGM groups can set goals to shift their sense of mastery (to improve positive affect), engage with a community that understands their needs (to improve social connection), and identify local resources that support their well-being (to improve coping and reduce the impact of discrimination on their well-being). Finally, STARS will promote the use of the safety plan by equipping peer mentors to discuss barriers to enacting the safety plan.

STARS will address theoretical mechanisms that can reduce the severity of suicidal ideation, including coping with discrimination and improving social support. STARS additions will include a module about promoting positive affect through behavioral activation, pleasant events scheduling, and safety plan content. STARS will address constructs of self-efficacy, knowledge, and attitudes about safety planning.

Figure 1. Conceptual model. STARS: Supporting Transitions to Adulthood and Reducing Suicide.



Intervention Components

STARS uses traditional multitier architecture in which the concerns are separated into presentation, service, and database *layers*. The administrative portal was written in React (Meta Platforms), whereas the mobile app is written in React Native, which allows us to build native apps for both Android and iPhone, reusing approximately 90% of the code between the 2 operating systems. Table 1 presents brief descriptions of the core components of STARS, aligned with the theoretical underpinnings for addressing stigma and changing behavior.

The adaptation of the existing iREACH content was guided by ADAPT-ITT (Table 2). The ADAPT-ITT model was developed to adapt evidence-based practices for circumstances or populations outside those included in the evidence base. The ADAPT-ITT model includes 8 phases. These include assessment, decision, adaptation, production, topical experts, integration, training, and testing. This framework is useful because implementation of evidence-based practices often requires modification to the innovation [53]. Following a framework such as ADAPT-ITT can speed the process of adaptation, while incorporating feedback from peer mentors and a technical expertise group (TEG) with expertise in LGBTQ+ health, youth development, and suicide prevention.

From September 2021 to September 2022, the team met weekly to review the existing content and features on the platform to identify the required modifications, to ensure readiness for the implementation of the pilot test (*assessment*). During the *decision* stage, we reviewed evidence-based practices and identified the components that were ready for adoption and those that needed to be adapted. For example, although SPI did not require adaptation, the research team built SPI into the app for STARS. We revised the iREACH content and interactive activities to address suicide prevention and reinforce EA-SGM groups' social support, coping with discrimination, and positive affect. Our review included both text and imagery and video content within the platform to ensure developmentally appropriate, contextually relevant, and culturally sensitive alignment with EA-SGM groups. Over the following months, the research team met weekly to discuss the features, design, and engagement desired within STARS *(administration)*. During these discussions, we reflected about whether the platform met the desired expectations for design and ease of use and

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incorporated feedback regarding its content and layout accordingly (Multimedia Appendices 2-6).

Table 2. Modifications to the intervention content using the assessment, decision, administration, production, topical experts–integration, training, and testing framework (8 steps).

Phase	Procedures
Assessment (months 1-8)	• Obtain iterative feedback about content adaptation from the research team and technical expertise group
Decision (months 2-8)	• Review the information obtained from the assessment and draft the revised intervention content (text, video, and activities) and measures
Administration (month 9)	• Elicit feedback through iterative testing and feedback cycles • Address reactions and make modifications
Production (months 2-12)	• Balance priorities while maintaining fidelity to core elements and underlying theoretical framework
Topical experts (month 10)	• Elicit expert review of the final curriculum and activities
Integration (months 11-12)	• Integrate content from experts and conduct readability tests • Translate curricula into a mobile platform
Training (months 11-12)	• Beta test the study procedures, recruit peer mentors, and train the staff • Begin recruitment for pilot testing
Testing (months 18-36)	• Pilot-test the intervention with 60 emerging adult sexual and gender minority individuals • Collect implementation and preliminary efficacy data • Analyze the data

During the *production* phase, our technical partner produced instances of the app based on the elicited feedback and began to iteratively test for platform stability, identification of bugs requiring modification, and ability to track engagement metrics. The test environment looked as similar to production as possible, so that changes and bug fixes could be tested and reliably expected to work when promoted to the production environment. The research team used the beta versions of STARS for internal usability testing. We worked with our technology partner to finalize the app and ensure its security using industry best practices.

Our TEG served as *topical experts*, offering their subject matter expertise on the content and activities incorporated into the app. After the TEG provided written comments, we integrated their comments and tested the readability of the finalized content using the Flesch-Kincaid Readability Test (average score 6.98, SD 1.8) [61].

During the *integration* stage, the research team worked with the technical partner to make the final refinements and modifications before launching the production server. We reviewed the production server instance to ensure that the layout works with different mobile devices and browser platforms as intended and that all data are captured and saved in the server as planned.

During the *training* stage, the research team worked on reviewing the study-related procedures and finalizing the protocols' operations manual. The recruiters were trained to fidelity in the process of describing the study to EA-SGM individuals who call to inquire about participation and suicide risk assessment as potential participants will indicate previous suicidal ideation in the past month. Research team members were trained in data management, which includes securely storing data, data protection, and proper data collection. All staff were trained in accordance with National Institutes of Health standards on recognizing and reporting adverse events.

The research team also finalized the peer mentor modules and began the recruitment and training of peer mentors using the existing training and fidelity protocols (Multimedia Appendix 1). STARS relies on peer mentors as care navigators to provide social support, reduce the impact of discrimination, connect youth to safe spaces, remind them to use their safety plan at the beginning and end of every session, and brainstorm and implement solutions to overcome obstacles to its use. For example, at each session, the peer mentor will check in on whether the participant used their safety plan and inquire about how it went, about barriers to its use or efficacy, and about whether any changes are needed to the safety plan. This approach offers a confidential and user-controlled opportunity to support EA-SGM groups in their transition to adulthood.

Peer mentor positions were posted on the web; applicants were asked to provide their curriculum vitae and a 1-paragraph description of any previous experiences with or interest in working with LGBTQ+ emerging adults (aged 18-24 years). This allowed for the selection of candidates who would be suitable as peers for the project. Once selected, peer mentors completed 12 hours of training with a licensed clinical psychologist, which included didactics, modeling, role-plays with feedback, and discussions about difficult topics that might emerge outside the planned content. Following training, they attended weekly group supervision for 1 hour. Peer mentors were trained to conduct 6 sessions (which were audio recorded) with participants to provide social support, reduce the impact of discrimination, promote positive affect, and reduce barriers to enacting the safety plans (refer to the peer mentor manual in

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Multimedia Appendix 1 for additional details). Staff identified measures of fidelity specific to each peer mentoring session that were assessed for each audio-recorded session. Peer mentors were paid on an hourly basis.

The peer mentors do not conduct SPI, but they help participants brainstorm ways to overcome obstacles to using SPI. Peer mentors receive booster trainings every 2 months to reinforce their skills and respond to emerging challenges [62]. Peer mentors' proficiency is monitored via audio-recorded role-plays using standard coding protocols. Peer mentor sessions occur on a Health Insurance Portability and Accountability Act–compliant telehealth platform.

Testing

The final ADAPT-ITT phase evaluates the intervention in a pilot trial described in the following section. A randomized clinical trial (N=60) is recruiting individuals aged 18 to 24 years who identify as sexual or gender minorities and who report past-month suicidal ideation. After completion of an interest survey and phone screening, participants complete a comprehensive eligibility assessment in person with a licensed clinician. All eligible participants complete SPI in an original, unadapted format. Then, participants are randomized to either the STARS or control group. The control group completes assessments, which include a survey and an interview, every 2 months (2-, 4-, and 6-month follow-up). Participants in STARS meet with a research assistant to download and complete an orientation to the STARS app and to schedule the peer mentoring sessions, conducted virtually. The STARS participants then complete the same assessment as the control group (at 2, 4, and 6 months). User data are collected from the STARS app, as is feedback from the peer mentors about the way that time was spent in their sessions.

Sample Size and Power Analysis

We plan to recruit 60 EA-SGM participants. A power analysis in Repeated Measures with Attrition: Sample Sizes for 2 Groups (5% attrition at each time point; 2-sided test; r=0.50 between tests; Cronbach α=.05; power=0.80) suggested that we would need 29 participants per group to detect a medium between-group effect size on suicidal ideation (Cohen d=0.60). Previous studies found that crisis response planning (a type of safety planning) had a between-group effect size ranging from 0.0 to 0.7 (at the 1-, 3-, and 6-month follow-up) compared with contracting for safety [39]. We anticipate that with the addition of important skills (coping with discrimination, social support, and positive affect) and peer support, a medium effect size improvement in suicidal ideation over safety planning alone is realistic and clinically meaningful.

There is controversy regarding the use of "pilot data" to estimate actual effect sizes [63]. The primary goal of this project is to determine our intervention's reach, feasibility, acceptability, and its implementation fidelity. Our secondary goal is to ensure that the critical parameters required to plan efficacy targets within a large trial are estimated. We seek to estimate key study parameters with sample means and proportions together with 2-sided 95% CIs and test the primary null hypotheses at the traditional 2-sided level α=.05. These data can help rule out unusually large or small effects by confirming that extrinsic effect sizes are contained within our CIs and help inform a future efficacy trial.

Engagement and Retention

Retention

We will make all efforts to retain consented participants. Our study retention plan draws on previously successful retention protocols to achieve at least an 80% retention rate. It is critical to obtain accurate follow-up contact information. We will use best practices to retain participants (eg, comprehensive locator information that includes participants' mobile phone number, email, Facebook and Twitter username, and contact information about 2 peers who could help us contact them), while being sensitive to undue disclosure of EA-SGM individuals participating in the study.

We also have a planned schedule of follow-up that consists of a variety of follow-up methods. Short time (2 months) between assessments will help us quickly address retention issues. A study-specific home page allows study staff to monitor participant progress at a glance, viewing steps or phases in the dashboard filtered by conditions such as record status, intervention arm, last log-in to the app, and so on. This dashboard facilitates participant retention via prompts to study staff to reach out to participants who have missed a specified number of study activities and by providing a secure platform to communicate with staff and deliver participant incentives. At each follow-up assessment, participants can update their contact information. This allows us to remain connected with participants and facilitates the delivery of reminders regarding upcoming study procedures.

Initially, a participant who does not respond to an electronic notification that a survey is due will automatically receive additional notifications 36 hours after the initial notification. If the participant has still not completed the assessment 24 hours after the third electronic notification, a research staff member will escalate contact intensity. Depending on the participant's preferences provided upon registration, they will be contacted initially through the preferred mode of recontact (eg, via SMS text message); if still unresponsive, other available modes (eg, phone call) will be used. Each contact is logged in an electronic retention system.

Incentives

Participants will be followed for 6 months after enrollment. We have designed our incentive schedule to encourage the completion of study assessments, in that after the baseline assessment, which is in person and for which participants are compensated US $50, each of the subsequent assessments pays the participant at an increasing rate to encourage them to complete future assessments. They will be compensated US $30 for completing the 2-month assessment, US $40 for the 4-month assessment, and US $50 for the 6-month assessment. This incremental compensation has proven highly effective in our previous cohorts. Neither our institutional review board (IRB) nor previous advisory boards have found this amount of incentive to be coercive. Rather, they have found it commensurate with what would be expected to compensate

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participants if they were engaged in face-to-face and web assessments that are similar in duration.

Outcomes

Overview

Assessments will be conducted on the web using REDCap (Table 3). All participants will complete web surveys every 2 months (2-, 4-, and 6-month follow-up surveys), which are similar to the baseline survey they completed in person.

Table 3. Measures for primary and secondary outcomes.

Outcome	Measures
Recruitment	
Recruitment and enrollment (Reach)	Advertisement and screening metrics
Primary outcomes	
Suicidal ideation (efficacy)	Columbia–Suicide Severity Rating Scale; Severity of Suicidal Ideation Subscale [57] (primary outcome); Intensity of Ideation Subscale (secondary outcome); Suicidal Behavior Subscale (secondary outcome); at baseline, we will assess lifetime and past-month suicidal thoughts and behaviors; and at follow-up assessments, we will assess suicidal thoughts and behaviors in the past 2 months
Secondary outcomes	
Safety Planning Intervention and STARS[a] app willingness (adoption)	Self-report of willingness to use and satisfaction with the Safety Planning Intervention and the STARS app and Short Intervention Evaluation Form [64]
Safety plan and STARS app use (participant implementation)	Self-reported use of the safety plan, STARS app log-in sessions, app session length, pages visited, and activities completed
STARS fidelity (peer mentor implementation)	Peer mentor session adherence and competence
Retention (maintenance)	Completion of evaluations
Expert and peer mentor perceptions (maintenance)	Qualitative interviews with the youth action group and technical expertise group
Mechanisms of action	
Social support and isolation	5-Item Scale of Parental and Peer Support [65], Interpersonal Needs Questionnaire–Reduced [66], and UCLA Loneliness Scale [67]
Positive affect	PANAS[b]-positive [68,69]
IBM[c] targets	Attitudes, norms, self-efficacy, and intentions to use safety planning [70]
Coping with discrimination	Coping with Discrimination Scale [71,72] and sexuality-related stressors [73]
Covariates	
Sociodemographics	Demographics and technology use [74]
Sexual behavior	Sexual Practices Assessment Schedule [21,75]
Alcohol and drugs	Alcohol Use Disorder Identification Test [76] and Alcohol, Smoking, and Substance Involvement Screening Test [77]
Homonegativity	Internalized homonegativity scale [78]
Gender-related stigma	Gender minority stress and resilience rejection subscale [79]
Perceived stress	Daily hassles over the past month [80]
Discrimination	Everyday Discrimination Scale [81,82]

[a]STARS: Supporting Transitions to Adulthood and Reducing Suicide.

[b]PANAS: Positive and Negative Affect Schedule.

[c]IBM: Integrated Behavioral Model.

Primary Outcomes

The RE-AIM framework guides our selection of efficacy and implementation indicators. Consistent with the type-1 hybrid design, the primary goal of our pilot study is to identify key indicators of preliminary efficacy, with a secondary goal of describing the implementation context.

Reach

We will track advertisement impressions (clicks, cost/click, and click-through rate), screening (number of participants who were

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screened, were eligible, and provided contact information and cost/eligible contact), and enrollment metrics (number of eligible participants who attend in-person visits and enroll). We will document the reasons for refusal among eligible individuals. We will compare reach across social media platforms.

Efficacy

The C-SSRS is a clinician-rated interview measure of the severity of suicidal ideation (primary outcome), intensity of ideation (secondary outcome), and suicidal behavior (secondary outcome) with strong psychometric properties that will be our primary efficacy indicators [57].

Adoption

We will evaluate changes in the intention to use the safety plan from baseline through all follow-up assessments. We also will examine satisfaction with and perceived usefulness of the components in their assigned arm. Participants will also complete the Short Intervention Evaluation Form [64] to elicit information about their experience (ie, was the intervention interesting, was it relevant, or did they learn from the intervention). For STARS participants, we will evaluate self-reported intention to use the STARS app and satisfaction with the app.

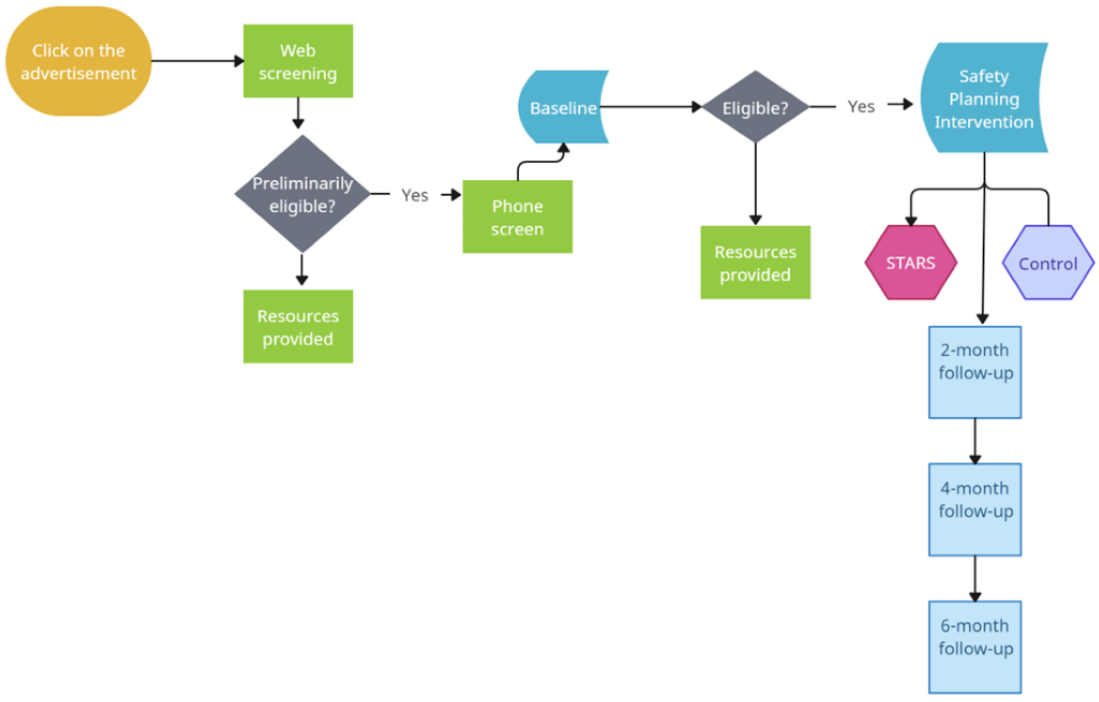
Implementation

To assess intervention engagement by *participants*, we will measure counts of log-in sessions to the app, app session length, pages visited, activities completed, and other functions used within the app, which can indicate intervention dosage. We will also collect the number, frequency, and duration of peer mentor sessions that participants requested and attended and assess self-reported frequency of use of the safety plan in both conditions. *Peer mentors* will complete a case report form after each session to document the topics discussed. Procedures for monitoring intervention adherence and competence include audio recording all sessions and coding for clinical skill or competence. We will interview the *youth advisory group, TEG, and peer mentor members* for their reflections about lessons learned, insights into potential modifications, and experienced challenges and opportunities gleaned during implementation. Semistructured interviews will ask about the intervention adaptation process and perceived impact of the intervention. Interviews will last 30 minutes, will be audio recorded, and transcribed. We will create a codebook of a priori and emergent themes including operational definitions of all codes and sample quotations. Then, 2 study team members will independently code the data; a third team member will review the coded sections and resolve discrepancies.

Maintenance

We will monitor retention over time as a marker of maintenance, with a criterion of ≥80% retention at the 6-month follow-up (refer to Figure 2 for the timeline). We will compare those who are lost to follow-up with study completers across baseline scores based on our key efficacy indicators and sociodemographic characteristics.

Figure 2. Timeline for participation. STARS: Supporting Transitions to Adulthood and Reducing Suicide.



Mediators of Intervention Effects

We will also measure mechanisms of action (Integrative Behavioral Model targets [70], social support, positive affect, and coping with discrimination) and key demographic and behavioral covariates.

Social Support

Social support from parents and friends will be measured separately using a 5-item emotional support scale, with items rated on a 5-point scale. The measure has strong convergent and divergent validity, test-retest reliability, and internal

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consistency. Participants will complete the UCLA Loneliness Scale [67], a 20-item measure of subjective experiences of loneliness, with items rated on a 4-point scale, reflecting the frequency with which a participant feels a particular way (often, sometimes, rarely, or never). The measure has strong convergent and divergent validity, test-retest reliability, and internal consistency. The Interpersonal Needs Questionnaire–Reduced [66] is a 15-item measure of perceived burdensomeness and thwarted belongingness. The measure has strong psychometric properties, including measurement invariance, divergent and convergent validity, and ability to predict future suicidal ideation.

Positive Affect

The Positive and Negative Affect Schedule–Positive Affect subscale [68] is a 10-item measure of positive affect over the past week, including enthusiasm, interest, determination, excitement, inspiration, alertness, activity, strength, pride, and attentiveness. Each item is rated on a Likert scale ranging from 1 (very slightly or not at all) to 5 (extremely). The Positive and Negative Affect Schedule has strong internal consistency and convergent and divergent validity.

Integrative Behavioral Model Questionnaire for Safety Planning

We will measure attitudes, norms, self-efficacy, and intentions regarding adoption of the safety plan using an adapted version of the Theory of Planned Behavior Questionnaire [83]. The measure has strong psychometric properties, including high reliability and validity.

Coping With Discrimination

The Coping with Discrimination Scale [71] is a 41-item measure assessing internalization (10 items), disengagement (5 items), drug and alcohol use (5 items), support seeking (5 items), resistance (6 items), resilience (6 items), and education or advocacy (8 items). Participants respond to these items using 6 response options, ranging from 1 (never like me) to 6 (always like me). Instructions for the measure are as follows: “This is a list of strategies that some people use to deal with their experiences of discrimination. Please respond to the following items as honestly as possible to reflect how much each strategy best describes the ways you cope with discrimination. There are no right or wrong answers.”

Covariates

We will measure the following constructs as covariates: sociodemographics (age, race and ethnicity, education, employment, income, sexual orientation, sex assigned at birth, and gender identity), sexual behavior, alcohol and drug use, internalized homonegativity, experiences of everyday discrimination, and perceived stress. These measures are presented in Table 3.

Statistical Analysis

Before conducting our multivariate analyses, we will examine the study variables using descriptive statistics and test for differences across demographic characteristics (eg, race and ethnicity, age, and education) using 2-tailed *t* tests, ANOVAs, and chi-square tests, as appropriate. As participants will be randomized to the 2 treatment groups, systematic baseline differences are not expected; however, if some parameters differ across conditions at baseline, they will be included as covariates in subsequent multivariate models. We will calculate descriptive summary statistics corresponding to the study variables at each visit to understand any temporal patterns and compare the 2 treatment groups in terms of average change from baseline after intervention (averaged across all 3 follow-up times).

In its simplest form, under the assumption of equivalence between the 2 randomized groups, we will compare differences from baseline to the 6-month outcomes across our outcome measures using 2-tailed *t* tests, ANOVAs, and chi-square tests, as appropriate. For repeated measures analyses, we will use the general framework of generalized linear mixed models to model the longitudinal outcomes. We will compare differences across the groups over time based on the C-SSRS suicidal ideation subscale, social support (a composite measure of the 5-Item Scale of Parental and Peer Support, Interpersonal Needs Questionnaire, and University of California, Los Angeles Loneliness Scale), coping with discrimination (a composite measure of Coping with Discrimination Scale and a measure of sexuality-related stressors), and positive affect (Positive and Negative Affect Schedule–Positive), noting that we will not be powered to detect differences in suicidal behavior; however, we will have sufficient power to detect changes in the severity of suicidal ideation. We will evaluate the preliminary evidence for associations between change in intervention targets, mechanisms, and suicidal ideation or behavior. We will examine differences in the rate of use of the safety plan and in retention by condition, and we will examine whether paradata from STARS (ie, frequency of peer mentoring sessions and using the app) correlate with safety plan use.

Missing Data

We will compare those who are lost to follow-up with study completers across baseline scores based on our key efficacy indicators (C-SSRS suicidal ideation and suicidal behavior subscales, social support, coping with discrimination, and positive affect) and on sociodemographic characteristics using linear regression. Web-based entry for all measures will help reduce missing data. We will manage missing data by applying likelihood-based methods that include partial information about participants who drop out prematurely and develop nonresponse adjustment and poststratification weights to account for survey nonparticipation. The use of expectation-maximization algorithm and multiple imputation approach in longitudinal analyses will help overcome missing data concerns when appropriate. When the missing-at-random assumption is not supported, we will not replace missing data to avoid bias.

Ethics Approval

The human participants’ considerations presented in this protocol are approved by the IRB of the University of Pennsylvania (protocol number 849500).

Results

This project began in September 2021. Preliminary study activities (eg, obtaining IRB approvals, hiring and training staff,

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and developing the study protocol and study-specific procedures) were completed in September 2022. During this period, we also worked with our technology partner (One Cow Standing), our youth advisory group, and a TEG to update and expand the intervention content related to suicide ideation; finalized and programmed all study tools; and established robust recruitment, retention, and engagement plans. Recruitment began in October 2022; we anticipate completing recruitment by September 2023. Final participant follow-up will be completed by February 2024, followed by data analysis. Study results will be disseminated in 2024.

Discussion

Summary

The proposed project is innovative in 3 ways. First, although evidence-based life skills programs target diverse racial and ethnic and urban or rural youth [84,85], to the best of our knowledge, ours will be the first life skills intervention designed to reduce suicide risk among a diverse sample of EA-SGM groups who are at risk for suicide by promoting positive affect, coping with discrimination, and improving social support. Although a study found that interventions targeting positive affect reduced suicidal ideation to a greater extent than those targeting negative affect [86], this has not been demonstrated among EA-SGM groups. Second, we will be among the first to tailor and study the effects of an e-delivered life skills intervention to reduce EA-SGM groups' suicidal ideation and behavior among sexual minorities. The life skills app will deliver tailored and interactive content and reinforce it with peer mentor support. Third, our intervention acknowledges that EA-SGM groups might require ongoing support in enacting their safety plan and leverages our previous success in teaching motivational interviewing to young lay workers to facilitate care navigation and support of vulnerable youth. The peer mentors' ongoing support in problem-solving obstacles to the use of the safety plan and reminding EA-SGM individuals to use their safety plan will serve as key implementation strategies to enhance the impact of this intervention.

Principal Contributions to the Field

In light of the difficulty in using "pilot data" to estimate effect sizes [63], the primary goal of this project is to determine STARS' reach, acceptability, and implementation fidelity. Our secondary goal is to estimate the critical parameters required to plan efficacy targets within a large trial. Although we anticipate having adequate power to determine the effects on suicidal ideation, we will not be powered to determine the effects on suicidal behavior, which will be the goal of a fully powered future R01. These data can help rule out unusually large or small effects by confirming that extrinsic effect sizes are contained within our CIs [63] and help inform a large-scale version of the intervention to test its efficacy in reducing suicidal ideation and behavior among EA-SGM groups.

Acknowledgments

The authors would like to acknowledge the members of their Community Advisory Board. The authors would also like to acknowledge the members of their technical expertise group. This project was supported by the National Institutes of Health (P50 MH127511; multiple principal investigators: GKB and MO).

Data Availability

Data will be deposited in the National Institutes of Health data repository.

Conflicts of Interest

GKB and MO receive royalties for the commercial use of the Columbia–Suicide Severity Rating Scale from the Research Foundation of Mental Hygiene Inc. MO serves as an advisor to Alkermes, Mind Medicine, Sage Therapeutics, St George's University, and Fundación Jimenez Díaz. Her family owns stock in Bristol Myers Squibb.

Multimedia Appendix 1
Peer mentor manual.
[PDF File (Adobe PDF File), 362 KB - resprot_v12i1e48177_app1.pdf]

Multimedia Appendix 2
Forums.
[PNG File , 100 KB - resprot_v12i1e48177_app2.png]

Multimedia Appendix 3
Goal setting.
[PNG File , 121 KB - resprot_v12i1e48177_app3.png]

Multimedia Appendix 4
Safety plan.

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[PNG File , 98 KB - resprot_v12i1e48177_app4.png]

Multimedia Appendix 5
Articles and activities.
[PNG File , 169 KB - resprot_v12i1e48177_app5.png]

Multimedia Appendix 6
Peer mentor scheduling.
[PNG File , 102 KB - resprot_v12i1e48177_app6.png]

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Abbreviations

ADAPT-ITT: assessment, decision, administration, production, topical experts–integration, training, and testing
C-SSRS: Columbia–Suicide Severity Rating Scale
EA-SGM: emerging adult sexual and gender minority
IRB: institutional review board
LGBTQ+: lesbian, gay, bisexual, transgender, queer, plus

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RE-AIM: reach, efficacy, adoption, implementation, and maintenance
SPI: Safety Planning Intervention
STARS: Supporting Transitions to Adulthood and Reducing Suicide
TEG: technical expertise group

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Protocol

Testing the Effects of App-Based Motivational Messages on Physical Activity and Resting Heart Rate Through Smartphone App Compliance in Patients With Vulnerable Coronary Artery Plaques: Protocol for a Microrandomized Trial

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Abstract

Background: Achieving the weekly physical activity recommendations of at least 150-300 minutes of moderate-intensity or 75-150 minutes of vigorous-intensity aerobic exercise is important for reducing cardiometabolic risk, but evidence shows that most people struggle to meet these goals, particularly in the mid to long term.

Objective: The Messages Improving Resting Heart Health (MIRTH) study aims to determine if (1) sending daily motivational messages through a research app is effective in improving motivation and in promoting adherence to physical activity recommendations in men and women with coronary heart disease randomized to a 12-month intensive lifestyle intervention, and (2) the time of the day when the message is delivered impacts compliance with exercise training.

Methods: We will conduct a single-center, microrandomized trial. Participants will be randomized daily to either receive or not receive motivational messages over two 90-day periods at the beginning (phase 1: months 4-6) and at the end (phase 2: months 10-12) of the Lifestyle Vulnerable Plaque Study. Wrist-worn devices (Fitbit Inspire 2) and Bluetooth pairing with smartphones will be used to passively collect data for proximal (ie, physical activity duration, steps walked, and heart rate within 180 minutes of receiving messages) and distal (ie, change values for resting heart rate and total steps walked within and across both phases 1 and 2 of the trial) outcomes. Participants will be recruited from a large academic cardiology office practice (Central Sydney

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Cardiology) and the Royal Prince Alfred Hospital Departments of Cardiology and Radiology. All clinical investigations will be undertaken at the Charles Perkins Centre Royal Prince Alfred clinic. Individuals aged 18-80 years (n=58) with stable coronary heart disease who have low attenuation plaques based on a coronary computed tomography angiography within the past 3 months and have been randomized to an intensive lifestyle intervention program will be included in MIRTH.

Results: The Lifestyle Vulnerable Plaque Study was funded in 2020 and started enrolling participants in February 2022. Recruitment for MIRTH commenced in November 2022. As of September 2023, 2 participants were enrolled in the MIRTH study and provided baseline data.

Conclusions: This MIRTH microrandomized trial will represent the single most detailed and integrated analysis of the effects of a comprehensive lifestyle intervention delivered through a customized mobile health app on smart devices on time-based motivational messaging for patients with coronary heart disease. This study will also help inform future studies optimizing for just-in-time adaptive interventions.

Trial Registration: Australian New Zealand Clinical Trials Registry ACTRN12622000731796; https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=382861

International Registered Report Identifier (IRRID): DERR1-10.2196/46082

(JMIR Res Protoc 2023;12:e46082) doi:10.2196/46082

KEYWORDS

adherence; coronary artery disease; coronary heart disease; digital health; health behavior; heart rate; messages; mhealth; microrandomized trial; mobile app; physical activity; smartphone; telehealth; user motivation

Introduction

Background and Rationale

Physical activity has been widely recognized as an effective intervention for improving cardiometabolic health [1,2]. Regular endurance exercise has been shown to reduce body weight and visceral adiposity, improve insulin sensitivity and glucose tolerance, lower blood pressure, and enhance lipid metabolism, all of which contribute to the prevention and management of atherosclerotic cardiovascular disease [3-6]. However, achieving sufficient compliance with physical activity recommendations poses a significant challenge, which can be attributed to various factors, including lack of motivation, skills, resources, and limited access to exercise facilities, among others [7].

The emergence of new technologies and digital products such as wearable devices, mobile apps, and mobile health (mHealth) platforms offers the potential for the delivery of customized educational and motivational material, which may increase compliance with physical activity interventions [8]. Smartphones and mobile apps are the first and second most frequently used digital products in clinical research [9], and with other sensors connected to digital platforms, are increasingly becoming an integral part of daily health care routine [10].

Passive monitoring of health parameters can be accomplished using wearable devices, which allow for nonintrusive data collection [11]. These technologies allow for the gathering of real-time data, the tracking of progress, and the delivery of messages that are timed to align with a person's daily routines and patterns of activity. This can provide a personalized and targeted approach to physical activity, which can help individuals be more motivated and engaged in regular physical activity [12,13]. To explore this further, we have designed a microrandomized trial (MRT) to investigate the impact of delivering motivational messages at different times of the day targeting physical activity compliance, duration, and intensity.

An MRT is a cutting-edge trial design for mHealth research. A unique feature of an MRT is that an individual can be repeatedly randomized multiple times throughout the duration of the study [14,15]. The overall aim is to fine-tune the mHealth intervention by analyzing the effects of the different intervention components (eg, behavioral prompts) on the activities of the participant (eg, physical activity compliance; Textbox 1). This random sequence within and between participants constitutes an MRT [16,17], with most MRTs contributing to the development of just-in-time adaptive interventions (JITAIs). JITAIs aim to deliver appropriate support tailored to individuals' needs at the precise moment it is needed [18,19].

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Textbox 1. What are the benefits of randomizing a participant multiple times over the duration of this trial?

Microrandomized trials (MRTs) are unique clinical trial designs suitable for studying interventions using mobile health technologies. They randomize interventions at multiple time points, allowing for dynamic treatment investigation. Key features include fine-grained granularity, personalization, and sequential decision-making. MRTs provide additional information such as temporal dynamics, contextual effects, individual response patterns, and treatment adaptation. These trials offer insights into personalized and effective interventions in the mobile health context.

The unique experimental design of an MRT allows for capturing data with the aim of developing sharp decision-making tools or rules for fine-tuning the sending of messages as notifications. The ability to randomize a participant multiple times in an MRT gives it its distinctive characteristic, which is not present in a traditional parallel-group randomized control trial, thereby allowing us to study:

- the effects of the intervention multiple times over a given time period;
- if the motivational messages sent as notifications have any near-term effect on engagement with the intervention components over the duration of the study;
- if this near-term effect changes over the two 90-day study periods; and
- if the effects of the motivational messages in phase 1 are similar to those in phase 2, thereby having a long-term effect.

Through analyzing the data from above, researchers will be able to optimize just-in-time adaptive interventions more effectively for notification delivery through apps encouraging physical activity in patients with coronary heart disease.

The main purpose of the Messages Improving Resting Heart Health (MIRTH) study is to determine if (1) sending daily customized motivational messages through a research app improves motivation and engagement with physical activity recommendations in men and women with coronary heart disease randomized to a 12-month intensive lifestyle intervention, and (2) the time of the day when the message is delivered impacts compliance with exercise training. This trial will be a crucial step in determining the potential of technology to support people in their efforts to maintain a physically active lifestyle, which can have a significant impact on the prevention and management of cardiometabolic abnormalities and atherosclerotic cardiovascular disease.

The primary objective of this study is to evaluate the immediate effectiveness of motivational messages aimed at promoting physical activity in adults with stable atherosclerotic cardiovascular disease. The secondary objectives include assessing the impact of message delivery time (ie, 6 AM, 11 AM, or 3 PM) on the immediate effectiveness of the intervention and investigating its long-term effectiveness over a 12-month period by comparing results at the midpoint and end of the study.

The primary hypothesis is (1) that participants will demonstrate an increase in steps taken within 180 minutes of receiving motivational messages compared to those who do not receive the messages. The secondary hypotheses are (2) that participants will exhibit an increase in physical activity duration and heart rate within 180 minutes of receiving motivational messages compared to those who do not receive the messages; (3) the proximal effect sizes of message are different at different times of a day (ie, 6 AM, 11 AM, or 3 PM); and (4) that there will be no difference in long-term outcomes between phase 1 (months 4-6 of the Lifestyle Vulnerable Plaque Study [LIVEPLUS]) and phase 2 (months 10-12 of the LIVEPLUS) of the study.

Previous Work

In the HeartSteps MRT study, research volunteers randomly received, through an app, contextually tailored physical activity notifications delivered up to 5 times per day at user-selected times [20]. During the 6-week trial, the implementation of a physical activity notification resulted in a significant 24% increase in average step count compared to no suggestion. However, the effect was not consistently maintained throughout the study, with higher compliance observed primarily at the beginning. Similarly, the 6-week DIAMANTE student study [21] demonstrated that motivational text messages based on a cognitive-behavioral approach led to a significant increase in daily step count, although the effect diminished over time. These findings highlight the need for further research to investigate the potential advantages of incorporating personalization and contextualization in text-messaging interventions, aiming to enhance the effectiveness of physical activity promotion [21]. Aguilera et al [22] explored the effects of text messages in alleviating depression and anxiety symptoms during the COVID-19 lockdowns in the United States in the StayWell at Home study. The study revealed a positive association between engagement in a text-messaging program rooted in cognitive-behavioral principles and the amelioration of depression and anxiety symptoms associated with the COVID-19 pandemic. The program involved the delivery of 2 messages per day over a period of 60 days and demonstrated significant engagement and effectiveness in enhancing mental well-being. These findings suggest that text-messaging interventions, when used as a standalone component of a comprehensive program, have the potential to serve as a valuable tool in public health initiatives targeting mental health concerns, facilitating improved health outcomes through increased engagement with the intervention.

Methods

Study Design

Overview

Figure 1 [23] provides an overview of the study design for the MIRTH MRT study. The intervention period consists of two 90-day periods, which are condensed into phases for the purposes of this protocol. Phase 1 corresponds to months 4-6 of the LIVEPLUS program, while phase 2 corresponds to months 10-12 (Figure 2). Throughout the study, participants are randomly selected at decision time points, which occur at 3 different times of the day: early morning (6 AM), late morning

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(11 AM), and early afternoon (3 PM). At the designated time point, each participant is randomly assigned to either receive or not receive the intervention component (motivational message) using a simple randomization method (Multimedia Appendix 1). The randomization process is independent of the participant's allocation from the previous day. To ensure allocation concealment, a central randomization algorithm is used. Computerized sequence generation will be used to conduct participant randomization. Given the nature of the intervention, participants will be aware of the messages they receive. Subsequently, the duration and type of physical activity performed will be evaluated. A research personnel will assist participants in downloading the study app, creating a profile, and providing a brief demonstration of the app's various functionalities. Detailed written instructions, along with a video tour of the app, can be accessed in the app's help section. Screenshots of the app are available in Multimedia Appendix 2.

Figure 1. Microrandomized trial design for the Messages Improving Resting Heart Health (MIRTH) study. Intervention randomization is followed by time randomization, as shown by R. Figure adapted from Golbus et al [23].

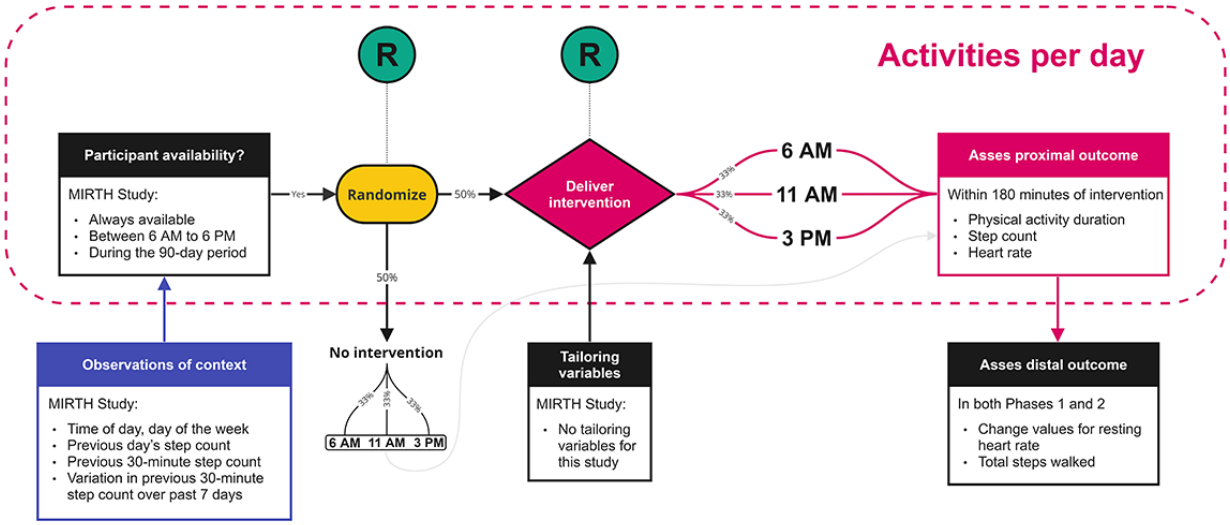
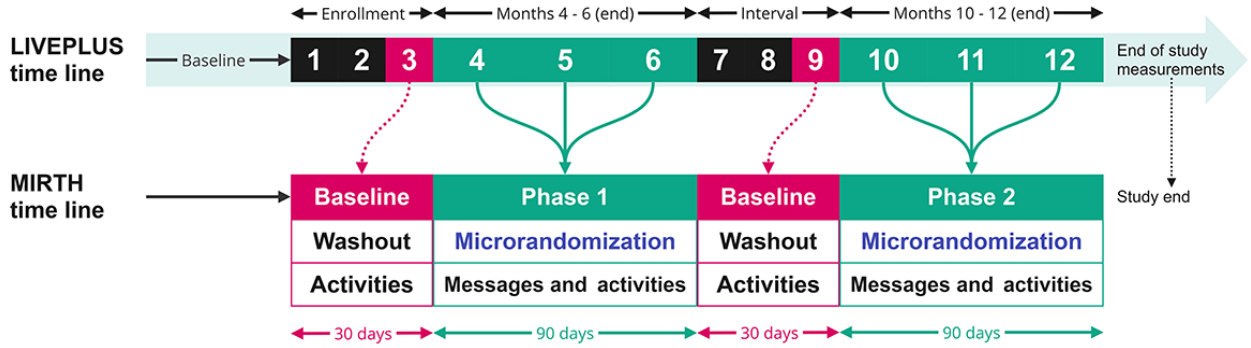


Figure 2. Time line of the Messages Improving Resting Heart Health (MIRTH) study, illustrating the participant flow and duration for each phase aligned with the Lifestyle Vulnerable Plaque Study (LIVEPLUS) time line. Baseline data collection for the MIRTH study will occur over a period of 1 month (30 days) at the ends of months 3 and 9 of the LIVEPLUS intervention. The collected data will include various metrics such as the average daily step count, duration, and heart rate from 6 AM to 6 PM. Additionally, we will also collect the average weekly physical activity duration. Activities refer to the LIVEPLUS component of the intervention (end-of-study measurements assessed at the end of month 12).



Study Population

The study will recruit adults aged 18-80 years with stable heart disease who have undergone a clinically indicated coronary computed tomography angiography scan at Royal Prince Alfred Hospital in Sydney, New South Wales, Australia, as previously described [24]. Only individuals with a confirmed positive diagnosis of a low attenuation plaque (quantifiable plaque within the –30 to 150 HU range) by 2 independent clinicians or researchers will be contacted for potential participation. Before collecting any participant data, informed written consent will be obtained. Volunteer self–opt-in will not be considered eligible for participation in the study.

Key Inclusion and Exclusion Criteria

The criteria listed in Textbox 2 were followed in selecting participants for the study.

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Textbox 2. Inclusion and exclusion criteria.

Inclusion criteria:

- Intervention group participants from the Lifestyle Vulnerable Plaque Study (Australian New Zealand Clinical Trials Registry ACTRN12620001151921)
- Adults who have access to and can competently use a smartphone (running iOS or Android)
- Presence of low-attenuation plaque on coronary computed tomography angiography
- aged 18-80 years
- BMI≥22.0 kg/m^2
- Have no contraindications for the Lifestyle Vulnerable Plaque Study
- Able to provide full, informed consent

Exclusion criteria:

- History or clinical manifestation of any other significant metabolic, hematologic, pulmonary, cardiovascular, gastrointestinal, neurologic, immune, hepatic, renal, or urologic disorders, or cancer that, in the opinion of the investigator, would make the candidate ineligible for the study
- Non–magnetic resonance imaging–compatible implanted devices or implants
- Estimated glomerular filtration rate less than 30 mL/kg/1.73 m^2
- Inability to exercise through a supine ergometer
- Claustrophobia
- Contraindications for adenosine: sinus node disease (eg, sick sinus syndrome and symptomatic sinus bradycardia), second- or third-degree heart blocks, unstable angina, bronchospasm (eg, asthma), heart transplant recipient, and history of seizure disorder
- Contraindications for glyceryl trinitrate: known nitrate hypersensitivity, severe anemia, severe aortic or mitral stenosis, and hypotension defined as resting systolic blood pressure equal to 89 mm Hg
- Not suitable for computerized tomography coronary angiography due to contraindications
- Psychiatric or behavioral problems (history of drug and alcohol abuse, eating disorder, etc)
- Breastfeeding or pregnant women, or those intending to become pregnant before the scheduled end of the intervention
- Concurrent participation in any other interventional study

Recruitment

The subsample for this study will be recruited from the intervention group of the LIVEPLUS (Australian New Zealand Clinical Trials Registry ACTRN12620001151921). Participants will be recruited from Central Sydney Cardiology and the Departments of Cardiology and Radiology at the Royal Prince Alfred Hospital in Camperdown, New South Wales, Australia. Eligible patients will be introduced to the study by their cardiologist. The research team will conduct a 30-minute informal web-based (Zoom) call to illustrate the study, which will include a presentation and an opportunity for participants to ask questions.

Baseline Assessment

The collection of participants' physical activity data will occur in a free-living setting, reflecting their daily life activities. The baseline assessment for enrollment into the MIRTH study will be conducted based on the baseline assessment previously described for the LIVEPLUS [24].

Trial Arms

In contrast to traditional randomized controlled trials, the MRT approach in this study enables each participant to serve as their own control. As a result, there is a single group of research participants who are randomly assigned on a daily basis to either the intervention group (receive message) or the control group (no message) in order to provide data.

Intervention

Participants in the study will receive messages as app notifications based on a random schedule. Each day during the intervention period, participants will be randomized to either receive or not receive the messages at a designated time point. Some of the messages included in the intervention have been previously used in the DIAMANTE study [25]. Additional messages were created in collaboration with a health psychologist (LA) who specializes in health behavior change. These messages were designed to incorporate various behavior change techniques (BCTs) based on established theories, such as providing information about health consequences, using cues and prompts, and encouraging problem-solving. The selection of BCT was guided by a validated and reliable BCT taxonomy to ensure their effectiveness [26]. Multimedia Appendix 3 provides a comprehensive list of the current messages, along with the BCT they incorporate and whether they target motivation or volition. Moving forward, we intend to expand this message bank using the same principles and guidelines that were used to develop the existing messages.

Examples of MIRTH messages include the following:

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1. "Physical activity is a great way to feel better overall, improve your cardiometabolic health, and lift your mood. Aim for at least 30 minutes of walking each day at a medium pace to see the benefits."
2. "Going for a walk can improve your mood and clear your mind."
3. "Can you find 30 minutes in your day to go for a walk? That is less time than it takes to watch one episode of a TV show."
4. "Do not worry if you are not as physically active as others. Focus on you and your own goals. Everyone is different."

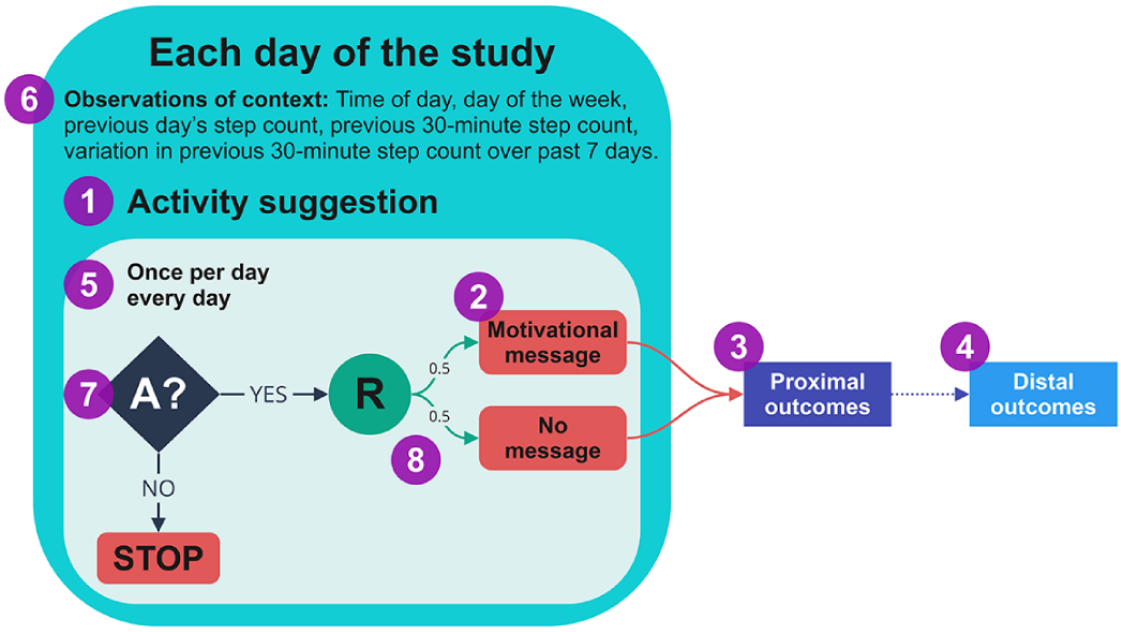
We will track participants' activity using the Fitbit Inspire 2 wrist-worn device, which connects to a smartphone through Bluetooth and collect the data using our custom-built LivePulse research app, available only in Australia on the App Store [27] (Apple) and Play Store [28] (Google).

Study Duration

The participant time line consists of 2 intervention periods lasting for 90 continuous days, spanning 4-6 months and 10-12 months (Figure 2). Throughout these intervention periods, participants will be required to wear Fitbit Inspire 2 wrist-worn devices continuously. Baseline data collection will take place for 1 month at month 3 before initiating the intervention for the 4-6–month study period. Another baseline data collection will occur at month 9 (natural baseline) for the 10-12–month study period.

Motivational messages will be randomly delivered to participants allocated to receive the intervention for that day at 3 different time points: 6 AM, 11 AM, or 3 PM (Figure 1). In the MIRTH study, specific exercises will not be prescribed through these messages. Participants have the freedom to choose the type, duration, and intensity of their physical activity. However, through the LIVEPLUS program, participants will receive a home-based program that aligns with the guidelines provided by the American College of Cardiology Foundation and the American Heart Association [29]. The following recommendations will be emphasized: (1) engaging in 30-60 minutes of moderate-intensity aerobic exercise, such as brisk walking, for at least five days, ideally 7 days per week; (2) enhancing daily physical activity through lifestyle activities (eg, taking walks during work, gardening, or household chores); and (3) incorporating resistance training into their routine at least two days per week. The delivery of messages will be monitored using app analytics to ensure successful delivery to participants (Figure 3).

Figure 3. Each day of the Messages Improving Resting Heart Health trial. Please follow the numbers in the figure caption to guide you: (1) intervention component: activity suggestion sent as push notifications to participants' smartphones as motivational messages. (2) Intervention options: motivational message (encouraging physical activity) or no message. (3) Proximal outcomes: physical activity duration, total step count, and heart rate, in the 180 minutes following a decision time point. (4) Distal outcomes: total step count and the change of resting heart rate during each 90-day study period. (5) Decision points: 6 AM, 11 AM, or 3 PM. (6) Observations of context: time of the day, day of the week, previous day's step count, previous 30-minute step count, variation in previous 30-minute step count over past 7 days. (7) Availability: participants are deemed to be always available between 6 AM and 6 PM during the 90-day period. (8) Randomization probabilities: participants who are available at a decision point are randomized with a 0.5 probability to (a) receive or (b) not receive a motivational message.



Outcome Measures

Primary Outcome

The number of steps walked within 180 minutes after either the message or no-message intervention is sent randomly at each decision-making time point (proximal).

Secondary Outcomes

The secondary outcomes are as follows: (1) the duration of time spent engaged in physical activity within 180 minutes after randomization at each decision-making time point (proximal short-term effect); (2) the change in heart rate within the next 180 minutes after receiving either the intervention or no intervention randomly (proximal short-term effect); (3) the

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average change values of resting heart rate within and across both phases 1 and 2 (distal long-term effect); and (4) the total number of steps walked within and across both phases 1 and 2 periods (distal long-term effect).

For the proximal analysis, which is based on an MRT design where each participant receives either control or intervention randomly at each selected decision time point over the study period, the proximal effect size of intervention (with-intervention vs without-intervention) is estimated. For the distal analysis, there is no control group; we only observe the total step count (total step counts accumulated over each phase) difference between phases 1 and 2 for each participant.

Statistical Analysis

The effect sizes of the proximal outcome variables will be determined based on improvements in the number of steps (hypothesis 1), physical activity duration, and heart rate (hypothesis 2) observed within 180 minutes following the randomization of messages at each decision time point. To estimate these effect sizes, we will use the weighted and centered least-squares method as proposed by Boruvka et al [30]. This approach is specifically designed for analyzing longitudinal data within the context of an MRT design [20]. The weighted and centered least-squares method used in this study is similar to multilevel models, which account for the nested structure of the data, with daily time points nested within participants. It also shares similarities with the generalized estimating equation method. While there is a within-participant correlation across time in the outcome, the independent working correlation matrix is considered, as the message intervention is a time-dependent factor. This approach leverages sequential randomization to estimate the causal effects of the intervention. The estimated intervention effects are robust and not biased, even when covariates are included to reduce the variance of the estimates.

The regression model used in this study includes several covariates: days in study (ranging from 1 to 90 days), message type (intervention messages versus control), and an interaction term between days and message type. The message variable will be converted into a binary variable (0 for control and 1 for intervention), and it will be centered using the corresponding randomization probabilities (eg, A-0.5, where A represents the binary message variable, with A=1 for intervention and A=0 for control). Different trends over days, such as constant, linear, or quadratic, can be considered to assess the proximal effect of intervention messages in the regression models.

To estimate the proximal effect sizes of messages at different time points (hypothesis 3), we will replace (A-0.5) by $(A-0.5)I_{6AM}$, $(A-0.5)I_{11AM}$, and $(A-0.5)I_{3PM}$ in the regression model. Here, $I_{6AM}=1$ indicates that the participant is randomized to the 6 AM time point, and 0 indicates otherwise.

Our goal is to examine the effect of messages at these specific time points (6 AM, 11 AM, or 3 PM), considering that messages are only received at 1 of the 3 time points. Therefore, assuming a constant trend, we can model the daily steps using the following equation:

$$Y = \beta_0 + \beta_1(A-0.5)I_{6AM} + \beta_2(A-0.5)I_{11AM} + \beta_3(A-0.5)I_{3PM}$$

Where Y=steps; β_0 is the expected number of steps; and β_1, β_2, and β_3 are the proximal effects of messages on steps at 6 AM, 11 AM, and 3 PM, respectively.

The effect size of the distal outcome variables will be assessed using a 2-tailed paired *t* test, assuming that there will be no significant difference in the long-term outcomes between phase 1 and phase 2 of the study (hypothesis 4).

Sensitivity Analyses

Sensitivity analyses will be conducted for hypotheses 1-3, considering the following factors:

1. The intervention's proximal effect size will be estimated by adjusting for additional baseline characteristics such as age, gender, and physical activity history. These characteristics can be included as covariates in the regression models.
2. The regression model estimating the proximal effect of the intervention will be based on participants who have at least 45 (50%) out of 90 days of data available.

In the case of positively skewed distributions of the primary outcome variables, the data will be transformed using logarithm or square root transformations. Before the transformations, a small decimal number (eg, 0.5) will be added to the zero values. This is done to address the issue of zero values in the data [20]. Missing data will be addressed using the full-information maximum likelihood approach [31].

Power

Sample size calculations were conducted using Liao et al [32] as a reference, and an R-shiny app [33] was used for this purpose. Based on the calculations, a sample size of 58 participants was determined for randomization over a 90-day period (Multimedia Appendix 4). The calculations were performed with 80% power and a significance level of 5%. For the proximal outcomes, which involve 1 decision time point per day over the 90-day study duration and a randomization probability of 0.5, it is anticipated that participants will have an average availability rate of 0.8 at each decision time point, following a constant trend. The proximal effect size is expected to follow a quadratic trend, with an initial value of 0 and an average value of 0.1. The maximum value is anticipated to occur on the 45th day. For the distal outcome, such as the change in resting heart rate within either phase 1 or phase 2, the sample size of 58 participants can detect a standardized effect size of 0.374 (small to medium effect size) based on a paired *t* test.

Data Exclusion

For activity suggestions, the interventional messages aim to promote physical activity, that is, walking. The primary outcome measure for each participant at each decision-making time point is the step count recorded within the subsequent 180 minutes after receiving a message. With 1 decision-making time point per day, this step count serves as the key data point for analysis. Detailed data management procedures have been outlined in

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the study's protocol to ensure proper handling, processing, and analysis of the collected data [24].

User Statistics

Fitbit data will be collected during participant visits, specifically scheduled to align with the 6th and 12th months of the LIVEPLUS. During these visits, the data from Fitbit devices will be downloaded and collated for further analysis (the time line described in Figure 2).

Ethical Considerations

In Australia, all human research is reviewed by an independent human research ethics committee. MIRTH's parent study LIVEPLUS received approval from the ethics review committee of the Royal Prince Alfred Hospital (RPAH) Zone of the Sydney Local Health District (protocol X20-0229 & 2020/ETH01273 on July 22, 2020). The original informed consent allows for secondary data analysis without additional consent. Before baseline testing, the research team will conduct a video call with potential participants to provide an overview of the study and address any questions or concerns. Any identifiable data obtained will remain confidential and encrypted on secure RPAH servers. Participants will be assigned a unique study ID number, and nonidentifiable data will be stored for at least 15 years. All deidentified data will be stored on university servers and only accessible by research staff through password-protected computers. The mobile app backs up data on both the smartphone and a web-based cloud server based in Sydney. While the app does not have a delete function, participants may request to have their data deleted from the cloud server. Access to mobile app data is restricted to the research team. There is no monetary compensation or amount for LIVEPLUS participants; however, participants who complete the 12-month period get to keep the Fitbit device used for physical activity monitoring.

Results

The LIVEPLUS trial received funding in 2020 and initiated participant enrollment in February 2022. Recruitment for the MIRTH trial began in November 2022. As of September 2023, two participants have been enrolled in the MIRTH study and provided baseline data.

Discussion

Overview

The MIRTH trial aims to conduct a comprehensive analysis of the impact of a customized mHealth app on smart devices, delivering a lifestyle intervention to patients with coronary heart disease. This intervention includes time-based motivational messaging, which can be used to develop a JITAI. The goal of this approach is to provide prompts and cues at the optimal time to enhance motivation and promote increased physical activity behavior among participants. Through this study, we aim to gain insights into the effectiveness of this intervention in improving motivation and achieving the desired objectives of the study.

During the 90-day study duration, participants may receive randomized physical activity suggestions at up to 90 time points. Considering both phase 1 and phase 2 of the trial, there is a maximum potential for 180 time points in total (90 days for each phase). Since we anticipate an equal distribution of intervention and control messages among participants (with a randomization probability of 0.5), it is statistically unlikely for any participant to receive the intervention at all 180 time points. However, we can use the two 90-day study phases to examine improvements in distal outcomes. Our analysis will involve comparing resting heart rate and step counts from baseline (months 3 and 9) to the end of each phase. Furthermore, we will assess distal outcomes by comparing monthly changes within a study phase and between the 2 phases. Based on our hypothesis, we anticipate that participants who receive the intervention messages will demonstrate an increase in physical activity behavior aligned with the recommended guidelines. Additionally, we expect to observe improvements in resting heart rate and overall cardiometabolic health at the 12-month time point. This study will serve as a foundation for integrating an MRT design into routine clinical digital health prescriptions, especially for populations where lifestyle behavior change facilitated by digital health interventions can improve or potentially reverse disease states. The physical activity data collected during the baseline time points are more likely to reflect habitual physical activity behavior. In future studies, the incorporation of a reinforcement learning algorithm can consider additional factors such as user location, local weather conditions, and undisclosed calendar information to deliver a personalized and gamified JITAI.

Strengths

This study introduces an innovative strategy to address physical activity behavior in patients diagnosed with coronary heart disease. It examines the timing of messages within each individual and their impact on outcomes. The study implements a layered digital intervention with minimal participant burden. It spans a longer duration of 180 days, divided into two 90-day periods. Furthermore, to our knowledge, this is the first MRT study to use incremental recruitment specifically for this population.

Limitations

The findings of this study may have limited generalizability to the broader population with cardiovascular disease due to the specific characteristics of the study participants. It is important to note that this study is not designed as a double-blind study, as both participants and researchers are aware of the content and frequency of the messages being delivered. However, the lack of blinding does not pose a significant disadvantage since the outcomes are objectively assessed through Fitbit data, minimizing potential bias in outcome evaluation. It should be noted that this study does not incorporate reinforcement learning in the algorithm, which limits our ability to examine time-varying states for potential moderation effects, such as participant activity levels on the intervention day or the preceding day. Given that the intervention component is delivered through personal electronic devices such as smartphones and Fitbit, it is important to acknowledge the

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potential for technical issues that could impact the reliability of step count records. These challenges may include supporting participants in resolving technical issues with limited in-person assistance. It is worth noting that, in certain instances, Fitbit devices have been known to register hand movements as step counts, which could introduce some measurement inaccuracies [34]. To address potential data collection issues, the research team and technical support will closely monitor and cross-validate the data collection process, ensuring any troubleshooting is promptly addressed. Participants will be informed if any data collection issues occur. The incremental recruitment approach used in this study limits the ability to make adaptive changes based on preliminary results from phase 1 to inform and improve the intervention in phase 2. This may impact the optimization of the intervention based on real-time feedback. The 180-minute window for assessing the effect of messages may not capture the true change in motivation. There could be delayed effects observed weeks after receiving the messages, such as lag effects. Finally, the lack of message sequencing or tailored content may result in participants who are already making progress receiving messages that target earlier stages of motivation.

Conclusions

The outcome of this study will provide preliminary insights into the value and efficacy of motivational messages in promoting physical activity behavior among patients with coronary heart disease in a community setting. The results will provide important data on the effectiveness of delivering physical activity motivational messages through a research study app. If proven effective, this approach could be implemented to enhance personalized care strategies, including the use of digital health interventions, for patients with coronary heart disease.

Acknowledgments

The authors would like to thank the study sponsors for their support. The authors would also like to extend thanks in advance to all participants who volunteered their time to be part of this and the parent study.

Data Availability

The data sets generated during and/or analyzed during this study will be made available from the corresponding author on reasonable request.

Authors' Contributions

SM, JX, BC, and LF conceptualized the study. SM, JX, BC, CMK, AM, and LF further built on the initial study plan. SM, CMK, and LA prepared the message bank, with LA verifying and amending the messages to suit the study cohort. SM drafted the study protocol and submitted it to Australian New Zealand Clinical Trials Registry for registration, with the draft reviewed by CMK, JX, and LF. SM drafted the protocol manuscript for publication, with all authors contributing to the draft. JX prepared the statistical analysis and power sections. RH contributed by adding the randomization sequence and inserting the message bank into the study app. IH and IW recruited participants. SM, CK, SAC, AM, TW, RH, LA, JX, BC, and LF reviewed the manuscript before submission. All authors revised the manuscript for relevant scientific content and approved the final version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
MIRTH randomization algorithm.
[ZIP File (Zip Archive), 3 KB - resprot_v12i1e46082_app1.zip]

Multimedia Appendix 2
Screenshots of the mobile App.
[ZIP File (Zip Archive), 1468 KB - resprot_v12i1e46082_app2.zip]

Multimedia Appendix 3
Messages for MIRTH.
[XLSX File (Microsoft Excel File), 13 KB - resprot_v12i1e46082_app3.xlsx]

Multimedia Appendix 4
Table 1. Sample size calculations (Liao et al. 2016) from the R-shiny app.
[DOCX File , 15 KB - resprot_v12i1e46082_app4.docx]

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Abbreviations

BCT: behavior change technique
JITAI: just-in-time adaptive intervention
LIVEPLUS: Lifestyle Vulnerable Plaque Study
mHealth: mobile health
MIRTH: Messages Improving Resting Heart Health
MRT: microrandomized trial
RPAH: Royal Prince Alfred Hospital

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Protocol

Testing a Model of Care for Patients on Immune Checkpoint Inhibitors Based on Electronic Patient-Reported Outcomes: Protocol for a Randomized Phase II Controlled Trial

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Abstract

Background: Management of severe symptomatic immune-related adverse events (IrAEs) related to immune checkpoint inhibitors (ICIs) can be facilitated by timely detection. As patients face a heterogeneous set of symptoms outside the clinical setting, remotely monitoring and assessing symptoms by using patient-reported outcomes (PROs) may result in shorter delays between symptom onset and clinician detection.

Objective: We assess the effect of a model of care for remote patient monitoring and symptom management based on PRO data on the time to detection of symptomatic IrAEs from symptom onset. The secondary objectives are to assess its effects on the time between symptomatic IrAE detection and intervention, IrAE grade (severity), health-related quality of life, self-efficacy, and overall survival at 6 months.

Methods: For this study, 198 patients with cancer receiving systemic treatment comprising ICIs exclusively will be recruited from 2 Swiss university hospitals. Patients are randomized (1:1) to a digital model of care (intervention) or usual care (control group). Patients are enrolled for 6 months, and they use an electronic app to complete weekly Functional Assessment of Cancer Therapy-General questionnaire and PROMIS (PROs Measurement Information System) Self-Efficacy to Manage Symptoms questionnaires. The intervention patient group completes a standard set of 37 items in a weekly PROs version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) questionnaire, and active symptoms are reassessed daily for the first 3 months by using a modified 24-hour recall period. Patients can add items from the full PRO-CTCAE item library to their questionnaire. Nurses call patients in the event of new or worsening symptoms and manage them by using a standardized triage algorithm based on the United Kingdom Oncology Nursing Society 24-hour triage tool. This algorithm provides guidance on deciding if patients should receive in-person care, if monitoring should be increased, or if self-management education should be reinforced.

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Results: The Institut Suisse de Recherche Expérimentale sur le Cancer Foundation and Kaiku Health Ltd funded this study. Active recruitment began since November 2021 and is projected to conclude in November 2023. Trial results are expected to be published in the first quarter of 2024 and will be disseminated through publications submitted at international scientific conferences.

Conclusions: This trial is among the first trials to use PRO data to directly influence routine care of patients treated with ICIs and addresses some limitations in previous studies. This trial collects a wider spectrum of self-reported symptom data daily. There are some methodological limitations brought by changes in evolving treatment standards for patients with cancer. This trial's results could entail further academic discussions on the challenges of diagnosing and managing symptoms associated with treatment remotely by providing further insights into the burden symptoms represent to patients and highlight the complexity of care procedures involved in managing symptomatic IrAEs.

Trial Registration: ClinicalTrials.gov NCT05530187; https://www.clinicaltrials.gov/study/NCT05530187

International Registered Report Identifier (IRRID): DERR1-10.2196/48386

(JMIR Res Protoc 2023;12:e48386) doi:10.2196/48386

KEYWORDS

patient-reported outcomes; model of care; immune-related adverse events; remote symptom management; self-management support; self-efficacy; health-related quality of life; eHealth; telehealth; support; self-management; symptom; monitoring; cancer; electronic health record; immune; detection; questionnaire; treatment

Introduction

Immune checkpoint inhibitors (ICIs) have increasingly become part of the standard treatment for multiple cancer types and stages, with the main benefits including superior overall survival rates [1-14]. Although ICIs are generally considered as well-tolerated, they may trigger immune-related adverse events (IrAEs), which can be severe and result in debilitating or fatal outcomes [15,16]. Treatment modality, cancer type, and patient characteristics appear to influence the likelihood of symptomatic IrAEs, which generally occur in 40%-80% of patients [10,15]. Combinations of ICI agents generally result in a higher incidence and severity of symptoms, with 55% of IrAEs being severe (grade 3 or higher) [15,17]. Even though the incidence of IrAEs appears to be positively correlated with superior objective response rates to ICIs, the occurrence of severe events may lower overall survival rates [2,18]. It is posited that solid tumors that exhibit high mutational burden elicit a stronger immune response, which may trigger more IrAEs [19,20]. Limited evidence suggests that skin, respiratory, renal, and hepatic IrAEs also appear to be correlated with melanoma, lung cancer, kidney cancer, and hepatocellular cancers, respectively, suggesting that different tumor types may increase the likelihood of specific IrAEs [21-23]. In addition, genetic risk factors such as allelic variations of *HLA-B* and mutations in the *TMEM162* gene are correlated with higher or lower likelihood of IrAEs [24]. Recent studies have highlighted that the potential chronicity of IrAEs could further burden patients and contribute to lower overall quality of life [16,25-27]. The timing of detection and intervention of IrAEs appears to play a key role in limiting their progression and outcome [10,15,28].

Although most IrAEs occur within the first 3-6 months of the start of treatment, some may develop after a year even when treatment has been discontinued [15,29,30]. In addition to the uncertainty of when they may manifest, IrAEs are heterogenous in their symptomatic presentation and are usually related to the affected tissue or organ [15]. Therefore, patients need to be ready to engage in self-care activities to self-monitor and self-manage symptoms they confront outside of the clinical environment during the multiple weeks between treatments [31].

As clinicians rely on patient recall to assess symptomatic adverse events, the time between visits and the clinician's own judgement may inadvertently contribute to an underestimation of their severity, frequency, and burden [32,33]. Collecting patient-reported outcomes (PROs) has become a standard to accurately describe symptomatic adverse events by avoiding some of the biases of clinician reporting, thus contributing evidence on safety, tolerability, and efficacy of cancer treatments [34,35]. Recent studies show that PRO data collected electronically can enable more timely interventions to support patients in managing symptoms, resulting in improvements in overall survival, health-related quality of life (HRQoL), symptom control, and patients' perceived self-efficacy [34,36,37]. Improvements and smaller declines in HRQoL have been observed when actionable PRO data are available to clinicians [38]. PROs can improve communication between patients and health care professionals by increasing the scope of symptoms addressed and how often they are discussed [34].

Clinical trials using electronic PROs (ePROs) in remote symptom management have noted how these data enable interventions that prevent complications related to cancer treatment, leading to similar or lower rates of hospital admissions and emergency care admissions than the current standard of care [36,37]. These models of care generally interpret ePRO symptom data that nurses use to provide personalized remote symptom management support to patients or that activate automated feedback through custom algorithms [36,37,39]. These interventions have seldom been detailed on the procedures put in place to monitor and manage ePRO symptom data. We thus hypothesized that a structured and standardized ePRO-based model of care, including remote monitoring and symptom management, using real-time data may reduce the time to detection of symptomatic IrAEs. This would, in turn, facilitate timely intervention and limit worsening of patients' HRQoL and perceived self-efficacy to manage their conditions. This randomized controlled trial (RCT), the IePRO

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(IrAEs monitoring through electronic PROs) trial, aims to verify the effect of an ePRO-based model of care on the time to detection of symptomatic IrAEs.

Methods

Project Context

The RCT described in this protocol is the third phase of the IePRO project, which began in the year 2020. The first phase focused on the development of a PRO measure based on the PRO version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) [40]. The development of this measure has been detailed in a previously published Delphi study [41]. The second phase was concerned with the development of the ePRO-based model of care being tested in the RCT [42]. This is a 2-arm RCT taking place in the ambulatory care oncology units of 2 university hospitals in French-speaking Switzerland since 2 years. Its overall aim is to compare an ePRO-based model of care that enables remote monitoring and management of symptoms to usual care for patients with cancer receiving ICIs exclusively for up to 6 months.

Study Population

Setting

Patients are being recruited in the Department of Oncology of the 2 university hospitals. They receive treatment and have same-day follow-up appointments at the hospitals' outpatient clinics. Both sites include tumor type–oriented clinical oncology teams with treatment strategies dictated by multidisciplinary tumor boards.

Eligibility Criteria

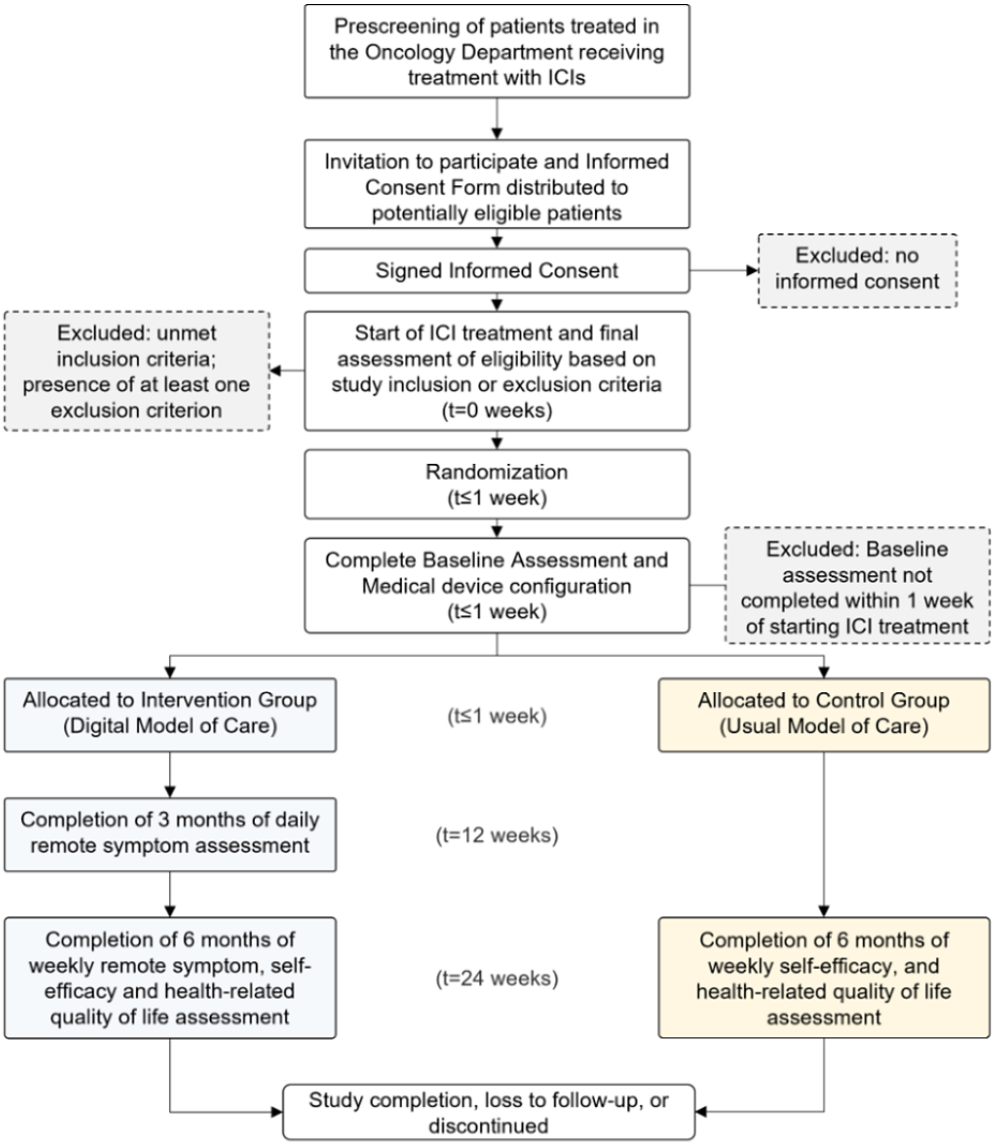
Participants fulfilling all the following inclusion criteria are eligible for this study: (1) patients 18 years old or older, (2) diagnosed with cancer, (3) starting or restarting systemic single- or dual-agent ICI monotherapy in neoadjuvant, adjuvant, consolidation, or palliative settings, and (4) providing informed consent as documented by the signature on the informed consent form. The presence of any of the following exclusion criteria will lead to participant exclusion: (1) patients self-declaring not being able to use the electronic app and complete the questionnaire in French, (2) patients with any psychological, familial, or sociological condition and linguistic limitation, potentially hampering compliance with the study protocol requirements or follow-up procedures, (3) patients restarting ICI therapy who have previously participated in this study, (4) patients with cognitive impairment, as declared in the patient record, and (5) patients participating in other interventional clinical studies.

Screening and Enrollment

Patients are identified by the local principal investigator and a team of sub investigators. Potentially eligible patients are approached after clinician appointments or during treatment. They are given the informed consent form (Multimedia Appendix 1), and a telephone call with a subinvestigator is scheduled within the following week to answer any questions or concerns. Patients are given at least 48 hours to consider participating in the study. Figure 1 shows the flowchart for patient enrollment in this study. Informed consent forms are collected during the patients' next hospital appointment. Patients can be enrolled in the study up to a week after ICI treatment has started. When eligible patients refuse to participate, their reason for refusal is anonymously recorded with their consent.

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Figure 1. Flowchart of the enrollment of the patients in this study. ICI: immune checkpoint inhibitor.



Study Design

Prior to randomization, subinvestigators collect demographic, medical history, and active treatment data from eligible consenting patients. Participants are randomized by subinvestigators using a web-based REDCap (Research Electronic Data Capture) form (version 12.4.21) [43]. The form has a randomization table (1 per site) using permuted block 1:1 randomization (block size of 4), independently prepared by the study biostatistician. Initially, the IePRO RCT was open to patients with melanoma and patients with lung cancer exclusively, and randomization was stratified by cancer type. Due to challenges in recruitment and following a protocol amendment in April 2022, this study was open to patients with all cancer types, and the stratification criteria were dropped. Blinding was not possible due to the nature of the intervention. Patients are informed that they will be randomly allocated to 1 of the 2 models of care: the standard model (control group) or the digital model (intervention group). The informed consent form and support documentation for the electronic app used to deliver the PRO questionnaires include these same conventions to further mitigate the adverse effects of the lack of blinding toward participants. Data collection instructions and reminders sent to clinicians caring for participants do not indicate which group the participant belongs to.

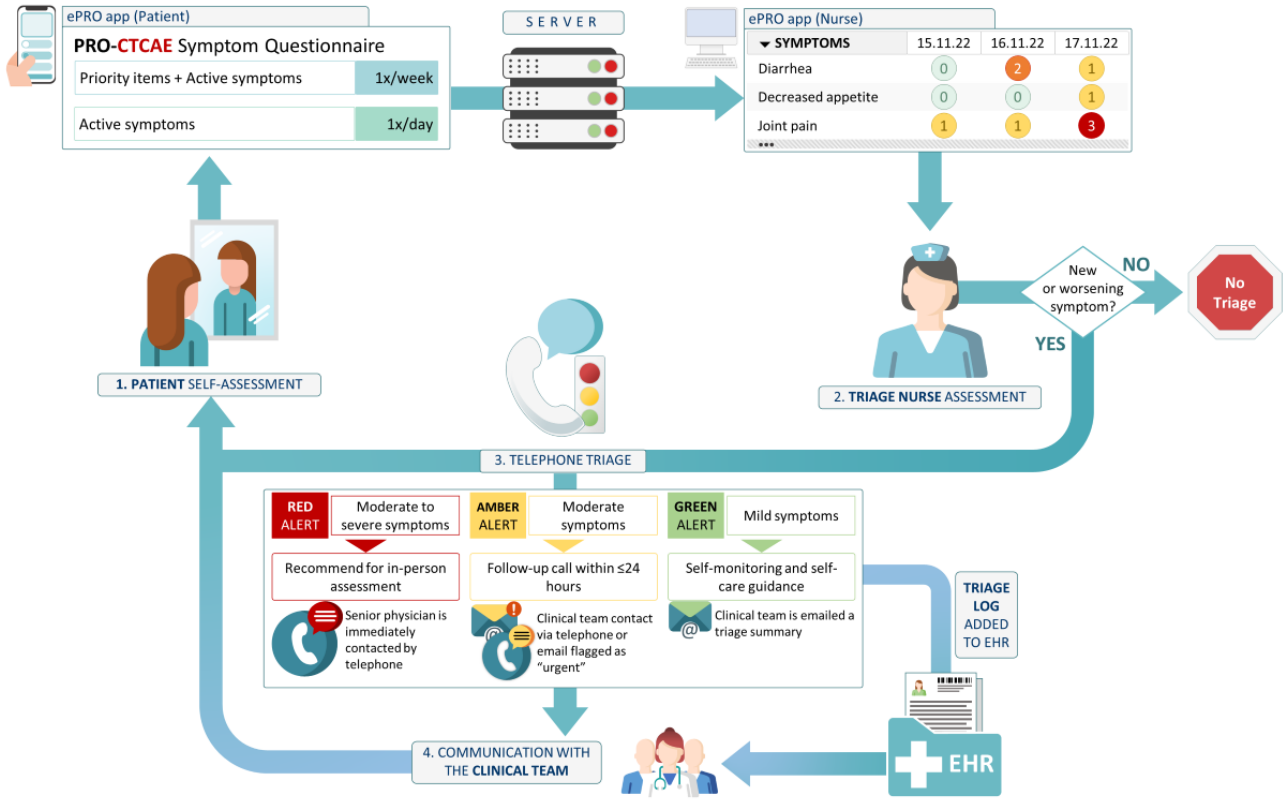
Patients in both groups obtain access to an electronic mobile app, which contains weekly questionnaires for HRQoL and self-efficacy to manage symptoms. An information sheet detailing how to navigate the app is also provided. Nurses and subinvestigators are available to assist patients in installing the app, registering and signing into an account, and replying to the baseline questionnaires in-person or over the phone. Patients in the intervention group have access to a symptoms questionnaire that is part of the intervention being tested. Automated reminders via emails or push notifications are sent to patients when a new questionnaire is available. Patients in both groups have the same number of scheduled clinician appointments—usually the same day and frequency of the ICI treatment—and are followed up for up to 6 months of ICI treatment.

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Intervention

The intervention of this RCT consists of a complementary model of care that uses ePROs to facilitate remote symptom management [42]. This model is represented in Figure 2. Patients in the intervention arm have access to a weekly PRO-CTCAE questionnaire through an electronic mobile app. Patients receive an email invitation to access the app and an information sheet explaining its interface. Once patients access the app, they are required to complete a questionnaire of predefined symptoms. During the first 3 months of the intervention, active symptoms are reassessed daily. When replying to a questionnaire, patients can add any other item of the full PRO-CTCAE item library, which are automatically added to the following daily or weekly questionnaires as well (see Multimedia Appendix 2). The rapid and sudden onset of IrAE and ICI's interference with pre-existing conditions and symptoms drove the decision to collect symptom data daily [10,28]. Due to the potential burden this sustained frequency could represent to patients, this was restricted to the first 3 months of the intervention. Patient replies are available in real time to the triage nurses. Two triage nurses at each site are notified via email when patients submit new replies or report severe symptoms, and they contact patients by telephone in the event of new or worsening symptoms. The nurses review patients' answers every working day from 8 AM to noon. Outside of these hours, usual care procedures apply.

Figure 2. IePRO (immune-related adverse events monitoring through electronic patient-reported outcomes) Model of Care: (1) When prompted by the mobile app, patients reply to a Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events symptom questionnaire via their own computer or mobile device. Data collected through the questionnaire are stored in a server controlled by the study sites. (2) Triage nurses are notified when patients have declared symptoms. (3) In the event of new or worsening symptoms, nurses initiate a telephone triage call with the patient. (4) Using the United Kingdom Oncology Nursing Society 24-hour triage tool, nurses determine the adequate course of action according to symptom severity and communicate the outcome of their assessments with the clinical team. The triage nurse's detailed assessment is recorded in a triage log stored in the electronic health record. EHR: electronic health record; ePRO: electronic patient-reported outcome; PRO-CTCAE: Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events.



Triage nurses perform an assessment of the reported symptoms with the United Kingdom Oncology Nursing Society 24-hour triage tool [44], which are graded on a CTCAE-based scale [45]. If patients report symptoms not covered by the PRO-CTCAE questionnaire, they are also addressed during these calls. The combination of symptoms may result in different types of color-coded alerts that tie into different recommendations. Mild symptoms generally result in green alerts, where self-care and self-monitoring instructions are warranted. Moderate symptoms requiring remote follow-up within the next 24 hours correspond to an amber alert. The presence of 2 or more amber alerts or of severe symptoms results in a red alert, where urgent in-person assessment is recommended. Triage nurses communicate with physicians via email or telephone according to the type of alert. A triage log detailing the symptom assessment, recommendations to the clinical team, and the actions taken to manage patient care is added to the electronic health record (EHR).

Patients are informed that this model of care is complementary to the usual care model. They are instructed by the triage nurses and subinvestigators in the clinical team that in the event of a symptom that causes them any level of concern and would lead them to seek medical assistance, they must contact their reference clinician or the on-call oncologist as usual. It is also

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clarified that the likelihood of being called by the triage nurse should never delay them from seeking medical assistance. In this sense, patients are reminded of these procedures at every telephone interaction with the triage nurses.

Electronic App (Medical Device)

This study is categorized as a clinical trial with medical device of risk category A1. It uses a web-based and mobile CE-marked app (Kaiku Health app) containing the PRO measures. The app is classed as a medical device that allows patients to submit their answers and access previous replies. Patients receive a summary of the reported symptoms detailing which of those improved, remained stable, or worsened. The app's security features were assessed and validated by the participating hospitals' information technology departments. Web-based and mobile versions of the app are identical in content and functionality. Patient data collected through the medical device are encrypted at rest and in transit and are subject to regular backups. Security updates are ensured by the app developer (Elekta AB). Two-factor authentication is activated for all patients.

Study Objectives and Outcomes

Primary Objective and Primary Outcome

The primary objective of the IePRO RCT is to compare the effect of an ePRO-based model of care to the current standard model of care on the delay between symptomatic IrAE onset and its detection by health care providers in patients with cancer treated with ICIs. The ePRO-based model of care complements the standard model of care with remote symptom monitoring via ePROs and remote symptom management via telephone triage calls done by oncology nurses. The primary outcome is the time-to-detection of IrAEs, as evidenced by a statistically significantly lower length of time when compared to that in usual care. Time to detection is the difference expressed in days between the IrAE detection date by the clinical team and the associated symptom's onset date according to the patient's self-report.

Secondary Objectives and Secondary Outcomes

The secondary objectives of this trial include assessing the effect of the ePRO-based model of care on the following secondary outcomes: (1) the delay between symptom onset and deployment of pharmacological interventions to manage symptomatic IrAEs by a statistically significant shorter or longer average time delay, (2) the type and amount of pharmacological interventions to manage symptomatic IrAEs by a statistically significant lower average dose, (3) the average maximum symptomatic IrAE grade by a statistically lower or higher average score, (4) the HRQoL through a statistically significant higher or lower overall score of the Functional Assessment of Cancer Therapy-General (FACT-G) questionnaire [46], (5) the perceived self-efficacy to manage symptoms through a statistically significant higher or lower score of the PROMIS (PRO Measurement Information System) Self-Efficacy for Managing Chronic Conditions–Managing Symptoms (short form 8a) [47], (6) overall survival at 6 months plotted using Kaplan-Meier estimates, using routine data collected in the EHR, and (7) description of the symptomatic IrAEs experienced by patients by type and grade according to version 5.0 of the National Cancer Institute's CTCAE [48]. Remote symptom management processes recorded by nurses will be described using (1) patient-reported symptoms triggering remote symptom management procedures using the composite grading algorithm for the PRO-CTCAE questionnaire [49] and (2) the type of issued triage alerts following triage procedures according to the United Kingdom Oncology Nursing Society 24-hour triage tool [44] and associated symptoms reported using the PRO-CTCAE questionnaire.

Exploratory Objectives

As exploratory objectives, the RCT will also describe the following in the intervention group: (1) symptoms reported via the PRO-CTCAE questionnaire that suggested the need for in-person intervention and patients received the intervention (true positives), (2) symptoms reported via the PRO-CTCAE questionnaire that suggested the need for in-person intervention but patients did not receive the intervention (false positives), (3) type of interventions required and provided for symptoms as reported in the triage log and the EHR, (4) symptoms reported via the PRO-CTCAE questionnaire that require an intervention beyond remote symptom management, (5) usability of the electronic app used to collect PRO symptom data and acceptability of the ePRO-based model of care, assessed through semistructured patient interviews, and (6) acceptability of the ePRO-based model of care assessed via semistructured individual interviews and focus groups with clinical nurse specialists, nurses, and physicians.

Sample Size Calculation

A sample of 29 health records of previously treated patients with melanoma who experienced IrAEs was used to estimate the required sample size. Patients with lung cancer were not considered for this calculation due to the lack of accessibility to symptomatic IrAE data in that population. Only records where the symptom onset was reported were included for this sample size calculation. In that record sample, the time interval between symptom onset and clinician detection of symptomatic IrAEs was estimated at 4.43 days, with an SD of 3.65 days. A 2-sample *t* test with a statistical power of 90% and significance level set at .05 determined that 138 participants would be required to detect a 2-day difference, assuming the same SD of 3.65 days. Given that similar studies have reported an attrition rate of 30%, the target sample size was adjusted to 198 patients [36,50].

Data Collection Methods

Demographic data and data relating to symptomatic IrAEs and their management for both control and intervention groups are collected through EHR review of the clinical oncologist's follow-up notes at each scheduled appointment with participants. Data from the EHR are recorded in REDCap electronic case report forms hosted in the server of the study sponsor's Clinical Research Center [51]. PRO data are collected through the Kaiku Health electronic app, which contains 3 questionnaires. The questionnaires were selected by the study's subinvestigator team, including a patient advocate (GS-B), by discussing matters of burden and of pertinence of the collected data to patients, and what data were actionable for the model of care.

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HRQoL data are collected via version 4 of FACT-G questionnaire, translated in French [46,52]. The questionnaire targets 4 domains: physical well-being, social or family well-being, emotional well-being, and functional well-being. Recall period, instrument scaling, scoring, and methods to handle missing data do not differ from the official administration and scoring guidelines [53]. The self-efficacy for managing symptoms is assessed weekly using the 8-item short-form French version of the PROMIS Self-Efficacy for Managing Chronic Conditions–Manage Symptoms measure [54]. Instrument scaling, scoring, and missing data handling also do not differ from the official scoring manual [55].

Symptom data in the intervention group are collected using a weekly PRO-CTCAE that includes symptom terms categorized as of the highest importance to monitor during ICI treatment. Thirty of the 37 symptom terms were identified through the Delphi study conducted in the first phase of the IePRO project [41]. The remaining 7 were selected by the IePRO project's clinical team and principal investigators. All PRO-CTCAE items were translated in French. Currently, no official guidelines exist on how to best analyze PRO-CTCAE data longitudinally [56]. In this RCT, we will follow guidance provided by Basch et al [49] to calculate a single composite numerical grade for PRO-CTCAE symptom terms to facilitate longitudinal analysis.

As previously stated, active symptoms are reassessed daily during the first 3 months of the RCT. This is done by modifying the standard PRO-CTCAE recall period from 7 days to 24 hours. Although modifications to the recall period of PRO-CTCAE items are not encouraged, this is specifically due to potential considerable measurement errors, as that period is extended [57]. Recent studies [58,59] have highlighted how PRO measures using 24-hour recall periods more accurately convey symptom burden and variability over a short period of time, particularly for symptoms such as constipation, diarrhea, nausea, and those related to the patient's emotional state. In patients treated with chemotherapy, shortened recall periods across different symptom PRO measures have enabled detection of clinically meaningful changes and were shown to be capable of detecting severe symptoms earlier [58,59]. Because some IrAEs can be fulminant and evolve in severity very quickly, daily reassessment of active symptoms could also support early detection and management. Although there is concern that the inclusion of all PRO-CTCAE items for daily assessment can be burdensome to patients, this concern addressed static questionnaires. In this intervention, questionnaires are dynamic and only active symptoms are reassessed daily to avoid overburdening patients.

To minimize missing data, the app requires respondents to provide a response before they are able to progress within the questionnaire. Patients receive automated reminders to reply to the questionnaires via email. In the event of early study discontinuation or withdrawal, all data collections, including PRO data, are halted. A semistructured interview guide based on the mHealth App Usability Questionnaire by Zhou et al [60] was developed to assess the usability of the ePRO app. Acceptability of the model of care will be assessed using an interview guide developed around the 7 constructs of acceptability of health care interventions as described by Sekhon et al [61]. Patient and individual staff interview data will be collected via audio recordings. Recordings will be transferred from the recording device's secure digital card to be stored in the corresponding site's local secured servers. Transcriptions of the recordings will be independently analyzed by 2 subinvestigators by using thematic analysis.

Statistical Methods

In this RCT, the null hypothesis postulates that there is no difference in the primary end point (delay between symptom onset and detection be clinical team) between the intervention and control groups. The primary outcome will be analyzed comparing groups by means of multivariable regressions, adjusting for cancer type, age, and treatment regimen, against a 1-sided hypothesis. Secondary outcomes will be analyzed using multivariate regression analysis, controlled for cancer type, treatment regimen, and age. All statistical analyses will be presented as effect measure plus 95% CI, using a significance level of 5%. Variations in HRQoL and self-efficacy scores will be assessed by adjusting to baseline measure. Overall survival at 6 months will be controlled for cancer type and stage. All data processing and statistical analyses will be performed in R statistical software (v4.2.2; R Core Team 2023) and Microsoft Excel for Microsoft 365 MSO (version 2302, 2023). In-questionnaire data completeness is compulsory, though potential errors in the app may nevertheless occur. In addition, data such as time points may prove difficult to collect. According to the type and amount of missing data, strategies including imputation methods, deletions, or dismissals will be considered. For the HRQoL and self-efficacy for managing symptoms questionnaires, missing data will be handled according to official guidelines [53,55]. For exploratory outcomes, descriptive statistics will be applied. Qualitative data of semistructured interviews will be analyzed by the subinvestigators. Interviews will be transcribed verbatim and analyzed through thematic analysis.

Patient and Public Involvement

A patient expert (GS-B) was involved from the initial stages of the design of this study. The patients helped define the outcomes of interest of the study; gave their feedback on its design, choice of instruments for PRO data collection, and choice of medical device; assisted in the creation of documents targeting patients such as the informed consent form and the information sheet for the medical device; and participated in the study's dissemination. Ten patients gave feedback on the medical device interface during its development phase.

Safety Reporting

The university hospitals participating in this study have signed a research agreement detailing each site's responsibilities and data access and management procedures to ensure compliance with the research protocol and data monitoring plan. All information related to the trial will be stored securely at the corresponding study site. Documents containing participant data will be identified by a coded identification number only to maintain patient confidentiality. The sponsor and medical device developer have entered a written data processing agreement that outlines the extent in which data processing can be handled by

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the developer. Upon trial completion or early withdrawal, patients' login credentials are deactivated, and PRO data are archived. The data archive is stored by the data manager and the sponsor of the study. Accessing encrypted data logs requires prior authorization from the sponsor-investigator. Trial monitoring activities are ensured by a data monitor for each site, following a clinical monitoring plan submitted alongside the research protocol to the competent ethics committee. Monitoring visits are scheduled to occur at 6, 12, 18, and 24 months (end of trial). Any study-related incidents are reported to the sponsor representative. Serious adverse events are reported to the competent ethics committee of the trial. Patients enrolled in the trial are covered by indemnity for negligent harm through the sponsor.

Ethics Approval

This study has been approved by the ethics committee of the Canton of Vaud, Switzerland (approval 2021-00301) and is conducted according to local regulations and the Declaration of Helsinki [62]. This trial is sponsored and led by the Lausanne University Hospital in Switzerland and registered at ClinicalTrials.gov (NCT05530187). Informed consent is obtained from all participants. Due to the nature of the intervention, this study is unblinded. Data are deidentified for data analysis purposes. No compensation was provided to patients participating in this study. In addition to the major amendment to the eligibility criteria, challenges brought by the COVID-19 pandemic (including site-imposed restrictions to conducting research not related to the pandemic) and resulting uncertainty on whether all the components of this trial could be deployed and thus its original outcomes assessed, further prevented this trial from being registered prospectively. Trial registration preceded any interim data analysis, and the original outcomes have been preserved.

Results

The first version of the research protocol of the IePRO RCT was approved in September 2021. In addition to 2 minor amendments, the latest version of the protocol contained a major amendment to the inclusion criteria, which was modified to include patients with any cancer type. This version was submitted and approved by the responsible ethics committee in April 2022. The current version of the protocol includes minor amendments that were approved in March 2023 (version 3.1 on September 22, 2022). All trial documents, including the protocol, site-specific informed consent form, and participant education materials, have been approved by the competent ethics committee. Patients have been actively recruited to this trial since November 2021, and this trial is projected to close by November 2023. The results of this trial will be published through abstracts, posters, presentations, and publications in peer-reviewed journals, when agreed to and reviewed by the principal investigators and the sponsor representative of the trial.

Discussion

The IePRO RCT is, to our knowledge, among the first trials to use PRO data to directly influence the routine care of patients treated with ICIs. Current guidelines argue that PRO measures can guide clinicians in monitoring patients at home, optimize patient interactions when the patients come to the hospital, and highlight symptoms that could improve or resolve through supportive care interventions [32]. Crucially, PROs can help identify active treatment-associated toxicities that, if unmanaged, may worsen and require complex care, impact quality of life, lead to treatment interruptions, and thus, ultimately, decrease survival [32,34].

Recent studies have shown the feasibility and acceptability of ePRO symptom monitoring systems to monitor IrAEs but have provided limited evidence of their impact on patient care and clinical outcomes [63]. IrAE investigation and management algorithms and the lack of integration and adaptability to routine care are among the key areas requiring improvement for the success of these interventions. The triage process in the IePRO model is a potential strength, as it provides nurses with a standardized procedure to investigate and manage symptoms, potentially decreasing variations in how care and information are provided, facilitating more consistent outcomes. In addition, the model of care was conceived with adaptability in mind, to be able to accommodate 2 tertiary hospitals. The adaptive structure of the PRO-CTCAE questionnaire focuses on active symptoms and enables patients with the choice of adding self-detected symptoms, while limiting the risk of increased burden, particularly due to more frequent data collection. It is possible that its weekly data collection may more accurately portray changes throughout treatment, as opposed to multiple-month intervals of measures of HRQoL and self-efficacy for managing symptoms.

Other limitations of this study are that the broad triggers for a telephone triage call (new or worsening symptom) may lead to a significant number of calls that may not always result in meaningful changes to how care is provided. A recent publication by Msaouel et al [64] has described adaptive and more granular alert thresholds that could prevent and alleviate clinician burden. Clinicians in similar studies have noted the time-consuming nature of ePRO data review, and these broad triggers may compound that burden further and limit clinician compliance to study procedures [65]. Tolstrup et al [66] attempted to empower patients with the decision to contact the hospital, though this may have discouraged computer-naïve patients from doing so even when symptoms were concerning, leading the authors to consider a proactive approach for future iterations of remote PRO monitoring. Integration with the EHR was complicated by the differences in EHR platforms across study sites and the short time interval between the finalized code for the mobile app and the start of the study. EHR integration is a major factor for ensuring successful implementation of ePRO monitoring [63], and it remains unclear if the measures implemented to mitigate the lack thereof will be successful.

Dropping tumor type and excluding ICI agents as stratification criteria constitute a major limitation of this study, as patient groups could present important differences that could influence the type, severity, and frequency of IrAEs. This consideration should guide future analysis of the data, and its impact will be addressed in future publications. More frequent measuring and

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the reactive nature of the intervention increase the risk of surveillance bias, as clinicians will be more aware of the challenges patients are experiencing. The intervention also does not allow blinding of patients who may alter their usual self-monitoring and self-care behaviors due to their awareness of the triage nurse's monitoring [66]. As this study is being deployed in 2 sites, tracking hospitalization and emergency room admissions for patients in the control group was outside the resources available to the study team. As a consequence, they were not included as secondary end points for this study, limiting insight on its efficiency to improved care. Overall survival measures were capped at 6 months due to limited resources to pursue a longer target, which could hinder the visibility of long-term effects of the model of care. Lastly, excluding patients who self-declare unable to use the electronic app and the lack of alternative means to self-report symptoms limit the comparability of this sample to the general population [36,67]. Despite these limitations, the IePRO RCT takes a pragmatic approach to symptom monitoring with ePRO data by not insulating its model of care from the existing resources the sites use to assist patients. Importantly, the IePRO RCT may further highlight the challenges patients treated with ICIs face outside the clinical setting, particularly as more data revealing the true burden of treatment-associated toxicities continue to emerge.

Acknowledgments

The authors are grateful to the clinicians, patients, patient-experts, and collaborators in the participating sites who have facilitated the development of this study and to Dr Sandra A Mitchell for her guidance in using the Patient-Reported Outcome version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE).

Data Availability

The data sets generated during or analyzed during this study are not publicly available due to its sensitive nature but are available from the corresponding author on reasonable request.

Authors' Contributions

ME and OM conceived the study's original concept and design. AMdSL, SC-L, CD, VA-L, SL, NM, GS-B, and AA later contributed to refining the design, instruments, and methods. The first draft of the manuscript was written by AMdSL, and all authors commented on the previous versions of the manuscript. Analyses will be conducted by the study biostatistician MC and AMdSL. ME is the sponsor representative of the Lausanne University Hospital for this study. All authors read and approved the final manuscript.

Conflicts of Interest

SC-L reports grants from Institut Suisse de Recherche Expérimentale sur le Cancer Foundation. GS-B reports grants from MSD France, grants from Novartis, and personal fees from Bayer, Melanoma Patient Network Europe, and Working Group of European Cancer Advocacy Networks outside the submitted work. OM reports grants and personal fees from Bristol Myers Squibb (BMS), MSD, Pierre-Fabre, Amgem; personal fees from Roche, Novartis, and Glasgow Smith Kline; and grants from Merck outside the submitted work. ME received institutional research grants from Kaiku Health and reports grants from BMS, Roche, and institutional fees as a scientific advisory board member or consultant from Roche outside the submitted work.

Multimedia Appendix 1
Informed consent form (in French).
[PDF File (Adobe PDF File), 355 KB - resprot_v12i1e48386_app1.pdf]

Multimedia Appendix 2
Symptom Questionnaire flowchart demonstrating how the electronic app uses symptoms that the patient declares as active to then requesting a reassessment in the following day by using a modified 24-hour recall period. It also shows how symptoms that emerge between weekly questionnaires are taken into account in the next weekly questionnaire even when the symptoms are no longer active.
[PDF File (Adobe PDF File), 284 KB - resprot_v12i1e48386_app2.pdf]

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Abbreviations

CTCAE: Common Terminology Criteria for Adverse Events
EHR: electronic health record
ePRO: electronic patient-reported outcome
FACT-G: Functional Assessment of Cancer Therapy-General
HRQoL: health-related quality of life
IePRO: immune-related adverse events monitoring through electronic patient-reported outcomes
ICI: immune checkpoint inhibitor
IrAE: immune-related adverse event
PRO: patient-reported outcome
PRO-CTCAE: Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events
PROMIS: Patient-Reported Outcomes Measurement Information System
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture

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Protocol

Pilot Testing of an mHealth App for Tobacco Cessation in People Living With HIV: Protocol for a Pilot Randomized Controlled Trial

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Abstract

Background: An estimated 40% of people living with HIV smoke cigarettes. Although smoking rates in the United States have been declining in recent years, people living with HIV continue to smoke cigarettes at twice the rate of the general population. Mobile health (mHealth) technology is an effective tool for people living with a chronic illness, such as HIV, as currently 84% of households in the United States report that they have a smartphone. Although many studies have used mHealth interventions for smoking cessation, few studies have recruited people living with HIV who smoke.

Objective: The objective of the pilot randomized controlled trial (RCT) is to examine the feasibility, acceptability, and preliminary efficacy of the Sense2Quit App as a tool for people living with HIV who are motivated to quit smoking.

Methods: The Sense2Quit study is a 2-arm RCT for people living with HIV who smoke cigarettes (n=60). Participants are randomized to either the active intervention condition, which consists of an 8-week supply of nicotine replacement therapy, standard smoking cessation counseling, and access to the Sense2Quit mobile app and smartwatch, or the control condition, which consists of standard smoking cessation counseling and a referral to the New York State Smokers' Quitline. The Sense2Quit app is a mobile app connected through Bluetooth to a smartwatch that tracks smoking gestures and distinguishes them from other everyday hand movements. In the Sense2Quit app, participants can view their smoking trends, which are recorded through their use of the smartwatch, including how often or how much they smoke and the amount of money that they are spending on cigarettes, watch videos with quitting tips, information, and distractions, play games, set reminders, and communicate with a study team member.

Results: Enrollment of study participants began in March 2023 and is expected to end in October 2023. All data collection is expected to be completed by the end of January 2024. This RCT will test the difference in outcomes between the control and intervention arms. The primary outcome will be the percentage of participants with biochemically verified 7-day point prevalence smoking or tobacco abstinence at their 12-week follow-up. Results from this pilot study will be disseminated to the research community following the completion of all data collection.

Conclusions: The Sense2Quit study leverages mHealth so that it can help smokers improve their efforts at smoking cessation. Our research has the potential to not only increase quitting rates among people living with HIV who may need a prolonged, tailored intervention but also inform further development of mHealth for people living with HIV. This mHealth study will contribute significant findings to the greater mHealth research community, providing evidence as to how mHealth should be developed and tested among the target population.

Trial Registration: ClinicalTrials.gov NCT05609032; https://clinicaltrials.gov/study/NCT05609032

International Registered Report Identifier (IRRID): DERR1-10.2196/49558

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KEYWORDS

addict; addiction; app; application; applications; apps; cessation; cigar; cigarette; cigarettes; HIV; mHealth; mobile health; quit; quitting; randomized controlled trial; RCT; smartwatch; smoker; smoking cessation; smoking; tobacco

Introduction

Overview

An estimated 40% of people living with HIV smoke cigarettes [1]. Smoking leads to many health problems among people living with HIV, including cardiovascular disease, pulmonary infections, bacterial pneumonia, chronic obstructive pulmonary disease, and cancer [2]. Lung cancer is the leading cause of death among people living with HIV taking antiretroviral therapy (ART) in the United States [1,3]. Although smoking rates in the United States have been declining in recent years, people living with HIV continue to smoke at twice the rate of the general population [3,4]. Quitting smoking can significantly decrease the risk of acquiring serious illnesses [2].

Mobile health (mHealth) technology is an effective tool for people living with a chronic illness, such as HIV. Currently, 84% of households in the United States report that they have a smartphone [5]. Due to the high rate of smartphone ownership and associated tech literacy, mHealth apps are an accessible and affordable means of delivering health care [6].

Although many studies have used mHealth interventions for smoking cessation [7-9], few studies have recruited people living with HIV [10-12]. As such, this study's team created the Sense2Quit app, using the Information Systems Research (ISR) framework [13], for people living with HIV who want to quit smoking. Through an iterative process with people living with HIV who were current or former smokers, as well as usability experts, we identified major themes associated with quitting smoking and developed and evaluated the Sense2Quit app to be used in our randomized controlled trial (RCT) starting in March 2023 [14,15].

Study Objective

The objective of this pilot RCT is to examine the feasibility, acceptability, and preliminary efficacy of the Sense2Quit app as a tool for people living with HIV who are motivated to quit smoking. This paper details the procedures that will take place during the Sense2Quit RCT.

Methods

Ethical Considerations

All study procedures were reviewed and approved by the Columbia University institutional review board (protocol number AAAT7031). Study participants will provide written informed consent and HIPAA (Health Insurance Portability and Accountability Act) authorization before enrolling in the study. Consent forms inform participants about (1) why the study is being carried out, (2) the things they will be asked to do if they are part of the study, (3) any known risks involved, (4) any potential benefit, (5) options other than taking part in this study that they have, and (6) the way their health information will be used and shared for research purposes. The study staff explains all procedures that will occur throughout the study and answers any participant questions before obtaining the participant's informed consent.

Confidential participant information will be assigned a code number and separated from any name or information that is identifiable. The research file that links a participant name to the code number will be kept on a password-protected computer, and only the investigator and authorized study staff will have access to the file. Any results disseminated from the study will be deidentified.

All participants will receive US $40 after completing baseline procedures, US $50 after completing their 4-week follow-up, and US $60 after completing their 12-week follow-up. All tokens of appreciation will be presented in the form of a Bank of America pay card.

Design

The Sense2Quit study is a 2-arm RCT among people living with HIV who are motivated to quit smoking. Sense2Quit is a 12-week pilot study to determine the feasibility and acceptability of the intervention. This study duration is comparable to other small pilot feasibility and acceptability studies [16-21]. Participants are randomized to either the active intervention condition, which consists of an 8-week supply of nicotine replacement therapy (NRT), standard smoking cessation counseling, and access to the Sense2Quit mobile app and smartwatch, or the control condition, which consists of standard smoking cessation counseling and a discussion about enrolling in the New York State (NYS) Smokers' Quitline, whereby the study team encourages the participant to contact the Quitline. Those who contact the NYS Quitline are eligible to receive an NRT supply, smoking cessation counseling, and other benefits, depending on their zip code [22]. Participants in the control arm do not receive NRT as part of the study because the study team determined that offering NRT would not be considered a true standard of care. Intervention participants will self-report NRT use on the follow-up visit surveys. Control participants will receive a sheet with information about the NYS Quitline and will self-report whether or not they contacted the Quitline during check-in calls with the study team. Participants in both conditions are scheduled for a baseline visit, a 4-week follow-up, and a 12-week follow-up. Participants are informed that the day of their baseline visit is their quit date; however, they are given the option to set their quit date on an established date within 1 week following their baseline appointment. Study team members will call participants in both arms to check in on a weekly or biweekly basis about their quitting process. The differences in study arms are presented in Table 1.

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Table 1. Intervention versus control study procedures.

Study procedure	Baseline	4-week follow-up	12-week follow-up
Intervention			
Survey	✓	✓	✓
Smoking cessation counseling	✓		
eCO[a] monitoring	✓	✓	✓
8-week supply of combination NRT[b]	✓		
Sense2Quit app and smartwatch	✓		
Control			
Survey	✓	✓	✓
Smoking cessation counseling	✓		
eCO monitoring	✓	✓	✓
NYS[c] Smokers' Quitline referral	✓		

[a]eCO: exhaled carbon monoxide.

[b]NRT: nicotine replacement therapy.

[c]NYS: New York State.

Recruitment and Eligibility

Targeted recruitment occurs through the posting of flyers in community-based organizations and the submission of web-based advertisements (ie, Craigslist and RecruitMe), as well as through snowball sampling [23] of study participants. Potential participants are instructed to call our office line or contact the study email to participate in screening procedures over the phone with a study team member. The eligibility criteria for this study are presented in Textbox 1.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- People living with HIV confirmed through medical records or pill bottles for antiretroviral therapy (ART) medications.
- Aged 18 years or older.
- Able to understand and read English.
- Current smoker (smokes at least five cigarettes per day for the past 30 days).
- Owns an Android smartphone.
- Not pregnant or breastfeeding (due to contraindications for nicotine replacement therapy [NRT]).
- Permanent contact information.
- Interested in quitting smoking within 30 days.
- Exhaled carbon monoxide (eCO) ≥5 ppm (parts per million) at baseline.

Exclusion criteria

- Use of tobacco products other than cigarettes (ie, vapes, electronic cigarettes [e-cigarettes], cigars, piped tobacco, chew, and snuff).
- Planning to move within 3 months of enrollment.
- Alcohol dependence as measured through the Alcohol Use Disorders Identification Test-Concise (AUDIT-C).
- Positive history of a medical condition that precludes nicotine patch use.
- Current use of NRT or other smoking cessation medications (eg, Chantix or Zyban).
- Current enrollment in another smoking cessation program
- A household member is also participating in the Sense2Quit study, as it can lead to study contamination [24].

Sample Size Calculation

This study is a pilot study, and therefore it is not powered to detect efficacy. In this pilot study, we propose a total sample of 60 (30 per arm group) with a 20% expected attrition rate. Therefore, this study is not powered to detect a significant difference between study arms. Instead, we estimated the precision of proportion estimates (cessation rates) for the given

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sample size (30 per arm). For the proposed sample size of 30 per group, we will have at least an 80% probability that the SE of the cessation rate estimates are ≤7%.

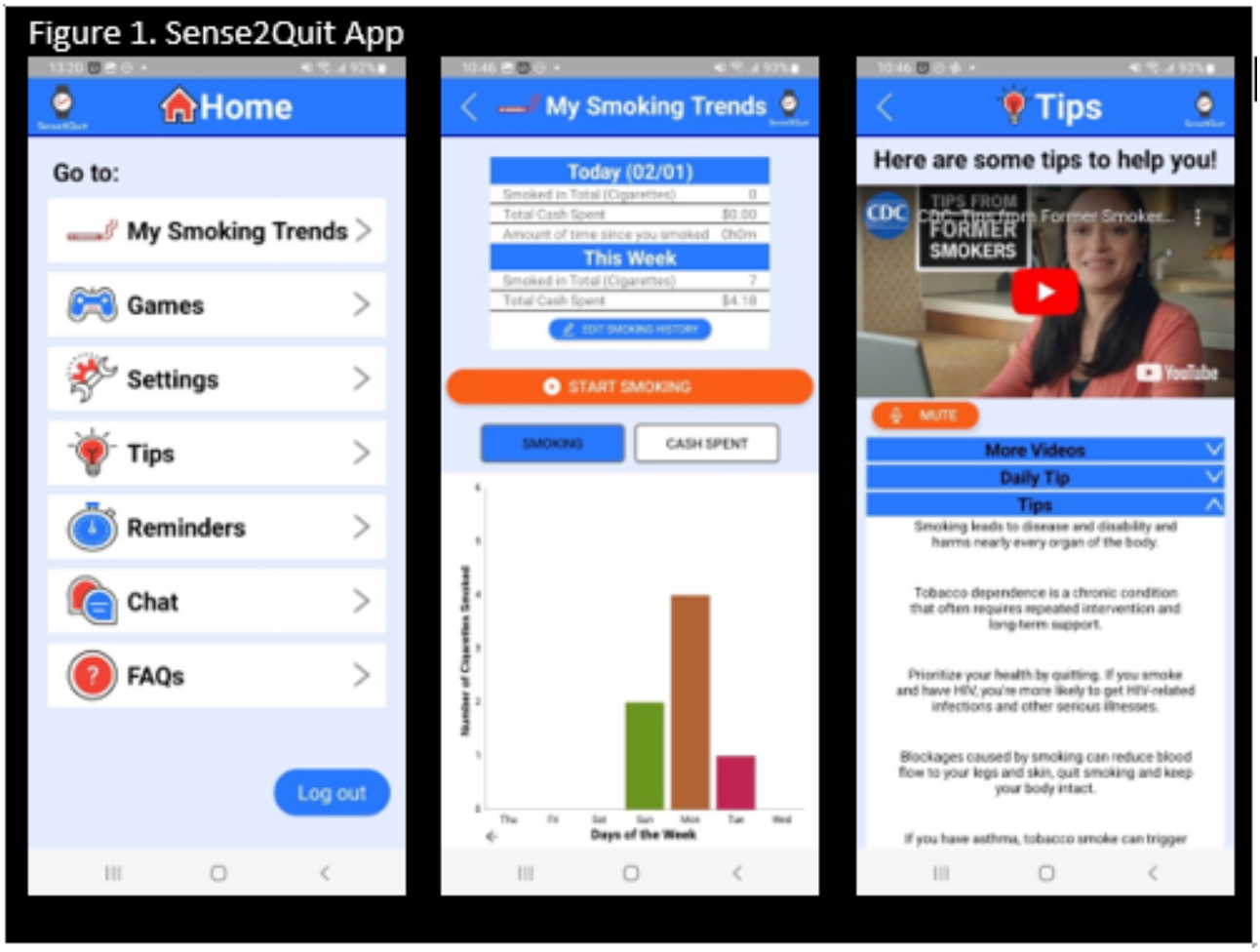
Randomization

Eligibility is confirmed at the in-person baseline visit. Participants confirm their HIV status by showing the study team their ART prescription or other medical records that provide HIV status. Smoking status is confirmed by the participant having an exhaled carbon monoxide (eCO) level of ≥5 ppm (parts per million). Upon confirmation of eligibility, participants complete the informed consent process and are randomized to the study group using a computer random number generator in Research Electronic Data Capture (REDCap). Study personnel are blinded to randomization before enrollment. Sex (assigned at birth)-stratified randomization is achieved through random-permuted blocks.

Description of the Intervention: Sense2Quit App

The Sense2Quit app (Figure 1) is a mobile app connected through Bluetooth to a smartwatch that tracks smoking gestures and distinguishes them from other everyday movements such as eating, drinking, etc. The ISR framework guided the development of the app and included an iterative process [14,15] where both people living with HIV, who were current or former smokers, and usability experts helped design, evaluate, and refine the Sense2Quit app. Findings from the formative work were used to inform the final Sense2Quit app, which was used in the RCT [14,15].

Figure 1. Sense2Quit app.



In the Sense2Quit app, participants can view their smoking trends, which are recorded through their use of the smartwatch, including how often or how much they smoke and the amount of money that they are spending on cigarettes, watch videos with quitting tips, information, and distractions, play Pac-Man and Tedroid (a game similar to Tetris [25]), set reminders, and communicate with a study team member.

Following enrollment in the study, participants who are randomized to the intervention arm receive a smartwatch and access to the Sense2Quit app. Participants are assigned a username (their study ID, SQ, followed by a number assigned chronologically) and can create a password for themselves. A study team member familiarizes the participant with the app, highlighting each component and feature. Participants can send a chat or call the study office whenever they have a question about the app or watch.

Study staff will encourage participants to wear their smartwatch on a daily basis so that it accurately captures smoking data. All smoking data will be displayed on the "My Smoking Trends" page of the app in the form of a graph. If the smartwatch incorrectly detects smoking, participants can click "Edit Smoking History" to update their smoking data for the previous

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week. Participants will be informed of the potential benefits of using the "Games," "Tips," and "Reminders" pages of the app, such as distracting themselves to overcome an urge to smoke by playing Pac-Man or Tetroid or watching a video. Additionally, tailored reminders can be set to overcome daily urges such as those surrounding morning coffee or a meal. Study staff will check in with participants throughout the study about any issues that arise while using the app, and participants will come into the office for a tech appointment when necessary.

Study Assessments

Participants are enrolled in person at the research office. After enrollment, participants in both arms complete study assessments at their baseline, 4-week, and 12-week follow-up visits, for a total of 3 study visits. Surveys are administered through Qualtrics (Qualtrics Experience Management [XM]) and gather information about participant demographics [26], tobacco use history, tobacco cessation (primary outcome: self-report of whether or not they have smoked or used other tobacco products in the last 7 days; number of quit attempts), illicit substance and alcohol use [27,28], predictors of tobacco cessation [29,30], cravings and withdrawal [31], psychosocial factors [32-34], markers of HIV/AIDS immune status [35], and pharmacotherapy use. All instruments used in the surveys have consistently demonstrated high reliability and validity [26-37]. The Health Information Technology Usability Evaluation Scale (Health-ITUES) and Post-Study System Usability Questionnaire (PSSUQ) will be used on the 12-week follow-up assessment to help us determine the acceptability of the intervention. We will ask participants in both arms how useful each of the intervention components was using the PSSUQ with a 7-point Likert scale (1=strongly agree to 7=strongly disagree) [37] and Health-ITUES with a 5-point Likert scale (1=strongly disagree to 5=strongly agree) [38].

Primary Outcome

The primary outcome is the percentage of participants with a biochemically verified 7-day point prevalence of smoking or tobacco abstinence. The 7-day point prevalence of abstinence is calculated as the percentage of participants who reported no smoking or tobacco use in the 7 days before their 12-week follow-up visits (self-report on survey whether or not they have smoked cigarettes, even just a puff, or used other forms of tobacco in the past 7 days), which is then biochemically verified by eCO collected at 12 weeks through a breathalyzer (Micro+TM basic Smokerlyzer, coVita). Participants with eCO levels <5 ppm will be classified as abstinent, while participants with eCO levels ≥5 ppm will be classified as not abstinent. Although we exclude participants who report use of tobacco products other than cigarettes at baseline, we anticipate that some participants may use other tobacco products during the study period. Thus, abstinence will be defined as having refrained from using not only cigarettes but also all tobacco products.

Statistical Analysis

This is a pilot study to assess feasibility, acceptability, and preliminary efficacy. To determine feasibility, we will examine retention rates, eligibility criteria, recruitment and enrollment rates, missing data, and study measures. Descriptive statistics will be used for the analysis of demographic characteristics. The rate of quit attempts will be calculated as the proportion of smokers who made a quit attempt (defined as no smoking for at least a 24-hour period); 7-day point prevalence abstinence will be calculated as the proportion of smokers who have not smoked or used tobacco products in the 7 days before the study visit (as reported in the 4- and 12-week follow-up surveys) and verified by an eCO level of <5 ppm. We will provide point estimates and corresponding CIs of these measures for each arm. Because of the small sample sizes, we will obtain Clopper-Pearson exact CIs based on the binomial distribution. Given the small sample size, the purpose of the arms is to monitor for unexpected, gross differences between the 2 groups. The preliminary efficacy of the intervention will be based on 7-day point prevalence abstinence at the 12-week follow-up survey. Participants lost to follow-up will be included as smokers because we will be missing follow-up data and cannot determine whether or not the intervention was effective. Since this is a pilot study, we will be focusing on the acceptability, demand, and limited efficacy testing of the intervention. Acceptability will be assessed by evaluating how the participants react to the intervention (using PSSUQ and Health-ITUES). The demand for the intervention will be assessed by gathering data on estimated use. The limited-**efficacy testing** will be conducted on a convenience sample with a short follow-up period and limited statistical power [39].

Results

Enrollment of study participants began in March 2023 and is expected to end in October 2023. All data collection is expected to be completed by the end of January 2024. Results from this pilot study will be disseminated to the research community following the completion of all data collection.

Discussion

Overview

Our planned study will test the effectiveness of the Sense2Quit app for smoking cessation among people living with HIV in New York City. This RCT will assess the difference in outcomes between the control arm, receiving smoking cessation counseling and Quitline referral, and the intervention arm, receiving smoking cessation counseling, an 8-week supply of combination NRT, and a smartwatch linked to the Sense2Quit app. This study plans to address a gap in the literature surrounding mHealth for people living with HIV who smoke.

Smartwatch technology has been developed and tested in interventional smoking cessation studies within the past decade, yet study samples have been small, and more testing is required to improve the accuracy of smoking detection [40-43]. Similarly, mHealth has been used for smoking cessation and has been found to be effective in the short term [44-51], with little evidence of efficacy in the long term [52]. A systematic review of quit-smoking apps in Android's Play Store and Apple's App Store found high rates of existing irrelevant or nonfunctioning apps and few apps with evidence-based support [53]. Thus,

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despite the large volume of apps to help users quit smoking that are currently on the market, few are likely to be effective.

Smoking cessation mHealth studies among people living with HIV are limited [12]. Tobacco cessation studies targeting people living with HIV have mostly consisted of automated messaging systems to intervene with smoking habits, motivational interviewing, and provision of pharmacotherapy [11,54-56]. In most cases, mHealth interventions for people living with HIV who smoke have been found to be more effective than face-to-face interventions [11], yet there is a need for more research on mHealth interventions which include interactive components such as communication with the study team or smoking cessation counseling [57]. Because people living with HIV are likely to have a shorter life span if they are chronic smokers [3], further research on effective quitting tools for people living with HIV is needed.

Although we found that people living with HIV in our focus groups were highly motivated to quit smoking due to health concerns, they identified needing additional interventions and support to successfully quit smoking amid everyday challenges and struggles [14]. With more than 350,000 apps currently on the market, mHealth technology is becoming widely known and used among people of all ages, races, and ethnicities [58,59]. mHealth technology is a promising tool across socioeconomic groups, as roughly 76% of low-income households (earning US $30,000 or less yearly) in the United States own a smartphone and indicate that their smartphone is their primary source of internet access [60,61]. Consequently, mHealth technology is a tool that is used in people's everyday lives and therefore can help with promoting health behavior change. This study will help us determine the potential of the Sense2Quit app to help people living with HIV quit smoking cigarettes. To our knowledge, the Sense2Quit study is the only existing study to use mHealth combined with a smartwatch to guide people living with HIV through their quitting process in New York City.

Limitations

This pilot study plans to recruit 60 people living with HIV in New York City who smoke cigarettes. As a result, the population may be too small to make generalizations about effective tobacco cessation techniques among people living with HIV in the short or long term. A second limitation is that although we will exclude people who use other tobacco products, such as cigars and vapes, we do not exclude people who may smoke other drugs, such as marijuana. This may result in incorrect smoking data for some participants. Participants will be instructed, however, on how to edit their smoking log in the app if incorrect data is shown.

Conclusions

The Sense2Quit study leverages mHealth so that it can help smokers improve their efforts at smoking cessation. Our research has the potential to not only increase quitting rates among people living with HIV who may need a prolonged, tailored intervention but also inform further development of mHealth for people living with HIV. This mHealth intervention also has the potential to address health inequities among people of different socioeconomic groups, as the majority of people in the United States own a smartphone and have access to apps. Finally, this study will contribute significant findings to the greater mHealth research community, providing evidence as to how mHealth should be developed and tested among the target population.

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Data Availability

The data sets generated during this study are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

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Abbreviations

ART: antiretroviral therapy
eCO: exhaled carbon monoxide.
Health-ITUES: Health Information Technology Usability Evaluation Scale
HIPAA: Health Insurance Portability and Accountability Act
ISR: Information Systems Research
mHealth: mobile health
NRT: nicotine replacement therapy
NYS: New York State
ppm: parts per million
PSSUQ: Post-Study System Usability Questionnaire
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture

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Protocol

Applying AI and Guidelines to Assist Medical Students in Recognizing Patients With Heart Failure: Protocol for a Randomized Trial

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Abstract

Background: The integration of artificial intelligence (AI) into clinical practice is transforming both clinical practice and medical education. AI-based systems aim to improve the efficacy of clinical tasks, enhancing diagnostic accuracy and tailoring treatment delivery. As it becomes increasingly prevalent in health care for high-quality patient care, it is critical for health care providers to use the systems responsibly to mitigate bias, ensure effective outcomes, and provide safe clinical practices. In this study, the clinical task is the identification of heart failure (HF) prior to surgery with the intention of enhancing clinical decision-making skills. HF is a common and severe disease, but detection remains challenging due to its subtle manifestation, often concurrent with other medical conditions, and the absence of a simple and effective diagnostic test. While advanced HF algorithms have been developed, the use of these AI-based systems to enhance clinical decision-making in medical education remains understudied.

Objective: This research protocol is to demonstrate our study design, systematic procedures for selecting surgical cases from electronic health records, and interventions. The primary objective of this study is to measure the effectiveness of interventions aimed at improving HF recognition before surgery, the second objective is to evaluate the impact of inaccurate AI recommendations, and the third objective is to explore the relationship between the inclination to accept AI recommendations and their accuracy.

Methods: Our study used a 3 × 2 factorial design (intervention type × order of prepost sets) for this randomized trial with medical students. The student participants are asked to complete a 30-minute e-learning module that includes key information about the intervention and a 5-question quiz, and a 60-minute review of 20 surgical cases to determine the presence of HF. To mitigate selection bias in the pre- and posttests, we adopted a feature-based systematic sampling procedure. From a pool of 703 expert-reviewed surgical cases, 20 were selected based on features such as case complexity, model performance, and positive and negative labels. This study comprises three interventions: (1) a direct AI-based recommendation with a predicted HF score, (2) an indirect AI-based recommendation gauged through the area under the curve metric, and (3) an HF guideline-based intervention.

Results: As of July 2023, 62 of the enrolled medical students have fulfilled this study's participation, including the completion of a short quiz and the review of 20 surgical cases. The subject enrollment commenced in August 2022 and will end in December 2023, with the goal of recruiting 75 medical students in years 3 and 4 with clinical experience.

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Conclusions: We demonstrated a study protocol for the randomized trial, measuring the effectiveness of interventions using AI and HF guidelines among medical students to enhance HF recognition in preoperative care with electronic health record data.

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(JMIR Res Protoc 2023;12:e49842) doi:10.2196/49842

KEYWORDS

medical education; clinical decision support systems; artificial intelligence; machine learning; heart failure; evidence-based medicine; guidelines; digital health interventions

Introduction

Computer-based diagnostic systems have played a critical role in both clinical practice and medical education, enhancing diagnostic accuracy and fostering the development of necessary knowledge and skills [1]. According to the Institute of Medicine's report [2], the use of informatics for clinical decision-making is an essential educational competency required for all health care professionals. However, the informatics landscape has undergone rapid advancement with the advent of deep learning in artificial intelligence (AI) and has revolutionized disease diagnosis, treatment delivery, and patient care [3-5]. Subsequently, AI-based tools become increasingly prevalent in health care, allowing health care providers to make informed clinical decisions for high-quality care and optimal patient outcomes [6-8].

As AI continues to be integrated into medical practice, it becomes inevitable for medical students, residents, and professionals to acquire the necessary skills for effective medical practice [9]. In 2021, Lomis et al [10] highlighted the importance of incorporating AI training across health care professions to maximize its benefits while mitigating the potential drawbacks in routine patient care. Mckinsey's report [11], titled "Transforming Healthcare with AI," emphasizes the need to implement this transformation within the realm of education and training. Moreover, AI training within the medical school curriculum is an active area of discussion and investigation [10,12,13]. With AI in the medical program, students have the opportunity to learn about the use of apps and limitations of AI in clinical practice and improve their ability to use AI-based tools to enhance patient care and decision-making.

In 1989, Iliad [14,15], a computer-aided diagnosis, was introduced to enhance diagnostic abilities, encompassing over 6300 disease manifestations and addressing 1300 diseases related to internal medicine. Iliad offered a unique diagnostic learning experience by simulating cases and guiding users through a series of decision-making processes encountered in clinical workups. It also provided tailored feedback at each decision-making of the clinical workups based on the user's performance. Lincoln et al [16] and Lange et al [17] demonstrated the improvement of diagnostic reasoning and a diagnostic error reduction among medical students and nurse practitioner students. Similarly, Friedman et al [18] confirmed enhanced diagnostic accuracy before and after using diagnostic consultation systems among medical students, residents, and physicians.

Despite the benefits of diagnostic systems, their integration into educational programs has been limited and has insufficient results [19,20]. Berner and McGowan [1] also pointed out that 1 contributing factor to limited educational usage is the stand-alone nature of these systems, which needs to be better integrated into existing clinical workflows. Conversely, Tolsgaard et al [21] observed that commercially available AI systems used in clinical settings are predominantly tailored to address specialized clinical challenges rather than assisting health care providers in skill enhancement. As a result, there is a gap in the development of health care professionals' ability to use such decision support systems to use algorithmically generated recommendations in their clinical decision-making responsibly.

Moreover, an overreliance on AI systems can lead to unintended errors due to automation bias [22], which refers to the tendency for individuals to place excessive trust in automated systems and disregard their own judgment, such as the failure of autopilot technology [23]. Without proper training on the responsible use of AI, health care professionals may unknowingly commit mistakes by relying too heavily on AI-based systems [24,25]. The lack of understanding and awareness of AI's limitations and potential biases can lead to errors in decision-making and patient care [26]. Health care professionals need the knowledge and skills to critically evaluate and interpret AI-generated recommendations, taking into account contextual factors and individual patient needs [27].

To mitigate the adverse effects and ensure the responsible use of AI, Tolsgaard et al [21] emphasized the importance of integrating learning sciences with clinical science and data science while developing new AI systems. This interdisciplinary approach aims to combine insights from educational research, clinical practice, and data analysis to design AI systems [28]. This approach enhances performance and fosters continuous learning and professional development. By integrating these disciplines, AI systems can be designed to provide appropriate feedback, facilitate reflective practice, and support the acquisition of clinical reasoning skills, promoting a balance between clinical practice and education in health care.

This paper is centered on demonstrating a study protocol, including a study design, a systematic procedure for case selection from electronic health record (EHR) data, and intervention designs to improve the recognition of patients with heart failure (HF) before surgery in a preoperative care clinical setting. HF is a common and serious chronic condition characterized by an abnormality in the structure and function of the heart, leading to reduced blood circulation throughout

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the body [29,30]. However, identifying patients with HF remains challenging due to its subtle and concurrent progression with other conditions and the lack of a single gold standard diagnostic test for HF [31,32]. Several algorithmic approaches have been recently published to improve HF detection, such as convolutional neural network with ECG [33-35], logistic regression [36], recurrent neural network [37], and transformer [38] models with EHR data.

The primary objective of this study is to measure the effectiveness of interventions aimed at improving HF recognition in preoperative care through a web-based clinical decision support (CDS) tool. The interventions are grounded in our previous research using traditional machine learning (ML) algorithms [39] and guideline-based diagnostic factors reviewed by clinical experts [40,41]. These interventions are algorithmically and manually synthesized from a large amount of EHR data for identifying HF. The secondary objective is to evaluate the impact of inaccurate ML recommendations in recognizing patients with HF, as compared to HF guideline-based recommendations. The third objective is to explore the relationship between the inclination to accept AI recommendations and the ability to accurately recognize HF using ML-based interventions.

Methods

Study Setting and Participants

Participants in this study are medical students to simulate the clinical task of preoperative surgical screening, targeting the recognition of HF as a specific educational objective using surgical cases performed at a tertiary hospital. This study's participants review surgical cases on our internally developed web-based CDS educational tool that displays deidentified EHR data, including clinical visits, diagnoses, procedures, vitals, laboratory, medications, imaging or studies, and clinical notes up to the day of surgery. To maximize the efficiency of case reviews, clinical data included in the CDS tool was tailored to preoperative care and cardiovascular diseases for screening HF. Irrelevant EHR data to this study (eg, administrative data, non-HF-related imaging) was excluded. This CDS tool was developed and deployed in a secure internal environment where study participants can access and review surgical cases.

The eligible students for participation in this study are medical students in their third (M3) or fourth (M4) year of medical school, who completed some coursework requirements and underwent clinical rotations. In addition, medical school graduates who have not yet started their residency program are eligible for inclusion. The rationale behind including senior medical students in this study is that accurate identification of HF using real-world EHR data needs a comprehensive understanding of clinical knowledge and skills acquired through coursework and clinical rotations.

This study is entirely on the internet and comprises two components as follows:

1. The first component entails an e-learning module, including an instructional video about the intervention and a short quiz, with an estimated completion time of 30 minutes.
2. The second component involves reviewing 20 surgical cases to evaluate the presence or absence of HF using EHR data, with an estimated completion time of 90 minutes.

Prior to reviewing the surgical cases, participants are required to complete a 5-question short quiz with all correct answers. They have the option to attempt the quiz multiple times if necessary. As this study is conducted on the internet, participants can complete this study at their own pace and at their own convenient time. Upon successful completion of this study, participants receive US $50 as a gift of appreciation.

Ethics Approval

This research study involving human subjects has received ethical approval from the institutional review board at the University of Michigan (HUM00207646). This approval indicates that this study's protocol, including research design, data collection methods, and informed consent, has been reviewed and considered to be in compliance with ethical standards for human subject research.

Study Design

The study design of this HF recognition study is a 3 × 2 factorial randomized trial that involves 3 intervention groups and the order exchange of 2 sets of surgical cases during the pre- and posttests. This study design allows us to measure the effectiveness of 3 interventions without introducing bias from surgical case selection in the pre- and posttests, summarized in Multimedia Appendix 1.

The rationale behind exchanging the order of 2 sets is to minimize the potential bias arising from differences in individual surgical cases. For example, if set A in the pretest contains 10 surgical cases that are more difficult than those in set B in the posttest, it would be challenging to attribute any improvements in accuracy solely to the interventions. Therefore, exchanging the order of the sets between the pre- and posttests ensures the measurement of unbiased interventions' effectiveness.

Furthermore, the use of random selection for the surgical cases is not suitable in this study due to the implementation of specific case selection criteria. The selection criteria aim to provide medical students with targeted learning opportunities to recognize HF through the review of surgical cases. The selection process is designed to ensure that the chosen cases offer valuable educational experiences and align with the intended learning objectives. Further details about the case selection are discussed in the later section dedicated to the systematic procedure for surgical case selection.

Prior to implementing the 3 × 2 factorial study design, a pilot study was conducted using a 3-arm study design. In this preliminary investigation, participants were asked to determine the presence or absence of HF before intervention access and then reassess the same surgical case after intervention access. However, this study design demonstrated an "anchoring effect," where participants tended to adhere to their initial clinical judgment. Therefore, it underestimated the effectiveness of the intervention. Consequently, the decision was made to adopt the 3 × 2 factorial design to overcome this limitation and provide a more accurate evaluation of the effectiveness of interventions.

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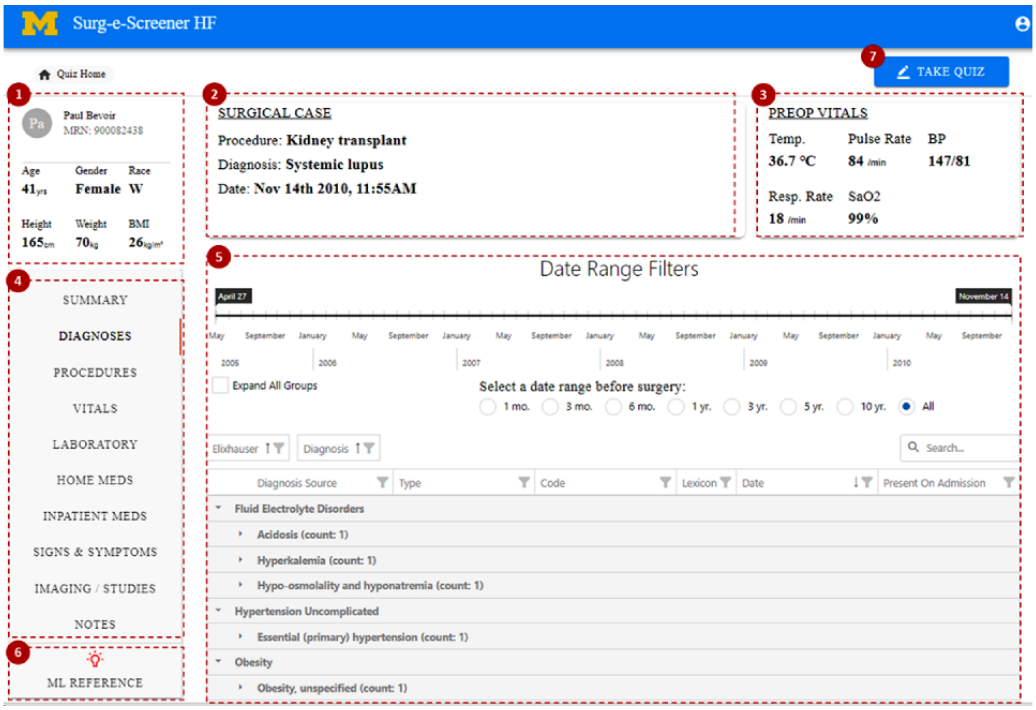
Interventions: ML_{DR}, ML_{IR}, and EB References

In order to measure the effectiveness of AI and guideline-based educational methods with 3 distinct interventions, the interventions need to provide essential information specific to the methods to enhance the ability to accurately recognize HF using patient data from the EHR.

The essential information is consolidated into a single *reference* page, which compiles risk factors associated with HF and method-specific recommendations (eg, HF yes or no, risk scores) to augment medical students' ability to recognize HF accurately. The risk factors are categorized into nine sections based on consultations with HF experts to improve the readability and comprehensibility of the interventions. These sections include (1) signs and symptoms, (2) past HF history, (3) past medical history, (4) surgical history, (5) medications, (6) physical exams, (7) test labs, (8) imaging or studies, and (9) ECG. A detailed description of the risk factors within each section can be found in Multimedia Appendix 2.

During the posttest phase, the intervention, represented by the reference page, is available to medical students who completed the first 10 surgical cases using only their clinical judgment during the pretest. In the posttest, the reference page is accessible through an ML or EB reference tab (6) in Figure 1 and can be accessed at any time while medical students review a surgical case. Further information about developing the ML model used in ML reference is included in Multimedia Appendix 3, and the details of the intervention differences are outlined as follows.

Figure 1. A web-based educational tool to review surgical cases, including (1) demographics (top left), (2) surgical case information (top middle), (3) preoperative vitals (top right), (4) subject domains (left side), (5) EHR data of a subject domain (center), (6) ML and EB intervention (left bottom). The intervention tab is only available during the posttest. After reviewing surgical cases, answer survey questions by clicking the (7) "TAKE QUIZ" button. EB: evidence based; EHR: electronic health record; ML: machine learning.



ML_{DR} Reference

The ML_{DR} reference provides a direct recommendation (DR), which is an output from the ML algorithm in the form of the presence or absence of HF, a dichotomous response. To achieve this, an optimal threshold is set to discriminate between positive and negative cases based on the estimated HF probability. The threshold configuration is critical in determining the sensitivity and specificity of the system. In this study, the optimal threshold was determined to be 38% based on the assumption that sensitivity and specificity are equally important. The ML_{DR} reference includes a brief explanation of the dichotomous recommendation, such as "this patient has a 98% chance of having HF, which is above the 38% threshold," to allow medical students to incorporate this into their clinical decision-making. It is important to note that the diagnosis of HF is a complex process that requires a thorough examination, and ML_{DR} reference offers a simple and efficient method to recommend the presence or absence of HF to medical students, along with a justification of the recommendation. The screenshot of ML_{DR} reference is in Multimedia Appendix 4.

ML_{IR} Reference

ML_{IR} reference offers an indirect recommendation (IR), which is a proxy of carrying HF risk, using the area under the receiver operating characteristic (AUROC), which comprises the true-positive rate (TPR) and false-positive rate (FPR). The AUROC plot, with TPR and FPR plotted along its axes, provides a comprehensive view of the model's performance across various thresholds. In contrast to ML_{DR} reference, which is limited to a single threshold, ML_{IR} reference shows the position of TPR and FPR on the AUROC plot when the threshold is defined as the predicted probability of HF for individual cases. For example, in the case of a surgical case with a high predicted

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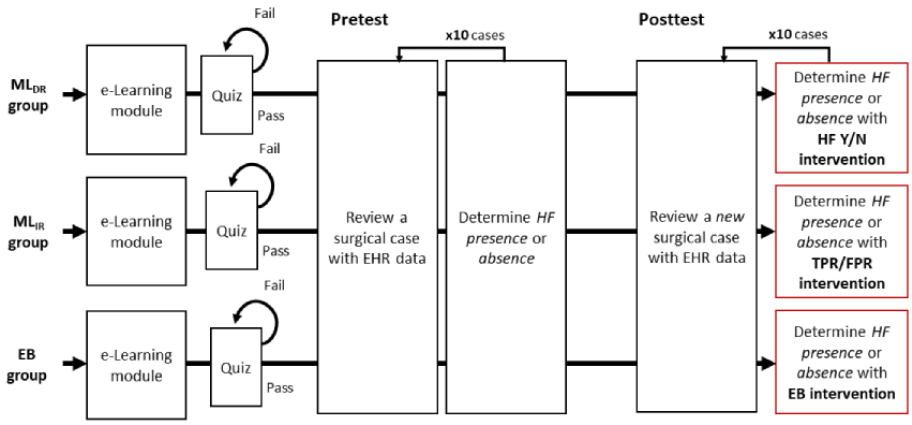
HF probability, ML_{IR} reference displays the corresponding TPR or FPR position on the AUROC plot, reflecting a high-level threshold equivalent to the predicted HF probability. This approach enables medical students to examine surgical cases with different TPR and FPR positions on the AUROC plot, thereby avoiding a *decision bias* toward a single threshold. The screenshot of ML_{IR} reference is in Multimedia Appendix 5. In short, ML_{DR} and ML_{IR} references adopt 2 distinct approaches to present direct and indirect recommendations to medical students while using the same underlying ML model.

EB Reference

The third intervention, *EB reference*, includes risk factors described in HF guidelines [42,43] and shows the presence or absence of these risk factors explicitly documented in EHR and clinical experts' impressions while reviewing the case from EHR. In our previous study [40], the 20 surgical cases were adjudicated by a consensus panel of HF experts (cardiologists, cardiac anesthesiologists, and critical care physicians) who indicated the explicit documentation of the risk factors in EHR as well as their impression of presence or absence of the risk factors. Unlike the risk factors from EHR data in ML references, this intervention uses the highest-quality evidence in the medical literature from various clinical studies and a consensus of domain experts to incorporate evidence-based practice into HF diagnostic recommendations. Further, because the HF recommendations in the guidelines [42,43] are intended to provide evidence-based recommendations for health care practitioners, they are presented in a way that is easy to *understand* and *acceptable* for clinicians. As such, the risk factors related to heart diseases are incorporated into medical education and training, resulting in less friction in clinical reasoning and decision-making. The screenshot of the EB reference is in Multimedia Appendix 6.

Each group in the HF recognition study is given access to one of the interventions during the posttest case reviews. After assignment to an intervention group, all participants reviewed the same 20 surgical cases, 10 surgical cases during the pretest phase, and then 10 new surgical cases during the posttest phase. The intervention is only accessible during the posttest. Figure 2 shows an overview of this study's participants for the three intervention groups: (1) ML_{DR} group, which receives direction recommendations indicating the presence or absence of HF; (2) ML_{IR} group, which receives indirect recommendations in the form of TPR, FPR, and AUROC plot; and (3) EB group, which receives expert-reviewed evidence-based risk factors from HF guidelines.

Figure 2. An overview of study participation using a 3 × 2 factorial study design. The participation includes an e-learning module, a short quiz, and 20 surgical case reviews. The order of 2 sets of 10 surgical cases is predetermined before the participant begins this study's activities. ML_{DR} group: a group of students who receive ML-generated risk factors and a direct recommendation of HF Y/N. ML_{IR} group: a group of students who receive ML-generated risk factors and an indirect recommendation of the likelihood of having HF from TPR, FPR, and AUROC. EB group: a group of students who receive HF expert-reviewed risk factors extracted from HF guidelines. AUROC: area under the receiver operating characteristic; EB: evidence based; EHR: electronic health record; FPR: false-positive rate; HF: heart failure; ML: machine learning; TPR: true-positive rate; Y/N: yes or no.



E-Learning Module

Prior to starting the surgical case review, participants are required to engage in a series of preparatory activities, including a web-based e-learning module that includes a 20-minute prerecorded instructional video, and a short quiz with 5 multiple-choice questions. The purpose of the e-learning module is to provide participants with the necessary knowledge and understanding to recognize patients with HF using the web-based tool. Given the diversity of participants' backgrounds and lack of familiarity with the new tool, this module offers educational materials and essential concepts that are fundamental to comprehending the interventions used to facilitate clinical decision-making.

The e-learning module focuses explicitly on facilitating participants' comprehension of machine learning concepts, including predicted risk scores, important features, thresholds, and evaluation metrics (eg, sensitivity, specificity, TPR, and FPR) for ML intervention groups. Additionally, the module covers the identification of risk factors contributing to HF, as outlined in the American Heart Association [42,44] and the European Society of Cardiology [43] HF guidelines, and Framingham criteria [45] for the EB intervention group.

In an attempt to confirm that subjects have viewed and comprehended the material presented in the prerecorded video, participants are required to complete a short quiz, which must be completed with a score of 100% (5 out of 5 questions). When

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questions are answered incorrectly, participants are instructed to review the material and revise their responses prior to proceeding to the next step. This e-learning module reduces variations in participants' prior knowledge and background to develop a standardized basis for evaluating surgical cases and measuring the effectiveness of interventions.

Surgical Case Selections

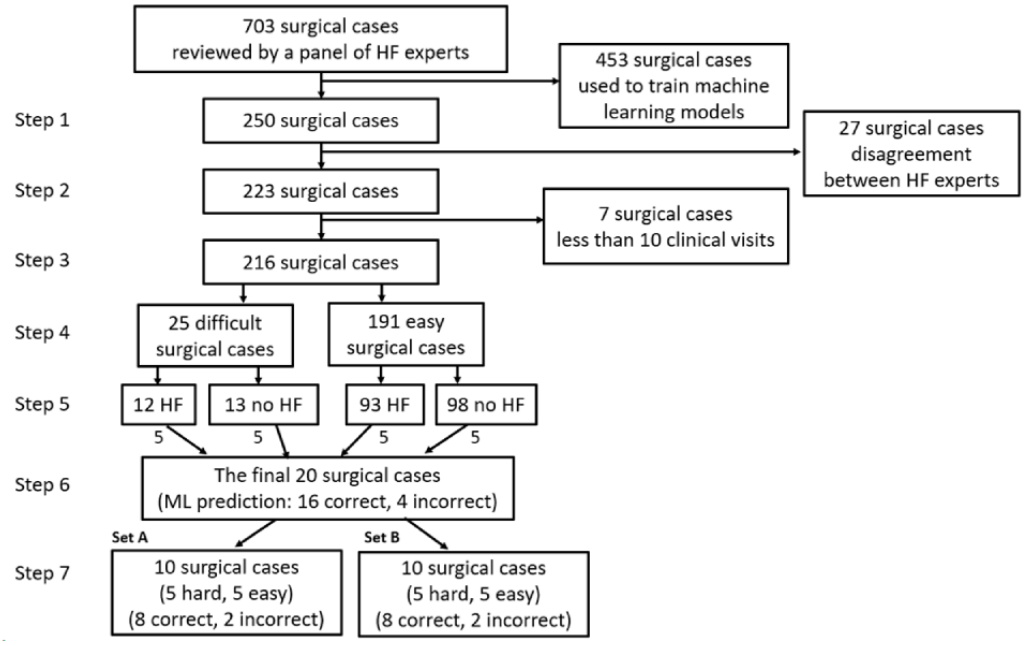
In our previous study [40,41], a consensus panel of HF experts, comprising cardiologists, cardiac anesthesiologists, and critical care physicians, assessed 1018 surgical cases, of which 703 were available during this study. These cases were part of a stratified subsample of 40,659 adult noncardiac surgical procedures between 2015 and 2019 at Michigan Medicine. Using a feature-based sampling process [46], 20 surgical cases were deliberately selected, considering factors, such as case complexity, expert consensus, ML performance, and HF outcomes. The 20 cases were divided into 2 sets, each consisting of 10 cases, for the use of pre- and posttests. Each set included an equal number of easy and difficult cases, as well as an equal representation of patients with and without HF.

The systematic sampling procedure for surgical case selection is illustrated in Figure 3. There are seven steps involved: (1) selecting cases from the holdout data set, (2) including cases that are consensus among expert reviewers, (3) including patients who had at least 10 clinical visits, (4) determining the level of difficulty from clinical diagnostic factors presented in EHR, (5) selection priority based on HF outcome, (6) consideration of ML performance (90% AUROC, 82% sensitivity, and 82% of specificity in our model), and (7) dividing cases into two sets for pre- and posttests. The more detailed descriptions of each step are included in Multimedia Appendix 7.

The implementation of a systematic methodology for case selection from EHR is critical, as the validation derived from this study could serve as a foundational cornerstone for scalability across diverse medical conditions. For example, diagnostic tasks using ML with expert-reviewed labels are potential candidates that could be integrated into this CDS tool by following the steps above, requiring only minor adjustments to accommodate unique clinical nuances. Thus, these ML-based tasks could be transformed into additional educational resources and presented to learners through this educational tool.

In the last step, surgical cases in set A and set B were presented to medical students in pre- and posttests to determine the presence or absence of HF. However, it does not guarantee equivalent difficulty levels, which is critical for evaluating intervention effectiveness. To mitigate the issue, we altered the order of sets in the pre- and posttests. Half of the participants received set A in the pretest and set B in the posttest, and vice versa for the rest of the participants, resulting in a 3 × 2 factorial design that ensured a balanced measurement of the interventions' effectiveness.

Figure 3. A systematic sampling procedure for the final 20 surgical cases with respect to the level of difficulty, positive and negative HF cases, and the ML performance from expert-reviewed surgical cases. HF: heart failure; ML: machine learning.



Sample Size and Recruitment Strategies

To assess the effectiveness of interventions with a power of 80% at a significant level of 5%, the total number of subjects needed is 75, with 25 subjects assigned to each group. This power analysis was conducted using a 1-sample *t* test using SPSS (version 28.0; IBM Corp), a statistical software package. The power analysis was based on our preliminary results, which indicated a mean difference of 0.08 and an SD of 0.13.

The recruitment for this study commenced in August 2022 and will continue until December 2023. The primary recruitment method involves sending a group email to year 3 and 4 medical students through faculty and academic curriculum coordinators, posting notices in various institutional newsletters and web-based bulletin boards, and distributing fliers. The recruitment started at a single institution and expanded to participants from other institutions.

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Furthermore, snowball sampling has been used, which asks for referrals from enrolled study participants. To encourage referrals, a referral-based lottery has been implemented for individuals who refer their friends and colleagues in year 3 or 4 medical students. This lottery is recurring quarterly, and the winner will be drawn each term and awarded a US $100 prize. In addition, we have implemented a sweepstakes for study participants who will enter for a chance to win US $500 worth of prizes to recruit more students.

Assignment of Interventions

To participate in this study, subjects must first complete a survey form providing information about their school year, clinical experiences, and their level of acceptance toward clinical recommendations made by both clinical experts and AI algorithms. As an individual's behavior and willingness to accept recommendations can significantly impact this study's outcome [47], the level of acceptance was included in the survey form for use in the subject assignment.

Upon registration, subjects are allocated to one of the intervention groups using a permuted block and stratification method [48]. This method involves stratifying subjects based on key characteristics and randomly assigning them across groups within a fixed size of blocks. For this study, the acceptance level of AI recommendations (≥50%) and medical institutions serve as the stratification criteria, with subjects being randomly assigned to intervention groups within each block of size 6. As a result, each block consists of 2 occurrences of 3 distinct interventions.

Data Collection

Upon completing the e-learning module, medical students begin reviewing 20 surgical cases. To assess the accuracy of recognizing patients with HF, medical students respond to a set of 3 survey questions for each case review. This survey is embedded in the web-based tool, which is accessible after reviewing EHR data and intervention information. Medical students have the option to revisit data points if needed to address the survey questions. As shown in Multimedia Appendix 8, 3 survey questions are presented to evaluate the ability of medical students to accurately identify the presence or absence of HF. The first question pertains to the final decision of HF presence or absence at the start of surgery, followed by a question on their level of confidence in their clinical decision. Finally, medical students are requested to check the type of information they use to inform their clinical decision-making process.

Outcomes

The primary outcome of this study is to assess the effectiveness of interventions in improving the accuracy of recognizing patients with HF, by measuring the mean difference of recognition accuracy before and after intervention in pre- and posttests. Specifically, this study will demonstrate the mean difference in HF recognition accuracy before and after accessing ML_{DR} ML_{IR}, and EB reference interventions.

The second outcome of this study is to evaluate the impact of accurate or inaccurate ML recommendations on medical students' clinical judgment to recognize the presence or absence of HF, compared to the EB intervention group. In addition, this study explores the differential effects of direct and indirect ML recommendations on clinical decision-making among students.

Lastly, this study measures the effect of the acceptance level of AI reported in the prescreening survey on the accuracy of recognizing HF using ML references. This exploratory outcome will provide valuable insights for enhancing the acceptability of AI tools.

Results

As of July 2023, 62 of the enrolled medical students have fulfilled this study's participation, including the completion of a short quiz and the review of 20 surgical cases. The recruitment process for these study participants began in August 2022 and will end in December 2023.

Discussion

Principal Findings

In this study protocol paper, we outlined a methodological approach for measuring the effectiveness of ML-based interventions, both direct and indirect recommendations, and EB intervention. The interventions were integrated with EHR data within a web-based educational tool to enhance the recognition of HF before surgery. Specifically, we demonstrated a novel randomized trial using a 3 × 2 factorial design, systematic procedures for surgical case selection, and 3 interventions using ML algorithms and HF guidelines using EHR data.

The demonstration of 3 × 2 factorial design (intervention type × order of prepost sets) represents a unique methodological contribution, enabling the measurement of intervention effectiveness through enrolling students in pre- and posttests. Prior work such as Lincoln et al [16] with medical students and Lange et al [17] with nurse practitioner students adopted a 2 × 2 × 2 mixed factorial design (disease sets × trained or untrained groups × replication) to evaluate diagnostic errors and posterior probability pertaining to the comprehensiveness of clinical workups. In contrast to Iliad, which offers feedback during training via simulated cases, our study provides an e-learning module designed to impart and apply synthesized information, grounded in AI or HF guidelines, to enhance diagnostic accuracy. With our proposed factorial design, the effectiveness of the synthesized information was measured before and after reviewing surgical cases derived from EHR.

Furthermore, this study protocol paper articulates a systematic procedure of selecting HF cases from expert-reviewed surgical cases in EHR, incorporating the difficulty level and positive and negative outcomes. We believe that this systematic procedure of case selection not only mitigates selection bias for this study but also offers a replicable framework for other diseases when expert-reviewed labels and EHR data are available. In addition, our approach has the potential of scalability to present algorithmically or manually synthesized information, along with other data available in EHRs, on other

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diseases. This is challenging for expert systems like Iliad, equipped with a knowledge base or inference engine [14,49].

Limitations

While this study provides a foundational approach to measure the effectiveness of enhancing HF recognition, it is important to note limitations with respect to a limited scope of findings and generalizability. Specifically, the target sample size of 75 participants (25 in each study arm) is adequate with a statistical power of 0.80 to measure the effectiveness of enhancing HF decision-making before and after intervention access. However, additional research questions, such as comparative effectiveness between ML and EB interventions, are limited in this study. Furthermore, this study was primarily conducted within an academic medical center that could be limited to a representative of medical schools in the United States. Despite this sample size constraint, our proposed study has the potential to inform future studies to broaden our understanding of how AI-based tools can be helpful for medical education and training.

Moreover, this study primarily focuses on intervention effectiveness, neglecting the essential facet of learner engagement and feedback mechanisms within the web-based tool. To enhance the effective learning outcomes in future iterations, the web-based decision support tool could incorporate real-time feedback upon each case completion, such as indicating the accuracy of case reviews and providing preannotated expert commentary on examined surgical cases. Additionally, offering structured guidance on interpreting AI-generated outputs is critical for accurately using predictive scores and in-depth analysis of misclassification instances. Integrating these postreview feedback mechanisms holds considerable promise for aiding learners in effectively leveraging AI-based tools for clinical decision-making.

The ML model used in this study was trained and evaluated on a stratified and manually reviewed data set, comprising patients who had developed HF and patients at high and low risk [40,41]. While stratification ensures the model learns various stages of HF progression, it may not accurately reflect the prevalence of HF estimated between 1.5% and 1.9% in the US population [50]. As a result, the model performance should be interpreted with caution when considering its use in a routine clinical setting and requires careful further examination. In this study, however, the deliberate inclusion of surgical cases for training the model with various complexities serves educational purposes effectively. This approach allows learners to gain experience in clear-cut positive or negative outcomes and also borderline cases, which are inherently challenging yet particularly informative.

Conclusions

In summary, this study protocol demonstrates a study design for measuring the effectiveness of interventions to enhance HF recognition among adult noncardiac surgical patients. Despite limitations of sample size and generalizability, this study serves as a foundational step toward a more comprehensive understanding of how AI techniques and evidence-based medicine can be synergistically used to advance both medical education and patient care outcomes.

Acknowledgments

The deployment of this study was possible with the extensive financial, infrastructure, and resource support provided by the University of Michigan. Several funding sources supported this study, including Research. Innovation. Scholarship. Education. (RISE) initiative, Michigan Institute for Computational Discovery and Engineering, Rackham Graduate Student Research Grant, and Aikens Innovation Academy from Frankel Cardiovascular Center. The Department of Learning Health Sciences offered unique opportunities to engage with professionals in health care, data, and implementation sciences. We thank Dr Karandeep Singh and Dr Zhenke Wu for their critical study reviews, and Dr Gretchen Piatt and Dr Anne Sales for their valuable insights in the realm of implementation science during this study's development. Additionally, during the RISE fellowship, the RISE team offered training sessions, ongoing support, and feedback to enhance my understanding of developing an AI-based tool for medical education. Notably, the core members of the RISE team, namely Dr Paula Thompson and Dr Nikki Bibler Zaidi, facilitated the training sessions and recommended developing relationships with relevant individuals for further guidance in order to obtain essential knowledge regarding the problem. With these supports, necessary connections were established with Dr Brian George, a surgeon whose insights into surgical consultation and workflow proved invaluable, and Dr James Woolliscroft, a professor of internal medicine and former dean of the medical school at Michigan Medicine, who provided valuable feedback on the overall study design and student recruitment processes. Lastly, the development and deployment of the web-based tool were feasible with the tremendous support from the Michigan Anesthesiology Informatics and Systems Improvement Exchange with the necessary IT infrastructure and resources to make this tool easily accessible to researchers and medical students. The use of ChatGPT (OpenAI, Microsoft Corporation) to improve the style of academic writing and grammar checking is disclosed in Multimedia Appendix 9.

Data Availability

Due to patient identification concerns and confidentiality, the data used for this study is not publicly available. Any request for data access may need additional approval from the institute review board at Michigan Medicine.

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Conflicts of Interest

HJ is currently an employee of Meta Platforms, Inc (aka Facebook). This research study was developed and deployed when HJ was affiliated with the University of Michigan.

Multimedia Appendix 1
A 3 x 2 factorial study design with three interventions and the set order of surgical cases. A study subject reviews a total of 20 surgical cases, 10 surgical cases in each pre- and post-tests. The mean difference in accuracy before and after accessing an intervention will be measured in each cell.
[DOCX File , 14 KB - resprot_v12i1e49842_app1.docx]

Multimedia Appendix 2
ML and EB Reference tables. The nine sections of heart failure–related risk indicators are categorized in the sequence of informed necessity for diagnosis.
[DOCX File , 22 KB - resprot_v12i1e49842_app2.docx]

Multimedia Appendix 3
A summary of developing and adopting a machine learning model in ML References.
[DOCX File , 13 KB - resprot_v12i1e49842_app3.docx]

Multimedia Appendix 4
ML_{DR} Reference: This intervention includes a direct recommendation based on heart failure (HF) probability, like HF or No HF. It also consists of the top 5 risk factors and the entire list in the reference table.
[DOCX File , 185 KB - resprot_v12i1e49842_app4.docx]

Multimedia Appendix 5
ML_{IR} Reference: This intervention includes the true-positive rate, false-positive rate, and area under the receiver operating characteristic plot. These will give a proxy of heart failure risk level but no direct recommendation. It also consists of the top 5 risk factors and the entire list in the reference table.
[DOCX File , 124 KB - resprot_v12i1e49842_app5.docx]

Multimedia Appendix 6
EB Reference: This intervention includes heart failure (HF) expert-reviewed presence or absence of risk factors listed in HF guidelines and HF expert's impression on the presence or absence of risk factors as reviewing a surgical case.
[DOCX File , 191 KB - resprot_v12i1e49842_app6.docx]

Multimedia Appendix 7
This is a detailed 7-step procedure to systematically select two sets of surgical cases from electronic health records taking into account factors such as case complexity, expert agreement, machine learning performance, and heart failure outcome.
[DOCX File , 14 KB - resprot_v12i1e49842_app7.docx]

Multimedia Appendix 8
The questionnaire that study participants are asked to answer after reviewing each case via the web-based educational tool.
[DOCX File , 15 KB - resprot_v12i1e49842_app8.docx]

Multimedia Appendix 9
The disclosure of the use of ChatGPT or other generative language models.
[DOCX File , 13 KB - resprot_v12i1e49842_app9.docx]

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Abbreviations

AI: artificial intelligence
AUROC: area under the receiver operating characteristic
CDS: clinical decision support
EHR: electronic health record
FPR: false-positive rate
HF: heart failure
ML: machine learning
TPR: true-positive rate

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Protocol

Improving Mild to Moderate Depression With an App-Based Self-Guided Intervention: Protocol for a Randomized Controlled Trial

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Abstract

Background: Depression is one of the most prevalent mental disorders and frequently co-occurs with other mental disorders. Despite the high direct and indirect costs to both individuals and society, more than 80% of those diagnosed with depression remain with their primary care physician and do not receive specialized treatment. Self-guided digital interventions have been shown to improve depression and, due to their scalability, have a large potential public health impact. Current digital interventions often focus on specific disorders, while recent research suggests that transdiagnostic approaches are more suitable.

Objective: This paper presents the protocol for a study that aims to assess the efficacy of a self-guided transdiagnostic app-based self-management intervention in patients with mild or moderate depression with and without comorbid mental disorders. Specifically, we are investigating the impact of the intervention on symptoms of depression, quality of life, anxiety symptoms, and mental health–related patient empowerment and self-management skills.

Methods: The intervention under investigation, MindDoc with Prescription, is a self-guided digital intervention aimed at supporting individuals with mild to moderate mental disorders from the internalizing spectrum, including depression. The app can be used as a low-threshold psychosocial intervention. Up to 570 adult patients will be randomized to either receive the intervention in addition to care as usual or only care as usual. We are including adults with a permanent residency in Germany and mild or moderate depression according to International Classification of Diseases, 10th Revision, criteria (F32.0, F32.1, F33.0, and F33.1). Clinical interviews will be conducted to confirm the diagnosis. Data will be collected at baseline as well as 8 weeks and 6 months after randomization. The primary outcome will be depression symptom severity after 8 weeks. Secondary outcomes will be quality of life, anxiety symptom severity, and patient empowerment and self-management behaviors. Data will be analyzed using multiple imputations, using the intention-to-treat principle, while sensitivity analyses will be based on additional imputation strategies and a per-protocol analysis.

Results: Recruitment for the trial started on February 7, 2023, and the first participant was randomized on February 14, 2023. As of September 5, 2023, 275 participants have been included in the trial and 176 have provided the primary outcome. The rate of missing values in the primary outcome is approximately 20%.

Conclusions: Data from this efficacy trial will be used to establish whether access to the intervention is associated with an improvement in depression symptoms in individuals diagnosed with mild or moderate depression. The study will contribute to expanding the evidence base on transdiagnostic digital interventions.

Trial Registration: German Registry of Clinical Trials DRKS00030852; https://drks.de/search/de/trial/DRKS00030852

International Registered Report Identifier (IRRID): DERR1-10.2196/46651

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KEYWORDS

depression; mobile app; intervention; unguided; transdiagnostic; randomized controlled trial; e-mental health; digital app; self-management; mental health; mHealth; mobile health; unguided digital intervention; public health; digital intervention; mobile phone

Introduction

In Germany, approximately 1 in 10 individuals experience depression in a given 12-month period [1]. Depression frequently co-occurs with other mental disorders; epidemiological data show that 61% of those with depression have at least 1 other mental illness [2]. This is supported by clinical evidence, where 69% of patients diagnosed with major depression also had at least 1 other Axis I diagnosis [3].

Health insurance billing data in Germany show a comorbidity rate of 50% within the group of mental disorders [4]. The most common combinations involve mood disorders (F3 group) and neurotic, stress, and somatoform disorders (F4 group) according to the International Classification of Diseases, 10th Revision (ICD-10), classification system [5].

The World Health Organization's World Mental Health Survey findings suggest that the majority of comorbid mental illnesses are a result of shared causal factors [6]. A study of the Dunedin Multidisciplinary Health and Development Study data also supports this conclusion [7], showing that across diagnostic categories mental illness can be broken down into 3 common higher-level factors (internalizing, externalizing, and thought disorders).

This finding may explain the transdiagnostic effects of many pharmaceutical and psychosocial treatments for a range of mental disorders [8,9]. As a result, mental health treatment approaches are shifting toward transdiagnostic interventions which are based on common underlying mechanisms of mental illness that have been proven to be effective across diagnoses [10]. Examples include the Unified Protocol [11] and the Common Elements Treatment Approach [12], which are increasingly replacing disorder-specific treatments.

Mental disorders are among the top 4 causes of healthy life years lost in Germany, with depression taking the first place within that group [13]. In 2015, the direct medical costs of depression in Germany were estimated at nearly €9 billion (US $8.4 billion) [14], while the loss of income due to depression throughout the European Union is approximately €176 billion (US $164 billion) per year [15].

Despite the high prevalence of depression and its significant direct and indirect costs, few receive specialized treatment. Health insurance billing data showed that while nearly 10% of insured individuals were diagnosed with an affective disorder at least once over a 3-year period, more than 80% of those affected remained with their primary care physician for the entire treatment [4]. On top, epidemiological data suggest that 3 out of 4 cases of major depression in Germany go undiagnosed and only 1 in 10 affected individuals receive evidence-based treatment as per national guidelines [16]. More recent data confirm this trend [17].

Treatment delay for depression can be attributed not only to limited resources among providers, but also to personal barriers such as low health literacy or negative attitudes toward seeking help. A desire to handle the issue alone and a low perceived need for treatment play a greater role in delaying treatment than structural barriers [18,19]. These factors hinder early detection, worsen the issue of underdiagnosis, and increase the risk of long-term symptom deterioration and chronicity [20].

Most people with depression in Germany receive treatment only from primary care physicians [4]. However, billing data from 2021 indicate that there are significant discrepancies between the frequency of mental illnesses in the general population as detected in epidemiological studies, and the diagnoses made by general practitioners [1,21,22]. While depression is diagnosed relatively in line with its frequency in the general population, anxiety disorders are underdiagnosed by as much as 75%. This suggests that comorbid disorders are likely not consistently recognized in primary care. This may be due to the difficulty of making a guideline-based diagnosis and differential diagnosis within the limited time frame of a general practitioner consultation, which typically lasts between 6 and 11 minutes [23,24].

Studies have found digital, cognitive-behavioral self-management programs to be effective for depression. Disorder-specific programs produce moderate to large effects on depression compared to waitlist controls [25-30]. Specifically, smartphone-based interventions have been shown to produce small to moderate effects [31]. The effect of self-guided transdiagnostic interventions on depression symptoms is comparable to the effect of disorder-specific interventions, with moderate to large effects on depression symptoms, and large effects on anxiety symptoms [32].

Interventions that include guidance by a mental health professional have larger effects [30,33-36], but there is also research showing no differences between guided and self-guided interventions [34,37-39]. Overall, self-guided interventions are more scalable due to lower costs and less human resources, making them more impactful for public health [40], especially when administered in primary care settings [41]. Other factors contributing to the variability in the results of self-guided interventions include study design characteristics including the use of clinical interviews [42], automated reminders [43], and the clinical setting [41], as well as participant characteristics like the severity of the disorder [34].

Meta-analyses confirm the effectiveness of digital interventions not only in reducing symptoms but also in improving quality of life [44] and there is also some evidence that such

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interventions can reduce self-stigma [45-47] and improve health-promoting behaviors [48].

Overall, digital interventions can help close the treatment gap for mental disorders including depression. In primary care settings, low-threshold transdiagnostic interventions appear to be most suitable, particularly due to the opportunity to address comorbid disorders, which are often overlooked in the setting, with the same intervention.

In a previous study on such a transdiagnostic intervention (MindDoc App) in people with mild or moderate symptoms of mental disorders from the internalizing spectrum [49,50], we detected small effects on depression symptoms (d=0.34) in both the overall sample (d=0.34) and a subsample of participants with depression symptoms above the diagnostic threshold (d=0.43). Small effects were also detected on quality of life (overall sample: d=0.19; subsample: d=0.31), anxiety symptoms (overall sample: d=0.22; subsample: d=0.24), and mental health–related patient empowerment and self-management skills (overall sample: d=0.29; subsample: d=0.41). Patient empowerment and self-management behaviors encompass a range of attitudes and behaviors that individuals exhibit in relation to taking control of their health and well-being, including seeking support, actively participating in health care decision-making, and adopting healthy habits.

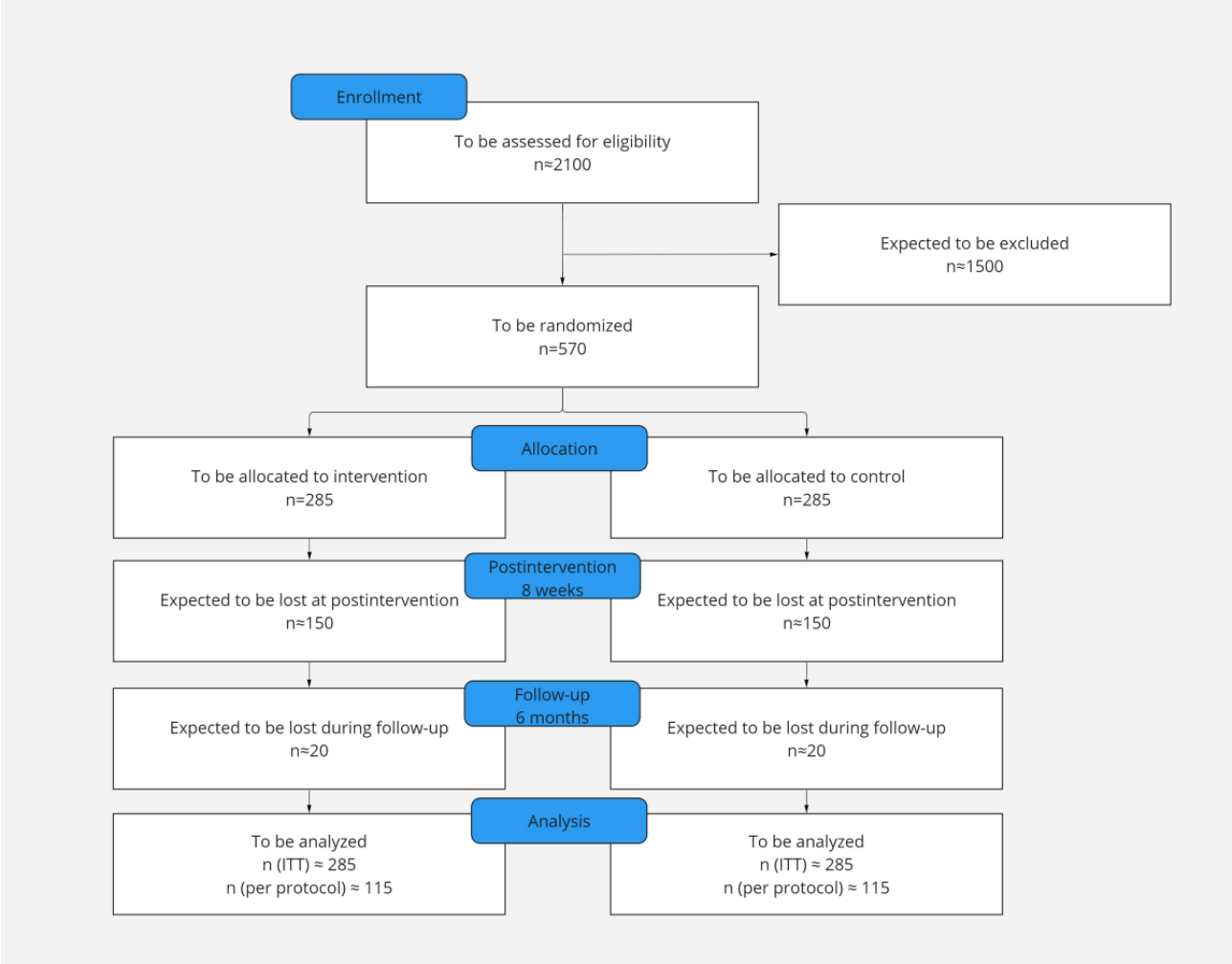
The aim of this study is to evaluate the intervention in a sample of individuals diagnosed with mild or moderate depression. Based on our previous findings, we expect the intervention to be associated with less severe symptoms of depression at the end of an 8-week intervention period compared with a waitlist control group. We will also examine intervention effects after 6 months, as well as intervention effects on quality of life, anxiety symptoms, and mental health–related patient empowerment and self-management skills.

Methods

Study Design

We are conducting a monocenter 2-arm randomized controlled trial with 3 assessment points (baseline, postintervention at 8 weeks, and follow-up at 6 months). Participants in the intervention condition will receive access to MindDoc with Prescription in addition to care as usual. Participants in the control condition will only have access to care as usual. Care as usual includes any form of treatment, including psychotherapy, unless psychotherapy has already been started or planned at the time of inclusion in the study. The study design is illustrated in Figure 1.

Figure 1. Study design. ITT: intention-to-treat.



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Procedures

Study participation includes a web-based screening, a diagnostic interview (baseline), 3 additional web-based surveys (baseline, postintervention, and follow-up) and a clinician rating (postintervention). In the intervention group, it additionally includes access to a digital health application (DiGA). The process is described in more detail below. All study data will be collected in an electronic data capture (EDC) system provided by Climedo Health GmbH in the form of electronic case report forms and electronic patient reported outcome forms.

Applicants first receive written information on the study procedure and must explicitly agree to participate in the study via electronic consent by ticking a number of checkboxes before they can proceed to the screening questionnaire. The responses are logged in the study database and can only be changed by the participants themselves. By ticking the checkboxes, they confirmed that they had thoroughly read and understood the information about the study procedures and data security measures (including information on how to contact the study team if they had questions) provided to them. This approach is General Data Protection Regulation (GDPR) compliant and was approved by the ethics committee.

After consent has been given, applicants proceed to a screening questionnaire, on which the majority of exclusion criteria are assessed. The applicants who do not fulfill any exclusion criteria are then invited to the diagnostic interview.

The diagnostic interview is conducted via telephone by a clinical psychologist or clinical psychologist in training. Before the actual interview begins, the participants are given another opportunity to ask questions about the study. They are also informed verbally once again that their participation is voluntary and that they can withdraw their consent at any time without giving reasons and without disadvantages. Immediately after the interview, applicants receive feedback on whether or not they can participate in the study.

The diagnostic interview is then followed by the actual baseline survey for the study. The link to the survey is sent to the participant's email address.

After the baseline survey has been completed, participants are randomized at the person level with 1:1 group assignment. Randomization is performed as block randomization in blocks of 4, 6, and 8, stratified by sex (male, female, and diverse), diagnosis (F32.0, F32.1, F33.0, and F33.1), and previous psychiatric or psychotherapeutic treatment (yes and no). Randomization lists were generated (1 per stratum) using Sealed Envelope [51] and directly integrated into the EDC system. Randomization is performed in a protected area of the EDC system that can only be accessed by authorized members of the study team without them having access to the randomization lists.

Participants will be notified of the results of the assignment via email. Participants assigned to the intervention group will immediately receive free access to the DiGA described below. Participants in the control group will receive free access to the DiGA after they complete their follow-up assessment.

In both groups, postintervention and follow-up assessments will take place after 8 weeks and after 6 months. The links to the respective surveys are sent to the participant's email address. The postintervention assessment also includes another telephone interview which is conducted by a clinical psychologist or clinical psychologist in training. Interviewers are blinded to the group assignment of the study participants.

If a participant fails to respond to a survey invitation, up to 5 reminders are sent within 14 days. If no response has been received after 28 days, the assessment will be marked as missing.

Eligibility Criteria

Overview

Eligibility criteria were selected to ensure an optimal fit of the study sample with respect to the subsequent implementation of the app in the German health care setting, to meet the requirements of the legal authorities, to minimize the impact of confounding variables, and to ensure comparability with other studies on self-guided digital interventions.

Inclusion Criteria

We are including adults with mild or moderate depression according to ICD-10 criteria (F32.0, F32.1, F33.0, and F33.1). Clinical interviews are conducted to confirm the diagnosis. Raters are clinical psychologists and clinical psychologists in training who are not part of the core study team. They administer the short version of the diagnostic interview for mental disorders [52], a short structured clinical interview for diagnosing mental disorders. The interview assesses current and lifetime diagnoses according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) and ICD-10.

Participants must also be fully legally competent, reside in Germany, and have sufficient German language skills. They must have access to their own smartphone (Android, version 6.0, Google, or iOS, version 13.0 or higher, Apple) and the internet, and be willing and able to use the app regularly and participate in the assessments.

Exclusion Criteria

We are excluding individuals who receive outpatient psychotherapy or inpatient treatment for a mental disorder at the point of enrollment or already have such a treatment planned to start within the next 8 weeks. We are also excluding individuals who report changes in antidepressant medication in the past 4 weeks, who report suicidal ideations, or who have a history of bipolar disorder, psychotic disorder, substance use disorder, or suspected substance use disorder. Individuals who report having used the MindDoc App or a comparable digital intervention in the past 12 months will also be excluded.

Recruitment

Participants are recruited via press releases, social media advertising, and cooperating primary care practices. Recruitment will take place over a period of at least 6 months. It is expected that about 2500 prospective participants will have to be screened, of whom 800 will be invited for a diagnostic interview to determine eligibility.

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Intervention

MindDoc with Prescription is a digital intervention aimed at supporting individuals with mild to moderate mental disorders from the internalizing spectrum, including depression. The app can be used as a low-threshold psychosocial intervention.

MindDoc with Prescription is a risk class I medical device according to Annex VIII, Rule 11 of the Medical Device Regulation (REGULATION (EU) 2017/745 on medical devices). Intended users include individuals with mild and moderate mental disorders.

The app consists of four key components: (1) continuous self-monitoring of symptoms and personal resources (journal), (2) personalized feedback on symptoms and coping strategies (insights), (3) regular overall assessments of emotional health (result), and (4) courses and exercises for psychoeducation and self-management (discover). All content was developed by licensed clinical psychologists based on established guidelines for the treatment of mental disorders.

The journal component allows users to log symptoms and personal information up to 3 times a day, with mood assessments and free text inputs. The insights section provides personalized feedback based on the information recorded in the journal. The result section provides an overall assessment of emotional health every 14 days, while the discover section offers courses and exercises on coping with symptoms, drawing on cognitive behavioral therapy, and other evidence-based treatments. Recommendations for relevant courses are provided based on users' journal entries. The app is designed to help patients understand and manage their symptoms, promoting self-sufficiency, and empowering them to take control of their mental health.

Participants can contact the study team and the MindDoc customer support by email at any time with questions about app use. Requests will typically be answered within 1 working day.

A detailed description of MindDoc with Prescription is provided in Multimedia Appendix 1. Instructions for use can be viewed on the app manufacturer's website [53].

Measures

Screening and Diagnostic Interview

The screening questionnaire is designed to assess the inclusion and exclusion criteria described above and includes the depression module of the Patient Health Questionnaire-9 (PHQ-9) [54,55] to assess depression symptom severity, the Alcohol Use Disorders Identification Test (AUDIT) [56] to assess problematic alcohol use, and the Drug Use Disorders Identification Test (DUDIT) [57] to assess drug use. It also contains questions on current and previous treatments and diagnoses, as well as questions on sociodemographic data.

The diagnostic interview is a shortened version of the short version of the diagnostic interview for mental disorders (Mini-DIPS) [52], a short structured clinical interview for diagnosing mental disorders. The interview assesses current and lifetime diagnoses according to DSM-5 and ICD-10 and is used to confirm that participants fulfill the diagnostic criteria for depression and to assess comorbidity.

Study End Points

Depression Symptom Severity

Depression symptom severity is assessed using the depression module of the PHQ-9 [53,58], a 9-item questionnaire that is part of the Primary Care Evaluation of Mental Disorders (PRIME-MD) diagnostic instrument for common mental disorders [54] and can be self-administered. The questionnaire evaluates each of the 9 DSM-5 diagnostic criteria for depression [59], with scores ranging from 0 (not at all) to 3 (nearly every day). The PHQ-9 is a reliable and valid tool for measuring depression, with a Cronbach α coefficient of .89.

Quality of Life

Quality of life is assessed with the Assessment of Quality of Life-8 Dimensions (AQoL-8D) [60]. The 35-item self-rating scale can be used to evaluate the impact of health care services on an individual's psychosocial quality of life. It measures 6 psychosocial functioning domains and physical autonomy, and has shown high reliability (with a Cronbach α score of .96) and convergent and predictive validity.

Anxiety Symptom Severity

Anxiety symptom severity is assessed with the Generalized Anxiety Disorder-7 (GAD-7) [58,61], which is a 7-item tool for detecting symptoms of generalized anxiety disorder as defined in the DSM-5. Each item is rated on a scale from 0 (not at all) to 3 (nearly every day), making it an effective and reliable way to screen for anxiety disorders and assess their severity in both clinical settings and research.

Patient Empowerment and Self-Management Behaviors

Patient empowerment and self-management behaviors are assessed with a questionnaire we have developed for our previous study [49,50]. It consists of 10 statement items assessing patient empowerment on a 6-point Likert scale (strongly agree, mostly agree, somewhat agree, somewhat disagree, mostly disagree, and strongly disagree) and 18 question items assessing the frequency of self-management behaviors in the past 8 weeks on a 6-point Likert scale (never, once in a while, less than half the time, more than half the time, most of the time, and all the time). The questionnaire has good internal consistency in data from a previously conducted study. The parallel analysis yields 2 components, and an exploratory factor analysis with 2 factors yields medium to high factor loadings of the respective items on their scales as well as low cross-loadings. Reliabilities (McDonalds ω) are in the good to very good range for both subscales as well as the total scale (ω (self-management)=0.87; ω (empowerment)=0.82; ω (total scale)=0.89). Furthermore, the overall scale of the instrument showed convergent validity in the form of significant correlations (P<.01) with further surveyed constructs from health literacy (knowledge of self-help measures: r=0.44, 95% CI 0.39-0.49; "first aid skills": r=0.38, 95% CI 0.33-0.43), with attitudes toward mental illness (positive attitudes toward help-seeking behavior: r=0.46, 95% CI 0.41-0.51; stigma toward mental illness: r=0.30, 95% CI 0.25-0.36), and with the "coping"

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(r=0.40, 95% CI 0.35-0.45) and "relationships" (r=0.37, 95% CI 0.31-0.42) subscales of the AQol-8D.

Other Measures

Depression symptom severity will also be rated by a clinician (clinical psychologist or clinical psychologist in training), using a short version of the Hamilton Rating Scale for Depression (HAM-D) with 6 items. The chosen version best differentiates between groups with and without treatment compared with other versions [62]. HAM-D is the most widely used clinician-administered depression assessment scale. The rating scale was supplemented with the Structured Interview Guide for the HAM-D (SIGH-D) [63,64]).

The therapeutic alliance is measured with a shortened version of the Working Alliance Inventory (WAI-SR) [65] is used, which contains the 8 items of the dimensions (process and goals).

Negative intervention effects were assessed with the Inventory for Balanced Assessment of Negative Effects of Online Interventions (INEP-ON) [66], which captures negative intervention effects from the patient's perspective. The questionnaire also assesses whether patients attribute these effects to the intervention or to other factors.

Confounding Variables

To estimate the influence of potential confounding variables, additional information is collected (see Textbox 1).

Textbox 1. Confounding variables to be investigated in secondary analyses.

Moderators (to be recorded before randomization)

- Duration of illness
- Gender and age
- Psychiatric comorbidity
- Type of depression (first-time, recurrent)
- Severity of depression (Patient Health Questionnaire-9 sum score at randomization)
- Prior treatment (antidepressant medication, outpatient psychotherapy, inpatient treatment or day treatment for a mental disorder, and comparable digital interventions for depression based on cognitive behavioral therapy)
- Personality functioning
- Health literacy

Mediators (to be recorded after 8 weeks and after 6 months, respectively)

- Outpatient visits with psychotherapists or psychiatrists
- Outpatient visits with general practitioners
- Outpatient visits with physicians of other specialties
- Inpatient treatment for mental disorders
- Changes in medication use between baseline and follow-up
- Use of other digital interventions addressing mental health between baseline and follow-up
- Use of alternative treatment methods (eg, acupuncture, osteopathy, homeopathy, and Reiki) between baseline and follow-up
- Use of low-threshold psychosocial services (eg, self-help groups, counseling centers, and social psychiatric service) or preventive services (eg, relaxation training) between baseline and follow-up
- Critical life events between baseline and follow-up

Personality functioning is assessed with the Level of Personality Functioning Scale-Brief Form (LPFS-BF) [67], a brief self-report measure that captures personality functioning in the domains of self and interpersonal pathology and is compatible with the assessment of severity of personality dysfunction according to ICD-11. The German version has high reliability and satisfactory validity. The severity of personality dysfunction was an important predictor of trial discontinuation in a previous study [50].

Health literacy was assessed with the Mental Health Literacy Questionnaire (MHLq) [68], a 29-item scale with 4 dimensions (knowledge about mental health problems, false beliefs or stereotypes, help-seeking and first aid skills, and self-help strategies). Results showed significant differences between individuals with more or less experience with mental health and good internal consistency for the overall outcome.

Safety End Points

To assess the safety of the intervention, the following adverse events were defined and recorded at 8 weeks and at 6 months, respectively: (1) new occurrence or worsening of suicidal ideations during the intervention and follow-up period (recorded via item 9 of the PHQ-9), (2) illnesses and injuries during the intervention and follow-up period (self-report), and (3) inpatient treatment during the intervention and follow-up period (self-report).

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Sample Size

The primary end point is the between-group difference in depressive symptoms (PHQ-9 total score) after 8 weeks. The effect regarding the primary end point will be determined by a 2-tailed *t* test. Based on the results of our previous study, an effect of *d*=0.4 (Cohen *d*) is expected and a dropout rate of up to 60% is assumed. A sample size of 570 participants is required to detect the expected difference at 85% probability and α=5% significance in both intention-to-treat and per-protocol analyses.

Data Management

Study Data

All study data are collected and stored in an electronic data capture system (Climedo) in the form of electronic case report forms and electronic patient reported outcome forms All data collected by means of the EDC provided by Climedo Health GmbH are processed and stored in data centers in Frankfurt am Main, operated by Amazon Web Services EMEA SARL (Luxembourg), which acts as an order processor for Climedo Health GmbH. Amazon Web Services is currently ISO 27001, ISO 27017, and ISO 27018 certified hosting provider. The ISO 27001 certification largely corresponds to the requirements of the German Federal Office for Information Security and is compatible with these (eg, BSI-200). ISO 27017 is an international standard for securing cloud services (Cloud Security), while ISO 27018 primarily relates to the protection of personal data (Cloud Privacy). All personal data are stored on servers in Germany. After completion of the data collection, the pseudonymized data will be exported by MindDoc Health GmbH and stored there in digital form for a period of 10 years in accordance with legal requirements.

All data collected from participants will be assigned an 8-digit code consisting of random numbers and letters. Personal information, including name and contact details, are only collected from those participants who do not meet any exclusion criteria in the screening.

A pseudonymization list of names assigned to codes is stored in a protected area of the electronic data capture system, only accessible to authorized members of the study team. The data are protected from unauthorized access, allowing for secure study procedures. The list will be destroyed after the study completion or after 10 years.

All data collected will be handled in accordance with national law and the GDPR. All personal and health data will be stored and handled in accordance with international and national data protection guidelines. Any publication derived from the personal data will be presented in such a way that it is impossible to identify individuals by referring only to group-level statistics. Participants have the right to request the deletion of their records prior to the destruction of the pseudonymization list without giving any reason.

App Data

To use the digital health app, participants must create a user account with a name and email address of their choice, stored separately by MindDoc Health GmbH. Passwords must meet minimum security standards that are checked in real time by an algorithm. Forgotten passwords cannot be recovered and a new password can be set through a link sent via email.

Using the app generates additional usage data (eg, answers, mood ratings, and course or exercise usage) stored by MindDoc Health GmbH. These data can be merged with study data in pseudonymized form using personalized access codes and a 16-digit user ID.

All data collected as part of the app are processed and stored in a high-security data center in Germany. The data center is operated by T-Systems International GmbH, Hahnstraße 43, 60528 Frankfurt am Main, Germany, which acts as an order data processor for MindDoc Health GmbH. All personal data are stored on servers in Germany. Separate consent is obtained for the processing of health data pursuant to Article 9 (2) lit h DS-GVO within the app, without which the app cannot be used. Irrespective of the right to data deletion pursuant to Art. 17 DS-GVO, the data collected in the app can be deleted from the server directly in the app in the “Settings → Data & Security” area at any time. Prior to this, they can be transferred to the user’s own device using an export function.

All communication between the user and the technical platform is automatically encrypted. The app communicates with the server over encrypted connections using transport layer security or hypertext transfer protocol secure, which prevents third parties from unauthorized reading of the data while it is being sent (ie, “in transit”). Both servers and databases are located behind firewalls to prevent access to data while it is being stored (ie, “at-rest”) or while it is being processed (ie, “in process”). In order to independently check system security, test attacks (penetration tests) are carried out at least once a year by an externally contracted IT security company on the servers provided and attempts are made to gain unauthorized access to them on a test basis.

Statistical Analysis

Data will be described using descriptive statistics (eg, frequencies, mean, median, SD, and IQR) and visualizations (eg, histograms, box plots, and bar charts). Assumptions for statistical tests will be checked (eg, normality by histograms and tests, sphericity by Mauchly test, and equal variance-covariance matrices by Box and Levene tests). App usage will be described according to previously proposed standards for reporting adherence to digital interventions [69], and include days of use and engagement with different features of the app.

Significant baseline group differences will be detected using χ^2 and *t* tests on baseline variables and accounted for in all analyses.

The intervention’s effectiveness will be analyzed using an intention-to-treat approach with multiple imputed data. Missing values from the postsurvey and follow-up survey of nonbinary end points will be imputed using all available information collected at baseline by applying an iterative Markov chain Monte Carlo method based on the initial group assignment. For this purpose, imputations will be calculated for 100, 150, 200, 300, 400, and 500 iterations. Then, the fraction of missing

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information (FMI) index will be determined for all multiply imputed data sets. The FMI ranges from 0 to 1 (where 1 means that 100% of the information required for the planned conclusions is missing) and is a reliable indicator of the validity of conclusions based on imputed data sets [70]. For the following analyses, the number of imputations that do not result in further improvement in FMI compared to previous imputations will be chosen. Statistical characteristics will be aggregated across the multiply imputed data sets using Rubin's rules. The comparison of intervention effects on all outcomes will be done using *t* tests.

In addition to the primary analysis, further sensitivity analyses will be performed. Analyses of intervention effects on all outcomes will be repeated using analysis of covariance, adjusted for baseline scores. In addition, per-protocol analyses excluding participants who violated the protocol will be conducted. The following protocol violations have been prespecified: (1) failure to download the app and complete the onboarding process in the intervention group, (2) reporting of using a similar digital health intervention during the intervention and follow-up period in the control group, (3) reporting of regular psychotherapy during the 8-week intervention period, and (4) noncompletion of postintervention or follow-up assessment. Subgroup analyses will be done to address potential heterogeneity.

To allow for adjustment of the sample size in this study (for lower dropout), an interim analysis can be performed. This can be done once the primary end point of 182 participants is available. With this sample size, the expected effect can be revealed with a probability of 85% at a significance level of α=10%. The interim analysis will be performed blinded, meaning that the variable "group membership" will be replaced by a dummy variable and the blinded data set will be analyzed by a person who is not part of the core study team and is unaware of the group assignment.

Ethical Considerations

This trial is conducted in compliance with the protocol, the Declaration of Helsinki and good clinical practice. The local ethical committee of Ludwigs-Maximilians-Universität München has approved the protocol (project 22-0984). Amendments to the trial protocol will be immediately communicated to the local ethical committee as well as the trial registry by the corresponding author.

No anticipated risks beyond normal daily life are associated with using the app and participating in the study. Temporary mood changes or increased stress may occur during mental health treatment. Based on preliminary studies with the DiGA, a medical benefit, including a reduction of depressive symptoms, can be assumed.

Participants will not receive compensation for participating in the study, but both groups will get free access to the intervention for a year, and those who complete assessments are eligible for a monthly prize draw for a €50 (US $52) voucher. All measures used in the study were selected both based on psychometric properties and the number of items in an effort to minimize participant burden.

The participants' physical, psychological, and social integrity will be protected. The participants have the option to refuse to answer questions, end participation at any time, and request data deletion (before their data have been anonymized) without any consequences.

If suicidal tendencies are suspected or present before randomization, applicants will not be eligible to participate in the study. If suicidal ideations are reported during the web-based screening process, participants will receive written information on available help resources. If suicidal ideations are detected during the diagnostic interview, the interviewer will conduct a crisis intervention and refer the applicant to the local crisis service.

Since suicidal ideations are among the symptoms of depression, they may occur during the intervention or follow-up period even in participants who did not report them at baseline. In this case, precautions will be taken: (1) participants will receive written information about help resources immediately after completing assessments and (2) the study team will be informed and a member will promptly contact participants to further assess the situation. If a crisis cannot be resolved or a participant cannot be reached, support from local emergency services will be sought and the participant's contact information will be shared with these services. Participants agree to this procedure upon enrollment in the study.

Patient and Public Involvement

Patients or the public were not involved in the design, conduct, reporting, or dissemination plans of our research, although user or patient feedback was an important source for the development and improvement of the mental health app investigated in this trial.

Dissemination

This trial aims to support the eligibility of MindDoc with Prescription for registration as a DiGA (Digitale Gesundheitsanwendung) for patients with mild to moderate depression under the Digitales Versorgungsgesetz (Digital Health Care Act). This law regulates the cost reimbursement by German statutory health insurances for digital health applications.

The publication plan includes a report on the effects of MindDoc with Prescription on outcomes, and a second publication on predictors of effectiveness in low-threshold mental health interventions. Results will be presented at conferences and authorship will be based on contributions.

Results

Recruitment for the trial started on February 7, 2023, and the first participant was randomized on February 14, 2023. As of September 5, 2023, a total of 275 participants have been included in the trial and 176 have provided the primary outcome. The rate of missing values in the primary outcome is approximately 20%.

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Discussion

Anticipated Findings

Data from this study will be used to establish whether access to an app-based, self-guided, transdiagnostic intervention addressing common mental disorders is associated with an improvement of depression symptoms in individuals diagnosed with mild or moderate depression and with or without comorbid mental disorders. It will also be used to investigate improvements in quality of life, anxiety symptoms, and patient empowerment and self-management behaviors in relation to access to the intervention.

The results will provide additional insights into the therapeutic alliance in digital interventions and also assess their safety by systematically collecting data on negative intervention effects.

The study will contribute to the evidence base on transdiagnostic digital interventions and at the same time provide information on what role primary care providers can play in facilitating the dissemination of digital mental interventions.

Limitations

A possible limitation of the study could be the composition of the sample. Since participants are recruited over various channels including press releases and social media advertising, it is possible that those with previous (positive) experience with psychotherapy or other psychological interventions are more likely to enroll than those who have not yet sought treatment. In our previous trial, almost 60% of the participants reported previous inpatient or outpatient treatment for a mental disorder. In this trial, we aim to mitigate the risk of an imbalanced sample by cooperating with primary care providers (general practitioners and family doctors) to recruit participants for the trial.

Another possible limitation could be a high dropout rate at postintervention or follow-up, as is common in self-guided interventions. While we determined the sample size accounting for that risk, we also implemented several mitigation measures to reduce dropout, including clinical telephone interviews at baseline and postintervention.

The study is conducted in Germany. Results may not be generalizable to other countries and health care systems, especially free-market health care systems.

Impact and Future Directions

With a focus on both symptom reduction and patient empowerment and self-management behaviors, the study will contribute to expanding the evidence base of transdiagnostic low-threshold digital interventions.

Furthermore, the study aims to provide insights into factors impacting the effectiveness of transdiagnostic digital interventions in mental health care. By examining potential moderators and predictors of outcomes, the study will inform decision-making in stepped care and improve mental health care.

General psychopathology and personality dysfunction have previously been shown to predict treatment response in digital interventions, rendering these factors as potential predictors of outcome in this trial. Further, improvement of mental health–related self-management skills and literacy through app usage may constitute an important mediating factor for change in psychopathology. In addition, the detailed assessment of help-seeking behavior and mental health care use may help to disentangle the direct and indirect effects of transdiagnostic digital interventions on mental health.

Acknowledgments

We would like to thank all users of the MindDoc App who provided us with feedback on their user experience through reviews and usability studies.

Data Availability

The data sets generated and analyzed during this study will be available from the corresponding author on reasonable request after the main results of the trial have been published in a peer-reviewed journal.

Conflicts of Interest

IB is the chief science and clinical officer at MindDoc Health GmbH. CD is a staff researcher at MindDoc Health GmbH.

Multimedia Appendix 1
Description of MindDoc with Prescription.
[PDF File (Adobe PDF File), 3912 KB - resprot_v12i1e46651_app1.pdf]

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Abbreviations

AQoL-8D: Assessment of Quality of Life-8 Dimensions
AUDIT: Alcohol Use Disorders Identification Test
DiGA: Digital Health Application
DSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
DUDIT: Drug Use Disorders Identification Test
EDC: electronic data capture system
FMI: fraction of missing information
GAD-7: Generalized Anxiety Disorder-7
GDPR: General Data Protection Regulation
HAM-D: Hamilton Rating Scale for Depression
ICD-10: International Classification of Diseases, 10th Revision
INEP-ON: Inventory for Balanced Assessment of Negative Effects of Online Interventions
LPFS-BF: Level of Personality Functioning Scale-Brief Form
MHLq: Mental Health Literacy Questionnaire
PHQ-9: Patient Health Questionnaire-9
PRIME-MD: Primary Care Evaluation of Mental Disorders
SIGH-D: Structured Interview Guide for the Hamilton Rating Scale for Depression
WAI-SR: shortened version of the Working Alliance Inventory

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Protocol

Optimization of a Transdiagnostic Mobile Emotion Regulation Intervention for University Students: Protocol for a Microrandomized Trial

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Abstract

Background: Many university students experience mental health problems such as anxiety and depression. To support their mental health, a transdiagnostic mobile app intervention has been developed. The intervention provides short exercises rooted in various approaches (eg, positive psychology, mindfulness, self-compassion, and acceptance and commitment therapy) that aim to facilitate adaptive emotion regulation (ER) to help students cope with the various stressors they encounter during their time at university.

Objective: The goals of this study are to investigate whether the intervention and its components function as intended and how participants engage with them. In addition, this study aims to monitor changes in distress symptoms and ER skills and identify relevant contextual factors that may moderate the intervention's impact.

Methods: A sequential explanatory mixed methods design combining a microrandomized trial and semistructured interviews will be used. During the microrandomized trial, students (N=200) will be prompted via the mobile app twice a day for 3 weeks to evaluate their emotional states and complete a randomly assigned intervention (ie, an exercise supporting ER) or a control intervention (ie, a health information snippet). A subsample of participants (21/200, 10.5%) will participate in interviews exploring their user experience with the app and the completed exercises. The primary outcomes will be changes in emotional states and engagement with the intervention (ie, objective and subjective engagement). Objective engagement will be evaluated through log data (eg, exercise completion time). Subjective engagement will be evaluated through exercise likability and helpfulness ratings as well as user experience interviews. The secondary outcomes will include the distal outcomes of the intervention (ie, ER skills and distress symptoms). Finally, the contextual moderators of intervention effectiveness will be explored (eg, the time of day and momentary emotional states).

Results: The study commenced on February 9, 2023, and the data collection was concluded on June 13, 2023. Of the 172 eligible participants, 161 (93.6%) decided to participate. Of these 161 participants, 137 (85.1%) completed the first phase of the study. A subsample of participants (18/172, 10.5%) participated in the user experience interviews. Currently, the data processing and analyses are being conducted.

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Conclusions: This study will provide insight into the functioning of the intervention and identify areas for improvement. Furthermore, the findings will shed light on potential changes in the distal outcomes of the intervention (ie, ER skills and distress symptoms), which will be considered when designing a follow-up randomized controlled trial evaluating the full-scale effectiveness of this intervention. Finally, the results and data gathered will be used to design and train a recommendation algorithm that will be integrated into the app linking students to relevant content.

Trial Registration: ClinicalTrials.gov NCT05576883; https://www.clinicaltrials.gov/study/NCT05576883

International Registered Report Identifier (IRRID): DERR1-10.2196/46603

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KEYWORDS

transdiagnostic; mobile intervention; microrandomized trial; mental health; emotion regulation; university students; mobile app; mobile phone

Introduction

Background

For young people, the years at university coincide with a transitional period of emerging adulthood [1,2]. This period is not only exciting but also a demanding and uncertain phase in life, and for some, it poses a great risk to their psychological well-being. Globally, it is estimated that between 12% and 50% of all university students are affected by mental health (MH) problems [3-5], the most common ones being anxiety, depression, and substance abuse disorder [3,4,6]. Because of the increased demands for MH support, traditional means of providing it, such as in-person counseling services, are difficult to achieve [7]. Even before the COVID-19 outbreak, which imposed additional challenges to student well-being [8,9], college counseling centers reported that they needed to continually adjust their operations to meet the demands for students' MH needs [10]. In-person MH support also does not fully fit the needs of all students. In fact, students who experience increased MH problems are especially less likely to seek help, and informal and web-based resources are preferred [11]. Moreover, students who experience higher levels of MH-related stigma are less inclined to use face-to-face MH services and are more open to digital tools such as MH mobile apps [12].

To help students navigate this transitional period of their life and equip them with skills relevant for and beyond university life, it is vital to develop preventive and therapeutic interventions that are easily accessible, can counteract MH-related stigma, and are at the same time cost-effective [13]. As part of a student well-being program introduced at Erasmus University Rotterdam (EUR) in 2019, a mobile app consisting of preventive self-guided MH tools is being developed. Its goal is to help students better manage their MH by supporting them in the development of adaptive emotion regulation (ER) strategies.

Digital tools supporting MH have been proven to be good solutions for existing barriers to care, such as long waiting lines and MH-related stigma, owing to their accessibility and ability to maintain students' privacy [14-16]. However, there are often substantial problems with the uptake (ie, use and acceptance) and actual effectiveness of these tools. Specifically, if the tool is not used for a recommended period, it is unlikely that it will have the intended effect [17,18]. Low uptake of interventions is often the result of a mismatch between technology and end users' needs [19]. Technology offers countless possibilities for its use, but if a product is not developed in line with the target user's needs (eg, values, goals, and abilities) or is not engaging and intuitive to use, the likelihood of such a product being integrated, accepted, and adopted by people is low [14,20]. Therefore, it is important to adopt user-centered eHealth design approaches, where the end user is involved across all stages of the design and development of the intervention as informant or co-designer and has a direct influence on both the outcome and the design process [21]. It is also essential to build a deeper understanding of how an intervention and its components function and under what circumstances they can be most beneficial for different users. This understanding can be helpful to tailor digital interventions to different types of users, optimizing their therapeutic benefits.

This paper describes the protocol for the optimization of a mobile app designed to improve students' MH, combining a microrandomized trial (MRT) [22,23] with semistructured interviews. The goals of this study are to examine whether the intervention and its separate categories (ie, groups of exercises rooted in different therapeutic approaches supporting ER) have the intended effects and how students engage with and perceive them. In addition, relevant contextual factors, such as emotional state and the time of day, that may have an influence on intervention effectiveness will be explored. The latter will support the development of the prototype of a recommendation system that will connect students to the relevant content in the app based on their needs and characteristics. Ultimately, the study results will support the optimization and further development of this mobile app, which will later be evaluated for its overall effectiveness in a randomized controlled trial (RCT).

MH Apps for University Students

The current generation of university students, consisting of millennials (those born between 1981 and 1996) and Generation Z (those born between 1997 and 2012), are considered digital natives. Research shows that these generations have developed specific behavioral characteristics owing to the influence of technology on their upbringing; for example, they communicate predominantly through web-based platforms, such as social media networks, because this provides quick and instant delivery of information [24]. This preference is not surprising, given that

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both young millennials and Generation Z highly value efficiency and the ability to perform multiple tasks at the same time [25]. These generations are digitally connected socially as well as informationally. They grew up in a society where information is instant and easily accessible, which in turn makes them prone to using more flexible learning methods and settings [25]. This explains why learning with the help of internet-based digital systems, such as games or mobile apps, attracts them [26]. Considering this generation's needs and behavioral characteristics, interventions delivered through mobile phones are a good fit.

Several systematic reviews and meta-analyses have attested that digital interventions have the potential to improve mental well-being among this population [14,15,27-29]. However, most of the scientifically tested digital interventions for this population focus on web-based technologies and less so on mobile technology [14]. Mobile technology enables observation of the immediate context (eg, emotional state, location, and heart rate) through experience sampling and sensors and offers the possibility to recognize an individual's needs and provide relevant support by using recommendation systems [30]. This permits greater precision in lending support at moments and under circumstances when an intervention is most useful and the person is receptive to it, which can play a crucial role in its uptake [30]. The fit between their needs and the delivered content was indicated to be an especially important feature among university students [18].

Despite the many advantages of digital technology in the field of MH, digital interventions struggle with low uptake and high attrition rates [31]. One of the main challenges is involving and keeping users engaged in the intervention over a longer time span [31,32]; for example, a study examining engagement patterns with trendy MH apps (≥10,000 downloads) found that user retention was only 3.9% two weeks after downloading the app [33]. The low uptake of digital MH interventions is considered one of the most potent barriers to beneficial effects on users' MH because the intervention cannot have the potential impact when users do not engage with it [13]. Among university students, the main barriers to the use of MH apps include privacy concerns and concerns about the credibility of information. They prefer MH apps that are safe and secure, user friendly, credible, informative, and fitted specifically to their needs [13].

The Mobile App for Students' MH

Intervention Development

The development of the mobile app was guided by the Center for eHealth Research (CeHRes) road map, an established framework for the development of eHealth tools [19,34] in which evidence and theoretical insights are intertwined with design methods. This road map emphasizes a human-centered participatory design process and iterative approach to eHealth tool development [19]. Following this approach, the mobile app was designed with university students consistently at the center of the process and involved at all stages, from the analysis of the problem and context (ie, contextual inquiry) to the technical operationalization of the intervention. Students acted as informants and co-designers of the intervention. At the early stages of the intervention development, focus groups were conducted with other relevant stakeholders, that is, university psychologists and study advisors who are in close contact with this population. The development process involved a thorough review of scientific literature and multiple rounds of expert sessions involving MH professionals and behavioral scientists to lay a strong evidence- and theory-based foundation for our intervention. In collaboration with serious game and interaction designers, all intervention concepts and designs were tested with end users using qualitative and quantitative methods and iteratively adjusted in line with the results.

A Transdiagnostic Approach to MH

The intervention incorporates a transdiagnostic approach to MH (ie, Unified Protocol for Transdiagnostic Treatment of Emotional Disorders [35]) and implements techniques from various therapeutic approaches, such as positive psychology [36], mindfulness [37], acceptance and commitment therapy (ACT) [38], self-compassion [39], and cognitive behavioral therapy [40], to accommodate the diverse needs and content preferences of the student population. Using a transdiagnostic approach implies operating outside the traditional psychodiagnostics boundaries (ie, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition categories), focusing on the factors that cause or maintain problems that students present with. Instead of restrictedly following protocols aimed at specific disorders, this app will provide evidence-based interventions in a flexible fashion and in line with the needs and preferences of individual students [41].

Targeted psychological factors include negative self-referential thoughts, rumination, experiences of prolonged negative emotional states, and lack of MH literacy. These factors have been highlighted in the scientific literature [35,42-45] as well as by students, university psychologists, and study advisors interviewed at the start of this project. Targeting these transdiagnostic factors has been shown promising in the reduction of depressive and anxiety symptoms [35], both of which are prevalent among the university student population [3,4].

Intervention Structure

The current version of the mobile app consists of a suite of MH interventions in the form of short exercises. The goal of these exercises is to teach students how to use adaptive ER strategies such as acceptance, self-soothing, and reappraisal instead of maladaptive strategies such as avoidance, suppression, and rumination. In the short term, this will help them manage their emotional responses to internal (eg, unhelpful thoughts) or external (eg, failing a test) events by improving their ability to adjust or change the intensity and duration of emotional states [46]. In addition, students are frequently prompted to evaluate their emotional states through ecological momentary assessments (EMAs), which enable them to practice self-awareness and self-monitoring. In the long run, improving self-awareness and adopting adaptive ER strategies can work preventively by decreasing the likelihood of developing serious MH problems such as anxiety and mood disorders [47].

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Our Vision for the Final Version of the App

For the final version of our MH app, we envision that students will be able to access multiple exercises at the same time and in any order and consume the content that is most relevant to their unique MH needs. Such a strategy has been previously proven successful in decreasing stress in university students in an Australian program for students called "thedesk" [48]. In addition, our app will include a recommendation system that will suggest exercises to students considering their unique characteristics, such as their goals, intervention preferences, MH state, momentary emotional state, the time of day, and individual app use history. The recommendation system introduces a potential solution to the low engagement and impact of the mobile intervention because efficiency, system responsiveness, and content relevance to users' needs are highly valued among this population and have been reported as lacking in available MH apps [18,49].

Intervention Optimization Using an MRT Method

To design an adaptive system of interventions responsive to users' needs, the optimization of their contents and delivery is crucial. This study will combine an MRT with user experience interviews, a novel study design that can provide information on which intervention is effective for whom and in what context [30].

An MRT can evaluate how different intervention components affect an individual in real time (ie, directly after they have used it), and it assesses how this effect varies over time (eg, an intervention may be effective at the beginning, but its effectiveness may decrease with time). In addition, this method can evaluate the moderating role of contextual factors (eg, current mood or the time of day) on the intervention effect, which is especially helpful when optimizing rules for intervention delivery [50,51]. Although it is a young method, an MRT has been successfully applied to evaluate dynamic and user-tailored eHealth interventions focused on weight management [52], smoking cessation [53], and MH [54]. Within the field of MH, NeCamp et al [55] investigated the optimal timing for delivering a mobile MH intervention to medical interns. The authors found that delivering an intervention when individuals experienced lower levels of MH indicated by low mood, poor sleep, and reduced activity was beneficial, whereas intervening when the individuals were doing well had a negative effect [55]. Another MRT study evaluated the impact of an ACT-based mobile intervention on distress symptoms (ie, depressive and stress symptoms) in first-generation university students [56], and the results suggest that interventions prompting mindful awareness and acceptance of internal experience (ie, thoughts, emotions, and physical sensations) were the most impactful for decreasing depressive symptoms. In addition, interventions delivered in the evening were more predictive of decreases in distress symptoms than those delivered in the morning [56]. Both studies signal the importance of considering contextual factors to optimize the impact of digital MH interventions.

Using MRT research design allows for the gathering of more granular and proximal insights about a given intervention, which cannot be captured through traditional RCT designs. In an MRT, unlike in a traditional RCT where individuals are randomized to an intervention or control group at the beginning of the trial, different intervention components (or no intervention) are repeatedly randomized to the participants at prespecified decision points. Thus, in an MRT, the randomization unit is not the participant but the intervention, and participants act as their own controls. Therefore, compared with an RCT, which focuses on between-participant effects, the MRT measures within-participant effects aggregated across participants. The decision point refers to the time of day at which an individual may or may not receive an intervention. Furthermore, the proximal outcome refers to the short-term goals of the intervention (ie, intervention targets) and is seen as the facilitator of the desired distal outcome of the intervention (ie, a mediator of the long-term outcome); for example, if the focus of an intervention is on increasing physical activity, a proximal outcome would be the number of steps taken within 30 minutes after an intervention was delivered, and the distal outcome would be the overall increase in physical activity at the end of the entire intervention period [51].

Finally, owing to repeated randomization, an MRT allows for the evaluation of the moderating role of contextual factors, such as current mood and time, on the proximal effects of the intervention [22].

Study Objectives

This study combines an MRT design with semistructured user experience interviews to achieve the following research goals.

Evaluation of the Proximal Effects of the Intervention

This study will experimentally evaluate whether the intervention as a whole and its separate intervention categories (ie, groups of exercises categorized into 5 therapeutic approaches) have the intended effects on participants' subsequent emotional states, which, in the long term, may have an impact on students' MH (eg, depressive and anxiety symptoms) and acquisition of ER skills [47], and whether these effects deteriorate over time. Increases in positive affect and decreases in negative affect when an intervention is received compared with when a control intervention is received are expected and considered effective. For exercises targeting unhelpful thoughts (ie, cognitive defusion [CD]), changes in thought believability and discomfort with the thought before and after the exercises will be observed, and unhelpful thoughts are expected to subside as a result of exercise completion.

Evaluation of Intervention Feasibility

The feasibility of the system will be examined by evaluating objective (ie, the pattern of interaction with the exercises) and subjective (ie, participant ratings and experience with the exercises) engagement behavioral patterns.

Evaluation of the Distal Outcomes of the Intervention

ER skills and level of distress (ie, stress as well as anxiety and depressive symptoms) will be evaluated before and after the intervention period for the purpose of safety monitoring and to inform the design of a follow-up RCT. In terms of safety, the results will be used to indicate whether negative changes in individuals' MH (ie, distress symptoms) occurred between

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baseline and the end of the intervention period. As there is no comparator group, the results will provide only an indication of a potential link between worsened (or improved) distress symptoms and the intervention, which will be further tested in a traditional RCT. In terms of RCT design, given the innovative nature of this intervention, there is no prior data available to estimate its effect size. Therefore, we will use the pre-post evaluation of distal outcomes in this study as a pilot evaluation of changes in the distal outcomes to estimate the potential effect size of the intervention. This estimate will be used to calculate the sample size for the standard RCT, where between-group changes in distal outcomes (ie, ER skills and distress symptoms) will be evaluated.

Exploratory Goal: The Impact of Contextual Moderators on Proximal Intervention Effects

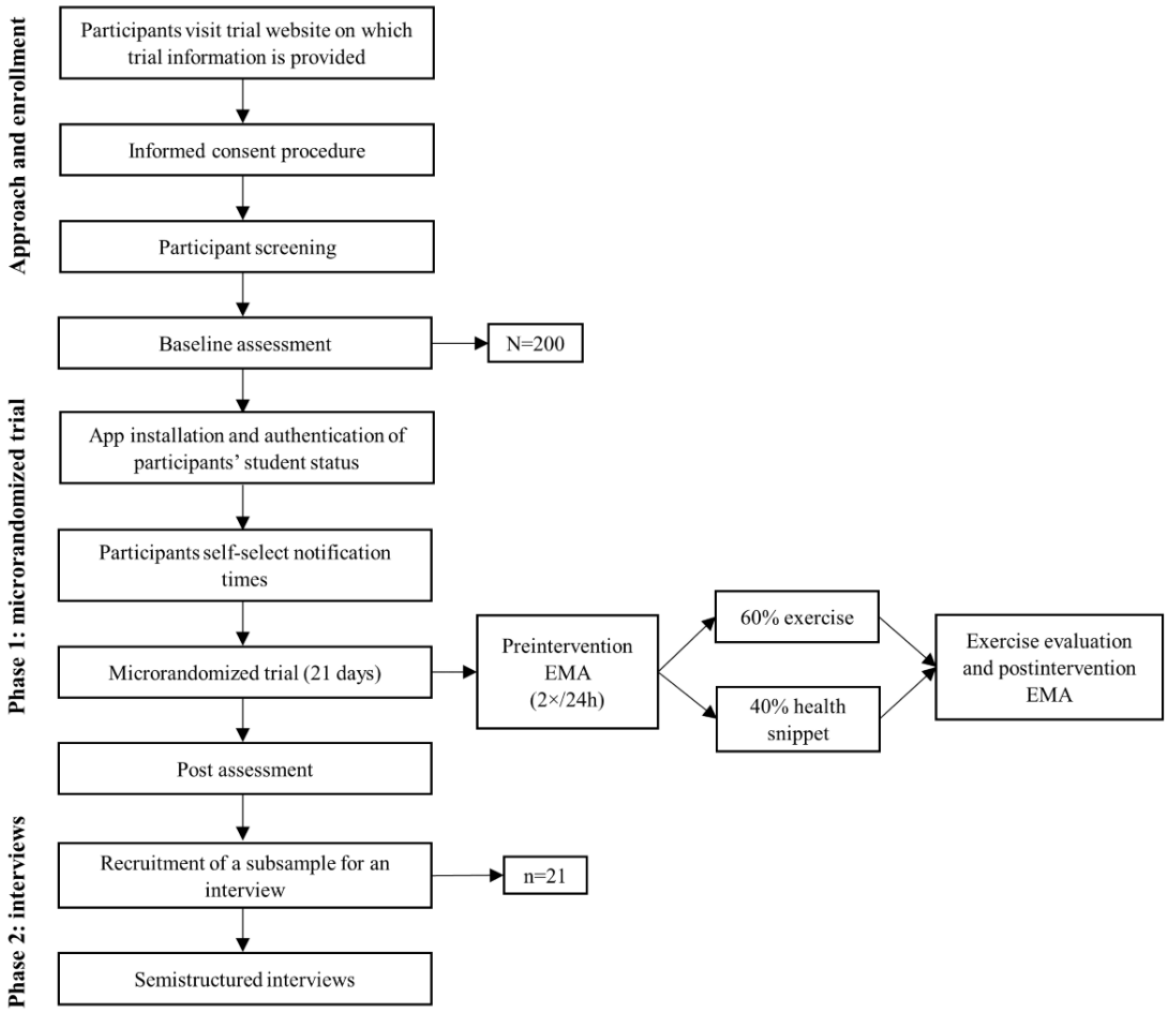
The role of the time of day, momentary emotional state, personality type, preferences, and intervention type as moderators will be explored to determine the context under which the intervention and its categories exercises are the most effective.

Methods

Study Design

This study uses an explanatory sequential mixed methods approach combining an MRT (phase 1) [22] with follow-up semistructured interviews (phase 2; refer to Figure 1 for an overview). During the MRT, the participants (N=200) will be randomized 2 times per day (morning and evening) to the intervention (ie, an exercise supporting ER; 60% probability) or to a control intervention (ie, a health snippet; 40% probability) over a span of 21 days. Data will be collected at baseline and at the end of the 3-week intervention period, as well as daily via the app before and after the completion of each assigned exercise or health snippet. The primary outcomes include changes in emotional states and engagement patterns with the intervention. For the exercises targeting unhelpful thoughts, differences in thought believability and discomfort before and after the CD exercises will be evaluated. The secondary outcomes include changes in the 4 distal outcomes—ER skills, perceived stress level, and levels of anxiety and depressive symptoms—which will be measured at baseline and at the end of the intervention phase (ie, after 21 days; refer to Table 1 for the measurement schedule).

Figure 1. CONSORT (Consolidated Standards of Reporting Trials) flow diagram of participants' progress through the mixed methods study integrating a microrandomized trial with semistructured interviews. EMA: ecological momentary assessment.



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Table 1. Overview of measurements performed during phase 1 (microrandomized trial).

	Day 1	Day 2 to day 22	Day 23
Emotional states		✓	
Thought believability and discomfort[a]		✓	
Demographics	✓		
Experience with MH[b] apps	✓		
Knowledge of approaches	✓		
Use of MH techniques	✓		✓
Ten-Item Personality Inventory	✓		
General Health Questionnaire-12	✓		
Patient Health Questionnaire-9[c]			✓
Generalized Anxiety Disorder-7	✓		✓
Perceived Stress Scale-14	✓		✓
Emotion Regulation Skills Questionnaire	✓		✓

[a]Thought believability and discomfort are measured only before and after the cognitive defusion exercises.

[b]MH: mental health.

[c]The Patient Health Questionnaire-9 is part of the eligibility screening questionnaire; it is not readministered at baseline.

In phase 2, semistructured interviews will be conducted with a subsample of participants (21/200, 10.5%) investigating their user experience. The results of the qualitative phase will be used to interpret the quantitative results, obtaining a well-rounded picture of how the mobile intervention is functioning and its feasibility.

Participants

Phase 1: MRT

Overview

A total of 200 students at EUR will be recruited. A web-based sample size calculator for MRT studies [57,58] was used to calculate the sample size based on the duration of the intervention period (21 days), expected availability intervention randomization probability (60%), and proximal treatment effect. We expect that participants will respond to approximately 70% of the prompts throughout the intervention period (ie, we assume a constant availability of 70%). Furthermore, we assume a linear effect of the intervention on the proximal outcome measures over time with an average size of 0.1 and an initial effect of 0 at the start of the study. In comparison with the large effect size for in-person therapy based on transdiagnostic approaches to emotional disorders [59], we assume a smaller effect size for our study, which is in line with the results of internet interventions for MH in university students [27] and with a similar MRT study protocol examining an ACT intervention [54]. On the basis of these assumptions, 126 participants will generate 80% power to detect the assumed effect with a significance level of .05. We will increase the participant number to 200 to account for a dropout rate of 40%, in line with average attrition rates for MH interventions delivered through smartphones [60].

Eligibility Criteria

Participants are eligible to participate in our study if they are currently enrolled at EUR, are aged between 18 and 27 years, own a smartphone with an active phone number, feel comfortable speaking and writing in English, and score between 5 (mild symptoms) and 19 (moderately severe symptoms) on the Patient Health Questionnaire-9 (PHQ-9) [61]. The last criterion was selected to ensure that participants in the study experience a certain degree of MH problems, thereby making the interventions in the app more relevant to them and allowing for the observation of intervention impact within a population that is likely to derive the greatest benefit from it. Participants who have experienced significant suicidal thoughts over the past month; have a medical diagnosis of psychosis or bipolar disorder, severe clinical depression, or anxiety disorder; or are undergoing psychopharmacological treatment or treatment with experimental drugs are ineligible for this study.

Phase 2: Semistructured Interviews

From the 200 participants included in the MRT study, 21 (10.5%) will be invited to participate in the semistructured interviews that will occur within 2 weeks of the completion of the MRT study. We expect that 21 participants will provide adequate saturation of themes [62,63]. The subsample will consist of participants with different intervention completion rates (low [<30%], medium [30%-70%], and high [>70%]) to gain a better understanding of engagement patterns and user experiences with the intervention. We aim to balance the sample across gender and study level (ie, bachelor's or master's course) using a purposive sampling strategy. Each adherence group would thus consist of 7 participants: 3 (43%) women, 3 (43%) men, and 1 (14%) nonbinary individual. We will attempt to ensure that this subsample comprises roughly equal proportions of bachelor's students and master's students. In case thematic saturation is not reached after interviewing 21 participants, we

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will attempt to recruit additional participants. However, should saturation be achieved before interviewing 21 participants, we may opt to stop recruitment earlier.

Intervention

Overview of the App Content

The intervention under study is delivered through the student well-being app developed by EUR in collaboration with IJsfontein, a media company specializing in serious game design. The version of the app used in this study consists of 3 core features building the intervention flow: (1) EMAs assessing participants' emotional states before and after engaging in the assigned exercise or control intervention, (2) a visualization of participants' emotional states acting as immediate feedback to EMA completion, and (3) a total of 20 exercises targeting different ER skills as well as 20 health facts (control intervention; refer to Multimedia Appendix 1 for example intervention pages).

The exercises are categorized into 5 intervention categories that correspond to the 5 therapeutic approaches integrated in this app: *upregulation of positive affect, mindfulness, CD, relaxation and breathing,* and *self-compassion* (refer to Textbox 1 [36, 37, 39, 64] for a list of the exercises). Each therapeutic approach is explained in an article available to participants when they engage in the corresponding exercise. The exercises are relatively short (each lasts between 3 and 12 min) and actionable in the moment. They were selected owing to their potential to directly regulate students' emotional states and can be completed without extensive exercise background knowledge. Each exercise includes a brief explanation of the rationale behind the exercise as well as debriefing information explaining how the exercise works in general and what the reason might be for experiencing discomfort upon its completion.

Textbox 1. Overview of the exercises classified into 5 intervention categories. The content of the exercises is grounded in the therapeutic principles of positive psychology [36], mindfulness [37], acceptance and commitment therapy [64], yogic breathing, and self-compassion [39].

Upregulation of positive affect

- 3 good things (adapted from Seligman et al [65])
- Savoring the present moment
- Positive self-talk

Mindfulness

- 5 senses exercise
- Tracking your thoughts in time (adapted from Hayes and Smith [66])
- Follow your breath (adapted from Hayes and Smith [66])
- Body scan

Cognitive defusion

- Milk, milk, milk (adapted from Hayes and Smith [66])
- Bad news radio (adapted from Hayes and Smith [66])
- Labeling (adapted from Hayes and Smith [66])
- Leaves on stream (adapted from Hayes and Smith [66])
- Naming and thanking your mind (adapted from Hayes et al [64] and Harris [67])
- Shape your thought (adapted from Hayes and Smith [66])

Relaxation and breathing

- Alternate nostril breathing
- Boxed breathing
- Diaphragmatic breathing
- Progressive muscle relaxation (adapted from Jacobson [68])

Self-compassion

- Self-compassion break (adapted from Germer and Neff [69])
- Talking to a friend (adapted from Germer and Neff [69])
- The compassionate friend (adapted from Germer and Neff [69])

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Intervention Categories

Upregulation of Positive Affect

Positive emotions play an important role in people's well-being. They alleviate the effects of negative emotions that are considered the root of anxiety and depressive disorders and promote resilience and positive MH [70-72]. Several meta-analyses have shown that positive psychology interventions targeting feelings of gratitude, savoring of experiences and sensations, and hope and meaning lead to improved well-being and reduced depressive and anxiety symptoms in both general populations and those considered vulnerable [73-75]. The goal of the exercises in this category is to encourage a focus on positive thoughts and away from negative ones in relation to the current situation or about oneself. These exercises may play an important role in enhancing student well-being because higher levels of positive affect are linked to better psychological and physical health [70,72,76].

Mindfulness

Mindfulness refers to present-moment awareness and the acceptance (ie, nonjudgment) of experience independent of one's emotional state [77,78]. Various studies have shown that being mindful is related to better mental [79,80] and physical [81-83] health in university students. Being in touch with the present moment enables one to react to a stressful situation in an adaptive way by using reappraisal or acceptance [38,77,84] instead of engaging in avoidant and ruminative behaviors. Being mindful helps one to endure a distressing experience by perceiving it as less unpleasant and shifts attention to the here and now rather than to the negative reaction to the current distressing event [85]. Supporting students to practice strategies that will enable them to nonjudgmentally engage with the present moment may help improve their ability to cope and flourish in the academic environment.

CD Technique

CD is defined as a process in which people look upon thoughts in a more objective manner and see them as separate from one's sense of self [86,87]. By contrast, cognitive fusion (the opposite to CD) is a state in which thoughts are perceived as the total truth and thus dominate and regulate one's behaviors and emotions, potentially leading to maladaptive and inflexible behavioral outcomes [88]. Cognitive fusion is especially maladaptive when people experience negative self-referential thoughts. These types of thoughts are related to elevated psychological distress among students [42] and constitute a risk factor for depression, anxiety [89], and eating disorders [90]. Targeting self-critical thoughts within this population is especially important because many students experience maladaptive perfectionistic tendencies characterized by unrealistic expectations of oneself and problematic evaluations of self-worth and performance [89]. Therefore, the intervention includes exercises that teach different CD techniques, such as deliteralization, labeling, and distancing.

Relaxation and Breathing

People can mitigate their emotional states by controlling their breathing [91]. Relaxation and breathing techniques help individuals to decrease their feelings of tension and anxiety, physically and psychologically, and to increase feelings of calmness and evoke relaxation responses that counteract physiological stress responses such as heart palpitations, shortness of breath, and muscle tension. These techniques have a long-standing tradition in psychotherapy and stress management programs [92]. To help students mitigate negative emotional states, such as stress, anger, and tension, the intervention offers breathing and relaxation exercises.

Self-Compassion

Self-compassion is considered an effective mood-stabilizing strategy [93]. It refers to the act of being kind, empathic, supportive, and understanding of oneself in moments of hardship. Those practicing self-compassion are less likely to use maladaptive ER strategies such as rumination and suppression and unhelpful behaviors such as self-criticism [94]. Self-compassion is considered a protective factor against academic stress [39,95], homesickness, depression, and problems in the transition to college [96,97]. Teaching students self-compassion techniques may help them stabilize their mood and make space to adaptively cope with the challenges presented by the academic environment.

Control Intervention

In the control intervention condition, participants receive short snippets of health information about, for example, nutrition, exercise, and sleeping habits. These health-related notions will be phrased in a general, impersonal, and informative fashion. For example, "Did you know that by sneezing the human body is getting rid of infected cells and an average sneeze will spread over 100,000 virus cells up to nine meters? On average, adults catch two to three colds each year. School-age children can have 12 or more colds in a year." Introducing health information as a control intervention condition will act as a placebo intervention with no effect on ER and keep participants engaged in the postintervention EMA evaluation when they are not randomized to an exercise. The health information might influence participants' emotional states but to a minimal extent.

Outcome Measures

Primary Outcomes

Changes in a Momentary Emotional State

Participants will be asked to evaluate 7 emotional states by answering the question "How [*affect*, eg, happy] do you feel at the moment?" on a scale ranging from 1 (not at all) to 5 (very much). The emotional states are combined into 2 categories of affect: negative (stressed, frustrated, sad, and fatigued) and positive (happy, energetic, and relaxed) [98]. The scores of the emotional states will be averaged per category for preintervention and postintervention EMA assessment. The 2 composite outcomes will be calculated by subtracting the results of the preintervention EMA from those of the postintervention EMA for the positive affect and negative affect categories.

Changes in Thought Believability and Discomfort

The CD exercises include a measure of thought believability and discomfort. Participants are asked to assess "How uncomfortable is the thought?" and "How believable (true) is the thought?" on a scale ranging from 1 (not at all uncomfortable

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or believable) to 100 (very uncomfortable or believable) [99] before and after they engage in the CD exercise.

Intervention Engagement

Objective engagement parameters are retrieved from app use analytics (ie, log data) and consist of exercise completion rate, average time spent per exercise, and the times when participants most frequently engaged in an exercise (morning or evening). Subjective engagement parameters of exercise likability ("How much did you like the exercise?") and helpfulness ("How helpful did you find the exercise?") scores measured on a scale ranging from 1 (not at all) to 100 (very much) are assessed at the conclusion of each exercise.

User Experience Evaluated in Semistructured Interviews

Participants' user experience with the intervention will be examined qualitatively in follow-up semistructured interviews with a subset of participants (refer to the *Participants* subsection). Students will first be asked to report on their experience with the whole intervention, followed by a discussion focusing on the separate intervention categories and exercises they engaged in during the trial. They will be asked which aspects of these exercises they liked, disliked, or found difficult to complete. Finally, they will be prompted to share what things they would like to see implemented in the further development of the intervention. Apart from this, the interviewees will be asked about their motivations to participate and general experience related to the study participation. The full interview protocol is available in Multimedia Appendix 2. Additional questions may be derived from the evaluation of engagement metrics. In particular, in the interviews, we might pay extra attention to exercises that were evaluated as unhelpful or unlikable to understand why and to figure out how they could be improved.

Secondary Outcomes

ER will be measured with the Emotion Regulation Skills Questionnaire [100], which evaluates 8 types of ER skills: awareness, sensation, clarity, understanding acceptance, tolerance, compassionate self-support, readiness to confront distressing situations, and modification of negative emotions. Each skill is assessed with 3 items rated on a scale ranging from 0 (not at all) to 4 (almost always). Apart from the scores on separate subscales, the Emotion Regulation Skills Questionnaire consists of a total score computed as the average of all items. Higher scores indicate higher ER skills.

Symptoms of depression and anxiety are measured with the PHQ-9 [61] and the Generalized Anxiety Disorder-7 (GAD-7) [101] questionnaire, respectively. The PHQ-9 consists of 9 items measuring depressive symptoms, and the GAD-7 is composed of 7 items measuring anxiety symptoms. Both questionnaires instruct participants to indicate how often they have been bothered by different symptoms over the last 2 weeks on a scale ranging from 0 (not at all) to 3 (nearly every day). The summed scores for the PHQ-9 range from 0 to 27 and for the GAD-7 from 0 to 21, with higher scores indicating higher levels of depressive and anxiety symptoms. The PHQ-9 is used both to screen for eligibility and to assess the baseline level of depression.

Stress levels will be assessed with the Perceived Stress Scale-14 [102], which consists of 14 items and instructs participants to indicate how often they felt or thought a certain way over the last month on a scale ranging from 0 (never) to 4 (very often). The summed scores range from 0 to 56, with higher scores indicating higher levels of perceived stress symptoms (refer to Table 1 for an overview of the measurement schedule).

Other Measures

Demographics information includes age; gender; university discipline of study (eg, law and medicine); study program (ie, bachelor's or master's); prior experience with MH apps (ie, use); and preknowledge and use of, and experience with, the therapeutic approaches included in this study. For the purposes of the recommendation system development, additional information on students' MH, vulnerability (eg, care duties and functional impairments), and personality traits is collected at the baseline only. These outcomes will be used to explore whether these factors play a role in recommending exercises to students.

Students' MH is screened with the General Health Questionnaire-12 (GHQ-12) [103]. The GHQ-12 consists of 12 items, each assessing the severity of an MH problem over the past few weeks using a 4-point scale (ranging from 0 to 3). The total scores range from 0 to 36, with higher scores indicating lower psychological well-being.

Personality traits are measured with the Ten-Item Personality Inventory [104], which assesses 5 personality dimensions: extraversion, agreeableness, conscientiousness, emotional stability, and openness to experience. Participants are asked to evaluate to what extent they agree with each statement on a scale ranging from 1 (disagree strongly) to 7 (agree strongly). An example statement is "I see myself extraverted; enthusiastic."

Study Procedure

Recruitment and Informed Consent Procedures

To secure a diverse sample in terms of gender and students' university discipline of study, participants will be approached through various pathways. Students who had subscribed to our user research participant pool over the last couple of years will be contacted via email. The study will be advertised on EUR's campus screens and social media platforms (ie, well-being website and Instagram account); in November 2022, it was advertised during a Student Well-being Week event. Promotional material for the study will be sent to students via communication and marketing offices and student associations.

Interested students will subscribe to the study via a QR code or hyperlink. Those subscribing to the study will be emailed a link to a web page with information for participants and will have 2 weeks to review the information and decide on participation. They will be invited to contact the researcher via phone or email for any study-related question. Students who are interested in participating can indicate this preference at the bottom of the web page and will be automatically directed to the digital informed consent form. Once the informed consent form is signed, participants are screened for eligibility.

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Phase 1: MRT

Eligible participants will fill in the baseline questionnaires and be asked to install the app on their mobile phones through which the intervention will be delivered over a period of 3 weeks.

Each student will receive a unique randomly generated user ID to access the app to protect their privacy. Participants' status as EUR students will be verified through the authentication of their student accounts. Once the authentication phase is concluded, participants will be asked to select 1 morning (7 AM to noon) and 1 evening (5 PM to 10 PM) time slot when they believe they are most likely to have time to complete the daily assessments and exercises (Multimedia Appendix 1).

During the intervention phase, participants are asked to complete the intervention flow (ie, preintervention EMA, followed by exercise or health snippet, followed by postintervention EMA) 2 times per day. The prompts (eg, "Good morning! Don't forget to take a moment for yourself." or "Psst, did you check your evening exercise for today?") to complete the flow will be sent to participants at the 2 self-selected time slots. Participants can self-initiate the intervention flow during each time frame by opening the app. If they complete the intervention flow before the self-selected time slot, the reminder for this time slot is skipped. Of note, participants must complete the preintervention EMA to be able to continue and complete the intervention flow. The intervention flow will be available to participants to complete between 7 AM and 2 PM (morning time slot) and between 5 PM and midnight (evening time slot). The completion of tasks in the app is not possible outside of the predetermined time slots. In addition, to ensure that the changes in emotional states are most likely a result of exercise completion rather than other factors, a time limit was set. Participants will have 30 minutes to complete the intervention flow; otherwise, they need to start the intervention flow from the beginning, starting with the preintervention EMA.

Every time participants fill in the preintervention EMA, they have a 60% chance of receiving an exercise and a 40% chance of receiving a health snippet. The 60:40 ratio was chosen to ensure a higher chance of receiving an intervention at every decision point. This strategy has been used in previous MRT studies too [51,52]. For this study, a simple randomization with replacement will be used. The randomization is carried out automatically within the app and is as follows: randomization of exercise (60% chance) or control intervention; if an exercise is chosen, a second randomization to the intervention categories follows (20% chance for each intervention category), followed by the random selection of 1 exercise within the randomized intervention category (equal chance across exercises); if a control intervention is randomized (40% chance), a second randomization takes place in which a health information snippet is selected. Participants will be asked to complete 42 preintervention EMAs and 42 postintervention EMAs in total during the study. They can receive an exercise 0 times, 1 time, or maximally 2 times in a day. On average, they will be prompted to engage in 1.2 exercises per day and 25.2 exercises throughout the study.

Upon the completion of either the exercise or the control intervention, the participants are asked to reassess their emotional state by completing the postintervention EMA. When assigned to an exercise, in addition to the postintervention EMA, participants will be asked to rate the likability and helpfulness of the exercise. When CD exercises are selected, participants will also complete the corresponding measures of thought believability and discomfort before and after the exercise.

Given that the primary objective of this study is to evaluate the functioning of the intervention rather than observe it in a naturalistic setting, we have implemented an adherence protocol to enhance completion rates and ensure high-quality data. To support participants in staying engaged, they will receive emails or telephone calls from researchers, depending on the number of missed sessions. The adherence protocol is presented in Multimedia Appendix 3.

Immediately after the intervention period is concluded, participants will complete the postintervention assessment, including the secondary outcome measures (refer to Table 1 for an overview of the measurements performed during phase 1 of the study).

Phase 2: Semistructured Interviews

In the second phase, semistructured interviews will be conducted with 21 (10.5%) of the 200 study participants. A purposive sampling strategy will be used to balance the sample across gender, study level, and the level of adherence during the MRT. Participants who consented to participate in the user experience interviews will be selected based on the aforementioned characteristics and contacted by the researcher to set up an interview session within 2 weeks of completing the follow-up questionnaire. The interviews will take place on the web or at the EUR behavioral laboratory and will last between 45 and 60 minutes. An overview of the study procedures is presented in Figure 1.

Ethical Considerations

The study has been approved by the EUR institutional review board (ETH2122-0677) and is registered at ClinicalTrials.gov (NCT05576883).

Participant informed consent will be obtained electronically. The participants will be informed about the study-related goals, procedures, potential benefits and risks, and compensation, as well as privacy and confidentiality aspects. Consenting to participate in interviews and allowing data use beyond the study's research goals (eg, educational purposes and further research) will be optional, and opting out will not preclude participation in phase 1 of the study.

To protect participants' privacy and confidentiality, the study procedures as well as research data servers and the app itself comply with the General Data Protection Regulation standards. Research data and personal data will be stored separately. Participants will be assigned unique identifiers, enabling linkage among data collected during the different study phases. Only the primary researchers will have access to the research data and identification key.

Finally, participants in this study will be compensated with digital vouchers for completing the assessments and participating in an interview. To incentivize participants to complete both

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assessments, the voucher for the baseline assessment is worth €5 (US $5.5), and, for the final assessment, it is worth €15 (US $16.2). The subsample of participants taking part in the semistructured interviews will receive a €10 (US $10.8) voucher to compensate them for their time. Those completing ≥80% of the EMAs during the intervention phase of the study will be included in a lottery, and 4 of them will be randomly selected to win a €50 (US $54.7) voucher each.

Data Analysis Plan

Preliminary analyses exploring the data set will be conducted, including descriptive statistics and exploratory graphing for all the variables of interest measured during the study, which will allow for the identification of outliers (eg, measurements or recording errors and logical inconsistencies in data). The key baseline variables (eg, sex) will be considered as plausible covariates in the planned analyses.

Primary Outcome Analysis

Effects of the Intervention on the Proximal Outcomes

The weighted and centered least squares method developed by Boruvka et al [105] to evaluate data from MRT studies will be used to estimate and test the causal excursion effects of the intervention on the proximal outcomes. This method assesses parameters in treatment effect models and allows for the inclusion of covariates that can reduce the variance of the treatment effect estimates. Similar to generalized estimating equations and multilevel models, this method can effectively manage nested data (ie, decision points nested within participants) and within-person dependencies across time in the outcome. A detailed explanation of the analyses is available in Multimedia Appendix 4 [23,51,105,106].

As a primary goal of this study, we will test the overall (average, across all decision points) effect of engaging in any intervention versus engaging in the control intervention on the emotional states measured with the postintervention EMA upon intervention completion. Furthermore, we aim to evaluate whether this effect deteriorates over time by estimating the interaction between the overall intervention effect and the day in the study.

As a subgoal, we will examine differences in the overall effect of engaging in a suggested intervention versus engaging in the control intervention on emotional states for each intervention category separately. We will control for the pretreatment scores of positive and negative affect measured by the preintervention EMA across all models. To account for repeated dependent measures, robust SEs will be calculated using a sandwich estimator, and because we are comparing multiple outcomes, the results will be controlled for multiple testing using Bonferroni correction, that is, we will divide the α value by the number of comparisons being made (ie, 2; hence, we will use α=.025).

Data may be missing if participants do not complete the EMAs before and after an exercise because without the completion of both measurements the observation for the proximal outcome will be missing. If no more than 10% of the data are missing, our primary analysis will be performed as a complete case analysis. If >10% of data are missing, the missing data will be handled by using multiple imputation approaches and outcome models averaged across imputations to adhere to the intention-to-treat principle.

Thought Believability and Discomfort Outcome

A multiple linear regression model will be applied to assess the effects of CD exercises on the level of thought believability and discomfort measured before and after CD exercise completion.

Feasibility Outcomes

Objective Engagement Patterns

Descriptive statistics of engagement metrics (ie, completion rate, average time spent, and the time of day when participants completed the exercises) per exercise and exercise categories will be examined to evaluate exercise performance and inform further design revisions. A linear mixed model will be used to analyze whether there is a relationship between the time of day and exercise completion rates.

Subjective Engagement Patterns

To gain insights into subjective engagement with the exercises, we will combine information on (1) the exercise likability and helpfulness ratings and (2) semistructured interviews with a subset of participants purposefully recruited based on their adherence levels (refer to the *Participants* subsection).

Exercise Likability and Helpfulness

For every exercise, average scores on likability and helpfulness scales are computed across all participants, with higher scores indicating higher levels of likability and helpfulness of the exercise. Exercises will then be ranked from the most liked and helpful to the least, informing on which exercises may be perceived as difficult by participants and pointing to potential design revisions of exercise content or user experience design.

Semistructured Interviews

Information gathered from semistructured interviews with a subsample of study participants will be analyzed using ATLAS.ti software (ATLAS.ti Scientific Software Development GmbH). A multistage standardized thematic analysis will be performed: familiarization with the data, generating preliminary codes, gathering potential themes, reviewing the themes, refining the themes and labeling them, and conducting the write-up of the analysis [107]. Two members of the research team will code the responses for process alignment [108]. In the analysis, we are interested specifically in participants' experiences with the different types of exercises, in what way these were helpful (or not), and whether participants were able to understand the different approaches and exercises embedded in the intervention (eg, ACT, CD, and self-compassion).

Secondary Outcome Analysis

Analysis of Distal Outcomes: ER Skills and Distress Symptoms

For estimating the effect of the intervention on participants' ER skills and levels of distress, we will apply a multiple linear regression model with the following covariates: gender, age,

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study year, preknowledge of therapeutic approaches, and intervention adherence (ie, number of completed exercises).

Analysis of Exploratory Outcome Analysis: Contextual Moderators

For the purposes of optimization of the mobile intervention app, exploratory analyses will be carried out to explore contextual factors, that is, the time of intervention delivery (morning vs evening), momentary emotional state, and vulnerability to MH problems indicated by higher scores on the GHQ-12, as potential moderators of perceived helpfulness and of the proximal effects on changes in emotional states among the intervention and intervention categories. Additional exploratory variables of interest include personality traits and gender. This information will help us form initial decision rules for the algorithm that is being designed for this intervention.

Results

The study commenced on February 9, 2023, and the data collection was concluded on June 13, 2023. Of the 172 eligible participants, 161 (93.6%) decided to participate. Of these 161 participants, 137 (85.1%) completed the first phase of the study. In the qualitative phase, interviews were conducted with 18 participants: 7 (39%) from the high-adherence group, 7 (39%) from the medium-adherence group, and 4 (22%) from the low-adherence group. Currently, the data processing and analyses are being conducted.

Discussion

Overview

This study will investigate the effectiveness and feasibility of digitally delivered therapeutic exercises designed to facilitate adaptive ER among university students. A secondary goal of this study focuses on the evaluation of distal outcomes, that is, changes in ER skills and distress symptoms as a result of the intervention, which will serve as a safety indicator and inform the sample size estimation of the RCT to follow. In addition, contextual moderators that could be relevant for the recommendation system that will link students to exercises relevant to their needs and preferences will be explored.

Compared with other methodologies used for intervention evaluation such as an RCT, the MRT design makes it possible to observe proximal changes in participants' emotional states directly after they complete an exercise, in addition to requiring fewer participants to achieve sufficient power to detect the proximal main effect of an intervention component [52]. This enables insight into the mechanisms of change (ie, changes in emotional states), elucidating on how the intervention and its components stimulate the desired benefits (ie, increase in ER skills and decrease in depressive and anxiety symptoms). Combining results from the MRT with information on user engagement patterns (ie, log data analytics) and user experience (ie, exercise ratings and user experience interviews) will help unpack the black box typical of studies of digital MH interventions, where often little is known about the mechanisms by which the interventions exert their benefit [109]. The combined results will also indicate intervention components that might need improvements or should be discarded when they play no significant, or possibly impeding, role in facilitating the desired change. This means that if an intervention category is perceived as unhelpful, unlikable, or unclear or was hardly used by participants, and when it was used, it showed a negative or no effect on proximal outcomes, the intervention category (or specific exercises) could be removed from the intervention library or redesigned. Furthermore, the use of a mixed methods approach not only offers the opportunity to gather valuable insight into how the current generation of students perceive and engage with digital MH interventions but also sheds light on how they receive the MRT as a method of evaluation. This information can help optimize future endeavors in the development and evaluation of tools for digital MH interventions. Finally, the results of exploratory analyses and the data set obtained in this study will be used to develop and train the recommendation algorithm, maximizing the likability and usefulness of exercises for users based on individual (ie, personality and MH status) and contextual (eg, the time of day and momentary emotional states) characteristics. Creating a system that can suggest content relevant to its users has been indicated as a top priority for university students to engage and remain engaged in an MH app [18]. Therefore, designing and implementing a recommendation system in the app may be crucial in improving its uptake and effectiveness.

All in all, this study will contribute to the optimization of the intervention content and the system functionalities (ie, recommendation system). An optimized version of the app will be evaluated in an RCT where the full-scale effectiveness on clinical outcomes (eg, ER skills as well as depressive and anxiety symptoms) will be examined.

Limitations

The results of this study will need to be considered in light of some limitations. First, this study relies heavily on students' self-reports of emotional states through EMA before and after completing an exercise. Therefore, the participant burden is considered relatively high. However, this was chosen because user research indicated that students do not like to be monitored and consider passive sensing tracking (eg, collection of location and acceleration data) as too invasive. This is in line with studies examining the acceptability of sensing technology among university students [110,111].

Second, in this study, participants are compensated for completing the baseline and follow-up assessments and for participating in the interview (when applicable). In addition, they are incentivized to complete the daily assessment by the prospect of inclusion in a lottery for a €50 (US $54.7) voucher when they achieve a completion rate of ≥80%. Therefore, this design only allows the evaluation of certain aspects of engagement, such as how participants interacted with the exercises and the average likability and helpfulness ratings. We cannot draw any firm conclusions about the actual engagement level with the intervention when used freely in a naturalistic setting.

Third, our mobile app combines various types of exercises based on different therapeutic approaches ranging from self-compassion to positive psychology. The exercises were

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designed in such a way that they can be completed in the moment, without users' preknowledge of the approach. In this study, we offer them materials educating them about the underlying exercise approach, but this is kept optional. There is a possibility that some exercises might be more effective when presented in combination with psychoeducational material. In addition, given the randomized nature of the exercises, participants might find some suggestions less appropriate when reporting certain states (eg, recommending an exercise belonging to the upregulation of positive affect category when participants report a high-stress state). However, the experimental goal of the study is to empirically examine how the exercises affect participants' emotional states and participants' reactions to the exercises (whether they like them or find them helpful) instead of drawing conclusions based on current psychological theories and our hunches. Current psychological theories seem to be insufficient to inform the development of mobile interventions that include high levels of interactivity and flexibility. This is because prevailing behavior change theories are still based on data providing information on static snapshots of behavior (ie, the predictions of behavior are based on pre-post evaluations) rather than accounting for contextualized and transitory changes in mood states and behavior at the granular level [112-114]. However, an MRT can address the limitations of traditional research methods, such as RCTs, which have shaped current behavior change theories. Specifically, an MRT offers a deeper understanding of the dynamics involved in health behaviors and behavior change, which are influenced by a myriad of contextual factors, including emotional states, physical context, social norms, and expectations [115]. These factors seem to play a role in intervention functioning [51,55,56]. Therefore, with this study, we hope to gather insights and draw experimentally informed conclusions regarding which intervention option is appropriate for whom and in what context.

Conclusions

In sum, the results of this study will inform further development of the content and system of the digital MH tool that is being developed for university students. The optimization method will help us optimize our mobile app and shed light on how different therapeutic approaches work and why. Such information will hopefully be valuable to the development of modern theories of behavior change because this design can provide information on how different therapeutic exercises influence ER in near time.

Acknowledgments

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Data Availability

The data collected in phase 1 of the study will be available in the Open Science Framework (OSF) data repository [116].

Authors' Contributions

TL, DR, RCMEE, MB, and DSM designed the study. TL, MB, and SK designed the approach to statistical analysis. TL prepared the study material, designed the intervention material, and collected the data. TL drafted the first version of the manuscript; all authors provided feedback and edited the manuscript. All authors reviewed and approved the final version of the manuscript before submission.

Conflicts of Interest

TL, RCMEE, DR, and MB are employed by Erasmus University Rotterdam and are directly or indirectly involved in the development of the intervention. All other authors declare no other conflicts of interest.

Multimedia Appendix 1
Examples of intervention pages of the app (called "Room").
[DOCX File , 3385 KB - resprot_v12i1e46603_app1.docx]

Multimedia Appendix 2
Protocol for the semistructured interview.
[DOCX File , 17 KB - resprot_v12i1e46603_app2.docx]

Multimedia Appendix 3
Adherence protocol.
[DOCX File , 20 KB - resprot_v12i1e46603_app3.docx]

Multimedia Appendix 4
The analytic method used for microrandomized trial data analysis.

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[DOCX File , 28 KB - resprot_v12i1e46603_app4.docx]

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Abbreviations

ACT: acceptance and commitment therapy
CD: cognitive defusion
CeHRes: Center for eHealth Research
EMA: ecological momentary assessment
ER: emotion regulation
EUR: Erasmus University Rotterdam
GAD-7: Generalized Anxiety Disorder-7

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GHQ-12: General Health Questionnaire-12
MH: mental health
MRT: microrandomized trial
PHQ-9: Patient Health Questionnaire-9
RCT: randomized controlled trial

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Protocol

A Multisite Electronic Health Record Integrated Remote Monitoring Intervention for Hypertension Improvement: Protocol for a Randomized Pragmatic Comparative Effectiveness Trial

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Abstract

Background: Hypertension is a major contributor to various adverse health outcomes. Although previous studies have shown the benefits of home blood pressure (BP) monitoring over office-based measurements, there is limited evidence comparing the effectiveness of whether a BP monitor integrated into the electronic health record is superior to a nonintegrated BP monitor.

Objective: In this paper, we describe the protocol for a pragmatic multisite implementation of a quality improvement initiative directly comparing integrated to nonintegrated BP monitors for hypertension improvement.

Methods: We will conduct a randomized, comparative effectiveness trial at 3 large academic health centers across California. The 3 sites will enroll a total of 660 participants (approximately n=220 per site), with 330 in the integrated BP monitor arm and 330 in the nonintegrated BP control arm. The primary outcome of this study will be the absolute difference in systolic BP in mm Hg from enrollment to 6 months. Secondary outcome measures include binary measures of hypertension (controlled vs uncontrolled), hypertension-related health complications, hospitalizations, and death. The list of possible participants will be generated from a central data warehouse. Randomization will occur after enrollment in the study. Participants will use their assigned BP monitor

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and join site-specific hypertension interventions. Cross-site learning will occur at regular all-site meetings facilitated by the University of California, Los Angeles Value-Based Care Research Consortium. A pre- and poststudy questionnaire will be conducted to further evaluate participants' perspectives regarding their BP monitor. Linear mixed effects models will be used to compare the primary outcome measure between study arms. Mixed effects logistic regression models will be used to compare secondary outcome measures between study arms.

Results: The study will start enrolling participants in the second quarter of 2023 and will be completed by the first half of 2024. Results will be published by the end of 2024.

Conclusions: This pragmatic trial will contribute to the growing field of chronic care management using remote monitoring by answering whether a hypertension intervention coupled with an electronic health record integrated home BP monitor improves patients' hypertension better than a hypertension intervention with a nonintegrated BP monitor. The outcomes of this study may help health system decision makers determine whether to invest in integrated BP monitors for vulnerable patient populations.

Trial Registration: ClinicalTrials.gov NCT05390502; clinicaltrials.gov/study/NCT05390502

International Registered Report Identifier (IRRID): PRR1-10.2196/45915

(JMIR Res Protoc 2023;12:e45915) doi:10.2196/45915

KEYWORDS

blood pressure; EHR; electronic health record; hypertension; hypertensive; improvement science; monitor; monitoring; randomized controlled trial; RCT; remote blood pressure monitoring

Introduction

Hypertension is a marked modifiable risk factor for many adverse health outcomes, with the highest attributable risk for cardiovascular disease and death [1]. About half of the US adult population has hypertension, with the majority having uncontrolled hypertension [2]. The inadequate treatment of hypertension for certain groups is a large source of health disparities [3]. Clinically, the diagnosis of hypertension is made using office-based blood pressure (BP) measurements at several week intervals [4] and confirmed with an out-of-office reading or using ambulatory BP monitoring [5,6], as there is growing evidence showing differences in BP measurements in the office compared to the home setting [7,8]. Variations in adherence to clinical guidelines on how to properly perform BP readings, patient anxiety, environmental factors, and "white-coat hypertension" all contribute to these differences [6,9]. Additionally, many studies have shown the superiority of home BP monitoring compared to office BP monitoring in terms of cardiovascular and renal outcomes, all-cause mortality [1,8,10,11], and patient empowerment and adherence to medical therapies for hypertension [12].

Although the benefits of home BP monitoring compared to office-based monitoring are well studied, optimal methods for obtaining home BP readings are less clear. A previous study showed improvements to systolic BP at 1 year after a self-monitoring and digital intervention involving a health care provider-managed lifestyle modification and medication titration approach compared to usual care [7]. Whereas a single-center study found no difference in BP change using an electronic health record (EHR)–connected smartphone device to record BP using a standard self-monitoring strategy [13]. This randomized, comparative effectiveness trial adds to the existing literature by including multiple sites and comparing an EHR-integrated monitor with automated BP data uploads to a standard self-monitoring approach.

In developing the protocol for this study, we used the eHealth Enhanced Chronic Care Model (eCCM) [14] to shape our theoretical understanding that remote BP monitoring can improve patients' and health care providers' "wisdom" [15,16] to provide interventions capable of improving hypertension control. This project aligns with a joint scientific advisory on hypertension control from the American Heart Association, the American College of Cardiology, and the Centers for Disease Control and Prevention, which argued for systems-level, population-health-level initiatives to control hypertension, involving the community around a patient, leveraging data from EHRs, and patient-provider engagement [17].

This manuscript was developed to describe the protocol for this pragmatic multisite study that evaluates whether an integrated BP monitor performs better at controlling hypertension than a self-reporting strategy. We define the roles and responsibilities of key partners, study design, key outcomes, and statistical analyses.

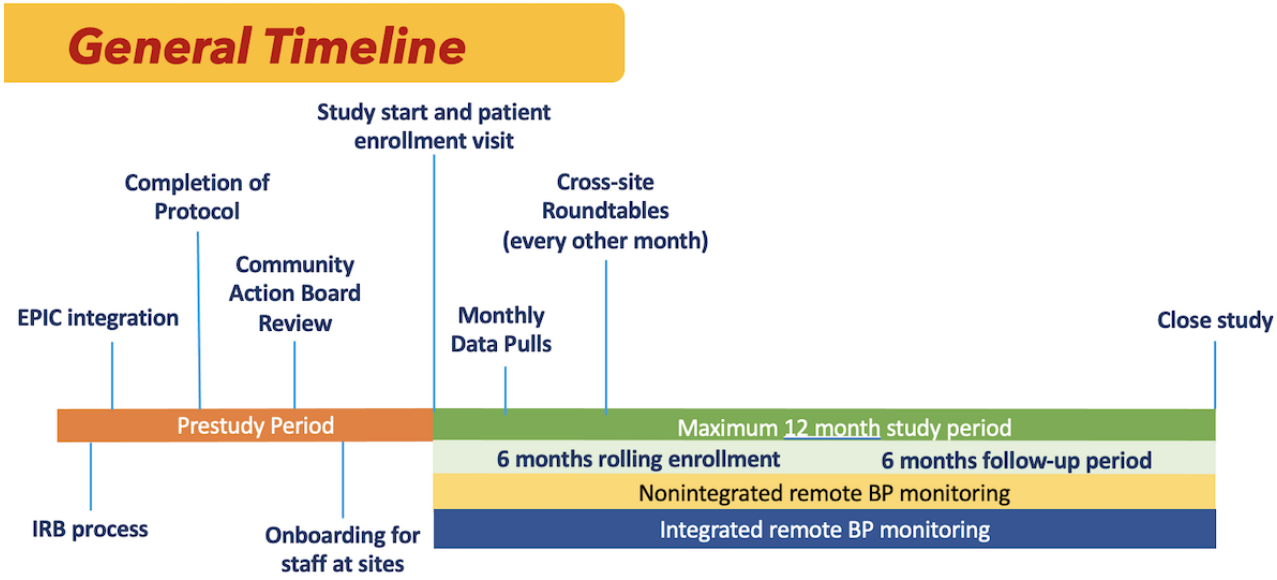
Methods

Setting and Study Design

The University of California (UC) Health System is a large academic health system serving a diverse patient population throughout California, the United States, and internationally. It includes teaching hospitals, affiliations with community health clinics, health professional schools, research centers, and other health care entities. This study protocol describes a randomized, comparative effectiveness trial that will be conducted at 3 of the UC Health System sites (UC Davis [UCD], UC Los Angeles [UCLA], and UC San Francisco [UCSF]). Figure 1 describes the general timeline. Enrollment will occur over 6 months after study initiation, and each participant will be followed for 6 months after enrollment.

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Figure 1. Timeline for the study. Participants will be followed for 6 months after enrollment date. BP: blood pressure; IRB: institutional review board.



Defining Key Partners and Study Preparation

The UCLA Value-Based Care Research Consortium (VBCRC) will lead the planning, implementation, and evaluation of this study in collaboration with the UCLA Department of Medicine Statistics Core, the UC Office of the President (UCOP), and each UC site. The UCLA VBCRC is a team that aims to improve value in health care through partnerships with health systems and researchers. The UCOP team will provide input into study design and feasibility, as well as funding for the study, including the BP monitors. Each UC site will have a designated site champion, program manager, and IT lead (Multimedia Appendix 1 details the responsibilities of these roles). The UCLA VBCRC team will facilitate regular meetings with representatives from each team, focusing on cross-site learning, troubleshooting implementation issues, and providing updates on progress. Further evaluation of cross-site variations, barriers to implementation, and understanding of patient experiences will be obtained from qualitatively coding and analyzing these regularly scheduled meetings with the sites.

In preparation for the study, the UCLA VBCRC met with a community action board consisting of representatives from community organizations serving large numbers of diverse members with hypertension to understand patient concerns and perspectives regarding this study. Overall, the community action board supported the need for this project but raised concerns regarding proper training for using the BP monitors for participants in the study. They also reiterated the importance of providing instructional materials at various education and literacy levels, as well as individualized support for participants when needed. This feedback was provided to the sites and the BP monitor company.

Site-Specific Hypertension Interventions

In addition to following core protocol instructions, each site will design and implement a hypertension intervention for both arms of the study. The study sites are given the autonomy to create their own site-specific hypertension intervention to fit their patient population needs and available resources. Table 1 compares interventions across each UC site, including whether the intervention is web-based only or hybrid (component of in-person and web-based), the main health care providers involved in the intervention, specific details about the intervention, discharge criteria from the program, and site-specific inclusions and exclusions.

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Table 1. Comparison of site interventions.

	University of California, Davis	University of California, Los Angeles	University of California, San Francisco
Web-based only, hybrid (in-person and web-based)	• Hybrid	• Web-based only	• Hybrid
BP[a] monitor distribution plan (eg, mail, in person, etc)	• Mailed directly to the patient	• Mailed directly to the patient	• Mailed directly to the patient
Main providers involved in the intervention	• Pharmacist	• Pharmacist • Patient service representative • Primary care provider • Program supervising physician	• Pharmacist • Primary care provider • Health care navigator
General structure of study arms	• Intervention: EHR[b] integrated remote BP monitor with pharmacist follow up • Control: nonintegrated BP monitor with pharmacist follow up	• Intervention: EHR integrated remote BP monitor + web-based patient portal • Control: nonintegrated BP monitor + web-based patient portal	• Intervention: EHR integrated remote BP monitor + usual care and follow-up • Control: nonintegrated BP monitor + usual care and follow-up
Frequency of BP checks	• There is no minimum per month. • Ideally, at least 16 per month.	• There is no minimum per month. • Ideally, at least 16 per month.	• There is no minimum per month; however, patients will receive daily reminders. • Ideally, at least 16 per month.
Site-specific intervention	• Initial visit (60 minutes): (1) The pharmacist will provide disease management (ie, monitor BP readings and help titrate medications accordingly). (2) Notify the PCP[c] of patient participation or access to monitor. • Clinic visits (1 minimum): (1) Before the pharmacist's intervention. (2) As needed to facilitate care plans and achieve BP goals	• Initial visit (40 minutes): (1) Review: PMH[d] relevant to treatment, calculate 10-year ASCVD[e] risk, labs, current BP management, diet and exercise, medication adherence, access to a home BP monitor, and BP measurement techniques. (2) Treatment: develop an individualized treatment plan, including starting antihypertensive medications, hypertension education, lifestyle management, and reviewing BP measurement techniques. (3) Communication: send a visit summary to PCP. (4) Visits performed by pharmacists or supervising program physicians. (5) Schedule: next visit in 2-4 weeks (monthly follow-up). • Follow-up visit (20 minutes): review the individualized treatment plan, home BP measurements, and access to medications (if any).	• Initial visit (40 minutes): (1) Review: PMH relevant to treatment, current blood pressure management, diet and exercise, labs, medication adherence, access to a home BP monitor, and BP measurement techniques. (2) Treatment: create an individualized plan that may include starting a new antihypertensive, dose adjustment, or tapering medications contributing to high BP, and set or reinforce target BP goals. (3) Schedule: next visit in 4 weeks. (4) Visits performed by a pharmacist, primary care doctor, nurse practitioner, or registered nurse. • Follow up: every 1-2 months.
Control group	• Self-report BP. Intervention is the same as above.	• Self-report BP. Intervention is the same as above.	• Self-report BP. Intervention is the same as above.
Discharge from the program	• BP at goal for 2 consecutive visits • Resistant hypertension criteria • Clinical concerns develop, for example, recurrent orthostatic symptoms with systolic BP <100 mm Hg, persistent changes in labs (electrolytes and GFR[f]), significant excursions in BP after confirming measurement technique, and unstable symptoms • BP is above goal after 6 months • The patient requests discharge	• BP at goal for 2 consecutive visits • Resistant hypertension criteria • Clinical concerns develop, for example, recurrent orthostatic symptoms with systolic BP <100 mm Hg, persistent changes in labs (electrolytes and GFR), significant excursions in BP after confirming measurement technique, unstable symptoms • BP is above goal after 6 months • The patient requests discharge	• BP is well controlled. • Patient request or lost to follow-up. • Complicating comorbid conditions develop

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	University of California, Davis	University of California, Los Angeles	University of California, San Francisco
Site-specific inclusion criteria	• None	• The participant must be active on the web-based patient portal.	• The participant must be active on the web-based patient portal.
Site-specific exclusion criteria (if any)	• None	• None	• None

[a]BP: blood pressure.

[b]EHR: electronic health records.

[c]PCP: primary care physician.

[d]PMH: patient medical history.

[e]ASCVD: atherosclerotic cardiovascular disease.

[f]GFR: glomerular filtration rate.

Eligibility, Inclusion, and Exclusion Criteria

A complete list of eligibility, inclusion, and exclusion criteria is listed in Textbox 1. Eligible participants must be 18 years of age or older, willing and functionally able to use the BP monitor, and have access to the web-based health care patient portal (with help from another person if needed). Participants will be included if they have had an outpatient visit within the last year and 2 readings of systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg within 6 months of each other, have a primary care physician within the health care system, and are taking three or fewer antihypertensive medications. There is no language preference or maximum age cutoff for this study.

Participants will be excluded if they had a recent BP measurement greater than or equal to 180/110 mm Hg (office BP) or greater than or equal to 175/105 mm Hg (self-monitored BP), have a history of conditions that could lead to refractory hypertension (Textbox 1), are currently incarcerated, are enrolled in home health, hospice, or a hypertension management program, have cognitive impairment that prevents them from participating in intervention activities, or have a white coat hypertension diagnosis. Individuals with BP measurements greater than or equal to 180/110 mm Hg (office BP) or greater than or equal to 175/105 mm Hg (self-monitored BP) will be excluded because they may have treatment-resistant hypertension or may need more intensive intervention than is being provided with this program.

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Textbox 1. Complete list of eligibility, inclusion, and exclusion criteria.

Eligibility criteria

- Aged 18 years and older.
- Must be willing and functionally able (with help from another person if needed) to perform remote blood pressure (BP) monitoring.
- Have access to the web-based health care portal (with help from another person if needed).

Inclusion criteria

- Have outpatient visit within the last 12 months, and have a previous visit within 6 months of inclusion outpatient visit with diagnosis of hypertension, defined as having 2 readings of systolic BP >140 mm Hg or diastolic BP >90 mm Hg
- Has at least one visit with primary care physician in prior year.
- Takes 0 or 3 antihypertensive prescriptions (can include pills with 2 different drugs so could be on 2 medications).

Exclusion criteria

- BP > 180/110 mm Hg (office) or > 175/105 mm Hg (self-monitored BP measurements)
- Pheochromocytoma
- Uncontrolled hypothyroidism or hyperthyroidism
- Renal artery stenosis
- Conn's syndrome
- End Stage Renal Disease (ESRD)
- Chronic Kidney Disease (CKD) Stage 3b (CrCL <45) and worse
- Transplant patients—used the code that if they ever had a transplant
- Pregnancy
- Severe aortic stenosis
- Hospice or end-of-life or palliative Care
- Left Ventricular Ejection Fraction (LVEF) <30%
- Acute cardiac event in the last 3 months (eg, myocardial infarction)
- Heart block and arrhythmias
- Recurrent or symptomatic hypotension (systolic BP <100 mm Hg or diastolic BP <60 mm Hg)
- Drug and alcohol abuse
- Orthostatic hypotension (drop in systolic BP >20 mm Hg)
- Other secondary causes of hypertension
- Receiving hypertension management from other services (home health, hospice, already enrolled in hypertension management program)
- White coat hypertension

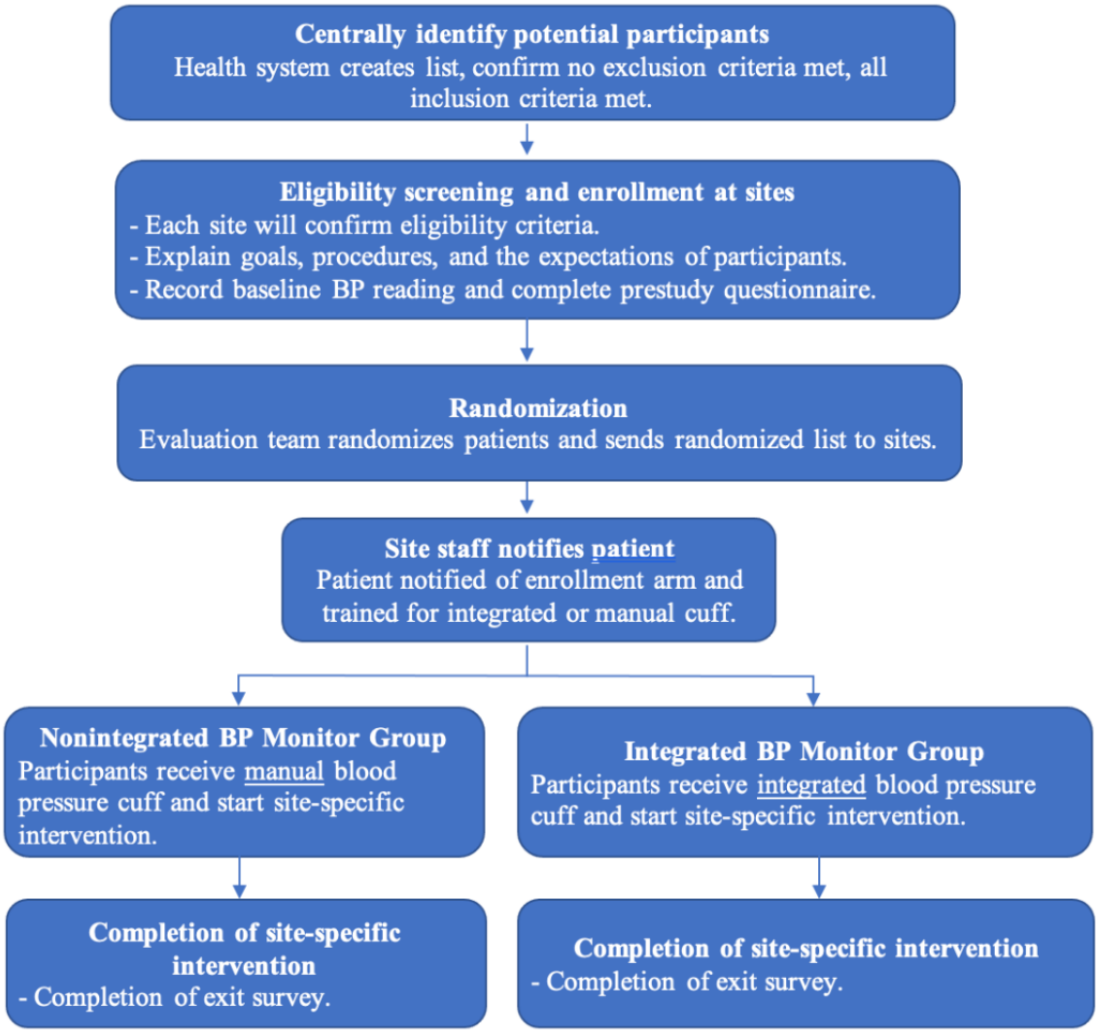
Enrollment, Randomization, and Study Initiation

Figure 2 describes the study phases, starting with the creation of the potential participant list obtained from the Center for Data-Driven Insights and Innovation (CDi2) and the UC Health Data Warehouse (UCHDW), verification of eligibility criteria, and study enrollment, which we aim to start in the second quarter of 2023. This study plans to enroll 660 participants (about 220 per site and 330 participants in each arm of the study). These power calculation estimates are based on previous literature reviews [18,19] to achieve an 80% power to detect a difference of 0.23 SDs and an anticipated 10% attrition rate. An enrollment script will be provided to each site (Multimedia Appendix 2). Randomization will occur after enrollment using a randomization allocation template within REDCap (Research Electronic Data Capture), a secure web-based platform designed to help capture data and operationalize research studies [20,21].

After enrollment and randomization, participants will receive their BP monitor (integrated or nonintegrated) and complete a prestudy questionnaire (Multimedia Appendix 3). Each UC site will then administer their site-specific hypertension intervention, which will be administered to both arms of the study. At the end of the 6-month follow-up period, a similar poststudy questionnaire evaluating participant experiences will be completed (Multimedia Appendix 4). Given the nature of the different BP management interventions, site representatives and participants will not be blinded to study arm assignments; however, the UCLA VBCRC evaluation team will be blinded.

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Figure 2. Study phases. BP: blood pressure.



Blood Pressure Monitors, Electronic Health Record Integration, and Operations

Both integrated and nonintegrated BP monitors Omron 5 Series Model, BP7250 (Omron Healthcare Inc) will be directly mailed to participants' homes, and participants will be asked to follow standard instructions for measuring BP.

EHR integration refers to the secure transfer of data from the remote BP monitor to the health system's electronic medical record through DataHub (Omron). The process of integration will occur in collaboration with site IT leads, Omron representatives, and the Redox (Redox Inc) team. Redox is a backend integration platform that provides a standardized method for receiving and sending data between health care EHR systems and technology vendors such as Omron Healthcare Inc. Though more time- and labor-intensive to implement, the Redox platform allows for the immediate upload of data into the EHR without the use of a mobile app. For all participants with the integrated BP monitor, BP measurements will be immediately available in the EHR for intervention.

In terms of operations, the integrated BP monitors will store measurements in the provided DataHub, which will then automatically transmit BP measurements to Redox. At the backend, these BP measurements in Redox will then be transmitted to the patients' medical records and stored as a flowsheet item in the EHR that can be acted upon by local site-specific interventions. In contrast, the nonintegrated BP monitor will require participants to self-report BP measurements to their health care provider through the site-specific web-based patient portal. Participant and staff training on how to use the integrated BP monitor, techniques for taking BP, and further technical support in multiple languages will be conducted by Omron representatives. Omron representatives will call the participant after the monitor has been delivered and follow a standardized script that includes asking the participant to take multiple BP measurements and ensuring BP readings are properly captured in the database.

Primary and Secondary Outcomes

The primary outcome is the difference in BP from baseline compared to 6 months between study groups (integrated vs nonintegrated BP monitor), defined as a continuous measure of BP in mm Hg. Secondary outcomes include a binary measure of controlled versus uncontrolled hypertension (where uncontrolled is defined as systolic BP >130 mm Hg or diastolic BP >80 mm Hg based on American College of Cardiology and American Heart Association Practice Guidelines [22]), hypertension-related health complications by the end of the study, including acute coronary syndrome (myocardial

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infarction), stroke (ischemic and hemorrhagic), decompensated heart failure, syncope, electrolyte abnormalities (hyponatremia, hypokalemia, and hyperkalemia), hospitalization, and mortality (all-cause). Hypertension-related health complications will be captured using International Classification of Diseases Ninth or Tenth Revision codes after the participants have started the study.

Statistical Analysis

For the primary outcome, linear mixed effects models will be used to compare changes from baseline home BP to 6 months from enrollment between the integrated and nonintegrated remote monitoring arms of the study. Models will include random site effects to account for the clustering of patients within sites. Models will adjust for demographic and clinical characteristics including age, sex, race, and ethnicity, as well as social vulnerability (the census tract Social Vulnerability Index). The evaluation of each arm will be based on a Wald test of the primary model term, and estimated differential changes will be reported along with a 95% CI. For the dichotomous secondary outcomes, we will use mixed effects logistic regression models with similar specifications and report differences in terms of odds ratios. A significance level of .05 will be used, and all analyses will follow the intention-to-treat principle. For patients who do not have a BP reading at 6 months, we will use the reading closest to 6 months, with a minimum 2-month period between the baseline and final reading [23,24]. Missing data will be handled through multiple imputations using pattern-mixture models. For the exploratory pre-post analysis, we will use linear mixed effects models to evaluate changes in BP. The analysis will be performed using SAS (version 9.4; SAS Institute Inc).

Ethical Considerations

The UCLA institutional review board (IRB) approved the study (IRB #22-000036) before study initiation on May 27, 2022, and agreed to serve as the IRB of record for UC Davis and UC San Francisco. All amendments to the protocol will be submitted for approval by the IRB. Results will be presented at clinical conferences and in the scientific literature. Based on findings from this study, similar remote BP monitoring programs may be disseminated to other UC sites not included in this study.

The UCLA VBCRC team will use Observational Medical Outcomes Partnership (OMOP) Common Data Models (CDM) in collaboration with CDi2 and the UCHDW to access BP data and secondary outcome measures from the EHR during the study period. The VBCRC team will monitor data quality at monthly intervals.

Results

All 3 clinical sites will begin enrolling participants during the second quarter of 2023. We anticipate the study to conclude in the first half of 2024 for all 3 sites. The results of this study will be available in 2024, and we aim to publish them by the end of 2024.

Discussion

Improving hypertension outcomes depends on timely and accurate BP measurements. This study is a pragmatic trial that focuses on clinical effectiveness, testing whether an integrated BP monitor is more effective than a nonintegrated BP monitor at BP improvement while documenting cross-site variation, barriers to implementation, and patient experiences.

One limitation to this study design is the risk of contamination across study arms; it is possible that providers taking care of patients in the integrated BP monitoring arm might escalate the level of care they provide to their patients in the nonintegrated arm, biasing the study to the null. Because the major difference between the study arms is the integration itself, we do not anticipate this to be a major limitation. Another limitation is the possibility of poor fidelity to the intervention; participants in both arms may choose to not actually take their BP, limiting the impact of the interventions. As a pragmatic trial of a quality improvement intervention, there are also limits to the types of data that can be collected; for example, we will not be collecting insurance type, primary language spoken, or telehealth use, all of which would be interesting to know whether these had a moderating effect on the intervention.

Overall, the findings from this study will inform health system decision makers in determining whether to invest resources in integrated BP monitoring for their patient populations. Additionally, it could support the development of programs to evaluate whether remote patient monitoring is a viable option, particularly for geographically dispersed populations.

Acknowledgments

The authors would like to recognize the University of California Office of the President for providing guidance and funding for this project, including the purchase of blood pressure equipment by Omron Healthcare Inc. We would also like to thank the participants for joining this study. CS was supported by a National Institute on Aging award (1K24AG047899-01) and the University of California, Los Angeles (UCLA) Clinical and Translational Science Institute National Institutes of Health (NIH)/National Center for Advanced Translational Science Grant (UL1TR001881). LHC received funding as a Clinical Translation Science Institute TL1 Fellow, Agency for Health Care Research and Quality Los Angeles Area Health Services Research Training Program Trainee, Gates Millennium Scholar (Bill and Melinda Gates Foundation), Cota Robles Fellow (UCLA Graduate Division), Progressive Vietnamese American Organization, board member, and policy co-chair. TCT reports a relationship with UCSF Partners in Care (Ron Rankin Grant) that includes funding grants related to telehealth; Mount Zion Health Fund Inc and Community Tech Network that include funding grants related to telehealth; and Epic Systems Corporation, which includes nonfinancial

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support and a position on the Epic System's Telehealth Advisory Council. DRL was supported by an NIH T32 research training grant.

Data Availability

The data sets generated during or analyzed during this study are available from the corresponding author on request.

Authors' Contributions

All authors contributed to the study conceptualization and development of study methods. SV provided biostatistical support. RP contributed to the data abstraction. DRL, MC, LHC, CWV, and CS drafted the manuscript, and all authors provided input and edits. JB, HW, CCM, MH, SAS, MMM, AD, KNP, MA, and PFB contributed to the development and implementation of the University of California, Los Angeles (UCLA) site intervention. TCT and LB contributed to the development and implementation of the UC San Francisco site intervention. HM, RG, and LP contributed to the development and implementation of the UC Davis site intervention. All authors approved the final draft and contents of this protocol manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Roles and Responsibilities.
[PNG File , 155 KB - resprot_v12i1e45915_app1.png]

Multimedia Appendix 2
Enrollment Invitation Script.
[PDF File (Adobe PDF File), 40 KB - resprot_v12i1e45915_app2.pdf]

Multimedia Appendix 3
Pre-Survey Questions.
[PDF File (Adobe PDF File), 47 KB - resprot_v12i1e45915_app3.pdf]

Multimedia Appendix 4
Post-Survey Questions.
[PDF File (Adobe PDF File), 46 KB - resprot_v12i1e45915_app4.pdf]

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Abbreviations

BP: blood pressure
CDi2: Center for Data-Driven Insights and Innovation
CDM: Common Data Models

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eCCM: eHealth Enhanced Chronic Care Model
EHR: electronic health record
IRB: institutional review board
OMOP: Observational Medical Outcomes Partnership
REDCap: Research Electronic Data Capture
UC: University of California
UCD: UC Davis
UCHDW: UC Health Data Warehouse
UCLA: UC Los Angeles
UCOP: UC Office of the President
UCSF: UC San Francisco
VBCRC: Value-Based Care Research Consortium

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Protocol

Online-Mediated HIV Pre-exposure Prophylaxis Care and Reduced Monitoring Frequency for Men Who Have Sex With Men: Protocol for a Randomized Controlled Noninferiority Trial (EZI-PrEP Study)

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Abstract

Background: Daily and event-driven HIV pre-exposure prophylaxis (PrEP) with oral tenofovir-emtricitabine is highly effective to prevent HIV in men who have sex with men (MSM). PrEP care generally consists of in-clinic monitoring every 3 months that includes PrEP dispensing, counseling, and screening for HIV and sexually transmitted infections (STIs). However, the optimal frequency for monitoring remains undetermined. Attending a clinic every 3 months for monitoring may be a barrier for PrEP. Online-mediated PrEP care and reduced frequency of monitoring may lower this barrier.

Objective: The primary objective of this study is to establish the noninferiority of online PrEP care (vs in-clinic care) and monitoring every 6 months (vs every 3 months). The secondary objectives are to (1) examine differences between PrEP care modalities regarding incidences of STIs, HIV infection, and hepatitis C virus infection; retention in PrEP care; intracellular tenofovir-diphosphate concentration; and satisfaction, usability, and acceptability of PrEP care modalities; and (2) evaluate associations of these study outcomes with sociodemographic, behavioral, and psychological characteristics.

Methods: This study is a 2×2 factorial, 4-arm, open-label, multi-center, randomized, controlled, noninferiority trial. The 4 arms are (1) in-clinic monitoring every 3 months, (2) in-clinic monitoring every 6 months, (3) online monitoring every 3 months, and (4) online monitoring every 6 months. The primary outcome is a condomless anal sex act with a casual partner not covered or insufficiently covered by PrEP (ie, “unprotected act”) as a proxy for HIV infection risk. Eligible individuals are MSM, and transgender and gender diverse people aged ≥18 years who are eligible for PrEP care at 1 of 4 participating sexual health centers in the Netherlands. The required sample size is 442 participants, and the planned observation time is 24 months. All study

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participants will receive access to a smartphone app, which contains a diary. Participants are requested to complete the diary on a daily basis during the first 18 months of participation. Participants will complete questionnaires at baseline and 6, 12, 18, and 24 months. Dried blood spots will be collected at 6 and 12 months for assessment of intracellular tenofovir-diphosphate concentration. Incidence rates of unprotected acts will be compared between the online and in-clinic arms, and between the 6-month and 3-month arms. Noninferiority will be concluded if the upper limit of the 2-sided 97.5% CI of the incidence rate ratio is <1.8.

Results: The results of the main analysis are expected in 2024.

Conclusions: This trial will demonstrate whether online PrEP care and monitoring every 6 months is noninferior to standard PrEP care in terms of PrEP adherence. If noninferiority is established, these modalities may lower barriers for initiating and continuing PrEP use and potentially reduce the systemic burden for PrEP providers.

Trial Registration: ClinicalTrials.gov NCT05093036; https://tinyurl.com/28b8ndvj

International Registered Report Identifier (IRRID): DERR1-10.2196/51023

(JMIR Res Protoc 2023;12:e51023) doi:10.2196/51023

KEYWORDS

pre-exposure prophylaxis; randomized controlled trial; telemedicine; HIV prevention; MSM; men who have sex with men; Netherlands; adherence; acceptability; usability

Introduction

Oral tenofovir (TFV) disoproxil combined with emtricitabine (FTC) is highly efficacious as pre-exposure prophylaxis (PrEP) for the prevention of HIV infection [1,2]. PrEP can be taken daily [3-5] or in an event-driven schedule by cisgender men or transgender and gender diverse people (TGDP) assigned male at birth, who are not taking exogenous estradiol-based hormones [6-8]. Globally, the standard of care generally entails in-clinic PrEP initiation and in-clinic monitoring visits every 3 months, including PrEP prescription and dispensing, counseling on PrEP adherence and other HIV prevention strategies, and HIV testing, and may include kidney function testing [8,9]. PrEP programs are recommended to integrate PrEP monitoring visits with testing for bacterial sexually transmitted infections (STIs) and for hepatitis B virus and hepatitis C virus (HCV) infections [8-12]. If combined with the recommended HIV testing frequency, such testing is commonly performed every 3 months, although in practice, the frequency of testing could depend on sexual behavior [8-12].

In-clinic PrEP care faces several challenges that stem from the recommended frequency of monitoring visits (every 3 months). Clients might have to take time off from work, school, or family obligations, and may incur travel costs for attending in-clinic visits [13-17]. Persons interested in PrEP may also feel burdened with perceived stigma [18,19], cultural or social insensitivity [16,20,21], and lack of privacy [14,15] at the clinic. Providers might have capacity problems at facilities owing to shortages of health care staff or budget constraints, and might be forced to limit the number of clients or prioritize certain clients [22-24]. These client and provider barriers may contribute to individuals not initiating PrEP or discontinuing PrEP, which in turn increases the risk of avoidable HIV infections [23,25].

Limiting the number of in-clinic visits by offering online-mediated PrEP care may address some of these barriers [8,26,27]. Different models of digital PrEP services had been implemented across income settings prior to the COVID-19 pandemic, and implementation accelerated since the start of the pandemic [8,26-29]. Online PrEP care generally includes a combination of the following components: telephone or video consultation to collect data regarding medical history, sexual behavior, and PrEP intake, which are needed for PrEP prescription and counseling [8,26-29]; specimen collection for HIV and STI testing at a local laboratory [30], at home using a self-sampling kit [31,32], or a combination of both [30,33]; and delivery of PrEP tablets at locations preferred by users (eg, at home, other addresses, or health facilities) [30,33]. Since online PrEP care involves less intensive contact between PrEP users and health care providers and thus less guidance on PrEP use, it could theoretically have an adverse effect on PrEP adherence. Studies so far have shown high acceptability of online PrEP services among PrEP users. However, these studies were small in scale and were predominantly descriptive in nature and thus did not provide rigorous evidence on PrEP adherence in comparison to the standard of care [29,34], with the exception of an ongoing randomized controlled trial in the United States [31]. In their study, the authors aimed to compare online PrEP care with the standard of care with respect to protective levels of tenofovir diphosphate (TFV-DP) in dried blood spots (DBSs), and the results of this study are still pending [31]. Other trials related to online PrEP care in the European context do not yet exist.

Limiting the number of in-clinic visits through a reduction in the frequency of PrEP monitoring may pose challenges for the timely screening of HIV and other STIs. Regular HIV testing during PrEP use is essential to identify breakthrough HIV infections in suboptimally adherent PrEP users and, rarely, in highly adherent PrEP users [35,36]. It allows for commencing HIV treatment as soon as possible and avoiding onward transmission and the development or transmission of drug-resistant strains. While the current guidelines recommend HIV testing every 3 to 6 months [8-12], few studies have formally investigated the impact of HIV screening frequency on PrEP adherence [8]. A lower frequency of contact moments and HIV testing may negatively affect PrEP intake. One randomized noninferiority trial in Kenya found similar PrEP adherence in adults with dispensing of PrEP every 6 months at

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the clinic combined with home-sampled HIV testing at 3 months after dispensing and in adults with dispensing of PrEP and HIV testing every 3 months at the clinic as the standard of care [37]. More evidence from other regions and from different groups of PrEP users is needed to further evaluate the implications of reduced frequency of monitoring. Particularly in high income settings with low HIV prevalence and high community-level PrEP uptake and PrEP adherence, HIV testing every 6 months might be sufficient. PrEP monitoring visits for men who have sex with men (MSM) in these settings are commonly combined with STI testing, but the optimal frequency of STI screening among MSM who use PrEP is unknown [2,22,38]. On the one hand, reducing the frequency of PrEP monitoring might lead to delayed diagnosis and treatment of asymptomatic STIs and onward transmission. On the other hand, it might avoid antibiotic use related to asymptomatic chlamydia and gonorrhea [39-41], and a lower STI screening frequency might be sufficient for MSM with lower levels of sexual activity.

The *E-Health for Zero Infections - facilitating access to and use of Pre-Exposure Prophylaxis in the Netherlands* (EZI-PrEP) study has been designed to assess whether online-mediated PrEP care and a reduced frequency of monitoring are noninferior compared to standard practice. The secondary research aims include assessing the effect of reduced monitoring frequency on HIV and STI testing behaviors and assessing whether the frequency of testing matches the level of behaviors associated with acquiring these infections. In the EZI-PrEP study, we will develop, implement, and evaluate an online-mediated PrEP care service and a less frequent monitoring schedule (every 6 months) among MSM and TGDP in 4 regions in the Netherlands. This paper describes the design and methods of the EZI-PrEP study.

Methods

Study Objectives

The primary objective of the EZI-PrEP study is to assess whether online-mediated PrEP care is noninferior to standard in-clinic care and whether monitoring every 6 months is noninferior to standard monitoring every 3 months. We defined the primary outcome measure as a condomless anal sex act with a casual partner during which PrEP was not used or insufficiently used (herein referred to as an “unprotected act”). Ideally, incident HIV infection would be the primary outcome, but this outcome is expected to be exceedingly rare for use in a clinical trial [42]. The outcome “unprotected act” can be regarded as a behavior that carries the most risk for HIV acquisition and is expected to occur frequently enough to serve as the primary outcome.

The secondary objective is to compare differences between PrEP care modalities in the incidences of bacterial STIs (ie, chlamydia, gonorrhea, and syphilis), HIV infection, and HCV infection; intracellular concentrations of TFV-DP; retention in PrEP care; total number of STI consultations (in addition to PrEP monitoring visits); and satisfaction, usability, perceived quality, acceptability, and time and cost investments of PrEP care.

Furthermore, to investigate how suitable the offered PrEP care modalities are for participants, we will study the associations of the sociodemographic, behavioral, and psychosocial predictors of PrEP adherence with all outcomes mentioned above, and assess whether these associations vary between study arms. More specifically, we will study the associations of unprotected acts with problematic alcohol and drug use, risk perception of acquiring STIs and HIV infection, and sexual compulsivity. Adequate PrEP adherence is key to its effectiveness in preventing HIV, and regular PrEP adherence counseling is therefore recommended. While ample evidence exists on the facilitators and barriers of medication adherence across different populations and settings [43] (eg, medication for the prevention and treatment of cardiovascular diseases [44], chronic disease management [45], and HIV treatment [46]), this remains an understudied topic for MSM who use PrEP. We are interested in how PrEP intake is integrated in daily life, what circumstances may lead to inadequate PrEP adherence, and whether these factors are associated with fewer contact moments between health care providers and PrEP users. We will therefore study the relationship between habit formation and PrEP intake. We will also analyze mental well-being (eg, positive and negative emotions, depression, stress, and anxiety) in relation to adherence and unprotected acts, and explore the mediating effects of personality-related variables (eg, emotion regulation, coping skills, conscientiousness, and resilience). Finally, we will investigate to what extent having a social environment, which is measured by social norms, loneliness, and support systems, is related to PrEP adherence and retention in PrEP care.

Study Setting

The EZI-PrEP study will be embedded in the government-funded National PrEP Pilot Program (NPP) that plans to run from August 2019 until July 2024 [47]. This program provides PrEP care to persons at high risk for HIV infection, notably MSM and TGDP, and is implemented by the sexual health centers (SHCs) of the public health service (PHS) regions throughout the Netherlands. The PrEP care offered consists of in-clinic monitoring visits every 3 months that are free of charge. PrEP tablets are provided at a reduced price of €7.50 (US $7.88) per 30 tablets (paid out-of-pocket by the PrEP user) and are provided only to those completing a monitoring visit. Following the Dutch PrEP guidelines applicable at the time when the study started (ie, April 15, 2019 [10]), each PrEP monitoring visit includes screening for HIV infection, bacterial STIs, and HCV infection, and, every 6 months, screening for kidney function (Table 1). It also includes counseling based on motivational interviewing techniques to stimulate informed and conscious decision-making by PrEP users in relation to their own sexual health, PrEP intake, and usage of other HIV-prevention strategies. PrEP naïve people are allowed to commence PrEP immediately after screening and counseling, and have to return to the SHC after the first month of PrEP use for repeat HIV testing. Three months after commencing PrEP, routine PrEP care begins with the first in-clinic monitoring visit (performed every 3 months). Individuals are allowed to test for HIV, STIs, and HCV free of charge in between regular PrEP monitoring visits at their own initiative. Individuals can freely

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choose and switch between daily or event-driven PrEP regimens. These guidelines have since been updated in 2022, with the most relevant modification being that the monitoring frequency may be adapted under certain individual cases [11].

Table 1. Overview of testing for HIV infection, sexually transmitted infections, hepatitis C virus infection, and kidney function as part of routine pre-exposure prophylaxis care for each EZI-PrEP study visit at sexual health centers in the Netherlands (based on Dutch national pre-exposure prophylaxis guidelines; April 19, 2019).

Laboratory measurement	Inclusion	Months								
		1	3	6	9	12	15	18	21	24
HIV	✓	✓[a]	✓	✓	✓	✓	✓	✓	✓	✓
Syphilis	✓		✓	✓	✓	✓	✓	✓	✓	✓
Chlamydia trachomatis	✓		✓	✓	✓	✓	✓	✓	✓	✓
Neisseria gonorrhoeae	✓		✓	✓	✓	✓	✓	✓	✓	✓
HCV[b]	✓		✓	✓	✓	✓	✓	✓	✓	✓
Creatinine	✓			✓		✓		✓		✓
Proteinuria	✓			✓		✓		✓		✓

[a]Only pre-exposure prophylaxis starters and restarters have a pre-exposure prophylaxis monitoring visit at month 1.

[b]HCV: hepatitis C virus.

In the Netherlands, PrEP can also be obtained through a general practitioner, although, in this instance, neither PrEP tablets nor laboratory testing are fully reimbursed by the Dutch health insurance. The Dutch insurance system has an obligatory deductible excess, meaning that the first €385 (US $404) of health care costs, including laboratory testing ordered by primary care providers, are paid for out-of-pocket. Moreover, knowledge and willingness to prescribe PrEP varies across general practitioners. Most people who are using or want to use PrEP in the Netherlands therefore procure PrEP through the NPP. This program has been capped at 8500 PrEP users, which has resulted in individuals being placed on waiting lists to obtain PrEP from the NPP [24].

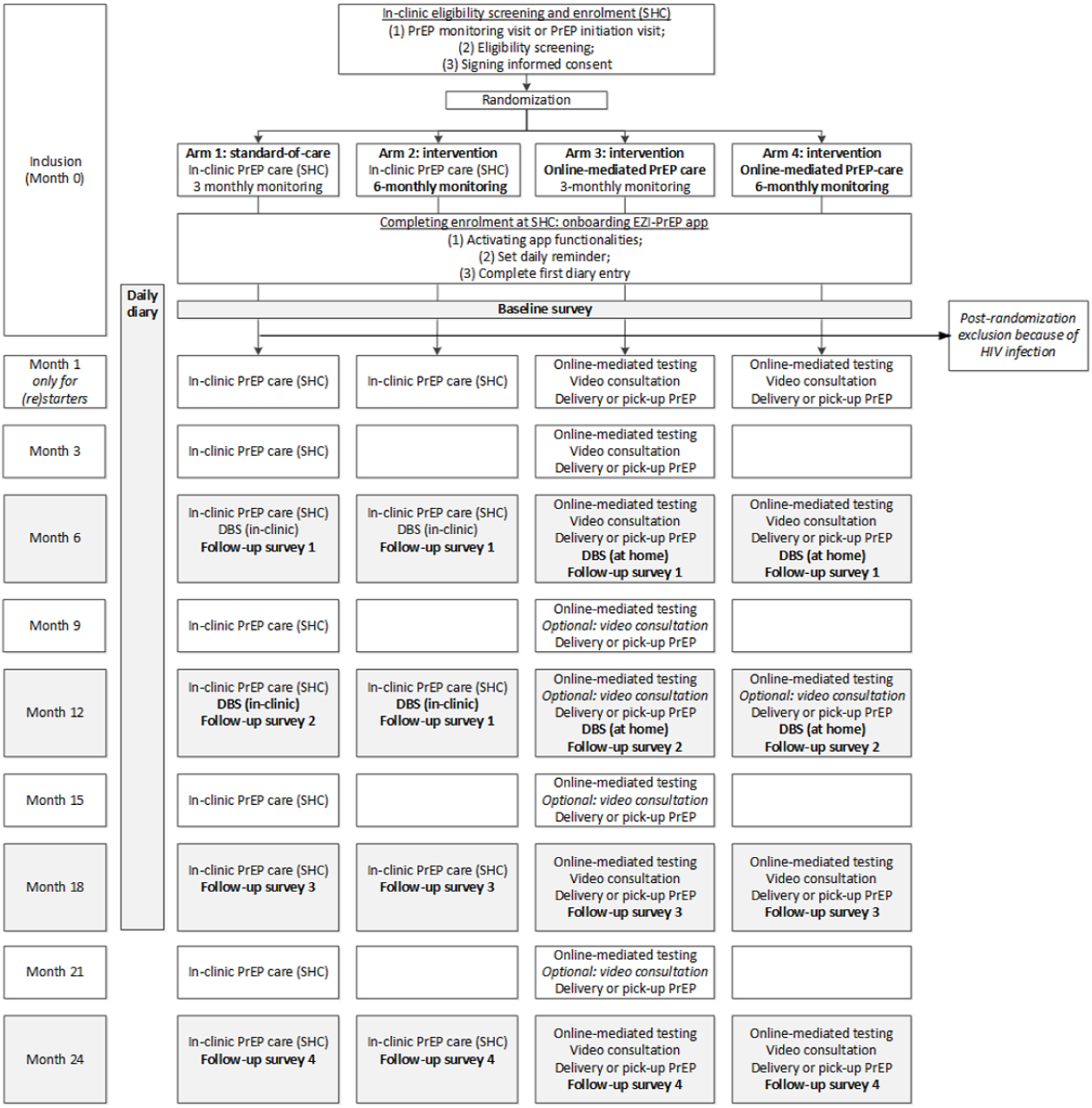
Study Design

The EZI-PrEP study will be a 2×2 factorial, 4-arm, open-label, multi-center, randomized, controlled, noninferiority trial. Study participants will be randomized to 1 of 4 arms: (1) in-clinic monitoring every 3 months (standard of care), (2) in-clinic monitoring every 6 months, (3) online monitoring every 3 months, or (4) online monitoring every 6 months (Figure 1). The study will be implemented at SHCs in Amsterdam, Rotterdam-Rijnmond, Haaglanden, and Gelderland-Zuid (Figure 2). For each individual participant, the planned observation time is 24 months, starting after eligibility screening and enrollment.

All study participants will receive access to a smartphone app (the “EZI-PrEP app”), which contains a diary. Participants will be required to complete this diary daily during the first 18 months of the study period. This information will be used to measure the primary outcome (ie, unprotected acts). DBSs will be collected at months 6 and 12. Routine clinical data registered during PrEP monitoring visits and any additional STI testing or treatment visits from inclusion until the final monitoring visit at month 24 will be retrieved from the national STI surveillance system. Participants will be requested to complete 5 questionnaires (at baseline and at 6, 12, 18, and 24 months) to collect data on PrEP intake; sexual behavior; psychosocial characteristics; and the experiences, acceptability, and usability of the interventions. We will extract automatically registered data on app usage from the app.

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Figure 1. EZI-PrEP study flowchart. DBS: dried blood spot; EZI-PrEP: E-Health for Zero Infections - facilitating access to and use of Pre-Exposure Prophylaxis in the Netherlands; PrEP: pre-exposure prophylaxis; SHC: sexual health center.



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Figure 2. Map of the Netherlands with EZI-PrEP study sites. EZI-PrEP: E-Health for Zero Infections - facilitating access to and use of Pre-Exposure Prophylaxis in the Netherlands; PHS: public health service.



Study Population

We aim to include 442 individuals who are already using PrEP through the Dutch NPP or will be starting or restarting PrEP. Individuals starting PrEP are PrEP naïve (herein referred to as "PrEP starters"), whereas individuals restarting PrEP are persons who have used PrEP more than 6 months prior to inclusion and will recommence PrEP at inclusion (herein referred to as "PrEP restarters"). Both groups of individuals need to have a monitoring consultation after 1 month of starting or restarting PrEP as part of standard-of-care procedures and are therefore grouped in the protocol as "PrEP starters or restarters." Our intention is that at least 25% of study participants will be PrEP starters or restarters.

The eligibility criteria will be as follows: (1) being eligible for the Dutch NPP (Textbox 1) [45]; (2) being 18 years or older; (3) living in the catchment area of a participating PHS; (4) being able to complete informed consent, medical history, the daily diary, and questionnaires in English or Dutch; (5) having an email address; (6) owning an iOS or Android mobile phone capable of running the study app; (7) having daily access to an internet connection; (8) being able to make online payments; and (9) providing informed consent. The exclusion criteria will be as follows: (1) having an HIV infection; (2) being advised by a physician to wait with starting or restarting PrEP (PrEP starters or restarters) or being advised to stop with PrEP (current PrEP users) for more than 1 month, such as in the case of decreased kidney function with an estimated glomerular filtration rate (eGFR) of less than 60 mL/min/1.73m^2 or other kidney problems, or chronic use of medication that interacts with TFV/FTC; (3) being advised to have in-clinic monitoring every 3 months, such as in the case of adverse mental health conditions or life circumstances, chronic or acute hepatitis B virus infection, or other medical conditions that require special attention when using PrEP or may need a referral, such as osteoporosis or other bone diseases; and (4) participating in another clinical trial or research project related to HIV prevention.

Textbox 1. Eligibility criteria of the Dutch national pre-exposure prophylaxis pilot program (Dutch national pre-exposure prophylaxis guidelines dated April 15, 2019).

Men who have sex with men or transgender and gender diverse people who in the 6 months prior to the pre-exposure prophylaxis (PrEP) request or PrEP consultation:

- Had anal sexual intercourse without a condom with a male partner having an unknown HIV status
- Had anal sexual intercourse without a condom with a male partner having a known HIV-positive status and a detectable viral load
- Was diagnosed with a rectal sexually transmitted infection or syphilis
- Received a prescription for HIV postexposure prophylaxis

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Recruitment

We will recruit participants mainly at the SHCs of the participating PHSs. Current PrEP users will be recruited during regular PrEP monitoring visits by a health professional (usually a nurse or a physician). Individuals who are starting or restarting PrEP will be recruited from the waiting lists for PrEP care via email, SMS text messaging, or a phone call and routine communication channels of the respective SHC. The enrollment visit will be scheduled together with the first PrEP consultation. To support the recruitment efforts of the SHCs, we developed a website [48] and promotional materials for distribution to SHC clients. In addition, depending on the recruitment rate in the participating SHCs, we plan to conduct 3 advertising rounds on the MSM dating platform Grindr, targeting potential participants living in the catchment areas of the 4 participating PHSs. All promotional materials and advertisements will link to the EZI-PrEP website page with a short application form.

Enrollment Procedures

In preparation of the enrollment visit, potential participants will receive an email with the patient information folder and will be asked to download the EZI-PrEP study app. The enrollment interview will begin with a regular PrEP consultation at the SHCs, which will be combined with eligibility screening (Figure 1). Noneligible individuals will continue or commence routine PrEP care. Eligible individuals will be guided through study procedures and asked to sign an informed consent form, and will be subsequently randomized to 1 of the study arms. Each participant will then onboard the EZI-PrEP app and complete the diary for that day to ensure understanding of the questions asked in the diary. This first diary entry will not be used for analysis because it is completed in the presence of a health care worker. The enrollment interview will be finalized with scheduling of the next monitoring appointment and PrEP provision.

The Dutch PrEP guidelines allow for combining STI and HIV test specimen collection with PrEP dispensing, as long as a client can be easily reached to communicate HIV and STI test results [10,11]. In case of a positive HIV test result, the PrEP user will be notified immediately to discontinue their PrEP and will be referred to HIV care. This strategy may lead to postrandomization exclusion from the EZI-PrEP study within 1 week after randomization.

Randomization

Participants will be randomized (stratified by PHS and by PrEP experience, that is, those starting or restarting PrEP, and current PrEP users) to 1 of 4 study arms in permuted blocks of 4. Randomization will be performed by a statistician of PHS Amsterdam who is not part of the EZI-PrEP study team at initiation of the study, using Stata Intercooled 15.1 (StataCorp). Sequentially numbered and colored nontransparent envelopes will be made, containing a code for the study arm. Each PHS will receive 2 sets of envelopes, red ones for those starting or restarting PrEP and blue ones for current PrEP users. During the enrollment interview, in the presence of the participant and dependent on their PrEP experience, the health care provider will open the next envelope to reveal the study arm and study number.

Interventions

PrEP Care Every 6 Months

Participants in arms 2 and 4 (Figure 1) will receive PrEP care every 6 months. All study participants, irrespective of study arm, will be allowed to get screened free of charge for HIV and STIs in between scheduled PrEP monitoring visits (eg, after a partner notification for an STI or in case of STI-related symptoms). To allow for monitoring in between testing, we will ask participants to visit the SHC where they receive PrEP care.

Online PrEP Care

Participants in arms 3 and 4 (Figure 1) will receive online-mediated PrEP care that mimics in-clinic PrEP care. Figure 3 depicts the process of online-mediated PrEP care. First, participants will access an established online HIV and STI test request platform for MSM called Testlab [49]. On this platform, participants will complete standard intake questions for a PrEP consultation. The number of PrEP tablets needed until the next monitoring date will also be reported. All medical information will be stored in the electronic patient files. Participants reporting STI symptoms at the scheduled online monitoring visit will be asked to visit the clinic for physical examination and treatment.

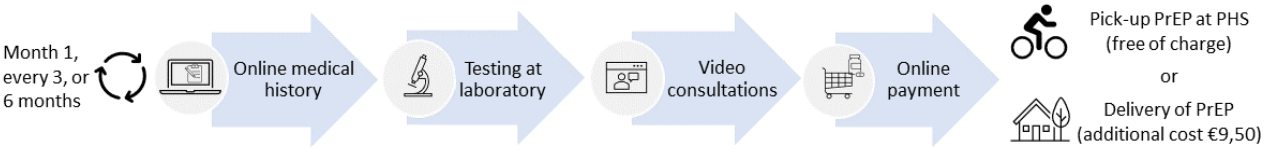
The participant will then receive a lab order from the Testlab platform to visit one of the connected laboratories to provide samples for HIV infection, STI, HCV infection, and kidney function testing (Table 1). Negative test results for HIV infection, STI, and HCV infection; normal kidney function test results; and positive test results for bacterial STIs will be communicated via the Testlab platform. Treatment of bacterial STIs will occur in the clinic at SHCs. In case of a positive test result for HIV or HCV, or a decreased kidney function, participants will receive a phone call to make an appointment on the same day.

To provide counseling on sexual well-being, PrEP intake, and other HIV prevention strategies, a video consultation will take place. These video consultations will become optional after 6 months. The continuation of video consultation will be based on shared decision-making between the participant and the SHC health care provider. Self-reported medical history and testing for HIV infection, STIs, HCV infection, and kidney function will remain mandatory for PrEP provision. For the purpose of the study, a mandatory video consultation will take place at 18 and 24 months to inform participants about study procedures that change at those time points (Figure 1).

Participants in the online arms may opt for home delivery of PrEP tablets, for which a service fee of €9.50 ($9.98) will be requested and will require an online payment. Pick up of PrEP tablets from the SHC will also be possible without any additional cost. The SHC physician will determine the number of tablets that a participant is able to obtain based on the intended PrEP regimen and the number of tablets requested by the participant in the self-reported medical history.

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Figure 3. Process of online-mediated EZI-PrEP care. It should be noted that 6 months after inclusion, the video consultations will become optional, and PrEP provision will then be based on online (self-reported) medical history and test results. A currency exchange rate of €1=US $1.05 is applicable. EZI-PrEP: E-Health for Zero Infections - facilitating access to and use of Pre-Exposure Prophylaxis in the Netherlands; PHS: public health service; PrEP: pre-exposure prophylaxis.

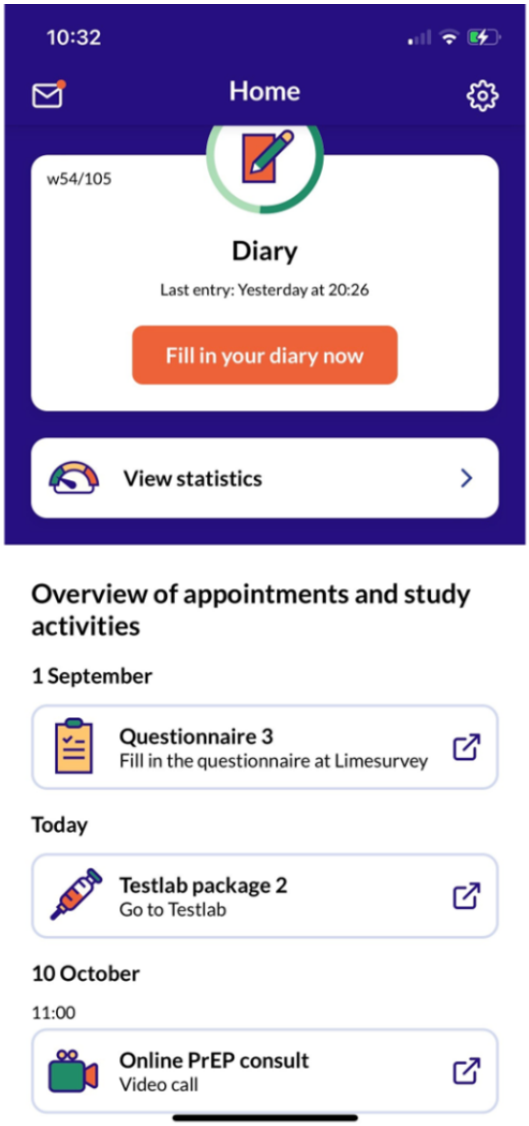


EZI-PrEP Applications

EZI-PrEP App

All participants will get access to the free-of-charge, password-protected EZI-PrEP app through the Apple and Google Play stores. App functionalities will depend on their allocated mode of PrEP care provision. All participants will have access to the daily diary, the summary of data entered in the diary, and a timeline with an overview of upcoming PrEP monitoring visits and study questionnaires (Figure 4). Participants receiving online PrEP care will also receive access to the online-mediated test request platform, video consultation software, and PrEP payment module. All functionalities will be immediately accessible by clicking on the activity in the timeline of the app via a single sign on. All participants will be able to receive messages in the app from SHC health care workers and study staff, but will not be able to send messages via the app (Figure 4).

Figure 4. Homepage of the EZI-PrEP app. It should be noted that Testlab package 2 and online PrEP consultation are only visible to EZI-PrEP participants in arms 3 and 4. Arm 3: online monitoring every 3 months; Arm 4: online monitoring every 6 months; EZI-PrEP: E-Health for Zero Infections - facilitating access to and use of Pre-Exposure Prophylaxis in the Netherlands; PrEP: pre-exposure prophylaxis.



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EZI-PrEP Administration Portal

The EZI-PrEP app and all functionalities, except for the diary, will be controlled by SHC health care workers and EZI-PrEP study staff via a web portal that uses a cloud platform to exchange data with the EZI-PrEP app. The administration portal will be used to activate participant accounts, with functionalities enabled according to the study arm allocation. The portal will include an event planner to register the date and time of in-clinic visits, online-mediated testing, and video consultations, and activate the PrEP payment module upon entering the number of tablets that can be obtained by the online participants. The portal will also be used for scheduling questionnaires and, for online participants only, to activate home delivery of a DBS home sampling kit. In-app messages will be sent via the administration portal as well. Health care workers will be able to only access the accounts of participants receiving PrEP care at their SHCs.

Laboratory Procedures

Laboratory procedures will be performed according to routine STI and PrEP care clinical protocols, which may slightly differ across study sites. A detailed description of the laboratory procedures at each study site can be found in Multimedia Appendix 1.

Data Collection Methods

EZI-PrEP Diary

To minimize recall bias and increase the accuracy of self-reported PrEP intake, casual anal sex, and condom use, participants will be requested to complete a daily diary for primary outcome measurement [50]. Completing the diary may be burdensome for certain participants and could result in less motivation to remain in the study. Minimizing the length of the diary collection period could help maintain sufficient motivation to complete the diary and continue study participation. During the first 18 months of the study, each participant will be completing 4 to 6 daily questions. These diary questions ask about PrEP use, sexual behavior of the previous day, and current mood. The first question (“Do you use daily or event-driven PrEP?”) will be asked once and set as default (ie, prefilled) until the participant changes to a different regimen, which can be selected in a new diary on the following day. The second question (“How many PrEP pills did you take?”) will need to be answered with 0, 1, or 2. In case of 1 or 2 tablets, the third question will be prompted (“At what time did you take PrEP?”), which will need to be answered with a specific time. The fourth question (“Did you have anal sex with a casual partner?”) will need to be answered with yes or no. If yes is answered, the fifth question (“Did you use a condom every time?”) will be prompted, which will need to be answered with yes or no. The sixth question (“How do you feel today?”) will need to be answered on a discrete scale with 5 options, ranging from 1 (depicted by a red sad face) to 5 (a green happy face). Participants will be allowed to change their answers until automatic submission of the diary when the final question is answered. The average expected duration of completing the daily diary is 90 seconds.

The diary that is completed on a given day will ask about PrEP intake and sexual behavior of the day before, which is indicated on the top of the screen. If a participant forgets to enter their information in the daily diary, they will be allowed to retrospectively fill in information, but only for the past 2 days.

To increase diary completion adherence, we will send automated daily notifications at 10 AM Central European Time (CET); however, it will be possible to deactivate this reminder in the settings of the app. If a participant has not completed their diary for 7 days, an email with a reminder and explanation of the importance of the diary for the study will be sent. After 14 days, another reminder that the diary is crucial for the study will be sent to the participant and to the PHS where they are under care, so that the importance of diary completion can be discussed in the upcoming monitoring visit. Being unable to complete the diary will not be considered as a reason to end participation in the study.

DBS Collection

We will collect DBSs to measure intracellular concentrations of TFV-DP and emtricitabine-triphosphate (FTC-TP). Blood will be spotted on Whatman 903TM Protein Saver Cards (GE Healthcare Bio-Sciences Corp). For participants receiving in-clinic PrEP care, study nurses will collect whole blood via phlebotomy and spot this onto the DBS card during the 6- and 12-month PrEP monitoring visits. Participants receiving online-mediated PrEP care will receive a DBS home sampling kit after completing their PrEP monitoring visit at months 6 and 12. This kit contains the DBS card with 5 spots, 2 contact-activated lancets (2.0-mm BD Microtainer), an alcohol wipe, a gauze wipe, 2 band aids, a grip seal bag, a desiccant sachet with a humidity indicator (MiniPax, Multisorp Technologies), a preposted envelope, and paper instructions with a QR code to an instruction video. Participants will be requested to send the completed DBSs in the preposted envelope to the Amsterdam regional microbiology laboratory. All DBS cards will be stored at −20°C at the Amsterdam regional microbiology laboratory and shipped in batches for analysis to Skaggs School of Pharmacy and Pharmaceutical Sciences (University of Colorado Anschutz Medical Campus). Owing to financial constraints, only DBS cards from daily PrEP users will be analyzed. The procedure to measure TFV-DP and FTC-TP in DBSs has been described previously [51]. The results will not be reported back to the participants. For participants with incident HIV infection, the most recent DBS prior to infection will be analyzed for TFV-DP, FTC-TP, and HIV RNA

Clinical Data

We will obtain the clinical data of all PrEP and STI consultations of study participants between enrollment and study completion from the Dutch national SHC surveillance database (SOAP). During every consultation at the SHC, data are collected on the following: (1) sociodemographic characteristics (age, gender, highest educational level, country of birth, and country of birth of parents); (2) sexual behavior and STI/HIV risk factors (number of sex partners, condom use, group sex, use of alcohol and drugs during sex, sex work, having been a victim of sexual violence, and sex partners from STI or HIV endemic countries); (3) reason for consultation (partner notification, STI-related

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symptoms, PrEP, and STI testing); (4) PrEP use (history of PrEP use, reasons for stopping PrEP, and number of PrEP tablets provided); and (5) HIV infection, STI, and HCV infection testing and diagnosis. Data on kidney function and proteinuria will be retrieved from the electronic patient files.

Study Questionnaires

The first 4 questionnaires (ie, at baseline, and 6, 12, and 18 months) will ask about PrEP intake, sexual behavior, risk perception related to STIs and HIV infection, and STI testing at facilities other than SHCs. We will include several psychosocial measurements in the questionnaires (summarized in Table 2). The questionnaire at month 12 will include questions on social norms with respect to PrEP use, loneliness, and the presence of social support systems. To investigate the usability and acceptability of the PrEP care modality, we will include questions based on Davis' model of technology acceptance [52] at months 6, 12, and 18. These questionnaires will also include questions regarding experiences with PrEP care and to what extent participants felt supported in their PrEP use. To assess the usability and acceptability of online-mediated PrEP care specifically, we will include the system usability scale [53] at month 18 for online study participants. We will also ask them to rate the different steps during their online PrEP care. The fifth (and last) questionnaire, at month 24, will focus on the quality of PrEP care within the EZI-PrEP study and in the Netherlands in general, as well as the time and cost investments of study participants in receiving PrEP care.

Table 2. Overview of psychosocial measurements within the EZI-PrEP study in each survey round.

Scale	Abbreviation	Aspect measured	Baseline survey (month 0)	Follow-up survey			
				Month 6	Month 12	Month 18	Month 24
Self-reported habit index	SHI	Habit formation	✓	✓	✓	✓	
Patient Health Questionnaire-9	PHQ-9	Severity of depressive symptoms	✓	✓	✓	✓	
Generalized Anxiety Disorder Assessment	GAD-7	Generalized anxiety disorder	✓	✓	✓	✓	
Sexual compulsivity scale	SCS	Sexual compulsivity	✓		✓		
Alcohol Use Disorders Identification Test	AUDIT	Problematic alcohol use	✓			✓	
Drug Use Disorders Identification Test	DUDIT	Problematic drug use	✓			✓	
Perceived stress questionnaire	PSQ20	Perceived stress		✓	✓	✓	
Brief Resilience Scale	BRS	Resilience		✓			
Cognitive Emotion Regulation Questionnaire	CERQ-short	Coping skills			✓		
HEXACO[a] Personality Inventory-Revised	HEXACO-PI-R	Conscientiousness			✓		

[a]HEXACO is an acronym for "Honesty-humility," "Emotionality," "Extraversion," "Agreeableness," "Conscientiousness," and "Openness to experience."

Data Analysis

Primary Outcome

The primary outcome ("unprotected act") will be assessed using daily self-reported data on sexual behavior, pill intake, and condom use. We will use all available data, meaning that observation time and all data of those who are lost to follow-up or have dropped out will be included until their last day in the study. We will determine, for each day of follow-up, whether a condomless anal sex act with a casual partner took place. We will also determine whether sufficient PrEP pills were taken around the time of this condomless anal sex act. Using this information, the condomless anal sex act will be considered as either unprotected or not. We will then calculate the total number of unprotected acts (n) and the total person-years of observation. Incidence rates per 100 person years will be calculated by dividing the sum of all unprotected acts by the sum of person-years of observation and multiplying the result by 100. We will calculate the incidence rates among participants of online PrEP care (arms 3 and 4), in-clinic PrEP care (arms 1 and 2), monitoring every 6 months (arms 2 and 4), and monitoring every 3 months (arms 1 and 3). Two main analyses will be conducted in which we will test the ratio of the incidence rates of unprotected acts for (1) online PrEP care versus in-clinic PrEP care and (2) monitoring every 6 months versus monitoring every 3 months. The analyses will be based on crude unadjusted incidence rate ratios.

A noninferiority trial intends to demonstrate that one intervention is not unacceptably worse than a comparison intervention [54]. To do so, the lower limit of the 95% CI (or 2-sided 97.5% CI) should not extend beyond a predefined margin, which is referred to as the noninferiority margin. In this study, noninferiority will be tested using a 1-sided test based on maximum likelihood estimators with a type 1 error at 0.0125 (ie, with 2 comparisons using Bonferroni corrections=0.025/2) [40] and a noninferiority ratio of 1.8. If the upper 2-sided 97.5%

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CI of the incidence rate ratio is below 1.8, we will conclude that the intervention arms are noninferior to the comparator arms.

To determine whether the incidence rates change over time, we will model the number of unprotected acts as a function of 1-month intervals using Poisson regression (or negative-binomial regression, if the standard deviation is far greater than the mean of the outcome, ie, overdispersion) and test for changes in time using a Wald χ^2 test. We will test for the interaction between time and intervention arm.

Secondary Outcomes

We will assess intracellular concentrations of TFV-DP and FTC-TP using DBSs collected at month 12 in all participants using daily PrEP. The lower limit of detection is determined as 25 fmol/punch and 50 fmol/punch for TFV-DP and FTC-TP, respectively. The distribution of the intracellular concentrations of TFV-DP and FTC-TP will be compared between daily PrEP users in (1) online PrEP care versus in-clinic PrEP care and (2) monitoring every 6 months versus monitoring every 3 months, using a rank-sum test. In a secondary analysis, the log-transformed values will be compared using a linear regression.

The incidence rates of HIV infection and TFV/FTC-resistant HIV infection, and the incidence rates of bacterial STIs (ie, chlamydia, gonorrhea, and syphilis), HCV infection, and eGFR of less than 60 mL/min/1.73m^2 will be assessed. The incidence rates are calculated by dividing the number of diagnoses by the person-years of observation. The incidence rates will be compared for (1) online PrEP care versus in-clinic PrEP care and (2) monitoring every 6 months versus monitoring every 3 months.

Retention in PrEP care is defined as having had a PrEP prescription no longer than 8 months ago. Participants will be considered lost to follow-up when they do not complete a PrEP monitoring visit at month 18 within 2 months of the planned date. They will be regarded as lost to follow-up from the date of the last contact with the study (ie, completed a diary, questionnaire, or consultation). We will compare proportions of participants who are retained in PrEP care or are lost to follow-up for (1) online PrEP care versus in-clinic PrEP care and (2) monitoring every 6 months versus monitoring every 3 months, using the Pearson χ^2 test.

Satisfaction with PrEP care will be compared between study arms. Furthermore, we will analyze how usability of the online PrEP service differs between online-mediated PrEP care every 3 months and every 6 months. For these analyses, we will use the Wilcoxon signed-rank test of the Likert score outcomes.

We will investigate the associations between sociodemographic and psychosocial determinants and the incidence rates of unprotected acts; HIV infection, STIs, and HCV infection; retention in PrEP care; and loss to follow-up. A wide range of parameters, mentioned in the Data Collection Methods section, will be included in our analyses. The analyses will involve logistic models, Cox proportional hazards models, and Poisson regression models.

Power and Sample Size Calculation

We assume that the primary outcome measure of unprotected acts will be Poisson distributed with the total number per 100 person-years given as an incident rate (λ) and the total time during monitoring (t). We define the incidence rate in the experimental arm as λ_e and the incidence rate in the control arm as λ_c. We aim to reject the null hypothesis that the ratio λ_e/λ_c is greater than or equal to a predetermined noninferiority ratio (r). We consider that a noninferiority ratio of 1.8 is able to preserve clinically acceptable noninferiority bounds with increasing λ.

In a previous PrEP study in the Netherlands (Amsterdam PrEP demonstration project [“AMPrEP study”]), the overall incidence rate of unprotected acts was 78/100 person-years [50]. The AMPrEP study included participants with a high number of sex partners and very high incidence of bacterial STIs. Participants of the NPP have reported fewer casual sex partners and have a lower incidence of bacterial STIs [55]. The EZI-PrEP participants are therefore expected to have fewer unprotected sex acts than the AMPrEP participants. We expect the incidence rate of unprotected acts in the experimental arm (λ_e) and control arm (λ_c) to be at least 36/100 person-years. We also assume a median monitoring time of 18 months. Using a Bonferroni-corrected 1-sided type 1 error of 0.0125 (=0.025/2 for a total of 2 comparisons), we will need 368 participants to have 90% power to demonstrate noninferiority using the test statistic based on maximum likelihood estimators from Stucke and Kieser [56]. If λ is higher than 36/100 person-years, we will have sufficient power to demonstrate noninferiority. Considering expected loss to follow-up, we have increased the target sample size by 20%, and thus, the total required sample size is 442.

Ethical Considerations

This study has been approved by the medical ethics committee of the Amsterdam University Medical Centers (file number 2020_154 - NL74494.018.20). The trial has been registered at ClinicalTrials.gov (number NCT05093036).

Results

The results of the primary outcome assessment are expected by Fall 2024. Completion of the 24-month questionnaire and retrieval of STI data are expected by Fall 2024. Analysis of secondary outcomes will be conducted in 2024 and 2025.

Discussion

We have designed the EZI-PrEP study in order to assess whether online-mediated PrEP care and a reduced frequency of monitoring are noninferior compared to standard practice. In this study, we will develop, implement, and rigorously evaluate an online-mediated PrEP care service and a less frequent monitoring schedule (every 6 months) among MSM and TGDP in 4 regions in the Netherlands. Studies in countries with concentrated HIV epidemics and PrEP programs for MSM show the potential of PrEP programs to reduce population-level HIV incidence [57,58]. Reducing the number of in-clinic visits may

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reduce the burden of PrEP care and might help increase uptake and improve retention. Additionally, it may improve access to PrEP as it may make more resources available and enlarge capacity at facilities providing PrEP. Online-mediated PrEP care and monitoring every 6 months are promising options to reduce in-clinic PrEP visits, but it is unclear how this affects PrEP adherence. Since both modalities involve less intense contact between PrEP users and health care providers, and thus less guidance in PrEP use, it could theoretically have an adverse effect on PrEP adherence. The EZI-PrEP study will be able to provide evidence on the efficacy and safety of online-mediated PrEP care and PrEP care every 6 months compared to standard in-clinic PrEP care every 3 months in terms of PrEP adherence as a proxy for HIV risk. If these services are found to be noninferior, both online access to PrEP and reduced monitoring frequency could become viable evidence-based PrEP care options.

The EZI-PrEP study will contribute crucial data to the ongoing debate on optimal HIV and STI screening frequency for MSM who use PrEP. By comparing incidence rates of HIV infection, STIs, and HCV infection between the 3-month and 6-month monitoring study arms, we will provide evidence on the impact of testing every 6 months on STI diagnosis and treatment. If noninferiority in terms of PrEP adherence is concluded and STI incidence rates are similar between the 6-month and 3-month monitoring arms, a stronger case can be made to offer PrEP monitoring every 6 months as the standard of care. If STI incidence rates are not similar between the study arms, we will be able to examine to what extent this is related to particular sociodemographic, sexual behavior, or psychosocial factors and advise on implementation accordingly. EZI-PrEP study participants will be allowed to test for HIV, STIs, and HCV in between regular PrEP monitoring visits at their own initiative. The EZI-PrEP study will also be able to quantify the extent to which in-between visits occur among PrEP users receiving monitoring every 6 months.

Since adherence to the PrEP intake regimen is crucial for its effectiveness [3,5-7], having a thorough understanding of enabling and disenabling factors of PrEP adherence is important. The EZI-PrEP study will provide new insights on the associations between sociodemographic and psychosocial variables on the one hand and PrEP adherence on the other hand. Insights into the role of such sociodemographic and psychological factors in the context of adherence may be used to further improve the content or conduct of PrEP consultations and inform interventions that support PrEP adherence. Furthermore, we will investigate the relationship of these factors with PrEP adherence, STIs, retention, and satisfaction with PrEP care, according to the study arm. The results of these analyses could be used to determine if these new PrEP care modalities should be implemented widely or should be offered to specific subpopulations.

The main methodological challenge of this study is the measurement of the primary outcome measure, which is based on self-reported PrEP intake and sexual behavior. In the AMPrEP study, it was found that reporting of daily data decreases over time, which may confront us with a substantial amount of missing data. We will therefore implement an intensive scheme of reminders. Additionally, the diary in itself may cause behavioral changes (ie, Hawthorne effect). For instance, PrEP intake may be affected due to the daily reminder to complete the diary. Completing the diary on a daily basis might also be too burdensome for some participants, and as a result, their motivation to complete the study could be low. However, because of randomization, any effect of daily diary entry on behavior or participation is not expected to differ across the 4 arms. A major strength of our study is that it is embedded in routine PrEP care, which increases the generalizability of study outcomes and will provide a realistic perspective on the implementation of 2 new PrEP care modalities. If these modalities are found to be noninferior, they can be easily implemented in routine care using the workflows developed in this study and applied to the 4 participating PHSs. Furthermore, combining monitoring every 6 months and online-mediated PrEP care in this trial offers a unique opportunity to study real-life implementation of these PrEP modalities.

In conclusion, the results of the EZI-PrEP trial will provide evidence on the noninferiority of online-mediated PrEP care compared to in-clinic care and the noninferiority of monitoring every 6 months compared to monitoring every 3 months in terms of PrEP adherence. It will also provide insights into screening every 6 months for HIV infection, STIs, and HCV infection among MSM who use PrEP, and thereby will contribute to the literature on the optimal STI screening frequency among PrEP users. Moreover, the study will investigate to what extent these PrEP care modalities are appealing to PrEP users in general and if particular PrEP users would benefit more from these modalities than others. Finally, the study will provide insights into the sociodemographic and psychosocial factors that influence PrEP adherence. The EZI-PrEP study aims to inform policymakers and sexual health centers in deciding which strategies would be appropriate for PrEP care. The findings will contribute to accessible, low-cost, scalable, and sustainable PrEP care.

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Data Availability

Data sharing is not applicable to this article as no data sets have been generated or analyzed.

Authors' Contributions

UD, MFSvdL, EH, MP, AB, AM, LC, ARF, FvH, and MLGB conceptualized and designed the EZI-PrEP (E-Health for Zero Infections - facilitating access to and use of Pre-Exposure Prophylaxis in the Netherlands) trial. UD, MFSvdL, JW, KY, SB, HMG, JMB, KV, and MLGB were involved in the development of the online pre-exposure prophylaxis care trajectory, smartphone app, administration panel, and website, and organized the implementation of the study. MLGB drafted the manuscript. All authors read and approved the final manuscript.

Conflicts of Interest

UD received unrestricted research grants and speaker fees from Gilead Sciences, paid to his institute. MFSvdL participated in Advisory Boards of Merck Sharp & Dohme, for which fees were paid to his institute. MFSvdL received a research grant from GlaxoSmithKline, paid to his institute. EH received unrestricted research grants from Gilead Sciences, paid to her institute. MP received unrestricted research grants and speaker/advisory fees from Gilead Sciences and Merck Sharp & Dohme, all paid to her institute. All other authors declare no competing interest.

Multimedia Appendix 1
Laboratory procedures at each study site.
[DOCX File , 16 KB - resprot_v12i1e51023_app1.docx]

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Abbreviations

AMPrEP: Amsterdam PrEP demonstration project
DBS: dried blood spot
eGFR: estimated glomerular filtration rate
EZI-PrEP: E-Health for Zero Infections - facilitating access to and use of Pre-Exposure Prophylaxis in the Netherlands
FTC: emtricitabine
FTC-TP: emtricitabine-triphosphate
HCV: hepatitis C virus
MSM: men who have sex with men
NPP: National PrEP Pilot Program
PHS: public health service
PrEP: pre-exposure prophylaxis
SHC: sexual health center
STI: sexually transmitted infection
TFV: tenofovir
TFV-DP: tenofovir-diphosphate
TGDP: transgender and gender diverse people

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Protocol

Use of Immersive Virtual Reality Spaces to Engage Adolescent and Young Adult Patients With Cancer in Therapist-Guided Support Groups: Protocol for a Pre-Post Study

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Abstract

Background: For adolescents and young adults, a cancer diagnoses can magnify feelings of social isolation at an inherently vulnerable developmental stage. Prior studies have highlighted the importance of peer groups during cancer treatment. Support groups help foster connection and resilience, but patients find in-person participation difficult due to a variety of factors. Additionally, physical changes brought on by cancer makes these patients hesitant to meet in person. The COVID-19 pandemic magnified these difficulties. Virtual reality (VR) allows for the creation of a therapist-curated, computer-generated social space that potentially enables support groups for this population.

Objective: This protocol describes a pilot study examining the efficacy, feasibility, and acceptability of a social VR support group intervention for adolescent and young adult patients with cancer.

Methods: We approached 20 participants aged 17-20 years, and 16 agreed to participate. Moreover, 1 participant dropped out due to hospitalization. Participants attended virtual, professionally facilitated support groups using Meta Quest VR headsets. The groups consisted of 4 participants and 1 facilitator, amounting to a total of 22 individual sessions. Each session lasted 45-60 minutes and took place weekly for 4-6 weeks. The primary aim of this study was to collect quantitative and qualitative data on the feasibility and acceptability of the intervention. Feasibility was measured through session participation rates and overall retention rates. The acceptability of the intervention was explored through brief in-person interviews with participants at the end of the final intervention session. The secondary aim of this study was to collect data on the preliminary efficacy of the intervention in decreasing symptoms of participant depression and anxiety and increasing positive affect and resiliency.

Results: In total, 15 patients aged 17-20 years participated in 22 sessions between November 5, 2019, and July 8, 2021. The median age was 19 (IQR 17-20) years. Overall, 10 (62%) participants identified as male, 5 (31%) as female, and 1 (6%) as transgender female. Furthermore, 5 (31%) participants identified as Hispanic, 1 (6%) identified as non-Hispanic Asian, 3 (19%) identified as non-Hispanic Black, 6 (38%) identified as non-Hispanic White, and 1 (6%) identified as other race or ethnicity. Hematologic malignancies or bone marrow failure was the most common diagnosis (8/16, 50%). The mean attendance rate was 72.8% (SD 25.7%) and retention was 86.7% (SD 0.35%). Moreover, 45% (10/22) of sessions had to be postponed by a week or more due to unexpected participant scheduling issues.

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Conclusions: The use of VR to deliver psychosocial support for adolescents and young adults with cancer may reduce common barriers associated with attending in-person peer support groups while improving quality-of-life measures. The data from this study will inform future studies focused on conducting VR support groups in other rare disease populations, including older adults with cancer.

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KEYWORDS

cancer; virtual reality; support groups; peer support; adolescent; young adult; resilience; adolescents and young adults; oncology; therapist-guided support; social isolation; support system; psychosocial support; barrier; quality of life

Introduction

Background

Approximately 90,000 adolescents and young adults were diagnosed with cancer in 2020, with around 9000 having lost their lives [1]. In the group of patients aged 15-39 years, a cancer diagnosis brings unique medical and psychosocial needs. Complications of treatment are both medical and psychosocial and include infection, fatigue, hair loss, mouth sores, anxiety, infertility, depression, boredom, and isolation. Feelings of social isolation, depression, and anxiety are magnified in this group as their life experiences violently diverge from those of their peers. Support from caregivers and interactions with adolescents and young adults going through a similar experience improves the quality of life for this population [2].

One of the most requested and effective psychosocial interventions for this population are peer support groups, whether in person or via videoconference [3,4]. These groups give adolescents and young adults with cancer the opportunity to shed the defining attribute of their cancer diagnoses and engage with peers who have had similar experiences while finding true empathy among peers. Despite the clear benefits of these groups and patients' desire to participate in them, personal communications with various adolescents and young adult cancer centers and personal experience in attempting to organize these groups have proven the difficulty of assuring in-person attendance. The reason for this is multifold, including active immunosuppression; prolonged hospitalizations; geographic constraints; and patients' other responsibilities to their schools, families, and jobs. In addition, the inherent physical changes brought on by an adolescents and young adult cancer diagnoses make these patients less willing to meet in person or show themselves on a screen.

Potential Technologic Approaches to Solve the Problem of Poor Adherence

Although support groups have traditionally been conducted through real time face-to-face gatherings, a lack of access due to distance, time, and transportation has long been cited as one of the most prominent barriers to support group participation and adherence [5]. For individuals with long-term health conditions, such as cancer, these barriers are further amplified [6]. The past decade has seen the steady development of virtual support groups that use the communication technology of virtual worlds to overcome the logistical barriers presented by face-to-face meetings [7,8]. In addition to minimizing logistical barriers, virtual support groups offer further affordances including anonymity, which may facilitate disclosure, autonomy, and help-seeking [9], whereby users can control how much they share and with whom. In the case of persistent online worlds including social media, the asynchrony of participation allows individuals to access the service whenever they choose [10]. Although the COVID-19 pandemic propelled mainstream acceptance of videoconferencing software such as Zoom (Zoom Video Communications) as a convenient tool for remote social connection, the use of live videoconferencing for support groups is not well defined in the literature, although initial reports of its use during the pandemic show it has promise as a solution to the logistical barriers to attendance [11].

Social virtual reality (VR) is an emerging technology in which multiple users can interact with one another in a shared, immersive 3D virtual environment [12]. Compared to other forms of virtual interaction that mainly support screen-mediated communication (including videoconferencing, social media, and persistent online social worlds), social VR is characterized by full-body tracked avatars. These avatars enable real-time embodied interaction that is similar to face-to-face communication in that it includes verbal *and* nonverbal interactions such as voice, gestures, proxemics, gaze, and facial expression [13]. The opportunity for embodied and immersive experiences mediated through VR technology has the potential to replicate people's everyday activities and is likely to play a role in forming and maintaining interpersonal relationships. Given that VR can be used from the convenience of one's own home, or even their hospital bed, support groups offered through social VR settings overcome logistical barriers of physical distance and immunosuppression while still maintaining much of the nuance of nonverbal communication and physicality that are seen as hallmarks of in-person support.

Previous VR Studies in Adolescents and Young Adults, Cancer, and Telemedicine

Multiple studies have demonstrated the benefits and viability of using VR as an intervention in the pediatric and adolescent and young adult health care setting. In a group of pediatric patients with cancer aged 10-17 years undergoing chemotherapy, it was found that patients' self-reported symptom distress immediately after chemotherapy was significantly lower when they used VR with 1 of 3 distractive experiences (CD ROM-based scenarios: Magic Carpet, Sherlock Holmes Mystery, and Seventh Guest viewed via a head-mounted display) as compared to a session during which they did not use VR [14].

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Another adolescent cancer group showed equally promising effects on pain and discomfort using a VR experience during lumbar puncture in the form of a distracting video viewed via a head-mounted display [15]. In a group of pediatric patients using distractive VR while undergoing chronic wound care, pain and anxiety as measured by patients, caregivers, and nurses was significantly lower during and after dressing changes in the VR group versus the group receiving standard distractions; additionally, the time to complete each dressing change was significantly less in the VR group. The distractive VR came in the form of the Ice Age 2: The Meltdown game. In the game, players control "Sid the Sloth," who slides down a snowy path while trying to collect acorns and avoid obstacles [16].

Prior studies in adolescents and young adults have illustrated the utility of group-based interventions in this particular age demographic. For example, in a group of 15 adolescents and young adults with type 1 diabetes, hemoglobin A_{1C} improved after participation in peer support groups with a psychologist [17]. More significantly, in the Adolescents and Young Adult Health Outcomes and Patient Experiences study [18], adolescents and young adults with cancer who did not receive, but reported needing support groups, were about 4 and 13 times as likely to report needs for talking about their cancer experience with family and friends and meeting peer survivors, respectively.

Given the proven viability, benefits, and safety of VR in the health care setting, as well as the importance of support groups in the adolescent and young adult population, the combination of these 2 interventions may provide increased psychosocial support for adolescents and young adults with a recent cancer diagnosis.

Commercially Available Social VR Platforms

Over the past 5 years, social VR apps such as VR Chat, AltspaceVR, Horizon Worlds, and Rec Room have emerged as a few exemplars of social VR platforms where people meet, interact, and socialize in new and more immersive ways using a head-mounted display and hand-tracking hardware. Many social VR platforms can be characterized by customizable avatars and persistent virtual worlds, with some platforms emphasizing opportunities for world customization while others favor social gaming or large-scale events such as concerts. Most platforms provide users with an opportunity to create private rooms or environments that only designated "friends" can access, as well as public worlds or spaces where anyone can interact. These platforms continue to attract more users and improve both in interaction quality, features, and ease of use, with many futurists predicting that VR social interaction will become the next major technological evolution for computer-mediated human communication. Indeed, the social VR market is expected to grow at a 14.1% compound annual growth rate between 2021 and 2027 [19].

While many commercially available social VR apps do exist, this project required a specific platform that was (1) Health Insurance Portability and Accountability Act (HIPAA) compliant, (2) easy to use, (3) contained minimal distractions within the experience, (4) used high-quality spatial audio, and (5) facilitated the expression of subtle body language through player avatars. For this study, we used the Foretell Realities platform, as described within the *Methods* section of this paper.

Study Aims

The primary aim of this study is to evaluate the feasibility and acceptability of a VR intervention to facilitate support groups for adolescents and young adults with cancer. Intervention feasibility is examined through the number of sessions completed by participants and participant retentions rates at the end of this study. The acceptability of the intervention will be examined through participant interviews conducted at the end of the last VR session and solicited feedback at the end of each individual session.

We hypothesize that our intervention will be feasible as measured by overall participation rates of >50% and retention rates of >50%. These numbers were chosen in the context of historical data showing adolescent and young adult patient participation in clinical trials to fall at less than 20% [20,21] and only 41% of Americans with mental health disorders initiating treatment services, with just 33% engaging in enough services for them to be deemed adequate [22]. Our secondary aim is to collect data on the preliminary impact of the intervention on participants' depression, anxiety, positive affect, and resilience skills. We hypothesize that participants will report a significant decrease in symptoms of depression and anxiety and an increase in positive affect and resiliency skills as measured by standardized patient report instruments from baseline to immediately after intervention. The results of this aim are beyond the scope of this paper and are currently being reviewed for submission of a subsequent mixed methods analysis.

Methods

Ethical Considerations

Formal evaluation and adoption of novel human interventions at major institutes include the need for proper and thoughtful assessment by first, a Protocol Review Committee (PRC) to ensure appropriate scientific rigor and then, an institutional review board (IRB) to ensure participant safety. The formal goal of the PRC is to ensure "assessment of the scientific rationale and merit of a proposed study in addition to protocol design, safety parameters, and biostatistical analysis to determine that high quality and appropriate designs have been incorporated" [23]. In the case of this study, the PRC of review was that of Yale Cancer Center, which consists of voting members from various scientific and epidemiologic disciplines. All procedures were approved first by the PRC and then by the Yale University IRB (ID#2000023701). The participants did not receive any compensation.

Data Collection

The following personal identifying and medical information were collected: email address, phone number, diagnoses, diagnoses date, end of treatment date (if relevant), treatment modalities, gender identity, race and ethnicity, and insurance status. All data collected from the assessments were entered by participants directly into the secure web-based system, Qualtrics (Qualtrics International Inc), which is Yale's enterprise-wide

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data management system or directly onto deidentified paper questionnaires, depending on participant choice. This ensured participant confidence that their data would remain confidential. Written consent was obtained via signature from all the participants before their participation, as detailed in the *Study Population and Study Flow* section.

The confidentiality of assessment data was assured by assigning a unique identifier to each participant once they registered for this study. A document linking this study's identifiers to the patient's name was maintained by the principal investigator (PI) and was destroyed upon the completion of data collection. All computer data were password protected and all nondigital data (including consent forms) were stored in locked cabinets.

Study Design

This pilot study uses a pre-post design to evaluate the feasibility, acceptability, and preliminary efficacy of a social VR support group intervention for adolescent and young adult patients with cancer. The team was led by a team with expertise in adolescent and young adult cancer, onco-psychology, social VR, adolescent development, and clinical trial design and evaluation.

Study Population and Study Flow

Recruitment

Candidates for this study were identified through the Yale University School of Medicine's Pediatric Hematology and Oncology Department and adolescent and young adult clinic. The Director of the adolescent and young adult clinic is the PI and one of the treating oncologists at Yale New Haven Hospital who has firsthand knowledge of the potential participants, participants' medical and psychiatric histories, and social situations. The PI consulted with the candidate's primary treating oncologist, other health care providers, and their psychosocial team to assist in determining if a participant was an appropriate candidate for this study. Candidates were considered eligible to participate if they met the following criteria: (1) between 13 and 30 years of age, (2) actively receiving treatment for cancer or completed treatment for no more than 1 year prior to enrollment, (3) English speaking, and (4) able to don a head-mounted display. Exclusion criteria included (1) not English speaking; (2) the lack of reliable access to the internet; and (3) patients who are prone to motion sickness or are experiencing nausea, vomiting, seizures, or other health problems that the medical team deem them unstable to participate. If all inclusion criteria were met and no exclusion criteria were noted, the PI approached the family or patient for study participation.

If a participant was of age to sign the consent form, consent was obtained directly from the participant. In the case of participants under 18 years of age, youth's assent was obtained along with legal guardian permission from the participant's legal guardian. If permission could not be obtained from the patient or their parent or legal guardian, the participant was not enrolled. Consent (or assent and permission) were sought after the research protocol and the risks of participation in this study were fully explained. All participants and participants' families were encouraged to read the appropriate forms and ask questions about any aspect of this study that was not clear. Participants were reminded that they could withdraw from this study at any time if desired and that the decision to not participate would have no impact on their care or relationship with the physicians or investigators.

Assessments

To evaluate the preliminary impact of this study, we collected assessment data at 2 time points: prior to the beginning of the first VR group session (baseline) and immediately after the final session.

To assess participants' depression, anxiety, and positive affect, we used PROMIS (Patient-Reported Outcomes Measurement Information System) questionnaires. The pediatric PROMIS short forms (version 1.0; Depressive Symptoms 8a July 28, 2016 [8 questions]; Anxiety 8a July 27, 2016 [8 questions]; and Positive Affect 8a July 14, 2016 [8 questions]) were used for participants 17 years of age and younger while the adult short forms (Depression 8a June 26, 2016 [8 questions]; Anxiety 8a June 2, 2016 [8 questions]; and Positive Affect 15a July 18, 2017 [8 questions]) were used for participants 18 years of age or older [24-26]. These surveys have been validated in pediatric and adolescent patients with cancer as well as in children and adolescents in other health care settings [24,27].

To assess resilience, we used the Connor-Davidson Resilience Scale (25 questions), which has been validated in multiple settings, including in young adults and in the outpatient psychiatric context [28,29].

Brief In-Person Interviews

We conducted brief in-person interviews with participants at the end of the final VR group session to explore participants' perceptions of the acceptability of the intervention. Participants were also encouraged to write out their responses to the open-ended questions after the interview if they had additional thoughts or comments that they would like to contribute (see Textbox 1). Responses were recorded as field notes by the group moderator in a secured Microsoft Word document.

Textbox 1. Open-ended questions for in-person interviews.

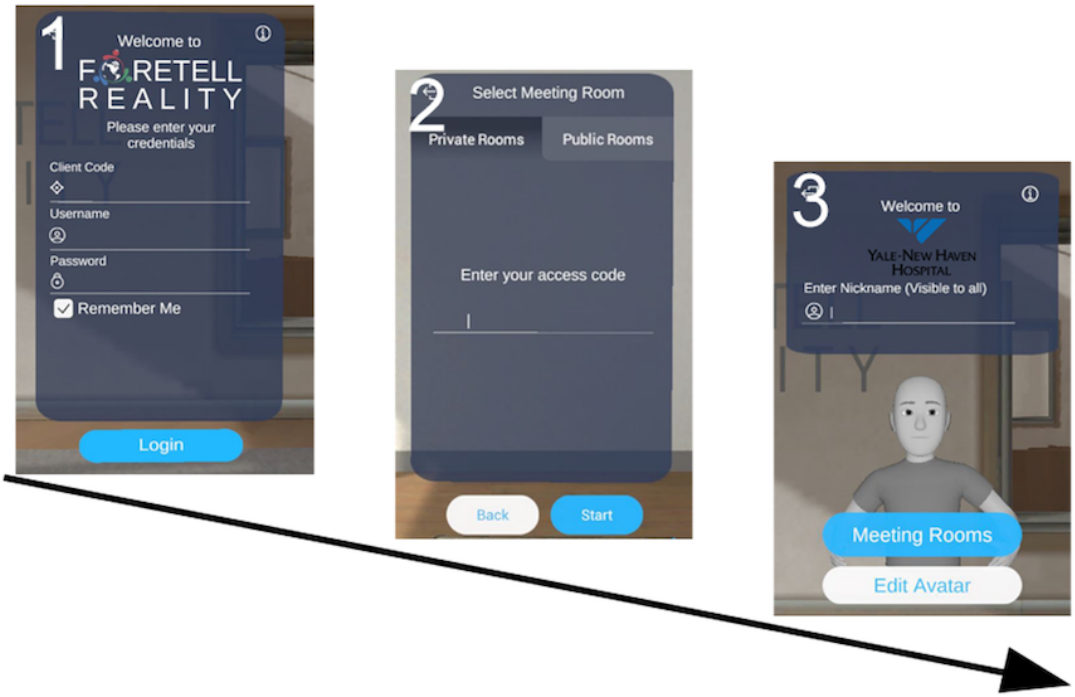
- Did you experience any physical or emotional discomfort during the virtual reality (VR) session – specifically, nausea or anxiety?
- Is there anything you would drastically change about the virtual environment in which we met – for example: colors, virtual items, or general surroundings?
- Do you feel there were any distractions preventing you from fully participating in the session?
- Would you like to see more opportunities to interact with each other, for example, through games or the ability to share digital media (photos, music, etc.)?
- Is there anything else you would like to share about the experience you just had?

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Description of Intervention

Foretell Reality is a social VR platform that leverages VR technologies to bring people together for meaningful interaction in a virtual space. After a simple and secure sign-in process, invitees share the same immersive environment, as depicted in Figure 1. Participation can occur from anywhere in the world with an internet connection. The environment used in our intervention is that of a therapeutic space with participants seated in a circle (Figure 1). Though not tested as part of our pilot, optional activities directed by facilitators such as simple games (eg, "catch the ball"), drawing in 3 dimensions, joint viewing of 360 videos and pictures, presentation of documents, meditation, and physical exercise (eg, stretching or chair yoga) are available [30]

Figure 1. Sign-in process and example of the immersive therapeutic space.





Seated in a circle, users feel a sense of social presence in VR. This is achieved through the tracked body movements and hand gestures of users' customized 3D avatars, as well as spatial audio communications. Users can mask their voices and choose nicknames that allow for complete anonymity, which can help remove barriers to vulnerability. The platform is HIPAA

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compliant, does not store any identifiable personal information, is protected by individual login usernames and passwords, and requires special access codes to enter private meetings.

Working with Foretell Reality allowed us full control and customization of the features we chose to include in our support groups and provided us close support and training for our professional personnel and patients. For example, to ensure a calming and familiar environment where patients could focus on the session at hand, a room was created to resemble the Adolescents and Young Adults Lounge at Yale New Haven Hospital with minimal distractions. We specifically requested that features such as the ability to pass a ball around the room and move away from the seated area were turned off. Limiting movement around the room ensured a low likelihood of introducing experiences that could result in motion sickness.

Study Procedure

Participants enrolled in this study were assigned to a support group on a first come first serve basis, assuming they met enrollment criteria. Groups were run one at a time with subsequent groups only enrolling after the previous group completed all sessions. Upon enrollment, patients were briefly oriented to the headset and software and given their sign in information.

During a support group session, 4 adolescent and young adult patients with cancer used the Meta Quest 1 (Meta Platforms, Inc; previously Oculus Quest 1) VR headset—a portable, low cost (US $300 manufacturer's suggested retail price) piece of hardware running Foretell Studios (Foretell Studios) software—to participate in 6 virtual, professionally facilitated support groups. Participants received brief training on hardware and software use when the hardware was initially distributed prior to the start of the support groups. Participants also received a brief operating manual. The rules of engagement (Textbox 2) were reviewed with each participant prior to their enrollment.

Textbox 2. Rules of engagement.

- Share only what you feel comfortable sharing.
- What is discussed in group, stays in group (unless there are concerns about safety).
- Be respectful/everyone should have an opportunity to share/speak.

Each support group session included 4 patients, a facilitator, and a research assistant (or the PI). The patients and facilitator were represented by a customized avatar, each with a chosen name displayed floating above their head. The research assistant or PI did not have a visible avatar, but participants were made aware that study personnel were potentially observing each session via VR headset or desktop computer. Participants were informed that the VR headsets could be used in the patients' homes, inpatient hospital room, or any other space that had an active Wi-Fi signal and was convenient, private, and desirable for the patient. The 4 participants in each group were curated by the facilitator of the group in order to ensure the grouping of appropriate ages and development levels. In total, 4 separate groups of 4 participants each were assembled for a total of 16 participants and a goal of 22 individual support group sessions (the number of sessions was increased from 4 to 6 after string feedback from group 1). Each session lasted 45-60 minutes and was scheduled with a goal of occurring once weekly for 6 weeks. Sessions were postponed if fewer than 2 participants were available to participate during any 1 scheduled session.

Support groups were facilitated by an appropriately credentialed and trained clinical psychologist, psychiatrist, or social worker or their trained designees who reviewed the "Rules of engagement" (Textbox 2) prior to each session.

Once a group completed their last session, headset disinfection was done following methods of those described in a paper published by Roberts et al [31] using isopropyl alcohol wipes on all high-touch surfaces.

Safety

With the introduction of any new technology, it is important to consider all possible malfunctions and emergent scenarios. All participants were given 2 phone numbers at the beginning of each session: the direct phone number to the facilitator and the direct phone number to the observing or on-call research assistant or PI. Additionally, the facilitator had an emergency phone number for each participant, as well as the physical location from which the participant was participating. While the hardware and software being used in this trial has been extensively tested and is commercially available, we developed troubleshooting and emergency intervention (Multimedia Appendix 1) protocols that were given to all participants. The greatest concern that we felt had to be addressed was that in an immersive, remote setting where patients are addressing topics with significant risk of inducing posttraumatic stress disorder, depression, and anxiety, it was important that they could find support immediately and at any time. In addition, given the new technologies we were dealing with, it was important that tech support was also available at any point during the session.

Statistical Analysis

Quantitative Analysis

Descriptive statistics were obtained for each of the categorical variables pertaining to participant characteristics, including age, type of cancer diagnosis, documented gender identity within the electronic medical record (EMR), documented race and ethnicity within the EMR, and documented insurance status within the EMR. Attendance data were collected for each of the participants within each support group to evaluate attendance rates. Participants' scores for the Connor-Davidson Resilience Scale and each of the PROMIS domains (positive affect, anxiety,

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and depression) before and after the support group will be compared using a 2-tailed *t* test with 95% CI. All statistical analyses will be completed using Stata (version 16.0; StataCorp).

Qualitative Analysis

Participant responses of the open-ended questions during the brief in-person interviews were recorded as field notes by the research coordinator and organized in a secure Word document. Using a grounded theory approach [32], we will use the rigorous and accelerated data reduction (RADaR) technique [33], which is used to organize, reduce, and analyze qualitative data. The RADaR technique is a rigorous, systematic approach to qualitative analysis that provides an expedited and user-friendly way of organizing, reducing, coding, and analyzing qualitative data. The RADaR technique is often used to manage smaller pilot projects that use grounded theory [27].

Results

Enrollment

Between November 5, 2019, and July 8, 2021, a total of 20 participants aged 17-20 years were approached to be a part of this study, and 16 agreed to participate. Reasons cited for not agreeing to participate included the lack of time and lack of interest. No patients expressed concerns around using the VR headset itself.

The enrollment of group 1 was completed in November 2019, in February 2020 for group 2, in August 2020 for group 3, and in May 2021 for group 4. Of note, groups 3 and 4 were enrolled amid the COVID-19 pandemic, and group 2 was recruited just before and subsequently ran during the pandemic. This resulted in prolonged times between group enrollments due to risks of COVID-19 being spread by unnecessarily returning to clinic for study consents, orientation, and headset exchange.

Sample Demographics

The patients who enrolled had a median age of 19 (IQR 17-20) years. Overall, 62% (n=10) were male and 31% (n=5) were female, with 1 (6%) patient who identified as transgender female. In total, 5 (31%) participants identified as Hispanic, 1 (6%) identified as non-Hispanic Asian, 3 (19%) identified as non-Hispanic Black, 6 (38%) participants identified as non-Hispanic White, and 1 (6%) identified as other, as described in Table 1.

Table 1. Participant demographics and characteristics (n=16).

Characteristics	Value
Age (years), median (IQR)	19 (17-20)
Documented gender identity in EMR[a], n (%)	
Male	10 (62)
Female	5 (31)
Transgender female	1 (6)
Documented race and ethnicity in EMR, n (%)	
Hispanic (all races)	5 (31)
Non-Hispanic Asian	1 (6)
Non-Hispanic Black	3 (19)
Non-Hispanic White	6 (38)
Other	1 (6.)
Documented insurance status in EMR, n (%)	
Medicaid	7 (44)
Private	9 (56)
Type of cancer or disorder, n (%)	
Hematologic malignancies or bone marrow failure	8 (50)
Solid tumor	6 (38)
Central nervous system tumor	2 (12)

[a]EMR: electronic medical record.

Participation rates for each of the groups are shown below in Table 2. Group 1 was only scheduled for 4 total sessions, and future groups were increased to 6 sessions due to overwhelming requests from the first group to increase the total number of sessions. Of note, 1 of the participants in group 2 (g2p2) had a lengthy hospitalization shortly after they consented to this study. Given the inability of the hospital internet bandwidth or hot spot to support the system, they were unable to participate in any of the sessions—this hurdle was later remedied with a long-term evolution hot spot. Additionally, part of group 2's and all of group 3's and group 4's sessions occurred during the COVID-19 pandemic. Further, 45% (10/22) of sessions needed to be postponed by a week or more, but only 18% (4/22) by more than 2 weeks.

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Defining retention as attending any of the first 3 sessions in combination with any of the last 3 sessions, all but 2 patients met the criteria (g3p2 and g4p4) for a retention rate of 86.7% (SD 0.35%). Patients g3p2 and g4p4 described scheduling issues and the lack of interest as reasons for attrition.

Table 2. Participation rates.

Group and participant ID	Sessions attended, n (%)
Group 1 (n=4 sessions)	
g1p1	4 (100)
g1p2	3 (75)
g1p3	4 (100)
g1p4	4 (100)
Group 2 (n=6 sessions)	
g2p1	5 (83)
g2p3	3 (50)
g2p4	5 (83)
Group 3 (n=6 sessions)	
g3p1	4 (67)
g3p2	1 (17)
g3p3	5 (83)
g3p4	6 (100)
Group 4 (n=6 sessions)	
g4p1	4 (67)
g4p2	5 (83)
g4p3	3 (50)
g4p4	2 (33)

Discussion

Principal Findings

This protocol review describes the implementation of social VR support groups for a rare disease population with substantial participation (72.8%, SD 25.7%) and retention rates (86.7%, SD 0.35%). These rates compare favorably to historical data describing outpatient mental health attrition rates ranging widely with a range of 25% to 75% in children and adolescents [34]. Prior to the launch of our VR-based approach, and despite expressing a desire to participate in support groups, our adolescent and young adult cancer social worker was unable to convince any significant number of patients to return to the hospital for in-person groups. With the VR group option, however, we had a generally successful experience with manageable hurdles to implementation. No sessions needed to be canceled due to purely technical issues. We had no patients refuse to participate due to consent concerns and enthusiastic patients and families expressed a desire for expanded groups to include more sessions as well as requests for opportunities for caregivers to participate in their own groups.

The process of protocol development and review, however, have revealed an academic and health care system unprepared for the incoming wave of digital health interventions and subsequent implementation. PRCs and IRBs are designed to be led by experts and laypersons versed in the proposed interventions and familiar with the expected timelines and processes required for a smooth launch. These committees are required and helpful check points prior to the launch of any clinical trial at the Yale Center for Clinical Investigation. As this trial involved cancer patients with cancer, these committees have had substantial experience reviewing, recommending amendments to, and launching clinical trials involving early and late phase pharmaceutical trials. A supportive care trial involving cutting edge digital technologies requires an entirely different set of experience and skills. As a result, approval for what is a relatively benign intervention took more than 9 months, multiple protocol revisions, expansion, and the need to incorporate multiple outside entities including technology and psychologic experts to ensure scientific merit and safety. Due to this experience, we recommend an ad hoc digital health subcommittee be put in place at institutes interested in pursuing such digital interventions.

At a minimum, we propose that a digital health intervention protocol review and human protection committee would incorporate the expertise of digital privacy experts, software or hardware developers, and psychologists versed in the effects of immersive reality. To expedite a review, this committee would act as a first line, prior to submission to the PRC and subsequently the IRB. Given the inherent risks of health data (including biometric data) collection during the use of digital

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interventions, the committee would ensure appropriate security protocols are in place to ensure HIPAA compliance. With the increasing disconnects in the speed between technologic advancement and academic processes, they would additionally ensure that the technologies being studied are the most up to date and not soon to be outdated. Finally, this committee would be cognizant of the significant potential psychologic effects of immersive technologies and be prepared to address them.

Additional institutional barriers experienced included in-hospital networking protocols that limited the use of certain security approaches used by Foretell's software. Subsequently, the hospital wireless network was not a viable solution. Fortunately, we were able to secure a reliable (long-term evolution) connection via mobile hot spot router, which was used for connection when study participants were in the hospital.

These barriers revealed challenges that may arise in attempting to implement similar interventions in more rural areas and counties other than the United States. While network speed demands are not high (we found no difficulty running sessions with upload and download speeds in the 10-30 Mbps range), reliability and stability are important. We anticipate that other high-income countries with a robust and reliable internet infrastructure should be successful in similar approaches. The expansion of this study will be looking specifically at non–English-speaking populations, rural populations, and populations defined as low socioeconomic status.

A noted limitation to this study is that participants were told that they may be observed by a team member other than the facilitator (PI or research assistant) during their sessions. This may have influenced how a participant behaved or what was said during a session. To mitigate this concern, observers were made invisible during the sessions and there was no indication of whether the observer was present or not. Given that the social worker themselves was present, visible, and participating in avatar form in every session, we suspect that any bias that may have been introduced by knowing an additional observer may be there was likely mitigated.

A final barrier to safe implementation of the above protocol was safe disinfection of the headsets themselves. This study coincided with the COVID-19 pandemic, so finding a safe way to continue offering support groups was essential. Concurrent with this project, we conducted an examination of VR equipment disinfection protocols, the results of which appear in the *Journal of Medical Internet Research* [31]. Despite initial excitement over ultraviolet disinfection, isopropyl alcohol or quaternary ammonium products were ultimately found to be most effective. Future studies should examine best uses and methodologies for an ultraviolet disinfection approach.

Conclusions

Here we have presented an in-depth review of the creation and implementation of a novel, social VR-based intervention for an underserved, rare disease group. We have demonstrated feasibility through participation and retention and described pain points in implementation including the need for appropriate review committees, intrahospital network infrastructure, and disinfection needs.

These results and experiences have given us confidence to expand the trial to additional centers throughout the United States. The greater number of patients in more diverse populations with cancer will allow us to better assess feasibility in non–English-speaking populations, rural populations, and populations with low socioeconomic status. The expanded numbers will also offer greater power to identify effects on fear, anxiety, depression, resilience, and feelings of connectedness. In addition, we have started groups with the Yale Gender clinic, enrolling transgender and gender-diverse patients to examine the intervention's effects on such measures as gender dysphoria, psychological flexibility, and self-esteem.

As immersive technologies and opportunities for innovative telehealth models emerge, it will be important to find their appropriate places within the clinical landscape. Populations with rare diseases seeking peer-based social support appear to be a viable and enthusiastic group with which to start.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Emergency procedures.
[DOCX File , 14 KB - resprot_v12i1e48761_app1.docx]

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Abbreviations

EMR: electronic medical record
HIPAA: Health Insurance Portability and Accountability Act
IRB: institutional review board
PI: principal investigator
PRC: Protocol Review Committee
PROMIS: Patient-Reported Outcomes Measurement Information System
RADaR: rigorous and accelerated data reduction
VR: virtual reality

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Protocol

Effects of a Virtual Reality Game on Children's Anxiety During Dental Procedures (VR-TOOTH): Protocol for a Pilot Randomized Controlled Trial

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Abstract

Background: Dental fear and anxiety (DFA) is a condition that affects approximately one-quarter of children and adolescents. It is a significant cause for pediatric patients to avoid dental care later in adulthood. Lack of patient cooperation due to DFA can create an environment of stress, often obligating dentists to end appointments prematurely and consider alternative pharmacological treatment options. Virtual reality (VR) use during dental care, providing an immersive experience through sensory stimuli, is potentially an additional nonpharmacologic tool to better manage DFA in children with special health care needs (SHCN) undergoing dental procedures.

Objective: This pilot study aims to assess the feasibility and acceptability of VR immersion as a tool to reduce DFA in pediatric special needs patients undergoing dental procedures. The study also aims to gain insight on parent and health care provider perspectives on the use of VR during dental appointments.

Methods: This pilot randomized controlled trial study will follow a parallel design including 2 groups: a control group (clinic's standard care using a wall TV) and an experimental group (using a VR game). We will randomize 20 participants to either group. Recruitment will be carried out at the dental clinic of the Centre Hospitalier Universitaire Sainte-Justine, a tertiary-quaternary care center that mostly serves pediatric patients with SHCN. The primary outcome will be patient recruitment rates and completion rates of planned procedures. DFA in children will be assessed using both an observation-based proxy assessment with the Venham Anxiety and Behavior Rating Scale and physiological assessments using parameters such as change in heart rate and levels of salivary alpha-amylase as a stress biomarker before and 10 minutes after the procedure. Sociodemographic characteristics, measures of the levels of parent and health care professional satisfaction, occurrence of side effects, and any deviation from normal procedure length will also be collected. Descriptive statistics, nonparametric tests, and effect sizes will be used for demographic and clinical variables and to present parent and health care professional satisfaction levels as well as procedural time.

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Results: This study will be conducted from May 2023 to May 2024, with results expected to be available in December 2024.

Conclusions: The pilot study will provide insight on the feasibility and acceptability of VR use in clinical dentistry to reduce DFA for pediatric patients with SHCN. This study will guide future research on VR use in pediatric dentistry and can serve as a framework for a larger randomized clinical trial.

Trial Registration: ClinicalTrials.gov NCT05898100; https://classic.clinicaltrials.gov/ct2/show/NCT05898100

International Registered Report Identifier (IRRID): DERR1-10.2196/49956

(JMIR Res Protoc 2023;12:e49956) doi:10.2196/49956

KEYWORDS

virtual reality; pediatrics; children; dentistry; procedures; fear; anxiety; child; pediatric; dentist; dental; tooth; teeth; oral; anxious; immersion; immersive; RCT; randomized; controlled trial

Introduction

Dental fear and anxiety (DFA) is a condition that affects approximately 13.3% to 29.3% of children and adolescents and is a significant cause of patients avoiding dental care [1,2]. In children, DFA is also associated with a lower oral health–related quality of life [3]. Although the etiology of DFA is multifactorial, often stemming from both exogenous and endogenous sources, a previous traumatic dental experience is the most predictive factor for DFA [4,5]. A study by Ten Berge et al [6] stated that the majority of DFA experienced by adults stems from poor dental experiences as children. These findings highlight the importance of keeping each dental experience a positive one for pediatric patients. Short-term distress during appointments that is not managed properly can accumulate into poor dental experiences and, in turn, reinforce DFA into adulthood [7]. The long-term effects of these poor dental experiences as children can lead patients to avoid seeking proper dental care in the future [8].

Dental patients with special health care needs (SHCN) are defined as patients requiring additional time and special consideration when receiving treatment due to medical, physical, cognitive, or developmental conditions [9]. The population includes children with behavior (eg, autism spectrum, anxiety, attention deficit hyperactivity disorder), congenital (eg, trisomy 21, congenital heart disease), developmental (eg, cerebral palsy), systemic (eg, childhood cancer, sickle cell disease), or cognitive disorders (eg, intellectual disability) [9]. Children with SHCN face more barriers to dental care than the overall population [9]. Barriers include external factors (transportation, cost, inadequate dental facilities) and internal factors (fear and poor tolerance) [9,10]. Many children with SHCN are cared for by dentists in the community or, more often, in hospital dental clinic settings [9]. They experience more DFA, which can result in more difficult dental visits [9]. The importance of providing well-rounded care and making each dental visit a positive one for pediatric patients with SHCN is crucial for promoting a good oral health routine, as well as improving their oral health transitioning into adulthood [9].

Understanding and assessing DFA in children are important for delivering successful dental care with high satisfaction in this age group. Among the vast number of assessment method options available today, self-report assessment, parental proxy assessment, observation-based assessment, and physiological assessment are the 4 major types for DFA in children [11]. In the recent literature, salivary alpha-amylase, an enzyme correlated with both adrenaline and noradrenaline, has also been used as a marker for autonomic nervous system activity and stress [12].

Factors in the dental setting that trigger DFA include the loud sounds of dental instruments, presence of strangers examining the oral cavity, and the fear of pain [13]. Of these, the biggest trigger of DFA is the anticipation and use of local anesthesia injections [5,13]. Although necessary to provide adequate pain control during certain treatments, local anesthesia injections are understandably uncomfortable [5]. For children, the initial injection combined with the feeling of numbness during the procedure is especially distressing [5]. Pharmacological agents, combined with light to moderate sedation, or general anesthesia can also be considered for noncooperative patients; these options are often time-consuming and confer a higher cost as well as health risk [1]. In the current literature, audiovisual distractions such as tablets or TV screens have been used as additional distraction techniques rather than just traditional tell-show-do distraction, with overall positive results [14]. However, there is a lack of interactivity with these techniques, and as a result, they produce less immersive environments with distraction for the children [15]. Lack of patient cooperation due to DFA often obliges dentists treating pediatric populations to end appointments prematurely and sometimes without completing the planned procedure. Treating an anxious and fearful patient can create an environment of stress for the clinician and associated dental team [1].

Particularly when treating children with SHCN, extra time and tools are needed to provide comfortable dental care. Depending on the child's diagnosis, some have hypersensitivity to external stimuli such as loud noises, aversion to specific tastes, and difficultly straying from usual daily routines [16]. A study by Pagano et al [16] showed that the use of augmented reality was well suited for patients with autism spectrum disorder in preparation for their dental visits. Additionally, a systematic review by Cunningham et al [17] concluded that virtual reality (VR) is a promising tool in dentistry, especially for the population of children with autism spectrum disorder or other special needs.

VR is defined as an artificial environment that is experienced through sensory stimuli [18]. It is a modern tool that can immerse patients in a "game" or "world." Commonly used in

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the medical field to help distract patients during unpleasant procedures such as vaccination, cast removal, and short bedside interventions, it has proven to be effective at decreasing procedural anxiety and providing a more positive experience for patients [19]. Among the limited existing literature, the use of VR to manage anxiety during dental procedures has shown positive results. A recent clinical trial by Alshatrat et al [15] concluded that VR is an effective tool for reducing anxiety in young children during dental procedures. Moreover, a previous study by Ram et al [20] showed that both parent and clinician satisfaction was high using audiovisual glasses as distraction for children during dental treatments. However, clinical VR research in pediatric dentistry is limited, especially with special needs populations. VR use in pediatric dentistry offers the potential to add a nonpharmacologic tool to a clinician's toolbox. A clinical study on the use of VR during dental appointments with pediatric patients with SHCN would allow a better understanding of the effect of VR on DFA in this population and possibly facilitate dental procedures.

Aims of the Study

The aims of the study are twofold: (1) assess the feasibility and acceptability of VR immersion as a tool to reduce DFA in pediatric patients with SHCN undergoing dental procedures and (2) gain insight on parent and health care provider perspectives on the use of VR during dental appointments.

Objectives

The primary research objectives are to determine (1) the feasibility and acceptability of VR distraction for children with special needs requiring dental procedures, (2) compare parent and health care professional satisfaction levels between the VR distraction group and the clinic's standard mounted TV showing cartoons, and (3) observe the preliminary effects of VR distraction on reducing patient anxiety during dental procedures compared with standard nonpharmacological behavior management.

The secondary objectives of this study are to compare the following between the VR distraction group and the clinic's standard mounted TV showing cartoons: (1) physiological parameters (pulse and oxygen saturation), (2) the occurrence of side effects, (3) dental procedure length, (4) the number of retakes of dental procedures due to DFA, and (5) salivary amylase levels.

Methods

Design

This randomized controlled trial pilot study will follow a parallel design including 2 groups: a control group (mounted wall TV playing cartoons) and an experimental group (VR intervention during the dental procedure).

Sample and Setting

This pilot will include 20 participants, totalling 10% of the expected 200 children to be included in the final study. All participants in this pilot study will be allocated in an equal ratio of 10 per group. Recruitment will be carried out at the dental clinic of the Centre Hospitalier Universitaire Sainte-Justine, a pediatric hospital in Montreal, Canada. This clinic mostly serves patients with SHCN such as craniofacial abnormalities, autism spectrum disorder, cancer, and others. Pediatric patients with SHCN represent around 80% of the total clientele of this clinic, while the rest is comprised of otherwise healthy patients with dental traumas and other dental emergencies.

Inclusion Criteria

Children participating in this study will have to meet the following criteria: (1) aged 6 years to 17 years; (2) recommended by the dentist to participate; (3) required to undergo any dental procedure; and (4) accompanied by a parent or a legal guardian who can understand, read, and write in either French or English.

Exclusion Criteria

Participants will be excluded from this study if they meet the following criterion: have epilepsy or any other conditions preventing them from using VR. Non-SHCN patients will not be excluded from the study, but this information will be collected. Patients with a strong history of motion sickness will not be excluded from this study, but this information will be collected and additional monitoring will be provided. The use of medication (opioid and non-opioid analgesic, antiemetic, anxiolytic, or any other drugs) prior to the procedure within the last 4 hours will not exclude participants from this study, but this information will be collected during the pre-intervention questionnaire. Patients having undergone previous dental procedures in the past will not be excluded.

Randomization and Allocation

Randomization will be done through the electronic REDCap (Vanderbilt University) system. Allocation to either intervention will be randomized by an independent biostatistician from the Applied Clinical Research Unit (URCA). To equalize participants in both arms, permuted block randomization with a randomly selected block size design will be used to randomize participants to the intervention [21]. Access to the randomization list will only be granted to the biostatistician, and allocation will be concealed using REDCap to reduce selection bias.

Interventions

Control Treatment

The control group will only receive a care-as-usual approach. This includes a television mounted on the wall showing cartoons and the use of pharmaceutical treatment during the procedure such as the use of injected local anesthesia. In the event of noncooperation during the appointment, any retakes or rescheduling of appointments will be compiled by the resident dentist. One parent will be permitted to be present in the room during the procedure as part of the clinic's usual protocol, and their presence will be recorded. Children allocated to the control group will be offered the possibility to try the VR game after the study period if they choose to do so.

Experimental Treatment

The experimental group will be provided the VR video game "Dental Dream" designed specifically for this study. Pharmaceutical treatment, such as the use of injected local

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anesthesia, during the procedure will be used if the procedure requires it. Children will be able to play for the entire duration of the dental procedure. “Dental Dream” aims to reduce anxiety in children aged 6 years to 17 years old by means of immersive distraction. The VR headset offers children the ability of viewing the game they are playing in real time while simultaneously obstructing the partial view they would normally have of the procedure. In the event of noncooperation during the appointment, any retakes or rescheduling of appointments will be compiled by the resident dentist. One parent will be allowed in the room during the dental procedure, and their presence will be recorded.

Developed by Paperplane Therapeutics, “Dental Dream” is an easy-to-play, immersive VR video game tailored for the pediatric population and approved by a team of health care professionals in pediatric care. The simplified no-success game allows it to be enjoyable no matter the child’s video game experience, and its point-and-shoot arcade style also allows for easy understanding and fast immersion in the game. Positioning is normally a challenge for VR as it is very position-specific, needing a semi-fowler's angle of 30°-45° to function properly. “Dental Dream” was designed specifically for this study with the specific horizontal position needed for dental procedures in mind. “Dental Dream” is designed to be supported by the Pico Neo 4 VR headset.

Children playing the game will be immersed through a virtual environment where they will be able to use a remote in one hand to target floating and static objects in the VR game. The objective of the game is to throw balls at targets such as balloons, trolls, and diamonds to gain points. The “Dental Dream” game uses an on-rail feature guiding the child through space with a new eye tracking technology developed within the headset in order to help the child navigate the same way head movement normally would in classic VR, making it easier for dental procedures where head movement is restricted. These features also aim to reduce cybersickness.

The preliminary version of the VR headset has been tested in clinic on staff—the size and volume of the Pico Neo 4 headset do not hinder delivery of dental care as it is smaller than usual VR headsets.

Study Time Points

Sociodemographic data will be assessed before the intervention at baseline (T0) to establish a baseline using a simple questionnaire completed by the parent or legal guardian present while sitting in the waiting room. Salivary alpha-amylase samples will be collected at T0 and after the intervention/procedure (T2; Multimedia Appendix 1). Measures of specific dental procedure–related anxiety and uncooperative behavior will be assessed at T0, during the procedure (10 minutes from the start; T1), and immediately after the end of the procedure (T2). Physiological parameters will be measured at T0, during the intervention (T1), and T2. Data on occurrence of side effects will be assessed and monitored at all times for the duration of this study. All clinical monitoring will be performed by the dental resident on site. Measures of parent or legal guardian and health care professional satisfaction will be assessed at T2.

Measures and Outcomes

Sociodemographic Characteristics

Sociodemographic characteristics will be provided by the parent or legal guardian in the waiting room prior to the intervention and will include information such as age, sex, ethnicity, and the procedure needed. Other information will also include any medication taken within the last 24 hours (name, class, and posology) that could have an impact on the conclusions of this study.

Primary Outcomes

To measure feasibility and patient acceptability, we will record patient recruitment rates, completion rates of planned procedures, and satisfaction. As this is a population of children with SHCN, we estimate 50% of patients will agree to participate during recruitment, and we expect a completion rate of planned procedures of 75%.

Measures of Primary Outcomes

Parent or legal guardian satisfaction with the intervention will be assessed using a visual analog scale (VAS; 0-10, where 0 is very dissatisfied and 10 is very satisfied) and the question recommended by the Pediatric Initiatives on Methods, Measurement and Pain Assessment in Clinical Trials (PedIMMPACT): “Considering anxiety relief, side effects and emotional recovery, how satisfied were you with the intervention used to manage DFA experienced by your child?” [22] (Multimedia Appendix 2). The parent or legal guardian will respond according to their satisfaction level.

Health care professional satisfaction with the intervention will be assessed using a VAS (ranked from 0-10, where 0 is very dissatisfied and 10 is very satisfied) as well as a 6-question satisfaction questionnaire (each answer will be given a score of 1, 2, 3, or 4 based on the choice of answer: Fortement en désaccord, En désaccord, En accord, Fortement en accord, respectively) and will result in a final score between 6 and 24 (Multimedia Appendix 3).

DFA scores will be evaluated using the Venham Anxiety and Behavioral Rating Scale [23]. It is an observation-based assessment by proxy for DFA and is among the most frequent behavior scoring models for DFA [23] (Multimedia Appendix 4). It is composed of 2 scales used to assess the anxiety and uncooperative behavior of children in the dental setting. The scale is also found under the name Clinical Anxiety Scale/Uncooperative Behaviour Rating Scale or Venham Clinical Cooperation Scale and Venham Clinical Anxiety Scale and has been used as an anxiety rating scale in other studies that have evaluated the efficacy of VR distraction for the management of DFA [11,24,25]. Both consist of a 6-point scale, with 6 defined behavioral levels that range from 0 to 5. The highest score defines the highest anxiety level or lack of cooperation [23]. A high degree of reliability has been observed for both scales, even for an untrained observer [23,26]. The scale points are measured by proxy and anchored in objective, specific, and readily observable behavior. The research assistant indicates the participant’s behavior by picking a number from 0 to 5 according to the scale; thus, for each participant, 2 scores

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on the levels of anxiety and cooperation with the dental procedure will be obtained at T0, T1, and T2. Venham et al [27] reported that the scale is a reliable and valid scale and provides an interval-level measurement. The scale has been a useful instrument for assessing a child's response to dental stress. The anxiety score and uncooperative score will both be evaluated at T0 (baseline), during the procedure at 10 minutes after the beginning of the procedure (T1), and after the completion of the procedure (T2). The videos will be reviewed by 2 independent evaluators who will provide a score for the anxiety of each child during the procedure. Scores will be compared afterwards. The same scales will be used during observation of the child's behavior using the video recordings by a separate member of the team. Both evaluations (when available depending on consent) will allow for inter-rater agreement to be calculated.

Secondary Outcomes

The secondary outcomes will be (1) changes in physiological parameters (such as heart rate and pulse oximetry) during and after the intervention compared with baseline, (2) occurrence of side effects, (3) deviation from the normal procedure length, (4) rescheduling of procedures in the event cooperation is impossible, and (5) salivary amylase levels.

Measures of Secondary Outcomes

The secondary outcomes will be measured as described here. Physiological parameters will be continuously measured using the Nellcor pulse oxygen saturation meter (Covidien), an approved and validated device. The occurrence of side effects will be collected from arrival on site to discharge from the study using a checklist of common side effects experienced while using VR and also related to dental medication. The length of the procedure will be measured and collected for every participant and will be compared with the average duration for a similar procedure that will have been measured prior to the study by the clinic's personnel. Rescheduling of procedures in the event that cooperation is impossible will be noted. Salivary amylase levels, as a stress biomarker, will be measured before and after the dental procedure as described in the following section.

Measurement of Salivary Amylase

Saliva samples will be collected from all children in this study at 2 different study time periods: before (T0) and after (T2) the intervention. Salivary alpha-amylase has been recognized and validated as a reliable and specific marker for autonomic nervous system activity and has been proposed as an alternative biomarker for stress [12]. Alpha-amylase sampling has been performed in previous studies to evaluate DFA for children undergoing dental procedures [28-30]. Alpha-amylase, as a salivary biomarker, can be considered an important and noninvasive tool for assessment of anxiety-related events, such as dental extraction and other treatment, for children [28,31].

Salivary samples will be collected using a sterile dental cotton swab from under the tongue 10 minutes before and 10 minutes after the procedure and stored immediately within a sterile vile in a research-specific on-site freezer. Samples will be collected by the dental resident and taken to the laboratory. Results will be entered in REDCap for analysis after the study.

Table 1 provides an overview of which questionnaires will be answered by which respondents during the study.

Table 1. Questionnaires and corresponding respondents.

Questionnaires	Respondents
Parent or legal guardian satisfaction	Parents or legal guardians
Health care professional satisfaction	Health care professional
Anxiety score, physiological parameters	By proxy through research assistants

Study Proceedings Including Data Collection

Participants will be identified by the resident dentist through the appointment scheduling system as requiring any dental procedure. Since DFA can arise from multiple different procedures such as simple cleaning to teeth extraction, dentists at the clinic will identify possible participants to include based on their cooperation, personality, and fears. An individual independent to the study will review consent with participants and parents. Written consent by the parents or legal guardian—including the child's assent—will be obtained on arrival at the clinic the day of the procedure while completing the preprocedural questionnaire.

After verifying that the participant meets all the inclusion and exclusion criteria, the dental resident will log into REDCap only 10 minutes before the start of the intervention to minimize the risk of bias toward the intervention and to obtain the group allocation and announce it to the participant. Because of the nature of VR, no blinding of staff, participants, and parents or legal guardians will be possible. Baseline data collection prior to the dental procedure, including the sociodemographic questionnaire, recording of physiological parameters, and salivary alpha-amylase sampling, will take approximately 15 minutes to complete. The VR headset will be adjusted for the child's size, and approximately 5 minutes will be allotted for children to familiarize themselves with the room, equipment, and game before the start of the procedure.

The intervention will last the entire time of the dental procedure, and the duration will be recorded for every patient. DFA assessment by proxy using the Venham Anxiety and Behavioral Rating Scale will be performed on site by the dental resident present and will also be filmed (if consent was given) to be evaluated by another member of the team at a later date.

As per the clinic's protocol, if a child becomes restless and cooperation is impossible, the child will be held by his or her parents for the remaining duration of the procedure if it cannot be safely stopped at that time or if the procedure is considered

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an emergency. If the procedure can be safely stopped, rescheduling will be discussed with the parents including the possible need for sedation. The involvement of parents will be recorded as well as any other distractions used during treatment such as the use of stickers, teddy bears, or music.

All side effects and medication used will be recorded. The former will be transmitted to the ethics committee if needed. As VR has the potential to cause nausea, dizziness, and motion sickness, should participants experience any of these, they will be dealt with according to the clinic's protocols. If participants experience adverse side effects and the attending dentist and dental assistant have been informed, the treatment will be safely discontinued. All instruments in the mouth will be removed. The VR device will be removed from the participant. The dental chair will be placed in a comfortable position, and the patient will rest until they feel comfortable and recovered. The option of continuing the treatment (without the VR headset) or postponing the treatment to another day will be discussed. Postprocedure salivary alpha-amylase sampling and completion of questionnaires regarding parent and health care professional satisfaction levels after the dental procedure will take approximately 20 minutes. Equipment used by children will be disinfected before the next participant arrives.

Statistical Analysis

Analysis will be conducted using the SAS (SAS Institute) statistical analysis software (version 9.4). Descriptive statistics, by treatment, will be conducted for demographic and clinical variables and will be used to present sociodemographic and clinical data, parent and health care professional satisfaction levels, and procedural time. Due to a small sample size, we will also assess effect sizes.

For the pilot project, we plan to perform descriptive analyses of the sample as well as comparative analyses between the 2 groups. Nonparametric tests for procedural type, age, parental presence, parental and health care satisfaction levels, and baseline (T0) anxiety score measurement will be used to assess the composite outcome for mean salivary cortisol level and mean difference in anxiety score (using the Venham Clinical Cooperation Scale and Venham Clinical Anxiety Scale) between the experimental and control groups at T2. Analyses will be carried out according to the intention-to-treat principle, with a significance level (α) of .025, considering Bonferroni's correction.

For secondary outcome analyses, nonparametric tests adjusted for procedural type, age, and parental presence will be used to assess the mean procedural length at T2 using the VAS and 6-item tailored questionnaire, respectively. Comparison of dichotomous variables including the necessity for procedural retakes, use of other nonpharmacological interventions, and the occurrence of side effects will be assessed using the Cochran-Mantel-Haenszel test.

The study data will be recorded in the REDCap system belonging to URCA. The data manager associated with URCA and independent of the study will be responsible for the storage of the recorded data. However, a URCA biostatistician independent of the study will be responsible for the data analysis. The data analysis plan will be discussed with the principal investigator (SLM). Interjudge correlations will be conducted for the video tape analysis. Two judges will independently rate the anxiety measure on the videotapes. Subsequently, we will conduct intraclass correlation coefficient analyses to compare the scores for each of the recruited patients between the 2 judges.

Ethical Considerations

Approval by the Ste-Justine Hospital research board of ethics (#2023-4985) was obtained in March 2023. An individual independent to the study will review consent with participants and parents. The information and consent form will be signed by one of the parents on the day of the visit. Upon enrollment, children are assigned codes used on all data collection forms to protect their confidentiality. Only the dental resident and the principal investigator will have access to the log that links the study codes to the participants. Patient-identifying information is kept separate from the case reports and is linked to study enrollment by a study ID number. The consent form also identifies all the information that may be collected during this study and details the use of videos that may be needed for further behavior evaluation using proxy scales with the possibility to opt out. All data collected by paper forms the day of the intervention will subsequently be transferred into REDCap. No recording of the child's screen nor their game inputs will be collected. The intervention will be filmed and recorded, as the use of proxy scales will need further evaluation of the child's behavior. As per usual, all information such as links between patient identifiers to study ID and paper copies of forms and questionnaires will be kept stored and double locked for 7 years (starting from the end of trial) at the principal investigator's office at the research center.

Results

This study will be conducted from May 2023 to May 2024, with results expected to be available in December 2024. The findings of the study will be disseminated through peer-reviewed publications.

Discussion

The results of the study will allow us to gain insight on the feasibility and acceptability of the intervention and on the satisfaction of parents and health care professionals regarding the use of VR as a tool to reduce anxiety in pediatric dentistry, especially in children with SHCN. Due to the limited clinical studies about VR and pediatric SHCN populations in dentistry, this pilot study will guide potential future, larger, clinical trials.

Challenges and Limitations

Individual experience with VR varies immensely, as some children may love to have an active distraction during dental treatment, while others may prefer to be present in the moment. As such, we acknowledge that the acceptance of VR use during dental treatment is a tool that may be useful for a certain population within a patient pool. Like all other distraction tools used in the dental setting, proper screening and patient selection are crucial during treatment planning. Moreover, the game

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design used during the study was created specifically for our study, so the results of our study may not be able to be extrapolated to a different setting with a different game design.

Conclusion

The results of the study could be used to help us to better understand how VR distraction can reduce DFA in children with special needs and the acceptability of its use by parents, patients, and health care professionals during dental procedures. The results can be used as preliminary data for a future clinical trial on the use of VR in dentistry with special needs patients. In addition, this study will possibly allow for more comfortable and less traumatic dental care for pediatric patients. By exploring new avenues for behavior and anxiety management tools for pediatric dentistry, this study and its results will provide improved patient-centered care.

Data Availability

Once the pilot study is completed, the authors confirm that the data supporting the findings of this study will be available through the clinicaltrials.gov repository. In addition, data will be available within a future publication and its supplementary materials.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Study time points and data collection.
[DOCX File , 15 KB - resprot_v12i1e49956_app1.docx]

Multimedia Appendix 2
Parental satisfaction questionnaire.
[DOCX File , 43 KB - resprot_v12i1e49956_app2.docx]

Multimedia Appendix 3
Healthcare professional satisfaction questionnaire.
[DOCX File , 16 KB - resprot_v12i1e49956_app3.docx]

Multimedia Appendix 4
Venham anxiety and behavioral rating scale.
[DOCX File , 20 KB - resprot_v12i1e49956_app4.docx]

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Abbreviations

DFA: dental fear and anxiety
SHCN: special health care needs
URCA: Applied Clinical Research Unit
VAS: visual analog scale
VR: virtual reality

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Protocol

Behavioral Activation for Comorbid Depression in People With Noncommunicable Disease in India: Protocol for a Randomized Controlled Feasibility Trial

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Abstract

Background: The increasing burden of depression and noncommunicable disease (NCD) is a global challenge, especially in low- and middle-income countries, considering the resource constraints and lack of trained human resources in these settings. Effective treatment of depression in people with NCDs has the potential to enhance both the mental and physical well-being of this population. It will also result in the effective use of the available health care resources. Brief psychological therapies, such as behavioral activation (BA), are effective for the treatment of depression. BA has not been adapted in the community health care services of India, and the feasibility of using BA as an intervention for depression in NCD and its effectiveness in these settings have not been systematically evaluated.

Objective: Our objective is to adapt BA for the Indian NCD context and test the acceptability, feasibility, and implementation of the adapted BA intervention (BEACON intervention package [BIP]). Additionally, we aim to test the feasibility of a randomized controlled trial evaluation of BIP for the treatment of depression compared with enhanced usual care.

Methods: Following well-established frameworks for intervention adaptation, we first adapted BA (to fit the linguistic, cultural, and resource context) for delivery in India. The intervention was also adapted for potential remote delivery by telephone. In a randomized controlled trial, we will be testing the acceptability, feasibility, and implementation of the adapted BA intervention (BIP). We shall also test if a randomized controlled feasibility trial can be delivered effectively and estimate important parameters (eg, recruitment and retention rates and completeness of follow-up) needed to design a future definitive trial.

Results: Following the receipt of approval from all the relevant agencies, the development of the BIP was started on November 28, 2020, and completed on August 18, 2021, and the quantitative data collection was started on August 23, 2021, and completed

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on December 10, 2021. Process evaluation (qualitative data) collection is ongoing. Both the qualitative and quantitative data analyses are ongoing.

Conclusions: This study may offer insights that could help in closing the gap in the treatment of common mental illness, particularly in nations with limited resources, infrastructure, and systems such as India. To close this gap, BEACON tries to provide BA for depression in NCDs through qualified NCD (BA) counselors integrated within the state-run NCD clinics. The results of this study may aid in understanding whether BA as an intervention is acceptable for the population and how feasible it will be to deliver such interventions for depression in NCD in South Asian countries such as India. The BIP may also be used in the future by Indian community clinics as a brief intervention program.

Trial Registration: Clinical Trials Registry of India CTRI/2020/05/025048; https://tinyurl.com/mpt33jv5

International Registered Report Identifier (IRRID): DERR1-10.2196/41127

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KEYWORDS

adaption; behavioral activation; cancer; cardiovascular disease; cultural; culture; depression; diabetes; feasibility; India; language; linguistic; mental disorder; mental health care; mental health; non-communicable disease; Patient Health Questionnaire; PHQ; randomized controlled feasibility trial; respiratory; retention; social; stroke; therapy; treatment

Introduction

Noncommunicable diseases (NCDs), also known as chronic diseases, tend to be of long duration and are the result of a combination of genetic, physiological, environmental, and behavioral factors. NCDs are the leading cause of mortality in the world, much of which is premature and avoidable [1,2]. The largest population-based study conducted in India on the prevalence of depression found that 15.1% of urban South Indians were depressed. The most frequent symptom was a depressed mood (30.8%), followed by fatigue (30%), whereas less frequently occurring symptoms included suicidal thoughts (12.4%) and speech and motor retardation (12.4%) [3]. Another study conducted in South India shows patients with ischemic heart disease and hypertension were more likely to exhibit somatization and depression symptoms, whereas patients with diabetes mellitus, those with hypertension, and those with ischemic heart disease were more likely to exhibit anxiety symptoms [4]. According to a study on comorbid depression in NCDs among older patients conducted in Punjab, India, 58.1% of study participants had depression, of which 34.1% had severe depression. Generalized anxiety disorder (GAD) was found to be present in 38.7% of cases, with 19.7% falling into the severe category. In 37.8%, GAD and depression were both identified [5]. There is increasing evidence that comorbid mental health conditions, such as depression, can greatly affect people with physical health conditions [6]. For example, people with NCDs are 2-3 times more likely to experience depression [2]. As the population grows in number and becomes older, more people with physical and mental illnesses are living longer. These persistent disorders are closely related. Several key modifiable risk factors for NCD, such as a poor diet, inactivity, smoking, and hazardous alcohol use, are made worse by poor mental health. A person is more likely to have one or more chronic illnesses if they have a mental illness, which is a risk factor for NCD [3].

The presence of depression worsens NCD symptoms, adversely impacts the quality of life, and increases the financial burden for patients and their families [2]. Therefore, it is important to recognize and treat depression to improve the overall management of NCDs and improve health, quality of life, and economic outcomes for these patients.

There is an identified need to integrate mental health care in NCD care settings to help address the high burden of comorbid depression with NCDs. However, there is a notable gap worldwide between the number of people in need of mental health care and those who receive treatment. This “treatment gap” is especially high in low- and middle-income countries (LMICs) [7,8]. It is recognized that depression management is not standardized across services and is often not available at all.

Another reason for this treatment gap would be that in developing nations, stigma is a significant barrier to people seeking care for mental health issues. Those who are stigmatized may expect to be treated unfairly and with contempt by others, which may encourage them to use unhealthy coping techniques such as withdrawal or secrecy. This tendency has been noted in research conducted in LMICs, such as Ethiopia and India. One option would be to incorporate areas of mental health treatment that influence the development of stigma, such as successful task-shifting programs, peer and health worker-delivered therapy, and case management [9]. Task shifting is a strategy that has been shown to be successful in helping to address this shortage of specialists, whereby nonspecialist health workers are trained to deliver interventions that would usually be provided by specialists [10]. This approach is supported by the World Health Organization’s (WHO’s) Mental Health Gap Action Program (mhGAP) [11].

Behavioral activation (BA) is an evidence-based, simple, structured psychotherapy for the treatment of depression, initially developed in the 1970s. BA aims to break the negative cycle of aversive behaviors and low mood by increasing engagement in activities that are associated with positive reinforcement. BA therapy is delivered by a trained practitioner, usually over a series of face-to-face therapy sessions, with “homework” tasks that are agreed upon with the person with depression to be undertaken between sessions. BA can be delivered through a number of sessions over digital and telephone platforms as well as in person [2,12,13].

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Although there is interest in using BA for depression in people with NCDs, evidence for the effectiveness of this approach has not been clearly established. A systematic review conducted in 2011 found only 8 randomized controlled trials of BA in long-term conditions (with study sample sizes ranging from 20 to 105) [14]. A total of 3 trials targeted stroke; another 2 were in dementia and 1 in breast cancer. The remaining 2 included studies targeting older residents in nursing homes but did not specify the comorbid physical conditions. Since the publication of that review, the "Integrating Depression and Diabetes Treatment" (INDEPENDENT) study, a randomized controlled trial of BA delivered through a multicomponent care model in India, has shown effectiveness and cost-effectiveness for the treatment of depression in people with diabetes. However, the study intervention was complex and multifaceted, combining collaborative care, decision support, and population health management. It remains uncertain whether a briefer intervention like BA is effective for the treatment of depression in NCDs in LMICs [15].

This study aims to address this evidence gap by (1) adapting BA for the Indian NCD context; (2) testing the acceptability, feasibility, and implementation of the adapted BA intervention (BEACON intervention package [BIP]); and (3) testing the feasibility of a randomized controlled trial evaluation of BIP for the treatment of depression compared with an enhanced usual care (EUC) package.

Methods

Intervention Adaptation

The purpose of this step was to ensure the BA intervention content and delivery were appropriate for the Indian NCD's cultural, linguistic, and resource context. The initial content was based on treatment manuals and workbooks from previous adaptations of BA for multimorbidity and delivery by lay counselors in the United Kingdom [16] and India [17]. The research team also looked at training packages from the WHO mhGAP [11] relevant to the delivery of BA and formative research exploring the implementation of BA in similar settings in South Asia [18].

Following adaptation frameworks, including cultural adaptation [19,20], and taking this information into account and in discussion with experts within the National Institute of Mental Health and Neuro Sciences (NIMHANS) and the wider BEACON team, the materials, plans for delivery, and training package were adapted. Revisions to the package were made through expert panel reviews, co-design workshops with NCD counselors, and feedback sessions from NCD patients and caregivers. Major revisions included modification of the workbook as a flipbook with less text and more pictures, simplification of the BA counselor's manual, and preparation of a separate session log instead of homework tasks in between session follow-ups. The training package for the BA counselors was modified in collaboration with a BA expert from the United Kingdom.

The finalized BIP comprised a BA counselor's manual, a session log, and a flipbook for the patient participants. The intervention could be delivered remotely by telephone over 6 sessions lasting approximately 30-40 minutes each. The training of the BA counselors focused on developing skills in communication, establishing therapeutic relationships, and using the manual and materials to deliver therapy sessions. The task of adapting BA for the Indian NCD context has already been completed.

Feasibility Trial

Objectives

The objectives of the feasibility trial are to (1) test the acceptability, feasibility, and implementation of the adapted BA intervention (BIP) and (2) test if a randomized controlled feasibility trial can be delivered effectively and estimate important parameters needed to design a future definitive trial.

This will be achieved by answering the following research questions (RQs): (1) what are the recruitment and retention rates for participants in the trial? (2) What is the feasibility and acceptability of the proposed randomization and data collection procedures? (3) To what degree can the BIP be implemented as planned? (4) What is the acceptability of the BIP from the perspective of study participants and BA counselors?

Design

A randomized controlled feasibility trial with the nested process and economic evaluations was conducted over 12 months. The Gantt chart can be found in Multimedia Appendix 1.

The 2 trial arms are the intervention arm (BIP) and the control arm (EUC).

Setting

In 2010, the Ministry of Health and Family Welfare, Government of India, launched the National Programme for Prevention and Control of Cancer, Diabetes, Cardiovascular Diseases, and Stroke (NPCDCS). This includes the prevention and management of NCDs at district and subdistrict-level facilities. These facilities provide services for screening, treatment, or referral of patients with NCD but do not, at present, include the integrated detection and management of mental disorders. They do not yet cover all districts in the country [21].

The setting for the BEACON study is a district in Kolar, Karnataka, South India, where it was possible to explore the integration of mental and physical health care based on several pragmatic considerations, including the availability of NCD services that are part of the government health system and the engagement of key stakeholders. Therefore, to better understand the health system at the study site, a survey of the organizational capacity in the study area was conducted, along with interviews with the NCD counselors and the patients who visit the health facility. Following this, the selection of health care facilities was based on (1) the provision of NCD services, (2) the availability of health care staff such as NCD counselors and nurses to identify the patient participants for the study (by administering the Patient Health Questionnaire [PHQ-2]) [22], a screening tool to identify those who need further assessment for depression), (3) the engagement and support of senior managers, and (4) a sufficient number of patients with NCD attending the facility. Facilities were part of

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government-supported health services and were within a reasonable travel distance of the research team's base to make the study feasible.

Since most NCD services are limited to providing care for cardiovascular and chronic lung diseases and diabetes (excluding cancer), the study focused on these disorders. Finally, a total of 6 NCD clinics were chosen for data collection.

Eligibility Criteria for Trial Participants

The eligibility criteria for this study are given in Textbox 1.

Textbox 1. Inclusion and exclusion criteria for the study.

Inclusion criteria

- Aged 18 years or older.
- Diagnosed with cardiovascular disease, chronic respiratory disease, or diabetes (type 1 or 2).
- Current diagnosis of depression (confirmed with a Patient Health Questionnaire [PHQ-9] [23] score of ≥10).
- Willing to participate and able to attend therapy sessions in person or by telephone.
- Other mental or physical illness comorbidities will not be a reason to exclude unless the patient is judged to be too unwell to participate.

Exclusion criteria

- Already receiving psychotherapy for depression. Being on antidepressant medication will not, however, be a reason to exclude.
- Lacking the capacity to provide informed consent.
- Unable to take part in therapy because of cognitive impairment or the severity of a mental or physical illness.

Intervention Arm

Participants in the intervention arm will receive the BIP, delivered by trained nonmental health specialists (BA counselors) who will be specifically recruited for the study. BA counselors will be supervised by a mental health specialist.

The BIP will be delivered over 6 sessions lasting 30-40 minutes over a period of 6-12 weeks, with a minimum of one week between sessions. All sessions will be delivered remotely, by telephone. An alternate telephone number will be collected at the time of recruitment to ensure the unhindered delivery of BA sessions to the client.

The components of BIP include structured sessions where participants, with the BA counselors, plan and identify 3 types of activities. The first one includes routine and necessary activities that are done either regularly or on a daily basis, for example, getting fresh, taking a bath, cooking, doing household chores, etc. Second, social activities involve interacting with other people, for example, meeting or chatting with people from the neighborhood, etc. And third, pleasurable activities include activities that one enjoys and has fun with. For example, reading a newspaper or book, watching television (serials and movies), etc. The BA counselor and the participant will both have a flipbook for guidance and a better understanding of the activities during the session, as it contains a pictorial representation of each type of activity. The BA counselor will follow a manual and maintain the session logs of the participants. The BA counselor in the session log will not only maintain the session details but also keep a record of the daily activities done by the participants and the mood associated with doing these activities through telephonic follow-up in between the sessions. Another reason this is done is to check if the participants are doing the activities or if they are facing any challenges while doing them.

Control Arm

Participants in the control arm will receive an EUC leaflet describing depression and its treatment and signposting, including providing contact details (addresses and telephone numbers) to help access usual care for depression. They will also be provided with 1-time brief advice on the same from the research assistants (RAs) remotely.

Outcomes

The outcomes for the feasibility trial relate to (1) the acceptability and feasibility of recruitment and data collection and (2) the acceptability, feasibility, and implementation of the BIP.

Outcomes relating to the feasibility and acceptability of recruitment and data collection are (1) the rates of recruitment into the trial and retention at 3 months (RQ1), (2) the proportion of participants recruited who are randomized (RQ2), and (3) the completeness of data collection (percentage of planned measures completed) (RQ2) at:

- Baseline: demographic data, depression symptoms—PHQ-9 [23], negative emotional state of depression—depression subscale of Depression Anxiety and Stress Scale (DASS-21) [24], GAD-7 [25], health-related quality of life (EQ-5D-5L) [26], measures of potential mediators, for example, knowledge, intention, beliefs of 3 activities (routine and necessary, social, and pleasurable activities), and questions on how doing these activities will affect their NCDs, Premium Accredited Activation Scale (PAAS) [27], and adverse events.
- 3 months: depression symptoms—PHQ-9 [23], negative emotional state of depression—depression subscale of DASS-21, GAD-7 [25], health-related quality of life (Euroqol-EQ-5D-5L) [26], measures of potential mediators, for example, knowledge, intention, and beliefs of 3 activities (routine and necessary, social, and pleasurable activities),

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and questions on how doing these activities affected their NCDs, PAAS [27], and adverse events.

Outcomes relating to the acceptability, feasibility, and implementation of the BIP are described below in the process evaluation.

Trial Sample Size

The sample size is set to enable reliable estimation of recruitment and retention rates and to adequately explore the feasibility of data collection and intervention delivery in this feasibility trial. A total of 56 participants will be recruited for this study. This should be adequate to estimate a participation rate of 20% and a follow-up rate of 80% to within a 95% CI (with SD of 5% and 10%, respectively).

Trial Recruitment and Consent Procedures

The BEACON study flowchart can be found in Multimedia Appendix 2.

Participating sites were asked to implement depression screening by NCD health care staff, such as NCD counselors and nurses, using the PHQ-2 [22], as part of routine clinical practice. The PHQ-2 is a simple screening tool with minimal training and time requirements. The training was provided by the study team, and staff were asked to use the PHQ-2 with every patient attending the NCD service.

Staff (NCD counselors and nurses) will be asked to give information about the study and screen the patients for PHQ-2 [22] after obtaining their written consent. The participants who scored ≥3 will be qualified for the next level of screening. Those who indicated they were interested in participating in the feasibility trial were approached by RAs for the next level of screening by administering the PHQ-9 [23].

Recruitment of the willing participants by RAs was done remotely by telephone, mobile phone, internet, or video calling, as was convenient for the participant. Accordingly, verbal informed consent will be obtained before administering the PHQ-9, along with consent for participation in the feasibility trial. Those screening positive for depression on PHQ-9 (score ≥10) were invited to participate in the feasibility trial and provided detailed information about the purpose of the study and trial procedures either face-to-face or remotely. Furthermore, a suicide risk assessment was conducted at this point, where the participant was asked whether they have had thoughts of harming themselves or wished they were dead in the past week. If they say no, then the recruitment process will continue. Final verbal consent for participating in the trial will be obtained. The BEACON patient information sheet and consent forms can be found in Multimedia Appendix 3.

But if the answer is yes to the question of whether they have had thoughts of harming themselves or wished they were dead in the past week, then further questions on plans, actions, and prevention are to be asked, and based on the responses, the participants will be categorized into level A (mild), level B (moderate), and level C (severe). Three-week follow-ups by the RAs will be done, and then the decision on whether to recruit the patient or not will be made by the research team. The details about the safety considerations followed in the trial can be found in Multimedia Appendix 4.

Participants were free to withdraw consent and leave the trial at any time without giving a reason. They were able to withdraw by letting any member of the research team know that they wished to do so. If a participant withdrew consent to participate, no further data were collected from them. However, data collected up to the point of withdrawal were retained and used in the analysis, except where withdrawal of consent for the use of this data is explicit, in which case all data will be destroyed.

Randomization

Once consent has been secured, eligible participants complete a baseline questionnaire and are then randomized (BIP or EUC) by the trial manager or research fellow who will be based at the central office. Participants will be allocated in a 1:1 ratio using simple randomization without stratification. Treatment allocation was concealed from the study team at the point of recruitment using an automated computer data entry system, administered remotely by York Trials Unit, and using a computer-generated randomization sequence generated by an independent statistician (using Stata; version 16 or later; StataCorp).

Quantitative Data collection

Baseline and 3-month follow-up data were collected by RAs. The SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) schedule of enrollment, interventions, and assessments can be found in Multimedia Appendix 5. Quantitative data were collected with predesigned and tested data collection forms, using tablets to improve efficiency and minimize the risk of errors in data entry. Data will be anonymized, replacing identifiable personal data with unique study participant identification numbers, with the key only available to the local research team, principal investigator, and manager. Data will be secured and transferred safely, in line with the University of York data management policies and procedures. The completed SPIRIT checklist can be found in Multimedia Appendix 6.

Quantitative Data Analysis

Analyses will be conducted using Stata software. The number of participants who were screened, randomized, treated, and followed up for the primary outcome (PHQ-9) [23] will be reported in a CONSORT (Consolidated Standards of Reporting Trials)-style flowchart [28]. The number of study completers, by trial arm, will be calculated as a proportion of the number randomized at baseline.

The proportion of baseline and outcome measures completed out of those planned and presented by the treatment allocation arm will also be calculated. The normality of the data will be assessed, and based on that, an independent *t* test or Mann-Whitney *U* test will be used to compare the intervention and the EUC arm.

Process Evaluation

The 3 key functions of a process evaluation (mechanisms of impact, context, and implementation) will underpin our approach for the feasibility trial [29]. The qualitative inquiry will be used

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in combination with quantitative data to gain a more complete picture.

Survey (Implementation and Mechanisms of Impact)

To capture the views and experiences of participants, all participants will complete a brief quantitative survey at a 3-month follow-up. Participants in the intervention arm will be asked about their engagement with and acceptability of BIP, views on remote delivery, as well as the perceived impact on their depression symptoms. Control arm participants will answer these questions in relation to the EUC leaflet. Participants in both trial arms will also complete some questions to assess the acceptability of trial processes.

Potential mediators of intervention impact will be measured at baseline and 3 months: intentions, beliefs about capabilities, and beliefs about outcomes. These have been selected to reflect the hypothesized mechanisms of action of BA [30].

Qualitative Data Collection: Interviews (Implementation, Mechanisms of Impact, and Context)

A subsample of 16 participants will be interviewed. We will purposively sample to ensure a mix of participants (intervention and control arms, men and women, aged 60 years or younger and aged 60 years or older, and completed or dropped out of BIP). The interviews will seek in-depth feedback on the topics explored in the brief survey as well as explore individual and context barriers and drivers to performing the 3 types of activities (routine and necessary, social, and pleasurable).

Once delivery of the BIP is completed, a group interview will be conducted with the 4 BA counselors to explore their experiences, including the acceptability of the interventions and the barriers and drivers to delivery, including contextual factors such as remote delivery.

All interviews will be conducted in the local language, face-to-face using topic guides, and digitally audio-recorded. A hermeneutics approach, which encourages participants to discuss features of the intervention to elicit data on their experience and evaluation of its delivery or receipt, will be used with trial participants, family members, and health care staff [31].

Trial participants will provide written informed consent for these interviews within their trial consent.

Fidelity Index (Implementation)

Fidelity in delivering BIP will be assessed using a fidelity index. This index consists of 2 subindices, namely, the adherence index, which assesses adherence to delivering the content of the 6 BIP sessions, and the interaction index, which assesses the level of counselor-participant with which the intervention was delivered. Both indices are scored on a 3-point Likert scale (0=not implemented, 1=partially implemented, and 2=fully implemented).

All BIP sessions will be audio-recorded. We will then perform the fidelity checks by reviewing the audio recording of a subsample (n=18) of sessions. These sessions will be purposefully selected to include a mix of sessions 1-6, delivered by all BA counselors early and late in the feasibility trial.

Fidelity Data Analysis

The quantitative data from the fidelity index and questionnaire will be analyzed using descriptive statistics, including means and SD for continuous variables and absolute and relative frequencies for categorical variables.

Qualitative Data Analysis

Interviews will be transcribed verbatim, translated into English, and analyzed using the Framework Approach [32], which is particularly useful for understanding and improving programs and policies and when multiple researchers are working with the data [33]. Excel (Microsoft Corp) software will aid in data handling.

Integration of interview findings with respective questionnaire data will be done using a “triangulation protocol” [34]. Methodological triangulation, where more than one research method or data collection technique is used [35], will be used in this study.

Economic Evaluation

The feasibility of undertaking a full cost-effectiveness analysis will be assessed. This will primarily investigate the acceptability and resource use associated with capturing data for a cost-effectiveness evaluation in the full trial.

The team will capture costs associated with depression in NCD, such as delivery or receipt of the BIP. Costs will include the time to deliver the BIP and the cost of the materials used. And the costs of training the BA counselors to deliver the BIP will be calculated. Training requires the “staff time” of the trainer plus staff travel costs. Staff time is based on the salary of the trainer and allocated on a cost-per-minute basis, plus costs of materials.

Diaries to capture resource use, to be completed by patients and BA counselors, will be developed by the research team. Participants will be asked to complete these on a monthly basis for 3 months.

A pro forma to capture the costs of delivering the BIP incurred by the host organization will be completed by service managers, including staff salaries, time, and costs of estates and materials. An average cost per case per trial arm for treatment and the control group will be calculated.

Health service use will be assessed by asking pretested questions on contacts with doctors and nurses, hospital admissions, pharmacy visits, drug use, etc.

Quality of life will be assessed using a quality of life questionnaire (EQ-5D-5L) at baseline and 3 months. This information can be used as a quantitative measure of health outcomes as judged by the individual respondents. A higher score represents a better-perceived health state. The data will be checked for completeness.

Data Management

The following data will be collected from feasibility trial participants (at baseline and 3-month follow-up): demographic data and validated instrument measurements of mental and physical health. The process evaluation of the feasibility trial

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will collect data from interviews with trial participants and BA counselors, a sample of audio-recorded BIP sessions, and drop-out data. Health economic data will be collected to provide evidence of the costs of providing the BIP in the host institution.

All study data will be stored in accordance with the General Data Protection Regulation and the University of York data management policies. Electronic data will be password-protected and stored on secure servers at the country's partner institutions and the University of York.

Unique study identification (ID) numbers, allocated by the research team, will be used to anonymize data on electronic documents containing data from the trial and interviews. Paper-based documents, for example, consent forms and hard copies of transcripts, as well as any research participant personal data collected, will be stored in locked filing cabinets at the partner institutions.

Study documents (paper and electronic) at the research sites will be retained in a secure (locked when not in use) location during and after the study finishes. Interview recordings will be transferred from the digital recorder to a secure server as soon as possible after the interview has taken place. Once the transferred recording has been checked to ensure audibility, the original will be deleted from the digital recorder. All essential documents, including source documents (eg, transcripts), will be retained for a minimum period of 10 years after study completion, in accordance with the University of York Research Data Management Policy. This is deemed to be sufficient time for any queries arising from the findings to be answered, for example, queries arising from the publication of the findings. They will be retained in secure locations (locked when not in use) at the University of York and at the partner institutions.

The Department of Health Sciences at the University of York has a backup procedure approved by auditors for disaster recovery. There will be a separate archive of electronic data performed at the end of the study to safeguard the data and comply with regulatory requirements. The access, use, and storage of sensitive or confidential data will be conducted in accordance with the University of York Data Security Policy and Handling Sensitive Data Guidance. All sensitive or confidential data used for BEACON will be encrypted.

Data Monitoring

Data will be monitored for quality and completeness by the delegated researchers at the study site, followed by a second check by researchers at the University of York using verification, validation and checking processes. Missing data will be pursued until the study's end unless it causes any distress to the participant contacted. Data will be reported to the Health Ministry Screening Committee and Ethics Committee as required.

Adverse Events

Working with a potentially vulnerable group of participants has many ethical implications. We have addressed them in our ethics application. The main adverse events anticipated in this study, both during the recruitment phase and during the delivery of the BIP, are self-harm and suicide risk. Therefore, standard operating procedures to address these adverse events will be adapted by the study team.

Informed Consent

As the recruitment is done at 2 levels, written consent will be obtained at first-level screening using PHQ-2 [22] by the staff (NCD counselors and nurses) and verbal consent for the next level screening using PHQ-9 [23] by the RAs.

Privacy and Confidentiality

Data will be anonymized, replacing identifiable personal data with unique study participant identification numbers, with the key only available to the local research team and the principal investigator.

Community Engagement

A community advisory panel will provide community engagement and involvement for the duration of the study. This panel consists of patient and family representatives and community and voluntary sector advocates interested in improving the care of common mental disorders and NCDs. The panel has already given feedback on:

- The accessibility and feasibility for patients of the proposed BIP intervention, including remote delivery.
- Delivery of BA counseling by the NCD counselors.
- The acceptability of proposed methods for the feasibility trial.

The feedback and suggestions were incorporated into the intervention development and delivery plans of the study. The panel will continue to provide feedback, providing an important perspective on the delivery of the study and its findings.

Dissemination

Feasibility study results will be disseminated by engaging end users of our research, including policy makers and commissioners, by holding knowledge transfer and dissemination events at key stages. Lay summaries and fact sheets of findings are distributed using social media, newspapers, and a project website, alongside publications in academic journals, to reach a range of audiences.

Ethical Considerations

Ethics and other relevant approvals on the protocol have been secured from the University of York Health Sciences Research Governance Committee (HSRGC/2020/418/B; November 27, 2020); the Health Ministry Screening Committee, India (2020-9330; June 12, 2020); and the ethics committee, NIMHANS's Behavioral Sciences Division (NIMHANS/EC [BEH. SC.DIV.] 22nd MEETING/2OI9; February 3, 2020). The trial is also registered under the Clinical Trial Registry of India (CTRI/2020/05/025048; May 6, 2020).

Approvals for necessary amendments adjusting to the COVID-19 pandemic situation have been provided by the institutional ethics committee, Behavioral Sciences Division, NIMHANS.

The following amendments are made to the protocol:

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- In the first amendment to the protocol dated September 25, 2020, the focus group discussions and interviews as part of the survey of organizational capacity were shifted from face-to-face to telephonic mode.
- In the second amendment to the protocol dated May 15, 2021, the recruitment process was shifted from face-to-face to telephonic mode, and NCD counselors were involved in preliminary screening. A total of 4 BA counselors of the same cadre as the NCD counselors were recruited into the study to deliver the BA sessions.
- In the third amendment to the protocol dated January 27, 2022, process evaluation interviews are to be conducted at 8 weeks instead of 12 weeks, that is, immediately after the participants in the intervention group complete their 6 BA sessions and in the control group at 8 weeks after the participants receive their brief advice from the RAs postbaseline assessment.

Participants in the intervention group will receive INR 250 (US $3.01) per session, and participants in the EUC group will receive INR 250 (US $3.01) for attending the one-time brief advice.

Results

The BIP was developed beginning on November 28, 2020, and it was finished on August 18, 2021. The quantitative data-gathering process began on August 23, 2021, and was finished on December 10, 2021, following the acquisition of approval from all pertinent agencies. Process evaluation (qualitative data) collection is ongoing. Both the qualitative and quantitative data analyses are ongoing.

Discussion

Overview

This research study overall aims to address the evidence gap regarding the use of BA for depression in people with NCDs by adapting BA interventions to the Indian context, testing the acceptability, feasibility, and implementation of adapted BA intervention, and testing the feasibility of a randomized controlled trial evaluation of BIP for the treatment of depression compared with EUC.

Effective treatment of depression in NCDs offers the potential to improve mental and physical outcomes for this population and, additionally, maximize the efficient use of health care resources. To bridge the treatment gap globally, psychological therapies must be scaled up, which necessitates their effective use in many cultural contexts. An increasing number of studies have examined the degree to which cultural adaptation enhances the acceptability and effectiveness of psychological therapies among populations from various cultural backgrounds. The data are still unclear at this stage because there are not enough studies that analyze the many types of changes involved in cultural adaptation [36]. If shown to be effective, the approach of integrating treatment for a mental disorder within NCD care will also provide the opportunity to harness physical health resources to reduce the large mental health treatment gap, reduce stigma for people with mental illness, and add to the data on cultural adaptation of interventions such as BA.

Several of the issues with conventional psychological therapy may be resolved through remote therapy. Because of their accessibility and simplicity, telephone-based therapies are a popular research topic in the field of therapeutic communication and may provide important advantages. Data suggests that a therapeutic connection and successful treatment outcomes may not require the colocation of a patient and therapist. Nonetheless, the evidence is scant in both amount and quality [37]. Therefore, this study might provide evidence of how well BA can be delivered remotely and whether this approach can be further scaled up.

If the feasibility trial demonstrates that the BIP is feasible and potentially beneficial, we will be able to make further adaptations to the BIP and test the intervention in a full trial.

Limitations

Given the COVID-19 situation, BA counselors of the same cadre as the NCD counselors were recruited into the study to deliver the BA sessions, which can be a drawback as there is no sense of familiarity, which might affect intervention delivery.

Future Directions

This work will support a future definitive trial evaluation of BA for depression in NCD in India.

Conclusions

This study has the potential to provide evidence that would be useful to bridge the treatment gap for mental disorders, especially in resource-, infrastructure-, and system-constraint countries such as India. BEACON attempts to deliver BA for depression in NCDs through trained NCD (BA) counselors integrated within the NCD clinics to reduce this gap. The findings from this study will help understand the impact of the BA intervention for depression in NCD in countries such as India. Also, the BIP may serve as a culturally validated intervention package for the Indian population for future use.

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Data Availability

All data generated or analyzed during this study are included in this study and its Multimedia Appendices.

Authors' Contributions

NS is responsible for the conceptualization of the study. DE, AK, PM, CEH, GN, GNR, PM, and KC planned the phase I research, whereas the methodology for phase II research was planned by NS, AK, PM, CEH, CJ, and HJ. AK is the principal investigator. The investigation was done by AK, RZ, NAB, and CVD. Manuscript writing was undertaken by RZ, AK, HJ, and CJ. All authors reviewed and approved the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Beacon feasibility trial Gantt chart.
[XLSX File (Microsoft Excel File), 103 KB - resprot_v12i1e41127_app1.xlsx]

Multimedia Appendix 2
Beacon study flow chart.
[PDF File (Adobe PDF File), 105 KB - resprot_v12i1e41127_app2.pdf]

Multimedia Appendix 3
Beacon patient information sheet and consent forms.
[DOCX File , 726 KB - resprot_v12i1e41127_app3.docx]

Multimedia Appendix 4
Safety considerations.
[PDF File (Adobe PDF File), 321 KB - resprot_v12i1e41127_app4.pdf]

Multimedia Appendix 5
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) schedule of enrollment interventions and assessments.
[DOCX File , 16 KB - resprot_v12i1e41127_app5.docx]

Multimedia Appendix 6
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist.
[DOC File , 127 KB - resprot_v12i1e41127_app6.doc]

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Abbreviations

BA: behavioral activation
BIP: BEACON intervention package
CONSORT: Consolidated Standards of Reporting Trials
DASS-21: Depression Anxiety and Stress Scale
EUC: enhanced usual care
GAD: generalized anxiety disorder
INDEPENDENT: Integrating Depression and Diabetes Treatment
LMICs: low- and middle-income countries
mhGAP: Mental Health Gap Action Program
NCD: noncommunicable disease
NIMHANS: National Institute of Mental Health and Neuro Sciences
NPCDCS: National Programme for Prevention and Control of Cancer, Diabetes, Cardiovascular Diseases, and Stroke
PAAS: Premium Accredited Activation Scale
PHQ-9: Patient Health Questionnaire-9
RA: research assistant
RQ: research question
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
WHO: World Health Organization

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Protocol

Assessing the Efficacy and Safety of a Digital Therapeutic for Symptoms of Depression in Adolescents: Protocol for a Randomized Controlled Trial

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Abstract

Background: Depression is a serious, prevalent, recurrent, and undertreated disorder in adolescents. Low levels of treatment seeking and treatment adherence in this age group, combined with a growing national crisis in access to mental health care, have increased efforts to identify effective treatment alternatives for this demographic. Digital health interventions for mental illness can provide cost-effective, engaging, and accessible means of delivering psychotherapy to adolescents.

Objective: This protocol describes a virtual randomized controlled trial designed to evaluate the efficacy and safety of a self-guided, mobile app–based implementation of behavioral activation therapy, SparkRx, for the adjunct treatment of symptoms of depression in adolescents.

Methods: Participants are recruited directly through web-based and print advertisements. Following eligibility screening and consenting, participants are randomly assigned to a treatment arm (SparkRx) or a control arm (assessment-enhanced usual care) for 5 weeks. The primary efficacy outcome, total score on the 8-item Patient Health Questionnaire (PHQ-8), is assessed at the end of the 5-week intervention period. Additional participant-reported outcomes are assessed at baseline, the postintervention time point, and 1-month follow-up. The safety of the intervention is assessed by participant report (and legal guardian report, if the participant is younger than 18 years) and by patterns of symptom deterioration on the PHQ-8, as part of a larger clinical safety monitoring protocol. The primary efficacy outcome, total PHQ-8 score at the postintervention time point, will be compared between SparkRx and enhanced usual care arms using mixed effect modeling, with baseline PHQ-8 and current antidepressant medication status included as covariates. Secondary efficacy outcomes, including the proportion of participants exhibiting treatment response, remission, and minimal clinically significant improvement (all derived from total PHQ-8 scores), will be compared between groups using chi-square tests. Symptom severity at 1-month follow-up will also be compared between arms. Planned subgroup analyses will examine the robustness of treatment effects to differences in baseline symptom severity (PHQ-8 score <15 or ≥ 15) and age (younger than 18 years and older than 18 years). The primary safety outcome, the number of psychiatric serious adverse events, will be compared between trial arms using the Fisher exact test. All other adverse events will be presented descriptively.

Results: As of May 2023, enrollment into the study has concluded; 223 participants were randomized. The analysis of the efficacy and safety data is expected to be completed by Fall 2023.

Conclusions: We hypothesize that the results of this trial will support the efficacy and safety of SparkRx in attenuating symptoms of depression in adolescents. Positive results would more broadly support the prospect of using accessible, scientifically validated, digital therapeutics in the adjunct treatment of mental health disorders in this age range.

Trial Registration: ClinicalTrials.gov NCT05462652; https://clinicaltrials.gov/study/NCT05462652

International Registered Report Identifier (IRRID): DERR1-10.2196/48740

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(JMIR Res Protoc 2023;12:e48740) doi:10.2196/48740

KEYWORDS

randomized controlled trial; depression; adolescent; youth; mental health; digital therapeutic; behavioral activation; cognitive behavioral therapy; virtual trial; efficacy; treatment; digital health; intervention; mental illness

Introduction

Depression is among the most prevalent mental health disorders in adolescents and young adults [1,2], with global rates rising sharply in the past decade [3]. Symptoms of the disorder can contribute in significant ways to the disruption of social and familial relationships, decreased quality of life and physical health, poor academic and occupational outcomes, and increased risk of substance abuse and self-harm [4-11]. Alarmingly, suicide is now among the leading causes of death in this age group [12-14], highlighting a critical need for the development and deployment of effective and accessible treatments to affected individuals.

Despite the high rate of depression among adolescents, levels of treatment seeking and adherence are low for both psychotherapy and pharmaceutical treatment [15-17], likely due in part to concerns over privacy or stigma [18,19] and side effects [20,21], respectively. Simultaneously, access to effective mental health care is often limited [22-24], with a documented shortage of mental health providers [25-27], long waitlists [28-33], and prohibitive treatment costs [34,35]. For young patients, logistical barriers may also exist for seeking or accessing traditional forms of care, such as limited caregiver time, and conflicting responsibilities, such as school and other activities. An evidence-based self-guided psychotherapy program delivered via personal mobile device may be a promising and scalable option as an adjunct to the standard of care; such a program, if effective, would be expected to overcome many of the existing limitations in access to mental health care, adherence, and safety. As with other digital health interventions, such a program could be less stigmatizing, leading to higher rates of engagement and self-disclosure [36-39].

Cognitive behavioral therapy (CBT), a recommended form of treatment for adolescent depression by the American Academy of Pediatrics, has been shown to be effective when implemented in a digital format [40-42]. Behavioral activation, a key component of CBT, may be particularly well suited for deployment as a digital therapeutic, as it is fundamentally individualized, self-driven, and self-monitored. Specifically, behavioral activation emphasizes engagement in adaptive and personally meaningful activities to increase feelings of reward, mastery, or goal advancement; additional components focus on techniques for reducing harmful or avoidance behaviors commonly associated with depression [43-46]. Importantly, evidence supports behavioral activation therapy on its own as efficacious in the treatment of depression [47]. SparkRx (Limbix Health, Inc), an investigational mobile app–based digital therapeutic, was developed to deliver behavioral activation programming and psychoeducation to adolescents with symptoms of depression as an adjunct to usual care.

This randomized controlled trial (RCT) is designed to test the efficacy and safety of SparkRx. To test the efficacy of the intervention, we will compare self-reported symptom severity (total score 8-item Patient Health Questionnaire [PHQ-8] [48]) between adolescents who receive SparkRx and adolescents who continue their usual care for symptoms of depression. We hypothesize that the SparkRx group will exhibit (1) lower PHQ-8 scores at the postintervention time point, (2) higher rates of treatment response defined as a 10-point decrease in PHQ-8 score from baseline, (3) higher rates of remission defined as a postintervention PHQ-8 score less than 5, (4) lower PHQ-8 scores at 1-month follow-up, and (5) higher rates of clinically meaningful reduction in symptom severity, defined as a 5-point or greater reduction in PHQ-8 score from baseline to postintervention. We also hypothesize that SparkRx users will, on average, demonstrate a minimal clinically important difference at the postintervention time point, defined as a 5-point reduction from baseline. To test the safety of SparkRx, the number of serious adverse events (SAEs) reported during the intervention period will be compared between treatment groups. We hypothesize that participants who receive SparkRx will report no more of these events than those who continue their usual care for symptoms of depression.

Methods

Study Overview

This parallel-group, superiority, and single-blind (investigator) RCT compares the efficacy and safety of an investigational digital therapeutic (SparkRx) with assessment-enhanced usual care (eUC) for symptoms of depression in adolescents (13-21 years). Participants are randomly assigned to receive 5 weeks of access to either SparkRx or a control app with no therapeutic content in addition to continuing their usual care for symptoms of depression. Participant-reported efficacy outcomes are obtained at baseline, weekly during the intervention period, at the postintervention time point, and at 1-month follow-up. Safety is monitored throughout study participation using a combination of explicit assessment of symptom deterioration and side effects and triage of other incoming information for potential clinical concerns. The RCT is conducted entirely virtually. Study procedures were preregistered on ClinicalTrials.gov (NCT05462652). The study is overseen by an independent Data and Safety Monitoring Board.

Ethics Approval

Study procedures were approved by the Advarra institutional review board prior to participant enrollment (Pro00061682).

Sample Size

G*Power [49] was used to calculate the estimated sample size based on the primary outcome—total PHQ-8 score at postintervention. Using a 2-sample *t* test approach and assuming

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a 2-tailed α set at .05, a total of 200 participants (100 in each study arm) was estimated to provide 80% power to detect a moderate effect size of at least *d*=0.4. Given an anticipated 10% rate of attrition, the target sample size was determined to be 220 (110 randomized to each trial arm).

Participants

The inclusion criteria are assessed via self-report and legal guardian report (if applicable, ie, participant is under the age of 18 years) and include (1) aged 13-21 years; (2) PHQ-8 score ≥5 at eligibility screening; (3) English fluency and literacy; (4) access to a compatible smartphone (or other device) and operating system (ie, capable of installing the app from the Google Play or Apple App Store) and regular internet access (most app content is usable offline, but internet access is required to submit weekly check-in PHQ-8 and safety data); (5) willing and able to provide informed consent or assent and, if required, have a legal guardian willing and able to provide informed consent; (6) under the care of a US-based licensed health care provider and willing and able to provide contact information for the provider and sign a Health Insurance Portability and Accountability Act (HIPAA) release that allows Limbix to contact provider; (7) willing and able to provide the information required for study enrollment (eg, all responses to initial PHQ-8 assessment and current antidepressant medication status); and (8) located in the continental United States, Hawaii, or Alaska and not planning to leave the United States during the study period (through 1-month follow-up assessments, up to 11 weeks after eligibility screening).

The exclusion criteria are assessed via self-report and legal guardian report (if applicable) and include (1) a diagnosis of (or treatment for) bipolar disorder, posttraumatic stress disorder, psychotic disorder, substance use disorder, or eating disorder within the 12 months prior to eligibility screening; (2) recent change in psychotropic medication (past 30 days) or plans to change psychotropic medication or other treatment for a mental health disorder during the 5-week intervention period; (3) recent participation (past 60 days) in or plans to initiate participation in any other mental health intervention research during the intervention period; (4) suicide attempt within the past year; (5) active suicidal ideation with intent; (6) having a sibling in the study; (7) previous participation in user testing or clinical testing of SparkRx; and (8) any other condition, comorbidity, or event that may prevent the potential participant from adhering to the protocol or benefitting from the intervention (eg, coercion or low level of cognitive functioning) or will prevent investigators from being able to ensure safety.

Recruitment, Consent, and Screening

Recruitment is conducted through direct advertisement, including web-based and print media advertisements, flyers, word of mouth, and health care provider referrals. Potential participants (and legal guardians, if applicable) are directed to a study website where they can evaluate their preliminary eligibility to participate and sign up for a videoconferencing-based consent and onboarding session if they are preliminarily eligible to participate. During the session, potential participants and legal guardians (if required) provide informed consent or assent. The consent form provides information about the potential uses and disclosures of participant data, as well as the security practices for maintaining data. Specifically, the consent form provides a description of the parties who may gain access to participant data (eg, Data and Safety Monitoring Board, US Food and Drug Administration, and third-party vendors required for the operation of the study app and web platform). Third-party vendors are required by contract to maintain the confidentiality of participant data and to follow applicable data protection laws. Participants are informed that study staff will protect information from disclosure to others to the extent required by law but are obliged to share information under certain circumstances, such as in cases of suspected abuse, or indications of imminent harm to self or others. The consent form also discusses the risk of a loss of confidentiality and describes a few of the security features in place to reduce the likelihood of such a breach, including firewalls and end-to-end data encryption. Following consenting procedures, participants complete a screening/baseline PHQ-8 assessment and are screened for all remaining eligibility criteria. For potential participants younger than 18 years, self-report confirmation of eligibility is conducted privately with the minors and again with their legal guardians to increase the likelihood that sensitive information relevant to determining ineligibility (eg, active suicidal ideation with intent) is disclosed. Research coordinators confirm the licensure of participants' health care providers in the National Provider Identifier registry and inform providers of their patients' participation in the study via phone message. Eligible participants are enrolled into the study, complete baseline assessments, and receive instructions for downloading their assigned study app onto their mobile device. Participants are also provided with a safety plan template [50] and instructions for use as a personal resource.

Randomization With Stratification

A permuted block randomization schedule is used to randomly assign participants in a 1:1 ratio to either the treatment arm or the control arm. Stratification factors for randomization include baseline total PHQ-8 score (<15 or ≥15) and current antidepressant medication use (yes or no).

Intervention Arms

Overview

Participants are randomized to receive either the treatment app (SparkRx) or a control app (eUC). Both apps deliver weekly questionnaires for participants to complete. User guides for each app include instructions on app usage, study team contact information, crisis resources, and troubleshooting help.

Treatment Arm: SparkRx (Investigational)

SparkRx is a 5-week, self-guided multilevel program based on clinically validated behavioral activation protocols [44,45] to treat adolescent symptoms of depression (see Multimedia Appendix 1). In the first level, participants learn about the deleterious cycle of negative mood triggers and behavioral avoidance patterns in depression and practice identifying their negative mood-behavior patterns by tracking their mood in the app. In the second level, participants learn to distinguish between "Up" and "Down" activities and value-based activity scheduling

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is introduced. In the third level, participants practice scheduling activities to perform outside of the app. Push notifications remind and encourage participants to log their moods, complete their scheduled activities, and review each activity and their mood after scheduled activity times have elapsed. Participants engage in guided problem-solving to overcome challenges in the completion of their scheduled activities. In levels 4 and 5, participants learn mindfulness techniques to combat avoidance patterns and develop an action plan to maintain gains after SparkRx program completion. Levels and tasks within each level progress in a linear fashion (ie, each task or level must be completed to progress to the next task or level). Participants are encouraged to complete 1 level per week, though they are at liberty to complete the levels at their own pace without penalty. Certain on-demand resources can be accessed in the app at any time, including crisis resources.

Control Arm: eUC

Usual care is broadly defined as any of the existing treatment options for symptoms of depression, including active monitoring of depressive symptoms and suicidality, supportive counseling by a health care provider, psychosocial support interventions, collaborative care (eg, facilitation of parental and patient self-management, referral for peer support or other community, or school-based behavioral health programs), psychoeducation, complementary and alternative medicine approaches, psychotherapy (eg, behavioral treatment, interpersonal therapy, or CBT), pharmacotherapy for mood problems, visit to a primary care provider, behavioral or mental health specialist or therapist, counselor or coach for a mood disorder. It also includes the option of obtaining no treatment for symptoms of depression. For purposes of this study, usual care is considered enhanced (eUC) by prompting participants to complete a weekly PHQ-8 assessment and side effect screen (Participant Symptom Check) in the control mobile app, providing a safety plan template, and clinician-based safety monitoring (with corresponding clinical reach out, as needed).

Blinding (Investigator)

Study staff and investigators are not directly involved in the collection of any efficacy outcome data. These data are collected directly from participants through the study app and a secure web portal. The proprietary electronic data collection system used in this trial (Limbix Synapse) enables selective blinding or unblinding of designated individuals; thus, study staff who enroll participants, monitor assessment completion and send reminders to complete assessments, and directly correspond with participants about technical difficulties are not exposed to any data fields that contain implicitly or explicitly unblinding information.

Randomization is performed automatically upon entry of relevant data fields into Synapse during enrollment, and the deployment of assigned interventions takes place without the need for study staff involvement and without exposure of treatment assignments to study staff. Specifically, all participants download a single study app onto their mobile devices. Content specific to a participant's assigned treatment arm is displayed only after they log in to the app for the first time and confirm that study staff are unable to see their mobile device screen. Participants are asked not to reveal their assigned treatment arm in communications with study staff.

Study coordinators and clinicians involved in safety monitoring are unblinded to treatment assignment by necessity, as monitoring includes a review of freeform text entered into only the SparkRx app, clinical reach out in response to identified safety concerns, and the identification and categorization of adverse device effects (see the *Safety Monitoring* section for details). Unblinded study staff are instructed not to discuss treatment allocation or any potentially unblinding information with blinded study team members.

Assessments

Overview

Assessments take place at baseline, weekly during the intervention period, at the postintervention time point, and at 1-month follow-up (see Table 1 for the schedule of assessments). Baseline assessments are completed during the consent and onboarding session prior to mobile app download. Participants complete weekly assessments during the intervention period in their assigned mobile app. In-app push notifications and text messages are sent to remind participants to complete these assessments within a 4-day response window. Participants in the treatment arm are unable to continue engaging with content in the app until they have completed (or actively skipped) the weekly assessment or until their response window for a given week has closed. Legal guardians (if applicable) complete weekly proxy assessments in a secure web portal and receive reminders to do so. At the postintervention time point (immediately following the intervention period) and again at 1-month follow-up, participants (and legal guardians, if applicable) complete assessments in a secure web portal. The window for completion of postintervention and 1-month follow-up assessments is 2 weeks. Participants who do not complete 1-month follow-up assessments within the 2-week window are considered lost to follow-up. No collateral reports are obtained for participants older than 18 years.

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Table 1. Schedule of assessments.

	Eligibility screening	Baseline	Weekly during the intervention period	Postintervention	1-month follow-up
Medication use screener	✓				
Patient Health Questionnaire[a,b]		✓	✓	✓	✓
Demographics and medical history questionnaire[a]		✓			
Behavioral Activation for Depression Scale–Short Form		✓		✓	✓
Generalized Anxiety Disorder–7		✓		✓	✓
Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire[a]		✓		✓	✓
Absenteeism questionnaire[a]		✓		✓	✓
Health care utilization questionnaire[a]		✓		✓	✓
Participant symptom check[a]			✓	✓	✓
Systems Usability Scale				✓	
User Engagement Scale–Short Form				✓	

[a]A legal guardian proxy is additionally administered when participants are younger than 18 years.

[b]A single Patient Health Questionnaire–8 is administered to participants at the consent and onboarding session for purposes of both eligibility screening and baseline assessment.

Primary Outcome

The primary outcome is depressive symptom severity as measured by the PHQ-8, an 8-item participant-reported measure used to screen for depression and to establish depression severity [48]. The PHQ-8 was selected as the primary end point to align closely with a tool used for initial screening (and severity assessment) of depressive symptoms in clinical practice. Whereas the 9-item Patient Health Questionnaire is often used in clinical settings, the PHQ-8 (which drops an item related to suicidality) is commonly used in research contexts that are not geared toward clinically responding to reports of suicidality [48].

The total score ranges from 0 to 24, with a higher score indicating greater depression symptom severity. Scores of 5, 10, 15, and 20 represent thresholds for mild, moderate, moderately severe, and severe symptom severity, respectively; here, we define the minimal clinically important difference to be a 5-point reduction in total score from baseline [51,52].

Secondary Outcomes

The total PHQ-8 score will also be used to compute the trial's secondary outcomes, which include the (1) proportion of participants meeting criteria for intervention response, defined as a 50% reduction in symptoms from baseline to postintervention [47,53-56]; (2) proportion of participants meeting criteria for remission, defined as a score less than 5 at the postintervention time point [53,57]; (3) depressive symptom severity at 1-month follow-up; and (4) proportion of participants meeting criteria for a clinically meaningful reduction in symptom severity, defined as a 5-point or greater reduction in PHQ-8 score from baseline to the postintervention time point.

Tertiary and Exploratory Outcomes

As described below, a series of additional participant- and legal guardian–reported assessments are collected to investigate the potential effects of the SparkRx digital therapeutic on other clinical and functional domains, as well as its perceived usability and degree of engagement.

Anxiety symptoms are assessed with the Generalized Anxiety Disorder–7 (GAD-7) scale. The GAD-7 is a validated 7-item participant-reported assessment for generalized anxiety disorder [58]. The total score ranges from 0 to 21, with a higher score indicating greater anxiety symptom severity.

Quality of life will be assessed with the Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q), a 15-item participant-reported self-administered questionnaire that captures life satisfaction over the past week [59]. Each question is rated on a 5-point scale from 1 (very poor) to 5 (very good). The first 14 items are summed to form a total score, with higher scores indicating higher quality of life. The 15th item ("Overall, how has your life been?") is a stand-alone item. For participants younger than 18 years, a legal guardian proxy version of the PQ-LES-Q is administered to legal guardians.

Depression-associated behavior is assessed with the Behavioral Activation for Depression Scale-Short Form (BADS-SF). The BADS-SF [60] consists of 9 participant-reported questions assessing behavioral activation and avoidance over the previous week, each rated on a 7-point scale ranging from 0 (not at all) to 6 (completely). This form can be used to track changes in behaviors that are targeted by behavioral activation therapy. It examines changes in areas such as activation, avoidance or rumination, work or school impairment, and social impairment.

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The total score ranges from 0 to 54, with higher scores indicating higher activation.

The usability of the mobile app is assessed with the participant-reported System Usability Scale (SUS) [61]. The SUS consists of a 10-item questionnaire with 5 response options for respondents, ranging from strongly agree to strongly disagree. User engagement is assessed with the User Engagement Scale–Short Form [62], a participant-reported, statistically reliable measure that is tailored to the specific device being tested (ie, the study app). The form has 12 items and uses a 5-point Likert scale to evaluate domains such as aesthetic appeal, focused attention, perceived usability, and reward. Each subscale score ranges from 1 to 5, with higher scores indicating higher levels of each scale. The total score also ranges from 1 to 5, with higher scores indicating more engagement.

Absenteeism is assessed with study-specific adaptations of the absenteeism and presenteeism questions of the World Health Organization's Health and Work Performance Questionnaire [63] that solicit information from participants (and legal guardians, if applicable) about missed time at work or school attributable to the participant's mental health condition over the past 4 weeks.

Finally, the use of health care resources is evaluated with a brief questionnaire assessing the use of health care resources such as hospital visits and medical appointments over the past 4 weeks.

Treatment Compliance Outcomes

Treatment compliance for those assigned to use SparkRx is assessed descriptively by examining the rates of module and program completion, as well as the amount of time spent in the app over the course of 5 weeks and the number of participants who engaged with the app on each day of the intervention period.

Safety Monitoring and Safety Outcomes

Safety Monitoring

Safety is monitored during consent and onboarding sessions and throughout study participation. In this trial, clinical concerns are defined as any negative experiences or symptoms reported by a participant or a legal guardian, whether or not they are thought to be associated with participation in the study. Examples of clinical concerns include past or current suicidal ideation, self-harm, worsening of depression symptoms, new symptoms, changes in medication or treatment status, or hospitalizations. Sources for potential clinical concerns include (1) freeform text input into the SparkRx app or study questionnaires; (2) communication from participants or legal guardians to study staff during the consent and onboarding session or study participation; (3) patterns of responses to PHQ-8 assessments, as defined below; and (4) responses to the Participant Symptom Check that is deployed to participants (and legal guardians, if appropriate) weekly during the intervention period, at the postintervention time point, and at 1-month follow-up. Responses to PHQ-8 assessments are considered to be clinical concerns if they suggest (1) temporary clinical deterioration, defined as a PHQ-8 score >15 that reflects a 5-point or more increase from baseline, or (2) sustained elevated symptom severity, defined as a total PHQ-8 score greater than 20 for 2 or more consecutive weeks. In addition, a built-in algorithm in the SparkRx app compares all freeform text input into the app to a defined list of risk words and phrases. When a match occurs, the participant receives a pop-up alert directing them to the crisis resources page; study staff are automatically notified about potential clinical concerns involving the use of risk words or phrases. All identified clinical concerns are logged by a study staff member and reviewed by a study clinician daily. If clinical involvement for a logged clinical concern is indicated for the purpose of clinical safety management or to investigate the presence of a possible adverse event (AE), the study clinician contacts the participant and legal guardian (if applicable) to further evaluate clinical status and make determinations regarding continued participation in the study.

AE Classification

AEs, per the US Food and Drug Administration's guidance [64], are identified from logged clinical concerns during regular reviews by the study clinician. Each AE is then preliminarily categorized by expectedness, seriousness, and the likelihood of relatedness to the SparkRx app ("not possible," "possible," "probable," or "definite"), as well as whether it constitutes a psychiatric or nonpsychiatric occurrence.

Given the trial population, the following AEs are classified as "expected": (1) passive or active suicidal ideation, with or without intent to act; (2) clinically significant deterioration in depressive symptoms, including temporary clinical deterioration as defined in the *Safety Monitoring* section; (3) nonsuicidal self-injury ideation; and (4) nonsuicidal self-injury not resulting in the need for medical care or intervention. All other types of AEs are classified as "unexpected."

Definitions of AE seriousness and adverse device effects follow the guidance provided by the International Organization for Standardization 14155:2020. "Psychiatric" AEs constitute experiences that are related to the presence of a mental disorder, symptom of a disorder, or issue, as defined in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) [65].

Following preliminary categorization by a study clinician, a second independent clinician, not otherwise associated with the study, completes the final categorization of all AEs.

Statistical Analysis

Overview

Efficacy and safety analyses will be conducted by an independent statistician external to the sponsor organization who is otherwise not involved in the design or conduct of the trial. A statistical analysis plan, finalized prior to the conclusion of data collection, will be followed that includes detailed provisions for the handling of missing data. The plan will be made public as part of results reporting on ClinicalTrials.gov (NCT05462652).

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Populations

The primary population for all analyses is defined according to the intention-to-treat (ITT) principle, whereby all participants will be included according to their assigned study arm at baseline, regardless of adherence to study protocol.

Secondary analyses of the primary and secondary outcomes will be conducted with the following additional populations: (1) a modified ITT population will exclude from analysis participants who were found to not meet eligibility criteria after randomization and individuals without any postrandomization data. This population is included to ensure that effects are observed with the appropriate intended sample. In addition, this population allows for the handling of missing data without the need to impute values based solely on baseline data. (2) A per-protocol population will include individuals who complete, at minimum, the postintervention PHQ-8 assessment and, for participants in the SparkRx arm, meet a minimum engagement threshold of completing 2 app modules. This population is intended to estimate treatment effects in participants who adhere to the study and treatment protocol. (3) A moderate-severe population will include participants from the ITT population whose baseline PHQ-8 score was 10 or greater. This population is intended to ensure that efficacy outcomes are not masked by floor effects.

Analysis of Primary and Secondary Outcomes

A mixed effect model with an appropriate correlation matrix will be implemented to evaluate the effect of treatment on PHQ-8 scores at the postintervention time point. Time point, treatment arm, time point by treatment interaction, baseline PHQ-8 score, and antidepressant medication status will be included in the model as fixed effects. For analysis of the ITT population, missing PHQ-8 total scores will be imputed with multiple imputation within treatment arm under the assumption that data are missing at random; 20 imputed data sets will be analyzed independently and then combined [66]. As a sensitivity analysis, this model will be repeated without imputation using the modified ITT population, which includes only participants with at least 1 postbaseline data point.

For descriptive purposes, the mean change from baseline (and 95% CIs) in the SparkRx arm will be estimated to determine whether the change in this group meets or exceeds criteria for minimal clinically important difference (a 5-point improvement) and whether a 5-point change was contained or surpassed by 95% CI.

To analyze the secondary outcomes, we will compute the number and proportion of participants meeting the criteria for intervention response, remission, and clinically meaningful reduction in severity at postintervention and compare the rates between treatment arms using chi-square tests. If counts are low, Fisher exact tests will be used. As above, the 20 imputed data sets will be analyzed independently and combined. All tests will be 2-tailed.

Control of Type I Error in Primary and Secondary Outcome Analyses

The primary outcome analysis, conducted with the ITT population, will be tested with a 2-tailed α set at .05. To control for multiple comparisons, a serial gatekeeping approach will be applied, whereby the secondary outcomes will be tested only upon obtaining a significant primary outcome test and in the order in which they are listed in the Secondary Outcome section (see above). All subsequent outcomes will be considered to be nonsignificant following the first *P* value greater than α=.05.

Additional Planned Analyses of the Primary and Secondary Outcomes

Analyses will be repeated within the 4 subgroups: aged <18 years at enrollment, aged ≥18 years at enrollment, baseline PHQ-8 score <15, and baseline PHQ-8 score ≥15. *P* values will be reported; however, because the protocol was not powered for comparisons within such subgroups, they should be considered purely descriptive.

Analyses of Tertiary and Exploratory Outcomes

Appropriate models (eg, analyses of covariance) will be used to compare continuous clinical outcomes (eg, GAD-7, BADS-SF, PQ-LES-Q, and legal guardian PHQ-8 proxy) at the postintervention time point between treatment arms. Baseline scores will be included in models as appropriate. Changes in health care utilization and absenteeism from baseline to postintervention will be examined descriptively.

Moderation analyses will test whether demographic and other participant features (eg, baseline PHQ-8 score, antidepressant medication use, sex or gender, and age) influence the effects of treatment on PHQ-8 outcomes. Mediation analyses will be used to determine whether the degree to which participants engaged with SparkRx (eg, module completion rate) explains its effect on PHQ-8 scores. The usability and engagement of the SparkRx app (SUS and User Engagement Scale–Short Form) will be examined descriptively.

Analysis of Safety Outcomes

The rate of psychiatric SAEs (irrespective of device relatedness) derived from the Participant Symptom Check (side effect screen) and PHQ-8–based deteriorations will be compared between SparkRx and eUC groups using the Fisher exact test. For purposes of this comparison, psychiatric SAEs reported via app freeform text will be excluded, as freeform text is unique to the SparkRx arm.

Control of Bias

As Limbix Health Inc is the sponsor-investigator of this trial, there is a risk of bias due to study staff's conflicts of interest. This risk is mitigated in a number of ways. First, the efficacy end points are participant reported and digitally input by the participant directly into a password-protected, web-based assessment portal or into their study app. After the baseline session, data are not collected in the presence of study staff members. Thus, study staff members will not be directly involved in the capture of efficacy data. Except in cases of clinical reach out to ensure participant safety, all communication with study participants will be conducted by study staff blinded

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to treatment assignments to prevent bias. Second, to reduce bias related to the collection of safety outcomes, an independent clinician with no other role in the study nor conflict of interest will review all AEs and provide final classifications of AE seriousness and device relatedness for use in data analysis. Third, an independent statistician will conduct statistical analyses for the study based on a Statistical Analysis Plan to be finalized prior to data transfer.

Results

As of May 2023, enrollment into the study has concluded; 223 were participants randomized. The analysis of the efficacy and safety data is expected to be completed by Fall 2023.

Discussion

Expected Findings

While SparkRx is based on well-validated therapeutic behavioral activation protocols for depression, this RCT represents one of the first assessments of their efficacy in treating symptoms of depression as deployed to adolescents via a self-guided mobile app. For our primary outcome, we hypothesize that participants assigned to the SparkRx arm will report lower total PHQ-8 scores at postintervention compared to those in the eUC arm. For our secondary outcomes, we hypothesize that there will be higher rates of intervention response, remission, and clinically meaningful reduction in severity in the SparkRx arm than in the eUC arm. In addition, we expect to observe a durable effect of SparkRx as indicated by significantly lower PHQ-8 scores at 1-month follow-up in participants who received the SparkRx app compared to those who did not. Similarly, we hypothesize that participants in the treatment arm will report experiencing fewer symptoms of anxiety, greater quality of life, and higher levels of behavioral activation (lower levels of behavioral avoidance) at the postintervention time point than participants in the control arm. Finally, we anticipate that there will be statistically no more psychiatric SAEs in the SparkRx arm than in the eUC arm, supporting the overall safety of the SparkRx intervention.

Potential Problems

Poor adherence and low levels of engagement are common challenges with self-guided digital therapies [67]. As such, user engagement was a primary goal in the development of the SparkRx intervention [68]; the app was co-designed with a teen advisory council and iterated through rounds of user research and diary studies among adolescents with and without depression symptoms. For this trial, a few additional strategies are being implemented to encourage adherence to the study protocol. In addition to SparkRx push notifications that encourage engagement with the app and scheduled activities, both automatic and manual text messages are sent to remind participants to complete assessments. Adherence is also incentivized by compensation that is tied to discrete study components (attending the onboarding session and completing each set of questionnaires).

Dissemination

The primary results of this trial will be submitted to a peer-reviewed journal, irrespective of magnitude or direction of effect, and findings will be presented at scientific conferences. A lay report of findings will also be prepared for dissemination to trial participants (upon request) and to broader audiences.

Conclusions

During this mental health crisis, adolescents are in urgent need of accessible and quality care. Digital therapeutics, such as SparkRx, can bring such care to those who might otherwise have to wait months to see a provider or who face barriers to receiving care, such as high costs or stigma against traditional mental health treatment. To our knowledge, this is the first digital therapeutic offering CBT-based content specifically designed for adolescents with symptoms of depression, and this RCT is the first fully powered test of the efficacy of SparkRx. Support for our hypotheses would increase not only the scientific evidence base for SparkRx specifically but also more broadly for the model of using self-guided, adjunct digital therapeutics in the treatment of mental health disorders in adolescents.

Acknowledgments

Limbix Health, Inc developed SparkRx and funded this work. Employees of Limbix Health, Inc developed the study protocol, conducted the clinical trial, and reviewed or approved this manuscript for publication.

Conflicts of Interest

All authors are employed by the sponsor, Limbix Health, Inc, and have a financial stake in the company.

Multimedia Appendix 1
Screenshots depicting aspects of the SparkRx app (including psychoeducational programming, mood logging, and value-based activity scheduling and tracking).
[DOCX File , 1402 KB - resprot_v12i1e48740_app1.docx]

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Abbreviations

AE: adverse event
BADS-SF: Behavioral Activation for Depression Scale–Short Form
CBT: cognitive behavioral therapy
DSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
eUC: assessment-enhanced usual care
GAD-7: Generalized Anxiety Disorder–7
HIPAA: Health Insurance Portability and Accountability Act
ITT: intention-to-treat
PHQ-8: 8-item Patient Health Questionnaire
PQ-LES-Q: Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire
RCT: randomized controlled trial
SAE: serious adverse event
SUS: System Usability Scale

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Protocol

Usability and Efficacy of Artificial Intelligence Chatbots (ChatGPT) for Health Sciences Students: Protocol for a Crossover Randomized Controlled Trial

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Abstract

Background: The integration of artificial intelligence (AI) into health sciences students' education holds significant importance. The rapid advancement of AI has opened new horizons in scientific writing and has the potential to reshape human-technology interactions. AI in education may impact critical thinking, leading to unintended consequences that need to be addressed. Understanding the implications of AI adoption in education is essential for ensuring its responsible and effective use, empowering health sciences students to navigate AI-driven technologies' evolving field with essential knowledge and skills.

Objective: This study aims to provide details on the study protocol and the methods used to investigate the usability and efficacy of ChatGPT, a large language model. The primary focus is on assessing its role as a supplementary learning tool for improving learning processes and outcomes among undergraduate health sciences students, with a specific emphasis on chronic diseases.

Methods: This single-blinded, crossover, randomized, controlled trial is part of a broader mixed methods study, and the primary emphasis of this paper is on the quantitative component of the overall research. A total of 50 students will be recruited for this study. The alternative hypothesis posits that there will be a significant difference in learning outcomes and technology usability between students using ChatGPT (group A) and those using standard web-based tools (group B) to access resources and complete assignments. Participants will be allocated to sequence AB or BA in a 1:1 ratio using computer-generated randomization. Both arms include students' participation in a writing assignment intervention, with a washout period of 21 days between interventions. The primary outcome is the measure of the technology usability and effectiveness of ChatGPT, whereas the secondary outcome is the measure of students' perceptions and experiences with ChatGPT as a learning tool. Outcome data will be collected up to 24 hours after the interventions.

Results: This study aims to understand the potential benefits and challenges of incorporating AI as an educational tool, particularly in the context of student learning. The findings are expected to identify critical areas that need attention and help educators develop a deeper understanding of AI's impact on the educational field. By exploring the differences in the usability and efficacy between

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ChatGPT and conventional web-based tools, this study seeks to inform educators and students on the responsible integration of AI into academic settings, with a specific focus on health sciences education.

Conclusions: By exploring the usability and efficacy of ChatGPT compared with conventional web-based tools, this study seeks to inform educators and students about the responsible integration of AI into academic settings.

Trial Registration: ClinicalTrails.gov NCT05963802; https://clinicaltrials.gov/study/NCT05963802

International Registered Report Identifier (IRRID): PRR1-10.2196/51873

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KEYWORDS

artificial intelligence; AI; health sciences; usability; learning outcomes; perceptions; OpenAI; ChatGPT; education; randomized controlled trial; RCT; crossover RCT

Introduction

Background

The integration of artificial intelligence (AI) into the education field has led to many possibilities, benefiting both educators and students [1]. AI takes on various roles as an intelligent tutor, a collaborative learning partner, a valuable tool, and even an adviser in influencing educational policies [2,3]. The multidimensional role of AI in education, as demonstrated by the potential for dynamic and adaptive learning experiences, aligns with ChatGPT's capacity to operate as a valuable educational tool. ChatGPT is a generative AI that can generate complex answers to questions asked by the user. It has been described as a tool offering numerous benefits in the field of education [4]. It serves as a platform for enhancing students' writing skills through features such as text completion, translation, and summarization tools. Educators can integrate ChatGPT into their courses to customize the learning journey for their students by considering their preferred learning methods and existing proficiency levels [4].

An exploratory survey examining the use of ChatGPT in various domains, including education, health care, and research, revealed both positive and negative impacts [5]. On the positive side, ChatGPT was found to level the playing field for students facing language challenges, enhance comprehension by providing additional details, and offer valuable assistance in crafting writing assignments. However, the study also uncovered negative consequences, such as the potential for inaccuracies, concerns about replacing hard work with automated solutions, and the possible discouragement of critical thinking skills. In addition, questions remained regarding academic integrity and students' willingness to disclose their use of ChatGPT. These findings emphasize the need for careful consideration and guidance when integrating AI technologies such as ChatGPT into various fields [5].

It is crucial to acknowledge that integrating AI into education can result in unintended consequences [6]. The use of ChatGPT, while presenting remarkable potential, has sparked discussions regarding its potential negative implications. Concerns have been raised regarding its potential to promote academic dishonesty, stifle creativity, and diminish critical thinking abilities [7]. Numerous legitimate concerns encompass a spectrum of challenges. These include the potential for generating inaccurate content and ethical dilemmas such as the imminent risk of bias, instances of plagiarism, and complex copyright matters [8]. The findings of a systematic review exploring the application of ChatGPT in health care education, research, and practice revealed that ethical concerns were prevalent in 33 out of 60 records. These concerns, particularly the risk of bias and plagiarism, often revolved around data privacy and security issues [8]. This underscores the significance of investigating students' perceptions of ethics and accountability concerning the use of ChatGPT in health sciences.

Within the health sciences domain, the successful use of AI relies on several key factors. First, usability is paramount. For example, chatbots and AI programs designed to simulate conversations with human users must be user-friendly, ensuring that students, health care professionals, and patients can interact effortlessly. Second, efficiency is critical because these chatbots should streamline processes, reduce workload, and provide rapid and accurate responses [9]. Finally, the overall effectiveness of these chatbots plays a pivotal role, as they need to deliver tangible benefits such as improved patient care, enhanced diagnostic accuracy, and increased efficiency in health care operations. Consequently, the usability, efficiency, and overall effectiveness of chatbots in health sciences are vital aspects that warrant careful consideration and optimization for their successful integration into the field [8].

In this study, the term *usability* is defined as "a quality attribute that assesses how easy user interfaces are to use." The word *usability* also refers to "methods for improving ease-of-use during the design process" [10]. The 5 components of usability are learnability (how easy is it for users to accomplish basic tasks the first time they encounter the design?); efficiency (once users have learned the design, how quickly can they perform the tasks?); memorability (when users return to the design after a period of not using it, how easily can they reestablish proficiency?); errors (how many errors do users make, how severe are these, and how easily can they recover from them?); and satisfaction (how pleasant is it to use the design?) [10]. The evaluation of ChatGPT's usability will be conducted in health sciences students, as assessing the usability of this AI holds significance due to the potential impact on adopting this technology in the training of these students.

Over the past few years, extensive research has investigated the usability of ChatGPT across various domains. A study assessing ChatGPT's usability in formal English language learning revealed promising outcomes. The findings showed that

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ChatGPT is an effective tool for formal English language education, excelling in various learning tasks encompassing conversation, writing, grammar, and vocabulary enhancement [11]. A systematic mapping study examining the usability of chatbots and human-computer interaction systems examined the field exhaustively, drawing on numerous references. Of the 170 studies that met the inclusion criteria, 21 were primary studies. The authors' conclusions highlighted the emerging nature of chatbot usability research, which mainly comprises surveys, informal experimental studies, and usability tests. They emphasized the need for more formal experiments to rigorously gauge the user experience, leveraging these findings to design guidelines that prioritize usability [12]. To our knowledge, no randomized controlled trial (RCT) has assessed the usability and students' perceptions of ChatGPT use within the health sciences.

Study Objectives

Primary Objectives

We aim to explore the usability and effectiveness of ChatGPT compared with conventional web-based tools as a supplementary assistance tool to enhance undergraduate health sciences students' learning experiences and outcomes.

Secondary Objectives

Our secondary objectives are to (1) explore students' perceptions and experiences with ChatGPT as a learning tool; (2) explore the potential benefits of or barriers to using ChatGPT to improve students' writing abilities in the health sciences; and (3) investigate students' perceptions of accountability, ethical considerations, and equity concerns related to the use of AI in education.

Study Hypotheses

The study's hypotheses are as follows:

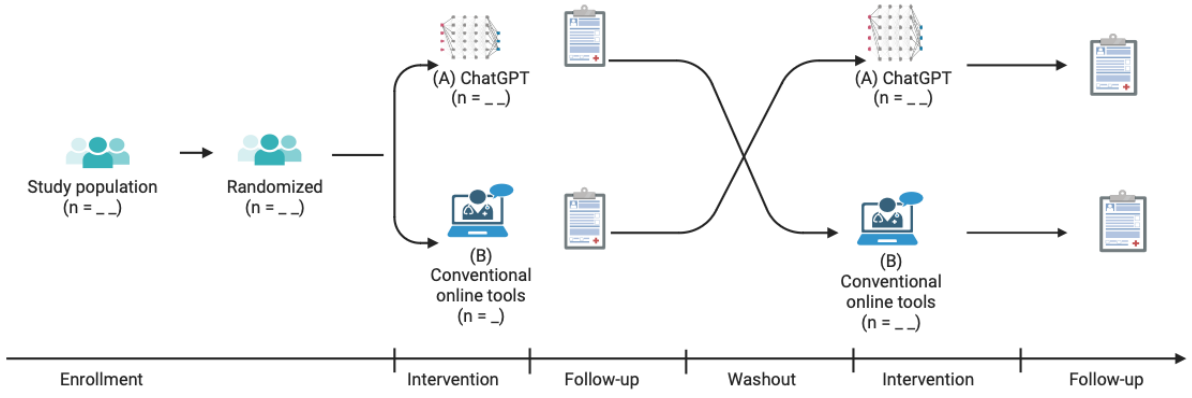
- *Null hypothesis:* there is no significant difference in technology usability and learning outcomes between students who use ChatGPT (group A) and those who use conventional web-based tools (group B) for accessing resources and completing assignments.
- *Alternative hypothesis:* there is a significant difference in technology usability between students who use ChatGPT (group A) and those who use conventional web-based tools (group B) for accessing resources and completing assignments.
- *Exploratory hypothesis:* the learning outcomes of students who use ChatGPT (group A) will significantly differ from those of students who use conventional web-based tools (group B) for completing their assignments. This hypothesis proposes that the choice of intervention (ChatGPT or conventional web-based tools) may influence the learning outcomes and explore the interaction between usability and learning outcomes.

Methods

Study Design

We will use a randomized crossover design to ensure equity in the learning experience for all students. This involves assigning students to use ChatGPT (group A) or conventional web-based learning tools (group B) to access resources and assist them in completing their assignments (Figure 1). To address the potential biases associated with the reporting of results using RCT design, we will adhere to 2 specific guidelines: the CONSORT (Consolidated Standards of Reporting Trials) and its extensions. The CONSORT statement was introduced in 1996 to enhance the quality of clinical trial reporting [13]. However, critics observe that the reporting of crossover trials has been inconsistent and incomplete. To address this issue, the CONSORT 2010 statement was extended to provide recommendations for reporting randomized crossover trials, including a specific checklist [14]. This CONSORT extension for crossover trials includes 14 additional items aimed at improving the reporting of such trials. Furthermore, our report will also draw upon the CONSORT-AI, an extension of the CONSORT 2010 statement published in 2020, which focuses on the evaluation of RCTs involving AI [15].

Figure 1. Crossover randomized controlled trial study design on the usability and efficacy of ChatGPT for health sciences students.



Setting

This crossover RCT will be conducted on the web and will include health sciences students who are registered in a course on chronic diseases and disability, a third-year undergraduate course at Carleton University in Ottawa, Canada.

Eligible participants will receive comprehensive information about the trial, including the study's purpose and procedure,

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through both verbal communication and written materials. To address ethical concerns regarding power dynamics between those responsible for the study and those who may be involved in student teaching and assessment (ie, professors) and students, we opted to involve an individual who is independent of the research team in the recruitment process (ie, a teaching assistant [TA] not involved in other aspects of the study). This decision aims to minimize any potential bias or influence that could arise from direct professor involvement in the recruitment and research. By introducing a TA to be involved in recruitment, we strive to create a more equitable research environment and mitigate any power imbalances that may exist between professors and students. This approach helps ensure that the study is conducted fairly and unbiasedly, fostering a research environment that prioritizes equal opportunities for all participants. Both groups will simultaneously work on an assignment.

Participants

Inclusion Criteria

The inclusion criteria consist of health sciences undergraduate students who are aged ≥18 years and of any gender identity at Carleton University, Canada. They must be registered in a course on chronic diseases and disability during fall of 2023.

Students who responded to the advertisements and consented to participate in the study will be included. Participant recruitment will involve the TA who is not associated with the research project and does not hold any power or authority over the students. The research assistant (RA) will be responsible for overseeing the consent process. They will ensure that informed consent is obtained from the students voluntarily and without undue influence.

Exclusion Criteria

Students who do not provide informed consent are not included in the study.

Recruitment

Recruitment will be conducted in September 2023, followed by interventions and assessments in October and November 2023. All students registered in the course will participate in the learning activities (ie, course assignments) included in this study, as these activities are mandatory for completing the course. They will be asked to give their informed consent for the data generated by their participation in the course assignments to be used for the purposes of the study and for web-based questionnaires to be sent to them to gather information about their learning experience while performing the assignments.

The students will be identified from the class list in Brightspace (Desire2Learn; the digital learning environment of the course), and all students who express their consent will be eligible for inclusion. Upon providing consent, the students will receive an invitation email containing instructions to access and complete the web-based questionnaires through the Qualtrics platform (Qualtrics International Inc). If there is no response within 2 weeks of the initial invitation, a follow-up reminder email will be sent to nonresponding students.

Sample Size

Recently, Luna et al [16] evaluated the performance of an AI compared with that of a group of physiotherapists in a squat exercise–related quiz and found that the AI demonstrated a sensitivity of 84% in providing correct responses. Assuming a minimum sensitivity of 50% as the null hypothesis, we estimated that 45 participants need to be evaluated to obtain a sample that represents the alternative hypothesis of this study with 90% power and 95% confidence (Fleiss method with continuity correction). Considering the possibility of sample loss from the first to the second intervention, we added an additional 10% added to this sample, totaling 50 students. The sample size was calculated using OpenEpi (version 3.01) [17].

Randomization and Allocation Concealment

The participants will be allocated randomly to one of the 2 sequences: ChatGPT (A), followed by conventional web-based tools (B), or conventional web-based tools (B), followed by ChatGPT (A). The allocation of participants into sequences (AB or BA) will be determined through computer-generated randomization in an allocation ratio of 1:1. The research team responsible for analyzing the data will be kept blind to the participants' group assignments. The research team will generate the allocation sequence, and the TA will enroll the participants and assign them to the intervention. The trial will adhere to established procedures to maintain separation between staff that take outcome measurements and staff that deliver the intervention [13,14].

Intervention and Measurement

During the initial phase of the study, participants assigned to sequence AB will use ChatGPT (experimental intervention: group A) to complete their assignments, while participants assigned to sequence BA will use conventional web-based tools (control intervention: group B) and serve as a control group. In the subsequent period, the interventions will switch between the 2 groups. Students will not know which one is the "intervention of interest" and which one will be the "comparator." As mentioned above, the learning activity to be assessed in this project is part of the mandatory course activities. This means that all students will receive a grade for this assignment. Therefore, the instructor will not be able to determine which students have or have not participated in the study. Students' acceptance to participate in this study only gives permission to the research team to use their data for research purposes, but all students will be assessed for this work as part of the course. The course instructor will not be responsible for grading the assignments associated with the intervention. The TA will be responsible for grading assignments and assigning a unique number code to each participating student, which will be linked to their names. This coded information will be sent to the RA to preserve anonymity throughout the process. The RA will receive the graded assignments, the student names, and their respective codes from the TA. The RA will collect the grades of the student participants and submit them to the research team members responsible for the analysis. It is important to note that the research team, which includes the course instructor, will not have access to the participants' names. Only the grades and the

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participant codes will be accessible for analysis. The research team, including the course instructor, will perform the data analysis based solely on the provided grades and participant codes, without access to any identifiable information. This further ensures that anonymity is strictly maintained throughout the analysis phase.

Experimental Intervention

In this study, the intervention of interest is the use of ChatGPT by students to complete their assignments. As part of this intervention, students will be given a period of 6 days to use it for assignment completion. Along with the assignment instructions, participants will receive an ethical guideline and specific guidelines on how to use ChatGPT effectively (Multimedia Appendices 1 and 2) [18-23].

Control Intervention

In this study, the control intervention is the use of conventional web-based tools by students to complete the assignment. In this intervention, they will receive instructions on how to complete the assignment using conventional web-based tools available on the internet, without the use of ChatGPT or other generative AI platforms “and” or “or” tools. They will have a timeframe of 6 days to complete the assignment using these conventional web-based tools. Similar to the participants in the experimental intervention, they will also be required to fill out a survey on technology usability, providing feedback on their experience with the web-based tools.

Washout Period

The purpose of the 21-day washout period is to mitigate or minimize any potential carryover effects from the intervention. The term *carryover effect* refers to the persistence of the previous intervention’s effect or the impact of the initial intervention that extends beyond its duration and influences the subsequent intervention’s effect. By incorporating a washout period, we aim to ensure a clearer distinction between the effects of each intervention and minimize any potential interference or bias [24].

The available evidence on determining the appropriate washout period to eliminate the carryover effect effectively is limited. The conventional approach for determining the washout period is often based on the concept of 5 half-lives of the specific drug involved [25]. To address the carryover effect in this study, we used 2 strategies. First, we implemented a washout period of 21 days between interventions. This time gap was intended to allow for a sufficient delay to minimize the memory of the previous intervention and any lingering effects from the previous intervention. In addition, for the second intervention, the investigators carefully selected a different topic from the assignment to ensure that students would not easily recall specific details from the previous intervention. Furthermore, the research team ensured that the assignment content for the second intervention had similar complexities and requirements to maintain consistency across the study.

Outcomes and Measurements

The outcome measures will be (1) the usability of the technological tools (ChatGPT or conventional) for completing the assignments (primary outcome), (2) the participants’ perception of these tools as support for learning, and (3) the learning outcomes (secondary outcomes). Outcomes and measurements will be collected at 2 points: at the first follow-up, that is, after the first intervention (experimental or control) in the initial phase, and at the second follow-up, that is, after the second intervention (experimental or control) in the final phase (Figure 1).

Usability

Participants in the experimental intervention (AI-ChatGPT intervention) will also be asked to fill out a survey regarding their perception of using generative AI as an assistance tool to complete their assignments. This survey aims to gather insights into their thoughts, opinions, and attitudes toward using AI in their learning experiences. Participants will have the opportunity to share their feedback on the effectiveness, benefits, challenges, and overall satisfaction while using AI for assignment completion. Their responses will provide valuable information on AI technology’s perceived value and acceptance in enhancing their learning experience. Participants in the control intervention (conventional tools) will complete the same survey, but regarding the usability of the conventional tools.

The System Usability Scale (SUS) will assess the participants’ perceptions of usability. The SUS is a valid questionnaire [26] and will be administered at the end of the interventions and when participants cross over to the other assistance tool (AI-ChatGPT or conventional web-based tools without AI). The SUS is commonly used in numerous studies to assess the effectiveness and usability of new technologies, including in the education field [27-29]. A recent systematic review of home-based telerehabilitation software systems for remote supervision revealed that the SUS tool was the most frequently used measure or tool across the studies examined [28]. This scale has been translated into several languages, including the American Sign Language [30-32]. The SUS questionnaire was originally developed as a “quick and dirty” tool, with the goal of providing a fast and nonintrusive assessment experience for participants [26]. The SUS consists of 10 items formulated as affirmative statements, for which users indicate their level of agreement or disagreement on a 5-point Likert scale (1=strongly disagree; 5=strongly agree). For the odd answers (1, 3, and 5), we will subtract 1 from the score that the user answered; for the even answers (2 and 4), the score will be subtracted from 5. The values of the 10 questions will be added and multiplied by 2.5. The final score can range from 0 to 100. Internal consistency will be calculated using Cronbach α per item and overall. This scale allows for the assessment of outcomes and comparisons within and between the 2 interventions (Table 1).

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Table 1. Overview of outcome measures.

Outcome measure	Variable or scale	Measure	Analysis method
Primary			
Usability (SUS[a])	Continuous, nominal, ordinal, and 5-point Likert-type scale[b]	• 0-100 (SUS score: >68=above average and <68=below average) • The individual scores of the participants for each question are transformed into a new number, which is then aggregated and multiplied by 2.5 to convert the initial range of scores from 0-40 to a new range of 0-100.	The frequencies, means, and SD of each item of the SUS scale will be calculated and compared using the McNemar or chi-square and Wilcoxon tests, respectively. In addition, each group's usability scores and grades will be correlated using Spearman correlation.
Secondary			
Perception of AI[c]	Continuous, nominal, ordinal, and 5-point Likert-type scale	• The questionnaire consists of four sections: (1) sociodemographic information; (2) AI literacy exploration of positive learning experiences with AI; (3) examination of negative experiences associated with AI use; and (4) an assessment of the potential for discussing accountability, fostering student leadership, and addressing ethical and equity concerns pertaining to the use of AI.	Fisher exact or Pearson chi-square test will investigate the associations between the categorized scales and sociodemographic characteristics.
Learning outcomes	Continuous	• Students' grades on both interventions. Score range (0-100)	Mean, SD

[a]SUS: System Usability Scale.

[b]5=Strongly agree, 4=agree, 3=neither agree nor disagree, 2=disagree, and 1=strongly disagree.

[c]AI: artificial intelligence.

Perception of Ethics and Accountability

After the intervention with ChatGPT, the students will be asked to fill out a web-based survey about their perception of their AI experience. The survey will use multiple-choice questions, short open questions and a 5-point Likert scale, using closed-ended response options. This response format ensures enhanced objectivity and enables appropriate discrimination to address the research objectives effectively. A closed-ended Likert scale also promotes the participants' comprehension and active engagement with the study. The questionnaire consists of four sections: (1) a sociodemographic information; (2) AI literacy exploration of positive learning experiences with AI; (3) an examination of negative experiences associated with AI use; and (4) an assessment of the potential for discussing accountability, fostering student leadership, and addressing ethical and equity concerns pertaining to the use of AI. One question of this survey was taken from a Swedish questionnaire about the use and views among university students about chatbots and other AI for learning. Qualtrics software will be used for survey design and data collection, as this software passed a security assessment of Carleton University, and its server is located in Montreal, Quebec, Canada.

The SUS survey is expected to take approximately 2 minutes to complete, whereas the perception survey is anticipated to be completed in approximately 10 minutes. By collecting data at multiple points in the study (2 points), we can evaluate the effects of each intervention and any potential carryover effects during the crossover period. In addition, it provides an opportunity to measure changes in outcomes within individual participants as they switch from one intervention to another.

Data Analysis

This study aims to compare the 2 interventions in terms of usability, student perception, and learning outcomes. The crossover design allows for within-group and between-group comparisons, enabling a comprehensive analysis of students' perceptions of the use of the intervention and its impact on their learning, as well as the effects of the intervention on their learning outcomes.

The use of an identification code will anonymize data. The data set will be exported from the datasheet and imported into the SPSS software (version 28.0; IBM Corp) for Mac, where the data will be subjected to analysis with a confidence level of 95%. Descriptive statistics, including the calculation of frequencies, will be performed on the sociodemographic variables of the students. The usability scale and grades at each assessment time will be summarized using mean and SD. The nonparametric Wilcoxon test will be used to compare the differences between these variables.

The frequencies, means, and SDs of each item of the SUS scale will be calculated and compared using the McNemar or chi-square and Wilcoxon tests, respectively. In addition, the usability scores and the grades of each group will be correlated using Spearman correlation.

For the analysis of perception and usability outcomes, we will use the Spearman correlation coefficient to assess the relationship between the 2 scales. This statistical approach was chosen to measure the strength and direction of the associations between variables when the data may not conform to a linear pattern. Using the Spearman correlation coefficient, we aim to better understand how perceptions and usability factors are

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interrelated, providing a robust basis for our research findings and conclusions. To assess the internal consistency of the scales, Cronbach α coefficient will be calculated for both constructs and for each individual item.

To categorize the students into groups of low and high performance (using a cut-off value of 80) and classify the SUS scale into high and low usability groups (with a cut-off value of 50), appropriate statistical tests will be applied. Specifically, Fisher exact test or Pearson chi-square test will investigate the associations between the categorized scales and sociodemographic characteristics.

Ethical Considerations

This study has obtained ethical approval from Carleton University Research Ethics Board-B, ethics clearance ID: 119784, ensuring strict adherence to participant confidentiality, anonymity, informed consent procedures, and data protection, in compliance with applicable institutional and ethical guidelines. No identifiable data will be included in any part of the research. Participants will be given the opportunity to enter a drawing for gift cards valued at US $25 each, specifically for completing the surveys.

Results

Data collection took place in October and November 2023; the anticipated results are scheduled for publication in 2024. We anticipate several key findings. First, randomization is expected to have groups with closely matched demographic characteristics, ensuring a balanced starting point for our analysis. Second, we anticipate that usability will be significantly higher for the ChatGPT intervention than for conventional methods, reflecting the potential benefits of AI-assisted learning. In addition, regarding ChatGPT's use in assignments, we expect to observe students expressing concerns about data privacy and plagiarism, consistent with prior literature findings on these issues. The potential correlation between usability and learning outcomes is a significant aspect to consider in our study. Understanding how usability impacts learning outcomes not only is critical for this study but also lays the foundation for future investigations. By quantifying the effect sizes of both the learning and usability effects in this study, we can better inform the calculation of sample sizes for larger RCTs on this topic. These data will be invaluable for designing robust experiments and ensuring that our research can provide meaningful insights into the relationship between usability and educational outcomes.

Furthermore, it is our anticipation that despite these concerns, learning outcomes will remain consistent across both interventions. We expect to observe that while these concerns may be raised, the overall effectiveness and educational benefits of ChatGPT are not compromised. Our study seeks to determine whether these anticipated results are confirmed. These data will contribute to a better understanding of the potential impacts of integrating AI into health sciences education.

This study is expected to contribute to the identification of key areas and challenges concerning the use of AI as an educational tool, specifically examining its benefits and challenges for students. By doing so, it aims to facilitate the establishment of comparable frameworks for future academic endeavors. In addition, the findings will enlighten educators about the potential advantages and barriers associated with integrating AI into educational activities for university students.

We expect this study's findings to be disseminated through multiple channels. The study will undergo a rigorous peer review process for publication in a reputable, peer-reviewed journal. Subsequently, the results will be initially shared with the community in the health sciences department, ensuring timely access for the scientific community. Furthermore, we intend to submit the results of this study to relevant national conferences to provide a platform for knowledge exchange and engagement with a broader audience.

Discussion

Overview

This study will compare the use of ChatGPT and web-based conventional tools in terms of usability, student perception, and learning outcomes. ChatGPT is expected to be perceived as more usable than conventional tools. However, we anticipate that both groups will achieve similar learning outcomes. Furthermore, our findings may align with those of previous studies that underscore the significance of AI in education, albeit with concerns related to data privacy, as students increasingly recognize the importance of AI in their learning experiences.

This study is expected to provide details on students' perceptions of using AI to perform their learning assignments. The results of this study will be compared with those of the literature. In recent years, there has been a growing body of research on AI, focusing on its applications in various fields, including medical education, health care, radiography, and ophthalmology [5,33,34]. Many of these studies use cross-sectional and qualitative research methods to explore the perspectives and attitudes of professionals and students [33,35,36]. Despite variations in the specific field of study, some common themes emerge from this research. These themes include a generally positive attitude toward AI's potential benefits, a widespread lack of formal AI education among participants, concerns about data privacy and ethical implications, and a clear and urgent need for structured AI education to be integrated into relevant curricula [33,35]. These studies collectively underscore the importance of preparing individuals in these fields for the increasing role of AI in their respective domains.

A study focused on assessing medical students' knowledge, attitudes, and perceptions of AI chatbots in health care revealed that while medical students generally held positive attitudes toward AI, they also had data protection and monitoring concerns. Students expressed a desire for more comprehensive AI education integrated into their medical curriculum, emphasizing the importance of preparing them for AI's role in health care [35]. A systematic review of the utility of ChatGPT, an AI-based conversational large language model, in health care education, research, and practice highlighted numerous benefits and emphasized the need for a code of ethics and responsible use guidelines for AI chatbots, such as ChatGPT in health care

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and academia, to maximize their potential while addressing limitations and risks [8]. A Canadian study explored how undergraduate medical students in Canada perceive AI in medical education. The survey conducted with 486 students from all 17 Canadian medical schools revealed that while there was a consensus that AI will be important in future medicine and should be formally taught, many students believed that there are currently insufficient educational opportunities related to AI. Interviews with students echoed these concerns, emphasizing the need for AI integration into the medical curriculum to better prepare future physicians for the changing health care landscape [33].

These studies have provided valuable insights into students' and professionals' knowledge, attitudes, and perceptions regarding AI and AI chatbots in health care and related fields. They generally indicate positive attitudes toward AI's potential benefits, along with concerns about data privacy and the need for structured AI education. However, it is essential to acknowledge that these studies have limitations, including potential biases inherent to their study designs. Therefore, further research is needed to delve deeper into the utility and students' perceptions of AI chatbots, such as ChatGPT, in health care and academia. To address these gaps and gain a more comprehensive understanding, we plan to conduct a crossover RCT. This proposed study will enable us to systematically investigate the effectiveness and user perceptions of ChatGPT in specific health sciences and educational contexts while controlling for potential biases and limitations observed in previous studies.

Limitations and Strengths

Although this study possesses several strengths, it anticipates limitations. First, the sample size may restrict the generalizability of the findings to a broader population of health sciences students. However, this constraint is balanced by the advantages of a focused investigation within a specific academic institution, allowing for in-depth exploration. Second, the relatively short intervention period may limit the ability to capture long-term effects or changes in participants' perceptions over time. Nevertheless, this controlled timeframe allows for a rigorous assessment of immediate impacts. Moreover, although the study specifically examines the use of ChatGPT, acknowledging the limitation of generalizability to other AI tools, it contributes to the existing body of knowledge in this field. Finally, participants' self-reported data, including their perceptions and experiences, may introduce response bias. However, this method aligns with the quantitative nature of the research and provides rich insights into participants' perspectives. Despite these anticipated limitations, this study's strengths lie in its focused investigation, controlled timeframe, and quantitative approach, all of which contribute valuable insights into the usability, perceptions, and potential benefits of using AI in health sciences education.

It is important to note that the next phase of this study, which involves subsequent qualitative data collection and analysis, is strategically designed to address some of these limitations. By investigating participants' experiences and perceptions through focus groups, the next phase of the study aims to provide a more comprehensive understanding of the long-term effects, nuanced challenges, and potential benefits associated with AI use in health sciences education. This approach complements the quantitative phase of the study presented in this protocol and enhances the overall robustness of the study's findings, thereby mitigating some of the anticipated limitations.

Acknowledgments

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Data Availability

The data sets used and analyzed during this study are available from the corresponding author upon reasonable request.

Authors' Contributions

MV, DK, and J-OD conceptualized this study. MV drafted the protocol, with critical inputs from J-OD, DK, MR, PGBS, and DR. All authors contributed to the study design and manuscript drafting. MV drafted the first and last versions of the manuscript. All authors have read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Tips to interact with artificial intelligence.
[DOCX File , 18 KB - resprot_v12i1e51873_app1.docx]

Multimedia Appendix 2
Guidelines for equitable use of artificial intelligence.
[PDF File (Adobe PDF File), 140 KB - resprot_v12i1e51873_app2.pdf]

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Abbreviations

AI: artificial intelligence
CONSORT: Consolidated Standards of Reporting Trials
RA: research assistant
RCT: randomized controlled trial
SUS: System Usability Scale
TA: teaching assistant

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Protocol

Design Research to Embed mHealth into a Community-Led Blood Pressure Management System in Uganda: Protocol for a Mixed Methods Study

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Abstract

Background: Uncontrolled hypertension is a leading risk factor for cardiovascular diseases. In Uganda, such diseases account for approximately 10% of all deaths, with 1 in 5 adults having hypertension (>90% of the hypertensive cases are uncontrolled). Although basic health care in the country is available free of cost at government facilities, regularly accessing medication to control hypertension is difficult because supply chain challenges impede availability. Clients therefore frequently suspend treatment or buy medication individually at private facilities or pharmacies (incurring significant costs). In recent years, mobile health (mHealth) interventions have shown increasing potential in addressing health system challenges in sub-Saharan Africa, but the acceptability, feasibility, and uptake conditions of mobile money approaches to chronic disease management remain understudied.

Objective: This study aims to design and pilot-test a mobile money–based intervention to increase the availability of antihypertensive medication and lower clients' out-of-pocket payments. We will build on existing local approaches and assess the acceptability, feasibility, and uptake of the designed intervention. Furthermore, rather than entering the study setting with a ready-made intervention, this research will place emphasis on gathering applied ethnographic insights early, which can then inform the parameters of the intervention prototype and concurrent trial.

Methods: We will conduct a mixed methods study following a human-centered design approach. We will begin by conducting extensive qualitative research with a range of stakeholders (clients; health care providers; religious, cultural, and community leaders; academics; and policy makers at district and national levels) on their perceptions of hypertension management,

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money-saving systems, and mobile money in the context of health care. Our results will inform the design, iterative adaptation, and implementation of an mHealth-facilitated pooled financing intervention prototype. At study conclusion, the finalized prototype will be evaluated quantitatively via a randomized controlled trial.

Results: As of August 2023, qualitative data collection, which started in November 2022, is ongoing, with data analysis of the first qualitative interviews underway to inform platform and implementation design. Recruitment for the quantitative part of this study began in August 2023.

Conclusions: Our results aim to inform the ongoing discourse on novel and sustainable pathways to facilitate access to medication for the management of hypertension in resource-constrained settings.

Trial Registration: German registry of clinical trials DRKS00030922; https://drks.de/search/en/trial/DRKS00030922

International Registered Report Identifier (IRRID): DERR1-10.2196/46614

(JMIR Res Protoc 2023;12:e46614) doi:10.2196/46614

KEYWORDS

Uganda; hypertension; mobile health; mHealth; mobile money; pooled financing; medication availability; human-centered design; mixed methods; mobile phone

Introduction

Background

Globally, noncommunicable diseases (NCDs) are becoming the leading cause of death [1]. Further exacerbated by aging populations, NCD-associated mortality is expected to exceed infectious and respiratory causes of death by 2030 [2]. Cardiovascular diseases (CVDs) make up 13% of the mortality rate in sub-Saharan Africa (SSA) and account for the largest proportion (37%) of deaths caused by NCDs [3], adding to a double burden of communicable diseases and NCDs. Although the age-adjusted CVD mortality rates are lower in SSA than in high-income countries, the absolute number of CVD-related deaths in SSA has increased significantly in the past three decades, largely due to rapid urbanization, population growth, aging, dietary and lifestyle changes [4,5].

The successful management of CVDs requires controlling common risk factors (such as hypertension and diabetes) and ensuring that access to required medications is stable. The latter point is particularly challenging in settings marked by scarcity. In Uganda, an estimated 26.4% of adults have high blood pressure, and another estimated 36.9% of the country's population are estimated to be prehypertensive (with a blood pressure reading of >120/80 mm Hg) [6]. Among those who are prehypertensive, approximately one third could become hypertensive within 4 years [7]. Although basic health care is meant to be available free of cost at government facilities across the country, the availability of essential medicines for conditions requiring long-term management, including hypertension, is generally low [8-10]. Clients who do not receive treatment at government facilities must buy prescribed medicines at private health facilities or pharmacies, where prices tend to be 3 to 4 times higher than at public facilities [11]. Out-of-pocket payments represent 39% of the total health care expenditures in Uganda [12], often exceeding the resources of many households and causing noncompliance with prescribed regimens [13-15]. The resulting regular disruptions in long-term medication schedules can result in uncontrolled blood pressure associated with a high CVD risk.

However, uncertainty remains in terms of potential interventions to sustainably address gaps in NCD care in SSA in general and Uganda in particular. Several novel approaches have been recently trialed, including community health worker (CHW) mobilization in South Africa [16] and medication adherence clubs in Kenya [17]. Other novel approaches have explored mobile health (mHealth) to target medication adherence (eg, SMS text message reminders for tuberculosis medication [18] or an electronic app for self-monitoring in Uganda [19]). Dialogue within our team (comprising anthropologists, epidemiologists, clinicians, nurses, community outreach workers, community leaders, and policy makers) therefore guided us toward mHealth solutions with a particular focus on mobile money, given that medication adherence is greatly affected by financial resources [20].

Mobile money, which refers to payments made via a digital wallet on a mobile device, has been evaluated in several studies for health interventions in SSA to address health system challenges in agile ways, including mobile money transfers to pay transportation costs for patients with cancer in Malawi [21] or to facilitate health insurance uptake in Kenya [22]. In Uganda, mobile money programs across the country have provided a savings mechanism to many people who were previously unable to access formal bank accounts; in 2021, approximately 71% of individuals were registered for a mobile money account [23] (compared with 29% of individuals having access to a formal bank account [24]). However, although a range of sectors have used mobile money approaches to facilitate payment for, among others, school fees, bills, water or food [25,26], application in the context of health interventions in Uganda has so far been limited.

To the best of our knowledge, no interventions have yet explored the potential of mobile money approaches in alleviating financial difficulties for hypertension treatment. Although the interest in mHealth interventions in general is rising, and the potential of mobile money for economic equality in particular is high [27], their application might be associated with implementation challenges, with scholars highlighting the complexity of mHealth interventions, particularly in relation to accessibility [28]. However, person-based development strategies have shown

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promising results in terms of increasing the interventions' acceptability and feasibility [29,30], but these strategies remain underused when exploring the potential of mobile money approaches to chronic disease care. This study seeks to fill this gap in the literature by applying human-centered design (HCD) to co-design and test an mHealth blood pressure management intervention in rural Uganda, assessing the design process as well as intervention uptake and viability.

Study Objectives

This study aims to codevelop (with end users and implementers) an integrated mobile money–based solution for antihypertensive medication delivery and to assess the platform's feasibility, acceptability, and effectiveness.

The specific study objectives are as follows:

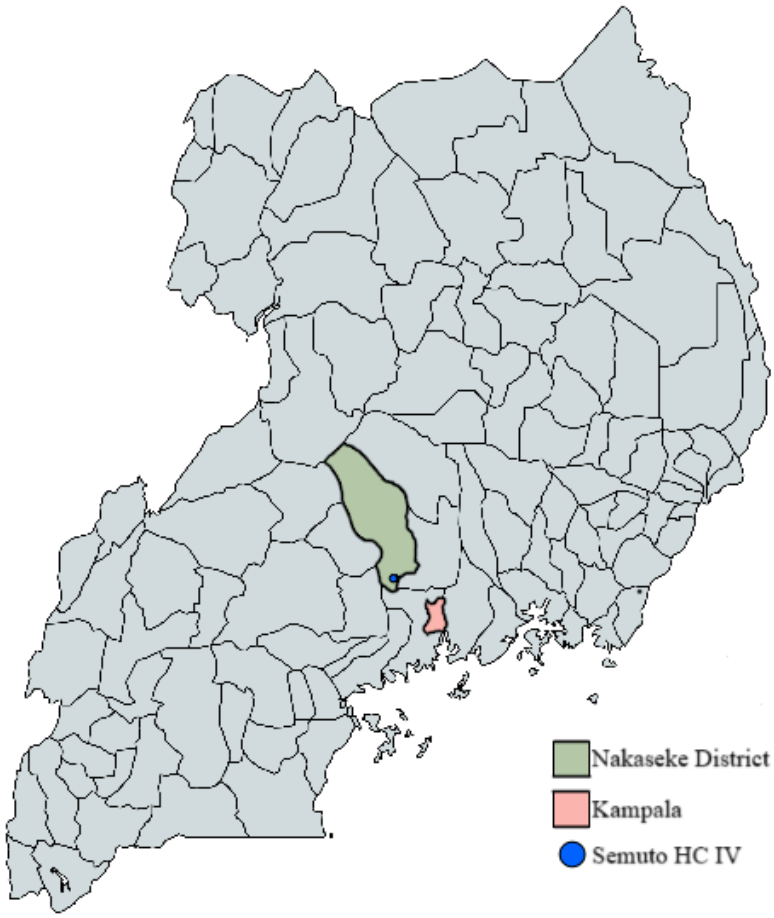
1. Understanding client, provider, and intervention implementer perspectives on financing schemes and mHealth interventions that are meant to increase medication availability and uptake among clients with NCDs (work package [WP] 1a).
2. Developing together with end users a prototype for a mobile phone–based solution to increase the availability and uptake of antihypertensive medication and assessing the development and design process (WP 1b and WP 2).
3. Testing the prototype and evaluating end users' and health providers' experiences with 2 versions of the prototype, including how users make and evaluate payment management decisions (WP 3) and whether 1 version is more effective than the other.

Methods

Study Setting

This design research study will take place in rural Nakaseke district, Uganda, with a population of 29,400 [31] (Figure 1). Nakaseke administratively belongs to the central region of Uganda, where an estimated 28.5% of the population are hypertensive [6]. Our study will focus on clients within Semuto Health Center IV, chosen during an early formative phase of research because the center has initiated an alternative, promising approach to manage blood pressure, which is described in the following subsection.

Figure 1. Map of Uganda highlighting the location of our study setting: Nakaseke district and Semuto Health Center (HC) IV.



Semuto Health Center IV's Alternative Approach: A Community-Led Pooling Strategy

Recognizing the challenges of medication supply, the clients and staff of a designated NCD treatment unit at Semuto Health Center IV collectively initiated a client self-help financing scheme wherein clients living with hypertension were invited to pay 2000 Ugandan shillings (US $0.54) per clinic visit, and clients living with diabetes were invited to pay 7000 Ugandan shillings (US $1.87) per clinic visit. These funds were then pooled to purchase medication. This initiative sought to increase medication availability by buying in bulk via a wholesale

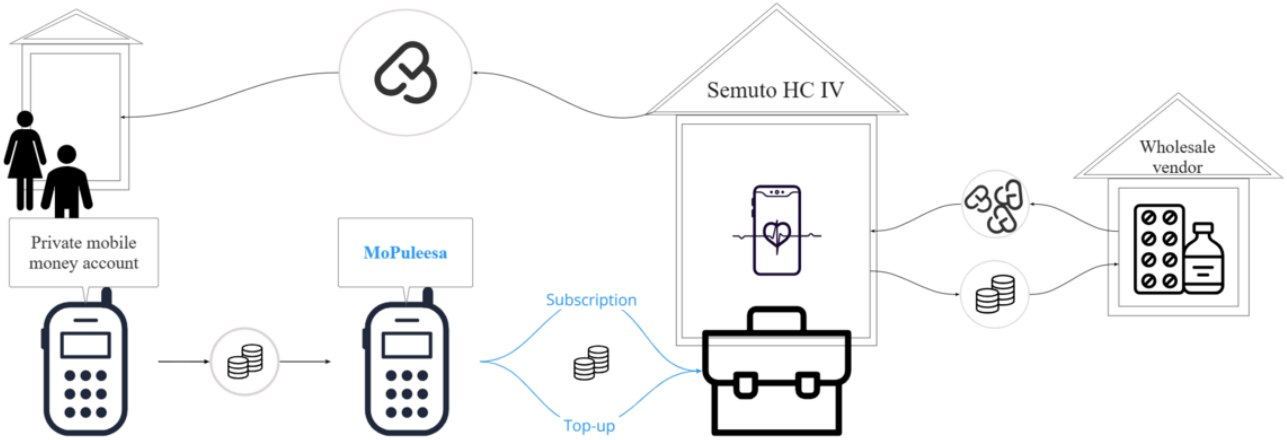
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vendor, which is a more cost-effective approach than purchasing medication from a retail vendor. Payment was voluntary; those who contributed to the pool could draw on the additional allotment, whereas those who did not contribute could access government-supplied medication. Beyond purchasing blood pressure medication, excess funds were also used to purchase equipment such as batteries or glucose strips. The scheme, although promising, was not reliably generating sufficient funds to ensure a continued supply of medications and proved challenging in terms of paperwork, accounting, and management. A nurse was assigned the task of purchasing medication from a central pharmacy in the capital, Kampala, but real-time knowledge regarding the amount of funding available complicated her purchasing trips. Furthermore, the clinic staff struggled to track who had made or not made payments, which would affect who could draw from the specially purchased pool of medication.

Semuto Health Center IV Approach 2.0: The MoPuleesa Intervention

Building on the paper-based approach of Semuto Health Center IV, we will digitize and expand the existing system, drawing on insights from community members, software programmers, anthropologists, social scientists, health care providers (HCPs), mHealth implementers, policy makers, and local leaders with an aim to create a continual flow of money to secure medication availability. The proposed money flow is illustrated in Figure 2.

Figure 2. Flow of money from the client via their mobile health wallet to the Health Center (HC) and medication flow back to the client.



The central component of the co-designed intervention will be the mHealth wallet (illustrated as the *MoPuleesa feature phone* in Figure 2 [*puleesa* means "pressure" in the Luganda language]), which will allow clients to deposit the money they wish to save for their health care expenses via their private mobile money accounts. Others (eg, family members) who are themselves not users of the system can also remotely contribute to a client's mHealth wallet. Clients will be prompted to transfer money from their account to the clinic pool to facilitate bulk medication purchasing via 1 of 2 ways: either allowing for a specific amount of money to be automatically transferred from a marked savings account via direct deposit at predetermined and fixed intervals (the *subscription approach*) or independently transferring amounts of their own choosing at any time within a 1-month period (the *top-up approach*), shown by the corresponding arrows in Figure 2. Clients using the subscription approach who want to change the subscription amount or frequency can approach the designated clinic staff in person at the health center. For the top-up approach, clients can choose the timing themselves but can only contribute the exact amount needed to avail drug coverage each month; excess contributions will not be transferred to the following months. Core principles guiding our design and implementation efforts are the engagement of CHWs for community commitment, the use of mHealth technologies not requiring costly infrastructure at an individual level, and the integration of the designed intervention into existing clinic structures via a multidisciplinary team.

To facilitate end-user buy-in, we will work with CHWs, who are volunteers serving as intermediaries and communication links between clients and medical facilities within their own communities, which often imbues them with considerable trust, experience, and communicational skills [32,33]. In our study, we will include CHWs not only for outreach and recruitment purposes but also as key informants who can provide valuable insights on setting and intervention design, supporting a sustainable outreach that in turn might enhance the engagement of the community with the intervention and assist regular contributions.

For the integration of a novel technology, we acknowledge the need for easy accessibility by all members of the community; therefore, the platform does not rely on users having their own smartphone or an internet connection. Instead, following successful examples [34,35], all system functions will be accessible from feature phones via unstructured supplementary service data (USSD) menus, which operate via service and control commands in a mobile network. To access the USSD menu, users will be able to either register their own mobile phone number or receive a new SIM card in their name upon study enrollment (with which they can access their personal account via the mobile phones of CHWs, other clients, or any friend or family member). For validation purposes, the study team will routinely conduct on-site user research with stakeholders and end users to ensure that the envisioned flows and developed prototypes fit the needs of end users. Following

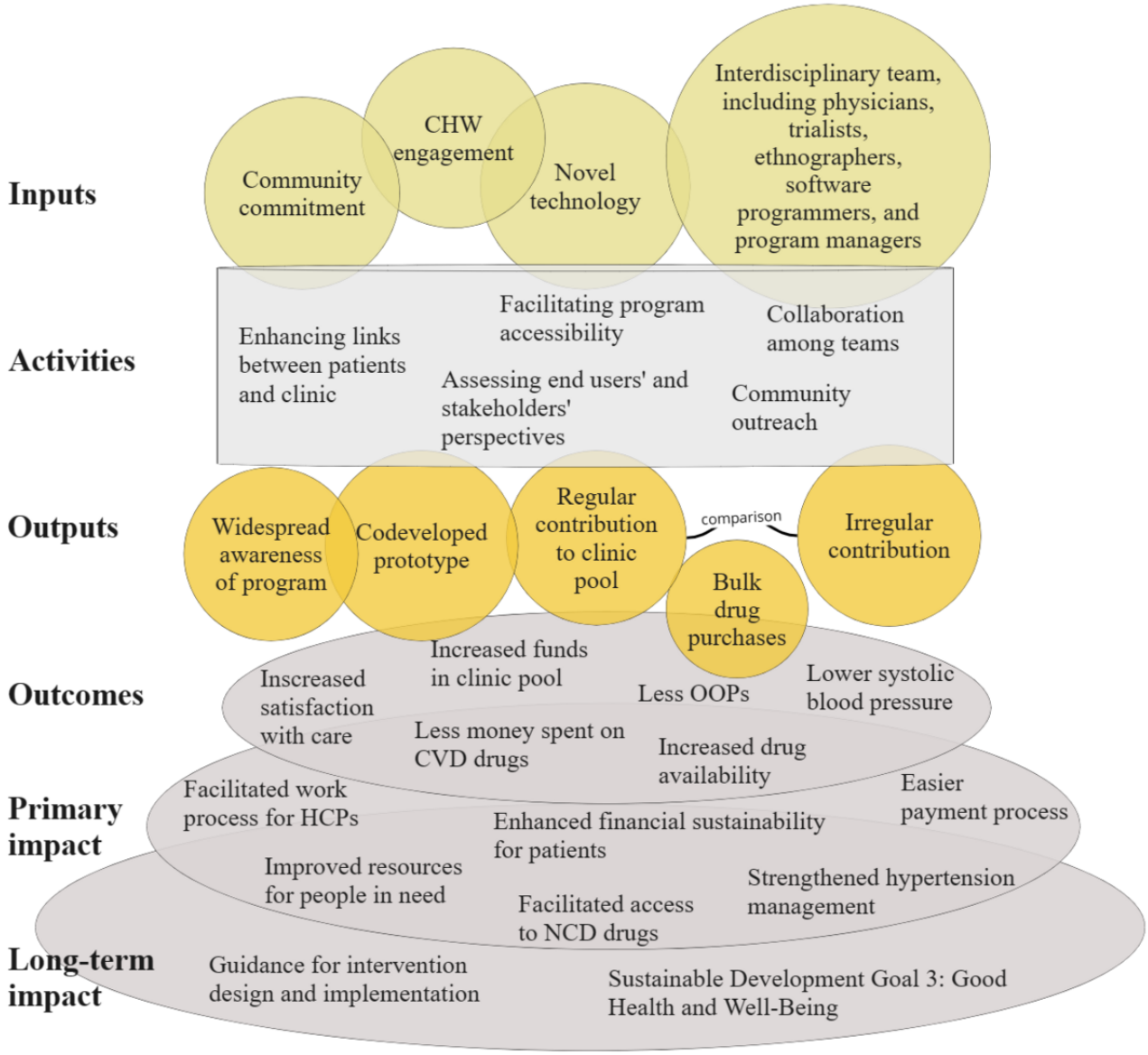
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the tenets of HCD, this validation process is directly integrated into the prototype codevelopment and product design.

Theory of Change

Building on the envisioned MoPuleesa intervention approach, Figure 3 summarizes key inputs, activities, and causal pathways that underpin our design and implementation work, serving as a guide to understand how the intervention will lead to the desired outcomes and impact.

Figure 3. Theory of change illustrating inputs and activities, with expected outputs, outcomes, and impact. CHW: community health worker; CVD: cardiovascular disease; HCP: health care provider; NCD: noncommunicable disease; OOP: out-of-pocket payment.



We theorize that the mHealth platform will foster a regular influx of money into the pooled system, which will allow the clinic to purchase antihypertensive medication in bulk via designated channels (medication purchase by the health center directly from wholesale vendors shown in Figure 2), thereby reducing costs for individual clients (compared with out-of-pocket purchasing of medication at pharmacies) and facilitating a sustainable, stable supply of medication. Considering a possible scale-up of this intervention and learning from our design and implementation process, we envision a long-term impact (shown in the increasingly larger circles in the lower part of Figure 3) on the well-being of patients with hypertension and on scientific intervention design efforts. Our envisioned methodological approaches to achieve this goal and the overarching study objectives are outlined in detail in the following subsections.

Methodology

Originating in computer science, artificial intelligence, and ergonomics, HCD has more recently begun to inform how public health actors design and implement health interventions [36]. In the HCD approach, end users are involved in all stages of the design process and have influence on the final product of the intervention, with the implicit rationale that engaging users facilitates implementation success [37]. HCD begins with developing a thorough understanding of the status quo in

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question to define an issue that will be addressed. On the basis of this understanding, researchers and end users together develop an idea for a potential product or intervention (empathize, define, and ideate). As this process continues, researchers elicit feedback to iteratively adapt the envisioned solution to end users' needs and expectations to maximize the fit of the developed prototype to the setting at hand (prototype). Finally, the developed product is pilot-tested (test).

As a design-driven study, this research did not begin with a predetermined intervention in mind; instead, we sought to capture the nature of the challenge and potential solutions, identified as promising, in similar settings. We use the HCD approach to identify product priorities and intervention approaches and to codevelop product prototypes together with end users. Once a final product is identified, it will be evaluated quantitatively for efficacy, usability, and desirability.

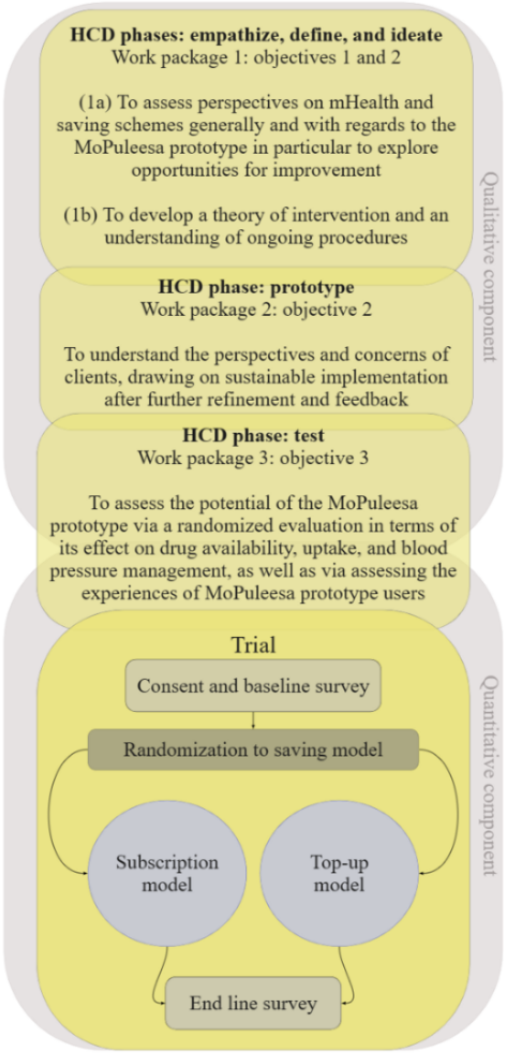
To provide maximum experience and expertise, we will leverage the multidisciplinarity of our team throughout the project with a focus on trust, communication, and team identification within the team to facilitate collaborative work [38]. Our team includes ethnographers and social scientists who will ensure context sensitivity and qualitative insight into end users' and stakeholders' experiences, preferences, and perspectives; local clinical research leaders who will tap into context expertise and communication channels; medical professionals, including biomedically trained clinicians, who will assess the medical aspects and health benefits of the intervention and gain insight into the local health system; NCD-focused trialists who can meaningfully incorporate quantitative results that can guide further research directions; and, finally, software programmers and experts in the technical aspects of the project who will guide successful implementation, identify opportunities, and make the intervention as up to date and innovative as possible.

Research Design

This study will follow a mixed methods exploratory sequential design [39] in line with established recommendations for HCD studies [40,41]. In a first step, the design approach will allow us to qualitatively explore stakeholder perceptions, experiences, and recommendations in the setting at hand, informing key design decisions in accordance with specific study objectives 1 and 2. Although formative research revealed the essential challenge of accessing drugs in the study setting and recognized mobile money as a potential solution, qualitative data are needed to inform the design and operationalization of the platform, anticipate potential difficulties and facilitators, and assess clients' willingness to accept the approach. Building on these qualitative results, while maintaining core trial design and rationale, we will refine and finalize the concluding quantitative component aimed at pilot-testing the intervention in the form of a randomized controlled trial (study objective 3). Sequentially combined, these methods will allow us to ideate and design an intervention adapted to the specific study context, as well as allow for evidence-based conclusions regarding the prototype's potential in facilitating sustainable hypertension care. Figure 4 highlights the overlap of research activities and WPs across the HCD phases.

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Figure 4. Summary of all study phases and methods (including trial details) corresponding to specific study objectives. HCD: human-centered design; mHealth: mobile health.



HCD Phases

Empathize, Define, and Ideate: WP 1

WP 1 is divided into 2 phases, both informed by the tenets of HCD. In the first phase (WP 1a), we will conduct in-depth interviews (IDIs) and focus group discussions (FGDs). The IDIs will facilitate the capture of clients' personal perspectives on, and experiences with, blood pressure management and hypertension, mHealth, savings schemes, and the existing paper-based scheme that inspired this work. We will explicitly probe on more nuanced facets such as trust and transparency. In addition to IDIs, we will conduct FGDs to determine how groups such as HCPs, clients, and CHWs negotiate the trade-offs and opportunities of different approaches to hypertension management and care, including the proposed intervention. Within the FGDs, the envisioned platform use process will be explained to participants step by step, and feedback will be gathered. We will collectively determine intervention facets, such as how the intervention should be explained or presented within a community, who should be responsible for enrolling clients and troubleshooting challenges, what foreseeable challenges respondents see with the intervention, and how these should be circumnavigated or addressed. Finally, within WP 1a, we will examine field notes from the previous phases of formative research, where we collected information on CVD management in Nakaseke region from NCD clients and HCPs; these notes will bolster our own recall of the system in place at Semuto Health Center IV and its development, which can inform how we can build a meaningful product.

In a second phase (WP 1b), we will conduct nonparticipant semistructured observations of client-provider interactions and clinic processes, as well as IDIs with higher-level stakeholders. The observations will be conducted by research team members working in Nakaseke district who will already have interacted with clients and providers on site; this will allow us to understand actual behaviors and current workflows regarding hypertension management and care in the study setting (including, eg, how client-provider interactions and medication procurement or delivery currently take place). Using an observation checklist, we will examine how health services related to blood pressure management are currently provided and how clients are handled at Semuto Health Center IV. In addition, we will gather information on the locations and processes of medication prescription, storage, and delivery. In the stakeholder IDIs, we will capture insights from policy makers, academics, and public health actors at community and

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national levels to determine the feasibility, opportunities, and potential pitfalls of our proposed intervention, both with regard to our target setting and when considering how to scale-up our intervention. Table 1 summarizes the individual activities conducted in WP 1a and WP 1b.

Table 1. Methods used in work package (WP) 1: in-depth interviews, focus group discussions, and document analysis.

Activities	Participants	Themes	Purpose
WP 1a			
IDIs[a] (n=20-40)	Clients visiting the NCD[b] clinic at Semuto Health Center IV	• Hypertension management and care • Mobile health • Money-saving schemes • Feedback on early concepts for the intervention	To identify essential facets to include in the prototype
FGDs[c] (n=5)	Clients and CHWs[d]	• Perspectives on planned intervention • Communities' hypertension experiences and perspectives	To identify possible facilitators and barriers to intervention implementation
Document analysis	Field notes	• Field notes from formative research phase	To gather information on what has informed the existing approaches and identify key stakeholders
WP 1b			
Semistructured observations (n=3-5 clinic days)	HCPs[e], clients, and staff at the health center	• Client-provider interaction (n=10) • Clinic processes • Medical examination • Medication procurement and delivery • Locations of medication supplies, output, or storage	To understand current workflows regarding NCD management and care
IDIs (n=10-20)	Academics, implementers working on CVDs[f] or mHealth[g] interventions, and policy makers	• Development and implementation of mHealth interventions • Research on NCD management • Current health care services	To develop a theory of intervention for implementation and scale-up

[a]IDI: in-depth interview.

[b]NCD: noncommunicable disease.

[c]FGD: focus group discussion.

[d]CHW: community health worker.

[e]HCP: health care provider.

[f]CVD: cardiovascular disease.

[g]mHealth: mobile health.

Prototype: WP 2

WP 2 (Table 2) aims at finalizing the design prototype and preparing for pilot testing. To collect detailed feedback from end users and ensure that the final product aligns with their expectations, we will present a first MoPuleesa prototype on mobile devices to the end users. Luganda-speaking research team members on site will conduct think-aloud exercises, which will allow a much more targeted refinement of the prototype to address emerging barriers or challenges [42]. Think-aloud exercises are used to track a participant's thoughts while using a platform and to capture their problem-solving process [43]. After a short practice phase, participants are asked to comment on each step they take while using the platform and to say out loud what thoughts come to mind [42]. To minimize potential biases, data collectors will be asked to not interrupt the exercise and not interact with participants during the exercise unless they stop speaking (whereupon participants will be encouraged to continue speaking). Furthermore, we will capture local policy makers' and local leaders' feedback on the prototype and envisioned implementation processes via IDIs to further refine the prototype and identify potential difficulties and facilitators for rollout.

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Table 2. Methods used in work package 2: think-aloud exercises and in-depth interviews.

Activities	Participants	Themes	Purpose
Think-aloud exercises (n≤40)	Clients, HCPs[a], CHWs[b] (who have or have not used a version of the prototype before)	• Interaction with latest prototyped platform • Usability of platform features	To refine the prototype to address emerging barriers or challenges
IDIs[c] (n≤20)	Key stakeholders (policy makers and local leaders)	• Latest prototype version • Benefits and barriers • Implementation process	To incorporate further concerns and perspectives

[a]HCP: health care provider.

[b]CHW: community health worker.

[c]IDI: in-depth interview.

Test: WP 3

In WP 3 (Table 3), we will pilot-test the final prototype. For the qualitative component of this WP, we will conduct IDIs with clients who were particularly engaged in previous interviews or who suggest during trial administration that they would like to expand on their responses in more detail to get a full understanding of their perspectives on the design and implementation process. In addition, to provide guidance on best practice approaches to co-designing mHealth interventions with end users, we will conduct IDIs with key stakeholders involved in this process, including health center staff, software developers, and members of the study team.

Quantitatively, we will assess differences between the top-up and subscription contribution options, as well as the impact of the intervention on service use, user satisfaction, intervention uptake and funds contributed, and clients' blood pressure readings, in a 2-arm between-participants parallel randomized controlled trial.

Participants will be randomized to 1 of the following 2 intervention arms (for the randomization plan, refer to the *Sample, Sampling, and Data Collection* subsection):

Table 3. Methods used in work package 3: in-depth interviews and randomized controlled trial.

Exercise	Participants	Themes	Purpose
Qualitative			
IDIs[a] (n=5-7)	Clients (particularly engaged in previous interviews or suggested during survey administration that they would like to expand on their responses in more detail)	• Expectations toward the prototype • Perception of implementation process	To assess experiences with the finalized prototype
IDIs (n=10-15)	Key stakeholders involved in the implementation process (health center staff, software developers, and members of the study team)	• Team communication • Implementation process • Problem-solving	To provide guidance on best practice approaches to co-designing mHealth[b] interventions with end users
Quantitative			
Trial (sample size: 250-350 clients)	All clients who have given consent to participate in the trial and take up a money-saving model	• Baseline and follow-up survey • Kano questionnaire [44] • Aggregation of clinic data	To gather information on trial participants

[a]IDI: in-depth interview.

[b]mHealth: mobile health.

Arm 1: subscription-based model, where individuals will be given the opportunity to enroll in a medication-specific mobile money savings account where they can deposit money over the course of the month. If clients reach the minimum amount needed to purchase medications for the following visit, the money will be automatically debited from their savings account at the end of each month.

Arm 2: top-up payment model, where clients can actively make mobile money transfers to the health facility throughout the month for the purchase of medication in the subsequent month without the option to make marked contributions for several months in advance.

Main Hypothesis

For the comparison between these 2 subscription approaches (specifically study objective 3), we draw on ongoing discourses in the literature regarding the chances and challenges of monetary contribution approaches for various purposes. Our considerations included findings regarding the differences between restrained commitment accounts and flexible liquid accounts that suggest greater willingness to save with less account flexibility in cases where clients self-report awareness of their own limited saving discipline [45]. In addition, several scholars have suggested that marked savings accounts, similar to our proposed subscription-based model where clients can

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save money to cover automatically deducted monthly medication costs, increase utility costs for the later repurposing of already made marked savings and thereby can increase overall savings made for the intended purpose [46,47]. Furthermore, Fisher and Anong [48] have found that long-term saving motives as well as low risk tolerance might add to regular savings. Transferred to the setting at hand, this suggests that marked savings combined with regular and automated contributions might be preferred to ensure sustainable contribution and treatment.

When testing the developed prototype, our main hypothesis therefore is that the subscription model, combining benefits from committed, semiliquid, and long-term savings possibilities, will lead to more clinic visits, more intervention take up, and greater funds contributed to the health facility for the purpose of purchasing essential medications. We argue that, thanks to the ability to save dedicated funds in small increments for the explicit purpose of accessing a guaranteed medication stock, individuals in the subscription arm will be more likely to contribute to, and pick up, antihypertensive medications than individuals in the top-up payment arm. We will test whether this will lead to monetary savings (eg, individuals receive their medications through the public facility at a lower total cost than when purchasing out of pocket from a private pharmacy) and improved health (eg, individuals will be more consistent with picking up their medication and thus have improved blood pressure). We will evaluate the effect of the subscription model compared with that of the top-up payment model based on the outcomes listed in Table 4.

Table 4. Outcomes.

Category	Outcome	Measurement
Primary outcome	• Number of NCD[a] clinic visits as well as number of medication pickups	Health facility records
Implementation and medication outcomes	• Percentage of people who take up funding models • Total amount contributed to the clinic funds	Directly from MoPuleesa platform
Long-term health outcome	• Systolic and diastolic blood pressure readings	Collected through CHWs[b] and health facility records
User experience outcome	• User satisfaction	Questions on user satisfaction in baseline and follow-up surveys

[a]NCD: noncommunicable disease.

[b]CHW: community health worker.

Participants will be asked to fill out a questionnaire at baseline and after 6 months that will address care-seeking behavior, the consistency of medication pickups, health-related money-saving routines, and the perceptions of care quality. At baseline, the questionnaire will also include sociodemographic characteristics. At 6 months, the questionnaire will further include questions about the feasibility and acceptability of the intervention, as well as a short series of platform attribute or Kano-style questions (the Kano model describes the relationship between product attributes and user satisfaction or disapproval to determine the relative importance of product features [44]). In addition, we will use data routinely collected at clinic level (demographic data, blood pressure readings, and height and weight measurements) and via the MoPuleesa prototype (money contributed and medication ordered) as detailed in Table 4.

Participants and Inclusion Criteria

Across all WPs, the respondent groups include HCPs at facility and community levels (medical doctors and clinic staff), CHWs working in the community, community members and key stakeholders (religious and local leaders, members of pooled financing schemes, and academics), clients (diagnosed with hypertension and living within the catchment area of Semuto Health Center IV), and decision makers (policy makers and ministry of health representatives). In the final WP, we also include study team members involved in intervention design, implementation, and evaluation processes as respondents.

Ethnicity, race, political orientation, religion, and class are not criteria for inclusion or exclusion in this study. Respondents must be aged ≥18 years to participate. Persons who are incapacitated (mentally challenged or physical disability: hearing and speech impaired) are excluded from this study. Textbox 1 summarizes the inclusion and exclusion criteria for this study.

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Textbox 1. Study inclusion and exclusion criteria.

Inclusion criteria (aged ≥18 y and having given informed consent)

- Health care providers: community health workers, medical doctors, clinic staff working at Semuto Health Center IV or in community outreach in Nakaseke district, etc
- Local key stakeholders: religious and local leaders, members of financing schemes, academics, etc
- Clients: clients who have been diagnosed with hypertension and are registered at Semuto Health Center IV
- Decision makers: policy makers, ministry of health representatives, health insurance representatives, district administrators, etc
- Study team members: individuals involved in the intervention design, implementation, and evaluation

Exclusion criteria

- Refusing or withdrawing informed consent
- Not responding to invitations to participate
- Persons who are incapacitated (mentally challenged or physical disability: hearing and speech impaired)

Sample, Sampling, and Data Collection

Qualitative Components

For the qualitative components of this study, we expect to recruit a maximum of 160 individuals. In line with the tenets of saturation (new data cease to provide fundamentally novel insights) [49] and information power [50], our sample size will be determined as data are collected. The aforementioned estimate is based on experience and an effort to achieve a justifiable trade-off between collecting high-quality data and minimizing strain on the target populations (eg, individuals to be interviewed) [51].

We will use purposive sampling [52] for WP 1 and WP 2 to gain a range of perspectives. Local leaders, policy makers, and academics will be contacted and recruited through the official communication channels for the respective health facility or office or via the established channels of African Community Center for Social Sustainability (ACCESS) Uganda. Health care professionals will be contacted through the respective clinics or when conducting structured observations once the clinics have agreed to participate. We will use snowball sampling [53] as necessary to contact additional participants.

For clients, convenience sampling [52] will be used. Clients will be approached during structured observations in the clinic areas where they await NCD care (waiting time: minimum 30 min). As clinic days for NCD care are conducted once a week at the health facility, clients will additionally be purposively recruited via local HCPs guiding the study team toward a range of clients who represent different types of background characteristics using the sampling criteria: age group (those aged >50 y and those aged <50 y), gender (male and female), and condition (hypertension, diabetes, or both). The study will be briefly introduced using an information sheet. If clients signal interest to participate, contact information will be exchanged to schedule an IDI. All IDIs and FGDs will take approximately 60 minutes and will be conducted by researchers and research assistants, including CHWs who work in the area but not in the study setting. All research assistants will have gone through a 5-day training program in qualitative research and interviewing and will work together as teams of 2 people representing a moderator and a notetaker. Research assistants will be provided with interview guides that will be refined in group sessions during the 5-day training period and pilot-tested on 2 days with participants within the study setting.

Quantitative Component

For the quantitative component, we anticipate enrolling between 200 and 350 clients. Client recruitment will follow the same procedures as those outlined in the previous subsection. This number was not the result of a detailed power calculation; rather, it was determined and constrained by the total client population from which we can recruit. Specifically, based on our discussion with the administrators of the NCD study clinic at Semuto Health Center IV, the clinic currently serves approximately 380 clients who meet the aforementioned inclusion criteria. Thus, we realistically expect to enroll 200 to 350 clients based on exact attendance during the study period and refusal rates.

Sample Size Estimation

On the basis of the range of recruited participants, we estimate the following minimal detectable effects (Table 5). For these calculations, our primary outcome is the number of clinic visits for medication pickups. On the basis of the 6-month study duration, this can range from 0 to 5 visits (individuals are asked to come once a month), which we will analyze as a count variable using Poisson regression. We additionally set an α of 5% and a power of 80%, with a 2-tailed *t* test for all estimates, and show the minimal detectable effects across a range of possible control counts (the number of visits for pickups among the voluntary contribution group in a range from 1 to 5) and sample sizes (ranging between 200 and 350). The minimum detectable effect is expressed as a rate ratio and measures the percentage increase in mean visits for the subscription contribution (intervention 1) compared with those for the voluntary contribution (intervention 2) over the 6-month study period.

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Table 5. Minimum detectable effect size across sample sizes and base rates.

Mean number of visits in the voluntary contribution (intervention 2) group	Minimum detectable effect size			
	200[a]	250[a]	300[a]	350[a]
1	1.44	1.39	1.35	1.32
2	1.30	1.27	1.24	1.22
3	1.24	1.22	1.20	1.18
4	1.21	1.19	1.17	1.16
5	1.19	1.16	1.15	1.14

[a]Total sample size (50% intervention 1 and 50% intervention 2).

Randomization

Participants will be randomized to be offered either the subscription model or the top-up contribution payment model and assigned to the different models by study team members after the initial recruitment at the facility and upon providing informed consent. The allocation sequence for the random assignment of the intervention was developed by an independent statistician. Individuals are randomly assigned in a 1:1 ratio. We use stratified randomization by sex and day of recruitment, with participants randomized in blocks of 4 to maximize balance between treatment and control. The allocation is concealed because assignment is based on a random draw from a box such that an individual's assignment is only revealed after they physically draw a slip.

Randomization Implementation

The quantitative research team developed the allocation sequence, and the research assistants enroll participants into the study. After enrollment into the study, each participant will be assigned to a particular arm by drawing concealed slips labeled either direct payment or savings from a box on the day of their recruitment into the study.

Blinding

The allocation sequence of assigning the intervention will be concealed from the research team until the moment of assignment. This will prevent selection bias when assigning participants to study arms. However, because of the nature of this intervention, blinding of neither the research team nor the participants will be possible once the program has started.

Data Management

The research study data manager will guide the data management responsibilities for this study. This study's quantitative data will be collected using both paper and electronic case report forms, whereas qualitative data will be collected using audio recorders. Transcripts and field notes from the qualitative work as well as the paper case report forms will be kept under lock and key and will be overseen by the principal investigators. The transfer of participant-related data, if any, will be carried out in pseudonymized form; third parties will not have access to original data. REDCap (Research Electronic Data Capture; Vanderbilt University) will be used to enter, store, and manage quantitative data. To ensure that quality data are collected, the REDCap platform will provide an interface for data entry (an audit trail to track all changes within the database). In addition, automated validation checks will be embedded within the study database. The study data manager will share data queries generated from the accruing data with the research team on a biweekly basis.

Data Analysis

Qualitative Data Analysis

Data generated from the qualitative interviews will be transcribed verbatim and analyzed using NVivo software version 14 (Lumivero) following a five-step framework approach: (1) *familiarization with the data*, (2) *identifying a thematic framework*, (3) *indexing*, (4) *charting*, and (5) *mapping and interpretation* [54]. This will help us generate an understanding of stakeholders' experiences with the prototype. After the completion of the intervention prototype, a detailed analysis plan for this study will be developed. To adapt and inform our design and implementation processes, we will conduct systematic debriefings after each day of qualitative data collection. In weekly team meetings, we will share the first findings from these debriefings with all team members to adjust platform features to end users' needs and facilitate implementation steps within the community.

Quantitative Data Analysis

We will summarize participant demographic characteristics and assess baseline balance between those randomized to the top-up and subscription arms. We will then assess the effect of offering the subscription model on the number of clinic visits with medication pickups (the main outcome) by comparing differences between those *offered* (including those who were offered and did not take up) the subscription model and those *offered* the top-up contribution model. As not all individuals will take up the offer, this will represent the intention-to-treat effect. We will estimate this effect using Poisson regression models. Next, we will assess the effect of the amount of money an individual contributed on the number of visits they attend. We will do this using a Poisson instrumental variable regression approach, where we use the random assignment as an instrument for the amount of money contributed. Finally, we will assess the effect of the random assignment to the different contribution arms on the proportion of individuals who take up the contribution model (the implementation outcome) using linear probability models and the effect on systolic and diastolic blood pressure readings using linear regression models.

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Statistical Analysis

The baseline characteristics of participants will be compared between the 2 arms using medians and IQRs for continuous variables and proportions for categorical variables. Outcomes will be analyzed by both the intention-to-treat and per-protocol analysis methods using mixed effects Poisson regression methods for the primary outcomes. We will adjust for baseline imbalances for both the primary and secondary analyses, and both unadjusted and adjusted analyses will be presented. All our regression models will additionally control for baseline patient characteristics such as age, sex, and income to increase the precision of the treatment effects. We will not only conduct a complete case analysis but also present the results using multiple imputation as sensitivity analyses. Missing data on outcomes and key covariates will be assessed before analyses. Where applicable (missingness >10%), we will implement multiple imputation methods appropriate for random effects models. Two-tailed *P* values of ≤.05 will be considered to indicate statistical significance. Analysis will be performed with Stata software (version 17; StataCorp LLC). We will not conduct any interim analysis for this study.

Ethical Considerations

The study protocol was approved by the institutional review board of the Medical Faculty, Heidelberg University, Heidelberg, Germany (S-299/2022) and the Makerere University School of Biomedical Sciences Research and Ethics Committee (SBS-2022-175), Kampala, Uganda. The study has been registered at the Uganda National Council for Science and Technology (HS2445ES). Protocol modifications will be communicated to both ethics committees, the Uganda National Council for Science and Technology, and the German Clinical Trials Register. All participants will provide written informed consent before their enrollment in the study. Consent will be obtained by the study research team.

Dissemination of Findings

We will disseminate the findings from all study phases via established academic channels (eg, peer-reviewed publications and conference contributions). Furthermore, we will hold dissemination workshops with local stakeholders and policy makers to ensure transparent communication; to discuss the impact the intervention has had on local medication availability, purchase, and distribution; and, in the case of proof of concept, to explore the potential for scaling up and replicating our intervention.

Results

This study was granted funding by the German Federal Ministry of Education and Research via the German Alliance for Global Health Research in April 2021 for a duration of 24 months, with an extension of 8 months until December 2023. The funders have no role in study design or analysis. As of August 2023, the first part of qualitative data collection had been finalized (with 55 IDIs and 4 FGDs conducted with clients, HCPs, CHWs, local leaders, and policy makers), and qualitative data analysis is underway. The results from the ongoing qualitative phase have informed platform design and implementation in accordance with the HCD principles outlined previously. In addition, the results are providing insights into current practices and understandings in the target population regarding topics such as NCDs, community-led health financing, and mHealth approaches. The findings are expected to be published in early 2024.

The randomized controlled trial for pilot-testing the final intervention prototype was registered in December 2022, paving the way for recruitment, which started in August 2023 and is ongoing. The results from the quantitative trial are expected to be published in summer 2024.

Discussion

Expected Observations

Hypertension is a key risk factor for CVDs and significantly contributes to morbidity and mortality across the globe, but accessing the required long-term care remains challenging, especially in low-resource settings. In this study protocol, we outlined how we will work with clients, providers, and other key stakeholders in a rural Ugandan setting to build on a community-led self-help financing scheme for facilitating access to antihypertensive medication. Following the tenets of HCD, we will rapidly iterate and refine an mHealth platform to incorporate end-user feedback across all stages of the design process.

Efforts to bolster sustainability and fairness in access to health care have a long history in global health. The large-scale multisectoral declaration of Alma Ata in 1978, aiming at adequate health care provision for everyone by 2000, has been criticized for the lack of follow-up on implemented goals and its selectiveness in the addressed diseases [55]. Placing a larger emphasis on the principle of strengthening primary health care, the Bamako Initiative of 1987 aimed at the integration of communities in attempts to facilitate health care financing. However, this initiative is widely considered to have failed, and it has been criticized for its top-down approach or in some instances increasing financial burden on some of the populations classified as the most disadvantaged [56]. In the aftermath of these large-scale efforts, researchers and implementers have highlighted still-open questions regarding pathways to avoid selectiveness in primary health care, to prevent shifts toward the private sector when client charges are introduced, and to meaningfully engage communities in implementation and follow-up [57]. In our study, we will contribute to providing answers to these questions, combining qualitative and quantitative approaches in the HCD design to gain insights into the perspectives and experiences of local stakeholders and end users.

In response to the lessons learned in the context of the previous efforts highlighted in this paper, we aim to build on a system initiated locally with already existing stakeholder buy-in, rather than implementing a new intervention created outside the study setting. We focus on a bottom-up approach to work with local realities and learn from clients' and providers' past experiences, and we have conducted extensive formative research in the study setting to inform the research and implementation

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activities presented in this protocol. The results of this study may inform future research on the potential of design research as a means to build on locally sourced approaches with high existing stakeholder buy-in.

Addressing Reported Challenges

mHealth approaches in resource-constrained settings are often accompanied by many difficulties that could hinder their acceptance and uptake (eg, incomplete mobile phone access owing to lack of a personal mobile phone, charging challenges, or theft) [58]. Some studies report difficulties for mHealth interventions that rely on a stable network connection or complex digital software [28,59,60]. To facilitate accessibility and overcome the challenges reported by fellow researchers, the MoPuleesa platform is based on a simple USSD menu that can be operated from any feature phone without internet access. It is also linked to a SIM card that can be accessed via different devices and can be locked in case of theft. This way, we hope to contribute to the potential of digital technologies for health care to reach resource-limited areas. Furthermore, research has shown that trust and risk assessment play a crucial part in enhancing the uptake of mHealth interventions and mobile money acceptance [61]. Moreover, service quality and confirmed expectations in turn seem to increase confidence in an intervention [62]. We want to investigate these components within our quantitative evaluation to provide thorough feedback on the variables for intervention uptake and use.

Community financing approaches should consider mandatory contributions to facilitate sustainability [63]. However, end users and implementers in the context of our formative research have voiced concerns that in our setting, mandatory contributions might result in a decrease of community engagement and continual intervention uptake. Similar findings have been reported from research conducted in Nigeria [64]. As health care should be available free of cost at government facilities in Uganda, mandatory contributions might be perceived as unfair and an additional, often prohibitive burden. Instead, formative research in our setting has shown that a financing scheme led by the community can spark substantially more trust and willingness to participate if it is an optional addition to governmental health coverage. Despite the potential of such community-driven efforts, a tension remains between creating a program that is flexible in terms of contribution (as desired by clients who are contending with seasonal harvests and uneven employment) and building a program that is rigid in its contribution requirements (as desired by health providers who are trying to forecast bulk purchasing needs). To strike a balance between maintaining acceptability of the community-initiated financing program and facilitating a sustainable influx of funds, our comparators for pilot-testing the developed intervention will be based on 2 voluntary contribution approaches that differ in their rigidity.

To further facilitate a sustainable influx of money, previous studies have highlighted the importance of affordability and the amount of trust placed in the operating administrators [65]. In addition, both previous studies and our formative research have found that the acceptability of financing schemes might increase if contributors are closely involved in the creation and the management of a scheme [66]. Therefore, in our study, we aim to bolster trust by engaging CHWs, HCPs, and other local stakeholders throughout intervention design and rollout, and suggested contribution amounts will be determined based on conversations with both clients and providers.

Finally, the success of pooled financing approaches strongly depends on the number of regular contributors [67]. After proof of concept of our intervention, 1 key challenge to achieve long-term sustainability will therefore be to scale platform integration and participation to maintain the constant influx of money required for bulk medication purchasing. To explore options for scale-up at clinic level, we will continually engage stakeholders to discuss possibilities in the case of proof of concept to expand platform integration to include other NCDs requiring long-term management (eg, diabetes) according to local priorities. As a first step toward informing policies and the potential scale-up of our intervention in the Ugandan setting, we will engage local policy makers in qualitative interviews to discuss the wide-range potential and adaptability of our program. We plan for further engagement of these key stakeholders through dissemination workshops at the conclusion of data collection to ideate on how to further develop and grow our program.

Limitations

With this study being a design study, the available sample size and limited generalizability owing to the specificity of patients with hypertension at 1 health facility might prove not to be sufficient to establish large-scale statements regarding intervention efficacy. Therefore, in the case of proof of concept, we encourage further randomized testing of the developed intervention with representative populations to allow for more robust interpretation and recommendations. Although the specific setting of an established dedicated NCD clinic and a patient-initiated money-saving program is one of our study's' key strengths, it could also prove to be a potential limitation in terms of transferability to settings with less ideal conditions. Although restricted, recent project development addressing NCDs in this region has emphasized the potential of HCD, mHealth, and community-led intervention to guide future policy decisions [68]. We will therefore refrain from making sweeping statements across settings but encourage further research on these topics in other contexts.

Conclusions

Our study will contribute to filling a gap in the literature by investigating the design and implementation of an mHealth intervention based on an existing community-led financing scheme. We hope to spark discourse and inform future research on the potential of design research in exploring novel approaches to facilitate sustainable access to medication in resource-constrained settings. We also aim to broaden the scope of established practices for community involvement in the design and implementation of interventions by focusing on their potential for expanding end user–driven solutions already established in the field.

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Data Availability

All data collected in the context of this study will be managed at the African Community Center for Social Sustainability (ACCESS) research facility in Nakaseke, Uganda. Data sharing will take place in compliance with the ACCESS data sharing policy and established procedures. Third-party researchers who are interested in the data must complete and sign data sharing agreements. Decisions on data sharing will be made on a case-by-case basis by the investigators upon reasonable request. Individuals granted database access will be expected to use the data to answer the questions clearly outlined in the data sharing agreement.

Authors' Contributions

JVE, TB, FK, SK, RK, and SM conceived of the study. JS, J Wachinger, RM, MN, J Wafula, RI, IW, JC, IS, JVE, TB, FK, SK, NS, CKN, RK, and SM conceptualized the study. JS and J Wachinger led the ethical and administrative approval processes in Germany. RM, J Wafula, and IW led the ethical and administrative approval processes in Uganda. JS, MN, and CKN prepared data collection plans and conducted data collection training. JS led manuscript writing and prepared the first draft. J Wachinger and SM supported and supervised manuscript writing. RM, MN, RI, IW, JC, IS, JVE, TB, FK, SK, NS, CKN, and RK provided feedback on the manuscript and study design. All authors have read and approved the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

ACCESS: African Community Center for Social Sustainability
CHW: community health worker
CVD: cardiovascular disease
FGD: focus group discussion
HCD: human-centered design
HCP: health care provider
IDI: in-depth interview
mHealth: mobile health
NCD: noncommunicable disease
REDCap: Research Electronic Data Capture
SSA: sub-Saharan Africa
USSD: unstructured supplementary service data
WP: work package

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Protocol

Repetitive Transcranial Magnetic Stimulation With and Without Text4Support for the Treatment of Resistant Depression: Protocol for a Patient-Centered Multicenter Randomized Controlled Pilot Trial

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Abstract

Background: Treatment-resistant depression (TRD) is the inability of a patient with major depressive disorder (MDD) to accomplish or achieve remission after an adequate trial of antidepressant treatments. Several combinations and augmentation treatment strategies for TRD exist, including the use of repetitive transcranial magnetic stimulation (rTMS), and new therapeutic options are being introduced. Text4Support, a text message–based form of cognitive behavioral therapy that allows patients with MDD to receive daily supportive text messages for correcting or altering negative thought patterns through positive reinforcement, may be a useful augmentation treatment strategy for patients with TRD. It is however currently unknown if adding the Text4Support intervention will enhance the response of patients with TRD to rTMS treatment.

Objective: This study aims to assess the initial comparative clinical effectiveness of rTMS with and without the Text4Support program as an innovative patient-centered intervention for the management of patients diagnosed with TRD.

Methods: This study is a multicenter, prospective, parallel-design, 2-arm, rater-blinded randomized controlled pilot trial. The recruitment process is scheduled to last 12 months. It will involve active treatment for 6 weeks, observation, and a follow-up period of 6 months for participants in the study arms. In total, 200 participants diagnosed with TRD at rTMS care clinics in Edmonton, Alberta, and rTMS clinics in Halifax, Nova Scotia will be randomized to 1 of 2 treatment arms (rTMS sessions alone or rTMS sessions plus Text4Support intervention). Participants in each group will be made to complete evaluation measures at baseline, and 1, 3, and 6 months. The primary outcome measure will be the mean change in the scores of the Patient Health Questionnaire-9 (PHQ-9). The secondary outcome measures will involve the scores of the 7-item Generalized Anxiety Disorders Scale (GAD-7), Columbia-Suicide Severity Rating Scale (CSSRS), and World Health Organization-Five Well-Being Index (WHO-5). Patient data will be analyzed with descriptive statistics, repeated measures, and correlational analyses. Qualitative data will be analyzed using the thematic analysis framework.

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Results: The results of the study are expected to be available 18 months from the start of recruitment. We hypothesize that participants enrolled in the rTMS plus Text4Support intervention treatment arm of the study will achieve superior outcomes compared with the outcomes of participants enrolled in the rTMS alone arm.

Conclusions: The application of the combination of rTMS and Text4Support has not been investigated previously. Therefore, we hope that this study will provide a concrete base of data to evaluate the practical application and efficacy of using the novel combination of these 2 treatment modalities.

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KEYWORDS

repetitive transcranial magnetic stimulation; treatment-resistant depression; cognitive behavioral therapy; Text4Support; text messaging; major depressive disorder

Introduction

Background

Major depressive disorder (MDD) is one of the most prevailing mental health conditions, which affects about 300 million people globally [1]. MDD is considered the second leading cause of years lived with disability, and it was associated with an estimated worldwide loss of over 63 million healthy years in 2010 [2,3]. The lifetime prevalence of MDD stands at 15% [4], with a substantial socioeconomic impact and an estimated annual cost of about US $236 billion and €91 billion (US $96 billion) in the United States and Europe, respectively [5,6]. The lifetime prevalence of MDD within the Canadian population stands at 9.9% [7], with an estimated annual economic cost of about US $12 billion [8]. Data demonstrate that among MDD patients who receive first-line treatment, about 50% fail to achieve remission, with two-thirds requiring further treatment trials before they can reach the state of remission [9,10].

Most MDD patients may respond to treatment modalities, which include conventional psychopharmacology, psychotherapy, and electroconvulsive therapy. However, about one-third of patients fail to respond to these treatment modalities and hence are diagnosed with treatment-resistant depression (TRD) [11,12]. Owing to the heterogeneity of MDD and the absence of clear biological predictors of what constitutes a response to a specific treatment agent, there is a high chance of any patient with treatment failure being classified as treatment resistant [13,14].

The concept of TRD spans over decades [15]. While many definitions of TRD have been proposed in the literature, the consensus appears to center on the failure of an MDD patient to respond to 2 adequate trials of recommended antidepressant pharmacotherapy [16]. However, the term “adequate response” may be in contention regarding the precise meaning of what constitutes “adequate.” Generally, it has been argued that “TRD” may not be the best term to describe the nonresponse to therapeutic modalities in patients with MDD [16]. Instead, the term “difficult-to-treat depression” has been proposed in the literature. It has the added benefit of preventing MDD patients from feeling that their condition is impossible to treat with the recommended treatment modalities [17]. In Canada, TRD is diagnosed based on nonresponse to at least two antidepressant medications from different classes [18].

Data in the literature suggest that TRD is characterized by a disproportional socioeconomic burden for affected individuals, their relatives, and the health care system in general [19]. TRD presents with a higher direct and indirect medical cost than MDD, which is responsive to therapeutic interventions. This medical cost increases with the severity of TRD [20-23]. Compared with other depressive conditions, TRD leads to at least about 12% more outpatient attendance, is associated with about twice the chances of hospitalization, and is associated with the use of up to about 3 times more psychopharmacological medications [22]. Evidence in the literature suggests that the overall medical cost for hospitalization among patients with TRD is about 6 times greater compared to that among patients without TRD [22]. Similarly, the total cost of a TRD episode among patients with TRD is about 2.7 to 5.8 times higher compared to that among patients without TRD. This difference in cost is due to a longer duration of TRD episodes coupled with a greater rate of usage and a higher cost per treatment visit among patients with TRD [23]. Furthermore, the overall depression-related cost among patients with TRD is estimated to be about 19 times greater compared to that among patients with other depressive conditions [22]. Data suggest that up to about 47% of depression-related costs are attributed to TRD in the United States alone [21,24].

TRD is associated with several risk factors, which include physical or psychiatric conditions, such as anxiety disorders, personality disorders, and hypothyroidism; drug interactions; sociodemographic risk factors, such as individual education attainment and gender; and other external issues affecting ill health [21,25-27]. Furthermore, bipolarity is considered a major factor in TRD based on the inadequate management of bipolar diathesis in MDD, which is diagnosed as unipolar [26,28,29]. Again, TRD is characterized by a greater risk of comorbidities of both psychiatric and medical conditions, an increased risk of suicides, and impairment in normal functioning such as impaired quality of life and social functioning [20,30-32]. Due to its recurrent nature, an estimated 80% of patients with TRD relapse within 1 year after remission of their symptoms [30].

The prevalence of TRD varies significantly across the literature (12%-55%) [21,33-35]. In the United States alone, the estimated annual prevalence of medication-treated MDD was 8.9 million adults, of which 2.8 million (30.9%) had TRD [24]. A study that evaluated the prevalence and burden of TRD among patients with MDD in 4 Latin American countries (Argentina, Mexico,

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Colombia, and Brazil) revealed that 29% of the study participants with MDD were resistant to medication. The results demonstrated a TRD prevalence of 33% in Argentina, 21% in Mexico, 32% in Colombia, and 40% in Brazil [19]. In Europe, data from a multicenter study of patients with TRD suggested a prevalence rate of 41% among patients with MDD, while in the United Kingdom, a study conducted on patients treated for MDD in a primary care setting demonstrated that 55% of the patients had TRD [36,37]. In Canada, the prevalence of TRD is about 21.7%. However, there were no differences in prevalence between men and women or among ethnic groups [18]. The wide variation in prevalence estimates is not unconnected with the variation in the definition and criteria for classifying TRD in the literature.

Treatment Options for TRD

Since the idea of TRD was established in 1974 [38,39], there has not been any straightforward standardized technique made available for the management of TRD; however, several studies have been conducted to evaluate the optimum treatment modalities for the same [40,41]. Many different psychopharmacological and nonpharmacological agents have been proposed and considered for the management of TRD. These treatment strategies may consist of psychopharmacological options, such as switching, augmentation, combination, and optimization of antidepressant medications [42]. Other comprehensive strategies include electroconvulsive therapy [43], psychotherapy [44], exercise [45], deep brain stimulation [43], light-based therapy [45], yoga [45], and transcranial magnetic stimulation (TMS) [43].

Use of Repetitive TMS in the Treatment of TRD

TMS was developed in the late 1980s [46]. Subsequently, researchers came up with newer techniques to deliver multiple pulses of TMS in shorter intervals referred to as repetitive TMS (rTMS) [47]. Thereafter, several studies were conducted to evaluate the efficacy of rTMS for the management of MDD [48] and other psychiatric conditions. rTMS is effective in the management of TRD, with response rates ranging from 30.6% to 64.7% [49-54]. In 2002, the application of rTMS for the management of TRD was approved by Health Canada [16].

rTMS is a noninvasive brain stimulation treatment modality that is deemed to be a valuable and promising treatment technique for TRD [55]. Two main protocols of rTMS are mostly used in the management of TRD: low-frequency (≤1 Hz) rTMS targeting the right dorsolateral prefrontal cortex and high-frequency (5-20 Hz) rTMS targeting the left dorsolateral prefrontal cortex [56]. Studies have argued that there is no significant difference in the efficacy of low-frequency rTMS and high-frequency rTMS in the management of patients with MDD. However, high-frequency rTMS seems better suited in clinical practice owing to the placebo effect [57,58]. The rTMS protocol of choice commonly used in suicide interventions (a common feature of TRD) is high-frequency rTMS [59,60]. The evidence in the literature in support of rTMS as a suicide reduction treatment intervention is modest and yet promising. Although there have been variations in the rTMS protocol among studies, several studies have demonstrated reductions in the rates of suicidality, with remission rates ranging from 40% to 65% in patients diagnosed with depressive disorders [59-63].

A standard session of rTMS for the management of TRD may consist of 20 to 30 daily treatment sessions for 4 to 6 weeks [64]. The administration of rTMS does not require an anesthetic agent and hospitalization, and thus, it is more accessible compared to electroconvulsive therapy in the management of TRD. Furthermore, rTMS application is deemed safe and tolerable, with no serious adverse effects among users [65].

Digital Technology Used in the Treatment of TRD

Though many treatment interventions for depressive conditions have been proposed in the literature, it is quite obvious that the traditional face-to-face means of delivering mental health care alone will not be enough to meet the demands for health care services, given the high prevalence of MDD and TRD, without any hope or likelihood of a decrease any time soon [66]. According to the 2012 Canadian Community Health Survey on Mental Health, about 2.3 million Canadians mentioned among other things that the barriers hindering them from accessing quality mental health care include a lack of a readily available care system, stigma, and high cost of health care services [67,68]. There has been a significant advancement in the development of digital technologies for the provision of health care in recent decades [69]. In particular, mobile digital information and communication technologies continue to advance at an exponential rate, making it possible to communicate, obtain information, and access care services with ease.

There is evidence in the literature in support of the therapeutic efficacy and cost-effectiveness of these digital technologies, such as tele-mental and e-mental health services, with the potential of enhancing easy access to health care and thereby helping to reduce the decades-old problem of unmet treatment needs and the wide treatment gap for mental conditions, particularly TRD [70,71]. These useful technological methods of health care delivery include smartphone apps, text messages, and email messaging [71,72]. In 2019 alone, about 97% of the world's population lived in communities with coverage of mobile cellular signals [73]. This exponential growth of mobile networks and phones has greatly opened new opportunities for health care delivery and health promotion, with a significant improvement in mobile health within recent years [74]. A global survey conducted in 2015 demonstrated that Canada, among Western countries, is in the high internet use group, with about 90% of Canadians using internet services and 67% owning a smartphone [75]. In 2022, internet usage among individuals aged 15 years or above in Canada increased to 95% from 92% in 2020. Notably, there was a significant rise in usage among those aged 75 years or older, with an increase from 62% in 2020 to 72% in 2022 [76].

Technology-enabled cognitive behavioral therapy–based programs have been increasingly acknowledged as innovative, accessible, cost-effective, and acceptable ways of delivering psychological treatments to patients and the general public with mental health problems [77]. An estimated 99% of all messages received on mobile phones are opened, and about 90% of all text messages end up being read within 1 to 3 minutes of

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reception [78]. Thus, providing an affordable means of accessing care could help close the psychological treatment gap for patients with TRD [79].

Text4Support is one of the supportive text messaging programs in the ResilienceNHope [80] suite delivered by the Global Psychological eHealth Foundation [81]. The program allows users to receive daily supportive text messages, which have been written by a team of cognitive behavioral therapists and mental health professionals in collaboration with users of mental health services. The aim of this Text4Support depression program is to positively enhance the mood of patients with clinical depression. The program operates using positive reinforcement to correct distorted or negative thought patterns.

Evidence in support of the therapeutic efficacy of supportive text messaging exists from randomized controlled trials (RCTs) on supportive text messaging for the management of MDD conducted in Canada [82] and Ireland [83]. In these trials, patients with MDD were offered twice daily supportive text messages in addition to their usual care. Overall, there were significantly greater reductions in the symptoms of MDD among patients in the intervention group than among those in the control group receiving only usual care. After 3 months, the study in Canada demonstrated a statistically significant difference in the mean Beck Depression Inventory-II (BDI-II) score between the intervention group and the control group (mean change of −7.6, 95% CI −13.2 to −1.9; Cohen *d*=0.67) in favor of the intervention group [82]. Similarly, the RCT conducted in Ireland demonstrated a statistically significant difference in the BDI-II score between the intervention group and the treatment as usual group (mean change of −7.9, 95% CI −13.06 to −2.76; Cohen *d*=0.85) in favor of the intervention group [83]. User satisfaction with the Text4Support intervention and related programs has been assessed and reported in several other studies [79,84]. About 83% of users of the Text4Mood program reported an overall improvement in their mental health conditions, which they attributed to receiving daily supportive messages [79].

This study seeks to investigate the combined effect of an rTMS intervention with and without a text message–based cognitive behavioral therapy program (Text4Support) in patients diagnosed with TRD. The study also aims to generate effect size data for these interventions, which will help inform sample size and power calculations for a full-scale randomized clinical trial.

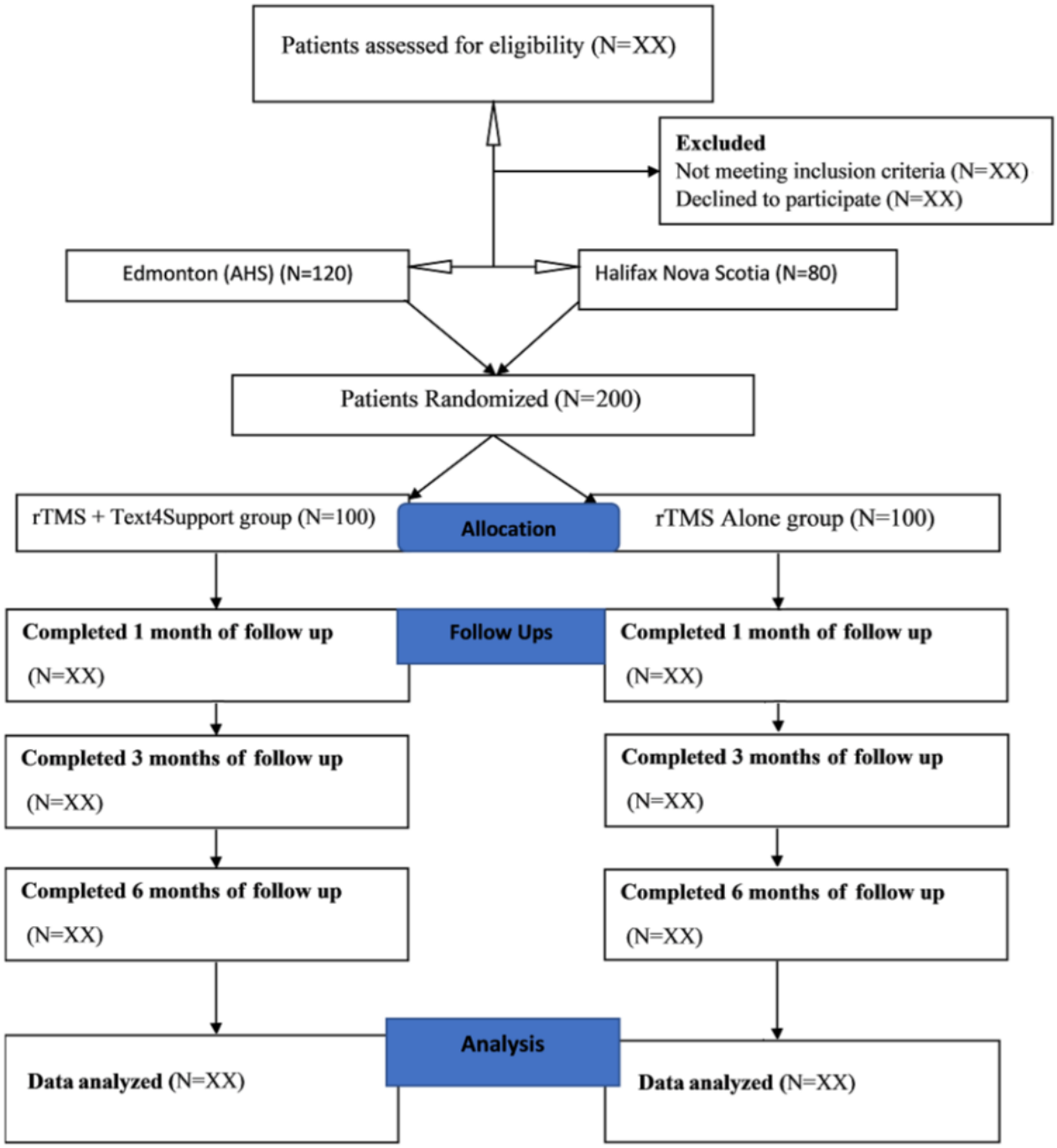
Methods

Study Design and Setting

This study is a multicenter, prospective, parallel design, 2-arm, rater-blinded randomized controlled pilot trial. Participants will be randomly assigned to 1 of 2 treatment conditions. The first condition includes rTMS sessions combined with Text4Support. The second condition includes treatment as usual (rTMS sessions alone). The recruitment process is scheduled to last 12 months. It will involve active treatment for 6 weeks and follow-up with observation periods of 6 weeks, and 3 and 6 months for participants in both arms of the study. Figure 1 presents the CONSORT (Consolidated Standards of Reporting Trials) flowchart for the project. Participants will be recruited from 4 different centers for this project. Two centers (the Addiction and Mental Health Clinic and the Alberta Day Hospital) are from the large sociodemographically diverse city of Edmonton in Alberta, Western Canada. The remaining 2 centers are in Halifax and Annapolis Valley in Nova Scotia, Canada. Table 1 presents the proposed timelines for this project.

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Figure 1. CONSORT (Consolidated Standards of Reporting Trials) flowchart. AHS: Alberta Health Services; rTMS: repetitive transcranial magnetic stimulation.



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Table 1. Gantt chart displaying project timelines.

Milestone	Year 1				Year 2	
	Q1	Q2	Q3	Q4	Q1	Q2
Milestone 1: Recruitment and training of trainees in psychiatry, and setting up of infrastructure for the delivery of Text4Support						
1.1. Advertising and recruitment of a trainee in psychiatry who will support the research/evaluation of the project component, apply rTMS[a], and facilitate the delivery of Text4Support	✓					
Milestone 2: Recruitment of study participants						
2.1. Recruitment, baseline assessment, and randomization		✓	✓			
2.2. Assignment into 1 of the 2 arms of the study		✓	✓			
2.3. Delivery of Text4Support and rTMS to participants		✓	✓	✓		
Milestone 3: Follow-up assessment of study participants						
3.1. Follow-up assessment of individual study participants				✓	✓	
3.2. Follow-up satisfaction survey of participants in all groups				✓	✓	
Milestone 4: Data compilation, data analysis, and preparation of reports, publications, and presentations						
4.1. Data compilation		✓	✓	✓	✓	✓
4.2. Data analysis		✓	✓	✓	✓	✓
4.3. Preparation of reports, publications, and presentations						✓

[a]rTMS: repetitive transcranial magnetic stimulation.

Participants

We aim to randomize 200 patients (Edmonton/AB=120 and Halifax/NS=80) in this study.

Inclusion Criteria

The inclusion criteria are as follows: (1) Age 18 years or above; (2) Diagnosis of MDD based on the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition criteria, and failure of at least two standard antidepressant treatments during the current episode; (3) Good understanding of the English language; (4) Possession of a smartphone, and ability to receive and read text messages; and (5) Ability to consent, and willingness to provide written informed consent.

Exclusion Criteria

The exclusion criteria are as follows: (1) Age less than 18 years; (2) Diagnosis (current unless otherwise stated) of a neurological disorder (including a history of seizures), a primary or secondary tumor in the central nervous system, cerebrovascular disease, stroke, cerebral aneurysm, or movement disorder; (3) Diagnosis of a current psychotic disorder, such as substance-induced psychosis, psychotic disorder due to a medical condition, or MDD with psychotic features at the time of screening; (4) Diagnosis of a current personality disorder that may hinder participation in this research or may have the potential of affecting cognition and the ability to fully participate in the study; (5) Presence of a learning disability as identified through medical history or by the investigator during the assessment process; (6) Involvement in any drug or device clinical trial within the last 6 weeks before the screening visit or involvement in another clinical trial for the duration of this study; and (7) Identification of or the sudden appearance of any condition identified by the investigators to have the potential to hinder the progress and completion of the trial, or be a confounding factor for the outcome assessment.

Sample Size Calculation

This study is a pilot study with no standardized data documented on the effect size, which could aid in power and sample size calculations. We will therefore use data that can be generated from the study participants recruited within the existing protocol. This approach is accepted for pilot studies that consist of novel interventions, such as this, and this method has been described by Haynes et al [85] as using “the participants I can get.” In this regard, the study will be limited to a sample size of about 200 (120 from Edmonton and 80 from Halifax), with 100 participants recruited in each of the study arms. Since TRD is characterized by periods of relapses and depressive attacks, we anticipate a certain number of eligible patients to decline to enroll in the study or even drop out before the completion of the study.

Recruitment Process

Participant eligibility will be determined by the rTMS specialist team within the various centers. If found eligible for inclusion in the rTMS program, the patient will be approached by a member of the study team to introduce the study. A copy of the information leaflet will be provided to patients to have a detailed insight into the study processes. Once the patients agree to take part in the study, they will be asked to sign a consent form. The signing of the consent form and recruitment process will be conducted face-to-face at the various study sites during the week of the rTMS eligibility assessment of the participants, which usually occurs 1 week before the rTMS sessions begin. Participation in the study is by choice, and a participant can decide to withdraw at any time without providing a reason. To withdraw from the study, participants can contact the research coordinator to communicate their decision to discontinue their

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participation in the study. Once withdrawn, the study will not collect any new information about them, and if deemed fit, the said participants may approach the research team to withdraw all data collected on them before the study data are analyzed or disseminated.

Randomization and Blinding

A simple randomization technique will be employed using a single sequence of random assignments. The simple randomization will be performed using a computer-generated Excel sheet (Microsoft Corp). To ensure balance (1:1), the randomization will be stratified by using permuted blocks. The codes generated will then be transmitted via text message by an independent statistician directly to a blinded researcher's password-protected phone line with a secure online backup. This process will occur for enrollment as each participant signs the consent form.

Since blinding of participants in this study is impossible, their treatment allocation will be made known to them right after the randomization process. Primary outcome assessors will not be granted access to the database that contains the randomization codes, and they will not be involved with all discussions concerning the study participants and may be blinded to the treatment arm allocations. The data that would be generated from the study will undergo a blind review for the reason of finishing the planned analysis.

Interventions

Study participants will be randomized to 1 of 2 treatment interventions (rTMS alone or rTMS plus Text4Support). During the introductory visit to the study sites, participants in both arms of the study will be given a detailed orientation about the rTMS application, and all procedures and activities within each visit will be explained to them. As part of their participation in the rTMS program, all patients will be made to complete some standard measures. Participants will be invited to the various rTMS clinics a week before the commencement of the rTMS sessions to enable them to undergo motor threshold (MT) assessment. MT assessment is essential in that it aids in the selection of the required stimulation intensity for each patient for inclusion in the treatment. It is a measure of the minimum intensity of TMS output needed to elicit a motor response in the participating TRD patients in at least 50% of all attempts.

All MT assessments will be conducted by the rTMS team of experts within the rTMS clinics in the various treatment centers, and the team may involve psychiatrists, nurses, and other health care professionals with the requisite training to perform the assessments. Each TMS assessment session will take about 3 to 5 minutes, and the total time will be within 35 to 45 minutes. This visit timeline will be the same for all study participants. Overall, all study participants will be scheduled to receive 30 sessions of rTMS treatment for 6 weeks according to the schedule pre-established by the Alberta Health Services' Strategic Clinical Network for Addiction and Mental Health and Nova Scotia Health. The rTMS protocol includes low-frequency (1 Hz) inhibitory stimulation targeting the right dorsolateral prefrontal cortex at 120% MT, with 20 trains (60 pulses/train at 60 s) and a total pulse of 1200 for 20 minutes, and high-frequency (10 Hz) excitatory stimulation targeting the left dorsolateral prefrontal cortex at 120% MT, with 75 trains (intertrain interval of 11 s) and a total pulse of 3000 for 19 minutes. The study will use the MagVenture rTMS machine with a figure-of-8 coil. The angle between the coil and the head will be measured at 45 degrees. The cortex area will be targeted by using the 5-cm technique. The prefrontal cortex stimulation site will be determined as 5 cm anterior further ahead of the motor strip in the parasagittal line. Regarding the issue of adherence to the treatment protocol, the rTMS team of experts will contact each patient to remind them of their sessions whenever they default in order to ensure adherence to the treatment. The patients will be continuously monitored, and an attending nurse will remain with each patient during the whole session, checking on any expected side effects. Complete treatment will be considered as attending at least 25 out of 30 sessions.

Additionally, participants in the rTMS plus Text4Support group of the study will be assisted by a study team member to register into the Text4Support program. The process will require all participants in this arm of the study to input their phone numbers into the Text4Support platform, which will be used to deliver daily messages. Starting a day after enrollment, participants will receive daily supportive text messages designed by mental health therapists, clinical psychologists, psychiatrists, and mental health service users. These messages will be based on cognitive behavior therapy principles crafted to positively enhance the mood of users with depressive symptoms and other related mental health problems of concern. The messages will be preprogrammed into a software program that will deliver the messages automatically to the participants' mobile phones at 10 AM (Mountain Time) and 12 PM (Atlantic Time), and each participant will receive these messages continuously for 6 weeks.

Hypothesis

We hypothesize that participants enrolled in the rTMS plus Text4Support treatment arm of the study will achieve superior outcomes compared with the outcomes of participants enrolled in the rTMS treatment alone arm of the study in terms of all outcome measures that will be assessed.

Data Collection and Follow-Up Assessment

All study participants who provide informed written consent and agree to participate in the study will be asked to complete a baseline assessment questionnaire that captures both demographic and clinical information. Study participants will also be asked to complete various follow-up assessments related to primary and secondary outcome measures at 6 weeks, and 3 and 6 months from enrollment. All self-completed surveys will be completed online on tablets or on participants' cell phones. Clinician-rated scales will be completed either face-to-face at the study sites or over the phone/video conference with the help of a blinded researcher. All follow-up survey links will be delivered to participants' cell phones at the designated time points. Two reminder text messages will be sent a day apart to encourage participants to complete the follow-up surveys. Participants who do not complete the online surveys despite receipt of 2 reminder text messages will be contacted by a research team member to ascertain if there are any barriers to

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survey completion and if any assistance is needed. Qualitative data collection will be in the form of a patient experience questionnaire and a key informant interview via telephone, which will be conducted at 3 and 6 months. Data related to participants' clinic or program attendance rates and use of health services will be compiled from administrative records by a blinded researcher at 6 months.

Outcome Measures

The primary outcome measure for the study will be changes in the mean score of the Patient Health Questionnaire-9 (PHQ-9) [86] from baseline to the specified time points for the intervention and control groups. With 9 items, the PHQ-9 is half the length of many other depression measures, has comparable sensitivity and specificity, and is made up of the actual 9 criteria upon which the diagnosis of depressive disorders is based according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. This instrument has the potential to establish major depressive disorder diagnosis, as well as grade the severity of depressive symptoms [86]. The PHQ-9 has good psychometric qualities with high internal consistency, and Cronbach α values of .86 and .89 were obtained in a study that included 2 separate patient populations [87]. The secondary outcome measure will include the 7-item Generalized Anxiety Disorders Scale (GAD-7) [88]. The GAD-7 score is calculated by assigning scores of 0, 1, 2, and 3 to response categories. The GAD-7 total score for the 7 items ranges from 0 to 21, with a score of 0-4 indicating minimal anxiety, 5-9 indicating mild anxiety, 10-14 indicating moderate anxiety, and 15-21 indicating severe anxiety. The GAD-7 has excellent internal consistency (Cronbach α=.92) and test-retest reliability (intraclass correlation=0.83) [88]. The screen version of the Columbia-Suicide Severity Rating Scale (CSSRS) [89] will be included to measure the suicidal ideation of participants. The CSSRS is made up of 6 questions. Users are required to respond "Yes" or "No" to whether they have thought about suicide, have acted or plan to act, or have attempted or plan to attempt suicide. Each of the 6 questions evaluates a different component of the respondent's suicidal ideation severity and behavior. This measuring tool is scored as low, moderate, or high risk, depending on positive answers (Yes) to the various questions. If a respondent answers positively (Yes) to question 2, the respondent is instructed to respond to questions 3-5. If a respondent answers "No" to question 2, the respondent may skip to question 6. Responding "Yes" to any of the 6 items may imply a need for referral to a mental health care professional, but responding "Yes" to question 4, 5, or 6 indicates a high risk. The CSSRS intensity of ideation subscale has good internal consistency, with Cronbach α values ranging between .73 and .93 [89]. Additionally, the World Health Organization-Five Well-Being Index (WHO-5) [90] will be employed to measure the quality of life of participants. The WHO-5 is a psychometrically robust questionnaire with high internal consistency (Cronbach α=.923) [91]. The WHO-5 is a short questionnaire made up of 5 simple and noninvasive questions, which assess the subjective well-being of respondents. A respondent is asked to rate how well each of the 5 statements applies to them within the last 14 days. Each of the 5 items is scored from 5 (all of the time) to 0 (none of the time). The raw score therefore theoretically ranges from 0 (absence of well-being) to 25 (maximal well-being). To translate the scores to percentages (from 0 [absent] to 100 [maximal]) as required by scales measuring health-related quality of life, the raw score is multiplied 4. The outcome measures and time points for the study are demonstrated in Table 2.

Table 2. Client-oriented outcome measures and time points.

Variable type and construct	Tool	Rater	Time points assessed			
			Baseline	1 month	3 months	6 months
Symptom variables						
Depression	Patient Health Questionnaire (PHQ-9)	Client	✓	✓	✓	✓
Anxiety	Generalized Anxiety Disorders Scale (GAD-7)	Client	✓	✓	✓	✓
Suicidal ideation	Columbia-Suicide Severity Rating Scale (CSSRS)	Clinician	✓	✓	✓	✓
Functional variables						
Quality of life	World Health Organization-Five Well-Being Index (WHO-5)	Client	✓	✓	✓	✓

Data Analysis

SPSS Version 26 (IBM Corp) will be used to analyze all quantitative data in accordance with the CONSORT guidelines [92]. Following an intention-to-treat approach, data will be analyzed with descriptive statistics, repeated measures, and correlational analyses. Descriptive data for baseline parameters will be presented using frequencies and percentages among the 2 intervention groups and compared using the chi-square test for categorical variables and the independent sample *t* test for continuous variables. The type of intervention (rTMS alone and rTMS plus Text4Support) will be considered the independent variable, while the scores of the various scales at each time point (6 weeks, and 3 and 6 months) will be considered the dependent variables for each of the analyses. Baseline scores of the respective scales will be used as covariates in the analyses.

To compare the effectiveness of the treatment interventions for the management of TRD among participants, the 1-way between-group analysis of covariance (ANCOVA) comparing changes in the mean scores from baseline to 6 weeks, and 3 and 6 months for all measures will be employed. Preliminary checks will be conducted to ensure there is no violation of the assumption of normality, linearity, homogeneity of variance,

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homogeneity of regression slopes, or reliable measurement of the variate before ANCOVA is conducted. For participants with missing data, the last observation will be imputed before performing sensitivity analyses of covariance to explore the impact of the imputation of data loss on the PHQ-9 and the secondary measures at each time point.

The chi-square test or Fisher exact test will be employed to compare the prevalence of depression symptoms using the PHQ-9, the prevalence of anxiety symptoms using the GAD-7, suicidal ideations using the CSSRS, and quality of life using the WHO-5 between the 2 intervention groups at all time points in the overall sample.

Furthermore, a paired *t* test will be used to examine the changes in the mean scores of the PHQ-9, GAD-7, CSSRS, and WHO-5 at baseline and 6 weeks for participants who complete the instruments at both time points. Frequencies and percentages will be used to report categorical variables, while mean scores, confidence intervals, and effect sizes will be used to report continuous variables. The 2-tailed α-level criterion for statistical significance will be set at $P \leq .05$.

Qualitative data obtained through audio recordings from participant focus group discussion sessions will be transcribed and analyzed using thematic analysis aided by NVIVO software [93]. Data analysis will be both deductive and inductive. After familiarization with the transcripts obtained, 2 researchers will independently conduct the initial coding, and subsequently, the final coding criteria will be agreed by the 2 researchers. This will be followed by an iterative review of emerging themes as informed by the research questions. The final sets of themes and subthemes in relation to the overall study aims will be reported and supported with verbatim quotes.

Ethical Considerations

The study will be conducted according to the Declaration of Helsinki (Hong Kong Amendment) [94]. The study participants will be made to provide informed consent before their inclusion in the study. The research team will strictly adhere to the protection of participants' health information according to the structure laid down by the 2 major health institutions (Alberta Health Services and Nova Scotia Health Authority). An independent monitor will be assigned by the research team to monitor the progress of the research, ensure the completeness of informed consent and data safety, and liaise with the ethics committee. Although not anticipated, serious adverse events will be reported to the Research Ethics Committee. The study has received ethical clearance from the Health Ethics Research Board of the University of Alberta (Pro000122696) and the Nova Scotia Health Research Ethics Board (REB File #: 1028488).

Results

The study is registered at ClinicalTrials.gov (registration number: NCT05570344). The study is yet to commence recruitment of participants. The study results are envisioned to be available 18 months from the start of recruitment. The results are expected to be disseminated at different levels, including practitioners, health care organizations, and academics/researchers. Before the study ends, the team of investigators will organize an engagement plan to discuss the practicability and effectiveness of the study.

Discussion

Overview

The findings from the study will provide the data needed to assess the initial effectiveness of rTMS plus Text4Support for individuals diagnosed with TRD. Though there are several pieces of evidence in the literature in support of the effectiveness of rTMS in TRD, the data generated regarding rTMS application are relevant only when it is used as a single treatment modality. However, the concomitant application of psychotherapy with rTMS is limited. Therefore, we hope that this novel project will provide a concrete base of data to enable the evaluation of the wider-scale practical application and efficacy of the combination of rTMS and Text4Support. To the best of our knowledge, this study will be the first clinical trial to investigate the combined effect of these 2 interventions. Owing to the limited availability of data regarding this specific area of treatment, another objective will be to generate effect size information for these interventions to aid future power and sample size calculations for a full-scale RCT.

Strengths of This Study

This study has several strengths. First, since this RCT will be conducted in a naturalistic clinical care setting, translation of the results to clinical practice will be easier. Regardless of the outcome of this trial, the findings can inform clinical decision-making and aid in choosing the right treatment for a patient with TRD. Second, this study will have a longer follow-up duration than other rTMS trials. Since data up to 6 months from the start of the study will be available, the durability of the treatment effects of rTMS in the longer term can be evaluated. Third, randomizing participants will ensure that participants in the 2 treatment arms have similar psychiatric morbidity at baseline. Moreover, the blinding of all primary outcome assessors to the primary outcome measures will ensure the elimination of rater bias in the outcome measures.

Limitations

As eligible patients will ultimately decide on whether they want to join the study, a major limitation may be selection bias, which will potentially result in the selection of highly motivated patients. This may affect the ability to achieve a good study sample size and power. Another limitation may be associated with possible variabilities in illness duration and concomitant treatments being received by patients outside the rTMS treatment, which could have confounding effects on the outcomes of our interventions.

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Conflicts of Interest

None declared.

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Abbreviations

ANCOVA: analysis of covariance
BDI-II: Beck Depression Inventory-II
CONSORT: Consolidated Standards of Reporting Trials
CSSRS: Columbia-Suicide Severity Rating Scale
GAD-7: 7-item Generalized Anxiety Disorders Scale
MDD: major depressive disorder
MT: motor threshold
PHQ-9: Patient Health Questionnaire-9
RCT: randomized controlled trial
rTMS: repetitive transcranial magnetic stimulation
TMS: transcranial magnetic stimulation
TRD: treatment-resistant depression
WHO-5: World Health Organization-Five Well-Being Index

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Protocol

Analgesic Effect of Intraoperative Intravenous S(+)-Ketamine During Total Knee Arthroplasty Surgery: Study Protocol for a Randomized Controlled Clinical Trial

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Abstract

Background: Total knee arthroplasty (TKA) is currently the main treatment for end-stage knee disease. The number of cases of TKA in China increased from 53,880 in 2011 to 374,833 in 2019, representing a 5.9-fold increase. Moderate to severe pain often occurs after TKA, which seriously affects postoperative rehabilitation, patient satisfaction, and overall outcome. Multimodal analgesia is considered the ideal solution. Adequate postoperative analgesia can not only reduce pain, opioid consumption, and, consequently, opioid-related adverse events, but can also reduce the length of hospital stay and costs and improve rehabilitation and patient satisfaction.

Objective: Effective multimodal pain management in the early postoperative period is essential for anesthesiologists. Additional studies have demonstrated that a low-dose intravenous infusion of ketamine can be administered as an adjuvant drug to alleviate acute postoperative pain. Therefore, we aim to appraise the efficacy and safety of intraoperative intravenous injection of S(+)-ketamine to relieve acute pain after TKA in older patients.

Methods: This is a protocol for a randomized, placebo-controlled trial. A total of 144 participants aged 65 years and older undergoing TKA will be randomly allocated into the S(+)-ketamine and placebo groups in a 1:1 ratio. S(+)-ketamine or the placebo will be intravenously administered at 0.3 mg/kg/h during the operation by anesthesiologists. Blinded evaluation by trained investigators will be completed at 2 hours, 24 hours, and 48 hours after surgery. The primary outcome measure will be the numeric rating scale score at rest and movement at 24 hours after surgery. The secondary outcomes will include the numeric rating scale scores at rest and movement at 2 hours and 48 hours after surgery, the number of patients who require additional analgesics during the first 48 hours after operation, the total consumption of opioids or nonsteroid anti-inflammatory drugs during the first 48 hours after operation, and adverse events at 2, 24, and 48 hours after operation.

Results: The protocol was registered at Clinical Trials.gov on February 26, 2022. It was performed in accordance with the approved guidelines and regulations of the participating institutions. Recruitment began in April 2022. Data collection is expected to conclude in September 2024. Study completion is expected in December 2024.

Conclusions: A randomized, controlled, clinical study was designed to observe the analgesic effect of intraoperative intravenous administration of a lower dose of S(+)-ketamine (0.3 mg/kg/h) in older patients after TKA surgery. The protocol will appraise the efficacy and safety of intraoperative intravenous injection of S(+)-ketamine to relieve acute pain after TKA in older patients who may benefit from the administration of S(+)-ketamine.

Trial Registration: ClinicalTrials.gov NCT05289050; https://clinicaltrials.gov/ct2/show/NCT05289050

International Registered Report Identifier (IRRID): DERR1-10.2196/53063

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KEYWORDS

analgesic; S(+)-ketamine; total knee arthroplasty surgery; older patients, multimodal pain management

Introduction

Total knee arthroplasty (TKA) is currently the main treatment for end-stage knee disease. The number of cases of TKA in China increased from 53,880 in 2011 to 374,833 in 2019, representing a 5.9-fold increase [1]. Moderate to severe pain often occurs after TKA [2], which seriously affects postoperative rehabilitation, patient satisfaction, and overall outcomes [3,4]. Multimodal analgesia is considered the ideal solution. Adequate postoperative analgesia can not only reduce pain, opioid consumption, and, consequently, opioid-related adverse events, but can also reduce the length of hospital stay and costs and improve rehabilitation and patient satisfaction [5].

Opioids are effective for acute postoperative pain, but they have numerous adverse effects (eg, respiratory depression and nausea), especially in older patients. In addition, the use of excessive opioids may pose a risk of opioid addiction [6]. Despite encouraging results and rapid recovery after the use of perioperative local infiltration analgesia and nerve block agents, pain management can be further optimized [7]. Therefore, effective multimodal pain management in the early postoperative period is essential for anesthesiologists.

Ketamine has been widely used in anesthesia to relieve postoperative pain. It mainly acts on the N-methyl-D-aspartate (NMDA) receptor to produce sedative, analgesic, and anesthetic effects [8,9]. S(+)-ketamine is an effective S-enantiomer of racemic ketamine with a greater affinity than ketamine (approximately 2- to 4-fold) for NMDA receptors, thereby producing stronger sedative and analgesic effects and fewer adverse events, and it has been used to prevent central sensitization [10-13]. Opioids, such as remifentanil, may lead to hyperalgesia and more analgesic requirements. A clinical study showed that IV ketamine improved the analgesic effect of fentanyl and lessened hyperalgesia [14].

Aggressive management of TKA pain has multiple benefits, such as shortening the length of hospital stay, preventing postoperative complications, and accelerating patient recovery [15]. Therefore, S(+)-ketamine requires further investigation, and the following questions must be addressed: What is the ideal dosage of S(+)-ketamine infusion for the prevention of postoperative acute pain? Can older patients experience a beneficial effect after surgery? To answer these questions, a randomized, controlled, clinical study was designed to observe the analgesic effect of intraoperative intravenous administration of a lower dose of S(+)-ketamine (0.3 mg/kg/h) in older patients after TKA surgery.

Methods

Objective and Trial Design

This clinical study was designed to observe the analgesic effect of a lower intravenous dose of S(+)-ketamine (0.3 mg/kg/h) in patients after TKA surgery.

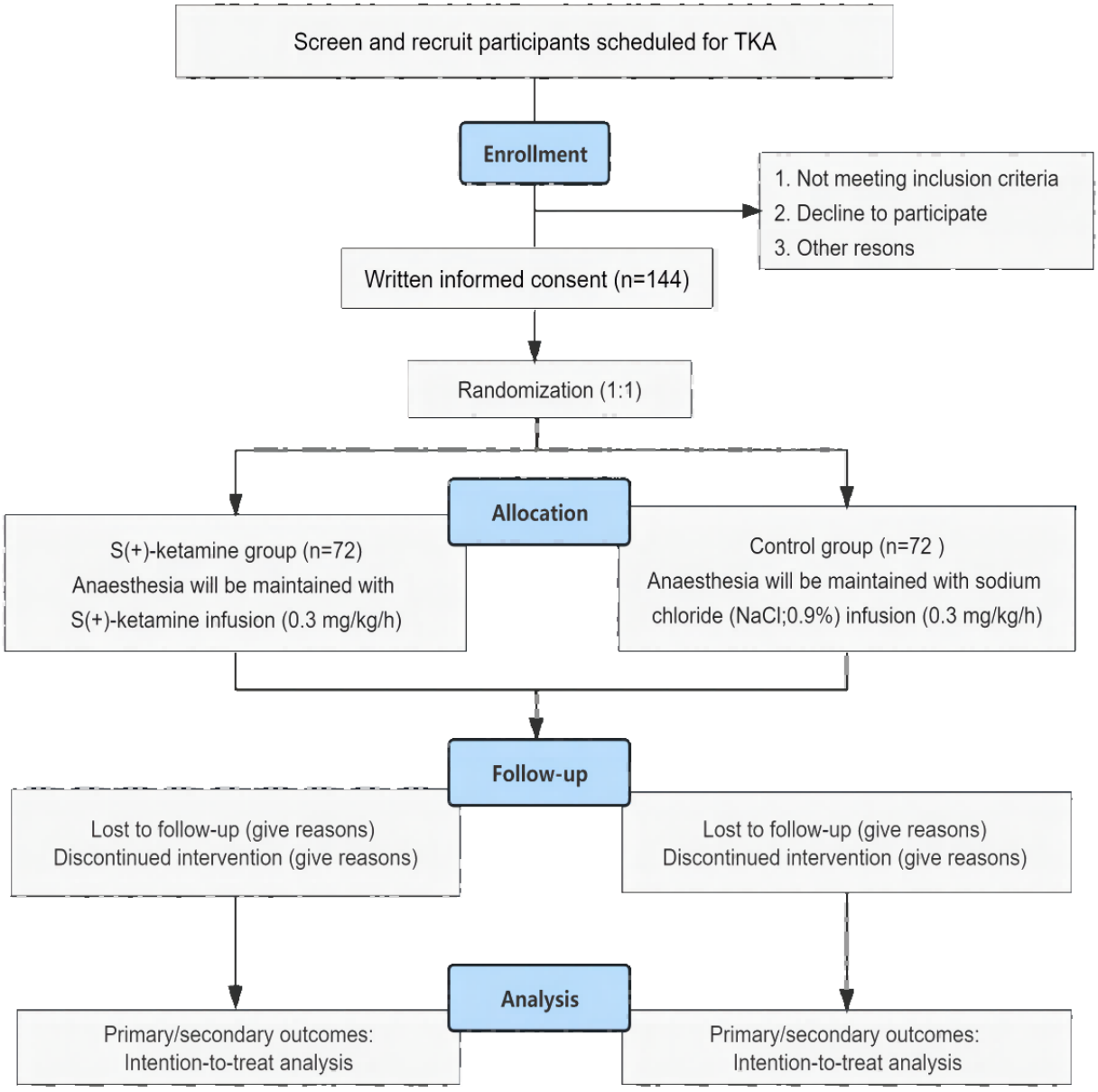
This is a single-center, randomized, single-blind, controlled, clinical trial in older patients undergoing TKA under general anesthesia. Eligible patients will be randomized to receive S(+)-ketamine (n=72) or a placebo equivalent, 0.9% sodium chloride (n=72), in a ratio of 1:1. Patients will be randomized using a computer-generated list. The anesthetist nurse and the pharmacist will not be blinded and will not partake in the following research, but the follow-up evaluators will be blinded in the trial.

Recruitment and Study Setting

A researcher with a detailed understanding of the study protocol (ie, study objective, inclusion and exclusion criteria, and benefits and risks for patients) will present the protocol to the patients and answer any questions in a concise and comprehensive manner. All patients are required to provide written consent before surgery (Figure 1).

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Figure 1. Consolidated standards of reporting trials flow diagram describing patient progress throughout the study. TKA: total knee arthroplasty.



Inclusion Criteria

The inclusion criteria include patients who have an American Society of Anesthesiologists physical status of I-III; understand the study in detail and voluntarily sign the informed consent form; are to be treated with TKA surgery under general anesthesia; are 65 years or older, regardless of sex; can communicate normally; have no contraindications to drugs, such as midazolam, fentanyl, and S(+)-ketamine; and have a body mass index between 18 kg/m^2 and 30 kg/m^2.

Exclusion Criteria

The exclusion criteria include patients who have increased intracranial or intraocular pressure, severe hypertension, severe psychiatric disease and mental system diseases, severe respiratory diseases, hyperthyroidism, liver or kidney dysfunction, or an allergy to midazolam, fentanyl, or S(+)-ketamine; are unwilling to participate in the study; or misuse alcohol or drugs.

Intervention

Preanesthetic Preparation

An experienced anesthesiologist will participate in the management of the entire perioperative period. Patients will be randomly assigned to the intravenous S(+)-ketamine intervention group or placebo equivalent (0.9% sodium chloride) control group. All patients will be continuously monitored with pulse oximetry, noninvasive blood pressure, and electrocardiogram. General anesthesia induction will be provided after saphenous nerve block is performed with 0.375% ropivacaine (20 ml) by ultrasound guidance.

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Induction and Maintenance of Anesthesia

All patients will undergo anesthetic induction administered by an experienced anesthesiologist per the protocol using dexamethasone (10 mg), midazolam (0.01-0.05 mg/kg), sufentanil (0.2-0.4 μg/kg), etomidate (0.15-0.3 mg/kg), and atracurium (0.3-0.6 mg/kg). A laryngeal mask airway will be inserted followed by muscle effective relaxation. Patients in both groups will be given ondansetron hydrochloride (8 mg) intravenously during anesthesia induction to prevent postoperative nausea and vomiting.

For patients in the S(+)-ketamine group, anesthesia will be maintained with S(+)-ketamine infusion (0.3 mg/kg/h), sedation will be maintained with propofol infusion (4-12 mg/kg/h), and analgesia will be maintained with remifentanil (0.15-0.3 μg/kg/min). The sufentanil dose at induction and the rate of intraoperative remifentanil and propofol infusions are at the discretion of the anesthesiologist in charge of the patient. The assessment of the depth of anesthesia will be based on clinical evaluation. S(+)-ketamine infusion will be stopped 15 minutes before the end of surgery. Propofol and remifentanil infusion will be stopped at the end of surgery. For the control group, other procedures will be consistent; however, S(+)-ketamine (0.3 mg/kg/h) will be replaced by intravenous sodium chloride (0.9%) infusion (0.3 mg/kg/h).

Intraoperative Management

Hypertension will be defined as an intraoperative systolic blood pressure exceeding 20% from the baseline value, and hypotension will be defined as 20% of the baseline value. Norepinephrine should be administered if the patient has hypotension and a heart rate (HR) >90 beats per minute; dopamine should be administered when the patient has hypotension and an HR <50 beats per minute; urapidil hydrochloride should be administered if the patient has hypertension and their HR is normal; and atropine should be administered if the patient has normal blood pressure and a HR <50 beats per minute. The dosages are to be determined by the patient's sensitivity to drugs to maintain stable circulation.

Outcome Measures

Primary Outcome Measure

The primary outcome is the numeric rating scale (NRS) score at rest and during movement 24 hours after surgery in the surgical ward. The NRS is widely used to assess pain intensity after surgery. The NRS is evaluated on an 11-point scale (no pain: NRS=0; mild pain: 0<NRS<4; moderate pain: 4≤NRS<7; severe pain: 7≤NRS<10; worst pain imaginable: NRS=10).

Secondary Outcome Measures

The secondary outcomes are as follows:

1. The NRS score at rest and during movement at 2 hours after surgery.

2. The NRS score at rest and during movement at 48 hours after surgery.

3. The cumulative consumption of opioids, such as pethidine, sufentanil, and morphine, during the first 48 hours after the operation.

4. The number of patients who required additional analgesics, such as opioids (pethidine, sufentanil, or morphine) or nonsteroid anti-inflammatory drugs (acetaminophen or diclofenac) during the first 48 hours after the operation.

5. The total consumption of opioids (pethidine, sufentanil, and morphine) or nonsteroid anti-inflammatory drugs (acetaminophen and diclofenac) during the first 48 hours after the operation.

6. The incidence of nausea and vomiting and adverse central nervous system events at 2, 24, and 48 hours after the operation.

The use of rescue analgesic drugs (types, administration times, and doses) and any adverse side effects (yes or no) will be recorded.

Participant Timeline

The participant timeline is shown in Table 1.

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Table 1. Schedule of enrollment, interventions, and assessments for the trial.

	Study period						
	Enrollment	Allocation	Postallocation				Close-out
Time points[a]	$-t_1$	0	t_1	t_2	t_3	t_4	t_5
Enrollment							
Eligibility screen	X						
Informed consent	X						
Allocation		X					
Interventions							
S(+)-ketamine			X	X	X	X	
Normal saline			X	X	X	X	
Assessments							
NRS[b] pain score					X	X	X
Postoperative opioid[c] consumption					X	X	X
Patients who required additional analgesics					X	X	X
Postoperative nausea					X	X	X
Postoperative vomiting					X	X	X
Nightmares					X	X	X
Hallucinations					X	X	X
Dizziness					X	X	X
Itchy skin					X	X	X

[a]The following time points were used: $-t_1$, preoperative assessment; 0, entering the operating room; t_1, after induction; t_2, end of surgery; t_3, 2 hours after surgery; t_4, 24 hours after surgery; and T_5, 48 hours after surgery.

[b]NRS: numeric rating scale.

[c]Opioids included pethidine, sufentanil, or morphine.

Safety

The main adverse effects of S(+)-ketamine alone are neuropsychiatric symptoms, such as dizziness. Therefore, S(+)-ketamine is usually used with midazolam and propofol to decrease its psychoactive effects. All adverse events related to this research will be investigated and recorded by research personnel from the time patients sign the informed consent to the end of follow-up. The investigator will decide whether to continue the study according to the status of the patient. Any serious adverse events will be treated with appropriate interventions and submitted to the principal researcher and the Medical Ethics Committee within 24 hours.

Ethical Considerations

This study has been approved by the Medical Ethics Committee of the First Affiliated Hospital of Shandong First Medical University under approval number YXLL-KY-2021 (077) and will be performed in accordance with the approved guidelines and regulations of the participating institutions. The study was registered at ClinicalTrials.gov (NCT05289050) on February 26, 2022. Informed written consent will be obtained from all patients before inclusion in the study. Because the involvement of the patients is voluntary, the study can be stopped at any time.

Data Management

The basic information of the patients before surgery and the dosage of drugs used during the operation will be collected by the anesthesiologists participating in surgical anesthesia, and the follow-up data after surgery will be provided by independent researchers. Each data point related to the study will be entered into the case report form to improve data completeness and accuracy, and electronic data will be collected and analyzed by statisticians. All the clinical trial materials will be stored securely.

Statistics

The SD will be described for measurement data that follow a normal distribution, and the median (IQR) will be described for measurement data that do not conform to a normal distribution. The student *t* test will be used to compare continuous and normally distributed variables, and the Mann-Whitney U test will be used to compare nonnormally distributed variables. Counts (percentages) will be described for categorical variables using χ^2 analysis or Fisher exact tests for compilation.

Both primary and secondary outcomes will be based on an intention to treat analysis. SPSS 22.0 software (IBM) will be used for statistical analysis, and a P value of <.05 will be considered to be statistically significant.

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Sample Size

The minimum clinically important difference (MCID) can be used to guide the noninferiority margin for clinical trials and to determine the sample size in a clinical trial [16,17]. The NRS pain score ranges from 0 (no pain) to 10 (worst pain imaginable). The MCID for the NRS that was used for the calculation of the study sample size was 1.3; however, some studies suggest that an MCID of 1.5 or 2 is appropriate [18-20]. The sample size would have been too small if we choose an MCID of 2. Considering a 10% withdrawal or dropout rate, a sample size of 72 patients per group was calculated, with a power of 80%. The MCID determined 1.5 as statistically significant, with an SD of 3 at the 5% bilateral significance level.

Results

The protocol was registered at ClinicalTrials.gov (NCT05289050) on February 26, 2022. It was performed in accordance with the approved guidelines and regulations of the participating institutions. Recruitment began in April 2022. Data collection is expected to conclude in September 2024. Study completion is expected in December 2024. As of December 2023, we have enrolled 132 patients.

Discussion

TKA is increasingly performed in geriatric patients to cure pain, deformation, and the inability to walk normally caused by knee arthritis. The total number of TKA procedures may increase by 401% in 2040 compared to that in 2014 [21]. Poor management of acute pain after TKA increases the risk of complications, such as venous thrombosis, an inability to exercise effectively, and pneumonia. Currently, there is a consensus that inadequate postoperative pain control measures are being implemented, especially in older patients. Opioids are the main treatment for relieving TKA postoperative pain [22]. Considering the side effects of opioids, appropriate multimodal medication projects are required to decrease postoperative opioid use and improve effects with decreasing pain levels in geriatric patients. Ketamine can suppress the pathway of central sensitization and secondary postoperative hyperalgesia and has been proposed as a component of multimodal analgesia for various surgical procedures [23]. Ketamine in subanaesthetic doses is available as an adjuvant to the standard regimen of opioids, presenting prominent analgesic and opioid-sparing effects without adverse effects [24]. Some studies have shown that low-doses of S(+)-ketamine can reduce the incidence of side effects (eg, the induction of hypotension) and high doses of opioids through its sympathetic stimulation, analgesia, and antagonism of the NMDA receptor [25,26]. Similarly, a meta-analysis demonstrated that the administration of low-dose ketamine can decrease total opioid use and pain scores over 2 days and may also reduce postoperative nausea and vomiting. This has been attributed to reductions in total opioid administration, leading to decreased opioid-associated nausea and vomiting [27,28]. Another meta-analysis demonstrated that perioperative intravenous ketamine reduced postoperative opioid consumption by 8 mg morphine equivalents per day [29].

Additional studies have demonstrated that a low-dose intravenous infusion of ketamine can be administered as an adjuvant drug to alleviate acute postoperative pain, while the guidelines for ketamine for postoperative acute pain have found grade B evidence to advocate perioperative ketamine as an adjuvant [15,30].

Although low-dose S(+)-ketamine has been shown to be beneficial in pain management after various surgeries, there is no consensus regarding the effectiveness of an S(+)-ketamine analgesic combined with opioids in older patients with knee arthroplasty. In addition, the appropriate administration duration and dose of S(+)-ketamine to achieve pain relief in older patients are unknown. A randomized controlled trial will be conducted to assess the efficacy and safety of an intraoperative intravenous low-dose of S(+)-ketamine for pain management in older patients undergoing TKA.

The design of our protocol has several limitations. First, this is a single-center study with a relatively small sample size, and only older patients undergoing TKA will be enrolled, which limits the generalizability of our outcomes. Second, the end of our follow-up is 48 hours postoperatively. A longer follow-up is necessary to demonstrate the long-term effects and safety of S(+)-ketamine.

In conclusion, we will appraise the efficacy and safety of the intraoperative intravenous injection of S(+)-ketamine to relieve acute pain after TKA in older patients who may benefit from the administration of S(+)-ketamine.

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Data Availability

The data sets used or analyzed during the trial will be made available from the corresponding author on reasonable request.

Authors' Contributions

SYD wrote the main manuscript text. LD reviewed the article. LNC and XS prepared the figure. LG and FZ prepared the table. JL searched the literature.

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Conflicts of Interest

None declared.

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Abbreviations

HR: heart rate
MCID: minimum clinically important difference
NMDA: N-methyl-D-aspartate receptor
NRS: numeric rating scale score
TKA: total knee arthroplasty

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Protocol

Effect of Baduanjin Qigong on Sleep Quality and Hyperarousal State in Adults With Chronic Insomnia: Protocol for a Randomized Controlled Trial

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Abstract

Background: Chronic insomnia (CI) is a mind-body disease that is commonly defined as a state of having disturbed daytime activities due to poor nighttime sleep quality. Baduanjin qigong (BDJQG) is widely used for CI in China. However, there is little scientific evidence to evaluate its effects on the hyperarousal state, which is closely associated with improved sleep quality.

Objective: The objective of the trial is to assess the therapeutic effects of BDJQG on sleep quality in patients with CI.

Methods: A randomized controlled trial will be conducted on 86 patients, who will be divided into a BDJQG group and a cognitive behavioral therapy for insomnia group at a ratio of 1:1. Interventions in both groups will be given to the participants 7 times a week for 8 weeks, and the participants will be followed up for 4 weeks. The primary outcome is the change in the Pittsburgh Sleep Quality Index from baseline to week 8. The secondary outcomes are the changes in the Hyperarousal Scale, Insomnia Severity Index, Fatigue Scale-14, wrist actigraphy, salivary cortisol level, and functional magnetic resonance imaging from baseline to week 8. All main analyses will be carried out on the basis of the intention-to-treat principle.

Results: This study was funded from January 2023. As of the submission of the manuscript, there were 86 participants. Data collection began in April 2023 and will end in January 2024. Data analysis is expected to begin in January 2024, with the publication of results expected in February 2024.

Conclusions: This study will present data concerning the clinical effects of BDJQG on CI. The results will help to demonstrate whether BDJQG is an effective therapy for improving sleep quality in association with a decreased hyperarousal level as a possible underlying mechanism. This study will provide much-needed knowledge for complementary and alternative therapy for patients with CI.

Trial Registration: China Clinical Registration Agency ChiCTR2300069241; https://chictr.org.cn/bin/project/ChiCTR2300069241

International Registered Report Identifier (IRRID): PRR1-10.2196/53501

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KEYWORDS

Baduanjin qigong; chronic insomnia; functional magnetic resonance imaging; hyperarousal; randomized controlled trial

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Introduction

Chronic insomnia (CI) is the most common clinical sleep disorder. It is characterized by persistent challenges in initiating or maintaining sleep; suboptimal sleep quality; and impairments in daytime functioning, including fatigue, attention deficit, and emotional instability [1]. The prevalence of CI in the general population varies between 9% and 12%, with transient insomnia symptoms reported by 22% to 35% of individuals [2]. The widely recognized classification framework for sleep disorders, the *International Classification of Sleep Disorders, Third Edition*, stipulates specific criteria for diagnosing CI. Specifically, the diagnosis of CI necessitates the presence of insomnia symptoms for a minimum duration of 3 months, with no fewer than 3 associated symptoms, which may encompass manifestations such as fatigue, irritability, and compromised work, school, or social performance [3]. While CI is classified as a sleep disorder, its pathophysiological underpinnings suggest a prevailing state of hyperarousal during both sleep and wakefulness phases [4]. Evidence of the hyperarousal phenomenon in individuals with insomnia encompasses elevated levels of cortisol and adrenocorticotropic hormone during the initial stages of sleep and discernible thalamic responses determined through functional magnetic resonance imaging (fMRI) [5].

Several pharmaceutical agents, including benzodiazepines, benzodiazepine agonists, and certain antidepressants, have demonstrated efficacy in the short-term management of insomnia [6]. However, these pharmacological interventions carry inherent risks related to the sedative properties. The risks encompass an elevated propensity for falls; cognitive confusion; and the potential for the development of tolerance, dependence, and withdrawal effects when used for extended periods [7]. Cognitive behavioral therapy for insomnia (CBTI), regarded as the first-line treatment for insomnia, has proven its effectiveness in addressing CI in adults. It consistently ameliorates clinical symptoms associated with insomnia, producing clinically meaningful effects [8]. Nevertheless, the accessibility of CBTI remains challenging for patients, primarily due to the limited availability of specialized practitioners, which hinders its ability to adequately meet clinical demands [9]. Several complementary and alternative medicine modalities, including traditional Chinese herbal medicine [10], acupuncture [11], and qigong, have exhibited efficacy in the treatment and prevention of insomnia, effectively mitigating symptoms such as fatigue and depression.

Qigong is a component of traditional Chinese medicine characterized by its integrated approach, involving breath control, physical movement, and meditation techniques. Notably, extant research has furnished evidence supporting the beneficial effect of qigong on various facets of health among individuals with insomnia, including the enhancement of sleep quality [12,13], alleviation of symptoms related to anxiety and depression [14,15], and modification of sleep-wake patterns as corroborated by actigraphy assessments [16].

The nomenclature “Baduanjin qigong” (BDJQG) was first documented in *Yi Jian Zhi* by Hong Mai during the Northern Song Dynasty, indicating that this mind-body practice has a history spanning over 800 years [17]. This modality is renowned for its holistic approach, characterized by facilitating overall coordination, unblocking meridians, harmonizing the mind and body, and assisting the body in achieving a relative equilibrium between the yin and yang elements. The safety and efficacy of BDJQG have garnered empirical support through numerous clinical trials, rendering it a widely embraced therapeutic approach for diverse chronic ailments [18-20]. For example, an illustrative meta-analysis has indicated that BDJQG, particularly when integrated with mindfulness techniques, is effective in alleviating musculoskeletal pain and enhancing the overall sleep quality in individuals with chronic conditions [21]. Furthermore, BDJQG comprises 8 distinct movements that are easy to learn. If its efficacy is proven, its wider use could be promoted.

Previous investigations into insomnia treatment have primarily centered on enhancing sleep quality but have often overlooked the assessment of daytime functioning. In contrast, our previous research findings suggested that qigong exhibits efficacy both in ameliorating sleep quality and in enhancing daytime functioning [22].

Remarkably, assessments of the hyperarousal state have been conspicuously scarce in previous trials. In this study, we intend to comprehensively evaluate hyperarousal from a multidimensional perspective, encompassing cognitive functions (evaluated through the Hyperarousal Scale [HAS]), cortical activities (scrutinized through fMRI), and hypothalamic-pituitary-adrenocortical (HPA) axis functioning. Salivary cortisol level (SCL), known to correlate with various sleep parameters [23], will be measured, given that hyperarousal in insomnia is associated with heightened cortisol secretion. Previous empirical evidence has directly indicated that BDJQG may induce changes such as increased melatonin levels and decreased cortisol levels, which are indicative of reduced wakefulness-related factors [24]. These physiological markers will be meticulously monitored as potential indicators of BDJQG’s effect on the HPA axis.

Building upon the insights gleaned from previous research and considering the plausible role of BDJQG in attenuating hyperarousal, we have formulated a randomized, open-label, parallel-controlled trial to systematically investigate the therapeutic efficacy of BDJQG concerning both sleep quality and hyperarousal state in individuals with CI.

Methods

Aims and Study Design

The primary objectives of this open-label, parallel, noninferiority randomized controlled trial (RCT) will be 2-fold:

1. To ascertain whether BDJQG can yield improvements in the primary outcome, which is sleep quality, and the secondary outcomes, encompassing an array of measures spanning various domains, including hyperarousal state, severity of insomnia, and levels of fatigue. These improvements will be evaluated in comparison to CBTI.
2. To explore the potential efficacy of BDJQG as a therapeutic intervention for CI and its potential association with a

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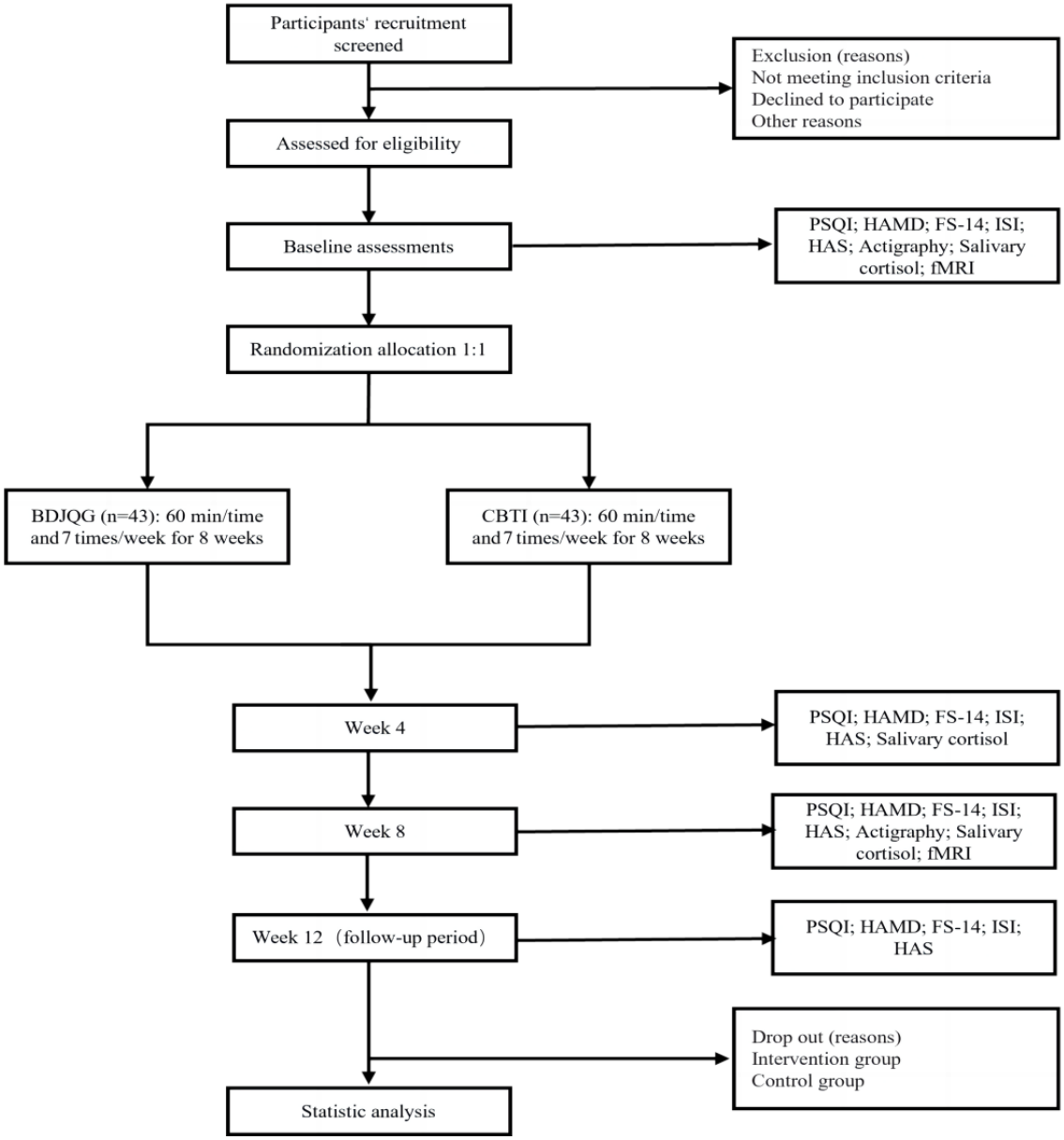
reduction in hyperarousal levels, which may serve as an underlying mechanistic pathway. This exploration will be facilitated through correlation analyses.

Study Setting

Participants will be recruited from the Shanghai Municipal Hospital of Traditional Chinese Medicine. Eligibility for inclusion will be determined by 2 orthopedic surgeons based on predefined inclusion and exclusion criteria. Participants who are determined to be eligible and provide written informed consent will be randomly allocated to either the BDJQG group or the CBTI group in a 1:1 ratio. The BDJQG group will undergo BDJQG treatment, while the CBTI group will receive cognitive behavioral therapy for insomnia. Both groups will undergo an 8-week-long treatment program, consisting of 1 supervised session per week at Shanghai University of Traditional Chinese Medicine and the remaining 6 days of the week completed at home. The study will span a total of 13 weeks, comprising a 1-week-long screening period, an 8-week-long treatment phase, and a subsequent 4-week-long follow-up period.

Assessments using various scales will be conducted at baseline, the 4-week intervention mark, the 8-week intervention mark, and the 4-week follow-up. SCL will be measured at baseline, the 4-week intervention mark, and the 8-week intervention mark. Actigraphy and fMRI assessments will be administered at baseline and the 8-week intervention mark. Figure 1 gives a visual representation of the research process, and Table 1 shows an overview of the study's time points.

Figure 1. Flowchart of the study design. BDJQG: Baduanjin qigong; CBTI: Cognitive behavioral therapy for insomnia; fMRI: functional magnetic resonance imaging; FS-14: Fatigue Scale-14; HAMD: Hamilton Depression Scale; HAS: Hyperarousal Scale; ISI: Insomnia Severity Index; PSQI: Pittsburgh Sleep Quality Index.



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Table 1. Chart of the trial's time points.

Research process	Baseline (week 0)	Intervention period (weeks 1-8)	Intervention period (week 4)	Intervention period (week 8)	Follow-up (week 12)
Inclusion criteria	✓				
Exclusion criteria	✓				
Informed consent	✓				
Randomization and allocation	✓				
Intervention		✓			
PSQI[a]	✓		✓	✓	✓
HAMD[b]	✓		✓	✓	✓
ISI[c]	✓		✓	✓	✓
HAS[d]	✓		✓	✓	✓
FS-14[e]	✓		✓	✓	✓
Actigraphy	✓			✓	
Salivary cortisol	✓		✓	✓	
fMRI[f]	✓			✓	
Adverse events		✓		✓	✓
Working practice record		✓		✓	✓

[a]PSQI: Pittsburgh Sleep Quality Index.

[b]HAMD: Hamilton Depression Scale.

[c]ISI: Insomnia Severity Index.

[d]HAS: Hyperarousal Scale.

[e]FS-14: Fatigue Scale-14.

[f]fMRI: functional magnetic resonance imaging.

Participants' Eligibility Criteria

Textbox 1 shows the inclusion, exclusion, and withdrawal criteria.

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Textbox 1. Inclusion, exclusion, and withdrawal criteria.

Inclusion criteria

Participants meeting the following criteria will be included:

- Chronic insomnia based on established diagnostic criteria (*International Classification of Sleep Disorders, Third Edition*), including a report of sleep initiation or maintenance problems, adequate opportunity and circumstances to sleep, daytime consequences, and duration of at least 3 months, with a frequency of at least 3 times per week
- Insomnia Severity Index score between 8 and 21
- Age between 20 and 55 years and male or female sex
- Hamilton Depression Scale score ≤14
- No treatments for insomnia, including medication and acupuncture, received during the past month
- Right-handedness
- Understanding the process of this study and agreeing to participate and sign the consent form

Exclusion criteria

Participants meeting any of the following criteria will be excluded:

- Severe pain or systemic diseases (endocrine system diseases, motor system diseases, autoimmune diseases, infectious diseases, and metabolic diseases such as diabetes mellitus) that affect sleep
- History of metal, head surgery, and implantation of any metal or other contraindications for functional magnetic resonance imaging
- Insufficient language skills and mobility to perform Baduanjin qigong
- Major depressive disorder, anxiety disorder, panic disorder, or other mental disorders, and alcohol or caffeine addiction
- Pregnancy, breastfeeding, or planning to become pregnant

Withdrawal criteria

Participants meeting the following criteria will be excluded after the start of the trial:

- Occurrence of an adverse event related to the research
- Participant's personal request

Interventions

The two arms of the trial are (1) the intervention arm (BDJQG) and (2) the control arm (CBTI).

Intervention Arm (BDJQG Group)

BDJQG consists of 8 forms, which are shown in Multimedia Appendix 1. A qigong teacher from Shanghai University of Traditional Chinese Medicine, who has been involved in qigong education for at least 5 years, will be in charge of the concentrated supervision of the exercise and correction of the exercise posture for 1 hour every Sunday throughout the intervention period. The teacher will first lead a 5-minute stretching and relaxation exercise session to be done before the qigong exercise; and they will then introduce and demonstrate each movement, explain precautions, and answer the participants' questions for 5 minutes. Then, the teacher will give individual guidance to each participant by correcting their movements. This will last for 30 minutes. Finally, all participants will be told to practice qigong together for 20 minutes. The participants will be asked to practice at home for 30 minutes on the remaining 6 days of the week, to practice on WeChat (Tencent) cluster video at 6 PM daily, and to practice under video supervision. Private video surveillance will be carried out if this is deemed appropriate by an individual participant. A "practice log" will be distributed, to be filled in after each exercise. The entire treatment will last for 8 weeks. The BDJQG intervention will be in line with the descriptions provided in the study by Xie et al [25].

Control Arm (CBTI Group)

The CBTI protocols used in this study are based on the comprehensive guide titled *Cognitive Behavioral Treatment of Insomnia: A Session-by-Session Guide* [26]. The participants assigned to the CBTI group will undergo an 8-week-long cognitive behavioral therapy program for insomnia, guided by an experienced psychotherapist, with each session spanning 1 hour and occurring weekly. Additionally, the participants will be provided with a "practice log" to document their activities and progress after each video session.

Follow-Up Period

An 8-week-long follow-up will be conducted subsequent to the conclusion of the trial, during which the participants will resume their regular lifestyles. However, it is imperative that all of the participants maintain a record of their daily exercise or study activities. To facilitate this, WeChat will be used as a platform for the participants to periodically capture and share photos, providing the researchers with a comprehensive account of their daily exercise or study routines. Upon the culmination of the follow-up period, a reassessment of several metrics, including the Pittsburgh Sleep Quality Index (PSQI), Insomnia Severity

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Index (ISI), HAS, and Fatigue Scale-14 (FS-14), will be conducted. The objective of this follow-up assessment is to evaluate the enduring or long-term effects of BDJQG on individuals with insomnia, as elucidated in a study conducted by Guan et al [27].

Quality Control

The specific movements and the corresponding intensity levels used in the BDJQG regimen will be meticulously tailored to individual prescriptions, with variations designed to minimize disparities. Preceding the commencement of the experimental phase, each participant will undergo a structured training program spanning 3 days, administered by a traditional Chinese medicine practitioner with a minimum of 5 years of clinical experience. This training regimen is intended to impart standardized BDJQG movements to ensure uniformity and precision among the participants.

Outcomes

Primary Outcome (PSQI)

The primary outcome is the change in PSQI from baseline to week 8. The PSQI is a comprehensive self-report instrument comprising 19 items aimed at evaluating sleep quality and disturbances experienced within a 1-month time frame. These items collectively contribute to the generation of 7 distinct "component" scores, encompassing assessments of subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. The sum of the scores derived from these 7 components yields a singular global score. The total global score spans a range from 0 to 21, with a lower global score indicative of a higher quality of sleep [28].

Secondary Outcomes

The secondary outcomes include the changes in ISI, HAS, FS-14, actigraphy, SCL, and fMRI from baseline to week 8.

ISI Instrument

The ISI is a self-report instrument encompassing 7 items intended to assess various aspects of insomnia, including the challenges associated with falling asleep and maintaining sleep, overall sleep satisfaction, daytime functioning, impaired attention attributable to sleep disturbances, the degree of distress caused by insomnia-related symptoms, and the level of preoccupation with insomnia-related concerns. Each of these aspects is evaluated on a 5-point scale. The cumulative ISI score ranges from 0 to 28 points and is categorized as follows: 0-7=absence of insomnia; 8-14=mild insomnia; 15-21=moderate insomnia; and 22-28=severe insomnia [29].

HAS Instrument

The HAS comprises 26 self-report items designed to gauge a range of cognitive and behavioral factors associated with heightened information processing, propensity for introspection, tendencies to engage in deep emotional reflection, and heightened responsiveness to unforeseen stimuli, all of which are postulated to be indicative of cortical arousal [30]. Elevated scores on this scale are suggestive of an increased state of arousal. Consequently, the HAS serves as a valuable tool for assessing the effect of interventions on cognitive and somatic hyperarousal levels [31].

FS-14 Instrument

Fatigue is a prominent consequence of CI, as consistently documented in previous research studies [32,33]. The FS-14 is a self-report assessment tool comprising 14 items designed to capture both physical and mental aspects of fatigue. On this scale, a higher score is indicative of a more pronounced and debilitating level of fatigue.

Actigraphy

The ActiGraph GT9X Link (Actigraphy LLC) will be worn on the participants' wrists to record sleep quality by noting sleep awakenings, total sleep time, sleep onset, sleep latency, and efficiency of sleep. Subsequent analysis of sleep conditions and sleep quality will be executed using the ActiLife6 software (version 6.8.1; Actigraphy LLC) [34]. The participants will be instructed to wear the device continuously for 3 consecutive days, both before and after the 8-week-long intervention period.

SCL Measurement

SCL will be quantified using the enzyme-linked immunosorbent assay (ELISA) methodology. Sampling will be conducted at 4 distinct time points during the day, namely upon awakening [35], 30 minutes after awakening [36], before sleep (30 minutes before bedtime) [37], and immediately before bedtime [38] (with the timing adjusted to fall within the range of 9 PM to 1 AM, contingent on each participant's self-selected bedtime). This collection process will be carried out during 3 distinct cycles, namely at baseline, 4 weeks, and 8 weeks.

Saliva samples will be gathered using a Salivette collection system (hygienic saliva collection; Sarstedt) [36] and stored in a –20 °C freezer until they undergo analysis using the General Cortisol ELISA Kit (RK00639; ABclonal) [39]. The participants will be provided with specific instructions not to engage in eating, drinking, toothbrushing, or strenuous physical activity within the 30-minute interval preceding each saliva sampling session.

fMRI Examination Procedure

fMRI data will be acquired from all of the participants using a 3.0-T Trio Siemens System (SIEMENS AG) at the Yueyang Hospital of Integrated Traditional Chinese and Western Medicine affiliated with the Shanghai University of Traditional Chinese Medicine, Shanghai, China. A total of 30 participants will be scanned under the following conditions: repetition time=1900 ms; effective echo times=2.93 ms; sagittal slices=188; thickness/skip=1.2/0.6 mm; field of view=256 × 256 mm^2; matrix=240 × 256 mm^2; voxel size=1.0 × 1.0 × 1.0; phase encoding direction=A >> P; and flip angle=90°. The participants will be requested to rest for 10 minutes with their eyes closed, and they will be requested not to think about anything before the scan. They will be asked not to move the head during data acquisition. We will acquire 242 3D image volumes with the following parameters: repetition time=2000 ms; effective echo times=30 ms; section thickness=1 mm; sagittal slices=32; field of view=256 × 256 mm^2; matrix=64 ×

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64 mm^2; and flip angle=90°. Both groups of participants will be examined before and after treatment.

Sample Size

The following 2 hypotheses are related to the differences between the 2 groups:

- Hypothesis 1: $\mu_1 = \mu_2$
- Hypothesis 2: $\mu_1 \neq \mu_2$,

where μ_1 is the PSQI mean score of the 8-week treatment in the BDJQG group, and μ_2 is the PSQI mean score of the 8-week treatment in the CBTI group.

The required sample size has been calculated using an estimation formula based on the difference between 2 sample means and SDs (PSQI, which is assessed using composite points of sleep quality). Therefore, in a study with this sample size, the difference between the BDJQG group and the CBTI group will be considered, and the conservative comparison method by Bonferroni will be adopted. In this study, it is expected that the BDJQG group will be 1.78 points better than the CBTI group in the PSQI scale mean score. The final calculated difference and SD of the 2 groups of the PSQI mean scores were calculated [40]. On the basis of 0.9 power to detect a significant difference (α=.025; 1-sided), 34 participants will be required for each group.

The following formula was used to calculate the sample size in this trial:



Given that an attrition rate of ~20% is anticipated, our target enrollment will be 43. Therefore, a total of 86 participants should be recruited for this RCT.

Recruitment

To attain the requisite participant enrollment necessary to achieve our predetermined target sample size, recruitment will be conducted within the Shanghai area. These endeavors will encompass the dissemination of recruitment materials through posters, promotion through WeChat public accounts, engagement with individuals attending outpatient clinics, and outreach to those using medical examination centers.

Randomization and Blinding

Following a postbaseline assessment, the eligible participants will be randomly allocated to the BDJQG group and the CBTI group, adhering to a 1:1 equal proportion allocation. A randomization list will be meticulously generated by a skilled statistician using a computer program (Strategic Applications Software, version 9.1.3; SAS Institute Inc). The generated random sequences will be sequentially numbered by the statistician, who serves as the architect of the randomization sequence. Subsequently, the sequences will be placed within opaque envelopes by a designated project manager, uninvolved in the recruitment process. These sealed envelopes will ultimately be delivered to the research team.

Before implementing the random assignment procedure, the research team will diligently record the particulars of each participant at the clinical center. These records will encompass the participant's information, such as name, date of birth, participant and center codes, and the inclusion date. Following a meticulous review of the participant's information by the research team to ascertain eligibility, a sequence will be randomly drawn from the envelope. The selected sequence will be applied to label the participant's data, designating the participant's assignment to one of the study groups. This information will then be conveyed to the respective participants.

It is noteworthy that, due to the specific nature of the intervention approach, this study is an open trial, with only the statistical analysis experts being kept blinded, as delineated in the research conducted by Cheng et al [41].

Adverse Events and Assessment of Safety

Adverse events (AEs) encompass any untoward and nonsignificant occurrences, namely abnormal experimental findings, symptoms, or illnesses that transpire during the course of the study, irrespective of their causal relation to the intervention. It is important to note that numerous authors have attested to the relative safety of qigong as an approach to addressing various health conditions, including hypertension, with no records of severe AEs. In the event of any unexpected AEs, categorized as functional abnormalities brought about by the intervention, such as symptoms like headache, dizziness, vertigo, head distension, tinnitus, chest tightness, aggravated shortness of breath, heart palpitations, muscular soreness or pain, profuse cold perspiration, irritability, neurasthenia, hallucinations, paranoia, or psychological stress—regardless of their treatment association—prompt notification will be made to the nearest affiliated Shuguang Hospital physician. The physician will then conduct an assessment and initiate appropriate medical intervention.

In instances where serious AEs are encountered, the investigator will promptly report the incident to the primary investigator and the ethics committee to collectively determine whether the affected participant should be withdrawn from the study and the associated treatment. The investigator will earnestly strive to avert and manage any potential harm that may arise during the course of the study. If, following the assessment by the expert committee, the AE is determined to be linked to the qigong treatment, the research team will assume responsibility for covering the cost of treatment and providing appropriate financial compensation for any damage arising from the trial. This comprehensive approach to describing AEs and ensuring the assessment of safety closely adheres to the framework delineated in the study conducted by Guan et al [27].

Data Management and Monitoring

Upon recruitment, the participants' identities will be replaced with numerical codes to safeguard their privacy. Data collection will be conducted at baseline, week 4, and week 8. This process will entail the involvement of 2 proficient data specialists who will be responsible for transcribing the paper-based records into a unified database while meticulously verifying the accuracy of the entered data. Ultimately, both the paper records and encrypted electronic files will be securely stored and redundantly backed up by the research leader. These records will be retained

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in storage for a period of 3 years following the conclusion of the study.

The oversight of the study will be carried out under the purview of the ethics committee of the Shanghai Municipal Hospital of Traditional Chinese Medicine. Importantly, the members of this committee have been carefully vetted to ensure they possess no conflicts of interest pertaining to this study. The principal investigators will retain unfettered access to all study results and will have the final authority to decide on the termination of the study. Furthermore, they will extend the privilege to project team members to disseminate the trial's findings through the publication of research papers.

Statistical Analysis

The collected data will meticulously be entered into Microsoft Excel (Microsoft Corporation), and subsequent statistical analysis will be conducted using SPSS software (version 18.0; SPSS Inc). Continuous variables will be summarized using the mean value and SD, with the median and IQR used for variables exhibiting nonnormal distributions. Categorical variables will be presented as frequencies or percentages.

For within-group comparisons, paired 2-tailed *t* tests will be used. Between-group differences will be analyzed through 2-sample, independent-sample *t* tests, with effect sizes computed using Cohen *d* statistics. Furthermore, demographic characteristics, baseline measurements, and changes in measurements from baseline to study completion between the 2 groups will be analyzed using 2-sample, independent-sample *t* tests. In cases where baseline measurements exhibit disparities, analysis of covariance will be implemented to account for these variations when comparing the 2 groups.

The clinical overall efficacy evaluation will be based on a nonparametric test for 2 independent samples. In instances of limited participant numbers within a specific subject or in the presence of missing data, the Mann-Whitney *U* test will be used to assess differences between the groups. A statistical significance level of $P<.05$ will be used, signifying statistical significance when this threshold is met.

Ethical Considerations

This study will adhere to the principles outlined in the Declaration of Helsinki, ensuring that no additional harm or risks are imposed on the participants. The study has been meticulously designed in compliance with the Standardized Protocol Items, encompassing the recommendations for interventional trials (SPIRIT [Standard Protocol Items: Recommendations for Interventional Trials]) checklist, and has received approval from the ethics committee of Shanghai Municipal Hospital of Traditional Chinese Medicine (2023SHL-KY-17-01). Furthermore, the study has been duly registered in the Chinese Clinical Trials Registry in 2023 (ChiCTR2300069241). The information presented in this report is derived from protocol version 1.0. Before the commencement of the trial, the participants will undergo a comprehensive orientation session regarding the study protocol and their associated responsibilities. This briefing will encompass a detailed explanation of the required physical examinations and relevant precautions. Of paramount importance, the participants will be unequivocally apprised that their engagement in the study is entirely voluntary, and they retain the prerogative to decline participation or withdraw at any juncture without any impact on their medical care or other associated benefits. Notably, if a participant opts to withdraw from the study, any previously collected data will remain intact and be incorporated into the final analysis. To initiate any study-related interventions, explicit written informed consent will be diligently obtained from each participant. A designated research assistant will be entrusted with the responsibility of securing informed consent from all participants. Separate informed consent forms have been developed for the collection of magnetic resonance imaging and saliva samples. Furthermore, all participants will be asked for their consent for the potential publication of identifying information or images within an internet-based open publication, in accordance with established ethical guidelines. The study data will be anonymous or deidentified. Upon the conclusion of the study, the patients will be extended an invitation to continue their 4-week follow-up period at the Shanghai University of Traditional Chinese Medicine, located in Shanghai, China. The 8-week BDJQG program is an enduring initiative, and the participants will maintain their eligibility to engage in this program. Should they desire to do so, the participants can opt to attend BDJQG or CBTI classes free of charge following the culmination of their participation in the study. As an additional incentive to bolster follow-up participation, the participants will be furnished with a large gift pack that will include specialized topical pain patches, a wellness pot, and ¥300 (US $41.98) at the conclusion of the follow-up evaluation. This provision is aimed at enhancing their enthusiasm for continued participation in the follow-up phase.

Results

This study was funded from January 2023. As of the submission of the manuscript, there were 86 participants. Data collection began in April 2023 and will end in January 2024. Data analysis is expected to begin in January 2024, with the publication of results expected in February 2024.

Discussion

Overview

The impact of insomnia extends beyond individual challenges, significantly affecting both personal and societal domains, encompassing physical and mental health, social progress, and economic facets. Regrettably, despite its considerable debilitating effects, effective treatments for insomnia have remained elusive. Moreover, there is limited application of evidence-based interventions aimed at alleviating symptoms and enhancing patients' overall functioning. Therefore, the quest for a cost-effective and efficacious insomnia remedy is of paramount importance. Numerous studies have underscored the effectiveness of qigong and related therapies in ameliorating insomnia, although these investigations have primarily centered on efficacy and largely overlooked the underlying mechanisms. Furthermore, there is a scarcity of rigorous studies to affirm the clinical effects of BDJQG exercises on insomnia-induced hyperarousal.

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The primary objective of this trial is to probe the efficacy of BDJQG in addressing sleep quality and hyperarousal state associated with CI. The trial's efficacy indicators will encompass both subjective and objective aspects, such as sleep duration and quality as evaluated by the PSQI and wrist actigraphy, daytime functioning as assessed by the FS-14, physiological changes linked to the HPA axis determined through cortisol level measurements, and cortical activities monitored through fMRI. This study aims to establish a connection between the effect of BDJQG on CI and its potential impact on hyperarousal state, measured across multiple dimensions. A diagram to illustrate the mechanism of change before and after the intervention is shown in Multimedia Appendix 2. This novel approach marks the first endeavor in a clinical trial of CI to explore both the clinical effects and the plausible underlying mechanisms associated with BDJQG.

fMRI serves as a vital tool to assess changes in cortical hyperarousal, a phenomenon observed in individuals with insomnia. The thalamus is the switch that controls wakefulness [42]. Patients with insomnia disorder demonstrate decreased thalamic connectivity with the left amygdala, parahippocampal gyrus, putamen, pallidum, and hippocampus across wakefulness [43]. Previous studies have shown that qigong can affect the brain response [22,44-46]. This trial strives to bridge the existing knowledge gap by combining fMRI, which investigates arousal responses spatially within the brain, with wrist actigraphy, enabling the temporal monitoring of arousal status. This combined approach will enhance our ability to comprehensively elucidate the shifts in arousal experienced by individuals with insomnia.

The strengths of this protocol are manifold. First, it represents the inaugural RCT delving into the effects of qigong, specifically BDJQG, on hyperarousal among individuals with insomnia. The findings emerging from this trial will enrich the existing body of research on qigong for the management of insomnia. Second, BDJQG's accessibility and versatility, enabling indoor or outdoor practice by individuals or groups without necessitating specialized sports facilities or equipment, make it an appealing intervention. Third, BDJQG's dual benefits of physical and mental conditioning render it suitable for individuals across diverse age groups.

Nonetheless, this study exhibits certain limitations. First, the challenge of achieving blinding in nonpharmaceutical trials, wherein participants are aware of the treatment they receive, could potentially introduce bias into the results. However, rigorous measures have been implemented to ensure that laboratory technicians, data managers, and statisticians remain detached from the recruitment and participant processing phases. Furthermore, recent meta-epidemiological research has indicated no substantial differences in estimated treatment effects between trials with and without patient blinding. Second, the recruitment criteria limit participants to those aged between 20 and 55 years without severe CI, possibly limiting the generalizability of the results to other age groups. Third, as this is a single-center study, it will not recruit participants from diverse regions. Nevertheless, recruitment strategies will encompass community outreach and internet-based channels to diversify the participant pool and minimize regional bias. Therefore, we are prepared to follow up with a multicenter study to provide more adequate evidence.

Conclusion

This study is poised to provide valuable data regarding the treatment of CI through BDJQG. Its outcomes will help elucidate whether BDJQG is an efficacious approach for enhancing sleep quality and explore its potential mechanistic associations. We will scrutinize the hypothesis that BDJQG's effect on insomnia may be linked to its capacity to mitigate hyperarousal states. The findings of this trial hold the potential to guide more informed and selective use of BDJQG as an insomnia treatment modality in the future.

Acknowledgments

We thank Rui-ping Wang and Guan-wu Li for their contributions to the development of this protocol. This study is funded by the Young Gifu Scholars Support Program and the National Natural Science Foundation of China (grants 82105038 and 82374610). It is important to note that the funding body has no involvement in the design of the study, data collection, analysis, interpretation of results, manuscript preparation, or the decision to submit the report for publication. FY and YLY are co-corresponding authors on this article.

Data Availability

The data sets analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

CQX reviewed the literature and wrote the manuscript. FFX and JWM wrote and revised the manuscript. HYY revised the manuscript. FY and YLY designed and revised the manuscript. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
The detailed movements of the Baduanjin qigong.

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[PDF File (Adobe PDF File), 494 KB - resprot_v12i1e53501_app1.pdf]

Multimedia Appendix 2
Chart of mechanisms of change before and after the intervention.
[PDF File (Adobe PDF File), 97 KB - resprot_v12i1e53501_app2.pdf]

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Abbreviations

AE: adverse event
BDJQG: Baduanjin qigong
CBTI: cognitive behavioral therapy for insomnia
CI: chronic insomnia
ELISA: enzyme-linked immunosorbent assay
fMRI: functional magnetic resonance imaging
FS-14: Fatigue Scale-14
HAS: Hyperarousal Scale
HPA: hypothalamic-pituitary-adrenocortical
ISI: Insomnia Severity Index
PSQI: Pittsburgh Sleep Quality Index
RCT: randomized controlled trial
SCL: salivary cortisol level
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Protocol

A Machine Learning Model to Predict Patients' Adherence Behavior and a Decision Support System for Patients With Metastatic Breast Cancer: Protocol for a Randomized Controlled Trial

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Abstract

Background: Adherence to oral anticancer treatments is critical in the disease trajectory of patients with breast cancer. Given the impact of nonadherence on clinical outcomes and the associated economic burden for the health care system, finding ways to increase treatment adherence is particularly relevant.

Objective: The primary end point is to evaluate the effectiveness of a decision support system (DSS) and a machine learning web application in promoting adherence to oral anticancer treatments among patients with metastatic breast cancer. The secondary end point is to collect a set of new physical, psychological, social, behavioral, and quality of life predictive variables that could be used to refine the preliminary version of the machine learning model to predict patients' adherence behavior.

Methods: This prospective, randomized controlled study is nested in a large-scale international project named "Enhancing therapy adherence among metastatic breast cancer patients" (Pfizer 65080791), aimed to develop a predictive model of nonadherence and associated DSS and guidelines to foster patients' engagement and therapy adherence. A web-based DSS named TREAT (treatment adherence support) was developed using a patient-driven approach, with 4 sections, that is, Section A: Metastatic Breast Cancer; Section B: Adherence to Cancer Therapies; Section C: Promoting Adherence; and Section D: My Adherence Diary. Moreover, a machine learning–based web application was developed to predict patients' risk factors of adherence to anticancer treatment, specifically pertaining to physical status and comorbid conditions, as well as short and long-term side effects. Overall, 100 patients consecutively admitted at the European Institute of Oncology (IEO) at the Division of Medical Senology will be enrolled; 50 patients with metastatic breast cancer will be exposed to the DSS and machine learning web application for 3 months (experimental group), and 50 patients will not be exposed to the intervention (control group). Each participant will fill a weekly medication diary and a set of standardized self-reports evaluating psychological and quality of life variables (Adherence Attitude Inventory, Beck Depression Inventory-II, Brief Pain Inventory, 13-item Sense of Coherence scale, Brief Italian version of Cancer Behavior Inventory, European Organization for Research and Treatment of Cancer Quality of Life 23-item Breast

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Cancer-specific Questionnaire, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, 8-item Morisky Medication Adherence Scale, State-Trait Anxiety Inventory forms I and II, Big Five Inventory, and visual analogue scales evaluating risk perception). The 3 assessment time points are T0 (baseline), T1 (1 month), T2 (2 months), and T3 (3 months). This study was approved by the IEO ethics committee (R1786/22-IEO 1907).

Results: The recruitment process started in May 2023 and is expected to conclude on December 2023.

Conclusions: The contribution of machine learning techniques through risk-predictive models integrated into DSS will enable medication adherence by patients with cancer.

Trial Registration: ClinicalTrials.gov NCT06161181; https://clinicaltrials.gov/study/NCT06161181

International Registered Report Identifier (IRRID): DERR1-10.2196/48852

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KEYWORDS

adherence; metastatic breast cancer; decision-making; personality; risk-predictive model; decision support system; oral therapies; machine learning; behavior; cancer; breast cancer

Introduction

Adherence to Oral Anticancer Treatments

Metastatic breast cancer (MBC) is an incurable disease, wherein the available medications are primarily focused on deferring disease progression and symptom mitigation, thereby prolonging survival rate as well as preserving the quality of life (QoL) and psychological well-being [1,2]. The clinical advancements achieved in anticancer treatments have increased the survival rates of patients with MBC. The 5-year survival rate of patients with MBC is around 38% [2]. Notwithstanding, several studies [3-6] have shown that adherence to anticancer treatments is a critical issue in the disease trajectory of patients with breast cancer, especially regarding oral anticancer treatments (OATs), which are intensely demanding because patients are responsible for assuming medications according to the medical prescriptions, thereby increasing the risk of not appropriately taking the therapy [7].

From a theoretical perspective and according to the World Health Organization's recommendations [8], medication adherence might be explained by a set of mutual and interconnected determinants incorporating (1) sociodemographic (eg, age, gender, socioeconomic status), psychocognitive, and social variables (eg, psychological well-being, social support); (2) disease and treatment-related characteristics (eg, cancer stage, prognosis, dosage, side effects); (3) attitudes, beliefs, and values; (4) health literacy and knowledge; and finally (5) health care system–related factors [7,9,10]. Accruing evidence have highlighted that patients with advanced cancer might report significant levels of nonadherence because in case of some cancers such as MBC, the patients have to change the type of treatments or dosage frequently and they experience a high level of fear of cancer spread [3]. For example, Yerrapragada and colleagues [6] reported nonadherence to tamoxifen in patients with MBC, ranging between 30% and 85% and further reducing over time. In addition, patients with MBC reported several barriers to the daily management of OAT, such as emotional (eg, worry, depression) and physical distress related to the side effects (eg, fatigue, weakness, sleep disturbance, emotional burden, pain) and lack of knowledge about their disease. Further, patients might experience a lack of control and a lack of perceived benefits during the disease pathway, and they may experience difficulty in managing therapy [3,6]. Other studies have shown that patients with MBC experience modest QoL due to the related treatment side effects, financial burden affecting therapy discontinuation, and a significant level of nonadherence [4,7]. Marshall and colleagues [4] observed that patients with MBC who frequently report treatment concerns rather than treatment benefits are less likely to be adherent to prescriptions, as well as patients who experience a more significant number and severity of side effects tend to have more medication worries that could negatively impact adherence.

Risk-Predictive Models and Decision Support Systems

Given the impact of nonadherence on clinical outcomes and the associated economic burden on the health care system [11,12], finding effective ways to increase treatment adherence is particularly relevant. Patients who adopt nonadherent behaviors need support in managing oral therapies and in overcoming individual and systemic barriers and roadblocks [5]. Notwithstanding, the dynamics influencing adherence to OATs are understudied in the cancer field [13], and a comprehensive model of the risk determinants of nonadherence is not currently available, particularly for targeted therapies and novel generations of hormonal therapy [14]. Besides, a shared definition of medication adherence and satisfactory assessment tools is not acknowledged, which vary in terms of accuracy and reliability [14-17], even in the explicit case of the equivalent treatment protocol and diagnosis [13,18]. Because of the direct costs of nonadherence (eg, survival rate, health-related QoL for patients with MBC) and the indirect costs for the health care system (eg, economic burden), it is mandatory to identify potential risk factors of nonadherence to OATs and to define personalized interventions supporting adherence during the clinical pathway in patients with MBC.

Consistently, defining, measuring, and developing a comprehensive model of medication adherence based on real-world data predictive models is a crucial clinical, psychological, social, and economic challenge. Machine learning has become an integral part of the health care industry—from biomedical research to the delivery of health care services. Compared to traditional statistical methods, machine learning provides numerous advantages such as increased flexibility,

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prediction accuracy, possibility of automation, and processing of big data. Prediction models for adherence have already been developed and tested in various scenarios [19-22]. If adequately reported, these models can help guide treatment decision-making, improve patient outcomes, and streamline perioperative health care management. Considering the complexity of medication nonadherence in patients with MBC, it is critical to identify patients at risk of nonadherence and carry out timely, precise, and tailored interventions to improve their adherence. Through machine learning models, it is possible to provide personalized prediction on medication adherence for a given patient, supporting adherence and performing a specific intervention [22,23].

A growing body of studies have underlined that eHealth technologies (eg, mobile apps, web-based solutions, wearables) might be helpful tools to foster patient management and engagement in clinical decisions during the cancer pathway [24]. Different web-based solutions based on educational and behavioral interventions have been developed for patients with breast cancer to foster medication adherence [25,26]. For example, the Multinational Association for Supportive Care in Cancer has developed an educational and teaching tool for patients with cancer receiving OATs that is composed of different educational sections aimed at assessing general patient knowledge about their treatment protocol and drug information (eg, side effects), skills in the management of therapy, possible strategies to manage nonadherence occurrences, and a specific questionnaire section to evaluate patient comprehension [26]. Moreover, Omaki and colleagues [27] have developed a patient decision aid named "My Healthy Choices" to foster adherence to pain treatments, assessing the environmental and personal risks and setting patient treatment priorities.

Nevertheless, no study has been conducted on patients with MBC to foster medication adherence to OATs through the clinical care pathway based on designing and developing a decision support system (DSS), integrating risk predictive models and educational and training tools. The information embedded in a DSS solution designed and developed according to the needs of patients with MBC might enable users to be better informed, develop more accurate expectations of the benefits and harms, and increase participation in the decision-making processes and medication adherence [28]. Evidence shows that, when implemented on web or mobile apps, DSS may support patients and physicians by improving adherence to medical treatments [27,29,30].

The Pfizer Project (65080791)

Drawing from the theoretical framework described above, we present and explain the study protocol of a prospective, randomized controlled study that is nested in a large-scale international project named "Enhancing Therapy Adherence Among Metastatic Breast Cancer Patients" (Pfizer 65080791) aimed to develop a predictive model of nonadherence and an associated DSS and guidelines to foster patients' engagement and therapy adherence among patients with MBC concerning oral chemotherapy, endocrine therapy, supportive care, and the treatment of comorbidities. Consistently, the Pfizer Project (65080791) has been organized into 2 different studies to achieve the key goal. A retrospective study has been designed and a model has been developed to predict adherence to OATs, which use existing physiological, clinical, and QoL data available in the European Institute of Oncology (IEO; Milan, Italy). More in-detail, multimodal retrospective data have been retrieved from patient electronic health records by using natural language processing in a sample of 2750 patients with MBC (from 2010 to 2020). Data included in the analysis have been sociodemographic variables, diagnosis, biochemical and medical tests, procedures and medical history, treatment programs, treatment side effects, comorbidities, and familiarities. Concerning adherence to the treatment protocols, data included the following dimensions: initiation of the treatment, interruption of treatment, and skipped treatment doses. Furthermore, a prospective study is designed to assess the effectiveness of a DSS web-based solution and to enrich the predictive power of the machine learning model to forecast adherence behavior in patients with MBC. The tuning of the model permits adding additional predictors (personality traits, self-efficacy for coping with cancer, sense of coherence, pain, anxiety, depression, risk perception, and QoL) known to influence medication adherence behavior and that are not available retrospectively [10]. These data are used to improve the predictive power of the machine learning model and its capacity to profile patients' adherence behaviors and to provide an individual risk value of nonadherence.

Methods

Primary End Point Analysis

The primary end point was to assess the effectiveness of the DSS web-based solution and the machine learning web application in promoting adherence to OATs in a sample of 100 patients with MBC at 3 months. The adherence is evaluated using the number of pills taken divided by the number of pills prescribed. Further, the adherence is assessed using behavioral measures: the 8-item Morisky Medication Adherence Scale (MMAS-8) [31] and Adherence Attitude Inventory (AAI) [32].

Secondary End Point Analysis

The secondary end points were to identify clinical (comorbidities, presence of pain, tumor type, type of treatment), psychological (personality traits, anxiety, depression, self-efficacy for coping with cancer, sense of coherence, and risk perception), and QoL variables predicting patients' adherence to OATs. These variables are used as predictors for evaluating nonadherence to OATs among patients with MBC and for enriching the preliminary version of a machine learning model developed in the retrospective study. Our initial machine learning models that are evaluated as an intervention in this study were built based on variables extracted from clinical notes by using natural language processing. Once the data collection for this study is complete, we will also use the data collected to improve our initial machine learning models. Data for the secondary end points are collected using the European Organization for Research and Treatment of Cancer QoL Questionnaire Core 30 (EORTC-QLQ-C30) [33,34], European Organization for Research and Treatment of Cancer QoL 23-item Breast Cancer-specific Questionnaire

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(EORTC-QLQ-BR23) [35], and the Brief Pain Inventory (BPI) [36]. To evaluate psychological variables, we used the State-Trait Anxiety Inventory (STAI-Y) [37,38], Beck Depression Inventory-II (BDI-II) [39,40], Big Five Inventory (BFI) [41], Brief Italian version of Cancer Behavior Inventory (CBI-B/I) [42,43], 13-item Sense of Coherence scale (SOC-13) [44], and risk perception (using 2 visual analogue scales) [45,46].

Study Design

Treatment Adherence DSS

The first version of the web-based DSS, namely, TREAT (treatment adherence support) was designed and developed in the first year of the Pfizer Project (65080791) by using a patient-driven approach. The development phase was systematized in 5 steps. First, a systematic review of the literature was conducted to explore the main issues related to the interventions fostering adherence in patients with breast cancer [47]. Second, 4 focus group studies with 19 patients with MBC (mean age [years] 55.95, SD 6.87; range 46-70) with different metastasis localizations were implemented in order to explore patients' unmet needs related to the MBC disease and knowledge about the adherence, barriers, roadblocks, and resources related to OATs and to examine the role of technologies and decision support as aids fostering adherence behaviors during the care pathway [45]. The first and second steps informed the third step in which a preliminary set of mock-ups of TREAT using Wikimedia technology was shaped. TREAT was developed as a web-based application accessible by patients through a web link, without personal registration, and in Italian according to the patient's user approach. The information contained in TREAT was constructed using the international guidelines for patients with MBC (eg, European School of Oncology-European Society for Medical Oncology 2nd international consensus guidelines for advanced breast cancer) [1,46]. Further, the information was organized using different setups (written text, figures, flowcharts, graphs, and tables). In the fourth step, this preliminary version was revised by an internal and multidisciplinary review group (oncologists, psychologists, technicians, and patients). Finally, the TREAT's revised version was translated and published.

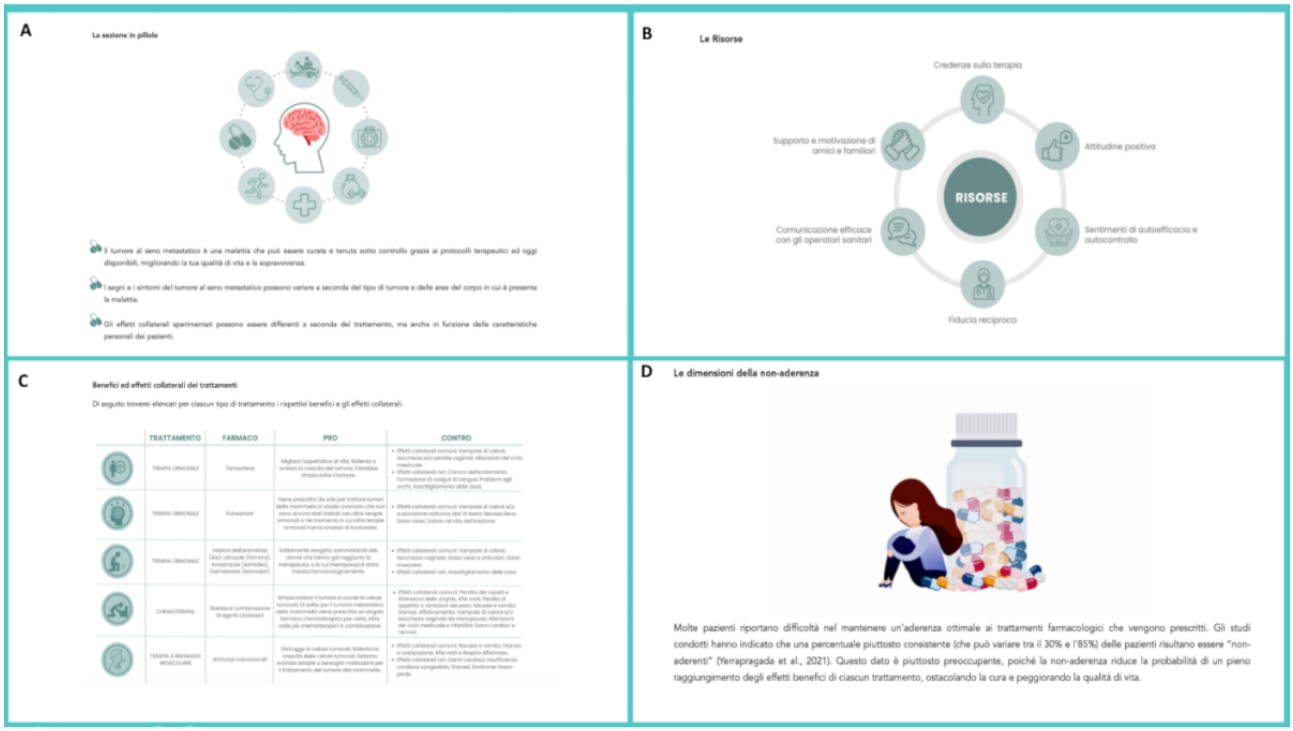
Currently, TREAT is organized into 4 key sections. Section A on metastatic breast cancer provides information on MBC disease (eg, definition, clinical management), physical consequences (eg, pain, weight loss, lack of energy), psychological consequences (eg, anxiety, depression, fatigue), anticancer treatments and the associated side effects, and benefits that can be experienced during the care pathway. Section B on adherence to cancer therapies discusses the meaning of nonadherence and its consequences, incidence in the population with cancer, and determinants of medication adherence according to the World Health Organization's approach. Section C on promoting adherence provides information about the resources (eg, personal beliefs, social support, trust in the health care providers), barriers (eg, distress, inadequate knowledge) of medication adherence, and the different available interventions (eg, educational, affective, behavioral) to promote patients' adherence. Further, TREAT delivers specific self-managed suggestions to mitigate potential risk factors associated with nonadherence and an example of a specific training based on a goal-setting approach. In Section D, that is, My Adherence Diary, patients are invited to write a free-text diary reporting doubts, concerns, thoughts, and behaviors related to their disease and therapies, sharing this information with their oncologists in the following clinical consultation (Figures 1-2).

Figure 1. The 4 main sections of the decision support system in Italian. Section A: metastatic breast cancer; Section B: adherence to cancer therapies; Section C: promoting adherence; Section D: my adherence diary. The screenshot with the decision support system, namely, "TREAT - Supporting Therapy Adherence" is shown in the center.



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Figure 2. Screenshots of the decision support system, exemplifying some examples of the information nested in different sections of the system (A, B, C, D). A. "The Section on Pills" refers to a short summary enclosed at the end of each section of the decision support system reporting the key themes (renamed pills) discussed in the section. B. "Resources" is a flowchart on the main resources that can improve medication adherence. C. "Benefits and side effects of the treatments" is a table that shows the action of each anticancer treatment, type of drug, expected benefits, and side effects. D. "The adherence dimension" is a written text that informs about the dimension of nonadherence in the population with cancer.



We also developed a machine learning application, which will be tested with the DSS. This application focuses on models to predict adherence risk factors and used data extracted from the electronic health records of the IEO. Specifically, the machine learning models focused on 2 outcomes: short-term and long-term side effects as well as physical status and comorbid conditions. We evaluated the models predicting performance by utilizing metrics such as area under the curve, precision, recall, sensitivity, specificity, κ, and positive and negative predictive values. Based on these criteria, we identified the top performing models, which were integrated into a web application built using the Shiny open source framework for the R statistical language (R Core Team) [48]. We designed this application for shared decision-making sessions between patients and oncologists. It also uses the Shapley interpretable machine learning algorithm, which offers insights into the specific risk factors that played a role in predicting outcomes for individual patients.

Participants

A sample of 100 patients enrolled consecutively in May 2023 in the IEO at the Division of Medical Senology with an MBC diagnosis. The enrollment started in May. Specifically, the observed outcomes of 50 patients with MBC exposed to the DSS (experimental group) and 50 patients with MBC not exposed to the intervention (control group) are evaluated.

Inclusion and Exclusion Criteria

The inclusion criteria were female patients with MBC, 18 years of age and older, with a prescription of oral treatment (eg, oral chemotherapy, endocrine therapy, cyclin-dependent kinase 4/6 inhibitors), having internet access and a personal smartphone or tablet, and ability to read and sign informed consent. The exclusion criteria were the presence of any primary psychiatric or neurological conditions.

Procedure

Randomization

Patients who signed the informed consent are given a unique identifier and assigned to either the control or intervention arm in a 1:1 ratio. First, the system asks to confirm all the inclusion and exclusion criteria. Then, an independent researcher generates a random sequence using the statistical language R (R Core Team 2020). Our randomization schedule involves an undisclosed blocking size that the data science team calculates without stratification. A patient is considered randomized when the randomization system assigns the patient an identification number according to a pre-established randomization list. We have created 2 different groups: the experimental group (n=50), in which each participant receives the link for the DSS and is trained to use the DSS for 3 months; and the control group (n=50), in which each patient receives standard care and suggestions bolstering adherence. Among all participants, the personal nonadherence risk is calculated through the preliminary version of the machine learning model to predict patients' nonadherence behavior.

Recruitment and Follow-Up

Patients admitted to the Division of Medical Senology of the IEO are enrolled by the oncologist during the formal clinical consultation. Patients are enrolled even if they already had oral treatments in the past and they are switching to a new one. The patients who show interest in this research have a phone call

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with a trained psychologist to receive further information about the Pfizer study. If patients decide to participate in this study, the psychologist plans a consultation to receive informed consent and a preliminary assessment. Patients are informed that TREAT will not replace the clinical consultation. However, it should help manage oral treatment and improve adherence through education using evidence-based information. Patients may decide to discontinue their participation in the trial without any penalties. Patients who refuse to participate in this study are asked to complete a short refusal survey regarding the main reasons for not participating and their demographic information in order to assess the potential differences among the participants. Furthermore, patients have to contact the pertaining division for any necessity. Data are collected by the REDCap (research electronic data capture) platform and stored centrally by the IEO.

Measures

Assessment of Nonadherence to OATs

This study uses the operational definition of adherence provided by the International Society for Pharmacoeconomics and Outcomes Research Medication Compliance and Persistence Work Group, which defines adherence as "the extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen" [49]. Coherently, the nonadherence to OATs is evaluated using a prospective method [15] by weekly medication diaries and 2 self-reported measures.

Adherence Medication Diary

A weekly paper diary is given to patients to monitor their medication intake. The diary will assess if medications are taken as prescribed and the possible reasons for not taking pills (eg, side effects, forgetfulness, no pill refill). The data collected refer to the number of pills not taken per week and the number of pills established according to the patient medical prescription protocol per week as well as planned interruptions. Further, the diary evaluates and monitors the side effects, their intensity (from 0 to 10) associated with the therapy intake, and their emotions, thoughts, behaviors, and consequences.

MMAS-8 Self-Report Questionnaire (© 2006 Donald E Morisky)

The MMAS-8 scale [31,50,51] is an 8-item self-report questionnaire evaluating treatment adherence (forgetfulness, medication-taking behavior, adverse effects, and problems) (Cronbach α=.83). The first 7 items have dichotomous responses (0=Yes, 1=No), and the last includes a 5-point Likert scale response [52].

AAI Self-Report Questionnaire

The AAI is a 28-item self-report questionnaire on a 5-point Likert scale response (from "does not fit" to "perfect fit") evaluating treatment adherence (Cronbach α=.80) [32]. The AAI is organized into 4 subscales: cognitive functioning (evaluating the ability to remember issues and tasks related to adherence in the short and long term), patient-provider communication (evaluating thoughts, attitudes, feelings, and ideas related to adherence between patient and medical provider), self-efficacy (evaluating the belief in one's ability to adhere to medication and a history of similar success), and commitment to adherence (evaluating the determination to overcome obstacles to achieve adherence).

Demographic, Clinical, Emotional, and QoL Assessments

Considering that adherence to OATs is explained by a set of mutual and interconnected determinants, a comprehensive pool of self-reported measures is administered to identify the psychological predictors of nonadherence in patients with MBC.

Patient Demographic and Clinical Variables

Age, gender, education, marital status, cancer diagnosis and staging, oncological treatments, BMI, alcohol and smoking habits, and comorbid medical disorders are collected through electronic medical records.

STAI-Y Self-Report Questionnaire

The STAI-Y is a 40-item self-report questionnaire on a 4-point Likert scale (Cronbach α=.89). The STAI-Y evaluates both trait anxiety (20 items) and state anxiety (20 items) [37,38].

BDI-II Self-Report Questionnaire

The BDI-II is a 21-item self-report questionnaire on a 4-point Likert scale response evaluating depression (Cronbach α=.89). The BDI can be administered to adults and adolescents aged 13 years and older [39,40].

CBI-B/I Self-Report Questionnaire

The CBI-B/I is a 12-item self-report questionnaire on a 7-point Likert scale response (from not all confident to totally confident) evaluating self-efficacy for coping in patients with cancer (Cronbach α=.84). The CBI-B/I is composed of 4 subscales: coping and stress management, maintaining independence, managing affect, and participating in medical care [42,43].

SOC-13 Self-Report Questionnaire

The SOC-13 is a 13-item self-report questionnaire on a 7-point Likert scale response (Cronbach α=.76). The SOC-13 is composed of 3 subscales: comprehensibility, manageability, and meaningfulness [44].

BPI Self-Report Questionnaire

The BPI is a 9-item self-report questionnaire evaluating pain intensity during the past 24 hours (Cronbach α=.91) [36].

EORTC-QLQ-C30 Self-Report Questionnaire

The EORTC-QLQ-C30 is a self-report questionnaire composed of 28 items on a 4-point Likert-type scale (ranging from not at all to very much) and 2 items, that is, general global health status and QoL on a 7-point Likert-type scale (ranging from very poor to excellent) [33,34]. The EORTC-QLQ-C30 provides information on 3 areas: functional (physical, role, cognitive, emotional, and social), symptoms (appetite loss, fatigue, pain, nausea, constipation-diarrhea, dyspnea, and insomnia), and global health status or QoL (Cronbach α=.85) [32,33]. Further, the EORTC-QLQ-B R23 for patients with breast cancer has been used previously (Cronbach α=.87) [34,35].

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BFI Self-Report Questionnaire

The BFI is a 44-item self-report questionnaire on a 5-point scale (from disagree strongly to strongly agree) that assesses 5 dimensions of personality: openness to experience (Cronbach α=.78), conscientiousness (Cronbach α=.81), extraversion (Cronbach α=.87), agreeableness (Cronbach α=.81), and neuroticism (Cronbach α=.82) [41].

Risk Perception

Risk perception is evaluated using 2 visual analogue scales (from 0 to 100): one for the objective and one for the subjective risk perception. These items were developed using the Weinstein approach [45,46].

Timeline

There are 3 assessment time points. At the baseline (T0), all patients fill a set of validated measures (MMAS-8, AAI, STAI-Y forms I and II, BDI-II, CBI-B/I, SOC-13, BPI, EORTC-QLQ-C30, EORTC-QLQ-BR23, BFI, and visual analogue scale). The expected time to complete all the given questionnaires at baseline is approximately 40 minutes. Access to DSS is given to the experimental group for 3 months. At T1 and T2, the following questionnaires are filled: MMAS-8, AAI, STAI-Y form I, BDI-II, CBI-B/I, EORTC-QLQ-C30, and EORTC-QLQ-BR23. Further, all patients have to fill a weekly adherence medication diary for 3 months. Variables that are not sensitive to change, for example, personality (BFI) and anxiety traits (STAI-Y form II) are collected only at T0. Each month, all participants receive a brief telephone interview in which they are monitored for adherence to the research protocol. Two psychologists perform the monthly telephone interview to monitor the filling out of the questionnaires and the medication adherence diary supporting patients with MBC in this task, barriers, and concerns related to the study participation. At T3 (3 months), all behavioral and psychological measures are filled, and an interview (online or vis-à-vis) is performed.

Calculation of Sample Size

The sample size calculation was based on estimates for the effectiveness of TREAT as the primary outcome, assuming that the final analysis would be performed with a 2-sample 2-sided *t* test, a power of 96.4%, an α of .05, a standard deviation of 1.2, and a minimal difference in outcomes of 0.51 (effect size of 0.42) based on the patients' self-reported satisfaction with the treatment decision [53]. Under these considerations, the final sample size was calculated to be 100 patients with MBC, with 50 individuals per group (50 patients with MBC exposed to DSS and 50 patients with MBC not exposed to the intervention). This sample size is expanded to 120 when a 20% attrition rate is used.

Statistical Considerations

Exploratory Analysis

Our exploratory analysis will start with a visual exploration of all variables to evaluate the frequency, percentage, and near-zero variance for categorical variables (eg, gender, cancer stage); distribution for numeric variables (eg, age); and their corresponding missing value patterns [54]. Near-zero variance is found when a categorical variable has a small percentage of a given category and will be addressed by recategorization. We will consider variable transformations such as logarithmic, Box-Cox, or categorization of numeric variables that do not present a normal distribution. Missing values will be handled through imputation algorithms followed by sensitivity analyses to verify whether our results are stable with and without imputation [53]. Comparisons for the exploratory analysis will be conducted through analysis of variance (2-sided *t* tests being a category of analysis of variance) and chi-square tests (Fisher exact test when any cell presented a frequency below 5).

Propensity Score

For residual confounding after randomization, we will use propensity scores based on inverse probability of treatment weighting [55]. We will first assess the covariate balance between control and intervention groups through standardized mean differences and differences in proportion. Covariates will include the patient demographic and clinical variables. Values greater than 0.1 will signal an imbalance in covariates. Next, we will use inverse probability of treatment weighting generated through logistic regression to balance the covariates [56]. Once we achieve covariate balance, we will estimate the effect for each outcome by using a double robust approach.

Generalized Linear Models

Additional analyses will be run using generalized linear models with a Gaussian distribution family (multiple linear regression) being adjusted for randomization baseline imbalances. These models will evaluate the association between all previously reported outcomes (the number of pills taken during the prescribed interval, MMAS-8, AAI, STAI-Y, BDI-II, CBI-B/I, SOC-13, BPI, EORTC-QLQ-C30, EORTC-QLQ-BR23, BFI, and risk perception) and the intervention (TREAT and machine learning web application), accounting for the baseline differences. We will build one model for each combination of predictor and outcome, where the outcome will be the dependent variable (Y) and the predictor will be the independent variable (X), adjusted for the covariates unbalanced at baseline. We will also evaluate models with a Poisson or negative binomial distribution for non–normally distributed outcomes. Results will be reported as predicted means along with 95% CIs.

Ethics Approval

This study is compliant with the recommendations outlined in the Helsinki Declaration [57] and the Council for International Organizations of Medical Sciences guidelines [58], as well as with the principles of biomedical ethics reported in the Belmont report [59]. This study presents a fair balance between risks and benefits for study participants and future patients affected by the same condition. No physical risks directly related to participation in the research are expected. Although psychological risks are not expected, in case these raised from participation, psychologists responsible for the study will promptly intervene and take care of the patient. Regarding the benefits, given the impact of nonadherence on clinical outcomes, finding effective ways to increase treatment adherence is particularly relevant for the community of patients with MBC, thus playing a role in the improvement of the patient's general well-being. The principle of self-determination is also respected.

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A devoted informed consent form is signed by participants before participation. Signing the informed consent form is preceded by a dialogic consent process necessary to ensure informed, voluntary, and awareness of participation in research. Regarding the respect for privacy, this study is performed according to the General Data Protection Regulation (Regulation EU, 2016/679) [60]. All data are collected in a pseudoanonymized form. Data are treated confidentially and used only by the collaborators in this study for scientific purposes related to what is stated in the research protocol. The retrospective study was approved by the IEO ethics committee (R1595/21-IEO 1704). The prospective study was approved by the IEO ethics committee (R1786/22-IEO 1907).

Results

The recruitment process started in May 2023 and is expected to be concluded on December 2023. Data analysis will be performed between 2023 and 2024. This project has been funded by a Pfizer grant: Enhancing therapy adherence among patients with metastatic breast cancer (65080791).

Discussion

Expected Findings

Adherence to anticancer treatment is fundamental in the clinical management of patients with MBC, as adherence can lead to a series of crucial clinical outcomes (eg, prolonged survival time, better monitoring and management of side effects, improvement of QoL) [1-6]. Studies on implementing machine learning to foster medication adherence as well as the development of shared DSSs are quite recent [23].

We believe that our study might achieve 3 milestones in the clinical care of patients with MBC with regard to adherence to OATs. Concerning the primary end point, implementing a shared and integrated DSS web-based solution might be an essential strategy for patients with MBC to enhance their health knowledge and understanding of medication nonadherence issues and to learn behavioral strategies to overcome individual, disease-related, and organizational barriers impacting adherence behaviors. This expected result is coherent with the results of other studies on patient decision tools, highlighting that such engines might improve patients' participation and health knowledge in the care pathway [61]. Regarding the secondary end point, this prospective study will contribute to refining the initial risk-predictive model of adherence attained from the retrospective study, informing about specific (inner and external) predictors of adherence behavior during the MBC care pathway that were not considered in the preliminary version of the model. This should provide a more comprehensive and systematic definition of medication adherence for OATs in patients with MBC, defining an interrelated and evidence-based list of predictors. Data will define a final risk-predictive model of adherence and enable the identification of specific patient populations at risk of nonadherence. The earlier identification of patients with poor adherence using our machine learning web application will permit the development of tailored psychological and behavioral interventions to foster adherence by dealing with individual barriers and needs according to the risk profile. Finally, the information retrieved by the risk-predictive models might support oncologists' treatment decisions, allowing them to better understand the hindered reasons behind a complex adherence trajectory.

Limitations of This Trial

Despite the key contributions of this study in the field of the medication adherence to OATs among patients with MBC, some limitations have to be acknowledged. First, the questionnaires used to refine our risk-predictive model might cause cognitive burden and general fatigue among participants. However, a monthly telephone interview has been introduced as a mitigation risk strategy. The interview is aimed to support participants in filling out the questionnaires and medication adherence diary and to manage barriers and concerns related to this study. Related to this aspect, the second limitation concerns the recall bias that might be generated using self-report measures. Further, self-report measures might overvalue adherence compared to the other prospective methods such as the Medication Event Monitoring System. However, the weekly medication diary method, in which patients have to report a detailed and systematic description of pill counts, side effects, and barriers related to the management of the therapy and missed doses, can aid in providing a more comprehensive picture of medication adherence. Moreover, as highlighted by Shah and colleagues [15], the diary has a higher accuracy and minor recall bias and permits the evaluation of subjective information (eg, emotions, thoughts, worries, behaviors, expectations) related to the medication coherently with the processual model of the adherence used in this research protocol [8]. Third, a monthly follow-up and a 3-month end point have been established, considering the type of diagnosis, high variation in the prognosis, and shifting in the lines of treatment due to cancer progression or declining physical functioning. This short end point might affect a deep understanding of the efficacy of our DSS in the long term. However, previous studies have used correspondent follow-ups and end points [13]. Fourth, as observed by other studies on patients with MBC [14], an additional risk that should be considered is related to the overestimated adherence rate. Patients participating in clinical trials are highly motivated, possibly leading to greater adherence to the OATs prescribed. Fifth, the initial version of the machine learning web application was not able to directly predict patient adherence. Instead, it predicted adherence risk factors, including short-term and long-term side effects, as well as physical status and comorbid conditions. This is a limitation of the data we used to build this initial version of the model, as it was not possible to reliably identify adherence patterns. However, predicting adherence risk factors can still provide insights that can assist in improving OAT adherence during shared decision-making sessions between physicians and patients.

Conclusions

Considering the poor evidence on OATs and the need to develop validated instruments to evaluate medication adherence to improve patient clinical outcomes [14,16], the development of integrated and shared DSSs able to foster adherence behaviors and to profile patient adherence risks might have key impacts on clinical practice and patient health-related QoL, thereby

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enabling the early identification of high-risk populations and enriching knowledge about the implementation of machine learning models in clinical practice.

Acknowledgments

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This project has been funded by a Pfizer grant: Enhancing therapy adherence among patients with metastatic breast cancer (65080791).

Data Availability

Data will be available from the corresponding author on reasonable request.

Authors' Contributions

GP, MM, RP, and EM conceived and designed this study. GP coordinated this study. RP, LT, MV, and AM performed statistical analyses. MM, GES, VS, RP, LT, MV, AM, EM, EF, MP, and GP handled the drafting and writing of the manuscript. All authors have read and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

AAI: Adherence Attitude Inventory
BDI-II: Beck Depression Inventory-II
BFI: Big Five Inventory
BPI: Brief Pain Inventory
CBI-B/I: Brief Italian version of Cancer Behavior Inventory
DSS: decision support system
EORTC-QLQ-BR23: European Organization for Research and Treatment of Cancer Quality of Life 23-item Breast Cancer-specific Questionnaire
EORTC-QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
IEO: European Institute of Oncology
MBC: metastatic breast cancer
MMAS-8: 8-item Morisky Medication Adherence Scale
OAT: oral anticancer treatment
QoL: quality of life
REDCap: research electronic data capture
SOC-13: 13-item Sense of Coherence scale
STAI-Y: State-Trait Anxiety Inventory
TREAT: treatment adherence support

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Protocol

Digital Support Systems to Improve Child Health and Development in Peru: Protocol for a Randomized Controlled Trial

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Abstract

Background: Children living in low and middle-income countries (LMICs) are at greater risk for experiencing adversities that can undermine their health and early development. Recently launched digital early childhood development (ECD) programs attempt to support families with young children in their home environments using digital technologies. However, relatively little is known regarding the effectiveness of these new technologies.

Objective: The goal of this study is to rigorously assess the reach, effectiveness, and cost-effectiveness of a newly developed digital ECD platform called Afini. The Afini platform was designed to support parents of young children in low-resource settings to improve ECD and interact with caregivers through messenger services and a chatbot.

Methods: This is a 3-arm cluster randomized controlled trial. In total, 2471 caregivers and their 3- to 9-month-old children were enrolled in the study across 164 study clusters in the San Marcos, Cajabamba, and Cajamarca provinces of Peru. Clusters of participants were randomly assigned to 1 of 3 groups: a control group (72 community clusters and 980 caregiver-child dyads), a home visit intervention group (20 community clusters and 316 caregiver-child dyads), and an Afini intervention group (72 community clusters and 1175 caregiver-child dyads). Families in the control group receive no focused ECD intervention. The home visit group is receiving biweekly home visits by a trained field staff following the national ECD program (*Programa Nacional Cuna Más*) curriculum and training guidelines. Caregivers in the Afini group are receiving ECD activities and advice through the digital platform. The primary study outcome is children's overall development at the age of 2.5 years, using the internationally validated long form of the Global Scales for Early Development. Secondary outcomes include caregiver engagement; caregiver mental health; screen time; as well as caregiver reports of children's motor, cognitive, language, and socioemotional development measured through locally piloted and validated tools.

Results: Enrollment started in September 2021 and ended in March 2023. Endline assessments will take place between August 2023 and September 2024.

Conclusions: This study is, to our knowledge, the first to rigorously assess the effectiveness and cost-effectiveness of digital ECD technologies in LMICs. Given the large number of children in LMICs currently receiving only limited external support, the evaluated platform has the potential to improve the short- and long-term well-being of millions of children and their parents globally.

Trial Registration: ClinicalTrials.gov NCT05202106; https://clinicaltrials.gov/ct2/show/NCT05202106

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KEYWORDS

child development; digital support; parenting; Peru; child; children; childhood; parent; parents; parenting; education; support; parental; cost; low income; low resource; digital health; platforms; pediatric; pediatrics; eHealth; e-health; RCT; RCTs; randomized; controlled trial; development; scalable

Introduction

According to the World Health Organization, early life adversity affects more than 250 million children younger than 5 years, making it more difficult for them to reach their developmental potential [1,2]. Chronic poverty, malnutrition, and high exposure to infectious diseases undermine children's development in their early years [1] and limit their physical and cognitive development over time. The most recent estimates suggest that 30% of children younger than 5 years in low and middle-income countries (LMICs) are stunted [3], and 37% of children aged 3-4 years display deficits in their cognitive or socioemotional development [4]. Interventions targeted at this early life stage are crucial for creating environments that support healthy development [5-8] and ensuring children's long-term economic and overall well-being [9].

Home visiting programs have emerged as one of the most promising and popular approaches for improving child health and well-being in both high- and low-income settings [10], with successful implementation in Bangladesh [11], Brazil [12], Colombia [13], Jamaica [14,15], Pakistan [16], Peru [17], and South Africa [18]. These programs involve training community agents on child development and having them meet with mothers or parents weekly, biweekly, or monthly to discuss their children's overall well-being. They provide practical guidance to caregivers on creating a healthy and developmentally stimulating environment in the home. Home visiting programs usually have a structured curriculum containing essential child health and development topics that are covered during each home visit. Despite consistently positive impacts on maternal [19,20] and child well-being [21,22], most countries have not adopted home visiting programs at scale due to the high cost and logistical efforts associated with them. In Peru, the state-run national early childhood development (ECD) program (*Programa Nacional Cuna Más* [PNCM]) provides a crèche-based intervention in urban and periurban settings and traditional home visits by trained agents in rural settings [17,23,24].

The rapid rise in cell phone coverage globally [25] and the introduction of mobile computing devices such as smartphones and tablets have created new opportunities for health and social systems to engage with patients and parents at scale [26-28], resulting in a rapid growth in the development of software apps for these platforms [29-34]. Additionally, new mobile phone contracts that offer low-income families access to basic messaging software (such as WhatsApp and Facebook messengers) without formal data contracts have also contributed to the expansion. Such light messenger-only data plans allow users to share information, pictures, and videos on messaging platforms without incurring any cost per message or upload. In our pilot study, 84.4% (152/180) of families owned a smartphone and 94% (169/180) had internet connectivity at home [35]. In this setting, new artificial intelligence (AI)–based ECD technologies using automated chatbots to interact with caregivers of young children seem to be a potentially attractive new option to support parents and their children.

In this project, we will test whether one of these newly developed digital platforms, called Afini [36], can be effective at improving children's development in a remote population in high-altitude rural Andean Peru. Through this study, we wish to assess the reach, impact, and scalability of the newly developed Afini platform as a tool for improving children's early development; the subaims are to (1) improve the functionality and usefulness of the Afini platform through qualitative and quantitative feedback and to integrate of state-of-the-art machine learning algorithms, (2) assess the cost and cost-effectiveness of Afini platform as a tool, and (3) disseminate the findings to our targeted population and reach out to the policy makers for further scalability of digital platform initiatives on ECD.

Methods

Study Setting

The study is conducted in 3 provinces of the Cajamarca region (San Marcos, Cajabamba, and Cajamarca) in the Northern Andes of Peru. The altitude in the study area ranges between 1900 and 3900 m above sea level. The region is predominantly rural and has a large share of low-resource and remote households engaged in farming, making it representative of many rural and periurban settings in Andean South America. The majority (80%) have regular access to social media platforms [35]. Communities were classified in accordance with the Peruvian National Institute of Statistics and Informatics as urban (communities with >2000 inhabitants with contiguous and grouped homes forming streets) or rural (scattered or grouped houses of up to 2000 inhabitants per community [37]). The study area is partially covered by PNCM.

Study Design

The study was designed and adapted based on a field-testing phase completed over a period of 5 months from February to July 2021. During the test phase, we conducted a mixed method feasibility pilot to test the reach, reception, and use of the Afini parenting platform. Specifically, we (1) systematically assessed internet connectivity in the greater study region, (2) conducted focus groups and in-depth interviews to adapt Afini to the local cultural context, and (3) assessed use over time and satisfaction

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with Afini in a sample of 280 mothers with children up to 2 years of age and smartphone access [35].

The study was designed as a 3-arm parallel cluster randomized controlled trial to assess the Afini platform's effectiveness in improving ECD outcomes relative to a control group receiving no additional intervention as well as relative to a home visit group receiving an ECD home stimulation intervention (gold standard). The trial enrolled 2471 caregivers and their 3- to 9-month-old children across 164 community clusters from September 2021 to March 2023. As described above, communities were randomly assigned to the three study groups: (1) a control group receiving no additional ECD support (72 community clusters and 980 caregiver-child dyads), (2) a home visit intervention group receiving a biweekly home visit by a trained field staff following the national ECD program PNCM curriculum and training guidelines (20 community clusters and 316 caregiver-child dyads), and (3) the Afini intervention group receiving ECD activities and advice through the digital Afini platform (72 community clusters and 1175 caregiver-child dyads).

Description of the Study Groups and Intervention

Control Group

The control group comprises families that receive the regular level of mother and newborn child health care in the region. They have not been benefitting from any ECD program or intervention, but they may have sought assistance regarding parenting from within their network. This study group is only visited once at the beginning (baseline survey) and once at the end of the study (endline survey and assessment).

Home Visit Intervention Group

Home visits are considered the gold standard for enhancing child health and development in LMICs [21]. Families in the home visit intervention group (home visit group) receive support through biweekly home visits following the nationally developed and validated curriculum of the national ECD program PNCM. The PNCM program offers home visits to low-income families residing in rural areas (*Servicio de Acompañamiento a Familias*) and daycare services in urban settings (*Servicio de Cuidado Diurno*) [23]. Specifically, all families in the home visit group are receiving biweekly home visits by our trained field staff from when their children turn 6 months until endline assessments at approximately 2.5 years of age. Trained staff members visit families at home every 2 weeks. During these visits, they follow a structured (age-specific) curriculum to educate parents on engaging in educational activities and games for daily interaction with their children, actively play with the child, and provide parents with a set of age-appropriate toys every 3 months. The toys and activities were designed in Peru to promote their children's psychomotor, cognitive, language, and socioemotional development.

Afini Intervention Group

Caregivers in the Afini intervention group (Afini group) were introduced to the Afini digital system on Facebook Messenger during the study baseline visit. During the initial setup, families registered the child's day of birth and other demographics for Afini to recommend a first educational activity.

After this initial visit, caregivers received automated weekly alerts with personalized content from Afini over Facebook Messenger. Specifically, the Afini system sent weekly reminders to engage in age-specific, health- and development-promoting activities as well as general information on child development and the child's progress. Afini was available for families 24/7, and families could request up to 4 personalized educational activities for their child, ask for advice, or ask any questions related to child development to the Afini chatbot system at any time. The personalization of content works based on the child's age, initial child development assessment on the platform, and user preferences (ratings) for each educational content.

After approximately 1 year, caregivers in the Afini group will receive a short home visit to ensure they can still connect to the system. Caregivers continue to use Afini independently until they are visited at the end of the study (endline survey and assessment).

The Afini platform is a digital parental support platform for children younger than 5 years in LMIC settings. The platform can be accessed via Facebook Messenger, WhatsApp, or an independent Afini app. Once connected, the Afini content recommender system uses AI to learn about individual children's needs and recommends content or ideas for activities that caregivers can practice at home together with their child. The platform tracks child development and caregivers can contact the assistant chatbots at any time to receive general advice on child development and parenting. Afini offers over 1500 age-specific, health- and development-promoting activities, articles, and tips to caregivers. Afini's educational activities, tips, and content are designed in a fun, simple way and with materials that are commonly found at home. All Afini contents offered to caregivers in the Afini group were developed by early development experts and revised by local experts in Cajamarca [35].

Ancillary Studies

In order to assess whether the usage and impact of Afini can be improved through incentives, a total of 20 study clusters among the 72 Afini intervention clusters were randomly selected for additional top-up intervention. Within these 20 clusters, all caregivers with a prepaid phone plan with either Claro or Bite phone operators were eligible to receive small biweekly data credit transfers with a value of between US $0.8 and US $2. The credit transfers can be used for unlimited access to WhatsApp and Facebook Messenger for 1-3 days, depending on the provider; the monetary value of US $2 corresponds to half a kilo of chicken at a local market. We will assess the marginal impact on the use and development of these incentives as well as their relative cost-effectiveness.

In addition, and to increase the generalizability across the country, we added a comparison group composed of families participating in the existing governmental PNCM program. These families were screened during the enrollment of the main trial and excluded due to their participation in another ECD program; they became eligible for the ancillary study. This

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PNCM comparison group comprises 237 caregiver-child dyads and is treated the same as a natural control group without intervention. This group was not randomly selected or assigned and will thus mostly be used for descriptive purposes and to provide further context for this study. In summary, the project thus included 2471 trial participants and 237 comparison group participants, totaling 2708 project participants.

Sample Size Calculations

The study is powered to detect a 0.25 SD difference in normalized child development *z* scores (mean 0, SD 1) at the age 2 years between the Afini group and the control group and a difference of 0.5 SD in *z* scores between the home visit group and the control group. These calculations are based on the following assumptions: (1) an average of 15 (SD 5) children per village or study cluster, (2) an intraclass correlation of 0.12, (3) α=.05, and (4) an attrition rate of 15%. The estimated normalized effect size of 0.5 SD was based on 2 recent reviews of ECD home visiting programs [10,16]. We conservatively anticipate the Afini platform to only reach about half the target population and, thus expect an intention-to-treat effect size of 0.25 SD. Our assumptions regarding intraclass correlations, number of children per cluster, and attrition rates are based on a recently completed ECD-focused study in the same area [17].

Recruitment

Recruitment occurred continuously over 18 months with a target to enroll 2460 caregiver-child dyads. To identify potential children, the local health facilities' birth registries from San Marcos, Cajamarca, and Cajabamba were used. All children between 3 and 9 months of age identified during the recruitment period in the study catchment area were eligible. All families that complied with the eligibility criteria were visited in person by study staff and invited to participate. The only reasons for exclusion were if the (1) caregiver and child intended to migrate outside the study area within the next 12 months, (2) child had a diagnosis of congenital abnormalities or a disability such as deafness or blindness (as reported by the caregiver), and (3) child already participated in the national PNCM program and did not belong to the PNCM comparison group. The study was built on a long-standing relationship of the research team with the regional and local health centers that facilitated recruitment.

Randomization Process

Stratified constrained randomization was used to ensure both spatial and covariate balance across groups. As study strata, 3 study provinces (Cajamarca, Cajabamba, and San Marcos) were used. Within each stratum, communities were allocated with ratios 3.6:1:3.6 for the control group, home visit group, and the Afini group, resulting in a final sample of 72 clusters in both the control group and Afini group and 20 clusters in the home visit group. A total of 1000 potential cluster allocations were randomly drawn using the Stata SE (version 16.0; Stata Corp) software package. We then chose the allocation minimizing mean differences across the 3 arms concerning variables such as cluster population size, cluster number of births, cluster altitude, household cell phone ownership, education of caregiver, and household wealth. Information on these covariates was obtained from governmental sources and validated by our field staff.

Primary and Secondary Outcome Measures

The primary study outcome will be children's overall development at the age of 2.5 years. Children's development will be assessed using the long form of the Global Scales for Early Development (GSED) [38]. The GSED is a new global open access tool designed to provide a standardized method for measuring the development of children up to 36 months of age in low-resource settings. We will use the long form of the GSED tool, which allows for a direct assessment of children's development through trained assessors.

Secondary outcomes include (1) caregiver-reported early child development in motor, cognitive, language, and socio-emotional domains; (2) quality of a caregiver-child relationship; (3) screen time with and without a child being present; (4) primary female caregiver's parenting behaviors; (5) parenting attitudes; and (6) mental health. Table 1 summarizes the measures to be collected at baseline and endline—all measures will be applied to the full sample, that is, to all participants independent of their random group assignment. Given that children were very young at baseline (6 months on average), detailed assessments of child development and caregiver-child interactions seemed unlikely to yield much insight at baseline. For overall child development, we used a caregiver report (Caregiver Reported Early Development Instruments [39]) at baseline and will use a more detailed direct observation tool (GSED) at endline. Sociodemographic factors collected at baseline will be used as controls in the final analysis.

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Table 1. Overview of constructs and measures used at baseline and endline.

Construct and measures	Time of assessment
Child development (assessment)	
Child assessment (GSED[a] Long Form) [38]	Endline
Child development (parent report)	
CREDI[b] Long Form [39]	Baseline
CREDI Short form [39]	Endline
Parent-child relationship quality	
Observation of Mother-Child Interaction [40]—adapted version	Endline
ARI - CP 2-5[c] questionnaire [41] adapted short form	Endline
Child information	
Nutrition, health and health insurance status, participation in ECD[d] programs	Baseline and endline
Anthropometrics	
Child weight at birth (reported)	Baseline
Child weight and height (measured)	Endline
Household demographics	
Household composition and assets; education, age, and so on of mother and father	Baseline
Economic activity	
The main occupation for parents, membership in government support programs and COVID-19 support	Baseline
Negative household events	
Household shocks questionnaire	Endline
Phone network or internet availability and use	
Availability of phone, knowledge and use of apps, money spent on the phone, and phone use	Baseline
Digital literacy	
Digital Literacy Scale [42]	Baseline
Satisfaction with Afini (Afini group) and phone use	
Use and satisfaction with Afini and phone use	Endline
Stimulation materials and experiences	
Family Care Indicators [43]	Baseline and endline
Parenting behaviors, attitudes, and knowledge	
Parenting questionnaire (under development)	Endline
Maternal social support	
Social support questionnaire	Baseline and endline
Maternal mental health	
Depression, Anxiety, and Stress scale [44]	Baseline and endline
Location	
GPS data	Baseline and endline

[a]GSED: Global Scales for Early Development.

[b]CREDI: Caregiver Reported Early Development Instruments.

[c]ARI - CP 2-5: Attachment Relationship Inventory Caregiver Perception 2-5 years.

[d]ECD: early childhood development.

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Data Collection

Baseline Assessments

Upon caregivers' consent, all caregivers completed a baseline survey, including household demographics, household structure, household poverty and income, educational attainment, child assets, household member interactions with the child, caregiver mental health, social support, and digital literacy. The baseline survey also collected data on the child's age, sex, twin status, gestational length, birthweight, and attendance of daycare or other child- and household-supporting services as well as children's early development using the Caregiver Reported Early Development Instruments tool [39].

End-of-Study Assessments

The endline surveys will occur when children reach 2.5 years of age, which will begin in September 2023. Table 2 shows an overview of the study timeline.

Table 2. Study timeline and project activities.

Time period	Description of project activities
July 2020 to January 2021	Study setup, software development, and ethics board approval
February to July 2021	Field testing and finalizing tool development and high-frequency feedback to the programming team
September 2021 to March 2023	Enrollment and baseline survey of 2471 small children and their caregivers in the main trial plus 237 small children and their caregivers in the comparison group (total 2708 project participants)
September 2021 to August 2024	Parenting interventions
August 2023 to September 2024	Endline survey and assessments
October 2024 to February 2025	Data analysis
March 2025	Study dissemination event

The end-of-study assessment will involve gathering information on child development, maternal mental health, mother-child interactions, and parenting attitudes toward the child. To measure the primary outcome, we will use the GSED assessment tool [38]. Secondary outcomes include (1) caregiver-reported early child development in motor, cognitive, language, and socioemotional domains; (2) the quality of a caregiver-child relationship; (3) screen time with and without the child being present; (4) primary female caregiver's parenting behaviors; (5) parenting attitudes; and (6) mental health. Table 1 provides details on the instruments used.

Additional Data Collection

To monitor and ensure the quality of the Afini platform, we collect data on users' platform usage and interactions with the system for the Afini group. These data include activities dispatched to the users, users' ratings, and feedback on the activities and questions asked. This data access is restricted to the service developers and maintainers and associated with an anonymized internal ID. Through these data, we identify users that have been "recently active" in the platform, which we define as having interacted with the service in any way in the past 15 days. A randomly selected subset of households in the Afini group, qualifying as "recently active," receives a small biweekly data credit transfer (US $0.8 to US $2.0) to evaluate a potential increase in the use of the platform through small rewards. The data transfer cost and value depend on the service provider (Claro and Bitel) and the aggregator used to perform the credit transfer (Reloadly and DTOne), with these costs increasing within that range from the start of the reward program.

Home Visits

For each home visit, a short visit form was completed to document the time and date, topics covered, and toys delivered. Additionally, we collected information about the play environment, the toys available, and the interactions between the caregiver and the child at the time of the visit.

Table 3 provides an overview of all study activities. Recruitment and baseline surveys started in the third quarter of 2021. Given the prerandomization of clusters to treatment, interventions were initiated directly after baseline in September 2021, gradually increasing sample sizes in all arms. Recruitment was completed in January 2021, and the first households were scheduled to complete the endline assessment (and exit the study) in September 2023. Interventions will continue (with a steadily decreasing number of households) until the last household completes the endline survey and exits the study in late 2024.

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Table 3. Overview of study activities[a].

Study activity	Year and quarter															
	2021				2022				2023				2024			
	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Data collection																
Baseline survey			✓	✓	✓	✓	✓	✓	✓							
Afini user data collection			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Home visit logs			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Endline data collection											✓	✓	✓	✓	✓	
Interventions																
Home visits			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Afini system use			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

[a]Summarizes data collection and intervention activities. Each cell corresponds to a quarter in the 2021-2024 period. Active data collection periods and active intervention periods are marked with a ✓.

Statistical Analysis

After confirming the psychometric reliability and validity of our key variables, we will perform a descriptive analysis (means and percentages) for the main characteristics and calculate prevalence and proportions for the primary outcomes. We will use standard linear regression models to assess the impact of the 2 intervention arms on child development. The primary outcome variable will be overall development as measured by the GSED, normalized to a developmental *z* score with a mean (0, SD 1) in the global reference population. Our primary empirical approach will be intent-to-treat, that is, comparing average outcomes across the 3 arms (independent of intervention compliance) with average outcomes in the control group. We will also conduct additional per-protocol analyses measuring mean differences between compliant children in the intervention arms with compliant children in the control group. For the home visit group, compliance will be defined as receiving at least 18 out of the 36 anticipated visits over the 18-month intervention period. Compliance with the Afini intervention will be defined as having interacted with the system at least once per month for at least 6 months in the observation period. Cluster-robust standard errors will be used to account for the cluster-level randomization of the intervention. Separate models will be estimated with and without baseline covariates.

Specifically, we will assess and control for household factors, caregiver factors, and child factors. Structural equation modeling will be used to test subgroup and mediation effects.

We will calculate the intervention's cost-effectiveness by comparing the developmental outcomes observed in the 2 intervention arms to the average developmental levels in the control arm to the costs of the 2 interventions per child.

Ethical Considerations

The study was approved by the University Peruana Cayetano Heredia institutional review board in Lima, Peru (SIDISI: 202522-Ref 030-03-21) and the Ethics Commission for Northwest and Central Switzerland (EKNZ: AO_2021-00002). All participants signed an informed consent before participating in any project-related activity. Verbal consent was asked for key informant interviews and focus group discussions during the pilot phase. The nature of the study was thoroughly explained to all participants, and all questions were answered before obtaining informed consent. Community leaders and local authorities are aware of the study.

Results

As shown in Table 2, enrollment and baseline data collection were completed in March 2023, and endline assessments were launched in September 2023. Table 4 shows descriptive statistics for the baseline sample by study arm. On average, children were 5 months old at baseline, 49.9% (1223/2452) were female, 8.1% (199/2452) had low birthweight (<2500 g at birth), and 97.5% (2391/2452) of children had a child health card. On average, mothers were 28 years old and considered literate. Fathers were slightly older, with an average age of 31.5 years at baseline, and had slightly higher education levels than mothers. The average household consisted of 2.5 adults and 1 additional child (sibling).

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Table 4. Descriptive statistics.

Characteristics	Control (n=962)			Home visits (n=315)			Afini (n=1175)		
	Observations, n	Clusters, n	Mean (SE)	Observations, n	Clusters, n	Mean (SE)	Observations, n	Clusters, n	Mean (SE)
Child age (months)	959	67	5.0 (0.11)	315	19	5.1 (0.22)	1169	78	5.1 (0.10)
Child is female	954	67	0.51 (0.02)	314	19	0.48 (0.03)	1172	78	0.50 (0.01)
Child has a health card	959	67	0.98 (0.01)	315	19	0.97 (0.01)	1169	78	0.98 (0.01)
Child born <2500 g	949	67	0.08 (0.01)	308	19	0.10 (0.02)	1152	78	0.08 (0.01)
CREDI[a] score	950	67	43.0 (0.066)	307	19	43.0 (0.163)	1163	78	43.2 (0.065)
Mother's age (years)	945	67	27.7 (0.26)	311	19	28.6 (0.48)	1155	78	28.0 (0.22)
Mother is literate	941	67	0.98 (0.01)	307	19	0.97 (0.01)	1151	77	0.99 (0.004)
Mother education level	944	67	3.2 (0.08)	310	19	3.2 (0.23)	1154	78	3.4 (0.08)
Father's age (years)	843	66	31.2 (0.26)	277	18	32.1 (0.52)	1027	76	31.6 (0.26)
Father is head of household	844	66	0.94 (0.01)	277	18	0.94 (0.02)	1026	76	0.94 (0.01)
Father education level	832	66	3.5 (0.07)	267	18	3.5 (0.22)	1007	76	3.7 (0.07)
SES[b] index	957	67	2.9 (0.12)	315	19	3.1 (0.29)	1169	78	3.2 (0.12)
Stimulation index	868	66	3.4 (0.06)	285	19	3.4 (0.14)	1076	78	3.5 (0.06)

[a]CREDI: Caregiver Reported Early Development Instruments.

[b]SES: socioeconomic status.

We anticipate completing the endline assessments in September 2024 and presenting final trial results to the local and national governments in Peru in early 2025.

Discussion

Principal Findings

In this study, we present the design and setup of a cluster randomized trial to evaluate the effectiveness and cost-effectiveness of Afini, a digital platform that provides digital support to children from 0 to 7 years of age. The trial compares the developmental improvement achievable through the Afini platform to developmental improvements achievable through home visits, which currently are considered the gold standard in this field. While home visits offer the advantage of personal interactions with caregivers, the main benefits of new technologies, such as Afini, lie in their flexibility. Using a chatbot and AI system, Afini efficiently and automatically takes into account the caregiver's and child's preferences. It then offers age-specific recommendations for development-promoting activities that parents can undertake with their children whenever they have the time for such interactions. The platform also provides advice on early child development, well-being, and health similar to the contents typically delivered through ECD home visits.

The proposed trial is innovative and timely for several reasons. Due to the rapid global increase in cell phone coverage [25], there are now unprecedented opportunities for health and education systems to interact with patients and families and intervene at scale effectively and efficiently [31,33,34]. These advances have paved the way for the development and use of parenting support platforms as a means of engagement [26,30,43,45,46]. However, several key questions must be addressed before such platforms can be used in remote and resource-constrained settings. These include understanding their reach and actual impact on child development. Additionally, it remains unclear whether these technologies can be scaled to populations with limited digital literacy.

Understanding the extent to which digital platforms can reach low-income communities and families is crucial for understanding the feasibility and effectiveness of digital platforms in addressing the needs of vulnerable populations. During our formative research, we were particularly concerned about the challenges related to technology access, internet connectivity, and affordability. However, our early findings indicated that the large majority of mothers with young children had internet and smartphone access. Furthermore, 2 months after baseline, 84% of mothers reported using the platform at least once, and 87% rated it as useful [35]. Similar studies conducted in LMICs have also reported high acceptance of digital parenting interventions [47,48] and good reach for mobile health interventions to improve maternal and child health [31,34]. However, the majority of existing data on digital parenting support interventions during early childhood has been collected in high-income countries [27,30,33,43]. While those studies show promise in parenting outcomes and engagement, such as enhancing parental self-efficacy [49,50], data from LMIC contexts are largely missing. Furthermore, to date, limited data exist on digital parenting interventions' impact on child development, with few randomized controlled trials [51], and many studies still in the piloting stages, with small samples, or in ongoing data collection [52-54].

Our second question revolves around the impact of digital platforms on caregiver-child interactions and child development in low-resource communities. Caregiver-child interactions are

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vital for a child's early development, and it is important for a digital platform targeting households in low-resource communities to facilitate positive and developmentally appropriate caregiver-child interactions. A study conducted in the United States examined the availability and quality of the apps in app stores and found very few apps offering tailored materials to parents instead of promoting generic guidance that may have limited usefulness in certain contexts [55]. However, several pilot studies demonstrated that digital interventions are feasible, engaging, and cost-effective ways for delivering developmental education to families, particularly in enhancing language-promoting behaviors [56,57]. A recent review highlighted the potential of mobile health and apps to promote early language development as well, although it raised concerns about the frequency and consistency with which parents will access and use digital interventions in their daily lives [58].

From a policy perspective, scalability is maybe the most critical aspect to consider when evaluating a digital platform. It is important to assess whether the platform can be successfully extended to other settings and populations beyond the initial study in the rural Andes. This becomes especially relevant when there is a possibility of limiting access for subsets of the population with varying levels of digital literacy, particularly in the absence of guidelines or follow-up assistance. Initial data collected in the study area showed that smartphone access and connectivity are almost universal [35]. While there have been limited studies demonstrating scalability thus far, it is essential to identify any unanticipated limitations or challenges that may arise during implementation and adherence, particularly in populations with diverse levels of digital literacy.

The proposed study has some limitations. First, while all intervention content was carefully adapted and is thus optimized for the local context studied, the materials used (and results obtained) may not directly work and translate to other settings. Second, our study is only able to follow-up children for about 2.5 years and can thus only give short-term treatment effects that may not fully capture long-term gains for treated children. Third, our intervention focused primarily on a broad measure of child development and did not offer specific insights into more narrow areas of early childhood health such as nutrition or emotional development. Future studies will be needed to address these issues.

Conclusions

This trial will provide valuable insights into the impact and scalability of tailored digital ECD platforms, particularly in reaching remote and vulnerable populations in low- to middle-income settings, and address challenges faced by home visiting models, such as cost and sustainability. We wish to demonstrate the platform's effectiveness, especially among diverse population groups with varying levels of digital literacy. This is crucial for designing effective future interventions.

Acknowledgments

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Data Availability

The data sets generated and analyzed during this study are available from the corresponding author on reasonable request. All trial data will be made publicly available upon completion of the trial and analysis.

Conflicts of Interest

None declared.

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Abbreviations

AI: artificial intelligence
ARI-CP 2-5: Attachment Relationship Inventory Caregiver Perception 2-5 years
ECD: early child development
GSED: Global Scales for Early Development
LMIC: low and middle-income countries
PNCM: Programa Nacional Cuna Más

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Protocol

A Relationship-Based Resilience Program for Promotores: Protocol for a Randomized Controlled Waitlist Trial

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Abstract

Background: Community service providers (CSPs) play an integral role in the health care of low-income Hispanic or Latinx (HL) communities. CSPs have high-stress frontline jobs and share the high-risk demographics of their communities. Relational savoring (RS) has been associated with lower cardiovascular reactivity and psychosocial benefits, with particular promise among HL participants. In this study, we aim to identify RS's potential in promoting CSPs' cardiometabolic health and, in so doing, having broader impacts on the community they serve.

Objective: This randomized controlled waitlist study aims to examine the effect of an RS intervention on (1) CSPs' cardiometabolic health (cardiometabolic risk factors and outcomes) and (2) CSPs' threats to leaving the workforce.

Methods: We will recruit a sample of 80 CSPs from community health agencies serving low-income HL populations. Participating CSPs will be randomized into an experimental or a waitlist control. Participants will complete 1 or 2 baseline assessment batteries (before the intervention), depending on the assigned group, and then complete 2 more assessment batteries following the 4-week RS intervention (after the intervention and at a 3-mo follow-up). The RS intervention consists of guided reflections on positive moments of connection with others. Electrocardiogram data will be obtained from a wearable device (Polar Verity Sense or Movisens) to measure heart rate variability. The primary outcome is cardiometabolic health, consisting of cardiometabolic risk (obtained from heart rate variability) and cardiometabolic health behaviors. The secondary outcomes include CSPs' threats to leaving the workforce (assessed via psychological well-being), intervention acceptability, and CSPs' delivery of cardiometabolic health programming to the community (exploratory). Analyses of covariance will be used to examine the effects of RS on cardiometabolic health and on CSPs' threats to leaving the workforce, comparing outcomes at baseline, postintervention, and at follow-up across participants in the experimental versus waitlist group.

Results: The study has been approved by the University of California, Irvine, Institutional Review Board and is currently in the data collection phase. By May 2023, 37 HL CSPs have been recruited: 34 have completed the baseline assessment, 28 have completed the 4 intervention sessions, 27 have completed the posttreatment assessment, and 10 have completed all assessments (including the 3-mo follow-up).

Conclusions: This study will provide valuable information on the potential of RS to support cardiometabolic health in HL CSPs and, indirectly, in the communities they serve.

Trial Registration: ClinicalTrials.gov NCT05560893; https://clinicaltrials.gov/study/NCT05560893

International Registered Report Identifier (IRRID): DERR1-10.2196/51427

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KEYWORDS

psychosocial intervention; relational savoring; cardiometabolic health; community service providers; Hispanic or Latinx; CSP

Introduction

Background

Ethnic and racial disparities in cardiometabolic health within the United States have been widely documented [1-5]. Racial-ethnic minoritized and historically underrepresented groups, including Hispanic or Latinx (HL) Americans, face higher cardiometabolic risks, such as obesity, diabetes, hypertension, and dyslipidemia, than non-HL White Americans [6,7]. According to data obtained from the National Health Interview Survey of 2018, HL adults are 1.3 times more likely to die from diabetes and 70% more likely to be diagnosed with diabetes by a physician than non-Hispanic White (NHW) adults [8]. Similarly, HL Americans are 1.2 times more likely to be obese than NHW Americans, whereas HL women are 20% more likely to be overweight than their NHW counterparts [9]. The etiology of cardiometabolic risk disparities in racial-ethnic minoritized communities, including low-income HL communities, is multifactorial and includes socioeconomic, behavioral, and environmental factors. Cultural and language barriers, lack of health care access, and differences in education and employment opportunities contribute to these disparities [1,5,10]. Community service providers (CSPs), also called *promotores de salud*, are members of the community who provide culturally appropriate health education and information, offer support and care, and advocate for the community's health needs [11]. These roles empower HL CSPs to help community members overcome or withstand the barriers that contribute to health inequalities.

Through culturally accessible programming, CSPs help prevent and manage chronic diseases, including cardiometabolic diseases, in the communities they serve. Indeed, CSPs play a significant role in reducing health risks and disease burden as well as in the management of various health problems, including hypertension, diabetes, HIV infection, cancer, and cardiovascular disease [12-16]. Community interventions led by CSPs have been proven to effectively lower cardiometabolic risk factors in HL communities while being affordable and well received by community members [12-16]. These include, among others, prevention programs targeting diabetes and obesity, which effectively impact risk factors such as blood pressure, low-density lipoprotein cholesterol, triglycerides, insulin, sedentary behaviors, and one's weight [12-16]. There are many advantages to CSPs belonging to the same communities they serve, including cultural and linguistic understanding, trust, credibility, and rapport. All of this contributes to community members' engagement and retention in interventions that improve health outcomes and provide long-term support. However, sharing the same demographic characteristics also means that HL CSPs face the same high cardiometabolic risks as the community members they serve. In fact, it is often the case that CSPs are individuals who themselves have experienced health challenges and have learned to manage their conditions (eg, diabetes, HIV). In addition to providing support to others, as they have been trained to, their own health concerns might still require monitoring and self-management. Furthermore, the high-stress nature of their occupations may further amplify health risks. This is especially true when considering the extensive stress that the COVID-19 pandemic brought to frontline health care workers, including CSPs. In support of this assertion, a qualitative analysis found that the pandemic affected CSPs' work and daily life, leading to psychological and social stress [17].

CSPs, along with all frontline health care professionals (HCPs) during the pandemic, experienced acute psychological distress and associated effects [17]. A study analyzing the role of CSPs in the COVID-19 pandemic response reports that CSPs faced significant exposure to stress and grief, among other difficulties [18]. In addition, HL communities, as well as other minoritized communities, were more likely to be exposed to the SARS-CoV-2 virus, to experience severe forms of COVID-19, and to face higher mortality rates [19,20]. Understandably, this led to catastrophic financial and social consequences in low-income HL communities. Owing to the comprehensive support that CSPs provide to community members, which addresses not only physical health but also various financial and social needs (eg, unemployment, housing insecurity, food insecurity, domestic violence, and language barriers to navigate legal paperwork), CSPs carried a significant burden [17]. Considering the fact that they are at higher risk for negative health outcomes (eg, diabetes, high blood pressure, and overweight) based on demographics alone and the role they played during the pandemic, which led to heavy workloads and high stress, CSPs may face substantial risk for cardiometabolic disease. Nevertheless, to the best of our knowledge, there have been no interventions aimed at protecting cardiometabolic health specifically in CSPs.

By placing enormous demands on CSPs, the aftereffects of COVID-19 have placed CSPs at risk of professional burnout, endangering their abilities to deliver this care [17,21]. CSPs play a crucial role in the health of underserved communities, but to carry out their greatly needed service, there must be a system that promotes and protects their health and well-being. Supporting CSPs is a matter of equity; in response to the health care system failure to adequately support medically underserved communities, the CSP model represents these communities' efforts to promote health and build resilience. Although no previous studies have specifically examined how CSPs' physical and psychological well-being relates to the quality and reach of their services, researchers have investigated how burnout in other HCPs affects the quality and safety of the care they provide [22,23]. In line with theory, a meta-analysis comprising 210,669 HCPs concluded that burnout (depersonalization, emotional exhaustion, and reduced personal accomplishment) is negatively associated with quality (perceived quality and patient satisfaction) and safety of care [22]. Similarly, in a systematic literature review, burnout among physicians was associated with decreased productivity, as evidenced by the number of sick days, hours worked, number of patients seen, and intent to leave the profession [23]. Considering these relationships between

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HCPs' burnout and reduced productivity, impaired quality of care, and reduced safety of the care provided, it is reasonable to expect similar associations between CSPs' well-being and the reach and quality of the services delivered to the community. As such, interventions designed to promote CSPs' well-being and prevent their burnout are a necessity.

Relational Savoring: A Culturally Congruent Approach

Relational savoring (RS), based on positive psychology and attachment theory, is a brief intervention in which one deeply reflects on a positive emotional experience involving a moment of connection with another person [24]. The underlying premise is that focusing on a memory of positive connection will augment the meaning and positive emotion associated with this interpersonal experience [24]. Through this process, one's sense of psychological agency, fulfillment, and satisfaction are enhanced [24]. Similarly, per attachment theory, experiences of felt security such as *safe haven* (a time when an attachment figure provided care of comfort) and *secure base* (a time when the support provided by an attachment figure allows one to take a risk one would not have taken otherwise) in our early relationships constitute the basis of later socioemotional health [25]. As such, moments of closeness recalled in an RS intervention include times when one supported (secure base) or comforted (safe haven) another person and felt deep positive emotions such as joy, peace, satisfaction, or love [24]. For CSPs, experiencing interpersonal connectedness when helping members of their community is a common occurrence [26], thereby underscoring the cultural congruence of this intervention. RS has the potential to prolong and enhance the attention given to these moments, helping CSPs lower stress and motivating them to continue engaging in their meaningful and necessary work.

Although RS has not previously been tested with CSPs or HCPs, other interventions rooted in positive psychology, such as the Web-based Implementation for the Science of Enhancing Resilience (WISER) intervention, have been found to decrease burnout and depression and support work-life integration in neonatal intensive care unit HCPs [27]. The WISER intervention includes 6 modules, 2 of which are titled "Three Good Things" and "Relationship Resilience" and refer to reflecting on 3 positive moments that occurred that day and reflecting on positive interactions, respectively. Considering RS's focus on reflecting and enhancing positive emotions linked to a relational memory, there are considerable similarities with these 2 modules of WISER. Likewise, support for the RS intervention exists in its prior findings with other samples. Findings across studies with parent-child dyads, long-distance couples, older adults, and male adolescents in residential treatment have shown that RS can improve emotional states, psychological agency, relational schemas, and relationship satisfaction compared with control conditions [28-32]. Likewise, the RS intervention shows promise in affecting physical health by impacting health behaviors and lowering heart rate [29,31]. In addition, previous studies report that RS might be especially effective in HL populations because of its compatibility with cultural values [28]. Considering the potential of RS in positively impacting psychological and physical health in different populations, as well as evidence suggesting cultural computability, it is worth exploring its effect among HL CSPs.

In this study as well as in previous studies [26,28-32], while maintaining its core characteristics, the RS intervention is tailored to our priority population of HL-serving CSPs. This was done based on discussions held between the investigative team and the CSPs regarding what brings them meaning in relation to the job. Furthermore, the results of a qualitative study of *promotores'* experiences during the pandemic revealed important insights regarding the meaning derived from work as well as the unique challenges posed by working during the pandemic [17]. The challenges reported included enduring their own and their community's losses, which placed them at risk of compassion fatigue or vicarious traumatization, along with feelings of grief and anxiety [17]. However, by being able to provide help to the community during difficult times, their work also provided a source of agency and meaning [17]. Therefore, in this investigation, RS focuses on assisting CSPs' recall moments of connection with community members while doing their work and engaging with the community.

Finally, the participants in this study are all CSPs who serve the HL community, with most of them being HL themselves. Although we recognize that *Hispanic* and *Latinx* refers to individuals with origins in different countries, racial backgrounds, and levels of acculturation, there are cultural values that seem to be shared across communities of Latin American origin. Shared values include, among others, *simpatía*, the inclination toward emotional positivity or warmth and the avoidance of negativity or conflict with others, and *familismo*, valuing close family connections above the individual or self [33,34]. Considering that RS focuses on finding and reflecting on moments of warmth and connection, this intervention is culturally compatible with HL populations without the need for substantial tailoring [24]. In agreement, a previous study reported that HL mothers, but not non-HL mothers, showed a greater response to an RS intervention than to a personal savoring intervention [24]. Likewise, besides cultural congruence, HL CSPs share the fact that their job is caring for and supporting community members. In other words, CSPs' day-to-day interactions with members of their communities may lead to various moments of connection that can be used throughout the RS intervention [26]. As such, the characteristics of their job may facilitate engagement with RS.

CSPs are required to support low-income HL communities' health. If their physical and psychological well-being are at risk, their ability to reach community members through their programming is compromised. Considering the challenges endured in the pandemic and the risk factors associated with both their demographic characteristics and their job responsibilities, there is a need for interventions that support HL CSPs' well-being. Bearing in mind this intervention's compatibility with CSPs' occupation and cultural background, RS holds immense potential.

Objectives

This study aims to analyze the effects of an RS intervention on (1) HL CSPs' cardiometabolic health (cardiometabolic risk and health behaviors) and (2) the risks of CSPs leaving the

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workforce. We hypothesize that compared with participants assigned to the waitlist control condition, those in the RS condition will exhibit the following health improvements:

- 1a. Exhibit lower cardiometabolic risk (lower heart rate variability [HRV]) during a discrimination stressor task
- 1b. Report more favorable cardiometabolic health behaviors pertaining to sleep, exercise, and diet
- 2a. Show reduced threats to CSPs leaving the workforce (greater work satisfaction and psychological agency and lower burnout)
- 2b. Exploratory hypothesis: That introduction of the RS intervention into agencies will result in greater engagement, as evidenced by the following: agencies will show increases in their demonstrated reach to community members through their health programing (ie, fewer absent days, more health-related events offered, larger community attendance at their events, and larger retention of community members in their programs) during the period following the introduction of RS as compared with the 6 months preceding the introduction of RS

Methods

Ethical Considerations

In conducting this study, careful attention was given to the ethical considerations that guide the treatment of research participants, ensuring the protection of their rights, privacy, and well-being throughout the study.

1. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the University of California, Irvine, Institutional Review Board (UCI IRB #1596).
2. Informed consent: All participants gave their informed consent for inclusion before they participated in the study.
3. Privacy and confidentiality protection: All identifiable data collected were removed and replaced with a code. A securely maintained list links this code to the identifiable information, and is kept separately from the research data. All research data are maintained in a secure location at the University of California, Irvine, to which only authorized individuals have access. The data are stored electronically on a cloud and an external drive in an encrypted, password-protected file. Video or audio recordings are stored in a secure location; these data are transcribed and deidentified before analyses.
4. Compensation: The CSPs are compensated for their participation in the study, with compensation broken down as follows: US $30 for baseline visit 1, US $40 for baseline visit 2 (waitlist control group only), US $25 for each intervention session (total US $100), US $40 for posttreatment session, and US $50 for the follow-up visit. Overall, participants can earn US $220 or US $260 depending on the assigned group (experimental vs control). Participants can choose to receive the compensation via Venmo (PayPal, Inc) or as a physical or web-based gift card.

Eligibility Criteria and Recruitment

All participants will be CSPs employed at partner community health agencies, including Latino Health Access (LHA), Dignity Health, and other agencies, to be recruited throughout our enrollment period. Participating agencies and CSPs will serve HL communities and will be located throughout the United States. Inclusion criteria include being aged ≥18 years and working (for payment or as a volunteer) as a CSP serving low-income HL families. Given that this pilot study is intended to test RS on a new population, we identified a sample size (n=80) that would allow us to identify a signal but not a statistically significant ($P<.05$) effect. This study aimed to generate a pilot study that could be used to support an adequately powered randomized controlled trial.

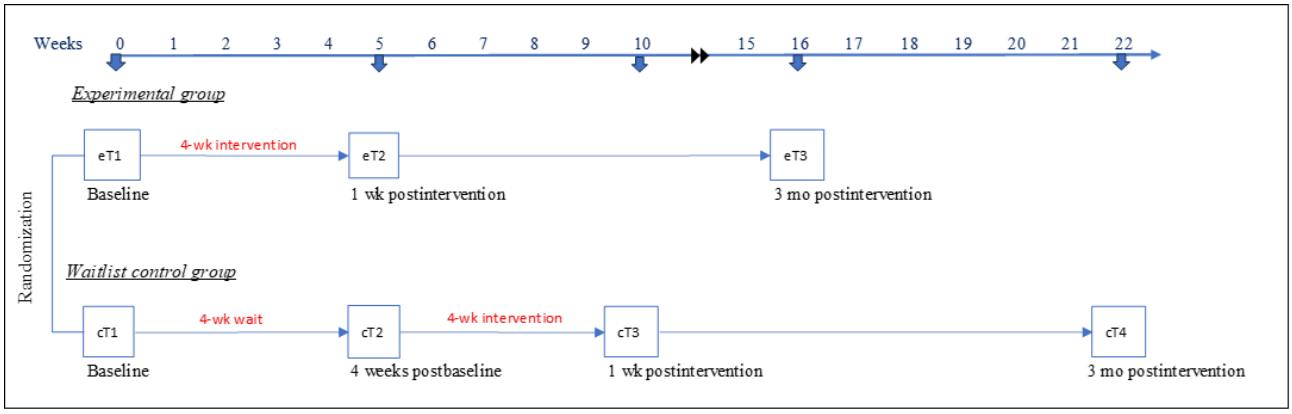
Participants will be recruited both offline and via email through their agencies, which will post advertisements in English and Spanish at their facilities, announce the opportunity in staff meetings and via email, and facilitate introductions between the research team and the CSPs. Interested participants will contact research personnel.

Randomization and Overview

In this randomized controlled waitlist design (ClinicalTrial.gov identifier NCT05560893), the CSPs will be randomly assigned to an experimental group or a waitlist group. Both groups will complete an identical assessment battery (assessing health behaviors and psychological well-being) and complete stressor tasks (assessing cardiometabolic risk) before the intervention, after the intervention, and at a 3-month follow-up. The experimental group will receive the RS intervention (4 sessions, 1/wk) 1 week after the baseline assessment (Figure 1). The waitlist group will complete the baseline assessment, wait 4 weeks, complete a second baseline assessment, and 1 week later receive the RS intervention. After completing the RS intervention, the participants in both the experimental and waitlist groups will complete the postintervention assessment 1 week later and a follow-up 3 months later.

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Figure 1. Randomization and timeline.



Measures

Primary Outcomes

All the constructs and measures assessed are summarized in Table 1.

All assessments are available in both English and Spanish. Cardiometabolic health, as indicated by cardiometabolic risk and cardiometabolic health behaviors, will be the primary outcome and will be measured before the intervention, after the intervention, and at the 3-month follow-up. Cardiometabolic risk will be measured via HRV in response to a stressor task. The stressor task will consist of a discrimination stream-of-consciousness (SOC) task [35,36], where participants will talk for 4 minutes about an occasion where they felt discriminated against. Before completing the SOC task, participants will complete a questionnaire [36] that will provide them with a list of commonly occurring discrimination events from which they can select an event that has occurred to them. Vagally mediated HRV will be calculated from the variability of the interbeat intervals obtained from electrocardiogram (ECG) data. ECG data will be recorded using a Polar Verity Sense heart rate monitor or Movisens device, small wearable devices that the participants will place in their arm or chest, respectively, during the stressor task and at rest (before and after the stressor task baseline measures). Favorable cardiometabolic health behaviors include behaviors pertaining to sleep, exercise, and diet and will be assessed using the Pittsburgh Sleep Quality Index [37], the International Physical Activity Questionnaire–Short Form [38], the Food Behavior Checklist [39], the 36-Item Short Form Health Survey [40], and 2 self-developed scales (subjective assessment of overall health and impairment owing to overall health).

The measures and tasks used to assess the primary outcome, cardiometabolic health, are described in the following sentences:

1. Everyday Discrimination Scale: the participants will complete a Spanish version of the Everyday Discrimination Scale [36], a 9-item scale that assesses the frequency and the attribution of discrimination experiences (eg, In your day-to-day life, how often are you treated with less respect than other people are?) to assist them in identifying a discrimination experience to speak about in the SOC task. Items are rated on a scale of 0 (never) to 5 (almost every day), with higher scores indicating a higher frequency of discrimination experience. Previous studies have demonstrated good reliability and validity in HL samples [41].

2. SOC task: after a 2-minute baseline task (sitting with no stimuli), the participants will be asked to select an experience of discrimination to focus on for a SOC task. To help them do this, the participants will complete a brief questionnaire of common discrimination experiences, followed by a 5-minute interview to help them select among the experiences reported on the questionnaire. This cardiovascular reactivity task is modeled after a SOC task previously used in our laboratory [35], modified to be ecologically relevant to this population. The SOC task will ask the participants to speak for 4 minutes about the discrimination experience, focusing on the thoughts and feelings they had. The participants will then complete a 2-minute resting-recovery task wherein they will speak about a positive memory. The prompt for the SOC task is as follows (prompt translated to Spanish and available in English and Spanish, based on participant's preference):

> *For the next four minutes, I would like for you to please discuss in detail your experience during this time that you have identified when you felt [insert discrimination experience here]. Please discuss your thoughts, feelings, hopes, and concerns about the experience. Remember, there are no right or wrong answers, so please say whatever comes to mind. Your job is to talk continuously about anything that comes to mind about this experience for the 4-minute period. We will record your responses because how you are thinking and feeling about this experience is very important to us.*

3. Pittsburgh Sleep Quality Index: the participants will report on their sleep quality using the Spanish version of the Pittsburgh Sleep Quality Index [42], a 10-item measure that assesses sleep quality and duration. Items (eg, How many hours of actual sleep do you get at night—this may be different than the number of hours you spend in bed?) are rated on a scale of 0 to 3, whereby higher scores reflect more sleep disruption. Previous studies have demonstrated good reliability and validity in HL samples [43].

4. Food Behavior Checklist: the participants will report on their diet using the Food Behavior Checklist for Spanish speakers [39], a 16-item questionnaire that measures basic dietary behaviors, including the frequency of fruit, vegetables, juice,

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and low-fat dairy consumption; food insecurity; shopping; and cooking techniques. Previous studies have demonstrated good reliability and validity in HL samples [44].

5. Thirty six-Item Short Form Health Survey: the participants will report on their overall health using a Spanish version of the 36-Item Short Form Health Survey [40], a 36-item quality of life measurement that assesses 8 health-related domains, including physical functioning, role limitations because of physical problems, bodily pains, general health perceptions, vitality, social functioning, role limitations because of emotional problems, and perceived mental health. Previous studies have demonstrated good reliability and validity in HL samples [45].

6. Subjective assessment of overall health: the participants will report on their subjective assessment of their overall health by answering a 2-item scale designed for this study. Items assess perceptions of health (eg, Compared with men or women of your age, how would you define your health?) and are rated on a scale of 0 (bad) to 5 (excellent).

7. Impairment owing to overall health: the participants will report on impairments owing to their overall health by answering a 2-item scale designed for this study. Items assess behaviors related to health (eg, During the past 3 months, how many times have you missed school or work for physical or health problems?) and are rated on a scale from 0 (never) to 5 (>10 times).

8. International Physical Activity Questionnaire—Short Form: the participants will report on their exercise habits using a Spanish version of the International Physical Activity Questionnaire–Short Form [38], a 7-item scale that assesses the duration and intensity of physical activities undertaken over the previous 7 days, including the number of hours engaged in physical activity at different intensities, including walking, moderate-intensity activities, and vigorous-intensity activities.

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Table 1. Outcomes: constructs and measures assessed.

Outcomes and constructs	Measures assessed
Primary outcome: cardiometabolic health	
Cardiometabolic risk	
Stressor-level heart rate variability	• Everyday Discrimination Scale • SOC[a] task
Cardiometabolic health behaviors	
Sleep quality	• Pittsburg Sleep Quality Index
Diet	• Food Behavior Checklist
Overall health	• 36-Item Short Form Health Survey
Subjective assessment of overall health	• Self-Developed Scale
Impairment due to overall health	• Self-Developed Scale
Exercise	• International Physical Activity Questionnaire–Short Form
Secondary outcomes	
CSPs'[b] threat to leaving the workforce (psychological well-being)	
Psychological well-being	• Brief Symptom Inventory
Emotion	• Self-Assessment Manikin
Closeness to community	• Inclusion of Other in the Self Scale–Community Version
Trauma history	• Traumatic Life Events Questionnaire
Burnout	• The COVID-19 Burnout Scale • Maslach Burnout Inventory
Job satisfaction	• Job Satisfaction Survey
Psychological agency	• Coder-rated measures based on SOC
Reflective functioning	• Coder-rated measures based on SOC
Intervention acceptability	
Savoring uptake	• Self-developed questionnaires
Intervention acceptability	• Self-developed questionnaires
Community reach	
Number of days CSPs worked	• Information obtained from agency
Number of health-related events offered	• Information obtained from agency
Retention of community members in programs	• Information obtained from agency
Community attendance at events	• Information obtained from agency

[a]SOC: stream-of-consciousness.

[b]CSP: community service provider.

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Secondary Outcomes

Secondary outcomes include threats to CSPs leaving the workforce, which will be assessed via psychological well-being (ie, agency, burnout, and job satisfaction) and intervention acceptability. For these secondary outcomes, we will use the Brief Symptom Inventory-18 [46], the Self-Assessment Manikin [47], the Inclusion of Other in the Self Scale–Community Version (IOS-C) [48], the COVID-19 Burnout Scale [49], the Maslach Burnout Inventory [50], the Traumatic Life Events Questionnaire [51], and the Job Satisfaction Survey [52]. RS intervention acceptability and savoring uptake will be assessed via self-developed questionnaires. All these will be assessed before the intervention, after the intervention, and at the 3-month follow-up.

Finally, the CSPs' delivery of cardiometabolic health programming to the community will be measured in an exploratory manner. This will be assessed via the number of days the CSPs worked, the number of health-related events offered, the retention of community members in the programs offered by the CSPs, and the number of community members attending the events. Data from the time following the introduction of RS will be compared with those from the 6 months preceding the introduction of RS. This information will be obtained from the health agencies' institutional data. It is worth mentioning that these measures are not a reflection of the CSPs' effectiveness, given that the CSPs may meet with fewer community members at any given time yet effectively support them in improving their health outcomes. Likewise, given different structures or job tasks across agencies (eg, leading groups, doing outreach, and follow-ups), there might be differences in how these measures are analyzed in the future. The collection of these data will not enable us to detect differences between the intervention and waitlist control groups. We intend to collect these data on the CSP's delivery of health programming to lay the groundwork for a more in-depth future investigation of the impact of RS.

The measures and tasks used to assess the secondary outcomes are described in the following sentences:

1. Brief Symptom Inventory: the participants will report on their psychological well-being using the Spanish version of the Brief Symptom Inventory-18 [46], an 18-item measure assessing depression (eg, During the past week including today, how much were you distressed by feelings of worthlessness?), anxiety (eg, During the past week including today, how much were you distressed by nervousness or shakiness inside?), and somatization. Items are rated on a 5-point scale ranging from 0 (not at all) to 4 (extremely). Previous studies have demonstrated good reliability and validity in HL samples [53].
2. Self-Assessment Manikin: the participants will report on their emotions using the Self-Assessment Manikin [47], a widely recognized nonverbal pictorial measure that assesses emotional states, valence, and arousal levels using pictures to represent how a participant is feeling in response to stimuli.
3. IOS-C: the participants will report on closeness to the community using IOS-C [48]. This single-item pictorial measure uses Venn‐like diagrams—each diagram represents different degrees of overlap of 2 circles, progressing through 7 equal steps, representing lower and higher levels of closeness as the circles overlap more and more. The Inclusion of Other in the Self Scale has good test-retest reliability and convergent validity and has been used in samples with a large percentage of HL participants [54].
4. Traumatic Life Events Questionnaire: the participants will report their trauma history using the Spanish version of the Traumatic Life Events Questionnaire [51], a 23-item scale measuring whether an individual has experienced a wide range of traumatic events, including sexual assault, exposure to combat, or the unexpected death of a loved one, on a scale ranging from 0 (never) to 4 (≥5). Previous studies have demonstrated good reliability and validity in HL samples [55].
5. The COVID-19 Burnout Scale: the participants will report on their COVID-19 related burnout using the COVID-19 Burnout Scale [49], a 10-item scale that measures burnout feelings related to the pandemic. Items (eg, When you think about COVID-19 overall, how often do you feel hopeless?) are scored on a scale ranging from 0 (never) to 6 (all the time).
6. Maslach Burnout Inventory: the participants will report on their occupational burnout using a Spanish version of the Maslach Burnout Inventory [50], a 22-item scale that measures occupational exhaustion, depersonalization, and level of personal accomplishment related to work. Items (eg, I have become more callous to people since I have started doing this job) are scored on a scale ranging from 0 (never) to 6 (every day). Previous studies have demonstrated good reliability and validity in HL samples [56].
7. Job Satisfaction Survey: the participants will report on their job satisfaction using the Spanish version of the Job Satisfaction Survey [52], a 36-item assessment measuring attitudes related to the job and aspects of the job. Items (eg, I feel I am being paid a fair amount for the work I do) are scored on a scale ranging from 1 (disagree very much) to 6 (agree very much). Previous studies have demonstrated good reliability and validity in HL samples [57].
8. Savoring uptake: after completing the intervention, the participants will reflect on the savoring experience using the savoring uptake questionnaire that was developed for this study. The 6-item questionnaire measures the frequency at which participants have engaged in savoring since their last session, how useful they found savoring, how valuable they found savoring, whether they would recommend the program to others, and whether they would like to continue savoring on their own time. Items are scored on a scale ranging from 1 (not at all likely, useful, or valuable) to 5 (extremely likely, useful, or valuable).
9. Intervention acceptability: the participants will report on the acceptability of the RS intervention by completing the Relational Savoring Acceptability Questionnaire, a 14-item assessment created for this study to capture how participants feel before they begin the program (eg, I expect the program will improve my feelings about my work) and how they

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feel after they complete the program (eg, The program improved my health and well-being) on a scale ranging from 1 (strongly disagree) to 5 (strongly agree).

Intervention

Consistent with prior work, the RS intervention will involve 4 weekly sessions, each lasting approximately 30 minutes, consisting of 2 phases: memory selection and memory reflection (Textbox 1).

Textbox 1. Relational savoring: intervention phases.

Phases and steps

- Memory selection
  - Recall a few memories of positive connectedness or attachment content when helping community members.
  - Participants describe these memories and interveners ask follow-up questions designed to reveal the level of specificity, positivity, connectedness, and potential for spoiling in the memories.
  - Interveners select one specific memory with the best content for the next phase.
- Memory reflection (5-step guided reflection)
  - Sensory reflection (eg, Where were you? What did your surroundings look like? What could you hear?)
  - Emotion reflection (eg, What did you feel?)
  - Meaning making (eg, What did you think?)
  - Future-oriented reflection (eg, What do you think will happen in the future thanks to this connection?)
  - Mind-wandering reflection (eg, What else comes to mind?)

RS is a manualized intervention that has been adapted to allow CSPs the opportunity to savor memories of providing care to community members to enhance their sense of connectedness to the community [24,28]. In this study, as in previous studies, the intervention will be delivered by paraprofessionals (eg, undergraduate and postbaccalaureate students) [28]. Previous studies have shown that the intervention can be administered with high fidelity by paraprofessionals with a low level of clinical training (4 h of didactic training plus approximately 4 h of practice-based training) [28].

At the beginning of RS, the CSPs will complete a 1-minute mindfulness exercise, which is consistent with prior studies [28,29]. Next, during the first phase of the RS intervention (*memory selection*), the CSPs will be guided to generate memories of the times when they felt closeness, connection, or joy when they were able to support, encourage, or protect community members. The participant will be guided to select a memory with substantial attachment content (ie, secure base and safe haven memories). Alternatively, if the participant is unable to produce a memory explicitly related to safe haven or secure base content, they may select a memory involving a moment of positive connectedness or togetherness [28]. Then, during the second phase (*memory reflection*), the CSPs will engage in a 5-step guided process, where they will reflect on sensations, emotions, and cognitions associated with the selected moment. Sessions will be conducted via Zoom (Zoom Video Communications, Inc) by trained bilingual and bicultural research assistants in the participant's language of choice (Spanish or English). The RS sessions will be recorded and transcribed to assess themes that emerge during the savoring sessions and to analyze therapist fidelity and therapist-client relationship quality. In addition, immediately before and after each intervention session, the participant will complete a 2-question survey assessing the participant's mood (Self-Assessment Manikin) and perceived closeness to the community (IOS-C) [47,48].

Data Analytic Plan

Descriptive statistics will be used to analyze the demographic characteristics of our sample population. A series of analyses of covariance will be conducted to examine the effects of RS on HRV, health behavior, psychological well-being, threats to CSPs leaving the workforce, and the reach of CSPs' cardiometabolic health programming. We will compare outcomes at baseline, immediately postintervention, and at the 3-month follow-up across participants in the experimental versus waitlist group. HRV at baseline will be included as a covariate in analyses examining HRV, and all analyses will examine a range of potentially confounding covariates for potential use in analyses (eg, age, BMI, and socioeconomic status; those that are significantly associated with key study variables will be included as covariates in hypothesis testing). Effect sizes will be examined in all analyses. With a sample size of 80, it will be possible to detect small-to-moderate effects (yielding an effect size d=0.24) of RS on the CSPs' cardiometabolic health, threats of CSPs leaving the workforce, and the delivery of cardiometabolic health programming. As stated in the *Eligibility Criteria and Recruitment* section, our goal is not to detect statistically significant effects but rather to look for effect sizes to inform future studies.

Results

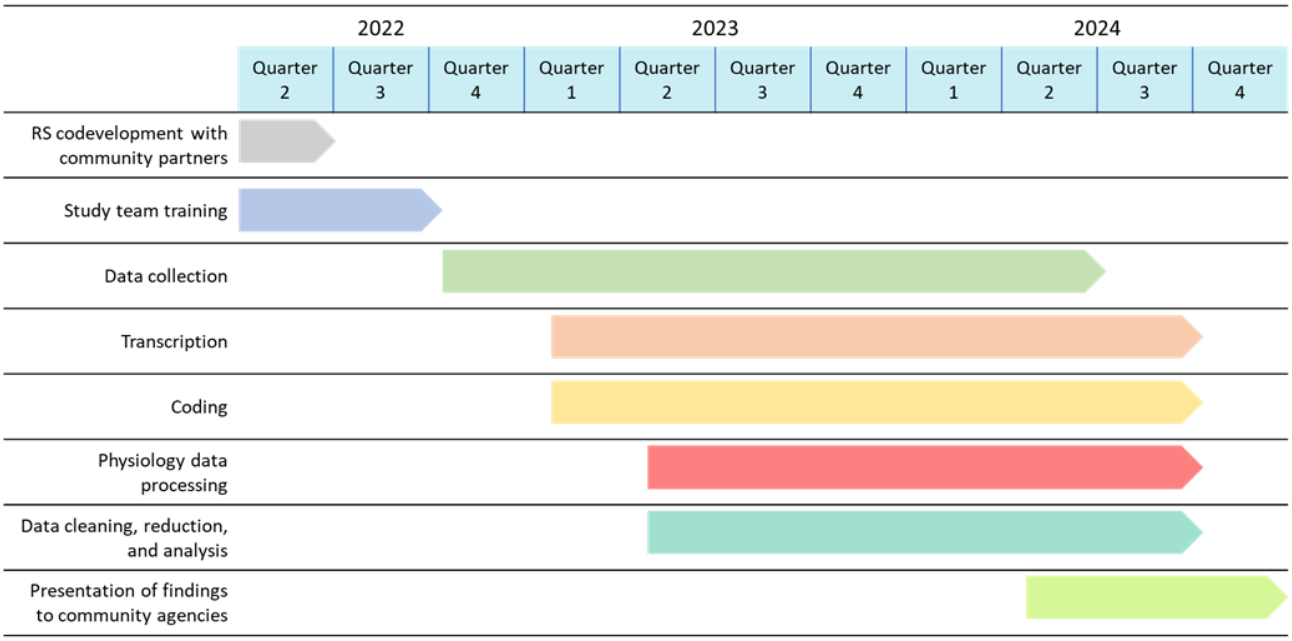
We expect that 80 CSPs will complete this study. The study was approved by the institutional review board in July 2022. CSPs from community agencies began participating in the study in October 2022, with 79 CSPs enrolled by November 2023.

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The data collection process is expected to continue until May 2024 and will include participants from LHA, Dignity Health, Green Madison Park, Orange County Health Promoters, and potentially from additional partner community agencies serving low-income HL communities. Transcription; coding; physiological data processing; and data cleaning, reduction, and analysis will occur throughout the following months and after the completion of data collection (Figure 2). We expect to publish our findings during the fourth quarter of 2024.

We will answer our central research questions using statistical analyses. In addition to these central analyses, we anticipate using qualitative methods to examine savoring sessions and discrimination SOC recordings for the themes that emerge (eg, nature of work, sources of strength or stress, and recurring topics). These qualitative analyses have the potential to reveal important information about HL CSPs, an understudied and important population.

Figure 2. Study timeline. RS: relational savoring.



Discussion

Expected Findings

This study will provide valuable information on the potential of RS to positively impact cardiometabolic health in HL CSPs and, indirectly, in the communities they serve. By improving cardiometabolic health behavior and lowering HRV, RS can reduce the risk of cardiovascular disease in CSPs. Simultaneously, supporting CSPs' well-being and engagement can improve the community's cardiometabolic health. Theoretically, if CSPs are healthy both psychologically and physically, their risk of leaving the workforce is reduced, and more community members will be reached and impacted by CSPs' cardiometabolic health programming. This is particularly important in the context of communities' recovery following the COVID-19 pandemic and considering the unique ability of CSPs to reach community members in ways that the health care system is unable to do. Therefore, RS interventions aimed at CSPs have the potential to influence well-being and cardiometabolic health at both individual and community levels.

Importantly, RS appears to be compatible with both HL CSPs' cultural background and the characteristics of their job. This is evidenced by previous studies reporting greater benefits of RS in HL (vs non-HL) participants [28]. Likewise, CSPs are in constant interaction with community members, mostly in the context of CSPs providing some sort of support (eg, information, resources, and socioemotional support) [17,26]. This may facilitate engagement with the memories preferred for the RS intervention: moments where the participant helped or comforted others (safe haven) or when the participant provided support or encouragement (secure base) [24]. Congruence with both culture and occupation makes RS a particularly promising approach to support this population, especially when considering additional factors pertaining to the delivery of the intervention.

The use of culturally centered language is an important aspect to be considered in the delivery of psychosocial interventions [58]. As previously mentioned, the prompts generated for the RS intervention in this study were conducted in collaboration with our partner community health agency, LHA, to ensure culturally and linguistically appropriate wording. Relatedly, authors have contended that bilingual clinicians, rather than interpreters, are preferred to achieve optimal outcomes [58]. In this study, all participating CSPs are given the option of completing the intervention either in English or Spanish. Accordingly, RS is delivered by bilingual and bicultural trained paraprofessional interviewers, which may facilitate the use of culturally centered language throughout the interventions.

As previously mentioned, in this study, RS is delivered by paraprofessionals. Data from past studies have shown that RS can be administered at high fidelity by interveners who have had a low level of clinical training [28], such as interveners who are undergraduate college students and interveners who are

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promotores (trained community workers without formal education in mental health). This suggests that RS could be effectively implemented in settings without the need of professional health personnel, suggesting great promise as a highly scalable intervention. The data from this study will provide an opportunity to further examine RS intervener training, which could have important implications pertaining to this intervention's potential for dissemination. The fact that we are delivering RS via telehealth further facilitates the interventions' reach and potential impact. The flexibility offered by the remote setup reduces participant burden by avoiding a commute to and from a specific location, while broadening the timeframe in which the intervention can take place throughout the day both for participants and interviewers [59]. Likewise, this allows for participation throughout the country.

If RS is shown to be effective in supporting HL CSPs' cardiometabolic health and psychological well-being, it could be implemented within the broader context of HL community health agencies' personnel (employed and volunteer). In a more encompassing sense, once the CSPs have completed the intervention, they could potentially be trained as facilitators and conduct the intervention with community members. Although the cultural congruence between RS and HL values may boost its efficacy in our priority population, RS has the potential to support CSPs from other non-HL low-income communities. Medically underserved communities that rely heavily on community health agencies, such as those served by the CSPs participating in this study, may be particularly benefited by interventions such as RS that show great portability.

Limitations

We anticipate that our study has limitations, some associated with the fact that the study will be conducted virtually, with participants usually at home or at their job location. Although remote sessions have advantages, it has been reported that it may be necessary to contact additional participants to reach enrollment and compliance goals in remote (vs in-laboratory) studies [60]. This is in addition to the fact that overall research recruitment has been affected since the pandemic. Likewise, the technology (devices, programs, and internet connection) needed to conduct remote studies can be unreliable, as has been found in previous studies [60]. Regarding the cardiovascular data, technical difficulties with the wearable devices and logistical issues in their delivery might result in missing ECG data, particularly given that the participants themselves will be tasked with deploying the devices. Given that one of the broader goals of the project is to provide information regarding the feasibility of the approach, any information yielded through this effort will be useful. However, missing data will preclude us from being able to understand the impact of RS on cardiometabolic health. Finally, we recognize that the planned analyses may be considered simple, yet this is what the sample size will afford. Furthermore, the data we can collect is limited to that which is feasible for the community agencies with whom we collaborate. These compromises accompany community-engaged work.

Conclusions

Although considerable efforts are being made to expand the CSP model, it is necessary to ensure that the CSP workforce is adequately supported. The RS intervention holds immense potential in supporting HL CSPs' overall health, specifically in lowering cardiometabolic risk. As such, RS could be used as a tool to promote resilience and support health in the growing number of CSPs. By supporting CSPs' individual well-being, community health is strengthened. Our study will provide important contributions regarding the therapeutic effects of this psychosocial intervention in HL CSPs, who are particularly susceptible to cardiometabolic risks because of the COVID-19 pandemic, and consequently, on the communities they serve.

Acknowledgments

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Data Availability

As data collection for this project is still ongoing, the complete data sets pertaining to this study are not yet available. Once the study is finalized, the data sets generated during this study will be available from the corresponding author upon reasonable request.

Conflicts of Interest

None declared.

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Abbreviations

CSP: community service provider
ECG: electrocardiogram
HCP: health care professional
HL: Hispanic or Latinx
HRV: heart rate variability
IOS-C: Inclusion of Other in the Self Scale–Community Version
LHA: Latino Health Access
NHW: non-Hispanic White
RS: relational savoring
SOC: stream-of-consciousness
WISER: Web-based Implementation for the Science of Enhancing Resilience

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Protocol

Teaching Adolescents With Type 1 Diabetes Self-Compassion (TADS) to Reduce Diabetes Distress: Protocol for a Randomized Controlled Trial

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Abstract

Background: Adolescents living with type 1 diabetes (T1D) often experience diabetes distress (DD), a construct distinct from depression or anxiety that refers to the negative emotions that arise from living with and managing diabetes. Self-compassion, which involves being open to one’s own suffering and treating oneself with the same care one would show to loved ones, is associated with better psychological and clinical outcomes among individuals with T1D. Self-compassion is a skill that can be taught and therefore represents an opportunity for intervention.

Objective: The overall aim of this study is to assess the effectiveness of a web-based mindful self-compassion for teens (MSC-T) intervention on improving DD, anxiety, depression, diabetes-related disordered eating, and suicidal ideation experienced by youth with T1D (aged between 12 and 17 years) compared with a waitlist control group (standard of care). We will also explore (1) if the effect of the MSC-T intervention changes over time, (2) if the MSC-T intervention has a positive impact on measures of glycemic control, and (3) if the effect of the MSC-T intervention differs based on self-reported gender.

Methods: We will conduct a single-center, parallel-group randomized controlled trial of 140 adolescents with T1D followed for 12 months. Participants will be randomly allocated (using hidden allocation) in a 1:1 ratio to either the MSC-T intervention or the waitlist control group. Our primary outcome is DD, as measured by the Problem Areas in Diabetes-Teen (PAID-T) version at 3 months. Secondary outcomes, assessed at 3 and 12 months, include anxiety (Generalized Anxiety Disorder 7-item [GAD-7]

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scale), depression (Patient Health Questionnaire-9 [PHQ-9]), diabetes-related disordered eating (Diabetes Eating Problem Survey-Revised [DEPS-R] version), and suicidal ideation (using 1 question from the PHQ-9).

Results: Study recruitment began in October 2022 and was completed in March 2023, with a total of 141 participants enrolling. Data collection will be ongoing until March 2024. The first results are expected in June 2024.

Conclusions: This study will be the first randomized trial to assess the effectiveness of the web-based MSC-T intervention on adolescents with T1D. Given that adolescence is a period where individuals are typically required to assume more responsibility for their diabetes care, providing adolescents with the tools they need to better manage the stress that often accompanies T1D management is paramount.

Trial Registration: ClinicalTrials.gov NCT05463874; https://clinicaltrials.gov/study/NCT05463874

International Registered Report Identifier (IRRID): DERR1-10.2196/53935

(JMIR Res Protoc 2023;12:e53935) doi:10.2196/53935

KEYWORDS

anxiety; depression; diabetes distress; disordered eating; mental health; mindful self-compassion; pediatrics; randomized controlled trial; type 1 diabetes

Introduction

Background and Rationale

Adolescence constitutes a critical developmental period during which youth establish their autonomy while grappling with the social, emotional, and physical challenges of becoming young adults. This period represents a time of tremendous vulnerability, during which psychiatric and mood disorders often manifest [1]. Adolescence is even more challenging for youth with type 1 diabetes (T1D), as they contend with the daily challenges of disease management in addition to the developmental challenges inherent to this phase of development.

Diabetes distress (DD) is an emotional construct that refers to the negative emotions that arise from living with and managing diabetes. The majority of youth with T1D experience some level of DD [2,3], with adolescent females experiencing greater DD than males [4-6]. More than one-third of youth with T1D suffer from substantial DD [7]. DD is apparent in youth for many reasons, including fear of stigma from peers [8], feeling overwhelmed by their diabetes regimen [9], and worry of hypoglycemia and long-term complications of a potentially fatal condition [9].

Self-compassion, a positive psychological construct, involves being open to one's own suffering and treating oneself with the same care one would show to loved ones [10]. Youth can have varying degrees of innate self-compassion [11]. Higher levels of self-compassion are associated with lower levels of distress in youth with other chronic medical conditions [12], and it is a psychological characteristic that correlates with favorable outcomes, including psychological well-being, self-care, and hemoglobin A_{1c} (HbA_{1c}) among individuals with diabetes [13].

Among adults with diabetes, an intervention to increase self-compassion resulted in reductions in DD [14]. However, this relationship has yet to be shown in youth with T1D. Self-compassion interventions lead to better psychological well-being and decreased psychopathology in healthy adolescents and those with some chronic conditions [15,16]. Since self-compassion is a modifiable behavior on which one can be trained [17,18], we have a largely untapped opportunity for intervention among youth with T1D.

Mindfulness-based therapy has led to short-term improvements in self-reported stress among adults and emerging adults with T1D [19]. However, a sole focus on mindfulness is not sufficient, as it does not provide enough training around active self-comforting in suffering. Mindfulness also does not provide the aptitude to address the feelings of failure and self-blame that are common among youth with T1D [20]. Therefore, our goal is to study the effects of a psychological intervention combining mindfulness and self-compassion (mindful self-compassion for teens [MSC-T]) on DD among youth with T1D.

Objectives

Our primary objective is to compare DD at 3 months among youth with T1D who participated in the MSC-T intervention to those in a waitlist control group. Our secondary objectives are to (1) compare anxiety, depression, diabetes-related disordered eating, and suicidal ideation at 3 months among youth with T1D who participated in the MSC-T intervention with those in the waitlist control group; and (2) compare DD, anxiety, depression, diabetes-related disordered eating, and suicidal ideation at 12 months among youth with T1D who participated in the MSC-T intervention with those in the waitlist control group. Finally, our exploratory objectives are to (1) explore if the effect of the MSC-T intervention changes over time throughout the 12-month follow-up period, (2) compare glycemic control (HbA_{1c} and time in range) among adolescents with T1D who participated in the MSC-T intervention to those in the waitlist control group, and (3) explore if the effect of the web-based MSC-T intervention on DD differs based on self-reported gender.

Hypotheses

We hypothesize that adolescents who participate in the MSC-T intervention will report lower DD, anxiety, depression, diabetes-related disordered eating, and suicidal ideation at 3 months compared with the waitlist control group.

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Methods

Ethical Considerations

This study was reviewed and approved by the local Research Ethics Board at the Children's Hospital of Eastern Ontario (CHEO; protocol 22/09E, approved July 17, 2022). Following an introduction from a member of the participant's circle of care, in line with requirements outlined in the Personal Health Information Protection Act, a member of the research team will obtain written informed consent, either in person or remotely, using our REDCap (Research Electronic Data Capture; Vanderbilt University) system [21,22]. Participants will consent on their own behalf and will be compensated with gift cards for completing the study questionnaires (US $15 for baseline, US $20 for week 8, US $30 for month 3, US $30 for month 6, and US $35 for month 12) and up to 15 volunteer hours.

Study Design

We will conduct a single-center, parallel-group randomized controlled trial assessing the effect of a web-based MSC-T intervention on DD in adolescents with T1D followed for 12 months, compared with a waitlist control group (standard of care).

Participants and Recruitment

We will recruit 140 adolescents with T1D, aged between 12 and 17 years, from the Diabetes Clinic at CHEO in Ottawa, Ontario, Canada.

Inclusion and Exclusion Criteria

The inclusion criteria and exclusion criteria for this study are presented in Textbox 1.

Textbox 1. The inclusion and exclusion criteria.

Inclusion criteria

- Aged between 12 and 17 years.
- Diagnosed with type 1 diabetes (T1D) ≥6 months before enrollment.
- Ability to provide informed consent.

Exclusion criteria

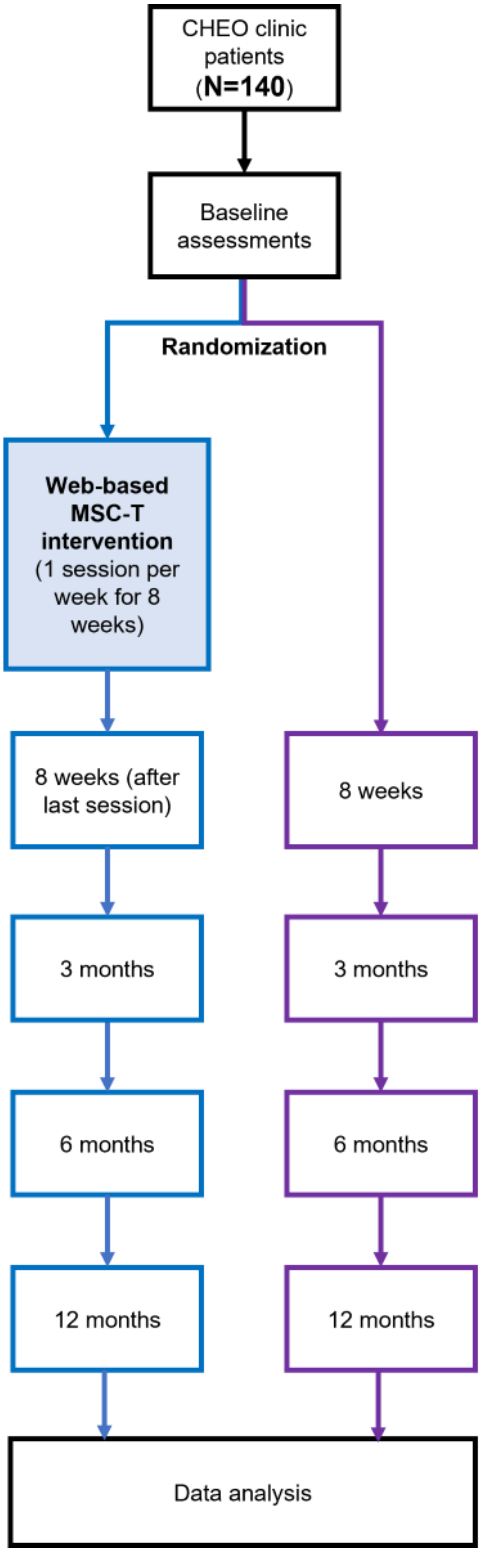
- Inability or unwillingness to provide informed consent.
- Inability to speak English with enough fluency to complete all study-related tasks.
- Presence of an intellectual disability that would preclude participation in the mindful self-compassion for teens (MSC-T) intervention, as assessed by the treating physician.
- A lifetime diagnosis of a psychotic or bipolar disorder given by a clinician (these often involve intensive treatments with psychological and pharmacologic implications, which may confound our results).
- Presence of acute suicidality at the time of enrollment.
- Active participation in another mental health intervention trial.

Trial Intervention

As shown in Figure 1, participants from the diabetes clinic at CHEO will be randomized to the MSC-T intervention group or the waitlist control group (standard of care).

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Figure 1. Schematic overview of the study. CHEO: Children's Hospital of Eastern Ontario; MSC-T: mindful self-compassion for teens.



Intervention Group

The MSC-T intervention (Textbox 2) teaches the participants to be open to, rather than disconnected from, their own suffering and treat themselves with the same care they would show to a friend [10]. The program consists of 8 weekly interactive sessions, each lasting 1.5 hours (a total of 12 hours). The program will be led by our collaborators (KB and AL), who are trained, experienced MSC-T instructors. Each session will begin with a brief mindful art activity, which provides a transition to the class. Classes include developmentally appropriate hands-on exercises, videos, games, mindful movement, music meditation, and between-class practice assignments to solidify practices. The session content and structure were reviewed by our people with lived experience collaborators (SH and OI).

MSC-T program fidelity will be determined by (1) assessing the change in self-compassion between baseline and 8 weeks and (2) assessing if the required topics for each MSC-T session

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were covered and activities performed. Self-compassion will be assessed using the Self-Compassion Scale for Youth, a psychometrically valid and reliable measure of self-compassion for adolescents [23]. To ensure the respective topics are appropriately covered in the MSC-T sessions, a member of the study team will complete a fidelity assessment during each session.

Participants' satisfaction and acceptability of the intervention will be evaluated using an intervention satisfaction survey, similar to what has been previously used to determine satisfaction with the web-based MSC-T program [18].

Textbox 2. Program summary (sessions and topics) for mindful self-compassion for teens (MSC-T) intervention.

Week 1

- Discovering mindful self-compassion: introduction to concepts of mindfulness and self-compassion; safety measures for class established; and both informal and formal practices are introduced.

Week 2

- Paying attention on purpose: concepts of mindfulness, wandering mind, and default mode network are discussed; mindful eating, "soles of the feet," and "palm of the hand" meditations are presented.

Week 3

- Lovingkindness: "lovingkindness" is defined and lovingkindness practice is introduced; participants create their own lovingkindness phrases; adolescent brain development is discussed.

Week 4

- Self-compassion: this exercise encourages teenagers to turn from the "inner critic" toward the "compassionate voice," and music meditation is introduced.

Week 5

- Self-compassion versus self-esteem: the difference between these 2 is elucidated, and the perils of social comparison are discussed.

Week 6

- Living deeply: core values exercise; "giving and receiving" meditation is introduced.

Week 7

- Managing difficult emotions: "soften, soothe, and allow" practice is introduced; tools to contend with anger and unmet needs are practiced; and 2 developing systems of the adolescent brain are explained.

Week 8

- Embracing your life with gratitude: gratitude and self-appreciation practices are presented, and the wrap-up of the course takes place through writing a letter to oneself.

Waitlist Control Group

Participants in the wait-list control group will receive standard-of-care treatment as usual. Following the conclusion of the experimental protocol, participants in this group will be given the opportunity to complete the 8-week web-based MSC-T program.

Randomization Procedures

We will use the randomization module in REDCap [21,22] to allocate participants to their group. The randomization table will be created by a study team member who is not directly involved in patient recruitment or data collection using R (R Core Team) [24]. The trial coordinator will generate the allocation for each participant following obtaining informed consent and completion of the baseline assessments (ie, there will be hidden allocation).

Participants will be randomly allocated to either the MSC-T intervention group or the waitlist control group using a 1:1 ratio block randomization. We will stratify each block by age group (12-14 years [early adolescence] or 15-17 years [middle adolescence]). The cohort will be divided by these age groups to deliver the intervention with the goal of fostering a developmentally appropriate and open environment. Stratification by age group is therefore necessary to ensure an equal age distribution between the treatment groups, since the developmental age of a participant could impact their response to the intervention [25]. We will also randomly vary the block size, with blocks of either 6 or 8, to prevent prediction of group allocation as participants are accrued [26].

Data and Outcome Measures

We will collect the following demographic information at baseline: age, postal code (to determine socioeconomic status using neighborhood-level material and social deprivation indices [27,28]), optional self-reporting of gender identity (participants will be presented with a range of options [29,30]; Table 1), race or ethnicity, and indigeneity [31] (Table 2), and participant's

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social context (living arrangements, etc). Medical history will be collected at baseline, and at intervals, it will be reviewed at each follow-up visit to determine if participants have been newly diagnosed with a serious mental illness (exclusion or withdrawal criteria).

Table 1. Gender reporting options to be presented to participants. The presented gender reporting options are in line with accepted standards for determining gender identity in research [29,30]. Participants will be informed that the provision of this information is voluntary and that they will be allowed to select more than one.

Self-reported option	Analysis group
Male	Male
Female	Female
Transgender	Will depend on if another option is selected
Transgender boy or transgender male	Male
Transgender girl or transgender female	Female
Genderqueer	Gender diverse
Gender expansive	Gender diverse
Androgynous	Gender diverse
Nonbinary	Gender diverse
Two-spirited	Gender diverse
Third gender	Gender diverse
Agender	Gender diverse
Not sure or questioning	Gender diverse
Other	Will depend on free text
Prefer not to say	Will be excluded from gender analysis

Table 2. Ethnicity and Indigenous identity questions and responses to be presented to participants. The categories are in line with accepted standards for reporting ethnicity from the Canadian Institute for Health Information [31]. Participants will be informed that the provision of this information is voluntary and that they will be allowed to select more than one. Participants will be asked to answer the following question: "In our society, people are often described by their race or racial background. These are not based in science, but our race may influence the way we are treated by individuals and institutions, and this may affect our health and health outcomes related to diabetes. Which category or categories best describe you? Check all that apply."

Response category	Examples
Black	African, African Canadian, and Afro-Caribbean descent
East Asian	Chinese, Japanese, Korean, and Taiwanese descent
Indigenous (First Nations, Inuk/Inuit, Métis)	First Nations, Inuk or Inuit, and Métis descent
Latin American	Hispanic or Latin American descent
Middle Eastern	Arab, Persian, and West Asian descent (eg, Afghan, Egyptian, Iranian, Kurdish, Lebanese, and Turkish)
South Asian	South Asian descent (eg, Bangladeshi, Indian, Indo-Caribbean, Pakistani, and Sri Lankan)
Southeast Asian	Cambodian, Filipino, Indonesian, Thai, Vietnamese, or other Southeast Asian descent
White	European descent
Other category	Includes options not described above
Do not know	N/A[a]
Prefer not to answer	N/A

[a]N/A: not applicable.

Our primary outcome, DD, has been shown to be the psychological construct most related to metabolic outcomes in adolescents with T1D [3]. DD will be measured using the Problem Areas in Diabetes-Teens (PAID-T) version [32], a validated measure to evaluate diabetes-specific emotional distress in adolescents with high internal consistency (Cronbach α=.96) [32]. It consists of 26 items, each scored on a 6-point ordinal scale, allowing for the calculation of an overall distress score of 26-156, with scores of <70, 70-90, and >90 representing none-to-mild, moderate, and severe DD, respectively [33]. The

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PAID-T has excellent psychometric properties [34], is sensitive to change from behavioral intervention [35], and is a commonly used measure to assess DD in adolescents [7,36].

Our secondary outcomes are anxiety, depression, diabetes-related disordered eating, and suicidal ideation. Symptoms of anxiety will be measured using the Generalized Anxiety Disorder 7-item (GAD-7) scale, a self-report tool to detect clinically significant anxiety symptoms. The GAD-7 is scored from 0-21, with 0-4, 5-9, 10-14, and 15-21 indicating minimal, mild, moderate, and severe anxiety symptoms, respectively [37]. It has been validated in adolescents [38] and has previously been used to assess adolescents with T1D [39,40].

Symptoms of depression will be measured using the Patient Health Questionnaire-9 (PHQ-9) by self-report [41]. The PHQ-9 is a valid and reliable screening tool for identifying adolescents meeting the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for major depression [41]. Scores range from 0-27, and in adolescents, scores of 0-4, 5-10, 11-14, 15-19, and ≥20 indicate absence of, mild, moderate, moderately severe, and severe depression, respectively [41].

Symptoms of diabetes-related disordered eating will be measured using the Diabetes Eating Problem Survey-Revised (DEPS-R) version [42], a diabetes-specific measure of disordered eating symptoms that is valid for use in adolescents with T1D [42]. The DEPS-R is scored from 0-80, with higher scores indicating more disordered eating behaviors, and a score of ≥20 is suggestive of disordered eating behaviors [42]. The use of a diabetes-specific tool to measure disordered eating is important, as generic measures may overestimate the prevalence of disordered eating symptoms given that diabetes management involves an emphasis on food intake and carbohydrate counting and that insulin restriction is not captured in generic measures [43].

Suicidal ideation will be assessed using 1 question on the PHQ-9, which asks the respondent if they have had thoughts that they would be better off dead or of hurting themselves in the previous 2 weeks. This question is scored on a scale from 0 (not at all) to 3 (nearly every day). In line with previous use of the PHQ-9 [44], we will consider any score of >0 to be indicative that suicidal ideation is present.

Our exploratory outcomes are the effects of time, HbA_{1c}, time in range, and effect of gender. We will assess whether the effect of the MSC-T intervention on DD changes over time by exploring the interaction of time (ie, study time point) with DD. We will assess both HbA_{1c} and time in range, as not all our clinic patients wear a continuous glucose monitor (CGM), which is necessary to calculate time in range (>70% of our clinic patients wear a CGM).

HbA_{1c} is a measure of the average blood glucose levels over the previous 3 months and is a routinely followed biochemical marker used to gauge metabolic control in individuals with T1D. We will explore changes in HbA_{1c} over the duration of our trial, as mental health morbidity has been associated with higher HbA_{1c} levels [45,46]. Time in range is a metric that denotes the proportion of time that a person's glucose level is within a desired target range, calculated using a CGM. A total of 14 days of data from CGM provides a good approximation of glucose data [47]; time in range will allow us to evaluate the glucose control at the various time points. We will collect CGM data at all study visits. Given the web-based nature of the trial combined with the high proportion of our clinic population that uses CGM, which is a more reliable measure of metabolic control [48], we will minimize additional blood collection by recording results from clinically collected HbA_{1c} at baseline and 1 year.

Safety Parameters and Description of Risk

All the mental health outcomes being assessed are self-reported by participants directly into the study database. The principal investigator or delegate and study coordinator will be immediately alerted through an automated REDCap algorithm when (1) an individual self-reports as having suicidal ideation >0 on question 9 of the PHQ-9 or (2) an individual intentionally does not fill out the suicidality question on the PHQ-9. The principal investigator, delegate, or study coordinator will contact the participant's endocrinologist or the endocrinologist on call, who will conduct a same-day risk assessment using the Ask Suicide-Screening Questionnaire (ASQ) [49]. If the participant is judged to have acute suicidality or suicidal ideation as per the ASQ, the assessor will either suggest a referral to the emergency department or contact the psychiatrist on call, who will suggest clinical follow-up as appropriate. The assessor will report the results of the ASQ screening back to the study coordinator within 1 day. Participants with acute suicidality as per the ASQ will then be excluded or withdrawn from the study.

Trial Management

To foster an environment where the participants feel comfortable, the web-based MSC-T intervention will be conducted with groups of 12-18 participants of the same age group [18]. To ensure that there is no exclusion of youth based on socioeconomic status or access to technology, participants who do not have a computer, laptop, tablet, or webcam to attend the web-based sessions will be loaned a study tablet, and mobile internet devices will be provided to those who do not have high-speed internet at home. All participants will receive a subsidy to offset the cost of increased home internet use for the duration of the study. To maximize participant engagement, the trial coordinator will provide weekly reminders for the duration of the program through SMS text messages or email, depending on the participant's preference.

At each follow-up visit (Table 3), the study coordinator will review the interim medical history using a study case report form and have the participants complete the study questionnaires.

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Table 3. Schedule of activities.

Procedures	Baseline	8 weeks (±2 weeks)	3 months (±2 weeks)	6 months (±4 weeks)	12 months (±4 weeks)
Informed consent	✓				
Baseline demographics questionnaire	✓				
Problem Areas in Diabetes-Teen version (diabetes distress)	✓	✓	✓	✓	✓
Self-compassion Scale for Youth (self-compassion)	✓	✓	✓	✓	✓
Intervention satisfaction survey[a]		✓			
Patient Health Questionnaire (depression and suicidality)	✓	✓	✓	✓	✓
Generalized Anxiety 7-item scale (anxiety)	✓	✓	✓	✓	✓
Diabetes Eating Problem Survey-Revised version (eating disorders)	✓	✓	✓	✓	✓
Hemoglobin A_{1C}	✓				✓
Time in range	✓	✓	✓	✓	✓
Review interval medical history	✓	✓	✓	✓	✓

[a]The intervention satisfaction survey will be given to the participants in the mindful self-compassion for teens (MSC-T) intervention group only.

Engagement of People With Lived Experience of T1D

To ensure that this study is feasible, interesting, and relevant to youth with T1D, we have engaged and plan to continue to engage with people with lived experience throughout all stages of the study. We have 2 people with lived experience as collaborators (SH and OI), both of whom are former patients of the CHEO diabetes clinic, who will help spearhead engagement strategies. Multimedia Appendix 1 provides more information about our people with lived experience engagement activities.

Equity, Diversity, and Inclusion Considerations

We have considered gender and diversity in all aspects of this study, from recruitment through to knowledge translation. Multimedia Appendix 2 [4-6,50-52] provides more information about our equity, diversity, and inclusion considerations.

Statistical Plan

Sample Size

Our target sample size is 70 participants per group (140 participants total). This sample size achieves 80% power to detect group differences of 12 points or more [53] using a 2-sided significance level of 5% [26]. In this calculation, we assumed a mean PAID-T score of 73 in the waitlist control group with a SD of 26 [54]. A 30% attrition rate, based on previous relevant trials [55], was also considered.

Statistical Analysis

For the MSC-T and waitlist control groups, the following will be summarized using descriptive statistics: participant baseline characteristics, mental health outcome measures, and self-compassion score responses from each study time point, and for the MSC-T group, we will summarize the results of the intervention satisfaction survey and session attendance.

Our main analyses will be performed based on the intention-to-treat principle. We will also complete per-protocol analyses where we will exclude participants based on nonadherence to the intervention (defined as attending fewer than 6 out of 8 MSC-T sessions, in line with previous work done using MSC-T [56]).

Primary Analysis for the Primary Outcome

The primary outcome will be analyzed using a linear regression model adjusted for age and baseline DD to assess the effect of the MSC-T intervention on DD at the 3-month time point. We will adjust for age to account for the variability in the developmental stage of each participant, which may impact their response to the mindful self-compassion (MSC) program. We will also account for baseline levels of DD as we are assessing the change in DD from baseline to 3 months.

Secondary Bayesian Analysis for the Primary Outcome

Although our trial is powered to detect a moderate effect size of 12 points on the PAID-T, we acknowledge that a smaller effect size is still clinically meaningful. Bayesian methods focus on providing plausible values for the intervention effect that are compatible with both the observed data and previous knowledge and beliefs. Bayesian analysis enables the use of both noninformative priors that minimize the influence of priors on the statistical inference and informative priors that are guided by existing evidence or a range of collective expertise from investigators regarding the belief or skepticism of the intervention's efficacy. Thus, a secondary Bayesian analysis will complement our frequentist analysis in the interpretation of our randomized trial results [57]. Following existing Bayesian analysis reporting guidelines [58], we will conduct a prespecified Bayesian linear regression analysis to examine the probability that the MSC-T intervention reduces DD in a clinically meaningful way compared with the control group based on the trial results.

The main objective of the Bayesian analysis is to determine the posterior probability (also known as an updated probabilistic belief) that the MSC-T intervention (1) affects PAID-T scores

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and (2) reduces DD by between-group differences on the PAID-T of 7-15 points (eg, effect size of 0.27-0.5), given the prior distributions of the treatment effect and the observed data from the trial. We considered an effect size of 0.27 as the minimum threshold for potential clinical relevance, given the strong relationship between DD and clinical outcomes [3], and based on the expert opinions of our team of experienced diabetologists.

To reflect our uncertainty around the effect of the MSC-T intervention, we will use a range of priors representing varying degrees of enthusiasm and skepticism (Multimedia Appendix 3). In the Bayesian regression analysis, noninformative priors will be used for nuisance parameters, including the regression intercept terms and the parameters that do not quantify the MSC intervention effectiveness. The convergence of Bayesian estimation will be examined using trace plots and the R^ convergence index with a cut-off of 1.01 [59]. With the trial data, we will estimate the 95% credible intervals using Markov chain Monte Carlo (MCMC) sampling techniques with at least 2 parallel chains [58] and report the estimated posterior probabilities for different magnitudes of treatment effects as specified in Multimedia Appendix 3. The analysis will be conducted in R statistical software [24], and Bayesian analysis will be performed using Stan MCMC (Stan Development Team) [60].

Analyses for Secondary Outcomes

Linear regression models and generalized linear regression models (for binary or categorical secondary outcomes), adjusting the same covariates as the primary analysis, will be used to assess the effect of the MSC-T intervention on our secondary outcomes of (1) depression, anxiety, disordered eating symptoms, and suicidal ideation at 3 months; and (2) DD, depression, anxiety, disordered eating symptoms, and suicidal ideation at 12 months.

Analyses for Exploratory Outcomes

To explore the effect of the MSC-T program on DD over time, we will use the 3-, 6-, and 12-month data to fit a linear mixed effects model, adjusted for time, age, baseline DD, an interaction term for time and group, and a random intercept (to account for repeated measures).

Exploratory outcome HbA_{1c} at 12 months will be modeled in a linear regression adjusted for age and baseline HbA_{1c}. Linear mixed effects models, adjusted for age, baseline time in range, and a random intercept, will be used to assess the effect of the MSC-T intervention on the repeated measure time in range. Interaction terms between group and gender will be included in a separate model to investigate how the MSC-T intervention differs based on self-reported gender (collapsed to male, female, and gender-diverse for the purposes of analysis) at the primary end point.

Sensitivity Analysis on Missing Data

Differences in characteristics between participants with no recorded outcome measurements and those with at least 1 recorded follow-up measurement will be assessed. For participants with at least 1 available data point, we will input missing outcome data following best-case and worst-case scenarios, where best-case is defined as successfully achieving clinically meaningful improvement in PAID-T scores and worst-case is defined as failure to achieve clinically meaningful improvement in PAID-T scores.

Results

Study recruitment began in October 2022 and was completed in March 2023, with 141 participants enrolling in the trial. Data collection will be ongoing until March 2024. The first results are expected in June 2024.

Discussion

Expected Findings

In this study, we will evaluate MSC-T as a way to improve DD and mental health outcomes among adolescents with T1D. We will also explore the impact of the MSC-T intervention on glycemic control. In adolescents with T1D, psychological interventions have largely targeted improvement in diet and insulin regimen adherence and strategies to cope with specific stressors [61]. While some approaches, including cognitive behavioral therapy (CBT), have shown promise for improving diabetes management, there is limited evidence that these traditional approaches translate to improved coping with distress [61]. A recent review [62] on the use of CBT for stress and coping in youth with T1D showed conflicting results, with a number of studies showing no improvement in stress [63] or DD [64]. CBT may also highlight potential causes of distress related to diabetes that the teenager has not yet considered without providing adequate skills and practices to manage these emotions [64].

We hypothesize that the combination of mindfulness and self-compassion practices in the MSC-T program will result in improved DD and mental health outcomes for adolescents enrolled in the program. We also anticipate that these improvements may translate to improved clinical outcomes through glycemic control.

Strengths and Limitations

To our knowledge, this is the first randomized controlled trial using the MSC-T intervention to address DD in adolescents with T1D. One of our instructors (KB) is a person with lived experience of T1D; having an instructor who is also a person with lived experience of the condition has been identified as a key component in previous studies using MSC interventions [56]. The longer-term follow-up of 12 months is also a clear strength. Throughout adolescence, youth are typically required to become more independent with their diabetes self-management while receiving diminished support from their caregivers. Mental health morbidity, including DD, is associated with poor glycemic control, diabetic ketoacidosis, and hypoglycemia in youth with T1D [7,65,66]. The MSC-T program will help adolescents with T1D develop skills to better cope with their emotions around managing their diabetes.

There are, however, some potential limitations to this study. The trial is single-blind; participants and the trial coordinator

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are not blinded to their assignment group. However, the statistician conducting the primary analysis will be blinded to participant allocation to the MSC-T intervention or waitlist control group. Given that the intervention is web-based, it does require the use of high-speed internet and a device that has webcam functionality, which may make it difficult for some youth to attend should these items be lacking. However, in Canada and the United States, over 96% [67] and 95% [68] of youth and emerging adults own smartphones, respectively, suggesting that if the program were to be scaled nationally or internationally, attending such a program would be feasible for the majority of North Americans.

Conclusions

Our proposed research has the potential to lower DD among youth with T1D by increasing their mindfulness-based self-compassion. We expect that our work will enhance the psychological well-being of youth with T1D, providing them with self-compassion skills to face adversity as they develop into young adults, ultimately leading them to live happier and healthier lives. If effective, further research should be done toward the implementation of MSC-T into standard clinical care for youth with T1D through partnerships with diabetes organizations.

Acknowledgments

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Authors' Contributions

M-ER and SD designed the trial, and together with AA, BMF, EBG, GSG, KK, YO, SL, JS, NS, and CZ, they contributed to the recruitment plan, selection of outcome measures, safety plan, trial management plan, and data analysis plan. KB developed the intervention and, together with AL, administered it. CP attended all intervention sessions to ensure participant safety in her capacity as a licensed psychologist. SH and OI reviewed all aspects of the protocol through their lens as people with lived experience. All authors read and approved the final manuscript and have agreed to be accountable for all aspects of the work.

Conflicts of Interest

KB is a cocreator of Mindful Self-Compassion for Teens. CZ reports grants to the institution from Tandem Diabetes Care and Advisory Board membership for Dexcom. M-ER reports grants to the institution from Ascendis Biopharma, Ipsen Biopharmaceuticals, and QED Therapeutics, Inc. The remaining authors have nothing to disclose.

Multimedia Appendix 1
Plan for engagement of people with lived experience (PWLE) of type 1 diabetes.
[DOCX File , 13 KB - resprot_v12i1e53935_app1.docx]

Multimedia Appendix 2
Equity, diversity, and inclusion (EDI) considerations.
[DOCX File , 51 KB - resprot_v12i1e53935_app2.docx]

Multimedia Appendix 3
Characteristics of reference prior probability distributions representing prior beliefs about primary outcome effect size.
[DOCX File , 14 KB - resprot_v12i1e53935_app3.docx]

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Abbreviations

ASQ: Ask Suicide-Screening Questionnaire
CBT: cognitive behavioral therapy
CGM: continuous glucose monitor
CHEO: Children's Hospital of Eastern Ontario
DD: diabetes distress
DEPS-R: Diabetes Eating Problem Survey-Revised

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DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
GAD-7: Generalized Anxiety Disorder 7-item
HbA1c: hemoglobin A1c
MCMC: Markov chain Monte Carlo
MSC: mindful self-compassion
MSC-T: mindful self-compassion for teens
PAID-T: Problem Areas in Diabetes-Teen
PHQ-9: Patient Health Questionnaire-9
REDCap: Research Electronic Data Capture
T1D: type 1 diabetes

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Protocol

Follow-Up of Patients With Axial Spondyloarthritis in Specialist Health Care With Remote Monitoring and Self-Monitoring Compared With Regular Face-to-Face Follow-Up Visits (the ReMonit Study): Protocol for a Randomized, Controlled Open-Label Noninferiority Trial

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Abstract

Background: Patients with chronic inflammatory joint diseases such as axial spondyloarthritis have traditionally received regular follow-up in specialist health care to maintain low disease activity. The follow-up has been organized as prescheduled face-to-face visits, which are time-consuming for both patients and health care professionals. Technology has enabled the remote monitoring of disease activity, allowing patients to self-monitor their disease and contact health care professionals when needed. Remote monitoring or self-monitoring may provide a more personalized follow-up, but there is limited research on how these follow-up strategies perform in maintaining low disease activity, patient satisfaction, safety, and cost-effectiveness.

Objective: The Remote Monitoring in Axial Spondyloarthritis (ReMonit) study aimed to assess the effectiveness of digital remote monitoring and self-monitoring in maintaining low disease activity in patients with axial spondyloarthritis.

Methods: The ReMonit study is a 3-armed, single-site, randomized, controlled, open-label noninferiority trial including patients with axial spondyloarthritis with low disease activity (Ankylosing Spondylitis Disease Activity Score <2.1) and on stable treatment with a tumor necrosis factor inhibitor. Participants were randomized 1:1:1 to arm A (usual care, face-to-face visits every sixth month), arm B (remote monitoring, monthly digital registration of patient-reported outcomes), or arm C (patient-initiated care, self-monitoring, no planned visits during the study period). The primary end point was disease activity measured with the

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Ankylosing Spondylitis Disease Activity Score, evaluated at 6, 12, and 18 months. We aimed to include 240 patients, 80 in each arm. Secondary end points included other measures of disease activity, patient satisfaction, safety, and cost-effectiveness.

Results: The project is funded by the South-Eastern Norway Regional Health Authority and Centre for the treatment of Rheumatic and Musculoskeletal Diseases (REMEDY), Diakonhjemmet Hospital, Norway. Enrollment started in September 2021 and was completed with 242 patients by June 2022. The data collection will be completed in December 2023.

Conclusions: To our knowledge, this trial will be among the first to evaluate the effectiveness, safety, and cost-effectiveness of remote digital monitoring and self-monitoring of patients with axial spondyloarthritis compared with usual care. Hence, the ReMonit study will contribute important knowledge to personalized follow-up strategies for patients with axial spondyloarthritis. These results may also be relevant for other patient groups with inflammatory joint diseases.

Trial Registration: ClinicalTrials.gov NCT05031767; hpps://www.clinicaltrials.gov/study/NCT05031767

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KEYWORDS

spondyloarthritis; inflammatory joint disease; telemedicine; remote monitoring; remote care; self-management; randomized controlled trial; cost-effectiveness

Introduction

Background

Chronic inflammatory joint diseases (IJDs), including axial spondyloarthritis (axSpA), rheumatoid arthritis (RA), and psoriatic arthritis (PsA), often affect young patients. Most patients are treated with disease-modifying antirheumatic drugs (DMARDs). These patients are scheduled for regular follow-up visits in specialist health care, which can be time-consuming, especially for those active in the workforce. Patients have also reported that in this mode of regular follow-up the health care professionals (HPs) only see a narrow timeframe of their disease course, with important changes often taking place between visits [1].

Details on axSpA

The primary effects of axSpA occur in the sacroiliac joints and the spine, where the main concerns are back pain and spinal stiffness. Some patients experience arthritis and enthesitis and may also have extramusculoskeletal manifestations, such as uveitis, psoriasis, and inflammatory bowel disease [2]. The prevalence of axSpA is 0.3% to 1.4%, and the onset is typically in the third decade of life, with an equal gender distribution [3]. As a consequence of spinal inflammation, structural damage may occur, resulting in limited spinal mobility [3]. Furthermore, high disease activity may affect health-related quality of life with work impairment and a substantial socioeconomic load [4].

The treatment of axSpA is individualized according to the patient's needs, disease manifestations, and level of inflammation. The treatment goals include symptomatic relief, maintaining flexibility of the spine, maintaining or improving function and work ability, and preventing disease-related complications [2,5]. First-line treatment consists of exercises and the use of nonsteroidal anti-inflammatory drugs (NSAIDs). Regular exercises and physical activity are recommended for symptom relief and reduced disease activity [5,6]. A recent study demonstrated that patient-reported flares are associated with impaired physical activity [7]. NSAIDs also reduce pain and stiffness, with doses adjusted to symptom severity [2,5]. Second-line treatment includes the use of DMARDs, usually tumor necrosis factor inhibitors (TNFis) [5], which in most patients leads to a rapid, substantial, and sustained improvement of symptoms, inflammation, and physical function [2], enabling participation in the workforce and in daily activities [4,5].

Follow-up of patients with axSpA treated with TNFi includes long-term monitoring of disease activity, clinical findings, and laboratory tests, with a treat-to-target strategy usually aimed at inactive disease or low disease activity as measured by the Ankylosing Spondylitis Disease Activity Score (ASDAS) <2.1 [5,8,9]. Patients are reviewed regularly during face-to-face visits by a rheumatologist or a rheumatology nurse in specialist health care. The frequency of monitoring is individualized depending on the disease severity. At most clinics, the patients can request extra visits when they experience increased disease activity (flares).

In recent years, technology has opened up for remote monitoring through the digital collection of patient-reported outcomes (PROs) and the use of tools for supporting medical decisions. Patients may receive remote care or self-monitor their disease and receive remote support from HPs when needed [10]. Together with treat-to-target strategies, remote care may improve clinical outcomes [11]. The timing of face-to-face or digital visits may be individualized [11], which may increase patient satisfaction. Patients living in both rural and urban areas with limited access to health care services may experience increased access to health care services if they are offered digital follow-up [12,13]. Remote monitoring and self-monitoring may be a step toward more personalized and potentially better follow-up of patients with axSpA. Remote care may reduce the need for visits to specialist health care and thus be cost-effective.

Prior Work

The effect, user satisfaction, and resource use of new follow-up regimens should be evaluated before their implementation in usual clinical care. Previous studies on remote monitoring in patients with other chronic diseases, such as cardiovascular disease, lung disease, and diabetes mellitus, have shown

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beneficial results on clinical outcomes [14]. However, a recent systematic review found little or no effect of resource use in specialist health care services [15].

There is limited research on the remote follow-up of IJDs [16-18]. A few studies on patients with RA and PsA in low disease activity or remission found similar disease activity in patients followed by remote monitoring and usual care [10,19], and patient satisfaction with remote care was high [1,20]. Furthermore, patients have reported that self-monitoring of the disease enables them to see the connection between behavioral factors (eg, taking medications and lifestyle choices) and disease concerns [1]. However, a survey regarding the use of digital technology during the COVID-19 pandemic revealed that HPs considered remote care inferior to face-to-face visits [21]. In a recent study, both patients and HPs considered remote care inferior to face-to-face visits, but remote care was convenient for patients in relation to reduced traveling and waiting times [22]. In studies on patients with RA and PsA, the relative cost-effectiveness has shown conflicting results [23,24]. There is limited research on the sustainability of remote follow-up and self-monitoring in patients with axSpA.

Aim of This Study

The primary aim of the Remote Monitoring in Axial Spondyloarthritis (ReMonit; Multimedia Appendix 1) study is to determine whether 2 new follow-up strategies for patients with axSpA—remote monitoring or patient self-monitoring—are noninferior to the conventional follow-up strategy with regular prescheduled face-to-face visits to maintain low disease activity over time. Second, we aim to evaluate patient satisfaction, HP satisfaction, safety, and cost-effectiveness of the 3 follow-up strategies (Figure 1). Our hypothesis is that remote monitoring and patient self-monitoring are noninferior to traditional follow-up with regular face-to-face visits in maintaining low disease activity and that these new follow-ups are associated with patient and HP satisfaction, safety, and cost-effectiveness.

Figure 1. Logo of the Remote Monitoring in Axial Spondyloarthritis (ReMonit) study.

Comprehensive data collection allows for analyses of willingness to use, adherence to remote care among patients, fluctuations in disease activity, and associations between disease activity and physical activity.

Methods

Study Design

The ReMonit study is a 3-armed, single-center, parallel-group, noninferiority randomized controlled trial (RCT) designed to investigate whether 2 new follow-up strategies for patients with axSpA are noninferior to conventional follow-up for maintaining stable low disease activity (NCT05031767; registered on September 2, 2021).

Study Settings, Population, and Recruitment

Patients were recruited between September 2021 and June 2022 from the outpatient clinic at the Division of Rheumatology and Research, Diakonhjemmet Hospital, Oslo, Norway. Eligible patients (axSpA with stable treatment with TNFi and low disease activity [ASDAS <2.1]) were identified from the waiting list for regular follow-up visits and were sent information about the ReMonit study and a consent form, along with an invitation to a visit with a rheumatologist. At the visit, patients willing to participate were screened according to the inclusion and exclusion criteria (Textbox 1).

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Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Participants were eligible to be included in the study only if all the following criteria applied
  - Male or female aged >18 years of age at screening
  - Diagnosis of axial spondyloarthritis (axSpA) according to the Assessment of Spondyloarthritis International Society classification criteria for axSpA [25]
  - Stable medical treatment with tumor necrosis factor inhibitors for the last 6 months
  - Inactive disease or low disease activity (Ankylosing Spondylitis Disease Activity Score <2.1) at inclusion
  - Capable of understanding the Norwegian language and of providing informed consent.

Exclusion criteria

- Medical conditions
  - Major comorbidities, such as severe malignancies, severe diabetes mellitus, severe infections, uncontrollable hypertension, severe cardiovascular disease (New York Heart Association class III or IV), severe respiratory diseases, or cirrhosis
  - Indications of active tuberculosis
  - Pregnant or nursing
- Diagnostic assessments
  - Abnormal renal function, defined as serum creatinine >142 µmol/L in female participants and >168 µmol/L in male participants or glomerular filtration rate <40 mL/min/1.73 m2
  - Abnormal liver function (defined as alanine transaminase >3 times the upper normal limit) and active or recent hepatitis
  - Leukopenia, thrombocytopenia, or both
- Other
  - Severe psychiatric or mental disorders, alcohol abuse or other substance abuse, language barriers or other factors which makes adherence to the study protocol impossible.

Ethical Considerations

This study was approved by the Norwegian Regional Committee for Medical and Health Research Ethics (229187) as well as the data protection official (DS-00372) and the local research committee at Diakonhjemmet Hospital. The ReMonit study was conducted according to the Declaration of Helsinki. The Norwegian Regional Committee for Medical and Health Research Ethics approved the collection of data (age, gender, diagnosis, comorbidities, medication, disease activity, laboratory measurement, level of education, work status, and smoking habits) from nonparticipating patients attending a screening visit, both screening failures, and patients unwilling to participate in the RCT, if the patients gave their informed consent. These data will be used to evaluate potential selection bias in patient recruitment.

Randomization and Blinding

The included patients were allocated in a 1:1:1 ratio among the 3 study arms (Textbox 2). A statistician and a secretary, not involved in patient screening or enrollment, provided a computer-generated block randomization list (random block size of 6, 9, or 12 patients) and prepared sealed, opaque envelopes containing information on study arm assignment. Participants and treating clinicians are not blinded to the group allocation, but the statistician that will perform the primary outcome analyses is blinded.

Textbox 2. Study arms.

Arm A (usual care): conventional follow-up strategy with prescheduled face-to-face visits at the hospital every 6 months, with an assessment of blood tests, patient-reported outcomes (PROs), and joint examination

Arm B (remote monitoring): hospital health care professionals (HPs) perform remote monitoring of PROs, the HP contacts patients if the PRO score indicates disease flare or if the patient requests an appointment with HPs

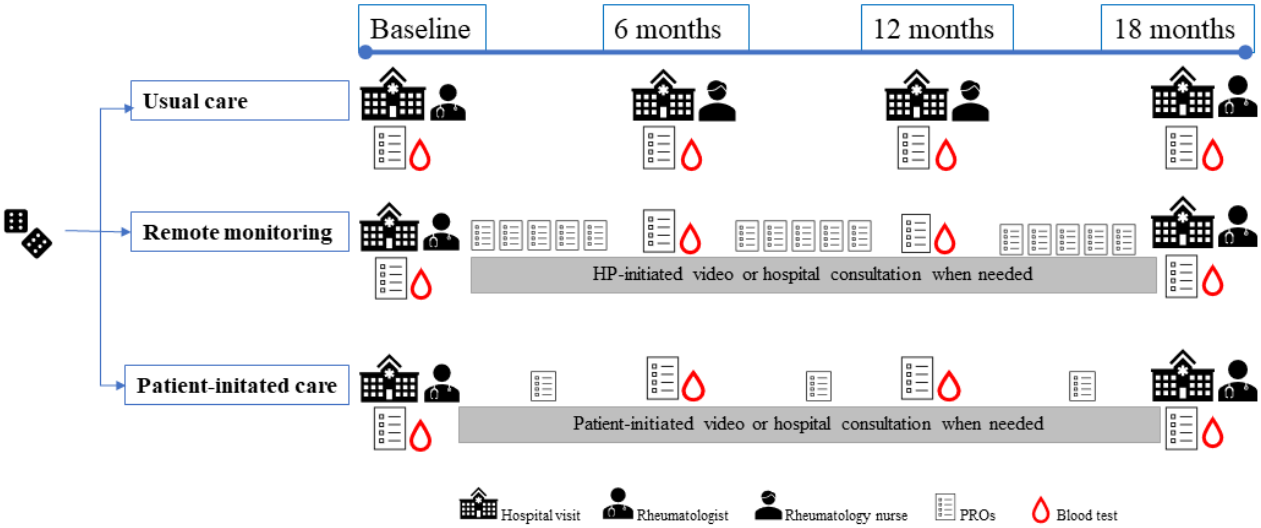
Arm C (patient-initiated care): self-monitoring by the patients with no prescheduled visits or remote monitoring, the HP contacts the patient if the patient requests an appointment with HPs

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Intervention and Follow-Up

The follow-up for arms A, B, and C lasts for 18 months with data collection at baseline and 6, 12, and 18 months (Figure 2).

Figure 2. Illustration of the Remote Monitoring in Axial Spondyloarthritis (ReMonit) study design. CRP: c-reactive protein; HP: health care professional; PRO: patient-reported outcome.



Digital Monitoring: MyDignio App and Dignio Prevent Platform

Dignio AS offers digital solutions for remote care in the health care system, is certified according to international standards of information security, and has approval for communication of health data in Norwegian health care services [26]. All communication through the software is encrypted and in compliance with the current legislation.

The patients download the MyDignio app on their smartphone or tablet and can report on PROs and manually report data, such as laboratory measurements, in the app. Several instruments can be integrated into the Dignio system, including measurements of physical activity. The HPs can monitor the patient-reported data and measurements on the web-based Dignio Prevent platform, and PROs and measurements can be displayed as graphs or histograms. The MyDignio app and the Dignio Prevent platform also provides the possibility of asynchronous chats between patients and HPs and synchronous communication with video consultations.

In this study, the patients use MyDignio for reporting PROs in the intervention arms B and C and HPs use Dignio Prevent for monitoring PROs in arm B, as described in detail in subsequent sections. Physical activity registered as steps and heart rate is recorded by a smartwatch connected via Bluetooth to a smartphone or tablet that synchronizes data via MyDignio. We also used Dignio for short communication for the patients in arms B and C, such as to send messages reminding patients on completing regularly reported PROs (arms B and C), regular blood sampling, and a link to a questionnaire every 6 months.

Description of the Study Arms

Usual Care: Arm A

Patients underwent conventional prescheduled face-to-face visits with an experienced rheumatology nurse at 6 and 12 months and with a rheumatologist at 18 months (study end), with a review of disease-related concerns, blood test results, joint examination as well as recording medication use, and adverse events. Patients who are unable to attend to a visit are offered a rescheduled visit. Patients can call the study nurse if they experience significant symptom worsening or adverse events.

Remote Monitoring: Arm B

No visits are prescheduled between the baseline visit and study-end visit. Patients download the MyDignio app on their smartphone or tablet and receive a brief introduction from the study coordinator. For monitoring, the patients receive a monthly SMS text message reminder for reporting PROs, which includes the Patient Global Assessment (PGA) and whether they experience a flare (significant worsening of disease-related symptoms). If the PGA is scored ≥3 or they answer “yes” or “uncertain” on the flare question, they are asked to report disease activity using the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) [27]. These PRO reports are monitored daily (Monday to Friday) by a study nurse via Dignio Prevent, where patients that need attention are highlighted based on predefined values for the outcomes (Table 1). If patients do not report the PROs, Dignio Prevent alerts the study coordinator who sends a reminder using Dignio. Patients can send messages to the HPs through the app or call the study nurse if they experience significant symptom worsening or adverse events.

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Table 1. Indication for the health care professionals (HPs) to contact a patient in the remote monitoring study arm.

Indication	Definition	Action
Significant worsening	• Yellow flag: BASDAI[a] ≥4 in the monthly PRO[b] reporting • Red flag: BASDAI ≥8 in the monthly PRO reporting	The study nurse contacts the patient to evaluate if a visit is needed
The patient has requested to be contacted by the HP	• The patient sends a message in MyDignio app asking to be contacted by HP	The study nurse contacts the patient to evaluate if a visit is needed

[a]BASDAI: Bath Ankylosing Spondylitis Disease Activity Index.

[b]PRO: patient-reported outcomes.

Patient-Initiated Care: Arm C

No visits are scheduled between the baseline visit and study-end visit. Patients in arm C download the MyDignio app on their smartphone or tablet and receive a brief introduction from the study coordinator. The patients receive an SMS text message reminder for reporting PROs every third month (PGA and patient-reported flare, the same as that reported monthly in arm B), but the PROs are not monitored by HPs. If patients do not report the PROs, Dignio Prevent alerts the study coordinator who sends a reminder using Dignio. Patients can send messages to HPs through the app or call the study nurse if they experience significant symptom worsening or adverse events.

Medical Treatment

At inclusion, all eligible patients were on stable medical treatment with TNFi for the last 6 months, and TNFi were continued for patients in all 3 study arms. If, during the study, patients experience a minor worsening of disease-related symptoms, they can initiate or intensify treatment with NSAIDs. Patients experiencing a significant worsening of the disease (identified either at a visit with a nurse in arm A, registered by digital monitoring in arm B, or by the patient contacting the study nurse in either of the arms) are offered a face-to-face visit with a rheumatologist within 2 weeks to evaluate the treatment regimen. The dose of TNFi may be adjusted or if TNFi therapy fails, switching to another TNFi (or an interleukin-17 inhibitor) is considered. In the case of switching treatment, the patient is offered a face-to-face follow-up visit 3 months later to ensure the effectiveness and tolerability of the new medication.

Study Assessments Schedule

Research data are collected throughout the study, separately from the remote monitoring data collected with the My Dignio app in study arm B. The main data collection time points are at baseline and at 6, 12, and 18 months (study end) for all patients (Table 2). Data are collected through interviews by a rheumatologist and a study nurse, self-reports by patients in digital questionnaires, physical examinations by a rheumatologist or a study nurse, laboratory assessments or blood samples, and a physical activity tracker or smartwatch. A qualitative substudy with individual interviews will be conducted after the end of the study.

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Table 2. Schedule of activities.

Procedure	Screening	Baseline	Intervention period (remote monitoring or visits)				Extra visits and early discontinuation
			Every month	6th-month follow-up	12th-month follow-up	18th month, study end	
Inclusion and exclusion criteria	✓						
Fulfil ASAS[a] criteria	✓						
Physical examination including the heart and lungs	✓						
Informed consent	✓						
Randomization		✓					
Safety laboratory tests[b]		✓		✓	✓	✓	✓
CRP[c] and ESR[d]		✓	✓[e]	✓	✓	✓	✓
Clinical examination of disease activity, including enthesitis (heel) and peripheral arthritis		✓		✓[f]	✓[f]	✓	✓
Vital signs		✓					
Medical history		✓					
Demography		✓					
Lifestyle		✓					
eHealth literacy		✓					
Patient Global Assessment		✓	✓[g]	✓	✓	✓	✓
Patient-reported outcomes		✓	✓[g]	✓	✓	✓	✓
Medication		✓		✓	✓	✓	✓
Adverse event review				✓	✓	✓	✓
Physical activity monitoring			✓[h]	✓[h]	✓[h]		
Reason for discontinuation[i]							✓

[a]ASAS: Assessment of Spondyloarthritis International Society.

[b]Measured at baseline and every 3 months throughout the study as recommended due to treatment with tumor necrosis factor inhibitors. Blood samples are analyzed by the patient's general practitioner or at the Diakonhjemmet Hospital, whatever is the most convenient for the patients. The following blood samples will be analyzed: hemoglobin, red blood cells, white blood cells with differential count, platelets, creatinine, and alanine transaminase.

[c]CRP: c-reactive protein.

[d]ESR: erythrocyte sedimentation rate.

[e]Only the subgroup (n=12) in the remote monitoring arm (arm B) that received a home-based C-reactive protein instrument.

[f]At 6 and 12 months, only in the usual care arm (arm A).

[g]Patients in the remote monitoring arm (arm B) will complete a brief questionnaire each month, and patients in the "patient-initiated care" arm (arm C) will complete a brief questionnaire only every 3 months.

[h]Only patients in the remote monitoring arm (arm B) and patient-initiated care arm (arm C) from inclusion or randomization until 12 months.

[i]Only at the early discontinuation visit.

Interview With a Rheumatologist and a Study Nurse

Information on medical history and fulfillment of the Assessment of Spondyloarthritis International Society classification criteria is obtained at baseline by a rheumatologist. Information on medication is recorded at baseline, extra visits, study end, and early discontinuation in all groups as well as at the 6- and 12-month visits in arm A. The dosage and frequency of TNFi and concomitant medication is recorded. The use of NSAIDs, oral or injected glucocorticoids, and analgesics for residual pain (paracetamol or opioids) has received particular attention. Adverse events are reported at all follow-up visits. At the end of the study, the patients will be asked about their preference for future follow-up strategies.

Digital Questionnaires

All patients completed digital questionnaires at baseline and 6, 12, and 18 months and at extra visits and early discontinuation. Data collections were handled by questionnaires created with Nettskjema, a survey solution developed and hosted by the

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University of Oslo. At baseline, patients reported demographic data, lifestyle factors (smoking and physical activity), educational level, work status, travel distance, travel time, and way of transport to the hospital. The patients also responded to questions regarding experience with digital technology and eHealth literacy through 20 items from 4 domains of the eHealth Literacy Questionnaire; domain 1, using technology to process health information; domain 3, the ability to actively engage in digital services; domain 4, feel safe and in control; and domain 5, motivated to engage with digital services (response options ranged from 1—strongly disagree, to 4—strongly agree) [28].

Several PROs on disease activity, functional status, sleep quality, health-related quality of life, and patient satisfaction with care and physical activity are reported at baseline and 6, 12, and 18 months; extra visits; and early discontinuation (Table 3). The patients also report, in line with the Assessment of Spondyloarthritis International Society recommendations [29], on the use of medication for spondyloarthritis (TNFi, NSAIDs, and steroids) and if TNFi has been taken as recommended.

Table 3. Patient-reported secondary outcomes at baseline and 6-, 12- and 18-month data collection time points, at extra visits, and at early discontinuation.

Patient-reported outcome	Measurement scale
PGA[a]	• NRS[b] 0-10
Pain assessment	• NRS 0-10
Joint pain assessment	• NRS 0-10
BASDAI[c] [27]	• 6 items, NRS 0-10
BASFI[d] [30]	• 10 items, NRS 0-10
Flare[e]	• Yes, no, or uncertain • If yes or uncertain, which date the flare occurred and number of days it lasted
Change in disease activity last 6 months[e]	• 7-point scale ranging from “much worse” to “much better”
Change in activity impairment last 6 months[e]	• 7-point scale ranging from “more activity impairment” to “improved ability to performed daily activities”
WPAI[f] item no. 6: activity impairment last week [31]	• 1 item, NRS 0-10
Pittsburgh Sleep Quality Index: sleep disturbances due to pain [32]	• 1 item • 4-point scale from “not during the past month” to “3 or more times a week”
EQ-5D-5L [33,34]	• 5 items • 5-point scale • + Health index, VAS[g] 0-100
The patients’ satisfaction with care [35]	• 1 item • 5-point response options ranging from “very satisfied” to “very dissatisfied”
Patient-reported physical activity [36]	• 3 items • Frequency (never, less than once, once, 2 to 3 times, or ≥4 times per week) • Duration (less than 15, 15-30, 31-60, or ≥60 min) • Intensity (no sweat, sweat, or exhausted)

[a]PGA: Patient Global Assessment.

[b]NRS: numeric rating scale.

[c]BASDAI: Bath Ankylosing Spondylitis Disease Activity Index.

[d]BASFI: Bath Ankylosing Spondylitis Functional Index.

[e]Not reported at baseline.

[f]WPAI: Work Productivity and Activity Impairment questionnaire.

[g]VAS: visual analog scale.

In arm A, patients receive a link to the digital questionnaires by SMS text messages a few days ahead of the 6-, 12-, and 18-month visits. Participants in arms B and C receive a digital reminder through the MyDignio app at the time of data collection at 6 and 12 months, with a link to the digital questionnaire, but the link is sent by SMS text messages for the 18-month visit. The study personnel carefully monitor the data collection to ensure completeness and contact nonresponders by SMS text messages or phone calls.

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Physical Examinations

Vital signs are examined at baseline (Table 2). A joint examination is performed at baseline, extra visits, study end, and early discontinuation in all arms and at 6- and 12-month visits in arm A.

Laboratory Assessments

Standard care blood samples (Table 2; hemoglobin, red blood cells, white blood cells with differential count, platelets, creatinine, and alanine transaminase) are analyzed as a safety procedure when using TNFi. Patients in arms B and C are asked to report the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) values at 6 and 12 months if measurements are performed by their general practitioner. A subgroup of 12 patients in arm B are asked to perform home-based measurements of CRP each month, in connection with the monthly reporting of PROs. The CRP level is measured using the QuikRead go instrument [37], and the patients register the CRP value in the MyDignio app.

Registration of Physical Activity

The patients in arms B and C are asked to wear a water-resistant smartwatch (Garmin Vivosmart 4) for physical activity monitoring, for example, the number of steps and heart rate during daytime, and data are transferred to Dignio. They are instructed to wear this smartwatch for at least 10 hours during the day, but they can wear it all day and night should they want to. Patients who do not want to wear this smartwatch can still participate in the study in the allocated arm.

Qualitative Substudy

A qualitative substudy with observations and individual semistructured interviews will be conducted after the study ends to gain in-depth insight from patients and HPs on their experiences with remote monitoring. We are planning to conduct interviews with 15 to 20 patients and 5 to 8 HPs. The interview will be recorded through Nettskjema and sent encrypted to Services for Sensitive Data at the University of Oslo.

Outcomes

Primary Outcome

The primary outcome of the study is low disease activity, defined as ASDAS <2.1, and will be evaluated by point prevalence across the 6-, 12-, and 18-month data collection time points. ASDAS is calculated from 4 PROs on patients' experience of back pain, joint pain or swelling, duration of morning stiffness, and PGA during the last week (reported on a visual analog scale, 0-100, 0 being best and 100 being worst) and CRP or ESR, where $ASDAS_{CRP}$ is the preferred measure.

The formula for $ASDAS_{CRP}$ is as follows: 0.12 × back pain + 0.06 × duration of morning stiffness + 0.11 × patient global + 0.07 × peripheral pain or swelling + 0.58×Ln(CRP + 1)). The formula for $ASDAS_{ESR}$ = 0.08 × back pain + 0.07 × duration of morning stiffness + 0.11 × patient global + 0.09 × peripheral pain or swelling + 0.29 × $\sqrt{}$(ESR) [38,39]. In this study, we will calculate $ASDAS_{CRP}$; however, if CRP is missing and we have the value for ESR, $ASDAS_{ESR}$ will be used.

Secondary Outcomes

Secondary outcomes include other measurements of disease activity (eg, ESR, CRP, BASDAI, PGA, change in PGA, pain and joint pain assessment, flare, swollen and tender joint count, presence of heel enthesitis, extramusculoskeletal manifestations, and use of medication), functional status (Bath Ankylosing Spondylitis Functional Index, change in activity impairment, and work productivity and activity impairment item no 6), and sleep quality (Pittsburgh Sleep Quality Index: sleep disturbances due to pain). Furthermore, patient satisfaction with care will be evaluated.

Rates and types of adverse events and serious adverse events are recorded throughout the study at all follow-up visits, extra visits, early discontinuation, and study-end visits by structured interviews and reported in the electronic case report form (eCRF). If an adverse event is considered to be related to the treatment of the patient, the patient's medical treatment is evaluated by a rheumatologist and changed if needed or recommended. Recording adverse events, use of medications such as painkillers, and possible use of antibiotics can provide information on the safety of the 3 follow-up arms.

Substudies

Assessment of the EQ-5D-5L, time for patient being absent from work and potential travel costs related to consultations, time and costs related to patient monitoring (phone calls from patients to nurse or rheumatologist, telephone consultations, video consultations, and face-to-face visits), and health care use (in primary and secondary health care) will provide information on health care use and will allow for evaluation of cost-effectiveness.

All patients will at baseline self-report their experience with digital technology and eHealth literacy. Patients will report on satisfaction with care (Table 3), and patients in arm B will also report on their experiences on reporting monthly disease activity at the 18-month follow-up [40,41].

This qualitative substudy with observations and individual semistructured interviews will provide in-depth insight from patients and HPs on their experiences with remote monitoring.

The close measurement of disease activity by PGA and the monthly CRP for the subgroup in arm B will allow for analyses of fluctuations in disease activity over time. Self-reported physical activity (Table 3) and the measurement of physical activity with smartwatches in arms B and C will provide data to analyze the potential associations between disease activity and physical activity.

Linkage to Registers

The ReMonit project has approval to link data with several national registers in Norway: KUHR (register of national financing support for patients in health services in Norway by Norwegian Directorate of Health), FD-trygd (register of work status, sick leave, and disability pension by Statistics Norway), NPR (register on health information on patients having received treatment or waiting for treatment in specialist health care in Norway by Norwegian Directorate of Health), and NorPD (register of prescription of drugs dispensed from pharmacies,

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Norwegian Prescription Database by Norwegian Institute of Public Health). These data can provide information for the cost-effectiveness analyses.

Statistics

Sample Size and Power Considerations

On the basis of data from the NOR-DMARD database (an ongoing longitudinal observational study of the effectiveness of treatment of IJDs with biological disease-modifying antirheumatic drugs in clinical practice, ClinicalTrials.gov NCT01581294) [42], we expect approximately 88% of the usual care patients to have low disease activity at the end of the study. We estimate that 74 patients in each arm will give a power of 80% to conclude that at least one of the alternative follow-up strategies is noninferior to usual care. This assumes a noninferiority margin of 15%, no actual difference between the groups, and an analysis based only on one time point. By collecting the primary end point at 3 time points (and not only at the end of study) for each participant, the power will increase, and a group size of 80 participants should have sufficient power, even with 15% dropout or missing data.

Statistical Analyses

This study will compare the point prevalence of low disease activity (ASDAS <2.1) in the remote monitoring (arm B) and patient-initiated care (arm C) arms to that of usual care (arm A). A monitoring regime will be deemed noninferior to usual care if it can be shown that its low disease activity prevalence is no more than 15 percentage points below that of usual care. In addition, we will test the noninferiority of patient-initiated care to remote monitoring using the same 15% margin. This test will be done only if patient-initiated care is shown to be noninferior to conventional care (a hierarchical test) and thus will not inflate the 5% false positive rate.

The statistical analysis plan will be finalized, signed, and dated before data locking. Demographics, baseline characteristics, efficacy, and safety variables will be summarized using descriptive statistics. Efficacy (both primary and secondary endpoints) and safety analyses will include data from all randomized patients who started the allocated intervention by completing at least one questionnaire and blood test results after randomization, the full analyses set. Robustness analyses will be performed in the per-protocol set, which includes all randomized patients meeting the study entry criteria who followed the study protocol (meeting appointments and reporting data as described in the follow-up regimen of arms A, B, and C).

Primary Analyses

The primary end point, the point prevalence of ASDAS <2.1, will be analyzed by mixed effect logistic regression. The analysis will be based on follow-up data from 6-, 12-, and 18-month data collection time points and will include the randomization group as the main covariate. Sensitivity analyses will include additional covariates such as age, gender, and disease characteristics. The estimates of between-group differences in point prevalence will be based on adjusted risk differences [43]. The noninferiority of remote monitoring to usual care will be evaluated by the CI for the between-group difference in low disease activity (point) prevalence, with a similar approach for patient-initiated care versus usual care [44].

Secondary Analyses

Analyses of secondary effectiveness end points will be presented using point estimates of between-group differences along with their 95% CIs. Continuous and binary outcomes will be analyzed using mixed effects linear and logistic regression, respectively. Cost-effectiveness of the 2 new follow-up strategies will be evaluated primarily with a health care perspective. If the new follow-up strategies are considered noninferior to usual care, cost-minimization analyses may be relevant. Otherwise, calculations of quality-adjusted life-years, determination of the incremental or decremental cost-effectiveness ratio, and the assessment of cost-effectiveness using the cost-effectiveness acceptability curve may be considered. Details of the analyses will be described in the statistical analyses plan.

Missing Data

In the ReMonit study, the primary end point will be collected at 3 time points for each patient, and only patients with at least 1 assessment of the primary end point will be included in the final analyses (the full analyses set). For the main analysis, missing values of the primary end point will not be imputed, as the mixed effect analysis provides unbiased effect estimates, provided the missing data are missing-at-random. Alternative treatments for missing values of the primary end point will be entertained as sensitivity analyses.

Data Registration, Monitoring, and Storage

Data are reported in the eCRF and stored safely at Services for Sensitive Data provided by the University of Oslo [45]. Guidance on the completion of eCRFs is provided in the investigator brochure and eCRF. The regular self-reported disease activity in arms B and C, the CRP measurements performed by the subgroup of patients, and the data on physical activity from the smartwatch are reported in the MyDignio app.

The investigator must permit study-related monitoring and regulatory reviews, audits, and inspections. The investigators will monitor the data collection to ensure completeness. The study personnel will be closely monitoring the data collection needed for the primary outcome, ASDAS (PROs and CRP), at 6, 12, and 18 months. If data are not reported, the patients will be reminded at least 3 times, either through the MyDignio app, an SMS text message, or a phone call.

Study Termination

The end of the study was the completion of the 18-month visit. However, patients may withdraw from the study at any time point. Patients with early termination are asked to participate in a study-end visit—a face-to-face visit or a telephone or video consultation. They are then offered regular follow-up at the outpatient clinic as before inclusion in the ReMonit study.

Results

The project is funded by the Norwegian South-Eastern Regional Health Authority and the Centre for Treatment of Rheumatic

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and Musculoskeletal Diseases (REMEDY), Diakonhjemmet Hospital, Norway.

Patient screening and recruitment began in September 2021, and inclusion was completed in June 2022. The last 18-month study-end visit will be conducted in December 2023. At present, all included patients were followed up according to the outlined schedule.

Discussion

Principal Findings

Patients with IJDs are often followed up in specialist health care for many years. Alternative follow-up strategies with either digital remote monitoring or self-monitoring may be a step toward a more personalized follow-up. By eliminating the need for patients to travel to visits, the ReMonit study aims to enhance accessibility to health care and save valuable time for participants. Furthermore, alternative follow-up strategies may reduce the demands on the health care services [46]. There are few studies evaluating digital follow-up in IJDs [18], and to our knowledge, this trial is among the first to evaluate the effectiveness, satisfaction, safety, and cost-effectiveness of remote digital monitoring and self-monitoring of patient with axSpA.

Patients

Among the IJDs, we considered patients with axSpA to be the most suitable for remote follow-up and self-monitoring, as disease activity is measured by ASDAS, which is based on PROs together with CRP and not based on a clinical examination. Moreover, treatment is focused on alleviating symptoms. We decided to include only patients treated with TNFi because these patients require follow-up in specialist health care. Furthermore, many patients with axSpA are relatively young, usually without comorbidities, and often experience few side effects of TNFi, which minimizes safety issues. Most patients with axSpA are young and participate in the workforce, making remote follow-up especially attractive in this patient group.

Single-Center Study

The ReMonit study is a single-center study conducted at the Department of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway. This department is responsible for the largest number of patients with IJDs in Norway. The greater Oslo area is the most densely populated area in Norway. Most patients have short to moderate travel distances to the outpatient clinic. Hence, being allocated to either of the study arms, with face-to-face visits (controls) or remote follow-up (intervention), would be acceptable for most of the screened patients and minimize selection bias at inclusion. The potential benefits of saved costs related to fewer face-to-face visits (transport costs, time use, and absenteeism from work) will probably be greater elsewhere in Norway than in this study.

Randomization and Blinding

Treating clinicians are not blinded to group allocation. It could have been possible, by having 2 separate HP teams, but would be challenging in terms of study logistics as well as very resource demanding and regarded unfeasible. Blinding of the patients is not possible because the patients need to know the allocated follow-up strategy. However, the patients will not be informed of the primary outcome measures to minimize their influence on the primary outcome. Furthermore, treating clinicians will not know the ASDAS (primary outcome) of the patients during follow-up.

Study Design

The noninferiority design was chosen because the new follow-up strategies are likely to be less resource demanding (both for patients and HPs) but not be superior to conventional follow-up in maintaining low disease activity. The included patients are well treated with TNFi with an ASDAS <2.1 at inclusion. We cannot expect improvement of disease activity in either of the study arms, and it is unlikely to obtain superiority of the point prevalence of ASDAS <2.1 in the intervention groups. This assumption is based on data from the NOR-DMARD database [42], which showed that 88% of patients with axSpA using TNFi with ASDAS <2.1, remained at ASDAS <2.1 2 years later without change of medication in traditional face-to-face follow-up.

Primary Outcome

Our main goal is to assess whether these new follow-up strategies are associated with low disease activity over time; hence, it is meaningful to assess the primary outcome, ASDAS, at several time points. There are 2 validated measurements of disease activity of patients with axSpA: ASDAS and BASDAI [27,38]. The ASDAS is the newest and is based on both PROs and objective measurements of inflammation (CRP or ESR) and is the recommended instrument for assessing disease activity when monitoring patients [5,47,48]. Thus, ASDAS was chosen as the primary outcome measure and BASDAI as a secondary outcome measure. Other measures of disease activity are included as secondary objectives together with the measure of functional status measured by the Bath Ankylosing Spondylitis Functional Index, which will provide more comprehensive information about disease activity.

Secondary Outcomes

We believe that the evaluation of secondary end points in the ReMonit study is important with regard to the clinical implications of the study results. Even if this study shows noninferiority of the primary outcome with the 2 new follow-up strategies, the success of the follow-up strategies is also dependent on patient satisfaction and safety issues, such as adverse events or the use of painkillers. Follow-up with remote monitoring or self-monitoring may not be relevant to implement if there are increased negative effects compared with usual care.

Selection of Participants

On the basis of prior research and also from clinical experience, where patients at the outpatient clinic often ask for an alternative follow-up rather than face-to-face visits, we hypothesize that patient satisfaction will be high in the remote monitoring and self-monitoring groups [1]. At recruitment, we motivated all patients fulfilling the screening criteria to participate (also patients not interested in digital follow-up) to obtain a representative study sample and avoid selection bias by only

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recruiting patients especially interested in digital follow-up. It was underscored that patients in all the study arms can ask for a face-to-face visit with a rheumatologist when they need it.

Safety and Adverse Events

Some patients may experience increased pain or disease activity and a reduced effect of TNFi, and in this case, the patients are instructed to ask for an extra visit. It is possible that some patients in the intervention arms will not ask for an extra visit even when experiencing worsening of the disease and instead increase the use of painkillers. We will register the use of NSAIDs and other painkillers to detect increased use, and we will consider this as a possible adverse event of the intervention. A consequence of increased pain may be reduced sleep quality that will be captured from the reported PROs. The linkage to the Norwegian Prescription Database will provide information on the use of sleeping pills.

Substudies

Another consequence of not detecting increased disease activity might be increased sick leave. Linkage to FD-trygd (register of work status, sick leave, and disability pension) and patient reports will provide information about possible differences in sick leave between the study arms. As all patients use TNFi, an immunosuppressant, they are at increased risk of infection. We will collect information on the use of antibiotics through patient reports and receive information from the Norwegian Prescription Database to assess whether there are differences in the use of antibiotics between the intervention and control groups.

We hypothesize that patients with remote follow-up and self-monitoring will spend less time on disease-related follow-up. However, there is a possibility that patients need closer follow-up in primary health care when follow-up in specialist health care is less close. Furthermore, fewer prescheduled visits may result in more unscheduled telephone or face-to-face visits. Thus, it is important to analyze the cost-effectiveness of the different follow-up regimen when designing future sustainable follow-up strategies.

Data collection will also provide the opportunity to perform other analyses. Before the implementation of digital follow-up, it is important to explore eHealth literacy and the attitude toward digital follow-up [46]. This will provide important information on facilitators and barriers to remote care and may explain why digital health service implementations work or fail. The qualitative substudy with individual interviews will be conducted after the RCT to gain in-depth insights from patients and HPs on their experiences with remote monitoring. Interviews will explore potential implications for patients' empowerment, acceptability of remote monitoring, and patients' views on the frequency and content of remote monitoring. Observations will provide insight into the interaction and communication between patients and HPs with remote follow-up and face-to-face visits.

In arm B, remote monitoring, the patients will self-report on disease activity once a month, and a subgroup will also measure CRP monthly. These data will provide valuable information about how disease activity and inflammation vary over time. The frequent reporting of PROs will provide an opportunity to investigate the optimal frequency of collecting PROs, which is important when designing future follow-up strategies. Frequent registration of disease activity and the tracking of physical activity and heart rate allow for evaluating fluctuations in disease activity and physical activity over time and if flares can be predicted based on changes in monitored physical activity level.

Conclusions

In conclusion, the ReMonit study will evaluate whether remote digital monitoring or self-monitoring is a clinically effective, safe, and sustainable future follow-up strategy for patients with axSpA. The ReMonit study will contribute to the current knowledge on new follow-up strategies, which may result in improved and more personalized follow-up strategies for patients with axSpA, and potentially lead to reduced costs for the patients and the society.

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Data Availability

The full trial protocol (version 1.1; date: 23.12.22) is available from the corresponding author upon request. At present, data sharing is not applicable.

Authors' Contributions

IJB, ATT, GB, SH, EKK, SL, GJM, EM, SAP, JS, EEKT, ADT, LG, EAH, and NØ made substantial contribution to designing the study. IJB and NØ drafted the manuscript. JS provided statistical expertise, IJB, ATT, GB, SH, EKK, SL, GJM, EM, SAP, JS, EEKT, ADT, LG, EAH, and NØ made critical revision of the manuscript, approved the final manuscript, and agreed to be accountable for all aspects of the work.

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Conflicts of Interest

IJB has received consultation fees from Novartis outside the submitted work. GB has received consultation fees from UCB outside the submitted work. SAP has received consultation fees from Boehringer Ingelheim and Pfizer and a research grant from Boehringer Ingelheim outside the submitted work. LG has received grants from AbbVie, Biogen, Lilly, Novartis, and UCB; personal fees from AbbVie, Amgen, BMS, Celltrion, Galapagos, Janssen, Lilly, MSD, Novartis, Pfizer, Sandoz, and UCB; and nonfinancial support from AbbVie, Janssen, MSD, Novartis, Pfizer, UCB, and Viatris outside the submitted work. EAH has received grants from the Research Council of Norway during the conduct of the study and for the last 36 months outside of the submitted work, as well as speaker or consultant fees from Pfizer, AbbVie, Gilead, UCB Pharma, Galapagos, Eli Lilly, Novartis, and Boehringer Ingelheim. ATT, SH, EKK, SL, GJM, EM, JS, EEKT, ADT, and NØ have no conflicts of interests.

Multimedia Appendix 1
Aim of the Remote Monitoring in Axial Spondyloarthritis (ReMonit) study.
[PDF File (Adobe PDF File), 118 KB - resprot_v12i1e52872_app1.pdf]

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Abbreviations

ASDAS: Ankylosing Spondylitis Disease Activity Score
AxSpA: axial spondyloarthritis
BASDAI: Bath Ankylosing Spondylitis Disease Activity Index
CRP: c-reactive protein
DMARD: disease-modifying antirheumatic drug
eCRF: electronic case report form
ESR: erythrocyte sedimentation rate
HP: health care professional
IJD: inflammatory joint disease
NSAID: nonsteroidal anti-inflammatory drug
PGA: Patient Global Assessment
PRO: patient-reported outcome
PsA: psoriatic arthritis
RA: rheumatoid arthritis
RCT: randomized controlled trial
ReMonit: Remote Monitoring in Axial Spondyloarthritis
TNFi: tumor necrosis factor inhibitor

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Protocol

FLASH Radiotherapy for the Treatment of Symptomatic Bone Metastases (FAST-01): Protocol for the First Prospective Feasibility Study

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Abstract

Background: In preclinical studies, FLASH therapy, in which radiation delivered at ultrahigh dose rates of ≥40 Gy per second, has been shown to cause less injury to normal tissues than radiotherapy delivered at conventional dose rates. This paper describes the protocol for the first-in-human clinical investigation of proton FLASH therapy.

Objective: FAST-01 is a prospective, single-center trial designed to assess the workflow feasibility, toxicity, and efficacy of FLASH therapy for the treatment of painful bone metastases in the extremities.

Methods: Following informed consent, 10 subjects aged ≥18 years with up to 3 painful bone metastases in the extremities (excluding the feet, hands, and wrists) will be enrolled. A treatment field selected from a predefined library of plans with fixed field sizes (from 7.5 cm × 7.5 cm up to 7.5 cm × 20 cm) will be used for treatment. Subjects will receive 8 Gy of radiation in a single fraction—a well-established palliative regimen evaluated in prior investigations using conventional dose rate photon radiotherapy. A FLASH-enabled Varian ProBeam proton therapy unit will be used to deliver treatment to the target volume at a dose rate of ≥40 Gy per second, using the plateau (transmission) portion of the proton beam. After treatment, subjects will be assessed for pain response as well as any adverse effects of FLASH radiation. The primary end points include assessing the workflow feasibility and toxicity of FLASH treatment. The secondary end point is pain response at the treated site(s), as measured by patient-reported pain scores, the use of pain medication, and any flare in bone pain after treatment. The results will be compared to those reported historically for conventional dose rate photon radiotherapy, using the same radiation dose and fractionation.

Results: FAST-01 opened to enrollment on November 3, 2020. Initial results are expected to be published in 2022.

Conclusions: The results of this investigation will contribute to further developing and optimizing the FLASH-enabled ProBeam proton therapy system workflow. The pain response and toxicity data acquired in our study will provide a greater understanding of FLASH treatment effects on tumor responses and normal tissue toxicities, and they will inform future FLASH trial designs.

Trial Registration: : ClinicalTrials.gov NCT04592887; http://clinicaltrials.gov/ct2/show/NCT04592887

International Registered Report Identifier (IRRID): DERR1-10.2196/41812

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(JMIR Res Protoc 2023;12:e41812) doi:10.2196/41812

KEYWORDS

bone metastases; FLASH; proton therapy; external beam radiotherapy; palliative radiotherapy; extremities; pain relief; ultra-high dose rate; radiation therapy; cancer treatment; toxicity; oncology; radiotherapy

Introduction

Background

FLASH is an emerging radiation treatment modality that has shown promise for improving the therapeutic ratio by potentially reducing normal tissue toxicity when compared to conventional radiotherapy. FLASH treatment is delivered at ultrahigh dose rates of at least 40 Gy per second, which is approximately 1000 times the dose rate of conventional radiotherapy. In our study—the first clinical trial of FLASH—10 subjects will undergo FLASH treatment for painful bone metastases in the extremities, using a proton radiotherapy system.

The bone, liver, and lungs are the most common sites of metastases from cancer [1]. The pain caused by bone metastases can be severe and debilitating and compromises the quality of life of patients [2,3]. A multimodal approach is often required to adequately manage bone metastases [3], and this does not always adequately control pain.

Subjects with painful bone metastases benefit from radiation therapy [3-8]. Radiotherapy palliation for bone metastasis pain can reduce the use of analgesics [9], enhance mobility, and improve quality of life [10-12]. For painful bone metastases, a standard-of-care radiotherapy regimen is 8 Gy of radiation delivered in 1 fraction (a single treatment) via a medical linear accelerator [4]. Because of the toxicities inherent with ionizing radiation, achieving a favorable therapeutic ratio (balancing radiation-induced damage to the tumor while sparing normal tissue) is a key goal of radiotherapy prescriptions and planning for both radical treatment and palliative treatment.

Study Intervention

Multiple preclinical models have shown that FLASH therapy, when compared to conventional radiotherapy, results in the increased protection of healthy tissue and cells and has equal or greater tumor cell kill rates [13-17]. Research is ongoing to understand the mechanisms underlying the observed benefits of FLASH. Data suggest that the lower levels of toxic oxygen reactive species in normal tissues may explain why less side effects may be produced by FLASH than by conventional radiotherapy [18]. The normal tissue–sparing effects of FLASH have been observed in several tissues and animal models, including mouse intestines [19], mouse skin [20], mouse lungs [21], mouse brains [18], and cat and pig skin [22].

Irradiating mouse lungs in vivo, Favaudon et al [21] found that a higher FLASH dose was required to induce radiation pneumonitis and fibrosis than the dose required for conventional radiotherapy (30 Gy for FLASH vs 17 Gy for conventional radiotherapy). Furthermore, tumor control was more easily achieved with FLASH. The tumor control rates were 70% at 27 Gy in FLASH and 20% at 15 Gy in conventional radiotherapy. At 27 Gy in FLASH, no pneumonitis was observed, whereas significant pneumonitis was observed at 15 Gy in conventional radiotherapy [21]. Similarly, Montay-Gruel et al [18] treated mouse brains in vivo. Subsequent follow-ups revealed that neurocognitive impairment developed in the 10-Gy conventional radiotherapy group but not in the 10-Gy FLASH group. Similarly, Cunningham et al [23] demonstrated that FLASH proton pencil beam scanning irradiation minimized radiation-induced leg contracture and skin toxicity in mice.

To our knowledge, there is only 1 peer-reviewed report [24] on the use of FLASH in humans—a case report of a single subject with cutaneous T-cell lymphoma who underwent extensive prior skin radiotherapy. This individual was treated with a single 15-Gy dose of FLASH, using electrons for a recurrent cutaneous lymphoma lesion. The lesion had a complete response to treatment, with minimal toxicity to the surrounding skin.

A standard of care for the radiotherapy palliation of painful bone metastases is 8 Gy of photon radiation delivered by a medical linear accelerator. Although there is no commercially available medical linear accelerator capable of delivering FLASH dose rates, some cyclotrons, which generate proton radiation for medical treatments, are capable of FLASH dose rates when operated in research mode. Our study will be carried out in a proton treatment facility delivering FLASH dose rate treatment to subjects with painful bone metastases in the extremities.

Rationale and Risk Benefit

The implementation data acquired in this first-in-human investigation will contribute to developing the clinical workflow for FLASH and making this technology routinely available to radiation oncologists and their patients.

The prescription dose and fractionation in this study are the same as those in the standard of care for the palliation of bone metastases—8 Gy of radiation delivered in a single treatment [4]. A single radiotherapy fraction of 8 Gy was also used to administer conventional radiotherapy in prior clinical studies [25,26]. Based on the early data indicating that FLASH may be capable of controlling tumors as effectively as conventional radiotherapy [25,26], it is expected that the subjects with painful bone metastases treated using this study protocol will receive the same pain control benefit as that received by patients treated with conventional radiotherapy.

The subjects' experience of treatment and the follow-up schedule were designed to be very similar to those of standard-of-care conventional radiotherapy. Some of the study activities will occur during regular visits that the subjects will have as part of their oncologic care. Thus, the time and social burden imposed by study participation will be minimal. FLASH will only be delivered to targets in the extremities, which are distant from visceral organs at higher risk of radiation toxicity. In this study, normal tissue toxicity due to FLASH is expected

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to be no more than (and potentially less than [21]) that historically observed with conventional radiotherapy. Toxicities of conventional radiotherapy have been evaluated in a prior benchmark multi-institutional prospective randomized clinical trial [9], in which a cohort of 455 patients (433 and 354 patients analyzed for acute and late toxicities, respectively) was treated with 8-Gy, single-fraction conventional radiotherapy for the palliation of painful bone metastases. Toxicities were scored using the Radiation Therapy Oncology Group (RTOG) acute and late morbidity Criteria [27]. Late toxicity (occurring >90 days after radiotherapy) was "rare (4%)," and no patients in the cited study had any grade 4 to 5 acute or late toxicities. The most common toxicity was gastrointestinal. Gastrointestinal toxicity should not be relevant to our feasibility study because radiotherapy will be delivered to the extremities, and no portion of the gastrointestinal tract will be in the radiation field. The acute toxicity that is most likely to occur in this study is radiation dermatitis within the irradiated field. In the prior cited study, of the 433 patients, there were 15 (3%) grade 1, 1 (<1%) grade 2, and no grade 3 acute skin toxicities. Hematologic and "other" (not specified in the prior studies) acute toxicities also occurred in the cited trial.

Methods

Trial Design

This clinical trial is a first-in-human feasibility study of proton FLASH (trial registration number: NCT04592887). Up to 10 adult subjects will undergo FLASH on a proton therapy system operated in research mode. Each subject will undergo FLASH treatment for up to 3 painful bone metastasis sites in the extremities. The feasibility of the clinical workflow will be evaluated. A combination of physician-reported and patient-reported outcomes will be used to assess toxicities and pain relief at scheduled time points throughout the study for the duration of the study participants' lifetime or until they are lost to follow-up.

Objectives

The primary objectives are to assess the workflow feasibility of FLASH therapy in a clinical setting and the toxicities of treatment. The secondary objective is to assess pain relief at the treated site(s).

Setting

This clinical trial will be conducted at the Cincinnati Children's/University of Cincinnati Health Proton Therapy Center—an academic hospital in Cincinnati, Ohio.

Oversight and Compliance

The protocol was reviewed and approved by the US Food and Drug Administration (FDA) prior to participation by any subjects. This research will be conducted on a modified proton therapy device under an investigational device exemption (IDE) approved by the FDA.

Ethics Approval

The FAST-01 protocol was reviewed and approved by the Cincinnati Children's Hospital Institutional Review Board (reference ID: 2020-0030) prior to participation by any subjects.

Recruitment

Patients presenting for palliative radiotherapy to bone metastases will be screened for potential inclusion. In addition, copies of a flier (Multimedia Appendix 1) inviting patients to inquire about the study will be posted.

The radiation oncologists and their staff involved in the study will administer the informed consent procedures for the patients.

Enrollment and Replacement

Enrollment for the study is expected to take 12 months.

All inclusion criteria must be met, and none of the exclusion criteria may be present for a patient to be eligible for the study (Textbox 1). After patients consent to participate in the trial (Multimedia Appendix 2), the investigator will determine whether the patient meets the eligibility criteria, and the results of the screening process will be compiled at the investigational site. No eligibility exceptions will be considered. All patients will be considered regardless of race or gender.

Eligible patients can have 1 to 3 painful bone metastases of the extremities, excluding metastases involving the feet, hands, and wrists. Other bone metastases may be treated with conventional radiotherapy while the patient is participating in the study. Patients who have more than 3 painful bone metastases of the limb bones that require treatment are more likely to have generalized pain, which could confound the measurement of pain relief (ie, the response to treatment).

Patients may continue to take steroids during their participation in the clinical trial, if prescribed by their physician. Steroid medication is optional and at the discretion of the prescribing physician.

Because proton range and dosimetry are less certain in the presence of metal, patients with bone fractures or metal implants in the treatment field will be excluded from this study. Patients who will receive cytotoxic chemotherapy within 1 week prior to or 1 week following their planned radiation treatment will also be excluded because concurrent cytotoxic chemotherapy could affect the tissue response to radiation.

Patients interested in participating in the study will be asked to read, understand, and sign the informed consent document, consistent with institutional practices. Patients who meet all eligibility criteria and sign the consent document may proceed onto the study.

If the subject leaves the study for any reason before the next scheduled follow-up visit is completed, the investigator will document the reason(s). In addition, the investigator will attempt to record the overall score of patient-reported pain and scores for pain specifically in treated site(s), use of pain medications, and adverse events (AEs).

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Textbox 1. Eligibility criteria.

Inclusion criteria

- Patient age ≥18 years
- Life expectancy of >2 months (per the judgement of the investigator)
- ≤3 painful bone metastases that are in the extremities but are not in the feet, hands, or wrists
- Bone metastases that can be treated using predefined treatment field sizes (7.5 cm × 7.5 cm, 7.5 cm × 10 cm, 7.5 cm × 12 cm, 7.5 cm × 14 cm, 7.5 cm × 16 cm, 7.5 cm × 18 cm, and 7.5 cm × 20 cm), without overlap of radiation fields
- Patients who are able to comply with the protocol
- Provision of signed and dated informed consent form

Exclusion criteria

- Patients who are pregnant or nursing
- Prior radiotherapy to the treatment site(s)
- Patients whose painful bone metastasis sites requiring treatment are all in ineligible treatment sites for FLASH, such as lesions of the feet, hands, or wrists or lesions that are not in the extremities
- More than 3 painful bone metastases of the limbs requiring palliative radiotherapy
- Tumor lysis of >50% of the circumferential bone cortex or other factors considered to place the subject at significant risk of pathologic fracture
- Patients with bone fractures
- Patients with metal implants in the treatment field
- Patients who will receive cytotoxic chemotherapy within 1 week prior to or 1 week following their planned radiation treatment
- Prior local therapy modality to the treatment site(s) within 2 weeks of study enrollment
- Patients with pacemakers or other implanted devices at risk of malfunction during radiotherapy
- Patients at known risk of enhanced normal tissue sensitivity to radiotherapy due to inherited predisposition or documented comorbidity that might lead to hypersensitivity to ionizing radiation
- Patients with any other medical condition or laboratory value that would, at the discretion of the investigator, preclude the patient from participation in this clinical investigation
- Patients enrolled in any other clinical studies that the investigator believes to be in conflict with this clinical investigation

An investigator may withdraw a subject's participation in the study because of the following reasons: patients meeting an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation; significant noncompliance with the study procedure; and the occurrence of an AE, a laboratory abnormality, or any other medical condition or situation such that continued participation in the study would not be in the best interest of the subject.

Subjects who sign the informed consent form and subsequently withdraw or are withdrawn from the study prior to receiving FLASH therapy will not be counted toward the study participant limit and will be replaced. Subjects who sign the informed consent form, receive FLASH therapy, and subsequently withdraw or are withdrawn from the study will be counted toward the study participant limit and will not be replaced.

Imaging and Treatment Plan Selection

Each subject will undergo computed tomography (CT) simulation imaging for the area(s) encompassing the treatment targets. Prior to the acquisition of the CT simulation image, the subject will be fitted with an immobilization device, such as a Vac-Lok bag (MED-TEC Inc); this will be used at simulation and for reproducing the subject's positioning at the time of treatment.

The CT simulation images will be transferred to the Eclipse treatment planning workstation (Varian). The target site(s) will be delineated on the transferred images by one of the radiation oncologist investigators. An expansion (margin) of ≥5 mm will be added to the target to create a planning target volume (PTV).

For each of the FLASH treatment sites, plans will be chosen from a predefined library of single-field, 250-MeV transmission beam plans for different field sizes. The largest treatment field available for this study is 7.5 cm × 20 cm. If it is determined at the time of CT simulation or during treatment planning that the target would be inadequately encompassed by the available fields, then the subject no longer meets the eligibility criteria for the study (Textbox 1) and should be removed from the study and replaced.

The predefined plans are designed to deliver a radiation prescription of 8 Gy in a single fraction at a dose rate of ≥40 Gy per second to the PTV. The volume of the PTV receiving 90% of the prescribed dose shall be ≥90%, and the dose to 10% of the PTV will not exceed 110% of the prescription dose. Because a transmission beam is being used, a relative biological effectiveness of 1.0 will be used for the dose calculation, as there is no Bragg peak within the body.

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FLASH Treatment

The treatment plan will be transferred from the ARIA Oncology Information System (Varian) to the proton therapy system console for patient-specific quality assurance (QA) and FLASH radiotherapy delivery. Treatment will be carried out on a ProBeam proton therapy system (Varian). This FDA-cleared proton therapy system will be modified under an IDE to deliver the transmission-beam proton radiation at a FLASH dose rate.

Clinical site staff with appropriate qualifications will be trained on device usage and clinical study operations. The FLASH delivery will be performed in accordance with written instructions and training. QA procedures will be completed to verify that the dose delivered is as prescribed. On each day of treatment, but prior to the subjects' treatments, QA procedures for the radiotherapy system (machine QA) will be performed to confirm the FLASH dose and the dose rate constancy of the proton delivery system [28]. Additionally, patient-specific QA will be performed per institutional practices for all subjects, using, for example, standard film and ion chamber dosimetry procedures.

At the time of treatment, subjects will be positioned on the treatment couch as planned at the time of their simulation visit. Image guidance will be used to verify that the target is in the correct position for treatment.

Assessments

Overview of Assessments

The following assessments will be conducted over the course of the study and according to the schedule of activities (Table 1). The choice of follow-up visit time points was informed by the study designs of Chow et al [29] and Hartsell et al [9]. Questionnaires will be completed as permitted by the subjects' clinical status.

Table 1. Schedule of assessments during the study.

Steps	Enrollment and baseline[a]	FLASH treatment (day 1)[b]			Post-FLASH treatment follow-up		Follow-up
		Before FLASH	FLASH	After FLASH	Day 2[c]	Days 2-11[c]	Each visit[d]
Patient screening	✓						
Informed consent	✓						
Computed tomography simulation	✓						
Eligibility determination	✓						
Subject and tumor characteristics	✓						
Subject evaluation	✓	✓					✓
Pain flare questionnaire		✓			✓	✓	
Pain response questionnaire		✓					✓
FLASH workflow			✓				
Adverse events				✓	✓		✓

[a]Approximately 1 to 2 weeks before computed tomography simulation.

[b]≤7 days after computed tomography simulation.

[c]The assessments associated with these visits will be completed remotely.

[d]After FLASH treatment (day 1), follow-up visits will occur on day 15 (±2 business days), month 1 (±5 business days), month 2 (±10 business days), month 3 (±10 business days), and every 2 months (±10 business days) thereafter until subject death or loss to follow-up.

FLASH Assessment

The following will be documented for each treatment: time that the subject is on the treatment table, any delays in study treatment related to the investigational device (excluding delays due to subject or facility factors not related to study treatment), and any device deficiency.

For each subject, workflow feasibility will be judged as not successful if the total treatment time, measured as subjects' time on the treatment table, is >1 hour or there is a delay related to the investigational device (excluding delays due to subject or facility factors that are not related to the study treatment) of more than 7 business days from simulation to study treatment.

For this study, a *device deficiency* is defined as an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors, and inadequate labeling [30].

In the event of interruption to treatment during FLASH, the remaining portion of the treatment should resume, as the system will correctly execute the remainder of the plan such that the full dose of 8 Gy will be delivered to the target volume. Based on reliability testing, treatment interruption is unlikely to occur.

Baseline Characteristics

Baseline characteristics will be assessed before the subjects' simulation CT and include subject and tumor characteristics.

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The subjects' characteristics are age, gender, performance status, history of medical comorbidities or autoimmune disorders, diagnosis date, and prior cancer-directed treatments.

The tumor characteristics are histology, anatomic location of the original primary tumor, anatomic location of the treatment site(s), target lesion size, target lesion extent of bone circumferential involvement (if available), and metastasis type (ie, lytic, blastic, or mixed).

Pain Flare

Transient flare in bone pain at a site treated by radiotherapy is a known acute toxicity of palliative radiotherapy for painful bone metastases in some patients [31,32].

Per the methodology of Chow et al [29], flares in bone pain due to radiation will be assessed by using the Pain Flare Questionnaire (Multimedia Appendix 3), which will be administered on day 1 to day 11. *Pain flare* is defined as either of the following: a minimum of a 2-point increase in the worst pain score for the treated site without a reduction in analgesic intake or a ≥25% increase in analgesic intake based on daily oral morphine equivalence without a reduction in the worst pain score. If the worst pain score before treatment was 9 or 10, the criteria for pain flare are met if the follow-up worst pain score is 10 and reported as worse than the worst pain before treatment with no decrease in analgesic intake. To distinguish pain flare from progression of pain, the worst pain score and analgesic intake have to return to baseline levels during the 11-day (day 1 to day 11) period. The incidence of pain flare will be determined both as the percentage of patients and as the percentage of metastatic treatment sites. Consistent with the Chow et al [29] study, we will document the use of steroid medication.

Data on use of pain medication will be collected, and changes in pain medication use will be evaluated at baseline, during each of the first 10 days after treatment, and during follow-up visits (day 15, month 1, month 2, month 3, and long-term). The percentage of subjects requiring narcotics, nonnarcotic analgesics, and no pain medications will be assessed and compared to literature values from prior clinical trials.

Pain Response

Patient-reported pain scores (overall) at baseline and posttreatment (day 15, month 1, month 2, month 3, and long-term) will be assessed, using the Brief Pain Inventory (BPI) Short Form questionnaire (Multimedia Appendix 4). Patient-reported pain scores for each treated site will be assessed using the Treated Sites Pain questionnaire (Multimedia Appendix 5).

The BPI Short Form questionnaire was selected to permit the results of this study to be compared with prior published results that were obtained by using this instrument [9]. Per the methodology of Hartsell et al [9], the worst pain scores in the BPI Short Form and the Treated Sites Pain questionnaire will be used to assess treatment response.

A *complete response* will be defined as having no pain at 3 months after radiation therapy, a *partial response* will be defined as a pain score that is at least 2 points lower than the initial response, a *stable response* will be defined as a 1-point change in pain score in either direction, and a *progressive response* will be defined as a pain score that is at least 2 points higher than the initial score [9].

The percentage of patients and the percentage of metastatic treatment sites having complete, stable, and progressive responses will be determined.

Subject Evaluations

Study personnel will review pain medications (including steroid medications), performance status, and findings of physical examinations involving the skin or other normal tissues at the planned treatment site(s) during subject evaluations. The physical evaluation will include photographs of skin at the entry and exit sites of the beam. These should include an image that encompasses the entire anatomic region treated (upper leg, lower leg, upper arm, and lower arm), with close-up photographs of the skin at each treated area(s) if the treated area(s) can be readily identified.

The investigator or a delegate who is a study physician, nurse, physician assistant, or advanced registered nurse practitioner will evaluate and manage AEs. All AEs, regardless of severity or attribution, from the time of treatment and throughout the subjects' participation in the trial will be captured in the study data. It is expected that most AEs in the study population will be due to underlying cancer and non-FLASH treatments, which will be managed by nonstudy personnel. The investigator (or the person to whom the task is delegated by the investigator) will grade each AE and determine whether the AE is serious per the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The investigator will document whether the AE is attributable to FLASH radiotherapy delivery.

The anticipated AEs for this study are the previously documented AEs [9] associated with the treatment of bone metastases via 8 Gy of radiation in 1 fraction at a standard dose rate. It is expected that most frequently seen study-related toxicities will be associated with the skin. Radiation dermatitis will be managed at the study site through outpatient treatment by the investigators or their designees, using an appropriate combination of topical emollients, topical steroids, topical antibiotics, and dressings as deemed necessary by the investigator or designee. For other AEs that might occur, such as the pathologic fracture of the treated bone (a known complication of the disease process), patients will be referred to the appropriate specialist for management.

It is desirable to have in-person follow-up visits. However, in the event of a subject's inability or reluctance to travel (given the COVID-19 pandemic), it is acceptable to carry out remote follow-up visits. In these circumstances, subject evaluation may be carried out by using remote visits, record reviews, or a combination thereof. Photographs of the treatment site may be taken at home by caregivers, and physical evaluations will be carried out to the extent that is feasible via telehealth.

Toxicities that are rated by the investigator as possibly, probably, or definitely related to FLASH radiotherapy will be used for assessing the toxicity of the FLASH treatment. A *dose-limiting toxicity* (DLT) is defined as a toxicity grade of $^{3}3$ that is

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possibly, probably, or definitely related to FLASH radiotherapy. The number of DLTs will be monitored throughout the duration of the study.

End of Study

At the end of a subject's participation in the study, the investigator will document the reason for the end of the study and will attempt to record patient-reported scores for overall pain and for the pain specifically in the treated site(s), the use of pain medications (including steroid medications), and AEs (including skin and other normal tissue toxicities).

Statistical Analysis

Owing to the small planned sample size, no formal statistical calculations will be performed. The sample size of 10 subjects was determined in consultation with regulatory authorities. Where appropriate, descriptive statistics will be used to analyze the results.

Privacy and Confidentiality

All efforts will be made to remove patient-identifying information and deidentify the data. Only the minimum necessary information regarding the patients' health records and treatment while participating in this study will be collected. All reasonable efforts will be made to protect the privacy of the patients.

Data Collection, Management, and Monitoring

Standardized electronic case report forms and case report form completion guidelines will be created for the collection of study data. These case report forms will include fields for documenting unintended effects of trial interventions or trial conduct, such as AEs, device issues, and protocol deviations.

The study data will be entered into a commercial electronic data capture system designed for clinical research. Automated edit checks, queries, and audit trails are built into the system to ensure accurate data collection. A secure, central storage site provided by the sponsor will be used to collect study DICOM data and photographs.

Data will be transmitted from the study site to the electronic data capture system via a secure internet connection and by using industry-standard encryption modalities. Data access will be password protected.

All data will be reviewed by a clinical monitor from the sponsor or a representative of the sponsor to ensure acceptable accuracy and completeness. The principal investigator will maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. After study closure, the investigator will maintain all source documents and study-related documents.

Stopping Rules

Enrollment will cease and the study data will be reviewed by the study committee (principal investigator and coinvestigators) and by the Cincinnati Cancer and Blood Disease Institute Data Safety Monitoring Board (DSMB) if any of the following occurs: 3 subjects experience a DLT, 3 subjects are on the treatment table for more than 1 hour, 3 subjects have a delay in study treatment related to the investigational device (excluding delays due to subject or facility factors not related to the study treatment) of more than 7 business days from simulation to treatment, or a major device malfunction in dose delivery (as indicated by the dose monitoring system) occurs. The DSMB is independent of the sponsor.

Results

FAST-01 opened to enrollment on November 3, 2020, and the final patient signed the informed consent document on October 1, 2021.

Data collection will continue for the lifetime of the study participants or when they withdraw from follow-up. Interim results, including the conclusions of the workflow feasibility analysis, are expected to be published in 2022. The final study results will be published upon completion of the study, which may run from 1.5 years to several years, depending on the duration of subject participation.

Discussion

This first-in-human study investigates the use of ultrahigh dose rate proton FLASH therapy for the single-fraction treatment of painful bone metastases in the extremities in a routine clinical setting. Numerous preclinical studies have shown that FLASH therapy reduces radiation-related toxicities when compared to conventional radiotherapy. In this trial, we anticipate that the feasibility of FLASH therapy in a clinical setting will be demonstrated. Additionally, we hypothesize that radiation-induced toxicity will be limited and that pain relief will be similar to historical comparators.

The sample size of 10 subjects in this clinical trial is common in first-in-human device studies, and it was the sample size agreed upon with the US FDA as part of an IDE approval.

This study will use single-fraction treatment delivered at a dose rate of ≥40 Gy per second for the enrolled subjects. Single-fraction radiotherapy for the treatment of bone metastases has been shown to be effective in prior investigations. In 2005, a prospective, phase 3, randomized RTOG study compared the efficacy of multiple-fraction radiotherapy (300 cGy/fraction × 10 fractions) with single-fraction radiotherapy (800 cGy/fraction × 1 fraction) for the treatment of painful bone metastases. The results indicated comparable efficacy for the two fractionation schedules [9]. Based on ongoing reviews of the clinical evidence [4,9,33], single-fraction, 8-Gy radiotherapy remains a standard of care for the palliation of bone metastasis, and it was therefore selected as an appropriate course of treatment for an initial clinical trial of FLASH. The use of this fractionation for the FLASH treatment enables comparison with the data from prior investigations that used photon radiation and conventional dose rates.

AEs attributed to FLASH will be compared with those observed in the prior RTOG randomized trial [9]. In that study, toxicities were scored by using the RTOG acute and late morbidity criteria. That grading system has since been supplanted by the CTCAE system. For skin toxicities, which are expected to be

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the most common treatment-related toxicity in our clinical study, the RTOG skin and CTCAE radiation dermatitis scoring systems are very similar, and direct toxicity comparisons can be made between our study and historical studies.

The BPI questionnaire (both the long and the short form questionnaires) was originally developed for patients with cancer and consists of a set of standardized questions for describing pain, pain medication use, and the interference of pain in the patients' lives. The BPI has been recommended as an appropriate tool for measuring pain from metastatic bone disease [34], and using it makes it possible to consider the data from this study in the context of historical data. Similarly, the pain flare questionnaire chosen for use in this evaluation is the same instrument used by Chow et al [29] in a prior study evaluating the use of steroids in combination with radiotherapy for the palliation of bone metastases.

FAST-01 is designed as a first-in-human trial involving 10 patients requiring palliative radiotherapy to the extremities. This low-risk clinical setting is ideal for the initial evaluation of this new technology. Favorable results would support the further investigation of FLASH therapy for other clinical indications. Future research could include treating lesions nearer to sensitive normal tissues and evaluating curative dose regimens.

Acknowledgments

This study is sponsored by Varian, a Siemens Healthineers Company. For more information, contact LL (lisa.levine@varian.com).

Joseph Speth (University of Cincinnati and Cincinnati Children's Hospital, Cincinnati) contributed to the protocol development. Sponsor employees Heike S Hausen and Kathleen T Campbell (Varian) contributed to manuscript development, and Vidhya Krishnamurthi, Aaron Marshall, Adam Harrington, and Michael Folkerts (Varian) contributed to the technical development and discussions that made the proton FLASH treatment possible. The Cincinnati investigators had final authority on journal selection and the content for publication and provided final approval of the versions for submission and publication.

Data Availability

Data sharing is not applicable to this manuscript, as no data sets were generated or analyzed during the development of the protocol described herein. Once data collection begins, all investigators will have access to anonymized patient-level data.

Conflicts of Interest

ECD has received small honoraria from Varian Speakers Bureau for a February 2022 virtual talk. ZX is a principal investigator of a preclinical research grant from Varian, a Siemens Healthineers company. The grant goes to the author's institution. MS is a private investigator on a pre-clinical research grant from Varian, a Siemens Healthineers company; the grant goes to the author's institution. JW, CMC, KR, LL, RS and DK are employees of Varian, and CBS is a Varian Medical Systems consultant. JP is the principal investigator of a multi-investigator research program contract between his institution and Varian Medical Systems; the funding goes to the author's institution. JP's institution also receives funding for the execution of FLASH clinical trials. JP does not receive honoraria or other forms of payment from Varian Medical Systems, and the author follows their institutional policy toward conflicts of interest in this consultant role. JB is a principal investigator of a research grant from Varian Medical Systems; the grant funding goes to the author's institution. JB is also a consultant for Varian, involved in its application to the Food and Drug Administration for FLASH radiotherapy. The author follows the policy of his institute in terms of the conflicts of interest in this consultant role. The remaining authors have no conflicts of interest to declare.

Multimedia Appendix 1
Trial recruitment flier.
[PDF File (Adobe PDF File), 177 KB - resprot_v12i1e41812_app1.pdf]

Multimedia Appendix 2
Consent form.
[PDF File (Adobe PDF File), 423 KB - resprot_v12i1e41812_app2.pdf]

Multimedia Appendix 3
Pain flare assessment.
[PDF File (Adobe PDF File), 123 KB - resprot_v12i1e41812_app3.pdf]

Multimedia Appendix 4
Overall pain assessment.
[PDF File (Adobe PDF File), 271 KB - resprot_v12i1e41812_app4.pdf]

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Multimedia Appendix 5
Treated Sites Pain questionnaire.
[PDF File (Adobe PDF File), 389 KB - resprot_v12i1e41812_app5.pdf]

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Abbreviations

AE: adverse event
BPI: Brief Pain Inventory
CT: computed tomography
CTCAE: Common Terminology Criteria for Adverse Events
DLT: dose-limiting toxicity
DSMB: Data Safety Monitoring Board
FDA: Food and Drug Administration
IDE: investigational device exemption
PTV: planning target volume
QA: quality assurance
RTOG: Radiation Therapy Oncology Group

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Protocol

Neural Correlates of the DEEPP (Anti-suicidal Response to Ketamine in Treatment-Resistant Bipolar Depression) Study: Protocol for a Pilot, Open-Label Clinical Trial

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Abstract

Background: Suicide is among the top 10 leading causes of death worldwide. Of people who died by suicide, the majority are diagnosed with depression. It is estimated that 25%-60% of people with bipolar depression (BD) will attempt suicide at least once, and 10%-15% will die by suicide. Several treatments, such as lithium, clozapine, electroconvulsive therapy, and cognitive behavioral therapy, have been shown to be effective in treating suicidality. However, these treatments can be difficult to tolerate or may take months to take effect. Ketamine, a glutamate N-methyl-D-aspartate antagonist, has been shown to have rapid antisuicidal effect and antidepressant qualities, and is thus a promising intervention to target acute suicidality in patients with BD. However, the biological mechanism underlying its therapeutic action remains poorly understood. Enhancing our understanding of underlying mechanisms of action for ketamine's effectiveness in reducing suicidality is critical to establishing biological markers of treatment response and developing tailored, personalized interventions for patients with BD.

Objective: This is an open-label clinical trial to test the safety and feasibility of repeated ketamine infusions to treat acute suicidality. The primary objective is to test the safety and feasibility of ketamine intervention. The secondary objective is to examine ketamine's potential neurophysiological mechanisms of action by assessing cortical excitation and inhibition to determine potential biomarkers of clinical response. Other objectives are to evaluate the effect of ketamine on acute suicidality and other clinical outcomes, such as depressive symptoms and quality of life, to inform a future larger trial.

Methods: This open-label clinical trial aims to test the safety and feasibility of repeated ketamine infusions in patients with BD for suicidality and to assess ketamine's neurophysiological effects. A sterile form of racemic ketamine hydrochloride will be administered over a 40-minute intravenous infusion 2 times per week on nonconsecutive days for 4 weeks (8 sessions). We will recruit 30 adults (24-65 year olds) over 2 years from an academic psychiatric hospital in Toronto, Canada.

Results: This study is currently ongoing and actively recruiting participants. So far, 5 participants have completed the trial, 1 is currently in active treatment, and 8 participants are on the waitlist to be screened. We anticipate initial results being available in the fall of 2023. This proposal was presented as a poster presentation at the Research to Reality Global Summit on Psychedelic-Assisted Therapies and Medicine, held in May 2022 in Toronto, Canada.

Conclusions: Developing effective interventions for acute suicidality in high-risk populations such as those with BD remains a major therapeutic challenge. Ketamine is a promising treatment due to its rapid antidepressant and antisuicidal effects, but its underlying neurophysiological mechanisms of action remain unknown.

Trial Registration: ClinicalTrials.gov NCT05177146; https://clinicaltrials.gov/ct2/show/NCT05177146

International Registered Report Identifier (IRRID): DERR1-10.2196/41013

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(JMIR Res Protoc 2023;12:e41013) doi:10.2196/41013

KEYWORDS

bipolar depression; suicidality; ketamine intervention; neurophysiological markers of response

Introduction

Background and Rationale

Suicide is among the top 10 leading causes of death, with progressively increasing rates and is a critical public health issue [1]. Bipolar depression (BD) is a serious psychiatric condition with a high mortality rate due to suicide [2]. Between 25% and 60% of those with BD will attempt suicide at least once, and 10%-15% will die by suicide [3-5]. Several interventions, such as lithium, clozapine, electroconvulsive therapy, and cognitive behavioral therapy, have demonstrated antisuicidal properties [4,5]. However, as polypharmacy is common in patients with bipolar illness [6], adding another treatment can be difficult to tolerate, or new treatments may take months to take effect. Therefore, there is an urgent need to develop robust interventions to treat suicidality in patients with BD rapidly. In addition, establishing biological markers of treatment response is critical in developing personalized, tailored treatment interventions.

A paradigm shift from a monoamine hypothesis to a plasticity-based hypothesis of depression represents a substantial advancement, where accumulating evidence suggests that glutamatergic or excitatory neurotransmission system dysfunction plays a pivotal role in depression [7-9]. There are 3 classes of glutamate-gated ion channels such as α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid, and kainite and *N*-methyl-d-aspartate (NMDA) receptors that transduce the postsynaptic signal [7]. NMDA receptors are distributed throughout the brain and are fundamental to excitatory neurotransmission and the normal functioning of the central nervous system (CNS) [7,8]. Ketamine is the first clinically used NMDA receptor antagonist with a primary mechanism of action closely linked to the blockade of the NMDA receptor at the phencyclidine site, which mediates excitatory synaptic transmission through the CNS [8-10].

Developing effective interventions for acute suicidality in high-risk populations, such as BD, remains a major therapeutic challenge. Ketamine is a promising treatment modality due to its rapid antisuicidal [11,12] and antidepressant [13] effects, with numerous studies demonstrating its safety and efficacy in subanesthetic doses administered over 40-minute intravenous (IV) infusions [11-13]. Despite growing interest in ketamine interventions in depressive disorders, our understanding of ketamine's underlying neurophysiological mechanisms of action, especially concerning suicidality, remains very limited.

Noninvasive brain stimulation neurophysiological tools, such as transcranial magnetic stimulation (TMS), offer an opportunity to study human brain cortical physiology mechanisms in vivo with high temporal resolution [14]. The combination of TMS with a CNS pharmacological agent, such as ketamine, will provide a platform to explore the neurophysiological basis of the impact of ketamine on brain physiology, an important piece of work toward identifying neurobiomarkers of treatment response. Until present, only some studies have attempted to examine the excitatory and inhibitory circuits by using a range of TMS protocols during infusion of incremental doses of ketamine [15-17], primarily using very low ketamine doses or single doses in healthy volunteers. Currently, the prediction of the therapeutic response in those with mood disorders as measured by changes in cortical excitability continues to be in very early stages and has not been systematically tested, making this proposal uniquely positioned among other neurophysiological studies on ketamine and TMS. Our group has previously demonstrated impaired GABA (gamma-aminobutyric acid) inhibition from the motor cortex in patients with depression, a finding that was most pronounced in patients with treatment-resistant depression [16,18,19]. In addition, Croarkin et al [19] demonstrated impaired NMDA receptor–mediated excitation in depression.

Objectives

The primary objective of this open-label pilot clinical trial is to examine the safety and feasibility of repeated subanesthetic doses (0.5-0.8 mg/kg) of ketamine administered over 40-minute IV infusions in patients with BD to treat acute suicidality. The secondary objective is to analyze the potential impact of ketamine on neurophysiological markers associated with cortical excitation and inhibition as a proxy of NMDA receptor activity in the cortex. Our scientific group has successfully applied TMS-electromyography (EMG) and TMS-electroencephalogram (TMS-EEG) paradigms to assess cortical activities in patients with psychiatric issues [15,18]. Thus, we will use these paradigms to investigate the impact of ketamine on cortical activities in patients with BD and suicidality. We have previously reported that intracortical facilitation is abnormal in depression [14,18] and is closely associated with NMDA receptor–mediated neurotransmission [9,18]. This study will evaluate cortical excitation and inhibition pre- and postketamine course in patients with BD and suicidality to determine a biological target of ketamine treatment response. We will use a TMS-EMG paradigm to investigate the impact of ketamine on cortical excitation via intracortical facilitation and cortical inhibition via short-interval cortical inhibition paradigms [19-21]. Next, we will compare the effect of ketamine on resting-state cortical oscillation via EEG. These results will provide important evidence for the role of NMDA receptors in cortical physiology, which may serve as a ketamine biomarker and would be a crucial breakthrough in determining potential predictors of clinical response for suicidality in patients with BD.

Trial Design

The DEEPP (Anti-suicidal Response to Ketamine in Treatment-Resistant Bipolar Depression) study is designed as an open-label pilot clinical trial to assess (1) the feasibility of a series of IV ketamine infusions to treat suicidality in patients

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with BD and (2) ketamine's neurophysiological markers associated with cortical excitation and inhibition.

Methods

Study Setting

Potential participants will be recruited from 1 site, specifically the Centre for Addictions and Mental Health, a large academic center located in Toronto, Ontario, Canada, over 2 years.

Eligibility Criteria

Inclusion criteria are patients who (1) meet criteria for bipolar disorder according to DSM-V (Diagnostic and Statistical Manual of Mental Disorders, 5th edition) criteria as confirmed by the Mini-International Neuropsychiatric Interview (MINI) [22]; (2) meet criteria for a current depressive episode, confirmed with the 24-item Hamilton Rating Scale for Depression (HRSD-24) score of 14 and above [23]; (3) experiencing suicidal ideation as defined by a score of 9 or higher on the Scale for Suicide Ideation (SSI) [24,25]; (4) capable of providing consent; (5) outpatients; (6) able to speak and understand English; and (7) aged 24-65 years, inclusive.

Exclusion criteria are patients who (1) have a history of a substance use disorder within the past month or a lifetime history of ketamine substance use disorder, as confirmed by the MINI; (2) concomitant major unstable medical illness (eg, poorly controlled hypertension, enlarged prostate, renal- or urinary-related issues, the presence of cardiac decompensation/heart failure, results of liver function tests [alanine transaminase and aspartate transaminase] are 3 times or greater than the upper limit of normal readings); (3) pregnancy or the intention to become pregnant or breastfeeding during the study as confirmed by self-report. Female participants of reproductive potential must be willing to use a medically acceptable method of birth control which includes highly effective (eg, approved hormonal contraceptives, intrauterine device, tubal ligation) or double barrier (eg, male condom with a diaphragm, male condom with cervical cap) methods of contraception or abstinence if that is the usual and preferred lifestyle of the participant; (4) DSM-V diagnosis of any primary psychotic disorder, obsessive-compulsive disorder, posttraumatic stress disorder (current), unipolar depression, other subtypes of depressive disorders, or current psychotic symptoms as confirmed by the MINI; (5) current episode meeting criteria for mania/hypomania or mixed episode as per DSM-V criteria on the MINI or as determined by the study team; (6) primary diagnosis of severe personality disorder as assessed during the initial consultation with a study psychiatrist prior to study entry; (7) any significant neurological disorder (eg, a space occupying brain lesion, a history of stroke, a cerebral aneurysm, a seizure disorder, Parkinson disease, Huntington chorea, multiple sclerosis) as assessed through medical history review during the initial consultation with a study physician prior to study entry; (8) requiring a benzodiazepine with a dose equivalent to lorazepam 2 mg/day or higher; (9) being on any anticonvulsant (eg, lamotrigine, topiramate, carbamazepine) or opioid medication due to the potential of these medications to limit the efficacy of ketamine; (10) cognitive or physical impairment that may potentially interfere with IV ketamine administration or participants' ability to stay in the same place for a 2-hour monitoring supervision as assessed through medical history review during the initial consultation with a study physician prior to study entry; (11) any intracranial implant (eg, aneurysm clips, shunts, cochlear implants) or any other metal object within or near the head, excluding the mouth, that cannot be safely removed given that we will be using TMS-EMG/EEG; (12) inability to secure escort to accompany them back home after ketamine sessions; or (13) any known allergy to ketamine or any component or ingredient of the ketamine preparation.

Discontinuation Criteria

Participants will be discontinued from the study if they cannot safely continue the study based on any of the following criteria: (1) experience clinically significant worsening of depressive symptoms (50% increase in HRSD-24 scores from baseline on 2 consecutive ratings); (2) require in-patient hospitalization due to the presence of clinically significant suicidal ideation with imminent intent or attempted suicide; (3) develop clinically significant worsening of mood or physical symptoms (assessed by a study physician); (4) miss over 2 consecutive treatments during the study without the cause; (5) develop any medical illness that may be unstable; (6) experience a seizure; (7) become pregnant, or (8) withdraw consent.

Intervention

Drug Characteristics, Distribution, and Storing

A sterile form of racemic ketamine hydrochloride (DIN: 02246795, 02246796) will be dispensed through the Centre for Addiction and Mental Health (CAMH) pharmacy. Ketamine will be administered intravenously over a 40-minute infusion using a Baxter FA-2021-056 pump. The CAMH research pharmacy will order the investigational product from the supplier (Sandoz Canada Inc) on behalf of the research team with the study investigator's authorization and will be responsible for the receipt and responsible destruction of the investigational product. As per the manufacturer's recommendation, the investigational product will be stored between 15°C and 30°C, protected from light and heat, and discarded within 28 days of initial use. Only dedicated medical personnel will have access to the investigational product and pick it up from the locked and password-protected storage on the day of the treatment. All treatment sessions will be delivered at CAMH's Temerty Centre for Therapeutic Brain Intervention, a dedicated clinic providing electroconvulsive therapy to patients and thus equipped with a highly trained medical team.

Drug Administration and Scheduling

Ketamine will be administered 2 times per week for 4 weeks (a total of 8 treatment sessions). The dosing schedule will be determined based on the patient's weight, clinical response, and tolerability (Table 1). The first treatment session dose will be calculated based on 0.5 mg/kg. Doses in this trial will range between 0.5 and 0.8 mg/kg.

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Table 1. Intervention schedule.

Week	Session, intervention, and dosing
1	• Start-up (first) dose to assess tolerability; 0.5 mg/kg intravenous infusion over 40 minutes
	• Second infusion session (dose adjustment, if needed, 0.5-0.8 mg/kg)
2	• Third infusion session (40 minutes; dose adjustment, if needed, 0.5-0.8 mg/kg)
	• Forth infusion session (40 minutes; dose adjustment, if needed, 0.5-0.8 mg/kg)
3	• Fifth infusion session (40 minutes; dose adjustment, if needed, 0.5-0.8 mg/kg)
	• Sixth infusion session (40 minutes; dose adjustment, if needed, 0.5-0.8 mg/kg)
4	• Seventh infusion session (40 minutes; dose adjustment, if needed, 0.5-0.8 mg/kg)
	• Eighth infusion session (40 minutes; dose adjustment, if needed, 0.5-0.8 mg/kg)

Dose Adjustment

If the first session is tolerated well and the patient has no side effects, the dose can be further increased up to (but not exceeding) 0.8 mg/kg. Participants will have a weekly follow-up with the study's physician. The study physician will determine the exact doses on a case-by-case basis based on treatment tolerability, safety, and clinical response. From principal investigator's (PI) previous clinical experience treating patients with ketamine, dose adjustment occurs within the first 1-3 sessions, and patients continue with stable doses following sessions 2 and 3. However, dose adjustment can also occur after session 3 if the participant experiences side effects with repeated infusions. The procedure around dose adjustment is a part of this trial's feasibility; this information will be collected by the study physician during weekly follow-ups and incorporated into the research protocol for further studies in the future.

Monitoring Schedule

All patients will stay on-site for the administration and monitoring period, calculated as 2 hours from the start of IV infusion per consensus guidelines in ketamine administration. Patients will stay in a separate private space and be provided with noise-cancellation headphones and an eye mask to minimize environmental disruptions. Patients will be closely monitored by available trained personnel, with a medical doctor present on-site for the entire supervision period. Specifically, IV induction will be performed under the direct supervision of an anesthesiologist or delegate and psychiatrist, who will remain present on-site for the entire duration of the 40-minute ketamine infusion. Trained personnel are available on-site to closely monitor the postinfusion period, where vital signs (ie, heart rate, blood pressure, oxygen saturation level) will be monitored every 30 minutes. Each patient will be closely monitored for the entire IV infusion duration and the postinfusion period for at least 2 hours. The overall time per treatment session is at least 2 hours starting from the time of infusion initiation. This includes the 40-minute infusion period and 80 minutes for postinfusion monitoring. Any adverse events will be managed by the medical team administering the treatment. If required, appropriate medications will be provided to manage treatment-related side effects and any adverse events as defined by clinical site policies and regulations. Clinical and neurophysiological assessments will be administered according to the trained research personnel's schedule for study visits. There is a total of 16 study visits in this trial, which includes treatment sessions and follow-ups.

Potential Risks and Mitigation Strategies

Given the potential risks described below, trained medical personnel will be present during the administration and for the entire duration of the 2-hour monitoring period.

Ketamine is classified as a schedule I controlled substance due to its potential for abuse and addiction and can be abused in a number of ways, including via injection, snorting, or orally. Ketamine can produce vivid dreams and a feeling that the mind is separated from the body, referred to as "dissociation." Regular users of ketamine can become tolerant to the dissociative effects of the drug, meaning an increasing amount is needed to achieve the same effect. Drug-related risks include (1) psychiatric symptoms such as fatigue, dizziness, anxiety, visual and auditory disturbances, panic attacks, increased irritability, and changes in mood and behavior; (2) medical symptoms such as transient increases in blood pressure and heart rate, an increase in the need to urinate, headaches, vision changes, chest pain, shortness of breath, confusion, memory impairment, anaphylaxis; and (3) a rare risk of dependency. To address these risks, in this trial, ketamine will be dispensed by the research pharmacy and administered by a trained medical professional, and the patient will receive close supervision and monitoring. Doses are individually calculated, and treatment sessions are structured to prevent tolerance building. Patients will be strongly discouraged from using ketamine outside of the context of this trial and will be informed that they can be discussed with the study physician if they have questions.

IV route–associated risks are infiltration, hematoma, air embolism, phlebitis, extravascular drug administration, and intraarterial injection. Most of these complications are transient and resolve with conservative monitoring. An intraarterial injection is rare but as threatening. An anesthesiologist is present

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on-site for the IV infusion and will attend if needed, per site rules and regulations.

Clinical Assessment Risks

Answering multiple questions at times can be distressing. These adverse reactions are mostly brief, transient, and rarely have long-term implications.

TMS-EMG/EEG Risks

Single-pulse TMS is now in routine clinical diagnostic use in hundreds of neurophysiological laboratories worldwide. The ability of TMS to noninvasively stimulate brain areas presents a significant advance beyond techniques that require the invasive method of direct cortical or transcranial electrical stimulation. Magnetic fields pass through the scalp and skull without the impedance encountered by direct electrical stimulation, permitting enhanced control over the site and intensity of stimulation. The induced electrical current is well below that which is expected to cause harm to nervous tissue; thus, stimulation at <1 Hz carries virtually no risk of seizure and is therefore classified as a nonsignificant risk device. In numerous studies, single-pulse TMS has been found to pose no significant health risk to properly screened healthy volunteers.

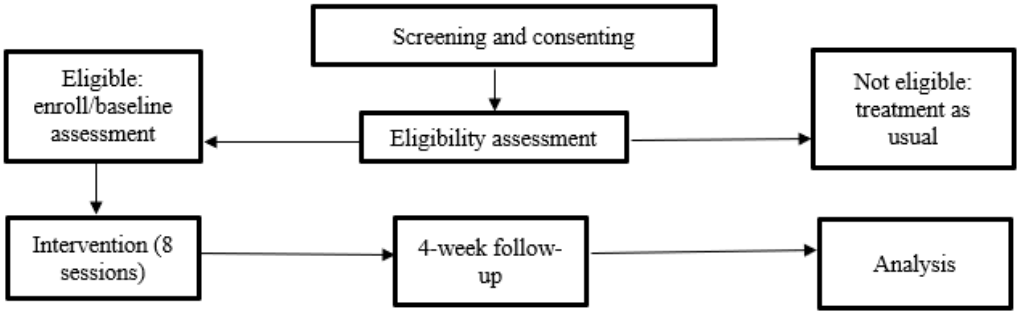
Outcomes

The primary outcome of this pilot trial is to examine the safety and feasibility of repeated subanesthetic doses (0.5-0.8 mg/kg) of ketamine administered over 40-minute IV infusions in patients with BD to treat acute suicidality based on recruitment numbers, attrition rate, and a number of adverse events in the trial. The secondary outcome is to analyze the potential impact of ketamine on neurophysiological markers associated with cortical excitation and inhibition as a proxy of NMDA receptor activity in the cortex. The tertiary outcomes are to assess the intervention's potential effect on clinical outcomes, such as acute suicidality, depressive symptoms, and quality of life.

Participant Timeline

We intend to recruit 30 participants, adults 24-65 years old, diagnosed with BD and experiencing suicidal thoughts in their current episode, over the duration of 2 years from 1 site (CAMH). The trial period is shown in the CONSORT (Consolidated Standards of Reporting Trials) diagram (Figure 1).

Figure 1. Flowchart of the study design.



Sample Size

We calculated our sample size based on this study design, which is to test the safety and feasibility of ketamine infusions. We calculated that a minimum sample size of 30 participants is needed for the proposed investigation.

Recruitment

This is a single-site open-label pilot safety and feasibility study that will be conducted at the CAMH. The CAMH is a large urban academic institution offering psychiatric care to a diverse population across the province. We intend to recruit participants through CAMH General Division Ambulatory services, which annually provides over 500 consultations for mood-related concerns. The study's PI is a staff psychiatrist and clinician-scientist in General Division who provides outpatient services to a large population with mood disorders at local and provincial levels. PI is also an interventional psychiatrist working as a part of the Therapeutic Brain Intervention Centre, seeing many patients with treatment-resistant and severe mood disorders. She is also US certified in ketamine interventions and a member of the American Society for Ketamine Physicians (ASKP). This study group has extensive experience with recruiting patients for clinical trials as the PI of this study and coinvestigators are clinician-scientists who provide care to a large number of patients with mood disorders within the context of clinical trials. Thus, we believe recruiting 30 participants over 2 years is feasible.

In addition to group expertise, we will utilize a CAMH-wide recruitment strategy, specifically the Clinical Engagement and Research Recruitment (CLEARR) model, where all new referrals to the CAMH clinics are prescreened, and all patients are informed about clinical research at the time of their initial clinical assessment. The study site will make efforts to recruit a representative and ethnically diverse sample. CAMH services a very diverse inner-city population through numerous satellite clinics in several minority neighborhoods throughout the city. Toronto has diverse cultural representation as almost 75% of its population, aged 15 and older, have direct ties to immigration. In this study, we anticipate our recruitment will follow the ethnic distribution of White/non-Hispanic 50%, Asian 20%, Southeast Asian 15%, Black/non-Hispanic 10%, and Hispanic 5%. We also expect that 60% of our population enrolled at the CAMH site will be female based on our prior experience with clinical trials at the CAMH.

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Data Collection Methods

Data will be collected on a baseline assessment, weekly during the course of IV ketamine, within a week after the completion of the intervention, and following 4 weeks for a final follow-up. Assessments will include psychiatric assessment, physical examination, and clinical assessments through manualized validated clinical scales (Multimedia Appendices 1 and 2).

Psychiatric assessment will include a consultation with a study physician to confirm a diagnosis. Demographic information, medical and psychiatric history, and concomitant medications will also be included.

A *physical examination* will include a physical exam performed by a study physician or a delegate, and blood work and electrocardiography for medical clearance according to standard clinical procedures also be reviewed by the study physician. Blood tests will include complete blood count with differential tests (white blood cells, red blood cells, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, red cell distribution width, mean platelet volume, platelet, nucleated red blood cell count, neutrophil count, lymphocyte count, monocyte count, eosinophil count, basophil count); blood chemistry test, including liver function (alanine transaminase and aspartate transaminase), kidney function (blood urea nitrogen and creatinine), and electrolytes (sodium, potassium, chloride, and phosphate); and thyroid function (thyroid-stimulating hormone). Study participants' blood pressure will also be monitored before, during, and after treatment.

Clinical assessments will include (1) the MINI to clarify psychiatric inclusion and exclusion criteria; (2) the Antidepressant Treatment History Form (ATHF) to clarify on inclusion and exclusion criteria [26]; (3) the SSI will be administered at screening, baseline, weekly, and after treatment to confirm eligibility and to assess changes as a secondary outcome measure; (4) the HRSD-24, which will assess changes in depressive symptoms and will be administered at the baseline and after treatment; (5) the Young Mania Rating Scale (YMRS), which will be used to evaluate mania/hypomania symptoms at screening and throughout the study for eligibility and safety monitoring purposes [27]; and (6) World Health Organization Disability Assessment Schedule (WHODAS 2.0), which will be used as a standard measure of disability promoted and used at baseline and after treatment to assess changes in individual level of functioning [28].

Neurophysiological assessments will include (1) the Transcranial Magnetic Stimulation Adult Safety Screen to assess potential TMS risk factors; and (2) TMS-EMG/EEG. Our neurophysiological measures have been established and have a high test-retest reliability (ie, intraclass correlation >0.9) [18,19]. Data analysis will be performed using semiautomated methods developed and validated by our group [29]. TMS pulses will be administered to the left dorsolateral prefrontal cortex using a 7-cm figure-of-eight coil and 2 Magstim 200 stimulators (Magstim Company Ltd) connected via a BiStim module, and motor-evoked potential data will be collected using commercially available software (Signal; Cambridge Electronics). Each TMS session will include the establishment of the individual threshold for stimulation of motor cortex, and dorsolateral prefrontal cortex localization will be performed according to previously published methods [29,30]. The resting motor threshold will be determined by applying single pulses of TMS to the motor cortex while the coil is placed at the optimal position to elicit motor-evoked potentials from the right abductor pollicis brevis muscle. The resting motor threshold is defined as the minimum stimulus intensity that elicited a motor-evoked potential of >50 μV in more than 5 of the 10 trials [30].

TMS-EMG will be recorded from the abductor pollicis brevis with Ag-AgCl electrodes placed over the belly of the muscle. The signal will be amplified (Model 2024F; Intronix Technologies Corporation), filtered (band-pass 2 Hz-5 kHz), digitized at 5 kHz (Micro 1401; Cambridge Electronics Design), and stored in a laboratory computer for offline analysis. The participants will be instructed to relax throughout the study. Trials contaminated with voluntary muscle activity will be discarded.

TMS-EEG

EEG will be used to evaluate TMS-induced cortical evoked activity. EEG recordings will be acquired through a 64-channel EEG system [30]. A 64-channel EEG cap will be used to record the cortical signal, and 4 electrodes will be placed on the outer side of each eye and above and below the left eye to closely monitor the eye movement artifact. All electrodes will be referenced to an electrode placed on the vertex positioned posterior to the Cz (midline central) electrode. Direct current EEG signals will be recorded with a 20-kHz sampling rate and with a low-pass filter of 300 Hz, which in pilot experiments was shown to avoid saturation of amplifiers and minimize the TMS-related artifact. The EEG data will be downsampled to a 1-kHz sampling frequency and segmented concerning the TMS stimulus such that each epoch includes a 1000-ms prestimulus baseline and a 1000-ms poststimulus activity. Epochs will be baseline corrected concerning the TMS-free prestimulus interval. The baseline-corrected poststimulus intervals (approximately 25-1000 ms) that are not contaminated by TMS artifact will be extracted and digitally filtered using a zero-phase shift 1-100-Hz band-pass filter (48 dB per octave). Records will be manually reviewed at this stage, and trials contaminated with muscle activity, movement, and TMS artifacts will be excluded from further analysis. Finally, the average signals at each recording site will be computed from the movement-free epochs (approximately 80 trials per participant) and fed into an automated eye-blink correction algorithm [30]. The eye-blink–corrected average EEG waveforms will be imported into MATLAB (The MathWorks Inc), and further analyses will be carried out using the EEGLAB toolbox [31]. Furthermore, methods in this approach will be conducted according to previously published combined TMS-EEG studies [29-31].

Data Management

The REDCap (Research Electronic Data Capture) software will be used for data collection and overall study data management throughout this project. REDCap is a secure, web-based clinical data management and electronic data capture system and database. It is built and distributed by Vanderbilt University,

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with a local instance installed on a central CAMH server overseen by the CAMH REDCap Operations Committee. All data are stored on-site and backed up daily. The system is developed and managed in compliance with HIPAA (Health Insurance Portability and Accountability Act), PIPEDA (Personal Information Protection and Electronic Documents Act), and FDA21 CFR (US Food and Drug Administration Code of Federal Regulations Title 21) Part 11 regulations, providing functions such as defined user roles and privileges, user authentication and encryption, electronic signatures, deidentification of protected health information, comprehensive auditing features to record and monitor access and data changes, and a validated software development life cycle. This system will collect data, design electronic case report forms, data entry, monitor and clean, and query and export data sets for statistical analysis.

Statistical Methods

Baseline participant characteristics will be reported and described using summary statistics—mean and SD for continuous data and number and proportion for categorical data. As the primary outcome is to assess feasibility, we will report on (1) recruitment numbers and attrition rates; (2) the number of individuals who experience side effects, and (3) the overall number and type of side effects. For neurophysiology, we will use an independent *t* test (paired 1-tailed) to compare components of TMS-evoked responses in the left dorsolateral prefrontal cortex in TMS-EEG data. In addition, we will apply a nonparametric cluster-based permutation test to investigate any significant changes in overall EEG channels. We will conduct a paired 1-tailed *t* test of the SSI and HRSD-24 scores from baseline to week 4 and monthly follow-up to assess preliminary clinical outcomes. We will also report the standardized mean difference as a measure of effect size (small: 0.2; medium: 0.5; large: 0.8).

Monitoring

Trial Monitoring

We will perform internal quality management of study conduct, data collection, documentation, and completion through proactive study monitoring using our team-based monitoring approach. Monitoring will be conducted prior to, during, and after the study concludes to ensure that good clinical practice is maintained. All data monitoring, auditing, and harms reporting will be performed according to CAMH Research Ethics Board and regulatory standards. The study investigator and delegated research personnel will monitor study participants according to the study protocol and continually assess the patient for adverse outcomes; all adverse events will be assessed in real-time to determine if they meet the criteria for a “serious adverse event” and how the event was “related” to the study intervention.

Harms

Adverse events occurring as of the first administered dose of the investigational product and 30 days after the last administered dose will be collected. All reported adverse events will be followed up to the resolution, or an appropriate posttrial follow-up plan will be determined. Serious unexpected adverse drug reactions will be reported as required by Health Canada, the Food and Drug Regulations—Division 5. For this pilot trial, all relevant adverse events and all serious adverse events will be reported to the Research Ethics Board directly if they meet applicable reporting requirements.

Auditing

At the time of this publication submission, the study also passed the CAMH Quality Assurance internal auditing process. Quality control procedures will be implemented beginning with the data entry system, and data quality control checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated for clarification/resolution.

Research Ethic Approval

This study has received CAMH Research Ethics Board (approval number 179-2020) and Health Canada (approval number NOL251577) approvals.

Consent

We will obtain informed consent from each participant who agrees to participate in the trial. Patients meeting the criteria will be referred to the research analyst/study coordinator to discuss the study purpose, procedures, potential risks, and rights as research participants. Consent forms describing the study intervention, study procedures, and risks will be given to each participant, and written documentation of informed consent will be required prior to completing the initial screening visit and starting the study intervention. Once consent is obtained, the research personnel will confirm that inclusion and exclusion criteria are met before proceeding with baseline testing. Patients will be informed that they can withdraw participation at any point during the study. The participants will be given a copy of the information and consent documents for their records. The informed consent process will be documented, and the form will be signed before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing that the quality of their medical care will not be adversely affected if they decline to participate in this study (Multimedia Appendix 3).

Confidentiality

Data confidentiality and confidentiality of the identities of the individuals participating in this study will be strictly maintained. Data forms that include identifying information will be kept in locked cabinets. Only the unique ID number assigned by the research coordinator will be used to represent participants during data entry, data transfer, data analysis, or other file management procedures. All information linking their identity will be kept separate from the research records. All information entered into a computer will be stored in a password-protected and encrypted file format on a secure server. If any participant withdraws from the study, any research information recorded for or resulting from the participant prior to the date that the participant formally withdrew consent will continue to be stored and used (in the manner described above) for research purposes (and will be disclosed by the investigators); however, no new data will be collected. Withdrawing from the study will not have any consequences for the participant. Participants’ identities will not be revealed in the publication or presentation of any results from this study.

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Access to Data

The data sets generated during and/or analyzed during this study are not currently publicly available due to the ongoing trial but will be available from the corresponding author upon reasonable request.

Dissemination Policy

The results of this study will be disseminated through publications and presentations at the scientific conferences.

Results

This study is currently ongoing and actively recruiting participants. So far, 5 participants have completed the trial, 1 is currently in active treatment, and 8 participants are on the waitlist to be screened. We anticipate initial results being available in the fall of 2023. This proposal was presented as a poster presentation at the Research to Reality Global Summit on Psychedelic-Assisted Therapies and Medicine, held in May 2022 in Toronto, Canada.

Discussion

Expected Findings

Developing effective interventions for acute suicidality in high-risk populations such as BD remains a major therapeutic challenge. Ketamine, an NMDA receptor antagonist, represents a promising intervention due to its rapid antidepressant and antisuicidal effects [11]. However, our understanding of its underlying neurophysiological mechanisms for suicidality in BD is limited. TMS-EMG and TMS-EEG can be used to produce a reliable neurophysiological measure of NMDA receptor–mediated neurotransmission [15]. To our knowledge, this is the first study to investigate the safety/feasibility and neurophysiological changes of repeated 40-minute ketamine infusions to treat suicidality in patients with BD. Results from this study will (1) inform the development of a larger, adequately powered randomized controlled trial to test the feasibility of a series of IV ketamine infusions to treat suicidality in patients with BD and (2) determine potential neurophysiological markers of clinical response.

Limitations

In general, a lack of a control group and a small sample size are limitations in ketamine clinical trials. However, given that this is a pilot open-label clinical trial, the sample size is sufficient (ie, the goal is not to assess generalizability or statistical significance). The lack of blinding in the control group is a common concern in ketamine trials because a placebo with comparable effects does not exist, and it is impossible to ensure blinding to the full extent. Because the study is conducted at a single site of a large psychiatric academic facility, the results may not be fully transferable to a broader population; however, the study will provide preliminary data on feasibility and safety to be used in a larger, adequately powered and controlled trial. Moreover, a small sample size may not allow drawing any meaningful conclusions around neurophysiological markers of response; however, results will inform a further larger clinical trial where we can test neurophysiological markers more accurately.

Clinical Significance

BD is an incapacitating psychiatric condition with high mortality rates due to suicide, where 25%-60% of patients will attempt suicide at least once in their lifetime, and about 10%-15% die by suicide. Current treatment options for suicidality are very limited. Subanesthetic doses of ketamine have been shown to have rapid antisuicidal effects [5]; however, research exploring ketamine's biological targets of treatment response remains limited. This study will provide preliminary data on the feasibility of repeated IV ketamine infusions to treat suicidality in patients with BD and investigate potential neurophysiological mechanisms to identify the biomarkers of clinical response.

Acknowledgments

This study has been funded partly by the 2020 Discovery Fund Seed Funding, an award supported by a generous philanthropic donation dedicated to the innovation required to solve major challenges in the effective diagnosis and treatment of mental illness.

Authors' Contributions

YK is the lead of this project as a principal investigator. DV, TK, and AT will monitor recruitment and treatment sessions. DB is a mentor and senior author who will assist with trial monitoring and access to facilities and trained personnel. RZ will assist with data analysis. All authors will work on the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) flowchart.
[DOCX File , 18 KB - resprot_v12i1e41013_app1.docx]

Multimedia Appendix 2
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist.

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[PDF File (Adobe PDF File), 163 KB - resprot_v12i1e41013_app2.pdf]

Multimedia Appendix 3
Participant consent form.
[PDF File (Adobe PDF File), 229 KB - resprot_v12i1e41013_app3.pdf]

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Abbreviations

ASKP: American Society for Ketamine Physicians
BD: bipolar depression
CAMH: Centre for Addiction and Mental Health
CLEARR: Clinical Engagement and Research Recruitment
CNS: central nervous system
DEEPP: Anti-suicidal Response to Ketamine in Treatment-Resistant Bipolar Depression
DSM-V: Diagnostic and Statistical Manual of Mental Disorders, 5th edition
EEG: electroencephalography
EMG: electromyography
FDA21 CFR: US Food and Drug Administration Code of Federal Regulations Title 21
GABA: gamma-aminobutyric acid
HIPAA: Health Insurance Portability and Accountability Act
HRSD-24: 24-item Hamilton Rating Scale for Depression
IV: intravenous
MINI: Mini-International Neuropsychiatric Interview
NMDA: N-methyl-d-aspartate
PI: principal investigator
PIPEDA: Personal Information Protection and Electronic Documents Act
REDCap: Research Electronic Data Capture
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
SSI: Scale for Suicide Ideation
TMS: transcranial magnetic stimulation
WHODAS 2.0: World Health Organization Disability Assessment Schedule
YMRS: Young Mania Rating Scale

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Protocol

The Effect of Prophylactic Intravenous Amiodarone Administration on Reperfusion Ventricular Fibrillation in Patients With Left Ventricular Hypertrophy Undergoing Cardiopulmonary Bypass Surgery: Protocol for a Randomized Double-Blind Clinical Trial

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Abstract

Background: Ventricular fibrillation (VF) is a common arrhythmia that occurs after the release of aortic cross-clamp (ACC) in patients undergoing cardiopulmonary bypass (CPB) surgery. Repeated defibrillation and long duration of VF could increase myocardial injuries. In patients with left ventricular hypertrophy (LVH), VF is easier to occur and more difficult to be terminated. Amiodarone, known as class III antiarrhythmic agent, has the prominent properties of converting VF and restoring the sinus rhythm. Before ACC release, administration of amiodarone has been confirmed useful to reduce occurrence of VF. However, few studies are focused on the effect of amiodarone before ACC release on reducing VF in patients with LVH.

Objective: This study aimed at determining the efficacy of prophylactic intravenous amiodarone administration on reperfusion VF after release of ACC in patients with LVH undergoing CPB surgery.

Methods: This will be a prospective, randomized, double-blind, placebo-controlled trial. The trial will enroll 54 patients with LVH aged 18-75 years who will undergo CPB surgery. All eligible participants will be randomly allocated to either the amiodarone or placebo group by using the block randomization in a 1:1 ratio. The primary end point will be the incidence rate of VF 30 minutes after ACC release and be assessed using the Fisher exact test. All data will be analyzed in accordance with the intention-to-treat principle.

Results: The study began in August 2022, and the data collection will take place for the next 2 academic years. As of this writing, 21 participants have already been recruited for the study.

Conclusions: With this trial, we are hoping to demonstrate that prophylactic infusion of amiodarone before ACC release could reduce the occurrence of reperfusion VF in patients with LVH.

Trial Registration: ClinicalTrials.gov ChiCTR2000035057; https://www.chictr.org.cn/showprojen.aspx?proj=57145

International Registered Report Identifier (IRRID): DERR1-10.2196/40115

(JMIR Res Protoc 2023;12:e40115) doi:10.2196/40115

KEYWORDS

amiodarone; cardiopulmonary bypass; left ventricular hypertrophy; ventricular fibrillation

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Introduction

Background

Ventricular fibrillation (VF) is commonly seen after aortic cross-clamp (ACC) release during cardiopulmonary bypass (CPB) surgery [1]. It has been reported that the incidence rate of VF after ACC release ranges from 45% to 100% [1-6]. Left ventricular hypertrophy (LVH) has been found to increase the incidence rate of VF after ACC release, which is more difficult to be terminated [7]. Internal electrical defibrillation is an effective method to eliminate VF but repeated shock and long duration of VF could aggravate myocardial injury and reduce the patient's prognosis [8].

There are different factors leading to VF after ACC release including surgical trauma, insufficient myocardial protection, inadequate intracardiac deairing or left ventricular vent, abnormal electrolyte and acid-base metabolism, delayed rewarming before ACC release and myocardial reperfusion injury after ACC release, etc. Among these, myocardial reperfusion injury is the main reason resulting in VF after ACC release [9]. The ischemia of cardiomyocytes could cause the increase in extracellular potassium ions. When the blood supply is restored, the uneven recovery of extracellular potassium ions makes the cell membrane potentially unstable, which would easily lead to increased self-discipline or triggered arrhythmias [10]. At the same time, myocardial ischemia-reperfusion can increase intracellular calcium levels, resulting in delayed depolarization of cardiomyocytes and triggered electrical activity, which also induces ventricular arrhythmias. Furthermore, α-adrenergic receptors are activated in reperfusion cardiomyocytes over a short period of time, contributing to increased myocardial autonomic activity and intracellular calcium levels [11]. The ischemic cardiomyocytes gradually and slowly recover their activities after the blood resupply, during which they are prone to reentrant arrhythmias, and the effective refractory period of cardiomyocytes in ischemic regions decreases, which also provides conditions for the occurrence of reentrant arrhythmias [12]. Therefore, both reentrant and nonreentrant arrhythmias play a role in the occurrence of ischemia-reperfusion VF.

Long duration of VF has many side effects on cardiomyocytes after ACC release. A study showed that coronary artery blood supply was redistributed during VF, which resulted in subendocardial myocardial ischemia and cardiac dysfunction [13]. With the prolongation of VF duration, the resistance of subendocardial vessels increased gradually, which worsened the subendocardial ischemia of cardiomyocytes. Besides, myocardial edema also developed with the long duration of VF [14]. The ventricular wall tension and venous pressure would increase during VF and higher perfusion pressure would be required to achieve normal blood supply in CPB. Frequent and irregular myocardial contractions and increased pressure in the cardiac cavity could result in a higher oxygen consumption of myocardium. The abovementioned factors lead to the imbalance of oxygen supply and demand in myocardium, which seriously destroy the function of cardiomyocytes. Moreover, Khuri et al [15] discovered that metabolic acidosis was more severe in cardiomyocytes during VF and the postoperative mortality rate was higher in a group of patients. Creatine kinase–myocardial band (CK-MB) is a specific marker of myocardial injury. After ACC release, the postoperative CK-MB of patients with VF was significantly higher than that of patients without VF, and the degree of elevation was 75% related to the duration of VF [16].

Defibrillation could also damage the myocardium. Doherty et al [17] found that when the energy of defibrillation was more than 30 J, the damage of cardiomyocytes increased and the blood flow in cardiomyocytes decreased. Multiple defibrillations significantly increased myocardial damage compared with single defibrillation. The shorter time interval of each defibrillation also resulted in greater myocardial injuries. It was observed under electron microscope that the gaps between myocardial intercalated discs increased after defibrillation, thus affecting the myocardial contractile function. A clinical study showed that myocardial injury markers, cardiac troponin T, cardiac troponin I, and CK-MB were significantly elevated after cardiac shock, which further confirmed the myocardial injury owing to internal electrical defibrillation [18].

In patients with LVH, the volume of cardiomyocytes expands, but the corresponding coronary arteries do not increase, resulting in absence of subendocardial capillaries. The end-diastolic pressure and systolic cardiac function also increase, leading to increased myocardial oxygen consumption. These histological changes give rise to the imbalance of myocardial oxygen supply and demand, and ischemia of subendocardial myocardium, which reduces the tolerance of myocardium to ischemia-reperfusion [19]. Owing to the special structure of LVH, the perfusion fluid of CPB could not completely reach the subendocardial cardiomyocytes. Compared with the normal heart, the effect of myocardial protection during CPB is usually inadequate. The incidence of VF after ACC release increased significantly, and the energy and frequency of cardiac shocks in hypertrophic myocardium increased as well [20]. Thus, reducing the occurrence of VF has an important clinical significance.

Amiodarone is a class III antiarrhythmic agent with multiple electrophysiological effects, which has been used clinically in the management of both atrial and ventricular arrhythmias. Through hepatic metabolism, amiodarone is transformed to desethylamiodarone, which has the property of antiarrhythmic effects. Amiodarone is highly lipid soluble and is widely stored in fat, muscle, skin, liver, and lungs with a very long elimination half-life, averaging about 58 days [21]. The predominant antiarrhythmic effect of amiodarone is the inhibition of IKr and IKs channels leading to a prolongation of myocardial repolarization homogeneously. Amiodarone also slows heart rate and atrioventricular nodal conduction through inhibiting calcium channels and β-receptors. In addition, it also prolongs refractoriness and reduces intracardiac conduction velocity by blocking sodium channel [22,23]. It has been confirmed that intravenous amiodarone could protect myocardium from ischemia-reperfusion and prevent VF caused by reperfusion [24-26]. During ischemia-reperfusion, amiodarone can improve the metabolic efficiency of cardiomyocytes and reduce the

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repolarization dispersion of cell membrane, which is one of the main factors causing ventricular arrhythmias.

Previous studies have shown the effectiveness of amiodarone on reducing the incidence rate of VF after ACC release [2,3,27,28]. Samantaray et al [3] reported that during coronary artery bypass grafting surgery, 150 mg of amiodarone was given 3 minutes before aortic opening, which decreased the incidence of VF after ACC release compared with the placebo-controlled group. However, in the study of Ayoub and colleagues [2], the administration of amiodarone 2 minutes before aortic opening failed to reduce the incidence of VF after ACC release during coronary artery bypass grafting surgery, but lidocaine instead reduced the occurrence of VF. Mauerman et al [27] also found that neither 300 mg of amiodarone nor 1.5 mg/kg of lidocaine reduced the occurrence of VF. Furthermore, the study of Yilmaz et al [28] showed that both 300 mg of amiodarone and 1.5 mg/kg of lidocaine decreased VF after ACC release compared with the placebo-controlled group, but there was no significant difference in reducing VF between amiodarone and lidocaine groups. Although the results from the abovementioned clinical studies are controversial, they generally hint that amiodarone has a therapeutic effect on reperfusion VF after ACC release.

In a case report of Morita et al [7], a 66-year-old female patient underwent aortic valve replacement due to severe aortic stenosis, and preoperative transthoracic echocardiogram showed the thickness of ventricular septal and left ventricular posterior wall up to 18 mm. Refractory VF after ACC release occurred and lidocaine infusion and multiple cardiac shocks were both ineffective. Thereafter, 150 mg of amiodarone was given through the root of aorta, and finally VF was terminated by one defibrillation. Suzuki et al [20] also reported a similar case of using amiodarone in terminating reperfusion VF during cardiac surgery. There is only a clinical trial about amiodarone in reducing reperfusion VF in patients with LVH [29]. In this trial, patients with LVH undergoing aortic valve replacement were randomly assigned to receive a bolus of 150 mg of amiodarone plus maintenance dose of 30 mg/hour or a bolus of 1 mg/kg of lidocaine plus maintenance dose of 1 mg/kg/hour after anesthetic induction. The incidence rate of VF was significantly lower in the amiodarone group than in the lidocaine group (20.6%, 7/34 vs 50%, 17/34, P=.02). Meanwhile, amiodarone could reduce the level of interleukin-6 and tumor necrosis factor after operation. In addition to the abovementioned studies, no more studies were focused on this area.

Objective

The objective of this study is to explore the outcomes of prophylactic intravenous amiodarone administration on reperfusion VF after ACC release in patients with LVH undergoing CPB surgery.

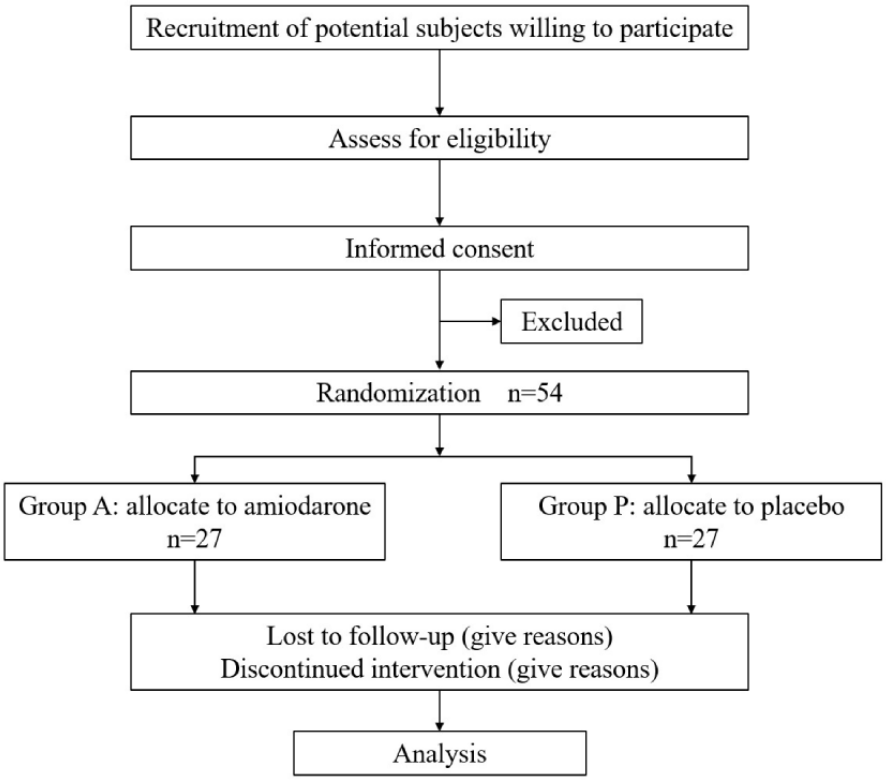
This study also concentrates on the effect of amiodarone on hemodynamic state after weaning from CPB in patients with LVH, which few previous studies have examined.

Methods

Study Design and Setting

This study is a prospective, single-center, randomized, double-blinded, placebo-controlled clinical trial to investigate effect of perioperative intravenous amiodarone on reperfusion VF after release of ACC in patients with LVH undergoing CPB. The study will be conducted in the First Affiliated Hospital of Nanjing Medical University, Nanjing, China. A schematic of the trial protocol is presented in Figure 1.

Figure 1. Trial flow chart.



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Study Population

Fifty-four patients who meet the eligibility criteria will be recruited and randomly divided into 2 groups, including amiodarone group (group A) and placebo-controlled group (group P), 27 cases in each group. Informed consent will be obtained from all participants (Textbox 1).

Textbox 1. Inclusion and exclusion criteria of participants.

Inclusion criteria

Patients included in the trial are as follows:

- Subjects undergoing cardiopulmonary bypass surgery
- Aged between 18 and 75 years
- With left ventricular hypertrophy diagnosed by transthoracic echocardiogram preoperatively
- American Society of Anesthesiologists class I-III

Exclusion criteria

Patients fulfilling one or more of the following criteria will not be included:

- Preoperative use of class I or III antiarrhythmic drugs
- Corrected QT interval of ≥480 milliseconds or QT of ≥500 milliseconds
- Left ventricular ejection fraction <30%
- With thyroid dysfunction
- With electrolyte imbalances
- With hepatic or renal dysfunction
- With pulmonary interstitial fibrosis
- Allergic to amiodarone
- Undergoing emergency surgery
- Undergoing redo surgery

Randomization and Blinding

Thirty minutes before ACC release, the enrolled participants who meet the eligibility criteria will be randomly allocated in a 1:1 ratio to 2 groups, namely, group A (treated with amiodarone) and group P (placebo control). Block randomization will be used with a block size of 4, which will be implemented with SPSS (version 22.0; IBM Corp) by an independent statistician, and the randomization numbers will be given to an external data manager with no involvement in the study procedures and concealed on password-protected computer.

When a patient meets the eligibility criteria, the external data manager will return the corresponding allocation to the nurse anesthetist. The drugs will be prepared by the nurse anesthetists according to the allocation information, packaged with the same looking and labeled with numbers, and injected by the anesthesiologists. Both anesthesiologists and patients will be blinded to the regimen. The anesthesiologist will be notified of the study group by the nurse anesthetists in case of emergency. However, the nurse anesthetists have no role in assessing the treatment actions, analyzing, or interpreting the data.

Interventions

Treatment Regimen of Amiodarone

Thirty minutes before ACC release, the trial drugs will be administered through the central venous line. In group A, 150 mg of amiodarone will be diluted to 20 mL normal saline and pumped in 5 minutes. In group P, 20 mL normal saline will be pumped in 5 minutes (Table 1).

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Table 1. Schedule for enrolment and intervention per cluster.

Time point[a]	Enrollment	Allocation	Close-out			
	$-t_1$	0	t_1	t_2	t_3	t_4
Enrollment						
Eligibility screen	✓[b]					
Informed consent	✓					
Allocation		✓				
Interventions						
Group A[c]			✓			
Group P[d]			✓			
Assessments						
Baseline demographic information	✓					
Primary end point[e]				✓		
Secondary end point[f]				✓	✓	✓

[a]Time point: t_1: baseline; t_1: intervention period, 30 minutes before aortic cross-clamp (ACC) release; t_2: 10 minutes after ACC release; t_3: 15 minutes after weaning from cardiopulmonary bypass; t_4: the end of surgery.

[b]✓: refers to crucial events at corresponding points in time.

[c]Group A: amiodarone group.

[d]Group P: placebo-controlled group.

[e]Primary end point: occurrence of ventricular fibrillation (VF).

[f]Secondary end point: t_2: the number and maximum energy of defibrillations to terminate VF; t_3: heart rate, mean arterial pressure, mean pulmonary arterial pressure, central venous pressure; t_4: the total dosages of vasoactive agents.

Anesthesia Protocols

All the patients will fast for 8 hours and abstain from water for 4 hours preoperatively and receive standardized general anesthesia. In the operating room, the patients will be routinely monitored including 5-lead electrocardiograph, peripheral blood oxygen saturation, invasive arterial blood pressure, bispectral index (BIS), and end tidal CO_2, which will be recorded every 3 minutes in each patient's electronic medical record. The induction of anesthesia will be performed as follows: 0.05 mg/kg midazolam, 0.3 mg/kg etomidate, 0.15 mg/kg cis-atracurium, and 4-6 μg/kg fentanyl. Approximately 5 minutes after induction, patients will be intubated and ventilated to maintain the end tidal CO_2 at 35-45 mm Hg. Then, the ultrasound-guided central vein catheterization will be conducted via the right internal jugular or subclavian vein. Swan-Gans catheter will be floated to pulmonary artery through the right internal jugular. Thereafter, transesophageal echocardiogram will be inserted for the intraoperative cardiac estimations. The patients continued receiving anesthesia by inhalation of sevoflurane 1%-2% and continuous pump of propofol 1-2 mg/kg/hour, dexmedetomidine 0.5 μg/kg/minute, and cis-atracurium 0.05-0.1 mg/kg/hour. The total dosage of fentanyl will be 30-50 μg/kg. During continuation of anesthesia, the BIS will be maintained between 40 and 60. Inotropic agents, vasopressors, vasodilators, or fluid administration will be applied to achieve the following hemodynamic status: a mean blood pressure of 50-80 mm Hg, cardiac index (CI) ≥2.2 L/min/m^2, and urine output ≥1.0 mL/kg/hour.

Surgical and CPB Procedures

The surgical procedures will be performed via median sternotomy with heparinization and standard CPB. The cannulation sites for CPB are at the discretion of the cardiac surgeon and dependent on the operation. The aortic cannulation is obtained with a patient size–appropriate cannula. Venous cannulation is obtained with a single 2-stage cannula in the right atrium or separate cannula in the superior and inferior vena cava. Anticoagulation is started with 400 μg/kg of heparin and maintained according to an activated clotting time of >480 seconds. CPB is initiated using a membrane oxygenator and the circuit is primed with 1500 mL of acetate Ringer solution and 200 mL of 50% human serum albumin. Patients are perfused by a nonpulsatile roller pump at a flow rate of 2.0-2.4 L/minute/m^2 and with mean arterial pressure (MAP) of 50-80 mm Hg. Moderate systemic hypothermia around 30-32 °C is maintained during CPB. Myocardial protection is achieved using intermittent antegrade or retrograde infusions of histidine-tryptophane-ketogluterate cardioplegia. Cardioplegic infusion is repeated every 120 minutes or when electrical activity of the heart is detected. After weaning from CPB, reversal of heparin is achieved with protamine.

Management of VF

Thirty seconds before ACC release, 1 mg/kg of esmolol will be given to all patients. When VF occurs after ACC release, internal electrical defibrillation with 20 J will be performed in the first attempt. If not successful, the second defibrillation with 20 J will be attempted after reusing 0.5-1 mg/kg of esmolol. If VF

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persists, the third defibrillation with 30 J will be performed after giving 1 mg/kg of lidocaine. If VF termination is not achieved, the fourth defibrillation with 40 J will be attempted after administration of 50 mg of amiodarone. If VF still exists, administration of 100 mg of amiodarone and defibrillation with 50 J will be repeated until VF terminates.

End Points

The primary end point is the incidence rate of VF 10 minutes after ACC release. The secondary end points include the duration of VF, the number and maximum energy of defibrillations needed to terminate VF, the use of other antiarrhythmic agents, and epicardial temporary pacemakers after ACC release. Besides, the secondary end points also include heart rate, MAP, mean pulmonary arterial pressure, central venous pressure and CI 15 minutes after anesthetic induction and weaning from CPB, and the speed of vasoactive agents at the end of CPB and surgery and their total dosages.

Sample Size Estimation

The sample size is calculated based on the primary end point: the incidence rate of VF 10 minutes after ACC release using PASS (version 15.0; NCSS). According to the published studies, the incidence rate of VF after ACC release ranges from 45% to 100% [1-6]. We assumed that the incidence rate of VF 10 minutes after ACC release would be 70% in the placebo-controlled group and amiodarone could decrease the rate to 30%. To reach statistical significance with a power of 80% and an α value of .05 (2-sided), 21 patients are assessed to be needed in each group. Assuming a 20% dropout or missing data rate, we will recruit 27 patients in each group for a total of 54 patients.

Statistical Analysis

All data will be analyzed using SPSS (version 22.0; IBM Corp) and in accordance with the intention-to-treat principle, beginning immediately after randomization. All statistical tests will be considered significant if $P<.05$. Only 2-sided tests will be used. Baseline characteristics will be described and compared by using the Fisher exact test for the categorical variables and 2-sample *t* test or Wilcoxon rank sum test depending on the normality of the data distribution for the continuous variables. The continuous variables will be described by mean and SD values if normally distributed or median and interquartile range if not. The normality of distributions will be checked graphically and using the Kolmogorov-Smirnov test. If there is a violation of distribution assumption, appropriate transformation will be used. The categorical variables will be expressed as frequencies and percentages.

For the primary end point, the incidence rate of VF 10 minutes after ACC release will be compared by using the chi-square test. For the secondary end points, heart rate, MAP, mean pulmonary arterial pressure, central venous pressure, and CI will be compared between 2 groups by using a repeated measures ANOVA model during the 2 observation times. Other continuous secondary end point variables will be compared between 2 groups by using a 2-sample *t* test or a Wilcoxon rank sum test depending on the normality of the data distribution. The chi-square test or Fisher exact test will be used to compare categorical secondary end point variables.

If data are missing at random, the analyses will be carried out using multiple imputations. The multiple imputation procedure will be based on all available data for that patient and be conducted using the chained equation approach. If data are not missing at random, the analyses will be conducted using available data with appropriate interpretational reservations. We will also evaluate the data using the intention-to-treat principle and per-protocol data set and compare the analysis results to estimate reliability of our analytical results.

Adverse Events Observation

During trial agent infusion, if the mean arterial pressure is less than 50 mm Hg, 20-40 μg of norepinephrine will be administered through the CPB venous reservoir. After recovery of the autonomous cardiac rhythm, if the heart rate is <60 bpm or a type II second-degree or third-degree atrioventricular block develops, 0.5-1 mg of atropine will be used intravenously, and if it does not work, epicardial temporary pacing will be performed. If the QT interval is >440 milliseconds or the corrected QT interval is >400 milliseconds, 0.5-1 mg of atropine will be given to increase heart rate to >70 bpm and blood potassium will be ensured at >4.0 mmol/L.

Data Collection and Management

The data will be collected from paper case report forms (manually counter checked with source files by the data entry personnel) by the investigator and given to the statistician to analyze the data. The data will be recorded by their specific ID number instead of participant's name throughout the study unless otherwise specified. Access to data will be restricted to the investigators who signed the confidential disclosure agreement or to the institutional or governmental auditors during the study. All original documents and files will be archived for at least 5 years to allow inspection after the trial has ended. The process will be monitored by the Institutional Ethics Committee of the First Affiliated Hospital of Nanjing Medical University.

Ethical Considerations

This study has been approved by the Institutional Ethics Committee of the First Affiliated Hospital of Nanjing Medical University (2020-SR-175) and registered with the Chinese Clinical Trial Registry (ChiCTR2000035057). Informed consent will be obtained from all participants before recruiting to the study.

Results

The study began in August 2022, and the data collection will take place for the next 2 academic years. To obtain the total study sample, a total of 54 participants will be recruited. At present, 21 participants have already been recruited for the study.

Discussion

The clinical trial is designed in order to investigate the efficacy of prophylactic intravenous amiodarone administration on

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reperfusion VF after release of ACC in patients with LVH undergoing CPB surgery.

Reperfusion VF is a common arrhythmia encountered after ACC release in patients undergoing CPB surgery. Repeated defibrillation and long duration of VF could increase myocardial oxygen consumption, damage cardiomyocytes, and decrease the patients' prognosis postoperatively. In patients with LVH, cardiac protection is often not as effective as the normal heart during CPB, and thus reperfusion VF is easier to occur and more difficult to be terminated.

Amiodarone, known as class III antiarrhythmic agent, has the properties of converting VF and restoring the sinus rhythm and can also be administered in patients with structural heart diseases. Before ACC release, administration of amiodarone has been confirmed useful to reduce occurrence of reperfusion VF. However, few proofs supported the effect of amiodarone before ACC release on reducing VF in patients with LVH. With this trial, we are hoping to further demonstrate that prophylactic infusion of amiodarone could reduce the occurrence of reperfusion VF in patients with LVH.

The limitation of this study may include the following aspects. First, this is a single-center trial with Asian patients in which there might be a selection bias. Second, the sample size is relatively small. However, according to the clinical experience in our center, the incidence of reperfusion VF is similar to those documented in the literature. So, the sample size could prove our hypothesis. We hope that in the future, a multicenter clinical trial with larger sample size could be performed to further elucidate this problem.

This study is believed to provide more proof regarding how to avoid reperfusion VF in patients with LVH undergoing CPB surgery, reducing myocardial damages occurred in those patients.

Data Availability

Access to data will be restricted to the investigators who signed the confidential disclosure agreement or to the institutional or governmental auditors during the study. All original documents and files will be archived for at least 5 years to allow inspection after the trial has ended.

Conflicts of Interest

None declared.

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Abbreviations

ACC: aortic cross-clamp
BIS: bispectral index
CI: cardiac index
CK-MB: creatine kinase-myocardial band
CPB: cardiopulmonary bypass
LVH: left ventricular hypertrophy

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MAP: mean arterial pressure
VF: ventricular fibrillation

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Protocol

A Text Messaging–Based Support Intervention to Enhance Pre-exposure Prophylaxis for HIV Prevention Adherence During Pregnancy and Breastfeeding: Protocol for a Randomized Controlled Trial

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Abstract

Background: Cisgender women in Kenya are at elevated risk of HIV acquisition during pregnancy and post partum. Acute HIV infection during pregnancy and breastfeeding accounts for approximately one-third of all vertical HIV transmissions. The World Health Organization recommends offering oral tenofovir-based pre-exposure prophylaxis (PrEP) to pregnant and postpartum women who are HIV negative but at substantial and ongoing risk for HIV acquisition. PrEP delivery for pregnant and postpartum women is expanding within routine maternal child health clinics in Kenya. However, approximately half of pregnant women discontinue PrEP within 30 days of initiation. Therefore, it is crucial to develop PrEP adherence strategies that enhance support for adherence when peripartum events and health issues pose challenges to sustaining PrEP adherence.

Objective: We are conducting a randomized controlled trial to determine the effect of a bidirectional communication platform named Mobile Solutions for Women's and Children's Health (mWACh), which utilizes two-way SMS text messaging between patients and remote nurses to support PrEP adherence and address maternal health concerns in real time during the peripartum period.

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Methods: The mWACh-PrEP study is a randomized trial designed to support PrEP adherence during the peripartum period by comparing mWACh-PrEP to the standard of care (ie, in-clinic adherence counseling) among women who are HIV negative and initiating PrEP. Purposive sampling was used to select 5 facilities offering PrEP in antenatal clinics in Kisumu and Siaya Counties, and block randomization will be used to divide participants into groups. Participants in the intervention arm will receive a customized messaging curriculum via SMS text messages targeted toward their particular perinatal stage. The primary outcome, PrEP adherence at 6 months post partum, will be evaluated using a log-binomial regression model, adjusting for imbalanced baseline characteristics. Based on a previous study of directly observed dosing conditions, we will use a hair tenofovir concentration cutoff of 0.038 ng/mg (corresponding to 7 doses/week) as the primary adherence outcome measured at 6 months post partum (binary outcome). Qualitative interviews and cost-effective analyses will be conducted to understand the feasibility, acceptability, and economic impact of the intervention.

Results: Enrollment began in March 2022 and is projected to continue until July 2023, with follow-up through March 2024. The study results are expected to be reported in 2025.

Conclusions: This trial will provide insights into using mobile health to enhance PrEP adherence among pregnant and postpartum mothers. Additionally, the findings will have implications for the use of mobile health technology to improve adherence to other daily medications during the peripartum period.

Trial Registration: ClinicalTrials.gov NCT04472884; https://clinicaltrials.gov/ct2/show/NCT04472884

International Registered Report Identifier (IRRID): DERR1-10.2196/41170

(JMIR Res Protoc 2023;12:e41170) doi:10.2196/41170

KEYWORDS

pre-exposure prophylaxis; text messaging; text message; mobile technology; PrEP adherence; adherence; prevention; pregnancy; pregnant; breastfeeding; maternal; randomized; RCT; peripartum; patient-provider; postpartum; HIV prevention; SMS; HIV; mHealth; mobile health

Introduction

Background

Young cisgender women in East and Southern Africa have a high incidence of HIV, which persists during pregnancy and the postpartum period, with evidence of an over 2-fold increased acquisition risk during these periods [1,2]. HIV infection among pregnant women also negatively impacts infants. Moreover, acute HIV infections during pregnancy and breastfeeding account for approximately 26% of all vertical HIV transmissions [3,4]. Globally, 150,000 infants were newly infected with HIV in 2019 [5], substantially above the global goal of 20,000 new infections among children by 2020. To protect women and children and eliminate vertical transmission, the World Health Organization (WHO) recommends offering daily oral tenofovir (TFV)-based pre-exposure prophylaxis (PrEP) to pregnant and postpartum women who are HIV negative and at substantial ongoing risk for HIV as part of a comprehensive HIV prevention package [6].

PrEP provision to pregnant and breastfeeding women may prevent primary maternal HIV infections and help eliminate vertical HIV transmission globally. Kenya is a world leader in PrEP implementation for pregnant and postpartum women within maternal and child health (MCH) settings [7,8]. In a study integrating PrEP delivery within antenatal care (ANC) [9], most pregnant Kenyan women at risk of HIV acquisition accepted PrEP when offered during ANC [8]. However, >50% of pregnant women discontinued PrEP within 30 days of initiation [8]. Compared to nonpregnant women, pregnant women more frequently reported side effects, which often overlap with common pregnancy symptoms, as a reason for discontinuing PrEP [8,10,11] and less frequently had detectable tenofovir diphosphate (TFV-DP) levels in dried blood spots (DBS) collected at follow-up visits (52% vs 70%) [12], suggesting suboptimal adherence. Studies among women living with HIV found that motivation for antiretroviral therapy (ART) adherence wanes after breastfeeding cessation when the risk of vertical transmission diminishes [13-15]. In qualitative studies, women's reported motivation for PrEP in pregnancy was driven by the desire to have an infant who is HIV negative [10,11]. Postpartum PrEP adherence may be reduced if a mother perceives the medication is only beneficial to her infant, similar to ART adherence patterns among postpartum women living with HIV [13-15]. Moreover, remembering to take PrEP pills may be difficult with the additional demands of newborn care [16]. PrEP effectiveness depends on adherence [17-19]; therefore, PrEP programs must now focus on improving prevention-effective adherence to maximize reductions in HIV incidence [12].

Mobile health (mHealth) technologies for public health have enormous potential to support HIV prevention and adherence among at-risk populations [20-22], including in Kenya, where cell phone ownership among women is very high at ~90% [23]. SMS text messaging–based interventions have demonstrated effectiveness in increasing adherence to ART among people living with HIV [24-27] and better treatment outcomes among women living with HIV during the peripartum period [28]. More recently, the role of SMS text message–based strategies in supporting PrEP adherence has been investigated among men who have sex with men and transgender women in the United States [29,30]. SMS text message interventions have the potential to improve PrEP adherence and could be used to address issues faced by women using PrEP via real-time texting with a health worker [31-35].

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Our team developed a bidirectional communication platform, Mobile Solutions for Women's and Children's Health (mWACh), utilizing two-way SMS text messaging between patients and remote nurses to support ART adherence and MCH among peripartum women [36]. The mWACh intervention was feasible, acceptable, and effective at improving selected ANC outcomes, including improving ART adherence among pregnant women initiated on ART and maternal and infant birth outcomes and adherence to contraceptives [37-39]. We adapted mWACh to send PrEP-tailored, Information-Motivation-Behavioral Skills (IMB) Model–based SMS text messages to facilitate adherence among pregnant women who initiated PrEP. In a nonrandomized pre- and posttest pilot, mWACh-PrEP recipients were more likely to persist with PrEP use (42% vs 22%) and to self-report high adherence (73% missed <1 pill/week vs 55%) [31]. Nurses adequately addressed issues raised by participants on PrEP use and side effects via text message.

It is essential to develop PrEP adherence strategies for pregnant women that address PrEP side effects that may overlap with pregnancy symptoms and enhance support for adherence when peripartum life events and health issues pose challenges to sustained PrEP adherence. Therefore, we are conducting a randomized controlled trial (RCT) to determine the effect of mWACh-PrEP on PrEP adherence during pregnancy and the postpartum period.

Study Objectives

The mWACh-PrEP trial (NCT04472884) aims to improve PrEP adherence among peripartum women using an IMB-informed approach. Our overall goal is to determine the effect of the mWACh-PrEP tool on PrEP adherence during pregnancy and the postpartum period among women at high risk for HIV acquisition who initiate PrEP within ANC and to estimate the cost-effectiveness for potential scale-up. We hypothesize that the mWACh-PrEP tool will improve PrEP adherence among women at risk for HIV, be acceptable to patients and providers, and be cost effective.

Methods

Study Design

We are conducting a nonblinded individual-level RCT comparing 2 arms of PrEP adherence to determine the effect of the mWACh-PrEP tool on PrEP adherence among pregnant women at risk for HIV acquisition initiating PrEP within ANC clinics.

Study Setting and Population

Facility Selection Process

The study is being conducted in 5 public health facilities offering routine MCH services within Kisumu and Siaya Counties in Kenya. The facilities were selected based on high HIV prevalence areas, existing infrastructure, established rapport, and discussions with the Kenyan Ministry of Health and the local government of Kisumu County.

Participant Eligibility Criteria

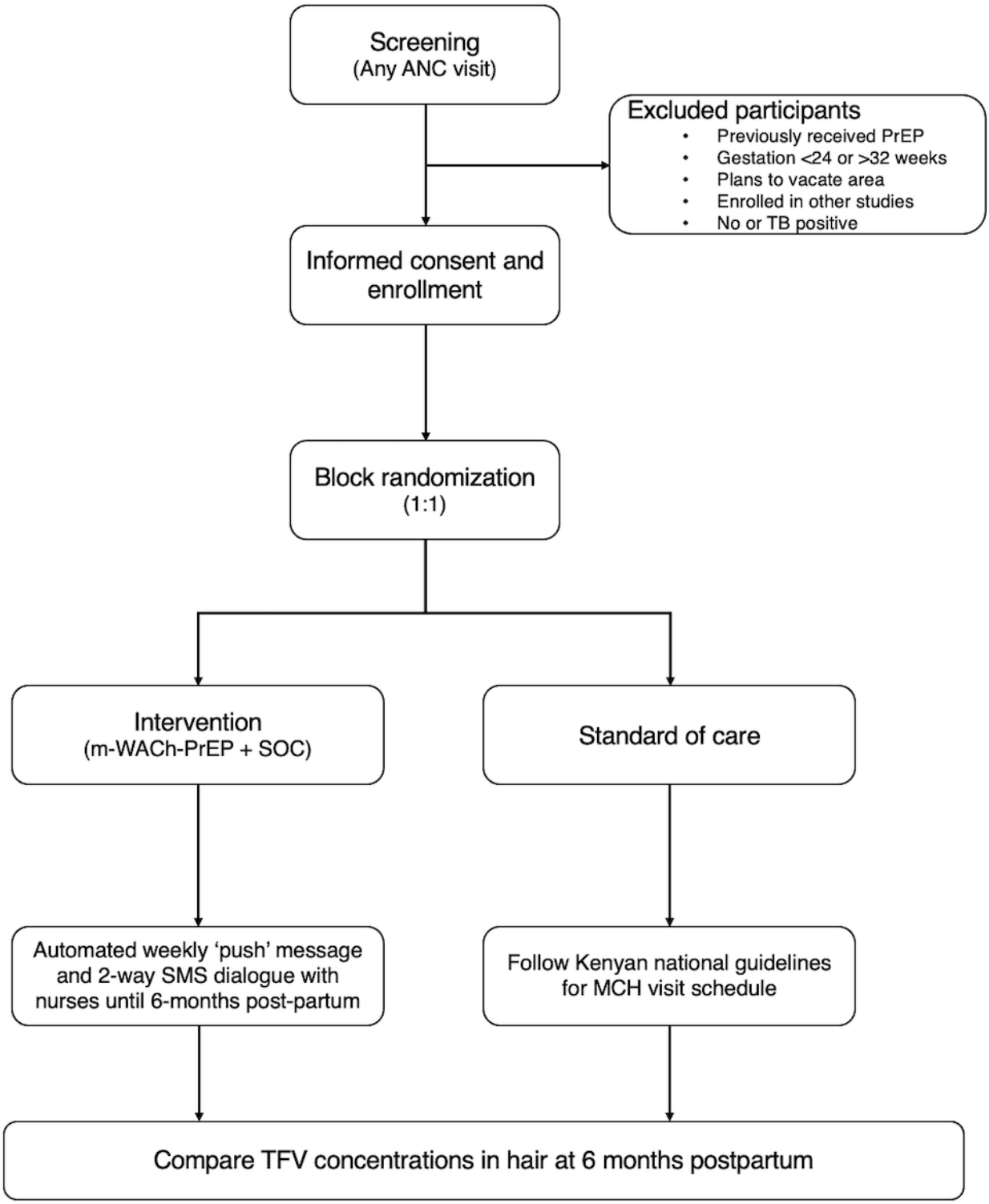
Participating facilities are enrolling 600 pregnant women who are HIV negative (300 in each arm), between 24 and 32 weeks of gestational age (to allow for adequate follow-up during pregnancy), and receiving ANC at MCH clinics. Gestational age is ascertained using the last menstrual period and fundal height measurement, which is part of the routine care for women in this region. Eligibility criteria include HIV and tuberculosis negative, HIV acquisition risk score ≥6 (translating to HIV incidence 7.3 per 100 person-years) [40], initiated PrEP during routine ANC clinic in the participating clinics, ≥18 years, has access to a cell phone, plans to reside in the area for at least 1 year post partum, and plans to receive postpartum and infant care at the study clinic.

Randomization Arms

Two PrEP adherence models are compared: standard of care (SOC) comprising in-clinic adherence counseling only versus SOC plus the mWACh-PrEP tool. All women receive routine MCH care and PrEP services that include health education, clinical assessments, safety monitoring, screening for sexually transmitted infections (STIs), and treatment per national guidelines (including expedited partner treatment for those with STI diagnoses), HIV risk reduction counseling, assessment of psychosocial barriers, and standard in-clinic adherence counseling per national guidelines. Participants randomized to SOC receive in-clinic counseling on PrEP. Participants randomized to the intervention arm are registered in the mWACh-PrEP system, a bidirectional SMS text message communication platform that sends PrEP-tailored, theory-based, preprogrammed texts on PrEP adherence weekly during pregnancy and the postpartum period, in addition to receiving SOC services (Figure 1).

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Figure 1. Screening, enrollment, and follow-up procedure for this study. ANC: antenatal care; MCH: maternal and child health; mWACh: Mobile Solutions for Women's and Children's Health; PrEP: pre-exposure prophylaxis; SOC: standard of care; TB: tuberculosis; TFV: tenofovir.



Randomization

Block randomization using a 1:1 allocation in random-sized blocks stratified by recruitment site is being used to ensure a balanced allocation of each arm within sites. Before randomization, study nurses ensure all routine PrEP initiation services and study enrollment procedures are complete. Treatment allocation (mWACh-PrEP or SOC) for each consented participant is done by the study nurses within the individual's health facility using Research Electronic Data Capture (REDCap; Vanderbilt University). The randomization code is stored in an electronic format, and once assigned, it is unblinded. The randomization key for the database is restricted to the data manager and statistician.

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Study Procedures

Main Study

Participant Screening and Recruitment

Pregnant women initiating PrEP as part of routine care are approached by the study staff while waiting for ANC and invited to participate in the study. Participants undergo screening, and all eligible participants who express interest undergo an informed consent process at the ANC clinic before the initiation of study procedures. Information on facility volume, clients approached, clients screened, and participants enrolled are reported daily by the study staff. Reasons for nonparticipation are captured from those who decline.

Enrollment Visit Data Collection

At enrollment, electronic questionnaires are administered to capture demographic, pregnancy, and medical history; mental health status; HIV results; risk perception; risk assessment; partner characteristics; PrEP attitudes; expected maternity care; health literacy; and COVID-19 experiences. Socioeconomic status is measured using the validated standard Demographic and Health Survey (DHS) Wealth Index [41]. Health literacy is assessed using the standard DHS panel of 8 items across 4 domains (capacity to interpret, obtain, understand, and make appropriate health decisions) [41]. Intimate partner violence (IPV) is assessed using the Hit, Insult, Threaten, Scream scale [42]. Symptoms of depression are assessed using the Edinburgh Postpartum Depression Scale and the Patient Health Questionnaire 9, which has been validated in Kenya [43]. An HIV acquisition risk score validated among pregnant and postpartum Kenyan women is used to assess the risk for HIV [40]. Additional data abstracted from the MCH clinics and PrEP records include details on PrEP initiation, confirmation of syphilis, and HIV test results.

SOC Arm Enrollment Visit and Study Procedures

Per national guidelines, all women initiated on PrEP in both arms receive in-clinic counseling on the benefits of sustained PrEP adherence at enrollment and subsequent refill clinic visits, HIV risk reduction, and assessment of psychosocial barriers.

Intervention Arm Enrollment Visit and Study Procedures

Participants randomized to the intervention arm are registered in the mWACh-PrEP SMS text messaging system with their preferred name for messaging, messaging language (ie, English, Kiswahili, or Dholuo), and day of the week and time for SMS text message delivery. Once registered, the participants receive weekly automated "push" messages on the day/time of their choice from enrollment until they are 6 months post partum. All automated "push" messages include the participant's nickname, clinic, and nurse name; an educational message or actionable advice targeting PrEP adherence and continuation and/or MCH topics; and a question related to the content. Through multiple messaging tracks, participants receive messages targeted to their perinatal status as well as supportive messages if they decide to discontinue or restart PrEP. SMS text message topics include adherence encouragement (IMB domain: motivation), PrEP efficacy and safety (IMB domain: information), self-efficacy for prevention of HIV, support for potential PrEP side effects, behavioral skills (eg, tips for remembering PrEP medications; IMB domain: behavioral skills [44,45]), and visit reminders (Figure 2)**.** Participants have the option to respond to automated messages or extemporaneously contact the study nurses at any time. Study nurses encourage participants to respond with concerns and questions (Figure 3). Participants have access to a two-way dialogue with remote nurses until their 6-month postpartum visit. Participants are free to voluntarily exit autonomously by texting "STOP," thereby ending all communication. All messaging is free to the participant using a reverse-billed short code. The mWACh system also includes multiple features to support study management and personalized counseling based on the participant's psychosocial status (Table 1).

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Figure 2. Conceptual model adapted from the Information-Motivation-Behavioral Skills (IMB) Model. mWACh: Mobile Solutions for Women's and Children's Health; PrEP: pre-exposure prophylaxis.

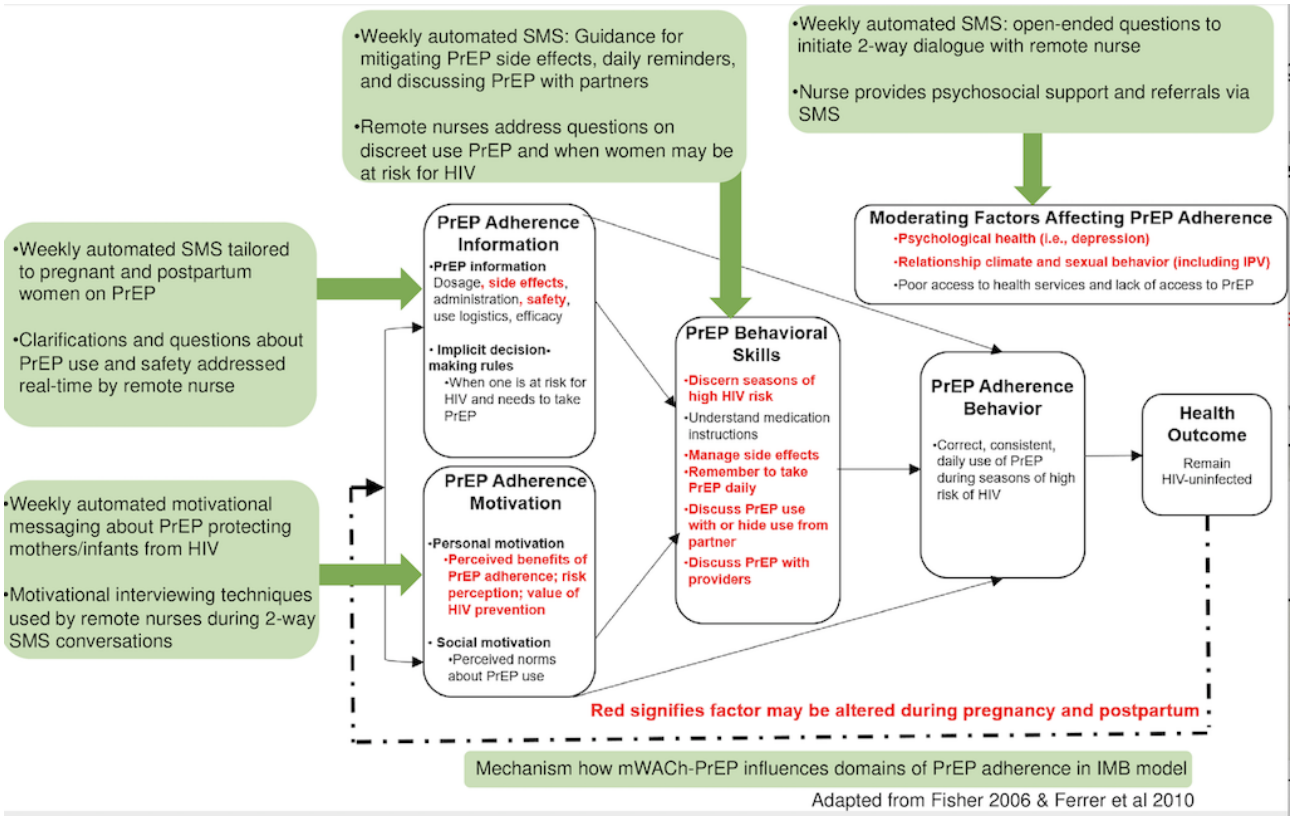
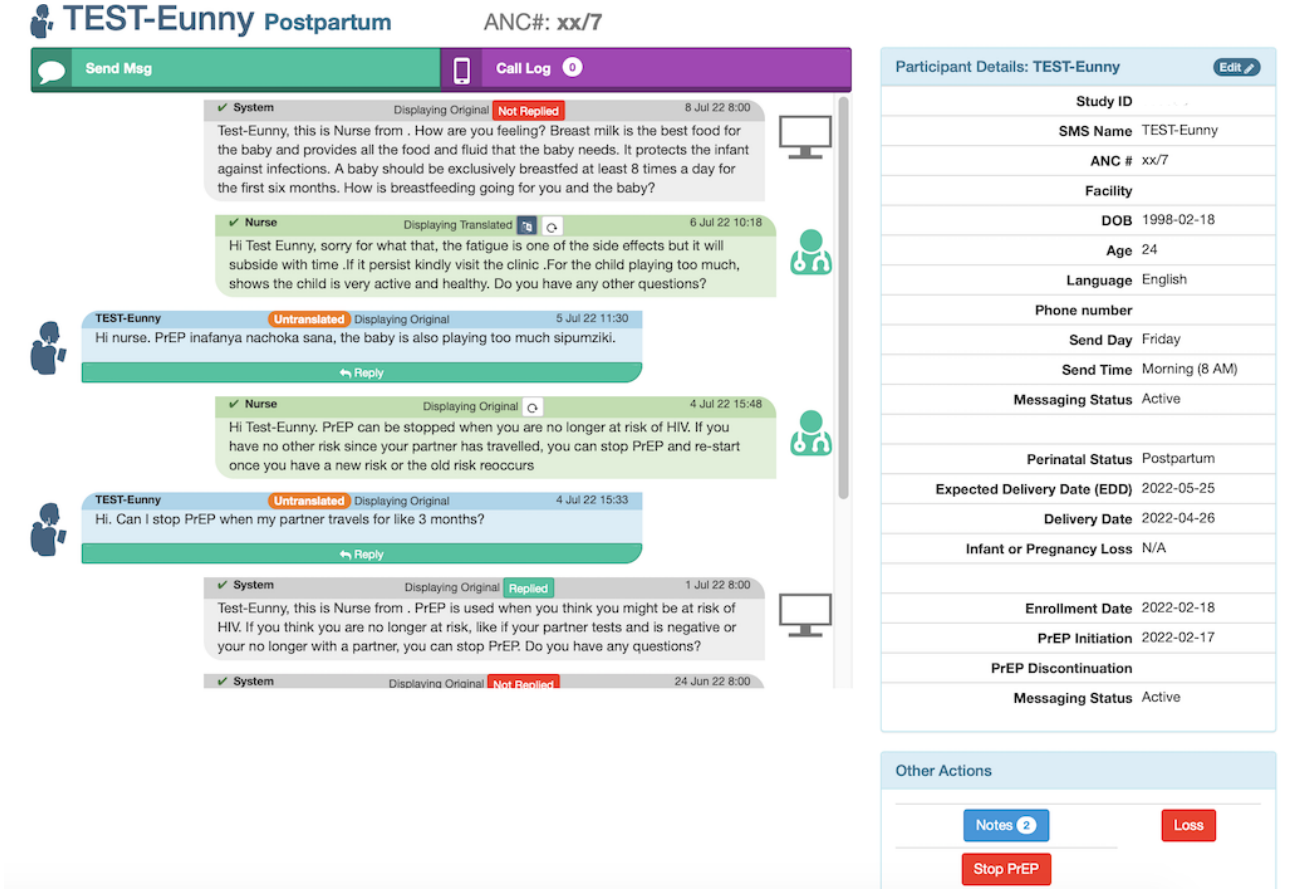


Figure 3. Screenshot of the SMS messaging system. PrEP: pre-exposure prophylaxis.



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Table 1. Example mWACh[a]-PrEP[b] SMS text messages based on the IMB[c] model.

Construct	Week	Example messages
Information		
Dosage	2 weeks after PrEP initiation	{name}, this is {nurse} from {clinic}. There are some misconceptions about PrEP in the community. People should not only take the PrEP pill just before potential exposure to HIV. Rather, it should be taken every single day for it to build up in your system and offer protection against HIV. Is there anything else that you have heard about PrEP in the community?
Side effects	2 weeks after PrEP initiation	{name}, this is {nurse} from {clinic}. A few PrEP users may experience side effects related to PrEP. Most side effects lessen after the first few weeks of use once the body is used to the medication. Please let us know if you are having any side effects. We can help you manage them or know if it is okay to continue.
Safety	19 weeks after PrEP initiation	{name}, this is {nurse} from {clinic}. PrEP is very safe and one of the ways you can protect yourself from HIV. With this pill, you can keep yourself safer from HIV. Are you still taking the medication? Do you have any questions or concerns?
Use logistics	4 weeks postpartum	{name}, this is {nurse} from {clinic}. At this time, you may have a lot to deal with as you adjust to having a newborn. Remember to continue taking care of yourself to prevent HIV by consistently taking PrEP. Do you have any questions?
Efficacy	1 week after PrEP initiation	{name}, this is {nurse} from {clinic}. PrEP is very effective at preventing you from getting HIV. For this effectiveness to be achieved, it is important to take the medication for the first 7 days after initiation without being exposed and thereafter daily. You can use condoms or abstain during this period. Do you have any concerns about PrEP?
Motivation		
Perceived benefits of adherence	4 weeks after PrEP initiation	{name}, this is {nurse} from {clinic}. PrEP is very effective at preventing you from getting HIV if you take it every day. It also helps prevent HIV in your baby if you are pregnant. If you miss too many doses it may not work. Are you having any challenges taking the medication?
Risk perception	17 weeks after PrEP initiation	{name}, this is {nurse} from {clinic}. PrEP is used when you think you might be at risk of HIV. If you think you are no longer at risk, like if your partner tests and is negative or you are no longer with a partner, you can stop PrEP. Do you have any questions?
Value of HIV Prevention	15 weeks after PrEP initiation	{name}, this is {nurse} from {clinic}. You are doing a great job taking care of yourself. Deciding to take PrEP is an important way to protect yourself from HIV. It is also important to be tested regularly. Do you have any questions about PrEP?
Behavioral Skills		
Discern seasons of high HIV risk	6 weeks after PrEP initiation	{name}, this is {nurse} from {clinic}. Some women choose to discontinue PrEP for many reasons. It is okay to stop the medication if you decide. We would want to know why people stop PrEP. Have you stopped taking PrEP? If you have why did you stop?
Remember to take PrEP daily	8 weeks after PrEP initiation	{name}, this is {nurse} from {clinic}. It can be difficult to take medications every day especially if you are trying to be discrete. Many people ask a friend to help remind them, set a timer on their phone, or take it with a meal. You can also put it in a different container you can carry with you in private. How do you remember to take your medication? Do you have any challenges taking it every day?
Manage PrEP use in relation to partner	9 weeks after PrEP initiation	{name}, this is {nurse} from {clinic}. PrEP enhances the power you have to make an independent decision regarding preventing yourself from HIV as you do not have to rely on your partner for this decision. Do you have any questions about PrEP?
Moderating Factors		
Psychological health	3 weeks after PrEP initiation	{name}, this is {nurse} from {clinic}. Sometimes new mothers can feel sad, anxious, or worried all the time. This happens to many women and can cause crying and difficulty sleeping. Are you having any of these problems?

[a]mWACh: Mobile Solutions for Women's and Children's Health.

[b]PrEP: pre-exposure prophylaxis.

[c]IMB: Information-Motivation-Behavioral Skills.

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Data Collection at Follow-up Visits

Study participants are followed up until 9 months post partum to ascertain sustained PrEP adherence at 3 months after cessation of SMS text messages. All study visits for both arms will be aligned with Kenyan national guidelines for standard ANC and infant immunization visit schedules: monthly visits during pregnancy until delivery and then after delivery at 6 weeks, 14 weeks, 6 months, and 9 months post partum. At each visit, nurses administer questionnaires to assess sexual behavior; infant outcomes; IPV; symptoms of depression; and PrEP attitudes, use, and adherence. PrEP use disclosure is assessed at each follow-up visit by asking participants whether they have disclosed to anyone that they use PrEP and, if so, to whom they disclosed this (Table S1 in Multimedia Appendix 1).

Additional data on infant growth, birth weight, estimated gestation at birth, diagnosed preterm birth, and serial growth are abstracted from medical records. Additionally, *z* scores are calculated using WHO AnthroPlus software. Data on birth outcomes (stillbirth, pregnancy loss, mortality, or congenital anomalies) and birth length are abstracted from the MCH medical record or interview.

Laboratory Procedures

A combination of red blood cells from DBS and hair samples is used to assess PrEP adherence. A strong correlation between dosing frequency and TFV levels in hair has been demonstrated [46], and significant correlations were also seen between hair, plasma, peripheral blood mononuclear cells, and red blood cell levels (in DBS) of PrEP drugs or metabolites [47,48]. Plasma levels reflect exposure over the past 1 to 3 days [49] and are highly susceptible to intraindividual variation; therefore, measuring hair drug levels is a unique approach to determining drug exposure over a longer period [50,51]. DBS are collected from a finger or heel prick from all mothers and infants at all study visits for future assessment of TFV-DP and emtricitabine triphosphate in red blood cells.

Hair samples will be collected from participants at pregnancy follow-up visits and from both the participants and their babies at postpartum follow-up visits. These hair samples will be analyzed for TFV using validated liquid chromatography-tandem mass spectrometry methods at the University of California San Francisco (UCSF) Hair Analytical Lab (HAL). The UCSF HAL found that TFV concentrations in the hair under directly observed dosing conditions are similar by sex, and the same adherence benchmarks can be used for both women and men [50]. Additionally, hair TFV levels have not been shown to alter in pregnancy [51].

Data Management

The study staff is trained on data collection using REDCap and communication with participants in the intervention arm using the two-way mWACh-PrEP platform to send, receive, and respond to SMS text messages. Baseline and follow-up data are collected and stored electronically via REDCap, transported via a secure socket layer, and only accessible by authenticated users. Designated study staff generate weekly reports on study progress, performance indicators, adverse events, and troubleshooting problems. All study laptops used to collect data and study databases are encrypted and password protected. All data collected in this study will be available free of charge after registration to access or download files on a study-related website (URL to be determined) after the completion of primary analyses.

Data Analyses

Sample Size

The sample size was calculated to detect a difference between trial arms dependent on the frequency of PrEP adherence in the SOC arm of the cohort. Prior data from our PrEP in pregnancy studies indicate that the frequency of detectable PrEP drug levels is approximately 50% among pregnant women who initiate PrEP in MCH clinics within fully programmatic settings [12]. Since this study will exclusively enroll women who initiate PrEP in MCH, we anticipate that adherence will be similar or slightly higher. Assuming a PrEP adherence estimate of 50% in the SOC arm at 6 months post partum and a sample size of 600 (randomized 1:1), we will have 80% power to detect a minimum detectable difference of 12% between arms in PrEP adherence in the mWACh arm, assuming 15% attrition and a 2-sided test with a Cronbach α of .05 (Table S2 in Multimedia Appendix 1).

Statistical Methods and Analyses

The primary outcome, PrEP adherence at 6 months post partum, will be assessed in an intention-to-treat analysis comparing randomization arms mWACh-PrEP versus SOC. Enrollment characteristics will be compared between randomization arms to assess the balance between arms and control for any imbalanced factors. Based on a previous study of directly observed dosing conditions, we will use a hair TFV concentration cutoff of 0.038 ng/mg (corresponding to 7 doses/week) as the threshold of detection for the primary adherence outcome measured at 6 months post partum (detectable/nondetectable binary outcome) [52]. Protective PrEP drug level thresholds for cisgender women have not been established; however, current WHO and Kenyan national guidelines recommend daily (7 doses/week) oral PrEP for cisgender women. A log-binomial regression model will be used to estimate the relative risk, adjusting for any imbalances in baseline demographic, clinical, or behavioral characteristics between arms. Missing primary outcomes or loss to follow-up will be assumed nonadherent. To evaluate the sustained effect of mWACh-PrEP on PrEP-taking habits after the SMS text messaging intervention ends, the same model will be used to analyze our secondary outcome of PrEP adherence at 9 months post partum (3 months after cessation of mWACh-PrEP messaging).

Qualitative Analyses

Focus group discussions and semistructured in-depth interviews will be conducted to evaluate potential barriers and facilitators to the acceptability and feasibility of mWACh-PrEP implementation within routine ANC delivery settings (Figure 4). To evaluate personal experiences with the mWACh-PrEP intervention, a purposively selected sample of study participants will be recruited to participate in in-depth interviews. In-depth interviews will explore community, dyadic, and individual

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factors influencing decision-making and how these influence individual perceptions of and experiences with mWACh-PrEP use. To gather perspectives on the mWACh-PrEP scale-up, we will invite the study's community advisory board (CAB) and county-level health officials overseeing ANC-PrEP programs to participate in focus group discussions. These focus group discussions will elicit perspectives on foreseeable barriers and facilitators of larger-scale implementation of mWACh-PrEP based on individual, community, and health system factors.

Discussions will be conducted in English, Kiswahili, or Luo depending on participants' preferences and be guided by prepiloted topic guides with the flexibility to explore additional probes and newly emerging content as necessary. All in-depth interviews and focus group discussions will be audio recorded, transcribed, and translated to English for analysis as necessary. Thematic analysis will be used to identify key elements of the patient/provider experience, including convenience, comfort level, and satisfaction of the mWACh-PrEP model, that influence intervention acceptability, feasibility, and potential scale-up.

Figure 4. Schematic of qualitative purposive stratified sampling approach (N=70). PrEP: pre-exposure prophylaxis.

		PrEP adherence		
		Non adherent at 6 months	Adherent at 6 months	
			Non adherent at 9 months	Adherent at 9 months
mWACh status	Responded to <10% of SMS	Non responder; non adherent *(n=10)*	Non responder; waned adherence *(n=10)*	Non responder; persistent adherence *(n=10)*
	Responded to >25% of SMS	Responder; Non adherent *(n=10)*	Responder; waned adherence *(n=10)*	Responder; persistent adherence *(n=10)*
	Declined registration	*(n=10) Sampled regardless of adherence status*		

Cost-effectiveness Analysis

Overview

We will project the cost-effectiveness of implementing mWACh-PrEP intervention within ANC compared to the SOC per averted disability-adjusted life year (DALY) using a payer perspective and collect intervention costs from expense reports, staff, and expert interviews. Costs will be divided into mutually exclusive categories, including personnel, equipment, supplies, buildings and overhead, and start-up. We will convert the local currency, Kenyan shillings, to US dollars. Sensitivity analyses will be conducted to identify influential assumptions.

Costing

Time and motion observation of intervention activities will be conducted to calculate staff time and resources necessary for the mWACh-PrEP intervention. A research assistant (RA) will collect data on the time and motion of patient/provider interactions to inform costs and productivity assumptions. The RA will also conduct a survey with health care workers to assess daily responsibilities associated with the mWACh-PrEP intervention, including time to send and respond to client SMS text messages and routine service provision. Research time (eg, administering study questionnaires) and other research costs will be separated from programmatic costs.

Modeling

We will parameterize a previously developed mathematical model with cost and outcome data from the mWACh-PrEP trial and project the averted HIV infections, HIV-related deaths, and DALYs associated with scaling up the mWACh-PrEP intervention in Kenya. We will calculate the incremental cost-effectiveness ratio as the difference in costs divided by the difference in effects (DALYs) for the intervention compared to SOC over a 20-year period. Costs and benefits will be discounted annually at 3%.

Secondary and Exploratory Analyses

Secondary outcome analyses will include sustained PrEP adherence by determining levels of detectable TFV in the hair at 9 months post partum, adherence cofactors, STI incidence, and prevention-effective adherence (time-varying alignment of adherence with risk behaviors). Exploratory analyses will include HIV incidence, perinatal outcomes, and expedited partner treatment outcomes by randomization arms (Table S3 in Multimedia Appendix 1).

Ethics Approval

Ethical approval was obtained from the institutional review board of the University of Washington (STUDY00010797) and the Kenyatta National Hospital Ethics and Research Committee (P319.05/2021). This study was registered at ClinicalTrials.gov. (NCT04472884). Any critical protocol deviations, adverse events, and future modifications will be communicated promptly

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to these organizations. Additional permissions will be sought from all participating clinical sites.

Informed Consent

A written informed consent before recruitment is administered to all study participants, with each receiving a copy of the signed form. Additional permission will be obtained for audio recording and note-taking during the qualitative interviews.

All participants are informed that their participation is voluntary, and they can stop receiving the SMS text messages at any time by contacting the study staff or texting "STOP," which will cease communication between the study staff and the participant. All study staff is trained in protecting human participants and the clinical and emotional needs of pregnant and postpartum women on PrEP. The MWACh system is point-to-point encrypted; therefore, only study team members can access it through a password-protected laptop stored in a locked office. All data are deidentified and kept in password-protected databases in a locked study office that is accessible only to study personnel.

Patient and Public Involvement

A CAB has been established in Kisumu County to review the study objectives, methodology, and other study activities. The team comprises local community leaders, women from the community, the Kenyan Ministry of Health, and county health representatives from MCH departments. The CAB is anticipated to meet 2 times per year to review this study's progress. An external advisory panel (EAP) has been established to oversee the data and safety of study participants by reviewing study aims, statistical analysis plan, and progress. EAP meetings will be routinely convened to review study enrollment, retention, data missingness, and pooled study outcomes. Study results will be disseminated through peer-reviewed journals, technical reports, policy briefings, and oral presentations at relevant local and international conferences. Additionally, we will present results to clinical experts and policy advisors at the local county level, the Kenyan Ministry of Health, and the WHO. Routine hybrid meetings in the form of progress updates with CABs engaged in the study activities, facility staff, and study collaborators will be conducted to share study progress and findings.

Results

Study enrollment began in March 2022 and is projected to continue until July 2023, with patient participant follow-up through March 2024. The study results are expected to be reported in 2025.

Discussion

Anticipated Findings and Implications

This intervention study aims to determine the effect of the mWACh-PrEP tool on PrEP adherence among pregnant and breastfeeding women at high risk for HIV acquisition who initiate PrEP during ANC. The primary outcome is adherence at 6 months, while the secondary outcomes include sustained adherence at 3 months after cessation of the SMS text messaging intervention and other HIV and MCH indicators. This is the first intervention that aims to enhance PrEP adherence among women in the peripartum period research, and we anticipate that our findings will inform clinical practice for PrEP delivery during the peripartum period by providing effectiveness data on an mHealth PrEP adherence tool tailored for the peripartum period.

Study Strengths and Limitations

This is the first intervention study aiming to improve PrEP adherence among peripartum women using an IMB-guided approach tailored to pregnant and postpartum women on PrEP for HIV prevention. The development of adherence strategies for periods during and after pregnancy can have implications for other daily medications taken during pregnancy and the postpartum period when medication side effects overlap with typical symptoms, and life events pose challenges to sustained adherence. Furthermore, collected microcosting data will guide researchers and policy makers on the cost of scale-up and use of mHealth and the IMB-informed approach.

Daily oral tenofovir disoproxil fumarate (TDF)/emtricitabine is currently the only medication with a label indication as PrEP in Kenya and the only regimen recommended by the WHO for cisgender women. While several novel PrEP agents are being tested, including long-acting injectable cabotegravir (CAB-LA) [53], forthcoming results are still years away, and it will take longer for CAB-LA to reach pregnant or lactating women as there is no safety evaluation underway in these populations. Similarly, event-driven PrEP (ED-PrEP) is not approved by the US Food and Drug Administration. Moreover, WHO guidelines explicitly state that ED-PrEP is not appropriate for cisgender women, citing effectiveness concerns in this group [54]. Therefore, daily oral TDF/emtricitabine will likely remain the PrEP SOC for pregnant and breastfeeding women for several years. Because this is a programmatic RCT, the characterization of some secondary and exploratory outcomes will be limited. This design was intentional to optimize program/policy relevance. Costing data will be collected to understand how additional time spent by nurses on the intervention in already busy health facilities may potentially affect scale-up.

Dissemination Plan

To provide insights on the effects of mWACh-PrEP, we will communicate the study protocol, progress report, and results to the scientific community and policy makers. This will guide the clinical management of pregnant women who choose to initiate PrEP, informing future scale-up of the intervention as a population-level program. Dissemination of the results will potentially improve communication between researchers, ethical bodies, and policy makers and strengthen collaborations between participating partners through technical reports and policy briefings. For the scientific community, we will publish our findings in peer-reviewed journals and present them at international scientific conferences. Presentations and progress reports regarding the study will be shared with study participants and presented to the public at the facility level and to the Kenyan Ministry of Health.

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Conclusion

This study will inform clinical practice and contribute to advancing strategies to enhance PrEP and other daily medication adherence during pregnancy and the postpartum period, which are both critical periods for MCH. If our mWACh approach positively affects MCH outcomes (eg, birth and infant outcomes), it could be readily integrated into other mHealth platforms aiming to improve MCH in the future. The study will also contribute to an mHealth adherence tool for pregnant women on PrEP with the goal of enhancing PrEP use and ultimately reducing HIV incidence in this important population that is disproportionately affected by HIV.

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Data Availability

The data sets generated and analyzed during this ongoing study are available from the corresponding author upon reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Tables S1-S3.
[DOCX File , 893 KB - resprot_v12i1e41170_app1.docx]

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Abbreviations

ANC: antenatal care
ART: antiretroviral therapy
CAB: community advisory board
CAB-LA: long-acting injectable cabotegravir
DALY: disability-adjusted life year
DBS: dried blood spots
DHS: Demographic and Health Survey
EAP: external advisory panel
ED-PrEP: event-driven pre-exposure prophylaxis
HAL: Hair Analytical Laboratory
IMB: Information-Motivation-Behavioral Skills
IPV: intimate partner violence
MCH: maternal and child health
mHealth: mobile health
mWACh: Mobile Solutions for Women's and Children's Health
PrEP: pre-exposure prophylaxis
RA: research assistant
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
SOC: standard of care
STI: sexually transmitted infection
TDF: tenofovir disoproxil fumarate
TFV: tenofovir
TFV-DP: tenofovir diphosphate
WHO: World Health Organization

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Protocol

Effectiveness of an Individualized Exergame-Based Motor-Cognitive Training Concept Targeted to Improve Cognitive Functioning in Older Adults With Mild Neurocognitive Disorder: Study Protocol for a Randomized Controlled Trial

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Abstract

Background: Simultaneous motor-cognitive training is considered promising for preventing the decline in cognitive functioning in older adults with mild neurocognitive disorder (mNCD) and can be highly motivating when applied in the form of exergaming. The literature points to opportunities for improvement in the application of exergames in individuals with mNCD by developing novel exergames and exergame-based training concepts that are specifically tailored to patients with mNCD and ensuring the implementation of effective training components.

Objective: This study systematically explores the effectiveness of a newly developed exergame-based motor-cognitive training concept (called “Brain-IT”) targeted to improve cognitive functioning in older adults with mNCD.

Methods: A 2-arm, parallel-group, single-blinded randomized controlled trial with a 1:1 allocation ratio (ie, intervention: control), including 34 to 40 older adults with mNCD will be conducted between May 2022 and December 2023. The control group will proceed with the usual care provided by the (memory) clinics where the patients are recruited. The intervention group will perform a 12-week training intervention according to the “Brain-IT” training concept, in addition to usual care. Global cognitive functioning will be assessed as the primary outcome. As secondary outcomes, domain-specific cognitive functioning, brain structure and function, spatiotemporal parameters of gait, instrumental activities of daily living, psychosocial factors, and resting cardiac vagal modulation will be assessed. Pre- and postintervention measurements will take place within 2 weeks before starting and after completing the intervention. A 2-way analysis of covariance or the Quade nonparametric analysis of covariance will be computed for all primary and secondary outcomes, with the premeasurement value as a covariate for the predicting group factor and the postmeasurement value as the outcome variable. To determine whether the effects are substantive, partial eta-squared (η^2_p) effect sizes will be calculated for all primary and secondary outcomes.

Results: Upon the initial submission of this study protocol, 13 patients were contacted by the study team. Four patients were included in the study, 2 were excluded because they were not eligible, and 7 were being informed about the study in detail. Of the 4 included patients, 2 already completed all premeasurements and were in week 2 of the intervention period. Data collection

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is expected to be completed by December 2023. A manuscript of the results will be submitted for publication in a peer-reviewed open-access journal in 2024.

Conclusions: This study contributes to the evidence base in the highly relevant area of preventing disability because of cognitive impairment, which has been declared a public health priority by the World Health Organization.

Trial Registration: ClinicalTrials.gov NCT05387057; https://clinicaltrials.gov/ct2/show/NCT05387057

International Registered Report Identifier (IRRID): DERR1-10.2196/41173

(JMIR Res Protoc 2023;12:e41173) doi:10.2196/41173

KEYWORDS

cognition; cognitive impairment; effectiveness; exercise; exergame; neuroplasticity; neurosciences; technology; training

Introduction

Background

Aging is typically accompanied by structural [1,2] and functional [2-4] brain changes associated with a gradual decline in physical [5] and cognitive [1,3,6] abilities. Decline in cognitive functioning exists on a continuum from healthy aging to pathological conditions, such as “mild cognitive impairment” (MCI) or “dementia” [7-9]. MCI has evolved over the last decades [8] and was incorporated in the latest Diagnostic and Statistical Manual of Mental Disorders 5th Edition (DSM-V) and the International Classification of Diseases 11th Revision, as mild neurocognitive disorder (mNCD) [10-13]. Although slightly different definitions have been used in the literature, the core criteria remain [7,8]. According to DSM-V, mNCD is characterized by: “(A) Evidence of modest cognitive decline from a previous level of performance in one or more cognitive domains [...]; (B) cognitive deficits do not interfere with the capacity for independence in everyday activities [...]; (C) Cognitive deficits do not occur exclusively in the context of delirium. (D) Cognitive deficits are not better explained by another mental disorder (eg, major depressive disorder, schizophrenia)” [12]. In individuals with mNCD, deterioration in episodic memory and executive function represent the most prevalent cognitive impairment [14] and are associated with structural [7,15] and functional [7,15,16] brain changes. In addition to cognitive decline, individuals with mNCD may also experience problems in motor function [17,18], impaired balance [18], a higher fall risk [17,19], or difficulties in everyday functioning [20-22]. However, individuals with mNCD retain their capacity for independence in everyday activities [12].

In 2021, over 55 million people were living with major neurocognitive disorder (MNCD; also referred to as “dementia” [12]) [23]. The pooled prevalence of mNCD increases with age and is estimated to be approximately 16% [24], more than twice as high as the prevalence of MNCD [23,25]. The global increase in life expectancy [26] and insufficient levels of physical activity [27] serve as important risk factors for cognitive decline [9,24,28-30] and are expected to boost the incidence and prevalence of mild to major neurocognitive disorders (MNCD). Moreover, individuals with mNCD are at an increased risk of developing dementia. The annual conversion rate of mNCD to MNCD is approximately 4.9 in community settings and 9.6 in specialist clinical settings [31]. Between 14% (clinical population) and 31% (community-based cohort) revert to normal cognitive function [32]. Nonetheless, the pooled progression rate is estimated to be 34%, which is more than twice as high as the pooled reversion rate of 15% [24]. Consequently, the worldwide prevalence of dementia is expected to nearly double over the next 20 years [25]. To counteract this development, the World Health Organization has declared the prevention of disabilities caused by cognitive impairment a public health priority [33].

Individuals with mNCD may represent an optimal target population for pharmacological and nonpharmacological interventions [7]. However, no pharmacological treatment that effectively decelerates or prevents the progression from mNCD to MNCD or decreases the impact of cognitive decline on functioning exists [34-37]. The American Food and Drug Administration recently approved a new but controversial pharmacological agent (aducanumab) to treat individuals with mNCD due to Alzheimer disease (AD) [38,39]. In Europe, Biogen Netherlands BV withdrew its application for marketing authorization of Aduhelm for the treatment of early stages of AD due to insufficient data [40]. Evidence for other pharmacological treatment options (eg, cholinesterase inhibitors, antihypertensive, anti-inflammatory, or lipid-lowering medication, or hormone therapies) and nutritional supplements is largely insufficient and does not support their use for improving cognitive performance, slowing down cognitive decline, or reducing the risk of developing dementia [41-46]. Several nonpharmacological interventions, such as lifestyle changes that target modifiable risk factors such as diabetes mellitus [47-49], hypertension [47-49], obesity [49], depression [49,50], physical [29,49] or cognitive inactivity [30,49], or smoking [49,51], may hold promise for slowing down cognitive decline or reducing the risk of developing dementia [52]. It has been estimated that up to half of the world’s cases of AD, the leading cause of m-MNCDs [12]—may be attributable to these 7 potentially modifiable risk factors [49]. A 10%-25% reduction in these risk factors is estimated to reduce AD prevalence by up to 3 million individual cases worldwide [49]. As physical inactivity is associated with most other modifiable risk factors, an increase in physical activity is believed to have an impact on m-MNCD prevalence [49]. In addition, the theory of cognitive reserve suggests that, “education and mental stimulation throughout life may lower risk of AD and dementia by helping to build a ‘cognitive reserve’ that enables individuals to continue functioning at a ‘normal’ level despite experiencing neurodegenerative changes” [49,53,54]. According to recent network meta-analyses, nonpharmacological interventions

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targeting modifiable risk factors, such as physical and cognitive exercises, outperform pharmacological therapies [55,56]. It can be hypothesized that a shift from pharmacological to nonpharmacological interventions with multi-domain treatment strategies, including physical exercises and cognitive stimulation, may lead to better results [9,36].

Aerobic training [57-59] and multicomponent physical exercises [57,59,60] are beneficial exercise modes for cognition in patients with NCDs, whereas cognitively engaging exercises appear to have the strongest effect on cognition [61,62]. Combined motor-cognitive training seems to be the most effective type of training for improving cognitive functioning in older adults with mNCD [61,63-65]. These findings are consistent with the "guided-plasticity facilitation" framework [66-68]: physical exercise enhances brain metabolism and promotes neuroplastic processes, whereas these changes in brain plasticity are guided by cognitive stimulation [66,67,69]. Combined motor-cognitive training can be categorized into "sequential," "simultaneous-additional," and "simultaneous-incorporated" motor-cognitive training [68]. Incorporating cognitive tasks into motor tasks is more beneficial than "classical" dual-task approaches or sequential motor-cognitive training in terms of stabilizing neuroplasticity effects [68].

Technological innovations (eg, exergames) provide new options to engage older adults with mNCD in (simultaneous-incorporated) motor-cognitive training [70]. "Exergaming is defined as technology-driven physical activities, such as video game play, that requires participants to be physically active or exercise in order to play the game" [71]. When exergames are specifically designed and implemented with a purpose beyond play, it is a "serious game" [72,73]. Exergame-based interventions are highly accepted in individuals with mNCD and increase training adherence and engagement by facilitating training motivation and satisfaction [74]. Furthermore, exergaming offers "the unique opportunity for patients to interact in an enriched environment, providing structured, scalable training opportunities augmented by multi-sensory feedback to enhance skill learning and neuroplasticity through repeated practice" [75], an additional advantage compared with conventional motor-cognitive training. There are consistent positive effects on cognitive functioning, favoring exergaming in people with m-MNCD [74]. Nonetheless, it is currently difficult to draw reliable conclusions about the effectiveness of exergaming in preventing and treating neurocognitive disorders because of the substantial variations in exergame-based training [74]. Gavelin et al [63] synthesized smaller effects on cognitive outcomes for exergaming (standardized mean difference [SMD] 0.13, 95% CI −0.22 to 0.44) compared with sequential (SMD 0.25, 95% CI −0.05 to 0.55) or simultaneous (SMD 0.45, 95% CI 0.11-0.78) motor-cognitive training in individuals with mNCD compared with passive control groups [63]. To the best of our knowledge, 11 studies have investigated exergame-based motor-cognitive training in older adults with mNCD [76-86]. Most of these studies used commercially available exergame systems [76-82], where the training content was not specifically developed for individuals with mNCD. In addition, only one of these studies applied training that individually prescribed content based on a patient's cognitive abilities [82]. This may explain the small effect findings of Gavelin et al [63], and points to opportunities for improvement in the application of exergames in individuals with mNCD by developing novel exergames and exergame-based training concepts that ensure the implementation of effective training components specifically tailored to the requirements and needs of individuals with mNCD [87]. It seems fair to state that purpose-developed exergames and exergame-based training concepts specifically targeting individuals with mNCD and implementing effective training components will have larger effects on individuals with mNCD.

Prior Work

We developed an exergame-based motor-cognitive training concept ("Brain-IT") specifically for older adults with mNCD. It was developed using the "Multidisciplinary Iterative Design of Exergames: A Framework for Supporting the *Design* section, Development, and Evaluation of Exergames for Health" [88]. The target group, therapists, and experts from different fields were involved in the development process to ensure that the training met the requirements and needs of older adults with mNCD and to foster the usability and acceptance of the approach in "real life." This interactive and participatory design and development process allowed the identification of the key requirements for exergame design as well as the training characteristics. These formed the basis for determining the components of the resulting "Brain-IT" training concept. It ensures the implementation of effective training components and is specifically tailored to the requirements and needs of older adults with mNCD. A detailed description of this design and development process is outlined in a previously published methodological paper that contains our complete training concept with sufficient details to allow full replication [89].

The original "Brain-IT" training concept was already shown to be feasible, usable, and highly accepted in our pilot feasibility randomized controlled trial (RCT), including a small sample of older adults with mNCD (n=18; under peer review; registered at ClinicalTrials.gov NCT04996654). Minor modifications were incorporated to further optimize the "Brain-IT" training concept, making it applicable for the systematic evaluation of effectiveness in samples of older adults with mNCD.

Explanation and Choice of Comparators

According to a recent systematic review summarizing worldwide available clinical practice guidelines and consensus statements, recommendations for the treatment and management of individuals with mNCD can be classified into 4 categories: interventions for risk reduction, pharmacological interventions, nonpharmacologic interventions, and counseling. Recommendations for nonpharmacological interventions mainly include physical and cognitive activity interventions; however, the specific training characteristics (eg, frequency, intensity, type, volume, and progression) are not specified [90].

In line with these recommendations, in Switzerland, usual care for mNCD typically includes treating medical conditions other than mNCD (eg, diabetes mellitus and depressive symptoms), controlling comorbidities (eg, hypertension and obesity), and

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managing risk factors (eg, smoking habits and physical and cognitive inactivity). In this regard, usual care may include medication, recommendations for changing lifestyle habits (eg, living a cognitively, physically, and socially active life), physiotherapy to treat specific health problems, such as back pain or mobility problems, occupational therapy, or day clinic visits. This justifies the selection of usual care as the control intervention.

Objectives and Hypotheses

This study explores the effectiveness of the "Brain-IT" training in improving global cognitive functioning in older adults with mNCD. With this, we aim to obtain a sufficiently precise estimate of the treatment effect to minimize the sample size needed for a future full-scale RCT.

- Null Hypothesis ($H_0$0): In older adults with mNCD, the addition of the "Brain-IT" training to usual care has no significant effect on global cognitive functioning compared with usual care.
- Alternative Hypothesis (H_A): In older adults with mNCD, the addition of the "Brain-IT" training to usual care results in differing effects on global cognitive functioning compared with usual care.

As secondary objectives, the effects of the "Brain-IT" training on (a) domain-specific cognitive functioning (ie, learning and memory, complex attention, executive function, and visuospatial skills), (b) brain structure and function, (c) spatiotemporal parameters of gait, (d) instrumental activities of daily living (IADL), and (e) psychosocial factors (ie, QoL [quality of life], and levels of depression, anxiety, and stress), and (f) cardiac vagal modulation (ie, resting vagally-mediated heart rate variability [vm-HRV]) in older adults with mNCD as compared with usual care will be explored. (B) Brain structure and function will be evaluated to explore the possible underlying neural changes in training in relation to adaptations in cognitive performance. The following hypotheses are formulated for the remaining outcomes:

- Null Hypothesis (H_0): In older adults with mNCD, the addition of the 'Brain-IT' training to usual care has no significant effect on (a) domain-specific cognitive functioning, (c) spatiotemporal parameters of gait, (d) IADL and (e) psychosocial factors (ie, QoL, and levels of depression, anxiety, stress), and (f) cardiac vagal modulation (resting vm-HRV) compared with usual care.
- Alternative Hypothesis (H_A): In older adults with mNCD, the addition the "Brain-IT" training to usual care results in differing effects on (a) domain-specific cognitive functioning, (c) spatiotemporal parameters of gait, (d) IADL, (e) psychosocial factors (ie, QoL, and levels of depression, anxiety, and stress), and (f) cardiac vagal modulation (resting vm-HRV) compared with usual care.

The rationale and description of the specific hypotheses for (c) spatiotemporal parameters of gait are explained in more detail in the section "Methods—Outcomes—Secondary Outcomes—Spatiotemporal Parameters of Gait."

Methods

This study protocol (version 1.0; July 20, 2022) was developed in accordance with established guidelines from the "SPIRIT 2013 Statement: Defining Standard Protocol Items for Clinical Trials" [91,92] (see the checklist in Multimedia Appendix 1).

Ethics Approval

All the study procedures will be performed in accordance with the Declaration of Helsinki. The study protocol was approved by the Ethics Committees of Zurich and Eastern Switzerland (EK-2022-00386).

Trial Design and Study Setting

A 2-arm, prospective, parallel-group, single-blinded (ie, outcome evaluator of pre- and postintervention measurements blinded to group allocation) RCT with a 1:1 allocation ratio (ie, intervention: control), including 34 to 40 older adults with mNCD, will be conducted between May 2022 and December 2023. The control group will proceed with usual care as provided by the (memory) clinics where the patients are recruited, while the intervention group will perform a 12-week training intervention according to the "Brain-IT" training concept in addition to usual care (see section "Methods—Interventions"). The study was registered at clinicaltrials.gov before the start of patient recruitment (NCT05387057; date of registration: May 18, 2022; see Table 1 for details) and will be reported according to "The Consolidated Standards of Reporting Trials (CONSORT) 2010 statement" [93] and elaboration paper [94]. The study setup is multicentric (Zurich and St. Gallen) and national (Switzerland).

After recruitment and providing written informed consent (see section "Methods—Recruitment"), participants will be screened on eligibility (see section "Methods—Eligibility Criteria"), and premeasurements will be scheduled for all eligible participants. Pre- and postintervention measurements will take place within 2 weeks before starting and after completing the intervention. For participants recruited in Zurich, preintervention measurements will take place at ETH Hönggerberg (Robert-Gnehm-Platz 1, CH-8093 Zurich). For participants recruited in St. Gallen, premeasurements will take place at the Eastern Switzerland University of Applied Sciences (Vadianstrasse 29, CH-9000 St Gallen). The measurements will take approximately 90 minutes. For all participants with no contraindications to magnetic resonance imaging (MRI), an additional appointment to conduct an MRI scan (duration: approximately 1 hour [including preparation]) at University Hospital Zurich (Rämistrasse 100, CH-8006 Zurich) will be scheduled. All measurements will be led by 2 investigators from our research team trained in the application of the measurement techniques and protocols. Pre- and postintervention measurements will be scheduled to occur at approximately the same time of the day (±2 h) for each participant. To minimize the influence of transient confounding effects on HRV, all participants will additionally be instructed verbally and in writing to follow a normal sleep routine the day before the experiment, to avoid intense physical activity and alcohol consumption within 24 hours before measurements, and to refrain from coffee–or caffeinated drinks as well as food

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consumption at least 2 hours before measurements [95]. After completing premeasurements, participants will be randomly allocated to the intervention or control group and will be instructed about their respective intervention procedures (see section "Methods—Interventions"). For participants in the intervention group, the exergame device will be installed in their homes; they will receive safety instructions and will be familiarized with the exergame training system. Subsequently, the study intervention will be started (see section "Methods—Interventions—Intervention Group"). After completing the 12-week intervention period, postintervention measurements will be performed for both groups. No compensation will be granted to the participants, but detailed feedback on individual performance as well as the study outcomes in general will be provided at the end of the trial. Figure 1 summarizes the study procedures.

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Table 1. Overview of trial registration data.

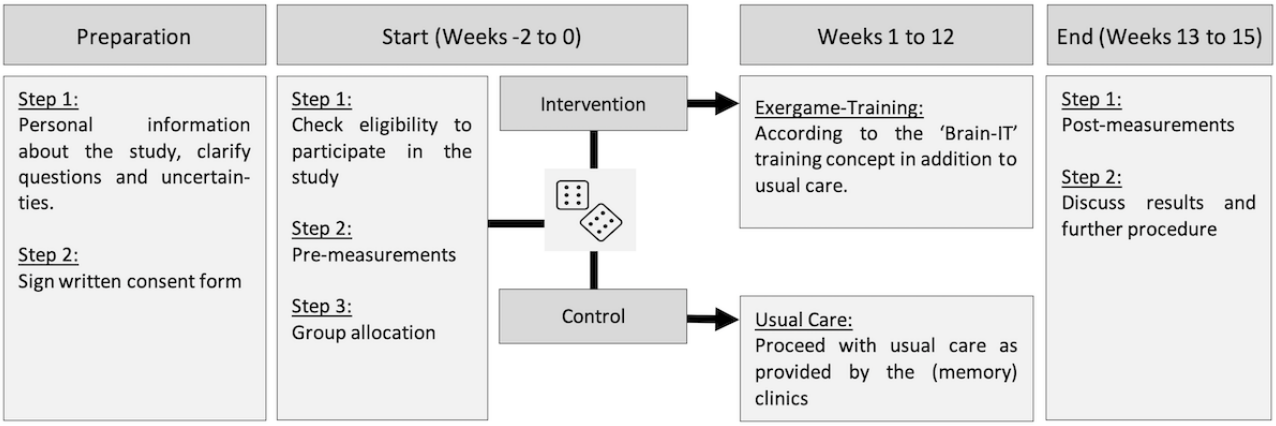
Data category	Information
Primary registry and trial identifying number	ClinicalTrials; NCT05387057
Date of registration in primary registry	May 18, 2022
Secondary identifying numbers	N/A[a]
Sources of monetary or material support	Synapsis Foundation—Dementia Research Switzerland
Sponsor-investigator	Prof Dr Eling D. de Bruin, Motor Control and Learning Group – Institute of Human Movement Sciences and Sport, Department of Health Sciences and Technology, ETH Zurich, Leopold-Ruzicka-Weg 4, Zurich, Switzerland, eling.debruin@hest.ethz.ch and Department of Health, OST – Eastern Swiss University of Applied Sciences, Vadianstrasse 29, St. Gallen, Switzerland, eling.debruin@ost.ch
Contact for public queries	Patrick Manser; Motor Control and Learning Group – Institute of Human Movement Sciences and Sport, Department of Health Sciences and Technology, ETH Zurich, Zurich, Switzerland; patrick.manser@hest.ethz.ch
Contact for scientific queries	Patrick Manser; Motor Control and Learning Group – Institute of Human Movement Sciences and Sport, Department of Health Sciences and Technology, ETH Zurich, Zurich, Switzerland; patrick.manser@hest.ethz.ch
Public title	Effectiveness of a Novel Exergame-Based Training Concept for Older Adults with Mild Neurocognitive Disorder
Scientific title	Effectiveness of an Individualized Exergame-based Motor-Cognitive Training Concept Targeted to Improve Cognitive Functioning in Older Adults with Mild Neurocognitive Disorder–A Randomized Controlled Trial
Countries of recruitment	Switzerland
Health conditions or problems studied	Older adults with mild neurocognitive disorder
Interventions	Control group: The control group will proceed with usual care as provided by the (memory) clinics where the patients are recruited. Intervention group: Participants in the intervention group will perform a 12-week training intervention according to the newly developed “Brain-IT” training concept in addition to their usual care.
Key inclusion and exclusion criteria	Key inclusion criteria: • (1=mNCD) clinical diagnosis of “Mild Neurocognitive Disorder” OR (2=sMCI) patients sMCI • German speaking • Able to stand at least for 10 min without assistance Exclusion criteria: • Mobility impairments that prevent experiment participation • Presence of additional, clinically relevant (ie, acute or symptomatic) neurological disorders • Presence of any other unstable or uncontrolled diseases (eg, uncontrolled high blood pressure, progressing or terminal cancer)
Study type	• Study type: Interventional • Primary purpose: Prevention • Study phase: N/A • Interventional study model: Randomized, Parallel Assignment • Masking: Single blind
Date of first enrollment	June 22, 2022
Target sample size	40
Recruitment status	Recruiting
Primary outcomes	Changes in global cognitive functioning (Time Frame: both, the pre- and the postintervention measurements of the primary outcome will take place within 2 weeks before starting or after completing the intervention)

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Data category	Information
Key secondary outcomes	• Changes in Learning and Memory • Changes in Complex Attention • Changes in Executive Function • Changes in Visuospatial Skills • Changes in Brain Structure and Function • Changes in Spatiotemporal Gait Parameters • Changes in instrumental activities of daily living • Changes in Psychosocial Factors • Changes in vagally-mediated Heart Rate Variability • For all secondary outcomes: (Time Frame: both, the pre- and postintervention measurements of the primary outcome measurement will take place within 2 weeks before starting or after completing the intervention)

[a]N/A: not applicable.

Figure 1. Graphical overview of the study procedures. The cubes are used to illustrate the randomization process (variable block randomization (ie, block sizes=4, 6, 8) with a 1:1 allocation ratio stratified by sex and per institute (study center), as described in section "Methods–Randomization").



Recruitment

Older adults with mNCD will be recruited between May 2022 and September 2023 in collaboration with (memory) clinics in a larger area of Zurich and St. Gallen. Suitable patients will either be identified from medical records and patient registries of (memory) clinics, or from recent diagnostics performed by medical doctors or therapists authorized to search for medical records. Alternatively, suitable patients will be identified by an informant (ie, health care professionals) based on suspicion of MCI in one of their patients (see *Methods—Eligibility Criteria* section). Identified patients will be verbally informed about the study and will receive leaflets by their physicians or therapists containing key information about study participation and researchers' contact details. If patients are interested in being informed about the study in detail, they will be asked to provide consent to share their contact details with the research team and will be contacted by phone or email by a trained investigator of the study team. In case of initial interest in participating in the study, all interested subjects will be fully informed about the study procedures in-person (at the interested persons' home or at one of the study centers, depending on their preferences) by providing verbal explanations and an information sheet. After sufficient time for consideration (ie, at least 24 hours after handing out the study information sheet, but on average around 1 week), suitable patients willing to participate in the study will provide written informed consent in a second in-person meeting with one of the trained investigators of the study team at the home of the interested persons or at one of the study centers. After providing written informed consent, participants will be fully screened for eligibility (see section "Methods—Eligibility Criteria"), and premeasurements will be scheduled.

Eligibility Criteria

All eligibility criteria are detailed in Textbox 1.

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Textbox 1. Description of all eligibility criteria.

Inclusion criteria

- Participants fulfilling all the following inclusion criteria were eligible:
  - (1=mild neurocognitive disorder) clinical diagnosis of "mild neurocognitive disorder" according to International Classification of Diseases 11th Revision [13] or Diagnostic and Statistical Manual of Mental Disorders 5th Edition [12] OR (2=screened for mild cognitive impairment [sMCI]) patients sMCI according to the following criteria: (1) informant (ie, health care professional)-based suspicion of MCI confirmed by (2) an objective screening of MCI based on the German version of the using the quick mild cognitive impairment screen [96] with (2A) a recommended cut-off score for cognitive impairment (MCI or dementia) of <62/100 [97], while (2B) not falling below the cut-off score for dementia (ie<45/100 [97]).
  - Speaking German
  - Able to stand at least for 10 minutes without assistance

Exclusion criteria

- The presence of any of the following criteria led to exclusion:
  - Mobility impairments (ie, gait and balance) that prevent experiment participation
  - Presence of additional, clinically relevant (ie, acute or symptomatic or both) neurological disorders (ie, epilepsy, stroke, multiple sclerosis, Parkinson's disease, brain tumors, or traumatic disorders of the nervous system)
  - Presence of any other unstable or uncontrolled diseases (eg, uncontrolled high blood pressure and progressing or terminal cancer)
- COVID-19–specific risk factors (according to the Swiss Federal Office of Public Health) are additional exclusion criteria. In case of COVID-19–specific exclusion criteria, participation in the study will only be allowed when the patients' treating physician provides written informed consent allowing participation in the study despite the presence of COVID-19–specific exclusion criteria. COVID-19–specific exclusion criteria include:
  - High blood pressure (self-reported; systolic ≥140 mm Hg or diastolic ≥90 mm Hg)
  - Chronic respiratory condition
  - Uncontrolled type 2 diabetes
  - Condition or therapy that weakens the immune system
  - Unstable cardiovascular disease
  - Cancer (present or under treatment)
  - Serious obesity (BMI≥40 kg/m^2)

Interventions

Control Group

The control group will proceed with the usual care provided by the (memory) clinics where the patients are recruited. As described in section "Introduction—Choice of comparators" and based on clinical practice guidelines [90], in Switzerland, usual care is highly individual, varies between (memory) clinics where patients are recruited, and it is unclear whether patients comply with the recommendations of their clinicians. Therefore, details about all structured or guided usual care activities or both, as well as medication intake, will be assessed in both the intervention and control groups. If there are relevant between-group differences in usual care, these differences will be accounted for in the analysis and discussion of results.

Intervention Group

Participants in the intervention group will perform a 12-week training intervention in addition to their usual care (as provided by the [memory] clinics where patients were recruited). The training will be prescribed according our "Brain-IT" training concept. This motor-cognitive training concept represents a guideline for applying exergame-based motor-cognitive training by standardizing the training characteristics (eg, training frequency, intensity, and duration) as well as the structure and content of the training, whereas the exergame device and the specific games used within each of the defined neurocognitive domains can be replaced by alternative exergames. In this project, our training concept was implemented using the "Senso (Flex)" (Dividat AG). This platform was found to be suitable for the "Brain-IT" training [87] and is a widely used means for motor-cognitive training within geriatric populations, physiotherapy, and rehabilitation in Switzerland. The original "Brain-IT" training concept has recently been published with sufficient detail about the exergame components as well as the exercise and training characteristics (ie, including all predefined levels of task demands as well as the detailed progression rules) to allow full replication (ie, consider supplementary file 3 of [89]). Some minor modifications were implemented in the "Brain-IT" training concept for use in this study, based on the findings of our pilot feasibility RCT (under peer review; registered at ClinicalTrials.gov NCT04996654). This will be complemented in cases in which suitable new games become available throughout the study. The final (modified) "Brain-IT"

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training concept will be published with the manuscript reporting the results of this study, and will additionally provide specific information that would theoretically allow adaptation of the training to other hardware and software solutions. To ensure replicability, the "Brain-IT" training concept was planned and will be reported using the Consensus on Exercise Reporting Template [98].

For an overview, the "Brain-IT" training concept consists of individually adapted multidomain exergame–based simultaneous motor-cognitive training with incorporated cognitive tasks that is adopted with a deficit-oriented focus on the neurocognitive domains of (1) learning and memory, (2) executive function, (3) complex attention, and (4) visuospatial skills. Each participant is instructed to train 5 times per week for 24 minutes per session, resulting in a weekly training volume of 120 minutes. All training sessions are planned to take place at participant's homes using the "Senso Flex" hardware (Dividat AG; CE certification pending; see left side of Figure 2). The "Senso Flex" is a home-based version of the "Senso" (Dividat AG; CE certification; see right side of Figure 2). It consists of a 1.11×0.99 m rollable mat that is plugged into a portable computer and a frontal television (or other screen) at home. Both systems divide the pressure-sensitive stepping area into five fields: (1) center (home position), (2) front, (3) right, (4) back, and (5) left. The device detects the participants' position and timing of movements to interact with different game scenarios programmed in the training software. Weight shifting, walking on the spot, and steps in 4 directions (ie, front, right, back, and left) enable interaction with and control of the exergame scenarios displayed on a frontal screen. Visual, auditory, and somatosensory (vibrating platform; only available on the "Senso") feedback is provided in real time to enrich the game experience. Various games are available for training different neurocognitive domains (more details on how the device is implemented in our training concept have been provided [89]).

Adherence to the training will be monitored (see section "Outcomes—Other Outcomes—For the intervention group," ie, exergame training), and participants will be actively motivated and reminded to adhere to the training by the person responsible for supervision and correspondence with the respective study participant. Upon the request of participants, training can be paused for a maximum of 2 weeks (eg, because of holidays).

Figure 2. Exergame Device used as means to implement the "Brain-IT" training concept in this study: "Senso Flex" for home-based use (left side) and its stationary version ("Senso" for stationary use in physiotherapies, nursing homes, or rehabilitation clinics (right side). Photos provided by Dividat AG.



Outcomes

Overview

To ensure comparability of the study outcomes, global cognitive functioning will be assessed as the primary outcome. As secondary outcomes, domain-specific assessments evaluating the key neurocognitive domains (as defined in [10] in line with DSM-V [12] and according to recommendations [7]) of (1) learning and memory; (2) complex attention; (3) executive function; and (4) visuospatial skills, as well as brain structure and function, spatiotemporal parameters of gait, IADL, psychosocial factors (ie, QoL, and levels of depression, anxiety, and stress), and cardiac vagal modulation (resting vm-HRV) will be assessed. Table 2 provides an overview of all endpoints.

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Table 2. Overview of all primary and secondary outcome measures, outcome variables and interpretation guide.

Outcome measures	Outcome variables	Interpretation guide
Primary		
	Global cognitive functioning	
Quick mild cognitive impairment screen [96,99]	Total point score	Improvement=↑[a]
Secondary		
	Learning and memory	
Subtest "logical memory" of the Wechsler Memory Scale—fourth edition [100,101]	Total point score part 1—free recall	Improvement=↑
Subtest "logical memory" of the Wechsler Memory Scale—fourth edition [100,101]	Total point score part 2—free recall	Improvement=↑
Subtest "logical memory" of the Wechsler Memory Scale—fourth edition [100,101]	Total point score part 2—recognition	Improvement=↑
PEBL[b] digit span forward [102-104]	Total point score	Improvement=↑
PEBL digit span forward [102-104]	Maximum span	Improvement=↑
	Complex attention	
PEBL trail making test—part A [102]	Completion times	Improvement=↓[c]
PEBL trail making test—part A [102]	Number of errors	Improvement=↓
Subtest "Go-NoGo" of the test of attentional performance [105]	Median reaction time (ms)	Improvement=↓
Subtest "Go-NoGo" of the test of attentional performance [105]	Number of errors	Improvement=↓
	Executive function	
HOTAP picture-sorting test part A [106]	Combi score (ie, sum of the points divided by the time they needed to arrange the cards) (points×min^{-1})	Improvement=↑
PEBL digit span backward [102-104]	Total point score	Improvement=↑
PEBL digit span backward [102-104]	Maximum span	Improvement=↑
PEBL trail making test—part B [102,104]	Completion time (s)	Improvement=↓
PEBL trail making test—part B [102,104]	Number of errors	Improvement=↓
	Visuospatial skills	
PEBL-Mental Rotation Task [102,104,107]	Median reaction time of correct answered trials (ms)	Improvement=↓
PEBL-Mental Rotation Task [102,104,107]	Performance (number of correct answered trials)	Improvement=↑
	Brain Structure and Function	
3D isotropic T1-weighted MRI[d] scan	Gray matter volume of defined key regions of interest (mm^3)	Improvement=↑
3D isotropic T1-weighted MRI scan	White matter volume of defined key regions of interest (mm^3)	Improvement=↑
Diffusion Tensor Imaging MRI scan	Mean diffusivity of defined key regions of interest	Improvement=↓
Diffusion Tensor Imaging MRI scan	Fractional anisotropy of defined key regions of interest	Improvement=↑

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Outcome measures	Outcome variables	Interpretation guide
Resting state T*2-weighted blood oxygen level-dependent fMRI[e]	Individual functional connectivity maps between the hippocampal seed and the defined key regions of interest	Improvement=↑
Task-based T*2-weighted blood oxygen level-dependent fMRI	Individual functional connectivity maps between the hippocampal seed and the defined key regions of interest	Improvement=↑
	Spatiotemporal parameters of gait	
Gait analysis[f] [108]	Walking speed (m/s)	Improvement=↑
Gait analysis	Stride duration (ms)	Improvement=↓
Gait analysis	Stride length (cm)	Improvement=↑
Gait analysis	Stance phase duration (ms)	Improvement=↓
Gait analysis	Swing time (ms)	Improvement=↓
Gait analysis	Single support time (ms)	Improvement=↓
Gait analysis	Double support time (ms)	Improvement=↓
	IADL[g]	
Amsterdam IADL questionnaire [109]	T- score	Improvement=↑
	Psychosocial factors	
Quality of life-Alzheimer disease [110-112]	Overall score	Improvement=↑
Depression, anxiety and stress scale-21 [113-117]	Overall score—subscale depression	Improvement=↓
Depression, anxiety and stress scale-21 [113-117]	Overall score—subscale anxiety	Improvement=↓
Depression, anxiety and stress scale-21 [113-117]	Overall score—subscale stress	Improvement=↓
	Resting vagally–mediated Heart Rate Variability	
resting vm-HRV[h] measurement[i] [118]	Mean R-R time interval (ms)	Improvement=↑
Resting vm-HRV measurement	Root Mean Square of successive RR interval differences	Improvement=↑
Resting vm-HRV measurement	Percentage of successive RR intervals that differ by more than 50 ms (%)	Improvement=↑
Resting vm-HRV measurement	Absolute power of the high-frequency (0.15-0.4 Hz) band (ms^2)	Improvement=↑
Resting vm-HRV measurement	Relative power of the high-frequency (0.15-0.4 Hz) band (nu)	Improvement=↑
Resting vm-HRV measurement	Poincaré plot SD perpendicular to the line of identity (ms)	Improvement=↑

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Outcome measures	Outcome variables	Interpretation guide
Resting vm-HRV measurement	Parasympathetic nervous system tone index	Improvement=↑

[a]Higher values or an increase over time indicate better functioning or improvement in the respective study endpoint.

[b]PEBL: psychology experiment building language.

[c]Lower values or a decrease over time indicate better functioning or improvement in the respective study endpoint.

[d]MRI: magnetic resonance imaging.

[e]fMRI: functional magnetic resonance imaging.

[f]Instrumented gait analysis using a figure of 8 walking path [108] at preferred walking speed using BTS G-WALK (BTS Bioengineering SpA, Garbagnate Milanese, Italy) inertial sensor attached with semielastic belt to the lower back of the participant.

[g]IADL: instrumental activities of daily living.

[h]vm-HRV: vagally-mediated heart rate variability.

[i]5 min resting vm-HRV measurement with heart rate monitor (Polar M430) and sensor (Polar H10) analyzed using Kubios HRV Premium (Kubios Oy, Kuopio, Finland, version 3.4) [118].

Primary Outcome

The German version of the quick mild cognitive impairment (Qmci) screen will be used to assess global cognitive functioning [96,99]. The Qmci has been validated against the standardized Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-cog) [96,119], which is considered the gold standard for assessing the efficacy of antidementia treatments [120-122]. The Qmci was shown to "correlate strongly, significantly and correspondingly over time to the standardized ADAS-cog and that both are equally sensitive with similar responsiveness to deterioration over time" [119], "suggesting that the Qmci could be substituted for a more detailed neuropsychological instrument in clinical trials" [96,119]. Furthermore, it is accurate in differentiating mNCD from normal cognition and MNCD [119]. In this regard, it has also been externally validated and has shown a higher level of accuracy, sensitivity, and specificity than commonly used tests such as the (Standardised) Mini Mental State Exam ([S]MMSE) and the Montreal Cognitive Assessment for detecting cognitive impairment (MCI and dementia) [123]. In comparison to the (S)MMSE and Montreal Cognitive Assessment, the Qmci includes a more detailed scoring system and a logical memory task that allows the Qmci to detect more subtle cognitive abnormalities and avoid ceiling effects [123]. Qmci was scored as the point rate out of a maximum score of 100. It consists of 6 subtests: orientation (10 points), registration (5 points), clock drawing (15 points), delayed recall (20 points), verbal fluency (20 points), and logical memory (30 points) [99,124]. Qmci will be administered and evaluated according to published guidelines [99].

To the best of our knowledge, the smallest unit of clinically meaningful change has not yet been determined for the Qmci. However, changes in Qmci scores were very similar to changes in standardized ADAS-cog scores. Longitudinal data of more than 360 patients with m-MNCD were analyzed for responsiveness of the Qmci and the standardized ADAS-cog [125] by calculating standardized response mean from baseline to scores obtained at 1, 3, 6, 9, and 12 months. The mean change between months 1 and 12 was 5 points (SD 7.56) for the standardized ADAS-cog scores, and 5.41 points (SD 10.02) for the Qmci. The paired-samples *t* test showed no statistically significant difference in standardized response means for standardized ADAS-cog and Qmci (t_{357}=0.32; *P*=.75) [119]. Therefore, it is anticipated that the smallest units of clinically meaningful changes between these 2 measures are similar. For the standardized ADAS-cog, the minimal clinically relevant change is estimated to be 3 points for individuals with mNCD compared with ≥4 points based on previous recommendations made by a consensus committee of the Food and Drug Administration for patients in more advanced stages [126,127]. Therefore, it is assumed that a change of ≥3 points in the Qmci score can be regarded as a clinically meaningful change.

Secondary Outcomes

Learning and Memory

Learning and memory will be assessed using the German version of the subtests "logical memory" of the Wechsler Memory Scale—fourth edition (WMS-IV-LM) [100,101] and a computerized version of the digit span forward (DSF) test (psychology experiment building language [PEBL; PEBL-DSF]) [102-104].

The WMS-IV-LM measures auditory verbal contextual learning and memory with excellent reliability and validity [101]. The validated older adults battery (aged 65 years or older) of the German version of the WMS-IV-LM [100,101,128] will be used for all participants. The test will be instructed, conducted, and evaluated according to the standardized administration and scoring manual [100]. During the 20 to 30 minutes retention phase, unrelated assessments (eg, gait analysis, questionnaires) will be performed that do not interfere with memory.

The PEBL-DSF test assesses immediate recall and will be executed using the PEBL Test battery software [version 2.1 (2), with default settings] [102-104]. Participants were required to remember and repeat the digit sequences presented on the screen. Span length covers 2 to a maximum of 8 digits. For each digit span, 2 trials will be presented before increasing the sequence length (in case at least one of the 2 trials is completed correctly). For every correct replication of a digit sequence, 1 point will be scored, summing up to a total point score. In addition, the length of the longest correctly repeated digit sequence will be recorded as the maximum span. Instructions will be presented on the screen and will be explained verbally to each participant before starting the test.

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Complex Attention

Complex attention will be assessed using a computerized version of the Trail Making Test—Part A (PEBL-TMT-A) [102,104] and the subtest "Go-NoGo" of the Test of Attentional Performance (test of attentional performance [TAP] Go-NoGo) [105].

The TMT-A is a valid and reliable neuropsychological test for assessing psychomotor processing speed and visuo-perceptual abilities [129-134]. A computerized version of the TMT-A PEBL Test battery software [version 2.1 (2), with default settings] will be used [102,104,135]. Participants will be verbally instructed, and a short practice session will be conducted before starting the test. The completion time will be limited to 300 seconds. Completion times (seconds; including time for error correction) and the number of errors will be measured.

The TAP (version 2.3.1, PSYTEST, Psychologische Testsysteme, Herzogenrath, Germany) is a valid and reliable computerized test battery to assess various attentional and executive functions [105,136], with norm values for healthy older adults provided by the supplier [105,137]. The TAP Go-NoGo will be used to assess selective attention and inhibition. The test form "1 of 2" will be instructed, conducted and evaluated according to the standardized protocol of the manufacturer. The median reaction time and number of errors will be measured [105].

Executive Function

Executive function will be assessed considering planning (ie, using the HOTAP picture-sorting test part A [106]), working memory (ie, using a computerized version of the Digit Span Backward test; PEBL Digit Span Backward [PEBL-DSB]) [102-104], and cognitive flexibility (ie, using a computerized version of the Trail Making Test-Part B [PEBL-TMT-B] [102,104]).

HOTAP picture-sorting test part A [106] will be used to measure planning ability. A set of photo cards containing actions typical of everyday life (eg, making coffee, washing clothes, and grocery shopping) will be presented. Participants will be verbally instructed to sort photo cards on which the individual substeps of these typical everyday actions are depicted. The test will be conducted according to the manufacturer's standardized protocol. The outcome variable is a combination score calculated as the sum of points divided by the time needed to arrange the cards [106].

The PEBL Digit Span Backward (PEBL-DSB) [102-104] test will be used to assess the short-term working memory capacity. It will be instructed, administered, and scored identical to the PEBL-DSF, but participants will have to remember and repeat the digit sequences in reverse order.

The TMT-B is a valid and reliable neuropsychological test for assessing cognitive flexibility [129-134]. It consists of 25 randomly allocated circles distributed over a sheet of paper. A computerized version of the TMT-A (PEBL Test battery software [version 2.1 (2), with default settings]) will be used [102,104,135]. It will be instructed, administered, and scored identical to the PEBL-TMT-A.

Visuospatial Skills

Visuospatial skills will be tested using a computerized version of the classic Shepard and Metzler mental rotation task [138]. The PEBL-Mental Rotation Task (PEBL-MRT) will be executed using PEBL Test battery software [version 2.1 (2), with default settings] [102,104,107]. Instructions will be presented on the screen and will be explained verbally to each participant before starting the task. Pairs of differently rotated 2D polygons will be presented simultaneously on the screen. Participants need to decide as quickly as possible whether the 2 presented objects are identical (ie, pressing <Lshift> on the keyboard) or different (ie, pressing <Rshift> on the keyboard). Median reaction time of correct answered trials as well as performance (number of correct answered trials) are an indicator for mental rotation ability [107,138]. Trials with reaction times less than 0.2 seconds or greater than 13 seconds will be excluded from the data analysis [107].

Brain Structure and Function: Data Acquisition

Brain structure and function will be evaluated by MRI using a 3.0 Tesla Philips whole-body scanner (Philips Medical Systems, Best, and Netherlands) to explore possible underlying neural changes of training in relation to adaptations in cognitive performance. Only participants having no contraindications to MRI (ie, any MRI-incompatible metallic parts within the body, metallic or electronic implants [eg, heart pacemaker, brain pacemaker, and cochlear implants], and strong claustrophobia) will be measured. During measurements (duration=approximately 35 min), participants will lay comfortably in the MRI scanner and will be asked to avoid head movements. Data will be collected according to the Canadian Dementia Imaging Protocol (CDIP) [139] for comparison with other studies. The CDIP was developed to harmonize MRI acquisitions in the context of studying primary and secondary causes of morbidity of neurodegeneration in a wide range of neurological pathologies related to aging [139]. First, the following parts of the core CDIP will be applied: anatomical imaging (1.) and connectivity and functional imaging (2. – 3.) [139]:

- a 3D isotropic t1-weighted (t_1w) scan (duration=6.5 minutes) for assessing fine anatomical detail and brain atrophy (voxel size=1.0×1.0×1.0 mm^3) with an acceleration factor of 2 (TFE-Sense: 2);
- diffusion tensor imaging (DTI; duration=6 minutes) for assessment of white matter microstructural integrity and connectivity, with resolution 2.0×2.0×2.0 mm^3, a minimum of 30 uniformly distributed directions with b=1000 second/mm^2, (EPI-Sense 2-32 directions; we use the vendor-provided directions set), and an acceleration factor of 2; and
- a resting state fMRI (duration=9 minutes) for assessment of functional networks and pathways using a T^*_2-weighted blood oxygen level-dependent-sensitive sequence, with resolution of 3.5×3.5×3.5 mm^3, repetition time=2110 milliseconds, 300 volumes over time, and slice order=ascending.

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During resting-state fMRI data acquisition, participants will be asked to fixate on a cross displayed on the screen. At the end of this scan, participants must respond to written instructions by button press to check whether they were awake during the measurement.

In addition, task-based (event-related) fMRI measured with an episodic memory task (face-occupation matching task; duration: approximately 10 min) will be conducted. The face-occupation matching task was described in [140] and has been used in fMRI [141]. It was shown to robustly activate the hippocampus bilaterally and provide a differential signal for correct and incorrect trials [141]. The task was adapted specifically for older adults with mNCD [142] and will be run in PsychoPy (version 3.2.4) [143]. It includes 6 rounds, each containing (1) an encoding phase, (2) a retention phase, and (3) a retrieval phase including a cued recall task and a recognition task (see Figure 3 for an overview).

During the *encoding* phase, 5 face-occupation pairs will be presented in each round in a randomized order. A total of 30 face-occupation pairs (15 different face-occupation combinations) will be presented (Figure 3). Photographs of unfamiliar faces of older adults with neutral expressions were derived from the FACES database [144] and will be equally balanced over sex. Each face-occupation pair will be shown for 3.5 seconds. To ensure that participants view both faces and occupations, they will be asked to indicate whether each respective occupation "suits" (ie, pressing a button with their right index finger) or does not suit the presented face (ie, pressing a button with their right middle finger).

During the *retention* phase, 5 silhouettes will be presented in randomized order in each round. A total of 30 silhouettes will be presented. Each silhouette will be shown for 3.5 seconds. Participants will be asked to indicate by button press whether each silhouette corresponds to a woman (pressing a button with their right index finger) or a man (pressing a button with their right middle finger).

In the *retrieval* phase, a cued-recall task will be performed followed by a recognition task. In the cued recall task, participants will be asked to decide which of 2 educational degrees (ie, study [pressing a button with their right index finger] or apprenticeship [pressing a button with their right middle finger]) the previously encoded occupation of the person matched. In the recognition task, participants will have to decide between correct and distractor occupation via a button press (right index finger or right middle finger). For both the tasks, the response window will be 3.5 seconds. The photographs will be presented in the same order as those in the encoding phase.

The same recording parameters as in resting-state fMRI will be used. There are 4 alternative task conditions (ie, other face-occupation pairs). The task condition will be randomly allocated using random.org [145], while ensuring that 2 different conditions are used in the pre- and postintervention measurements for each participant.

Figure 3. Graphical overview of the episodic memory task (face-occupation matching task).



Brain Structure and Function: Data Analysis

Processing and volumetric segmentation of t_1w morphological data is performed using the longitudinal pipeline of the FreeSurfer software package (version 7.2.0 or newer with default parameters) [146,147], as described in [148]. Gray matter volumes and WMVs are determined for the following key regions of interest (ROIs): total brain (ie, total brain volume without ventricles [brainsegvolnotvent] from the aseg file), hippocampus, dorsolateral prefrontal cortex, PFC, and anterior cingulate cortex (ACC). Similar to Anderson-Hanley et al [77,78], we will combine the following regions to obtain the defined key ROIs of the dorsolateral prefrontal cortex, PFC, and ACC, because these are not directly extracted using the FreeSurfer software package: dlPFC=frontal middle gyrus and sulcus from the Destrieux et al [149] atlas; ACC=rostral and caudal anterior cingulate cortices from the Desikan et al [150] atlas; PFC=ACC+medial orbitofrontal and transverse frontopolar regions [151].

DTI data will be processed using the TractoFlow pipeline [152,153], a diffusion MRI tractography processing pipeline based on Nextflow [154] and Singularity [155], for human brain tractography reconstruction. In patients with m-MNCD, DTI abnormalities are concentrated in the posterior regions, whereas the most reported regions of DTI alterations are the temporal lobes, with a particular emphasis on the parahippocampal white matter and posterior cingulum [156,157]. Therefore, MD and FA will be calculated for the parahippocampal white matter and posterior cingulum, defined as key ROIs for this study. In addition, tract-based spatial statistical analysis will be performed to study white matter changes at voxel-to-voxel (whole-brain)

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levels. Tract-based spatial statistical analysis is based on a general linear model and will be performed using FSL's randomization tool [158] with 5000 permutations to correct for multiple comparisons (P<.05, corrected). All results will include threshold-free cluster enhancement [159]. The threshold-free cluster enhancement correction method is somewhat similar to cluster-based thresholding but is generally more robust and avoids the need for an arbitrary initial cluster-forming threshold. Two contrasts will be computed at the individual and group levels, testing for positive and negative differences in FA and MD parameters pre- and postintervention. We will include age and sex as key covariates in the general linear model.

Data of *resting state and task-based fMRI* will be preprocessed to minimize data artifacts from thermal noise of MRI, system noise of the MR hardware, and subject-related noise resulting mostly from head motion [160]. The preprocessing steps will include slice time correction, motion correction, coregistration, and spatial smoothing (Gaussian kernel with 7 mm full width at half maximum) of the signal [161]. For functional connectivity (FC) analysis, preprocessed resting-state functional data will be analyzed using the latest release of the Functional Connectivity Toolbox (currently CONN 21a; [162,163]) in SPM12. The CONN utilizes a component-based noise correction method (CompCor) that increases selectivity and sensitivity and allows a higher degree of interscan reliability [164]. In addition to the described preprocessing steps, a band-pass filter (0.01-0.1 Hz) will be applied to remove linear drift artifacts and high-frequency noise. The CONN also accounts for outlier data points and movement time courses as nuisance regressors. The 6 motion parameters, WM and CSF, will be included as regressors of no interest, thereby reducing noise and signals that are unlikely to reflect neuronal activity related to FC. Age and sex will be included as key covariates of no interest. Significance was set at P<.05 with Family Wise Error-level correction for multiple comparisons (with P<.05 2-sided false-discovery rate correction) [163].

Bilateral hippocampal masks were selected as seeds from an Anatomical Automatic Labeling template [165]. Individual FC maps for the hippocampal seed will then be generated based on correlations between the mean signal time course within each seed region and the rest of the brain, similar to Suo et al 2016 [166], with the following selected key ROIs (ie, brain regions related to cognitive functioning, similar to Zhong et al [167]): precuneus or posterior cingulate cortex, medial prefrontal cortex, medial temporal lobe, angular gyrus, lateral temporal cortex, and medial, lateral, and inferior parietal cortex.

Spatiotemporal Parameters of Gait

Spatiotemporal parameters of gait will be evaluated to explore whether the addition of the "Brain-IT" training to usual care effectively improves gait. The gait of individuals with mNCD differs from that of healthy controls in terms of (among others; 1) slower single-task gait speed at the preferred walking speed (m/s) [18,168], (2) longer stride duration (ms) [18,168], (3) shorter stride length (cm) [18,168], (4) longer stance time (ms) [168], (5) longer swing time (ms) [168], (6) longer single support time (ms) [168], and (7) longer double support time (ms) [168]. Furthermore, individuals with mNCD typically show greater variability and coefficient of variation of gait parameters compared with cognitively healthy individuals [168].

According to the literature summarized above, we assume that an effective intervention leads to an (1) increase in single-task gait speed at the preferred walking speed, (2) decrease in stride duration, (3) increase in stride length, (4) decrease in stance time, (5) decrease in swing time, (6) decrease in single support time, and (7) decrease in double support time.

On the basis of this, we have elaborated our alternative hypotheses in more detail. It is hypothesized that in older adults with mNCD, the addition of the "Brain-IT" training to usual care results in differing effects on (c_1) single-task gait speed at the preferred walking speed, (c_2) stride duration, (c_3) stride length, (c_4) stance time, (c_5) swing time, (c_6) single support time, and (c_7) double support time compared with usual care.

Spatiotemporal gait parameters will be assessed using a BTS G-WALK (BTS Bioengineering SpA, Garbagnate Milanese, Italy) inertial sensor attached with semielastic belt to participants' lower back. The BTS G-WALK sensor delivers valid [169-171] and reliable [169,172] spatiotemporal gait parameters. All the acceleration data will be sampled at a frequency of 100 Hz. Data will be transmitted for analysis through Bluetooth 3.0, connection to the software program BTS G-Studio (BTS Bioengineering SpA, Italy). A gait-analysis protocol consisting of a figure of 8 walking path (ie, distance between cones of approximately 8 m) will be applied [108]. At least 50 consecutive gait cycles are required to ensure the reliability of the spatial and temporal parameters of gait variability [173]. Therefore, participants will perform 5 to 10 repetitions of the figure of 8 walking path at the preferred walking speed, depending on their walking speed and stride length. Comparative quantitative reference values for healthy older adults are available [174].

IADL Functioning

IADL functioning will be assessed using the Amsterdam IADL questionnaire short version, German for Switzerland, which has demonstrated good psychometric properties [109]. In addition, the original version of the Amsterdam IADL questionnaire was sensitive to longitudinal changes [175] and has been recommended for use in research settings [176]. The closest informant (eg, spouse, child, or friend) will fill out the questionnaire twice (within 2 weeks before the study participant starts or completes the intervention). Each item is scored on a 5-point Likert scale ("no difficulty" to "unable to perform"). Scoring is based on the item response theory. Item response theory latent trait levels are transformed to a T-score, with a range from 20 to 80, a mean of 50, and an SD of 10. A higher t score indicates better functioning [109].

Psychosocial Factors

QoL will be evaluated in interview format using the Quality of Life-Alzheimer Disease (QOL-AD) scale [110]. The QOL-AD is a valid and reliable self-report 13-item scale assessing various domains of QOL in cognitively impaired patients [110,177]. The German version of the QOL-AD scale, which has high test-retest reliability and good construct validity [111,112] will

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be used. Administration and evaluation will follow standardized instructions [112,178]. Comparable values are available for individuals with mNCD [179].

Levels of depression, anxiety and stress will be assessed using the short version of the Depression, Anxiety and Stress scale-21 (DASS-21) [113-115]. The DASS-21 has high reliability and good convergent and discriminant validity [113,180]. The validated German version of the DASS-21 will be administered and scored according to guidelines and scoring template [116,117]. Normative data of the 3 subscales are available and suggest cut-off scores of 10, 8, and 15, indicating significant depression, anxiety, or stress, respectively [116]. Comparative values for individuals with mNCD are available [181].

Cardiac Vagal Modulation (Resting Vagally-Mediated Heart Rate Variability)

To determine resting vm-HRV, all participants will be instructed to sit in a comfortable position on a chair without speaking, both feet flat on the floor with knees at a 90º angle, hands on the thighs (ie, palms facing upward), and eyes closed [95]. Measurements will be performed in a quiet room with dimmed light at room temperature. Data will be collected using a heart rate monitor (Polar M430) and sensor (Polar H10). The initial acclimatization phase will last for 5 minutes followed by a 5-minute resting measurement, the recommended standard duration for short-term recordings [95,182]. The start of the resting measurement will not be announced to the participants [95].

For resting HRV measurements, a sampling rate of 1000 Hz will be used to provide a temporal resolution of 1 milliseconds for each RR interval [183]. R-R data recordings will directly be transmitted to the Kubios HRV Premium (Kubios Oy, Kuopio, Finland, version 3.4) for analysis. Kubios HRV is a scientifically validated software for HRV analysis and has achieved the gold standard status in research [118,184-186]. The automatic beat correction algorithm and noise handling provided by the software will be used to correct for artifacts or ectopic beats. This algorithm has been validated for measurements at rest [184]. After removing interbeat-interval time series nonstationarities by detrending analysis using the smoothness priors method approach (settings: detrending method=smoothing priors, Lambda=500, f_c=0.035 Hz), the mean values of mainly vagal-mediated HRV indices will be calculated for each segment. For this purpose, the mean R-R time intervals (mRR; ms), root mean square of successive RR interval differences (ms), percentage of successive RR intervals that differ by more than 50 milliseconds (%), absolute power of the high-frequency (0.15-0.4 Hz; high frequency [HF]) band (ms^2), relative power of HF (in normal units; HF [n.u.] = HF [ms^2] / (total power [ms^2]—very low frequency; 0.00-0.04 Hz [ms^2]), and Poincaré plot SD perpendicular to the line of identity (SD1; ms) will be considered [95,182,187-189]. In addition, the parasympathetic nervous system tone index (parasympathetic nervous system index) will be calculated to compare parasympathetic nervous system activity with normal resting values [189].

Other Endpoints

Safety Endpoint Variables

A protocol will be kept of all (serious) adverse events.

Baseline Factors

Baseline factors are collected through demographic data, including age, sex, height, weight, BMI, years of education, physical activity behavior (ie, measured with the German version of the International Physical Activity Questionnaire Short Form—short form [190,191] and analyzed according to published guidelines for data processing and analysis of International Physical Activity Questionnaire Short Form—short form [192]), clinical subtype (ie, mNCD due to AD, mild Frontotemporal NCD, mNCD with Lewy Bodies, or mild vascular NCD), medication intake, and changes in medication intake between pre- and postintervention measurements.

Adherence and Compliance Protocol

For the intervention group (ie, exergame training):

- Adherence Protocol (number of sessions completed per week per participant; automatically assessed in the Exergame Training Software) to calculate the mean adherence rate (%) = number of training sessions attended / total number of training sessions offered; calculated as the average of each participant's weekly adherence with a maximum of 100%.
- Compliance Protocol (training time completed per week per participant; automatically assessed in the Exergame Training Software) to calculate the mean compliance rate (%) = training duration attended (min) / total training duration offered (min), calculated as the average of each participant's weekly compliance, with a maximum of 100%.

Participant Timeline

Table 3 provides an overview of the participant timeline.

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Table 3. Participant timeline.

Time	≥2 days before pre-measurements	≥1 day before pre-measurements	Week−1 to 0	Week 1-12	Week 13-14	Week 15
Visit	Information	Consent and screening	Premeasurements	Intervention period	Postintervention measurements	Postintervention information
Location	At the interested persons' home or at one of the study centers, depending on their preferences	At the interested persons' home or at one of the study centers, depending on their preferences	At one of the study centers	At the participants' homes	At one of the study centers	At the participants' homes or at one of the study centers, depending on their preferences
Oral and written information	✓					
Written informed consent		✓				
Inclusion and exclusion criteria		✓				
Primary outcome:Qmci[a] (~5 min)			✓		✓	
Secondary outcomes: • WMS-IV-LM[b] (~15 min) • PEBL[c]-DSF[d] and DSB[e] (~5 min) • PEBL-TMT-A and B[f] (~5 min) • TAP Go-NoGo[g] (~5 min) • HOTAP-A[h] (~5 min) • PEBL-MRT[i] (~5 min) • MRI[j]-Scan (~60 min) • gait Analysis (~5 min) • IADL[k] (~15 min) • QOL-AD[l] (~5 min) • DASS-21[m] (~5 min) • resting vm-HRV[n] (~12 min)			✓		✓	
Baseline Factors (~5 min)			✓			
Safety endpoints			✓	✓	✓	
Adherence and Compliance to the Training Protocol				✓		
Study intervention				✓ (Study visits only applicable for exergame-group)		
Discuss individual results						✓

[a]Qmci: quick mild cognitive impairment screen.

[b]WMS-IV-LM: subtest "logical memory" of the Wechsler Memory Scale–fourth edition.

[c]PEBL: psychology experiment building language.

[d]DSF: digit span forward.

[e]DSB: digit span backward.

[f]TMT-A and B: Trail Making Test Part A and B.

[g]TAP Go-NoGo: subtest "Go-NoGo" of the test of attentional performance.

[h]HOTAP-A: HOTAP picture-sorting test part A.

[i]MRT: mental rotation task.

[j]MRI: magnetic resonance imaging

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[k]IADL: instrumental activities of daily living.

[l]QOL-AD: Quality of Life-Alzheimer Disease.

[m]DASS-21: Depression, Anxiety and Stress scale-21.

[n]vm-HRV: vagally-mediated heart rate variability.

Sample Size

The optimal sample size was justified based on Whitehead et al [193], and the following assumptions: the future main (full-scale) RCT will be planned with identical design and primary outcome as this study, with a two-sided type 1 error rate of 5% and a statistical power of 80%.

Our pilot feasibility RCT revealed a medium effect size (η^2_p=0.080; under peer review; registered at ClinicalTrials.gov NCT04996654). The observed medium effect size is slightly higher than the pooled evidence of exergame-based or combined motor-cognitive training interventions in older adults with NCD on global cognitive functioning. For exergame-based interventions in individuals with mNCD, Wang et al [194] reported a medium SMD of 0.57 (*P*=.21, 95% CI −0.32 to 1.47; *k*=1; n=20, compared with cognitively active control), while Gavelin et al (2021) reported an SMD of 0.13 (*P*>.05, 95% CI −0.22 to 0.48; *k*=2; n=109, compared with passive control) [63]. Stanmore et al [195] reported a small pooled effect of Hedges *g*=0.340 (*P*=.02, 95% CI 0.06-0.62; *k*=6; n=193) for patients with cognitive impairment. Further meta-analytic results for individuals with mNCD are limited to simultaneous motor-cognitive training with reported small-to-medium effect sizes, including SMDs of 0.45 [61], 0.48 [196], 0.531 [61], and 0.69 [197]. On the basis of this, a medium effect size of a SMD of 0.5 seems reasonable and is anticipated. This leads to a justified optimal sample size of n=14 per arm.

In our pilot feasibility RCT, we observed an attrition rate of 20% (under peer review, registered at ClinicalTrials.gov NCT04996654). This is consistent with recent systematic reviews synthesizing mean attrition rates of 17% (range, 0 to 59%) [198] in physical training interventions, 10% for combined motor-cognitive training interventions [199], and 15% (range 0%-31%) [200] for exergame-based interventions for patients with m-MNCD. Therefore, an attrition rate of 20% is anticipated. To ensure an adequate number of participants, a wide upper safety margin for an attrition rate of up to 40% is selected.

On the basis of these considerations, we will aim to recruit 17 to 20 older adults with mNCD per group, leading to a total sample size of 34 to 40. This will provide a sufficiently precise estimate of the treatment effect to minimize the sample size needed for a future full-scale RCT [193].

Randomization

Sequence Generation

Participants will be randomly allocated to the intervention or control group. Variable block randomization (ie, block sizes=4, 6, and 8) with a 1:1 allocation ratio stratified by sex and institute (study center) will be used.

Allocation Concealment Mechanism

To ensure allocation concealment, random allocation will be computer generated using a validated variable block randomization model implemented in the data management system Castor EDC (Ciwit BV) [201].

Implementation

Randomization process will be set up by PM before starting patient recruitment. PM will also oversee the enrollment of participants. Participants will individually be assigned to the intervention or control group by the investigator responsible for supervision and correspondence with the respective study participant after completing premeasurements. Randomization allocation can be viewed in eCRFs by investigators who have been assigned right to do so. The eCRF is implemented in the Castor EDC data management system [201]. None of the investigators performing postintervention measurements will have access rights to view the randomization allocation in eRCFs.

Blinding

Outcome evaluators of pre- and postintervention measurements will be blinded to the group allocation (single blinding). To ensure blinding and blind-keeping of outcome assessors, detailed study-specific guidelines for all relevant procedures related to blinding and blind-keeping of outcome assessors have been established, which will be followed by all involved study investigators. For data assessed throughout the intervention period (ie, only applicable to the intervention group), blinding of investigators is not possible. The blinding of participants will also not be possible because usual care will be used as a control intervention.

Participant Retention

Once a patient is included, a trained investigator will be assigned as the person responsible for supervision and correspondence with the respective study participant and will make all reasonable efforts to achieve participant's retention in the study. Examples include providing written information sheets and reminders about study appointments, involving carers or relatives as personal support for study participants, and providing assistance with travel to the study center. Specifically, in the intervention group, each participant is provided with a training manual that is individually adapted to ensure that they use the training system correctly.

Data Management

All study investigators will be thoroughly trained for all study procedures according to the Guidelines of Good Clinical Practice and in line with detailed working instructions and a data management plan (Multimedia Appendix 1). In short, local principal investigators are in charge for methodological standards and quality of data collection using data management system Castor EDC (Ciwit BV) [201]. The data management

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plan specifies standard procedures for data management, evaluation, and storage. All data entries will be cross-checked by a second investigator before exporting for analysis. Range checks for data values were preprogrammed for data entry into the eCRFs. To minimize bias during the assessment of all clinical outcome measures, detailed working instructions were prepared, including standardized measurement procedures and standardized instructions of participants for all measurements.

Statistical Methods

Statistical analysis will be executed using R (The R Foundation), in line with RStudio (RStudio Inc). For demographics as well as training adherence and compliance, all collected data will be included (ie, including data of dropouts up to the time point of their withdrawal). For primary and all secondary outcomes, the data of all participants who completed pre- and postintervention measurements, regardless of protocol adherence, will be included in the statistical analyses. Questionnaire scores will be regarded as ordinal data. Data will be reported as mean (SD) values for continuous parametric data and median (IQR) values for continuous nonparametric data.

For all outcomes, descriptive statistics will be computed first. Normality distribution of data will be checked using the Shapiro-Wilk test. The level of significance will be set to $P \leq .05$ (2-sided, uncorrected).

For all demographic variables, between-group differences (ie, intervention vs control) will be tested using an independent *t* test or Mann-Whitney *U* test in case the data are not normally distributed. For primary and secondary outcomes, the assumption of homogeneity of variance will be checked using Levene test. In case all assumptions for a 2-way analysis of covariance (ANCOVA) are met, effectiveness of the "Brain-IT" training will be analyzed using a two-way ANCOVA with the premeasurement value as covariate for the predicting group factor and the postmeasurement value as outcome variable [202]. If not all assumptions are met, the Quade nonparametric ANCOVA will be used. Because of the stratification by sex in the randomization process, no sex-specific statistical analysis will be computed. However, if there are relevant between-group differences in sex distribution or other demographic variables, these will be included in the statistical analyses as additional covariates. To determine whether the effects are substantive, partial eta-squared (η^2_p) effect sizes will be calculated for all primary and secondary outcomes. Effect sizes will be interpreted as small ($0.01 \leq \eta^2_p < 0.06$), medium ($0.06 \leq \eta^2_p < 0.14$), or large ($\eta^2_p > 0.14$) [203].

Statistical analysis will be performed by PM after data collection is completed. As this is a small-scale RCT, no interim analysis will be performed.

Monitoring

External monitoring will be performed at three time points: (1) before starting recruitment (site initiation visit); (2) after inclusion of 10 participants (routine monitoring visit); and (3) after completing all postintervention measurements and database lock (close-out visit) by Dr Ruud Knols (Physiotherapy and Occupational Therapy Research Centre, Directorate of Research and Education, University Hospital Zurich). Monitoring activities will be performed according to the ICH-GCP and according to a detailed monitoring plan that is based on adaptations of the "Monitoring Plan Template" of the Swiss Clinical Trial Organization to meet study-specific requirements.

Ethics and Dissemination

Research Ethics Approval and Protocol Amendments

The study protocol was approved by the Ethics Committees of Zurich and Eastern Switzerland (EK-2022-00386). Any substantial amendment to the study protocol will have to be approved by the Ethics Committees of Zurich and Eastern Switzerland, and the trial registration at clinicaltrials.gov (NCT05387057) will be updated accordingly. Any substantial amendments to the study protocol that may occur after publication of this study protocol will be reported in the final publication of the study results.

Consent or Assent

As described in detail in section "Methods - Recruitment", suitable patients willing to take part in the study will provide written informed consent in a second in-person meeting with one of the trained investigators of the study team at the interested persons home or at one of the study centers, depending on their preferences.

Confidentiality

Measures to ensure data confidentiality are detailed in the data management plan (Multimedia Appendix 1).

Access to Data

As detailed in the data management plan (Multimedia Appendix 1), anonymized data sets from this project that underpin a publication will be deposited in the Zenodo repository and made public after completing data collection.

Ancillary and Posttrial Care

In the event of study-related damage or injuries, the liability of the institution ETH Zurich provides compensation, except for claims arising from misconduct or gross negligence. Insurance is covered by ETH Zurich public liability insurance (Police Nr 30/4.078.362 of "Basler Versicherung AG"). After completion of study participation, all participants will be offered to use the training device at their own responsibility, either by purchasing a "Senso Flex" (if market launch of the "Senso Flex" has already taken place at that time) or by using a "Senso" in one of a nearby physiotherapies, nursing homes or rehabilitation clinics offering the system.

Dissemination Policy

Each participant will be informed of their personal results by providing a written report summarizing the patients' relevant results. The report will be handed out in person and explained by a trained investigator to ensure that the patients understand their results. In addition, upon request, an information letter will be sent to participants at the end of the study to inform them about the findings obtained in this study.

A manuscript of the results will be published in a peer-review open-access journal as well as on ResearchGate and original

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data sets will be made available in a publicly accessible repository. Standard journal authorship criteria will be applied; there will be no use of professional writers. In addition, the results of this study will be disseminated via open-access journal articles and conference presentations to inform health care professionals, the public, and other relevant groups about the study results and the knowledge gained.

Results

Upon the initial submission of this study protocol, 13 patients were contacted by the study team. Four patients were included in the study, 2 were excluded because they were not eligible, and 7 were being informed about the study in detail. Of the 4 included patients, 2 already completed all premeasurements and were in week 2 of the intervention period. Data collection is expected to be completed by December 2023. A manuscript of the results will be submitted for publication in a peer-reviewed open-access journal in 2024.

Discussion

Principal Findings

This RCT will systematically evaluate the effectiveness of a newly developed nonpharmacological exergame-based training targeted at improving cognitive functioning in older adults with mNCD. The results of this study should provide information on whether the addition of our modified and improved exergame-based training (according to the "Brain-IT" training concept) to usual care is effective in improving global cognitive functioning, and a future full-scale RCT is warranted. The study will thus contribute to the evidence base in prevention of disability because of cognitive impairment, which has been declared a public health priority by the World Health Organization [33].

Comparison With Prior Work

Technological innovations (eg, exergames) provide new options to engage older adults with mNCD in (simultaneously-incorporated) motor-cognitive training [70]. So far, only 1 study has applied exergame-based training that was individualized content-wise based on the cognitive abilities of older adults with mNCD [82]. Furthermore, most previous studies used commercially available exergame systems [76-82], where the training content was not specifically developed for individuals with mNCD. These studies have shown rather limited effects on global cognitive functioning [63], although combined motor-cognitive training seems to be the most effective type of training for improving cognition in older adults with mNCD [61,63-65].

Limitations

There are some limitations to this RCT that must be mentioned. First, we will only explore the effectiveness of the addition of the "Brain-IT" training concept to usual care. In line with this, the sample size for this RCT was justified to provide a sufficiently precise estimate of the treatment effect to minimize the sample size needed for a future full-scale RCT [193]. As a result, the statistical analyses will most probably be insufficiently powered, and confirmatory studies are needed following this study. Second, usual care interventions are assessed by self-report of patients. To counteract possible biased information, the study team will ask specific questions about whether participants are engaged in typical usual care interventions (as described in section "the Methods and Materials section—Interventions—Control Group") and actively involve participants' proxies when collecting this information. Third, patients screened for MCI according to predefined criteria are recruited in addition to patients with a clinical diagnosis of mNCD, which will increase the heterogeneity of the study population. In line with this, in our project, we aim to investigate an individualized exergame-based training concept not only to treat clinically diagnosed patients with mNCD but also to prevent progression to dementia in individuals at risk who might not have been diagnosed (yet).

Conclusions

This study will contribute to the evidence base in the highly relevant area of prevention of disability because of cognitive impairment, which has been declared a public health priority by the World Health Organization.

Acknowledgments

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Authors' Contributions

PM was responsible for the conception and writing of the study protocol under the supervision of EdB. LM and AS contributed to magnetic resonance imaging methodology, and FB contributed to the recruitment strategy and eligibility criteria for participants. All authors have contributed to the revision of the manuscript. All authors have read and approved the submitted version of the manuscript.

Conflicts of Interest

None declared.

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Multimedia Appendix 1
Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 checklist and data management plan.
[PDF File (Adobe PDF File), 322 KB - resprot_v12i1e41173_app1.pdf]

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Abbreviations

ACC: anterior cingulate cortex
AD: Alzheimer disease
ADAS-cog: Alzheimer's Disease Assessment Scale-Cognitive Subscale
ANCOVA: analysis of covariance
CDIP: Canadian Dementia Imaging Protocol
DASS-21: Depression, Anxiety and Stress Scale-21
DSF: digit span forward
DSM-V: Diagnostic and Statistical Manual of Mental Disorders 5th Edition
DTI: diffusion tensor imaging
FC: functional connectivity
HF: high frequency
IADL: instrumental activities of daily living
MCI: mild cognitive impairment
MNCD: major neurocognitive disorder
mNCD: mild neurocognitive disorder
MRI: magnetic resonance imaging
PEBL: psychology experiment building language
Qmci: quick mild cognitive impairment
RCT: randomized controlled trial
ROI: region of interest
SMD: standardized mean difference
TAP: test of attentional performance

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Protocol

Physiological and Psychological Effects of Parent-Delivered Traditional Thai Massage in Children With Autism: Protocol for a Randomized Controlled Trial

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Abstract

Background: Although many autistic children receive massage as a complementary therapy, it is not included in evidence-based practice for autism because evidence of its efficacy is lacking. Further, prior studies have failed to identify objective indicators of core symptoms or elucidate their mechanisms.

Objective: We developed a parent-delivered traditional Thai massage (TTM) intervention for children with autism, aiming to experimentally determine whether children with autism truly experience positive effects from parent-delivered TTM and determine possible mechanisms of the observed effects.

Methods: A 2-armed, parallel randomized controlled trial was conducted between February 2022 and June 2022. Forty-eight children with autism (aged 7-12 years) were recruited from the Hainan Special Education School and randomly assigned to either a parental TTM or control group at a ratio of 1:1 based on random numbers generated with Online Research Randomizer. The generated sequences were concealed in an opaque envelope. Individuals in the parental TTM group received 16 parent-delivered TTM sessions over 8 weeks at the school's health room after school, and the control group maintained a normal daily routine. Outcomes were assessed on admission, after 8 weeks, and at a 2-month follow-up and included the effect of massage treatment on autism symptoms, measured with the Autism Treatment Evaluation Checklist score (evaluated by parents and a blinded teacher), physiological parameters (ie, heart rate variability and gait), and the Parenting Stress Index, Fourth Edition–Short Form.

Results: We finished all data collection on June 20, 2022. Data analysis will be started, and we expect to publish results in 2023.

Conclusions: This study will provide further evidence for massage treatment of autism and provide support for family-based care.

Trial Registration: Chinese Clinical Trial Registry ChiCTR2100051355; https://tinyurl.com/3dwjxsw5

International Registered Report Identifier (IRRID): DERR1-10.2196/41839

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KEYWORDS

autism; massage; randomized controlled trial; protocol

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Introduction

Background

Autism is a neurodevelopmental disorder that affects central nervous system development. The core symptoms are characterized by social interaction and social communication deficits and restrictive-repetitive behavior patterns [1]. The disorder is not associated with any particular culture, ethnicity, race, or socioeconomic group [2]. The majority of individuals with autism also have motor disorders, sensory disorders, anxiety, hyperactivity, sleep disorders, or autonomic nervous system (ANS)-associated disorders [3-5]. The prevalence of autism has risen rapidly in the last decade. An assessment commissioned by the World Health Organization in 2012 estimated the global prevalence of autism to be approximately 1% [6]. An updated report from the US Centers for Disease Control and Prevention showed that 1 in 44 children aged 8 years was estimated to have autism spectrum disorder (ASD) [7]. A survey found that the incidence of autism among children in China was comparable to that in Western countries [8].

A variety of motor disorders are common in autism [9]. Postural [10] and gait abnormalities [11,12] can appear as early as infancy [13] and persist into childhood [14,15] and adulthood [16]. Previous studies showed that motor impairment may result in atypical movement [17] and limit social interaction [18] due to sensory integration impairment [16]. This could, in turn, lead to the development of core autistic symptoms [18,19] and reduced quality of life [20].

The core symptoms of autism can be explained in part by ANS dysregulation [3,21,22]. Messina et al [23] found sympathetic activity, such as heart rate variability (HRV; the variation in time between each heartbeat), which is controlled by the ANS, may be considered an important tool for autism assessment. Measurements of HRV are considered to be the standard noninvasive method for assessing ANS function [23] and have also been suggested to be a valuable situation-specific marker of the effective regulation of children's binary social interactions [24]. Previous reports showed that tonic HRV was significantly reduced in children with ASD compared with typically developing children [22,25]. Lory et al [25] suggested that ANS disorders in autism may lead to atypical attentional responses to sensory stimuli.

Atypical sensory responses (hyper- or hyporeactivity to sensory stimuli) are present in 90% of children with autism [26] and have been listed in the core diagnostic criteria for autism in the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, with abnormal tactile responses commonly reported [27]. Thye et al [19] reviewed the evidence of a relationship between sensory and social behavior in autism, especially in terms of touch and tactile processing irregularities, and concluded that it may be associated with social dysfunction.

Prior Work

Massage is a touch-based therapy [28] defined as the use of the hands, feet, arms, or elbows to touch or manipulate the body surface of the person being massaged for healing and maintenance purposes [29]. Massage originates from human instinct and was developed as a kind of technology by the ancients. Historical records of massage therapy date back 3000 years, and massage therapy is mentioned in the earliest medical book in China, the *Huangdi Neijing* (*The Yellow Emperor's Classic of Internal Medicine*), which recorded the theory of Chinese medicine and massage theory. The value of massage as a form of therapy has been recognized throughout history by ancient civilizations in China, India, Japan, Thailand, and, later, the ancient Egyptians, as well as the Greeks and Romans [30]. Since then, massage therapy has been continuously developed and applied, and is widely used in clinical practice to relieve pain, eliminate fatigue, and promote rehabilitation. A review by Field [31] outlined the clinical implementation of massage theory in recent years. Massage has recently been employed as a complementary therapy in the treatment of autism. It has been reported that 11% to 16% of people with autism receive massage therapy [32]. Initial studies in this area of research suggest that massage might have positive impacts on social communication [33,34], stereotypic behavior [35,36], sensory profiles [37,38], and language ability [39,40] in autism. According to research findings, positive touch stimuli can increase oxytocin release [41,42]. Oxytocin is known to be involved in ANS circuit regulation [41], which affects both emotional and social processes [43]. Suitable pressure stimulation is the critical feature of massage, and stimulation of pressure receptors has been shown to result in increased vagal activity. Increased vagal activity is associated with slower heart rate and enhanced attentiveness [31].

Traditional Thai massage (TTM) is believed to have ancient origins and has 3 distinctive features: deep pressure massage, work on meridian (energy) lines, and stretching of the affected muscles and joints. TTM is widely used in health care [44,45] and rehabilitation [46,47]. The results of studies conducted to date suggest that TTM may facilitate immediate and short-term improvement in HRV [48,49] and some gait parameters in nonautistic patients [50,51]. Since an increase in HRV reflects a state of relaxation due to parasympathetic activity induced by TTM, patients either with or without autism can relax and reduce their restrictive-repetitive behavior patterns. Consequently, they should improve their gait pattern and speed. TTM has also been effectively used in the rehabilitation of children with disabilities by the Bangkok Foundation for Children with Disabilities [52]. However, we only found one study [53] that reported the effects of TTM administered by masseurs on autistic behavior, and its methodology and conclusions were questionable [54]. It appears that more research is needed to explore the effects of TTM on autism by using both subjective and objective evaluation.

Furthermore, the refractory and lifelong nature of autism has profound implications for parents of autistic children and evidence shows that parents of children with autism experience more parenting stress than parents of nonautistic children or children diagnosed with other disabilities [55,56]. One recent review suggested that family-based interventions for mental disorders in children are becoming increasingly important, with more positive outcomes when parents are involved in the treatment [57]. Previous research revealed that parents who engaged in a massage-based intervention not only satisfied family-based care needs [58] but also showed relieved anxiety

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[42] and strengthened parent-child bonding [37,38,59]. The effects of TTM delivered by the parents of autistic children on these outcome measures have not been verified. This study aims to assess the effects of parental-delivered TTM in children with autism by evaluating changes in symptoms and physiological parameters (ie, gait and HRV). The primary objective of the study is to assess the effectiveness of parental TTM in improving symptoms of autism according to the Autism Treatment Evaluation Checklist (ATEC). Secondary objectives are to evaluate instant and cumulative effects of the parental TTM intervention via an assessment of gait and HRV and explore the relationship between symptom improvement and observed changes in physiological parameters. The tertiary objective is to examine changes in levels of parental stress after parents have administered the TTM intervention. The following four research questions will be addressed: (1) Do core symptoms significantly improve (ie, does ATEC score improve) in autistic children after parental TTM in comparison with the control group? (2) Do HRV and gait indicators significantly improve in children with autism after parental TTM? (3) Is ATEC score improvement related to observed changes in physiological parameters? (4) How does parental stress change throughout the intervention period, as measured by the Parenting Stress Index, Fourth Edition–Short Form (PSI-4-SF)?

Methods

Participants

Inclusion Criteria

The following inclusion criteria were applied to select autistic children: they had autism diagnosed by a child psychologist, were aged 7 to 12 years, were not already receiving systemic massage therapy, and were able to follow instructions. The children's primary caregivers met the following criteria: they had been providing ≥1 year of childcare, were able to communicate with the massage trainer, and were able to read the questionnaire. Teachers met the following inclusion criteria: they served as primary caregivers for autistic children at school, had provided care for at least one semester, and were willing to participate in research.

Exclusion Criteria

This study applied exclusion criteria to 3 groups of people: the autistic children, their parents, and their teachers. For autistic children, the following exclusion criteria were applied: contraindications to TTM, such as fractures, fever, or psychoactive medication, and administration of other specialized interventions during the experimental period. Parents were excluded if they were not available at the allotted time. Further, teachers with insufficient time to complete the questionnaire were excluded.

Sample Size

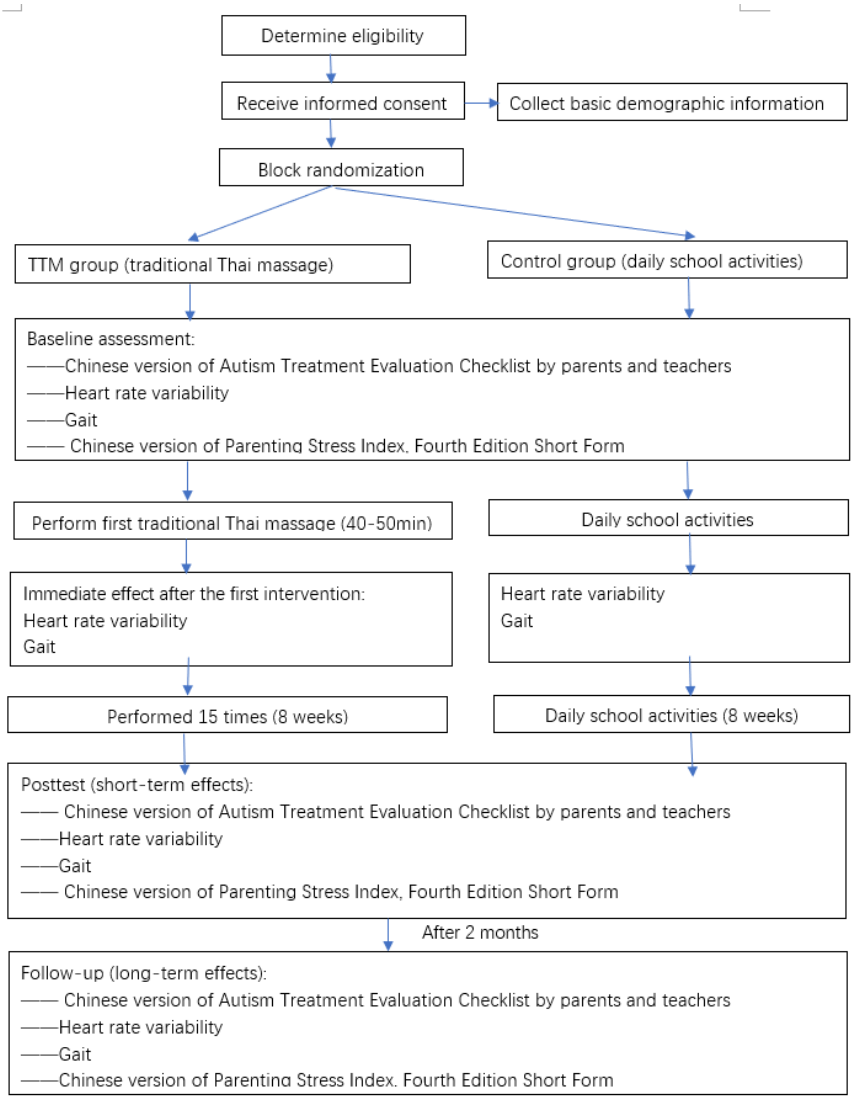
The sample size calculation was based on research by Najafabadi et al [60]; no previous study has used both an autism massage intervention and the ATEC scale. The standard deviation of the social ATEC scores of the 2 groups was used to calculate the sample size needed to achieve a power of 80% and a 2-sided significance level of 5%. A dropout rate of 10% was assumed to determine the principal of intention for estimating the final sample size needed. According to a previously reported formula [61], a total of 48 participants were recruited for the study.

Design and Setting

A randomized controlled trial (RCT) was conducted between February 2022 and June 2022. Participants were recruited from the Hainan Special Education School in Hainan Province, China. A recruiting poster and presentation were posted on the bulletin board at the school. Figure 1 depicts a flowchart of the study protocol prepared according to the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines [62] (Multimedia Appendix 1). Before recruiting the participants, informed consent forms (Multimedia Appendix 2) were sent to the parents via the teachers, and if the parents agreed to participate, they signed the form and submitted it to a designated box within 2 days. The children with autism who could communicate with their parents also gave either verbal or written informed consent.

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Figure 1. Flowchart depicting the study design.



Randomization

Forty-eight participants (aged 7-12 years) from grades 1 to 6 were randomly assigned to parental TTM and control groups by random numbers generated with Online Research Randomizer (Geoffrey C Urbaniak and Scott Plous). The random numbers were then concealed in an opaque envelope.

Blinding

Since the massage intervention took place after school hours, parents brought their children to the health room, which is located far from the teaching building. Teachers were blinded to the group assignments of the children included in the study. Parents were asked to refrain from discussing the intervention to prevent contamination of the control group. Data collectors were also unaware of group placement.

Ethical Considerations

This study complies with the ethical standards of the relevant national and institutional guidelines on human experimentation and was approved by the Khon Kaen University Ethics Committee for Human Research (HE642167). The study followed the Helsinki Declaration. Results will be published in a peer-reviewed journal and presented at domestic and international academic conferences to further promote communication. This protocol was registered with the Chinese Clinical Trial Registry (ChiCTR2100051355).

Researchers provided parents with information about the study and obtained informed consent from them while their children were in school. The parent or guardian signed the document and returned it to the school researcher or the teacher. Before the study, the parents were responsible for asking their children about their willingness to participate in the study. Children whose parents provided informed consent took part in the study. The researchers explained the study methods verbally to the children and parents and demonstrated the tests that would be performed on the children; the teachers and parents observed each child's reaction to determine if the child consented or not before the test.

In the massage group, the participants were paid US $7 for each TTM session. In the control group, each volunteer participated in the evaluation 4 times and was paid US $7 each time. The decision was made that after data collection was finished, if good results were obtained in the parental TTM group, the control group would also be given training in TTM. Each teacher

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volunteer who participated in the 3 stages of assessment received US $30 for each stage.

Intervention

Children assigned to the TTM group received sixteen 40-to-50-minute parent-delivered TTM sessions over an 8-week period (2 sessions per week) in the health room of the school after school had finished. Gifts and rewards were given to parents and children to increase intervention adherence rates. The control group maintained a normal daily routine when in school.

TTM Training

The parents of autistic children who were enrolled in the study took part in 3 TTM training sessions. Each 3-hour session was hosted by experts at the health room of Hainan Special Education School. Parents of participants in the intervention group were trained in TTM by an experienced traditional Thai masseur with a massage qualification until they became able to perform the experimental intervention. Thereafter, the massage trainer monitored the parents to ensure that they continued to perform TTM properly at each session.

TTM Procedure

The TTM method involves pressure massage and muscle stretching. Pressure massage involves massaging with the thumbs and pressing with the palms until slight muscle resistance is felt. The children may feel slight muscle tightness, but the massage should not be painful. The masseur will maintain pressure for 5 to 10 seconds and then release it to allow energy or blood to flow freely around the massage area; this is repeated 2 to 3 times for each body part. Muscle stretching includes the masseur observing the children and asking them whether they feel that the stretch is too deep; if the stretch is acceptable, they hold the appropriate position for 15 to 30 seconds [63]. The 9 steps of TTM are based on standard practice. However, they have been modified for this patient population: gentle touch is used to facilitate relaxation and promote social communication, motor control, and a sense of confidence in and love for the children. Starting from the head and continuing to the limbs easily promotes relaxation. Stretching at the end of the session is one of the principles of TTM.

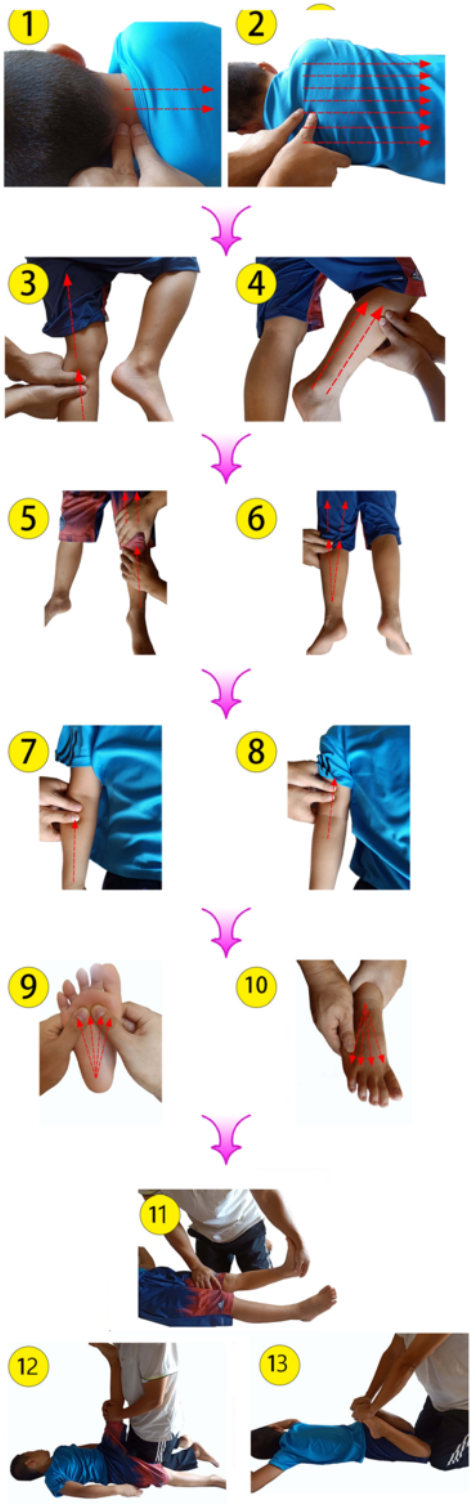
In the starting position, the children lie on their side with the upper leg bent at the knee forming a 90° angle with a pillow placed under the head and a straight lower leg. The parent performing the massage kneels or sits behind the child. Massage strategies for distinct massage types should be performed as described in Table 1 and Figure 2.

Table 1. Traditional Thai massage procedures for children with autism and the order in which they are performed.

Target area	Description of procedure
1. Neck (lateral position)	Massage is started in the neck region and extends along the back muscles toward the lumbar area. Massage is performed along the side of the neck toward the shoulders.
2. Back and waist	The paravertebral muscles, which are close to the thoracolumbar spine, are massaged toward the waist level. There are 3 lines of massage. One is started on the upper back near the spinous processes of T1 to L5 on each side of the back. The second line is about 1 cm along the side of the first one. The third line is about 1 cm along the side of the second one. A pressing massage style should be applied on the 3 lines, which should be initiated in the thoracolumbar region and continue toward the top of the sacrum.
3. Inner thigh (straightened legs)	Thumb pressure should be applied to the medial side of a straightened leg from the Achilles tendon toward the groin (along the line in panel 3 of Figure 1). This type of massage should be performed along 2 massage lines. The first massage line extends along the medial side of the leg, and the second massage line extends along the backside of the leg.
4. Outer leg massage (on the bent leg side):	Both hands are placed on the lower leg of the child. The lateral part of the lower leg should be pushed down using the thumb. This massage style should be applied from the area above the lateral malleolus and continued to the side of the knee joint. The top of both knees are pressed toward the middle of the hip. Outer leg massage should be performed along the 2 massage lines. The first line extends along the front of the leg, and the second line is positioned slightly behind the first line.
Repeat on opposite side	The child lies on the other side and procedures 1 to 4 are repeated.
5. Leg (supine position)	Massage is performed in front of the ankle to near the groin.
6. Leg massage (prone position)	Massage is initiated behind the heel around the Achilles tendon and continues toward the gluteal and hamstring muscles.
7. Arm	With the child in a prone position, thumb pressure is applied along the back of the lower and upper arm toward the shoulder. The procedure is then repeated on the other arm. In the supine position, push massage is applied upward from the center of the forearm and along the center of the arm toward the axilla.
8. Foot (supine position)	A foot massage is performed by applying pressure from the heel to all 5 toes. Then, the tip of each toe should be pulled gently.
9. Muscle stretch (the appropriate position is held for 15 to 30 seconds)	With the child in a supine position, the heel is stretched and the child's foot is lifted until tension is felt. In the prone position, the child's knees are flexed as much as possible by applying gentle pressure to the soles of the feet.

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Figure 2. Traditional Thai massage procedure: (1) neck massage, (2) back and waist massage, (3) inner thigh massage, (4) outer leg massage, (5) leg massage in the supine position, (6) leg massage in the prone position, (7, 8) arm massage, (9, 10) foot massage, and (11-13) muscle stretching. The procedure is performed in the numbered order.



Fidelity

The fidelity measurement represents the number of times parents use massage with their children, incorporating any adjustments to the massage technique made by the expert. More than 90% attendance is expected, and the expert will correct improper technique in real time.

Primary Outcome Measurement: ATEC

The ATEC questionnaire was developed by Dr Bernard Rimland and Dr Stephen M Edelson at the Autism Research Institute in the United States in the mid-1990s to help researchers and parents evaluate the effectiveness of various treatments for autistic children and adults [64]. It is not used to diagnose autism. It comprises 4 subscales: speech, language, and

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communication; sociability; sensory and cognitive awareness; and health and physical behavior. The maximum score is 179, with higher scores indicating autism of increased severity. The sensitivity and specificity of the Chinese version of the ATEC total scale and its subscales have been determined to range from 0.922 to 0.987 and 0.803 to 0.887, respectively; the scale has also been determined to have high reliability [65].

Secondary Outcome Assessments

Gait

Gait was measured using a wearable BTS G-Walk device (BTS Bioengineering Company). Experimental gait data were collected at a frequency of 100 Hz and transmitted to a computer via a Bluetooth connection. All gait parameter measurements have been determined to have high test-retest and intertrial reliability (intraclass correlation coefficient: 0.728-0.969 and 0.84-0.99, respectively) [66,67]. Wireless internet was required for the gait tests, which were carried out on a flat surface that measured at least 10 × 10 m. Prior to performing the test, the height of the participant was entered, and an adjustable elastic band was placed around the participant's waist. When taking the test, participants stood in place for a few seconds. After confirming that the sensor was connected to the computer via Bluetooth and the connection was stable, each child volunteer followed a marked 7-m path back and forth while walking normally. Teachers or parents were allowed to provide verbal cues but not physical assistance.

HRV Measurement

UBiomacpa (version 1; Biosense Creative) was used to detect the activity of the autonomic nervous system. The HRV test was carried out in an independent, quiet room at an ambient temperature of 26 °C. Before starting the test, the tester ensured that the equipment was properly connected. After receiving TTM, the autistic children were placed in a sitting position with a pulse sensor attached to their left index finger, and they underwent an HRV test for 2 minutes that was administered by a physiotherapist. When the test was complete, the device automatically generated a data report via a connected computer.

PSI-4-SF Assessment

The PSI-4-SF consists of 36 items in the following 3 dimensions: parent distress, parent-child dysfunction interaction, and difficult child [68]. The Chinese version of the PSI-4-SF has an internal consistency and reliability that ranges between 0.92 and 0.95 for each subscale. For the whole scale, the value is 0.97, indicating that this scale has good consistency and stability [69].

Data Collection, Management, and Analysis

IBM SPSS (version 25; IBM Corp) will be used for data analysis. Missing outcome data will not be imputed in the analysis, but the multiple imputation method will be used to explore the potential impact of missing data on outcomes. Demographic data will be expressed as means with standard deviation and percentages. $P<.05$ will be considered statistically significant. Holm correction of P values will be applied for multiple comparisons to compare the immediate effects of TTM for autistic children and effects in the short and long term. The primary outcome is the ATEC score, which will use generalized estimating equations. Time will be the covariate and the model will include group, time, and the group × time interaction. A 2-tailed paired t test or Wilcoxon signed-rank test will be used to test ATEC score, HRV, and gait parameters, as well as PSI-4-SF score changes within each group after testing for normal distribution. The relationship between physiological effects and ATEC results will be evaluated using a correlation test. A coefficient value <0.4 indicates a low degree of correlation, a value between 0.4 and 0.7 indicates a medium degree of correlation, and a value >0.7 indicates a high degree of correlation between variables.

Two trained assessors will be responsible for data collection, electronic double entry of the data, and management of the database. A team from the Key Laboratory of Data Science and Smart Education at Hainan Normal University, which is independent of the study team, will be responsible for data monitoring.

Harms

No adverse events from TTM interventions have been reported in previous studies. Furthermore, in both intervention and control groups, data collection did not cause physical harm to the children and did not create psychological, social, or financial risks. If there is a risk of affecting the body (ie, pain or injury) or mind (ie, dissatisfaction, discomfort, hate, or boredom) of any participant, we decided to temporarily suspend or stop that individual's participation and data gathering. Moreover, if any severe adverse events, such as death or other medical occurrences resulting in hospitalization, were to occur during the massage intervention sessions, the researcher planned to terminate the intervention and immediately report the event to the nearest local hospital in China. The researchers will report whether any such adverse events occurred to the ethics committee as required and describe them in the final paper.

Confidentiality

The research group will keep the data confidential, and the research group will use passwords to record and access data. In this study, only the research group will have access to the data, and the research group will not state the names of the participants under any circumstances if the study results are published in a journal. The participants' personal information will be stored in a specific file with a preset code.

Ancillary and Posttrial Care

Participants could contact the researchers during the trial or 1 month after participation ended. Plans were made for participants with serious adverse events to receive a timely and appropriate response.

Patient and Public Involvement

The patients and public will not be involved in the design, conduct, reporting, or dissemination of this research.

Results

We finished all data collection on June 20, 2022. Data analysis will be started, and we expect results to be published in 2023.

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The normal distribution of the data will be determined before descriptive statistics for all variables are calculated. The participants' demographic information will be reported as descriptive data. The primary outcomes will be expressed as continuous variables, and generalized estimating equations will be used to evaluate the effect of TTM on the children (via the ATEC score) at 3 time points: immediate, short term, and long term. Changes in physiological parameters (ie, HRV and gait parameters) after the intervention will be analyzed. Further, the relationship between ATEC score and physiological parameters will be identified with a correlation analysis. Finally, changes in parental stress throughout the intervention period will be investigated with the PSI-4-SF.

Discussion

This study aims to assess the effects of parent-delivered TTM in children with autism by evaluating changes in symptoms and physiological parameters (ie, gait and HRV). In practice, massage has previously been used to treat autism. However, this treatment has not been included in evidence-based practice for autism due to the lack of long-term, extensive scientific research to supports its use. At present, studies of interventions have mainly focused on qigong massage and tui na massage. Furthermore, we found that outcome measures in most prior studies were based on questionnaires and scales evaluated before and after the intervention, and that there was a lack of studies that explored the mechanisms that underlie core symptom improvement. Presumably, massage adjusts the body and mind via sensory processes [70,71] and neural and hormonal regulation (eg, changing oxytocin levels).

In comparison with prior work, this will be the first RCT to explore parental TTM in terms of its physiological and psychological effects on children with autism. We will use objective indices to investigate possible mechanisms underlying the observed effects. Our study may highlight the value of complementary and alternative therapies for adjunctive treatment of autism to enhance family-based interventions. Both parents and blinded teachers will be evaluated for effects that might cause bias. Finally, the variability of massage manipulation by parents was minimized by expert training, examinations, and supervision.

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Data Availability

Data sharing is not applicable to this study as no new data were generated or analyzed. The data sets generated or analyzed after the experiments will be made available from the corresponding author on reasonable request.

Authors' Contributions

HR and WE contributed to conceptualization. HR, WE, and CA contributed to design and methodology. HR contributed to investigation. HR and HW contributed to writing the original draft and revision.

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT guidelines.
[DOCX File , 31 KB - resprot_v12i1e41839_app1.docx]

Multimedia Appendix 2
Parents' consent form.
[PDF File (Adobe PDF File), 174 KB - resprot_v12i1e41839_app2.pdf]

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Abbreviations

ANS: autonomic nervous system
ASD: autism spectrum disorder
ATEC: Autism Treatment Evaluation Checklist
HRV: heart rate variability
PSI-4-SF: Parenting Stress Index, Fourth Edition–Short Form
RCT: randomized controlled trial
TTM: traditional Thai massage

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Protocol

Nitric Oxide on Extracorporeal Membrane Oxygenation in Neonates and Children (NECTAR Trial): Protocol for a Randomized Controlled Trial

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Abstract

Background: Extracorporeal membrane oxygenation (ECMO) provides support for the pulmonary or cardiovascular function of children in whom the predicted mortality risk remains very high. The inevitable host inflammatory response and activation of the coagulation cascade due to the extracorporeal circuit contribute to additional morbidity and mortality in these patients. Mixing nitric oxide (NO) into the sweep gas of ECMO circuits may reduce the inflammatory and coagulation cascade activation during ECMO support.

Objective: The purpose of this study is to test the feasibility and safety of mixing NO into the sweep gas of ECMO systems and assess its effect on inflammation and coagulation system activation through a pilot randomized controlled trial.

Methods: The Nitric Oxide on Extracorporeal Membrane Oxygenation in Neonates and Children (NECTAR) trial is an open-label, parallel-group, pilot randomized controlled trial to be conducted at a single center. Fifty patients who require ECMO support will be randomly assigned to receive either NO mixed into the sweep gas of the ECMO system at 20 ppm for the duration of ECMO or standard care (no NO) in a 1:1 ratio, with stratification by support type (veno-venous vs veno-arterial ECMO).

Results: Outcome measures will focus on feasibility (recruitment rate and consent rate, and successful inflammatory marker measurements), the safety of the intervention (oxygenation and carbon dioxide control within defined parameters and methemoglobin levels), and proxy markers of efficacy (assessment of cytokines, chemokines, and coagulation factors to assess the impact of NO on host inflammation and coagulation cascade activation, clotting of ECMO components, including computer tomography scanning of oxygenators for clot assessments), bleeding complications, as well as total blood product use. Survival without ECMO and the length of stay in the pediatric intensive care unit (PICU) are clinically relevant efficacy outcomes. Long-term outcomes include neurodevelopmental assessments (Ages and Stages Questionnaire, Strength and Difficulties Questionnaire, and others) and quality of life (Pediatric Quality of Life Inventory and others) measured at 6 and 12 months post ECMO cannulation. Analyses will be conducted on an intention-to-treat basis.

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Conclusions: The NECTAR study investigates the safety and feasibility of NO as a drug intervention during extracorporeal life support and explores its efficacy. The study will investigate whether morbidity and mortality in patients treated with ECMO can be improved with NO. The intervention targets adverse outcomes in patients who are supported by ECMO and who have high expected mortality and morbidity. The study will be one of the largest randomized controlled trials performed among pediatric patients supported by ECMO.

Trial Registration: Australian New Zealand Clinical Trials Registry ACTRN12619001518156; https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=376869

International Registered Report Identifier (IRRID): DERR1-10.2196/43760

(JMIR Res Protoc 2023;12:e43760) doi:10.2196/43760

KEYWORDS

extracorporeal membrane oxygenation; randomized controlled trial; children; nitric oxide; child; RCT; ECMO; neonate; neonatal; infant; baby; babies; life support; mortality; pulmonary; cardiovascular; heart; lung

Introduction

Extracorporeal membrane oxygenation (ECMO) has gained widespread acceptance as a rescue treatment for refractory cardiovascular and respiratory failure among neonates, children, and adults [1-3]. While morbidity and mortality in ECMO are predominantly affected by the severity of preexisting disease, the contribution of iatrogenic factors to patient-centered outcomes is becoming increasingly recognized [4]. Despite major improvements in ECMO devices, the exposure of host blood to large artificial organ surfaces, mechanical cell stress, and reperfusion injury result in the activation of the coagulation system and generate a severe inflammatory response [5]. Studies on extracorporeal circuits (including bypass circuits) have shown that hypoxic-ischemic injury and the release of damage-associated molecular patterns trigger an inflammatory cascade closely related to sepsis-induced systemic inflammatory response syndrome. It is characterized by endotoxin release, leukocyte and complement activation, and widespread activation of inflammatory mediators, resulting in endothelial leak, increased oxygen consumption, and organ dysfunction [6]. Both intrinsic factors and extrinsic factors, such as exposure to injured tissue, contribute to excessive inflammation and coagulation system activation and may be further aggravated by cross talk across the complement and coagulation systems [7]. Therefore, it is not surprising that thrombosis and hemorrhage remain among the most common complications seen with ECMO [8].

These ECMO-related side effects expose patients to substantial morbidity and can lead to death or devastating long-term outcomes, even if the primary reason for requiring ECMO has been resolved. Importantly, some pediatric data show that more than 85% of patients who die during or after their ECMO run have developed either bleeding or clotting complications [9].

Nitric oxide (NO) mediates anti-inflammatory host responses and regulates both endothelial functions as well as microvascular inflammation. The mixing of NO into the sweep gas that runs into the oxygenator in neonates and children undergoing cardiopulmonary bypass has been investigated in several pilot studies with promising results, and a large randomized controlled trial (RCT) has recently been published [10-13]. In this trial, the effects of NO used in a bypass circuit for pediatric cardiac surgery were tested [13]. No effect on mortality or on the duration of ventilation was observed, though the safety of NO was high. The treatment duration on cardiopulmonary bypass is a few hours, whereas ECMO support lasts days to weeks, making the 2 clinical scenarios not directly comparable. In addition, mixing NO into the sweep gas (at 30, 50, and 80 ppm) in an animal model of ECMO significantly reduced the host response, with suppression of tumor necrosis factor α (TNF-α) and interleukin (IL)-6 expression (Fraser J, unpublished data, April 2023). A single-center observational study using historical controls reported the safety and outcomes of NO at 20 ppm mixed into the sweep gas of the ECMO oxygenator. The authors observed a lower blood product administration and a marginal improvement in the survival of patients on NO compared to the historical controls without any NO. There are no randomized studies on the effect of NO mixed into the oxygenator on patients treated with ECMO.

The Nitric Oxide on Extracorporeal Membrane Oxygenation in Neonates and Children (NECTAR) study was designed to investigate in a randomized clinical trial whether mixing NO into the sweep gas in neonates and children treated with ECMO is feasible (recruitment, randomization, and protocol compliance) and safe (accurate NO delivery and methemoglobin levels). Efficacy will be tested by measuring ECMO-free days (the number of days that patients spend alive and free from ECMO is censored at 30 and 90 days) and by assessing the inflammatory host response and coagulation activation. We hereby describe the NECTAR trial protocol.

Methods

The NECTAR trial is an investigator-initiated, 50-patient, open-label, single-center, pilot RCT with neonates and children who require ECMO support.

Study Setting

A tertiary pediatric intensive care unit (PICU) in Australia with approximately 30 ECMO runs annually.

Participants

Eligible children will be identified during the clinical deterioration typically seen prior to ECMO support commencement, such as progressive respiratory, cardiovascular, and cardiorespiratory failure, including cardiopulmonary arrest. If the situation permits, prospective consent will be sought;

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otherwise, delayed consent or consent to continue the approach will be applied.

Inclusion Criteria

All infants and children (birth to ≤16 years) that are commenced on ECMO will be eligible for inclusion in the study if there is the ability to obtain prospective consent or consent to continue from parents or guardians. In addition, infants or children that are commenced on ECMO at the colocated Neonatal Intensive Care Unit will be eligible for inclusion in the study. Patients who are commenced on ECMO outside of these units will not be eligible for the study.

Exclusion Criteria

Neonates and children treated with ECMO who were retrieved to the PICU on ECMO, those with preexisting methemoglobinemia (methemoglobin [MetHb]>3%), and patients managed on a ventricular assist device only without an oxygenator were present in the ECMO circuit.

Randomization and Blinding

Treatment group allocation will be performed using a web-based REDCap electronic data capture tool hosted by The University of Queensland [14,15]. A randomization sequence using variable block randomization with a 1:1 ratio was uploaded into REDCap prior to the screening of the first patient. Randomization is stratified by veno-arterial (VA) versus veno-venous (VV) support. Where conversion of VV to VA or VA to VV occurs, patients will remain in the initial randomization allocation and strata. When a second ECMO run is commenced, the patient will be randomized again.

Consent

Prospective consent will be sought from the parents or guardians of any child for whom a decision to be commenced on ECMO has been made. Where possible, this consent will be obtained before the commencement of ECMO. However, due to parental stress and cognitive overload at the time of cannulation, consent can also be obtained following randomization under the consent to continue model (termed “delayed consent” previously) [16]. Prior to or after ECMO commencement, parents will be provided with study information, including printed study flyers and links to web-based study documentation.

Blinding of the Intervention

Blinding is not possible, as the NO delivery device makes a distinctive noise during standard operation. Further, the NO levels need to be adjusted depending on sweep flow, which requires nurses by the side to identify whether NO is being delivered or not.

Interventions

Infants and children will be randomly assigned to receive either NO or standard care. Those allocated to the intervention (NO) will receive 20 ppm of NO mixed into the sweep gas running into the oxygenator during their ECMO run. The NO concentration will be maintained at 20 ppm using a NO delivery system (Sokinox, Maquet), or a similar device. Continuous sampling of NO and NO_2 concentrations is performed by the Sokinox machine by gas aspiration after the NO injection site. Patients allocated to the standard study arm will receive the standard oxygen-air mix in the ECMO oxygenator as per institutional practice and protocol.

Relevant Concomitant Coagulation Management and Intensive Care Treatment

Apart from mixing NO into the sweep gas flow of the ECMO system, no other patient management parameters will be changed, and institutional practices and protocols will be followed. Methods and goals of anticoagulation will remain unchanged for any other ECMO management and treatments, such as decisions to decannulate, ventilation support, inotrope management, fluid intake, fluid removal practices, or antimicrobial or immunological treatments.

Safety Data Monitoring

A data and safety monitoring board (DSMB) will monitor the conduct of the study and the accrual of data. The DSMB will consist of a chairperson (experienced in clinical trials), a pediatric intensivist, a cardiac surgeon, and a statistician. The DSMB will be independent of the study investigators and will monitor adverse events in the study as well as ensure the validity and timeliness of the data collection. The DSMB may advise the Chief Investigator to terminate the trial, which would necessitate safety concerns in this step. The DSMB is expected to meet at least 4 times during the study period.

Monitoring

The study team will be responsible for all documentation of the study nurse’s and the investigator’s training records and credentials. All consent forms will be reviewed by the study team. The perfusion data collection forms will be compared to the source documentation to ensure both the completeness and accuracy of the data. All severe adverse events will be recorded and reported to the local Human Research and Ethics Committee (HREC) as per the institutional guidelines.

Ethics Approval

This protocol and the informed consent document, and any subsequent modifications, have been reviewed and approved by the human research ethics committee (reference number HREC/18/QCHQ/49018). This study will be conducted in compliance with this version of the protocol. Any change to the protocol document or informed consent document that affects the scientific intent, study design, patient safety, or anything that may affect a participant’s willingness to continue in the study is considered an amendment, and therefore will be written and filed as an amendment to this protocol or the informed consent document. All protocol deviations will be reported to the principal investigator, recorded in REDCap, and reported to HREC. Protocol deviations and violations will be assessed for clarification by the principal investigator. The study was approved by the local HREC (HREC/18/QCHQ/49018) and has been registered with the Australian New Zealand Clinical Trials Registry (ACTRN12619001518156). The NECTAR trial commenced recruitment in August 2020

Sample Size

The NECTAR trial is a pilot RCT with the main focus on feasibility, safety, and exploration of efficacy. A sample size

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of 50 patients has been chosen in line with the recommendations for pilot studies that anticipate a medium effect size for a continuous primary outcome for the main trial [17].

Data Collection, Management, and Analysis

Data Collection

Baseline variables (demographics, primary diagnosis, comorbidities including syndromes), precannulation disease severity, precannulation surgery (such as cardiac surgery), cannulation technique, primary and secondary end points, as well as predetermined physiological variables of interest, will be recorded and entered prospectively into a purpose-built REDCap database [14,15]. Treatment that is administered continuously (such as heparin or inotropes) will be recorded as maximal values that were maintained for at least 4 hours. Physiological and blood parameters will be recorded precannulation, at 1, 12, and 24 hours post cannulation, and daily thereafter. The duration of circulatory, renal, and ventilatory support on and off ECMO will be recorded. Gross functional performance assessment will be recorded upon admission to the PICU and upon discharge from the hospital [18].

Participant data confidentiality will be ensured by the study coordinator, the research staff, and the institution sponsoring the trial. All data, as well as the study protocol and any other information that this trial may generate, will be held in strict confidence.

Biobanking

Blood samples for inflammatory and coagulation pathway activation will be collected prior to cannulation, as well as at 1, 12, and 24 hours post commencement of ECMO. These samples will be frozen using standard operating procedures and batch tested.

Results

Study Outcomes

The NECTAR trial is a pilot RCT; hence, it will focus on safety and feasibility outcomes in addition to exploring efficacy outcomes as described in Textbox 1. This work was supported by grants from the Children's Hospital Foundation, Brisbane, Australia, and by a grant from the Thrombosis and Hemostasis Society of Australia. The results are expected to be published at the end of 2023 or early 2024.

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Textbox 1. Main study outcomes and secondary analyses for the Nitric Oxide on Extracorporeal Membrane Oxygenation in Neonates and Children (NECTAR) trial.

Main study outcomes

- Feasibility outcomes
  - Monthly recruitment rate
  - Randomized to screened patient ratio
  - Compliance with the study protocol (with particular focus on the timing of the initiation of nitric oxide (NO) and the maintenance of NO for the duration of the study)
- Safety outcomes
  - Failure rate of gas delivery
  - Carbon dioxide control of patients
  - Methemoglobin levels
- Efficacy outcomes
  - Host systemic inflammation levels at 1, 12, and 24 hours
  - Coagulation system activation and consumption
  - Clotting and bleeding complications
  - Rate of clotting and bleeding events

Secondary outcomes

- Survival without extracorporeal membrane oxygenation (ECMO), censored at 30 and 90 days post randomization. Patients dying within 30 and 90 days of presentation will be considered as 0 days, to account for the competing effect of mortality on ECMO-free survival.
- Survival free of pediatric intensive care unit (PICU; censored at 30 and 90 days)
- Hospital length of stay post randomization
- Median daily blood product usage
- Complement system activation
- Child neurodevelopment, function, and quality of life at 6 and 12 months, as measured by:
  - Ages and Stages Questionnaire (<5 years of age) OR Strength and Difficulties Questionnaire (>5 years of age)
  - Pediatric Quality of Life Inventory
  - Pediatric Emotional Distress Scale (2-5 years) OR Children's Revised Impact of Events Scale (>5 years)
  - Behavior Rating Index of Executive Functioning – Preschool (2-5 years) OR Behavior Rating Index of Executive Functioning – 2 (>5 years)
  - Vineland Adaptive Behavior Scale
- Parent functioning at 6 and 12 months, as measured by:
  - Parenting Stress Index – Short Form
  - Kessler-6
  - Primary Caregiver – Post Traumatic Stress Disorder Scale

Feasibility Outcomes

The focus will be on the monthly recruitment rate, the randomized to screened patient ratio, and protocol adherence, that is, how many blood collection points, computer tomography scans of oxygenators, and daily indirect oxygenator clot measurements (by extracorporeal life support assessment monitor) were completed.

Safety Outcomes

There will be a focus on sweep gas delivery failure related to NO administration. Specifically, an arterial oxygen saturation of less than 80 due to a sweep gas interruption related to NO administration or carbon dioxide control outside of 30 to 50 mm Hg due to NO administration will be recorded as a safety event. The methemoglobin (MetHb) levels during the time of ECMO will be measured, and events above 3% related to NO administration will be noted.

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Efficacy Outcomes

Host inflammation and complement components will be assessed before cannulation and at 1, 12, and 24 hours post cannulation by determining serum concentrations of C-reactive protein, procalcitonin, IL-1b, IL-6, IL-8, IL-10, and TNF-α. At the same time points, coagulation system activation will be assessed by measuring the international normalized ratio (INR), prothrombin time (PT), activated partial thromboplastin time (APTT), thromboelastography (TEG), antithrombin, soluble CD40L, P-selectin, platelet factor 4 levels, and ADAMTS13 release (see Textbox 2). A single measurement of Von Willebrand factor at initiation followed by daily measurements will be performed. After the initial 24 hours, further daily laboratory testing will include D-Dimers, TEG, INR, PT, APTT, anti Xa and activated clotting time (by TEG), and plasma-free hemoglobin. Clotting and bleeding complications and the rate of clotting and bleeding events will be measured. Clotting events are defined as the need to change ECMO circuit componentry due to high transmembrane pressures, high D-Dimers, or high free plasma hemoglobin. Bleeding rates will be measured by both the amount of bleeding per day as well as the daily requirement for blood product administration.

Textbox 2. Coagulation, inflammation, and complement system measurements.

Coagulation system measurements

- Change in granule (soluble CD40 ligand and P-selectin) and chemokine (platelet factor 4) levels released by activated platelets
- ADAMTS13 release
- Change in van Willebrand factor concentrations during and after the extracorporeal membrane oxygenation (ECMO) run

Changes in inflammatory and complement system activation

- Change in C-reactive protein, procalcitonin, interleukin (IL)-1b, IL-6, IL-8, IL-10, and tumor necrosis factor α (inflammatory mediators) levels; Complement (C)1q, Complement Factor B, Complement Factor H, C5a, C9, and Mannose-Binding Lectin (classic and alternate complement pathways); and C3, C3 and CH50.

Secondary Clinical Outcomes

The secondary clinical outcomes include mortality at 30 and 90 days. ECMO-free and PICU-free survival censored at 30 and 90 days post randomization, length of stay at the hospital post randomization, average daily blood product usage, complement system activation with measurements of complement (C)1q, C5a, C9, C3, C4, complement factor B, complement factor H, and Mannose-binding Lectin, as well as neurodevelopmental function and quality of life at 6 and 12 months, will be considered (Textbox 3).

Textbox 3. Subanalyses for the Nitric Oxide on Extracorporeal Membrane Oxygenation in Neonates and Children (NECTAR) trial.

- Cardiac, respiratory, and extracorporeal membrane oxygenation–assisted cardiopulmonary resuscitation outcomes (proportions alive at 30 and 90 days for each group)
- Circuit duration (time to decannulation or time to circuit change) per treatment group
- Renal function measured as creatinine and urine output changes during extracorporeal membrane oxygenation (ECMO) per treatment group
- Renal replacement treatment on ECMO (type of renal replacement therapy, duration of slow continuous ultrafiltration, type of filter, and duration of filter viability)
- Incidence of seizures diagnosed during ECMO or up to 48 hours after decannulation
- Transmembrane oxygenator pressure assessment every 24 hours
- Oxygenator clot volume as assessed by the extracorporeal life support assessment monitor
- Oxygenator clot volume (by computer tomography imaging)
- Hemolysis (plasma-free hemoglobin) per treatment group
- Mean daily heparin dose per kg required to meet target anticoagulation per treatment group

Subanalyses

We will further investigate the oxygenator's function and structure. The former will be done by postoxygenator blood gas sampling, and the latter by oxygenator clot volume assessment by computer tomography scanning. Outcomes by age group (<28 days, 28 to 365 days, and greater than 365 days) will be analyzed.

Statistical Analysis Plan

Analysis Plan

Descriptive statistics will be used to report the baseline characteristics of the total study cohort and each subgroup. The primary efficacy outcome measure investigating days free of ECMO will be analyzed using quantile regression incorporating treatment group and VA or VV support (stratification variable) as fixed effects, with the treatment group effect estimate and 95% CI reported (assuming the data is abnormally distributed).

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Exploratory subgroup analysis by cardiac, respiratory, and ECMO-assisted cardiopulmonary resuscitation support will be performed. Analysis of secondary outcomes includes comparisons of measurements and proportions, with confidence intervals of differences as the major method of presentation. The primary analysis will be by intention-to-treat. If appropriate, per-protocol analyses will be performed as well and compared to the intention-to-treat. Statistical significance will be set at the .05 level and no adjustment for multiple comparisons will be made, noting the exploratory nature of the analysis. CIs will be generated using quantile regression for abnormally distributed continuous data, a 2-sided *t* test for normally distributed data, and a test of 2 proportions for binary data.

Long-term Outcomes

Neurodevelopmental and functional outcomes (using phone interviews and web-based questionnaires) will be documented at baseline (assessment of premorbid function during PICU admission) using the test battery described in Table 1. Assessments will focus on neurodevelopment, quality of life, executive functioning, adaptive behaviors, functioning, and parental outcomes. Assessments will occur at 6 and 12 months post cannulation. The following will be used for children younger than 5 years (for respective neurodevelopmental assessment areas): (1) ages and stages questionnaire, (2) pediatric emotional distress scale, and (3) behavior rating index of executive functioning for preschoolers. For all other children (and other neurodevelopmental function assessments), the following will be used: (1) strengths and difficulties questionnaire, (2) children's revised impact of events scale, (3) vineland adaptive behavior scale, (4) pediatric cerebral performance category, (5) pediatric outcome performance category, and (6) pediatric quality of life inventory. For parental outcomes, the Kessler scale, as well as the Primary Carer – Post Traumatic Stress Disorder and Parenting Stress Index – Short Form will be used.

The neurodevelopmental outcomes will be reported separately from the main study.

Table 1. Long-term outcome measures at 6 and 12 months after pediatric intensive care unit discharge.

Measure	<5 years of age	≥5 years of age
Neurodevelopment	Ages and Stages Questionnaire (ASQ)	Strengths and Difficulties Questionnaire (SDQ)
Quality of life	Pediatric Quality of Life Inventory	Pediatric Quality of Life Inventory
Distress	Pediatric Emotional Distress Scale (2-4 years) (PEDS)	Children's Revised Impact of Events Scale (≥5 years) (CRIES)
Executive functioning	Behavior Rating Index of Executive Functioning for Preschoolers (2-4 years) (BRIEF-P)	Behavior Rating Index of Executive Functioning (≥5 years) (BRIEF)
Adaptive behavior	Vineland Adaptive Behavior Scale (VABS)	VABS
Functioning	Functional Status Score (FSS), Pediatric Cerebral Performance Category (PCPC), and Pediatric Outcome Performance Category (POPC)	FSS, PCPC, and POPC
Parent outcomes	Kessler (K6), Primary Carer – Post Traumatic Stress Disorder (PC-PTSD), and Parenting Stress Index – Short Form (PSI-4-SF)	K6, PC-PTSD, and PSI-4-SF

Adverse Events

Given the severity of the underlying disease leading to the requirement for ECMO, patients are expected to have a high rate of adverse events unrelated to the study intervention. Events that are in the expected range of adverse events during standard treatment will therefore not be reported as related to the study intervention, as previously described [19]. Adverse events that are likely related to the study intervention will be reported. Adverse events likely related to NO delivery during ECMO support, such as failure to deliver sweep gas to the oxygenator, poor patient carbon dioxide control due to sweep gas failure, and increased MetHb (MetHb >3%) at any of the blood gas sampling points, will be reported [11,12]. Death will be reported as an adverse event and will be assessed as to whether it may be related to the study intervention. The study team, together with the treating physician, will assess each patient's case and make an initial assessment of whether death occurred due to the intervention. The final assessment is to be confirmed with the DSMB.

Discussion

Principal Findings

The NECTAR trial will be the first RCT to assess the effect of NO on bleeding, clotting, and inflammatory complications in neonates and children supported on ECMO. It will establish the feasibility and safety of the procedure to allow the design of a trial powered for patient-centered outcomes.

Children requiring ECMO support continue to have a very high mortality risk. Both bleeding and clotting events are significantly associated with mortality and morbidity in this group of patients, and—in combination with inflammatory activation—they continue to pose a challenge to which no therapeutic answer has been found to date. The addition of NO to the sweep gas to reduce bleeding, clotting, and inflammatory complications is a promising therapeutic approach that has so far only been tested in vitro, in historical comparisons, or in RCTs on cardiopulmonary bypass settings rather than ECMO. Given the anticipated high safety of the intervention, the approach has the potential to improve patient-centered short- and long-term outcomes.

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Limitations

The patient group requiring ECMO is very heterogeneous, and due to the pilot study size, achieving a normal distribution of risk factors in the 2 study groups may be unlikely. In addition, this pilot trial is not powered to assess associations between the intervention and clinical outcomes such as ECMO-free survival. It is designed to test the feasibility, safety, and efficacy of such an intervention and the conduct of such a study while exploring clinical and laboratory data in relation to the study groups.

Conclusions

Inflammatory and coagulation system activation of patients during ECMO support remains a major contributor to ECMO-related morbidity and mortality. NO may be an effective treatment for children supported on ECMO to mitigate inflammation and coagulation system activation. Data from the NECTAR pilot study will inform the design of a larger, definitive trial.

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Data Availability

Deidentified participant data will be shared upon reasonable request after the publication of the original paper. Data will be available for use if the request is approved by the appropriate institutional review board and the Trial Steering Committee and a signed data access agreement is in place.

Authors' Contributions

The first draft of the protocol was written by ACM and LS. KG wrote the section on statistical analyses. The final study protocol was established with input from LS, ACM, KJ, KG, JR, AB, PSV, DL, and AS. ACM prepared the final protocol manuscript, which was reviewed and approved by all authors.

Conflicts of Interest

ACM, LS, DL, KJ, KG, JR, and AB have no conflicts of interest to declare. AS has received grants from Fisher and Paykel.

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Abbreviations

APTT: activated partial thromboplastin time
DSMB: data and safety monitoring board
ECMO: extracorporeal membrane oxygenation
HREC: Human Research and Ethics Committee
IL: interleukin
INR: international normalized ratio
MetHb: methemoglobin
NECTAR: Nitric Oxide on Extracorporeal Membrane Oxygenation in Neonates and Children
NO: nitric oxide
PICU: pediatric intensive care unit
PT: prothrombin time
RCT: randomized controlled trial
TEG: thromboelastography
TNF-α: tumor necrosis factor α
VA: veno-arterial
VV: veno-venous

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Protocol

Repeat Ivermectin Mass Drug Administrations for Malaria Control II: Protocol for a Double-blind, Cluster-Randomized, Placebo-Controlled Trial for the Integrated Control of Malaria

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Abstract

Background: The gains made against malaria have stagnated since 2015, threatened further by increasing resistance to insecticides and antimalarials. Improvement in malaria control necessitates a multipronged strategy, which includes the development of novel tools. One such tool is mass drug administration (MDA) with endectocides, primarily ivermectin, which has shown promise in reducing malaria transmission through lethal and sublethal impacts on the mosquito vector.

Objective: The primary objective of the study is to assess the impact of repeated ivermectin MDA on malaria incidence in children aged ≤10 years.

Methods: Repeat Ivermectin MDA for Malaria Control II is a double-blind, placebo-controlled, cluster-randomized, and parallel-group trial conducted in a setting with intense seasonal malaria transmission in Southwest Burkina Faso. The study included 14 discrete villages: 7 (50%) randomized to receive standard measures (seasonal malaria chemoprevention [SMC] and bed net use for children aged 3 to 59 months) and placebo, and 7 (50%) randomized to receive standard measures and monthly ivermectin MDA at 300 µg/kg for 3 consecutive days, provided under supervision to all eligible village inhabitants, over 2 successive rainy seasons. Nonpregnant individuals >90 cm in height were eligible for ivermectin MDA, and cotreatment with ivermectin and SMC was not permitted. The primary outcome is malaria incidence in children aged ≤10 years, as assessed by active case surveillance. The secondary safety outcome of repeated ivermectin MDA was assessed through active and passive adverse event monitoring.

Results: The trial intervention was conducted from July to November in 2019 and 2020, with additional sampling of humans and mosquitoes occurring through February 2022 to assess postintervention changes in transmission patterns. Additional human

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and entomological assessments were performed over the 2 years in a subset of households from 6 cross-sectional villages. A subset of individuals underwent additional sampling in 2020 to characterize ivermectin pharmacokinetics and pharmacodynamics. Analysis and unblinding will commence once the database has been completed, cleaned, and locked.

Conclusions: Our trial represents the first study to directly assess the impact of a novel approach for malaria control, ivermectin MDA as a mosquitocidal agent, layered into existing standard-of-care interventions. The study was designed to leverage the current SMC deployment infrastructure and will provide evidence regarding the additional benefit of ivermectin MDA in reducing malaria incidence in children.

Trial Registrations: ClinicalTrials.gov NCT03967054; https://clinicaltrials.gov/ct2/show/NCT03967054 and Pan African Clinical Trials Registry PACT201907479787308; https://pactr.samrc.ac.za/TrialDisplay.aspx?TrialID=8219

International Registered Report Identifier (IRRID): DERR1-10.2196/41197

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KEYWORDS

malaria; ivermectin; mass drug administration; mosquito; Anopheles; endectocide; cluster-randomized; clinical trial; seasonal malaria chemoprevention; transmission

Introduction

Background and Previous Studies

Widespread implementation of new malaria control tools since the turn of the century has dramatically reduced malaria parasite transmission and malaria-related morbidity and mortality across the globe, especially in African countries. Improved access to vector control interventions (indoor residual spraying [IRS] and insecticide-treated bed nets [ITNs]), point-of-care diagnostics (rapid diagnostic tests [RDTs]), and efficacious treatment (artemisinin-based combination therapies) have all contributed to this success. ITNs appear to have made the most dramatic impact, with models estimating that 68% of the decline in *Plasmodium falciparum* prevalence in Africa between 2000 and 2015 could be attributed to this vector-focused intervention [1]. In addition to these tools, the use of intermittent preventive treatment in pregnancy (IPTp) and seasonal malaria chemoprevention (SMC) have contributed to morbidity reductions. IPTp entails the administration of at least 3 antenatal doses of sulfadoxine-pyrimethamine (SP) to pregnant women living in malaria endemic regions. SMC, implemented primarily in the seasonal Sahel region of West Africa, entails the use of amodiaquine (AQ) and SP in children aged 3 to 59 months, administered over 3 days during each month of the rainy season [2]. Studies suggest that SMC is very effective in reducing malaria morbidity, with reductions in incidence of up to 70% [2]; the target age group was recently widened to include all age groups at risk of severe disease, and several countries are already piloting or implementing SMC in all children aged <10 years [2]. In most settings, Ministries of Health (MoHs) work with local communities to deliver SMC door to door over 4 months, even though other delivery approaches and tailoring of the number of months of administration are being discussed and implemented in different regions [2].

Unfortunately, despite these impactful interventions, gains against malaria have been uneven across Africa and have largely stagnated or reversed since 2015 [3]. Given the major contribution of vector control interventions to malaria control, it is not surprising that widespread mosquito resistance to the insecticide classes being used in ITNs and IRS (including pyrethroids, carbamates, and organophosphates) and behavioral avoidance (biting outdoors, resting outdoors, or biting at times when individuals are not sleeping under ITNs) are principal reasons for this stagnation in gains. For example, despite high SMC and ITN coverage, Burkina Faso remains as one of the countries with the highest malaria burden, as all major malaria vectors are resistant to pyrethroids [4].

In light of these challenges, it is clear that additional control methods are needed against the *Anopheles* vector. A promising option is the use of endectocides, drugs that kill both endoparasites (such as parasitic worms) and ectoparasites (such as fleas, lice, and mosquitoes) that feed on treated hosts [5-8]. The most well studied of these is ivermectin, a semisynthetic avermectin derivative that was first licensed in 1981 and has been administered for decades at a dose of 150 to 400 µg/kg once or twice a year as mass drug administrations (MDAs) to treat and eliminate onchocerciasis, lymphatic filariasis, and scabies [9]. Importantly, it has a broad spectrum of activity that also targets invertebrate-specific ligand-gated ion channels, hyperpolarizing their neurons and causing flaccid paralysis, death, and other sublethal effects [10]. Our team and others have pioneered the development of ivermectin as a novel malaria transmission control tool through laboratory and natural field experiments [11-14] and recent clinical trials [15-17], including a recent cluster-randomized trial (Repeat Ivermectin MDA for Malaria Control [RIMDAMAL]; conducted by our group) of repeated low-dose (150 µg/kg) ivermectin MDA during the rainy season in Burkina Faso that reduced malaria incidence by 20% in children aged <5 years [18].

Goal of This Study

Although RIMDAMAL supported the potential impact of repeated MDA with ivermectin on malaria incidence, the doses and frequency were not optimized for either maximizing efficacy or ease of implementation. In particular, low-dose ivermectin is unlikely to achieve sufficient and sustained drug levels to reduce malaria transmission if given monthly. On the basis of pharmacokinetic and pharmacodynamic modeling, we determined that a repeated monthly dose of 300 µg/kg daily for 3 days would be expected to achieve sufficient blood levels to have a clinically relevant impact on malaria rates in children

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[1,7,19]. In addition, to facilitate the implementation of repeated ivermectin MDA on a wide scale, we hypothesized that combining the delivery of SMC (already standard practice in most of Sahel) with ivermectin would facilitate the deployment of our intervention and provide a multifaceted and layered approach for malaria control, targeting both the parasite and the mosquito simultaneously, which is critical to making further gains toward reducing the burden of malaria [1,7,20]. Therefore, we designed the RIMDAMAL II trial, a double-blind, cluster-randomized, and placebo-controlled trial for integrated control of malaria. The trial aims to assess the impact of a combined approach of repeated ivermectin MDA and SMC on malaria incidence in children compared with that of repeated placebo MDA and SMC. The trial was implemented in the high-transmission, highly seasonal Diébougou region of Southwest Burkina Faso, the same general location as RIMDAMAL.

Methods

Study Design Overview

RIMDAMAL II is a double-blind, placebo-controlled, cluster-randomized, and parallel-group trial (ClinicalTrials.gov: NCT03967054; pactr.org: PACT201907479787308) designed to determine the efficacy of adding seasonal ivermectin MDA to the standard-policy malaria control measures in Sahel (SMC in children aged 3 to 59 months, long-lasting ITN coverage, and IPTp), for reducing the incidence of uncomplicated malaria episodes among children in enrolled villages (Figure 1). The study includes 14 randomized villages (n=7, 50% control and n=7, 50% intervention clusters). The primary end point is the incidence of malaria over 2 consecutive ivermectin MDA intervention seasons in children aged ≤10 years (Figure 2).

Figure 1. Overall study design showing which groups received each malaria control intervention and which age demographic constituted the active case detection (ACD) cohort [1]. IPTp: intermittent preventive treatment in pregnancy; MDA: mass drug administration; PD: pharmacodynamics; PK: pharmacokinetics; SMC: seasonal malaria chemoprevention; SP: sulfadoxine-pyrimethamine.

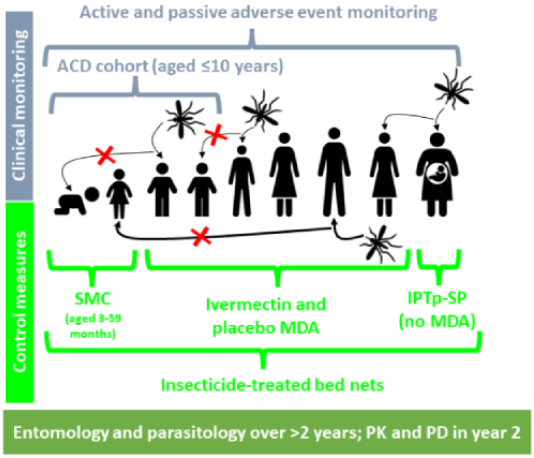
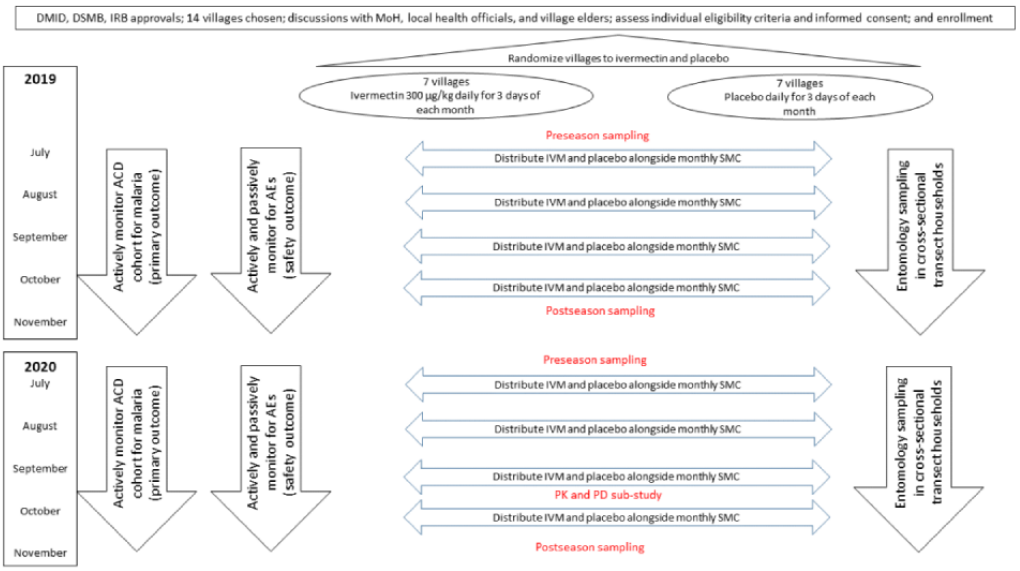


Figure 2. Diagram of study interventions and follow-up for primary and secondary outcomes. ACD: active case detection; AE: adverse event; DMID: Division of Microbiology and Infectious Diseases; DSMB: Data Safety Monitoring Board; IRB: institutional review board; IVM: ivermectin; MoH: Ministry of Health; PD: pharmacodynamics; PK: pharmacokinetics; SMC: seasonal malaria chemoprevention.



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Study Objectives

Primary Objective

Primary objective is to assess the impact of a combined approach of repeated ivermectin MDA and SMC on malaria incidence in children aged ≤10 years (active case detection [ACD] cohort; assessed weekly), with the purpose of testing the superiority of ivermectin compared with placebo for reducing malaria incidence. Our hypothesis is that ivermectin MDAs (the intervention), coinciding with standard-of-care control procedures in Burkina Faso (4 SMC rounds during the rainy season, maximum ITN coverage, and IPTp), will significantly reduce the incidence of childhood malaria (defined in the following sections) in the intervention arm compared with the control arm (standard-of-care control measures without ivermectin MDA).

Secondary Objectives

Secondary objectives include the following:

1. Safety—To measure whether ivermectin MDAs will increase harms for the participants (ie, safety of repeated administrations of high-dose ivermectin)
2. Entomology—To measure entomological indices between the intervention and control arms and over the time of the intervention phase (mosquito survival rate after blood feeding, mosquito population age structure, *Plasmodium* species sporozoite rate, and human exposure to *Anopheles* mosquito bites) between the intervention and control arms
3. Parasitology—To measure the parasitological indices obtained from blood samples collected during the active case surveillance of cohort children between the intervention and control arms and over the time of the intervention phase, including asexual parasite prevalence, species, density, multiplicity of infection, and molecular force of infection (mFOI)
4. Pharmacokinetics and pharmacodynamics—To characterize the pharmacokinetics and pharmacodynamics of ivermectin across the age spectrum and the relationship between ivermectin pharmacokinetics and its entomological effects via membrane feeds

Study Setting

The study was conducted in villages surrounding the town of Diébougou, situated in the Southwest region of Burkina Faso. The region has highly seasonal intense malaria transmission, typically lasting from June to October or November. SMC was also routinely administered in this region for the 4 months of the rainy season (July to October) to all eligible children aged 3 to 59 months. Village residents represent multiple diverse ethnic Burkinabé groups including Dagara, Mossi, Dioula, and others. Previous entomology studies in the area demonstrated that the primary vector responsible for malaria transmission is *A gambiae sensu strictu* with secondary contributions largely from *A funestus* and *A coluzzii* [18,21,22]. The primary means of subsistence are farming, livestock rearing, and trading.

Village and Household Selection

In this region, families typically reside in clustered, grouped homes that consist of extended family households. As a first step, a catchment area for potential clusters within the Diébougou health district was determined using Google Earth Pro (version 7.3.6.9345; Google LLC) that was roughly square in shape (approximately 35 km^2), bounded to the north by the Bougouriba river, to the east by road N12, to the south by the road from Tiankora to Tomena, and to the west by an artificial line that went north from Tomena to the Bougouriba river. Using these satellite images, population centers in this catchment area were outlined based on an analysis of housing structures and an approximation of the number of concessions (extended family households) within each population center. In total, 147 villages or sectors were identified from this analysis, each consisting of between 5 to >100 households. Artisanal gold mining operations were also identified using the maps. From this final map, 18.4% (27/147) of the villages (clusters) were selected based on the following criteria: (1) clusters were accessible to the clinical team during the rainy seasons via motorcycles, which would be their primary mode of transport, providing them with safe road access and allowing them to conduct field visits and return to the field station in Diébougou in 1 day; (2) clusters were at least 2 km away from an artisanal gold mine for the safety of the study team and to minimize contamination from mosquito and human movement to and from these areas; (3) clusters had clearly defined boundaries, allowing field technicians to sample from a single cluster easily without inadvertently including households from neighboring villages; (4) clusters were accessible by study car and no more than 2 km away from an accessible road to facilitate emergency transport of participants to the hospital if necessary; (5) based on an estimated 8 individuals per household, selected clusters had between 20 and 50 households—this was estimated to provide an average of approximately 100 cohort children per cluster, which would enable a single nurse to care for each cluster; and (6) clusters were at least 2 km away from any other enrolled cluster to avoid contamination from mosquito migration. As a final step, in April 2019, the study team selected the final 52% (14/27) of the villages (clusters) based on visits to each village to verify satellite data, household numbers, and village boundaries. All finalized villages and households were enumerated and mapped using handheld GPS devices.

Before the rainy season of year 2, following the review of GPS satellite mapping data, it was determined that a small number of households in a subset of villages were not enrolled in 2019 despite being located at the outer boundaries of participating villages. Owing to their proximity to enrolled households and location within the initial intended catchment area, these households were added to the potential list for enrollment and approached in year 2.

Study Enrollment and Informed Consent

Before village engagement, approvals were attained from the *Comité d'Ethique Institutionnel pour la Recherche en Santé*, *Comité d'Ethique pour la Recherche en Santé*, and MoH through the *Comité Technique d'Evaluation des Essais Cliniques*, followed by permission from regional health authorities (*Directeur Régional de la Santé* and *Médecin Chef de District*). Following these approvals, community engagement began first with village chiefs and elders and the *Agent de santé*

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Communitaire (ASC) and subsequently with village residents. All eligible village residents were asked to enroll, which encompassed people of all ages, genders, and reproductive capabilities. Inclusion criteria for enrollment were residence in the study village and ability to understand the information and provide consent or assent. Exclusion criteria for receiving the intervention included (1) sleeping outside of the study village for ≥3 nights per week; (2) height <90 cm; (3) current receipt of SMC; (4) permanent disability or serious medical illness that prevents or impedes study participation and comprehension; (5) pregnancy (screened for in women of childbearing age—12 to 45 years—using a pregnancy urine rapid test the week before each MDA) and older women who have not yet reached menopause; (6) breastfeeding, if the infant is within 1 week of birth; (7) known allergy to ivermectin; (8) possibility of *Loa loa* infection, as assessed by travel history to Angola, Cameroon, Chad, Central African Republic, Congo, Democratic Republic of the Congo, Equatorial Guinea, Ethiopia, Gabon, Nigeria, and Sudan; or (9) enrollment in any other active clinical trials. For the ACD cohort, inclusion criteria were residence in the study village, aged ≤10 years, and parent or guardian consent. Exclusion criteria for the ACD cohort included (1) sleeping outside the study village for ≥3 nights per week or (2) permanent disability or serious medical illness that prevents or impedes study participation.

Eligibility for ACD was determined at the beginning of each intervention season and retained for the remainder of that season:

1. Newborns were eligible for inclusion.
2. Children who turned 11 years during an intervention season remained eligible for the ACD cohort for the remainder of that season.
3. If a participant aged out of the ACD cohort in the first season, they were not eligible for the ACD cohort in the second season.

Eligibility for SMC was determined by the MoH community workers and not by the RIMDAMAL II study team. Participants may age out of SMC (>59 months) in the first season and become eligible for MDA (height ≥90 cm and aged >59 months) in the second season. They did not become eligible for MDA during the season in which this occurred, that is, individuals had to be ≥90 cm at the beginning of the season to receive ivermectin during that season. Cotreatment with ivermectin or placebo and SMC was not allowed during the study because no data were available about the safety of coadministration.

Informed consent was obtained through a multitiered process. After obtaining the permissions stated previously, the head of each household was approached by the study team. Informed consent was obtained from all willing heads of households. Following consent of the head of household, individual consent was obtained from each willing villager. For those aged <18 years, the consent of a parent or guardian was obtained, and for those aged between 12 and 17 years, an additional assent was obtained. Informed consent procedures were repeated before the year-2 intervention season for any potential new villagers who were not present for the informed consent process before the beginning of the study in year 1. Obtaining consent was also an ongoing process throughout the trial, and any participant who refused treatment or wished to withdraw from the study was able to do so without prejudice.

Cross-sectional Transect Household Selection

A subset of villages and households was selected for more intensive sampling of both humans and mosquitoes to enhance parasitological and entomological secondary studies. Before the beginning of the trial, 6 villages were chosen at random by the study pharmacist, who was unblinded, such that 3 (50%) villages were intervention clusters and 3 (50%) villages were control clusters. Within each of these villages, 8 households were chosen based on GPS mapping and location on spatial transects (east-west and north-south). Households closest to the transects were selected based on location: 2 innermost and 2 outermost households on each transect (8 households per village; 48 households in total). Selected households were subject to more frequent cross-sectional sampling of all individuals living in the household (regardless of age) and to intensive entomological sampling.

Trial Medication and Interventions

The intervention, ivermectin or ivermectin placebo (Iver P; Laboratorio Elea; 6-mg tablet) at 300 µg/kg dose estimated by height bands, was administered orally for 3 days to eligible individuals who are not receiving SMC. Per the package insert, dosing of ivermectin or placebo was according to height:

1. 90 to 119 cm (15-25 kg)=1 tablet per day for 3 days
2. 120 to 140 cm (26-44 kg)=2 tablets per day for 3 days
3. 141 to 158 cm (45-64 kg)=3 tablets per day for 3 days
4. >158 cm (65-84 kg)=4 tablets per day for 3 days

Ivermectin tablets were stored in a temperature-controlled room at *Institut de Recherche en Sciences de la Santé* in Bobo-Dioulasso until the beginning of each intervention season and then brought to the temperature-controlled field-based pharmacy in Diébougou. Ivermectin or placebo were administered on a monthly schedule from approximately July to October (4 rounds) as a 3-day course to all eligible individuals according to exclusion and inclusion criteria. The intervention period lasted 2 rainy seasons (one in 2019 and another in 2020). The interventional drugs were administered by the study team via the door-to-door delivery method. Whenever possible, dispensing of ivermectin MDA was conducted alongside community health workers distributing SMC to the same households. In the week before each MDA, the study team members requested a urine pregnancy test for any women of childbearing age (12-45 years) or who had not yet reached menopause. For those who were pregnant or did not agree to pregnancy testing, ivermectin was not administered for that round of MDA. Directly observed therapy was conducted for initial doses, whereby the first day of treatment of each month were handled by the study team. If a participant was not available, the dose was left with the village ASC to be provided to the participant later in the day. MDA on the second and third days were also observed, if possible, with doses provided to the ASC for any missing participants. Any doses that were observed and vomited within 30 minutes were readministered. The status of whether doses were observed was recorded for each participant. For all participants who received MDA, active

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surveillance was conducted on the following day to assess for any adverse events (AEs). Participants were encouraged to consume ivermectin with water and to avoid food for 2 hours after dosing, even though this was not enforced in practice.

IRS was not administered in these villages in the 7 years before the study, aside from a single village that received Actellic 300CS (Syngenta AG) in 2017, and no IRS was deployed during the study. All study villages (14/14, 100%) were part of the periodic MoH ITN distribution cycle, having received pyrethroid ITNs within 2 years before the beginning of the study via mass distribution campaigns. Following the initiation of the study, the MoH relayed that villages in the Diébougou health district were expected to receive new Interceptor G2 ITNs, which were ultimately deployed in October 2019. These new long-lasting insecticidal nets (LLINs) are made with 2 different insecticides (chlorphenapyr and α-cypermethrin) to circumvent the prevalent pyrethroid resistance seen among anophelines in Burkina Faso and much of sub-Saharan Africa.

SMC was provided and distributed by the MoH. It was administered monthly from July to October (for 3 consecutive days) with SP and AQ (eg, SPAQ-CO; Guilin Pharmaceutical). SMC was dosed as 500/25 mg SP and 153 mg AQ for children aged 12 to 59 months and 250/12.5 mg SP and 76.5 mg AQ for children aged 3 to 11 months. As per standard practice in Burkina Faso, the first dose (AQ and SP) is directly observed by MoH staff, and doses on days 2 and 3 (AQ only) are provided to the parents or guardians to administer at home. For pregnant women, IPTp is provided by the MoH and followed World Health Organization policy, which recommended at least 3 treatments, 1 month apart, starting in the second trimester (eg, Fansidar; Roche; 500/25 mg SP per tablet; 3-tablet dosage=1500/75 mg SP).

Ivermectin was also administered to all villages as part of the yearly MDA elimination campaigns, at a single dose of 150 µg/kg orally. According to MoH district leaders, study villages received ivermectin MDA as a single dose for eligible individuals from September 2, 2019, to September 7, 2019, and from November 10, 2020, to November 19, 2020, meaning that study participants received an extra dose of ivermectin 150 µg/kg during the intervention rounds in 2019 and 1 month after the intervention rounds in 2020. Ivermectin MDA was administered by the MoH and not by the study team.

Outcome Measures

Primary Clinical Efficacy Outcome

The primary outcome is the incidence of malaria episodes in the ACD cohort, which comprised children aged ≤10 years, as assessed by active case surveillance by study team nurses assigned to each village and required to visit each child a minimum of once per week during the intervention phases. In this field setting, malaria incidence in children is the most clinically relevant outcome measure for an antivector intervention that targets blood-feeding mosquitoes, and its reduction following repeated ivermectin administration has been validated in our previous RIMDAMAL study [18]. Study nurses were instructed to visit each child weekly to monitor for malaria episodes. At each visit, malaria was defined as a temperature ≥37.5 °C (axillary or equivalent at another site) or history of fever in the last 24 hours with a positive RDT for *Plasmodium* of any species. Study nurses and physicians routinely visited local clinics serving the study villages to capture malaria cases in study participants that were not detected during weekly monitoring in the villages.

Secondary Outcomes

Secondary outcomes include the following:

1. Safety and tolerability—AE monitoring occurred throughout the intervention periods in both years through active and passive case surveillance. AE monitoring occurred for all enrolled participants, regardless of age, and will be further characterized by their relationship to the intervention and as serious AEs based on their severity. Active AE monitoring entailed assessments 24 hours following each dose of MDA in all participants available at the time of a nurse's visit and weekly visits for children in the ACD cohort. Nurses conducted passive AE monitoring over the course of the week during routine study activities.
2. Entomology—Entomological outcomes include the following. (1) *Human biting rate (HBR)*—this is defined as the number of mosquitoes captured per person per period. For aspirated, indoor-resting, blood-fed mosquitoes, HBR is calculated by dividing the house or household catch by the number of humans living in that house or household. For host-seeking mosquitoes caught in light traps placed next to individuals sleeping in tents (outdoors) or under bed nets (indoors), HBR is simply the catch number per person. (2) *Sporozoite rate*—a representative proportion of mosquitoes captured per period and per mosquito species will be tested for the prevalence of infection with *Plasmodium* sporozoites through genetic testing of their heads and thoraces. (3) Changes in participants' antibody responses to *Anopheles* saliva proteins—paired sets of antibodies from individual participants will be tested for binding to *Anopheles* saliva proteins, and the binding change per person over the study period will be calculated. (4) *The survival of blood-fed mosquitoes*—blood-fed mosquitoes were collected per period, brought back to the field insectary, and held for 3 days to measure their survivorship over that time. A subset of blood-fed mosquitoes from cross-sectional households was stored for the assessment of mosquito biting preference [23].
3. Parasitology—Parasitological outcomes include the following. (1) *Parasite prevalence*—parasite prevalence will be assessed for both *P falciparum*and non-*falciparum* species. (2) multiplicity of infection (also sometimes referred to as complexity of infection) is defined as the number of unique clones per individual at the time of diagnosis of malaria infection. (3) *mFOI* (also sometimes further subclassified as molecular force of blood-stage infection) is defined as the number of new *Plasmodium* clones acquired over time that were not present in the preceding intervals.
4. Pharmacokinetics and pharmacodynamics—Outcomes include (1) the pharmacokinetic profile of ivermectin in 3 different age groups (5-10 years, 11-18 years, and >18 years) sampled over 28 days and (2) the relationship

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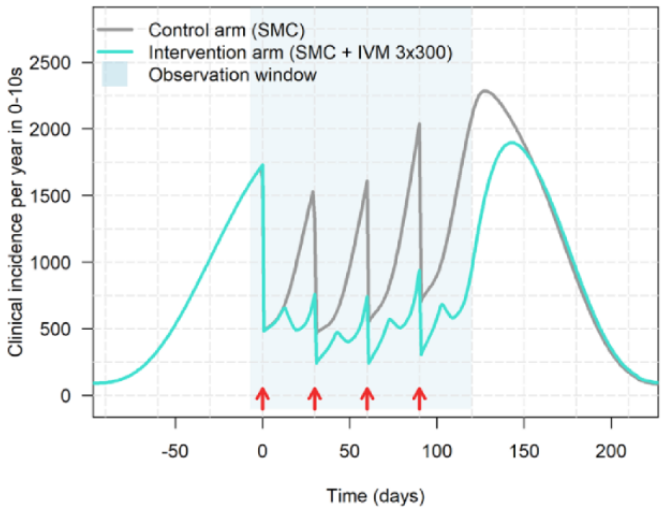
between ivermectin plasma concentration and mosquitocidal effects over time via membrane feeds.

Power and Sample Size Considerations

The primary end point for the trial is the incidence rate of malaria episodes in children aged ≤10 years, as assessed by active case surveillance by study nurses with weekly visits to each child, starting at the first round of MDA in year 1, continuing for 4 months and beginning again with the fifth round of MDA in year 2, and ceasing 4 weeks after the last round of MDA. The dosing regimen, sample size, and power for RIMDAMAL II were guided by the Malaria Transmission model developed at Imperial College, London [24], and are based on data from the RIMDAMAL and Efficacy and Safety of High-Dose Ivermectin for Reducing Malaria Transmission (IVERMAL) trials [1,17-19,25]. The model predicts an effect size in the intervention arm over the control arm of 43% (Figure 3). Calculations assume seasonal incidence rates (per year) of approximately 1.06 and 0.60 in the control and intervention arms, respectively, thus corresponding to an incidence rate ratio of 0.60/1.06=0.57 (ie, incidence rate reduction of 0.43). The initial sample size evaluation shows that RIMDAMAL II has 80% power with 6 villages per arm and 48 children per cluster, assuming a coefficient of variation between clusters of 0.22, which was informed by variation in RIMDAMAL. However, shortly before trial initiation, the sample size was increased from 12 to 14 villages (7 per arm) with approximately 100 children per village or cluster. In a recently published simulation study, the large sample size provides >90% power in the statistical models that were considered for the primary analysis of trial results [26].

This effect size and resulting sample size calculations assumed a moderate level of LLIN coverage with a low-efficacy net owing to high levels of pyrethroid resistance in the region. However, during study planning, it emerged that Interceptor G2 ITNs were to be distributed toward the end of the first year of the intervention. Updating the modeled incidence rates by assuming that the new ITNs would result in an additional 30% reduction, while also increasing the number of children per cluster, meant that even with new LLIN distribution, the number of clusters was still adequate to achieve 80% power.

Figure 3. Initial modeled impact of 4 monthly rounds of seasonal malaria chemoprevention (SMC) compared with 4 monthly rounds of SMC and ivermectin (IVM) 3×300. The resulting annualized incidence rates over the observation window were 1.06 in the control arm and 0.60 in the intervention arm.



Randomization and Blinding Procedures

The randomization unit was the study village (cluster). Before a public randomization event, the study pharmacist, who is the only nonblinded member of the study team, initiated the masking procedure in private, whereby 14 identical cards were made with the numbers 1 to 14 written on them, and these were placed in a container, mixed, and then randomly pulled from the container. In total, 7 numbered cards were randomly placed in each of 2 other containers labeled *ivermectin* or *placebo*. The results of this masking were identically recorded on 3 separate documents, signed by the study pharmacist, and sealed in 3 opaque envelopes kept by the study pharmacist and the 2 principal investigators until the unblinding to be performed after the intervention phase and database cleaning is complete. Following the masking procedure, a public randomization event was conducted before the initiation of the study at the facilities of the district health authority, which was attended by the district medical director, representatives of each village, and members of the study team. At this event, each village's representative randomly drew 1 card from an opaque container that contained 14 identical cards, except for the numbers 1 to 14 marked on them, and each representative signed and dated a document with the record of the number they drew next to the name of their village. This randomization key was copied for the principal investigators, and the original document was given to the study pharmacist, who used it to match the village to the intervention (ivermectin or placebo) previously assigned to each number during the masking procedure.

The study pharmacist was in charge of the drug stock rooms, and he allocated the tablets for each MDA round according to the original randomization throughout the trial. Drug was distributed in sealed containers labeled with the number code. All study personnel, apart from the pharmacist, remained blinded throughout the study.

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Study Procedures

Enrollment

Enrollment forms were completed after obtaining consent from all participants in years 1 and 2 and recorded on study tablets. Year-2 enrollment forms included a reassessment of eligibility criteria and captured additional information about the village participants who were not eligible for MDA owing to them sleeping in the village ≥3 nights per week. Baseline pre-MDA filter paper samples were obtained from a subset of ACD participants in year 1 from each village and from all study participants in year 2.

ACD Cohort Follow-up

Active case surveillance was conducted by study nurses visiting each enrolled ACD cohort child weekly following the beginning of the first MDA and ending 30 days following the last MDA of the season. At each visit, the nurse recorded patient information in the electronic case record form, measured the child's temperature, recorded whether either a history of fever in the past 24 hours or current fever was present, and obtained a blood sample by capillary finger prick method (for RDT, blood smear slide and filter paper [Whatman 3MM] samples were collected). The RDT detected both parasite-derived histidine-rich protein 2 and lactate dehydrogenase (SD Bioline Malaria Ag Pf/Pan; Abbott). All clinical decisions were made based on the RDT result, and if positive for either antigen, results were recorded, and participants were treated with artemether-lumefantrine, according to the Burkina Faso MoH guidelines. Episodes of malaria were classified as complicated based on standard World Health Organization criteria [2]. Patients with complicated malaria were referred to the district hospital immediately. Routine visits were made to local clinics and hospitals to determine whether any participant required management for any AEs that were not captured during routine village-based surveillance.

During each weekly visit, the nurse inquired about any AEs following the receipt of MDA doses or during any intervening time since the last visit. Passive AE monitoring was performed if AEs were communicated to the nurse during other nonstudy visit encounters. Household surveys were performed over the course of the study to ascertain the use of malaria control measures and gather other demographic and social information. In year 2, infection prevention and control measures were implemented to limit the risk of COVID-19 among study staff and participants. Measures included the use of personal protective equipment and the purchase and use of washing stations within each village.

AE Monitoring

As noted previously, active and passive AE monitoring occurred in all enrolled villagers, regardless of age. Study nurses and physicians were trained on how to monitor, record, and report AEs. In addition, AEs were followed to resolution when feasible. Severity assessments by the study physicians were performed in consultation with the study nurses and on-site physicians. AEs were graded on a 5-point scale and grouped according to body system and preferred terms using Medical Dictionary for Regulatory Activities. Relationship to the study intervention was determined by the study physician and reviewed by the study's principal investigators before unblinding.

Cross-sectional Transect Household Assessments

Before the beginning of MDA 1 in year 1, cross-sectional households were visited to complete a baseline questionnaire and collect a capillary finger prick sample on filter paper. In year 1, additional blood samples were obtained on filter paper in the middle of the season and approximately 4 weeks following the last MDA. In year 2, filter paper samples were obtained from all cross-sectional household participants before each MDA and 4 weeks following the last MDA. In addition, before and after each season, a hemoglobin measurement was performed using point-of-care HemoCue. Entomology collections in cross-sectional households are described in the following sections. Cross-sectional questionnaires were administered to ascertain the use of malaria control measures and to assess housing and environmental aspects related to malaria risks.

Parasitological Assessments

Parasite prevalence and speciation will be determined using molecular assays on DNA extracted from filter paper samples using established methods. *P falciparum* clonality (complexity of infection and mFOI) will be assessed using either length-polymorphic markers or single nucleotide polymorphism–based genotyping using deep amplicon sequencing [27,28].

Entomological Assessments

Mosquito sampling was conducted in a subset of cross-sectional villages, within the cross-sectional transect households only. Overall, 2 sampling methods were used; the first method was indoor aspirations of resting mosquitoes collected in the morning in all cross-sectional household sleeping rooms, and the second was light traps placed in 1 cross-sectional household located in the center of the village to collect host-seeking anophelines overnight. For the light traps, one was placed outdoors hanging under the rain tarp of a camping tent that was occupied by a sleeping person, and another was placed indoors hanging next to a person sleeping under a bed net. Mosquito sampling intervals occurred in these 6 cross-sectional villages over the course of a week and were conducted 1 week after each MDA and 3 weeks after each MDA for a total of 16 sampling intervals across the entire intervention period.

Pharmacokinetics and Pharmacodynamics Assessments

In October 2020, following the third round of ivermectin MDA, a pharmacokinetics and pharmacodynamics substudy was performed for individuals residing in 6 villages (n=3, 50% intervention and n=3, 50% control villages). In total, 178 participants were enrolled in the substudy, approximately 90 each from the intervention and control villages, with all team members except the pharmacist blinded to the village study arm. Participants were enrolled to achieve roughly equal numbers from three age groups: (1) 5 to 10 years, (2) 11 to 18 years, and (3) >18 years. Sparse pharmacokinetics sampling was conducted for each individual at up to 7 time points over 28 days, with additional blood collected for entomological and safety assessments (chemistries and blood counts).

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Pharmacokinetics data will be analyzed using nonlinear mixed effects modeling, and entomological assessments will be performed using membrane feeds on participant plasma.

Data Management

Data were gathered in an electronic data capture system (REDCap [Research Electronic Data Capture; Vanderbilt University] database system). All electronic case report forms containing participant demographic and clinical data (active case surveillance data on the children cohort and AE data for all participants) were entered on password-protected tablets that were maintained and updated daily by the clinical team working at the field site. Only the study team will have access to the source data. Long-term maintenance of the participant codes is held only by the study's principal investigators on password-protected computers and files. Database records were individually checked for inconsistencies and cross-checked with the study team and other data sources, as applicable. Study data devoid of identifiers will be provided to the research community following the publication of the primary outcomes.

Ethics Approval and Regulatory Oversight

Institutional review board approvals were obtained and maintained from the Colorado State University (19-9144H/1691), Yale Human Investigations Committee (under a Streamlined, Multisite, Accelerated Resources for Trials Institutional Review Board Reliance platform agreement with the Colorado State University; 2000024138), *Comité D'Ethique Institutionnel Pour La Recherche en Sciences de La Santé* (A031-2018), *Comité D'Ethique Pour La Recherche en Santé* (2019-01-009), and *Comité Technique D'Examen Des Demandes D'Autorisation D'Essais Cliniques* (2019-0580). The protocol was approved by the National Institutes of Health Division of Microbiology and Infectious Diseases (protocol number 18-0007). An independent data and safety monitoring board was convened by the Division of Microbiology and Infectious Diseases. Protocol violations and serious AEs were reported to the abovementioned regulatory bodies according to institutional requirements. An independent study monitor (an in-country contract research organization, CliMAfrica-CRO, Burkina Faso) provided external monitoring for the study, beginning before study initiation and until completion of the study. The CONSORT (Consolidated Standards of Reporting Trials) extension for cluster trials will be completed and made available at the time of reporting primary study results for publication.

Statistical Analysis

Primary Clinical Outcome

We will use an intention-to-treat analysis method for our primary clinical outcome, which is the incidence rate in children in the ACD cohort [26]. Person time will be defined in 7-day consecutive intervals, with ≥1 visits occurring during each interval considered as a single eligible person week. A Poisson mixed effects regression model with a village-level random effect will use the counts of malaria episodes with exposure time (modeled as an offset) in each participant to estimate the malaria incidence rate for all participants in the intervention and control villages. The primary analysis will be adjusted for other covariates such as ITN use and participant age. The estimate for the primary analysis is the exponentiated coefficient for the treatment covariate across both seasons. This rate ratio is the ratio of malaria incidence rate in the treatment villages to the rate in the control villages. The model will be fit with a Kenward Roger *df* correction to account for the limited number of clusters. The primary conclusion about the relative efficacy of ivermectin MDA will be based on the treatment effect coefficient, its 95% CI, and *P* value testing difference from 0 (rate ratio of 1). The primary analysis method and model were selected based on the results of a simulation study of the statistical properties of many models that have been proposed for the analysis of cluster-randomized trials using count-based outcomes [26].

The primary analysis will evaluate the efficacy of ivermectin treatment as described previously. The robustness of this conclusion will be evaluated through analyses that will adjust for other covariates and assess the strength of the rate ratio in key subgroups. Sensitivity analysis will be performed to assess the impact of censoring a participant's time at risk for 14 days following the diagnosis and treatment of malaria owing to the impacts of treatment on risk of recurrent malaria.

Subgroup analyses will be performed to help inform the mechanism of action of ivermectin and determine whether the effects are similar across important subgroups. Subgroups include (1) children aged 0 to 3 months, who receive neither SMC nor intervention; (2) children aged 3 to 59 months, who receive SMC only; (3) children aged >59 months but are <90 cm in height, and therefore do not receive SMC or the intervention; and (4) those who receive MDA only (height ≥90 cm and aged ≤10 years).

Safety Analysis

Safety analysis will be assessed by relative risk (RR) in the following groups: (1) all participants were followed actively and passively for AEs, and the risk ratios of AEs of those in the intervention versus control clusters will be compared; (2) ACD-cohort SMC-treated children only—RR of AEs in children who receive SMC and live in ivermectin-treated clusters versus those who receive SMC and live in placebo-treated clusters; (3) ACD-cohort ivermectin-treated or placebo-treated children only—RR of AEs in those children receiving ivermectin MDA versus those receiving placebo; and (4) non-ACD participants who were enrolled in the study were followed actively for 24 hours after each study intervention and then passively for the rest of the MDA round.

Results

Consent process and recruitment for the study began on July 13, 2019. The first round of MDA began on July 26, 2019, and the last round of MDA in year 1 began on October 16, 2019. MDA in year 2 began on July 20, 2020, and the last round of MDA began on October 12, 2020. SMC and ivermectin MDA distribution occurred on the same days for all MDA except MDA 1 in 2019, in which ivermectin MDA was delayed relative to SMC by 2 days. Statistical analysis will be conducted once the database is completed, cleaned, and locked, and the clinical trial protocol is publicly available. The study team will be

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unblinded after the clinical trial protocol and statistical plan is finalized and publicly available.

Discussion

Principal Findings

With gains in malaria stagnating since 2015 and reversals being seen in several countries, particularly in sub-Saharan Africa, novel control methods are urgently needed [3]. Novel interventions in conjunction with other measures will likely be needed, as no single intervention is expected to have a sufficient, durable, and sustainable impact to reduce malaria morbidity and mortality in the long term. Previous studies by our group and others demonstrated that ivermectin, when used at 150 µg/kg, similar to doses used for MDA campaigns to eliminate lymphatic filariasis, onchocerciasis, and scabies (150-400 µg/kg), showed lethal and sublethal effects on mosquitoes following blood meal ingestion [15,29-32]. The same dosage was then shown to affect malaria incidence when administered more frequently (every 3 weeks) in the RIMDAMAL trial [18]. Modeling studies have demonstrated that a monthly regimen of 300 µg/kg administered on 3 consecutive days is likely to have a significant impact on malaria incidence [1]. The safety and mosquitocidal impact of this regimen were recently demonstrated in a randomized trial of adults with malaria living in Kenya [17].

RIMDAMAL II builds on these insights and will assess whether the high dose of ivermectin MDA, when administered in operational conjunction with SMC delivery, is associated with significant reduction in malaria incidence in children aged <10 years, as compared with standard interventions alone (SMC and ITN use). Malaria incidence was chosen as the primary outcome, as this was felt to reflect a meaningful outcome measure that could have an impact on policy decisions. The study is cluster randomized and placebo controlled, with all study investigators being blinded to intervention allocation, which is a rigorous design to test the community-level impact of this novel intervention. The study intervention was also conducted over 2 seasons and involved both active and passive follow-up of AEs for all enrolled participants, thus providing a strong evidence base to assess the safety of repeated high-dose ivermectin for malaria transmission reduction. Secondary outcomes will provide parasitological, entomological, and pharmacokinetic outcome measures to further enhance our understanding of the mechanisms by which ivermectin may exert its effects. Additional sampling in the year following the intervention will provide information on any postintervention effects of ivermectin MDA.

Community-level trials are subject to several challenges during planning and execution. The identification of appropriate clusters that are sufficiently distanced from one another to avoid contamination and of appropriate size to enable rigorous surveillance of all participants can be challenging, but it also reflects the reality of spatial demographics in rural African settings. During the planning stages, attempts were made to identify ideal villages for inclusion, while balancing with practical limitations in the field (refer to previous sections).

Cluster-randomized, community-based trials are also open to external factors that can challenge the execution phases of the study. During RIMDAMAL II, the COVID-19 pandemic spread around the globe just before the beginning of the second intervention season. In recognition of the potential impact that the COVID-19 pandemic could have on multiple aspects of the study (safety of the staff and participants, availability of supplies, ability to differentiate malaria and COVID-19, etc), extensive discussions and preparations occurred before year 2 of the study. Efforts included the training of the staff on appropriate infection prevention and control measures, purchase and shipment of personal protective equipment from the United States to Burkina Faso, and purchase of handwashing stations for each village. At the conclusion of year 2 of the intervention, there was no overt evidence of COVID-19–related clinical impacts in our enrolled villages; however, precise data on COVID-19 case counts in the region were not available.

A second challenge was the decision by the Burkina Faso MoH and certain research partners to deploy ITNs with different insecticide chemistries in Southwest Burkina Faso. In the region of Diébougou, new Interceptor G2 ITNs were deployed in October 2019, at the end of year-1 intervention season. The timing of distribution created challenges and opportunities, which will be assessed in the analysis, as both year-1 and year-2 outcomes largely occurred under the use of deltamethrin and chlorphenapyr or α-cypermethrin nets.

RIMDAMAL II will be the first cluster-randomized trial to directly assess the impact of repeated high-dose ivermectin MDA on malaria incidence. The trial uses high-dose, monthly ivermectin coupled operationally with SMC, and the assessment of primary outcome includes children who received only SMC (those aged 3-59 months) and those who received only ivermectin (and no SMC; those aged 60 months to 10 years). Statistical analysis planning supports the adequacy of the cluster size and the approach to assess the primary outcome [26]. The study encountered challenges with the emergence of COVID-19 globally and the deployment of ITNs with new chemistries locally in year 2. Following the final analysis and dissemination of results, if the intervention is found to be efficacious and safe, the design will facilitate the potential consideration of this multilayered novel approach for malaria control in seasonal high-transmission settings.

Conclusions

RIMDAMAL II will be the first cluster-randomized trial to directly assess the impact of repeated high-dose ivermectin MDA on malaria incidence in children. The results will inform policies and future studies on the use of mosquitocidal agents as novel components for malaria control.

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Acknowledgments

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Data Availability

Data for the trial will be made available on the Clinical Epidemiology Database Resources [33].

Authors' Contributions

BDF, SP, and RKD conceived of the study. SP and BDF drafted the manuscript. AFS and GC served as the study coordinators. AS was the primary medical officer and oversaw the field activities. BDF and RKD oversaw the design and entomology activities. TM, BDF, AS, LG, MC, and SP oversaw the creation and management of the database. MW oversaw laboratory management at Yale. TB assisted with the study design. SR, CLJ, HCS, and JK provided the modeling and statistical analysis plan. KR performed regulatory oversight.

Conflicts of Interest

In October 2020, BDF and SP joined the Scientific Advisory Board as consultants for the IMPACT project being run by MedinCell. RKD and AFS are investigators for the IMPACT project. BDF also performed a 1-time consultation for Lyndra Therapeutics Inc in July 2020.

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Abbreviations

ACD: active case detection
AE: adverse event

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AQ: amodiaquine
ASC: Agent de santé Communitaire
CONSORT: Consolidated Standards of Reporting Trials
HBR: human biting rate
IPTp: intermittent preventive treatment in pregnancy
IRS: indoor residual spraying
ITN: insecticide-treated bed net
IVERMAL: Efficacy and Safety of High-Dose Ivermectin for Reducing Malaria Transmission
LLIN: long-lasting insecticidal net
MDA: mass drug administration
mFOI: molecular force of infection
MoH: Ministry of Health
RDT: rapid diagnostic test
REDCap: Research Electronic Data Capture
RIMDAMAL: Repeat Ivermectin Mass Drug Administration for Malaria Control
RR: relative risk
SMC: seasonal malaria chemoprevention
SP: sulfadoxine-pyrimethamine

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Protocol

Exercise Training to Improve Brain Health in Older People Living With HIV: Study Protocol for a Randomized Controlled Trial

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Abstract

Background: With the advent of antiretrovirals, people living with HIV are living near-normal lifespans. However, people living with HIV are at greater risk of experiencing cognitive impairment and reduced brain integrity despite well-controlled viremia. A robust literature supports exercise interventions as a method of improving cognition and structural brain integrity in older individuals without HIV. The effects of exercise on cardiometabolic, neurocognitive, and neural structures in middle-aged to older people living with HIV are less well known, with few prospective studies examining these measures.

Objective: This prospective randomized clinical trial will examine the effects of a 6-month exercise training intervention compared to a 6-month stretching intervention (control) on cardiorespiratory fitness, physical function and strength, cognition, and neuroimaging measures of brain volumes and cerebral blood flow in people living with HIV.

Methods: Sedentary middle-aged to older people living with HIV (ages≥40; n=150) with undetectable HIV viral load (<20 copies/mL) will be enrolled in the study. At the baseline and final visit, fasting plasma lipid, insulin, glucose, and brain neurotrophic factor concentrations; cardiorespiratory fitness; cognitive performance; brain volumes; and cerebral blood flow via a magnetic resonance imaging scan will be measured. Participants will be randomized in a 2:1 ratio to either the exercise or control stretching intervention. All participants will complete their assigned programs at a community fitness center 3 times a week for 6 months. A professional fitness trainer will provide personal training guidance at all sessions for individuals enrolled in both arms. Individuals randomized to the exercise intervention will perform endurance and strength training exercises, while those randomized to the control intervention will perform stretches to increase flexibility. A midpoint visit (at 3 months) will assess cognitive performance, and at the end point visit, subjects will undergo cardiorespiratory fitness and cognition testing, and a magnetic resonance imaging scan. Physical activity throughout the duration of the trial will be recorded using an actigraph.

Results: Recruitment and data collection are complete as of December 2020. Data processing, cleaning, and organization are complete as of December 2021. Data analysis began in January 2022, with the publication of study results for primary aims 1 and 2 expected by early 2023.

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Conclusions: This study will investigate the effects of a 6-month aerobic and resistance exercise training intervention to improve cardiometabolic risk factors, cognitive performance, cerebral structure, and blood flow in sedentary people living with HIV. Results will inform clinicians and patients of the potential benefits of a structured aerobic exercise training program on the cognitive, functional, and cardiometabolic health status of older people living with HIV. Assessment of compliance will inform the development and implementation of future exercise programs for people living with HIV.

Trial Registration: ClinicalTrials.gov NCT02663934; https://clinicaltrials.gov/ct2/show/NCT02663934

International Registered Report Identifier (IRRID): DERR1-10.2196/41421

(JMIR Res Protoc 2023;12:e41421) doi:10.2196/41421

KEYWORDS

cardiorespiratory fitness; cognition; exercise; HIV; magnetic resonance imaging; resistance training

Introduction

Overview

In the era of combination antiretroviral therapy (cART), people living with HIV are living near-normal lifespans [1]. Despite this, cognitive impairment is still prevalent in people living with HIV, even in those with well-controlled viremia [2]. Current adjunctive therapies to cART, such as cognitive training or other medications designed to treat comorbid conditions (ie, anticholinergics and lithium), have not demonstrated significant benefit in improving cognition and quality of life in people living with HIV. Consequently, there is a critical need for the development of adjunctive therapies that improve cognition in people living with HIV.

The effects of aerobic and resistance exercise (EXS) training interventions on physical and brain health have been well documented in people without HIV. These interventions are especially important in older adults, as older individuals tend to exhibit more sedentary lives than younger individuals [3]. Improved physical functioning and physical fitness have been reported in older people without HIV who completed exercise intervention programs [4-7]. Older adults have also demonstrated improvements in cardiorespiratory health (ie, VO_2 maximum [VO_{2max}], the maximum rate of oxygen consumption during exercise) after completing an exercise program [8]. Reviews of the extant literature reveal that exercise intervention programs improve cognitive performance or slow cognitive decline, specifically in domains such as attention, processing speed, executive function, and memory [9-12] in both clinical populations (mild cognitive impairment and Alzheimer's disease) and otherwise healthy older adults. Neuroimaging indices of brain integrity also improve in response to engagement in structured exercise interventions in older adults. Specifically, increased brain volumes [13,14], changes in cerebral blood flow (CBF) [15-17], and improved brain network connectivity [16,18,19] have been observed in individuals completing exercise interventions. These results are particularly evident in the frontal and temporal regions (including the hippocampus), each of which is critical for executive function, learning, and memory.

Research into the efficacy of an exercise intervention in improving physical and brain health in people living with HIV is less established. Longitudinal intervention studies have primarily focused on physical health outcomes, with evidence of improved blood pressures (BPs), cardiorespiratory fitness ($VO_{2\ max}$), inflammatory markers, physical strength, and body composition in people living with HIV following completion of an EXS training program or other activity programs, such as yoga [20-25]. The relationship between exercise and cognitive outcomes in people living with HIV has primarily been assessed using association studies and self-reported levels of physical activity. The effects of self-reported exercise or physical activity on cognitive function in the setting of HIV have produced conflicting results, with both positive [26-30] and null findings [31] reported. Because these studies did not include an intervention component, a causal effect of exercise on cognition was not able to be established.

Few studies have used neuroimaging to examine the effects of exercise on structural brain integrity in people living with HIV. While one cross-sectional study reported larger putamen volumes in a group of physically active people living with HIV compared to sedentary people living with HIV [30], to our knowledge, there have been no prospective studies examining neuroimaging markers of brain integrity before and after completion of an EXS training intervention in older people living with HIV. Therefore, the purpose of this clinical trial is to examine the effects of a 6-month EXS training intervention (vs a stretching control group) on cardiorespiratory and physical function, plasma markers of cardiometabolic risk and neurotrophic peptides, cognitive performance, and neuroimaging metrics in a sample of sedentary older people living with HIV who are on a stable cART regimen and virologically well controlled.

Aims

The primary objective of this study is to compare the effects of supervised EXS training versus a social-interaction stretching (SIS) group on brain health in people living with HIV aged ≥40 years.

Aim 1

The aim is to examine the effects of exercise training on cognitive function in people living with HIV aged ≥40 years.

Hypothesis 1a

A 26-week EXS program will enhance cognitive function (domain-specific executive function, attention, and memory) more than an SIS program in physically inactive people living with HIV.

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Hypothesis 1b

Greater improvements in cardiorespiratory fitness and physical function (daily physical activity, muscle strength, and muscle mass) in the EXS group will be associated with better cognitive performance.

Aim 2

The aim is to examine the effects of exercise training on brain structural and functional measures in people living with HIV aged ≥40 years.

Hypothesis 2a

A 26-week EXS program will associate with improved brain structural and functional measures (CBF and brain volumetrics) more than an SIS program in physically inactive people living with HIV.

Hypothesis 2b

Greater changes in physical function (daily physical activity, cardiorespiratory capacity, muscle strength, and muscle mass) in the EXS group will be associated with increases in CBF and larger brain volumetrics.

Hypothesis 2c

Improved neuroimaging changes will be associated with enhanced cognition in people living with HIV.

Exploratory Hypothesis

Improvements in brain integrity due to EXS will be accompanied by reduced systemic inflammation and improved glucose regulation.

Methods

Participants

All study visits are conducted at Washington University in St. Louis. Participants are recruited from local clinic referrals, flyers posted in pharmacies, food pantries, and advocacy groups in addition to word of mouth. Our team has also met with caseworkers and physicians to introduce them to this study.

Inclusion criteria are as follows: age 40-80 years, sedentary lifestyle (defined as structured exercise for less than 2 hours per week for the last 6 months), known HIV infection, on a stable cART regimen with an undetectable plasma HIV RNA (<50 copies/mL) for at least 12 months prior to enrollment, able to receive a magnetic resonance imaging (MRI) scan, and able to attend 3 EXS or SIS sessions a week over 6 months. It should be noted that the study inclusion criteria originally only enrolled older people living with HIV older than 50 years. However, due to difficulty in enrolling this population, the study opened enrollment to people living with HIV older than 40 years during the final year of enrollment.

Exclusion criteria are as follows: history of serious cardiovascular or cerebrovascular disorder (ie, stroke and uncontrolled hypertension), pulmonary disease, or significant neurological disorders; substance use disorder within the last 6 months; pregnant or breastfeeding; currently prescribed anticoagulants or medications known to affect glucose and lipid metabolism (other than statin medications); or any other medical condition that, in the opinion of the principal investigator, makes the patient unsuitable for inclusion in the study (eg, severe psychiatric illness).

Study Visits

Baseline Visit 1

Cardiovascular Visit

After obtaining informed consent from each volunteer and after 10 minutes of rest, BP, heart rate (HR), temperature, waist circumference (mid-way between right costal margin and anterior superior iliac crest), height (by using a stadiometer), weight, and fasting blood glucose level (Accucheck) are collected. Female participants are administered a urine pregnancy test (McKesson Consult Diagnostics, manufacturer #5000) before testing begins.

Whole-body dual-energy x-ray absorptiometry (DXA) scan is performed on a GE-Healthcare Lunar I scanner. DXA outcome variables, quantified through the use of Encore Software (version 16), include BMI, total mass, lean mass, fat mass, android and gynoid mass, visceral adipose tissue mass, and fat tissue mass for each arm, leg, and the trunk.

Once the DXA is completed, an intravenous tube is placed in the participant's arm for the blood draw (see Bloodwork section below). Once blood is collected, an electrocardiogram machine (Case V6.73) is obtained. The study physician then conducts a medical history and physical examination.

After the electrocardiogram, the participant completes a graded maximal exercise test on a recumbent cycle ergometer with concurrent indirect calorimetry (ParvoMedics True One System) with a 2-way valve and mouthpiece (Hans Rudolph Inc) in order to measure VO_2. Test workload is initiated at 20 W. Once exercise starts, the participant is asked at 1-minute intervals to rate their perceived exertion on a scale of 6-20, and the resistance is increased by 10-20 W every minute until volitional exhaustion. HR is recorded once every minute, while BPs are collected every 2 minutes. After the session, the participant is monitored for 5 minutes until BP reaches baseline value. Maximal $VO_{2\ max}$ (mL O_2/kg/min) is recorded as the highest VO_2 reached during the test. Exercise tests are considered maximal if the participant reaches ≥85% projected peak HR (220 – age) or respiratory exchange ratio ≥1.1 [32].

After testing, an actigraph (ActiGraph GT3X+) is attached to the nondominant wrist of each subject to record daily physical activity. This actigraph is initialized using the ActiLife v6.13.4 program and set to start recording 1 hour after the end of the study visit with a sampling rate of 100 Hz. The actigraph is worn continuously for 1 week and is collected at baseline visit 2. Once returned, actigraph data are downloaded and integrated into a 60-second epoch-length format to be analyzed using ActiLife. Average time spent sedentary, lightly active, moderately active, vigorously active, and in moderate-to-vigorous physical activity are the primary outcome variables generated by the ActiLife scoring program.

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Bloodwork

Fasting (12 hours) samples are collected during the cardiovascular visit and sent to the Core Laboratory for Clinical Sciences, Barnes Jewish Hospital, Washington University in St. Louis; Quest Diagnostics; or Temple University for processing. The following measures are reported from these samples: comprehensive metabolic panel and lipid panel, C-reactive protein, complete blood count, hemoglobin A1C, insulin and c-peptide, insulin-like growth factor 1, CD4 T-cell count, CD8 T-cell count, HIV RNA viral load, interleukin-6, C-X-C motif chemokine ligand 10, vascular endothelial growth factor, apolipoprotein E, leptin, neopterin, adiponectin, as well as archived plasma and serum. For serum, blood is allowed to clot for 30 minutes and then centrifuged at 2000×*g* at 4 °C for 10-15 minutes before aliquoting and storing in 80 °C freezer. For plasma, samples are centrifuged at 1500×*g* at 4 °C for 10 minutes before aliquoting and storing in 80 °C freezer.

Baseline Visit 2

MRI Scan Visit

One to 2 weeks after the initial visit, MRI scanning and neuropsychological (NP) evaluation are performed. An MRI safety form is completed before the scan to ensure there are no contraindications. Participants complete a urine drug screen (Alere Multi-drug Screen Test Panel; DOA-3104) before the scan. Scans are conducted on a 3T Siemens Prisma scanner using a 20-channel head coil. Collected scans include a T1, 3D-pseudo continuous arterial spin labeling, blood oxygenation level–dependent scan for resting state functional connectivity, diffusion basis spectrum imaging, and fluid-attenuated inversion recovery. For anatomical and pathological analysis, high-resolution magnetization-prepared rapid acquisition and T2 scans are acquired. Arterial spin labeling is acquired using a standard sequence (repetition time =3500 seconds, echo time =9 milliseconds, 90° flip angle, voxel size=3.4×3.4×5 voxels, 64×64 acquisition matrix, 22 axial slices with a 1-mm gap). We use pipelines developed by the Washington University in St. Louis Central Neuroimaging Data Archive and FreeSurfer software (version 5.3) to process the imaging data. Brain volumes and CBF are the primary outcome variables generated from MRI scan data. Additional data acquired from the performed sequences, including blood oxygenation level–dependent scan and diffusion basis spectrum imaging data, are considered in secondary analyses.

NP Testing

Participants complete the questionnaires and NP testing after the MRI. Web-based questionnaires assessing mental health, substance use, sleep quality, and subjective memory performance are first administered using an iPad (iPad Air 2, model MH182LL/A; Table 1). Following the questionnaires, the NP testing begins with allowances for breaks when needed. Most tests are administered in paper and pencil format, with some tests administered on the iPad. Questionnaires and NP testing take 2-3 hours to complete (Textbox 1).

Table 1. Questionnaires administered at baseline and end point visits.

Domain and questionnaire	Function
Substance use	
KMSK[a]-Lifetime [33]	Quantify lifetime heaviest use of alcohol, tobacco, marijuana, cocaine, heroin, and opiates
KMSK-30 Day [33]	Quantify use of alcohol, tobacco, marijuana, cocaine, heroin, Rx benzodiazepines, illicit benzodiazepines, Rx opiates, illicit opiates, illicit barbiturates, amphetamines, and methamphetamines in past 30 days
Fagerstrom Test for Nicotine Dependence [34]	Nicotine dependence
Sleep	
Pittsburgh Sleep Quality Index [35]	Measures quality and patterns of sleep
Activities of daily living	
Patient Assessment of Own Functioning [36]	Measures perceived daily functioning impairments
Activity	
International Physical Assessment Questionnaire [37]	Measure of physical activity
Patient-Centered Assessment and Counseling for Exercise [38]	Assess physical awareness
Mood	
Beck Depression Inventory-II [39]	Measures characteristic attitudes and symptoms of depression
Centers for Epidemiologic Studies-Depression Scale [40]	Measures self-reported symptoms associated with depression
Memory	
Prospective Retrospective Memory Questionnaire [41]	Self-report measures of prospective and retrospective memory slips in everyday life.

[a]KMSK: Kreek-McHugh-Schluger-Kellogg scale.

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Textbox 1. Neuropsychological (NP) test battery. All tests are completed at baseline and end point NP visits. Tests denoted with a "*" are also completed at the midpoint NP visit.

Learning and memory domain

- Hopkins Verbal Learning Test–Revised* [42]
- Brief Visuospatial Learning Test Revised* [43]

Prospective and retrospective memory domain

- Virtual week program [44]

Executive function domain

- Action Fluency* [45]
- Trail-Making Test B* [46]
- Letter Number Sequencing* [47]
- Paced Auditory Serial Addition* [48]
- Color Word Inference Test–Stimuli 3* [49]
- Digit Span-Backwards [47]
- Medication Management Task–Revised [50]
- Wisconsin Card Sorting Task [51]
- Rey-Osterrieth Complex Figure–Copy* [52]

Psychomotor or processing speed domain

- Trail Making Test-A* [46]
- WAIS-III Symbol Search [47]
- Digit Span* [47]
- Digit-Symbol Substitution Test* [47]

Language domain

- FAS fluency* [53]
- Animal fluency [54]

Motor and fine motor domain

- Grooved Pegboard (dominant and nondominant hand)* [55]
- Finger tapping*
- Timed Gait
- Grip strength

Premorbid IQ

- Wide range achievement test 3–reading and recognition [56]

Study Arm Randomization

Group randomization is performed after all baseline appointments are completed and the participant is determined to be safe to exercise. A randomization program is employed by the study senior statistician to assign group membership with a 2:1 ratio in EXS and SIS arms, respectively. All study staff directly involved with participant testing are blinded to the randomization; only the personal trainer is aware of the study arm designation. All participants are instructed not to disclose their randomization to study staff.

Interventions

Overview

Each participant is familiarized with the gym facility where the intervention takes place. At the first session, participants are given a Polar chest HR monitor and then instructed to complete a 5-minute warm-up (options include walking on the indoor track, stationary cycling, elliptical, or treadmill). After warm-up, participants complete a 6-minute walk test [57] as an assessment of cardiovascular fitness. Distance walked in meters during the 6-minute period is recorded. The 6-minute walk test is repeated several times throughout the course of the study intervention

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for all participants, at intervention visits 20, 40, 60, and at the final visit.

For all subsequent intervention visits, HR is recorded through use of the Polar chest HR monitor, and the 5-minute warm-up is completed before beginning the EXS or SIS session.

Participants are scheduled for 3 intervention visits per week, with all visits supervised by the personal trainer. A participant's intervention is complete after 26 weeks have elapsed. Adherence is defined as the participant completing ≥80% of the expected 78 intervention visits.

EXS Intervention

After the 5-minute warm-up, the participant has the option to start either the cardiorespiratory training portion or resistance training portion first, followed by the other for the second half of the daily session. Resistance training covers a full-body workout including 3 lower body and 4 upper body areas, with exercises including leg press, knee extension, knee flexion, seated row, chest press, latissimus dorsi pulldown (lat pulldown), and triceps extension. A combination of guided motion machines and free weights is used.

At the second gym session, a 1-repetition maximum (1RM; measured in pounds) is assessed for each of the major muscle group stations (leg press, lat pulldown, seated row, and chest press) to establish peak muscular strength. The rate of perceived exertion scale (1-10) is used to measure intensity. The 1RM is reevaluated after each month.

During the course of the EXS intervention, the trainer begins the resistance training program with weight for each exercise set to 60% of each 1RM. Three sets of 8-10 repetitions are completed for each exercise for the first 3 months. The trainer increases the weights to 70% of the reevaluated 1RMs for the final 3 months. A rest period of 2 seconds is allowed between each repetition, 1-2 minutes of rest is allowed between each set, and 2-4 minutes of rest between each exercise station or machine.

Cardiorespiratory training includes brisk walking on the indoor track, stationary cycling, treadmill, and elliptical machines. Participants may use a combination of different cardiorespiratory machines to reach their target duration and HR. Target HR begins at 50% of the heart rate reserve (HRR) as assessed during the initial cardiorespiratory testing. Throughout the study, the target HR increases to 85% of the participants' HRR. Duration is progressively increased from 10 to 40 minutes of continuous exercise as the participant acclimates to the exercise program. Intensity is increased as exercise yields a lower HR than previously observed or by 5%-10% per month. After each session, the participant cools down to bring their HR to a comfortable level that would allow conversation. The trainer then demonstrates a stretching routine that covers the major muscle groups of the body (quadriceps, hamstrings, hips or glutes, chest, back, shoulders, and triceps).

SIS Intervention

The SIS group serves as a control group against which to gauge the effects of aerobic and resistance training on brain integrity. Participants in this group follow the same intervention schedule and timeline as the EXS group. SIS participants are supervised by the same personal trainer and receive the same amount of attention and class interaction as participants in the EXS program. This group receives instructions on stretching, range of motion (RoM), limbering, and toning, but intensity is less than that achieved in the EXS group. Activities will focus on flexibility enhancement. As the participant's level of flexibility increases, stretches with increasing levels of difficulty are incorporated into the program.

For the stretching intervention, the participant begins with the 5-minute warm-up. During the second session, the trainer conducts RoM testing for hip flexion, shoulder flexion, ankle dorsi, and plantar flexion on both sides of the body using a goniometer. The RoM is reevaluated after each month.

During each SIS visit, the trainer demonstrates and provides a list of stretches that may include but are not limited to the following muscle groups: hamstrings, gluteals, lower back, upper back, chest, calves, shoulders, triceps, and arm and wrists. Participants complete 10-12 stretches with 30-60 second intervals for each stretch. These stretches are repeated 2-3 times on each side of the body during each session. HR is maintained between the established resting HR and 50% of the HRR.

Midpoint (3-Month) Visit

Once the participant has completed 3 months (36-40 gym visits), a midpoint visit is scheduled. At the midpoint visit, an abbreviated NP battery is administered (see Textbox 1). This battery includes tests that were administered during the baseline NP testing, with alternative versions of NP tests used when available. Additionally, the participant is again provided an Actigraph to be worn for 1 week in order to assess daily activity during participation in the study.

End Point (6-Month) Visit

Once the intervention portion (78 sessions) is completed, the end point (6-month) visits are scheduled. End point visits are repeats of the baseline visits 1 and 2, with the cardiovascular testing visit occurring first. The DXA scan and $VO_{2\,max}$ test are completed, fasting blood samples are collected, and the participant is given an Actigraph to wear on the nondominant wrist for 1 week. After 1 week, the participant returns for the follow-up MRI and NP testing visit. Upon completion of the study, participants are given a 6-month membership to a local fitness facility.

Midpoint and end point visits are completed for all participants, regardless of assigned intervention.

Secondary End points

This study aims to also identify key implementation factors needed for scale-up of an EXS program in older people living with HIV from a single site to HIV clinics at multiple institutions. In order to gain a sound understanding of contextual factors that affect implementation of an EXS program for older, sedentary people living with HIV, we are conducting interviews and focus groups with staff and participants at several time periods during the intervention. This allows us to (1) tailor aspects of the program to coincide with reported barriers to implementation, (2) develop strategies to enhance adherence,

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and (3) make recommendations for future intervention strategies based on modifiable psychosocial characteristics of people living with HIV as they progress through the intervention.

Planned Recruitment and Power Analyses

The recruitment goal for this study is 150 older participants living with HIV, with 100 randomized to the EXS intervention and 50 participants randomized to the SIS control intervention. With this sample size, we calculated 80% power to detect an effect size (Cohen *d*=0.49) in the primary analyses (aim 1 hypotheses *a* and *b*; aim 2 hypothesis *a*). Anticipating a 20% dropout rate at 26 weeks (final EXS n=80; SIS n=40), we would have 80% power to detect an effect size (Cohen *d*=0.55). For aim 2 hypothesis *b*, and anticipating a 20% dropout rate, we would have 80% power to detect a predictor explaining R^2=0.10 or 10% of the variation in the outcome.

Statistical Analyses

For aim 1, planned statistical analyses include *t* tests examining change in cognition (domain and global cognition *z* scores), cardiorespiratory fitness, physical function, and questionnaire data from the baseline to end point visits between the EXS and SIS groups. This analysis uses all randomized participants under the intent-to-treat paradigm. Additionally, linear models are used to determine the mediating effect of the cardiorespiratory fitness and physical function markers on the change from baseline in domain and global cognition *z* scores by including these markers, together with group assignment, as predictors in the model.

For aim 2, similar analyses are conducted to those as described for aim 1, with brain volumetrics and CBF values used in place of cognitive performance. Brain volumes are adjusted for intracranial volume. Linear regression analyses are conducted to examine relationships between changes in brain volumetrics or CBF and changes in cognitive performance from baseline to end point visits.

For the exploratory hypothesis, linear regression models are used to examine relationships between changes in inflammatory or metabolic markers and changes in brain volumetrics, CBF, or cognitive performance. Group assignment is included as a predictor in the model.

Ethics Approval

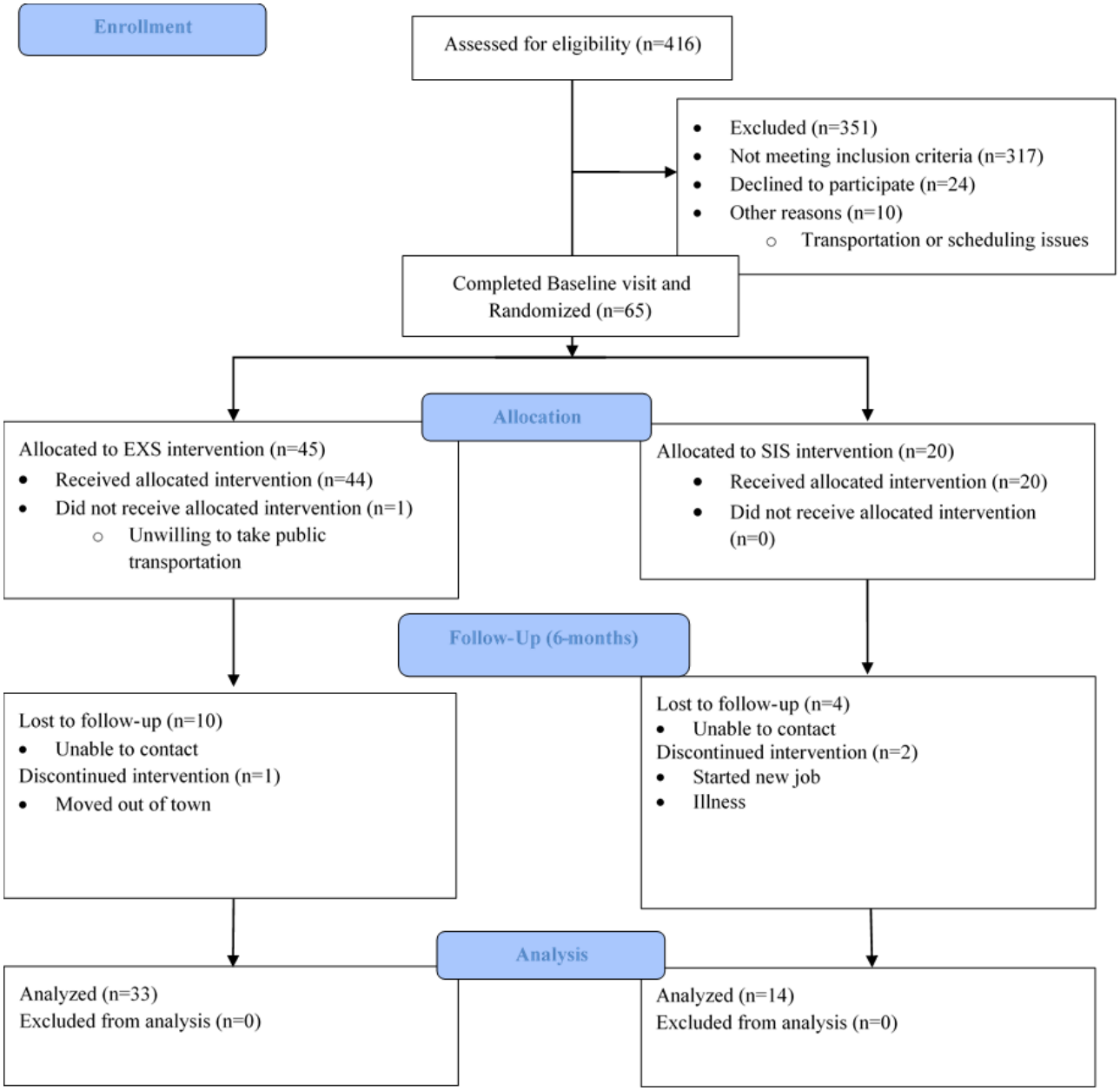
Before completing any study procedures, all participants provided written informed consent that was approved by the Institutional Review Board at Washington University in St. Louis (IRB #201508002). All study procedures were in accordance with the ethical standards described by the Helsinki Declaration. Study participants are assigned an identification number, allowing all stored records to be deidentified. Deidentified data are kept in a locked file room or stored in a password-protected database on a password-protected computer. All participants are monetarily compensated for their participation, prorated to each study visit or gym visit completed, up to US $815. Participants can withdraw from the study at any point.

Results

Recruitment and data collection are complete as of December 2020 (Figure 1). Recruitment and data collection were paused between March 2020 and September 2020 due to the COVID-19 pandemic and again paused in November 2020 due to increasing COVID-19 cases. Consequently, the decision was made to terminate the recruitment phase due to limited time for any newly enrolled participants to complete the 6-month intervention. Baseline study participant demographic and clinical characteristics are provided in Table 2. A total of 65 individuals were enrolled and randomized at a baseline visit, with 47 completing the study. As of July 2022, the study remains open for data processing and analyses. Data processing, cleaning, and organization are complete as of December 2021. Data analysis began in January 2022, with publication of study results for primary aims 1 and 2 expected by early 2023.

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Figure 1. CONSORT (Consolidated Standards of Reporting Trials) flow diagram of study enrollment. EXS: aerobic and resistance exercise; SIS: stretching.



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Table 2. Baseline demographic and clinical characteristics by intervention group.

	EXS[a] group (n=45)	SIS[b] group (n=20)	*P* value
Age (years), mean (SD)	56.5 (5.7)	56.5 (5.9)	.99
Education (years), mean (SD)	12.9 (2.4)	13.9 (2.2)	.14
Sex (male), n (%)	32 (71)	18 (90)	.10
BMI, mean (SD)	30.5 (7)	28.9 (5.7)	.39
Ethnicity (African American), n (%)	29 (64)	14 (70)	.81
Recent CD4 T-cell count (cells/mm^3), median (IQR)	581 (474-817)	561 (362-771)	.47
CD4 nadir T-cell count (cells/mm^3), median (IQR)	195 (22-312)	47 (25-358)	.84
CD8 T-cell count (cells/mm^3), median (IQR)	809 (489-1079)	689 (577-1035)	.50
Duration of HIV infection (months), mean (SD)	225.4 (117.6)	259 (94.3)	.27

[a]EXS: aerobic and resistance exercise.

[b]SIS: social-interaction stretching.

Discussion

Exercise interventions have demonstrated beneficial effects on physical fitness and brain integrity in middle-aged to older adults without HIV infection [4-7]. However, few studies have examined these relationships in people living with HIV. Adjunctive therapies designed to improve brain integrity are needed as the population of people living with HIV over the age of 50 years continues to grow and experience cognitive impairment and decline despite cART and well-controlled viremia. This study was designed to examine the effects of a 6-month exercise intervention on cardiometabolic risk, cardiorespiratory and physical fitness, cognitive performance, and neuroimaging metrics of brain integrity in a sample of sedentary people living with HIV aged ≥40 years on stable cART and who are virologically well controlled.

This study has several important strengths that underlie its potential contributions to the field of therapeutic interventions for older people living with HIV. First, this study recruits a sizeable sample of sedentary people living with HIV, primarily over the age of 50 years, to complete an exercise intervention or an attention control program involving stretching. To date, the few interventional studies examining effects of an exercise program in people living with HIV have included a relatively small number of individuals, limiting the generalizability of the results, and have primarily been conducted in younger (age ≤40 years) individuals. However, people living with HIV aged >50 years are estimated to make up over half of all individuals currently living with HIV in the United States [58] and are at a higher risk for cognitive impairment compared to younger individuals [59,60]. Additionally, this group of people living with HIV is well characterized in terms of physical health, blood inflammatory markers, cognitive ability, and brain imaging, allowing for in-depth analyses examining the effects of the EXS intervention on these outcomes. The 6-month duration of the intervention with midpoint data collection also allows for the potential capture of both acute and long-term effects of exercise on the brain in people living with HIV. Finally, the inclusion of a focus group will help inform future exercise programs for people living with HIV by assessing the feasibility of such programs barriers and facilitators for enrollment and retention, as well as predictors of successful adherence to the program.

This study design does have inherent challenges. Recruitment and retention are challenges for any prospective study requiring lifestyle changes for a long duration. Our inclusion and exclusion criteria require a participant to be healthy enough to safely participate in a 6-month supervised exercise program, limiting its generalizability; however, this requirement selects a population who are potentially the most likely to tolerate and complete the study intervention and therefore benefit from participation. Finally, the nature of the study may also introduce a recruitment bias into the sample, as people living with HIV who are willing and able to travel to the study site 3 times a week for 6 months during normal working hours may have baseline differences in socioeconomic status, physical health, and cognitive ability than people living with HIV who are not able to meet these requirements. However, by focusing recruitment on a diverse sample (eg, sex, race or ethnicity, education level, and cognitive ability) and by using group interviews to systematically assess these obstacles, we hope to broaden the generalizability of this intervention to a larger proportion of the population living with HIV. Results gained from this study will help inform clinicians as to possible benefits gained from prescribing an exercise program to middle-aged to older people living with HIV who may be experiencing cognitive issues, as well as help advise the development and implementation of future exercise programs for people living with HIV.

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Data Availability

The data sets generated and analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

WTC, DNR, FV, KEY, RHP, and BMA conceptualized the study and contributed to the writing of the manuscript. SAC, BMN, AR, and EW contributed to data collection, data processing, and writing of the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

1RM: 1-repetition maximum
BP: blood pressure
cART: combination antiretroviral therapy
CBF: cerebral blood flow
DXA: dual energy x-ray absorptiometry
EXS: aerobic and resistance exercise
HR: heart rate
HRR: heart rate reserve
MRI: magnetic resonance imaging
NP: neuropsychological
RoM: range of motion
SIS: social-interaction stretching
VO2 max: VO2 maximum

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Protocol

Motivational Interviewing for Enhancing Self-care in Patients With Heart Failure: Protocol for a Randomized Controlled Trial

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Abstract

Background: Heart failure (HF) is characterized by an increasing prevalence, representing a public health problem and a significant cause of morbidity and mortality. Self-care is a cornerstone approach for optimizing therapy for patients with HF. Patients play a crucial role in managing their condition, given that several adverse health outcomes might be avoided with adequate self-care. In this regard, the literature describes motivational interviewing (MI) as highly favorable for treating chronic diseases, with promising results supporting its efficacy in enhancing self-care. Moreover, caregivers' availability constitutes a fundamental supporting factor among the strategies to improve self-care behaviors in people with HF.

Objective: The primary study aim is to test the efficacy of a structured program, including scheduled MI interventions, in improving self-care maintenance in the 3-month follow-up from the enrollment. Secondary aims comprehend the assessment of the effectiveness of the above intervention on secondary outcomes (eg, self-care monitoring, quality of life, sleep disturbance) and the corroboration of the superiority of caregivers' participation to the intervention over the program administrated only to individual patients in enhancing self-care behaviors and other outcomes at 3, 6, 9, and 12 months from the enrollment.

Methods: This study protocol designed a prospective, parallel-arm, open-label, 3-arm, controlled trial. The MI intervention will be administered by nurses trained in HF self-care and MI; the education program will be provided to nurses by an expert psychologist. Analyses will be performed within the framework of intention-to-treat analysis. Comparisons between groups will be based on an alpha of 5% and 2-tailed null hypotheses. In the case of missingness, analyzing the extent of the missingness and identifying underlying mechanisms and patterns will guide imputation methods.

Results: The data collection was started in May 2017. We completed the data collection with the last follow-up in May 2021. We plan to perform data analysis by December 2022. We plan to publish the study results within March 2023.

Conclusions: MI enhances potential self-care practices in patients with HF and their caregivers. Although MI is effectively largely employed either alone or combined with other treatments and is administered in different settings and ways, face-to-face interventions seem to be more effective. Dyads with higher shared HF knowledge are more efficient in promoting self-care adherence behaviors. Moreover, patients and caregivers may perceive proximity with health care professionals, resulting in a

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better ability to follow the received health professionals' directions. The scheduled in-person meetings with patients and caregivers will be exploited to administer MI, respecting all the safety regulations for infection containment. The conduction of this study may support changes in clinical practice to include MI to improve self-care for patients with HF.

Trial Registration: ClinicalTrials.gov NCT05595655; https://clinicaltrials.gov/ct2/show/NCT05595655

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KEYWORDS

cardiology; cardiovascular; clinical trial; heart failure; motivational interviewing; randomized; heart; self-care; randomized controlled trial

Introduction

Heart failure (HF) is defined as "a clinical syndrome with symptoms and or signs caused by a structural and/or functional cardiac abnormality and corroborated by elevated natriuretic peptide levels and or objective evidence of pulmonary or systemic congestion" [1]. HF is characterized by an increasing prevalence and burden, representing a public health problem and a major cause of morbidity and mortality [1,2]. Globally, the overall estimated incidence of HF disease is 1-4 cases per 1000 person-years, with a prevalence of 10-30 cases per 1000 persons [3]. The incidence of the disease in Europe is about 5 per 1000 person-years, with a prevalence of 1%-2% in adults [4]. The prevalence of HF increases significantly with age: 6.6% of men with HF are aged 60 to 79 years, and 10.6% are aged 80 years and older [5].

Due to the impact of the disease, some authors have defined HF to be the "global outbreak" of the 21st century about 25 years ago [6,7]. An estimated 64.3 million people worldwide are affected by HF [7]; the growing and aging of the population, the high survival rate after an acute coronary event, and the effectiveness of secondary prevention and drug treatment result in a constant increase in the number of patients living with HF [4,7-9]. HF is most frequently diagnosed in patients who are hospitalized and 65 years and older [10]. People surviving at 1 and 5 years of follow-up have increased by about 20% compared to 1950-1970s [11]; however, 5-year mortality is still high, resulting in 24.4% for people aged 60 years and 54.4% for people aged 80 years [5].

Outcomes related to HF have improved in recent years [4]. Thus far, hospitalization and rehospitalization still impact the health care system; treating patients with HF costs US $30 billion every year, and this figure is destined to grow further, reaching US $70 billion by 2030 in the United States [5]. Once HF is first diagnosed, patients are readmitted to the hospital about once a year; this trend contributes to increasing health care resource consumption and worsens patients' quality of life (QoL) [7,12]. Moreover, HF is associated with considerable morbidity and mortality [13]. A 60- to 90-day mortality from diagnosis is about 10% in patients with HF; 1-year mortality is about 36% [14].

Self-care is a cornerstone approach for optimizing therapy for patients with HF [15]. Self-care is defined as an active, cognitive process through which people engage to maintain their health (self-care maintenance) and recognize and manage signs and symptoms (self-care monitoring and management, respectively) [16]. Precisely, self-care maintenance is defined by behaviors to preserve physical and psychological status, self-care monitoring encompasses behaviors about the ability to recognize signs and symptoms, and self-care management consists of the ability to manage signs and symptoms when they occur [17,18]. The consequences of inappropriate self-care behaviors can be dramatic, resulting in emergency hospital admissions, recurrent hospitalizations, and preventable complications. Poor adherence to treatments and improper disease management are the main causes of the exacerbation of HF [19-21]. In this regard, patients play a key role in the management of their condition, given that several negative health outcomes might be avoided with effective self-care [20,22].

Caregivers' availability constitutes a key supporting factor among the strategies to improve self-care behaviors in people with HF [23]. Studies involving patients with HF and their caregivers [24-26] report that self-care in HF is a "dyadic phenomenon" [27]: informal caregivers, such as a family member or a close friend, are fundamental in contributing to HF patients' self-care, as they provide tangible and emotional support and cooperation [23]. Caregivers tend to adapt their conduct based on patients' ability to care for themselves: they may act by reminding self-care behaviors or replacing the patient in the self-care process.

Many international studies have tested interventions to improve self-care in patients with HF involving caregivers to enhance the effectiveness of educational interventions [25,28,29]. Among the interventions reported in the literature, motivational interviewing (MI) has been described as highly favorable for treating chronic diseases, with promising results supporting its efficacy in enhancing self-care [30]. This intervention is a directive client-centered counseling approach for eliciting behavioral change by helping people to explore and resolve ambivalence. MI considers several critical factors in improving self-care in patients with HF and is based on brief interventions, which are feasible in several health care settings [30,31].

A recent study involving patients with HF and their caregivers tested the efficacy of MI in improving self-care maintenance, self-care management, and self-care confidence in adults with HF at the 3-month assessment after enrollment [32]. In this study, a 1-year follow-up was also performed, and the MI was performed only once. The influence exerted by caregivers on self-care behaviors employed by patients was also assessed using a 3-arm design [32]. More precisely, in the first arm, MI

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was administered to patients only; in arm 2, MI was administered to patients and caregivers; and in arm 3, participants received usual care (standard education). The study demonstrated that MI performed by trained nurses effectively improved self-care in patients with HF, especially in the arm where it was administered to both patients and caregivers [32]. However, the 1-year follow-up showed that the effects of MI on self-care confidence and on proxy measurement of specific self-care behaviors, such as physical activity and functioning, did not last over 3 months if administered only one time [32]. Similar results emerged from a recent meta-analysis [33].

Thus far, it is still unclear if administrating face-to-face MI more than once over 1 year might stabilize the positive effects of MI on self-care behaviors in patients with HF, and additional evidence is required to determine whether performing a MI on the dyad (patients and caregivers) is better than applying MI only to the individual patient [33]. For these reasons, this study protocol designed a prospective, parallel-arm, open-label, 3-arm, controlled trial for purposing the following aims: (1) to test the efficacy of a structured program including scheduled MI interventions in improving self-care behaviors (specifically, self-care maintenance) among patients with HF at 3 months from the enrollment; (2) to test the effect of a structured program including scheduled MI interventions on secondary outcomes (eg, self-care monitoring, QoL, sleep disturbance) at 3, 6, 9, and 12 months from the enrollment; and (3) to corroborate the superiority of the caregivers' participation to the structured program including scheduled MI interventions over the program administrated only to individual patients in enhancing self-care behaviors.

Methods

Trial Design

This is a prospective, parallel-arm, open-label, 3-arm, controlled, and superiority randomized controlled trial (RCT). This protocol was designed and reported following the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2013 statement: defining standard protocol items for clinical trials (see Multimedia Appendix 1).

Sample and Setting

Outpatients referred to the heart failure clinic and inpatients at discharge after hospitalization for HF will be enrolled in the study. The single center where the study will be implemented is the IRCCS Policlinico San Donato, northern Italy. The recruitment strategy will be based on enrolling patients continuously until the predetermined sample size is achieved.

Randomization, Allocation Concealment, and Blinding

Patients and caregivers will be randomized into 3 study arms by a computer software program that generates the random sequence. A simple randomization algorithm will be used to generate the sequences, and the randomization list will be concealed by using cloud-based software with restricted access only to the statistician who developed the randomization list and who will not be involved in the data analysis.

In the control group, patients receive MI, and caregivers receive traditional educational treatment. In the first interventional arm, MI will be used to reinforce the education of patients and caregivers will receive standard education. In the second interventional arm, MI will be used to reinforce self-care education in patients and caregivers. The standard educational approach will be adopted for all patients and caregivers and will be based on the preidentified informational materials about self-care in patients with HF.

The nature of the intervention does not allow researchers to employ the blindness of participants and investigators because the interventionist and the enrolled subjects will be aware of the allocated arm; in this regard, the study is considered open-label. However, blinding will be employed in the outcome assessment as the outcome assessors will have to follow predefined standard operative procedures that encompass their blinding in assessing self-care. Furthermore, blinding will be ensured during the data entry process and analytics. Data will be managed with the Research Electronic Data Capture (REDCap) platform, a secure, web-based software application and workflow methodology designed to collect and manage data for research studies.

Inclusion and Exclusion Criteria

The following inclusion criteria will be used for patients: being 18 years and older, diagnosis of HF with New York Heart Association (NYHA) Class II-IV, no acute coronary events within 3 months, consent to participate in the study, score ≤ 2 to at least 2 items of the Self-Care of Heart Failure Index 6.2 (SCHFI 6.2) at baseline [34], scores on Six Item Screener >4 [35], living at home, understanding of spoken and written Italian. The exclusion criteria for patients will be severe cognitive impairment (score 0-4 on the Six-item Screener) [35], acute coronary events that occurred within 3 months, living in nursing homes or residential settings, and caregivers unwilling to participate in the study.

The following inclusion criteria will be used for caregivers: being 18 years or older, being the primary informal caregiver identified by the patient, consent to participate in the study, and understanding of spoken and written Italian. Their unavailability will give the exclusion criterion for caregivers to participate in the study.

Instruments and Outcomes

The measurements for patients will be based on collecting sociodemographic and clinical characteristics data (eg, age, gender, NYHA class), SCHFI 6.2 [34], Heart Failure Somatic Perception Scale to assess patient's ability to feel the symptoms of HF [36], Six Item Screener to identify subjects with cognitive impairment [35], Kansas City Cardiomyopathy Questionnaire (KCCQ) to assess HF-specific QoL [37], Mutuality Scale (MS) to assess the feeling of intimacy and positive relationship between patient and caregiver [38], 12-Item Short Form Survey (SF-12) to measure generic health-related QoL [39], Pittsburgh Sleep Quality Index (PSQI) to assess sleep quality [40], Hospital Anxiety and Depression Scale (HADS) to detect depression and anxiety [41], Montreal Cognitive Assessment (MoCA) to detect

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mild cognitive impairment [42], and Charlson Comorbidity Index (CCI) to assess comorbidities [43].

The measurements for caregivers will be based on collecting sociodemographic data (eg, age, gender, marital status, and relationship with the patient), the Caregiver Contribution to Self-care of Heart Failure Index (CC-SCHFI) to measure the caregiver contribution to self-care in patients with HF [44], SF-12 [39], MS [38], Caregiver Preparedness Scale to assess how the caregiver feels prepared to care [45], HADS [41], Multidimensional Scale of Perceived Social Support to assess the level of social support perceived by patients with HF in managing the disease [46], and PSQI [40].

All the tools used to assess both patients' and caregivers' outcomes are constituted by validated and widely used instruments. The SCHFI 6.2 [34] is an instrument adopted to assess patients' self-care, which is the primary outcome. It is a widely used scale that comprises 3 subdimensions: self-care maintenance, self-care management, and self-care confidence. A 0 to 100 score can be attributed to each dimension; scores higher than 70 indicate an adequate self-care level. The SCHFI 6.2 [34] will also be used to assess the self-care maintenance at 6, 9, and 12 months from enrollment. Several additional secondary outcomes will be evaluated at a patient level using the measurements described below.

The Heart Failure Somatic Perception Scale is the instrument used to measure physical HF symptoms. It is an 18-item Likert scale that assesses the extension of the discomfort due to symptoms perceived by patients in the week before assessment. The score for each item can range from 0 (*I did not have the symptom*) to 5 (*extreme discomfort*). Once scores are summed, higher values indicate higher symptoms bothersomely.

The Six Item Screener [35] is adopted to identify cognitive impairment or dementia; patients' assessment using this tool requires a 3-item recall test, and it only takes 1 to 2 minutes to be administered: the subject should be able to repeat the 3 items initially and recall them after 5 minutes. The number of errors recorded in patients' answers is used as a cutoff point. The KCCQ [37] assesses physical function, symptoms, social function, self-efficacy, and QoL in patients with HF. The KCCQ is a 23-item Likert scale used to measure the health status responsive to changes in clinical condition. The KCCQ scoring regarding health status can range from 0 to 100: 0-24 indicates very poor to poor; 25-49 poor to fair; 50-74: fair to good; and 75-100 good to excellent.

The MS is a 15-item Likert instrument used to measure mutuality from the patient's or the caregiver's perspective. Each item can range from 0 to 4. The mean of all item scores constitutes the overall scale score; higher scores indicate better mutuality. The SF-12 [39] is a practical, reliable, and valid tool adopted to measure physical and mental health status. It is a 12-item short-form health survey with eight domains and 1 or 2 items per domain: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health. The Physical Component Summary (PCS) and Mental Component Summary (MCS) scores are composed of each health domain score. Scores range from 0 to 100; higher scores indicate better physical and mental health functioning. A score of 50 or less on the PCS-12 determines the physical condition; a score of 42 or less on the MCS-12 indicates "clinical depression."

The PSQI [40] is a self-report questionnaire used to screen patients for the presence of significant sleep disturbance experienced in the month before the assessment. The measure consists of 19 individual items, creating 7 components that are summed to obtain a global PSQI score ranging from 0 to 21; higher scores indicate worse sleep quality. The HADS [41] is a 14-item measure used to detect anxiety and depression in patients. Items are rated on a 4-point scale. The HADS produces 2 scales, 1 for anxiety (HADS–A) and 1 for depression (HADS–D); anxiety and depression are confirmed by scores equal to or greater than 11.

The MoCA is used to detect mild cognitive dysfunction. It assesses different cognitive domains: attention and concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation. Scores on the MoCA range from 0 to 30; a score of 26 and higher is considered normal. The CCI [43] predicts 10-year survival in patients with multiple comorbidities. The updated index of 12 comorbidities predicts in-hospital mortality; the severity of comorbidity is categorized into 3 grades: mild, moderate, and severe, with CCI scores of 1-2, 3-4, and ≥5, respectively.

The following tools have been used to evaluate the caregivers' specific secondary outcomes. The CC-SCHFI [44] comprehends 10 items that assess the caregiver's contribution to maintaining a stable condition and 10 items that assess the caregiver's ability to monitor and recognize symptoms of HF decompensation, implement adequate treatments, evaluate those treatments, and help patients to take part in each phase of the self-care process. Each measure uses a 4-point Likert response scale with a score from 0 to 100; higher scores indicate a higher contribution to self-care.

The Caregiver Preparedness Scale is an instrument that consists of 8 items that ask caregivers how prepared they feel to handle multiple domains of caregiving. Responses are rated on a 5-point Likert scale with scores ranging from 0 to 4. The scale is scored by calculating the mean of all items. Higher scores indicate higher caregiver preparedness. The Multidimensional Scale of Perceived Social Support is a 12-item scale of perceived appropriateness of the support offered by family, friends, and significant other. The measure uses a 5-point Likert scale. The score can range from 12 to 84, and a higher score indicates greater social support perceived by the caregiver.

Intervention and Participant Timeline

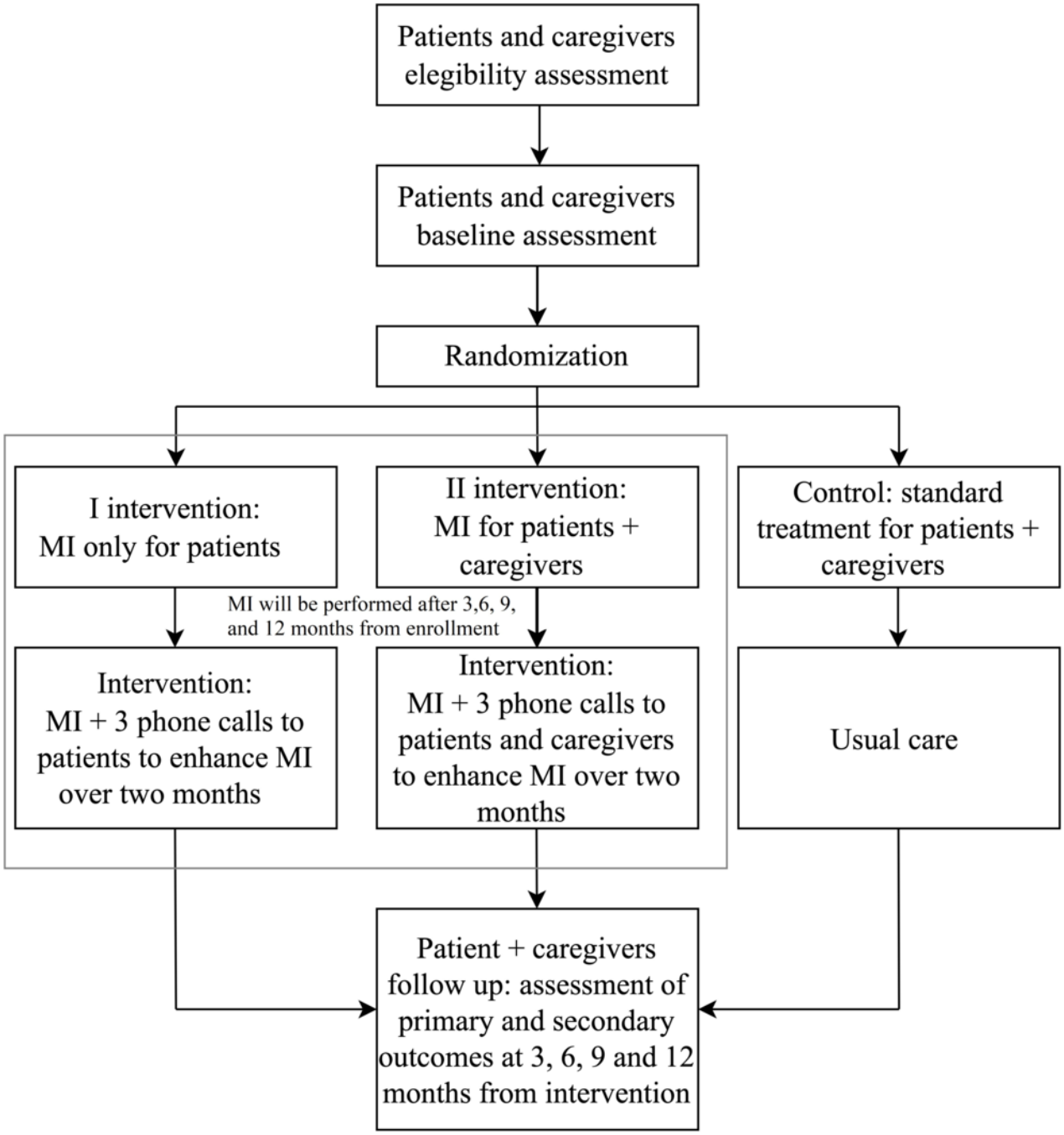
All patients meeting the inclusion criteria and not any exclusion criteria will be randomized by the researchers responsible for the study after having signed a consent form. Patients will be informed about the single allocation and will not be aware of the randomization list and allocation sequence. The intervention will be administered by nurses trained in HF self-care and MI.

The study flowchart is shown in Figure 1. In the first interventional arm, the MI intervention will be administered to patients only, and caregivers will receive standard education.

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MI is used to reinforce areas of inadequate self-care (eg, low physical activity or not having a low-salt diet) and to agree with the patients on the steps to be adopted to modify their behavior. MI focuses on a tailored patient approach to improve patients' adherence to self-care behaviors. The intervention will last approximately 30 minutes. Thereafter, the nurse who performed the MI will contact the patients over the phone 3 times every 2 weeks from the first MI during the first 2 months after MI to strengthen the intervention. Then, the intervention will be used again after 3, 6, 9, and 12 months from enrollment. After each MI session, both patients and caregivers will be asked to complete the follow-up questionnaires post enrollment as described in the "Instrument" section. In the second interventional arm, MI intervention will be administered both to patients and caregivers. The intervention will be administered to the dyad in 1 session, and patients and their caregivers will receive the reinforcing educational treatment calibrated on the specific lacking areas of patients' self-care behaviors. After each MI session, both patients and caregivers will be asked to complete the follow-up questionnaires post intervention. In the control group, the dyads will receive only traditional educational treatment and complete the questionnaires after 3, 6, 9, and 12 months of follow-up post intervention. Enrolled dyads will be monitored by the research team responsible for recruitment and follow-up.

Figure 1. Study flowchart. MI: motivational interviewing.



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Training for Nurses

Nurses will participate in a training program to acquire the competence to conduct a MI. The education program will be provided to nurses by an expert psychologist.

Sample Size Calculation

For determining sample size, based on a recent literature review [33], it was hypothesized that both experimental arms would show an improvement in self-care maintenance, and the adequacy of self-care maintenance scores in the experimental arm was shown in approximately 50% (n=250) of patients. Current Italian data indicated that roughly 20% (n=238) of Italian adults with HF reported adequate scores of self-care maintenance (scores higher than 70 are considered adequate) [47,48]. For this reason, the sample size estimation was based on a 2-sample proportions test: the expected proportion in experimental arms was equal to 50% of adequate scores (proportion 1) versus 20% of the adequate score in the control group based on the current descriptive literature (proportion 2, delta=30%). Setting alpha at .05 and power at 0.90, the number per group to identify significant differences was equal to 52. Therefore, as the study has 3 arms, 156 participants are required to test the differences in proportions between groups. Given the likelihood of a 15% rate of dropouts as per previous studies [32], the total sample size was equal to 180 diads (n=60 per arm). A consecutive screening and enrollment will be performed.

End Points

The end points of this study are designed for the specific aim focused on testing the efficacy of a structured program, including scheduled MI interventions, in improving self-care maintenance. Precisely, the primary end point is the difference between self-care maintenance levels between the 2 groups in the 3-month follow-up. The secondary end points are the differences between self-care maintenance, self-care monitoring, and self-care management at 6, 9, and 12 months of follow-up after enrollment.

Statistical Analysis

Analyses will be performed within the framework of intention-to-treat analysis. Sociodemographic and clinical characteristics will be summarized and compared between groups in the baseline. For the primary end point, the differences between proportions of adequate self-care maintenance in the 3-month follow-up will be assessed using the chi-square test (or the Fisher exact test if adequate) and performed to compare the first experimental arm (MI delivered only to patients) and control group and between the second experimental arm (MI delivered to the dyad) and control group.

In addition, beyond the comparison between proportions aimed to detect clinically meaningful differences between groups, the standardized 0-100 scores of self-care maintenance will be compared using a 1-way ANOVA with post hoc comparisons adjusting the significance according to Bonferroni. A stepwise logistic regression model based on a dichotomic outcome (adequate self-care vs inadequate self-care scores) will be used to encompass the effects of clinical and sociodemographic covariates in determining the association between the group and the proportion of adequate self-care. The first step of the stepwise approach will include the trial group as an independent variable to determine the odds ratios, highlighting the associations between each group and the dichotomic outcome. The second step will allow authors to include the covariates that show significant linear relationships with the outcome to adjust the associations described in the first step. This model will be evaluated using goodness-of-fit tests, such as the Hosmer-Lemeshow test. The same approach will be used by considering the standardized 0-100 scores of self-care maintenance as the dependent variable and, therefore, in the framework of multiple linear regression. While the logistic regression will provide an association between the adequacy of self-care maintenance and the arm by accounting covariates for adjusting the estimate, the multiple linear regression will highlight the amount of variance explained by belonging to each arm, accounting for the same covariates used in the logistic regression.

The analytical strategy for testing the secondary end points will be the same adopted for the primary end point. In addition, in the framework of time-to-event analysis, the cumulative probability of shifting from inadequate to adequate self-care (ie, the event will be defined as each shift from self-care maintenance scores under 70 to scores equal to or greater than 70) at 6, 9, and 12 months of follow-up after enrollment will be described using Kaplan-Meier curves and inferentially tested using log-rank tests.

The aims focused on testing the effect of the structured program based on MI interventions on secondary outcomes (eg, self-care monitoring, QoL, sleep disturbance) at 3, 6, 9, and 12 months from the enrollment and corroborating the superiority of the caregivers' participation to the MI interventions over the MI interventions administrated only to individual patients in enhancing self-care behaviors are not used for determining specific end points. Therefore, the analytical plan for assessing those aims will be based on exploratory analyses based on comparing the secondary outcomes scores between the study arms.

In the case of missingness, analyzing the extent of the missingness and identifying underlying mechanisms and patterns will guide imputation methods. If missing at random criteria will be plausible, multiple imputations based on random effect models will be considered for missingness >5% of the outcome assessments at each time point of the trial. Inferential analyses will be based on an alpha of 5% and 2-tailed null hypotheses using Stata 17 (StataCorp).

Ethical Considerations

The study protocol and template consent forms have been reviewed and approved by the Ethical Committee of San Raffaele Hospital (approval #74/INT). Also, the study protocol has been registered at ClinicalTrials.gov (NCT05595655). Any amendments to the protocol will be submitted to the committee. Patients and caregivers will have to sign the informed consent forms before the randomization. Patients and caregivers may leave the study at any time. The withdrawal from the study will not imply any prejudice, as fully documented and explained in the informed consent. The full protocol will be available freely.

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Results

The data collection was started in May 2017. We completed the data collection with the last follow-up in May 2021. We plan to perform data analysis by December 2022. We plan to publish the study results within March 2023.

Dissemination

Data collected during the study will be considered the property of the principal investigator and the promoter. Participants' sensitive data will be processed according to the current privacy legislation. Study results may be published in peer-reviewed journals or submitted to relevant national and international conferences. The data monitoring committee will be constituted of professional monitors identified by the institution and the principal investigator. The monitoring process will encompass all the procedures to guarantee proper transparency and study conduction. No competing interests will be presented by the data monitoring committee.

Discussion

The general aims of this RCT will be to test the effectiveness of a program of MI interventions in improving self-care behaviors among patients with HF and the caregiver's contribution to self-care and to assess the extent to which caregivers' participation in a program of MI interventions impacts on enhancing self-care behaviors employed by patients. Moreover, this study aims to describe the patient's clinical course and to evaluate the persistence of the results achieved over 1-year time. Several secondary outcomes resulting from questionnaires administered to patients and caregivers will be considered as well, such as sleep quality [40] or HF-specific QoL [7]. Although this study may seem like the Motivational Interviewing to Improve Self-care in Heart Failure Patients (MOTIVATE-HF) study [32], we would like to highlight a difference detectable in the intervention setting administered to patients and caregivers. In fact, in this RCT the interventionist will meet up with the dyad 5 times over 1 year, while in the MOTIVATE-HF study [32] the dyad met up face-to-face with the interventionist only once, and the intervention was bolstered via phone calls. We believe that an intervention including more face-to-face administration would be more powerful in acting on the outcomes of interest.

Although MI is effectively largely used either alone or combined with other treatments and is administered in different settings and ways (ie, patients' homes; over the telephone; and in hospitals, clinics, or nursing homes), face-to-face interventions seem to be more effective [49]. There is rationale to believe that a more intensive intervention program would even ameliorate and better support patients' self-care behaviors. Moreover, involving caregivers in this intensive intervention program would make them feel more participatory and aware of the patient's care process, recognizing their pivotal role in disease management and enhancing their knowledge about HF disease. Besides, dyads with higher shared HF knowledge are more efficient in promoting self-care adherence behaviors [29]. Moreover, both patients and caregivers may perceive proximity with health care professionals, resulting in a better ability to follow the received health professionals' directions [50]. Self-care is built up on attitudes, behaviors, knowledge, and self-efficacy, and the literature suggests that HF self-care management is more challenging than self-care maintenance and is enhanced by the presence of a caregiver who needs to be properly trained and involved [50,51].

This study protocol presents some limitations that need to be pointed out. First, the monocentric design could affect the generalizability of the results, and the nature of the intervention does not permit a double-blind study design. Moreover, the rather short follow-up (1 year) does not give correct estimates of the lifetime effects of the intervention. Lastly, study participants might be healthier than the average person with HF, as they are usually health conscious with a better lifestyle.

The COVID-19 pandemic still causes mobility restrictions for the population to control infection spread; in particular, people living with a disease, such as patients with HF, are forced to be followed up with remotely by health care professionals to reduce the risk of infection [52,53]. This paradigm shift based on telemedicine and remote monitoring may be fundamental to preventing HF from worsening during circumstances discouraging outpatient visits [52]. However, when circumstances permit, patients' encounters with health care professionals are recommended to guarantee a periodic proper assessment for early signs of worsening disease [54]. The in-person meetings with patients and caregivers will be exploited to administer MI, respecting all the safety regulations for infection containment.

Conclusion

MI potentially enhances self-care practices in patients with HF and their caregivers. The conduction of this study may support changes in clinical practice to include MI to enhance the self-care of patients with HF.

Acknowledgments

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Data Availability

All data relevant to the study are available on reasonable request to the corresponding author.

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Authors' Contributions

FD and RC conceptualized the study. All authors developed the first draft of the manuscript and are involved in the data collection. All authors contributed to the development of the study protocol and approved the final draft of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2013 checklist.
[PDF File (Adobe PDF File), 92 KB - resprot_v12i1e44629_app1.pdf]

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Abbreviations

CCI: Charlson Comorbidity Index
CC-SCHFI: Caregiver Contribution to Self-care of Heart Failure Index
HADS: Hospital Anxiety and Depression Scale
HF: heart failure
KCCQ: Kansas City Cardiomyopathy Questionnaire
MCS: Mental Component Summary
MI: motivational interviewing
MoCA: Montreal Cognitive Assessment
MOTIVATE-HF: Motivational Interviewing to Improve Self-care in Heart Failure Patients
MS: Mutuality Scale
NYHA: New York Heart Association
PCS: Physical Component Summary

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PSQI: Pittsburgh Sleep Quality Index
QoL: quality of life
RCT: randomized controlled trial
SCHFI 6.2: Self-Care of Heart Failure Index 6.2
SF-12: 12-Item Short Form Survey
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Protocol

Management of Hypertension Using a Plant-Based Diet Among Farmers: Protocol for a Mixed Methods Study

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Abstract

Background: Farmers in Indonesia have a high risk for hypertension owing to their lifestyle and working environment. Diet management is a solution to reduce hypertension, and Indonesia has natural resources in the agricultural sector that could help manage hypertension. Optimizing vegetable and fruit intake in a plant-based diet (PBD) could help maintain blood pressure among farmers in Indonesia.

Objective: This study aims to explore the health problem of hypertension and the characteristics of local food sources to formulate a PBD menu for treating hypertension, as well as assess the prevalence of hypertension, level of acceptability of a PBD, and associated sociodemographic factors. Further, we want to examine the effectiveness of a community-based nursing program for managing hypertension using a PBD.

Methods: We will use the exploratory sequential mixed methods approach. There will be a qualitative study (phase I) in 2022 and a quantitative study (phase II) in 2023. We will analyze data using a thematic framework in phase I. In phase II, the study will involve (1) questionnaire development and validation; (2) examination of the prevalence of hypertension, the level of acceptability of a PBD, and the associated factors; and (3) a randomized controlled trial. We will recruit farmers with hypertension who meet the study criteria. Moreover, in phase II, we will invite expert nurses and nutritionists to assess the face and content validity of the questionnaire. We will use multiple logistic regression models to estimate the associated sociodemographic factors and the level of acceptability of a PBD. Furthermore, a linear generalized estimating equation will be used to estimate the parameters of a generalized linear model with a possible unmeasured correlation between observations from different time points for systolic and diastolic blood pressure.

Results: A model PBD for hypertension management is expected to be developed. In 2022, we will collect information on hypertension and the characteristics of local food sources for managing hypertension, and will formulate a PBD menu to treat hypertension among farmers. In 2023, we will develop a questionnaire to assess the acceptability of a PBD to manage hypertension among farmers, the prevalence of hypertension, and the sociodemographic factors associated with hypertension among farmers. We will implement a community-based nursing program for managing hypertension using a PBD among farmers.

Conclusions: The PBD model will not be readily available for other agricultural areas since validation of local food variation is required to design the menu. We expect contributions from the local government to implement the intervention as one of the policies in the management of hypertension for farmers in the agricultural plantation areas of Jember. This program may also be implemented in other agricultural countries with similar problems, so that hypertension can be optimally treated among farmers.

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KEYWORDS

hypertension; farming; plant-based diet; nursing

Introduction

Hypertension contributes to 12.8% of the total 7.5 million deaths worldwide [1]. The prevalence of hypertension in Indonesia is 33.4% [2], while in East Java province, it is 20.43% [3]. Farming communities have a high risk of health problems [4], including hypertension [5-7]. Hypertension among farmers in Indonesia has reached 36.1% [8]. Our previous study found that the incidence of hypertension among farmers in agricultural areas was 35.8% [9]. This shows the magnitude of the problem of hypertension among farmers, and there is a need for the management of care using an agricultural health nursing (agronursing) approach to realize the health status of farmers.

Agronursing can facilitate occupational health and safety among farmers [9]. Farmers' health problems are generally caused by a lack of knowledge and skills in health management, which can lead to hypertension [10]. Most farmers with hypertension have a low level of education, so skills in self-care management are lacking [11]. Hypertension among farmers is also caused by an unhealthy lifestyle [9] and inadequate nutrition [12]. High consumption of unhealthy foods among farmers, such as high-sodium foods [6], and low knowledge about diet [13] can increase the risk of hypertension in farmers. Therefore, dietary management with a plant-based diet (PBD) needs to be introduced, and the basic principles of hypertension nursing care for farmers need to be developed.

Natural agricultural resources should be considered in the management of hypertension among farmers. The basic principles of hypertension care among farmers should be developed through optimizing the agricultural sector's potential by consuming a PBD that prioritizes vegetables and fruits [14]. Therefore, it is necessary to formulate the basic concepts and principles of a PBD in nursing care management for farmers with hypertension based on the agronursing approach.

The agronursing approach to treat hypertension among farmers focuses on promotive and preventive measures to reduce the risk of disease occurrence or disease worsening from previous conditions [15]. Moreover, it focuses on the health status of individuals in carrying out their work (in this case, farmers who work in fields) in order to improve overall health (physically, mentally, and socially) [16]. The PBD concept is expected to be able to overcome the problem of hypertension among farmers in agricultural areas, which is synergistic with the culture and local wisdom of the agricultural population. Therefore, the objectives of this study are as follows: (1) to explore the health problem of hypertension among farmers and the characteristics of local food sources of vegetables and fruits that can be used in a PBD to manage hypertension; (2) to examine the prevalence of hypertension, the level of acceptability of a PBD, and the associated factors among farmers; and (3) to examine the effectiveness of a community-based nursing program for the management of hypertension using a PBD among farmers.

Methods

Study Overview

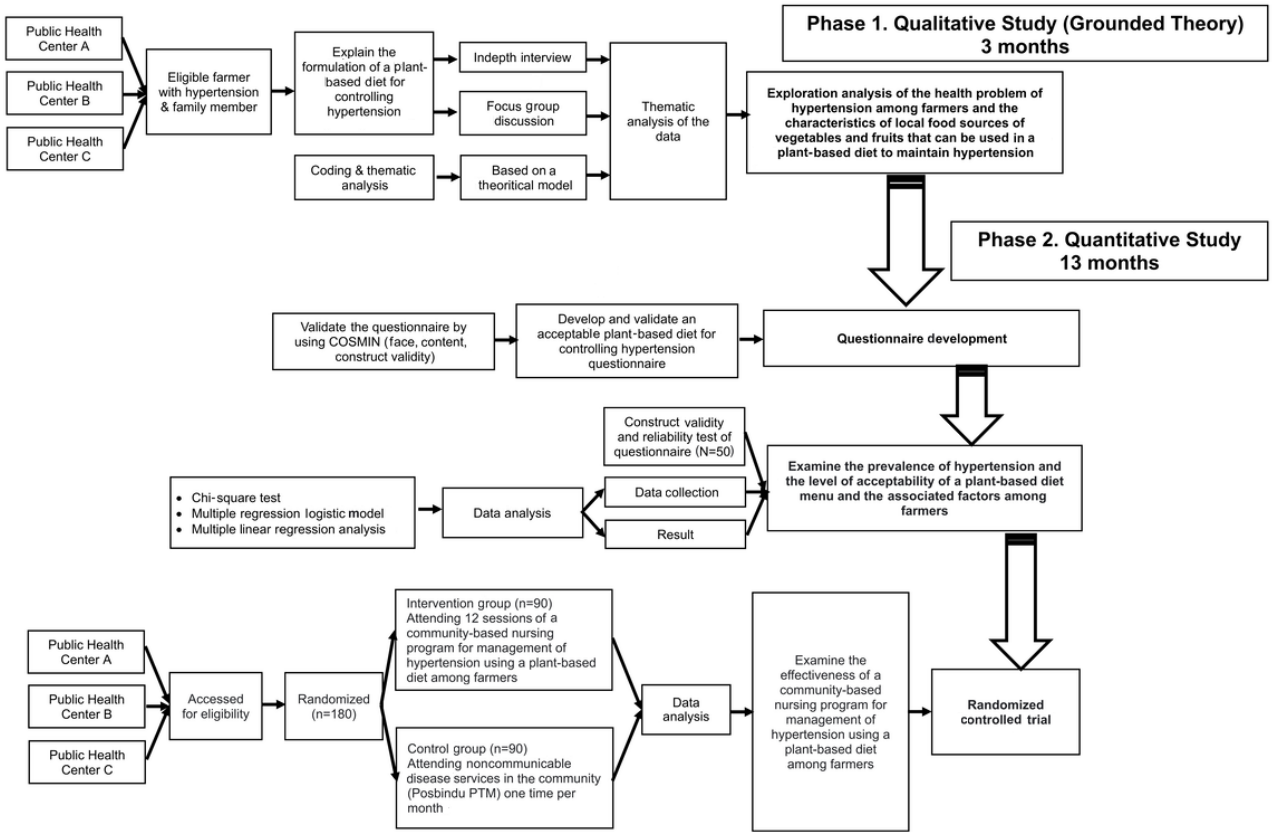
The exploratory sequential mixed methods approach will be used to achieve the research objectives in the following 2 phases: qualitative study (phase I) and quantitative study (phase II) (Figure 1). In phase I, we will explore the health problem of hypertension among farmers and the characteristics of local food sources of vegetables and fruits that can be used in a PBD to manage hypertension through semistructured interviews. Then, we will formulate a PBD menu to treat hypertension among farmers.

In phase II, we will conduct a quantitative study. In this phase, the following 3 activities will be performed: (1) we will develop and validate a questionnaire as the assessment instrument; (2) we will examine the prevalence of hypertension, the level of acceptability of a PBD, and the associated sociodemographic factors among farmers; and (3) we will examine the effectiveness of a community-based nursing program for managing hypertension using a PBD among farmers.

This study will use farmers with hypertension and their families in the planning of phases I and II.

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Figure 1. Study overview. COSMIN: consensus-based standards for the selection of health measurement instruments; Posbindu PTM; Pos Pembinaan Terpadu Penyakit Tidak Menular.



Phase I: Qualitative Phase

Overview

We will perform a semistructured interview involving farmers with hypertension and the family members of eligible participants to address the research objectives. The qualitative study will provide insights on health problems related to hypertension and the characteristics of local food, and will help formulate a PBD to control blood pressure from the perspective of agricultural health nursing care services. After undergoing training in conducting qualitative studies, 5 investigators (TS, HR, FK, IR, and RAY) will conduct interviews in the field.

Setting

This study will recruit eligible participants selected from 3 public health centers (PHCs) in Jember, East Java Province of Indonesia. Jember, East Java Province is a province representing Indonesia's agricultural sector. It is known that Jember Regency is an agricultural area, and most of its people make a living as farmers or work in agriculture. The agricultural land in Jember Regency is very fertile. Therefore, most land in Jember Regency is used for agriculture and plantations. This is very suitable as the main livelihood of the people of Jember Regency is related to the agricultural sector.

Jember Regency is considered one of the rice barns of East Java Province, reflecting that the agricultural sector plays an important role (leading sector) in the economy of Jember Regency, and it can be said that Jember has an agrarian economic structure. Since Jember's economy is generally based on agriculture, the maintenance and management of natural resources are very important, and it is hoped that the economic development carried out is oriented toward environmentally sound development. Regarding cultivations, all areas except the city center have food crops; the slopes of Mount Argopuro have plantations of tea, coffee, cocoa, and rubber; the slopes of Mount Raung have plantations of coffee and tobacco; and central to southern areas have plantations of tobacco, sugarcane, and coconut. In Jember, 42.9% of the population has jobs in agriculture [17]. Based on data [18] released by BPS Kabupaten Jember, the population of Jember Regency in 2020 was projected to reach 2,536,729 people, consisting of 1,264,968 male residents and 1,271,761 female residents, and the population density in Jember Regency in 2020 reached 770.26 people/km^2.

Participants

The inclusion criteria for recruiting the purposive sample are as follows: (1) farmers aged 20-65 years from other parts of East Java Province, Indonesia (citizens) living in 3 PHCs of Jember; (2) residents living in 3 PHCs of Jember; (3) those with hypertension; (4) those who consume fruits and vegetables to control their blood pressure; (5) those who attend the Integrated Health Center (IHC) for noncommunicable diseases (NCDs) in the community; and (6) those having and living with family for care provision. We will exclude older people who are not citizens of Indonesia and those who are unwilling to be interviewed or unable to communicate clearly due to language problems. To obtain more insights on the acceptability of a PBD, the family members of eligible farmers with hypertension will be included in the interview. The inclusion criteria are as

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follows: (1) employment as a farmer; (2) age 45-65 years; (3) presence of grade I/II hypertension according to the Eighth Joint National Committee on Prevention, Detection, and Treatment of High Blood Pressure (JNC VIII) criteria; and (4) presence of relatives who stay in the same house with their parents or take care of their parents by helping them with preparing food or assisting them in daily routines. We will exclude farmers with hypertension having other chronic diseases (diabetes mellites, chronic kidney disease, heart disease, and stroke).

Sampling Process

Phase I is estimated to last 3 months. The snowball sampling method will be used to recruit participants. The investigators (TS, HR, FK, IR, and RAY) will recruit participants in Jember based on the inclusion and exclusion criteria. The interviewees will be asked to recommend other eligible participants among farmers and their family members who wish to participate in this research. Investigators will contact eligible participants to explain the study details, confirm their interest in participating, and determine their preferred interview method (eg, individual interview or focus group discussion). Payment of US $10 will be made to participants for participating in this study (online transfer to their bank accounts).

Data Collection

Phase I will involve the following 2 data collection methods: in-depth interviews and focus groups using semistructured interview guides. Further, in-depth interviews may be conducted with certain respondents who have attended the previous focus group interviews to gain more perspectives and clarify the focus groups' findings. Each focus group will consist of 4 to 6 participants. An earlier scoping review conducted by the same research team will help identify health problems related to hypertension among farmers. Then, we will explore the characteristics of local food sources to manage hypertension and formulate a PBD. The findings will provide additional information for developing the interview guides and questions (eg, "Can you describe your health problem related to your hypertension?" "How would you control your blood pressure with a plant-based diet?" "What kinds and contents of local foods would you use for controlling hypertension?" "How would you formulate a plant-based diet menu to control hypertension?" "What do you expect from a plant-based diet?" and "Would you adopt a plant-based diet? If yes, why? If no, why not?"). The preliminary semistructured interview guides, which contain open-ended questions and probes to explore the acceptability of a PBD, will be pilot tested.

We plan to interview the farmers and the family members of eligible farmers with hypertension. We will recruit 30 participants initially, but the final sample size for this qualitative study will be determined when data saturation is reached, for example, when additional data collection reveals no substantial new information. Each in-depth interview will take between 30 and 45 minutes, and the focus group interview will take around 45 to 60 minutes. Before the interviews, participants will provide their sociodemographic and related information, such as age, education, occupation, income, insurance, and health condition. Information about this research, including the hypertension problem and the characteristics of local foods used in a PBD, will be explained to all participants in Bahasa Indonesia before they are asked to provide informed consent. All interviews will be conducted in the Bahasa Indonesia language and will be audio recorded. Investigators will take down field notes, and transcripts will be translated line by line into English. All data will be translated into English to allow discussions with non-Indonesian researchers.

Qualitative Data Analysis Plan

Interviews will be video recorded, and all data will be transcribed verbatim. Data in Bahasa Indonesia will be translated into English for co-investigators who are only proficient in English. Qualitative data will be analyzed to identify a thematic framework [19], guided by a theoretical model of a PBD for controlling hypertension in farmers [20]. The emerging codes will be analyzed thematically according to the framework if they are coherent. The team members will repeatedly read each document and transcript to familiarize themselves with the whole data set and ensure the accuracy of the transcription reviews. Codes will be applied to raw data and then grouped into clusters to generate themes. Consensus on the codes and themes must be reached among at least three of the investigators (TS, HR, FK, IR, and RAY). The data will be compared in an ongoing manner to identify the true meaning of the data. Member checking and investigator reflexivity will be used to increase the credibility and reliability of the data. Data credibility will be enhanced through further analysis of interview and field notes, and views from the different categories of farmers having different sociodemographic backgrounds (eg, those with different grades of hypertension), as well as through triangulation involving multiple investigators. The content of the interviews will be shared with some participants, and their feedback on the findings will be sought for validation purposes (respondent validation). Investigators involved in the data analysis will collect and explain their biases or assumptions during data analysis and interpretation (reflexivity). Raw data, interpretations, and conclusions will be discussed with peers (peer debriefing). Confirmability will be enhanced by keeping an audit trail of the audio/video files, electronic documents, original field notes, and translations [21].

Phase II: Quantitative Phase

Activity 1: Questionnaire Development and Validation

Overview

In activity 1, we will develop a questionnaire of an acceptable PBD for controlling hypertension, according to the qualitative data in phase I. The quotations from raw data will become questionnaire items, themes will become scales, and codes will become variables. A Likert score will be used for measurement (range of 1 to 4 points), which will determine the levels of expectations and acceptability. Based on the scores of the items or the summed scores, expectations and acceptability can be categorized into the following 3 categories: affordable, accessible, and achievable. Categorization will be performed using a statistical formula. If the data are normally distributed, the grade level will be based on the mean value; otherwise, the median will be used ($X <$ mean/median – 1 SD; mean/median – 1 SD $< X <$ mean/median + 1 SD; mean/median + 1 SD $< X$).

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The questionnaire will have the following 2 sections: (1) sociodemographic characteristics of hypertension and (2) acceptable PBD for controlling hypertension. The instructions and descriptions of the definition, concept, and criteria of a PBD will be provided at the beginning of the questionnaire. The Pender Health Promotion Model will guide the questionnaire's qualitative analysis and item design. After performing a member check and assessing face and content validity with an expert committee, we expect the final version of the questionnaire. The expert committee will include investigators with expertise in qualitative research (HR), statistical analysis (FK), public health (TS), and research methodology (RAY and IR).

Validation and Reliability

A cognitive debriefing involving 10 people to further assess the face and content validity of the questionnaire will be performed (5 expert nurses on hypertension and 5 nutritionists). Feedback will be discussed by the expert committee, and it will determine the appropriateness and completeness of the questionnaire and ethical considerations in the process. The next analysis step is the COSMIN (consensus-based standards for the selection of health measurement instruments) checklist developed in an international Delphi study to estimate the quality of selected measurement instruments. It measures internal consistency, reliability, measurement error, content validity (as well as face validity), structural validity, hypothesis testing, cross-cultural validity (the 3 aspects of construct validity), criterion validity, and responsiveness. Based on the checklist, items will be sorted by experts in the group to establish face, content, and construct validity in activity 1. The duration to finish the questionnaire is estimated to be less than 30 minutes. Further validation of the questionnaire will be conducted in activity 2. Cronbach alpha will be applied to prove the internal consistency (0.70 or higher is considered as good) of the expectations and acceptability questionnaire. Exploratory factor analysis using principal component analysis will be performed to examine the structural validity of the expectations and acceptability questionnaire separately.

In addition, the Kaiser-Mayer-Olkin test of sampling adequacy, the Bartlett test of sphericity, and the scree plot will be used to check the unidimensionality of the expectations and acceptability questionnaire. The convergence criteria will be set at an eigenvalue above 1. Construct validity (hypothesis testing) will be tested when comparing the responses to the expectations or acceptability of 1 item (yes or no). We hypothesize that the highest tertile expectation will be associated with willingness measured by a repeat measurement value of at least 2.0. The highest tertile acceptability will be related to willingness measured by a repeat measurement value of at least 3.0. It is also hypothesized that expectations and acceptability will correlate at a coefficient of at least 0.4. One-month intrarater test-retest reliability will be assessed in a random sample of at least 50 older people throughout the data collection period in activity 2.

Activity 2: Survey

Overview

In activity 2, we will conduct a survey to identify the prevalence of hypertension, the level of acceptability of a PBD, and the associated sociodemographic factors among farmers. We will use the questionnaire developed in activity 1. Written informed consent will be obtained, and each participant will be required to indicate agreement for participation before filling out the questionnaire and submitting it.

Setting

To obtain a representative sample according to the criteria that have been set, we will select 3 PHCs located in agricultural areas in Jember, East Java, Indonesia. The PHCs we have selected include Banjarsengon, Sukorambi, and Panti. There are quite a lot of farmers in the Panti area, with 14,322 active farmers having quite complex hypertension problems [22]. Farmers in Banjarsengon and Sukorambi also show a similar condition. These 3 PHCs are expected to have a sufficient number of farmers with hypertension who could respond and complete the questionnaire.

Participants

The criteria for recruiting our representative sample are as follows: (1) farmers aged 20-65 years from other parts of East Java Province, Indonesia (citizens) living in 3 PHCs in Jember; (2) residents living in 3 PHCs in Jember; (3) those with grade I/II hypertension according to the JNC VIII criteria; (4) those who attend the IHC for NCDs in the community; and (5) those having and living with family for care provision. We will exclude (1) farmers with psychiatric disorders that may impair their ability to answer or complete the questionnaires and (2) farmers with cognitive impairment.

Sample Size Estimation

The sample size will be determined based on a G*Power analysis. Since no previous similar study has been conducted, this study takes the best estimate of the minor difference in the proportion of expectations and acceptability of a smart nursing home among elderly people to be at 10%. Using G*Power 3.1.2 (Institute for Experimental Psychology in Dusseldorf Germany) with 0.90 power and significance at a 2-sided α of .05, the estimated sample size is 263.

Measures

To meet the study objectives, the questionnaire will consist of the following sections: (1) sociodemographic characteristics and (2) the level of acceptability of a PBD to treat hypertension among farmers. The sociodemographic characteristics will include age, gender, marital status, education (no formal education, elementary school, middle school, and high school or higher), household monthly income per capita (less than US $65.82, US $65.82-131.65, US $131.66-197.47, and over US $197.47), duration of hypertension (years), grade of hypertension based on the JNC VIII criteria, and living condition (with children or a spouse). In section 2 of the questionnaire, a 4-point Likert scale will be used to assess the level of acceptability of a PBD to treat hypertension among farmers. Expectations will be measured as follows: 1, strongly disagree;

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2, disagree; 3, agree; and 4, strongly agree. A higher score will indicate a higher level of acceptability of a PBD to treat hypertension among farmers. The association of sociodemographic factors with the different categories of expectations and acceptability will be determined through statistical analysis.

Sampling Process

Representative research respondents will be selected by collecting available data on public health services. Farmers with hypertension are listed as regular patients in the Posbindu PTM (Pos Pembinaan Terpadu Penyakit Tidak Menular) program of the public health services. The data obtained will be assessed in a random process to select respondents using a simple random sampling technique. We will use a randomizer application that is available online to select respondents. Respondents selected from the randomizer application will then be included in the list of research respondents. We will follow the activities of the Posbindu PTM program as well as meet with research respondents who have been selected to be able to collect research data. We will print out the questionnaire and give it to the research respondents to fill out. Our team will assist farmers in filling out questionnaires to ensure that the questionnaires given are filled out completely and accurately.

Analysis Plan

The data from the questionnaire will be inputted into SPSS (IBM Corp) for analysis. We will perform data cleaning to check each data point from the questionnaire and ensure there are no missing data from the entire questionnaire. We will only use completed questionnaires for analysis. After the data cleaning process is complete, we will perform the data analysis process.

We will use descriptive statistics to describe the characteristics of the respondents and the level of acceptability of a PBD to treat hypertension among farmers according to data distribution. Numerical variables will be shown as means and standard deviations or medians and interquartile ranges, while categorical variables will be shown as absolute frequencies and percentages. We will use the chi-square test to examine the sociodemographic factors associated with farmers' different categories of acceptability. With the 95% CI, a *P* value of <.05 will be considered statistically significant.

We will use multiple logistic regression models to estimate the associated and independent factors from the sociodemographic factors and the level of acceptability of a PBD among farmers. In the case of a low event rate and low sample size for expectations and acceptability in the definite form, we may recode them into tertiles and use the lowest score category as the reference group. Alternatively, we may conduct multiple linear regression analyses with the 2 dependent variables as continuous variables. We will also include any independent factors with a *P* value <.20 from the univariable regression analysis in the multiple regression analysis. Multicollinearity between independent variables will be checked according to a tolerance value <0.4 (variance inflation factor ≥2.5). In the presence of multicollinearity, we will select the more critical or essential variables from clinical perspectives for use in the final regression analysis. We will check all models, check Q-Q plots for normality, check residual plots for linearity, and check homogeneity assumptions, as well as assess model fitting.

Activity 3: Randomized Controlled Trial

Overview

In activity 3, we will perform a randomized controlled trial (RCT) on the effectiveness of a community-based program for managing hypertension using a PBD among farmers. We will evaluate the effectiveness of a PBD menu for the outcomes (blood pressure and acceptability of a PBD) of farmers with hypertension.

Design

An RCT will be performed for the community-based program in 2 groups (with pretest and posttest) using the CONSORT (Consolidated Standards of Reporting Trials) guidelines. An RCT is preferred to reduce selection bias [23]. Participants in this study will be randomly allocated to either the control or intervention group. The control group will receive a standard health education intervention for managing hypertension, while the intervention group will receive the PBD formula. A single-blind technique will be used so that participants will be unaware if they are in the control or intervention group.

Participants

The target population of this study is farmers with hypertension from 3 PHCs in Jember, East Java, Indonesia. Three PHCs have been chosen to represent the characteristics of agricultural areas with a high hypertension problem. The 3 PHCs have implemented the Integrated Health Program (IHP) for NCDs.

Inclusion and Exclusion Criteria

The inclusion criteria are as follows: farmers aged 45-65 years with stage I hypertension (systolic blood pressure [SBP]: 140-159 mmHg and diastolic blood pressure [DBP]: 90-99 mmHg) according to the JNC VIII criteria, farmers performing appropriate work, and those providing a commitment to attend the study for 3 months. We will exclude those who have experienced stroke as they are not eligible for participation, those with hypertension of stage II or higher, those taking medications, and those who have been hospitalized.

Sample Size Determination

The sample size will be determined using a traditional sample size calculation based on the McNemar test. The sample size in the McNemar test in this study should fulfill the following criteria: (1) directional hypothesis for 1 tail; (2) magnitude of expected change using the odds ratio (OR; OR=2); (3) alpha value of .05; and (4) required power of 0.8 or higher. The OR and the proportion are expected to change as a result of the intervention. Considering a 2-tailed approach, an effect size of 2.0 at an α value of .05 and power of 80%, and a change in 75% of the population as a result of the intervention, 96 participants would be needed to detect the effect.

Randomization

Initially, public health nurses (PHNs) will visit the study areas and make announcements about the study for farmer participation. The recruitment will be open for 6 months. Farmers will visit the PHC and will be provided an explanation

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of the study. Informed consent will be obtained, and farmers will be randomized using a computer-generated number. The allocation sequence will be concealed from the researchers and farmers. The computer-generated number system will randomize the initial name of the farmers from the PHC. The PHNs from the PHC will then obtain informed consent and manage the study groups.

Outcome Measures

The main outcome measures in this study are SBP and DBP, which will be measured using a standard protocol employing a stethoscope and sphygmomanometer after stabilizing subjects for more than 10 minutes. Measurements of SBP and DBP (mmHg) will be categorized according to the JNC VIII criteria to determine hypertension for participants aged >18 years [24]. The length of work per day, time of rest during working, and hours of sleep per day will be assessed among the farmers. These factors will be measured as they can influence blood pressure among farmers, according to a previous study [2]. Manual blood pressure measurement is usually performed using a mercury device or a calibrated needle (aneroid). SBP and DBP are determined through auscultation by listening for the appearance and disappearance of Korotkoff sounds in the brachial artery. Blood pressure measurements will be taken after a 14-minute rest period, during which the researcher and the participant will have a conversation to reduce tension associated with the "white coat" effect. Measurements will be taken at the same time (ie, 8 AM before activities) with the same tool. Participants will be told not to wear clothes that are too thick. Blood pressure test results will be more accurate if the cuff is placed directly over the skin. Participants will be told to empty their bladder before measurement. For the measurement, participants will be told to sit with their arms on a table so that the elbows are in line with the heart, the back is well supported by the back of the chair, and the feet are on the floor.

Data Collection Plan

At baseline, sociodemographic data, including age, gender, education level, smoking, hours of work, rest during working, and hours of sleep per day, will be obtained using a self-administered questionnaire. For measuring SBP and DBP at the PHC, participants will sit in a chair and relax for 10 minutes. Then, PHNs will measure blood pressure at least twice. If the blood pressure values obtained in the second measurement differ from the values in the first measurement by ≥10 mmHg, a third measurement will be carried out. The 2 measurement values with the smallest difference will be averaged to obtain the final value [24].

Intervention Group Arm

The intervention group will receive a community-based intervention program involving a PBD.

Control Group Arm

The control group will receive a standard education intervention through the IHC for NCDs and available health services that can be accessed every month in the community.

Intervention

The intervention group will receive a PBD formulated by the researchers. Farmers will consume the plant-based food 3 times per week. For the PBD, we will adopt a standard protocol from previous studies [1]. Therefore, we have decided to provide the PBD for 6 months.

In the control group, participants will receive education on health and safety on attending the IHP for NCDs, and they will adopt healthy behaviors according to the health education. As they will receive health education, they will be able to lead a healthy life in the agricultural environment, with occupational health and safety.

In both study groups, health education will be provided before the program, which will include information on how to manage a healthy lifestyle while working as farmers, including diet, exercise, rest, and sleep, and how to address blood pressure problems among farmers. Participants will receive this health education in a single session for 60 minutes at the first screening meeting. All participants will receive a manual book on a healthy lifestyle in an agricultural setting.

The blood pressure of participants in both study groups will be maintained. If the blood pressure increases to hypertension stage II or above, appropriate treatment will be provided by the medical doctor in the PHC and the participant will be excluded from the study. Data will be obtained at registration and at the pretest and posttest assessments. For blood pressure data, we will use rounded values, with values ending in 0-4 being rounded to "0" and values ending in 6-10 being rounded to "10" (eg, 120-124 mmHg will be rounded to 120 mmHg, 125 mmHg will be used directly, and 126-130 mmHg will be rounded to 130 mmHg).

Data Analysis Plan

SPSS version 22.0 (IBM Corp) will be used for the analysis. The significance level will be set as $P<.05$. Numerical data will be presented using means and standard deviations, while categorical data will be presented using frequencies and percentages. Furthermore, a linear generalized estimating equation (GEE) will be used to estimate the parameters of a generalized linear model with a possible unmeasured correlation between observations from different timepoints for SBP and DBP (comparing pretest and posttest).

Ethical Considerations

This study has received ethical approval from the Ethics Committee for Research Involving Human Subjects, Faculty of Dentistry of Universitas Jember (approval number: 1548/UN25.8/KEPK/DL/2022, with an amendment on June 29, 2021) and conforms to the requirements of the World Medical Association's Declaration of Helsinki. All the participants will provide written informed consent before their inclusion.

This study will use descriptive analytics in health and community service units with a quantitative approach through surveys and qualitative interviews at health and community service units. This research will not cause harm to the participants. Each participant will provide informed consent. We will give autonomy rights to prospective participants.

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Participants will be provided an explanation of the study, including the objectives, benefits, implementation process, and participant rights. Participants will be informed that there is no risk of harm if they do not participate in the study or leave the study while the research process is in progress.

The study will pay attention to safety aspects for both the researchers and participants, and will be performed according to the applicable COVID-19 protocol. The interviews will be adjusted according to the participants' time. Participants will receive compensation (transportation fee) and food for each data collection. The design of this study involves an intervention group and a control group, and we will try to minimize the occurrence of unwanted incidents during the implementation of the intervention. We will provide leaflets containing educational materials for a PBD when the last measurement is taken. Participants in the control group will be offered a discussion session after reading the leaflet provided, but there is no compulsion to join the discussion session. All participants in the intervention group will receive the same intervention regardless of ethnicity, religion, and race.

The confidentiality of the participants' data will be maintained, and the identity of the participants will not be disclosed. The data obtained will only be used for research purposes. To keep participants' data confidential, the survey sheet will have a special code that does not display the personal data. Moreover, a statement will be provided that qualitative study data are anonymous or deidentified. Furthermore, a brief description of the protections in place will be provided.

Results

This research has been funded by DRPTM Kementerian Pendidikan, Kebudayaan, Riset dan Teknologi Skema Riset Penelitian Dasar Unggulan Perguruan Tinggi (PDUPT) in 2022 (0277/E5/AK.04/2022). The research started in May 2022, and phase I of the study is scheduled to begin in May 2023, with a total research duration of 2 years. A model PBD for the management of hypertension is expected to be developed from using local food–related agronursing services. In 2022, we will collect data on hypertension and the characteristics of local food sources to manage hypertension, and formulate a PBD menu to treat hypertension among farmers. A thematic analysis of the qualitative data of farmers in the agricultural sector will be performed. In 2023, we will develop a questionnaire to assess the acceptability of a PBD to manage hypertension among farmers, the prevalence of hypertension, and the sociodemographic factors associated with hypertension among farmers. Furthermore, we will introduce a community-based nursing program for the management of hypertension using a PBD among farmers.

Discussion

Contributions of the Study

This paper describes a protocol for the management of hypertension using a PBD among farmers. We hypothesize that the formulation of the PBD concept can overcome the problem of hypertension among farmers in agricultural areas, which is synergistic with the culture and local wisdom of the agricultural population. The findings of this study may contribute to the development of a better solution for hypertension among farmers in Indonesia and may be relevant to a special group of readers interested in this research. It is believed that innovations of the intervention can be used and integrated to promote nursing care within the fields of health assessment, activities of daily living, and care management, which could improve the quality of life and quality of care for farmers in agricultural areas.

The concept of a PBD as a solution for hypertension is based on meeting the nutritional needs of plant-based proteins and minimizing intake from animal and processed sources [24]. Maximized intake of nutrients in a PBD involves high intake of fiber, vegetable protein, vitamins, polyphenols, and unsaturated fatty acids, and low intake of sodium. Food processing in a PBD can be adapted to the culture and habits of the local community to facilitate the consumption process and maintain consistency in the implementation of the process. A PBD is expected to provide considerable benefits to overcome hypertension in farmers. Optimal nutrition and fiber in a PBD will provide strong protection for organ systems in the body and will help systems to work synergistically to reduce inflammation and oxidation in the body [19].

A PBD model will provide farmers with an alternative solution that has independent, safe, and comfortable features for their needs. It could also be used to adapt and transform existing hypertension programs for farmers and their family members. With a better understanding of farmers' expectations and acceptability of a PBD model in public health, researchers, stakeholders, and policymakers may be able to effectively develop a complete model that incorporates appropriate technologies and integrates relevant medical services, and yet remains affordable to benefit the majority of farmers. This would facilitate the transformation of traditional hypertension interventions to smart and local interventions, which include necessary skill sets or required training for PHNs and other health care professionals to meet expectations.

The findings of this study will be presented at conferences and published in peer-reviewed journals. We will publish the results of this research in academic journals. We will also present this research at national and international conferences. The data from this study will be presented in a research report to the Ministry of Cultural Education, Research and Technology, and Higher Education on the BIMA system dashboard (BIMA – Kemdikbudristek) as restricted data. In addition, research data will be reported to the Institute for Research and Community Service, University of Jember (organizer in research activities). Furthermore, the research results of the first year and second year will be presented in a manuscript. The manuscript will be submitted to a reputable international journal in the areas of hypertension and NCD management.

Disseminating our study findings will significantly contribute to the advancement of science and holistic nursing services for farmers with hypertension in the community.

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Limitations of the Study

This study will examine the effectiveness of a community-based nursing program for the management of hypertension using a PBD among farmers in Indonesia. However, this protocol may have some limitations. First, the program requires participant compliance for carrying out regular training to maintain blood pleasure, and some participants may drop out of this study for various reasons, such as noncompliance with the consumption of a PBD. Therefore, a dairy is required to continuously monitor the diet. Second, the measurement of blood pressure may be biased because of different enumerators and sphygmomanometers. This can be minimized by interrater enumerator measurements and instrument calibration.

Conclusion

We believe the findings of this research will be beneficial for farmers in the agricultural and plantation areas of Jember, who experience hypertension. We will compile the results of our research by comparing and discussing the results in terms of the results of previous similar studies. Future research is expected to improve the results of this study in terms of determining the preparation of hypertension management using a PBD for farmers. We expect contributions from the local government to implement the intervention as one of the policies in the management of hypertension for farmers in the agricultural plantation areas of Jember. This program may also be implemented in other agricultural countries with similar problems, so that hypertension can be optimally treated among farmers.

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Authors' Contributions

All authors have critically reviewed and approved the final draft and are responsible for the content of the manuscript. TS contributed to conceptualization, methodology, validation, formal analysis, investigation, resources, data curation, writing – original draft, writing – review and editing, supervision, project administration, and funding acquisition. RAY contributed to conceptualization, methodology, validation, formal analysis, investigation, resources, data curation, writing – original draft, and writing – review and editing. HR contributed to validation, formal analysis, investigation, data curation, and writing. IR contributed to validation, formal analysis, investigation, data curation, and writing – original draft. FK contributed to validation, formal analysis, and investigation.

Conflicts of Interest

None declared.

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Abbreviations

DBP: diastolic blood pressure
IHC: Integrated Health Center
IHP: Integrated Health Program
JNC VIII: Eighth Joint National Committee on Prevention, Detection, and Treatment of High Blood Pressure
NCD: noncommunicable disease
OR: odds ratio
PBD: plant-based diet
PHC: public health center
PHN: public health nurse
RCT: randomized controlled trial
SBP: systolic blood pressure

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Protocol

Improving Cognitive Function Through High-Intensity Interval Training in Breast Cancer Patients Undergoing Chemotherapy: Protocol for a Randomized Controlled Trial

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Abstract

Background: More than 75% of patients with breast cancer treated with chemotherapy experience cognitive impairments (eg, memory and attention problems), commonly known as *chemo-brain*. Exercise, especially aerobic high-intensity interval training (HIIT), is associated with better cognitive function in healthy populations. However, clinical trials testing the impact of exercise interventions on chemotherapy-induced cognitive decline in patients with cancer are lacking, and the mechanisms through which exercise could improve cognitive function are unclear.

Objective: The objective of the Improving Cognitive Function Through High-Intensity Interval Training in Breast Cancer Patients Undergoing Chemotherapy trial is to examine the effects of HIIT on cognitive function in patients with breast cancer undergoing chemotherapy.

Methods: This 2-arm, single-center, pilot randomized controlled trial will randomize 50 patients with breast cancer undergoing chemotherapy to HIIT or attention control. The HIIT group will perform a supervised 16-week, thrice-weekly intervention, with each session including a 5-minute warm-up at 10% maximal power output (POmax), 10 sets of alternating 1-minute high-intensity (90% POmax) and 1-minute recovery (10% POmax) intervals, and a 5-minute cooldown (10% POmax). The attention control group will receive a stretching program with no exercise components and be asked to maintain their exercise levels for 16 weeks. The primary outcomes of the study are executive function and memory measured using the National Institutes of Health toolbox and resting-state connectivity and diffusion tensor imaging microstructure evaluated using magnetic resonance imaging. The secondary and tertiary outcomes include cardiorespiratory fitness, body composition, physical fitness, and psychosocial health. The study has been approved by the institutional review board of the Dana-Farber Cancer Institute (20-222).

Results: The trial was funded in January 2019, with recruitment started in June 2021. As of May 2022, a total of 4 patients have consented and been randomized (n=2, 50% to exercise; n=1, 25% to control; and n=1, 25% nonrandomized). Trial completion is expected in January 2024.

Conclusions: This first-of-its-kind study incorporates a novel exercise intervention (ie, HIIT) and comprehensive cognitive measures. If positive, our findings will establish the pilot efficacy of HIIT on chemotherapy-induced cognitive function in patients with breast cancer, providing the foundation for future larger phase-II and phase-III trials to confirm the findings and potentially establish HIIT as a standard of care for women undergoing chemotherapy for breast cancer.

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Trial Registration: ClinicalTrials.gov NCT04724499; https://clinicaltrials.gov/ct2/show/NCT04724499
International Registered Report Identifier (IRRID): DERR1-10.2196/39740

(JMIR Res Protoc 2023;12:e39740) doi:10.2196/39740

KEYWORDS

cognitive function; high-intensity interval training; exercise; breast cancer; chemotherapy; magnetic resonance imaging; MRI

Introduction

Background

Breast cancer is the most commonly diagnosed cancer among women in the United States, with approximately 280,000 new cases each year [1]. Advances in breast cancer treatment have increased breast cancer–specific and overall survival for women with early-stage breast cancer, but side effects of therapy affect quality of life and functional status during and after cancer treatment. In particular, up to 75% of patients with breast cancer treated with chemotherapy experience treatment-related cognitive impairments commonly referred to as *chemo-brain* [1,2]. Although *chemo-brain* is often associated with chemotherapy, similar cognitive changes may also present as a result of the cancer itself or conditions resulting from cancer treatment (eg, pain and infection). These alterations in memory, concentration, and other cognitive abilities may represent long-term effects that diminish the quality of life of patients with breast cancer and increase the risks of patient morbidity and mortality [3,4].

Although the neurological mechanisms underlying *chemo-brain* remain unresolved, previous studies have demonstrated an association between physical activity, such as walking or cycling, and enhanced cognitive function in patients who have undergone chemotherapy treatment [5-7]. High-intensity interval training (HIIT) in particular has been shown to improve cognitive flexibility, executive function, and psychological well-being in both older adults and youths [8-11]. This exercise modality consists of brief periods of intense exercise interspersed with recovery intervals and is a safe and feasible exercise approach for patients with breast cancer undergoing chemotherapy [12-14]. However, the impact of HIIT on cognitive function in women undergoing chemotherapy for breast cancer remains unknown.

Objectives

The primary aim of the Improving Cognitive Function Through High-Intensity Interval Training in Breast Cancer Patients Undergoing Chemotherapy (CLARITY) trial is to examine the impact of a 16-week HIIT exercise intervention on cognitive function assessed using the Montreal Cognitive Assessment, the National Institutes of Health (NIH) toolbox, and quantitative magnetic resonance imaging (MRI) of the brain. We hypothesize that executive function and memory scores will be higher after exercise compared with baseline and the attention control (AC) group and that participants in the HIIT intervention will have enhanced functional brain connectivity and structural white matter tracts compared with baseline and the AC group. The secondary aims are to examine the effects of HIIT on body composition; biomarkers related to metabolic dysregulation, inflammation, and cardiotoxicity; physical fitness and function; and quality of life and psychosocial outcomes in patients diagnosed with early-stage breast cancer undergoing chemotherapy. We hypothesize that participants in the HIIT intervention will have improved body composition and psychosocial health compared with baseline and the AC group.

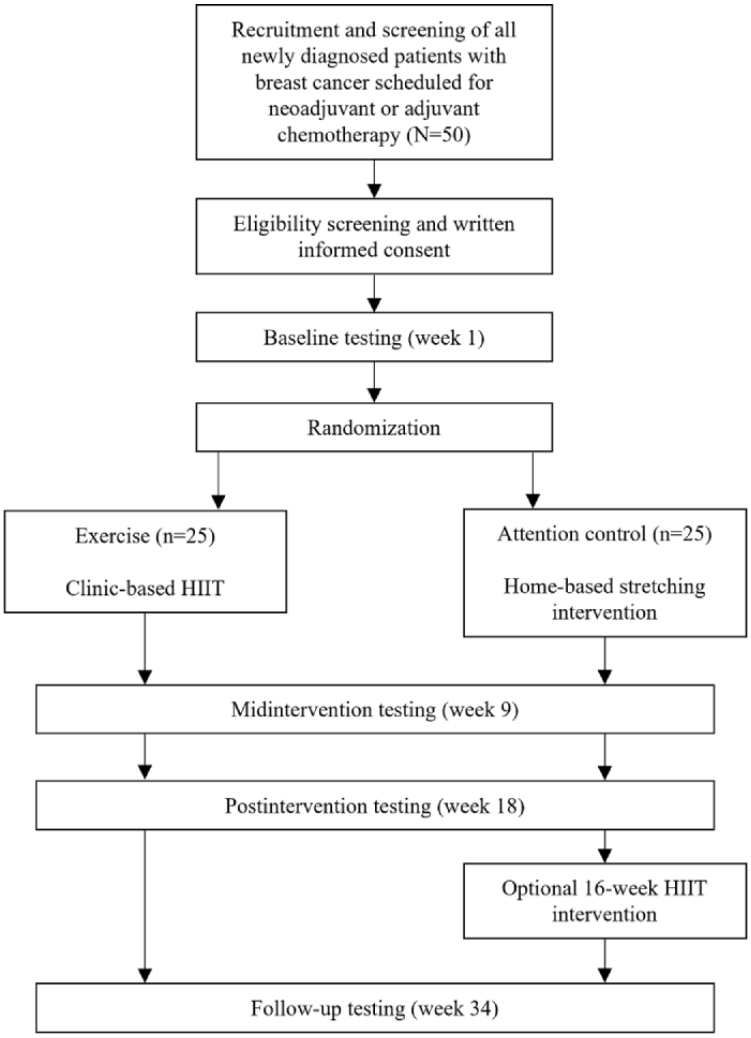
Methods

Study Design

The CLARITY trial is a 2-arm randomized controlled trial underway at the Dana-Farber Cancer Institute (NCT04724499). Outcomes are measured at baseline (week 1), midintervention (week 9), after the intervention (week 18), and at follow-up (week 34; HIIT group only; Figure 1). A total of 50 women diagnosed with breast cancer who are chemotherapy-naïve are randomized either to a 16-week clinic-based HIIT intervention or an AC group who will be provided with a 16-week flexibility intervention. After the initial 16-week intervention period, the HIIT group completes a further 16-week follow-up period of self-directed exercise. The AC group does not complete the follow-up period and is instead offered the HIIT program. Only the AC participants who choose to partake in the HIIT program complete testing at the follow-up point (week 34).

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Figure 1. Study schema of the Improving Cognitive Function Through High-Intensity Interval Training in Breast Cancer Patients Undergoing Chemotherapy trial. HIIT: high-intensity interval training.



Participant Eligibility

Women are eligible if they are (1) newly diagnosed with breast cancer, (2) planning to receive neoadjuvant or adjuvant chemotherapy (regardless of duration and regimen of drug), (3) aged >18 years, (4) nonsmokers (within the previous 12 months), (5) inactive (defined as <60 minutes of structured exercise per week), (6) cleared by their clinicians for exercise, and (7) English-speaking. Exclusion criteria include (1) having a second malignancy or metastases; (2) pregnancy; (3) weight loss of >10% within the past 6 months; (4) having any uncontrolled comorbidity, condition, or contraindication that may prevent participation in high-intensity exercise; (5) having a pacemaker or any implantable device not safe for MRI; (6) claustrophobia; and (7) having a history of coronary heart or artery disease, chronic or acute congestive heart failure, or history of systolic or diastolic insufficiencies.

Recruitment and Informed Consent

Participants are currently being recruited through clinician referral and screening of patient lists at the Dana-Farber Cancer Institute, Boston, Massachusetts, as well as by way of advertisements in patient waiting rooms, the Partners Rally Platform, and other relevant breast cancer community newsletters and servers. Pending accrual rate, potential additions to recruitment efforts to boost enrollment include offering travel compensation for testing visits for those who live outside the city and offering exercise sessions at additional satellite locations. All participants require clinician clearance before being formally screened via phone. Phone screening comprises 2 short questionnaires to determine eligibility: the Godin Leisure Time Questionnaire [15] to assist in determining the participant's current exercise levels and the Physical Activity Readiness Questionnaire [16] to confirm the participants' health status and how this relates to undertaking an exercise program. Upon confirmation of eligibility and interest, participants consent via wet or electronic signature.

Ethics Approval

Approval of the trial protocol was obtained from the institutional review board at the Dana-Farber Cancer Institute (20-222).

Randomization and Blinding

After baseline testing, participants are randomly allocated to either the HIIT or AC group using a 1:1 ratio and a permuted blocked design with varying block sizes where investigators are blinded to this process. The study biostatistician and coinvestigator (HU) prepared the randomization list before study start-up, after which the investigators access through a web-based application to conduct randomization and

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subsequently verbally inform the participants of their group allocation. Testers and participants are blinded to group allocation during baseline testing. Owing to the nature of the intervention and logistical limitations, participants and study staff cannot be blinded to the intervention allocation.

Measurements

Overview

Testing is completed on 2 consecutive days at baseline, after the intervention, and at follow-up, with only 1 day required for testing at midintervention. At baseline, the first testing day may occur before the first dose of chemotherapy or within 10 days of the first infusion. The second day of testing is completed within 1 to 6 days of testing day 1 and may occur after the first cycle of chemotherapy. All measures are collected at all time points unless otherwise specified, and study staff members trained in exercise oncology will be supervising and leading all the tests unless otherwise specified (Table 1).

Table 1. SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) flow diagram for timeline of study visits for the Improving Cognitive Function Through High-Intensity Interval Training in Breast Cancer Patients Undergoing Chemotherapy trial.

Time point[a]	Week 0	Week 1-17	Week 9	Week 17 or 18[b]	Week 17-34	Week 34[c]
Enrollment						
Eligibility screen	✓					
Phone screen	✓					
Informed consent	✓					
Allocation	✓					
Exercise screening	✓					
Interventions						
HIIT[d]		✓				
Attention control		✓			✓ (optional)	
Assessments						
Executive function and memory	✓			✓		✓
MRI[e]	✓			✓		✓
Blood biomarkers	✓		✓	✓		✓
Anthropometrics	✓		✓ (no DEXA[f])	✓		✓
Cardiorespiratory fitness	✓		✓	✓		✓
Muscle strength	✓		✓	✓		✓
Physical function	✓		✓	✓		✓
Psychosocial measures	✓		✓	✓		✓
Peripheral neuropathy	✓		✓	✓		✓
Lymphedema assessment	✓		✓	✓		✓
Shoulder function and range of motion	✓		✓	✓		✓
Dietary intake	✓		✓	✓		✓
ActiGraph	✓		✓	✓		✓
Activity logs		✓			✓	

[a]Week 0: enrollment and baseline assessment; week 1 to 17: intervention period; week 9: midpoint assessment; week 17 or 18: postintervention assessment; week 17 to 34: follow-up period; week 34: follow-up assessment.

[b]Depends on whether a participant has any exercise sessions to make up.

[c]Only for the high-intensity interval training group and the attention control participants who choose to complete the high-intensity interval training program during the follow-up period.

[d]HIIT: high-intensity interval training.

[e]MRI: magnetic resonance imaging.

[f]DEXA: dual-energy x-ray absorptiometry.

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Primary Outcomes

Executive Function and Memory

To assess executive functioning and abilities, we use the NIH toolbox [17] and the Montreal Cognitive Assessment to assess global cognition; both tests are conducted at baseline, after the intervention, and at follow-up. From the NIH toolbox, the following tests are administered: Auditory Verbal Learning Test for immediate recall (memory), Picture Sequence Memory Test for episodic memory, Oral Reading Recognition for language, flanker task for executive function and attention, List Sorting Test for working memory, Oral Symbol Digit Test for processing speed, Dimensional Change Card Sort Test for executive function, and Pattern Comparison for processing speed. We also include an episodic memory composite that is derived from tests supported by the hippocampus and surrounding medial temporal lobe [18].

Resting-State Connectivity and Structural Diffusion Tension Imaging Connectivity

The MRI (Table 2) is conducted at baseline, after the intervention, and at follow-up by authorized MRI personnel. All imaging is performed on a single Siemens 3T Prisma MRI system with a 32-channel head coil. 3D T1 magnetization-prepared rapid acquisition with gradient echo imaging (1-mm isotropic voxels and 6-min, 38-s gradient time) is performed as the primary anatomic imaging sequence. Automated brain region segmentation is performed using the open-source FreeSurfer program (Martinos Center for Biomedical Imaging) [19] with manual correction [20]. Segmentation is used for primary volumetric analyses [21,22]. We examine the amygdala-hippocampus complex and thalamic and ventricular volumes and perform an exploratory comprehensive volumetric analysis. Multishell diffusion tensor imaging (DTI) is performed with 107 directions obtained in both the anteroposterior and posteroanterior directions (2-mm slice thickness and 6-min, 7-s gradient time each). DTI data are processed using the open-source 3D Slicer program (The Slicer Community) [23]. This technique enables traditional DTI analyses that are considered measures of cerebral microstructure and axonal and myelin pathology [24,25]. This technique also enables more novel analyses of free-water imaging [26], neurite orientation dispersion and density imaging [27], and diffusion kurtosis imaging [28], which can help evaluate for neuroinflammation and vasogenic and cytotoxic edema. Resting-state functional MRI (fMRI) is performed and analyzed using the Resting-State fMRI Data Analysis Toolkit (Hangzhou Normal University) [29]. We are examining the intrinsic network connectivity between the prefrontal cortex and hippocampus in addition to seed voxels in the posterior cingulate and precuneus of the default mode network [30].

Table 2. Magnetic resonance imaging parameters for the Improving Cognitive Function Through High-Intensity Interval Training in Breast Cancer Patients Undergoing Chemotherapy trial.

Sequence	Flip angle	Voxel size (mm^3)	TE[a] (ms)	TR[b] (ms)	Acceleration	Extra notes
3D T1 MPRAGE[c]	8	0.8 × 0.8 × 0.8	2.22	2400	GRAPPA[d] factor 2	Inversion time: 1000 ms
DTI[e]	78	1.5 × 1.5 × 1.5	89.20	3930	None	107 gradient directions both AP[f] and PA[g]
rsfMRI[h]	52	2.0 × 2.0 × 2.0	37.00	800	None	AP direction

[a]TE: time to echo.

[b]TR: time to repetition.

[c]MPRAGE: magnetization-prepared rapid acquisition with gradient echo.

[d]GRAPPA: Generalized Autocalibrating Partially Parallel Acquisitions.

[e]DTI: diffusion tensor imaging.

[f]AP: anteroposterior.

[g]PA: posteroanterior.

[h]rsfMRI: resting-state functional magnetic resonance imaging.

Secondary Outcomes

Blood Biomarkers

A trained phlebotomist performs a fasting blood draw, obtaining both serum-separating tubes and EDTA samples. After being processed and aliquoted, the blood serum and plasma samples are stored in a −80 °C freezer for later batched analysis. Analysis of bloods through commercially available kits (Thermo Fisher Scientific) will be used for leptin, adiponectin, insulin, estradiol, matrix metalloproteinases, tissue inhibitors of metalloproteinases, interleukin-6, sex hormone–binding globulin, tumor necrosis factor-α, brain natriuretic peptide, N-terminal probrain natriuretic peptide, cardiac troponin I, and C-reactive protein. These biomarkers were selected based on their potential mechanistic role in how exercise may affect cognitive function [31-34].

Anthropometric Measures

Height (cm), weight (kg), and waist and hip circumference (cm) are assessed according to standard procedures [35], with height and weight used to calculate BMI (kg/m^2). Body composition is assessed using bioelectrical impedance (Tanita 780), providing both appendicular and whole-body measures of fat and lean mass (kg).

Cardiorespiratory Fitness and Exercise Capacity

To assess maximal oxygen consumption (VO_{2max}) and accurately prescribe the exercise intervention, a maximal cardiopulmonary exercise test is completed on a cycle ergometer (ErgoSelect

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100; Ergoline) using an incremental ramp protocol [36]. Participants complete a 5-minute warm-up at a resistance of 40 W and then proceed into an incremental ramp protocol increasing 10 W every minute until volitional fatigue. Cadence is kept between 60 and 80 revolutions per minute. Heart rate (HR; FT4; Polar USA) and rate of perceived exertion (Borg scale 1-10) are recorded every minute and at the end of the test. Expired gas analysis (TrueOne 2400; ParvoMedics, Inc) is used to measure VO_{2max}. The results of this test are used to calculate the target maximal power output (POmax) in watts for the high-intensity and recovery intervals of the HIIT program. In addition, the 6-minute Walk Test is used to estimate exercise capacity [37,38]. Participants will be instructed to walk as far as they can in 6 minutes up and down a 10-m walking course within a hallway. The distance achieved in 6 minutes will be measured in meters.

Muscular Strength

Muscular strength is assessed using an estimated 1-repetition maximum (RM) from 10-RM of leg press, leg extension, and leg curl (SportsArt and Matrix Fitness). Participants perform 1 to 2 warm-up sets of 6 to 8 repetitions. The participant proceeds to complete sets of 10 repetitions with increasing weights in each set until volitional fatigue is reached on the 10th repetition; a maximum of 3 sets are used to reach 10-RM. The weight of the participant's 10-RM is recorded in kilograms and used to estimate 1-RM using validated equations [39,40]. Isometric handgrip strength is measured in the dominant upper limb (Camry Digital Hand Dynamometer). Participants perform 3 trials in a standing position with their arms down by their side, with the highest result used for analysis.

Physical Function

Physical function is assessed using the Short Physical Performance Battery (SPPB) [41], Timed Up and Go (TUG) [42], gait speed [43], Margaria stair climb [44], and sit-to-stand [45] tests. The SPPB comprises three sections: (1) balance with feet together, semitandem, and full tandem is held for up to 10 seconds with no support (only 1 attempt is given for each position, and the time in seconds to complete it is recorded); (2) usual gait speed over 4 m is timed, where the participant completes 2 attempts with the fastest time (seconds) recorded; and (3) chair stand, where the time (seconds) to complete 5 chair sit-to-stands is recorded, and only 1 attempt is given after a familiarization practice. Each section of the SPPB is given a score dictated by performance to then provide a summary score. The TUG test times how fast it takes a participant to stand up from a chair, walk around a cone placed 3 m away from the chair where they start, and end in a seated position. Participants attempt the TUG 3 times after a familiarization practice, where the average of the 3 trials is calculated. Gait speed is assessed over a 6-m flat surface where the time to walk the 6-m course at a usual and fast pace is recorded. In total, 2 attempts for each speed are completed. The Margaria stair climb is completed in a stairwell of 10 stairs. The participant walks or runs up the stairs as fast and safely as they can. The time (seconds) the participant takes from stair 3 to stair 9 is recorded; 3 attempts are given after a familiarization practice, where the average time of the 3 trials is calculated. Power (kg) is calculated from the stair climb using a validated equation [44]. The sit-to-stand test involves participants completing as many sit-to-stands as possible from a seated chair position to a standing position with full hip extension in 30 seconds; 1 attempt is given, with the number of full movements with correct technique recorded.

Psychosocial Measures

Health-related quality of life is assessed using the Functional Assessment of Cancer Therapy-Breast, which has an internal consistency coefficient of Cronbach α=.90 [46]. This is a 37-item questionnaire specifically designed for patients with breast cancer and measures the following 5 domains: physical, social, emotional, and functional well-being and a breast cancer subscale. Cancer-related fatigue is assessed using the Brief Fatigue Inventory, which has an internal consistency coefficient of Cronbach α=.96 [47]. This is a 6-item questionnaire that produces a global fatigue score by averaging all the items of the Brief Fatigue Inventory. Depressive symptoms are assessed using the Center for Epidemiologic Studies Depression Scale, which has an internal consistency coefficient of Cronbach α=.82 [48,49]. This is a 20-item questionnaire designed to measure a participant's current level of depressive state using the following 6 scales reflecting major facets of depression: depressed mood, feelings of guilt and worthlessness, feelings of helplessness, psychomotor retardation, loss of appetite, and sleep disturbance. The State-Trait Anxiety Inventory is a 40-item questionnaire, which will be used to examine anxiety. The State-Trait Anxiety Inventory has an internal consistency coefficient of Cronbach α=.86 to .95 [50]. Sleep quality will be assessed using the Pittsburgh Sleep Quality Index, which has an internal consistency coefficient of Cronbach α=.83 [51,52]. This is a 19-item questionnaire evaluating 7 domains—subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction—and provides a global score. The impact that pain has on quality of life will be assessed using the Brief Pain Inventory-Short Form, which has an internal consistency coefficient of Cronbach α=.81 to .89 [53,54]. This is a 9-item questionnaire and has been validated for use in patients with breast cancer [53]. Finally, barriers to recruitment and exercise adherence are assessed using the Barriers to Recruitment Participation Questionnaire and Exercise Benefits/Barriers Scale, which have an internal consistency coefficient of Cronbach α=.93 [55,56]. The Barriers to Recruitment Participation Questionnaire is a 17-item questionnaire, and the Exercise Benefits/Barriers Scale is a 43-item questionnaire.

Peripheral Neuropathy

Peripheral neuropathy is measured using two tests: (1) the Semmes-Weinstein Monofilament Examination and (2) vibration testing using the on-off method [57-59]. For both tests, participants are seated in an upright position with their eyes closed and socks and shoes off. The Semmes-Weinstein Monofilament Examination is used to evaluate protective sensation at 2 sites—pad of the great toe (foot) and pad of the index finger (hand)—with the nylon monofilament applied 4 times to each site. The vibration sensation is evaluated by applying a tuning fork to the bony prominences of the great toe, thumb, and medial malleolus. Correct identification of the side

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of the body and on-off vibration sensation for the respective tests is recorded.

Lymphedema Assessment

Lymphedema is assessed using geometric arm volume calculations on both upper limbs [60]. We calculate arm volume using circumferential measurements taken at the following anatomic landmarks: axillary fold, halfway between the axillary fold and antecubital fossa, antecubital fossa, halfway between the antecubital fossa and wrist, and wrist. Circumferential measurements are taken with a constant-tension tape measure. Calculations for limb geometric volume are done using the frustum (truncated cone) volume, as described by Taylor et al [60]. A percentage difference between the lymphedema limb and the uninvolved limb is calculated to determine the amount of lymphedema. Lymphedema has been defined in recent literature as a >10% difference in volume calculation for the arm compared with the uninvolved upper extremity [60].

Shoulder Function and Range of Motion

Upper-body function is assessed using the Y Balance Test Kit (Move2Perform) [61]. Participants begin in a 3-point plank position on the toes or knees depending on ability. The tested shoulder is the supporting limb placed on the connecting block, the nontesting limb is placed on the medial block, and the feet are placed shoulder-width apart. From this position, the participant uses their nontesting limb to move each reach block one at a time in the medial, inferolateral, and superolateral directions in a controlled manner as far as they can and then return to the starting position. The test is performed 3 times on each side with a 30-second rest between trials. The reach distance in each direction is recorded, where the highest value in each direction is used to calculate an average composite score.

Bilateral upper-body strength and power are assessed through the seated medicine ball throw [62]. Participants are instructed to sit on the floor with their head, shoulders, and back against the wall and legs extended; legs may be bent if ability does not allow for full extension. To calculate a relative throwing distance, arm-reach distance is measured from the wall in meters. Using a 2-kg medicine ball covered in chalk, the participant performs a chest pass holding the ball with both hands and throwing it forward in a straight line as far as they can with head, shoulders, and back maintaining full contact with the wall. A measuring tape is used to measure the distance from the wall to the most proximal point of the chalk mark, with the participant's reach distance subtracted to provide a final distance in meters. In total, 3 test trials will take place after a practice throw with a 1-minute rest between each trial. The average of the 3 trials will be calculated.

Shoulder function is assessed through the shoulder performance test using the following tasks: overhead reach, hand behind the head, and hand behind the back. All movements are completed in a standing position starting with the arms by the side. The time (seconds) taken to complete the respective tasks using the correct technique 20 times is recorded. Each task is repeated to the right and left.

Upper-body function is assessed using the closed kinetic chain upper-extremity stability test [63]. Participants begin in a 3-point plank position on the toes or knees, depending on ability, with hands 36 inches (91.4 cm) apart, shoulders perpendicular to hands, and feet hip-width apart. From this position, the dominant hand reaches across the body, touches the nondominant hand, and returns to the starting position. Subsequently, the same movement is performed by the nondominant hand. Participants are instructed to perform as many alternating touches as possible in 15 seconds while maintaining the correct push-up position. In total, 3 trials occur after familiarization, with 45 seconds of rest in between each trial.

Shoulder active range of motion (AROM) is measured on both upper limbs. Using a goniometer (EZ Read; Jamar), AROM is assessed in external rotation at 0°, external rotation at 90°, forward flexion, and abduction [64,65]. The participant stands for all tests except for external rotation at 90°, where the participant is lying on the ground with knees bent and feet hip-width apart. The starting position of the measured limb is dictated by the AROM being tested. The participant is asked to actively perform the required motion with the angle of movement recorded in degrees. In total, 3 active trials are performed after the tester passively moves the participant's limb in the tested motion.

Physical Activity and Sedentary Behavior

Physical activity and sedentary behavior are assessed using the ActiGraph wGT3X-BT (ActiGraph LLC) at baseline, after the intervention, and at follow-up only. Patients wear the accelerometer on their hip for 7 consecutive days, excluding water-based activities and sleep. ActiLife software (ActiLife 6; ActiGraph LLC) is used to analyze the ActiGraph data. Only wake wear time is used, with a minimal data collection period set for inclusion in the analysis of 4 days of at least 600 minutes per day. Nonwear time is excluded from the analysis, defined as ≥90 minutes of consecutive zeros with a 2-minute spike tolerance [66]. Commonly used cutoff points among patients with cancer will be used to classify sedentary time (<100 counts per minute), light physical activity (100-1951 counts per minute), and moderate to vigorous physical activity (≥1952 counts per minute) [67-69].

Covariates

Participant Characteristics

Participant demographic and medical history data are collected at baseline with the administration of a study-tailored questionnaire. In addition, patients complete the Socioeconomic Status Questionnaire to determine economic demographics, education level, and socioeconomic status [70]. Changes in demographic and medical history data (eg, medical conditions, medication, and cancer treatment) will be monitored throughout the study period and confirmed at each testing time point.

Dietary Intake

Recent dietary patterns are assessed using the automated self-administered 24-hour dietary assessment tool [71]. Participants complete 3 assessments at home on 2 weekdays and 1 weekend day, recording all food and drinks consumed during the previous 24-hour period.

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Physical Activity Logs

The AC group completes a daily activity log throughout the 16-week intervention. During the supervised exercise sessions, the HIIT group is asked about their physical activity completed outside the supervised sessions over the previous week. In addition, they complete daily activity logs during the follow-up period. In the activity logs, the participants are asked to record the type of exercise performed, the time spent performing the exercise, the intensity of the exercise bout (rate of perceived exertion [Borg scale 1-10] or average HR for the HIIT group if they are wearing an HR monitor), and the day of the week in which it was completed.

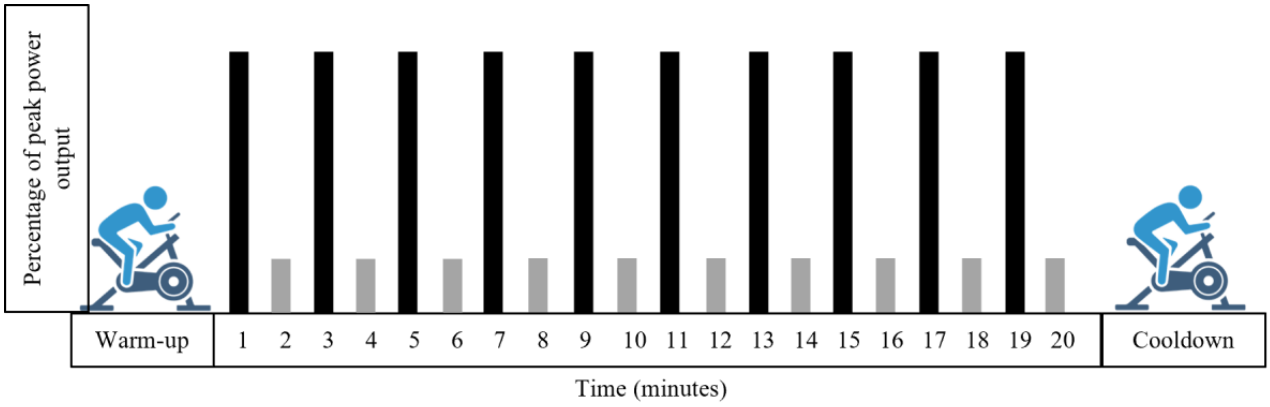
Intervention

HIIT Group

Participants randomized to this group partake in a clinic-based HIIT program using a cycle ergometer 3 days per week for 16 weeks under the supervision of a trained exercise oncology specialist. Before beginning the exercise session, participants undergo a screening procedure to ensure that they are fit to participate. Participants are permitted to participate in the exercise session if they present with normal body temperature (≤100 °F or ≤37.8 °C), resting HR (absence of bradycardia, <60 beats per minute; or tachycardia, >100 beats per minute), and resting blood pressure (≤200/120 mm Hg). In addition, participants complete the Exercise-Induced Feeling Inventory [72] before and after the HIIT session to assess the participants' feeling state changes after exercise and self-motivation to adhere to an aerobic exercise regimen. Participants also complete the Therapy-Related Symptom Checklist [73], a 25-item questionnaire, to assess and identify patient-reported symptom occurrence and severity.

The cycle-based HIIT exercise session consists of a 5-minute warm-up period at 10% of POmax (watts; calculated from the cardiopulmonary exercise test) followed by a 20-minute stimulus period consisting of alternating high-intensity interval bouts at 90% POmax (based on individual fitness level) with a recovery bout at 10% at a 1 minute:1 minute (work:recovery) ratio (Figure 2). Following the stimulus period, participants complete a 5-minute cooldown at 10% POmax (watts). An HR monitor wristwatch and transmitter are used to measure HR before exercise and at every minute during warm-up, exercise, and cooldown. Exercise sessions are completed with at least one full day of rest in between each session and are not to be completed on days when the participant has a chemotherapy infusion. Weekly goals will be set by the study staff for each participant based on their symptoms and how they feel overall, allowing for tailored sessions to accommodate individual fitness ability and treatment burden.

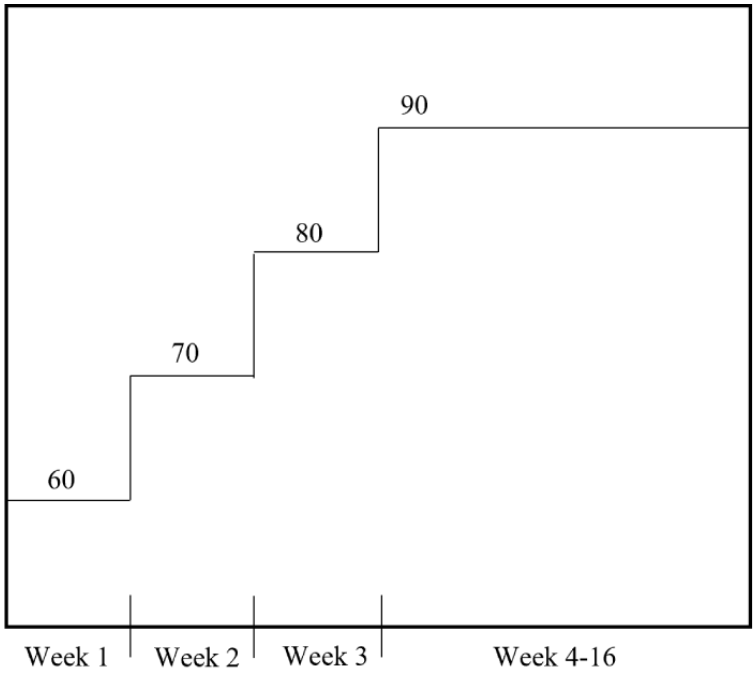
Figure 2. Example of a high-intensity interval training session and the high and low intensities performed.



Exercise intensity is gradually increased within the first 4 weeks of the intervention, whereby the participants begin the high-intensity interval bouts at 60% POmax, increase by 10% each week until 90% is reached, and then maintain at 90% for the remainder of the intervention (Figure 3). If a participant is unable to achieve compliance with the prescribed HIIT program, a moderate-intensity interval training (MIIT) program is substituted as an alternative exercise prescription. A single session is considered noncompliant if the number of high-intensity bouts achieving the target power output is <80% (eg, if ≥3 high-intensity bouts do not reach the prescribed power output). If 3 concurrent exercise sessions are reported as noncompliant, the participant is offered the MIIT program instead. Within the MIIT program, participants continue to complete intervals at a 1 minute:1 minute (work:recovery) ratio; however, the high-intensity bout is replaced with a moderate-intensity power output target. The intensity of the moderate interval is calculated as a percentage of the individual's estimated VO_{2max} and will be selected according to the highest intensity that the participant may tolerate or complete. After the aerobic exercise session, the participants will perform 1 set of 3 to 4 static stretching exercises held for 30 seconds.

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Figure 3. High-intensity bout progression over the course of the 16-week high-intensity interval training intervention.



AC Group

Participants randomized to this group perform a home-based flexibility intervention 3 days per week for 16 weeks. The stretching protocol consists of the same stretching exercises as in the HIIT program. As flexibility exercises are low-intensity, low-impact, and low-volume, minimal caloric expenditure is expected. To increase compliance [74] and aid in the standardization of the home-based stretching [75], participants are provided with an instructional booklet of the flexibility exercises. Participants are asked to enter these stretching bouts into the daily activity log in addition to the other self-directed exercise sessions performed. Participants in the AC group are offered to participate in the same experimental exercise condition (HIIT) after the first 16-week study period; if they do not choose to participate in the HIIT program, they are not required to complete follow-up testing and are finished with the study after the first 16 weeks. The AC participants who choose to take part in the HIIT protocol after the initial 16 weeks return at the follow-up testing time point for final testing, which serves as post-HIIT testing.

Intervention Adherence

Participant adherence to the HIIT program is measured using (1) percentage and number of prescribed sessions attended (participants must attend ≥80% of the 48 sessions to be considered compliant with the HIIT program; eg, ≥38 sessions) and (2) average minutes of exercise per week (participants must complete ≥80% of the prescribed 90 minutes per week; eg, ≥72 minutes per week). To support adherence throughout the intervention, flexible hours are offered for exercise sessions, including before or after normal working hours and on weekends. In addition, all participants are given an additional 2 weeks beyond the 16-week intervention period to make up for any exercise sessions missed because of illness, work, or travel. Participants are provided with monetary compensation for each MRI completed and parking validation for every visit to the Dana-Farber Cancer Institute.

Adverse Events

Any expected and unexpected adverse events are or will be reported to the principal investigator, who then subsequently reports to the institutional review board of the Dana-Farber Cancer Institute. Serious events must be reported within 24 hours of occurrence or finding out about the event. All adverse events, both serious and nonserious, and deaths that are encountered from the initiation of the study intervention, throughout the study, and within 30 days of the last study intervention are followed to their resolution or until the principal investigator assesses them as stable or determines the event to be irreversible or the participant is lost to follow-up. The presence and resolution of adverse events are documented on the appropriate case report form and recorded in the participant's medical record.

Data Monitoring and Management

Data are monitored internally within the Dana-Farber Cancer Institute for timeliness of submission, completeness, and adherence to protocol requirements. Monitoring begins at the time of participant registration and will continue during protocol performance and completion. The study team collects, manages, and performs quality checks of the data. Potential audits or inspections may be conducted by the principal investigator or their designated representatives. All data are stored on a secure network drive using REDCap (Research Electronic Data Capture; Vanderbilt University), a Health Insurance Portability and Accountability Act–compliant web-based application hosted by Partners HealthCare Research Computing, Enterprise Research Infrastructure & Services, on password-protected computers. Any hard-copy data are stored in locked filing cabinets in card-access facilities. The results of this study will be presented in publication, conference, and invited speaker formats.

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Sample Size Calculation

We will enroll 50 patients with breast cancer (n=25, 50% per group) in this study. We estimate that the dropout rate will at most be 20%. Assuming a 20% dropout, data from 40 (n=20, 50% per group) patients will be available for the analyses. With this sample size, we will be able to estimate within-group means for our outcome variables with a 95% CI of –0.47 to +0.47 SD units and mean differences between groups with a 95% CI of –0.64 to +0.64 SD units. Although the primary objective of the analysis for this pilot study is not to detect a between-group difference but to estimate the effect size for designing a subsequent confirmatory study, we also calculated a detectable effect size for the between-group comparison for reference. This sample size offers 80% power to detect a between-group difference at a .05 2-sided α level when the difference is 0.91 SD units.

Statistical Analysis

Analyses will reflect the trial hypotheses that involve comparisons of HIIT and AC. Initial descriptive analyses will evaluate baseline comparability between the 2 intervention groups using the 2-sample, 2-tailed *t* test or 2-sample Wilcoxon test for continuous variables and the chi-square test or Fisher exact test for categorical variables. The primary analysis variables will be changed from baseline to week 16 of neuroimaging and cognitive function measures. Summary statistics (mean, SD, median, IQR, minimum, and maximum) will be used to describe the distribution of the variables. The mean and median will be reported along with the corresponding 95% CIs. Paired tests will be performed for these continuous outcomes for each group to assess whether there is a significant difference between baseline and week 16 in each group. For between-group comparison, a 2-sample *t* test will be performed. Analysis of covariance will also be used to assess the intervention effect on those continuous outcomes (changes from baseline to week 16), adjusting for patient baseline characteristics and other clinical covariates, including any participant who is required to switch to MIIT. Furthermore, those who are transferred to the MIIT group will be included in the HIIT group in the primary analysis based on the intention-to-treat principle. As an exploratory analysis, we will identify baseline factors of the patients who are likely to be transferred to the MIIT group. We will then exclude those who are transferred to the MIIT group and compare the HIIT and AC groups adjusting for factors that affect the transfer from HIIT to MIIT. Chi-square tests will be used for group comparison of binary outcomes (eg, the occurrence of adverse events). The magnitude of the intervention effect on binary outcomes will be summarized using odds ratio and the corresponding 95% CI. For each analysis, a 2-sided *P* value of <.05 will be considered statistically significant. As this is a pilot study, we will not adjust for multiple testing. Linear mixed-effects models will be used to estimate the trajectories of those repeatedly measured continuous outcomes across the intervention to assess group differences and explore the impact of potential prognostic factors (eg, body weight, age, fat mass, race, and menopausal status) on outcomes. Linear mixed-effects models will also be used for exploratory analysis of potential neuroimaging biomarkers. The primary analysis will include all completed outcome assessments (regardless of whether the woman stayed on the intervention), inviting those who drop out of the intervention to return for outcome assessments. The only missing data would be of those who drop out of the intervention and do not return for outcome assessments. Preliminary analyses will compare women who do and do not contribute to this analysis of baseline characteristics. A sensitivity analysis will include multiple imputations of all missing outcome data, including those patients who have missing assessments.

Results

The CLARITY study was funded in January 2019 (American Institute of Cancer Research); however, recruitment was delayed until June 2021 as a result of the COVID-19 pandemic. As of May 2022, we have enrolled 4 patients in the study (n=2, 50% to exercise and n=1, 25% to control), with the fourth patient providing consent but withdrawing before baseline testing owing to chemotherapy not being pursued. In total, 50% (1/2) of the exercising patients also withdrew at week 6 of the intervention because of changes in time commitment. Recruitment is due to be completed in January 2024, with the primary results expected to be published in August 2024.

Discussion

Expected Findings

The CLARITY trial is the first randomized controlled trial to examine the impact of HIIT on cognitive function in patients with breast cancer undergoing chemotherapy. We hypothesize that undertaking HIIT will lead to improved executive function and memory scores and advance the current scientific knowledge regarding exercise and chemotherapy-induced brain function by incorporating (1) HIIT as an effective intervention that can enhance cognitive function; (2) multidimensional yet novel approaches to assess the effects of exercise on *chemo-brain*, such as fMRI, DTI, and the NIH toolbox; and (3) important secondary outcomes to provide a comprehensive understanding of the links between exercise and chemotherapy, including body composition, biomarkers related to metabolism, inflammation, cardiotoxicity, physical fitness and function, and quality of life and psychosocial outcomes.

Most patients with breast cancer experience cognitive decline during chemotherapy (up to 75%) [76,77], which may linger after treatment and even increase the risk of morbidity and mortality [78]. The onset of chemotherapy-induced cognitive decline has been an important clinical issue over the last few decades; however, the underlying mechanisms and potential interventions that can address cancer-related cognitive decline are still largely under investigation [3]. A promising nonpharmacological intervention is to engage in active physical movement, and a body of evidence supports the association between higher physical activity levels and improved cognitive function in patients with cancer [79]. A recent nationwide cohort study of 580 patients with breast cancer and 363 age-matched controls reported that patients who met the physical activity guidelines (ie, 150 minutes per week of moderate to vigorous physical activity) during chemotherapy showed significantly better self-reported cognitive function than those who did not

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meet the guidelines [80]. Nevertheless, the impact of exercise interventions on cognitive function in women receiving chemotherapy for breast cancer is not known. Previous exercise oncology trials have reported the preliminary benefits of exercise for cognitive function, but the overall quality of studies has been poor [79], warranting rigorously designed exercise clinical trials to explore the efficacy and mechanisms of exercise and cognition outcomes in patients with cancer undergoing chemotherapy treatment.

There are potential biological mechanisms to explain the benefits of exercise for chemotherapy-induced cognitive function. Exercise induces the expression of neurotrophic and neuroprotective markers, including brain-derived neurotrophic factor [81] and vascular endothelial growth factor [82], which contribute to "neurogenesis" in certain brain areas (eg, the hippocampus), leading to an enhancement of memory space and consolidation [83]. This mechanism is particularly plausible given that the hippocampus can be degenerated by toxic chemotherapy agents [84,85], whereas exercise has shown to not only improve hippocampus-dependent cognitive capacities but also increase the volume of the hippocampus [86-89]. Furthermore, neurological degeneration is significantly influenced by inflammatory markers [90], and exercise training can create a systemic anti-inflammatory environment to fight against and restore chemotherapy-induced cognitive decline [91-93].

Prior work has suggested that HIIT has significant potential to address chemotherapy-induced cognitive decline. For example, HIIT significantly improved cognitive responsiveness when compared with continuous moderate aerobic exercise in healthy young adults [94]. HIIT resulted in shorter reaction times and better response accuracy than continuous moderate-intensity exercise, suggesting that HIIT-induced neural adaptations redistribute neural resources to efficiently accomplish goal-directed behavior during cognitively demanding tasks. The observed decrease in P3 amplitude from fMRI following HIIT along with enhanced behavioral outcomes may indicate the implementation of greater efficiency in neuroelectric function. In addition, HIIT has successfully improved cognitive performance in patients with multiple sclerosis with reduced cognitive performance [95] and cancer-related fatigue in patients with breast cancer [14]. Furthermore, HIIT has shown superior effects on cognitive function (ie, verbal memory and executive functions) when compared with continuous moderate-intensity exercise in older adults [8] and individuals with Parkinson disease [96]. Therefore, HIIT may have the unique capacity to improve cognitive function in patients undergoing breast cancer chemotherapy.

Of importance, HIIT is a clinically proven, safe, and cost-effective intervention [97,98]. A recent study investigating HIIT in patients with heart failure with reduced ejection fraction revealed that the number of adverse events was not statistically different between the HIIT and moderate-intensity exercise group [99]. Furthermore, lower volumes of HIIT compared with moderate continuous-intensity exercise elicit better cardiovascular and physical fitness outcomes such as VO_{2max}; therefore, it is a time-efficient exercise option that promotes greater gains in cardiovascular outcomes [98]. During chemotherapy, the optimal type, timing, and intensity of exercise interventions are unclear. As such, the exercise protocols examined during chemotherapy in previous breast cancer studies are varied, with many using aerobic interventions with common exercise prescriptions, including 3 to 5 times per week of 30-75 minutes of moderate-intensity (40%-70% predicted maximum HR) continuous exercise rather than the on-off interval strategy of HIIT [100]. Given the potential barrier of compliance to regular exercise participation during chemotherapy in patients with breast cancer, HIIT is an intriguing option for increasing cardiovascular benefits with shorter exercise duration, which serves as an efficient alternative to traditional endurance-based exercise training [12].

The strengths of our study include the randomized controlled design, comprehensive set of cognitive and biomarker measures, and the inclusion of delayed exercise for the AC group to enhance the retention rate. We also acknowledge that our study has several weaknesses. There is potential recruitment bias, such as participants in our study who are already interested in exercise and, therefore, relatively more fit than other patients with breast cancer undergoing chemotherapy who are not keen to participate in such exercise studies. In addition, the clinic-based setting of our intervention may not be reproducible in other intervention settings, such as home-, remote-, or community-based exercise programs. Upon publication of positive findings of this pilot study, future studies would be beneficial to understand effective dissemination strategies within the standard of care and the best timing of implementation of HIIT for patients with breast cancer undergoing chemotherapy to prevent chemotherapy-induced cognitive decline.

Conclusions

The CLARITY trial is a first-of-its-kind study that incorporates a novel approach using a high-intensity exercise intervention (ie, HIIT), comprehensive cognitive measures (ie, quantitative fMRI and the NIH toolbox), and important secondary outcomes (ie, biomarkers, physical fitness and function, and psychosocial health). This study is anticipated to contribute to the current evidence on the role of HIIT in managing cognitive function and various patient-reported outcomes in patients with breast cancer undergoing chemotherapy and will establish the pilot efficacy to inform future larger phase-II and phase-III trials to confirm the findings.

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Data Availability

Data sharing is not applicable to this paper as no data sets were generated or analyzed during this study.

Conflicts of Interest

None declared.

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Abbreviations

AC: attention control
AROM: active range of motion
CLARITY: Improving Cognitive Function Through High-Intensity Interval Training in Breast Cancer Patients Undergoing Chemotherapy
DTI: diffusion tensor imaging
fMRI: functional magnetic resonance imaging
HIIT: high-intensity interval training
HR: heart rate

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MIIT: moderate-intensity interval training
MRI: magnetic resonance imaging
NIH: National Institutes of Health
POmax: maximal power output
REDCap: Research Electronic Data Capture
RM: repetition maximum
SPPB: Short Physical Performance Battery
TUG: Timed Up and Go
VO2max: maximal oxygen consumption

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Protocol

Developing a System of Health Support for Young People Experiencing First-Episode Psychosis: Protocol for a Co-design Process

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Abstract

Background: People living with psychosis face a substantially increased risk of poor psychological well-being and physical health and premature mortality. Encouraging positive health behaviors from an early stage is crucial to the health and well-being of this population but is often overshadowed by symptom management within early intervention services.

Objective: Experience-based co-design is a participant-centered approach that aims to combine service user narratives with service design methods to design systems of support for health and well-being. This study aims to use experience-based co-design principles to co-design a system that supports the health and well-being of young people experiencing first-episode psychosis (FEP), which considers the lived experience of these people within the context of early intervention services. We also aim to develop a set of principles to guide future systems to support the health and well-being of young people experiencing FEP.

Methods: Up to 15 young people living with FEP aged 16 to 24 years who are service users of early intervention services in psychosis, their immediate support networks (family or friends), and health professionals involved with early intervention services in psychosis will be invited to participate in a series of co-design workshops. Data will be collected in various forms, including expressive forms (eg, art and spoken word) and traditional methods (interview transcription and surveys), with phenomenographic and thematic analyses being used to understand these data. Furthermore, the co-design process will draw upon indigenous (Māori) knowledge and the lived experience of mental health services from the perspectives of the members of the research team. The co-design process will be evaluated in terms of acceptability from the perspective of service users via rating scales and interviews. The study will be conducted within the Lower North Island in Aotearoa New Zealand.

Results: Data collection will be performed between August 2022 and February 2023. Drawing from extended consultations with service users and service providers, we have developed a robust co-design process with which we intend to collect rich qualitative and quantitative data. The results of this process will be used to create a system of support that can be immediately applied and as preliminary evidence for funding and resource applications to deliver and evaluate a “full” version of the co-designed system of support.

Conclusions: The co-designed system of support and accompanying set of principles will offer a potentially impactful health and well-being intervention for young people experiencing FEP in Aotearoa New Zealand. Furthermore, making the co-design process transparent will further the field in terms of providing a blueprint for this form of participant-focused research.

Trial Registration: Australian New Zealand Clinical Trials Registry (ANZCTR) ACTRN12622001323718; https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=384775&isReview=true

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KEYWORDS

psychosis; health; well-being; co-design; lived experience; early intervention

Introduction

Background

The physical health of people living with serious mental illness is worse than that of the general population [1]. Cardiovascular disease is more prevalent in this population, and life expectancies are shortened on average by 25 years, a sobering statistic described as the "scandal of premature mortality" [2]. Ultimately, serious mental illness, particularly psychosis, has been identified as a significant independent risk factor for poor cardiovascular health and increased mortality [3]. Although antipsychotic medication has been implicated in the elevated risk of cardiovascular disease [4-6], modifiable risk factors such as smoking, substance use, poor diet, and insufficient physical activity also play an important role. The relationship between mental illness and poor physical health highlights the holistic nature of health such that physical and mental aspects (among other equally important parts such as social and spiritual well-being) are deeply interconnected [7]. Failure to support the health of people living with psychosis has led to international calls for interventions that prioritize both physical and mental health, with health behaviors as a key point of leverage [8].

The timing of these interventions is crucial. There is a critical window of opportunity to provide support for young people experiencing their first-episode psychosis (FEP) in maintaining positive health behaviors [9]. However, in a review of lifestyle interventions for people experiencing FEP, Gates et al [10] highlighted the lack of such programs, and even less are those programs that are based on robust evidence and theory in Aotearoa New Zealand (NZ). A lack of support for the physical health of people experiencing psychosis has been noted as a major source of inequity [1].

The long-term effectiveness of any health intervention depends on its feasibility within a given health service, which itself relies on the uptake and engagement by the target group and those who support them (eg, family and carers). A major factor in the acceptability of a lifestyle intervention is the extent to which it is suitably adapted to the specific population. People experiencing FEP may encounter barriers to health behaviors related to antipsychotic medication (eg, metabolic issues and effects on energy levels), psychological factors (eg, motivation and self-efficacy), stress, and a lack of support [11,12]. They are also likely to prioritize their own goals over those imposed on them by health services. Therefore, elucidating and addressing such barriers and understanding the goals of people experiencing FEP are crucial for intervention success.

Valuing lived experience positions service users as "experts by experience." As such, the personal experience of living with mental distress and using mental health services provides unique and essential insight into how to best serve the users of these services. Early and authentic involvement with people with lived experience can lead to enhanced credibility, quality, and relevance of services and to a greater sense of empowerment and agency for the service users involved in the development process [13-15]. Working alongside experts by experience is increasingly recognized as being crucial to service development, both within the mental health sector [13,14] and specifically with people experiencing psychosis [15].

Support from service providers is also necessary for the long-term sustainability of a new health intervention [16]. Frontline providers are responsible for implementing the intervention beyond the life of the project, as well as directly influencing the extent to which participants change their behaviors [17]. Therefore, when developing an intervention, we must understand how the intended intervention outcomes align with providers' service objectives, as well as the extent to which they can be adequately resourced and implemented in practical terms. By addressing these factors, we increase the likelihood of ongoing intervention success by encouraging service providers to "buy-in" [16].

Co-designing interventions alongside participants and service providers effectively optimizes intervention feasibility, uptake, and sustainability [18,19]. An additional benefit of co-design is that it supports participants' self-determination by providing them with an opportunity to exercise autonomy in terms of their physical health care [20]. To date, co-designed interventions that support the physical health of people experiencing FEP have been missing in Aotearoa NZ [1]. This research responds to global calls to develop such interventions [8] while aligning with localized health service contexts.

Research Objectives

Obtain Narratives Regarding the Lived Experience of Young People Being Healthy During FEP

How do young people experiencing FEP define health (ie, what "health" looks like and what components contribute to a healthy life)? What are the key barriers and facilitators to achieving positive health? What is missing in the current health care system or community that can support a healthy life?

Develop a System of Support for Leading a Healthy Life

Alongside service users, their family or support people and service providers cocreate a system of support, including specified components (eg, physical activity sessions or access to peer support groups) and format (eg, in-person or web-based connecting events).

Create a Set of Principles to Guide Early Intervention Health Care

Using data obtained across all stages of the co-design process, we aim to distill a set of principles that participants think should

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guide the support of young people experiencing FEP. For example, such principles might include collaboration, social connections, action, listening, or autonomy.

Devise a Strategy for the Future Delivery of a System of Support

Furthermore, we aim to obtain an understanding of the resources that are needed to deliver the components that have emerged from the co-design process and to create a plan to obtain these resources, whether internally from the existing health care system or externally from community, project, or research grants.

Methods

Design

An experience-based co-design (EBCD) approach [18] will be used to understand the lived experiences of service users experiencing FEP and to design an effective system of support for service users of early intervention services in psychosis (EISP). An iterative approach is an important aspect of EBCD because it allows for the reflection and hypothesis testing of prototype solutions [21].

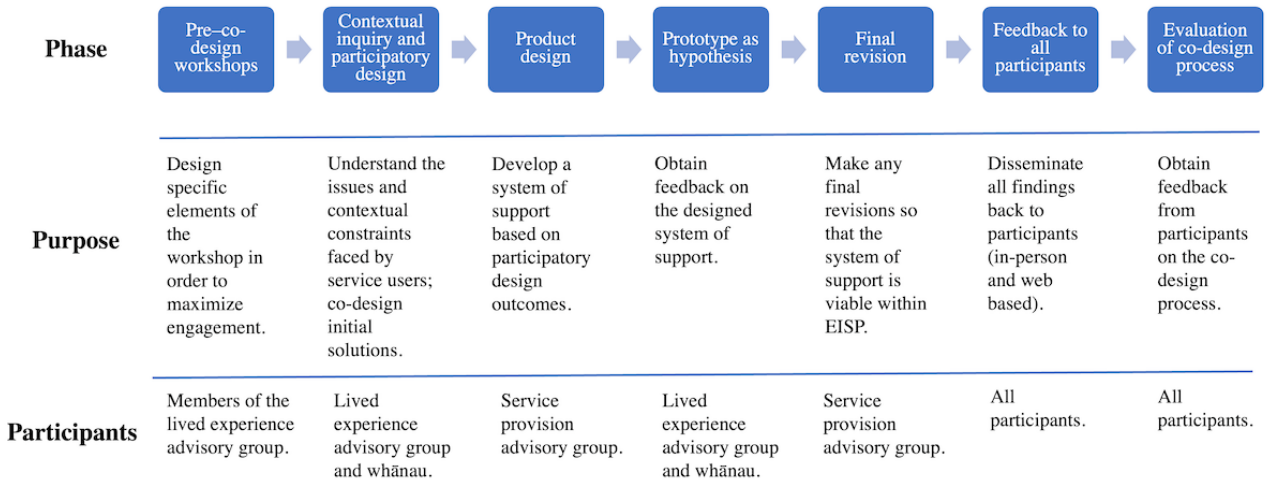
The co-design process will include five key phases:

1. Contextual inquiry (understanding the context, including issues faced by participants and contextual constraints).
2. Participatory design (working with service users and service providers to identify initial solutions).
3. Product design (working with the service provision advisory group to develop a support system based on participatory design outcomes).
4. Prototype as hypothesis (asking service users to approve or provide comment on the developed system of support).
5. Final program revision.

For the purpose of this project, contextual inquiry and participatory design will be combined into one phase. In addition, a pre–co-design focus group with prospective service user participants is used to design the co-design workshops. Following these phases, the co-designed system of support will be presented to all stakeholders, and an audit will be conducted to identify the resources required to deliver and evaluate the system of support. Service users, their close supporters (eg, family members and other support people), and staff within the EISP will be consulted via a combination of interviews and focus groups across these phases. Involving service users and their support group in the design process will provide them with opportunities to exercise autonomy in their own health care, while service providers will offer critical insights regarding the intervention feasibility and will support future implementation success.

An overview of the co-design process and the involvement of the participants at different stages are summarized in Figure 1.

Figure 1. Overview of the co-design process.



Context

Critical to conducting research in Aotearoa NZ is the duty to uphold Te Tiriti o Waitangi (the Māori version of the Treaty of Waitangi), which recognizes shared governance between the Indigenous people of Aotearoa NZ and the British Crown as well as a responsibility for supporting Māori health. Failure to do so in the past is exemplified by the overrepresentation of Māori with FEP and psychosis [22]. This co-design project works in partnership with a Māori agency, Toi Tangata, to ensure that the project is informed by mātauranga Māori (Māori knowledge) so that the resulting system of support is culturally responsive and safe for Māori with FEP in Aotearoa NZ.

Furthermore, this project takes place against a background of change to Aotearoa NZ health service delivery. This change involves the dissolution of 20 district health boards into a larger unifying health board and the establishment of an independent Māori Health Authority. Relevant to this project, the reform has been identified as a catalyst for change toward strengthening primary health care contextualized to local communities and improving the way services are used and accessed [23].

Adopting a Māori Lens for Co-design

This project embeds Māori principles, which enable approaches that are engaging and creative. For example, a key principle is the process of whakawhanaungatanga (relationship building) to create a space in which participants feel safe to tell their

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stories and narratives. Indeed, this narrative storytelling aspect is another key principle of Māori-based approaches, with pūrākau (stories) relating to one's own individual experiences being an important way to create meaning. The key features of this project that align with this approach are the use of water (wai) as a metaphor (Figure 2) and allowing participants to tell their story in different creative ways so that they are understood by their peers and researchers (Multimedia Appendix 1).

Furthermore, this research is guided by the Māori model of health, Te Whare Tapa Whā, that conceptualizes health as a whare (house) with its stability dependent on the 4 walls of well-being: tinana (physical), hinengaro (mental), wairua (spiritual), and whānau (social) health [7]. This model is inherently holistic compared with typical Western-influenced models, such that it acknowledges the importance of the dynamic relationship between the many dimensions of well-being. This holistic approach has the potential to benefit all clients of health services, including those who identify as Māori. Embedding Te Whare Tapa Whā and Māori principles into the project process and design is a strengths-based approach to incorporating mātauranga Māori into health care, rather than solely focusing on Māori health deficits.

Figure 2. "Navigating the Puna" framework used to guide contextual inquiry. Translations from Māori to English: "Moemoeā" is often used to mean "dreams and aspirations"; "mauri" often refers to one's "life force or essence". Copyright League of Live Illustrators, New Zealand.



Research Team and Partners

Researchers from the University of Otago and Te Herenga Waka Victoria University of Wellington are coleading this project. Other team members include a project manager and 3 early career researchers employed as research assistants or assistant research fellows. Throughout the research team, there are varying degrees of lived experiences of FEP and mental distress. Given the existing discrimination of people living with mental illness or distress in employment (both perceived and objective) [24,25], this was an opportunity to increase the research capacity within the workforce in terms of early career researchers with lived experience of FEP and mental distress, as well as to bring in crucial lived experience perspectives to the research process.

The Māori health agency Toi Tangata has codeveloped the co-design process alongside the research team and will

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cofacilitate the workshops. In addition, the League of Live Illustrators will be embedded in some workshops to provide live interactive note-taking in the form of illustrations. Partners within the EISP will be project facilitators and assist with participant recruitment (service users, family members, and service providers).

A steering group will guide project decision-making from procedural and policy perspectives to maximize project impact. Steering group members include clinical and academic psychiatrists, representatives of nongovernment advocacy organizations, and both Māori and non-Māori public health researchers.

Participants

Lived Experience Advisory Group

This is the primary participant group. The community of young people experiencing FEP is heterogeneous in terms of cultural background, gender, and education. The research team will work closely with the EISP to identify participants within their services who are representative of these demographic characteristics.

Whānau

Recognizing the wider network of people who support young people experiencing FEP, we will seek the perspectives from service users' whānau. Whānau is a Māori word that is often translated to "family members"; however, whānau can also refer more widely to close family friends or people who support another person. Therefore, the word whānau is used throughout this manuscript to refer to both family members and people who support service users (in a nonprofessional capacity).

Service Provision Advisory Group

The service provision advisory group will consist of health professionals who support service users in some professional or voluntary capacity, which may include psychiatrists, clinical psychologists, occupational therapists, and pharmacists, who have experience in treating, managing, and supporting young people experiencing FEP. It is anticipated that they will mostly be working within the EISP (and therefore have an internal understanding of mental health services), but participation will also be open to people working in an adjacent supportive capacity (eg, nutritionists, physical activity providers, and community support workers).

The iterative procedure means that these groups will be consulted at least twice during the co-design process.

Recruitment

For the lived experience advisory group, study information will be relayed to EISP service users via posters, email, newsletters, and caseworkers working within EISP. In terms of sample size, approximately 125 clients are engaged with early intervention FEP services in the target catchment area. We aim to recruit up to 15 clients from this pool.

For the whānau workshop, members of the lived experience advisory group will be asked to identify their supporters and pass on the study information to them. We aim to recruit 1 whānau member per participant in the lived experience advisory group.

The project team will recruit service provision advisory group members through their existing networks and local early intervention symposia. Study information will also be circulated to relevant experienced health professionals via EISP staff team meetings, newsletters, and email.

Participant Remuneration

Our group recognizes that a co-design process that truly values the opinions and narratives of service users and their whānau should compensate them in a way that recognizes them as experts in their own health care. As such, members of the lived experience advisory group will receive NZ $100 (US $62) in vouchers as compensation for their time. In addition, these participants will be offered a choice of a framed print or tote bag depicting an illustration produced during the first workshop. Whānau participants will receive NZ $50 (US $31) for attending the single 2-hour workshop.

Members of the service provision advisory group who are employees of mental health services will not be remunerated, as participation is interpreted as part of their employment. Any members of the service provision advisory group who are engaged as volunteers and not in a professional capacity will be offered remuneration in line with service users and their whānau.

Co-design Workshop Format

Overview

The workshop format was developed in collaboration with members of the lived experience advisory group, the research team, and partners over a series of meetings. Together, this group contained expertise in the lived experience of psychosis and EISP, community engagement, mātauranga Māori, and co-design. A key objective in designing these workshops was to ensure that as many participants as possible have the opportunity to engage meaningfully with the project.

Two key decisions in the design were whether the workshops should include all participants (ie, service users, whānau, and service providers) or whether they should be separated into 3 distinct workshops and where the workshops should be held (ie, in-person or web-based workshops and specific location if in person).

Combined or Separated Groups

The group decided that the lived experience advisory group, their whānau members, and the service provision advisory group would each attend separate workshops, thus enabling frank and open discussions regarding service users' health and related barriers and not being inhibited by the presence of another group. However, the lived experience advisory group will be given the option of being accompanied by a whānau member or caseworker for support at each workshop they attend. One-to-one interviews (either web-based or in-person interviews) will be offered to members of the lived experience advisory group who are uncomfortable speaking within group situations or unable to attend workshop times.

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Platform and Location

With regard to choosing web-based versus in-person workshops, members of the lived experience advisory group indicated a preference for in-person workshops to maximize engagement and relationship building. Feedback regarding whānau members was that they were often employed full time and had time and travel constraints. Therefore, whānau members will be invited to a web-based evening workshop during the contextual inquiry and participatory design phases.

Many members of the service provision advisory group are health professionals with time constraints in terms of their clinical duties. For workshops involving this group, in-person attendance will be offered for the first relevant session (product design) to create initial engagement and investment in the project. The second round of sessions involving the advisory group (product revision) will be offered as a web-based workshop and survey.

The venue chosen for the co-design and similar workshops involving service users is important in terms of setting participant expectations and creating a sense of security and willingness to share experiences. The research team considered the balance between being in a familiar space that was well known to service users (ie, EISP clinical services) and the need for a space that was not directly associated with a clinical setting, thus increasing the likelihood that participants would feel free to share their experiences (ie, in a neutral venue). It was decided that rooms at the University of Otago campus will be used for the first workshop involving the lived experience advisory group. For whānau, this did not apply because the workshop will be held on the web. For the advisory group, the venue will be EISP clinical service centers.

Workshop Facilitation

The workshops will be cofacilitated by diverse members of the project team across all the co-design phases. All facilitators have significant experience in facilitating workshops in community settings, including with young people experiencing FEP, whānau members, and service providers. Notably, several facilitators have lived experience of FEP and mental distress. This will create an opportunity for positive role modeling and increased the relatability of the workshop content. The workshop design draws from contact-based antistigma and discrimination intervention models, which have been used to guide efforts to counter stigma toward mental distress in Aotearoa NZ [26,27].

Although lived experience–directed antistigma interventions typically target groups who hold the power to discriminate, the model here also functions to alleviate internalized stigma for participants who experienced FEP. The power of the contact model [27] draws on the principles of all group members having equal status and providing the opportunity for relationship building, active cooperation, and the pursuit of a mutual goal. Other members of the facilitation team have extensive knowledge and experience in incorporating the Māori worldview into co-design processes.

Ethics Approval

The project has been approved by the University of Otago Health Ethics Committee (ref H22/048) and has undergone a Māori consultation in line with guidelines pertaining to research based in Aotearoa NZ. Considering that workshops may be used to address potentially sensitive health-based topics and thus present a small risk of psychological distress, an experienced clinical psychologist (not directly associated with EISP) will also attend sessions involving the lived experience advisory group to meet the ethical guidelines regarding psychological safety. The project has also been registered with the Australian NZ Clinical Trials Registry ACTRN12622001323718.

Results

Details of the co-design workshops are summarized in Multimedia Appendix 1.

Phase 1a: Contextual Inquiry and Participatory Design With the Lived Experience Advisory Group

The illustrated framework ("Navigating the Puna"; Figure 2) was developed by research team members with lived experience of mental distress, the Māori co-design partners (Toi Tangata), and artists from the League of Live Illustrators. The illustration encompasses the main objectives of contextual inquiry and participatory design (eg, experiences of health, barriers to and facilitators of health and well-being, and how health and well-being can be supported). "Navigating the Puna" is based on mātauranga Māori in that the puna (fountain or spring) represents the person with a lived experience of FEP. The illustration will be used as a framework to guide the first workshop with the lived experience advisory group (workshop 1a).

Contextual inquiry with the lived experience advisory group will seek to understand (1) how young people conceptualize health while living with FEP, (2) what constitutes a healthy life and the barriers and facilitators to leading a healthy life, and (3) the contextual constraints they encounter.

A phenomenographic approach will be used to provide participants in the lived experience advisory group the opportunity to express their experiences in a way that is meaningful to them and not constrained to typical focus group–style data collection. Phenomenography is "a qualitative research approach used to describe variations in people's experiences through their own discourse, not to derive general principles of how things appear but to make known the way(s) experiences can be commonly understood" [28], with the goal of discovering different ways of understanding the experience of phenomena [29-31].

In line with this approach, participants will be offered several platforms to describe their experiences. Opportunities will include writing or audio recording their experiences in the form of stories, simple descriptions, or voice notes. A data wall will be set up to which participants can contribute post-it notes at any point during the workshop as ideas occur. Alternative creative outputs include drawings, paintings, poetry, and clay sculptures. There has been an increasing trend in using creative

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and art-based approaches in health care, for example, photovoice, visual artistic methods such as drawing and painting, and literary arts such as poetry and storytelling [32-39]. All these are accepted approaches for collecting phenomenographic data [29].

When possible, photos of creative outputs will be taken, and participants will be asked to provide a brief description of the output in their own words to aid later interpretation and analysis. Members of the research team will also collect data through a process of interactive note-taking using a whiteboard that will be visible to the participants throughout the day. These notes will be collated and photographed at the end of the workshop.

Data will be analyzed using an approach aligned with both thematic analysis [40] and phenomenographic analysis [41]. These approaches share a common process that is characterized by several stages: (1) familiarization (data are reviewed taking note of initial ideas); (2) identification (data that are related to the phenomenon being described are identified); (3) sorting (identified data are organized into "pools of meaning" according to similarities); (4) contrasting and categorizing (themes are contrasted, and categories are generated with descriptions); and (5) reliability checking (a portion of the data coded by independent researchers will be checked for intercoder reliability).

The result will be a collection of themes regarding service users' experiences of health and well-being while living with FEP and facilitators of and barriers to leading healthy lives.

For the participatory design aspect of the workshops (for both 1a and 1b), ideas with regard to possible program components, features, or structures that participants create will be noted, collated, and taken through to phase 2 with the service provision advisory group.

Phase 1b: Contextual Inquiry With Whānau

A web-based focus group will be held with whānau to explore their experiences of supporting a young person living with FEP and their perspectives on what additional supports are required from health care services. This focus group will be audio recorded and analyzed using thematic analysis as described in the previous section. The findings from phase 1b will supplement the themes identified from the lived experience advisory group.

Phase 2: Product Design With Service Provision Advisory Group

An in-person focus group will be held, and the sessions will be audio recorded. Key areas that will be addressed include participants' experiences in supporting young people living with FEP in terms of maximizing health and well-being, perceived barriers to and facilitators of positive health behaviors, and any other aspects that they see as being relevant.

A summary of findings from the previous workshops with the lived experience advisory group and their identified whānau will be presented. Participants will be asked to respond to the proposed solutions to ascertain which features and components they see as feasible in the context of the existing EISP and which of these may be feasible in the future. Participants will be asked to identify other potential approaches to supporting health and well-being that align with the initial design solutions proposed by the lived experience advisory group.

The research team will collate these responses and integrate them with the initial co-designed system of support from the previous workshops, resulting in a "prototype" support system or program.

Phase 3: Prototype as Hypothesis With the Lived Experience Advisory Group

A web-based focus group with the lived experience advisory group will be held, and sessions will be audio recorded. The prototype will be presented to participants, who will be asked to provide feedback in terms of the acceptability and likelihood that they would use it. Participants will also be asked to identify any issues that they foresee with the prototype and any revisions to overcome such issues. Any omissions in terms of requested features, components, or formats will be explained.

The research team will collate these responses and integrate them to create a new revised version of the system of support or program.

Phase 4: Final Revision With the Service Provision Advisory Group

Feedback will be sought on the revised version of the system of support or program in the form of a web-based survey. The system or program is presented in full as a web-based static document, and the feedback sought will pertain to the feasibility of the various features in the form of 1 to 10 rating scales. For features that are deemed unfeasible, participants will be asked to provide a rationale for this. Participants will be able to leave open-text feedback on each feature or program as a whole.

Post–Co-design Reflection and Presentation of Findings

The project team will produce a final version of the system or program that will account for the data and feedback offered by all participants. This will be presented to all participants and invited guests during a seminar.

Evaluation of the Co-design Process

Members of the lived experience advisory group will be asked to provide feedback on the co-design process. Feedback will be sought at the final program presentation, with an option to provide web-based feedback. Specifically, feedback will be sought regarding (1) the extent to which participants felt like their autonomy was supported during the co-design process, (2) the extent to which participants came away with a sense of hope for their own lives and for their health care, (3) whether participants felt listened to throughout the process, and (4) to what extent participants feel confident that change might happen as a result of the co-design workshop.

This feedback will be collected using rating scales (eg, "On a scale of one to ten, how much confidence do you have that change might occur as a result of this co-design process?").

Regarding autonomy and feelings listened to, the Healthcare Climate Questionnaire (HCCQ) will be used. The HCCQ also contains questions pertaining to perceptions of being listened

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to by facilitators (eg, "The workshop facilitators listened to how I would like to do things regarding my health").

Postproject Audit

The research team will work with project facilitators at the EISP and health care managers to identify a minimal deliverable version of the system or program and if necessary, identify potential sources of funding to deliver and evaluate a "full" version of the system or program (eg, research grants, internal health care funding, and Ministry of Health grants). This audit will take the form of a discussion group and feedback via e-mails.

Discussion

Overview

This project has four objectives: (1) to understand the lived experiences of young people in being healthy during FEP, (2) to develop a system of support for leading a healthy life, (3) to create a set of principles that guide early intervention health care for young people experiencing psychosis, and (4) to devise a strategy for the future delivery of a system of support for health and well-being within this community. To achieve these objectives, an EBCD approach will be undertaken, within which we will work alongside and listen to key stakeholders (service users with lived experiences, their whānau, and service providers) through a series of workshops. The results of this project will provide us with (1) a richer understanding of the lived experiences of young people living with FEP, (2) a co-designed system of support for health and well-being, (3) a set of guiding principles for developing such systems of support, and (4) a clear strategy for delivering and evaluating the co-designed system.

This co-design project responds to the lack of interventions aimed at supporting the health of young people experiencing FEP [8]. Close collaboration with experts in the lived experience of FEP and mātauranga Māori works to ensure the relevance of, and engagement with, the co-design process and the resulting support system by end users in Aotearoa NZ. This approach answers the calls for health care research and services to genuinely engage with indigenous (Māori) knowledge systems in a collaborative rather than prescriptive and tokenistic manner [42]. This collaborative approach also works alongside EISP service providers to support the longevity of the end product beyond the life of the project.

Limitations

This project is specific to the context of Aotearoa NZ. Although it provides a useful example of how to engage with young people with lived experiences of FEP, Indigenous stakeholders, and EISP providers, careful consideration is needed when working outside of this specific context. In addition, the authors acknowledge that young people experiencing FEP engage in a wide variety of services. This project is co-designed specifically with young people at the stage of FEP and with EISP providers. Therefore, reproducing this study with other services and with persons at a different stage of diagnosis may likely produce a different result. Given that physical health inequities are experienced by people with serious mental illnesses in broader terms [8], further research is needed to investigate how this approach may be applied to people with other diagnoses and service providers.

A further limitation is that although the power of the contact model is named as a key guiding framework for the co-design process, a true representation of this model would have resulted in combined group discussions (ie, service providers, service users, and whānau). However, our priority was to create a safe space for service users to discuss, and owing to the explicit request of the service users within our consultation round, we decided to keep these stakeholder groups separate, resulting in a power of contact model adapted to suit our primary participants.

This protocol provides an example of how health professionals and researchers can engage in the co-design process toward a more collaborative way of working and participant-centered support. It is our hope that the results of this project will address the inequities that young people experiencing FEP face and improve their health and well-being. Furthermore, we hope that the guiding principles produced by this project can be applied to develop similar support systems in communities outside the area in which this research takes place.

Acknowledgments

Toi Tangata provided significant support by working with members of the lived experience team to design and facilitate co-design workshops, in addition to deepening the authors' understanding of Māori knowledge, worldview, and language throughout the project development. The League of Live Illustrators cocreated the materials used to frame the co-design workshops alongside the lived experience team and Toi Tangata. Early intervention in psychosis services provided significant support in recruiting all project participants. The authors acknowledge and thank the members of the lived experience team who were fundamental in developing the co-design process. The project is funded by a Lottery Health New Zealand project grant. The salary of the lead author is funded by the University of Otago Division of Health Sciences Postdoctoral Fellowship awarded for the purpose of this research.

Data Availability

The data collected in this study will be deidentified and made openly available in Figshare [43].

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Co-design workshops details.
[DOCX File , 21 KB - resprot_v12i1e44980_app1.docx]

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Abbreviations

EBCD: experience-based co-design

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EISP: early intervention services in psychosis
FEP: first-episode psychosis
HCCQ: Healthcare Climate Questionnaire
NZ: New Zealand

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Protocol

Addressing the Shortage of Health Professionals in Official Language Minority Communities to Strengthen Retention Strategies for the Benefit of New Brunswick Francophone and Acadian Communities: Protocol for a Mixed Methods Design

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Abstract

Background: COVID-19 has highlighted already existing human resource gaps in health care systems. New Brunswick health care services are significantly weakened by a shortage of nurses and physicians, affecting regions where Official Language Minority Communities (OLMCs) reside. Since 2008, Vitalité Health Network (the "Network"), whose work language is French (with services delivered in both official languages, English and French), has provided health care to OLMCs in New Brunswick. The Network currently needs to fill hundreds of vacant physician and nurse positions. It is imperative to strengthen the network's retention strategies to ensure its viability and maintain adequate health care services for OLMCs. The study is a collaborative effort between the Network (our partner) and the research team to identify and implement organizational and structural strategies to upscale retention.

Objective: The aim of this study is to support one of New Brunswick health networks in identifying and implementing strategies to promote physician and registered nurse retention. More precisely, it wishes to make 4 important contributions to identify (and enhance our understanding of) the factors related to the retention of physicians and nurses within the Network; determine, based on the "Magnet Hospital" model and the "Making it Work" framework, on which aspects of the Network's environment (internal or external) it should focus for its retention strategy; define clear and actionable practices to help the Network replenish its strength and vitality; and improve the quality of health care services to OLMCs.

Methods: The sequential methodology combines quantitative and qualitative approaches based on a mixed methods design. For the quantitative part, data collected through the years by the Network will be used to take stock of vacant positions and examine turnover rates. These data will also help determine which areas have the most critical challenges and which ones have more successful approaches regarding retention. Recruitment will be made in those areas for the qualitative part of the study to conduct interviews and focus groups with different respondents, either currently employed or who have left it in the last 5 years.

Results: This study was funded in February 2022. Active enrollment and data collection started in the spring of 2022. A total of 56 semistructured interviews were conducted with physicians and nurses. As of manuscript submission, qualitative data analysis

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is in progress and quantitative data collection is intended to end by February 2023. Summer and fall 2023 is the anticipated period to disseminate the results.

Conclusions: Applying the "Magnet Hospital" model and the "Making it Work" framework outside urban settings will offer a novel outlook to the knowledge of professional resource shortages within OLMCs. Furthermore, this study will generate recommendations that could contribute to a more robust retention plan for physicians and registered nurses.

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KEYWORDS

human resource shortage; retention; health care professional; health care provider; shortage; health care professionals' retention; registered nurse retention; physicians' retention; retention factors; Francophone communities; linguistic minorities; rural communities; minority; minorities; language; rural; ethnic; French; Francophone; Acadian; Canada

Introduction

Background

In Canada and elsewhere, COVID-19 has highlighted the human resource gaps already present in health care systems. In New Brunswick, health care services are weakened by a shortage of registered nurses and physicians, mainly affecting rural areas, where Francophone and Acadian communities are concentrated and considered as Official Language Minority Communities (OLMCs) [1]. These OLMCs have greater social and health disparities (eg, smoking and obesity) [2] and are older than their Anglophone counterparts, which are the majority population in New Brunswick [3,4]. In other words, being part of a linguistic minority group is a potential barrier to health care and services access and makes people vulnerable to health inequities [3-5].

Since 2008, a total of 2 health networks have been providing health services and care to the population of New Brunswick: Vitalité Health Network (the "Network") and Horizon Health Network. They are required by the Regional Health Authorities Act to provide services to users in the official language of their choice (English or French). It is worth mentioning that the same law stipulates that the language of operation of Horizon Health Network is English, whereas it is French for the Vitalité Health Network. The Network, our partner, covers 4 geographic regions, 3 of which are in rural areas where many Acadian and Francophone communities reside. The fourth zone includes a more urban area, where both health networks provide health services. The New Brunswick population currently totals 775,610 citizens, 30% of whom report French as their first language [6]. The Network manages and delivers health care and services to Francophone citizens in the province, representing approximately 241,100 people living in the 4 geographic territories [6]. It has approximately 7700 part-time and full-time employees, including 560 physicians [7].

The latest data show that there are 100 vacant physician positions [8] and 200 vacant registered nurse positions [9]. For the past year, a shortage of staff has caused the closure of the obstetric services in the Restigouche region [10]. Also, the departure of oncologists has recently affected the Dr Georges-L.-Dumont University Hospital Centre in Moncton. Several media papers have addressed these issues [11]. Provincial projections predict a critical shortage of more than 1300 registered nurses in the next 5 to 7 years, and approximately 35% of family physicians will retire [12]. Given these staff shortages, combined with the global COVID-19 pandemic, it is imperative to strengthen the Network's retention strategies to ensure its viability and reduce the health disparities in OLMCs.

Theoretical Frameworks

The conceptual framework is based on the "Making it Work" framework [13,14] and the "Magnet Hospital" model [15], in addition to the delivery of health care services in OLMCs. The inclusion of the linguistic minority variable will lead us back to our objectives or research questions and will provide theory-based results, increase credibility, and foster transferability to practice settings [16].

The "Making it Work" Framework

The "Making it Work" framework, which focuses on rural and remote recruitment and retention, is based on 9 key strategic elements that primarily address determinants of the environment that are grouped under 3 main activities (ie, planning, recruiting, and retaining) and are briefly described [13,17] (see Figure 1). The Network's Board of Directors decided in 2020 to take a closer look at this framework, which has been the focus of a framework in Northern Ontario [14,18]. The framework was launched in 2011 by an international collaborative, addressing the challenges of recruiting and retaining health professionals in rural and remote northern settings and has been the focus of the Northern Ontario School of Medicine, which has sites throughout the north of Ontario, 1 being in the OLMC of Sudbury [19].

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Figure 1. Making it Work framework (adapted from École de médecine du Nord de l'Ontario [20], which is published under Creative Commons Attribution 4.0 [CC BY 21]).



Planning thus involves assessing the population's health needs and aligning service delivery models with them [17]. This task also includes developing job profiles for the professionals the organization wishes to recruit, including skills specific to working in rural and remote settings [17]. *Recruitment* focuses on sharing information about the work environment, practice, population served, and available housing in the area [17]. Recruiting also involves consideration of community engagement and support for the professional's family, such as employment opportunities for the spouse. Finally, elements included in the *retention* component of the model are related to team cohesion, professional development, and training [17].

In total, 5 conditions are contingent on the success of the framework [17,22]: acknowledgment of the unique challenges of rural and remote areas (eg, the unique aspects of living and working in these areas compared to urban settings), engagement of communities and consideration of their perspectives (in workforce planning or policy-making), adequate investments (targeting professional development and training internships, in particular), an annual cycle of activities (as opposed to actions driven by urgency) that promote recruitment and retention (like attention-drawing job descriptions or performance standards), and finally, continuous monitoring and evaluation (to modify interventions based on experiences and improve quality to meet the needs of the population). Conjointly, these conditions promote the establishment of a stable and appropriately qualified professional workforce in rural and remote communities, in this case, the OLMCs.

The Magnet Hospital Model

The Magnet Hospital model emerged in the early 1980s when the American Academy of Nursing appointed a task force to

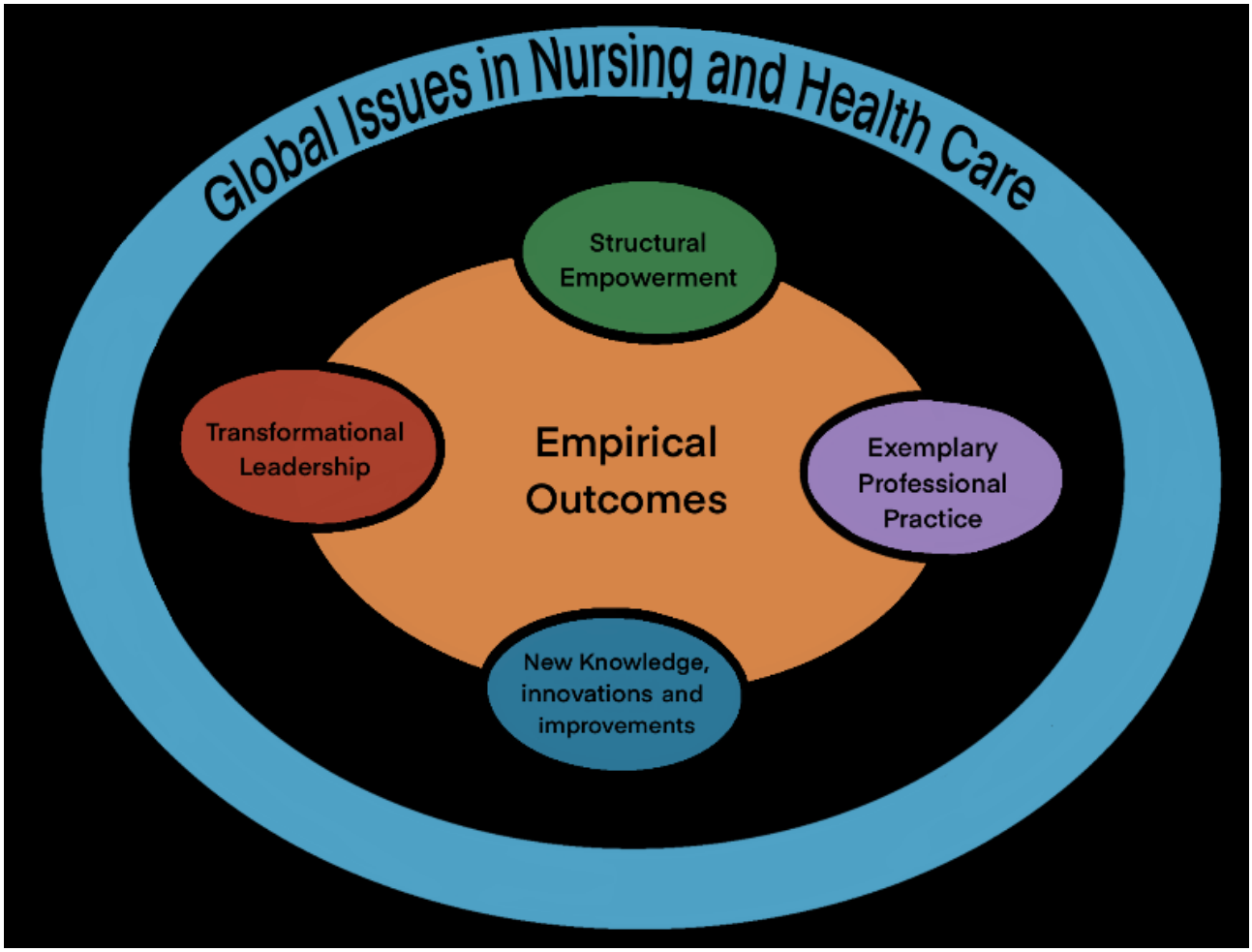
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study the facilitating factors and barriers to professional nursing practice in hospitals [15]. McClure et al [23] revisited the work done by these forerunners, focusing on organizational culture and quality of care:

> *We found that all these settings had a commonality: their corporate cultures were totally supportive of nursing and of quality patient care. What we learned was that this culture permeated the entire institution. It was palpable, and it seemed to be almost a part of the bricks and mortar. Simply stated, these were good places for all employees to work (not just nurses), and these were good places for patients to receive care. The goal of quality was not only stated in the mission of these institutions, but it was lived on a daily basis.* [p. 199]

Thus, the Magnet Hospital model, or the "magnet" hospital, means "literally, the ability to retain and attract staff, and figuratively, the ability to foster well-being to their patients" [24]. The evolution of this model over the past few decades led to the model presented in Figure 2.

Figure 2. An evaluation of the nursing practice environment and successful change management using the new generation Magnet Hospital model [25].



The model [25] in Figure 2 builds on areas that are primarily part of the work environment: (1) transformational leadership (ie, "magnet" managers at all organizational levels), (2) exemplary professional practices (eg, the ethic of caring), (3) structural empowerment (eg, decentralized decision-making), (4) new knowledge, innovation, and improvements (eg, research- and evidence-based decision-making), and (5) empirical outcomes (eg, quality of care and organizational goals) [25,26]. These components cannot be separated from the overall context, relating to, for example, the global pandemic, and all have implications for employee retention, optimal service delivery, and quality of clinical care [27,28].

Shortage of Health Care Professionals and Access to Health Care in OLMCs

The shortage of registered nurses and physicians is particularly acute in rural areas, where are concentrated OLMCs [1,3]. These regions have difficulty attracting and retaining professionals who generally do their training and start working in urban settings [29]. Also, a preference for acute care clinical settings in urban areas and the mobility of professionals make recruitment and retention challenges difficult to overcome by rural and remote OLMCs [30].

A study [30] has shown that one of the factors affecting the retention of professionals in OLMCs is the quality of the work environment. For example, the quality of social ties, the sense of belonging, the diversity of the environment, both ethnic and

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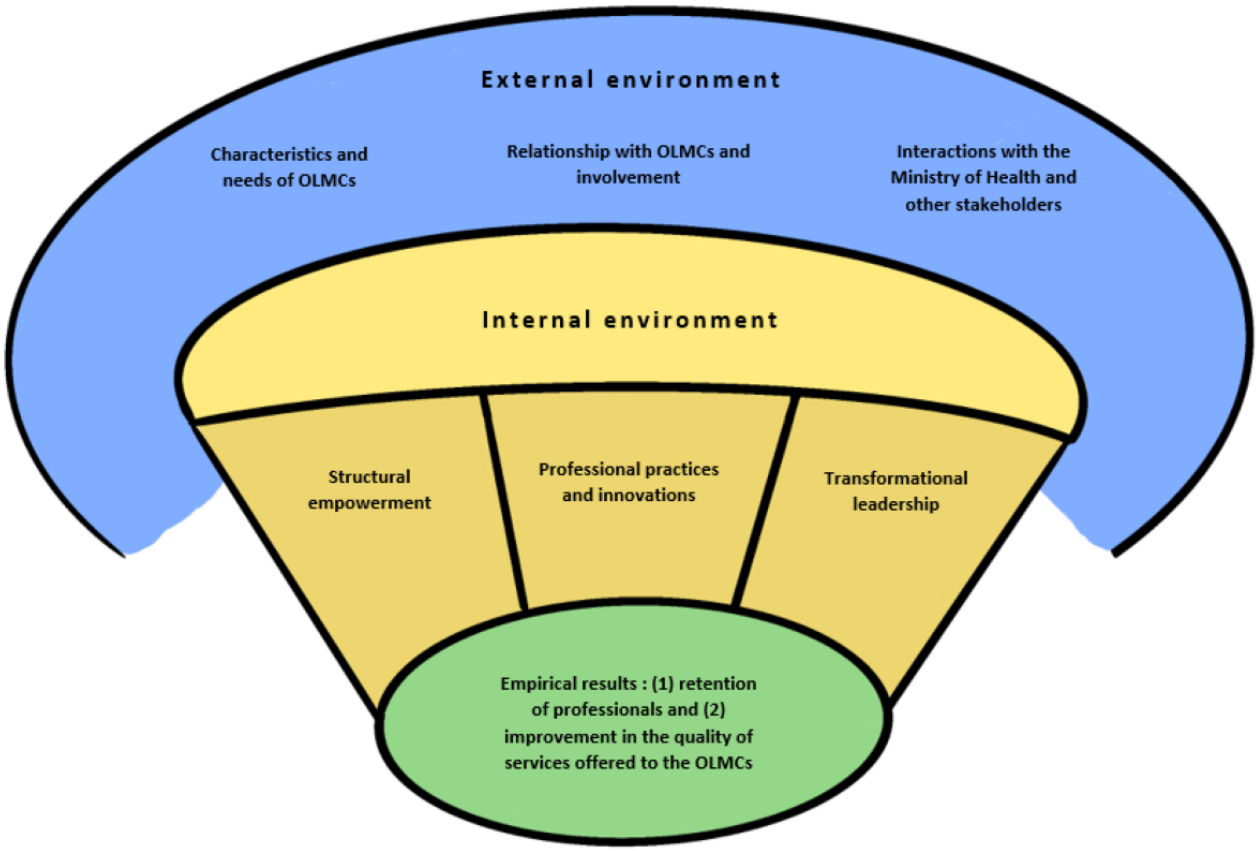
linguistic, and the working conditions influenced their desire to remain in their position [30].

For OLMCs, a shortage of registered nurses and physicians can lead to inadequate access to health services and negatively impact initiatives to meet their health needs, such as those in prevention and promotion [31,32]. The provision of quality and safe health care services to OLMCs is, in other words, linked to the availability of competent professional resources [33]. Furthermore, studies have shown that the challenges to offering services to the linguistic minority group are due to the lack of professionals who are able to provide these services within OLMCs [34,35]. The smaller pool of bilingual professionals can thus have consequences on the health of these communities [36-38].

Conceptual Framework and Research Questions

The conceptual framework presented in Figure 3 shows that varied factors in the internal and external environment influence the retention of registered nurses and physicians. The "Magnet Hospital" model provides key work environment components for understanding the retention capacities of these health professionals that are also essential to quality patient care, whereas the "Making it Work" concept helps us analyze the retention factors through the lens of strategic elements crucial to accessing high-quality health services in rural and remote environments.

Figure 3. Factors influencing the retention of Registered Nurses and Physicians Working in OLMCs. OLMCs: Official Language Minority Communities.



The internal environment of the health organization (in yellow in Figure 3) has three components: (1) structural empowerment, (2) professional practices and innovations, and (3) transformational leadership. *Structural empowerment* refers to a structure that is decentralized and debureaucratized [39]. This component includes recognition measures such as awards or scholarships for innovative projects [40] and employee satisfaction with salary, workload, and work-life balance. It also considers other vital elements such as competitive pay, adequate staffing, a sense of control over decision-making and practice, and perceived stress levels [15,24].

Professional practices and innovations are associated with a philosophy of excellence in care that emphasizes evidence-based skills and best practices, a focus on quality improvement through innovative approaches, and the value placed on professional development [15,39]. This component indicates the importance of ensuring that resources are available to new employees like mentorship, access to advice, and other resources to help with their integration. A collaborative relationship between registered nurses and physicians and autonomy based on professional standards are all part of this component [15,27]. Ethical values in caring and transparency are linked to better care for people needing health care and services while helping with their self-fulfillment [24].

Transformational leadership refers to close supervision that is characterized by a manager who is visionary, respectful, attentive to their collaborators, stimulating, and mobilizing [24,41]. To counteract burnout, the caring approach to management prioritizes social ties and team cohesion as well as dialogue and trust [41]. In addition, the practice of supportive

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management must take place in a stimulating work environment to be effective.

The external environment of the health organization (in blue in Figure 3) is made up of three main dimensions: (1) the characteristics and needs of OLMCs; (2) the relationship established between the health organization and the OLMCs, and their involvement in attracting and retaining professionals; and lastly (3) interactions with the Department of Health and other relevant actors (such as training institutions).

The *characteristics and needs of OLMCs* focus on the particularities of the populations served by the health organization. In New Brunswick, the territory served by the Network is composed primarily of Francophone and Acadian populations, many of which are in rural areas. These citizens are generally more disadvantaged in terms of socioeconomic status and are older than elsewhere in the province or the country [42]. The health needs of the OLMCs served by the Network differ from one health zone to another and even from one city to another and must be reevaluated on an ongoing basis. A service model that does not meet the needs of rural and remote communities can lead to burnout and job dissatisfaction for its employees [14].

The *involvement of OLMCs* in efforts to counter the departure of health professionals is reported in the literature on the "Making it Work" concept [13,14]. While the involvement of rural and remote communities is crucial when recruiting health care professionals [14], policies that encourage their active and ongoing participation are also essential to ensure the retention and stability of medical personnel [43].

The interactions with the *Department of Health and other relevant actors* go hand in hand with the involvement of OLMCs, as it is linked to the relational dynamics in the planning stage between the health organization and other key players, particularly the Department of Health, training institutions, and nongovernmental organizations. Decisions made by actors of the external environment, sometimes outside the control of the Network, can affect the intention to stay of professionals. Furthermore, without adequate investments, such as in professional development, efforts remain focused on solving urgent problems (vacancies) at the expense of an ongoing strategy to ensure the stability of the skilled workforce [17].

Finally, the empirical results (in green in Figure 3) are influenced by “what’s going on” in the environment (internal and external) of the health care organization. Factors emanating from these 2 spheres affect the commitment and retention of registered nurses and physicians responsible for improving the quality of services offered to OLMCs.

Main and Specific Objectives

The overall objective of this study is to support one of New Brunswick health networks in identifying and implementing concrete strategies that take into consideration its environment to promote physician and registered nurse retention.

Two specific objectives are derived from the general research objective: (1) to identify current staffing trends and examine the turnover rate in each geographical zone of the Network to determine where the most significant challenges are with recruitment and retention; (2) to identify and understand the factors that affect the retention of physicians and registered nurses (a) at the operational level, to determine the factors that make the Network’s environment (internal and external) attractive, such as the working and living conditions of professionals, and (b) at the strategic level, to make concrete and valuable recommendations to our main partner, the Network.

Methods

Methods Overview

This study will use a sequential mixed methods design that combines quantitative and qualitative approaches [44]. This design offers a more comprehensive technique to better understand phenomena and nuance data interpretation [45].

Initially, secondary data will be compiled within existing sources to identify current organizational trends and inform our qualitative data collection strategy. In other words, the quantitative analysis of secondary data will guide the qualitative approaches’ recruitment process. Specifically, we will assess job vacancy and turnover rates for nurses and physicians to target the more problematic geographical zones and departments concerning retention. Turnover rates are commonly evaluated as an indicator of retention of hospital staff, and it is especially used for nurses [46-48]. When turnover rates are chronically high, it may indicate that staff working in that hospital unit are not satisfied at work [46] or that the work environment is not favorable to psychological well-being [48]. Research on turnover rates indicates average annual turnover rates for nurses are between 14% and 27% in Canada [49]. This finding is supported by data worldwide that found the average turnover rate for nurses to be between 15% and 36% [50,51]. For this study, we will use job turnover rates as a guide to target the areas that are more or less successful with retention.

As a secondary indicator for retention, vacant positions will also be analyzed for nurses and physicians within the Network. Using a similar strategy, the job vacancy rate will be assessed as an indicator for retention [52]. The 2 indicators, the turnover and job vacancy rates, will be analyzed together to target areas within the Network that are doing well with retention and areas with retention challenges.

We will then target these areas to recruit participants for individual and group discussions as described in section “Qualitative Approach: Data Collection and Analysis.” For physicians, position turnover rates are less reported, and researchers generally use the intention to leave as a proxy for turnover rates [53]. Of the little data available, the average turnover rate for physicians is between 4% and 25% [54].

Quantitative Approach: Data Collection and Analysis

Component 1 (quantitative secondary data analysis): to achieve specific objective 1, secondary data from the Network will be used to illustrate the proportions and the tendencies in physician and registered nurse vacancies by zone in the Network. It will also measure the extent of the current shortage and determine if there are significant differences between regions and sectors (eg, psychiatry and obstetrics) to identify those that are more

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successful than those that are less successful. The data from the past 5 years related to age and gender, the number of years of service in the Network at the moment of departure, family status, type of professional (specialist vs generalist), hospital unit or service area, and geographic area will be analyzed. Information on turnover rates for physicians and registered nurses for the past 5 years will be compiled and analyzed from the Regional Plan of Physician Workforce descriptive data collected by the Network's Medical Services. To supplement this information, data from the Network's Human Resources Department regarding medical and nursing staff who have left their positions will be used. From these data, a profile of professionals who have left the Network can be created to tailor retention strategies and improve their effectiveness.

Since we plan to use secondary data on job vacancies and turnover rates, we will be limited to the data already collected and may face an information gap. Some team members have used quantitative approaches in their research for several years. Faced with sometimes incomplete databases, the team may have to develop data collection tools to collect more quantitative data to supplement the secondary data provided by the Network. At this time, the approach considered is a web-based survey to target employees (nurses and doctors) working at the Network and people (nurses and doctors) who have left. If a survey is used, validated questions will be used to measure factors that impact job satisfaction and intention to leave the current workplace [55-57]. The survey design will be multiple choice questions with a 7-point Likert scale to maintain validation from previous studies.

The statistical analysis for specific objective 1 will be discussed first. Next, we will conduct bivariate and multivariate correlational analyses to assess the influence of the factors comprised in our conceptual framework over health professionals' intention to stay. Considering that participants' sociodemographic characteristics (ie, sectors, gender, age, education, and years of service) may influence the relationships between the variables under study (ie, factors comprise in our conceptual framework), analyses will be conducted to determine the magnitude of their effect [58].

Qualitative Approach: Data Collection and Analysis

Component 2 (qualitative data): to achieve specific objective 2, qualitative data will be collected through semistructured interviews, focus groups, and a document review, including gray literature such as media reports.

Semistructured Interviews

The interview guides were developed to take into consideration the factors listed in the conceptual framework (Figure 3). Participants will be asked to share their views on topics such as job satisfaction, autonomy in decision-making, leadership, and language used at work. The first set of semistructured interviews (approximately 30) will be conducted with physicians and registered nurses who have left the Network in the past 5 years. The second set of semistructured interviews (approximately 30) will be conducted with these same 2 types of professionals the Network currently employs. In sum, the data will be used to understand whether the reasons for retention and departure are more related to the external environment or whether they result from the internal environment. The specific number of semistructured interviews and focus groups is subject to change, depending on data saturation, that is, when the ability to obtain additional new information has been attained, and further coding is no longer needed [59]. If necessary, we will adjust our recruitment efforts to ensure gender participation that represents diversity in the work environment, considering that the proportion of women is higher than men in the health sector. The interviews will be completed on the web or in person to respect certain COVID-19 prevention strategies and enhance a better understanding of the current retention realities across the province (ie, rural and urban regions). There are 2 exclusion criteria for our study: physicians and registered nurses who have left the Network for more than 5 years and those who have retired.

Focus Groups

The focus groups, which will also allow the achievement of specific objective 2, will be held with 5 to 10 participants in 4 different groups and with 2 distinct types of participants: leadership team and Board of Directors and Network managers. Participants will be asked about retention challenges in the workforce, strategies for retaining physicians and registered nurses, relationships with the Health Department and other stakeholders, and the involvement of OLMCs in retention efforts. The focus groups will be conducted at 3 different times (beginning, mid-term, and end of the study). The first focus group will be conducted at the very start of the project with key informants (leadership team, the executive team, and members of the governance team) to enhance the understanding pertaining to the factors responsible for past and current staff shortages. The last focus group, held at the end of our study with the same key informants, will be to mitigate and discuss retention strategies to enhance workplace satisfaction among nurses and physicians. In contrast, the 2 midpoint focus groups will target the Network's management staff, more specifically: the first group in a service area where retention rates have been identified as low and the second group in a service area where retention rates have been identified as high. The information gathered in these latter 2 focus groups will be used to better understand the factors that influence physician and nurse retention in particular areas.

Document Review

A document review is another strategy that complements our data collection. Thus, documentary sources will allow us to corroborate the information obtained through our interviews and focus groups. We believe the document review will also be used to mark key retention milestones for the Network (province announcements, new internal regulations, procedures, etc). Different types of governance or administrative documents will be analyzed: Network and Department of Health annual reports, action plans, regulations, bills, etc. Since the Network does not have total control over the external and internal factors of its environment and since these can influence the retention of professionals, we consider it worthwhile to conduct a media review to understand their impact. The period for the document

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and media analysis is from March 2008, when the Network was created, to December 2022, when our data collection ended.

In terms of qualitative analysis, the data analysis approach used in the study is descriptive, where an initial analysis emerges from the respondents' words, using a thematic approach to analysis [44,60]. Coding will be done iteratively in collaboration with other members of the research team using a predeveloped codebook. The team will code the same transcripts and then compare initial findings to help ensure intercoder reliability. Braun and Clark [60] approach to thematic analysis will be used to explore the current state of retention. The approach will also rely on a direct thematic analysis based on the "Magnet Hospital" model and "Making it Work" framework.

Ethics Approval

The project was approved by both ethical research boards: the Vitalité Health Network (101574) and the Université de Moncton (2122-105). A detailed consent form will be explained orally and in writing to all participants. Informed consent will be obtained for all participants before taking part in the individual interview and focus groups. The importance of privacy and confidentiality protection for the research team will also be expressed to all participants, as one of our research partners is their current or past employer. Thus, each participant will be given a numerical code to preserve their anonymity. The code will be kept in a locked cabinet that only the 2 primary researchers can access. As for result reporting, such as in publication or recommendation reports, it will be done so the participants cannot be identified.

Recruitment

Participants in the current workforce will be identified using a "snowball" technique [61]. Initial meetings with physicians and registered nurses associated with the Network should allow us to identify additional participants from these 2 disciplines who can inform us about the shortage of professional resources within the organization. A research team member will contact potential participants by phone or email to explain the research project and solicit their participation.

For respondents who have left the Network, we will seek the Network's Human Resources support to identify potential candidates. Human Resources Department will then send an email to them, including the invitation to participate and specifying that the research is independent of the employer and that the latter will not have access to the data. The study details and the information on how to join the research team will be included in this invitation message. This procedure will ensure that no confidential employee information will be transferred to the research team. A CAD $20 (US $14.68) gift card will be offered to interview and focus group participants.

Results

This study was funded in February 2022 by the Canadian Institutes of Health Research. Active enrollment and data collection started in the spring of 2022. A total of 56 semistructured interviews were conducted with physicians and nurses who are currently working for the network or have left in the past 5 years. The data collection for both quantitative and qualitative is intended to end by February 2023. Summer and fall 2023 is the anticipated period to disseminate the results locally, nationally, and internationally.

Discussion

According to the World Health Organization, there is a global shortage of more than 7 million health professionals [62]. The uneven distribution of professional resources contributes to significant health disparities between rural and urban communities [62,63], and may be associated with economic stagnation and social decline in communities located in rural areas [64,65]. The province of New Brunswick is no exception to this situation, and the Network needs to effectively address its health workforce staff shortages as it may affect its viability.

Through the application of the "Making it work" and "Magnet Hospital" frameworks outside of urban settings, this study will contribute globally to the current reflection on the professional resources shortages within OLMCs [1]. The results of this study will help our partner (the Network) in identifying and implementing concrete strategies to promote physician and registered nurse retention by considering the particularities of its environment. It will allow the Network to replenish its strength and vitality by questioning issues such as autonomy [66], job satisfaction [40,67], and attachment to the community [42,68].

The results of this study will be published in a peer-reviewed open-access journal to increase public dissemination of the findings. The different knowledge dissemination activities will raise awareness among coresearchers and decision makers on the importance of addressing professional shortages in rural areas, especially within OLMCs.

The main limitation of this research is the availability of physicians and registered nurses due to pandemic fatigue and shortages in staffing. A second limitation to be considered in this study, pertaining to organizational systems and retention among physicians and nurses, is social desirability. Although confidentiality and anonymity will be respected and always enforced during the study, there is the potential and willingness to answer questions in a manner that will be viewed favorably by others (social desirability bias) [69]. A third limitation is related to the secondary data on job vacancies and turnover rates and the fact that we are constrained by the information that is already collected by the Network.

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Acknowledgments

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Conflicts of Interest

None declared.

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Abbreviations

OLMC: Official Language Minority Community

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Protocol

Combining Intensive Rehabilitation With a Nonfunctional Isokinetic Strengthening Program in Adolescents With Cerebral Palsy: Protocol for a Randomized Controlled Trial

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Abstract

Background: Cerebral palsy is the most common brain injury in the pediatric population. Patients with cerebral palsy present different affectations such as decreased muscle strength, gait deviations, impaired proprioception, and spasticity. Isokinetic strengthening programs combined with intensive rehabilitation may improve muscle strength and therefore gait efficiency.

Objective: The primary aim of this randomized controlled trial is to compare the effect of an intensive rehabilitation combined with a nonfunctional isokinetic progressive strengthening program to an intensive rehabilitation alone on gait parameters and muscle strength in patients with cerebral palsy. Another goal of this study is to determine whether adding an isokinetic program to intensive rehabilitation is more effective than intensive rehabilitation alone at decreasing spasticity and improving joint position sense in patients with cerebral palsy.

Methods: A total of 30 adolescents with spastic diplegia cerebral palsy (Gross Motor Function Classification System levels I to III) will be randomized, by an independent researcher, into a 3-week intensive rehabilitation and isokinetic progressive strengthening group or an intensive rehabilitation control group. Gait parameters, muscle strength, spasticity, and knee joint position sense will be assessed. These variables will be evaluated at baseline (T0) and at the end of the intervention (T1). The intensive rehabilitation will consist of physiotherapy sessions twice a day and hydrotherapy and virtual reality gait training once a day. The isokinetic training group will have a total of 9 supervised isokinetic strength training sessions focusing on knee flexors and extensors with different execution speeds.

Results: The protocol has been accepted by the French National Ethics Committee in October 2022. The inclusion of patients will start in November 2022.

Conclusions: The combination of intensive rehabilitation with an isokinetic program on knee flexors and extensors has not been studied yet. The findings of this study may determine if an isokinetic strength training program of knee flexors and extensors is beneficial for the improvement of gait parameters, muscle strength, spasticity, and joint position sense in adolescents with spastic diplegia.

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KEYWORDS

isokinetic; cerebral palsy; gait analysis; spasticity; muscle strength

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Introduction

Background

Cerebral palsy is considered the most common brain injury in the pediatric population [1]. Motor impairments are commonly observed in adolescents with cerebral palsy [2]. Sensory impairments, cognitive disorders, epilepsy, and nutritional deficiencies are also often found in patients with cerebral palsy [2]. Cerebral palsy prevalence ranges from 1.5 to 2.5 cases per 1000 births and does not differ within different western countries [3]. Spasticity is regularly described as the most common motor impairment in the cerebral palsy population and is characterized by an increased stretch reflex. Spasticity is movement dependent, increasing with a higher velocity [4]. Spasticity is often measured through an isokinetic dynamometer to passively stretch the targeted muscles [4-6].

Muscle strength is commonly decreased in adolescents with cerebral palsy. Quadriceps and hamstring muscles are important to perform daily activities such as standing, walking, and climbing stairs [7]. Knee extensor strength is described as a good indicator of total lower limb muscle strength. Isokinetic dynamometry is the gold standard to measure muscle strength [6]. Isokinetic dynamometry has been described as a reliable tool to measure quadriceps and hamstring muscle strength in children with cerebral palsy [6]. Isokinetic dynamometry can also be used within a reeducation program to increase muscle strength in children with cerebral palsy [6]. An isokinetic strength training program focusing on knee flexors and extensors has shown some promising results in improving muscle strength in children with cerebral palsy [8]. MacPhail and Kramer [8] did not find any improvement in gait parameters in patients with cerebral palsy after an isokinetic program focusing on knee flexors and extensors. However, they did not implement such a program within an intensive rehabilitation program. A recent systematic review has shown that an isokinetic strength training program focusing on knee flexors and extensors improves muscle strength, mobility, and gait in patients with stroke [9]. Functional power training has been shown to be effective training to improve muscle strength, walking capacities, and resting somatosensory cortical activity in children with cerebral palsy [10-12]. Power training exercises such as walking, sit-to-stand, and side-walking should form part of an intensive rehabilitation program. Medium-speed concentric and eccentric isokinetic training is considered strength training, whereas low-speed isokinetic training produces hypertrophy [13]. Finally, high-speed isokinetic training is described as power training [13].

Gait deviations are frequently observed in adolescents with cerebral palsy due to motor impairment. Gait speed, stride length, step width, and stance time are important factors for an effective gait [14,15]. Lower limb muscle fatigue is commonly observed in patients with cerebral palsy and drastically affects their gait abilities and distances [16,17]. Usually, patients with cerebral palsy receive physiotherapy treatment for long periods; however, decreased muscle strength of the lower limbs has been shown to be associated with impaired gait function in children with cerebral palsy. Therefore, treatment for patients with cerebral palsy should focus on strengthening lower limb muscles to improve gait parameters [15,18].

Proprioception has been defined as the ability of an individual to integrate sensory signals from mechanoreceptors, allowing him to determine the position of a joint in space and its movement [19]. Knee proprioception is provided by afferent signals that are located inside or around the joint [19,20]. Its functions are to protect the knee joint against excessive injurious movement, stabilize the knee during static postures, and coordinate complex movements [19-21]. Wingert et al [22] have shown that children with cerebral palsy who present with gait disturbances have poorer proprioception than typically developing children. Over the last decade, 2 different proprioception assessment techniques have been described in the literature [21]: joint position sense and joint motion sense. Strength training has been described as an effective intervention to improve proprioception in children with cerebral palsy [23].

Intensive rehabilitation has been shown to be an effective program to improve functional motor outcomes in children with cerebral palsy [7,24-26]. A recent practice guideline to improve physical function in children with cerebral palsy has shown that a high enough dose of practice is required in order to improve motor abilities [26]. Jackman et al [26] have shown that intensive blocks of therapy were better than low-dose regular therapy in order to improve motor abilities in patients with cerebral palsy. Elgawish and Zakaria [27] have shown that intensive physiotherapy is more effective than standard physiotherapy in improving gross motor function in children with spastic diplegia. Bleyenheuft et al [24,25] have shown that an intensive training protocol including upper and lower extremities was effective in improving lower extremity function in children with unilateral and bilateral spastic cerebral palsy. In a meta-analysis, Moreau et al [28] have shown that gait training is an important component of rehabilitation to improve gait parameters, such as gait speed, in children with cerebral palsy. In their clinical guideline, Jackman et al [26] have shown that 30 to 40 hours of practice are required to improve motor abilities. Combining intensive rehabilitation with an isokinetic strengthening program has not been studied yet.

Objectives

The primary aim of this randomized controlled trial is to compare the effect of intensive rehabilitation combined with an isokinetic progressive strengthening program to intensive rehabilitation alone on gait parameters and muscle strength in patients with cerebral palsy. Another goal of this study is to determine whether adding an isokinetic program is more effective than just intensive rehabilitation in decreasing spasticity and improving joint position sense in patients with cerebral palsy.

Methods

Study Design

This study will be a prospective randomized controlled trial. Adolescents with spastic diplegia cerebral palsy will be randomized by an independent researcher through a computer-based method into an isokinetic training group (IG)

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or a control group (CG). The block randomization method will be used to keep the number of subjects in each group equal. The IG will receive a 3-week isokinetic strengthening program together with intensive rehabilitation, and the CG will only follow the intensive rehabilitation. Patients will not be informed if they are part of the intervention or the CG. Outcome measures will be done at baseline (T0) and at the end of the intervention (T1). The protocol has been accepted by the French National Ethics Committee (IDRCB: 2022-A00431-42).

Sample Size

Sample size calculation was realized using G*POWER statistical programming (version 3.1.9.2; Franz Faul): power ($1-\alpha$ error P)=.85, α=.05, effect size=1.1, with a 2-tailed for a comparison of 2 independent groups. This calculation was based on the results of a pilot study based on ratio improvement following 2 specific interventions in patients with cerebral palsy. It will take 15 participants in each group to complete this study.

Participants

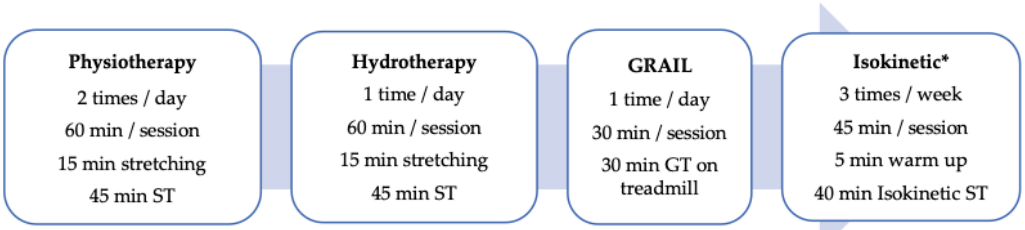
A total of 30 pediatric patients will be recruited from the Institut St Pierre, France. The inclusion criteria for this study will be adolescents aged from 11 up to 18 years with a diagnosed spastic diplegia cerebral palsy, patients with walking abilities (Gross Motor Function Classification System levels I to III), the ability to activate knee flexors and extensors voluntarily, and cognitive abilities to understand the instructions. The exclusion criteria for this study will be cardiovascular disorders; fractures of any type; history of hip subluxation, dislocation, or important scoliosis (>40° of curvature); surgery of the lower limb within the last year; botulinum toxin injection within the last 3 months; significant contracture of the knee flexors and extensors (less than 90° of knee active range of motion [ROM]); and insufficient understanding of the French language. All the participants and their legal tutor will be informed of the study procedures in agreement with the ethical standards of the Helsinki Declaration and will sign an informed consent.

Intensive Rehabilitation

The intensive rehabilitation will be conducted over a 3-week period. All participants will follow the intensive rehabilitation. Physiotherapy will be performed twice a day. Hydrotherapy and virtual reality gait training will be performed on a daily basis. During the 3 weeks of rehabilitation, the IG and CG will practice for a total of 59 and 52 hours, respectively. The hourly repartition can be found in Figure 1.

Physiotherapy sessions are expected to last for 60 minutes and will include lower limb stretching exercises and strengthening of the lower extremities (Table 1). All exercises realized during a typical physiotherapy session are described in Table 2. Hydrotherapy sessions will last for 60 minutes and will include stretching exercises, aerobic exercises, and strengthening of the lower extremities (Table 3). Hydrotherapy exercises are realized with water up to the patient's belly. All exercises realized during a typical hydrotherapy session are described in Table 2. The virtual reality gait training will last for 30 minutes in total and will focus on improving different gait parameters with video games. Another aim of the virtual reality training will be to perform balance exercises. Perturbations will be added to challenge participants. All exercises realized during a Gait Real-time Analysis Interactive Lab (GRAIL) session are described in Table 2. The same video games will be performed for every adolescent (Table 4). A summary of all exercises performed during the intensive rehabilitation is presented in Figure 2.

Figure 1. Rehabilitation program with the total amount of training. During the 3 weeks of rehabilitation, the isokinetic training group and control group will respectively perform a total of 48 hours and 41 hours of active training. *Only performed by the isokinetic training group. GRAIL: Gait Real-time Analysis Interactive Lab; GT: gait training; ST: strength training.



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Table 1. Characteristics and rehabilitation volume for the physiotherapy sessions.

Interventions and exercises	Sets, n	Repetitions (seconds), n	Contraction types
Stretching			
Triceps surae	2	20	N/A[a]
Quadriceps	2	20	N/A
Hamstrings	2	20	N/A
Iliopsoas	2	20	N/A
Strengthening			
Foot plantar flexion with elastic band	6	10	CON[b] and ECC[c]
Foot dorsiflexion with elastic band	6	10	CON and ECC
Sit to stand	6	10	CON and ECC
Knee flexion with elastic band	6	10	CON and ECC

[a]N/A: not applicable.

[b]CON: concentric realized as fast as possible.

[c]ECC: eccentric maintained for 2-3 seconds.

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Table 2. Description of intensive rehabilitation sessions performed by adolescent in both groups.

Interventions and exercises	Description	Resistance added
Physiotherapy		
Stretching		
Triceps surae	Patient in supine position. PT[a] is pushing the patient foot in dorsiflexion with the knee extended as much as possible	N/A[b]
Quadriceps	Patient in prone position. PT is bending the patient knee and maintaining the patient hip against the table	N/A
Hamstrings	Patient in supine position. PT is maintaining the patient knee extended and adding as much hip flexion as possible. The opposite leg must stay extended on the table	N/A
Iliopsoas	Patient in supine position on the lower part of the table. PT is maintaining a hip extension with a knee flexion. The opposite leg is placed on the chest of the PT	N/A
Strengthening		
Foot plantar flexion	Patient in supine position with knee extended. Ankle placed in dorsiflexion. Elastic band placed around the ball of the foot and help by the patient	Resistance band of various resistances
Foot dorsiflexion	Patient in supine position with knee extended. Ankle placed in plantar flexion. Elastic band placed around the instep of the foot and held by the PT	Resistance band of various resistances
Sit to stand	Patient seating on a chair and push with his feet on the ground to stand	Dumbbells from 5 kg to 10 kg
Knee flexion	Patient in prone position with knee extended. Elastic band is placed around patient ankle and held by the PT	Resistance band of various resistances
Hydrotherapy		
Stretching		
Triceps surae	Patient standing against the pool. One lower limb in front of the other. Both feet on the ground with the back foot in maximal dorsiflexion	N/A
Quadriceps	Patient standing against the pool. Holding one lower limb and bending toward knee flexion while the other hand is stabilizing against the pool.	N/A
Iliopsoas	Patient kneeling against the pool. One knee against the ground and the other one bended. Pushing his gravity center forward	N/A
Strengthening		
Forward walking	Patient standing and walking forward at high intensity inside the swimming pool with water up to the belly.	Resistance band
Backward walking	Patient standing and walking backward at high intensity inside the swimming pool with water up to the belly.	Resistance band
Side walking	Patient standing and walking from side to side at high intensity inside the swimming pool with water up to the belly	Resistance band
Calf raises	Patient standing against the pool with water up to the belly. Pushing against the ground toward maximal plantar flexion and going back to the ground slowly	Water resistant weight
Squat	Patient standing against the pool with water up to the belly. Squatting up to 90 degrees of knee flexion and back to the initial position	Water resistant weight
GRAIL[c]		
Gait training		
Rope bridge	Patient standing on a treadmill. 4 markers are placed on posterior and anterior superior iliac spine. A self-paced mode is used to let the patient walk at a comfortable speed	Sway: level 1 to 3; pitch: level 1 to 3; encounters: level 1 to 3
Step on it	Patient standing on a treadmill. 2 markers are placed on both lateral malleoli. Treadmill speed is set based on gait analysis assessment.	Increasing step length and decreasing step width
Balance		
Perturb	Patient is standing on the treadmill. Anteroposterior and mediolateral stimuli are produced from the treadmill.	Automatic mode starting from level 1 to 5

[a]PT: physiotherapist.

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[b]N/A: not applicable.

[c]GRAIL: Gait Real-time Analysis Interactive Lab.

Table 3. Characteristics and rehabilitation volume for the hydrotherapy sessions.

Interventions and exercises	Sets, n	Repetitions (seconds), n	Contraction types
Stretching			
Triceps surae	2	20	N/A[a]
Quadriceps	2	20	N/A
Iliopsoas	2	20	N/A
Strengthening			
Walking forward	6	30	N/A
Walking backward	6	30	N/A
Side walking	6	30	N/A
Calf raises	5	10	CON[b] and ECC[c]
Squats	5	10	CON and ECC

[a]N/A: not applicable.

[b]CON: concentric realized as fast as possible.

[c]ECC: eccentric maintained for 2-3 seconds.

Table 4. Characteristics and rehabilitation volume for the Gait Real-time Analysis Interactive Lab sessions.

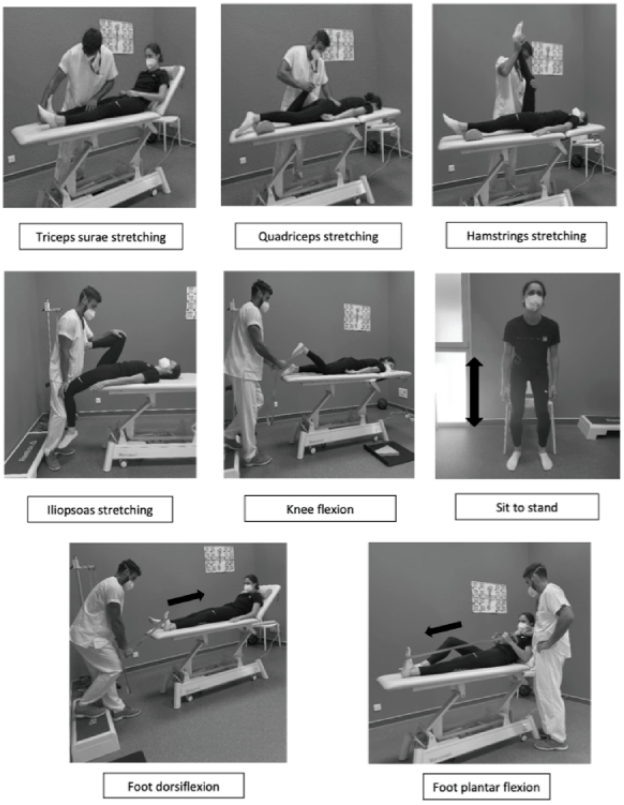
Exercises	Aim	Sets, n	Duration (minutes[a]), n	Parameters
Rope bridge	Walk on treadmill with perturbations	4	2	Sway, pitch, and encounters
Perturb	Stand on the treadmill with perturbation to improve balance	4	2	Automatic mode
Step on it	Walk on the treadmill with targets to hit to improve step width and length	4	2	N/A[b]

[a]Minutes for the time for each exercise; seating breaks of 1 minute are respected between each sets.

[b]N/A: not applicable.

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Figure 2. Images of the guidelines for the intensive rehabilitation program and the isokinetic strength training program. Both groups will follow the exact same intensive rehabilitation program. Only the isokinetic training group will follow the isokinetic strength training program. *Knee flexors and extensors are trained at various speeds in concentric and eccentric modes with different intensities depending on the training week.



Isokinetic Training Intervention

The IG will also receive a total of 9 supervised isokinetic training sessions over 3 weeks based on given guidelines for isokinetic training [29-31]. Adolescents will train between 70% and 80% of the maximal value in Newton-meter reached during the test at the different speeds (Table 5). A visual feedback will be displayed to the participants, with a frame range showing the target strength to reach for every set. A rest time of at least 24 hours between sessions will be observed for every participant. Based on MacArdle et al's [13] findings, 1 single training session will consist of 3 sets of 5 repetitions at a speed of 30 degrees/s concentrically, 3 sets of 8 repetitions at 120 degrees/s concentrically, and 3 sets of 3 repetitions at 30 degrees/s eccentrically. Therefore, strength, hypertrophy, and power will be performed. One repetition consisted of a complete knee extension and flexion, based on the ROM reached during the first assessment. A 90-second rest will be respected between each set. Every session will be preceded by a 5-minute warm-up and followed by a 5-minute cooldown. All exercises realized during isokinetic sessions are shown in Figure 2. One session is expected to last for approximately 45 minutes [29,30,32]. A summary of the exercises performed in the isokinetic strengthening program is presented in Figure 2.

Table 5. Isokinetic strengthening program for the intervention group.

Weeks	Sets, n	Intensity, %[a]	Contraction type
1 and 2	3	70	CON[b] and ECC[c]
3 and 4	3	75	CON and ECC
5 and 6	3	80	CON and ECC

[a]Percentage from maximal reached value at each speed.

[b]CON: concentric.

[c]ECC: eccentric.

Primary Outcomes

Strength

Muscle strength will be assessed with an isokinetic dynamometer (CON-TREX, MJ Multijoint module, Medimex, CMV AG). Patients will be installed as described previously. Patients will perform an aerobic warm-up for 5 minutes and stretching of the quadriceps and hamstring prior to the test. The ROM will be set based on the extension abilities of the patients. Knee flexors and extensors will be assessed in a concentric mode for 3 repetitions at a speed of 30 degrees/s, 5 repetitions at a speed of 120 degrees/s, and for 8 repetitions at a speed of 180 degrees/s; in an isometric mode at 45° of knee flexion for

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5 seconds; and in an eccentric mode for 3 repetitions at a speed of 30 degrees/s. The isokinetic equipment is shown in Figure 2.

Between the 2 concentric, the isometric, and the eccentric tests, 90 seconds of recovery will be allowed. Verbal encouragement will be provided for all participants during the entire test. The highest value in Newton-meter, the maximum reached speed in degrees/s, and the total work produced in joules will be considered for data analysis.

A recent meta-analysis from Muñoz-Bermejo et al [6] showed good to excellent levels of reliability of isokinetic dynamometer in measuring knee extensors and knee flexors strength in children with cerebral palsy, with an interclass correlation coefficient (ICC) ranging from 0.7 to 1 in the dominant and the nondominant lower limb.

Gait Assessment

Patients will perform a walking test on the GRAIL (Motekforce Link). The GRAIL technology consisted of a split-belt treadmill with integrated force plates, an incurved virtual reality screen, and a 3D motion capture system (VICON). The treadmill is built with a self-paced mode, allowing patients to walk at a comfortable speed during the entire test.

Spatiotemporal parameters such as gait speed, stride length, step width, and stance time will be recorded during the walking test. Gait speed (m/s) is defined as the average speed recorded during the entire test after removing the first and last seconds to undo the acceleration and deceleration phenomena. Stride length (cm) is defined as the average anteroposterior distance between heel strikes of the same lower limb. Step width (cm) is defined as the average mediolateral distance between both feet. Stance time (s) is defined as the time between heel strike and toe-off from the same lower limb.

Kinematics data will also be collected through the 3D motion capture system. A total of 22 markers will be placed on patients' lower limbs following the human body model, which has been described as a valid method to measure kinematics [33]. Hip, knee, and ankle ROM will be captured during the entire gait assessment in the sagittal, transversal, and horizontal planes. Electromyography activity will be recorded for both lower limbs using surface electrodes on 2 important muscles. The rectus femoris and biceps femoris will be recorded. These 2 muscles are important for knee function, including extension and flexion.

A 6-minute walking test (6MWT) will also be performed on the GRAIL. The treadmill will be set to the self-paced mode. Patients will be asked to walk during the entire test. The total distance reached during the test will be registered for data analysis. Performing the 6MWT on the GRAIL technology has shown good construct validity and reproducibility [34,35]. The Borg scale will also be measured before and after the 6MWT for every patient as an indicator of the level of exertion perceived during the test [34,35].

Secondary Outcomes

Spasticity

Spasticity within knee flexors and extensors will be assessed with an isokinetic dynamometer (CON-TREX, MJ Multijoint module, Medimex, CMV AG) by applying a passive movement at a speed of 180 degrees/s to stretch the muscles. Patients will be installed on the isokinetic seat with 80° of hip flexion, 90° of knee flexion, and no restriction within the ankle joint. The mechanical axis of the dynamometer will be aligned with the lateral epicondyle of the femur. The tibial pad will be placed 3 cm above the lateral malleolus. The trunk and the thigh of the patients will be stabilized with belts. Both limbs will be assessed for 10 consecutive times from 90° to 25° of knee flexion and back to 90°. A 60-second rest break will be respected between each movement. The patient will receive the instruction to rest as much as possible during the entire movement. Prior to the spasticity test, a filter for gravity correction will be applied based on the patient's limb weight. The isokinetic dynamometer will record the forces, angles, and speed during the entire movement. The first and last 5° of each movement will be excluded from the data analysis to avoid errors from the effect of inertia [24]. The test will be interrupted if the force, in Newton, applied to the dynamometer is greater than half the patient's body weight. Patients will be instructed to stop the test if they feel any pain or are scared [36].

The peak resistive torque will be calculated at baseline and after a 3-week intensive training program within both groups. In the knee, the peak resistive torque has shown good relative reliability at a speed of 180 degrees/s, with an ICC of 0.86 for knee extensor peak torque and an ICC of 0.80 for knee flexor peak torque [36].

Knee Joint Position Sense

Knee JPS will be assessed with an isokinetic dynamometer (CON-TREX, MJ Multijoint module, Medimex, CMV AG). Patients will be installed as described previously. The patient's resting position will be set to a preselected joint angle of 45° of knee flexion. Knee JPS will consist of the position-reposition angle difference of the dominant leg. The angular speed for the repositioning task will be set at 2° per seconds as described by El Shemy [37]. Prior to the test, every adolescent will participate in a practice session to become familiar with the task. For the test, the patient's limb will first be placed at a knee angle of 45° for 10 seconds, and then the lower limb will go back to 90° of knee flexion. Finally, the dynamometer will move the lower limb through extension at the same speed. Once patients feel that they have reached the target position again, they will press the button and stop the test. Patients will be blindfolded, and the test will be performed in quiet surroundings to eliminate visual and auditory stimuli. The test will be performed 3 consecutive times, and the mean will be calculated for data analysis.

Data Analysis

Descriptive statistics will be used to describe gender, age, and Gross Motor Function Classification System. Primary and secondary outcomes will be analyzed in the same way. The assumption of normality will be checked by visual inspection

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of the q-q plot and the box plot of the data within groups. A Shapiro-Wilks test will also be performed on the data within groups. The homogeneity of variance will be checked using Levene test.

If the data are normally distributed, an independent *t* test will be carried out for each variable to see if there are differences between the experimental and control groups. The 95% CI for the mean differences will be determined. Pearson *r* will be used to calculate the effect size.

If the data are not normally distributed, a Wilcoxon rank-sum test will be used for each variable to determine if there are any significant differences between groups. Pearson *r* will be calculated as a measure of effect size.

The data analysis will be performed using SPSS (25.00, IBM Corp). For the data analysis, the researchers will use a 95% CI, considering all those variables with a *P* value of less than .05 to be statistically significant.

Ethics Approval

This research is promoted by the Institut St-Pierre, France. A parent or legal tutor together, with participants, will fill out a written consent. All participants will join this study voluntarily and will be informed that they can stop their participation at any time. Full data will be available only to members of the research team, and anonymization of the data will be done prior to publication. Written observation reports will be registered during the entire trial by the investigators. Adverse events will be reported to the medical practitioner and the trial sponsor. Unexpected serious adverse events will be transferred to the ethical committee within 15 days. Trial results will be published in academic journals and presented at conferences worldwide. Participants, their families, and health care professionals will have the option to receive a summary of the study results. The study will be conducted in accordance with the Declaration of Helsinki, and the protocol has been approved by the Comité de protection des personnes Sud-Méditerranée II (CPP 222 B21) IDRCB 2022-A01790-43. The date of approval was October 3, 2022.

Results

The protocol was accepted by the French National Ethics Committee in October 2022. The inclusion of patients will start in November 2022. Data collection is expected to be completed in June 2024. The results of the trial are expected to be available by the end of 2024.

Discussion

Principal Findings

This study will evaluate the effects of intensive rehabilitation combined with an isokinetic progressive strengthening program on gait parameters, muscle strength, spasticity, and joint position sense. Both groups will receive the same intensive rehabilitation, and the intervention group will also have an isokinetic program. The findings of this study may determine if an isokinetic strength training program of knee flexors and extensors is beneficial to improve gait parameters, muscle strength, spasticity, and joint position sense in adolescents with spastic diplegia. Positive findings are expected for this clinical trial. If this is the case, isokinetic strength training programs should be considered as a complementary intervention for patients with cerebral palsy.

It has been decided to measure and strengthen knee flexors and extensors, as they have been described as good indicators for total lower limb muscle strength [6,38]. Strength training programs have been designed and tested on children with spastic diplegia [30,39,40]. Aye et al [40] have shown an improvement in muscle strength, gait parameters, and gross motor function measure after a strength training program for hip and knee extensors. In their study, MacPhail and Kramer [8] have shown that an isokinetic strength training program focusing on knee flexors and extensors could significantly improve strength in patients with cerebral palsy. MacPhail and Kramer [8] did not find significant improvement in gait parameters following an isokinetic strength training program. However, they did not implement such a program within an intensive rehabilitation program.

Limitations

The intensive rehabilitation program could not be longer than 3 weeks due to school, and a longer period of time might be important to improve gait functions and muscle strength in patients with cerebral palsy.

The total amount of training was not kept equal for both groups due to the isokinetic training program, and this might have an influence on the results.

Conclusions

Nowadays, there is missing information about the effects of an intensive rehabilitation program combined with an isokinetic strength training program on gait parameters. The combination of intensive rehabilitation with an isokinetic program on knee flexors and extensors has not been studied yet. Positive findings of this study may suggest that an isokinetic strength training program should be implemented within the traditional treatment of children with spastic diplegia.

Data Availability

The data are not publicly available, as they have not been collected yet. The data will be uploaded to publish this paper.

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Authors' Contributions

MG participated in the conceptualization together with BZ and KP. MG and BZ conducted the methodology. The validation was done by KP, BS, and LB. MG, BZ, and FC designed the original draft preparation. BS and KP reviewed the manuscript. KP and LB supervised the protocol. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
CONSORT-eHEALTH checklist (V 1.6.2).
[PDF File (Adobe PDF File), 82 KB - resprot_v12i1e43221_app1.pdf]

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Abbreviations

6MWT: 6-minute walking test
CG: control group
GRAIL: Gait Real-time Analysis Interactive Lab
ICC: interclass correlation coefficient
IG: isokinetic training group
ROM: range of motion

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Protocol

Memantine for Refractory Obsessive-Compulsive Disorder: Protocol for a Pragmatic, Double-blind, Randomized, Parallel-Group, Placebo-Controlled, Monocenter Trial

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Abstract

Background: Obsessive-compulsive disorder (OCD) is a psychiatric syndrome characterized by unwanted and repetitive thoughts and repeated ritualistic compulsions for decreasing distress. Symptoms can cause severe distress and functional impairment. OCD affects 2% to 3% of the population and is ranked within the 10 leading neuropsychiatric causes of disability. Cortico-striatal-thalamo-cortical circuitry dysfunction has been implicated in OCD, including altered brain activation and connectivity. Complex glutamatergic signaling dysregulation within cortico-striatal circuitry has been proposed in OCD. Data obtained by several studies indicate reduced glutamatergic concentrations in the anterior cingulate cortex, combined with overactive glutamatergic signaling in the striatum and orbitofrontal cortex. A growing number of randomized controlled trials have assessed the utility of different glutamate-modulating drugs as augmentation medications or monotherapies for OCD, including refractory OCD. However, there are relevant variations among studies in terms of patients' treatment resistance, comorbidity, age, and gender. At present, 4 randomized controlled trials are available on the efficacy of memantine as an augmentation medication for refractory OCD.

Objective: Our study's main purpose is to conduct a double-blind, randomized, parallel-group, placebo-controlled, monocenter trial to assess the efficacy and safety of memantine as an augmentative agent to a selective serotonin reuptake inhibitor in the treatment of moderate to severe OCD. The study's second aim is to evaluate the effect of memantine on cognitive functions in patients with OCD. The third aim is to investigate if responses to memantine are modulated by variables such as gender, symptom subtypes, and the duration of untreated illness.

Methods: Investigators intend to conduct a double-blind, randomized, parallel-group, placebo-controlled, monocenter trial to assess the efficacy and safety of memantine as an augmentative agent to a selective serotonin reuptake inhibitor in the treatment of patients affected by severe refractory OCD. Participants will be rated via the Yale-Brown Obsessive Compulsive Scale at baseline and at 2, 4, 6, 8, 10, and 12 months. During the screening period and T4 and T6 follow-up visits, all participants will undergo an extensive neuropsychological evaluation. The 52-week study duration will consist of 4 distinct periods, including memantine titration and follow-up periods.

Results: Recruitment has not yet started. The study will be conducted from June 2023 to December 2024. Results are expected to be available in January 2025. Throughout the slow-titration period, we will observe the minimum effective dose of memantine, and the follow-up procedure will detail its residual efficacy after drug withdrawal.

Conclusions: The innovation of this research proposal is not limited to the evaluation of the efficacy and safety of memantine as an augmentation medication for OCD. We will also test if memantine acts as a pure antiobsessive medication or if memantine's ability to improve concentration and attention mimics an antiobsessive effect.

Trial Registration: ClinicalTrials.gov NCT05015595; https://clinicaltrials.gov/ct2/show/NCT05015595

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International Registered Report Identifier (IRRID): PRR1-10.2196/39223

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KEYWORDS

obsessive-compulsive disorder; refractory patients; antiglutamatergic agents; glutamate; augmentation medication; memantine; double blind; parallel group; placebo; OCD; psychiatric; distress; symptoms; neuropsychiatric; disability; overactivity; drug; treatment; Alzheimer; cognitive; titration; medication; mental health; psychiatric disorder

Introduction

Background

Obsessive-compulsive disorder (OCD) is one of the most disabling neuropsychiatric disorders, characterized by repetitive and intrusive thoughts (obsessions) and repeated ritualistic behaviors (compulsions) that are performed by affected individuals to decrease distress [1]. It is estimated that 2.5% to 3% of the general population are affected by OCD [2], which has some sex-related features [3]. Moreover, in the last decade, evidence suggests significant neuropsychological deficits—independent of severity, comorbidity, and medication—in patients with OCD [4,5]. Several studies suggest impairments in executive function, processing speed, sustained attention, and nonverbal memory [6-11].

Prior to the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) [12], OCD was included as an anxiety disorder because patients commonly reported anxiety as a symptom [13]. However, in the DSM-5, OCD was moved to its own distinct section—*Obsessive-Compulsive and Related Disorders*—because the condition was considered to be more closely related to other disorders [14].

Typically, OCD is determined by obsessions (irrational beliefs) and compulsions that are rational avoidance responses activated by these irrational beliefs. Recent data [15,16] instead suggest that the mechanism underlying OCD can be found in an interference in the balance between the habit learning system and the goal-directed system. The habit learning system is founded on historical information, independent of past rewards, potentially resulting in behavioral inflexibility even in light of rapid changes in the environment. On the other hand, the goal-directed system applies control over habits in response to changes, including changes in response to the assessment of actions and outcomes. A study conducted by Voon and colleagues [17] found that patients with OCD made choices generally based on a model-free approach (habit learning system) rather than a model based on a goal-directed system.

In the current habit hypothesis of compulsivity, compulsions result from a deficit of goal-directed actions, rather than being driven by irrational beliefs. In line with this much more behavioral account of the disorder, OCD was inserted in the new *Obsessive-Compulsive and Related Disorders* chapter of the DSM-5.

Recurrent circuits that connect the cerebral cortex to the basal ganglia, which are termed *cortico-striatal-thalamo-cortical circuitry* (CSTC) *loops*, are involved in habits. CSTC dysfunctions, as structural abnormalities, alter brain activation and connectivity [18,19] and seem to be implicated in OCD. According to this hypothesis, the hyperactive or hyperconnected CSTC loops are self-exciting in a runaway positive feedback loop [20,21], resulting in the need to perform compulsions, which in turn reinforces habits and increases the urge to perform compulsions [22].

The primary neurotransmitter involved in the CSTC model of OCD is glutamate [23]; it also has a fundamental role in neuronal plasticity, learning, and memory [24]. Excessive levels of glutamate in the brain area can stimulate glutamate receptors, resulting in hyperactivity or even excitotoxicity in neurons; in pathological conditions, glutamate can act as a neuronal excitotoxin, resulting in rapid or late neurotoxicity [25].

In support of this hypothesis, a large mega-analysis and meta-analysis of imaging data found age-related changes in brain structures, suggesting that OCD is underpinned by complex, nonlinear neurodevelopmental mechanisms [26,27].

The pathophysiology of OCD indicates aberrant glutamatergic signaling, with reduced glutamatergic concentrations in the anterior cingulate cortex and increased glutamatergic concentrations in the striatum and orbitofrontal cortex [28]. Moreover, both ionotropic glutamate receptors and metabotropic glutamate receptors are linked in virtually every form of learning in the brain, including habit learning [15,29]; are localized in brain circuitry; and are candidates in the pathophysiology of OCD. Several studies show evidence of altered glutamate homeostasis in OCD, with higher levels of glutamate in the cerebrospinal fluid of patients with OCD compared to those of healthy controls [30,31]. Genetics studies suggest an association between polymorphisms of glutamate-associated genes and the development of OCD [32-34]; in particular, OCD in families has been associated with a polymorphism of the gene that codes for N-methyl-D-aspartic acid receptors [32].

Conventionally, guidelines suggest the use of medications that act on serotonergic pathways, such as serotonin reuptake inhibitors (SRIs) and, in particular, selective SRIs (SSRIs), for OCD. Even if the exact mechanisms of their actions remain mysterious, it seems that SRIs exert their effects by influencing CSTC [35]. Unfortunately, it is estimated that around 30% to 60% of patients with OCD do not attain remission after taking SRIs [5]; even when switching to another SSRI, clomipramine, or an atypical antipsychotic, around 30% of patients remain untreated for refractory symptoms.

Given the role that glutamate appears to play in the dysregulation of OCD, glutamatergic drugs could be potential candidates for an OCD therapy augmentation strategy. Glutamate-modulating drugs seem to be potential therapeutic agents for other psychiatric disorders, such as depression, bipolar

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disorder, and suicidality, that have high comorbidity with OCD [36-38].

In light of the new evidence, several authors have focused their interest on the use of glutamate-modulating agents in patients with refractory OCD. Indeed, some studies that used memantine; riluzole; ketamine; or nutritional supplements, such as inositol and N-acetylcysteine, suggested promising benefits for these kinds of patients [39].

Several randomized controlled trials (RCTs) on the effects of glutamate-modulating drugs on OCD were conducted. A review conducted by Marinova and colleagues [39] showed that memantine seems to have a positive effect on refractory symptoms as an augmentation medication for OCD.

Due to substantial differences in treatment resistance, comorbidity, age, and gender among patients [39], at the moment, it is premature to recommend the use of glutamatergic drugs for refractory symptoms, since more studies are needed to confirm the use of this pharmacological approach for OCD augmentation therapy [40]. Moreover, randomized placebo-controlled trials with larger study populations are necessary in order to draw definitive conclusions on the utility of glutamate-modulating drugs for OCD.

Identifying and confirming the efficacy and safety of new therapeutic approaches for OCD could also be very useful for the purpose of early intervention in patients. Even if there are not sufficient data to support a progression of brain changes, it is likely that early intervention could help to reduce damage resulting from neurotoxicity [41].

Objectives

The main purpose of our study is to conduct a double-blind, randomized, parallel-group, placebo-controlled, monocenter trial to assess the efficacy and safety of memantine—a low- to moderate-affinity, noncompetitive N-methyl-D-aspartic acid receptor antagonist [40] that is currently approved for the treatment of Alzheimer disease—as an augmentative agent to an SSRI in the treatment of moderate to severe OCD. The second aim of the study is to evaluate the effect of memantine on the concentration and attention abilities of patients with OCD. The third aim is to investigate if responses to memantine could be modulated by variables such as gender, symptoms subtypes, and the duration of untreated illness.

Methods

This protocol has been reported according to the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) statement requirements (Figure 1). The complete SPIRIT checklist is available in Multimedia Appendix 1.

Figure 1. Spirit figure.

	STUDY PERIOD							
	Enrollment	Allocation	Postallocation					Closeout
TIMEPOINT	$-T_1$	0	T_1	T_2	T_3	T_4	T_5	T_6
ENROLMENT:								
Eligibility screen	X							
Informed consent	X							
Recruitment form	X							
Allocation		X						
INTERVENTIONS:								
[Memantine Titration]		◆—	—	—	—	—	—◆	
[Placebo]		◆—	—	—	—	—	—◆	
ASSESSMENTS:								
Y-BOCS	X		X	X	X	X	X	X
WAIS-IV Digit	X					X		X
Trial Making Test	X					X		X
Digit and Corsi Span	X					X		X
Corsi Block Tapping test	X					X		X
Rivermead Behavioral Memory Test	X					X		X
Babcock Story recall test	X					X		X
Stroop Task	X					X		X
Tower of London	X					X		X
Modified Five-Point Test	X					X		X

Trial Design

A double-blind, randomized, parallel-group, placebo-controlled, monocenter trial will be conducted over 52 weeks at the outpatient clinic of the Department of Human Neurosciences, Sapienza University of Rome. The study population will include patients diagnosed with moderate to severe OCD according to the diagnostic criteria of the DSM-5 who consecutively access the OCD outpatient clinic of the Department of Human Neurosciences, Sapienza University of Rome. The investigators

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will be academic research assistants and psychiatrists with experience in OCD.

We will enroll patients who meet the diagnostic criteria of the DSM-5 [12] for moderate to severe OCD, and those with a Yale-Brown Obsessive Compulsive Scale (Y-BOCS) [42] score of >21 will be selected for inclusion in the study. The Y-BOCS, which will be used to evaluate treatment efficacy, is a well-validated, 10-item rating scale that is widely used to measure the severity of OCD symptoms. Participants will be rated with the Y-BOCS at baseline and at 2, 4, 6, 8, 10, and 12 months.

During the screening period and T4 and T6 follow-up visits, all participants will undergo an extensive neuropsychological evaluation. We will assess processing speed by using the Wechsler Adult Intelligence Scale, Fourth Edition, Digit Span [43]; attention by means of the Trial Making Test [44]; computerized alertness and go/no-go task memory by using the Digit and Corsi Span [45], a modified version of the Corsi Block-Tapping Test [46], the story recall portion of the Rivermead Behavioral Memory Test [47], and a modified version of the Babcock Story Recall Test [48]; and executive functions by means of the Stroop task [49], a modified version of the Tower of London test [50], and the Modified Five-Point Test [51].

Ethical Considerations

The study will be conducted in accordance with the Declaration of Helsinki and its subsequent revisions. Written informed consent will be obtained from all eligible participants, following the complete description of study details. Participants will be informed about their freedom to withdraw from the trial anytime without any negative effect on their therapy. The study was approved for a grant by Sapienza University of Rome (grant RM11916B7477A1B6), approved by the local ethics committee (protocol number: 0784/2022), and registered on ClinicalTrials.gov (trial number: NCT05015595).

Only patients legally capable of giving their consent can participate in the study. The investigator will be responsible for the correctness of the recruitment procedure and will be asked to use comprehensible verbal communication when providing information to the patients. Before entering the study, patients will be fully informed about the purposes of the research; possible benefits; any potential, personal, reasonable risks or discomforts; and the expected duration of their participation in the trial. The investigator will also clearly inform the patients that they can leave the study at any time and for any reason, without giving an explanation, and that discontinuation would not, in any case, deteriorate the patients' relationship with the physician or the possibility of receiving alternative therapies.

Before recruitment, a copy of the informed consent form and personal data processing consent form will be given to the patients, together with any needed clarification. Sufficient time will be given to enable the patients to decide whether they will participate in the study. Moreover, we intend to also seek approval from the Institutional Review Board of Sapienza University of Rome.

Participants

The inclusion criteria are as follows: a psychiatrist diagnosis of current moderate to severe OCD based on the DSM-5, a Y-BOCS [42] score of >21, an age of 18 to 55 years, patients in therapy with a stable SSRI for at least 3 weeks prior to enrollment, and written informed consent.

The exclusion criteria are as follows: substance dependence, an IQ of <70, comorbid psychiatric disorders, pregnant or breastfeeding women or women who intend to become pregnant during the period of the study, and concomitant treatments (repetitive transcranial magnetic stimulation, cognitive behavioral therapy, or other glutamate-modulating drugs).

Interventions

This is a protocol for a double-blind, randomized, parallel-group, placebo-controlled, monocenter trial in patients with OCD. The trial will include 1 active memantine dose arm and 1 placebo arm.

The trial will consist of the following four distinct periods:

- Screening: the screening period may last up to 4 weeks for each eligible patient.
- A 32-week, double-blind, up-titration treatment period (from T0 to T4): after screening, patients who meet all eligibility criteria will be randomly assigned to 1 of 2 arms (memantine or placebo) in a 1:1 ratio. Following baseline assessments, each patient will receive a daily dose of memantine or the placebo (up to 20 mg/day).
- An 8-week, double-blind, down-titration treatment period (from T4 to T5): at T4, the dose of memantine or the placebo will be reduced to 10 mg per day due to safety reasons, before the end of treatment (T5).
- Follow-up period (from T5 to T6): after the 40-week, double-blind treatment period, patients will be asked to come back for the follow-up visit (T6) 8 weeks after the end of the treatment (T5; Figures 2 and 3).

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Figure 2. Study Flow-chart.

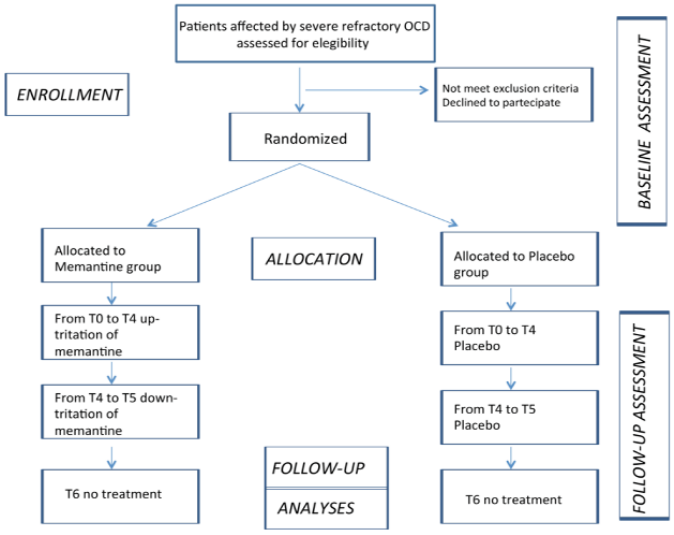
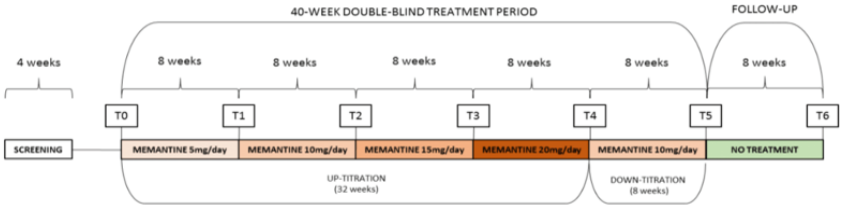


Figure 3. Study Timeline.



Recording of Adverse Events

The investigator will carefully monitor the patients' symptoms and signs, which will be either spontaneously reported or detected, throughout the whole study period up to the last visit scheduled in the study protocol. On a case-by-case basis, a prolonged observation period may be requested.

Adverse events that occur during the clinical trial will be assessed by the investigator in terms of their seriousness and relationship with the investigational product, and the principal investigator will be notified.

As soon as a severe adverse event occurs, an ad hoc form for severe adverse events will be completed, in accordance with the European Union regulation about pharmacovigilance in clinical research [52]. If, for any reason, the disadvantages of participation appear to be significantly greater than those foreseen, the investigator will inform the principal investigator and the bodies providing ethical oversight to evaluate trial discontinuation for the patient.

Sample Size

The sample size was calculated by using the G*Power 3.1.9.2 software (Heinrich-Heine-Universität Düsseldorf) [53]. By using the ANOVA repeated measures test with a within-between group interaction approach (considering changes in Y-BOCS scores as the primary outcome), an α of .5, a power $(1 - \beta)$ of 0.85, 2 groups (SSRI and memantine group vs SSRI and placebo group), and 7 measurements (T0 to T6); and by assuming a correlation of 0.5 among repeated measures and a nonsphericity correction ε of 1, we determined that a total sample size of 20 participants (10 in each group) will be necessary to achieve a moderate effect size (f=0.25).

Randomization and Blinding

Placebo and memantine tablets will be identical in shape, color, weight, and scent. We will prepare in advance a computer-generated random number sequence for random group assignment. Treatment allocation will be concealed from the patients, from the physicians rating the patients, and from the statistician. Separate individuals will be responsible for randomization and the rating of patients.

Data Collection and Quality Control

Patients will be enrolled after the physician in charge and a supervisor check the patient information regarding the inclusion and exclusion criteria. The data of all participants, including those who are discontinued or dropped from intervention protocols, will be collected according to the study protocol. Quality control will be performed by an external data manager (recruited exclusively for this project).

Statistical Methods

Descriptive statistics for baseline characteristics and the measurements at each time point will be calculated. For the primary objective, a repeated measures ANOVA approach will be used to detect between- and within-group differences in Y-BOCS variables. P values of <.05 will be considered statistically significant. Data will be analyzed by using SPSS version 20 (IBM Corp).

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Results

Recruitment will start in June 2023, and data collection is expected to end in 2024. Results are expected to be available in January 2025. We also intend to make publications available in 2025, and the results of our trial will also be presented at conferences.

Discussion

Overview

In light of the possible role of glutamatergic signal dysregulation in OCD, it is possible to find, among glutamatergic drugs, candidates for an OCD therapy augmentation strategy.

This has motivated the use of glutamate modulators in patients who are unresponsive to standard pharmacotherapeutic approaches. Several RCTs that used glutamate-modulating agents, such as memantine, riluzole, N-acetylcysteine, and glycine, reported promising benefits [38,54,55]. In particular, 4 RCTs were conducted that used memantine (vs a placebo) as an augmentative agent to SRIs in the treatment of moderate to severe OCD [56].

Marinova and colleagues [39] reported that memantine was the compound that most consistently showed a positive effect, as an augmentation medication, on OCD in their study. A critical letter [40] exposed some concerns on this conclusion and proposed that, in light of some methodological gaps, it is necessary to conduct more studies on the use of memantine as an OCD augmentation therapy.

Limitations

Our outpatient clinic—a center specializing in OCD—is an academic service of the Department of Human Neurosciences, Sapienza University of Rome. This could represent a limitation—patient selection bias—due to patients' access to the center's services. Moreover, our study will use a small sample size due to the limits of service access and the inclusion criteria.

Conclusion

To the best of our knowledge, only 4 RCTs have been conducted in recent years that investigated the effects of memantine in patients with refractory severe OCD; our trial will be the first one of its kind in Italy. The innovation of this research proposal is not limited to the evaluation of the efficacy and safety of memantine as an augmentation medication for OCD. Through slow titration and follow-up, we will also observe the minimum effective dose of memantine and its residual efficacy after drug withdrawal by using an 8-week follow-up procedure. In addition, by measuring potential executive function impairments during the study period, we might confirm whether memory and attention are modulators of overall clinical improvement. In other words, we will test if memantine, being an antiglutamatergic agent, acts as a pure antiobsessive medication or if memantine's ability to improve concentration and attention mimics an antiobsessive effect.

Data Availability

The data generated and analyzed during this study will be available from the corresponding author on reasonable request, following the completion of the trial and publication of the main outcomes paper, and will be included in any published articles.

Authors' Contributions

AM, MP, AT, and CDL contributed to the conception and design of the research. AM and MP will evaluate the patients. ADV and FD will assign the patients to the two groups. AM and MP drafted the manuscript. All authors critically revised the manuscript, agreed to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist.
[PDF File (Adobe PDF File), 113 KB - resprot_v12i1e39223_app1.pdf]

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Abbreviations

CSTC: cortico-striatal-thalamo-cortical circuitry
DSM-5: *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*
OCD: obsessive-compulsive disorder
RCT: randomized controlled trial
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
SRI: serotonin reuptake inhibitor
SSRI: selective serotonin reuptake inhibitor
Y-BOCS: Yale-Brown Obsessive Compulsive Scale

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Protocol

Effects of Semisupervised Exercise Training on Health Outcomes in People With Lung or Head and Neck Cancer: Protocol for a Randomized Controlled Trial

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Abstract

Background: Lung or head and neck cancers are known for their high prevalence and mortality rates. Chemotherapy and radiotherapy are usually recommended as cancer treatment for these malignancies; however, they can negatively impact both the physical and mental status of patients. Hence, it is reasonable to consider resistance and aerobic exercise training to prevent these negative health outcomes. Further, several factors prevent patients from attending outpatient exercise training programs, and, therefore, a semisupervised home-based exercise training program may be seen as a well-accepted alternative.

Objective: The aim of this study will be to investigate the effects of a semisupervised home-based exercise training program on physical performance, body composition, and self-reported outcomes; changes in the initial cancer treatment dose prescribed; number of hospitalizations at 3, 6, and 9 months; and 12-month survival in people with primary lung or head and neck cancer.

Methods: Participants will be randomly allocated to the training group (TG) or control group (CG). The TG will undergo semisupervised home-based resistance and aerobic exercise training throughout their cancer treatment. The resistance training will be performed using elastic bands (TheraBand) twice a week. The aerobic training (ie, brisk walk) will be performed for at least 20 minutes per day outdoors. The equipment and tools used during the training sessions will be provided. This intervention will start the week before treatment commencement, will be performed throughout the duration of the treatment, and will continue for 2 weeks after treatment completion. The CG will undergo usual care (ie, cancer treatment with no formal exercise prescription). Assessments will take place 2 weeks before the beginning of the usual cancer treatment and 2 weeks after treatment completion. The measures of physical function (peripheral muscle strength, functional exercise capacity, and physical activity), body composition, and self-reported outcomes (symptoms of anxiety and depression, health-related quality of life, and symptoms related to the disease and treatment) will be collected. We will report on any change in the initial cancer treatment dose prescribed; number of hospitalizations at 3, 6, and 9 months; and 12-month survival.

Results: In February 2021, the clinical trial registration was approved. Recruitment and data collection for the trial are ongoing (as of April 2023, 20 participants had already been randomized), and findings of this study are likely to be published late in 2024.

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Conclusions: This exercise training as a complementary treatment for patients with cancer is likely to promote positive effects on the health outcomes assessed, over and above any change in the CG, and prevent the reduction of initial cancer treatment dose prescribed. If these positive effects are shown, they will likely impact long-term outcomes such as hospitalizations and 12-month survival.

Trial Registration: Brazilian Clinical Trials Registry (ReBEC) RBR-5cyvzh9; https://ensaiosclinicos.gov.br/rg/RBR-5cyvzh9.

International Registered Report Identifier (IRRID): PRR1-10.2196/43547

(JMIR Res Protoc 2023;12:e43547) doi:10.2196/43547

KEYWORDS

lung neoplasms; head and neck neoplasms; drug therapy; radiotherapy; exercise; muscle strength; lung cancer; neck cancer; head cancer; aerobic exercise; pulmonary; neoplasm; ENDT; ear nose throat; ear, nose, and throat; RCT; oncology; outpatient; cancer treatment; Eastern Cooperative Oncology Group; ECOG; HRQoL; quality of life; QoL; physical activity

Introduction

Background

Worldwide, lung or head and neck cancers are the most common cancers and the main causes of death each year [1,2]. Because of the direct effect of these cancers on the respiratory system, management and rehabilitation may be substantially similar [3]. The usual cancer treatment options are surgery, chemotherapy, radiotherapy, or a combination of these treatments [4]. Although having positive effects, these treatments also have side effects, such as fatigue [5,6] and a decrease in functional exercise capacity [7], muscle mass [8], and muscle strength [8,9], which will ultimately affect physical activity and health-related quality of life (HRQoL) [10,11]. Therefore, complementary interventions that could minimize these side effects are needed [7].

Studies have demonstrated that exercise promotes benefits to this population [7]. Improvements have been reported in physical function, body composition, psychosocial function, sleep quality, fatigue, HRQoL [12], and muscle strength [7] after completion of an exercise program. When used as a complementary treatment to usual cancer treatment, exercise has been shown to maximize chemotherapy completion in women with breast cancer and men with prostate cancer [13,14].

Exercise training has been shown to be safe and have positive effects on health outcomes in people with lung or head and neck cancer [15]. Taking into account these positive effects [16,17], as well as the fact that exercise is a low-cost treatment modality that attenuates symptoms related to cancer treatment, it is imperative that exercise training is delivered as a complement or adjunct to medical treatment [15-17].

Distance- and travel-related costs are factors that influence the patient's enrollment and attendance to exercise, and home-based exercises seem to be an option that can overcome these barriers. Although being a feasible alternative [18-20], home-based exercises should be semisupervised to ensure safety and adherence, as well as maximize training efficacy. As there is limited data on the effects of a semisupervised home-based exercise program in people with lung or head and neck cancer, this randomized controlled trial aims to investigate the protective effect of semisupervised home-based exercise training on physical function, body composition, and self-reported outcomes in people with primary lung or head and neck cancer. In addition, we will also report on changes in the initial cancer treatment dose prescribed; number of hospitalizations at 3, 6, and 9 months; and 12-month survival.

Hypotheses

We hypothesize that the semisupervised home-based exercise training as a complementary treatment will promote positive effects on physical function, body composition, and self-reported outcomes in these patients during the cancer treatment. It is also expected that the initial usual cancer treatment dose prescribed will be maintained because of the benefits of the exercise training, leading to fewer hospitalizations and greater survival in patients who underwent the exercise training program.

Methods

Study Design

This will be a single-blind (outcome assessor), 2-arm randomized controlled trial. The study will be conducted at a cancer hospital. The study protocol has been developed following the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2013 checklist guidelines.

Ethics Approval

The trial has received approval from the health research ethics committee of the Regional Cancer Hospital of Presidente Prudente (HRCPP; 26123119.5.0000.8247), which complies with the Declaration of Helsinki. Written, informed consent to participate will be obtained from all participants.

Data Collection and Management

The information collected about participants is individually identifiable by members of the research team only. Each participant will be allocated a unique numeric code (ID number) such that all stored electronic data (eg, databases and data files) will not contain identifiable data until the completion of the study. All confidential information is stored in locked filing cabinets, and only deidentified data will be presented or published.

Study Population

Participants will be recruited from the outpatient clinic before cancer treatment commencement. The inclusion criteria will be as follows: diagnosis of primary lung or head and neck cancer;

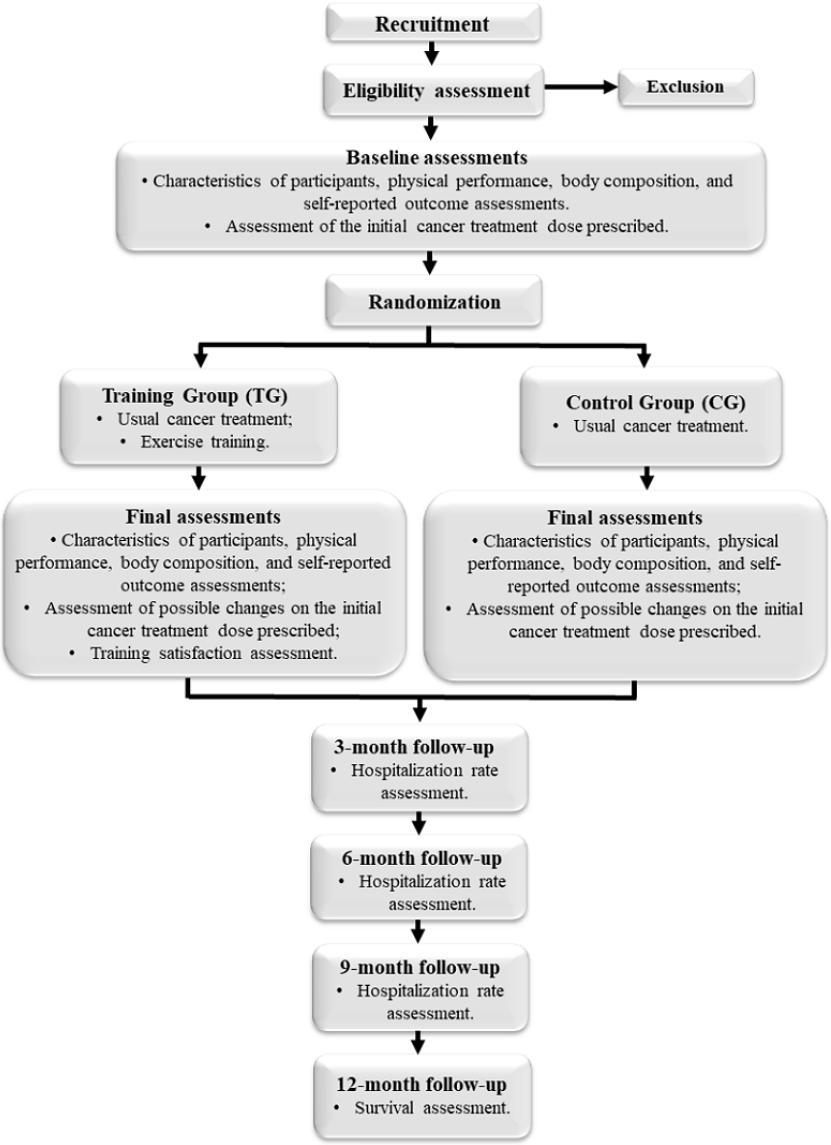
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older than 18 years; referred for cancer treatment including radiotherapy, chemotherapy, or both; Eastern Cooperative Oncology Group performance status score between 0 and 2; life expectancy (physician-rated) of >6 months; and sufficient functional literacy or having a support person who can help with reading the instructions for the home-based exercise program. The exclusion criteria will be as follows: people referred for cancer surgery or palliative care; symptomatic brain or bone metastasis prohibiting participation in exercise training; and unstable metabolic, musculoskeletal, or cardiovascular disease.

Experimental Design

The flow of participants through the study is presented in Figure 1, and the overview of the data collection is given in Table 1. First, people referred to usual lung or head and neck cancer treatment (chemotherapy or radiotherapy) will be assessed on 2 nonconsecutive days. On assessment day 1, participants' characteristics and past medical history will be collected, and data on physical activity, symptoms of anxiety and depression, HRQoL, and symptoms related to treatment and disease will be assessed via validated questionnaires. Subsequently, peripheral muscle strength will be assessed via digital dynamometry. On assessment day 2, measures of body composition (octapolar Inbody 720; Biospace) and functional exercise capacity will be undertaken, including the 6-minute walk test (6MWT), time up and go test (TUG), and 1-minute sit-to-stand test (1STS). After assessment day 2, participants will be randomly allocated to either the training group (TG) or the control group (CG). A third visit will be scheduled for those allocated to the TG, where the exercise training protocol will be explained and demonstrated, and the participants will be familiarized with the training equipment and tools. Participants in the CG group will undergo usual cancer treatment (chemotherapy and radiotherapy) and will be instructed to keep their routine activities during the study period. They will also receive phone calls every 15 days (throughout the course of their cancer treatment) to discuss any issues related to cancer treatment and their participation in the study.

Figure 1. Experimental design of the study.



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Table 1. Overview of the information collected at baseline, during the intervention, at the end of the study, and at the follow-ups.

Outcome	Assessment	Baseline	During intervention	Final	Follow-up (3, 6, and 9 months)	Follow-up (12 months)
Characteristics of the participants	By interview	✓		✓		
Functional capacity	6MWT[a]	✓		✓		
Functional capacity	TUG[b]	✓		✓		
Functional capacity	1STS[c]	✓		✓		
Physical activity	IPAQ[d]	✓		✓		
Body composition	Bioimpedance spectroscopy (octopolar InBody 720; Biospace)	✓		✓		
Anxiety and depression	HADS[e]	✓		✓		
HRQoL[f]	EORTC QLQ-30[g]/QLQ-LC13	✓		✓		
Symptoms related to the treatment and disease	MSAS-BR[h]					
Cancer treatment dose prescribed	Via the participant's medical records	✓				
Cancer treatment dose completed	Via the participant's medical records			✓		
Hospitalization rate assessment	Via telephone calls				✓	
Survival rate assessment	Via telephone calls					✓

[a]6MWT: 6-minute walk test.

[b]TUG: time up and go test.

[c]1STS: 1-minute sit-to-stand test.

[d]IPAQ: International Physical Activity Questionnaire.

[e]HADS: Hospital for Anxiety and Depression Scale.

[f]HRQoL: health-related quality of life.

[g]EORTC QLQ-30: European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire.

[h]MSAS-BR: Memorial Symptom Assessment Scale (Portuguese version).

Two weeks after completion of the cancer treatment, participants will be reassessed (ie, repetition of the 2 days of assessments described above). Data on changes in the initial cancer treatment dose prescribed will be collected during the intervention period. Participants (or their support person) will receive phone calls at 3, 6, 9, and 12 months after the reassessment date. The number of hospitalizations at 3, 6, and 9 months as well as 12-month survival will also be recorded.

Randomization, Concealment, and Blinding

The randomization sequence will be generated on a web-based platform [21] and concealed using opaque envelopes. This process will be conducted by a researcher who is not involved with participant recruitment, assessment, or data management and analysis. The assessor will be blinded to group allocation. Assessments and patient recruitment will be blinded to the therapeutics.

Procedures (TG and CG Intervention)

Participants in both groups (TG and CG) will undergo usual cancer treatment that does not include any formal exercise prescription. Those allocated to the TG will perform resistance and aerobic exercises that will be individually prescribed.

TG Intervention

The semisupervised home-based exercise training program will start 1 week before commencement of cancer treatment and will finish 2 weeks after completion of the cancer treatment. Semisupervision will include an exercise diary, daily SMS text messaging, and frequent phone calls. A previous study [22] reported that people who underwent semisupervised home-based exercise training did not have any adverse event during the training program. The resistance and aerobic training will be guided by an exercise diary developed by the research team; see Multimedia Appendix 1 for more details. Participants in the TG will be instructed to complete the diary on a daily basis with information on the exercises they performed. They will also be provided with a pulse oximeter (G-Tech Portable Oled) and the modified Borg scale to assess and record their peripheral capillary oxygen saturation and the Borg dyspnea score, respectively, before and after the exercise training session. Participants will be asked to avoid exercise training if resting oxygen saturation is <90%. Resistance training will be performed twice a week and aerobic training will be performed 7 days a week. Participants will also receive a daily SMS text message reminding them to perform the exercises and will be contacted (via a phone call) every 7 to 14 days.

To ensure participants' safety during the exercise program, blood tests will be performed every second week to monitor

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platelet count and hemoglobin levels. Exercise training will be paused when there is fever (>38 °C) [23], infection, hemoglobin level <8 g/dL [24,25], and psychological instability or clinical complications [26].

Resistance Training

Participants in the TG will perform semisupervised home-based resistance training using elastic bands (TheraBand, green color, moderate resistance) [26]. Exercises for the following muscle groups will be included: elbow flexors, knee flexors, and knee extensors (2 sets of 10 repetitions with a 1-minute interval) [27]. The exercise intensity will be adjusted using the modified Borg scale (the participant must maintain dyspnea between 4 and 6, ie, moderate intensity) [22]. Regarding progression of the exercise prescription, if the participant is able to perform more than 2 sets of 10 repetitions and report a Borg dyspnea score <4, an increment of 5 repetitions will be prescribed for the following session using the same elastic band resistance [28]. Subsequently, the intensity progression will be to 3 sets of 10 repetitions and then 3 sets of 15 repetitions. Participants will be contacted via a phone call (or in person, if needed) every 7 to 14 days to assess the need for increased training intensity. This protocol was developed based on previous studies of exercise training in people with cancer [22,26-28] as well as of resistance training with elastic bands in people with chronic obstructive pulmonary disease [29,30].

Aerobic Training

For the aerobic training, participants will perform a brisk walk outside, starting with 20 minutes daily (equivalent to 1.5 km) [28], and will be asked to maintain a Borg dyspnea score between 4 and 6 (moderate intensity) [31]. Therefore, this training will be equivalent to approximately 3.5 metabolic equivalents [28]. Participants will be provided with a pedometer (Power Walk PW-610; Yamax) as a feedback tool for the aerobic training. Participants will be instructed to try to achieve at least 150 minutes of aerobic training weekly. The modified Borg scale will also be used to titrate the intensity of the aerobic training (if symptoms of dyspnea are <4 on the Borg scale, an extra 5 minutes will be prescribed for the following week). If more than 150 minutes of weekly aerobic training is achieved, the participants will be instructed to increase their walking speed but maintain a Borg dyspnea score between 4 and 6. This protocol has been developed based on previous studies of physical training for people with cancer [26,28].

CG Intervention

Participants in the CG will undergo usual cancer treatment with no formal exercise prescription and will be instructed to keep routine activities during the study period. They will also receive phone calls every 15 days to discuss any issues related to cancer treatment and their participation in the study.

Outcome Measures (Assessments)

Characteristics of Participants

Participant characteristics will be collected of age, gender, height, body weight, cancer type and stage, number of cycles per session as well as dose of chemotherapy or radiotherapy prescribed, and self-reported comorbidities.

Primary Outcome

Peripheral Muscle Strength

Peripheral muscle strength will be assessed via the force gauge digital dynamometer (Instrutherm DD-300), and the results will be expressed in newtons. The participants will be instructed to perform elbow flexion (at 180°), knee flexion (at 90°), and extension (at 90°) movements resisted by a steel cable coupled to the dynamometer. The measurement will be repeated 5 times with an interval of 1 minute between attempts, and the highest value among the 3 closest measurements will be recorded [32].

Secondary Outcomes

Functional Exercise Capacity

Functional exercise capacity will be assessed via the 6MWT and the 1STS. The 6MWT will be performed in accordance with the guidelines established by the American Thoracic Society and European Respiratory Society [33]. Two tests will be performed, with at least 30 minutes of rest between them, and the best performance (ie, 6-minute walk distance) will be reported. The reference values developed for the Brazilian population will be used [34].

The 1STS test will also be used to evaluate the functional exercise capacity. Two tests will be performed, with 1 minute of rest between them, and best performance (ie, number of sit-to-stand repetitions) will be reported [35].

Mobility

Mobility and the capacity to perform routine activities will be assessed by the TUG. The TUG has also been used to assess risk of falls, and the performance in the TUG is determined by the time spent to complete the test [36,37].

Physical Activity

The International Physical Activity Questionnaire will be used to assess self-reported physical activity. The variable from the International Physical Activity Questionnaire that will be used is time spent in physical activity [38].

Body Composition

Body composition will be assessed via bioimpedance spectroscopy (octopolar InBody 720; Biospace) following the manufacturer's instructions. Data will be electronically imported to Excel (Microsoft Corp) using the software Lookin'Body (version 3.0; Biospace) [39]. The following variables will be assessed: intracellular water, extracellular water, total body water, basal metabolic rate, protein mass, skeletal muscle mass, bone mineral content, fat mass, and body weight.

Symptoms of Anxiety and Depression

Symptoms of anxiety and depression will be assessed via the Hospital for Anxiety and Depression Scale. This scale comprises 14 questions, divided into 2 subscales: anxiety and depression. The final score indicates probably not anxiety or depression, questionable or doubtful anxiety or depression, and probable anxiety or depression [40].

Health-Related Quality of Life

HRQoL will be assessed using the European Organization for Research and Treatment of Cancer Core Quality of Life

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Questionnaire (EORTC QLQ-30) [41]. The specific module for lung cancer (QLQ-LC13) [42] will also be used. Higher scores in physical scales and global health scales indicate greater HRQoL, whereas higher scores in symptoms scales indicate worse symptoms and poorer HRQoL [41].

Symptoms Related to the Treatment and Disease

The Memorial Symptom Assessment Scale (Portuguese version) will be used to assess symptoms related to the treatment and disease. This scale comprises items related to psychological and physical symptoms [43].

Other Measures

Any change in the initial cancer treatment dose prescribed will be investigated via the participant's medical records. Participants (or their support person) will receive phone calls at 3, 6, 9, and 12 months after the reassessment date. The number of hospitalizations at 3, 6, and 9 months as well as 12-month survival will also be recorded. Satisfaction with the semisupervised home-based exercise training program will be assessed using a questionnaire that comprises 2 questions [44]. Participants will rate, on a scale ranging between 0 and 10, their satisfaction with performing the exercise training program and how valuable the exercise training program was for them. Higher scores indicate greater satisfaction.

Sample Size Calculation

The sample size was determined using published data on the effectiveness of exercise training in improving peripheral muscle strength in patients with cancer [45]. Forty participants will be needed to detect a between-group difference of 72 (SD 71) newtons on the specific primary outcome: knee extensors' muscle strength [46] (power of 80%, adopting an α of 5%). This calculation accounts for 30% loss to follow-up.

Data Management and Analysis

The statistical software SPSS (version 23.0; IBM Corp) will be used. The distribution of the data will be assessed by the Shapiro-Wilk test. Continuous data will be expressed as either mean (SD) or median (IQR) according to their distribution. The criteria that define the exclusion of the participant from the final data analysis will be (1) initiation of palliative care or (2) substantial physical impairment due to hospitalization during the intervention period. For data that are normally distributed, both within- and between-group differences will be assessed using the 2-way repeated measures ANOVA. Between-group differences will be reported as the mean difference and 95% CI [47,48]. For data that are not normally distributed, within-group differences will be assessed using the Wilcoxon test, whereas between-group differences will be assessed using the Mann-Whitney *U* test. To evaluate the effect size between groups, the Cohen *d* test will be used. For all analyses, a *P* value of <.05 will be considered significant. The within-group change from baseline to postintervention will be assessed via either a 2-tailed paired *t* test or the Mann-Whitney *U* test. The chi-square test will be used to analyze hospitalization frequency at 3, 6, and 9 months, and the hazard ratio will be used to report on 12-month survival. Analyses will be undertaken according to the intention-to-treat principle.

Results

In February 2021, the clinical trial registration was approved. Recruitment and data collection for the trial are ongoing, and the results of this study are likely to be published late in 2024.

Discussion

Potential Impact and Significance of the Study

This study protocol has been developed after a thorough literature search on exercise training for people with cancer, specifically lung or head and neck cancers. The implementation of this novel exercise training protocol, which will be based on a semisupervised home-based program delivered as a complementary treatment in people with lung or head and neck cancer, will investigate whether the program will promote a protective effect on physical function, body composition, and self-reported outcomes. Further, the study will also explore the effects of the program on any change in initial cancer treatment dose prescribed; hospitalizations at 3, 6, and 9 months; and 12-month survival.

Strengths and Limitations of the Study

This study will be a single-blinded (outcome assessor) randomized controlled trial in which participants allocated to the TG will undergo an individualized home-based exercise program. The study will be the first to include both people with lung cancer and those with head and neck cancer. In addition to reporting the effectiveness of the proposed intervention on important health outcomes, this novel study will also explore the effects of the proposed intervention on any change in the initial cancer treatment dose prescribed; hospitalizations at 3, 6, and 9 months; and the 12-month survival rate. As in any study in the field of exercise training, blinding of participants and personnel is very challenging, and in this case, it is not possible. The study will only be conducted in a single center, which may limit its external validity. However, the robust reporting of our methods will allow replication in future multicenter studies.

Contribution and Clinical Applicability

The proposed complementary semisupervised home-based exercise training program is of low cost. If shown to have a positive impact on the outcomes of interest, the program will likely impact long-term outcomes such as hospitalizations and 12-month survival and is likely to be implemented in routine-practice cancer exercise or pulmonary rehabilitation programs delivered in settings such as outpatient clinics, rehabilitation centers, and community programs.

Conclusions

The proposed exercise training program as a complementary treatment for patients with lung or head and neck cancer is likely to promote positive effects on the physical and mental health outcomes assessed, over and above any change in the CG, and prevent the reduction of initial cancer treatment dose prescribed, which will likely impact long-term outcomes such as hospitalizations and 12-month survival. If shown to be effective at improving outcomes, the semisupervised exercise training

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protocol is likely to be implemented in clinical practice across many cancer and pulmonary rehabilitation programs worldwide.

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Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during this study.

Authors' Contributions

IG, VC, FFDL, and EMCR contributed to the development of the exercise protocols presented in this study and to the writing and commented on all versions of this study protocol. IG, EMCR, KP, ERMF, DGR, and NI are involved in recruiting and collecting data. IG, VC, FFDL, KP, and EMCR will conduct the analysis. All authors approved the final version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Exercise diary.
[PDF File (Adobe PDF File), 150 KB - resprot_v12i1e43547_app1.pdf]

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Abbreviations

1STS: 1-minute sit-to-stand test
6MWT: 6-minute walk test
CG: control group
EORTC QLQ-30: European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire
HRCPP: Regional Cancer Hospital of Presidente Prudente
HRQoL: health-related quality of life
QLQ-LC13: European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire–Lung Cancer 13
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
TG: training group
TUG: time up and go test

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Protocol

Efficacy of Naprapathy in Brachial Plexus Injury: Protocol for a Randomized Clinical Trial

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Abstract

Background: Clinical rehabilitation for brachial plexus injury is difficult in terms of chronic pain and dysfunction. Physiotherapy is considered a routine intervention for rehabilitation. Common physical therapy may require a variety of instruments. One approach that does not need instruments, but belongs to the field of complementary and alternative medicine, is naprapathy. Naprapathy, also called Tuina in China, has been applied in rehabilitation after brachial plexus injury for a long time. Naprapathy can relieve chronic neuropathic pain, promote local blood circulation, and improve body edema. Naprapathy can passively help improve motor functions in patients with peripheral nerve injury. However, the efficacy of naprapathy in improving rehabilitation after brachial plexus injury is unclear.

Objective: This study aims to evaluate the additional value of naprapathy when combined with conventional physical therapy for the treatment of brachial plexus injury.

Methods: This will be a single-center randomized controlled trial. A total of 116 eligible patients with brachial plexus injury will be randomly divided into an experimental group (naprapathy plus physical therapy group) or a control group (physical therapy group). The participants will be followed up for 4 weeks of treatment. Observation outcomes will include the visual analog scale score, upper limb index, electromyography findings, and adverse reactions, among others. The measuring points for outcomes will be the baseline and the completion of treatment. In addition, a quality control group independent from the research team will be set up to control the quality of the trial. Finally, the data will be analyzed using SPSS software (version 21.0; IBM Corp).

Results: The study is recruiting participants. The first participant was enrolled in September 2021. As of January 2023, a total of 100 participants have been enrolled. The trial is expected to be completed by September 2023. The study protocol was approved by the Ethics Review Committee of Yue Yang Hospital affiliated with the Shanghai University of Traditional Chinese Medicine (2021-012).

Conclusions: One limitation of this trial is that we will be unable to achieve strict double-blinding because of the features of naprapathy. The trial aims to contribute reliable evidence for decision-making in naprapathy for treating brachial plexus injury.

Trial Registration: Chinese Clinical Trial Registry ChiCTR2100043515; http://www.chictr.org.cn/showproj.aspx?proj=122154

International Registered Report Identifier (IRRID): DERR1-10.2196/46054

(JMIR Res Protoc 2023;12:e46054) doi:10.2196/46054

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KEYWORDS

naprapathy; brachial plexus injury; traditional Chinese medicine; study protocol; clinical rehabilitation; chronic pain; physical therapy; randomized controlled trial; neuromusculoskeletal; acupuncture; moxibustion; Tuina; TCM; pain; edema; blood circulation; brachial plexus; spinal cord; limb; electromyography; EMG

Introduction

Brachial plexus injury (BPI) is one of the most challenging problems in modern medicine because of its high disability rate, surgical difficulty, and complex sequelae [1]. It is mostly caused by injuries such as a motorcycle accident, birth injury, bruising, puncture injury, fracture, dislocation, and lung apex tumor resection [2-5]. Sensory impairment or muscle paralysis and atrophy, which cause partial or complete upper limb motor and sensory dysfunction, may place a great burden on the patient's life and mental health [6,7]. With the development of microsurgical technology in recent decades [8], great progress has been made in the treatment of BPI, especially in terms of surgical treatments [9,10], allowing good conditions for the functional recovery of patients' limbs to be provided. There are also some rehabilitation methods, such as medium-frequency electrical stimulation, infrared irradiation, ultrasound therapy, and so forth, but the effects are not satisfactory [11,12].

The ability of an injured nerve to regenerate is closely related to the repair time, with 1 to 3 months after injury being considered the “golden period” for nerve repair [13]. However, with a delayed diagnosis, the prognosis is poor. Surgical repair is only performed in preparation for the treatment of BPI; rehabilitation is the beginning of treatment and is necessary after surgery [14]. Due to differences in the condition of patients with BPI, physical therapy should be used to relieve pain, eliminate swelling, prevent scar adhesion, and joint contracture; promote nerve regeneration; and prevent muscle atrophy and joint stiffness [15,16].

At present, physical rehabilitation therapies commonly used after BPI, such as neuromyoelectric stimulation, intermediate frequency electrotherapy, and hand function training [17-19], have certain effects on upper limb function, but the effect of rehabilitation on hand function remains limited.

Naprapathy (also called Tuina therapy in traditional Chinese medicine) [20] consists of physical stimuli acting on the human body through manipulation to cause physiological responses in tissue fibers. Through the regulation of nerve reflexes and body fluids, therapeutic effects on damaged areas can be achieved. Naprapathy can promote capillary dilation, increase blood circulation, and improve muscle blood circulation such that the condition of damaged tissue can be improved and the tissue will be repaired [21]. Swelling and cramping can also be reduced or alleviated. Our previous study showed that naprapathy can improve the pain threshold in rats with neuropathic pain caused by BPI, increase the expression of β-endorphin and gamma-aminobutyric acid in the reward circuit in the brain [22], and relieve chronic neuropathic pain in rats. These findings may represent one of the neurological mechanisms of naprapathy. Naprapathy not only exerts an analgesic effect but also provides a certain comfort for patients. Patients with BPI are also willing to undergo naprapathy in the clinic. However, there is a lack of clinical research on naprapathy in the treatment of BPI. Therefore, we designed this randomized controlled trial (RCT) to evaluate the additional effects of naprapathy when combined with conventional physical therapy on pain and hand motor function in patients with BPI.

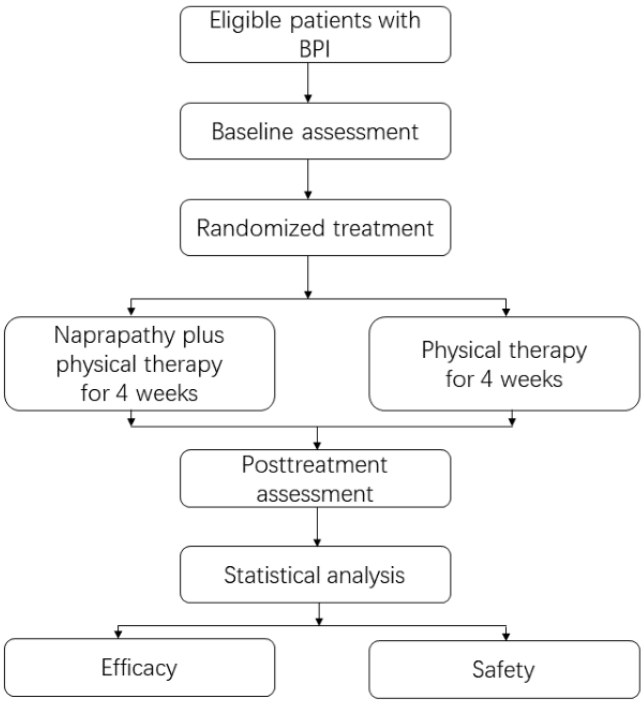
Methods

Study Design

This clinical trial will be an open-label RCT designed to compare naprapathy plus physical therapy and physical therapy in treating BPI. This protocol has been registered on the Chinese Clinical Trial Registry (2100043515) and will be performed in accordance with the Declaration of Helsinki. The study flowchart is shown in Figure 1.

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Figure 1. Study flowchart. BPI: brachial plexus injury.



Study Setting of Recruitment

Recruitment will be carried out at Yue Yang Hospital affiliated with the Shanghai University of Traditional Chinese Medicine. A total of 116 participants with BPI will be enrolled. Recruitment will be carried out through social platforms and outpatient departments. The study team will educate physicians about the study, focusing on those who do the surgery for patients with BPI. If the patients meet the inclusion criteria and are willing to participate in the trial, they will be asked to provide written informed consent. Then, they will be randomized into the naprapathy plus physical therapy group (group A) or the physical therapy group (group B) by LZ and BP.

Ethics Approval

The study protocol was approved by the ethics review committee of Yue Yang Hospital affiliated with the Shanghai University of Traditional Chinese Medicine (2021-012). Any changes including eligibility criteria, outcomes, and so forth should be reported to the Ethics Review Committee. The ethics committee of Yueyang Hospital affiliated with the Shanghai University of Traditional Chinese Medicine will audit the whole procedure during the clinical trial conducted independently from investigators and the funder. The participants signed the informed consent and agreed to the primary and secondary analyses of their data without additional consent. All the study data are deidentified. This trial has also been registered in the Chinese Clinical Trial Registry (2100043515). The results of the preliminary study will be published in a professional journal.

Patient and Public Involvement

Patients and the public are involved in the design of the study. They reviewed the study proposal and attended the design meetings. Patients and the public will be included in all research communications.

The inclusion criteria are as follows: (1) aged 18 to 70 years; (2) BPI diagnosed by history, physical examination, electromyography, or surgical exploration more than 2 weeks after nerve surgery; (3) agreement to provide written informed consent.

The exclusion criteria are as follows: (1) concurrent damage to major organs, such as the heart, kidneys, liver, and so forth; (2) severe cardiovascular or cerebrovascular disease, liver or kidney dysfunction, metabolic disease, or mental illness; (3) chronic illness, physical discomfort, frailty, severe neurosis, or pregnancy; (4) primary brachial plexus pain or brachial plexus neuritis; (5) brachial plexus pain due to cervical spondylosis, tennis elbow, carpal tunnel syndrome, frozen shoulder, biceps tenosynovitis, thoracic outlet syndrome, or other secondary causes.

The participants will be withdrawn if they have the following: (1) missing or incomplete patient treatment records, which would affect the final data analysis; (2) treatment with other methods at the same time; (3) any severe adverse reactions or other emergent symptoms during the treatment (such as aggravation of disease or severe depression and the need for special treatment).

Randomization

In this clinical trial, a total of 116 participants with BPI will be randomly assigned to either group A (naprapathy plus physical therapy) or group B (physical therapy) at a 1:1 ratio. The random sequence will be generated using SAS software (version 9.3; SAS Institute, Inc). The coauthors randomizing the participants are not linked to any statistical work.

Interventions

The treatment plan of this trial is based on naprapathy in clinical rehabilitation for the treatment of BPI. Participants in group A

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will receive naprapathy in addition to physical therapy, while participants in group B will receive physical therapy only. Treatment in both groups will last 4 weeks. The interventions in this trial involve rigorous naprapathy and physical therapy schedules. To ensure the compliance of naprapathy practitioners and physical therapists with their schedules, they will be asked to undergo pretrial training, after which they will be required to pass an entrance examination to participate in this trial. All included naprapathy practitioners and physical therapists will have at least 5 years of practical experience in clinical rehabilitation.

Physical Therapy

All participants will receive physical therapy, such as neuromyoelectric stimulation by a transcutaneous electrical nerve stimulator (TENS 21, Homer Ion), medium-frequency electrotherapy by a medium-frequency electrical stimulator (ES-521, Ito), and continuous passive motion by an upper limb continuous passive motion joint rehabilitation device (2029, DJO), once each day for 5 continuous days in a week. Each therapy session will last for 40 minutes and will be performed 5 times a week (from Monday to Friday) for a total of 20 sessions in 4 weeks.

Naprapathy

For patients with total BPI, the patient will take a sitting position. The naprapathy practitioner will stand on the affected side and first apply Yizhichan (one-finger Zen) (Figure 2) pushing manipulation and press-kneading manipulation at Fengchi (GB 20, affected side), cervical Jiaji points (EX-B2, affected side), Jianjing (GB 21, affected side), Jianyu (LI 15, affected side), Quchi (LI 11, affected side), Waiguan (SJ 5, affected side), and Hegu (LI 4, affected side). Then, the practitioner will apply rolling manipulation (Figure 3) from the affected shoulder to the upper limb and grasping manipulation (Figure 4) on the neck, shoulder, and upper limb. Finally, the hand-shoulder shaking (Figure 5) method will be applied to help soothe the joints. Within the allowable safety range of the affected limbs, the joints of the upper limbs will be passively moved.

For patients with upper trunk BPI, the naprapathy practitioner will apply Yizhichan pushing and press-kneading manipulations at Fengchi (GB 20, affected side), Yunmen (LU 2, affected side), Quchi (LI 11, affected side), Shousanli (LI 10, affected side), Hegu (LI 4, affected side), Yangxi (LI 5, affected side), Sanjian (LI 3, affected side), Yuji (LU 10, affected side), and Laogong (PC 8, affected side). The other methods will be the same as above.

For patients with lower trunk BPI, the naprapathy practitioner will apply Yizhichan pushing and press-kneading manipulations at Tianzong (SI 11, affected side), Jianzhen (SI 9, affected side), Waiguan (SJ 5, affected side), Yangchi (SJ 4, affected side), Jianwaishu (SI 14, affected side), Xiaohai (SI 8, affected side), Yanglao (SI 6, affected side), Yanggu (SI 5, affected side), and Houxi (SI 3, affected side). The other methods will be the same as above.

The duration of each naprapathy session will be 20 minutes and will be performed 5 times a week (every Monday to Friday) for a total of 20 sessions in 4 weeks. If there are any adverse events, the treatment will be suspended, and the investigator will decide whether to terminate the treatment.

All the acupoints used in this study are shown in Figures 6 and 7.

Figure 2. Yizhichan pushing manipulation.



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Figure 3. Rolling manipulation.

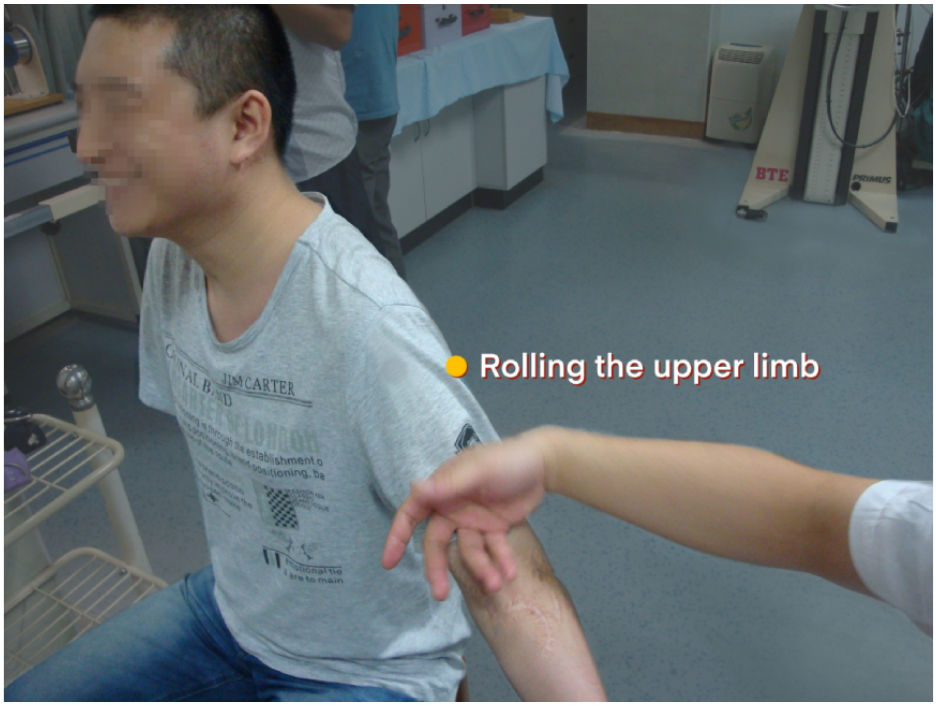


Figure 4. Grasping manipulation.

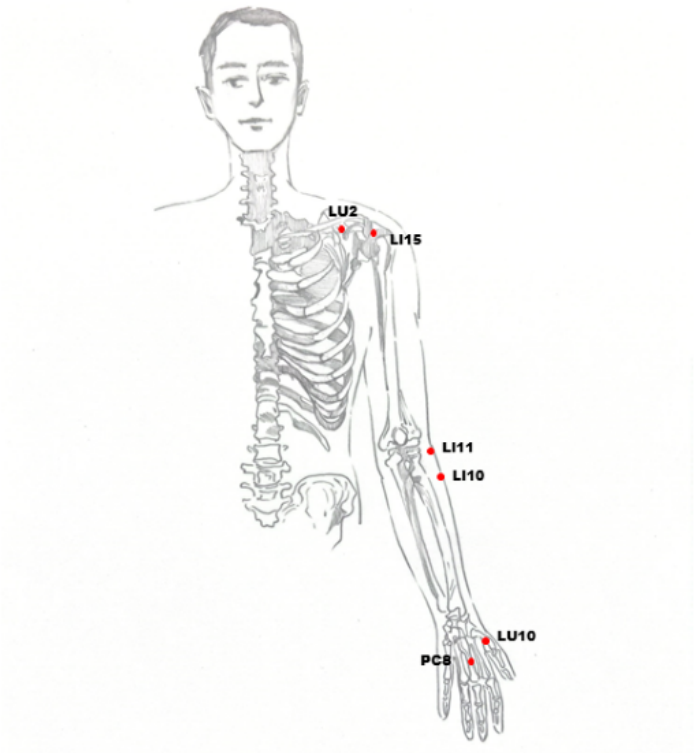


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Figure 5. Shaking manipulation.

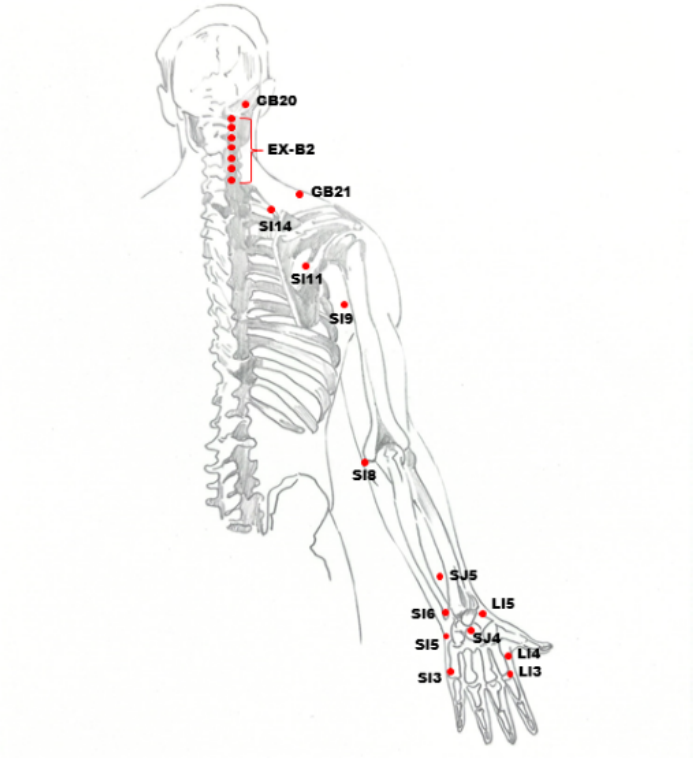


Figure 6. Illustration of acupoints (front).



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Figure 7. Illustration of acupoints (back).



Outcomes

Primary Outcome Indicator

The primary outcome measure will be the change in visual analog scale score relative to baseline at 4 weeks.

Secondary Outcome Indicators

The secondary outcomes will include the upper limb motor function score according to the Brunnstrom functional assessment and electromyography findings.

Time Points of Outcome Measurement

Outcomes will be evaluated at 2 time points: baseline and at the completion of treatment. An overview of the outcomes measured at the different time points is shown in Table 1.

Table 1. Case data collection timetable.

Time point	Baseline	Posttreatment
Written informed consent	✓	
Concomitant treatment	✓	
Disease history	✓	
History of medication	✓	
Brunnstrom functional assessment	✓	✓
VAS[a]	✓	✓
EMG[b] examination	✓	✓
Participant self-evaluation		✓
Adverse events		✓
Safety analysis		✓

[a]VAS: visual analog scale.

[b]EMG: electromyography.

Assessment of Safety and Adverse Events

According to clinical experience and the literature, naprapathy may cause several kinds of adverse events, such as subcutaneous hematoma, edema, skin bruising, local pain, and fainting. Among these adverse events, subcutaneous hematoma and edema are the most common. Naprapathy-related safety and adverse events will be carefully recorded using case report

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forms. Adverse events should be reported to the ethics committee of Yueyang Hospital affiliated with the Shanghai University of Traditional Chinese Medicine. The Ethics Committee has the right to stop the intervention of the participant.

Data Collection and Management

All our measures will be free of charge to ensure complete participation in the follow-up evaluation. Case report forms will be completed in paper form and stored by the Shanghai University of Traditional Chinese Medicine. Data will be collected according to Table 1 by investigators, and personal information about the enrolled participants will be kept in Yueyang Hospital in order to protect confidentiality in the whole trial. The ethics committee of Yueyang Hospital affiliated with the Shanghai University of Traditional Chinese Medicine will audit the trial every 12 months and will establish a data monitoring committee, which is independent from the funder and has no competing interests. The data will be stored in the clinical trial public management platform and ready for public inquiry after the trial. A quality control group independent from the research team will be set up to control the quality of this study.

Sample Size

Our previous study indicated that 58.5% of patients with BPI showed improvements in upper extremity function and muscle strength [23]. In this clinical trial, the rate of upper extremity function recovery is expected to be 75% in the naprapathy group and 55% in the physical therapy group. With α=.05 and β=.01, a total of 52 participants will be needed, as calculated using SPSS software (version 21.0; IBM Corp). According to the previous study, a 10% withdrawal rate will also be considered; therefore, each group will include at least 58 participants.

Statistical Analysis

All data will be analyzed by researchers using SPSS (version 21.0) software. Data will be expressed as the mean (SD) or median (IQR). First, the data will be tested for normality and homogeneity of variance; if the data meet the requirements for a normal distribution, the homogeneity of variance will be analyzed by the *F* test. In the case of heterogeneity, the corrected *t* test will be used. If the requirements for normality and homogeneity of variance are not satisfied, the rank-sum test will be used. If the sphericity test yields a *P* value less than .05, indicating that the assumption of sphericity is violated, we will perform multivariate analysis. A statistically significant result (P<.05) for the time factor will indicate that the measurements show a trend of changing over time. A statistically significant (P<.05) interaction between time and group will indicate that in addition to the effect of time, there are differences between the groups. If a *P* value is less than .05, the difference will be considered statistically significant, indicating a difference in the results between the two groups. If a *P* value is greater than .05, then the difference will not be considered statistically significant, indicating no difference in the results between the two groups. Cohen *d* (sample size) will also be used to compare differences between groups, and the generalized linear model will be applied to explore differences in outcomes between groups.

For safety analysis, adverse event data are generally expressed as the number of events and the percentage of cases involved in the adverse event.

Results

This study was funded by The National Natural Science Foundation of China and the Shanghai Health Commission. Yue Yang Hospital affiliated with the Shanghai University of Traditional Chinese Medicine approved the study protocol in February 2021. The first participant was enrolled in September 2021. As of January 2023, a total of 100 participants have been enrolled. The trial is expected to be completed by September 2023.

Discussion

Due to methodological design problems, the quality of currently available clinical studies on naprapathy for BPI is relatively low. Therefore, this study is designed as an RCT to evaluate the additional effects of naprapathy when combined with physical therapy on BPI in terms of pain and upper extremity motor function.

Additionally, this single-center trial will provide reliable data for our future multicenter RCTs. Participants will receive 5 treatments a week, which is the most common frequency for external traditional Chinese medicine treatments for rehabilitation after BPI.

One limitation of this trial is that we will be unable to achieve strict double-blinding because of the features of naprapathy. Other limitations include manpower, material resources and funds, and short follow-up time, and it is expected that the future study will extend the follow-up time. Naprapathy relies on the intervention of the naprapathy practitioner, and future trials could be designed with a sham naprapathy placebo group.

This study aims to provide reliable evidence for naprapathy in the treatment of BPI and will compensate for the lack of related research on clinical efficacy.

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The authors thanks Yaqi Wang for assistance with the illustrations of anatomical landmarks and Xiaoyi Qu for valuable discussion. This study is financially supported by funds from the Shanghai Health Commission (20204Y0490) and The National Natural Science Foundation of China (82105041). The funding organizations offers peer review for the design of the study.

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Authors' Contributions

ZL and FG designed the study as principal investigators. BX, AM, LZ, and YH participated in the design of the study and drafted the manuscript. BX, LZ, BP, and YH are responsible for the recruitment and treatment of patients. All authors have read and approved the final manuscript.

Authors ZL (lzy1855@aliyun.com) and FG (gufeiking@163.com) are co-corresponding authors for this article.

Conflicts of Interest

None declared.

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Abbreviations

BPI: brachial plexus injury
RCT: randomized controlled trial

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Protocol

Effectiveness of Silver Diamine Fluoride for Early Childhood Caries Among Children Aged 24 to 72 Months: Protocol for a Randomized Controlled Trial

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Abstract

Background: Dental caries is a serious public health issue globally. It is one of the most prevalent chronic disease in children worldwide. An important public health concern is the existence of one or more decayed, missing, or filled tooth surfaces in any primary teeth of preschool children. Early childhood caries (ECC) can be halted with the use of silver diamine fluoride (SDF) solution. Previous research has indicated that it may have a preventive impact in the treatment of ECC. It is well known that 38% silver diamine fluoride (SDF) is helpful at preventing dental caries. On the other hand, there is not enough evidence on SDF's ability to prevent caries in primary teeth. To date, no well-planned clinical study has been carried out to investigate SDF's impact on caries protection.

Objective: The study's objective is to evaluate and compare the efficacy of 12%, 30%, and 38% silver diamine fluoride in preventing ECC in children aged 24 to 72 months in Mangaluru Taluk.

Methods: This is a single-center, randomized, active-controlled, parallel-group pragmatic trial. Children attending preschool in Mangalore Taluk aged 24 to 72 months will be included in the study. There will be three study groups: group 1 will receive 12% SDF semiannually; group 2 will receive 30% SDF semiannually; and group 3 will receive 38% SDF semiannually. After 6 and 12 months, the principal examiner will conduct a clinical examination of the teeth with a visual and tactile assessment. The effectiveness of the various concentrations of SDF will be determined after 12 months.

Results: The research was funded in September 2020, and data collection started in September 2022. As of February 2023, 150 participants have enrolled in the study. The project is still underway, and it is expected to be completed in December 2023.

Conclusions: Uncertainty surrounds the efficacy of 38% SDF in preventing ECC. Consensus-Based Clinical Case Reporting (CARE) guidelines recommending the use of SDF for ECC prevention will be modified if the findings are as expected. Additionally, since the findings will be broadly disseminated, more nations will implement the use of SDF, easing the burden of ECC on the entire world. Future research on the treatment and prevention of ECC will benefit from the study results. If SDF is successful in preventing caries in a classroom or community context, it will mark an important turning point for preventive dentistry.

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Trial Registration: Clinical Trial Registry of India CTRI/2020/02/023420; https://tinyurl.com/3ju2apab
International Registered Report Identifier (IRRID): PRR1-10.2196/46144

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KEYWORDS

silver diamine fluoride; children; caries; childhood; dental; dentist; oral health; child; pediatric; RCT; randomized; fluoride; prevention

Introduction

Background

Dental caries is a complex, bacteria-driven, chronic, site-specific, and significant process brought on by a physiological imbalance between minerals in teeth and the fluid in plaque [1]. It is a progressive condition that results from the demineralization of dental enamel caused by the acids generated during the metabolism of sugars by cariogenic bacteria [2] and is one of the most prevalent chronic childhood illnesses; in developing nations, many decayed teeth go untreated. The World Health Organization (WHO) estimates that there are an average of 2.4 decaying, missing, and filled teeth per person worldwide. Dental caries continues to be a significant problem in the majority of developed nations, impacting 60% to 90% of school-aged children. In many industrialized nations, there have been encouraging trends in the fight against pediatric dental caries. In India, where more than 70% of the population lives in rural areas with few health services and restorative therapy is expensive, parents tend to neglect their children's dental needs, leading to untreated dental caries [1].

The term early childhood caries (ECC) has been used to describe the presence of one or more decayed, restored, or missing primary teeth in a child younger than 6 years [3]. The American Dental Association has classified the presence of one or more decayed, missing, or filled tooth surfaces in any primary tooth in a preschool-aged child as a major public health concern. If ECC is not addressed, it may affect a person's quality of life in terms of dental health, as well as their body weight, growth, attendance at school, and academic achievement. Measures to prevent and treat severe ECC are essential for both general and dental health because it is a major indicator of adult caries [4].

Poor oral health–related quality of life, low BMI, bad scholastic results, and high absenteeism from school are just a few of the harmful impacts of untreated dental caries that can have an impact on physical development. Due to their vulnerability and reliance on their caretakers for both nutritional requirements and mouth cleanliness, children are most at risk of developing dental caries. Dental caries frequently exhibits no symptoms in its early phases, but if left unchecked, it can cause excruciating pain and potentially fatal infections [3].

ECC prevalence varies from population to population. The illness is most prevalent and severe in East Asia, where prevalence rates in children aged 3 years range from 36% to 85%. In India, 44% of children aged between 8 and 48 months have ECC. Despite tremendous advancements in the field of caries control in recent decades, a high prevalence of ECC in young infants has been observed. It is thus a major social concern; disease control can be accomplished if the demographic groups with the greatest needs are identified. The prevalence of ECC overall in India is 49.6% according to an analysis of all included studies. While in Karnataka state, the prevalence of ECC was reported to be 48.79% [5].

The current cost of treating oral diseases, such as dental caries, places a heavy financial burden on both households and health care providers. Additionally, because of the high expense of dental treatment, elderly adults, socially excluded groups, and children living in poverty are more likely to develop oral diseases. Moreover, even if people have access to therapy, the current course of action for children with severe caries includes giving them local anesthesia to ease their pain and worry. Such treatments have been linked to poor oral health, dental anxiety, and a higher risk of dental caries in children's permanent teeth in later life. In order to prevent and manage caries and encourage health and well-being, new, accessible, and equitable methods are required [6].

Nonrestorative intervention is a potential alternative method for treating caries in primary molars. Silver diamine fluoride (SDF) has been used successfully to stop the progression of carious lesions in people who cannot tolerate invasive treatment, including children, the elderly, people with medical conditions, and people who require additional care and support. Even though the mechanism of action of SDF is debatable, SDF treatment has been shown to support tooth desensitization and to arrest carious lesions through dentinal tubule blockage, cariogenic bacterial death, remineralization of the demineralized tooth, and inhibition of dentinal collagen degradation. Hence, SDF is a cost-effective, reliable, secure, and efficient caries-prevention substance [6].

Japan authorized the use of silver diamine fluoride (SDF) as a medication in the 1960s. It has been used for many years to cure dental caries in China, Australia, Brazil, Argentina, and Australia. The US Food and Drug Administration authorized the first SDF product for use in the country in 2014. Since 1969, SDF has been used to prevent tooth decay in young children's primary teeth and pit and fissure caries in developing permanent molars, as well as to treat root caries in geriatric patients. In addition to treating caries, SDF is also used to sterilize infected root canals and treat dental hypersensitivity. It can be applied directly to a carious lesion to arrest the spread of caries or to a caries-prone surface to prevent caries [7].

Although some drawbacks of SDF have been reported, such as staining, its safety has been strongly backed by the fact that not a single untoward event has been connected to its use since it was introduced in Japan. Recent Hong Kong–based randomized controlled studies showed that SDF can decrease carious lesions

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among children, if SDF is administered twice a year at a concentration of 38%. This method is advised because it can arrest caries without leading to excessive staining. However, after 6 months, it was discovered that a single application of SDF at a concentration of 38% was effective in halting dentinal caries in the primary anterior teeth of preschoolers [6].

SDF has the ability to prevent discomfort, sepsis, and the requirement for extractions if applied early, when the cavity is evident but has not yet resulted in permanent pulpal injury. A 38% SDF solution is more efficient than a solution with a lower concentration, and biannual application is superior to annual application. The use of SDF encourages participation and community support from parents who do not seek dental consultation for their children. Additionally, silver-modified atraumatic restorative therapy is an appealing option that improves treatment results. SDF can increase accessibility and equity in dental care, particularly for people from low socioeconomic backgrounds [6].

A study done by Fung and colleagues in 2018 [8] compared 12% and 38% SDF and found that decay was more substantially arrested when using the higher concentration. Neither that report nor the clinical trial registry listing provides the details of product origin. Further, the investigators did not independently verify the concentrations, making it impossible to generalize from their findings. More research is required to completely evaluate the efficacy of SDF and identify the most effective concentration in order to set guidelines. This study will add on to existing literature, as the SDF product used in our study has not been trialed before. The procedure can be used in basic care settings and could ease the population's burden of untreated tooth decay. SDF has the potential to play a significant role in comprehensive and successful preventative initiatives to achieve the UN Sustainable Development Goals. We hypothesize that both 12% and 30% SDF will have comparable efficacy with 38% SDF.

Objective

To assess and compare the effectiveness of 12% SDF, 30% SDF, and 38% SDF for treatment of early childhood caries among children aged 24 to 72 months in Mangaluru Taluk.

Methods

Trial Design and Protocol Development

This is a single-center, randomized, active-controlled, parallel-group pragmatic trial. This clinical trial protocol's design and report adhere to the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) declaration. The trial schedule is shown in Figure 1.

Figure 1. Schedule of enrollment, intervention, and assessment of groups that received 38%, 30%, and 12% silver diamine fluoride.

Time point	Enrolment	Allocation	Post allocation	
	-T1	*Month 0*	*Month 6*	*Month 12*
Enrolment				
Eligibility screening	✓			
Informed consent	✓			
Allocation		✓		
Interventions				
38% Silver diamine fluoride	✓	←	—	→
30% Silver diamine fluoride	✓	←	—	→
12% Silver diamine fluoride	✓	←	—	→
Assessments				
Arrested caries		✓	×	×
Caries progression		✓	×	×

Study Setting

The study is being carried out at preschools of Mangaluru Taluk, South India. The dental examinations are performed after receiving confirmation of participation from preschool teachers or caregivers, and informed consent forms (Multimedia Appendix 1) are sent to the parents of the eligible children. Signed parental consent is collected before the intervention starts.

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Participant Selection

Children attending preschools in Mangalore Taluk aged from 24 to 72 months are included. Additional inclusion criteria are as follows: at least one soft caries lesion (ie, cavitated active caries lesion) that is small (less than half of the mesial or distal or less than one-third of the buccal, lingual, or occlusal surfaces). The exclusion criteria are pulpal exposure, history of pain, nonvital teeth, swelling or fistula, silver allergy, arrested caries or inactive lesions, teeth at the period of shedding, restored teeth, secondary caries, fluorosis, enamel hypoplasia, uncooperative behavior, physical or mental disability, and a lack of signed informed consent.

Baseline and Follow-up Oral Examinations

Before conducting the trial, the principal investigator was trained and calibrated by experienced dental public health specialists in the Caries Assessment Spectrum and Treatment (CAST) index. Training and calibration sessions included theoretical aspects and were followed by clinical examination of a group of 10 subjects from the outpatient department. The subjects were reexamined by the principal investigator and the guide (an experienced dental public health specialist) after 1 week. The κ coefficient values for intraexaminer and interexaminer reliability were 0.88 and 0.80, respectively, reflecting a high degree of conformity in the observations.

The examinations in this study are performed by a single examiner with the help of a recording device in preschools in Mangaluru Taluk. The study sample comprises 3 groups of children aged 24 to 72 months. After baseline examination, eligible children are randomly allocated to 1 of the 3 groups using the lottery method. Group 1 receives 12% SDF semiannually, group 2 receives 30% SDF semiannually, and group 3 receives 38% SDF semiannually. Dental caries will be measured using the CAST index [9].

A CAST score of 0 is given to sound teeth (ie, with no visible evidence of a distinct carious lesion); a score of 1 for pits or fissures that are at least partially covered with a sealant material; a score of 2 for cavities that have been restored with a direct or indirect restorative material; a score of 3 for distinct visual change in the enamel only or clearly visible caries-related discoloration, with or without localized enamel breakdown; a score of 4 for internal caries-related discoloration in the dentine, with the discolored dentine visible through the enamel, which may or may not exhibit a visible localized breakdown; a score of 5 for distinct cavitation into the dentine with the pulp chamber showing intact pulp; a score of 6 for involvement of the pulp chamber with distinct cavitation reaching the pulp chamber or with the presence of only root fragments and abscess or fistula; a score of 7 for pus-containing swelling or a pus-releasing sinus tract related to a tooth with pulpal involvement; a score of 8 for teeth that have been removed because of dental caries; and a score of 9 for teeth that do not match any of the above descriptions.

All tooth surfaces, including the buccal, lingual, mesial, distal, and occlusal surfaces for posterior teeth, are evaluated for caries. Miller's criterion is used to assess whether active caries are present; Miller's criterion suggests that a carious lesion is termed active if a blunt University of North Carolina–15 probe can easily enter it; a carious lesion is defined as halted when the dentine cannot be penetrated.

The size of the lesion is categorized as small or large at the tooth-surface level (less than one-third of the buccal, lingual, or occlusal surface, or less than half of the mesial or distal surface).

Intervention

Drug Description

The SDF in this study is Caries Stop (Biodinamica); it was used at product concentrations of 12%, 30%, and 38%. The investigators did not independently verify the concentrations stated by the manufacturer. The product is composed of fluoridric acid, silver nitrate, ammonia hydroxide and deionized water.

Application of SDF

Primary teeth that have cavities are separated and kept dry using cotton rollers. A plastic dish is prepared that contains 1 drop of SDF. Using a tiny brush, the SDF is administered to the carious lesion for 2 minutes. The excess is eliminated by gently wiping with another cotton pellet. The children are requested to avoid any dietary intake for an hour after application. At 6 months after the first application, a second application will be carried out. After 6 and 12 months, the principal examiner conducts a clinical examination of the teeth with a visual and tactile assessment. After a year, the efficacy of the various SDF concentrations will be evaluated.

Outcome Measure

The primary outcome measure is caries arrest at the twelfth month of application of SDF. The secondary outcome measure is the caries increment (ie, CAST index).

Effect Modification

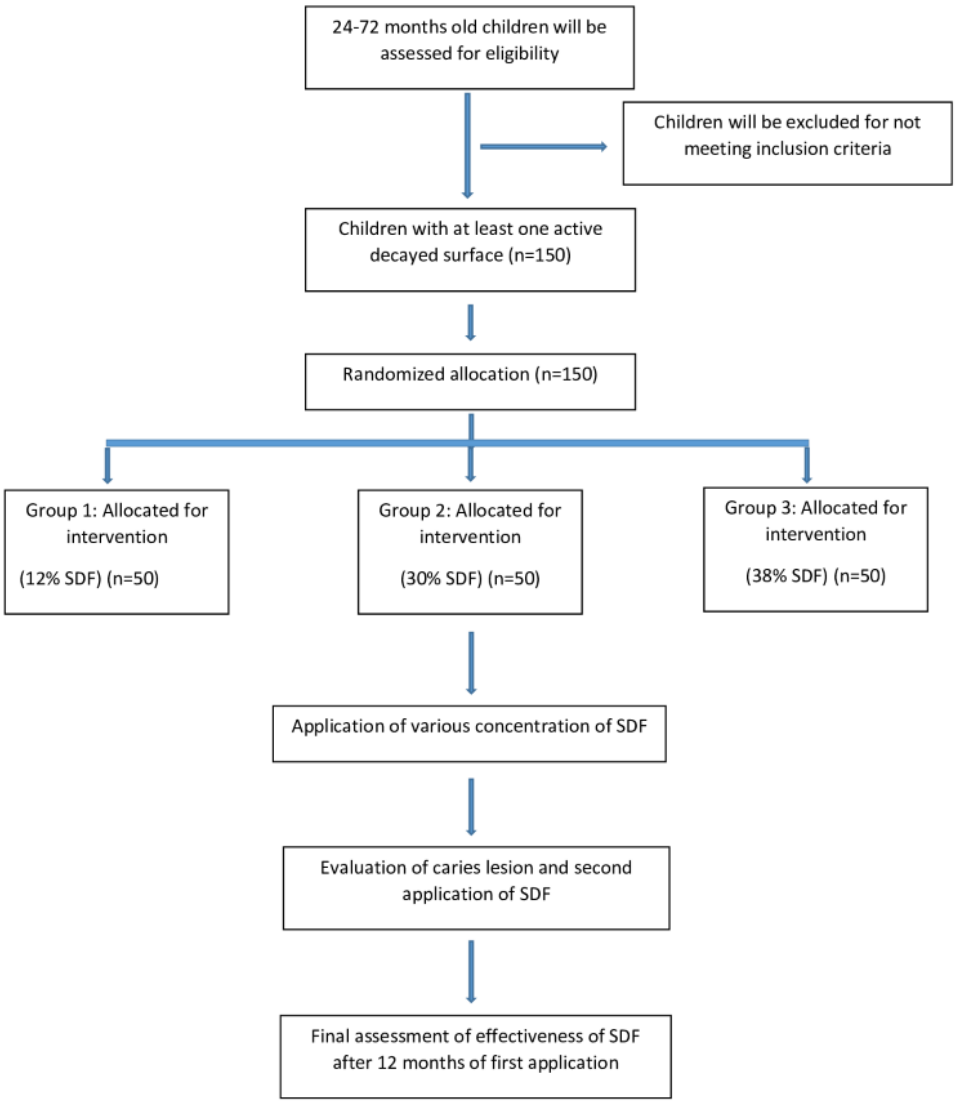
A parental questionnaire is administered at baseline regarding the children's oral hygiene habits (eg, tooth brushing), fluoride agent use (eg, fluoride toothpaste), dietary habits (eg, bottle feeding), and source of drinking water.

Randomization and Treatment Allocation

The study is being conducted in preschools in Mangaluru Taluk. Multistage random sampling was used to select the preschools, with the following stages: (1) Mangaluru Taluk was divided into north and south zones; (2) preschools in Mangaluru Taluk were divided into government schools, government-aided private schools, and non–government-aided private schools; and (3) children were selected randomly from 437 preschools (n=218 from the south zone and n=219 from the north zone). Children were randomly allocated to 1 of the 3 groups using the lottery method. The study sample comprises 150 students aged from 24 to 72 months attending preschools in Mangaluru Taluk, including 50 students in group 1 (12% SDF semiannually), 50 students in group 2 (30% SDF semiannually), and 50 students in group 3 (38% SDF semiannually), as shown in Figure 2.

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Figure 2. Enrollment and allocation of sample. SDF: silver diamine fluoride.



Random Allocation, Concealment, Masking, and Blinding

Allocation concealment was done using the sequentially numbered opaque sealed envelope method. A random code for each participant was put in an opaque package as part of a randomization system. Masking is used for the products, which are indistinguishable in terms of consistency, packaging, and labeling. The researchers applying the products are unaware of what product is being applied. A dentist's aide opens the envelope, and the materials are then prepared after the child's designated actions in accordance with their group allocation. The children and parents are blinded regarding their grouping. The principal examiner, who is blinded to the participating children's group assignment, performs a clinical evaluation of the children at baseline and at semiannual follow-up exams. The dentist's aide is unblinded to the interventions and aids in allocating the participants to the principal examiner. The participant's allocated intervention during the trial will be revealed to the principal examiner only after the follow-up is completed.

Sample Size Estimation

Based on the previous studies, the anticipated proportion of sound occlusal surfaces at baseline that develop into cavitated dentin lesions at the 30-month follow-up is approximately 25% [3].

Sample size calculation was performed with G* Power 3 (Heinrich-Heine-Universität Düsseldorf). Based on a 5% level of significance, power of 80%, effect size of 0.63, and 3 groups, the required sample size is 120, including 40 in each group. Considering a drop-out rate of 20%, the final sample size is 150, as shown by the following equation: final sample size = ND = N / (1 – d), where *N* is the sample size before drop-out, *d* is the expected drop-out rate, and *ND* is the sample size considering drop-out. Thus, ND = 120 / (1 – 0.2) = 120 / 0.8 = 150, and the total sample required for intervention is 150 (50 in each group). The allocation ratio is 1:1:1. The participants are allocated to the 3 groups equally.

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Statistical Analysis

Data analysis will be done using SPSS (version 23.0; IBM Corp). Continuous variables will be presented as the mean (SD). Categorical variables will be presented as frequencies and percentages. To confirm normality, the Shapiro-Wilk and Kolmogorov-Smirnov tests will be used. A one-way analysis of variance (ANOVA) statistical test will be used to compare the means of continuous outcome variables if the data follow a normal distribution. Nonparametric tests (ie, the Kruskal-Wallis statistical test) will be used in the data analysis in cases when there is skewed distribution of data. Post hoc tests will be performed with an ANOVA or the Kruskal-Wallis test.

Binary logistic regression will be performed. The dependent variable will be whether the lesion is arrested or not at the 12-month examination, and the independent variables will include the children's oral hygiene habits (eg, tooth brushing), fluoride agent use (eg, fluoride toothpaste), dietary habits (eg, bottle feeding), and source of drinking water.

Ethical Considerations

Ethical approval has been obtained from the Institutional Review Board (Ethics Committee II) of Yenepoya (Deemed to be University) for protocol version 3 (YEC2/175). Research aides will serve as contact people and be involved in all phases of the trial. Parents or legal caretakers of the children are given an information sheet outlining the purpose of the study, the specifics of the research, and the processes after the principals consent to participate in the study. Parents are informed of the side effects of the treatment, notably staining of the tooth. Their queries regarding the side effects are addressed. Before beginning this trial, informed consent is obtained. The participants, including the children and their guardians, are free to withdraw at any time during the study. They are also allowed to pursue additional dental care according to their own decisions and financial means.

Caries assessment is done with aseptic precautions and without any harm to the patient. The application of 12% SDF, 30% SDF, or 38% SDF is also done with aseptic precautions and without any harm to the patient. If any complications take place, the child is treated free of charge by the principal investigator.

The study data will be deidentified for privacy and confidentiality protection. No compensation will be offered to the study participants.

The drugs were sponsored by Biodinamica. This drug company has no role in the research.

The Drug Controller General of India does not normally restrict the use of topically applied drugs. Currently, there are also no official guidelines announced for SDF use by dental professional associations or research bodies [10].

Risks of the Study

There are no major known risks to the study. Minor risks, such as black stains on the carious tooth surface or temporary stains on the skin, will occur. Temporary stains on the skin disappear within 48 hours without treatment.

Withdrawal Criteria

During semiannual applications, clinical examination for caries will be done. If any pulpal involvement or abscess is noticed, appropriate treatment will be provided by the principal investigator. The children will be given the right to refuse or withdraw at any point in time.

Maximum Dose and Safety Margin

The margin of safety for dosing is of paramount concern. The typical lethal dose, 50% (LD 50), for oral administration is 520 mg/kg. One drop (25 µL) contains 9.5 mg SDF and is sufficient to treat 5 teeth. The dose will be 0.95 mg/kg, and assuming that the smallest children with caries weigh between 10 kg and 15 kg, the relative safety margin for administering a whole drop to a child weighing 10 kg is therefore 380 mg/kg LD 50 / 0.95 mg/kg dosage, for a 400-fold safety margin. The actual dose will probably be much lower. One drop (25 µL) per 10 kg per treatment session is the suggested upper limit. The largest applied dose for 3 teeth is 2.37 mg, allowing for more than 400 applications [11].

Adverse Effects

Information on adverse effects of SDF treatment—including tooth or gum pain, gum swelling, gum bleaching (ie, becoming whiter), and systemic toxicity (nausea, vomiting, and generalized discomfort)—is collected through a parental questionnaire within a week of SDF or placebo application at baseline and at 6- and 12-month follow-ups. If there is an acute systemic illness associated with SDF treatment, the parents are asked to immediately contact the principal investigator by telephone. Oral examinations will also be performed at baseline and at 6- and 12-month follow-ups. An examiner will evaluate the hard and soft tissues to establish changes and visible alterations during the clinical examination. All changes will be recorded on a case report form.

Results

The research was funded in September 2020, and data collection started in September 2022. As of February 2023, 150 participants were enrolled in the study. The project is still underway and is expected to be completed in December 2023. The findings of this study will be beneficial for future studies and the management of early childhood caries.

The information obtained from the study will be submitted to the institution and to the concerned authorities. The details of the study will be published in journals and presented at conferences.

Discussion

Principal Aims

The purpose of this single-center, randomized, active-controlled, 3-arm pragmatic trial is to evaluate and compare the efficacy of 12%, 30%, and 38% SDF in preventing early childhood caries in children aged 24 to 72 months. We are using 38% SDF, which is thought of as the standard of care for preventing ECC, in a

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positive control group to determine if 30% and 12% SDF are superior.

Our hypothesis is that 38% SDF will have a superior effect compared to 30% and 12% SDF in stopping ECC, because it has a fluoride concentration that is much higher (44,800 ppm) than 30% (35,400 ppm) or 12% (14,100 ppm) SDF. The standard of care will be altered if the results are as expected. Because every child who enrolls in the study should have the right to obtain an efficient preventative strategy, there is no negative control group.

In this study, we evaluate the ability of 12%, 30%, and 38% SDF to arrest ECC. The use of SDF solutions in a clinical setting has been deemed safe, and the application process is noninvasive. Despite the fact that the participants in this study are recruited at a young age, few ethical questions have been raised.

In order to examine the efficiency of 12% and 38% SDF in halting dentin caries in the primary teeth of preschool children, Fung et al [8] undertook a randomized clinical experiment. Other recent research indicates that 38% SDF is more effective than 12% SDF. In a clinical trial, Vollú et al [12] compared the effectiveness of 30% SDF and atraumatic restorative treatment in halting dentine caries in the primary molars of preschoolers. Recent research revealed that 30% SDF could stop caries lesions with effects comparable to those of atraumatic restorative treatment.

The findings of this trial, performed in young children who are in good health, may not be generalizable to other populations of children, such as those who require special medical attention or are older, which is a limitation of this study. It will be necessary to perform additional research on the preventive impact of SDF in individuals with special health care requirements. The generalizability of the study will also be limited by the fact that clinical trials in different countries use different parameters for caries assessment.

The study outcomes will be widely disseminated, which should encourage the adoption of SDF in other nations and lessen the global burden of ECC. SDF may even become a crucial component of comprehensive and successful preventative programs to achieve the UN sustainable development goals.

Conclusions

The findings of this study will be beneficial for future studies on the management and prevention of ECC. If SDF is found to be effective in a school or community setting for caries prevention, it will be a significant milestone for preventive dentistry.

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Data Availability

The data sets generated during and/or analyzed during this study are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Informed consent form given to parents.
[PNG File , 191 KB - resprot_v12i1e46144_app1.png]

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Abbreviations

ANOVA: analysis of variance
CARE: Consensus-Based Clinical Case Reporting Guideline
CAST: Caries Assessment Spectrum and Treatment
ECC: early childhood caries
SDF: silver diamine fluoride
WHO: World Health Organization

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Protocol

The Effect of Positive Therapeutic Communication on Pain (POPAIN) and Anxiety During Arterial Blood Gas Standardized Procedures in the Emergency Department Compared to Traditional Communication: Protocol for a Monocentric Randomized Controlled Trial

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Abstract

Background: In the emergency department (ED), medical procedures, such as arterial blood gas (ABG) testing, can cause pain and high stress levels. However, ABG testing is a routine procedure assessing the severity of the patient's condition. To reduce the pain of ABG, several methods have been investigated without significant difference in pain perception. Communication, a key element of care, has shown a significant effect on pain perception. A positive communication strategy, including positive, kind, or reassuring words, can reduce pain perception, while negative words can raise this perception, causing discomfort, known as the “nocebo effect.” Although some studies have compared the impact of verbal attitudes, particularly in anesthesia and mainly with staff already trained in hypnosis, to the best of our knowledge, none have investigated the effect of communication in the emergency setting, where patients may be more suggestible to the words used.

Objective: In this study, we will investigate the effect of positive therapeutic communication on pain, anxiety, discomfort, and global satisfaction in patients requiring ABG compared to nocebo and neutral communication.

Methods: A single-center, double-blind randomized controlled trial (RCT) with 3 parallel arms will be conducted with 249 patients requiring ABG during their ED visit. Patients will be randomly assigned to 1 of 3 groups before receiving ABG: positive communication group, negative communication (nocebo) group, or neutral communication (neutral) group. The communication and the words used by the physicians during hygiene preparation, artery location, and puncture will be imposed in each group. The study will be proposed to each patient corresponding to the inclusion criteria. The physicians will not be trained in hypnosis or in positive therapeutic communication. The procedure will be recorded with audio recorders to test its quality. Intention-to-treat analysis will be performed. The primary endpoint is the onset of pain. The secondary outcomes are patient comfort, patient anxiety, and global satisfaction of the patient with the communication strategy used.

Results: On average, 2000 ABG procedures are performed each year in the EDs of hospitals. In this study, 249 patients are expected to be included. With a projected positive response rate of 80%, we intend to include 25 (10%) patients per month. The inclusion period began in April 2023 and will run until July 2024. We hope to publish the results of the study during the fall of 2024.

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Conclusions: To the best of our knowledge, this study is the first RCT assessing the use of positive communication on pain and anxiety in patients undergoing the ABG procedure in the ED. A reduction in pain, discomfort, and anxiety is expected when using positive communication. If the results are positive, this could be useful to the medical community and encourage clinicians to monitor their communication during care.

Trial Registration: ClinicalTrials.gov NCT05434169; https://clinicaltrials.gov/ct2/show/NCT05434169

International Registered Report Identifier (IRRID): PRR1-10.2196/42043

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KEYWORDS

pain; therapeutic communication; nocebo; emergency department; arterial blood gas; anxiety; positive therapeutic communication

Introduction

Pain, defined as a disagreeable sensory or emotional experience, is the most frequent symptom among patients admitted to the emergency department (ED). Karwowski-Soulié et al [1] estimate that this symptom can be observed in almost 80% of patients upon their arrival to the ED. Despite several international recommendations concerning pain management [2,3], pain in the context of an emergency often remains underestimated [4]. Medical procedures, such as venous or arterial blood collection, which are essential for diagnostic management and patient care, can also generate pain and a high level of stress for patients who are already weakened by their underlying condition [5]. This is known as "care-related pain" [6].

Arterial blood gas (ABG) sampling is necessary to assess the gravity of the patient's condition and is a procedure conducted routinely in the ED. In a medium-size hospital (30,000 hospitalizations per year), approximately 1000 ABG tests are conducted annually [7]. However, arterial blood collection is generally associated with pain and patient anxiety [8].

To decrease the perception of pain linked to the collection of arterial blood, several methods have been studied, such as applying a topical anesthetic cream (eg, lidocaine, xylocaine) or administering a subcutaneous injection of lidocaine prior to the procedure [9]. Given that arterial blood collection is often performed in emergency situations and that the anesthetic cream must be applied at least 1 hour before sampling, this method is not adapted to emergency practices. In a previous study, a subcutaneous injection of lidocaine did not allow a significant reduction in pain during radial artery puncture [10]. Similarly, another study using ultrasound guidance for arterial blood sampling did not show any significant decrease in pain, the rate of immediate complications, or physician satisfaction [11].

In addition to the therapeutic tools commonly used, communication is a key element of care [12]. In routine practice, caregivers inform patients that they are going to perform a potentially painful act. However, forewarning a patient that one will perform a painful act increases the perception of pain [13]. It has also been shown that a communication strategy including the use of positive, kind, or reassuring terms ("Let me reassure you…," "Are you comfortable?," "Are you warm enough?") can contribute to decreasing pain [14,15], while conversely, the choice of terms with a negative connotation ("Okay, this might sting," "Do not panic," "Are you in pain?," "Are you cold?") may increase the perception of pain and provoke a sense of discomfort [16]. In the latter case, this is known as the "nocebo" effect [15]. A communication strategy including reassuring terms, perceived by the brain as agreeable information, can reduce the pain perception. The objective of this strategy is that the painful message becomes less present as much as possible and that the patient benefits from a feeling of control. This procedure is widely used in hypnosis communication [17] and is based on a neurobiological rationale [18,19], that is, an increase in the secretion of endogenous opioids [20-25] affecting pain modulation networks [26] decreases transmission in the pain pathways [27,28], thus leading to a release of dopamine in the striatum [29]. This technique has already been shown to be of benefit in patient management [15,30] in various domains, such as anesthesia and pediatrics [15,31].

Arrival to the ED can induce a particular state of consciousness linked to anxiety and a heightened suggestibility of negative communication. Although several studies have compared the impact of verbal attitudes, notably in the domain of anesthesia and mainly with staff already trained in hypnosis, to the best of our knowledge, none have studied the effect of positive communication by caregivers or physicians among a patient population in the ED setting. Given the limited therapeutic options to relieve the pain and discomfort of blood collection performed in the ED, this study will investigate the effect of positive therapeutic communication on pain, anxiety, discomfort, and global satisfaction in patients requiring ABG compared to nocebo or neutral communication.

Methods

Study Design

This study will be a single-center, double-blind randomized controlled trial (RCT) with 3 parallel arms. To minimize bias during the intervention itself, the communication strategy will be clearly defined beforehand. The evaluator (any person [physician/student/other] assessing patient outcomes before and after arterial blood collection but playing no role in patient management in the ED or in the conducting of the procedure and without any knowledge of the study arm assigned to the patient at randomization) will be blinded to the strategy used.

Setting

Patients will be recruited at the adult ED of the Cantonal Hospital of Fribourg (HFR) in Switzerland. On average, 2000 ABG procedures are performed each year in the ED of the HFR.

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Population and Sample

The inclusion criteria are as follows:

- Patients over 18 years of age
- Patients scheduled to undergo radial artery blood collection during their visit to the ED in order to pursue routine care
- Free and informed consent obtained from the patient

The exclusion criteria are as follows:

- Patients incapable of judgment
- Patients with conditions that render them unable to participate in the intervention in this study (eg, cognitive impairment, major hearing loss without the use of hearing aids, acute psychiatric disorders, under intravenous or oral sedation)
- Patients with an insufficient understanding of the French language, as defined by self-evaluation
- Patients in critical situation requiring immediate resuscitation
- Local anesthesia (subcutaneous, transdermal patch) at the point of ABG puncture
- Patients already treated with anxiolytics or sedatives during care in the ED

Recruitment and Screening

Potentially eligible patients for inclusion in the study will be identified by residents who will inform the senior physician responsible for triage (triage doctor [TD]) in the ED at the initial stage of patient management if arterial blood collection is required for medical care. The senior TD (triage medical consultant regulating the flow of activity in the ED, who can be a physician investigator) will proceed with recruitment as follows: “We have explained to you that we need to perform a blood gas test on a sample of blood from the wrist artery. At present, we are conducting a study to examine the patient experience with this procedure. In this context, if you accept to participate in our study, another person will ask you some questions before and after sample collection. You are free to participate and to withdraw at any point of time during the study. If you refuse, there will be no modification of your care in the ED. The data collected will be coded, and your name or any other personal information that could identify you will be removed. The entire procedure will be recorded using an audio recorder.”

The study will be proposed to all eligible individuals from among participants available 24 hours a day, 7 days a week. With a projected positive response rate of 80%, we intend to include 25 patients per month. To achieve the desired sample size, we would need 12 months to finalize study inclusion.

Data Collection

The clinician in charge of the patients will determine the indication for ABG testing according to the rules of good practice in emergency medicine (hypotension and shock, dyspnea and respiratory insufficiency, intoxication, metabolic and acid-base disorders, renal insufficiency, polytrauma, convulsions, disorders of the state of consciousness). Patients in critical situations requiring immediate resuscitation will be excluded from the study because of the impossibility of waiting for the time necessary for screening/inclusion/randomization before ABG testing, the immediate vital prognosis being engaged.

Following verification of the inclusion criteria and patient agreement, the patient will be included in the study by the senior MRT. The latter will collect written signed informed consent forms after the procedure, which will be stored in a dedicated file cabinet and locked by 1 of the physician investigators (physicians with a role in the concept, implementation, or organization of the study). The forms will then be filed in a file reserved for this purpose and stored in a secure location by the physician acting as the principal investigator (PI).

Next, the patient will be randomized to 1 of the 3 study arms by an administrative reception agent, who will use Research Electronic Data Capture (REDCap) software (Vanderbilt University) to assign the patient to a randomization arm. To maintain the blinding of those involved in the study, the administrative reception agent will give the participating physician an opaque envelope containing randomization arm details and an audio recorder. The participating physician (resident performing arterial blood collection, who can concomitantly manage the medical aspect of the patient) will only be able to open the envelope once they are in the patient booth in order to maintain the blinding of the senior MRT. They will perform arterial blood collection according to the communication method generated by the randomization arm and will be the only person aware of the patient groups.

The senior MRT will also communicate the patient ID to the evaluator. Data collection, as well as the case report form (CRF), will be completed by the evaluator before the beginning of the recording and after completion of the procedure. Data will be collected with the help of the electronic patient record and the questions asked to the patient before and after the ABG procedure. Thus, the patient will be blinded to the specific intervention status.

Implementation of Arterial Blood Collection

Sample collection will be performed in the patient booth. The booth door will be closed, and the shutter lowered during the intervention to allow noise and visual isolation. Only the physician performing the intervention and the patient will be in the booth during the procedure. At that time, the physician will open the envelope with their back to the patient at the same time as they prepare the material for the arterial puncture. They will then perform arterial blood collection by using 1 of the different standardized communication methods according to the group assigned to the patient: therapeutic positive communication, neutral, or nocebo. The physician assistants participating in the study have not received any training in hypnosis or in-depth instruction in positive therapeutic communication. They will carry out the intervention in all 3 study arms.

Before performing the procedure, the participating physician will switch on the audio recorder and record their conversation with the patient. The recording will start just before sampling. When the collection procedure is terminated, the participating physician will stop recording, place the text and the audio

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recorder in the envelope, and give it to the senior MRT. The evaluator will then come to collect the audio recorder and evaluate patient outcomes by using the CRF intended for this purpose.

Arterial blood collection will be conducted in a seated position for all 3 groups. The patient will be in a supine position, with the forearm comfortably placed on a small table. The needle used for blood collection will be a 25-gauge needle without local anesthetic. This method of sampling is identical to the one used in daily practice in the ED of the HFR.

In the event of failure of the first puncture, the physician in charge of the patient will be able to use other terms corresponding to the assigned intervention group. In the event of 2 puncture failures by the participating physician, the patient will be excluded from the study.

Case Report Form

The following data will be collected and included in dedicated CRFs. The paper CRF will contain a first part with the date of the screening, the name of the medical officer who will perform the screening, the inclusion and exclusion criteria, whether the patient has been informed orally, and whether they have provided oral consent. The medical officer will confirm whether the inclusion and exclusion criteria have been met and, if so, indicate the number of the envelope containing the random allocation to 1 of the 3 study arms; this number will be the patient's ID in the study.

Once the patient is included in the study, the assessor will fill in the second part of the paper CRF before the ABG procedure: the name of the assessor, educational level, native language (French/Swiss German/German/Italian/Portuguese/other), tobacco, diabetes, first 3 outcomes, vitals (blood pressure, heart rate, respiratory rate), and time data on the ABG procedure.

After the ABG procedure, the evaluator will fill in the third part of the paper CRF, containing the 5 outcomes, the level of overall satisfaction, the vitals (blood pressure, heart rate, respiratory rate), the number of arterial punctures observed on the skin, and the type of words used by the doctor during the procedure according to the patient.

The fourth part of the paper CRF certifies that the patient has received the complete information about the study, whether the patient has consented, and, if they have consented, whether they have received a copy of the signed informed consent form.

The fifth part of the paper CRF contains the following information extracted directly from the patient's file: age, sex, first and last names of the attending physician, duration of the ED visit (difference between admission and discharge from the ED, difference between admission to the ED and the patient's placement in the cubicle), reason for admission to the ED (Swiss emergency triage scale [U1-U4]), list of emergency reasons, BMI (weight/(height in m × height in m), and the patient outcome after the emergency stay (inpatient/outpatient/death).

The evaluator will confirm the accuracy of the data collected.

Intervention Groups

During each step of the sampling (identification, disinfection, sampling) for the ABG procedure, the physician involved will communicate with the patient with a preestablished speech according to the assigned study arm. Communication sentences for each intervention group are presented in Table 1. In the case of failure of the first puncture, the intervening doctor will be able to use the second set of sentences corresponding to the assigned intervention group (also in Table 1).

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Table 1. Study arms.

Study arm	Intervention/treatment
Positive therapeutic communication: Solicit the subconscious mind of the patient by asking questions that are not focused on the ABG[a] procedure. This process allows to divert the attention of the brain to more pleasant information and thus modulate the painful information. This is a standardized intervention with precise phrases.	The positive therapeutic communication group physician will say: • During identification of the arterial blood collection site: "Are you comfortably installed?," "How old did you say you were?," etc • At the time of disinfection: "How did you get to the hospital?," "What day is it?," etc • At the time of puncture: "What is the noise of the lights at your home?," "Does your car still go to the shops?," etc
Nocebo: Use of words with a negative connotation (words used frequently in daily practice in the ED[b])	The nocebo group physician will say: • During identification of the puncture site: "That's where I am going to prick you," "I am looking for the place where I will prick," etc • At the time of disinfection: "Watch out, it is cold," "It is disagreeable," "I am disinfecting the site," etc • At the time of puncture: "Watch out! I am going to prick…1, 2, 3…I am pricking," "Watch out, this is going to hurt, I am pricking," etc
Neutral: Use of words defined as neutral (ie, no negative or positive connotation but based on the description of precise facts)	The neutral group physician will say: • During identification of the site: "I am taking your pulse," "I am identifying the artery," etc • At the time of disinfection: "I am disinfecting the site," "I am cleaning your skin," etc • At the time of puncture: "I am taking the sample," "I am performing the puncture," etc

[a]ABG: arterial blood gas.

[b]ED: emergency department.

Positive Therapeutic Communication Arm

The first 2 sentences allow the gesture to be accompanied by reassuring words and positive words, while the last sentence involves the patient's subconscious by asking a question not focused on the procedure (confusion). This allows the brain to divert attention to more pleasant information and thus modulate the painful perception.

A study of a similar design, "Hypnosis and Communication Reduce Pain and Anxiety in Peripheral Intravenous Cannulation: Effect of Language and Confusion on Pain During Peripheral Intravenous Catheterization" (KTHYPE) [15], has already evaluated the impact of these sentences during the placement of a venous catheter in patients undergoing surgery and demonstrated its beneficial effects.

All the short phrases in this protocol are inspired by the KTHYPE study and have been adapted for the population and context of our study.

Nocebo Arm

The use of words with negative connotations would cause more pain and anxiety [13,18]. Warning a patient that they are going to undergo a potentially painful procedure can potentiate discomfort. In current practice, these are the words most used by emergency teams. The stress associated with the emergency consultation could further amplify the painful experience and the impact of these words by the state of hypersuggestibility that it induces.

Neutral Arm

The use of neutral terms allows precisely describing the procedure to the patient and informing them of the course of the treatment without using words with negative connotations (pain, stinging, unpleasant).

Hypotheses

The principal hypothesis is as follows: Pain perceived during the collection of an arterial blood sample in the ED is lower when it is performed using positive therapeutic communication compared to neutral or nocebo communication.

The secondary hypotheses are as follows:

- Discomfort perceived during the collection of an arterial blood sample in the ED is lower when the procedure is conducted using positive therapeutic communication compared to neutral or nocebo communication.
- Anxiety perceived during the collection of an arterial blood sample in the ED is lower when the procedure is conducted using positive therapeutic communication compared to neutral or nocebo communication.

Outcomes

The primary outcome is pain: self-evaluation of the maximum pain felt by the patient during the collection of an arterial blood sample on the Verbal Rating Scale (VRS: 0=no pain to 10=the worst imaginable pain) just before the beginning of the procedure and during the procedure (question asked during the 3 minutes after the procedure) [14,31,32].

The secondary outcomes are as follows:

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- Comfort: self-evaluation of patient comfort using a simple comfort VRS (0=no comfort to 10=the most comfort imaginable) just before the beginning of the procedure and 3 minutes after the procedure [33]
- Anxiety: self-evaluation of patient anxiety using a simple anxiety VRS (0=no anxiety to 10=the worst anxiety imaginable) just before the beginning of the procedure and 3 minutes after the procedure [34]
- Puncture failure: success of the first arterial puncture assessed by the accredited evaluator at the end of the procedure using the number of puncture points visible on the patient's skin (possible response: 1 puncture visible, yes/no)
- Global satisfaction with the communication strategy used: evaluation by the patient at the end of the procedure using a numeric scale of 0-10 (0=extremely dissatisfied to 10=extremely satisfied)

Statistical Analysis

Sample Size Calculation

With a significance level of .05, a power of 0.9, a difference in pain on the VRS of 1.5 (generally accepted as clinically significant) with an expected SD of 2.5 [35], and an attrition of 20% on the basis of a group-independent *t* test (a specific case of linear mixed effects models [LMMs]), we must include 83 patients in each group to show the efficacy of the intervention on pain by applying the Bonferroni correction (ie, a total of 249 patients).

Statistical Analysis Plan

First, descriptive statistics (frequencies and percentages for categorical data; means, SDs, medians, and IQRs for quantitative data) will be run for each measure of time for each group and the overall study sample. In addition, an analysis of nonresponses and patient dropouts will be conducted. Second, bivariate associations will be calculated to compare the groups at baseline (Pearson chi-square test, Fisher exact test, *t* test, and the Mann-Whitney test according to the distribution of variables). Third, to test the impact of the intervention on the different outcomes (hypotheses 1, 2, and 3), LMMs with patients, groups and physicians as a random effect will be performed to analyze changes over time. The participation of approximately 25 physicians is foreseen in this study. The models will be tested on all available data.

The effects of time, groups, and their interaction will be tested by controlling for sociodemographic characteristics and variables linked to health status. An intention-to-treat (ITT) analysis, per protocol (PP) and based on the analysis of communications (ie, the respect of the quality of the defined communication according to the protocol; see the next section), will be conducted. The Pearson chi-square test comparing the allocation defined in the protocol and the allocation following the analysis of communications will be performed. If necessary, a generalized LMM will also be used to explore the differences between the available measured variables (physicians having performed the ABG procedure, pain, etc). Statistical analysis will be performed on available data, and no imputation of missing data will be conducted. Given that our study will be conducted on a 1-to-1 basis with a member of the research team and on the basis of previous experience, we expect that the number of missing values will be low. Statistical analyses will be performed using the R (R Core Team and the R Foundation for Statistical Computing) and STATA version 12 (StataCorp); the level of significance will be set at P=.05.

Analyses of Communications

All communications will be recorded. We will listen to 30 communications at a time to evaluate the quality of each communication and to ensure that the communication corresponds to the defined study arm defined at the time of randomization. This evaluation will be performed until less than 10% of incorrect rankings are obtained. A physician external to patient management will reassign the patient groups based on a list of preselected keywords. This same physician will then (re)classify the patients into 1 of the following 3 arms: therapeutic positive communication, nocebo, or neutral.

The classification will be performed with the help of a list of 10 keywords provided to the external physician. Each list of 10 keywords will be associated with 1 of the 3 arms and will correspond to standardized phrases related to each arm. Thus, if the external physician finds 1 keyword associated with the nocebo arm, the patient will then be reclassified into the nocebo arm; if the external physician finds 1 keyword associated with the therapeutic positive communication arm but without any keywords associated with the nocebo arm, the patient will be classified into the therapeutic positive communication arm. If the physician does not find any keywords associated with these 2 arms, the patient will be classified into the neutral arm.

This classification will be conducted in parallel by 2 persons for the first 30 patients to evaluate the interrater reliability using Cohen κ. If $\kappa>0.90$, only 1 coder will continue to code the audio recordings. If not, 2 coders will continue to evaluate the communications; in the case of disagreement, a third coder will make the final decision.

The keywords associated with the nocebo group are as follows:

- Pain
- Cold
- Prick
- Do not panic.
- Are you in pain? I am going to prick.
- This is going to sting.
- Do not move, it won't be long.
- Do not be frightened.
- How do you feel?

The keywords associated with the therapeutic positive communication group are as follows:

- Be reassured.
- Are you comfortable?
- Are you relieved?
- I am going to place the drip.
- Have confidence.
- Take it easy.
- It will be fast.
- Do you feel well?

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These lists are likely to be adapted based on the audio recordings.

Ethical Considerations

Research Ethics Approval

The study protocol was approved by the Human Research Ethics Committee of the Canton of Vaud, Switzerland (no. 2022-00685).

All participants will receive an information letter presenting the study, its objectives, and its risks. Sufficient information will be provided to allow an informed decision to be made concerning their participation in the study. The senior TD responsible for recruitment will be at the disposal of patients to respond to any eventual questions that may arise. Given the specific context of medical care in the emergency setting, a reflection time of 15 minutes will be allocated to allow each participant to make a decision. Particular focus will be given to the primacy of the medical indication for arterial blood sampling and to the fact that this study is solely concerned with the patient perception of this procedure. In this context, we consider that the time of reflection is sufficient to allow free and informed consent. Following signature of the consent form and verification of the eligibility criteria, the patient will be included in the study. As the patient will be blinded to the intervention, the information letter will only explain our hypothesis concerning the importance of communication on the emotional level during a care episode, and no information will be provided on the 3 verbal attitudes or any other details, which might influence the patient's judgement.

In the event of the inability of a patient to provide informed consent in writing before the ABG procedure (eg, severe respiratory distress preventing them to write), verbal consent will be sufficient before inclusion and will be notified in writing on a consent sheet by the senior TD. Written consent will then be requested later after emergency care.

Data Monitoring

No data related to the research foreseen will be obtained via laboratory tests or invasive procedures. The sources of materials are as follows:

- Data of quantitative interviews, heteroadministered by the evaluator using a paper CRF. The data will then be entered into REDCap.
- Patient screening data collected by the senior TD.
- Data of audio recordings collected during the ABG procedure with the use of an audio recorder. Recordings will be transcribed for analysis in Microsoft Word.
- Patient information letters as well as the consent forms to be completed will be stored in a dedicated secure box for the study in the ED.

As this is a low-risk study, the following monitoring activities will be carried out by a person independent of the study and trained in good clinical practices and the protocol:

- A qualification visit will be conducted prior to the start of the study.
- The initiation visit will be conducted in the HFR ED in the presence of the PI and the research team.
- A follow-up visit after the inclusion of the first 3 participants will be carried out and if necessary repeated in the case of major problems encountered.
- Regular monitoring (minimum once every 3 months) will be carried out to (1) check that all patients have provided oral consent before inclusion and written consent after the procedure, (2) check that documents are stored according to the protocol (consents, paper CRFs, etc), (3) verify paper CRF data extracted from the patient records (at least 20% of data randomly selected), (4) verify the concordance of the information in REDCap and the information in the paper CRFs (at least 20% of the randomly selected data), and (5) verify the adequacy of the caregivers' communication with the allocation arm for the first 30 patients included. Control visits will be conducted if the actual communication differs from the allocation arm in more than 10% of cases.

Data Confidentiality

Data concerning the trial and the participants will be treated with the greatest-possible confidentiality and will only be accessible to authorized staff who need the data to fulfil their role within the context of the study. Participants will only be identified on the CRFs and other specific study documents by their unique IDs.

The production, transmission, storage, and analysis of personal health data in the context of this study will strictly respect current Swiss legal requirements concerning data protection and will be conducted in conformity with Ordonnance ClinO Art. 18. All lists of names (or other identifying information), personal IDs, and consent forms will be stored in a locked office at the HFR in the offices of the PI. Access to the initial lists and signed informed consent forms will be limited to the physician investigators (authors CLT, YG, and TS).

All electronic data will be recorded using only personal IDs in REDCap.

Quantitative interview data will be collected using paper CRFs. All participants will be identified only by study IDs. The list corresponding to identifying information and the study IDs will be stored in a file protected by a password and only be accessed by the physician investigators.

Data of physician communication during the ABG procedure will be recorded using a numeric recording machine. Audio files will be labelled only with the ID number and transferred to computers protected by a password to be stored electronically. Interviews will be transcribed in Word files containing only the ID number and then stored electronically on computers protected by a password and on secure servers at HFR. Following verification of the transcripts, the audio files will be erased.

Retention and Destruction of Study Data

All the study data will be archived for 10 years after termination of the study or premature termination. The signed informed consent forms will be kept at the HFR and immediately placed in secure locked cupboards. All paperwork (including printed data) will be archived for a minimum of 10 years after the end

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of the study in locked cupboards at the HFR. Participants who withdraw their consent or express the wish to end the research interview will be excluded from the study. Data collected until that time will be analyzed so as not to compromise the validity of the study, unless they request the deletion of their data.

Results

On average, 2000 ABG procedures are performed each year in the ED of the HFR. Recruitment for this RCT began in April 2023. In total, 249 patients are expected to be included. The inclusion period will run from April 2023 to July 2024.

Discussion

Summary

To the best of our knowledge, this is the first RCT that will investigate the effect of a positive communication over a routine procedure, such as ABG testing, in an emergency setting. Considering the KTHYPE study [15], a reduction in pain, anxiety, and discomfort can be expected when using positive communication.

Two of the ethical values in the medical field are beneficence and the objective to do no harm to the patient. However, although the nocebo effect of language is acknowledged today in specialties, such as anesthesiology, negative communication continues to be used daily in the ED, a particularly stressful setting with vulnerable patients. This makes it all the more important to study language tools in this environment, with the aim of standardizing and protocolizing caregivers' communication.

ABG testing is an investigation required in certain medical situations. The global experience of this procedure has often been described as disagreeable and can be improved [8]. The comfort and anxiety before and after sampling can be demonstrated. Today, no risk linked to the communication strategy has been documented, except for the usual inherent risks of arterial blood collection. The nocebo arm is nowadays commonly used in routine practice. If communication can lead to decreased pain, anxiety, and discomfort during this standard investigation, it will lead to changes in current practice. This method is easily used by even the most inexperienced doctors, and we hope that this will reduce their stress during the procedures.

Our study will also assess patient comfort and anxiety. These elements are of primary importance, as pain is frequent in emergencies and frequently underestimated (80% of patients [1]). The patient's anxiety and comfort level contribute to this pain, even if it has not been well documented. To interpret the results, we may compare the comfort and anxiety scores before and after the procedure. This will allow us to control for patients with chronic pathologies (eg, depression).

Strengths and Limitations

The main strengths of the study are its originality, the ease of implementation, and the rigorous methodological design, the last being based on a previously published study [15].

However, this study also has some limitations. First, the received communication policy may be different from the one intended to be used. To limit this bias and avoid any contamination of the arms due to inappropriate communication, all procedures will be recorded and replayed to verify whether the attributed group and the received communication scheme correspond. Second, this is a single-center study. The experience of the physicians performing the ABG procedure, although similar, is quite limited, which could interfere with the communication, as these inexperienced physicians may focus more on the correct technical execution of the ABG procedure than on the communication. In addition, nonverbal communication during the interview will not be studied. Third, other uncontrolled confusing factors could affect the results (eg, a long wait in the waiting room for the patient and overloaded service for the doctor), but we hypothesize that these factors may be similar in each group due to randomization and will thus limit the potential bias.

Conclusion

The Positive Therapeutic Communication on Pain (POPAIN) trial is an RCT assessing the effect of positive communication on pain, discomfort, and anxiety in patients undergoing ABG testing compared to neutral and nocebo communication. A reduction in pain, discomfort, and anxiety is expected when using positive communication. These results could be useful to the medical community and encourage clinicians to monitor their communication to reduce pain and anxiety in care. This method, if successful, could be easily implemented in other emergency departments.

Acknowledgments

This study was funded by the Cantonal Hospital of Fribourg. The authors gratefully acknowledge Pr Helene Beloeil (University Hospital of Rennes, France). She provided the protocol for the KTHYPE (Hypnosis and Communication Reduce Pain and Anxiety in Peripheral Intravenous Cannulation: Effect of Language and Confusion on Pain During Peripheral Intravenous Catheterization) study, which inspired the creation of our study. She also gave us advice on going to the Ethics Commission.

Data Availability

Once data are collected and ready for publication, they will be comprehensively presented in the manuscript. The results will be distributed in national and international scientific conferences and medical peer-reviewed journals.

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Authors' Contributions

TS had the idea for the study and was responsible for study design, and funding. CLT was responsible for drafting the protocol, writing it and obtaining ethics committee approval. Both TS and CLT contributed equally as first coauthor. YG, TS, CLT, and KI wrote and prepared the manuscript for publication. KI provided knowledge and input for statistical measures and outcome analyses. TS, CLT, YG, VR, and KI provided significant feedback on the manuscript and aided in the development of content.

Conflicts of Interest

None declared.

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Abbreviations

ABG: arterial blood gas
CRF: case report form
ED: emergency department
HFR: Cantonal Hospital of Fribourg
KTHYPE: Hypnosis and Communication Reduce Pain and Anxiety in Peripheral Intravenous Cannulation: Effect of Language and Confusion on Pain During Peripheral Intravenous Catheterization
LMM: linear mixed effects model
PI: principal investigator
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
TD: triage doctor
VRS: Verbal Rating Scale

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Protocol

Efficacy and Safety of Mizoribine for the Treatment of Refractory Nephrotic Syndrome: Protocol for a Multicenter, Controlled, Open-label, Randomized Controlled Trial

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Abstract

Background: Nephrotic syndrome that is resistant to steroid therapy is termed refractory nephrotic syndrome (RNS), a condition that is associated with an increased risk of end-stage renal disease. Immunosuppressants are used to treat RNS; however, prolonged use may lead to significant adverse effects. Mizoribine (MZR) is a novel agent used in long-term immunosuppressive therapy, which has few adverse effects, but data on its long-term use in patients with RNS are unavailable.

Objective: We propose a trial to examine the efficacy and safety of MZR compared with cyclophosphamide (CYC) in Chinese adult patients with RNS.

Methods: This is a multicenter, randomized, controlled interventional study with a screening phase (1 week) and a treatment phase (52 weeks). This study has been reviewed and approved by the Medical Ethics Committees of all 34 medical centers that are participating. Patients with RNS consent to participation, and are enrolled and randomized to an MZR group or a CYC group (1:1 ratio), with each group receiving tapering doses of oral corticosteroids. Participants are assessed for adverse effects, and laboratory results are collected at 8 visits during the treatment phase (weeks 4, 8, 12, 16, 20, 32, 44, and 52 [exit visit]). Participants are able to withdraw voluntarily, and investigators are required to remove patients when there are safety concerns or deviations from the protocol.

Results: The study started in November 2014 and was completed in March 2019. A total of 239 participants from 34 hospitals in China have been enrolled. Data analysis has been completed. The results are being finalized by the Center for Drug Evaluation.

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Conclusions: This study examines the safety and efficacy of MZR as a long-term treatment approach for Chinese adults with RNS. It is the longest lasting and largest randomized controlled trial to examine MZR in Chinese patients. The results can help determine whether RNS should be considered as an additional indication for MZR treatment in China.

Trial Registration: ClinicalTrials.gov NCT02257697; https://clinicaltrials.gov/ct2/show/NCT02257697

International Registered Report Identifier (IRRID): RR1-10.2196/46101

(JMIR Res Protoc 2023;12:e46101) doi:10.2196/46101

KEYWORDS

refractory nephrotic syndrome; mizoribine; cyclophosphamide

Introduction

Patients with nephrotic syndrome (NS) have the following classic triad of symptoms: heavy proteinuria, edema, and hypoalbuminemia [1]. Additional complications in these patients, such as venous thromboembolism, infection, and, less commonly, acute renal failure, can lead to catastrophic outcomes [2]. Patients with NS who are resistant to or dependent on corticosteroids for more than 4 to 6 months are considered to have refractory nephrotic syndrome (RNS), also referred to as steroid-resistant nephrotic syndrome, although RNS is a complex condition and there have been differences in how this term is used [3,4]. Almost all patients with NS who have proteinuria eventually progress to end-stage renal disease (ESRD) [3,5]. Because prednisone therapy often fails to provide complete remission of proteinuria, immunosuppressants may also be used to prevent or treat RNS [6]. Although several immunosuppressants (eg, cyclophosphamide [CYC], azathioprine, cyclosporine, and rituximab) can effectively treat proteinuria in patients with RNS [7,8], prolonged use of these drugs can lead to severe adverse effects (SAEs), such as sexual dysfunction, tumorigenesis, and renal dysfunction, and patients may also experience recurrence after discontinuation [9]. A novel immunosuppressant therapy that causes fewer side effects and that is suitable for long-term therapy is therefore needed for the treatment of RNS.

Mizoribine (MZR) was originally isolated from an ascomycete, *Eupenicillium brefeldianum*. Initial studies reported it had weak activity against *Candida albicans*, and subsequent studies confirmed it suppressed lymphocyte proliferation, and humoral and cellular immunity [10-12]. Other studies had examined its immunosuppressive effects and its use with other immunosuppressants for preventing rejection after kidney transplantation. Japan has approved MZR for the treatment of lupus nephritis, rheumatoid arthritis, and primary NS. Previous studies showed that MZR led to fewer SAEs, such as myelosuppression and hepatotoxicity, than other immunosuppressants [10,12]. Several clinical trials confirmed the clinical efficacy of MZR when it was used as a long-term therapy for the treatment of certain autoimmune diseases, such as lupus nephritis, rheumatoid arthritis, and primary NS [10,12]. Kawasaki et al [10] also reported that MZR was superior to corticosteroids in reducing proteinuria in patients with RNS and that the adverse effects (AEs) were similar in MZR and control groups. However, due to its relatively low efficacy, there is only limited data regarding the effect of MZR in patients with RNS, especially in adults with complex etiologies.

We propose a randomized, multicenter, controlled study to evaluate the efficacy and safety of MZR compared with CYC for the treatment of adults with RNS.

Methods

Ethical Considerations

This clinical trial is performed in accordance with the principles in the latest versions of the Declaration of Helsinki and Chinese Good Clinical Practice, and applicable clinical trial regulations. This study has been approved by the Medical Ethics Committee of the Chinese People's Liberation Army General Hospital on September 15, 2014 (C2014-042-01). Documents describing the study protocol, informed consent, safety monitoring policy, AEs, and management policies have been reviewed and approved with minor modifications by the Medical Ethics Committee. Approval of this trial has also been granted by appropriate Ethics Committees and the Center for Drug Evaluation (CTR20130299). Written informed consent for publication has been obtained from all participants.

Overview

This multicenter, randomized, controlled, open-label clinical study assesses the efficacy and safety of MZR in comparison with CYC for the treatment of RNS in adult patients. This clinical trial is performed at 34 centers in 27 cities in China.

The principal investigators at the 34 different sites receive patients from inpatient and outpatient settings who are referred and might be good candidates for participation. All potential candidates are carefully screened according to the inclusion and exclusion criteria. Those who qualify are approached by investigators for study enrollment. Study details, potential benefits, and potential risks of participating are explained in detail to all patients and to family members (if present), and all questions are answered. Patients who express full understanding and are willing to participate sign the informed consent documents, and these are co-signed by the investigators who recruit them. Each eligible and enrolled participant is offered US $15 as compensation for transportation expenses. The participants pay for all concomitant medications. The sponsor pays for the study medications and tests. The clinic visits and laboratory procedures are free of charge. The medical care needed for any AEs is also covered by the sponsor. All data are deidentified to protect patient confidentiality. The protected health information of all participants is entered by authorized staff or investigators into the electronic case report form in an electronic database that is managed by Tigermed Data

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Management. Any access to the system records or change of data in the electronic case report form after the original entry is automatically recorded, and each patient's protected health information is secured. All paper documents, such as consent forms, are collected and locked in the investigators' offices.

Key Study Objectives

The primary objective is to compare the therapeutic effect of MZR with CYC (the current standard therapy) for the treatment of RNS by analyzing overall and total remission rates in the different groups.

The secondary objective is to evaluate the efficacy and safety profiles of MZR for the treatment of RNS, including but not limited to clinical remission rate, progression rate, treatment failure rate (not achieving partial remission), 24-h urine protein, serum albumin, serum creatine, and estimated glomerular filtration rate (eGFR) as endpoints.

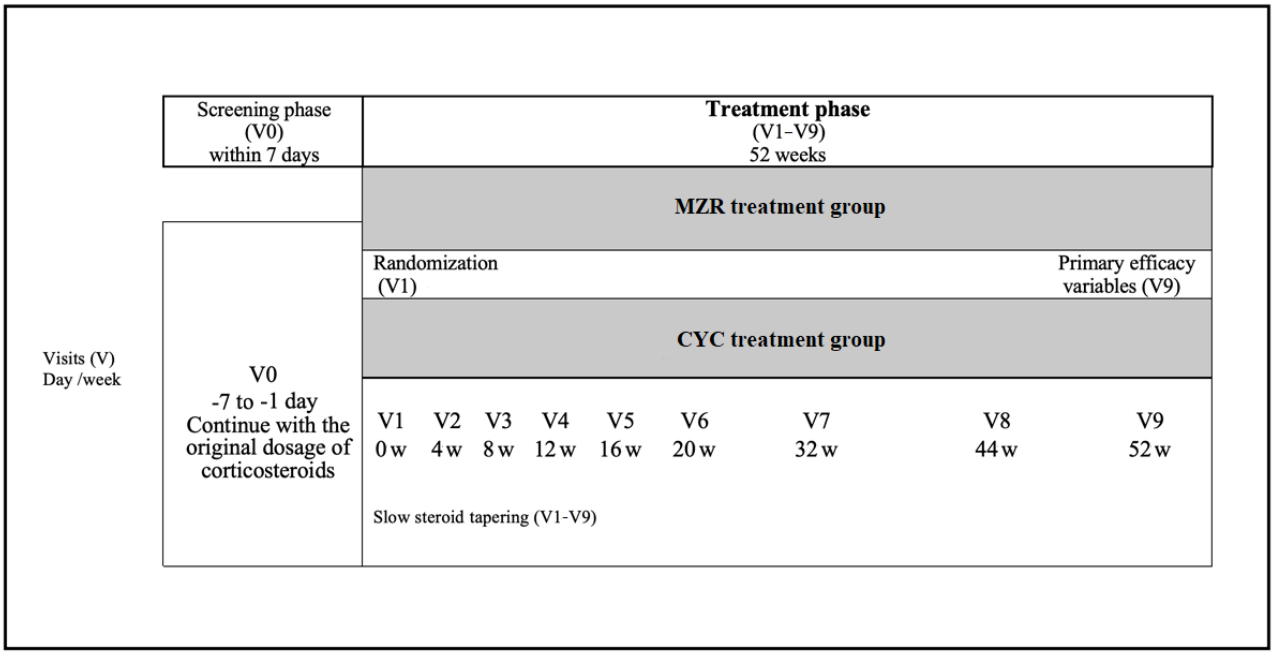
The exploratory objective is to evaluate the changes in high-sensitivity C-reactive protein (hs-CRP) levels in patients who receive MZR.

Trial Design

The specific aim of this study is to assess the hypothesis that MZR is not inferior to CYC for the treatment of RNS. This study consists of a 1-week screening phase followed by a 52-week treatment phase (Figure 1). Signed informed consent agreements are collected upon patient enrolment. The investigators have identified 238 eligible participants during the screening phase (visit 0; V0) according to the inclusion and exclusion criteria. Baseline information, including medical records, are obtained at this time. All enrolled participants are then randomized to an MZR group or a CYC group (1:1 ratio).

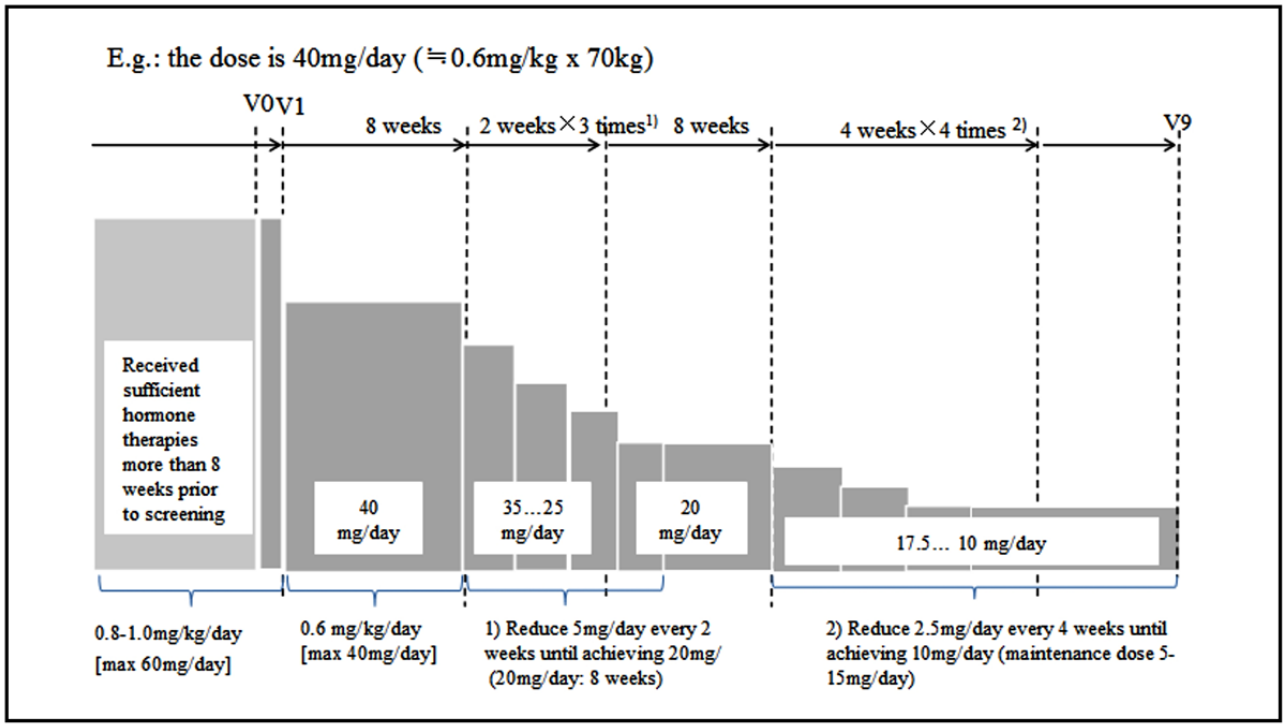
There are 9 visits (V1-V9) by each participant during the treatment phase, during which examinations are performed, AEs are evaluated, and samples are collected for laboratory tests performed at a central laboratory (Figure 2). Each visit is within 7 days of the scheduled date. All participants from both groups receive tapering oral corticosteroid therapy during the entire treatment phase (Figure 2). Patients in both groups receive specific doses of the treatment drugs in addition to corticosteroids. AEs and symptoms are closely monitored and documented. Participants are able to withdraw voluntarily, and investigators are required to remove participants when there is any concern regarding safety, according to the withdrawal protocol.

Figure 1. Study timeline. Randomization is performed on day 1 of V1. CYC: cyclophosphamide; MZR: mizoribine; V: visit.



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Figure 2. Plan for corticosteroid dose tapering. This example is for a dose of 40 mg/day (0.6 mg/kg x 70 kg). V: visit.



Eligibility Criteria

Inclusion Criteria

Patients are eligible for inclusion if they meet all of the following criteria: (1) Documentation of a confirmed diagnosis of NS; (2) Receipt of a renal biopsy within 1 year prior to screening, with a confirmed pathologic diagnosis of minimal change disease, immunoglobulin (Ig) A nephropathy, mesangioproliferative glomerulonephritis, membranous nephropathy (MN), or focal segmental glomerulosclerosis (FSGS), so that a planned subgroup analysis can be performed for these different pathological classifications; (3) Receipt of an adequate dosage of corticosteroids (0.8-1.0 mg/kg/day prednisolone or equivalent dose of another corticosteroid for more than 8 weeks [more than 12 weeks for FSGS]) based on the pathologic diagnosis mentioned in "inclusion criterion 2" before screening; (4) 24-h urine protein of 2.0 g or more at screening; (5) Male or female gender and age from 18 to 70 years upon signing the informed consent agreement; (6) Body weight between 40 and 80 kg at screening; and (7) Capacity and willingness to sign the informed consent document.

Exclusion Criteria

Patients are excluded if they have any of the following conditions: (1) NS caused by primary diseases other than those listed in "inclusion criterion 2" (eg, membranoproliferative glomerulonephritis); (2) NS from a secondary cause (eg, diabetic nephropathy, anaphylactic purpura nephritis, lupus nephritis, type B hepatitis-related nephritis, and renal amyloidosis); (3) History of allergy to MZR or CYC; (4) Receipt of an accumulated dosage of more than 3 g CYC during the 1 year before screening; (5) Receipt of immunosuppressants or any Chinese traditional medicine with immunosuppressive effects within 30 days before screening; (6) Receipt of disallowed therapeutic medications within 30 days before screening; (7) Receipt of plasma exchange therapy or immunoadsorption therapy within 30 days before screening; (8) Need for pentostatin or a live vaccine (not including the flu vaccine); (9) Receipt of renal replacement therapy; (10) Receipt of kidney transplantation; (11) Malignancy; (12) Severe hypertension (systolic blood pressure >160 mmHg or diastolic blood pressure >100 mmHg) that is not effectively controlled; (13) Low white blood cell count ($<3\times10^9$/L); (14) Elevated serum creatinine (SCr; >176.8 μmol/L [2 mg/dL]); (15) Elevated levels of liver enzymes (aspartate transaminase or alanine transaminase 3 times higher than the upper limit of normal); (16) Hepatitis B, hepatitis C, or HIV infection; (17) Other infections based on chest computed tomography; (18) Unsuitability to participate according to the investigators because of uncontrolled diabetes, central nervous system lupus, lupus encephalopathy, active psychosis, osteonecrosis of the femoral head, fulminant hepatitis, peptic ulcer, etc; (19) Pregnancy, breast feeding, or planning to become pregnant; and (20) Any other disease that may affect the evaluation of medication efficacy and safety.

Premature Withdrawal Criteria

Any participant who has signed the informed consent form and has initiated the study can be withdrawn prior to the last visit for any of the following reasons: (1) Withdrawal by the participant (the participant decides to withdraw during the screening or interventional phase); (2) Screening failure (the participant does not satisfy all inclusion criteria or meets one of the exclusion criteria at V0 and V1 [randomization visit]); (3) Protocol violation (the participant has a serious violation of the inclusion or exclusion criteria after the first dose of medication, uses a prohibited medication or prohibited therapy before the last planned visit, or has another major violation); (4) Pregnancy; (5) Poor compliance with the study medication

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(the participant has poor compliance with the protocol, including refusal of follow-up, laboratory tests, or treatments); (6) Investigators' decision (the investigators decide the participant has a medical condition, including those listed in the exclusion criteria, or has personal circumstances during the interventional phase that might cause substantial risk on continuing treatment; or the professional evaluations and decisions of the investigators do not allow the participant to follow the study protocol); (7) AE (the participant has any clinical AE or SAE according to the investigators' professional judgment; if an AE is not considered to be clinically related to the study medications or if the benefits of continuing treatment outweigh the risks, the treatment is continued at the discretion of the investigators; a low white blood cell count [$\leq 3\times10^9$/L] or an elevated aspartate transaminase or alanine transaminase level [>5 times the upper limit of normal] necessitates withdrawal); (8) Loss to follow-up (the participant fails to visit the study site for any reason before the last planned visit or by the end of the study); (9) Reaching an endpoint (progression to ESRD or doubling of SCr) at any time during the study; and (10) Others (difficulty for the participant to continue the study based on judgment of the principal investigator or co-investigators).

Randomization Strategy

Eligible participants are randomized to an MZR group or a CYC group in a 1:1 ratio using the Interactive Web Response System (IWRS) on day 1. A unique subject number is assigned to each participant. Stratification is according to pathological classification. When a participant who fails the screening is deemed eligible after rescreening by the investigators, the participant is allowed to enter the randomization before the end of enrollment.

Interventions

Study Medications

MZR

Participants in the MZR group start receiving MZR at V1. The oral dose is 50 mg per tablet, 3 times per day, corresponding to a total daily dose of 150 mg. Administration continues until V9 (Figure 1).

CYC

Participants in the CYC group start receiving CYC at V1. The dose is calculated as 0.5 to 1.0 g/m^2 body surface area, with a maximum dose of 1.0 g/day. Administration occurs from V1 to V8 (Figure 1).

Corticosteroids

All participants receive oral corticosteroid therapy (0.8 to 1.0 mg/kg/day prednisolone or an equivalent dose of methylprednisolone) during the screening phase. A dose of 0.6 mg/kg/day for 8 weeks begins at V1, and the maximum daily dosage is 40 mg. Starting from V3, the corticosteroid dose is tapered gradually, with a dose reduction of 5 mg every 2 weeks until the daily dose is 20 mg/day (if tolerated). Prednisolone (20 mg/day) or an equivalent dose of methylprednisolone is continued for 8 weeks. The dose is tapered by 2.5 mg every 4 weeks until the maintenance dose of 5 to 15 mg/day is attained at V9 (Figure 2).

Screening Period (V0)

The investigators obtain written informed consent from all participants prior to any intervention, and all participants are registered in the IWRS. During the screening period, participants are screened by the investigators for collection of relevant information. This information includes medical history, medications and previous therapies, and AEs (if any). Height, body weight, and vital signs are measured, and a 12-lead resting electrocardiogram (ECG) is obtained. Blood is collected for laboratory tests, including complete blood count (CBC), biochemistry, eGFR, hepatitis B surface antigen, hepatitis C virus antibody, HIV, IgG, and hs-CRP. A routine urine test for 24-h protein is performed. Women of childbearing age are tested for pregnancy (Multimedia Appendix 1).

Treatment Period (V1-V9)

V1 (Randomization Visit)

Each participant's laboratory results, physical examination results, medical history, medication history, and pathology reports are reviewed for evaluation of eligibility according to the inclusion and exclusion criteria before enrollment and randomization. Participants are then registered in the IWRS. If they qualify and are enrolled, appropriate doses of the study medication are dispensed, and the investigators provide information on how to take the medication and appropriate storage. The investigators also emphasize the importance of compliance, and request the return of all unused medications (Multimedia Appendix 1).

V2-V9

During this phase, all women of childbearing age return to the study center for pregnancy tests whenever they think there is a possibility of pregnancy. All participants are logged in to the IWRS when they visit the study center. Appropriate doses of the study medications are dispensed, and the investigators reinforce the importance of appropriate dosing and storage. The importance of compliance and the return of unused medications is also addressed, and detailed information regarding AEs is recorded. Pregnancy tests are routinely performed in all women of childbearing age. Laboratory tests, including CBC, biochemistry, eGFR, routine urine test, pregnancy test for women of childbearing age (V6 and V9), IgG, 24-h urine protein, and hs-CRP, are performed. Body weight and vital signs are measured at each visit, and a second ECG is performed at V9 (Multimedia Appendix 1).

Unscheduled Visit

Study participants who come to the study site for an unscheduled visit are documented as such. The reason for any unscheduled visit is documented in detail. Laboratory tests are performed if necessary, and vital signs, body weight, ECG, etc are assessed as needed. An urgent or emergent situation, such as potential pregnancy or disease progression, is evaluated and addressed by the study investigators.

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Premature Withdrawal From the Study (End of Study)

Any participant who is prematurely withdrawn from the study after confirmation receives an examination within 1 week from the withdrawal date, and this event is documented. The examination consists of necessary tests and other procedures that are recommended by the investigators and accepted by the participant.

The study design and items collected at all visits are summarized in Multimedia Appendix 1.

Outcome Measures

Primary Efficacy Variables

The primary efficacy variable is the total remission rate (%) and is based on data collected from each group at V9. The total remission rate is calculated as the sum of the complete remission rate (%) and the partial remission rate (%). Complete remission is defined as 24-h urine protein less than 0.3 g, and partial remission is defined as 24-h urine protein decline of more than 50% from baseline (V0) and value of less than 3.5 g.

Secondary Efficacy Variables

The secondary efficacy variables are the complete remission rate and partial remission rate of each group at V9; remission rate at V3, V6, V7, V8, and V9; treatment failure, defined as not achieving partial remission; and 24-h urine protein, serum albumin, SCr, eGFR (using the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] formula), and blood urea nitrogen values. The endpoint events are progression to ESRD or doubling of the SCr relative to baseline.

Exploratory Variables

The exploratory variables are the hs-CRP levels in each group at the different visits.

Safety Assessment

The safety of participants is actively monitored during the study. All events, including unplanned pregnancy, are documented and properly managed. The reportable events include but are not limited to SAEs (including death), pregnancy, important treatment-related AEs (granulocytopenia, infections, hemorrhagic cystitis, liver function impairment, hyperuricemia, malignancy, amenorrhea, alopecia, nausea, and vomiting), and AEs leading to study discontinuation.

Safety is monitored by asking participants about symptoms, and by assessment of physical examination results and laboratory test results (CBC, blood biochemistry, IgG, hs-CRP, pregnancy test, routine urine test, body weight, vital signs [blood pressure, pulse, and body temperature], chest computed tomography, and 12-lead ECG).

Statistical Plans

The sample size calculation is based on a noninferiority comparison of the MZR and CYC groups regarding the total remission rate after treatment, and is to be calculated using SAS (SAS Institute). Studies of RNS assumed the total remission rate in each group was 60% [13,14] and the risk ratio of MZR to CYC was 1.0. Thus, we include 119 participants in each group based on the following assumptions: total remission rate of 60% for each group, noninferiority difference ratio of 0.674, power of 80%, 1-sided significance level of 2.5%, and dropout rate of 20%.

The full analysis set (FAS) includes all participants who are randomized and treated with at least one dose of the study medication and who have received at least one posttreatment efficacy assessment. The per-protocol set (PPS) includes all FAS participants who have no major protocol violation. The safety set includes all randomized participants who receive at least one dose of the study medication and have at least one safety assessment.

The primary and secondary efficacy outcomes are assessed and analyzed. A noninferiority test of total remission is performed in the PPS population by comparing the 2 groups at V9, and relative risk ratios and 2-sided 95% CIs are calculated. A secondary analysis of the primary efficacy variable is performed in the PPS at the end of the study and in the FAS at V9. The number of participants who achieve total remission in the PPS is calculated in each group at each visit. The secondary efficacy variables are analyzed using descriptive statistics. The safety assessment is performed in the safety set population. The incidences of AEs in the 2 groups are compared. Subgroup analysis is performed as necessary, such as exploratory outcome analysis using hs-CRP and other variables.

Results

The study began in November 2014 and was completed in March 2019. A total of 239 participants from 34 hospitals in China were enrolled. Data analysis has been completed. The results are being finalized by the Center for Drug Evaluation.

Discussion

NS is caused by abnormally increased protein leakage from the kidneys into the urine [15]. In adults, proteinuria greater than 3.5 g/1.73 m^2 per day is considered nephrotic. The incidence of NS in the general population is about 1 per 100,000 [16]. The manifestations of NS are more complex in adults than children, because adults experience a wider variety of primary and systemic diseases, making management more difficult.

MN, FSGS, and minimal change disease are the most common causes of idiopathic RNS in adults [17-20]. Diabetes mellitus is the most common cause of secondary NS, and other causes include systemic lupus erythematosus, hepatitis B or C, amyloidosis, and multiple myeloma [2]. The pathogenesis of secondary NS differs from that of primary NS in that treatments for primary NS focus on the primary disease. Steroid hormone regimens and immunosuppression strategies also differ for primary and secondary NS. Thus, we exclude patients with secondary NS from this study. A potential limitation of this study is that the pathologic types of RNS may be concentrated in a few common pathologic types in Chinese patients, such as MN.

RNS remains poorly understood but is currently considered immune mediated because many patients respond to immunosuppressive drugs [21]. The immune mechanisms

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underlying the pathophysiology of RNS may include systemic T- or B-cell dysfunction [22]. In particular, cytokines produced by T cells are thought to act on the slit diaphragms of renal podocytes and increase protein permeability [23]. Alkylating agents, such as CYC, can inhibit T cells and B cells, have a wide range of applications in RNS, and are often used as positive controls in clinical studies. However, CYC and other traditional alkylating agents can cause myelosuppression, infertility, bladder cancer, leukemia, skin cancer, and hemorrhagic cystitis [24]. The optimal regimen to be used for immunosuppression in patients with RNS is uncertain, and many clinical trials are evaluating different therapeutic schedules for patients with different pathological types of RNS. Calcineurin inhibitors mainly inhibit T cells and can induce remission, but there is nearly a 50% risk of relapse after cessation of calcineurin inhibitors in patients with idiopathic MN [25]. Rituximab is a B-cell–depleting agent, and when used alone, it can induce disease remission and can cause few SAEs [26].

MZR was originally isolated as an antibiotic agent that had activity against *C. albicans*, and subsequent studies reported it had strong immunosuppressive activity in various animal experimental models [11]. MZR is an imidazole nucleoside, and its metabolite, MZ-5-P, selectively inhibits inosine monophosphate synthetase and guanosine monophosphate synthetase, resulting in the complete inhibition of guanine nucleotide synthesis without incorporation into nucleotides. MZR also has selective inhibitory effects on inosine 5-monophosphate dehydrogenase, an enzyme that functions in de novo purine nucleotide synthesis. MZR thus suppresses cell-mediated and humoral immune responses by suppressing T- and B-lymphocyte proliferation via the inhibition of guanosine monophosphate synthesis [27,28]. This mechanism is similar to that of CYC, but MZR is associated with fewer AEs. Two previous small head-to-head trials of specific agents compared the relative effectiveness and safety profiles of MZR and CYC in adult patients with MN [29,30]. Both studies showed that MZR reduced albuminuria and had a good safety profile.

Accordingly, this clinical trial evaluates the efficacy and safety of MZR in comparison with CYC for the treatment of RNS in Chinese adults with glomerular diseases. It is a multicenter, randomized, controlled trial, and we assess the efficacy of MZR based on changes in total proteinuria, eGFR, and AEs.

There is no universal treatment regimen used for adults with primary NS, although corticosteroids are beneficial in pediatric patients. Adults with NS usually receive conservative management and steroid treatment when conservative therapies fail [16,31]. However, the long-term use of immunosuppressants for the treatment of RNS may lead to SAEs, with unclear benefits. MZR appears to cause less severe AEs and provides good outcomes when used to treat other immune-related conditions, such as lupus nephritis, disorders after kidney transplantation, and primary nephritic syndrome [10,12,32,33]. However, there is currently insufficient evidence regarding its efficacy and safety for the treatment of RNS.

The proposed study examines the efficacy and safety of MZR as a long-term treatment approach for adults with RNS. It is so far the largest randomized controlled trial to examine MZR in China. The trial lasted about 1 year, and frequent follow-ups have been used to monitor efficacy and AEs. Confirmation of the efficacy and safety of MZR could lead to the improved management of adults with RNS and could improve our understanding of the pathology of RNS caused by different renal diseases.

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Data Availability

The data sets generated during this study are not publicly available due to the incomplete clinical analysis but will be made available by the corresponding author on reasonable request.

Authors' Contributions

ZD, JZ, ZX, ZN, YH, HL, GJ, XS, LZ, and XC discussed and designed the trial. ZD drafted the manuscript. XC and LZ are the principal investigators. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Study design and items collected at different visits.

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[DOCX File , 26 KB - resprot_v12i1e46101_app1.docx]

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Abbreviations

AE: adverse effect
CBC: complete blood count
CYC: cyclophosphamide
ECG: electrocardiogram
eGFR: estimated glomerular filtration rate
ESRD: end-stage renal disease
FAS: full analysis set
FSGS: focal segmental glomerulosclerosis
hs-CRP: high-sensitivity C-reactive protein
Ig: immunoglobulin
IWRS: Interactive Web Response System
MN: membranous nephropathy
MZR: mizoribine
NS: nephrotic syndrome
PPS: per-protocol set
RNS: refractory nephrotic syndrome
SAE: serious adverse effect
SCr: serum creatinine

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Protocol

Conditioning of the Cortisol Awakening Response in Healthy Men: Study Protocol for a Randomized Controlled Trial

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Abstract

Background: The hormone cortisol plays important roles in human circadian and stress physiology and is an interesting target for interventions. Cortisol varies not only in response to stress but also as part of a diurnal rhythm. It shows a particularly sharp increase immediately after awakening, the cortisol awakening response (CAR). Cortisol can be affected by medication, but it is less clear whether it can also be affected by learning. Animal studies have consistently shown that cortisol can be affected by pharmacological conditioning, but the results in humans have been mixed. Other studies have suggested that conditioning is also possible during sleep and that the diurnal rhythm can be conditioned, but these findings have not yet been applied to cortisol conditioning.

Objective: The objective of our study was to introduce a novel avenue for conditioning cortisol: by using the CAR as an unconditioned response and using scent conditioning while the participant is asleep. This study investigates an innovative way to study the effects of conditioning on cortisol and the diurnal rhythm, using a variety of devices and measures to make measurement possible at a distance and at unusual moments.

Methods: The study protocol takes 2 weeks and is performed from the participant's home. Measures in week 1 are taken to reflect the CAR and waking under baseline conditions. For the first 3 nights of week 2, participants are exposed to a scent from 30 minutes before awakening until their normal time of awakening to allow the scent to become associated with the CAR. On the final night, participants are forced to wake 4 hours earlier, when cortisol levels are normally low, and either the same (conditioned group) or a different (control group) scent is presented half an hour before this new time. This allows us to test whether cortisol levels are higher after the same scent is presented. The primary outcome is the CAR, assessed by saliva cortisol levels, 0, 15, 30, and 45 minutes after awakening. The secondary outcomes are heart rate variability, actigraphy measures taken during sleep, and self-reported mood after awakening. To perform manipulations and measurements, this study uses wearable devices, 2 smartphone apps, web-based questionnaires, and a programmed scent device.

Results: We completed data collection as of December 24, 2021.

Conclusions: This study can provide new insights into learning effects on cortisol and the diurnal rhythm. If the procedure does affect the CAR and associated measures, it also has potential clinical implications in the treatment of sleep and stress disorders.

Trial Registration: Netherlands Trial Register NL58792.058.16; https://trialsearch.who.int/Trial2.aspx?TrialID=NL7791

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International Registered Report Identifier (IRRID): DERR1-10.2196/38087

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KEYWORDS

conditioning; cortisol; cortisol awakening response; sleep; olfactory learning

Introduction

Background

The hormone cortisol has far-reaching effects throughout the body, mainly influencing metabolism but also being involved in systems as varied as the immune system [1], memory [2,3], and the sleep-wake cycle [4]. Cortisol is secreted from the adrenal gland as the end product of the hypothalamic-pituitary-adrenal (HPA) axis, a system of cascading secretions that originate in the hypothalamus. Cortisol is perhaps best known for its role in the stress response [5], and thus is often called the "stress hormone" in everyday parlance. However, cortisol does not just fluctuate in response to stress; it also follows several rhythms, including a diurnal rhythm. Cortisol levels are highest in the early morning and decline throughout the day and evening, with levels increasing again in the second half of the night [6]. A visual representation of a typical rhythm is shown in Figure 1. The onset of pulsatile secretion varies, but a strong peak is seen in cortisol increase in the period immediately after awakening in most participants [7]. This peak is referred to as the cortisol awakening response (CAR). The CAR has been extensively studied and has been shown to be generally consistent in size within an individual [7,8] but also influenced by situational variables [9], such as sleep duration in the preceding night [10]. Befitting the role of the stress hormone, the most reliable of the situational variables are stress-related [11]. Reviews of relevant studies suggest that the CAR is partially responsible for preparing the body in anticipation of the events and challenges of the day ahead [9,10]. Anticipation of a stressful and challenging day may lead to an increased CAR [12], while an intervention that reduces stress showed a corresponding decrease in the CAR [13]. Meanwhile, patients with severe amnesia, presumably not expecting anything from the coming day, seem to show no CAR at all [14].

Apart from stress and diurnal rhythms, cortisol levels can also be influenced more directly by medical interventions, whether intentionally or as a side effect. For example, sumatriptan is a serotonin receptor agonist taken to help with migraines, but it also reduces serum levels of adrenocorticotropin, and will reduce cortisol levels as a result [15]. Corticosteroids, such as dexamethasone, are a synthetic form of natural cortisol and can be used as cortisol replacement or to treat inflammation. Because cortisol is one part of an interconnected system, these types of medication can have indirect effects. Increased serum cortisol levels will normally trigger negative feedback to the hypothalamus and pituitary, the first links in the HPA axis, which leads to serum cortisol levels decreasing [16]. Corticosteroids trigger the same mechanism, which means that taking them lowers cortisol levels in the long term. Thus, it is always important to consider the timeframe and downstream effects when estimating the effect of any form of medication on cortisol levels.

Once the body is familiar with the effects of cortisol-affecting medication, learning processes can modulate their effects. These generally arise through the process of classical conditioning. Classical conditioning occurs when a natural reaction, the unconditioned response, which is normally caused by a stimulus termed the unconditioned stimulus (UCS), is repeatedly paired with a different, traditionally neutral stimulus. Once an association is established, the paired stimulus, known as the conditioned stimulus (CS), may evoke a response even when the UCS is not present; in this case, the response is known as the conditioned response [17]. These principles can be applied to cortisol-affecting medication. After repeated pairings, the CS will "remind" the body of the UCS and evoke either the cortisol change produced by the medication or a compensatory feedback mechanism [18,19]. A review of human and animal studies [20] found that this type of pharmacological conditioning was effective in animals, with 13 out of 15 studies finding the expected effect but less often tested and not as effective in humans. Of the human studies performed on this topic, 2 used medication that indirectly affects cortisol levels as a UCS: Benedetti et al [21] used sumatriptan, which reduces cortisol levels, while Petrakova et al [22] used corticotropin-releasing hormone, an upstream factor in the HPA axis. In the study by Benedetti et al [21], participants were injected with sumatriptan on 2 consecutive days, and on the third day, they received a saline injection presented as a 50/50 chance of sumatriptan or saline. Cortisol levels on the third day decreased in response to the injection in this group, while no effect was observed in the group that received the same injection without the previous 2 days of conditioning. Petrakova et al [22] used 2 conditioning trials 3 days apart, where participants received a distinctly flavored and colored drink combined with an injection of corticotropin-releasing hormone. After another 3 days, the participants were tested with a saline (placebo) injection on 2 subsequent days. Compared with a control group that also received saline injections in the conditioning phase, the participants showed an increase in cortisol during conditioning, but not in response to saline.

Two other studies relied on a direct increase in cortisol. Sabbioni et al [23] used dexamethasone, a glucocorticoid, while Tekampe et al [19] used hydrocortisone. In both cases, the CS was a strongly flavored drink combined with oral intake of the UCS on 3 occasions during the conditioning period. The results here are mixed again. Both studies indicate that cortisol increased after conditioning, but the results are inconclusive because of low power or group differences at baseline, respectively. On the basis of the 4 studies investigating this topic, it remains unclear to what extent and in what situations cortisol levels are

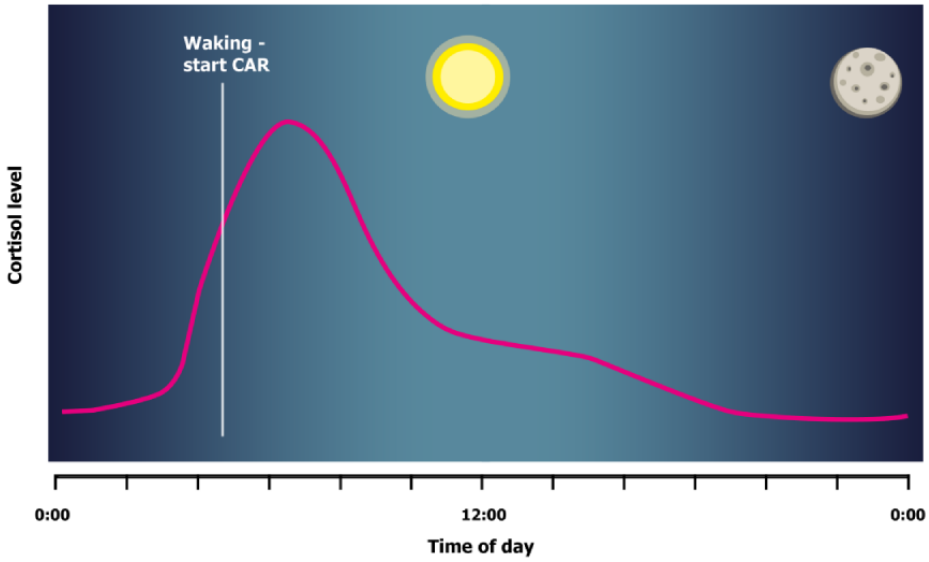
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subject to classical conditioning in humans. It may be worthwhile to test cortisol conditioning in other situations.

Association learning is generally performed while the learner is fully conscious, but a line of studies suggests that it is also possible during sleep. A series of studies by the same research group [24-26] have shown that associations between a scent and another stimulus can be formed during sleep. While these stimuli are relatively subtle, they can lead to relevant behavioral effects; 1 study found that coupling the scent of smoke with an aversive stimulus for one night led to a modest reduction in smoking for several days afterward [25]. Odors seem to be particularly suited for this type of learning, because they do not wake sleeping individuals but seem to reduce arousal and wakefulness [27] and seem to function as a strong memory stimulus in general [28]. This idea is supported by other exploratory studies suggesting that presenting a scent during sleep can reactivate memories. For example, 1 study had participants perform a problem-solving task in the evening and simultaneously present a scent. On the subsequent night, some participants were reexposed to the scent, and these participants imagined and applied more creative solutions to the problem the next day compared with participants who received a different or no scent [29]. The authors suggest that this effect was the result of reactivating memory of the task during sleep. Another study [30] similarly presented a scent during sleep that was also present during a task performed the evening before, in this case using a visual memory task. In addition, while the scent was presented, functional magnetic resonance imaging measures were taken to examine brain activity. The results showed that the presentation of the scent activated the hippocampus, known for its role in declarative memory, and improved memory performance the following day, suggesting that scents presented during sleep can reactivate memories and influence objective outcomes.

Two animal studies have indicated that this type of learning may apply not only to associations relevant outside of sleep but also to the workings of the diurnal rhythm itself. In 1 study, a CS that was previously associated with light exposure was found to be able to trigger behavioral awakening patterns and awakening-related activity in the suprachiasmatic nucleus [31]. In another study, a stimulus linked to light deprivation was able to trigger increased melatonin levels related to the start of sleep [32]. To our knowledge, these results have not been replicated in humans. However, 1 publication suggests that the diurnal pattern of cortisol concentration can be influenced by learning [33]. When participants were informed that they would be awoken 3 hours before normal, they showed an anticipatory increase in adrenocorticotropin several hours before awakening. This response was not present when the participants were not given any warning, regardless of whether they were awoken 3 hours before normal or simply allowed to keep sleeping. This suggests that the human diurnal rhythm may be subject to learning effects just as it is in animals.

Figure 1. Stylized representation of a typical change in cortisol levels over a 24-hour period. CAR: Cortisol Awakening Response.



Objective

This study builds on these separate lines of evidence by investigating whether the CAR can be conditioned during sleep and moved to an earlier point in the night. Manipulation of the CAR could help evoke the benefits associated with a high CAR, such as a more alert and prepared awakening on busy days, or a low CAR, such as a more restful awakening. The association between cortisol and the diurnal cycle may indicate that such effects could be helpful in normalizing the sleep-wake cycle when it has been disturbed, as seen in conditions such as seasonal affective disorder [34] or delayed sleep phase disorder [35]. These effects are especially valuable considering that they could be evoked without the use of medication and the associated side effects.

Owing to the interindividual reliability and strength of the CAR, it has the potential to be an effective unconditioned response. By exposing participants to a distinctive odor in the half hour before awakening, we expect that an association can be created between the cortisol increase in this period and the distinctive scent. According to the principles of classical conditioning, the scent alone should also be able to evoke an increase in the CAR

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and potentially accompanying feelings of wakefulness, even when administered hours before the regular time of awakening.

Methods

Ethics Approval and Dissemination

The study was approved by the Medical Ethics Committee of the Leiden University Medical Centre, Leiden, the Netherlands (case NL62812.058.017), who will be notified of major changes. The study is performed in accordance with the principles of the Declaration of Helsinki and Dutch Medical Research Involving Human Subjects Act (WMO). The study was preregistered at the Dutch trial register [36]. The results will be disseminated in peer-reviewed journals, international conferences, and the PhD thesis of the first author.

Participants

Participants are recruited from the local Dutch population and compensated with €100 (US $110.25) for participation. Flyers displaying a summary of the study inclusion criteria and procedures as well as the compensation amount are disseminated on social media through word of mouth by students and teachers, in university buildings, and in local student housing. Owing to the novel and exploratory nature of the study design, no sufficiently similar studies are available to form the basis of a power analysis. Studies on similar topics have used different outcome measures and statistical analyses and thus do not offer a usable comparison. Therefore, it was decided to run a pilot study and include as many participants as possible within the grant-permitted timeframe, which resulted in 50 inclusions and 42 participants completing the full protocol. It should be noted that the most similar studies available use a comparable number of participants [24,25,37].

To avoid confounding in the measurement of the CAR by menstrual cycle or age [38], only male individuals between the ages of 21 and 34 years are included, and participants are excluded if their answers during screening indicate obesity (defined as BMI >30 kg/m^2), brain damage, or HPA axis–related endocrine disorders (Cushing disease or Addison disease). Participants currently taking medication (including glucocorticoid medication) or who have a habit of heavy drinking or recreational drug use are also excluded. Participants are screened for severe somatic or psychiatric conditions that would interfere with the study protocol using the Mini-International Neuropsychiatric Interview Plus (MINI-Plus) [39]. To ensure a regular sleep pattern, participants are screened using the Pittsburgh Sleep Quality Index (PSQI) [40] and excluded if they experience jetlag or participate in shift work up to 1 week before participation. To ensure that participants are able to properly detect the scents used in the study, they are excluded if they indicate that they have olfactory impairments. Participants are also excluded if they report allergies or sensitivity to perfume or similar substances that might indicate an adverse reaction to the scents used in the study or if they show an allergic reaction to the scents in the course of the study.

Ongoing health and stress are checked at several points from 1 week before participation up to the conclusion of the study, and participants are encouraged to report any changes between these points. Participation is stopped if a participant uses glucocorticoid medication, has high levels of stress, or falls ill during the study period. The participants are asked to refrain from alcohol and drug use for the duration of the study. Caffeine use is permitted for consistency with existing habits but is monitored. They note their regular awakening time and are requested to set their alarm at exactly the noted time and maintain a steady sleep rhythm for the duration of the study. All participants sign an informed consent before participation.

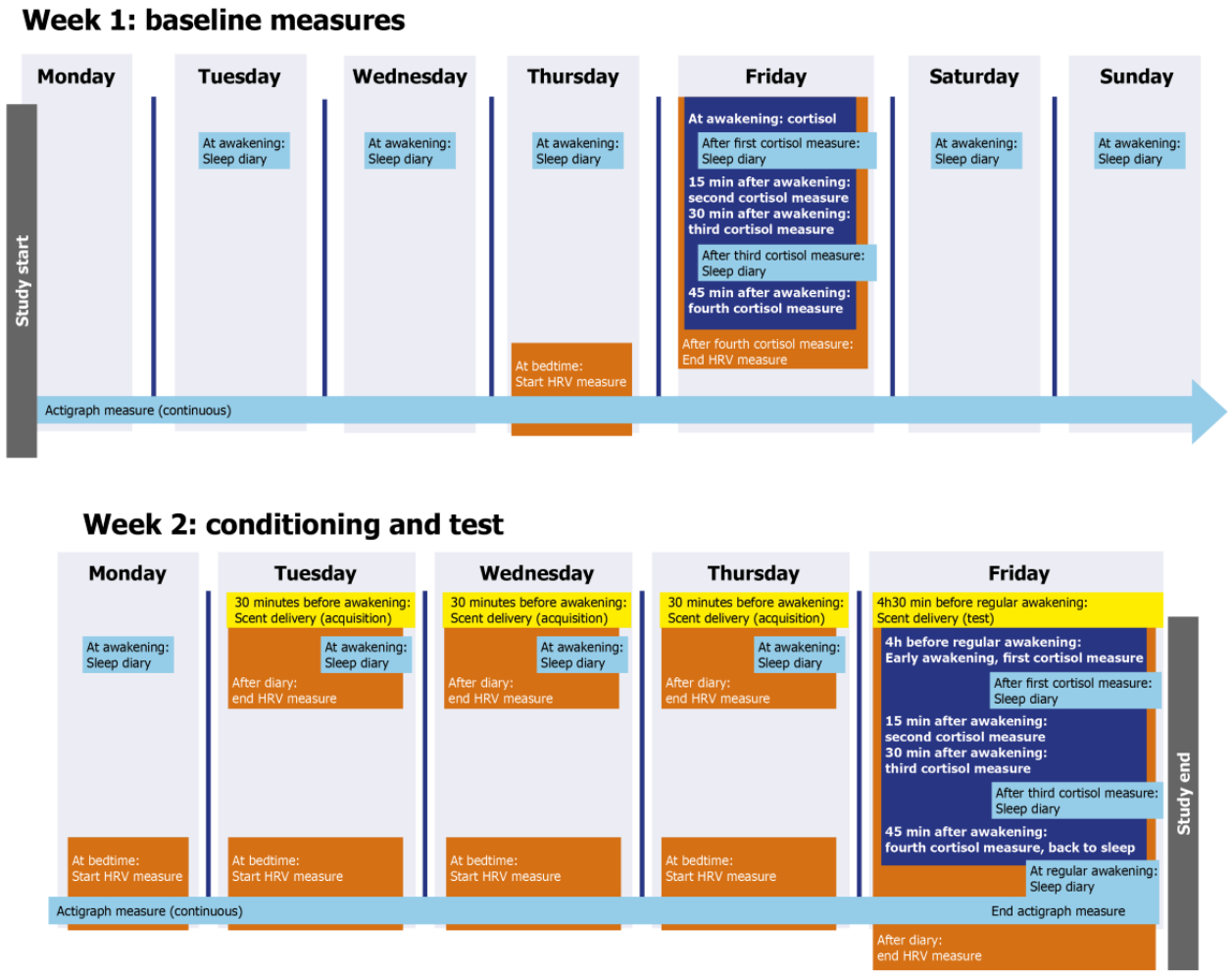
Upon inclusion, participants are randomized to the experimental or control group through a pregenerated random number list, set to randomize in blocks of 4. Owing to procedural constraints (see the *Procedure* section), the study is single-blinded. Participants are not informed about the existence of a control group or the purpose of the study until the debriefing at the end of the study; instead, they are told that the study examines the effect of certain scents on sleep.

Design

The study design is summarized in Figure 2. Participants follow a 2-week protocol, with all measurements taking place in their own homes. The first week functions as a baseline measure. In the second week, the scent conditioning takes place on Tuesday through Thursday morning. Participants are exposed to a scent half an hour before awakening, with the aim of conditioning the scent to the CAR. The 30-minute interval was chosen to match the CAR in length and to increase the chance that the participant is still asleep for the length of the scent presentation, while still clearly preceding the CAR and minimizing the time between CS and CAR. It is presupposed that the CAR naturally functions as an unconditioned response to daylight and other zeitgebers that set the diurnal rhythm that serves as the UCS. The final night of the study functions as the test phase. To test whether conditioning has taken place, participants in the experimental group are asked to set their alarm 4 hours earlier than normal, and the scent device releases the trained scent half an hour before this time. This way, the CS is present, while the UCS is not. Participants in the control group wake up at the same time, but for them, the scent has surreptitiously been replaced the previous day with a different, novel scent, so that neither the CS nor the UCS is present. We expect that in the experimental group, the scent (CS) will evoke the CAR and lead to an increase in cortisol levels. While the process of awakening may lead to an increase in cortisol levels in both groups, the presence of the CS would cause this increase to be more pronounced in the experimental group.

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Figure 2. Study design of the protocol conditioning the cortisol awakening response. See Design and Procedure section for details on the content of each measurement. HRV: heart rate variability.



Measurements

Scent Delivery System and Scents Used

Scents are delivered using the Air/Q-100 and Air/Q-160 devices and accompanying scent cartridges (Prolitec Inc). The scents used in the study were “Blue Wood” (Prolitec reference 9083) and “Marsala” (Prolitec reference 9141), with the latter used as the control scent during the last night for the participants in the control group and the former for all other instances. The scents were previously piloted to ensure that they were sufficiently distinctive. The devices release the scent at intervals of approximately 2 minutes every 9 minutes. The exact length of the delivery was dependent on the settings of the device, which were adjusted to the size of the participant’s bedroom based on the manufacturer’s suggestions. Custom-made containers were used to muffle the noise generated by the scent delivery devices.

Physiological Measures

Cortisol Awakening Response

Participants take saliva measures themselves on 2 consecutive Fridays of the experiment to measure cortisol levels. A total of 4 samples are taken each week: immediately after awakening, 15 minutes after awakening, 30 minutes after awakening, and 45 minutes after awakening. Participants are instructed not to eat, brush their teeth, smoke, exercise, shower, or drink anything other than water between awakening and taking the final sample to avoid any contamination of the samples or confounding of cortisol values [38]. Saliva is collected using sealed swabs designed for cortisol collection (Salivettes; Sarstedt AG and Co). Cortisol is assessed in saliva with a competitive electrochemiluminescence immunoassay using a Modular Analytics E602 immunoanalyzer (Roche Diagnostics). Cortisol activities are measured and expressed in nmol/L. Participants track the times when they take the saliva measures in a smartphone app, using a phone that they receive from an experimenter and use throughout the study to allow the researchers to verify that they were awake and took the required samples at the correct time. Because cortisol samples remain stable at varying temperatures for up to 5 days [41], participants were not required to cool or freeze the samples once collected. Samples were retrieved by a researcher and frozen on the same day they were collected.

The cortisol measure requires participants to be awake, but the scent conditioning procedure operates for half an hour before the participant wakes. To investigate whether the conditioning procedure has an effect before awakening, heart rate variability

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and actigraphy measures are included that operate throughout the night. These measures also allow for an additional check for whether the participant did indeed awake at the scheduled time.

Heart Rate Variability

Heart rate is measured using Polar H7 and H10 heart rate sensors (Polar Electro Oy) connected to the Heart Rate Variability Logger smartphone app [42] using the same phone as the one required for registering cortisol measures. Participants equip themselves with the heart rate monitor before going to bed on the first Thursday and every day of the second week, so that it stays on throughout the night. On days when they perform the saliva measures, the monitor is kept on until the end of those measures (ie, 45 minutes after awakening) so that any changes in heart rate that accompany the change in cortisol levels during this period can also be measured.

Actigraphy

Actigraphy is performed using Motionwatch 8 wearable motion detectors (CamNtech Ltd). Measures are taken over the entire 2-week period with 1-minute epochs.

Questionnaires

All questionnaires used have previously been found to have adequate validity and reliability.

For screening, the participants complete the PSQI [40]. Scores of 5 or higher indicate poor sleep and are used as an exclusion criterion. In addition, participants are screened for mental disorders using the MINI-Plus [39,43] and excluded if they meet the criteria for any disorder.

Several personality characteristics are measured upon inclusion, to check for possible interaction with the main outcome. Specifically, the questionnaires used are the extraversion and neuroticism scales of the Eysenck Personality Questionnaire [44,45] to measure extraversion and neuroticism, the Depression Anxiety Stress Scale-21 (DASS-21 [46]) to measure symptoms of depression and anxiety, the Life Orientation Test–Revised [47] to measure optimism, the Perceived Stress Scale [48] to measure general appraisal of stress, and the Morningness-Eveningness Questionnaire [49] to measure chronotype.

Every day of the study, immediately after awakening or after the first saliva measure, participants complete a web-based diary on their phone or PC, which includes several questionnaires. To measure positive and negative affect, the Positive and Negative Affect Schedule (PANAS [50,51]) is used. Stress is measured using a custom-made Numerical Rating Scale (NRS) asking participants to score themselves between 0 (“not at all”) and 100 (“very much”) on 7 stress-related words [19,52]. Vitality is measured using the Subjective Vitality Scale (SVS [53]), and fatigue using the fatigue subscale of the Checklist Individual Strength (CIS [54]) adjusted to measure the current state of fatigue.

The sleep diary also includes custom-made daily questions about habits that indicate or may influence sleep quality and patterns. Participants are asked about their meal times; their intake of caffeine, alcohol, tobacco, medication, and recreational drugs; sporting activities; the time at which they fell asleep the previous night and the time at which they awoke in the morning; any nighttime awakenings; and their perceived sleep quality.

Procedure

An experimenter screens interested applicants through a telephone interview consisting of questions about relevant exclusion criteria (*Participants* section) and vocal administration of the PSQI (no data are saved). If participants meet the criteria, a follow-up screening session at Leiden University is scheduled to obtain written informed consent, perform a more elaborate check of mental and physical health, and to further explain the procedure and schedule meetings. This screening session consists of several questions about sleep, stress, and health and the Mini-International Neuropsychiatric Interview (MINI) plus international psychiatric interview. Participants who pass the screening also complete the Eysenck Personality Questionnaire – Revised Short Scale, Life Orientation Test–Revised, DASS-21, Perceived Stress Scale, and Morningness-Eveningness Questionnaire in this session. To ensure that the participants know how to take a sample of their saliva, they practice using the swabs used in the study under the supervision of a member of the research team.

The procedure of the actual experiment takes place over a period of 2 weeks, always starting on a Monday and ending on the second Friday. All measurements are performed at the participants’ homes; an experimenter visits the participants at several points to deliver and take equipment, check on participants’ health and stress, offer instructions on study procedures, and check whether all measurements have been completed successfully. Participants indicate their regular time of awakening before the experiment starts and instructed to set their alarm for this time for every day of the study. They are instructed to try to fall back asleep if they wake earlier than the indicated time. However, if they are fully awake, they should start all measurements at the earlier time of awakening.

The measures begin once an experimenter delivers the equipment on Monday of the first week. Participants are checked for exclusion criteria, instructed in the procedure for the coming days, and put on the actograph watch. The (waterproof) actograph watch will be worn continuously until the study ends, barring special circumstances such as high-contact sports or interactions with sensitive equipment where the watch could cause an issue, in which case it can be removed for the duration of the activity. Up until the evening of Thursday of week 1, participants fill in the web-based diary each morning at awakening and indicate their wake and sleep times on the actograph. Thursday evening, they put the heart rate monitor around their chest and wear it for the following night. On Friday morning, when waking up at their regular time of awakening, the first saliva measure is taken. Participants then complete the morning’s sleep diary, followed by another saliva measure 15, 30, and 45 minutes after awakening. An additional diary, where the PANAS, Stress NRS, SVS, and CIS-fatigue are completed again, is taken after the third saliva measure. After the last saliva measure, the participants remove the heart rate monitor. An experimenter arrives later in the day to take saliva measures for analysis.

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During the weekend and on the morning of the following Monday, participants only complete the web-based sleep diary and indicate their sleeping times on the actograph. On Monday, an experimenter arrives to install the scent delivery system. This device has been preprogrammed to deliver the distinctive scent 30 minutes before the participant's regular awakening time. Participants continue to complete the diary and use the actometer in the second week, and starting Monday evening, they also wear the heart rate monitor every night. An experimenter comes by again on Thursday to reset the scent delivery system to go off 4 hours earlier than previously, that is, 4 and a half hours before regular awakening. The experimenter also checks the participant's experience with the scent device at this time and notes if the participant had any unexpected reactions or has woken up early. Unbeknownst to the participant, if the participant is in the control group, the cartridge containing the scent is also switched for a different cartridge containing a different scent. The participant is instructed to set their alarm 4 hours earlier than normal and perform saliva measures at the new time of awakening and 15, 30, and 45 minutes later. They also use the web-based diary to complete the PANAS, Stress NRS, SVS, and CIS-fatigue directly after the first and third saliva measures. After the final saliva measure, the participants are allowed to return to sleep. They awake at a time of their choosing the following morning and only at that point remove the heart rate monitor. Their only remaining activity that day is a final diary filled in at a time of the participant's choosing. Later that day, an experimenter picks up the saliva samples and all equipment, including the actometer that the participant can at that point remove, and debriefs the participant about the true aim of the study and their group assignment.

Data Management

Self-reported data will be entered electronically by participants and checked for completion throughout the study at each experimenter visit. These data will be stored on a secure server that produces daily backups. Saliva samples are stored securely in a freezer at Leiden University Medical Center until study completion. All data are handled in compliance with the Leiden University Data Management Policy (available at request). Personal data are kept separate from the research data, and the file connecting the 2 is secured and only accessible to the study staff. Owing to low risk, external monitoring was deemed unnecessary by the ethical review committee, but a department data manager will monitor the data during the study and check the data package for completeness at study completion. Data will be stored locally for a period of 15 years after study completion and will be uploaded to the Data Archiving and Networked Services database to be accessed at request.

Statistical Analysis

The data will be checked for outliers and all relevant assumptions. If cortisol values deviate strongly from normality, a log transformation will be performed. An α level of .05 will be used for all analyses, and an effect size (Cohen *d* or partial eta squared, as appropriate) will be calculated for all effects.

Sensitivity analyses will be performed to investigate the effect of including participants who do not show a CAR in week 1 (defined as an increase of at least 2.5 nmol/L above baseline [8]) and the effect of including participants with incomplete data.

A conditioned effect on cortisol values can be defined in 2 ways: by a higher increase in the CAR from baseline (first week) to evocation (second week) for the experimental group (same scent on evocation) than the control group (different scent on evocation), and by a higher increase in the initial cortisol value (first measure of the CAR) from baseline (first week) to evocation (second week) in the experimental group than in the control group. Therefore, 2 separate analyses will be performed. For the first definition, cortisol levels over each day will be transformed into a single score by computing the area under the curve with respect to the first value (area under the curve with respect to increase [7]). We will then perform a linear mixed-model analysis with week (baseline vs evocation) and group (experimental vs control) as fixed factors. For the second definition, we will again perform a linear mixed-model analysis, replacing the area under the curve with respect to increase value with the first cortisol value after awakening. To check for confounding variables, sociodemographic and personality variables will be included as random factors in both the analyses.

Linear mixed models are also used to analyze the secondary outcomes. Heart rate variability measures 30 minutes before awakening and 45 minutes after awakening will be analyzed separately. In both cases, week (baseline vs evocation) and group will again be fixed factors. For the secondary psychological outcomes affect, stress, vitality, and fatigue, the measurement time (0 vs 30 minutes after awakening) is added as an additional fixed factor.

Finally, multivariate regression will be used to explore the possible moderating or mediating role of psychological variables (affect, personality, and perceived stress) on the effects of conditioning.

Results

Data collection started on June 24, 2019, and we encountered difficulties owing to the COVID-19 pandemic. Data collection was closed on December 24, 2021, with 50 inclusions and 42 participants completing the full 2-week protocol. The results will be published separately at a later date when the data analysis is completed.

Discussion

The design of this study is intended to classically condition the CAR by repeatedly presenting a scent in the half hour immediately before awakening, immediately before the CAR normally occurs. If the conditioning is successful, participants should respond to the CS with higher cortisol levels even when it appears in the middle of the night, when cortisol levels are normally far below the morning levels. The outcomes of this study could offer more insight into learning during sleep, learning influences on physiological processes, and manipulating the diurnal rhythm. These findings may also aid in the treatment of sleep rhythm and cortisol disorders.

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This study uses a novel design that combines the finding that conditioning is possible during sleep [24,25] with the idea that the diurnal rhythm itself could be conditioned [31,32]. While other studies have investigated whether cortisol levels are subject to classical conditioning [19,21-23], all of them have used an external UCS to adjust cortisol levels rather than relying on changes brought upon by the natural diurnal rhythm. Even animal studies that relied on less invasive stimuli kept the animals under artificial lighting conditions that are impossible to replicate in daily human life [31,32]. Should the alternative approach of this study be successful in conditioning the CAR, this could indicate that it is not necessary to rely on medication or highly demanding procedures to influence cortisol levels.

Should the conditioning procedure used in this study be successful in affecting subjective wakefulness measures, then a similar conditioning procedure has potential use in the treatment of sleep disorders. The primary target group would likely be those patients who do not respond to or cannot participate in existing behavioral therapies. Pharmacological therapies currently prescribed for this purpose are not always ideal solutions; many, such as benzodiazepines, do more to deregulate than help the sleep cycle and feature unpleasant side effects and risks of dependence [55].

On the other hand, the conditioning procedure could fail to affect cortisol. This may be due to the novel aspects of the study design. For example, using the stimuli associated with the diurnal rhythm may prove to be less reliable than inducing effects on cortisol through medication; the existing animal studies that relied on this [31,32] may not generalize to humans. Timing the test phase in the middle of the night will hopefully expose the effect because the CAR is not present in the control group, but there are indications that cortisol will still show an increase around an earlier time of awakening as long as the participants are aware that they will awake at the earlier time [33]. There is also the risk that the presence of the scent, the knowledge of having to wake, or the sound of the scent device would cause participants to wake up before the predetermined time. This would cause the scent and CAR to overlap, potentially affecting the conditioning procedure. If the participants do wake up, they could also consciously process the scent. While the debate on the role of consciousness in conditioning is ongoing and beyond the scope of this paper [56], what exactly is learned under these conditions is no doubt different than when asleep. Even if the conditioning procedure still led to an increase in cortisol, the conditioning might not be unconscious or physiological. Therefore, we endeavored to reduce the chances of this occurrence by selecting good sleepers as participants and reducing the noise as much as possible. If the participants do wake up, actigraphy and heart rate variability measures should show this.

Apart from factors specific to this study's design, a null result may indicate that pharmacological conditioning of cortisol levels in humans may not be feasible in general. The mixed results in existing studies might be the result of underlying confounds or sample fluctuations; several early studies rely on relatively small samples or groups [21,23] or suffer from unexpected baseline differences [19]. We hope that this study will avoid these issues and offer more clarity. The difficulties so far could also indicate that any effect of conditioning on cortisol is small and easily overshadowed by confounds. If the effect is too small or unreliable to be of use in clinical applications, further investigations may not be warranted.

Allowing participants to perform all measures themselves at home will invariably lead to a loss of control over the measurement situation, resulting in overall noisier data and an increased likelihood of missing or inaccurate measurements compared with a laboratory environment. Testing in a laboratory would have also allowed us to perform more continuous measures, such as daily cortisol sampling. However, such a setting would also highly increase participant burden, and sleep in a controlled medical environment has been shown to affect sleep measures in a way that does not occur for at-home measurements [57]. Therefore, we chose to focus on a home setting with fewer measurement points, relying on the reliability of the CAR [9] and stringent participant selection to still provide reliable data. Allowing measures to be taken at home also ensures that the results of the study are generalizable to real-life situations in a way that laboratory measures are not, thus ensuring maximal external validity.

Only healthy young men are included in this study. This selection is performed to prevent possible confounding effects of the menstrual cycle, gender, age, stress, and illness. However, it should be noted that the effects of some of these confounds are small [38] and the findings are often heterogeneous. For example, while some studies find differences in CAR in different phases of the menstrual cycle [58,59], others do not [60,61], and even when there are effects, they are limited to 1 phase differing from all others. Those few studies that cover a large age range show mixed results regarding the effect of age [8,60]. The effect of smoking is similarly equivocal [7,60,62,63]. Because this study uses a novel procedure and the exact size of the expected effect is uncertain, and because testing in the home environment is already going to produce additional noise, precautions have been taken to exclude any additional sources of interference. Thus, we have chosen to control for these factors, even if their effects may be small. However, should the current design produce the expected effect, broadening the type of participants in follow-up studies will greatly help generalizing the results. Extending the design to women may be especially valuable, not only because this is the largest excluded group but also because the CAR tends to be larger in women [7,8,64], which may make it easier to evoke through conditioning.

In conclusion, an innovative study design has been presented to investigate whether the CAR can be classically conditioned during sleep. The design of this study offers a unique first look at the potential of using natural diurnal changes in physiological conditioning. The results of this study will provide clarification on the currently murky topic of the conditioning of cortisol levels and, if positive, can inspire future additive treatment for sleep disorders.

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Data Availability

Data sharing is not applicable for this paper as no data sets were generated or analyzed during this study.

Conflicts of Interest

None declared.

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Abbreviations

CAR: Cortisol Awakening Response
CIS: Checklist Individual Strength
CS: conditioned stimulus

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DASS-21: Depression Anxiety Stress Scale-21
HPA axis: Hypothalamus-Pituitary-Adrenal Axis
HRV: heart rate variability
MINI-Plus: Mini-International Neuropsychiatric Interview Plus
NRS: Numerical Rating Scale
PANAS: Positive and Negative Affect Schedule
PSQI: Pittsburgh Sleep Quality Inventory
SVS: Subjective Vitality Scale
UCS: unconditioned stimulus

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Protocol

Ascertaining the Career Intentions of Medical Students (AIMS) in the United Kingdom Post Graduation: Protocol for a Mixed Methods Study

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Abstract

Background: Among doctors in the United Kingdom, there is growing sentiment regarding delaying specialist training, emigrating to practice medicine abroad, or leaving the profession altogether. This trend may have substantial implications for the future of the profession in the United Kingdom. The extent to which this sentiment is also present in the medical student population is not well understood.

Objective: Our primary outcome is to determine current medical students' career intentions after graduation and upon completing the foundation program and to establish the motivations behind these intentions. Secondary outcomes include determining which, if any, demographic factors alter the propensity to pursue different career paths available to a medical graduate, determining which specialties medical students plan on pursuing, and understanding current views on the prospect of working in the National Health Service (NHS).

Methods: The Ascertaining the Career Intentions of Medical Students (AIMS) study is a national, multi-institution, and cross-sectional study in which all medical students at all medical schools in the United Kingdom are eligible to participate. It was administered via a novel, mixed methods, and web-based questionnaire and disseminated through a collaborative network of approximately 200 students recruited for this purpose. Both quantitative and thematic analyses will be performed.

Results: The study was launched nationally on January 16, 2023. Data collection was closed on March 27, 2023, and data analysis has commenced. The results are expected to be available later in the year.

Conclusions: Doctors' career satisfaction within the NHS is a well-researched topic; however, there is a shortage of high-powered studies that are able to offer insight into medical students' outlook on their future careers. It is anticipated that the results of this study will bring clarity to this issue. Identified areas of improvement in medical training or within the NHS could be targeted to improve doctors' working conditions and help retain medical graduates. Results may also aid future workforce-planning efforts.

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KEYWORDS

medical students; NHS; National Health Service; career intent; attitude; opinion; workforce; workforce planning; medical education; career; doctor; medical training; medical graduate; cross-sectional; thematic analysis; degree; rotation

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Introduction

Background

In the United Kingdom, medical degrees typically last for 5 or 6 years, depending on whether one elects to pursue an additional year in the awarding of an intercalated degree. Alternatively, for previous degree holders, there is a 4-year accelerated medicine course. Upon the completion of their medical degree, graduates are provisionally registered with the General Medical Council (GMC). Graduates then enter the mandatory 2-year United Kingdom Foundation Programme (UKFP), consisting of rotations in various settings and specialties. After the first year of the UKFP, graduates are awarded full medical registration with the GMC. Doctors who have completed the UKFP are then able to pursue further training, which may be in very specialized fields, for example, ophthalmology or neurosurgery, or broader pathways such as general practice or internal medicine training [1].

Historically, the vast majority of UKFP graduates pursued specialty training immediately after completing their foundation program; for instance, in 2010, the proportion of graduates entering further training upon completing Foundation Year 2 was 83.1%. However, the UKFP Office career destination report revealed that this number had fallen to only 34.9% of doctors in 2019 [2]. The UKFP Office has not repeated the survey since, so it is difficult to surmise how these statistics may have changed in the interim.

In comparison to most other Organization for Economic Co-operation and Development countries, the United Kingdom has fewer doctors per capita [3]. One of the ways the British government has attempted to combat this issue is through the opening of new medical schools as well as increasing student capacity in existing medical schools [4,5]. The aim of the Ascertaining the Career Intentions of Medical Students (AIMS) study is to understand the effectiveness of this approach: are the factors encouraging graduate doctors to seek alternatives to medicine in the United Kingdom, or in its entirety, also present in the undergraduate population?

AIMS also endeavors to investigate the reasons behind students' intentions to both enter and leave the standard training pathway and attempt to identify any demographic and background information that might increase the propensity to leave training.

A British Medical Association survey of 8000 senior doctors determined that 44% of National Health Service (NHS) consultants in England plan to leave or take a break from working in the NHS over the next year [6]. Similarly, a recent survey of 4553 junior doctors in the NHS reported that 4 in 10 plan to leave the NHS, with 33% of these wanting to immigrate to another country to work [7]. Broader literature supports these findings, with a 40-year survey series of junior doctors highlighting that the desire to remain in UK medical practice was lower in 2015 than had ever been recorded [8]. Additionally, in 2021, nearly 10,000 doctors relinquished their license to practice in the United Kingdom, making up nearly 1 out of 10 of the total UK doctor workforce [5,9]. We aim to determine if this trend, found in both junior and senior doctors alike, may also manifest in the intentions of medical students yet to even enter the profession.

The study invites participants to share their views on many aspects of working in the NHS and how the prospect of working in the NHS could be improved. Data collected from this study could prove helpful in addressing some of the concerns of those making up the future of the profession. In Australia and New Zealand, a questionnaire is distributed each year where the medical deans of medical schools in the country survey final-year medical students and collect data on their background, medical school experience, and any early geographical and specialty preferences for their future career [10]. The information gained has had a lasting positive impact on curriculum development and future medical workforce planning. Additionally, it has assisted in workforce distribution and helped to plan specialist training pathways to meet the career interests of trainees and the public's health needs.

The AIMS study is a national, multi-institutional, and cross-sectional study. AIMS endeavors to understand the factors involved in medical students' decision-making around their future careers. Specifically, we are interested in students' current career plans and why they may or may not intend to pursue specialty training or a medical career in the United Kingdom. We are also hoping to understand current views on the prospect of working in the NHS.

Study Objectives

Primary Objectives

This primary objectives are to determine current medical students' career intentions after graduation and upon completing the foundation program and to ascertain the motivations behind these intentions.

Secondary Objectives

Secondary objectives are as follows:

- To characterize the backgrounds of medical students intending to:
  - emigrate to practice abroad
  - leave medicine permanently
  - undertake further study or a career break
  - not going into further medical training immediately after degree completion or foundation training
- To determine which specialties medical students plan on pursuing
- To analyze medical students' views on how the prospect of working in the NHS could be improved

Methods

Study Design

AIMS is a national, multi-institutional, and cross-sectional study of medical students. Participants' responses will be recorded via a web-based survey platform. The survey contains 71 items, but participants will not view all of them as their visibility depends on their previous answers. The shortest question sequence involves 30 items, and the longest involves 43 items. Questions are structured using a combination of Likert scale

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matrices, multiple-choice options, and free-text entry to broaden the capture of sentiment nuance and improve precision in the data. Data collection began on January 16, 2023, and was completed on March 27, 2023. A full project timeline can be found in Table 1. This timeline will be approached with a level of flexibility, such as for centers with logistical obstacles to data collection.

Table 1. Project timeline.

Dates	Activity
December 12, 2022, to January 9, 2023	Recruitment of collaborators throughout all UK medical schools via social media and communication with medical schools and societies
January 10, 2023, to January 15, 2023	Training of collaborators
January 16, 2023, to March 27, 2023	Study runs nationally for approximately 2 months
March 28, 2023, to June 1, 2023	Data analysis and manuscript preparation

The survey consists of multiple sections. Section 1 of the survey involves a background and demographic section, which all participants will answer. Consent is also obtained in this section. Section 2 focuses on participants' career intentions immediately after graduation and after foundation training (for those entering it). Section 3 invites participants to explore the factors behind their decision-making. Section 4 surveys which specialties the participants are currently inclined to pursue. The final section includes a free-entry text box where participants are invited to articulate how the prospect of working in the NHS could be improved and a question to obtain consent for follow-up studies.

The complete 71-item questionnaire can be found in Multimedia Appendix 1.

To identify gaps in knowledge and inform the aim of the project, a review of existing literature was conducted, including similar questionnaires and qualitative studies on students' and doctors' perspectives. Feedback from senior clinical staff was also obtained. Questions were revised based on the comments received, aiming to ensure they were as nondirective and comprehensive as possible while remaining unencumbering so as to maximize the number of responses for statistical power.

The survey will be hosted on the Qualtrics survey platform (Qualtrics XM), a General Data Protection Regulation (GDPR)–compliant web-based survey platform that supports both mobile and desktop devices. The survey will be distributed through university mailing lists, student society social media pages, conferences, and personal and medical school social media platforms (such as Facebook, Instagram, LinkedIn, and Twitter). To maximize distribution across the United Kingdom, a national network of approximately 200 AIMS Collaborative members was recruited, representing all medical schools in the United Kingdom. Each member will be asked to liaise with their medical school dean to distribute the survey through official channels and advertise it at regular intervals over the collection period from January to March.

Study Population

All current students in all years at UK medical schools recognized by the GMC and the Medical Schools Council are eligible to participate in the study. A list of eligible medical schools and approved programs can be found in Multimedia Appendix 2. It is worth noting that we have excluded schools that, although approved by the GMC, have not yet admitted their first cohort of students since they have no medical students to participate.

Data Collection

The survey will be disseminated primarily through medical student collaborators recruited prior to the study launch. These collaborators will ensure that their medical school is formally engaged at an early stage of this study and will be primarily responsible for disseminating this questionnaire among students at their medical school.

Ethics Approval

Ethical approval was granted by the University of Cambridge Research Ethics Committee (reference PRE.2022.124) on January 5, 2023.

To obtain informed consent, a participant information sheet (Multimedia Appendix 3) will be made available to all participants. This information sheet will explain the rationale and purpose of the study, emphasizing its voluntary nature and the anonymity and confidentiality of participants. It will be made clear on the study materials and on the first page of the questionnaire that submitting responses provides consent for data usage. Additionally, the first question of the survey will obtain consent, and it will be mandatory to complete. Consent can be withdrawn at any time, during or after completing the questionnaire, by contacting the study lead. Email addresses will only be collected and stored for participants who provide explicit consent to this in the final question of the survey. Email addresses will be kept separate from the responses to survey questions, ensuring anonymity.

The anonymous responses will be collected and stored on the secure web-based server, Qualtrics. Survey data will be extracted from Qualtrics and stored in a password-protected Microsoft Excel (version 16.71; Microsoft) file accessible only to the central study team. The University of Cambridge standards for data handling will be followed for all data management and record-keeping.

Participants will not receive compensation for completing the questionnaire. However, participants who provide their contact information will be entered into a prize draw, with one randomly selected individual receiving a cash prize of £300 (US $370.10) at the time of prize draw, at the end of data collection.

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Data Analysis

A sample size calculation was performed, and it was determined that a minimum of 8026 participants are needed to have a confidence level of 95% that the results of the survey are within 1% representation of the total medical student population. This calculation used a population size for UK medical students acquired via a Freedom of Information request to the GMC.

The study will adhere to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines for cross-sectional studies [11]. Descriptive statistics and comparisons between student year groups and other participant characteristics will be used. Appropriate statistical tests will be applied for these comparisons, such as the chi-square test (for categorical variables) and Student *t* test (for continuous variables). For free-text questions yielding qualitative data, a thematic analysis will be conducted using the reflexive approach of Braun and Clarke [12]. Data analysis will be performed using Microsoft Excel and RStudio (version 4.2.1; RStudio, PBC).

Results

Following study completion, teleconferences will be conducted with all collaborators to share and discuss the data analysis undertaken and the study results. Following this, it is intended that results will be presented at local, regional, national, and international conferences. In addition, the results will be disseminated via publication in a peer-reviewed medical journal. All collaborators will be given PubMed-citable collaborative coauthorship under the institutional name "the AIMS Collaborative". We will have a hybrid authorship list of named authors and the institutional collaborative.

Following study completion, medical school collaborators will be able to request their institution-specific data and the analysis performed on said data from the AIMS steering committee. This data will be anonymized. The fully anonymized data set will be made publicly available.

Data collection is currently underway, with the study having launched nationally on January 16, 2023. Data collection was closed on March 27, 2023, and data analysis has commenced. The results are expected to be available later in the year.

Discussion

Previous Literature

Although there have been (1) studies exploring which specialties junior doctors or medical students intend on pursuing [13-18], (2) studies that focused on career intentions of those pursuing one specialty or exploring factors that attract them to one specific specialty [19-35], (3) studies specifically focused on reasons why doctors are leaving the United Kingdom [36-40], (4) studies exploring how medical students and junior doctors feel about specific aspects of working within the NHS [41-44], and (5) studies investigating the desire for a career break post Foundation Year 2 (also known as the "F3") [45-47], there have been no recent, high-powered studies explicitly aimed at medical students, irrespective of current career ambitions or seniority, investigating overall career intentions and correlating it with demographic factors and medical student seniority. There has been one similar study, although it focuses entirely on medical students and their intentions to leave the NHS, which is limited by its low power and lack of subanalysis regarding student seniority and demographic factors [48]. We aim to address these limitations. Additionally, this study will be the first of a series of follow-up surveys of medical students, thus being the first longitudinal study of medical students' career intentions of its kind.

Strengths

Owing to its rigorous collaborator recruitment plans with the aim of high participant recruitment, this study will provide an accurate representation of medical students' intentions regarding practicing in the United Kingdom or abroad, as well as their preferred specialties. This information can be valuable for workforce planning.

The study will determine the current undergraduate consensus on several aspects of working in the NHS, which could help future policymakers prioritize change and better prepare medical schools' junior students for the reality of such aspects.

This study will determine which, if any, of the included demographic factors alter the propensity to pursue different career paths available to a medical graduate, providing insights into potential disparities.

Limitations

The study is limited by its snapshot nature, as it does not capture changes in career intentions over time. However, it is our intention to follow up with consenting participants and determine how their career intentions may have changed.

It is possible that those already intending to exit the profession, emigrate, or are dissatisfied with the current circumstances will be more likely to complete the survey. To mitigate this, we have recruited approximately 200 collaborators who will distribute the survey in their respective medical schools, targeting all medical students. Additionally, the promotional material and the questions have been written not to imply any particular outcome is predicted or sought.

Challenges in recruiting collaborators or ensuring sufficient student responses may impact the achievement of the study's national goals.

The study's response options for each question may be limited, potentially affecting the comprehensiveness of the data. However, an extensive literature review, peer survey testing, and input from senior clinicians provide confidence that the survey will capture the majority of students' career intentions and opinions. Additionally, a free-text box allows participants to express their views more freely.

This study presents a unique opportunity to accurately assess how medical students view their current career prospects and assess the feasibility of potentially implementing a regular, census-like survey of UK medical students to assist the government's efforts in workforce planning and addressing grievances within the workforce, therefore resulting in higher job satisfaction.

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Acknowledgments

This work was supported by Queens' College, University of Cambridge. The institution has had no role in the design of the study, the collection, analysis, and interpretation of data, or in writing the manuscript.

Data Availability

The data sets generated and analyzed during this study will be made publicly available once the study is completed.

Authors' Contributions

TF was responsible for conceptualization, obtaining funding and ethical approval, and drafting the manuscript. TF and AMC were responsible for designing the survey. All authors were responsible for editing and revising the manuscript. RH was responsible for supervision. All authors have read and approved the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
AIMS (Ascertaining the Career Intentions of Medical Students) survey.
[PDF File (Adobe PDF File), 482 KB - resprot_v12i1e45992_app1.pdf]

Multimedia Appendix 2
List of eligible medical schools.
[PDF File (Adobe PDF File), 65 KB - resprot_v12i1e45992_app2.pdf]

Multimedia Appendix 3
Participant Information Sheet.
[PDF File (Adobe PDF File), 104 KB - resprot_v12i1e45992_app3.pdf]

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Abbreviations

AIMS: Ascertaining the Career Intentions of Medical Students
GDPR: General Data Protection Regulation
GMC: General Medical Council
NHS: National Health Service
STROBE: Strengthening the Reporting of Observational Studies in Epidemiology
UKFP: United Kingdom Foundation Programme

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Protocol

Evaluation of Lactobacillus Coryniformis K8 Consumption by Health Care Workers Exposed to COVID-19 (LactoCor2 Project): Protocol for a Randomized Controlled Trial

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Abstract

Background: *Lactobacillus coryniformis* K8 CECT5711 has immune-modulating properties, enhances the immune response to viral antigens leading to the production of specific antibodies, and has anti-inflammatory activity, which may help to prevent uncontrolled inflammatory processes leading to respiratory and other organ failures.

Objective: The purpose of this study is to evaluate the effect of the consumption of a probiotic strain on the incidence and severity of COVID-19 in health personnel who carry out their professional work among patients with infection or suspected infection by SARS-CoV-2.

Methods: This is a double-blind randomized clinical trial in which the experimental group will receive a capsule of *L coryniformis* K8 per day (3×10^9 colony former units/day), and the control group will receive a daily placebo capsule consisting of maltodextrin. A sample size of 314 volunteers was calculated. Volunteers must meet the following inclusion criteria: older than 20 years and active health personnel caring for patients with COVID-19, including all professionals such as medical doctors, nurses, and caretakers at the 2 referral hospitals that treat patients with COVID-19. The main outcome of the clinical trial will be the incidence of symptomatic infection by SARS-CoV-2 in personnel who care for patients with suspected or confirmed COVID-19.

Results: The study had to be extended to the 2 referral hospitals that treat patients with COVID-19 in the province of Granada (Andalusia, Spain); Hospital San Cecilio and Hospital Virgen de las Nieves. A total of 255 individuals met the inclusion criteria and were randomly assigned to one of the 2 groups.

Conclusions: The results of this randomized controlled trial will provide valuable information regarding the administration of *L coryniformis* K8 against COVID-19, including whether there are fewer infectious processes due to this virus or, in case of occurrence, whether the disease is milder in participants taking the probiotic strain.

Trial Registration: ClinicalTrials.gov NCT04366180; http://www.clinicaltrials.gov/ct2/show/NCT04366180

International Registered Report Identifier (IRRID): RR1-10.2196/37857

(JMIR Res Protoc 2023;12:e37857) doi:10.2196/37857

KEYWORDS

COVID-19; coronavirus; Lactobacillus; health care workers; Lactobacilo; trabajadores de la salud; SARS-CoV-2; probiótico

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Introduction

Humans have consumed lactic bacteria throughout history, but it was at the beginning of the 20th century when this consumption was first related to beneficial properties for health [1]. From that moment on, multiple studies both in vitro and in vivo have shown the beneficial effects that the consumption of this type of bacteria, called probiotics, has on health. Effects such as the improvement of intestinal function [2,3], prevention of intestinal infections [4], and immunomodulation have been widely demonstrated [5]. In addition to these beneficial effects, the consumption of probiotics has been related to a reduction in the incidence and severity of respiratory infections [4,6].

Oral administration of lactic acid bacteria has been associated with an increase in innate and acquired immune responses [7,8]. The consumption of certain strains has been shown to induce an increase in IgA related to the anti-infective properties of probiotic bacteria in diarrhea [9,10]. Innate immunity is increased through an increase in the proportion and activity of phagocytic cells of the immune system, such as monocytes and neutrophils. The function of natural killer cells is also enhanced by the consumption of probiotic bacteria [11]. Activation of the innate immune system is essential, as it produces cytokines that will lead to more specialized activation of the specific immune response. It has been suggested that it is through this mechanism that probiotic bacteria activate the immune response, thus being able to function as adjuvants in vaccination processes [12].

The European Food Safety Agency (EFSA) has published guidelines on how studies should be conducted to demonstrate the effect of a probiotic or natural ingredient on the immune system. Among its recommendations is the use of vaccination protocols that demonstrate how the administration of the probiotic translates into an improvement in the response to an antigen [13]. Recently, a study carried out at the Center Institute of Food Science and Technology and Nutrition of the Spanish National Research Council demonstrated that the administration of *Lactobacillus coryniformis* K8 CECT5711 increases the response of specific antibodies against hepatitis A in a vaccination protocol against this virus [14]. In addition, a certain effect on memory T-helper lymphocytes was observed, which increased in the probiotic group with respect to baseline values (mean 660, SD 223 cells/µL vs mean 551, SD 213 cells/µL). These results highlight the potential of this probiotic strain to improve the immune response against viral antigens.

To evaluate this activity that boosts the immune response, another study was carried out in an older population. This population is more susceptible to infections due to the characteristic immunosenescence of age. A total of 98 older people residing in nursing homes participated in this study. The volunteers received a daily capsule of *L coryniformis* K8 CECT5711 (3×10^9 colony former units/day) for 2 weeks prior to being vaccinated against the flu or a placebo. The percentage of seroconversion was higher in the group receiving the probiotic than in the control group (93.1% vs 72.7%; *P*=.04). During the months of October to April, the volunteers were monitored, and the incidence of local symptoms associated with respiratory infections (sore throat, cough, and nasal congestion) was 48% lower in the group that received the probiotic strain than in the control group (*P*=.007). Furthermore, the consumption of analgesics was significantly reduced in this group by 86% (*P*=.008) [15]. This latest study corroborates the strain's ability to improve the immune response against viral antigens even in the older population.

We are currently experiencing a pandemic due to COVID-19 (the English acronym for COVID-19), which started in the Chinese city of Wuhan in December 2019. Having reached more than 100 territories, the disease was declared a pandemic by the World Health Organization on March 11, 2020 [16]. The number of confirmed cases continued to grow until reaching 5,371,660 cases worldwide on May 22, 2020. In Spain, at the end of May 2020, despite the containment measures initiated in early March, more than 235,772 cases were registered, and of these patients, more than 27,940 died [17].

The COVID-19 infection produces flu-like symptoms, including fever, dry cough, dyspnea, myalgia, and fatigue. In severe cases, it is characterized by pneumonia, acute respiratory distress syndrome, and septic shock, which lead to death in approximately 3% of those infected. Transmission occurs through small droplets that are emitted when speaking, sneezing, or coughing by a carrier and pass directly to another person through inhalation or by contact with contaminated objects in the recipient's nasal and ocular mucous membranes. Symptoms start after approximately 7-20 days of exposure, and prevention at the population level consists of frequent hand washing, disinfecting surfaces with alcohol, and avoiding close contact with other people [15].

Some drugs have been proposed as antiviral treatments, such as hydroxychloroquine, lopinavir, ritonavir, and others; severe pneumonia is treated with broad-spectrum antibiotics. There is no up-to-date, effective treatment for the COVID-19 infection.

An article published in March 2020 shows how the immune response to the COVID-19 virus is similar to the response generated by the influenza virus [18]. Some authors propose the use of probiotics as a strategy to mitigate the effects of viruses [19].

Health care workers (HCWs) are at increased risk of COVID-19 infection due to close contact with highly infectious patients as well as exposure to undiagnosed or subclinical infected cases. The stress and physical exhaustion associated with the pandemic may also impact the immune response of HCWs [20]. A recent study examined 97 studies and found that approximately 11% of patients with COVID-19 were people with underlying disease [21]. This represented a considerable percentage of all COVID-19 cases [22]. Although the number of severe cases and mortality among HCWs was lower than in other populations [21], the number of COVID-19 cases has led to a shortage of HCWs, thus adding an extra burden to the fight against this pandemic.

It has been suggested by several authors that probiotics could play a role in preventing and alleviating the severity of COVID-19 due to their immune-modulating, anti-inflammatory, antioxidant, and antiviral properties [23-25]. The *Loigolactobacillus coryniformis* K8 CECT 5711 strain has been

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shown to have the immune-modulating capacity in adults [26] and children [27,28]. Research has shown that this strain causes an increase in hepatitis A virus antibody levels after oral administration in healthy adults as part of hepatitis A vaccination [14]. A study in older people found that the administration of *L coryniformis* K8 strengthened the immune response to influenza vaccination and reduced symptoms associated with respiratory infections [15]. A recent randomized controlled trial conducted with nursing home residents showed the benefits of *L coryniformis* K8 in the COVID-19 pandemic. This is because it may enhance the specific immune response following COVID-19 infection and also aid vaccine-specific responses among the older population [29].

In this context, it is proposed that the immunomodulatory properties of *L coryniformis* K8 CECT5711 might be useful for COVID-19 management.

Methods

Aim of the Study

The objective of this study is to evaluate the effects of the consumption of *L coryniformis* K8 on the incidence and severity of symptomatic infection by SARS-CoV-2 and the severity of COVID-19 in HCWs who carry out their professional work among patients with infection or suspected infection by SARS-CoV-2 at 2 referral hospitals that treat individuals with COVID-19 in the province of Granada (Andalusia, Spain).

Description of Treatments

The administration of the experimental product and the placebo will be carried out in the form of a gelatin capsule that will have the same weight, consistency, and color.

The Experimental Group will receive hard gelatin capsules that will contain 3×10^9 colony forming units of *Lcoryniformis* K8 (120 mg), 10 mg magnesium stearate, and 120 mg maltodextrin.

The control group will receive hard gelatin capsules that will contain magnesium stearate (10 mg) and maltodextrin (220 mg). Individuals from both groups will take 1 capsule a day (preferably with dinner).

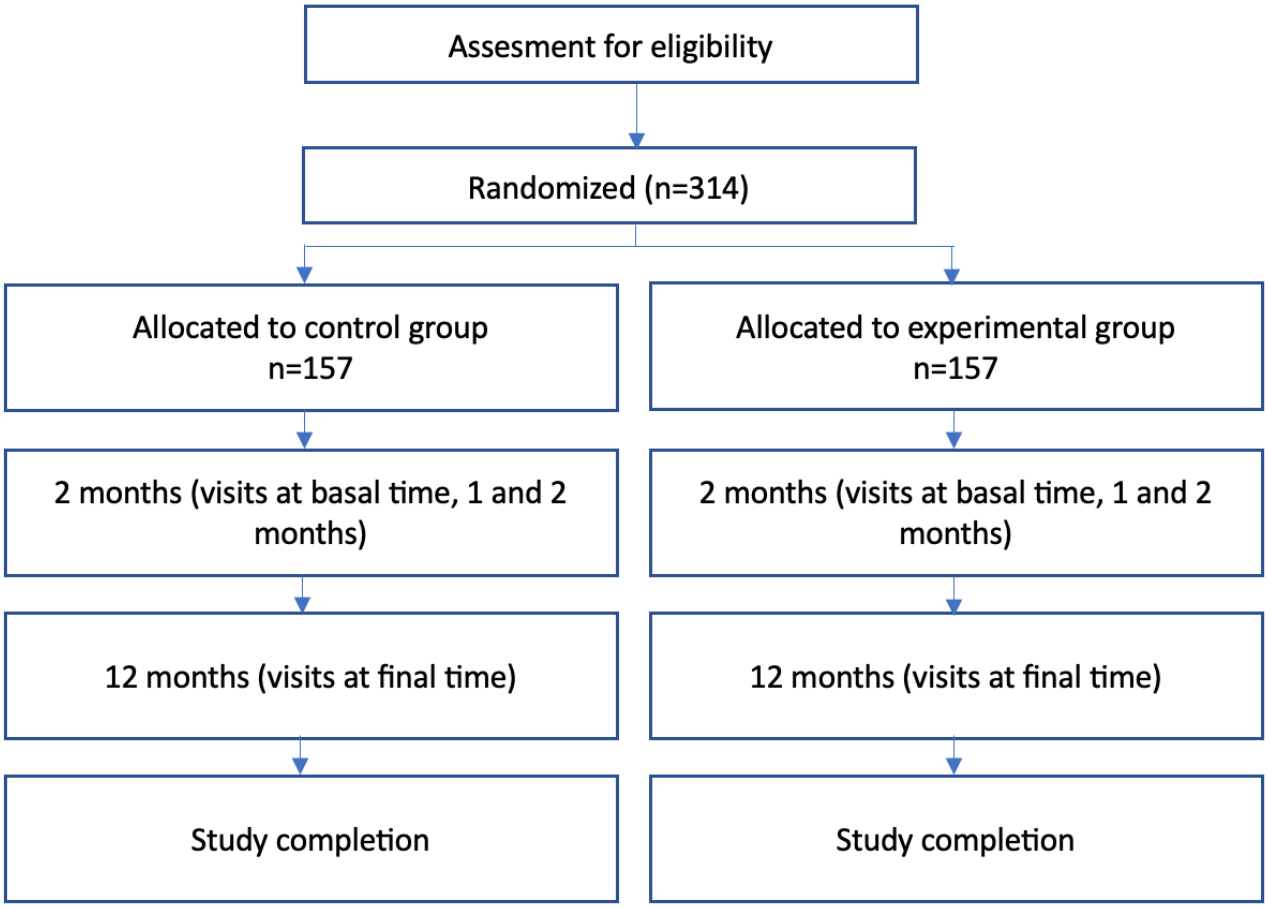
Capsules for the probiotic and placebo will be provided by Biosearch Life (Granada, Spain).

Study Design

The study is a nutritional, randomized, double-blind, controlled, and parallel-group observational prospective cohort study. Volunteers will be distributed into 2 groups: a control group and an experimental group. The study will be performed as shown in Figure 1.

The trial has been registered on ClinicalTrials.gov (NCT04366180).

Figure 1. Study flowchart.



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Ethics Approval

This clinical research protocol has been prepared with full understanding and in accordance with the standards of Good Clinical Practice in accordance with CPMP/ICH/135/95, the Declaration of Helsinki (64th General Assembly, Fortaleza, Brazil, October 2013), ISO 14155, and all relevant national guidelines. All investigators participating in the study are appropriately qualified. The protocol was approved by the Research Ethics Committee for the province of Granada (3/2020_P_054; CEIM/CEI Province of Granada). Volunteers will be included in the study after informed written consent is obtained.

Participants, Intervention, and Outcomes

Inclusion Criteria

The inclusion criteria included individuals older than 18 years and active HCWs, including all professional categories such as medicine, nursing, and caretaking, who attend cases classified as positive or suspicious for COVID-19 in the emergency department, intensive care unit (ICU), or in the wards designated to care for such patients; and the ability to complete the surveys and having signed the informed consent.

Exclusion Criteria

The exclusion criteria excludes individuals with a positive test for COVID-19 confirmed by polymerase chain reaction or serology, individuals with concomitant pathology such as HIV, transplantation, active cancer, or other active immunosuppression, and women who are pregnant or intend to become pregnant in the subsequent months.

Recruitment

The recruitment of participants will take place at the San Cecilio University Clinical Hospital and at the Virgen de las Nieves University Hospital in Granada among HCWs with high exposure to patients with COVID-19.

Randomization, Allocation, and Blinding

Patients will be randomly allocated to a control group or experimental group in a 1:1 ratio by the block randomization method with a block size of 4. Participants and investigators will be blinded to the treatment allocation during the course of the intervention. The blind will be broken after statistical analysis is completed.

Capsules for the control and experimental groups will be provided in white containers labeled with a random number.

Intervention

Participants meeting the inclusion criteria will be randomly assigned to the control or experimental group. During the intervention, participants will be asked to ingest a capsule per day with some food (preferably with dinner). Follow-up visits will be scheduled at the beginning, midpoint (1 month), and end of the intervention period (2 months). At the first visit, baseline data (age, sex, lifestyle, medication, concomitant diseases, and current symptoms) will be collected. At follow-up visits, data about symptoms, medication, and adverse effects will be recorded (Table 1).

Table 1. Detailed study procedures.

Visits (V) per week (W)	V1 (W0)	V2 (W4)	V3 (W8)	V4 (12 months)
Informed consent form	✓			
Inclusion or exclusion criteria	✓			
Randomization or allocation	✓			
Treatment distribution	✓			
Basal data	✓			
COVID-19 test	✓	✓[a]	✓	
Symptoms questionnaire		✓	✓	
Medication questionnaire	✓	✓	✓	
Adverse effects questionnaire		✓	✓	
Return of unconsumed capsules			✓	
Evaluation of the immune response to the vaccine				✓

[a]COVID-19 test data would be collected only if performed.

Outcomes Measures

Primary Outcomes

The main outcome will be the incidence of symptomatic SARS-CoV-2 infection confirmed by polymerase chain reaction or serology in HCW caring for patients with suspected or confirmed COVID-19 at the San Cecilio Clinical University Hospital and at the Virgen de las Nieves University Hospital.

Secondary Outcomes

Incidence of hospital admissions caused by SARS-CoV-2 infection, the incidence of ICU admissions caused by SARS-CoV-2 infection, the incidence of pneumonia caused by SARS-CoV-2 infection, the incidence of the need for oxygen

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support, the incidence of gastrointestinal symptoms, days with a body temperature of >37.5 °C, days of persistent cough, days of persistent feeling of fatigue, and use of pharmacological treatments. Data for mild symptoms will be recorded daily in the notebook of the volunteer, and, in the case of hospitalization, data will be collected by investigators from medical histories.

In addition, the immune response and side effects of the COVID-19 vaccine in these HCWs will be assessed. Data will be collected on the vaccines received by the HCWs, including the name and type of vaccine, doses received, date of vaccination, and immune response of the HCWs.

Withdrawal, Dropout, Discontinuation, and Compliance

Withdrawal will be allowed at any time during the trial. Investigators may recommend discontinuing the trial if, in their opinion, staying in the study would be detrimental to the participant's well-being. This decision must be based on the appearance of an adverse effect that will be duly included in the case report form.

Volunteers will return the unconsumed capsules. Compliance ≤80% of the total will be considered a violation of the protocol and will be considered dropouts.

Adverse Effects

L coryniformis species are included in the Qualified Presumption of Safety list published by the EFSA, which guarantees safety for consumption [30]. On each visit, it will be monitored for adverse effects, which will be recorded in the patient's medical history and evaluated by the principal investigator. In the event of serious adverse events considered related to the experimental product, the researcher will inform the health authorities and the Clinical Research Ethics Committee involved in the clinical trial.

Sample Size

Given that the current rates of infection among health professionals worldwide are very different, the sample size has been based on the comparison of 2 independent proportions for the use of the chi-square test. For an α of 5% and a power of 80%, taking a percentage of affected individuals in the control group of 15% and 10% as the minimum meaningful difference to be detected, a sample of 157 per branch would be necessary, taking into account a loss of 10% of participants.

Statistical Analysis

Due to the urgency of the circumstances of the pandemic, the statistical methods have not been fully planned. A statistical analysis plan will be prepared during the execution of the study and before the closure of the database. The statistical methods to be used, the strategy to be followed in the case of missing values, and the tables and figures to include in the statistical report will be described in detail.

The sample size has been calculated assuming 10% dropouts. It is not planned to replace withdrawal participants. Intention-to-treat analysis will be carried out, taking into account all the data of the recruited volunteers, even if they have not completed the intervention.

In general, the data will be presented as absolute frequencies and percentages in the case of qualitative variables. For the quantitative variables, central tendency statistics, such as the mean and median, and dispersion statistics, such as the SD, IQR, minimum and maximum values, and to indicate the shape of the distribution, shape measures such as coefficients of skewness and kurtosis, will be used. In the case of ordinal variables, depending on the number of categories, one form or another of description will be used. In all cases, a column that includes the number of volunteers with available data must be added to the data presentation table. The analyses will be divided by randomization group.

To analyze the comparisons between groups, parametric tests (Student *t* test or ANOVA) and nonparametric tests (Mann-Whitney *U* or Kruskal-Wallis) will be used for continuous variables according to the characteristics of the study variables (assumption normality), while for categorical variables, chi-square tests or Fisher exact tests will be used.

In the case of between-visit comparisons of continuous variables, parametric tests (Student *t* test for paired data or repeated measures ANOVA) and nonparametric tests (Wilcoxon or Friedman) will be used, as appropriate, according to the characteristics of the study variables (assumption of normality) and the number of visits to be compared, while the categorical variables will be compared using the McNemar test. The effect size will be estimated using CIs.

The significance level of the statistical tests used will be .05. All calculations will be performed with the SPSS statistical software package (version 26; IBM Corp).

For the analysis of adverse events, a descriptive analysis (frequencies and percentages) will be carried out throughout the study, presenting a list of the adverse events grouped according to severity. These events will be listed by volunteer and randomization groups.

Adverse events and concomitant medication will be coded using a standardization system. In the case of adverse events, the most current version of the MedDRA system will be used, and for concomitant medication, the ATC code will be used.

Data Management

To further ensure the accuracy and reliability of the collected data, a thorough process of data cleansing will be implemented before computerization at the coordinating center in Granada, Spain. Any errors or inconsistencies identified during this process will be rectified or clarified with the relevant source documents or database managers. The source documents and databases will also be subjected to regular data cleansing procedures to maintain their integrity throughout the minimum 5-year retention period after the study's conclusion. Additionally, any personal information will be carefully screened and removed as part of the data cleansing process to guarantee anonymity and confidentiality.

Dissemination

Communications and scientific reports that emerge from this study will be carried out under the responsibility of the principal investigator in agreement with the associated investigators.

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Publication rules will follow international recommendations. The findings will also be shared with national health authorities.

Authorship will follow the guidelines established by the International Committee of Medical Journal Editors [31], which require substantive contributions to the design, conduct, interpretation, and reporting of a trial.

Results

The study had to be extended to the 2 referral hospitals that treat COVID-19 cases in the province of Granada (Andalusia, Spain), Hospital San Cecilio and Hospital Virgen de las Nieves because the projected recruitment was not sufficient for the objective of the study and it was necessary to expand the sample obtained in order to reach as close as possible to the calculated sample. Finally, 255 volunteers were recruited and randomly distributed into 2 groups: the control group (n=128) and the probiotic group (n=127). In order to measure additional secondary outcomes, the project was kept open by collecting data related to vaccines and immune responses. The study started in July 2020, with the first part of the study ending in September 2020. In order to measure additional secondary outcomes, the project was kept open by collecting data related to vaccines and immune responses until September 2021. We will start analyzing responses in July 2023, with publication of results expected in the second half of 2023.

Discussion

Principal Findings

This study is conducted to evaluate the efficacy of the effects of *L coryniformis* K8 consumption on the incidence and severity of COVID-19 in HCWs working with SARS-CoV-2–infected or suspected patients in referral hospitals for patients with COVID-19 in the province of Granada. This randomized controlled trial aims to study whether the consumption of *L coryniformis* K8 will reduce the incidence of SARS-CoV-2 infection in the staff caring for patients with suspected or confirmed COVID-19 disease at the San Cecilio University Hospital and Virgen de las Nieves University Hospital. For this purpose, the incidence of hospital admissions caused by SARS-CoV-2 infection, both in the general hospitalization area and in the ICU area, will be studied in HCWs caring for SARS-CoV-2–infected patients.

It is important to determine the prevalence of pneumonia caused by SARS-CoV-2 infection and the need for oxygen supply to these patients. The presence of fever will be studied, and the number of days will be quantified, as well as the persistence of cough and feeling of fatigue. On the other hand, it will also be assessed whether these workers have needed pharmacological treatment.

This intervention aims to shed light on the use of probiotics to enhance the immune effect against SARS-CoV-2. In addition, this intervention study aims to contribute to the understanding of the effect of taking probiotics to improve the immune response to vaccines against SARS-CoV-2. An article published in March 2020 shows how the immune response to the COVID-19 virus is similar to the response generated by the influenza virus [18]. When the immune system works properly, the first barrier to SARS-CoV-2 is the innate response. This innate response, characterized by interferon and cytokines, which are small proteins responsible for symptoms such as fever, headaches, and muscle pain, has 2 functions: to slow down the replication and spread of the virus until the specific immune response (which, when it is a virus that has not been previously contacted, takes approximately 2 to 3 weeks) is activated. The specific immune response is what will stop and ultimately eliminate the infection. This specific response also controls the innate response in order to prevent excessive activity from damaging the tissues. When this response works in a correct and coordinated manner, the infection is overcome, showing symptoms more or less similar to those of the flu. However, in an older population experiencing dysfunction of the age-related immune response, called immunosenescence, or in a population in which the response appears to be poorly coordinated, the innate response occurs later or is ineffective, giving the virus time to replicate and spread and delaying the activation of the specific response. Before the massive invasion of tissues, the innate response exaggeratedly damages tissues, causing respiratory failure and failure in other organs, such as the kidney. Given this situation, some authors speak of 3 disease states that require different approaches: an asymptomatic state, a second state with nonsevere symptoms, and a third state with severe respiratory symptoms and a high viral load. During the first 2 states, a specific immune response is required to eliminate the virus and prevent the disease from progressing to state 3. In this phase, strategies to enhance the immune response are important. However, in state 3, when the immune system has failed and the virus has spread, the damage to the tissues causes a massive inflammatory response; the strategy should be aimed at controlling that inflammation [27]. Several clinical trials have evidenced the positive effects of certain probiotic strains on the prevention of respiratory tract infections. In fact, some authors propose the use of probiotics as a strategy to mitigate the effects of SARS-CoV-2 [19]. Mechanisms that would be involved in a positive effect of probiotic treatments on respiratory viruses include enhancement of the intestinal epithelial barrier, competition with pathogens for nutrients and adhesion to the intestinal epithelium, production of antimicrobial substances, and modulation of the host immune system [19]. *L coryniformis* K8 CECT5711 has immunomodulatory properties that could be useful for COVID-19 management. On the one hand, we have previously discussed its ability to improve the immune response against viral antigens, leading to the production of specific antibodies [14,15]. On the other hand, the strain has been shown in animal experiments to have anti-inflammatory capacity in models of inflammation [3,27]. This anti-inflammatory activity would also be of interest in the case of COVID-19, as it could help prevent uncontrolled inflammatory processes from leading to respiratory and other organ failure.

The working hypothesis is that the administration of *L coryniformis* K8 will stimulate the immune response of people exposed to COVID-19, acting as an adjuvant that contributes to developing an effective response against the virus, and therefore fewer infectious cases are presented due to this virus

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or, in the event of an occurrence, the disease is milder among the participants taking the probiotic strain.

The high degree of exposure among HCWs puts them at high risk of contracting the virus. If we add to this situation the fact that the stress and physical overexertion caused by the pandemic can affect the immune response, the risk increases even more. The study has been designed to demonstrate if the consumption of these probiotic bacteria might contribute to reducing the level of incidence, or at least the severity of infection, in this population.

Conclusions

Further knowledge in this area could lead to an improvement in the immune response of HCWs to noninfection with SARS-CoV-2 or to a reduction of symptoms in cases of infection. This would ensure that HCW workforces are not impaired in their ability to cope with SARS-CoV-2 and that those infected with SARS-CoV-2 are able to return to work more quickly than those who do not take probiotic supplements.

Acknowledgments

We thank all participants for their valuable contributions. We would especially like to thank the managing directors of the San Cecilio and Virgen de las Nieves University Hospitals.

Data Availability

The data sets generated during this study are available from the corresponding author upon reasonable request.

Authors' Contributions

All authors participated in the writing and reading of the manuscript and approved the final version.

Conflicts of Interest

None declared.

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Abbreviations

EFSA: European Food Safety Agency
HCW: health care worker
ICU: intensive care unit

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Protocol

Feasibility and Effectiveness of an Intervention to Reduce Intimate Partner Violence and Psychological Distress Among Women in Nepal: Protocol for the Domestic Violence Intervention (DeVI) Cluster-Randomized Trial

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Abstract

Background: Intimate partner violence (IPV) disproportionately affects people in low-and middle-income countries (LMICs), such as Nepal. Women experiencing IPV are at higher risk of developing depression, anxiety, and posttraumatic stress disorder. The shortage of trained frontline health care providers, coupled with stigma related to IPV and mental health disorders, fuels low service uptake among women experiencing IPV. The Domestic Violence Intervention (DeVI) combines the Problem Management Plus counseling program developed by the World Health Organization with a violence prevention component.

Objective: This study aims to implement and evaluate the feasibility, acceptability, and effectiveness of DeVI in addressing psychological distress and enabling the secondary prevention of violence for women experiencing IPV.

Methods: A parallel cluster-randomized trial will be conducted across 8 districts in Madhesh Province in Nepal, involving 24 health care facilities. The study will include women aged 18-49 years who are either nonpregnant or in their first trimester, have experienced IPV within the past 12 months, have a 12-item General Health Questionnaire (GHQ-12) score of 3 or more (indicating current mental health issues), and have lived with their husbands or in-laws for at least 6 months. A total sample size of 912 was estimated at 80% power and $\alpha<.05$ statistical significance level to detect a 15% absolute risk reduction in the IPV frequency and a 50% reduction in the GHQ-12 score in the intervention arm. The health care facilities will be randomly assigned to either the intervention or the control arm in a 1:1 ratio. Women visiting the health care facilities in the intervention and control arms will be recruited into the respective arms. In total, 38 participants from each health care facility will be included in the trial to meet the desired sample size. Eligible participants allocated to either arm will be assessed at baseline and follow-up visits after 6, 17, and 52 weeks after baseline.

Results: This study received funding in 2019. As of December 29, 2022, over 50% of eligible women had been recruited from both intervention and control sites. In total, 269 eligible women have been enrolled in the intervention arm and 309 eligible women in the control arm. The trial is currently in the recruitment phase. Data collection is expected to be completed by December 2023, after which data analysis will begin.

Conclusions: If the intervention proves effective, it will provide evidence of how nonspecialist mental health care providers can address the harmful effects of IPV in resource-constrained settings with a high burden of IPV, such as Nepal. The study

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findings could also contribute evidence for integrating similar services into routine health programs in LMICs to prevent IPV and manage mental health problems among women experiencing IPV.

Trial Registration: ClinicalTrials.gov NCT05426863; https://clinicaltrials.gov/ct2/show/NCT05426863

International Registered Report Identifier (IRRID): DERR1-10.2196/45917

(JMIR Res Protoc 2023;12:e45917) doi:10.2196/45917

KEYWORDS

intimate partner violence; intervention; violence prevention; mental health; cluster-randomized trial; depression; anxiety; posttraumatic stress disorder; low-income country; women; Nepal

Introduction

Background

Intimate partner violence (IPV) against women is a significant public health problem worldwide [1]. IPV encompasses various behaviors, such as physical, psychological, and sexual harm or controlling behavior, primarily perpetrated by male partners/husbands, ranging from verbal abuse to assaults and even murder [2]. Worldwide, one-third of women experience physical or sexual violence, often perpetrated by their intimate partners [3]. The COVID-19 pandemic has exacerbated this problem, with approximately 50% of women aged 15-49 years reporting that they either experienced violence themselves or knew someone who did [4]. Low- and middle-income countries (LMICs), including Nepal, witness higher rates of IPV. During the first wave of the pandemic, gender-based violence among women and girls increased by 2.7% in Nepal compared to the prepandemic period [5]. A nationwide survey conducted in Nepal found that 26% of ever-married women aged 15-49 years had experienced physical, sexual, or emotional violence from their husbands/partners at least once in their lives, with physical violence being the most prevalent form (23%) of IPV (Figure 1) [6]. Among Nepal's 7 provinces, Madhesh Province (formerly known as Province 2) has the highest prevalence (37%) of spousal violence/IPV [6].

IPV is a prevalent form of violence against women and is linked to various adverse health and socioeconomic outcomes for survivors. Women who experience IPV are 2.5 times more likely to develop mental and neurological issues, such as depressive symptoms and disorders, suicidal ideation and behavior, and poor psychological adjustment, than those who have not experienced IPV [2]. A systematic review found that pregnant women who have experienced domestic violence (IPV or violence perpetrated by another family member or both) are 3 times more likely to experience postnatal depression [7]. Moreover, there is an increased risk for mental health problems, communicable diseases, health risk behaviors, and reproductive health issues, including pregnancy-related complications [2,7]. A cross-sectional study conducted in Nepal in 2017, involving 397 married women, reported that those who had experienced IPV at any point in their lives were nearly 5 times more likely to have depression compared to those who had never experienced IPV [8]. Common mental disorders significantly contribute to functional impairments and disabilities and severely impact one's quality of life [9]. Recent studies have demonstrated a bidirectional relationship between mental health issues and victimization. For example, research linking depression and posttraumatic stress disorder (PTSD) resulting from IPV also indicates an increased risk for future victimization [10].

Despite increasing recognition of the mental health and social needs of women who have experienced or are experiencing IPV, the programs or interventions aimed to address their needs are still in infancy, particularly in resource-constrained countries. The literature indicates that the shortage of trained health care providers, leading to poor recognition of violence against women, particularly IPV episodes, coupled with the reluctance of women to disclose and seek support for their experiences with violence has made it difficult to manage IPV and its consequences [11-13]. About two-thirds of the women experiencing violence in Nepal never seek help or tell anyone [6] probably due to low expected support, stigma, and fear that the violence will increase. Mental health is not a national priority in Nepal, reflected by the low availability of mental health services (only 1.5 beds per 100,000 people for in-patient care [14]) and almost nonexistent services in rural areas. Investment in human resources for mental health is extremely low: 0.68 psychiatrists and 0.17 psychiatric nurses per 100,000 people (ie, 200 psychiatrists and 50 psychiatric nurses in total to serve almost 30 million people [14]), which is significantly lower than the average of 6 mental health workers per 100,000 population in LMICs and 70 mental health workers per 100,000 population in high-income countries [15]. This indicates an urgent need for developing interventions that are effective in reducing IPV and associated mental health consequences, while improving access to health care services that do not require highly trained professionals.

On a positive note, growing evidence suggests that psychological interventions delivered by nonspecialist mental health care providers are effective in reducing psychological distress among women experiencing IPV [12]. The World Health Organization (WHO) Mental Health Gap Action Programme includes evidence-based psychological interventions for priority mental health conditions to be delivered by nonspecialists in primary health care settings in LMICs. One promising example developed by WHO is a low-intensity 5-session counseling program known as Problem Management Plus (PM+) [16]. PM+ is a nonintrusive technique for managing stress and solving problems, strengthening social support, and sustaining change. This intervention is based on established cognitive behavioral therapy and problem-solving techniques to manage depression, anxiety, and stress regardless of cause and has been evaluated in randomized controlled trials and found to be effective at reducing psychological distress among women experiencing

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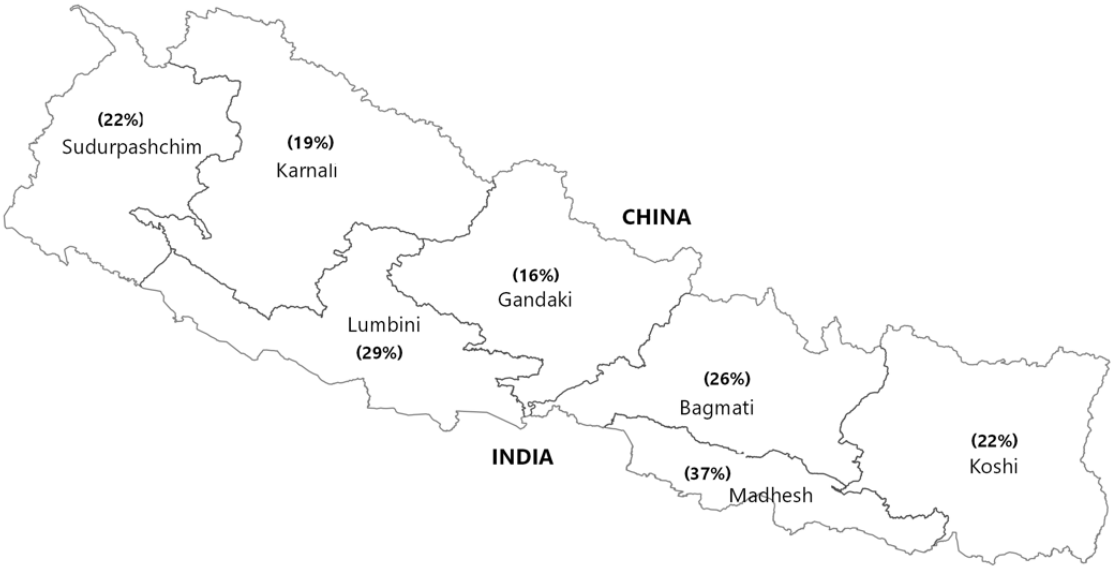
IPV in Kenya [12] and improving mental health outcomes in conflict settings in Pakistan and earthquake-affected communities in Nepal [17,18].

In high-income countries, several interventions have been introduced to prevent or reduce the effects of IPV [11,19], including counseling interventions, using empathetic listening and psychotherapies, which have demonstrated promising results [11,19,20]. IPV interventions ideally incorporate the development of a safety plan for women to rescue themselves from difficult situations of violence [11,19,20].

The PM+ intervention primarily focuses on managing the consequences of violence on mental health, but it lacks comprehensive components that specifically address the root cause, namely the violence itself. To bridge this gap, the Domestic Violence Intervention (DeVI), proposed in this study protocol, was developed by augmenting PM+ with other violence prevention elements, such as education on the cycle of violence and its impact on health, development of a safety plan, and empowerment-based counseling. Components such as areas of safety, choice making, and problem solving [20,21] were adapted from previous studies [22-24].

The name of the intervention, "DeVI," an integrated, multicomponent tool, is a neutral term that will be used throughout the trial while communicating with the research team and the participants. In Nepali, and originating from Hinduism, *devi* means *goddess* or *supreme woman deity*.

Figure 1. Map of Nepal showing the percentage of married girls and women aged 15-49 years who have experienced physical, sexual, or emotional violence committed by their spouse [6].



Study Aim

This study aims to implement and evaluate the feasibility, acceptability, and effectiveness of DeVI in addressing psychological distress and enabling the secondary prevention of violence for women experiencing IPV through a cluster-randomized trial. The program will be delivered through nonspecialist mental health care providers in public health institutions to increase the feasibility and applicability of such interventions in an LMIC setting. The study will be conducted in Madhesh Province, Nepal, which has the highest-reported prevalence of spousal violence/IPV [6].

Specific Objectives

The study aims to achieve the following objectives:

- Objective 1: Assess the feasibility of DeVI in health care facilities in Nepal by exploring the views of key stakeholders, health care providers, and local women in the community.
- Objective 2: Train nonspecialist mental health care providers in the delivery of DeVI among women experiencing IPV.
- Objective 3: Explore participants' and health care providers' experiences with DeVI and the opportunities and challenges encountered during implementation.
- Objective 4: Measure the effectiveness of DeVI in addressing and resolving psychological distress, reducing the occurrence of IPV, and developing safety strategies for women experiencing IPV.
- Objective 5: Measure the impact of training health care providers in DeVI on their knowledge, attitudes, skills, and stigma toward IPV and the social and health-related consequences of IPV.

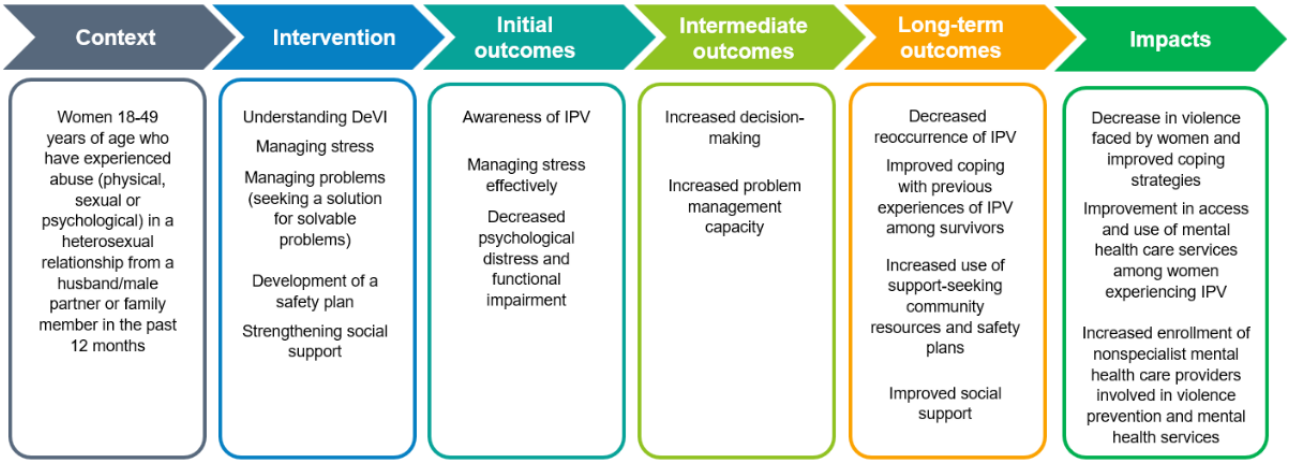
Conceptual Framework of the Study

DeVI will be administered to women who have a history of any form of IPV (physical, sexual, or psychological) and are experiencing or have experienced psychological distress. The primary aim of this intervention is to decrease exposure to IPV and IPV-related distress. The intervention aims to enable women to cope with previous experiences of IPV and manage their situation better, strengthen mental well-being, and prevent revictimization (ie, protect participants from future harm). The intervention also aims to aid in the participants' development of a personal safety plan and strategies, encourage the identification of available support (of any form) in the

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community, and use it effectively, when needed. Participants who show severe mental impairment, have suicidal thoughts, or are at risk of suicide after participating in the intervention will be handled per the risk management plan. Figure 2 depicts the conceptual framework of this study in brief.

Figure 2. Conceptual framework of DeVI, including expected outcomes. DeVI: Domestic Violence Intervention; IPV: intimate partner violence.



Methods

Ethical Considerations

This study was approved by the Ethical Review Board of the Nepal Health Research Council (approval no. 852/2019), and permission was obtained from the Ministry of Health and Population, the Health Directorate of Madhesh Province, and all study sites. The study will follow the *Ethical and Safety Recommendations for Intervention Research on Violence against Women* developed by WHO [25]. Participation in the study is voluntary, and participants have the right to refuse or withdraw at any point without providing a reason. Written informed consent will be obtained from all participants. In cases where participants are unable to read or write, a witness will be present during the consent process. Women needing more time to decide will be asked to communicate their decision during their next health care facility visit. Given the sensitivity of IPV/domestic violence, speaking openly about such experiences can be challenging due to shame, stigma, fear, and pressure. To address this, intervention implementers will receive training to create a comfortable environment where survivors of violence can feel at ease sharing their experiences. Further, the intervention will be conducted in a private room.

Study Design and Setting

This study is designed as a 2-arm parallel cluster-randomized trial comparing the study outcomes in the intervention arm to those in the usual standard-of-care (control) arm. The study protocol has been devised in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines for cluster-randomized trials [26].

The trial will be conducted across 8 districts of Madhesh Province, Nepal, which has the highest prevalence of IPV and poorer sexual and reproductive health outcomes indicators compared to other provinces [6]. Although the legal age of marriage under Nepali law is 20 years [27], women in Madhesh Province tend to marry 4 years earlier and are less likely to be literate than women in other provinces [6]. Poor socioeconomic conditions, low awareness of personal and human rights, poor quality of life, and traditional norms are contributors to IPV [28] and are common in Madhesh Province.

The study will be carried out in 24 health care facilities (only public hospitals and selected primary health care centers), both rural and urban, since these types of facilities constitute a major proportion of facilities available in the province that provide a range of services to the public and are visited by patients from diverse backgrounds. Some of the selected public hospitals, typically at the district level or higher, also offer integrated services for survivors of violence through 1-stop crisis management centers. These specialized centers offer a platform for women and care providers to exchange information regarding available measures to combat violence against women, as well as referrals for additional legal services, if necessary, and will enhance our comprehension of the effectiveness of interventions within the current context.

A total of 63 frontline female health care providers (eg, nurses and auxiliary nurse midwives [ANMs]) were trained to deliver DeVI: 33 (52%) health workers from the intervention sites and 30 (48%) health workers from the control sites. Of these, 9 (27%) health workers from the intervention sites and 8 (27%) from the control sites received training to be backups for the intervention implementation or data collection if the primary implementor or data collector was unavailable due to unforeseen circumstances, such as transfer to another health care facility, illness, or pregnancy.

Formative Assessment and Consultation Workshop

A formative assessment was conducted during a preliminary site visit before the commencement of the trial in order to explore the behavior, experiences, opinions, and knowledge of key stakeholders, health care providers, and women experiencing IPV/domestic violence. A qualitative approach using focus group discussions (FGDs), in-depth interviews (IDIs), and key informant interviews (KIIs) was followed to collect data for the formative assessment. The key stakeholders included were women experiencing IPV/domestic violence, local health care providers, women seeking care in the outpatient department,

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representatives from various community-based organizations, and individuals/experts from federal and provincial levels. A total of 21 interviews, including 15 (71%) IDIs with health care providers, 3 (14%) IDIs with women visiting the outpatient department, and 3 (14%) KIIs with the stakeholders, and 1 FGD with women experiencing IPV were conducted in Nepali by trained field interviewers.

The FGD explored the women's knowledge, attitudes, and opinions about IPV/domestic violence, as well as personal experiences of violence and its mental, physical, and social impacts. The FGD further explored the challenges these women faced while coping with past experiences of violence, along with barriers to and facilitators of seeking help from a victim's perspective. IDIs with local health care providers focused on existing models of care for women experiencing IPV/domestic violence and their perceptions, experiences, and challenges in managing IPV/domestic violence. IDIs with women seeking care explored their general perspectives of IPV/domestic violence. KIIs with various key stakeholders from different community-based organizations and local nongovernmental organizations (NGOs) explored their role, perceptions, and challenges in preventing and managing IPV/domestic violence. Furthermore, these interviews explored health care providers' suggestions and feedback on DeVI's ability to address psychological distress issues and reduce the recurrence of IPV/domestic violence in communities in which they have been working.

National-level consultation workshops with experts in the field of IPV and mental health were also conducted. Their feedback on the study intervention and tools was acknowledged, and our intervention was updated accordingly. Findings from the formative assessment and consultation workshops were used to adapt the data collection tools and intervention according to the local, social, and cultural context and the participants' knowledge about the topics. Additionally, these findings helped the study team customize the training to be provided to intervention implementers and data collectors at the local health care facilities.

Validity and Reliability of the Tools

All the tools used in this study are standardized and have been used and validated previously in South Asian contexts, including Nepal [17, 29-31]. The tools were translated into Nepali and local languages (Bhojpuri and Maithili), which were reviewed by respective subject and language experts. The validity and reliability of these translated tools were further assessed during pretesting. Pretesting was conducted within a small sample of local working teams, including survivors of violence, and the tools were amended accordingly.

Training of the Study Team

Public health experts, psychiatrists, and staff working on violence against women provided all the field team members (staff nurses and ANMs) involved in the study with specific training in an interactive way, ensuring active participation in the study. The intervention implementers received 10-day training primarily focused on DeVI, the integrated, multicomponent intervention, and were briefed about the types of violence, their prevalence and impact, and the status of women in Madhesh Province. The implementers were also thoroughly trained in implementing the intervention, conducting sessions, and using flipcharts, brochures, worksheets, templates, and forms. In addition, they were trained in the importance and maintenance of confidentiality and ethical considerations. Furthermore, they were trained in how to build trust with the participants, such as approaching them politely, and how to create a comfortable and friendly environment for basic counseling and intervention. While delivering the intervention, the implementers may feel strong emotions and stress, so they were trained to handle their own stress. Although each participant will receive the intervention in a separate, private room at a health care facility, the intervention implementers were also trained to divert the topics to maternal/reproductive health–related issues if interrupted by the person accompanying the participant, such as the woman's spouse/in-laws. Participants will also be informed about such diversions.

Data collectors for both arms received 3-day training in approaching the participants, following ethical guidelines, maintaining confidentially, determining eligibility, using various tools and techniques for data collection, getting oriented with Research Electronic Data Capture (REDCap) data collection software, and sharing data with the central team. They were also trained in using screening, baseline, and follow-up tools.

Participants and Recruitment

Sample Size

Based on the sample size calculation, a total of 912 eligible women (456, 50%, in each arm) will be included in the study. This sample size for the cluster-randomized trial was calculated considering 80% power to detect 15% absolute risk reduction in the IPV frequency in the intervention arm at a statistical significance level of $\alpha<.05$ [32]; we estimated a 50% reduction in mental health problems in the PM+ group, as measured with the 12-item General Health Questionnaire (GHQ-12) [33]. The minimum number of clusters required in each arm was 6, which was later increased to 11 to ensure an efficient trial design [34]. The number of clusters was further increased to 12 to account for dropouts at the cluster level [34]. Finally, a total of 24 clusters (12, 50%, intervention and 12, 50%, control clusters) were included, and 38 eligible women from each cluster regardless of the arms will be enrolled in the study.

Recruitment

Participants will be recruited using different approaches, including direct recruitment by asking women visiting health care facilities for maternal and reproductive health services by trained ANMs and nurses. In addition, women visiting the hospital-based 1-stop crisis management centers will also be approached for the study. Furthermore, female community health volunteers and community leaders may also disseminate information about the study to the community in any gatherings, such as mothers' groups, community meetings, or health-related events.

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Eligibility and Screening

The inclusion criteria for the participants are as follows: (1) women aged 18-49 years; (2) those self-reporting experience of abuse (physical, sexual, or psychological) in a heterosexual relationship, involving their husbands/male partners or other family members, occurring within the past 12 months; (3) women who are nonpregnant or in the first trimester; (4) those with a minimum score of ≥3 on the Psychological Distress Scale (measured with sthe GHQ-12) [35]; and (5) those living with their husbands or in-laws for at least 6 months. Women will be excluded if they (1) have severe cognitive impairment, (2) are seeking treatment for life-threatening emergency care, (3) or are at imminent risk for suicidal ideation and attempt. A questionnaire that helps in determining these eligibility criteria will be formulated and used specifically for the purpose of screening women for eligibility. Women who are at imminent risk for suicidal ideation and attempt will be referred to a psychiatrist.

Retention of Study Participants

Contact information of the participants, alternative contact persons, and preferred times for making phone calls for safe contact will be collected in order to keep in touch with them. If a participant absconds from a scheduled session or follow-up, the intervention implementer will try to contact her over the phone and encourage her to attend all sessions and follow-ups. If the participant is still absconding or cannot be contacted over the phone, the intervention implementer will contact female community health volunteers to follow up with the participant personally or over the phone. Female community health volunteers properly informed by the intervention implementer will then personally visit the participant at home following ethical guidelines [25]. All ethical guidelines [25] described in detail in the *Ethical Considerations* section will be considered while following up with participants to continue and complete the intervention. However, participants will be clearly informed that they are free to withdraw from the trial at any time without giving reasons.

Randomization and Blinding

From a sampling frame of 43 health care facilities available in Madhesh Province, a total of 24 (56%) facilities were selected based on the flow of women seeking various health-related services. The selection process involved randomization of health care facilities using a computer-generated random number table, ensuring a 1:1 ratio of intervention and control clusters (12, 50%, intervention and 12, 50%, control clusters). Each health care facility represents 1 cluster.

Participants visiting the intervention sites will be recruited into the intervention arm, while those visiting the control sites will be recruited into the control arm. To maintain blinding, both participants and health care facility staff will be completely unaware of the information pertaining to the 2 different arms, as well as the arm to which their respective health care facility belongs. However, it may not be possible to conceal this information from the study team responsible for the study design. Therefore, the study will be unmasked during data monitoring, evaluation, and analysis.

DeVI: An Integrated Multicomponent Intervention

This intervention is structured into 5 weekly sessions, where each session lasts for about 90 minutes. The first session includes general information about DeVI, components to understand the cycle of violence, and its potential health impacts. Following this, the second session focuses on common health problems caused by IPV, mental health consequences, the purpose of managing stress, and techniques for managing stress. The third session emphasizes on strategies to help women manage their situation and develop their own customized problem management strategies. This session aims to improve participants' ability or skills to solve and manage practical problems that may be influenced by other factors or changed by conflict in the family or unsolvable problems, such as employment. These problems are managed considering the participants' existing personal strengths, resources, or support. This is followed by exploring safety-planning behaviors and preparing a customized safety plan in the fourth session. The last session involves exploring social support and assisting participants in planning to strengthen the social support identified. The contents of DeVI are detailed in Table 1.

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Table 1. Contents of DeVI[a].

Intervention session	Contents of PM+[b] [16]	Additional components of DeVI
Session 1: understanding the muticomponent intervention	Introduction and confidentiality	General information about DeVI
	Before-intervention PSYCHLOPS[c] assessment	IPV[d] and domestic violence, the cycle of violence, and its common impacts on health
Session 2: common consequences of IPV and domestic violence and managing stress	During-intervention PSYCHLOPS assessment and general review	Information about common health problems associated with IPV/domestic violence
	Purpose of managing stress	Details about the common mental health consequences of IPV/domestic violence
	Explanation and demonstration of some common stress management techniques	Case of a women experiencing IPV/domestic violence
	Strategies to manage stress	
Session 3: managing problems	During-intervention PSYCHLOPS assessment and general review	Behavioral activation, during which participants will be encouraged to gradually re-engage with pleasant and task-oriented activities to improve mood and functionality
	Strategy for managing problems and its usefulness	
	Practice of the problem-managing strategy through a case example	
	Application of the strategy in solving practical problems identified by participants	
	Plan to solve the identified problems	
	Practice of stress management techniques	
Session 4: development of a safety plan	During-intervention PSYCHLOPS assessment and general review	Safety behavior assessment
		Safety-planning behaviors applicable to the participants' context
		Barriers to and facilitators of using safety behaviors
		Preparation of a safety plan in times of need
		Information about applying for legal protection orders
		Filing criminal charges
Session 5: strengthening social support and referrals	During-intervention PSYCHLOPS assessment and general review	Distribution of an information booklet that details updated contact information or locally available organizations that offer different services to women experiencing IPV
	Available social support	
	Assisting participant in making plans and approaches for strengthening social support identified	

[a]DeVI: Domestic Violence Intervention.

[b]PM+: Problem Management Plus.

[c]PSYCHLOPS: Psychological Outcome Profiles.

[d]IPV: intimate partner violence.

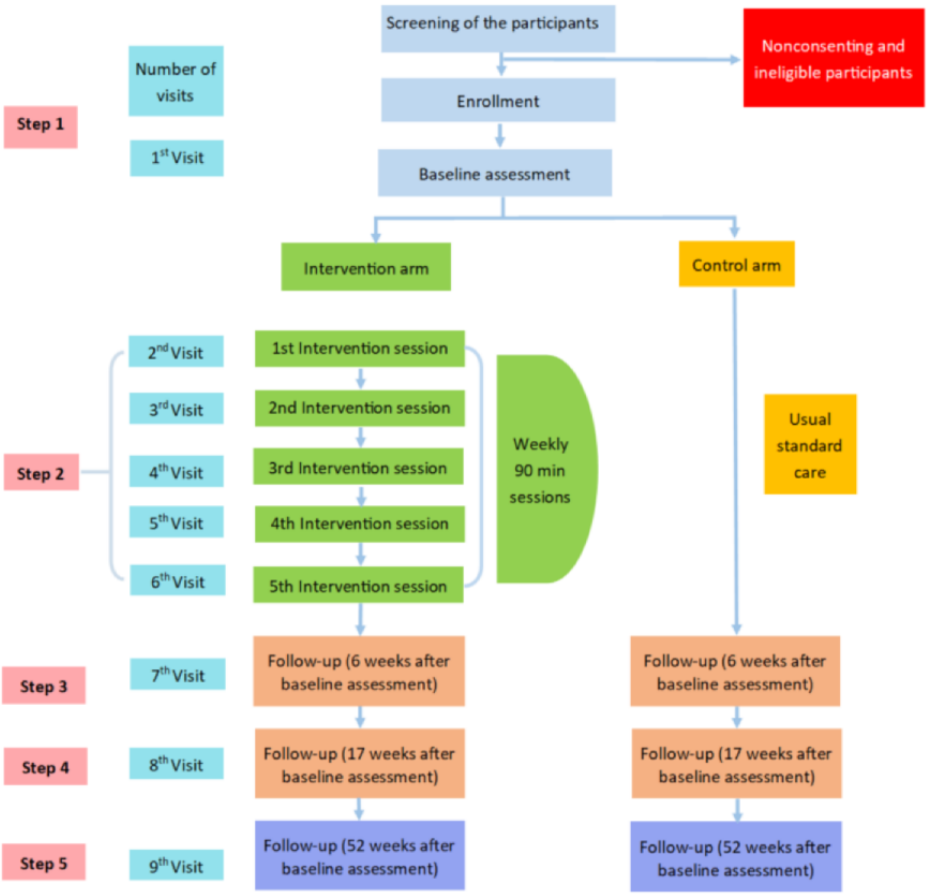
Procedure

Trained ANMs and nurses will be referred to as data collectors and intervention implementers, respectively. Their role throughout the study will be to approach women visiting health care facilities and screen them using a questionnaire for willingness to participate and eligibility. The study process is illustrated in Figure 3.

Data collectors will provide detailed information about the study to potential eligible participants and obtain written informed consent for a baseline assessment. Once consent is obtained, data collectors will conduct a baseline assessment. The baseline assessment will take about 30-45 minutes, which will be carried out in a separate room at the health care facilities. Participants will be made aware that refusal to participate will not have an impact on any type of support that they receive outside of the study. The detailed steps of study activities are listed in Table 2.

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Figure 3. Flowchart of the study process.



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Table 2. Detailed steps of study activities at the cluster level.

Steps and arms	Timing	By whom	Determined by	Rationale	Outcome
Screening					
Both intervention and control arms	N/A[a]	Data collectors	Data collectors	To screen eligible participants for the study. Data collectors will inform participants about the study and obtain written informed consent.	N/A
Enrollment and baseline data collection					
Both intervention and control arms	N/A	Data collectors	Data collectors	Baseline data collection will help track the impact of the intervention.	Assessment of primary outcomes (psychological distress and occurrence of IPV[b]/domestic violence) at baseline
DeVI[c]					
Intervention arm only	90 minutes/week for 5 weeks	Intervention implementers	Intervention implementers	To implement the intended intervention in the intervention arm.	N/A
Intervention arm only	After session 5	Data collectors	Data collectors	To assess participants' perception toward the intervention.	Exit interview to assess participants' satisfaction and suggestions
Follow-up					
Both intervention and control arms	6, 17, and 52 weeks after baseline in both arms	Data collectors	Data collectors	To compare baseline data with follow-up data between control and intervention arms.	Impact of the intervention on primary outcomes and secondary outcomes, such as a change in social support
Follow-up of absconding participants					
Both intervention and control arm	N/A	Female community health volunteers	Data collectors and intervention implementers	Female community health volunteers to contact absconding participants over the phone or in person to reduce the attrition rate as much as possible.	Assessment of other outcomes, such as reasons for absconding

[a]N/A: not applicable.

[b]IPV: intimate partner violence.

[c]DeVI: Domestic Violence Intervention.

Intervention Arm

After the baseline assessment, study participants will be referred by data collectors to intervention implementers, whose role is to deliver the intervention package once a week, with each session lasting around 90 minutes. The intervention package aims to prevent the recurrence of IPV/domestic violence and address psychological distress among participants. During each session, intervention implementers will administer the Psychological Outcome Profiles (PSYCHLOPS) form, a mental health and social functioning tool. Before-intervention PSYCHLOPS data will be collected in session 1, and during-intervention PSYCHLOPS data will be collected in sessions 2-5. At the end of each session, the intervention implementer will schedule the participant's next session. The intervention implementers will guide and encourage the participants to develop personalized plans and strategies for managing their problems, create a safety plan, and fully use existing community organizations and social support.

Enhanced Standard Care or the Control Arm

Control arm participants will receive standard care provided by the local health care facilities, depending on what they seek care for, and they will also receive an information booklet. Any participant with severe psychological distress or at risk for suicide will immediately be referred to a psychiatrist. Psychiatrists can provide remote counselling over the phone to the participant and, if necessary, also visit the participant in person. The study team will arrange the time, schedule, and consultation fees for the psychiatrist in both study arms, particularly for severe cases involving suicidal ideation identified during screening. Further, if the participant prefers to visit a psychiatrist herself, she will be provided with the travel cost.

Information Booklet

Both intervention and control arms will receive an information booklet that contains updated contact information for referral services in the study area. Further, they will receive information about the psychological distress resulting from IPV/ domestic

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violence and available services in the local context for psychological and legal support. Ahead of the study, the study team contacted and coordinated with concerned NGOs or community organizations working in the field of prevention of violence against women or management of mental health problems in the study area to ensure that women have safe places to visit in case of an emergency or difficulty.

Follow-up Assessments

Follow-up surveys will be conducted at 3 time points: 6 weeks after baseline assessment (ie, 1 week postintervention), 17 weeks after baseline assessment (ie, 12 weeks postintervention), and 52 weeks after baseline assessment (ie, 47 weeks postintervention). The data collection tools for follow-up will be similar to those for baseline assessments. However, in the last follow-up, participants will be asked questions and will be expected to contribute to the assessment of any sustained effects of DeVI on the prevention of revictimization and improvement in coping strategies against IPV. An exit interview will be conducted after intervention session 5.

IDIs will be conducted with health care providers from the intervention arm during or after the intervention to explore their experiences and perspectives of DeVI and program implementation. Health workers will be mobilized to identify suitable participants in the community, and those who provide written informed consent will be contacted for confidential interviews, preferably at the health care facility, both during and after the intervention.

Adverse Events and Risk Management

There are some potential risks to participants, such as escalation of violence, as they reside at the same household as the perpetrator. Participants will be briefed about safety behaviors and contact numbers of local authorities and the study team (ie, health care providers, psychiatrists) that they may seek help from when in need. If any participants are in grave danger and do not want to go home, they will be referred to local shelter homes managed by different community organizations and NGOs.

If any other unprecedented harm or risk arises affecting the involved participants in any study arm, data collectors and intervention implementers from each site will notify the project coordinator immediately and manage the situation per guidance from the study team, depending upon the intensity of the adverse event. Adverse events would include a marked increase in suicidal thoughts, the death of the participants, suicide attempts, serious violence, the need for prolonged hospitalization, disability/incapacity, and any other life-threatening events. The study team will also assess these factors throughout the study period.

Any participant who is at risk for severe injury or who displays severe psychological distress and needs help from a specialist will be referred to a psychiatrist by the study team. Intervention implementers will receive the necessary help and guidance from the study team for risk management at respective sites. If any adverse event is reported by a participant or observed at any stage of the study by the data collector or intervention implementer, the study team will record all the necessary details in an adverse reporting form. This form, which is designed by integrating the adverse event form developed by WHO and the National Institutes of Health (NIH), will be used to capture adverse event details of individual participants throughout the study [25].

Outcomes Measures

Primary Outcomes

The primary outcomes are psychological distress and the frequency and intensity of IPV/domestic violence. IPV/domestic violence will be assessed using the modified WHO multicountry questionnaire [36]. This instrument synthesizes women's experience of physical, sexual, and psychological violence, as well as controlling behavior by husbands/male partners, and also measures the severity of IPV/domestic violence. Psychological distress will be measured with the GHQ-12 [35] and the 9-item Patient Health Questionnaire (PHQ-9) [37]. Both tools have been translated and clinically validated in Nepal. The GHQ-12 has a cut-off score of 0.5, with sensitivity 85.6%, specificity 75.8%, positive predictive value 86.7%, and negative predictive value 84% [38]. Similarly, the PHQ-9 has a cut off score of ≥10, with sensitivity 94%, specificity 80%, positive predictive value 42%, and negative predictive value 99% [39].

Secondary Outcomes

The secondary outcomes are safety planning, use of community resources, social support, impaired functioning, symptoms of PTSD, personally identified problems, and health service use. Health care providers' capacity to identify IPV/domestic violence to provide women experiencing IPV/domestic violence with risk mitigation services will also be assessed. Details of instruments and assessments for primary and secondary outcomes, including follow-up time, are provided in Tables 3-5.

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Table 3. Overview of instruments and assessments for specific objectives concerning women experiencing IPV[a]/domestic violence.

Study objective and tool	Baseline (T_1)[b]	Follow-up after baseline		
		6 weeks (T_2)	17 weeks (T_3)	52 weeks (T_4)
Objective 1: Assess the feasibility of DeVI[c] in health care facilities in Nepal by exploring the views of key stakeholders, health care providers, and local women in the community.				
Formative assessment (details have been mentioned in the *Formative Assessment and Consultation Workshop* section)	0[d]	0	0	0
Objective 4: Measure the effectiveness of DeVI in addressing and resolving psychological distress, reducing the occurrence of IPV, and developing safety strategies for women experiencing IPV.				
Husband/male partner/domestic violence assessment	1[e]	1	1	1
GHQ-12[f] [35]	1	1	1	0
Hospital Anxiety Depression Scale [40], PHQ-9[g] [37], PTSD[h] CheckList – Civilian Version, Multidimensional Scale of Perceived Social Support [41], WHO[i] Disability Assessment Schedule [42]	1	1	1	0
Safety Behavior Checklist, use of community resources	1	1	1	1

[a]IPV: intimate partner violence.

[b]T: time point.

[c]DeVI: Domestic Violence Intervention.

[d]0: not applicable.

[e]1: applicable.

[f]GHQ-12: 12-item General Health Questionnaire.

[g]PHQ-9: 9-item Patient Health Questionnaire.

[h]PTSD: posttraumatic stress disorder.

[i]WHO: World Health Organization.

Table 4. Overview of instruments and assessments for objective 5 (measure the impact of training health care providers on DeVI[a] on their knowledge, attitudes, skills, and stigma toward IPV[b] and the social and health-related consequences of IPV) concerning health care providers.

Tools	Pretraining	Posttraining	Follow-up 1 (T_2)[c]	Follow-ups (T_3 and T_4)
Modified PREMIS[d] [43]	1[e]	1	0[f]	0
MAKS[g], Social Distance Scale [44], perceived dangerousness of the mental health patients [44]	1	1	0	1
In-depth interviews with health care providers	0	1	1	1

[a]DeVI: Domestic Violence Intervention.

[b]IPV: intimate partner violence.

[c]T: time point.

[d]PREMIS: Physician Readiness to Manage Intimate Partner Violence Survey.

[e]1: applicable.

[f]0: not applicable.

[g]MAKS: Mental Health Knowledge Schedule.

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Table 5. Overview of instruments and assessments for specific objectives concerning health care providers and women experiencing IPV[a]/domestic violence.

Study objective	Tool	Session					Follow-up	
		1	2	3	4	5	1 (T_2)[b]	2 (T_3)
Objective 4: Measure the effectiveness of DeVI[c] in addressing and resolving psychological distress, reducing the occurrence of IPV, and developing safety strategies for women experiencing IPV.	PSYCHLOPS[d] [16]	1[e]	1	1	1	1	1	1
Objective 3: Explore participants' and health care providers' experiences with DeVI and the opportunities and challenges encountered during implementation.	Process evaluation	0[f]	0	0	0	0	1	1
Objective 3: Explore participants' and health care providers' experiences with DeVI and the opportunities and challenges encountered during implementation.	Exit interview of participants	0	0	0	0	1	0	0

[a]IPV: intimate partner violence.

[b]T: time point.

[c]DeVI: Domestic Violence Intervention.

[d]PSYCHLOPS: Psychological Outcome Profiles.

[e]1: applicable.

[f]0: not applicable.

Other Outcomes

Health care providers will be asked to respond to questionnaires, such as the modified Physician Readiness to Manage Intimate Partner Violence Survey (PREMIS), the Mental Health Knowledge Schedule (MAKS), the Social Distance Scale, and the perceived dangerousness of mental health patients pre- and posttraining to assess the impact of training on the health care providers' knowledge and attitude. Further, MAKS and the perceived dangerousness of mental health patients will be assessed during integrated multicomponent supervision (approximately 90 days posttraining). Exit interviews will be conducted among 180 participants by data collectors in the absence of intervention implementers after the completion of all 5 sessions in a separate room by adopting a mixed methods approach. This will help determine changes postintervention and any aspects that need to be changed. This will also help assess the satisfaction and acceptability of DeVI from the participant's point of view.

Quantitative Data Collection for the Trial

Quantitative data will be collected electronically using REDCap software [45] and various data collection tools by data collectors in computer-based tablets at different time points. If any technical problem arises during electronic data collection, paper-based data collection will be performed. Each health care facility will be provided with a computer-based tablet with an updated questionnaire for data collection.

Data collection tools will include structured surveys and standard validated tools. The structured surveys will include questions on participants' personal information (date of birth, ethnicity, address, contact information, and preferred time to call) and sociodemographic characteristics. The data collection tools in this study are standard international tools widely used and validated in different countries. However, some terminologies and contents have been contextualized to suit the Nepali context. The data will be collected at 4 different time points, once at baseline and at 3 follow-up time points (see Figure 3 for details). In addition, the PSYCHLOPS form will be filled in at the 5 intervention sessions.

Qualitative Data Collection

Qualitative interviews will be conducted by purposively selecting participants to learn more about their perspectives toward DeVI. IDIs will be conducted with randomly selected intervention implementers to understand their challenges in implementing the intervention sessions and their suggestions for improving the applicability and sustainability of DeVI. A deeper understanding of their needs will help the study team alter the intervention approach and activities in the future. The qualitative process assessment will also help assess the acceptability of DeVI, which is key for scale-up and integration into routine services.

Data Management and Analysis

Quantitative Data Analysis

Electronically collected data will be securely stored in a central office cloud, accessible only to designated study team members. Paper-based data pertaining to the study will be secured in a locker and retrieved from data collectors during central study team monitoring. Regular checks will be conducted to ensure data accuracy and quality, with necessary feedback provided to the data collectors. The primary measure of intervention effects will be based on intention-to-treat analyses. Multilevel analysis will be conducted to account for DeVI's impact on primary and secondary outcomes, adjusting for clustering at the health center level [46]. The model will consider intervention × time interactions to assess the differential effects of DeVI on changes in outcomes from baseline to the final follow-up. Cluster-level variables will also be compared between intervention and control arms since randomization is based on health care facilities.

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Furthermore, the study will assess variations in outcome measures of interest between urban and rural areas.

The knowledge, perception, and preparedness of both intervention implementers and data collectors will be assessed before and after the training through pre-, post-, and follow-up tests. Quantitative data will be analyzed using STATA 15 software.

Qualitative Data Analysis

Qualitative interviews will be conducted in Nepali and audio-recorded with the participants' consent. The recordings will be stored on a password-protected device. Transcription will be carried out in Nepali, and then the transcripts will be translated into English. The transcripts will undergo thorough review and validation against audio recordings to ensure accuracy. Qualitative content analysis will be performed. Independent researchers will initially conduct open coding, followed by discussion within the study team. Agreed-upon codes will be grouped into categories and themes, which will be developed and finalized based on the study objectives.

Monitoring and Evaluation

The monitoring committee will comprise a study principal investigator, coinvestigators, and other independent experts who will oversee the study's implementation and data collection. Any deviations from the protocol will be identified and documented during monitoring. The team will monitor and supervise field activities and communicate over the phone every day and visit all the study sites every month. The monitoring activities will be aided by checklists, tools, and manuals. Regular communication, both oral and written, will facilitate ongoing monitoring and updates among data collectors, intervention implementers, and other study members at the central offices.

Process Evaluation

Concurrently with the trial, we will conduct process evaluation following the implementation component of the UK Medical Research Council's guidance [47] in order to enhance comprehension of the DeVI's acceptability among both women experiencing violence (reach) and health care providers. Additionally, we will assess the study's adherence to the intended plan. The evaluation also aims to explore the barriers to and facilitators of DeVI (adaptations) from the perspective of health care providers, providing information about the possibility of its future sustainability and scalability, considering its effectiveness.

This process evaluation is based on the hypothesis that health care providers can identify women experiencing violence with mild-to-moderate psychological distress and that they can deliver planned counseling sessions and inviting women for further sessions and follow-ups on predetermined dates and times. This evaluation also hypothesizes that health care providers will allocate time for delivering the sessions in intervention sites, as well as conducting baseline and follow-up assessments in both intervention and control sites, in addition to their regular duty.

A mixed methods approach will be used for the process evaluation. Qualitative data will be collected through in-depth interviews with data collectors and intervention implementers at different time points. Quantitative data will be collected using an observation checklist and a 3-month follow-up period. The IDIs with health care providers will explore their experiences in, barriers to, and facilitators of recruiting and retaining women, as well as providing suggestions for improvement. Similarly, the observation checklist will help track their progress and status in the trial thus far, while the practice questionnaire will assess changes in their practice regarding violence identification and management. The practice questions will be derived from the practice section of the PREMIS questionnaire, which was previously used during training as a pretest. Qualitative data will be analyzed using thematic analysis [48], while quantitative data will be simply analyzed using descriptive analysis.

The process evaluation will uncover unforeseen insights, propose solutions, and introduce innovative approaches that encompass diverse aspects and perspectives of health care providers engaged in the trial. Moreover, should the trial deviate from its predetermined trajectory, we will diligently work to enhance the program by addressing areas requiring improvement, facilitating, overcoming barriers, ensuring resource availability, and effectively managing the time of health care providers.

Periodic monitoring will involve conducting site observations, observing intervention sessions with participant consent, and keeping track of participants. Regular meetings will be held between the study team and field teams to exchange updates and monitor progress. Adverse events related to the intervention will be reviewed periodically. The study team will cross-check the collected data for accuracy and completeness. Any identified errors during data monitoring will be promptly addressed through communication with the field teams for correction.

Dissemination of Findings

Study findings, along with policy recommendations for enhanced collaboration between key stakeholders and increased coverage of IPV/domestic violence and mental health services for women, will be disseminated to relevant provincial and national stakeholders and authorities. The study results and recommendations will reach a wider audience through policy briefs, press releases, workshops, conferences, and scientific publications.

Results

The trial received funding from the Swedish Research Council in 2019. The goal is to recruit 456 eligible women in each arm. As of December 29, 2022, a total of 269 eligible women were enrolled from the intervention sites and 309 eligible women from the control sites. The trial is currently in the recruitment phase. Data collection is expected to be completed by December 2023. Data analysis will begin shortly after obtaining all the data following the established plan. Regular data cleaning and monitoring are being conducted every day.

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Discussion

Summary

This cluster-randomized trial aims to implement and evaluate the acceptability, feasibility, and effectiveness of DeVI in addressing psychological distress and enabling the secondary prevention of violence for women experiencing IPV. These interventions will be administered by trained nonspecialist mental health care providers in Madhesh Province, Nepal, at the health care facility level. As of December 29, 2022, the study had enrolled 59% (n=456) of eligible women from the intervention sites and 68% (n=456) of eligible women from the control sites. In low-income settings, such as Nepal, mental health specialists are scarce. Therefore, if this study proves effective, it could provide scientific evidence supporting the integration of mental health services into routine health care facilities in Nepal. This integration aims to prevent the recurrence of violence and address mental health issues among survivors of violence. Additionally, the study can offer valuable insights into how nonspecialist mental health care providers can address mental health problems and violence among women experiencing IPV/domestic violence. DeVI aims to improve access for marginalized women, particularly those who are hard to reach and have experienced IPV/domestic violence, while facing mental health challenges. Throughout the intervention, health care providers and survivors of violence will collaborate actively to address violence and enhance the women's mental well-being. They will develop customized strategies for self-management of these issues. Investing in women's health is considered a cost-effective strategy to improve the nation's overall well-being [49].

We hypothesize that addressing the needs of women experiencing IPV/domestic violence will enhance their mental stability and reduce long-term health risks associated with violence. This study will contribute to bridging existing knowledge gaps by generating scientific evidence for regional policy makers, given the limited availability of data on mental health issues in resource-constrained settings.

The results from DeVI will hopefully support the integration of mental health services into routine health programs in Nepal. It could also add evidence to the global knowledge base on how and whether nonspecialist mental health care providers can be mobilized in addressing mental health problems in settings where IPV/domestic violence prevalence is high and human resources scarce. In addition, if this cluster-randomized trial is proven effective, this concept can be replicated in other LMICs following contextual adaptation and testing in each setting and target population.

Limitations

Women experiencing violence and eligible for our study may refrain from providing consent due to the fear that their husbands or male partners will subject them to further abuse upon discovering their participation. The dropout rate may be higher due to the associated stigma and the fear of family members, society, and perpetrators. In a patriarchal society, such as Nepal, women are typically accompanied by their in-laws or husbands when seeking basic services at health care facilities, which creates reluctance to disclose issues related to violence or participate in the study.

Conclusion

This trial aims to present vital evidence for mitigating the impact of intersecting violence and mental health issues among women in Nepal. If the intervention is found to be effective, the study has the potential to offer significant contributions and insights into how nonspecialist mental health care providers can address problems related to IPV and mental health among survivors in low-income settings.

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Data Availability

Data sharing is not applicable to this paper as no data sets will be generated or analyzed during this study.

Authors' Contributions

KD conceived and designed the study. RS, DS, DM, and AME made substantial contributions to the study design, and KD and RS drafted the manuscript. All the authors revised the manuscript critically for intellectual content and have read and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

ANM: auxiliary nurse midwife

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DeVI: Domestic Violence Intervention
GHQ-12: 12-item General Health Questionnaire
FGD: focus group discussion
IDI: in-depth interview
IPV: intimate partner violence
KII: key informant interview
LMIC: low-and middle-income country
MAKS: Mental Health Knowledge Schedule
NGO: nongovernmental organization
PHQ-9: 9-item Patient Health Questionnaire
PM+: Problem Management Plus
PREMIS: Physician Readiness to Manage Intimate Partner Violence Survey
PSYCHLOPS: Psychological Outcome Profiles
PTSD: posttraumatic stress disorder
WHO: World Health Organization

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Protocol

Effects of Melatonin on Glycemic Variability in Type 2 Diabetes Mellitus: Protocol for a Crossover, Double-Blind, Placebo-Controlled Trial

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Abstract

Background: Glycemic variability is recognized as a significant factor contributing to the development of micro- and macrovascular complications in individuals with type 2 diabetes mellitus (T2DM). Numerous studies have shown that melatonin, a hormone involved in regulating various biological rhythms, including those related to glucose regulation, such as hunger, satiety, sleep, and circadian hormone secretion (ie, cortisol, growth hormone, catecholamines, and insulin), is deficient in individuals with T2DM. This raises an important question: Could melatonin replacement potentially reduce glycemic variability in these patients? This warrants investigation as a novel approach to improving glycemic control and reducing the risk of complications associated with T2DM.

Objective: We aimed to investigate whether melatonin replacement in individuals with T2DM who supposedly have melatonin deficiency can positively impact the regulation of insulin secretion rhythms and improve insulin sensitivity, ultimately resulting in a reduction in glycemic variability.

Methods: This study will use a crossover, randomized, double-blind, placebo-controlled trial design. Patients with T2DM in group 1 will receive 3 mg of melatonin at 9:00 PM in the first week, undergo a washout period in the second week, and receive a placebo in the third week (melatonin-washout-placebo). Group 2 will be randomized to receive a placebo-washout-melatonin sequence (3 mg). Capillary blood glucose levels will be measured at 6 different times before and after meals during the last 3 days of the first and third weeks. The study aims to compare the mean differences in blood glucose levels and the coefficient of glycemic variability in patients receiving melatonin and placebo during the first and third weeks. After analyzing the initial results, the number of needed patients will be recalculated. If the recalculated number is higher than 30, new participants will be recruited. Thirty patients with T2DM will be randomized into the 2 groups: melatonin-washout-placebo or placebo-washout-melatonin.

Results: Participant recruitment took place between March 2023 to April 2023. In all, 30 participants were eligible and completed the study. We expect that patients will show different glycemic variability on the days they receive placebo or melatonin. Studies on melatonin and glycemic control have shown both positive and negative results. We hope that there will be a positive outcome regarding glycemic variability (ie, a reduction in glycemic variability), as melatonin has a well-described chronobiotic effect in the literature.

Conclusions: This study aims to determine whether melatonin supplementation can effectively reduce glycemic variability in patients with T2DM. The crossover design is necessary due to the multiple variables involved in the circadian variations of glucose, including diet, physical activity, sleep parameters, and pharmacological treatments. The relatively low cost of melatonin and its potential role in reducing the severe complications associated with T2DM have motivated this research effort. Furthermore, the indiscriminate use of melatonin in current times makes conducting this study essential to evaluate the effect of this substance in patients with T2DM.

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Trial Registration: Brazilian Registry of Clinical Trials RBR-6wg54rb; https://ensaiosclinicos.gov.br/rg/RBR-6wg54rb
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KEYWORDS

type 2 diabetes mellitus; glycemic control; melatonin; randomized controlled trial; cross-over studies; T2DM; glucose; glycemic variability; circadian rhythm

Introduction

Despite recent advances in medical technology and treatments for type 2 diabetes mellitus (T2DM), the prevalence of this disease is still increasing exponentially worldwide [1]. According to the International Diabetes Federation, the number of adults with T2DM globally was expected to rise to 463 million in 2019 and 700 million by 2045, with a significant impact on public health, society, and the economy [2]. Effective treatment of T2DM is crucial in avoiding complications and improving overall health outcomes for patients. In recent years, the management of T2DM has evolved significantly due to the discovery of new therapeutic targets and the development of new drugs with different mechanisms of action [3]. Additionally, nondrug interventions that impact glycemic control have become increasingly important in the management of T2DM [4,5]. Dietary modification, physical activity, weight management, and stress management have long been recommended. In addition to lifestyle modifications and medication, the role of good quality sleep in managing T2DM has become increasingly recognized by health care professionals. The American Diabetes Association's 2017 position statement underscored the significance of adequate sleep in the management of T2DM and brought attention to the detrimental effect that sleep disturbances can have on glycemic control [6]. Melatonin, a hormone linked to the circadian rhythm, may be the pathophysiological link between sleep changes and glycemic control [7]. This hormone synchronizes our waking, sleeping, hunger, and satiety times, as well as other biological functions, such as insulin secretion. Previous studies found that melatonin production is reduced in T2DM [8-10]. While some papers have suggested that melatonin replacement may have benefits for glycemic control, the results of these studies have been conflicting, with some studies not showing significant benefits [11-14]. How can such differences be explained? The impact of melatonin on glycemic control may depend on several factors, including the timing and duration of use, as well as individual genetic variations, such as *MT2* melatonin receptor polymorphisms [15,16] Mutations in the *MT2* receptor gene have been associated with altered glucose metabolism and insulin sensitivity and may impact the effectiveness of melatonin supplementation in improving glycemic control. Some studies have suggested that individuals with *MT2* receptor mutations may experience an increase in glycohemoglobin levels following melatonin use, unlike those without this mutation.

Assessing variations in glucose throughout the day, instead of just the average glycohemoglobin level, is an important aspect of investigating the potential impact of melatonin on glycemic control. In this work, we will not evaluate the role of melatonin in average glucose (glycohemoglobin) level, but on variations in glucose level throughout the day. Our proposal is to determine whether melatonin influences the circadian rhythm of glucose in patients with T2DM. Currently, no study has evaluated whether melatonin has such a role.

Glycemic variations throughout the day depend on central and peripheral control of insulin secretion and sensitivity. Previous studies have linked the action of melatonin on *MT1* and *MT2* receptors to insulin secretion and sensitivity [17]. Our hypothesis is that melatonin replacement in people with T2DM who are melatonin deficient may have a positive role in the regulation of insulin, cortisol, and the rhythms of other secretions. If this hypothesis is correct, melatonin replacement may reduce the range of blood glucose variation throughout the day. It has already been demonstrated that wide circadian glucose variation in patients with diabetes mellitus can be a stress and inflammation factor and lead to chronic complications of the disease that occur when glycohemoglobin is elevated [18,19]. Thus, this study asks, Could melatonin replacement in these melatonin-deficient patients attenuate these glycemic oscillations? The objective of this research project is to assess whether melatonin supplementation can reduce glycemic variations throughout the day in patients with T2DM.

Methods

Study Design

This prospective, crossover, double-blind, randomized, placebo-controlled study was approved by the ethics committee of the Federal University of Minas Gerais. The study will be conducted at an endocrinology outpatient clinic run by the research physician (WM) in the city of Belo Horizonte, Brazil. Thirty patients will participate in the initial phase of this work. These patients will be randomized to 2 groups: a placebo-washout-melatonin (3 mg) group, which will receive a placebo for 7 days, followed by 7 days without the study medication (washout period) and 7 days of melatonin (3 mg); and group 2, the melatonin-washout-placebo group, which will receive melatonin (3 mg) for 7 days, followed by 7 days without the study medication (washout period) and 7 days of placebo. When 15 patients are allocated to one of the possible intervention orders (placebo followed by melatonin or melatonin followed by placebo), 15 patients will be allocated to the other, not-yet-complete intervention order. Patients will be instructed to use the study medication at 9:00 PM. Patients will receive guidance on diet and physical activity to be followed during these 3 weeks. On the fifth, sixth, and seventh days of the first week and the fifth, sixth, and seventh days of the third week, the patients will use a glucometer to monitor fasting capillary

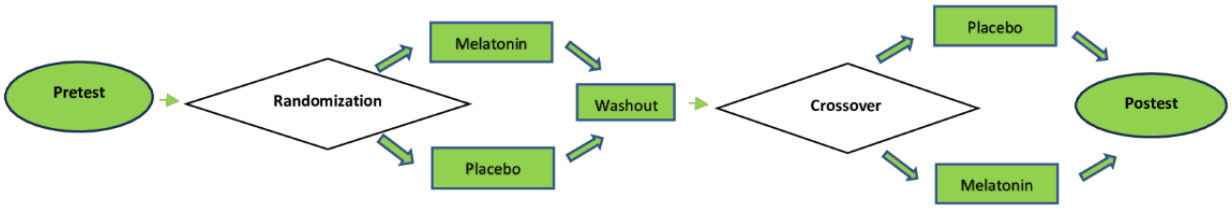
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blood glucose before breakfast, 2 hours after breakfast, before lunch, 2 hours after lunch, before dinner, and 2 hours after dinner. The primary outcome analyzed in this study will be the variability of pre- and postprandial glycemia. The result will be compared between 2 periods: with placebo and with melatonin.

Blinding

Medicine bottles containing melatonin or placebo will be numbered 1 and 2, not necessarily in that order. The individual responsible for assigning the numbers will be the sole person with knowledge of which bottles contain melatonin and which contain placebo. All other people involved in this project (patients, medical researchers, statisticians, and assistant personnel) will be blind in relation to the substances. Upon completion of the statistical analysis, the researchers will be informed as to which bottle contained melatonin and which contained placebo. Figure 1 shows a flowchart of the study.

Figure 1. Flowchart.



Glycemic Variability and Crossover Studies

Crossover studies present an advantage over parallel group studies: comparing 2 or more interventions in the same individual reduces possible biases related to differences between groups. Such a design is suitable for chronic diseases and for testing drugs that control a disease but do not cure it. Curing a disease in one period of the study would make it meaningless to use another drug or even a placebo in the following period. When studying an outcome that is influenced by several variables, this design allows for a more reliable comparison with a smaller sample. This is the case for assessing glycemic variability in patients with T2DM. Glycemic variability in patients with T2DM can be influenced by several factors, including medications, duration of diabetes, age, diet, and physical activity. In the evolution of the treatment of diabetes mellitus, there has been an effort to develop drugs that reduce variability in glycemia: dipeptidyl peptidase 4 (DPP-4) inhibitors, GLP1 (glucagon-like peptide 1) analogues, and ultra-slow insulins. Patients with T2DM are treated with a diverse combination of the available drugs. For this reason, pairing groups for a comparison of glycemic variability would be a complex task. Added to this are individual differences in diet and physical activity. Thus, a crossover study is more suitable for the purpose of this work.

Melatonin and the Carryover Effect in Crossover Studies

Crossover studies should include an adequate washout period, that is, a period in which there is a break from the initial intervention until the beginning of the next intervention. In this work, we propose a period of 1 week for the washout. Questions to examine include whether that time is adequate and whether effects of the initial intervention in the first week remain in the third week. As melatonin has a short half-life (10 to 60 minutes), we believe that its influence will not be present in the third week of the study in the group that uses it initially; a washout period of 1 week thus seems sufficient [20]. Therefore, after a week without using any substance, the initial intervention will not influence the proposed intervention in the third week.

Glycemic Variability

Glycemic variability refers to fluctuations in blood glucose levels over time. It can be short-term, in self-monitored evaluations of (pre- and postprandial) capillary blood glucose; it can also use the gold standard method, continuous blood glucose monitoring, in which nocturnal blood glucose fluctuations are recorded every 5 minutes [21,22]. There is little correlation between the average variability in glycemic amplitude measured by continuous glucose monitoring and by self-monitoring; however, the latter method can be used for structured assessments of short-term glycemic variability in a day and between different days. The calculation of glycemic variability by this method can also be performed using SDs or even the coefficient of variation. A glycemic variation coefficient of less than 36% is considered level E evidence to separate stable from unstable glycemic control [21]. This measure is considered most effective to assess glycemic variability; however, comparing glycemia between different days is more effective with the mean of daily differences (MODD). This measure is obtained by determining the difference in blood glucose measured at the same time in a 24-hour interval. An additional computer program is used for this measurement, and it cannot be obtained only by continuous capillary blood glucose monitoring devices [21]. In this work, we will use pre- and postprandial capillary glycemia monitoring to determine the glycemic variability of patients with T2DM. In addition to the low cost of the method, we believe that this method gives the work an aspect of a real-life study and therefore greater clinical relevance.

Inclusion and Exclusion Criteria

Patients will be included in this project according to the following criteria: (1) T2DM duration more than 1 year, (2) age greater than or equal to 40 years, (3) family history of T2DM, and (4) glycohemoglobin between 7% and 10%. Inclusion criterion 1, a T2DM duration of more than 1 year, was chosen because in the first year after diagnosis, patients might not yet have achieved baseline glycemic control. Some patients may have significant improvement in beta-cell glucotoxicity in the first year, with reduced blood glucose levels, and therefore have

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very wide blood glucose variations from one week to the next because of this improvement. Inclusion criterion 2, the age limit, was established based on the fact that most individuals with T2DM are aged over 40 years. In this way, we avoid including individuals who have autoimmune or genetic diabetes in the study. Item 3 is important because it further homogenizes our patients. We know that T2DM has a strong hereditary component, unlike other types of diabetes. Item 4, limiting the glycohemoglobin value range to 7% to 10%, was established with the objective of homogenizing glycemic variability among our patients, as it is known that glycemic variability increases with an increase in glycohemoglobin.

The following patients will be excluded from this study: (1) pregnant women, (2) patients who have recently (within 3 months) used corticosteroids or other hyperglycemic medications, (3) patients who have conditions that significantly alter glycemic stability (such as renal failure, recent acute coronary syndrome, and other diseases, such as cancer and liver failure). Also excluded will be (4) patients who refuse to participate in this research at any point and (5) patients who have uncontrolled diabetes with symptoms of polydipsia, polyuria, or weight loss that require other measures, such as the use of insulin for glycemic control, in addition to diet, physical activity, and medications already in use. Finally, we will exclude from this study (6) patients at high risk for severe sleep apnea, (7) patients with depression, (8) patients with alternating work shifts, and (9) patients who have epilepsy, a condition that can worsen with the use of melatonin.

Most of these exclusion criteria function to limit conditions that generate very high glycemic variability. It is unlikely that the use of melatonin will be able to reduce glycemic variability induced by corticoids, for example. Patients at high risk for sleep apnea, patients with depression, and patients with alternating work shifts were excluded due to studies that show the negative influence of these conditions on glycemic control. Specific studies with these populations seem more adequate for the purpose proposed here.

Ethical Aspects

Participants involved in this study will be required to sign an informed consent form that has been drafted in compliance with the Declaration of Helsinki [23]. The wording of the consent form was initially sanctioned, together with the entire project outlined herein, by the ethics committee of the Federal University of Minas Gerais (CAAE: 31990720.7.000.5149). The invitation to participate in this study will be extended during routine consultation at the office of an endocrinology physician (WM). Participants, if they meet the inclusion criteria, will be volunteers. There will be no payment. All research objectives, as well as potential risks pertaining to the use of melatonin, will be explained. We will emphasize, however, that melatonin is a low-risk substance with few side effects. A possible risk is daytime drowsiness, but this is unlikely given the very short half-life of the drug and the low dose used.

Randomization

Patients will be randomized into two groups. Group 1 will use the substance contained in bottle 1 in the first week, will not use any substance in the second week (the washout period), and will use the substance contained in bottle 2 in the third week. Group 2 will use the substance contained in bottle 2 in the first week, will not use any substance in the second week (the washout period), and will use the substance contained in bottle 1 in the third week.

Patients will be divided into these groups according to the result of rolling a die. Those who roll a number from 1 to 3 will be in group 1, while those who roll a number from 4 to 6 will be in group 2. When the number of participants in a group reaches 15, patients will be automatically allocated to the other group until it includes 15 participants. The project researcher will know which patients will use bottle 1 or 2 in the first and third weeks but will not know which bottle contains placebo and which contains melatonin.

Interventions

Patients will use melatonin in the first week and placebo in the third week or placebo in the first week and melatonin in the third week, according to the randomization described. On days 5, 6, and 7 of the first and third weeks of the study, patients will measure fasting capillary blood glucose levels 2 hours after breakfast, before lunch, 2 hours after lunch, before dinner, and 2 hours after dinner. Patients will also receive guidance on diet and physical activity to be followed during these 3 weeks. In the second week, patients will undergo a washout period. At the end of the study, the patients will return to the office with their capillary blood glucose results. At this point, they will be asked whether they experienced excessive daytime sleepiness at any point in the study and whether they suspected at any time whether a substance was the placebo or melatonin.

Procedures

Patients with T2DM will be selected to take part in this study during routine consultations held in an outpatient endocrinology clinic. At the end of the consultation, the endocrinologist, when verifying that the patient meets the inclusion criteria, will ask the patient if they are interested in participating in research on diabetes and melatonin. This question will be followed by reading the informed consent form. All stages of the research will be explained to the patient. This includes the research period, the use of a placebo substance and melatonin, the need to perform capillary blood glucose measurement 6 times a day for 3 days in the first week and 3 days in the third week, the washout period, and the delivery of capillary blood glucose results after the 3 weeks of the project. If the patient agrees to participate in the project, the researcher will ask them to sign the free and informed consent form. A copy of this form will be given to the patient. Next, the researcher will ask the patient to roll a die. Patients who roll a number from 1 to 3 will be in group 1 and will be included in the group that uses the following sequence: bottle 1, washout, bottle 2. Those who roll a number from 4 to 6 will be included in group that uses the following sequence: bottle 2, washout, bottle 1. After allocating the patient to one of the groups, the project researcher will fill in the research record, which will contain the epidemiological, clinical, and laboratory data of the patient, including age, gender, duration of diabetes, history of epilepsy, insulin use (or not), STOP-Bang (snoring, tiredness, observed apnea, high blood

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pressure, BMI, age, neck circumference, and gender) questionnaire results, weight, height, BMI, abdominal circumference, and glycohemoglobin value. After this step, the patient will be guided on the diet and physical activity regimens to be carried out during the 3 weeks of the project. Patients will be instructed to perform 30 minutes of physical activity 5 times a week during the 3 weeks of the project. After this guidance, patients will receive a glucometer, strips for measuring capillary blood glucose, and lancets to take home. In addition, patients will be given a form to record capillary blood glucose values. At the end of the third week, the patient will return with the blood glucose values.

Primary and Secondary Outcomes

The primary end point of this study will be the difference in mean variability of the patients' blood glucose levels between the first and third weeks of the study. The data will be acquired by computing the average of the variance between the total blood glucose levels obtained in these weeks.

As a secondary outcome, we will evaluate the mean disparities in glycemia at each time interval, namely fasting, 2 hours after fasting, before lunch, 2 hours after lunch, before dinner, and 2 hours after dinner. This assessment aims to determine whether the use of melatonin has any discernable impact on blood glucose fluctuation at specific times of the day.

In order to analyze the effect of melatonin after a greater number of days of use, we will perform a specific analysis of the glycemic variability measured on the last day of glycemic measurement in the first and third weeks.

We will also perform a categorical analysis that will take into account the coefficient of variation of blood glucose levels during the use of placebo and during the use of melatonin. We will consider this value to be stable if it is less than 36% and unstable if it is higher than 36%. We will evaluate whether the coefficient of variation was stable or unstable in the week in which melatonin was used.

Sample Size

The sample size will be 30 patients. As referenced in the literature, when the SD and population frequencies of a given variable are not known, a pretest should be performed with 30 to 40 patients, and data from this group should be considered a population estimate [24]. After collecting blood glucose data for the first and third weeks, the mean glycemic variability and the SD will be calculated so that the sample size can be recalculated. This is necessary because there are no similar studies in the literature. If the recalculated sample size is less than 30, no new participants will be needed and the study will be concluded. If the new sample size is greater than 30, new patients will be recruited until the new, larger sample size is reached.

Statistical Analysis

If quantitative variables adhere to a normal distribution, as represented by the Gaussian curve, their central tendency will be expressed as mean and their dispersion will be quantified by the SD. If the distribution of these variables does not follow a normal distribution, then their central tendency will be described by the median and their dispersion will be characterized by the 25% and 75% quartiles. The Shapiro-Wilk test will be used to assess normality. Categorical variables will be presented using both absolute frequencies and percentages.

Statistical analyses of normal quantitative variables, both before and after the intervention, will be conducted using a paired 1-tailed *t* test. When the distribution is not normal, the Wilcoxon test will be used. The study will have 2 intervention tails: placebo-washout-melatonin and melatonin-washout-placebo. Comparison of blood glucose levels will be performed between the time when the patients used melatonin and the time they used placebo.

The patients will be compared with one another based on the capillary blood glucose results obtained during the first and third weeks.

The epidemiological, clinical, and laboratory data of the patients will be compared between groups 1 and 2 in order to evaluate whether the randomization process has generated groups that lack statistical differences that may influence the research results.

The significance level will be .05 and the software of choice will be SPSS (version 20.0; IBM Corp).

Results

Participant recruitment took place between March 2023 to April 2023. In all, 30 participants were eligible and completed the study. Upon selection of these patients and completion of the 3-week research period, a statistical analysis was conducted on the variability of capillary blood glucose levels during the first and third weeks. Subsequently, these data were used to determine the required sample size (n) necessary to draw valid conclusions regarding the proposed research objectives. Furthermore, in addition to the capillary blood glucose values, the data types presented in Table 1 will be scrutinized to ensure the absence of statistical discrepancies between groups 1 and 2. The study was approved by the Brazilian Registry of Clinical Trials (RBR-6wg54rb) on March 7, 2023. Figure 2 shows a sample table of how the results will be presented.

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Table 1. Epidemiological, clinical, and laboratory data (n=30).

Characteristics	Values
Participants	n
Age (years)	Mean or median
Sex (female)	n, %
Insulin users	n, %
BMI (kg/m^2)	Mean or median
Abdominal circumference (cm)	Mean or median
Duration of diabetes (years)	Mean or median
STOP-Bang[a] (score)	Mean or median
Glycohemoglobin (%)	Mean or median

[a]STOP-Bang: snoring, tiredness, observed apnea, high blood pressure, BMI, age, neck circumference, gender.

Figure 2. Sample table showing how results will be reported. Unpaired-sample *t* tests or Wilcoxon tests will be used.

Results	Placebo	Intervention	*P* value (95% CI)
Sum of the differences between all pre- and postprandial blood glucose levels			
Sum of the difference between pre- and postprandial blood glucose levels (breakfast glucose level)			
Sum of the difference between pre- and postprandial blood glucose levels (lunch glucose level)			
Sum of the difference between pre- and postprandial blood glucose levels (dinner glucose level)			
Sum of the difference between all pre- and postprandial blood glucose levels on the last day of blood glucose measurement			
Glycemic variability coefficient			

Discussion

Anticipated Findings

The role of melatonin in the glycemic control of T2DM patients has been studied for a number of years [25]. However, studies on the role of melatonin in glycemic variability are not available. Our work does not aim to assess the impact of melatonin on glycohemoglobin levels, but rather its effect on glycemic variability. The hypothesis was tested based on the fact that melatonin, as a hormone, plays a crucial role in regulating circadian rhythms. This notion is logical to us, given that a hormone whose secretion is primarily nocturnal, such as melatonin, governs numerous biological rhythms [26]. Our findings could signify a great advance in the management of T2DM, as it would provide a new therapeutic target: deficient melatonin production in affected individuals. The primary aim of this work is present a new approach toward managing and preventing chronic complications in patients diagnosed with T2DM.

Limitations

The limitations inherent in this study pertain to an analysis of glycemic variability conducted over a short span: only a few days after intake of melatonin or placebo. The effectiveness of melatonin in reducing glycemic variability might occur with longer use.

A second limitation of this study is derived from the fact that endogenous melatonin peaks in the middle of the night. The exogenous melatonin administered to patients in this study will not reproduce the physiological rhythm of endogenous melatonin.

A third limitation is the fact that patients may have diet and physical activity fluctuations between weeks 1 and 3 of the study, despite the guidance given initially, which might interfere with glycemic variability.

A fourth limitation of this study is the fact that we will not assess the prevalence of the *MTNR1B* mutation, which can determine a poorer glycemic response to melatonin use.

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Conclusions

The study of glycemic variability in patients with T2DM is fundamental for the prevention of chronic complications of the disease. Melatonin is a substance involved in biological rhythms, including those related to glucose control, such as insulin secretion. The existing knowledge that patients with T2DM produce a smaller amount of melatonin motivated us to test the replacement of this hormone as an instrument for greater glycemic stability. As glycemic variability is influenced by several variables, we conclude that a crossover design will be more suitable than a paired-group design for this study to evaluate the role of melatonin in glycemic stability.

Data Availability

The data sets generated during and/or analyzed during this study will be made available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

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Abbreviations

DPP 4: dipeptidyl peptidase 4
GLP1: glucagon-like peptide-1
MODD: mean of daily differences
STOP-Bang: snoring, tiredness, observed apnea, high blood pressure, BMI, age, neck circumference, gender
T2DM: type 2 diabetes mellitus

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Protocol

Colorectal Cancer Screening Decision Based on Predicted Risk: Protocol for a Pilot Randomized Controlled Trial

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Abstract

Background: Incidence of and mortality from colorectal cancer (CRC) can be effectively reduced by screening with the fecal immunochemical test (FIT) or colonoscopy. Individual risk to develop CRC within 15 years varies from <1% to >15% among people aged 50 to 75 years. Communicating personalized CRC risk and appropriate screening recommendations could improve the risk-benefit balance of screening test allocations and optimize the use of limited colonoscopy resources. However, significant uncertainty exists regarding the feasibility and efficacy of risk-based screening.

Objective: We aim to study the effect of communicating individual CRC risk and a risk-based recommendation of the FIT or colonoscopy on participants' choice of screening test. We will also assess the feasibility of a larger clinical trial designed to evaluate the impact of personalized screening on clinical outcomes.

Methods: We will perform a pilot randomized controlled trial among 880 residents aged 50 to 69 years eligible to participate in the organized screening program of the Vaud canton, Switzerland. Participants will be recruited by mail by the Vaud CRC screening program. Primary and secondary outcomes will be self-assessed through questionnaires. The risk score will be calculated using the open-source QCancer calculator that was validated in the United Kingdom. Participants will be stratified into 3 groups—low (<3%), moderate (3% to <6%), and high (≥6%) risk—according to their 15-year CRC risk and randomized within each risk stratum. The intervention group participants will receive a newly designed brochure with their personalized risk and screening recommendations. The control group will receive the usual brochure of the Vaud CRC screening program. Our primary outcome, measured using a self-administered questionnaire, is appropriate screening uptake 6 months after the intervention. Screening will be defined as appropriate if participants at high risk undertake colonoscopy and participants at low risk undertake the FIT. We will also measure the acceptability of the risk score and screening recommendations and the psychological factors influencing screening behavior. We will also assess the feasibility of a full-scale randomized controlled trial.

Results: We expect that a total sample of 880 individuals will allow us to detect a difference of 10% (α=5%) between groups. The main outcome will be analyzed using a 2-tailed chi-squared test. We expect that appropriate screening uptake will be higher in the intervention group. No difference in overall screening uptake is expected.

Conclusions: We will test the impact of personalized risk information and screening recommendations on participants' choice of screening test in an organized screening program. This study should advance our understanding of the feasibility of large-scale risk-based CRC screening. Our results may provide insights into the optimization of CRC screening by offering screening options with a better risk-benefit balance and optimizing the use of resources.

Trial Registration: ClinicalTrials.gov NCT05357508; https://www.clinicaltrials.gov/study/NCT05357508

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International Registered Report Identifier (IRRID): DERR1-10.2196/46865

(JMIR Res Protoc 2023;12:e46865) doi:10.2196/46865

KEYWORDS

colorectal cancer screening; personalized screening; risk communication; shared decision-making; screening behavior; Switzerland

Introduction

Background

Colorectal cancer (CRC) is the third most common cancer after breast and lung cancers [1]. In 2020, CRC affected approximately 2 million people worldwide and caused 900,000 deaths. In Switzerland, every year, 4500 people are diagnosed with CRC, of whom 1760 die from CRC [2]. However, CRC can be effectively prevented by screening that allows detection and removal of early-stage cancers and precancerous lesions [3-5]. The 2 most frequently offered screening options are colonoscopy and the fecal immunochemical test (FIT). Colonoscopy is more sensitive, especially for polyps [6,7], but it carries risks of bleeding and perforation [8,9]. It also requires an onerous bowel preparation; can be embarrassing for patients; and, as a population-level screening test, requires a large number of gastroenterologists. The FIT is less costly and noninvasive, can be performed at home without preparation, and has higher acceptance [6,10]. The impact of the FIT on CRC mortality over multiple rounds of screening is likely similar to colonoscopy [7,10], and it seems to decrease CRC incidence by approximately 33% [11].

Major risk factors for CRC are advanced adenoma, increasing age, and a small number of rare genetic syndromes [5]. Multiple other factors related to environment and lifestyle influence CRC incidence and can also contribute to one's risk of developing CRC [12]. One of the best-performing risk calculators is the open-source tool QCancer [12], developed in the United Kingdom and validated on 2 large cohorts of 3.6 million and 2.1 million patients [13,14]. It performed well in comparison with other algorithms [14,15].

Currently, in Switzerland and many other countries, the population is divided into 2 groups: people at average risk of CRC and those at very high risk of CRC because of a personal history of advanced adenomas or CRC, a familial history of CRC, symptoms concerning for cancer, or rare genetic syndromes [5]. Individuals at very high risk are offered regular surveillance colonoscopies and are not part of organized screening programs. However, the population at average risk is not homogeneous and could be broken up into at least 3 groups: high, moderate, and low risk. In 2019, the BMJ Rapid Recommendations team [12] made a weak recommendation against screening for individuals with a CRC risk of <3% in the next 15 years using the QCancer calculator [12]. However, because zero risk does not exist, recommendations against screening are questionable. Nevertheless, the threshold of <3% risk can be used to recommend the FIT and not colonoscopy. In clinical practice, patients with a risk of >6% in the next 15 years are generally offered colonoscopy surveillance. Thus, 6% risk can be considered a threshold for the high-risk level. These cutoffs could optimize the use of colonoscopy resources, which are limited. The majority of people are at low risk (approximately 60%; J Usher-Smith, PhD, email, June 21, 2020). Offering them colonoscopy results in its overuse and risk of complication for the individuals who are less likely to benefit from screening. On the contrary, reorienting individuals at low risk to the FIT would reduce the number of individuals who choose colonoscopy as a screening test and, therefore, reduce waiting time for those at high risk. Given that the ultimate aim of screening is to diminish mortality, colonoscopies should be reserved for people at high risk because differences in risk reduction between colonoscopy and the FIT become more pronounced for this population [16].

However, the impact of personalized screening on the screening test choice remains unclear. A meta-analysis has shown that personalized risk communication alone does not improve the overall uptake of screening tests [17]. Indeed, communicating personalized risk without giving clear screening recommendations may have no influence on screening behavior or even decrease it. This is in accordance with the view that providing people with threatening information only can decrease desired health behaviors if people cannot cope with the threatening information. However, the studies included in the meta-analysis did not address the choice between the FIT and colonoscopy and contain some important methodological discrepancies.

Objectives

In summary, personalized screening may offer people better risk-benefit balance in CRC screening and optimize the use of limited colonoscopy resources. However, there is limited knowledge about how the communication of risk and screening recommendations affects CRC screening behaviors. The primary aim of this trial is to study the effect of communicating individual CRC risk score and screening recommendations on appropriate screening uptake at 6 months in individuals stratified into 3 groups: low, moderate, and high risk of developing CRC in the next 15 years. Screening will be considered appropriate if the participant undertakes the test that is adapted to their risk level. Our hypotheses are as follows:

- Compared with the control group, individuals at low risk receiving the intervention will be more likely to undertake the FIT.
- Compared with the control group, individuals at high risk receiving the intervention will be more likely to undertake colonoscopy.
- Individuals at moderate risk receiving the intervention will have the same screening behavior as the individuals in the control group, that is, approximately 50% will be more likely to undertake the FIT, and approximately 50% will be more likely to undertake colonoscopy [18].

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We expect no difference in overall screening uptake.

Moreover, we will calculate the participation rate and proportion of individuals eligible for our study. We will also perform subgroup analyses and explore anxiety related to the information about the participants' risk level.

Methods

The trial's protocol follows the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines and the CONSORT (Consolidated Standards of Reporting Trials) statement for randomized controlled trials, as well as the CONSORT-EHEALTH (CONSORT of Electronic and Mobile Health Applications and Online Telehealth) checklist [19,20] (Multimedia Appendix 1). The trial was registered on ClinicalTrials.gov (NCT05357508) on May 3, 2022, before the enrollment of the first participant.

Study Design and Setting

We will perform a 2-arm randomized superiority controlled trial with participants randomized 1:1 in 2 arms: intervention and usual care. Participants, but not the investigators, will be blinded. The statistician performing the primary outcome analyses will be blinded to group assignments. The trial will be nested in the Vaud CRC screening program.

We used a *patient and public involvement in research* approach throughout by involving 5 members of the target population (residents of the canton of Vaud, Switzerland, aged between 50 and 69 years) in all aspects of the project. This collaboration allowed us to develop materials for our participants that were acceptable, easily understood, and pretested before the trial started. These 5 members will participate in the interpretation and dissemination of the results.

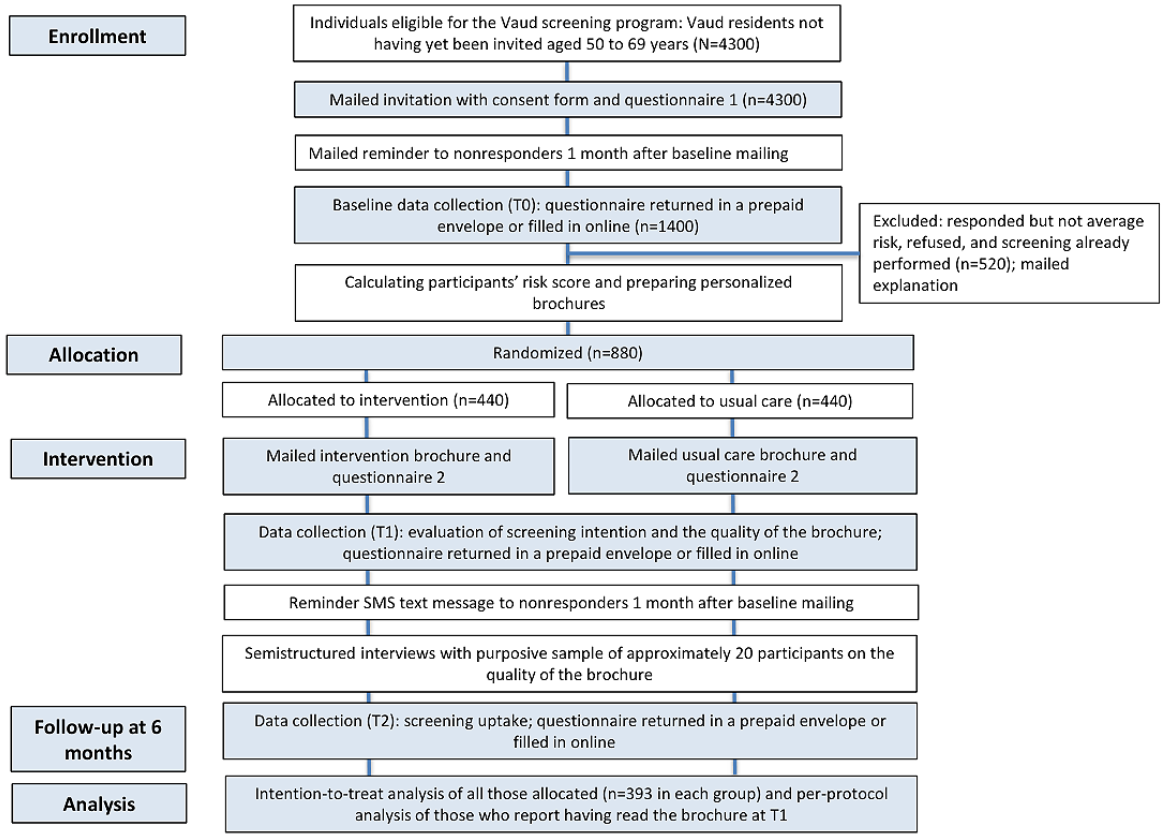
Participants

We plan to send out 4300 invitations to recruit 880 eligible participants (Figure 1). Refer to Textbox 1 for the inclusion and exclusion criteria.

Our exclusion criteria allow for the exclusion of individuals at very high risk of CRC (Textbox 1), enabling us to avoid inviting to the study those who are ineligible for the Vaud screening program. Individuals at very high risk are identified using a questionnaire to screen for current symptoms of possible CRC, personal history of CRC or polyp requiring surveillance, inflammatory bowel disease, and genetic syndromes.

Participants can stop their participation at any time without providing any justification. They will be informed that screening uptake is not mandatory and that withdrawal of consent will not affect their subsequent participation in the Vaud screening program.

Figure 1. Planned CONSORT (Consolidated Standards of Reporting Trials) diagram for the pilot randomized controlled trial. T1: intervention and secondary outcome data collection; T2: follow-up at 6 months (primary outcome and secondary outcome data collection).



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Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Being a resident of the Vaud canton, Switzerland
- Aged between 50 and 69 years
- Not having yet been invited to the Vaud colorectal cancer (CRC) screening program (this program was gradually rolled out between 2016 and 2022)

Exclusion criteria

- Current new symptoms suggestive of CRC
- Personal history of CRC, inflammatory bowel disease, or advanced adenoma or other polyps requiring colonoscopy surveillance at intervals of <10 years
- High-risk familial syndromes for CRC (ie, Lynch syndrome or familial polyposis)
- Having undergone colonoscopy within 9 years or having undertaken the fecal immunochemical test within 1.5 years
- Being unable to participate in follow-up at 6 months

Procedure

The study will be conducted in the following 3 phases:

- T0: recruitment and baseline data collection
- T1: intervention and secondary outcome data collection
- T2: follow-up at 6 months (primary outcome and secondary outcome data collection)

At T0, an invitation letter, a consent form, and the baseline questionnaire (questionnaire 1) that allows us to verify the eligibility criteria and calculate the CRC risk score will be sent to the potential participants by the Vaud CRC screening program. The ID codes for the participants will be generated using the IDGenerator, a software tool that was specifically developed for epidemiological and clinical trials [21]. The risk score will be calculated for all eligible individuals who return the signed consent form; subsequently, they will be randomized to either the intervention group or the control group. All individuals who do not respond within 1 month after the first mailing will receive a reminder.

At T1, enrolled participants will receive the intervention or a usual care brochure (in accordance with their group allocation), questionnaire 2, and an information sheet that they can provide to their general practitioner and pharmacist regarding their participation in the study. The participants who do not respond to questionnaire 2 within 2 weeks will be sent a reminder. Qualitative interviews will be conducted with willing participants at this time.

Six months after the intervention, at T2, participants will be contacted again to measure their screening behavior using questionnaire 3. Their responses will be accepted up to 8 months after the intervention. In case of nonresponse within 2 weeks, they will receive a reminder.

All 3 questionnaires, information materials for the participants, and the consent form will be available in both paper and electronic formats. Participants can choose the format that is more convenient to them. All data will be entered into the REDCap (Research Electronic Data Capture; Vanderbilt University) platform [22,23].

Refer to Table 1 and Figures 1 and 2 for procedure details.

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Table 1. Schedule of enrollment, intervention, and assessments.

	Study period			
	Enrollment	Allocation	After the allocation	
	T0[a]	0	T1[b]	T2[c]
Enrollment				
Informed consent	✓			
Eligibility screening	✓			
Calculation of the risk for CRC[d]	✓			
Allocation		✓		
Intervention				
Mailing of the intervention brochure			✓	
Mailing of the usual care brochure			✓	
Assessments				
Baseline variables: eligibility, risk factors for CRC, previous screening recommendations from a GP[e], knowledge about screening for CRC, demographics, and contact information	✓			
Main outcome variables: FIT[f] uptake, colonoscopy uptake or appointment for colonoscopy				✓
Secondary outcome variables				
Intention for screening	✓		✓	✓
Results of the undertaken screening test				✓
Self-efficacy for screening tests			✓	
Emotional reaction to the received risk score			✓	
Perceived barriers to screening			✓	✓
Perceived benefits from screening			✓	
Perceived susceptibility for CRC			✓	
Quality of the brochure and acceptability of the screening recommendations			✓	
Qualitative interviews				
Clarity, completeness, and credibility of the information in the brochure, brochure's usefulness for decision-making, and suggestions about brochure design			✓	✓
Motivation for undergoing a specific screening test			✓	✓

[a]T0: recruitment and baseline data collection.

[b]T1: intervention and secondary outcome data collection.

[c]T2: follow-up at 6 months (primary outcome and secondary outcome data collection).

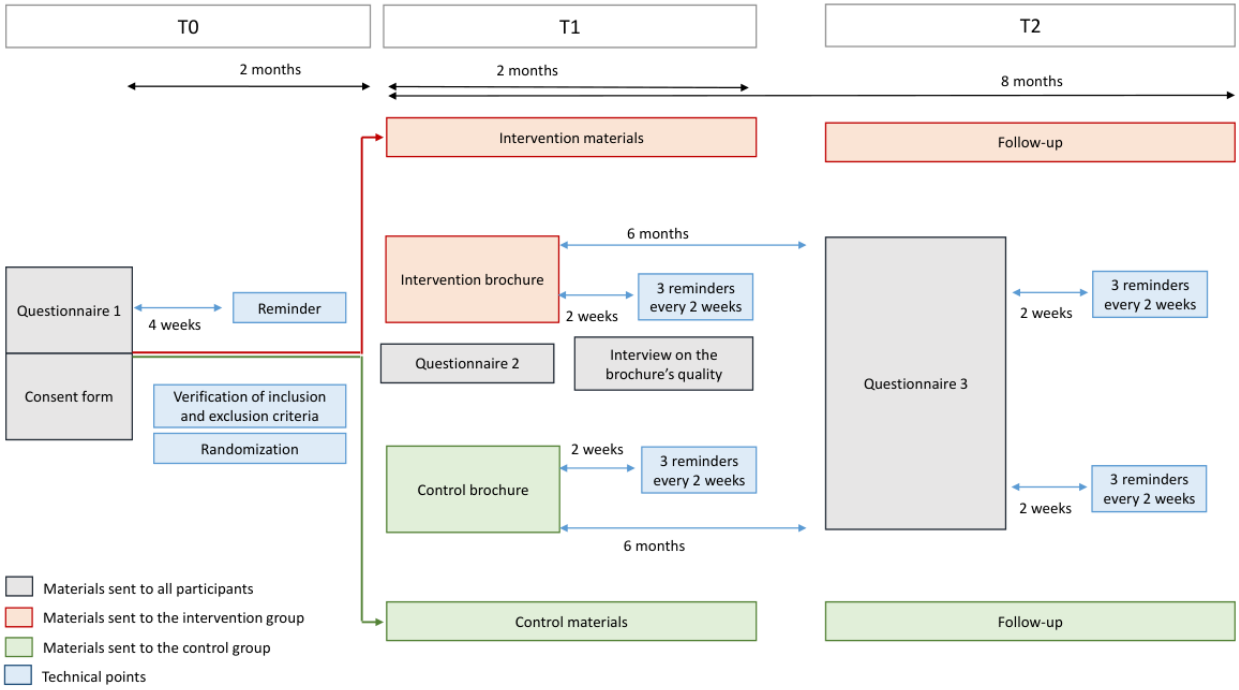
[d]CRC: colorectal cancer.

[e]GP: general practitioner.

[f]FIT: fecal immunochemical test.

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Figure 2. Detailed procedure of the study. T0: recruitment and baseline data collection; T1: intervention and secondary outcome data collection; T2: follow-up at 6 months (primary outcome and secondary outcome data collection).



Outcome Measures

The primary outcome measure is the self-reported appropriate screening uptake 6 to 8 months after the intervention (T2), measured using a short self-administered questionnaire. As waiting times can be long for screening colonoscopies [18], participants who have fixed a colonoscopy appointment will be counted as having undergone a colonoscopy. For the secondary outcome measures, refer to Textbox 2, and for the additional measures, refer to Textbox 3.

Refer to Multimedia Appendix 2 for the English version of the questionnaires and Multimedia Appendix 3 for the French version.

Textbox 2. Secondary outcome measures.

- Self-reported overall screening participation measured at T2 (follow-up at 6 months): on the basis of the participants' responses at T2, we will calculate the proportion of those who have completed any colorectal cancer (CRC) screening test (fecal immunochemical test or colonoscopy)
- Participation in the study at 6 weeks after the invitation letter was sent out: we will calculate the number of fully completed electronic or paper questionnaires
- Eligibility for the Vaud CRC screening program at 6 weeks after the invitation letter was sent out: we will calculate the proportion of those who are eligible for the Vaud screening program (eg, not up to date with screening, not in colonoscopy surveillance, and no personal CRC history)
- Self-reported anxiety related to the intervention and control materials measured at T1 (intervention) using 6 items inspired by the State-Trait Anxiety Inventory [24]
- Linkage to the Vaud CRC screening program assessed at 3 to 6 months after the primary outcome measurement: we will calculate the proportion of study participants who consent and whose screening status is obtained from the Vaud CRC screening program
- Linkage to the Vaud cancer registry up to 10 years after the primary outcome measurement: we will calculate the proportion of study participants who consent and whose cancer status is obtained from the Vaud cancer registry (a long time frame has been chosen in view of the delay in updating the cancer registry records and interest in cancer outcomes several years after the primary outcome measurement)

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Textbox 3. Additional measures.

At T0 (baseline)

- Intention for screening
- Preferences for screening test
- Capacity to participate in screening (no serious health conditions preventing participants from undergoing screening)
- Previous screening recommendations of general practitioner
- Knowledge about screening for colorectal cancer (CRC)
- Demographics

At T1 (intervention)

- Perceived susceptibility to CRC
- Perceived benefits of, and barriers to, screening
- Perceived self-efficacy for screening tests
- Participants' opinions regarding the quality of the brochure
- Acceptance of the provided screening recommendations

At T2 (follow-up at 6 months)

- Participants' barriers to screening (only those who were not screened)

Theoretical Framework for Understanding the Choice of Screening Test

Several of our outcomes are based on the health belief model [25], which posits that people are more likely to adopt a health-related behavior if they believe that they are vulnerable to the illness (perceived susceptibility) and that the illness is dangerous (perceived severity). Indeed, according to a recent meta-analysis [26], risk appraisals had a small to moderate effect on both the intention to adopt a health-related behavior and the behavior itself. However, the effect sizes for intention and behavior were nearly doubled in size when the interventions aimed at increasing participants' self-efficacy and perceived efficacy of the recommended behavior [26].

We believe that participants' screening behavior will largely depend on their perceived susceptibility to CRC as well as their beliefs about their self-efficacy and the efficacy of screening. These elements have been included in our intervention materials.

CRC Risk Calculation and Risk Levels

The personalized 15-year CRC risk score will be calculated using the QCancer calculator [27]. The QCancer calculator is an open-source algorithm that was developed in the United Kingdom and validated on 2 large cohorts of 3.6 million and 2.1 million patients [28,29]. The QCancer algorithm is based on variables that were available from the patients' primary care electronic health records. This covers many risk factors for CRC such as age, sex, and personal and family histories of cancers. However, diet and physical activity, which are 2 potentially important CRC risk factors, were not included in the algorithm because the information about them was not routinely collected and included in electronic health records [14]. The QCancer score was chosen because it was developed on a European population, it predicts CRC instead of advanced neoplasia, and it performed well in a large prospective validation study [13]. Despite some limitations, a systematic review showed that the QCancer score allows assigning an individual to the correct risk group with a probability of approximately 70% [14,15]. Although its predictive performance is not perfect, the QCancer risk score gives a good estimation of an individual's risk level and allows the delivering of personalized recommendations for screening.

For this study, we modified the original algorithm slightly. Our adapted version includes the following factors to calculate the participants' risk score: age; sex; tobacco and alcohol consumption; family history of CRC; personal history of breast cancer, uterine cancer, cervical cancer, or ovarian cancer for women and personal history of lung cancer, oral cancer, or blood cancer for men; having type 2 diabetes; and BMI values.

Ethnicity, postal code, ulcerative colitis, and colonic polyps will not be used in our adapted algorithm. Ethnicity and postal code have not been validated by studies for use in Switzerland and likely have different effects on CRC risk here than in the United Kingdom. For this reason, the option "White or not stated" will be used by default for all participants, and the field for postal code will be left blank. As our exclusion criteria include advanced adenoma and inflammatory bowel disease, we will indicate that our participants had neither ulcerative colitis nor colonic polyps. We have conducted tests to ensure the robustness of the QCancer score without these elements.

The obtained participant risk scores will be divided into 3 risk levels: low risk (<3%), moderate risk (3% to <6%), and high risk (≥6%).

These cutoffs are related to screening recommendations made to the participants and were based on the evaluation of risk and benefits related to the screening options.

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Intervention and Usual Care Materials

The intervention consists in communicating to the participants their 15-year CRC risk score and recommending the screening test most appropriate for their risk level using specially designed brochures (refer to Multimedia Appendix 4 for the English version of the brochure and Multimedia Appendix 5 for the French version). The intervention brochure is available in the following 3 categories: low CRC risk (<3%), with a recommendation to undertake the FIT; moderate CRC risk (3% to <6%), with a recommendation to either undertake the FIT or colonoscopy; and high CRC risk (≥6%), with a recommendation to undertake colonoscopy.

The intervention brochure provides the 15-year CRC risk score in comparison with that of an *average person* who has a similar profile; for example, an individual who has a CRC risk of 2% (low risk) receives the following message: "According to our estimations, 2 out of 100 people with the same profile as yours will get colon cancer in the next 15 years."

This message is accompanied by a graphic representation of the risk score and the risk level. Refer to Multimedia Appendix 4 (English version) and Multimedia Appendix 5 (French version) for more information.

Clear screening recommendations presented in the intervention brochure aim to increase participants' perceived self-efficacy for screening tests. We thus expect that participants at high risk will perceive that they are more susceptible to CRC and, therefore, will be more likely to undertake colonoscopy, which is the most accurate CRC screening test. By contrast, the participants at low risk are expected to perceive their susceptibility to CRC as lower and opt for the noninvasive FIT. To prevent the participants at low risk from declining screening, the brochure informs that zero risk does not exist and strongly recommends undertaking the FIT. No strong recommendations will be made to participants at moderate risk; therefore, the FIT and colonoscopy will be presented in the brochure as equal screening options.

To increase the participants' perceived response efficacy, our intervention materials emphasize information about the advantages of the recommended test for their risk level. However, the intervention brochure does present an alternative to screening, thus offering a choice to the participants. Moreover, all intervention group participants will receive an information sheet suggesting that they discuss their risk level with their general practitioner.

The intervention brochure will contain recommendations corresponding to the risk level of each participant only. We expect that this will facilitate the understanding of the provided information, minimize reading effort, and enhance adherence to our recommendations. Refer to Table 2 for more information about the content of each brochure category. For the sake of brevity, the intervention brochures will not communicate the side effects or sensitivity of the tests. Both the FIT and colonoscopy are screening tests commonly used in Switzerland and are considered safe and efficient to significantly reduce CRC mortality if undergone within the recommended period (the FIT every 2 years and colonoscopy every 10 years).

The control brochure represents the usual brochure that the Vaud screening program provides to individuals eligible for CRC screening. This brochure recommends screening to all individuals beginning at age 50 years and presents both the FIT and colonoscopy as equal options. This brochure does not include either a personalized risk score or specific screening recommendations. This suggests that, in the control group, the screening tests will be chosen according to the participants' preferences or after discussion with their primary care physician rather than in accordance with their risk level.

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Table 2. The different kinds of information presented in the printed materials.

Information presented in the brochure	Intervention brochure			Control brochure
	High risk	Low risk	Moderate risk	
Information about CRC[a]	Yes	Yes	Yes	Yes
Information about screening benefits	Yes	Yes	Yes	Yes
Explanation concerning risk levels and how they can be calculated	Yes	Yes	Yes	No
Personalized risk score	Yes	Yes	Yes	No
Screening recommendations	Personalized: colonoscopy recommended; the FIT[b] as an alternative	Personalized: the FIT is recommended; colonoscopy as an alternative	Personalized: the FIT and colonoscopy are equal options	General: the FIT and colonoscopy are equal options
Explanations why recommended tests are appropriate	Yes	Yes	Yes	No
Short instructions about how to undertake the FIT and how to prepare bowel for colonoscopy	Yes, instructions for colonoscopy only	Yes, instructions for the FIT only	Yes, instructions for both tests	Yes, instructions for both tests
Warning that risk increases with age and encouraging statements to maintain a healthy lifestyle	Yes	Yes	Yes	No
Suggestion to consult a physician if cancer symptoms occur	Yes	Yes	Yes	Yes
Information about health insurance coverage of the screening tests	Yes	Yes	Yes	Yes

[a]CRC: colorectal cancer.

[b]FIT: fecal immunochemical test.

Qualitative Interviews

Semistructured qualitative interviews will be conducted by telephone with a purposive sample of approximately 20 participants using a previously elaborated interview guide until we achieve thematic saturation. The interviews are based on the user-experience "honeycomb" framework described by Morville [30], and they aim to obtain detailed information about the quality of the brochure and the acceptability of the provided screening recommendations. We will be especially interested in the following information: (1) whether the brochure is useful for decision-making about the screening tests; (2) whether participants feel that the brochure improved their knowledge about CRC and screening; (3) whether the information is clear, easy to understand, and credible; and (4) whether the brochure satisfies the participants or whether they have suggestions to improve it.

Purposive sampling will be based on study arm, sex, age, risk level, knowledge of the French language, and reported preferences for the screening test.

Randomization and Blinding

Randomization will be carried out automatically via the REDCap randomization module programmed by the trial statistician. We will apply a stratified block randomization strategy with a block factor of 8 to prevent a possible imbalance between the control and intervention groups, especially among participants at high risk. The participants will be blinded to the group allocation. They will be told that the study compares 2 slightly different brochures about CRC screening options; however, the nature of the intervention will not be disclosed. The investigators will not be blinded, but, owing to the automatic randomization, they will not be able to influence the participants' group allocation. The analysis of the main study outcome will be performed by the trial statistician who will be blinded to the participants' allocation.

Ethics Approval

The study protocol (project ID 2021-02431) was approved by the ethics committee of the canton of Vaud on March 2, 2022. All the important protocol modifications will be documented and communicated to the ethics committee along with the intermediate and final reports.

Steering Committee and Trial Monitoring

The trial is supervised by a steering committee composed of a gastroenterologist, a general practitioner, an epidemiologist, and psychologists, as well as experts in shared decision-making and statistical modeling. The members of the steering committee are in charge of approving the trial's methodology and data analysis plan, and they also contribute in the preparation of oral and written communication materials.

The trial is monitored by an institutional team for trial monitoring that is independent from the trial sponsor and competing interests. The monitoring team will check the quality of collected data as well as conformity with the study protocol. At least 3 site visits are planned, following recommendations from the Swiss Clinical Trial Organization for low-risk trials.

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Statistical Analyses

Sample Size Estimation

We expect that 60% of the eligible individuals will be at low risk for CRC, 30% at moderate risk, and 10% at high risk, based on approximate calculations carried out with the UK biobank cohort. The actual distribution of CRC risk factors, and hence 15-year risk scores, in the Vaud population eligible for the screening program is not known.

We also expect that in the intervention group, individuals will be more likely to undertake the appropriate screening test, whereas in the control group, the choice of screening test will not differ among the risk levels (Table 3).

Thus, to detect a difference of 10% (ie, between 46% and 56%) at α=5%, a sample size of 392 individuals in each arm is required to reach 80% power. Assuming approximately 10% attrition, we plan to recruit 440 individuals in each arm (a total of 880 individuals). Our estimation of 10% attrition is based on the results of previous longitudinal studies conducted in the canton of Vaud.

We will invite individuals who have not previously been invited to the Vaud CRC screening program. At the time of sending out the invitation, we will not know whether they are eligible for screening, principally because they may already be up to date with screening or may have had a high-risk polyp needing colonoscopy surveillance. Thus, we plan to send out approximately 4300 invitations; we expect 1400 (32.56%) to respond. Of these 1400 participants, we anticipate that 880 (62.86%) will be eligible for the study (Figure 1). In case of a low response rate, we will send out an additional 2000 invitations.

Table 3. Hypothesized size of each group as a proportion of the eligible population and predicted changes in screening choices with personalized recommendations. Group sizes have been chosen to provide sufficient statistical power.

Arm and risk level	Eligible population, %	Choose colonoscopy, %	Choose FIT[a], %	None, %	Colonoscopy, n/N	FIT, n/N	None, n/N	Overall uptake, %	Appropriately screened, % (n/N)	Overall proportions by randomization
Control (n=392)										
Low	60	34.9	34.9	30.2	82/235	82/235	71/235	70	35 (82/235)	Appropriate screening: 46% (179/392)
Moderate	30	34.7	35.6	29.7	41/118	42/118	35/118	70	71 (83/118)	Overall uptake: 70%
High	10	35	35	30	14/39	14/39	11/39	70	35 (14/39)	—[b]
Intervention (n=392)										
Low	60	20.4	49.8	30.2	48/235	117/235	71/235	70	50 (118/235)	Appropriate screening: 56% (220/392)
Moderate	30	34.7	35.6	29.7	41/118	42/118	35/118	70	70 (82/118)	Overall uptake: 70%
High	10	50	25	25	20/39	10/39	9/39	75	50 (20/39)	—

[a]FIT: fecal immunochemical test.

[b]Not available.

Data Collection

Trial personnel will be trained in good clinical practices and data management. The research team will be provided with the precise guidelines for the inclusion and exclusion criteria, data collection and analysis, and the handling of missing data.

For data collection, we will use 2 validated questionnaires or questionnaires pretested in previous studies. All study materials, including questionnaires, have been reviewed and approved by our citizen advisory group.

All answers to the questionnaire in paper format will be manually entered into the REDCap platform, and 20% of the entries will be checked by another member of the research team. Qualitative interviews will be conducted by a trained team member, recorded, and transcribed. For quality assurance, dual independent coding will be used for 20% of the transcripts, purposively selected. Data triangulation will be used as relevant. Investigator triangulation will also be conducted.

Quantitative and qualitative data will be coded using unique participant identifiers previously generated via the IDGenerator [21]. Paper questionnaires and consent forms will be stored in the investigator site file. Coded data and participant identification lists will be stored separately. Participants' data will be accessible to authorized personnel only.

Although our trial presents low risk for participants, we will collect information about adverse events; for instance, we will collect information about rectal bleeding or hospitalization after colonoscopy and participants' anxiety related to the intervention and control materials, as well as the adverse events registered by the Vaud screening program. Serious adverse events will be documented and reported within 24 hours to the sponsor-investigator of the study. Serious adverse events that

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could be attributable to the trial intervention will be reported to the ethics committee within 15 days.

Quantitative Data Analysis Plan

The study data will be summarized across all participants by group and by risk level. Continuous and count variables will be summarized as mean (SD) or median (IQR) and categorical variables as number (percentage). To test randomization quality, differences on the baseline variables will be examined using a 2-tailed *t* test for continuous variables and a 2-tailed chi-squared test for categorical variables.

Self-reported appropriate screening uptake will be analyzed using a 2-tailed chi-squared test and controlled for the CRC risk level. Data analysis will be performed using R statistical software (R Foundation for Statistical Computing) [31] and Stata 16 software (StataCorp LLC) [32].

For the primary outcome, participants lost to follow-up will be considered as having refused to participate in screening. If there seems to be differential loss to follow-up between the intervention and control groups, we may perform multiple imputation based on baseline factors as an exploratory analysis. For other secondary outcomes, data will be considered missing completely at random.

Qualitative Data Analysis Plan

For qualitative analysis, we will use the user-experience "honeycomb" framework described by Morville [30]. This approach was used to test health education applications, a decision aid tool [33-36], and the systematic review library of the Cochrane Collaboration [37]. For the purposes of our study, we will use the following 5 (of 7) dimensions:

- Useful: whether the brochure is useful for decision-making about the screening test
- Valuable: whether the brochure improves participants' knowledge about CRC and screening
- Credible: whether the information in the brochure is perceived as credible
- Usable: whether the information is clear and easy to understand
- Desirable: whether the participants are satisfied by the brochure or whether they have suggestions about how to improve it

The qualitative data will be analyzed using MAXQDA software (VERBI Software GmbH) [38].

Results

Overview

As of September 2022, a total of 515 participants had been enrolled in the trial and sent intervention or control materials. Six months later, 98.8% (509/515) of the enrolled individuals were sent the follow-up questionnaire. Data collection was completed on July 24, 2023 (6-8 months after the intervention).

We expect that the proportion of participants who complete the screening test appropriate to their risk level will be higher in the intervention group than in the control group, except for the individuals at moderate risk. The proportion of participants at moderate risk in the intervention group is expected to be the same as that of the participants in the control group in screening test choice because both tests are suggested as equal options.

We do not expect any difference in anxiety between the intervention and control groups. A Cochrane review of interventions similar to ours has shown that there was a nonsignificant trend toward decreased anxiety with risk information (standard mean difference in anxiety 0.13, 95% CI −0.29 to 0.03) [17].

Our intervention does not aim to enhance overall screening uptake; therefore, we do not expect any difference between the groups.

Dissemination of Results

We plan at least 5 open-access publications based on the trial data. Intermediate and final reports will be sent to the funding institution and to the ethics committee. Participants will be informed about the results of the trial on request. We communicate regularly with the Vaud organized CRC screening program and will encourage it to implement components of this approach if it is found effective.

Suggestions for oral communications and publications as well as names of authors will be discussed during the meetings of the steering committee. The principal investigator should be considered for the role of lead author. Disputes regarding authorship will be settled by the principal investigator and the steering committee.

Discussion

Testing the Impact of Risk Communication and Recommendations on Screening Behavior

Although many experts have recommended personalized CRC screening as a means of optimizing the risk-benefit balance for individuals and improving the use of scarce gastroenterology resources, this approach has not been implemented to date in an organized screening program. This study aims to demonstrate the effect of personalized information materials on individuals' choice of screening test to assess the feasibility of a larger trial evaluating the effect of personalized screening recommendations on clinical outcomes such as advanced neoplasia detection rate and CRC screening uptake. The trial addresses a current need of the Vaud screening program to demonstrate to the public and to physicians that individuals at low risk can be safely directed toward the FIT.

This trial is one of the rare studies that tests the impact of risk communication and recommendations on screening behavior. Although it may seem evident that communicating individuals' risk level would influence their screening behavior, previous studies have shown increased knowledge but little effect on test choice [17]. This presents a potential limitation in the implementation of personalized screening programs: unless these programs restrict the choice of participants, risk calculation may have no effect.

There are other means of personalizing CRC screening. Several strategies rely simply on participants' sex or race. In Sweden

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and Norway, different cutoffs are used to define a positive FIT result requiring colonoscopy [39]. In Germany, colonoscopy screening is recommended at age 50 years for men and age 55 years for women. The American Gastroenterology Society recommends screening at a younger age (45 years) for African Americans. Another approach is to use quantitative FIT results below the positivity threshold but above 0 to define shorter intervals between FITs [40]. We chose to use multiple factors to define baseline risk following recommendations from the BMJ Rapid Recommendations team [12] and because of the strains on colonoscopy capacity in the canton of Vaud [18].

The strengths of this study include its *patient and public involvement in research* approach for the development of study materials; nesting within an organized screening program; population-based sampling to obtain the estimates of participation in the general population; both quantitative and qualitative evaluations, which should permit us to obtain a preliminary estimate of not only efficacy but also acceptability and potential improvements; the use of theory (the Health Belief Model [25]) to inform the intervention and evaluation; and randomization and rigorous design for a pilot study.

Potential weaknesses include the need for informed consent beyond what is typically needed in an organized screening program, which could decrease participation and increase selection bias. As such, we might underestimate eventual participation and overestimate acceptance, assuming that we preferentially include persons motivated to be screened. This selection bias could exclude populations considered more vulnerable, such as individuals with poor health literacy. However, the study materials were written, to the extent legally possible, using plain language. We did not translate the study materials into other languages, but all invitations from the screening program are also in French, with other languages only available on request. The Vaud screening program requested that we not invite individuals already participating in screening at regular intervals with the program because screening recommendations made in the study may differ from those made by the program and thus create confusion. We sought to avoid inviting for this study individuals who had not participated after being sent an invitation to the program, fearing that our participation rate would be too low. As a result, our sample population is heavily weighted toward younger age groups (those aged 50-54 years), and we may have a larger-than-expected proportion of participants at low risk of CRC.

Conclusions

We are evaluating the effect of communicating individualized CRC risk information and screening recommendations on the choice of screening test in an organized screening program that currently performs the FIT and colonoscopy in a ratio of approximately 50:50. We hypothesize that we can increase FIT use among individuals at low risk and increase colonoscopy use among individuals at high risk, improving the risk-benefit balance of CRC screening. These results will be valuable to screening programs around the world with either a high use of colonoscopy, such as in the canton of Vaud, or FIT programs that may fail to recognize individuals at high risk who could derive additional benefit from colonoscopy over the FIT.

Acknowledgments

The authors would like to thank Cyril Ducros, head of the Vaud cancer screening program; Sandra Mordacci-Boldini, administrative coordinator of the program; and all program team members for their contribution in the development of the original concept of the study and study logistics. The authors would also like to thank the members of the citizen advisory group who greatly contributed in the development of the study materials for participants.

Data Availability

The data sets generated and analyzed during this study are available from the corresponding author on reasonable request.

Conflicts of Interest

M-AD has contributed to the development of Option Grid patient decision aids. EBSCO Information Services sells subscription access to Option Grid patient decision aids, and M-AD receives consulting income from EBSCO Health as well as royalties. RA is the main recipient of 2 grants related to colorectal cancer screening from the Swiss Cancer Research Foundation (Health Services Research; HSR-4366-11-2017) and the Swiss National Science Foundation (National Research Program 74; NFP74 407440_167519) “Smarter Health Care.” RA is also an unpaid member of the expert committee of the organized screening program in Bern, Switzerland, with an advisory role as expert. IL-V has received several grants evaluating (risk-based) colorectal cancer screening from nonprofit organizations.

Multimedia Appendix 1
CONSORT-EHEALTH (Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth) checklist.
[PDF File (Adobe PDF File), 1146 KB - resprot_v12i1e46865_app1.pdf]

Multimedia Appendix 2
Questionnaires (English version).

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[PDF File (Adobe PDF File), 1462 KB - resprot_v12i1e46865_app2.pdf]

Multimedia Appendix 3
Questionnaires (French version).
[PDF File (Adobe PDF File), 2232 KB - resprot_v12i1e46865_app3.pdf]

Multimedia Appendix 4
Intervention and control brochures (English version).
[PDF File (Adobe PDF File), 2699 KB - resprot_v12i1e46865_app4.pdf]

Multimedia Appendix 5
Intervention and control brochures (French version).
[PDF File (Adobe PDF File), 11140 KB - resprot_v12i1e46865_app5.pdf]

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Abbreviations

CONSORT: Consolidated Standards of Reporting Trials
CONSORT-EHEALTH: Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth
CRC: colorectal cancer
FIT: fecal immunochemical test
REDCap: Research Electronic Data Capture
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Protocol

Evaluating the Effectiveness of the Housing First for Youth Intervention for Youth Experiencing Homelessness in Canada: Protocol for a Multisite, Mixed Methods Randomized Controlled Trial

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Abstract

Background: Emerging evidence at the international level suggests that the Housing First approach could improve the housing stability of young people experiencing homelessness. However, there is a dearth of literature in Canada on whether the Housing First intervention for young people experiencing homelessness can improve outcomes including housing stability, health and well-being, and access to complementary supports. Adapted from the original Housing First model, Housing First for Youth (HF4Y) was developed in Canada as a rights-based approach tailored specifically for young people aged 16 to 24 years who are experiencing or are at risk of homelessness.

Objective: The Making the Shift Youth Homelessness Social Innovation Lab is testing the effectiveness of the HF4Y intervention in Canada. The objective of this study is to determine whether the HF4Y model results in better participant-level outcomes than treatment-as-usual services for young people experiencing homelessness in 2 urban settings: Ottawa and Toronto, Ontario. Primary outcomes include housing stability, health and well-being, and complementary supports, and secondary outcomes include employment and educational attainment and social inclusion.

Methods: The HF4Y study used a multisite, mixed methods, randomized controlled trial research approach for data collection and analysis. Eligible participants included young people aged 16 to 24 years who were experiencing homelessness or housing precarity. The participants were randomly assigned to either the treatment-as-usual group or the housing first intervention group. Survey and interview data in Ottawa and Toronto, Ontario are being collected at multiple time points (3-6 months) over 4 years to capture a range of outcomes. Analytic strategies for quantitative data will include mixed-effects modeling for repeated measures and logistic models. A thematic analysis will be used to analyze qualitative data based on participants' narratives and life journeys through homelessness. Furthermore, program fidelity evaluations are conducted within each HF4Y program. These evaluations assess how well the intervention aligns with the HF4Y model and identify any areas that may require adjustments or additional support.

Results: The HF4Y study has received human participant research ethics approval from the Office of Research Ethics at York University. Recruitment was conducted between February 2018 and March 2020. Data collection is expected to be completed at both sites by March 2024. A preliminary analysis of the quantitative and qualitative data collected between baseline and 24 months is underway.

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Conclusions: This pilot randomized controlled trial is the first to test the effectiveness of the HF4Y intervention in Canada. The findings of this study will enhance our understanding of how to effectively deliver and scale up the HF4Y intervention, with the aim of continually improving the HF4Y model to promote better outcomes for youth.

Trial Registration: International Standard Randomized Controlled Trial Number (ISRCTN) ISRCTN10505930; https://www.isrctn.com/ISRCTN10505930

International Registered Report Identifier (IRRID): DERR1-10.2196/46690

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KEYWORDS

youth homelessness; Housing First for Youth; Canada; randomized controlled trial; RCT; Making the Shift

Introduction

Background

Youth homelessness has become a social problem in Canada that does not lend itself to a straightforward solution. Young people who experience homelessness (aged 13-24 years) account for approximately 20% of the total population experiencing homelessness in Canada, with 6000 to 7000 young people experiencing homelessness on any given night [1]. Pathways into youth homelessness are diverse and essentially emerge as the outcome of a complex and intricate interplay between individual and relational risk factors (eg, family crises and trauma), structural circumstances (eg, poverty and the lack of affordable housing), and systems failures (eg, fragmented service and program delivery) [2,3]. To effectively reduce and end youth homelessness, it is necessary to identify best practices and program interventions that address the unique needs of developing adolescents and young adults.

To date, studies have mostly focused on evaluating the different models of housing and support programs that serve adults experiencing homelessness, particularly those with mental health and substance use disorders [4]. Among such programs, the Pathways model known as Housing First gained currency in the 1990s, largely because of its demonstrated efficacy in reducing homelessness for individuals experiencing chronic homelessness and serious mental illness [5]. The underlying premise of the Pathways model was that individuals experiencing homelessness should be placed in housing as quickly as possible without conditions or prerequisites such as sobriety or medication adherence. The well-established, evidence-based body of research on the Pathways model lent further support to its success, with many cities adopting the model to address homelessness [6-9].

Within the Canadian context, the national At Home/Chez Soi project initiated in 2008 the largest randomized controlled trial (RCT) of the Housing First intervention, with many studies stemming from this research project [10-15]. The Mental Health Commission of Canada implemented the Housing First model in 5 cities (Vancouver, Winnipeg, Toronto, Montreal, and Moncton) with >2200 individuals who were experiencing homelessness. The 1-year and 2-year findings of the At Home/Chez Soi project across various sites provided compelling evidence that the Housing First intervention is an effective approach that helps individuals experiencing homelessness and who have serious mental illnesses exit homelessness more quickly compared with other treatment-as-usual (TAU) services [11,12,16,17].

However, as discussed by Goering et al [10], it remains unknown whether the Housing First intervention is effective and can be replicated among young adolescents with diverse racial and sociodemographic backgrounds, particularly within the Canadian context where Indigenous youth experiencing homelessness are overrepresented [3]. In addition, although Kozloff et al [14] presented promising results that the Housing First model can be "a viable intervention to promote housing stability in homeless youth with mental illness," they suggested that modifications be made to the model to better meet the needs of youth, as their findings indicated that the application of the model to young people did not significantly improve other primary outcomes in the treatment group (eg, community integration and substance use).

With these considerations in mind, Housing First for Youth (HF4Y) was developed in Canada as an adaptation of the original Housing First model and is based on the understanding that the causes and conditions of youth homelessness are distinct from those affecting adults; therefore, the solutions must likewise be youth focused [18-22]. This means that HF4Y is designed specifically to meet the needs of young adults who are at risk of or experience homelessness by providing them with age-appropriate supports including housing. As a rights-based approach, HF4Y rests on the philosophy that "all people deserve housing and that adequate housing is a precondition for recovery" [23]. The core principles of the HF4Y model provide a framework for developing the interventions that are needed to help young people successfully transition to adulthood in a safe and planned way. These core principles are as follows [20]:

1. A right to housing with no preconditions: as a rights-based and youth-centric approach, HF4Y does not require youth to fulfill any precondition, such as sobriety or abstinence, to qualify for receiving housing support.
2. Youth choice, youth voice, and self-determination: this principle speaks to providing opportunities for youth to be in control of their own lives and encouraging them to make informed decisions when it comes to deciding where they want to live, rather than having this imposed on them (in real-world practice, eg, if a young person cannot live in cooperative housing with shared rooms, case workers need to discuss and work on a solution to accommodate the youth

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living on their own by finding a place that is suitable for the young person and within their budget).

3. Positive youth development and wellness orientation: as a strength-based approach, the HF4Y model extends beyond assessing risk and vulnerability by recognizing the assets and strengths of young individuals to build self-esteem and a positive sense of self.
4. Individualized, client-driven supports with no time limits: as youth have diverse pathways into homelessness, the program model is client-driven to ensure culturally appropriate services are offered to youth that also accommodate the spectrum of sexual orientation and gender identities with no time limits.
5. Social inclusion and community integration: HF4Y promotes social inclusion by building youth's life skills and strengthening their existing relationships or by providing opportunities for them to meaningfully participate in community activities and engage with school and the labor market.

There is emerging evidence on the effectiveness of HF4Y at the international level [24-26]; however, little is known about the effectiveness of the HF4Y model in Canada, particularly considering that interventions and programs based on the HF4Y model must strictly adhere to the model's core values and principles to qualify as an HF4Y intervention [20]. This paper describes the research protocol of a 4-year comprehensive study that will contribute to the evidence base on the effectiveness of HF4Y through a rigorous program of developmental and outcomes evaluations. This will enhance our understanding of how to effectively deliver the HF4Y intervention and what outcomes are likely to be expected, with the aim of continually improving the HF4Y model to promote better outcomes for youth.

Making the Shift Youth Homelessness Social Innovation Lab

A key challenge in addressing youth homelessness is to determine what works, for whom it works, and in what context [27]; thus, how we frame "youth homelessness" is of paramount importance. In the Canadian context, youth homelessness refers to "the situation and experience of young people between the ages of 13 and 24 who are living independently of parents and/or caregivers, but do not have the means or ability to acquire a stable, safe, or consistent residence" [3]. The youth population experiencing homelessness is diverse, with Indigenous, 2SLGBTQA+ (2-spirit, lesbian, gay, bisexual, transgender, queer [or questioning], asexual, and additional groups), and Black youth being overrepresented, meaning that our interventions need to be implemented with a focus on equity, diversity, and inclusion [3].

Focusing specifically on the prevention of youth homelessness (ie, reducing inflow into homelessness and returns to homelessness), the Making the Shift (MtS) Youth Homelessness Social Innovation Lab is coled by A Way Home Canada and the Canadian Observatory on Homelessness, which is housed at York University. MtS supports the facilitation of sustainable exits from homelessness by identifying, developing, prototyping, testing, evaluating, and mobilizing innovations in policy and practice through the implementation of demonstration projects. Blending experimental program delivery with research and evaluation, the demonstration projects include 15 sites across Canada in 12 communities in Alberta, British Columbia, Newfoundland and Labrador, and Ontario. These projects are intended to expand the knowledge and understanding of innovative approaches to preventing and ending youth homelessness by using design thinking and producing scientific evidence to truly meet the needs of those served. The demonstration projects also help determine how and whether a proposed policy or intervention works—known as establishing "proof of concept"—which can later be used to inform policy and provide knowledge for "scaling" successful models beyond the original communities.

As part of the MtS Youth Homelessness Social Innovation Lab, 3 demonstration projects on HF4Y are currently being implemented by community agencies in Ottawa, Toronto, and Hamilton in Ontario, Canada. In each of the cities, agencies that work with youth experiencing homelessness are implementing and operating the HF4Y program, consistent with the model developed by Gaetz et al [21]. Each testing site focuses on specific populations of young people experiencing homelessness. Although Ottawa focuses on youth currently experiencing homelessness, Toronto focuses on youth exiting the child welfare system as a preventive intervention.

In Hamilton, an RCT design is not being used as it does not align with the values of Indigenous knowledge and traditions. Instead, a hybrid model is being implemented; it is called *Endaayaang* and combines the core principles of HF4Y with Indigenous ways of knowing and cultural practices. In Canada, Indigenous youth include 3 distinct cultural groups, that is, First Nations, Metis, and Inuit. Youth from these communities are overrepresented in the population of youth experiencing homelessness because of the history of colonialism (including practices aimed at eradicating Indigenous cultural traditions such as residential schools and the 1960s Scoop); involvement with child protection services; and the presence of intersecting forms of oppression, intergenerational trauma, and marginalization [28-30]. The adaptation of the HF4Y program necessitates the inclusion of Indigenous leadership in the program for it to succeed. Therefore, an Indigenous-led methodology that adopts a hybrid approach combining Western and Indigenous methodologies and ways of knowing is being used [31]. This approach combines elements from the settler-developed HF4Y model with Indigenous ways of knowing and cultural practices, rooted in the understanding that Indigenous youth must experience a sense of belonging within their community and have access to cultural and spiritual guidance from Elders and Traditional Knowledge Keepers to achieve positive outcomes.

The demonstration projects intend to help build an evidence base for youth homelessness prevention in Canada and to inform work on youth homelessness internationally. The research protocol described in this paper focuses on the models being implemented at the HF4Y sites in Toronto and Ottawa. The *Endaayaang* program model, which incorporates Indigenous epistemology, vernacular knowledge, and Indigenous-led research methodologies, will be described separately.

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Study Objectives

The HF4Y study seeks to engage relevant stakeholders and communities in a collaborative research and knowledge translation process throughout all stages of the project. The stakeholders include young people with lived experiences of homelessness, Indigenous communities, the agencies engaged in the homelessness sector and delivering interventions, and the broader network of service providers for youth experiencing homelessness in each city. On the basis of an equity lens, this study also intends to address the intersectional needs of racialized, Indigenous, and 2SLGBTQA+ youth populations as well as youth with disabilities. Together, this collaboration aims to achieve the following objectives:

1. To determine whether the HF4Y model results in better participant-level outcomes than TAU services for young people experiencing homelessness in 2 urban settings (Ottawa and Toronto) with respect to (1) housing stability; (2) health and well-being; (3) complementary supports such as social functioning and life skills (4) engagement in education, training, and employment; and (5) social inclusion.
2. To identify the critical components of the HF4Y model and what modifications are needed to effectively serve particular communities and subpopulations (eg, youth exiting the child welfare system, Indigenous youth, and 2SLGBTQA+ youth).
3. To identify the main pathways into youth homelessness or precarious housing situations and understand the key challenges young people experience in terms of recovery, the ability to thrive, and housing precarity. This will allow policies, practices, and program interventions to be improved to better serve the needs of youth experiencing homelessness.

It should be noted that the relationship between these objectives can be framed in a complementary manner, which helps improve the HF4Y program to better respond to the needs of youth experiencing homelessness.

Methods

Study Design

The HF4Y study uses a longitudinal, multisite, mixed methods RCT research approach for data collection and analysis. The choice of using an RCT design was consistent with the relevant body of clinical trials at the intersection of homelessness, social policy, and health [16,32,33], particularly the At Home/Chez Soi national project [10]. RCT studies are widely regarded as the highest standard for studying causal relationships between interventions and outcomes [34,35]. Despite their limitations, such as population availability, missing data, and participant dropouts [36], RCTs can successfully minimize a substantial portion of the inherent biases commonly observed in other study designs.

There is a growing recognition of the importance of integrating qualitative approaches in RCTs [37]. The choice of incorporating a qualitative inquiry in this study was intended to gain insights from youth participants during the implementation phase to better understand the effects of the HF4Y interventions and how they are experienced by recipients. Therefore, the results of the qualitative inquiry and RCT can be integrated to draw meaningful conclusions about the efficacy of the HF4Y intervention.

Each of the 2 site-specific HF4Y demonstration projects was tailored to reflect the needs of the target population as well as the unique local environments and cultural contexts at hand. At both the Ottawa and Toronto sites, 2 groups were created: an intervention group that received housing first (HF intervention) and a control group that received TAU services. At both sites, the participants randomized to the HF intervention group receive housing and support, consistent with the HF4Y program model [20,21], including the provision of a housing subsidy for the duration of the study (4 years). Youth participants are offered a range of housing options with no treatment preconditions (eg, in-place crisis, transitional, supportive, or scatter-site housing with mobile supports), and they receive an array of case management services related to housing retention, well-being, income and employment, education, and social inclusion as well as complementary supports. Participants randomized to the TAU group do not receive the HF intervention but generally have access to supports and regular housing programs in the community that are available for young people, potentially including income support, drop-ins, physical and mental health clinics, emergency shelters, and transitional housing or longer-term housing. Participants in this group are provided with an information package about both housing and supports and are invited to use the field office or participating service agency as a resource.

Partnership and Public Involvement

The HF4Y research study actively engaged community partners and youth with a lived experience of homelessness throughout the design and implementation process. Forming a partnership with key stakeholders, including community agencies, was pivotal to advancing the goals of the study while allowing for a more meaningful collaboration between researchers and service providers. It was important that the study be delivered in partnership with local agencies, as the ultimate aim was to build practical knowledge and an evidence base for the HF4Y intervention. Combining on-the-ground knowledge with insights provided by a large body of stakeholders, including service providers, policy makers, researchers, and youth with lived experience, was an underlying ethos that undergirded the development of the original HF4Y program model guide [20].

The collaboration between researchers and 2 key organizations, namely, the Street Youth Planning Collaborative (Hamilton) and the National Learning Community on Youth Homelessness, played a central role in shaping and executing this study. In particular, the input from young individuals with lived experience was crucial and highly valued during this collaborative process. The findings of this study will also be shared with the youth participants and community partners who actively participated in the research.

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Ethical Considerations

The study's human participant research protocol was approved by the Office of Research Ethics at York University (2017-382).

The eligible participants are provided with informed consent forms that contain information about the study, participants' rights, expectations, potential risks and benefits, the amount of compensation, and the resources and services available for them during the study. Informed consent is also solicited from participants for each follow-up survey or interview. Participants are compensated for their participation in the research depending on the length of the sessions they attend. For the intervention group, 90-minute appointments are being remunerated with CAD $50 (US $37) per session, and shorter appointments of 30 minutes are being remunerated with CAD $25 (US $18.5) per session. For the TAU group, 90-minute appointments are being remunerated with CAD $60 (US $44.4) per session, and shorter appointments of 30 minutes are being remunerated with CAD $35 (US $25.9) per session. Qualitative interviews last approximately 60 to 90 minutes, and participants in both the intervention and control groups receive CAD $50 (US $37) per interview.

The privacy and confidentiality of participants will strictly be followed to the fullest extent possible by the law. All identifying information collected will be treated as strictly confidential. The names of the participants will not be used to identify the data at any stage of the research. Each participant will instead be identified by a number code on every survey, recording, and transcript to ensure privacy. The participants ID list, linking the participants' names with their unique identifiers, will be kept electronically on a password-protected computer in the locked office of the principal investigator at the Canadian Observatory on Homelessness at York University. This participants ID list will be kept separate from all other data and will only be accessible to the research team enlisted in the study's human participant research protocol. The participants ID list will be kept in the event that any participant wishes to withdraw from the study following data collection. In terms of data analysis, the research team will only be working with deidentified data, and all findings will be presented at the aggregate level. For the purpose of research dissemination, no identifying information about the participants themselves or the names of participating agencies and organizations will be shared in publications or presentations.

Participants' Recruitment

The recruitment process began by identifying eligible youth across the demonstration sites, which included young people aged 16 to 24 years who were experiencing homelessness or housing precarity consistent with the Canadian definition of youth homelessness [3]. However, because of concerns over participants not reaching the age of majority to be able to participate in the HF4Y research study, the age range was set between 16 and 24 years. Owing to different operational procedures, each community agency included additional criteria in terms of recruiting participants.

Potential study participants came from the pool of young people who accessed homelessness services and associated sectors (eg, child protection services, youth mental health or addictions services, law enforcement, or corrections). Each site determined additional inclusion criteria to address existing gaps in local service delivery as well as individualized recruitment strategies based on local prioritization processes and budgeting limitations. For example, the Ottawa site recruited youth aged 18 to 24 years who were experiencing homelessness, including young people living in a shelter, couch surfing, or sleeping outdoors. The Toronto site recruited youth experiencing homelessness (or at risk of experiencing homelessness) aged 17 to 24 years who had been in or were transitioning out of the provincial child welfare system.

To identify eligible participants to be recruited for the study, outreach activities began with local agencies and providers who were in contact with young people experiencing homelessness in Ottawa. Community representatives from each site developed a strategy to work with potential referral sources and inform them about the study. Strategies to ensure adequate participation in the study included seeking referrals from a wide range of services accessed by each site population. In Ottawa, these included local youth shelters, drop-in centers, city prioritization lists (ie, by-names list), and other local service agencies delivering programs for youth experiencing homelessness. In Toronto, youth were primarily referred by Youth in Transition workers who work with youth exiting the child welfare system, in addition to the types of referral sources used in Ottawa. Researchers and service delivery teams followed site-specific strategies for informing referral agencies (eg, outreach, posters, and meetings with key staff), identifying prospective participants, making contact to ascertain participant interest, and carrying out screening processes.

Recruitment for the study started in February 2018 in Ottawa and was completed in November 2019, with 86 participants enrolled in the study. In Toronto, the first participants were recruited in June 2018, and the final group of youth was admitted to the study in March 2020, with 62 youth participants in total. At the initial interview, participants were guided through an informed consent process and then asked to complete a baseline evaluation (interview and survey) before receiving a notification of the group assignment.

Data Collection and Randomization

Survey and interview data in Ottawa and Toronto are being collected at multiple time points over the course of 4 years to capture a range of outcomes, as listed in Table 1. Data collection is expected to be completed at both sites by March 2024. The data collection procedures follow a sequential, mixed methods design [38], which involves a 2-phase process starting with the quantitative data collection, followed by a qualitative phase to help provide a deeper understanding of the survey responses and quantitative results based on participants' personal narratives and life journeys through homelessness.

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Table 1. Core outcome areas, domains, measures, and interval schedule.

Core outcome areas, variables, and domains	Measures and instruments	Interval
Housing stability[a]		
Obtaining and maintaining housing with reduced stays in emergency shelters	Residential timeline follow-back [39][b]	3 months[c]
Knowledge and skills regarding housing and independent living	Casey-Ansell Youth Life Skills Assessment (adapted) [40]	6 months
Health and well-being[a]		
Perceptions of health and well-being	World Health Organization Quality of Life-Brief Form [41]	6 months
Behavioral health	Global Appraisal of Individual Needs–Short Screener [42]	6 months
Food security	Food Security Survey [43]	6 months
Psychological functioning	Brief Symptom Inventory [44]	6 months
Substance use patterns	Ontario Student Drug Use and Health Survey [45]	6 months
Self-efficacy	General Self-Efficacy Scale [46]	6 months
Complementary supports[a]		
Life skills	Casey-Ansell Youth Life Skills Assessment (Adapted) [40]	6 months
Access to necessary nonmedical services	Diagnostic interview	6 months
Hope for the future	Herth Hope Index [47]	6 months
Legal and justice issues	Diagnostic interview	6 months
Resilience	The Resilience Scale-14 [48]	6 months
Education and employment		
Participation in education and training	VTLFB[d] and education [13]	3 months
Educational achievement	Diagnostic interview	24 months
Participation in the labor force	VTLFB and employment	3 months
Financial security	VTLFB and income	3 months
Social inclusion		
Family and natural supports	Multidimensional Screener of Perceived Social Support	6 months
Sense of belonging to the community	Psychological Community Integration Scale [49]	6 months
Engagement in cultural and meaningful activities	Physical Community Integration Scale [50]	6 months

[a]Primary outcomes domains.

[b]The residential timeline follow-back (RTLFB) is designed to assess various aspects of housing status and stability. In this study, it serves to incorporate point-in-time assessments and longitudinal evaluations of participants' housing stays and transitions. It allows building a chronological record of each respondent's residential history between successive interviews. In addition, the RTLFB collects information about the type of residence, the individuals the participants are living with, and the reasons for moving in and moving out during the specified period. The records obtained from the RTLFB will be analyzed to gain insights into the specific places where young people stayed during the study, as well as the reasons for their moves in and out of different residences. This information will contribute to a comprehensive assessment of the effectiveness and impact of the HF4Y intervention on their housing stability and overall well-being.

[c]The measures and intervals listed will be used at the interval indicated to collect data over 48 months (eg, the residential timeline follow-back is being used every 3 months for 48 months).

[d]VTLFB: vocational timeline follow-back.

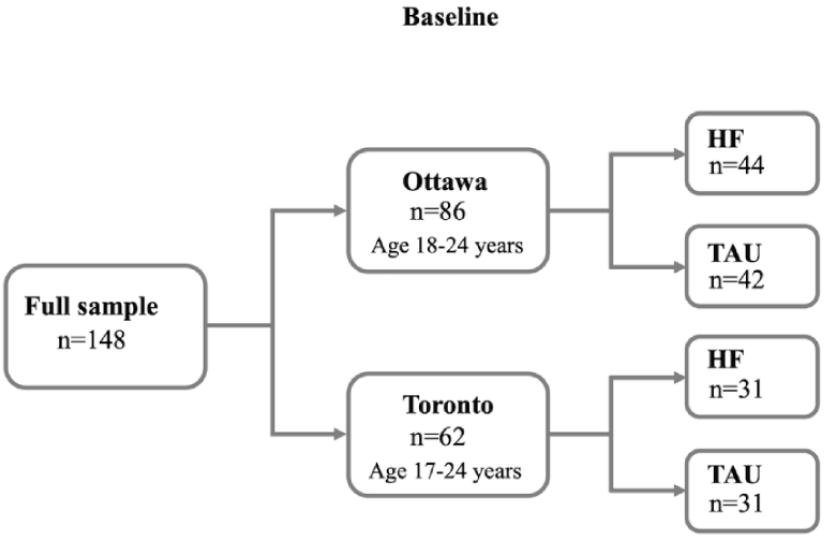
It was expected that baseline differences would exist across sites, reflecting the diverse demographic, socioeconomic, and ethnoracial background of participants based on regional characteristics. To achieve representativeness in the RCT sample, homogeneous sampling was used [38], which targeted several shared characteristics including age range (youth aged 16-24 years) and those who were experiencing homelessness or were at risk of homelessness. For each site, a minimum of 63 participants needed to be recruited for the study to be able to detect an effect size of 0.5 between the TAU group and the intervention group for the primary outcome domains, given α=.05 and β=.20. However, the total number of participants recruited was 148 to account for an attrition rate of 25%, following similar RCT-designed studies [11,17].

The participants were assigned through strict randomization to either the TAU or HF intervention groups. Research assistants sealed assignments in envelopes ordered by participant identification number according to a randomization sequence generated through a web-based random sequence generator.

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Once the baseline interview was completed, the participants received a notification of the group assignment in a sealed envelope along with an information sheet. In Ottawa, 44 youths were assigned to the HF intervention group and 42 were assigned to TAU group. In Toronto, the number of participants in the HF intervention and TAU groups was equal (n=31; Figure 1). After group assignment, research assistants connected the participants assigned to the HF intervention group to the program service provider. Participants randomized to the TAU group were informed about the available services in the community. All participants were informed of the schedule of research follow-up appointments and were invited to use the research field office or the participating service agency as a resource center. All participants were provided with a pamphlet on existing services in the community.

Figure 1. Housing First for Youth randomized controlled trial study design HF: housing first; TAU: treatment-as-usual.



Housing and Supports Services

Participants randomized to the HF intervention group receive housing and support in accordance with the HF4Y model's framework and core principles [20,21]. The program staff were extensively trained on the intervention requirements to ensure fidelity to the model. Supports offered include the provision of a housing subsidy, such that participants spend ≤30% of their income on housing based on the private rental market. Participants may also live in social, supported, or alternative housing with no treatment preconditions (eg, in-place crisis, transitional, supportive, or scatter-site housing with mobile support), in which case the rent supplement is not required. The provision of support services is not bound by any preconditions (eg, housing readiness, sobriety, and engagement in other treatment), although participants agree to be visited in their unit a minimum of once per week by program staff for a length of time that is appropriate to their level of need.

It is important to note that although a range of housing options is available in both Ottawa and Toronto, the immediate access to specific options may vary. Factors such as demand, capacity, and funding influence the availability of each option. Resource limitations or eligibility criteria may result in some options being more readily available than others.

The intervention services young people receive within the HF4Y model, including a housing rent subsidy and a range of supports delivered via housing-based case managers, are designed to bridge the financial gap and enhance young people's ability to secure suitable housing, such as private market rentals, which they may not be able to afford on their own. In addition, housing-based case managers provide support in navigating housing processes while ensuring that young people are aware of their housing prospects. These supports include providing young people with comprehensive information about the various housing options available in the community as well as facilitating discussions with youth on the advantages and disadvantages of each option, including any potential constraints in accessing their preferred types of housing. Through these conversations, young people actively participate in the decision-making process, enabling them to select the type of housing, neighborhood, and level of services that best align with their individual needs and preferences. This means that young people can also reassess their needs and make adjustments to their housing options as required. This approach empowers young individuals, promotes informed decision-making, and supports their personal growth and development.

The HF4Y model offers a wide array of support services related to housing retention, well-being, income and employment, education, and social inclusion as well as complementary supports such as peer support that are offered by providers who are based off-site. These support services are individualized and tailored specifically to participants' needs, preferences, and cultural backgrounds. Adapted from the Pathways model [5], the support services are provided in the home or community, using mostly intensive case management, which is appropriate for individuals with moderate mental health needs and linked them primarily to 1 case manager rather than a team. In the HF4Y program model [20-22], an intensive case management model should be established in the range of 7 to 10 youths per case manager, with 7 being the ideal number to produce the most desired, optimal outcomes for youth. Case managers work with participants to obtain and maintain housing and to navigate

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referrals to external services (eg, mental health support and medical services).

Compared with the HF intervention group, no active intervention is introduced to the TAU group. However, participants may continue to access existing supports and housing available in each community, including income support, drop-ins, physical and mental health clinics, emergency shelters, transitional housing, and longer-term housing. As both Ottawa and Toronto are urban centers with agencies that deliver housing services targeted to young people, it is recognized that some individuals in the TAU group may over time, through new or existing programs, access some of the same services being offered to the HF intervention group. It is also likely that the usual care service patterns will differ between cities.

Participant Retention

Participation retention is a major concern, particularly in RCT studies where receiving maximum response rates and compliance with the research protocol is pivotal to their success. In this longitudinal study, enrolling young people experiencing homelessness and housing precarity was a particularly difficult task because of their involvement in a variety of competing activities, such as school and meeting their basic needs. In addition, barriers such as unstable housing and frequent transitions have made it difficult for youth to maintain a consistent mode of communication over time. The COVID-19 pandemic in February 2020 compounded these challenges, as it disrupted the efforts made to establish and maintain contact with youth.

Existing literature suggests strategies to minimize participant attrition, which broadly include baseline tracking procedures such as collecting detailed information on the participant's location and follow-up procedures, including sending reminders to conduct follow-up interviews [51-53]. Consistent with the literature, this study uses an array of techniques to maintain contact with hard-to-reach participants, which include building rapport, supplementing traditional tracking methods (eg, phone, email, social media, and known associates) with new technologies, and offering financial incentives. More importantly, as data collection is still underway, a key factor is cultivating an appreciation of the contribution of the respondents as experts. Such a "participant-centered" approach [54] ensures that participants are aware of the impact of their participation in the outcomes and success of the study, thereby increasing the likelihood that they will continue to be engaged in the study. Although the existing body of research suggests varying rates of retention depending on the types of strategies used, ranging from 65% to 85% [53], this study aims to keep approximately 75% of the participants engaged in the study over 4 years.

Outcome Areas and Measures

Building on the existing body of research including the At Home/Chez Soi national study, primary outcomes were selected to reflect the unique characteristics of youth experiencing homelessness and to measure the effectiveness of the HF4Y program interventions that are consistent with the program's core principles and the detailed service delivery model [20,21,55]. In evaluating complex interventions, there are a range of factors that likely have an impact on housing stabilization, including sufficient and stable income, health and well-being, involvement with the justice system, involvement in education and employment, and social inclusion [56,57]. The core primary outcomes are thus selected to assess the effectiveness of HF4Y interventions on housing stability (as defined by a joint function of the number of days housed and the number of moves), health and well-being (mental and physical health status), and access to complementary supports, with secondary outcomes consisting of participation in education and employment and social functioning, as listed in Table 1 [55]. Multimedia Appendix 1 provides a comprehensive description of the measures.

In Ottawa and Toronto, interviews and surveys designed to collect quantitative data were administered at baseline, and each follow-up takes place at specific time points (3-6 months) over 4 years. At entry into the study (baseline), youth participants were interviewed using a range of questions aimed at collecting demographic data, physical health conditions, access to care, housing retention (using residential timeline follow-back), and employment (using vocational timeline follow-back; refer to Multimedia Appendix 1 for a detailed description of the interview measures). Following the interview, the participants were administered a battery of survey measures for physical and mental health and well-being, social inclusion, self-esteem and self-efficacy, resilience, hope, quality of life, and a measure reflecting complementary skills that impact the various domains (Table 1). In-person and phone-based follow-up quantitative interviews are being conducted at 3- or 6-month intervals depending on the instrument used. Since the onset of the COVID-19 pandemic, interviews and surveys with youth participants have been conducted remotely via Zoom (Zoom Video Communications) or phone. The number and timing of interview sessions were decided based on two factors: (1) the intention to evaluate longer-term outcomes and trajectories of change for each participant and (2) the recognition that participants may miss appointments owing to the nature of their situation and issues. This may be even more pronounced in the TAU group that has no interaction with the intervention, and, therefore, a potentially weaker incentive to attend appointments as scheduled.

The collection of primary data is mostly achieved through interviews conducted via Zoom or phone, with a mixture of both paper- and computer-based survey methods. Each interview appointment takes approximately 30 to 60 minutes to complete, and the participants are compensated for their time. Computer-based surveys administered through the *Qualtrics* survey platform are entered into a secure central database using wireless technology. Hard-copy data are stored securely following double-lock procedures at each site, and electronic backups are stored on cloud-based, secure, institutional network–based storage. Several strategies are being used to ensure optimal data quality: (1) using validated and reliable tools for susceptible youth populations; (2) using a cross-site protocol for data management, data entry, quality checking, and cleaning; (3) practicing common data-checking routines at each site through monthly multisite data quality committee meetings; (4) training interviewers for face-to-face and web conferencing

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interaction with participants; and (5) fielding interviewer questions centrally and making decisions where necessary across both RCT sites.

Following a sequential mixed methods approach [38], a subset of 20 youths per group at each RCT site was randomly selected (10 participants from the HF intervention group and 10 from the TAU group) to participate in a narrative interview, once at 6 months and later at 18 months. Demographic data of participants successfully recruited into the qualitative study were then assessed to ensure balance in demographic variables including age, gender identity, and ethnoracial background.

The purpose of this qualitative research inquiry is (1) to supplement the quantitative data collected with respect to the effectiveness of the HF4Y program and (2) to help identify areas that need improvement for future scaling of the HF4Y program. This qualitative approach is also intended to allow us to understand the lived and living experiences of study participants in their own words through life story (or "narrative") interviews. For the large majority of youth participants, homelessness is not the product of a single event, but it is seen as a journey in which individual agency and life decisions take center stage. The qualitative interviews follow a semistructured format and include questions that are mapped onto the quantitative outcome domains. The follow-up interviews help understand how youths' lives have changed during the RCT and what things may have contributed to those changes. These interviews specifically inquire about the types of services within and outside the HF4Y program that participants are currently receiving. They also explore the types of services participants require but are not currently receiving as well as their perspectives on the helpfulness or limitations of the services they are accessing.

Analytical Procedures

HF intervention and TAU groups will be compared within each RCT site; although if it is determined that no significant differences exist between the 2 sites in terms of sociodemographic characteristics and outcome measures collected at baseline, the TAU and intervention groups will be combined accordingly across sites to increase the power of the study. There will be an interim analysis using 2-year quantitative data, with the final analyses based on the 4-year data. It is expected that certain participants might not adhere to the protocol or could discontinue their involvement owing to health issues or fatigue arising from repeated assessments. As deviations from the protocol are inevitable and likely to occur in real-time practice [58-60], there exist a number of approaches that can preserve the integrity of the randomization process including an intention-to-treat analysis, which considers all participants initially randomized in the study.

In addition, certain participants may be more likely not to respond to surveys, or certain questions might be more likely to have missing responses. With respect to missing data, 3 common mechanisms can be observed: missing completely at random, missing at random, and missing not at random [61,62]. For data missing completely at random, single imputation methods can be used to address the missing values, albeit with a tendency to provide conservative estimates of the treatment effect; for example, missing values can be replaced with the last observed values or the mean values. For data missing at random and missing not at random, multiple imputation can be used, which produces a more accurate and less biased estimate of the treatment effect [63].

For continuous outcome measures, differences between the intervention and control groups will be examined by using mixed-effects modeling for repeated measures. For binary outcomes, logistic models will be used, and negative binomial modeling will be used for all count outcome measures to account for any possible overdispersion in the data. Sociodemographic characteristics collected at baseline will be entered into the models as covariates, and the interaction between time and intervention will be considered to capture the interaction effects. All quantitative analyses will be conducted in SPSS (IBM Corp) and R studio (Posit) software packages with power set at 80% (α=.05 and β=.20) to detect an effect size of 0.5 between the TAU and intervention groups for the primary outcome domains.

Qualitative data will be assessed through thematic analyses to identify common themes related to outcomes and to analyze the underlying intervention process, consistent with the approaches suggested by Miles et al [64] and Saldaña [65]. The qualitative data provide a rich source of the narratives regarding young people's experiences with homelessness, housing instability, and interaction with the HF4Y program itself. Interviews will be transcribed and imported into NVivo (QSR International) software for analysis. Rather than focusing on preexisting theoretical constructs using an a priori method, an emergent, bottom-up approach will be used for coding [64]. The process of coding will shift back and forth from the key narratives provided by the participants to the researcher's interpretation of the meaning of those narratives, which will be documented through the researcher's analytic memos. Recurring patterns gleaned from the codes will be grouped as themes and will be thematically classified under broader themes. The final set of themes will be summarized and presented in a table, where representative quotes from transcripts will be paired with themes as textual evidence.

In addition to the quantitative and qualitative analyses, each agency is responsible for completing monthly reports that provide important metrics for all participating youth, including demographic information and key indicators such as the number of youth housed during the month and the number of youth who exit a program. Furthermore, program fidelity evaluations are conducted within each HF4Y program. These evaluations assess how well the intervention aligns with the HF4Y model and identify any areas that may require adjustments or additional support.

Data Access

Quantitative data are entered directly into laptops configured specifically for the project and are stored using a contracted service provider who will manage data storage for the study on an off-site, centralized server with high levels of physical network security. No data are stored on the hard drive, and after entry, the hard copies are kept in secure storage at each site. Access to the data is limited to authorized users only, using a multilevel permission protocol.

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Results

The HF4Y study has been registered with the International Standard Randomized Controlled Trial Number (ISRCTN10505930). Human participant research ethics approval has been obtained from the Office of Research Ethics at York University. Recruitment was conducted between February 2018 and March 2020. Data collection is expected to be completed at both sites by March 2024, and preliminary analysis of data collected between baseline and 24 months is underway. The preliminary findings of the study will be published through public-facing reports at 24 months, and these results will be generated from deidentified and aggregate-level data (final results will be reported at 48 months). These reports will be made publicly available for the broader network of community partners and all levels of government (federal, provincial, and municipal), and they will be hosted virtually for a larger readership. Furthermore, several peer-reviewed, scholarly publications will be published based on the study's findings in top-tier journal outlets with an open-access option. During the course of the study, research vignettes and blog posts will highlight the ongoing progress of the research project and discuss the lessons learned, and this will be followed by a number of webinars and presentations at major national and international conferences. In addition, as part of the MtS project and in the context of what we have learned from implementation science [66-70], a robust training and technical assistance capacity has been developed to enable the spread and scaling of the HF4Y program. In particular, an iterative interaction between research and practice enhances service design and contributes to the continuous quality improvement of training and technical assistance.

Discussion

Strengths and Limitations

As the first pilot RCT to test the effectiveness of the HF4Y intervention in Canada, this study's strength lies in its approach to engaging participants and community partners in the study design while using a sequential, mixed methods design during the quantitative phase, followed by a qualitative phase. However, this study has some limitations. A larger sample size would make the study's findings more robust in terms of aggregate-level analyses. The current sample size could potentially limit the generalizability of our results. Participant dropouts, missed intervals, and noncompliance between the HF intervention and TAU groups could also affect the outcomes. Furthermore, RCT studies have limitations including issues related to low sample sizes, external validity, and missing data, which are applicable to this study.

Public Health Implications

The findings of this study will help build an evidence base on the impact of HF4Y through a rigorous program of developmental and outcomes evaluations. The findings will have potential public health implications for youth experiencing homelessness or housing precarity, as housing stability is central to preventing homelessness and addressing the range of physical and mental health issues resulting from housing instability [55]. Consistent with the emerging evidence at the international level [24,26], we anticipate an increase in housing stability and a reduction in homelessness, followed by longer periods of housing retention in the HF4Y intervention groups compared with the TAU group. This could lead to enhanced physical and mental well-being, improved social functioning, and increased community integration while allowing participants to meaningfully engage in education and employment opportunities. In addition, improved housing quality and increased housing stability are likely to lead to a reduction in the use of hospitals and emergency services as well as improved clinical outcomes, such as psychiatric symptoms and substance use, and reduced involvement in the criminal justice system.

Conclusions

Although there is emerging evidence on the efficacy of HF4Y globally [24-26], there is limited knowledge about its effectiveness specifically in Canada. This knowledge gap is significant because the HF4Y interventions and programs in Canada must adhere closely to the model's core values and principles to be recognized as true HF4Y interventions. This study will contribute to our understanding of how to effectively deliver and scale up the HF4Y intervention, with the aim of continually improving the HF4Y model and promoting better outcomes for youth.

The HF4Y pilot study will provide an evidence base for transforming policy and program interventions to address youth homelessness. This requires a shift away from solely managing the crisis and toward prioritizing prevention, which entails supporting those who are experiencing or at risk of homelessness to regain stable housing. By empowering individuals to sustain their housing, the HF4Y demonstration project actively seeks to engage youth in education and cultivate their sense of inclusion in the community, thereby creating a foundation for long-term health and well-being.

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Data Availability

The data sets generated and analyzed during this study are available upon request. External researchers must make a formal request to use the data sets and agree to the policies and procedures set forth by the Making the Shift. Inquiries and requests can be sent to the corresponding author.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Psychometric descriptions of the measures used in the randomized controlled trial study.
[DOCX File , 28 KB - resprot_v12i1e46690_app1.docx]

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Abbreviations

2SLGBTQA+: 2-spirit, lesbian, gay, bisexual, transgender, queer (or questioning), asexual, and additional groups
HF: housing first
HF4Y: Housing First for Youth
MtS: Making the Shift
RCT: randomized controlled trial
TAU: treatment-as-usual

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Protocol

Vitalizing Community for Health Promotion Against Modifiable Risk Factors of Noncommunicable Diseases (V-CaN) in Rural Central India: Protocol for a Hybrid Type II Implementation Effectiveness Trial

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Abstract

Background: Low- and middle-income countries are facing the emerging burden of chronic noncommunicable diseases (NCDs). Apart from loss of human lives and premature deaths, NCDs result in huge costs for treatment to individuals and the health system. Although NCDs develop in later life, the risk factors begin at an early age. The key to the control of the global epidemic of NCDs is primary prevention based on comprehensive community-based programs.

Objective: This study aims to develop, implement, and evaluate the effect of a participatory health promotion initiative utilizing the existing mechanisms of Village Health Nutrition and Sanitation Committees (VHNSCs), women's self-help groups (SHGs), and schools on modifiable risk factors for NCDs among young people aged 10-30 years.

Methods: The proposed type II hybrid effectiveness implementation cluster randomized field trial will be conducted in the catchment area of 4 primary health centers (PHCs) in Wardha district, India, comprising 100 villages with a population of 144,000. Each PHC will be randomly allocated to one of the 3 intervention arms or the control arm. The 3-intervention arm PHCs will utilize a unique strategy with either VHNSC or SHG members or school students as change agents for health action against common modifiable NCD risk factors. This study will be implemented in 3 phases from January 2022 to December 2024. First, the preparatory phase for baseline assessments includes anthropometry, behavioral and biochemical risk factors for NCDs, and participatory development of the health promotion intervention modules. Second, the implementation phase will focus on capacity building of the change agents and implementation of the participatory health promotion initiative. The implementation will include organization of community-based events, 6-monthly participatory assessment of change, and preparation of a sustainability and exit plan toward the end of this phase. Third, the evaluation phase will consist of studying the effectiveness of each intervention strategy in the reduction of risk factor prevalence at the population level.

Results: We will assess 12,000 (3000 in each arm) randomly selected individuals for behavioral risk factors and 1600 (400 in each arm) individuals for biochemical risk factors during baseline as well as endline assessments. Difference in differences,

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ANOVA or multivariate analysis of covariance, and regression analysis will be performed to assess the effectiveness of the interventions. Qualitative methods such as focus group discussions and stories of change will be documented and analyzed using thematic framework analysis. The implementation outcomes will be reported using the PRISM (Practical Robust Implementation and Sustainability Model) RE-AIM (Reach, Effectiveness, Adoption, Implementation, Maintenance) framework. The results are expected to be published by mid-2025.

Conclusions: This study will show the magnitude of risk factors for NCDs, its determinants, feasibility, effectiveness of community-based interventions, and health promotion models for NCD prevention.

Trial Registration: Clinical Trials Registration India CTRI/2020/10/028700; https://ctri.nic.in/Clinicaltrials/showallp.php?mid1=47597&EncHid=&userName=V-CaN

International Registered Report Identifier (IRRID): DERR1-10.2196/42450

(JMIR Res Protoc 2023;12:e42450) doi:10.2196/42450

KEYWORDS

noncommunicable diseases; action research; implementation research; community-based participatory research; salutogenesis; primary prevention

Introduction

Background

Low- and middle-income countries such as India are facing the emerging burden of chronic noncommunicable diseases (NCDs) while still struggling with the unfinished agenda of improving maternal and child health, nutrition, and infectious disease spread [1]. The burden of cardiovascular diseases, chronic respiratory diseases, diabetes, cancer, and mental disorders is predicted to increase significantly in the next 25 years [1]. NCDs are estimated to account for about 75% of all deaths in India by 2030 [1]. Cancer deaths are projected to double from 2004 to 2030, and cardiovascular disease deaths are predicted to increase from 2.7 million in 2004 to 4 million in 2030 [1]. Apart from high costs to the health system, NCDs result in high out-of-pocket expenditure. The overall economic burden of NCDs in India is estimated to amount to approximately 5%-10% of the gross domestic productivity, thus imposing huge social and economic costs, impeding not only health improvements but also economic progress and social development of the country [2]. Evidence suggests that NCDs disproportionately impact people at younger ages and are increasingly afflicting the poorer segments of the society [2,3].

The National Family Health Survey has shown that throughout India, over 10% of the population aged 15 years and older have elevated blood sugar levels and over 20% of the population have elevated blood pressure levels [4,5]. Various studies [6-9] have highlighted the need of early interventions for the primary and secondary prevention of NCD-related risk factors. For instance, a study in Central India reported that the prevalence of hypertension was 5.75% among adolescents, which highlights the need for blood pressure and nutritional monitoring among adolescents [6]. Overweight or obesity has been reported in 4.3% of schoolchildren in Wardha, with a dietary deficiency in 57% of the adolescent girls [7]. Metabolic syndrome (clustering of abdominal obesity, hypertension, disturbed glucose metabolism, and dyslipidemia) has been reported in 9.3% of the rural adult population in India [8]. A recent review from low- and middle-income countries highlights the role of community-based interventions through health-promotion initiatives in reducing the risk factors related to NCDs. Such interventions significantly reduce the risks ranging from lifestyle and diet modifications, smoking, alcohol, etc [9].

The key to the control of the global epidemic of NCDs is primary prevention based on comprehensive community-based population-wide programs. There is a common agreement that community empowerment is crucial for the success of such programs, and partnerships among different stakeholders are required to provide effective pathways for the design and delivery of NCD prevention and control programs. Although India counts on different national programs to control NCDs, the gaps in implementing these programs and a clear strategy of what works and how to implement it at the local level is lacking. Notably, health promotion is a common component in all these programs [2,9,10]. Indian states such as Tamil Nadu and Kerala have piloted efforts around NCD prevention and control through various health promotion activities [11]. Although some community-based interventions have been conducted in India, there is a great variation in terms of the components of the interventions and the target population. However, to have a population-level impact and to reach communities in the periphery, the health promotion component of the NCD programs needs to be adapted to the local context [2,9].

Few studies [12-17] focusing on lifestyle intervention programs at the community level have shown considerable benefits in terms of promoting health education through healthy diets, increasing physical activity, and screening for diabetes prevention and control [12]. A community-based study in Gujarat targeting adults for the prevention and control of diabetes, consisting of health education sessions provided by trained community health workers, led to improved knowledge of diabetes and cardiovascular diseases and a reduction in the overall blood pressure in the studied population [13]. A community-based program in India for NCD prevention and control in Ballabgarh district was evaluated by Krishnan et al [14]. Volunteers and schoolteachers were trained in addition to communication campaigns, camps, and reorientation of health services at the community level. The intervention led to better management of NCDs at health facilities [14].

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Several school-based health education programs in India have successfully reduced the rates of both tobacco experimentation and offer of tobacco by peers [15,16]. School-based educational programs can significantly influence children's behavior in inculcating healthy lifestyle practices. A school-based intervention called MARG (medical education for children or adolescents for realistic prevention of obesity and diabetes and for healthy aging) showed a significant increase in the intake of healthy foods, decrease in the intake of fried and fatty energy-dense foods, and increase in the physical activity and time spent on outdoor games along with improvements in glycemic parameters and lipid profiles [17]. The MYTRI (Mobilizing Youth for Tobacco-Related Initiatives in India; 2002-2007) project consisted of randomized controlled intervention trials that established the effectiveness of school health interventions in reducing tobacco use among Indian adolescents by reducing current tobacco use and their future intentions to use tobacco and by enhancing their health advocacy skills [16].

Several studies [18-22] have also emphasized the potential of self-help groups (SHGs) in improving health-related outcomes at the population level, especially in terms of knowledge, attitude, and practice of healthy behaviors for NCDs as well as other health-related conditions. VHNSCs were constituted under the National Rural Health Mission in India to enable community participation in health-related activities, formulate village health action plans, and implement and monitor the same in the villages. The VHNSC is responsible for the health of the villagers, and they are mandated to undertake preventive, promotive, and curative health activities at the village level [23].

In this study, we aim to develop, implement, and evaluate the effects of a participatory health promotion initiative utilizing the existing mechanisms of VHNSC, women's SHGs, and schools on behavioral as well as biochemical modifiable risk factors for NCDs (obesity or overweight, tobacco use, stress, unhealthy diet, physical inactivity, harmful use of alcohol, high blood pressure, high blood sugar, and increased blood cholesterol) among young people in the age group of 10-30 years.

Rationale of This Study

Randomized clinical trials have documented that lifestyle changes can prevent NCDs [24]. However, there is limited evidence, particularly in India, whether such strategies are applicable at the community level, that is, in a real-life setting. The emphasis of our proposed study is to strengthen the primary prevention of NCDs, which is often neglected under the current national health programs. Our proposed study will utilize a health promotion approach as indicated in the Ottawa Charter for Health Promotion [25] and will make efforts to empower and enable young people aged 10-30 years to exercise control and take care of their own health. Our study will focus on young people aged 10-30 years, as this age group is not covered under the National Programme for Prevention & Control of Non-Communicable Diseases (NP-NCD), and it is during this phase of life that NCD-related risk factors begin, which become habits during later years and thus become difficult to change and lead to chronic diseases. Apart from focusing on the commonly emphasized risk factors of tobacco, alcohol, and physical activity, this study will include locally feasible and acceptable strategies to reduce stress, which often is not accounted for in NCD prevention. This study will be implemented in collaboration with the district health system, utilizing the existing mechanisms of Village Health Nutrition and Sanitation Committee (VHNSC), women's SHGs, and schools by using the principles of participatory development and therefore much more likely to be acceptable to the community and sustainable eventually. The NP-NCD currently emphasizes early diagnosis and prompt treatment and at times tends to overlook the primary prevention. Our study, which is the first of its kind in central India for health promotion against NCD risk factors among young people aged 10-30 years, will help strengthen the primary prevention component under the NP-NCD. The proposed study has the potential of producing a community-based health promotion model for the prevention of NCDs through the life cycle approach, and thus, has every chance of leading directly to improvements in population health.

Methods

Study Design

The proposed study will be a type II hybrid effectiveness implementation cluster randomized field trial that will be implemented in a rural area of Wardha district of Maharashtra, India, which also is a part of the field practice area of the Department of Community Medicine, Mahatma Gandhi Institute of Medical Sciences, India. This study will be performed in the catchment areas of 4 primary health centers (PHCs) of Wardha block, namely, Anji, Kharangana, Talegaon, and Waifad. As per the census of 2011, there are around 100 villages in this study area with a population of approximately 144,000 people. However, the census towns (as per census 2011) in the study area will be excluded [26]. This study will be performed from January 2022 to December 2024.

Randomization

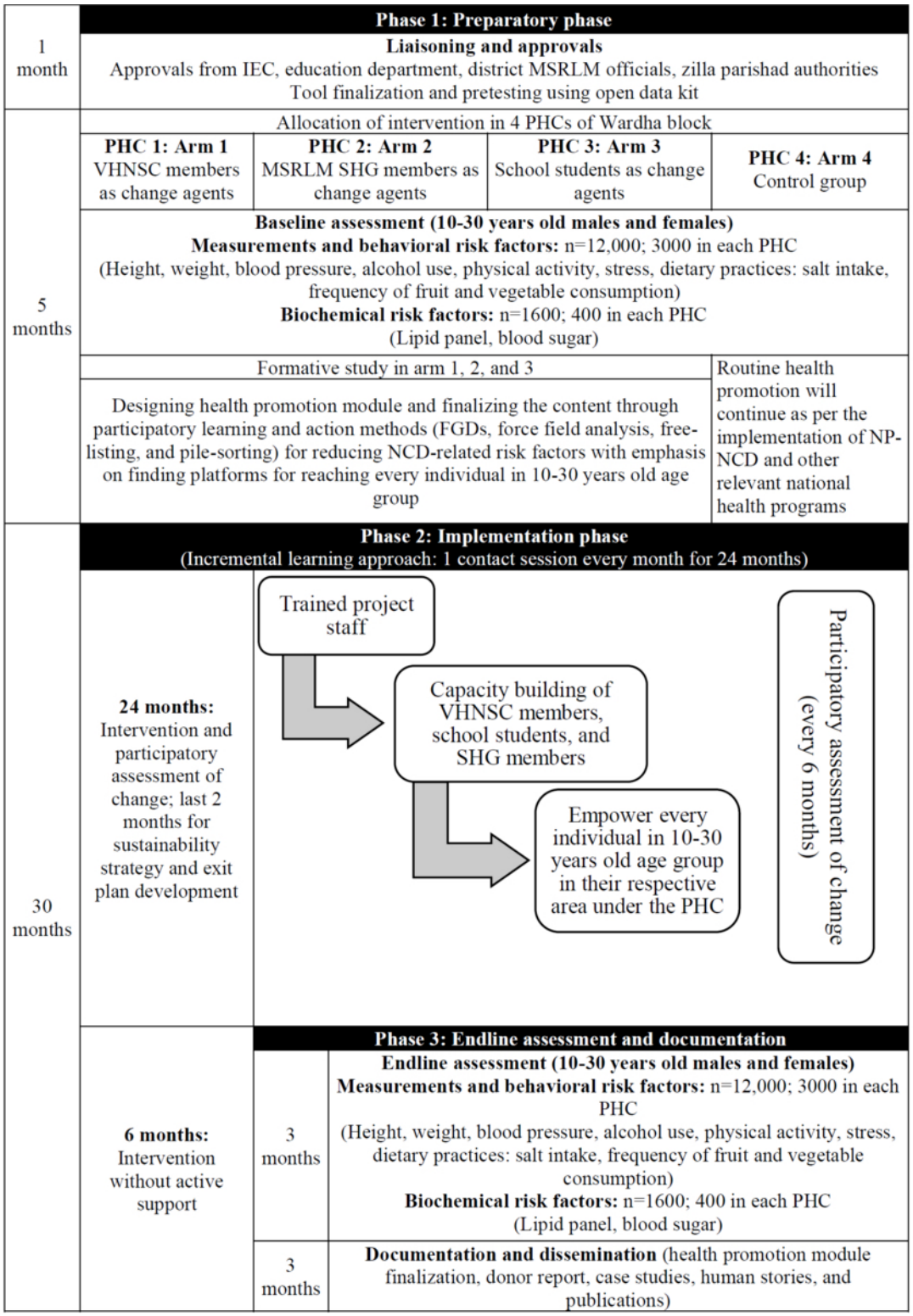
The proposed study will have 4 arms: 3 intervention arms and 1 control arm. The unit of randomization would be PHCs and each of the 4 PHCs will be randomly allocated using a simple randomization technique through the lottery method to 1 of the 3 intervention arms or to the control arm. The primary strategy in this study would be health promotion by creating change agents. The 3 intervention arms would differ in the source of change agents. The 3 interventions in this proposed study would be with (1) school students as change agents, (2) VHNSC members as change agents, and (3) women's SHG members as change agents.

Study Implementation Plan

This study will be implemented in collaboration with the district health system. As per randomization of the study arms, the existing mechanisms of VHNSC, women's SHGs, and schools would be utilized for study implementation by using the principles of participatory development in a phased manner as depicted in Figure 1 and as described below.

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Figure 1. Study flowchart showing the phases and respective activities. FGD: focus group discussion; IEC: institutional ethics committee; MSRLM: Maharashtra State Rural Livelihood Mission; NCD: noncommunicable disease; NP-NCD: National Programme for Prevention & Control of Non-Communicable Diseases; PHC: primary health center; SHG: self-help group; VHNSC: Village Health Nutrition and Sanitation Committee.



Phase 1: Preparatory Phase (6 Months)

The preparatory phase will include liaising and seeking administrative approvals, staff recruitment, baseline data collection, and a formative study for developing the health promotion module.

Liaising and Seeking Administrative Approvals (First Month)

The preparatory phase will include seeking approval from the institutional ethics committee and concerned district authorities from health, education, zilla parishad, and livelihood mission departments. Piloting of data collection tools and planning for baseline data collection will be performed.

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Baseline Data Collection (Second Month to Fourth Month)

A baseline assessment of the prevalence of NCD-related modifiable risk factors, that is, obesity, addiction, stress, and dietary practices, including salt consumption, physical activity, and hypertension or prehypertension will be conducted using the STEPS approach developed by the World Health Organization (WHO) [27]. The study questionnaires will include sociodemographic details, NCD risk factor survey, stress questionnaire, anthropometry, and blood pressure measurements. The details of these tools are given in a later section. Sample size was estimated separately for behavioral and biochemical risk factors by using G*power software (version 3.1; Institute for Experimental Psychology) for behavioral as well as biochemical risk factors.

Sample Size for Behavioral Risk Factors

We hypothesize that our interventions would reduce the modifiable behavioral risk factors for NCDs by 25% over a period of 3 years. With an assumption of the lowest prevalence of NCD-related risk factors at 13% [6-8,28,29] to detect the aforesaid difference, with 95% CIs, power of 80%, intracluster correlation coefficient of 2, an approximate sample of 12,000 participants, that is, 3000 in each arm, was calculated. Sample size was estimated using the lowest risk factor prevalence, as it gives the maximum possible sample size. We will utilize stratified random sampling (stratified by gender) to select the study participants. The sampling frame will be prepared from the already existing health and demographic surveillance system, which is established by the Department of Community Medicine, Mahatma Gandhi Institute of Medical Sciences, in 5 PHCs (including the study PHCs) covering around 113 villages and a population of about 120,000 people. The health and demographic surveillance system is updated every 6-12 months, and data from the most recent round will be used for the abovementioned purpose.

Sample Size for Biochemical Risk Factors

An approximate sample of 1600 participants, that is, 400 in each arm, has been estimated. This sample size will help to detect an effect size of 10% mean difference from baseline with 90% power, 95% CIs, assuming 10% sample wastage. These 1600 participants would be a randomly selected subset of the 12,000 respondents (as specified for assessing the change in behavioral risk factors). The random sampling will be performed using the "sample_n" function of "dplyr" package in R software (version 4.1.2; R Foundation for Statistical Computing).

Inclusion and Exclusion Criteria

All individuals in the age group of 10-30 years, as selected through the sampling procedure described earlier who or whose parents or guardians give written informed consent, will be included in this study for evaluation of the intervention. Those experiencing severe illness or chronic diseases will be excluded from the study since their behavioral and biochemical risk factors may be influenced by their diseased status.

Formative Study for Developing the Health Promotion Module (Second to Sixth Month)

Formative research using qualitative methods and participatory learning and action techniques will be performed, which will help us in understanding the current practices pertaining to NCD-related risk factors and help us identify the possible opportunities and mechanisms to implement the intervention. Focus group discussions, force-field analysis, free-listing, and pile-sorting will be performed to understand the community perceptions on NCD-related risk factors, their prevention, and control. Based on the findings of the formative study, the health promotion module will be developed. These modules will be central to the participatory health promotive interventions to be implemented in the next phase. The health promotion module will have incorporated monthly session plans that will be implemented through monthly contact sessions in an incremental learning approach. The health promotion module will also emphasize deciding strategies for reaching every young person in the age group of 10-30 years and its delivery mechanisms. The strength of this strategy will be that the concerned stakeholders will be able to identify and implement initiatives that are acceptable and feasible to them (eg, stress mediation strategies, local strategies for increasing consumption of locally available and easy to access nutritious food, promotion of physical activity).

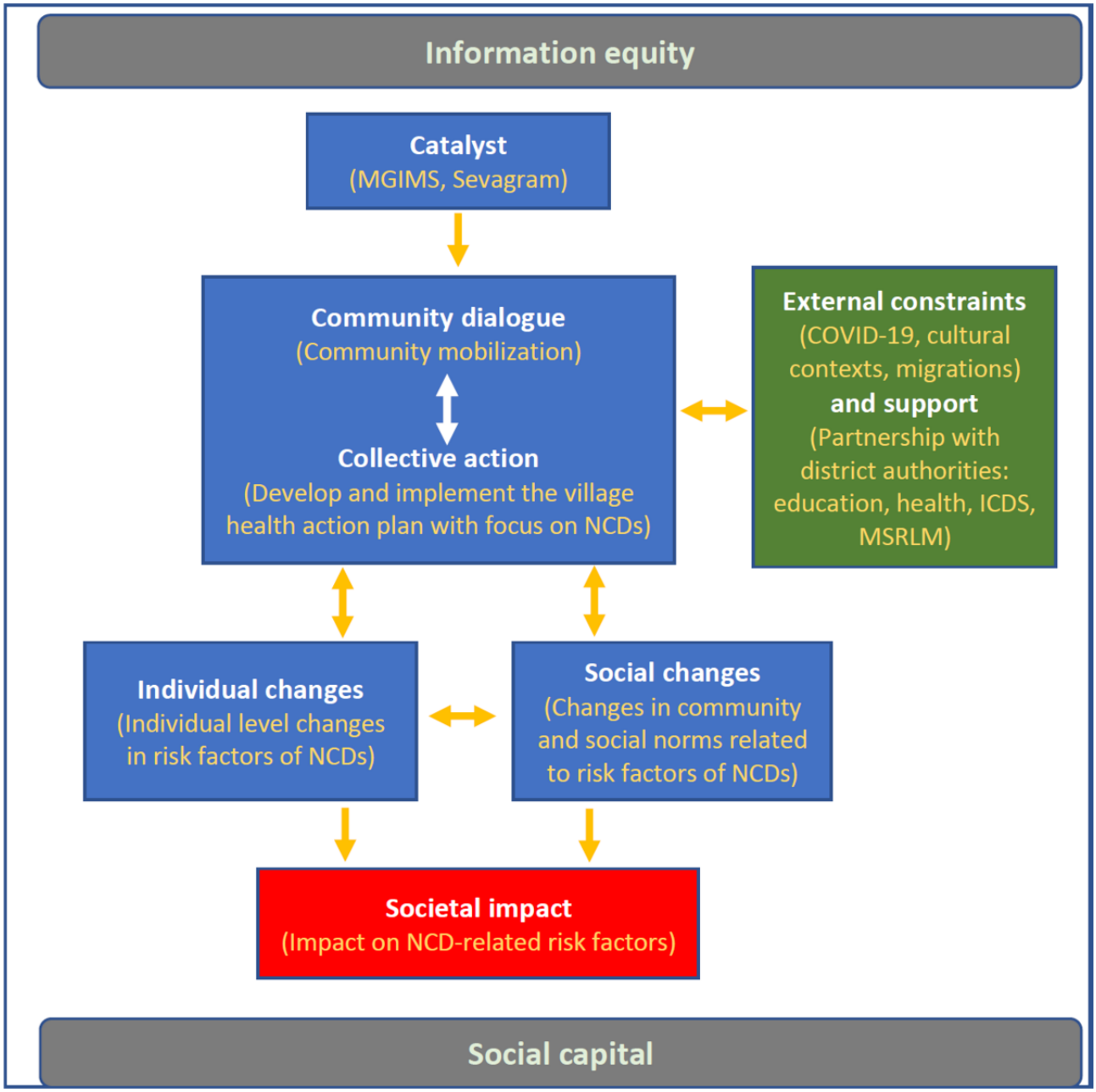
Phase 2: Intervention Phase (30 Months)

Design

The intervention phase will include the implementation of the participatory health promotion initiative based on the integrated model of communication for social change (Figure 2) [30]. Of the total duration of 30 months, 24 months will be active intervention through the study and 6 months will be the intervention without active support to assess the sustainability of the intervention. VHNSCs, although mandated to undertake preventive, promotive, and curative activities at the village level since many years, now need further capacity building to undertake such activities. The capacity of the existing VHNSCs will be used to implement the village health plan against NCDs in coordination with various community-based organizations such as SHGs, farmer groups, and adolescent groups. As discussed earlier, the health promotion module will be implemented in the community through VHNSCs, school students, and SHG members as change agents. The population in all the 4 arms will continue to receive routine care through the existing government programs for NCDs. However, no additional activities will be conducted in the control arm in this study.

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Figure 2. Adaptation of the integrated model of communication for social change in this study (adapted from Figueroa et al [30], which is published under Creative Commons Attribution 4.0 International License [31]). ICDS: Integrated Child Development Services; MGIMS: Mahatma Gandhi Institute of Medical Sciences; MSRLM: Maharashtra State Rural Livelihood Mission; NCD: noncommunicable disease.



Formation of Vitalizing Community for Health Promotion Against Modifiable Risk Factor NCD (V-CaN) Clubs

The key implementation strategies through these change agents in the intervention arms will be the formation of the Vitalizing Community for Health Promotion Against Modifiable Risk Factors of NCD (V-CaN) clubs for developing and implementing an NCD-specific health action plan for their own villages, undertaking various community-based events for health promotion, celebration of V-CaN days for spreading awareness, and creation of a social norm. The formation of these V-CaN clubs will be facilitated by the study team, and the change agents in their respective arms will be encouraged to form V-CaN clubs in their village with representation from all concerned stakeholders from that village to help disseminate and promote the learnings of the participatory health promotion module.

These V-CaN clubs will focus on preparing NCD-specific health action for themselves. The V-CaN clubs will also give emphasis on relieving stress through locally acceptable and feasible stress meditation strategies. A monthly meeting of these V-CaN clubs will be conducted to review monthly activities and ensure prompt health actions. As specified earlier, there will be no additional activities (V-CaN club formation) in the control arm; however, the population in the control arm will continue to receive routine care through the existing government program, that is, NP-NCD.

NCD-Specific Health Action Plan

The V-CaN club members will be expected to make a health plan against NCDs to take the learning from the monthly sessions forward. The health plan will focus on reaching every person in the age group of 10-30 years in their area. It will also

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include activities that they will undertake during the next 2 years for bringing about behavior change in young people. The plan will focus on identifying and implementing initiatives that are acceptable and feasible to the local community for motivating the community to indulge in pro-health behavior as described above.

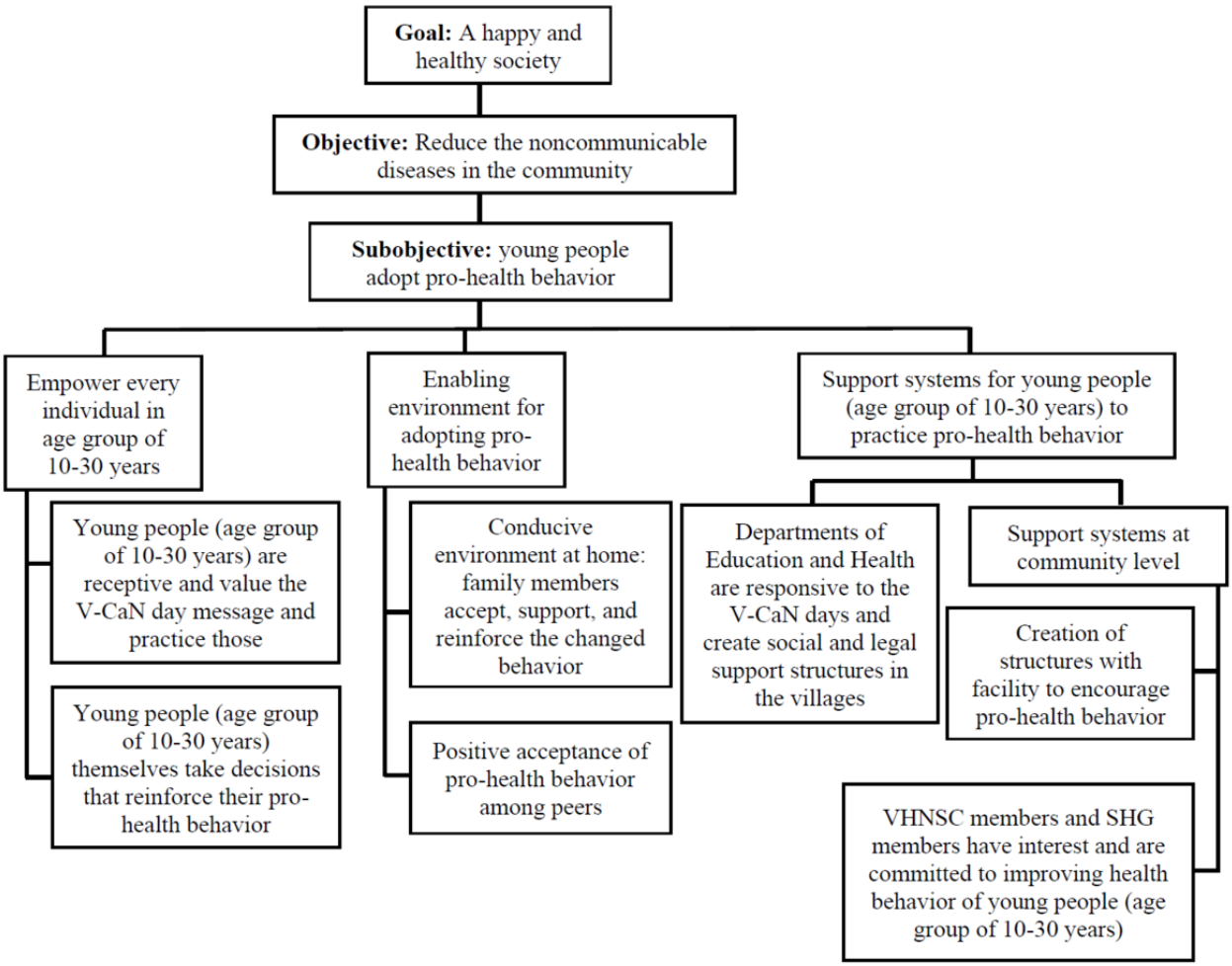
Organizing V-CaN Days

A V-CaN day (Melawa) will be organized in all the intervention villages and schools once in every 6 months with the objective to facilitate the behavior change process in the participants to (1) give up tobacco and alcohol consumption habits, if any, (2) eat a proper balanced diet, and (3) indulge in physical activity every week. The activities on the V-CaN day will be arranged in collaboration with village level health functionaries, namely, VHNSCs, ASHA (Accredited Social Health Activist), and AWW (Anganwadi worker). The effort will be to emphasize the harmful effects of the NCD risk factors by using modes such as exhibitions, role plays, demonstrations, and participatory games. Efforts will be taken to maximize the participation in these V-CaN day celebrations.

Sustainability Strategy and Exit Plan

An exit plan will be prepared in consultation with the V-CaN clubs regarding how to sustain the initiative after the implementation phase of the study. Each V-CaN club will be facilitated to prepare a plan for mobilizing resources for continuing the activities of V-CaN club. In the last 6 months of the implementation phase of the study, the activities will continue without any active support from the study staff. The sustenance of activities for the next 6 months will be monitored and documented through the study and will be a proxy indicator of the sustainability of the intervention. Factors affecting sustainability will be studied through doer (villages or schools that are able to sustain) and non–doer analyses (villages or schools that are not able to sustain). We have developed a theory of change (Figure 3) and a results framework (Table 1) for the study that will be used for monitoring and evaluation (process, output, and effect) of the study and documenting the change.

Figure 3. Theory of change for this study. SHG: self-help group; V-CaN: Vitalizing Community for Health Promotion Against Modifiable Risk Factors of Noncommunicable Diseases; VHNSC: Village Health Nutrition and Sanitation Committee.



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Table 1. Results framework for the proposed Vitalizing Community for Health Promotion Against Modifiable Risk Factors of Noncommunicable Diseases (V-CaN) study.

Questions	Answers	Key assumptions
What is the problem you are trying to solve?	• Enabling every young person to adopt a pro-health behavior	• Quality and longevity of the intervention
Who is your key audience?	• All young people aged 10-30 years	• Young people are receptive and value the V-CaN[a] day messages and practice them
What is your entry point for reaching your key audience?	• VHNSC[b] members, school students, MSRLM[c] SHG[d] members	• Health and education departments are responsive to V-CaN days and give due priority to them • VHNSC members, school students, and MSRLM SHG members have interest and are committed to improving the health behavior of young people
What steps are needed to bring about the change?	• Receiving administrative approvals • Necessary supplies and logistics • Training of trainers (supervisors) • Training and capacity building of VHNSC members, school students, and MSRLM SHG members • Reaching all young people aged 10-30 years through identified approaches	• VHNSC members, school students, and MSRLM SHG members are able to tide over the social norms or restrictions and conduct or participate in V-CaN day activities
What is the measurable effect of your work?	Impact • Obesity or overweight • Prehypertension • Hypertension • Pro-health behavior of all young people Effect • Decreased prevalence of prehypertension or hypertension • Decreased prevalence of overweight or obesity • Increased frequency and consumption of fruits and vegetables • Increased level of physical activity • Decreased stress levels • Decreased tobacco use • Decreased alcohol use • Decreased salt intake Output • V-CaN days held (number conducted or number planned) • V-CaN clubs formed • Proportion of young persons (10-30 years) reached	• Master trainers have interest and are committed to improving the health behavior of young people • Good quality in-system trainings are planned and conducted • Master trainers are able to transfer the skills to VHNSC members, school students, and MSRLM SHG members
What are the wider benefits of your work?	• Decreased prevalence of noncommunicable diseases	• Young people have the necessary family and social support to engage in pro-health behavior
What is the long-term change you see as your goal?	• A healthy and happy society	• Stakeholders are young children and their parents, panchayat raj institution members, VHNSC members, school students, and MSRLM SHG members

[a]V-CaN: Vitalizing Community for Health Promotion Against Modifiable Risk Factors of Noncommunicable Diseases.

[b]VHNSC: Village Health Nutrition and Sanitation Committee.

[c]MSRLM: Maharashtra State Rural Livelihood Mission.

[d]SHG: self-help group.

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Participatory Assessment of Change

Concurrent evaluations using the participatory method of web (spider) diagram will be performed every 6 months to assess behavior change among the young people.

Phase 3: Endline Assessment and Documentation (6 months)

Endline surveys and assessments for the effectiveness of health intervention measures will be performed in both the intervention and control groups. Case studies and human stories of change will be documented.

Data Collection and Statistical Analysis Plan

Data Collection Tools

The data collection instrument will be designed based on the WHO-STEPwise tool for NCD risk factor surveillance during baseline as well as endline assessments [27]. The WHO-STEPwise approach to the surveillance of NCD risk factors uses a standard survey instrument and a methodology that can be adapted to different country resource settings. It will be suitably modified to meet the objectives of this study and will be pilot tested. Data will be collected on Android-based tablets by using a survey solution platform developed by the World Bank through individual surveys. Anthropometry, physical measurements, and biochemical assessments will also be conducted in young people in the age group of 10-30 years. The data collection tools will consist of (1) baseline demographic information about individuals in households (age, gender, education, occupation, socioeconomic status, etc); (2) health behaviors consisting of tobacco use in smoked and smokeless form, alcohol consumption, dietary pattern (consumption of fruits, vegetables, salt, etc), and physical activity; (3) stress measurements of the study participants by using the perceived stress scale-10 that has already been used and validated in India [32,33]; (4) physical measurements, which will include measurements of height, weight, and blood pressure; and (5) biochemical assessments, which will include fasting blood sugar and lipid profile.

Operational definitions of health behaviors and procedures for physical measurements and biochemical assessments will be as per the standard procedures in the WHO-STEPwise tool for the NCD risk factor surveillance. Height and weight will be measured as described in the WHO STEPwise surveillance module. For blood pressure measurements, all the readings will be recorded by trained personnel to reduce the interobserver variation. Training in all relevant techniques will be given, including care for avoiding expectation error and digit preference. The forearm will be kept at the level of the heart. The sphygmomanometer will also be kept at the level of the heart. Two readings of blood pressure will be taken: one at the beginning of the assessment and the second at midway in the assessment. If the first 2 readings differ by more than 5 mm Hg, an additional reading will be taken and the average of the 3 readings will be noted. For blood sugar and lipid profile, 5 mL of fasting venous blood sample will be collected and transferred to the central laboratory of the institute for further processing and reporting [34]. As specified in the methodology earlier, all the measurements would be performed on 12,000 participants, except for biochemical assessments, which will be performed for a random subset of 1600 participants from among the larger cohort of 12,000 participants. However, a separate random sampling will be performed as specified earlier for the endline assessment as well.

Statistical Analysis Plan

The primary outcome variable for this study would be the prevalence of various modifiable NCD risk factors as compared to baseline. Descriptive analysis will be performed using proportions with 95% CIs. For the quantitative information, difference in differences analysis using *Z*-test for differences between proportions of independent samples and ANOVA or multivariate analysis of covariance will be used to find out the effectiveness of the intervention between the intervention and the control groups. Here, the 3 interventions will be evaluated independently to demonstrate the feasibility and efficacy of each of the 3 intervention modalities. In addition, multivariate regression will be performed for finding the determinants of the risk factors, and exploratory factor analysis will be performed to explain the observed variances between intervention and control groups. For the qualitative data, thematic content analysis will be performed.

Quality Assurance

A 3-member project steering committee will be formed for technical guidance and overall quality assurance of the study. The committee will consist of a senior public health professional, a member of the district administration, and a health communications expert. Standard operating procedures will be developed for measurements of blood pressure, height, and weight. Standard and calibrated ISO-marked nonmercury automated sphygmomanometers will used throughout the study to minimize the instrumental error. Height and weight will be measured using standard calibrated electronic weighing scales and stadiometer. Similarly, standard operating procedures will be developed for blood collection and transport of samples for fasting blood sugar and lipid profile estimation. Blood sugar and lipid profile estimation will be performed in the National Accreditation Board for Testing and Calibration Laboratories–accredited central laboratory of the institute. Approximately 5% backcheck of the filled forms will be performed by study assistants for ensuring the quality of data collection. Supportive supervision checklists will be prepared for concurrent quality monitoring for monthly meetings of V-CaN clubs and V-CaN days.

Ethics Approval

This study has been registered with Clinical Trials Registration India prospectively on October 28, 2020. Ethics approval has been obtained from the institutional ethics committee, Mahatma Gandhi Institute of Medical Sciences, before the start of the trial vide letter MGIMS/IEC/COMMED/79/2020. A written informed consent will be taken from all adults before enrolling in this study. For schoolchildren and adolescents, written consent will be taken from their parents and verbal assent from the participants. Treatment of study participants diagnosed with hypertension during screening will be ensured at the respective PHC. If needed, a referral to the appropriate higher center will

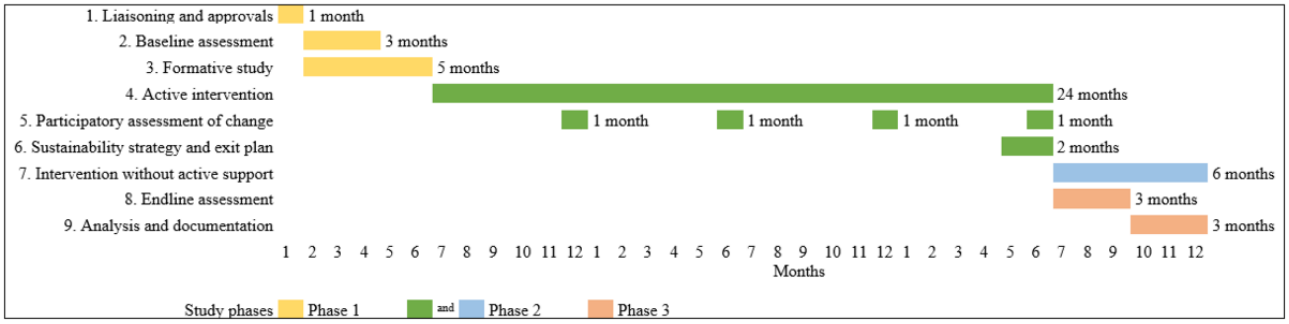
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be given to the study participants. Study participants will be interviewed and examined in private; women or adolescent girls will be examined in the presence of another female. The information in the study records will be kept strictly confidential. The identity of the study participants will be kept confidential by assigning them a unique identification number. Anonymized data would be used for scientific publications. Data quality will be checked before analysis.

Results

This study will be performed over a course of 3 years, as described in Figure 4, and the results are expected to be ready to be published or disseminated by mid-2025. Our findings will be disseminated through scientific publications in peer-reviewed journals, academic seminars, national and international conferences, and administrative stakeholders at the district, state, and national levels. Special dissemination strategies will be conducted at community and school levels through local-level gatherings and meetings.

Figure 4. Timelines for the proposed study.



Discussion

Our study is one of its kind trying to focus on reducing the exposure to risk factors related to NCDs in young people in the age group of 10-30 years. The findings of this study will provide us with evidence based on exposure prevention and lifestyle modification at a stage when exposures become habits and subsequently the lifestyle.

Expected Outcomes

This study will help to find out the magnitude of the problem of risk factors for NCDs in rural areas, its determinants, and the feasibility and effectiveness of a community-based trial. This study will also provide insights into the positive influences and barriers for behavioral change communication. The findings of this study will help us to develop a community-based health promotion model for the prevention of NCDs through the life cycle approach. Thus, the proposed research has every chance of leading directly to improvements in population health. We will use the PRISM (Practical Robust Implementation and Sustainability Model) RE-AIM (Reach, Effectiveness, Adoption, Implementation, Maintenance) framework to assess the implementation outcomes as outlined in Tables 2 and 3 so as to facilitate its translation into policy and practice [35,36].

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Table 2. Description of the PRISM (Practical Robust Implementation and Sustainability Model) contextual domains and elements incorporated in the study.

PRISM[a] domains	Elements of PRISM domains
Program (intervention)	
Organizational perspective	• Readiness of the institute, government administration, and investigators • Coordination and collaboration between MGIMS[b] and district authorities of health, MSRLM[c], and education departments as well as interdepartmental collaboration • Strong evidence base of behavioral risk factors targeted in the study • Estimated high burden of NCDs[d] in future • Usability and adaptability of the community mobilization process • Mechanism for addressing barriers of study staff
Individual (beneficiary) perspective	• Community-centered interventions • Community empowerment to adopt healthy behavior • Addressing barriers of beneficiaries in participation and adoption of behavior change during V-CaN[e] days/monthly V-CaN meetings • Feedback of results to be shared
Recipients	
Organizational characteristics	• Schools, VHNSCs[f], MSRLM SHGs[g]—implementation climate across the 3 intervention arms • Developing and implementing village health action plans through V-CaN clubs • Trainings given under the study • Keeping the group motivated as a whole to work toward healthy behavior • Existing community norms • Time management for study-related activities along with primary objectives of the organization • Decision-making
Individual (beneficiary) characteristics	• Keeping the group members motivated to work toward healthy behavior • Knowledge and beliefs of individuals • Competing interests of individuals
Implementation and sustainability infrastructure	• Universally existing infrastructure of schools, VHNSCs, and SHG networks • Dedicated study team for study duration and V-CaN clubs for future sustainability • Participatory approach for preparing health promotion modules and planning of interventions • Scope of flexibility/creativity as per the village health action plan prepared under the study • Exclusively dedicated time duration for studying sustainability • 6 monthly participatory assessments of change and program evaluation at the end of the study
External environment	• Existing national program for NCDs (NP-NCD[h]) • Competing health agenda and priorities • Migrations • Behavioral/cultural acceptability for pro-health behavior • Community resource mobilization

[a]PRISM: Practical Robust Implementation and Sustainability Model.

[b]MGIMS: Mahatma Gandhi Institute of Medical Sciences.

[c]MSRLM: Maharashtra State Rural Livelihood Mission.

[d]NCD: noncommunicable disease.

[e]V-CaN: Vitalizing Community for Health Promotion Against Modifiable Risk Factors of Noncommunicable Diseases.

[f]VHNSC: Village Health Nutrition and Sanitation Committee.

[g]SHG: self-help group.

[h]NP-NCD: National Programme for Prevention & Control of Non-Communicable Diseases.

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Table 3. Description of the RE-AIM (Reach, Effectiveness, Adoption, Implementation, Maintenance) critical outcome indicators to be assessed.

RE-AIM[a] dimensions	RE-AIM indicators
Reach	• Characteristics of participants, that is, students, SHG[b] members, VHNSCs[c] (eg, age, gender, education) and comparison of characteristics across the 3 arms • Participation rates (as proportion of all eligible/approached) • Dropout rates
Effectiveness	
Primary	• Change in the prevalence of risk factors related to NCDs[d] • Feasibility of each intervention for reduction of risk factor prevalence
Secondary	• Characteristics of individuals who comply with the behavior change versus noncompliers • Change in the prevalence of obese/overweight individuals, patients with hypertension or prehypertension, patients with diabetes or prediabetes • Change in the mean blood pressure/blood sugar/serum cholesterol levels of population
Adoption	• Proportion of V-CaN[e] club monthly meetings held/V-CaN days celebrated out of committee • Reasons for missed V-CaN club meetings/V-CaN day celebrations (comparison across the 3 arms)
Implementation	• Fidelity of intervention sessions (trainings, V-CaN meetings, V-CaN days) • Content delivery and satisfaction of beneficiaries • Best practices, innovations, and improvisation in the 3 arms
Maintenance	• Sustainability and exit plan • Proportion of villages delivering the interventions during the last 6 months of the study period without active support of the study team • Enabling and inhibiting factors for maintenance/discontinuation and adaptation

[a]RE-AIM: Reach, Effectiveness, Adoption, Implementation, Maintenance.

[b]SHG: self-help group.

[c]VHNSC: Village Health Nutrition and Sanitation Committee.

[d]NCD: noncommunicable disease.

[e]V-CaN: Vitalizing Community for Health Promotion Against Modifiable Risk Factors of Noncommunicable Diseases.

Future Plans Based on Expected Outcomes

This study will be a value addition to strengthen the primary prevention component under the NP-NCD and Rashtriya Kishor Swasthya Karyakram, as it is going to be implemented in collaboration with the district health system, utilizing the existing mechanisms of VHNSC, community-based organizations, and frontline health workers. If proven effective, the possibility to implement the health promotion modules in the control PHC will also be explored at the end of the study. Further advocacy with the administration will be performed for scaling up of the intervention.

Strengths and Limitations of This Study

This cluster randomized study will provide rich evidence regarding prevention of common modifiable risk factors against NCDs. Moreover, outcome evaluation is performed in a very large sample, thereby minimizing the possibility of random errors in the results. Simple random sampling will ensure minimal selection bias. The inbuilt concept of community mobilization and preparation of an exit plan may also lead to sustenance of the program, thereby ensuring the perceived benefits to reach the people even beyond the study duration. External generalizability of this study will be limited only for rural areas with similar profiles and not for urban or tribal areas.

Acknowledgments

This study has been approved and will be funded by the Indian Council of Medical Research, New Delhi, vide letter 5/4/8-23/CD/AVR/202 l-NCD-ll.

Data Availability

After the completion of the proposed study, the findings will be published in a peer-reviewed journal. The data from this study may be available with the authors and will be accessible on request from the corresponding author.

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Conflicts of Interest

None declared.

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Abbreviations

ASHA: Accredited Social Health Activist
AWW: Anganwadi worker
MARG: medical education for children or adolescents for realistic prevention of obesity and diabetes and for healthy aging
MYTRI: Mobilizing Youth for Tobacco-Related Initiatives in India
NCD: noncommunicable disease
NP-NCD: National Programme for Prevention & Control of Non-Communicable Diseases
PHC: primary health center
PRISM RE-AIM: Practical Robust Implementation and Sustainability Model Reach, Effectiveness, Adoption, Implementation, Maintenance
SHG: self-help group
V-CaN: Vitalizing Community for Health Promotion Against Modifiable Risk Factors of Noncommunicable Diseases
VHNSC: Village Health Nutrition and Sanitation Committee
WHO: World Health Organization

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Protocol

Effects of a Community Health Worker–Led Health Literacy Intervention on Lifestyle Modification Among Patients With Hypertension and Diabetes in the City of Harare, Zimbabwe: Protocol for a Cluster Randomized Controlled Trial

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Abstract

Background: Hypertension and diabetes are among the most common noncommunicable diseases in Zimbabwe. These 2 conditions are largely prevented and controlled by lifestyle modifications, such as healthy eating habits, physical activity, and avoiding the use of tobacco and alcohol.

Objective: This study aims to evaluate the effects of a community health worker (CHW)–led health literacy intervention on lifestyle modification among patients with diabetes and hypertension in the City of Harare, Zimbabwe, in terms of (1) adherence to recommended lifestyle changes, (2) blood pressure and blood glucose levels, and (3) medication adherence.

Methods: This is a 6-month–long cluster randomized controlled trial, which will be conducted in primary health care clinics in the city of Harare. A total of 14 clinics will be randomly allocated into either the intervention or control group. A total of 680 (49 participants per clinic) adult patients with hypertension and diabetes will be enrolled for the trial. Participants in the intervention arm will receive a simple health literacy intervention on lifestyle modification, which will be delivered by trained CHWs, while those in the control arm will receive usual care. The intervention consists of 4 face-to-face interactive educational sessions and monthly support visits by trained CHWs and will be carried out over a period of 6 months. The primary study outcomes will be blood pressure and blood glucose levels and levels of adherence to the recommended lifestyle modifications. Other outcomes will include adherence to medication. Data management and analysis will be done using Epi Info software, and the data will be analyzed using the intention-to-treat principle.

Results: Recruitment of study participants commenced on June 1, 2023, and was completed on July 30, 2023. Baseline data are being collected after participants' recruitment, and the final data collection will be completed by January 31, 2024.

Conclusions: There is an information dearth regarding the effectiveness of CHW-led interventions for the management and control of hypertension in Zimbabwe. Our study offers an opportunity to show the effectiveness of CHWs in addressing the gaps in the management of hypertension and diabetes. The findings from our study will provide crucial evidence on the effectiveness and feasibility of a simple intervention delivered by CHWs in resource-constrained areas.

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KEYWORDS

hypertension; diabetes; community health worker; lifestyle modification; cluster randomized controlled trial; protocol; Harare; Zimbabwe; RCT; randomized controlled trial; hypertensive; blood pressure; CHW; diabetic; Africa; healthy lifestyle; health literacy

Introduction

Hypertension and diabetes are among the leading causes of morbidity, disability, and premature death worldwide. In 2019, diabetes was the direct cause of 1.5 million deaths worldwide, and 48% of all deaths due to diabetes occurred before the age of 70 years [1-3]. An estimated 1.28 billion adults aged 30-79 years worldwide have hypertension, with an estimated 46% being unaware of their condition. The prevalence of both hypertension and diabetes has been increasing more rapidly in low- and middle-income countries, compared to high-income countries. This is a cause for concern in these countries, considering their already high burden of communicable diseases [1,3].

Studies have shown links between hypertension and diabetes [4-6]. For instance, hypertension is more common in patients with diabetes, and similarly, diabetes is also more common in patients with hypertension than in the general population [4]. Previous studies have reported that hypertension occurs in 50% to 80% of patients with type 2 diabetes [5]. These two conditions are predominantly lifestyle related, as they are highly associated with risk factors like obesity, stress, excessive salt intake, physical inactivity, excessive alcohol intake, and smoking [3,6,7]. Therefore, prevention, control, and management of these two conditions involve lifestyle modifications. The recommended lifestyle changes include weight reduction, healthy eating, reducing alcohol consumption, regular physical exercise, and quitting smoking [8-10].

Lifestyle modification poses a challenge for patients with hypertension and diabetes, and several studies have demonstrated high noncompliance with the recommended lifestyle modifications worldwide [11]. Although studies have shown that nonadherence to recommended lifestyle modifications is influenced by several factors, inadequate knowledge and lack of support have constantly been highlighted as major contributing factors [12-17]. Therefore, there is a need for educational interventions to assisst patients with hypertension and diabetes in adopting the reccommended lifestyle modifications easily. In most instances, counseling about the reccommended lifestyle modification is done by physicians and nurses as part of their routine clinical care [14]. However, in resource-limited settings, where there is a shortage of health care workers, effectively counseling patients on the reccommended lifestyle modifications poses a challenge [18]. As a result, there is a need to explore other cost-effective strategies to ensure the effective counseling of patients regarding lifestyle modifications. Task-shifting to community health workers (CHWs) has been proven as one such cost-effective and sustainable approach in chronic disease prevention and control, particularly in areas with limited economic and health care resources [15,16,18].

CHWs are voluntary public health workers who are trusted members of the community they serve [17]. They play a crucial role in primary and tertiary prevention of diseases, particularly in low- and medium-income countries. According to the Alma Ata Declaration on Primary Health Care, CHWs are the cornerstone of health promotion, as they facilitate community members' participation in health programs [19]. Overall, CHWs build individual and community capacity to manage chronic conditions by increasing health knowledge and self-sufficiency through a range of activities, such as outreach, community education, informal counseling, social support, and advocacy [20-22]. In Zimbabwe, CHWs primarily provide community-based care, but for many years, their efforts have been focused on home-based care for people living with HIV and tuberculosis, with limited focus on addressing noncommunicable diseases (NCDs) [21]. This shows the need to continuously come up with effective CHW-led interventions for the management of common NCDs.

We have developed a simple CHW health literacy intervention on lifestyle modification, and we have designed a study to evaluate the effects of the intervention among patients with hypertension and diabetes in the city of Harare, Zimbabwe. This paper describes our research design and discusses the rationale of our study. We hypothesize that the intervention will have a positive effect on (1) adherence to recommended lifestyle modifications, (2) adherence to medication, as well as (3) blood glucose and blood pressure levels.

Methods

Study Design

The study is a cluster randomized controlled trial, which will be conducted in the city of Harare in Zimbabwe from June 2023 to January 2024. The design, implementation, and reporting of the study are based on the recommendations from CONSORT (Consolidated Standards of Reporting Trials) statement on cluster randomized controlled trials [23]. The cluster randomized controlled trial will have a 6-month follow-up period and will consist of 1 intervention arm and 1 control arm.

Study Setting

The study will be conducted in 14 primary health care clinics in the city of Harare; these clinics were purposefully selected from a total of 39 health facilities (12 polyclinics, 6 family health services clinics, 15 satellite clinics, and 2 infectious diseases hospitals) in the city. The 14 facilities that have been selected for the study are the ones that offer comprehensive services, including curative services, chronic pain care, maternal and child health services, HIV prevention services, and community health services. These clinics are in the high-density suburbs of the city, with each clinic serving a population of 80,000-100,000 people, the majority of whom are socioeconomically disadvantaged. The 14 health facilities will

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be randomly allocated into either the intervention or the control arm. Thus, each study arm will comprise 7 health facilities.

Interventions

The intervention arm will receive the CHW-led health literacy intervention, while the control arm will receive usual care.

CHW-Led Health Literacy Intervention for Lifestyle Modifications

The intervention was designed by the principal investigator (PI), and its development entailed two processes, as follows: (1) conducting a scoping review of the literature on CHW-based interventions for hypertension and diabetes and (2) validating the content through consultations with 10 experts (ie, 3 health promotion officers, 2 nutritionists, 2 medical doctors, 1 Diabetes Association of Zimbabwe official, 1 pharmacist, and 1 nurse). The intervention is based on the constructs of the Health Belief Model [24], and thus, it aims to (1) convey the consequences of the patient's poor adherence to recommended lifestyle modifications, (2) communicate to the patient the list of recommended lifestyle modifications and highlight the benefits, (3) provide assistance in identifying and reducing barriers to adopt the recommended lifestyle modifications, and (4) develop cues to action for the patient.

This intervention consists of face-to-face educational sessions and support visits to patients and will be delivered by trained CHWs. A total of 4 educational sessions will be conducted at either the patient's home or the primary care clinic, through which the patient is routinely monitored. The first session will be held at the clinic on the day of recruitment. The second and the third sessions will be held at either the clinic or the patient's home, as preferred by the patient. The fourth session will be a home visit, where the CHW will visit the patient in their home to provide support and follow-up. After the fourth educational session, the CHWs will continue to make monthly home visits to the patient.

In terms of content, in the first session, the CHW will educate the patient on the recommended lifestyle modifications and the consequences of nonadherence. In the second session, focus will be on the patient's barriers to adopting recommended lifestyle modifications and ways to overcome them. At the end of this session, patients are expected to write down their own plan for lifestyle modifications on a card, which they will then place in a visible location in their home. This will serve as a cue to action. The second session will be highly interactive, compared to the first session. The third and fourth sessions will be supportive and evaluation sessions during which the CHW assesses whether the patient has been following the action plan established in the second session. In the fourth session, which will be conducted at home, available family members will be involved to support the patient, and this will serve as another cue to action for the patient and will also help to build the patient's self-efficacy. Any deviations from the plan will be discussed and ways to correct will be explored. The monthly home visits conducted after the fourth educational session will serve as support visits, where the CHW will continue to reinforce the importance of adhering to lifestyle modifications.

In terms of timing, the first session will be conducted on the day of recruitment, and the second session will be scheduled a week after the first session. The third session will be conducted 2 weeks after the second session, and the fourth session will also be conducted 2 weeks after the third session. A month after the fourth session, the patients will receive monthly home visits at a date and time convenient for them. Each educational session will last 45-60 minutes, while the monthly support visits will last 10-15 minutes.

To ensure that the intervention adheres to the protocol and maintains study fidelity, the CHWs who will deliver educational sessions will undergo a 1-day training; this training will be conducted by the PI, 1 nurse, and 1 health promotion officer from the city of Harare. The CHWs will be given notes on the recommended lifestyle modifications, to which they will refer when conducting educational sessions. All the CHWs participating in the study have been working as CHWs for periods ranging from 5 to 30 years, and upon their initial recruitment as CHWs, they underwent an 8-week training program. They will also receive refresher trainings as needed, in accordance with the guidelines for CHWs in Zimbabwe [21,25].

Usual Care

The usual care for patients with diabetes and hypertension in the city of Harare involves patients coming to the clinic for monthly reviews and medication collection. Patients also receive counseling on medication adherence and recommended lifestyle modifications, particularly on the day when they are diagnosed and start their medication. Although there is no formalized CHW intervention, CHWs are involved in the continuum of care when patients fail to report for their monthly reviews for 3 consecutive months. Additionally, patients may seek consultation with CHWs in their communities, as needed. Table 1 summarizes the interventions that will be implemented in this study.

Table 1. Summary of study interventions.

Component	Control arm (usual care)	Intervention arm (community health worker–led health literacy intervention)
Main components	Health education session on the importance of adhering to medication and lifestyle modifications on the day medication is initiated by a nurse or doctor and monthly drug pickups at local health facilities	Usual care and 4 interactive educational sessions and monthly home visits by community health workers
Theoretical background of educational sessions	None	Health Belief Model [24]
Role of community health workers	Follow-up when the patient misses clinic appointments for 3 consecutive months	Continuous support in the management and control of diabetes and hypertension

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Randomization

All 14 targeted health facilities will be randomly allocated to either the intervention or the control arm. Each arm will consist of 7 clinics. The randomization process will be conducted by an official from the city of Harare, from the City Health Department, who will not be part of the study staff. The randomization process will be done using the simple randomization technique, based on computer-generated random numbers. To reduce bias and improve study fidelity, group allocation will be concealed to the data collectors until the completion of baseline data collection.

Inclusion and Exclusion Criteria

All adults aged 18 years and older, with a confirmed diagnosis of hypertension and diabetes, residing within the targeted health facility's catchment area, and capable of providing written informed consent will be eligible for enrollment.

Exclusion criteria will include the following: (1) individuals having hypertension- and diabetes-related complications that cannot be managed in a primary care setting, (2) individuals who are pregnant or planning to become pregnant during the course of the trial, (3) individuals who will not be able to stay within the catchment area of the clinic where they are enrolled for the duration of the trial, and (4) individuals who will not be able to give consent for any reason, such as severe mental health disorders.

Recruitment of Participants

Participants will be recruited by trained research assistants every day of the 1-week recruitment period. The recruitment process will be done concurrently at control and intervention sites. Baseline data will be collected on the day of the recruitment, and research assistants will not be aware of group allocations during the recruitment and the baseline data collection periods.

Outcome Measures

The outcome evaluation for this study will be based on data collected both at baseline and during the postintervention follow-up (after 6 months). Data collection tools will be identical for data collection at both periods and include information on patient's demographics, disease history, lifestyle behaviors, medication use, primary use of health care services, and hospitalizations. Height, weight, waist circumference, glycosylated blood glucose levels, and blood pressure will also be measured.

The primary study outcomes will be blood pressure and blood glucose levels as well as levels of adherence to recommended lifestyle modifications. Other outcomes will include changes in medication adherence and additional health-related outcomes, such as frequency of hospitalization or the occurrence of complications.

Assessment of Primary and Secondary Outcomes

A consolidated interviewer-administered questioner comprising of all measures (as detailed in Multimedia Appendix 1) will be used to collect data. The interviewer-administered questionnaire consists of 5 sections, as follows: section A (sociodemographic characteristics), section B (details of the patient's condition), section C (blood pressure, BMI, and glycosylated hemoglobin [HBA_{1c}] measurements), section D (adherence to lifestyle modifications), and section E (adherence to medication).

Lifestyle Modifications

Patients' levels of adherence to recommended lifestyle modifications will be assessed using self-reported questions adapted from the Hypertension Self-Care Activity Level Effects Scale (H-SCALE) questionnaire. The H-SCALE is a validated self-reported questionnaire for assessing self-care practices for hypertension prevention and control [26]. The questionnaire assesses 5 key recommended lifestyle modifications (ie, low-salt diet, physical activity, smoking cessation, weight management, and abstinence from alcohol) as well as adherence to medication. Table 2 shows how each recommended lifestyle modification will be assessed based on the H-SCALE.

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Table 2. Assessment of lifestyle modifications using an interviewer-administered questionnaire adapted from the Hypertension Self-Care Activity Level Effects Scale (H-SCALE).

Recommended lifestyle modification	The WHO[a] recommendation	Assessment method
Weight reduction and management	Maintain normal body weight (BMI 18.5-24.9 kg/m^2)	First, the patient's BMI will be assessed based on the patient's height and weight. All patients with a BMI above 24.9 will be considered as overweight. Second, 10 questions will be used to assess activities undertaken to manage weight through dietary practices, such as reducing portion size, making food substitutions, and exercising to lose weight. Participants who say yes to 5 or more questions will be nonadherent to recommended weight management practices.
Reducing dietary salt intake	Reduce dietary salt intake to less than 2400 mg of sodium per day or less than 6000 mg sodium chloride per day.	A total of 6 questions will be used to assess practices related avoiding salt while cooking and avoiding foods high in salt content. Patients who answer yes to 3 or more questions will be considered as nonadherent to a low salt diet.
Reducing dietary fat intake	Avoid foods high in cholesterol and fat content	A total of 2 questions will be used to assess practices related to avoiding foods high in cholesterol and fat content. Patients who answer yes to any 1 question will be considered as nonadherent to a low fat or cholesterol diet.
Increasing fruit and vegetable consumption	Consume 5 servings (equivalent of 5 tablespoons) of vegetables and 3 servings (equivalent of to at least 3 fruits) of fruits every day.	A total of 2 questions will be asked to assess adherence to fruits and vegetables. Patients who answer yes to any 1 question will be considered as adherent to a high fruit and vegetable diet.
Smoking	Avoid smoking	Smoking status will be assessed by 1 question. All patients who answer yes to the question will be considered nonadherent to nonsmoking recommendations
Moderation in alcohol consumption	Limit alcohol consumption to no more than 2 drinks (eg, 24 oz of beer, 10 oz of wine, or 3 oz of 80-proof whiskey) per day in men and no more than 1 drink per day in women and lighter-weight persons.	Alcohol intake will be assessed using 2 questions. Participants who answer yes to any 1 of the questions will be considered nonadherent to the alcohol recommendation moderation.
Physical activity	Engage in regular aerobic exercises, such as brisk walking for at least 30 minutes per day, for at least 5 days a week.	Physical activity will be assessed by 1 question. Participants who answer yes to the question will be considered as being adherent to the physical activity recommendation.

[a]WHO: World Health Organization.

Hypertension and Diabetes Control

Patient's hypertension and diabetes control will be assessed by blood pressure and HbA_{1c} measurements, respectively. Blood pressure of 140/90 mm Hg or higher will be considered uncontrolled hypertension, while an HbA_{1c} level above 8% (53 mmol/mol) will be considered uncontrolled diabetes [27].

Adherence to Medication

Patients' adherence to medication will be assessed using a widely used and validated tool, the 8-item Morisky Medication Adherence Scale (MMAS-8) [28-31]. The MMAS-8 consists of 8 questions that assess patients' adherence to medication. Patients who score 8 points on the MMAS-8 will be considered to have high adherence, and patients who score 7 and 6 will be considered to have medium adherence; those scoring less than 6 points will be classified as having low adherence.

Other Health Outcomes

Other health outcomes, such as hospitalization and the occurrence of diabetes and hypertension complications, will be assessed from the patients' clinic records.

Sample Size

Based on the recommendations for sample size calculation for cluster randomized controlled trials with a fixed number of clusters [32], a total of 680 participants will be required for the trial. Therefore, the study will comprise 14 clusters, with 49 participants per cluster. The sample size was calculated using the following parameters, obtained from the review of literature: 80% study power, 0.5 effect size, 1 SD, 0.05 coefficient of variation, and 20% lost to follow-up adjustment.

Data Collection and Management

Recruitment of participants started in June 2023. Baseline data were collected during the recruitment of participants. Follow-up data will be collected after 6 months, in January 2024. Data will be collected using the research assistants' smartphones. The questionnaire will be uploaded onto the phones and the REDCap platform will be used for storing and managing the data. The computer system that will be used for storing the data will be password protected so that the data will only be accessible to authorized individuals. Patients will be assigned unique identifying numbers at the beginning of the study and the same number will be used in the follow-up data collection period. Data will be managed according to the International Conference on Harmonisation Guidelines for Good Clinical Practices [33].

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To minimize errors, range checks and skip patterns within data entry screens will be used. Data will be backed up on a password-protected external hard drive as well as on Google Drive.

Data Analysis

Data analysis will be performed using the Epi Info (Centers for Disease Control and Prevention) software. The primary analysis will be conducted under the intention-to-treat principle. For individual outcomes, proportions will be compared using the chi-square test, and continuous measures will be compared using 2-tailed *t* tests. Stratified analysis will be conducted to control for confounding and assess the effect modification by demographic variables and medication adherence. The effects of the intervention will be tested by ANOVA, which will allow adjustment for baseline differences between groups. Two-sided *P* values and 95% CIs will be used to determine statistical significance of results.

Ethical Considerations

Permission to carry out the study in the city of Harare clinics was obtained from the City Health Services Director. Ethical clearance was obtained from the University of Zimbabwe's institutional review board, the Joint Research and Ethics Committee (JREC/339/2022). Written informed consent will be obtained from all study participants. Confidentiality of the study participants will be maintained at all stages of the study.

All participants will be treated fairly, and they will not be intentionally subjected to any harm. During the study, all participants who present with any other health education needs that do not result in contamination of the study will be assisted. Those with complications or any other needs beyond the scope of the research team will be referred to appropriate HCWs. The knowledge that will be generated from this study will be disseminated to all pertinent stakeholders using various strategies, such as publications and feedback meetings.

Results

Recruitment of study participants commenced on June 1, 2023, and was completed on July 30, 2023. Baseline data are being collected after participant recruitment, and the final data collection will be completed by January 31, 2024.

Discussion

Expected Findings

Hypertension and diabetes are global health challenges that have placed significant burdens on health care systems in all nations [34]. The burden of chronic NCDs is rapidly increasing worldwide. Nevertheless, many countries, particularly low- and medium-income countries, do not have adequate health care resources to effectively deal with these prevalent health problems. Therefore, there is a dire need for effective interventions to tackle these challenges. These interventions rely on adequate human resources. However, in resource-limited countries like Zimbabwe, there is a shortage of health workers, and they are already overburdened with the management of infectious diseases, such as HIV or AIDS, tuberculosis, and diarrheal diseases. Therefore, task-shifting the counseling responsibilities for patients with chronic NCDs is one of the options that should be considered. The findings from our study will thus add to the body of knowledge needed for the development of interventions to address NCDs in resource-limited settings.

Evidence-based national and international guidelines on managing hypertension and diabetes are well-established, cost-effective approaches, suitable for adoption in resource-constrained settings, but they have not been adequately investigated [8]. Our study offers an opportunity to show the effectiveness of CHWs in addressing the gaps in the management of hypertension and diabetes. The use of CHWs to address the shortage of professional health care workers in the management of hypertension, diabetes, and other chronic NCDs has been widely recommended [35]. Evidence from several low- and medium-income countries indicates that this is a feasible and cost-effective strategy [36-38]. However, there is an information dearth regarding such evidence, specifically for the Zimbabwean setting, and particularly, in the urban setup. To the best of our knowledge, our study will be the first to assess the effectiveness of CHWs in improving the much-needed lifestyle modification among patients with hypertension and diabetes in the city of Harare. The findings from our study will provide evidence on the feasibility and effectiveness of a simple intervention delivered by the CHWs in resource-constrained areas. Overall, our study is vital to the achievement of Sustainable Development Goal target 3.4, which aims to reduce premature mortality from NCDs by one-third [39].

Strengths and Limitations

The strengths of our study include CHWs who are already integrated in the Zimbabwean primary health care system. The CHWs have prior experience in disseminating health education on various health topics, particularly prevention of diarrheal diseases and malaria, which are prevalent in the country. Additionally, the CHWs are routinely involved in follow-ups with patients who have hypertension and diabetes, ensuring they do not miss monthly checkups. Therefore, if successful, our intervention will modify and strengthen community-based management of hypertension and diabetes. Unlike most of the CHW-based interventions being implemented in other low- and middle-income countries, our intervention is based on a tested and tried health behavior model, the Health Belief Model [24]. Therefore, we envisage that the intended behavior change in the adoption of recommended lifestyles will be successful. Moreover, our intervention will be innovatively addressing some of the most challenging barriers to the management of chronic NCDs, such as human resources. Hence, if successful, this intervention can be potentially scaled up to the entire nation.

Nonetheless, there are weaknesses in our study, mainly emanating from the cluster randomized controlled trial design. First, our study does not involve blinding of study participants. Lack of blinding is one of the weaknesses inherent in cluster randomized controlled trials that include behavioral interventions. However, to reduce bias associated with lack of blinding, there will be partial blinding of data collectors during the collection of baseline data. The data collectors will not know

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the arm to which each clinic will belong. In addition, there is a possibility of information sharing among participants in the intervention and control group, since the suburbs in Harare are within close proximities. To limit the sharing of information, participants in the intervention group will receive a detailed explanation of the study's importance from the PI. There is also a possibility of social desirability bias in assessing lifestyle modifications. Participants may report what they perceive as the desired behavior rather than their actual behavior. However, the study will assess overall changes in blood glucose and hypertension levels as well as BMI, which are more objective outcome measures.

Conclusions

Our trial aims to evaluate the effects of a CHW-led health literacy intervention for lifestyle modifications among patients with diabetes and hypertension in Harare, Zimbabwe. Findings from our study will provide reliable evidence on the effectiveness of a simple community-based intervention in the management and control of the two most common NCDs in Zimbabwe. In summary, our study will contribute to the much-needed body of knowledge on the effectiveness of using CHWs in the management of chronic NCDs in resource-limited countries.

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NAK acquired a license to use the 8-item Morisky Medication Adherence Scale (MMAS-8) for this study from the scale developer, Dr Donald E Morisky. The MMAS-8 Scale, content, name, and trademarks are protected by US copyright and trademark laws. Permission for use of the scale and its coding is required. A license agreement is available from MMAR, LLC (http://www.moriskyscale.com).

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Data Availability

The consent and ethical approvals for this study do not have any restrictions on data sharing. Therefore, the data sets generated from this study will be made publicly available as supplementary files in all publications of the study results.

Authors' Contributions

NAK conceptualized the study and was responsible for drafting the initial manuscript, and the subsequent drafts, leading to the final version; SR, SS, and GTF reviewed the study proposal as well as the initial manuscript and its subsequent drafts. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Interviewer-administered questionnaire for collecting data.
[DOC File , 67 KB - resprot_v12i1e47512_app1.doc]

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Abbreviations

CHW: community health worker
CONSORT: Consolidated Standards of Reporting Trials
H-SCALE: Hypertension Self-Care Activity Level Effects Scale
HBA_{1c}: glycosylated hemoglobin
MMAS-8: Morisky Medication Adherence Scale-8
NCD: noncommunicable disease
PI: principal investigator

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Protocol

Optimizing Noninvasive Vagus Nerve Stimulation for Systemic Lupus Erythematosus: Protocol for a Multicenter Randomized Controlled Trial

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Abstract

Background: Systemic lupus erythematosus is a chronic, multisystem, inflammatory disease of autoimmune etiology occurring predominantly in women. A major hurdle to the diagnosis, treatment, and therapeutic advancement of this disease is its heterogeneous nature, which presents as a wide range of symptoms such as fatigue, fever, musculoskeletal involvement, neuropsychiatric disorders, and cardiovascular involvement with varying severity. The current therapeutic approach to this disease includes the administration of immunomodulatory drugs that may produce unfavorable secondary effects.

Objective: This study explores the known relationship between the autonomic nervous system and inflammatory pathways to improve patient outcomes by treating autonomic nervous system dysregulation in patients via noninvasive vagus nerve stimulation. In this study, data including biomarkers, physiological signals, patient outcomes, and patient quality of life are being collected and analyzed. After completion of the clinical trial, a computer model will be developed to identify the biomarkers and physiological signals related to lupus activity in order to understand how they change with different noninvasive vagus nerve stimulation frequency parameters. Finally, we propose building a decision support system with integrated noninvasive wearable technologies for continuous cardiovascular and peripheral physiological sensing for adaptive, patient-specific optimization of the noninvasive vagus nerve stimulation frequency parameters in real time.

Methods: The protocol was designed to evaluate the efficacy and safety of transauricular vagus nerve stimulation in patients with systemic lupus erythematosus. This multicenter, national, randomized, double-blind, parallel-group, placebo-controlled study will recruit a minimum of 18 patients diagnosed with this disease. Evaluation and treatment of patients will be conducted in an outpatient clinic and will include 12 visits. Visit 1 consists of a screening session. Subsequent visits up to visit 6 involve mixing treatment and evaluation sessions. Finally, the remaining visits correspond with early and late posttreatment follow-ups.

Results: On November 2022, data collection was initiated. Of the 10 participants scheduled for their initial appointment, 8 met the inclusion criteria, and 6 successfully completed the entire protocol. Patient enrollment and data collection are currently underway and are expected to be completed in December 2023.

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Conclusions: The results of this study will advance patient-tailored vagus nerve stimulation therapies, providing an adjunctive treatment solution for systemic lupus erythematosus that will foster adoption of technology and, thus, expand the population with systemic lupus erythematosus who can benefit from improved autonomic dysregulation, translating into reduced costs and better quality of life.

Trial Registration: ClinicalTrials.gov NCT05704153; https://clinicaltrials.gov/study/NCT05704153

International Registered Report Identifier (IRRID): DERR1-10.2196/48387

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KEYWORDS

vagus nerve stimulation; autonomic nervous system; computational models; systemic lupus erythematosus; vagus; vagal; nerve stimulation; noninvasive; RCT; randomized; lupus; inflammation; autoimmune; chronic; nerve; nerve damage; vagus nerve

Introduction

Background

The origin of autoimmune disease is a disruption of immune tolerance of self-antigens thought to occur in genetically susceptible individuals after exposure to environmental triggers. Possible environmental factors that predispose to autoimmunity include exposure to infectious agents, ultraviolet light, dietary components, chemicals, xenobiotics, toxins, and stress, as well as reduced exposure to factors that protect from the development of autoimmune diseases. Autoimmune diseases can be systemic or can affect specific organs or body systems including the endocrine system, gastrointestinal system, liver, neurological system, and musculoskeletal system and connective tissue [1].

Systemic lupus erythematosus (SLE) is a chronic systemic autoimmune disorder that commonly affects the skin, joints, kidneys, and nervous system. Abnormal activation and processing of cell death signals by the immune system trigger the release of nuclear debris from apoptotic and necrotic cells and stimulate the production of antinuclear antibodies (for example, anti-Ro and anti-DNA), with subsequent inflammation, organ damage, and pathology [2].

Many patients with SLE experience flares of disease activity interspersed with quiescent periods. The current understanding of the factors driving the different phenotypes and its pathogenesis in SLE is limited and directly affects treatment. The current therapeutic approach to SLE most commonly includes the administration of antimalarials, immunosuppressants, and biological agents. These treatments have allowed great progress to be made, and, currently, SLE-related mortality is 10% within 10 years, compared with the 1960s, when the mortality was 50% within 3 years, according to an analysis of a multisite, international SLE cohort [3]. However, these current medication options for SLE produce secondary effects, such as ocular toxicity, renal damage, risks of infections, hematological toxicities, gastrointestinal events, ovarian toxicities, and in particular, comorbidities associated with the long-term adverse effects of glucocorticoids in the musculoskeletal, cardiovascular, peripheral vascular, ocular, and metabolic domains [4].

A major hurdle to the treatment of autoimmune diseases is their heterogeneous nature. SLE is referred to as “the great imitator” because patients can experience a wide range of symptoms with varying severity [5] that appear to belong to other diseases. The heterogeneity of SLE presents challenges not only with diagnosis but also with treatment and therapeutic advancements. Broadly, manifestations of SLE include fatigue, fever, weight changes, lupus nephritis, and complications involving the following systems: musculoskeletal, gastrointestinal, pulmonary, cardiovascular, cutaneous, neuropsychiatric, hematological, and ocular.

The autonomic nervous system (ANS) is mainly composed of 2 primary branches: the sympathetic nervous system (SNS) and parasympathetic nervous system (PNS). The ANS exhibits complex central control and plays a critical role in mediating interactions between the nervous and immune systems and coordinates the interplay among cells, tissues, and organs throughout the body to maintain homeostasis via its widespread innervation of the glands, smooth muscles, and heart [6].

In many inflammatory diseases, dysautonomia manifests as an imbalance in the activity and reactivity of the SNS and PNS [7]. Increased sympathetic nerve outflow has been shown to activate pro-inflammatory cytokines and produce reactive oxygen intermediates, processes strongly implicated in the pathogenesis of SLE [2]. SLE was found to have SNS predominance or PNS dysregulation owing to decreased heart rate variability in patients with SLE. The prevalence of autonomic dysfunction ranges widely from 6% to 93% in patients with SLE [8]. Autonomic imbalance is related to an increased risk of developing cardiovascular disease—a major cause of morbidity and mortality in patients with SLE. Therefore, therapeutic strategies aimed at rebalancing the ANS may provide improved outcomes in patients with SLE.

Prior Work

Vagus nerve stimulation (VNS) stimulates the tenth cranial nerve, the longest nerve of the organism that links the central nervous system and body by innervating major organs, such as the heart, lungs, and gastrointestinal tract. The vagus nerve is a major component of the PNS that enables bidirectional communication between the brain and different organs of the body by transmitting and exchanging sensory and motor information. The vagus nerve has been shown to play a crucial role in regulating inflammation [9] by activating the cholinergic anti-inflammatory pathway, which reduces pro-inflammatory cytokine production, inhibits pro-inflammatory activity of immune cells, and promotes the release of anti-inflammatory molecules [10]. This process is mediated by the release of acetylcholine, which binds to alpha-7 nicotinic acetylcholine

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receptors on immune cells, such as macrophages and T-cells, and inhibits their pro-inflammatory activity [9]. This vagus nerve–mediated pathway has been shown to have potential therapeutic applications for a range of inflammatory disorders, including rheumatoid arthritis, inflammatory bowel disease, and sepsis [11-13].

Although invasive VNS has shown positive results for the treatment of multiple diseases [11-14], VNS device implantation is associated with multiple complications, such as hoarseness, bradycardia, coughing, shortness of breath, tingling, syncope, paresthesia, muscle pain, asystole, delayed arrhythmias, sleep apnea, and surgical trauma [15-17]. To avoid implant‐related complications, noninvasive VNS (nVNS) devices that stimulate the vagus nerve through transcutaneous stimulation were developed. nVNS has shown positive therapeutic results with no significant adverse events reported for a large collection of diseases [18-28].

Varying the waveform parameters of nVNS can dramatically change the therapeutic outcome. High-frequency nVNS has been shown to stimulate different vagal fibers than those stimulated by low‐frequency nVNS, resulting in different therapeutic effects [26,28-32]. The pulse width may have a different effect on patients; a short pulse width may produce significantly less overall activation in the human brain than long pulse widths. The stimulation intensity also plays an important role and can be delivered at the subsensory, sensory, or maximal tolerance levels. Other nVNS parameters, such as the output current and signal ON and OFF times, have unknown therapeutic effects. In addition to variations in the therapeutic response, the physiological response to a given nVNS configuration can suffer from significant inter and intrapatient variability. As a result, the optimal nVNS parameters for patients with SLE are unknown. To optimize the nVNS parameters for SLE treatment, computational models can be used to study complex physiological interactions of the vagus nerve and to predict therapeutic outcomes to different nVNS configurations. Computational models have been developed for invasive VNS [33-38] and nVNS [39-41]. However, these systems have yet to be put into the context of SLE [10].

Hypotheses and Aims

The discrepancy that exists in the use of nVNS parameters requires investigation to enable the appropriate administration of nVNS to patients with autoimmune diseases, such as SLE, for the improvement of ANS dysregulation. Therefore, the hypotheses of this study are as follows:

1. ANS dysregulation can be improved through the application of personalized nVNS.
2. At postintervention, the treatment groups (active and sham nVNS) will have different outcomes and scores.
3. Improved ANS function in patients with SLE can lead to better patient outcomes and increased quality of life.

Based on this premise, the aims of this clinical trial are as follows:

1. Collect data related to biomarkers, physiological signals, patient outcomes, and patient quality of life.
2. From the collected data, propose a computational model that can (1) identify the biomarkers and physiological signals related to SLE activity, (2) understand how the identified biomarkers and physiological signals change with different nVNS frequency parameters, and (3) include a decision support system with integrated noninvasive wearable technologies for continuous cardiovascular and peripheral physiological sensing for adaptive, patient-specific optimization of the nVNS frequency parameters in real time.
3. Validate the findings of Aranow et al [28], who found that the use of nVNS reduced pain and fatigue in patients with SLE.

Methods

Participants and Recruitment

Patients are recruited from the autoimmune disease outpatient clinics of the Hospital Clínic de Barcelona and Hospital Universitari Mútua Terrassa for a multicenter, national, randomized, double-blind, parallel-group, placebo-controlled, outpatient study. To compare our results with those of Aranow et al [28], a minimum of 18 adult patients (6 per study arm) is required. There is growing evidence that sex affects the pathophysiology, incidence, prevalence, development, and response to therapy in many diseases. In SLE, 90% of all diagnoses are in women [42], who are most commonly affected by clinical flares between the ages of 15 years and 44 years, or during childbearing years. Due to this disproportionality between sexes, this study aims to have a women:men ratio of 9:1, in keeping with SLE prevalence between sexes. The inclusion and exclusion criteria are summarized in Textbox 1.

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Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

1. Age ≥18 years
2. Diagnosis of systemic lupus erythematosus (SLE; defined by the American College of Rheumatology or Systemic Lupus International Collaborating Clinics [SLICC] criteria)
3. Musculoskeletal pain ≥4 on a nonanchored, 10-cm visual analog scale (VAS)
4. British Isles Lupus Assessment Group (BILAG) C on the musculoskeletal domain of the BILAG 2004
5. If on corticosteroids, stable dose of ≤10 mg/day (prednisone or equivalent) for at least 28 days before baseline
6. If on background immunosuppressive treatment, stable dose for at least 28 days before baseline
7. Able and willing to give written informed consent and comply with the requirements of the study protocol

Exclusion criteria

1. Treatment with rituximab within 1 year of baseline
2. Treatment with cyclophosphamide within 2 months of baseline
3. Expectation to increase steroid or immunosuppressive treatment
4. Antiphospholipid syndrome
5. Fibromyalgia (as defined by a score >13 on the fibromyalgia symptom scale)
6. Chronic fatigue syndrome
7. Treatment with an anticholinergic or sympathomimetic medication, including over-the-counter medications
8. Implantable electronic devices, such as pacemakers, defibrillators, hearing aids, cochlear implants, or deep brain stimulators
9. Joint replacement within 60 days prior to study enrollment or planned within the course of the study
10. Any planned surgical procedure requiring general anesthesia within the course of the study
11. Intra-articular cortisone injections within 28 days of the start of study
12. Chronic inflammatory disorders apart from SLE affecting the joints
13. Investigational drug or treatment during the 28 days or 7 half-lives of the investigational drug prior to the start of study drug dosing (day 0), whichever is the greater length of time
14. Active infection including hepatitis B, hepatitis C, or HIV at baseline due to high prevalence of neuropathy
15. Any condition that, in the opinion of the investigator, would jeopardize the participant's safety following exposure to a study intervention
16. Pregnancy or lactation
17. Hemoglobin <9.0 gm/dL (according to the most recent complete blood count)
18. Comorbid disease that may require administration of corticosteroid
19. Inability to comply with study and follow-up procedures
20. Known cardiac arrhythmia, severe cardiac disease, or neurodegenerative disease
21. Peripheral or autonomic nervous system involvement, including SLE-related neuropathies, toxic polyneuropathies, metabolic neuropathies (including diabetes)
22. Previous experience with vagus nerve stimulation devices

Screening

The screening period is set at 4 weeks and begins when the patient signs the informed consent form, which includes a full description of the study and procedures involved, patients' rights and responsibilities, and alternative treatments that are available if the patient does not decide to participate in the study. During the screening period, the investigators must confirm that the patient meets all inclusion criteria and no exclusion criteria for the study (see the Participants and Recruitment section). Eligible patients are randomized at week 0.

Patients who are registered for this trial may have one or more active symptoms of lupus but the investigators believe that their condition is stable enough to participate. This trial design permits patients to continue their regular immune suppressive therapies at stable doses, but they are not allowed to receive additional corticosteroids during the short duration of the protocol, even if they receive a sham intervention.

Intervention

At the second visit (week 0, baseline), after all assessments are completed and baseline laboratory samples are obtained according to the schedule of activities (see the Follow-Up

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section), patients are randomly assigned (1:1:1) to active (1 Hz or 30 Hz) or sham (placebo) nVNS. The rationale underlying the choice of 1 Hz and 30 Hz (minimum and maximum values of the nVNS treatment device) is based on the discrepancies found in the literature regarding the choice of a frequency value, as well as previous findings indicating that high and low frequencies of nVNS treatment stimulate different vagal fibers. The effect of VNS in epilepsy and depression is thought to be mediated through the activation of vagal afferent fibers via high-frequency (20-30 Hz) stimulation, whereas the activation of the cholinergic anti-inflammatory pathway has been found to be mediated through vagal efferent fibers involving low‐frequency (1-10 Hz) stimulation [29]. A study by Borovikova et al [30] found that VNS at 1 Hz frequency for 20 minutes was effective for the preferential recruitment of efferent parasympathetic fibers. Other reports have also shown that low-frequency (5 Hz) VNS is able to activate vagal efferent fibers [31]. In various studies of nVNS in inflammatory diseases, the amplitude was generally set individually to a constant tingling, nonpainful sensation. In these same studies, interestingly, 25 Hz [19,21,24,26] was the most frequently studied frequency, while other frequencies used were 100 Hz [23], 30 Hz [22], 5 kHz [32], and 1 Hz [12,25]. Only 2 studies have explored the low-frequency range to stimulate the vagal efferent fibers and thus, the cholinergic anti-inflammatory pathway. Straube et al [26] compared 25 Hz with 1 Hz in the treatment of chronic migraines and found a significantly larger reduction in headache days in the 1 Hz group.

Patients are blinded to the treatment allocation and are requested to refrain from discussing the details of their treatment with other patients, physicians, and clinic staff. The clinical coordinators are also blinded to the treatment allocation, and the responsible engineer instructs the patients on the proper use of the device. The study personnel have been designated to address the patient's questions and concerns as well as to record any side effects related to the use of the device.

Active or sham nVNS is administered for 5 minutes during 5 consecutive days in a similar schedule to the treatment followed by Aranow et al [28] (5 minutes during 4 consecutive days). Clinical assessments and laboratory samples are obtained at scheduled visits according to the schedule of activities. During the treatment period, in addition to randomized treatment, patients also continue their usual medication regimen for SLE, including background standard-of-care therapy (see the Participants and Recruitment section for more details).

nVNS is administered using a Parasym device (Parasym Ltd). The Parasym device is compliant with the relevant standards contained in the Medical Device Directive 93/42/EEC. The Parasym Device is CE marked and available for purchase by individuals of the European Union.

According to the available literature, adverse effects are scarce. Although a low incidence of skin irritation has been reported from using the Parasym device, no serious adverse events have been reported in the literature. In a systematic review, Redgrave et al [43] analyzed data from 1322 participants (across 51 studies) who received nVNS. This review found that only 2.6% of participants discontinued use due to side effects, and the most common side effect reported was skin irritation at the stimulation site that typically ceased shortly after use. The low rate of cardiac arrhythmias (0.3%) is noteworthy because cardiac arrhythmias are recognized as early and late complications of invasive VNS.

Follow-Up

Patients who complete the treatment period of the study will then attend weekly follow-up evaluations for 1 month. Subsequently, if the values of the measured biomarkers and scales of activity do not return to baseline levels ($P<.05$), additional follow-up evaluations will be performed at months 2 and 3. Patients who discontinue study treatment early will have the same posttreatment follow-up visits, unless the patient withdraws informed consent.

Primary and Secondary Outcomes

The primary outcome of this study will be the evaluation of the causal relationship among the waveform frequency of nVNS, physiological signals, and therapeutic effect of the treatment. Therefore, we will analyze clinical and physiological changes in patients with SLE after nVNS using different waveform frequency parameters between the exploratory study at the first visit (baseline) and 30 days after the first nVNS treatment session. The secondary outcome of this study will be a comparison between our results and those of Aranow et al [28]. Both outcomes fall under the overall objective of the Modelling and Control of Non-invasive Vagus Nerve Stimulation for Autoimmune Diseases (VaNeSA) project, aimed at developing a VNS platform with an integrated VNS decision support system, including an nVNS device and portable physiological sensors that will optimize nVNS waveform parameters to maximize the therapeutic effect and minimize unwanted side effects.

The therapeutic effect and side effects will be measured using clinical, neurophysiological, and analytical tests divided into 3 sections: serum biomarkers (Textbox 2), clinical activity indices (Textbox 3), and ANS assessment (Textbox 4).

Furthermore, the addition of continuous cardiovascular and peripheral physiological sensing offers a convenient tool for this investigation owing to the intimate relationship of the vagus nerve with the heart and peripheral physiology and the ubiquity of noninvasive wearable technologies. This will allow the capture of real-time information regarding the state of the patient and their response to nVNS, which will facilitate real-time predictions of physiological responses to nVNS. Physiological signals are evaluated using a Fitbit Charge 5 activity band (Textbox 5).

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Textbox 2. Serum biomarkers.

1. Complete blood count (CBC)
2. Erythrocyte sedimentation rate (ESR)
3. C-reactive protein (CRP)
4. Complement C3
5. Complement C4
6. Anti-double stranded DNA (anti-dsDNA)
7. Tumor necrosis factor (TNF)
8. High mobility group box 1 (HMGB1)
9. Interleukin (IL)-6, IL-10, and IL-1B
10. Intravesical interferon alpha (IFNα)

Textbox 3. Disease activity indices and outcome measures.

1. Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), British Isles Lupus Assessment Group 2004 (BILAG 2004) index
2. Physician's Global Assessment (PGA) and Patient's Global Assessment (PtGA)
3. 28-joint count
4. Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI)
5. Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F) and Fatigue Severity Scale (FSS)
6. Visual analog scale for pain (VAS Pain) and 11-point numeric rating scale
7. EQ-5D-5L, Lupus Quality of Life (LupusQoL), and Lupus Patient-Reported Outcome (LupusPRO) questionnaires

Textbox 4. Autonomic nervous system evaluation.

1. Cardiovagal evaluation: continuous electrocardiogram heart rate changes during deep breathing, Valsalva maneuver, and postural changes
2. Sympathetic evaluation: beat-to-beat blood pressure changes to Valsalva maneuver and postural changes
3. Heart rate variability (HRV): continuous electrocardiogram recorded at rest for 5 minutes for HRV analysis
4. Composite autonomic symptom scale 31 (COMPASS-31)

Textbox 5. Physiological signals measured with a Fitbit Charge 5.

1. Heart rate: heart rate and heart rate variability value every 5 minutes
2. Physical activity: steps, distance, and elevation every 5 minutes
3. Sleep: daily sleep duration and sleep quality

Schedule of Activities

In total, between 10 and 12 visits are scheduled. The activities of each of these visits are detailed in Table 1. In the first visit (V1), the screening session, each patient is provided with a Fitbit Charge 5 activity band and assessed for 90 minutes. The next treatment visits (V2-V6) will last between 15 minutes and 30 minutes. We will then conduct 2 telephone follow-ups (V8 and V9) of up to 15 minutes each. Subsequently, early (V7) and late (V10) posttreatment follow-ups will be conducted for 30 minutes. Finally, if the measured biomarker values and activity scales do not return to baseline levels ($P<.05$), a very late posttreatment follow-up of 1 or 2 visits (V11 and V12), each lasting 30 minutes, will be performed.

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Table 1. Activities of the study during the scheduled visits.

Details	Visit number											
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11[a]	V12[a]
Study day	–28	1	2	3	4	5	8	15	22	29	56	84
Activities												
Informed consent	✓											
Wearable	✓											
Demographics	✓											
Medical history	✓											
Physical examination	✓	✓	✓	✓	✓	✓	✓			✓	✓	✓
Substance use[b]	✓	✓					✓			✓	✓	✓
Nervous system evaluation	✓						✓			✓	✓	✓
Concomitant medications	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Review inclusion and exclusion criteria	✓	✓										
Adverse events		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Randomization		✓										
Investigational treatment administration		✓	✓	✓	✓	✓						
SLEDAI-2K[c]	✓	✓	✓	✓	✓	✓	✓			✓	✓	✓
BILAG-2004[d]		✓									✓	✓
PGA[e]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
PtGA[f]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
CLASI[g]	✓	✓	✓	✓	✓	✓	✓			✓	✓	✓
Tender/swollen joint count	✓	✓	✓	✓	✓	✓	✓			✓	✓	✓
FACIT-F[h]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
FSS[i]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
VAS[j] Pain	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
11-point NRS[k] scale	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
EQ-5D-5L		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
LupusQoL[l]		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
LupusPRO[m]		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
COMPASS-31[n]	✓						✓			✓		
CBC[o]	✓						✓			✓	✓	✓
ESR[p] and CRP[q]	✓						✓			✓	✓	✓
C3[r], C4[s], anti-dsDNA[t]	✓						✓			✓	✓	✓
TNF[u], HMGB1[v], IL[w]-6, IL-1B, IL-10	✓						✓			✓	✓	✓
IFNα[x]	✓						✓			✓	✓	✓

[a]Only if the values of the measured biomarkers and scales of activity do not return to baseline levels ($P<.05$).

[b]Caffeine, alcohol, or tobacco.

[c]SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index.

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[d]BILAG 2004: British Isles Lupus Assessment Group 2004.
[e]PGA: Physician's Global Assessment.
[f]PtGA: Patient's Global Assessment.
[g]CLASI: Cutaneous Lupus Erythematosus Disease Area and Severity Index.
[h]FACIT-F: Functional Assessment of Chronic Illness Therapy – Fatigue.
[i]FSS: Fatigue Severity Scale
[j]VAS: visual analog scale.
[k]NRS: numeric rating scale.
[l]LupusQoL: Lupus Quality of Life.
[m]LupusPRO: Lupus Patient-Reported Outcome.
[n]COMPASS 31: Composite autonomic symptom scale 31.
[o]CBC: complete blood count.
[p]ESR: erythrocyte sedimentation rate.
[q]CRP: C-reactive protein.
[r]C3: complement C3.
[s]C4: complement C4.
[t]anti-dsDNA: anti-double stranded DNA.
[u]TNF: tumor necrosis factor.
[v]HMGB1: high mobility group box 1.
[w]IL: interleukin.
[x]IFNα: interferon alpha.

Statistical Analysis

The Wilcoxon rank sum test will be used to compare the change in endpoints from baseline to day 7 and from baseline to day 21 in participants receiving active and sham nVNS. Spearman rank-order correlation will be used to assess the potential associations between endpoints. False discovery rate control will be used to mitigate the problem of a false positive rate error. Statistical analysis will be performed using the SciPy Python-based library.

Ethics Approval

This study is being conducted in compliance with the Declaration of Helsinki (Fortaleza, Brazil, October 2013). The study is being carried out in accordance with the protocol and with the relevant legal requirements, Law 14/2007 of July 3, on Biomedical Research. The study was approved by the Clinical Research Ethics Committee of the Hospital Clínic of Barcelona (protocol identifier: HB/2021/1286; approved March 14, 2022). Informed consent is obtained from all participants invited to participate in the study prior to the baseline visit. Data will be processed in accordance with ethical principles that guarantee the anonymity of the participants.

Results

The study is supported by the Spanish Ministry of Science and Innovation through grant PID2020-117171RA-I00 funded by MCIN/AEI/10.13039/501100011033 in July 2021. The data collection began on November 19, 2022. The clinical study staff have been engaged in activities including enrollment and data collection. As of March 1, 2023, a total of 10 participants had been admitted for their first appointment, 8 had met the inclusion criteria, and 6 had completed the treatment. Recruitment and data analysis are expected to be completed in December 2023.

Discussion

Overview

This study belongs to a collection of studies pertaining to the VaNeSA project. The overall goal of the VaNeSA project is to develop an nVNS platform with nVNS, an integrated nVNS decision support system, and physiological wearable sensors that will optimize nVNS waveform parameters to maximize the therapeutic nVNS effect while minimizing unwanted side effects.

This clinical trial is the first conducted in the VaNeSA project that will analyze the physiological signals, biomarkers, and clinical outcomes to determine the most effective measures to monitor, optimize, and personalize nVNS in patients with SLE. The ultimate aim of this study is to confirm that the application of personalized nVNS will improve ANS dysregulation, a possible driver of autoimmune disease, leading to better patient outcomes and quality of life. After this study, computational models to describe and predict the impact of nVNS on the ANS and clinical outcomes for patients with SLE will be created, implemented, and validated. The goal of developing computational models is the objective not only of this study but also of the framework project (VaNeSA project) in which there will be more clinical experimentation with other related diseases and other sets of nVNS parameters. The results obtained in this clinical trial will serve to determine the most appropriate approach for obtaining these models, but the idea is to condition the physiological responses of the treatment to the therapy administered so that we can develop a first prototype to induce the application of specific stimulation parameters to each patient. Although the creation of computational models depends on the overall quality of the final results, the initial plan is to use modelling algorithms using artificial intelligence techniques. We plan to implement a decision tree–based methodology since it seems to be one of the best alternatives, as their conditional

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control statements decompose complex data into more manageable parts. The validated computer models, a decision support system, and wearable physiological sensors will be integrated into an nVNS platform allowing for the optimization and personalization of nVNS therapy in real time. Finally, the nVNS platform will be tested and validated.

Limitations and Strengths

This randomized, double-blinded, placebo-controlled clinical trial is one of the first studies delving into the impact of nVNS on clinical outcomes for patients with SLE. The design is a parallel study used to ensure optimal blinding and adjust to the time constraints of the study. However, this study design is weaker than that of a crossover design. The nVNS sessions are being performed by the hospital staff, potentially limiting the willingness of patients to enroll in the study due to the frequency of required hospital visits but ensuring correct treatment delivery and safety (sham treatment, stimulation intensity, localization, and duration). Evidence from this trial will have a limited effect on the knowledge of the optimization of the nVNS parameters because only the frequency domain is evaluated while the remaining characteristic parameters of the nVNS will remain unknown. The small sample size may also pose a limitation in terms of sample representation and statistical power. Finally, in comparison with prior research, our study involves a comprehensive number of biomarkers and activity indices, including ANS and PNS evaluations, that will provide extensive baseline characterization and explore dose-response characteristics of nVNS, allowing nVNS to be contextualized for clinical use.

Conclusions

This study addresses the potential use of nVNS as an adjunctive treatment for SLE. The goal of the study is to provide information on the use of nVNS in SLE and move toward a patient-tailored therapeutic solution that can encourage the adoption of VNS technologies and thus expand the SLE population that can benefit from improved autonomic dysregulation, resulting in reduced costs and improved patient outcomes and quality of life.

Acknowledgments

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Data Availability

Deidentified participant data will be shared upon reasonable request after completion of the trial and publication of the study results. Data will be available for use if the request is approved by the appropriate institutional review board and the Trial Steering Committee and a signed data access agreement is in place.

Conflicts of Interest

None declared.

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Abbreviations

nVNS: noninvasive vagus nerve stimulation
PNS: parasympathetic nervous system
SLE: systemic lupus erythematosus
SNS: sympathetic nervous system
VaNeSA: Modelling and Control of Non-invasive Vagus Nerve Stimulation for Autoimmune Diseases
VNS: vagus nerve stimulation

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Protocol

Nursing Training for Early Clinical Deterioration Risk Assessment: Protocol for an Implementation Study

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Abstract

Background: During the hospitalization period, it is possible to observe considerable changes in the vital parameters of patients, which may require emergency interventions or intensive treatment. The alteration of signs and symptoms that lead to physiological instability that can worsen the clinical picture with progression to shock, respiratory failure, or cardiorespiratory arrest is currently defined as clinical deterioration. Identifying signs of clinical deterioration at an early stage can lead to substantial decreases in mortality rates, the need for emergency interventions, and unscheduled treatments in intensive care units. Identifying and appropriately referring patients who show signs of clinical deterioration can be facilitated by applying early warning systems that provide rapid responses. The nursing team is usually the first to identify clinical changes in patients. Although the literature demonstrates that early recognition of clinical deterioration is the key to early intervention and leads to better outcomes, we only sometimes pursue the most appropriate intervention.

Objective: This study aims to implement and evaluate an evidence-based professional training program designed for nurses and coordinated by a nurse using the "just-in-time" methodology and the National Early Warning Score 2 (NEWS2) to assess the risk of early clinical deterioration and appropriate referral in inpatient units of a public university hospital in southeastern Brazil.

Methods: This intervention protocol is structured according to the recommendations of the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) Declaration 2013. The type of training to be offered, "Just-in-Time Training," consists of a teaching modality that facilitates the delivery of a time-based and work-based education, with greater emphasis on providing on-the-job learning as needed. A qualitative stage will also be conducted through focus groups and interviews with nurses to verify the factors that influence the professional practice related to the early evaluation of the clinic. A script of previously tested questions will guide and standardize the different groups. The data will define the intervention's elements: the strategy, the type of training, the location, the teaching methodology, and the teaching material.

Results: The study has received authorization from the ethics committee, and participants will be recruited in July 2023. Data collection should be completed in October of the same year. The results obtained at the end of this research will be shared with the participating nursing team through the presentation of reports. In addition, the research results will be submitted to scientific journals and presented at international scientific conferences.

Conclusions: This study will support nurses and possibly other clinicians to improve their approach to early recognition of clinical deterioration in patients.

Trial Registration: Brazilian Registry of Clinical Trials RBR-5hq9y3k; https://ensaiosclinicos.gov.br/rg/RBR-5hq9y3k

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KEYWORDS

nursing; hospitalization; clinical deterioration; patient safety; early warning score; education

Introduction

A patient's clinical deterioration originates from physiological changes detected by monitoring vital signs, which can indicate early or potentially critical patients who need special monitoring in the wards [1,2]. Such changes can indicate a greater probability of cardiorespiratory arrest and lead to unplanned hospitalizations in intensive care units and death [3]. If there is a delay in the identification of these patients, it will result in delayed intervention and, therefore, in the increase of hospital mortality. The early identification of alterations in vital signs can facilitate greater efficiency in the care provided to the patient because the reduction in morbidity leads to a reduction in the length of hospital stays and lower expenditure on health, which can guarantee a better quality of care [1,4].

The nursing team is usually the first to identify clinical changes in patients. The nursing team comprises a diverse group of health care professionals collaborating to deliver patient care. This team typically includes registered nurses, licensed practical nurses or licensed vocational nurses, certified nursing assistants, nurse practitioners, nurse managers or supervisors, clinical nurse specialists, and additional support staff. These professionals possess specialized skills and training, allowing them to provide comprehensive care, administer treatments, monitor patient conditions, and fulfill administrative responsibilities. The composition of the nursing team may vary based on health care settings and specific patient needs.

The evaluation of vital signs is a routine activity of the nursing team in the hospital and is of extreme importance as it tracks the evolution of the clinical picture and the individual's health and can predict clinical deterioration. Intrinsically, nursing is linked to patient surveillance and monitoring changes that may indicate warning signs, and these factors are interlinked with survival outcomes in cases of in-hospital cardiorespiratory arrest. Therefore, the nursing team can predict these events early to increase patient safety and prevent this clinical deterioration [5].

Early recognition of clinical deterioration is the key to early intervention and can lead to better patient outcomes [5]. Early warning systems are designed to detect changes and activate rapid response teams to minimize complications resulting from the degradation of the patient's clinical condition before reaching a critical state of complex regression, which can be fatal [6]. Various systems have been described in the literature that use simple physiological parameters and routine assessments performed daily by nurses to manage the risk of degradation of the patient's clinical status by adapting the level of care they need [7]. These systems are used to identify and respond efficiently to the needs of patients in an acute situation or phase [8].

Considering the PICOT (Population, Intervention, Comparison, Outcome, and Time) approach [9], this training was designed with nurses working in a hospital setting as the population of interest, the implementation of a professional training program for early clinical deterioration risk assessment as the intervention, the standard practice without the professional training program (ie, pretraining and posttraining) as the comparison, the improved identification and appropriate referral of patients showing signs of clinical deterioration as the outcome, and before and after the implementation of the professional training program as the timeframe. Therefore, the following research question guided the development of this training: "In nurses working in a hospital setting, does the implementation of a professional training program for early clinical deterioration risk assessment (compared to standard practice without the program) improve the identification and appropriate referral of patients showing signs of clinical deterioration?"

Considering this research question and given the options available in the literature of instruments that aim to facilitate the assessment of clinical deterioration, we decided to develop a training project for nurses to assess early clinical deterioration in a university hospital through the use of an alert scale designed for early identification of signs of clinical deterioration in patients. This protocol aims to implement and evaluate an evidence-based professional training program designed for nurses and coordinated by a nurse using the "just-in-time" methodology and the National Early Warning Score 2 (NEWS2) to assess the risk of early clinical deterioration and appropriate referral in inpatient units of a public university hospital in southeastern Brazil.

Methods

This study was structured according to the recommendations of the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) Declaration 2013 (Multimedia Appendix 1) [10].

Trial Design and Settings

A quasi-experimental study of the type before and after, with a single arm, will be conducted with all nurses from inpatient units of a tertiary-level university hospital in the interior of the southeast of São Paulo to implement a training program to assess the risk of early clinical deterioration. This study aims to demonstrate causality between the proposed intervention and the nurses' ability to use the NEWS2 tool to assess the patient's clinical deterioration and provide appropriate referrals. Quasi-experimental designs are often used when assigning participants randomly to different groups is not feasible or ethical. This allows for intragroup comparison of outcomes (ie, comparing the pretraining and posttraining results in the same group). In this study, having only a subset of the staff receiving the training would not be feasible. Although a quasi-experimental design does not offer the same level of control as a randomized controlled trial, it can provide valuable

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insights into the effects of the training program because it offers a real-world evaluation of the intervention's impact within the specific setting and considers the practical constraints of implementation.

The trial was registered in the Brazilian Registry of Clinical Trials (ReBEC) with the number RBR-5hq9y3k. For the design of the method, the limits of the Guideline for Reporting Evidence-Based Practice Educational Interventions and Teaching (GREET) [11] were respected.

Eligibility Criteria

All assisting nurses allocated to the university hospital's clinical and surgical hospitalization units in the interior of São Paulo will be included. During the data collection period, nurses who are inactive or on health or maternity leave or vacation will be excluded because they cannot be invited to participate in the training due to labor legislation issues.

Intervention

The type of training to be offered, known as "Just-in-Time Training" (JITT), consists of an education modality that facilitates the delivery of time-relevant and work-based education, with a greater emphasis on teaching provision at work as needed [12]. JITT is a training approach that focuses on providing relevant and specific information to individuals when they need it to perform a task or solve a problem and is designed to provide immediate and targeted support, allowing nurses to acquire knowledge or skills quickly and efficiently. JITT is often used in contexts where time is limited and there is a need for spontaneous and on-demand learning. The effectiveness of the JITT method stems from several factors, such as punctuality, contextualization, and flexibility. By providing nurses with the correct information at a convenient time and place, JITT increases learning efficiency, minimizes continuums, and empowers individuals to quickly acquire the knowledge and skills they need to perform effectively in their specific tasks or problem-solving scenarios [12].

The JITT approach to recognizing and responding to patient deterioration has theoretical and educational relevance in its design. Education takes place in the clinical setting using real meetings with patients to guide the content. This approach is closely aligned with learning through a theory of practice, as the literature recommends [13]. In this perspective, workplaces are viewed as learning environments; optimizing the experiences provided by health workplaces, increasing learning potential, and promoting the involvement of workers can improve workers' ability to respond to future occupational challenges.

The training program developed for nurses was based on the intervention mapping [14] protocol that describes the path from problem identification to problem solution or mitigation. Each of the six stages of intervention mapping comprises several tasks, integrating theory and evidence. Completing tasks in one step creates a product that drives the subsequent step. Completing all steps serves as a model for designing, implementing, and evaluating an intervention based on theoretical, empirical, and practical information.

Needs Assessment: A Theoretical and Experiential Approach

The needs assessment will be gathered by reviewing the literature on nurses' knowledge and use of early deterioration tools. To use the experiential approach, a qualitative step will be conducted through the realization of focus groups and interviews with nurses from inpatient units to verify the factors that influence professional practice related to the early assessment of clinical deterioration. A script of previously established questions will guide and standardize the different groups (Textbox 1). The invitation to nurses will be made through a direct approach by verbal invitation from the researcher herself.

The interviews and focus groups will be based on a pre-established script (Textbox 2). All groups will have their audio recorded for future analysis, with the saturation criterion as a parameter for the decision to stop collection. The data collected in this phase will be evaluated through content analysis.

Textbox 1. Presentation of the project in the focus groups.

- Team presentation: 3 nurses.
- Aims: Invite nurses to participate in a project offering training on early assessment of clinical deterioration.
- Planning: After agreeing and signing the consent form, the nurses will participate in a 30-minute focus group meeting. Six months after the meeting, training will be offered. Those who participate will receive feedback and a certificate.
- Setting: Nursing Department, University Hospital.

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Textbox 2. Script to guide focus groups.

- Do you know what early assessment of clinical deterioration in patients is?
- Do you usually perform an early assessment of the clinical deterioration of patients admitted to the wards? If so, how?
- For you, what is the importance of this assessment in your daily work in the ward?
- Do you use data from early clinical deterioration assessment to guide the care plan of patients under your supervision? If so, what data? How?
- Do you think it is feasible to carry out an early assessment of the clinical deterioration of patients admitted to the wards?
- In your opinion, what factors can favor the early assessment of clinical deterioration of patients admitted to the wards?
- In your opinion, what factors can hinder the early assessment of clinical deterioration of patients admitted to the wards?
- How would you like to receive this training? Reflect and give your opinion on the best strategy, the type of training, location, teaching methodology to be used and teaching material.

Establishment of Training Objectives

Following the needs assessment stage, we will establish the training objective. The most appropriate content and training strategies for the target population and context should be identified at this stage. The data obtained will allow us to define the elements of the intervention, including the strategy, type of training, location, teaching methodology, and teaching material.

Intervention Strategy Proposal

In this stage, the content to be addressed, the methods design, and the strategies and means of communication will be defined.

Pretest

This phase will consist of a pretest of the intervention applied to a population subsample to verify operational aspects of the chosen content, strategy, and means of communication. This step aims to assess the adequacy and feasibility of the proposed intervention.

Preintervention Assessment

In this step, a questionnaire [15] will be used to assess the theoretical content related to each participating nurse's early assessment of clinical deterioration to compare the pretraining and posttraining results. The Brazilian version of the rapid response team (RRT) survey, which aims to explore nurses' knowledge and perceptions of RRTs, was translated and adapted into Brazilian Portuguese and validated (LBdA Lourenço and TM São-João, unpublished data). This instrument has 3 parts: part 1 contains 4 hypothetical case studies; in part 2, respondents must evaluate each factor according to its degree of importance; and in part 3, participants must include their basic information regarding characteristics and work history.

Although this tool has been widely used globally, no studies have been published on its psychometric properties. Assessing the psychometric properties of a measurement tool is relevant for ensuring its validity, reliability, and suitability for data collection in most research contexts. However, there are situations where a psychometric evaluation may be unnecessary, such as for well-established and widely used tools, especially those that do not measure psychosocial constructs (eg, the RRT survey). Once the tool has been extensively used, widely accepted, and has a solid empirical foundation in the literature, conducting a full psychometric assessment may not be necessary [16].

Implementation of the Intervention

The planned intervention will be implemented via the chosen method, and the participants will be informed in advance to allow for planning and effective participation.

Postintervention Assessment

In this step, the Brazilian version of the RRT survey will be reapplied to compare the pretraining and posttraining results and evaluate the effectiveness of the intervention.

Assessment of Suitability, Acceptability, and Quality of the Intervention

The nurses' assessment regarding the suitability, acceptability, and quality of the proposed intervention will be assessed through a self-answered, open-questions questionnaire. This questionnaire will have its content submitted for validation by specialists.

Criteria for Discontinuing or Modifying Allocated Interventions for a Given Trial Participant

Participants will be discontinued for not attending scheduled meetings or ending participation in the study during the intervention or data collection phase.

Strategies to Improve Adherence to Intervention Protocols and Procedures for Monitoring Adherence

An SMS text message will be sent to participants' telephones a day before the scheduled appointment, reminding them to attend the training.

Relevant Interventions That Are Permitted or Prohibited During the Trial

During the intervention, participants must not engage in any other training regarding clinical deterioration.

Outcomes

A form for analyzing the sociodemographic profile will be applied to nurses with the following variables: age, sex, education level, time of training, place, and time of work in the unit.

The effect of evaluating the theoretical content related to the early assessment of clinical deterioration by each participating nurse will be considered to compare the pretraining and posttraining results.

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Sample Size and Sampling

The minimum sample size was calculated according to the stages of data collection in the pretest and posttest. To evaluate the responsiveness of part 1 of the RRT survey comparing the scores from the two evaluation periods, a paired student *t* test was used. In this calculation, a significance level of 5% was assumed with a test power of 80% and an effect size of 0.50, which, according to Cohen [17], can be considered an effect size of medium degree. The calculation resulted in a minimum sample of 34 participants. To carry out this sample calculation, G*Power 3.1.9.2 software was used [18,19].

To assess the internal consistency of part 2 of the RRT survey, we referred to the recommendation proposed by the COSMIN (Consensus-Based Standards for the Selection of Health Measurement Instruments) initiative that at least 50 participants are necessary for a sample to be considered adequate when this measurement property is evaluated [20].

To evaluate assertiveness in filling out the NEWS2 before and after the intervention, the same methodology was proposed by the COSMIN initiative that at least 50 participants are necessary [20]. Thus, 50 participants will be included in the study to meet all the proposed objectives.

Recruitment

The human resources records of each eligible participant will be accessed through a list of registered nurses in floor units. Participants who engage in the study will be scheduled for a baseline appointment. On the appointed day, the interviewer will personally invite the participant and both will sign two copies of the research consent form.

Randomization and Allocation Concealment

Considering the nature of a JITT, no randomization will be conceived. All nurses allocated in floor units will be sequentially included according to their availability, schedule, and willingness to participate.

Implementation

The lead investigator will implement intervention strategies.

Blinding

This is not a blind study as both the lead investigator and participants will know they are receiving an intervention.

Data Collection

The experiment will be offered from July to December 2023 and include nurses who work in the clinical and surgical floor units.

Initially, a meeting will be held with the managers of the inpatient units to present the training program. Then, nurses will be recruited through an individual invitation to be offered by the researcher in the work units. After acceptance by the participants, a roster will be set up, together with the managers of the units, to assist in the organization of work rosters so that every position is covered when the nurses leave to participate in the training. Several training sessions will be made available in the morning, afternoon, and evening to carry out the training within the working hours of each nurse and according to what was described in the JITT method. The training sessions are structured to be 1 hour long and include the following steps: training presentation, signing of the informed consent form, application of the pretest, training, application of the posttest, and final evaluation. All nurses will participate in a single session and receive a participation certificate after completing all the steps described. The training will be carried out in a training room within the hospital.

Content analysis will be carried out during the qualitative phase (focal group). The most appropriate contents and strategies for nurses, as defined by them, will be combined to determine the elements of the intervention. Regarding the web-based questionnaire and the RRT survey, both of which are quantitative instruments, any increase in the score from the pretest to posttest will represent an improvement and, consequently, indicate the effectiveness of the intervention.

Data Management

The gathered data will be compiled in a spreadsheet using Excel 2010 (Microsoft Corporation) using double entry. In this spreadsheet, numerical encodings will be created for categorical variables. Quantitative variables will be inserted as collected. To avoid erroneous double entries or differences in the created codes, preset values for categorical variables will be used. The spreadsheet containing the data will be password-protected and solely accessible by the lead investigator.

Data Analysis

The data spreadsheet will be imported into SAS 9.4 software (SAS Institute). The results of the focus groups, as well as the preintervention and postintervention assessment questionnaires, will be submitted for content analysis.

Statistical Analysis

Qualitative variables will be described by calculating frequencies and percentages, and quantitative variables through position measurements and dispersion.

Comparisons between the two time periods concerning the score of the NEWS2 instrument and part 1 of the RRT survey instrument will be carried out using paired Student *t* tests or paired Wilcoxon tests [21], according to the data distribution. The distribution of data will be evaluated using the Shapiro-Wilk test.

The internal consistency of part 2 of the RRT survey instrument will be assessed using Cronbach α coefficient [22]. This coefficient ranges from 0 to 1, where values >.7 indicate that the measurements are reliable [23].

The statistical software SAS and SPSS (version 28; IBM Corp) will be used to carry out the analysis with a significance level of 5%.

Data Monitoring

No monitoring committee was established for this study because we understand it will bring minimal risk to participants, as described in the section Harms below. In addition, the protocol may be terminated early due to these minimal predicted risks.

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Harms

For this study, small risks and discomforts to participants are foreseen. Participants may feel uncomfortable during the encounters or while answering any questions about clinical deterioration, and they may need to know the answer.

Auditing

The following audit procedures will be considered: (1) compliance audits, by assessing the extent to which nurses are complying with the prescribed training protocol (ie, reviewing records, documentation, and training logs to verify if nurses have completed the required modules, attended relevant sessions, or fulfilled certification requirements); (2) knowledge assessments, by assessing nurses' understanding of the content; (3) skills evaluations, by observing and assessing nurses' performance of the specific skills or procedures required through direct observation, simulated scenarios, and practical assessments; (4) feedback surveys, to gather feedback from nurses about their training experience; and (5) quality assurance reviews of training materials, resources, and procedures, to ensure they align with evidence-based practices.

Ethical Considerations

The local Research Ethics Committee approved the study (Certificate of Submission for Ethical Review n. 37499220.9.0000.5404). All enrolled participants will sign the informed consent form, according to Resolution 196/96 of the National Health Council, when instructed about anonymity and the freedom to withdraw their consent at any time during the research. It should be noted that the database will not be sent abroad for analysis. The study was also registered in ReBEC (RBR-5hq9y3k).

The lead investigator shall keep research forms for 5 years, at which time they shall be incinerated. A multimodal dissemination strategy will be used to share findings with multiple stakeholders. Strategies will include scientific publications and presentations in the form of an expository and oral class in previously scheduled meetings with hospital managers and the participating nursing team, with the results obtained at the end of the training program implementation.

Results

Data collection will start in July 2023 with results expected in December of the same year. This study aims to describe a protocol for a professional training program developed for nurses so that they can implement early assessment of the risk of clinical deterioration and offer appropriate referrals. The protocol will also influence nursing managers and nurses in elaborating protocols and clinical practice because, as the first team to identify changes in the status of patients, the importance of nursing in detecting clinical deterioration is recognized.

The results obtained at the end of this research will be shared with the participating nursing team through the presentation of reports. In addition, we will submit the research results to scientific journals and present them at international scientific conferences.

Discussion

Innovative Protocol for Nurse Training in Early Detection of Clinical Deterioration

This study will describe a protocol for a professional training program designed for nurses to implement early risk assessment of clinical deterioration. This protocol is unprecedented and of great relevance, as some studies [24,25] have already demonstrated that the implementation of clinical deterioration evaluation directly impacts nurses in three areas of competence: (1) evaluation and care of patients (through the detection of clinical deterioration and development of skills and knowledge); (2) referring patients (through knowledge of the language and lines of communication in the referral process and deciding whether to seek help); and (3) coping experiences. Studies have also demonstrated that most patients who required hospitalization in intensive care units or who experienced cardiopulmonary complications exhibited signs of clinical deterioration hours before the event; more than 80% of these patients could be identified approximately 24 hours before these serious adverse events [26]. In this way, identifying patients who can benefit from intensive care units becomes crucial [26].

The development of this proposal is expected to implement a pioneering early warning system with Unicamp Clinical Hospital to increase the quality of care, improve indicators related to patient safety, and decrease the preventable hospital mortality rate.

Limitations

Some limitations pertaining to the study's design and methodology exist. The limited generalizability is a concern, as the study will be conducted in a specific public university hospital in southeastern Brazil, potentially limiting the applicability of the findings to other health care settings or regions. Potential selection bias is another limitation, as the recruitment process will not be randomized. The data collection period may restrict the gathering of a comprehensive and long-term data set.

The second set of limitations revolves around data collection and analysis. The qualitative stage involving focus groups and interviews with nurses introduces the possibility of self-reporting bias, where participants may provide socially desirable responses, or their recollections may not accurately reflect their actual practices. Finally, it is not possible to control or account for potential confounding factors, such as patient demographics or other interventions that may influence the outcomes.

Despite the acknowledged limitations, this paper provides a valuable contribution by outlining the design of a nurse-led intervention program that other health care professionals can replicate. The structured and systematically mapped intervention presented in this study offers the potential for improved resource allocation and results optimization. By enhancing nurses' ability to detect early signs of clinical deterioration and facilitating prompt and accurate interventions, this program holds promise for improving patient outcomes and increasing the likelihood of positive treatment outcomes.

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Some studies have demonstrated the effectiveness of using intervention mapping in nursing in planning and implementing interventions and evaluating results. The research subjects reported that the interventions allowed a better understanding of the studied models [27,28].

Conclusions

This study aims to contribute to advancing nursing practices in the context of clinical deterioration among inpatients. The intervention proposed in this research is grounded in established theoretical principles and is characterized by its cost-effectiveness and ease of implementation. Specifically tailored for adult patients in inpatient units, this program holds the potential to substantially enhance nurses' ability to accurately diagnose and promptly intervene in cases of early clinical deterioration. The paper introduces an evidence-based professional training program designed for nurses and led by a nurse, implementing a risk assessment protocol for early clinical deterioration within the inpatient units.

Data Availability

The data sets generated and analyzed during this study are available from the corresponding author upon reasonable request. Data and metadata will be made available in the University of Rhode Island Research Data Repository (DigitalCommons@URI) after the completion of the project and for 10 years.

Authors' Contributions

LBdAL idealized the primary concept of this study. The strategy was then conceived and refined by LBdAL and TMS-J. The protocol was written by LBdAL and TMS-J, with final revision by LBdAL, TMS-J, MdJM, and MdFNS.

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT 2013 checklist.
[DOCX File , 15 KB - resprot_v12i1e47293_app1.docx]

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Abbreviations

COSMIN: Consensus-Based Standards for the Selection of Health Measurement Instruments
GREET: Guideline for Reporting Evidence-Based Practice Educational Interventions and Teaching
JITT: Just-in-Time Training
NEWS2: National Early Warning Score 2
PICOT: Population, Intervention, Comparison, Outcome, and Time
ReBEC: Brazilian Registry of Clinical Trials
RTT: rapid response team
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Protocol

Evaluation of Incremental Validity of Casper in Predicting Program and National Licensure Performance of Undergraduate Nursing Students: Protocol for a Mixed Methods Study

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Abstract

Background: Academic success has been the primary criterion for admission to many nursing programs. However, academic success as an admission criterion may have limited predictive value for success in noncognitive skills. Adding situational judgment tests, such as Casper, to admissions procedures may be one strategy to strengthen decisions and address the limited predictive value of academic admission criteria. In 2021, admissions processes were modified to include Casper based on concerns identified with noncognitive skills.

Objective: This study aims to (1) assess the incremental validity of Casper scores in predicting nursing student performance at years 1, 2, 3, and 4 and on the National Council Licensing Examination (NCLEX) performance; and (2) examine faculty members' perceptions of student performance and influences related to communication, professionalism, empathy, and problem-solving.

Methods: We will use a multistage evaluation mixed methods design with 5 phases. At the end of each year, students will complete questionnaires related to empathy and professionalism and have their performance assessed for communication and problem-solving in psychomotor laboratory sessions. The final phase will assess graduate performance on the NCLEX. Each phase also includes qualitative data collection (ie, focus groups with faculty members). The goal of the focus groups is to help explain the quantitative findings (explanatory phase) as well as inform data collection (eg, focus group questions) in the subsequent phase (exploratory sequence). All students enrolled in the first year of the nursing program in 2021 were asked to participate (n=290). Faculty will be asked to participate in the focus groups at the end of each year of the program. Hierarchical multiple regression will be conducted for each outcome of interest (eg, communication, professionalism, empathy, and problem-solving) to determine the extent to which scores on Casper with admission grades, compared to admission grades alone, predict nursing student performance at years 1-4 of the program and success on the national exam. Thematic analysis of focus group transcripts will be conducted using interpretive description. The quantitative and qualitative data will be integrated after each phase is complete and at the end of the study.

Results: This study was funded in September 2021, and data collection began in March 2022. Year 1 data collection and analysis are complete. Year 2 data collection is complete, and data analysis is in progress.

Conclusions: At the end of the study, we will provide the results of a comprehensive analysis to determine the extent to which the addition of scores on Casper compared to admission grades alone predicts nursing student performance at years 1-4 of the program and on the NCLEX exam.

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KEYWORDS

communication; empathy; incremental validity; mixed methods; nursing school admissions; problem-solving; professionalism; situational judgement testing; undergraduate nursing students

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Introduction

Overview

There is an increased demand for registered nurses (RNs) with the increasingly complex health care system and aging population [1]. The strength of the global nursing workforce depends on the nursing education sector, and as a result, it is essential to invest in nursing education. Since the COVID-19 pandemic, there has been a 30% increase in applications to nursing programs [2]. Nursing education has limited resources to meet this demand [1], and there is increasing competition for seats [3]. The International Council of Nurses is concerned about this increased need for RNs and maintaining a high-quality workforce [2]. In their 2021 Strategic Workforce Plan for Nursing and Midwifery, the World Health Organization (WHO) stated that enough nurses need to be educated to have the "knowledge, competencies, and attitudes" to meet the population and health system's needs [4]. Optimizing admission procedures and admitting applicants that are the best fit for the profession is a way to invest in nursing education, develop the nursing workforce, and support the WHO global strategic direction. This paper describes a research protocol for a multiphase mixed methods study. The purpose of the study is to assess the effectiveness of a situational judgement test, Casper, as part of the admission decisions in the Bachelor of Science in Nursing (BScN Collaborative) program in predicting student performance during the program and on the National Council Licensure Examination (NCLEX).

Background

Admission criteria that accurately predict student success related to the performance of cognitive and noncognitive skills can help admit applicants with the prerequisites to develop nursing competencies. This can also help reduce the loss of invested resources from failure or attrition [3]. Cognitive skills refer to academic achievement and "involve the ability to understand complex ideas, to adapt effectively to the environment, to learn from experience, to engage in various forms of reasoning, to overcome obstacles by taking thought" [5]. Noncognitive skills comprise "personal traits, attitudes, and motivations" [6]. It is important to note that noncognitive skills usually involve mental processes such as decision-making, interpersonal skills, and emotional maturity, but they are more difficult to measure than cognitive skills (Textbox 1) [7].

Textbox 1. Description of key terms. Casper measures collaboration, communication, empathy, equity, ethics, motivation, problem solving, professionalism, resilience, and self-awareness.

Cognitive skills

- Academic achievements
- Ability to understand complex ideas, learn from experience, and reason [5]

Noncognitive skills

- Personal traits, attitudes, and motivation (eg, empathy) [6]
- Involve mental processes (eg, decision-making and interpersonal skills)

Situational judgment tests (SJTs)

- A methodology for assessing decisions in relation to underlying knowledge, skill, traits, and other attributes [8]

Casper

- A web-based SJT (90-110 minutes) that assesses noncognitive skills
- Test-takers respond to scenarios concerning what they would do and why
- Trained raters score the test
- Interrater reliability and intraclass correlations range from 0.84 to 0.94 [9]

Applicants who have appropriate decision-making skills that reflect capabilities related to noncognitive skills may be more suitable for the nursing profession. Noncognitive skills related to areas such as communication, empathy, problem-solving, and professionalism are essential to assume the roles of an RN (eg, advocate, coordinator of care, and educator) and deliver competent care to often complex patients and families across the life span in different settings (eg, acute care and the community).

There is strong evidence that cognitive ability predicts program success, but there is limited evidence related to noncognitive skills. The authors of a 2020 systematic review of 16 cohort studies explored preadmission criteria that predicted student success in undergraduate nursing programs in the United States. These authors reported that it was well established that cognitive predictors such as admission grade point average (GPA) predicted program success. Although not used as admission criteria, age, gender, and ethnicity also predicted success. Other possible predictors included grades on standardized tests, such as the Test of Essential Academic Skills. It is important to note that the definition of success used by most studies varied and was related to academic success, passing the licensure exam, attrition, program completion, and GPA in nursing and science courses. These authors contend that it is difficult to isolate a single variable as the best predictor of student performance, and it would be more reliable to use a combination of variables [1].

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No research has considered the predictive validity of noncognitive skills on student performance as well as the value of adding these criteria, that is, the incremental validity, to the nursing admission process. Incremental validity is defined as "the improvement obtained by adding a particular procedure or technique to an existing combination of assessment methods. In other words, incremental validity reflects the value of each measure or piece of information to the process and outcome of assessment" [10].

One possible approach for nursing admissions is using situational judgment tests (SJTs) to measure noncognitive skills, combining these results with cognitive criteria. SJTs are defined as "a methodology for assessing how an individual's underlying knowledge, skills, traits, and other attributes are expressed when making decisions about job-related scenarios" [8]. The use of SJTs has been identified as a valid approach for selecting medical school applicants concerning the performance of nonacademic skills. The authors of a systematic review of 30 studies (10 observational, 17 cohort with follow-up from 1-9 years, and 3 observational with longer follow-up) conducted a meta-analysis of 26 of these studies that reported validity correlations related to SJT and student performance. A pooled correlation was obtained of 0.32 (95% CI 0.26-0.39; $P<.001$) [11]. A total of 15 of the 17 studies that assessed the incremental validity of adding SJT found modest values of 5%-10% of additional variance accounted for (ie, the R^2 of regression models with and without SJTs differed by 5-10 percentage points). This suggests that there is value to adding SJTs, but SJTs alone cannot account for the outcomes assessed. The authors point out that this is a modest relationship but was considered in the context of medical school admissions, where many applicants are strong. Therefore, detecting slight differences is difficult [11].

The authors of a 2020 scoping review reported that no research was identified between 2006 and 2019 concerning using SJT for nursing school admissions [12]. A literature search did not identify any research published after 2019. Research is needed to explore the predictive nature of SJTs to inform nursing admissions decisions. Nursing admission committees need evidence of the incremental validity of admission criteria that can predict student success both academically and in noncognitive skills [13].

The BScN (Collaborative) program at Memorial University of Newfoundland (MUN) is a competitive program composed of 2 admission options: the 4-year option and the accelerated option. Over 600 applicants per year apply for 291 seats at 3 sites. Historically, admission decisions were primarily based on academic performance, but starting in 2021, the admissions process was modified to include Casper, a SJT that assesses noncognitive skills. The Casper score, the applicants' academic average, and references were used in the admissions decisions.

Casper is a web-based test developed by Acuity Insights that takes 90-110 minutes to complete. Test-takers are asked to respond to various scenarios that are designed to measure noncognitive skills concerning what they would do and why. The goal of these scenarios is to ascertain "behavioral tendencies" of individuals who are applying to programs that are person-centered. The test is divided into 2 sections: a video response section and a written response section. Trained raters score the test, and within 2-3 weeks of completion, the Casper score, converted to a *z* score, is sent to the program the applicant applied to. Casper assesses for the following noncognitive skills: collaboration, communication, empathy, equity, ethics, motivation, problem-solving, professionalism, resilience, and self-awareness. As noted above, these noncognitive skills are essential for nursing practice. The interrater reliability of Casper is strong, with intraclass correlations ranging from 0.84 to 0.94 across 55,988 applicants (Textbox 1) [9].

The goal of using Casper in our nursing program was to guide the admission of applicants with the best potential for success in the program and the profession. The need to include the assessment of noncognitive skills during the admissions process was further reinforced by findings of the 2016-2018 Employer Survey Report (prepared by BScN Collaborative Program), which raised concerns about recent graduates' performance in the clinical area with professionalism, empathy, communication, and problem-solving. These concerns were also highlighted in discussion with the College of Registered Nurses of Newfoundland and Labrador, the admissions committee, and faculty members.

This study proposes a mixed methods research (MMR) study to address and add to the knowledge related to predictors of success in a nursing program concerning noncognitive skills and program success. In particular, the predictive nature of Casper will be examined concerning optimizing admission decisions and admitting applicants with the greatest potential of completing the program, meeting the competencies of the nursing profession, and passing the NCLEX.

Purpose

The purpose of this multiphase MMR study is to assess the effectiveness of Casper as part of the admission decisions in the BScN (Collaborative) program in predicting student performance in years 1, 2, 3, and 4 of the program, and on the NCLEX, compared to academic performance alone. Overall academic success will be evaluated, as well as performance in psychomotor skills laboratory sessions and clinical settings. Problem-solving, empathy, and other skills are expectations in both types of settings, and all are expected to improve as students progress through the program.

The overarching MMR research question is, What is the effectiveness of the addition of Casper to admission decisions in predicting student success across the curriculum? The objectives of the quantitative and qualitative analysis and the integration of both are as follows:

1. To assess the incremental validity of Casper scores in predicting student performance with communication and problem-solving and student behavior related to professionalism and empathy at years 1, 2, 3, and 4 of the program, and on NCLEX performance, compared to academic ranking alone.
2. To examine clinical and laboratory faculty members' perceptions of student performance, challenges, and influences related to professionalism, empathy,

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communication, and problem-solving in psychomotor skills laboratory sessions and the clinical area.

Methods

Ethical Considerations

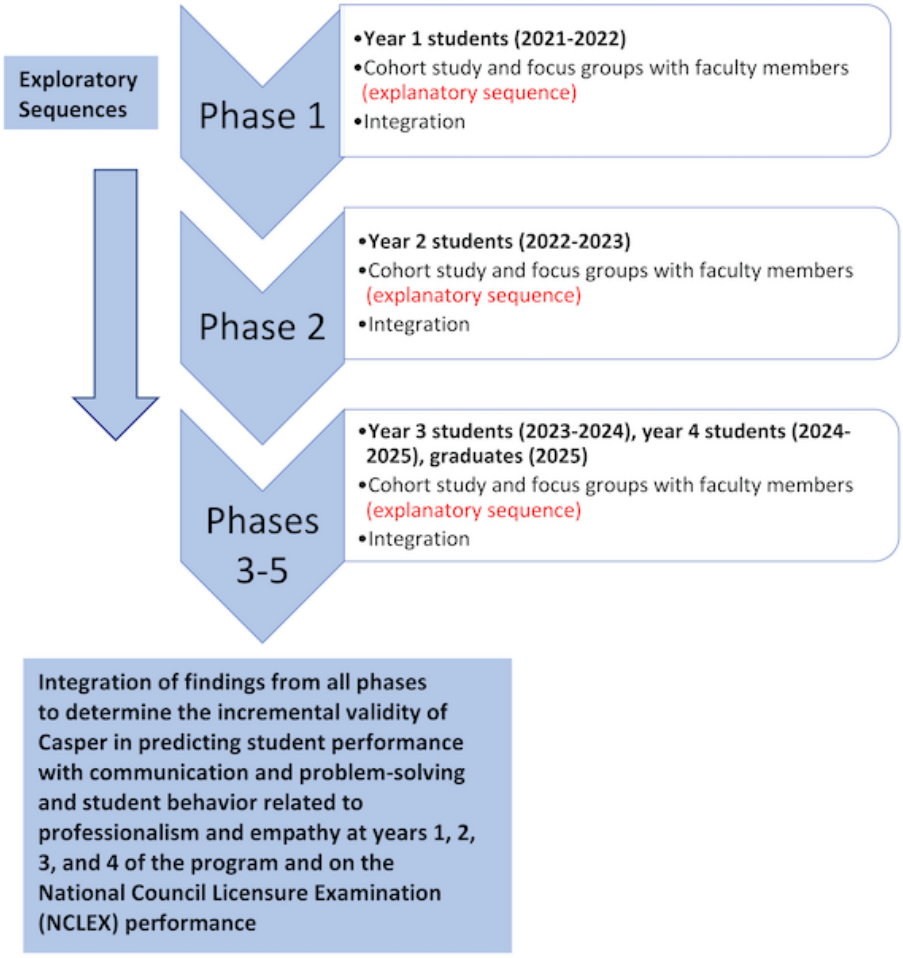
We obtained ethical approval (20222324) from the Newfoundland and Labrador Health Research Ethics Authority in February 2022, and this approval was renewed in January 2023.

Study Design and Setting

This study will use a multistage evaluation MMR study design with 5 phases and 2 embedded sequences (Figure 1). An interpretive description was used to guide the qualitative portion of the study. Both MMR and interpretive description are underpinned by pragmatism, and as such, both objective and subjective knowledge are valued and used to answer the research questions [14,15].

In each study phase, there is an embedded explanatory sequence whereby quantitative data collection (longitudinal cohort study) will be followed by qualitative data collection (focus groups). The goal of the qualitative interviews is to help explain the quantitative findings and gain a more robust understanding of student performance concerning professionalism, empathy, communication, and problem-solving. The other embedded sequence is an exploratory sequence, whereby what is learned in each phase will inform focus group questions in the subsequent phase.

Figure 1. Mixed methods model that illustrates the exploratory and explanatory sequences and points of integration.



Student Recruitment

In March 2022, all first-year students in the 4-year option and accelerated option at all 3 sites were invited to participate. These students were admitted in 2021 and were the first cohort to complete Casper as part of the admission process. Students who chose to participate will be followed through their program to the completion of the NCLEX exam. A faculty member at each site not associated with the study acted as an intermediary and introduced the study using a script. If students were interested, an investigator came to the class to further explain the study, and an information letter was provided to students. At that time, informed consent was obtained from students wanting to enroll, and the first set of questionnaires was completed. Students who chose not to enroll at that time were told that if they decided they would like to enroll, they could contact the research assistant within 1 week. It was explained to students in the consent form that participation (or not) would not affect any courses that they take in the nursing program; there were no known risks to participating in the study; all identifying information would be kept confidential; study data would be

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anonymized and safely stored using a secured drive; and only the research team would have access to the data.

A demographic profile was completed for each student (eg, age, gender, Canadian province or country of origin, and previous education). The student's Casper score and admission GPA for those who had completed university courses, or the high school average, were obtained through the Nursing Admissions Office. To access these data, a conditional agreement was reached between the university and the researchers.

Faculty Recruitment

Focus groups with clinical and laboratory faculty will be conducted at the end of each year of the program at a mutually convenient location and time. Recruitment is done by email using purposive convenience sampling. Emails will be sent to clinical and laboratory faculty that taught this group of students in the previous year. During the focus groups, we explore faculty perceptions of student performance, challenges, and influencing factors related to noncognitive skills in the laboratory and clinical settings. Written informed consent is obtained from participants in the focus groups. It is explained in the consent form that all information that identifies participants will be kept confidential, and only the research team has access to the data. As well, it is explained that there may be potential risks, including being uncomfortable sharing experiences in the context with others in the focus group. Every effort is made by the researchers to ensure participant comfort as well as safety during the focus group (eg, the researchers will ask the participants to respect the privacy of fellow participants and treat all information shared with the group as confidential).

Sample Size

To assess incremental validity, the R^2 of regression models, with and without SJTs, are compared to see if the addition of the SJT explains more of the variance found. The sample size of this study was calculated using the findings of a previous study [16] that assessed incremental validity using R^2 analysis. In it, researchers examined the incremental validity of adding SJTs to the use of a clinical problem-solving tool (CPST) for predicting performance in workplace simulation exercises as part of the selection process for postgraduate medical training. The researchers found that a regression model with CPST but not SJT explained 35% of variance (R^2=.35) whereas a model with both CPST and SJT explained 57% of the variance (R^2=.57) seen in the simulation scores. Their sample size of 135 was sufficient to detect this difference. Our target sample size is, therefore, 135, assuming we will see similar differences for the addition of SJT to admission grades (instead of CPST) on different outcomes. Few of the other studies reported in the systematic review by Webster et al [11] assessed outcomes similar to ours, few related to admission to medical schools, and most were conducted on very large (pooled) cohorts of medical students (N>1000) making it difficult to identify the minimum sample size required. No data are available related to nursing students. Assuming an attrition rate of 10%, which is normally seen in our program, 150 students will be recruited.

Quantitative Data Collection

This study has 5 phases, with quantitative data collection occurring in appropriate psychomotor skills courses during each academic year and at the end of each phase (ie, end of each year and after NCLEX completion). Figure 2 depicts the timeline for data collection.

Figure 2. Timeline for data collection (2022-2026).



Outcomes and Measures

The following outcomes, identified as concerns related to graduate performance and entry-level competencies of RNs, will measure nursing student performance: communication, problem-solving, empathy, professionalism, GPA and grades, and NCLEX success.

Communication is being evaluated during psychomotor testing in a nursing skills laboratory session using a tool developed for the study. One specific course was chosen for each year of the program. In these courses, students learn and practice foundational skills (eg, health assessment, basic care, and safe medication administration) and complex psychomotor skills (eg, complex dressings, care of chest tubes, and care of central lines). Nursing skills laboratory session testing is scenario-based

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and requires students to demonstrate effective communication skills (eg, verbal skills and documentation). Laboratory faculty who evaluate students during the psychomotor testing, use consistent rubrics for that course, and complete these tools based on the student's performance related to communication. The communication tool assesses whether students introduce themselves, use appropriate language, and complete appropriate documentation. There are additional criteria to assess if the testing involves a real person (eg, the student used appropriate listening skills). The possible range of scores for this assessment tool is 0-14, with higher scores indicating strong communication skills. Face validity was established by having faculty who have extensive experience conducting psychomotor assessments with nursing students review the tool to ensure the content was appropriate and relevant. The interrater reliability score was 100%. Laboratory faculty received training on how to complete the tool (Multimedia Appendix 1).

Problem-solving is being evaluated during psychomotor testing in a nursing skills laboratory session using a tool developed for the study. One specific course has been chosen for each year of the program. Nursing skills laboratory session testing is scenario-based and requires students to demonstrate effective problem-solving skills. Laboratory faculty who evaluate students during the psychomotor testing, using consistent rubrics for that course, will complete this tool based on the student's performance related to problem-solving. The problem-solving tool evaluates whether the student recognizes the problem, attempts to address the problem, and takes appropriate action to address the problem. The possible range of scores for this assessment tool is 0-6, with a higher score indicating strong problem-solving skills. Face validity was established by having faculty who have extensive experience conducting psychomotor assessments with nursing students review the tool to ensure the content was appropriate and relevant. The interrater reliability score was 94%. Laboratory faculty received training on how to complete the tool (Multimedia Appendix 2).

Empathy will be measured with the Jefferson Scale of Empathy (reliable and valid). This 20-item self-report scale takes approximately 10 minutes to complete and measures 3 constructs: "perspective taking," "compassionate care," and "standing in a patient's shoes." Each item is answered using a 7-item Likert scale (1=strongly agree and 7=strongly disagree). The scores can range from 20 to 140, with higher scores indicating stronger empathy [17].

Professionalism will be measured with an adapted Nurses Professional Values Scale-Three (NPVS-3; reliable and valid). This measurement is a 28-item self-report scale. The demographics questions were removed as the questions were either not appropriate for our context or the information would be obtained from the MUN Registrar's Office. Professional nursing values are evaluated using a 5-item Likert scale: not important (A), somewhat important (B), important (C), very important (D), and most important (E). Numeric values were assigned to each letter and added together to get the total score. The scores can range from 28 to 140. A higher score indicates a stronger nurse's professional value orientation [18].

For GPA and grades, GPA (yearly and cumulative) and marks in academic nursing courses will be obtained at the end of the academic year from the registrar's office.

For NCLEX success, data will be obtained from the College of Registered Nurses of Newfoundland and Labrador (CRNNL) regarding NCLEX success in terms of pass or fail. If available, as NCLEX scoring is changing, the overall performance (logit score) and performance on individual test categories (logit score) will be obtained. The CRNNL is the regulatory body and professional association for all RNs and nurse practitioners and the custodian for the National Council of State Boards of Nursing data. An agreement was signed between the researchers, MUN, and CRNNL to access the data.

Predictor Variables

Data will be collected on several predictor variables. Admission grades and Casper scores are the predictor variables of interest (ie, the independent variables to be assessed in terms of predictive and incremental validity). The other variables will be assessed and controlled for as potential confounders.

- Admission grades: the admission GPA will be obtained for students who had some postsecondary education before admission; the admission high school average will be obtained for students admitted directly from high school. These data will be obtained from the registrar's office.
- Admission Casper score: students complete Casper as part of their admissions application. Results will be obtained from the nursing admission office.
- Demographics: age, gender, province, and program of study (ie, 4-year option and accelerated option) and program site, as the BScN (Collaborative) program is offered at 3 sites. These data will be obtained from the nursing admissions office.

Quantitative Data Collection Procedures

At the end of each year of the program, the research assistant or researchers will meet with the students to complete the 2 pen and paper questionnaires: the Jefferson Scale of Empathy and the NPVS-3. The research assistant has been trained in data collection and the use of measurement tools. Students are monitored to ensure they are not talking to each other. As a thank-you for participating, students are given a CAD $10 (US $7.32) coffee card at each phase of data collection. The completed problem-solving and communication tools will be obtained directly from the laboratory instructors.

Completed questionnaires and tools at the sites are placed in a sealed envelope and sent to the MUN Faculty of Nursing Research Unit by courier. If there is a delay in sending the completed questionnaires by courier, the questionnaires are stored in a locked filing cabinet in one of the researcher's offices. Data will be obtained from the Registrar's Office, Nursing Admissions Office, and CRNNL at the appropriate times, using procedures established with each source.

Qualitative Data Collection

Qualitative data collection will occur at the end of each academic year. Figure 2 depicts the timeline for data collection. Both primary investigators (PIs) have expertise in qualitative

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research and experience in focus group facilitation. The PIs will conduct the focus groups at the MUN Faculty of Nursing and will provide instruction, guidance, and support for focus group facilitators at the other 2 sites. Focus group interviews with clinical and laboratory faculty will be recorded and transcribed verbatim. An interview guide is used (Textbox 2). Interpretive description will be used to guide data collection, and consistent with this approach, initial focus group questions were guided by the research purpose and objectives [17]. Subsequent interview guides will be developed based on the unfolding data analysis [19,20]. With interpretive description, the researcher goes beyond description and asks what it means, what I can do with these findings, and why it is important [15]. Quirkos (version 2.5.2; Quirkos), a qualitative software package, will be used to categorize the data to identify themes.

Textbox 2. Phase 1 faculty focus group questions.

Faculty focus group questions
1. Tell me about your experiences with students this past year in the clinical setting concerning communication, professionalism, empathy, and problem-solving.
2. Tell me about your experiences with students this past year in the laboratory setting concerning communication, professionalism, empathy, and problem-solving.
3. Did you experience any challenges related to communication, professionalism, empathy, and problem-solving?
4. What do you think influenced their performance in relation to communication, professionalism, empathy, and problem-solving?

Statistical and Analytic Plan

Descriptive statistics (eg, means and proportions), as appropriate for the data, will be used to describe the characteristics of the participants, including their GPAs and their scores on the different outcome measures. Stata (version 17; StataCorp) will be used to analyze the data. The data will be checked for the amount of missing data; if they are missing completely at random, and if warranted, multiple imputation will be used. Different analyses will be conducted to address each research objective, as described below.

For objective 1 (phases 1-5), hierarchical multiple linear regression will be conducted to determine if Casper is a significant predictor of each outcome (predictive validity) and if a model with both Casper and admission grade explains more of the variance for the outcome than a model without Casper (incremental validity). Each model assessed will contain both the Casper score and the admission average and include potential predictors and confounders (eg, GPA for the year, age, gender, province, program of study, and program site). Modeling will be conducted separately for students who entered directly from high school (admission grade=high school average) and those who had some postsecondary education before admission (admission grade=GPA for the postsecondary courses). The modeling will be repeated at the end of each year (years 1-4) for each of the yearly outcomes (ie, dependent variables): communication, problem-solving, empathy, professionalism, and GPA. The measures used will be the scores for that year.

For the first model that is tested, all the predictor variables will be entered into the model. The predictor variable with the highest *P* value ($P>.05$) will be dropped, and the model without this variable will be tested. The second model will be compared to the previous model using the likelihood ratio (LR) test. If the LR test is not significant ($P>.05$), the variable is not a predictor and needs to be assessed for confounding before being removed from the model. To assess confounding, the coefficient for the main exposure of interest is assessed to see if it changes when the potential confounder is taken out of the model. If it did, that variable would be considered a confounding variable and would be kept in the model. If the coefficient did not change, the variable is not a confounder and will be removed from the model. This process will be repeated, comparing it with the previous model, until all of the variables are tested and the final model has been established. To determine the incremental validity, the R^2 (ie, the percentage of variance explained by the model) for the final model and the R^2 for that model without the Casper score will be compared.

A similar analysis will be conducted in 2025 using logistic regression to determine if Casper is a significant predictor of NCLEX success (predictive validity) and if a model with both Casper and admission grade explains more of the variance for NCLEX success than a model without Casper (incremental validity).

For objective 2 (phases 1-5), under the direction of the methodological approach of interpretive description, the analytical framework, the three Cs (coding, categorizing, and concepts) will be used to conduct a thematic analysis of the data. The following 6 steps are used in this iterative process: initial coding, revisiting initial coding, developing categories, revising the initial list of categories based on additional review of the data, reviewing categories and subcategories, and developing themes (ie, concepts) [21]. The PIs will independently code the focus group data and reach consensus on the themes [19]. We will use verification strategies to incrementally build rigor throughout the qualitative phase of the project [19,22]. These strategies include methodological coherence (eg, ensuring the fit between methods of data collection and analysis with the research design) and concurrently collecting and analyzing data (eg, ensuring that future focus group questions are based on the analysis and findings of previous focus groups) [19,22]. Both PIs and other focus group facilitators are known to faculty participants. Another verification strategy, researcher responsiveness, offers the opportunity for the PIs to reflexively consider their influence on the research [19,22]. For example, debriefing after each focus group to explore how we questioned, probed, and, overall,

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facilitated the group to meet the goals of the research. These verification strategies will enhance the trustworthiness and credibility of the data [19,22,23].

The integration will occur after each phase is complete and at the end of the study.

- Explanatory sequences (end of phases 1-5): integration with this design aims to use the qualitative results to explain the quantitative data [14]. Each data set will be analyzed separately (ie, questionnaires completed by students, problem-solving and communication tools completed by faculty, and focus groups with faculty), and then the "fit of the data integration" will be analyzed. This refers to the coherence of the qualitative and quantitative findings; completing this analysis will result in a more comprehensive understanding of the findings. Three possible outcomes will be assessed. (1) Confirmation occurs when the findings from both data sets confirm the results of the other: the 2 data sources provide similar conclusions, and therefore, the results have more credibility. (2) Expansion occurs when the findings from the 2 data sets diverge and expand insights related to the findings. And (3) discordance occurs if the findings of qualitative and quantitative data sets are inconsistent or disagree [24].
- Exploratory sequences (end of phases 1-3): the goal of integration in an exploratory sequence is to build from one database to another [14]. In this study, what is learned in each phase will inform qualitative data collection for the focus group in the subsequent phase.

Results

This study was funded in September 2021. In March 2022, a total of 144 first-year students enrolled in the research, who will be followed throughout the nursing program to the completion of the NCLEX exam in 2026. A total of 3 focus groups with clinical and laboratory faculty were conducted in May 2022. Data analysis of year 1 data is complete, and data analysis of year 2 data has begun. STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines for cross-sectional research and COREQ (Consolidated Criteria for Reporting Qualitative Research) guidelines for qualitative research will be followed when results are presented [25,26]. The knowledge translation includes reports, presentations, and publications. Year 1 and a portion of year 2 data were presented at the International Council of Nurses Congress in July 2023.

Discussion

The results of this study may provide evidence to support the use of the SJT, Casper, to guide nursing admissions to optimize the selection of applicants who have the greatest potential of completing the nursing program and meeting the competencies of the nursing profession. Specifically, the results will show if Casper helps predict the performance of the 4 noncognitive skills that were measured (ie, communication, problem-solving, empathy, and professionalism) and success on the NCLEX. Identifying and selecting applicants who perform well in these areas will mean that individuals are selected who are a good fit for nursing and therefore may be more likely to remain in the program and be licensed to practice as an RN. This will, in turn, potentially improve the quality of the nursing workforce and patient care.

These findings will have implications for nursing education and administration concerning admissions procedures and whether the use, or continued use, of SJTs is warranted based on the available evidence. As well, the results of this study will hold implications for nurse researchers to further evaluate the use of SJTs such as CASPER. Consideration should be given to conducting a multisite study across several university schools of nursing and comparing student cohorts on outcomes measured by Casper (eg, communication and problem-solving) before and after the implementation of Casper.

There are several notable strengths. This is the first study to report on the predictive ability of situational judgment testing as part of nursing admission criteria. The recruitment of students at 3 nursing schools ensured that participants were representative of the target population. Also, using a multiphase MMR approach and integrating or merging quantitative and qualitative data allows for a more comprehensive answer to the research questions [14]. Concerning this study, using MMR provides a greater understanding across the years of student performance. It also increased understanding of the challenges and influences related to professionalism, empathy, communication, and problem-solving. Using focus groups as the data collection method in the qualitative phase allows for the development of rich, thick descriptions and, thus, ultimately, enhanced understanding of the concepts explored [27]. Finally, using regression in the analysis allows for control of confounding variables, compared to just correlations between Casper and admission grades with the outcomes.

There may be some possible limitations to this study. The first is the attrition of participants throughout the study. We anticipate that there will be some attrition from the study with student failure and withdrawal from the study or program throughout the 5-year study timeline. The COVID-19 pandemic has greatly influenced this cohort, and this may be found to be a contributing factor to attrition and student performance. The second limitation concerns variables that are measured with self-report (eg, professionalism and empathy). Although the tools used are valid and reliable, there is a potential for social desirability bias with these measures. Additionally, while focus groups for data collection are considered a strength, there is the possibility of power imbalances within the group, thus limiting the breadth and depth of the data [27,28]. This will be mitigated by facilitators, who will establish guidelines at the beginning of the focus group and provide opportunities for all participants to participate in the discussion, including the exploration of new ideas as they emerge. The final limitation concerns potential differences in the student experience across the 3 program sites. Although the same curriculum is offered to students at the 3 program sites, there may be some variability in school culture, clinical experiences, and curriculum delivery that could impact the outcomes that are measured. The program site will be controlled for in the regression analysis. These potential limitations will be taken into consideration when interpreting the results.

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The addition of a SJT such as Casper may be a strategy that could support admissions committees as they endeavor to admit students that have both the cognitive and noncognitive skills to be successful in a nursing program. SJTs have been widely used for medical education, but there is limited literature on their usefulness for nursing programs. This multistage evaluation mixed methods study will add to the literature about the predictive ability and incremental validity of the SJT Casper. The findings of this study will have implications for nursing education and research.

Acknowledgments

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Data Availability

The data sets generated and/or analyzed during this study are not publicly available due to participant confidentiality but are available from the corresponding author on reasonable request.

Authors' Contributions

KS prepared the first and second drafts. DM provided feedback on the first and second drafts and refined the third draft. RC provided feedback and read and approved the final version of the protocol. All authors participated in the revisions of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Communication tool.
[DOCX File , 19 KB - resprot_v12i1e48672_app1.docx]

Multimedia Appendix 2
Problem Solving Tool.
[DOCX File , 23 KB - resprot_v12i1e48672_app2.docx]

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Abbreviations

BScN: Bachelor of Science in Nursing
COREQ: Consolidated Criteria for Reporting Qualitative Research
CPST: clinical problem-solving tool
CRNNL: College of Registered Nurses of Newfoundland and Labrador
GPA: grade point average
LR: likelihood ratio
MMR: mixed methods research
MUN: Memorial University of Newfoundland
NCLEX: National Council Licensing Examination
NPVS-3: Nurses Professional Values Scale-Three
PI: primary investigator
RN: registered nurse
SJT: situational judgment test
STROBE: Strengthening the Reporting of Observational Studies in Epidemiology
WHO: World Health Organization

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Protocol

The Effects of Exercise on Synaptic Plasticity in Individuals With Mild Cognitive Impairment: Protocol for a Pilot Intervention Study

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Abstract

Background: Mild cognitive impairment (MCI) is a syndrome preceding more severe impairment characterized by dementia. MCI affects an estimated 15% to 20% of people older than 65 years. Nonpharmacological interventions including exercise are recommended as part of overall MCI management based on the positive effects of exercise on cognitive performance. Interval training involves brief intermittent bouts of exercise interspersed with short recovery periods. This type of exercise promotes cognitive improvement and can be performed in individuals with MCI. Synaptic plasticity can be assessed in vivo by the neurophysiological response to repetitive transcranial magnetic stimulation (rTMS). A method to assess synaptic plasticity uses an intermittent theta burst stimulation (iTBS), which is a patterned form of rTMS. Individuals with MCI have decreased responses to iTBS, reflecting reduced synaptic plasticity. It is unknown whether interval training causes changes in synaptic plasticity in individuals living with MCI.

Objective: This research will determine whether interval training performed using a cycle ergometer enhances synaptic plasticity in individuals with MCI. The three aims are to (1) quantify synaptic plasticity after interval training performed at a self-determined intensity in individuals with MCI; (2) determine whether changes in synaptic plasticity correlate with changes in serum brain-derived neurotrophic factor, osteocalcin, and cognition; and (3) assess participant compliance to the exercise schedule.

Methods: 24 individuals diagnosed with MCI will be recruited for assignment to 1 of the 2 equally sized groups: exercise and no exercise. The exercise group will perform exercise 3 times per week for 4 weeks. Synaptic plasticity will be measured before and following the 4-week intervention. At these time points, synaptic plasticity will be measured as the response to single-pulse TMS, reflected as the percent change in the average amplitude of 20 motor-evoked potentials before and after an iTBS rTMS protocol, which is used to induce synaptic plasticity. In addition, individuals will complete a battery of cognitive assessments and provide a blood sample from the antecubital vein to determine serum brain-derived neurotrophic factor and osteocalcin.

Results: The study began in September 2023.

Conclusions: The proposed research is the first to assess whether synaptic plasticity is enhanced after exercise training in individuals with MCI. If exercise does indeed modify synaptic plasticity, this will create a new avenue by which we can study and manipulate neural plasticity in these individuals.

Trial Registration: ClinicalTrials.gov NCT05663918; https://clinicaltrials.gov/study/NCT05663918

International Registered Report Identifier (IRRID): PRR1-10.2196/50030

(JMIR Res Protoc 2023;12:e50030) doi:10.2196/50030

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KEYWORDS

mild cognitive impairment; exercise; brain-derived neurotrophic factor; cognition; brain plasticity; repetitive transcranial magnetic stimulation; transcranial magnetic stimulation; magnetic stimulation; aging; interval training; intermittent theta-burst stimulation; repetitive transcranial magnetic stimulation; ageing; gerontology; geriatric; cognitive; physical activity; fitness; neurology; neuroscience; synapse; synaptic; plasticity; brain; neurotrophic; hormone; hormones; endocrinology

Introduction

Memory impairment has long been seen as a common consequence of aging, but it could be seen as mild cognitive impairment (MCI), a precursor of dementias such as Alzheimer disease. MCI is characterized by evidence of cognitive decline without a substantial disruption to completing everyday tasks [1,2]. Currently, 15% to 20% of people aged 65 or older are living with MCI [3]. About 10%-15% of individuals with MCI progress to dementia [3], exacerbating the concern for reduced social and functional capacities of such a large number of people and their increased rate of mortality [1,2].

Risk factors for MCI include older age, sedentary lifestyle, low number of years of education, and factors such as hypertension and obesity, various cardiovascular diseases, and neuropsychiatric conditions including depression and anxiety [1]. MCI is recognized as an intermediate phase between a healthy brain state and dementia; however, not all individuals diagnosed with MCI are certain to progress to dementia, and some may even revert to normal life [4]. The progression to dementia is often preceded by subtle difficulties in performing everyday activities [5] and can include diagnoses of subjective cognitive impairment [6], mild behavioral impairment [7,8], and psychiatric disturbances including anxiety [9,10], depression [11-13], and posttraumatic stress disorder [14,15]. Amidst ongoing challenges in developing disease-modifying drugs, nonpharmacological interventions including exercise are recommended as part of the overall MCI management [16] based on the positive effects of exercise on cognitive performance [17-23].

Exercise promotes cognitive improvement [24-32], and individuals living with MCI can participate in various forms of exercise [33,34]. Evidence also supports the notion that exercise interventions have a positive influence on different facets of cognitive function in MCI such as global cognitive functioning [30], immediate recall [22,26-28], delayed recall [26], and executive function [31,32]. However, not all studies report improvements in cognitive performance following exercise training [35-37]. Further, physical exercise may present challenges related to mobility and movement that limit the accessibility of the intervention to all individuals. Nonetheless, physical exercise is an affordable and alternative approach to alleviate symptoms of cognitive decline [17-22,38,39].

Interval training can involve intermittent bouts of exercise performed at either a prescribed or self-determined intensity, interspersed with short recovery periods [40,41]. The latter enables participants to determine their own pace that they deem appropriate and tolerable. They are typically encouraged to identify a pace that is physically challenging and to rate their effort level or perceived exertion. This type of training can be performed by participants with a wide age range who are both healthy and have conditions such as type 2 diabetes [42-44], coronary artery disease [45,46], and obesity [47]. Evidence that aerobic-based interval training can improve cognitive function [24-32] suggests that cognitive improvement could be induced by aerobic interval exercise via upregulation of pathways that promote synaptic plasticity.

Synaptic plasticity involves activity-induced changes in specific patterns of neural activity that alter the strength or efficacy of synaptic transmission, playing a considerable role in the acquisition of information and learning of new behaviors [48]. Synaptic plasticity is modeled by long-term potentiation (LTP) and long-term depression (LTD). LTP increases synaptic transmission as a consequence of high-frequency stimulation of excitatory synapses or the correlation of presynaptic activity and postsynaptic depolarization [48]. In contrast, LTD decreases the strength and efficacy of synaptic transmission [49]. A significant association has been found between LTP, LTD, and age-related cognitive decline. Animal models have shown that reductions in cognition due to age correlate with reductions in the LTP originating in the hippocampus [49].

In humans, synaptic plasticity, and more specifically, LTP-like effects can be assessed in vivo by delivery of transcranial magnetic stimulation (TMS) in protocols called intermittent theta burst stimulation (iTBS) and 5-Hz repetitive TMS (5-Hz rTMS). Both forms delivered over the motor cortex induce LTP-like effects as measured by short-term increases in the efficacy of the corticospinal pathway from cortex to muscle [50,51]. These effects are analogous to animal models of LTP since they are mediated by glutamate and require glutamate binding at *N*-methyl-D-aspartate (NMDA) receptors [51]. In humans, the decline in neuronal excitability and synaptic function seen with aging contributes to memory loss as well as sensory and motor deficits [52]. Thus, in humans, iTBS and 5-Hz rTMS are noninvasive tools to assess whether aging and MCI populations demonstrate synaptic plasticity and whether interventions such as exercise can enhance the magnitude of synaptic plasticity. Compared to age-matched controls, individuals with MCI demonstrate blunted synaptic plasticity as indicated by a reduced response to 5-Hz rTMS [53] and iTBS [54]. These effects are reflected as decreases in motor evoked potentials (MEP) when compared to healthy controls. Healthy controls demonstrate MEP facilitation, as expected, observed by an increase in MEP amplitude during the delivery of a 5-Hz train. In contrast, 5 Hz–induced MEP facilitation is not seen in individuals with MCI, suggesting deficits of glutamate pathways responsible for synaptic potentiation [53]. The delivery of iTBS has yielded similar results in patients with MCI, demonstrating a lack of MEP facilitation [54].

Brain-derived neurotrophic factor (BDNF) is a key regulator of processes crucial for cognition, particularly learning and memory [55-57]. The presynaptic release of BDNF influences

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the activation, trafficking, and expression of NMDA receptors as a result of enhanced calcium influx. This calcium influx is thought to allow for the release of BDNF at the postsynaptic terminal. Postsynaptic BDNF release is essential for presynaptic vesicle cycling, which increases synaptic plasticity, ultimately leading to improvements in cognitive functioning [58]. BDNF expression is correlated with cognitive function [57] and is consistently elevated following exercise in healthy older adults, suggesting that the rise in BDNF levels with long-term exercise may reduce mental deterioration in patients with MCI [55].

Exercise increases the secretion of hormones and other factors into the blood from organs such as skeletal muscle, bone, and liver [59-70]. Some of these are known to increase brain BDNF either directly or indirectly. A bone-derived hormone called osteocalcin (OCN), which plays a role in bone mineralization and glucose metabolism, increases following exercise [71-75] and increases BDNF transcription and the number of BDNF vesicles transported to the synapse [76,77]. OCN is carboxylated at 3 different residues and is found in the blood in both carboxylated and partially or fully decarboxylated forms. Acute exercise increases the partially or fully decarboxylated forms of OCN in serum [72-75].

The proposed research will determine whether interval training performed at a self-determined intensity will enhance synaptic plasticity in individuals with MCI. The three aims are to (1) quantify synaptic plasticity after interval training performed at a self-determined intensity in individuals with MCI; (2) determine whether changes in synaptic plasticity correlate with changes in serum BDNF, OCN, and with cognition; and (3) assess compliance to the exercise schedule.

Methods

Screening

To determine the eligibility of those who have reached out to the study team via advertisements, individuals will be contacted to schedule a phone interview. During the phone interview, individuals will be provided with the details of the study, and eligibility for TMS will be assessed via a TMS screening questionnaire. Individuals will also be asked whether they have been diagnosed by a health care professional or physician with "Mild Cognitive Impairment" or "Mild Neurocognitive Disorder?" If the individual answers "Yes," then they will be asked to provide a written medical note to confirm a diagnosis of MCI at the first scheduled session. In addition, the individual's eligibility to complete the exercise protocol will be assessed using the Canadian Society for Exercise Physiology Get Active Questionnaire (GAQ). If the individual has contraindications to the GAQ, the participant will be asked to contact their family doctor and acquire a medical note clearing them for participation. The parameters of the study, including the procedures and collection measures, will be explained verbally to the participant. If the participant agrees to participate in the study and has no contraindications to the GAQ and TMS screening questionnaire, a time will be arranged for the individual to undergo the experiment. Participants will provide informed written consent on the day of data collection prior to any testing, as well as verbal reaffirmation before each procedure. Researchers will determine the capacity to consent for all participants at the commencement of the study, using a modified University of California, San Diego Brief Assessment of Capacity to Consent questionnaire.

Ethical Considerations

Approval to conduct this study was granted by the Hamilton Integrated Research Ethics Board (ID # 14938) in partnership with Hamilton Health Sciences and conformed to the Declaration of Helsinki. In addition, this study has been registered and approved as a registered clinical trial on clincialtrials.gov (NCT05663918) in December 2022, a World Health Organization (WHO) accredited trial registry.

Power

This pilot study will recruit 24 participants aged 55-80 years old diagnosed with MCI. To determine this sample size, the following features were included in an a priori calculation using G*Power (Heinrich-Heine-Universität Düsseldorf), α=.05, Power (1-β)=0.9, and the effect size was calculated using Trebbastoni et al's findings [53].

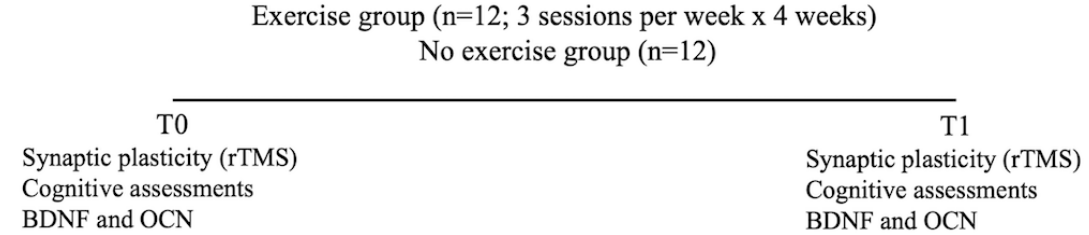
Experimental Design

Individuals will be recruited for assignment to 1 of the 2 equally sized groups: exercise or no exercise. The exercise group will perform the exercise intervention. The no exercise group will serve as the control.

Experimental Protocol

The dependent measures of synaptic plasticity, cognition, and venous blood BDNF and OCN, will be measured before and after the 4-week intervention (Figure 1).

Figure 1. Dependent measures will be obtained in all participants 2-3 days before (T0) and following the exercise intervention (T1). Synaptic plasticity assessed using transcranial magnetic stimulation, cognitive function assessed by neuropsychological battery, and blood draws for serum BDNF and osteocalcin will be performed before and immediately following the intervention. BDNF: brain-derived neurotrophic factor; OCN: osteocalcin; rTMS: repetitive transcranial magnetic stimulation.

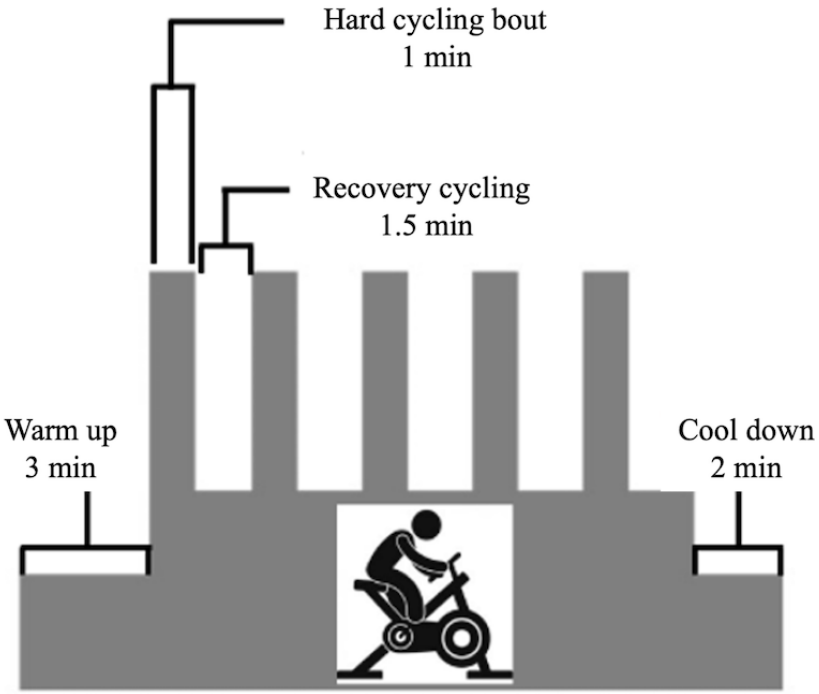


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Exercise Intervention

The exercise group will participate in 3 sessions per week of interval training performed at a self-determined intensity, using a cycle ergometer, for 4 weeks (12 sessions), in line with our previous experience in participant retention [41]. Ratings of perceived exertion (RPE) will be measured using Borg's 6-20 scale [78]. Participants will be asked to exercise on a stationary bike at an intensity whereby their RPE is deemed "challenging" to them. The perceived effort and RPE rating will likely be different for participants depending on their initial fitness and exercise tolerance. The important aspect is for an individual to feel that the exercise is challenging. The cycling protocol includes 5 one-minute bouts of maximum effort, interspersed with 1.5 minutes of recovery, which will involve cycling at a light intensity (Figure 2). Participants will also perform a 3-minute warm-up and a 2-minute cool-down for a total exercise duration of 17.5 minutes, as we have described [41,74,79]. RPE will be measured by asking the participant to provide their rating at the end of the last interval.

Figure 2. Self-determined intensity interval training protocol on cycle ergometer to be delivered to exercise group.



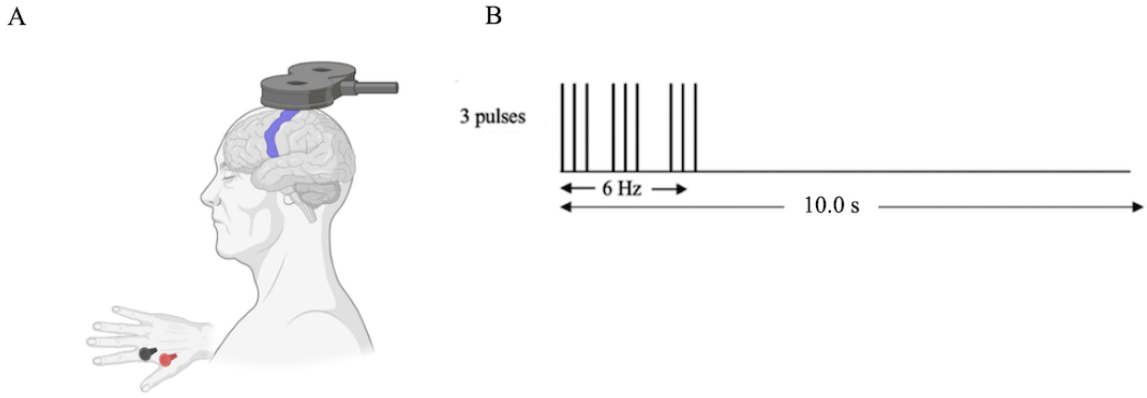
Dependent Measures

Synaptic Plasticity

Surface electrodes (9 mm AgCl) will be used to record activity from the first dorsal interosseous (FDI) muscle of the right hand. The active electrode will be placed over the muscle belly. To reduce signal noise, dry ground will be placed on the styloid process at the right wrist. Electromyography (EMG) signals will be magnified ×1000 and bandpass filtered between 20 and 2.5 kHz (Intronix Technologies Corporation Model 2024F). An analog-digital converter will be used to digitize data at 5 kHz (Power1401; Cambridge Electronics Design), prior to being analyzed using commercial software (Signal version 7.01; Cambridge Electronics Design). Repetitive TMS will be performed using a 70-mm inner diameter figure-of-8 coil with a Magstim Super Rapid^2 Plus Stimulator (Magstim). Biphasic magnetic pulses will be delivered over the primary motor area of the dominant hemisphere to find the optimal position for eliciting a MEP in the contralateral FDI muscle [80,81]. The hot spot of the right FDI muscle is defined as the location on the left motor cortex that, when stimulated with rTMS, consistently leads to the largest MEP in the muscle (Figure 3A). This point will be found and registered using Brainsight Neuronavigation and rTMS (Rogue Research).

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Figure 3. (A) Transcranial magnetic stimulation will be delivered over the primary motor area of the dominant hemisphere to find the optimal position for eliciting a motor evoked potential in the contralateral first dorsal interosseous muscle. (B) Intermittent theta burst stimulation parameters.



Participants will complete 3 maximal isometric contractions of the right FDI against an immovable structure. The duration of each contraction will be 5 seconds with a 30-second rest interval between trials. The largest EMG activity obtained from any of the 3 trials will be defined as the maximum voluntary contraction (MVC) of the FDI muscle for an individual. The level of EMG activity corresponding to 10% MVC will be displayed on an oscilloscope as a horizontal target line. Participants will be required to match the horizontal target line and maintain 10% MVC by contracting their right FDI during the acquisition of active motor threshold (AMT).

AMT will be defined as the lowest intensity required to evoke a MEP≥200 µV in 5 out of 10 consecutive trials while participants maintain approximately 10% MVC with their FDI [80,81]. This value will be determined using TMS_MTAT_2.0 freeware [82]. The stimulus intensity will be set to 37% maximum stimulator output, and 20 TMS pulses will be distributed over M1, specifically the FDI hot spot, with the stimulus intensity being adjusted after each subsequent pulse as advised by the MTAT software based on the presence or absence of an MEP on the previous trial [83]. Resting motor threshold (RMT) will be defined as the lowest intensity required to evoke a MEP≥50 µV in 5 out of 10 consecutive trials while participants maintaining the FDI at rest [80,81]. This value will be determined using TMS_MTAT_2.0 freeware.

To assess synaptic plasticity, an iTBS protocol (Figure 3B) will be delivered using biphasic pulses in bursts of 3 pulses delivered in 6 Hz trains that will last 2 seconds, followed by 8 seconds with no pulse delivered [50,84,85]. iTBS will be repeated for a total of 612 pulses at 80% of AMT [86]. To assess synaptic plasticity 20 MEPs will be delivered at 120% of RMT. The average of 20 MEPs will be recorded from FDI before and immediately following iTBS.

Cognitive Function

Cognitive functions will be assessed using the National Alzheimer's Coordinating Center Uniform Data Set Neuropsychological Battery, Version 3, comprised of the Montreal Cognitive Assessment, Semantic and Verbal Fluency, Trail-making Tests, Digit Span, Benson Complex Figure Test, and the Multilingual Naming Task.

Brain Derived Neurotropic Factor and Osteocalcin

Blood will be collected after ≥10-hour fast from an antecubital vein at T0 and T1 in red top BD Vacutainer collection tubes (Becton, Dickinson and Company, Franklin Lakes, NJ, USA). Red top tubes will be left to clot at room temperature for 45 minutes and subsequently centrifuged at 3488×g for 10 minutes at 4°C. Serum will be aliquoted into vials and stored at –80°C. Enzyme-linked immunosorbent assay (ELISA) assays will be carried out for the determination of serum BDNF (R&D Systems, Inc, Minneapolis, MN, USA) and total OCN (Human Osteocalcin ELISA kit KAQ1381). After incubation with 5 mg/ml hydroxylapatite (Invitrogen-Thermo Fisher Scientific, Carlsbad, CA, USA) to remove carboxylated OCN [87], serum uncarboxylated OCN will be measured by ELISA. Carboxylated OCN will be determined by subtracting uncarboxylated OCN from the total OCN [74].

Participant Experience

A Likert-type scale (0-4) will be given to participants to rate their enjoyment of the self-determined intensity interval training intervention (exercise group) and the overall research experience during the last visit (exercise and no exercise group).

Compliance

We will quantify the number of participants who demonstrate compliance with the exercise schedule. An individual is deemed 100% compliant if they attend all exercise sessions (3 times per week × 4 weeks=12 sessions). Attendance lower than this will be quantified as a percentage of the total number of sessions (out of 12).

Data Exclusion

Peak-to-peak amplitudes of the MEPs will be collected by the experimenter. Trials will be examined visually, and any trials presenting with EMG activity prior to TMS stimulus artifact will be discarded from the analysis. The remaining EMG data will be analyzed using Signal Software (Cambridge Electronic Design).

Statistical Analysis Plan

To investigate the difference in the magnitude of synaptic plasticity between groups, an unpaired *t* test will compare the percentage change in synaptic plasticity (from T0 to T1) between

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the 2 groups (exercise and no exercise). Similarly, the effect of exercise on serum BDNF and OCN levels will be assessed using an unpaired *t* test comparing the change in levels from T0 to T1. Significance will be set to =.05.

Results

As of September 2023, we are currently screening participants for eligibility to participate in the research. We anticipate to complete data collection and analysis by August 2025.

Discussion

Overview

This pilot project is the first to assess changes in synaptic plasticity following a 4-week, self-determined, interval exercise training in individuals with MCI. Individuals will be assigned to 1 of the 2 groups (exercise or no exercise). The exercise group will participate in 12 sessions of exercise across 4 weeks (3 sessions per week). The no exercise group will not participate in the exercise regime, instead, they will be asked to return 4 weeks after their initial visit. Measures of synaptic plasticity, cognition, BDNF, and OCN will be assessed at baseline and 4 weeks later.

Previous research has demonstrated the positive benefits of exercise in individuals diagnosed with MCI. The 12 weeks of resistance training in individuals with MCI improved attention and working memory, and elicited changes in EEG activity [30]. In addition, 2 days of aerobic exercise in MCI subjects improved memory recall [26]. The 12 weeks of aerobic exercise in subjects with MCI improved cognition as reflected by changes in the Mini Mental State Exam [34]. These findings provide evidence that aerobic exercise is capable of modifying cognition in individuals with MCI. It remains unknown whether these improvements in cognition are a result of increases in synaptic plasticity following aerobic exercise.

Our study aims to determine whether synaptic plasticity is modified following 4 weeks of self-determined interval exercise training. Further, we will determine whether any changes in synaptic plasticity correlate with changes in cognition, BDNF, or OCN levels. We anticipate that the exercise group will demonstrate an increase in synaptic plasticity after 4 weeks of exercise compared to the no exercise group. If synaptic plasticity increases in the exercise group, this will be interpreted as a mechanism by which exercise improves cognition in MCI. Further, we hypothesize a positive relationship between a change in synaptic plasticity and measures of serum BDNF and OCN.

A limitation of this study is the use of self-determined interval training, whereby participants determine their own level of exertion. Individuals living with MCI will have varying physical and cognitive abilities which may limit their capacity to perform exercise at an imposed intensity. However, previous research has shown that only individuals who increase their fitness over the exercise period exhibit increased serum BDNF levels [88]. We hope that our approach of tailoring the exercise to the individual will increase the feasibility and retention of the study, thus creating a realistic and effective exercise regimen for individuals with MCI. A second limitation is that we do not consider biological sex or gender in the randomization due to the small sample size. If the study is successful in providing data to support compliance and the exercise regime, it will inform a larger-scale study of exercise training in MCI with biological sex and gender included.

Conclusions

The data obtained from this research study will provide valuable insights into the compliance of a self-determined intensity interval exercise in the MCI population. Exercise provides an affordable and accessible opportunity to promote changes in cognition. This study will determine whether exercise alters synaptic plasticity in a population with impaired cognition.

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Data Availability

The data sets generated and analyzed during this study are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

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Abbreviations

AMT: active motor threshold
BDNF: brain-derived neurotrophic factor
ELISA: enzyme-linked immunosorbent assay
EMG: electromyography
FDI: first dorsal interosseous
GAQ: Get Active Questionnaire
iTBS: intermittent theta burst stimulation
LTD: long-term depression
LTP: long-term potentiation
MCI: mild cognitive impairment
MEP: motor evoked potential
MVC: maximum voluntary contraction
NMDA: N-methyl-D-aspartate
OCN: osteocalcin
RMT: resting motor threshold
RPE: rating of perceived exertion
rTMS: repetitive transcranial magnetic stimulation
TMS: transcranial magnetic stimulation
WHO: World Health Organization

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Protocol

Causes of Patient Nonattendance at Medical Appointments: Protocol for a Mixed Methods Study

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Abstract

Background: Approximately one-third of patient appointments in Danish health care result in failures, leading to patient risk and sizable resource *waste*. Existing interventions to alleviate no-shows often target the patients. The underlying reason behind these interventions is a view that attendance or nonattendance is solely the patient's problem. However, these interventions often prove to be ineffective and can perpetuate social biases and health inequalities, leaving behind patients who are more vulnerable or disadvantaged (in terms of social, economical, and linguistic factors, etc). A more holistic understanding of no-shows is needed to optimize processes, reduce waste, and support patients who are vulnerable.

Objective: This study aims to gain a deep and more comprehensive understanding of the causes, mechanisms, and recurring patterns and elements contributing to nonattendance at Danish hospitals in the Region of Southern Denmark. It emphasizes the patient perspective and analyzes the relational and organizational processes surrounding no-shows in health care. In addition, the study aims to identify effective communicative strategies and organizational processes that can support the development and implementation of successful interventions.

Methods: The study uses mixed quantitative-qualitative methods, encompassing 4 analytical projects focusing on nonattendance patterns, patient knowledge and behavior, the management of hospital appointments, and in situ communication. To address the complexity of no-shows in health care, the study incorporates various data sources. The quantitative data sources include the electronic patient records, Danish central registries, Danish National Patient Registry, and Register of Medicinal Product Statistics. Baseline characteristics of patients at different levels are compared using chi-square tests and Kruskal-Wallis tests. The qualitative studies involve observational data, individual semistructured interviews with patients and practitioners, and video recordings of patient consultations.

Results: This paper presents the protocol of the study, which was funded by the Novo Nordisk Foundation in July 2022. Recruitment started in February 2023. It is anticipated that the quantitative data analysis will be completed by the end of September 2023, with the qualitative investigation starting in October 2023. The first study findings are anticipated to be available by the end of 2024.

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Conclusions: The existing studies of nonattendance in Danish health care are inadequate in addressing relational and organizational factors leading to hospital no-shows. Interventions have had limited effect, highlighting the Danish health care system's failure to accommodate patients who are vulnerable. Effective interventions require a qualitative approach and robust ethnographic data to supplement the description and categorization of no-shows at hospitals. Obtaining comprehensive knowledge about the causes of missed patient appointments will yield practical benefits, enhancing the safety, coherence, and quality of treatment in health care.

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KEYWORDS

missed appointments; nonattendance; hospital appointments; Danish health care; prevention strategies; positive deviance; quality of treatment; mixed methods

Introduction

Background

Approximately one-third of all scheduled appointments at Danish hospitals do not succeed—that is, they are unattended by the patients [1]. An unattended or "missed appointment" is "when a patient does not show up for a scheduled appointment without sufficient notification, or any notification at all" [2,3]. At Odense University Hospital (OUH), for instance, every 20th patient does not show up for outpatient visits [1]. At Hospital Lillebælt, 12,424 cases of no-shows were registered during the first 7 months of 2018, which corresponds to approximately 4% of all appointments [4]. In the Capital Region, every fifth patient misses their hospital appointment [5]. No-shows are expensive owing to the large waste of resources that they entail. A single no-show costs health care between DKK 1500 and DKK 2000 (approximately US $227 to US $235). Bispebjerg Hospital spends DKK 40 million (approximately US $6 million) on nonattendances annually, whereas OUH spent as much as DKK 2.4 billion (US $380 million) on nonattendances in 2010 [6]. More importantly, no-shows increase the risk of patient errors and may seriously complicate patient treatment and continuity of care [7]. According to a Danish national report, "patients who do not show up for planned examinations, operations, etc., are a problem for the efficient use of resources in the healthcare system. It prevents other patients from arriving earlier, wastes staff time and prevents technology and operating theaters from being optimally utilised" [8].

The large number of no-shows for treatment in Danish hospitals has led to a lively debate among Danish politicians and in the daily press. So far, however, most papers that have addressed no-shows in outpatient and hospital appointments adopted an organizational perspective, ascribing no-shows to the faulty behavior of the patients (hence, referred to as "nonattendance"). It is the patient who "does not show up for hospital appointments," "has forgotten to cancel an appointment," or "is unable to show up for an appointment for other reasons" [5]. This is despite the fact that practices surrounding nonattendances vary significantly across various hospitals and sectors. At some clinics, it will be categorized as a missed appointment if a patient is at least 5 minutes late [2]. Such framing of the problem draws our attention toward individual behavior and no-shows as responsibilities of the patient and away from the structural and organizational shortcomings, which are responsibilities of the health care system. This perspective has been widely accepted among Danish policy makers, administrators, and health professionals, who generally view no-shows as a problem caused by patients. Some, for example, have suggested putting nonattending patients at the back of the queue for examination and treatment or giving them fines [9,10].

Most interventions to reduce nonattendance in Danish hospitals and outpatient clinics therefore target the patients: the introduction of web-based appointment systems, reminders via SMS text message, reminder letter, and so on. In Denmark and Great Britain, attempts have also been made to give the nonattendant patients fines. However, interventions such as fines are based on a lack of understanding of the health care system's own role in missed appointments, and their effect is limited [11]. Other studies have claimed that up to 40% of nonattendances in health care are actually caused by errors on the hospital's side [12,13]. It indicates that the many failures to attend hospital appointments may rather be "a symptom" of the shortage within the health care system itself to adequately accommodate patients who are more vulnerable. By "vulnerable patients" we mean those patients who have a low social capital or who belong to marginalized or socially excluded groups because of factors such as ethnicity, age (older people), language, low education level, low income, unemployment, housing conditions (eg, people experiencing homelessness), drug and alcohol addictions [14], people with complex illness (eg, type 2 diabetes) [15], and those individuals who do not have the capacity to take care of themselves (eg, children, people who are physically and mentally disabled, and people with mental illnesses) [14]. Vulnerability may also arise as a result of misunderstandings that lead to failure to fulfill the patient's needs. In other words, it arises in the encounter between the physician and the patient, for example, as a result of misunderstanding or dissimilar points of departure or beliefs for the patient and the physician or health system, or forms of treatment [16].

Despite this, we found no documented interventions that target the health care causes for missed appointments. In the numerous attempts to reduce nonattendances at hospitals in Denmark, the patients' perspective has also been lacking, and in general, we have very sparse knowledge about how relational and clinical factors affect patients' no-shows. National, empirical studies of relational and organizational causes of nonattendances are practically nonexisting. Most no-shows in the Danish health

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care system are registered automatically but rarely with documentation of the cause. The causes of nonattendance in, for example, electronic patient records (EPRs), which are a platform that integrates electronic health records from hospitals [17], are not fully documented or not documented at all. The EPR only provides response options that deal with patient causes—not the administrative or clinical causes.

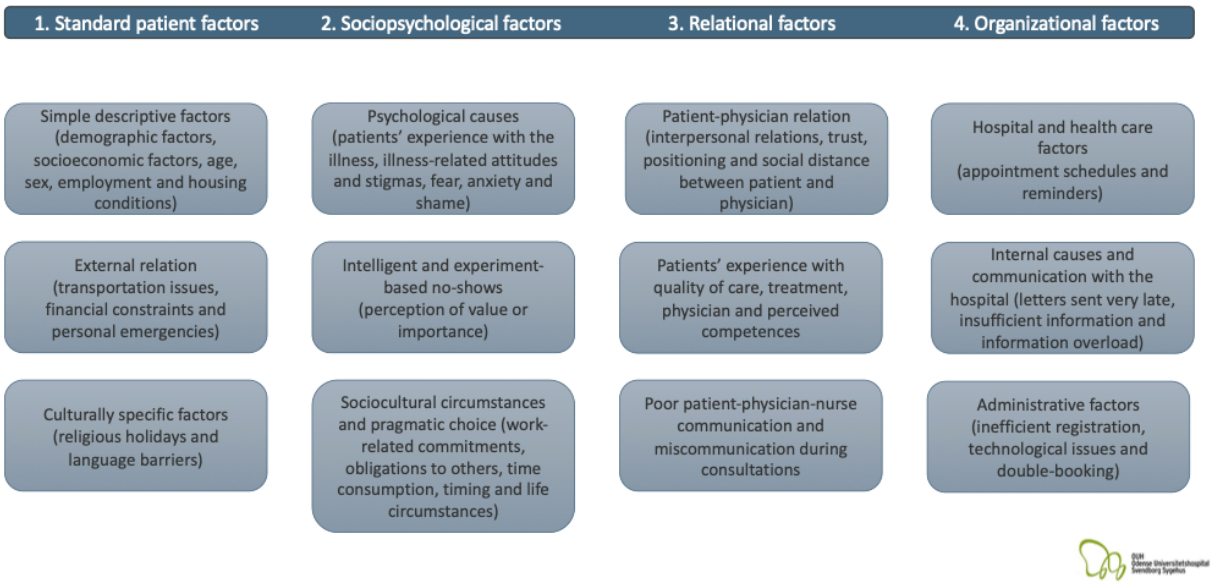
Previous studies that adopt the health care system perspective (with its fundamental understanding that patient are the ones who fail to attend hospital appointments) primarily focuses on (rather limited) sociodemographic descriptions of the patients who "do not show up" for hospital appointments (age, employment, socioeconomic status, ethnicity, etc). Furthermore, many studies have inadequate documentation or ambiguity regarding the reasons for these missed appointments. In addition, only a small number of studies have explored the patient perspective about this issue. Consequently, there is a lack of *a substantial body of research* that adequately explains the reasons behind no-shows. Our aim is to delve deep into the patient perspective and provide a more comprehensive understanding of no-shows at Danish hospitals.

Determinants of Nonattendance (Literature Review)

Overview

This project builds on previous studies of missed appointments or nonattendance and related interventions in hospitals and outpatient settings. Both Danish and international studies were included. In our review of literature, we have singled the following 4 key groups of factors and circumstances of "nonattendance" (refer to Figure 1).

Figure 1. Determinants for nonattendance.



Standard Patient Factors

A large number of studies of no-shows or nonattendances in health care—and particularly no-shows at Danish hospitals and outpatient clinics—focus merely on describing standard patient factors (such as age, sex, education, employment, etc), showing that there is a correspondence of nonattendance with sociodemographic factors such as age, ethnicity, sex, illness, insurance coverage, poor residence areas, socioeconomic status, timing of the appointment, travel time, transportation to and from hospital, and so on [18,19]. According to a Danish study, patients who fail to attend appointments are young people aged between 17 and 40 years, and they come from socially disadvantaged groups or from low-income housing areas, are unskilled, and have a high rate of unemployment [8]. The combination of long transport time and low income or low education are particularly intensifying when it comes to nonattendance [20]. Patients on social benefits, those with low income or short education, and those who have difficulty in finding transportation means (eg, lonely people) are also more likely to miss their appointments and have significantly more absences. Language (eg, patients who do not have Danish as their first language) and specific circumstances, such as religious holidays, may also be associated with nonattendance [8,19,21].

Sociopsychological Factors: Patient Knowledge, Risk Balancing, and Pragmatic Choice

Few qualitative studies of nonattendances similarly point toward themes such as balancing the costs and benefits of the individual attendance (intelligent compliance), lack of trust in the health care system, obligation to other people, stigmatization, anxiety, and patient's attitudes toward the health care staff and toward illness as possible causes of no-shows [22,23]. Studies of nonattendances among patients with chronic disease [23-26], for example, show that there is a direct connection between nonattendance and the patient's knowledge, attitudes, and behavior in relation to illness (eg, the patient's feeling about whether the medicine is working, the patient is not satisfied with the treatment, or the patient does not trust the physician's skills). Stigmatization (eg, obesity stigma) and shame can also act as barriers to comprehensive and effective treatment of type 2 diabetes and can be significant reasons for the patient's no-show for the appointment [27]; health-related anxiety was a primary factor in decisions to discontinue long-term follow-up care among young survivors of cancer [28]. The patient's

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willingness and unwillingness to meet up for hospital appointments may similarly depend on the patient's relation with and obligations toward other people (that are framed by norms and beliefs within a particular society), patient's previous experiences with and trust toward the health care system [29], perception about own position in relation to the physician's position and skills [30], and diagnosis [31]. Patients who are vulnerable may further lack the resources and social support they need to establish and maintain their appointments [28,30]. A recent Danish report on social inequality in health care encounters also shows that there are considerable differences in patients' skills and opportunities to search for health information themselves and absorb knowledge about health and illness, partly because patients with low socioeconomic status have low degree of social and cultural capital, which gives them few opportunities to seek knowledge via different sources, for example, internet, professional sources, and social networks [30]. Thus, in contrast to standard patient factors (age, education, housing, and ethnicity), this category is more about the interplay between the sociocultural and psychological factors (eg, moral values, obligations to others, fear, anxiety, and stigmas related to illness) and practical constraints that can influence peoples' pragmatic choice and capacity to attend a hospital appointment.

Relational Factors, Quality of Patient Consultations, and Patient's Relation With the Treating Clinician

Relational factors relate to social interactions and communication in patients' encounters with health professionals. It encompasses elements such as patients and health professionals' competencies, attitudes, and expectations toward the encounter and other communicative mechanisms that create social distancing and distrust between patients and health professionals [30]. The role of the quality of patient-physician conversations and the relationship that clinicians and the patient have before no-show has not been investigated in the Danish context. However, international studies have shown that the patient's perceptions about the treating physician may play an important role in nonattendance [32,33]. Clinical psychologists' patients had the lowest proportion of nonattendances (7.8%), followed by consultant psychiatrists (18.6%), specialist registrars (34%), and senior housekeepers (37.5%) [34]. Some referring physicians have significantly more nonattendances than others, just as patients who are treated by the youngest physicians are most likely not to show up for their appointments [35]. A large study from Australia showed that 50% of patient compliance is related to trust toward the treating physician [36], whereas other studies have shown that the failures to attend appointments were caused by insufficient communication from the physician, for example, when the physician did not explain sufficiently why the given appointment is important for the patient [33].

Organizational Factors and Errors in Hospital Communication

Organizational factors relate to the organization of the health care system and how the conditions in the system enable or prevent the accommodation of some patients [30]. International studies, for instance, reveal that minimum 35% to 40% of nonattendances at hospitals are caused by errors on the part of the hospital—errors in administration of patient appointments (letters not sent, wrong times, wrong bookings, wrong appointment places, changed agreements, very short notices, etc), insignificant or redundant hospital appointments, lack of availability, insulting behavior or speech, slow mail correspondence, and other administrative matters for which patients are not accountable [12,37,38]. A study of nonattendance at surgical control after trauma hospitalization showed, for example, that 37% of nonattendances were solely owing to the lack of communication about the appointment between the surgeon and nurse or between the medical team and the patient, which resulted in miscommunication [39] and not because the patients simply forgot the appointments, as other studies have claimed [40]. Another study claims that 41% of nonattendances are caused by errors on the part of the hospital [41].

The nonattendance rates can also differ significantly among different hospitals and among different units at the same hospital. The nonattendance rate in medical outpatient clinics in Denmark is 12% to 13% compared with 16% to 20% in England [41], and some specialties (eg, orthopedic surgery and type 2 diabetes) are systematically overrepresented among the high nonattendance rates, whereas others most often have low nonattendance rates (eg, in cancer treatment). Although it can be difficult to compare the nonattendance rates across units, both because the percentage can be estimated differently (per patient or per course of treatment and ≥1 nonattendances/course of treatment) and because there is a significant difference in the severity of illness (for instance, being a patient with cancer; being a patient with a chronic illness such as diabetes; or having a disease burden owing to, for example, multimorbidity) [26,42], we see that in chronical specialties, patients with low attendance compliance weigh heavily, whereas very few patients are represented in repeated rehospitalizations [41].

There is also evidence suggesting that comorbidity, an increased number of relationship problems, difficult consultations, and the lack of attendance affect the continuity of care [7,43]. Among the factors that prevent patients from attending, for example, asthma assessment consultations at hospitals are memory loss, reduced mobility owing to poor health, and frustration over the organization of the clinic that results in long waiting times and interruptions of treatment [44]. Attachment is also important for shaping and understanding the clinician-patient relationship and is essential for adherence to treatment and continuity of care [45], whereas social networks can be decisive when it comes to supporting patients who are vulnerable [46].

All of this supports our claim that nonattendance is a complexly determined behavior and is not something purely driven by the patient. To understand this complexity, we therefore need to look beyond purely descriptive patient factors and pay more attention to relational and organizational aspects of health care encounters that may result in no-shows. To further understand cognitive processes (decision-making) behind no-shows, we also need to investigate the relationship between the sociopsychological factors and pragmatic conditions and the patient's conceptual representations (knowledge and values) that influence the generation of no-shows. Such knowledge may also help to develop prevention approaches and interventions

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that are appropriate and relevant—that is, target specific causes for no-shows within a particular context and setting.

Interventions That Enhance Attendance

Interestingly, interventions targeting the specific causes for nonattendance at outpatient and hospital appointments work and can significantly reduce the number of nonattendances. We know of 5 well-documented, simple interventions that can reduce nonattendances at hospitals and ensure equality [41,47-49]. However, most interventions related to nonattendances are aimed at patients (they receive a reminder, can book an appointment themselves, or they receive a fine for not showing up) and are not related to the errors and deficiencies triggered by the health care system. A hand surgery clinic, for example, established an open outpatient clinic unit, where patients who missed to attend an appointment could themselves book a new appointment, thereby reducing nonattendance from 16% to 11% [41], whereas the pediatric ward in Viborg achieved analogous results by changing their guidelines and introducing a reminder via SMS text message [48]. A Cochrane review documents that SMS text message, e-mail, postage-paid reply envelopes, and self-booking outpatient clinics all significantly reduce nonattendances [50,51].

In Denmark, different hospital units are currently introducing web-based appointment systems to give patients more responsibility and better opportunity to make decisions about their appointments. Nevertheless, according to the staff, some patients experience barriers related to using web-based booking systems (low computer skills, ignorance of the web-based appointment, distrust of the internet, preference for verbal communication, etc) and may therefore be reluctant to use the system [52].

Having knowledge about the experiences and needs of the specific target group and in-depth insights into organizational processes and methods for creating relationships with and for the patient is, therefore, crucial not only for understanding why health care appointments fail but also for improving patient compliance and continuity of care and for supporting interventions that work well.

Aims of the Study

The intention of this project is to provide a deep and more comprehensive understanding of the causes, mechanisms, and recurring patterns and elements contributing to nonattendance at hospitals and outpatient clinics in Denmark. The key objectives are (1) to describe the pattern of nonattendance and patients' experiences thereof, (2) to identify managerial practices and interactional strategies that work or do not work well, and (3) to identify personal factors and administrative processes that can predict nonattendance and that can support appropriate implementation effort. Keeping this in mind, we ask the following research questions:

1. How do patients explain why they miss their hospital appointments?
2. What is the role of the quality of patient consultation and the physician-patient relationship before nonattendance for whether the patient attends their appointment?
3. How are no-shows handled by hospitals and medical professionals; what actions are taken (or not taken); and how does it affect the outcome, communication, time, and workload?
4. Which interventions do questions 1 to 3 offer possibilities for?

We, thus, put emphasis on some of the determinants presented previously and adding new ones, as we collect both quantitative and qualitative data. To pursue the research objectives, we propose a mixed methods design that combines research methods from health science, anthropology, cognitive science, humanistic interaction research, health care communication, and translational science.

Methods

Overview

Given that the goal of the project is to enhance an understanding of the problems and opportunities associated with missed hospital appointments, it is essential to grasp both the general patterns regarding the occurrence of patients' nonattendance in Danish hospitals, which are available and hold significance from an epidemiological and biostatistical perspective. In addition, we must delve into the atypical instances and trends of no-shows, which come to light through the use of ethnographic approaches. To address these goals, the project uses a mixed quantitative-qualitative approach and is divided into three phases:

1. Quantitative data collection and analysis
2. Qualitative data collection and analysis, organized into 3 subprojects
3. Identifying prevention strategies

In the first phase of the project period, the focus is on quantitative analysis. We will identify the recurring patterns of no-shows in the Region of Southern Denmark and the patients and hospital units eligible for the qualitative studies in the second, qualitative phase of the project. In the last phase, the achieved knowledge will be used to identify relevant prevention strategies and to design context-based, evidence-driven interventions that target specific causes of no-shows (refer to Figure 2 for an overview of the project design and aims of the study).

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Figure 2. Overview of the project design and aims of the study.



Quantitative Data Collection and Analysis

Description of the Study Population

The study population of this project comprises all patients who are residents in the Region of Southern Denmark and who were referred with at least 1 contact to a hospital in the period between January 1, 2018, and December 31, 2022. Patients who do not turn up for an appointment owing to death or immigration will be excluded from the study population.

Data for Analysis

To describe the patient population and the pattern of nonattendance, we will retrieve a series of information including the patient's age, sex, diagnostic codes for hospital contact, weight, height, smoking status, alcohol consumption, and information about planned and performed hospital examinations and treatments. In addition, we will investigate whether the patient's other personal factors, such as cohabitation, number of children, working status, socioeconomic status, and medical history affect the risk of nonattendance. Nonattendance at hospital appointments is our primary interest. Information about nonattendance will be retrieved from the EPR system. Information about planned and performed examinations are to be applied as explanatory background variables. This information will be retrieved from the EPR system. Information from the Danish central registries for all patients in the study population will be used to retrieve information about the civil and vital status of the patients and about immigration and emigration from the civil registration system. Furthermore, we will retrieve information about all previous hospital contacts from the Danish National Patient Registry and about prescriptions from the Register of Medicinal Product Statistics. The central registers from Statistics Denmark are tools for retrieving information about the patients' socioeconomic status and additional background variables.

Statistical Analyses

We will divide the patient population according to the nonappearance patterns on several levels: hospital level, department level, disease diagnosis level, and calendar time. The patient characteristics will be assessed according to these levels. We will use descriptive and more advanced analyses. *Chi-square tests* and *Kruskal-Wallistests* will be used to compare the baseline characteristics of the patients across different levels. To estimate the odds ratio for nonattendance, we will conduct both univariate logistic regression analyses and multivariate logistic regression analyses, where we will adjust for various combinations of adjustment variables (including age, sex, socioeconomic status, type of underlying disease, and cohabitation).

Qualitative Data Collection and Analysis, Organized Into 3 Subprojects

Description of the Study Population

The project uses the open approach, which means that units, medical professionals, and patients who are to be included in the qualitative study will be obtained through quantitative analysis. On the basis of the current picture, we will identify and investigate units (and practitioners) that are similar in clinical specialty but that lay on the opposite side of the spectrum regarding no-shows. We will further identify those patients whom we will follow throughout the course of their treatment and with whom we will conduct individual interviews to identify some important barriers and facilitators (even if we do not get hold of those patients who score highest on the no-show). To include ethnic minority individuals, an additional subgroup will be chosen among patients with an ethnic minority background who have been referred to the Migrant Health Outpatient Clinic at OUH during the same period. Ethnic minority individuals are often underrepresented in clinical studies [53] but are, as a rule, overrepresented among the

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nonattendances in survey studies—and often for reasons other than those of the majority population: the lack of knowledge about the purpose of control appointments, lack of reading skills, poor economy, transport barriers, and interpreting fees—that is, the fee that the patient has to pay for having an interpreter present during the consultation—are among the key reasons [54]. The inclusion of ethnic minority individuals is vital and will help to secure great validity and equality of the study. Only patients who agree to participate in the study will be included. Patients who die or move during the study period will be excluded from the study, unless we have obtained the necessary data.

Data for Analysis

To achieve more comprehensive data about missed appointments, we will investigate patient knowledge, attitudes and experiences related to missed appointments and identify to what extent organizational factors (tight day programs, excessive documentation, lack of time, etc) and relational dynamics (interpersonal relations between patient and physician or nurse, trust, empathy, attitudes, etc) contribute to the generation of no-shows and shape the pragmatic choice [55,56] and ways in which information is administrated and provided to the patient. It will provide a deep understanding of patient-related and disease-related factors, interactional dynamics, and organizational processes, which cause patients to miss their appointments at Danish hospitals and outpatient settings in the Region of Southern Denmark. It will also identify the role that the quality of patient consultations and the patient-physician relationship before nonattendance plays in the success or failure of attendances. This will help secure appropriate practices at hospitals and support the development of interventions based on situated data and the reasons for nonattendance. To meet the key goals, the qualitative part is divided into 3 independent but interrelated subprojects, focusing on patients' knowledge, attitudes, and behavior (subproject 1); decision-making and management of hospital appointments (subproject 2); and interpersonal relations and communication (subproject 3).

Subproject 1

The *patient's knowledge, attitudes, and behavior* subproject will examine the patient's lived experiences and perceptions about the quality and course of treatment and their reasons, motives, and motivations for not showing up for hospital appointments by drawing on patient-reported outcome data about physical and mental health symptoms and quality of life and on in-depth semistructured qualitative interviews with selected patients [57,58]. To help secure patient perspective, the analysis of the project involves patient and relative representatives who are members of the research committee at the Centre for Clinical Epidemiology and of Center for Research Together with Patients and Relatives (*Center for Forskning Sammen med Patienter og Pårørende*; ForSa-P) [59] throughout the study to discuss and comment on the main aspects of the study. They will receive upgrades of the study progress on a regular basis and will be included in the evaluation of study results and relevance. To include ethnic minority patients and gain insight into their experiences with hospital agreements (and possible side effects), 3 separate focus group interviews with patients referred to the Migrant Health Outpatient Clinic at OUH during the same period as the main cohort will be conducted. We will focus on patients within 3 different languages and ethnic backgrounds, as these will overlap for most participants: Arabic, Somali, and Farsi or Turkish, as these immigrant groups are the largest within the Danish context. The number of participants for each group will be limited to 8. The focus groups will be facilitated by a Doctor of Philosophy student and conducted with the assistance of an interpreter and will focus on barriers related to and implications of no-shows experienced by those patients.

Subproject 2

The *decision-making and management of hospital agreements* subproject will explore how no-shows are managed by hospitals, hospital units, and medical professionals and the implications it has for the number of registered cases and for the frequency of nonattendance. A Danish study has claimed that the health care system's capacity to accommodate some patients often relates to the limited resources within the health care system and may be explained by, for example, the time that is available for health professionals, their educational prerequisites for communicating with socially (and ethnically) diverse patients, and their knowledge about the available referential options and offers, which places demands on patients and any relatives to be able to navigate their course of treatment themselves [30]. The experience from a pilot study at OUH further shows that the management of hospital agreements often lies with the individual physicians and that certain structural factors (tight day programs, excessive documentation, and lack of time) can prevent the individual physicians from examining the individual cases further or contacting the absent patients. Moreover, physicians often use time to attend to other tasks. This raises the question about whether the time lost as a result of no-shows is actually wasted or whether opportunities arise instead to solve other tasks, such as, for example, documentation of patient progress or professional sparring.

To document how patient appointments and no-shows are managed locally (ie, when is the patient registered as "absent"; has the patient been contacted via phone and by whom; how many times should the patient be registered as "absent" before the case is closed; who closes the case; and what are the strategies, norms, and procedures; and what are the challenges?), this study will rely on systematic observations applied in cognitive ethnography [60,61]. Observation at the reception desk will be conducted by a research assistant or postdoc at 4 hospital units, identified in the first phase. They will be integrated into the clinic for a period of 1 month at each unit [58,60,62], producing a running record of mundane practices surrounding no-shows. To supplement observational data and secure their validity, the researcher will conduct individual semistructured ethnographic interviews [63] with medical secretaries and other medical professionals at each unit, to investigate their attitudes and how they handle no-shows (approximately 5-10 interviews at each site or unit, depending on the size of the unit). The study will be conducted in collaboration with the units, and the core informants will be identified by the researcher, in collaboration with the management team, in the course of fieldwork. We anticipate

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that the examination will enable us to identify gaps in the statistical data and provide insight into which actions are taken in connection with such situations. Administrator perspective can further provide key insights into organizational factors that influence no-shows. It can also help outline best practices, that is, define the managerial strategies that work best.

Subproject 3

The *interpersonal relations and communication* subproject will focus on patient consultations and examines how clinicians communicate with the patient in situated, real-time, real-life interaction. Communication (how we meet the patient; whether we manage to listen, communicate interest and care, and create security and trust; etc) is crucial to how patients experience their encounter with the health care system. Communication can both help to address nonattendance and cause it. It may also produce social inequality, for example, owing to patient's ethnicity, poor hygiene, or poor language skills [64] or owing to social distance between the patient and the treating physician [31], which may then contribute to the patient's no-shows. Subproject 3 seeks to examine the communicative strategies that may influence the patient-clinician relationship and trust (eg, time to listen, ability to read the patient or communication cues, ability to include and recognize the patient and the patient's needs, interruptions, etc). In contrast to subproject 2, which aims to map managerial strategies and challenges within respective hospital units and therefore focuses on communication more broadly ("a focus on equal access to care for all") than the patient-clinician relation, the objective of subproject 3 is to understand the extent to which the quality of patient consultation and the patient-clinician relationship (in particular, the one before no-show) plays a role in nonattendance. It therefore focuses more specifically on situated interactions and observations of live medical appointments between providers and patients, which can be examined through the application of video ethnography [65] and interpersonal dynamics that can contribute to a positive (or negative) dialectic relation between the clinician and the patient [66,67]. The video consultations will be conducted at 2 chosen hospital units, which will be identified based on quantitative analysis. The anticipated size of video sample is 60 to 100 patient consultations, depending on the number of participating units and medical professionals and the obtained consent. Combined with statistical data about the frequency of no-shows, these data may enlighten our understandings of the relational aspect of nonattendance. It may also help us to identify the strategies that work well.

Analytic Tools and Procedures

The 3 subprojects will share a common data pool consisting of ethnographic observational data (field notes), individual interviews with patients and practitioners, questionnaires regarding the patients' satisfaction with consultations or patient-reported outcomes, and video recordings of patient consultations. In the analysis of the data, we rely on phenomenological-hermeneutic tradition [58] and the thematic analysis used in traditional ethnography [68,69] and medical anthropology [33,70,71] and on cognitive ethnography [72], which is a method for studying distributed cognition in organizational contexts. A distributed approach means that cognitive processes (eg, decision-making) are examined in relation to the sociocultural context in which they occur, as opposed to classical approaches focusing on mental processes in individuals [60]. A cognitive ethnographic approach provides an opportunity to scrutinize both the conditions and the implications that the cognitive processes have in a particular organization. It allows to scrutinize no-shows as a dynamic dialogical process, that is, something that unfolds in the interaction among the patient, the health care professionals, and the environment. Cognitive ethnography can also provide insights into existing challenges in coordination of, for example, patient agreements across hospital units and across sectors (sector transition) and can be particularly useful in addressing situated choice and decision-making regarding no-shows. We analyze experiences, perceptions, and behaviors through the lens of medical anthropology, identifying the key themes, recurring patterns, variations, and contradictions within and across the data [73]. We draw on cognitive ethnography [74-78] when analyzing how no-shows are managed in the clinical setting [75]. In our analysis of video data, we rely on multimodal interactional analysis [79] and on embodied participation framework [66,80]. To better understand the multifaceted aspects of interaction, we treat consultations as a multiactivity setting, where people engage simultaneously in >1 activity, involving "complex configurations of spatiality (built spaces that both afford and constrain), materiality (objects, artefacts, tools, representations, etc), and participation (varying levels of involvement, shifting orientations, and more)" [66]. Taken together, the ethnographic data will provide more comprehensive knowledge about the reasons, patterns, and processes behind no-shows.

Identifying Prevention Strategies

This study intends to use a *positive deviance* approach to ensure the translation of the research to practice. The positive deviance method recognizes that within any society or organization, certain individuals or groups exhibit exceptional behavior and strategy that enable them to find better solutions to problems, despite having access to similar resources and facing similar or worse challenges. In other words, it focuses on those individuals (and, in our case, medical teams and hospital units) who demonstrate exceptional performance, despite facing the same constraints as others [81]. Positive deviance approach is increasingly used in health care organizations because it has the potential to solve many of the challenges faced by the organizations in the effort of enhancing quality [82]. A four-step process has been proposed to apply the positive deviation approach in health care: (1) positive deviations are identified using routinely collected data; (2) qualitative methods are used to generate hypotheses about how positive deviants succeed; (3) these hypotheses are tested in large, more representative samples; and finally, (4) the successful, positively deviant practices are widely disseminated [81,83].

Consistent with this approach, this part of the project aims to use the collected data to identify units, clinics, and individuals that exhibit exceptional performance and to identify practices and strategies that work well. Subsequently, a pilot study will be designed to test the effectiveness of the identified prevention strategies.

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Ethical Considerations

As of January 2023, the study was registered with the Danish Data Protection Agency—Datatilsynet (registry ID 22/54791) and with the Open Patient Data Explorative Network (registry ID OP_1800). Request for ethics approval was sent to the Regional Committees on Health Research Ethics for Southern Denmark [84]. The request has been given the case number 20222000–133. On October 26, 2022, the committee replied that, based on the available information, the committee has assessed that the project could not be considered as health science research with an obligation to report to the Health Research Ethics Committee System, as found in Committee Act Article paragraph 14, section 1. In the decision, emphasis has been placed on the fact that it appears to be a quality development project, where the trial-related procedures cannot be considered as an intervention within the meaning of the Committee Act. The project, therefore, falls outside the scope of the Committee Act's definition of a reportable health science research project. Pursuant to the Committee Act Article paragraph 14, section 2, questionnaire surveys and register-based research projects must only be reported to the Research Ethics Committee System if the project includes human biological material. If a health research project is to fall within the framework for reporting to the committee system, the project must, as found in the guidelines from the National Committee on Health Research Ethics, both have a health scientific purpose and involve intervention.

Results

Given that this paper is a study protocol, we do not yet have any results to report from the study. The study was funded by the Novo Nordisk Foundation and will be conducted for a period of 48 months (January 1, 2023, to December 31, 2026). The original title of the research application, funded by the Novo Nordisk Foundation, was "Non-attendant or not invited? A cross-disciplinary study about why healthcare appointments fail and how this can be prevented." As of January 2023, the request for permission to use information from patient records has been directed to the Region of Southern Denmark [85], in accordance with the Health Act (Sundhedsloven) Article §46, section 2, and Article §47, section 1. Recruitment commenced in February 2023. It is anticipated that the quantitative data analysis will be completed by the end of September 2023, with the qualitative investigation beginning in October 2023 and the first study findings being available by the end of 2024. An overview of the project timeline and key activities is presented in Figure 2.

Discussion

Expected Outcomes

We are proposing an ambiguous study design, combining national registries and EPR with a longitudinal ethnographic study to explore a broad range of no-shows management, patient-specific experiences, and relational dynamics that cause no-shows. Rather than focusing on purely descriptive factors, this study rests on the idea that "nonattendance" is a complex problem—it implies societal and communicative or interactive challenges that are also tied to relational, sociocultural, and organizational factors. It further assumes that the long-lasting, narrow focus on the patient as the major problem and the key cause for nonattendance has prevented effective interventions to reduce the nonattendance waste, and it has produced more inequality with respect to patients, who are vulnerable; lack resources; or have previously been overlooked, excluded, or stigmatized.

The study aims to fill the major gap of knowledge about no-shows in the Danish health care context. It addresses structural, relational, and pragmatic dimensions of no-shows to provide a broad and more operational knowledge base for unsuccessful encounters between patients and health care professionals. In addition to providing a holistic picture of no-shows within the Danish context, this study also aims to identify the personal and organizational factors and administrative strategies that work well. We anticipate that such knowledge will yield significant practical advantages for health professionals and can be foundational in scaffolding better-informed development and implementation of interventions and prevention approaches.

Limitations

Obtaining comprehensive and reliable data about no-shows can be challenging. The weakness of this study is that the registration of no-shows varies significantly across hospitals and even among units within the same hospital, and the quality of the data is not known. Hospital records may not always accurately capture the reasons for nonattendance, making it difficult to assess the underlying factors. Moreover, self-reported data rely on individual perceptions, attitudes, and beliefs. It may be biased and may not always provide an objective view of the reality [58,68]. To achieve more valid data, we combine methods such as ethnographic interviews [58], focus group interviews [86], systematic observations and video ethnography [65].

Implications for Practice

The project will offer a methodological and empirical contribution to health science, humanities scholars, and medical professionals. It will contribute new insight by involving the patient perspective and analyzing the relational and organizational processes around no-show at hospitals and outpatient clinics in the Region of Southern Denmark. By incorporating various data sources and by linking national registers, EPR data, and patient satisfaction questionnaires with rich ethnographic (and video) data, it will create a comprehensive and multifaceted data pool. Taken together, these data will strengthen Danish health care by providing new and more comprehensive knowledge about the reasons, patterns, and processes behind no-shows. More comprehensive knowledge about problems and intervention possibilities (1) can partly be used to make predictions about nonattendances; (2) can help to identify interventions grounded in specific causes that trigger failures at hospital appointments; and (3) can identify patient perspectives and strategies that can lead to interventions in health care interaction with patients who are vulnerable, where the risk of misunderstandings and missed appointments is high. This will yield significant practical advantages at least in 4 different ways, with potential for creating more appropriate and effective interventions. It will allow us to do the following:

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1. Identify specific areas within the health care system where interventions can be implemented to reduce resource wastage effectively
2. Address social inequalities related to missed appointments, ensuring that populations that are vulnerable receive equitable access to health care services
3. Enable active participation of the health care system by using patient-reported information and engaging in cocreation with patients to optimize resource allocation
4. Foster cross-sector collaboration, enhancing the overall coherence and quality of treatment

An approach to interventions that focus on "the good examples" can then be applied to others in the health care system and give clinicians and managements the opportunity to optimize organizational processes through targeted interventions. The project thus has the potential to reduce waste and clinical errors in health care, which will be beneficial for both the patients and the health care system. It also has the potential to cast light on how health care professionals can improve their skills for detecting potential nonattendants early in the process, for example, by articulating and responding to what matters to the individual patient.

In the future, the expanded model for determinants of no-shows could form the basis for algorithms created by machine learning, among other methods [87]. However, as artificial intelligence method of cogitation is mechanically distinct from human intelligence—computers lack emotion; thus, they cannot literally be courageous and their logic boards cannot process narrative [88]—jumping straight to machine learning is methodologically immature. It requires massive analytical resources, and it reproduces and intensifies the health care system's own misconceptions and the existing administrative and professional discourses behind no-shows [89,90].

Finally, the project will also contribute to a new Research Portfolio for Human Factors and Patient Safety, established as part of a collaboration between the University of Southern Denmark and OUH. The portfolio is the first of its kind in Denmark, and it will enable researchers in close cooperation with clinicians to test and implement successful interventions and to further develop original ways of communicating and collaborating, to produce a more informed scholarly understanding of nonattendances in health care and the interaction of core biological, social, and cultural factors.

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Data Availability

According to Danish legislation, our approvals to use register data for this study do not allow us to distribute or make patient data available to other parties. Any interested researchers may apply for access to data through an application to the Research Service at Statistics Denmark and at the Danish Health Data Authority. Moreover, access to data from the Danish health data authorities requires approval from the Danish Data Protection Agency. The authors of this project do not have special access privileges to the data used in this study. The data that support the findings will be available from the Centre for Research in Patient Communication, University of Southern Denmark, but restrictions apply to the availability of these data, which were used under license for this study, and thus are not publicly available. Data available from the authors could be made available upon reasonable request and with permission of the University of Southern Denmark.

Conflicts of Interest

None declared.

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Abbreviations

EPR: electronic patient record
ForSa-P: Center for Forskning Sammen med Patienter og Pårørende (Center for Research Together with Patients and Relatives)
OUH: Odense University Hospital

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Protocol

Transcranial Magnetic Stimulation for Reducing the Relative Reinforcing Value of Food in Adult Patients With Obesity Pursuing Metabolic and Bariatric Surgery: Protocol for a Pilot, Within-Participants, Sham-Controlled Trial

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Abstract

Background: Metabolic and bariatric surgery (MBS) is the most effective and durable obesity treatment. However, there is heterogeneity in weight outcomes, which is partially attributed to variability in appetite and eating regulation. Patients with a strong desire to eat in response to the reward of palatable foods are more likely to overeat and experience suboptimal outcomes. This subgroup, classified as at risk, may benefit from repetitive transcranial magnetic stimulation (rTMS), a noninvasive brain stimulation technique that shows promise for reducing cravings and consumption of addictive drugs and food; no study has evaluated how rTMS affects the reinforcing value of food and brain reward processing in the context of MBS.

Objective: The goal of the *Transcranial Magnetic Stimulation to Reduce the Relative Reinforcing Value of Food (RESTRAIN)* study is to perform an initial rTMS test on the relative reinforcing value (RRV) of food (the reinforcing value of palatable food compared with money) among adult patients who are pursuing MBS and report high food reinforcement. Using a within-participants sham-controlled crossover design, we will compare the active and sham rTMS conditions on pre- to posttest changes in the RRV of food (primary objective) and the neural modulation of reward, measured via electroencephalography (EEG; secondary objective). We hypothesize that participants will show larger decreases in food reinforcement and increases in brain reward processing after active versus sham rTMS.

Methods: Participants (n=10) will attend 2 study sessions separated by a washout period. They will be randomized to active rTMS on 1 day and sham rTMS on the other day using a counterbalanced schedule. For both sessions, participants will arrive fasted in the morning and consume a standardized breakfast before being assessed on the RRV of food and reward tasks via EEG before and after rTMS of the left dorsolateral prefrontal cortex.

Results: Recruitment and data collection began in December 2022. As of October 2023, overall, 52 patients have been screened; 36 (69%) screened eligible, and 17 (47%) were enrolled. Of these 17 patients, 3 (18%) were excluded before rTMS, 5 (29%) withdrew, 4 (24%) are in the process of completing the protocol, and 5 (29%) completed the protocol.

Conclusions: The RESTRAIN study is the first to test whether rTMS can target neural reward circuits to reduce behavioral (RRV) and neural (EEG) measures of food reward in patients who are pursuing MBS. If successful, the results would provide a rationale for a fully powered trial to examine whether rTMS-related changes in food reinforcement translate into healthier eating patterns and improved MBS outcomes. If the results do not support our hypotheses, we will continue this line of research to

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evaluate whether additional rTMS sessions and pulses as well as different stimulation locations produce clinically meaningful changes in food reinforcement.

Trial Registration: ClinicalTrials.gov NCT05522803; https://clinicaltrials.gov/study/NCT05522803

International Registered Report Identifier (IRRID): DERR1-10.2196/50714

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KEYWORDS

obesity; repetitive transcranial magnetic stimulation; food reinforcement; hedonic hunger; electroencephalography; metabolic and bariatric surgery

Introduction

Background

Metabolic and bariatric surgery (MBS) is currently the most effective long-term treatment for obesity and its comorbidities [1-3]. However, there is substantial individual variability in the magnitude and durability of these outcomes, and patients who adopt and sustain healthier behaviors achieve better outcomes [3,4]. As a proximal behavioral driver of initial weight loss is reduced energy intake [5-7], there is a need to understand the mechanisms that can be targeted to promote healthier eating behaviors for improved MBS outcomes.

Food reinforcement is an important determinant of energy intake in the context of obesity and MBS [5,8]. Food is a potent primary reinforcer that motivates the initiation of eating [8,9]. By consuming a variety of foods, people learn which foods are pleasant and develop preferences influenced by the sensory qualities of these foods (eg, smell and taste) [8,9]. Eating preferred foods activates brain reward pathways and the release of dopamine that, over time via conditioning processes, promote greater wanting and intake of these foods in the absence of physiological hunger [8-15]. Thus, foods with higher reinforcing value are likely to be consumed more frequently and in greater quantities than foods with low reinforcing value.

Given that foods with higher reinforcing value also tend to be palatable and calorie dense, it is not surprising that higher food reinforcement is related to higher energy intake and obesity [8,16-23]. The reinforcing value of a food can be determined by how much work a person will do (or the number of responses they will make) to access that food [8,18]. The food reinforcer is provided on a progressive-ratio work schedule such that after a person earns a portion of the food, it becomes much more difficult to access the next portion. To better mirror eating in daily life, which involves making choices about whether, what, and how much to eat, the reinforcing value of food can be assessed by providing a choice to work for either a portion of a specified food or an alternative reinforcer such as money (ie, the relative reinforcing value [RRV] of food). The point at which a person makes the choice to switch from working for food to working for money serves as an index of the reinforcing value of food [8,18]. Research using RRV measures has found that people with obesity work harder for food and find food more reinforcing than nonfood alternatives compared with those who have a healthy weight [8,16,18-23]; higher food reinforcement predicts obesity severity and weight gain [8,16,18-24], and the relationship between food reinforcement and obesity is mediated by energy intake [25], suggesting that high food reinforcement leads to excess weight via energy intake.

Reduction in food reinforcement seems to be one of the ways in which MBS effects changes in energy intake [5,26,27]. MBS-induced anatomical and metabolic alterations are hypothesized to reset how rewarding food stimuli in the mesolimbic dopamine system are processed, leading to reduced hedonic hunger (eating for pleasure in the absence of physiological hunger) and related eating behaviors [14,26,28-30]. Support for this hypothesis is derived from studies showing postoperative reductions in questionnaire-based measures of food-seeking behavior and appetite for highly palatable foods as well as from progressive-ratio behavioral tasks of the reinforcing value of sweet and fat candy [27,31,32]. Furthermore, neuroimaging research shows the postsurgical normalization of obesity-induced alterations in brain reward regions (ie, caudate nucleus, putamen, nucleus accumbens, pallidum, and amygdala), improvements in overall functional connectivity, and increased activation of executive regions (ie, dorsolateral prefrontal cortex and ventral anterior cingulate cortex) during response inhibition to high-caloric food [14,28,33].

However, the MBS modulation of the mechanisms that influence food reinforcement is variable, with some patients being more resistant to these effects than others [34,35]. A characteristic of this *resistant* phenotype is greater hedonic hunger and susceptibility to overeating [31,35]. Moreover, changes in food reinforcement seem to be only temporary, with the re-emergence of unhealthy eating behaviors typically occurring approximately 2 years (but as early as 6 mo) after MBS [28,29,36,37]. Thus, strategies are needed that can directly target the neural mechanisms of food reinforcement, ideally before MBS, to prevent suboptimal outcomes.

Noninvasive brain stimulation interventions, such as repetitive transcranial magnetic stimulation (rTMS), are increasingly used to target dysregulated brain reward circuitry in individuals who have substance use disorders (SUDs) and in those who are prone to overeating [14,38-44]. rTMS exerts its neuromodulatory influence via electromagnetic coils that generate repetitive magnetic impulses to induce small electrical currents within a focal area in the superficial brain tissue below the scalp directly under the rTMS coil [43]. The main neural target of rTMS treatment for SUDs and overeating is the left dorsolateral prefrontal cortex (l-dlPFC), which drives mesolimbic dopaminergic regions to initiate motivated behavior [14,43,45]. In both SUDs and dysregulated eating, the l-dlPFC is

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hypoactive, contributing to heightened sensitivity to the reinforcing properties of substances and food and the failure of inhibitory control systems to resist temptation to consume them [14,43,45]. The application of excitatory rTMS to the l-dlPFC can upregulate neuronal excitability and alter synaptic plasticity to promote the lowering of the threshold of engagement of this region during exposure to drug and food reinforcers [38-45]. rTMS at this location could affect inhibitory control processes (ie, *top-down* mechanisms) or reward processes (ie, *bottom-up* mechanisms) because the l-dlPFC has structural connections to reward regions such as the dorsal and ventral striata [46]. These neuromodulatory changes, in the context of food reinforcement, could reduce motivated responding to food reinforcers and enhance eating regulation [43,44]. This empirical question has yet to be addressed.

Although a growing number of studies suggest that rTMS can be effective for reducing food cravings (ie, intense desire for a specific food), including among individuals with obesity [43,44], no study to our knowledge has directly examined the effects of rTMS on motivation to obtain a specific food that is reinforcing [8]. Unlike food craving measures, the reinforcing value of food directly measures motivation to eat and eating behavior by assessing how much work a person will do to obtain access to a palatable food. Furthermore, because the natural environment involves making choices between competing food and nonfood reinforcers, it is important to assess not only how much work a person will do to obtain a food but also how they choose to allocate work between reinforcing food and nonfood options [8].

Objectives

Despite the potential benefit of rTMS for patients undergoing MBS, especially those who find food highly reinforcing and are at greater risk for overeating, no study has used rTMS in this clinical context. Thus, the *Transcranial Magnetic Stimulation to Reduce the Relative Reinforcing Value of Food (RESTRAIN)* study is the first to pilot-test the effects of excitatory rTMS applied to the l-dlPFC on food reinforcement using a validated RRV behavioral choice paradigm among patients who are pursuing MBS and have high levels of hedonic hunger. The aims are to compare the effects of active and sham rTMS on changes in the RRV of food via the behavioral choice task and the neuromodulation of reward via electroencephalography (EEG).

Methods

Ethical Considerations

The research and ethics described in this study have been reviewed and approved by the institutional review board (IRB) of Hartford Hospital (HHC-IRB 035431). The study protocol is registered at ClinicalTrials.gov (NCT05522803). All participants provide written informed consent after a thorough review of procedures and questions and are informed of their opportunity to opt out of the study at any time. All study data are deidentified. Participants are compensated at an hourly rate of US $20 for time spent in the laboratory and have the opportunity to earn an additional US $120 bonus for completing all study procedures.

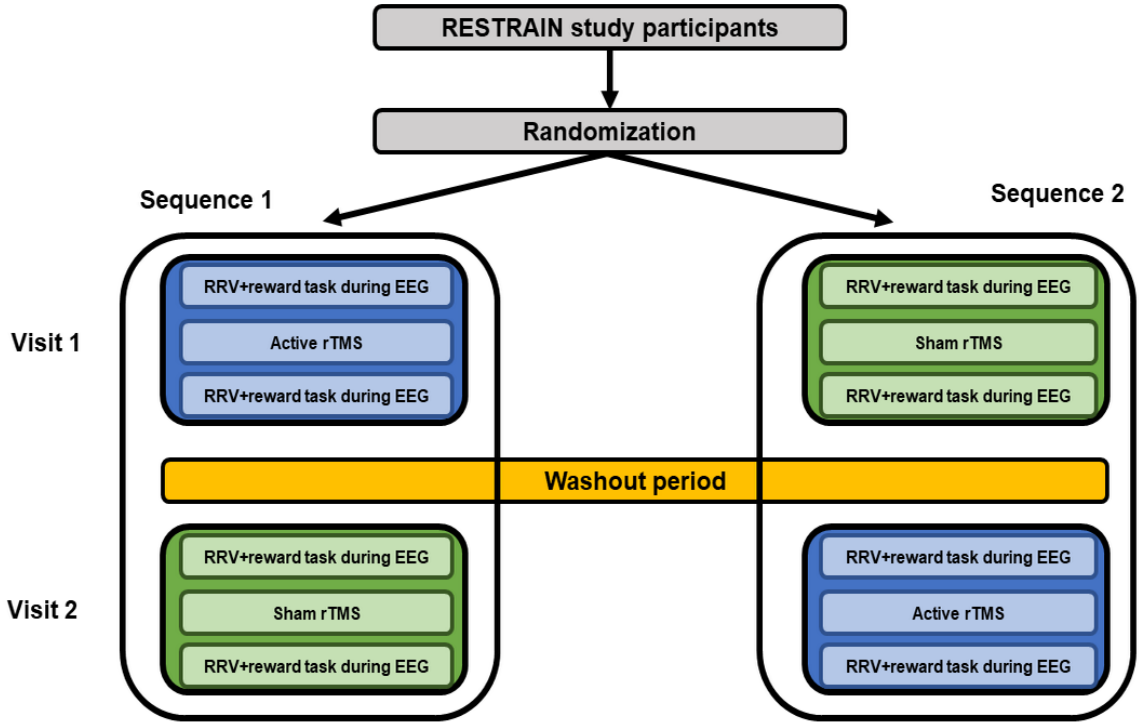
Design and Procedure Overview

A single-blind, within-participants, sham-controlled study is being conducted to perform an initial test of rTMS on the RRV of food, using a behavioral choice paradigm, and the neural modulation of reward, using an EEG (Figure 1).

Participants will attend 2 study visits that are separated by a washout period of at least 1 week (up to 4 weeks). Participants will receive active rTMS on 1 day and sham rTMS on the other day using a randomized and counterbalanced schedule. Participants will arrive at the laboratory fasted by 8 AM where they are asked to provide a urine sample for drug and pregnancy screening, complete an alcohol breath test, have their height and weight measured, and consume a standardized breakfast. During breakfast, participants will complete demographic, health history, and clinical behavioral and psychological questionnaires. After consuming breakfast, participants will complete a small sampling of 4 different palatable snack foods to determine which food will be used for the RRV measure for both study days. Participants will then complete the RRV measure and a reward task while an EEG is collected before rTMS (pre-rTMS EEG), receive rTMS, and complete the RRV measure and reward task again while an EEG is collected after rTMS (post-rTMS EEG). These procedures will allow for the comparison of pre- to posttest changes in the behavioral (RRV) and neural (EEG) modulations of reward between the active and sham rTMS conditions. Study procedures will be identical across study visits and conditions, except for certain baseline measures on the first day and the within-participant manipulation of active versus sham rTMS administration. A telephone follow-up to assess post-rTMS symptoms will be scheduled after the completion of each visit.

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Figure 1. The Transcranial Magnetic Stimulation to Reduce the Relative Reinforcing Value of Food (RESTRAIN) study design. EEG: electroencephalography; RRV: relative reinforcing value; rTMS: repetitive transcranial magnetic stimulation.



Participants

Adults pursuing a primary MBS procedure at the Hartford Hospital surgical and medical weight loss center who are aged 18 to 60 years, are able to give valid informed consent in English, are without cognitive impairment, fulfill clinical criteria regarding hedonic hunger, meet safety criteria for an EEG and rTMS, and habitually consume breakfast within 3 hours of waking up will be eligible to participate in this study.

Patients will be ineligible if they have a history of neurological disorders that would increase seizure risk from rTMS (eg, stroke, previous neurosurgery, and head trauma resulting in a significant loss of consciousness); a first-degree family history of epilepsy, schizophrenia, bipolar disorder, or neurological disorders with a potentially hereditary basis that affect rTMS safety or EEG measures; cardiac pacemakers, neural stimulators, implantable defibrillator, implanted medication pumps or sensors, intracardiac lines, or acute and unstable cardiac disease, with intracranial implants (eg, aneurysm clips, shunts, and electrodes) or other metal objects in the body; current use of any investigational drug with anti- or proconvulsive action or medications with psychotropic effects (eg, benzodiazepines) for a disease that is not currently stabilized or with disease symptoms present; a lifetime history of schizophrenia, bipolar disorder, mania, or hypomania; a history of myocardial infarction, angina, congestive heart failure, cardiomyopathy, stroke, or transient ischemic attack; participation in any rTMS sessions ≤2 weeks before enrollment; current pregnancy; a history of self-reported hypoglycemia owing to diabetes in the last 3 months; and allergies to foods that are provided during the research visits.

Screening, Recruitment, and Enrollment

Patients pursuing MBS will be recruited from the Hartford Hospital surgical weight loss center during the initial consultation visit for bariatric surgery. First, patients will receive an explanation of the study concept and a flyer from the surgeon during an office visit. Patients who are interested in being contacted by research staff for the study are asked to sign their name on the flyer and provided with a QR code to complete web-based screening questionnaires (refer to the following paragraphs). Patients will have the option of completing the screening questionnaires via REDCap (Research Electronic Data Capture; Vanderbilt University) at home on their own devices or over the telephone with a trained research assistant.

The screening measures that will be used to determine initial study eligibility are as follows:

1. *Power of Food Scale* (PFS) [47-49]: the PFS consists of 15 items, rated on a 5-point Likert scale, that assess preoccupation with an enhanced motivation to obtain and consume highly palatable foods across three separate but related domains—(1) food available, which assesses general thoughts about food; (2) food present, which assesses attraction to food that is directly available to a person; and (3) food tasted, which assesses desire for, and pleasure derived from, food when first tasted. PFS total and subscale scores are calculated by summing the item scores and dividing by the number of items. Higher PFS total scores relate to a higher drive to consume palatable foods. The PFS total score has good test-retest reliability, is internally consistent, is not affected by hunger states (consistent with the hedonic hunger construct), and is related to higher responsivity to food cues [47-50]. Given that there is no

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threshold to determine *high* PFS scores, we identify patients with high hedonic hunger levels as those who score ≥1 SD above the mean PFS total score (2.57, SD 0.45) obtained from a previous study involving a large clinical population of patients with obesity [48]. Thus, only patients who have a PFS total score of ≥3.00 are deemed initially eligible to participate.

2. *rTMS safety and appropriateness*: patients will be administered a questionnaire that the study team has previously used in clinical trials.
3. *Habit of eating breakfast*: patients will answer a question regarding whether they have a habit of eating breakfast in the morning within 3 hours of waking.
4. *Contact preference*: patients will indicate their preferred method of being contacted and provide permission to the research team to send the informed consent and Health Insurance Portability and Accountability Act (HIPAA) forms to their personal email account.

After patients complete the screening form, they will be contacted by the research assistant who will inform them of their eligibility, provide a short description of the study and answer any questions, confirm that they have no allergies to foods provided during the study visits, and schedule a remote verbal informed consent session using a hospital-approved Zoom (Zoom Video Communications, Inc) account.

The remote informed consent session will be conducted with the study research assistant, the patient, and a neutral witness who is not involved with the study. During the session, the research assistant will review the informed consent form with the patient in REDCap. If the patient is willing to participate, they will provide their verbal consent, which is documented on a progress note by the research assistant and the neutral third party. The research assistant and neutral third party will both sign hard copies of the informed consent and HIPAA forms. The patient will then be scheduled for their first study visit. When the patient arrives at the research center for this study visit, they will be asked to sign a hard copy of the informed consent and HIPAA documents.

Study Visits

Each participant will attend 2 study visits (each approximately 7 hours in duration) that are separated by a washout period of at least 1 week (up to 4 weeks). Participants will arrive at the research center between 7 AM and 8 AM after an overnight fast with no food or drink after midnight. Participants will undergo height and weight measurement, provide a urine sample (for drug or pregnancy screening), and consume a standardized breakfast (choice of 3 flavors of a soft-baked breakfast bar with gluten-free options, 2 flavors of yogurt, and orange or apple juice) that is equivalent to 12% of daily caloric needs based on weight and age. Both the standardized breakfast, which is consumed before the first RRV measurement, and the standardized snack (also providing 12% of daily caloric needs), which is consumed before the second RRV measurement, will be provided to diminish the potential influence of physiological hunger or food deprivation and the palatability of foods consumed on food reinforcement measured via the RRV measure [8,51]. During breakfast, participants will complete questionnaires, including the PFS, the Three-Factor Eating Questionnaire [52] (this measure assesses 3 aspects of eating behavior: cognitive restraint [tendency to consciously restrict or control food intake], disinhibition [tendency to overeat in the presence of palatable foods or other disinhibiting stimuli], and hunger [susceptibility to feelings of hunger]), the Food Craving Inventory [53] (this measure assesses subjective food cravings and the consumption of particular foods), Daily Activity Behaviors Questionnaire [54] (this measure assesses time spent in sleep, sedentary behaviors, and physical activity in the past 7 days), rTMS safety screen (this measure assesses the appropriateness of administering rTMS) [55], Patient Health Questionnaire-9 [56] (this measure assesses the severity of depression symptoms over the past 2 weeks), Adult ADHD Self-Report Scale [57] (this measure assesses symptoms related to attention-deficit/hyperactivity disorder), Edinburgh Handedness Inventory [58] (this measure assesses dominant handedness), and the Wide Range Achievement Test-4 [59] (this measure assesses fundamental reading, spelling, and math skills).

After completing the questionnaires, participants will be asked to sample 4 different palatable snack foods (ie, Doritos nacho cheese–flavored tortilla chips [Frito Lay], Lay's original potato chips [Frito Lay], Twix candy bars [Mars, Incorporated], and Chips Ahoy chocolate chip cookies [Mondelez International]) and rank their liking of each on a 100-mm visual analog scale anchored by *dislike very much* and *like very much* at either end. The food that participants rate as their most liked will be used for the RRV measure [60] at both study visits. After food sampling, participants will indicate their current levels of hunger and fullness using visual analog scales before being prepared for EEG procedures and completing the RRV measures and another reward task during the EEG procedure. Participants will consume a snack before undergoing rTMS to limit the potential effects of physiological hunger. After rTMS, they will complete the RRV and reward measures while an EEG is collected (RRV and reward measures as well as EEG and rTMS procedures are described in the following subsections). Participants will then be debriefed and monitored for any side effects, scheduled for their second study visit, compensated for their time, and discharged. After the washout period, participants return to the research center for their second visit. The washout period, identical testing procedures and environments, and counterbalancing procedures are intended to cancel out any carryover effects within the active and sham rTMS conditions. Procedures completed during the first study visit will be extended to the second study visit with the exception of randomization, height measurement, food sampling, and the completion of questionnaires used to determine study eligibility (ie, Patient Health Questionnaire-9, Wide Range Achievement Test-4, Adult ADHD Self-Report Scale, and Edinburgh Handedness Inventory). At the end of study visit 2, a brief rTMS blind assessment will be performed where the participant will be asked whether the rTMS session that day was active or sham. The participant will be asked to rate how confident they are in their choice on a scale ranging from 0 (*not at all confident*) to 10 (*very confident*).

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Primary and Secondary Outcome Measures

RRV of Food

The RRV of food will be measured by a validated behavioral choice questionnaire that asks participants to make a choice between receiving the food they rated as their most liked (ie, nacho cheese–flavored tortilla chips, original potato chips, candy bars, or chocolate chip cookies) and receiving money [60]. To determine how reinforcing food is in comparison with money, the behavioral choice questionnaire provides participants with 16 different choices, in which they make a choice between receiving the most liked food (100 kcal serving) and receiving the money (US $0.25). Each choice—food or money—is associated with a different number of button presses (using a tally clicker) required to gain access to the choice. Each of the 16 choices on the questionnaire requires the same number of button presses (ie, 20) for the money, whereas the number of button presses for the food increases with each choice. Choice 1 begins with 20 button presses for either the money or the food. The number of button presses required to receive the food increases in 20 response increments for choices 2 through 16. Thus, by choice 16, participants could have access to the food if they are willing to make 320 presses or receive the money for 20 presses. Participants will select whether they want money or food for choices 1 through 16. To produce valid responses, participants will be informed that they will be performing one of their choices by choosing 1 of 16 numbers from a hat, with the numbers representing the choice from the questionnaire (eg, if a participant randomly selects number 6, the participant will carry out the decision made for choice 6, which is either 120 button presses for the most liked food or 20 button presses for the money). After participants complete the number of button presses associated with the choice drawn, they will receive their choice (food or money). The reinforcing value of food is scored as the choice (1-16) when money is chosen instead of food. The higher the number associated with the choice of money, the higher the RRV of food. This measure has been shown to be valid and reliable for assessing the RRV of food [60].

Reward Task

Participants complete a version of the task described by Gehring and Willoughby [61] in which they choose between 2 monetary options (target stimuli) on each trial and then receive feedback indicating whether the choice resulted in winning or losing money on that trial. In this task, the target stimuli are 2 adjacent squares, each enclosing a number (5 or 25) representing a monetary value (in US cents). These stimuli remain on the screen until a choice is made between the left and right squares. Feedback stimuli follow the choice indicating the outcome of the participant's decision, that is, the chosen box turns either red or green to signify either a win or a loss (with red or green as the winning color counterbalanced across participants), and the unchosen box turns the other color (either green or red) to indicate what the outcome of the trial would have been had that box been chosen. The feedback stimulus appears for 1000 milliseconds, followed by a blank screen for 1500 milliseconds preceding the onset of the next trial. All 4 possible combinations of 5 and 25, (ie, 5-5, 5-25, 25-5, and 25-25) are evenly crossed with the 4 possible win or loss outcomes (ie, win-win, win-loss, loss-win, and loss-loss), resulting in 16 trial types; thus, although the participant's choice produces a designated outcome on each trial, signaled by the feedback, outcomes on future trials are not predictable from outcomes associated with prior choices (analogous to a roulette wheel or slot machine). Two sets of these 16 trial types, ordered randomly, are included in each block. Upon completion of a block, participants will receive feedback about their win or loss ratio within that block. The feedback received by the participant will elicit both a feedback-related negativity (FRN) and a reward positivity (RewP) when coupled with an EEG. The amplitude of the FRN largely indexes the relative loss presented in the feedback (ie, FRN amplitude is greater for trials where the participant loses 5 when the alternative was to gain 25 compared with losing 5 when the alternative was to gain 5). The amplitude of the RewP indexes the relative gain (ie, reward) presented in the feedback (ie, the RewP amplitude is greater in trials where the participant gains 25 when the alternative was to lose 25 compared with gaining 25 when the alternative was to lose 5). Extracting the underlying FRN theta (3-9 Hz) and RewP delta (<3 Hz) time-frequency power better measures these processes than amplitude alone.

EEG and rTMS Procedures

EEG Collection

For the EEG collection, participants are fitted with an elastic cap with embedded electrodes. These electrodes, once they are filled with gel, passively measure electrical brain signals during tasks at a very high resolution (5000 Hz). This high temporal resolution is the key advantage of an EEG as a measure, which produces robust and reliable brain measures across clinical populations. Measures will be collected using a BrainAmp MR Plus 64-channel electrode system (Brain Products GmbH) following standard manufacturer procedures. During data collection, participants will be seated in a comfortable chair 60 cm from the computer screen with access to a button-response box to perform the reward task.

rTMS Sessions

The rTMS sessions will be administered using a MagPro X100 including MagOption (MagVenture, Inc) stimulator equipped with a figure-eight coil. All sessions will be completed in the same laboratory that contains the EEG system used in this study [62]. During the rTMS sessions, participants will be seated comfortably in a chair and place their head on a chin rest for stabilization. Reducing head movement is essential for accurately placing and holding the rTMS coil during rTMS applications. Two separate coils that are similar in appearance and acoustic properties are available. One active unblinded coil will be used to determine the resting motor threshold (RMT); the other coil will be blinded (1 side active and 1 side sham) and used to deliver rTMS. The coils are calibrated quarterly against one another to ensure comparable output. Participants will be monitored throughout the study via staff interactions and a monitoring questionnaire assessing typical rTMS side effects (eg, headache).

After the scalp position closest to the motor representation (ie, the *motor hot spot*) is found, the RMT at this location will be

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determined. Using repeated single pulses, the coil will be moved to determine the optimal scalp position for producing visible contralateral movement in the first dorsal interosseous in the right hand. Pulses over this motor cortex location will be administered to identify the RMT using parameter estimation by sequential testing software [63]. The hot spot located during the initial rTMS session (study visit 1) will be saved in the neuronavigation system (Localite GmbH) and verified at the subsequent session (study visit 2), whereas the RMT will be measured from the hot spot at every session. In accordance with manufacturer instructions and accepted standards, hand motor cortex will be stimulated to obtain the RMT [64-66]. As the l-dlPFC is the target, the left hemisphere (right hand) will be used to determine the RMT.

The l-dlPFC will be targeted using the neuronavigation system (Localite GmbH) Montreal Neurological Institute coordinates (−50, 30, 36) thought to modulate the circuit implicated in reward processing. Over 2 sessions, participants will receive excitatory and sham rTMS sessions once in a single-blind fashion. Excitatory rTMS will consist of intermittent theta-burst stimulation parameters that include 3 pulses given at 50 Hz repeated every 200 milliseconds for a 2-second duration followed by 8 seconds of no stimulation. This sequence will be repeated for a total of 20 cycles, lasts 192 seconds, and delivers 600 pulses [67]. Magnetic field intensity will be set at medium intensity, gradually increasing to the goal of 100% of the participant's measured daily RMT.

The coil will be set accordingly (active vs sham) for each study day with the order counterbalanced within participant. The blinded coil has 2 sides that can be placed on the participant's head: 1 side active and 1 side sham (with shielding). These sides look identical to the research staff and the participant, but rTMS pulses are delivered only from the active side. The sham side of the coil is designed to mimic the auditory feedback and scalp pressure evoked by the active side of the coil. The MagVenture system also includes electrodes to be placed on the scalp, near the rTMS stimulation target. This scalp stimulation from the electrodes mimics rTMS administration (ie, causes similar discomfort) but does not modulate brain circuits as rTMS does, thus increasing the likelihood of maintaining the blind without affecting neural signals. The MagVenture sham system is the best commercially available system and can effectively mimic the discomfort of an active rTMS session. To avoid placebo effects, it will be emphasized to the participants that the sensation they feel is related to the stimulation of scalp nerves and muscles and that brain stimulation itself cannot be felt. Such procedures are effective in establishing these sham procedures [68]. Although the aforementioned efforts are taken to preserve the blind, it is possible that the participant will become unblinded to the condition during the study; therefore, a questionnaire assessing the blind and the pain felt will be administered to participants at the end of the study.

rTMS Safety Considerations

Although the anticipated risks and adverse events of rTMS are mostly low or minimal, life support equipment will be made available near the laboratory. All study team members who operate the MagVenture machine will have standard training for procedures, including training in rTMS device operation, supervised repeated practice in rTMS procedures, and testing for interrater reliability in RMT determination.

The rTMS monitoring questionnaire administration, staff observation, and interactions with participants will occur daily. If immediate medical intervention is required, the participant will be referred to an appropriate medical facility; an ambulance may be called as needed. Information on all adverse events will be recorded and reported to the IRB with each continuing review application. Unexpected or serious adverse events will be promptly reported to the IRB. Standard seizure monitoring procedures will be in place [69], and video recordings will be collected during rTMS sessions to help evaluate the session as needed for training or a review of adverse events. In the event a participant reports an rTMS-related symptom (most often, headache), the physician on the protocol will be consulted. If deemed necessary by the physician, a single dose of acetaminophen will be administered.

Statistical Analysis Plan

The statistical analysis will be conducted using Stata 18 (StataCorp LLC). All continuous measures will first be assessed for their distribution characteristics through the use of Shapiro-Wilk tests and the construction of histograms to determine whether assumptions are met for parametric analysis; if not, nonparametric alternatives will be used. Baseline clinical and demographic characteristics of participants will be assessed using descriptive statistical measures of central tendency and dispersion: means and SDs for those variables meeting assumptions for parametric analysis and medians, range, and IQRs for those not meeting assumptions. The primary outcome of changes in RRV (scores after rTMS−scores before rTMS) for both the active and sham conditions will be computed. Tests comparing the pre-post differences for the active and sham rTMS sessions will be conducted using 2-tailed paired *t* tests (if distributions are normal) or Wilcoxon signed rank tests if the assumptions of distribution are not met).

The EEG data, once collected, will be imported into the MATLAB platform (The MathWorks, Inc) for processing. Data will be filtered offline at 0.1 to 30 Hz and epoched (1000 ms before feedback to 2000 ms after feedback) to capture the FRN and RewP time windows and allow for time-frequency analyses (ie, reducing edge effects). Established preprocessing methods (eg, eye-blink correction, additional filtering, and bad-channel identification) will also be applied. Both theta (3-9 Hz) and delta (<3 Hz) power will be extracted and a principal component analysis applied. This data-driven approach helps separate meaningful segments of the time-frequency surface related to the FRN and RewP components. EEG data will be used to determine differences between active and sham rTMS on the neural modulation of reward [62,70,71]. Pearson and Spearman correlational coefficients will be used to evaluate the associations of clinical assessment measures with RRV and task-specific neural measures (eg, correlation between food craving scores and neural activation related to reward processing). We will control for any differences in hunger and fullness ratings before each RRV task in analyses examining changes in RRV.

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We do not anticipate any period effects (ie, when the outcome of interest changes with time irrespective of treatment effect) because the condition of the treatment is stable for both active and sham rTMS. Regarding carryover effects, we anticipate that the effect of a single session of rTMS will last no more than 24 hours (the washout period is >5 times the anticipated duration of effects).

Regarding participant and rTMS operator ratings of active versus sham rTMS, we will report descriptive data on the percentage of participants and operators who correctly identified the active condition. Such reporting on the success of blind manipulation is standard in the rTMS field.

Sample Size and Power Considerations

As this is an initial proof-of-concept pilot study, the sample size was based on guidelines for pilot studies and by practical considerations. Guidelines for an appropriate sample size for a 1-group pilot study suggest 10 to 12 participants [72,73]. Assuming 20% study attrition, we will enroll 12 patients to achieve an analyzable sample of 10 (83%) patients. The effect sizes found will be calculated and appropriate power calculations performed to determine the sample needed to fully power a subsequent study.

Results

Study recruitment began in December 2022. As of October 2023, a total of 52 patients have been recruited and screened, of whom 36 (69%) screened positive, and 17 (47%) were enrolled. Of these 17 patients, 3 (18%) withdrew before receiving rTMS, 5 (29%) withdrew after receiving rTMS, 4 (24%) are in the process of completing the protocol, and 5 (29%) completed the protocol. Analysis of data is planned for February 2024, with the manuscript expected to be submitted in April 2024.

Discussion

Principal Findings

Reduction in food reinforcement seems to be a principal way by which MBS lowers energy intake to promote weight loss and other health improvements [5,26,27]. However, the surgical modulation of the mechanisms that influence food reinforcement is variable, with some patients seeming to be more resistant to these effects than others [34,35]. This phenotype, characterized by high levels of hedonic hunger, can undermine MBS efficacy [31,35]. Patients pursuing MBS who demonstrate this high-risk eating phenotype may benefit from strategies that can directly target the neural mechanisms of food reinforcement.

This paper describes the protocol used in the RESTRAIN study. To our knowledge, this is the first study to perform an initial test of whether rTMS, a noninvasive procedure that delivers magnetic pulses to stimulate or inhibit nerve cells in the brain, can successfully target brain reward circuitry to diminish the reinforcing properties of food in patients pursuing MBS who are highly reinforced by food, more likely to overeat, and at risk for suboptimal surgical outcomes. Moreover, although previous studies have shown positive effects of rTMS on food cravings (ie, desire to consume a specific food) [44,45], this study is the first to directly examine the effects of rTMS on motivation to obtain and eat a well-liked food compared with a nonfood reinforcer using a validated behavioral choice task [8,60]. In addition, by measuring the acute rTMS-induced modulation of reward processing with EEG, this study has potential to provide novel insights into the neurobehavioral mechanisms of food reinforcement that can be targeted with rTMS and other interventions to improve eating regulation and weight outcomes after MBS as well as other obesity treatments. The data collected from this initial pilot trial will help determine the feasibility and acceptability of rTMS in patients pursuing MBS as well as an estimate of its effects on the RRV of food and EEG-measured reward processing. These data will be used to calculate the required sample size for a larger fully powered trial to test the effects of rTMS on eating regulation and relationships with weight change after MBS.

Limitations

Although the use of noninvasive brain stimulation techniques such as rTMS in the context of MBS is highly novel and potentially beneficial, some patients may not be open to rTMS and may prefer other treatment options (eg, psychotherapy and medications). Even if rTMS reduces food reinforcement, the scalability of rTMS for this purpose is not clear because rTMS can be costly and needs to be administered by highly trained operators. Although this study involves only 2 study visits to determine whether rTMS has an acute effect on food reinforcement, it is likely that a fuller course of treatment, such as that which has typically been recommended for treatment-resistant depression (ie, several d/wk for 4-6 wk) is required to produce durable changes [74]. Finally, there is a potential that the results do not support our hypotheses. In this event, the data collected will still be valuable in demonstrating the feasibility of conducting rTMS in patients pursuing MBS and provide a rationale for additional studies to determine whether there is an optimal number of rTMS sessions and pulses as well as stimulation locations that can yield clinically meaningful changes in food reinforcement within this patient population.

Conclusions

The RESTRAIN study is the first application of rTMS in MBS and the first study to use rTMS to target motivation to obtain food among people who have a strong drive to eat in response to the reward of palatable foods. Moreover, this study will measure the acute rTMS-induced modulation of brain reward processing with an EEG. If successful, the results would provide a rationale for a fully powered trial to test whether rTMS-related changes in food reinforcement translate into healthier eating patterns and improved weight and health outcomes after MBS. rTMS could potentially provide another treatment for patients who are experiencing suboptimal weight loss or significant weight regain owing to poor regulation of appetite and eating behavior.

If the results do not support our hypotheses, future studies will focus on whether it is possible to modify and refine rTMS to exert greater effects on food reinforcement and related outcomes.

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Acknowledgments

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Data Availability

Data generated or analyzed during the study will be included in the published articles and their supplementary information files. Individual participant data that underlie the results reported in future published articles will be made available, after deidentification, to investigators whose proposed use of the data has been approved by an independent review committee identified for this purpose.

Authors' Contributions

DSB and VRS are equal contributors in study conceptualization, design, execution, and evaluation. PKP, HAR, and CG made substantial contributions to the study concept and design. DSB and VRS wrote the manuscript, and all authors critically revised it and approved the final version.

Conflicts of Interest

DSB reports travel support from the International Federation for the Surgery of Obesity and Metabolic Disorders. All other authors declare no other conflicts of interest.

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Abbreviations

EEG: electroencephalography
FRN: feedback-related negativity
HIPAA: Health Insurance Portability and Accountability Act
IRB: institutional review board
l-dlPFC: left dorsolateral prefrontal cortex
MBS: metabolic and bariatric surgery
PFS: Power of Food Scale
REDCap: Research Electronic Data Capture
RESTRAIN: Transcranial Magnetic Stimulation to Reduce the Relative Reinforcing Value of Food
RewP: reward positivity
RMT: resting motor threshold
RRV: relative reinforcing value
rTMS: repetitive transcranial magnetic stimulation
SUD: substance use disorder

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Protocol

Effect of Electroacupuncture Versus Cognitive Behavioral Therapy for Perimenopausal Insomnia: Protocol for a Noninferiority Randomized Controlled Trial

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Abstract

Background: Perimenopausal insomnia (PMI) has a high global incidence, which is common in middle-aged women and is more severe than nonmenopausal insomnia. Effective treatments with fewer side effects and more consistent repeatable results are needed. Acupuncture, a therapy based on traditional Chinese medicine, is safe and may be effective for PMI. It is widely accepted in Western countries, and evidence supports the use of acupuncture as a main or supplementary therapy. Cognitive behavioral therapy is also used to improve sleep quality. It has structured sessions and has been recommended as a first-line treatment for insomnia (cognitive behavioral therapy for insomnia [CBT-I]) by the American Association of Physicians. However, few randomized controlled trials have been conducted to compare the effectiveness of these 2 therapies. This study will be performed in perimenopausal women with insomnia to determine the efficacy of electroacupuncture (EA) versus CBT-I.

Objective: This study aimed to compare the preliminary effectiveness and safety of EA and CBT-I for PMI through a randomized controlled noninferiority study design.

Methods: This study is designed as an assessor-blinded, noninferiority, randomized controlled trial. A total of 160 eligible participants with PMI will be randomly divided into 2 groups to receive either EA or CBT-I. Participants in the EA group will receive electroacupuncture for 8 weeks. The intervention will be delivered 3 times weekly for a total of 12 sessions and 2 times weekly for the next 4 weeks. Meanwhile, participants in the control group will undergo CBT-I (once a week) for 8 weeks. Treatment will use 7 main acupoints (GV20, DU24, EX-HN3, EX-HN18, EX-CA1, RN6, and RN4) and an extra 4 acupoints based on syndrome differentiation. The primary outcome is the Insomnia Severity Index. The secondary outcome measures are the Pittsburgh Sleep Quality Index; Menopause-Specific Quality of Life; Menopause Rating Scale; Hamilton Depression Scale; Hamilton Anxiety Scale; hot flash score; and the level of estradiol, follicle-stimulating hormone, and luteinizing hormone in serum. Sleep architecture will be assessed using polysomnograms.

Results: Participants are currently being recruited. The first participant was enrolled in January 2023, marking the initiation of the recruitment phase. The recruitment process is expected to continue until January 2025, at which point data collection will commence.

Conclusions: This trial represents a pioneering effort to investigate the efficacy and safety of EA and CBT-I as interventions for PMI. It is noteworthy that this study is conducted solely within a single center and involves Chinese participants, which is a

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limitation. Nonetheless, the findings of this study are expected to contribute valuable insights for clinicians engaged in the management of PMI.

Trial Registration: Chinese Clinical Trial Registry ChiCTR2300070981; https://www.chictr.org.cn/showprojEN.html?proj=194561

International Registered Report Identifier (IRRID): DERR1-10.2196/51767

(JMIR Res Protoc 2023;12:e51767) doi:10.2196/51767

KEYWORDS

perimenopausal insomnia; acupuncture; electroacupuncture; cognitive behavioral therapy; randomized controlled trial; CBT; sleep disorder; insomnia; perimenoupause; effectiveness

Introduction

Perimenopause is the period from the onset of menstrual irregularities to 1 year after amenorrhea has occurred and encompasses the physiological changes that occur before and after a woman stops menstruating [1]. During this period, women are prone to perimenopausal insomnia (PMI) due to fluctuations in estradiol, progesterone, and follicle-stimulating hormones that disrupt the central nervous control of the sleep-wake state [2]. The incidence of sleep disorders in perimenopausal women ranges from 43% to 48% [3], and in the United States, the incidence is 31% to 42% [4]. PMI seriously affects the quality of life and physical and mental health of perimenopausal women and is associated with the development of many diseases such as low immunity, diabetes, obesity, inflammation development, cardiovascular disease, mood disorders, cognitive dysfunction, and cancer [5-9].

In addition to PMI, perimenopausal syndromes are usually managed with menopausal hormone therapy (MHT) [10-12]. However, some patients are reluctant to choose MHT due to adverse effects [13], such as increasing the risk of uterine fibroids, breast cancer, and thrombosis [14,15]. The main reason for the increased incidence of breast cancer in patients taking hormones is related to the use of synthetic progestins such as dydrogesterone and 17α-hydroxyprogesterone derivatives in MHT regimens [16,17].

Cognitive behavioral therapy (CBT), as the first-line nonpharmacological treatment for insomnia, is an appropriate treatment for PMI without any concerns of drug-related side effects [18,19]. The focus is primarily on sleep problems, but CBT also targets stress, low mood, and vasomotor symptoms. Convincing effects of CBT for insomnia (CBT-I) in menopausal women have been found [20-22]. However, due to its limited availability in the community, the limitations of the psychological expertise of the operator, the high treatment costs, and the cognitive level of the patient, CBT has not been widely implemented in China [23]. It is, therefore, essential to develop treatment strategies to help patients manage PMI and improve their quality of life.

Acupuncture is widely practiced in the prevention and treatment of PMI [24] and is effective in the treatment of PMI and various sleep disorders through significantly reducing Pittsburgh Sleep Quality Index (PSQI) and Insomnia Severity Index (ISI) scores [25-27], improving sleep efficiency and overall nighttime sleep time in insomnia patients and reducing night-time wakefulness. Acupuncture is also a safe and effective treatment for perimenopausal depression with short- to medium-term efficacy [28].

Electroacupuncture (EA) therapy is a product of the combination of modern electrical stimulation and acupuncture therapy, with both stimulation effects, and can effectively and safely improve the sleep quality and quality of life of patients with PMI. Compared to CBT, EA is less expensive, simpler to administer, easier to promote, and has a high level of acceptability and enjoyment [29,30]. Despite the positive effects of EA on improving sleep, no studies have compared EA with CBT in women with PMI. We aimed to compare the effect of CBT-I versus EA for PMI and simultaneously evaluate the safety and acceptance of EA. We hypothesized that EA would not be inferior to CBT in patients with PMI.

Methods

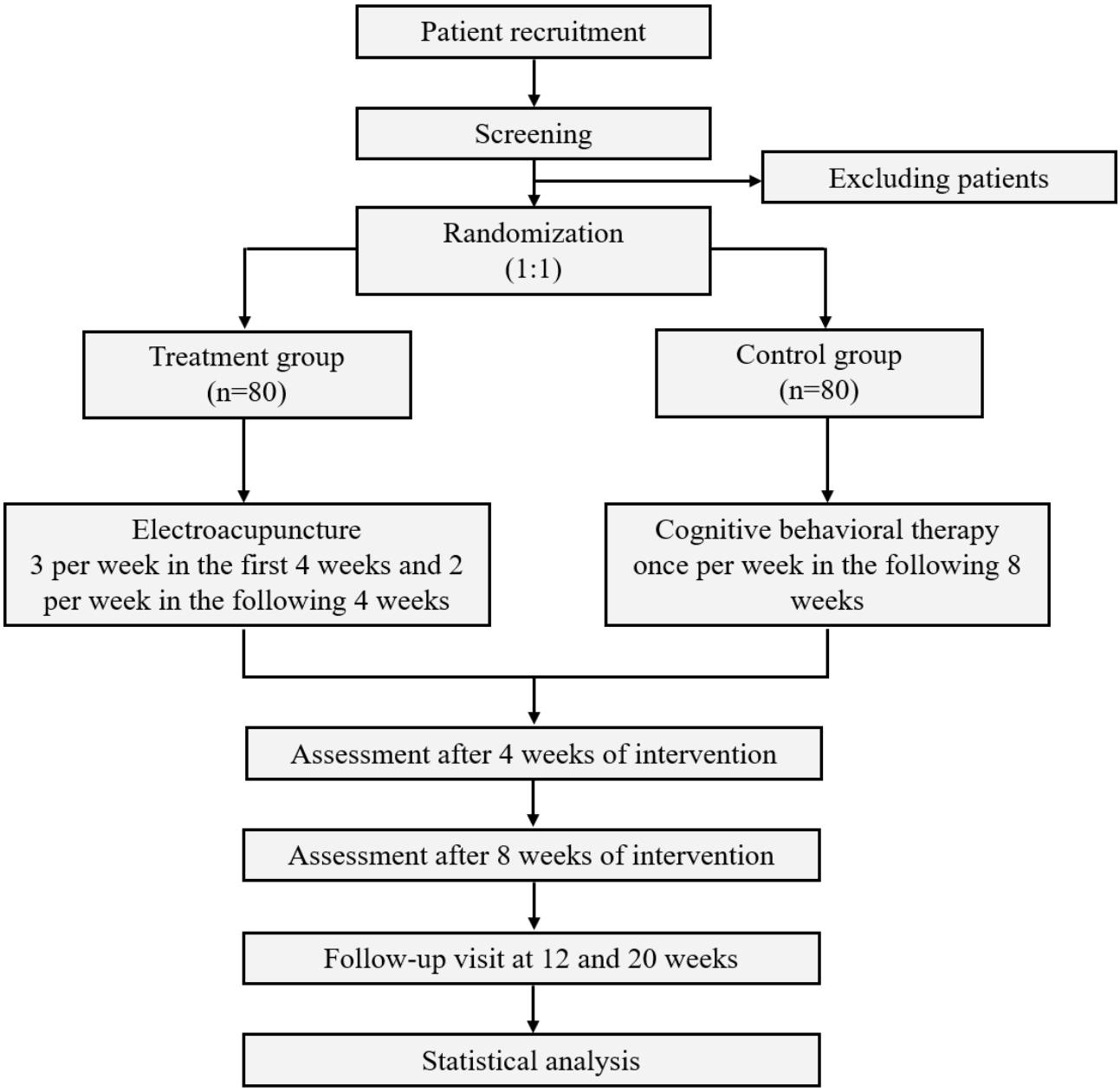
Study Design

This study is an assessor-blinded, randomized controlled trial. Participants will be randomized into the EA group or the control group in a 1:1 ratio. After the baseline assessment and informed consent has been obtained, a randomization number will be sent to the doctor. The statisticians and outcome assessors will be blinded to the allocation.

The duration of the trial is 21 weeks (Figure 1), including a 1-week baseline assessment period (weeks 0-1), an 8-week long treatment period (weeks 1-8), and a 12-week-long follow-up period (weeks 9-21) (Table 1). The trial will be conducted in accordance with the principles of the Declaration of Helsinki and has been approved by the ethics committee of the participating hospitals. The standard protocol items adhere to the Recommendations for Interventional Trials [31] and the checklist of SPIRIT (Standards for Reporting Interventions in Clinical Trials of Acupuncture) is presented in Multimedia Appendix 1).

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Figure 1. Flow diagram on the randomization of participants into the electroacupuncture and cognitive behavioral therapy groups.



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Table 1. Schedule of enrollment, interventions, and assessments for the electroacupuncture versus cognitive behavioral therapy study.

Schedule	Study period and time points (weeks)					
	Recruitment	Baseline	Treatment		Follow-up	
	1	0	4	8	12	20
Enrollment						
Eligibility screen	✓					
Informed consent form	✓					
Medical history	✓					
Allocation		✓				
Interventions						
Electroacupuncture	__[a]	__[a]	__[a]	__[a]	__[a]	__[a]
Cognitive behavioral therapy	__[b]	__[b]	__[b]	__[b]	__[b]	__[b]
Assessments						
Primary outcome						
ISI[c]		✓	✓	✓	✓	✓
Secondary outcomes						
MENQOL[d]		✓	✓	✓	✓	✓
PSQI[e]		✓		✓		
MRS[f]		✓		✓		
HAMA[g]		✓		✓		
HAMD[h]		✓		✓		
Hot flashes		✓		✓		
PSG[i]		✓		✓		
Serum sex hormone		✓		✓		
Others						
Adverse events			✓	✓	✓	✓
Patient compliance			✓	✓	✓	✓

[a]Patients in the treatment group will be treated with electroacupuncture for a total of 20 times.

[b]Patients in the control group will be treated with cognitive behavioral therapy for a total of 8 sessions.

[c]ISI: Insomnia Severity Index.

[d]MENQOL: Menopause-Specific Quality of Life.

[e]PSQI: Pittsburgh Sleep Quality Index.

[f]MRS: Menopause Rating Scale.

[g]HAMA: Hamilton Anxiety Scale.

[h]HAMD: Hamilton Depression Scale.

[i]PSG: polysomnograms.

Recruitment

This trial will be conducted at Yueyang Hospital of Integrated Traditional Chinese and Western Medicine affiliated with Shanghai University of Traditional Chinese Medicine from January 2023 to January 2025. In total, 160 participants will be recruited through posters, newspapers, and hospital websites. We will publish some advertisements in WeChat through the subscriptions of the acupuncture and gynecology departments. To reach the target sample size, lectures to publicize the project program will be given regularly.

Patients who sign up will initially be screened by phone and then asked to participate in a face-to-face interview to confirm whether they meet the criteria and to conduct further surveys. Written informed consent will be obtained before baseline outcome assessments and data collection.

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Participants

The sample size is based on the ISI. After 8 weeks of intervention, the mean ISI score baseline changes are approximately –7.7 (4.18) [21,32]. Assuming that the ISI score of the acupuncture group is slightly lower than that of the CBT group after 8 weeks of treatment, the ISI score should be no more than –2, with a noninferior effect threshold of –4 [33]—assuming that the single-side significant level is α=.025, power of the trial is 1 – β=.80, and the ratio between the EA group and the CBT-I group is 1:1. As calculated by PASS software (IBM Corp), each group requires 71 cases. Assuming that the dropout rate is 10%, the final sample size should be 160.

Eligible patients will be randomly assigned to either the EA or CBT-I group and will receive EA treatment or CBT-I consultation, respectively. The inclusion criteria are the International Classification of Sleep Disorders (Third Edition) criteria for insomnia disorder; women aged 40-60 years; according to STRAW+10 (Stages of Reproductive Aging Workshop + 10), signs of menopausal tendency that began to appear from clinical features, endocrinology, and biology until 1 year after final menopause; insomnia lasting for >3 months; total ISI score >14; and willingness to participate in the investigation and provide written informed consent prior to the trial.

The exclusion criteria are the use of menopause hormone therapy and sedative or antianxiety drugs; nonnatural menopause (due to surgery, radiation, and medication); any diseases that cause sleep disturbance; unknown causes of vaginal hemorrhage; diagnosis of mental disorders or any serious physical illness; receipt of CBT or acupuncture for insomnia; participation in any other clinical trial within the last 6 months; and pregnancy or lactation.

Randomization and Blinding

This study uses a randomized block design. Individual random numbers will be generated with SAS (version 9.4; SAS Institute). The random table is reproducible, and the random seeds will be recorded in the file. A researcher who will not interact with the participants during the recruitment or interventions will take charge of using sealed opaque envelopes to keep the randomized allocation sequence. The trial is designed to be open-ended, but the evaluators will be blinded to patient group assignments. The therapists who administer the treatment are not involved in the evaluation of the trial.

Control Design

An EA (treatment) group and a CBT (control) group will be set up. Parallel controls will be performed between the 2 groups. The CBT group will undergo first-line treatment recommended by the guidelines, and this study has a noninferiority design. The purpose of this clinical study will be achieved by comparisons with first-line therapy.

Interventions

The acupuncturist and psychologist have qualifications and 10 years of clinical work experience. All study participants will receive 7 days of training prior to the trial to familiarize them with the process. The therapist will send a message from a phone account assigned to the study to confirm the session 1 day in advance.

Treatment

Treatment group participants will receive acupuncture treatment from the same acupuncturist. The temperature of the treatment room will not be lower than 25 °C. Patients in the EA group will be treated with 0.25×25 mm and 0.25×40 mm disposable steel needles (Guizhou Andi Medical Instrument Co, Ltd).

Patients will be positioned supine after local skin disinfection with 75% alcohol wipes. The acupuncturist will insert needles into the GV20 (Baihui), DU24 (Shenting), EX-HN3 (Yintang), EX-HN18 (Anmian), EX-CA1 (Zigong), RN6 (Qihai), and RN4 (Guanyuan) acupoints as per the WHO Standard Acupuncture Point Locations [34]. KI3 (Taixi), KI7 (Fuliu), HT7 (Shenmen), and SP6 (Sanyinjiao) may also be used accordingly. KI3 and KI7 may be used for hot flashes; HT7 and SP6 are used for anxiety and depression. The needle is inserted with the double hand-needle insertion technique at a depth adjusted based on the standard permissible depth of insertion for each acupoint. The needle is then twirled, rotated, lifted, and thrust moderately until achieving the *deqi* sensation.

An electric stimulator will be placed on the pair of GV20 and EX-HN3 points with a continuous wave, 2.5 Hz, and 4-5 mA, for 30 minutes in each session. The other needles are retained for 30 minutes and manipulated for 10 seconds, twice every 10 minutes, with intermittent stimulation.

The needles will be removed with clean cotton balls to avoid bleeding. Each patient will receive 20 sessions over 8 weeks as follows: 3 per week in the first 4 weeks, every 2 days, with a 1-day interval; and 2 per week in the following 4 weeks, every 3 days, with a 2-day interval.

Control Group

The 8-week CBT-I intervention consists of 1 face-to-face session weekly for a total of 8 sessions with a certified psychologist. Each session will be 45 minutes at a fixed time including setting objectives, learning skills, class activities, and assigning homework. The CBT-I protocol covers typical CBT-I components. The first face-to-face session will include an introduction by the therapist and CBT. After assessing the patient's condition, the therapist will introduce the insomnia psychological patterns to stimulate the patient's intention for the therapy. In the second session, the therapist will set sleep restriction and stimulation control strategies based on the first conversation and carry out targeted sleep education. Starting with the third session, the therapist will map the patient's sleep diary and assess compliance to determine whether uptitration is allowed. Cognitive therapy for negative sleep beliefs will be performed from session 5. The principles of confidentiality, adherence, and autonomy will be followed throughout. At the end of each session, the therapist will assign homework to the participant and summarize the content of each treatment to provide skill consolidation and relapse prevention.

We will ensure patient confidentiality during the interview process and only mention the questions in treatment; no one

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shall disclose relevant information except the medical staff responsible for treatment. The client is expected to actively participate in the treatment process and, although there may be unforeseen events, we trust that the participant will adhere to the complete treatment process. Participants may leave the trial at any time during treatment. If, for some reason, the participant does choose to leave, there will be no effect on future treatment.

Ethical Considerations

The ethics committee has reviewed the research plan, informed consent form, and other relevant clinical trial documents (2021-088). This trial can only be carried out with the written consent of the ethics committee. If unforeseen problems arise during the study, these should be reported to the ethics committee immediately. Patient priorities, experience, and preferences were not involved in the development of the research question and outcome measures, the design of this study, or the recruitment to and conduct of the study. The results will be not disseminated to study participants.

Data Management

This experiment adopts electronic data management as described below and in the data management plan. The plan has been written by the data manager and will be carried out according to the described time, content, and methods. First, the data administrator will design the electronic case report form (eCRF) for the pilot study, a logic verification path is set according to the date verification plan, and the eCRF can be put into use only after passing a test and approval. The data in the eCRF are derived from the original record, and the data entry clerk enters the participant visit data as per the eCRF instructions. An inspector will then check the consistency of the eCRF data with the source data. All queries raised will be dealt with in a timely manner and addressed until the data is "clean." After the database record is signed by the main researchers, bidders, statistical analysts, and data managers, the data administrator will lock the database. The eCRF of each participant will be saved as a PDF electronic document. After the data analysis, the data administrator will close the database.

Quality Control

The trial will be conducted under the supervision of the Yueyang Hospital of Integrated Traditional Chinese and Western Medicine affiliated with the Shanghai University of Traditional Chinese Medicine. The clinicians in this trial have more than 10 years of clinical experience, and all the researchers will undergo training before the trial. A qualified clinical trial expert will be invited to monitor the study to identify any problems, examine the collected data, and control bias. Regarding quality control management, the data will be jointly managed through supervision, audit, and self-inspection. The procedures will be carried out in accordance with the relevant standard operating procedures.

Outcome Measures

The primary outcome will be a mean change in total ISI from baseline to the end of the 8-week intervention. The validated ISI that has a concise design, good reliability, and has become a recognized tool for clinical researchers to evaluate the efficacy of insomnia will be used [35,36]. The ISI is a self-reporting questionnaire, and 7 self-rated items are included that evaluate the severity and impact of insomnia on patients. The total ISI score ranges from 0 to 28 points. The higher the score, the more serious the degree of insomnia, which is classified according to the total score (0-7 points represent clinically nonsignificant insomnia, 8-14 points represent subthreshold insomnia, 15-21 points represent moderately severe clinical insomnia, and 22-28 points represent severe clinical insomnia).

The secondary outcomes include the Menopause-Specific Quality of Life (MENQOL); Menopause Rating Scale; PSQI; Hamilton Depression Scale (HAMD); Hamilton Anxiety Scale (HAMA); hot flash score; and the level of estradiol, follicle-stimulating hormone, and luteinizing hormone in serum. Sleep architecture will be assessed using deep learning on polysomnograms (PSG). The ISI and MENQOL are measured at randomization and 4, 8, 12, and 20 weeks after randomization. The other outcomes are measured before and 8 weeks after randomization.

Menopause Rating Scale is a reliable method to measure the severity of menopausal compliance and contains 11 items in 3 dimensions (psychological, somatic-vegetative, and genitourinary systems). Each symptom is given a score of 0, 1, 2, 3, and 4 according to severity; the total is the sum of the scores of each item [37,38].

The PSQI scale is used to assess the quality of sleep during the previous month [39]. The scale consists of 9 questions, and the overall score ranges from 0 to 21. The higher the score, the worse the sleep quality. PSQI can be used to calculate patient sleep onset latency, time in bed, wake after sleep onset, total sleep time, sleep efficiency, and record the medicine used. Therefore, the combination of sleep quality and quantity can be used to assess sleep conditions and identify any sleep disorders.

The HAMD was developed by Hamilton [40] in 1960 to test the severity of depression in participants. The scale evaluation method is simple and is most used in clinical practice. The time frame for the assessment is the last 1 week. Two trained assessors jointly examine and score the patient by means of a conversation. A version with 17 items will be used in this study with scores of 0-7 regarded as having no depressive symptoms, 8-17 regarded as having mild depression, 18-24 regarded as having moderate depression, and 25-52 regarded as having major depression.

The HAMA scale uses conversation, observation, and independent grading to rate anxiety in the previous week. There are 14 items, and anxiety is scored as 0 to 4 (0: none; 1: mild; 2: moderate; 3: severe, and 4: very severe). The total ranges from 0 to 56 points, and the higher the score, the more severe the anxiety symptoms [41]. HAMA can also be used to assess medication use and the effect of psychological intervention.

Participants will complete validated hot-flash daily diaries for 7 days at baseline and 8 weeks after randomization, by recording the number of hot flashes and severity (mild, moderate, severe, or very severe). A composite score is generated by multiplying the number of mild, moderate, severe, or very severe hot flashes

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by 1, 2, 3, and 4, respectively, and summing the values into one score [42].

MENQOL is used to record the symptoms experienced by participants in the past month or to evaluate the clinical efficacy of quality of life in menopausal women. MENQOL includes 29 items, each with a score of 0-6; 0 means the symptom has no impact, and 6 means extreme impact. The scale records symptoms in the 4 domains such as vasomotor, somatic symptoms, psychological symptoms, and sexuality. The higher the score, the worse the patient's quality of life [43].

PSG can objectively monitor sleep structure and efficiency, wakefulness, breathing, and periodic limb movements by recording the time off of lights; time in bed, total sleep time; sleep onset latency; wake-up time after sleep onset; total awake time from sleep onset to lights on; sleep efficiency; and sleep time in each period. Various physiological parameters such as electroencephalogram (EEG), electromyogram, electrooculogram, respiratory airflow, respiratory motion, and oxygen saturation are monitored [44,45]. Sleep staging will be performed by expert sleep technicians in nonoverlapping 30-second epochs as 1 of 5 stages such as wake, nonrapid eye movement (REM) stage 1, non-REM stage 2, non-REM stage 3, and REM.

Safety Assessment

All adverse events (AEs) will be recorded during the trial and ranked as mild (does not affect the normal function of the patient), moderate (affects normal function to a certain extent), or severe (significantly affects normal function). Acupuncture syncope, pain at the acupuncture point, bleeding, hematoma, or infection that may occur during acupuncture; patients developing symptoms that are significantly unrelated to the current disease, including an exacerbation of a preexisting disease; abnormalities in medical detection or physical examination that require clinical treatment or further examination; and injury or accident are considered as AEs.

Any medical conditions (eg, vertigo) and accidents should be reported as 2 different AEs. Abnormalities found by laboratory tests, when related to another reported event or that require clinical treatment or further investigation, should be described in the remark's column of the record and not treated as a separate AE.

Statistical Analysis

If statistical demographic data and other baseline characteristics are continuous variables, they will be represented by the mean (SDs) and median (IQR) values. We will also include count and grade data for frequency and composition ratios. Concomitant medications will be categorized using the Anatomical Therapeutic Chemical code, percentage of patients with concomitant medications, and the incidence of AEs will be compared using the χ^2 test or Fisher precision probability.

After 8 weeks of intervention, the change in the ISI score will be compared with the baseline. The subgroups and baseline are used as covariates to compare the differences between groups by analysis of covariance and the 2-sided 95% CIs of the least squares mean differences between groups. During each visit, the ISI score will be recorded, and mixed-effects model repeated measures will be used to compare the differences between groups. To compare 2 independent samples, a 2-tailed *t* test or nonparametric test will be used for continuous data, and chi-square or Fisher exact or nonparametric tests will be used for categorical data. The times and number of drugs that are taken by participants will be compared between groups using a rank sum test. When a covariance analysis is used for the primary efficacy indicator, missing values will be filled using the last observation carried forward method. When using the mixed-effects model repeated measures method for analysis, the missing data will not be filled. When an outlier is found, the main researcher, the applicant, and the statistician will discuss the processing method together before the database is locked. If necessary, the outlier value will be removed for sensitivity analysis.

Results

Recruitment of participants for the study is presently underway. The inaugural participant was enrolled in January 2023, signifying the commencement of the recruitment phase. It is anticipated that the recruitment process will persist until January 2025, at which juncture data collection will commence.

Discussion

Principal Findings

This will be the first randomized, noninferiority, EA-controlled trial to study the efficacy and safety of EA compared with CBT for PMI. Considering that drugs may cause adverse reactions such as feeling drowsy, lightheaded, and dizzy, medications need to be limited to the lowest necessary dose and shortest necessary duration and nonpharmacological therapies are reasonable to use [18].

CBT-I has a longer duration of treatment and is suitable for patients with cognitive impairment [46]. It is offered in various forms such as one-on-one or in groups via telephone, the internet, or books. During the COVID-19 pandemic, some evidence-based psychotherapy was provided to medical staff to relieve mental pressure and prevent the occurrence of psychological disorders [47]. Web-based CBT has been shown to be effective in treating and preventing many stress-related symptoms among health care workers. Web-based CBT has also shown strengths in breast cancer survivors with clinically significant sleep problems [48].

Actigraphy (ACT) and PSG are commonly used to monitor sleep in clinical studies [49]. We have chosen PSG to monitor sleep as an objective efficacy index, as it makes a comprehensive estimation by monitoring various physiological parameters such as EEG, electromyogram, ECG, respiratory airflow, respiratory motion, and oxygen saturation while being manually analyzed by a sleep technician. Thus, sleep architecture is shown without bias. In addition, PSG is the gold standard for the assessment and diagnosis of sleep disorders [50]. However, PSG must be performed in the laboratory under the supervision of a relevant technician, and the discomfort of the electrodes and harnesses necessary for PSG monitoring brings about the "first night

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effect" [51], which also has a higher cost than other tests. Rather than recording EEG activity, ACT combines body movement frequency with the help of gravity sensors [52]. Although ACT is economical and simple to wear, it has a distinct drawback in that it may overestimate sleep time and underestimate wake time [53].

Women who are undergoing menopause transition seem to report more sleep difficulties. The content of some hormone changes dramatically in this stage, which may be associated with decreased melatonin synthesis and secretion. Progesterone reduces arousal and can have a sedative effect, while estrogen increases the turnover of the neurotransmitter norepinephrine and, subsequently, increases time spent in REM sleep and decreases REM latency [54]. Many of the menopausal symptoms (eg, hot flashes and night sweating) are precipitating factors for insomnia, which are in relation to the occurrence of poor sleep quality in menopausal women. Hot flashes are one of the most typical menopausal symptoms and are highly associated with awakening perimenopausal women in particular [55]. Repeated exposure to menopausal symptoms that cause wakefulness at night may perpetuate insomnia symptoms through conditioned arousal.

Limitations

Our study protocol has some limitations. First, PSG brings discomfort to patients and reduces sleep quality. Although it is precise in the definition of wakefulness through accurate measurement with electroencephalography, PSG has insufficient validity for the assessment of wakefulness after sleep onset relative to wrist ACT. Second, we lack a follow-up assessment beyond 3 months. The durability of CBT-I is maintained 10 years after treatment [56]. Third, as our sample groups are going to be recruited from Shanghai, China, the inclusion of participants from different countries and regions would increase the persuasiveness of the trial results. The results may not be generalized to women who were taking certain medications, or who had certain gynecological surgeries (eg, hysterectomy and bilateral oophorectomy).

Conclusions

Acupuncture and CBT-I have been recommended in the guidelines [57]. Indeed, if the efficacy of EA is noninferior to CBT, it could become an empirically assessed viable option specifically suited to the needs of women with PMI. The results of this study will provide knowledge for clinicians in the treatment of PMI.

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Data Availability

The data sets generated in this study will be made available from the corresponding author. The study team will retain the exclusive use of the trial data until the publication of major outputs has been completed.

Authors' Contributions

YFC and XTY conceived the research plan. HXW and JH drafted the protocol and formed the analysis plan. YFC, XTY, HXW, XQS, YTZ, YR, Jing Hu, and Jia Hu coordinated the study. HXW and YFC recruited the participants. All authors participated in reading and approved the final paper.

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist.
[DOCX File , 41 KB - resprot_v12i1e51767_app1.docx]

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Abbreviations

ACT: actigraphy
AE: adverse event
CBT: cognitive behavioral therapy
CBT-I: cognitive behavioral therapy for insomnia
EA: electroacupuncture
eCRF: electronic case report form
EEG: electroencephalogram
HAMA: Hamilton Anxiety Scale
HAMD: Hamilton Depression Scale
ISI: Insomnia Severity Index
MENQOL: Menopause-Specific Quality of Life
MHT: menopausal hormone therapy
PMI: perimenopausal insomnia
PSG: polysomnograms
PSQI: Pittsburgh Sleep Quality Index
REM: rapid eye movement
SPIRIT: Standards for Reporting Interventions in Clinical Trials of Acupuncture

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Protocol

The Efficacy of Carbon Dioxide Paste in Alleviating Pain in Patients After Neck Dissection: Protocol for a Double-Blinded, Randomized Controlled Trial

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Abstract

Background: Head and neck cancers that cause severe aesthetic and functional disorders normally metastasize to the cervical lymph nodes. Patients with cervical lymph node metastasis are undergoing neck dissection. Shoulder complaints are common after neck dissection, with patients reporting symptoms such as pain, weakness, shoulder droop, and disability. However, no safe and effective treatment is available for this condition at present. We will conduct a double-blinded, randomized controlled trial to evaluate the efficacy of carbon dioxide (CO_2) paste in relieving pain in patients after neck dissection.

Objective: This will be the first clinical study to compare the efficacy of CO_2 paste with placebo in relieving postoperative pain in patients who underwent neck dissection.

Methods: We will perform this trial at the Kobe University Hospital in Japan. Patients will be randomized 1:1 into the CO_2 paste and control groups. Patients in the CO_2 paste group will have the CO_2 paste applied to the cervical surface skin for 10 minutes once per day for 14 consecutive days. The primary end point of the study is a change in the visual analog scale (VAS) scores of neck pain from baseline on day 1 (preapplication) to the end of drug application (day 15). Secondary end points include changes in the following parameters from baseline on day 1 to the end of drug application (day 15) or the study (day 29): neck pain VAS score (days 1-29), grip strength (days 1-15 and 1-29), VAS scores for subjective symptoms (the feeling of strangulation, numbness, swelling, and warmth in the neck and shoulder region) for days 1-15 and 1-29, whether the VAS score improved more than 30% (days 1-15), the arm abduction test (days 1-15 and 1-29), shoulder range of motion (abduction and flexion) for days 1-15 and 1-29, occurrence of skin disorders, and occurrence of serious side effects. Periodic monitoring will be conducted for participants during the trial. This study was approved by the certified review board of Kobe University.

Results: The intervention commenced in May 2021 and will continue until March 2024. The collected data will provide information on the efficacy of the CO_2 paste treatment. The primary end point will be compared using the Wilcoxon test, with the 1-sided significance level set at 5%. Each evaluation item will be summarized. Secondary efficacy end points will be analyzed to provide additional insights into the primary analysis. Findings based on the treatment effects are expected to be submitted for publication in 2025.

Conclusions: This trial will provide exploratory evidence of the efficacy and safety of CO_2 paste in relieving pain in patients after neck dissection.

Trial Registration: Japan Registry of Clinical Trials (jRCT) identifier: jRCTs051210028; https://jrct.niph.go.jp/en-latest-detail/jRCTs051210028

International Registered Report Identifier (IRRID): DERR1-10.2196/50500

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KEYWORDS

carbon dioxide; double-blind; neck dissection; pain; paste; postoperative; randomized controlled trial; surgery; surgical

Introduction

Postoperative wound pain in the head and neck region generally improves within 1-2 weeks after surgery. However, patients undergoing cancer treatment often experience continuous, persistent pain, which can cause physical and psychological distress. Surgery and radiation therapy often cause painful scarring and contractures. Musculoskeletal and neuromuscular disabilities after radiotherapy and surgical treatment are major causes of cancer treatment–related side effects. Disabilities in the head and neck region after cancer treatment are related to a patient's ability to communicate, eat, and work [1]. These changes reduce the functioning and social interaction of these patients [1,2].

Shoulder complaints are common (18%-77%) after neck dissection, even if the spinal accessory nerve has been preserved [3,4]. Symptoms such as pain, weakness, shoulder droop, and disability have been reported in patients after neck dissection [5,6]. Pain is an important factor affecting the quality of life (QOL) of cancer survivors [1,7]. Although various drug treatments are available for preventing or improving the management of chronic postsurgical pain [8-10], these treatments have side effects.

The exact etiology of persistent postsurgical pain remains unclear, but its causes are thought to involve neuropathy [11-13], inflammation [14,15], central sensitization [16,17], and ischemia [18-20]. In rats, decreased blood flow and tissue ischemia cause complex regional pain syndrome–like symptoms [18]. In addition, patients with peripheral arterial diseases experience chronic ischemic pain [20]. Thus, continuous postoperative pain may be reduced by improving the blood flow in the ischemic scar tissue.

We had previously reported the effects of transcutaneous application of carbon dioxide (CO_2) in a hydrogel as an absorption-promoting agent in healthy individuals and various animal models [21-23]. Transcutaneous application of CO_2 improves vascularization and exercise performance in rats; it also increases local oxygenation, causing the dissociation of oxygen from hemoglobin (Bohr effect) [23-25]. However, this method uses CO_2 gas, which is difficult to apply to the head and neck. In a recent study, we investigated the usefulness, safety, and feasibility of a CO_2 paste by analyzing the changes in blood flow in a phase 1 clinical study in healthy individuals [26]. The CO_2 paste reacted with water on the skin surface, could infiltrate CO_2 transcutaneously without the use of external CO_2 gas, and could be applied to the head and neck region. In the phase 1 clinical study, application of the CO_2 paste increased the blood flow in the skin and muscles, as observed by dynamic magnetic resonance imaging, and caused no adverse reactions.

This double-blind, randomized controlled trial aims to evaluate the efficacy and safety of CO_2 paste in decreasing postoperative neck pain in patients undergoing neck dissection.

Methods

Objectives

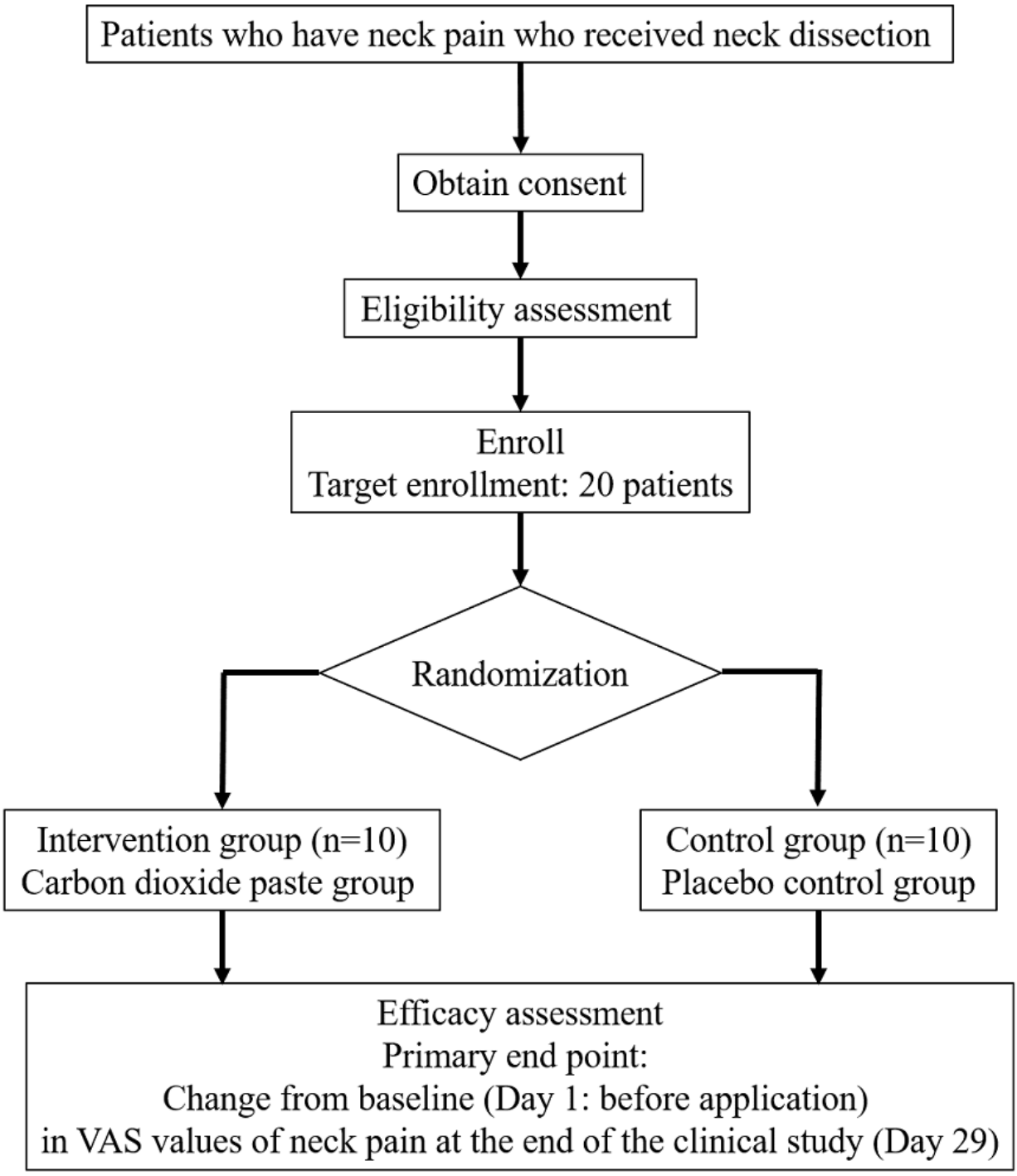
This study will examine whether the application of a CO_2 paste can reduce postoperative neck pain in patients receiving neck dissection in a double-blinded, randomized controlled trial. The primary objective is to estimate the within-patient differences in visual analog scale (VAS) scores for neck pain ranging from 0 (no pain) to 10 (worst pain) from baseline (day 1: before application) to the end of the study drug application (day 15). The secondary objectives are to evaluate the within-patient differences in the VAS scores for neck pain from baseline (day 1: before application) to the end of study drug application (day 15), grip strength from baseline to the end of the drug application (days 1-15) and the end of the study period (days 1-29), VAS scores for subjective symptoms (the feeling of strangulation, numbness, swelling, and warmth) from baseline to the end of the drug application (days 1-15) and the end of the study (days 1-29), arm abduction [27] from baseline to the end of the drug application (days 1-15) and the end of the study (days 1-29), and shoulder joint range of motion (abduction or flexion) from baseline to the end of the drug application (days 1-15) and the end of the clinical study (days 1-29). In addition, we aim to evaluate whether patients showed a ≥30% improvement in the VAS scores for neck pain from baseline to the end of the drug application (days 1-15) and the end of the study (days 1-29).

Study Design

This study has been designed as a single-center, placebo-controlled, double-blind, randomized controlled trial. The patient flowchart is shown in Figure 1. This study will be conducted at Kobe University Hospital. All data will be stored and archived at the data center of Kobe University Hospital. We will use Research Electronic Data Capture (REDCap; Vanderbilt University), an electronic data system for clinical research, to manage the data and protect confidentiality before, during, and after the trial. The study population will consist of patients undergoing neck dissection and will be selected based on the inclusion and exclusion criteria listed in Textbox 1. Patients will be recruited from Kobe University Hospital from May 24, 2021, to March 31, 2024. All patients will be asked if they wish to participate in the study and will be enrolled after obtaining written informed consent.

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Figure 1. Flowchart of participants. VAS: visual analog scale.



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Textbox 1. Inclusion and exclusion criteria for the study.

Inclusion criteria

- Aged 20 years or older
- Have complaints of postoperative neck pain after unilateral cervical dissection
- Between 6 months and 3 years after neck dissection
- A visual analog scale score of 1 or higher for neck pain
- Have given voluntary consent to participate in this clinical study

Exclusion criteria

- Hypersensitivity to drugs, including severe allergies
- Peripheral arterial disease, ischemia (Fontaine III-IV), and ischemic cerebral artery disease
- Heart failure (New York Heart Association IV) and ischemic heart disease (Canadian Cardiovascular Society functional classification 3-4)
- Female patients who are pregnant, lactating, wishing to become pregnant during the study period, or are fertile and cannot accept an effective contraceptive method
- Severe respiratory disease with oxygen saturation (SpO2) less than 90% at rest
- Skin ulcers larger than 4 cm × 4 cm × 1 cm or skin diseases making it difficult to apply the paste
- Deemed inappropriate for participation in this clinical study by the investigators

Randomization (Allocation)

Using the permutation random block method stratified by category, participants will be randomly assigned to either the CO_2 paste group or the placebo control group at a 1:1 allocation ratio. To ensure that blinding is maintained, the block size will not be disclosed. The allocation sequence for the randomization method will be generated by a biostatistician. All participants who provide consent to participate, fulfill the inclusion criteria, and do not meet any of the exclusion criteria will be randomized. The eligibility of each participant will be confirmed. A subject-enrollment confirmation form containing the eligibility judgment, randomization assignment results from the generated random sequence, and the enrollment number will be issued.

Experimental Drugs

The CO_2 paste (direCO_2t) is manufactured as an experimental drug at the CO2TECH, a limited liability company. The CO_2 paste contains 1,3-butylene glycol and other components, including sodium hydrogen carbonate, malic acid, sodium dihydrogen phosphate, an alkyl-modified carboxyvinyl polymer, and carboxyvinyl polymer. The placebo paste is a formulation in which the sodium bicarbonate in the CO_2 paste is replaced by a nonreactive material (sodium chloride).

Treatment and Assessment Schedule

Within 4 weeks of enrollment, the VAS score for neck pain will be evaluated 1 week before the administration of the experimental drug during the preobservation period. On the first day of treatment, body temperature, blood pressure, oxygen saturation, and pulse rate will be measured by a physician, dentist, or nurse before and after the application of the experimental drug. The paste will be applied at 0.2 g-0.3 g/100 cm^2 to the affected neck area once per day for 14 consecutive days. The duration of each application will be 10 minutes, and the paste will be wiped off after application.

Data Collection

The data collection schedules are presented in Table 1. The primary investigator or subinvestigator will enter the case report form (CRF) data for each participant into the electronic data capture (EDC) system. The principal investigator will confirm that the entered CRF data are complete and correct, electronically sign the CRF on the EDC system, and print out the signed CRF for filing. The CRF printout will be retained. If any queries about the CRF data are entered by the staff at the data center, the primary investigator or subinvestigator will be required to promptly respond to them.

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Table 1. Data collection schedule.

	Registration (within 4 weeks before allocation)	Preobservation (7±3 days before allocation)	Allocation day 1 (preapplication)	Allocation day 1 (postapplication)	Postallocation day 15+1 (finish application)	Postallocation day 29+3	Exclusion	Within 7 days after exclusion
Assessment of eligibility criteria	✓							
Obtain consent	✓							
Registration	✓							
Patient characteristics[a]	✓							
Allocation and start of the application			✓					
VAS[b] of neck pain		✓	✓	✓	✓	✓		
VAS values of subjective symptoms[c]			✓	✓	✓	✓		
Strength of grip			✓		✓	✓		
arm abduction test[d]								
Shoulder joint range of motion (abduction or flexion)								
Adverse events				✓	✓	✓	✓	✓
Vital sign[e]	✓		✓	✓	✓		✓	✓
Oxygen saturation (SpO_2)	✓		✓				✓	✓
Confirmation of days of application					✓		✓	

[a]Sex, date of birth, age, medical history, comorbidity, primary disease, TNM classification, the number of days after surgery, the range of neck dissection, preservation of sternocleidomastoid muscle, accessory nerve, and internal jugular vein, and the details of adjuvant therapy.

[b]VAS: visual analog scale.

[c]Strangulation, numbness, swelling, and warmth.

[d]Arm abduction test: up to 180˚ without pain or effort (5 points), up to 180˚ but with pain or effort (4 points), up to more than 150˚ but less than 180˚ (3 points), up to more than 90˚ but not less than 150˚ (2 points), up to approximately 90˚ (1 point), and up to less than 90˚ (0 point) [27].

[e]Body temperature, blood pressure, and pulse rate.

Main Outcomes

The primary end point for efficacy is the change in the VAS score for neck pain from baseline (day 1: before application) to the end of the study drug application (day 15).

The secondary efficacy end points are as follows:

1. Change in the VAS score for neck pain from baseline (day 1: before application) to the end of the clinical study (day 29).
2. Changes in grip strength from baseline to the end of the drug application (days 1-15) and the end of the study (days 1-29).
3. Changes in VAS scores for subjective symptoms (feeling of strangulation, numbness, swelling, and warmth) from baseline to the end of the drug application (days 1-15) and the end of the study (days 1-29).
4. Whether the VAS score for neck pain showed a ≥30% improvement from baseline to the end of the drug application (days 1-15) and the end of the study (days 1-29).
5. Change in arm abduction [27] from baseline to the end of drug administration (days 1-15) and the end of the study (days 1-29).
6. Change in shoulder joint range of motion (abduction and flexion) from baseline to the end of drug application (days 1-15) and the end of the study (days 1-29).

The secondary end point for safety is the presence or absence of adverse events such as skin disorders and serious diseases. The relationships among the interventions, outcomes, other assessments, and visits associated with the participants in this study are shown in Table 1.

Statistical Analysis

The primary objective of this clinical study was to evaluate the efficacy of the CO_2 paste versus the placebo in terms of the change in VAS scores for neck pain (the primary end point). For the comparison of the primary end point, the Wilcoxon test will be performed for the null hypothesis, “There is no difference in the change in VAS values for neck pain at day 15 between

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the placebo group and the CO_2 paste group." The significance level will be set at 5.0% (1-sided). Each evaluation item will be summarized. Secondary efficacy end points will be analyzed to provide additional insights into the primary analysis. No adjustment for multiplicity will be made in the analyses of the secondary efficacy end points. The significance level for hypothesis testing is 5% (2-sided) with 2-sided 95% CIs. The incidence and rate of disease will also be evaluated. The safety end point is the frequency of the occurrence of adverse reactions. Tables will be prepared for the end points, and exact 2-sided 95% CIs of the binomial distribution will be calculated for each group to estimate the proportions.

Sample Size Calculation

Most patients are expected to have a baseline VAS score of 2-3 cm. For the primary end point (the amount of change in VAS values for neck pain), we estimated that the mean difference in change between the CO_2 paste application and placebo groups would be 2 (SD 1.5) cm. A Wilcoxon test (a nonparametric test) will be performed considering the possibility that participants with a baseline score of less than 2 cm might be enrolled. The number of cases based on the Wilcoxon test can be calculated by multiplying the number of cases based on the *t* test [28]. Although the constant for multiplication is 1.045 in the case of a normal distribution, since the participants in this study were not assumed to be normally distributed, the number of cases was calculated by multiplying by 1.2. When conducting a *t* test with a 1-sided significance level of 5.0% and a power of 80%, a total of 7 participants were required per group. When the number of cases was multiplied by 1.2, the total number of cases was 8.4. Therefore, considering drop out cases, 20 cases would be sufficient to maintain power.

Monitoring for Human Rights, Safety, and Adequacy

Monitoring will be conducted periodically to check whether the human rights and safety of the participants are protected and to confirm that the regulatory requirements of the Clinical Trials Act are followed. To ensure an appropriate assessment, the principal investigator is responsible for dealing with personal data and items specified in the written procedure. Any requirements made by the ethics committee will be immediately announced to the participants by the study investigators.

Other Considerations

This study will be conducted without patient or public involvement. Neither the patients nor the public will be involved in the development of the research question, study design, or implementation of the trial. Patients will not be invited to develop patient-relevant outcomes, interpret the results, or participate in the writing or editing of the final manuscript. Since the interventions in this study are routine clinical procedures, the burden of the interventions will be assessed by the patients themselves.

Any protocol changes that affect the study conduct or participant risk-benefit profile will require approval from the relevant institutional review board, including changes in the objectives, design, sample size, participant characteristics, staff changes, or significant administrative features. Minor protocol corrections or clarifications that do not affect the study conduct or the participant risk-benefit profile will be viewed as administrative changes and documented internally. The study investigators will have full access to and ownership of all the data. Anonymized data will be made available to other interested investigators for additional analyses on reasonable request, following reports of primary outcomes and with an appropriate data use agreement. The findings of this study will be disseminated through scientific and professional conferences and a peer-reviewed journal.

Ethical Considerations

The study is being conducted in compliance with the principles of the Declaration of Helsinki (1996), the principles of good clinical practice, and all applicable regulatory requirements. This study has been approved by the Clinical Research Review Board of Kobe University (CRB5180009), and the trial has been registered with the Japan Registry of Clinical Trials (jRCT) (jRCTs051210028). All participants will be required to provide written informed consent before any study procedures are conducted. The participants will have the opportunity to review the consent form and confirm that they have fully understood the details of the study procedures. Secondary use of the data will occur only if the patients provide written informed consent for additional use of their data. Secondary use of the data will adhere to appropriate ethical review and approvals, as per institutional guidelines. No funding was received for this study, including institutional or departmental support. The study is not commissioned, externally peer reviewed.

Results

The subject recruitment began on May 24, 2021. The entry period for participants is up to March 31, 2024, three years after the jRCT registration. Data analyses of all enrolled participants will be conducted in 2024. This manuscript is based on the current version of the protocol (version 3.0), last updated on December 23, 2022.

The data sets generated in this study will be available on the jRCT website. The final report is expected to be published in a peer-reviewed journal in 2025. The findings will be disseminated through scientific and professional conferences and peer-reviewed journal publications in 2025.

Discussion

Expected Findings and Implications

This report describes the protocol for a study evaluating the application of CO_2 paste to patients who undergo neck dissection and experience postoperative complaints. A neck dissection is a surgical procedure performed to remove cervical lymph nodes. During surgery, the blood vessels are ligated to prevent bleeding. In addition, the internal jugular vein, which drains blood from important organs such as the brain, face, and neck, is removed depending on the type of neck dissection. These blood flow interruptions lead to wound ischemia and various postoperative symptoms or dysfunctions.

Pain, the main side effect of neck dissection, often aggravates patient QOL [1,7]. As its pathogenesis remains uncertain, a

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treatment strategy for postoperative pain has not yet been established. Analgesics such as nonsteroidal anti-inflammatory drugs and acetaminophen are commonly administered to relieve this pain. Nonsteroidal anti-inflammatory drugs show remarkable efficacy as painkillers; however, they are also associated with serious adverse reactions in the gastric mucosa and cardiovascular, hepatic, renal, and hematological systems [29]. Although almost all patients receive acetaminophen [30], those undergoing neck dissection continue to experience pain. Considering the limitations of drug therapy, effective treatment of every patient with postoperative pain is essential.

In a phase 1 clinical study, we reported that CO_2 paste application increases blood flow to the skin and muscles without any side effects [26]. Since transcutaneous CO_2 application induces angiogenesis by inducing an artificial Bohr effect, we hypothesize that this simple and adaptable treatment can alleviate side effects and improve the QOL of patients undergoing neck dissection.

This study will be the first to apply CO_2 paste to postoperative skin. Since it is composed of food ingredients, the CO_2 paste is considered to have few life-threatening side effects. However, there is no evidence on whether its application may induce dermatitis. Therefore, the occurrence of dermopathies such as erythema and exanthema should be carefully monitored during the trial. To address potential safety concerns, the CO_2 paste will be applied to the postoperative neck for only 10 minutes a day.

Through this study, we aim to determine the curative effect of CO_2 paste application on postoperative neck pain in patients undergoing neck dissection. Since the efficacy of CO_2 paste for neck pain has never been reported, this will be the first well-designed clinical evaluation study on this topic. Our primary hypothesis is that CO_2 paste application can reduce pain in patients undergoing neck dissection. We also expect that the application of this paste will reduce subjective symptoms, including feelings of strangulation, numbness, swelling, and warmth, and will improve grip strength, arm abduction, and shoulder joint range of motion (abduction and flexion).

Study Strengths and Limitations

We previously conducted a clinical trial on a small number of healthy individuals. To explore the adequacy and applicability of CO_2 paste application, this will be the first protocol to be performed as a phase 2, double-blinded, randomized controlled trial, evaluating the efficacy of CO_2 paste in a small number of patients with neck pain after neck dissection. Nonetheless, this clinical trial has some limitations that should be acknowledged. First, the number of evaluated patients is relatively small to conclusively determine the efficacy of the CO_2 paste. Second, since some patients underwent neck dissection as part of larger resections, a small amount of heterogeneity is expected. Finally, this study is limited by its short duration (28 days).

Conclusions

Considering the general condition of the patients and the side effects of drug therapy, postoperative pain after neck dissection is difficult to manage. Therefore, establishing a widely applicable treatment with fewer adverse effects is essential. The results of this study will provide valuable evidence for the future application of CO_2 paste to patients complaining of pain after neck dissection.

Acknowledgments

This trial is supported by CO2TECH, a limited liability company, which has provided the authors with both the CO_2 and the placebo paste. We would like to thank Editage for English language editing.

Data Availability

The data sets generated or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

All authors met the criteria of authorship as outlined in the International Committee of Medical Journal Editors and approved this manuscript for submission. Specific contributions were as follows: The conception or design of the work and the interpretation of the data for the work were done by TH, DT, YK, and MA; acquisition and revising the work critically for important intellectual content: TH, DT, YK, IS, NY, and MA; analysis: TH; and drafting the work: YT, TH, DT, YK, and MA. The final approval of the version to be published and the agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved were given by all the authors.

Conflicts of Interest

None declared.

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Abbreviations

CO_2: carbon dioxide
CRF: case report form
EDC: electronic data capture
jRCT: Japan Registry of Clinical Trials
QOL: quality of life
REDCap: Research Electronic Data Capture
VAS: visual analog scale

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Protocol

Sitafloxacin- Versus Moxifloxacin-Based Sequential Treatment for Mycoplasma Genitalium Infections: Protocol for a Multicenter, Open-Label Randomized Controlled Trial

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Abstract

Background: *Mycoplasma genitalium* is an emerging sexually transmitted pathogen associated with increasing antibiotic resistance. The current treatment guidelines recommend moxifloxacin-sequential therapy for macrolide-resistant *Mgenitalium* or strains with unknown resistance profiles. However, it is unclear whether sitafloxacin, a 4th-generation fluoroquinolone antibiotic, is effective against resistant strains.

Objective: This study aims to assess and compare the efficacy and safety of sitafloxacin- and moxifloxacin-based treatment regimens for managing *Mgenitalium* infections.

Methods: We will conduct this randomized controlled trial at multiple centers in Japan. Eligible participants include adults aged 18 years or older with a confirmed *Mgenitalium* infection, as determined through the nucleic acid amplification test. Patients will be randomly assigned using a stratified approach based on the treatment facility and infection site. The interventions comprise oral sitafloxacin (200 mg) daily for 7 days (with optional pretreatment of oral doxycycline, 200 mg, daily for up to 7 days), with a control group receiving oral doxycycline (200 mg) daily for 7 days followed by moxifloxacin (400 mg) daily for another 7 days. The primary outcome is the treatment success rate with a superiority margin of 10%, as confirmed through the nucleic acid amplification test. Secondary outcomes encompass changes in the bacterial load at the urogenital or rectal sites and the emergence of posttreatment-resistant mutant strains.

Results: Enrollment commenced in June 2023 and will conclude in December 2024, with findings anticipated by 2025. The expected success rates fall within the range of 80% for sitafloxacin and 42% for moxifloxacin against *Mgenitalium* carrying the G248T (S83I) mutation, based on previous studies. Accordingly, with a 5% significance level (2-sided) and 80% statistical power, we aim to recruit 50 participants per group, factoring in a 10% expected dropout rate.

Conclusions: This study will provide valuable insights into the efficacy and safety of sitafloxacin- versus moxifloxacin-based sequential therapy in treating *Mgenitalium* infections. These findings have the potential to influence clinical guidelines, favoring more effective therapeutic choices. The multicenter approach enhances the robustness of this study. However, a limitation is the potential insufficiency of statistical power to detect posttreatment-resistant mutant strains in each group, rendering posttreatment-resistance mutations a notable concern. In the future, we may need to increase the sample size to enhance power.

Trial Registration: Japan Registry of Clinical Trials (jRCTs031230111); https://jrct.niph.go.jp/en-latest-detail/jRCTs031230111

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KEYWORDS

bacteria; bacterial; clinical trial; clinical trials; controlled trials; doxycycline; drug; drugs; genital; genitalia; infection; medication; medications; moxifloxacin; Mycoplasma genitalium; pharmaceutic; pharmaceutical; pharmaceuticals; pharmaceutics; pharmacology; pharmacotherapy; pharmacy; quinolone resistance-associated mutation; randomized controlled trial; RCT; sexual transmission; sexually transmitted infection; sexually transmitted; sitafloxacin; STD; STI

Introduction

The increase in the number of resistant strains of *Mycoplasma genitalium* is a global concern. The global prevalence of *M genitalium* in the general population ranges from 1.3% to 3.9% [1]. The prevalence of macrolide resistance-associated mutations (MRMs) has increased over the decades [2]. Furthermore, regional variations in resistant strains have been observed, with the prevalence of MRMs in the American and Western Pacific regions exceeding that in European countries [2]. The prevalence of quinolone resistance-associated mutations (QRAMs) has been increasing in the Western Pacific regions, including Australia, New Zealand, China, and Japan, making these regions focal points for resistance mutations [3-7]. The current national guidelines recommend resistance-guided sequential therapy for *M genitalium* infections when macrolide resistance testing is available; otherwise, empiric sequential therapy is recommended, commencing with doxycycline followed by fluoroquinolone [8-11]. For macrolide-susceptible strains, sequential therapy involves an initial cycle of doxycycline treatment followed by azithromycin, whereas for macrolide-resistant strains, it entails an initial cycle of doxycycline treatment followed by fluoroquinolone. According to Australian studies, resistance-guided therapy with doxycycline followed by azithromycin attains a high efficacy of 92% to 95.4% against macrolide-susceptible strains, whereas doxycycline followed by moxifloxacin achieves a high efficacy of 95.4% against macrolide-resistant strains, and doxycycline followed by sitafloxacin demonstrates a high efficacy of 95% against macrolide-resistant strains [12-14]. However, the cure rate of fluoroquinolone-based therapies depends on the prevalence of QRAMs, which include *parC* and *gyrA* mutations. Specifically, S83 and D87 mutations in *parC*, as well as M95, G93, and D99 mutations in *gyrA*, have been linked to treatment failure with moxifloxacin and sitafloxacin [15-19]. Additionally, combined *parC* and *gyrA* mutations limit the efficacy of fluoroquinolone-based therapy more significantly than single mutations [19,20]. As sitafloxacin, a newer-generation fluoroquinolone, is not widely available, direct comparisons between moxifloxacin and sitafloxacin treatments are lacking. Sitafloxacin exhibits higher efficacy against QRAM-resistant strains [14,17,18] and demonstrates a lower minimum inhibitory concentration relative to moxifloxacin in QRAM-resistant strains based on minimum inhibitory concentration assays [17,18]. Murray et al [14] conducted a clinical study and demonstrated that sitafloxacin-based sequential therapy for the most common *parC* G248T (S83I) mutant strains achieved a higher success rate than moxifloxacin-based sequential therapy. However, as previously mentioned, they did not directly compare the 2 drugs but instead retrospectively compared them at different times. Given the fluctuating numbers of mutant-resistant strains in recent years, a randomized clinical trial would be a more suitable approach to investigate the efficacy of these 2 drug regimens [14,21].

In Japan, the prevalence of resistant strains is high [3,21]. Ando et al [3] reported that 89.6% of strains harbored MRMs, with 68.3% harboring *parC* mutations and 27% harboring *gyrA* mutations. Given the unavailability of resistance testing for MRMs and the high prevalence of strains harboring MRMs (89.6%), sitafloxacin is the preferred treatment for *M genitalium* infections at our facility. Ando et al [20] reported that sitafloxacin monotherapy cleared strains harboring wild-type *parC* and *gyrA*. In addition to resistant strains, sitafloxacin demonstrated high effectiveness (92.9%) in clearing strains harboring *parC* G248T (S83I) mutations and wild-type *gyrA*, with 41.7% of those harboring *parC* G248T (S83I) and *gyrA* mutations. In contrast, moxifloxacin-based therapy cleared 96.5% of the strains harboring wild-type *parC* and *gyrA* [19]. The regimens mainly comprised sequential therapy with doxycycline followed by moxifloxacin and combination therapy with doxycycline and moxifloxacin. However, for strains harboring *parC* G248T (S83I) mutations and wild-type *gyrA*, the effectiveness of moxifloxacin-based therapy was limited to 54.2%. For those harboring *parC* G248T (S83I) and *gyrA* mutations, the effectiveness was further reduced to 18.8% [19]. Both sitafloxacin and moxifloxacin are newer-generation quinolones that exhibit a comparable incidence of gastrointestinal side effects [22,23]. These agents are less frequently associated with tendon rupture than levofloxacin, a prevalent fluoroquinolone drug [24]. Considering that both are broad-spectrum antibiotics, their impact on de novo resistance and the environment remains unclear and requires vigilant monitoring. A 7-day course of doxycycline is generally used to treat sexually transmitted infections with mild side effects, such as gastrointestinal disturbances [25].

Accordingly, we propose to conduct a multicenter, open-label randomized controlled trial aimed at comparing the efficacy and safety profiles of sitafloxacin and standard moxifloxacin-based sequential treatments in managing highly resistant *M genitalium* infections.

Methods

Study Design

This study constitutes a comparative randomized open-label parallel-group trial assessing the efficacy of sitafloxacin- versus

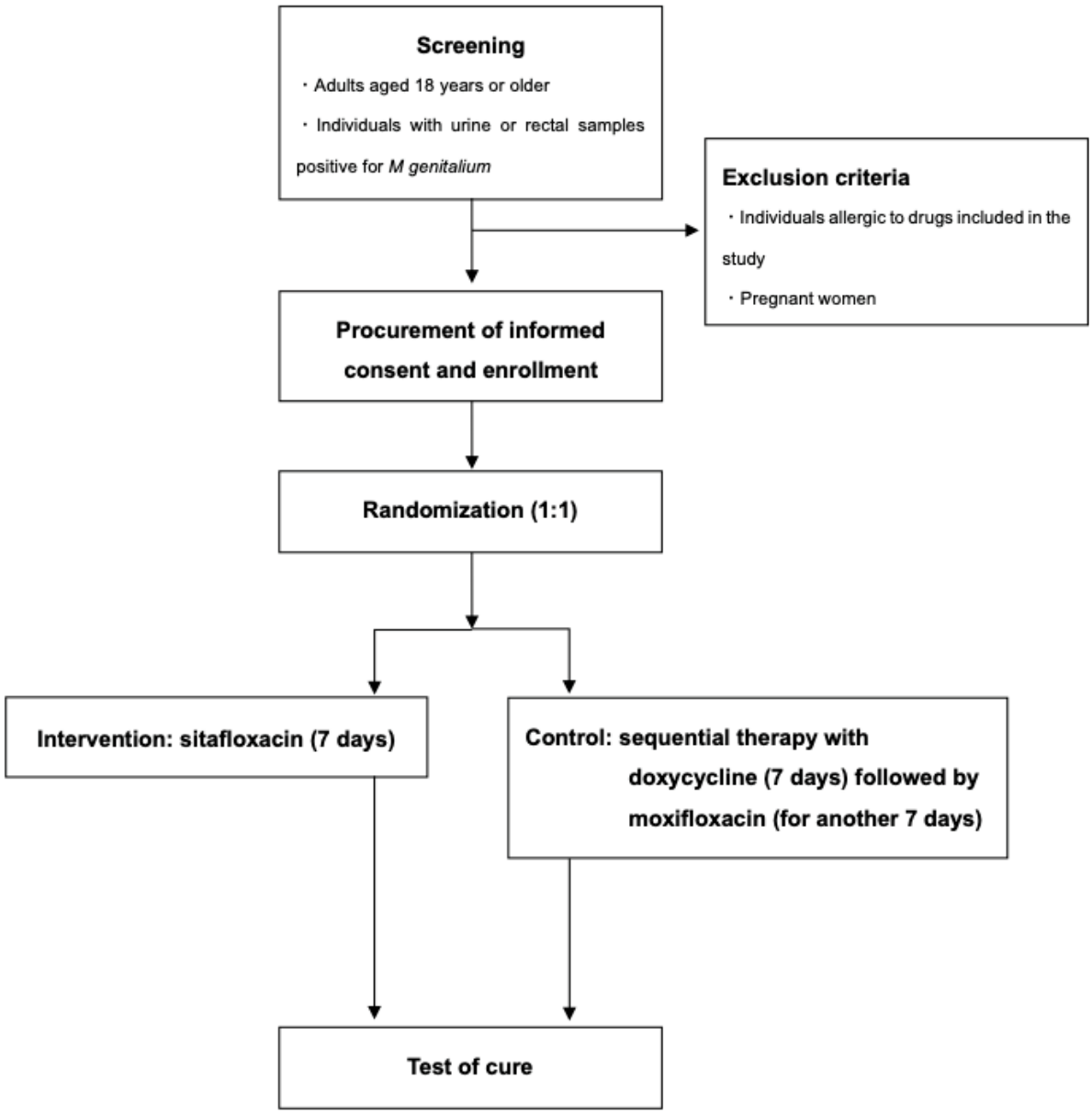
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moxifloxacin-based sequential treatment for *M genitalium* infections, particularly those involving resistant strains.

Population and Eligibility Criteria

Participants are currently being recruited at the Sexual Health Clinic, AIDS Clinical Center of the National Center for Global Health and Medicine, and Personal Health Clinic in Japan (Figure 1). The inclusion criteria include several aspects. First, participants must be adults aged 18 years or older. Second, the confirmation of the presence of *M genitalium* in an individual's urine or rectal samples is required through the nucleic acid amplification test (NAAT). Lastly, participants are obligated to provide written informed consent to partake in the study, with exclusion criteria covering individuals with known allergies to the study medications and pregnant women. Additionally, individuals deemed unsuitable for study participation by the attending physician based on various criteria or medical judgments will be excluded. Study participants who need antibiotics that are potentially effective for *M genitalium* infection. This includes quinolones other than the study drugs, as well as minocycline, pristinamycin, and nitroimidazole.

Figure 1. Study flow chart.



Randomization and Blinding

We will use a computer-based stratified randomization approach to ensure an equitable allocation of participants across different treatment groups, stratifying based on 2 factors: the facility where the study participants are enrolled and the anatomical site of *M genitalium* infection (categorized as the urethra, rectum, or a combination of both). Participants will be randomly assigned to groups at a 1:1 ratio. Blinding will not be implemented, as treatment success will be determined using the NAAT, an objective test. After randomization, patients will receive their respective treatments and will be scheduled for a follow-up test of cure 3 weeks after completing the regimen, with a permissible range of 10-100 days. The test-of-cure content of the positive sites will be assessed using the NAAT. When treatment fails, the number of short tandem repeats in

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the protein MG309 will be analyzed to differentiate a new infection from a persistent one, as previously reported [26].

Intervention

In the intervention group, participants will be administered 200 mg of oral sitafloxacin daily for 7 days. Additionally, 200 mg oral doxycycline daily for up to 7 days will be administered as pretreatment, depending on the severity, before the definitive diagnosis of *M genitalium*. Severity will be assessed based on patients' complaints.

In the control group, participants will be initially administered 200 mg oral doxycycline daily for 7 days, followed by 400 mg moxifloxacin daily for another 7 days.

Statistical Analysis

The sample size has been determined based on previous treatment success rates and specific assumptions. In a preliminary study, we determined that sitafloxacin achieved a treatment success rate of 92.9% against *M genitalium* with the *parC* G248T (S83I) mutation, in conjunction with wild-type *gyrA* [20]. Furthermore, sitafloxacin demonstrated a 78.9% success rate against strains carrying the *parC* G248T (S83I) mutation based on our preliminary data, and Murray et al [27] reported a moxifloxacin success rate of 41.2% against such strains. Accordingly, the success rates of sitafloxacin and moxifloxacin were anticipated to be 80% and 42%, respectively. With a 5% significance level (2-sided) and 80% statistical power for precise analysis, we aimed to enroll 50 participants per group (totaling 100 cases), considering the prevalence of the G248T mutation. Additionally, an expected dropout rate of approximately 10% was factored in, leading to a calculated sample size of 112 participants, evenly distributed across treatment groups, to robustly assess the efficacy of sitafloxacin and moxifloxacin against specific mutations in *M genitalium*.

Primary analyses regarding efficacy primarily rely on the full analysis set (FAS), which encompasses all registered participants, excluding ineligible participants and those not receiving the study drugs. To evaluate sensitivity, the analysis will be conducted for the per-protocol set, which consists of the study population, excluding cases of major protocol violations and discontinuations from the FAS. To evaluate safety, the analysis will be conducted for the safety analysis set, which includes all registered participants except those not receiving the study drug. Baseline characteristics of the study participants, both discrete and continuous, will be summarized. Discrete data will be presented as frequencies and percentages, whereas continuous data will be presented as descriptive statistics such as the mean and SD. Data will be analyzed with STATA (version 16.0; StataCorp), SAS software (version 9.4; SAS Institute), and R (version 4.1.2; R Foundation for Statistical Computing); the sample size calculation was done using Power Analysis and Sample Size 2022 (NCSS Statistical Software).

Efficacy Outcome

The primary outcome is the treatment success rate, defined as the absence of the pathogen, as indicated through the NAAT. We set the superiority margin at 10%. The secondary outcomes include the change in bacterial load from pre- to posttreatment and the emergence of posttreatment nucleotide polymorphisms in mutant strains compared with those in pretreatment samples. The bacterial load will be measured as previously reported [28]. For the primary outcome in the FAS, with or without the G248T (S83I) mutation, rates and their 95% CIs will be computed. The chi-square test will be used to assess the statistical significance of treatment success between groups. This primary analysis will also be conducted for participants with the G248T mutation in the per-protocol set. In terms of secondary endpoints, differences, and rates of change in the bacterial load will be analyzed using either the 2-tailed Student *t* test or the Mann-Whitney *U* test. The rate and 95% CI of posttreatment resistance mutations in the FAS group will also be estimated using the positive cure confirmation results.

Safety Outcomes

The side effects of each regimen will be reported during visit 2. Any unusual symptom or adverse reaction following the start of the regimens will be documented based on the division of the AIDS table for grading the severity of adult and pediatric adverse events (corrected version 2.1). Safety considerations include documenting adverse events, ranging from allergies and diarrhea to severe conditions such as aortic lesions, which are presented as frequency and group percentages for the safety analysis set.

Data Collection and Management

A case report form (CRF) will be prepared by the appropriate and authorized individuals (investigators and physicians). All data recorded in the CRF must be consistent with the original material unless the data are recorded directly in the CRF as source material. Data will be collected at each visit (Table 1). All study findings and documents will remain strictly confidential, and patients will be identified only by their patient number or birth date, never by name, to protect their anonymity. The following data will be collected: date of birth (age), sex, nationality, race, medical history, history of current disease, complications, and allergies. Additionally, body weight and height will be measured at the first visit, along with vital signs at each visit, including the level of consciousness, body temperature (°C), blood pressure (mm Hg), pulse rate (beats per minute), respiratory rate, and physical condition at every visit, assessed through inspection, palpation, auscultation, and percussion.

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Table 1. Study calendar.

Study activities	Screening	Visit 1 (day 1)	Visit 2 (day 28 or 35)[a]
Informed consent	✓		
Confirmation of eligibility (inclusion and exclusion)	✓		
Enrollment	✓		
Clinical characteristics	✓		
Physical findings	✓	✓	✓
Treatment		✓	
Adverse events			✓
Test of cure			✓

[a]Permissible range of 10-100 days.

Data Monitoring

No external data monitoring committee will be involved in this study. The first author will oversee the progression, completion of the intervention, and follow-up assessment of all participants.

Ethical Considerations

This trial was granted ethical approval by the National Center for Global Health and Medicine of Japan's certified review board (approval NCGM-C-004624-00) in October 2022, registered under jRCTs031230111. The study protocol and informed consent forms were approved by the local ethics committees at each study site before the commencement of the study. Adherence to human subject ethics review approvals was maintained in accordance with institutional guidelines. Informed consent was obtained from all study participants, with the process including clear communication about their right to opt out at any stage without penalty. The data collected during the trial were anonymized to ensure the privacy and confidentiality of participants. While no monetary compensation was provided, participants received the study drug and associated testing free of charge. This provision was documented and justified according to ethical standards and guidelines, ensuring voluntary participation and the integrity of the study.

Results

Enrollment began on June 1, 2023, and will continue until December 31, 2025, followed by participant follow-up. The findings of the study are expected to be released in 2025.

Discussion

Summary

The primary objective of this randomized controlled study is to determine the comparative efficacy and safety of sitafloxacin and moxifloxacin-based sequential treatments in managing *M genitalium* infections, with the primary outcome focusing on the clearance of the pathogen as confirmed by NAAT tests and the secondary outcomes considering bacterial load changes and posttreatment development of resistant strains. Based on previous studies, the expected success rates fall within the range of 80% for sitafloxacin and 42% for moxifloxacin against *M genitalium* carrying the G248T (S83I) mutation. Therefore, sitafloxacin is expected to demonstrate superior efficacy over moxifloxacin-based sequential therapy. The prevalence of strains harboring the G248T (S83I) mutation has increased in certain regions such as Australia, New Zealand, China, and Japan over recent years, with growing concerns in more areas such as the United States [29,30]. Accordingly, the outcomes of this study are poised to have a pivotal role in shaping the evolving treatment landscape for these pathogens, particularly the resistant strains, potentially influencing clinical practice. The multicenter design of this study also enhances its credibility by minimizing bias and broadening the applicability of our findings to a wider population.

Limitations

This study has some limitations. One notable concern is the limited power to detect de novo resistance following the completion of each regimen. Furthermore, our focus extends to urogenital and rectal infections. While previous studies have suggested reduced efficacy of azithromycin against rectal infections, no discernible difference in the effectiveness of sitafloxacin was observed [20,31]. The treatment of rectal infections remains a subject of debate; however, considering that rectal infections may serve as potential reservoirs, assessing their effectiveness at both sites is crucial. Third, determining the optimal treatment for strains with both *parC* and *gyrA* mutations remains challenging owing to limitations in currently available effective regimens [19,20]. Exploring other drugs, such as nitroimidazole, with different mechanisms should be considered [32]. Considering these considerations, future studies, potentially encompassing a broader range of comparative therapies and exploring combinations of various treatments, must be conducted to ensure the best possible outcomes for patients.

Conclusions

As the prevalence of *M genitalium* strains, particularly those with the G248T (S83I) mutation, increases globally, current research is imperative in guiding treatment.

When our hypothesis that sitafloxacin demonstrates superior efficacy over moxifloxacin-based sequential therapy holds, the study will have significant implications, potentially compensating for the practice, especially for resistant strains.

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Data Availability

Data sharing is not applicable to this article, as no data sets have been currently generated or analyzed in the study.

Authors' Contributions

NA conceived and designed the study and also drafted the original manuscript. All the authors contributed to the refinement and approval of this manuscript. All authors have final responsibility for the decision to submit the manuscript for publication.

Conflicts of Interest

None declared.

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Abbreviations

CRF: case report form
FAS: full analysis set
MRM: macrolide resistance-associated mutation
NAAT: nucleic acid amplification test
QRAM: quinolone resistance-associated mutation

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Protocol

Dobutamine and Goal-Directed Fluid Therapy for Improving Tissue Oxygenation in Deep Inferior Epigastric Perforator (DIEP) Flap Breast Reconstruction Surgery: Protocol for a Randomized Controlled Trial

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Abstract

Background: Breast reconstruction is an integral part of breast cancer care. There are 2 main types of breast reconstruction: alloplastic (using implants) and autologous (using the patient's own tissue). The latter creates a more natural breast mound and avoids the long-term need for surgical revision—more often associated with implant-based surgery. The deep inferior epigastric perforator (DIEP) flap is considered the gold standard approach in autologous breast reconstruction. However, complications do occur with DIEP flap surgery and can stem from poor flap tissue perfusion/oxygenation. Hence, the development of strategies to enhance flap perfusion (eg, goal-directed perioperative fluid therapy) is essential. Current perioperative fluid therapy is traditionally guided by subjective criteria, which leads to wide variations in clinical practice.

Objective: The main objective of this trial is to determine whether the use of minimally invasive cardiac output (CO) monitoring for guiding intravenous fluid administration, combined with low-dose dobutamine infusion (via a treatment algorithm), will increase tissue oxygenation in patients undergoing DIEP flap surgery.

Methods: With appropriate institutional ethics board and Health Canada approval, patients undergoing DIEP flap surgery are randomly assigned to receive CO monitoring for the guidance of intraoperative fluid therapy in addition to a low-dose dobutamine infusion (which potentially improves flap oxygenation) versus the current standard of care. The primary outcome is tissue oxygenation measured via near-infrared spectroscopy at the perfusion zone furthest from the perforator vessels 45 minutes after vascular reanastomosis of the DIEP flap. Low dose (2.5 µg/kg/hr) dobutamine infusion continues for up to 4 hours postoperatively, provided there are no associated complications (ie, persistent tachycardia). Flap oxygenation, hemodynamic parameters, and any medication-associated side effects/complications are monitored for up to 48 hours postoperatively. Complications, rehospitalizations, and patient satisfaction are also collected until 30 days postoperatively.

Results: Funding and regulatory approvals were obtained in 2019, but the study recruitment was interrupted by the COVID-19 pandemic. As of October 4, 2023, 34 participants have been recruited. Because of the significant delays associated with the pandemic, the expected completion date was extended. We expect the study to be completed and ready for potential news release

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(as appropriate) and publication by July 2024. No patients have suffered any adverse effects/complications from participating in this study, and none have been lost to follow-up.

Conclusions: CO-directed fluid therapy in combination with a low-dose dobutamine infusion via a treatment algorithm has the potential to improve DIEP flap tissue oxygenation and reduce complications following DIEP flap breast reconstruction surgery. However, given that the investigators remain blinded to group randomization, no comment can be made regarding the efficacy of this intervention for improving tissue oxygenation at this time. Nevertheless, no patients have been withdrawn for safety concerns thus far, and compliance remains high.

Trial Registration: Clinicaltrials.gov NCT04020172; https://clinicaltrials.gov/study/NCT04020172

(JMIR Res Protoc 2023;12:e48576) doi:10.2196/48576

KEYWORDS

breast cancer; breast cancer care; breast reconstruction; DIEP flap; dobutamine; epigastric perforator; implant-based surgery; flap surgery; flap oxygenation; fluid therapy; goal-directed therapy; oxygenation; perioperative care; tissue oxygenation; treatment algorithm

Introduction

Background

Over the last several decades, breast reconstruction has evolved to become an integral part of breast cancer care. In many countries, including Canada, access to breast reconstruction has become a quality indicator for breast cancer care [1]. There are 2 main types of breast reconstruction: alloplastic (ie, using implants), and autologous (ie, using the patient's own tissue). The main advantages of choosing autologous reconstruction include a soft, natural breast mound that can better match a natural breast. Additionally, autologous reconstruction is associated with a lower long-term risk of surgical revision compared to implant-based reconstructions. Patient-reported outcomes measured using the BREAST-Q module indicate improved long-term patient satisfaction following autologous tissue reconstruction [2]. The deep inferior epigastric perforator (DIEP) flap remains the gold standard in autologous breast reconstruction [3], as it generally results in lower donor-site morbidity and optimal outcomes [1,4,5]. The DIEP flap (Figure 1) uses the same lower abdominal island of skin and fat as the pedicled transverse rectus abdominis myocutaneous (TRAM) flap, with the advantage of sparing the rectus abdominis muscle, thus resulting in a lower incidence of abdominal wall laxity and weakness, less postoperative pain, and a shorter recovery period [4,6-10].

However, no surgical procedure is without potential complications. DIEP flap complications include fat necrosis, partial or total flap loss, and abdominal wall laxity or hernia. In a series of 758 DIEP flaps performed for breast reconstruction, 6% of patients were returned to the operating room (OR) for flap-related problems [6]. Partial flap loss occurred in 2.5% of patients and total flap loss in less than 1% [6]. Other complications included fat necrosis (13%), seroma formation at the abdominal donor site (5%), and abdominal hernia (0.7%) [6]. As noted, several complications stem from poor flap perfusion. The current evidence suggests that the rate of perfusion-related complications with DIEP flaps is relatively high and highly variable [11,12], with several factors potentially playing a role, such as patient selection, surgical technique, perioperative fluid management, level of hemodynamic control, and perioperative use of inotropes and/or vasopressors. Hence, providing optimal perioperative management for fluid administration and hemodynamic goals may have a significant impact on the long-term viability of the DIEP flap.

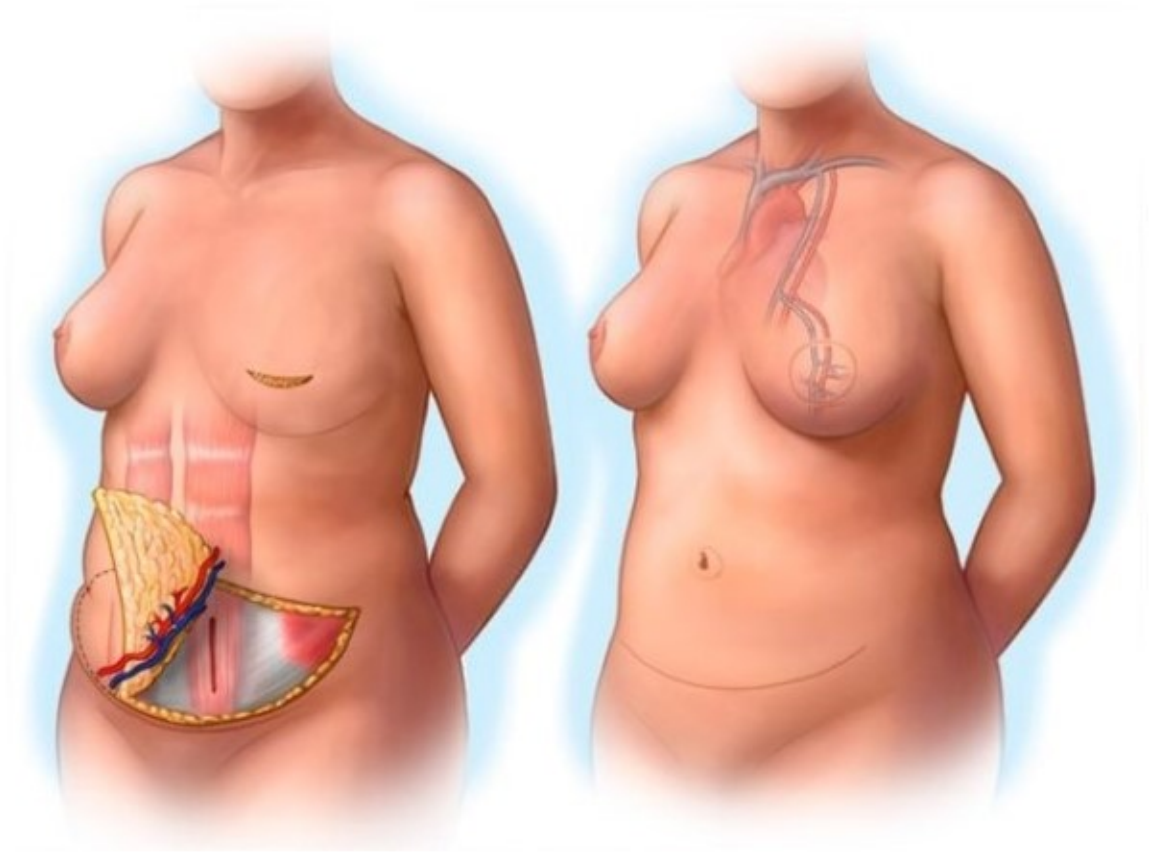
DIEP flaps are typically performed under general anesthesia. Vasoactive agents (eg, phenylephrine) commonly used to counteract the hypotensive effects of general anesthetics are often avoided in flap surgery due to concerns over vasoconstriction, which have been proven in animal models to consistently reduce the pedicle artery blood flow and microvascular perfusion of the flap [13]. Although definitive evidence is lacking in humans, a retrospective investigation suggests a trend toward increased partial flap loss in patients who received vasopressors compared to patients who did not [14]. Conversely, certain inotropes (eg, dobutamine, dopexamine) may be beneficial in enhancing peripheral oxygen delivery through increased cardiac output (CO) and a direct peripheral vasodilatory effect [15].

In DIEP flap surgery, maintaining normovolemia is of particular interest, as hypovolemia may lead to tissue hypoperfusion and hypervolemia may result in tissue edema, both of which can ultimately cause poor flap oxygenation. Indeed, a retrospective analysis of 354 free flaps for breast reconstruction revealed that the extremes of crystalloid infusion significantly predicted postoperative complications [16]. Yet, in current clinical practice, perioperative fluid therapy is commonly prescribed using subjective criteria, leading to wide variations in the total volume of crystalloid administered perioperatively. Therefore, CO monitoring to guide intravenous fluid management as part of a goal-directed hemodynamic therapy algorithm could significantly benefit this patient population. Notably, this approach has been studied for many years in various settings and has been shown to modify inflammatory pathways and improve tissue perfusion and oxygenation [15,17,18]. Specifically, a prospective analysis of 104 DIEP flaps comparing fluid-guided therapy by CO monitoring versus central venous pressure (CVP) found that the fluid input was not different between groups; however, patients in the CVP group had a smaller fluid output (blood loss, urine output, etc) and were in greater positive fluid balance, whereas the CO monitoring group had a reduced anesthetic time (despite similar surgical time between groups) and spent a mean of 1.9 days less in the hospital [19]. No differences were observed concerning core temperature

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or flap complications [19]. These findings suggest that meticulous fluid management and tight hemodynamic control, combined with select inotropes, may optimize flap perfusion.

Figure 1. Depiction of deep inferior epigastric perforator (DIEP) flap breast reconstruction surgery in which the lower abdominal island of skin and fat are used to form the tissue flap for breast reconstruction while sparing the rectus abdominis muscle. Although the muscle must be split to dissect out the perforating vessels, the muscle is not transferred. The deep inferior epigastric artery and vein, which provide the vascular supply for the free flap, are anastomosed to local recipient vessel using either the internal mammary or thoracodorsal arteries and veins. Image reproduced with permission from the Mayo Foundation for Medical Education and Research, all rights reserved.



Dobutamine (2 to 20 mcg/kg/min) is an inotrope widely used to treat cardiogenic shock and/or congestive heart failure. Its predominantly β-1 adrenergic receptor stimulatory effect increases inotropy and chronotropy and reduces left ventricular filling pressure. Dobutamine also has minimal β-2 adrenergic receptor effects, resulting in peripheral vasodilation. The net effect is increased CO and decreased systemic vascular resistance, with a generally imperceptible effect on blood pressure [20].

Purpose and Hypothesis

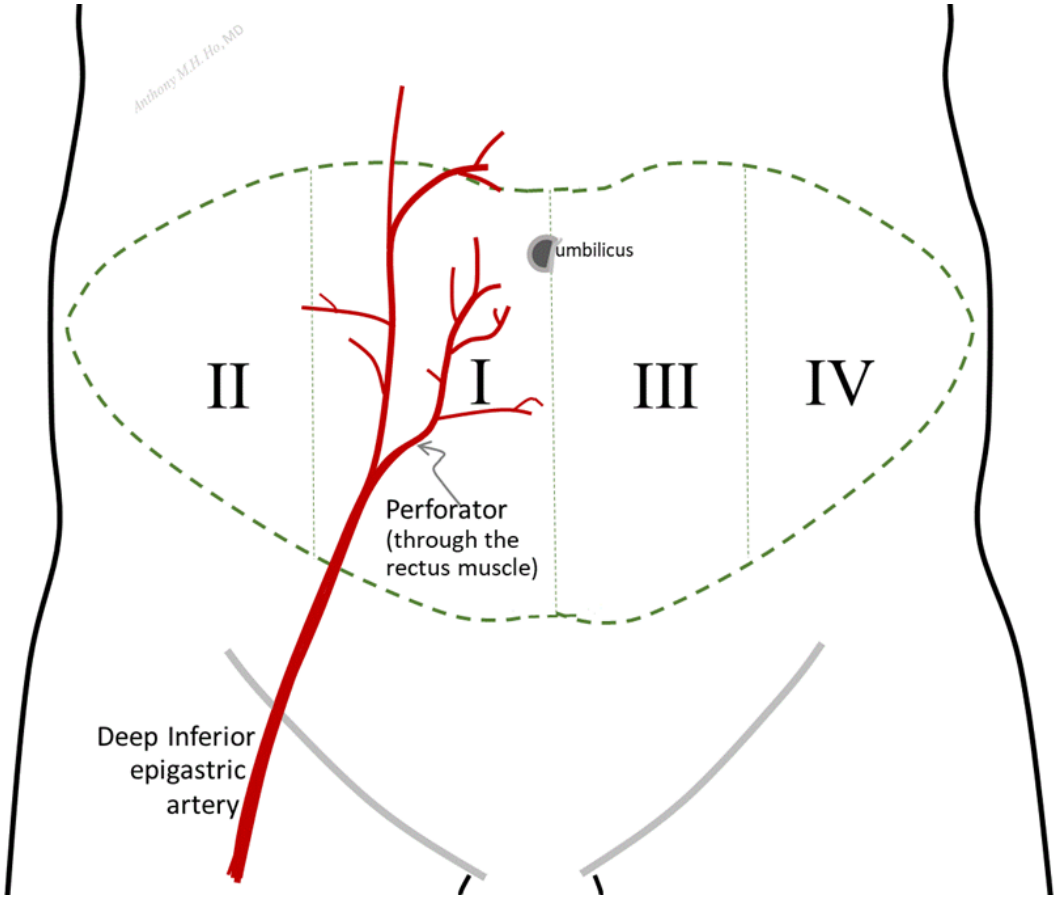
The purpose of this trial is to evaluate the effects of perioperative hemodynamic therapy (guided by CO monitoring) on tissue oxygenation during and after DIEP flap breast reconstruction surgery. We hypothesize that a low-dose, perioperative dobutamine infusion combined with goal-directed fluid therapy guided by CO monitoring will improve flap perfusion, and thus oxygenation, in patients undergoing DIEP surgery.

Objectives and Outcome Measures

The main objective is to determine whether the use of minimally invasive CO monitoring to guide intravenous fluid administration, combined with low-dose dobutamine infusion (via a treatment algorithm), will increase overall tissue oxygenation in patients undergoing DIEP flap surgery. The primary outcome is tissue oxygenation, measured via near-infrared spectroscopy (NIRS), 45 minutes following vascular reanastomosis of the DIEP flap within the perfusion zone farthest from the perforator vessels. This zone is the most vulnerable surgical area to ischemia and therefore the most likely to reflect the potential benefits of the proposed intervention. In the case of bilateral DIEP flaps, this zone will be assessed in both the left and right breasts. The zonal blood supply for DIEP flaps is depicted by Holm (Figure 2) [21]. Zone 1 includes the perforator vessel and is thus the most reliably perfused portion of the flap, while any flow across the midline can be less reliable than ipsilateral flow depending on the location of the perforators in zone 1. As aforementioned, the primary outcome will be tissue oxygenation within the zones farthest from the perforator vessels.

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Figure 2. Depiction of the Holm perfusion zones [21]. Zone I is well recognized for being the most richly perfused as it contains the perforator vessels. The use of this zone during deep inferior epigastric perforator (DIEP) flap breast reconstruction surgery may provide optimal tissue flap perfusion.



Our secondary outcomes include (1) tissue oxygenation at baseline (preoperatively), intra-operatively and 1, 2, 4, 8 hours postoperatively, as well as the morning of postoperative days 1 and 2; (2) the amount of intravenous fluids (crystalloids, colloids, blood products) and vasopressors (eg, phenylephrine, ephedrine, norepinephrine, etc) administered intraoperatively and up to 4 hours postoperatively; (3) the need for intraoperative surgical vascular reintervention (ie, reanastomosis); (4) laboratory measures including perioperative pH, serum lactate, and hemoglobin measures; (5) incidence of postoperative nausea and vomiting; (6) hospital length of stay; (7) any postoperative complications including infection, hematoma, and those resulting from flap malperfusion (ie, partial/total flap loss and fat necrosis); (8) the need for postoperative intervention for flap-related issues; (9) overall patient satisfaction; and (10) days alive and out of hospital, all up until 30 days postoperatively.

Methods

Ethical Considerations

This study received institutional ethics board approval (ANAE-341-19) on May 16, 2019, and Health Canada approval (control no 228403) on July 8, 2019. Moreover, it was registered on Clinicaltrials.gov (NCT04020172) on July 12, 2019. This study is being completed in compliance with the current protocol and the Guidelines for Good Clinical Practices. All data collected will be retained for 15 years in a form identified only by study identification numbers linked to the patient's identity through a master list kept separate from the data in a locked cabinet. Only study investigators and governing bodies for regulatory inspections/trial monitoring will have access to the confidential patient data. Should any significant protocol modifications be required that may impact participants' provision of consent or safety, this will be immediately shared with the participants, the ethics board, and Health Canada as appropriate. Such changes will also be documented on the Clinicaltrials.gov registry.

Participants and Recruitment

Overview

Patients scheduled for elective unilateral or bilateral delayed or immediate DIEP flap surgery at a medium-sized academic center will be recruited. Eligible patients will be approached at their preoperative surgical visit with the plastic surgeon (GM or WE). If patients are willing to participate, a research team member will obtain written informed consent after their assessment by the attending surgeon (Multimedia Appendix 1). In all cases, the anesthesiologist will be made aware of the patient's potential study involvement should there be any medical reasons warranting study exclusion.

Sample Size

There are few similar studies in the literature on which to base a valid sample size calculation. However, 1 randomized controlled trial (RCT) [15] compared 3 arms, two of which are similar to what we propose to study in terms of pharmacological intervention (ie, dobutamine/dopexamine) versus none (standard

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of care). Eight hours postoperatively, they noted a 1.75 kPa increase in cutaneous tissue oxygen partial pressure (PtO_2) in their stroke volume (SV) + dopexamine arm as compared to a 0.50 kPa increase in the SV-only arm. Using an SD of 1.0, α of 0.05, and a power of 80%, only 11 cases would be required per arm for these differences to attain statistical significance. However, this sample is rather small for valid statistical analyses [22], and because our groups are not identical to those available in the literature, we propose to increase the sample size to 20 per group. Notably, given that their SV group is tightly regulated (and therefore, likely superior) compared to our standard of care group, our sample size estimation is likely overly conservative.

Study Design, Randomization, and Blinding

Overview

This is a prospective RCT. A total of 40 participants will be randomized to one of 2 groups (n=20 per group) using a computer-generated randomization prepared by the institutional biostatistician. Patient randomization will be concealed in envelopes and opened only by the research staff (not otherwise involved with data collection) and/or the attending anesthesiologist prior to anesthesia induction. Blinding will be maintained until study completion and verification that all outcome data have been successfully collected for all study participants.

Surgical Procedure

Patients will be marked in the preoperative holding area for an abdominal-based free-flap breast reconstruction. All procedures are planned as a DIEP reconstruction. For most flaps, the goal is to include 1 to 3 perforators to optimize perfusion. In some cases, the DIEP flap may be converted to a muscle-sparing flap to achieve adequate arterial inflow and venous outflow to the tissue flap. Because the primary outcome is to look at perfusion of the flap most distant from the perforating vessels, in most cases, unilateral breast reconstructions will be performed, and perfusion zones 1, 2, and 3 included, according to the Holm classification (Figure 2). However, in patients with bilateral reconstructions, only Holm zones 1 and 2 will be included in a single flap. The supplying deep inferior epigastric vessels will be harvested at the level of the iliac artery and vein, and a microvascular anastomosis will be performed with the internal mammary artery and vein under a surgical microscope. A single artery and vein will be routinely anastomosed.

Approved Protocol

A tissue oximeter device (SnapshotNIR; Kent Imaging) will be used for all patients. This is a portable noninvasive monitor that measures tissue oxygen saturation using NIRS technology with the capability of saving images to allow for subsequent analyses. Measurements will be taken by holding the monitor at a standardized (30 cm) distance from the skin area where the oxygen levels are to be measured. Upon admission to the OR, preoperative baseline measurements (with patients breathing ambient air without supplemental oxygen) will be recorded over the abdominal flap tissue, followed by recordings immediately postinduction, 1-hour postinduction, when the abdominal flap is free (and still perfused by the chosen perforator arteries), before clamp removal postarterial reanastomosis, and 45 minutes following reanastomosis. All research personnel dedicated to this study will receive prestudy training on the perfusion zones and study outcomes to ensure that oxygenation measures are consistently taken from the same surgical region in relation to the perfusion zones (as described in Figure 2) throughout each case. In addition, the surgical team, led by authors GM and RWE, will assist with guiding the intraoperative oxygenation measurements with respect to flap location. However, the surgical team and attending anesthesiologist will be blinded to the Kent oxygenation measurements throughout the perioperative period, and surgery will be guided as per the standard of care. The ischemic period during which the flap is transferred (reflected by a fall in the oxygen saturation of the flap [23]) as well as the time of flap revascularization (characterized by increased oxygen saturation [23]) will be recorded. Upon completion of the surgical procedure, another NIRS-based monitor (Somanetics INVOS 5100C Cerebral/Somatic Oximeter; Medtronic) may be applied to the freshly reconstructed graft at the surgeon's discretion. If deemed appropriate, a sticker will be applied over the flap for continuous graft oxygenation monitoring up to 48 hours postoperatively. However, if the surgeon requires the entirety of the graft to be exposed for visual monitoring (as per the standard care), a sticker/sensor will not be applied. Nevertheless, postoperative measures will be routinely recorded at 1, 2, 4, and 8 hours postoperatively, as well as on the morning of postoperative days 1 and 2 using the Kent device. All measures will be consistently taken at the same location [24]. Note that continuous intraoperative monitoring with the Somanetics INVOS Oximeter is not possible, as the sensors cannot be sterilized.

All surgical procedures will be performed by one of the 2 surgeons (GM and RWE) to minimize variability in patient selection and surgical technique, both predictors of clinical outcomes in microsurgery [25]. Elective DIEP flap surgical procedures and anesthetic management will be completed in accordance with the standard of care. Perioperative management will be identical in both groups, apart from the hemodynamic monitoring for guiding intravenous fluid therapy and interventions as described below. In the OR, the ambient temperature will be set at 20^{o} C and standard monitors will be applied. Invasive monitoring in the form of an arterial line will be established as per the current practice. General anesthesia will be induced with propofol and fentanyl, followed by rocuronium to facilitate endotracheal intubation, and maintained with end-tidal sevoflurane (Et_{sevo}=1.5%-3%) and additional doses of fentanyl and/or hydromorphone administered at the discretion of the attending anesthesiologist. Extra doses of rocuronium will be administered throughout the case for muscle relaxation. A mean arterial pressure (MAP) ≥65 mmHg will be targeted throughout the perioperative period. Likewise, all patients will receive standard measures to maintain oxygen saturation (SpO_2 ≥95%), end-tidal carbon dioxide (Et_{CO2}) between 35 and 40 mmHg, hemoglobin (>8 g/dl), and a heart rate <100 beats per minute (BPM). A warming device (enFlow IV Fluid/Blood Warming System; GE Healthcare) will be used for intravenous fluids, along with a forced-air patient warming system (Bair Hugger Normothermia System; 3M) to maintain normothermia (core temperature between 36 and 37.5 ^{o}C).

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Arterial blood gasses will be checked every 2 hours (or more often at the discretion of the attending anesthesiologist) to specifically monitor the pH, SpO_2, partial pressure of oxygen (PaO_2) in arterial blood, partial pressure of carbon dioxide ($PaCO_2$) in arterial blood, base excess, hemoglobin, and lactate levels as surrogates for tissue perfusion perioperatively. Urine output will be recorded hourly. The total amount of vasopressor, perioperative fluid (crystalloids and albumin 5%), and blood products, if any, will be recorded. In addition, the following demographic and surgical characteristics will be included: age, BMI, preoperative hemoglobin and hematocrit levels, American Society of Anesthesiologists (ASA) classification, Charlson Comorbidity Index, and total surgical and anesthetic time. Subsequently, 4 mg prophylactic intravenous dexamethasone upon the induction of general anesthesia and 4 mg ondansetron 15 minutes prior to completion of the surgical procedure will be administered to prevent nausea and vomiting. All patients will be managed postoperatively in a high-dependency unit (level 2 critical care) and given an intravenous patient-controlled analgesia (IV-PCA) pump containing hydromorphone (or an alternative in the case of adverse reactions) for postoperative pain management, as per the current standard of care. The postoperative goals (up to 48 hours postoperative) will be similar to the intraoperative period, namely: MAP ≥65 mmHg (or within 20% of baseline), SpO_2 ≥95%, $PaCO_2$ between 35 and 45 mmHg, hemoglobin >8 g/dl, core temperature between 36 and 37.5 °C, and heart rate <100 BPM. Research personnel will call patients 30 days postoperatively to document any complications, hospitalizations, and overall satisfaction. If patients cannot be reached via telephone, the patient's family physician may be contacted and their medical record accessed to determine whether the patient experienced postoperative complications or required medical attention (as per the informed consent form).

Intervention Group

The intervention will commence from the induction of general anesthesia and continue until 4 hours after surgery. Ringer lactate (2 ml/kg/h) will be commenced upon admission to the OR to satisfy maintenance fluid requirements. CO and stroke volume index (SVI) will be measured by one of 2 CO monitors: (1) FloTrac system (Edwards Lifesciences Corp), which attaches to the arterial line already in place in this surgical population; or (2) Starling SV system (Cheetah Medical), a noninvasive CO monitor that utilizes 4 stickers placed on the patient's trunk. No more than 500 ml of intravenous fluid will be administered at anesthesia induction. In addition to the maintenance fluid described previously, patients will receive 250 ml fluid challenges with crystalloid as required until they are no longer fluid-responsive. Albumin 5% will also be allowed for fluid challenges at the discretion of the attending anesthesiologist. The absence of fluid responsiveness will be defined as the absence of a sustained rise in SVI of at least 10% for 20 minutes or more, at which point the patient will be considered fluid-optimized. At this point, a low-dose dobutamine infusion at a fixed rate (2.5 µg/kg/min) will be commenced and maintained until 4 hours postoperatively. The infusion rate will be halved and/or discontinued if the patient develops tachycardia (heart rate ≥100 BPM) for more than 30 minutes despite adequate anesthesia/analgesia and fluid status (based on the aforementioned intervention). Further fluid challenges will be performed by the attending anesthesiologist with the aim of maintaining maximal SVI throughout the case. Postoperatively, the patient will remain in the postanesthetic care unit (PACU) for a minimum of 4 hours (as per the current standard of care), after which the CO monitoring and the dobutamine infusion will be discontinued and the patient transferred to a level 2 step-down critical care unit. Ringer lactate at 2 ml/kg/h will be infused to satisfy maintenance fluid requirements until oral fluid intake is permitted by the surgical team, at which point the maintenance infusion will be stopped. Data collection and follow-up for such patients will be performed as per the standard of care.

Control Group

Patients in the control group will also receive a baseline infusion of Ringer lactate at 2 ml/kg/h to satisfy maintenance fluid requirements, which will commence upon admission to the OR. The anesthetic management will otherwise be according to standard practice. This will include 250 ml fluid challenges with a crystalloid administered at the discretion of the attending anesthesiologist, generally guided by pulse rate, arterial pressure, urine output, and/or core-peripheral temperature gradient. Albumin 5% will also be allowed for fluid challenges at the discretion of the attending anesthesiologist. No specific CO monitoring device will be used to guide fluid therapy; however, it will be present in the OR throughout the case to ensure adequate blinding of the surgical team and research staff regarding the 2 patient groups. Likewise, perioperative dobutamine will not be used unless clinically indicated to improve cardiac function, as it is not currently part of our standard practice in these surgeries, and there is no yet documented evidence to support its use in all DIEP flap patients. We expect this study to address this knowledge gap and provide evidence as to whether there is a benefit to using it routinely. Postoperative care will be similar to the intervention group (except for the CO monitoring and dobutamine infusion in PACU).

Inclusion and Exclusion Criteria

The inclusion and exclusion criteria for patient recruitment are outlined in Textbox 1.

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Textbox 1. Inclusion and exclusion criteria for the study recruitment.

Inclusion criteria

- Between 18 and 80 years of age
- Meet the American Society of Anesthesiologists (ASA) physical status classification I-III
- Undergoing elective unilateral/bilateral immediate or delayed deep inferior epigastric perforator (DIEP) flap surgery
- Cognitive ability to provide informed consent

Exclusion criteria

- Have dementia or neurological impairment
- Scheduled for DIEP flap combined with any other secondary surgical procedure
- Documented left ventricular dysfunction (ejection fraction < 40%)
- Contraindication to low-dose dobutamine
- BMI <18 or >40 kg·m-2
- Pregnant or lactating
- Renal insufficiency, with an estimated glomerular filtration rate (eGFR) <30 ml/min/1.73m2)
- Known liver insufficiency (ie, documented cirrhosis, coagulopathy, and/or encephalopathy of hepatic origin)

Premature Withdrawal and Discontinuation Criteria

One of the limitations of dobutamine infusion is tachycardia. The infusion rate will be halved and/or discontinued if a patient develops tachycardia (heart rate ≥100 BPM) for more than 30 minutes despite adequate anesthesia/analgesia and fluid status (based on the aforementioned intervention). If the reduced dose does not correct the tachycardia, the infusion will be turned off. In addition, if at any point the attending staff raises concerns about the patient being at an increased risk because of study participation, the intervention will be stopped and the patient removed from the investigation. Moreover, if the patient decides they want to withdraw their consent at any point prior to publication, they will be excluded from the study and none of the information collected from them will be used for research purposes. The study intervention only applies during surgery and potentially for up to 4 hours postoperatively. All study participants will be fully monitored for the duration of the study intervention and beyond for up to 48 hours postoperatively. They will have immediate access to any additional care or intervention if required.

If patients are withdrawn from the study, we will continue to enroll consecutively until we have met our stipulated sample size of 20 patients per group. For patients who are withdrawn, we will seek permission to retain any data collected (especially demographic information) for comparison between those who were not and those who were withdrawn to determine whether they differ in any respect.

Rescue Medication and Risk Management

All anesthesia and surgical procedures are according to the standard of care except for the low-dose dobutamine infusion intraoperatively and potentially up to 4 hours postoperatively, the use of CO monitoring to guide fluid administration intraoperatively and for up to 4 hours postoperatively, and noninvasive measurements of tissue oxygenation until 48 hours postoperatively. Patients will be intensively monitored, and medications will be administered as considered medically necessary. Conversely, no medications deemed medically necessary will be withheld because of study participation. The main potential side effect associated with dobutamine is tachycardia. To mitigate this risk, our protocol proposes a very low-dose infusion. In addition, the dobutamine infusion rate will be halved and/or discontinued if the patient develops tachycardia (heart rate ≥100 BPM) for more than 30 minutes despite adequate anesthesia/analgesia and fluid status. Additionally, all patients will be intensively monitored while in the hospital for any adverse events/complications, which will be carefully considered in terms of whether they are related to the study intervention or otherwise and action will be taken accordingly.

Adverse Event Reporting

Adverse events and serious adverse events (SAEs) will be monitored and documented. Study staff will mandatorily report all SAEs to the investigator for evaluation as soon as they become aware. All adverse events will be immediately and mandatorily reported to the Queen's University and Affiliated Teaching Hospitals Research Ethics Board and the Therapeutic Products Directorate of Health Canada, as per current guidelines.

If a patient experiences an adverse event due to study participation, medical care will be provided to them until resolution of the problem. Patients will be asked about satisfaction with healing and overall surgical care on the day of discharge. Patients will also receive a 30-day follow-up telephone call from research staff inquiring about complications and patient satisfaction.

Statistical Analysis

Data will be entered into REDCap (Research Electronic Data Capture; version 10.6.12; Vanderbilt University). Upon study completion, the data will be exported to SPSS software (version 29.0; IBM Corp) for analysis. Descriptive analyses, including mean, SD, median, and interquartile range for continuous data,

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as well as frequencies and percentages for categorical data, will be completed for all demographic and surgical characteristics and study outcomes. The underlying distributions of all continuous data will be assessed for normality using the Shapiro-Wilk test. Tissue oxygenation will be compared using independent sample *t* tests if the data are normally distributed and the Mann-Whitney *U* test in the event that they are not. Secondary outcomes will be compared between the 2 groups using the Fisher exact or Pearson chi-square tests (as appropriate depending on cell sizes) for categorical data and independent samples *t* tests (or the Mann-Whitney *U* test depending on the underlying distribution) for continuous data. Intent-to-treat analyses will not be conducted, and no adjustments will be made for missing data. Repeated measures analysis of variance (ANOVA), with the group as a factor, will be used to compare the tissue oxygenation over time (baseline, 1, 2, 4, and 8 hours postoperatively, along with baseline and postoperative day 1 and day 2 data). $P<.05$ will be used as the criteria for statistical significance, and no adjustment will be made for multiple comparisons. The possibility of a type I error will be acknowledged, and the actual *P* values will be presented for all comparisons.

Results

This project received funding and all regulatory approvals in 2019, but patient recruitment was interrupted by the COVID-19 pandemic and associated elective surgery cancellations. As of October 4, 2023, 34 participants have been successfully completed. Because of the significant delays associated with the pandemic, the expected completion date was extended, and we now expect study completion and publication (and potential news release as appropriate) by July 2024. Given that investigators remain blinded to group randomization, no statement can be made with respect to the study intervention in terms of tissue oxygenation at this point. At this time, investigators can only state that there have been no study withdrawals for safety concerns, no severe adverse events, and patient compliance remains high.

Discussion

Although no conclusions can be drawn at this time regarding the efficacy of the intraoperative CO monitoring/dobutamine infusion for improving tissue flap oxygenation in DIEP flap surgical patients, it is important to note that no patients have been withdrawn from the study due to safety concerns, there have been no complications attributable to the dobutamine infusion, and compliance remains high. These are important achievements that indicate that this study will be completed successfully within the projected time frame.

Because this is a single-center RCT, the generalizability of the results to all DIEP flap surgical patients may be limited and the numbers too small to make any determinations regarding rare adverse events. However, if we demonstrate that the intervention improves tissue oxygenation, the results from this trial will be used to plan (and acquire funds for) a large multicenter RCT to examine whether the altered oxygen levels have a detectable impact upon rare postoperative complications and for which the results would be generalizable to all DIEP flap surgical patients. Success with this highly novel approach could potentially lead to a change in the perioperative monitoring and management practices of DIEP flap surgical patients, with implications for improved long-term surgical success and patient satisfaction. Given that these microsurgical procedures are of such long duration and high complexity, any improvements in the surgical technique to improve long-term outcomes would be significant, particularly if the modifications are simple and short-term like those described with intraoperative CO monitoring and low-dose dobutamine infusion.

Acknowledgments

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Data Availability

Following study completion, the study results will be made publicly available on Clinicaltrials.gov (NCT04020172).

Authors' Contributions

GBM and AM-HH were involved in the conception, funding acquisition, methodology, data curation, writing the original draft, manuscript revision, and approval of the final version for submission. RP was involved in the funding acquisition, methodology, data curation, manuscript revision, and approval of the final version for submission. DD was involved in the supervision, data collection, data curation, manuscript revision, and approval of the final version for submission. JS and EV were involved in the data collection, data curation, manuscript revision, and approval of the final version for submission. JX and BS were involved in data curation, manuscript revision, and approval of the final version for submission. WMH was involved in the methodology, data curation, manuscript revision, and approval of the final version for submission. GM was involved in the conception, funding acquisition, methodology, data curation, writing the original draft, manuscript revision, and approval of the final version for submission. RWE was involved in the data curation, revision, and approval of final the version for submission. MM and RT were involved in the methodology, revision, and approval of the final version for submission. All authors made important intellectual contributions and approved the final version for submission.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Approved consent.
[DOC File , 599 KB - resprot_v12i1e48576_app1.doc]

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Abbreviations

ANOVA: analysis of variance
BPM: beats per minute
CO: cardiac output
CO2: carbon dioxide
CVP: central venous pressure
DIEP: deep inferior epigastric perforator
EtCO2: end-tidal carbon dioxide
Etsevo: end-tidal sevoflurane
IV-PCA: intravenous patient-controlled analgesia
MAP: mean arterial pressure
NIRS: near-infrared spectroscopy
OR: operating room
PaCO2: partial pressure of carbon dioxide
PACU: postanesthetic care unit
PaO2: partial pressure of oxygen
PtO2: tissue oxygen partial pressure
RCT: randomized controlled trial
REDCAP: Research Electronic Data Capture
SAE: severe adverse event
SpO2: oxygen saturation
SV: stroke volume
SVI: stroke volume index
TRAM: transverse rectus abdominis myocutaneous

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Protocol

The Primary Prevention of Poststroke Epilepsy in Patients With Middle Cerebral Artery Infarct: Protocol for a Randomized Controlled Trial

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Abstract

Background: Poststroke epilepsy poses a significant clinical challenge for individuals recovering from strokes, leading to a less favorable long-term outlook and increased mortality rates. Existing studies have primarily concentrated on administering antiseizure or anticonvulsant treatments only after the onset of late-onset seizures, without intervening during the epileptogenesis phase following a stroke.

Objective: This research protocol is designed to conduct a randomized controlled trial to assess whether the early, preventive introduction of low-dose antiepileptic drug therapy (levetiracetam [LEV] or perampanel [PER]) in patients who have experienced middle cerebral artery (MCA) infarction can reduce the risk of developing poststroke epilepsy (primary prevention).

Methods: Participants with MCA infarction, either with or without reperfusion treatments, will be recruited and promptly receive preventive intervention within 72 hours of the stroke occurrence. These participants will be randomly assigned to receive either PER (4 mg per day), LEV (1000 mg per day), or a placebo that matches the active drugs. This treatment will continue for 12 weeks after allocation. Brain magnetic resonance imaging will be used to confirm the presence of MCA territory infarction, and an electroencephalography will be used to ensure the absence of epileptiform discharges or electrographic seizures at the time of the stroke. All participants will undergo follow-up assessments for 72 weeks after allocation.

Results: The primary outcome under evaluation will be the incidence of poststroke epilepsy in the 3 groups following the 18-month study period. Secondary outcomes will encompass the time to the occurrence of the first seizure, the severity of seizures, any treatment-related adverse events, and the modified Rankin scale score at 3 and 18 months. Exploratory outcomes will involve comparing the effectiveness and safety of PER and LEV.

Conclusions: We anticipate that the intervention groups will experience a lower incidence and reduced severity of poststroke epilepsy compared to the control group after 18 months. We aim to establish evidence supporting the potential preventive effects of LEV and PER on poststroke seizures and epilepsy in patients with MCA infarction, as well as to explore the antiepileptogenic potential of both LEV and PER in patients with major ischemic strokes.

Trial Registration: ClinicalTrials.gov NCT04858841; https://clinicaltrials.gov/study/NCT04858841

International Registered Report Identifier (IRRID): DERR1-10.2196/49412

(JMIR Res Protoc 2023;12:e49412) doi:10.2196/49412

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KEYWORDS

poststroke epilepsy; middle cerebral artery infarct; seizure; randomized control trial; epilepsy; stroke; stroke survivor; prognosis; mortality; drug therapy; development; seizure severity; efficacy; heart attack; angina; cardiovascular; cardiology; cardiologist

Introduction

Background

Advances in stroke treatment have caused a considerable reduction in stroke mortality; however, the number of stroke survivors living with disability has increased significantly. Seizures and epilepsy related to ischemic stroke are common, and poststroke epilepsy is a significant clinical problem for stroke survivors. Stroke is the most common cause of epilepsy in older adults and for patients older than 65 years of age, and poststroke epilepsy accounts for 30%-50% of new-onset seizures [1]. The incidence of early seizures (occurring within the first 1-2 weeks of stroke) is 2.4%-5.4%, and the risk of poststroke late seizures (seizures occurring later than after 14 days of stroke) is approximately 7%-18% [1,2]. Late-onset poststroke epilepsy has a higher recurrence rate of up to 71.5% within 10 years after stroke [3]. Our previous study demonstrated that seizures during stroke increase overall morbidity and mortality [4]. The stroke severity, location (for example, middle cerebral artery [MCA] infarcts in our study), and the type of pathological changes, genetic factors, and pre- and postinjury exposure to nongenetic factors influence the susceptibility of patients with ischemic stroke [5,6]. The standardized morbidity rate of developing epilepsy is highest during the first year after stroke. In addition, higher National Institutes of Health Stroke Scale (NIHSS) score [7], cortical involvement, younger age, and central nervous system morbidities are associated with higher risk of poststroke epilepsy [1,8].

The effects of thrombolysis and thrombectomy on long-term poststroke epilepsy remain unclear. A retrospective evaluation of patients with thrombolysis found that 4% developed poststroke seizures during hospitalization and that death during admission was significantly more likely in those with seizures compared to those without seizures [9]. Another study found that 5.5% of patients receiving endovascular therapy had seizures between stroke onset and 3-month follow-up, and early seizures independently predicted a significantly unfavorable outcome [10]. Regarding early postthrombectomy seizures, 2.4% of patients with ischemic stroke treated with thrombectomy developed at least 1 seizure within 7 days of stroke onset, and the occurrence of seizures was associated with higher 90-day mortality and poorer functional outcomes [11]. For patients with stroke, receiving reperfusion treatments was not associated with acute symptomatic poststroke seizures or poststroke epilepsy [7,12].

Ethnicity may be an important factor in the development of poststroke seizures and epilepsy. The prevalence of poststroke seizures in patients without atrial fibrillation is higher in Australia than in China [13]. In Taiwan, 1 study found that atrial fibrillation may cause ischemic stroke that subsequently causes seizure and atrial fibrillation is associated with a higher rate of subsequent seizure [14]. One-year poststroke epilepsy risk is higher in patients staying in the ICU or in patients with seizure at stroke admission, atrial fibrillation, or cognitive impairment [15]. Late poststroke seizure recurrence is more common in patients of young age (younger than 65 years of age), of male sex, with large lesion seizure, or with partial-onset seizure [16].

Concept of Epileptogenesis

Antiepileptic drugs (AEDs) or antiseizure medications may prevent the recurrence of seizures but do not cure epileptogenesis. An epileptogenesis is the process by which the previously normal brain is functionally altered and biased towards the generation of abnormal electrical activity that induces chronic seizures [17]. It involves molecular, anatomical, or circuit-level alterations, such as cell death or dysregulation of an ion channel or neurotransmitter receptor and the impairment of intrinsic plasticity. How these different levels of alteration are regulated remains unclear. Studies have reported that the epigenetic factor chromodomain Y-like protein, a critical regulator of the initiation and maintenance of intrinsic neuroplasticity that works by regulating voltage-gated sodium channels [18], is involved, and epileptic neurons may also develop short- and long-term adaptive changes in sensitivity to gamma-aminobutyric acid (GABA)ergic neurotransmission [19], worsening excitatory or inhibitory imbalance and thus reducing the possibility of successful therapeutic approaches using traditional AEDs. Further, an increasing amount of research, including ours, suggests a major involvement of inflammation in epileptogenesis [20-22]. Seizure activity elicits the release of proinflammatory cytokines and activates immune responses.

We have studied medications with potential antiepileptogenesis effects in pilocarpine-induced seizure animal models, supporting the concept of antiepileptogenesis with intervention immediately following brain insult [21-23].

Studies Regarding Primary Prevention

The clinical trials aimed at the prevention of chronic epilepsy have often produced negative results because they mainly evaluated downstream clinical manifestations instead of monitoring early, specific molecular epileptogenic events and applying early intervention. A 1990 study on primary prevention of posttraumatic seizures with early use of phenytoin [24] indicated that phenytoin exerts a beneficial effect by reducing seizures only during the first week after severe head injury.

American Heart Association guidelines indicate that prophylactic AEDs are not recommended for the prevention of poststroke seizure [25] due to the lack of randomized control trials and some reports indicating that prophylactic AED therapy may be associated with poorer outcomes [26-28]. In addition, valproic acid therapy was found to be ineffective compared with a placebo in preventing the occurrence of late-onset seizures in patients with spontaneous and nonaneurysmal intracerebral hemorrhage [29]. Nevertheless, the lack of success in prophylactic AED therapy trials may be related to the use of traditional AEDs.

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Medications With Antiepileptogenetic Potential

Numerous AEDs exist. Based on our clinical experience and laboratory research [21,22,30-33], we have identified 2 newer AEDs with antiepileptogenesis potential. Levetiracetam (LEV), which exhibits a distinct synaptic vesicle modulating mechanism, has exhibited the potential in ameliorating epileptogenesis [1,34,35]. Our earlier research indicates that it has a broad spectrum of modulating neuronal excitability [30]. It exhibits no clinically relevant drug-drug interactions [36]. Perampanel (PER), a standard AED with a distinct mechanism of selective noncompetitive antagonism of alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-type receptors, is also effective in treating a wide spectrum of epileptic seizures and has a favorable tolerability profile [37]. Because it blocks glutamate excitotoxicity, PER is theoretically capable of modulating epileptogenesis and has demonstrated potential in ameliorating epileptogenesis [32,38,39]. Thus, it is potentially justified to evaluate whether early prophylactic administration of LEV or PER in patients with acute major stroke hampers the development of epileptogenesis and later poststroke epilepsy.

Methods

Overview

We will conduct a prospective randomized, triple-blind, and placebo-controlled study. To calculate the appropriate sample size, we took into account various factors including the population size, margin of error, confidence level, expected variance, number of patients with MCA infarcts admitted to our medical center annually, and potential loss rate. We used G*Power software (Heinrich-Heine-Universität Düsseldorf) to perform these calculations. Specifically, we used an effect size ranging from 0.25 to 0.4, α error probability of .05, power of 0.5, 3 groups, 2 measurements, and a correlation of 0.05 between repeated measures. The resulting total sample size ranged from 51 to 120. Based on the potential number of patients admitted to our medical center and the expected loss rate, we estimated that enrolling 180 cases would be reasonable.

Study Participants and Eligibility Criteria

We will recruit patients on the basis of the inclusion criteria of exhibiting acute MCA infarct and an NIHSS score of >8 (based on Diener Law) [40], confirmed using brain magnetic resonance imaging (MRI) studies during hospital admission within 72 hours of symptom onset. The exclusion criteria will be as follows: clinical history of major stroke; significant head injury; brain tumor; major psychiatric illness; progressive neurodegenerative disorder; central nervous system infection; epilepsy that may precipitate seizures; use of AEDs, including LEV or PER; being pregnant or lactating; history of inadequate medical compliance; or any other significant major systemic disease with safety concerns, as determined by a physician.

Intervention

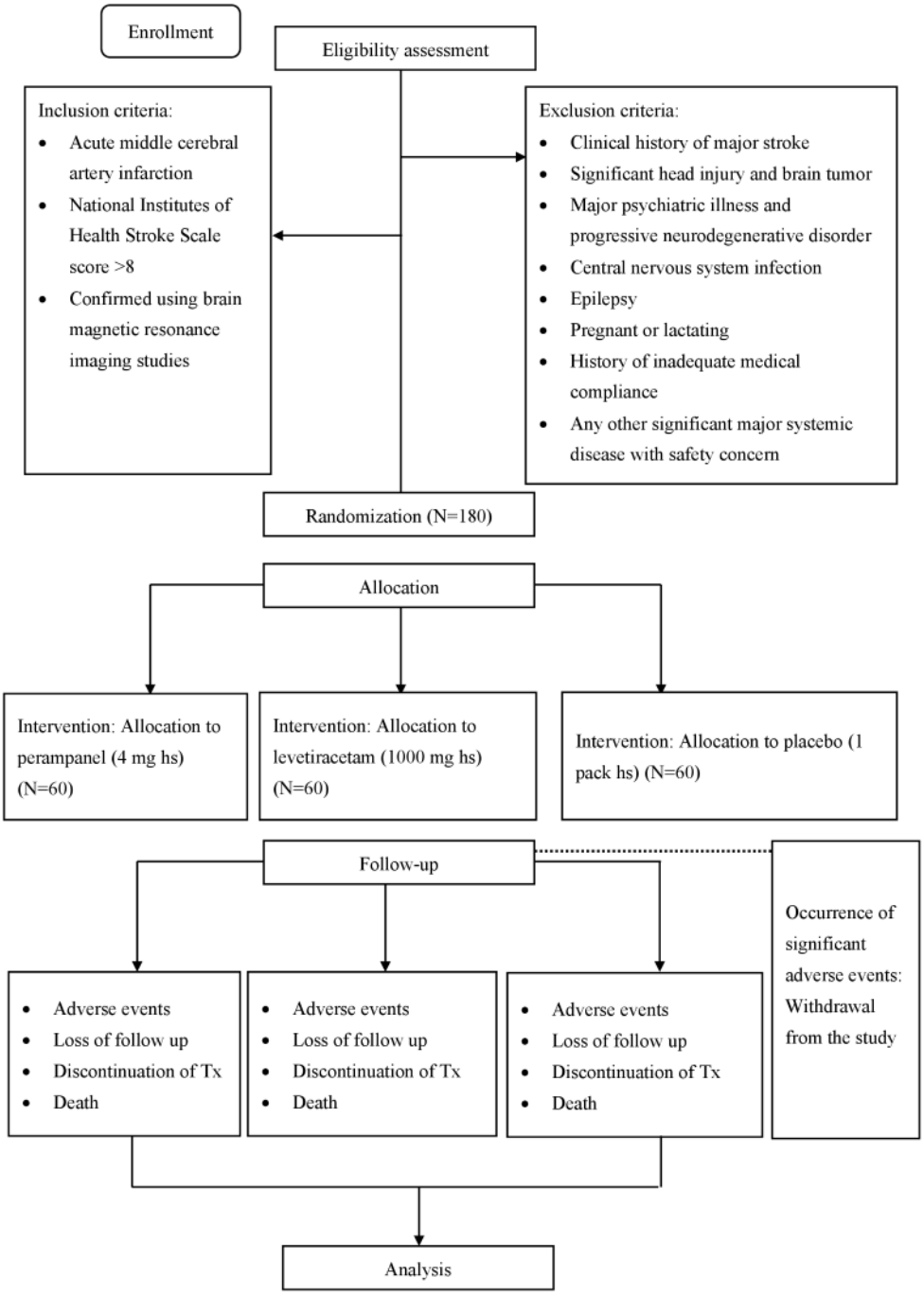
The participants will be divided into 3 groups: the control (placebo) group and the 2 experimental groups (LEV and PER). The patients, investigator, study assessors, and data analysts will remain blind to the treatment assignments from the time of randomization. Because we will conduct block randomization for group allocation, we anticipate that the percentage of patients receiving tissue plasminogen activator or intravenous thrombectomy will be similar in the 3 groups.

The major MCA infarctions typically require the early implantation of a nasogastric tube, and to account for the design of blinding, preventive drugs will be administered in powdered form. The study team works with pharmacists to ensure that medications for the experimental and control groups have similar color, fragrance, and taste. After being ground up, the drugs are packaged in identical medication bags, and a reminder label is affixed to the outer packaging to remind patients to take their medication regularly and for the appropriate duration.

The three groups are described as follows, and the study flowchart is shown in Figure 1: (1) For the control group, a placebo will be administered to patients, and we will maintain standard stroke care during hospital admission if no acute seizure occurs during this period. If an acute seizure occurs, unblinding will be performed, and we will administer AEDs not including LEV or PER; the patient will be maintained on these AEDs. (2) For the LEV group, we will prophylactically administer 1000 mg of LEV per day to patients from the first day of admission in addition to standard stroke treatment. The LEV treatment duration will be 3 months. (3) For the PER group, we will prophylactically administer 4 mg of PER per day to patients from the first day of admission in addition to standard stroke treatment. The PER treatment duration will be 3 months. (4) After the patient is discharged from the hospital, their respective medication will be administered orally for up to 3 months. (5) All patients will receive follow-up for 18 months, and the incidence of late-onset epilepsy will be documented. Seizure characteristics, including semiology, frequency, and severity, will be analyzed in the 3 groups. The relationship of seizure semiology to stroke-related localization will be verified. (6) For those who have acute seizures during hospital admission, unblinding will be performed, and either LEV or PER will be administered for treatment according to their group. The dosage will be adjusted according to real clinical needs. These patients will be treated as having epilepsy based on the 2016 definition of epilepsy [41] and be maintained on LEV or PER after hospital admission. The administration of LEV or PER to patients with acute seizures will still be considered prophylactic therapy because patients with acute seizures have a considerably higher risk of developing poststroke epilepsy. (7) Because up to 20% of patients with anterior circulation ischemic stroke may experience electrographic seizures during the acute stage of stroke without clinically overt seizures [42], we will arrange 1 routine electroencephalogram (EEG) at the acute stage for each patient. Prophylactic AED therapy will be administered according to the group the patient is allocated to if any electrographic seizure, including periodic lateralized epileptiform discharge (PLED), is identified in the EEG. (8) Unblinding will be implemented at 3 months, and the final analysis will be conducted at 18 months.

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Figure 1. Randomized controlled trial flow diagram. Tx: Treatment.



Randomization and Blinding

Block randomization of eligible participants will be performed to form the LEV, PER, and placebo groups. Blinding of participants, clinicians, and data collectors will be performed so that these individuals do not have access to group assignment details (Figure 2). Before accepting the case, the pharmacist, who is a nonresearch team member, sets the blocks and determines the distribution of random numbers using a random number table. The pharmacist is responsible for conducting all phases of the research. Additionally, the 3 topic groups can be equally distributed among participants through random assignment.

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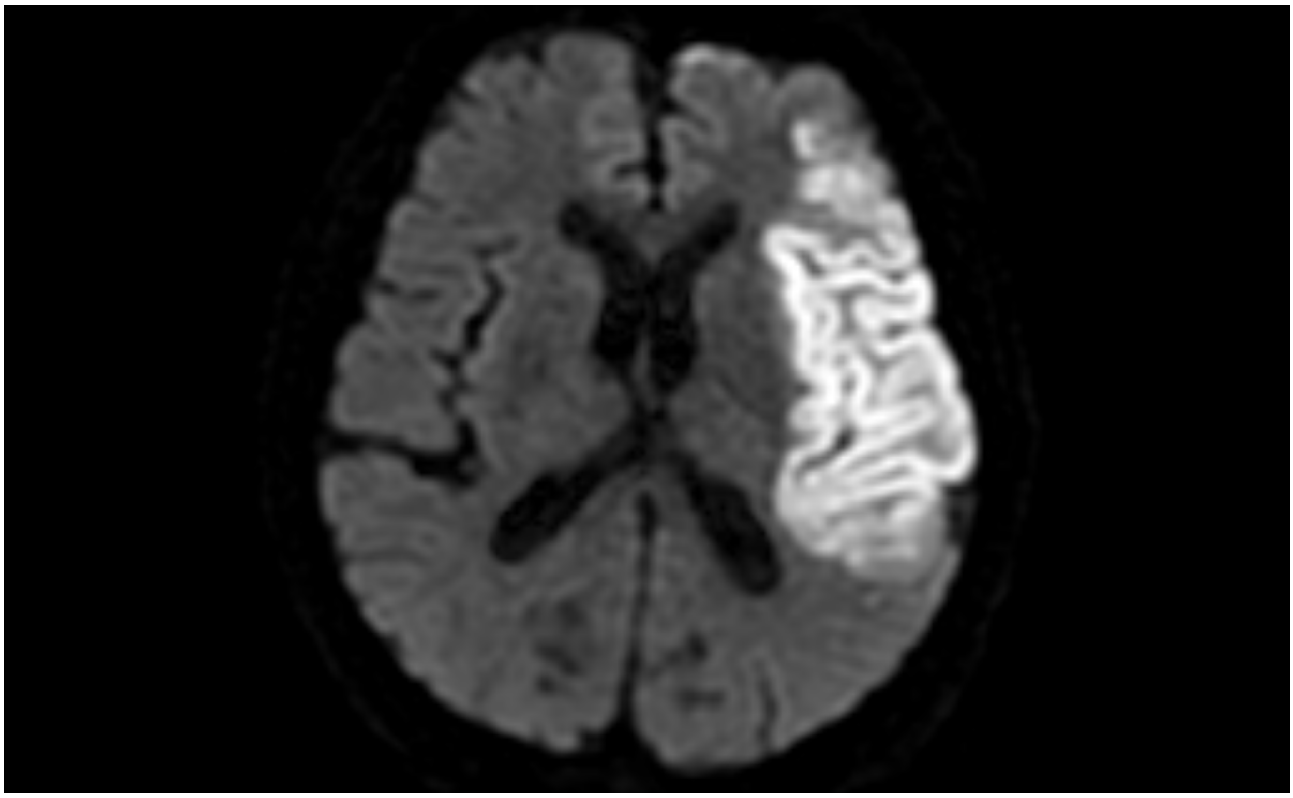
Figure 2. SPIRIT flow diagram: schedule of enrollment, interventions, and assessment procedures. EEG: electroencephalography; MRI: Magnetic Resonance Imaging; mRs: modified Rankin Scale; NIHSS: National Institute of Health Stroke Scale; SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials; TEAE: treatment-emergent adverse event; **: primary outcome; *: secondary outcome.

	Study period											
	Enrolment	Allocation	Intervention (time to week)			Post intervention (m=month)						Closeout
Timepoint	2020/08/01 to 2023/07/31	0	4	8	12	1	3	6	9	12	18	2023/01/31 to 2025/01/31
Enrolment												
Eligibility screen	✓											
NIHSS	✓											
Brain MRI	✓											
Informed consent	✓											
Allocation		✓										
Interventions												
Levetiracetam			✓	✓	✓							
Perampanel			✓	✓	✓							
Placebo			✓	✓	✓							
Assessments												
Demographics		✓										
Baseline EEG		✓										
Baseline mRs		✓										
Occurrence of seizure**			←	—	—	—	—	—	—	—	→	
Seizure severity**			←	—	—	—	—	—	—	—	→	
TEAE*			←	—	→							
Occurrence of death*			←	—	—	—	—	—	—	—	→	
Post-mRs*							✓				✓	

Procedure and Assessment

We will document patients with initial NIHSS scores of >8 [40]. For reperfusion therapy, we will also use a modified Rankin scale for treatment evaluation [43]. For each participant, we will use brain MRI to confirm MCA territory infarction and exclude that of other territories and lacunar infarction. The MRI image depicting the typical case with an MCA infarct enrolled in this study is displayed in Figure 3. Baseline EEG during admission prior to AED administration will be arranged to exclude patients with early or concurrent clinical or electrographic seizures (Figure 2).

Figure 3. A typical case with middle cerebral artery infarct enrolled in this study.



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Outcome Measures

Primary Outcome

The primary outcome measure will be the incidence of poststroke epilepsy and seizure severity at the end of the study period. Univariate ANOVA of the LEV, PER, and placebo groups will be performed. Intention-to-treat analysis will be performed. Participants will be followed up 1, 3, 6, 9, 12, and 18 months after stroke. If a seizure occurs during the prophylactic medication administration period, individual unblinding and adjustment of AEDs will be implemented. If a seizure occurs after the prophylactic medication administration period, ordinary medical care will be provided. We will record seizure type and duration after stroke onset at seizure occurrence (Table 1 and Figure 2).

Table 1. Summary of follow-up visits.

Visiting time	Within 3 days	3 months	6/9/12 months	18 months
NIHSS[a]	✓			
mRs[b]	✓			✓
MRI[c]	✓			
EEG[d]	✓			
Start of medication	✓			
TEAE[e]	✓	✓		
Occurrence of seizure	✓	✓	✓	✓
Occurrence of death	✓	✓	✓	✓

[a]NIHSS: National Institute of Health Stroke Scale.

[b]mRs: modified Rankin scale.

[c]MRI: magnetic resonance imaging.

[d]EEG: electroencephalograph.

[e]TEAE: treatment-emergent adverse event.

Secondary Outcomes

The secondary outcomes will include the duration until the occurrence of the first seizure, the severity of seizures, the safety and tolerance of the medication, and the overall stroke outcome. During the 18-month follow-up, we will record mortality, medication safety, and tolerability data at each visit. Stroke outcome will be measured using the modified Rankin scale at 3 and 18 months (Table 1 and Figure 2).

Statistical Analysis

Continuous variables will be assessed using a 2-tailed *t* test or ANOVA, followed by the Fisher least significant difference test. When data are not normally distributed, analyses will be performed using the nonparametric ANOVA Kruskal-Wallis H test followed by Dunn multiple comparison test for nonrepeated measures and the Friedman test for repeated measures. ANOVA will be used where sessions or quadrants will be treated as a within-subject factor and groups as a between-subjects factor. Analyses will be performed using a chi-square test, Yates chi-square test, or Fisher exact test for nominal variables. Differences will be considered statistically significant at a P value <.05, and actual P value will be reported, unless P<.001.

Ethical Considerations

This study received approval from the institutional review board (IRB) at National Cheng Kung University Hospital (A-BR-108-107). Each participant and their families were provided with a comprehensive verbal explanation of the study and were asked to provide informed consent, as authorized by the IRB. Participants completed their signatures on the consent forms to indicate their agreement to participate in the study.

The study data would be kept anonymous and deidentified to protect the participants' privacy. Participants were not offered any form of compensation or reimbursement for their involvement in this human subjects' research.

Results

Participant recruitment began on August 1, 2020 in National Cheng Kung University Hospital. Intervention, postintervention, and follow-up observation are still ongoing for the participants. The study is projected to be completed by January 31, 2025.

Discussion

Principal Findings

Although reports have not supported the role of prophylactic AEDs in the prevention of poststroke seizure because of a lack of randomized control trials, a lack of detected early clinical biomarkers, and worse outcomes with traditional AEDs, we will document the potential prophylactic effect of LEV and PER on poststroke seizures and epilepsy in patients with MCA infarct in this randomized clinical trial and determine the antiepileptogenic potential of LEV and PER in patients with major ischemic stroke in terms of seizure frequency and severity. We will also evaluate the safety and tolerability of these prophylactic treatments. This study will influence both stroke and epilepsy care considerably, including by potentially reducing

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long-term care costs and enhancing the quality of life of stroke survivors.

In addition to LEV, previous studies, including our own, have identified PER as a new AED with potential antiepileptogenic properties, attributed to its unique postsynaptic AMPA antagonism [32,38,39]. While it is not yet approved as a first-line treatment for focal epilepsy in many countries, this medication has potential and could be used at an early stage if our study confirms its effectiveness in prophylaxis against poststroke epilepsy.

The administration of AED or placebo for a period of 3 months is intended to intervene in the epileptogenesis phase, based on the relative duration of this phase observed in animal studies. Typically, the epileptogenesis phase in animal studies lasts for around 1 week, although this can vary depending on the animal model of seizure and epilepsy following brain injuries. By extrapolating from rat studies to human years [44], it is estimated that the epileptogenesis phase in rats is similar to around 3-4 months of human life. For the purposes of clinical feasibility, we administer a 3-month duration of AED.

In our trial to provide prophylactic treatment for epilepsy in patients who have not yet experienced seizures and are relatively vulnerable, particularly older patients who have endured stroke with multiple comorbidities, such as renal and liver diseases, we have opted for a relatively low medication dosage. Regarding the inclusion criteria, we do not enroll patients with severe renal or hepatic failure. However, we include patients who are already undergoing dialysis treatment. We assess the severity of liver disease using the Child-Pugh classification, with grade C being categorized as severe liver disease [45]. For the evaluation of renal disease severity, we use the National Kidney Foundation criteria, classifying stage 4 and above as severe renal disease [46]. In accordance with the renal dose adjustments for LEV [47], dosages vary depending on the level of renal impairment. For patients with mild renal impairment (glomerular filtration rate [GFR] 60-89 mL/min/1.73 m^2), the recommended dosage range is 1000-2000 mg per day. For those with moderate renal impairment (GFR 30-59 mL/min/1.73 m^2), the dose ranges from 500 to 1500 mg per day, while patients with severe renal impairment (GFR 15-29 mL/min/1.73 m^2) are prescribed doses of 500-1000 mg per day. For individuals undergoing hemodialysis, the recommended dosage is 500-1000 mg per day with an additional 250-500 mg postdialysis supplement.

Our decision regarding medication dosages is guided by the World Health Organization's Defined Daily Dose (DDD) guidelines [48] and our collective clinical experience. The DDD represents the estimated average daily maintenance dose for a drug when used for its primary indication in adults, taking into account our clinical expertise. For PER, the DDD is 8 mg, while for LEV, it is 1500 mg. In our study, we have chosen to administer PER at a dosage of 4 mg and LEV at 1000 mg. For LEV, this choice is driven by the fact that the majority of our recruited patients have normal renal function, with only a relatively small subset experiencing renal impairment (mild, moderate, or hemodialysis). To ensure randomization and maintain blinding in our triple-blind study, we have opted for a lower dose of 1000 mg per day. Of note, our blinding design excludes the use of postdialysis supplemental dosing.

According to the existing literature, late-onset seizures following a stroke typically exhibit a peak incidence between 6 and 12 months after the initial event [1]. Studies have shown that after an ischemic stroke, the highest risk for the occurrence of the first unprovoked poststroke seizure is observed during the initial follow-up year [5,49]. Furthermore, another study has reported the annual event risk of seizures after the first-ever ischemic stroke, indicating a risk of 6.3% after 1 year, 2.4% after 2 years, 1.3% after 3 years, and 0.3% thereafter [50]. Although the annual risk of seizures may indeed increase in subsequent years, given the highest risk observed during the first year and considering the practical feasibility of our protocol, we have chosen an 18-month follow-up period at this stage.

In terms of stroke severity, minor strokes (those with a small lesion size) are less likely to lead to the development of poststroke epilepsy. For each patient, we routinely arrange for MRI scans as a standard imaging procedure to assess the stroke, including its size, location, and the presence or absence of hemorrhagic transformation during admission. We do not typically perform brain computed tomography (CT) scans. It is worth noting that the absence of hemorrhagic transformation at the onset of the stroke does not eliminate the possibility of it occurring later during the acute stage. In the event of acute deterioration in neurological symptoms and signs, we arrange for follow-up brain MRI or CT scans and provide standard care.

In our protocol, we initiate treatment for patients with PLEDs. PLEDs have been considered to have a high association with seizures [51,52], and among the epileptiform abnormalities, the presence of lateralized periodic discharges was associated with a significantly increased risk of seizure [53]. In addition, PLEDs were associated with an acute process and occurred early during the course of the illness, with stroke being the main etiology [52].

While patients and research teams remain blinded to the allocated medications, the medication list, including cytochrome P450 inducers or inhibitors, is made available to study participants. This allows for vigilance regarding any potential drug-drug interactions. Moreover, given that our study involves a randomized controlled trial with blinding, which necessitates careful control over factors like color, size, and quantity of both the active drug and placebo tablets, the use of a powdered form is the most practical approach for conducting this trial. It is worth noting that the oral suspension form is only available for one of the medications, and furthermore, these oral suspension forms come in different colors. Additionally, the cost associated with preparing a placebo suspension in this context is prohibitively high. Regarding the issue of bioavailability, there has been no direct comparative study on bioavailability between the tablet and powdered forms. We do have clinical experience using the powdered form for patients who face challenges swallowing tablets or those reliant on nasogastric tubes. This practice is consistent with the medication package insert instructions. With their availability in multiple formulations in the future, these AEDs could serve as a potential drug for epilepsy prophylaxis during epileptogenesis.

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Conclusions

We anticipate that the intervention group will experience a lower incidence and severity of poststroke epilepsy than the control group. We will be able to document the potential prophylactic effect of LEV and PER in poststroke seizures and epilepsy in patients with MCA infarct and determine the antiepileptogenetic potential of LEV and PER in patients with major ischemic stroke.

Acknowledgments

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Data Availability

The data sets generated and analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

CWH led the effort to acquire funding from the National Science and Technology Council, Taiwan. YSC, PSS, and CWH formulated the research question, study protocol, and are conducting the trial. YSC prepared the first draft of the protocol paper, with contributions and editing of subsequent drafts by PSS, MCL, and CWH. All authors have read and approved the final study.

Conflicts of Interest

None declared.

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Abbreviations

AED: antiepileptic drug
AMPA: alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
CT: computed tomography
DDD: Defined Daily Dose
EEG: electroencephalogram
GABA: gamma-aminobutyric acid
GFR: glomerular filtration rate
IRB: institutional review board
LEV: levetiracetam
MCA: middle cerebral artery

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MRI: magnetic resonance imaging
NIHSS: National Institutes of Health Stroke Scale
PER: perampanel
PLED: periodic lateralized epileptiform discharge

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Protocol

Training Australian Dietitians in Behavior Change Techniques Through Educational Workshops: Protocol for a Randomized Controlled Trial

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Abstract

Background: The use of education alone as a technique to change behavior in interventions is usually insufficient, particularly in health interventions. Behavior change techniques have been shown to be effective in fostering positive changes in health behaviors such as diet and physical activity. The upskilling of health professionals can increase perceived capability and motivation toward eliciting change in clients' behaviors. However, to date, dietitians have received limited training in behavior change and have expressed a need for continuous professional development.

Objective: The study objectives are to (1) develop and evaluate the effectiveness and acceptability of two 2-hour behavior change workshops on changing dietitians behavior (ie, range of behavior change techniques used and frequency of use) across 3 time points; (2) determine if participation in these workshops will elicit changes in dietitians' perceived capability, opportunity, and motivation toward using behavior change techniques; and (3) determine the acceptability of the training and its application in practice by dietitians.

Methods: We will recruit registered dietitians (N=140) in Australia to participate in this randomized controlled trial. Participants will be randomly assigned to either the intervention or 3-month waitlist control condition and complete outcome measures at 3 time points: baseline, after the workshop, and follow-up at 3 months. Both groups will complete 2 workshops on behavior change that are guided by the COM-B (Capability, Opportunity, Motivation, and Behavior) Model and embedded with behavior change techniques. The primary outcome is changes in behavior, (ie, the range of behavior change techniques used and their frequency of use). Secondary outcomes include changes in perceived capability, opportunity, motivation, and preparedness as a health professional toward delivering behavior change techniques. The acceptability of the workshops will also be assessed after the workshop through the postworkshop survey and semistructured interviews. A series of 2-way repeated measures ANOVAs and regressions will be used. Qualitative data will be analyzed using thematic analysis.

Results: Participant recruitment commenced in June 2023. The results of the study are expected to be published in November 2024. The results will allow us to assess comparisons between the intervention and waitlist control groups, as well as changes in perceived capability, opportunity, motivation, and preparedness over a 3-month period. It will also provide an understanding of the acceptability of the training as a form of continuous professional development for dietitians.

Conclusions: If found to be effective, the results of this 2-arm randomized controlled trial will guide future training and continuous professional development for health professionals in changing behavior in practice. Our findings will contribute to our understanding of the application of behavior change techniques in practice with clients and identify components of COM-B where dietitians may need future support.

Trial Registration: ACTRN12623000525684; https://www.anzctr.org.au/ACTRN12623000525684.aspx

International Registered Report Identifier (IRRID): PRR1-10.2196/49723

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(JMIR Res Protoc 2023;12:e49723) doi:10.2196/49723

KEYWORDS

BCT; behavior change; COM-B; continuing education; dietitians; health professional; intervention; professional development; psychology; randomized controlled trial; training; workshop

Introduction

Chronic diseases such as cardiovascular disease, chronic obstructive pulmonary disease, cancer, and diabetes are among the most common noncommunicable diseases, which contribute to the burden of disease in Australia [1]. Approximately 38% of this burden of disease could be prevented by addressing behavioral determinants of disease such as overweight (including obesity) and dietary risk behaviors [2]. The majority of Australians do not meet the Australian government dietary guidelines for fruit and vegetable consumption, with almost 50% of adults eating fewer than 2 serves of fruit and 92% not eating the recommended 5 serves of vegetables daily [3]. Therefore, there is a need for behavior change interventions and health promotion across primary health care settings. However, while health professionals typically focus on education for clients, consumers, or patients (from here forward, any patient, client, or consumer will be referred to as clients), this is usually insufficient for facilitating behavior change and leads to missed opportunities in practice [4]. Behavior change techniques, which are considered the "active ingredients" of intervention design, have been shown to be more effective in improving client outcomes compared to those without, particularly in dietary interventions [5,6]. As such, it is important that health professionals are equipped with the capability and motivation to effectively facilitate behavior change among clients.

Brief opportunistic interventions in routine consultations have been effective for eliciting change in clients' behavior [7,8]. However, health care professionals report barriers to the implementation of behavior change techniques, such as poor confidence in individual skills and knowledge of behavior change, time constraints, priorities, and access to sufficient training [4]. Dietitians engaging in both in-person and telehealth consultations are in an optimal role where they can reach both metropolitan and rural clients to deliver health-behavior change interventions [9]. Additionally, many dietitians have expressed an unmet need for knowledge and skills in behavior change [10,11].

The understanding of behavior change theories and techniques can help health professionals understand behavior and the mechanisms that elicit or facilitate behavior change [12]. Theoretical models, such as the COM-B (Capability, Opportunity, Motivation, and Behavior) model [13] can provide a framework for identifying and explaining the factors enabling or hindering changes in behavior, which can guide intervention design for effective behavior change [14]. The COM-B model posits that an individual's capability (ie, physical and psychological capability), opportunity (ie, social and physical opportunity), and motivation (ie, reflective and automatic) interact in a bidirectional way and can explain behavior [14]. As such, interventions informed by these constructs have been effective in eliciting changes in knowledge and behavior [15,16], alongside the use of behavior change techniques [17,18]. Behavior change techniques can be considered the individual units or "active ingredients" that target components of behavior that need to change [6]. These components or units that form interventions can help us identify the parts of the intervention that work or do not work, providing valuable information for operationalizing effective intervention designs. The use of behavior change techniques can be effective in both changing the behavior of clients and health professionals [19,20]. For example, behavior change techniques such as goal setting, action planning, and self-monitoring have elicited behavior change in physical activity and food-related behaviors [21-24].

Despite the capacity of health professionals to foster behavior change in clients using behavior change techniques, no such training is consistently delivered to dietitians, particularly in formalized education [25]. Currently, the use of behavior change techniques used in dietary practice and dietary-based interventions is based around goal setting, problem-solving, social support, self-monitoring, and education-based techniques (eg, instructions on behavior and credible sources), which are consistent throughout the literature [5,26,27]. Therefore, the primary aim of the study is to develop and evaluate the effectiveness and acceptability of two 2-hour behavior change workshops on changing dietitians' behavior, that is, changes in the number and frequency of behavior change techniques dietitians use in practice. It is anticipated that the workshops will prompt dietitians to use a larger variety and frequency of using these techniques in practice between baseline, after the workshop, and 3-month follow-up. A secondary aim is to determine if attendance at these workshops will demonstrate an increase in dietitians' capability, opportunity, and motivation toward using these techniques. In these workshops, the use of behavior change techniques will underlie workshop material to target dietitians' barriers across capability (eg, persuasion around capability), opportunity (eg, identifying barriers and problem-solving), and motivation (eg, focus on past success). Therefore, we hypothesize that engagement in these workshops will predict dietitians' capability, perceived opportunity, and motivation toward using behavior change techniques from baseline and after the workshop to 3-month follow-up. Lastly, we also aim to determine the acceptability of the training.

Methods

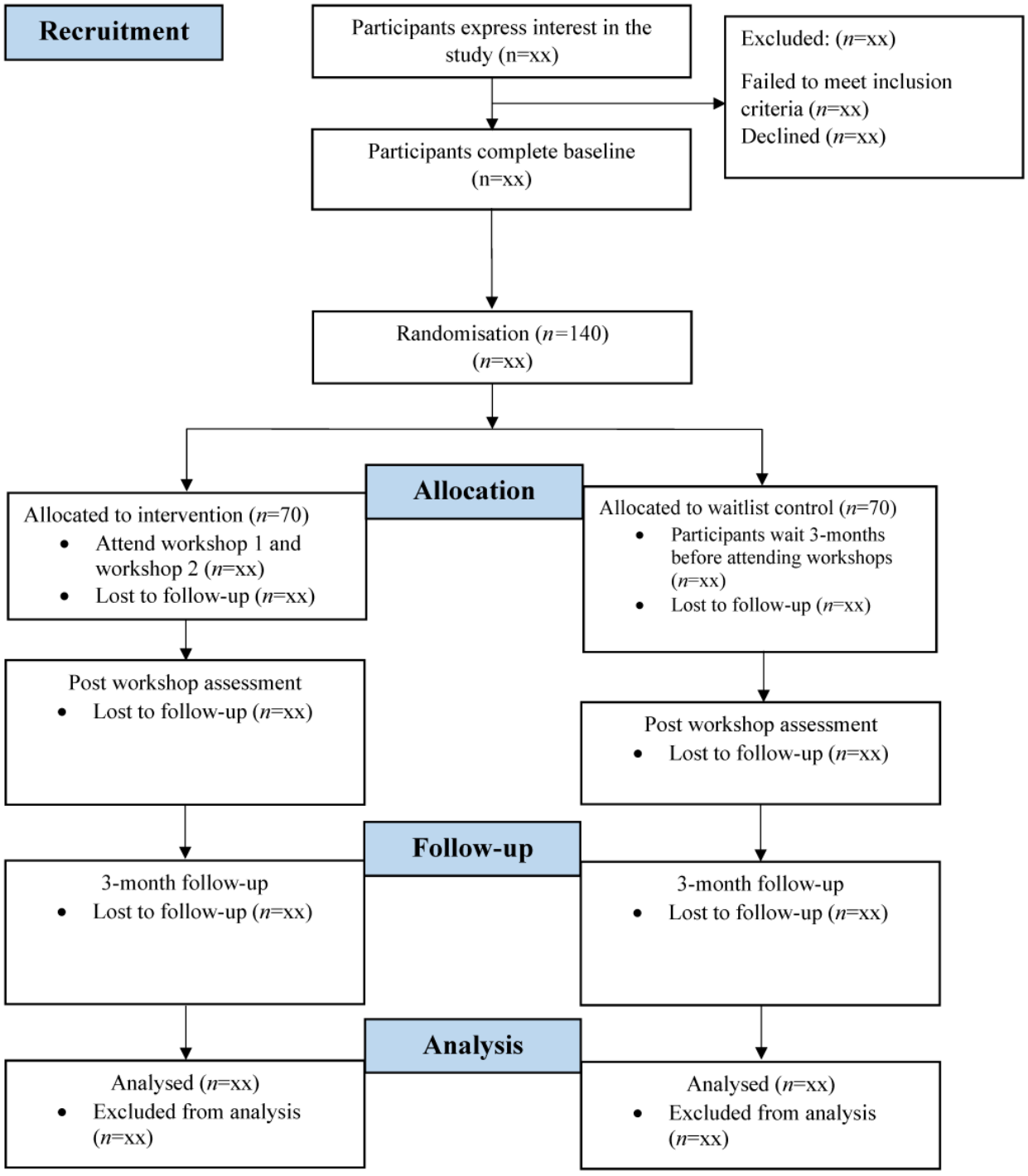
Study Design and Procedure

This study is a 2-arm randomized controlled trial with a 3-month follow-up. Participants will complete a questionnaire at baseline, immediately after the intervention, and 3 months after the intervention. Participants will express their interest to participate in the study through a Qualtrics survey. Informed consent will be obtained at the start of this survey. Following this initial survey, dietitians will be randomized in blocks of 4 into either the intervention or a waitlist control condition (1:1). Block

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randomization will be conducted with allocation concealment from the active research team through the use of sealed, opaque envelopes. Emails will be sent to participants with the initial baseline questionnaire, and they will be informed if they can participate in the workshops immediately or if their available workshop will be in 3 months. Once dietitians have been randomized and received their baseline questionnaire, they have been enrolled in the study as participants. Both groups will participate in both workshops and complete a questionnaire immediately after participation in the second workshop and at the 3-month follow-up. The waitlist control group will be debriefed after the final questionnaire regarding their allocation to the waitlist control group. Postworkshop data collected from the waitlist control group will also be included in the final data set. Figure 1 shows a flowchart for each group's progression in the trial. This protocol will adhere to the CONSORT (Consolidated Standards of Reporting Trials) and SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines for randomized controlled trials [28].

Figure 1. Outline of the trial.



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Participants

Participants will be dietitians who are currently working in Australia and hold full membership with Dietitians Australia. Participants will be recruited using purposive sampling, through both social media advertisements and newsletters directed through nutrition and dietetic organizations, and through snowballing. Recruitment of participants will be staggered over a 12-month period. A similar intervention in behavior change for health professionals found medium to large effect sizes for changes in mechanisms of change (eg, perceived knowledge) [16]. Therefore, anticipating medium to large effect sizes, a-priori analysis was conducted in G power (Axel Buchner; $F_{1,82}$=0.2; power =.80; α=.05) indicating that 42 participants in each group would be adequate [29]. This means a total sample size of 84. It is anticipated that there may be high attrition in this study. Therefore, we aim to recruit approximately 140 participants to ensure that if 50% of each group are lost to attrition, the proposed analysis will be sufficiently powered. This dropout rate of 50% is conservative given that similar interventions in training health professionals can report moderate (20%) to high (50%) attrition rates [20,30].

Intervention Components

The workshops have been developed and piloted by a research team of psychology researchers and dietitians with clinical and teaching experience (Textbox 1). The main objectives for these workshops are intended for dietitians to be able to (1) understand the importance of behavior change, (2) define the characteristics of the COM-B model, and (3) identify opportunities to and implement behavior change techniques in practice. The first workshop will focus on developing knowledge of behavior change and the COM-B model [13]. The second workshop is focused on providing dietitians with behavior change techniques from the behavior change taxonomy [6]. These techniques were based on those shown to be effective in dietary interventions [31] and were chosen based on the most relevant techniques for practical use by dietitians. These workshops will be delivered both remotely through Teams (Microsoft Corporation) and in person. The design of these workshops is informed by behavior change techniques to target participants capability, perceived opportunity, and motivation to use behavior change techniques. These are delivered through activities and group discussions to evoke reflection, awareness of their own behavior, and problem-solving to overcome the barriers that exist across their own capability, perceived opportunity, and motivation (Multimedia Appendix 1 [6,19,32-37]).

Textbox 1. Outline of workshops.

Workshop 1

- Understanding behavior
- Exploring behavior and behavior change
- Introduction to the Capability Opportunity Motivation-Behavior Model
- Case study
- Behavior change techniques
  - What are behavior change techniques?
  - Explore goal setting, problem solving, self-monitoring, and social support.
  - Case study in small groups behavior change technique

Workshop 2

- Behavior change techniques
- Further explore 9 additional behavior change techniques and how they might apply in practice (eg, pros and cons and reattribution).
- Case study in small groups
- Relapse management and prevention

Data Collection Methods

Once an expression of interest has been received through the Qualtrics survey, the participant will be asked to complete an initial baseline measure. In this baseline questionnaire, participants will be asked questions on their demographics (eg, age, gender, and highest level of qualification), current perceived knowledge and behavior (ie, use of behavior change techniques), the COM-B questionnaire [38], and preparedness as a health professional to deliver behavior change techniques. The same assessments (excluding demographics) will be repeated at the postworkshop and follow-up time points. At the postworkshop time point, the questionnaire will also include items on the acceptability of the workshops.

Outcomes

The primary outcome of this study will be behavior change, which will be operationalized in 2 ways for dietetic practice. These outcomes include (1) a change in the number of behavior change techniques used and (2) a change in the frequency of behavior change techniques used. This change will be measured across the 3 time points. While this may not be an absolute measure of behavior change technique delivery, however, any change will capture the range of techniques taken from the

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workshops, which may be more indicative of the dietitians' understanding and application of the COM-B model. To further capture the uniqueness of the behavior change techniques delivered by dietitians, the type of technique will also be measured across the 3 time points. Secondary outcomes include changes in perceived capability, opportunity, motivation, and preparedness as a health professional toward delivering behavior change techniques.

Measures

Behavior will be measured with two items to determine (1) the use of behavior change techniques and (2) the frequency of use. The first item asks participants "Which of the following behavior change techniques do you use in practice?" Participants will indicate which of the 14 techniques they have used by rating their answer as either yes, no, or unsure. A total of 14 techniques were chosen based upon techniques used for dietary behavior change in the literature [31], as well as consultations with an advisory group of dietitians to determine the appropriateness and practicality of the techniques. A composite score will be calculated to determine the number of techniques used. A second item will also be included to identify how frequently dietitians use these techniques in practice, for example, "How often do you currently use behavior change techniques when interacting with clients?" Participants will rate this item on a 5-point Likert scale from never (0) to always (4).

Capability, opportunity, and motivation will be measured using the COM-B questionnaire [38], which has been adapted for delivering behavior change techniques when interacting with clients in health contexts. This measure includes 6 items and 6 domains that reflect each component of the COM-B model as outlined by Michie et al [13]. Participants will rate their level of agreement with each item on an 11-point scale, with items ranging from strongly disagree (0) to strongly agree (10). An example item includes "I have the PHYSICAL opportunity to deliver behavior change techniques when interacting with clients (eg, time, the necessary materials, reminders, and space)."

Perceived knowledge will be measured using 3 items related to knowledge of behavior change techniques. Each item will be rated on a 7-point slider scale. Participants will rate their level of understanding of behavior change techniques and their knowledge of 9 categories of techniques from "no understanding" (1) to "perfect understanding" (7). These categories are described in the behavior change taxonomy [39]. Scores for each statement will be summed to create a total perceived knowledge score. Item 3 will ask participants to rate their level of agreement with 3 statements relating to the use of behavior change techniques (ie, if they have used them before and if they know why they are useful). These statements are rated from "strongly disagree" (1) to "strongly agree" (7). Perceived knowledge will be assessed at the 3 time points.

The preparedness of dietitians to deliver behavior change techniques will be measured using a 6-item scale. This scale has been used with health professionals, such as pharmacists [40]. This measure is to determine if dietitians feel they are equipped to deliver these techniques as part of their consultations. Statements will be rated on a 5-point Likert scale from (1) strongly disagree to (5) strongly agree. An example includes "Dietitians need training in communication skills to enable them to deliver a behavior change techniques."

Process Evaluation

The process evaluation will assess dietitians' acceptability of the 2 workshops. A total of 2 items will be included at the end of the postworkshop questionnaire, which was developed by Kothe and Mullan [41]. The first question will ask participants their level of agreeance on 14 keywords related to the facilitated workshops. For example, whether they felt the workshops were "needed, useful, appropriate, interesting, exciting, worthwhile, too short." These will be scored on a 5-point Likert scale. The second question asks participants how satisfied they were with the workshops, rated on a 5-point Likert scale ranging from "very dissatisfied" (1) to "very satisfied" (5). At follow-up, participants will also be invited to complete a one-on-one exit interview through Microsoft Teams. These interviews will allow us to assess the experience and impact of the intervention (eg, barriers and enablers) and explore the acceptability and feasibility of the workshops. Interviews will be guided by the COM-B model [13] and are expected to take 30-45 minutes each. In addition, participants who choose to withdraw from the study will also be invited to complete 3 short open-ended questions regarding their reason for withdrawing from the study. This will provide insights into noncompleters experiences and attitudes toward the intervention.

Statistical Analysis

Preliminary Analyses

Missing data will be managed during the data cleaning stage using case-wise deletion for missingness greater than 40%. Considerations for the use of multiple imputations as a method for addressing missing data will be made only if appropriate. Multiple imputation as a method for handling missing data is recommended for use in randomized controlled trials [42]. Assumption testing (eg, homogeneity of variances and normality) will also be conducted. If assumptions are not satisfied, appropriate transformations will be made. Dropout analyses using independent sample *t* tests (2-tailed) will identify any significant differences between participants who complete the study and those who drop out. Per protocol, intention-to-treat analyses will also be conducted as recommended for use in randomized controlled trials to reduce sample bias [43,44].

Primary and Secondary Outcomes

The primary and secondary outcome variables will be assessed at the baseline, postworkshop, and follow-up time points. A chi-square test will be used to assess if there are any differences between the intervention group and waitlist control at baseline. A 2-way repeated measures ANOVA will be conducted to compare the means between the intervention group and waitlist control group (between-subjects factor) over the 3 time points (within-subjects factor) for each of the primary and secondary variables. This analysis will be run to test for any time through conditional interactions. Demographics, such as age, gender, role of dietitian, and consultation delivery mode, will be included as covariates in the analysis. Multiple regression analyses will be used to determine whether changes (residual) in capability, opportunity, motivation, and health professional

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preparedness predict changes in behavior (range of use or frequency of use) at each of the 3 time points (while controlling for baseline behavior).

Qualitative Data

Interview data will be analyzed using thematic analysis to identify common themes concerning the impact of the intervention (eg, barriers or enablers experienced in practice) and to inform the acceptability and feasibility of the workshops [45].

Ethical Considerations

Ethics approval was granted for this study by the Human Research Ethics Office on January 20, 2023 (HRE2023-0026). This project has also been approved by the Human Research Ethics Committee (HRE2023-0026) and the Australian and New Zealand Clinical Trials Registry (ACTRN12623000525684). Informed consent to participate in the study will be received during the initial recruitment stage before any data collection. Dietitians who are interested in participating will follow a Qualtrics survey link to the participant information sheet that details their involvement in the trial. Following this information, participants will be asked to consent to participate in the study, and if they choose to withdraw from the study, they will also consent to being contacted with follow-up questions. The workshops provided will be freely accessible and are able to be recorded as continuous professional development under Dietitians Australia.

Research Data Plans

All research data collected as part of this project will be stored on the research drive of the university. Only the research team will have access to this data. Participant data will be collected and matched across the 3 time points based on their name, email address, and participant ID. All the data collected as part of this trial will remain confidential. After data collection, the 3 time points will be matched, and the data will be deidentified. Participants will be sent email reminders for each upcoming workshop and assessment.

Results

Participant recruitment commenced in June 2023. Recruitment will be staggered over 12 months. Data analysis will commence in 2024, with the anticipated publication of results in 2024.

Discussion

Principal Findings

This trial will examine the effectiveness and acceptability of two 2-hour behavior change workshops and, to our knowledge, is the first training workshop to promote behavior change techniques among dietitians. There is evidence to suggest that training health professionals is beneficial in improving capability and motivation for using behavior change techniques in practice [20,33]. It is important that health professionals are confident in eliciting and identifying opportunities to facilitate brief opportunistic interventions with the goal of developing long-term behavioral maintenance. The findings of this study will provide insights into effective strategies for training of allied health professionals, such as dietitians, which could inform efforts to incorporate behavior change education into either formalized training or continuous professional development.

Strengths and Limitations

A strength of this study is the use of a rigorous, co-designed process involving both experienced researchers in behavior change and a supervisory team of dietitians. Dietitians have been involved throughout the workshop design process and provided feedback to ensure terminology is consistent and information is tailored to nutrition and dietetic practice. Co-design provides valuable insights into stakeholders and consumer perspectives, allowing for a more targeted approach to intervention design [46]. A potential limitation that may arise during the study is that participants who do express interest are likely to have high motivation and potential knowledge of behavior change before the workshops. This may lead to only minor or no changes in capability, opportunity, and motivation, even if the workshops are effective, and may limit the generalizability of conclusions concerning uptake and interest in training.

Conclusions

The examination of the effectiveness and acceptability of this trial will inform strategies for continuous professional development in behavior change. If found to be effective and acceptable by dietitians, there is potential for future training and professional development programs across allied health professionals who are in opportunistic and client-facing roles to target chronic disease prevention and management [47,48]. Our findings will also contribute to our understanding of translating skills around behavior change techniques into practice with clients and identifying those components of COM where dietitians may need future support.

Acknowledgments

The authors would like to acknowledge the advisory group of dietitians from Curtin University who were involved in the planning and piloting of the workshops.

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Data Availability

The data sets generated during and analyzed during this study are not publicly available due to privacy and ethical restrictions but are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Behavior change techniques mapped to workshop material.
[DOCX File , 20 KB - resprot_v12i1e49723_app1.docx]

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Abbreviations

COM-B: Capability, Opportunity, Motivation, and Behavior
CONSORT: Consolidated Standards of Reporting Trials
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Protocol

FORWARD Study of GORE VIABAHN Balloon-Expandable Endoprostheses and Bare Metal Stents in the United States, European Union, United Kingdom, Australia, and New Zealand When Placed to Treat Complex Iliac Occlusive Disease: Protocol for a Randomized Superiority Trial

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Abstract

Background: The recommendations for the use of and selection of covered stent grafts in patients with aortoiliac occlusive disease are limited.

Objective: The GORE VBX FORWARD clinical study aims to demonstrate the superiority of the GORE VIABAHN VBX Balloon Expandable Endoprosthesis (VBX device) for primary patency when compared to bare metal stenting (BMS) for the treatment of complex iliac artery occlusive disease.

Methods: A prospective, multicenter, randomized control study in the United States, European Union, United Kingdom, Australia, and New Zealand will enroll patients with symptomatic, complex iliac artery occlusive disease. In this study, iliac artery occlusive disease is defined as a unilateral or bilateral disease with single or multiple lesions (with >50% stenosis or chronic total occlusion) each between 4 and 11 cm in length. In an attempt to more closely match real-world practices, patients with minor tissue loss (Rutherford class 5) and patients requiring hemodialysis will be included. Baseline aortoiliac angiography will be performed to assess target lesion characteristics and determine final patient eligibility. Once the patient is confirmed and guidewires are in place across the target lesions, the patient will be randomized in a 1:1 format to treatment with either the VBX device or a BMS. The BMS can be balloon- or self-expanding and must be approved for the iliac artery occlusive disease indication. Patients, the independent core laboratory reviewers, and Clinical Events Committee members will be blinded from the assigned treatment. Dual antithrombotic medical therapy is required through a minimum of 3 months post procedure. The primary end point is 12-month primary patency and will be adjudicated by an independent imaging core laboratory and Clinical Events Committee. Key secondary end points will be tested for superiority and include technical, acute procedural, and clinical success;

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changes in Ankle-brachial index; patient quality of life; primary patency; freedom from restenosis; primary-assisted patency; secondary patency; freedom from target lesion revascularizations; cumulative reintervention rate; amputation-free survival; survival; and change in Rutherford category. Study follow-up will continue through 5 years.

Results: Outcomes will be reported following study completion. Enrollment is anticipated to start in October 2023.

Conclusions: The results of this study will provide definitive, level 1 clinical evidence to clinicians on the optimal choice of stent device to use for the treatment of complex iliac artery occlusive disease. The FORWARD study is powered for superiority and includes only complex, unilateral, or bilateral lesions involving the common or external iliac arteries. This study is a multidisciplinary endeavor involving vascular surgery, interventional cardiology, and interventional radiology across multiple countries with a blinded core laboratory review of end points in hopes that the outcomes will be widely accepted and incorporated into practice guidelines for optimal treatment of patients with complex iliac artery occlusive disease.

Trial Registration: ClinicalTrials.gov NCT05811364; https://clinicaltrials.gov/study/NCT05811364

International Registered Report Identifier (IRRID): PRR1-10.2196/51480

(JMIR Res Protoc 2023;12:e51480) doi:10.2196/51480

KEYWORDS

iliac artery occlusive disease; VIABAHN VBX balloon expandable endoprosthesis; covered stent; stent graft; stent; randomized control trial; FORWARD; endoprosthesis; atherosclerosis; endovascular; stenting; occlusion; RCT; iliac occlusion

Introduction

Peripheral artery disease (PAD) of the lower extremities affects over 230 million adults worldwide and is the third leading cause of atherosclerotic morbidity behind coronary artery disease and stroke [1]. Symptomatic PAD, including lifestyle limiting claudication, rest pain, and tissue loss, is associated with significant disability, morbidity, and mortality. In the United States, the prevalence of PAD is estimated to be 7% to 10% [2,3], with approximately one-third involving the aortoiliac segment [4].

Endovascular treatment of aortoiliac occlusive disease (AIOD) has been proven to be a safe, durable, and efficient option compared to open repair, independent of the lesion Trans-Atlantic Inter-Society Consensus (TASC) II classification [5,6]. While balloon-expandable bare metal stents (BMS) have demonstrated acceptable technical success and 1-year primary patency in this location, balloon-expandable covered stents have arguably demonstrated more favorable primary patency through 12 months specifically in patients with complex TASC II C and D lesions [7,8]. Meta-analyses comparing BMS to balloon expandable covered stents suggest that covered stents may offer improved primary patency and freedom from reintervention, especially in more complex AIOD [9-11]. Randomized, controlled studies comparing balloon expandable covered stents and BMS in advanced AIOD, such as COBEST [12] and DISCOVER [13,14], have been conducted; however, limitations in these studies have prevented clear and conclusive outcomes. Despite only demonstrating a significant difference in binary restenosis in a subgroup analysis, the COBEST trial is widely referenced as the key evidence that supports the use of covered stents in advanced AIOD. While the COBEST trial subgroup analysis suggested a benefit to covered stenting, it should be considered hypothesis-generating for a future covered versus BMS comparative trial in complex iliac occlusive disease. The key limitations included a noninferiority design with minimal statistical power, limb-level randomization despite enrollment by TASC II classification, no independent core laboratory adjudication of end points, limited experience to 1 country (Australia), and limited follow-up to 18 months [12]. These limitations may contribute to the lack of additional recommendations for the use of covered stents in society consensus guidelines [15-17].

Though the Society of Vascular Surgery has published recommendations for the use of covered stent grafts in instances of severe calcification at risk of vessel rupture [15], there are no additional published guidelines on stent selection for AIOD [15,16,18]. The European Society for Vascular Surgery guidelines do recommend endovascular first treatment for patients with AIOD with severe comorbidities or in experienced teams if it does not compromise subsequent surgical options [16]. More recently, the DISCOVER trial compared the Advanta V12 (iCAST) to balloon-expandable BMS in “advanced” atherosclerotic disease of the common iliac artery [14]. This trial shares similar limitations to the COBEST trial [12] and focuses narrowly on the occlusive disease of the common iliac artery with a large proportion of TASCII A and B lesions (128/174, 73.5%) [14]. As a result, the DISCOVER trial failed to demonstrate any significant difference in primary or secondary outcomes at 2-year follow-up [14]. Other than the 5-year COBEST data [12], the literature for long-term, randomized comparison studies to serve as a guide for clinical practice for the treatment of AIOD remains limited.

The GORE VIABAHN VBX Balloon Expandable Endoprosthesis (VBX device) is a covered stent that has demonstrated favorable performance in patients with complex iliac occlusive disease. The FLEX Trial was a single-arm, nonrandomized study that reported a 1-year primary patency of 94.5%, with the overall cohort consisting of patients with kissing stents (57/134, 43%) and TASC C and D lesions (43/134, 32%) [8]. The GORE-sponsored FORWARD trial (ClinicalTrials.gov NCT05811364) is being conducted to demonstrate the superiority of treatment using the VBX device in patients with complex iliac artery occlusive disease when compared to BMS.

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Methods

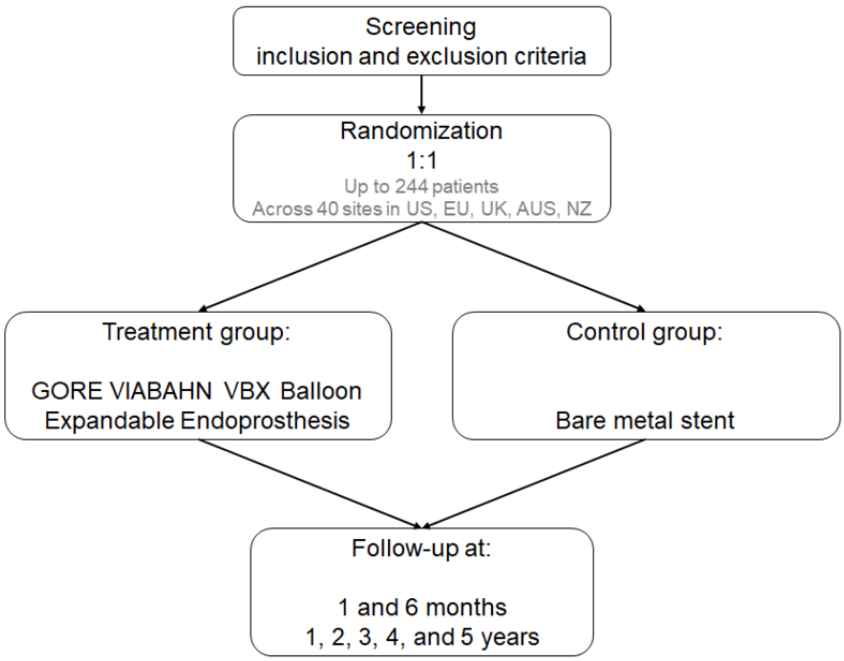
Study Design

The GORE VBX FORWARD clinical study is a prospective, multicenter, double-blind (patient, outcome assessor), randomized control trial comparing the VBX device to commercially available BMS in patients with complex iliac occlusive disease. The study is designed to randomize 244 patients at up to 40 sites across the United States, European Union, United Kingdom, Australia, and New Zealand.

Ethical Considerations

The study protocol will be reviewed and approved by the institutional review board or ethics committee at each of the study sites. Patients will provide written informed consent before undergoing any study procedures and will be considered enrolled. The study does not involve the collection of identifiable patient information. Human participants enrolled in this study will be compensated in the amount of US $75 for returns to the 1-month, 6-month, 2-, 3- and 4-year follow-ups and US $100 for returns to the 1-year and 5-year follow-ups. The study will be conducted according to Good Clinical Practice, the Declaration of Helsinki guidelines, and in compliance with ISO 14155 (International Organization for Standardization). The study (design illustrated in Figure 1) is registered with ClinicalTrials.gov (NCT05811364).

Figure 1. Study design schema. AUS: Australia; EU: European Union; NZ: New Zealand; UK: United Kingdom; US: United States.



Study Population

The inclusion and exclusion criteria for the study are detailed in Textbox 1. Patients eligible for enrollment will be 18 years or older and have a symptomatic complex iliac occlusive disease with de novo or restenotic lesions in the common or external iliac arteries and with unilateral or bilateral, single or multiple lesions (>50% stenosis or chronic total occlusion) each between 4.0 and 11.0 cm in length (Textbox 1). In addition, clarifications to the specific lesion are (1) bilateral common iliac artery lesions that require kissing stents with at least 1 lesion >4 cm, (2) unilateral common iliac artery lesions that extend into the external iliac artery with a total lesion length >4 cm, (3) unilateral common iliac artery lesion >4 cm that are fully occluded somewhere in the lesion, and (4) multiple unilateral discrete (noncontiguous) lesions each >4 cm.

Preoperative and intraoperative inclusion criteria include symptomatic claudication, rest pain, or minor tissue loss (Rutherford category 2 to 5); reference vessel diameters ranging from 5.0 to 13.0 mm; a sufficient (<50% stenotic) common femoral; a sufficient (<50% stenotic) deep or superficial femoral artery; and a minimum of 1 sufficient (<50% stenotic) infrapopliteal run-off vessel (Textbox 1).

Exclusionary criteria include life expectancy <1 year; pregnancy; known allergy to stent or stent-graft components; nondialyzing patients with severe chronic renal insufficiency; evidence of a systemic infection; known intolerance to antithrombotic medications, vascular surgery, or catheterization of the lower extremities within 30 days of randomization; previous stenting in the iliac arteries; surgical bypass in the target limb; and current participation in another investigative clinical study. Intraoperative exclusions include a lesion requiring adjunctive procedures to facilitate stent delivery (eg, atherectomy and lithotripsy); abdominal aortic artery lesion or aneurysm; lesion requiring stent placement within 2 cm of inguinal ligament; and outflow disease requiring concomitant interventions. In addition, exclusionary are patients with isolated common iliac artery stenosis of any length that can be treated with a single device. For example, common iliac artery stenosis that does not require kissing stents or extending into the external iliac artery (Textbox

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1) as these lesions are considered TASC A or B and would not be considered complex. While patients with bilateral disease are not excluded, those requiring concomitant procedures are excluded.

Textbox 1. Study inclusion and exclusion criteria.

Inclusion criteria

- The study population has been defined as adult patients presenting with symptomatic, complex iliac artery occlusive disease. Patients must present with de novo or restenotic lesions (post percutaneous transluminal angioplasty) in the common or external iliac arteries, and complex iliac artery occlusive disease defined as unilateral or bilateral single or multiple lesions (>50% stenosis or chronic total occlusion) each between 4 and 11 cm in length.

Preoperative:

- Aged 18 years or older at the time of informed consent signature
- Informed Consent Form is signed by the patient
- The patient can comply with protocol requirements, including follow-up
- The patient has symptomatic claudication, rest pain, or minor tissue loss (Rutherford category 2-5)

Intraoperative:

- The patient has de novo or restenotic lesions found in the common or external iliac arteries
- The patient has: Unilateral or bilateral single or multiple lesions (>50% stenosis or chronic total occlusion) each between 4 and 11 cm in length
- The patient has a target vessel diameter visually estimated to be approximately between 5 and 13 mm
- The patient has a patent (<50% stenosis) common femoral artery and at least 1 patent (<50% stenosis) femoral artery (deep or superficial)
- The patient has at least 1 sufficient (<50% stenotic) infrapopliteal run-off vessel

Exclusion criteria

Preoperative:

- Life expectancy <1 year
- The patient is pregnant at the time of informed consent
- The patient has a known allergy to stent or stent graft components (including nitinol, stainless steel, or heparin)
- The patient has severe chronic renal insufficiency (serum creatinine level >2.5 mg/dL) and not undergoing hemodialysis
- The patient has evidence of a systemic infection
- The patient has a known intolerance to antithrombotic medications that prevent compliance with study or control device instructions for use
- The patient has had vascular catheterization of the lower extremities within 30 days of randomization (excluding diagnostic angiograms for the study procedure)
- The patient has previous stenting in the iliac arteries
- The patient has a previous surgical bypass in the target limb
- The patient is currently participating in another investigative clinical study unless received written approval from the sponsor

Intraoperative:

- The patient has a lesion requiring drug-coated balloon angioplasty, atherectomy, lithotripsy, or any ablative device to facilitate stent delivery
- The patient has an abdominal aortic artery lesion or aneurysm
- The patient has a lesion that requires stent placement within 2 cm of the inguinal ligament
- The patient has isolated common iliac artery stenosis that can be treated with a single device (ie, common iliac artery stenosis that does not require kissing stents or extend into the external iliac artery)
- The patient has outflow disease that requires concomitant interventions (ie, common femoral endarterectomy or femoral/tibial revascularization)

Study Devices

The VBX device (W. L. Gore & Associates, Inc, Flagstaff, AZ; hereafter, VBX device) is comprised of a balloon-expandable stent graft with a balloon catheter delivery system. The VBX device is made of unconnected stainless-steel rings that are connected and enveloped by expanded polytetrafluoroethylene and fluorinated ethylene propylene film. The comparator device for the study is intended to be any commercially available BMS and can be balloon-expandable or self-expanding and must be approved for iliac artery occlusive disease indication. The use

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of interwoven stents or drug-eluting stents is not permitted in this study.

Study Procedures

Patient screening and preprocedural imaging (eg, duplex ultrasound, computed tomography angiography, and diagnostic angiogram) will be performed at the discretion of the investigator and per the institution's standard of care. Study measurements of medical history and demographics, laboratory workup, medication review, and physical examination will be collected. Vascular access, anticoagulation, and introduction of guidewires or catheters will be performed using the standard of care for iliac endovascular procedures at each institution. Baseline aortoiliac angiography will be performed to assess target lesion characteristics and determine final patient eligibility.

Randomization and Blinding

Once study eligibility is confirmed and guidewires are in place across the target lesions, the patient will be randomized (1:1 format) to treatment with either the VBX device or a BMS (balloon-expandable or self-expanding and approved iliac artery occlusive disease indication). Permuted block randomization will be used to promote balance on baseline characteristics across treatment groups. The investigator at each site will be required to select devices that are consistent with the assigned treatment group and proceed with device implantation following the manufacturer's instructions for use. Every effort will be made to limit the number of patient cross-overs (assigned treatment not performed).

Patients, the independent core lab reviewers, and Clinical Events Committee (CEC) members will be blinded from the assigned treatment. Given the nature of the procedure, the implanting investigator will not be blinded.

Index Procedure and Postprocedure

All device implantations will be performed in compliance with the instructions for use for vessel preparation, sizing, delivery, positioning, and deployment. Predilation of each target lesion may be performed with plain balloon angioplasty. After the deployment of the devices, a postdilation may be performed, and a final angiography will be obtained to assess the technical result. Use of closure devices or sheath removal performed in accordance with institutional standard of care is at the investigator's discretion. The procedure time (first incision to access site closure), anesthesia time, reference air kerma, and total fluoroscopic time will be recorded.

Secondary interventions to treat procedural complications requiring intervention will be performed at the discretion of the investigator and these postrandomized patients will continue to be followed at the protocol-specified intervals until study completion. Information about the angiographic images performed, devices and components used, the date of, and the adverse event leading to reintervention will be captured as part of the study record.

Discharge and Follow-Up

At discharge, dual antithrombotic medical therapy is required through a minimum of 3 months post procedure. Additional single antiplatelet therapy (aspirin, clopidogrel, or prasugrel) is required for patients currently prescribed anticoagulant therapy (oral anticoagulation or direct oral anticoagulant). After at least 3 months, antithrombotic medical therapy should be continued post procedure per the investigator's discretion. Patients will be evaluated by duplex ultrasound or angiography (if necessary) for patency at 1-month, 6-months, and annually through 5 years post randomization. Additional study assessments of ankle-brachial index (ABI) [19], Rutherford Classification [20], EQ-5D-5L Questionnaire [21], and the walking impairment questionnaire [22] will be captured.

End Points

The primary end point is 1-year primary patency and is defined as blood flow through the target lesion (no evidence of binary restenosis >50% or occlusion) without target lesion revascularization (TLR). Primary patency will be evaluated and adjudicated by the independent vascular Core laboratory. TLR events will be reviewed and adjudicated by the independent CEC (Table 1).

Secondary end points (defined in Table 1) will include technical success, acute procedural success, clinical success (through 30 days), changes in ABI (hemodynamic status), EQ-5D-5L, and walking impairment questionnaire through 5 years, and the following through 5 years: primary patency, freedom from binary restenosis, primary-assisted patency, secondary patency, freedom from TLR, cumulative reintervention rate (first and recurrent TLR), freedom from clinically-driven TLR, amputation-free survival, survival, and change in Rutherford category.

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Table 1. Study end point definitions.

Term	Definition
Primary patency	• Blood flow through the target lesion (no evidence of binary restenosis >50% or occlusion) without a TLR[a]
Binary restenosis	• Evidence of >50% restenosis or occlusion of the target lesions based on core laboratory adjudicated duplex ultrasound or angiography
Primary assisted patency	• Blood flow maintained (no evidence of occlusion) through the target lesion with or without a TLR
Secondary patency	• Blood flow through the target lesion with or without a TLR
Target lesion revascularization	• Endovascular or surgical intervention performed on the target lesions
Clinically driven target lesion revascularization	• Endovascular or surgical intervention performed on the target lesions in response to recurrent symptoms (increase ≥1 Rutherford category)
Amputation-free survival	• Freedom from major amputation (target limb, amputation above the metatarsals) and all-cause mortality
Survival	• Freedom from all-cause mortality
Technical success	• Deployment of device with <30% residual stenosis on final angiography
Acute procedural success	• Technical success and freedom from device or procedure-related SAE[b] requiring intervention
Clinical success	• Improvement from baseline of ≥1 Rutherford category and freedom from device or procedure-related SAE requiring intervention
Hemodynamic status	• Change in ABI[c] as compared to baseline
Rutherford category status	• Change in Rutherford category as compared to baseline
Quality of life assessments	• Change in EQ-5D-5L responses as compared to baseline • Change in WIQ[d] responses as compared to baseline

[a]TLR: target lesion revascularization.

[b]SAE: serious adverse event.

[c]ABI: ankle-brachial index.

[d]WIQ: walking impairment questionnaire.

Statistical Analysis

This study is designed to test the null hypothesis that the VBX device group will demonstrate a primary patency that is less than or equal to the BMS group at 1-year follow-up; versus the alternative hypothesis that the VBX device group will demonstrate a primary patency that is greater than the BMS at 1-year follow-up.

Sample Size Considerations

This study is designed with the assumption that 1-year primary patency will be 88% and 70% for the VBX device group and BMS group, respectively. The study assumptions are based on the FLEX clinical study data and a recent meta-analysis of covered stents and BMS (both balloon-expandable and self-expanding) in patients with TASC II C and D lesions with a minimum of 12-month follow-up [11].

A total sample size of 244 patients would be required to account for a 20% loss to follow-up in order to demonstrate statistical significance (α=.05) at a power of 88%.

Primary and Secondary End Point

The study analysis plan will include the following analysis populations: (1) intent-to-treat population (randomized patients categorized by assigned treatment); (2) as-treated population (randomized patients categorized by treatment received); and (3) per-protocol population. Primary patency at 1 year post implantation of the VBX device and BMS treatment groups will be analyzed with Kaplan-Meier estimates with separate estimates for each group. A 2-sided confidence interval of these estimates (α=.05) will be constructed to test the observed differences in primary patency rates between the treatment groups.

A comparative analysis of secondary end points will be performed. If the null hypothesis for the primary end point is rejected, key secondary end points will be evaluated for superiority using fixed sequential testing. In order, the secondary end points to be tested for superiority are cumulative target revascularization rate (first and recurrent events), the difference in mean ABI, and freedom from TLR.

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Time-to-event secondary end points will be analyzed with Kaplan-Meier estimates with separate estimates for each group. Categorical end points for each treatment group will be analyzed with chi-square tests, and continuous end points for the treatment groups will be analyzed with 2-sample *t* tests.

Trial Organization and Oversight

The Executive Steering Committee, consisting of multidisciplinary (vascular surgery, interventional cardiology, and interventional radiology) key opinion leaders, will provide study guidance and clinical oversight. The sponsor will provide study oversight in partnership with contract research organizations for database development, data monitoring, and independent review of study outcomes.

All imaging required by the study including duplex ultrasound and angiography, will be sent to the independent study core laboratory for centralized review and adjudication. An independent CEC will review and adjudicate potential end point–related events. For end point analysis, the sponsor will use data adjudicated by the core laboratory and CEC.

Results

Site enrollment is currently in process, and participant enrollment is anticipated to begin in October of 2023. Participant enrollment is expected to take up to 32 months. Once all participants are enrolled, follow-up will continue through 5 years.

Discussion

Progressive Standards

The literature for long-term, randomized comparison studies for the treatment of AIOD is limited and, therefore, there are no accepted, published guidelines regarding the selection of either bare metal or covered stents. The COBEST trial [12] is the reference data often cited supporting the use of covered stents in complex AIOD. However, the trial was a noninferiority study with minimal statistical power, limited experience in 1 country, only an 18-month follow-up visit, and no independent core laboratory review for adjudication of end points. Furthermore, the COBEST trial was designed to evaluate binary restenosis rather than primary patency. The DISCOVER trial [13,14] failed to show any benefit of covered stents in “advanced” common iliac artery disease across all end points, likely due to the majority of TASC II A and B lesions. The FLEX trial included patients with tortuous iliac arteries, severe calcification, chronic total occlusions, and those who required kissing stents at the aortic bifurcation [7]. Importantly, despite the inclusion of more challenging iliac pathology, the FLEX study demonstrated a 1-year patency of 94.5% for the VBX stent-grafts in the treatment of AIOD involving the common or external iliac arteries [8]. The physician-initiated long-term follow-up of the FLEX study [23], demonstrated a 5-year patency of 89.5% which appears significantly greater than the 5-year patency of 74.7% for covered stents in the COBEST study [12]. While these studies suggest that the primary patency of covered stents may be better than BMS for the treatment of complex AIOD, there is a lack of level 1 evidence and no clear consensus regarding the optimal stent selection in AIOD.

The objective of the FORWARD study is to demonstrate the superiority of the VBX device for primary patency when compared to BMS in complex iliac occlusive disease in a prospective, multicenter, randomized controlled trial. The data from this study aims to provide level 1 evidence that will significantly enhance therapeutic decision-making and help establish a standard of care to guide clinical practice for patients with symptomatic severe aortoiliac disease. The FORWARD study is powered for superiority and includes only complex, unilateral, or bilateral lesions involving the common or external iliac arteries. To mirror real-world practice more closely, patients with minor tissue loss (Rutherford class 5) and patients requiring hemodialysis will be included. This study is a multidisciplinary endeavor involving vascular surgery, interventional cardiology, and radiology across multiple countries with a blinded core laboratory review of end points in hopes that the outcomes will be widely accepted by all parties that treat symptomatic patients with complex AIOD.

Limitations

In the design of this study, multiple considerations were taken to curb the number of limitations. While the study intends to target complex diseases, the results may not be generalizable to populations with less complex diseases. This population is less frequent and may slow enrollment. The study is powered to demonstrate superiority at 1 year, however, longer-term outcomes are also clinically relevant. Additionally, due to the nature of the procedure, blinding of the implanting investigator is not possible which has the potential to induce bias.

Acknowledgments

Medical writing support was provided by Millie Hollandbeck (Phoenix, Arizona) and was funded by W. L. Gore & Associates, Inc (Flagstaff, AZ). Additional paper preparation assistance was provided by Chrystal Redding, an employee of W. L. Gore & Associates.

Data Availability

Data generated or analyzed during this study will be included in peer-reviewed publications. The data sets have yet to be generated or analyzed for this study because no participants have been enrolled.

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Conflicts of Interest

MLK is a consultant, advisor, or speaker for W.L. Gore & Associates, Inc. EJA is a consultant, advisor, or speaker for Abbott Vascular, Boston Scientific, W.L. Gore & Associates, Inc, Medtronic, Philips, and Shockwave Medical and receives support from Medalliance, REVA Medical. MMA is a consultant, advisor, or speaker for Philips, Boston Scientific, Terumo, W.L. Gore & Associates, Abbott, Bard, Cordis, Medtronic, CSI, Surmodics, Edwards, and Recor Medical and receives support from Boston Scientific, W.L.Gore, Abbott, Terumo, Recor medical, Reflow Medical, PQ Bypass, Alleviant, Ancora Heart, Med Alliance, Microport, Reva Medical, and Norvartis. AH is a consultant, advisor, or speaker for Boston Scientific, W.L. Gore & Associates, Medtronic, and Philips and receives support from Abbott, Bard-BD, Biotronik, Boston Scientific, Cagent, Cook, Efemoral, Endologix, Endospan, FluidX, W.L.Gore, Medtronic, Nectero, Philips, Reflow Medical, Shape Memory, Shockwave, Terumo, and TriReme. MMPJR is a consultant, advisor, or speaker for Medtronic, W.L. Gore & Associates, and Merit Medical and receives support from Medtronic, W.L. Gore & Associates, and Artivion. MS is a consultant, advisor, or speaker for W.L. Gore & Associates, Medtronic, Getinge Maquet, and Bentley. DBS is a consultant, advisor, or speaker for Cook, Medtronic, and W.L. Gore and receives funding from Boston Scientific, Cook, LimFlow, and W.L. Gore & Associates. ZC, HN, and AP are employees of W.L. Gore & Associates, Inc.

Multimedia Appendix 1
CONSORT 2010 Checklist.
[DOC File , 221 KB - resprot_v12i1e51480_app1.doc]

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Abbreviations

ABI: ankle-brachial index
AIOD: aortoiliac occlusive disease
BMS: bare metal stents
CEC: Clinical Events Committee
ISO: International Organization for Standardization
PAD: peripheral artery disease
TASC: Trans-Atlantic Inter-Society Consensus
TLR: target lesion revascularization
VBX device: GORE VIABAHN VBX Balloon Expandable Endoprosthesis

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Protocol

Intravenous Ascorbic Acid for the Prevention of Postreperfusion Syndrome in Orthotopic Liver Transplantation: Protocol for a Randomized Controlled Trial

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Abstract

Background: Liver transplantation is the last therapeutic option for patients with end-stage liver disease. Postreperfusion syndrome (PRS), defined as a fall in mean arterial pressure of more than 30% within the first 5 minutes after reperfusion of at least 1 minute, can occur in liver transplantation as a deep hemodynamic instability with associated hyperfibrinolysis immediately after reperfusion of the new graft. Its incidence has remained unchanged since it was first described in 1987. PRS is related to ischemia-reperfusion (I/R) injury, whose pathophysiology involves the release of several mediators from both the donor and the recipient. The antioxidant effect of ascorbic acid has been studied in resuscitating patients with septic shock and burns. Even today, there are publications with conflicting results, and there is a need for further studies to confirm or rule out the usefulness of this drug in this group of patients. The addition of ascorbic acid to preservation solutions used in solid organ transplantation is under investigation to harness its antioxidant effect and mitigate I/R injury. Since PRS could be considered a manifestation of I/R injury, we believe that the possible beneficial effect of ascorbic acid on the occurrence of PRS should be investigated.

Objective: The aim of this randomized controlled trial is to assess the benefits of ascorbic acid over saline in the development of PRS in adult liver transplantation.

Methods: We plan to conduct a single-center randomized controlled trial at the Hospital Universitario Ramo´n y Cajal in Spain. A total of 70 participants aged 18 years or older undergoing liver transplantation will be randomized to receive either ascorbic acid or saline. The primary outcome will be the difference between groups in the incidence of PRS. The randomized controlled trial will be conducted under conditions of respect for fundamental human rights and ethical principles governing biomedical research involving human participants and in accordance with the international recommendations contained in the Declaration of Helsinki and its subsequent revisions.

Results: The enrollment process began in 2020. A total of 35 patients have been recruited so far. Data cleaning and analysis are expected to occur in the first months of 2024. Results are expected around the middle of 2024.

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Conclusions: We believe that this study could be particularly relevant because it will be the first to analyze the clinical effect of ascorbic acid in liver transplantation. Moreover, we believe that this study fills an important gap in the knowledge of the potential benefits of ascorbic acid in the field of liver transplantation, particularly in relation to PRS.

Trial Registration: European Union Drug Regulating Authorities Clinical Trials Database 2020-000123-39; https://tinyurl.com/2cfzddw8; ClinicalTrials.gov NCT05754242; https://tinyurl.com/346vw7sm

International Registered Report Identifier (IRRID): DERR1-10.2196/50091

(JMIR Res Protoc 2023;12:e50091) doi:10.2196/50091

KEYWORDS

antioxidant therapy; antioxidant; ascorbic acid; blood; controlled trials; hepatic; ischemia; ischemic; liver transplantation; liver; postreperfusion syndrome; randomization; randomized controlled trial; RCT; reperfusion injury; reperfusion; surgery; surgical; transplant; transplantation; vascular; vitamin C; vitamin; vitamins

Introduction

Scientific Background and Explanation

The first liver transplant (LT) in the world was performed in 1963 [1], but the first successful transplant was carried out by Dr Starzl at the University of Pittsburgh in 1967 [2]. Until the introduction of immunosuppression with cyclosporine in the early 1980s, the survival rate of transplanted patients remained at 20% [3,4]. The 1-year and 5-year patient survival rates have increased to 85% and 70%, respectively, due to advances in surgical and anesthetic techniques and immunosuppression protocols. Despite these advances, hemodynamic changes during surgery remain a challenge for anesthesiologists.

One of the most serious changes during LT can occur at the time of graft reperfusion as an adverse hemodynamic situation known as postreperfusion syndrome (PRS), first described by Aggarwal et al [5] in 1987. They defined PRS as a deep and transient cardiovascular collapse immediately after graft reperfusion, with severe bradycardia, decreased mean arterial pressure (MAP) and systemic vascular resistance, severe arrhythmias, increased pulmonary artery pressure and central venous pressure, and even cardiac arrest. They defined it as a decrease in MAP of more than 30% within the first 5 minutes of graft reperfusion lasting at least 1 minute. The development of PRS is associated with decreased survival, an increased incidence of postoperative renal failure, early graft dysfunction, and the need for blood product transfusion in the setting of severe fibrinolysis [6-8]. Although it was first described in 1987, its incidence has not decreased over the past decades, ranging from 8% to 35% [9-11].

The intrinsic mechanisms of PRS are complex and not fully understood. Several theories have been proposed, including an abrupt accumulation of factors upon reperfusion, such as metabolic acidosis, hyperkalemia, hypokalemia, hypothermia, air emboli, and the release of vasoactive and proinflammatory mediators from both allograft and recipient, which are responsible for decreased systemic vascular resistance and myocardial depression [1,12-19]. During perfusion of the new graft, many proinflammatory cytokines are released from the new liver, such as tumor necrosis factor alpha and interleukins (ILs; IL-1, IL-2, and IL-8), and others from the patient (kallikrein and bradykinin). Other mediators have been found to be elevated after reperfusion (arginase, endotoxins, thromboxane, and monocyte chemoattractant protein-1), but the role of each of these mediators in the onset and severity of PRS is not known [18,20-24].

Ischemia-reperfusion (I/R) injury in LT is associated with graft dysfunction and decreased survival, but its exact role in PRS is controversial. I/R results in cell death due to lack of oxygenation, which occurs during the ischemic period and is exacerbated immediately after reperfusion by the release of proinflammatory cytokines and oxygen free radicals, activation of the complement system leading to sinusoidal vasoconstriction, and local hemoconcentration in the graft with the presence of neutrophils and platelets. All these mechanisms exacerbate the systemic inflammatory response (vasodilation and myocardial depression). The extent to which I/R contributes to the development of PRS and the severity of hemodynamic abnormalities is not entirely clear [25,26], but it seems logical to conclude that PRS is another manifestation of I/R injury. Several randomized controlled trials have been published using different drugs to prevent the onset of PRS (methylene blue, acetylcysteine, antifibrinolytics, and others). However, none of these have shown a beneficial effect.

On the other hand, there has recently been renewed interest in the use of high-dose vitamin C as a supportive treatment in patients with severe septic shock (metabolic resuscitation) [27]. Sepsis has been shown to decrease the levels of some vitamins, such as ascorbic acid, which has been associated with the development of multiorgan failure and death. Intestinal absorption of vitamin C is saturable, so the only way to increase its levels would be by intravenous administration. Tanaka et al [28] reduced resuscitation fluid volumes in patients with burns by administering high doses of intravenous ascorbic acid. This was a randomized controlled trial of 37 patients allocated to receive a dose of 66 mg/kg/hour of vitamin C versus saline during the first 24 hours of resuscitation. Although MAP and central venous pressure were similar at the end of the vitamin C or saline infusion, fluid administration was lower in the intervention group, and patients maintained higher urine output and developed less wound edema with a significant reduction in the duration of mechanical ventilation (12 days vs 21 days; P=.03).

Zabet et al [29] investigated the effect of high doses of vitamin C on vasopressor requirements in septic shock. As ascorbic acid is required for catecholamine synthesis [30], it was investigated

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whether it could be useful in shortening vasopressor weaning. A total of 24 patients with vasopressor-dependent septic shock were randomized to receive vitamin C at a dose of 25 mg/kg intravenously every 6 hours versus saline. The dose and duration of vasopressors were significantly reduced in the intervention group, as was mortality.

The most important study in septic patients was conducted by Marik et al [31], who used a combination of hydrocortisone, ascorbic acid (1.5 g every 6 hours), and thiamine (200 mg every 12 hours) in 47 patients with sepsis admitted to the intensive care unit with procalcitonin levels >2 ng/mL. The aim of thiamine was to prevent kidney oxalate accumulation. Mortality decreased in patients treated with vitamin C (P<.001). They were weaned from vasopressors earlier and received less intravenous fluid for resuscitation than the control group.

Vitamin C is safe even in very high doses. Fowler et al [32] conducted a safety study of intravenous ascorbic acid in 24 patients with severe sepsis (low dose 12.5 mg/kg every 6 hours vs high dose 50 mg/kg intravenously every 6 hours). No adverse events were observed. No adverse effects were reported in any of the above studies, including the study by Tanaka et al [28], in which the doses were very high (1.6 g/kg over 24 hours). Metabolism of vitamin C to oxalic acid could theoretically cause calcium oxalate nephropathy. However, this does not seem to be a real problem, as renal toxicity is dose-dependent and has only been reported at very high doses (>40 g/day) [33]. In addition, coadministration of thiamine would reduce the conversion of vitamin C to oxalate. In the study by Marik et al [31], the incidence of renal failure requiring renal replacement therapy was significantly lower in the intervention group (33% vs 10%; P=.02).

However, several meta-analyses have been published in recent years with mixed results. In most of them, a reduction in mortality, duration of mechanical ventilation, and hospitalization could not be demonstrated. However, a reduction in the sepsis-related organ failure assessment score and a shorter duration of treatment with vasoactive drugs is a common finding [34-38].

I/R injury plays a pivotal role in the development of graft dysfunction after liver transplantation, and excessive free radical production and massive depletion of endogenous antioxidants are common mechanisms underlying I/R injury. Ascorbic acid is an essential micronutrient involved in the antioxidant response and modulation of apoptosis and inflammation. These properties may, therefore, make it a potential strategy for reducing I/R injuries. In addition, its safety profile, low cost, and ease of administration favor its use in this scenario [39]. As discussed above, we can consider PRS as one of the clinical manifestations of I/R injury. Therefore, if we can prevent or at least attenuate I/R injury, we may be able to reduce the incidence of I/R injury.

Aim

The aim of the study is to determine the possible benefit of vitamin C in reducing the incidence of PRS in liver transplantation.

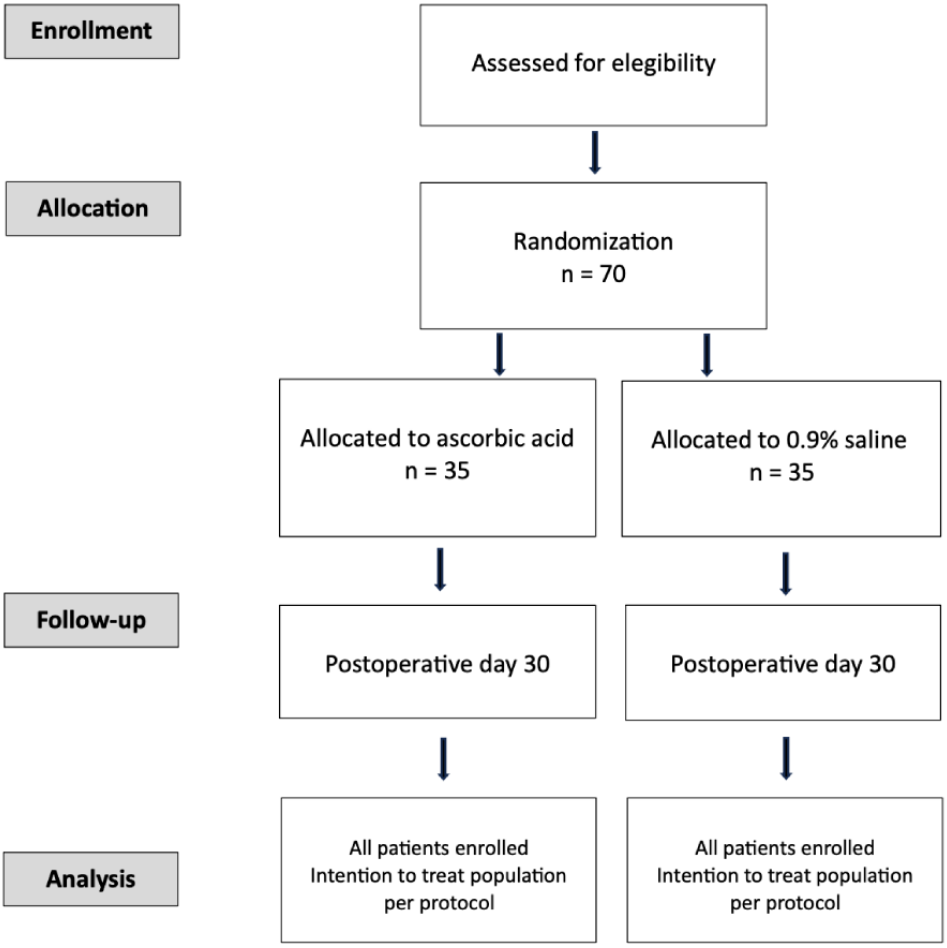
Methods

Study Setting

The trial has been designed in accordance with the updated CONSORT (Consolidated Standards of Reporting Trials), the Declaration of Helsinki, and the Good Clinical Practice guidelines issued by the Spanish regulatory authorities. The study will be conducted at a single center, the Hospital Universitario Ramon y Cajal in Madrid (Figure 1).

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Figure 1. CONSORT (Consolidated Standards of Reporting Trials) flow diagram.



Trial Design

This study is designed as a single-center, double-blind, randomized controlled trial. Participants will be randomized to receive ascorbic acid (intervention group) or saline (0.9%; control group). We will conduct a superiority analysis.

Eligibility Criteria for Participants

All patients over 18 years of age who are on the waiting list for liver transplantation may be eligible to participate in this study. The inclusion and exclusion criteria are detailed in Textbox 1.

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Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Aged between 18 and 67 years
- Waiting for a liver transplant
- Negative pregnancy test in women

Exclusion criteria

- Pregnancy
- Allergy to ascorbic acid
- Nephrolithiasis
- Glucose-6-phosphate dehydrogenase (G6PD) deficiency
- Hyperoxaluria
- Hyperuricemia
- Haemochromatosis
- Sickle cell anemia
- Serum creatinine >1.2 mg/dL (women) and 1.3 mg/dL (men)
- Split liver graft
- Acute liver failure
- Living donor liver transplantation
- Grafts from donation after circulatory death
- Treatment with indinavir, vitamin B_{12}, cyclosporine, iron, deferoxamine, or disulfiram

Study Procedures and Intervention

The intervention group will receive a dose of 1500 mg of intravenous ascorbic acid (vitamin C) diluted in 100 mL of 0.9% saline for 30 minutes, to be administered during the anhepatic phase of liver transplantation.

The control group will receive a dose of 100 mL of 0.9% saline for the same period and under the same conditions.

Outcome Measurements

The primary end point of the study is the percentage of patients who develop PRS after liver graft reperfusion. PRS is defined as a 30% decrease in MAP within the first 5 minutes after portal-clamp release that persists for at least 1 minute.

Textbox 2 contains the secondary variables that are also analyzed.

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Textbox 2. Secondary variables.

Secondary variables

- The percentage of patients with primary failure and early graft dysfunction. Primary graft failure is defined as the complete absence of liver graft function. The patient will not survive without retransplantation. In the case of early graft dysfunction, patient survival is likely and possible without retransplantation, although morbidity will be greater than in the case of normal function. The following Olthoff criteria are used for its definition (one criterion is enough):
  - Bilirubin ≥10 mg/dL on postoperative day 7.
  - International normalized ratio ≥1.6 on postoperative day 7.
  - Alanine aminotransferase or aspartate aminotransferase >2000 IU/mL in the first 7 postoperative days.
- Length of stay in the intensive care unit and hospitalization. The number of days spent in the surgical intensive care unit and the total number of days spent in the hospital.
- Dose and duration of catecholamines from the time of reperfusion.
- Length of time on mechanical ventilation (hours). Time to extubation of the patient.
- Vitamin C levels before transplantation and 12 hours after transplantation. Measurements are performed by high-pressure liquid chromatography with an ultraviolet detector.
- Levels of inflammatory markers (IL-1β, tumor necrosis factor alpha, IL-6, IL-8, and IFN-γ) before and after transplantation as measured by the high-sensitivity enzyme-linked immunosorbent assay technique.
- Development of postoperative kidney failure (acute kidney injury [AKI]) during the first week. AKI is defined as an increase in serum creatinine (SCr) ≥0.3 mg/dL within 48 hours or an increase in SCr × 1.5 times baseline; known or presumed to have occurred within the previous 7 days.
- Need for postoperative renal replacement therapy during the first week. Need for any type of renal replacement therapy during the first 7 days after transplantation, regardless of the technique used.
- Graft and patient survival 30 days after transplantation.

Participant Timeline

Patients will be monitored from randomization until day 30 post surgery. The team will collect variables daily through postoperative day 7 and a final visit on postoperative day 30. The research team will closely monitor adverse events, including onset, duration, intensity, progression, and outcome, to assess their relationship to the drug.

Sample Size Calculation

The current incidence of PRS at our center is 30%. Assuming a 50% decrease in PRS incidence (from 30% to 15%) with an α risk of 5% and a power of 80%, bilateral testing, and the Fleiss correction with a 10% loss rate, we require 268 participants (134 in each group). Due to the limited number of transplants per year in our center, achieving such a large sample will take 6-8 years. Given that this study will be conducted at a single center, the projected patient enrollment is 35 individuals per year, resulting in a final sample size of 70 participants. To attain 80% power with this sample, it is necessary to achieve a complete elimination of PRS. Although it is unlikely that such a reduction in the incidence of PRS would be achieved, we believe that this is a reasonable number of participants to show differences in the primary outcome that, although not reaching the desired statistical significance, would serve to justify a future multicenter randomized controlled trial. Participants will be randomly assigned to groups using a computer-generated sequence created by SPSS Statistics (SPSS Inc). The computer-generated sequence will allocate 35 participants to the ascorbic acid intervention group and 35 participants to the saline control group. To ensure independence, an unrelated staff member will enroll patients and prepare medication or saline upon arrival.

Analysis

Quantitative variables will be described using mean, median, SD, IQR, 95% CI, and range values. Quantitative data will be presented as absolute and relative frequencies. The significance level in any statistical test will be set at α=.05. Both groups will be assessed to ensure they are balanced in all variables.

A total of 2 populations will be established: one based on intention to treat and the other based on efficacy. The first population will consist of all participants randomized at the start and divided into 2 groups according to the corresponding randomization. The second population will consist of the participants who complete the protocol and end up in the same group in which they were randomized. All analyses will be conducted on both populations; however, the primary analysis will focus on the intention to treat the population. Statistical analyses will be performed using SPSS Statistics.

The comparison between participants who experienced PRS during the intervention will be performed using the chi-square test. Cohort proportions are compared using relative risk with 95% CIs. In a secondary analysis, we will adjust for potentially confounding factors related to the main outcome variable by using a multivariate technique. These factors include variables that showed significant differences (with $P \leq .20$) between the control and treatment groups and have been identified as potential confounds. When dealing with binary factors, we will assess the magnitude of association with odds ratios, while for ordinal or quantitative factors, we will use the Spearman correlation coefficient. A binary logistic regression analysis

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will be conducted to examine the presence of PRS. The control variable (ascorbic acid vs saline) and all variables resulting from the previous univariate analysis will serve as independent variables. The same procedure will be applied to secondary efficacy and safety analyses.

Monitoring and Quality Assurance

The data collected in the study will be coded, and only the principal investigator and collaborators will be able to access this information and link it to each patient's clinical history. The information will be stored in a database that adheres to current regulations on personal data protection, including Regulation (EU) 2016/679 of the European Parliament and of the Council of April 27, 2016, on Data Protection, and the Organic Law 3/2018 of December 5, on Personal Data Protection and Guarantee of Digital Rights. Only the data included in the medical file and related to the study will be subject to verification. This verification will be carried out in the presence of the principal investigator or collaborators, who have the responsibility to protect the privacy of data within the clinical records of the participants who take part in the clinical trial.

Therefore, the identity of the participant will not be disclosed to any other person except to the health authorities, when required, or in cases of medical emergencies. The Research Ethics Committees, the representatives of the Health Authority in matters of inspection, and the personnel authorized by the sponsor will only have access to verify the personal data, the procedures of the clinical trial, and compliance with good clinical practice (always maintaining the confidentiality of the information). The principal investigator and the sponsor will keep the data collected for the study for at least 25 years after its completion. Under no circumstances will the identities of study participants be disclosed at the time of publication of the results.

Ethical Considerations

This study has been registered in the European Union Drug Regulating Authorities Clinical Trials Database (EudraCT; 2020-000123-39) and at ClinicalTrials.gov (NCT05754242). The Ethics Committee of Hospital Universitario Ramo´n y Cajal and the Spanish Medicines and Health Products Agency (Agencia Espan˜ola del Medicamento y Productos Sanitarios [AEMPS]) have both approved this study protocol (AEMPS-20-0052).

This clinical trial will adhere to the ethical principles governing biomedical research on human beings and respect their fundamental rights in accordance with international recommendations included in the Declaration of Helsinki and its latest revision of Fortaleza (Brazil, 2013). The guidelines of AEMPS will also be followed, in addition to following national recommendations.

Participants will be given both oral and written information about how the study will be conducted, its objectives, the potential risks involved, and the guidelines to be followed during the monitoring period. If a patient satisfies the inclusion criteria and agrees to participate in the study, they will provide written informed consent. They are free to withdraw their consent and discontinue the study at any point and for any reason.

Results

The enrollment process began in 2020. A total of 35 patients have been recruited so far. Data cleaning and analysis are expected to occur in the first months of 2024. Results are expected by mid-2024.

Discussion

Overview

This study aims to show if ascorbic acid could be useful in preventing PRS during liver transplantation. Improved hemodynamic stability following graft reperfusion, combined with the potential antioxidant effects of vitamin C, may lead to enhanced outcomes in liver transplantation.

The potential protective effect of adding ascorbic acid to transplant preservation solutions before transplantation has been studied with promising results. However, there has been limited research on the benefits of intravenous vitamin C administration for the prevention of I/R injury in solid organ recipients. PRS may be considered a severe clinical manifestation of I/R injury in liver transplant recipients [25,26]. Therefore, we propose that ascorbic acid's antioxidant properties may play a protective role in preventing PRS during liver transplantation.

Vitamin C acts as an antioxidant. It reduces inflammation and modulates the immune response. It also increases the synthesis and sensitivity of endogenous vasopressors, acts as an enzymatic cofactor, and has bacteriostatic and antithrombotic properties [29].

The hallmark of PRS is a depressed state of the cardiovascular system. The pathophysiological mechanisms underlying PRS are thought to involve the release of proinflammatory mediators with vasodilatory effects by both graft and recipient [20-24]. Therefore, vitamin C may have beneficial effects in the prevention and treatment of I/R injury, potentially reducing the incidence of PRS.

We are aware that studies following Marik et al's [31] publication have reduced enthusiasm for the use of vitamin C in the treatment of patients with severe sepsis. In fact, its use is no longer recommended by the Surviving Sepsis Campaign guidelines. However, recent publications, including several meta-analyses, confirm the beneficial effects of this treatment in septic patients. These effects include reducing the number of days on vasopressors and improving the sepsis-related organ failure assessment score [34-38]. We believe that the administration of ascorbic acid to patients with sepsis could potentially have a positive impact, especially considering its minimal side effects. Additional prospective clinical trials are needed to definitively establish the benefits of this treatment in this specific patient population.

Likewise, treating and preventing I/R injury in solid organ transplant recipients may be helpful, given the beneficial effects of ascorbic acid demonstrated in some of these studies in patients with sepsis.

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This study is of particular importance because it is the first to evaluate the effects of administering ascorbic acid before reperfusion of the new liver graft to prevent PRS. It will also provide more information about the levels of inflammatory markers before and after reperfusion and how they change with the onset of PRS.

If the study shows positive results, the ideal dose to be used and the exact duration of treatment should be defined and could be applied to other types of solid organ transplantation.

This study aims to address the current gap in knowledge regarding the clinical effectiveness of administering vitamin C during solid organ transplantation, particularly in liver transplantation. We will provide valuable insights into this area of research through rigorous data analysis.

Strength and Limitation of the Study

The main limitation of the study, due to the limited number of participants planned, is that it may not achieve adequate statistical power to establish with sufficient scientific evidence whether vitamin C reduces the PRS and improves the results of LT. However, we believe that if positive results in favor of vitamin C are obtained, the trial would serve as the basis for a larger trial involving other transplant centers, which would allow us to demonstrate the benefit of vitamin C with enough statistical power. It is possible that we may not be able to control for additional variables that may bias the results, including those related to the surgical and anesthesia teams. A forthcoming multicenter trial could address this issue.

Acknowledgments

The authors would like to acknowledge that the researchers and collaborators in this study have not received any financial compensation. Any economic aspects related to the clinical trial are outlined in a contract between the Biomedical Research Foundation of Ramo´n y Cajal University Hospital (Instituto Ramo´n y Cajal de Investigacio´n Sanitaria [IRYCIS]) and the promoter of the study.

Data Availability

The data sets used or examined in this study will be accessible from the corresponding author upon request.

Authors' Contributions

LG, IdlH, and ME designed the study. LG, IdlH, MdCMG, JNV, and MARG performed the literature search. IdlH, LG, MdCMG, AMG, DPR, JV, and CFM recorded the data. LG and IdlH were the major contributors to writing this manuscript. All the authors participated in the design of the study and read, commented upon, and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

AEMPS: Agencia Espan˜ola del Medicamento y Productos Sanitarios
CONSORT: Consolidated Standards of Reporting Trials
I/R: ischemia-reperfusion
IL: interleukin
LT: liver transplant
MAP: mean arterial pressure
PRS: postreperfusion syndrome

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Protocol

Effectiveness of a Health Education Program for Patients Who Had a Stroke and Their Caregivers by Controlling Modifiable Risk Factors to Reduce Stroke Recurrence in a Tertiary Hospital in Bangladesh: Protocol for a Randomized Controlled Trial

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Abstract

Background: Stroke is a significant public health concern that causes severe and long-lasting disability. The recurrence of stroke is increasing due to lack of patients' knowledge and compliance with treatment to control modifiable risk factors and lifestyle changes. Health education can be an effective way to increase knowledge about behavioral changes in patients who had a stroke.

Objective: The aim of this study is to evaluate the effectiveness of a health education program in Bangladesh for patients who had their first stroke and their family caregivers in order to reduce the recurrence of stroke by controlling modifiable risk factors.

Methods: This is a parallel, open-label, prospective randomized controlled trial conducted at the National Institute of Neurosciences & Hospital in Dhaka, Bangladesh. We enrolled ≥18-year-old patients of both sexes who had a history of first stroke attack (transient ischemic attack, hemorrhagic stroke, lacunar stroke, atherothrombotic stroke, or cardioembolic stroke). We stratified patients into those aged <65 years and those aged ≥65 years and according to types of strokes for randomization. Our estimated sample size was 432. The intervention group receives face-to-face counseling on lifestyle modifications, blood pressure monitoring, and medication compliance–related health education during enrollment and monthly follow-ups. However, the control group receives only usual care from the hospital. The primary end point of this study is the reduction in the stroke recurrence rates at the end of the 12-month follow-up period. The secondary end points are to (1) assess the occurrence of all adverse events such as other cardiac events and all-cause mortality, (2) evaluate the status of the controlling modifiable risk factors such as blood pressure, glycated hemoglobin, and non–high-density lipoprotein cholesterol, (3) assess the knowledge related to stroke by using the investigator-developed questionnaire, (4) evaluate the lifestyle behavior related to stroke by using the investigator-developed questionnaire, (5) assess medication adherence, and (6) evaluate the quality of life of patients who had a stroke and their family caregivers. The evaluation points will be at baseline, 6 months, and 12 months for both groups.

Results: Patients' enrollment started on October 2022, and follow-up will be completed in March 2024. A total of 432 participants were included in both the intervention (n=216) and control groups (n=216). This study was approved by the institutional review board and the ethics review board of the National Institute of Neurosciences & Hospital (IRB/NINSH/2022/151) on August 30, 2022.

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Conclusions: Our health education program is expected to reduce the recurrence of stroke and improve the quality of life of patients who have had the first stroke. The results of this study will provide insights into the importance of health education for (self)-management and prevention of stroke.

Trial Registration: ClinicalTrials.gov NCT05520034; https://clinicaltrials.gov/ct2/show/NCT05520034

International Registered Report Identifier (IRRID): DERR1-10.2196/51178

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KEYWORDS

stroke; caregiver; recurrence of stroke; health education; Bangladesh; modifiable risk factor; recurrence; hospital; disability; lifestyle change; behavioral change; risk factor; quality of life; tertiary

Introduction

Background

Stroke is a major global health concern, ranked as the second highest cause of death in 2019 [1], with an estimate of 93.2-110.5 million people affected worldwide [2]. This debilitating condition causes long-term physical, mental, and social disability, leading to financial difficulties for patients and their families [2,3]. People are affected by stroke in both low-income and high-income countries, and most cases have been reported in older age groups [4,5], although it has also been reported in younger individuals, especially in low-income countries [6]. In 2019, the burden of stroke increased from 70% to 85% between 1990 and 2019, and the mortality rates rose by 43% during this period. Among them, 62.4% experienced an ischemic stroke, 27.9% had an intracerebral hemorrhage, and 9.7% had subarachnoid hemorrhage, with corresponding mortality rates of 4%, 0.36%, and 0.36%, respectively, resulting in a total death rate of 6% [2]. A meta-analysis of 26 studies from 1997 to 2019 found stroke recurrence rates ranging from 5.7% to 51.3% over 1-10 years, with a 1-year recurrence rate of 5.7%-17.7% [7]. The first 3 months following the initial attack are the most critical for recurrence [8]. Moreover, the meta-analysis indicated that factors such as diabetes mellitus, smoking status, peripheral artery disease, hypercoagulable state, depression, 24-hour minimum systolic blood pressure (BP), 24-hour maximum diastolic BP, age, family history of stroke, National Institutes of Health Stroke Scale score status, hypertension, and history of cardiac disease were found to influence the recurrence of stroke [9,10].

In Bangladesh, stroke is the topmost cause of death, accounting for 82.31 deaths per 100,000 people in 2019 across all age groups and genders [11], with prevalence of approximately 11.39 cases per 1000 people [4]. Among them, 79.7% experienced ischemic stroke, 15.7% had hemorrhagic stroke, and 4.6% were diagnosed with subarachnoid hemorrhage [4]. A hospital-based study in Bangladesh reported cumulative recurrence rates of 14.7% at 3 months, 15.3% at 6 months, 17.3% at 9 months, and 20% at 1 year, predominantly in individuals older than 75 years [8]. Male patients with hypertension, diabetes, and dyslipidemia had a higher risk of recurrence compared to females. Additional risk factors included hypertension (79.2%), dyslipidemia (38.9%), tobacco use and smoking (37.2%), diabetes (28.8%), ischemic heart disease (20.1%), atrial fibrillation (13.9%), and obesity (9.7%) [4].

Secondary preventive measures must be implemented that address comorbidities such as hypertension and diabetes through lifestyle modifications, surgical interventions, and pharmacological interventions to reduce the recurrence of stroke [12]. Health education interventions can effectively enhance knowledge, raise awareness, modify lifestyle behaviors, and control modifiable risk factors, ultimately improving the quality of life (QoL). A study demonstrated that a 6-month health education program reduced stroke recurrence rate by 50% at 30-month follow-up [13]. Furthermore, regular postdischarge checkups and early follow-ups are necessary to prevent complications and further recurrence. Many countries worldwide have implemented stroke prevention efforts [14]. A randomized controlled study showed that both face-to-face and telehealth education programs resulted in significant improvements in health behaviors related to physical activity, nutrition, low-salt diets, and medication adherence. Additionally, the intervention group exhibited decreased systolic BP and cholesterol levels [15,16]. Another similar study using a randomized controlled design found that a web-based stroke education program led to significant increases in exercise, reduced consumption of salty foods, increased intake of fruits and vegetables, enhanced sense of control, improved health motivation, and improved caregiver mastery. However, all these interventions did not result in significant reduction of stroke recurrence [17]. In Bangladesh, a significant challenge for patients who have had a stroke is the absence of a follow-up system after hospital discharge and lack of patient and family education during hospital stay or in postdischarge or primary care settings. As a result, low medication compliance and poor risk factor control have been reported among patients who have had a stroke in Bangladesh [18].

Study Objectives

The objective of this study is to evaluate the effectiveness of a health education program for patients who had their first stroke (transient ischemic attack, hemorrhagic stroke, lacunar stroke, atherothrombotic stroke, or cardioembolic stroke) and their family caregivers in order to reduce the recurrence of stroke.

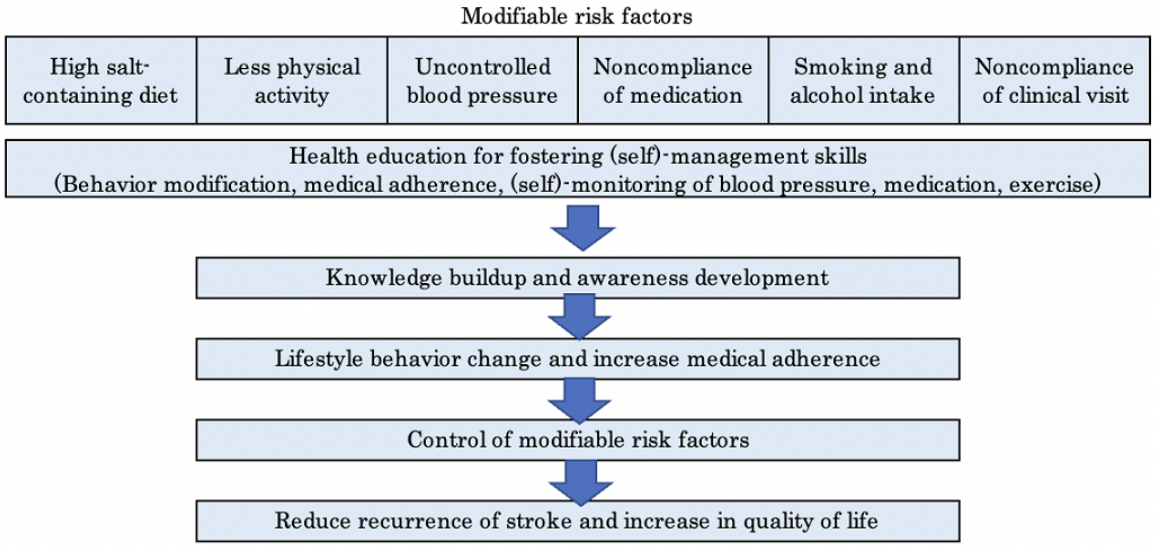
Study Framework and Hypothesis

In Bangladesh, lack of patient and family education during and after hospital discharge has led to poor follow-up, including low compliance with clinical visits, medications, and lifestyle changes, resulting in negative outcomes [18]. From the nursing perspective, this study aims to reduce recurrence by fostering (self)-management skills through health education on modifiable

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risk factors of stroke. After patients or caregivers acquire knowledge and are aware the importance of health care management, their lifestyle behaviors can be changed. (Self)-monitoring of BP, medications, and clinical visits will enhance adherence to treatment and consequently control for the risk factors, increase QoL, and reduce stroke recurrence. Therefore, we hypothesized that health education of patients who had their first stroke and their family caregivers could reduce the stroke recurrence rate by controlling the modifiable risk factors compared to patients who did not receive health education. Health education during the hospital stay of patients who had a stroke and their continuous care after discharge are essential. Therefore, we developed a conceptual framework (Figure 1) to illustrate the factors that influence the recurrence of stroke, and we conducted postdischarge education for patients and families to prevent the recurrence of stroke for the first time in Bangladesh. The American Heart Association and Canadian guidelines recommended healthy lifestyle and management of vascular risk factors for the secondary prevention of stroke [19,20]. Meta-analyses of randomized controlled trials on intensive control of systolic BP [21,22] and improved antiplatelet therapy [23] reported significant reduction in the recurrence of stroke. Lifestyle-related behaviors such as diet, physical activity, and smoking contribute to vascular risk factors of stroke; however, there is knowledge gap on if modifying these behaviors significantly reduce stroke recurrence in stroke survivors [19]. Moreover, there is evidence that positive lifestyle change in intervention studies focused on improving recurrence prevention behaviors [17], but it is not established if lifestyle changes can reduce stroke recurrence. Patients' medication adherence can be improved by providing information regarding the advantage of taking treatments, reminders, and (self)-monitoring [24]. Moreover, the (self)-management behavior of patients who had a stroke improved their self-efficacy, disease outcome, QoL, and self-satisfaction that could improve stroke recurrence [25]. It also increased patients' self-confidence and well-being [26].

Figure 1. Conceptual framwork.

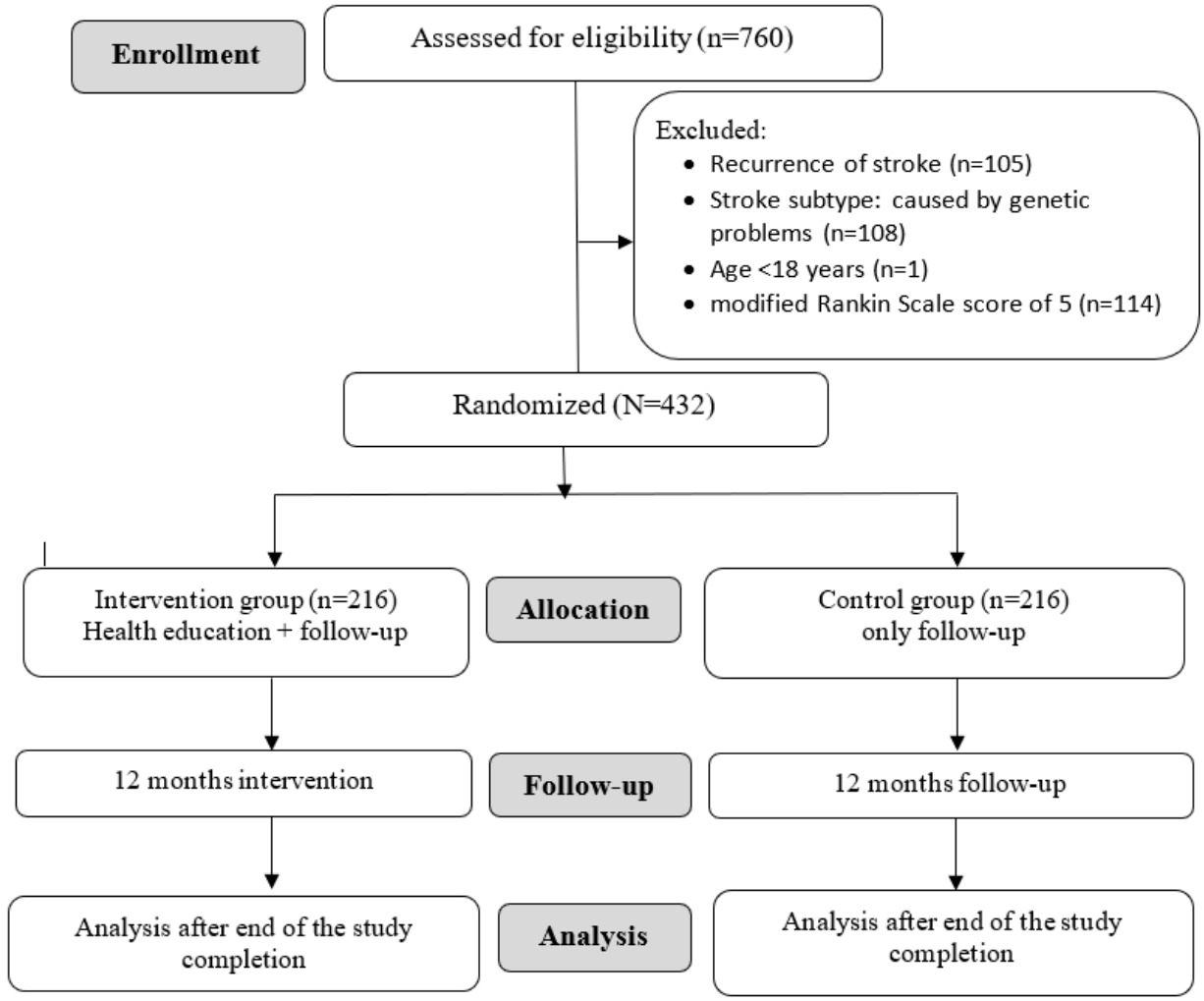


To enhance the knowledge and awareness of modifiable risk factors, we provided health education on various topics: (1) diet (reducing salt intake, maintaining a balanced diet, and managing weight) (Multimedia Appendix 1), (2) physical activity (increasing exercise or rehabilitation if patients are bedridden) (Multimedia Appendix 2), (3) smoking cessation and reducing alcohol consumption (Multimedia Appendix 3), (4) medication compliance and regular clinical visits (Multimedia Appendix 4), and (5) (self)-monitoring of BP (caregivers monitor BP if patients are unable to do so themselves) (Multimedia Appendix 5). Additionally, patients are educated about the importance of taking medication as prescribed and recognizing stroke symptoms. In Bangladesh, where the illiteracy rate is still high [27], the investigators developed an easy-to-understand study book named "Preventing Recurrence of Stroke: Friendly Health Education Booklet," featuring illustrations and photos tailored to Bangladeshi culture and lifestyle. Based on the study book, videos were produced to ensure that even illiterate patients and caregivers could understand the content and watch them repeatedly. Furthermore, a 45-minute hands-on training session is provided for better comprehension. To ensure adherence to these (self)-management activities, the investigators provide patients with a digital BP machine, a salt-measuring spoon, and a medication box that divides the medicines for 1 week into morning, afternoon, evening, and bedtime doses. These tools are accompanied by a health education booklet and video, as well as a (self)-monitoring notebook for patients to utilize at home. The (self)-monitoring notebook is designed for patients or family caregivers to record daily monitoring data, including medication, BP readings, and any notable observations for a duration of 12 months. Nurses regularly contact patients to ensure they are measuring and recording data correctly, explaining how to interpret BP readings and their implications. The investigators recognize the critical importance of daily (self)-monitoring of BP to promote awareness of the patients' condition and foster a sense of (self)-management. In Bangladesh, where the practice of measuring BP at home or even in hospitals is rare, investigators teach patients and

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caregivers how to measure BP, which is a new concept for the population who have never measured their BP levels before [28]. Another significant aspect is monitoring salt intake. The average daily salt consumption among Bangladeshi people ranges between 15 g/day and 21 g/day [29]. Due to the scarcity of processed and packaged foods in Bangladesh, where salt is the main seasoning, the concept of "measuring salt" is uncommon. Education on low-salt diets is virtually nonexistent in the country. Hence, it is crucial to teach individuals to comprehend and visualize "5 g of salt" by using a measuring spoon. Additionally, physical activities will be taught by a physical therapist.

Figure 2. CONSORT (Consolidated Standards of Reporting Trials) chart.



Methods

Study Design

This is an ongoing 12-month intervention study. This study follows a parallel (1:1), open-label, prospective, randomized controlled trial design, and adheres to the CONSORT (Consolidated Standards of Reporting Trials) guidelines [30]. The study flowchart is depicted in Figure 2. This study commenced in October 2022 and is expected to conclude in March 2024, with a total duration of 18 months. This trial is registered as ClinicalTrials.gov NCT05520034.

Study Site, Population, and Sample

This study was conducted at the National Institute of Neurosciences & Hospital (NINS&H) in Dhaka, Bangladesh. NINS&H is a state-run tertiary care hospital in Bangladesh that treats patients with neurological disorders. The inclusion criteria for enrollment encompassed individuals who experienced their first stroke attack, regardless of whether it was the ischemic or hemorrhagic subtype. In Bangladesh, ischemic stroke accounts for over three-quarters of cases [4], and health education can be effective for patients with ischemic stroke classified as modified Rankin Scale (mRS) scores 0-2. For hemorrhagic stroke, considering the impact of self-management, patients with an mRS score below 3 were included. However, in the context of Bangladesh, family caregivers often provide care, and if family education is considered, patients with an mRS score of 4 were also included. Additionally, we included patients who have an mRS score of 0-4, were 18 years of age or older, and of any gender. Moreover, due to the limited availability of emergency hospital beds in Bangladesh, patients with an mRS score of 0-2, particularly those with lacunar infarcts, are often treated as outpatients. Hence, we included outpatient care in

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our study. In cases where patients were unable to care for themselves and relied on the support of family caregivers, consent was obtained from the caregivers. Primary caregivers, regardless of gender, who were 18 years of age or older, and resided with the patients were recruited. The exclusion criteria consisted of patients with a history of stroke recurrence, stroke caused by genetic factors or injury or accident, multiorgan failure, terminal illness, or previous participation in other clinical trials. Patients with an mRS score of 5, indicating severe disability requiring constant nursing care, were excluded [31]. In such cases, health education and follow-up may not have a significant impact. Additionally, individuals younger than 18 years, mentally unstable, cognitively impaired (diagnosed cases), and family caregivers who did not reside with their patients were also excluded from this study. When patients were admitted as inpatients or visited the outpatient department of the hospital, investigators and the research assistant (RA) nurses reviewed the participants' admission or visiting files, including their current medications. Subsequently, the RA nurses visited the inpatient wards and brought the outpatients to a designated research room within the hospital.

Patient Enrollment

A total of 760 patients were screened, and among them, 432 patients were enrolled. We randomly allocated 216 patients to the intervention group and 216 patients to the control group. After completion of 12 months follow-up, we will analyze the data.

Randomization Schedule

A randomization schedule was used following the stratified randomization technique on a computer-generated series of numbers. On the basis of studies conducted in China [32,33], we stratified the patients into <65 years group and ≥65 years group, as the study site had no statistics about the age of the patients with recurrent stroke and types of strokes (hemorrhagic stroke, large artery atherosclerosis, cardioembolic, small vessel occlusion, lacunar, transient ischemic attack) because recurrence rates differed by the stroke type [6]. An experienced investigator who was not involved in this study generated the random allocation number by sequences. She distributed them in sealed opaque envelopes with serial numbers, which were kept in locked file cabinets in the hospital.

Study Procedure

Enrollment occurred over a span of 6 consecutive days during morning hours, excluding government holidays, within a week. After determining eligibility and obtaining consent, the RA nurses opened the sealed randomization envelope in the presence of the participants. They collected demographic information, conducted physical examinations, and filled up questionnaires (Table 1).

Table 1. Study activities.

Schedule	Intervention group	Control group
At baseline	• Data collection by RA[a] nurses through structured questionnaires • RA nurses provide knowledge-related health education before discharge or after the hospital visit: health education (face-to-face, 45 min) by RA nurse and exercise session by the physiotherapist • RA nurses perform physical examination: BP[b] level (systolic and diastolic) • Blood tests: HbA_{1c}[c], total cholesterol, and HDL cholesterol (calculate non-HDL cholesterol)	• Data collection by RA nurses through structured questionnaires • Provide usual practice • RA nurses perform physical examination: BP level (systolic and diastolic) • Blood tests: HbA_{1c}, total cholesterol, and HDL[d]-cholesterol (calculate non-HDL cholesterol)
Middle of study (6 months)	• Data collection by RA nurses through structured questionnaires • RA nurses provide refresher health education same as baseline • RA nurses perform physical examination: BP level (systolic and diastolic) • Blood tests: HbA_{1c}, total cholesterol, and HDL cholesterol (calculate non-HDL cholesterol)	• Data collection by RA nurses through structured questionnaires • Provide usual practice • RA nurses perform physical examination: BP level (systolic and diastolic) • Blood tests: HbA_{1c}, total cholesterol, and HDL cholesterol (calculate non-HDL cholesterol)
End of study (12 months)	• Data will be collected by RA nurses through structured questionnaires • RA nurses will perform physical examination: BP level (systolic and diastolic) • Laboratory tests: HbA_{1c}, total cholesterol, and HDL cholesterol (calculate non-HDL cholesterol)	• Data will be collected by RA nurses through structured questionnaires • RA nurses will provide health education at the end of the study, and a health education booklet will be given to them • RA nurses will perform physical examination: BP value (systolic and diastolic) • Laboratory tests: HbA_{1c}, total cholesterol, and HDL cholesterol (calculate non-HDL cholesterol)

[a]RA: research assistant.

[b]BP: blood pressure.

[c]HbA_{1c}: glycated hemoglobin.

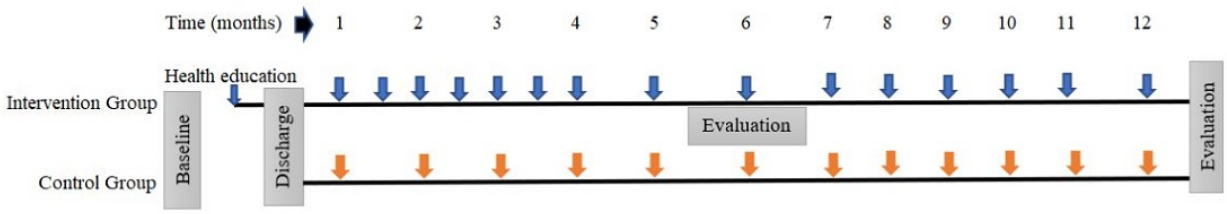
[d]HDL: high-density lipoprotein.

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Intervention Group Study Plan

After obtaining informed consent and baseline data, RA nurses provide health education through a booklet to patients and family caregivers and give them the booklet to follow the instructions at home. Subsequently, a video containing the risk factors of stroke and their management and prevention is shown to the patients and family caregivers. Health education sessions on booklet contents take around 20 minutes, and video show sessions take around 15 minutes. We provide these health education sessions 2 times after enrollment of the patients and 6 months after the follow-up visit in the hospital. Health education booklets guide patients on how to read food labels accurately for the prevention of stroke-related risk factors. Booklets have a reminder for the schedule date of the next clinic visits. There is also a notebook for recording daily health monitoring charts such as BP, exercise, and medication intake by the patients or caregivers. The video presentation includes simulation training on essential tasks such as how to measure BP and organize the medication boxes prescribed by physicians. We recommended placing the medications in our provided medication boxes to increase the adherence to doctors' guidelines for consumption and using salt-measuring spoons. After that, an assigned physiotherapist provides about 15-minute exercise orientation sessions to show how to do physical exercises at home. A repeated session is conducted by the physicians and RA nurses at 6-month follow-ups for their memorization. RA nurses provide motivational SMS texts every month to the patients and caregivers to remind patients to measure their daily BP, reduce salt intake, avoid oily and fatty foods, consume more fruits and vegetables, exercise regularly, and adhere to their medication regimen. Additionally, RA nurses provide refresher health education twice a month in the first 3 months and then monthly in the next 9 months over a phone call to obtain information about the health condition of the patients and document in the questionnaires. Patients receive a reminder phone call on the fifth month to visit the hospital for the sixth month follow-up visit. At the 6-month follow-up visit (middle of study), if the patient and family caregiver are not able to come for any reason, RA nurses collect data and provide refresher health education over a phone call (Figure 3).

Figure 3. Follow-up and evaluation timeline (months) of the intervention and control groups.



Control Group Study Plan

The control group participants receive a monthly telephone call for 1 year from RA nurses solely to gather information about the patients' health conditions and document the information in the questionnaires. At the fifth month, patients are reminded to visit the hospital for their sixth month follow-up visit (Figure 3). To mitigate the disadvantage faced by participants in the control group, after completing the study at the end point, they will be given the same health education booklet. If requested by the participants, a brief health education session will be provided based on the information contained in the booklet for their easy understanding.

Outcomes and Data Collection Procedure

Primary Outcome

The primary end point is the recurrence rate of stroke at 12 months.

Secondary Outcomes

The secondary outcomes are (1) all adverse events (stroke and other events), (2) changes in the values of modifiable risk factors of BP, glycated hemoglobin, non–high-density lipoprotein cholesterol, and (3) changes in the scores of knowledge related to stroke in the investigator-developed questionnaire (this questionnaire consists of 10 items with "no/wrong answer," "yes/correct answer," and "don't know" answers; the score ranges from 0 to 20, and a higher score indicates having better knowledge), (4) changes in scores in lifestyle behavior related to stroke in the investigator-developed questionnaire (this questionnaire consists of 14 items with a Likert scale to assess the frequency of behavioral changes; the score ranges from 0 to 37, and a higher score indicates having better lifestyle behavior), (5) changes in behavior in medication adherence by using Morisky Green Levine Medication Adherence Scale [34] (this questionnaire consists of 4 items with "yes=0" and "no=1" answers; the score ranges from 0 to 4, and a higher score indicates better compliance), and (6) changes in scores of QoL by using the QoL questionnaire (WHOQoL-BREF Bangla version [35]; each item scores from 1 [very poor or very dissatisfied] to 5 [very good or very satisfied] and ranges [mean of 2 items] from 1 to 5—a higher mean indicates a better QoL).

Operational Definitions for This Study

Recurrence of Stroke

Recurrent stroke is defined as a new stroke event occurring at least 28 days after the stroke incident [32], which is confirmed by the physician who treats and diagnoses the patients in this study.

Adverse Events

All adverse events (all causes of death, cardiovascular events) refer to all cases that need to be diagnosed, for example, recurrence of stroke, new onset of acute myocardial infarction

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and unstable angina, heart failure with hospitalization, and peripheral arterial disease with hospitalization—those that are confirmed by the physician who treats and diagnoses the patients in this study.

Sample Size

Stroke recurrence rate in Bangladesh was 20% within 1 year in 2019 [8]. A study that evaluated the effectiveness of health education in preventing the recurrence of stroke showed 50% reduction among the intervention group compared to the control group [13]. The expected proportion of outcomes from the intervention group was assumed as P1=0.10; P2 (proportion of outcome from control group)=0.20; α=.05 (2-tailed), 1-β=.80; Z1-α/2=Z, α=1.96; and Z1-β=Z, β=.84. We found that the estimated sample size was 196 for each arm (a total 392 for both arms). By considering 10% dropout, the total sample size was 432 (216 for each arm).

Study Preparation

Training of RA Nurses

Five RA nurses were recruited from NINS&H and another tertiary hospital, and 5 student nurses were recruited from 2 nursing schools for this study. Investigators provided protocol-specific theoretical and practical training to all RA nurses before the study initiation. They received training on physical measurements and were taught the motivational interviewing technique [36] to effectively encourage patients who had a stroke to adhere to instructions. We trained them how to educate patients to maintain daily activities and to send SMS text messages. Throughout the study, the RA nurses have been receiving monthly feedback sessions on the participants' health education materials.

Data Monitoring and Quality Assurance

The investigators (medical doctors) are directly involved in patient management. The investigators and the RA nurses have regular biweekly meetings for study purpose. Pretesting of the questionnaires was done among the patients (5% of the sample of 432) who did not participate in the main study. Additionally, for regular quality control purpose, investigators independently check 5% of the study participants' data on the same day by using field testing. The investigators check the process of taking consent, data collection, and physical examination by the RA nurses. The detected errors are corrected immediately at the field site. For any query, RA nurses consult with the investigators. RA nurses fill up the questionnaires and enter the data into a password-protected computer. Investigators check the data and resolve the queries.

Ethics Approval

This study was approved by the institutional review board and the ethics review board of the NINS&H (IRB/NINSH/2022/151). All participants were explicitly informed about the study goals, significance, risks, and benefits, and their rights to participate in the study prior to the requirement. To participate in this study was entirely voluntary, and participants can withdraw at any point from their participation.

Statistical Analysis

To compare the outcomes of the intervention group and the control group, we will conduct an intention-to-treat analysis and a full set analysis. A chi-square test will be performed for categorical data, and a 2-sided *t* test or Mann-Whitney *U* test will be employed for continuous variables, as appropriate, to compare the 2 groups. For the primary end point, the cumulative risk of recurrence and adverse events occurring in 12 months will be estimated using the Kaplan-Meier method and presented overall by age group and by stroke subtypes. For the secondary end points, an analysis of covariance will be conducted to assess the effect of the intervention on the outcomes by adjusting confounding variables. Changes in outcomes over time will be analyzed using repeated-measures analysis of variance as well as regression analysis. Friedman test will be performed to examine the changes within the groups. Associations between risk factors and outcomes will be tested using Cox proportional hazards models, adjusting for all baseline factors. Additionally, laboratory test and physical examination data will be analyzed using 2-sided *t* tests or 2-way repeated-measures analysis of variance, considering data normality. For the knowledge-related questionnaire, medication adherence–related questionnaire, and QoL, reliability checking will be performed, and total scores will be calculated. The significance level will be set at .05. Data analysis will be conducted using SPSS (version 26.0; IBM Corp).

Results

The enrollment of the participants was completed in February 2023, and the study follow-up and data collection will continue until February 2024. A total of 432 participants agreed to participate in this study, with 216 allocated to the intervention group and 216 to the control group. Data cleaning and analysis are expected to be completed in May 2024.

Discussion

Overview

This study describes the protocol for a randomized controlled trial that aims to develop awareness, enhance knowledge, and make behavioral changes through face-to-face health education and phone calls among individuals who had their first stroke and were discharged from hospitals admitted from different regions of Bangladesh. To the best of our knowledge, this is the first research study conducted in Bangladesh to measure the effectiveness of health education and monthly follow-ups over mobile phone in reducing the recurrence of stroke. One of the most significant barriers to the effective treatment of stroke is the lack of awareness and education about modifiable risk factors, its complications, and the optimal way to treat stroke, which can be addressed by providing health education and monthly follow-ups over mobile phone for knowledge generation. Further, creating an awareness and employing behavior change communications among patients with stroke can reduce the recurrence of stroke and increase their QoL. Although stroke management is a significant burden on health practitioners in low-resource settings, RA nurses can be an important and underutilized resource for patient education. RA

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nurses have been shown to be effective in assisting people in improving their health habits. An RA nurse intervention among patients with modifiable risk factors such as hypertension and diabetes can increase patients' awareness and help them control their BP and blood glucose levels. Monthly follow-ups as well as health education show a lot of potential in raising patient awareness and understanding of stroke disease as well as improving stroke knowledge.

Strengths

We implemented various strategies to empower patients and caregivers, including training on BP measurement, medication box usage, salt intake measurement using spoons, and health education booklets. Self-monitoring of BP is facilitated by providing patients with a BP machine for daily measurements, which is generally not practiced in Bangladesh. Medication compliance is assessed using medication boxes, and accurate salt intake measurement will be facilitated by providing salt-measuring spoons. Most of the participants are not aware of the benefits of regular medication and low salt intake. Health education materials such as booklets and videos in Bengali are tailored to accommodate both literate and illiterate patients and their caregivers. Participants and even health care providers had no understanding to date about the advantage of health education in the health care system in Bangladesh. NINS&H is the only referral hospital in Bangladesh that patients attend from all over the country. Thus, our study findings can be generalized to all the patients who had a stroke in Bangladesh.

Limitations

Our study has certain limitations. Although we provide education to the patients and their caregivers for their disease (self)-management at home, the level of education and understanding of each patient and his or her caregiver about the importance of monitoring risk factors would be different. This might influence the study outcomes. There will be heterogeneity at baseline in the level of illness, including level of consciousness, among patients with different subtypes of stroke. This could be a cause of outcome bias.

Conclusions

Stroke recurrence can be caused by different modifiable risk factors. Thus, early detection and management of these risk factors are crucial for preventing subsequent stroke recurrences and for lowering morbidity and death. If our results show an enhancement in the study outcomes among patients with stroke (mRS score 0-4), health education can be integrated with monthly follow-ups as an effective tool for preventing stroke recurrence at the national level in Bangladesh. Further, we can improve patient knowledge and motivate patients with stroke regarding their health care practices to improve their QoL. If this health education program results in significant improvements in the QoL of patients who have had a stroke, then this program can be introduced and implemented in the health care system of Bangladesh.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Salt intake guidelines and balanced diet guides.
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Multimedia Appendix 2
Physical activity education.
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Multimedia Appendix 3
Smoking and alcohol intake cessation education.

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Multimedia Appendix 4
Medication compliance.
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Multimedia Appendix 5
Blood pressure monitoring guidelines.
[PNG File , 1014 KB - resprot_v12i1e51178_app5.png]

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Abbreviations

BP: blood pressure
CONSORT: Consolidated Standards of Reporting Trials
mRS: modified Rankin Scale
NINS&H: National Institute of Neurosciences & Hospital

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QoL: quality of life
RA: research assistant

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Protocol

Developing and Implementing a Web-Based Relapse Prevention Psychotherapy Program for Patients With Alcohol Use Disorder: Protocol for a Randomized Controlled Trial

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Abstract

Background: Alcohol use disorder (AUD) is characterized by problematic alcohol use accompanied by clinically substantial distress. Patients with AUD frequently experience high relapse rates, and only 1 in 5 remain abstinent 12 months post treatment. Traditional face-to-face relapse prevention therapy (RPT) is a form of cognitive behavioral therapy (CBT) that examines one's situational triggers, maladaptive thought processes, self-efficacy, and motivation. However, access to this treatment is frequently limited due to its high cost, long waitlists, and inaccessibility. A web-based adaptation of RPT (e-RPT) could address these limitations by providing a more cost-effective and accessible delivery method for mental health care in this population.

Objective: This study protocol aims to establish the first academic e-RPT program to address AUD in the general population. The primary objective of this study is to compare the efficacy of e-RPT to face-to-face RPT in decreasing relapse rates. The secondary objective is to assess the effects of e-RPT on quality of life, self-efficacy, resilience, and depressive symptomatology. The tertiary objective is to evaluate the cost-effectiveness of e-RPT compared to face-to-face RPT.

Methods: Adult participants (n=60) with a confirmed diagnosis of AUD will be randomly assigned to receive 10 sessions of e-RPT or face-to-face RPT. e-RPT will consist of 10 predesigned modules and homework with asynchronous, personalized feedback from a therapist. Face-to-face RPT will comprise 10 one-hour face-to-face sessions with a therapist. The predesigned modules and the face-to-face sessions will present the same content and structure. Self-efficacy, resilience, depressive symptomatology, and alcohol consumption will be measured through various questionnaires at baseline, amid treatment, and at the end of treatment.

Results: Participant recruitment is expected to begin in October 2022 through targeted advertisements and physician referrals. Completed data collection and analysis are expected to conclude by October 2023. Outcome data will be assessed using linear and binomial regression (for continuous and categorical outcomes, respectively). Qualitative data will be analyzed using thematic analysis methods.

Conclusions: This study will be the first to examine the effectiveness of e-RPT compared to face-to-face RPT. It is posited that web-based care can present benefits in terms of accessibility and affordability compared to traditional face-to-face psychotherapy.

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KEYWORDS

mental health; alcohol use disorder; psychotherapy; eHealth; cognitive behavioral therapy; online; internet; treatment; electronic care

Introduction

Alcohol use disorder (AUD) is a mental health disorder that affects approximately 3.6% of the global population aged 15 to 64 years [1]. The disorder is highly prevalent and a major contributor to illness and mortality worldwide [2,3]. AUD is characterized by impaired control over alcohol use, leading to physiological dependence and negative psychological, social, and physical consequences [3,4]. The disorder is associated with many physical and psychiatric comorbidities, such as major depressive disorder, generalized anxiety disorder, liver cancer, and hypertension [2,5-7].

The rise in mental health challenges during the COVID-19 pandemic resulted in growing concerns over the health behaviors of individuals with AUD [8]. Stay-at-home orders presented complex relationships between financial issues, low social interaction, and anxiety about the future [9]. Moreover, the disruption to clinical services is believed to have contributed to increased relapse and subsequent negative health outcomes for people with AUD [10]. Kim et al [11] demonstrated that out of 182 participants with previous AUD, 23% increased their consumption during the lockdown. Additionally, 17% of the subjects abstained for an average of 19.5 months before relapsing during lockdown [11].

AUD treatments typically involve abstinence from alcohol due to the high failure rates and risks associated with controlled drinking approaches [12,13]. However, AUD is known as a "relapsing condition," since patients often relapse following abstinence [14]. Within the AUD framework, a lapse is defined as a single episode of drinking, whereas a relapse involves a return to a pattern of problematic drinking [15]. Stillman et al [16] found that relapse rates in people with AUD are approximately 60% to 80% after 3 months of treatment and 70% to 80% after 12 months post treatment. These rates highlight the importance of integrating relapse prevention into AUD treatment programs. These programs identify personal factors that contribute to relapse and offer helpful strategies to improve coping with cravings, and mood fluctuations, and identify triggers to decrease the rate and severity of relapses [17].

Psychosocial interventions are commonly used to treat AUD, with cognitive behavioral therapy (CBT) being one of the most studied psychological approaches [18,19]. CBT for AUD encourages abstinence in the presence of triggers and cravings by targeting maladaptive thought processes and behaviors [20,21]. This therapeutic approach has demonstrated greater efficacy compared to no treatment or minimal treatment [22]. Relapse prevention therapy (RPT) is a validated CBT treatment for AUD that targets both interpersonal and intrapersonal factors such as motivation and trigger identification. RPT also equips patients with coping strategies to use in situations where alcohol may be available [23-25]. The efficacy of RPT can vary depending on the substance used, personal factors such as income, and comorbid disorders [26,27]. However, despite the effectiveness of this type of therapy, financial issues, accessibility problems, and logistical problems may make it challenging for individuals to receive face-to-face care [28]. Moreover, individuals with AUD frequently experience shame and stigma surrounding their diagnosis, which can reduce treatment seeking in this population [29].

To address some of the issues of accessibility and availability, web-based adaptations of traditional face-to-face psychotherapy, such as internet-based CBT (e-CBT) have flourished in recent years. Web-based psychotherapy offers several advantages, such as not requiring office space, placing lower demands on therapists' time, improving accessibility, etc [30]. Although the literature has shown comparable effectiveness between web-based psychotherapy and face-to-face psychotherapy in the management of AUD [31], and face-to-face RPT has demonstrated beneficial effects in relapse prevention [12,24], web-based RPT (e-RPT) remains an understudied option for the management of AUD [32].

Therefore, this study proposes the development, study, and implementation of an e-RPT program for the management of AUD. The proposed program could be a viable solution to address the potential accessibility, stigma, and financial issues presented by traditional in-person therapies [32]. Thus, the primary objective of this study is to compare the efficacy of a secure e-RPT program to face-to-face RPT to decrease relapse rates in patients with AUD. Based on the evidence comparing face-to-face and web-based psychotherapies in other disorders, we hypothesize that both face-to-face RPT and e-RPT will have similar effectiveness in AUD symptom management, reducing alcohol consumption, and lowering relapse rates [33,34]. The secondary objective is to assess the effects of online treatment on quality of life, self-efficacy, resilience, and depressive symptomatology. The tertiary objective is to evaluate cost-effectiveness by comparing the amount of time an e-RPT therapist spends with each patient to the therapists administering face-to-face RPT. The results of this study will supplement the available literature and aid in the development of clinical recommendations for the management of AUD.

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Methods

Study Design and Participants

This is the protocol for a randomized controlled trial studying the efficacy of a novel e-RPT program. Participants (n=60) diagnosed with AUD will be recruited through physician referrals from Kingston Health Sciences Centre, family physicians, other health care providers, and self-referrals within Kingston, Ontario. After providing consent to participate in the study, a Mini International Neuropsychiatric Interview 7.0.2 (MINI) will be conducted to confirm the diagnosis of mild to moderate AUD [35]. The MINI is a diagnostic interview that assesses 17 common mental disorders by following the diagnostic criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth edition [35]. After the MINI, the Readiness to Change Questionnaire (RCQ) will be administered in an interview format to investigate the individual's desire to change their alcohol consumption [33]. In addition to the RCQ, participants will be asked questions listed in Textbox 1 to capture their history with AUD. Answers to these questions, along with the intake MINI, will be reviewed with the principal investigator (PI) to ensure that the participant meets eligibility criteria and to confirm the AUD diagnosis.

Textbox 1. The 6 additional interview questions to establish eligibility.

1. Have you been diagnosed with alcohol use disorder (AUD)?
2. If applicable, when were you diagnosed with AUD?
3. Are you currently enrolled in another relapse prevention program?
4. In the past month, how many times have you had an alcoholic beverage?
5. If applicable, how many drinks did you have on average in those times?
6. If applicable, how many drinks did you have per week on average in the past month?

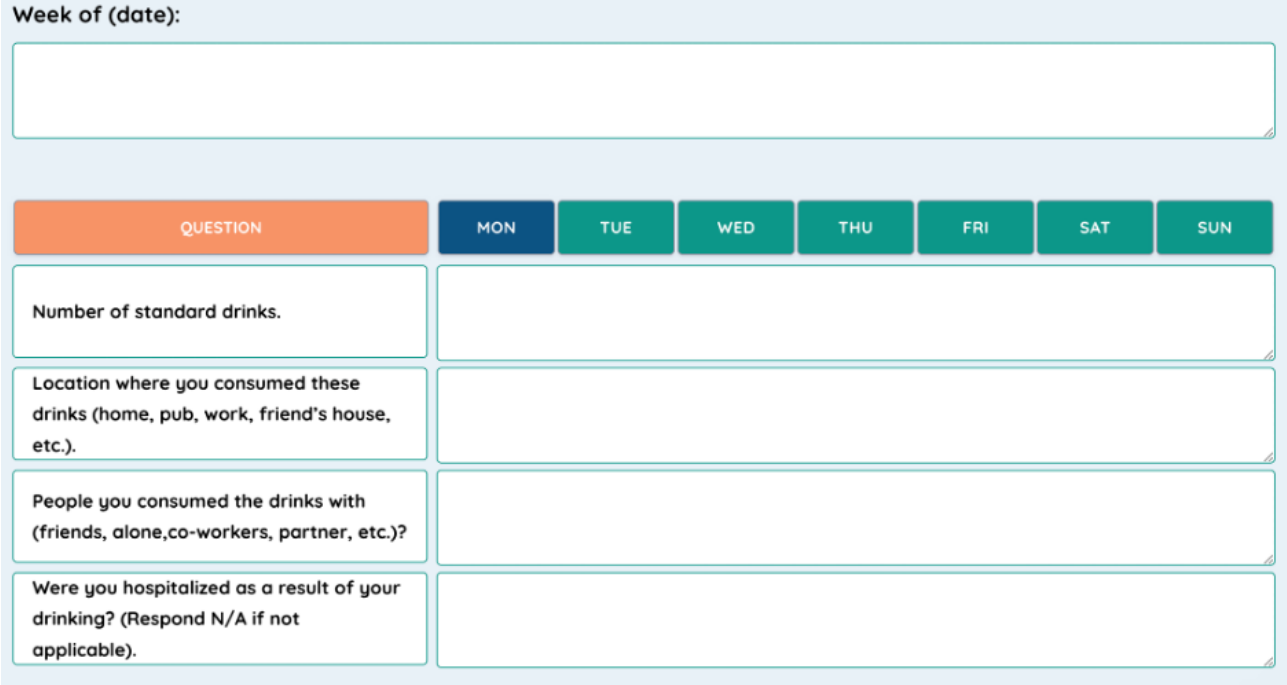
Participant inclusion criteria are being 18 years or older at the start of the study and having a diagnosis of mild to moderate AUD according to the MINI (2 to 5 MINI AUD symptom criteria) [20], competence to consent and participation, ability to speak and read English, and consistent and reliable access to the internet. Additionally, contemplation about stopping or having stopped consuming alcohol in the past 30 days is required. This will be assessed by the RCQ (participants should be in the contemplation or action stage according to the questionnaire) and by asking them about when they stopped drinking or began considering alcohol cessation [34,35]. Exclusion criteria are acute hypomanic or manic episodes, acute psychosis, other active substance use disorders classified as moderate or severe, active suicidal or homicidal ideation, untreated clinically substantial somatic symptoms or mental disorders, or current enrollment in another relapse prevention program. Additionally, men who consumed more than 4 drinks per day or 14 drinks per week and women who drank 3 drinks per day or 7 drinks per week in the past month will be excluded [36].

Procedure

Upon completion of the eligibility assessments, participants will be randomly assigned through a computerized system to one of the 2 groups: e-RPT or face-to-face RPT. Participants will be equally stratified (e-RPT n=30; face-to-face RPT n=30). These treatments will be delivered as an augmentation to treatment as usual (eg, medications, regular physician or clinician visits, referrals, or consultations that are conducted outside of this research study). The e-RPT program will be delivered through the Online Psychotherapy Tool (OPTT), a secure and interactive platform developed by the PI [37]. The face-to-face RPT program will be delivered through videoconference sessions using Microsoft Teams. Participants in the e-RPT and face-to-face groups will also have access to OPTT to access the triage module, the daily drinking diary (Figure 1), and assessment questionnaires.

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Figure 1. Daily drinking diary.



Triage Module

The triage module is a short module intended to introduce clients to the RPT program and the drinking diary. All participants in the e-RPT and face-to-face groups will complete this module before starting their respective treatments.

e-RPT

Participants in the e-RPT group will receive 10 predesigned online modules per week on the OPTT platform. Each module consists of approximately 30 slides and should have an estimated completion time of 45 minutes. At the end of each module, participants will be assigned homework to be completed before their next module is assigned. The therapists will submit personalized feedback by using session-specific therapy feedback templates. These structured templates standardize the quality of feedback across different patients and therapists. In previous studies, therapists have been able to effectively use these templates to prepare feedback in approximately 15-20 minutes [30].

This e-RPT program will focus on teaching essential cognitive and behavioral skills such as identifying maladaptive thought processes, increasing engagement in day-to-day activities, and developing strategies to reduce alcohol consumption. The content of the sessions is outlined in Table 1.

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Table 1. The program outline and session summary for the 10-week web-based and face-to-face relapse prevention program.

Session number	Session subject
1: Understanding addiction	• Introduces relapse prevention and what to expect from the course. The session explains what addiction is, including the symptoms, signs, consequences, and different types of addiction. Participants will create a SMART goal that they will try to achieve throughout the program. They will also share their personal experiences with addiction.
2: Exploring and strengthening your motivation	• Focuses on the 5 stages of motivation and the role of motivation in relapse prevention. Helpful techniques are discussed to help them reflect on and boost motivation throughout their recovery journey. Participants will create a pros and cons list about stopping alcohol use and reflect on different aspects of their ability to stop using alcohol.
3: Triggers	• Describes what triggers are and how to recognize them, including both internal and external triggers. This session also provides strategies to handle triggers through avoidance and careful planning. Participants will learn to identify their triggers and to be prepared for them if encountered.
4: Handling cravings and signs of relapse	• Presents skills for dealing with cravings as well as identifying and preventing a potential relapse. For instance, applying distraction methods during stressful situations decreases their urge to consume alcohol. Participants will also identify their warning signs by reflecting on previous relapse experiences.
5: The 5-Part Model	• The 5-Part Model will be explained, which highlights the importance of differentiating between our thoughts, feelings, physical reactions, and behaviors in stressful situations. Participants will complete the 5-Part Model using an example from their lives.
6: The Thought Record—Part 1	• Introduces the thought record and its relation to cognitive restructuration to highlight the connection between feelings, behaviors, and thoughts. This session focuses on the first 3 columns of the Thought Record (out of 7 columns). • The first 3 columns include the situation, followed by the feelings and automatic thoughts associated with the situation. Participants are asked to complete the first 3 columns of a thought record for a stressful situation they experienced within the past week.
7: The Thought Record—Part 2	• This session continues with the remaining 4 columns of the Thought Record, including gathering evidence in support of and against the identified automatic thoughts and finding alternative and balanced thoughts after examining the evidence. Participants will learn to challenge irrational thoughts using the thought record. They will also learn how to replace these irrational thoughts with more balanced and helpful ones. Participants have to complete a full thought record of a stressful situation related to their AUD within the past week.
8: Thinking errors and the Activity Record	• Explores irrational thinking and common thinking errors. This session also presents and highlights the importance of the Activity Record, a tool designed to record and plan weekly activities. Participants are asked to complete an activity record for an entire week.
9: Mindfulness and breathing techniques	• Presents mindfulness, breathing techniques, and other helpful skills to reduce urges and cravings associated with alcohol and to promote increased awareness. Participants are asked to incorporate one or more of these practices into their daily routines for a week and to reflect on how these practices made them feel. Participants will also identify which, if any, practices they found to be most effective.
10: Review	• This session is a review of the program. It summarizes all of the useful tools and techniques for relapse prevention that were described throughout the program. Participants are asked to reflect on the activities that they found to be the most effective throughout the sessions.

Face-to-Face RPT

Participants in the face-to-face intervention will meet with their therapist weekly through videoconferencing on Microsoft Teams [38]. During these 1-hour sessions, therapists will follow the same 10-week structure and content as e-RPT (Table 1). In contrast to e-RPT, where homework is written web-based by the therapist, the homework for the face-to-face sessions will be reviewed with the participant during the live session. At the end of each session, participants will receive the same homework and feedback as the e-RPT condition.

Training

Therapists for both e-RPT and face-to-face RPT will consist of research assistants who are trained in RPT and writing feedback. All therapists are trained by the PI, who is an expert in the electronic delivery of psychotherapy [30,39,40]. During training, the PI will closely guide the therapists through their first patient (assigning modules, reviewing homework, writing feedback, and conducting face-to-face sessions). All therapists will be supervised by the PI to ensure the quality and reliability of the treatment programs. To ensure the quality of the feedback, therapists will practice writing it using structured templates. All face-to-face sessions and feedback will be reviewed with the PI before being sent to the participants.

Outcome Measures

The primary objective of this study will be to determine if e-RPT has similar effectiveness to face-to-face RPT at reducing alcohol consumption and preventing relapses. This study defines relapse

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as either the consumption of at least 2.5 oz. of pure ethanol, which is around 4 and a half standard drinks (Canadian guidelines for standard drinks: 12 oz of beer with 5% ethanol, 12 oz of cider with 5% ethanol, 5 oz of wine with 12% ethanol, and 1.5 oz of spirits with 40% ethanol) [41,42] on one occasion or hospitalization because of alcohol drinking [43]. Therefore, to determine the effectiveness of this program, daily alcohol consumption will be recorded in a drinking diary accessible through OPTT. This diary will ask the participants to report how many drinks they consumed on each day of the week, where they had those drinks, with whom, and if their alcohol consumption resulted in hospitalization (Figure 1).

The study will also determine whether e-RPT and face-to-face RPT have a beneficial effect on self-efficacy, quality of life, resiliency, coping behaviors, and depressive symptomatology. These metrics will be assessed through the following scales: Situational Confidence Questionnaire (SCQ-100) [44], 14-item Resilience Scale (RS-14) [45], Coping Behaviors Inventory (CBI) [46], Patient Health Questionnaire (PHQ-9) [47], and Quality of Life Enjoyment and Satisfaction Questionnaire—Short Form (Q-LES-Q-SF) [48]. These assessment scales will be completed at study entry (baseline), amid the program (week 5), and post treatment (week 10). After the treatment period, we will conduct follow-up assessments with all our outcome measures at 3, 6, and 12 months. The amount of time that e-RPT therapists spend writing feedback compared to the 1-hour face-to-face session will be used as a measure of therapists' time efficiency and will be tracked on the OPTT platform.

Ethical Considerations

All components of this study were reviewed for ethical compliance by the Queen's University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board (File #: 6033212) in April 2022. Participants are only identifiable by an ID number, and all records are stored on a secure platform. Participant data is only accessible by the care providers, and anonymized data is provided to the analysis team. Participants can withdraw from the study at any point and request that their data be removed from the analysis. The research team will safeguard the privacy of the participants to the extent permitted by the applicable laws and their duty to report.

OPTT is compliant with the Health Insurance Portability and Accountability Act, Personal Information Protection and Electronic Documents Act, and Service Organization Control 2. All servers and databases are hosted in Amazon Web Service Canada cloud infrastructure to assure provincial and federal privacy and security regulations are met. OPTT does not collect identifiable personal information or IP addresses. OPTT collects anonymized metadata to improve service quality and provide advanced analytics to the clinician team.

Data Analysis

The data will be initially assessed for outliers, missing, and nonsensical variables. These variables will not be imputed, since they will be handled as missing. Similar studies that involved CBT and e-CBT demonstrated a dropout rate of up to 40% for both conditions once the study concluded [49]. Thus, this study will intentionally oversample the experimental and control groups to account for this dropout rate. Considering the effect size for face-to-face RPT reported by Harada et al [50] (2021) for CBI (effect size=0.65), a significance level of α=.05 and a power of 0.90, a sample size of 60 (30 per arm) would be sufficient to detect substantial changes from our interventions [51]. As this is the first study aiming to establish an e-RPT program for AUD, this sample size calculation relies on data from face-to-face RPT and takes into account the established effectiveness of online psychotherapy compared to face-to-face psychotherapy [30].

The analysis will begin by examining the data for missing, nonsensical, and outlying variables. The data will then be analyzed on a per-protocol basis, excluding missing data, and with intention-to-treat analysis to assess the clinical effects of the program on participants who dropped out prematurely. All calculations will be done using a 2-tailed significance level of α=.05, except for when a Bonferroni correction is needed. The demographic information of program completers and program dropouts will be compared using independent sample *t* tests to identify possible differences. A 2 by 3 repeated measures ANOVA of the primary (daily drinking and relapse) and secondary (SCQ-100, Q-LES-Q-SF, RS-14, CBI, and PHQ-9) outcomes will be conducted to test for the effects of the interventions (e-RPT or face-to-face RPT) throughout the 10-week treatment (0, 5, and 10-week assessment points). Linear regression (for continuous outcomes) and binomial regression analysis (for categorical outcomes) will be used to identify variables associated with outcome measures. Additionally, OPTT will collect usage statistics (ie, number of logins per day, amount of time spent logged in) and compare them to face-to-face metrics (ie, attendance to weekly 1-hour face-to-face sessions) to determine cost and time savings between the 2 programs. All statistical analyses will be conducted using IBM SPSS Statistics for Mac (version 24; IBM Corp).

Results

According to the literature on the efficacy of face-to-face psychotherapy compared to web-based psychotherapy in the management of AUD, we hypothesize that both e-RPT and face-to-face RPT will reduce alcohol consumption and relapse risk and improve secondary outcome measures (depressive symptomatology, self-efficacy, quality of life, and resilience) [44-47]. Recruitment and data collection are expected to end in October 2023. Data analysis will be concluded by December 2023, at which point the process of knowledge dissemination will begin, including but not limited to peer-reviewed publications, scientific presentations, grant proposals, and reports.

Discussion

This is a protocol for an RCT that aims to establish a novel e-RPT program to improve the mental health of patients with AUD. This program will teach effective coping techniques to maintain abstinence and reduce the risk of a relapse by applying the widely validated principles of CBT and relapse prevention [12,24,31,32,50]. Supporting the structure and design of this

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program, this study will apply the evidence gathered by Alavi et al [30,39,40] on the efficacy of e-CBT in managing other psychiatric disorders. Thus, this study hypothesizes that this novel e-RPT program will have a similar effectiveness as face-to-face RPT at maintaining long-term abstinence and reducing the risk of experiencing a relapse.

Psychosocial interventions are one of the most commonly used methods for the treatment of mental health disorders [18]. CBT is one of the most-studied approaches for treating AUD and involves one-on-one sessions between the patient and therapist [19]. These sessions work on overcoming cravings for drinking alcohol by developing strategies that help people abstain from consuming alcohol when cravings occur. When targeted to prevent or reduce the risk of relapses after an initial alcohol reduction program, this CBT approach becomes RPT. RPT involves addressing coping skills to decrease the risk of relapse [21,50]. Additionally, both interpersonal and intrapersonal factors are addressed so that patients can develop the skills necessary to aid in preventing relapse. For instance, through the development of coping mechanisms to respond effectively to stressful situations that otherwise could have led to relapse [12,50]. However, despite these benefits, there are many obstacles to receiving face-to-face psychotherapy, such as financial issues and logistical problems.

The strengths of this program and this study include the use of asynchronous psychotherapy through predesigned web-based modules. These web-based modules have been shown to increase therapy efficiency by allowing a web-based therapist to deliver care to 3 to 4 patients at a time compared to 1 synchronous session [30,39,40]. The use of a web-based platform like OPTT allows for the automatic and reliable collection of user analytics, which can then be used to continuously improve and optimize the delivery of web-based psychotherapy programs. Given that face-to-face RPT has been previously validated in the literature, this study hypothesizes that e-RPT will be effective at maintaining abstinence, reducing the risk of relapse and depression symptomatology, and improving quality of life, resiliency, and coping behaviors [12,24,31,32,50]. Furthermore, comparing our proposed e-RPT program to a validated face-to-face therapeutic approach (RPT) strengthens the design of this RCT and the conclusions that will stem from this evidence.

Despite the strengths of this program, the web-based mode of delivery of this program may have some potential limitations. The main limitation is that participation requires a reliable internet connection and sufficient technology literacy. This limitation could introduce biases in participant demographic characteristics. Thus, this study will analyze demographic factors through multiple sample *t* tests to determine if these factors could impact treatment outcomes. Additionally, due to the delivery mode and design of the program, it is not possible to conceal client allocation. Moreover, web-based psychotherapy is often characterized by a dropout rate of up to 40% by the end of the treatment [49,50]. To account for this without compromising statistical power, this study is intentionally oversampled.

The knowledge dissemination plan for this study includes publishing the outcomes of this study in a peer-reviewed, academic journal. The research team will also attend academic meetings and conferences to present these findings and commit to continuing education in the relevant research areas. Furthermore, the dissemination and application of knowledge will be further enhanced through the collaboration of the Canadian enterprise, OPTT Inc. Additionally, by providing this service to clinicians, the care capacity for accessible, affordable, and high-quality mental health care could be more rapidly scaled across Canada.

To conclude, online psychotherapy has the potential to allow for more services to be provided at a lower cost and with increased capacity and accessibility, but research on its applications to relapse prevention is limited. Therefore, the results of this study aim to supplement the literature on the use of online psychotherapy for the management of AUD and to validate the implementation of this e-RPT program. Thus, the findings from this study can help provide the stepping stones for the large-scale implementation of programs like this one and may provide family medicine clinics, specialists, mental health professionals, and insurance companies with a new, more affordable, and accessible mental health resource.

Acknowledgments

This study has been funded by the 2021 Queen's University Department of Psychiatry Internal Research Grant (Multimedia Appendix 1). The funding agency has no role in the study's design, execution, data collection, analysis, or interpretation.

Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed yet for the preparation of this protocol manuscript. Though the data sets generated during and analyzed in the randomized controlled trial will be available from the corresponding author on reasonable request.

Conflicts of Interest

NA and MO have cofunded the care delivery platform OPTT (Online Psychotherapy Tool) that is in use and have ownership stakes in OPTT Inc.

Multimedia Appendix 1

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Peer review report by Queen's University Department of Psychiatry Internal Research Grant Review (Kingston, Canada).
[PDF File (Adobe PDF File), 124 KB - resprot_v12i1e44694_app1.pdf]

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Abbreviations

AUD: alcohol use disorder
CBI: coping behaviors inventory
CBT: cognitive behavioral therapy
e-CBT: internet-based cognitive behavioral therapy
e-RPT: web-based relapse prevention therapy
MINI: Mini International Neuropsychiatric Interview
OPTT: Online Psychotherapy Tool
PHQ-9: Patient Health Questionnaire
PI: principal investigator
Q-LES-Q-SF: Quality of Life Enjoyment and Satisfaction Questionnaire—Short Form
RCQ: Readiness to Change Questionnaire
RPT: relapse prevention therapy
RS-14: 14-Item Resilience Scale
SCQ: Situational Confidence Questionnaire

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Protocol

Supporting Youth Vaping Cessation With the Crush the Crave Smartphone App: Protocol for a Randomized Controlled Trial

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Abstract

Background: The use of e-cigarettes, or vaping, has increased exponentially in the past decade, particularly among youth. Emerging evidence indicates growing nicotine dependence among youth, revealing historically higher rates of dependence among current e-cigarette users compared to rates seen in earlier research. Despite the urgent need for youth vaping cessation interventions, there is limited knowledge about the process of vaping cessation, and few evidence-based interventions are available to young people seeking support. A notable literature review on vaping cessation resources for young people recommended technology-based interventions, such as smartphone apps and SMS text messaging services, as a promising area of vaping cessation research and intervention development.

Objective: The primary aim of our study is to determine the effectiveness of the *Crush the Crave* app in supporting vaping cessation among youth recruited to the intervention arm via comparison with an assessment-only control group. The primary hypothesis is that participants in the intervention group—those using *Crush the Crave*—will be more likely to be abstinent at the 6-month follow-up point than participants in the assessment-only control arm.

Methods: A 2-arm, single-blind, parallel randomized controlled trial will be conducted over 12 months. Study invitations will be sent to 600 youth (age: 16-18 years) and young adult (age: 19-29 years) e-cigarette users and randomized between an intervention arm, which will be using *Crush the Crave* (n=300), and an assessment-only control arm (n=300) in a 1:1 ratio. The primary hypothesis is that participants in the intervention group—those using *Crush the Crave*—will be more likely to be abstinent at the 6-month follow-up point.

Results: Study recruitment began on March 4, 2022. Recruitment is anticipated to be completed in December 2022.

Conclusions: This protocol describes one of the first-ever randomized controlled trial studies to evaluate the effectiveness of an app-based intervention for supporting vaping cessation among youth aged 16 to 18 years and young adults aged 19 to 29 years. The findings from our trial will help increase our understanding of the process of vaping cessation among youth and provide evidence on the effectiveness of an app-based intervention in helping young people quit vaping. The trial results will also have implications in the development of current and future approaches to youth vaping cessation.

Trial Registration: OSF Registries osf.io/hmd87; https://doi.org/10.17605/OSF.IO/HMD87

International Registered Report Identifier (IRRID): DERR1-10.2196/42956

(JMIR Res Protoc 2023;12:e42956) doi:10.2196/42956

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KEYWORDS

e-cigarettes; vaping cessation; youth and young adult health; adult; youth; effectiveness; smartphone; application; vaping; cessation; assessment; intervention

Introduction

The use of e-cigarettes, or vaping, has increased exponentially in the past decade, particularly among young people [1,2]. Emerging evidence indicates growing nicotine dependence among youth, revealing historically higher rates of dependence among current e-cigarette users compared to rates seen in earlier research [3-5]. Several studies have documented the growing need for vaping cessation support among youth [4-10]. In 2019, young people who did not smoke accounted for a greater number of regular vapers (as opposed to *ever-vapers*) when compared to those who smoked [11]. The COVID-19 pandemic may have exacerbated these conditions, with research suggesting an increase in substance use, including vaping, among young people [9,12,13].

Despite the urgent need for youth vaping cessation interventions, there is limited knowledge about the process of vaping cessation, and few evidence-based interventions are available to young people seeking support [6,14]. To date, much of the clinical and public health guidance on vaping cessation is adapted from the literature on smoking cessation [6,8,14]. However, while there are several commonalities between smoking and vaping, there are important differences that have received relatively little attention. A narrative review published in 2021 identified the following three key differences between vaping and smoking dependence: (1) greater variability in vaping products than in cigarettes, (2) the discreetness and convenience of vaping, and (3) greater social acceptability of vaping among youth [6,8,14]. Knowledge of these differences can inform the development of vaping cessation interventions that are effective and acceptable among young people.

Previous work in intervention research and development identified technology-based interventions as a promising area for promoting youth vaping cessation [6]. Smartphone technology and mobile software apps are highly accessible, easily scalable, and cost-effective platforms for mental health interventions [15]. Globally, young people born after the year 2000 are the top smartphone users [16,17]. Consequentially, vaping prevalence is also greatest among those aged 18 to 24 years and 15 to 17 years [11,18,19]. In fact, the use of apps for addressing mental health and substance use among youth is well documented in the literature [20-23], with apps for vaping cessation being among the latest additions [24]. However, there is currently no empirically tested smartphone app that specifically targets youth vaping cessation [24].

This protocol describes one of the first-ever randomized controlled trial (RCT) studies to evaluate the effectiveness of an app-based intervention for supporting vaping cessation among youth. The first-ever RCT of a vaping cessation intervention was designed to evaluate the effectiveness of an SMS text messaging program called *This is Quitting* in helping young adults in the United States aged 18 to 24 years to stop vaping [8]. The trial results showed that an SMS text messaging program that provided interactive and tailored messages was successful in promoting vaping cessation among young adults [8]. However, this trial did not include youth aged 14 to 17 years, for whom vaping cessation is urgently needed, as participants [1,4,18]. In our study, 600 youths (aged 16-18 years) and young adults (aged 19-29 years) who vape will be recruited. The intervention is called *Crush the Crave*—a comprehensive, full-featured app for supporting youth vaping cessation (Figure 1).

Crush the Crave for vaping cessation was developed based on an earlier version of the app for smoking cessation [25-27]. An RCT of 1599 young adult smokers assessed *Crush the Crave* for smoking cessation and found that the 30-day point prevalence abstinence (PPA) at 6 months for the intervention condition (118/820, 14.4%) was not significantly different (odds ratio 0.82, 95% CI 0.63-1.08) from that for the control condition (132/779, 16.9%). However, the rate of abstinence was favorable when compared with the unassisted 30-day quit rates of 11.5% of young adults [28]. In addition, it was determined that 61% of the young adult smokers in the RCT were vaping. The increasing nicotine dependence and use of vapes among youth have prompted interest in developing an app for vaping cessation based on people's experiences with *Crush the Crave* for smoking cessation. *Crush the Crave* is a tracker app that tracks the following information: the number of vape-free days and the amount of money saved since quitting vaping, as well as triggers and cravings. The app also provides the following functions: tailored supportive messages and inspirational graphic images for quitting vaping, personalized quit plans, graphic performance feedback, digital awards for achieving milestones, the reporting of vaping triggers, assistance for dealing with cravings, and links to other supportive resources that can aid in vaping cessation.

The primary aim of our study is to determine the effectiveness of the *Crush the Crave* app in supporting vaping cessation among youth recruited to the intervention arm via comparison with an assessment-only control group. The primary hypothesis is that participants in the intervention group—those using *Crush the Crave*—will be more likely to be abstinent at the 6-month follow-up point than participants in the assessment-only control arm. Our trial is currently open for recruitment. The anticipated completion date for our study is March 2024.

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Figure 1. *Crush the Crave* app: comparison of the old version for young adult smoking cessation and the current version for youth vaping cessation.



Methods

Trial Design

A 2-arm, single-blind, parallel RCT will be conducted over 12 months. Study invitations will be sent to 600 youth and young adult e-cigarette users and randomized between an intervention arm, which will be using *Crush the Crave* (n=300), and an assessment-only control arm (n=300) in a 1:1 ratio. The trial protocol is registered with the Center for Open Science (registration digital object identifier: 10.17605/OSF.IO/HMD87). The trial protocol was developed in accordance with the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2013 checklist of recommended items for interventional trials [29].

Ethics Approval

The study is being conducted by the Ontario Tobacco Research Unit. Approval for the study protocol was obtained from the University of Toronto Office of Research Ethics (protocol number: 00038410).

Recruitment and Enrollment

Eligible participants are youth aged 16 to 29 years who live in Canada and have used nicotine e-cigarettes in the previous 30 days. Study participants will be recruited through the Vaping Dependence Cohort—an existing panel of youth enrolled in a prospective cohort study at the University of Toronto who provided consent for recontact in future studies at the Ontario Tobacco Research Unit. This panel is comprised of a broad sample of youth who self-reported current or past regular use of nicotine e-cigarettes. The use of nicotine e-cigarettes was assessed through a question that asked respondents if they had used e-cigarettes daily, in the past week, in the past month, in the past 3 months, or in the past year and if they had ever used an e-cigarette. This cohort was designed to balance recruitment by smoking status (*ever* or *never*), e-cigarette use (*ever* or *never*), and age (16-18 years or 19-25 years). Consequently, the prevalence of smoking, e-cigarette use, and younger participants was higher than what would be expected in a simple random sample of the population. An analysis controlling for the study design elements found that the within-group characteristics of the included youth were broadly consistent with expectations, which were based on a representative sample [9].

Informed Consent

After eligibility screening, participants must provide informed consent to proceed with study enrollment. The web-based consent form contains information about the study, the *Crush the Crave* app, participant eligibility, requirements and expectations for study participation, compensation, data collection, and plans for protecting participants and their privacy (ie, data deidentification), as well as the contact information of study staff and the University of Toronto Office of Research Ethics. Those who agree to participate in the study will receive an email containing a link to download the *Crush the Crave* app (sent to the email addresses they provided).

Compensation

Each participant in the intervention and control arms will receive compensation (CAD $10 [US $7.46] electronic gift card) upon completion of the baseline survey questionnaire and each time they complete a follow-up survey throughout the course of the study.

Randomization

Eligible participants will be identified from the Vaping Dependence Cohort. The *rand()* function in Excel (Microsoft Corporation) allowed for simple randomization; the top 50% highest numbers identified the participants that will receive invitations to use the *Crush the Crave* app. A research assistant from the Vaping Dependence Cohort will conduct the randomization and create a variable with a blinded key for the initial data analysis, which will allow the investigators and analyst to be blinded to the group allocation up until the data analysis is complete.

Interventions

Crush the Crave

An earlier version of the *Crush the Crave* app was developed for smoking cessation [22,25], incorporating fundamentals of persuasive technology [30] and recommended practices for addressing tobacco use and dependence [31]. This evidence

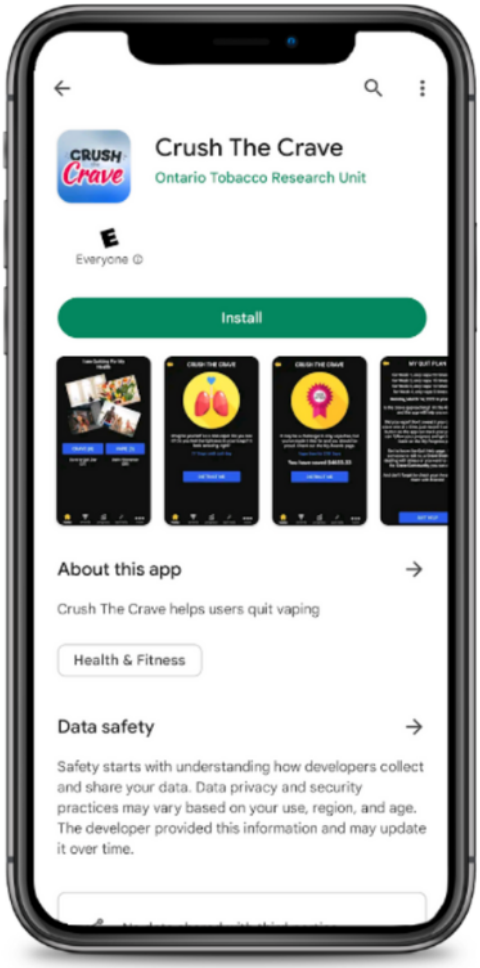
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base formed the foundation for the current version of the *Crush the Crave* app for vaping cessation (Figure 2), which was redesigned (using principles of co-design [32]) by a multidisciplinary team of tobacco control researchers, design researchers, and software developers. Youth and young adults who vape were also engaged in the co-design process through a series of focus groups (January to February 2020) and an intensive design research workshop called *VapeHack* (May 2020).

Like the original app for young adult smoking cessation, *Crush the Crave* for vaping cessation enables users to customize a quit plan. As a tracker app, *Crush the Crave* monitors the amount of money saved and the number of vape-free days since the user's quit date. This savings calculator is one of the most significant changes in this version of *Crush the Crave*, which involved the conversion of the money saved based on the number of cigarettes smoked in a day to the money saved based on the number vape pods used in a week (calculated as the number of vape-free days multiplied by the product of the average number of vape pods used each day and the price of vape pods in Canada). The previous version of the app had a health calculator that monitored users and informed them of the health milestones achieved since quitting smoking. In the current version of the app, the health calculator feature was removed as a reflection of the lack of definitive evidence on the health effects of vaping. Further development of *Crush the Crave* for vaping cessation will be halted during the trial.

The app also tracks cravings and vaping habits through a diary of vaping triggers that records when, where, and why vaping occurs. The app displays supportive messages and graphic images of encouragement in response to cravings and relapse, as well as direct links to evidence-based resources, such as quitlines. A visual representation of quitting progress over time is provided to users on the main page, and users have the ability to upload personalized pictures and verbal affirmations. *Crush the Crave* also gives users the ability to geotag where vaping and cravings occur, and this information is only viewable to the user. Other features include reminders or push notifications regarding the money saved, health improvements, and the achievement of goals; digital awards for reaching milestones; and supportive messages tailored to where users are in the quitting process.

Figure 2. *Crush the Crave* app on the Google Play Store.



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Assessment-Only Control

Based on an approach that is similar to the one used by Graham and colleagues [8], participants will be invited via email to complete the baseline assessment, and they will be invited to complete the follow-up assessment questionnaires asking about e-cigarette use and abstinence (as outlined in the following sections) at 3, 6, 9, and 12 months. At the end of the intervention period and following the last follow-up assessment, they will be invited to try the *Crush the Crave* app, if they are interested.

Data Collection

A baseline questionnaire will be sent to both the intervention group and the control group, using a self-administered web-based survey. This will collect comprehensive data on the history and characteristics of vaping (eg, vaping dependence, use of e-cigarettes, and self-confidence to quit), self-perceived addiction to vaping, health status (including mental health, mood, and perceived stress), and current and previous history of the use of other substances (combustible cigarettes, marijuana, alcohol, hookahs, and other tobacco products). The baseline survey will also ask questions on environmental factors and cessation goals. Self-reported demographic data (age, sex, gender and sexual orientation, province and country of residence, race and ethnicity, education, and marital status) will also be collected in the baseline survey.

A follow-up survey will be sent to the control and intervention groups at 3, 6, 9, and 12 months. Responses to the follow-up survey will be used to analyze any significant changes in vaping habits and differences between groups. The follow-up survey questionnaire includes items on cross-contamination and the use of cessation methods.

Outcome Measures

The primary outcome variable will be self-reported 30-day PPA at 3 months, operationalized as not having vaped, even a puff, in the last 30 days. The secondary measures include the intention to quit smoking in the next 6 months (*yes* or *no*), number of puffs per vaping session, number of vape sessions per day, and number of sessions in the past 30 days.

Process Measures

The mHealth (mobile health) App Usability Questionnaire [33] will be used to collect data on process measures from the intervention group. The mHealth App Usability Questionnaire collects data on the following three main constructs: ease of use and satisfaction (8 items), system information arrangement (6 items), and usefulness (7 items). Data from app analytics will also be used as process measures for the intervention group, including whether participants downloaded the intervention (*yes* or *no*), the frequency of use, the most frequently used features, and user reviews.

Qualitative interviews (n=25) will be conducted with participants in the intervention arm to gain insight on the usability and acceptability of the app. Interviews will be audio recorded and transcribed verbatim, and they will be analyzed in NVivo 12 (QSR International) by using a 6-step approach to thematic analysis, as proposed by Braun and Clarke [34].

Data Analysis Plan

Primary Outcome

Demographic and vaping characteristics (eg, vaping dependence, use of e-cigarettes, and self-confidence to quit) will be compared between groups at baseline. The intention-to-treat principle will be followed for statistical analyses, and all participants will be analyzed in the study arm to which they were randomized. Negative binomial regression with an identity function and robust SEs will be used to test between-group comparisons of the primary outcome variable—30-day PPA at follow-up. Multiple imputation via chained equations using the observed predictors of outcomes and the predictors of loss to follow-up will be performed to impute missing outcome data to correct for any potential bias caused by missing data. The imputation model will include age, sex and gender, education, marital status, province of residence, ethnicity, vaping dependence, self-confidence to quit, perceived stress, and the intervention group. The inverse of the adjusted risk difference will provide the number needed to treat.

The sample size of 600 (inclusive of both the control arm and the intervention arm) was selected to differentiate an effect size odds ratio of 1.60, assuming a base cessation rate of 5%, an α of .05, a power of 0.8, and a 75% (450/600) response rate.

Secondary Outcomes

For comparisons between secondary continuous outcomes and continuous outcomes, a linear regression with an identity function will be used. The secondary analysis of missing information will use the following two approaches to handle missingness: (1) imputation using the baseline observation carried forward or the classification of nonresponders as vapers in accordance with the Russell standard [35] and (2) imputation using the last observation of vaping status carried forward for nonresponders.

Process Analysis

For the process measures (whether participants downloaded the intervention, the frequency of use, satisfaction, and helpfulness), a chi-square test of association will be performed for binary and categorical variables, and for the ordinal variables approximating a normal distribution, a two-tailed *t* test for independent groups will be performed.

Results

Study recruitment began on March 4, 2022. Recruitment is anticipated to be completed in December 2022.

Discussion

Protocol Overview

This is the first-ever RCT study to evaluate the effectiveness of a smartphone app for supporting youth vaping cessation. The primary aim of our study is to determine the effectiveness of the *Crush the Crave* app in supporting vaping cessation among youth recruited to the intervention arm via comparison with an assessment-only control group. The primary hypothesis is that participants in the intervention group—those using *Crush the*

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Crave—will be more likely to be abstinent at the 6-month follow-up point than participants in the assessment-only control arm.

The *Crush the Crave* app was developed based on the best available evidence on vaping cessation and an empirical investigation on the effectiveness of an earlier version of the app for smoking cessation [22]. At the time of writing, 4 other clinical trial protocols for evaluating vaping cessation interventions among youth and young adults were registered on ClinicalTrials.gov. Of these, only 1 has been completed; the results are accessible in the published scientific literature and show that the intervention was successful (abstinence success rates of 16% for the intervention group and 8% for the control group) in encouraging young adults to stop vaping through an SMS text messaging program [8]. This study was useful in providing a benchmark for intervention effectiveness [8]. Of the 3 remaining protocols that are actively recruiting participants, 2 aim to evaluate the effectiveness of nicotine replacement therapy for vaping cessation among youth and young adults, and 1 aims to determine the effectiveness of a smartphone app called *Goal2QuitVaping*. Compared to the target sample size in our study (N=600), that of the Goal2QuitVaping study is relatively small (N=45).

Limitations

It is important to note the potential limitations in some aspects of the design and implementation of our trial. First, most notably, our trial was designed to include an assessment-only control group. We recognize that other app-based interventions for health are typically compared against other active controls or even other app-based interventions. Our methodology was adopted from the methodology used in the only completed trial (at the time of writing) of a technology-based vaping cessation intervention [8]. Second, our study focuses on evaluating the effectiveness of the intervention among youth and young adults who vape nicotine e-cigarettes. Given the recent rise in cannabis vaping among youth, interventions that focus on cannabis vaping will need to be developed and studied rigorously. Finally, we recognize that the active intervention is publicly available on the Apple and Google app stores and that participants in both trial groups may become aware of this fact during the trial. Cross-contamination measures will be put in place to assess awareness of and engagement with the *Crush the Crave* app among control group participants.

Conclusions

The findings from our trial will help increase our understanding of the process of vaping cessation among youth and provide evidence on the effectiveness of an app-based intervention in helping young people quit vaping. The trial results will also have implications in the development of current and future approaches to youth vaping cessation.

Conflicts of Interest

None declared.

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Abbreviations

mHealth: mobile health
PPA: point prevalence abstinence
RCT: randomized controlled trial
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Protocol

Feasibility of a Community-Based, Online, Peer-Supported Spinal Cord Injury Self-management Intervention: Protocol for a Pilot Wait-Listed Randomized Trial

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Abstract

Background: People with spinal cord injury (SCI) report feeling unprepared to manage their disability upon discharge to the community. This situation is exacerbated when they return to settings where self-management support and resources are sparse, thus increasing the risk of costly secondary conditions and rehospitalizations. These factors make a compelling case for implementing innovative community-based SCI self-management programs that empower and engage individuals with SCI. Using a community-engaged research (CEnR) approach, we developed a peer-supported SCI self-management intervention, known as PHOENIX (Peer-supported Health Outreach, Education, and Information Exchange), which integrates online educational content and support from peer navigators (PNs) through telehealth, to promote health and community participation after SCI.

Objective: The objective of this pilot study is to evaluate the feasibility and acceptability of PHOENIX and the study design, and to obtain estimates of the variability of relevant outcome measures.

Methods: We conducted a pilot randomized waitlist-controlled trial (n=30) in collaboration with the South Carolina Spinal Cord Injury Association (SCSCIA), our long-standing community-based nonprofit organization research partner. We recruited 4 PNs through our SCSCIA collaboration using its existing network of trained peer mentors. Our study design supported comparison of the following 2 randomly assigned groups: PHOENIX intervention group and waitlist enhanced usual care (EUC) group. The PHOENIX intervention was administered online by PNs over 16 weeks through scheduled “video visits.” The EUC group participated in the study for 16 weeks with usual community services and no navigation, and received 4 monthly newsletters from the SCSCIA on a variety of SCI-relevant topics. At the end of the waitlist period, the waitlist EUC group received the full PHOENIX intervention. Measures of feasibility included PN and participant recruitment and retention, PN workload, protocol adherence, and incidence of technical issues. We conducted qualitative interviews with participants and PNs to evaluate the acceptability of PHOENIX and the study design. Outcome measures, including community participation, quality of life, and the occurrence and subjective impact of medically serious secondary conditions and rehospitalizations, were assessed at baseline after randomization and at subsequent time points to allow between-group comparisons.

Results: PN hiring and training were completed in August 2018. Recruitment began in November 2018. A total of 30 participants were recruited across South Carolina, and 28 participants completed follow-up by August 2020. An analysis of the results is being finalized, and the results are expected to be published in 2023.

Conclusions: This study will provide valuable information to guide future research seeking to address unmet self-management needs and improve outcomes in individuals with SCI. Feasibility findings of this study will provide evidence from CEnR guided

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by people with SCI and SCI service providers to inform further development, testing, and dissemination of effective and scalable self-management strategies for people with SCI.

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KEYWORDS

spinal cord injury; peer support; self-management; telehealth; community engaged research; community participation

Introduction

Background

Spinal cord injury (SCI) is a life-altering event that results in varying degrees of paralysis, depending on the level and completeness of injury. According to the National Spinal Cord Injury Statistical Center, there are about 17,900 new SCI cases each year and about 296,000 people with SCI in the United States [1]. Presently, 87% of all people with SCI return to private noninstitutional residences in the community [2]. Individuals with SCI are among the most complex and costly patients to manage in the health care system, with approximately 30% of people with SCI being rehospitalized one or more times during any given year following injury. While the prevalence of SCI is relatively low in comparison with the prevalence of other chronic conditions, the costs are staggering. Estimates suggest that first-year postinjury health care and living expense costs average US $567,000 for individuals with paraplegia and US $1.16 million for quadriplegia, with estimated lifetime costs of up to US $5.16 million [1]. The treatment of secondary complications, such as pressure injuries and urinary tract infections, requiring rehospitalization further increases the cost.

Self-management is both a goal and a lifetime task after a traumatic disabling event such as SCI [3]. Individuals with SCI must engage in proactive self-care (eg, pressure relief, skin checks, and bladder and bowel care) to reduce the occurrence and severity of costly potentially preventable secondary conditions that can detract from community participation and reduce quality of life (QOL). Medical rehabilitation is an essential component of recovery and adaptation to life with SCI. However, the median rehabilitation length of stay has declined over the last 40 years from 98 days in the 1970s to 30 days currently [1]. Unfortunately, shorter rehabilitation results in reduced opportunities, before discharge to home, for education and practice in self-management skills that are essential to prevent common, albeit serious, postinjury secondary conditions. Rehospitalization and medically serious secondary conditions create risks for increased isolation, and decreased community participation and QOL [4,5].

People with SCI report feeling unprepared to manage their disability and its effects in an environment outside of the clinical setting [6]. This situation is exacerbated when they return to settings where self-management support and resources are sparse, thus increasing the risk of costly secondary conditions and rehospitalizations [7,8]. These factors make a compelling case for implementing innovative community-based SCI self-management programs that empower and engage individuals with SCI.

Intervention Overview

Our strategy to promote SCI self-management has consistently involved specially trained peer navigators (PNs). In the context of our studies, PNs are people with SCI who are informed about their condition, take an active role in their self-care, are trained in key self-management components, and have a desire to help others learn to navigate life with a new disability [9,10]. As our pilot work and other studies demonstrate, learning from peers is vital in rehabilitation from a disabling injury and adjustment to living with SCI [11-14]. Our peer navigation model was initially pilot tested as an in-person intervention delivered in participants' homes. However, given the issues of scalability and sustainability, scattered regional distribution of participants, access problems, and travel time and costs, we determined that a telehealth innovation was needed.

Our online PHOENIX (Peer-supported Health Outreach, Education, and Information Exchange) intervention evolved from lessons learned while piloting our in-person intervention. The primary goals of PHOENIX are to improve participants' community participation and QOL, and the secondary goals are to decrease the occurrence and subjective impact of medically serious secondary conditions and rehospitalizations. The 16-week PHOENIX intervention consists of 3 key components: (1) education on post-SCI self-care, and community resource navigation and use; (2) skill optimization through role modeling by the PN, tailored participant-centered behavioral goal setting, and action planning; and (3) information exchange through shared problem solving and decision support with the PN. The primary modalities to support the telehealth delivery of PHOENIX include (1) web-based multimedia educational content and (2) scheduled televideo interactions, using a telehealth platform, for knowledge and skill building and information exchange between participants and PNs with SCI.

The purpose of this study was to pilot test, in collaboration with our long-standing community partner, the South Carolina Spinal Cord Injury Association (SCSCIA), a structured, sustainable, technology-enhanced SCI PN intervention (ie, "PHOENIX") for statewide implementation across South Carolina. In congruence with the purpose of feasibility studies, the objective of this study was not to test the efficacy of the PHOENIX intervention but to determine whether the novel telehealth intervention and the study design could be feasibly implemented, and to obtain estimates of the variability of relevant outcome measures [15]. We designed a randomized pilot trial, using a waitlisted control group, to identify the potential logistical and methodological issues of both intervention implementation and study procedures in preparation for conducting a future full-scale randomized controlled trial [15]. We also sought to evaluate the PHOENIX intervention to obtain estimates of the variability

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of community participation and QOL (primary outcomes), and the occurrence and subjective impact of medically serious secondary conditions and rehospitalizations (secondary outcomes) to inform the design of an adequately powered future trial.

Methods

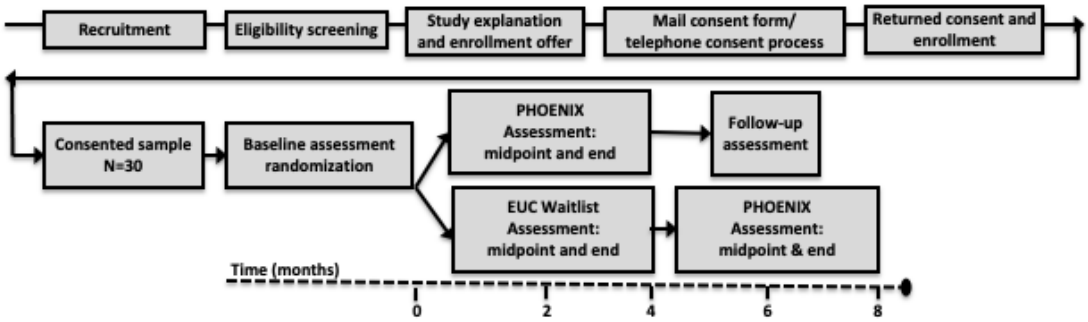
Community Engagement

Our approach reflected the Guidelines and Criteria for the Implementation of Community-based Health Promotion Programs for Individuals with Disabilities, including (1) use of an underlying theoretical framework; (2) implementation of process evaluation; (3) use of disability-appropriate outcome measures; (4) active involvement of people with disabilities in intervention development and implementation; (5) support of the personal beliefs, practices, and values of people with disabilities; (6) consideration of accessibility and barriers to program participation; and (7) sensitivity to financial constraints often experienced by people with disabilities [16]. A long-standing community-engaged research partnership between the principal investigator (SDN) and the SCSCIA supported this line of research. Over the course of our partnership, research activities have been guided by an active and empowered community advisory board comprised of community members with SCI, and representatives from agencies providing services to people with SCI. The advisory board participated in the conceptualization of PHOENIX and the development of multimedia content for the intervention to assure relevance and accessibility of the material. They also provided feedback on the structuring and layout of the online educational curriculum. The SCSCIA collaborated with the study team on (1) expansion and formalization of the PN training curriculum; (2) identification and recruitment of individuals who would serve well as PNs; (3) facilitation of PN training workshops; (4) periodic monitoring of PN performance; (5) assistance with participant recruitment; and (6) support to the principal investigator in addressing additional navigator training needs over the course of the study. It is also engaged in assisting with the dissemination of study results to nonacademic audiences in the community.

Study Design

Advisory board guidance was sought to address scientific rigor and logistics, as well as ethical concerns about condition assignment. We addressed these concerns through a randomized waitlist study design, so all participants received the intervention. Our study design supported the conduct of a pilot randomized (individual level) waitlist-controlled trial with 30 adults with SCI, comparing 2 groups: a waitlist enhanced usual care (EUC) group and a PHOENIX intervention group. At the end of the waitlist period, the EUC group received the full intervention (Figure 1).

Figure 1. Study design and flow. EUC: enhanced usual care; PHOENIX: Peer-supported Health Outreach, Education, and Information Exchange.



PN Recruitment, Training, and Retention

We recruited 4 PNs through our SCSCIA collaboration using its existing network of trained peer mentors. The PNs completed 2 full days of training on implementation of the PHOENIX intervention and working on a research team, which included completion of training in protecting human subjects, research ethics and compliance, and maintaining participant privacy and study data confidentiality. An additional full-day training was provided approximately 6 months after study initiation. To promote retention, all PNs were hired and paid as university employees. Additional retention strategies included scheduled weekly meetings with the team over the course of the study to address issues that arose in the navigation process and to provide ongoing support to PNs.

Ethics Approval

Institutional Review Board (IRB) approval (Medical University of South Carolina; number: Pro00071526) was obtained prior to the initiation of study participant recruitment. As the SCSCIA was determined to be engaged in research, a certificate of Federal Wide Assurance was obtained with a reliance agreement in place with the university IRB.

Inclusion and Exclusion Criteria

The inclusion criteria were as follows: (1) South Carolina resident; (2) ≥18 years old; (3) chronic paralysis due to traumatic SCI; (4) level and severity of paralysis requiring locomotion with a wheelchair for >6 hours/day; (5) living in a private residence; (6) accessible by mail, phone, or email; and (7) able to speak English. The exclusion criteria were as follows: (1) cognitive or mental impairment that would prevent informed consent; (2) level of injury requiring use of a ventilator; (3) unhealed stage III or IV pressure ulcer requiring bed rest; (4) acute serious medical illness at the time of screening that would inhibit participation in the intervention; and (5) plans to move out of South Carolina in the next 8 months.

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Number of Subjects

Our targeted sample was 30 adults with SCI from urban and rural regions across South Carolina. Consistent with guidance provided by Leon et al and Tickle-Degnen, our intent with this pilot study was not to estimate effect size, and our sample size was determined primarily by pragmatic reasons [15,17,18]. Sample size determination was based on estimates of workload for PNs. We expected that PNs could work with 2 study participants at a time during the first 8 weeks of the intervention that required weekly contact. For a sample size of 15 participants per group (intervention and waitlist control), the between-group difference in change scores for the relevant outcome measures for the intervention group versus waitlist control group was estimated with precision to range from ±7.6 to ±15.1 for SDs of difference scores ranging from 15.0 to 30.0 SD units.

Recruitment and Consent

Established collaborations, including the SCSCIA's network of peer support groups and relationships with SCI-related service providers and rehabilitation hospitals, supported recruitment of 30 adults with SCI from urban and rural regions across South Carolina. We announced the study through flyers, SCSCIA staff word of mouth, the SCSCIA Facebook page and other social media, and the SCSCIA website. Study announcements provided study team contact information to individuals interested in participating.

Once an individual responded to the call for participants, we conducted screening procedures to determine eligibility, thus following CONSORT (Consolidated Standards of Reporting Trials) guidelines to determine detailed information on recruitment flow. Eligible individuals were then provided with a brief study description, including randomization, and a general schedule of procedures to assess continued interest prior to conducting the informed consent process.

We offered 2 options for completing the informed consent process, by telephone or eConsent through REDCap (Research Electronic Data Capture). For telephone consent, eligible and interested individuals provided their full name and contact information. We then mailed 2 copies of the informed consent to the interested individuals and scheduled a time to complete the consenting process by phone, after which the participants signed and returned 1 signed copy of the consent. For eConsent, individuals interested in study participation provided their full name and contact information, including an email address, to which we sent a REDCap survey link containing the informed consent document. Study staff scheduled a time to complete the consenting process by phone, after which the participants signed the eConsent in REDCap. Upon submitting the eConsent, a REDCap trigger immediately notified the person obtaining consent, who then signed the document. Participants could download a copy of their executed informed consent directly to their own computer or request a copy be emailed or mailed to them.

Randomization

Once signed consent was received, participants were randomized and placed in the appropriate group in the REDCap database. Randomization was at the participant level, using the REDCap automated randomization feature. Following the completion of baseline measures, staff informed participants of their group assignment.

Intervention Delivery Platform

iTunes U

The iTunes U environment provided a private 1-way (ie, study participants did not enter any personal information into iTunes U) platform for the dissemination of multimedia educational content, including web links, documents, and videos, addressing topics in the PHOENIX curriculum (the educational videos are available online [19]). The educational content served as a source of information, as well as provided topics/themes for PN and participant discussions during the video visits. The educational content in iTunes U provided a library of resources available to PNs and participants, which was used to tailor the information provided, and an approach to address the relative learning needs of each participant.

Doxy.me

The low bandwidth televideo solution Doxy.me was used to facilitate the video visits between PNs and participants. Doxy.me is a Health Insurance Portability and Accountability Act–compliant, free, and secure telehealth solution that does not require downloads, plugins, or specialized hardware, and works natively on iPads through the Doxy.me app.

iPads

Once participants were assigned to PHOENIX, either at randomization or the end of waitlist, we assessed assistive technology needs, and participants were sent a kit by certified mail, which contained an iPad preloaded with PHOENIX educational materials, any required assistive technologies, and instructions on operation of the iPad. After we received confirmation that the iPad was received, study staff placed an initial call to assist iPad set up and provide information on the assigned PN who contacted the participant and initiated PHOENIX. The iPad provided a means for participants to access educational materials in iTunes U and engage in video visits using the Doxy.me app with PNs. In return for participants' time and effort for participating in the study, the study team transferred ownership of the iPad to the study participants, and they retained any additional assistive technologies provided to them at the end of the study. At the end of the study, the cellular data plan provided by the study was terminated, and participants were provided with suggestions for free Wi-Fi access in their community (eg, public library).

Intervention Implementation

PHOENIX was administered by the PN over 16 weeks. The first 8 weeks consisted of 6 educational modules (Table 1) and weekly televideo contact (ie, "video visits") via Doxy.me with the PN, followed by (weeks 9-16) biweekly scheduled video visits with the PN to address progress to goals; barriers encountered; skin, bladder, or bowel issues; or hospitalization since last contact. PHOENIX integrated the key skills of self-management as defined by Lorig et al: problem solving, decision making, resource utilization, formation of partnerships, action planning, and self-tailoring [3]. Developing participant

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self-efficacy in these essential skills through construction of action plans and facilitated goal setting supported a participant-centered approach to self-management. PNs facilitated and modeled methods to access community services and resources, as well as incorporated aspects of peer mentoring by helping the individual establish goals, served as a resource for advice and guidance, and modeled strategies to meet goals [20]. The intervention was designed to promote participant efficacy in achieving a desirable level of community participation and QOL through knowledge and skill building related to self-management, guided by motivation and support from PNs.

Table 1. PHOENIX[a] curriculum.

Week	Content/activity	PN role[b]
Week 1: Introduction to PHOENIX and SCI[c] 101	• What is PHOENIX? • Relationship building exercise • Brief PN video bios • Understanding your SCI • Initial personal goal setting	• Describe role of the PN • Share personal story • Engage peer in story sharing • Use action planning strategies to identify goals • Facilitate realistic goal setting and identifying potential barriers
Week 2: Getting what you need: Being an empowered consumer	• Self-advocacy skills • Knowing your rights • Active versus passive communication	• Role play • Facilitate discussion of a video • Assess progress to personal goal (PTPG) • Facilitate problem solving barriers
Week 3: Getting out there: Engaging community resources	• Identifying resources to support personal goal attainment • Initiate contact with a resource	• Assist with locating relevant resources • Support peer in engaging a resource • Assess PTPG • Facilitate problem solving barriers
Week 4: Staying healthy: Skin care and preventing pressure injury	• Skin care after SCI • Pressure injury prevention • Identifying a problem and taking action	• Evaluate knowledge/address gaps • Share personal experiences and strategies • Assess PTPG • Facilitate problem solving barriers
Week 5: Staying healthy: Preventing urinary tract infection (UTI)	• Bladder management after SCI • UTI prevention • Identifying a problem and taking action	• Evaluate knowledge/address gaps • Share personal experiences and strategies • Assess PTPG • Facilitate problem solving barriers
Week 6: Staying healthy: Bowel management	• Bowel management after SCI • Identifying a problem and taking action	• Evaluate knowledge/address gaps • Share personal experiences and strategies • Assess PTPG • Facilitate problem solving barriers
Weeks 7, 8, 10, 12, 14, and 16: Follow-up	• Video visit for action planning and goal support	• Share personal experiences and strategies • Assess PTPG • Facilitate problem solving barriers

[a]PHOENIX: Peer-supported Health Outreach, Education, and Information Exchange.

[b]PN: peer navigator.

[c]SCI: spinal cord injury.

Comparison Condition

The EUC waitlist group participated in the study for 16 weeks with usual community services and no navigation. Waitlist participants received 4 monthly newsletters from the SCSCIA on a variety of SCI-relevant topics. The newsletters contained contact information should participants need information or assistance. Following the end of waitlist assessment, waitlist participants crossed over to the PHOENIX intervention group. To compensate the waitlist participants for the completion of additional measures before crossover to PHOENIX and receiving the iPad, we provided US $50 payment for completing baseline and week 8 study measures.

Data Collection and Analysis: Feasibility

Assessment of feasibility was guided by Leon et al and Tickle-Degnen [15,18]. We assessed the feasibility of both the intervention and the study design and research procedures. Specific intervention and study components that were assessed, and their relevant quantifications are mentioned in Table 2.

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Table 2. Feasibility components and quantification.

Component	Feasibility quantification
Intervention component	
Navigator workload	Time logs (minutes per activity)
Retention	PN[a] attrition rate
Fidelity	Rates of adherence to intervention protocol by PNs
Adherence	Rates of adherence to intervention protocol by participants
Online module access (dosage)	Use statistics – number and duration of educational module access
Televideo access (dosage)	Use statistics – number and duration of televideo meetings
Technology	Rates of device and connectivity issues
Safety	Rate of adverse events
Study component	
Screening	Number screened per month
Recruitment	Number enrolled per month
Enrollment and consenting	Duration of enrollment and consenting process
Randomization	Proportion of screen eligible individuals who enrolled
Retention	Intervention versus waitlist attrition rates
Outcome assessments	Proportion of planned assessments completed; time to complete measures

[a]PN: peer navigator.

In addition to standard measures of feasibility, expanding the reach of PHOENIX across South Carolina using a telehealth approach removed the in-person procedures used in the original PN pilot, thus creating the need for study procedures that could be completed at a distance. We also evaluated the feasibility and logistics of our proposed screening, enrollment, and consenting procedures for use in a future larger trial with broader reach.

Part of our feasibility evaluation included determining the time required by PNs to complete navigation tasks through a telehealth platform. We closely monitored navigator workload and effectiveness. To support PN retention and closely monitor the PN experience, we held weekly team meetings, including the investigators, SCSCIA executive director, SCSCIA community outreach coordinator, and PNs, to assess and discuss issues uncovered by PNs in interactions with study participants and to provide support and guidance for addressing these issues. The proceedings of these meetings were audio recorded for later analysis and use in quality and process evaluation.

Intervention Fidelity

Standardized training of PNs and use of intervention manuals that listed session objectives and format, instructional resources, session content, and monitoring criteria supported fidelity in intervention delivery. Tracking logs in REDCap were completed by PNs at each study visit (Multimedia Appendix 1) and were used to monitor the dosage/fidelity of PNs' contacts, including frequency, length of contact, predominant interaction content, and participant progress. Feasibility will be evaluated by reporting 95% CIs on proportions and differences in proportions between the 2 groups for categorical feasibility measures, such as recruitment, retention, and adherence, and via 95% CIs for means and differences in means for continuous feasibility outcomes, including number of modules accessed, number of video visits completed, duration of video visits, etc.

Acceptability

We conducted postintervention evaluation surveys (Table 3) and interviews (Textbox 1) with participants, and a summative debriefing session with PNs to assess the usefulness, acceptance, and satisfaction regarding the waitlist study design and intervention components, as well as participant response burden for completing measures. Participants were asked about feedback regarding their experiences with engaging PNs, the use of the iPads and any other technology, the presence of any safety or comfort-related concerns about the study, and problems with the navigation process. The interviews and debriefing session were audio recorded, transcribed, and analyzed for process evaluation purposes, using the methods of qualitative content analysis.

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Table 3. Postintervention evaluation survey items.

Item	Response options
Please select the answer that best describes your feeling about each statement	
The length of partnership with my peer navigator was…	Too short, too long, or just right
The number of times I met with the peer navigator was…	Not enough, too often, or just right
How satisfied were you with the peer navigator?	Not, somewhat, or very
How satisfied were you with the educational materials?	Not, somewhat, or very
How satisfied were you with using iTunes U?	Not, somewhat, or very
How satisfied were you with using the iPad?	Not, somewhat, or very
How comfortable were you with video visits with the peer navigator?	Not, somewhat, or very
Please indicate how much the PHOENIX[a] program helped you in the following areas...	
My ability to speak up and advocate for my needs	No help, some help, or great deal of help
My knowledge about community resources & services	No help, some help, or great deal of help
My ability to access resources & services that I need	No help, some help, or great deal of help
My ability to make decisions that affect my health	No help, some help, or great deal of help
My ability to solve problems that arise	No help, some help, or great deal of help
Building a support system	No help, some help, or great deal of help
My ability to participate in activities that interest me	No help, some help, or great deal of help
Feeling I'm in control over my life	No help, some help, or great deal of help
My knowledge about spinal cord injury	No help, some help, or great deal of help
My ability to prevent pressure ulcers	No help, some help, or great deal of help
My ability to prevent urinary tract infections	No help, some help, or great deal of help
My ability to prevent bowel problems	No help, some help, or great deal of help

[a]PHOENIX: Peer-supported Health Outreach, Education, and Information Exchange.

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Textbox 1. Evaluation interview questions.

Questions

- What were your expectations for the PHOENIX (Peer-supported Health Outreach, Education, and Information Exchange) program before you began?
- What are the most helpful parts of the PHOENIX program in general?
- What are the least helpful parts of the PHOENIX program in general?

Now let's talk about using technology in PHOENIX.

First let's discuss the educational materials that were provided through iTunes U.

- Did you find these materials helpful?
- What did you like about them?
- What would make them better?
- Was any information missing?
- Describe your experience in using the iPad to video chat with the peer navigator.
- Describe any technology problems or challenges you experienced.
- Did you use the iPad to access other SCI (spinal cord injury) information on the internet? If yes, tell me more about this.

Now let's talk about your experience in working with the peer navigator.

- How would you describe the nature of your relationship with your peer navigator?
- What did you like about working with a peer navigator?
- What would make this experience better?
- Goal setting and following up on your goals with your peer navigator is an important part of the program. Tell me a little bit about your experiences with setting goals while you were in PHOENIX.
- Tell me about what you learned about self-advocacy while you were involved with this program.
- Describe any changes in your life with SCI that resulted from participating in PHOENIX.
- What suggestions do you have to make this program better?
- Do you have any other last thoughts that you would like to share?

Data Collection and Analysis: Outcomes

Baseline data collection occurred after randomization (week 0). In the intervention group, we collected outcome measures at the intervention midpoint (week 8) and end (week 16), and at follow-up (week 24). In the waitlist control group, we collected outcome measures at the same time points to allow preliminary between-group comparisons, including at baseline (week 0), waitlist midpoint (week 8), end of waitlist/preintervention (week 16), intervention midpoint (week 24), and intervention end (week 32) (Figure 1). We used REDCap for data collection and management. Participants were provided with a link to access the REDCap survey using their iPads. Contact information was provided to allow the option of phone administration for participants who were not able to complete the REDCap survey.

Measures

We used established instruments with reported validity and reliability in populations with SCI (measures and timing are detailed in Table 4). We used relevant item banks from the Spinal Cord Injury-Quality of Life (SCI-QOL) instrument developed for use with SCI populations, which builds on the Patient-Reported Outcomes Measurement Information System (PROMIS) and the Quality of Life in Neurological Disorders (Neuro-QOL) initiative [21]. We used short-form instrument options when available to minimize participant response burden.

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Table 4. Measures and timing.

Domain	Measures	Timing
Outcomes		
Community participation (objective)	Craig Handicap Assessment & Reporting Technique (CHART): Mobility subscale items [22,23]	All time points[a]
Community participation (subjective)	- Reintegration to Normal Living Index (RNL), 10 items [24-26] - SCI-QOL[b] Ability to Participate (ATP), 10 items; and Satisfaction with Social Roles (SRS), 10 items [27]	All time points[a]
Quality of life	SCI-QOL Positive Affect & Wellbeing (PAWB), 10 items [28]	All time points[a]
Secondary conditions and rehospitalizations	- SCI-QOL Pressure Ulcers Scale (PUS), 7 items [29] - Bladder Complications Scale (BCS), 5 items [30] - Bowel Management Difficulties Scale (BMD), 8 items [30] - Self-report incidence of PU[c], UTI[d], and rehospitalization	All time points[a]
Mediators		
Self-efficacy	Moorong Self-Efficacy Scale (MSES), 16 items [31,32]	All time points[a]
Social support	Medical Outcomes Survey-Social Support Scale (MOS-SSS), 19 items [33]	All time points[a]
Knowledge	Secondary conditions quiz, 10 items	All time points[a]
Moderators		
Demographics	Self-report	Baseline
SCI[e] information	Self-report	Baseline
Technology	Self-report	Baseline
Stigma	SCI-QOL Stigma, 10 items [34]	Baseline, end, and follow-up
Anxiety and depression	Hospital Anxiety and Depression Scale (HADS), 14 items [35]	Baseline, end, and follow-up

[a]All time points include weeks 0, 8, 16, and 24 for both groups, and week 32 for the waitlist group.

[b]SCI-QOL: Spinal Cord Injury-Quality of Life.

[c]PU: pressure ulcer.

[d]UTI: urinary tract infection.

[e]SCI: spinal cord injury.

Data Analyses

As this pilot study was intended to assess feasibility and was not a hypothesis testing study, no inferential statistical tests were proposed [15]. Descriptive statistics were calculated, as appropriate, for all variables for the total sample and within the PHOENIX and control groups. The primary purpose of this data analysis was to generate estimates of variability in the primary and secondary outcomes. The primary continuous outcome measures to be used to evaluate peer navigation efficacy in a future larger adequately powered trial are community participation (Craig Handicap Assessment & Reporting Technique [CHART], Reintegration to Normal Living Index [RNL], and SCI-QOL Ability to Participate [ATP] & Satisfaction with Social Roles [SRS]) and QOL (SCI-QOL Positive Affect & Wellbeing [PAWB]) scores, and the secondary outcome measures are occurrence and subjective impact of secondary conditions (SCI-QOL Pressure Ulcers Scale [PUS] & Bladder Complications Scale [BCS]) obtained at baseline and 2 and 4 months. In addition, within the PHOENIX group, the change from baseline to 6-month follow-up was assessed for community participation and QOL. We obtained 95% CIs for the unadjusted as well as adjusted mean change from pretreatment to posttreatment (baseline to 2 and 4 months) for primary and secondary outcome measures within each group and for differences in the change from pretreatment to posttreatment between the 2 groups (PHOENIX and EUC). Though CIs obtained as estimates of variability for the relevant outcome measures were wide, as expected from a feasibility study, they provided reasonable estimates as input for the determination of effect sizes in future trials. Given that estimates from small studies carry uncertainties for the calculation of sample size for future studies, we plan to carry out sensitivity analyses to assess deviations from variability assumptions, as suggested by Julious and Owen [36]. Future investigations will explore the effects of demographic (age, race/ethnicity, gender, education, income, and living situation) and clinical (injury level, injury severity, time since injury, stigma, anxiety, and depression) characteristics, as well as potential mediating (self-efficacy, social support, and patient activation) variables on community participation and QOL through inclusion as

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adjustment variables; thus, we piloted the collection of these variables in this study.

Results

PN training was completed and IRB approval for the study was obtained in August 2018. The first participant was enrolled in early November 2018. Due to the pattern generated by the automated randomization feature in REDCap, 8 out of 12 participants in the first wave of the study were randomized to the active intervention, and 4 were randomized to the waitlist arm. By the end of November, our PNs had reached their maximum capacity of 2 participants each; thus, we paused enrollment and placed interested individuals on a study enrollment waitlist. As consented participants completed the active intervention, additional participants were consented and enrolled. The final participant postintervention interview was completed in August 2020, and a debriefing focus group with PNs was completed in November 2020. Initial analysis of feasibility and outcome data was completed in September 2021. The study results have been disseminated to community partners involved in the development of the PHOENIX intervention, and the multimedia educational content (Figures 2 and 3) is available on the SCSCIA website via Vimeo [19] since the discontinuation of the iTunes U platform by Apple in 2021. The findings will be submitted to peer-reviewed journals and presented at academic conferences [37]. An analysis of the results is being finalized, and the results are expected to be published in 2023.

Figure 2. PHOENIX online educational content: Vimeo website landing page. PHOENIX: Peer-supported Health Outreach, Education, and Information Exchange.

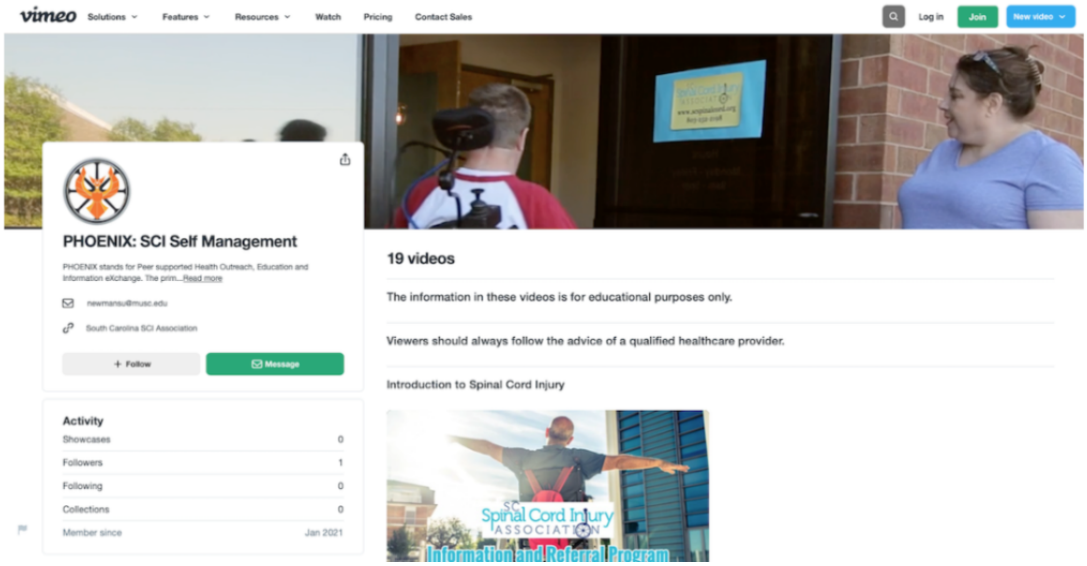
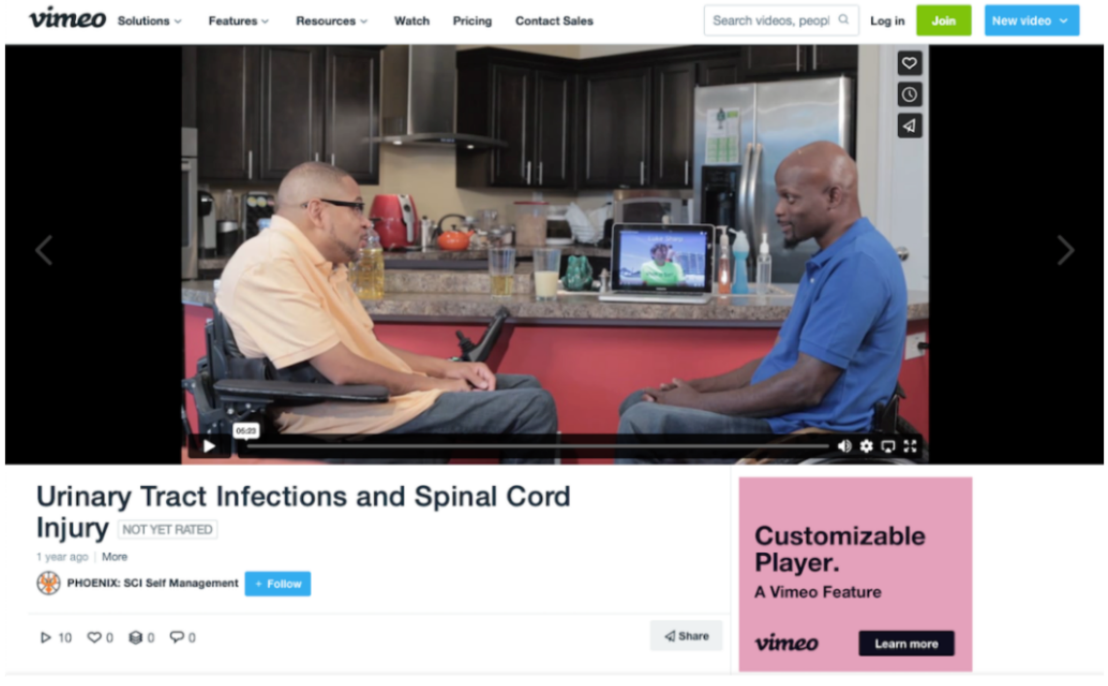


Figure 3. PHOENIX online educational content: Vimeo website educational video example. PHOENIX: Peer-supported Health Outreach, Education, and Information Exchange.



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Discussion

Principal Findings

Our research addresses an innovative combination of self-management and rehabilitation science, that is, the integration of peer-support, navigation, and telehealth to create an internet-based self-management intervention that is accessible, has extensive reach potential, and is designed to address the chronic consequences of an often permanently disabling injury with great individual and community burden. Use of a community-engaged research approach helps to ensure that the PHOENIX intervention is designed to be highly relevant to the unique needs of individuals with SCI, and that the study design and procedures are acceptable to the participant population. In congruence with the purpose of feasibility studies, the objective of this study is not to test for efficacy but to determine whether the PHOENIX intervention and the study design can be feasibly implemented, and to obtain estimates of the variability of relevant outcome measures. The field testing of the PHOENIX intervention through a randomized pilot trial using a waitlisted control group will facilitate the identification of potential logistical and methodological issues of both intervention implementation and study procedures. Specifically, our pilot trial is designed to evaluate aspects of feasibility and acceptability systematically, inform refinement of intervention components and delivery, and strengthen study procedures and processes required to conduct a robust future large-scale trial. Subsequent rigorous testing of the intervention will ultimately contribute to the scientific knowledge base regarding effective community-based self-management following a traumatic disabling injury, particularly those for which paralysis is central. This line of research will provide valuable information to support our long-term goal of developing an intervention that integrates online educational content and support from PNs through telehealth in order to promote effective self-management after SCI and ultimately increase the capacity of individuals with SCI to maintain health and participate in the community as desired.

Possible Challenges, Limitations, and Solutions

Designing and implementing a community-based trial using participatory methods with a historically vulnerable population while maintaining scientific rigor are quite challenging. We will attempt to maintain internal validity and minimize selection bias through randomization and by inviting all potentially eligible participants to join the study. We will report the demographic characteristics of our study participants and will compare these with published characteristics of the target group. We did not identify a specific time since injury in our recruitment criteria, as we did not want to eliminate the possibility of recognizing potentially unique needs related to SCI of a long duration. Regarding external validity, we recognize that the results of this pilot study cannot be generalized to the entire population with SCI but may be representative of the target population of people with SCI residing in the study area to the extent that those who volunteer to participate in our study sample are representative of this target population. We will monitor issues related to intervention fidelity and feasibility that can inform strategies to minimize threats to internal and external validity.

Conclusion

The results of this study will provide evidence from community-engaged research guided by people with SCI and SCI service providers to inform future development, refinement, testing, and dissemination of effective and scalable self-management strategies for people with SCI.

Acknowledgments

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Data Availability

The data sets analyzed during this study are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Example REDCap (Research Electronic Data Capture) form: Peer navigator documentation of study visits.
[PDF File (Adobe PDF File), 79 KB - resprot_v12i1e42688_app1.pdf]

Multimedia Appendix 2
Peer-review report by the National Institute on Disability, Independent Living, and Rehabilitation Research (NIDILRR) - Field Initiated Projects Program (Research) Grant Competition (Washington, DC).
[PDF File (Adobe PDF File), 1166 KB - resprot_v12i1e42688_app2.pdf]

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Abbreviations

EUC: enhanced usual care
IRB: Institutional Review Board
PHOENIX: Peer-supported Health Outreach, Education, and Information Exchange
PN: peer navigator
QOL: quality of life
REDCap: Research Electronic Data Capture
SCI: spinal cord injury
SCI-QOL: Spinal Cord Injury-Quality of Life
SCSCIA: South Carolina Spinal Cord Injury Association

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Protocol

Effectiveness of a Patient-Centered Assessment With a Solution-Focused Approach (DIALOG-A) in the Routine Care of Colombian Adolescents With Depression and Anxiety: Protocol for a Multicenter Cluster Randomized Controlled Trial

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Abstract

Background: Colombia is a middle-income country in South America, which has historically had high rates of mental health problems, coupled with a scarcity of mental health care. There is growing concern for the mental health of the adolescent population within this region. There is a significant treatment gap for young people, especially those living in the most vulnerable areas. DIALOG+ is a low-cost patient-centered intervention that can potentially improve the delivery of care and quality of life for adolescents with mental health problems.

Objective: This exploratory randomized controlled trial aims to evaluate the effectiveness, acceptability, and feasibility of an adapted version of the DIALOG+ intervention (DIALOG-A) in the community treatment of Colombian adolescents with depression and anxiety.

Methods: In total, 18 clinicians and 108 adolescents will be recruited from primary health care services in Bogota and Duitama, Colombia. Clinicians will be randomized 2:1 to either the intervention (12 clinicians:72 adolescents) or control group (6 clinicians:36 adolescents). In the intervention arm, clinicians will use DIALOG-A with adolescents once per month over 6 months. The control arm will continue to receive routine care. Outcomes will be measured at baseline, 6 months, and 9 months following randomization. Semistructured interviews with all clinicians and a subset of adolescents in the intervention arm will be conducted at the end of the intervention period. Quantitative and qualitative analysis of the data will be conducted.

Results: Trial recruitment was completed toward the end of October 2022, and follow-up is anticipated to last through to October 2023.

Conclusions: This is the first study to test an adapted resource-orientated intervention (DIALOG-A) in the treatment of adolescents with depression and anxiety attending primary care services. If the results are positive, DIALOG-A can be implemented in the routine care of adolescents with these mental health problems and provide valuable insight to other middle-income countries.

Trial Registration: ISRCTN Registry ISRCTN13980767; https://www.isrctn.com/ISRCTN13980767?q=ISRCTN13980767

International Registered Report Identifier (IRRID): DERR1-10.2196/43401

(JMIR Res Protoc 2023;12:e43401) doi:10.2196/43401

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KEYWORDS

randomised controlled trial; adolescent; mental health; depression; anxiety; telemedicine; primary health care; Colombia

Introduction

Background

Currently, an estimated 5.2 million adolescents are living in Colombia. During adolescence, physical, emotional, and social changes make individuals more vulnerable to mental health problems. Worldwide, and in Columbia, adolescence also marks the beginning of relationships and the emergence of sexuality, with a mature body capable of exercising it [1,2]. All these circumstances are intensified when adolescents live in an area with a history of conflict, displacement, inequality, poverty, violence, and lack of opportunities.

The internal conflict and violence experienced in Colombia for more than 50 years has led to the forcible displacement of 8.2 million individuals since 1985 [3], and a high proportion of the population is living in extreme poverty, which is currently estimated to be 12.2% (per the National Administrative Department of Statistics) [4]. This has contributed to fragile neighborhoods, particularly within urbanized inner-city areas, and deprived rural communities [3,4]. This complex picture has led to an increase in mental health illness among adolescents, including a rise in the prevalence of depression and anxiety, with a 1-year estimate of 4%-5% [5,6].

In Colombia, anxiety disorders are the most frequent, with an estimated prevalence of 15%-20%, and with rates reported to be as high as 31.9% among individuals aged between 13 and 18 years [7]. Similarly, rates of anxiety and depression are also commonly high among people aged 12 to 17 years. Using the Self-Reporting Questionnaire to assess this population, 13% of adolescents screened positive for depression [8,9].

Despite the high prevalence rates and long-term impacts of depression and anxiety, only half of the adolescents diagnosed with anxiety and depression in low- and middle-income countries (LMICs) access treatment, with a smaller percentage (20.5%) receiving at least the minimum standard of care. Consequently, less than 12% of adolescents in LMICs such as Colombia receive even minimally adequate treatment, pointing to an issue of both access and quality [10,11]. In Colombia, one of the most relevant barriers to mental health services delivery is a lack of sufficiently trained professionals [12,13]. Where resources are available, they tend to be distributed unevenly, concentrated in large cities, and fail to reach low-income or rural areas. Hence, low-cost, generic interventions that can be delivered by a range of staff (including those beyond the mental health system) are urgently needed to tackle depression and anxiety and ultimately improve adolescent health [14-16].

DIALOG+ is a technology-assisted and resource-orientated intervention based on quality-of-life research, patient-centered communication, and solution-focused therapy. Within DIALOG+, patients use a tablet to rate their satisfaction with 8 life domains (*mental health*, *physical health*, *job situation*, *accommodation*, *leisure activities*, *friendships*, *relationship with family/partner*, and *personal safety*) and 3 treatment aspects (*medication*, *practical help*, and *meetings with professionals*). This is followed by a 4-step solution-focused approach to identify and harness the existing resources available to the patient to address these concerns and improve their quality of life. This tool was established as an effective intervention for adults with mental health problems following a sustained program of research including multiple clinical trials [17-19].

Within a cluster randomized controlled trial (RCT) conducted across 6 European countries, regular use of the initial form of DIALOG+ over a year led to a better quality of life, fewer unmet needs, and higher treatment satisfaction for patients with psychosis. Following further modifications, DIALOG+, delivered once per month over 6 months, was compared to an active control in a pragmatic RCT involving 49 clinicians and 178 patients diagnosed with psychosis. Patients in the experimental group had a significant improvement in quality of life and lower general psychopathological symptoms after 3, 6, and 12 months. They also had fewer unmet needs and a better objective social situation. The effect size for improvements in quality of life ranged from 0.30 (95% CI 0.02-0.58) at 3 months to 0.32 (95% CI 0.06-0.58) at 12 months. Furthermore, DIALOG+ saved the National Health Service £1345 (US $1610.16) per patient, mainly due to fewer inpatient days required by the experimental group [17-19]. However, research has not assessed whether the intervention may also be effective for adolescents with common mental disorders.

Study Aims and Objectives

This planned exploratory cluster RCT sits within the context of a larger research program called “Building resilience in adolescence - improving quality of life for adolescents with mental health problems in Colombia (BRiCs).” This is a collaborative project between Queen Mary University of London (London, the United Kingdom) and the Pontificia Universidad Javeriana of Bogota (Bogota, Colombia), which aims to improve health outcomes and quality of life for the adolescent population with depression and anxiety in Colombia. During the initial phase of the project, semistructured interviews and focus groups were conducted alongside a pilot study to adapt the existing intervention (DIALOG+) for use with adolescents [20]. The new intervention is called DIALOG-A.

Given this background, the overall aim of this study is to evaluate the effectiveness of DIALOG-A in the community treatment of adolescents with anxiety and depression in Colombia.

Methods

Study Design and Setting

A multisite, exploratory cluster RCT will be conducted to assess the effectiveness, acceptability, and feasibility of DIALOG-A for adolescents with anxiety or depression. In total, 18 clinicians and 108 adolescents will be recruited from primary health care services in Colombia and outcomes measured at baseline, 6 months, and 9 months following randomization.

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The 3 sites included in this RCT in are based in 2 cities: Bogota and Duitama. Bogota is the capital city of Colombia, with 7.9 million inhabitants. Duitama, in contrast, is a small city of approximately 128,400 inhabitants in a rural location. Community mental health care is provided by primary health centers, which include an adolescent-friendly service. The population within Duitama is traditionally rural where poverty, alcohol intake, adult illiteracy, and family violence are common. Almost all the adolescents that use health services on this site belong to low socioeconomic status [21,22].

Participants

Inclusion Criteria

The inclusion criteria for clinicians will be as follows: (1) being aged 18 years or older, (2) having a medical qualification as a general practitioner or pediatrician, (3) having regular contact with adolescent patients with anxiety and depression, (4) having at least 3 months of experience in working with adolescents, and (5) having no plans to leave their current position within the next 6 months.

The inclusion criteria for adolescents will be as follows: (1) being aged 13 to 16 years; (2) currently experiencing anxiety and depression, which is defined as a cutoff score of ≥7 on the Self-Reporting Questionnaire [23]; and (3) having the capacity to provide informed assent.

Exclusion Criteria

The exclusion criteria for adolescents will be as follows: (1) having severe mental illness (psychosis, bipolar disorder, or schizophrenia), (2) having cognitive impairment or severe learning disability, and (3) being unable to speak and understand Spanish.

Recruitment and Informed Consent

Each study site will include a coordinator who will recruit the clinicians for the study. A research assistant will recruit the adolescents, guide all participants through the informed consent process, and assess the outcomes at 3 defined time points (baseline, 6 months, and 9 months post randomization). A wider administrative staff member will schedule the follow-ups and provide the clinicians' caseload to the research assistant to identify potential adolescent participants.

Clinicians

Each clinical site was identified from the national network of public and private primary care centers that provide care to the adolescent population of Colombia. An in-person meeting was arranged between the potential clinicians and study coordinators of each study site.

Eligible clinicians will provide their informed consent by signing and dating an electronic informed consent form via the Research Electronic Data Capture (REDCap) data management platform.

Adolescents

With the support of the administrative staff, research assistants will check each physician's caseload to identify adolescent patients who meet the inclusion criteria. Potentially eligible adolescents will be then invited to a one-on-one meeting with the local site's research assistant to discuss the study in more detail and answer any questions. This meeting will also be used to verify whether the inclusion criteria are met and to obtain informed assent and consent from the adolescents and their parents or guardians, respectively. During the study period, new referrals to the clinics will be screened for eligibility, and potentially eligible adolescents will be contacted by a research assistant.

Both the research team and the participants will keep a copy of the signed informed consent or assent form via REDCap. The researcher's contact details will be provided on the informed consent form to allow participants to raise any questions or concerns they may have throughout the study. This process will take place before any data collection begins.

Intervention

The enrolled clinicians will be contacted and invited to a web-based meeting on a free videoconferencing platform such as Zoom or Microsoft Teams with a researcher who will re-explain the objectives of the RCT and answer any questions or concerns that are raised.

Clinicians randomized to the intervention arm will use DIALOG-A with the adolescents once per month for 6 months. Clinicians allocated in this arm will receive a tablet, with the DIALOG-A app already preloaded. Each DIALOG-A session will last approximately 20 minutes and will take place face to face with the clinician. Where it is not possible for a face-to-face consultation to occur, a web-based consultation will be conducted in line with standard care procedures within the health care service. In each session, the clinician will ask the patient to rate all the domains on the DIALOG scale, which will then be followed by the 4-step solution-focused approach. After completing the 6-month intervention with the DIALOG-A app, clinicians and adolescents can continue using the intervention depending on their needs, and this will be documented and considered in the analysis.

Treatment-as-Usual Control

The intervention group will be compared to treatment-as-usual control. Clinicians in the control arm will follow the routine care provided for adolescents accessing primary care services. The frequency of the consultations during the duration of the RCT will vary depending on the clinical criteria of the respective clinician and the adolescent; however, this will be, on average, once per month.

Training and Supervision

All clinicians in the intervention arm will receive training in DIALOG-A through one-to-one web-based sessions with a researcher, which will take between 45 and 60 minutes. During these training sessions, clinicians are provided with reading material, instructions, and examples on how to use the DIALOG-A app with adolescents [24]. Clinicians can contact any member of the local research team for further sessions and for advice or support at any time of the RCT. Refresher training will be provided to clinicians in the intervention arm depending on their needs, with a minimum of 2 refresher sessions provided throughout the RCT.

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All clinicians allocated to either the intervention or control arms will receive training in the diagnosis and treatment of adolescent depression and anxiety through an asynchronous web-based course. These training sessions include academic passages on anxiety disorders, mental health disorders related to trauma and stress, and mood disorders, which are developed by adolescent mental health specialists from Pontificia Universidad Javeriana. Clinical cases and discussion forums will be available as well. A final quiz with a minimum passing score of 80% must be completed by participating clinicians.

Randomization

To reduce the potential for contamination, the unit for randomization will be the clinician. Clinicians will be randomized 2:1 to either the intervention (12 clinicians:72 adolescents; to have DIALOG-A sessions once per month for 6 months) or to the treatment-as-usual control group (6 clinicians:36 adolescents; appointments scheduled as and when needed, without DIALOG-A or specific assessments). For existing patients, who are already on the caseload, adolescent participants will be recruited and baseline assessments conducted prior to their clinician being randomized. Individuals who are new to the service and are not on the existing caseload of a clinician will be randomly assigned to either the intervention or control arm and then to an appropriate clinician, following completion of the baseline measures. We will record the number of adolescent participants who are recruited and individually randomized.

Clinicians and adolescents will not be blinded to allocation due to the nature of the intervention. However, to reduce bias, randomization will be carried out by a blinded independent statistician at the Unit for Social and Community Psychiatry, Wolfson Institute of Population Health, Queen Mary University of London. Baseline data collection will occur before randomization, and all research assistants involved in outcome data collection will be blinded to allocation. We will additionally record the number of postrandomization recruits; for example, individuals who were recruited after their clinician has been randomized.

Proposed Sample Size

A formal sample size calculation was not conducted as the primary objective is to collect data required for a full trial protocol, including the information needed for sample size calculation. Estimates for adequate sample sizes for exploratory trials range from 24 to 50 per arm, with at least 30 individuals required to estimate the SD of the outcomes. This exploratory trial will include 108 patients to provide usable estimates from each site. Unbalanced 2:1 randomization favoring the intervention will ensure sufficient data about the experience with the DIALOG-A intervention. Randomization will be stratified by the site to include 12 clinicians at the 3 study sites in Bogota and 6 at the study site in Duitama to reflect differences in population size and available resources.

Quantitative Data

All participants (clinicians and adolescents) will be asked to complete a sociodemographic questionnaire at baseline. Clinicians will be asked to rate the Clinical Global Impression questionnaire after every appointment.

The primary outcomes will be collected at 6 months, with a further follow up of 9 months post randomization—these include symptoms of depression measured using the 8-item Patient Health Questionnaire [25] and symptoms of anxiety measured using the 7-item Generalized Anxiety Disorder scale [26].

All secondary outcomes will be collected at baseline, 6 months, and 9 months (unless otherwise stated)—these include quality of life measured using the Manchester Short Assessment of Quality of Life [27], mental health symptom levels measured using YP-CORE [28], social support measured using the Multidimensional Scale of Perceived Social Support [29], empowerment measured using the Youth Efficacy/Empowerment scale [30], self-esteem measured using the Rosenberg Self-Esteem Scale [31], and economic outcomes measured using a modified Client Service Receipt Inventory [32].

In addition to the outcome data described above, we will collect process measures, including the number of DIALOG-A interventions performed, the date and duration of those sessions, the scores obtained on the DIALOG scale within each session, key topics discussed during the 4-step approach, and what actions were agreed upon. The DIALOG-A app on the tablet is able to capture the data required. This information will be synchronized to a server that the research team can access.

Qualitative Data

A subset of adolescent participants (n=20) and all clinicians (n=12) randomized to the intervention arm will be invited to complete an in-depth qualitative interview after the 6-month assessments (time point at the end of the intervention period) to capture and discuss their experience of delivering or receiving DIALOG-A. Interviews will focus on the barriers and facilitators of attending intervention sessions, suggested adaptations, trial procedures, practical implementation in the study sites, and potential processes of change. These interviews will be audio-recorded, transcribed verbatim, and further analyzed.

Statistical Analysis

The analysis of data will be discussed and agreed upon with the local and international research teams, with a statistical analysis plan developed by the statistician and signed off by trial steering committee. The local research team will take a leading role in the management and analysis of the data. Data analysis will not be conducted prior to signing off and blinding of the members of the research team, including the statistician responsible for the analysis, who will remain blinded throughout.

Quantitative Data Analysis

The number of approached and screened participants, those who refused participation, and those who could not be contacted will be recorded. The analysis will assess the number of intervention sessions received by participants and will collect data on dropouts (including reasons for dropping out, if available) from treatment, which will inform the assessment of the acceptability of the DIALOG-A intervention.

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Descriptive statistics will be reported for sociodemographic data for all participants. Nominal and ordinal data will be presented as proportions (frequencies), whereas continuous variables will be described using measures of central tendency and those of variability. The latter will be selected in accordance with observed data distributions (parametric or nonparametric), which will be evaluated through normality tests and histograms (probability functions). To assess the effectiveness of the intervention, means and SDs (or median and IQR values) over the 3 time points (baseline, 6 months, and 9 months) will be calculated, and analysis will test the significance of the differences between the means (or other parameters) of outcomes measured. The primary outcome will be the scores on the 8-item Patient Health Questionnaire and the 7-item Generalized Anxiety Disorder scale at 6 months. Mixed effects multivariable logistic regression analysis will be conducted to assess the effect of the intervention on the primary outcome, while controlling for clustering. A full analysis plan will be developed prior to data analysis, which will consider which covariates should be adjusted for in the model, along with methods for dealing with missing data. Quantitative data analysis will be conducted using Stata (version 17; StataCorp).

Qualitative Data Analysis

Qualitative data will be analyzed using thematic analysis following the guidance of Miles and Huberman and will be conducted using NVivo qualitative analysis software [33]. All interviews will be audio-recorded and transcribed verbatim. A researcher will remove all identifying information from the transcripts, including any references to patients, clinicians, or local services.

An inductive approach will be used to provide new insights and a richer understanding of the data without using preconceived categories. Two members of the research team will first familiarize themselves with the transcripts. Open coding will be used (making notes and headings in the text to describe the content). Similar codes will be grouped under themes, and the identified themes and subthemes will then be checked and refined. Interrater reliability in applying second-level codes (or categories) will be calculated for 20% of the data.

Reporting of Adverse Events

For this RCT, we will adopt the World Health Organization's definition for an adverse event: "Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment" [34]. Adverse events and the need for urgent safety measures are not anticipated.

Adverse Events

Any adverse events will be recorded in the main research file and in the participant's clinical records, if appropriate, and the participant will be followed up by the research team. We will establish an adverse event registration form based on REDCap in which research assistants can make a report of any adverse event for the RCT.

Serious Adverse Events

Serious adverse events are those that are "unexpected" and will be reported in accordance with the regulations of the research ethics committee (REC) and other relevant regulations in Colombia.

Urgent Safety Measures

In the case of urgent safety measures being required, the local principal investigator (PI) will inform the UK PI and the REC of the event per the REC and other relevant requirements and guidelines.

Quarterly Safety Reporting

The local PI will send over quarterly reports as required by the REC, using their existing templates and guidelines. These will be additionally monitored by the international trial steering committee, who will assume the role of a data monitoring and ethics committee.

Overview of the Safety Reporting Responsibilities

The local PI will ensure that safety monitoring and reporting are conducted in accordance with the requirements of the REC and any other relevant organizations or institutions that are involved in overseeing and monitoring research activities in Colombia.

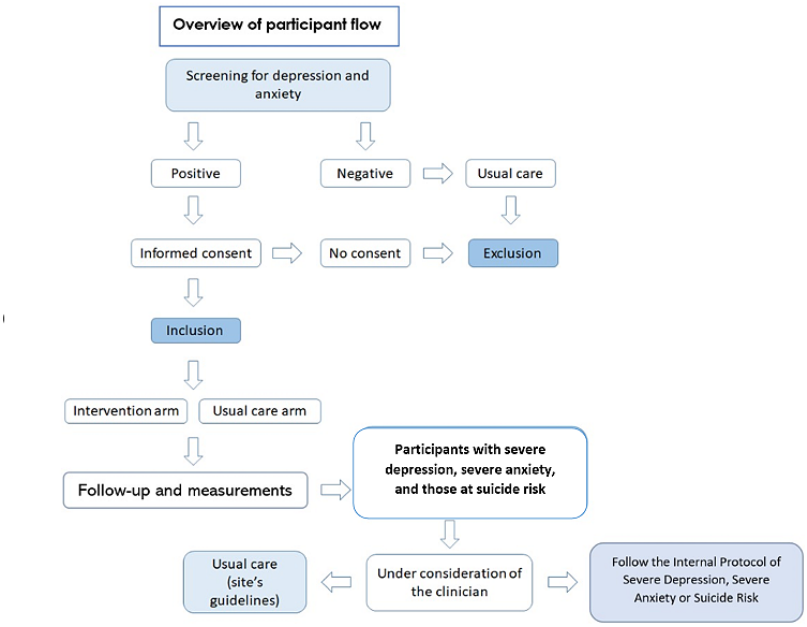
Safety and Suicide Risk Reduction

Participants who decline to participate but may have severe depression, severe anxiety, or are at a risk of suicide will be treated in accordance with each clinical site's procedures. For participants enrolled in the study who have been identified as having severe depression, severe anxiety, or being at a risk of suicide, the primary care physician will review and monitor the results of the screening. The participant will be managed in accordance with the primary care site's usual protocols and guidelines.

Additionally, if the participant meets the criteria for severe depression or anxiety, or is identified as being at risk of suicide, treatment may be either administered by or coordinated with a psychiatrist (in accordance with the Colombian clinical guidelines of best practices). According to the primary care physician, an optional case review could be performed by the academic psychiatrists involved in this study. Figure 1 summarizes the participant flow chart during the RCT.

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Figure 1. Withdrawal from the study.



Withdrawing From the Study

During the consent process, researchers will ensure that participants are aware of their right to decline participation at any stage of the research and that withdrawing participation will not affect their treatment or rights. Participants who withdraw will be able to ask that their data be destroyed and removed from the database if their withdrawal occurs before the start of data analysis.

If participants withdraw from the study, the research team will ask permission to contact them to take part in the postintervention qualitative interview to capture valuable information regarding reasons for withdrawal, which might be associated with the intervention. This will be explained to participants during the consent process, and participants' decisions to not be contacted for the postintervention interview will be respected. Participants who wish to withdraw from the intervention will also be asked if they wish to attend the follow-up research assessments, and their decisions to not participate will be respected.

If a participant wishes to withdraw from the study, researchers will record the date of withdrawal and reasons for withdrawal (if provided).

Ethics Approval

This study received approval from the local REC at Pontificia Universidad Javeriana in Bogota (approval number FM-CIE-0084-20). Consent forms from the parents or guardians and clinicians and assent forms from the adolescents will be obtained prior to the start of the study. Any changes to the protocol will be communicated to and approved by the local institutional review board and patients as appropriate.

Dissemination

The aims and impact of the program will be achieved through a comprehensive communication plan, which will inform the different stakeholders of the research findings as well as provide information relating to each of the program outputs. This will ensure that the new knowledge obtained translates into improved health outcomes. Target audiences include (but are not restricted to) adolescents and young people, policy makers, service managers, nongovernmental organizations, education, health and youth organizations, charities, and the public. To promote broader capacity building and initiate wider collaborations, we aim to disseminate findings across Colombia and the wider network with which Javeriana University is linked, the Latin American Clinical Epidemiology Network (LatinClen); and an additional network that Javeriana University is linked with, which trains young researchers in community mental health care across South America (RedMaristan).

International Trial Steering committee

An international trial steering committee has been set up, and the final protocol was approved by this committee. Lead investigators (CG and VB) are nonindependent members, alongside 6 independent members from the United Kingdom and Colombia. CG is the principal investigator in Colombia and VB is the principal investigator in the United Kingdom. The trial steering committee will periodically review the progress of the study and have agreed to take on the role of the data monitoring and ethics committee.

Results

Trial recruitment was completed toward the end of October 2022, and follow-up is expected to last through October 2023. We anticipate the outcomes of the trial will be reported by mid-2023 and the follow-ups by early 2024. The primary outcomes will be changes in depression [25] and anxiety [26] symptoms and the secondary outcomes will include changes in quality of life [27], mental health symptom levels [28], perceived social support [29], empowerment [30], self-esteem [31], and economic outcomes [32]. Furthermore, we will report on dropout rates and adverse events which take place during the trial.

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Discussion

Background

Depression and anxiety are leading causes of youth disability worldwide. This exploratory RCT will aim to repurpose an effective, low-cost intervention for the treatment of depression and anxiety in adolescence (DIALOG-A). The research focuses on Colombia where adolescents experience multiple stress factors such as internal displacement, violence, conflict, and deprivation. Improving the health outcomes of adolescents not only is a priority in its own right but also can aid the transferability of the intervention to other LMICs, where adolescents experience similar situations.

Strengths and Limitations

This study is the first to test the effect of DIALOG-A as a tool for use in primary care services for adolescents with depression and anxiety. One strength is the pragmatic design, which will enable us to adapt to the different logistics in the centers included in this RCT. One limitation, however, is that due to the characteristics of the intervention, blinding of the adolescent participants and clinicians will not be possible, which may result in the introduction of bias and a placebo effect. Additionally, the study is an exploratory study with unequal randomization (2:1 favoring the intervention). Although this will enable us to estimate potential interventions effects, a definitive trial will be needed to establish efficacy.

A potential benefit is that overall, the study has the potential to adapt a low-cost resource-orientated intervention for use in a vulnerable adolescent population. Additionally, for adolescents who will be involved in the testing of the modified intervention (DIALOG-A), this might lead to improved quality of life, social functioning, and symptoms. The RCT will also benefit the clinicians involved as they will be provided with training and supervision to enable them to implement the intervention. If results are successful, DIALOG-A can be implemented in the routine care of these adolescents in Colombia as it does not need the setting of new services or restructuring of preexisting organizations and is of low cost.

Acknowledgments

This study is funded by the Medical Research Council of the United Kingdom, the National Institute for Health Research of the United Kingdom, and UK aid (grant MR/S023674/1). These funding sources had no role in the design of the study and will not have any role in its conduction, interpretation, or dissemination.

Data Availability

Data will be available upon reasonable request. The approved consent forms did not specify that the data would be deposited in a public repository; hence, we will be unable to deposit the data. The deidentified participant data set will be made available from the corresponding author (VB, v.j.bird@qmul.ac.uk) upon reasonable request and subject to a data sharing agreement.

Authors' Contributions

VB, LO, and CG conceptualized the study. VB, DS, JR, and MR drafted the paper. All authors contributed to the refinement of the study protocol and approved the final version. All authors share responsibility for the submitted and published version. VB and CG obtained the funding for the study.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review report 1 by Medical Research Council (Swindon, United Kingdom).
[PDF File (Adobe PDF File), 35 KB - resprot_v12i1e43401_app1.pdf]

Multimedia Appendix 2
Peer review report 2 by Medical Research Council (Swindon, United Kingdom).
[PDF File (Adobe PDF File), 34 KB - resprot_v12i1e43401_app2.pdf]

Multimedia Appendix 3
Peer review report 3 by Medical Research Council (Swindon, United Kingdom).
[PDF File (Adobe PDF File), 34 KB - resprot_v12i1e43401_app3.pdf]

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Abbreviations

LMIC: low- and middle-income country
PI: principal investigator
RCT: randomized controlled trial
REC: research ethics committee
REDCap: Research Electronic Data Capture

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Protocol

Testing the Outcomes of a Smoking Cessation Smartphone App for Nondaily Smokers: Protocol for a Proof-of-concept Randomized Controlled Trial

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Abstract

Background: Nondaily smoking is a widespread, increasingly prevalent pattern of smoking, particularly in ethnic minority and vulnerable populations. To date, no effective treatment approach for this type of smokers has been identified.

Objective: This study aims to use a randomized controlled trial to evaluate proof-of-concept markers of the Smiling instead of Smoking (SiS) app, a smoking cessation smartphone app designed specifically for nondaily smokers. This app was developed iteratively and is now in its third version. Previous studies have demonstrated acceptability and feasibility when participants were onboarded in person (study 1) and remotely (study 2) and showed within-person changes in line with hypothesized mechanisms of change. This is the first randomized test of this app.

Methods: In total, 225 adult nondaily smokers will be asked to undertake a quit attempt while using smoking cessation support materials for a period of 7 weeks. Participants will be randomized to use the SiS smartphone app, the National Cancer Institute smartphone app QuitGuide, or the National Cancer Institute smoking cessation brochure "Clearing the Air." Participants will take part in a 15-minute scripted onboarding phone call during which study staff will introduce participants to their support materials. Survey links will be sent 2, 6, 12, and 24 weeks after the participants' initially chosen quit date. The primary outcome is self-efficacy to remain abstinent from smoking at treatment end, measured using the Smoking Self-Efficacy Questionnaire. Secondary outcomes cover several domains relevant to treatment development and implementation: treatment acceptability (eg, satisfaction with smoking cessation support, measured using the Client Satisfaction Questionnaire, and app usability, measured using the System Usability Scale); treatment feasibility (eg, measured using the number of days participants used the SiS or QuitGuide app during the prescribed treatment period); and, in an exploratory way, treatment efficacy assessed using self-reported 30-day point prevalence abstinence.

Results: Recruitment began in January 2021 and ended June 2022. The final 24-week follow-up was completed in January 2023. This trial is funded by the American Cancer Society.

Conclusions: This study is designed to test whether the prescribed use of the SiS app results in greater self-efficacy to abstain from smoking in nondaily smokers than commonly recommended alternative treatments and whether the SiS app treatment is

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acceptable and feasible. Positive results will mean that the SiS app warrants testing in a large-scale randomized controlled trial to test its effectiveness in supporting smoking cessation in nondaily smokers. The design of this study also provides insights into issues pertinent to smoking cessation smartphone app treatment development and implementation by measuring, in a randomized design, markers of treatment satisfaction, engagement with the technology and content of the treatment, and adherence to the treatment plan.

Trial Registration: ClinicalTrials.gov NCT04672239; https://clinicaltrials.gov/ct2/show/NCT04672239

International Registered Report Identifier (IRRID): DERR1-10.2196/40867

(JMIR Res Protoc 2023;12:e40867) doi:10.2196/40867

KEYWORDS

mobile health; mHealth; smartphone; smartphone app; smoking; smoking cessation; nondaily smoking; positive psychology; happiness; positive affect; clinical trial; feasibility; acceptability; app use; mobile phone

Introduction

Background

Cigarette smoking remains the number 1 cause of preventable disease and death in the United States, responsible for 16 million current cases of smoking-related diseases [1]. Although the prevalence of smoking has steadily declined over the past few decades, in part because of expansive public health efforts, taxation and indoor smoking policies, and accessibility to evidence-based cessation tools, the prevalence of nondaily smoking is steadily increasing. Currently, 25.4% of all adult smokers are nondaily smokers, a jump from 20.2% in 2008 [2]. Nondaily smoking has been a recognized public health issue for >10 years [3], yet the knowledge gap about treating nondaily smokers has remained largely unchanged, presenting a significant barrier to supporting this growing population of smokers in their cessation efforts [4]. However, knowledge has been gained that underscores the urgency of addressing nondaily smoking.

First, the detrimental health impact of nondaily smoking has now been clearly demonstrated. Nationally representative data have shown that, despite smoking a low number of cigarettes per month, nondaily smokers are exposed to substantial concentrations of carcinogenic nitrosamines [5]. Individuals who smoke as little as 6 to 10 cigarettes per month have a higher all-cause mortality risk than never smokers [6]. For individuals who smoke 11 to 30 cigarettes per month, the mortality risk compared with never smokers increases by 72%, and the median life expectancy decreases by 5 years [7]. Nondaily smokers are also at greater risk of cancer, heart disease, and respiratory disease [6].

Second, nondaily smoking is disproportionally prevalent in disadvantaged and vulnerable groups. Nondaily smoking is consistently highest among non-Hispanic Black individuals [8,9]. Nondaily smoking is also increasingly prevalent among adults with mental health and substance use problems [10], 2 groups with substantially higher smoking prevalence rates (35.8% in adults with serious psychological distress [11] and 65%-87% in individuals with substance use disorders [12]) than the general population (15.5%) [11]. Thus, failure to address nondaily smoking contributes to and further widens existing health disparities.

A promising method of engaging and meeting the needs of nondaily smokers are smartphone apps. Nondaily smokers are motivated to quit smoking, more so than daily smokers [13-15], with more recent and planned cessation efforts [14,16-18]. However, similar to daily smokers, nondaily smokers frequently fail in their quit attempts [19], demonstrating their need for smoking cessation support. Traditional treatment options fail to appeal to nondaily smokers, as evidenced by their lower rates of seeking or receiving formal smoking cessation treatment [13,14,20,21]. For nondaily smokers, many of whom resist labeling themselves as *smokers* [22-24], smartphone apps represent a low-barrier method for receiving smoking cessation support that invokes less treatment resistance than more traditional smoking cessation treatments [20].

Smartphone apps for smoking cessation have been increasingly prolific in recent years. Currently, there are an estimated 490 English-language smoking cessation apps on the market, downloaded an estimated 33 million times [25]. Despite this high number, a systematic review conducted in Australia found only 6 “high quality” smoking cessation smartphone apps [26]. None of these 6 identified apps specifically addressed nondaily smoking. A recent Cochrane review identified 5 randomized controlled trials (RCTs) on smoking cessation smartphone apps [27]. None of these tested apps addressed nondaily smoking.

To address this need, our team developed a smoking cessation smartphone app specifically for nondaily smokers, the “Smiling instead of Smoking” (SiS) app. Building on research that found that nondaily smokers did not view nicotine addiction as relevant to their efforts to quit but instead viewed themes related to a positive self-identity and wellness as more important [28], we built an app that focused on fostering the experience of positive emotions. This treatment approach was inspired by the development of positive psychotherapy for smoking cessation [29,30]. The app’s overall conceptual model, as described elsewhere [31,32], is based on Social Cognitive Theory [33], in which goal setting, self-efficacy, and knowledge are leveraged to support behavior change.

Our app development plan entailed a staged process consisting of 3 studies. In study 1, we tested feasibility and acceptability in a local sample of nondaily smokers [31]. In this study, nondaily smokers interacted with study staff in in-person meetings, both during onboarding to the app and 3 weeks after the prescribed app use period ended. The feedback gained from

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the study participants was used to make modifications to the app. In study 2, the feasibility and acceptability of version 2 of the app were tested, this time in a completely remote setting with nondaily smokers recruited nationwide [34]. Again, insights gained during this study were used to modify the app. In both studies, app use was high and sustained throughout the treatment period. Participants rated the app favorably in terms of its ease of use and usefulness. Longitudinal surveys demonstrated increases in the hypothesized direction for the underlying mechanisms of behavior change (ie, increased confidence, decreased urge to smoke, and less positive perceptions of smoking). Long-term self-reported abstinence rates were high (ie, 53% and 56% of the participants reported 30-day point prevalence abstinence at the 6-month follow-up in studies 1 and 2, respectively) [31,34]. These data supported the investment in a randomized trial.

Objectives

This study is study 3, which is a proof-of-concept RCT designed to test whether the SiS app successfully affects an early marker of smoking cessation success, namely, self-efficacy to abstain from smoking. We chose self-efficacy as our primary outcome variable as it is a causal component in many health behavior change theories and has been shown to be the primary mediator of conferring benefit in another mobile health (mHealth) intervention for smoking cessation, an SMS text messaging intervention [35]. The primary aim is to test for differences between randomized groups on the primary outcome, self-efficacy to remain abstinent, as measured at the end of treatment using the Smoking Self-Efficacy Questionnaire (SEQ-12) [36]. Self-efficacy to remain abstinent is hypothesized to be greater among participants in the SiS condition compared with 2 different but clinically relevant control conditions: the National Cancer Institute (NCI) smartphone app QuitGuide and the NCI smoking cessation brochure "Clearing the Air." The QuitGuide app was chosen as a comparator as it is a widely used, publicly available smoking cessation app that is part of the best-practice recommendations for treating smokers in the health care setting. Thus, it is a credible control for using a smoking cessation smartphone app. It controls for time, attention, and modality of delivery of smoking cessation support. Clearing the Air was chosen as an additional comparator as, to date, there is no evidence to demonstrate that QuitGuide confers smoking cessation benefits. Although widely used and endorsed, QuitGuide has never been tested against a treatment-as-usual (TAU) control condition. Thus, by including the Clearing the Air group in the design, this RCT tests whether app support provides better smoking cessation support than the standard of care and, if so, whether the SiS app does so more effectively than the QuitGuide app. The secondary aim is to test for differences between randomized groups on secondary outcomes pertaining to treatment acceptability; treatment feasibility; and, in an exploratory way, treatment effectiveness in terms of smoking cessation outcomes. Also measured were the impacts on secondary proof-of-concept efficacy markers: positive affect, desire to smoke, and attitudes toward smoking.

Methods

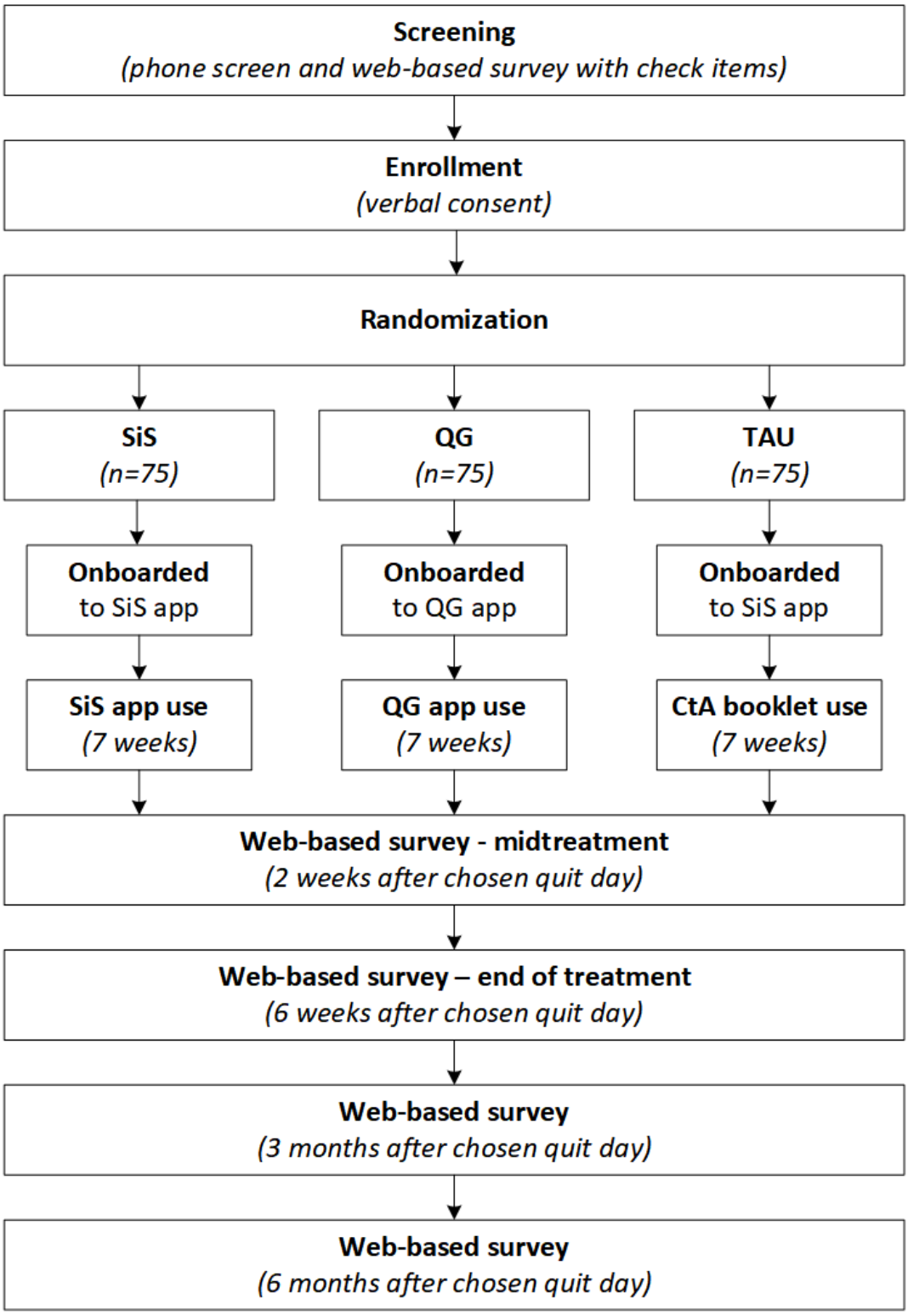
Overall Trial Design

Figure 1 shows the flowchart of this trial. This trial is a 3-group, randomized, fully remote, nationwide study. The trial aims to assess the efficacy of the SiS app version 3 in increasing smoking cessation self-efficacy in nondaily smokers compared with 2 control conditions representing current standards of care for providing low-barrier smoking cessation support. Participants in all treatment conditions will be asked to undertake a quit attempt while using smoking cessation support materials for a period of 7 weeks—1 week before and 6 weeks following their chosen quit date. Participants will be randomized to be onboarded to 1 of 3 conditions: the SiS smartphone app version 3, the NCI smartphone app QuitGuide, or the NCI brochure "Clearing the Air." The onboarding process is an approximately 15-minute–long scripted phone call during which study staff will guide participants through how to use SiS, QuitGuide, or Clearing the Air. The script is time-matched across conditions. In all 3 groups, the script covers setting the quit date, logging cigarettes, identifying triggers and strategies for those triggers, and managing challenging times. The onboarding process will conclude with study staff instructing participants to use SiS, QuitGuide, or Clearing the Air for the next 7 weeks.

Follow-up assessments are conducted via web-based surveys administered via REDCap (Research Electronic Data Capture; Vanderbilt University) [37] 2, 6, 12, and 24 weeks after the chosen quit date. Survey completion is remunerated at up to US $25 for the 2-, 12-, and 24-week survey (US $10 if check items are responded to incorrectly; these items are interspersed throughout the survey and ask participants to use the survey interface to indicate specific answers, eg, "Please set the slider to '0' to indicate 'not at all confident'") and US $50 for the 6-week survey, which is longer than the other surveys. The primary end point for this proof-of-concept RCT is end of treatment (ie, 6-week follow-up). The primary outcome is self-efficacy to remain abstinent from smoking, as measured by the SEQ-12 [36]. Secondary outcomes are shown in Table 1.

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Figure 1. Flowchart of the trial protocol. CtA: Clearing the Air; QG: QuitGuide; SiS: Smiling instead of Smoking; TAU: treatment as usual.



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Table 1. List of measure outcomes and their assessment schedule.

Type of measure and specific measure	Week of study				
	0	2	6	12	24
Primary outcome					
SEQ-12[a]	✓	✓	✓	✓	✓
Secondary outcomes					
Treatment acceptability					
Satisfaction with smoking cessation support (CSQ-8[b])			✓		
SUS[c] (SiS[d] or QG[e] only)			✓		
App likeability and satisfaction (SiS or QG only)			✓		
Treatment feasibility					
Self-reported amount of time spent applying content			✓	✓	✓
Use of smoking cessation strategies during treatment period			✓		
Use of positive psychology strategies during treatment period			✓		
Perceived impact of SiS, QG, or TAU[f] on quitting			✓		
Actual app use—continuously recorded (SiS or QG only)	✓	✓	✓	✓	✓
Self-reported app use—weeks 0 to 2 (SiS or QG only)		✓			
Self-reported app use—weeks 3 to 6 (SiS or QG only)			✓		
Exploratory treatment effectiveness outcomes					
Self-reported 30-day point prevalence abstinence	✓	✓	✓	✓	✓
Cigarette reduction	✓	✓	✓	✓	✓
Exploratory outcomes (ie, secondary proof-of-concept efficacy outcomes)					
Positive affect					
PANAS[g]	✓	✓	✓	✓	✓
Desire to smoke					
Brief QSU[h]	✓	✓	✓	✓	✓
Attitudes toward smoking					
ATS[i]	✓	✓	✓	✓	✓
DCB[j]-Short Form	✓	✓	✓	✓	✓

[a]SEQ-12: Smoking Self-Efficacy Questionnaire.
[b]CSQ-8: Client Satisfaction Questionnaire.
[c]SUS: System Usability Scale.
[d]SiS: Smiling instead of Smoking.
[e]QG: QuitGuide.
[f]TAU: treatment as usual.
[g]PANAS: Positive and Negative Affect Schedule.
[h]QSU: Questionnaire of Smoking Urges.
[i]ATS: Attitudes Toward Smoking Scale.
[j]DCB: Decisional Balance Inventory for Smoking.

Ethics Approval

This protocol is consistent with the CONSORT-EHEALTH (Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth) checklist [38]. This study was registered with ClinicalTrials.gov (NCT04672239) and approved by the Mass General Brigham Institutional Review Board (protocol 2020P003466).

Trial Participants

Participants who meet all inclusion criteria and pass the screening process will be included in the trial. The eligibility criteria are (1) age of ≥18 years, (2) smartphone ownership

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(Android or iPhone only), (3) current nondaily smokers who smoke at least weekly and no more than 25 out of the past 30 days, (4) lifetime history of having smoked ≥100 cigarettes, (5) willingness to make a smoking quit attempt as part of this study, and (6) currently residing in the United States. The screening process entails a screening phone call with study staff during which the eligibility criteria are assessed, followed by a web-based survey containing check items that test that screening participants are able to complete web-based surveys. Incorrectly completed check items render a participant ineligible for the study. Under unusual circumstances (eg, a participant reports a technical glitch to the study team), the study team will review the survey to evaluate the time spent on the survey and consistency of survey responses across phone-screen answers and the survey and across measures and, if consistent, may proceed with enrollment of the participant. Participants will also be required to provide contact information for 1 to 2 contacts who can assist study staff in locating participants for follow-up surveys. After screening, study staff will ask screening participants to choose their smoking cessation quit date. Study staff will then schedule the study enrollment call to occur 8 days before this date. Consent is obtained verbally during the enrollment phone call after nondaily smoking status is once again confirmed. A total of 225 nondaily smokers will be enrolled and randomized. To ensure adequate representation of racial and ethnic minorities, we will close enrollment to non-Hispanic White participants when 54.2% (122/225) of the planned total sample size have been enrolled as, nationwide, 54% of nondaily smokers are non-Hispanic White as per the 2014 National Health Interview Survey [39].

Randomization

Eligible participants will be randomly allocated in a 1:1:1 ratio to the 3 treatment conditions: SiS, QuitGuide, and Clearing the Air. Randomization is done using the PROC PLAN procedure in the SAS statistical software package (SAS Institute) with a block size of 4.

Treatment and Control Conditions

Participants in all treatment conditions are instructed to use the provided smoking cessation materials (ie, SiS, QuitGuide, or Clearing the Air) for 7 weeks starting on the day of their onboarding. They are also informed that they may use any additional smoking cessation support that they would like to use during this time.

Treatment Condition: SiS Smartphone App

Participants randomized to the treatment condition will use version 3 of the SiS smartphone app. We will first describe the app in its current form and then describe the ways in which version 3 differs from version 2. Adjustments that were made in transitioning from versions 1 to 2 are detailed in the study 2 outcome paper [34].

The SiS app is a smartphone app that engages participants in positive psychology exercises (Figure 2) and smoking cessation activities (Figure 3). It is part of an emerging generation of smoking cessation smartphone apps that provide smoking cessation tools within a specific therapeutic approach (eg, acceptance and commitment therapy [25,40]). In our case, the focus is on maintaining positive affect. Reduced positive affect during smoking cessation is a common experience of substantial magnitude [41]. The use of the SiS app seeks to offset this effect as experiencing positive affect during the process of smoking cessation is related to increased self-efficacy to abstain from smoking [42], decreased desire to smoke [43,44], and greater readiness to process self-relevant health information [45]. Engaging in positive psychology exercises is also pleasurable and, thus, may be a particularly effective way to keep users engaged with the app [31,34].

Each day, participants are asked to complete a positive psychology habit-building exercise. The goal of completing these exercises is for participants to develop a habit of noticing and savoring the positive experiences they encounter in everyday life. The app selects 1 of 3 exercises each day at random (ie, "3 Good Things," "Rose, Thorn and Bud," and "Savoring," as tested in prior work) [46]. If they have not completed this exercise by 7 PM, the app sends a push notification with a reminder to do so. App users are also encouraged to engage in a happiness-boost activity throughout the day as needed. The goal of the boost activity is to serve as a "rescue" activity during moments of craving or particularly low positive affect. Completing these activities is meant to provide a momentary boost in positive affect. To provide variety, the app randomly selects 1 of 11 possible happiness-boost activities each day as derived from the positive psychology literature. This differentiation between habit-building and boost activities was introduced in version 3. In version 2, there was a total of 5 happiness exercises. In study 2, participants commented that they would like to have more variety. Thus, in version 3, we limited the daily exercises to the 3 activities most suitable for habit-building and offered more variety through the introduction of boost activities. Throughout the app, information is provided to explain why participants are asked to complete positive psychology activities while quitting smoking, including through a feature called "Owl Wisdoms," which are push notifications that provide participants with relevant findings from the literature.

The smoking cessation content of the app is presented through the use of a number of app tools (Figure 3). The tools and information are in line with clinical practice guidelines for smoking cessation (ie, United States Clinical Practice Guidelines) [47] and are presented in a way that conforms to published recommendations for smoking cessation apps [48]. Each day, participants are asked to log their cigarettes or confirm that they were smoke-free. When participants log cigarettes, they are asked to indicate their reason for smoking by choosing from a list of common triggers or writing in their own response. After participants log cigarettes, they have access to a pie chart that offers personalized strategies matching their smoking triggers. Every 2 to 3 days, participants receive a push notification to complete a specific activity within the app that focuses on smoking cessation, called a "Behavioral Challenge." The timing of the "Behavioral Challenges" is anchored on the resettable quit date that participants specify in the app so as to provide participants with temporally appropriate smoking cessation activities as they progress. These "Behavioral Challenges" guide participants through the app's smoking

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cessation tools, which enable setting reminders, note keeping (ie, personal reasons for quitting), and using distractions to get through moments of craving (ie, a game called "Magma Bear") and provide information on the benefits of quitting smoking. For example, 5 days before their chosen quit date, participants receive a push notification to write down their personal reasons for quitting smoking; 2 days before the chosen quit date, they are asked to look at the pie chart of their triggers for smoking.

To make it easy for participants to remember what they should do on a given day, the SiS app version 3 provides an overview of all tasks required that day in a feature called "Today's Tasks" (Figure 4). This feature was added based on secondary data analyses of app use data collected during the SiS study 2 [49]. Results indicated that participants completed the assigned tasks with a relatively high completion rate (57% of behavioral challenges and 45% of daily happiness exercises). Tasks that were offered but not required were rarely completed (on <7 days). These findings suggested to us that prescriptive clarity may enhance app engagement and, thus, in SiS version 3, we incorporated a tool that enhances prescriptive clarity.

Figure 2. Screenshots of Smiling instead of Smoking version 3. The app prompts users to complete 1 happiness habit-building exercise every day and try out a happiness-boost activity, as needed. Information is provided throughout the app to explain the relevance of the positive psychology activities, including through a science-oriented feature called "Owl Wisdoms".

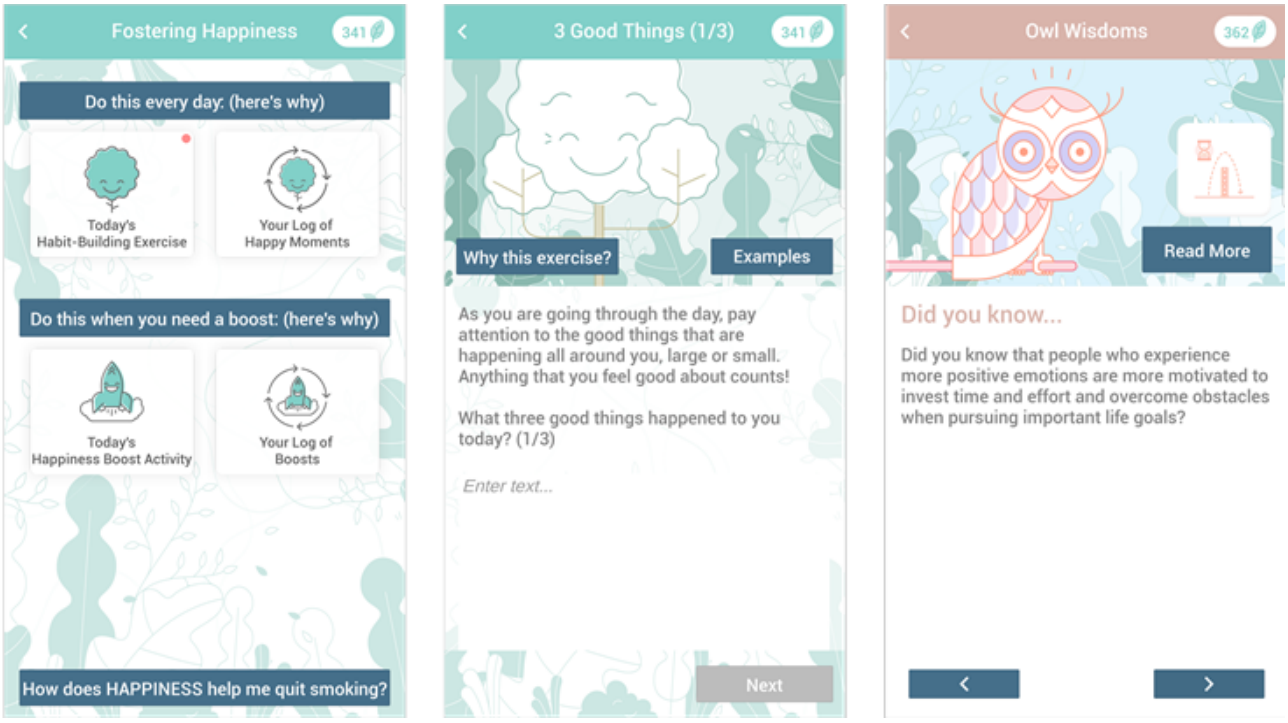
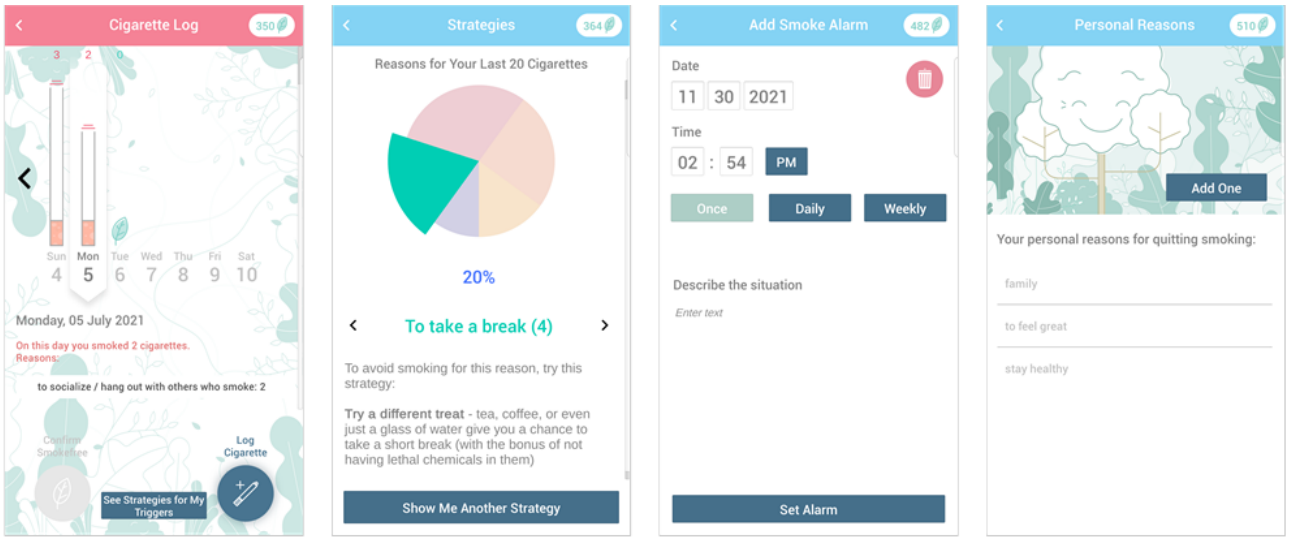
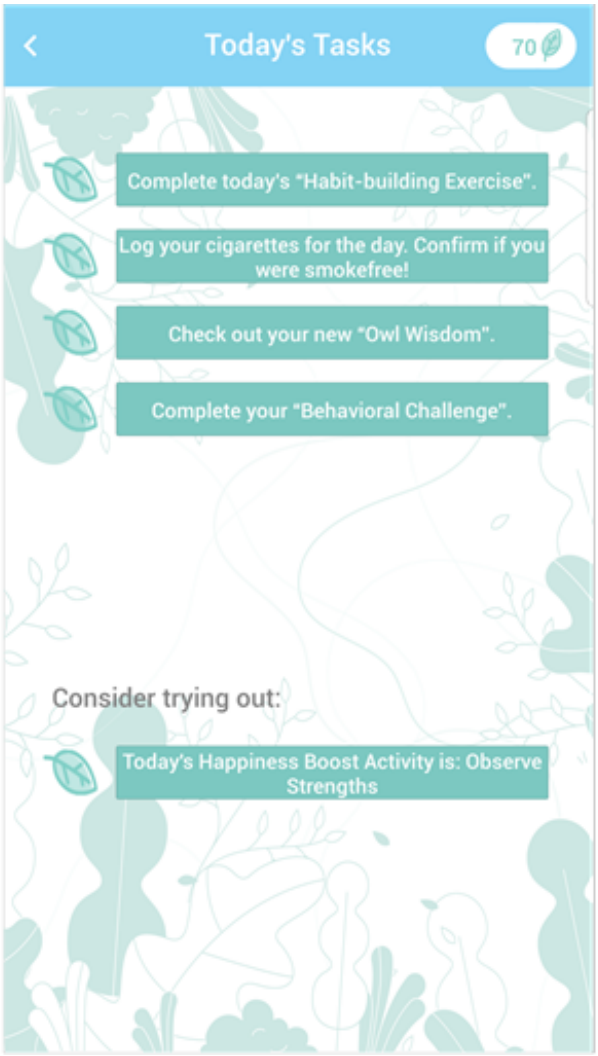


Figure 3. Screenshots from Smiling instead of Smoking version 3. While engaging in positive psychology content, app users are also prompted to complete smoking cessation activities within the app, including logging their cigarettes, which generates feedback on strategies for their triggers, and setting reminders to stay smoke-free, which reminds participants of their own personal reasons for quitting smoking.



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Figure 4. Screenshots from Smiling instead of Smoking (SiS) version 3. The "Today's Tasks" tool was added in version 3 of the SiS app to enhance prescriptive clarity.



Control Condition 1: NCI "QuitGuide" Smartphone App

Participants randomized to this control condition will use the NCI "QuitGuide" smartphone app. This smartphone app is 1 of 2 smartphone apps that the NCI currently has publicly available for use on their Smokefree.gov website. Referral to this website is recommended for treating smokers in health care settings [50]. QuitGuide is frequently used as a comparison app in smartphone app smoking cessation studies [40,51-55]. Although QuitGuide was not developed specifically for nondaily smokers, it targets both nondaily and daily smokers (ie, when downloading the app, users are asked to specify their smoking pattern, which includes both nondaily and daily patterns of smoking). Some SiS features have direct analogs in QuitGuide; others do not. The onboarding script leads QuitGuide users through the QuitGuide content in the same order as for SiS to the degree possible—setting the quit date (SiS and QuitGuide), happiness-promoting activities versus tracking mood and craving (SiS vs QuitGuide, respectively), guidance on quitting (via behavioral challenges in SiS vs "Learn to Quit" information in QuitGuide), logging cigarettes (SiS and QuitGuide), strategies for smoking triggers (pie chart in SiS and various graphs in QuitGuide), setting reminders (time-based in SiS and time- and location-based in QuitGuide), and as-needed tools (happiness-boost activities and suggested strategies in SiS vs tips in response to reporting craving or negative affect in QuitGuide). This control condition controls for time, attention, and modality of delivery of smoking cessation support.

Control Condition 2: NCI "Clearing the Air" Brochure

Participants randomized to this control condition will use the NCI booklet "Clearing the Air" [56]. This booklet has been used as a "treatment as usual" comparison condition in past RCTs evaluating phone-based mHealth smoking cessation technologies (ie, SMS text messaging). It remains a standard-of-care smoking cessation treatment today. Similar to SiS and QuitGuide, it is a low-barrier option for offering smoking cessation support. Unlike SiS and QuitGuide, it offers this support in a widely accepted booklet format rather than via mobile technology. During the scripted onboarding call, study staff will lead participants through the booklet's content in the same order as implemented in the SiS behavioral challenges (ie, reflecting on reasons to quit, informing about the benefits of quitting, logging smoking and its triggers, and formulating strategies for dealing with triggers). By comparing with this control group, it can be tested whether the SiS app provides an advantage over the currently existing standard of care. This is an important question for implementation.

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Measures

Primary Outcome Measure

Although, ultimately, the goal of engaging with a smoking cessation smartphone app is smoking cessation, we chose a process indicator toward that goal as the primary outcome of this proof-of-concept RCT. Namely, we selected self-efficacy to abstain from smoking as a process indicator of subsequent smoking cessation. Self-efficacy has been identified as the primary mediator through which an SMS text messaging intervention conferred smoking cessation benefits. Similar to our study, the latter trial used the "Clearing the Air" booklet as the control condition and showed that self-efficacy observed 1 month after the chosen quit date mediated group differences in smoking cessation at the 6-month follow-up [35]. In this study, self-efficacy to abstain from smoking will be measured using the SEQ-12 [36], a 2D 12-item self-report scale measuring a person's confidence in their ability to abstain from smoking when facing internal stimuli (eg, feeling depressed) and external stimuli (eg, being with smokers) on a 0 to 100 slider scale (ie, 0=*not at all confident that I can refrain* to 100=*extremely confident that I can refrain*). Scale scores are created by averaging across items and range from 0 to 100. Higher scores indicate greater self-efficacy to abstain from smoking.

Secondary Outcome Measures

This is the first randomized trial to evaluate the SiS app. As this is a proof-of-concept trial, our secondary aims cover several domains: treatment acceptability; treatment feasibility; and, in an exploratory way, treatment efficacy in terms of smoking cessation outcomes.

Treatment Acceptability

As an overall measure of treatment acceptability, we will assess participants' satisfaction with the smoking cessation support they will receive as part of the study. To this end, we will use the widely used Client Satisfaction Questionnaire. [57]. For this study, and with permission, we adjusted the wording of the introduction to this scale to clarify that the items refer to the smoking cessation support received as part of participating in this study. The wording of the 8 items will be used verbatim (eg, "How satisfied are you with the amount of help you received?"). Scores are summed across items and range from 8 to 32, with higher scores indicating greater satisfaction. For the 2 randomized groups using an app (SiS and QuitGuide), we will also assess the satisfaction with the apps from a technical standpoint. To this end, we will use the 10-item System Usability Scale, [58], as used in other studies on smoking cessation smartphone apps [59,60]. This 10-item scale provides a global view of subjective assessments of usability. To make clear that we are seeking feedback on the app and not on other aspects of the study, we have replaced the phrase "this system" (original scale) with "app" (modified scale; eg, "I found the app unnecessarily complex" 5-point Likert scale: 1=*strongly disagree* to 5=*strongly agree*). Scale scores range from 0 to 100, with greater scores indicating a more favorable perception of the usability of the app. To obtain an overall summary impression combining technical issues and smoking cessation support satisfaction, the survey will also include 2 stand-alone items: "How satisfied are you with the smoking cessation support this app provided you with?" (5-point Likert scale: 1=*very unsatisfied*, 2=*somewhat dissatisfied*, 3=*neither satisfied nor dissatisfied*, 4=*somewhat satisfied*, and 5=*very satisfied*) and "How much did you like using the smoking cessation app we asked you to use?" (5-point Likert scale: 1=*I strongly disliked using the app*, 2=*I somewhat disliked using the app*, 3=*I neither liked nor disliked using the app*, 4=*I somewhat liked using the app*, and 5=*I strongly liked using the app*). These scales and items will be assessed only once, at end of treatment (week 6).

Treatment Feasibility

To assess treatment feasibility, we will assess processes that are relevant across all 3 randomized groups and issues that are specific to app use. For all 3 groups, the end-of-treatment survey (week 6) will include scales to assess the degree to which participants applied the smoking cessation content delivered during treatment and the degree to which they practiced the type of positive psychology habits taught in the SiS app. Our hypothesis is that participants randomized to SiS will use taught smoking cessation strategies at least comparably with those in the QuitGuide and Clearing the Air groups and will use positive psychology strategies more frequently than QuitGuide and Clearing the Air participants, who are not taught these skills. We will assess the use of smoking cessation strategies using a list of 19 items developed for another randomized trial on smoking cessation [30]. Participants rate their agreement with statements about the support they received (eg, "I used the Smiling Instead of Smoking app/QuitGuide app/Clearing the Air pamphlet [logic-branched by treatment group] the way I was supposed to (in the days leading up to and following my quit attempt)") and the things they did while quitting (eg, "I avoided situations that would make me want to smoke"). Items are rated on a 5-point Likert scale (1=*strongly disagree* to 5=*strongly agree*). Higher scores indicate greater use of smoking cessation strategies. This scale also included items that referred to the positive psychology content of the intervention (eg, "I told myself that quitting smoking would eventually improve my moods, not make them worse" and "I focused on the good things that happened each day"). To assess the use of positive psychology techniques more directly, we will also use the Appreciation Scale [61]. This 18-item scale assesses the frequency with which one engages in thoughts and actions to heighten awareness of the blessings in one's life (eg, "I enjoy the little things around me like the trees, the wind, animals, sounds, light, etc.," rated on a 7-point frequency scale: 1=never to 7=more than once a day) and the degree to which one feels appreciative (eg, "I recognize and acknowledge the positive value and meaning of events in my life," rated on a 7-point agreement scale: 1=strongly disagree to 7=strongly agree). The score is created by sum scoring, with higher scores indicating a more appreciative mindset. As a subjective evaluation of the received treatment, participants will be administered 17 items to assess the impact of the treatment they received. The stem of the items is "The 'Smiling Instead of Smoking app, QuitGuide app, or Clearing the Air pamphlet [logic-branched by treatment group]..." which is followed by possible impacts (eg, "...gave me confidence that I can quit smoking," "...made me think it

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was worthwhile for me to quit," and "...helped me stay positive while quitting"). The same items were used to evaluate version 2 of the SiS app [34]. These scales and items will be assessed only once, at end of treatment (week 6). Finally, 1 treatment feasibility item will be administered in multiple surveys (weeks 6, 12, and 24). This item seeks to assess the degree to which participants engaged with the provided smoking cessation materials: "*During this past week, how much time did you spend applying or contemplating the content of the SiS app, QG app, or 'Clearing the Air'*?" (in minutes).

Regarding app use (SiS and QuitGuide groups only), passive data recording will be used that time-stamps each action participants take in the app. For QuitGuide, we will receive these data from the Smokefree.gov team. From these data, we will calculate the number of days the participants used the app during the treatment period. As objective reality and subjective experience can differ, the surveys will also ask participants to self-report app use. At week 2, they will be asked to report the number of days they used the app during weeks 0, 1, and 2. At week 6, they will be asked to report the number of days they used the app during weeks 3, 4, 5, and 6. In addition, they will be asked to self-report how many minutes per day they used the app.

Exploratory Treatment Effectiveness Outcomes

All surveys will include items to assess self-reported 30-day point prevalence abstinence. Participants will be asked the following—"what is your current smoking status?"—with the following options: "I smoke daily," "*I smoke non-daily (and have smoked in the past 7 days),*" "*I smoke non-daily (but have NOT smoked in the past 7 days),*" and "*I do not smoke at all.*" If a participant reports abstinence, they will then be asked, "have you been abstinent during the past 30 days?" (yes or no). If a participant does not report abstinence, they will be asked to indicate how many cigarettes they smoked over the past 7 days. From these data, we will code a binary indicator for self-reported 30-day point prevalence abstinence (yes or no) and calculate an indicator of cigarette reduction by subtracting the total number of cigarettes smoked in the week before baseline from the total number of cigarettes smoked in the past week.

Exploratory Outcomes (ie, Secondary Proof-of-concept Efficacy Outcomes)

Overview

As our secondary outcomes spanned several domains, including acceptability, feasibility, and exploratory estimates of gold-standard effectiveness markers, we designated secondary proof-of-concept efficacy outcomes as exploratory outcomes. Similar to our primary outcome, these outcomes measure constructs that, according to our conceptual model, should be affected by treatment and, in turn, should affect long-term smoking cessation. All these measures are self-report measures and are included in every survey. As proof-of-concept process markers, the primary end point of interest is the end of treatment. Treatment effects are hypothesized to have occurred at that point, with the hope that these impacts translate into subsequent smoking cessation success.

Positive Affect

The SiS app is designed to offset expected decreases in positive affect as smokers undertake a quit attempt [41]. Thus, if successful, positive affect should be higher among participants randomized to the SiS group by treatment end. To measure positive affect, we will use the 20-item Positive and Negative Affect Schedule [62]. Participants are given a list of 20 adjectives (eg, interested or distressed) and asked to rate to what extent they have experienced these states over the past week. Rating options range from 1 to 5 (1=*very slightly or not at all* to 5=*extremely*). A total of 10 items measure positive affect (ie, attentive, interested, alert, excited, enthusiastic, inspired, proud, determined, strong, and active), and the other 10 items measure negative affect. Positive affect items are sum scored to create the positive affect score, with a higher number reflecting a more frequent experience of positive affect.

Desire to Smoke

Previous research has indicated that experiencing positive affect during the process of smoking cessation is related to a decreased desire to smoke [43,44]. Although nondaily smokers are not nicotine-dependent, craving, or, rather, the desire to smoke, is the most common reason why nondaily smokers attempting to quit relapse to smoking during the 2 weeks after their chosen quit date [63]. Thus, reducing the desire to smoke is a meaningful outcome in supporting nondaily smokers with quitting. To measure the desire to smoke, we will use the 10-item Brief Questionnaire of Smoking Urges [64]. Participants rate items about their desire to smoke (eg, "A cigarette would taste good now" and "*I could control things better right now if I could smoke*") on a 7-point Likert scale (1=*strongly disagree* to 7=*strongly agree*). Items are sum scored to create the total score, with higher scores indicating a greater desire to smoke.

Attitudes Toward Smoking

Experiencing positive affect during the process of smoking cessation is related to greater readiness to process self-relevant health information, particularly information about the negative health effects of smoking [45]. In our previous studies on the SiS app, we conceptualized that this readiness would entail shifts in the appraisals of the pros and cons of smoking [31,34]. In these single-group studies, we found that positive appraisals of smoking decreased, as expected, but that negative appraisals stayed largely the same. In this study, we will measure these constructs in the same way, assessing both the participants' expectations of the effect of smoking on them using the Attitudes Toward Smoking Scale (ATS-18) [65] and the importance of these expectations on their decision to smoke using the Decisional Balance Inventory for Smoking (DCB)-Short Form [66]. The ATS-18 consists of 18 items that participants rate on a 5-point Likert scale (*1=strongly disagree* to *5=strongly agree*). These items address the adverse effects (eg, "Smoking is extremely dangerous to my health"), psychoactive benefits (eg, "A cigarette calms me down when I am stressed"), and pleasures (eg, "It feels so good to smoke") of smoking. The DCB consists of 6 items rated on a 0 to 100 slider anchored at 0=*not at all important* and 100=*extremely important* and asks participants the following: "HOW IMPORTANT is each statement to your decision to smoke

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RIGHT NOW?" Both the pros (eg, "Smoking cigarettes relieves tension") and cons (eg, "I'm embarrassed to have to smoke") of smoking are represented. For both the ATS-18 and DCB, items are sum scored to create subscale scores, with higher scores indicating greater endorsement.

Contextual Variables

At baseline, participants will be asked if they have ever tried to quit smoking (yes or no). If yes, they will be asked to indicate the number of previous quit attempts and what type of support they have used to quit smoking before (ie, group counseling, one-on-one counseling, quitline, web-based chat with a tobacco cessation specialist, website, social networking site for smoking cessation, SMS text message program, smoking cessation app, and medications). If they have previously used an app, they will be asked to indicate which one. In subsequent surveys, they will be asked which of these methods they have used since their onboarding call.

For descriptive purposes, the baseline survey will also include items on participants' demographics, past mental health diagnoses, smoking history, nicotine dependence (Fagerström Test for Nicotine Dependence), previous quit attempts, generalized self-efficacy (Generalized Self-Efficacy Scale), and personality (Single-Item Measures of Personality). Across time, also for descriptive purposes, participants will answer questions about their e-cigarette use, alcohol use, depression (Center for Epidemiological Studies Depression-10), generalized anxiety (Generalized Anxiety Disorder-7), capacity to experience pleasure (Snaith-Hamilton Pleasure Scale), optimism (Life Orientation Test-Revised, State Optimism Measure, and Brief State Optimism Measure), and coping style (Brief Coping Orientation to Problems Experienced).

Masking or Blinding

This proof-of-concept trial is not blinded. The same staff member who onboards participants to their smoking cessation materials may be the staff member reaching out via phone and email to remind participants to complete the surveys. However, contact with study staff is minimal and scripted. The initial survey invitations are automated using REDCap. Only surveys that are not completed within 3 days of the automated survey invitation will trigger a reminder email from the study staff, using an email template, and a phone call.

Sample Size

To select the sample size for this proof-of-concept trial, we were guided by one of the few mHealth smoking cessation studies that examined processes of smoking cessation over time. That study tested the effectiveness of an SMS text messaging intervention and, similarly to our study, used the "Clearing the Air" booklet as the control condition [67]. The study identified self-efficacy as the primary mediator of the observed salutary effect of the intervention on smoking cessation. Specifically, self-efficacy observed 1 month after the chosen quit date mediated group differences in smoking cessation at the 6-month follow-up [35]. The observed group difference between treatment and control at 1 month after the quit date on self-efficacy was Cohen d=0.66. Thus, we conservatively powered our proof-of-concept RCT to detect an effect size of Cohen d=0.50. As no trials have been published that test the effectiveness of QuitGuide, we assumed that QuitGuide would be as effective as Clearing the Air and that SiS would be more effective than either of them. Using SAS PROC POWER, we calculated that we would need a sample size of 64 per group to detect an effect of Cohen d≥0.50. Assuming a retention rate of 85%, we would need to enroll 75 participants per group to retain 64 by end of treatment. Thus, the total number of participants to be enrolled in this trial is 225 (3 randomized groups×75 participants to be enrolled in each group=225).

Analysis Plan

All successfully enrolled participants (ie, those who passed the screening process and were successfully onboarded to the assigned smoking cessation materials) will be included in the outcome analyses. Each follow-up survey will include 5 check items randomly interspersed throughout the survey. If a participant incorrectly responds to more than one of the 5 check items, this participant's entire survey for this time point will be considered unreliable and excluded from the analyses. If a participant incorrectly responds to only 1 of the 5 check items, the participant's data for the scale in which the error occurred will be considered unreliable and excluded from the analyses. All analyses will be conducted using SAS (version 9.4).

In this proof-of-concept RCT, the primary outcome is self-efficacy to abstain from smoking, as measured by the SEQ-12. The primary end point is end of treatment, which occurs 6 weeks after the originally chosen quit date. To test for differences between randomized groups, we will fit a fixed-effects repeated-measure model using PROC MIXED where observations are modeled as nested within persons. The predictors included in the model will be group (ie, SiS vs QuitGuide vs TAU), time (ie, baseline, week 2, week 6, week 12, and week 24), and the group×time interaction effect. A contrast statement will be used to derive the test statistic for the group comparison at week 6, our primary end point, given the overall longitudinal model. This contrast statement will test the null hypothesis that SiS=QuitGuide=TAU. If this null hypothesis is rejected (P<.05), we will conduct pairwise follow-up tests that compare the 3 possible pairwise comparisons (ie, SiS vs QuitGuide, SiS vs TAU, and QuitGuide vs TAU). Subscale scores can be computed for the SEQ-12 (ie, confidence to abstain from smoking in response to internal vs external triggers). For this trial, we consider the total SEQ-12 score as the primary outcome. We will also report outcomes on subscale scores.

The secondary outcomes of this proof-of-concept RCT are exploratory. Thus, we will not correct for multiple testing. We will fit 1 model per secondary outcome using an α of .05 for all analyses. To test for differences between randomized groups for outcomes that are assessed multiple times (ie, time spent applying content, app use, self-reported 30-day point prevalence abstinence, and cigarette reduction), our overall modeling approach will be the same as that for the primary outcome variable. That is, for each outcome, we will fit a fixed-effects repeated-measures model where observations are modeled as nested within persons. The predictors included in the model will be group, time, and the group×time interaction effect.

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However, the definition of the time effect varies across these secondary outcomes based on their assessment schedule. The distribution of the outcome variables also varies across these variables. Thus, we will implement this overall modeling approach for these variables but adjust the model to match the assessment schedule and distribution of the variable. To test for differences between randomized groups for outcomes that are only assessed at end of treatment (ie, satisfaction with smoking cessation support, system usability, app likeability and satisfaction, use of smoking cessation strategies, use of positive psychology strategies, and perceived impact of treatment), for each outcome, we will use a fixed-effects model where group is the only predictor and the score at end of treatment is the dependent variable. Histograms will be used to guide the selection of the most appropriate distribution. If the group effect is statistically significant (P<.05), we will conduct pairwise follow-up tests that compare the 3 possible pairwise comparisons (ie, SiS vs QuitGuide, SiS vs TAU, and QuitGuide vs TAU) using the Tukey adjustment. These follow-up analyses will not be necessary for secondary outcomes that are only assessed for the SiS and QuitGuide conditions.

For exploratory outcomes (ie, secondary proof-of-concept efficacy outcomes), we will use the same statistical approach as for the primary outcome but will match the analysis to the distribution of the variable under examination. For example, 30-day point prevalence abstinence will be a binary variable. Thus, we will use a binomial distribution with a logit link function.

Results

Recruitment began in January 2021 and ended June 2022 at this time. The final follow-up occured in January 2023. Specifically, the last partial follow-up response was collected on January 4, 2023, and efforts to obtain the rest of these participants' data ceased on January 6, 2023. We expect to publish the main outcomes of this study in summer 2023.

Discussion

This RCT will provide the first test of the SiS app versus relevant comparison conditions—the NCI smoking cessation brochure “Clearing the Air” and the NCI smoking cessation smartphone app QuitGuide. The primary outcome will be self-efficacy to remain abstinent, as measured using the SEQ-12. Secondary outcomes include treatment acceptability; treatment feasibility; proof-of-concept efficacy markers such as positive affect, desire to smoke, and attitudes toward smoking; and, in an exploratory way, treatment effectiveness in terms of smoking cessation outcomes. We hypothesize that participants using the SiS app will have higher self-efficacy to abstain from smoking than participants in either of the control conditions as the SiS app is specifically designed for nondaily smokers, whereas the other 2 comparison conditions are geared more generally toward daily smokers. In terms of acceptability and feasibility, we anticipate that participants using the SiS app will find the treatment at least as acceptable and feasible as the comparison conditions (ie, not worse). We further hypothesize that we may be able to detect differences in proof-of-concept efficacy markers as well as smoking cessation outcomes such that participants using the SiS app will have higher levels of positive affect, a lower desire to smoke, reduced prosmoking attitudes (eg, lower ratings of the psychoactive benefits of smoking, lower ratings of the pleasures of smoking, and lower ratings of the pros of smoking), and a greater self-reported 30-day point prevalence abstinence proportion at the end of treatment compared with both comparison conditions.

This study is innovative in several ways. First, the study results will indicate whether a fully powered test of the effectiveness of the SiS app is warranted. This is a vital contribution to future clinical trials. Currently, nondaily smoking is not addressed by clinical practice guidelines for smoking cessation and, thus, treatment recommendations for this increasingly prevalent pattern of smoking are not clear. Therefore, testing whether this novel treatment may warrant a larger, fully powered trial moves the field forward toward the critically important goal of providing empirically based smoking cessation support for nondaily smokers. This is especially important as other efforts to identify effective treatments for this group of smokers have so far been unsuccessful. Specifically, in recent years, nicotine replacement therapies have been tested, but studies have failed to show efficacy [68,69]. The SiS app uses a different treatment modality (mHealth rather than medication) and targets a different mechanism (bolstering positive affect rather than ameliorating withdrawal) and, thus, is a novel, promising treatment approach. If our study provides evidence that the SiS app promotes greater self-efficacy to abstain from smoking than the comparison treatments and if the study gives a positive indication of treatment acceptability and feasibility, we plan to submit a proposal for a fully powered RCT to test the efficacy of the SiS app in promoting smoking abstinence in nondaily smokers.

The results of this study will also be useful more generally to understand how people who smoke interact with smoking cessation self-help materials and how a smartphone app may confer benefits. This study includes numerous measures that provide insights into treatment acceptability and feasibility, both from the point of view of the user and based on observed behaviors that are passively recorded. The chosen measures address a diversity of aspects that are relevant to treatment development (eg, does the app successfully teach or prompt the use of smoking cessation behaviors? Does the app successfully engage users in positive affect–supporting behaviors?) and implementation (eg, do people like the treatment? Will they adhere to the treatment instructions? Do they perceive the treatment to be impactful?). To date, only a handful of studies have looked at these important indexes, and even fewer have done so in a randomized design.

A limitation of this study is the lack of biochemical verification of smoking status for entry into the study and to verify smoking abstinence at the end of treatment. At study entry, we will use several check items and consistency checks to evaluate whether interested participants are providing attentive, consistent, and detailed information about their current smoking behavior. This will increase the likelihood that participants entering the study are nondaily smokers. The lack of biochemical verification of smoking abstinence at end of treatment may inflate our estimates

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of smoking abstinence overall, but we do not expect that it will bias the comparison between treatment groups. In total, 2 strengths of the study are the efforts to recruit a diverse, representative sample of nondaily smokers and the use of 2 clinically relevant control groups that allow for the answering of different but equally important questions. With respect to recruitment, our efforts to ensure that we enroll a proportion of ethnic and racial minority participants that is representative of nationwide estimates will strengthen the generalizability of our results. With respect to the comparison groups we chose, in most health care settings, referral to smoking cessation apps is not provided. Although many such apps exist, only a handful have been tested empirically and, thus, the evidence base to support such a standard-of-care referral is slim. In these settings, providing written materials to support smoking cessation, such as the NCI booklet "Clearing the Air," remains a standard of care. Thus, comparing the SiS app with that control group answers the following question: would it be useful to change the standard of care to include referral to an app? This is an important practical question that can guide decision-making in health care settings. The other control group addresses the following scientifically relevant question: is the SiS app better than existing smartphone apps for smoking cessation? Although the NCI QuitGuide app has never been tested in a randomized trial designed to test its effectiveness, it is a widely used smartphone app and a recommended resource. Thus, it is an important benchmark that can help tease apart the effects of using a credible, well-designed app from the treatment mechanisms targeted and implemented in the SiS app. Note that this design also represents the first true test of QuitGuide against an established standard of care (ie, referral to "Clearing the Air"). Comparing QuitGuide to Clearing the Air provides insight into whether referral to this publicly available and widely used app is indeed beneficial to nondaily smokers.

Thus, we believe that this study will provide data to inform the next steps toward providing smoking cessation support for nondaily smokers while also providing important, multifaceted insights into smoking cessation smartphone app treatment development and implementation.

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Data Availability

The data sets generated during this study will be available from the corresponding author upon reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review report by Mentored Research Scholar Grant - American Cancer Society.
[PDF File (Adobe PDF File), 40 KB - resprot_v12i1e40867_app1.pdf]

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Abbreviations

ATS-18: Attitudes Toward Smoking Scale
CONSORT-EHEALTH: Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth
DCB: Decisional Balance Inventory for Smoking
mHealth: mobile health
NCI: National Cancer Institute
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
SEQ-12: Smoking Self-Efficacy Questionnaire

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SiS: Smiling instead of Smoking
TAU: treatment-as-usual

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Protocol

Leveraging mHealth and Patient Supporters for African Americans' and Latinxs' Engagement in HIV Care (LEAN): Protocol for a Randomized, Controlled, Effectiveness-Implementation Trial

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Abstract

Background: Despite substantial investments in ending the HIV epidemic, disparities in HIV care persist, and there is an urgent need to evaluate novel and scalable approaches to improving HIV care engagement and viral suppression in real-world settings.

Objective: This paper aims to describe a study protocol for a pragmatic type II hybrid effectiveness-implementation randomized controlled trial comparing existing standard of care clinic HIV linkage, adherence, and retention (LAR) protocols to a mobile health (mHealth)–enhanced linkage, adherence, and retention (mLAR) intervention.

Methods: The study will enroll 450 participants from clinics in Baltimore City. Eligibility criteria include being ≥18 years of age, having a new HIV diagnosis or being HIV-positive and out of care, or being HIV-positive and deemed by clinic staff as someone who could benefit from linkage and retention services. Participants randomized to the intervention receive mHealth-supported patient navigation for 12 months. Participants in the control group receive the referring clinic's standard of care patient support. The primary outcome is HIV virologic suppression at 12 months. A subset of participants will be interviewed at 12 months to learn about their HIV care experiences and, for those in the intervention arm, their experiences with the mLAR intervention. This protocol was developed in collaboration with the Baltimore City Health Department (BCHD) and the Maryland Department of Health (MDH) and with input from a community advisory board.

Results: Enrollment began on February 25, 2020. As of August 11, 2022, 411 of the 450 target participants had been enrolled.

Conclusions: Pragmatic implementation science trials designed with input from key stakeholders, including health departments and community members, can help evaluate the evidence for mHealth interventions to reduce HIV health disparities.

Trial Registration: ClinicalTrials.gov NCT03934437; https://clinicaltrials.gov/ct2/show/NCT03934437

International Registered Report Identifier (IRRID): DERR1-10.2196/42691

(JMIR Res Protoc 2023;12:e42691) doi:10.2196/42691

KEYWORDS

mHealth; HIV linkage to care; HIV virologic suppression; HIV continuum of care; adherence; implementation

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Introduction

Advances in HIV treatment have markedly improved clinical outcomes among people living with HIV [1]. The United States has an ambitious strategy to end the HIV epidemic by 2030, but persistent racial and ethnic disparities in HIV outcomes must be addressed to achieve this goal [2]. African American people represent 13% of the population but account for 42% of people living with HIV and are less likely to receive antiretroviral therapy (ART) or achieve virologic suppression compared to White people [3]. Latinx people have higher HIV rates than non-Hispanic White people and are at high risk for delays in diagnosis and linkage to care [3,4]. Delayed initiation of ART is associated with increased morbidity and mortality, and high viral load is the main predictor of HIV transmission [5-8].

Modeling studies suggest that reengaging people living with HIV into care and suppressing their viral load is one of the most important interventions to reduce HIV incidence in the United States [9,10]. HIV retention in care and virologic suppression rates above 80% are needed to sharply reduce HIV transmission, but in 2021, only 66% of people living with HIV in the United States were suppressed [3]. HIV clinics have implemented various strategies to improve retention in care and adherence to treatment, such as automatic reminder calls for upcoming appointments, intensive case management, or systematic reviews of patients to identify those who have fallen out of care [11]. Evidence suggests that increased contact with the clinic can improve retention in care but may not be enough for people with substance use disorders and other unmet needs [12]. Several personal and structural barriers to care have been identified, including difficulty with transportation to the clinic, lack of information and practical support in navigating the system, and cost [13,14].

HIV retention and adherence strategies could be enhanced with the use of evidence-based mobile health (mHealth) strategies that leverage mobile phones to improve health outcomes. Systematic reviews have found that mHealth interventions can promote engagement in care, adherence to ART, and virologic suppression [15-17]. These platforms can be programmed to send tailored messages, reminders, and alerts to patients and providers using algorithms that leverage existing data. A distinct potential advantage of mHealth platforms is the ability to securely facilitate patient-centered approaches to retention in care efficiently and without overburdening providers, with alerts for action designed to focus on areas that truly require provider input. Studies from Baltimore demonstrate the feasibility and acceptability of using mHealth approaches with diverse populations, including African American men who have sex with men, people who inject drugs, and foreign-born Latinx people [18-20]. However, additional evidence is needed on the relative benefit of mHealth interventions in real-world settings to justify routine investments in mHealth resources and technology.

This manuscript describes the Leveraging mHealth and Patient Supporters for African Americans and Latinxs in HIV Care (LEAN) study protocol for a pragmatic type II hybrid effectiveness-implementation randomized controlled trial. This trial will compare existing standard-of-care clinic HIV linkage, adherence, and retention (LAR) protocols to an mHealth-enhanced linkage, adherence, and retention (mLAR) intervention with the hypothesized finding of improved virologic suppression and engagement in care in the mLAR study arm. This protocol was developed in collaboration with the Baltimore City Health Department (BCHD) and the Maryland Department of Health (MDH) and with input from a community advisory board. The study will evaluate the effectiveness of an mHealth intervention integrated into clinical and public health operations and examine implementation mechanisms and outcomes to inform broader scalability and sustainability.

Methods

Study Setting

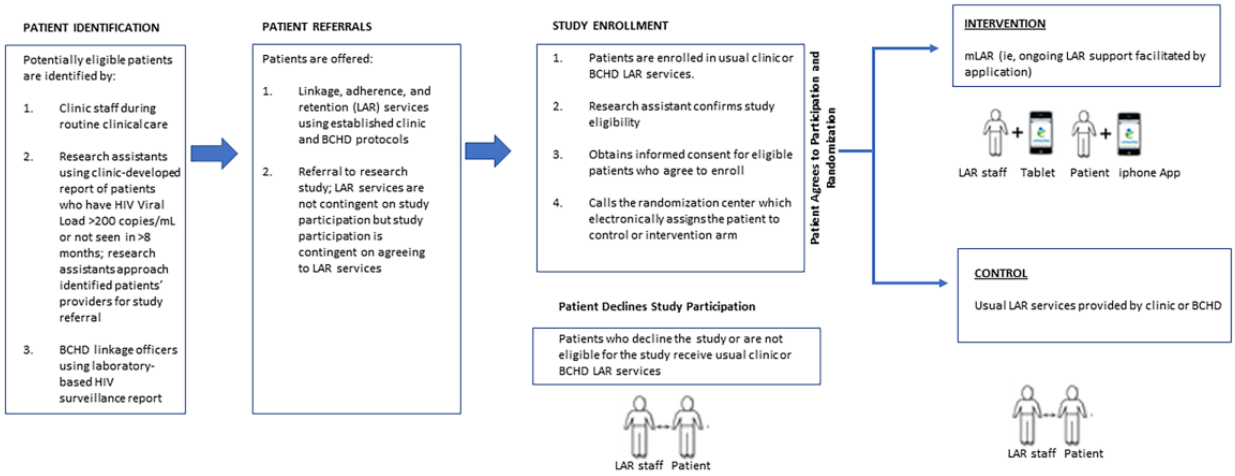
This is a collaborative study between the BCHD, MDH, and Johns Hopkins University conducted in Baltimore City. The HIV prevalence rate in Baltimore is among the highest in US metropolitan areas, and it is a city that faces profound health disparities. In Baltimore, African American people have an HIV prevalence that is 5 times higher than among White people and account for more than 80% of all HIV cases; Latinx people have a higher prevalence of HIV than White people and are at the highest risk for late HIV diagnosis among all racial and ethnic groups [21].

Study Design

This study is a pragmatic type II hybrid effectiveness-implementation [22,23] randomized trial comparing standard LAR services to mLAR services (Figure 1). The study was conceptualized through discussions with patients, providers, linkage officers, and health officials regarding barriers and facilitators to engagement in HIV care and ways to leverage technology into existing services and systems to facilitate provider-patient communication. Study activities were reviewed and approved by the Institutional Review Board at the Johns Hopkins School of Medicine (IRB00195120). The study was registered at ClinicalTrials.gov (NCT03934437).

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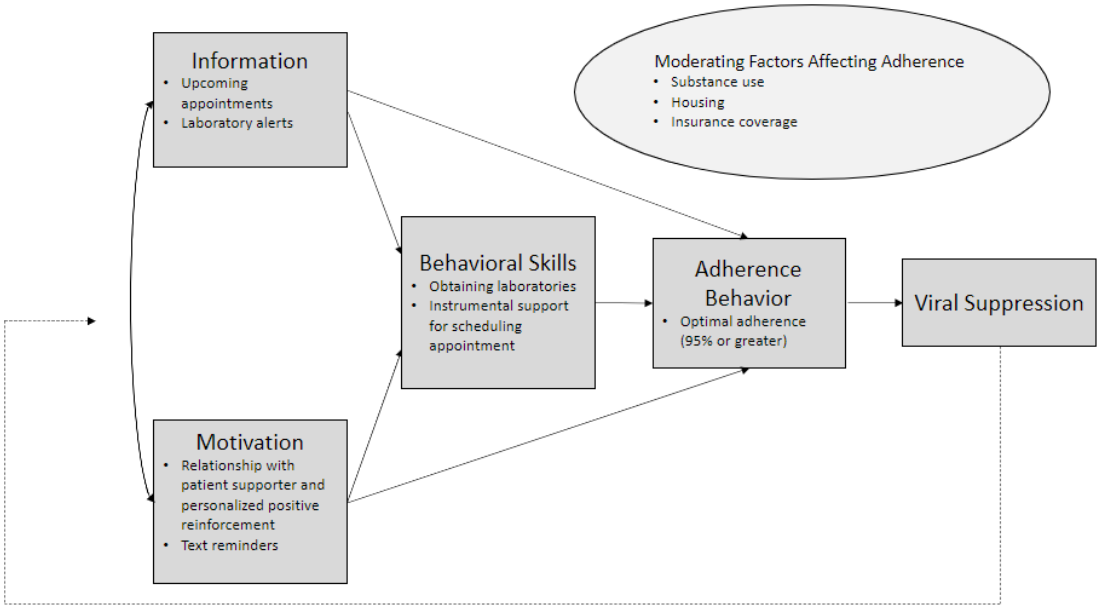
Figure 1. LEAN (Leveraging mHealth and Patient Supporters for African Americans and Latinxs in HIV Care) study design. BCHD: Baltimore City Health Department; LAR: linkage, adherence, and retention; mLAR: mobile health–enhanced linkage, adherence, and retention.



Conceptual Framework

The mLAR intervention was informed by the situated Information-Motivation-Behavioral Skills (IMB) Model of Adherence, an evidence-based and theory-driven approach to understanding ART adherence and engagement in care (Figure 2). The situated IMB model focuses comprehensively on the information, motivation, and behavioral skills factors that are conceptually and empirically linked to ART adherence and specifies individual and social factors that may moderate the relationship between the IMB model constructs and ART adherence. At its most general level, the IMB model asserts that someone who is informed about medication adherence (ie, appointment reminders and lab alerts), is motivated to act, and has the behavioral skills necessary to act effectively (ie, objective and perceived abilities, facilitated by patient supporters) is more likely to adhere to ART over time [24,25]. Social determinants of health, such as housing, and individual factors, such as depression and substance use, moderate adherence and can create barriers to gaining information, being motivated, and acquiring or adhering to ART. Figure 2 highlights examples of specific components of how the mLAR intervention provides information, motivation, and behavioral skills to promote ART adherence. Patient supporters try to address moderating factors, such as depression and substance use, by facilitating referrals to appropriate resources and maintaining close communication with the patient's case manager, as needed.

Figure 2. The situated Information-Motivation-Behavioral Skills (sIMB) Model of Adherence conceptual framework.



Formative Work and Community Engagement

Extensive discussions with stakeholders informed the study's implementation and app design. The BCHD and MHD expressed a strong preference for a pragmatic "real life" study so that results could be generalizable to public health practice. A steering committee of old and new partners included African American and Latinx individuals affected by HIV, HIV clinicians, clinic-based staff (ie, patient supporters), BCHD linkage team leaders, public health officials, and members of

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the nonprofit sector. The SC met monthly during the planning phase and then quarterly once data collection started. The SC provides guidance on all patient-facing aspects of the study, including app characteristics and use (ie, app name, app logo, materials to assist participants with using the app), participant referral and recruitment processes, study closeout for participants, and the in-depth interview guide. Ongoing SC meetings provide an opportunity to discuss challenges and brainstorm solutions. The app development team included JH researchers, members of the health department, and emocha Mobile Health software engineers who helped develop a Health Insurance Portability and Accountability Act (HIPAA)–compliant mHealth app to facilitate engagement in care. Adaptations to the app were also made in response to feedback from the community advisory board and in-depth interviews with participants and patient supporters. Based on community advisory board feedback, the app was named NxtSTEP.

Study Participants

Study Enrollment Criteria

Enrollment criteria include (1) being ≥18 years of age, (2) having the ability to provide consent, (3) having a new HIV diagnosis or being HIV-positive and "out of care" or being deemed by clinic staff as someone who could benefit from LAR services, and (4) living in Baltimore (within BCHD and Baltimore clinics' catchment areas).

Participating Clinic and Program Selection Criteria

Criteria for LAR program participation are (1) BCHD or other Baltimore-based HIV program, (2) has an existing HIV-focused LAR program, (3) has existing patient supporters as part of the LAR program, (4) does not use any formal mHealth component for patient supporters to communicate with patients (beyond basic telephone calls and texting), and (5) the leadership and staff of the LAR program must be willing to participate.

Recruitment

Study participants are recruited from participating programs in 1 of 3 ways (Figure 1): (1) participating clinics identify newly diagnosed patients with HIV, those who are out of care and those who clinic staff determine could benefit from LAR services, offer LAR services to these patients, and refer interested patients to the study; (2) research assistants use clinic-developed reports to identify patients who could benefit from LAR services and approach these patients' care providers during their regularly scheduled clinic visits or during hospitalization to refer interested individuals to the study; and (3) BCHD linkage officers use a laboratory-based HIV surveillance report from the state's enhanced HIV/AIDS Reporting System (eHARS) that identifies newly diagnosed patients with HIV or those who are out of care, and when these patients are offered linkage services, the linkage officer offers study referral.

LAR services are provided regardless of study interest, but individuals who would like to enroll must agree to LAR support. Individuals interested in study enrollment are referred to a research assistant, who confirms eligibility, describes study participant responsibilities, and obtains informed consent.

Randomization

After obtaining consent, the research assistant enters the participant's information into a Research Electronic Data Capture (REDCap) database [26,27], which has been programmed to randomly assign the patient to the control or intervention arm in a 1:1 ratio. The randomization schedule was generated by the study statistician, uses permuted blocks of varying sizes, and is stratified by whether the patient identified as Black or African American to ensure equal distribution of race in each study arm. Due to practical considerations, participants, clinic staff, and the study team are not blinded to arm assignment. Data analysis related to HIV clinical outcomes will be conducted in a blinded fashion.

Study Assessments

This is a pragmatic implementation trial with outcomes (eg, retention in care) that could be influenced by frequent study-related interactions, so study contact is minimized to a baseline visit where the research assistant obtains basic demographic and contact information and the reasons for referral to LAR services (ie, newly diagnosed, previously diagnosed but out of care, etc). A brief client satisfaction survey is conducted at the end of the 12-month follow-up period. Participants who agree to be contacted for an in-depth interview are randomly selected, aiming to capture both male and female participants in the control and intervention arms, including participants who did not use the app.

Participant Remuneration

All participants receive a US $50 incentive at initial enrollment in the study. Participants also receive US $20 for the completion of a client satisfaction survey and US $50 if they participate in an in-depth interview.

Study Arms

Overview

Patients are randomized to the control arm or the intervention arm. Participants randomized to the control arm will receive the usual LAR services as per clinic. Participants randomized to the intervention arm will download the NxtStep app to their personal phones (or the study phone if the participant does not own a compatible phone) and be onboarded for using the app with the research assistant. Subsequently, the intervention arm participants will use the app to communicate with their patient supporter at the clinic or BCHD and receive algorithm-driven alerts (Table 1).

Standard LAR Services

Below are descriptions of the standard LTCR services at each site.

BCHD Linkage to Care Program

BCHD has patient supporters called linkage officers who attempt to contact and provide linkage services to all Baltimore residents newly diagnosed with HIV or who are presumed to be out of care [28]. These patients are identified using the state's eHARS,

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which includes results for all HIV tests (including HIV viral load) conducted in Maryland, DC, and Virginia. An MDH algorithm generates weekly reports for the BCHD linkage team of new HIV diagnoses or out-of-care patients in Baltimore (defined as patients with a viral load >50,000 or no HIV labs for >12 months). The linkage officers attempt to contact patients on this list, and those who agree to be linked to HIV care by linkage officers are provided a same-day appointment and a warm handoff to clinical care (ie, the outreach worker drives the patient to the clinic of his or her choice).

Clinic-Based LAR Programs

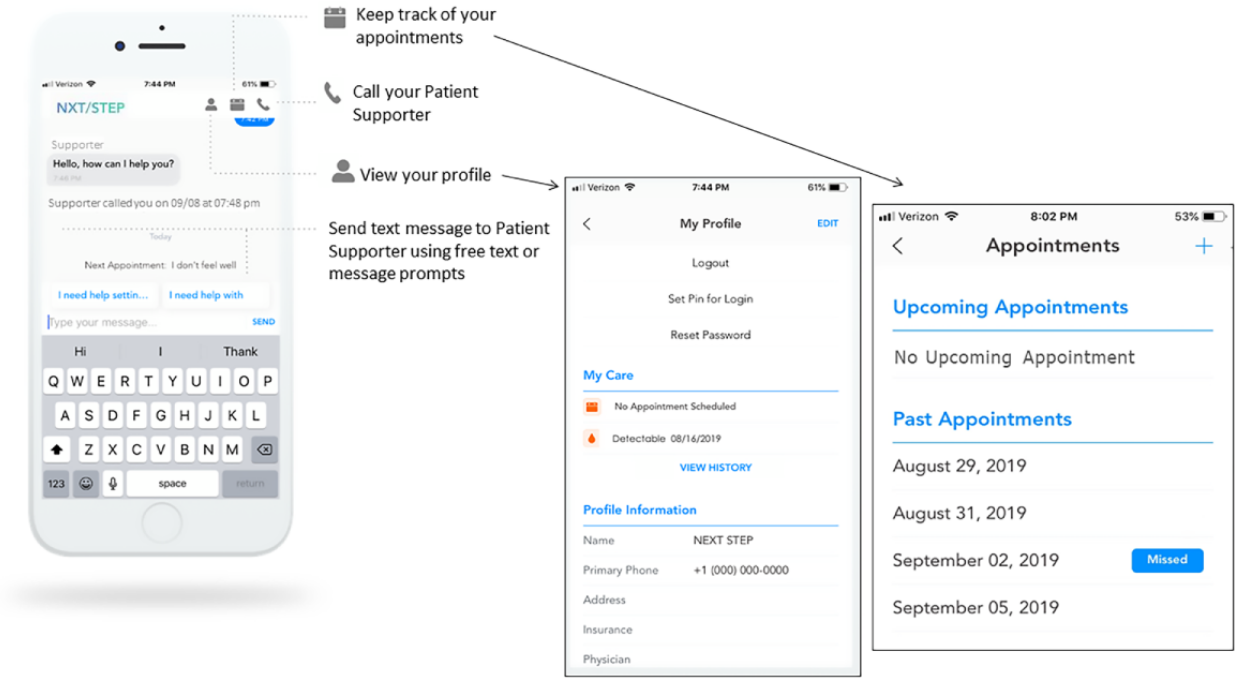
The Ryan White–funded HIV clinics currently participating in our study (Johns Hopkins Bartlett Clinic, BCHD Sexual Health Clinic, University of Maryland THRIVE Clinic, University of Maryland JACQUES Initiative) have patient supporters (called patient supporters, advocates, navigators, or health workers) who remind patients of upcoming appointments and act as a point of contact to help patients navigate their care. They help patients schedule appointments, lab visits, and medication refills. They also provide counseling and education to help patients self-advocate and connect to necessary services (eg, mental health services, substance use disorder treatment, or social services). Except for appointment reminders, which are intended to reach all patients, other services are delivered in response to patient or provider requests, not systematically to all patients. All clinics have rapid ART programs, and the patient supporters assist newly diagnosed patients through this process (quick appointment and introduction to the clinic). None of the programs provide home visits or services outside the clinic.

Intervention (mLAR)

This approach leverages existing LAR services at each study site and adds a novel mHealth component. The mHealth enhancement consists of 2 smartphone apps (NxtSTEP app), 1 for patients and 1 for existing patient supporters, to help facilitate communication on issues related to HIV care (eg, appointment scheduling, laboratory reminders, transportation), as well as patient-directed requests. The NxtSTEP app is designed to facilitate secure communication between the patient and patient supporters and to automate certain tasks, alerts, and reminders so that patient supporters can focus their efforts on patients at high risk of falling out of care (eg, calling a patient with a high viral load) rather than on time-consuming tasks not specifically targeted to high-risk patients (eg, general appointment reminders).

The NxtSTEP app has a viral load–driven algorithm using MDH HIV surveillance data that automatically alerts patient supporters and patients if the viral load is not suppressed (>200 copies/ml) or if more than 4 months have passed since the last viral load. This interval is consistent with HIV guidelines to monitor viral load at least every 3 to 4 months, or more frequently as clinically indicated, in patients who have not had sustained virologic suppression for more than 2 years [29]. In addition, patients are prompted to enter upcoming appointment dates in an app calendar, which allows for automatic reminders. Patient supporters are alerted if a patient does not have an upcoming appointment or if the patient missed their appointment. Patient supporters are trained to contact the patient alerted (lab alert, appointment alert, or patient message alert). Figures 3 and 4 show the patient and patient supporter's NxtSTEP views, respectively. Tasks, alerts, and action prompts are outlined in Table 1 for the patient app and in Table 2 for the patient supporter app.

Figure 3. Patient view of NxtSTEP app.



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Figure 4. Patient supporter view of NxtSTEP app.

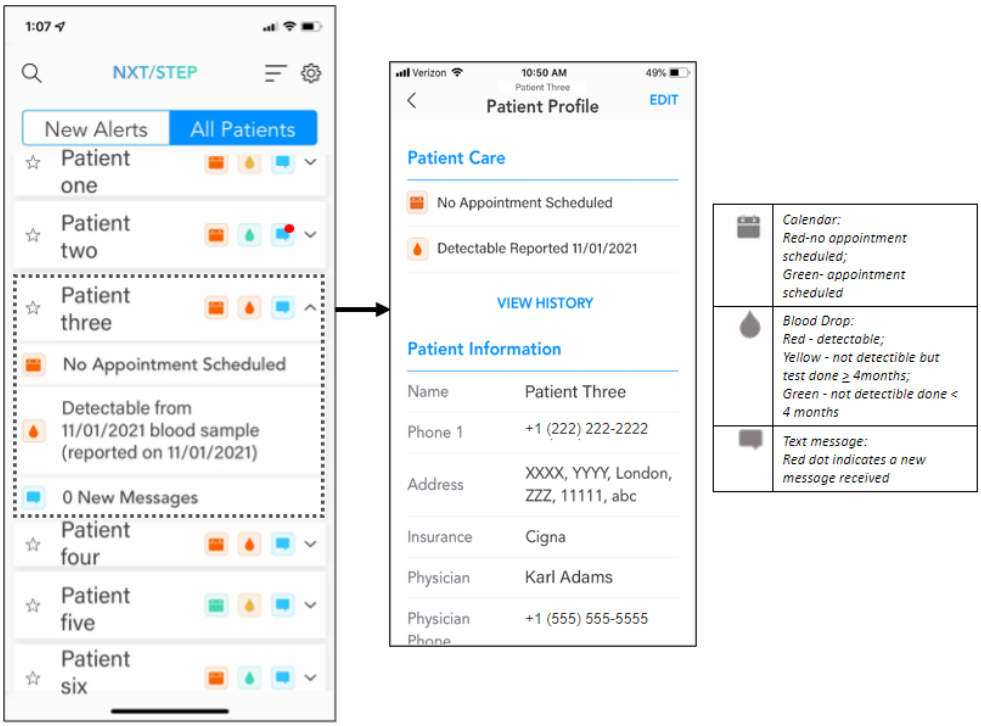


Table 1. Patient NxtSTEP app.

Task	Description	Patient support staff action
Appointment data	Tab to record the date, time, and place of an upcoming HIV care appointment	Patient support staff or patient can enter appointment data
Appointment reminders	Patient automatically receives reminders about upcoming appointments (3 days prior). The day after the scheduled appointment, patient receives the prompt, "Did you go to your appointment yesterday?" (Yes or No) If "Yes," patient received a message saying, "Great job keeping your appointments!"	Patient support staff contacts patient, if alerted (see Table 2)
Ability to directly message patient support staff	Patient can click on prompts (eg, "I need help setting an appointment" or "I need help with") or send a free text message to patient support staff	Patient support staff contacts patient, if alerted (see Table 2)
Control over messages	Patient has the option to type STOP if he or she prefers not to receive a type of message	Not applicable

Table 2. Patient support staff NxtSTEP app.

Task	Description	Patient support staff action
HIV data of participants in mLAR[a] arm	Participant viral load (dated) automatically uploaded from eHARS[b] (through BCHD[c] lab-based reporting surveillance protocols)	Value not applicable
Viral load status alerts	Automatic "out of care" alert if no viral load for >4 months or viral load >200	Patient support staff communicates with the participant. Contact attempts are recorded.
Automatic appointment alerts	Automatic alert if no next appointment is documented in the patient app. "Missed appointment" alert if patient responds 'No' or does not respond to prompt, "Did you go to your appointment yesterday?"	Patient support staff communicates with participant. Contact attempts are recorded.
Patient initiated direct messaging	Automatic alerts for all patient-initiated messages, for example, "Patient needs help with appointment," "Patient needs help with transportation," or if the patient has typed a request with free text.	Patient support staff communicates with participant. Contact attempts and outcomes are recorded. For social determinants (housing, transportation, and substance use), patient support staff assists patient with access to community and clinical-based resources.

[a]mLAR: mobile health–enhanced linkage, adherence, and retention.

[b]eHARS: enhanced HIV/AIDS Reporting System.

[c]BCHD: Baltimore City Health Department.

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NxtSTEP is available in English and Spanish. Spanish-speaking patients with limited English proficiency (LEP) are assigned a bilingual patient supporter who communicates with them in their preferred language. The study team had experience with cultural and linguistic adaptations of interventions and elicited feedback from the steering committee (see below) to ensure messages were tailored to the health literacy and language proficiency of the target population [30,31].

Outcomes

Clinical Outcomes

The primary outcome of the trial is virologic suppression at 12 months, defined as a viral load <200 copies/ml within a 6-month window (ie, 3 months before or after the 12-month follow-up). The secondary effectiveness outcome of the trial is retention in care at 12 months, defined as having a viral load within a 6-month window (ie, 3 months before or after the 12-month follow-up). Data for the primary and secondary outcomes will be obtained from the MDH surveillance HIV viral load data reported to eHARS. All laboratory assessments will be conducted as part of clinical care. Participants with a suppressed viral load (HIV RNA <200 copies/ml) within the follow-up period will be fully engaged in HIV care. While some individuals can maintain immune control over HIV in the absence of ART, this occurs in only <1% of infected persons [32].

Implementation Outcomes

Using a hybrid study design, we incorporated implementation science evaluation methods to assess important implementation questions [33]. Hybrid designs are efficient approaches to obtaining information that can help understand research findings in terms of internal validity and external generalizability and provide data to facilitate translating research into real-world policies and programs [34]. LEAN implementation processes will be evaluated in terms of core factors in the Reach, Effectiveness, Adoption, Implementation, and Maintenance (RE-AIM) approach (Table 3) [33] and informed by concepts from the IMB theoretical framework.

IMB framework dynamics will be explored through open-ended qualitative methods. The evaluation will engage the intervention's consumers (HIV-positive patients randomized to mLAR) as well as other stakeholder groups, including patient supporters, clinicians, and public health officials at the BCHD. Engaging this range of stakeholders will provide a holistic understanding of the barriers and facilitators to successfully implement the intervention, enhance service delivery, and assess the feasibility of scaling up the intervention if it is effective.

Table 3. Summary of mobile health–enhanced linkage, adherence, and retention implementation evaluation using the Reach, Effectiveness, Adoption, Implementation, and Maintenance approach.

Component	Research question	Assessment methods	Outcomes of interest
Reach	Who received the intervention?	• Program data • In-depth interviews	• Proportion of eligible patients successfully engaged in intervention. Differences between those reached and those not reached. Reasons why.
Effectiveness	What impact did the intervention have on patient-oriented outcomes?	• End-of-study viral load • In depth interviews	• Viral suppression • Engagement in care • Acceptability of the intervention
Adoption	Did the providers, patient supporters, and staff (implementers) adopt the intervention?	• Program data, in-depth interviews	• Frequency of contacts between patient supporters and patients. Services provided and received. Perceptions and attitudes of implementers.
Implementation	Was the intervention delivered as intended?	• Program data, in-depth interviews	• Program fidelity. Adaptation to design over time.
Maintenance	Was the intervention sustained and institutionalized over time?	• Program data, in-depth interviews	• Consistent implementation and effectiveness over time. Retention.

Client Satisfaction Survey

All participants (control and intervention, n=450) will be asked to complete a brief client satisfaction survey using a validated Client Satisfaction Questionnaire (CSQ-8) [35]. Participants in the intervention arm will be asked to complete the validated System Usability Scale to assess the acceptability and ease of use of the NxtSTEP app [36].

Qualitative Data

In-depth interviews will be conducted with 3 key stakeholder groups: patient supporters, study participants, and clinic leadership and public health officials. Interviews with patient supporters will occur before and 12 months after the implementation of mLAR to assess the nature of service delivery, client interactions and how this differs from standard linkage activities, barriers and facilitators of engaging out-of-care patients, challenges and solutions to the service delivery, and recommendations for service delivery improvements and expansion of reach. We will also conduct interviews with study participants randomized to the control or intervention arms. All participants will be asked about their experiences living with and engaging in HIV care, including facilitators and barriers to appointments and medication adherence, past experiences dropping out of care, impressions of HIV-related services they received, as well as recommendations for additional services. Participants randomized to the intervention arm will also be asked about

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their experience using the app, their satisfaction with features of the app such as the automated messaging they received, their motivation for engaging the patient supporter–delivered SMS text messages, their perception of the impact of app usage on their care, and their suggestions for other ways the mobile phone may facilitate HIV retention in care and adherence to medications. We will also assess facilitators and barriers to app use. Interviews with clinic leaders and public health officials will explore perceptions of the intervention's integration into linkage and engagement of care activities at clinics or the health department, as well as recommendations for service delivery improvements. These interviews will provide insights about policy, acceptability, political buy-in for the intervention, and the potential for sustainability and adoption in other settings going forward.

Process for Feedback and Intervention Refinement

During implementation, results from the interviews and client satisfaction surveys will be shared at regular intervals with patient supporters, program administrators at the BCHD, and the steering committee. Sharing these data will facilitate the use of the information for problem-solving, community engagement, and an opportunity to improve the quality of the intervention.

Statistical Procedures

We will conduct a test for the equality of proportions of virologically suppressed, not suppressed, or missing viral load individuals at 12 months between the 2 study arms, in line with the randomized design of the study. Secondary to this, and to adjust for any residual confounding, we will conduct a log-binomial regression using individual outcomes (yes or no suppressed) with the study arm as the main predictor and adjusting for patient demographic characteristics, socioeconomic status at baseline, and other factors. The observed virologic suppression in the control arm is higher than the estimate used in the design phase of the study. We will thus further conduct a difference-in-differences analysis to evaluate the effect of the study arm over time. This will be conducted using a log-binomial regression and will investigate the time (enrollment vs 12 months) by arm interaction term, adjusting for baseline sociodemographic covariates and robust standard errors to account for within-participant clustering.

A subgroup analysis will be conducted to assess the effects of the intervention among African American people and people of Hispanic or Latinx descent, and if most of our recruited participants come from 1 site, we will conduct a subgroup analysis focusing on this site alone. Sensitivity analysis using propensity-score weighting to adjust for imbalances in study arm allocation by site will be conducted.

Power Calculation

The reported virologic suppression or lack of a viral load measurement rate under standard of care among HIV-positive African American and Latinx people in Baltimore City is 33% [37]. In order to detect an improvement of 13%, such that 46% of the mLAR group have a viral load and achieve virologic suppression with 80% power at an α=5% level of significance, a total sample size of 442 (n=221 per arm) is required. A total of 450 participants will be enrolled in the study to account for participants who decide to withdraw from the study after enrollment. Because this is a pragmatic implementation study and the primary outcome is viral load obtained from surveillance data, patients who are lost to follow-up will still be included in the analysis. According to the protocol, patients who are lost to follow-up and do not have a viral load recorded in the surveillance database within the window period will be considered virologic failures.

Qualitative Data Analysis

Transcripts from in-depth interviews and key informant interviews will be entered and managed in Atlas.ti (Scientific Software Development GmbH). Separate coding schemes will be developed for HIV-positive patients (the control and intervention arms) and the other staff (patient supporters, program managers, and health officials). An iterative coding process will be used to conceptually name the data and reduce it to manageable units of information that cover broad and general categories. Codes will be informed by the questions in the qualitative guides, and new themes that emerge from the data will be analyzed through a constant comparison approach, allowing for themes to emerge and ensuring that the knowledge assembled from the observational data is not subjected to the ideas solely established through the interview guide. For each group, 2 coders will conduct open-coding on 3 transcripts to develop an initial coding scheme. The draft codebook will continue to be revised as needed as additional transcripts are coded and discussed. Once a final coding scheme is established, the transcripts will be systematically coded. Through weekly meetings, a team approach to data analysis will be used, whereby different analysts provide feedback on emerging interpretations and check emerging categories against the raw data. In this way, an "audit trail" will be used to help ensure the trustworthiness of findings, gather input from multiple perspectives, and enhance reliability.

Data Management and Quality Assurance

Data collected by the NxtSTEP app is sent in real time to a secure server, where linkage activities and data can be accessed through a simple web interface. Only authorized study personnel have access to this data. A triple level of data encryption is used to ensure confidentiality of data and HIPAA-compliance. Patient supporter devices and access to the patient supporter and patient apps are password protected. To further protect patients' confidentiality, the patient's app and messages to the patient include nonspecific terms without mention of HIV or other personal health information. Data will be cleaned at Johns Hopkins and deidentified before analysis.

Ethics Approval

This study was approved by the Johns Hopkins School of Medicine Institutional Review Board (IRB00195120).

Results

Study enrollment began February 2020 and was suspended in March 2020 until June 2020 due to the COVID-19 pandemic. As of August 11, 2022, 411 people had been enrolled in the study. Study enrollment of 450 participants was completed on December 1, 2022. Follow-up of these participants will continue

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until early 2024, and study assessment and data collection will be completed by January 31, 2024.

Discussion

This trial should provide evidence on whether an mLAR intervention improved viral suppression and engagement in care when compared to existing standard-of-care clinic HIV LAR protocols. Compared to prior work, this study will generate rigorous randomized, controlled trial-level evidence with hard biologic outcomes for an intervention used within real-world programs. Study strengths include the rigorous study design, multiple study sites, and a user- and community-informed app design and implementation. Study limitations include potentially imbalanced recruitment from the various study sites, COVID-19–related adaptations, and unforeseen technological challenges.

Informed by the community advisory board, we will implement (or develop) a robust dissemination plan that includes not only peer-reviewed publications and presentations at scientific conferences but also presentations among community-based organizations that offer HIV services and to city and state policy makers and funders of HIV programs.

The rigorous evaluation of a pragmatic HIV LAR to care approaches, especially in settings like Baltimore, where African American and Latinx people carry a disproportionate burden of HIV infections, is desperately needed. The results of this randomized study will contribute to the evidence on the effectiveness of an mHealth-enhanced LAR initiative implemented by the local health department and clinics that provide care to people living with HIV. Evidence supporting the feasibility, effectiveness, and implementation considerations of this intervention will be important for the BCHD and other health departments as they make decisions on the allocation of limited resources to address the HIV epidemic in their jurisdictions. As value-based reimbursement becomes the norm for payors including Medicare and Medicaid, this study will contribute to the evidence regarding insurance coverage for mHealth interventions to improve patient outcomes. The information will also be relevant to Ryan White officials responsible for allocating federal dollars to support clinical and ancillary services to improve HIV outcomes, particularly among patients who are uninsured or underinsured. Finally, and most importantly for patients and providers, the primary outcome of this study (virologic suppression) is directly related to improved clinical outcomes (improved survival and lower morbidity) and reduced HIV transmission in affected communities.

In summary, the LEAN trial seeks to test the impact of an mHealth-enhanced linkage to care, adherence, and retention strategies among vulnerable, mostly minority persons living with HIV in a real-world setting. If found to be effective, potential future directions for this intervention include scaling it up and adapting it to other settings as an important tool to reach HIV epidemic control.

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Data Availability

After completion of this study and publication of primary and secondary trial outcomes, a deidentified data set will be submitted for publication to JMIR Data.

Conflicts of Interest

Under a licensing agreement between emocha Mobile Health and the Johns Hopkins University, LWC, KRP, and JM-W are entitled to royalties on an invention described in this article. LWC and JM-W are also consultants to emocha Mobile Health. This arrangement has been reviewed and approved by Johns Hopkins University in accordance with its conflict of interest policies.

Multimedia Appendix 1
Peer-review report from Patient-Centered Outcomes Research Institute (PCORI).
[PDF File (Adobe PDF File), 396 KB - resprot_v12i1e42691_app1.pdf]

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Abbreviations

ART: antiretroviral therapy
BCHD: Baltimore City Health Department
eHARS: enhanced HIV/AIDS Reporting System
HIPAA: Health Insurance Portability and Accountability Act
IMB: Information-Motivation-Behavioral Skills
LAR: linkage, adherence, and retention
MDH: Maryland Department of Health
mHealth: mobile health
mLAR: mobile health–enhanced linkage, adherence, and retention

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Protocol

An mHealth Intervention to Reduce Gestational Obesity (mami-educ): Protocol for a Randomized Controlled Trial

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Abstract

Background: The World Federation of Obesity warns that the main health problem of the next decade will be childhood obesity. It is known that factors such as gestational obesity produce profound effects on fetal programming and are strong predictors of overweight and obesity in children. Therefore, establishing healthy eating behaviors during pregnancy is the key to the primary prevention of the intergenerational transmission of obesity. Mobile health (mHealth) programs are potentially more effective than face-to-face interventions, especially during a public health emergency such as the COVID-19 outbreak.

Objective: This study aims to evaluate the effectiveness of an mHealth intervention to reduce excessive weight gain in pregnant women who attend family health care centers.

Methods: The design of the intervention corresponds to a classic randomized clinical trial. The participants are pregnant women in the first trimester of pregnancy who live in urban and semiurban areas. Before starting the intervention, a survey will be applied to identify the barriers and facilitators perceived by pregnant women to adopt healthy eating behaviors. The dietary intake will be estimated in the same way. The intervention will last for 12 weeks and consists of sending messages through a multimedia messaging service with food education, addressing the 3 domains of learning (cognitive, affective, and psychomotor). Descriptive statistics will be used to analyze the demographic, socioeconomic, and obstetric characteristics of the respondents. The analysis strategy follows the intention-to-treat principle. Logistic regression analysis will be used to compare the intervention with routine care on maternal pregnancy outcome and perinatal outcome.

Results: The recruitment of study participants began in May 2022 and will end in May 2023. Results include the effectiveness of the intervention in reducing the incidence of excessive gestational weight gain. We also will examine the maternal-fetal outcome as well as the barriers and facilitators that influence the weight gain of pregnant women.

Conclusions: Data from this effectiveness trial will determine whether mami-educ successfully reduces rates of excessive weight gain during pregnancy. If successful, the findings of this study will generate knowledge to design and implement personalized prevention strategies for gestational obesity that can be included in routine primary care.

Trial Registration: ClinicalTrials.gov NCT05114174; https://clinicaltrials.gov/ct2/show/NCT05114174

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KEYWORDS

gestational obesity; mHealth; primary care; randomized controlled trial

Introduction

The World Obesity Federation warns that the main health problem of the next decade will be childhood obesity [1,2]. Obesity and its consequences have their origin in intrauterine life [3]. A study showed that the consumption of "junk" food (high in energy and poor in micronutrients) during pregnancy was a predictor of high birth weight and the child's future preference for foods high in fat, sugar, and salt [4]. The risk of obesity in childhood is increased if the mother has a high level of adiposity or develops gestational diabetes, or if the baby is not breastfed or experiences poor nutrition that leads to delayed birth [2]. Excessive gestational weight gain (eGWG) is a predictor of overweight and obesity in children in the short-, medium-, and long-term, with evidence of effects up to 21 years after delivery [5-7]. In this sense, according to Barker theory, nutrition and other environmental factors to which the mother is exposed during pregnancy alter intrauterine life [8]. Gestational obesity produces deep effects on the programming of the fetal genome, thereby inducing changes in the prenatal metabolism that extend to the postnatal period, which is also associated with increased susceptibility to developing cardiovascular and metabolic diseases in adulthood [5-7,9,10].

eGWG during early pregnancy has been repeatedly associated with increased adiposity in childhood and adolescence [11-15]. Thus, adequate maternal nutrition during pregnancy is the window of opportunity to strengthen the health status of the mother and fetus and reduce the risk of adverse birth outcomes, such as preterm birth and low birth weight associated with eGWG [16]. The first trimester of pregnancy is critical for short-term interventions to break the "transmission" of obesity from one generation to the next [17]. For many women, pregnancy is a powerful motivator for self-care, as they are more aware of personal risks and have a strong emotional response toward adopting risk-reducing behaviors [18]. Quantitative literature suggests that the key to maintaining a healthy pregnancy and the primary prevention of maternal-fetal complications is establishing healthy dietary behaviors during gestation [19,20]. Even though many women are aware of the importance of healthy eating during pregnancy, the lack of nutritional self-care knowledge represents a substantial barrier to weight control during this stage [21,22]. Nutrition education improves nutritional knowledge, thus influencing practices aimed at achieving adequate nutrition [22]. Several studies recommend the continuous use of educational interventions on nutrition during pregnancy in routine obstetric practice to improve the quality of life of pregnant women and their offspring [6,23-25]. Regarding this, a study performed on the Chilean population evaluated the efficacy of a low-intensity, high-coverage nutritional intervention at the primary health care level [26]. This high-coverage intervention included training health professionals on nutritional recommendations, counseling pregnant women on diet and physical activity, and appropriate referral to primary health care centers' dieticians. The study found that the intervention reduced gestational weight gain and has the potential for successful scale-up [26].

New strategies to engage the target population are required to maintain nutritional recommendations as a priority in the daily decision-making (top of mind) of pregnant women [27]. Interventions based on behavioral theories provide a greater understanding of the underlying mechanisms that determine health-related behavior change and have the potential to be more effective in promoting adherence to weight gain control [28]. The social cognitive theory [29,30] considers the social dimension of the individual since each individual has a belief system and the capacity for self-motivation and positive behavioral changes [29,31,32]. Therefore, technologies such as mobile phones can be useful to effectively address this problem. Mobile phone ownership is widespread among all sectors of society, regardless of socioeconomic status, which gives us the possibility to introduce the mobile health (mHealth) intervention as an important component of future health care practice [32].

mHealth programs are potentially more effective than face-to-face interventions since they make it possible to cover a larger part of the population; moreover, face-to-face interventions are more labor-intensive, time-consuming, and expensive. Furthermore, they are especially useful during public health emergencies, like the recent COVID-19 pandemic [33]. According to the World Health Organization, mHealth has been defined as "medical and public health practice supported by mobile devices, such as mobile phones, patient monitoring devices, personal digital assistants, and other wireless devices" [34]. Mobile phones are personal, portable, and connected devices [30]. This means that messages can be proactively delivered directly to people, while face-to-face activities or visiting a web page require "going" to look for the information, that is, the self-determined motivation of pregnant women. In this sense, a recent meta-analysis that included 12 randomized controlled trials (RCTs) conducted in an adult population of different ages and conditions demonstrates the efficacy of interventions based on mobile phone apps for weight loss [35]. The combined findings of 10 of the studies included in the meta-analysis showed a substantial reduction in BMI (−0.45 kg/m^2) and body weight (−1.07 kg) in the intervention group [35]. A recently published RCT that aimed to evaluate the efficacy of a digital health intervention on maternal and perinatal outcomes in pregnant women with obesity who attended the maternal-fetal department of the Hospital-Clinic of Barcelona [31] demonstrates that the digital intervention, which was delivered by the midwife through an app, including advice on gestational weight gain and physical activity, found that gestational weight gain was lower and physical activity increased in obese pregnant women in the intervention group [31]. Hence, we aim to evaluate the effectiveness of an mHealth intervention, based exclusively on mobile phone–delivered messages directed to the cognitive, emotional, and psychomotor

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behavior, called mami-educ, to reduce excessive weight gain in pregnant women who attend family health care centers in urban and predominantly rural areas (Figure 1). The intervention will last 12 weeks and consists of sending messages through the multimedia messaging system (MMS), with food education addressing the cognitive, affective, and psychomotor domains. According to the literature, the basic factors for adopting a healthy behavior are the perceived susceptibility to the perceived threat of a disease, the perceived consequence, such as severity, the perception of the positive benefits of the action, the perceived barriers to action, and the confidence in the ability to succeed, which is perceived as self-efficacy for action [36]. Thus, the messages that address the cognitive domain of learning are aimed at helping pregnant women understand the benefits of a healthy diet and the harm of a diet rich in fats and sugars during pregnancy, while the affective domain will address the beliefs, barriers, and opportunities to achieve the consumption of healthier foods and contribute to the health of the mother-child binomial. Behavior change is initiated and sustained when people feel that they can execute the desired behavior (ie, self-efficacy) and have a reasonable expectation that the behavior will lead to the desired outcome [37]. In this sense, the psychomotor domain seeks to promote self-efficacy by delivering messages about preparations with adequate nutrition for pregnancy and planning actions to avoid eGWG.

Figure 1. Schematic diagram of the proposed solution. The solution called "mami-educ" consists of sending cognitive, affective, and psychomotor messages through MMS to pregnant women that assist family health centers in urban and rural areas. MMS: multimedia messaging system.



Methods

Study Design and Participants

The design of the intervention corresponds to a classic RCT, a design that allows us to prospectively study pregnant women, in which it is intended to compare the effect of the intervention versus the control condition, to establish a cause-and-effect relationship. This design allows us to reduce the risk of comparability bias. The study will be carried out with pregnant women who control their pregnancy in Family Health Centers (CESFAM) of the Metropolitan Region (the capital city of Chile) and the Aconcagua Valley, Valparaiso Region (88 km to the north of the capital). The CESFAM work under the Comprehensive Health Model with a Family and Community Approach, focusing on prevention and health promotion, and are responsible for basic health care, including home care and health rehabilitation actions. These centers focus on families and communities, give importance to community participation, and work with a primary health team that attends to the whole family in health and sickness throughout the life cycle.

Control Group

Pregnant women enrolled in the prenatal control program receive routine care at the CESFAM.

Intervention Group

Pregnant women enrolled in the prenatal control program receive routine care at the CESFAM and messages on nutrition (intervention).

Inclusion Criteria

Chilean- or Spanish-speaking immigrant pregnant women older than 18 years who receive care at the 6 CESFAM in El Bosque, Metropolitan Region and in Segismundo Iturra CESFAM in San Felipe, Aconcagua Valley, Valparaiso Region; who have gestational ages ≤12 weeks (first trimester); who have a single pregnancy; who declare to have a normal pregnancy at the time of starting the intervention; who agree to be randomized; and who have voluntarily signed the informed consent can participate in this study. The pregnant women who participate in the study must have a mobile device that allows the use of MMS.

Exclusion Criteria

Exclusion criteria include multiple pregnancies, conditions requiring a special diet, participants with psychiatric illnesses or other prepregnancy pathology, and a history of recurrent miscarriages.

Sample Size Calculation

The total sample consists of 511 participants, which will be divided into 2 groups. In the El Bosque CESFAM, 280 pregnant women were recruited, with an estimated dropout rate of 30% (based on the pilot study carried out) to guarantee the required sample size of 210 pregnant women with a confidence level of 90% and a 5% error. At Segismundo Iturra CESFAM, 231 pregnant women were recruited, with the same estimated dropout rate, to ensure a sample size of 178 pregnant women with a confidence level of 90% and a 5% error. For the calculation of the sample size, the official records of the DEIS regarding the number of pregnant women between 20 and 44 years of age who were treated for prenatal control in the CESFAM of the El Bosque commune and Segismundo Iturra were considered. The recruitment period will be 6 months.

Randomization and Masking

The pregnant women who meet the inclusion criteria are invited to participate in the study, as are those who accept and sign the informed consent form. These pregnant women receive the link to the diagnostic survey on their telephones and are then randomized to be included in the intervention. At the end of each month of the recruitment period, the researchers will randomize the pregnant women who were recruited during that

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month. A stratified randomization will be carried out to ensure a sample that is as balanced as possible. The sample will be divided into 4 strata according to their pregestational weight, classifying them as underweight (BMI<18.5 kg/m^2), normal weight (BMI 18.5-24.9 kg/m^2), overweight (25-29.9 kg/m^2), and obese (BMI≥30 kg/m^2). Simple random selection will be carried out then by generating a table of random numbers without repetition, from 1 to n, and deciding a priori that it will be read from left to right, with even numbers assigned to the control group and odd numbers to the intervention group.

A single-blind study will be carried out since the CESFAM personnel who will oversee the recruitment will be blinded to the randomization of the subjects to avoid bias in routine care.

Procedures

The recruitment of pregnant women will be done for a period of 6 months. The study will end when all the participants with intervention have completed the 12-week message period.

Immediately after randomization, the researchers will send the MMS with the link that leads to a web-based survey. The survey will be the same for the control group and intervention group and will recollect demographic information, nutritional habits, and physical activity. Pregnant women in the intervention group who respond to the survey will receive the intervention messages by MMS.

Routine care visits will be scheduled usually by CESFAM's midwifery professionals. Such visits should occur monthly until the 28th week of gestation, biweekly during the 28-36 weeks of gestation, and weekly until delivery. During prenatal control, the nutritional evaluation is carried out according to the technical standard, and a referral to a nutritionist is made if necessary. These care visits may also include participation in the "Elige Vivir Sano" and "Chile Crece Contigo" programs and everything associated with the prenatal control program.

Intervention

The intervention consists of 3 MMS messages with nutritional information per week for 12 consecutive weeks. The messages were reviewed by a perinatal psychologist. The messages will be sent as follows: Monday at 3 PM, the message that addresses the cognitive domain will be sent; Tuesday at 3 PM, the message that addresses the affective domain will be sent; and Thursday at 3 PM, messages that address the psychomotor domain, together with the weekly user satisfaction survey, will be sent. This delivery scheme was validated in the pilot study that was carried out. The 12 topics related to nutrition during pregnancy will be addressed, 1 will be addressed per week, and 3 messages will be sent for each topic. At the beginning of each month, messages will be sent to pregnant women who were recruited during the immediately previous month. In the development of the project and to prevent pregnant women from incurring additional expenses for participating in the intervention, we will directly recharge the phones of the users who participate in the study.

Follow-up

The team of midwives will keep a record of the weight of the pregnant women who attend their prenatal checkups monthly. Therefore, the monitoring of the weight of both groups will be done through the midwives in order not to request sensitive data via MMS.

Dropouts

A record of the number of pregnant women who drop out of the study will be kept, as well as their characteristics for subsequent statistical analysis.

Primary and Secondary Outcomes

The primary outcome will be to assess the effectiveness of the mHealth mami-educ intervention in reducing the incidence of eGWG compared to routine care. Secondary outcomes will include identifying the barriers and facilitators influencing weight gain in pregnant women to compare the maternal outcome of pregnancy, in terms of complications developed during pregnancy (pre-eclampsia, gestational diabetes, and gestational hypertension), and the perinatal outcomes (prematurity and birth weight) of the pregnant women in the control and intervention groups.

Statistical Analysis

The data analysis plan will be governed by the intention-to-treat principle, as we will include all participants who were randomly assigned after recruitment, assuming that participants who drop out are treatment failures. The effectiveness of the treatment will be measured using the chi-square test (χ^2), comparing the intervention group with the control group in terms of the percentage of women who are classified as having excessive weight gain at the end of pregnancy. To confirm the effectiveness of the intervention, a significant decrease (P<.001) of women with eGWG in the intervened group will be expected. For data analysis, the statistical software GraphPad Instat 3.0b and GraphPad Prism 6.0f (GraphPad Software Inc) will be used. P<.001 (determined by a 2-sided test) will be considered statistically significant.

Ethics Approval

This research will be conducted in accordance with the Declaration of Helsinki. The study was approved by the Scientific Ethics Committee of the Aconcagua Health Service (protocol number: 26/2021, approved October 12, 2021) and the Scientific Ethics Committees of the South Metropolitan Health Service (protocol number: 07-27012022, approved February 7, 2022). Informed consent will be obtained from all participants invited to participate in the study before proceeding with the initial survey. The data will be treated respecting the ethical principles that guarantee the anonymity of the participants.

Results

The study was funded by the National Research and Development Agency of Chile in December 2021. The data collection began on May 2, 2022. Study staff have been engaged in activities associated with study including enrollment and data

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collection. As of November 30, 2022, a total of 222 pregnant women have been admitted for the first prenatal appointment, 127 meet the inclusion criteria, and 76 agree to participate and answered the diagnostic survey. The expected timeframe for completing recruitment and data analysis is November 2023.

Discussion

Principal Findings

It is well known that pregestational obesity has been recognized as a risk factor for several perinatal complications, such as fetal macrosomia, gestational diabetes, hypertensive disorders, failed induction, premature rupture of membranes, and cesarean section [38]. Nevertheless, this risk is increased when eGWG is present [39,40]. Prevention strategies in primary care are key to fighting this problem; in this regard, strategies that target behavior change by promoting self-efficacy have been proposed [37]. A recent study conducted focus groups with 66 women between 16 and 24 weeks' gestation [19], and the participants expressed that the difficulties in operationalizing the information in the guidelines and that provided by health care providers were one of the important barriers to self-care. For this reason, care providers' advice on nutrition and physical activity was perceived as minimal and ineffective. We propose the integration of social cognitive theory with mHealth to provide nutritional information to pregnant women in primary care. In this study, the structure of the messages addresses 3 learning domains (cognitive, affective, and psychomotor) that promote self-efficacy [37]. The hypothesis of this study is that the mHealth intervention called mami-educ is effective in reducing eGWG in pregnant women who attend family health care centers in an urban area and another predominant rural area. From a public policy perspective, effective health communication is very important; mHealth provides fast, easy-to-use, and cost-effective communication. We designed this study to address the gap in evidence-based primary prevention strategies regarding the use of mHealth to reduce eGWG. Overall, this proposal has the potential to reduce the incidence of perinatal complications through adequate gestational weight gain. To ensure the reproducibility of the study for future research and reduce the risk of comparability bias, the design of the intervention corresponds to a classic RCT. This design allows us to carry out a prospective study of pregnant women in which it is intended to compare the effect of the intervention versus the control condition to establish a cause-and-effect relationship.

The results of this study may serve to implement evidence-based primary prevention strategies and help a broader group of pregnant women maintain adequate weight gain during pregnancy and prevent pregnancy pathologies associated with obesity. This would ultimately influence health care costs. In Chile, it has been described that the cost of overweight and obesity increases to US $455 million by year, representing 2% of the total health budget, which means that obesity costs 4-fold higher than normal weight health care [41]. Through this observation, the projected health costs for 2030 related to overweight and obesity will reach 3.4% of the total health budget (US $3 billion). Furthermore, it is estimated that a weight reduction of 7%-10% in the obese population would translate into a 40% decrease in spending on obesity-associated comorbidities [42]. Thus, promoting adequate weight gain during pregnancy in women with obesity could improve maternal, fetal, newborn, and offspring health and could significantly reduce public health care costs. Lastly, the data collected in this study can play a central role in the development of public policies based on mHealth directed exclusively to the population of pregnant women.

Limitations

A limitation of this study is the reliance on smartphones to access interventions. In addition, the recruitment of pregnant women must occur during the first trimester of gestation, and this may be hindered because some pregnant women begin prenatal care in the second trimester. Another limitation is that the pregnant woman may decide not to interact with the messages by blocking the number of the intervention.

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Data Availability

The data sets generated and analyzed during this study will be available from the corresponding author on reasonable request following the completion of the trial and publication of the main outcomes paper.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Evaluation report.
[PDF File (Adobe PDF File), 207 KB - resprot_v12i1e44456_app1.pdf]

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Abbreviations

CESFAM: Centro de Salud Familiar
eGWG: excessive gestational weight gain
mHealth: mobile health
MMS: multimedia messaging system
RCT: randomized controlled trial

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Protocol

Testing the Impact of the #chatsafe Intervention on Young People's Ability to Communicate Safely About Suicide on Social Media: Protocol for a Randomized Controlled Trial

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Abstract

Background: Suicide is the leading cause of death among Australians. One commonly cited explanation is the impact of social media, in particular, the ways in which young people use social media to communicate about their own experiences and their exposure to suicide-related content posted by others. Guidelines designed to assist mainstream media to safely report about suicide are widespread. Until recently, no guidelines existed that targeted social media or young people. In response, we developed the #chatsafe guidelines and a supporting social media campaign, which together make up the #chatsafe intervention. The intervention was tested in a pilot study with positive results. However, the study was limited by the lack of a control group.

Objective: The aim of this study is to assess the impact of the #chatsafe social media intervention on young people's safety and confidence when communicating on the web about suicide.

Methods: The study employs a pragmatic, parallel, superiority randomized controlled design. It will be conducted in accordance with the Consolidated Standards of Reporting Trials statement over 18 months. Participants will be 400 young people aged 16-25 years (200 per arm). Participants will be recruited via social media advertising and assessed at 3 time points: time 1—baseline; time 2—8-week postintervention commencement; and time 3—4-week postintervention. They will be asked to complete a weekly survey to monitor safety and evaluate each piece of social media content. The intervention comprises an 8-week social media campaign including social media posts shared on public Instagram profiles. The intervention group will receive the #chatsafe suicide prevention content and the control group will receive sexual health content. Both groups will receive 24 pieces of content delivered to their mobile phones via text message. The primary outcome is safety when communicating on the web about suicide, as measured via the purpose-designed #chatsafe online safety questionnaire. Additional outcomes include willingness to intervene against suicide, internet self-efficacy, safety, and acceptability.

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Results: The study was funded in November 2020, approved by the University of Melbourne Human Research Ethics Committee on October 7, 2022, and prospectively registered with the Australian New Zealand Clinical Trials registry. Trial recruitment began in November 2022 and study completion is anticipated by June 2024.

Conclusions: This will be the first randomized controlled trial internationally to test the impact of a social media intervention designed to equip young people to communicate safely on the web about suicide. Given the rising rates of youth suicide in Australia and the acceptability of social media among young people, incorporating social media–based interventions into the suicide prevention landscape is an obvious next step. This intervention, if effective, could also be extended internationally, thereby improving web-based safety for young people not just in Australia but globally.

Trial Registration: Australian New Zealand Clinical Trials Registry ACTRN12622001397707; https://anzctr.org.au/Trial/Registration/TrialReview.aspx?id=384318

International Registered Report Identifier (IRRID): DERR1-10.2196/44300

(JMIR Res Protoc 2023;12:e44300) doi:10.2196/44300

KEYWORDS

suicide; young people; social media; intervention, sexual health, randomized-controlled trial

Introduction

Background

Suicide is the leading cause of death among Australians younger than 25 years, and rates have been increasing over the past 10 years [1]. The pathways that lead a young person to feel suicidal are complex and diverse; however, 1 commonly cited explanation for the recent rise in rates of youth suicide is the impact of social media [2].

Young Australians spend over 3 hours per day on social media, and this sometimes includes communicating with others about their own experiences of suicide and being exposed to suicide-related content posted by others [2-4]. While there are many potential benefits to communicating on the internet about suicide, such as the ability to seek and provide support from others in an accessible and nonstigmatizing manner [3,5], the potential for harm also exists. For example, there are concerns that certain types of content (eg, graphic information or images) may cause distress, lead to imitative suicidal behavior, and have been thought to contribute to suicide clusters [6]. In addition, young people may be exposed to expressions of suicide risk posted by others but feel ill-equipped to respond [7].

Guidelines designed to assist mainstream media outlets to report on suicide in a sensitive manner are widespread and have led to improved safety and quality of communication about suicide [8]. They also appear to be linked to a reduction in suicide rates [9]. However, until recently, no guidelines existed that targeted either social media or young people, who are now creators of their own content.

In response to this, we developed the #chatsafe guidelines [10], which were the first set of guidelines in the world specifically designed to better equip young people to communicate safely on social media about suicide. They were developed using the Delphi consensus method in partnership with young people, media, and suicide prevention professionals [11]. The guidelines consist of five sections: (1) things to consider before you post about suicide; (2) sharing your own thoughts, feelings, or experience with suicidal behavior; (3) communicating about someone you know who is affected by suicidal thoughts, feelings, or behaviors; (4) responding to someone who may be suicidal; and (5) memorial websites, pages, and closed groups.

The guidelines were supported by a national social media campaign designed to make the content of the guidelines more accessible to young people. The campaign was co-designed with young people from across Australia [12] and was initially rolled out nationally in 2019, reaching around 1.5 million young people. Together, the guidelines and campaign make up the #chatsafe intervention.

Aims and Hypotheses

The overall aim of the study is to assess the impact of the #chatsafe social media intervention on young people's safety and confidence when communicating on the internet about suicide. In this study, the treatment group who will receive the #chatsafe social media intervention will be compared to the control group who will receive social media content providing education on sexual health and well-being.

It is hypothesized that (1) At postintervention (T2), the treatment group will have higher mean scores than the control group on their understanding and compliance with the #chatsafe guidelines, as measured by the #chatsafe online safety questionnaire. Specifically, this will be assessed by improvements in their understanding of language to use or not use, support services available to them, how to share their own experiences of suicide safely, how to communicate about those who have died by suicide, and how to support someone that they are worried about. (2) At the postintervention time point (T2), the treatment group will have higher mean scores than the control group on self-reported (i) safety and confidence when communicating on the internet about suicide, (ii) willingness to intervene against suicide on the internet, and (iii) perceived internet self-efficacy. (3) It will be safe and acceptable to share the #chatsafe intervention with young people entirely via social media (assessed weekly throughout the intervention and postintervention [T2]). (4) Knowledge gains made in the intervention group at T2 will be maintained at T3.

Subgroup differences in perceptions toward the intervention and outcomes of the intervention (ie, gender, sexuality, age groups, and level of social media usage) will also be examined.

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Pilot Data

The #chatsafe intervention was tested in a pilot study in 2019-2020 [13]. The aims were to assess the acceptability, safety, and feasibility of the intervention as well as its impact on perceived self-efficacy, willingness to intervene against suicide on the internet, and safety of web-based communication about suicide. The study adopted a single-group pre- and posttest design. Participants were 189 young people aged 16-25 years recruited from 3 states in Australia via social media advertising. The intervention comprised 3 #chatsafe posts each week on the #chatsafe Instagram page. Participants were sent 1 post via direct message each week, for a period of 12 weeks. The results indicated that participants found the intervention acceptable. Participants also demonstrated improvements in perceived ability ($P<.001$) and intent to intervene against suicide ($P<.001$), and in several domains of internet self-efficacy, for example, problem-solving on the internet ($P<.001$). They also demonstrated improved web-based behavior, including monitoring their social media posts and responding directly to someone who may be suicidal.

Although these findings painted a promising picture, the pilot study was limited by the lack of control group. Therefore, the aim of this study is to test the efficacy of the #chatsafe intervention in a randomized controlled trial (RCT).

Methods

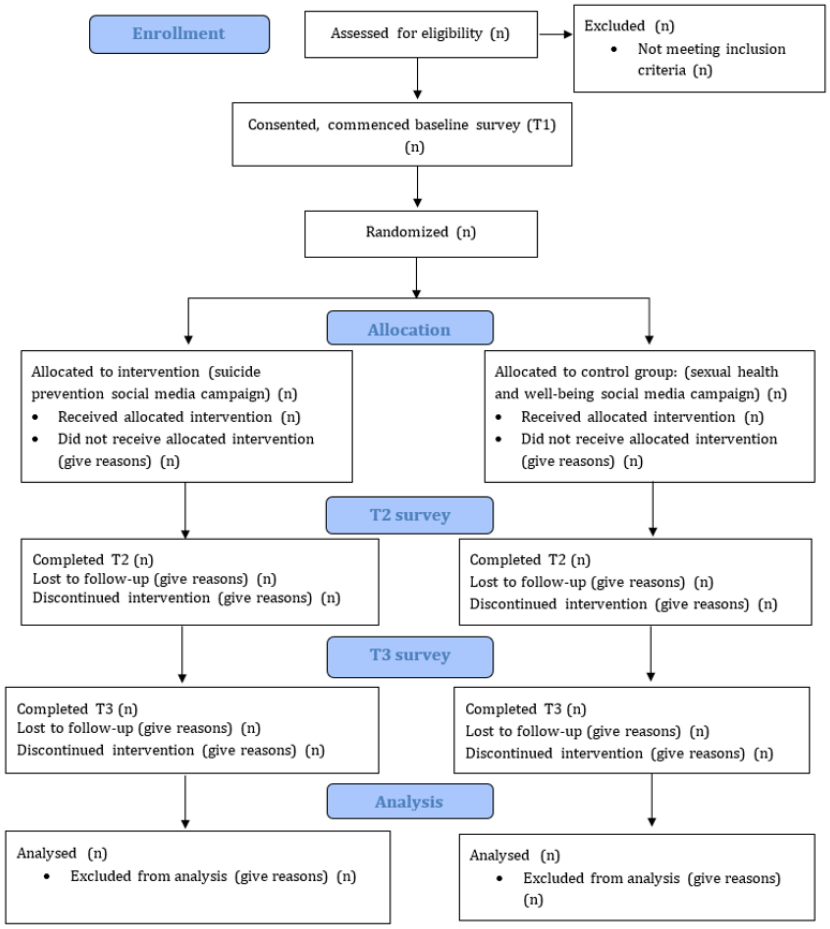
Study Design

The study uses a pragmatic, parallel, superiority randomized controlled design, where the intervention condition (the #chatsafe suicide prevention intervention) is compared to a control condition (sexual health content). It will be conducted over an 18-month period with up to a 12-month recruitment period and an 8-week intervention phase.

Participants will be assessed via self-report surveys at 3 time points: time 1 (T1)—baseline; time 2 (T2)—8-week postintervention commencement; and time 3 (T3)—4-week postintervention. In addition, participants will be asked to complete a short weekly survey to monitor safety and allow evaluation of each piece of social media content. All participants will be reimbursed for their time at a rate of Aus $45 (US $31.95) per hour.

The study is being led by researchers based at Orygen and the Centre for Youth Mental Health, University of Melbourne, Melbourne, Victoria, Australia. It will be conducted and reported in accordance with the Consolidated Standards of Reporting Trials statement [14] (Figure 1).

Figure 1. Consolidated Standards of Reporting Trials flow diagram of participants for enrollment, allocation, T1, T2, T3, and analysis stages.



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Participants and Recruitment

Participants will be 400 young people (200 per arm of the trial). Inclusion criteria are being aged between 16 and 25 years, living in Australia, having used social media to communicate about suicide or self-harm *or* having seen suicide- or self-harm–related information on social media, having not previously participated in a research study that was focused on evaluating suicide prevention or sexual health–related content on social media, considering oneself as being an active social media user, and being willing to share one's mobile phone number with the research team so that one can be contacted with regard to trial-related communications.

Participants will be recruited via social media advertising using Orygen's social media accounts. Young people who wish to participate will be directed to a brief self-assessment questionnaire to assess eligibility. They will then automatically be directed to a web-based consent form, which explains the key aspects of study involvement and consent process. This is followed by the T1 questionnaire, after which, participants will be randomly allocated to either the intervention group (#chatsafe intervention) or the control group.

The participant flowchart is shown in Figure 1.

Intervention

The intervention comprises an 8-week social media campaign. Intervention material will take the form of social media posts shared on public Instagram profiles created for the purpose of this study. As shown in Figure 1, the intervention group will receive the #chatsafe suicide prevention content, and the control group will receive the PROSPEct sexual health content. Both groups will receive 24 pieces of content; that is, 3 per week. All content will be delivered to participants' mobile phones via SMS text messaging via REDCap (Research Electronic Data Capture), an electronic data capture tool hosted at The University of Melbourne. A description of the #chatsafe intervention (group A) is provided in Textbox 1. The content is based on the #chatsafe guidelines and was developed in partnership with young people; examples are provided in Multimedia Appendix 1.

The control content will comprise 8 weeks of sexual health content (PROSPEct content). A description of the control content (group B) is provided in Multimedia Appendix 2, and examples from both the treatment and control conditions are shown in Multimedia Appendix 1.

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Textbox 1. The intervention content (group A, #chatsafe condition) by week.

Week 1: introduction

- Co-design—how the campaign was developed in partnership with young people
- Campaign overview: introduction to campaign learning objectives
- What is safe and unsafe communication about suicide?

Week 2: have you seen posts on the internet about suicide?

- What is safe and unsafe communication about suicide? (continued)
- What to do if you've seen content that you think is unsafe
- What happens when you report content online?

Week 3: sharing your own experiences of suicide on social media

- Sharing experiences in a way that is helpful to you
- Sharing experiences in a way that is helpful to others
- Content warnings

Week 4: asking someone if they are feeling suicidal

- Myth busting—it is safe to ask about suicide
- Things to do before you approach someone
- Asking the question

Week 5: navigating the conversation about suicide

- If they say yes—What you can say to someone in suicidal distress?
- What to say and do if they say no
- How to exit the conversation and looking after yourself

Week 6: when someone has died by suicide

- Safely sharing the news online
- Checking in on your friends (and yourself)
- Memorializing the deceased or communicating after the death

Week 7: helping a friend who has lost someone to suicide

- Checking in with yourself
- Planning how to approach your friend
- Helpful things to say or do to help a friend affected by suicide

Week 8: thank you and wrap up

- Available resources and supports
- Co-design
- Thank you

Study Outcomes

The primary outcome is safety when communicating online about suicide, as measured via the purpose-designed #chatsafe online safety questionnaire at T2. This measure was specifically designed for this purpose by 3 study authors (JR, LLS, and CC).

Secondary outcomes are (1) confidence when communicating on the internet about suicide, as measured via the purpose-designed #chatsafe online safety questionnaire at T2; (2) willingness to intervene against suicide on the internet, as measured via the Willingness to Intervene Questionnaire at T2 [15]; (3) internet self-efficacy, as measured by the Internet Self-Efficacy Questionnaire at T2 [16]; (4) safety of the weekly #chatsafe content, as measured by the purpose-built weekly evaluation and engagement survey; (5) acceptability of the #chatsafe intervention, as measured by the purpose-built T2 evaluation questions; and (6) safety of the #chatsafe social media intervention (as a whole), as measured by the number of (or absence of) adverse events recorded throughout the trial.

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Participant adverse events include (1) participant response to item 9 on the 9-item Patient Health Questionnaire [17] at baseline (time 1), time 2, or time 3. (2) Participant response to the 9-item weekly evaluation survey indicates distress, measured by participants selecting "very distressed" in response to the question "To what extent did you find the content this week distressing?" (3) Participant response to the T2 evaluation questionnaire indicates that a particular piece of campaign content made them feel distressed or at risk of suicide. (4) The participant directly contacts the research team via social media or email and reports distress or risk of harm to self. All adverse events will be responded to by the study team, in line with the study's safety management strategy. (7) Feasibility of the #chatsafe social media intervention was measured by campaign reach via social media analytics, and participant retention or attrition via audit of study enrollment and withdrawal logs. (8) Self-reported evaluations of the acceptability of receiving the #chatsafe social media intervention were measured by purpose-designed study questions. Exploratory outcomes are as follows: (1) subgroup differences (gender, age, previous exposure to, previous experiences of suicide and self-harm, and level of social media usage) at T2 and (2) self-reported open-ended evaluations of the safety, feasibility, and acceptability of receiving the PROSPEct social media intervention for sexual health promotion in the control group at T2.

Outcome Measures

Outcome measures together with the assessment schedule are presented in Table 1. Note that all participants complete the same questionnaires (T1, T2, T3, and purpose-designed 3-item weekly evaluation and engagement survey) regardless of the arm they are allocated to.

Table 1. Schedule of assessments and measures.

Measure	Baseline (T1, week 1)	Intervention (weeks 2-9)	Postintervention (T2, week 9)	Follow-up (T3, week 13)
Purpose designed #chatsafe online safety questionnaire	✓	N/A[a]	✓	✓
Patterns of Social Media Use Questionnaire (including 12 items to assess social media usage for the purposes of communicating about suicide and-self harm specifically)	✓	N/A	✓	✓
Perceived Internet-Self Efficacy Scale	✓	N/A	✓	✓
Willingness to Intervene Against Suicide Questionnaire	✓	N/A	✓	✓
Patient Health Questionnaire-9	✓	N/A	✓	✓
Purpose designed 7-items assessing exposure to, and personal experiences of, suicide and self-harm	✓	N/A	✓	✓
Purpose designed 9-item Weekly Evaluation and Engagement survey	N/A	✓	N/A	N/A
Purpose designed 1-item assessing participant reasons for withdrawal/noncomplete	✓	✓	✓	✓
Purpose designed 10-items assessing participants' evaluations of the intervention content immediately postintervention	N/A	N/A	✓	N/A
Sexual Health Capacity Scale	✓	N/A	✓	✓
Self-Efficacy Protective Sexual Behaviours Scale	✓	N/A	✓	✓
Sexual Health Questionnaire	✓	N/A	✓	✓

[a]N/A: not applicable.

Randomization and Treatment Allocation

Participants will be randomized to the intervention or the control group using block randomization with varying block sizes. The allocation ratio will be 1:1. The randomization schedule is computer generated by independent information technology personnel with guidance from the study statistician (MS). The schedule will then be implemented by a member of the study team (other than the statistician) into the REDCap database management software for allocating treatments to individual participants. Except for the study statistician, the study team members are not blinded to the treatment allocations. The study statistician will not have access to the randomization component of the database and will not be informed about the treatment allocations and will therefore remain blinded. As the study statistician will not be involved in any aspect of this study's operations other than data analysis, there are no circumstances we could foresee under which the study statistician would be required to be unblinded.

Statistical Analysis

At baseline, state of residence, postcode, age, Aboriginal or Torres Strait Island status, gender identity, sexual orientation, primary language spoken at home, cultural background, and educational and occupational background will be reported using descriptive statistics and will be checked for imbalance between trial arms. The moderating effect of gender (male, female, trans, and gender diverse), age group (ie, 16-20 and 21-25 years), time spent on social media, psychological distress, and previous experience of suicide and self-harm will be considered in analyses as covariates.

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Analyses will be performed on an intention-to-treat basis, where all individuals randomized will be included in the analysis by their allocated trial arm status regardless of whether they received all, part, or none of the intended treatments. For the primary analysis, we will use linear regression to estimate the difference in the mean changes between the intervention and control arms at T2 in the outcome safety when communicating online about suicide, as measured via the #chatsafe online safety questionnaire. This analysis will adjust for T1 scores. Multiple imputation will be used to address attrition bias, with 50 imputation samples generated using chained equations. We will conduct 2 sensitivity analyses. One sensitivity analysis will be undertaken using complete cases only (ie, repeating the primary analysis but only analyzing participants who have complete T1 and T2 data). The second sensitivity analysis will use multiple imputation and include the following potential moderating factors as covariates: gender (male, female, transgender, and gender diverse), age group (ie, 16-20 and 21-25 years), time spent on social media, psychological distress, and previous experience of suicide and self-harm.

The secondary outcomes at T2 and T3 will be analyzed based on the primary analysis and the 2 sensitivity analyses. We will use linear regression for continuous outcomes, logistic regression for binary outcomes, and negative binomial regression for counts.

Potential iatrogenic effects will be analyzed on a weekly basis and will serve as an interim analysis throughout the course of the study. If the weekly content is assessed as “very distressing” by more than 20% of participants per week, the safety monitoring committee (SMC) will be consulted, and the content may be withdrawn. The acceptability of each week’s content will be analyzed and reported as descriptive statistics (frequencies and percentages).

Sample Size and Statistical Power

This is the first study to investigate the #chatsafe intervention in an RCT and the first to use the proposed measures. As such, there are no previous data to guide the possible effect of the intervention, and therefore the sample size is required; however, a sample of ~400 participants (200 per arm) should be sufficient to assess the primary study outcome with a 5% significance level and 80% power.

The pilot study [13] recruited a total of 507 participants within a 3-month period, resulting in a final sample of 189 young people who completed all 3 time points. Note that the intervention period for this study was 12 weeks compared to 8 weeks in this study. As such, data from the pilot study on rates of recruitment and attrition indicate that the recruitment period of up to 12 months will be more than sufficient to achieve the required sample size.

In an effort to reduce attrition, all participants will be sent a SMS text message by a research team member halfway through the intervention period (week 4), as well as at T2 and T3 if they have not completed their survey 4 days after being sent their survey. This will encourage participants to complete their survey if they have not already done so and will provide them the opportunity to raise any concerns or questions.

Ethical Considerations

The study has been approved by the University of Melbourne Human Research and Ethics Committee (ID 2022-24238-32907-3). All participants will be required to provide written consent prior to commencement of the study.

The study will be carried out in accordance with the principles contained in the Declaration of Helsinki and the Australian National Health and Medical Research Council (NHMRC) National Statement on Ethical Conduct in Human Research and the NHMRC Australian Code for the Conduct of Research. In addition to being assessed at T2, safety will also be tracked using the weekly evaluation and engagement survey to identify any distress that is attributed to the intervention (see Table 1). Previous distress and suicide risk will be deemed as that reported during the baseline assessment. Further relevant risk will not be reported unless adverse events are reported by the participant or other study team members, which are deemed to possibly having been caused by study activities such as distress because of the intervention or because of interaction with the study team.

As per the pilot study, an SMC has been established. The main purpose of the committee is to oversee the safety of the trial. It comprises the study Chief Investigator (JR), members of the study team, as well as an Orygen Sponsor Operations representative, a statistician, a clinician, and a subject-matter expert. An initial meeting will be held prior to the commencement of recruitment to review the study risk assessment and the determination of safety oversight procedure. The research team will meet fortnightly for the duration of the trial, and a standing function of these meetings will be to review safety incidents and refer any relevant matters to SMC. All members of the SMC will be convened on a study-specific basis (ie, any time a serious safety concern is raised). The SMC will make recommendations as to appropriate risk assessment and mitigation measures, including but not limited to decisions as to whether the study should be amended or put on hold.

Finally, detailed safety protocols have been established and overseen by the trial psychologist (SR) and Orygen’s Sponsor Operations team (Multimedia Appendix 3).

Youth Participation

Young people have been involved in the preparation of this study in multiple ways. First, the entire #chatsafe program of work has been conceptualized, designed, and conducted in partnership with young people. The #chatsafe guidelines were created using the Delphi consensus method, with young people as an expert panel [11]. The first #chatsafe social media campaign was cocreated in partnership with over 140 young people [12].

The study was presented to Orygen’s Youth Research Council in November 2021, and feedback on intervention development and study conduct was obtained. A total of 3 co-design (N=46) and 1 user testing (N=10) workshops were conducted in April and May 2022 to help create the trial content. A total of 3 youth advisors helped to develop the participant information consent form and the #chatsafe online safety questionnaire. Finally, we are currently recruiting 2 paid youth advisors to this study to assist with participant recruitment and engagement. At the end

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of the study, they will assist with the interpretation and dissemination of the study findings, including conference presentations and journal articles.

Results

The funding for this project was awarded in November 2020 by the Australian Research Council; however, progress was delayed down due to the impacts of the COVID-19 pandemic. Approval from the University of Melbourne Human Research and Ethics Committee was provided in October 2022. Recruitment into the trial began in November 2022 and study completion is anticipated by June 2024. The trial is registered with the Australian and New Zealand Clinical Trials Registry (ACTRN12622001397707).

Discussion

This will be the first RCT internationally to test the impact of a social media intervention designed to better equip young people to communicate safely on the internet about suicide.

Social media platforms are commonly used by young people to communicate about suicide. While users rarely set out to cause harm to themselves or others, the potential for harm exists [18,19]. Therefore, it is essential that young people are adequately equipped to safely communicate on the internet about suicide. Guidelines regarding safe reporting of suicide exist for mainstream media [20]; however, until recently, no such guidelines have been developed by, and for, young people. Also, existing media guidelines do not specifically address the challenges and opportunities offered by social media. Although media campaigns are gaining traction in the suicide prevention sector, to date, they have not been developed with young people in mind nor have their impact on behavior change, in particular among young people, been tested.

The development of the #chatsafe intervention not only addresses these gaps, but it also represents a paradigm shift. It shifts the narrative away from advising young people to avoid engaging in suicide-related communication on social media—a strategy that is clearly not working—toward an approach that seeks to better equip young people to communicate safely. The guidelines themselves have already had significant traction not just in Australia but also internationally. They have been adapted for 11 additional countries and downloaded around 120,000 times [21]. In addition to being freely available on the Orygen website, they are also available via both the Facebook and Instagram Safety Centers, thereby significantly extending their reach [22,23]. The social media content has been widely disseminated via platforms such as Instagram, Facebook, Snapchat, and YouTube. There are few suicide prevention interventions that have the potential to be delivered at scale in this way.

This study proposes a rigorous and novel methodology. Until now, research into suicide and social media has been largely cross-sectional in nature and has examined the association between social media use and suicidal thinking. No studies have tested suicide prevention interventions delivered via social media using robust research designs. This study will build on a previous pilot study (La Sala et al, unpublished data) and will provide a robust evidence base for this work.

This work is timely. Given the rising rates of youth suicide in Australia and the acceptability of social media among young people, incorporating social media–based interventions into the suicide prevention landscape is an obvious next step. This intervention, if effective, could also be extended to international settings, thereby improving online safety for young people not just in Australia but globally.

Acknowledgments

The study received funding from the Australian Research Council (DP210101097). The #chatsafe project also receives funding from the Commonwealth Department of Health under the National Suicide Prevention Leadership and Support Program. JR is funded by an NHMRC Investigator Grant (ID2008460) and a Dame Kate Campbell Fellowship from the University of Melbourne. LLS is funded by a Suicide Prevention Australia post-doctoral fellowship. SR is funded by an NHMRC Career Development Fellowship (APP1158881) and a Dame Kate Campbell Fellowship from the University of Melbourne. JP is funded by a National Health and Medical Research Council Investigator Grant (GNT1173126) and a Dame Kate Campbell Fellowship from the University of Melbourne. MS is a recipient of an Australian Research Council Future Fellowship (FT180100075) and a Dame Kate Campbell Fellowship from the University of Melbourne.

Data Availability

All data analyzed during this study will be included in any published articles (and their supplementary information files). The participants of this study did not give written consent for their data to be shared publicly, so due to the sensitive nature of this research, supporting data are not available.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Intervention content examples.

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[DOCX File , 428 KB - resprot_v12i1e44300_app1.docx]

Multimedia Appendix 2
The control content.
[DOCX File , 14 KB - resprot_v12i1e44300_app2.docx]

Multimedia Appendix 3
Overview of safety management strategy.
[DOCX File , 19 KB - resprot_v12i1e44300_app3.docx]

Multimedia Appendix 4
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[PDF File (Adobe PDF File), 112 KB - resprot_v12i1e44300_app4.pdf]

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Abbreviations

NHMRC: Australian National Health and Medical Research Council
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
SMC: safety monitoring committee

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Protocol

Evaluation and Management of Dyspnea in Hypermobile Ehlers-Danlos Syndrome and Generalized Hypermobility Spectrum Disorder: Protocol for a Pilot and Feasibility Randomized Controlled Trial

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Abstract

Background: Dyspnea is a prevalent symptom in individuals with hypermobile Ehlers-Danlos Syndrome (hEDS) and generalized hypermobility spectrum disorder (G-HSD), yet its contributors have not been identified. One known contributor to dyspnea is respiratory muscle weakness. The feasibility and effectiveness of inspiratory muscle training (IMT) in combination with standard-of-care rehabilitation (aerobic, resistance, neuromuscular stabilization, and balance and proprioception exercises) in improving respiratory muscle strength and patient-reported outcomes in patients with hEDS or G-HSD have not been evaluated.

Objective: This study aims to evaluate dyspnea, respiratory muscle strength, and patient-reported outcome measures (PROMs) in hEDS or G-HSD compared with healthy controls and to assess the feasibility of a randomized controlled trial of IMT and standard-of-care rehabilitation for improving respiratory muscle strength, exercise capacity, and PROMs compared with standard-of-care rehabilitation in hEDS and G-HSD.

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Methods: The study will include 34 participants with hEDS or G-HSD and 17 healthy, age- and sex-matched controls to compare respiratory muscle structure and function and PROMs. After baseline assessments, participants with hEDS or G-HSD will be randomized into the intervention group and provided IMT combined with Ehlers-Danlos Syndrome standard-of-care rehabilitation or into the usual care group, and provided only standard-of-care rehabilitation for 8 weeks. The intervention group will be prescribed IMT in their home environment using the POWERbreathe K5 IMT device (POWERbreathe International Ltd). IMT will comprise 2 daily sessions of 30 breaths for 5 days per week, with IMT progressing from 20% to 60% of the baseline maximal inspiratory pressure (MIP) over an 8-week period. Feasibility will be assessed through rates of recruitment, attrition, adherence, adverse events, and participant satisfaction. The primary pilot outcome is MIP change over an 8-week period in hEDS or G-HSD. Secondary outcomes will include the evaluation of dyspnea using Medical Research Council Scale and 18-point qualitative dyspnea descriptors; diaphragmatic thickening fraction using ultrasound; respiratory muscle endurance; pulmonary function; prefrontal cortical activity using functional near-infrared spectroscopy; aerobic capacity during cardiopulmonary exercise testing; quality of life using Short Form-36; and scores from the Depression, Anxiety, and Stress scale-21. These measures will also be performed once in healthy controls to compare normative values. Multivariable regression will be used to assess the contributors to dyspnea. Paired 2-tailed *t* tests will be used to assess the changes in MIP and secondary measures after 8 weeks of IMT.

Results: Study recruitment began in August 2021 and, with several disruptions owing to COVID-19, is expected to be completed by December 2023.

Conclusions: This study will provide a better understanding of the factors associated with dyspnea and the feasibility and effectiveness of IMT combined with standard-of-care rehabilitation. IMT may be a novel therapeutic strategy for improving respiratory muscle function and patient-reported outcomes in individuals with hEDS or G-HSD.

Trial Registration: ClinicalTrials.gov NCT04972565; https://clinicaltrials.gov/ct2/show/NCT04972565

International Registered Report Identifier (IRRID): DERR1-10.2196/44832

(JMIR Res Protoc 2023;12:e44832) doi:10.2196/44832

KEYWORDS

Ehlers-Danlos Syndrome; generalized hypermobility spectrum disorders; inspiratory muscle training; rehabilitation; exercise; mobile phone

Introduction

Background

Ehlers-Danlos Syndrome (EDS) is a group of hereditary connective tissue disorders characterized by multisystem manifestations involving musculoskeletal and nonmusculoskeletal domains [1]. Currently, the International Classification of EDS and related disorders includes 14 subtypes based on a set of clinical criteria, with the most common subtype being hypermobile EDS (hEDS), which comprises 80% to 90% of EDS cases [1-3]. Patients who present with symptomatic generalized joint hypermobility and chronic pain but do not meet the International 2017 classification criteria are classified as having generalized hypermobility spectrum disorder (G-HSD) [3]. The clinical manifestations of the disease vary according to the EDS subtype, and our understanding of this disorder has evolved to recognize multisystem manifestations beyond the musculoskeletal system, including gastrointestinal, neurological, cardiovascular, and respiratory involvement [1]. These manifestations arise from abnormal collagen or proteins that bind collagen that affect the connective tissue throughout the body [1]. Given the multisystem nature of hEDS and G-HSD, several symptoms such as pain and fatigue may contribute to reduced health-related quality of life (HRQL), physical deconditioning, anxiety, and depression [4-8].

Respiratory Manifestations in EDS and G-HSD

Our research group and others have recently highlighted that respiratory manifestations are common in hEDS and G-HSD and include, but are not limited to, dyspnea, cough, asthma, and respiratory muscle weakness [2,9]. The collagen abnormalities lead to impairments throughout the respiratory system, which may contribute to the respiratory abnormalities observed in this population [2,10]. In individuals with hEDS, the prevalence of dyspnea is estimated to be approximately 50% [11]. Dyspnea has been described in a few studies on individuals with G-HSD, but its prevalence and determinants have not been well characterized [12]. A study reported that up to 26% of the patients with G-HSD presented with cardiorespiratory manifestations such as dyspnea, palpitations, and chest pain, which were commonly attributed to autonomic dysfunction [13].

Respiratory symptoms in EDS and G-HSD have also been associated with worse outcomes such as lower physical activity levels and function. Individuals with EDS or G-HSD experienced increased dyspnea while walking on a flat level compared with healthy controls [12]. Furthermore, a study investigating physical activity levels between patients with hEDS or G-HSD with autonomic dysfunction and those without autonomic dysfunction observed that autonomic dysfunction was associated with exercise intolerance, which is often attributed to increased symptoms of dyspnea and chest pain [14]. Postural orthostatic tachycardia syndrome, a more severe form of autonomic dysfunction, has also been observed to be associated with dyspnea, chest pain, and impairments in HRQL [15,16]. Thus, respiratory manifestations in individuals with hEDS or G-HSD have important consequences on exercise tolerance, HRQL, and functional abilities.

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Contributors to Dyspnea in hEDS and G-HSD

Functional impairments in respiratory muscle weakness occur in >75% of individuals with hEDS and can result in dyspnea and a restrictive pattern of ventilation [11]. The diaphragm is the main respiratory muscle, and alterations in collagen can lead to impairments in the respiratory muscle structure and function [17]. Respiratory muscle weakness has also been associated with lower vital capacity, which may contribute to dyspnea [18,19]. Thus, strengthening the respiratory muscles through modalities such as inspiratory muscle training (IMT) may improve dyspnea and pulmonary function [20].

Some individuals with hEDS or G-HSD have been observed to have chest wall deformities and increased rates of asthmatic symptoms, which can contribute to dyspnea and peripheral airway abnormalities [12,21,22]. There is also an increased tendency for dynamic airway collapse despite normal chest imaging, which highlights altered lung mechanics, including airway pressures and lung volumes [12]. Furthermore, deconditioning has been described as a contributor to low physical activity levels in the population with EDS or G-HSD as a consequence of increased joint laxity, pain, and peripheral muscle weakness [23]. Physical deconditioning may further exacerbate dyspnea and contribute to low exercise tolerance [23]. In conditions such as chronic obstructive pulmonary disease (COPD), cortical neural activity in the prefrontal cortex (PFC) has been shown to be associated with dyspnea and exercise intolerance and may be another contributor to dyspnea in hEDS or G-HSD [24,25]. Modalities such as functional near-infrared spectroscopy (fNIRS) have been used to assess PFC activity in individuals experiencing dyspnea during exercise testing [24]. Taken together, respiratory muscle weakness, peripheral airway changes, physical deconditioning, and autonomic dysfunction may contribute to the multifactorial nature of dyspnea in hEDS or G-HSD. These factors can be evaluated clinically and may help us understand the mechanisms that contribute to dyspnea and, importantly, tailor effective respiratory management strategies.

IMT and Standard-of-Care Rehabilitation

IMT has been established as an effective intervention for improving respiratory muscle structure and function in populations with chronic lung diseases [26,27]. A study observed that among 104 individuals with hEDS, 80 (77%) individuals had respiratory muscle weakness [11]. After 6 weeks of IMT, respiratory muscle strength measured with sniff nasal inspiratory pressure improved by 20% (pre-IMT intervention: mean 41, SD 17 cm H_2O vs post-IMT measurement: mean 49, SD 18 cm H_2O; $P<.001$) in patients with hEDS. Furthermore, the 6-minute walk distance improved by 13% (pre-IMT measurement: mean 455, SD 107 m vs post-IMT measurement: mean 515, SD 127 m; $P=.003$) along with forced expiratory volume in 1 second by 10% (pre-IMT measurement: mean 94%, SD 14% vs post-IMT measurement: mean 103%, SD 11%; $P=.01$). Thus, IMT may be an effective intervention for improving respiratory muscle strength, lung function, and exercise capacity in patients with hEDS or G-HSD.

Physical rehabilitation involving whole-body exercises such as aerobic and strength training has been shown to improve dyspnea in healthy populations and populations with chronic lung diseases such as COPD and idiopathic pulmonary fibrosis [28-31]. In a meta-analysis of 14 randomized controlled trials (RCTs), resistance training and endurance training were associated with improved dyspnea tolerance during exercise training, along with resting dyspnea levels, in patients with COPD [30]. This is often attributed to improved physical fitness owing to exercise training, which increases the efficiency of the muscles and decreases the level of ventilatory demand [30]. Unlike other populations, research on the effects of exercise training on individuals with hEDS or G-HSD is in its early stages, with only 5 RCTs performed in this area to date [32]. Following rehabilitation, in patients with hEDS or G-HSD, improvements have been observed in exercise capacity, muscle strength, mood, HRQL, and performance of daily activities [32].

Although the IMT RCT highlighted the safety and feasibility of IMT in hEDS, the study did not evaluate the mechanisms of dyspnea or assess diaphragm structure and function [11]. Furthermore, physical activity and other concurrent training, which may provide synergistic beneficial effects on respiratory symptoms and exercise capacity, were not considered. Several studies on chronic lung disease have demonstrated that IMT in combination with whole-body exercises, such as aerobic exercise, offers synergistic benefits on respiratory muscle strength and endurance and exercise capacity in comparison with whole-body exercises alone [23,33,34]. IMT alone has been shown to be an effective intervention in populations with asthma, populations with COPD, and populations with interstitial lung disease for improving maximal inspiratory pressure (MIP), respiratory muscle endurance, and diaphragm function [26,27,35] and thus may be an effective strategy in the population with hEDS or G-HSD.

The efficacy of both IMT and standard-of-care rehabilitation in ameliorating dyspnea and improving aerobic capacity and respiratory muscle structure and function in the population with hEDS or G-HSD has not been investigated to date. It is also unclear whether IMT in combination with standard-of-care rehabilitation is a feasible intervention, specifically for the population with hEDS or G-HSD, given the increased comorbidities. Furthermore, the efficacy of IMT has only been evaluated in hEDS and yet to be studied in G-HSD. This study aims to address these gaps.

Study Aims

The aims of this study are (1) to compare respiratory muscle strength and patient-reported outcome measures (PROMs) between individuals with hEDS or G-HSD and healthy, age- and sex-matched controls, as well as evaluate the main contributors to dyspnea in individuals with hEDS or G-HSD, and (2) to assess the feasibility of an RCT of IMT and standard-of-care rehabilitation (aerobic, resistance, neuromuscular stabilization, and balance and proprioception exercises) for improving respiratory muscle strength, exercise capacity, and PROMs compared with standard-of-care rehabilitation in hEDS or G-HSD.

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Hypotheses

We hypothesize that (1) individuals with hEDS or G-HSD will have lower respiratory muscle strength, higher peripheral airway resistance, lower HRQL, and higher anxiety and depression levels than age- and sex-matched healthy controls and that (2) the delivery of IMT and standard-of-care rehabilitation will be feasible and result in a significant improvement in respiratory muscle strength (MIP) over an 8-week period.

Methods

Study Design

Participants with hEDS or G-HSD will complete assessments at baseline (T_0; Table 1) and will be randomized into the intervention arm (IMT and standard-of-care rehabilitation) or usual care group (standard-of-care rehabilitation). The standard-of-care rehabilitation at the GoodHope EDS Clinic at Toronto General Hospital comprises active exercise training involving aerobic, resistance, neuromuscular stabilization, and balance and proprioception exercises, and is a part of the GoodHope Exercise and Rehabilitation Program (GEAR) [36].

Age- and sex-matched healthy controls will undergo the same T_0 assessments as those that the EDS and G-HSD intervention and usual care groups will undergo. The respiratory muscle structure and function, dyspnea, exercise capacity, and collected PROMs will be compared. Only the participants with hEDS or G-HSD (intervention and usual care groups) will repeat the T_0 assessments after 8 weeks, as described in the subsequent section on assessments.

Table 1. Summary of study measurements.

Measurement	Baseline assessments[a]	
	Intervention and usual care groups	Healthy control group
Dyspnea		
Medical Research Council Dyspnea Scale	✓	✓
18-Point Qualitative Dyspnea Scale	✓	✓
Pulmonary function tests		
Oscillometry	✓	✓
Spirometry and lung volumes	✓	✓
Respiratory muscle endurance[b]	✓	✓
Maximal respiratory pressures	✓	✓
Diaphragmatic measures	✓	✓
PROMs[c]		
Health-related quality of life: Short Form-36	✓	✓
Mood: Depression, Anxiety, and Stress scale	✓	✓
Physical activity volume: Godin Leisure-Time Exercise Questionnaire	✓	✓
Demographic questionnaire	✓	✓

[a]All baseline measures will be repeated after 8 weeks for the participants with hypermobile Ehlers-Danlos Syndrome or generalized hypermobility spectrum disorder.

[b]Respiratory muscle endurance will be repeated at 4 weeks.

[c]PROM: patient-reported outcome measure.

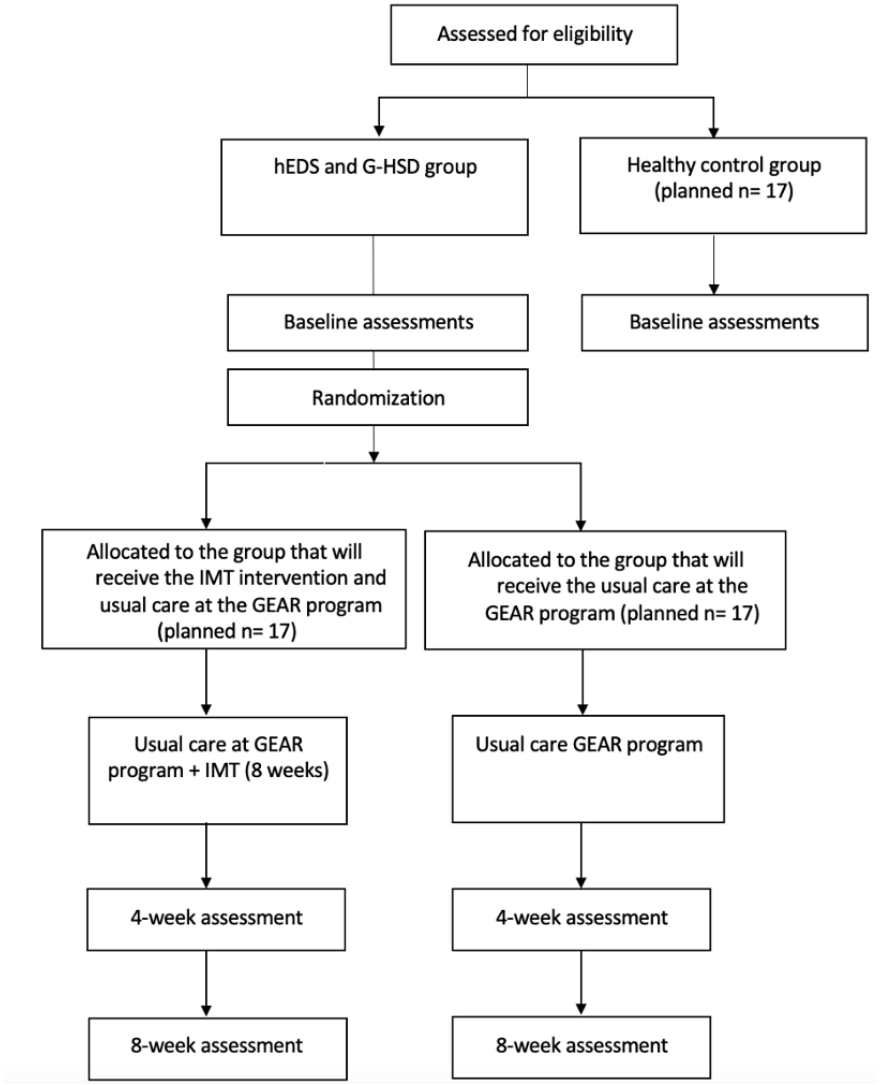
Ethics Approval

Ethics approval has been obtained from the research ethics board at the University Health Network (ID: 20-6346.0) and University of Toronto (ID: 42667). The study has been registered at ClinicalTrial.gov (NCT04972565).

Written informed consent will be obtained from all participants before the commencement of any research activities. The Standard Protocol Items: Recommendations for Interventional Trials, the CONSORT (Consolidated Standards of Reporting Trials) statement, and the Consensus on Exercise Reporting Template will be used [37-39]. Refer to Figure 1 for the CONSORT flow diagram.

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Figure 1. CONSORT (Consolidated Standards of Reporting Trials) flow diagram with healthy controls. GEAR: GoodHope Exercise and Rehabilitation Program; G-HSD: generalized hypermobility spectrum disorder; hEDS: hypermobile Ehlers-Danlos Syndrome; IMT: inspiratory muscle training.



Recruitment and Screening

Participants with hEDS or G-HSD will be recruited from the GEAR program at Toronto General Hospital, which is a major teaching hospital in Toronto, Canada. The GEAR program evaluates approximately 12 new participants per month. Potential participants are screened for study eligibility by exercise professionals who are part of the GEAR program. The research team will confirm the eligibility criteria, discuss study participation, and obtain consent among interested participants. The study flow of participants is shown in Figure 1.

Participants With hEDS or G-HSD

The sample will comprise adult individuals (aged ≥18 years) diagnosed with hEDS or G-HSD by the EDS medical team at Toronto General Hospital based on the 2017 diagnostic criteria [3]. Participants will be included if they have started their participation in the GEAR program within 4 weeks.

The following exclusion criteria will be applied:

1. Diagnosis of other subtypes of EDS (eg, classical and vascular)
2. Have a cardiac pacemaker, defibrillator, neuromuscular disease, severe autonomic dysfunction, or other cardiovascular manifestations limiting exercise or other exercise contraindications
3. Recent respiratory infection (<1 month) or known diagnosis of obstructive or restrictive parenchymal disease
4. History of pneumothorax, acute otitis media (fluid behind the eardrum), or rupture of tympanic membranes, given the risk owing to IMT
5. Participation in formal exercise training or IMT program within the last 3 months
6. Insufficient English fluency to provide informed consent or inability to follow study protocols
7. Self-reported pregnancy
8. No internet access for IMT or web-based assessments

Healthy Controls

Healthy adults (aged ≥18 years) will be age- and sex-matched with the participants with EDS and G-HSD. Individuals will be excluded from the study if they meet the following criteria:

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1. Diagnosis of a respiratory, cardiovascular, or musculoskeletal condition that may contribute to exercise limitation
2. Presence of cardiac pacemaker or implantable defibrillator
3. Insufficient English fluency to provide informed consent or inability to follow study protocols
4. Self-reported pregnancy
5. Active smoker (cigarettes or marijuana)

Assessments

At T_0, the participants with hEDS and G-HSD will undergo pulmonary function tests (PFTs), cardiopulmonary exercise test (CPET) with fNIRS on the PFC, PROMs, and diaphragm ultrasound. The same assessments will be performed for healthy controls. Please refer to Table 1 for a detailed list of T_0 measurements. At 4 weeks, respiratory muscle endurance assessment will be repeated for the participants with hEDS and G-HSD. All T_0 assessments, including PFTs, CPET, PROMs, and respiratory muscle endurance assessment, will be repeated at 8 weeks for the participants with hEDS and G-HSD.

The following tests will be used to assess the primary and secondary outcome measures in the PFT laboratory at Toronto General Hospital.

Respiratory Parameters

Assessment Using PFTs

Spirometry and Lung Volumes

Forced expiratory volume in 1 second, forced vital capacity, total lung capacity, and lung volumes (tidal volume, inspiratory capacity, expiratory reserve, and residual volumes) will be evaluated in accordance with the American Thoracic Society guidelines before CPET [40].

Oscillometry

This will be performed before other PFTs according to the European Respiratory Society Guidelines, as previously described [41,42]. Oscillometry provides detailed information regarding respiratory mechanics by measuring respiratory impedance, a complex sum of respiratory resistance, and reactance [43]. This technique uses sound waves to capture disturbances in airway resistance and can be a more sensitive marker of peripheral airway obstruction than spirometry [44,45]. Because it is performed during normal breathing, oscillometry is independent of effort and is not influenced by respiratory muscle strength. We will follow the quality assurance and control guidelines developed by our group using the tremoflo device (Thorasys) [46].

Respiratory Muscle Strength

MIP and maximal expiratory pressure will be evaluated using the American Thoracic Society standards. These measures will be repeated 3 times, and the highest value (cm H_2O) that is 10% within the lower measures will be used [47,48].

Respiratory Muscle Endurance

The threshold loading device (Threshold IMT trainer [Philips]) [49] will be used to evaluate respiratory muscle endurance. We will assess the time that can be sustained at respiratory endurance at 30% of MIP obtained as part of the T_0 measures after a brief familiarization session with the loading device. The maximum endurance that the threshold loading device can reach is 41 cm H_2O. The endurance assessment will be repeated within 5 minutes if the participant stops the protocol early (<1 minute) because of severe coughing or lack of familiarity with the loading device. The maximum endurance that participants will be asked to perform is 15 minutes. Oxygen saturation will be concurrently monitored with pulse oximetry during the assessment.

Diaphragm Ultrasound

While the participant is in semirecumbent position, the research coordinator will place an ultrasound probe perpendicular to the chest wall in the 8th or 9th intercostal space between the anterior and midaxillary lines using a 5-13 MHz transducer (GE Logiq e Laptop Ultrasound System [GE Medical Systems]) [50]. Bright-mode ultrasound will be used to visualize the diaphragm, and motion-mode ultrasound will be used to assess the amplitude of the cranio-caudal diaphragmatic excursion during quiet and deep breathing. Diaphragm thickness will be measured as the distance between the leading edges of the diaphragmatic pleura and peritoneum at resting end expiration and after peak inspiration. Thickening fraction, an established marker of diaphragm strength, will be calculated as follows: ([diaphragm thickness at end expiration–diaphragm thickness at peak inspiration] divided by diaphragm thickness at end expiation) × 100 [50].

Assessment Using CPET

Overview

Symptom-limited CPET will be performed on a cycle ergometer (Elema), with exhaled gas measurements captured breath by breath, as routinely applied in our PFT laboratory. Testing will start with 2 minutes of complete rest on the bike, followed by unloaded pedaling for 2 minutes, and then exercise intensity will be increased by 10 to 20 W per minute using a ramp protocol. Blood pressure, 12-lead electrocardiogram, and peripheral oxygen saturation will be continuously monitored. Inspiratory capacity, tidal volumes, and respiratory rate will be measured throughout the exercise to assess for any dynamic hyperinflation and ventilatory reserve. Heart rate (HR) response, peak aerobic capacity, oxygen pulse (measure of cardiac stroke volume), and minute ventilation (product of tidal volume and respiratory rate) will be collected throughout the exercise and up to 2 minutes after test completion with unloaded pedaling, with percent predicted values reported. HR recovery (difference between peak HR and HR 1 minute after exercise) and the chronotropic response index ([peak HR – resting HR × 100] / [220 – age] – [resting HR]) will be collected as a measure of autonomic function [51-53]. Chronotropic incompetence is the inability to decrease HR after exercise or the inability to reach 80% of the maximal age-predicted HR because of abnormal sympathetic activation [51]. Symptom intensity for breathing and leg discomfort with exercise will be measured at rest and every 3 minutes throughout the exercise using the Borg dyspnea [54] and leg fatigue scales [55]. The reasons for exercise cessation will be ascertained from the participants (ie, dyspnea, leg fatigue, both, or other). To ensure participant safety before

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CPET, 12-lead electrocardiograms will be performed for both the participants with hEDS or G-HSD and healthy controls.

Assessment Using fNIRS

fNIRS is a noninvasive method that uses continuous optical topography to evaluate increases in oxygenated hemoglobin levels, an indicator of PFC activity that has been suggested to be associated with dyspnea [56-58]. The change in oxyhemoglobin and deoxyhemoglobin will be monitored using the Artinis fNIRS device (Artinis Medical Systems) [59], which will be secured over the participant's forehead, with the center of each sensor pad vertically aligned with the iris. Light intensity data at 2 wavelengths (730 and 850 nm) will be obtained during CPET from the left and right sides of medial PFC and dorsolateral PFC using a cognitive optical brain imaging software at a sampling frequency of 4 Hz. Detector gain settings will be adjusted for light intensity, and filters will be applied to attenuate the physiological artifacts of respiration and pulse.

Assessment Using PROMs

Dyspnea

The Medical Research Council (MRC) dyspnea scale [60], Borg dyspnea scale [54], and 18-item qualitative dyspnea descriptors will be used [61]. This will allow us to evaluate the quantitative and qualitative changes in respiratory symptoms.

1. *MRC dyspnea scale*: the MRC dyspnea scale (1-5) will be used to assess the effect of breathlessness on daily activities at T_0 [60]. It allows patients to indicate the extent to which breathlessness limits their daily functioning [60].
2. *Borg dyspnea scale*: the highest score on a 10-point Borg scale at the beginning and end of CPET will be measured. The participants will also be asked to indicate their daily Borg dyspnea score before and after their IMT practice in their participant logs [62].
3. *Qualitative dyspnea descriptors:* the qualitative dyspnea descriptors scale comprises a list of 18 dyspnea descriptors. Qualitative descriptors of dyspnea will be ascertained at T_0 and at the end of CPET [61].

Exercise Behaviors and Physical Activity

Exercise behaviors will be measured using the 3-item Godin Leisure-Time Exercise Questionnaire—Leisure Score Index, which is a reliable and validated measure for this population [63]. This index assesses the frequency of mild, moderate, and strenuous bouts of leisure physical activity performed for at least 15 minutes over the past week. In addition, physical activity will be measured using a tracking device (Fitbit), which will record daily steps and active minutes for the study participants with hEDS or G-HSD [64,65].

Measurement of HRQL

The Short Form-36 Health Survey (version 1.0) will be used to assess generic HRQL [66]. It comprises 8 health domains that contribute to 2 physical and mental component scores (ranging from 0 to 100), with higher scores representing better HRQL. A 5-point change in the physical component scores or mental component scores is considered clinically significant [66].

Depression, Anxiety, and Stress

The Depression, Anxiety, and Stress scale has 21 items to assess mood (depression, anxiety, and stress) and has been administered to patients with hEDS [8]. It has acceptable to excellent internal consistency, and normative data are available [67].

Anthropometric Measures

Standard anthropometric measures will be captured for all the participants. Height, weight, waist circumference, and BMI information will be collected for the participants with hEDS or G-HSD from the electronic patient charts. The same measures will be collected for healthy controls during the T_0 assessments.

Clinical Assessments

We will abstract standard GEAR program measures from the medical charts for all the participants with hEDS or G-HSD: 6-minute walk distance, lower extremity function (5-repetition sit-to-stand test), hand-grip strength, Bristol questionnaire, and Godin Leisure-Time Exercise scale. The Beighton score [68], Charlson comorbidity index [69], and medications such as opioids that can impact dyspnea will be abstracted from chart review.

Sociodemographic Parameters

We will abstract information on demographics such as age, ethnicity, sex, employment status, education level, and lifestyle factors (eg, smoking status) from the medical charts for the participants with hEDS or G-HSD. Demographic data will be collected from healthy controls via a demographic survey.

Randomization

After T_0 assessments, the participants will be randomly allocated to the intervention or usual care group using a 1:1 ratio stratified by hEDS or G-HSD. The allocation of the participants to their groups will be randomized (blocks of 2 to 4) using shuffled, opaque envelopes by a biostatistician. The study participants and the research team and coordinator supervising the IMT will be aware of the group assignments.

Study Arms

Overview

The participants in both the intervention and usual care groups will receive the standard-of-care rehabilitation in the GEAR program. Those in the intervention group will receive IMT in addition to the GEAR program components, as shown in Table 2.

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Table 2. Summary of the study procedures.

Study groups	IMT[a] intervention group with participants with hEDS[b] or G-HSD[c] (n=17)	Usual care group with participants with hEDS or G-HSD (n=17)
Standard of care—GEAR[d] program: baseline (T_0), 4 weeks from T_0 (T_1), 8 weeks from T_0 (T_2), and 20 weeks from T_0 (T_3)	• Aerobic, resistance, neuromuscular stabilization, and balance and proprioception exercises [36]	• Aerobic, resistance, neuromuscular stabilization, and balance and proprioception exercises [36]

Baseline assessment (details provided in Table 1)	• Baseline assessment: explanation of equipment and tracking
	• IMT device POWERbreathe K5
	• IMT and exercise logs and Fitbit device and instructions
	• Fitbit device and instructions
	• Exercise logs
		• Baseline assessment:
		  • Fitbit device and instructions
		  • Exercise logs

Study intervention: 8 weeks	• 2 daily IMT sessions of 30 breaths (<5 minutes per session) for 5 days per week, up to 8 weeks • IMT starting at 20% of MIP[e] (up to a maximum of 60%) • Intensity progressed by 5% to 10% if the median weekly Borg dyspnea score is <7 • Web-based supervision by the study team • Weekly check-in with the study coordinator	• N/A[f]
Follow-up: week 4 time point	• Study assessments will be performed at week 4 from the home environment. Exercise logs and respiratory muscle endurance will be assessed	• Study assessments will be performed at week 4 from the home environment. Exercise logs and respiratory muscle endurance will be assessed
End point: week 8 time point	• Study assessments conducted at baseline will be performed again at week 8 in the PFT[g] laboratory. Collection of logs, Fitbits, and IMT device (POWERbreathe K5) will be done at the end of the study	• Study assessments conducted at baseline will be performed at week 8 in the PFT laboratory. Collection of logs, Fitbits, and IMT device (POWERbreathe K5) will be done at the end of the study.

[a]IMT: inspiratory muscle training.

[b]hEDS: hypermobile Ehlers-Danlos Syndrome.

[c]G-HSD: generalized hypermobility spectrum disorder.

[d]GEAR: GoodHope Exercise and Rehabilitation Program.

[e]MIP: maximal inspiratory pressure.

[f]N/A: not applicable.

[g]PFT: pulmonary function test.

Usual Care Group

The standard-of-care rehabilitation in the GEAR program comprises 8 weeks of aerobic, resistance, neuromuscular stabilization, and balance and proprioception exercises performed in the home environment [1]. The participants in the GEAR program attend in-person or web-based exercise training sessions at the following intervals: T_0, 4 weeks from T_0, 8 weeks from T_0, and 20 weeks from T_0 to observe maintenance [46]. The GEAR program comprises three major elements: (1) an individualized home-based rehabilitation and exercise therapy, (2) education on the self-management of hEDS or G-HSD symptoms, and (3) a community resource engagement plan. These components are delivered by a team of physiotherapists and kinesiologists.

Intervention Group (IMT)

The participants in the intervention group will receive an individual and personalized prescription for an IMT program for 8 weeks. This IMT program will use the POWERbreathe K5 IMT device in the participants' home environment combined with the standard-of-care rehabilitation as part of the GEAR program, as described earlier. A research coordinator will facilitate these training sessions and monitor the participants via the web for the first 3 sessions in the first week and once a week from weeks 2 to 8. Over 8 weeks, 2 daily IMT sessions of 30 breaths (<5 min/session) will be performed for 5 days per

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week, starting with 20% of the participants' T_0 MIP up to a maximum of 60%. This protocol was developed based on the previous literature on IMT applied in lung transplant candidates at our center [70-72]. The total workload per session (product of inspiratory muscle force and inhaled volume expressed in Joules) will be abstracted from the IMT device. Additional variables abstracted from the device will include inspiratory muscle load (cm H_2O), mean power per breath (W), and mean volume per breath (Liters).

The participants will be asked to record their resting and post-IMT Borg dyspnea scores for 5 days of the week (2 sessions per day), along with any side effects for each session. The median Borg dyspnea score for the previous week will be reviewed by the research coordinator, and IMT intensity will be increased by 5% to 10% of the T_0 MIP if the median weekly Borg dyspnea score is <7 (very severe breathlessness with IMT) [54].

The participants will be asked to maintain IMT diaries to assess adherence. They will receive instructions and feedback on how to optimize their home training efforts based on direct observation of their IMT with the POWERbreathe K5 device and review of IMT workload from the device. They will have the possibility to schedule additional sessions with the study team during the week, if further support is needed.

Trial Outcomes

Estimates of Intervention Feasibility

Study feasibility will be assessed through recruitment rate, attrition, IMT program adherence, safety, and satisfaction (Textbox 1).

Textbox 1. Feasibility estimates.

- Recruitment
  - We will evaluate the recruitment rate as the number of participants who consented and enrolled relative to the total number of eligible patients approached for eligibility assessment by the research coordinator. The reasons for nonparticipation in the study will be documented. A successful recruitment rate will be defined as 20% in this study.
- Retention
  - Retention will be evaluated through participant attrition throughout the intervention period. For each arm of the study, the retention rate will be assessed by measuring the number of participants who completed all assessments compared with the number of participants who enrolled and randomized. A successful retention rate will be defined as ≥80% in this study.
- Adherence
  - Adherence to inspiratory muscle training (IMT) in the intervention group will be tracked electronically and through participant logs (number of completed sessions of 30 breaths out of 10 planned sessions per week) with the IMT device over the 8-week period. Adherence will also be assessed during weekly communications with participants as well as through completed daily IMT logs, which will capture IMT training days and IMT prescription (percentage of maximal inspiratory pressure). These data will also be verified after the IMT device is returned. The number of completed IMT sessions will be reviewed from the recordings on the device.
  - The physical activity and exercise behaviors prescribed through the GoodHope Exercise and Rehabilitation Program will be monitored in both the intervention and usual care groups. Daily step counts will be assessed from the Fitbit device. The participants with hypermobile Ehlers-Danlos Syndrome or generalized hypermobility spectrum disorder will be asked to download the Fitbit app on their smartphones or tablets. A 1-page document highlighting the key steps for setting up the Fitbit tracker will be provided. We will also work with the participants via the web to set up the device if any problems arise. The exercise behaviors of the study participants in both groups will be reviewed using the self-reported exercise logs, which capture the exercise type, frequency, intensity, and duration on a daily basis. At the end of the baseline assessment, the study participants in both the usual care and intervention groups will be provided with documents explaining the maintenance and use of the study devices (eg, Fitbit, respiratory muscle endurance trainer, and IMT device for the intervention group).
- Safety
  - The participants will log any adverse effects during the IMT program, which will be reviewed weekly by the research coordinator. Adverse effects are rare; however, symptoms previously observed during IMT include mild chest discomfort, worsening respiratory symptoms (eg, dyspnea), and possibly nausea related to hyperventilation [73]. The participants will also be strongly encouraged to immediately contact a member of the research team if they notice any adverse events. Study personnel will also inquire about chest discomfort or delayed-onset muscle soreness during IMT in weekly meetings to adjust IMT prescriptions and ensure tolerability of training intensity.
- Satisfaction
  - Participation satisfaction and motivation to engage with the IMT program will be assessed in the intervention group using a standardized questionnaire administered at weeks 1, 4, and 8 after study enrollment.

Primary Pilot Outcome

The primary pilot outcome will be the change in MIP over the 8-week study period to demonstrate the efficacy of IMT, which has been shown to be an important physiological measure in several IMT studies [11,26,35,73].

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Secondary Outcomes

The secondary outcome measures evaluated will include dyspnea, respiratory muscle structure and function, mood, and HRQL assessed at T_0 and 8 weeks, as shown in Table 3.

Table 3. Study outcomes.

Outcome	Assessment measurement	Time point
Primary outcome		
Respiratory muscle strength	MIP[a] (cm H_2O)	Baseline (T_0) and 8 weeks (T_2)
Secondary outcomes		
Pulmonary function		
Spirometry and lung volumes	FEV1[b] (L), FVC[c] (L), TLC[d] (L), RV/TLC[e] (%)	Baseline (T_0) and 8 weeks (T_2)
Oscillometry	Oscillometry: respiratory impedance, reactance, and resistance	Baseline (T_0) and 8 weeks (T_2)
Respiratory muscle endurance time	Time (seconds) using the Philips Threshold trainer at 30% of baseline MIP	Baseline (T_0), 4 weeks (T_1), and 8 weeks (T_2)
Diaphragm structure and function	Diaphragm thickness and thickening fraction	Baseline (T_0) and 8 weeks (T_2)
PROMs[f]		
Dyspnea	MRC[g] scale ratings, Borg dyspnea scale ratings, and Qualitative Dyspnea Scale ratings	Baseline (T_0) and 8 weeks (T_2)
Exercise and physical activity volume	Godin Leisure-Time Exercise Questionnaire scores	Baseline (T_0) and 8 weeks (T_2)
HRQL[h]	SF-36[i] scores	Baseline (T_0) and 8 weeks (T_2)
Depression, anxiety, and stress	Depression, Anxiety, and Stress scale scores	Baseline (T_0) and 8 weeks (T_2)
Cardiopulmonary exercise parameters		
Aerobic and anaerobic capacity	Peak aerobic capacity, anaerobic threshold, breathing reserve, and cycling power output	Baseline (T_0) and 8 weeks (T_2)
HR[j] response and chronotropic response	HR recovery (HR at 1 minute after CPET[k] – HR at the end of CPET) and chronotropic response index adjusted for age ([peak HR – resting HR × 100] / [220 – age] – [resting HR])	Baseline (T_0) and 8 weeks (T_2)
Neural activity during exercise (prefrontal cortex)	Oxyhemoglobin and total hemoglobin concentration changes	Baseline (T_0) and 8 weeks (T_2)

[a]MIP: maximal inspiratory pressure.

[b]FEV1: forced expiratory volume in 1 second.

[c]FVC: forced vital capacity.

[d]TLC: total lung capacity.

[e]RV/TLC: residual volume/total lung capacity ratio.

[f]PROM: patient-reported outcome measure.

[g]MRC: Medical Research Council.

[h]HRQL: health-related quality of life.

[i]SF-36: Short Form-36.

[j]HR: heart rate.

[k]CPET: cardiopulmonary exercise test.

Statistical Analysis

Proposed Data Analyses

For objective 1, we aim to compare respiratory muscle structure and function and PROMs between patients with hEDS or G-HSD and healthy controls and to evaluate the main correlates with dyspnea in patients with hEDS or G-HSD. Descriptive statistics will be used for continuous variables (mean and SD or median and IQR), and frequencies will be used for categorical variables. We will use multivariable regression analysis to compare any differences between groups across respiratory parameters and PROMs, adjusted for EDS subtype (hEDS or G-HSD). We will explore the associations with peak Borg dyspnea scores during CPET using multivariable regression, with possible determinants being MIP, diaphragm thickening fraction, PFC activity, and PFT parameters.

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For objective 2, we aim to assess the feasibility of IMT and standard-of-care rehabilitation for improving respiratory muscle strength, exercise capacity, and PROMs compared with standard-of-care rehabilitation alone in patients with hEDS or G-HSD. Descriptive statistics will be used to summarize program adherence, recruitment, participant satisfaction, attrition, and safety in the hEDS or G-HSD study groups. Estimates of within- and between-group differences at T_0, 4 weeks, and 8 weeks will be reported using means and 95% CI. Paired *t* tests and *t* tests will be used to compare the changes in the primary pilot outcome (MIP) and secondary measures over the 8-week study period within and between the 2 randomized groups.

Sample Size

Objective 1

With the prevalence of dyspnea (MRC score: 2 out of 5) in 50% of the patients with hEDS and G-HSD, we estimate that 75% of the patients with hEDS will report a Borg dyspnea score of ≥4 (moderate dyspnea) compared with 25% of healthy controls after cardiopulmonary exercise, as previously observed at our center [74]. Thus, with a sample size of 34 patients with hEDS or G-HSD and 17 healthy controls, we will have 90% power to observe a significant difference in moderate dyspnea (α level=.05). Furthermore, given an estimate of 10 participants for each covariate in multivariable regression modeling, we reckon that enrollment of 34 participants with hEDS or G-HSD will allow us to explore at least 3 determinants of dyspnea in our models.

Objective 2 (Primary Pilot Outcome)

Given an estimated MIP comparable with that of moderate COPD patients (mean 51, SD 15 cm H_2O), we anticipate a mean increase of 10 (SD 3.5) cm H_2O in MIP in the IMT and exercise training group compared with the hEDS or G-HSD usual care group (exercise training alone; 5 cm H_2O) [75]. Assuming a maximum attrition rate of 20% among the 34 RCT participants with hEDS or G-HSD, we will have 90% power (α=.05) to observe a significant difference in MIP with 17 participants per group.

Data Management and Quality Assurance

Our research team is trained in the measurement protocols and has expertise in performing physical assessments and PROMs in individuals with respiratory conditions. The research team has critically appraised the peer-review comments from the 2020 GoodHope Ehlers-Danlos Syndrome foundation grant (Multimedia Appendix 1) and has incorporated them into the study protocol. Most of the study assessments will be conducted at the PFT laboratory of Toronto General Hospital by experienced respiratory technicians. All equipment (ultrasound, fNIRS, and oscillometry) has been applied in the laboratory setting previously. In addition, our research team has expertise in conducting web-based assessments in the participants' home environment, including IMT, given the COVID-19 environment.

The research coordinator will guide the participants through each step of the study process. Standard operating procedures will be generated for each step related to data collection, data entry, and data handling. The research coordinator will ensure accuracy by periodically auditing the data in our research database. Although the research coordinator will attempt to have the participants complete the entirety of the assessments and questionnaires, if there are unanswered questions or missing data, the data will not be imputed, and analysis will be performed on the available data.

The current institutional and national research ethics guidelines will be followed to ensure data privacy, security, and protection. Participant data will only be accessible by the research study team, and participants will be assigned a random participant ID, which will be linked to all the data. All the study data will be securely stored on a password-protected server. In the event of inappropriate data breaches, the following actions will be undertaken: (1) prevent further breach of information and attempt to retrieve breached information and (2) notify the institutional research ethics board immediately. Further action might be taken according to the recommendations from the research ethics board. Modifications to the study protocol will be approved by the research ethics board before implementation, communicated to funding agencies, and outlined in future publications.

Results

This research was funded in January 2021, and study enrollment began in August 2021 and will continue until December 2023. As of January 2023, a total of 4 participants with hEDS or G-HSD in the intervention group and 4 participants in the usual care group have completed the study, with 5 other participants with hEDS or G-HSD enrolled. A total of 11 healthy controls have completed the study. The results will be submitted for publication once data collection and assessments are complete.

Discussion

Summary

This study will help characterize the multifactorial nature of dyspnea experienced by individuals with hEDS and G-HSD. Given the known impairments in respiratory muscle strength in this population, this study will allow us to assess the synergistic effects of IMT and standard-of-care rehabilitation on dyspnea, PROMs, and exercise capacity, which have not been previously characterized. The findings of this study will inform the feasibility of a larger study using IMT and standard-of-care rehabilitation that will be appropriately powered to assess the effects of IMT on PROMs and clinical outcomes. Furthermore, this study has the potential to inform our understanding of the mechanistic effects that IMT may have on diaphragm structure and function, lung physiology, and neurocognitive adaptations in this population.

The literature describing respiratory manifestations in EDS and G-HSD has generally been limited to a few observational studies and case series involving mainly 4 subtypes: classical EDS, vascular EDS, hEDS, and G-HSD [2,9]. We chose to focus on the population with hEDS, as hEDS comprises the major subtype of EDS, and there is also a study highlighting respiratory muscle weakness and effectiveness of IMT [11]. The population with

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G-HSD was also chosen, as G-HSD is defined to be on the continuum of EDS and represents one of the most common diagnoses in our GEAR rehabilitation program, and the respiratory sequelae of G-HSD have not been well characterized [3]. Another important consideration factored into our selection of the EDS population was the risk of pneumothorax, which is generally lower in individuals with hEDS and G-HSD than in those with other subtypes. Thus, the inclusion of patients with hEDS and patients with G-HSD is owing to the representation of the majority (>90%) of the patients with EDS followed in our program.

We hypothesize that IMT and standard-of-care rehabilitation will provide a positive synergistic effect on respiratory muscle function, PROMs, and clinical outcomes. IMT has been shown to improve dyspnea by increasing respiratory muscle strength [76]. In addition, aerobic and strength training has been shown to increase the strength of the respiratory and limb muscles and improve oxygen use, ventilatory efficiency, and exercise capacity [20,31]. Furthermore, IMT can have positive effects on dyspnea through neurocognitive adaptations [77]. Breathing exercises may induce motor-sensory neural adaptations in the diaphragmatic and respiratory muscles, which can improve dyspnea tolerance [77]. It is also postulated that improvements in exercise capacity and dyspnea levels through IMT may result in greater independence in daily activities and improved HRQL [78]. Despite the proposed beneficial effects of IMT, the ideal duration remains to be determined, with 8 weeks chosen for this study based on the recommendation that a duration of at least 6 weeks is required to derive respiratory muscle adaptations [79-81].

Owing to the COVID-19 environment, a large proportion of research assessments and in-person care visits have transitioned to a web-based environment [82,83]. Patients often express concerns about the possibility of COVID-19 exposure and travel expenses for in-person assessments. Furthermore, the GEAR program has also adapted its format, with a proportion of web-based training sessions performed. Thus, we are closely monitoring enrollment numbers and if recruitment proves to be challenging because of the requirement for in-person visits, we will be able to amend the protocol to allow assessments to be performed via the web. In fact, most of the assessments in this study can be administered via the web, including all PROMs, respiratory muscle endurance testing, and IMT with electronic tracking on the device itself. The results of this study will demonstrate the potential of performing web-based IMT, especially with the emergence of tele-rehabilitation programs.

Limitations

This study has several limitations that need to be highlighted. First, our study focuses on hEDS and G-HSD, which represent most EDS disorders in our program. However, the findings may not be generalizable across less prevalent EDS subtypes (eg, classic EDS or vascular EDS). Second, all participants in this RCT will be enrolled in the GEAR program, and we anticipate that any differences in training volumes or physical activity levels will be negligible between the groups after randomization, but any differences over the 8-week IMT program will be explored. Third, we are unable to monitor adherence to the GEAR program in the intervention group. Moreover, IMT may not be suitable for all participants because of time restrictions, training preferences, and work-school schedules. However, the web-based environment provides participants with the flexibility to uptake the IMT program that best suits their schedules.

Conclusions

This study aims to provide a better understanding of the contributors to dyspnea in hEDS or G-HSD and highlight the association between dyspnea and respiratory muscle function, PROMs, and exercise capacity. The combination of IMT and standard-of-care rehabilitation training may provide a novel therapeutic strategy to improve respiratory muscle function and PROMs. A better understanding of the feasibility and efficacy of IMT and standard-of-care rehabilitation will provide insight into the use of IMT in the population with EDS and the population with G-HSD, given a shift toward tele-rehabilitation programs in the COVID-19 environment. This research will pave the way for future studies to evaluate respiratory management strategies in this population.

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Data Availability

The study data will be made available for review after trial completion and publication upon reasonable request from the corresponding author.

Authors' Contributions

DR conceived the study and participated in the design of the protocol and development of the intervention. DR, EG, LM, LL-H, WDR, CWC, CMR, DK, EH, KC, SR, DSM, and NM are the grant holders. SN coordinates the study under the direct supervision

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of DR. SN, ECP, and NAK are responsible for the implementation of the study. SN supervises the inspiratory muscle training home-based exercise program. DR and NAK helped draft this manuscript. ECP, SN, EG, LM, LL-H, WDR, CWC, CMR, DK, EH, KC, SR, SM, DSM, HC, and NM provided expert advice and reviewed the protocol. All the authors approved the final manuscript for submission.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review report from the 2020 GoodHope Ehlers-Danlos Syndrome Foundation grant competition.
[PDF File (Adobe PDF File), 122 KB - resprot_v12i1e44832_app1.pdf]

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Abbreviations

CONSORT: Consolidated Standards of Reporting Trials
COPD: chronic obstructive pulmonary disease
CPET: cardiopulmonary exercise test
EDS: Ehlers-Danlos Syndrome
fNIRS: functional near-infrared spectroscopy
GEAR: GoodHope Exercise and Rehabilitation Program
G-HSD: generalized hypermobility spectrum disorder
hEDS: hypermobile Ehlers-Danlos Syndrome
HR: heart rate
HRQL: health-related quality of life
IMT: inspiratory muscle training
MIP: maximal inspiratory pressure
MRC: Medical Research Council
PFC: prefrontal cortex
PFT: pulmonary function test
PROM: patient-reported outcome measure
RCT: randomized controlled trial
T0: baseline

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Protocol

Effects of a Salutogenic Healthy Eating Program in Type 2 Diabetes (the SALUD Study): Protocol for a Randomized Controlled Trial

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Abstract

Background: Healthy eating can improve the course of type 2 diabetes mellitus (T2DM) considerably. As changing eating behaviors in everyday is challenging, there is a need for a nutritional strategy with an eye for everyday life of people with T2DM. A theory centered around the everyday life context is salutogenesis. Salutogenic principles have been operationalized in a new nutritional program for T2DM on food literacy and well-being: the Salutogenic Intervention for Type 2 Diabetes (SALUD) program.

Objective: This study aims to describe the protocol of the invention study that will examine the quantitative and qualitative effects of the SALUD program.

Methods: A semiblinded randomized controlled trial will be performed in the Netherlands. A sample size of 56 (including a 30% dropout rate) people with T2DM has been calculated, of whom half (n=28, 50%) will follow the SALUD program (intervention) and half (n=28, 50%) will receive usual care (control). Recruitment strategies consist of advertisement via local health care professionals, posters, social media, and local newspapers. The SALUD program consists of 12 weekly web-based group sessions under the supervision of a certified lifestyle coach. Fidelity of the delivery is guaranteed by selecting a salutogenic coach, use of an intervention manual, training of the coach, weekly evaluation forms, and recording several sessions. The theoretical salutogenic principle of the intervention is mobilizing 2 important psychosocial resources required for organizing healthy eating in everyday life: self-identity and social support. Measurements will be performed at 3 times: at baseline (T0), after 12 weeks (postintervention; T1), and after 24 weeks (follow-up; T2). The primary outcome is food literacy, measured with the self-perceived food literacy scale questionnaire (expected effect size=0.9). Secondary outcomes are self-efficacy, quality of life, sense of coherence, diet quality, body weight, BMI, and waist-hip ratio. All outcomes will be tested with linear mixed models, following an intention-to-treat approach and standard principles of randomized controlled trials. In addition, a qualitative analysis will be performed.

Results: The proposed study will provide useful information on the effects of a salutogenic program on healthy eating and well-being in people with T2DM in everyday life. Recruitment started on October 1, 2021. The intervention participants followed the SALUD program between January and August, 2022. The acquisition of the data was completed on August 1, 2022; publications are expected in 2023.

Conclusions: This study will be one of the first salutogenic interventions for T2DM, which will provide valuable information on what salutogenic intervention entail. The SALUD program may serve as a concrete, web-based tool. The combination of

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quantitative and qualitative measures allows a comprehensive evaluation of effects. These insights can be used for further optimalization of T2DM interventions.

Trial Registration: Netherlands Trial Registry, NL8963; https://trialsearch.who.int/Trial2.aspx?TrialID=NL8963

International Registered Report Identifier (IRRID): DERR1-10.2196/40490

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KEYWORDS

salutogenesis; lifestyle; nutritional intervention; diabetes type 2; randomized controlled trial; RCT; patient centered; empowerment; resilience

Introduction

Background

Healthy eating is important for the disease course and quality of life (QoL) of people with type 2 diabetes mellitus (T2DM) [1]. Healthy eating may lower hemoglobin A_{1c} (HbA_{1c}) to a similar extent as medical treatments for T2DM [2,3]. In some cases, healthy eating can put the disease in remission [4-12]. However, people with T2DM indicated that implementing healthy eating recommendations in their everyday lives is challenging [5,7,8].

Several strategies are available to support people with T2DM with healthy eating. The strategies approach healthy eating in dissimilar manners that could be broadly categorized as dietary prescription, lifestyle counseling, and behavioral therapies [13]. Dietary prescription is characterized by a "top-down" and biomedical approach: the therapist actively provides the solution in the form of a strict calorie-restricted diet, and the main goal is to achieve weight loss or improved HbA_{1c} levels (eg, [12]). In lifestyle counseling, the participant has a more active role: the therapist provides lifestyle education, meal plan templates, and personalized advice to implement nutritional recommendations. The main goal is adherence to a healthy lifestyle (eg, the Look AHEAD [Action for Health in Diabetes] trial [14] and the Diabetes Remission Clinical Trial [DIRECT]; [15]). Behavioral counseling is characterized by a more "bottom-up" and holistic approach: the starting point is the participant's preferences; the goals and approaches are collaboratively planned. The therapist has an enabling role in the process: stimulating the participant's problem-solving abilities and self-efficacy by motivating and supporting the participant. The main goal is achieving a mindset that favors healthy lifestyle behaviors (eg, [16]).

All of these strategies have been successful in initiating health benefits such as weight loss and improved HbA_{1c} levels [12,16,17] but have struggled with maintaining the benefits in the long term [8,18-21]. Even after the most well-known T2DM interventions—the Look AHEAD [14] and the DIRECT trial [15]—health benefits gradually disappeared. The Look AHEAD trial (restricted caloric intake using portion-controlled meal plans, calorie-counting techniques, and meal replacements combined with moderate physical activity) demonstrated average weight loss of 8.6% (SD 6.9%) in the intervention participants, but half of the initial weight loss was regained after 5 years of follow-up [22,23]. The DIRECT trial (a very low–calorie diet, followed by stepwise food reintroduction) demonstrated that almost half of intervention participants achieved T2DM remission at 12 months, but this percentage declined to 36% at 24 months [24].

Most previous studies used dietary description or lifestyle counseling strategies. These strategies either included strict (ie, very low–calorie) diets or were performed in highly controlled research settings (intensive intervention regarding diet and physical activity combined with frequent contact with health care providers) [12,25,26]. However, people may experience difficulties when they return from these clinical and controlled research settings to their everyday lives. In everyday life, healthy eating requires a scale of personal and social resources, ranging from practical cooking skills to personal agency [27-29]. It is not only about *what* people eat but also *why* and *how* they eat: the ability to prepare food, social economic resources, the food environments, social support, self-image, mental health, etc. This may explain why the Mediterranean diet is considered as one of the healthiest diets with (long-term) health benefits [30]; the Mediterranean diet is not a strict diet, rather *a way of life* that includes seasonal cooking, freshly cooked meals, and socializing with others [31].

Objectives

Hence, there seems to be a need for a strategy with an eye for everyday life of people with T2DM to promote long-term healthy eating. A health theory centered around the everyday life context is salutogenesis. Applying salutogenesis to nutritional research leads to the assumption that healthy eating is not regarded as a central goal in life but as a resource for greater enjoyment of life [32]. It requires to accept a holistic viewpoint on health and real-life complexity as starting points for conducting and evaluating nutritional interventions. In salutogenesis, health results from the continuous everyday life interactions between the individual and the social, economic, cultural, physical, mental, and biochemical stressors [33]. The central concept in salutogenesis is the sense of coherence (SoC), which is the individual capability to mobilize and use health-promoting resources [33]. Understanding the *resources* that facilitate coping with these stressors in a health-promoting manner can help to unravel underlying principles of creating health [34]. Salutogenesis guided the development of the Salutogenic Intervention for Type 2 Diabetes (SALUD) program [35].

The aim of this study protocol is to outline the randomized controlled trial (RCT) in which the SALUD program is compared with the Dutch usual care for T2DM. The theoretical principle behind the program is mobilizing 2 important

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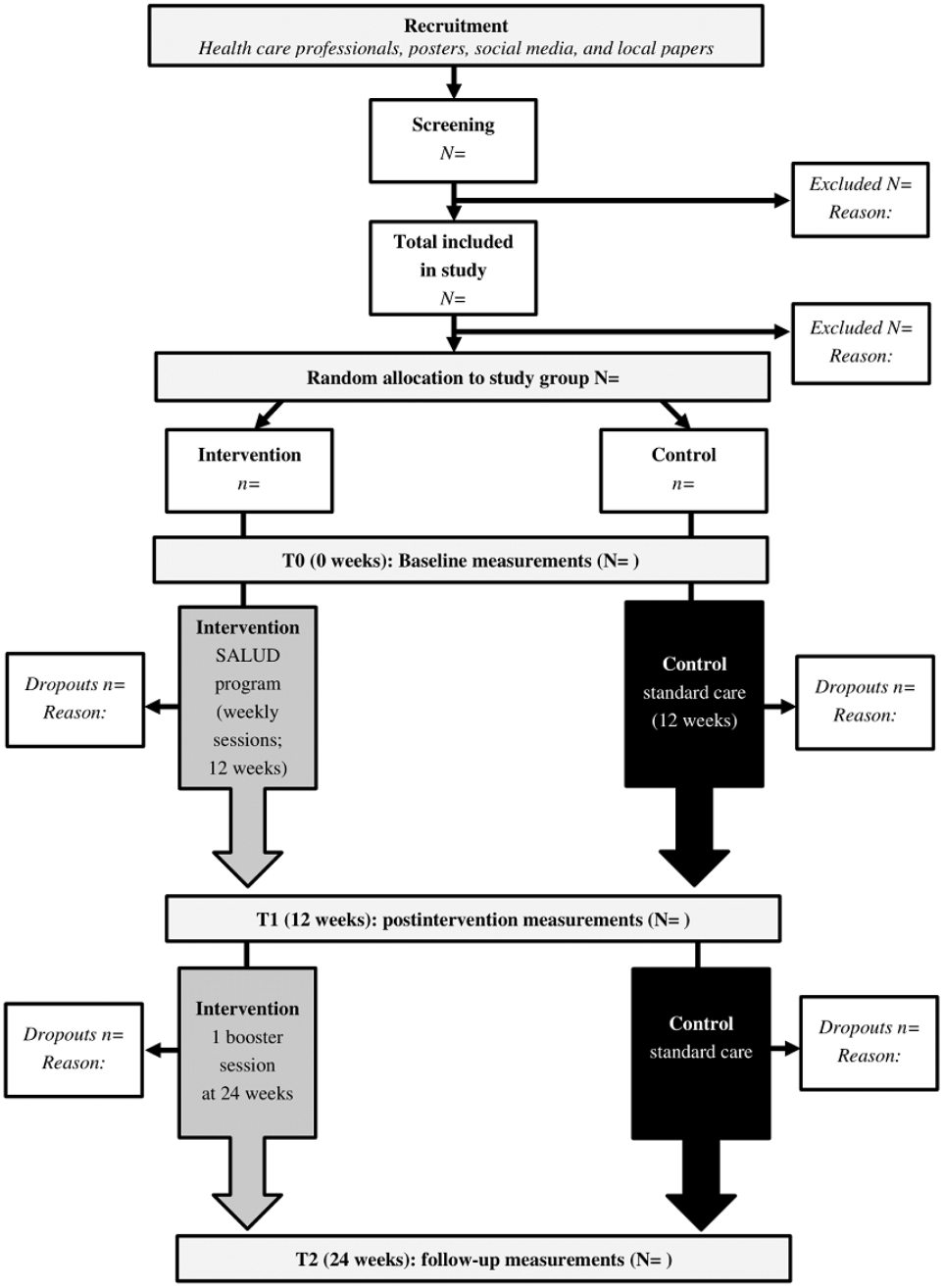
psychosocial resources required for organizing healthy eating and improved well-being in everyday life: self-identity and social support [35]. The present hypothesis is that mobilizing these resources will initiate a process of empowerment, leading to improved food literacy (direct effect) and improved health (indirect effects). Food literacy is the capability to navigate different food situations to make healthy eating choices [36], which is important for healthy eating and well-being in the long term. It is a measure that combines all relevant aspects for healthy eating in everyday life, that is, knowledge, skills, and behaviors. Hence, the primary objective is to determine the effect of the SALUD intervention on food literacy. Diet quality as well as several physical and psychosocial outcomes will be evaluated as secondary outcomes.

Methods

Study Design

A 2-arm, semiblinded RCT will be conducted with 56 people with T2DM in the Netherlands. The whole study duration will be 24 weeks, with measurements planned at baseline (T0), after 12 weeks (postintervention; T1), and 24 weeks (follow-up; T2). Participants will be randomly allocated to the intervention group (SALUD program) or to the control group (usual T2DM care [37]). The SALUD program will consist of 1 individual intake session (at the start), group sessions for 12 consecutive weeks, and 1 booster session (at 24 weeks). The study procedure is outlined in Figure 1.

Figure 1. Salutogenic Intervention for Type 2 Diabetes (SALUD) study procedure.



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Ethics Approval

Medical Ethical Committee Oost-Nederland has granted medical ethics approval for this study on August 8, 2021 (Medical Ethical Committee number 2021-12949).

Trial Registration

The study has been registered at Netherlands Trial Registry with registration number NL8963 [38] (registered on October 12, 2020).

Participants

The target population consists of Dutch-speaking men and women with T2DM. Inclusion criteria are as follows: officially diagnosed with T2DM by a general practitioner (GP); aged ≥18-75 years; fluent in Dutch, competent to make own decisions; and in possession of a computer device with internet connection. Exclusion criteria are as follows: pregnant, lactating, or intention to become pregnant in the upcoming 6 months; severe chronic illnesses or condition or comorbidities (other than T2DM, eg, kidney failure, severe form of chronic obstructive pulmonary disease [gold III or IV], heart failure [class 2-4], cancer, dementia, or severe depression); bariatric surgery in the past; and eating disorders (eg, anorexia or bulimia).

Recruitment

Participants are recruited via posters in GP practices, advertisements in local papers, social media, and websites of national diabetes organizations. In addition, several local GPs and practice nurses approach clients during regular health appointments or via phone or mail. Before commencement, all participants receive the information brochure that explains the study in detail and a phone call from the investigator for further explanation. At least 7 days after the phone call, participants sign an informed consent form and send it to the investigators before the start of the study. Participants are informed (written and verbally) that they will be randomly allocated to either the intervention or control group.

Randomization and Blinding

Randomization of participants will be performed by an independent researcher (not involved in the study) with use of a web-based randomization tool. The data analysis for the primary outcome will be run blinded by an independent researcher. Treatment codes will be broken after finalization of the data analyses. Participants and researchers are not blinded during the measurements owing to the nature of the intervention.

Intervention: SALUD Program

Theory Operationalization

For the development of the SALUD program, 3 main principles of salutogenesis were operationalized:

- The participant as a whole: in salutogenesis, health is a complex and dynamic concept incorporating multiple aspects of well-being that relate to the whole person [39]. This requires interventions that aim to improve multiple aspects of health. Hence, in the SALUD program, physical and psychosocial health are valued equally.
- The participant's active involvement: to facilitate the mobilization of health resources, intervention strategies should be adjusted to real life to increase the chance of successful implementation of newly adopted behaviors in everyday life. This can only be done successfully and respectfully when people with T2DM and their health care providers are actively involved in the development of interventions. Hence, people with T2DM, health care professionals, and scientists of different disciplines provided their perspectives multiple times during intervention development (the participatory developmental process has been described by Polhuis et al [35]). The participatory developmental process revealed that self-identity, social support, food literacy, disease acceptance, and stress management were crucial resources to enable healthy eating in everyday life.
- The participant's individual learning process: salutogenesis complements traditional information-providing approaches by supporting individuals in a learning process to mobilize personal and environmental health-promoting resources to cope with stressors. Hence, the strategy of the intervention was to enhance the generalized resistance resources (GRRs) and specific resistance resources (SRRs) for enabling healthy eating through a reflective and empowering approach. The main strategy was based on mobilizing the GRRs self-identity and social support; session themes were based on the identified SRRs food literacy, disease acceptance, and stress management (Table 1).

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Table 1. Summary of the Salutogenic Intervention for Type 2 Diabetes (SALUD) program sessions.

Session topic	Setting	Goals
0. Intake	Coach and participant one on one (web-based)	• Getting to know the participant; personal history, motivations, and goals
1. Building trust	Coach and peer-group (web-based)	• Establishing a safe place • Social bonding
2. Goal setting	Coach and peer-group (web-based)	• Formulating at least one personal Specific, Measurable, Achievable, Relevant, and Time-Bound (SMART) health goal
3. Food literacy I	Coach and peer-group (web-based)	• Reflection • Question hour with a dietician • Setting up an individualized diabetes-proof week menu • Practical skills for meal planning, grocery shopping, and cooking
4. Food literacy II	Coach and peer-group (web-based)	• Reflection • Learning and sharing recipes (SALUD recipe book)
5. Stress management	Coach and peer-group (web-based)	• Reflection • Stress management • Diabetes-related stress • Mindfulness exercises (body scan and breathing exercises)
6. Nature break	Coach and peer-group (web-based)	• Reflection • Stress management • Boosting positive emotions • A mindful, individual walk outside (20 minutes)
7. Measuring progress	Coach and peer-group (web-based)	• In-depth reflection, evaluation, and adjustment of health goals • Social support
8. Social support	Coach and peer-group (web-based)	• Involve partner or friend in the health process • Opportunity for partners or friends to ask questions about program or health • Social support
9. Self-identity	G Coach and peer-group (web-based)	• Reflection • Why do you eat what you eat? • Values and life goals • Disease acceptance • Social support: question hour with role model
10. Open session	Coach and peer-group (web-based)	• The participants choose the topic of this session during session 7
11. Measuring progress	Coach and peer-group (web-based)	• In-depth reflection, evaluation, and adjustment of health goals • Social support • Long-term health strategies
12. Festive closure	Coach and peer-group (web-based)	• Reflection on personal learning trajectory • Boosting positive emotions • Long-term health strategies
13. Booster session	Coach and peer-group (web-based)	• Reflection and sharing of experiences over the past 12 weeks • Social bonding • Long-term commitment to a healthy lifestyle

Setting

The SALUD program takes place in a web-based group setting (7-8 participants per group) under supervision of a certified and experienced lifestyle coach. The communication platform Microsoft Teams (Microsoft) is used for hosting the sessions. The job of lifestyle coach in the Netherlands entails coaching and motivating people to sustainable lifestyle changes regarding nutrition, physical activity, sleep, and stress. Certified lifestyle coaches are extensively trained in various communication and coaching techniques. They have basic knowledge of lifestyle-related diseases, physiology, and nutrition. The current coach has been externally hired for the study by the authors and is not part of the research team. The coach is specifically

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experienced in group coaching (>5 years), particularly people with T2DM. The participants will be divided into separate groups on different days (based on their availability), all under supervision of the same coach.

Content

The SALUD program consists of 1 individual intake session (at the start), 12 weekly group sessions, and 1 booster session. Each weekly session has its own theme and goals (summary in Table 1). The sessions' themes are based on the GRRs and SRRs that were identified during the participatory intervention development: self-identity, social support, food literacy, disease acceptance, and stress management. A "learning by experience" approach will be used to equip participants with practical tools and skills. The coach uses several reflective (on- and off-screen) exercises related to diet, health, stress, and life during each session. The sessions are intended to be highly interactive and informal. Most sessions end with a practical home exercise (eg, "cook a new recipe this week"). A registered dietician will be invited to 1 of the sessions to answer specific nutrition-related questions. In 2 of the sessions, participants are encouraged to bring an important person (their best friend, partner, neighbor, or family member). Session 10 is deliberately left "open" to provide the participants with the opportunity to choose a topic based on their needs. More details about the intervention content can be found in the study by Polhuis et al [35].

Fidelity of Delivery

Fidelity of the intervention delivery is assured by the following:

- selecting a coach in line with salutogenic principles, that is, whole person view on health and a participatory and empowering way of coaching
- using a program manual in which the program's core (salutogenic) values, the sessions, the exercises, and goals are outlined
- thoroughly discussing with the coach about the (salutogenic) approach of the program before the start of the study
- weekly evaluating forms that will be filled in by the coach after each session to keep track of deviations from the manual and feedback of participants
- weekly checkups between the coach and the principal investigator (KP) to evaluate the previous session and to discuss the upcoming session
- recording a (small) number of sessions (with permission of the participants).

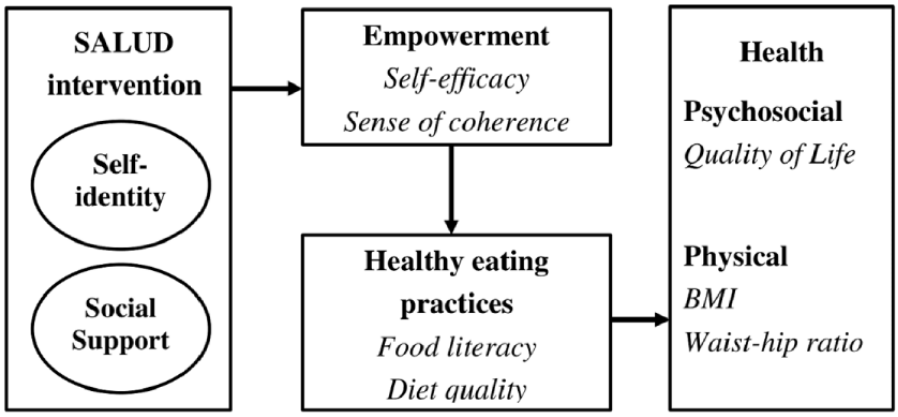
Control: Usual T2DM Care

The participants in the control group receive the usual Dutch T2DM care according to the Dutch General Practitioners Association (Nederlands Huisartsen Genootschap) protocols [37]. The usual care of T2DM is based on medical treatment, education, and lifestyle advice. Newly diagnosed persons and persons who require insulin administration are referred to a dietician by the GP. In some cases, the GP recommends a referral to a psychologist for help with dietary advice or to a physical therapist to help with physical activity. The GP refers to a specialist in case of complications (such as retinopathy and nephropathy). Generally, a person with T2DM has 4 quarterly checkups with the practice nurse and 1 yearly checkup with the GP. However, the exact frequency of the appointments depends on the specific agreements between the health care provider and the patient.

Quantitative Evaluation

The primary outcome is food literacy; secondary outcomes are self-efficacy, QoL, SoC, diet quality (Dutch Healthy Diet Index 2015 [DHD-15 index]), body weight, BMI, and waist-hip ratio (WHR). Self-efficacy and SoC are measured to evaluate the empowerment process of the SALUD program; diet quality to assess changes in nutritional intake; QoL to assess effects on psychosocial health; and body weight, BMI, and WHR to assess the effects on physical health (Figure 2). All measurements take place at the participants' homes.

Figure 2. Proposed mechanism of action of the Salutogenic Intervention for Type 2 Diabetes (SALUD) program.



Food Literacy (Self-perceived Food Literacy Scale)

The self-perceived food literacy scale (SPFLS) [36] is used to determine the capability to make healthy food choices in different contexts, settings, and situations. The SPFLS is a relatively new tool developed by Dutch researchers and validated among healthy Dutch adults (with a high internal reliability; Cronbach α=.80) [36] as well in people who underwent kidney transplant [36,40]. In the general population and in the patients who underwent kidney transplant, higher food literacy was associated with a healthier nutritional intake [36,40]. The SPFLS scale is proven to be capable of distinguishing between different populations [36,40]. The

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SPFLS contains 29 items related to 8 domains: food preparation skills, resilience and resistance, examining food labels, daily food planning, healthy budgeting, and healthy food stockpiling, healthy snack manners, and social and conscious eating. Response options include a 5-point Likert scale (1="not at all/never" to 5="yes/always"), eventually providing a score between 29 and 145. A higher score indicates higher food literacy. Domain scores and a total score are computed for each participant. Permission to use the SPFLS in this research has been formally granted by the developers of the SPFLS.

Self-efficacy (Dutch General Self-Efficacy Scale)

The Dutch General Self-Efficacy Scale (DGSES) [41] is a unidimensional free accessible questionnaire that measures the confidence someone has in their own abilities to cope with external challenges. The original DGSES was developed in German and is currently adapted to 32 languages [41]. Internal consistencies yielded typically Cronbach α between .76 and .90 [41]. Criterion validity is documented in numerous correlation [41]. The DGSES consists of 10 questions related to how people generally think and act. The response options include a 4-point Likert scale (1=completely false; 4=completely true), eventually providing a score between 10 and 40, with a higher score indicating higher self-efficacy. A total score will be computed for each participant.

QoL (World Health Organization Quality of Life Questionnaire)

The Dutch and abbreviated version of the World Health Organization Quality of Life-100 (WHOQOL-100) questionnaire is used to determine how people perceived their QoL over the last 2 weeks [42]. The abbreviated WHOQOL-100 is known as WHOQOL-BREF. The WHOQOL-BREF has been validated by comparing it with the original WHOQOL-100 domain scores (domains scores correlate at around 0.9 with the original) [43]. Internal validity is high (Cronbach α>.70) [44]. The WHOQOL-BREF contains a total of 26 questions that assess 5 domains of health and well-being: general perceived QoL, physical health, psychological health, social relationships, and environment. Response option includes a 5-point Likert scale (1=not at all; 5=extremely true), eventually providing a score between 26 and 130. Higher scores denote better QoL. A score is computed for each QoL domain as well as a total QoL score. Permission to use the Dutch version has been granted by the World Health Organization.

SoC (13 Items of the Orientation to Life Questionnaire)

The Dutch version of the 13 items of the Orientation to Life Questionnaire (SoC-13) is used to assess the participants' SoC [34]. The SoC measures to what extent participants perceive the world as comprehensible, meaningful, and manageable. The SoC-13 has been validated in multiple countries with a high internal validity (Cronbach α between .70 and .92 [45]). The Dutch version is validated among Dutch adults (Cronbach α=.86; based on the validation study of Swan, E, unpublished data, June 2013). Response options include a 7-point Likert scale (1=very often; 7=almost never), eventually proving a score between 13 and 91, with a higher score indicating a stronger SoC. Domain scores for manageability, comprehensibility, and meaningfulness as well as a total SoC score are computed for each participant. Permission to use the SoC-13 has been granted to the authors.

Diet Quality (DHD-15 Index)

The DHD-15 index is used to assess the diet quality via a scoring system based on the Dutch food-based dietary guidelines [46]. The DHD-15 index is a relatively short food frequency questionnaire consisting of 40 questions. The DHD-15 index has been validated with 24-hour recalls and food frequency questionnaire data among Dutch adults with a Dutch dietary pattern [46]. The DHD-15 index calculates a score for 16 food components: vegetables, fruit, wholegrain products, legumes, nuts, dairy, fish, tea, fats and oils, coffee, red meat, processed meat, sweetened beverages and fruit juices, alcohol, salt, and unhealthy food products (snacks and cookies). Each component is scored on a scale ranging from 0 (implies nonadherence) to 10 (optimal adherence), eventually providing a total score between 0 and 160. A higher score indicates a more optimal diet quality (ie, a diet in line with the Dutch dietary guidelines). For the calculation of the scores, specific cutoff and threshold values were used as suggested by Looman et al [46]. A separate score for each component as well as a total score will be calculated. Formal permission to use the DHD-15 index was granted by the developers to the authors.

Anthropometry

Body weight is measured at the participant's home with use of a scale (type: UC-411PBT-C) that measures to 2 decimals precisely. The scale will be calibrated before each measurement. The researcher makes sure the measurements are performed in similar circumstances (time of the day, placement of the scale, and layers of clothing). In addition to weight, height is measured once (during the first measurement). The scale calculates BMI (BMI [kg/m^2]=*body weight [kg]/height [m]*^{2}) and estimates fat percentage (%), muscle mass (kg), and basal metabolic rate (kcal).

Waist Circumference and WHR

Waist circumference and WHR are simple and useful measures of fat distribution. The measurements are performed according to the instructions of the World Health Organization [47]. In short, the participant must stand with arms at the sides, feet positioned close together, and weight evenly distributed across both feet. The measurement is performed at the end of a normal expiration. The researcher uses a measuring tape to measure the midpoint between the lower margin of the least palpable rib and the top of the iliac crest to determine waist circumference. Hip circumference is measured around the widest portion of the buttocks, with the tape parallel to the floor. All measurements are performed at the same time of the day (morning, afternoon, or evening). WHR is calculated using the following formula: *WHR=waist circumference (cm)/hip circumference (cm)*. A healthy WHR is considered ≤0.90 for men and ≤0.85 for women [47].

Participant Characteristics

A questionnaire consisting of personal contact details (name, age, address, phone number, and email), living situation,

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ethnicity, educational level, and clinical details (disease duration, medication use, and smoking [past and present]) is filled out during screening.

Qualitative Evaluation

Consecutive to the 12th session, participants are invited to a focus group to provide feedback and share their personal experiences with the program. The participants' partners are also invited to the focus group. One week before the focus group, the coach instructs the participants to bring an object that symbolizes their experiences with the SALUD and to think about what they liked or disliked about the program. The focus groups will be video recorded and used for qualitative effect analysis of the program. In the video recording, all participants (and partners) are asked to provide informed consent to record the session and to use the video recording for qualitative analysis. The following sample question will be used:

- If you were the program director of SALUD, what would you change? Why?
- Would you recommend SALUD to other people? Why? Why not?
- What did SALUD mean to you? Which parts were valuable/useful for you?
- Which elements of SALUD were not valuable/useful for you?
- Did you change things in your everyday life because of SALUD (eg, daily life, interactions with others, and the way you think)? Why?

The video recording will be transcribed ad verbatim and pseudonymized. Two researchers of the research team analyze the transcripts independently. First, the transcripts are read and reread to engage with the data. Then, the transcripts are open coded on a descriptive and interpretative level. More specifically, transcripts will be coded on active components of the intervention, the mechanism of action, health-promoting resources, and the influence on everyday life. Subsequently, the codes are clustered in preliminary themes. Then, the 2 researchers compare and discuss the preliminary themes until consensus is reached. The overarching themes are the result of various discussions between the researchers. The themes will be displayed with pertinent participant quotes and detailed interpretative commentary. The Dutch quotes will be translated into English by a professional translator.

Sample Size Calculation

Sample size calculation is based on the known mean value and SD of the SPFLS (food literacy measure) for the Dutch general population [36]. There are no RCTs with lifestyle interventions in the scientific literature that assessed food literacy (measured with SPFLS or another measure for food literacy) as a primary outcome. However, as RCTs evaluating lifestyle interventions that targeted psychosocial outcomes such as self-efficacy have demonstrated effect size of between 1.1 and 1.7 [48,49], it seemed reasonable to expect an effect size of 0.9. With use of the Cohen *d* calculation for effect size, an anticipated mean of 4.20 SPFLS score in the intervention group, and an anticipated mean of 3.83 (SD 0.41) in the control group is expected at T1 (based on references values [36]). With a standard power of 80% and a significance level of 5%, a total of 19 participants per group (38 participants in total) are needed. Adding a 30% dropout rate, the ideal sample size was set at 28 participants per group (56 in total).

Statistical Analyses

Statistical analyses are carried out using IBM SPSS Statistics for Windows, version 28 (released in 2021; IBM Corp). Two-sided *P* values <.05 are regarded as statistically significant. Analyses are performed with the intention-to-treat principle, meaning that all patients were analyzed in their original allocation group regardless of the extent to which they followed the intervention. Dropouts are counted, and reasons for dropping out are recorded. If missing is completely at random, all available data at T0 (baseline), T1 (12 weeks), and T2 (24 weeks) are used to conduct the analyses. If missing is at random, multiple imputation techniques are used to impute the missing data.

Scores are calculated for multiple-item instruments (ie, DGSES, WHOQOL-BREF, SoC-13, DHD-15 index, and SPFLS). Randomization will be checked, and variables will be normalized if needed. Descriptive statistics are performed to tabulate mean (or median) values of all study characteristics and baseline values of the independent variables. Chi-square tests (for categorical variables) and 2-tailed *t* tests (for continuous variables) are used to compare the descriptive statistics between study groups and to identify potential covariates. Data are tabulated as mean (SD) or median (IQR) if skewed. Categorical data are presented as n (%) where appropriate.

According to a strict data analysis protocol, primary and secondary outcomes are tested with mixed models. Secondary outcomes are also tested if the primary outcome is not statistically significant. The analyses scripts will be written by the researchers; the analysis of the primary outcome will be run by an independent researcher who is blind to the intervention code. Assumptions for mixed models are checked. The mixed models will test the difference compared with baseline in the scores and values (ie, dependent variables) between intervention and control (ie, independent variable) at T1 and T2. Fixed effects are the treatment condition, time, and the covariates; random effects are the repeated measures per participant at T0, T1, and T2. Multiple models are tested; a crude model, and additional models that are adjusted for confounders commonly adjusted for in literature (eg, sex, age, education, and BMI). Variables that statistically significantly differed at baseline are also included in a model as covariates. The final results are presented in a table displaying the estimated marginal means, 95% CIs, and *P* values for the treatment effect for all primary and secondary outcomes.

Incentive

All participants receive a financial compensation of €150 (US $159.5) after completion of the study (ie, after finishing the last measurements at T2). The financial compensation is calculated based on the time commitment and invasiveness of the measurements.

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Data Management

The handling of personal data complies with the European Union General Data Protection Regulation, the Dutch Act on Implementation of the General Data Protection Regulation (in Dutch: Uitvoeringswet Algemene Verordening Gegevensbescherming), and the Findability, Accessibility, Interoperability, and Reusability principles. Participants are assigned a unique participant identifier number (ie, a random 4 digits number) that does not change during the study to ensure that data cannot be tracked back to the participants. This number is linked with the name, address, and date of birth of the participant. The identifier number is used on raw and processed data files. The file that contains the link between the participant's information and the participant's identifier number is stored on a password-secured location during the study. Participants indicate in the informed consent form whether their data may be used for other studies. If a participant indicates that they do not allow further use of their data, their data will be removed from the file that can be requested for future research. The file with the link between the participant identifier number and the personal data of the participant will be destroyed after finalizing the data files for future research.

Results

The project of which this study is part of received funding from the Edema-Steernberg Foundation in November 2016. Recruitment started on October 1, 2021. The intervention participants followed the SALUD program between January and August, 2022. The acquisition of the data was completed on August 1, 2022. The data analysis and publications are expected at the end of 2023.

Discussion

This study will be one of the first salutogenic interventions for T2DM. Both the quantitative and the qualitative effect analyses are expected to provide valuable insights for further optimalization of interventions in people with T2DM.

Strengths and Limitations

A first strength of this study includes the RCT design, especially because previous Dutch "diabetes reversal" interventions have been evaluated via an observational pre- and posttest design [4,50]. Furthermore, there is also a shortage of evaluating salutogenic programs via RCTs [51]. Although RCTs are considered the gold standard for intervention evaluation, the RCT design has also some limitations for this particular study. The SALUD program is difficult to fit the experimental framework of an RCT, as it is a multicomponent intervention that cannot be strictly standardized [52-54]. Furthermore, RCTs are limited when the implementation context is a determinant of the result [52-54]. In the SALUD study, the success of the program will be dependent on the extent to which the program integrates with the everyday lives of the participants. Nevertheless, RCTs can be helpful for evaluating multicomponent interventions if close attention is paid to contextual factors via qualitative analysis [54]. Hence, a second strength is the proposed qualitative evaluation. This will increases the value of this RCT as it may help to understand the "black box" of the SALUD program (eg, the active components of the SALUD intervention, participant satisfaction, and points of improvement) [54]. In addition, the qualitative evaluation together with the quantitative evaluation may gather new insights regarding the theory of salutogenesis [51,54]. A third strength is that participants can follow the program on the web in the comfort of their own home: it saves the participants' time and travel efforts. Considering the recent COVID-19 pandemic, it is also a safe manner of group interactions, and the group sessions can continue during a possible lockdown. It also provides valuable information on how to perform a group-based coaching program in a web-based setting. A third strength is the open and flexible nature of the SALUD program, which provides the lifestyle coach opportunities to tailor the program to situational factors and individual needs. A final strength is the inclusion of both physical and psychosocial health measurements that enable assessment of the program's effect on different dimensions of health. However, because of limited budget, the study does not include HbA_{1c} and blood measurements to assess T2DM management.

A limitation is the limited follow-up period. Ideally, measurements would be repeated over 1, 5, or even more years to determine whether the program led to sustainable change. However, the current Dutch university and funding structures make it difficult to execute such long-term research projects (eg, temporary research contracts). Challenges the study may face are the recruitment; owing to the COVID-19 pandemic, health care professionals are overflooded with work and are short staffed. Especially in the case of a new infection peak, health care professionals may be unable to assist in the recruitment of participants. Furthermore, the intervention might be specifically suited for more motivated people because of the time investment and because self-identity and self-reflection require a proactive attitude. This might cause dropouts in the intervention group.

Conclusions

The proposed study will provide useful information on the effects of a salutogenic program on healthy eating and well-being in people with T2DM in a daily life setting. The SALUD program—if effective—may serve as a concrete, web-based tool to empower people with T2DM and guide them toward a healthier dietary pattern for the long run. In addition, the study may provide valuable information on what salutogenic interventions entail as well as new insights regarding the theory of salutogenesis. The combination of quantitative and qualitative measures allows a comprehensive evaluation of the intervention's effects.

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Acknowledgments

The authors thank the Edema-Steernberg Foundation for the possibility to execute this study. This study received funding from the Edema-Steernberg Foundation. The Edema-Steernberg Foundation is a Dutch nonprofit organization that stimulates multidisciplinary nutrition research.

Data Availability

All pseudonymized data will be stored for 10 years on a password-protected server of Wageningen University. If other researchers wish to use the data, they have to send a request to the principal investigator. If the request is approved, the principal investigator will grant a copy of the file.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review report and author comments from the Edema-Steernberg Foundation.
[PDF File (Adobe PDF File), 17 KB - resprot_v12i1e40490_app1.pdf]

Multimedia Appendix 2
Peer review report and author comments from the Edema-Steernberg Foundation.
[PDF File (Adobe PDF File), 174 KB - resprot_v12i1e40490_app2.pdf]

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Abbreviations

AHEAD: Action for Health in Diabetes
DGSES: Dutch General Self-Efficacy Scale
DHD-15 index: Dutch Healthy Diet Index 2015
DIRECT: Diabetes Remission Clinical Trial
GP: general practitioner
GRR: generalized resistance resource
HbA_{1c}: hemoglobin A_{1c}
QoL: quality of life
RCT: randomized controlled trial
SALUD: Salutogenic Intervention for Type 2 Diabetes
SoC: sense of coherence
SoC-13: 13 items of the orientation to life questionnaire
SPFLS: self-perceived food literacy scale
SRR: specific resistance resource
T2DM: type 2 diabetes mellitus
WHOQOL-100: World Health Organization Quality of Life-100
WHR: waist-hip ratio

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Protocol

A Brief Intervention for Improving Alcohol Literacy and Addressing Harmful Alcohol Use Among Women Attending an Australian Breast Screening Service (Health4her): Protocol for a Hybrid Effectiveness-Implementation Trial

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Abstract

Background: Alcohol consumption is a major modifiable risk factor for female breast cancer, even in small amounts. However, awareness of this risk remains low. National breast screening programs are uniquely positioned to provide timely and targeted health information and behavior change strategies to improve alcohol literacy and reduce consumption. A breast screening service is a novel health care setting for brief alcohol intervention, with the potential for extensive reach.

Objective: This study aimed to conduct a formative evaluation with breast screening service consumers to understand the need for, and acceptability of, brief alcohol intervention in the breast screening setting and collaboratively design a brief alcohol intervention (Health4Her); to test the effectiveness of Health4Her in improving knowledge of alcohol as a breast cancer risk factor (primary outcome), improving alcohol literacy, and reducing consumption among women attending a breast screening service; and to examine the implementation strategy through process evaluation.

Methods: This was a hybrid type II effectiveness-implementation trial comprising a randomized controlled trial (RCT) alongside a mixed methods program evaluation guided by applicable elements of the Reach, Effectiveness, Adoption, Implementation, and Maintenance framework and Consolidated Framework for Implementation Research. Formative evaluation comprised a retrospective analysis of alcohol consumption data (n=49,240), a web-based survey (n=391), and focus groups and interviews (n=31) with breast screening service consumers. Women attending routine mammography, drinking at any level, were recruited to the single-site, double-blind RCT (n=558), and completed a baseline assessment before randomization (1:1) to receive Health4Her (alcohol brief intervention + lifestyle information) or control (lifestyle information) via animation on an iPad. Follow-up assessments were performed 4 and 12 weeks after randomization. The process evaluation included evaluation of trial administrative data, participant quantitative (n=497) and qualitative feedback (n=30), and site staff qualitative feedback (n=11).

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Results: This research was funded in March and May 2019. Data collection for the formative evaluation and trial recruitment occurred between January and April 2020 and February and August 2021, respectively, with finalization of follow-up data collection in December 2021. Quantitative process evaluation data were collected during trial implementation, and collection of participant and staff feedback was finalized in December 2021. Results of the retrospective analysis of alcohol consumption data from breast screening service consumers is anticipated to be published in March 2023 and the results of the RCT to be published in March 2023.

Conclusions: This study is anticipated to generate new substantial knowledge on the alcohol consumption and literacy needs of women attending breast screening and the extent to which these can be addressed using a novel, tailored brief alcohol intervention. The study design permits the evaluation of the effectiveness and implementation of Health4Her to predict and facilitate uptake in breast screening services.

Trial Registration: ClinicalTrials.gov NCT04715516; https://clinicaltrials.gov/ct2/show/NCT04715516

International Registered Report Identifier (IRRID): RR1-10.2196/44867

(JMIR Res Protoc 2023;12:e44867) doi:10.2196/44867

KEYWORDS

alcohol; alcohol literacy; alcohol brief intervention; breast cancer; women's health; randomized controlled trial; hybrid effectiveness-implementation trial; protocol

Introduction

Background

Globally, alcohol use is a major modifiable risk factor for breast cancer in women, accounting for 4.4% of breast cancer cases and 10% of breast cancer deaths [1,2]. Meta-analyses demonstrate a dose-response relationship between alcohol and breast cancer [3-5] with the relative risk of breast cancer increasing by 4%, 23%, and 61% for light, moderate, and heavy alcohol consumption, respectively [3]. Lifetime and current alcohol consumption have been found to contribute to an increased risk of breast cancer [6-8]. In particular, alcohol consumption after the age of 40 years is strongly and independently associated with breast cancer risk [7]. Among women with a history of breast cancer, alcohol intake of <1 standard drink per day has been associated with an increased risk of breast cancer recurrence or development of a second primary breast cancer [9].

Despite strong evidence, awareness of the alcohol–breast cancer link has remained surprisingly low [10]; recent Australian and international estimates indicate that only 16% to 20% of the population accurately identifies alcohol consumption as a risk factor for breast cancer [11,12]. In Australia, per capita alcohol consumption is declining [13]; however, risky alcohol consumption (based on 2009 Australian Alcohol Guidelines, consuming >2 Australian standard drinks per day) has remained stable among women aged ≥40 years and has even increased among women aged between 50 and 69 years [14]. Furthermore, a prospective cohort study of Australian women with newly diagnosed first episode of invasive breast cancer found that the proportion of women drinking at the time of diagnosis and 2 years after diagnosis remained stable at 71%, with 1 in 6 women continuing to drink in excess of the national alcohol guidelines that were in place at the time (ie, >2 standard drinks per drinking day) after breast cancer diagnosis [14,15]. Despite this, alcohol consumption among middle- to older-age individuals is often underrecognized as an area of concern [16,17] and has largely been absent from breast cancer prevention strategies and health promotion.

Internationally, computerized brief alcohol interventions (ie, feedback on personal drinking levels compared with age and gender norms, alongside information about alcohol risks and harms) have received strong empirical support as a simple, cost-effective method of addressing alcohol consumption and reducing related harm in primary care populations [18]. Computerized brief alcohol interventions offer a low-cost, labor- and time-efficient approach that has the potential to overcome some of the issues with implementation in busy health care environments [19,20]. Meta-analyses show that a single computerized intervention session is effective in reducing alcohol consumption and improving health-related knowledge, attitudes, and intentions [18,21] and has the potential for wide reach.

Population-based screening programs can provide a window of opportunity to receive relevant targeted health information. Approximately 43 million women participate in population breast screening programs annually in Australia, the United States, and the United Kingdom. An intervention offered within an already established national breast screening program, which could provide information on alcohol and breast cancer risk alongside behavioral change strategies, has the potential to improve women's alcohol literacy, reduce alcohol consumption, and have extensive reach. Some recent research suggests that integrating brief alcohol interventions into breast screening services is perceived by clients as acceptable [20,22]; however, the effectiveness of such an approach is yet to be established.

Objectives

The aims of this research were to (1) conduct a formative evaluation with breast screening service consumers to understand the need for, and acceptability of brief alcohol intervention in the breast screening setting and collaboratively design a brief alcohol intervention (Health4Her) with women in this setting; (2) test the effectiveness of Health4Her in improving knowledge of alcohol as a breast cancer risk factor (primary outcome), improving alcohol literacy, and reducing

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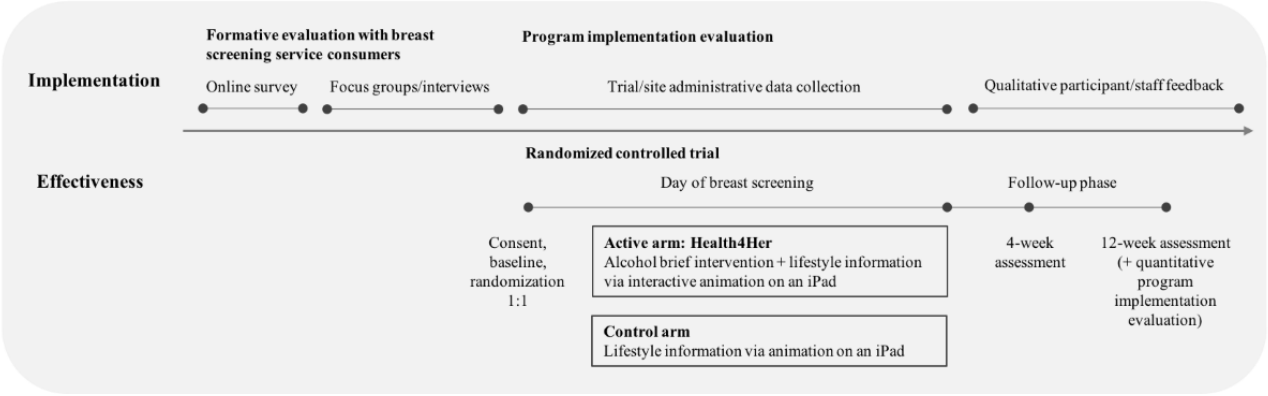
consumption among women attending a breast screening service; and (3) examine the implementation strategy through process evaluation to accelerate the translation of this research into practice.

Methods

Study Design

This was a hybrid type II effectiveness-implementation trial [23,24] comprising a randomized controlled trial (RCT) alongside a mixed methods program evaluation (Figure 1), guided by applicable elements of the Reach, Effectiveness, Adoption, Implementation, and Maintenance (RE-AIM) framework and Consolidated Framework for Implementation Research (CFIR) [25,26]. A mixed methods quantitative and qualitative formative evaluation comprised a retrospective analysis of cross-sectional alcohol consumption data from a large sample of breast screening service consumers, a web-based survey, and focus groups and interviews with subsets of breast screening service consumers. The single-site, parallel group, double-blind RCT was designed to evaluate whether the Health4Her intervention is effective in improving knowledge of alcohol as a breast cancer risk factor, improving alcohol literacy, and reducing consumption among women attending a breast screening service. A mixed methods quantitative and qualitative process evaluation examined the implementation strategy via the evaluation of trial and site administrative data, quantitative and qualitative feedback from trial participants, and qualitative feedback from breast screening site staff. The RCT protocol followed the Standard Protocol Items: Recommendations for Interventional Trials guidelines (Multimedia Appendix 1) [27] and the Template for Intervention Description and Replication checklist (Multimedia Appendix 2) [28].

Figure 1. Study design.



Formative Evaluation

Setting

Researchers conducting the formative evaluation were based at Turning Point, a national addiction treatment and research center in Melbourne, Australia. To collect qualitative data from breast screening service consumers, focus groups were initially conducted on-site and replaced with telephonic interviews conducted from the end of March 2020 to comply with social distancing requirements owing to the COVID-19 pandemic.

Participants

The first component of the formative evaluation comprised a retrospective analysis of deidentified cross-sectional alcohol and sociodemographic data (collected from May 2010 to November 2019) from 49,240 women who are members of Lifepool [29], a large convenience sample of women living in Victoria, Australia, who are recruited predominantly through the state-wide BreastScreen program. For the web-based survey, 391 participants were recruited through an email invitation circulated to randomly sampled batches of Lifepool members, stratified by age, based on an anticipated response rate of 25% (total invitations e-mailed, n=1412). Women who participated in the web-based survey and were living in the Melbourne region were invited to register for participation in a focus group or interview at the end of the survey. In addition, purposive sampling was employed to recruit women living in the Melbourne region who reported drinking 3 to 4 (or more) standard drinks, 3 to 4 (or more) days per week (based on the data collected at cohort entry), to participate in a focus group or interview (additional invitations, n=199; focus group or interview participation, n=31). As with all components of this study, women with or without a history of breast cancer were able to participate.

Data Collection

For the retrospective analysis of Lifepool data, there were data available on participants' typical and heavy alcohol consumption patterns over the previous 12 months (eg, "In the last 12 months, how often did you have an alcoholic drink of any kind?" and "In the past 12 months, how often have you had more than 4 standard drinks in a day?") [30]. Sociodemographic (ie, age, education, country of birth, and identifying as being of Aboriginal and/or Torres Strait Islander descent) and health-related (ie, hours per week of moderate-intensity physical activity, BMI, menopausal status, breast cancer diagnosis, first-degree relative breast cancer history, and smoking status) variables were also examined. Postcode data were used to derive the geographical remoteness [31] and relative socioeconomic advantage [32] variables, as defined by the Australian Bureau of Statistics.

The web-based survey, developed by the research team and tested with a convenience sample of women employees at Turning Point, collected demographic information (eg, age and

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education) and data on women's knowledge of breast cancer risk factors, breast cancer information sources, the acceptability of receiving cancer risk information in various health settings, and alcohol consumption patterns. Participants' typical and heavy alcohol consumption patterns over the previous 12 months was measured using quantity-frequency items (eg, "In the last 12 months, how often did you have an alcoholic drink of any kind?" and "On a day that you have an alcoholic drink, how many standard drinks do you usually have?") [30]. A visual standard drinks guide was provided alongside alcohol consumption questions to increase response accuracy and equivalence across participants.

Qualitative focus groups were facilitated by a senior research assistant, IV, and cofacilitated by at least one other researcher (ie, JG, CB, or PS). IV conducted the interviews. The semistructured focus group and interview schedule gathered information regarding women's views in relation to breast cancer risk, alcohol consumption, other lifestyle factors, information needs, and attitudes toward receiving health information in different health settings. Women participated in a collaborative design activity where they provided feedback on and generated ideas for the design of the brief alcohol intervention prototype (eg, format, alcohol messaging), as well as the planned research procedures.

Data Analyses

Summary data from the retrospective analysis of Lifepool data and the web-based survey were expressed as counts and proportions or means and SDs. For the retrospective analysis of Lifepool data, sociodemographic and health-related characteristics were compared among women drinking within or exceeding the limits set by national alcohol guidelines for weekly and daily consumption. Associations were explored using logistic regression (categorical variables, dummy coded) and linear regression (continuous variables); in separate models, each characteristic dependent variable was regressed onto the alcohol guideline independent variables. Analyses were performed using Stata (version 17; StataCorp LLC). A *P* value <.001 (2-sided) was used as the level of significance for statistical analyses.

For qualitative data, focus groups and interviews were audio-recorded and transcribed verbatim by a professional transcribing company and organized using NVivo 20 (QSR International) according to the relevant domains of the RE-AIM and CFIR frameworks. Deductive thematic analysis was conducted using the framework method [33].

Reimbursement

To optimize participation in the formative evaluation, there was an incentive of an Aus $1 (US $0.69) donation to breast cancer research for every web-based survey completed and an Aus $10 (US $6.91) donation for focus group or interview participation.

RCT Protocol

Setting

This RCT was conducted at Maroondah BreastScreen, an Eastern Health Service and part of the Victorian National Breast Cancer Screening Program in Melbourne, Australia.

Participants and Eligibility Criteria

Women who underwent routine mammography on Tuesdays and Fridays between February and August 2021 were invited to participate in the study after their appointment. Women received their usual appointment reminder emails with additional information to inform them about the study in advance. Study posters were displayed in the waiting and screening rooms, and verbal information about the study was provided by the radiographers and reception staff. A text message reminder informing women about the study the day before their appointment was introduced, in addition to the email, in May 2021. The inclusion and exclusion criteria are presented in Textbox 1. Women drinking at any level of alcohol consumption (including women who do not drink) were eligible to participate. This approach served to negate any stigma and potential unblinding that may occur by including only women who consume alcohol or drink at risky levels.

Textbox 1. Eligibility criteria.

Inclusion criteria

- Female
- Attending routine mammography
- Aged ≥40 years
- English as a first language or fluent
- Regular access to a telephone
- Able to provide informed consent to participate
- Any level of alcohol consumption (including women who do not drink)

Exclusion criteria

- Hearing impairment sufficient to prohibit a telephone interview
- Pregnancy (also an exclusion from screening)
- Unable to read or comprehend English at a level to provide informed consent or receive the brief intervention

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Randomization and Blinding

Randomization was performed immediately after screening assessment, with the next consecutive allocation revealed on the protected spreadsheet. Participants were randomly assigned to the intervention or control group at a 1:1 allocation ratio. Randomization used standard computer-generated permuted blocks of a variable-size scheme. A randomization list was generated at the start of the study by a data scientist and linked to a unique identification code. The data scientist generating the random allocation sequence played no other role in the study. The study was described as a trial of two types of women's health promotion that minimized the trial's alcohol focus and concealed allocation to the intervention arm. Researcher 1, who administered the corresponding intervention per a priori generated randomization list, was not blinded to trial allocation. Researcher 2, who performed the 4- and 12-week telephone assessments, was blinded to trial allocation throughout trial data collection and may only have been unblinded once quantitative program implementation evaluation feedback was sought from trial participants before closing the 12-week call (ie, data collection that did not require blinding). Given the nature and content of the intervention and the outcome assessments, emergency unblinding procedures were deemed unnecessary.

Interventions

Overview

Interventions were delivered on an iPad using a prototype of a brief eHealth intervention (ie, researcher-administered screening alcohol questions, intervention administered by the researcher for the participant to view alone). The brief eHealth intervention model was chosen to minimize disruption to the service workflow and the need for human resources to be implemented within the busy breast screening environment. Take-home study-branded earphones were provided to each participant to view the animation privately. The Qualtrics web-based survey platform that hosted the baseline alcohol questions and intervention tracked the time participants spent viewing the intervention, permitting oversight of the intervention completion.

Active Condition: Health4Her Alcohol Brief Intervention + Lifestyle Information

The active arm received 4 minutes of brief alcohol intervention and 3 minutes of lifestyle health promotion related to modifiable breast cancer risk factors (physical activity and maintaining a healthy weight). A take-home pamphlet summarizing the alcohol information presented during the intervention was provided along with a pamphlet on nutrition to maintain a healthy weight.

The Health4Her intervention was developed in accordance with brief alcohol intervention principles [34,35], applied behavior change approaches [36-39], and findings from our formative research with breast screening service consumers. The brief alcohol intervention comprised personalized feedback and comparison to gender and age drinking norms, negative-framed messaging around alcohol risks and harms, positive-framed messaging on the health benefits of reducing alcohol intake, and alcohol harm-reduction strategies (Table 1). There were 2 versions of the Health4Her intervention, whereby messages relating to personalized normative feedback varied depending on whether participants reported that alcohol use exceeded national alcohol guidelines.

Table 1. Examples of messages included in brief intervention.

Brief intervention and applied behavior change approach	Example of message received
Personalized normative feedback	
Not exceeding Australian Alcohol Guidelines for weekly consumption	"You indicated that you are drinking within the recommended amount of 0 to 10 standard drinks per week. You're doing a good thing for your health—the less you choose to drink, the lower your risk of alcohol-related harm."
Exceeding Australian Alcohol Guidelines for weekly consumption	"You indicated that you are drinking above the recommended limit of 10 standard drinks per week. You are drinking more alcohol than three-quarters of Australian women your age, and the amount you are drinking is putting your health at risk."
Negative-framed messaging	"Did you know that alcohol is a carcinogen, meaning that it's consumption can cause cancer in humans? And there's now strong evidence that drinking alcohol increases your risk of breast cancer."
Positive-framed (or gain-framed) messaging	"The less you choose to drink, the greater the immediate and longer-term health benefits."
Alcohol harm-reduction strategies	"Here are some strategies to get you started: keep track of how much you're drinking by checking the label of any bottle or can for the number of standard drinks it contains. Plan your alcohol-free days for the week ahead, and challenge yourself to add an extra alcohol-free day."

Control condition: Lifestyle Information

The control arm received 3 minutes of lifestyle health promotion to increase knowledge of how to improve women's health and reduce breast cancer risk, not inclusive of alcohol information. Lifestyle health promotion focused on physical activity and maintaining a healthy weight and was developed to be relevant to women attending breast screening services as 2 recognized modifiable breast cancer risk factors [40,41]. A take-home pamphlet on nutrition to maintain healthy weight was also provided.

Choice of Comparator

Participants in the control arm received lifestyle health information to reduce breast cancer risk through animation and a take-home pamphlet on nutrition to maintain a healthy weight. As confirmed through the formative evaluation, embedding brief alcohol intervention within lifestyle information offered to all women attending breast screening provided the opportunity

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to target harmful alcohol consumption in a discrete, nonstigmatizing way and increased Health4Her's relevance for all women. As such, lifestyle information in the control condition was also provided in the intervention condition. This also served to maintain equivalence across the treatment conditions. Data from several studies suggest that alcohol assessment reactivity (ie, mere exposure to screening and baseline alcohol questions can prompt awareness and behavioral self-regulation) can bias trial results toward the null and lead to underestimation of the true effects of interventions [42,43]. While participants in the control arm were anticipated to experience some benefits from trial participation and alcohol assessments, it was expected that the effects on primary and secondary end points would be less than those observed for the intervention arm.

Outcomes

Primary and secondary outcomes of the RCT are detailed in Textbox 2.

Textbox 2. Trial outcomes.

Primary outcome

- Change in the proportion of participants accurately identifying alcohol as a clear risk factor for breast cancer at 4-week postrandomization

Secondary outcomes

- Change in the proportion of participants drinking ≤10 standard drinks per week (ie, within current Australian Alcohol Guidelines) [44] at 4 week and 3 months postrandomization (14-day timeline follow-back [TLFB]) [45]
- Among participants who (1) have consumed any alcohol in the past 2 week and (2) drink >10 standard drinks per week at baseline: change in the proportion of participants drinking ≤10 standard drinks per week at 4 week and 3 months postrandomization (TLFB) [45]
- Change in alcohol consumption at 4 week and 3 months postrandomization (TLFB, Australian Institute of Health and Welfare alcohol frequency quantity items) [45-47]
- Among participants who (1) have consumed any alcohol in the past 2 week and (2) drink >10 standard drinks per week at baseline: change in alcohol consumption at 4 week and 3 months postrandomization (TLFB, Australian Institute of Health and Welfare alcohol frequency quantity items) [45-47]
- Health literacy (attitudes): change in participants' attitudes regarding alcohol and breast cancer risk at 4-week postrandomization (adapted from previous literature) [48]
- Health literacy (knowledge): change in the proportion of participants accurately identifying (1) the amount of alcohol in an Australian standard drink; (2) the number of standard drinks in an average restaurant serve of red wine; (3) the maximum number of standard drinks per week recommended by current Australian Alcohol Guidelines (multiple-choice and open-ended questions, adapted from previous literature) [10] at 4-week postrandomization.
- Health literacy (access to health information): proportion of participants who have accessed health information on (1) alcohol harms, (2) alcohol and breast cancer risk, and (3) alcohol harm-reduction at 4-week postrandomization.
- Change in general health at 4 week and 3-month postrandomization (12-item Short-Form Health Survey) [49]
- Change in quality of life at 4 week and 3-month postrandomization (European Health Interview Survey-Quality of Life-single item) [50]

Informed Consent, Enrollment, and Participation

After the breast screening appointment, women who were interested in participating in or learning more about the study were introduced to the on-site researcher (researchers held, at a minimum, an honors degree in Psychology, Population Health, or related discipline), who provided a copy of the participant information and consent form, provided a verbal explanation of the trial (aims, procedures, risks, and benefits), and answered any participant questions (Table 2). Women were advised that they could withdraw from the study at any time and that their decision to participate or withdraw would not affect their relationship with Maroondah BreastScreen or Eastern Health. For women interested in participating in the study, the researcher confirmed their eligibility and obtained verbal or written informed consent (time-dependent), which included consent for the possible future use of participants' deidentified data for related projects.

The researcher then conducted a brief baseline assessment and random allocation by manually administering the iPad to play the corresponding animation according to (1) randomization and (2) if allocated to the active arm, delivery of version the intervention consistent with the participant's level of alcohol consumption. The study explanation, informed consent, screening, baseline assessment, and participation were brief, taking approximately 15 minutes per participant (Table 2).

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Table 2. Standard Protocol Items: Recommendations for Interventional Trials schedule of enrollment, interventions, and assessments.

	Time point		
	Baseline (Maroondah BreastScreen)	Follow-up (telephone)	Follow-up (telephone)
	Day 1	4 weeks	12 weeks
Enrollment			
Verbal information and provision of trial information sheet	✓		
Informed consent (written or verbal; time-dependent)	✓		
Eligibility and demographic information	✓		
Randomization	✓		
Intervention			
Active condition: Health4Her alcohol brief intervention + lifestyle information	✓		
Control condition: lifestyle information	✓		
Assessment[a]			
Knowledge assessment of breast cancer risk factors, including alcohol	✓	✓[b]	
14-day timeline follow-back [45]	✓	✓	✓
Australian Institute of Health and Welfare alcohol frequency and quantity items [46,47]	✓	✓	✓
Assessment of alcohol literacy	✓	✓	
European Health Interview Survey-Quality of Life (single item) [50]	✓	✓	✓
Short Form Health Survey [49]	✓	✓	✓
Assessment of physical activity [51] and fruit and vegetable consumption [52]	✓	✓	✓

[a]Alcohol assessments were nested among general health and lifestyle questions to conceal alcohol focus.

[b]Primary outcome.

Follow-up and Lost to Follow-up

Follow-up assessments were conducted by researcher 2 via telephone calls (<15-minutes duration) at 4 and 12 weeks after randomization, wherein baseline measures were repeated (Table 2). Participants who could not be contacted after 5 attempts were deemed missing at that data collection time point. For participants lost to follow-up at 4 weeks, the researcher attempted contact at 12 weeks following the same procedure.

Schedule of Enrollment, Interventions, and Assessments

The schedule of enrollment, interventions and assessments is outlined in Table 2.

Reimbursement

Trial participants went into a draw to win one of the 10 Aus $100 (US $69.48) supermarket vouchers to optimize the follow-up response rate [42]. The participants received no direct financial or other consideration (ie, in kind contribution) to participate in this trial.

Outcome Measures

Outcome measures of the randomized controlled trial are shown in Table 3.

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Table 3. Standard Protocol Items: Recommendations for Interventional Trials schedule of enrollment, interventions, and assessments.

Data collected	Method
Screening	
Eligibility and demographic information	Brief standard demographic characteristics (eg, age and education) and inclusion and exclusion information collected through structured questions.
Primary outcome	
Knowledge assessment of breast cancer risk factors	Participants were asked to demonstrate their knowledge of breast cancer risk associated with 6 factors (eg, family history of breast cancer, physical inactivity, antiperspirant deodorant use, alcohol, processed meats, and excess weight) by selecting from a set of scaled-response options: (1) a clear breast cancer risk factor with strong, consistent evidence; (2) a possible risk factor with some evidence; (3) not a proven risk factor with too limited evidence to determine risk; or (4) do not know. Primary outcome was the proportion of participants identifying alcohol as a clear breast cancer risk factor at 4 weeks. Adapted from Cancer Australia's 2018 definitions of breast cancer risk factors and previous research with breast screening service consumers [48,53].
Secondary outcomes	
Alcohol[a]	
14-day TLFB[b]	Alcohol consumption over past 14 days assessed with TLFB [45]. TLFB also informed personalized feedback provided in the alcohol brief intervention.
AIHW[c] alcohol frequency and quantity items	Past-month frequency of alcohol consumption and volume of alcohol consumption on a typical drinking day assessed with 2 items from the AIHW National Drug Strategy Household Survey [46,47].
Assessment of alcohol health literacy	Adapted from previous research with breast screening service consumers, participants were asked about (1) attitudes to alcohol and breast cancer risk [48]; (2) alcohol health knowledge (eg, amount of alcohol in a standard drink, number of standard drinks in an average restaurant serve of alcohol, maximum number of standard drinks recommended by current health guidelines) [10]; and (3) access to alcohol and breast cancer health information [54]. Questions were presented in multiple-choice, open-ended, or statement (ie, 5-point Likert scale from strongly agree to strongly disagree) formats.
Health and well-being	
European Health Interview Survey-QOL[d] single item	QOL rated as single item on 5-point Likert scale from very poor to very good [50].
SF-12[e]	SF-12 used as a brief measure of general health [49].
Physical activity duration [51,52] and consumption of vegetables and fruit [52]	Brief physical activity and vegetable and fruit intake questions included to ensure blinding of participants. Questions adapted from the Australian Bureau of Statistics and previous research [51,52].

[a]Alcohol assessments were nested among general health and lifestyle questions to conceal the trial's alcohol focus.

[b]TLFB: timeline follow-back.

[c]AIHW: Australian Institute of Health and Welfare.

[d]QOL: quality of life.

[e]SF-12: 12-item Short-Form Health Survey.

Data Collection and Management

Baseline data were collected by researcher 1 (on-site at Maroondah BreastScreen) and follow-up data were collected by researcher 2 (via telephone). A description of the trial schedule of the assessments can be found in Tables 2 and 3. An electronic case report form was completed for each participant using REDCap (Research Electronic Data Capture; Vanderbilt University) [55], hosted on a secure server and managed by Eastern Health IT Services with individual access via a secure login, and accessible only to approved members of the research team. REDCap stored screening and trial data, as well as identifiable data, including participant names and contact information. Identifiers were flagged in REDCap to provide additional protection for these data during data exports (ie, identifiers were automatically removed from all exported material generated by REDCap). Spreadsheets containing reidentifiable information (ie, for the purpose of conducting follow-up assessments; timeline follow-back data, which could not be collected using REDCap) were protected with unique passwords. Hardcopy data were stored and secured in a locked cabinet on-site at Turning Point. Upon completion of trial data collection, data were transferred from the electronic case report form and other source documents (eg, timeline follow-back spreadsheets) to Stata and R statistical software (R Foundation for Statistical Computing) packages for analyses. Protected health information (ie, participant name and contact information) was not exported. All data collected during this study will be

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retained by the research team for at least 5 years, as outlined in the Australian Code for the Responsible Conduct of Research.

Power and Sample Size

Power and sample size estimates were carried out using PS: Power and Sample Size Calculation (version 3.1.2; Vanderbilt University) [56], assuming a type 1 error probability of <.05, 2-tailed, and equal-sized groups. Power calculations were based on the primary end point and the change in the proportion of participants who accurately identified alcohol as a clear risk factor for breast cancer. On the basis of the data from our web-based survey of breast screening service consumers (n=391) conducted as part of the study's formative evaluation, the proportion of participants identifying alcohol as a clear risk factor for breast cancer at baseline was estimated to be 22%. On the basis of a related study examining the effects of a public health campaign on awareness of the alcohol-breast cancer link [57], the response rate for participants receiving an alcohol brief intervention was estimated to be ≥12% greater at 34% at 4 weeks postrandomization. Accounting for 20% attrition at the follow-up, a sample of at least 548 participants (274 per arm) was estimated to provide 80% power to reject the null hypothesis.

Statistical Analysis Plan

Data were collated, cleaned, and validated in a database that was locked before analysis. No interim analyses were planned to be conducted, and as no substantial harm was anticipated from this trial, no formal stopping guidelines were specified. All statistical tests were 2-tailed, with the α level set at .05, and analyses were conducted using the most appropriate procedures in Stata or R All randomized participants were included in the analyses (ie, intention-to-treat) for primary and secondary outcomes. Sociodemographic characteristics will be summarized and reported by intervention arm. Analyses examined change in outcomes over time (4 weeks, 12 weeks, or 4 and 12 weeks; pre-specified for each outcome) relative to baseline. The Generalized Linear Mixed Model approach with fixed effects for treatment and time, their interaction, and random effects for subjects and assessments within subjects was applied to examine the treatment effect of the intervention on all outcomes. For outcomes assessed at a single postrandomization time point, the models were equivalent to traditional logistic regression. For consumption outcomes, subgroup analyses were conducted with participants exceeding national guidelines for weekly consumption. Mixed models are robust to missingness under the assumptions of missing at random and missing completely at random, thereby maintaining analyses based on intention-to-treat principles. For outcomes with 2 time points, Cochran-Mantel-Haenszel tests were examined.

Trial Monitoring

The trial's chief investigators performed the function of a Trial Steering Committee, because they had the technical expertise necessary to oversee all aspects of trial conduct (eg, monitor compliance with the protocol, provide ethical and clinical governance, provide standardized training and other means of quality control, and monitor trial arm fidelity). Given the minimal risks of harm associated with this brief intervention, a formal data-monitoring committee was not considered necessary. Regular liaison between the immediate research team and the principal investigator occurred to permit discussion of day-to-day trial progress and any potential concerns. The broader research team met intermittently to review the overall progress of the project and conduct the trial. Data audits were conducted at periodic intervals and were led by the trial manager.

Protocol Amendments

Protocol amendments were approved by the Eastern Health Human Research Ethics Committee. No major changes to the protocol were implemented without prior approval and there were no modifications to the intervention during the trial.

Adverse Events

The risk of harm or discomfort to participants during this trial was anticipated to be minor and transient, in line with the research team's experience conducting brief alcohol intervention research (eg, minor distress responding to questions about alcohol consumption). The research team monitored possible adverse effects throughout the trial.

Participant Withdrawal and Discontinuation

All participants were advised that they had the right to withdraw consent at any time and without consequences. Withdrawal of consent could occur verbally or in written form (ie, email or text message correspondence), and participants could elect to remove all of their previously collected data or consent for further data collection. No further contact was initiated by the research team once the participants withdrew consent.

Ancillary and Posttrial Care

Participants were advised during enrollment and at the end of participating in their allocation intervention that they should continue to engage with health care as usual while participating in the study and to contact their primary care provider if their participation in this study raised concerns about any aspect of their health (ie, alcohol use, general health, breast cancer risk).

Program Implementation Evaluation

Setting

Researchers conducting the process evaluation were based at Turning Point, with telephone or videoconferencing used to collect feedback from trial participants and breast screening staff.

Participants

The first component of the process evaluation comprised quantitative feedback about the health information received (Health4Her and control) and its implementation from the 497 women who participated in the 12-week follow-up assessment and responded to the program evaluation questions. Qualitative data about the Health4Her intervention and its implementation were collected from in-depth semistructured telephone interviews conducted with 30 participants after trial. A nested sample design was used to select a subsample of participants for the qualitative interviews [58]. All women were asked if they would be interested in being contacted for an optional qualitative telephone interview. From those who consented to

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participate in this extra component of the study, systematic random sampling was used to contact participants who (1) were randomized to the active arm and (2) reported drinking alcohol at baseline to arrange an interview. Of this sample, 9 women were purposively sampled from participants who were drinking above the Australian Alcohol Guidelines at baseline assessment and who had consented to the optional interview.

Staff feedback about the intervention and implementation was obtained via 3 videoconferencing focus groups with 11 Maroondah BreastScreen staff members (managers=2, radiographers=6, and reception staff=3) held at the completion of the trial. All staff members who were interested in participating in a focus group and who were available on the day a focus group was being run were able to take part.

Data Collection

Applicable elements of the RE-AIM framework [26] guided the development of the quantitative participant feedback schedule, the semistructured participant interview, and interpretation of participant feedback to understand the Health4Her intervention's reach (eg, participants' use of health information and reach of information beyond trial participants [distributed health literacy]), efficacy (eg, intervention acceptability and perceived benefits), and implementation (eg, intervention delivered via iPad). Some elements of the CFIR [25] were also used to understand the characteristics of the intervention (eg, format and delivery) and outer setting (eg, existing health campaigns and intervention needs) from the perspectives of participants to identify factors influencing successful implementation.

Applicable elements of the CFIR [25] were used to guide the development of the semistructured staff focus group schedule and interpretation of staff feedback to understand the outer setting (eg, client needs and resources) and inner setting (eg, Maroondah BreastScreen culture, implementation climate, compatibility, and resources). Elements of the RE-AIM framework [26] were also used to understand reach and efficacy relative to staff facilitating intervention delivery (eg, letting women know about the intervention in advance), adoption (eg, factors predicted to affect the uptake of the Health4Her intervention at other breast screening services), and maintenance (eg, factors that facilitate long-term uptake of the Health4Her intervention).

Guided by the RE-AIM framework [26], the process evaluation also included the evaluation of trial and service administrative data collected during implementation (eg, intervention reach and uptake, such as the rate at which women participate in the trial of women invited to participate, reasons for nonparticipation when available, participant characteristics including health inequity factors [culturally and linguistically diverse background; lesbian, gay, bisexual, transgender, intersex, queer, and other LGBTIQ+ status; experiencing disability; low education; and living alone], intervention reach beyond trial participants [distributed health literacy], and COVID-19 impact on operations).

Data Analyses

Summary data from quantitative trial and service data and participant feedback were expressed as counts and proportions or means and SDs. For participant and staff qualitative data, interviews and focus groups were audio-recorded and transcribed verbatim by a professional transcribing company and organized using NVivo 20 according to the relevant domains of the RE-AIM and CFIR frameworks. Deductive thematic analysis was conducted using the framework method [33].

Ethics Approval

This research was conducted in accordance with the Declaration of Helsinki, the 2007 National Health and Medical Research Council National Statement on Ethical Conduct in Human Research (updated 2018), the 2000 Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95), and the International Council for Harmonisation Good Clinical Practice Guidelines. This protocol and informed consent processes for each element of the research were approved by the Eastern Health Human Research Ethics Committee (LR19-011-50551) and the Monash University Human Research Ethics Committee (21,395). The trial was preregistered with ClinicalTrials.gov (NCT04715516) on January 20, 2021.

Results

This research was funded in March 2019 (Eastern Health Foundation Research and Innovation Grant) and May 2019 (VicHealth Impact Research Grant). Data collection for the formative evaluation was conducted from January to April 2020 (retrospective analysis of alcohol consumption data from Lifepool, n=49,240; web-based survey with breast screening service consumers, n=391; focus group and interviews with breast screening service consumers, n=31). Trial recruitment was conducted from February to August 2021 (n=588), with follow-up data collection finalized in December 2021. Quantitative process evaluation data were collected during trial implementation, and the collection of participant and staff feedback was finalized in December 2021 (participant quantitative feedback, n=588; participant qualitative feedback, n=30; and breast screening site staff feedback, n=11). We anticipate that the results of the retrospective analysis of alcohol consumption data from Lifepool (part of the mixed methods formative evaluation) will be published in March 2023. We anticipate that the results of this RCT will be published in March 2023. The program evaluation (comprising the preimplementation web-based survey and focus groups and interviews with subsets of breast screening service consumers and mixed methods process evaluation using trial and site administrative data and feedback from trial participants and breast screening site staff) is also planned for publication.

Discussion

Anticipated Findings

Previous research has found brief alcohol interventions to be effective in increasing alcohol-related knowledge and reducing alcohol consumption in primary care and other settings [34,59]. This is the first known hybrid effectiveness-implementation

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trial to examine the benefits of a novel, tailored alcohol brief intervention among women attending the breast screening setting. The study design permits an extensive mixed methods program evaluation alongside a RCT to provide a sound understanding of the factors affecting implementation of the Health4Her intervention to predict and facilitate uptake in practice. The RCT is anticipated to provide evidence that Health4Her intervention increases the proportion of women accurately identifying alcohol as a breast cancer risk factor, improving alcohol literacy more broadly (ie, increasing the proportion of women accurately identifying the amount of alcohol in an Australian standard drink, the number of standard drinks in an average restaurant serve of red wine, and the maximum number of standard drinks per week recommended by current Australian Alcohol Guidelines), and reducing alcohol consumption. The breast screening appointment can act as a window of opportunity to increase engagement with breast cancer risk reduction information; this research will generate new substantial knowledge on the alcohol consumption and alcohol literacy needs of this population and the extent to which these can be addressed using a low-cost, scalable intervention, with the potential to contribute to the prevention of alcohol-attributable breast cancer and the related burden of disease and quality of life among this population.

Strengths and Limitations

The hybrid type II effectiveness-implementation trial design, guided by applicable elements of the RE-AIM [26] and CFIR frameworks [25], represents a key strength of this study. The integration of quantitative and qualitative data occurring at each level of the implementation evaluation [60] will build upon the outcomes of the RCT to provide real-world indicators of program implementation, to accelerate the translation of this research into practice. The RCT used a double-blind design; a typical limitation of brief alcohol intervention studies with hazardous drinkers in primary care settings is the bias introduced by difficulties with participant blinding [61]. One limitation of this research is the risk of assessment reactivity, where mere exposure to alcohol questions prompts awareness and behavior self-regulation in the trial's control group and can bias trial results toward the null and lead to underestimates of true intervention effects. In the design of the RCT, alcohol knowledge and consumption outcomes were interspersed with general lifestyle questions to minimize the salience of the trial's alcohol focus. However, control group assessment reactivity may still occur. An additional limitation is that this initial trial was powered to identify a change in knowledge of alcohol as a breast cancer risk factor and not alcohol consumption per se. Still, this study will provide preliminary data on consumption end points, rates of missing data, and participant attrition, providing important estimates for future scaled-up research.

Conclusions

The benefits of brief alcohol interventions have been demonstrated in primary care and other settings; however, their effectiveness and implementation in the breast screening setting remain to be explored. The Health4Her intervention, targeting alcohol literacy and harmful consumption among women attending the breast screening setting, has huge potential for scalability and is particularly relevant considering the increasing prevalence of risky drinking among middle- to older-age women and strong evidence that even very light alcohol consumption increases breast cancer risk. This study will evaluate both the effectiveness and implementation of Health4Her intervention to predict and facilitate uptake in breast screening services.

Dissemination Plan

The findings of this research will be disseminated to funding bodies and other relevant stakeholders, published in peer-reviewed journals, presented at national and international conferences, and presented via public talks and media and social media.

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Data Availability

Only approved members of the research team had access to the final trial data set. Data were not shared, as there was no participant permission or ethics approval to do so, other than for related projects conducted by the research team.

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Authors' Contributions

JG, VM, and DIL were responsible for the conceptualization of the study. JG, VM, DL, MG, RB, LS, PB, and DIL were responsible for funding acquisition and study methodology. JG, VM, DL, MG, RB, and DIL were responsible for study supervision and coordination. PS, CB, and IV were responsible for data collection and qualitative analyses. CG performed formal analyses of quantitative data. The manuscript was originally drafted by JG, PS, CB, IV, and DIL. All authors reviewed, provided feedback on, and approved the final manuscript.

Conflicts of Interest

All authors declare no conflicts of interest.

Multimedia Appendix 1
Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines.
[DOC File , 126 KB - resprot_v12i1e44867_app1.doc]

Multimedia Appendix 2
Template for Intervention Description and Replication (TIDieR) checklist.
[DOCX File , 35 KB - resprot_v12i1e44867_app2.docx]

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Abbreviations

CFIR: Consolidated Framework for Implementation Research
LGBTIQ+: lesbian, gay, bisexual, transgender, intersex, queer, and other
RCT: randomized controlled trial
RE-AIM: Reach, Effectiveness, Adoption, Implementation, and Maintenance
REDCap: Research Electronic Data Capture

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Protocol

Enhancing the Cardiovascular Safety of Hemodialysis Care Using Multimodal Provider Education and Patient Activation Interventions: Protocol for a Cluster Randomized Controlled Trial

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Abstract

Background: End-stage kidney disease (ESKD) is treated with dialysis or kidney transplantation, with most patients with ESKD receiving in-center hemodialysis treatment. This life-saving treatment can result in cardiovascular and hemodynamic instability, with the most common form being low blood pressure during the dialysis treatment (*intradialytic hypotension* [IDH]). IDH is a complication of hemodialysis that can involve symptoms such as fatigue, nausea, cramping, and loss of consciousness. IDH increases risks of cardiovascular disease and ultimately hospitalizations and mortality. Provider-level and patient-level decisions influence the occurrence of IDH; thus, IDH may be preventable in routine hemodialysis care.

Objective: This study aims to evaluate the independent and comparative effectiveness of 2 interventions—one directed at hemodialysis providers and another for patients—in reducing the rate of IDH at hemodialysis facilities. In addition, the study will assess the effects of interventions on secondary patient-centered clinical outcomes and examine factors associated with a successful implementation of the interventions.

Methods: This study is a pragmatic, cluster randomized trial to be conducted in 20 hemodialysis facilities in the United States. Hemodialysis facilities will be randomized using a 2 × 2 factorial design, such that 5 sites will receive a multimodal provider education intervention, 5 sites will receive a patient activation intervention, 5 sites will receive both interventions, and 5 sites will receive none of the 2 interventions. The multimodal provider education intervention involved theory-informed team training and the use of a digital, tablet-based checklist to heighten attention to patient clinical factors associated with increased IDH risk. The patient activation intervention involves tablet-based, theory-informed patient education and peer mentoring. Patient outcomes will be monitored during a 12-week baseline period, followed by a 24-week intervention period and a 12-week postintervention

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follow-up period. The primary outcome of the study is the proportion of treatments with IDH, which will be aggregated at the facility level. Secondary outcomes include patient symptoms, fluid adherence, hemodialysis adherence, quality of life, hospitalizations, and mortality.

Results: This study is funded by the Patient-Centered Outcomes Research Institute and approved by the University of Michigan Medical School's institutional review board. The study began enrolling patients in January 2023. Initial feasibility data will be available in May 2023. Data collection will conclude in November 2024.

Conclusions: The effects of provider and patient education on reducing the proportion of sessions with IDH and improving other patient-centered clinical outcomes will be evaluated, and the findings will be used to inform further improvements in patient care. Improving the stability of hemodialysis sessions is a critical concern for clinicians and patients with ESKD; the interventions targeted to providers and patients are predicted to lead to improvements in patient health and quality of life.

Trial Registration: ClinicalTrials.gov NCT03171545; https://clinicaltrials.gov/ct2/show/NCT03171545

International Registered Report Identifier (IRRID): PRR1-10.2196/46187

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KEYWORDS

hemodialysis care; patient peer mentoring; telehealth; digital checklist; team training; cluster randomized controlled trial; pragmatic trial

Introduction

Background

End-stage kidney disease (ESKD) occurs when a person's kidneys are severely damaged and can no longer function independently. Patients with ESKD require dialysis or transplantation to survive. In 2020, 480,516 Americans (61.3% of patients with ESKD) received outpatient, facility-based hemodialysis (also known as in-center hemodialysis) [1]. This includes 109,107 new patients undergoing hemodialysis in 2020 [1]. Diabetes and hypertension are the leading causes of ESKD in the United States [1]. Accordingly, most patients with ESKD have multiple chronic conditions, including cardiovascular disease. In particular, ventricular hypertrophy and varying degrees of heart failure are common among patients on dialysis, compounded by the effect of intermittent fluctuations in blood volume during intermittent (eg, thrice weekly) hemodialysis [2]. The annual mortality rate among patients on dialysis in the United States has increased by nearly 17% during the COVID-19 pandemic in 2020. However, more than half of the deaths were owing to cardiovascular disease [1]. Patients on hemodialysis also experience low quality of life [3] and considerable pain, fatigue, social restrictions, and distress [4-7].

Patients on hemodialysis treated in a dialysis treatment facility typically receive dialysis treatment sessions 3 times a week, for 12 hours per week. On average, 20% of sessions become unstable, most commonly from low blood pressure, or *intradialytic hypotension* (IDH) [8-11]. IDH, a form of cardiovascular and hemodynamic instability, affects half of all patients on hemodialysis [8-11]. IDH may precipitate cramping, dizziness, vomiting, fainting, and fatigue [4,12,13]. The chief causes of IDH are removal of more fluid in a single session than a patient can tolerate, or removal of fluid faster than a patient can tolerate [14]. In the face of preexisting diminished cardiovascular reserves, this often results in hemodialysis instability and repeated myocardial hypoperfusion with resultant cardiac wall motion abnormalities, a phenomenon referred to as *myocardial stunning* [15-17]. Evidence shows that such fluid removal may be responsible for injury resulting from hypoperfusion in other organs, including the central nervous system (eg, repetitive neurological injury leading to cognitive dysfunction) [18].

Cardiovascular and hemodynamic instability during hemodialysis sessions may be preventable. Session stability is determined by the interplay between multiple factors, many of which are modifiable. At the patient level, these factors include decisions regarding sodium and fluid intake and skipping or shortening sessions [19]. Moreover, because early intervention in an IDH episode is important to prevent worsening, patients can notify providers of related symptoms, such as nausea, vomiting, dizziness, or muscle cramping, facilitating prompt provider-based interventions such as placing the patient in the Trendelenburg position [20]. Clinician practice patterns influencing session stability include the physician's decisions regarding the patient's target posthemodialysis weight (sometimes called "estimated dry weight", or "EDW" in practice) and prescribed treatment time and how often these are revisited. Facility-level policy or practice decisions such as a threshold for fluid removal speed (ultrafiltration rate [UFR]) and flexibility toward adding an extra session per week for specific patients are also potentially modifiable factors.

Owing to the relatively recent scientific consensus regarding the cardiovascular harm of rapid fluid removal [21], hemodialysis care providers may not always routinely incorporate cardiovascular and hemodynamic stability into their patient care decisions. In other words, providers regularly choose hemodialysis session lengths, fluid removal targets, and UFRs in ways that affect cardiovascular and hemodynamic stability, perhaps without direct attention to this factor. To provide a better foundation for such decisions, a consensus statement from Medical Directors of United States hemodialysis facilities called for trials of methods for improving patient fluid management [22], we address this call in our research.

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Objectives

We will independently evaluate and compare the effects of 2 facility-level interventions (multimodal provider education and patient activation interventions) on the cardiovascular and hemodynamic stability of hemodialysis care. Briefly, the multimodal provider education intervention includes a tablet-based checklist and team training for dialysis facility staff. The patient activation intervention includes tablet-based educational modules and peer mentoring. We pursue our study objectives through the following specific aims:

1. Aim 1: To conduct a cluster randomized controlled clinical trial to test and compare the effects of 2 hemodialysis facility-level interventions on the primary outcome of hemodialysis session stability over an intervention period of 24 weeks and a postintervention follow-up period of 12 weeks.
2. Aim 2: To test and compare the effects of 2 hemodialysis facility-level interventions on secondary patient-centered clinical outcomes, including patient symptoms, fluid adherence, hemodialysis adherence, quality of life, hospitalizations, and mortality over the same time frame.
3. Aim 3: To identify factors associated with the successful implementation of the interventions and ways in which implementation may influence intervention effectiveness.

Hypotheses

Our main study hypothesis is that hemodialysis session stability will significantly improve with either multimodal provider education or patient activation interventions, and that multimodal provider education will show a greater magnitude of improvement. This hypothesis is based on our expectation that some patients on hemodialysis might refuse or be unable to participate in the peer mentoring component of the patient activation intervention, potentially leading to greater reach of the provider intervention. We will test this main hypothesis and explore this potential explanation of any differential improvement as part of our planned sensitivity, mediation, and moderation analyses.

Methods

Study Design

We have translated 2 evidence-based interventions from their previous applications in inpatient safety (checklists [23] and team training [24]) and chronic disease self-management interventions (peer education and mentoring [25,26]) into the outpatient hemodialysis care context [27-29]. We will conduct a cluster randomized controlled clinical trial in 20 dialysis facilities to independently test and compare the effectiveness of each of the 2 interventions for improving the primary outcome of hemodialysis session stability, measured as the occurrence of IDH during a given session. The cluster randomized controlled trial design [30] is most appropriate to our goal of improving routine hemodialysis care. Because pragmatic intervention studies are most suited to supporting health care-related decision-making [31], the effectiveness of the interventions will be assessed under the usual conditions in which they will be applied [31]. The study will also use outcome data already gathered routinely by hemodialysis facilities [32].

Facilities will be randomized in a 2 × 2 factorial design. We selected this design because it is statistically efficient in providing a control group for testing each intervention. Furthermore, this design facilitates the comparison of the interventions' relative magnitudes of the effects and their potentially synergistic or antagonistic effects.

For aim 1 activities, the primary outcome, IDH occurrence, will be monitored for 12 weeks before the intervention (baseline period) for 24 weeks during the intervention period and for 12 weeks after the intervention period (follow-up period). We will also assess the effects of the interventions on secondary outcomes, including patient symptoms, fluid adherence, hemodialysis adherence, quality of life, hospitalization, and mortality (aim 2). The implementation of the interventions will also be assessed (aim 3).

Ethics Approval

This study has obtained institutional review board (IRB) approval for a waiver of informed consent and waiver of Health Insurance Portability and Accountability Act (HIPAA) authorization based on the "no more than minimal risk with potential direct benefits" to patients and the study's pragmatic nature (HUM00125305).

Study Organization and Partners

This study is led by a research team at the School of Information, Medical School, and the School of Public Health at the University of Michigan, Ann Arbor, United States. The study's data coordinating center, based in the Kidney Epidemiology and Cost Center at the School of Public Health, will receive deidentified patient data from a large dialysis provider organization to which all facilities in the study will belong. The National Kidney Foundation (NKF), a partner in the study, created patient educational module content and will recruit and train peer mentors for facilities assigned to the patient activation study arms. The patient activation intervention application used by peer mentors and their patient mentees will be developed by collaborators at the University of California, Irvine and at a telehealth platform company, VSee Inc. Funding for this study has been provided by the Patient-Centered Outcomes Research Institute.

Eligibility and Recruitment of Facilities

A total of 20 hemodialysis facilities were recruited from the following regions in the United States: Midwest, Northeast, Southeast, and Southwest. Facility inclusion criteria were as follows: (1) outpatient hemodialysis facilities, (2) at least 70 adult patients (aged ≥21 years) who were permanent patients at the study facility, (3) not currently involved in another study, and (4) no operational or administrative reasons that would make the trial difficult to implement at that site. Hemodialysis facility staff and providers will not be participants in the research (ie, data will not be collected from or about individual staff to answer the study research questions). Facilities were stratified by county poverty rate and then randomly selected to prevent

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one region or arm of the study from having a different socioeconomic status profile than the others.

Eligibility and Recruitment of Patients

As this is a pragmatic trial, we aim to include all nonvulnerable (see definition of vulnerable below in this section) in-center patients at participating hemodialysis facilities. The trial was designed so as not to exclude any patient, including women and minorities to the extent they are represented at the hemodialysis facilities from the age group of ≥21 years. We will only exclude vulnerable patients, including those below the age of 21 years; prisoners; those with a cognitive barrier; those deemed vulnerable by the clinical manager, medical director, or social worker; and those who are unable to comprehend the patient information sheet because of lack of facility in reading English or Spanish. Following prior pragmatic research in hemodialysis care [33] and the study's IRB review results, the study uses an "opt out" process for using patient clinical data to determine test facility-level and patient-level outcomes. Each patient will have the opportunity to opt out of having their data used in the study for outcome monitoring as part of aim 1 and 2 activities. The University of Michigan will manage the opt-out process and provision of study information remotely with the assistance of facility staff. Each patient will be given an information sheet by dialysis facility staff; these staff will also be provided an IRB-approved script to use when providing patients with the information sheet. Facility staff will record that each patient has received the information sheet and if they have verbalized a decision to opt out of the study. The information sheet will also provide a 1-800 telephone number to call the University of Michigan research team to learn more about the study or opt out of the study at any time if they desire. Patients may opt out of the study at any time, but patients in facilities assigned to the provider intervention arms of the study will still benefit from multimodal provider education as this is a facility-level intervention that does not involve specific patients.

For the patient activation intervention only, we will randomly select patients, in succession, who are not vulnerable or have not opted out of the overall study, until the target number of patients in a facility accept peer mentoring. That is, every time a patient declines to participate, we will choose another patient randomly until the enrollment target is reached. On the basis of prior studies [34-36], we estimated a retention rate of at least 73% for the peer mentoring intervention.

Detailed Intervention Description

Multimodal Provider Education Intervention

As Figure 1 shows, the provider intervention is informed by the Theory of Planned Behavior, commonly used in practice change interventions involving clinicians [37,38], including a study assessing the adoption of a patient safety checklist [39]. Using this model, we predict that changes in perceived behavioral control and behavioral intentions [40,41] resulting from the training will change providers' fluid management practice patterns (including use of the checklist), which will in turn reduce rates of hemodialysis session instability.

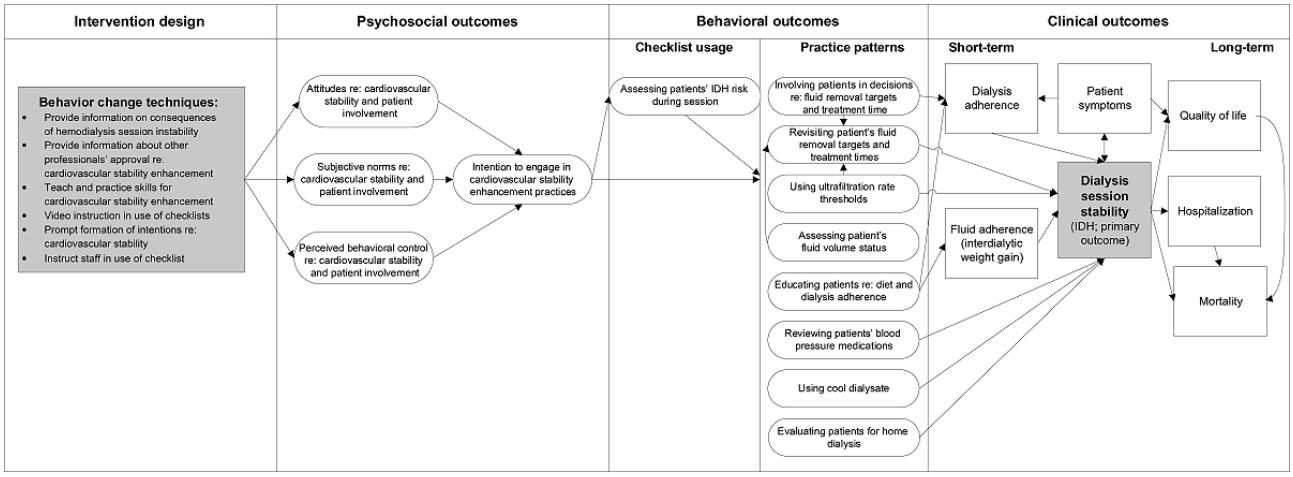
There are 2 components to the provider intervention. The first component consists of 4 training modules that will be completed by nurses, patient care technicians, dieticians, and social workers in the study facilities. The goals of these sessions were as follows: (1) to educate facility staff on the risks of IDH, (2) to promote recognition of IDH risk factors and opportunities for prevention and early intervention, and (3) to instruct staff in use of the checklist. Staff training will be implemented by the project coordinators at University of Michigan. It will include 2 self-paced modules available on web through the facility's access to a web-based learning management system and 2 synchronous web-based meetings between the project coordinators and staff at the facilities randomized to receive the provider intervention (Textbox 1 provides an overview of the staff training sessions).

In addition, physicians, nurse practitioners, and physician assistants who are not part of the hemodialysis facility staff, but who round in study facilities, will have access to a 1-hour asynchronous web-based training module. This training program reviews the purpose of the study and its scientific rationale. It also prepares them for potential treatment changes that facility staff, particularly nurses, may discuss with the provider as a result of using the checklist.

The second intervention component is the IDH prevention checklist [27], which will be provided on tablet computers (Figure 2). The checklist aims to identify patients at increased risk of IDH; it is to be completed by a nurse for each patient's hemodialysis treatment with verbal input from the patient and patient care technician as indicated. The checklist has 4 items that may be associated with increased IDH risk: 2 pertaining to the past 5 treatments and 2 pertaining to the current session. If any risk factors are identified, a list of suggestions based on the evidence-based literature on how to prevent IDH will be presented. Suggestions include measures for preventing IDH in the current hemodialysis session (ie, placing the patient in a modified Trendelenburg position) as well as longer-term changes that may require a physician's input (ie, adjusting the patient's estimated dry weight or providing additional counseling on sodium restrictions). The data collected through the checklist will not identify the patient or the staff member, but the use will be automatically logged on a HIPAA-compliant server, including the facility, date, time, items displayed, and items clicked.

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Figure 1. Theory-based model of behavior change for multimodal provider education intervention. IDH: intradialytic hypotension.

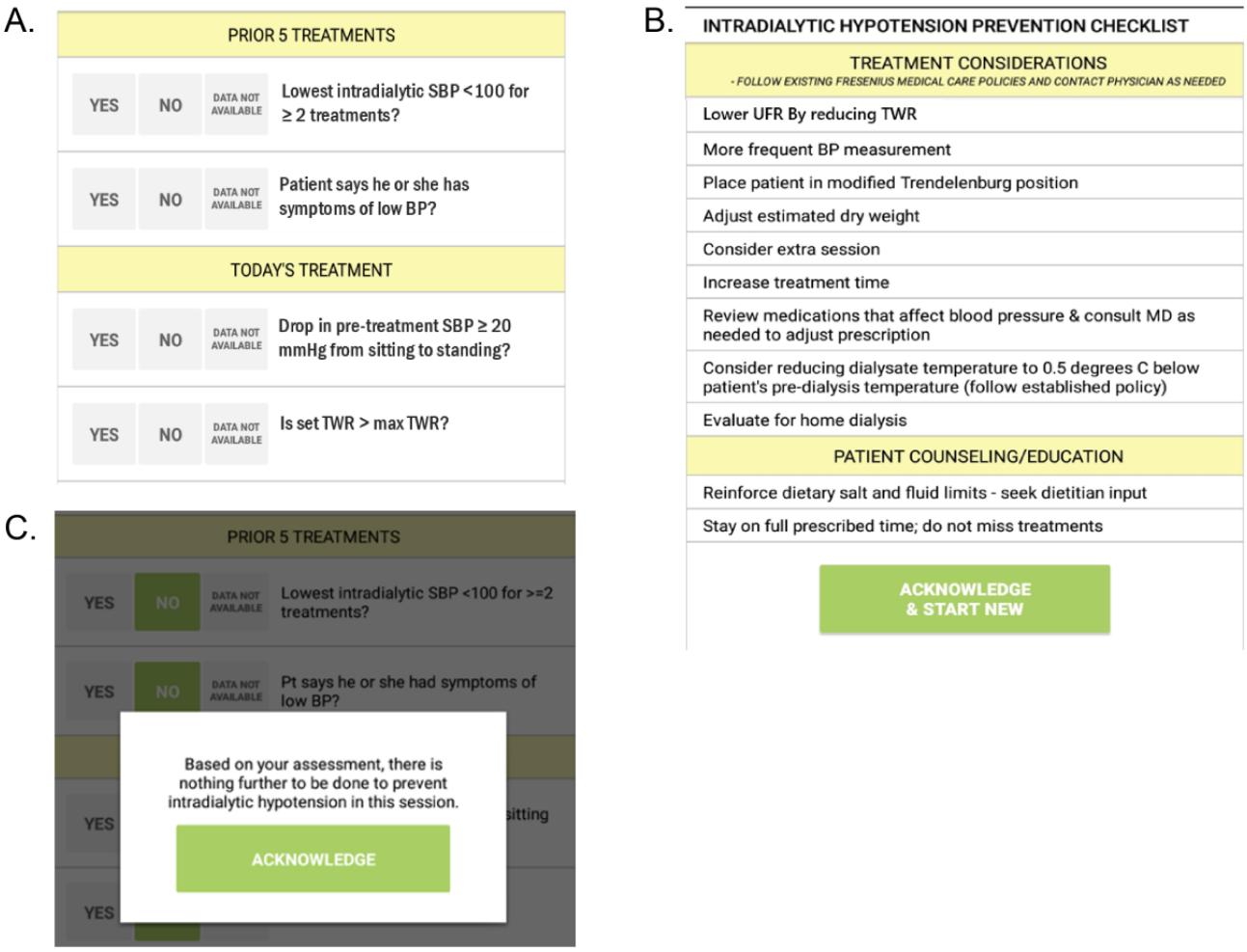


Textbox 1. Overview of the staff training intervention.

- The first training is a self-paced module through the learning management system available to the facilities. It will introduce the Dialysafe project goals and study design. Staff will refresh their knowledge on consequences of intradialytic hypotension (IDH) and identify the training requirements of their assigned study group.
- The second training is designed for active participation and discussion from the providers. Staff will consider the most susceptible points in time for patients to experience cardiovascular instability, including IDH. The training will review principles of weight and blood pressure measurement per existing facility policy. The audience will be introduced to how the nurse will use the Dialysafe IDH prevention checklist to systematically evaluate every patient for IDH risk early in the session, and how to make changes to the hemodialysis session if the patient is found to be at risk.
- In the third training, staff will review actions for increasing cardiovascular and hemodynamic stability for patients at higher risk of IDH. Key points of this training include the importance of frequently assessing a patient's dry weight and making changes as necessary, the need to review blood pressure medications, and the use of cool dialysate. These topics are some of the methods that can be used to prevent IDH; providers will also be given time to reflect on and discuss other measures they have found effective. Finally, staff will review their role in IDH prevention and consider times when they might discuss making changes to a patient's hemodialysis sessions. They will also reflect on their experience with the Dialysafe IDH prevention checklist.
- Staff training part 4 is a 15-question multiple-choice quiz hosted on the learning management system.

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Figure 2. Intradialytic hypotension (IDH) prevention checklist. A) Questions asked at each dialysis session to all patients in clinics assigned to the provider intervention. B) Suggested actions for dialysis care team if any questions from the checklist (A) are answered "yes" or "data not available." C) Screen displayed if ALL questions from the checklist (A) are answered "no ". BP: blood pressure; SBP: systolic blood pressure; TWR: target weight removal; UFR: ultrafiltration rate.



Approaches to Encouraging Participation and Retention for Provider Intervention

Several implementation strategies will be used to promote the successful adoption of the provider intervention. All facilities randomized to this intervention will appoint a *study champion* who will help convey positive messages about the study, including staff training and checklist implementation. Each of these facilities will also form an operations committee, which will include the study champion, an area manager, patients, and others selected to represent different organizational levels and perspectives, as intervention implementation will be enhanced by the early involvement of staff at various levels [42].

Checklists are more likely to be effectively used if accompanied by training that addresses the *why* and *how* questions regarding their implementation [43-46]. Therefore, the second provider training includes how to use the checklist and its associated rationale. The third training includes dedicated time for discussing the ways in which the checklist has or has not been integrated into the facility workflow to promote the sharing of learning and process improvements [47].

Notably, both components of the multimodal provider education intervention offer incentives for completion. We plan to offer incentives to staff in facilities that consistently use the checklist. For each month of intervention, facilities that achieve a 90% checklist completion rate will be provided lunch. Facilities that achieve a 90% checklist completion rate for the entire study will receive a certificate of recognition that can be posted in an area visible to staff and patients.

Facility-level incentives include the fact that study facilities that participate in trainings 2 and 3 and meet the requirements will receive one "Diamond" toward its 5-Diamond status. The 5-Diamond Patient Safety Program is a national initiative. The 5-Diamond Patient Safety Program was designed to assist dialysis centers with safety standards through continuous learning modules for frontline clinicians. Participating dialysis facilities are required to complete a series of safety modules each year to earn or renew their 5-diamond status, and annual participation in the 5-Diamond Patient Safety Program is already undertaken at all hemodialysis facilities in this study. In addition to the facility's diamond status, nurses and patient care technicians who attend these training sessions will be offered optional continuing education unit credit. Physicians and advanced practitioners will also be able to earn continuing medical education or continuing nursing education credit by watching the 1-hour training video described previously.

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Therefore, successful completion of the provider training offers both facility-level and individual-level incentives.

Patient Activation Intervention

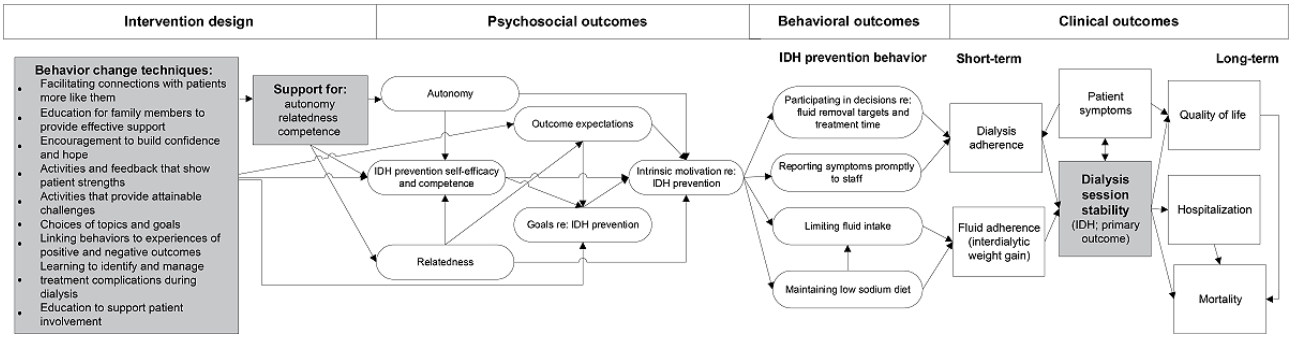
The patient activation intervention includes both internet-based educational modules and peer mentoring. Both intervention components were designed using Social Cognitive Theory and Self-determination Theory [28]. Social Cognitive Theory [48-50], an approach with strong empirical support in evidence-based interventions, is a key framework underlying the patient intervention. Social Cognitive Theory emphasizes the predictive power of *self-efficacy*, or confidence in one's ability to perform an action, in the likelihood of performing that action (Figure 3). This theory has led to successful peer-based chronic disease interventions [51,52]. The design of the educational modules is also informed by Self-determination Theory [53], which proposes that people are more likely to engage in a behavior when they are intrinsically motivated to perform it. Intrinsic motivation emerges when one finds an activity enjoyable or satisfying, as is the case when one's psychological needs are met when performing that activity. Self-determination Theory highlights three psychological needs: (1) autonomy (the need to feel in control of one's life), (2) competence (the need to feel effective in dealing with situations one encounters), and (3) relatedness (having meaningful relationships or having a sense of belonging in a community).

The patient activation intervention will be digitally available on tablets shipped to patients for use at home and shipped back to the university upon intervention completion. The patient activation intervention is delivered through 5 modules to be completed roughly 1 week apart from one another. Each module focuses on a different aspect of preventing IDH (Table 1 provides a detailed summary of the module's content and related behavioral goals). Each module includes the following elements: (1) a slide deck presented as an informational video; (2) an optional quiz about the video content; (3) patient experience stories presented as short video clips; (4) a goal-setting feature; (5) the option to view or email supplemental NKF handouts and suggested apps; (6) a peer mentoring session lasting 20 minutes to 1 hour supported by a discussion guide for mentors; and (7) an action plan with patient-identified goals, values, and steps to overcome barriers. The action plans will be completed by the peer mentor and emailed to the patient after the mentoring session. Multimedia Appendices 1 and 2 provide screenshots of the digital modules.

Peer mentoring sessions will be delivered via a secure, HIPAA-compliant videoconferencing platform. The intervention extends an existing peer mentoring program offered by NKF. NKF Peer Mentors are trained patients with ESKD who volunteer to support other patients. Mentors can speak from their own experience about the challenges of life on hemodialysis; thus, patients often view mentors as relatable, credible, and accessible information sources [51,54-56]. Mentors can serve as role models to encourage positive health behavior change as they share their experiences [55]. In this study, mentors will receive additional training on study-specific information and motivational interviewing. Accordingly, during the sessions, peer mentors will use discussion guides that implement motivational interviewing [57] principles based on Self-determination Theory [53]. Motivational interviewing involves encouragement, exploration of feelings, and personalized goal setting. It has been effective across clinical contexts [58-63] including for behavior change [64,65].

NKF is recruiting, training, and supporting mentors for involvement in the study. The mentors will receive study-specific training in addition to standard peer mentor training offered by NKF. Peer mentor training will be divided into 10 self-paced training modules, with one live, internet-based training session for role plays and mentor skill assessment. Training will include information on: (1) the role of the peer mentor; (2) hemodynamic stability; (3) listening and communication skills, including motivational interviewing techniques; (4) sharing experiences and strategies; (5) confidentiality and boundaries; and (6) program logistics such as using multimedia tools, intervention fidelity, and record keeping. After mentors have completed all the training modules, they will be matched with ≥1 mentees who have consented to participate in the program as part of the intervention at their facility.

Figure 3. Theory-based model of behavior change for patient intervention. IDH: intradialytic hypotension.



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Table 1. Interactive education modules for patient intervention.

Topic	Content	Behavioral goals
Getting enough dialysis	• How dialysis makes patients feel better • Importance of removing fluid and preventing fluid overload	• Attending dialysis sessions for the full length of time • Understanding benefits of attending lengthened or supplemental dialysis sessions as needed • Identifying values that will help with goal setting
Feeling better with less salt or sodium	• Why people on dialysis need a low-sodium diet • How to read a food label • Examples of low and high sodium foods	• Maintaining a diet that is low in sodium • Tracking sodium intake
Making fluid restrictions work for you	• Why people on dialysis need to limit fluid intake • Ways to decrease thirst and track fluid intake	• Maintaining a level of fluid intake that will optimize interdialytic weight gain • Becoming aware of usual interdialytic weight gain • Tracking fluid intake • Discussing symptoms of fluid overload with the dialysis team • Discussing the need for longer or extra sessions if experiencing fluid overload symptoms
Feeling better on dialysis and having easier sessions	• Strategies to prevent low blood pressure and other symptoms of fluid removal • Steps to correct low blood pressure • Why it is helpful to check blood pressure at home	• Recognizing symptoms of IDH[a] • Reporting IDH symptoms and episodes to staff • Tracking blood pressure at home • Notifying staff of changes in true body weight
Getting more involved in your care	• Patient roles and responsibilities as a member of the health care team • Roles and responsibilities of other dialysis team members	• Actively participating in decisions with providers regarding fluid removal targets, ultrafiltration rates, and treatment times • Asking questions of the dialysis team relevant to session stability • Share concerns related to health and care, emotional well-being, and upcoming procedures with the dialysis team

[a]IDH: intradialytic hypotension.

Approaches to Encouraging Participation and Retention for Patient Intervention

Although participant retention is an issue in virtually any trial, patients on hemodialysis are likely to experience fatigue, pain, and other symptoms; thus, there is a greater than average risk of patients not completing the intervention. Therefore, we will offer incentives [61] for both mentors and mentees to encourage completion of all 5 peer mentoring sessions. Mentors will receive US $100 per patient with whom they work and US $15 for completion of the peer mentoring satisfaction survey. Mentees will receive a total of US $120 for completing the entire mentoring program and peer mentoring satisfaction survey. Although mentors will be paid upon completion of the mentoring sessions, mentees will be paid on a per-session basis at an escalating rate (US $10 for session 1, US $15 for session 2, US $20 for session 3, US $25 for session 4, and US $50 for session 5 and completion of the satisfaction survey).

In addition, we will use several general evidence-based retention strategies: issuing reminders before a scheduled mentoring session [66], monitoring satisfaction with the study [67] via the planned peer mentoring survey (Multimedia Appendix 3 provides the survey instruments), and keeping the response burden for patient data collection very low [68].

Data Collection

For aim 1 and 2 activities, most of the data used in this study are already routinely documented within the electronic health record of participating hemodialysis facilities. Additional information gathered during this study will be minimal because of the study's pragmatic nature.

Primary Outcome

Our primary outcome is hemodialysis session stability, specifically IDH, which is measured every session using blood pressure cuffs worn by patients. The primary indicator of IDH, based on direct blood pressure measurements after the start of the session, will be sitting systolic blood pressure (SBP) falling below 100 mm Hg (using the lowest SBP during the session) if starting SBP ≥100 mm Hg.

Secondary measures of IDH based on direct blood pressure measures will include the lowest (minimum) valid SBP below 100 mm Hg during the session if starting SBP is ≥100 mm Hg; the number of SBP measurements <100 mm Hg (using raw blood pressure measures, time of blood pressure measurement, and starting SBP) if the starting SBP is ≥100 mm Hg; and whether the sitting SBP falls below 90 mm Hg (using the lowest SBP during session) if starting SBP ≥100 mm Hg.

Justification of Selection of Primary Outcome

IDH is linked to symptoms such as cramping, dizziness, vomiting, fainting, and fatigue [4,12,13,69] and increased risk of other outcomes important to patients including cardiovascular disease [70], hospitalization [71], and mortality [72-74]. IDH is a top-10 priority outcome (of 33 ranked) for patients on hemodialysis [75]. Patients express concern about the receipt of insufficient hemodialysis or administration of fluids in cases of IDH [69].

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There is a lack of consensus on IDH definitions; however, for the purposes of this study, we use the threshold of SBP <100 mm Hg. As documented in the literature, a drop in SBP to <100 mm Hg is associated with a higher probability of patient-reported negative symptoms [76]. Even in asymptomatic events, intervention at this threshold has the potential to prevent repetitive multi-organ tissue ischemia [77] and further decline to dangerously low levels of SBP <90 mm Hg [71,72]. A lower threshold (eg, SBP <90 mm Hg or the occurrence of symptoms or clinical interventions) would not be appropriate for this study as we aim to prevent organ damage and negative patient experiences [5].

Secondary Outcomes

The patient-centered secondary outcomes are described in the following subsections.

Interdialytic Weight Gain

Facilities record this measure of fluid gain between hemodialysis sessions by measuring the difference between patients' pre- and posthemodialysis weights at each hemodialysis session. This outcome is important to patients as high fluid gains are linked to symptoms such as bloating and shortness of breath [78]. High fluid gains are associated with fluid overload, which is a leading cause of hospitalizations in patients on hemodialysis [79,80]. High fluid gains are also associated with mortality risk, particularly from cardiovascular causes [81,82]. Interdialytic weight gain is a top-20 priority outcome (of 33 ranked) for patients on hemodialysis [75].

Hemodialysis Adherence

Facilities routinely collect data on hemodialysis adherence [83]. We will use 3 measures: number of minutes of prescribed hemodialysis time missed per week, number of missed sessions per week, and total missed session time.

Patient Symptoms

Symptoms during the hemodialysis session are a priority outcome for patients [84]. Symptoms such as severe fatigue and cramping are reported in 50% and 30% of hemodialysis sessions, respectively [4]. We will create a patient symptom burden measure combining symptom frequency and severity for each of the following symptoms that are often indicative of IDH, if they occur during or after the hemodialysis session (not prehemodialysis): nausea, vomiting, abdominal pain, dizziness, muscle cramps, headache, chest pain, shortness of breath, palpitations, diaphoresis, and blurred vision. Patients may report symptoms to the dialysis team or nurses to assess symptoms at each hemodialysis session and document them at that time. We will also add the symptoms listed on the Kidney Disease Quality of Life survey to the patient symptom burden measure. We will also calculate the proportion of sessions with each symptom using date and time of session.

More than 40% of patients feel that they have not fully recovered even after returning home after hemodialysis [4]. As an indicator of both fatigue and energy and hemodialysis-free time, this is one of the most important outcomes to patients on hemodialysis (first and fourth of 33 ranked) and more important to patients than to health care providers [75,85]. Therefore, two additional questions will be answered in the electronic health record documentation during the midweek hemodialysis session for all patients in the study:

1. After your last dialysis session, how long did it take you to recover enough to do the things you normally do on a nondialysis day?
2. Did the patient make a request today regarding their fluid removal goal?

The first question was created in consultation with the dialysis provider's patient advisory committee and our study's patient partners and builds on past research [86]. Responses to this question will also be used as a secondary outcome for patient symptoms alone and in combination with the patient symptom burden measure described earlier.

Health-Related Quality of Life

This important patient-reported outcome [87] will be measured before and after the intervention. Health-related quality of life is a longer-term measure that reflects symptom patterns and other key life dimensions, including physical functioning, emotional well-being, pain, and energy levels [88]. The suffering represented by low health-related quality of life predicts outcomes that matter to patients, including hospitalization [89] and mortality [89,90].

We will use the 36-item Kidney Disease Quality of Life (KDQOL-36 version 1) [91,92], which has good internal consistency based on α scores [92]. This instrument is required annually for all patients on hemodialysis in the United States [93]. The KDQOL results will be provided twice for each patient from the following surveys: (1) the latest survey within 12 months before the start of the study intervention and (2) the earliest survey within 12 months after the start of the intervention.

Hospitalizations

We will gather these data from the facility's records for all patients within the study period. Hospitalizations represent a period of heightened symptoms and lost functioning among patients; patients describe hospitalizations as extremely distressing, and they are a top-21 priority outcome for patients on hemodialysis (of 33 ranked) [75].

Secondary analyses of these data will assess hospitalizations by cause using hospital discharge diagnosis (eg, fluid-related or cardiovascular causes, COVID-19), number of hospitalizations per patient, and length of hospitalization.

Mortality

This has been provided as a key example of a patient-centered outcome [87] and will be gathered from the facility's patient records.

Aims 1 and 2: Supplementary Data Collection

Practice Patterns Survey

In keeping with the precedent set by the International Dialysis Outcomes and Practice Patterns Study [94], in which several of our team members were involved, we will use practice patterns [94] surveys (Multimedia Appendix 4). These will be

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delivered at all study facilities during the facility preparation period before the intervention starts and again at the end of the 24-week intervention period. These surveys will also serve as manipulation checks [95] that will allow us to determine whether practice changes occurred at intervention sites while not occurring at the no intervention sites. Accordingly, the survey results will allow us to assess whether the interventions worked as intended. Surveys will be provided to both the nurse manager and the medical director.

Peer Mentoring Satisfaction Survey

After the 5 mentoring sessions, both mentees and mentors will receive a satisfaction survey (Multimedia Appendix 3). The results will be analyzed to identify mentees' experiences with the multimedia educational modules and peer mentoring and the mentors' experiences with the digital tools, training, and support. We will share the aggregate results with NKF so that they can make program adjustments if needed.

Aim 3: Data Collection for Assessment of Intervention Implementation

Aim 3 activities will seek to identify variation in implementation approaches adopted within different study facilities and to characterize differences in intervention acceptance and workflow integration. These analyses will help with understanding any potential differences in intervention effects between sites and with identifying and responding to any emergent implementation challenges throughout the trial. We will collect implementation data in all intervention facilities. Data collection activities will not require additional meetings; study staff at University of Michigan will gather data from provider intervention training parts 2 and 3 (10 facilities) and operations committee meetings (15 facilities). No audio or video recordings will be made of any of the meetings or sessions.

At the provider intervention training sessions, UM study staff will take descriptive field notes. The study staff will inform attendees that they will take notes, the purpose of the notes, and that comments made during meetings may be tied to a staff member's role; however, staff names will not be recorded. The field notes will document the following:

1. Staff questions during the sessions.
2. Staff members' stated reactions to the interventions.
3. Discussions in which the staff talk about their plans for, and experience with, integrating the provider intervention into their workflows.

To assess usability of the checklist and patient intervention technologies, we will analyze use data, with attention to compiling the following metrics: (1) time spent on each page, (2) number of abandoned checklist sessions and videoconferencing or patient education module sessions, and (3) pages and click-through patterns preceding abandonment. We will present and discuss these data in operations committee meetings. We will also record any staff comments and concerns about the checklist.

The operations committee meeting agendas will also include a small number of questions directly related to study intervention implementation (Multimedia Appendix 5). UM study staff will record answers in descriptive field notes. These questions will be for facility staff, and study staff will ask them after patient representatives have left the meeting.

Data Analysis

Statistical Power

We calculated the statistical power for the study for the primary outcome of hemodialysis session stability. We assumed that a minimum of 60 patients on hemodialysis will be observed for at least 60 hemodialysis sessions and the primary outcome will be the proportion of unstable sessions, which we treat as a continuous variable. We assume that these proportions among patients in a facility are normally distributed with mean 0.20 in the control group and mean between 0.16 and 0.17 in the intervention group (a difference *d* of 0.034-0.043), with SD (or *sigma*) assumed to be in the range of 0.08-0.10. We conservatively assume 60 patients per facility (ie, a total of 60 × 20 facilities=1200 patients). The power calculation is robust to changes in number of patients (m), as the calculation of K (number of clusters) only increases by ~1 if m is increased to 90 [96]. We assume the intraclass correlation coefficient for hemodialysis facilities to be 0.10. We also assumed a significance level of 0.05 in all calculations. If the SD is as large as 0.10, we can detect a difference of 0.043 (ie, 20% vs 16%) with 81% power. In other words, if the smallest variance estimate is correct (sigma=0.08), we have 91% power to detect a 4% difference and 80% power to detect a 3% difference (Table 2).

Table 2. Power to detect difference in intradialytic hypotension (IDH) rates. The power is shown to detect a difference in IDH rates (D) between groups with at least (k) number of facilities, assuming 2 possible SDs (sigma).

Detectable IDH rate difference, D	SD, sigma	Number of facilities, k	Power, %
0.034	0.08	10	80
0.034	0.10	10	61
0.040	0.08	10	91
0.043	0.10	10	81

Overall Analytical Approach

Our 2 × 2 factorial trial is designed to answer the following four treatment comparison questions (Table 3):

1. Provider education versus no provider education (assumes no interaction between the interventions)

Cells ([A+B] vs [C+D])–*F* test comparison

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2. Peer mentoring versus no peer mentoring (assumes no interaction between interventions)

Cells ([A+C] vs [B+D])–*F* test comparison

Note that all data will be reused in the comparisons for 1 and 2. This shows a key advantage of the 2 × 2 design: it allows testing 2 interventions for the "price of one." Furthermore, if an interaction is observed (question 4 below), then the effect of one intervention can be estimated at each level of the other intervention.

3. Comparative effectiveness of provider education alone versus peer mentoring alone

B versus C–*F* test comparison. The head-to-head comparison of the magnitude of effect for the 2 interventions is actually comparing only the interventions alone, in the absence of the other ones.

4. Are there synergistic or antagonistic effects between the provider education and peer mentoring interventions?

The purpose of this test is to determine whether the effect of one intervention differs depending on the presence of the other intervention. The test compares:

- Cells ([A−C]−(B−D)]–*F* test comparison to examine the effects of provider education intervention with and without the presence of the patient activation intervention.
- This is equivalent to ([A−B]−[C−D]), which examines the patient activation intervention with or without provider education.

Table 3. A 2 × 2 factorial trial design with facility and patient sample sizes for treatment comparisons.

	Patient activation intervention, number of facilities (number of patients)		Total, number of facilities (number of patients)
	Yes	No	
Provider education			
Yes	A—5 (300)	B—5 (300)	10 (600)
No	C—5 (300)	D—5 (300)	10 (600)
Total	10 (600)	10 (600)	20 (1200)

This interaction test will provide power to detect strong synergistic or antagonistic effects. It is a statistically efficient approach valuable for studying health care interventions, where rigorous evaluation is typically expensive [97].

Aim 1 Analyses

For aim 1, the outcome is a dichotomous measure of hemodialysis session stability. This outcome will be collected through digitally recorded blood pressures in all hemodialysis sessions of all patients at each facility who have not opted out of the study during the study period. For the continuous outcome measure of the proportion of unstable sessions, we will use linear mixed models to compare individuals in facilities in the 2 treatment arms to individuals in the nonintervention facilities. Random effects for facility clustering will be accounted for using the MIXED procedure in SAS (SAS Institute). As a sensitivity analysis, we will also examine hemodialysis session stability as a dichotomous (yes or no) variable and analysis will be carried out on the longitudinal data set using logistic regression with a random effect for both patients and facilities, using the GLIMMIX procedure in SAS. The random effects will model the correlations among the measurements at each level.

Three secondary analyses are planned for this aim. The first will test the treatment effects in a similar model but adding adjustment for any covariates found to be unbalanced between treatment groups in preliminary analyses. The next secondary analysis will test the interaction between the 2 interventions to detect a possible synergistic or antagonistic effect. The third will be a secondary analysis of patient proportion with IDH before versus after the intervention phase to test whether the intervention effects are maintained. The basic analysis is a paired comparison of percentage of IDH before versus after the intervention phase begins, with adjustments for length of intervention phase (24 wks) and follow-up phase (12 wks).

In additional sensitivity analyses, we will examine the effect of patient compliance and noncompliance rates (ie, the percentage of patients who accept peer mentoring and checklist adherence for provider intervention) on the results. The sensitivity analyses aimed to assess the robustness of the conclusions based on the analyses of the primary outcome, specifically to determine whether the findings hold under different methods of defining the primary outcome. Thus, we will conduct sensitivity analyses for the secondary measures of session instability described in *Data Collection* section. As part of this, because we will know the dates and causes of hospitalizations and death by cardiovascular- or fluid-related causes, we will identify those events that took place on days in which dialysis was administered. Accordingly, we will conduct a sensitivity analysis of the primary outcome of dialysis session stability both with, and without, those events on dialysis days included. For the primary outcome analyses, we will also conduct a sensitivity analysis without the sessions of patients who begin that session with a sitting predialysis SBP of 100 to 110 mm Hg and whether the sitting SBP falls below 90 mm Hg (using the lowest SBP during session) if starting SBP ≥100 mm Hg.

Aim 2 Analyses

Aim 2 incorporates 6 secondary outcome measures, which we will analyze at the individual level and summarize at the facility level. The interdialytic weight gain, symptom and quality of life analyses, based on continuous outcome measures, will be carried out using mixed models (the MIXED procedure of SAS). Note that the quality of life analyses will be based on data from 2 time points, one before intervention and one during the intervention, rather than session-specific data as analyzed for

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the other outcomes. Analyses of missed or shortened hemodialysis sessions will use logistic regression for longitudinal data. Analyses of hospitalizations and mortality will use logistic regression for the individual-level data. As part of these models, we will test IDH-related variables (eg, recent IDH and frequency of IDH in the past month) as potential predictors. In addition, we will conduct as-treated analyses for the peer mentoring intervention whereby only patients who received peer mentoring are compared with patients in the other treatment arms, with adjustment for the same factors as in the intent-to-treat analyses.

Aim 3 Analyses

Field notes compiled from provider training sessions 2 and 3, as well as the operations committee meetings, will be used to identify and understand barriers to implementing the interventions. Using NVivo (QSR International) qualitative data analysis software, we will also analyze data thematically [98] to identify and explain the types of implementation barriers and facilitators. We will use these qualitative analyses as supplementary explanations as we seek to explain the results of the trial, especially if there are differences in effectiveness between facilities implementing the same interventions. If necessary, modifications will be made while the trial is ongoing.

Heterogeneity of Treatment Effects and Mediation Analyses

The primary analysis will examine average treatment effects, but we will also examine the heterogeneity of treatment effects (HTE) on IDH rate for a variety of covariates, particularly those that are characterized by differential outcomes among patients on hemodialysis. Covariates of interest include demographics such as age, race [99], level of education [99], literacy, presence of comorbidities, and heart rate variability. Supporting these HTE analyses, greater benefits from peer mentoring for African Americans were found in a trial conducted by our advisory partner, the Michigan branch of the NKF [34]. Depending on the sample size obtained for each of the covariates of interest, either a subgroup analysis or an analysis including interaction terms will be used to examine HTE. Only two-way interactions between the treatment indicator and each of the covariates will be analyzed.

The second part of these analyses aims to identify mechanisms of action for the interventions, such as changes in patient or practitioner behavior and session characteristics; these changes in behavior will identify important pathways for improvement in reducing IDH. However, these analyses are not intended to be used for causal inferences. Each potential mediator (Textbox 2) will be tested separately, without adjusting for other mediators, although associations between mediators can be assessed separately for improved interpretation.

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Textbox 2. Potential mediators of dialysis session stability.

Patient-level variables

- Patient session instability prevention behavior
- Fluid management practice patterns
- Number and categories of medications patient is taking
- Fluid adherence (interdialytic weight gain)
- Dialysis adherence
- Patient symptoms (burden and recovery time)
- Hospitalizations for cardiovascular or fluid-related causes
- Quality of life

Session level variables

- Treatment time delivered
- Average session ultrafiltration rate
- Use of cool dialysate
- Use of sodium modeling
- Use of ultrafiltration modeling
- Ultrafiltration variability for the whole session, or until intradialytic hypotension incident
- Sitting-to-standing change in systolic blood pressure (SBP)
- Starting SBP
- Slope of changes in SBP over the whole session, or until intradialytic hypotension incident
- Values and times of lowest and highest SBP readings during session
- Patient request regarding fluid removal
- Fluid adherence (interdialytic weight gain)
- Previous achievement of postdialysis target weight
- Previous session instability

Results

This study began enrolling participants in early 2020 but was paused during the COVID-19 pandemic. The study began in May 2022, and the first facilities began enrolling patients in January 2023. Intervention start dates will be staggered such that 4 facilities (1 from each intervention arm) start at once, while the next 4 facilities will begin preparation to join the study. The first 8 facilities will complete the intervention and follow-up data collection period in November 2023. The remaining 12 facilities will begin on a staggered timeline with follow-up data collection ending in November 2024.

Discussion

Principal Findings

The enhancement of the hemodynamic stability of hemodialysis is a critical concern for clinicians owing to study findings about the problem of hemodialysis-induced cardiovascular harm [20,100] and owing to vociferous calls for reform in fluid management practices in hemodialysis care [101-104]. A consensus statement from Medical Directors of United States hemodialysis facilities reflects this concern [22].

However, with a lack of clear guidance regarding hemodynamic stability enhancement, approaches to hemodynamic stability in hemodialysis care are variable. The current practice includes educating patients regarding appropriate fluid intake, individualized treatment targets and fluid removal goals, regular monitoring and assessment during dialysis treatments, regular medication reviews, intervening as IDH emerges, and management of emergent symptoms. However, there are also wide facility-level variations in IDH rates, demonstrating the ability of practice patterns to influence cardiovascular session stability. For instance, IDH prevalence varied between 11.1% and 25.8% in a study of 13 US facilities [11]. In that study, it was demonstrated that facility was also a significant predictor of IDH with odds ratios between 0.608 and 1.468 after adjustment for patient characteristics.

Although the high prevalence of dialysis instability demands change, hemodialysis providers lack critical guidance for preventing IDH in usual practice. Our evidence-based approach contends that to prevent unstable hemodialysis sessions, optimal fluid management must be at the forefront of typical care practices. In line with a growing body of evidence, we support gentle adjustment of posthemodialysis target weights and prolongation of treatment time prescriptions, regular assessment

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of patient fluid volume status, lower UFR (preferably <10-12 mL/kg/hr), and early intervention if a patient begins to show signs of instability. We do so while continuing to emphasize lower interdialytic weight gain and a low-sodium diet to reduce thirst, and thus fluid intake [83,105-109]. We also promote use of interventions such as use of cool dialysate, blood pressure medication review, and evaluation of patients for home dialysis, as appropriate (Figure 1). To facilitate this fluid management–focused practice, our intervention translates successful patient safety interventions and patient behavior interventions from inpatient and chronic disease care settings, respectively, to the outpatient hemodialysis context.

Novelty of This Study

Although checklists for patient safety have been growing in popularity in health care organizations in the United States and internationally, they have primarily been used in inpatient settings, particularly surgery [110-112] and critical care [113,114]. However, a recent trial on a checklist for hemodialysis care infection control [115,116] and another recent pilot in Canada [117] illustrated that hemodialysis care is an outpatient context that is well suited for checklist implementation. When combined with staff training, our novel application of checklists to hemodialysis care makes it an innovative and promising approach to care improvement.

Patient involvement in safety is encouraged by national and international stakeholder organizations [118-121]. Patient involvement is particularly promising in the context of efforts to improve hemodialysis session stability because patients already make daily decisions such as how much sodium and fluid to consume and whether to shorten or skip hemodialysis sessions—often without realizing the corresponding cardiovascular and hemodynamic stability implications. However, few studies to date have examined the potential for patient involvement in the prevention of hemodialysis session instability as a complication of hemodialysis care [119,122].

Outside hemodialysis care, practices designed to encourage patient involvement in the prevention of health care complications have seen mixed success in producing behavior change [123]. This is likely because of lack of education and support in prior initiatives [124-126]. Furthermore, prior efforts have been rarely grounded in validated theories of behavior change [123], relying instead on simple information provision, such as personalized care records [127] and verbal or written instruction [128-130]. Rarely have interventions explicitly used health behavior change theory, a component of our evidence-based intervention that increases its likelihood of success. Furthermore, although multimodal engagement strategies have been advocated [131], no intervention trial has examined the potential for patients to assist each other in preventing health care complications.

Supporting a peer-based approach to promoting hemodialysis session stability, there has been growing interest in peer-based health care approaches as trials have shown benefits in health outcomes [125-128] and behavior [129-131]—including complex health behaviors relevant to IDH, such as diet change [128,132]. Therefore, through an innovative application of peer mentoring, we aim to support the cardiovascular and hemodynamic stability of hemodialysis by helping patients become more actively engaged in treatment and self-care decisions that affect their cardiovascular well-being. We will address patients' frequent lack of information to help them meaningfully participate in hemodynamic stability–related decisions such as fluid removal targets, session length, and frequency. Our preliminary studies showed that some patients already try to influence their treatment targets and speed to reduce distressing symptoms and that patients with ESKD share strategies for making hemodialysis more tolerable [132]. Trained peer mentors are in an excellent position to provide this information systematically and in a manner that is accessible, actionable, and influential. Thus, our innovative approach meets important patient needs while enhancing the likelihood of success in mobilizing patients to engage in behaviors that will increase hemodialysis session stability.

Study Limitations

The study is being conducted in the United States in collaboration with one large hemodialysis facility chain. Although this may limit generalizability, we note that hemodialysis care in the United States is predominately provided by 2 large facility chains, one of which is a study partner. This study partner has >2000 facilities, which suggests the potential for substantial reach if the intervention proves successful. Study facilities were stratified by region and county poverty level, ensuring representation of facilities from 4 US regions and varied patient populations in the study. Furthermore, this study, as with other pragmatic trials, is dependent on care providers' data entry as part of routine care. In an effort to support completeness of study data, some training of staff in data collection will be undertaken as part of the facility staff onboarding process. This study will leverage a robust data infrastructure used for ongoing clinical trials.

Conclusions

The effects of provider and patient education on patient-centered clinical outcomes will be analyzed, and the findings will be used to inform further improvements in patient care. Improving the hemodynamic stability of hemodialysis sessions is a critical concern for clinicians and patients, and educating providers and patients is predicted to lead to improvements in patient health outcomes and quality of life.

Acknowledgments

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Data Availability

The data sets generated during or analyzed during this study are not publicly available because of concerns about patient identifiability and confidentiality. The patient information sheet provided to patients at the outset of the study clarifies that their information will not be shared in a raw form with anyone except the University of Michigan research team.

Conflicts of Interest

DC and RW are employees of Fresenius Medical Care. MA and KCD are employees of the National Kidney Foundation.

Multimedia Appendix 1
Patient intervention interactive modules—general website design.
[PNG File , 180 KB - resprot_v12i1e46187_app1.png]

Multimedia Appendix 2
Patient intervention interactive modules—educational module design.
[PNG File , 166 KB - resprot_v12i1e46187_app2.png]

Multimedia Appendix 3
Peer mentoring satisfaction surveys.
[DOCX File , 19 KB - resprot_v12i1e46187_app3.docx]

Multimedia Appendix 4
Practice patterns surveys.
[DOCX File , 27 KB - resprot_v12i1e46187_app4.docx]

Multimedia Appendix 5
Operations committee discussion questions.
[DOCX File , 15 KB - resprot_v12i1e46187_app5.docx]

Multimedia Appendix 6
Peer review report from PCORI Funding Announcement: Large Pragmatic Studies to Evaluate Patient-Centered Outcomes - Improving Healthcare Systems (Patient-Centered Outcomes Research Institute, USA).
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Abbreviations

ESKD: end-stage kidney disease
HIPAA: Health Insurance Portability and Accountability Act
HTE: heterogeneity of treatment effects
IDH: intradialytic hypotension
IRB: institutional review board
NKF: National Kidney Foundation
SBP: systolic blood pressure
UFR: ultrafiltration rate

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Protocol

Digital Guardian Angel Supported by an Artificial Intelligence System to Improve Quality of Life, Well-being, and Health Outcomes of Patients With Cancer (ONCORELIEF): Protocol for a Single Arm Prospective Multicenter Pilot Study

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Abstract

Background: According to Europe’s Beating Cancer Plan, the number of cancer survivors is growing every year and is now estimated at over 12 million in Europe. A main objective of the European Commission is to ensure that cancer survivors can enjoy a high quality of life, underlining the role of digital technology and eHealth apps and tools to achieve this.

Objective: The main objective of this study is the development of a user-centered artificial intelligence system to facilitate the input and integration of patient-related biopsychosocial data to improve posttreatment quality of life, well-being, and health outcomes and examine the feasibility of this digitally assisted workflow in a real-life setting in patients with colorectal cancer and acute myeloid leukemia.

Methods: A total of 60 patients with colorectal cancer and 30 patients with acute myeloid leukemia will be recruited from 2 clinical centers: Universitätsmedizin der Johannes Gutenberg-Universität Mainz (Mainz, Germany) and IRCCS Istituto Romagnolo per lo Studio dei Tumori “Dino Amadori” (IRST, Italy). Psychosocial data (eg, emotional distress, fatigue, quality of life, subjective well-being, sleep problems, and appetite loss) will be collected by questionnaires via a smartphone app, and physiological data (eg, heart rate, skin temperature, and movement through step count) will be collected by a customizable smart wrist-worn sensor

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device. Each patient will be assessed every 2 weeks over their 3-month participation in the ONCORELIEF study. Inclusion criteria include patients with the diagnosis of acute myeloid leukemia or colorectal cancer, adult patients aged 18 years and older, life expectancy greater than 12 months, Eastern Cooperative Oncology Group performance status ≤2, and patients who have a smartphone and agree to use it for the purpose of the study. Exclusion criteria include patients with a reduced cognitive function (such as dementia) or technological illiteracy and other known active malignant neoplastic diseases (patients with a medical history of treated neoplastic disease are included).

Results: The pilot study started on September 1, 2022. As of January 2023, we enrolled 33 patients with colorectal cancer and 7 patients with acute myeloid leukemia. As of January 2023, we have not yet started the data analysis. We expect to get all data in June 2023 and expect the results to be published in the second semester of 2023.

Conclusions: Web-based and mobile apps use methods from mathematical decision support and artificial intelligence through a closed-loop workflow that connects health professionals and patients. The ONCORELIEF system has the potential of continuously identifying, collecting, and processing data from diverse patient dimensions to offer health care recommendations, support patients with cancer to address their unmet needs, and optimize survivorship care.

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KEYWORDS

eHealth; artificial intelligence; quality of life and well-being; supportive cancer care; mobile phone; cancer support; artificial intelligence–based recommendations

Introduction

Background

Cancer is the second leading cause of death worldwide, and 10 million deaths in 2020 were attributed to cancer [1]. In 2020, a total of 2.7 million people in the European Union were diagnosed with cancer, and another 1.3 million people lost their lives to it, including over 2000 young people [2].

According to the Europe's Beating Cancer Plan, the number of cancer survivors is growing every year and is now estimated at over 12 million in Europe [3]. The Europe's Beating Cancer Plan aims to ensure that patients with cancer, survivors of cancer, their families, and caregivers can enjoy a high quality of life (QoL), highlighting the role of digital technology and eHealth app and tools to achieve this objective. In the last decade, there has been an increasing use of eHealth (ie, the broad use of health information and communication technologies and networks to enhance patient-centered care delivery) in the delivery of patient-centered cancer care [4,5]. Among the tools that have been used are smartphone apps, wearable devices, SMS text messaging, and internet-delivered interventions [5]. However, there has been little use of artificial intelligence (AI) in psycho-oncology research.

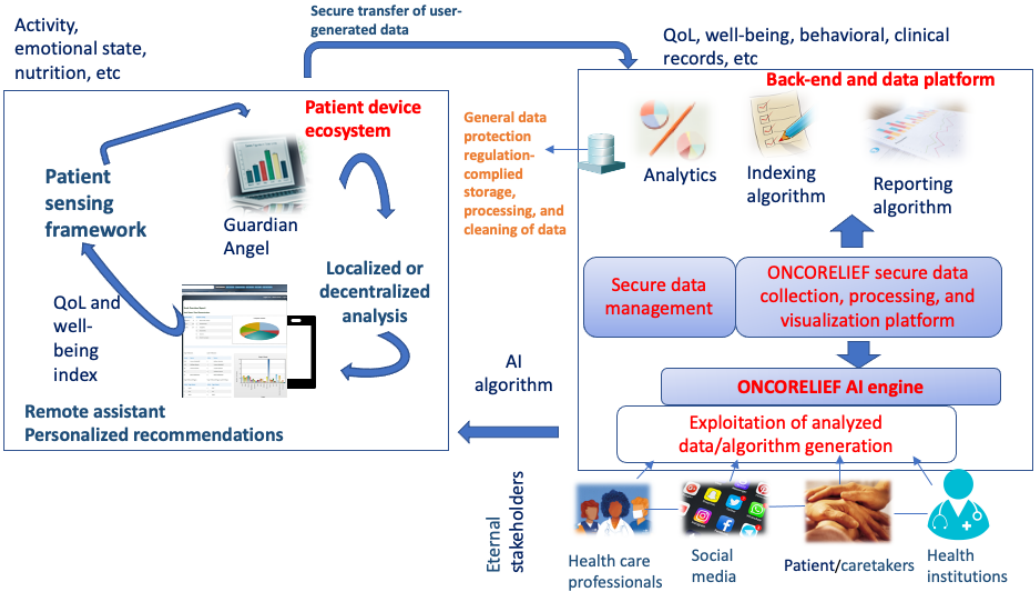
ONCORELIEF is a European project funded by EU Horizon 2020 (grant 875392) whose main objective is the development of a user-centered AI system to facilitate the input and integration of patient-related biopsychosocial data to improve posttreatment QoL, well-being, and health outcomes. Measurable parameters include patient-reported outcomes about their unmet needs (eg, emotional distress, fatigue, sexual problems, and sleep quality), physiological data monitored by a wearable device (eg, heart rate and skin temperature), and demographic and health status data from medical records. This objective is achieved by establishing a workflow that connects health professionals and patients by means of assisting digital solutions.

Concept and Study Architecture

The way that the connection between health professionals and patients is done is presented in Figure 1, which illustrates the concept and architecture of ONCORELIEF with its 5 technological components: the Guardian Angel app, the back-end and data platform, the Big Data and AI engine, the QoL and well-being index, and the sensing framework.

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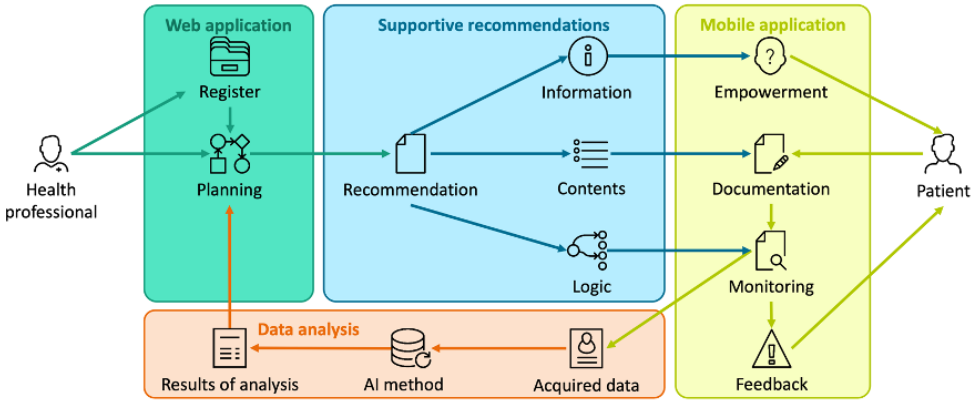
Figure 1. ONCORELIEF concept and architecture. The 5 main technological components of ONCORELIEF are the Guardian Angel—this is an app, compatible with portable devices operating with iPhone operating system and Android built upon the AI models generated by the ONCORELIEF platform; the back-end and data platform—this is where all the data are collected, processed, and used to deliver the services of the ONCORELIEF platform; the Big Data and AI engine—this resides on top of the back-end platform and exploits the insight derived from the analyses of the data as well as it is responsible for the interaction with the users of the Guardian Angel; the QoL and well-being index—this is used to monitor the QoL and well-being status and progress of the different users; and the sensing framework—this is the unobtrusive and pervasive, wearable, and embedded sensing ecosystem of the patient for data collection. AI: artificial intelligence; QoL: quality of life.



Novelty of the Study

A main innovation of ONCORELIEF is that all data will run on a digitally assisted workflow of posttreatment supportive patient care supported by an AI system (see Figure 2) [6]. This workflow comprises the planning of supportive recommendations with a web-based app by the health professional, the documentation and monitoring of recommendations with a mobile app by the patient, and analyzing the AI-based data of the achieved progress as preparation for the next planning step.

Figure 2. General AI solution approach with the core components and main information flows. The thick arrows indicate the main process steps of the approach. (Icons: Line icons [iconsmind.com] and Windows 8 icons [icons8.com]). AI: artificial intelligence.



The specific realization of this approach depends on the circumstances of the application scenario, such as the preferred level of detail of the recommendations, the information contents of the acquired data, and the amount of reference data available for the training of AI methods. The realization would feature a provision of suitable supportive recommendations by the register, adequate concepts for their documentation and monitoring, and an appropriate selection of AI methods for data analysis. In this sense, the ONCORELIEF pilot study features text-based informative recommendations, the documentation of recommendation outcomes with standardized health questionnaires and vital parameter data measured with wearable sensor devices, and a data analysis with methods from statistics and statistical learning such as automated classification and artificial neural networks, respectively.

The ONCORELIEF pilot study is designed with the aim to examine the feasibility of this digitally assisted workflow in a real-life setting on 2 quite different types of cancer: colorectal cancer and acute myeloid leukemia. These represent cancers with different biological characteristics, different treatment pathways, and specific patient needs [7-10]. In this paper, we describe the study protocol of a multicenter pilot study. There

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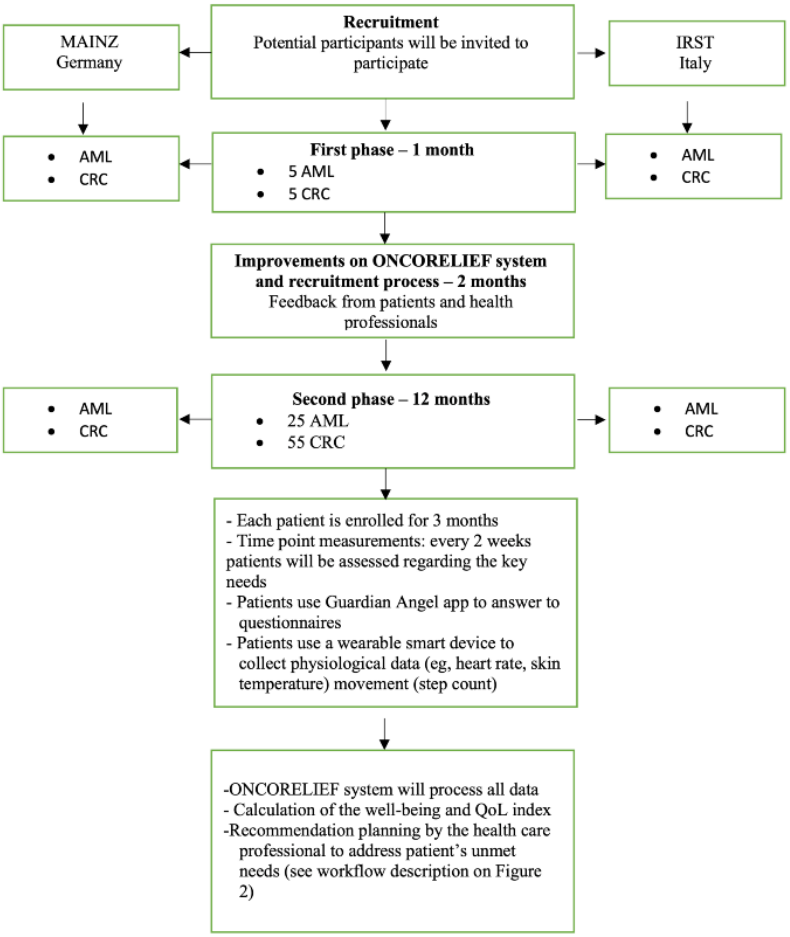
are four key questions to be examined: (1) It is feasible to assess the unmet needs of patients with cancer, after-treatment, through questionnaires included in a smartphone app (ie, Guardian Angel)? (2) It is feasible to collect physiological (eg, heart rate) and behavioral (eg, movement through step count) data from a wearable smart device connected with the app? (3) It is feasible to generate, with the support of AI, a composite and ongoing QoL and well-being Index that indicates continuously the balance of met and unmet needs of patients with cancer? (4) It is feasible to deliver timely recommendations for patients based on patients' data inputted from the Guardian Angel app and a wearable device?

Methods

Study Design

This 2-group pilot study is aimed to evaluate the feasibility of the ONCORELIEF system in real-life clinical settings for patients with colorectal cancer and acute myeloid leukemia. It will run in two phases: (1) a prepilot phase is a 1-month training of the entire system. A total of 10 patients (5 with acute myeloid leukemia and 5 with colorectal cancer) will be enrolled and provided with the ONCORELIEF digital tools (ie, the Guardian Angel app and the wearable device). Based on the feedback of patients and health professionals, improvements will be made to the entire system over a period of 2 months. (2) The second phase will last 12 months (see Figure 3).

Figure 3. The flow of patients throughout the study. AML: acute myeloid leukemia; CRC: colorectal cancer; IRST: Istituto Romagnolo per lo Studio dei Tumori; QoL: quality of life.



Clinical Centers

The study will be conducted in 2 clinical centers: Universitätsmedizin der Johannes Gutenberg-Universität Mainz (Mainz, Germany) and IRCCS Istituto Romagnolo per lo Studio dei Tumori "Dino Amadori" (IRST, Italy).

Study Participants

Inclusion criteria include (1) patients with the diagnosis of acute myeloid leukemia or colorectal cancer, (2) adult patients aged 18 years and older, (3) life expectancy greater than 12 months, (4) Eastern Cooperative Oncology Group performance status [11] ≤2, and (5) patients who have a smartphone and agree to use it for the purpose of the study.

Exclusion criteria include (1) patients with a reduced cognitive function (such as dementia) or technological illiteracy and (2) other known active malignant neoplastic diseases (patients with a medical history of treated neoplastic disease are included).

Recruitment and Enrollment

Figure 3 describes the flow of patients throughout the study. All patients will be treated and monitored for their disease according to the local clinical practice, and no changes in

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treatment or follow-up will be decided based on participation in this study. At IRST Italy, patients in follow-up at clinical sites for acute myeloid leukemia or colorectal cancer disease and those considered eligible by the study oncologists will be invited to participate in this research. The oncologist will inform patients of the aims and procedures of the study. At Mainz, patients are prescreened by the treating health care professional (HCP) for eligibility and are introduced to the study by the HCP during their regular clinic visits. If the patient is interested, the HCP will give the patient's name and the time of the next clinic visit to the study coordinator or study nurse. At the patient's next visit, the study coordinator will meet the patient and enroll the patient by following the enrollment procedures.

All patients will be informed that the participation is voluntary and that they are allowed to interrupt their participation whenever they want and for any reason. This will not prejudice the patient's subsequent care. Patients will also be informed about relevant data protection and privacy legislation. A written, signed, informed consent form from the patient must be obtained before study entry. After signing informed consent, patients will be registered into ONCORELIEF electronic data capture system. Only deidentified data will be collected, including the data collected by the app or wearable device. Each patient will be assigned a unique alphanumerical ID, and only clinical site staff will have access to patients' personal data and reidentification key. The anticipated total number of recruited patients will be 30 acute myeloid leukemia and 60 colorectal cancer for the 2 study phases. Therefore, for the pilot phase, an additional 25 patients with acute myeloid leukemia and 55 patients with colorectal cancer will be enrolled in total across clinical sites. Mainz will attempt to recruit about two-third of the patients, that is, up to 20 patients with acute myeloid leukemia and up to 40 patients with colorectal cancer. IRST is expected to recruit 20 patients with colorectal cancer (1 site in Italy, IRST IRCCS) and 10 patients with acute myeloid leukemia. However, due to the COVID-19 health crisis, fewer patients are coming to the clinic and the number might have to be adjusted. Patients are enrolled for 3 months.

Demographic, Medical, and Treatment Data

The clinical variables regarding medical and treatment data will be obtained from the patient's medical records. The following data will be recorded for each patient at study entry through an electronic data capture system: (1) demographics include age, gender, weight, educational background, occupation, and family status; (2) medical and medication history include relevant medical and medication history and acute myeloid leukemia or colorectal cancer history including date of diagnosis, type, treatments, and disease status at study entry; (3) baseline conditions (comorbidities and symptoms) assessment; (4) history of oncological treatments and any residual toxicity relating to prior or current treatment; (5) performance status (Eastern Cooperative Oncology Group); and (6) physical examination.

Instruments and Measures

Wearable Device and the Sensing Framework

The sensing infrastructure is an essential part of the ONCORELIEF ecosystem due to its role in providing and managing the data flow for all patients. The sensing framework describes the parameters that can be obtained from the wearable multisensor device as well as the ways to connect to them and encompasses four fundamental elements: (1) the whole set of smart sensors in the wearable device that includes sensors relevant both to the physiological parameters as well as to behavioral data (step count), (2) the patient's smartphone ONCORELIEF mobile app (the patient-centered Guardian Angel app) (3) interim sensor data storage and further processing (AI algorithms for stress level based on heart rate variability parameters), and (4) ability of real-time (or almost real-time) data transmission from the wearable device via the Guardian Angel mobile app to the ONCORELIEF cloud.

The customizable smart wrist-worn sensor device developed by a partner of this project, MCS Datalabs, is equipped with diverse sensors. It is able to monitor vital data (optical heart rate = pulse rate and oxygen saturation by photoplethysmography and skin temperature) and motion data from a 3D accelerometer (step count as an output of the sensor). The wrist-worn device is configured and customized to meet the defined data and security requirements.

Psychosocial Instruments

Before the selection of the instruments for measuring patient needs, we selected the key needs that should be assessed for each type of cancer. The aim of this selection was to reduce the number of needs as much as possible to diminish the patients' burden and make it possible to assess these needs through the Guardian Angel app and from the wearable. We started by identifying all needs documented in the scientific literature for acute myeloid leukemia and colorectal cancer, which resulted in a first list of needs. Next, the ONCORELIEF clinical partners (IRST and Mainz) filtered the needs based on the following criteria: (1) is it a common need (ie, affecting >10% of patients with the corresponding condition)? (2) can patients or caregivers self-report this need? (3) does the need have "intensity levels" or "grades" (1-5, or 1-10, or so on) or is it just "binary" (yes or no)? (4) is there more than one potential intervention available for this need? (5) could potential interventions bring noticeable improvement within the period of the pilot? (6) could this need be related to urgent care with action that needs to be taken in a very short timeframe? (7) is there a high risk from using AI (or training AI) for this need? (8) is this need a "must-have" patient need? From the app of these criteria resulted a final list of key needs presented in the first column of Table 1. Some needs are common to both cancers (anxiety, depression, fatigue, and subjective well-being) and others are specific, as shown in Table 1. Each patient will be assessed every 2 weeks over the 3-month participation in the ONCORELIEF study.

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Table 1. Patient key needs and questionnaires.

Patient needs	Questionnaire	Description
Anxiety	Hospital Anxiety and Depression Scale (HADS) [12-14]	HADS is a 14-item measure designed to assess anxiety and depression. This study focuses only on the 7 items of anxiety (HADS-A). Each item is endorsed on a Likert-type scale (0-3), and the score obtained ranges from 0 to 21.
Depression	Patient Health Questionnaire-9 (PHQ-9) [12-14]	The PHQ-9 is the 9-item depression module from the full PHQ. The PHQ-9 score can range from 0 to 27, since each of the 9 items can be scored from 0 (not at all) to 3 (nearly every day).
Fatigue	Brief Fatigue Inventory (BFI) [15-17]	BFI is a 9-item measure to assess the subjective report of cancer-related fatigue severity and the impact of fatigue on daily functioning. BFI uses an 11-point scale (0="no fatigue" to 10="fatigue as bad as you can imagine") to measure each specific symptom.
Appetite loss	EORTC-QLQ C30[a] [18]	Assessed by the appetite loss item from EORTC-QLQ C30. In the past week, have you lacked appetite? (from 1=not at all to 4=very much).
Subjective well-being	World Health Organization Well-Being Index (WHO-5) [19]	WHO-5 is a generic global rating scale measuring subjective well-being. Each of the 5 items is scored from 5 (all of the time) to 0 (none of the time). The raw score ranges from 0 (absence of well-being) to 25 (maximal well-being).
Lack of sexual interest (only acute myeloid leukemia)	EORTC-SHQ-C22[b] [20]	The EORTC SHQ-C22 is a 22-item scale designed to assess the physical, psychological, and social aspects of sexual health in patients with cancer and survivors of cancer. Each item is scored a 4-point Likert scale (not at all to very much).
Sleep problems (only acute myeloid leukemia)	Insomnia Severity Index (ISI) [21-23]	The ISI is composed of 7 items that evaluate sleep problems (the last item evaluates the level of distress caused by the sleep problem). Each of these items is rated on a 5-point Likert scale (not at all to extremely), and the time interval is "in the last 2 weeks." Total scores range from 0 to 28, with high scores indicating greater insomnia severity.
Sore mouth (only acute myeloid leukemia)	EORTC-OH15[c] [24]	The EORTC-OH15 assesses oral health quality of life in patients with any type of cancer. It has 15 items, containing one 8-item OH-QoL[d] scale, 3 single items (sticky saliva or mouth soreness or sensitivity to food or drink), and two 2-item contingency scales regarding use (yes or no) and problems with dentures and reception of (yes or no) and satisfaction with information.
Colitis (only colorectal cancer)	EORTC-QLQ-CR29[e] [25]	The European Organization for Research and Treatment of Cancer developed the colorectal QoL module as an adjunct to the generic EORTC QLQ-C30. This module consists of 4 scales and 19 individual items.
Hand-foot syndrome (only colorectal cancer)	EORTC-QLQ CIPN20[f] [26]	The EORTC QLQ-CIPN20 is the common method for determining chemotherapy-induced peripheral neuropathy symptoms.
Neuropathy (only colorectal cancer)	EORTC-QLQ CIPN20	Same as previous scale.

[a]EORTC-QLQ C30: European Organization for Research and Treatment of Cancer Core Quality of Life questionnaire.

[b]EORTC-SHQ-C22: European Organization for the Research and Treatment of Cancer Sexual Health Questionnaire.

[c]EORTC-OH15: European Organization for the Research and Treatment of Cancer—Oral Health Questionnaire.

[d]QoL: quality of life.

[e]EORTC-QLQ-CR29: European Organization for Research and Treatment of Cancer—colorectal quality of life module.

[f]EORTC-QLQ CIPN20: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire—Chemotherapy-Induced Peripheral Neuropathy 20-item scale.

The selection of the instruments for measuring the psychosocial needs described in Table 1 was based on three criteria: (1) sound reliability and construct validity, (2) reduced number of items, and (3) have already been translated and validated into Italian and German.

Measurement of the QoL and Well-being Index

The QoL and well-being composite index has a hierarchical structure of three levels: (1) global, (2) domains, and (3) needs. The first level represents the total QoL and well-being score. The second level includes 3 different need domains (emotional distress, psychophysiological, and physical). For example, the "emotional distress" domain includes the needs "depression" and "anxiety." See Table 2 that presents the grouping of needs into domains and the instruments to assess the needs for each type of cancer, acute myeloid leukemia and colorectal cancer.

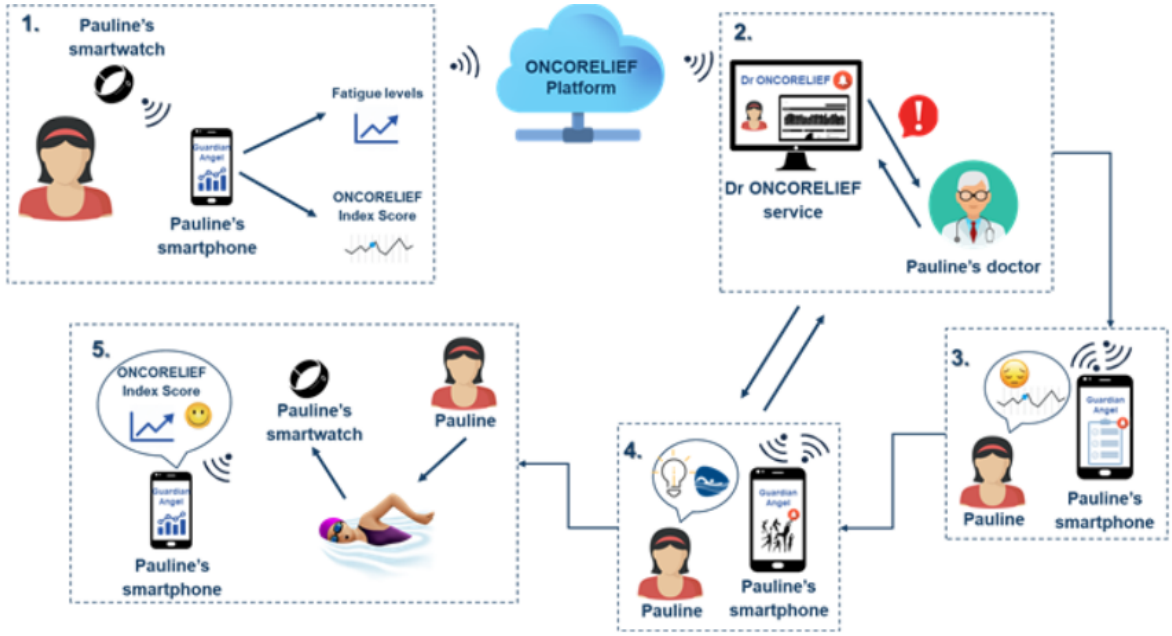
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Table 2. Domains and key needs assessed for each type of cancer.

Domain	Acute myeloid leukemia needs	Colorectal cancer needs
Emotional distress	• Depression • Anxiety	• Depression • Anxiety
Psychophysiological	• Sleep • Fatigue • Lack of sexual interest	• Fatigue
Physical symptoms	• Sore mouth • Appetite loss	• Colitis • Appetite loss • Peripheral neuropathy • Hand-foot syndrome
Well-being	• Well-being	• Well-being

The different scores at each level will provide a set of metrics that will allow to identifying and monitoring QoL and well-being of patients with cancer. This multilevel approach will provide information about what domain or domains (eg, emotional distress) related with patient needs (eg, depression, anxiety) must be improved or to identify differences by gender, type of cancer, and country at the 3 levels. The global index results from averaging the scores of each domain, which are based on the scores obtained in each patient's key needs. The QoL and well-being global score is converted on a 0-1000 scale and will allow a qualitative appreciation, which will range between 400 (very poor) and 900 or higher (very good). Clinical and psychosocial recommendations coming from the ONCORELIEF system are analyzed and decided by the health professional and are focused on specific needs rather than the overall score. However, it is expected that a positive change in specific unmet needs will be reflected positively on the QoL and well-being index global score. Below we describe a user scenario illustration based on a fictitious case (see Figure 4) as an example of how the ONCORELIEF digitally assisted workflow may hopefully work in a real-life setting.

Figure 4. Pauline case illustration.



User Scenario Illustration

Shortly after Pauline was diagnosed with stage 2 colorectal cancer, she had surgery followed by chemotherapy as adjuvant treatment. She accepted the opportunity to use the ONCORELIEF Guardian Angel app, although she didn't particularly like the idea of entering much data into an app. Over time, the Guardian Angel app, having connected with her smart device, identified patterns, which had been correlated with the early onset of fatigue in patients like Pauline: she napped more than before and was less active. Additionally, her ONCORELIEF QoL and well-being global score had dropped from 700 to 500. Her HCP got notified of these patterns through the ONCORELIEF service and, after some consideration, sent a message to the patient. When Pauline got notified the next day, she read the accompanying text and realized from the color coding on her app that her QoL and well-being index score had dropped further, and upon further investigation, she read that it was 500 because of early fatigue and some mild depressive symptoms. It then occurred to her that this may have been the

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reason behind her low motivation and her reluctance to get up and go to work in the morning. She gave consent for her new information to be shared with her HCP and was provided with a few minutes' worth of reading material, which made her feel somewhat better since she realized this is relatively common and not a huge cause of concern. Her HCP, after viewing the report on Pauline's responses as well as her recent history via ONCORELIEF, gave a recommended intervention: gradual exercise increase and get support from psycho-oncology services. The HCP agreed and soon enough Pauline had the recommendation on her Guardian Angel app. She felt OK but not great—but then read that the exercise coach would motivate her based on her achievements but also that her exercises would be tailored to her unique needs and preferences. The accompanying content offered a variety of exercises: since she had not had an ostomy surgery and did not have a stoma bag, she could also swim in the local pool, and she liked that idea. Pauline started tracking her swimming sessions simply with a couple of taps at a time. The psycho-oncologist assessed Pauline's depressive cognitions and beliefs and her lack of motivation and pleasure in doing daily activities and suggested some stress management skills to cope with depression. After a few weeks, both Pauline and her HCP could see her ONCORELIEF Index QoL and well-being score increasing slowly but steadily to 700.

Ethics Approval

The protocol, informed consent, and any accompanying material provided to the patient were submitted to the ethical board of IRST (CEROM, Comitato Etico della Romagna, case number Prot. 8528/2021) and Mainz (Ethik-Kommission der Landesärztekammer Rheinland-Pfalz, case 2021-16122) for review. The pilot study was approved by both ethical boards. Any modifications made to the protocol, informed consent, or material provided to the patient after receipt of the Ethics Committee approval must also be submitted by the investigator to the committee in accordance with local procedures and regulatory requirements. It is the responsibility of the investigator to obtain written informed consent from each subject prior to entering the trial or, where relevant, prior to evaluating the subject's suitability for the study.

The investigators will ensure that this study is conducted in full conformity with the current revision of the Declaration of Helsinki (last amended 64th WMA General Assembly, Fortaleza, Brazil, October 2013), with relevant regulations and with the ICH Guidelines for Good Clinical Practice E6 (R2), and other relevant local legislation.

Results

The ONCORELIEF project started in January 2020 and will end in June 2023. The pilot study started on September 1, 2022. As of January 2023, we enrolled 33 patients with colorectal cancer and 7 patients with acute myeloid leukemia. As of January 2023, we have not yet started the data analysis. We expect to get all data in June 2023 and expect the results to be published in the second semester of 2023.

Discussion

Principal Findings

The main objective of ONCORELIEF is the development of a user-centered AI system to facilitate the input and integration of patient-related biopsychosocial data to improve posttreatment QoL, well-being, and health outcomes. We hope that this project will be feasible and will provide patients and health professionals with a valuable tool to improve the holistic rehabilitation of patients with cancer. There has been increasing use of eHealth tools in health care in general [5] and in patients with cancer in particular [4,27,28], but the main innovation of ONCORELIEF is that all data of patients with cancer will run on a digitally assisted workflow of posttreatment supportive patient care supported by an AI system. The core concept of the ONCORELIEF proposal is based on the collection of biopsychosocial patient data to provide patient-centered care and better support services to patients with cancer and survivors of cancer. ONCORELIEF will enable identifying, collecting, harmonizing, modeling, and eventually processing and analyzing data from diverse channels and domains, using Big Data and AI techniques to develop services and features that will be offered to all cancer stakeholders, with the aim to serve them with a continuous monitoring and assistance app, toward increasing the awareness of their QoL and well-being status. The overall output of ONCORELIEF has the potential to provide insights for HCPs and caregivers, as well as for patients, and to deliver recommendations toward more effective psychosocial support. Patients may be more motivated to improve their health and hasten their way back to normal, through the adoption of healthy lifestyles and stress management skills. The power of ONCORELIEF lies on a holistic model of health, capturing ongoing data from diverse sources (eg, patient-reported outcomes through a smartphone app, physiological signals from a wearable smart device, and demographic and medical data from health records) involving the biological, psychological, and social dimensions of the patient with the potential to offer the patient just-in-time recommendations to cope with the unmet needs and challenges of the cancer journey.

Strengths

The strengths of the study are as follows: the platform and patient-assessment profile are continuously updated and is available 24/7, the study has the potential of less demand of medical consultations since ONCORELIEF gives support to the patient all the time, and the study contributes to better clinical outcomes.

Limitations

The limitations of this study are resistance from some patients who are not familiar with digital devices, eHealth tools and procedures are not yet integrated into hospitals' data evaluation and recording systems, and platforms and systems such as ONCORELIEF may emerge as extra tools that can be felt as complications in the day-to-day life of HCPs.

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Acknowledgments

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Data Availability

Data sharing is not applicable to this paper as no data sets were generated or analyzed during this study.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Project Evaluation (Peer-Review by European Commission).
[PDF File (Adobe PDF File), 197 KB - resprot_v12i1e45475_app1.pdf]

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Abbreviations

AI: artificial intelligence
HCP: health care professional
IRST: Istituto Romagnolo per lo Studio dei Tumori “Dino Amadori”
QoL: quality of life

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Protocol

Telehealth-Based Music Therapy Versus Cognitive Behavioral Therapy for Anxiety in Cancer Survivors: Rationale and Protocol for a Comparative Effectiveness Trial

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Abstract

Background: Cancer survivors represent one of the fastest growing populations in the United States. Unfortunately, nearly 1 in 3 survivors experience anxiety symptoms as a long-term consequence of cancer and its treatment. Characterized by restlessness, muscle tension, and worry, anxiety worsens the quality of life; impairs daily functioning; and is associated with poor sleep, depressed mood, and fatigue. Although pharmacological treatment options are available, polypharmacy has become a growing concern for cancer survivors. Music therapy (MT) and cognitive behavioral therapy (CBT) are evidence-based, nonpharmacological treatments that have demonstrated effectiveness in treating anxiety symptoms in cancer populations and can be adapted for remote delivery to increase access to mental health treatments. However, the comparative effectiveness of these 2 interventions delivered via telehealth is unknown.

Objective: The aims of the Music Therapy Versus Cognitive Behavioral Therapy for Cancer-related Anxiety (MELODY) study are to determine the comparative effectiveness of telehealth-based MT versus telehealth-based CBT for anxiety and comorbid symptoms in cancer survivors and to identify patient-level factors associated with greater anxiety symptom reduction for MT and CBT.

Methods: The MELODY study is a 2-arm, parallel-group randomized clinical trial that aims to compare the effectiveness of MT versus CBT for anxiety and comorbid symptoms. The trial will enroll 300 English- or Spanish-speaking survivors of any cancer type or stage who have experienced anxiety symptoms for at least 1 month. Participants will receive 7 weekly sessions of MT or CBT delivered remotely via Zoom (Zoom Video Communications, Inc) over 7 weeks. Validated instruments to assess anxiety (primary outcome), comorbid symptoms (fatigue, depression, insomnia, pain, and cognitive dysfunction), and health-related quality of life will be administered at baseline and at weeks 4, 8 (end of treatment), 16, and 26. Semistructured interviews will be conducted at week 8 with a subsample of 60 participants (30 per treatment arm) to understand individual experiences with the treatment sessions and their impact.

Results: The first study participant was enrolled in February 2022. As of January 2023, 151 participants have been enrolled. The trial is expected to be completed by September 2024.

Conclusions: This study is the first and largest randomized clinical trial to compare the short- and long-term effectiveness of remotely delivered MT and CBT for anxiety in cancer survivors. Limitations include the lack of usual care or placebo control

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groups and the lack of formal diagnostic assessments for psychiatric disorders among trial participants. The study findings will help guide treatment decisions for 2 evidence-based, scalable, and accessible interventions to promote mental well-being during cancer survivorship.

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KEYWORDS

oncology; anxiety; cognitive behavioral therapy; music therapy; telehealth; cancer survivorship; mental health; digital health; mobile phone

Introduction

The Burden of Anxiety During Cancer Survivorship

With advances in oncology care, the number of cancer survivors in the United States is expected to increase dramatically and exceed 22 million by the end of this decade [1]. A meta-analysis identified anxiety as one of the most common mental health issues faced by cancer survivors [2]. Compared with the general population, cancer survivors experience higher rates of anxiety [2-5], and up to one-third of them experience clinically meaningful anxiety symptoms [3,5-9]. Characterized by restlessness, muscle tension, and worry that is difficult to control, anxiety is a highly disruptive symptom associated with poor sleep [10], depressed mood [11-13], and fatigue [14-17]. Anxiety also contributes to poor treatment adherence [18-20] and increased health care expenditures [21,22]. As a primary driver of poor quality of life among cancer survivors [23-26], anxiety is an important issue to address in this rapidly growing population.

Although pharmacological treatment options for anxiety are available [27], polypharmacy is a growing concern among cancer survivors [28-31]. Compared with the general population, cancer survivors have much higher rates of polypharmacy, with 64% taking ≥5 unique medications [30]. One-third of survivors receive at least 1 psychotropic medication (eg, anxiolytics and antidepressants), and nearly 1 in 6 survivors report using ≥2 classes of psychotropic medications [31]. Psychotropic polypharmacy is associated with poor quality of life, impaired physical and mental functioning, financial toxicity, and higher risk of side effects and drug interactions [31]. These challenges of polypharmacy highlight the need for nonpharmacological treatment options for anxiety during cancer survivorship.

Cognitive Behavioral Therapy: An Effective First-Line Treatment for Anxiety

Cognitive behavioral therapy (CBT) is an evidence-based, nonpharmacological intervention delivered by licensed mental health professionals [32,33]. The American Society of Clinical Oncology (ASCO) [27] and the National Comprehensive Cancer Network (NCCN) [34] recommend CBT for treatment of anxiety in patients with cancer. Informed by the cognitive behavioral model of anxiety, CBT focuses on the relationship between thoughts, behaviors, and emotions and how thoughts and behaviors can exacerbate or reduce anxiety [35-37]. The therapeutic components of CBT consist of psychoeducation on anxiety, relaxation techniques, cognitive restructuring, and strategies for planning activity engagement and managing realistic worries [38,39]. Meta-analyses demonstrated moderate to large effects of CBT on anxiety symptoms in patients with cancer and cancer survivors relative to control conditions, with effect sizes ranging from 0.42 to 1.10 [40-43]. CBT is widely considered an effective first-line treatment for anxiety in people affected by cancer [27,34].

Despite the established effectiveness of CBT, studies have demonstrated that 20% to 25% of CBT participants fail to complete a full treatment course [44,45] and 37% do not achieve clinically meaningful improvements in anxiety symptoms [46,47]. Furthermore, social stigma surrounding psychotherapy exists in some demographic groups and cultures, and research shows that underserved racial or ethnic groups are more likely than White patients to delay, avoid, or drop out of mental health treatments [48,49]. These challenges of CBT highlight the importance of studying other nonpharmacological treatments that are not only effective but also culturally acceptable to diverse cancer survivors.

Music Therapy: An Evidence-Based Anxiety Treatment With Increasing Availability at Cancer Centers

Music therapy (MT) is a nonpharmacological, evidence-based intervention in which board-certified music therapists engage patients in personally tailored experiences with music to achieve therapeutic goals [50]. These experiences range from music-guided relaxation to more active forms of musical engagement, including singing and improvising music [50]. The social-cognitive processing model of emotional adjustment in cancer is one of several possible models that informs the use of MT for anxiety management in cancer survivors [51]. Supported by empirical studies [52,53], this model conceptualizes the cancer treatment journey as a disruptive, trauma-like experience that must be cognitively processed in a supportive social context for healthy emotional adaptation to occur [51,52]. A growing body of research demonstrates the capacity of MT to influence these social-cognitive processes central to anxiety. Interactive music experiences have been shown to build social connections and promote a sense of belonging [54-56]. Prior studies also suggest that MT provides novel, creative outlets (eg, through songwriting) to cognitively process past traumatic experiences that may otherwise be difficult to verbalize [57,58]. In addition to its social-cognitive effects, musical engagement has been shown to modulate brain regions (ie, amygdala) [54] and biological systems (ie, hypothalamic-pituitary-adrenal axis [59-61] and autonomic nervous system [62-65]) responsible for emotional regulation

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and implicated in anxiety and mood disorders [66-69]. Importantly, ethnographic and phylogenetic research has identified music as a defining characteristic of humankind across many cultures worldwide [70,71]. The multicultural presence of music supports the potential of MT to resonate with a diverse population of cancer survivors.

MT has a growing evidence base for cancer symptom management [72-75] and is recommended by ASCO [76], NCCN [34], and the Society for Integrative Oncology [77,78] as a treatment option for anxiety in cancer populations. A recent Cochrane review (81 trials, N=5576) found that MT was associated with a large reduction in anxiety symptoms compared with usual care [79]; MT is also offered at approximately 75% of the National Cancer Institute (NCI)–designated Comprehensive Cancer Centers and 55% of community-based cancer programs [80]. Owing to its growing evidence base and availability, MT represents a promising alternative to CBT for the treatment of anxiety.

Digital Transformation of Health Care During COVID-19: A Timely Opportunity to Improve Access to Mental Health Resources

In the past 2 decades, the percentage of US adults who use the internet has increased from 52% to 90% [81]. Approximately 59% to 79% have access to home broadband internet services [81] and 37% use smartphones as their primary access to the internet [82]. Cancer centers across the country are increasingly leveraging digital technology to monitor and manage symptoms remotely [83]. The COVID-19 pandemic accelerated these digital trends, and the use of videoconferencing for telehealth services increased by 8700% at the peak of the pandemic [84].

Although key disparities in digital access and literacy remain [85], the widespread adoption of videoconferencing offers a promising platform for reducing barriers to mental health services. Therapists have successfully used videoconferencing to deliver MT remotely to military populations [86-90] and patients with autism [91]. Therapists have also used videoconferencing to deliver MT services to inpatient [92,93] and oncology settings [94]. At the outset of the pandemic, the American Music Therapy Association and other MT professionals rapidly developed and implemented telehealth guidelines and resources to facilitate the telehealth-based delivery of MT services to patients isolated at home [92,95]. Many music therapists have shifted their clinical practices to web-based platforms [96,97]. There is also an extensive body of research (>100 trials) on internet-delivered CBT interventions [98,99], and studies have consistently demonstrated that CBT delivered remotely is as effective and acceptable as in-person treatments for anxiety [100]. Thus, both MT and CBT are equipped for the digital health care landscape, with unique potential for scalability to reduce barriers to mental health services.

Gaps in the Evidence: Treatment Dilemmas Facing Patients and Clinicians in the New Digital Health Care Landscape

Although CBT is widely considered a first-line treatment for anxiety, not all individuals are able to complete a full treatment course [44,45] or achieve meaningful improvements in their symptoms [46,47]. People may also be reluctant to pursue CBT because of the sociocultural stigma surrounding psychotherapy in different groups and communities [48,49]. For individuals who do not respond or do not wish to pursue CBT, evidence is lacking on whether MT is an effective, noninferior treatment alternative to CBT.

To inform treatment decision-making, the American Psychological Association, in its resolution on the Recognition of Psychotherapy Effectiveness, has called for “continued and further research on the comparative effectiveness” of CBT and other psychotherapeutic interventions [101]. Furthermore, as health care continues to undergo rapid digital transformation, there is a critical need for additional research into telehealth interventions. Although CBT research has compared remote delivery versus traditional in-person formats, few studies have compared telehealth-based CBT with other telehealth interventions, such as MT [98,100]. In their systematic review of digital health interventions for cancer survivors, Harris et al [83] emphasized that “one size may not fit all” and there is a “need to identify who is most likely to benefit from digital interventions.” Comparative effectiveness research on different telehealth-based treatments (ie, CBT vs MT) is essential to guide timely and patient-centered decision-making and help patients and clinicians navigate this new digital health care landscape.

The Music Therapy Versus Cognitive Behavioral Therapy for Cancer-Related Anxiety Trial: Study Aims and Hypotheses

The Music Therapy Versus Cognitive Behavioral Therapy for Cancer-related Anxiety (MELODY) trial seeks to address the following aims:

The primary aim is to determine the comparative effectiveness of telehealth-based MT versus telehealth-based CBT for anxiety and comorbid symptoms in cancer survivors.

- *Hypothesis 1(a)*: MT will be noninferior to CBT in treating anxiety symptoms among survivors at week 8 (end of treatment) and week 26 (long-term follow-up).
- *Hypothesis 1(b)*: Compared with CBT, MT will be associated with significantly greater improvement in fatigue co-occurring with anxiety.
- Exploratory hypothesis: Survivors may have unique experiences with MT and CBT for anxiety during cancer survivorship.

The secondary aim is to identify patient-level factors associated with greater anxiety symptom reduction after MT and CBT.

- *Hypothesis 2*: Specific sociodemographic characteristics (eg, age, sex, race, and education) or psychological attributes (ie, expectancy) will be associated with treatment response to MT or CBT.

Methods

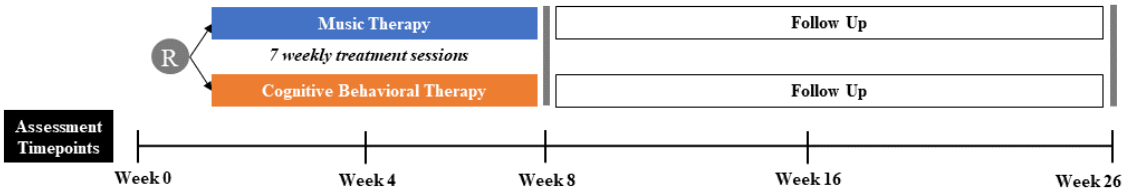
Study Design

The MELODY study is a 2-arm, parallel-group, pragmatic randomized clinical trial that aims to compare the effectiveness

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of MT versus CBT for anxiety and comorbid symptoms in a diverse and heterogeneous sample of 300 cancer survivors (Figure 1). This study will be conducted at the Memorial Sloan Kettering Cancer Center (MSK), an NCI-designated Comprehensive Cancer Center, as well as the Miami Cancer Institute (MCI) and Drexel University. These sites were chosen in part for their potential to help recruit a diverse study population. Interventions will be delivered weekly via Zoom (Zoom Video Communications, Inc) over 7 weeks. Study assessments will be administered at baseline and at weeks 4, 8, 16, and 26. This study will be conducted in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines for nonpharmacological interventions [102], the reporting guidelines for music-based interventions [103], and the National Institutes of Health Protocol Template for Behavioral and Social Sciences Research [104]. This study has also been registered at ClinicalTrials.gov (NCT05215353).

Figure 1. Study schema.



Ethics Approval

The study was approved by the institutional review board (IRB) at MSK on December 22, 2021 (IRB: 21-516). MSK serves as the IRB of record for both MCI and Drexel University.

Eligibility Criteria

The eligibility criteria were designed to be broad and consistent with a pragmatic design while ensuring participant safety and scientific rigor. Participants are eligible if they are English- or Spanish-speaking, are aged ≥18 years, have a prior cancer diagnosis of any type or stage, are free of oncological disease, have a score of ≥8 on the anxiety subscale of the Hospital Anxiety and Depression Scale (HADS), report anxiety symptoms lasting at least 1 month, and have access to Zoom and a quiet or private location. Participants will be excluded if they had completed active cancer treatment (eg, surgery, radiation, and chemotherapy) less than 1 month before enrollment; however, participants receiving maintenance hormonal or targeted therapies will be allowed to enroll. Participants will also be excluded if they have active suicidal ideation, bipolar disorder, schizophrenia, or substance abuse; have a score of ≥10 indicative of cognitive impairment on the Blessed Orientation-Memory-Concentration; or received a treatment course of ≥7 MT or CBT sessions for anxiety symptoms within the last 6 months.

Recruitment

This study will use a multimodal recruitment strategy that comprises population-based methods, clinician referrals, and community outreach and engagement, which are described as follows:

1. Population-based methods: MSK and MCI patient databases will be queried to identify survivors who meet basic eligibility criteria. MSK catchment areas include urban and suburban locations in New York, Long Island, and New Jersey, whereas MCI catchment areas include urban and suburban locations in South Florida with access to a large Hispanic population. Drexel University investigators will query the Pennsylvania Cancer Registry to identify potential participants from rural populations. A recruitment letter will be sent to the potential participants identified on these databases and registries. The recruitment letter will introduce the study and include instructions for interested persons to contact the study team.
2. Clinician referrals: potential participants will also be identified and referred by clinicians at MSK, MCI, or other health care settings. To facilitate referrals, the study team will educate clinicians about the study, focusing on those who care for cancer survivors.
3. Community outreach and engagement: information about the study will also be posted on social media outlets, ClinicalTrials.gov, and public-facing websites. The study team will also present the study at scientific conferences, cancer survivorship support groups, community organizations, and other patient advocacy groups.

The goal of this multimodal approach is to enroll a diverse sample that includes traditionally underrepresented sociodemographic groups. The recruitment strategies were developed jointly by the study team and the patient and stakeholder advisory board, which includes patient advocates, cancer survivors, community leaders, and clinical stakeholders. Diverse study representation will facilitate careful exploration of the differences between participant subgroups to inform personalized decision-making.

Once interested and potentially eligible participants are identified, the research staff will schedule them for an initial screening visit. If participants meet the basic eligibility criteria, they will then be scheduled for a telehealth visit with a study clinician to confirm their eligibility. If a participant is deemed eligible, the research staff will explain the study procedures and request informed consent. Once consent is obtained, the participants will complete the baseline assessments.

Randomization

After completing the baseline assessments, participants will be randomized using MSK's secure computer system that ensures full allocation concealment. Randomization will be 1:1 (MT:CBT) using randomly permuted blocks of random length, which are stratified by study site, current anxiety medication use (yes or no), and preferred language (English or Spanish).

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The principal investigator and biostatistician will be blinded to treatment assignments.

Interventions

Treatment Course

Study participants will receive 7 weekly 60-minute MT or CBT sessions over the first 7 weeks. All sessions will be delivered remotely through Zoom's Health Insurance Portability and Accountability Act (HIPAA)–compliant, encrypted, and passcode-protected videoconferencing software. Although the duration of these types of treatments may vary in real-world settings, this study will match the MT and CBT groups for patient-therapist contact time to ensure rigorous comparative effectiveness comparison.

MT Protocol

MT will be delivered by board-certified music therapists. The MT protocol is based on the neuroscience of music [54,105], the social-cognitive processing model [51,52], the scientific literature on MT [72], and the clinical and research experience of the study team [106]. Healthy psychological adjustment during cancer survivorship requires the processing of feelings and thoughts related to one's cancer journey in a supportive context [51,52]. Therefore, the intervention protocol is structured to build patient-therapist rapport and allow for greater emotional expressivity and deeper cognitive processing. Guided by the social-cognitive processing model [51,52], the first few sessions will focus on building a trusting relationship with the therapist, whereas the later sessions will focus on the cognitive processing of cancer-related experiences and current fears, worries, and hopes, using playlist creation and songwriting as an outlet for reflection, expression, and meaning making. Research also suggests that patients prefer receptive modes of engagement during their initial exposure to MT [75,107]. As such, the early sessions will focus on receptive techniques (eg, music-guided stress management), and the later sessions will progress to more active MT techniques (eg, songwriting). The protocol includes homework activities in between sessions to promote self-management skills (eg, the use of music-guided deep breathing), strengthen social connections (eg, sharing meaningful songs with loved ones), provide outlets for cognitive processing (eg, writing or reflecting on themes for song lyrics), and serve as transitions to the subsequent sessions.

CBT Protocol

The CBT protocol is based on the scientific literature [32,33] and the clinical and research experience of the study team [108]. CBT therapists will include licensed social workers because they are the most commonly employed mental health providers in cancer care and, therefore, reflect the real-world practice and implementation of CBT in oncology settings [109]. Informed by the cognitive behavioral model of anxiety, CBT focuses on addressing the thoughts and behaviors that exacerbate or reduce anxiety [35-37]. The protocol consists of psychoeducation on anxiety, relaxation techniques, cognitive restructuring, and strategies for planning activity engagement and managing realistic worries [38,39]. These components target the somatic symptoms of anxiety (eg, muscle tension) as well as the thoughts (eg, "What if my next scan is bad?") and behaviors (eg, excessive symptom monitoring) that trigger and exacerbate anxiety. Once identified, these problematic thoughts and behaviors are replaced by thoughts and behaviors that prevent and reduce anxiety. Each session will follow a consistent format that includes an overview of the session content, review of the homework exercise from the prior session, information on a new skill for managing anxiety, discussion of the upcoming homework exercise, and a plan for completing the exercise before the next session. Patients will receive a workbook with materials for each session and homework activities that promote practice of the skill learned during the session.

Interventionist Training and Treatment Fidelity

All interventionists will be trained about the specific research protocol and educated on the importance of adherence to the protocol methods. The interventionists will be either English speaking or bilingual in English and Spanish. The training of study interventionists will include didactic information on anxiety in cancer survivors and review of intervention materials. Interventionists will be provided with ongoing supervision over the course of the trial. During the trial, the CBT and MT sessions will be recorded and stored on secure, encrypted MSK servers. To ensure that study therapists adhere to the treatment protocol, document treatments appropriately, and maintain fidelity to the core functions of the intervention, the session recordings for the first 2 patients seen by a therapist will be reviewed. The review of session recordings will be based on treatment fidelity checklists outlining the core intervention components. If a therapist adheres to at least 80% of the treatment fidelity checklist items, then subsequent fidelity monitoring will be reduced to 2 randomly selected session recordings per patient. Deviations from the MT or CBT protocols will be discussed with study therapists during supervision meetings, and strategies will be suggested to minimize the number of deviations. Therapists who fail to adhere to at least 80% of the treatment fidelity checklist items will be retrained. Similar treatment fidelity strategies have been successful in other MT [106] and CBT trials [108,110] of patients with cancer conducted by the study team.

Study Assessment Procedures

Overview

Patient-reported outcomes (Table 1) will be completed on the web using Research Electronic Data Capture (REDCap; Vanderbilt University) [111]. Participants will also have the option to complete these study assessments on paper or over the telephone with research staff. Study assessment materials will be available in English or Spanish. Patient-reported outcome measures for anxiety, comorbid symptoms, and quality of life have been validated in Spanish [112-117]. Where needed, Spanish translation of other assessments took place in standard forward and reverse translation.

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Table 1. Summary of patient-reported outcomes.

Primary or secondary	Name of outcome	Validated instrument	Time points (weeks)
Primary	Anxiety	HADS[a]	0, 4, 8, 16, and 26
Secondary	Depression	HADS	0, 4, 8, 16, and 26
Secondary	Fatigue	BFI[b]	0, 4, 8, 16, and 26
Secondary	Insomnia	ISI[c]	0, 4, 8, 16, and 26
Secondary	Pain	BPI[d]	0, 4, 8, 16, and 26
Secondary	Cognitive dysfunction	FACT-Cog[e]	0, 4, 8, 16, and 26
Secondary	Quality of life	PROMIS–Global Health[f]	0, 4, 8, 16, and 26
Secondary	Treatment expectancy	METE[g]	0 and 8
Secondary	Treatment preference	Treatment preference Scale	0 and 8
Secondary	Music reward	BMRQ[h]	0
Secondary	Mental health stigma	SSRPH[i]	0
Secondary	Generalized anxiety disorder	GAD-7[j]	0

[a]HADS: Hospital Anxiety and Depression Scale.

[b]BFI: Brief Fatigue Inventory.

[c]ISI: Insomnia Severity Index.

[d]BPI: Brief Pain Inventory.

[e]FACT-Cog: Functional Assessment of Cancer Therapy–Cognitive Function.

[f]PROMIS–Global Health: Patient-Reported Outcomes Measurement Information System–Global Health.

[g]METE: Mao Expectancy of Treatment Effects.

[h]BMRQ: Barcelona Music Reward Questionnaire.

[i]SSRPH: Stigma Scale for Receiving Psychological Help.

[j]GAD-7: Generalized Anxiety Disorder 7-Item Scale.

Anxiety

The primary outcome is severity of anxiety symptoms, as assessed using the HADS anxiety subscale. The reliability, validity, and factor structure of this 7-item subscale has been established in patients with cancer with a Cronbach α of .83 [118,119]. A score of ≥8 indicates the presence of anxiety symptoms. Research has identified a minimal clinically important difference (MCID) of 1.7 points [120]. The HADS anxiety subscale will be administered at baseline and at weeks 4, 8, 16, and 26.

Comorbid Symptoms and Quality of Life

Given that anxiety is strongly associated with depressed mood [11-13], fatigue [14-17], insomnia [10], pain [121], and cognitive dysfunction [122], these comorbid symptoms will be assessed using validated instruments. Depressive symptoms will be assessed using the HADS depression subscale (Cronbach α=.79) [118,119]. Fatigue will be assessed using the Brief Fatigue Inventory (BFI), a 9-item scale that has been validated in cancer populations with a Cronbach α of .96 [123]. Insomnia symptoms will be assessed using the Insomnia Severity Index [124], a 7-item instrument validated in cancer populations with a Cronbach α of .90 [125]. Pain severity and pain-related interference will be assessed using the Brief Pain Inventory (BPI). The BPI has been demonstrated to be a reliable, valid, and responsive measure with a Cronbach α of .77 to .91 [126]. Cognitive difficulties will be assessed using the Functional Assessment of Cancer Therapy–Cognitive Function (FACT-Cog), version 3, a 37-item questionnaire with 4 subscales (perceived cognitive impairments, impact on quality of life, comments from others, and perceived cognitive abilities). The FACT-Cog is a reliable instrument validated in cancer populations with a Cronbach α of .89 [127]. The FACT-Cog instrument will only be administered to participants who reply "YES" to the following question at baseline: "Are you experiencing difficulties with memory, concentration, or other cognitive abilities?" As anxiety is a key determinant of quality of life in cancer survivors [23-26], the Patient-Reported Outcomes Measurement Information System–Global Health (PROMIS–Global Health) will also be administered. This validated measure contains 2 domains related to quality of life: mental health (Cronbach α=.86) and physical health (Cronbach α=.81) [128]. These measures will be administered at baseline and at weeks 4, 8, 16, and 26.

Treatment Expectancy

The Mao Expectancy of Treatment Effects (METE) is a 4-item instrument originally developed as the Acupuncture Expectancy Scale to measure outcome expectancy. It has demonstrated validity and reliability (Cronbach α=.82) and is correlated with patient self-reported efficacy and satisfaction [129-131]. Prior research has also demonstrated that outcome expectancy is

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associated with treatment response [129,132,133] and can, therefore, help inform personalized treatment decisions. The score ranges from 4 to 20, with higher scores indicating greater expectancy of benefit. This measure has been adapted for the MELODY study to assess patient expectancy of MT and CBT. The METE will be administered at baseline before receiving treatment. It will also be administered at week 8 to explore whether the expectancy changes after the treatment process.

Treatment Preference

As participants may have different preferences toward mental health treatment based on health beliefs or prior experiences with interventions, they will be asked at baseline whether they prefer MT or CBT or none [134]. Their preferences will also be assessed at week 8 to explore whether preferences change after their experiences with either MT or CBT.

Music Reward

Prior research has demonstrated variability in how people derive reward and pleasure from music, which may affect their experience with MT [135]. Therefore, the Barcelona Music Reward Questionnaire will be administered at baseline to assess the level of reward associated with music. This instrument has been validated with a Cronbach α of .92 [135].

Stigma of Receiving Psychological Help

In some groups and cultures, there is stigma associated with mental health needs, which may affect treatment experiences [48,49]. Therefore, the Stigma Scale for Receiving Psychological Help will be administered at baseline. This instrument has been validated (Cronbach α=.72) in different cultures to assess the stigma associated with receiving psychological health from mental health providers [136,137].

Covariates

Sociodemographics (eg, age, sex, race or ethnicity, and education) and other relevant clinical characteristics (eg, cancer type, stage, treatment history, and time since cancer diagnosis) will be collected at baseline. The Generalized Anxiety Disorder 7-Item Scale (GAD-7) will also be administered as a diagnostic screen for generalized anxiety disorder at baseline [138]. The use of medications prescribed for anxiety (eg, antidepressants, anxiolytics, hypnotics, and sedatives) will be tracked using weekly medication diaries at weeks 0, 8, and 26.

Semistructured Interviews

It may be difficult to capture the impact of MT and CBT using quantitative measures alone. Methodological experts recommend mixed methods approaches to understand patient experiences with health interventions [139-141]. Thus, qualitative method specialists will conduct 45-minute, semistructured individual interviews over the phone at week 8 (end of treatment). To reach thematic saturation from interviews, the research team will purposively sample 30 survivors in each treatment arm to be interviewed (N=60), aiming for balance across age, sex, race, ethnicity, and treatment response. Interviews will be conducted shortly after the intervention period to enhance the recall of personal experiences during therapy sessions. Interviews will be conducted using a semistructured guide that covers the following topics: (1) acceptability: treatment satisfaction, usefulness of the intervention, barriers and facilitators to session attendance, and adherence to and engagement with between-session assignments; (2) impact on anxiety symptoms and coping: perceived benefits and harms of the intervention on anxiety and comorbid symptoms, how one copes with stress and anxiety, integration of learned skills into daily life, and plans for maintaining anxiety management skills; (3) digital literacy and experience: views toward technology, comfort level with telehealth, and transfer of acquired digital skills to other aspects of daily living; and (4) unexpected experiences: unanticipated benefits, harms, or insights from engaging with the interventions. The interview guide will include flexibility in asking probing questions to enable participants to elaborate on their experiences. All the interviews will be audio-recorded and transcribed for thematic analysis.

Analytical Approach

General Description

Analyses will be conducted using the intention-to-treat principle (ie, participants will be analyzed according to their randomly assigned treatment group regardless of dropout or treatment adherence status). Given that CBT is widely recognized as a first-line therapy for anxiety, the study team opted to test the noninferiority of MT to CBT, with the goal of understanding whether MT can be an appropriate treatment option for patients who lack CBT access or do not wish to pursue CBT. To provide complementary information for treatment decision-making, the study team will also test which intervention is superior for addressing fatigue and other symptoms co-occurring with anxiety. For all specific aims, the main analytical tool will be a linear mixed-effects model (LMM) because the primary outcome (anxiety) and secondary outcomes (fatigue, depression, insomnia, pain, cognitive dysfunction, and health-related quality of life) are repeated continuous outcomes over time [142]. This statistical procedure takes into account within-subject correlations from repeated measurements in the same subjects and allows the estimation of between-group differences without necessitating the exclusion of participants with missing data. The general template of each LMM will model the outcome as a function of the treatment arm and assessment time (categorical), controlling for the randomization stratification variables (baseline anxiety medication use, preferred language, and study site) and including a subject-specific random intercept. The general LMM template will be tailored to test the specific aim hypotheses by adding interaction terms (eg, time-by-intervention) and additional covariates of interest to the model and by reparametrizing the assessment time variable to focus on specific contrasts.

Aim 1—Hypotheses 1(a) and 1(b)

Outcome measure trajectories will be plotted by randomization arm over time. Each outcome measure will be summarized at each assessment time by treatment arm using descriptive statistics. Comparisons between randomization arms with respect to changes in symptom outcomes will be based on specific coefficients from time-by-arm interactions added to the general LMM template described above in the *General Description* section. Specifically, the model will include all time points (categorical) at which the outcome was assessed (baseline and

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weeks 4, 8, 16, and 26), and the time-by-arm interaction will include multiple coefficients corresponding to the time-by-arm interaction at each discrete postbaseline time point. However, statistical inferences will focus on the interaction coefficients at 8 and 26 weeks, which are interpreted as the differences between arms in change from baseline to 8 and 26 weeks, respectively. For hypothesis 1(a), the 2 primary end points are HADS anxiety score changes at 8 weeks and 26 weeks. On the basis of the LMM coefficients for the time-by-arm interaction at weeks 8 and 26, 2 tests will be performed to determine whether MT is noninferior to CBT at reducing the HADS anxiety subscale score within a noninferiority margin of 0.35 SD for both comparisons. The noninferiority of MT to CBT will be tested at a significance threshold of $P<.025$ for each comparison, controlling the overall type I error at $P=.05$ for the primary end point comparisons. For hypothesis 1(b), a similar LMM evaluating BFI scores over time will be used to test whether the MT arm had significantly greater improvement in fatigue (BFI score) compared with the CBT arm at weeks 8 and 26. In contrast to the primary end point noninferiority comparisons, these tests will be superiority tests. For other comorbid symptoms (eg, depression and insomnia) and quality of life, the methods described for hypothesis 1(b) will be used to compare the treatment arms. Given that a small number of cancer survivors may experience disease recurrence during the 26-week study, sensitivity analyses will be performed, excluding those individuals who experienced a recurrence during the study period. These sensitivity analyses will not replace the primary analysis.

Aim 2—Heterogeneity of Treatment Effect

An essential part of patient-centered care is recognizing that not all patients will respond to treatments the same way. As such, exploratory, hypothesis-generating heterogeneity of treatment effect (HTE) analyses will be conducted to identify patient-level factors associated with treatment response to either MT or CBT by incorporating 6 relevant variables (sex, race, ethnicity, education, outcome expectancy, and time since cancer diagnosis) and variable-by-intervention interaction terms in the mixed-effects model described above in the *Aim 1—Hypotheses 1(a) and 1(b)* section. These 5 exploratory LMM-based analyses will be guarded against inflated type I error owing to multiple testing by adjusting the variable-by-intervention interaction *P* values for the false discovery rate [143,144]. This type of subgroup analysis, although patient centered, may need to be interpreted with caution and cannot replace the primary analyses. The evaluation and reporting of HTE analyses will be based on the approach proposed by Kent et al [145]. However, recognizing other factors may also contribute to treatment responses, the study team will also apply Bayesian [146,147] and machine learning [148,149] methods, which can identify HTE and subgroups based on multiple variables simultaneously and are potentially more powerful than traditional univariate methods.

Qualitative Analyses

All interviews will be transcribed verbatim and imported into MAXQDA 2022 (VERBI Software) for analysis. The semistructured interviews will be analyzed using theoretical thematic analysis procedures as per the guidelines by Braun and Clarke [150,151]. Such an analysis is aimed at identifying patterns driven by an a priori theoretical framework or research questions. Themes will be identified using a semantic approach in which themes are derived from "the explicit meaning of the data and the analyst is not looking for anything beyond what a participant has said" [150]. Two coders will code the interview transcripts. To ensure the trustworthiness of the analysis, the primary coder will code each transcript, whereas the secondary coder will code 30% of the transcripts. Coding discrepancies will be resolved through discussion until consensus is reached. The codes will then be organized into categories, reviewed, and subsequentially organized into broader themes. Interviews from each treatment arm will be analyzed separately and then compared for convergence and divergence. The themes will be linked to patient-reported outcomes to explore whether specific themes vary according to the magnitude of change in the HADS anxiety score. To augment the HTE analyses, the study team will also explore whether qualitative themes differed by subgroup (eg, sex, race, ethnicity, education, outcome expectancy, and time since cancer diagnosis) within each treatment group.

Missing Data

As the only certain way to avoid biases from missing data is to collect complete data [152], the study team will strive to minimize missing observations by using study procedures that reduce participant burden. Participants who experience difficulties completing assessments on the web will have the option to complete assessments on paper or over the telephone with the research staff. Participants with time constraints or other barriers to completing outcome assessments will be given the option to complete only the primary outcome, that is, the HADS scale. Participants who withdraw from treatments will be encouraged to continue completing the outcome assessments. Reasons for withdrawal will be recorded for those who completely withdraw from the study. Given that missing data are inevitable in a prospective study, sensitivity analyses will be performed to assess the impact on the results of adjusting for patient disease progression or death, and analytical strategies that are as robust as possible to data losses will be applied. The study team will first explore whether missingness is associated with observed variables (eg, randomization arm and baseline outcome measures) by comparing patients with complete and incomplete data. Notably, the LMMs described previously will include patients with incomplete data under the missing at random assumption. However, the exploration of the data may deem the missing at random assumption to be inappropriate. Multiple imputation and pattern mixture models are well-established methods for addressing these issues [153,154]. Sensitivity analyses will be performed to evaluate the robustness of the LMM results by refitting the models after imputing the missing week 8 and week 26 outcomes using multiple imputation.

Sample Size and Power

The sample size is based on the primary hypothesis that MT is noninferior to CBT for anxiety reduction at weeks 8 and 26. Two tests will be performed to determine whether MT is

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noninferior to CBT at reducing HADS anxiety at weeks 8 and 26, each with a noninferiority margin of Cohen *d*=0.35 SD for both comparisons. These comparisons will be based on the LMM coefficients for the time-by-arm interaction at weeks 8 and 26; however, the power calculation is based on 2-sample *t* tests of differences between the arms in their change scores. Therefore, the power estimate is conservative, that is, in the LMM-based analysis, there will be slightly higher power than the power calculation presented below, with all other assumptions held constant. Assuming 150 participants are randomized to each arm, 15% attrition, and a 1-sided significance threshold of *P*=.025 (controlling the overall type I error at 0.05 for our 2 primary end point comparisons), there will be 80% power to find MT noninferior to CBT with respect to the HADS anxiety subscale scores at weeks 8 and 26 within a noninferiority margin of Cohen *d*=0.35 SD.

The noninferiority margin was informed by a large study that used multiple rigorous methods to empirically estimate a difference of 1.7 points as the MCID for the HADS scales [120]. In preliminary data from CBT recipients with baseline HADS anxiety subscale scores ≥8, the SD for the HADS anxiety subscale score was 4.2 at week 8 [110]. In addition, in a large acupuncture trial of cancer survivors, among 159 patients with baseline HADS anxiety subscale scores ≥8, the HADS anxiety subscale score SD was 4.0 during follow-up [155,156]. On the basis of these studies, it is assumed that the HADS anxiety subscale score SD will be approximately 4.2. Dividing the raw-score MCID of 1.7 points by 4.2 yields a standardized difference, that is, Cohen *d*=0.40. The noninferiority margin of Cohen *d*=0.35 SD is smaller than the standardized MCID (Cohen *d*=0.40) of the HADS anxiety subscale; as such, the noninferiority margin and statistical approach will find MT to be noninferior to CBT only if MT is not meaningfully worse than CBT.

Regarding the sample size for the qualitative analyses, the number of participants required to draw meaningful conclusions from semistructured interviews is determined by saturation, that is, the point at which existing themes are fully understood and no new themes emerge through further data collection [157]. Prior research has indicated that thematic saturation can typically be obtained with <15 interview participants, although these findings were based on relatively homogeneous samples [158]. Given that this study is enrolling a more heterogeneous population, the plan is to conduct 30 interviews in each treatment arm to better capture the diverse perspectives.

Results

The MELODY study was funded by the Patient-Centered Outcomes Research Institute in July 2021. The IRB at MSK approved the study protocol in December 2021. The first study participant was enrolled in February 2022. As of January 2023, a total of 151 participants have been enrolled. Enrollment is expected to be completed by February 2024, and data collection is expected to be completed by September 2024.

Discussion

Cancer survivors represent one of the fastest growing populations in the United States [1]. Unfortunately, nearly 1 in 3 survivors experience anxiety symptoms as a long-term consequence of cancer and its treatment [3,5-9]. Although pharmacological treatment options are available, polypharmacy has become a growing concern for cancer survivors [28-31]. CBT is an established first-line treatment for anxiety [32,33,159], but not all individuals respond or wish to use CBT [45,47-49]. Although MT has a growing evidence base for anxiety in cancer populations [72-75], it remains unclear how MT compares with CBT as a treatment alternative. The MELODY study will address this evidence gap by determining the comparative effectiveness of telehealth-based MT and telehealth-based CBT for anxiety in cancer survivors. This study will intentionally support enrollment access for racially and ethnically diverse populations of English- or Spanish-speaking survivors from urban, suburban, and rural settings to improve the generalizability of the findings and to inform future efforts to reduce the disparities in survivorship care. By focusing on telehealth-based interventions, this study will capitalize on the accelerating digital trends in health care and society at large, helping patients and clinicians to navigate a growing array of remotely delivered care options.

Despite its novelty and strengths, the MELODY study has some limitations. First, the study lacks a usual care or waitlist control group and therefore cannot control for Hawthorne effects or regression to the mean; however, both MT [72-75] and CBT [40,43,160] have demonstrated effectiveness for anxiety symptoms in cancer populations. Second, although the study participants are screened for the presence of generalized anxiety disorder, they do not undergo a formal diagnostic interview for psychiatric disorders. Third, this study focuses on treating anxiety symptoms rather than an anxiety disorder. However, cancer care guidelines are often based on symptom severity rather than psychiatric diagnoses [161]. Furthermore, research indicates that anxiety symptoms are associated with poor quality of life and other problematic outcomes in cancer populations, even if symptoms do not meet the criteria for an anxiety disorder [23,162]. Thus, by focusing on symptoms, this study will align closely with clinical guidelines and enroll more patients who could potentially benefit from interventions.

In conclusion, the MELODY study is the first and largest randomized clinical trial to compare the short- and long-term effectiveness of remotely delivered MT and CBT for anxiety symptoms in cancer survivors. This trial has the unique potential to produce timely findings on 2 evidence-based, scalable, and accessible interventions to promote mental well-being during cancer survivorship.

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Conflicts of Interest

KMM serves as a research consultant for OncoHealth. The other authors disclose no conflicts of interest related to the content of this manuscript.

Multimedia Appendix 1
Peer-review report from PCORI Funding Announcement: Assessment of Prevention, Diagnosis, and Treatment Options - Comparative Effectiveness Research (Patient-Centered Outcomes Research Institute, USA).
[PDF File (Adobe PDF File), 200 KB - resprot_v12i1e46281_app1.pdf]

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Abbreviations

ASCO: American Society of Clinical Oncology
BFI: Brief Fatigue Inventory
BPI: Brief Pain Inventory
CBT: cognitive behavioral therapy
CONSORT: Consolidated Standards of Reporting Trials
FACT-Cog: Functional Assessment of Cancer Therapy–Cognitive Function
GAD-7: Generalized Anxiety Disorder 7-Item Scale
HADS: Hospital Anxiety and Depression Scale
HIPAA: Health Insurance Portability and Accountability Act
HTE: heterogeneity of treatment effect
IRB: institutional review board
LMM: linear mixed-effects model
MCI: Miami Cancer Institute
MCID: minimal clinically important difference
MELODY: Music Therapy Versus Cognitive Behavioral Therapy for Cancer-related Anxiety
METE: Mao Expectancy of Treatment Effects
MSK: Memorial Sloan Kettering Cancer Center
MT: music therapy
NCCN: National Comprehensive Cancer Network
NCI: National Cancer Institute
PROMIS–Global Health: Patient-Reported Outcomes Measurement Information System–Global Health
REDCap: Research Electronic Data Capture

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Protocol

My Health, My Life, My Way—An Inclusive Web-Based Self-management Program for People With Disabilities Living With Chronic Conditions: Protocol for a Multiphase Optimization Strategy Study

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Abstract

Background: Individuals with disabilities living with chronic health conditions require self-management programs that are accessible, sustainable, inclusive, and adaptable. Health coaching is an effective approach to promoting behavior change in self-management. Health coaching combined with telehealth technology has the potential to improve the overall quality of, and access to, health services.

Objective: This protocol outlines the study design for implementing the My Health, My Life, My Way intervention. The study will assess the feasibility, acceptability, and preliminary efficacy of the intervention for people with disabilities and optimize it.

Methods: The My Health, My Life, My Way study is a 4-arm randomized controlled trial evaluating the delivery of a 6-month intervention involving telecoaching, inclusive educational content, and technology access for 200 individuals with chronic conditions and physical disabilities. This study uses the engineering-inspired multiphase optimization strategy (MOST) framework to evaluate intervention components and assess whether a combination or lack of individual elements influences behavior. Participants will be randomized to 1 of 4 study arms: scheduled coaching calls and gamified rewards, no scheduled coaching calls and gamified rewards, scheduled coaching calls and flat rewards, and no scheduled coaching calls and flat rewards.

Results: The My Health, My Life, My Way study was approved by the institutional review board of the University of Alabama at Birmingham, and recruitment and enrollment will begin in May 2023. Data analysis is expected to be completed within 6 months of ending data collection. This clinical trial protocol was developed based on the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2013 statement.

Conclusions: The My Health, My Life, My Way study will help to optimize and improve our understanding of the feasibility and efficacy of a web-based self-management program for people with physical disabilities and chronic conditions. More specifically, My Health, My Life, My Way will determine which combination of interventions (coaching calls and gamification) will result in increased participation in self-management programming. The My Health, My Life, My Way intervention has the potential to become a scalable and novel method to successfully manage chronic conditions in people with disabilities.

Trial Registration: ClinicalTrials.gov NCT05481593; https://clinicaltrials.gov/ct2/show/NCT05481593

International Registered Report Identifier (IRRID): PRR1-10.2196/31694

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KEYWORDS

telehealth; health coaching; artificial intelligence; chronic conditions; mobile phone

Introduction

Background

The Centers for Disease Control and Prevention (CDC) defines chronic diseases as conditions that last ≥1 year and require ongoing medical attention or limit activities of daily living or both. In the United States, 6 in 10 adults are reported to have at least 1 chronic condition, whereas 4 in 10 adults are reported to have ≥2 chronic conditions [1]. The prevalence statistics of these individual conditions, which include diabetes, heart disease, and stroke, present an even more disturbing picture; for example, diabetes affects 12.2% of the overall American adult population and 25.25% of the population aged >65 years [1,2]. Similarly, approximately 1 in 3 deaths in the United States are attributed to heart disease, stroke, and other cardiovascular diseases [3]. In 2020, the CDC identified chronic diseases as the leading causes of death and disability as well as the leading drivers of annual health care costs of US $3.5 trillion [1].

Although physical disabilities increase the risk of developing chronic conditions, the inverse also occurs [4,5]. In fact, chronic conditions are the leading causes of disability [1]; for example, a report on the top causes of disability among adults in the United States found arthritis, heart conditions, and diabetes among the top 6 causes of disability [6]. This bidirectional relationship between disabilities and chronic conditions is indeed well documented. Diabetes is associated with a substantial increase in the risk of mobility disability [4]. Among older participants with diabetes (aged ≥60 years), diabetes was correlated with a 2- to 3-fold increased odds of not being able to perform each task of walking one-fourth of a mile, climbing stairs, or doing housework among both men and women [2]. In brief, chronic conditions and disability exist in a tightly knit closed loop, with the onset of any of these factors exposing the individual to increased risk for the other.

Current science has enabled multiple approaches to managing chronic disease conditions [7,8]. Approximately two-thirds of chronic disease management is conducted in primary care settings globally, whereas approximately one-fifth is conducted in community-based settings [9]. An extensive review of 145 chronic disease management studies notes that self-management support is the most frequently used intervention approach and the most effective strategy [7]. A meta-analysis specifically focused on chronic disease self-management strategies for diabetes, hypertension, and osteoarthritis spanning 53 randomized controlled trials concludes that these programs are indeed effective for people with diabetes or hypertension [10].

Within these programs, multiple approaches have been used to implement self-management programs. Health coaching is one of the most common and cost-effective mechanisms of delivering self-management programming [11-13]. Health coaches are health care professionals who are trained in relevant areas of focus based on the disease or condition being managed. Positive aspects of health coaching include removal of barriers and increased retention with human interactions that support individualized interventions. Health coaching can be conducted either synchronously or asynchronously, which further allows individualization to meet participant needs. However, health coaching has 2 challenges—resources and availability of time spent with participants—both of which affect the scalability of health coaching [14]. In addition to health coaching, gaming features incorporated into telehealth interventions have the capability to promote adherence and compliance and warrant adoption in disability-related self-management programs. Such features include obtaining points, participating in challenges or competitions, social communication, and person-centered customizations such as avatars. There is broad appeal to incorporating gaming elements into self-management programs for individuals with physical disabilities [15].

Although self-management programs are effective for behavior change in managing health conditions, individuals with physical disabilities who also experience chronic conditions lack inclusive and accessible self-management programming to positively affect their own behavior change. People with disabilities experience barriers that are different from those experienced by people without physical disabilities, including nutritional and dietary concerns, as well as barriers to physical activity (PA) participation. More specifically, these barriers include lack of accessible environments, appropriate equipment (eg, wheelchair accessibility), and low health literacy and knowledge [16-19]. As there are few studies evaluating the impact of self-management programs on individuals with physical disabilities, there is a demand to provide and optimize holistic self-management programming to those with physical disabilities who also experience chronic conditions.

In the goal to improve chronic disease management for people with disabilities, we propose the development of an inclusive telecoaching self-management program. To make the telecoaching approach sustainable and scalable, artificial intelligence techniques are used to reduce the time that health coaches spend communicating with each participant.

Objectives

This study is structured to serve as the optimization phase of the multiphase optimization strategy (MOST) framework and involves efficient randomized experimentation to estimate the effectiveness of individual intervention components and identify the optimal intervention package to improve the primary outcome, health-related quality of life after 6 months [20,21]. We will specifically focus on the physical functioning and emotional well-being subscale scores. The feasibility and acceptability of the My Health, My Life, My Way intervention will also be studied. This study protocol has been developed by using the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2013 statement [22]. It has been registered at ClinicalTrials.gov (NCT05481593).

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Methods

Study Overview

Coaching Calls

Telehealth programs provide several advantages for individuals who want to improve their overall health and promote positive behavior change [23]. A substantial advantage of such programs is scalability or widespread availability, which allows participants to engage domestically or internationally. Many of these programs use human-to-human interactions to deliver web-based content to their clients or patients. In addition, some programs now implement artificial intelligence in conjunction with human interactions; for example, certain health care industries use chatbots to provide satisfactory and engaging interactions. A chatbot is a software platform that mimics human interaction with individuals using text or voice capabilities across different technologies, such as computers and smartphones. Within the literature, there is an acceptable level of satisfaction with using chatbot technology [24,25]. Because of the perceived benefits of telehealth programs using human interactions as well as web-based chatbots, it is necessary to evaluate whether scheduling coaching calls are necessary for successful self-management of chronic conditions. Each study arm in this project will incorporate either scheduled coaching calls or no scheduled coaching calls. Those receiving scheduled coaching calls will receive weekly calls with trained health coaches. Although individuals not receiving coaching calls will not have regular contact with a health coach, these participants can still contact health coaches using texting, chatting, or calling to initiate on-demand communication with the health coaching team.

Gamification

Gaming technologies have displayed a high level of adherence and engagement characteristics, and this has led to the gamification of telehealth interventions. Gamification refers to the use of game design elements in nongame contexts and is being used across a variety of telehealth interventions to promote treatment adherence [15]. Within telehealth intervention, gamification elements provide immediate feedback, continuous progress reporting, points, badges, levels, challenges, competitive components, and avatar and profile functionality [15]. There is a broad appeal to including gamification elements in telehealth studies for multiple reasons, such as (1) supporting transition to increased levels of intrinsic motivation, (2) deliverability through multiple technology streams, (3) appeal across different audiences, and (4) appeal in health and fitness industries [15]. However, the impact of gamification features on redeemable rewards is unclear [26]. More specifically, it is unknown how individuals' intrinsic motivation will be affected by redeemable rewards. Within this study, participants will receive either gamified rewards or flat rewards. For those receiving gamified rewards, there will be an increase in the number of redeemable points the longer adherence and participation are maintained. Those receiving flat rewards will receive a fixed number of points for regular participation in the intervention. Elements of participation include but are not limited to logging in to the platform, interacting with the educational content, and watching multimedia content. These variations in rewards will inform whether gamification features alone promote a shift from extrinsic to more intrinsic motivation and whether this is associated with increased adherence and engagement or whether financial incentives are necessary to promote study adherence.

MOST Framework

Telehealth intervention studies typically use randomized controlled trial designs. However, telehealth interventions are comprehensive packages that include components such as coaching calls, educational content, texting, email, and mobile apps. Randomized controlled trials fail to reveal which components are responsible for any behavior change elicited during the intervention; rather, they only show whether the intervention package as a whole had any effect. Therefore, it is necessary to know which elements of telehealth interventions are needed or should be removed for a more efficient telehealth intervention. To optimize the My Health, My Life, My Way program, the MOST framework will be used to assess which study elements (coaching calls and gamification) elicit behavior change. The MOST framework, derived from engineering principles, is an efficient method to gather information on each intervention component or package and investigate whether the presence or absence of a component has an impact on the performance of other components [20,21,27]. Within this study, we will assess coaching calls (scheduled or on demand) and gamification (scaled rewards or flat rewards).

Intervention Design

The My Health, My Life, My Way study is a 2 × 2 randomized factorial experiment. By using the MOST framework, we can evaluate the effectiveness of different combinations of features within the My Health, My Life, My Way program, such as fixed versus gamified rewards and scheduled versus on-demand coaching calls. Eligible participants will be randomly assigned to one of four groups: (1) scheduled coaching calls with gamified rewards, (2) scheduled coaching calls with rewards independent of gamification, (3) no scheduled coaching calls with gamified rewards, and (4) no scheduled coaching calls with rewards independent of gamification (Table 1). For the study, 4 weeks is considered a month, thereby making the study duration 24 weeks. Study activities involving participants with disabilities will be conducted primarily on the web nationally in the United States.

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Table 1. Research design.

Gamified rewards	Coaching calls	
	Scheduled coaching calls	No scheduled coaching calls
Gamification-based rewards	Scheduled coaching calls with gamified rewards	No scheduled coaching calls with gamified rewards
Rewards independent of gamification	Scheduled coaching calls with rewards independent of gamification	No scheduled coaching calls with rewards independent of gamification

Sample Size

We will use a 2 × 2 factorial design for this MOST trial (detailed in the Intervention Design subsection). Our sample size and power calculations for the primary outcome (health-related quality of life) assume an overall 2-sided type I error rate of 5%, 80% power, and an analysis of covariance–based approach with 2 independent dichotomous factors (ie, each factor has 2 levels). We will assume an attrition rate of 20%, with 160 (80%) participants completing the study (referred to as completers) from 200 participants enrolled. Under these assumptions, we will have 80% power to detect at least a minimally detectable difference (Cohen *d*) of 0.36 for the main effect or 0.18 in terms of the standardized regression coefficient. In these calculations, we assume a conservative correlation of 0.6 between the baseline covariate and outcome, which is similar to that in a previous study by Froehlich-Grobe et al [4]. In addition, 12 participants will be enrolled for pilot-testing the My Health, My Life, My Way program [28].

Recruitment

Recruitment will be conducted on the web nationally through the National Center on Health, Physical Activity and Disability (NCHPAD) website and its associated social media. The NCHPAD website has approximately 45,000 site visits per month, with most of the internet traffic flowing from the United States (74%). Through these mechanisms, interested individuals will be directed to a website landing page that will have promotional media content and information about the study. From here, participants will be directed to a separate link through the Health Insurance Portability and Accountability Act (HIPAA)–compliant REDCap (Research Electronic Data Capture; Vanderbilt University) platform [29,30] and complete a screening eligibility form. If deemed eligible, the participants will be sent an electronic consent form to be completed using REDCap. On the basis of our recruitment methods, we expect that approximately 400 individuals will be screened for eligibility.

Allocation

Participants will be randomized into 1 of 4 study arms in a 1:1:1:1 allocation ratio using a computer-generated randomization procedure. The allocation sequence will be implemented after the baseline survey is completed. The computer-generated randomization process will be implemented in REDCap after the data from the baseline survey are completed using REDCap. This will trigger the allocation procedure to randomly assign participants to 1 of the 4 study arms. The health coach will be notified about the randomization through the telecoaching dashboard and will inform the participants about their randomization into the My Health, My Life, My Way intervention or the attention control arm during the orientation call.

Blinding (Masking)

The principal investigator and primary statistician will be blinded to the randomization of the participants into the study arms. All other study staff will be unblinded for purposes of recruitment, consent, orientation calls, welcome calls, and coaching calls. There are no circumstances in which the principal investigator or statistician will become unblinded during this protocol.

Eligibility Criteria

Eligible participants must meet the following inclusion criteria: (1) aged ≥18 years; (2) self-reported diagnosis of heart disease, chronic lung disease, hypertension, or type 2 diabetes; (3) living with a permanent physical disability such as spinal cord injury, spina bifida, multiple sclerosis, or stroke; (4) speak and read English; and (5) availability of a smartphone or computer. To screen for permanently impaired mobility, we will use the National Health and Nutrition Examination Survey (NHANES; physical functioning) [31].

The exclusion criteria are as follows: (1) current enrollment in any structured intervention, (2) severe cognitive impairment, (3) major cardiac event in the past 12 months, (4) resting tachycardia, (5) renal failure, (6) severe peripheral neuropathy, (7) active treatment for cancer in the past 12 months, and (8) having both visual and hearing impairments (either is acceptable).

Participant Timelines and Intervention Duration

The study duration for those enrolled in the study will be 6 months (24 weeks), regardless of study arm allocation. Participants assigned to groups with scheduled coaching calls will receive scheduled weekly coaching calls. Those assigned to a group without scheduled coaching calls will have access to health coaches during the study and be able to communicate with the health coaches as needed.

Study Survey Packets

After enrolling in the study, participants will automatically be electronically delivered a REDCap link to a survey packet. This survey packet will include demographics and outcome measures (Table 2). Participants will be asked to complete this survey packet 3 times during the 6-month study period (excluding the demographics in the first survey packet). The surveys should take approximately 20 minutes to complete at each time point. The time points include baseline, 3 months, and 6 months.

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Table 2. Measures of effectiveness.

Variables[a]	Instruments	Time points
Health-related quality of life	Enabled version of 36-item Short Form Health Survey (primary outcome)	Baseline, 3 months, and 6 months
Physical activity	Godin Leisure-Time Exercise Questionnaire	Baseline, 3 months, and 6 months
Physical activity	Minutes, steps, and related data from Fitbit	Continuous
SE[b] for managing symptoms	PROMIS[c] Item Bank v1.0–Self-Efficacy for Managing Chronic Conditions–Managing Symptoms–Short Form 4a	Baseline, 3 months, and 6 months
SE for managing daily activities	PROMIS Item Bank v1.0–Self-Efficacy for Chronic Conditions–Managing Daily Activities–Short Form 4a	Baseline, 3 months, and 6 months
SE for managing sleep disturbance	PROMIS Item Bank v1.0–Sleep Disturbance–Short Form 4a	Baseline, 3 months, and 6 months
Psychosocial Illness	PROMIS Item Bank v1.0–Psychosocial Illness Impact-Positive–Short Form 8a	Baseline, 3 months, and 6 months
SE for managing emotions	PROMIS Item Bank v1.0–Self-Efficacy for Managing Chronic Conditions–Managing Emotions–Short Form 4a	Baseline, 3 months, and 6 months
SE for managing social interactions	PROMIS Item Bank v1.0–Self-Efficacy for Managing Chronic Conditions–Managing Social Interactions–Short Form 4a	Baseline, 3 months, and 6 months
Emotional distress	PROMIS Item Bank v1.0–Emotional Distress-Depression–Short Form 4a	Baseline, 3 months, and 6 months
SE for managing medications and treatments	PROMIS Item Bank v1.0–Self-Efficacy for Managing Chronic Conditions–Managing Medication and Treatment–Short Form 4a	Baseline, 3 months, and 6 months
SE for managing sleep-related impairments	PROMIS Short Form v1.0–Sleep-Related Impairment–Short Form 4a	Baseline, 3 months, and 6 months
Dietary intake	Short Healthy Eating Index	Baseline, 3 months, and 6 months
Medication adherence	Medication Adherence Rating Scale and Beliefs About Medication Questionnaire	Baseline, 3 months, and 6 months
Usability	Health Information Usability Evaluation Scale and System Usability Scale	Three months and 6 months

[a]In addition to the variables listed in the table, primary care visits, pharmacy visits, physical therapy and occupational therapy visits, emergency visits, and hospitalizations in the last 3 months (self-reported) will also be taken into account.

[b]SE: self-efficacy.

[c]PROMIS: Patient-Reported Outcomes Measurement Information System.

Welcome Call

After the first survey packet is electronically delivered to participants, study team members will contact the participants by telephone. The purpose of this call is to welcome them into the program and explain the program elements. During the call, the staff will inform the participants that they will receive a technology package in the upcoming days.

Randomization

A randomization sequence will be generated and stored within REDCap, which assigns a participant to 1 of the 4 study arms of the My Health, My Life, My Way study. Randomization will occur only after the baseline survey packet is complete.

Overview of the Intervention

Orientation Call

After the welcome call and randomization, a study health coach will be notified through REDCap that a participant has been randomized to one of the study arms and will conduct an orientation call with the participant. The purpose of this call by the health coach is to introduce themselves to the participants as their primary health coach and to schedule the first weekly coaching call. For those not receiving scheduled coaching calls, the health coach will inform participants that they can contact the coaching staff during the study to ask questions related to the educational content provided on the platform.

Intervention Package

All participants, regardless of study arm allocation, will receive an intervention package that will include a PA tracker (Fitbit; Google LLC) and access to a telehealth platform. The Fitbit tracker will be shipped to the participants after randomization. The telehealth platform will be a central location for educational content (videos, articles, etc) for participants to access during the study. Those with conversational agents (eg, Amazon Echo) will be provided access to a My Health, My Life, My Way specific program that can operate with their home device. This package will be used for intervention delivery and not for outcome measurements.

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Educational Content and Health Coaching for the Study Arms

The study arms for the My Health, My Life, My Way study with the coaching calls for all groups will be guided by a prepared outline of inclusive educational content that will be delivered to the participants through the telehealth platform. This content will be delivered at the beginning of each week. The educational content will be created and adapted for individuals with physical disabilities by experts and delivered to the participants as multimedia content. There will be generalized educational content applicable to all participants. On the basis of a specific physical disability as well as specific health conditions, education-specific content will be tailored to each individual. For those receiving scheduled coaching calls, the content discussed will include nutrition and eating habits, exercise and PA, and medication adherence. Questions outside the scope of the health coaching content will be dealt with by the study clinician. If the study team determines that the questions indicate that it is necessary to collect a participant's detailed medical profile, the participant will be guided to communicate with their primary care physician. Finally, the health coach will address other health-related questions that the participant may have. For each call, the health coach will be able to record notes on the telehealth platform regarding topics discussed with the participant for future calls, as needed.

Telehealth Platform

The My Health, My Life, My Way telehealth platform will be used by participants throughout the duration of the study. On the platform, participants will be able to access educational multimedia content (videos and articles), track and log medication use, create and track health-related goals, and access food- and nutrition-related information. In addition, participants will be able to view upcoming health coaching calls and contact the health coaching team using the messaging feature of the platform.

Participant Study Activities

Gamification Component

All participants, regardless of gamification variation, will be able to obtain points and badges on the platform. Participants can check their points status at any time during the study by logging in to the platform to view an itemized list for all badges and points. In addition, participants will be provided email notifications for all gamification updates. All activities, such as viewing and reading educational content and logging in to the platform, will automatically be updated on the platform. Health coaches will encourage participants to engage on the platform regularly. Those not receiving scheduled coaching calls who exercise the on-demand coaching option will be encouraged by a health coach to use the platform regularly.

Health Coaching Component

Those receiving scheduled health coaching calls will be able to view upcoming calls on the platform. In addition, email and SMS text messaging notifications will be provided to remind participants of all scheduled coaching calls. Scheduled coaching calls will occur once per week and are expected to last up to 60 minutes. Those who will not receive scheduled coaching calls will still have access to the study platform. Within the platform, participants will be able to contact health coaching staff if they desire on-demand coaching. With this on-demand coaching function, participants can discuss any questions regarding educational content on the platform.

Exit Interviews

After the study duration, up to 30 participants from the My Health, My Life, My Way program will be contacted for a follow-up interview to obtain their experiences and feedback with the My Health, My Life, My Way telehealth platform. These interviews will be conducted on the web.

Data Collection Methods

Outcome Measures

Primary and secondary outcome measures will be assessed at baseline, 3 months, and 6 months (after the intervention). The primary clinical outcome measure is health-related quality of life; the secondary outcome measures are described in Table 2 along with the primary outcome measure.

Health-Related Quality of Life

The primary outcome measure is health-related quality of life. This will be measured by using the 36-item Short Form Health Survey, enabled version (SF-36E). More specifically, the physical functioning section of the SF-36E has been modified, which uses disability-friendly inclusive language for individuals with mobility impairments [4].

All other measures, including demographic data and secondary outcome measures, will be retrieved and automatically stored through electronic surveys delivered by REDCap. All self-reported items within the questionnaires will be mandatory to prevent missing data. The questionnaire packet will be delivered electronically to the participants during the study.

PA Measurements

To measure PA, participants will complete the Godin Leisure-Time Exercise Questionnaire. This 3-item questionnaire asks questions related to strenuous, moderate, and light exercises performed during the past 7 days [32]. In addition, activity counts and time spent in PA will be collected from the participant's Fitbit device.

Self-efficacy for Managing Symptoms

Participants will complete the Patient-Reported Outcomes Measurement Information System (PROMIS) Item Bank v1.0–Self-Efficacy for Managing Chronic Conditions–Managing Symptoms–Short Form 4a, which is a 4-item survey that assesses confidence in managing symptoms associated with their chronic health condition [33].

Self-efficacy for Managing Daily Activities

To assess confidence in handling daily activities, participants will complete the 4-item PROMIS Item Bank v1.0–Self-Efficacy for Chronic Conditions–Managing Daily Activities–Short Form 4a [33].

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Self-efficacy for Managing Sleep Disturbances

Participants will complete the PROMIS Item Bank v1.0–Sleep Disturbance–Short Form 4a, which is a 4-item survey that evaluates sleeping habits during the previous 7 days [33].

Psychosocial Illness

To assess self-efficacy for managing psychosocial illness, participants will complete the PROMIS Psychosocial Illness Impact-Positive–Short Form 8a [33]. This questionnaire includes 8 items that evaluate psychosocial illness before and after an illness.

Self-efficacy for Managing Emotions

To assess the ability to manage emotions, participants will complete the PROMIS Item Bank v1.0–Self-Efficacy for Managing Chronic Conditions–Managing Emotions–Short Form 4a [33]. This survey includes 4 items regarding the ability to manage emotions while experiencing chronic health conditions.

Self-efficacy for Managing Social Interactions

Participants will complete the PROMIS Item Bank v1.0–Self-Efficacy for Managing Chronic Conditions–Managing Social Interactions–Short Form 4a [33]. This 4-item survey will assess an individual's perceived ability to engage in meaningful social interactions.

Emotional Distress

To assess self-efficacy for managing depression, participants will complete the PROMIS Item Bank v1.0–Emotional Distress-Depression–Short Form 4a [33]. This survey includes 4 questions about participants' emotions within the past week.

Self-efficacy for Managing Medications and Treatment

To assess confidence in managing medications and treatment, participants will complete the 4-item PROMIS Item Bank v1.0–Self-Efficacy for Managing Chronic Conditions–Managing Medications and Treatment–Short Form 4a [33].

Self-efficacy for Managing Sleep-Related Impairments

Participants will complete the PROMIS Short Form v1.0–Sleep-Related Impairment 4a to evaluate overall sleep quality during the previous 7-day period [33].

Dietary Intake

Participants will complete the Short Healthy Eating Index (sHEI) survey, which is a 23-item survey that evaluates nutritional habits, such as fruit and vegetable consumption, water intake, and sugar consumption [34].

Medication Adherence

To measure medication adherence, participants will complete the Medication Adherence Rating Scale (MARS). The MARS is a general, 10-item binary questionnaire that asks questions related to regularly taking medication [35]. Medication adherence will also be measured using the Beliefs About Medication Questionnaire (BMQ). The BMQ is an 18-item questionnaire that includes Likert-style questions regarding personal beliefs about how medications influence daily living [36].

Telehealth Dashboard Usability

To measure the usability of the telehealth dashboard, participants will complete the System Usability Scale (SUS) and the Health Information Technology Usability Evaluation Scale (Health-ITUES). These Likert scales include items asking about the dashboard's effectiveness (ability to complete tasks), efficiency (level of dashboard use), and satisfaction (subjective reactions to the dashboard) [37,38].

Medication and Dosage

Participants will be asked to provide current medications and dosages throughout the study duration to control medication data during the statistical analysis.

Feasibility Measures

This study will obtain measures related to the feasibility and acceptability of the My Health, My Life, My Way intervention on self-management for individuals with disabilities who also experience chronic conditions. Measures will include process, resource, scientific, and management feasibility outcomes. All elements of intervention delivery will be collected, including but not limited to adherence, retention, attrition, coach and participant communication needs, staff preparation, and adverse events. Obtaining these measures will inform future considerations in the delivery of a web-based self-management program for people with disabilities.

Data Management

All data collected will be entered directly into REDCap and stored. Participants will be assigned a participant number upon enrollment in the study. Only approved study personnel will have access to the REDCap program, where data will be stored. Data checking will involve confirming that surveys, questionnaires, and health coaching calls are completed.

Statistical Methods

All statistical analyses will be conducted in an intent-to-treat manner at the individual level taking into account the correlated nature of data (multiple time points for every participant). Statistical significance will be evaluated at a type I error rate of 5%. Quality control will include descriptive and graphical approaches to summarize baseline characteristics of all key variables. With respect to data, we will begin by systematically cleaning and verifying all collected data, as well as examining ranges, missing values, and provenance. The significance tests conducted for the primary outcome are all specified a priori and modest in number. Consistent with published guidelines for statistical reporting, exact *P* values (rather than, eg, "$P<.05$" or "NS" [not significant]) will be reported [39]. This allows readers who may have their own opinions about multiple testing corrections, configurations of a family of hypotheses, and costs of type I errors to set the significance level to know the raw, uncorrected result and make their own judgments about statistical significance [40,41]. As Saville [42] noted, in multiple comparison issues, there is no right answer, and each investigator must ultimately "cut the Gordian knot" themselves. To evaluate the potential systematic variation among the study arms, key variables such as age, race, sex, disability type, and physical function at baseline will be examined and compared

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for relationships with study arms. If a potential confounder is found to differ meaningfully among the groups and if we find that the inclusion of the covariate improves the corrected Akaike information criterion (AIC), it will be included as a covariate in our analyses. We will estimate and test the effects of the 4 individual intervention components by means of a full factorial experiment. First, we will fit a linear mixed model to account for correlated data, to check whether each factor has a significant effect on outcome change across the time points (baseline and 6 months). For each of the 2 components, we will determine whether there is a difference in change across time using baseline as the reference cell (ie, 6 months vs baseline). This would be considered the main effect of each component on the pre-post difference. However, statistically, these effects will be modeled as component-by-time interactions, with the 6-month outcome as the primary end point. We will also include interactions among the components (eg, factor 1 × factor 2 × time interaction). In terms of multiple testing, given that this is a pilot project (ie, an exploratory and not confirmatory trial), we will estimate the false discovery rate and false discovery proportion based on the *P* values for all outcomes.

Our 3-pronged approach involves minimizing missing data, leveraging the maximum likelihood–based approach or the multiple imputation approach under the assumptions of ignorability (ie, missing-at-random [MAR] assumption), and conducting multiple sensitivity analyses assuming MAR as well as missing not at random [43,44]. Analytically, our choice of mixed models to account for the repeated nature of the data will allow us to handle missing data for the primary and secondary outcomes under the assumptions of MAR. The MAR mechanism is ignorable when mild regularity conditions are satisfied. Such inferences can proceed by analyzing the observed data only, without explicitly addressing a form of the MAR mechanism. Missing data in other independent variables (mediators or other covariates) will be handled through the expectation-maximization algorithm coupled with bootstrapping for SEs, which will give maximum likelihood–based imputation under the MAR assumption [43].

Data Monitoring

This project is a pilot feasibility and efficacy study that has a duration of 6 months and only involves minimal risks. Therefore, we believe that a data monitoring committee is not necessary. The principal investigator will be responsible for protocol fidelity and data collection throughout the study. The biostatistician will oversee data analysis in preparation for publication.

Harms

The My Health, My Life, My Way study will monitor all adverse events. Adverse events will be assessed for severity and causality and reported to the institutional review board and all other relevant regulatory bodies as needed.

Auditing

All elements of the study protocol will be evaluated at regular intervals (ie, weekly, monthly, or quarterly) to ensure proper and consistent adherence to the study design and implementation. Elements of auditing will include checklists; coaching call logs; audio recordings or coaching calls; content resource banks; telehealth platform reviews and event logs; review of participant food, PA, and medication, as well as time spent on the platform and in regular team meetings to discuss participant progress; educational content provided during health coaching calls; and protocol adherence.

Protocol Amendments

Any protocol changes deemed necessary by the principal investigator or study team will be submitted as amendments to the university's institutional review board, and we will only apply changes after approval.

Ethics Approval

This protocol has been approved by the institutional review board of the University of Alabama at Birmingham (IRB-300009485).

Consent or Assent

All consent processes will be conducted on the web through predetermined screening questionnaires provided through the website landing page and REDCap link. If a participant is deemed eligible through the web-based process, an electronic consent form will be sent to the participant to complete. Only approved study staff will have access to completed records of the consent form.

Confidentiality

Personal information will be collected in this study. All personal information shared, such as demographic details, will be collected and stored through REDCap. Only approved study staff will have access to securely stored personal information. All information will be subject to the university's institutional review board and the policies of affiliated entities surrounding confidentiality.

Results

Overview

The My Health, My Life, My Way protocol was funded in September 2020 and has been approved by the university's institutional review board and registered at ClinicalTrials.gov (NCT05481593). The telehealth platform (dashboard and educational content) and website landing page are being developed by the study technical support team. Research personnel are developing the database (REDCap) that will store data and communication mechanisms (ie, emails and SMS text messaging notifications). We project that enrollment for the study will begin in May 2023, with data analysis being completed within 6 months of completing data collection.

Dissemination Policy

The results of this study will be disseminated publicly through publication in peer-reviewed journals and presented at regional and national conferences.

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Discussion

Many Important Implications

The aim of this paper was to detail the study protocol used to develop a web-based self-management program for individuals with physical disabilities who also experience chronic conditions by using artificial intelligence techniques. The incorporation of variations in coaching calls and gamification will be evaluated to determine which combination of intervention components is the most effective for personal self-management. As the My Health, My Life, My Way program will be implementing a 4-arm protocol using the MOST design, many important implications can be drawn based on the findings of this study. The findings will assess what resources are required by self-management programs to maintain high levels of adherence and engagement. For coaching calls, if scheduled coaching calls are not as effective at promoting self-management as on-demand coaching calls, this would result in a reduced demand for excess resources, including the number of health coaches, monetary expenses, training, and daily availability of health coaches. If scheduled coaching calls are shown to be more effective than on-demand coaching calls, future web-based self-management programs should consider bolstering the resources to provide appropriate health coaching with qualified health coaches. Within the gamification context, the results from this study will inform future programming for individuals with physical disabilities who also experience chronic conditions. If gamified rewards are shown to be more effective than the fixed rewards model, self-management programs should consider using appropriate methods to promote extrinsic motivation by providing desirable incentives for behavior change. If fixed rewards are shown to be more effective than gamified rewards, this could indicate that a participant's intrinsic motivation to improve their self-management is more important than extrinsic rewards such as redeeming increasing monetary incentives to promote behavior change.

As multiple barriers hinder a person's ability to successfully manage chronic conditions, My Health, My Life, My Way aims to create a sustainable, scalable, accessible, implementable, sustainable, and inclusive self-management program for people with disabilities, which currently does not exist. This study will examine the feasibility and preliminary efficacy of My Health, My Life, My Way for individuals with physical disabilities who also experience chronic conditions using mobile apps and web-based applications, telehealth coaching sessions, and educational multimedia material. As part of the development process of My Health, My Life, My Way, we have conducted extensive focus groups with stakeholders with physical disabilities who also experience chronic conditions to obtain their perspectives on the proposed program and plan to implement relevant changes during further development. In addition, in line with the protocol, My Health, My Life, My Way is built upon a prior protocol evaluating the effectiveness of a web-based diabetes management program for individuals with physical disabilities [45]. The My Health, My Life, My Way study will also focus on quality-of-life measures during the intervention and will include qualitative interviews conducted after the intervention to provide a holistic evaluation of the program as a viable mode for self-management of chronic conditions. Next, to reduce barriers experienced by people with disabilities, the My Health, My Life, My Way program will be conducted completely on the web, with all coaching sessions taking place over the telephone, thereby allowing all participants to engage in the program and manage their health conditions in a home environment.

Limitations and Strengths

This protocol includes limitations. First, we are using self-reported measures to collect data on participant perceptions about their physical and mental health. Therefore, we are relying on participants' responses to be truthful when they answer all the surveys. The surveys we will use in this study have been shown to be reliable and valid in assessing physical and mental health outcomes. Second, My Health, My Life, My Way is using a web-based platform that participants will use to access multimedia content; therefore, those without internet capabilities will be unable to participate.

This study will add to the current literature to improve the quality of web-based self-management programs. In addition, not only will My Health, My Life, My Way determine how coaching calls and gamification variations affect behavior, but this program is also designed to be inclusive for those who experience physical disabilities, considered an underserved population. Finally, the findings from this study will inform how future self-management programs can be created and tailored to populations consisting of individuals with disabilities.

Acknowledgments

This study was funded by the National Institute on Disability, Independent Living, and Rehabilitation Research (90DPGE0017).

Data Availability

The data generated or analyzed during the study will be available from the corresponding author on reasonable request.

Authors' Contributions

EE, AZ, and MT contributed substantially to the conception and design of the work, drafted and revised the manuscript critically for important intellectual content, were responsible for the final approval of the version to be published, and agree to be accountable for all aspects of the work. AK, AW, TM, and AC were responsible for the design and analysis of the work, revised the work

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critically for important intellectual content and for final approval of the version to be published, and agree to be accountable for all aspects of the work.

Conflicts of Interest

TM has received consulting fees from The Obesity Society, PLOS One, and Novo Nordisk.

Multimedia Appendix 1
Peer-review report by the National Institute on Disability, Independent Living, and Rehabilitation Research (NIDILRR) - Disability and Rehabilitation Research Program (DRRP) (Washington, DC).
[PDF File (Adobe PDF File), 374 KB - resprot_v12i1e31694_app1.pdf]

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Abbreviations

AIC: Akaike information criterion
BMQ: Beliefs About Medication Questionnaire
CDC: Centers for Disease Control and Prevention
Health-ITUES: Health Information Technology Usability Evaluation Scale
HIPAA: Health Insurance Portability and Accountability Act
MAR: missing at random
MARS: Medication Adherence Rating Scale
MOST: multiphase optimization strategy
NCHPAD: National Center on Health, Physical Activity and Disability
NHANES: National Health and Nutrition Examination Survey
PA: physical activity
PROMIS: Patient-Reported Outcomes Measurement Information System
REDCap: Research Electronic Data Capture
SF-36E: 36-item Short Form Health Survey, enabled version
sHEI: Short Healthy Eating Index
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
SUS: System Usability Scale

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Protocol

Sensor-Controlled Digital Game for Heart Failure Self-management: Protocol for a Randomized Controlled Trial

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Abstract

Background: Heart failure (HF) is the leading cause of hospitalization among older adults in the United States. There are substantial racial and geographic disparities in HF outcomes, with patients living in southern US states having a mortality rate 69% higher than the national average. Self-management behaviors, particularly daily weight monitoring and physical activity, are extremely important in improving HF outcomes; however, patients typically have particularly low adherence to these behaviors. With the rise of digital technologies to improve health outcomes and motivate health behaviors, sensor-controlled digital games (SCDGs) have become a promising approach. SCDGs, which leverage sensor-connected technologies, offer the benefits of being portable and scalable and allowing for continuous observation and motivation of health behaviors in their real-world contexts. They are also becoming increasingly popular among older adults and offer an immersive and accessible way to measure self-management behaviors and improve adherence. No SCDGs have been designed for older adults or evaluated to test their outcomes.

Objective: This randomized clinical trial aims to assess the efficacy of a SCDG in integrating the behavioral data of participants with HF from weight scale and activity tracker sensors to activate game progress, rewards, and feedback and, ultimately, to improve adherence to important self-management behaviors.

Methods: A total of 200 participants with HF, aged ≥45 years, will be recruited and randomized into 2 groups: the SCDG playing group (intervention group) and sensor-only group (control group). Both groups will receive a weight scale, physical activity tracker, and accompanying app, whereas only the intervention group will play the SCDG. This design, thereby, assesses the contributions of the game. All participants will complete a baseline survey as well as posttests at 6 and 12 weeks to assess the immediate effect of the intervention. They will also complete a third posttest at 24 weeks to assess the maintenance of behavioral changes. Efficacy and benefits will be assessed by measuring improvements in HF-related proximal outcomes (self-management behaviors of daily weight monitoring and physical activity) and distal outcomes (HF hospitalization, quality of life, and functional status) between baseline and weeks 6, 12, and 24. The primary outcome measured will be days with weight monitoring, for which this design provides at least 80% power to detect differences between the 2 groups.

Results: Recruitment began in the fall of 2022, and the first patient was enrolled in the study on November 7, 2022. Recruitment of the last participant is expected in quarter 1 of 2025. Publication of complete results and data from this study is expected in 2026.

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Conclusions: This project will generate insight and guidance for scalable and easy-to-use digital gaming solutions to motivate persistent adherence to HF self-management behaviors and improve health outcomes among individuals with HF.

Trial Registration: ClinicalTrials.gov NCT05056129; https://clinicaltrials.gov/ct2/show/NCT05056129

International Registered Report Identifier (IRRID): DERR1-10.2196/45801

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KEYWORDS

heart failure; digital game; self-management; mobile phone; older adults

Introduction

Background

More than 6 million adults in the United States live with heart failure (HF), a condition that is the leading cause of hospitalization among older adults in the United States [1]. Despite substantial advances in treatment and management, the current estimated annual cost is US $32 billion, which is projected to rise to US $69 billion by 2030 [2]. There are major regional disparities among individuals diagnosed with HF in the southern United States, with a mortality rate 69% higher than the national average [3,4].

Self-management behaviors are important for patients with HF to help reduce serious adverse sequelae and outcomes [5]. For example, weight gain is an initial warning sign of volume overload in patients with HF; by monitoring their weight daily, patients may receive prompt treatment for their weight gain, which can help avoid clinically significant exacerbations (odds ratio 0.42, 95% CI 0.23-0.76) [6,7]. Similarly, physical activity is linked to clinically significant improvements, such as improved myocardial function (P=.02) and functional capacity (P<.001) [8] and reduced depressive symptoms [9]. By self-managing these 2 critical elements, patients with HF experienced improved quality of life (QoL) and reduced health care use and cost in high-quality research studies [10,11]. Conversely, poor HF self-management may delay recognition of severe HF symptoms and result in more frequent hospitalizations, impaired functional status, and poorer QoL [12].

Despite its importance, persistent adherence to critical self-management behaviors continues to remain a challenge for patients with HF [13,14]. Patients have poorer adherence to weight monitoring and physical activity than to other self-management behaviors [15]. Thus, there is a need for novel approaches to support and motivate patients with HF to self-manage these critical behaviors. Interventions that are remote, resource conservative, and can be used in home may help address the widening geographical [3,4] and racial [16] health disparities in HF outcomes. Wearable technologies, mobile health apps, and sensor devices offer substantial promise in that they are portable, scalable, and allow for continuous observation and motivation of health behaviors in real-world contexts. Despite these benefits, the adoption of these technologies is low; abandonment is common [17], and longitudinal studies, especially in the context of chronic health conditions, are rare. Although the potential of wearables and digital sensor technologies for HF to improve care and outcomes has been acknowledged [18] and proven [19,20], the studies exploring their use in practice have largely been limited in size and scale [21].

Objectives

One promising approach to increasing adherence to self-management behaviors in patients with HF is to leverage the use of digital technologies such as sensor-controlled digital games (SCDGs). SCDGs synchronize data on behaviors from sensors, such as wearable devices, with a mobile gaming app, allowing game progress, rewards, incentives, and personalized feedback (eg, reduce fluid intake or contact a physician) based on real-time contextual information (eg, weight gain or concerning symptoms) [22]. To promote change and its maintenance, SCDGs can also incorporate immersive stories [23], active learning [24], and social connections [25]. SCDGs are not only affordable, portable, and scalable, but they are also enjoyable and easy to use. Furthermore, prior research has indicated that they can also contextualize health behaviors [26], motivate behavioral changes, and improve health outcomes [27]. Thus, SCDGs offer an immersive and accessible way to objectively measure self-management behaviors and improve adherence [28]. Our previous research [29] conducting an SCDG intervention with 38 adults (aged ≥55 years) with HF from Texas and Oklahoma demonstrated improvements in weight monitoring and physical activity, and the intervention showed a high rate of acceptability (92%) from participants.

In this clinical trial, we have updated the SCDG intervention and will evaluate its efficacy for improving HF outcomes by integrating behavioral data of participants with HF from weight scale and activity tracker sensors to activate game progress, rewards, and feedback.

Methods

Study Design

This study is an efficacy clinical trial, using a prospective, 2-group randomized (1:1) controlled design in which an SCDG playing group with sensors and tracking apps (intervention group [IG]) will be compared with a sensor-only group (control group [CG]) that receives only the app that tracks weight monitoring and physical activity. In a sample of 200 individuals with HF, who are aged ≥45 years (n=100 per arm), benefits will be assessed by measuring improvements in HF-related proximal outcomes (self-management behaviors of daily weight monitoring and daily physical activity) and distal outcomes (HF hospitalization, QoL, and functional status) between baseline and weeks 6, 12, and 24. We will also apply mixed methods to

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assess IG and CG participants' perceptions of intervention and behavior adherence.

Study Setting

We will enroll 200 patients in this study, 100 each in the IG and CG. To recruit patients, we are contracting with Trialfacts [30], a web-based recruiting company. Participants will be recruited from 7 southern states of the United States to address prominent geographic health disparities in HF [3,4]. These states are Alabama, Arkansas, Georgia, Louisiana, Mississippi, Oklahoma, and Texas, where people experience higher HF rates than the rest of the country.

Eligibility Criteria

Participants must be aged ≥45 years (lifetime risk for HF is high for the age group of 45-95 years) [1]; have been hospitalized for HF in the last 12 months (to reduce the variance in recovery from a recent HF hospitalization); and be classified as class I, II, or III per the New York Heart Association's HF classes [31] (thus ensuring recruitment of those who would benefit the most from self-management interventions). They must also be fluent in English, able to pass a mini–cognitive screening assessment [32], and able to walk independently without using a walker or other assistance. Exclusion criteria include (1) having severe visual or tactile impairments (eg, legal blindness or severe arthritis), which might make using smartphones and sensor devices difficult; (2) having undergone a heart transplantation or implantation of a durable mechanical circulatory support device in the past; (3) having a history of renal failure (which adversely affects HF prognosis); or (4) being diagnosed with an end-stage or terminal illness (eg, cancer). The study is registered at ClinicalTrials.gov (NCT05056129).

Ethics Approval and Informed Consent

The protocol was approved by the Institutional Review Board of the University of Texas, Austin (STUDY00001438), on February 18, 2022. Informed consent will be obtained from all eligible participants through a phone call before baseline surveys are sent and data collection begins. After a member of the research team reads the consent form and solicits questions, participants will receive the consent form via email and be requested to provide their digitally signed consent form through the REDCap (Research Electronic Data Capture; Vanderbilt University) web-based survey database. Participants who prefer to sign a physical copy will be mailed a consent form. This approach will allow participants sufficient time to follow-up with questions and discuss the study with their family or friends before officially signing the consent form. Our team will make it clear to participants that they may decline to answer specific questions or terminate their involvement in the study at any time.

Enrollment and Randomization Procedures

Participants will be assigned to either the IG or CG through computer-automated randomization. These assignments will be stratified based on sex (male, female, or other) and age (45-64 years or ≥64 years) to ensure balance in the study design. The allocation sequence for permuted block randomization with random block sizes of 4 and 6 was created by a statistical analyst who is not connected to the participant enrollment process. The allocation sequence will be uploaded to REDCap, which will automatically assign the participants to groups when they are enrolled in the study. The research team will be blinded to assignment group or maintained in a way that ensures the separation of intervention implementation from evaluation, thus reducing any potential bias (eg, ascertainment bias) in the collection and analysis of outcome data. For example, data collectors will not be a part of the intervention delivery team. Similarly, participants will be blinded to their group assignment, as both groups use digital tools. All participants will be provided with the same informed consent form that includes general terms such as *digital health tools* to enable blinding of participants to their group assignment.

Intervention Description

The SCDG, which will be used by the IG in this study, is a smartphone app called Heart Health Mountain, which is available on both iOS and Android platforms. The design of the game was guided by behavioral change mechanisms using the concepts of motivation, ability, and trigger from the Fogg behavioral model and self-determination theoretical frameworks, as described in detail in a previous study [33]. This app has already been developed by a multidisciplinary team and tested through initial usability and feasibility studies and is described in detail elsewhere [28,29]. Several screenshots from the SCDG are pictured in Figure 1.

Figure 1. Screenshots from the different interfaces that make up the different levels within the sensor-controlled digital game.



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The SCDG fosters relatedness by involving a narrative, the goal of which is to help the game avatar avoid rehospitalization using game points, earned via the participants' demonstration of competence or ability in real-time behaviors, in game tasks that help maintain the avatar's optimal HF health status. The participants' real-time behaviors of weight monitoring and physical activity will be tracked by off-the-shelf sensors and an app (Withings Pulse HR tracker, Body scale, and Health Mate app; Withings app). The data from the Withings sensors will then be routed to our SCDG app.

The digital game paired with sensors will enable objective tracking of real-time behaviors such as physical activity and weight monitoring and provide personalized, contextually relevant feedback (eg, reduce fluid intake or call a physician for weight gain) as triggers to motivate engagement in and generate habit formation of HF-related self-management behaviors. The game is adaptive to real-time behaviors; for example, participants' step goals automatically adapt each week to encourage a tolerable physical activity level based on a rank-ordered algorithm [34].

Control Description

The CG will use the same Withings devices over the same period but will not have access to the SCDG. Real-time behaviors of weight monitoring and physical activity will be tracked by the Withings Pulse heart rate tracker, Body scale, and Health Mate app. However, the data from the Withings sensors will not be routed to the SCDG. Instead, the CG will receive the same educational content that is presented in the SCDG in a paper format by mail. This study design feature will allow us to isolate the SCDG effect from the other features of behavioral motivation.

Remote Study Procedures

All research activities will be conducted at participants' homes. Participants will be directed to engage in research activities through remote means (email, phone call, or video calls). Participants will be asked to provide a convenient time for a research team member to contact them.

Participants in both the IG and CG will receive their Withings devices by mail, along with information on how to install the HealthMate app and connect the devices. The IG will also receive instructions on how to install the SCDG app (Table 1).

Table 1. Components of interventions received by the intervention group (IG) and control group (CG) participants.

Devices and apps	IG	CG
Withings weight scale and activity tracker	✓	✓
Withings HealthMate app for sensor data tracking	✓	✓
SCDG[a] app with progress of game, messages, and incentives tailored to participant's real-time HF[b] self-management behaviors	✓	
Standard evidence-based HF educational content [35,36] embedded in SCDG	✓	
Standard evidence-based HF educational content [35,36] provided in paper format		✓

[a]SCDG: sensor-controlled digital game.

[b]HF: heart failure.

Participants in both groups will receive remote training from a member of the study team on how to install and use the devices. This remote training (ie, over Zoom [Zoom Video Communications] or FaceTime [Apple iOS]) was also successfully provided in our feasibility study [29]. After 3 days, both the groups will receive a follow-up email from the interventionist to summarize participants' study tasks and provide contact information in case of troubleshooting needed while using the devices and apps.

Both groups will use the devices for 24 weeks. A dashboard was developed to track the time stamps of behavior data that were last synced by the participants to identify participants without any behavior data for >3 days. On a different page, the dashboard also shows the time stamps of the last time each participant in the IG opened the SCDG app. An unblinded team member aware of troubleshooting procedures and following a protocol to communicate similarly with participants in both groups will reach out to participants in both groups who have not had any behavior data from their devices synced in 3 days. This member would follow-up with participants in both groups daily for 3 business days. In case of no response, they will reach out to the alternative contact person listed by the participant.

Randomized Controlled Trial Data Collection

All the survey data will be collected using the REDCap web-based survey system. After completing the baseline survey, all participants will complete the first and second posttests at 6 and 12 weeks for assessment of the *immediate effect of the intervention* and will complete the *third* posttest at 24 weeks after the first week for assessment of the *maintenance of behavioral changes*. Survey links will be sent via text messages to participants at 4 time points through automated events programmed in the REDCap survey system. In addition, daily sensor data will be obtained from the Withings server, and the game playing data will be obtained from a backend server hosted on Amazon Web Services. The steps, weight, and game state data will also be stored in a MongoDB database. All variables will be measured at all follow-ups using the instruments described in detail in Table 2.

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Table 2. Data collected and operationally defined, with time points.

Variables	Instrument or measure	Time point (weeks)
Baseline characteristics		
Sociodemographic	Sociodemographic and Upstream Risk Questionnaire [37,38]	Baseline
Clinical	Hospital discharge summary (medications, comorbidities, and ejection fraction)	Baseline
Weight monitoring frequency in the past week	1-item question using Likert scale	Baseline
Depressive symptoms	Patient Health Questionnaire-2 [39,40][a,b]	Baseline and 6, 12, and 24
Ability		
HF[c] self-management knowledge	30-item Atlanta Heart Failure Knowledge Test (Cronbach α=.84) [41][d]	Baseline and 6, 12, and 24
HF self-efficacy	6-item Section C Self-Care of HF Index (Cronbach α=.88) [42][d]	Baseline and 6, 12, and 24
Trigger		
Engagement with SCDG[e] and features	Backend game state logs of IG[f] participants; Intrinsic Motivation Inventory [43] and Qualitative Interviews	6, 12, and 24; 12
Motivation or behavior outcomes		
Number of days of weight monitoring (primary)[g]	HealthMate app logs [44] in IG and CG[h]	6, 12, and 24
Daily physical activity steps	HealthMate app logs [44] in IG and CG	6, 12, and 24
Daily physical activity intensity (light, moderate, or intense)	HealthMate app logs [44] in IG and CG	6, 12, and 24
HF self-management behaviors	9-item European Heart Failure Self-care Behavior Scale (Cronbach α=.80) [45][b,d]	Baseline, 6, 12, and 24
Patient outcomes		
Functional status	23-item Kansas City Cardiomyopathy Questionnaire [46][b,d]; functional status (Cronbach α=.93) [46]; QoL[i] (Cronbach α=.78) [46]	Baseline and 6, 12, and 24
QoL	Participant self-report	Baseline and 6, 12, and 24
HF hospitalization	Participant self-report and confirmed through hospitalization discharge summary and health care provider	Baseline and 6, 12, and 24

[a]A total of 90% sensitivity in patients with HF and reliable prognostic prediction of mortality and rehospitalization.

[b]Established validity using correlation with other instruments or clinical ratings in known groups.

[c]HF: heart failure.

[d]Established reliability using interitem correlations and test-retest. Instruments take 30-55 minutes to complete when administered together.

[e]SCDG: sensor-controlled digital game.

[f]IG: intervention group.

[g]Outcome measure.

[h]CG: control group.

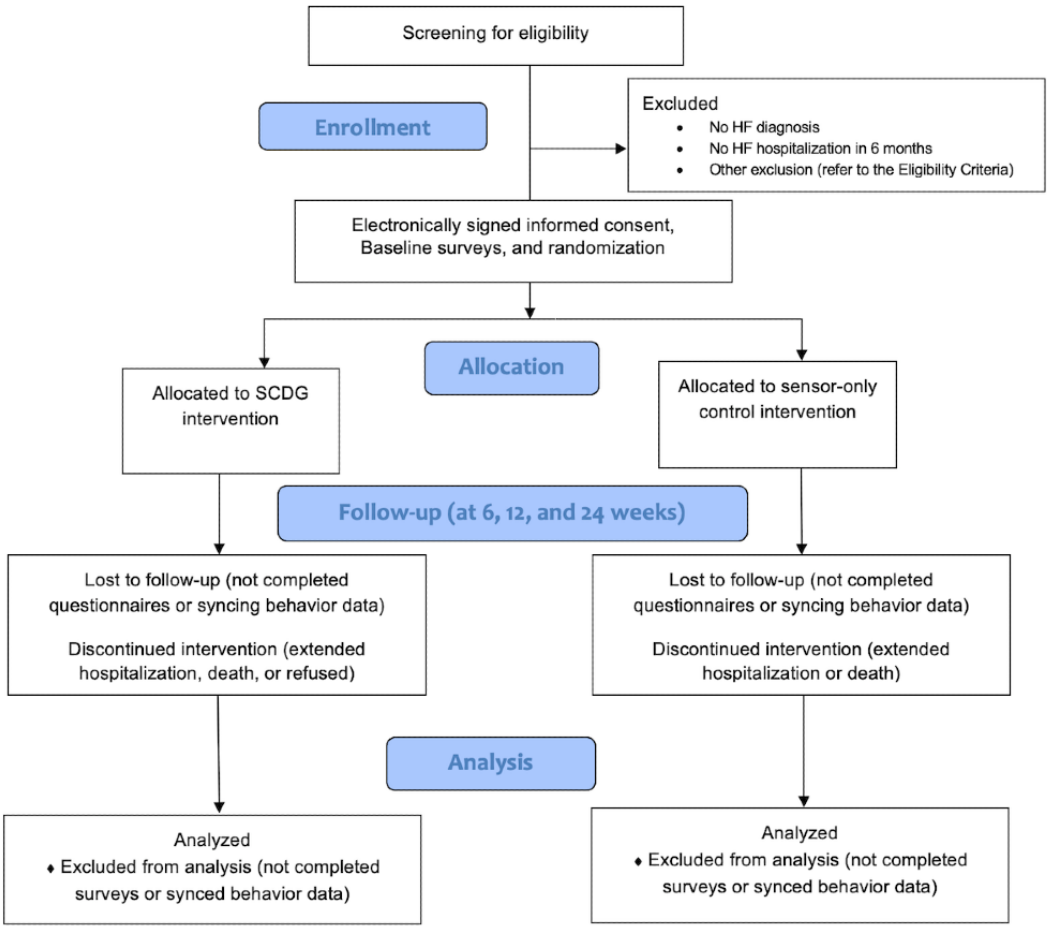
[i]QoL: quality of life.

The incentive of a gift card worth US $10 will be provided for the completion of surveys at each data collection time point (baseline and 6, 12, and 24 weeks) through Tango, a digital gift card disbursement system [47], as a reward for their effort. All participants will retain the scale and tracker till the end of the study.

An overview of the study's phases is mapped in Figure 2.

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Figure 2. Study flow diagram. HF: heart failure; SCDG: sensor-controlled digital game.



Participant Data Protection

We will take measures to ensure the best possible protection of participant data. Each participant will receive a unique identifier as well as a pseudonym identifier to use for their Withings account so that no personal or identifying information is connected to the account. The option to share contacts, location data, or photos from the game and the Withings app will be disabled. Withings is also subject to the European Union General Data Protection Regulation, which include strict policies against sharing of data or other misuse of data without participant knowledge or consent. Participants' unique identifiers, rather than their personal information, will be connected to their behavioral and survey data as well as any data shared or presented externally. To protect participants' privacy, a 6-digit unique identification number and dummy email addresses will be generated for the profile information required by the HealthMate app.

Baseline demographic and clinical data will include sex (male, female, or other), race and ethnicity, marital status, age, level of education, medications, depressive symptoms, hospitalizations, and HF-relevant phenotype data such as ejection fraction and comorbidities.

Outcomes Measured

The outcome measures that we will use in the study are delineated and described in the following subsections.

Primary Outcome

The primary outcome assessed will be the *number of days reporting the HF self-management behavior of weight monitoring*: The data collection time frame will be 6, 12, and 24 weeks. This outcome will be measured by collecting the number of days with weight-monitoring data. These measures will be collected from the sensor logs within the Withings server from the HealthMate app [44] for the IG and CG.

Secondary Outcomes

We will assess a variety of secondary outcomes in the study. These outcomes are listed below.

1. *Daily physical activity steps*: The data collection time frame will be 6, 12, and 24 weeks. This outcome will be measured by collecting the number of daily cumulative steps days. Daily average total will be calculated weekly for 6, 12, and 24 weeks. These measures will be collected from the sensor logs within the Health Mate app [44] for the IG and CG.
2. *Daily physical activity intensity*: The data collection time frame will be 6, 12, and 24 weeks. This outcome will be measured by collecting the intensity level of daily physical activity. Averages will be calculated weekly for 6, 12, and 24 weeks. These measures will be collected from the sensor logs within the Health Mate app [44] for the IG and CG.
3. *Self-report HF self-management behaviors*: The data collection time frame will be baseline and 6, 12, and 24

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weeks. This instrument will be the 9-item European Heart Failure Self-care Behavior Scale, which gives a standardized score from 0 to 100 (every item is given an equal weight), with a higher score indicating better self-care. Items are rated on a Likert scale ranging from 1 to 5. For calculating the standardized score, each item is reverse coded and then computed using the following formula: *(sum of all ever-coded items − 9) × 2.7777*. Cronbach α was .80 for the European Heart Failure Self-care Behavior Scale-9 and showed convergent validity with routine self-care behaviors and symptom response behaviors in the Self-Care of Heart Failure Index instrument [45].

4. *HF-related QoL*: The data collection time frame will be baseline and 6, 12, and 24 weeks. The instrument used will be items 13 to 15 from the Kansas City Cardiomyopathy Questionnaire (KCCQ). Values for the QoL domain range from 0 to 100, with higher scores indicating better QoL. The domain score will be transformed to a 0 to 100 range by subtracting the lowest possible scale score, dividing by the range of the scale, and multiplying by 100. Cronbach α was .78. The KCCQ is sensitive to clinical changes in HF compared with similar QoL instruments and had a significant, high correlation with the New York Heart Association HF classification (P<.001).
5. *HF-related functional status*: The data collection time frame will be baseline and 6, 12, and 24 weeks. Items 1 to 12 on the KCCQ will be used. Values for the functional status summary score ranged from 0 to 100, with higher scores indicating a better QoL. Summary score will be transformed to a 0 to 100 range by subtracting the lowest possible scale score, dividing by the range of the scale, and multiplying by 100. Cronbach α of the KCCQ for measuring functional status was excellent at .93. The scale demonstrated criterion validity with a high correlation with the New York Heart Association HF classification and the 6-minute walk test [46].
6. *Number of cardiac hospitalizations*: The data collection time frame will be baseline and 6, 12, and 24 weeks. This measure will be obtained through participant self-report through REDCap surveys and will be confirmed by hospitalization discharge summary and health care provider.
7. *HF self-management knowledge*: The data collection time frame will be baseline and 6, 12, and 24 weeks. The instrument used will be the 30-item Atlanta Heart Failure Knowledge Test [41]. Each correct answer is scored as 1 point, with no additional weighting of items; correct responses are then summed. Incorrect or skipped questions are awarded 0 points. Total scores range from 0 to 30. Higher scores indicate better knowledge of HF. Content validity ratings on relevance and clarity ranged from 0.55 to 1.0, with 81% of the items rated from 0.88 to 1.0. Reliability by Cronbach α was .84 for patients. Construct validity was demonstrated by directly correlating knowledge with clinical and self-care outcomes including dietary sodium consumption, medication adherence, and health care use.
8. *HF self-efficacy*: The data collection time frame will be baseline and 6, 12, and 24 weeks. The instrument used will be the 6-item Section C Self-efficacy section of the Self-Care of Heart Failure Index [42]. Scores on the self-efficacy scale will range from 0 to 100, with higher scores reflecting better self-efficacy. To standardize scores, the following formula will be used: *(sum of Section C items − 6) × 5.56*. Cronbach α was .88, with good evidence of construct validity and contrasting group validity.

To assess the facilitators and barriers impacting engagement of IG and CG participants with the SCDG and sensor-only interventions for HF self-management behavior adherence, we will use the convergence triangulation mixed methods design (including both quantitative and qualitative components) [48]. We will collect a survey informed by the Intrinsic Motivation Inventory [43] from all 200 participants at the 12-week follow-up assessment. In parallel, we will use random sampling to invite a subset (n=40) of IG and CG participants (20 per group) to participate in qualitative phone interviews at the end of 12 weeks. Interviews will be conducted by trained study staff, audio taped, and thematically coded by participant number to protect confidentiality. Participants will receive US $10 as an incentive to participate in the qualitative interview.

Adverse Event Collection and Handling

Participants will be monitored for anticipated and unanticipated adverse events from the time they sign the study consent until 30 days after the final study visit. Participants will be provided with contact information of a research team member to inform them of any adverse events that occur. In addition, the study team will monitor the adverse events that arise during data collection. A communication protocol was developed to report adverse events to appropriate research personnel, including the development of a phone tree. Serious adverse events will be reported to the Institutional Review Board associated with the University of Texas Austin within 24 hours of being informed of the incident. Unanticipated problems will be reported by the principal investigator (KR) to the Data Safety Monitoring Committee, the funding agency, and the Institutional Review Board within 15 days of the event. The Data Safety Monitoring Committee will meet the principal investigator and study staff to review adverse events once a year and as needed to address any adverse events that need to be addressed immediately.

Should any conditions present harm to the participant if they continue with the intervention, they will either be withdrawn from the intervention or asked to take a break from the intervention until the condition subsides. These conditions will be assessed on a case-by-case basis, with the principal investigator (KR) making the final decision. All adverse events, protocol deviations, and reportable information will be entered into the REDCap database.

Statistical Analysis

We have estimated the sample size for the primary outcome in our feasibility study for the 12 weeks study duration. All secondary outcomes will be examined on an exploratory basis. Analyses will be performed in an intent-to-treat manner.

General Considerations

Cronbach α coefficients will be computed for each multi-item scale, with Cronbach α≥.70 denoting acceptable consistency.

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In outcome analyses, we will control for the possible effects of the biological variables of age and sex, prespecified as potentially strong predictors of outcomes. Statistical significance will be Cronbach α=.05 for primary and secondary analyses. Descriptive statistics will be computed for study variables to assess missingness, out-of-range values, and features of variable distributions including floor and ceiling effects. For testing and quantification of treatment effect with respect to primary and secondary outcomes, the IG and CG will be compared following the intention-to-treat principle.

Missing Data

We expect missingness of items and other data to be minimal at baseline. Follow-up measures may be missing either because of formal dropout or failure to respond to contact from our research team. In all cases, we will assume missingness at random. For missing values at baseline, single (when <5%) or multiple (when ≥5%) imputation will be used. For more extensive missing data, especially at follow-up, we will use multiple imputation strategies when the analyses are based on generalized estimating equations [49] with sensitivity analyses to determine the effects of imputation. Sensitivity analyses will focus on which variables are used in imputation and on deviations from the missingness at random assumption (which must be parameterized, as this statistical assumption is not formally testable with the data) [50]. For missing outcomes in linear mixed models, imputation is not required because the analysis is based on maximum likelihood. However, missing predictors in mixed models will require single or multiple imputation.

Measuring Outcomes

For the primary outcome of days with weight monitoring, binary weight-monitoring data (yes or no) will be summed over days for each of the 24 weeks during which data are collected. Data will be analyzed with a linear model for binomial-like data with an effect of time (ranging from 1 to 24) and a time-by-treatment effect. We do not need a treatment main effect owing to randomization, which implies no treatment effect at time=0. Primary outcome treatment effect at 12 weeks can then be estimated from the model as a difference in mean weight-monitoring days (out of 7) comparing the IG with the CG. The model will be fitted with generalized estimating equations [51], using the matrix-adjusted estimating equations method to estimate model correlation over repeated measures within a subject and using a bias-corrected sandwich variance estimator [52]. The model will allow for overdispersion relative to the binomial variance, yielding correct statistical descriptions of the data and inference. We will consider exchangeable, exponential decay and a combination of the 2 correlation structures. Finally, (1) we mention that the linear (vs the logistic) model is valid for binomial data, especially when the binomial parameter is not near 0 or 1 and yields an interpretable treatment effect on the scale of "number of weight-monitoring days," and (2) we will maximize power by analyzing all 24 weeks of data, although we aim to extract the 12-week mean difference as the primary contrast of interest.

For the secondary outcome of physical activity, as measured by the number of steps, data will again be aggregated (summed) by week. As the measures are counts, we will use a log link and variance proportional to the mean (as with the Poisson distribution), allowing for an overdispersion parameter. Analysis will then emulate that for the number of weight-monitoring days. The log link will yield coefficients that, when exponentiated, will be interpreted as relative mean numbers of steps, which, given the expected between-person variability, will be more interpretable than a mean difference on the natural scale. For secondary outcome measures of HF self-management knowledge, self-efficacy, HF-related functional status, and QoL measured 4 times over the multiple data collection time points, we will use linear mixed effects models [53] with random slopes and intercepts to capture the association over time in the repeated measures within participant, estimating the treatment effect from the model at each of 6, 12, and 24 weeks.

Sample Size and Statistical Power

For a 1:1 randomization scheme (IG:CG), we aim to recruit 100 participants per group and allow for 25% attrition (some of which will be recovered through the treatment of missing data). We would like to detect a weight-monitoring rate of at least 80% (5.6/7) of days per week, as patients with HF who completed ≥80% of weight diaries were found to have significantly reduced odds for HF-related hospitalizations compared with patients who completed <80% of weight diaries [7]. In our planned analysis, we aim to use weekly data for weeks 1 through 24, fitting a flexible (eg, df=2) trend for the mean number of days (out of 7) in which participants complete weight monitoring, and thereby extracting the estimate at 12 weeks for each of the IG and CG. Using all 24 weeks of data represents an efficient use of data by exploiting a smooth time trend, by leveraging the positive correlation among the repeated measures on a given individual, and by offering the opportunity to handle missing time points through imputation or weighting of the nonmissing longitudinal data. For power estimation, because we are not sure about the form of the model based only on pilot data and because pilot data are relatively sparse for purposes of estimating within-subject correlation, we *conservatively* (in the sense that true power is expected to be greater) use aggregated pilot data just across weeks 7 to 12 (42 days) to estimate the mean and variance of $\hat{a}$, where a is the average within-group probability of engaging in weight monitoring on any given day. Owing to the strong day-to-day correlation within subject, the total number Y of weight-monitoring days is considerably overdispersed relative to the binomial distribution, such that for a given subject in a given group, the mean of Y is $42a$ and the variance of Y is $42Øa(1 - a)$, where $Ø$ is an overdispersion parameter. In our pilot data, we estimated $Ø$=17.5; these values yield 2-group power calculations comparing IG weight-monitoring rate, a_{IG}, with CG weight-monitoring rate, a_{CG}, under within-group sample size n=75. If a_{IG}=0.80, then we will have 90% power to detect differences between a_{IG} and a_{CG}, as small as 0.14 (SD 0.12; ie, a_{CG} as big as 0.66, SD 0.68), yielding strong power from our longitudinal design. Owing to the need to estimate the overdispersion parameter, these calculations were custom coded by our team in R (R Foundation for Statistical Computing) [54].

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Qualitative Coding and Analysis

Survey analysis will include descriptive statistics of counts and frequencies for the scale items and thematic analysis for the open-ended survey responses [55,56]. Verbatim transcripts will be created; they will be coded and examined using thematic analysis and Dedoose (SocioCultural Research Consultants) [57] software to enable examination of themes overall. Finally, the quantitative and qualitative results will be merged [48] to provide insights on the weight monitoring, physical activity, sensor use, and SCDG-playing behaviors of participants with HF; facilitators and barriers affecting participant engagement with sensors or SCDG for HF self-management behavior adherence; as well as future improvements and design modifications of the SCDG. The facilitators and barriers affecting engagement in sensor-based digital health interventions will be published in a secondary analysis publication.

Results

A CONSORT (Consolidated Standards of Reporting Trials) flow diagram will be reported. The clinical trial was initiated on October 24, 2022, and the first participant was enrolled on November 7, 2022. Recruitment of the last participant is anticipated in quarter 1 of 2025. Full trial results are planned to be published by 2026.

Discussion

Principal Findings

Our SCDG intervention addresses a substantial challenge, that is, to develop an affordable and scalable technology-assisted intervention to facilitate persistent adherence to self-management behaviors by adults with HF to improve QoL, functional status, and health outcomes and, ultimately, to reduce the burden of HF worldwide. We hypothesize that 12 weeks of playing the SCDG will result in greater behavioral changes in key self-management indicators of HF outcomes in adults aged >45 years compared with a CG that uses only sensors.

The recent rapid rise in the use of smartphones across demographic groups has enabled the scalability of innovative digital health interventions to promote HF self-management behaviors across diverse groups [58]. Although interventions such as digital games for health can be easily deployed to address geographic disparities in HF outcomes experienced by populations in southern US states, there is a lack of systematic research on the effectiveness of digital game interventions to promote evidence-based self-management behaviors of individuals with HF with conflicting priorities or in unsupportive environments. Current digital health interventions with unobtrusive monitoring capabilities allow the gathering of relevant contextual data to tailor and adapt interventions without overburdening participants through cumbersome data collection [59]. This study protocol was informed by our feasibility randomized controlled trial study, in which we demonstrated the remote implementation of a smartphone-based intervention using a digital game and sensors among participants in 18 counties in Texas and Oklahoma [29]. Combining digital games and sensors holds the potential to offer a powerful way to improve treatment adherence [60,61]; sustain healthy behaviors; and make health care more participatory, personalized, predictive, and preventive, as defined by precision medicine [62]. The lessons from this initial study provide a strong foundation to test our intervention with individuals with HF in 7 southern US states. Therefore, we hypothesize that 12 weeks of playing the SCDG will result in greater behavioral changes in key self-management indicators of HF outcomes in adults aged >45 years compared with a CG that uses only the sensors.

Strengths

Developing a dashboard that will allow easier visualization of behavioral data from all participants will provide us with the opportunity to intervene immediately in the event of absent or unsafe levels of behavioral data. In addition, fully remote study procedures will enhance the accessibility of HF research to participants living in rural or remote areas that are far from large HF centers in cities.

Limitations

Self-selection bias may be a limitation of this study as participation is voluntary, and participants already comfortable with using technology might be especially motivated to participate in digital intervention studies.

Dissemination Plan

We will disseminate our study findings to target an audience that cares for patients with HF and will benefit from the lessons learned through our study. This includes disseminating our findings through (1) peer-reviewed health technology–related journals such as *Games for Health Journal* or *Journal of Medical Internet Research* and clinical journals such as *Journal of Cardiovascular Nursing* or *Journal of Cardiac Failure*; (2) annual research conferences conducted by the Heart Failure Society of America, American Heart Association, Society of Behavioral Medicine, American Medical Informatics Association, and Gerontological Society of America; (3) local and regional nursing organizations such as Texas Public Health Association's monthly webinars and similar organizations in other southern US states; (4) scheduled continuing education sessions or monthly meetings conducted by HF clinics for their staff; and (5) local and regional support groups for patients with HF. In addition, all peer-reviewed and accepted manuscripts will be uploaded either by the investigator or by the journal (for those journals that perform this function) to the National Library of Medicine's PubMed Central in accordance with the National Institutes of Health Public Access Policy.

Conclusions

Nevertheless, this project will generate insight and guidance for scalable and easy-to-use digital gaming solutions to motivate persistent adherence to HF self-management behaviors and improve health outcomes among individuals with HF.

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Data Availability

Although the final data set comprising questionnaire and qualitative data will be stripped of identifiers, we believe that there remains the possibility of deductive disclosure of participants with unusual characteristics. Thus, we will make the data and associated documentation available to users only under a data-sharing agreement that provides for (1) a commitment to using the data only for research purposes and not to identify any individual participant, (2) a commitment to securing the data using appropriate computer technology, and (3) a commitment to destroying or returning the data after analyses are completed. After reviewing the purpose of the data request to ensure that it is consistent with the original project goals and verifying that the request meets approval from the Institutional Review Board, deidentified data may be shared with researchers as soon as possible but no later than within 1 year from the completion of the funded project period for the parent award or upon acceptance of the data for publication, whichever is earlier.

Conflicts of Interest

MO is the owner of Good Life Games, Inc, a company that develops health games for hire, which provided the prototype game images for this study.

Multimedia Appendix 1
Peer review report.
[PDF File (Adobe PDF File), 154 KB - resprot_v12i1e45801_app1.pdf]

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Abbreviations

CG: control group
CONSORT: Consolidated Standards of Reporting Trials
HF: heart failure
IG: intervention group
KCCQ: Kansas City Cardiomyopathy Questionnaire
QoL: quality of life
REDCap: Research Electronic Data Capture
SCDG: sensor-controlled digital game

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Protocol

Evaluating the Efficacy of Web-Based Cognitive Behavioral Therapy for the Treatment of Patients With Bipolar II Disorder and Residual Depressive Symptoms: Protocol for a Randomized Controlled Trial

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Abstract

Background: Bipolar disorder (BD) is a highly prevalent psychiatric condition that can significantly impact every aspect of a person's life if left untreated. A subtype of BD, bipolar disorder type II (BD-II), is characterized by long depressive episodes and residual depression symptoms, with short-lived hypomanic episodes. Medication and psychotherapy, such as cognitive behavioral therapy (CBT), are the main treatment options for BD-II. CBT specific for BD-II involves the recognition of warning signs, potentially triggering stimuli, and the development of coping skills to increase euthymic periods and improve global functioning. However, access to in-person CBT may be limited by several barriers, including low availability, high costs, and geographical limitations. Thus, web-based adaptations of CBT (e-CBT) have become a promising solution to address these treatment barriers. Nevertheless, e-CBT for the treatment of BD-II remains understudied.

Objective: The proposed study aims to establish the first e-CBT program specific for the treatment of BD-II with residual depressive symptoms. The primary objective of this study will be to determine the effect of e-CBT in managing BD symptomatology. The secondary objective will be to assess the effects of this e-CBT program on quality of life and resilience. The tertiary objective will involve gathering user feedback using a posttreatment survey to support the continuous improvement and optimization of the proposed program.

Methods: Adult participants (N=170) with a confirmed diagnosis of BD-II experiencing residual depressive symptoms will be randomly assigned to either the e-CBT and treatment as usual (TAU; n=85) group or the TAU (n=85) control group. Participants in the control group will be able to participate in the web-based program after the first 13 weeks. The e-CBT program will consist of 13 weekly web-based modules designed following a validated CBT framework. Participants will complete module-related homework and receive asynchronous personalized feedback from a therapist. TAU will consist of standard treatment services conducted outside of this research study. Depression and manic symptoms, quality of life, and resiliency will be assessed using clinically validated symptomatology questionnaires at baseline, week 6, and week 13.

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Results: The study received ethics approval in March 2020, and participant recruitment is expected to begin in February 2023 through targeted advertisements and physician referrals. Data collection and analysis are expected to conclude by December 2024. Linear and binomial regression (continuous and categorical outcomes, respectively) will be conducted along with qualitative interpretive methods.

Conclusions: The findings will be the first on the effectiveness of delivering e-CBT for patients with BD-II with residual depressive symptoms. This approach can provide an innovative method to address barriers to in-person psychotherapy by increasing accessibility and decreasing costs.

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KEYWORDS

bipolar disorder; cognitive behavioral therapy; depression; eHealth; electronic care; internet; mental health; psychotherapy; treatment; web-based therapy

Introduction

Bipolar disorder (BD) is a highly prevalent affective psychiatric condition that affects nearly 2% of the global population [1-5]. It is characterized by chronic mood swings fluctuating from mania or hypomania to depression, which often cause significant impairment both socially and occupationally. The manic or hypomanic component involves 3 days or more of persistently elevated mood, recklessness, grandiosity, decreased need for sleep, reduced ability to concentrate, and irritability [2,4,6-8]. The depressive component involves 2 weeks or more of persistently low mood, anhedonia, poor appetite and sleep, reduced ability to concentrate, agitation or motor slowness, and suicidal ideation [4,8]. There are 4 main types of BD that are differentiated by the type, frequency, and severity of the mood episodes. Bipolar I disorder requires at least one manic episode, whereas bipolar disorder type II (BD-II) is characterized by depressive and hypomanic episodes. Cyclothymic disorder involves the presence of depressive and hypomanic states that do not meet diagnostic criteria and last a minimum of 2 years. Lastly, BD with mixed features is characterized by depressive and elevated moods simultaneously [2,4]. Unlike other types of BD, individuals with BD-II tend to experience longer and more persistent depressive episodes, sometimes with residual depressive symptoms, which are further exacerbated by the negative consequences of their hypomanic episodes [8].

Misdiagnosis and delayed treatment are common for individuals with BD, which can result in serious and sometimes irreversible outcomes. These outcomes can include more frequent and severe mood episodes, intellectual disability, loss of independence, and loss of ability to function [2,4,6,7,9-12]. Although mood-stabilizing medication remains the first line of treatment for BD, the beneficial effects of psychosocial treatments, particularly cognitive behavioral therapy (CBT), are now widely recognized [13]. Furthermore, the use of psychotherapy for the management of BD-II has evolved significantly over the past few decades [8]. CBT targets negative or dysfunctional thought patterns and behaviors through cognitive and behavioral restructuring techniques. These techniques aim to help the individual develop healthier or more balanced thought patterns (cognitive restructuration), which can then be applied in day-to-day life (behavioral restructuration). This can help with reducing psychiatric symptomatology and decreasing depressive episode duration along with increasing euthymic periods and improving global functioning and quality of life [14-20]. Furthermore, CBT specific for BD-II often includes techniques to practice acceptance, recognize warning signs of an upcoming mood episode, recognize potentially triggering stimuli, and develop an action plan with helpful steps and considerations to follow before, during, and after a mood episode [8,14,16,17,19,21,22].

However, several barriers prevent the broader uptake of CBT and other in-person psychotherapy options, including high costs, low availability, long waitlists, stigma against psychiatric interventions, and geographical and physical limitations [11]. Thus, web-based adaptations of traditional in-person CBT (e-CBT) have become promising alternatives due to their lowered cost, time effectiveness, flexibility, privacy, and convenience [14,23-25]. Additionally, e-CBT has been shown to increase help-seeking behaviors among patients and to have similar effectiveness at reducing psychiatric symptomatology as in-person CBT [11,14,26-28]. e-CBT programs often include weekly assignments for the participants and may be either fully self-guided or guided with asynchronous support from an assigned therapist [14]. Despite these benefits over in-person CBT, e-CBT options specific to BD remain significantly understudied and underdeveloped, and very few e-CBT programs have focused on BD-II [15-19,29].

To supplement this gap in the literature and guide clinical practice, this will be an open-label randomized controlled trial studying the effectiveness of a novel e-CBT program specific for BD-II in addition to treatment as usual (TAU; e-CBT + TAU). This program will be developed with the help of individuals with lived experience of BD-II to ensure applicability and accuracy. Thus, the primary objective of this study will be to determine the changes in BD symptomatology (hypomanic and depressive symptoms) of participants receiving e-CBT + TAU compared to participants receiving only TAU. Based on the evidence comparing e-CBT specific for BD to psychoeducation, attention controls, and TAU [16,17,19], this study hypothesizes that adding this e-CBT program to TAU will result in better symptom management than TAU by itself. The secondary objective will be to assess the effects of this

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e-CBT program on quality of life and resilience. The tertiary objective will involve gathering user feedback using a posttreatment survey to support the continuous improvement and optimization of the proposed program.

Methods

Participants

This is the protocol for a randomized controlled trial studying the efficacy of a novel e-CBT program. Participants (N=170) diagnosed with BD-II experiencing residual depressive symptoms will be recruited from the Mood and Anxiety Clinic at Providence Care Hospital, Kingston Health Sciences Center, family physicians, other health care professionals, and self-referrals within Ontario, Canada. Additionally, recruitment efforts will be carried out through flyers in social gathering areas (eg, coffee shops, college campuses), media advertisements, and expert end user referrals. After providing consent to participate in the study, the participants will complete a Mini International Neuropsychiatric Interview 7.0.2 (MINI) with a trained research assistant [30]. The MINI assesses 17 common psychiatric conditions following the diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) [30]. Inclusion criteria include being 18 years or older at the start of the study, a diagnosis of BD-II based on the MINI assessment, a Montgomery-Åsberg Depressive Rating Scale (MADRS) score of mild to moderate depression symptomatology (MADRS score 7-34), competence to consent and participate, ability to speak and read English, and consistent and reliable access to the internet [14,31-33]. Exclusion criteria include acute hypomanic or manic episodes, acute psychosis, severe alcohol or substance use disorder, and active suicidal or homicidal ideation. Additionally, individuals who are currently receiving or have received CBT in the past 6 months will be ineligible to avoid confounding treatment effects.

Procedures

Eligible participants will be randomly assigned to either a 13-week e-CBT program in addition to TAU (n=85; e-CBT + TAU group) or TAU only (control group; n=85). If interested, participants in the control group will be offered access to the e-CBT program after completing 13 weeks as part of the control group. The e-CBT program will be delivered as an augmentation to TAU through the Online Psychotherapy Tool (OPTT), a secure and interactive platform developed by the principal investigator (PI) [14,34]. TAU will consist of medications, regular physician or clinician visits, referrals, or consultations that are conducted outside of this research study.

e-CBT Specific for BD-II

Participants in the e-CBT group will receive weekly predesigned web-based modules for 13 weeks. Each module will consist of approximately 30 slides and should take an estimated 45 minutes to complete. Each participant will be assigned a therapist to communicate with them asynchronously through the OPTT platform. In addition, the modules include weekly homework for the participants, which will be submitted directly through OPTT to the assigned therapists. The therapists will then use the OPTT platform to provide personalized feedback using session-specific therapy feedback templates. These feedback templates were developed under the guidance of the PI (NA) to standardize the quality and content of the feedback across different patients and therapists. Furthermore, in previous studies conducted by the PI, these feedback templates have been used to prepare personalized feedback in approximately 15-20 minutes [14,33,35,36].

The proposed e-CBT program will be developed to teach core CBT concepts (ie, the 5-part model, automatic thoughts, the thought record, cognitive and behavioral restructuration) and concepts specific to the management of BD-II [8,14,35,37]. These BD-II–specific concepts include techniques to practice acceptance, recognize warning signs of an upcoming mood episode, recognize potentially triggering stimuli, and develop an action plan with helpful steps and considerations to follow before, during, and after a mood episode [8,14,16,17,19,21]. Additionally, individuals with lived experience of BD-II will be recruited to help in module development and review the modules for applicability and accuracy.

Training

Research assistants trained in the delivery of CBT and writing feedback will be assigned as therapists for the e-CBT group. The PI, who is an expert in the web-based delivery of psychotherapy and CBT [14,33,35-37], is involved in the training of the therapists to ensure the quality and reliability of the treatment programs. Training will involve weekly workshops and a CBT training video with a quiz at the end. To further ensure that the therapists are well prepared, the co-PI (MY) will closely guide the therapists through their first patient (assigning modules, reviewing homework, writing feedback, and answering questions using the OPTT platform). Furthermore, all therapists will use predesigned session-specific feedback templates to secure the quality of the feedback, which will be reviewed by the co-PI before being sent to the participants. To avoid a conflict of interest, the PI will not be involved in writing or supervising feedback.

Outcome Evaluation

The primary outcome of this study will be to determine the change in BD symptomatology (hypomanic and depressive symptoms) of participants receiving e-CBT + TAU compared to participants receiving TAU only. This will be measured through clinically validated symptomatology questionnaires, including the MADRS and the Young Mania Rating Scale (YMRS) [31,32]. The secondary outcome will be to assess the effects of this e-CBT program on quality of life and resilience. These metrics will be assessed using the Quality-of-Life Enjoyment and Satisfaction Questionnaire-Short Form (Q-LES-Q-SF) [38] and the 14-item Resilience Scale (RS-14) [39]. All questionnaires will be completed through OPTT at baseline, week 6, and week 13. Subsequent to the treatment period, follow-up assessments will be conducted for all the outcome measures at 3, 6, and 12 months. The tertiary outcome will involve gathering user feedback using a posttreatment survey. This posttreatment survey will be sent to all participants who completed the e-CBT program and will consist of questions related to their experience going through the modules and using

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the OPTT platform. Also, it will collect any additional feedback and suggestions to support the continuous improvement and optimization of the proposed program.

Ethics Approval

This study has been reviewed for ethical compliance by the Queen's University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board (File Number 6028658) in March 2020. Participant data is only accessible to the health care professionals; otherwise, participants will only be identified by their study ID, and all records will be stored on a secure platform. As part of the consent process, participants are informed that they can withdraw from the study at any time and request for their data to be removed from the analysis. The research team will safeguard the data and privacy of the participants to the extent permitted by the applicable laws and duty to report.

OPTT is compliant with the Health Insurance Portability and Accountability Act, Personal Information Protection and Electronic Documents Act, and Service Organization Control-2. Also, to assure provincial and federal privacy and security regulations are met, all servers and databases are hosted in the Amazon Web Service Canada cloud infrastructure. OPTT only collects anonymized metadata used in service quality analysis; no identifiable personal information or IP addresses are collected.

Data Analysis

Initially, all data will be examined for missing, nonsensical, and outlying variables. Missing data will be treated as missing and not imputed (ie, will be analyzed on a per-protocol basis). However, an intention-to-treat analysis will be conducted to determine the clinical effects of the e-CBT program on participants who dropped out. Based on previous experience with CBT and e-CBT in similar patient populations, the anticipated dropout rate is up to 30% by the end of the treatment or TAU phases [14,33,35,37,40]. Given the likelihood of participant dropout or withdrawal, the study sample has been purposely oversampled to obtain meaningful and statistically significant results at the end of the study. Considering the effect size for e-CBT reported by Todd et al [19] for the reduction of depression symptomatology (effect size=0.44), a significance of $P<.05$ and a power of 0.80, a sample size of 170 (85 per arm) would be sufficient to detect significant changes from this intervention [14,19,33,35,40,41]. As this is the first study aiming to establish an e-CBT program specific for BD-II, this sample size calculation relies on data from e-CBT specific for BD (all types). It takes into account the established effectiveness of web-based psychotherapy [14].

A 2-tailed significance level of $\alpha=.05$ will be used for all calculations, except when a Bonferroni correction is needed. Possible differences between program completers and noncompleters will be determined by comparing the respective demographic information using independent sample *t* tests. A 2-by-3 repeated measures ANOVA of the primary (BD symptomatology: MADRS and YMRS) and secondary (Q-LES-Q-SF and RS-14) outcomes will be conducted to compare the effects of e-CBT + TAU to TAU only throughout the 13-week treatment course (0-, 6-, and 13-week assessment points). Variables associated with outcome measures will be determined using linear regression (continuous outcomes) and binomial regression analysis (categorical outcomes). The data collected from the posttreatment survey will be analyzed qualitatively with 2 reviewers to identify common themes and specific areas for improvement. All statistical analyses will be conducted using SPSS Statistics for Mac, version 28 (IBM Corp).

Results

The literature comparing the efficacy of e-CBT specific for BD to psychoeducation, attention controls, and TAU has shown that e-CBT specific for BD is effective at reducing BD symptomatology (depression and mania or hypomania symptoms) and improving quality of life [16,17,19]. Thus, this study hypothesizes that adding this e-CBT program to TAU will result in better symptom management (reduction of BD symptomatology and improvement of quality of life) than TAU by itself. The study received notice of funding acceptance through the Queen's University Department of Psychiatry Internal grant in December 2019. Participant recruitment will begin in February 2023 using targeted advertisements and physician referrals (see Methods). Complete data collection and analysis from all phases are expected to conclude by December 2024. All procedures and outcomes have been and will be reported using the CONSORT (Consolidated Standards of Reporting Trials) and TIDieR (Template for Intervention Description and Replication) Report Guidelines [42]. This study has been registered through the ClinicalTrials.gov system (NCT04664257).

Discussion

This is a protocol for an RCT that aims to establish the first e-CBT program for the management of BD-II with residual depressive symptoms. This program will cover helpful coping techniques to increase euthymic periods and improve global functioning by applying the widely validated principles of CBT [14-20]. Based on literature evidence, previous clinical trials conducted by NA, and the use of a validated therapy approach, this study hypothesizes that this novel e-CBT program will have similar effectiveness as face-to-face CBT for the management of BD-II with residual depressive symptoms [14,33,35-37].

The management of BD-II involves the use of mood-stabilizing medications and psychosocial interventions [13]. Thus, given the proven efficacy of CBT for a variety of psychiatric conditions, the development of CBT for the management of BD-II has become a growing area of research [8]. CBT for BD-II usually involves face-to-face sessions with a therapist and covers techniques to practice acceptance, recognize warning signs of an upcoming mood episode, recognize potentially triggering stimuli, and develop an action plan [14-20]. However, access to in-person CBT faces significant barriers, including high costs, low availability, long waitlists, stigma against psychiatric interventions, and geographical and physical limitations [11]. Also, despite advances in the development and validation of web-based adaptations of CBT for other psychiatric conditions

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[14,15,20], e-CBT options specific for the treatment of BD-II remain understudied [15-19]. This presents an important gap in the literature with potentially detrimental consequences for individuals with this condition.

The strengths of this novel e-CBT program and of this study include the use of a validated approach for the delivery of interactive, predesigned web-based modules with the asynchronous guidance of a therapist through the OPTT platform [14,33,35-37]. Also, by taking advantage of the web-based medium, this program has the potential to improve accessibility, cost, time effectiveness, flexibility, privacy, and convenience. For instance, previous studies have shown that asynchronous psychotherapy, through the use of predesigned web-based modules, allows therapists to deliver care to 3-4 patients in the same time as a traditional hour-long in-person session [14,33,35-37]. Furthermore, using the OPTT platform, this study will be able to reliably collect user analytics, which allows for the improvement and continuous optimization of e-CBT program delivery. Additionally, by comparing this proposed program to a validated therapeutic approach (face-to-face CBT for the management of BD-II) [14-20], the design of this study should provide helpful evidence for the validation of e-CBT for the management of BD-II with residual depressive symptoms.

Moreover, the knowledge dissemination plan for this study includes the publication of the findings in a peer-reviewed academic journal. The findings will also be presented broadly through academic meetings and conferences. Thus, this plan ensures the commitment to continuing education in the relevant research areas. Also, collaboration with the Canadian enterprise OPTT Inc. will enhance the dissemination and application of knowledge. Additionally, by providing this service to clinicians, the care capacity for accessible, affordable, and high-quality mental health care could be more rapidly scaled across Canada.

Though this study has some potential limitations that mainly stem from the web-based mode of delivery of this program, the main limiting factor is that participants would need a reliable internet connection and sufficient technology literacy to participate. In turn, this could introduce biases in participant demographic characteristics. To account for this, this study will analyze demographic factors through multiple sample *t* tests to identify the impact of these factors on treatment outcomes. Additionally, the design of this study is limited by the lack of therapist and client blinding. However, due to the delivery mode and design of the program, it is not possible to conceal client allocation. Furthermore, web-based psychotherapy is often characterized by significant dropout rates, with some studies reporting a dropout rate of up to 30% by the end of the treatment or TAU phases [14,33,35,37,40]. Hence, this study is intentionally oversampling to account for this potential high dropout rate without compromising the statistical power of this study.

In conclusion, this study recognizes the significant potential of web-based psychotherapy as a tool that can lower costs and increase capacity and accessibility in mental health care, as well as the lack of available web-based psychotherapy options for individuals with BD-II. Therefore, the results of this study aim to fill an important gap in the literature through the development, implementation, and validation of a novel e-CBT program for the management of BD-II with residual depressive symptoms. Additionally, these results aim to inform clinical practice and health care policy to support the widespread implementation of web-based psychotherapy, with potential benefits to the care capacity and performance of the health care system.

Acknowledgments

This study was funded by a 2020 Queen's University Department of Psychiatry Internal Grant. The funding agency has no role in the study design, execution, data collection, analysis, or interpretation.

Data Availability

Data sharing is not applicable to this paper as no data sets were generated or analyzed yet for the preparation of this protocol manuscript. Though, the data sets generated and analyzed in the randomized controlled trial will be available from the corresponding author on reasonable request.

Conflicts of Interest

NA and MO have cofounded the care delivery platform in use (ie, OPTT) and have ownership stakes in OPTT Inc. NA will be involved in web-based modules design, therapist training, and study design and methodology. MO will oversee the study design and methodology. RM has received consulting and speaking honoraria from AbbVie, Eisai, Janssen, Lallemand, Lundbeck, Neonmind, and Otsuka, and research grants from CAN-BIND, CIHR, Janssen, Nubiyota, OBI and OMHF.

Multimedia Appendix 1
Peer review report by Providence Care Centre Research Innovation Grant (Kingston, Canada).
[PDF File (Adobe PDF File), 147 KB - resprot_v12i1e46157_app1.pdf]

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Abbreviations

BD: bipolar disorder
BD-II: bipolar disorder type II
CBT: cognitive behavioral therapy
CONSORT: Consolidated Standards of Reporting Trials
e-CBT: web-based adaptations of cognitive behavioral therapy
MADRS: Montgomery-Asberg Depressive Rating Scale
MINI: Mini International Neuropsychiatric Interview 7.0.2
OPTT: Online Psychotherapy Tool
PI: principal investigator
Q-LES-Q-SF: Quality-of-Life Enjoyment and Satisfaction Questionnaire-Short Form

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RS-14: 14-item Resilience Scale
TAU: treatment as usual
TIDieR: Template for Intervention Description and Replication
YMRS: Young Mania Rating Scale

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Protocol

A Biological Approach to Building Resilience and Wellness Capacity Among Police Exposed to Posttraumatic Stress Injuries: Protocol for a Randomized Controlled Trial

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Abstract

Background: Law enforcement officers are routinely exposed to hazardous, disturbing events that can impose severe stress and long-term psychological trauma. As a result, police and other public safety personnel (PSP) are at increased risk of developing posttraumatic stress injuries (PTSIs) and disruptions to the autonomic nervous system (ANS). ANS functioning can be objectively and noninvasively measured by heart rate (HR), heart rate variability (HRV), and respiratory sinus arrhythmia (RSA). Traditional interventions aimed at building resilience among PSP have not adequately addressed the physiological ANS dysregulations that lead to mental and physical health conditions, as well as burnout and fatigue following potential psychological trauma.

Objective: In this study, we will investigate the efficacy of a web-based Autonomic Modulation Training (AMT) intervention on the following outcomes: (1) reducing self-reported symptoms of PTSI, (2) strengthening ANS physiological resilience and wellness capacity, and (3) exploring how sex and gender are related to baseline differences in psychological and biological PTSI symptoms and response to the AMT intervention.

Methods: The study is comprised of 2 phases. Phase 1 involves the development of the web-based AMT intervention, which includes 1 session of baseline survey measures, 6 weekly sessions that integrate HRV biofeedback (HRVBF) training with meta-cognitive skill practice, and 1 session of follow-up survey measures. Phase 2 will use a cluster randomized control design to test the effectiveness of AMT on the following prepost outcomes: (1) self-report symptoms of PTSI and other wellness measures; (2) physiological indicators of health and resilience including resting HR, HRV, and RSA; and (3) the influence of sex and gender on other outcomes. Participants will be recruited for an 8-week study across Canada in rolling cohorts.

Results: The study received grant funding in March 2020 and ethics approval in February 2021. Due to delays related to COVID-19, phase 1 was completed in December 2022, and phase 2 pilot testing began in February 2023. Cohorts of 10 participants in the experimental (AMT) and control (prepost assessment only) groups will continue until a total of 250 participants are tested.

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Data collection from all phases is expected to conclude in December 2025 but may be extended until the intended sample size is reached. Quantitative analyses of psychological and physiological data will be conducted in conjunction with expert coinvestigators.

Conclusions: There is an urgent need to provide police and PSP with effective training that improves physical and psychological functioning. Given that help-seeking for PTSI is reduced among these occupational groups, AMT is a promising intervention that can be completed in the privacy of one's home. Importantly, AMT is a novel program that uniquely addresses the underlying physiological mechanisms that support resilience and wellness promotion and is tailored to the occupational demands of PSP.

Trial Registration: ClinicalTrials.gov NCT05521360; https://clinicaltrials.gov/ct2/show/NCT05521360

International Registered Report Identifier (IRRID): PRR1-10.2196/33492

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KEYWORDS

posttraumatic stress injuries; autonomic modulation training; resilience; wellness promotion; public safety personnel; police; heart rate variability; heart rate variability biofeedback; respiratory sinus arrhythmia

Introduction

Background

Law enforcement officers are routinely exposed to hazardous, disturbing events that can impose severe stress and long-term psychological trauma. Upward of 42% of public safety personnel (PSP) report one or more mental health symptoms [1]. Accumulated stress and posttraumatic stress injuries (PTSIs) result in chronic physical and mental health disorders, including anxiety, depression, substance abuse, and cardiovascular disease [2,3]. PTSI is also related to reduced occupational performance, absenteeism, and risky behavior, with implications for both police and public safety [4,5]. Recent empirical research and government reports have highlighted a mental health and suicide crisis among various PSP sectors in Canada [6-8]. The accumulated evidence forms an urgent call for evidence-based programs that build resilience and wellness capacity in order to prevent PTSI symptoms before they manifest as severe, chronic, diagnosable disorders in PSP.

Biological Resilience: The Missing Piece

Existing PTSI prevention and resilience promotion interventions tailored to PSP not only show limited effectiveness but also do not consider sex and gender as central determinants of health and variables of importance [5,9,10]. Further, most traditional interventions are focused on addressing cognitive, emotional, and behavioral components without addressing the underlying neurophysiological mechanisms that erode resilience [2,11-14]. Typically, when a person encounters stress (either real or imagined), they will experience characteristic changes in the autonomic nervous system (ANS), including increased sympathetic nervous system (SNS) activation that elevates heart rate (HR) and respiration and a withdrawal of parasympathetic nervous system (PNS) activation. When stress has abated, PNS activation will lower heart and breathing rates and blood pressure, helping the body to return to reparative and restorative functioning [15].

Advances in physiology and neuroscience demonstrate that resilience is maintained by healthy ANS functioning. Disruptions in ANS functioning can be observed by objectively and noninvasively measuring 2 biological indices [13,14,16]: heart rate variability (HRV) and respiratory sinus arrhythmia (RSA). HRV is the variation in the time between successive heartbeats and depends primarily on the extrinsic regulation of HR by the balance between the SNS and PNS branches of the ANS [17,18]. If the time between heartbeats is rather constant, HRV will be low, whereas if the time varies, HRV will be higher. When a person is at rest, a high HRV signals good health because it represents a physical indicator of autonomic flexibility in responding to challenges [18,19]. In contrast, low resting HRV signals an imbalance in autonomic function, such as in clinical cases of anxiety and psychopathology, where there is an overactivation of the sympathetic branch and a weakening of parasympathetic influence over the heart [20]. RSA refers to the synchronization of HRV with breathing such that HR speeds up during inhalation (shortening the time between heartbeats) and slows during exhalation (lengthening the time between heartbeats) [21,22]. Increasing RSA builds physical wellness capacity by strengthening an individual's long-term reserves, which is theorized to occur via multiple pathways (ie, baroreflex control, blood pressure regulation, and efficiency of pulmonary gas exchange) [21,23].

There is evidence to suggest sex can influence ANS functioning, as indicated by differences in HRV and RSA at rest [24]. These findings have direct implications for evaluating and understanding biological resilience and the effectiveness of psychophysiological interventions. Policing is known to be both intensely stressful [25] and a hypermasculinized profession [26,27], both of which have significant consequences for women's professional experiences of stress and health. What remains to be seen is whether sociocultural gender and related occupational stressors (eg, gender discrimination and harassment) might contribute to differences in biological functioning and the effectiveness of physiologically focused wellness interventions.

Biological Resilience Training: Heart Rate Variability Biofeedback

Research reveals a connection between respiration, arousal, and emotional control, such that how a person breathes sends signals to regions in the brainstem and forebrain that modulate arousal [28]. For example, periods of slow breathing are associated with SNS suppression and PNS stimulation, which may underlie the anxiety- and stress-reducing effects of RSA [28]. For nearly 3 decades, Lehrer and Gevirtz [21] have pioneered and refined a

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cardiorespiratory intervention called heart rate variability biofeedback (HRVBF). During HRVBF, a person is shown visual feedback of their beat-by-beat HR data while engaging in slow breathing with the goal of maximizing RSA. For clinically effective treatment, it is not sufficient to simply instruct a person to breathe slowly. Rather, HRVBF technology is required to identify the precise breathing rate for maximizing individual RSA and to condition this rate through training [29,30].

In collaboration with expert police practitioners as well as medical and academic experts in psychophysiological risk and resilience, the lead author developed the International Performance Resilience and Efficiency Program (iPREP), an in-person resilience program that improves occupational health and performance by addressing the unique acute and chronic stressors faced by police [31-33]. This program has been refined across 6 grant-funded multimethod studies with over 300 police participants measuring objective psychophysiological and behavioral data [31-40]. The components of the currently proposed intervention are based upon the same core scientific principles and validated intervention methods as iPREP, including mental health awareness and support [2] and psychophysiological techniques (ie, HRVBF) to promote resilience by conditioning adaptive HRV, RSA, and HR functioning [30,41,42]. Research has shown that the autonomic modulation techniques instructed during iPREP result in significant, long-term reductions in occupational errors and improvements in officers' ability to recover quickly from acutely stressful events when completed during scenario-based, in-person training [31-33].

Objectives

The aim of the proposed study is to develop (phase 1) and test (phase 2) if a web-based delivery of autonomic modulation training (AMT) can reduce symptoms of PTSI and build psychological wellness capacity and physiological resilience in police officers with similar effectiveness as in-person training. An additional novel scientific contribution of this protocol includes an examination of sex and gender in baseline biological and psychological presentations of PTSI among police and in response to a resilience-building intervention.

Hypotheses

Self-reported PTSI Symptoms and Resilience

The following 3 hypotheses were proposed:

- H1: Symptoms of PTSI will be significantly reduced following the completion of the AMT intervention.
- H2: Functional wellness capacity and resilience will be significantly improved following the completion of the AMT intervention.
- H3: Sex and gender differences in PTSI will be observed at baseline and postintervention assessments.

Specifically, we expect that self-identified females will report more symptoms of PTSI and lower resilience at baseline, a greater reduction of PTSI symptoms, and a greater increase in resilience at follow-up than self-identified males. Gender role stress, discrimination, and harassment will be explored as moderators of PTSI symptoms at baseline and in response to the AMT intervention.

Objective Biological Indicators of PTSI Symptoms and Resilience

The following 4 hypotheses were proposed:

- H4: Resting HRV will significantly increase following the completion of the AMT intervention.
- H5: RSA will significantly increase following the completion of the AMT intervention.
- H6: Recovery from acute stress will significantly improve following the completion of the AMT intervention.
- H7: Based on inconsistencies in the extant literature, we will conduct exploratory analyses of any potential sex and gender differences in HRV, RSA, and acute stress recovery at baseline and postintervention assessments.

Methods

Ethics Approval

This protocol has been approved by the University of Toronto's Social Sciences, Humanities, and Education Research Ethics Board (Protocol #39478).

Design

Capitalizing on the numerous long-standing professional relationships between study coinvestigators and police populations of interest, phase 1—development of the AMT intervention—will use an integrated knowledge translation (iKT) approach to generate user-informed content [42]. To test the effectiveness of the AMT intervention (phase 2), a cluster randomized control trial with parallel assignment will be used on several cohort samples of active-duty Canadian police officers. This study has been registered with ClinicalTrials.gov (NCT05521360).

Recruitment

We aim to test the AMT intervention on a sample of approximately 250 frontline police officers in rolling cohorts of 10-15 participants (half AMT, half waitlist control) from geographically representative police services across Canada. A power analysis was conducted using G*Power software [43] and found that a minimum total sample size of 128 participants was required (effect size f=0.25, α=.05, power=0.80, number of groups=2, number of repeated measures=2). However, we plan to oversample officers by sex and mitigate possible attrition based on the principal investigator's previous experience with conducting longitudinal research on police officers [31-33]. A small laboratory-based prepilot sample (n=10) will test equipment reliability, accuracy, and integration of HR monitors with HRVBF and learning management system (LMS) platforms. An initial pilot cohort 1 (n=30) will then test the AMT intervention in the population of interest (ie, law enforcement officers) using a combined laboratory-remote paradigm to validate the implementation of study procedures. These participants will also be invited to participate in a poststudy focus group as per the study protocol (see iKT Focus Groups in Procedures) to optimize the intervention (ie, content and delivery) and overall study procedures to provide

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stakeholder- and user-informed feedback. When all user feedback has been incorporated, all subsequent participants will be tested fully remotely and in accordance with the randomized control trial procedures and group allocation.

Participants will be recruited in several ways: (1) partnering police services will provide a link to the web-based study hosted on the confidential University of Toronto (ie, not police-related) servers to members via email, announcements, and internal media postings with encouragement to participate; (2) the research team will visit police services and other related fora (eg, industry meetings and conferences) to hold recruitment and information days where eligible officers may sign up for the study; (3) our knowledge user (MLV) and expert police practitioner collaborator (PS) will facilitate recruitment of law enforcement officers through targeted media attention, networking, and professional outreach activities; (4) supporting stakeholder groups will facilitate communication and recruitment with users and law enforcement officers. Based on delays due to the COVID-19 pandemic, the order in which partner organizations are recruited and tested is subject to change based on availability and current public health guidelines.

Interested participants will be directed to a web-based consent form on a secure site that will detail the study aims, eligibility criteria, intervention protocol, allocation and procedures for experimental and control groups, risks and benefits, and other information related to their rights as a research participant (ie, confidentiality and contact information for PIs and the institutional ethics board). Participants will provide their informed consent by clicking on a link that will take them to an eligibility screening survey that will collect the following identifiable information: full name, mailing address (for equipment shipping and incentive payment), personal email address (for correspondence with the research team that is not monitored or accessible by the participants' police agency), and demographics including sex at birth, gender, age, ethnicity, police service (to verify active duty status against publicly available directories), role, years of service as a police officer, and confirmation that they are not currently on extended medical leave. Participants deemed eligible for the study will be provided with deidentified usernames and passwords to access the preintervention assessment (see phase 2 procedures).

Inclusion and Exclusion Criteria

Inclusion criteria included adults (aged 18 years or older) currently employed as active duty (ie, not retired or on an extended medical or disability leave) frontline law enforcement officers fluent in English. Exclusion criteria include non-Canadian law enforcement officers, police administrators, civilian employees (ie, nonsworn members), and officers that do not have regular access to a computer with internet access to complete the web-based AMT intervention. Scores on self-reported mental health screening tools completed during the preintervention sessions will be used to match the assignment of participants to experimental or control groups but will not be used to exclude participants based on established cutoff scores for high or severe PTSI symptoms.

Procedures

Phase 1: AMT Development

Using an iKT approach, the multidisciplinary research team will consult with police practitioners to tailor AMT content (ie, graphics and recruitment materials) and promote participation and adherence to the AMT intervention by advising on procedural aspects of the research study (ie, feasibility, accessibility, understandability, and relevance). The AMT intervention is comprised of 2 components—HRVBF training and meta-cognitive coping skills.

HRVBF Training

Based on an established and publicly available protocol [30], HRVBF has shown significant efficacy in treating a wide variety of disorders, including general anxiety disorder [44-46], major depressive disorder [47-51], hypertension [52-54], asthma [29,55,56], pain [57-61], and posttraumatic stress disorder (PTSD) [62]. Recent meta-analyses revealed a large effect size for HRVBF on reducing symptoms of self-reported anxiety and stress [63] and a moderate effect for HRVBF and paced breathing across targeted physical symptoms and measures of functioning [64]. The original protocol is intended for in-person delivery, and this project will test the effectiveness of web-based HRVBF delivery among police officers. Therefore, the protocol will be formatted for web-based delivery and presented on an LMS using a commercially available HRVBF app paired with a wearable HR monitor.

Meta-cognitive Coping Skills

Integrated with HRVBF training, psychoeducational modules will be developed to help individuals cultivate meta-cognitive coping skills, defined as the awareness and understanding of one's own thought processes and learning how to manage the assessment of one's own experiences, correctly identify demands and resources, and regulate the appraisal of experiences using attentional and cognitive techniques [2]. Participants will also receive training on developing effective coping skills, including the ability to garner social support from family or friends, engage in positive relationships, and seek professional help when needed. Further, participants will receive training on emotion regulation, such as directing thoughts in the service of reducing demands or increasing resources, the ability to express emotions appropriately and keep them in perspective, and the ability to stay aware of policy and procedures under stress. These meta-cognitive coping skills are rooted in cognitive behavioral therapy principles that have been tested digitally [2] and will be developed in consultation with licensed psychiatrists and clinical coinvestigators (NA).

Research ethics approvals, data sharing agreements with partner institutions, and the procurement of equipment to record HRV and HRVBF will also be finalized during this phase of the study.

Phase 2: Testing the Efficacy of the AMT Intervention

Overview

The ention assessment, 6 weeks of AMT sessions, and a postintervention assessment. Once participants are deemed eligible for the study, they will be issued a unique deidentified

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username to access the web-based study, which will be hosted on secure LMS and survey platforms (eg, Qualtrics).

Session 1: Preintervention Assessment (1.5 Hours)

During this session participants will complete self-reported baseline measures of: (1) PTSI, including the Personal Health Questionnaire (PHQ-8) for major depressive disorder, General Anxiety Disorder Scale (GAD-7), Depression, Anxiety, and Stress Scale (DASS-42), PTSD checklist (PCL-5), Alcohol Use Disorder Identification Test (AUDIT), Perceived Stress Scale (PSS), and Personal Burnout Subscale of the Copenhagen Burnout Inventory (CBI) [65-71]; (2) resilience and well-being using the Brief Coping Orientation to Problems Experienced Inventory (Brief-COPE), Resilience Scale for Adults (RSA-33), Brief Resilience Scale (BRS), White Bear Suppression Inventory (WBSI), Perseverative Thinking Questionnaire (PTQ), Ultra Brief-Penn State Worry Questionnaire (UB-PSWQ), and Ultra Brief-Rumination Response Styles (UB-RRS) Questionnaire [72-78]; (3) functional wellness and occupational stress using the Sheehan Disability Scale (SDS), Good Health Practices Scale (GHPS), COVID-19 adapted version of the Holmes Rahe Stress Inventory (COVID-19 HRSI), World Health Organization Disability Assessment Scale (WHODAS 2.0) [79-82], operational and organizational subscales of the Police Stress Questionnaire (PSQ) [83], and Lam Employment Absence and Productivity Scale (LEAPS) [84]; and (4) sex and gender-relevant data using the Workplace Gender Discrimination Scale (WGDS) and Gender Experiences Questionnaire (GEQ) [85,86]. Global ratings of stress will be asked at the beginning of each AMT session using a sliding visual analog scale of 0 (not at all stressful) to 10 (extremely stressful) in response to 2 questions: “How stressful was this past week?” and “How stressed are you right now?.” Data will be immediately tabulated to randomly assign participants matched on demographic and outcome variables to either the experimental AMT intervention group that will continue with sessions 2-8 of the protocol or to the waitlist control group that will only be responsible for the first part of session 2 and all of session 8 (postintervention assessment).

Upon completion of session 1, participants will be asked if they want to continue in the study. This secondary “reconsent” is designed to conserve shipment of expensive study equipment (approximately USD $550 total) and retain eligible participants that demonstrate commitment to adhering to the study protocol. If participants agree to continue, they will receive a notification in their personal email confirming their mailing address and will be shipped necessary study materials, including compensation for completing session 1, a wearable HR monitor and chest band, a device equipped with the HRVBF app (an iPad), and a prepaid envelope to return all equipment at the end of the study. Once participants confirm receipt of their equipment in the mail, they will gain access to session 2.

Session 2: Baseline Physiological Assessment and Introduction to AMT (40-60 Minutes)

All participants will be taught via web-based video modules how to apply the wearable HR monitor and configure the HRVBF app. The wearable HR monitor will automatically record date and time-stamped physiological data upon contact with the skin via the chest band and will communicate with the HRVBF app via Bluetooth. All HRV data will be stored locally on the HRVBF app and study device, which will be mailed back to the research team at the end of the study period. In the first part of this session, both experimental and control participants will provide baseline resting HRV and RSA data that will be recorded while participants engage in a 7-minute neutral activity (eg, listening to prerecorded sounds) that does not stimulate arousal or relaxation (N Quigley, unpublished data, 2019). To assess recovery from an acute stressor, participants will perform web-based versions of the Paced Auditory Serial Addition Test (PASAT) [87] and the emotional Stroop task [88], both of which have been shown to induce significant sympathetic arousal but do not simulate traumatic material [28].

Following these baseline physiological assessments, participants in the experimental group will continue with the rest of their session (15-20 min) and begin the AMT intervention. Participants in the control group will not have any programming until session 8 (postintervention assessment).

AMT Intervention Sessions 3-7 (45-60 Minutes Each)

These sessions will be completed by participants in the experimental group only. The content of each AMT session will be modified from the Lehrer et al [30] HRVBF protocol and informed by practitioner, knowledge user, and stakeholder-informed design workshops to adhere to iKT principles and fit a web-based format [42]. Participants will use the HRVBF app linked via Bluetooth to their HR monitor to engage in paced breathing exercises, view their RSA progress and live HRVBF data, engage with psychoeducational content on the LMS, and complete their homework assignments (ie, paced breathing practice at least twice a day as per protocol) [30]. Participants will also view short video lectures, text, and educational content, and engage in practical exercises during each session. Participants will receive weekly emails with practice reminders and links to useful resources, including links to YouTube videos of their preferred breathing pace. Participants will learn about meta-cognitive and coping skills as they can help mitigate stress in operational, organizational, and personal contexts to foster holistic resilience and well-being.

Session 8: Postintervention Assessment (2 Hours)

All participants will receive an email reminder 1 week before the final session, which will be completed by both experimental and control participants. It will begin by obtaining objective physiological measures at rest, including HRV (7-minute neutral task), RSA (paced breathing), and recovery from acute stress (PASAT and Stroop tasks). Next, participants will complete the same self-reported questionnaires as in session 1 to assess changes in self-reported PTSI, resilience and well-being, occupational and operational stress exposure, and sex and gender-relevant data (see hypotheses). Participants in the control group will be asked if they would like to complete the AMT intervention. If so, they will be provided access to sessions 3 to 7 and will be asked to complete a second postintervention assessment (session 8) after completing the AMT intervention. Incentive payments will be processed as participants drop out or complete study assessments.

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iKT Focus Groups

Following cohort 1, we will invite participants to take part in iKT Focus Groups to generate user-informed feedback on the web-based AMT intervention and identify potential sex and gender differences in the user experience. Focus groups will be led by our sex and gender expert (RR) and use a semistructured, purposive, snowball sampling design. Half-day focus groups will be held in person, with dedicated focus groups for female and male participants to provide sex-stratified samples. We will limit focus groups to 5 participants, as previous research shows groups of 4-6 ameliorate the effects of "over sharing" or domineering participants, as well as participants who may feel intimidated and become silent within larger groups [89,90]. Groups will also include officers of the same rank, a sampling stratification strategy designed to help ensure interaction with others that are not perceived as threatening and with whom an individual's experience may also resonate [90,91]. Focus group discussions will last between 60 and 120 minutes and will be voice-recorded to preserve their accuracy during transcription.

Outcomes

In accordance with our hypotheses, PTSI (H1) will be measured by the PHQ-8, GAD-7, DASS-42, PCL-5, AUDIT, PSS, CBI, and self-reported stress visual analog scale. Self-reported resilience and well-being (H2) will be measured by the Brief COPE, RSA-33, BRS, WBSI, PTQ, UB-PSWQ, and UB-RRS. Functional wellness capacity and occupational stress will be measured by the SDS, GHPS, COVID-19 HRSI, WHODAS 2.0, PSQ, and LEAPS. Sex will be measured by self-reported sex at birth (male, female, or other); gender is measured by self-identification as male, female, nonbinary, or other (with the option to self-report) or "prefer not to disclose." Sex and gender-related experiences will be measured by the WGDS and GEQ (H3 and H7). Changes in resting HRV (H4) will be measured by time and frequency domain parameters based on data collected from the wearable HR monitors (eg, high- and low-frequency HRV, low- or high- frequency ratio, and the Root Mean Square of Successive Differences, [RMSSD]) as recommended in the standards of practice for HRV analysis [17]. RSA (H5) will be measured by obtaining respiratory frequency. Greater power at the respiratory frequency indicates a higher level of RSA and will be analyzed using the gold standard HRV analysis program, Kubios [92]. Recovery from acute stress (H6) will be measured following completion of the web-based PASAT and emotional Stroop Tasks. Acute stress recovery will be assessed via a time-domain measure of HRV (RMSSD) [17].

Data Security and Analyses

Any personally identifiable information provided in the eligibility questionnaire will be downloaded and immediately deleted from web-based platforms, stored offline in encrypted files on password-protected computers at the University of Toronto accessible only by members of the primary research team approved by the lead principal investigator (JPA), and will not be shared with collaborators or participating police organizations. Data collected on the LMS and secure survey platforms (ie, pre- and postintervention assessments and responses to intervention exercises) will be matched to a deidentified user ID. Physiological data gathered by the wearable HR monitor and HRVBF app will be stored locally and will not be transferred to publicly accessible third-party cloud-based servers. Rather, participants will mail the equipment back to the research team, which will match the deidentified data offline. The key code linking participants' personal information and deidentified user IDs will only be stored on secure servers at the University of Toronto and will be destroyed once the participant completes or withdraws from the study, has received their compensation, and all deidentified data files have been matched.

Physiological data will be transferred to a 2-time Canada Research Chair in Health Informatics and Big Data expert coinvestigator (CM) via a secure virtual private network (VPN) tunnel and housed on a private cloud-based Big Data analytics platform located within the *Compute Ontario Advanced Research Computing* equipment at the Centre for Advanced Computing (Queen's University). CM will design the data management, cleaning, and analysis protocols necessary to construct the big data pipeline to process the large amount of continuous data, including matching the time stamps on the physiological data to significant event markers in the AMT intervention (eg, questionnaires, PASAT, and emotional Stroop tasks) and on the HRVBF app (eg, paced breathing exercise). Preprocessed data will then be sent back to the primary research team (JPA, PMD, and SCS) via a secure VPN tunnel and housed on the secure internal University of Toronto server (RES-NAS) for the statistical analyses described below using bespoke syntax and code on various software platforms (eg, Kubios, MatLab, and SPSS). Data from iKT focus groups will be stored in RR's secure data web-based Al Fresco space and hard copies in her triple-locking filing cabinet in her office at the Memorial University of Newfoundland.

To test the effectiveness of the AMT intervention on reducing PTSI symptoms and improving resilience, we will conduct prepost analyses of the self-reported PTSI (H1) and resilience measures (H2) using separate repeated measures analyses of covariance (ANCOVAs) accounting for demographic covariates for normally distributed data, and ranked repeated measures ANCOVAs for nonnormally distributed data [93]. Variables including sex, gender (H3), age, years of service, and geographic service region (eg, urban or rural; East, Central, or West) will be included as covariates.

To test the effectiveness of the AMT intervention on improving biological indicators of resilience, prepost analyses of resting HRV parameters (H4), RSA (H5), and recovery from acute stress (H6) will be separately assessed using repeated measures ANCOVAs with sex, gender (H7), age, years of service, and geographic service region as covariates. To determine which factors significantly predict greater changes in biological outcome measures, hierarchical linear regression analyses will be undertaken with self-reported measures and demographic variables entered as predictors in the models. We will also compare weekly changes in HRV and RSA as measured during AMT module exercises with repeated measures ANCOVAs. A main effects analysis of the "time" variable will explore the potential incremental benefit of AMT training and identify at what point during the 6-week intervention significant biological

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changes occur. Computational approaches to analyzing and visualizing biological indices of resilience will be led by CM, including integration of cardiac (eg, HRV) and respiratory (eg, RSA) rhythms to elucidate patterns of desynchronization before, during, and following AMT.

To explore sex and gender-based contributions to self-report (H3) and objective indices (H7) of PTSI and resilience, the above analyses will include sex and gender as covariates or predictor variables with sex-stratified samples. These findings will clarify any sex-related differences in baseline and postintervention rates of PTSI and resilience among law enforcement officers and whether there are any sex-related differences in the magnitude of treatment effects (H3). Moderated regression analyses will test whether the AMT intervention affects the relationship between sex and PTSI symptoms and resilience. Multiple comparisons will be adjusted with Bonferroni corrections, where applicable.

Qualitative analyses of the transcribed data obtained from the iKT focus groups will be led by the sex and gender coinvestigator (RR) with the assistance of graduate students and postdoctoral fellows, with the aim of identifying sex- and gender-based considerations for developing effective occupational health interventions tailored to police officers and other PSP groups. Qualitative data analysis will use an inductive, comparative approach without initially arriving at any definitive, substantive, or theoretical conclusions about what the data reflect interpretatively with a lens on sociology and criminology [94]. Themes will emerge through the dynamic interaction of participants. Coding will be performed using NVivo qualitative analysis software (Lumivero), allowing for comparison across sessions [89] and the emergence of prominent themes through the tracking of coding “nodes” both across and within groups. Regular research team meetings will ensure that thematic development emerges in a consistent and reliable manner and help to ensure the hermeneutically attuned validity of the data [90].

Results

The study received notice of funding acceptance in March 2020. In February 2021, ethics approval was obtained from the University of Toronto’s Social Sciences, Humanities, and Education Research Ethics Board (Protocol #39478) and was renewed in February 2023. Phase 1 of the study (AMT Development) was completed in December 2022. Participant recruitment for phase 2 began with the pilot cohort in February 2023 via advertisements through partnering stakeholders (see Recruitment section). As of April 2023, 7 pilot participants were actively registered for the AMT intervention. Knowledge dissemination for phase 1 was completed in March 2023 at an annual meeting of the public safety wellness team grant holders and is planned for 1 scientific (May 2023) and 1 practitioner (October 2023) conference. iKT focus groups will take place following the completion of each sufficient cohort (see the iKT Focus Groups section above).

Discussion

Based on the extant and precedent literature, we predict that the stated hypotheses will be confirmed following the execution of the proposed protocol. Specifically, we anticipate significant reductions in PTSI symptoms and improvements in physiological indicators of health and resilience following the completion of the 6-week web-based AMT intervention. We also anticipate sex- and gender-based differences in pre- and postintervention outcomes, such that self-identified females will report higher PTSI symptoms and lower resilience at baseline and a greater reduction of PTSI symptoms and greater increase in resilience at follow-up than self-identified males. The direction and magnitude of sex- and gender-based differences in physiological outcomes are not currently specified, given the novelty of these analyses. Insights derived from iKT focus groups will supplement the quantitative sex- and gender-based analyses (H3 and H7).

AMT fills an existing gap in the applied research literature supporting evidence-informed prevention and intervention programs for PSP exposed to PTSI, such that AMT aims to measure and strengthen objective biological resilience [12]. Specifically, we are developing a tool that integrates wearable technology, real-time app-based visualized biofeedback tailored to an individual’s biological rhythms, and confidential web-based resources that meet the needs of accessibility and availability expressed by PSP organizations and governmental agencies [16]. Furthermore, our project addresses population-specific needs, including stigma reduction and gendered perspectives on occupational and organizational stress from female officers. By delivering our program on an LMS platform that can be accessed remotely in the privacy of one’s own home, we are providing officers with a secure and accessible wellness promotion intervention and resources that they might not otherwise seek out. This project will also contribute substantial new knowledge to the scarce literature about how sex and gender are related to biological indicators of PTSI and resilience (ie, HRV and RSA). Specifically, analyses will reveal the directionality and strength of interactions between sex and gender and physiological resilience outcomes (eg, what was thought to be sex-based differences in HRV may be related to gender norms and gender stress; see [95]). Our study provides a well-powered design to sufficiently address the persistent knowledge gap in this area.

AMT techniques have previously garnered high “buy-in” from participating police officers because the intervention provides tangible, real-time, biological evidence of occupational and health improvement from the very first HRVBF session [31-34]. Buy-in is further promoted by potentially relieving some symptoms early on without having to wait until the end of the intervention. Further, AMT directs focus on more “physical” rather than “psychological” symptoms to reduce the association of PTSI with potential weakness or occupational inadequacy among police, which has been previously noted [33,96].

Pending significant results, AMT can be delivered alone or in tandem with other psychotherapeutic treatments, such as cognitive behavioral therapy, to provide PSP services with an

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attractive suite of resilience and wellness capacity interventions that reduce PTSI symptoms and save operating costs (eg, maintenance fees for multiple participant licenses) [97]. The intervention, if found to be effective, can be implemented on a larger scale with affordable, commercially available wearable technology (eg, FitBit and Apple iWatch) and apps (eg, HRV Trace and HRV Train) [98].

Rapid and direct knowledge dissemination to various stakeholders (eg, police organizations, unions, and professional and nonprofit first responder organizations such as The Haven, Badge of Life Canada, Ontario Women in Law Enforcement, and Wounded Warrior) will be facilitated by knowledge users' (MLV and PS) capacities as retired PSP, board members, and English-French bilingual contributors to police periodicals including "The Blue Line." In addition to this protocol, several research articles will be prepared based on the planned objectives and analyses identified above. High-impact peer-reviewed journals in relevant fields (eg, Psychophysiology, International Journal of Environmental Research and Public Health, and Policing) that provide open access options will be prioritized. Research findings on the pilot (n=30) and complete data sets (n=250) will be disseminated at scientific (Association for Applied Psychophysiology and Biofeedback, Society for Psychophysiological Research) and applied practitioner conferences (Law Enforcement and Public Health, Canadian Institute for Military and Veteran Health Research, Canadian Association of Chiefs of Police, Canadian Association of Police Educators) to distribute new knowledge generated to the widest audience possible.

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Data Availability

To protect the privacy and confidentiality of participants, which are comprised of active-duty Canadian police officers, the data sets generated or analyzed during this study are not publicly available, but deidentified or aggregated data may be available from the principal investigator (JPA) on reasonable request.

Authors' Contributions

All authors have read and approved the submitted version of this manuscript. JPA, PMD, RR, and CM wrote the first draft of the manuscript. JPA, PMD, SCS, and CM wrote the final draft of the manuscript. JPA was responsible for conceptualization. NA, GA, CB, CM, RR, PS, and MLV were involved in consultation, coinvestigation, and final manuscript edits.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review from the Canadian Institutes of Health Research (CIHR).
[PDF File (Adobe PDF File), 248 KB - resprot_v12i1e33492_app1.pdf]

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Abbreviations

AMT: autonomic modulation training
ANCOVA: analysis of covariance
ANS: autonomic nervous system
AUDIT: Alcohol Use Disorder Identification Test
BRS: Brief Resilience Scale
CBI: Copenhagen Burnout Inventory
COVID-19 HRSI: COVID-19 adapted version of the Holmes Rahe Stress Inventory
DASS-42: Depression and Anxiety Stress Scale-42 Item
GAD-7: General Anxiety Disorder Scale-7 Item
GEQ: Gender Experiences Questionnaire
GHPS: Good Health Practices Scale
HR: heart rate
HRV: heart rate variability
HRVBF: heart rate variability biofeedback
iKT: integrated knowledge translation
iPREP: International Performance Resilience and Efficiency Program
LEAPS: Lam Employment Absence and Productivity Scale
LMS: learning management system
PASAT: Paced Auditory Serial Addition Test
PCL-5: PTSD Checklist (DSM-5)
PHQ-8: Personal Health Questionnaire-8 Item
PNS: parasympathetic nervous system
PSP: public safety personnel
PSQ: Police Stress Questionnaire
PSS: Perceived Stress Scale
PTQ: Perseverative Thinking Questionnaire
PTSD: posttraumatic stress disorder
PTSI: posttraumatic stress injury
RSA: respiratory sinus arrhythmia
RSA-33: Resilience Scale for Adults-33 Item
SDS: Sheehan Disability Scale
SNS: sympathetic nervous system
UB-PSWQ: Ultra Brief-Penn State Worry Questionnaire
UB-RRS: Ultra Brief-Rumination Response Styles
WBSI: White Bear Suppression Inventory
WGDS: Workplace Gender Discrimination Scale
WHODAS 2.0: World Health Organization Disability Assessment Scale 2.0

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Protocol

A Comprehensive Self-Management Intervention for Inflammatory Bowel Disease (CSM-IBD): Protocol for a Pilot Randomized Controlled Trial

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Abstract

Background: Despite pharmacological treatment, individuals with inflammatory bowel disease (IBD) experience a variety of symptoms, including abdominal pain, fatigue, anxiety, and depression. Few nonmedical self-management interventions are available for people with IBD. A validated comprehensive self-management (CSM) intervention is effective for patients with irritable bowel syndrome who can have symptoms similar to those of individuals with IBD. We created a modified CSM intervention tailored to individuals with IBD (CSM-IBD). The CSM-IBD is an 8-session program delivered over 8-12 weeks with check-ins with a registered nurse.

Objective: The primary objective of this pilot study is to determine the feasibility and acceptability of study procedures and the CSM-IBD intervention and to evaluate preliminary efficacy on quality of life and daily symptoms for a future randomized controlled trial. Additionally, we will examine the association of socioecological, clinical, and biological factors with symptoms at baseline and response to intervention.

Methods: We are conducting a pilot randomized controlled trial of the CSM-IBD intervention. Participants aged 18-75 years who are experiencing at least 2 symptoms are eligible for inclusion. We plan to enroll 54 participants who will be randomized (2:1) into the CSM-IBD program or usual care. Patients in the CSM-IBD program will have 8 intervention sessions. Primary study outcomes include the feasibility of recruitment, randomization, and data or sample collection, as well as the acceptability of study procedures and interventions. Preliminary efficacy outcome variables include quality of life and symptoms. Outcomes data will be assessed at baseline, immediately post intervention, and 3 months post intervention. Participants in the usual care group will have access to the intervention after study participation.

Results: This project is funded by the National Institutes of Nursing Research and reviewed by the University of Washington's institutional review board. Recruitment began in February 2023. As of April 2023, we have enrolled 4 participants. We expect the study to be completed by March 2025.

Conclusions: This pilot study will evaluate the feasibility and efficacy of a self-management intervention (a web-based program with weekly check-ins with a registered nurse) that aims to improve symptom management in individuals with IBD. In the long term, we aim to validate a self-management intervention to improve patient quality of life, reduce direct and indirect costs related to IBD, and be culturally appropriate and accessible, particularly in rural and underserved communities.

Trial Registration: ClinicalTrials.gov NCT05651542; https://clinicaltrials.gov/ct2/show/NCT05651542

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KEYWORDS

inflammatory bowel disease; self-management; symptom management; pilot; intervention; randomized controlled trial

Introduction

Background and Rationale

Inflammatory bowel disease (IBD; including ulcerative colitis and Crohn disease) is a chronic immune-mediated disease of the gastrointestinal system that impacts individuals worldwide. Patients with IBD are often diagnosed at a young age and experience a lifetime of disease management, with symptoms including diarrhea, pain, fatigue, urgency, anxiety, and depression [1,2]. These symptoms result in suffering, substantial health care costs, and indirect costs related to work and school impairment, with fatigue being the most common reason for work absenteeism [3]. Health care providers are often not trained to manage noninflammatory symptoms, and with improved medications such as biologics and small molecule therapy, the disconnect between patient symptoms and management is widening [4,5]. Our team has a comprehensive solution to help patients with irritable bowel syndrome manage symptoms and improve self-management skills that can be adapted for an IBD population to address the urgent need for symptom management.

Within the United States, approximately 3.1 million individuals have a diagnosis of IBD [6]. As societies become more westernized, IBD incidence and prevalence have increased worldwide [7]. IBD affects men and women equally, although ulcerative colitis is slightly more common in males and Crohn disease is slightly more frequent in females [8]. In the past, it was thought that IBD occurred less frequently in racial and ethnic minorities compared with whites; however, this gap is narrowing with an increased incidence of IBD among African American and Asian individuals [9]. Therefore, with growing incidence and prevalence worldwide and among racial and ethnic minority populations, IBD represents a growing health problem demanding tailored, culturally appropriate, and effective interventions.

Immunosuppressive therapy can be effective in achieving control of endoscopic inflammation from IBD; yet, patients can experience symptoms while they await response to therapy or in the setting of refractory disease [10,11]. Patients can also have chronic symptoms, even after achieving remission, due to damage from chronic disease, altered surgical anatomy, or co-occurring functional symptoms [12]. While immunosuppression is essential in achieving and maintaining endoscopic remission for patients with moderate-severe IBD, other interventions are needed to improve symptom management and quality of life.

Symptom-directed medical therapies (eg, antidiarrheals, antiemetics, antispasmodics, and neuromodulators) offer symptom relief for some but are not effective for everyone and offer limited benefit for symptoms such as pain and fatigue. Nonpharmacological interventions such as dietary modification, relaxation techniques, and cognitive behavioral therapy (CBT) have been shown to improve symptoms [13,14], but teaching patients how to implement these interventions is time-consuming and impractical to achieve in a routine clinic visit. Some clinics have used an IBD specialty medical home model, which can reduce hospitalizations and emergency department visits as well as increase the quality of life [15]. Yet, patient access to providers who are experienced in these interventions and care delivery systems can be limited, especially in rural and underserved communities [16,17].

As the majority of a patient's time is spent outside of the clinic, there is a need to empower patients with the skills to manage their disease. Self-management refers to the day-to-day management that individuals must engage in while living with a chronic condition [18,19]. Among individuals with other chronic conditions, self-management programs are effective in reducing hospitalizations, days in the hospital, and fatigue while increasing self-reported health [20,21]. Despite the effectiveness of self-management programs among other chronic condition populations, few effective self-management interventions exist for individuals with IBD [22]. A systematic review identified 6 self-management randomized controlled trials conducted among individuals with IBD (representing 1715 patients) [22]. However, only half of the interventions improved health-related quality of life or reduced disease activity at 12 months. Psychological outcomes were reported by 2 studies, and 1, which used a written self-management plan developed with a clinician, failed to demonstrate an improvement in depression and anxiety [23,24].

An existing comprehensive self-management (CSM) intervention that provides patient education on nonmedical interventions for symptom management (eg, dietary modification, stress reduction, and CBT) has been shown to improve quality of life and decrease abdominal pain in patients with irritable bowel syndrome [25-27]. Furthermore, the intervention reduced anxiety, depression, fatigue, and extraintestinal pain and improved self-reported sleep compared to usual care [28,29]. To date, CSM interventions have not been routinely used in patients with IBD. Because there is a significant overlap between symptoms of irritable bowel syndrome and those of IBD, we hypothesized that adapting the CSM intervention to a population of individuals with IBD may also be effective (CSM-IBD). However, this remains to be tested.

Objectives

The objectives of this pilot randomized controlled trial are to (1) determine the feasibility and acceptability of study procedures (recruitment, randomization, and data and sample collection) and CSM-IBD; (2) compare CSM-IBD to usual care on changes from baseline to 3 months post intervention in

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quality of life and daily symptoms (fatigue, sleep disturbance, psychological distress, gastrointestinal symptoms) among IBD patients and (3) explore the association of socioecological factors (age, sex, race, ethnicity, or diet), clinical phenotype (medications, disease distribution, and disease activity), and biological signatures (microbiome and calprotectin) with symptoms at baseline and response to intervention (post intervention).

Methods

Study Design

The proposed study is a 2-arm pilot randomized controlled trial that follows the Consolidated Standards of Reporting Trials and Standard Protocol Items: Recommendations for Interventional Trials guidelines [30,31]. In a 2:1 ratio, 54 participants will be randomized (intervention=36 participants; usual care=18 participants). This randomization scheme was selected to maximize data collection and information regarding the intervention group. The intervention will take place over 8 sessions. The participants will be blinded to the study hypotheses. Web-based self-reported questionnaires will be used to reduce detection bias.

Theoretical Framework

This study is guided by the Individual and Family Self-Management Theory (IFSMT) [32]. The IFSMT has 3 dimensions: context, process, and outcomes. It posits that interventions can influence the context and process (Figure 1). The context includes not only the individuals with IBD but also the complexity of the condition or treatment, individual factors (eg, age and sex), and social determinants of health such as food access and environmental settings, which can influence self-management skills and the ability to self-manage. In the IFMST, the process includes knowledge and beliefs (patient activation), self-regulation skills and abilities, and social facilitation and support (see Table 1 for the IFSMT process and CSM-IBD content). The IFSMT process of knowledge and beliefs includes Bandura self-efficacy theory, in which the intervention enhances self-efficacy (an individual's belief in their capacity to execute behaviors) and thus improves self-management [33,34]. Specific strategies and approaches used within the intervention are based on the expansive literature on CBT [35,36]. By impacting both the context and process, the intervention can influence the outcome to decrease symptoms and improve quality of life.

Figure 1. Individual and Family Self-Management Theory.

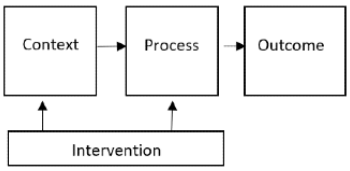


Table 1. IFSMT[a] self-management processes and CSM-IBD[b] content.

IFSMT process	IFSMT description	CSM-IBD content
Knowledge and beliefs	• Factual information • Self-efficacy • Goal congruence	• "When to contact your provider" • Introduction to strategies • Explanation of self-management • Personalized goals
Self-regulation skills and abilities	• Goal-setting, self-monitoring, reflective thinking • Decision-making, planning and action • Self-evaluation • Patient activation	• Abdominal breathing • Alternative thinking • Passive or active progressive muscle relaxation • Cognitive distortions • Sleep patterns, sleep hygiene • Pain management
Social facilitation	• Social influence • Support	• Eating out • Travel

[a]IFSMT: Individual and Family Self-Management Theory.

[b]CSM-IBD: comprehensive self-management for inflammatory bowel disease.

Study Population

Participants are individuals seeking care for their IBD at the University of Washington (UW). Inclusion criteria include participants who (1) have a health care provider diagnosis of IBD as reported in the electronic medical record, (2) report at least 2 current, active symptoms (Short Inflammatory Bowel Disease Questionnaire [SIBDQ] equal or less than 4 ["some of the time"] on any 2 items), (3) are 18 to 75 years old, and (4) are able to read and write in English. Participant exclusion criteria include (1) pregnant individuals, (2) significant co-occurring mental or physical conditions that would impact study participation, (3) surgery or hospitalization within the past month, or (4) living outside of Washington State.

CSM Intervention

The 8-session CSM includes patient education about self-management of symptoms using CBT, relaxation training,

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and diet counseling. The intervention will be delivered digitally with skill videos, readings, and homework, as well as a weekly phone call or Zoom check-in with a nurse trained in CBT. For each session, participants will review information and practice skills on the session topic. The content for each session is outlined in Table 2. The weekly phone calls are designed to provide accountability and support for achieving the session goals and to enable individuals to ask questions about the content. The estimated time of completion is 8 weeks; however, participants will have 12 weeks to complete the sessions to allow for unexpected events. Intervention fidelity will be monitored using fidelity checklists and through the evaluation of a random selection of 20% of participants.

Also of note, the original CSM intervention was administered as a paper workbook with weekly hour-long sessions with a trained advanced practice nurse. To improve accessibility and feasibility, we have adapted the intervention to be administered as a web-based intervention with weekly phone call check-ins with a CBT-trained nurse. This unique approach expands the feasibility and reach of the intervention by enabling patients who may live in rural or underserved areas to access the intervention content. To be appropriate for the IBD population, the session 1 disease content was modified to include the role of inflammation, the importance of endoscopic remission, and information on when to contact their health care provider. The intervention content was reviewed by patients and health care providers.

Table 2. Comprehensive self-management for inflammatory bowel disease (CSM-IBD) by session.

Session	Content
Introduction and tracking symptoms session	• "When to contact your provider" • Introduction to IBD[a] • Introduction to strategies and self-management • Personalized goals and social support
Abdominal breathing and stress session	• Role of stress • Abdominal breathing
Problem-solving and travelling session	• Alternative thinking or problem-solving • Travelling
Healthy thought patterns session	• Healthy thought patterns • Automatic thoughts
Sleep and physical intimacy session	• Sleep tracking • Sleep hygiene • Physical intimacy
Pain management and quick relaxation session	• Pain management • Passive or active progressive muscle relaxation
Healthy eating, tracking, and trigger foods session	• Tips for healthy eating • Eating out
Comprehensive plan session	• Developing a comprehensive plan

[a]IBD: inflammatory bowel disease.

Usual Care

The intervention group will be compared to a usual care group of participants who meet the same eligibility criteria. Due to a current lack of standardization in managing IBD within the clinic setting, a usual care patient group most accurately reflects current practice.

Study Outcomes

Feasibility Outcomes

Feasibility will be evaluated for study procedures (recruitment, randomization, and data and sample collection) and the CSM-IBD intervention.

1. Recruitment: the number and percentage of participants prescreened, approached, screened, and enrolled.
2. Randomization: we will assess dropout rates between the CSM-IBD and usual care.
3. Data collection: the quality of data will focus on the data completeness of questionnaires; missing data will be reported as a percentage of missing data and the time point at which missing data occurred. Bivariate comparisons will be made between individuals with and without missing data. Information on sample collection time, transit time, and processing time will be obtained.
4. Sample collection: we will report how many participants collected biological samples on the planned date and the length of time from sample collection to arrival at the laboratory.
5. Intervention feasibility: measured with the Feasibility of Intervention Measure, in which participants respond to 4 questions on a 5-point Likert scale from 1=completely

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disagree to 5=completely agree at the end of the intervention [37].

Acceptability Outcomes

A semistructured interview guide will be used to assess the acceptability of study procedures as well as the acceptability and satisfaction with the CSM-IBD. For instance, questions will probe for clarity of instructions, the burden of study procedures, and satisfaction with intervention content and delivery. Transcripts from participant interviews will be coded by 2 individuals using open coding methods to evaluate intervention acceptability. The use of CSM-IBD strategies will be assessed at 3 months post intervention by asking participants how often they use each strategy, with response options as: not at all or rarely, occasionally (at least 1 day a week), often (at least 2 days a week), very often (at least 4 days a week), or almost always [38]. Participants will complete the Acceptability of Intervention Measure, which includes 4 questions rated on a 5-point Likert scale from 1=completely disagree to 5=completely agree [37]. Satisfaction will also be measured with the 8-item Client Satisfaction Questionnaire [39].

Primary Outcomes

Quality of Life

The SIBDQ is a 10-item questionnaire that evaluates the quality of life. Participants respond on a 7-item Likert scale from all the time to none of the time. Total score range: 10 to 70 [40].

Symptoms

Symptoms are measured using a numeric rating scale where participants report the severity of the symptom from 0=not present to 10=worst possible. Symptoms include abdominal pain, anxiety, bloating, constipation, depression, diarrhea, fatigue or tiredness, passing gas, sleepiness during the day, stress, and urgency. See Multimedia Appendix 1 for a copy of the IBD Symptom Scale.

Secondary Outcomes

1. Process variables [41,42]
   - Self-Efficacy for Managing Chronic Disease: a 6-item self-report scale. Participants report ranging from not at all confident to totally confident [21].
   - Index of Self-Regulation: a 9-item scale to measure an individual's level of self-regulation [43].
   - Patient Activation Measure: a 13-item scale that assesses patients' beliefs, knowledge, and confidence in managing their health [44,45].
2. Biological signatures: stool samples will be collected by participants and stored immediately in home freezers (–20 °C) before transport to the UW School of Nursing Biobehavioral Laboratory. Samples will be stored at –80 °C until batch processing.
   - Gut microbiome: fecal microbial communities will be characterized using metagenomic shotgun sequencing on the Illumina MiniSeq or NextSeq platforms (Illumina, Inc) [46,47].
   - Fecal calprotectin: fecal calprotectin is a biomarker used to measure inflammation in the gut and will be assessed using an enzyme-linked immunosorbent assay [48].
3. Socioecological factors were selected based on the National Institute for Nursing Research's common data elements and include sex, gender, age, race or ethnicity, education level, employment, marital or partner status, household size, and neighborhood (urban or rural, zip code). Dietary intake can influence the composition of the gut microbiome and symptoms [49]. At the time of the stool collection, subjects will complete a detailed 3-day food record (Fred Hutchinson Cancer Research Center Nutrition Assessment).
4. The clinical phenotype will be obtained from the electronic medical record: type of disease, time since diagnosis, history of bowel surgery, disease distribution (measured by the Montreal Classification), medications, and disease activity (Harvey Bradshaw Index for Crohn Disease [50] and Simple Colitis Activity Index for Ulcerative Colitis [51]; <5 indicates remission).
5. Health care use will be evaluated from the electronic medical record and patient self-report, including emergency department use, hospitalizations, outpatient visits, laboratory tests, imaging, and procedures, as well as providers' nonclinical time spent managing patients.

Participant Timeline

Multimedia Appendix 2 presents the schedule of enrollment, interventions, and assessments based on the Standard Protocol Items: Recommendations for Interventional Trials guidelines. All procedures will occur remotely; data collection will occur digitally through REDCap (Research Electronic Data Capture; Vanderbilt University), a secure Health Insurance Portability and Accountability Act (HIPAA)–compliant database [52,53]. Individuals meeting eligibility criteria and interested in the study will be asked to sign a consent form and HIPAA form prior to participating in the study. All participants will complete baseline questionnaires (socioecological factors and disease information). Participants will collect a stool sample at home using a stool sample collection kit (instructions and researcher contact information will be provided); a 3-day food record will be collected starting 2 days before the stool sample collection. The stool samples will be placed in home freezers and returned to the School of Nursing Biobehavioral Laboratory. Participants will be provided with ice packs, a Styrofoam mailing box, and return labels. Stool samples will be stored at –80 °C until batch processing.

Following baseline data collection, participants will be randomly assigned to the 8-session CSM-IBD or usual care. Immediately post intervention, participants will complete questionnaires, collect a stool sample, and report a 3-day food record. Three months post intervention, participants will complete questionnaires and participate in a qualitative data collection interview. In addition, participants will report whether or not they are continuing the self-management skills learned in the intervention. Semistructured interviews will be conducted to understand the participants' perspective on procedural burden and suggestions to improve the intervention, including satisfaction with the intervention (see Multimedia Appendix 3). Interviews will be recorded and transcribed. Participants will

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be compensated for each assessment completed (baseline, immediately post intervention, and 3 months post intervention). To increase retention, participants in the usual care group will be provided access to the intervention upon study completion. Participants can continue the study despite not completing all data collection assessments and all intervention sessions.

Sample Size

Based on recommendations for preliminary studies [54], we aim for data on 54 participants (36 intervention and 18 usual care). The sample size is appropriate for assessing feasibility and acceptability (aim 1). For aim 2, we will be able to detect fairly large effect sizes of 0.81 with 80% power. For aim 3, there will be 80% power to detect a correlation of 0.45. As a pilot study, the project is not powered to detect differences or correlations unless they are large.

Recruitment

Overview

Participant recruitment will take place at the UW Inflammatory Bowel Disease Clinics. The UW sees a large number of patients with IBD and serves as a tertiary care clinic for patients with IBD in the Washington, Oregon, Alaska, Montana, and Idaho regions. Recruitment may occur in three different settings: (1) in a clinic, (2) virtually (via telephone, email, or mail), and (3) by posting on the Institute of Translational Health Sciences website. All individuals will be informed that participating or not participating will not influence the care that they receive.

In a Clinic

Weekly prescreening will occur to determine if participants with scheduled IBD clinic appointments may be eligible for the study. The goal of prescreening is to enable purposeful sampling of patients based on demographic (eg, age and race) and disease characteristics (eg, disease activity). Individuals who are eligible will receive a flyer containing the study purpose and contact information from either their health care provider or study staff (depending on feasibility and current COVID-19 restrictions). Individuals will have time to review the study information. Participants can call study staff or complete a REDCap survey to express their interest and complete screening questions.

Virtually

The team may contact potential participants via phone, email, or mail if in-person recruitment becomes difficult or not feasible. All contact will follow the UW's institutional review board guidelines for cold contact recruitment. Those expressing interest in the study will call study staff for more information and then complete additional screening questions.

Institute of Translational Health Sciences Website

Information regarding the study will be posted on the UW Institute of Translational Health Sciences website. Interested individuals can complete the contact form to be contacted by study staff and can complete screening questions digitally.

In all instances, the purpose of the study, study design, and length of time to complete the study will be discussed. To assess participants' understanding of study procedures, individuals will be asked to briefly describe the study. Interested individuals will complete additional screening questions to confirm whether patients meet the specified inclusion and exclusion criteria. Screening questionnaires may be completed over the phone or electronically via REDCap, based on patient preference. Those meeting inclusion or exclusion criteria will be invited to participate in the study, sign a consent form, and begin data collection. Throughout the entire process of informed consent, from the first contact with the patient, the potential participants are able to ask any questions or delay making a decision. This screening and recruitment process will continue until the target sample size has been reached.

Intervention Allocation

A computer adaptive randomization procedure using a modification of the minimization method proposed by Pocock and Simon [55] will be used to balance groups based on SIBDQ at baseline. Once the data are entered into the computer, the computer program will return the participants' group assignment.

Statistical Analysis

Feasibility

The number and percentage will be calculated for participants who were prescreened, approached, screened, and enrolled (recruitment). We will assess dropout rates between the CSM-IBD and usual care (randomization). Quality of data will focus on the data completeness of questionnaires; missing data will be reported, and bivariate comparisons will be made between individuals with and those without missing data (data collection). We will report how many participants collected biological samples within the desired timeframe (sample collection). The mean and SD will be reported for the Feasibility of Intervention Measure (intervention feasibility).

Acceptability

Transcripts from participant interviews will be coded by 2 individuals using open coding methods (acceptability and satisfaction). In addition, numbers and percentages will be reported for participants who continue to use self-management strategies 3 months post intervention.

Primary Outcomes

Data from the 2 follow-up time points (immediate and 3 months post intervention) will be analyzed together using linear mixed models for each of the outcomes. For example, one model will have a change in the quality of life from baseline to immediate and 3 months post intervention as the outcomes, subject as a random effect, time (immediate or 3 months) as a within-subject fixed factor, and treatment group as an across-subject fixed factor. Baseline quality of life will be included as a covariate in the model, as will any baseline variables that differ between the 2 treatment groups. The parameter for the treatment group factor will provide an estimate of the treatment effect, that is, the difference between the treatment groups in mean change in the quality of life, and a 95% CI on the estimated difference will be computed. We hypothesize participants in the CSM-IBD will report a greater reduction in symptoms compared to those in usual care. A second model will also include an interaction between group and time to test whether the treatment effect is

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different at the 2 post intervention times. Additional analyses will estimate treatment effects separately for men and women.

Secondary Outcomes

Analyses of microbiome data will use 3 summary measures—Shannon diversity, richness, and *Firmicutes/Bacteroidetes* ratio—as well as the relative abundance of bacterial families (eg, family Ruminococcaceae) and genera and will control for the read count. For diet, we will focus on protein and fiber intake, as our previous work has indicated these may be important dietary intake components related to the gut microbiome. First, we will examine the associations between socioecological, clinical phenotype, and biological signatures with symptoms at baseline in the total sample using Pearson correlation or Spearman rank correlation based on measure distributions. Scatter plots will be used to visually display these associations. Second, we will examine associations between socioecological, clinical phenotypes, and biological signatures at baseline and response to intervention in the intervention group. Response to intervention is conceptualized as an increase of 8 points on the SIBDQ scale (quality of life) [40] or a 50% decrease from baseline in the GI symptom score [27]. Among the intervention group, we will use the *t* test and chi-square test to compare socioecological factors, clinical phenotypes, and biological signatures among patients with and without a response to treatment.

Monitoring

This study has been classified as a minimal-risk study. The principal investigator has the responsibility for study oversight, including patient safety and data quality, as well as submitting reports to the funder and the institutional review board. Due to the low-risk nature of the CSM-IBD, we do not anticipate any adverse events or serious adverse events. The data safety and monitoring team will meet quarterly to review the study. The team will monitor accrual, withdrawals, data quality, timeliness of data submission, protocol compliance, and the types and frequency of adverse events and serious adverse events. No interim analysis or stopping rules are currently planned. However, if any adverse events or serious adverse events are reported, the data safety and monitoring team will meet within a week to discuss the event and any potential changes needed to the study procedures.

Ethics and Dissemination

Data Management

Study data will be collected and stored on REDCap. Participants will be assigned a unique study identification number. Only study members will have access to the data through a password-protected system and will have access to the least amount of data required for their position using limitations in REDCap user rights. The study will use ongoing quality control procedures during data collection, storage, and processing, including the use of the REDCap data quality module.

Ethics Approval

The institutional review board at the UW approved this protocol (STUDY 00015210) and determined the study to be minimal risk. This study is registered in ClinicalTrials.gov (NCT05651542). Any amendments to the study will be reviewed by the institutional review board and subsequently updated in the ClinicalTrials.gov registry. Participants in the usual care group will be offered access to the CSM-IBD intervention after they complete the 6-month data collection.

Dissemination

Study findings will be disseminated through presentations and publications to clinicians and researchers. Findings will be reported to the community through lay presentations and social media. Individuals will be eligible for authorship based on the International Committee of Medical Journal Editors' recommendations. The study will provide the basis for future research on self-management interventions. The findings of the study will be used to refine the intervention and develop a full-scale trial with additional recruitment sites throughout diverse geographical regions.

Patient Involvement

This study is informed by a patient advisory group that was convened for the purpose of providing advice and oversight for the study.

Results

This pilot randomized controlled trial was funded by the National Institute of Nursing Research (K23NR020044) in April 2022. Recruitment began on February 20, 2023. As of April 2023, we have enrolled 4 participants. We expect the study to be completed by March 2025.

Discussion

Expected Findings

This project is focused on evaluating the feasibility, acceptability, and preliminary efficacy of a CSM intervention for improving the quality of life and symptoms among individuals with IBD. We expect that overall participants will find the intervention acceptable and feasible, as mixed methods systematic review reported that greater than 75% of participants in IBD-related telehealth and mobile health interventions reported satisfaction with the intervention [56]. We also anticipate receiving feedback from participants on ways to improve the intervention.

Further, we expect to find preliminary signals of efficacy. A similar CSM intervention implemented in individuals with IBS showed reductions in anxiety, depression, abdominal pain, fatigue, and extraintestinal pain and improvements in sleep and quality of life [25-29]. A recently published study of a digital health program in IBD reported promising improvements in stress and energy levels, with a participant retention rate of 40% [57]. We hope that our approach of incorporating weekly check-ins will lead to higher retention rates. Findings from the study will be used to refine the intervention and develop a full-scale trial that will incorporate additional recruitment sites from diverse geographical regions. In future trials, we plan to collaborate with a variety of clinical practice settings, including community-based and academic settings.

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Strengths and Limitations

Individuals participating in a pilot self-management intervention may be more interested in or engaged in research and self-management than a general clinic population. Additionally, recruitment is currently focused on an academic medical setting, which may have a more medically refractory group of patients. Thus, expanding recruitment to other sites (eg, community sites) may assist with generalizability. To enhance its feasibility and reach, the intervention has been adapted into a web-based format.

Future Directions

If CSM-IBD proves effective, further research into predictors of response to CSM would be warranted, including assessing the correlation with the microbiome, histology, or co-occurring illness (eg, depression and anxiety). Other future directions include consideration for implementation barriers and facilitators. Future work may consider multilevel interventions that can impact the health care system level to promote self-management and quality of life.

Conclusions

The results of this study will inform the development of a full-scale clinical trial to examine the impact of CSM-IBD compared to usual care. If the intervention demonstrates acceptability and efficacy, it could be deployed in a variety of practice settings to improve patient self-management of IBD.

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Data Availability

The data sets generated during this study will be deposited in a publicly available repository at study completion.

Conflicts of Interest

SL receives grant and research support from the following: AbbVie Pharmaceuticals, Janssen Pharmaceuticals, Inc, Takeda Pharmaceuticals, Inc, Bristol Myers Squibb Pharmaceuticals, Inc, Pfizer Pharmaceuticals, Inc, Atlantic Pharmaceuticals, Ltd, Gilead Sciences, Inc, Tetherex Pharmaceuticals, Arena Pharmaceuticals, and Shield Therapeutics PLC, and is a consultant for UCB Pharma, Cornerstones, Janssen Pharmaceuticals, Inc, Takeda Pharmaceuticals, Inc, and Eli Lilly Company. KC-S has been a consultant for Pfizer Pharmaceuticals, Inc, Takeda Pharmaceuticals, Inc, AbbVie Pharmaceuticals, and Bristol Myers Squibb Pharmaceuticals, Inc. LK is co-founder and equity owner of Trellus Health and a consultant to Pfizer, Eli Lilly, Takeda, and Ardelyx. For the remaining authors, no conflicts of interest were declared.

Multimedia Appendix 1
IBD Symptom Scale.
[DOCX File , 24 KB - resprot_v12i1e46307_app1.docx]

Multimedia Appendix 2
Schedule of enrollment, interventions, and assessments—SPIRIT figure. CSM-IBD: comprehensive self-management for inflammatory bowel disease; SIBDQ: Short Inflammatory Bowel Disease Questionnaire.
[PNG File , 55 KB - resprot_v12i1e46307_app2.png]

Multimedia Appendix 3
End of Study Interview Questions.
[DOCX File , 21 KB - resprot_v12i1e46307_app3.docx]

Multimedia Appendix 4
Peer-review report by the National Institute of Nursing Research Initial Review Group (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 694 KB - resprot_v12i1e46307_app4.pdf]

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Abbreviations

CBT: cognitive behavioral therapy
CSM: comprehensive self-management intervention
CSM-IBD: comprehensive self-management for inflammatory bowel disease
HIPAA: Health Insurance Portability and Accountability Act
IBD: inflammatory bowel disease
IFSMT: Individual and Family Self-Management Theory
SIBDQ: Short Inflammatory Bowel Disease Questionnaire
UW: University of Washington

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Protocol

Rationale, Design, and Methods for the Sedentary Behavior Reduction in Pregnancy Intervention (SPRING): Protocol for a Pilot and Feasibility Randomized Controlled Trial

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Abstract

Background: Adverse pregnancy outcomes (APOs) identify cardiovascular disease risk, but few effective interventions are available. High sedentary behavior (SED) has recently been associated with APOs, but very few randomized controlled trials (RCTs) have tested SED reduction in pregnancy.

Objective: The Sedentary Behavior Reduction in Pregnancy Intervention (SPRING) pilot and feasibility RCT addresses this gap by testing the feasibility, acceptability, and preliminary pregnancy health effects of an intervention to reduce SED in pregnant women. The objective of this manuscript is to describe the rationale and design of SPRING.

Methods: Pregnant participants (n=53) in their first trimester, who are at risk for high SED and APO and without contraindications, are randomized in a 2:1 ratio to an intervention or control group. SED (primary outcome) and standing durations, and steps per day, are measured objectively in each trimester for 1 week with a thigh-mounted activPAL3 accelerometer. SPRING also seeks to demonstrate feasibility and acceptability while estimating preliminary effects on maternal-fetal health outcomes assessed during study visits and abstracted from medical records. The pregnancy-customized intervention promotes daily behavioral targets of less than 9 hours of SED and at least 7500 steps, achieved via increased standing and incorporating light-intensity movement breaks each hour. The multicomponent intervention provides a height-adjustable workstation, a wearable activity monitor, behavioral counseling every 2 weeks (through videoconference), and membership in a private social media group. Herein, we review the rationale, describe recruitment and screening processes, and detail the intervention, assessment protocols, and planned statistical analyses.

Results: This study was funded by the American Heart Association (20TPA3549099), with a funding period of January 1, 2021, and until December 31, 2023. Institutional review board approval was obtained on February 24, 2021. Participants were randomized between October 2021 and September 2022, with final data collection planned for May 2023. Analyses and submission of results are expected for winter of 2023.

Conclusions: The SPRING RCT will provide initial evidence on the feasibility and acceptability of an SED-reduction intervention to decrease SED in pregnant women. These data will inform the design of a large clinical trial testing SED reduction as a strategy to reduce APO risk.

Trial Registration: ClincialTrials.gov NCT05093842; https://clinicaltrials.gov/ct2/show/NCT05093842

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International Registered Report Identifier (IRRID): DERR1-10.2196/48228

(JMIR Res Protoc 2023;12:e48228) doi:10.2196/48228

KEYWORDS

pregnancy; behavioral intervention; pilot and feasibility trial; sedentary behavior; physical activity; mobile phone

Introduction

Background

Cardiovascular disease (CVD) remains the number one health threat in women [1]. Adverse pregnancy outcomes (APOs), such as hypertensive disorders of pregnancy, gestational diabetes, and preterm birth, affect up to 20% of pregnant women and are recognized as major risk factors for latent and future CVD [2,3]. Though research to disentangle the contributions of prepregnancy risk factors from APOs on future CVD risk is ongoing, interventions that prevent APOs as a target for reducing CVD offer immediate and possibly long-term benefits. Effective preventative therapies, however, remain elusive [4]. Moderate- to vigorous-intensity physical activity reduces APO risk [5,6], but less than 1 in 4 pregnant women achieve guidelines [7]. This likely reflects that pregnant women report unique exercise barriers such as fatigue, pain, medical restriction, and concern for the baby [8].Therefore, more feasible lifestyle strategies to prevent APOs are needed.

One such strategy could be reducing sedentary behavior (SED), which is defined as low-intensity behavior that occurs in a seated, reclined, or lying posture [9]. Considering barriers to more intensive physical activity during pregnancy, replacing SED across the day with standing and light-intensity physical activities may be more achievable. Excessive SED has been related to an increased risk of CVD and mortality in general populations, even after accounting for moderate- to vigorous-intensity physical activity [10]. Though sparse data on SED during pregnancy exist, our laboratory recently completed a small cohort study among 120 pregnant women that objectively measured SED and physical activity during each trimester [11]. We found that, on average, pregnant women had approximately 9.5 hours per day of SED, which is higher than the general population [12]. Further, using trajectory analysis, women with a pattern of very high SED across pregnancy (approximately 11 hours per day) versus low SED (approximately 8 hours per day) had 6.76 (95% CI 1.20-38.14) higher odds of experiencing an APO [11]. Of interest, women in the low and medium SED groups (approximately 8 and 9 hours per day, respectively) had no excess risk of APO, indicated a possible threshold effect. Similar threshold effects were observed for time spent standing and in the number of steps per day such that only women in the very low trajectory groups had excess risk. Importantly, moderate- to vigorous-intensity activity was not associated with APO outcomes, bolstering support for a strategy of reducing SED by increasing standing and daily steps as a novel intervention target to improve pregnancy health. Yet, few randomized clinical trials (RCTs) testing SED reduction interventions are available, especially in pregnant women.

The Sedentary Behavior Reduction in Pregnancy Intervention (SPRING) pilot and feasibility study, funded by the American Heart Association (20TPA3549099), seeks to address these research gaps. SPRING is an RCT that tests the feasibility, acceptability, and preliminary effects of a novel intervention designed to reduce SED and improve all-day activity patterns among pregnant women at high risk for APOs.

Objectives

The SPRING study's specific aims are to (1) evaluate the effect of SPRING versus control on objectively measured SED (*primary outcome*, *hypothesized to decrease*), standing (*hypothesized to increase*), and steps per day (*hypothesized to increase*); (2) evaluate the feasibility and acceptability of SPRING, including recruitment, retention, outcome assessment rates, intervention fidelity, and program evaluation; and (3) estimate the preliminary effects of SPRING versus control on maternal-fetal health outcomes including composite APOs (hypertensive disorders of pregnancy, gestational diabetes, and preterm birth), maternal blood pressure and glucose, psychosocial outcomes, gestational age at birth, and infant birth anthropometrics.

Methods

Study Design Overview

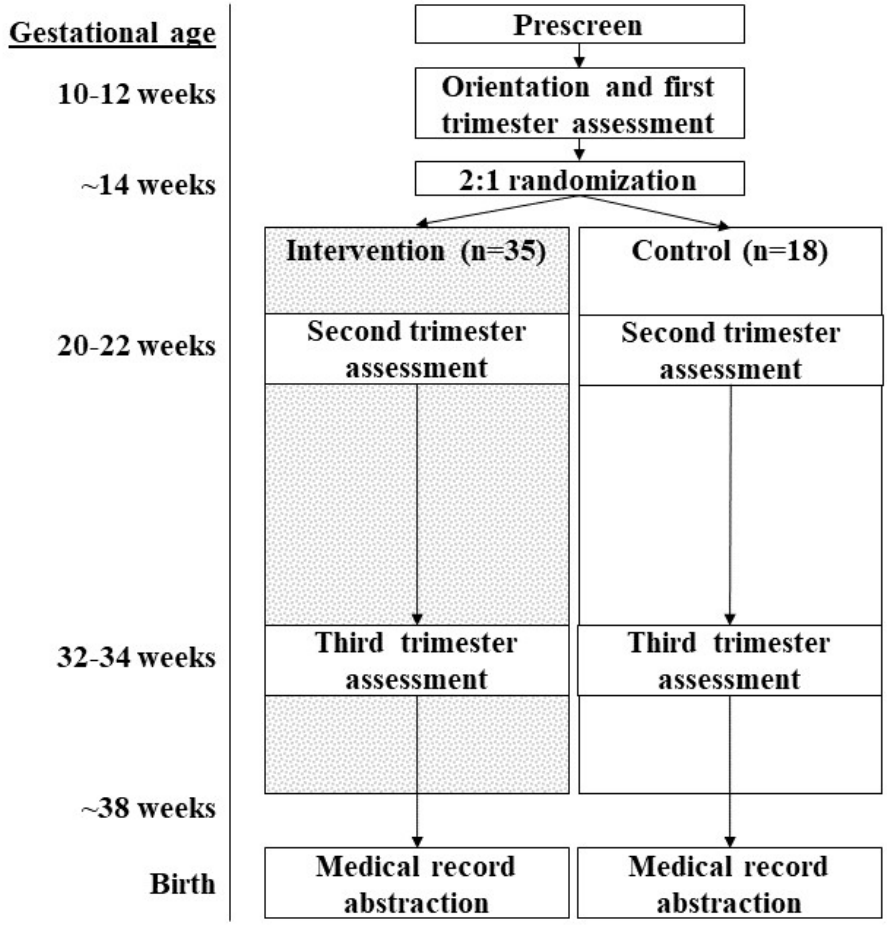
In the absence of established SED-reduction interventions or guidelines in pregnant women, a pilot and feasibility RCT among pregnant women with higher risk for SED and APOs was chosen as the first logical step to determine if the intervention could successfully reduce SED by increasing standing and steps per day across pregnancy. Figure 1 describes the timeline of study assessments and intervention procedures (SPIRIT [Standard Protocol Items: Recommendations for Intervention Trials] checklist [13] available in Multimedia Appendix 1). The SPRING pilot and feasibility trial is registered on ClincialTrials.gov (NCT05093842).

Potential participants complete baseline assessments and begin the 1-week baseline activity monitoring protocol between 10 weeks 0 days (10^0 weeks) and 12 weeks 6 days (12^6 weeks) of gestation. Upon receipt of valid activity monitoring data with a completed time-use diary and clearance to participate from the participant's prenatal care provider, pregnant women are randomized in a 2:1 ratio to either a multicomponent SED-reduction intervention or a usual care control group. Beginning at approximately 14 weeks of gestation, participants randomized to the intervention group begin the active intervention, which lasts through 38 weeks of gestation or until the participant gives birth, whichever occurs first. Participants randomized to the usual care control arm do not receive the intervention but are mailed a Fitbit Luxe after giving birth.

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Participants in both groups complete assessments in each trimester and are remunerated US $40 for completing the first trimester (baseline) assessment between 10^0 and 12^6 weeks, US $50 for completing the second-trimester assessment between 20^0 and 22^6 weeks of gestation, and US $60 for completing the third-trimester assessment between 32^0 and 34^6 weeks of gestation. After participants give birth, maternal-fetal outcomes are abstracted from medical records by trained clinical staff.

Figure 1. Participant flowchart across the study protocol.



Ethics Approval

All research procedures were approved by the University of Pittsburgh Human Research Protection Office (STUDY20110193).

Eligibility Criteria

Eligibility criteria for the SPRING Study are listed in Textbox 1. We recruit participants in their first trimester of pregnancy who are at risk for high levels of SED and who have at least 1 risk factor for APO. These criteria reflect an early gestational age when we can intervene meaningfully across pregnancy and higher SED appropriate for modification (ie, reduction) to reach the levels that we have found to be associated with better pregnancy outcomes [11]. The criteria of having at least 1 risk factor for APO relate to our long-term goal to test whether our intervention can reduce APO risk; therefore, we sought to evaluate feasibility and preliminary effects in this specific population. Lastly, to allow for our exploratory outcome assessment using prenatal records of maternal-fetal outcomes, participants are required to consent to abstraction either through our affiliation with the University of Pittsburgh Medical Center or through separate medical record release if they are receiving prenatal care elsewhere.

Participants younger than 18 years or older than 45 years are excluded to avoid an inability to provide consent and more complicated pregnancies with advanced age, respectively. Those with preexisting hypertension or diabetes are excluded because existing management of these conditions could affect our study outcomes (eg, prenatal blood pressure and glucose test results). Any other contraindications to exercise during pregnancy or severe mobility limitation are also exclusionary since the intervention asks participants to increase standing and daily steps. We also require participants to receive clearance for participation in the intervention from their prenatal care provider as an additional safety precaution. Lastly, those participating in other interventional research that could confound our study outcomes are excluded to reduce bias or contamination.

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Textbox 1. Eligibility criteria.

Inclusion criteria

- Gestational age:
  - Between 10 weeks 0 days and 12 weeks 6 days of gestation
- At risk for high sedentary behavior (meets at least one of the following criteria):
  - Primarily sitting, full-time desk job (more than 30 hours per week)
  - Primarily sitting, part-time desk job (less than 30 hours per week) and reports sitting at least half of the time during nonwork days
  - Does not work and reports sitting at least three-fourths of the time
  - Reports no more than 6000 steps per day from a wearable activity monitor
- Risk factor for adverse pregnancy outcome (APO; meets one of the following criteria):
  - Nulliparity
  - History of APO
  - Prepregnancy BMI of 30 kg/m^2 or greater
  - Age of 35 years or older
- Medical record access:
  - Plans to deliver at the University of Pittsburgh facility or willing to provide consent for medical record release of prenatal care and birth records

Exclusion criteria

- Young or advanced maternal age:
  - Younger than 18 years; older than 45 years
- Chronic hypertension:
  - Resting blood pressure of 140/90 mm Hg or greater or antihypertensive medication use
- Pregestational diabetes:
  - Type 1 or type 2 diabetes, prior to pregnancy
- Contraindication to exercise:
  - Serious medical conditions such as underlying cardiac disease, severe anemia, chronic bronchitis, poorly controlled hyperthyroidism, or seizure disorder
- Severe mobility limitation:
  - Self-report of inability to walk 2 blocks or climb a flight of stairs
- No prenatal care provider clearance:
  - Unable to obtain a signed permission form from a prenatal care provider to participate in the intervention
- Other research intervention:
  - Participating in another health-related intervention study that could affect study outcomes
- Travel plans restricting participation:
  - Plans to travel that limit ability to fully participate in the study protocol

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Recruitment and Screening

Recruitment Methods

Participants are recruited from within approximately 50 miles of the University of Pittsburgh's main campus in Pittsburgh, Pennsylvania. A variety of recruitment methods are used, including the University of Pittsburgh Clinical and Translational Science Institute's Pitt+Me research registry and targeted emails sent to the university community. In addition, recruitment messages from the study physician are sent to patients at the University of Pittsburgh Medical Center's (UPMC) Maternal Fetal Medicine clinic who meet eligibility requirements through the MyUPMC mobile app. Finally, flyers are placed in patient-facing areas of Magee-Womens Hospital of UPMC, the largest birthing hospital in the Pittsburgh region.

Screening, Orientation, and Informed Consent

Interested participants are directed to complete a web-based screening questionnaire using Research Electronic Data Capture (REDCap) [14,15]. The screening questionnaire contains a detailed summary of the study, a request for electronic consent to answer screening questions, and specific questions about the candidate's current pregnancy, risk factors for APO, SED exposure and habits, chronic diseases, medications, and contact information. Trained study staff assess initial eligibility based on the answers to the screening questionnaire and, if a candidate is deemed ineligible, they are informed at that time. Candidates who appear to be eligible during initial screening are invited to a web-based videoconference orientation where the study is described in detail, verbal informed consent is obtained, and then an electronic informed consent document is signed by the participant and study personnel conducting the informed consent. Finally, a detailed medical and reproductive history questionnaire is administered to determine final eligibility.

Randomization

A randomization ratio of 2:1 (2 intervention to 1 control) was chosen to provide more robust data to evaluate the feasibility and acceptability of our intervention and assessment protocols [16]. To help achieve balance over time, blocks of 6 were selected, and 9 blocks of computer-generated, randomly ordered sets were placed sequentially into sealed, numbered envelopes by a blinded study personnel. These envelopes were then provided to the unblinded study personnel (principal investigator and interventionist) and kept in a secure location.

Participant randomization begins with the blinded study coordinator notifying the principal investigator that a participant is eligible and has completed all baseline assessment procedures. The study investigator then opens the next sequential envelope and records the randomization assignment and date in the randomization log. The principal investigator then contacts the participant to inform her regarding her randomization assignment, describe next steps, ensure that the participant comprehends that the intervention and assessment study procedures are separate, and reinforce the importance of continued participation in either group.

Outcome Assessments

Study outcome assessments are conducted by trained, blinded study personnel and occur via web-based videoconference once per trimester of pregnancy (Table 1). Any necessary assessment materials are mailed to participants prior to study visits.

SED and physical activity are measured in each trimester. Objective assessment of activity patterns is conducted using a thigh-mounted activPAL3 monitor (PAL Technologies, Glasgow) worn for 24 hours over 8 days. This protocol is the best-practice methodology for field monitoring of SED and standing [17], and we have shown it to be a valid measure of moderate- to vigorous-intensity physical activity in pregnant women [18]. Participants wear the monitor on the anterior upper thigh for 8 days, with removal only for swimming activities. Concurrently, participants are asked to record periods of work, nonwork, sleep, and nonwear in a diary for accurate data processing. Participants are verbally instructed regarding procedures for correct monitor wear at each virtual assessment visit, including visual verification of correct placement. Detailed written instructions on monitor wear and diary completion are also provided. The activPAL3 24-hour event data are downloaded and cleaned by removing periods of sleep and nonwear; remaining valid wear time is used to calculate average daily durations of time spent in SED (total and in prolonged bouts of at least 30 and 60 minutes), standing, and stepping. Daily frequency of steps and sit-stand transitions are also averaged across days. Lastly, to estimate moderate- to vigorous-intensity physical activity, time with a stepping frequency of at least 75 steps per minute and 100 steps per minute are averaged across valid wear days from daily summary data. Averages are calculated overall and during working times (if applicable). Data are considered valid with at least 5 days of at least 10 hours of waking wear time recorded [19].

Self-reported SED and physical activity are assessed using the Pregnancy Physical Activity Questionnaire [20], with questions regarding proportion of time spent in SED during work and nonworking times added to improve the accuracy of self-reported SED assessment [21].

Blood pressure is assessed virtually during study assessment visits in each trimester using a validated oscillometric monitor [22]. Either a UA-611 monitor (A&D Medical) that was provided as part of prenatal care at the University of Pittsburgh Magee-Womens Hospital or a study-provided BP7250 monitor (Omron Healthcare Inc) is used. Participants use the same monitor and cuff for all visits. During the virtual assessment, participants first provide verbal confirmation of abstention from caffeine and nicotine for 1 hour prior. Then, participants place the cuff on the left upper arm and complete a supervised 5-minute quiet rest with their arm supported at chest level, back supported against a chair, and feet flat on the floor or other support with ankles and knees uncrossed. After the rest, the participant initiates the measurement by pressing the start button with the blood pressure monitor facing the video camera and visible only to the assessor (to reduce participant reactivity). The assessor leads the participant through 3 measurements, taken with a 1-minute rest in between, and records blood pressures and heart rates in the database prior to informing the

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participant of all values. The average of the second and third measurements is used for analysis.

Demographics, medical history, reproductive history, and medication use are collected at baseline using a standardized form. Anthropometry is assessed at baseline via self-reported height and prepregnancy weight, which are subsequently verified through medical record abstraction (described later). To capture changes that occurred following randomization, updates to demographics (eg, new employment) are reported in a questionnaire and changes to medical history or medication use (eg, a new diagnosis or starting, stopping, or changing dosage of medications) are assessed during an interval medical history review at each follow-up visit.

Table 1. Data collection schedule.

	Randomization			
	Baseline	Second trimester	Third trimester	Birth
Outcomes				
Objective SED[a] and activity (activPAL3)	✓	✓	✓	
Self-reported SED and activity	✓	✓	✓	
Blood pressure (remote observation)	✓	✓	✓	
Demographics and medical or reproductive history	✓			
Changes in demographics or medical history		✓	✓	
Dietary intake	✓	✓	✓	
Social support, SED and activity expectations, and barriers	✓	✓	✓	
Mood, stress, depression, quality of life, and sleep	✓	✓	✓	
Adverse events		✓	✓	
Maternal-fetal health outcomes				✓
Feasibility and acceptability				
Recruitment, screening, and enrollment	✓			
Expectations and experience joining SPRING[b]	✓			
Intervention fidelity and adherence		✓	✓	
Completion of assessment procedures	✓	✓	✓	
Program evaluation			✓	

[a]SED: sedentary behavior.

[b]SPRING: Sedentary Behavior Reduction in Pregnancy Intervention.

Dietary intake is assessed at each visit using the Diet Screening Questionnaire, a semiquantitative questionnaire that measures typical dietary habits [23]. Psychosocial behavioral targets and outcomes are measured at baseline and each follow-up visit via web-based self-report questionnaires. Validated questionnaires assessing behavioral targets of the intervention include the Sitting during Pregnancy Barriers and Outcome Expectations Questionnaire [24], Expected Outcomes and Barriers for Habitual Physical Activity [25], the Multidimensional Scale of Perceived Social Support [26], and Social Support for Exercise [27]. Validated questionnaires assessing possible psychosocial effects of the intervention include the Profile of Mood States [28], the Centers for Epidemiologic Studies Depression Scale (CES-D) [29], the Perceived Stress Scale [30], Health-Related Quality of Life for Nausea and Vomiting during Pregnancy [31], and the Pittsburgh Sleep Quality Index [32].

Adverse events are collected systematically at follow-up assessment visits by blinded study personnel. Details of new or worsening medical conditions, including pregnancy-related adverse events, are recorded and classified regarding severity and relationship. In addition, ongoing assessment of adverse events in the intervention group is conducted by intervention staff. All adverse events are reviewed by the principal investigator and, if needed, the study physician for accuracy, possible relationship to the intervention, and to make any necessary modifications or terminate participation in the intervention.

Pregnancy health and maternal-fetal outcomes are abstracted from the participant's medical record of prenatal visits and labor and delivery notes. Maternal outcomes extracted include gestational weight gain, clinic-measured blood pressures, pregnancy complications including APOs, glucose screening values, and tolerance tests (if available), and labor and delivery details. Fetal outcomes include gestational age at birth, anthropometrics, and complications. All abstractions are reviewed by a second reviewer and discrepancies are resolved. The study's maternal-fetal medicine physician coinvestigator (AH) confirms all APOs and a random sample of healthy pregnancies for accuracy.

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Feasibility and Acceptability

Feasibility and acceptability are also assessed through a variety of methods across the study period (Table 2). Screening outcomes are recorded prospectively including recruitment sources and yield, eligibility rates and ineligibility reasons, and rates of enrollment. We also administer a study-developed questionnaire at baseline (prior to randomization) to assess participant expectations, motivations, and experiences when enrolling in the SPRING RCT. Rates of valid assessment completion are also prospectively recorded. Intervention fidelity with respect to delivery, receipt, and enactment [33] is assessed at each intervention contact (see Intervention Content and Schedule section). A final web-based program evaluation assesses acceptability and includes 22 short-answer, ranking, and multiple-choice questions. The evaluation is distributed after the last intervention lesson to intervention participants only and aims to evaluate participants' perceptions regarding their health, usefulness of the intervention components, general satisfaction and acceptability of the intervention, and suggestions for improvement.

Table 2. Description of intervention components.

Component	Socioecological level	Description
Height-adjustable workstation [34]	Environment	A height-adjustable workstation is selected based on participant preference, occupational status, and the home or office setting. Study staff deliver and, if needed, install the workstation. This component supports the SPRING[a] study goals to alter posture frequently and increase standing time.
Facebook group [35]	Interpersonal	A private Facebook group for SPRING participants and intervention staff offers an opportunity to discuss shared experiences of reducing SED[b] during pregnancy and provide social support between participants. Participants are asked to join the private group after a web-based group social support lesson that includes a handful of other participants with a similar due date. Participants agree to community guidelines about respectful interaction on the page, and all activity is monitored by the intervention team. Study staff posts to the group twice per week with content aiming to provide information, engage members in discussion, and engender social support across participants.
Behavior coaching [36]	Individual or interpersonal	Participants engage in up to 13 videoconference contacts across the second and third trimesters of pregnancy. The interventionist delivers scripted lessons and check-ins (content described in more detail in Table 3) and uses motivational interviewing or problem-solving to help participants choose strategies for SED reduction and self-monitoring, set goals for standing, stepping, and movement breaks, and overcome barriers. Before each contact, the interventionist gathers the participants' objective activity data from the previous 14 days recorded by the wearable activity monitor (described below) to guide discussions. Most lessons are delivered one-on-one, except for 1 social support lesson during the fourth contact (~18th week of gestation) that includes a small group of 2-4 intervention participants with a similar due date.
Wearable activity monitor [37]	Individual	Participants are given the choice of receiving a new Fitbit Luxe or are allowed to continue the use of a personal Fitbit or Apple Watch. This flexibility of wearable choice reflects our previous experience that participants sometimes strongly preferred to continue use of their current wearable. Participants either share credentials (Fitbit) or grant shared access to their activity data (Apple Watch) so that the interventionist can review the participants' objective data. Participants are encouraged to wear the monitor during all waking hours and use the associated smartphone app to self-monitor their daily steps and adherence to daily movement break goals. The monitors are set up to alert participants if they have been inactive over the past hour during a participant-selected daytime interval. Participants are instructed to respond to an inactivity alert by taking a movement break, for example, a 2- to 3-minute walk or another light-intensity activity break. This component supports the study goals of breaking up prolonged SED and accumulating steps across the day.
Self-monitoring [37]	Individual	Participants are instructed to track the targeted behaviors to support behavior change and accurately report it to the interventionist during contacts. Participants are encouraged to use their wearable activity monitor app to track hourly movement breaks and daily step goals. To track standing, participants are offered paper or electronic diaries or are allowed to choose a preferred method, for example, smartphone app.

[a]SPRING: Sedentary Behavior Reduction in Pregnancy Intervention.

[b]SED: sedentary behavior.

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Table 3. Schedule and content of the SPRING[a] study behavioral intervention lessons.

Intervention contact	Gestational week	Intervention content
Lesson 1: Education (90 minutes)	14	• Orientation to SPRING study • Review of physical activity recommendations during pregnancy [36] • Education about the health risks of SED[b] with review of participant's objective SED and steps from the baseline assessment [38] • Introduction to SPRING behavioral targets • Height-adjustable workstation use and ergonomic safety • Use of wearable activity monitor for inactivity prompts and step tracking • Choose self-monitoring strategies • Goal setting for standing, movement breaks, and daily steps [39]
Check-in (15 minutes)	16	• Check for contraindications • Evaluation of fidelity (delivery, receipt, and enactment) [33] • Discuss goal attainment and, if needed, problem-solving [40,41] • Goal setting for the next 2 weeks
Lesson 2: Social support (30 minutes)	18	• The only behavioral lesson that occurs as a group, including 2-4 intervention participants with a similar due date (ie, "due date group") • Discussion of social support for behavior change at the individual and community level • Introduction to community-level support via the private Facebook group [35] • Goal setting for community-level engagement
Check-in	20	• Described in gestational week 16
Lesson 3: Know your cues (45 minutes)	22	• Check-in (described above) • Discuss stimulus control and environmental re-engineering [42] • Evaluate daily activity patterns using the activity tracker app and apply concepts to identify inactivity patterns or creating barriers to achievement • Goal setting for pregnancy-specific stimulus control strategies
Check-in	24	• Described above
Lesson 4: Progress review (45 minutes)	26	• Check-in (described above) • Guided self-reflection on progress for standing, movement breaks, and step goals [38,43] • Review of progress comparing the objective SED and steps data from second-trimester assessment to baseline levels • Goal setting for improvement or maintenance of standing, movement breaks, and daily step goals in the third trimester
Check-in	24	• Described above
Lesson 5: Motivation (45 minutes)	30	• Check-in (described above) • Introduction to concepts of internal motivation and behavior change adherence [44,45] • Guided activity to identify study-specific values • Goal setting and reflection on intrinsic motivation
Check-in	32	• Described above
Lesson 6: Lapses do not have to be collapses (45 minutes)	34	• Check-in (described above) • Discussion of behavior change maintenance, relapse theory, and prevention [39] • Goal setting for strategies to improve long-term maintenance of SED reduction or change
Check-in	36	• Described above
Check-in	38	• Described above

[a]SPRING: Sedentary Behavior Reduction in Pregnancy Intervention.

[b]SED: sedentary behavior.

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Intervention

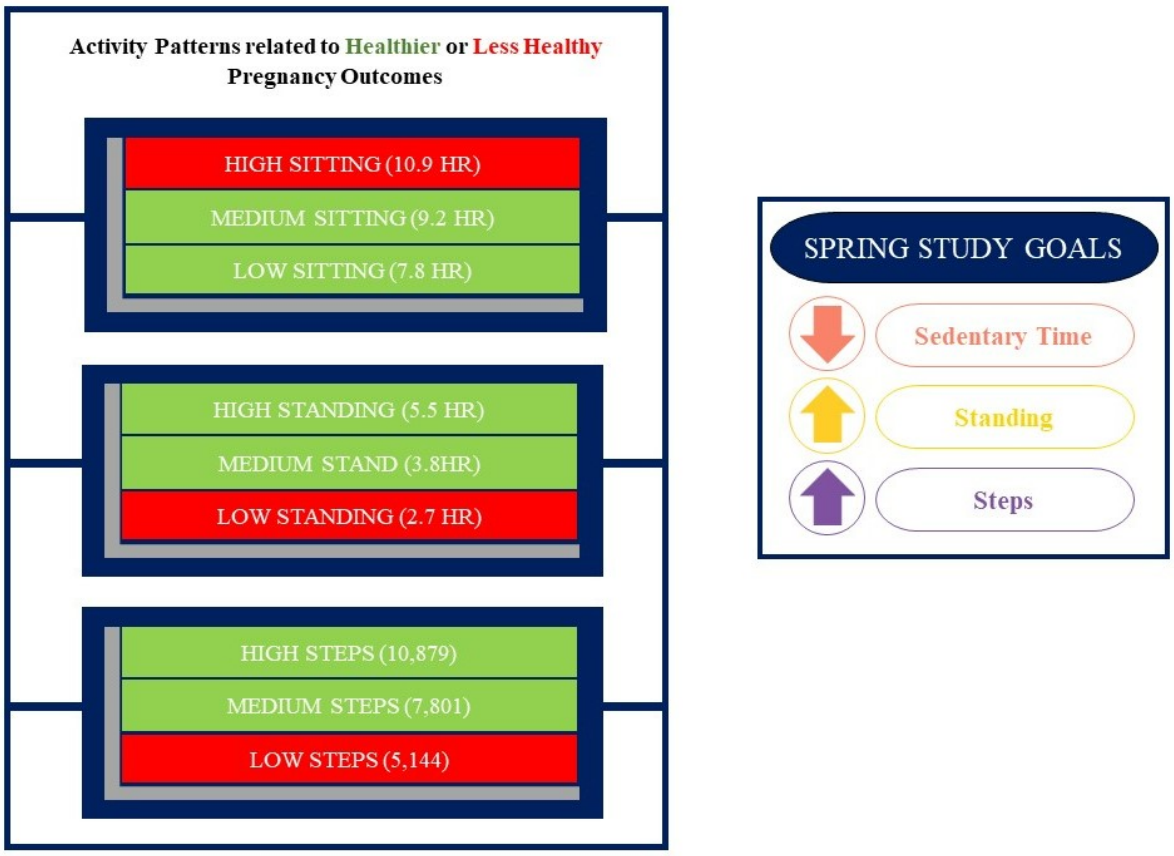
Intervention Content and Schedule

SPRING developed behavioral targets informed by the specific patterns of SED, standing, and daily steps that were associated with lower APO risk in our observation cohort of pregnant women [11]. Specifically, we observed threshold effects whereby engaging in SED for approximately 9.2 hours per day or less, standing for approximately 3.8 hours per day or more, and accumulating approximately 7801 steps per day or more were the activity patterns associated with a significantly lower risk of an APO [11] along with other maternal and fetal health benefits [46-48]. We also considered additional data from our observational research regarding determinants, barriers, attitudes, and outcome expectations related to SED during pregnancy. Findings from these studies suggested that pregnancy-related physical symptoms such as nausea and fatigue along with work-related sitting were the most commonly reported barriers to reducing SED [24]. Using objectively measured SED data, we also found that desk jobs and fewer children aged 5 years or younger in the home emerged as the factors that are most strongly associated with SED during pregnancy [49]. We then used these data to adapt our existing SED-reduction interventions in nonpregnant adults [50-52] to the new population of pregnant women at high risk for SED and APOs.

Thus, with the overall goal of reducing SED to less than 9 hours per day, we set evidence-based behavioral targets for our intervention as follows: (1) increase standing time by 2-3 hours per day with a daily total target of at least 4 hours per day; (2) increase light-intensity movement across the day, achieving at least 7500 steps per day; and (3) increase steps by at least 250 per hour (up to 8 hours per day). An example of the graphics used to convey these behavioral targets in the participant-facing intervention materials is presented in Figure 2. To facilitate behavior change toward these standing and step targets in our intervention group, we developed an evidence- and theory-based, multicomponent intervention strategy across 3 levels of the socioecological model (Table 2) [34,35,37,40].

The schedule and content of the behavioral coaching lessons are described in Table 3. Safety and fidelity of the intervention are assessed at each contact by measuring contraindications [36], delivery (provision of intervention components), receipt (self-report of intervention components working properly), and enactment (self-report of self-monitoring and goal achievement) [33].

Figure 2. Intervention behavioral targets.



Control Group

Participants assigned to the control group are asked to continue their typical behavior for the duration of their pregnancy and are provided with a general handout regarding recommended physical activity during pregnancy [36] but received no further intervention materials. After delivery, control participants are mailed a report of their objective activity levels that were previously measured during the study assessments and a Fitbit Luxe.

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Statistical Analysis

Analytic Strategy for Aim 1 and the Exploratory Aim

We will use Stata (StataCorp) for all analyses with an intention-to-treat philosophy. First, participant flow will be summarized using a Consolidated Standards of Reporting Trials diagram for randomized trials [53]. Second, descriptive statistics will be computed for variables by treatment group and time point. Third, the baseline measures will be compared between the 2 groups using independent samples *t* tests, Wilcoxon rank sum, chi-square, or Fisher exact tests, as appropriate. While significant differences are not expected, any found will be considered in sensitivity analyses. Next, main analyses will fit a series of linear mixed models with follow-up continuous outcomes as the dependent variable (eg, SED); intervention group (intervention or control), follow-up time (eg, second and third trimester), and group × time as fixed effects; baseline value of outcomes as fixed-effect covariates; and a participant random effect to account for multiple observations from the same participant over time. Mean contrasts will estimate the between-group difference at each follow-up time point. Similar methods will be used for the other activity variables (eg, standing and steps). Analysis of the exploratory aim will use similar methods, with logistic regression for dichotomous outcomes (eg, APOs). We will first consider the use of multiple imputation to account for missing data, but we will perform additional sensitivity or exploratory analyses to ensure robustness and extend our findings, for example, complete-data-only or last-value-carried forward strategies for missing data.

Analytic Strategy Aim 2

For the recruitment feasibility outcomes, we will calculate frequencies of recruitment method use and yields; rates of screening contacts, consent, eligibility, and randomization; reasons for ineligibility; and characteristics of enrolled participants. Benchmarks will be 42 (80%) for retention and 40 (95%) of the retained participants for valid outcome assessments. Intervention fidelity will be calculated based on intervention contacts with an overall average benchmark of 30 (85%) of each intervention contact competed. Quantitative or semiquantitative acceptability and program evaluation data will be summarized descriptively. Open-ended questionnaires will be analyzed using a constant comparison method to identify salient categories, themes, and patterns via open coding, iterative review and codebook generation, code linking into similar categories, and final integration into themes [54].

Sample Size Considerations

The primary outcome of this study is a change in SED. Based on our pilot data that suggest lower SED protects women from APOs [11], we calculated sample size requirements assuming the following: a between-group SED difference of 1 hour (SD 56 minutes) per day, a 2:1 randomization ratio to enhance recruitment and increase program evaluation and feasibility data, 90% power, and α=.05. This yielded a required sample size of 42 (28 intervention and 14 control). A final sample size of up to 53 (35 intervention and 18 control), inflated by 20%, was adopted to account for attrition.

Results

The SPRING study was funded as an American Heart Association Transformational Project Award, which began on January 1, 2021, and ends on December 31, 2023 (20TPA3549099; Principal Investigator: BBG). Institutional review board approval was obtained on February 24, 2021. Participants were recruited over approximately 1 year, with the first subject being randomized on October 4, 2021, and the final participant being randomized on September 9, 2022. The last research assessment visit occurred on January 20, 2023. Abstraction of maternal-fetal health outcomes has a planned completion date of May 31, 2023, data analysis is planned to be completed by June 30, 2023, and submission of primary outcomes to a scientific journal is planned for September 30, 2023.

Discussion

In summary, the SPRING pilot and feasibility RCT is testing the effects of our evidence-based SED-reduction intervention to modify SED, standing, and steps as well as determining whether our approach is feasible and acceptable among pregnant women at risk for high levels of SED and APOs. The multilevel intervention targets an activity pattern that we have found to be associated with a lower risk of APOs in observational research. To achieve these targets, our intervention approach synthesized our previous findings on determinants of SED during pregnancy with successful strategies for SED reduction intervention in nonpregnant adults. Our final exploratory aim will begin to assess the effects of our intervention on pregnancy health outcomes, including APOs. These data, including our planned in-depth feasibility, acceptability, and intervention program evaluation and clinical outcomes, will be critical for designing a fully powered RCT where we can test an optimized SED-reduction intervention for pregnant individuals. This next trial will importantly have maternal-fetal health measures (eg, APOs) as the primary outcomes so that we can understand whether our approach should be recommended as an alternative to standard moderate- to vigorous-intensity physical activity recommendations of 20-30 minutes per day. If ultimately successful, our intervention that targets reducing SED through an increase in standing and daily steps during pregnancy could offer a novel, more feasible strategy for preventing APOs and improving immediate and long-term cardiovascular health in women.

Acknowledgments

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Data Availability

Data generated from the SPRING study will be available upon reasonable request, with the permission of study investigators, and execution of a data use agreement.

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT (Standard Protocol Items: Recommendations for Intervention Trials) checklist.
[DOCX File , 22 KB - resprot_v12i1e48228_app1.docx]

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Abbreviations

APO: adverse pregnancy outcome
CES-D: Center for Epidemiologic Studies Depressive Scale
CVD: cardiovascular disease
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
SED: sedentary behavior
SPIRIT: Standard Protocol Items: Recommendations for Intervention Trials
SPRING: Sedentary Behavior Reduction in Pregnancy Intervention
UPMC: University of Pittsburgh Medical Center

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Protocol

Detecting Clinically Relevant Emotional Distress and Functional Impairment in Children and Adolescents: Protocol for an Automated Speech Analysis Algorithm Development Study

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Abstract

Background: Even before the onset of the COVID-19 pandemic, children and adolescents were experiencing a mental health crisis, partly due to a lack of quality mental health services. The rate of suicide for Black youth has increased by 80%. By 2025, the health care system will be short of 225,000 therapists, further exacerbating the current crisis. Therefore, it is of utmost importance for providers, schools, youth mental health, and pediatric medical providers to integrate innovation in digital mental health to identify problems proactively and rapidly for effective collaboration with other health care providers. Such approaches can help identify robust, reproducible, and generalizable predictors and digital biomarkers of treatment response in psychiatry. Among the multitude of digital innovations to identify a biomarker for psychiatric diseases currently, as part of the macrolevel digital health transformation, speech stands out as an attractive candidate with features such as affordability, noninvasive, and nonintrusive.

Objective: The protocol aims to develop speech-emotion recognition algorithms leveraging artificial intelligence/machine learning, which can establish a link between trauma, stress, and voice types, including disrupting speech-based characteristics, and detect clinically relevant emotional distress and functional impairments in children and adolescents.

Methods: Informed by theoretical foundations (the Theory of Psychological Trauma Biomarkers and Archetypal Voice Categories), we developed our methodology to focus on 5 emotions: anger, happiness, fear, neutral, and sadness. Participants will be recruited from 2 local mental health centers that serve urban youths. Speech samples, along with responses to the Symptom and Functioning Severity Scale, Patient Health Questionnaire 9, and Adverse Childhood Experiences scales, will be collected using an Android mobile app. Our model development pipeline is informed by Gaussian mixture model (GMM), recurrent neural network, and long short-term memory.

Results: We tested our model with a public data set. The GMM with 128 clusters showed an evenly distributed accuracy across all 5 emotions. Using utterance-level features, GMM achieved an accuracy of 79.15% overall, while frame selection increased accuracy to 85.35%. This demonstrates that GMM is a robust model for emotion classification of all 5 emotions and that emotion frame selection enhances accuracy, which is significant for scientific evaluation. Recruitment and data collection for the study were initiated in August 2021 and are currently underway. The study results are likely to be available and published in 2024.

Conclusions: This study contributes to the literature as it addresses the need for speech-focused digital health tools to detect clinically relevant emotional distress and functional impairments in children and adolescents. The preliminary results show that our algorithm has the potential to improve outcomes. The findings will contribute to the broader digital health transformation.

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KEYWORDS

mental health; predictive modeling; machine learning; artificial intelligence; social determinants of health; speech-recognition; adverse childhood experiences; trauma and emotional distress; voice marker; speech biomarker; pediatrics; at-risk youth

Introduction

Background

The increase in the rates of mental health problems among the pediatric population predates COVID-19. According to the Substance Abuse and Mental Health Services Administration and US Department of Health and Human Services Centers for Disease Control and Prevention [1]:

> *Between 2016 and 2020, the number of children ages 3-17 years diagnosed with anxiety grew by 29% and those with depression by 27%. In 2020, suicide was the second leading cause of death for young people aged 10-14 and 25-34, and among the top 9 leading causes of death for people ages 10-64.*

There has been an increase in suicide rates among children and adolescents [2], especially in low-income communities [3]. The meta-analysis of 29 studies with a total of more than 80,000 participants indicated an increase in emergency room visits by 22.3% and reported that 1 out of every 4 adolescents is experiencing clinically relevant depressive and anxiety symptoms, which was double the rate of prepandemic levels [4].

The need to focus on young people is partly related to the onset of mental disorders, which usually starts during a person's early developmental stages, and almost half of all mental health conditions are present before 14 years of age. Trauma plays a role in more than three-quarters of youth experiencing mental health disorders [5]. The early onset of the disease for Black, Indigenous, people of color, and other marginalized communities is related to the high rate of the experience of trauma, which is generational, and partly due to a history of discrimination, poverty, and poor access to quality mental health care. One way to account for the incidents and the severity of trauma is the use of Adverse Childhood Experiences (ACE). ACE scores tend to be higher for families from lower socioeconomic status [6]. ACE identifies a more expensive account of trauma, including the role of divorce and parental incarceration, and substance abuse. ACE score of 4 or more is likely related to symptoms of trauma, including aggression, self-harm behavior, posttraumatic arousal, and inattention, as well as neurobiological, developmental, and social delays [7]. Consequences across the lifespan include disrupted neurodevelopment and socioemotional and cognitive impairment. ACE also exacerbates the chances of future drug abuse, poor physical health, and early chronic disease, disability, and mortality [8].

The current behavioral health care system is falling short in addressing the crisis in the mental health needs of children and adolescents. In addition to the shortage of health care providers, the accurate diagnosis of mental disorders by humans requires extensive training, experience, and resources. Therefore, low-resourced communities have been experiencing a severe lack of experienced mental health providers, while the need for mental health services and the severity of patients remains disproportionately high. There is a need for technology-based and accessible tools for early intervention mechanisms for emotional distress in children and adolescents [9]. As a marker of emotional distress, speech or voice indicators have been used to understand the state of the mood and condition in health care [10]. Previous studies have already underlined the value of speech-based detection mechanisms in mental health. In earlier works, Scherer et al [11] followed 379 patients. They found that acoustic and linguistic measurements from voice samples achieved 85%-93% accuracy in classifying patients as suicidal, mentally ill but not suicidal, or neither. Mota et al [12] used a 2- to 5-minute free speech session and voice analysis method to predict (with 100% accuracy) whether an individual is at risk of first-episode depression. These examples and literature show the potential of speech analysis in detecting psychological distress and mental health issues [13-15]. Speech-based digital health technologies can assist health care providers in identifying children in need and aid in the delivery of appropriate and timely services to families in the community [16]. Specifically, such mechanisms can be used for early intervention, which can delay the onset and reduce the probability of developing the disorder [17]. Such prevention and mental health interventions can divert this population from future mental health issues and other high-risk behaviors [18].

In this study, we aim to develop and test a speech analysis algorithm to detect clinically relevant emotional distress and functional impairments in children and adolescents with diagnosable mental health disorders.

Theoretical Background

Archetypal Voice Categories

A significant problem for identifying speech emotions is the need to classify a collection of appropriate emotions to be identified as automatic emotion recognizers. Linguists have identified inventories of the emotional states that are occurring the most in our lives [19]. Several scholars agree with the "palette principle," which states that any emotion can be broken down into primary emotions, such as how each color is a mixture of simple colors. In this framework, the primary emotions are anger, happiness, fear, neutral, and sadness. These are the most visible and distinct feelings in our lives, and therefore, these emotions are called archetypal [20]. Given the role of emotions in human communication and decision-making, intelligent human-machine interfaces must respond appropriately to human emotions [20].

Automated emotion recognizers can be seen as devices assigning emotional states to category labels. The detection and identification of emotions in speech involve not only signal processing and interpretation methods but also psychological, linguistic, and emotional interpretation [20]. As a result of the

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rich voice data that can be identified, the focus on archetypal emotions—anger, happiness, fear, neutral, and sadness—is usually justified as a way of making finer distinctions [21]. On this premise, 2 forms of knowledge are included in the communication structure of human speech. The first type is more direct and communicates using spoken sentences. The second type is more passive and uses implicit, nonverbal signals to convey the message. We focus on understanding negative and nonnegative emotions from implicit and nondirect voice signals. This form of communication represents emotional distress and can help identify human emotions at a deeper level.

Theory of Psychological Trauma Biomarkers in Speech

Among all the biomarkers under development, speech stands out as an attractive candidate because it is affordable, noninvasive, and nonintrusive. Speech has the potential for applicability to a cohort of patients with various emotional or behavioral disorders from multiple cultural and linguistic backgrounds [20]. This capability is achieved by selecting only prosodic and acoustic features commonly existing in human speech and using them for predicting everyone's emotional distress and negative emotion [19]. This speech clustering emotion is assisted initially by traditional clinical diagnosis and at least 3 scientifically validated surveys: ACE, Patient Health Questionnaire 9 (PHQ-9), and Symptom and Functioning Severity Scale (SFSS) [22].

The link between trauma or stress and voice types is related to changes in the autonomic nervous system, including the disruption of speech-based characteristics partly due to muscle tensions. For example, evidence points to a connection between neural activity in the gamma-aminobutyric acid neurotransmitter, susceptibility to depression, and changes in muscle tonality [23]. Changes related to muscle tonality produce distinct utterances, thereby indicating the presence of negative mood or depressive symptoms [24]. Additionally, emotional states have a temporal structure. For example, people with bipolar depression or chronic anxiety may be in intense emotional states for months or years or have negative emotions for weeks [25]. On the other hand, emotions such as anger and excitement may be transient and last only for a few minutes. Emotions, therefore, have a broad meaning and a narrow sense. Overall, meaning reflects the long-term emotions underlying it, and the narrow sense applies to the mental stimulation that motivates people to behave in the short term [26]. To correctly identify the level of emotional distress, the algorithm needs to identify the underlying emotions of the behavioral/emotional disorder severity.

Methods

Participants

Participants are recruited from 2 mental health care centers that focused primarily on children and adolescents from low-income communities. The participants receive mental health services paid for by Medicaid, the Children's Health Institute Program, and the Department of Children and Family Services. The participants are children aged 5-18 years and those who have been referred for behavioral health services through schools, DJJ, and child protective agencies.

Ethical Considerations

The study received ethical board approval for a multisite pilot involving children and adolescents. We will receive written and informed consent from participants. The activities for patients enrolled in the study include data collected using multiple surveys and a voice sample. The surveys include structured and unstructured voice samples based on a reading selected by the research team. All the study contents are approved by the ethical board.

Data Collection

Using a software application, we use the TQI app [27] to collect voice samples from youth receiving mental health and family preservation services at the point of care. The app and data collection process include the concurrent administration of a scientifically validated, SFSS [28]. The patient's emotional disorder severity is confirmed based on the scores of the SFSS, ACE, and PHQ-9, as well as the patient's diagnosis and other clinical information from the patient's treatment history. For every voice sample collected, the pilot has a diagnosis or multiple, current procedural terminology code, and the therapist's clinical input. These data serve to categorize voice sample data into distinct categories and train voice-based machine learning (ML) algorithms to distinguish children in need and at high risk. The innovation is focused on families with low socioeconomic status, in whom ACE are common.

Data are collected by trained therapists (n=15). An Android mobile app is used to collect speech samples, SFSS, PHQ-9, and ACE scale responses. Each therapist receives a 5-hour in-person training about app installation and access, data (SFSS, voice sample) collection using the app, compliance and parameters, the process of the reward program, communication, and real-time technical support. Data are collected from patients every week as part of the mental health or other family-based intervention visits. Visits occur in a suitable (private) location at home (including foster and group homes) or school as part of a state's commitment to access services. Data are collected virtually as part of the shift in services secondary to the COVID-19 pandemic. Initially, identified target patient group demographics are shared in Table 1.

Voice samples are collected using the TQI app. To elicit speech for recording and analysis, patients are asked to choose from a subset of readings. Patients' reading is recorded for up to 90 seconds—a clock feature in the app signals when the time is up. Voice samples are stored in a separate deidentified database that will allow 3 to 4 psychologists to label the voice sample independently. SFSS, PHQ-9, and ACE responses are collected using the same app. The app scores the surveys immediately and makes the results available to the therapist to share with their patients if it is clinically appropriate; the availability of the data in real time is intended to close the gap in transparency, accountability, and family engagement.

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Table 1. Identified target patient group demographics.

Characteristics	Values (N=420), n (%)
Gender	
Female	136 (32)
Male	147 (35)
No gender disclosed	137 (33)
Ethnicity	
Hispanic	115 (27)
Caucasian	66 (16)
Black	93 (22)
Asian	2 (0.5)
No ethnicity disclosed	144 (34)

Data Processing

Data Preparation

Preprocessing speech samples, that is, segregating the voiced region from the silent and unvoiced portion of an utterance, is a crucial step in developing reliable voice analysis. Most of the speech-specific attributes are present in the voiced part of speech, and our algorithm learns emotion only based on the voiced portion as opposed to the whole segment. To extract the active voice from our samples, an open-source voice activity detection (VAD) algorithm called "WebRTC VAD" [29] is used in preprocessing. WebRTC VAD is a power-based VAD algorithm that extracts the features such as spectral energy and zero crossing rate during a short time frame of 30 milliseconds and feeds them into a decision tree trained by a large voice data set to decide the voice activity. As the clinical data collected from the app contains different levels of noise, we chose a high aggressiveness for our VAD in order to clean the data into voiced utterances.

Feature Extraction

Feature analysis is made by applying a shifting Hamming window of 25.6-minute length frames of the speech signal. Within each frame, the signal is approximately stationary. We then estimate the spectrum by calculating the discrete Fourier transform for each segment with N-point FFT (Fast Fourier transform) of 256 samples. For each analysis frame, we extract time domain feature, spectral features, and Mel-frequency cepstrum coefficient.

The time domain features extracted are zero crossing rate, energy, and entropy. Pitch and energy information are the most prominent features, as they can identify emotion based on the tension of vocal folds and subglottal air pressure. The time elapsed between 2 successive vocal fold openings is called a pitch period, while the vibration rate of the vocal folds is the fundamental frequency. Smaller pitch periods, that is, higher velocities of airflow, are associated with emotions like happiness, while longer pitch periods are linked to harsher emotions like anger. The spectral features extracted are entropy, spread, flux, and roll-off. The alterations in estimations of spectral spread over the frequency range and entropy in speech have been proven to be strongly linked to the diagnoses of clinical depression [30].

The Mel-frequency cepstrum coefficient extracted from the speech is a representation of linear cosine transform of a short-term log power spectrum of the speech signal on a nonlinear Mel scale of frequency. The incorporation of these coefficients in the feature vector is useful in the identification of paralinguistic content in speech. This extraction is of the type where all the characteristics of the speech signal are concentrated on the first few coefficients. A probability model algorithm is used to classify speech and to derive a prediction of the speaker's emotions.

Emotional Frame Selection

Feature extraction procedures produce a quantified collection of attributes. However, emotion recognition is still challenging as we do not understand the correlation between certain features and certain emotions. To better analyze and understand the correlation, we use a Gaussian mixture model (GMM) to perform frame selections. The key intuition is that emotions are usually more concentrated on certain words. While we are not studying emotion from a semantics perspective, it does help us to locate emotionally rich frames and study their features.

We perform GMM clustering on frame features in an utterance. The cluster means are visualized with multidimensional scaling, projecting the Euclidean distance between all clusters onto 2D map. We repeat the process for all emotion categories except neutral. Drawing inspiration from intuition, we deem frames close to the origin on the projection map to be less discriminative and frames on the outer ring to be more discriminative. By using the selected frames, inputs become more condensed hence boosting the classification accuracy.

Machine Learning Models

Gaussian Mixture Model

Our first model takes an unsupervised parametric clustering approach. The GMM is a parametric probability density function consisting of several single Gaussian distributions [31]. It is an unsupervised soft clustering technique that is widely used for speech and speaker classification, audio classification, audio segmentation, and so forth. A GMM approach was used, where

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speech emotions were modeled as a mixture of Gaussian densities. The model is parameterized by 2 types of values: the mixture component weights and the component mean and variances or covariances. For a model with K components, the kth component has a mean vector of length k and k × k dimensional covariance matrix. The mixture component weights are defined such that the total probability distribution normalizes to 1. If the component weights are not learned, they are viewed as an a priori distribution over components. If they are learned, they are the a posteriori estimates of the component probabilities given the data.

In the first step (expectation or E), the expectation of the component assignments for each data point is calculated. In the second step (maximization or M), the expectations calculated in the E step are maximized. This iterative process repeats until the algorithm converges, giving a maximum likelihood estimate. Alternating between which values are assumed fixed or known, maximum likelihood estimates of the nonfixed values can be calculated efficiently.

To ensure GMM's performance, we extract features from audio samples that have a satisfying discriminate capacity. We apply Fisher discriminant ratio [32] for the feature selection process. Fisher discriminant ratio is a significant measure for features to be used in classification. For our task, Fisher discriminant ratio indicates how separable the clusters for different emotions are. The top features include energy below 250 Hz, median and minimum of F1 formant frequency, a median of F0 formant frequency, and the variation of the duration of energy plateaus (represents speech rate). Other features used in our analysis include linear predictive coding coefficients and Mel-frequency cepstrum coefficients. Linear predictive coding coefficients is a robust, reliable, and accurate linear representation of speech that takes into consideration the vocal tract and glottal pulse characteristics of voiced speech [33]. Mel-frequency cepstrum coefficients is extracted on a nonlinear scale of frequencies that are altered to closely resemble human hearing capabilities [34]. As we are aiming at children's stress detection with varying age differences across all children patients, it is important to note the difference in the vocal cord between gender and age groups.

There are 2 general approaches for GMM parameter estimation methods: the maximum likelihood approach and expectation-maximization (EM) estimation [35]. The ML method constructs a most likely model to fit for all of the current observations. Since there is no way to ensure unbiased data collection regarding mental health, the ML method poses an unrealistic assumption on the data set. Comparatively, EM is a far superior method to cope with this so-called missing data problem, where we assume only a subset of the features is observed. The EM algorithm consists of 2 iterative steps. Expectation or the E-step made an initial guess for the model parameter concerning missing data, using current estimates, and conditioned upon observed data. The maximization (M-step) then provides a new estimate increasing the above expectation.

The entire iterative process repeats until the algorithm converges, giving a maximum likelihood estimate. Intuitively, the algorithm works because knowing the component assignment Ck for each xi makes solving for model parameters easy while knowing the model parameters and makes inferring the probability of point xi belonging to component Ck easy. The expectation step corresponds to the latter case, while the maximization step corresponds to the former. Thus, alternating between which values are assumed fixed or known, maximum likelihood estimates of the nonfixed values can be calculated efficiently.

Recurrent Neural Network and Long Short-Term Memory

Our second model takes on a different approach to learning, where it employs a supervised learning scheme. The primary motivation for using a recurrent neural network is the idea that they can connect previous information to the present, such as using features extracted from previous frames of the signal to understand the present frame [30]. A long short-term memory network is a special kind of recurrent neural network (RNN) capable of learning long-term dependencies. It uses memory cells and gates to control whether the information is memorized, output, or forgotten [30]. The gating mechanism is used to control information flow by pointwise multiplication. There is a cell to memorize information within the unit. The long short-term memory (LSTM) incorporates cell states at several different time points prior to the current frame using a linear combination, which is computed using an attention mechanism where the weights of data points are learned. This configuration implies an assumption that the current state depends on the state of the previous time step. Thus, emotion patterns are learned by not only correlating the features to the labels independently but also taking the change in features in time into consideration.

Recurrent neural network is a potent tool to extract features in speech recognition, audio scene detection, and so forth. Unlike artificial neural networks, RNN forms a directional graph along a temporal sequence, which registers temporal information throughout the learning process. RNN has proven to be extremely powerful in speech- or audio-related tasks [20,21,23,24] due to the temporal nature of speech. Emotion poses a similar temporal feature to speech, so we wish to create an RNN-based neural network for our task. There has been some research using RNN/LSTM networks for emotion classification. LSTM units are capable of learning long-term dependencies and avoid vanishing gradient problems. With more and more clinical data flooding our database, we are quite positive about what RNN can achieve for our task.

Results

Overview

The institutional review board approved the study in July 2021. Recruitment and data collection for the study were initiated in August 2021 and are currently underway. The study results are likely to be available and published in 2024.

Testing With a Public Data Set

The proposed models are first trained and tested on large public voice data sets to validate the model's ability of emotion classification. These data sets are the Toronto emotion speech set, Ryerson audio-visual database of emotional speech and song, and Surrey audio-visual expressed emotion, which have

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simulated emotions provided by professional actors [36]. The voice samples are split into training and testing sets, with a ratio of 85:15 for each of the 5 emotions. The models are trained both with utterance level features and with emotion frame selection to demonstrate the effectiveness.

Based on the results (Table 2), GMM with 128 clusters shows an evenly distributed accuracy across 5 emotions. With utterance level features, GMM achieves an accuracy of 79.15% in total and with frame selection of 85.35%. This demonstrates that GMM is a robust model for emotion classification of all 5 emotions, and emotion frame selection enhances the accuracy of all emotions, which is significant for scientific evaluation. The RNN-LSTM model also shows an evenly distributed accuracy over the emotions, with 79.6% overall accuracy on utterance level and 86% overall accuracy on emotional frames. With emotion frame selection, accuracy on emotions is enhanced but for fear.

Table 2. Accuracy testing results (%) for emotions with the public data set.

Emotions	GMM[a] utterance (%)	GMM frame selection (%)	RNN[b] utterance (%)	RNN frame selection (%)
Neutral	81.68	89.97	86	87
Happy	75.77	82.50	76	88
Sad	73.61	80.10	73	88
Angry	82.52	87.27	84	96
Fear	81.6	85.89	79	71
Overall	79.15	85.35	80	86

[a]GMM: Gaussian mixture model.

[b]RNN: recurrent neural network.

Clinical Data

During this study, we plan to collect and test our model with a clinical data set. Due to the potential variance of the sample size of available clinical data and the richness of emotions that may differ in the pediatric population, training with clinical data is necessary with GMM. For the public data set, our models yield unbiased classification accuracy across all emotion categories. GMM and RNN results are on par, and both could take advantage of the frame selection process to boost accuracy by 6.2% and 6.4%, respectively. Yet, GMM and RNN-LSTM approaches traditionally require a large amount of training data to achieve the best results. Therefore, the clinical data set is aimed to be diverse and large enough to meet the requirement for the training data set. Nevertheless, the results show that our approach is effective for adult human emotion recognition.

For the clinic data set, the performance drop in children's emotion recognition is expected, especially for the data trained on adult speech and tested on children's speech. It may demonstrate the difference between adults' and children's vocal quality. For models trained on clinical data sets, the performance depends on data sample size and quality. In addition, children's voice quality between 6 and 18 years of age is different across gender as well as age groups. It indicates that the training data set is required to be clustered into separate groups. Another parameter to consider is the natural bias in the data set. Since voice samples are collected from patients, they could be biased toward negative emotions, especially fear, anger, and sad categories.

Discussion

Principal Findings

Our study aims to develop and test a speech analysis algorithm to detect clinically relevant emotional distress and functional impairments in children and adolescents with diagnosable mental health disorders. More specifically, the study proposal focused on developing an ML model for a feature extraction that is used for discriminating clinically relevant emotions from speech utterances. The ML model we built also achieved its goal of emotion classification and frame selection for pediatric patients with mental health disorders.

The clinical voice samples provided a wealth of information that can indicate mental status and overall emotional functioning [10], and our study is building on top of earlier evidence on predicting mental conditions [11], including depression and emotional distress [13-15]. Therefore, we anticipate that our study findings will contribute to the literature in terms of understanding the current landscape and building evidence to develop an automated speech analysis algorithm to detect emotional distress and functional impairment.

Even though the study data collection is ongoing, preliminary testing with a public data set showed promising results. The study developed a robust emotion recognition algorithm for 5 classes of emotion based on open-source data sets with 79.14% accuracy using probabilistic models. Compared to the literature, we have promising scores in terms of accuracy with the public data set [11]. A GMM-based speech emotion classification algorithm is used with 3 public adult speech corpora.

Developing a more accurate model requires addressing the problem of biased samples; currently, all the voice samples are collected from youth in mental health services with known mental health diagnoses. The average score of ACE for this sample population (N=420) is 5 out of 10; less than 13% of the US population has an ACE score of 4 or higher [37]. Furthermore, some of the youths display regional Southern American accents, African American Vernacular English, as well as accents related to the fact that English is not their first language. While this gives us the opportunity to build a unique

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clinical data set from youth from low-income communities, a skewed data set may decrease the accuracy of the algorithm to detect and score the severity of negative emotions.

Limitations

The study presents several limitations. First, the quality and variability of speech data, including background noise and speech disorders, can affect the accuracy and reliability of biomarkers. Second, the sample population may not be representative to the greater US population, limiting the generalizability of findings. Finally, legal and regulatory considerations, including privacy rules and compliance with regulations, must be reviewed based on the state and jurisdictions, and may limit the use of the algorithm. The latter must be considered to protect participants and ensure the lawful use of data.

Implications and Future Work

In the United States, there are several bottlenecks in the current system of mental health care that technology can address immediately. First is a quick and accurate measurement of the severity of the mental health problem, keeping in mind that all planned interventions depend on the accuracy of symptom severity. Technology, like voice and artificial intelligence, that can make objective measurements of severity can be integrated with limited disruption to the workflow. They can play a significant role in triaging youth to the appropriate level of services proactively and effectively. As we transition to a knowledge-based economy and adjust to the digital industrial revolution, the mental health system of care can no longer afford to resist technology as one part of improving treatment outcomes While automation is routinely adopted in other sectors of the economy, the semimanual workflow of the current mental health system of care accounts for inefficiency in care and provider burnout. For example, mental health providers spend 40% of their time documenting, equivalent to 2 days out of the 5-day workweek that they cannot provide patient services.

Artificial intelligence, automation, and data analytics will be an integral part of the future of mental health services. Adoption of this technology will require the design of user-friendly interfaces, such as the TQI app, that can help mitigate clinician technophobia [38]. Because of the anticipated lack of qualified providers, health care organizations and school systems need to adopt innovation to address quality and cost. As a result, we expect to see the prevalence of innovative technologies continue to rise as payers and other stakeholders demand evidence-based services and data demonstrating treatment outcomes. The shift to value-based care is from payment based on service provided to payment based on outcomes. The providers that will thrive in this new service landscape must use technologies to improve clinical accuracy, workflow productivity, and efficiency. This will help service organizations not only to identify and track high-risk children but also to improve treatment outcomes. A significant percentage of patients in child protective services and covered by Medicaid and other state expenditures come from low-resourced communities. Such solutions will mitigate the severe shortage of highly trained mental health providers in these communities and address health outcome disparities.

The current student-to–school counselor ratio for most school systems is 300 students to 1 counselor. Some schools have a contractual agreement with virtual behavioral health providers to lessen this burden for their staff. The technology could play an influential role in integrating services and breaking down silos. Collaboration between mental health care providers, pediatric primary care, schools, and other stakeholders has been shown to be effective in the early identification and treatment of mental health conditions.

Conclusions

The integration of digital mental health innovations is crucial in addressing the ongoing mental health crisis among children and adolescents. Speech-based digital biomarkers that can be collected via a user-friendly interface hold promise for identifying emotional distress and functional impairments in this population. The findings will contribute to the broader digital health transformation and pave the way for proactive and collaborative mental health care practices.

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Data Availability

Data sharing is not applicable to this study as no data sets were generated or analyzed during this study. Preliminary work was completed using a public data set, and the data set is cited in the manuscript.

Conflicts of Interest

YA is the founder and CEO of TQIntelligence and the principal investigator for the NSF SBIR Phase I grant. The company, TQIntelligence, has also been the recipient of an award from the Google Black Founders Fund that partially funded this research. The company was also awarded a patent for this technology (serial No. 17/550,544) a year and a half after this study.

Multimedia Appendix 1

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Peer review reports.
[PDF File (Adobe PDF File), 20 KB - resprot_v12i1e46970_app1.pdf]

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Abbreviations

ACE: adverse childhood experiences
EM: expectation-maximization
GMM: Gaussian mixture model
LSTM: long short-term memory
ML: machine learning
PHQ-9: Patient Health Questionnaire 9
RNN: recurrent neural network
SFSS: Symptom and Functioning Severity Scale
VAD: voice activity detection

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Protocol

A Smartphone-Delivered Program (Anathema) to Promote the Sexual Health of Older Adults, Colorectal Cancer Survivors, and Stroke Survivors: Protocol for a Feasibility Pilot Randomized Controlled Trial

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Abstract

Background: Despite the prevalence of sexual distress and dysfunction in older adults in general and stroke and colorectal cancer survivors in particular, access to specialized care is limited by organizational barriers and stigma, embarrassment, and discrimination. The internet allows reaching services that would otherwise be difficult or impossible to reach, and as smartphones are personal (intimate) technologies, they are a promising vehicle to close this gap. However, research focusing on smartphone-delivered sexual health promotion programs is scarce.

Objective: This study aims to assess the acceptability, feasibility, and preliminary efficacy of Anathema, an 8-week, iOS/Android smartphone–delivered, individually tailored, cognitive-behavioral sexual health promotion program developed to improve relationship and sexual satisfaction, sexual functioning, sexual distress, sexual pleasure, and health-related quality of life (HRQoL) in older adults, colorectal cancer survivors, and stroke survivors compared to treatment as usual in a waiting-list control condition.

Methods: Two-arm, parallel, open-label, waiting list, feasibility, pilot randomized controlled trials (RCTs) will be conducted involving older adults, stroke survivors, and colorectal cancer survivors. The primary outcomes are the acceptability, usability, and feasibility of Anathema. Sexual function, relationship and sexual satisfaction, sexual pleasure, sexual distress, anxiety, depression, and HRQoL are the secondary outcomes. This study has been reviewed and approved by the ethics committees of Instituto Português de Oncologia do Porto Francisco Gentil, Europacolon Portugal, Faculty of Psychology and Educational Sciences, University of Porto, and Sigmund Freud University (approval numbers: CES218R/021, CES19/023, and 2022/01-05b).

Results: This project is funded by the European Commission through the Active and Assisted Living (AAL) Programme (reference: AAL-2020-7-133-CP) from April 2021 to December 2023. Recruitment for the pilot RCTs started on January 2023 in Portugal, Austria, and the Netherlands and is currently ongoing. As of May 2023, we randomized 49 participants in the trials. We expect to complete the RCTs in September 2023. The results on the acceptability, feasibility, and preliminary efficacy of Anathema are expected in the second semester of 2023. We expect Anathema to be highly accepted by the populations under study; to prove feasible to scale up to parent RCTs; and to be potentially efficacious in improving sexual functioning, relationship and sexual satisfaction, sexual distress, sexual pleasure, and HRQoL in older adults, colorectal cancer survivors, and stroke survivors compared to treatment as usual in a waiting-list control condition. The study results will be published in open-access venues according to COREQ (Consolidated Criteria for Reporting Qualitative Research) and CONSORT EHEALTH (Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth) guidelines.

Conclusions: The study results will inform the refinement and scale-up of Anathema. Anathema's wider-scale implementation can potentially promote the sexual health of largely neglected user groups such as older adults, colorectal cancer survivors, and stroke survivors.

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KEYWORDS

colorectal cancer; internet interventions; smartphone; older adults; participatory design; randomized controlled trial; stroke; survivors

Introduction

Background

Sexual health is an integral component of general health [1]. It is significantly related to physical and psychological health, as well as to the perception of well-being and health-related quality of life (HRQoL) [1-3]. Being sexually active has been reported to be associated with improved mental health, increased heart rate variability, and lower risk of certain cancers and coronary events, resulting in lower annual death rates [4]. However, the aging process frequently threatens the experience of a positive, healthy, and fulfilling sex life [5].

Due to physiological and psychosocial changes, older adults are at higher risk of developing sexual difficulties when compared to the general population [6,7]. Frequent problems affecting older women include decreased libido, lack of vaginal lubrication, and orgasmic difficulties. Among older men, erection problems, reduced sexual desire, and an inability to reach climax are the most reported sexual difficulties [5-7]. Previous studies focusing on the predictors of such conditions in both sex groups [5] have identified interpersonal and attitudinal factors, mental health conditions (eg, depression), and physical health conditions as being strongly associated with sexual problems. In this regard, colorectal cancer [8] and stroke [9] are examples of prevalent acquired medical conditions highly associated with older age, which may result in significant impairments in sexual functioning and satisfaction [10,11].

Studies targeting colorectal cancer survivors [12,13] often reported a decrease in the frequency of sexual intercourse, a high incidence of sexual problems (ie, low sexual desire, and arousal and orgasm difficulties), and a significant decrease in survivors' sexual satisfaction after cancer treatment. Identified risk factors for sexual dysfunction include being diagnosed with low rectal cancers, undergoing abdominoperineal resection, having a stoma, and prior treatment with radiotherapy [13]. Moreover, male sex, older age, individual and partner distress, and comorbidities have been reported to be associated with increased sexual disorders in colon cancer survivors [12]. The literature also suggests that sexual difficulties in colorectal cancer survivors span the continuum of care [14].

Among stroke survivors, research reports a high prevalence of sexual dysfunction [15]. The etiology of poststroke sexual dysfunction is multifactorial, and it includes organic (eg, lesion site, comorbidities, medication, etc) and psychosocial factors (eg, anxiety, depression, fear of recurrence, etc) [15]. Common clinical presentations of sexual dysfunction in female survivors include decreased libido, lack of vaginal lubrication, arousal problems, and orgasmic dysfunction [11,15,16]. Male survivors often report decreased libido, sexual activity, and coitus frequency, as well as erectile and ejaculatory dysfunctions [11,15,16]. These difficulties also manifest in stroke survivors with an absent or mild physical impairment, with nearly half experiencing decreased libido, coitus frequency, sexual arousal, orgasm, and sexual satisfaction [11,16]. This finding suggests that changes to prestroke relationships and roles, communication difficulties between partners, taboo and stigma, negative beliefs and attitudes toward sexuality, and perceived social norms may disrupt sexual expression in stroke survivors, leading to decreased sexual satisfaction and poor HRQoL outcomes [11,17].

Despite the prevalence of sexual distress and dysfunction in older adults in general and stroke and colorectal cancer survivors in particular, access to specialized care is limited, and sexual health remains a largely neglected component of treatment [18]. Recent reviews [19-21] have identified a lack of available information concerning sexual issues, a lack of education and training of health care professionals on sexual health, poor quality of the relationship between patients and health professionals, and misalignment between their perspectives on the importance of sexual health as important barriers to accessing sexual health support. Negative societal views and beliefs toward sexual health, stigma, embarrassment, and discrimination were also identified as major factors hindering access to sexual health support and treatment among older adults and other chronic disease groups [19-21]. Finding alternative ways of facilitating access to evidence-based sexual health support that is tailored to the unmet needs of older adults, colorectal cancer survivors, and stroke survivors in a nonstigmatizing manner is, therefore, critical to overcome barriers to treatment-seeking and promote their sexual health.

Because smartphones are personal (intimate) technologies that, augmented with internet connections, allow reaching services that would otherwise be difficult or impossible to reach, they are a promising vehicle to close this gap. However, research focusing on internet-delivered interventions for sexual health is scarce [22]. Most studies addressing such programs focused on male and female sexual dysfunctions in adult populations [23], and only a few targeted sexual difficulties related to chronic conditions. A recent systematic review [24] of mobile health interventions for sexual health among adults with chronic diseases reported no studies with interventions delivered through smartphones. All analyzed studies used a website for intervention delivery, failing to leverage the advantages of mobile devices in this context, namely, "convenience, privacy, anonymity, and more interactive treatment for sexual dysfunction" [24]. Still, the evidence suggests that internet-delivered sex therapy is effective in improving psychosexual outcomes in chronic patients [24].

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Among these, cancer is the most frequently researched condition [25-27], with studies including patients with gynecological [28,29], breast [29-32], prostate [33], and colorectal cancers [28]. The findings of these studies suggest that internet-delivered interventions for sexual health are feasible, acceptable, and potentially effective in improving sexual health in cancer survivors [25,27]. Reviewed studies have reported improvements in sexual function and activity [28,29,31]; sexual arousal and pleasure [30]; sexual, intimacy, and relationship satisfaction [34,35]; and sexual distress [28,30]. Furthermore, the positive effects of these interventions in cancer survivors are likely to persist in the long term [34].

However, previously conducted studies vary greatly in sample size, intensity, and program length, and further research is necessary to attest the feasibility and efficacy of internet-delivered interventions for sexual health among different target cancer populations, including colorectal cancer populations, and the use of digital technologies like smartphones.

To the best of our knowledge, no study has yet assessed the efficacy of internet-delivered interventions to promote sexual health in stroke survivors or older adults. Nevertheless, professionally guided online sexual rehabilitation programs were identified as highly consensual in a recent Delphi study involving stroke survivors, their partners, clinicians, and researchers [36], underlining the pertinence of developing and testing internet-delivered sexual health promotion programs targeting stroke survivors.

To address the research and supportive care gaps mentioned above, we developed, in the context of a European project named *Anathema – Technology for ageless sexual health*, an 8-week, iOS/Android smartphone–delivered, individually tailored, cognitive-behavioral, sexual health promotion program to improve relationship and sexual satisfaction, sexual function, sexual distress, sexual pleasure, and HRQoL in older adults, colorectal cancer survivors, and stroke survivors (for further details on Anathema's development and structure, please see [37]). This project is funded by the European Commission through the Active and Assisted Living (AAL) Programme. This report presents the research protocol that will support the assessment of Anathema's acceptability, feasibility, and preliminary efficacy in the 3 target populations compared to treatment as usual (TAU) in a waiting-list control (WLC) condition. The findings of this study will support Anathema's future scale-up, implementation, and commercialization, and ultimately facilitate access of older adults, colorectal cancer survivors, and stroke survivors to sexual health support.

Objectives and Hypothesis

This study aims to assess the acceptability, usability, feasibility, and preliminary efficacy of Anathema in older adults, colorectal cancer survivors, and stroke survivors compared to TAU in a WLC condition.

We hypothesize that Anathema will be highly accepted by study participants and prove feasible to scale up. We also expect Anathema to preliminarily show more efficacy in improving relationship and sexual satisfaction, sexual functioning, sexual distress, sexual pleasure, and HRQoL in the study populations compared to TAU in a WLC condition.

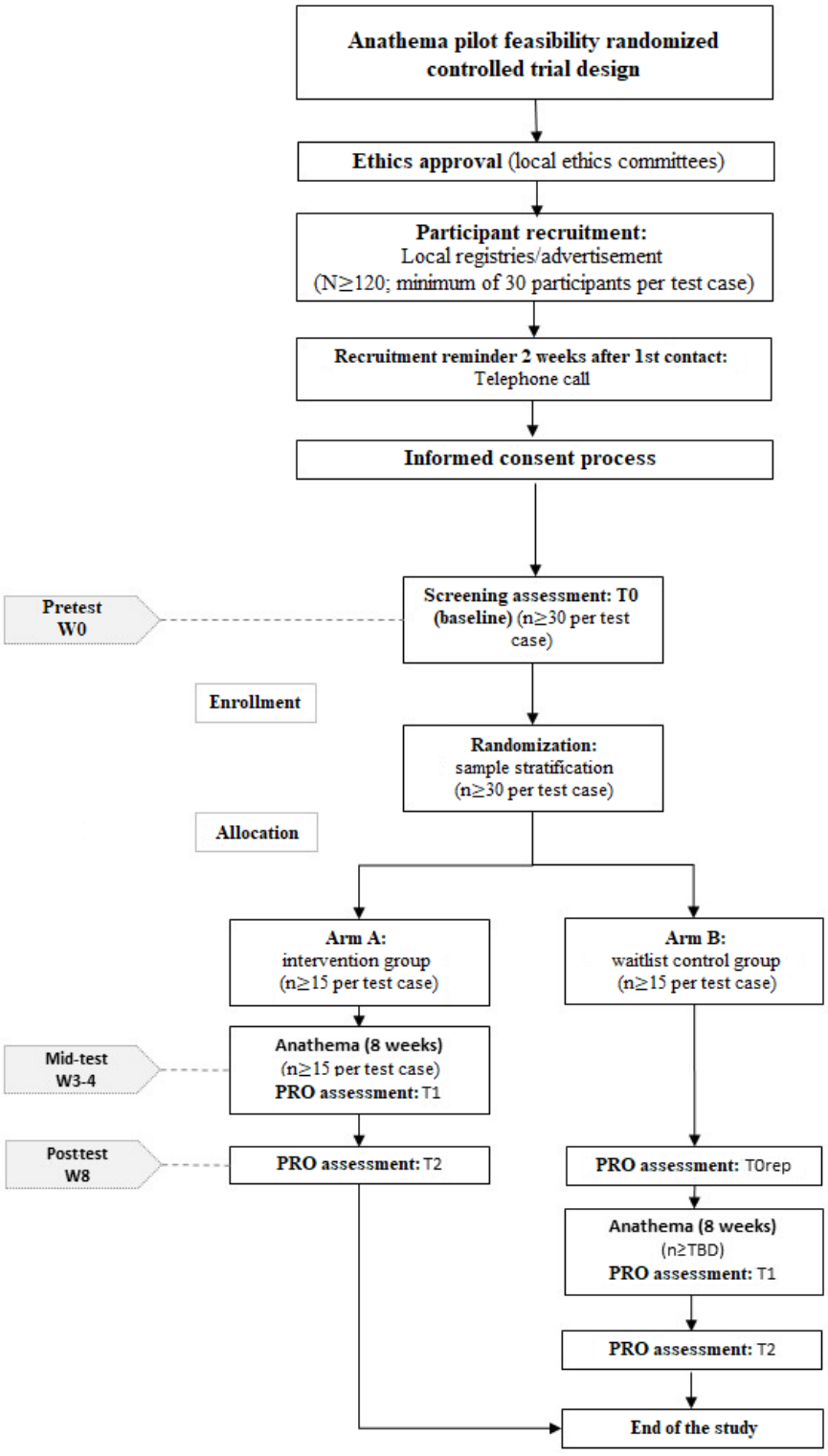
Methods

Study Design

Two-arm, parallel, open-label, waiting list, feasibility, pilot randomized controlled trials (RCTs) (Figure 1) will be conducted with older adults, stroke survivors, and colorectal cancer survivors. We will have 1 test case per target population, where different service models (unguided, guided, or blended care) will be tested. The feasibility pilot trials will be performed to identify weaknesses in the study design, test the data collection process, estimate sample sizes, and assess the feasibility of the parent RCTs. The acceptability of Anathema by study participants; the structure, format (ie, unguided, guided, and blended), and content of the study intervention; and between-group differences will also be preliminarily evaluated through this design.

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Figure 1. Anathema study design. PRO: participant-reported outcome; TBD: to be determined.



Ethics Approval

This study has been reviewed and approved by the ethics committees of Instituto Português de Oncologia do Porto Francisco Gentil (IPO-Porto) (approval number: CES218R/021, and CES19/023), Europacolon Portugal, Faculty of Psychology and Educational Sciences, University of Porto (approval number: 2022/01-05b), and Sigmund Freud University.

Study Population and Research Sites

This research will target 3 study populations: older adults, colorectal cancer survivors, and stroke survivors. Older adults will be recruited in the Netherlands and Austria. Colorectal cancer survivors and stroke survivors will be recruited in Portugal. A minimum of 30 participants [38,39] per target group is expected to participate in the study trials.

The criteria presented in Textbox 1 will be used to check eligibility for participation in the study:

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The study will be conducted at 5 different research sites: Unie KBO in the Netherlands; Instahelp in Austria; and IPO-Porto, Europacolon Portugal, and Centro de Reabilitação Profissional de Gaia in Portugal. Sites invited to participate were selected owing to their working standards and resources.

Textbox 1. Eligibility criteria for Anathema's feasibility randomized controlled trials.

Inclusion criteria

- All target groups: Ability to provide informed consent; age ≥55 years; all gender identities, sexual orientations, relationship statuses, and sexual practices at the time of the study; absence of severe psychiatric comorbidity (psychotic or bipolar disorders, severe depression, and substance abuse); single or partnered; no unstable medical conditions precluding participation in a sexual health promotion program; no concurrent therapy to alleviate problems with sexuality or intimacy, or cognitive-behavioral therapy for other psychological issues; ongoing regular psychoactive medication accepted if the dosage has been stable during the last 3 months; daily access to the internet and ability to perform basic use of a smartphone; and no concurrent participation in any other interventional study or clinical trial.
- Specific for colorectal cancer survivors: History of histologically confirmed colorectal cancer; an interval of ≥6 months from primary adjuvant treatment completion (surgery, chemotherapy, or radiotherapy); no previous treatment for another type of cancer (except for cervix carcinoma in situ or basal cell carcinoma); and disease-free at the time of study entry.
- Specific for stroke survivors: Confirmed diagnosis of stroke (hemorrhagic or ischemic) based on clinical examination and imaging, as assessed by a neurologist; and absence of severe cognitive issues or dementia.

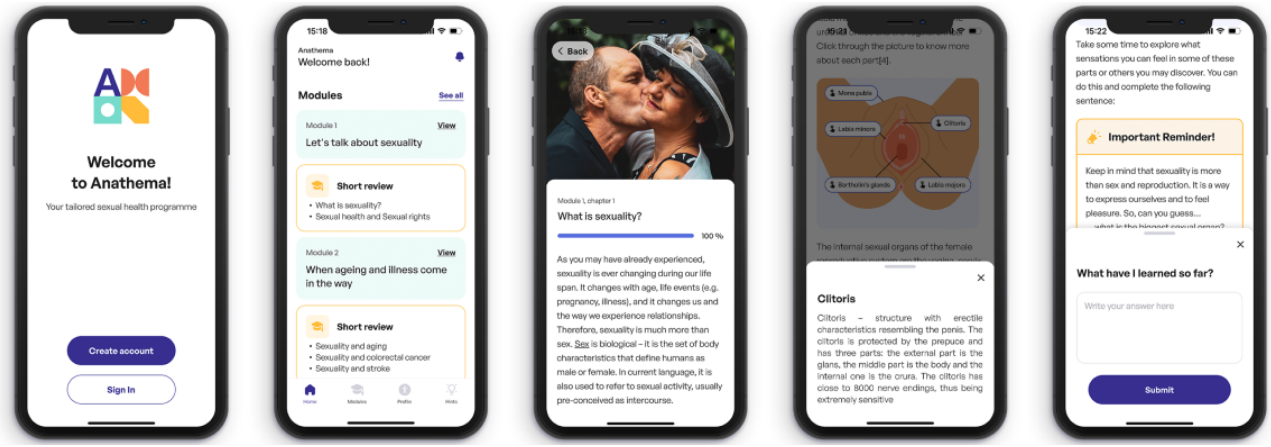
Exclusion criteria

- All target groups: Age <55 years; inability to co-operate and provide informed consent; current severe, uncontrolled systemic disease or mental disorder; parallel ongoing psychological treatment; ongoing regular psychoactive medication if the dosage has been changed during the last 3 months; no access to the internet; inability to use a smartphone and the internet; parallel ongoing participation in another interventional study or clinical trial; and assessment by the investigator to be unable or unwilling to comply with the requirements of the protocol.
- Specific for colorectal cancer survivors: Colorectal cancer not histologically or cytologically confirmed; history of other malignancy within the last 5 years; and metastasized colorectal cancer.
- Specific for stroke survivors: Unconfirmed stroke diagnosis; and severe cognitive impairment or dementia.

Study Intervention and TAU

Anathema (Figure 2) is an 8-week, iOS/Android smartphone–delivered, individually tailored, cognitive-behavioral sexual health promotion program developed to improve relationship and sexual satisfaction, sexual functioning, sexual distress, sexual pleasure, and HRQoL in older adults, colorectal cancer survivors, and stroke survivors.

Figure 2. Anathema app overview.



The program was created using a participatory design approach [40], involving its primary (older adults, colorectal cancer survivors, and stroke survivors), secondary (psychologists and sexologists), and tertiary end users (managers of care homes, day-care centers, or clinics). Anathema's development followed an agile development framework [41] and was based on peer-review sources (eg, [12,42-49]) and user research insights (eg, [37]). The program adopts a transdiagnostic structure, featuring sexual health promotion strategies considered appropriate for the different populations under study. Its central components are psychoeducation, cognitive restructuring, mindfulness, communication skills training, exercises to promote sexual sensation awareness and erotic repertoire, and masturbatory and sensate focus exercises. Anathema is structured into 5 modules to be completed for up to 8 weeks. A detailed description of Anathema's structure and content is provided in Table 1.

Regarding human support, Anathema may be delivered using 3 service models. The subtypes are as follows: unguided or self-guided (the primary end user follows all the intervention programs on her/his own with no support from a clinical psychologist), guided (the intervention program incorporates

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clinical psychologists' synchronous or asynchronous support, guidance, and feedback via email, chat, etc), and blended (treatment programs that combine face-to-face or videoconference sessions with online treatment modules in an integrated and sequential format). An iOS/Android app co-developed in the context of this project will be used to deliver the self-guided version of the intervention to older adults in the Netherlands. In this approach, no clinical psychologist-participant contact is foreseen. This app will also guide colorectal cancer and stroke survivors throughout the program in Portugal. Synchronous (eg, voice and chat) and asynchronous (eg, email) communication channels will be available to provide participants with guidance and support weekly and upon request. The blended-care format intervention will be delivered to older adults in Austria via an iFrame to be made available on the Instahelp platform [50]. In this case, the developed modules will be combined with 3 videoconference sessions (at the onset, mid, and conclusion of the intervention) focusing on the clarification of the intervention's content and strategies to be implemented. Upon request, sessions are also possible for participants requiring additional support from clinical psychologists.

In this research, TAU refers to the routine sexual health care participants would receive at the recruitment sites. Therefore, the type of TAU received may vary and include pharmacologic treatment or psychosocial support. WLC participants will be informed that they are free to access any form of support during the study and encouraged to seek professional help in case they experience symptomatic deterioration or other difficulties. WLC participants will be offered the same treatment protocol applied to the experimental group after completion of the program (approximately 8 weeks from baseline).

Table 1. Anathema's structure and content.

Module	Intervention components	Content
Let's talk about sexuality? (week 1)	• Psychoeducation	• Concepts underlying sexuality • Male and female anatomies and erogenous zones • Sexual response and sexual pleasure • Sexual health, sexual rights, and their importance • Activities: Setting my personal goals within Anathema, and I get pleasure from…
When aging and illness come in the way (week 2)	• Psychoeducation (tailored to each study population)	• Successful aging • Sexual expression in older age • Physiological, cognitive, and emotional changes in older age • Sexual problems and sexual dysfunction in older age • Biopsychosocial changes associated with colorectal cancer (CRC) and stroke, and their impact on survivors' sexual health • Activities: Practicing self-compassion, and identifying and classifying the changes I experience in my sexual life due to aging, CRC, or stroke
Emotional and physical intimacy (weeks 3-6)	• Psychoeducation • Cognitive restructuring • Mindfulness • Communication skills training • Sensate focus	• Sexual beliefs, thoughts, and emotions, and their impact on sexuality • Identifying, evaluating, and modifying maladaptive thinking • Interpersonal relationship and communication issues commonly associated with aging, CRC, and stroke • Restoring interpersonal relationships and intimacy • Activities: Rational disputation, diary of thoughts and emotions, practicing mindfulness, identifying and overcoming relationship stressors, improving communication, and sensate focus
Exploring one's sexuality (week 7)	• Psychoeducation • Mindfulness exercises • Sexual skills training	• Giving and receiving pleasure: eroticism, masturbation, and intercourse • Sex aids and strategies to enhance sexual pleasure and satisfaction • Activities: Practicing mindfulness and identifying treatment options
Planning for a long-term fulfilling sex life (week 8)	• Relapse prevention	• Overview of Anathema and progress evaluation • Strategies to maintain progress and prevent setbacks • Promotion of a healthy lifestyle as key to better sexual health • Activities: Managing therapeutic progress, and strategies to enhance sexual pleasure and satisfaction

Measures

Primary Outcome Measures

The primary outcomes in this study are the acceptability, usability, and feasibility of Anathema. To assess Anathema's acceptability, participants will self-report on the appropriateness and usefulness of the intervention's content, length, usability, and service delivery model, using a self-developed 5-point Likert scale and the System Usability Scale [51].

Anathema's feasibility-specific measures include recruitment, randomization, retention, and adherence rates (Table 2). Postintervention semistructured interviews will also be conducted to gather further data on Anathema's usefulness, usability, and feasibility, as perceived by participants.

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Table 2. Primary outcome measures.

Outcome	Metrics
Acceptability	• Self-developed 5-point Likert scale assessing the appropriateness and usefulness of the intervention's content, length, usability, and service delivery model • Postintervention semistructured interviews
Usability	• System Usability Scale [51]
Feasibility	Recruitment: • Number of participants screened per week • Number of screening failures • Number of participants enrolled per week • Proportion of recruited participants opting to enroll Randomization: • Proportion of eligible participants who access Anathema following randomization • Proportion of eligible participants who complete at least one module of Anathema Retention: • Proportion of participants who complete T0 (baseline) measures • Condition-specific completion rates following randomization (completion is defined as ≥50% of modules accessed at least once) • Proportion of participants initiating baseline measures who complete T1 (midtest) and T2 (posttest) measures Adherence: • Proportion of participant dropouts from each intervention condition • Proportion of participant withdrawals from the study • Postintervention semistructured interviews

Secondary Outcome Measures

Sexual function, relationship and sexual satisfaction, sexual pleasure, sexual distress, anxiety, depression, and HRQoL are secondary outcome variables in this research. A summary of the secondary outcome measures to be used in this study is presented in Table 3. Participants will not be invited to fill in all the listed measures, since secondary outcome measures will be tailored to participants' gender, sexual orientation, and condition.

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Table 3. Secondary outcome measures.

Measure	Construct	Number of items	Dimensions	Rating scale	Cutoff points	Psychometric properties	Translation/adaptation to the target populations
Sociodemographic and clinical background questionnaires tailored to each target group	N/A[a]	11	N/A	N/A	N/A	N/A	Original version developed in Portuguese (Portugal) by the research team and translated to Dutch and German.
Mini-International Neuropsychiatric Interview (MINI) [52]	Mental disorders	16 modules (branching tree logic items)	Multidimensional	Dichotomous rating scale	N/A	Cohen k=0.7	Translated and adapted to Portuguese (Portugal), Dutch, and German.
Patient Health Questionnaire (PHQ-9) [53]	Depression	9	Unidimensional	4-point Likert scale	Mild depression (<5), moderate depression (6-10), moderately severe depression (11-15), and severe depression (>15)	α=.86	Translated and adapted to Portuguese (Portugal), Dutch, and German.
Generalized Anxiety Disorder Screener (GAD-7) [54]	Anxiety	7	Unidimensional	4-point Likert scale	Normal anxiety (<5), mild anxiety (5-9), moderate anxiety (10-15), and severe anxiety (15-21)	Primary care setting (α=.92); general population (α=.89)	Translated and adapted to Portuguese (Portugal), Dutch, and German.
World Health Organization Quality of Life: Brief Version (WHO-QoL-BREF) [55]	Quality of life	26	Multidimensional	5-point Likert scale	N/A	.66<α<.84	Translated and adapted to Portuguese (Portugal), Dutch, and German.
Global Measure of Sexual Satisfaction (GMSEX) [56]	Sexual satisfaction	5	Unidimensional	7-point Likert scale	N/A	α=.94	To be translated and adapted to Dutch and German in the context of this research.
Global Measure of Relationship Satisfaction (GMREL) [56]	Relationship satisfaction	5	Unidimensional	7-point Likert scale	N/A	α=.95	To be translated and adapted to Dutch and German in the context of this research.
Sexual Pleasure Scale (SPS) [57]	Sexual pleasure	3	Unidimensional	7-point Likert scale	N/A	α=.84	To be translated and adapted to Dutch and German in the context of this research.
International Index of Erectile Function (IIEF) [58]	Sexual function	15	Multidimensional	0-5 or 1-5 numeric rating scale	≤25 expresses risk of sexual dysfunction	α>.70 for all domains	Translated and adapted to Portuguese (Portugal), Dutch, and German.
Female Sexual Function Index (FSFI) [59]	Sexual function	19	Multidimensional	0-5 or 1-5 numeric rating scale	≤26 expresses risk of sexual dysfunction	α>.9 for all domains	Translated and adapted to Portuguese (Portugal), Dutch, and German.
Sexual Distress Scale (SDS-R) [60]	Sexual distress	13	Unidimensional	5-point Likert scale	N/A	α>.85	Translated and adapted to Portuguese (Portugal), Dutch, and German.

[a]N/A: not applicable.

Study Procedures

Compliance With Laws, Regulations, and Ethical Standards

The study will comply with the following laws, regulations, and ethical standards: the International Conference on Harmonisation (ICH) E6 Guideline for Good Clinical Practice (GCP), the Declaration of Helsinki (October 1996), Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation), as well as the following Portuguese Decree-laws: Lei n.º 58/2019 (Assegura a execução, na ordem jurídica nacional, do Regulamento (UE) 2016/679 do Parlamento e do Conselho, de 27 de abril de 2016, relativo à proteção das pessoas singulares no que diz respeito ao tratamento de dados pessoais e à livre circulação desses dados); Lei n.º 21/2014 (Lei da Investigação Clínica), de 16 de Abril; Lei n.º 73/2015, de 27 de julho (Primeira alteração à Lei n.º 21/2014, de 16 de abril, que aprova a lei da investigação clínica, no sentido de fixar as condições em que os monitores, auditores e inspetores podem aceder ao registo dos participantes em estudos clínicos); Regulamento n.º 258/2011 (nos termos do artigo 77.º do Estatuto

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da Ordem dos Psicólogos Portugueses, aprovado pela Lei n.º 57/2008, de 4 de Setembro, a Ordem elabora, mantém e atualiza o Código Deontológico da Ordem dos Psicólogos Portugueses); and Linhas de Orientação para a Prestação de Serviços de Psicologia Mediados por Tecnologias da Informação e da Comunicação (TIC) da Ordem dos Psicólogos Portugueses.

In Austria, clinical psychologists will follow the Ethics Guideline from the Federal Ministry of Labour, Social Affairs, Health, and Consumer Protection. The practice of the profession of clinical psychology and health psychology in Austria is regulated by the Psychologists Act 2013, Federal Law Gazette I No. 182/2013. The Code of Professional Conduct, in the form of an ethics guideline, supplements and concretizes the professional duties laid down in the Psychologists Act 2013 and serves to safeguard and promote the professional ethics of the members of the profession. The professional and ethical principles are based on the Meta Code of Ethics of the European Federation of Psychologists' Associations (EFPA) as follows: (1) respect for the dignity and rights of the person, (2) competence, (3) responsibility, and (4) integrity. The most recent version (as of May 21, 2021) was updated in February 2020.

The study will follow ISO standards TC314 (Ageing committees) and 82304-2 (Health and wellness apps), as noted in the AAL Guidelines for Ethics, Data Privacy, and Security, as they are also relevant.

However, due to the openness that a participatory design approach brings to research projects, fixed regulations and ethics guidelines may not suffice for Anathema. Therefore, an in-action ethics [61] approach, whereby the entire consortium is called to define the project ethos, eliciting values that the project should stand for and that should guide decisions in case the answer to ethical dilemmas falls outside normative ethics principles, is being adopted.

Study Initiation

The pilot feasibility trials will be initiated in February 2023. The study duration will be approximately 12 months. A study initiation visit will be performed to present the research protocol, train the local study teams, and adjust the study procedures to site specificities. A training course targeting the study psychologists will be delivered before the onset of the recruitment period to train them on Anathema's key components, structure, and delivery, as well as on the study procedures. This course will be delivered online by certified psychologists and sex therapists.

Recruitment

Recruitment procedures will follow a multicenter strategy, as different consortium partners have access to different study populations. Unie KBO in the Netherlands, and Instahelp and Sigmund Freud University in Austria will be responsible for recruiting older adults. In Portugal, IPO-Porto and Europacolon will be responsible for recruiting colorectal cancer survivors. Centro de Reabilitação Profissional de Gaia will be responsible for recruiting stroke survivors in Portugal. With the support of local study team members, potential study participants will be identified by reviewing patient files at each site or following advertisements of the studies in institutional newsletters, social networks, or newspapers.

Consent Process

All participants will provide informed consent before any study-specific assessments and procedures are performed. Regardless of the implemented recruitment strategy, a local study team member will perform the first contact to secure the participants' permission to be approached by the researchers. Copies of the study information sheet and informed consent forms will be provided for analysis and discussion. Subjects self-referring to participate (eg, following the study's advertisement) will be directly contacted by the study team to provide any required clarifications before giving their consent. After informed consent is obtained, screening and baseline assessment procedures may occur.

Screening and Baseline Assessments

Screening and baseline assessments will be conducted by certified psychologists or psychology students supervised by the study team. The abovementioned outcome measures will be used for this purpose (Table 3). Participants fulfilling the eligibility criteria for the study will then be further assessed via a diagnostic interview. The Mini-International Neuropsychiatric Interview (MINI) [52] will structure this process. Participants with severe mental disorders will be referred to psychology departments at study sites or community mental health services.

Enrollment and Randomization

Participants fulfilling all eligibility criteria will be registered and randomized. Simple randomization will be performed by an independent statistician, using a computerized program. Older adults in Austria, and colorectal cancer and stroke survivors in Portugal will be submitted to subsequent simple randomization so that they are randomly assigned to one of the study psychologists. Colorectal and stroke survivors will be guided by study psychologists from SexLab, and older adults in Austria will have access to blended support provided by clinical psychologists from Instahelp. Older adults in the Netherlands will not be submitted to this second randomization procedure, given that they will get access to the self-guided version of the program. Participants randomized to Arm A (experimental condition) will receive immediate access to Anathema. Participants assigned to the WLC condition will gain access to the program approximately 8 weeks after randomization and after being submitted to a second baseline assessment to confirm their eligibility for the study.

Study Intervention Delivery and Assessment

After randomization, participants will gain access to Anathema either via the co-developed app (older adults in the Netherlands, and colorectal cancer and stroke survivors in Portugal) or the Instahelp platform (older adults in Austria). At this stage, the 3 abovementioned service models will be tested for acceptability, feasibility, and preliminary efficacy.

The self-guided model will be tested with older adults in the Netherlands. Participants will gain access to the treatment modules every week, being prompted to complete the modules in approximately 1 week. If participants fail to complete the

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modules in the specified time frame, a reminder will be sent. Upon completion, participants will receive access to the following module. The preliminary efficacy of the intervention will be assessed at midtest (T2) and after the completion of the program at posttest (T3), using the measures listed above.

The guided model will be trialed by colorectal cancer and stroke survivors in Portugal. Participants will gain access to the intervention after a preliminary online or telephone appointment is conducted with their assigned study psychologist. This first e-appointment aims to discuss the program's structure, report the baseline findings, and tailor the intervention according to participants' needs and preferences. Once clinical psychologists and participants reach an agreement, the selected modules will be prescribed and made available weekly to the participants. Participants will be prompted to complete the modules in approximately 1 week. Within 24 hours of module completion, the study psychologists, based on the reported outcomes, will assess participants' progress and determine whether it is appropriate or not for the participants to proceed to the next module. If so, participants will receive access to the following module. If not, study psychologists will instruct participants on what needs to be completed to advance to the next module. The preliminary efficacy of the intervention will be assessed at midtest (T2) and after the completion of the program at posttest (T3), using the measures listed above.

The blended model will be assessed by older adults in Austria. Participants will gain access to the intervention after a preliminary 60-minute videoconference appointment is conducted with their assigned study psychologist. This first appointment aims to discuss the program's structure and tailor the intervention according to participants' needs and preferences. Once clinical psychologists and participants reach an agreement, the selected modules will be prescribed and made available every week to the participants. Participants will be prompted to complete the modules weekly. Within 24 hours of module completion, the study psychologists, based on the reported outcomes, will assess participants' progress and determine whether it is appropriate or not for the participants to proceed to the next module. If so, the participants will receive access to the subsequent module. If not, clinical psychologists will instruct participants on what needs to be completed to advance to the next module. Online videoconference appointments will be conducted at the onset of the program (session 1), at week 3/4 (session 2), and at the end of the program (session 3) to blend self-care work and asynchronous support with therapeutic videoconference synchronous support. During the videoconference appointments, study psychologists will assess participants' progress, instruct participants on how to implement treatment strategies, and determine whether it is appropriate or not for participants to proceed with the program. Upon request, sessions are also possible for participants requiring additional support from clinical psychologists. Still, they are limited to 5 extra sessions, at a maximum of 1 per week and for approximately 40 to 50 minutes. If an extra videoconference session is requested, it will replace the scheduled asynchronous session to avoid redundancy. The preliminary efficacy of the intervention will be assessed at midtest (T2) and after the completion of the program at posttest (T3), using the measures listed above (Table 3).

Discontinuation of Participation

Participants may withdraw from the study at any time and for any reason, without any consequences, or be dropped from the study by the research team if a severe aggravation of baseline measures occurs. In this case, the participant will be referred to psychology services at study sites or specialized resources in the community. The main reason for withdrawal will be registered, and a final assessment will be performed whenever the participant agrees with it. Participants who are lost to follow-up may be replaced to ensure a balanced number of participants in each study arm.

Data Handling and Storage

All data to be collected within the scope of Anathema will be completed by participants via the Anathema app and through regular outcome assessments. Questionnaire data will be collected through LimeSurvey [62] and Microsoft Office Forms. These surveys will exclude personal information and IP storage, so that confidentiality and anonymity are ensured. Each participant will be assigned a random user, and this will be used by researchers to identify the participants and their survey responses during the study. Feasibility and trial-related data will be monitored via TrialMonitor [63], a software tool that scaffolds the creation of personalized web dashboards for monitoring participants in technology-enabled field trials. Data will be kept confidential and will be stored in compliance with physical infrastructure and software requirements imposed by the European Union (EU), namely the EU Regulation 2016/679 of The European Parliament and of the Council of April 27, 2016, on the protection of natural persons with regard to the processing of personal data and on the free movement of such data. The questionnaire responses and data from the application will be stored in a secure database that is not accessible from the outside world without proper authorization. The data will be protected by multiple layers of security to ensure that it remains confidential and can only be accessed by authorized personnel. The database will be regularly backed up to ensure that the data are not lost in case of any unforeseen events. Additionally, strict protocols will be in place to track and monitor any access to the data, to ensure that the data are only being used for authorized purposes. All communication related to Anathema will take place within the developed platform, so no confidential information is sent unencrypted and via third-party programs.

Regarding physical infrastructure, data will be stored in servers that are physically located on the premises of Associação Fraunhofer Portugal Research in Porto, Portugal. These servers are situated in a locked server room that is equipped with a key and card-keypad access control system, and is accessible to only authorized personnel. A dedicated division of IT technicians, working at Associação Fraunhofer Portugal Research, is responsible for the maintenance of the hardware equipment (servers and network), ensuring that all equipment is constantly running and is redundant (various hardware backups ensure continuity if one system fails). The software on the servers is updated constantly. Additionally, full backups of the system

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are performed on a daily basis and stored at a different location than the live servers. These backups are encrypted. The server operating system is Linux-based, and the operating system installation is dedicated only to the platform services. Encrypted (https/Transport Layer Security) protocols will be used in all data communication between the servers and the users, as well as in peer-to-peer audio/video chat. The key to produce the code that allows the indirect identification of the participants will be deleted 5 years after the end of the study, as mandated by Deliberação n. 1704/2015 (Deliberação da Comissão Nacional de Proteção de Dados Aplicável aos tratamentos de dados pessoais efectuados no âmbito de Investigação Clínica).

Instahelp uses 3 different security mechanisms to protect data from external access: (1) encryption of data before transmission (end-to-end encryption), (2) secure data transmission (Transport Layer Security), and (3) 2-factor authentication. The widely used and recognized LibSodium cryptography library is used to encrypt the data. Each individual chat message is encrypted with a symmetric space key based on the Salsa20 (64-bit) method. In addition, each message is checked for tampering after transmission using message authentication via Poly 1305MAC. The hosting of the web server (including the implementation on the server side) and the database are provided by the IT service provider 1&1 in Frankfurt (Germany).

Analysis

Descriptive statistics (ie, means, percentages, frequencies, etc) will be used to characterize the study sample and report on acceptability, usability, and feasibility quantitative measures. Acceptability and feasibility assessments will also be based on the qualitative data collected during the postintervention interviews. Qualitative data will be thematically analyzed [64].

To evaluate Anathema's preliminary efficacy, we will first perform independent sample *t* tests and chi-square analysis to assess potential baseline differences between participants randomized to the experimental and control arms. Second, we will calculate the differences between the experimental group and the control condition for secondary outcomes. Data analysis will be performed according to the intention-to-treat principle and resorting to a mixed-models approach [65]. Effect sizes (Cohen *d*) [66] and the 95% CI will be calculated to measure the treatment magnitude for continuous outcomes. Finally, clinical significance will be assessed using the Jacobson & Truax method [67]. All statistical analyses will be conducted in IBM SPSS for Windows (IBM Corp).

Results

The European Commission funds the project Anathema through the AAL Programme (reference: AAL-2020-7-133-CP) from April 2021 to December 2023. Recruitment for the pilot RCTs started on January 2023 in Portugal, Austria, and the Netherlands, and is currently ongoing. As of May 2023, we randomized 49 participants in the trials. We expect to complete the RCTs in September 2023. The results on the acceptability, feasibility, and preliminary efficacy of Anathema are expected in the second semester of 2023.

Considering that the development of Anathema involved a participatory design approach [40] and included primary, secondary, and tertiary end users, we expect it to be highly accepted by older adults, colorectal cancer survivors, stroke survivors, mental health professionals, and sexual health experts. We also expect it to prove feasible to scale up to parent RCTs and to be potentially efficacious in improving the relationship and sexual satisfaction, sexual pleasure, and HRQoL of older adults, colorectal cancer survivors, and stroke survivors compared to TAU in a WLC condition. Study results will be published in open-access venues according to COREQ (Consolidated Criteria for Reporting Qualitative Research) [68] and CONSORT EHEALTH (Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth) [69] guidelines.

Discussion

This study is designed to assess the acceptability, usability, feasibility, and preliminary efficacy of Anathema in decreasing sexual distress and improving sexual function, relationship and sexual satisfaction, sexual pleasure, and HRQoL in older adults, colorectal cancer survivors, and stroke survivors when compared to TAU in a WLC condition. We expect this feasibility study to prove that the adopted methodology is sound, feasible, and coherent with participants' expectations and needs. We also expect Anathema to be potentially efficacious in improving the relationship and sexual satisfaction, sexual pleasure, and HRQoL of older adults, colorectal cancer survivors, and stroke survivors compared to TAU in a WLC condition.

To our knowledge, this is the first study evaluating the acceptability, feasibility, and preliminary efficacy of a smartphone-delivered sexual health promotion program targeting older adults that also caters to the unmet specific sexual health needs of colorectal cancer and stroke survivors, and is an important contribution to this knowledge field. Furthermore, the obtained results will add to the evidence on the acceptability, feasibility, and effectiveness of internet-delivered sex therapy in cancer [25-27] and chronic disease patients [24]. The results will also inform Anathema's refinement and the methodology used in future parent RCTs testing the effectiveness of the sexual health promotion program in the 3 target populations.

If proven acceptable, feasible, and preliminarily effective, Anathema will be made available to participants, and health care and research organizations to be used free of charge in health care and future research. Anathema is expected to be an important self-care tool to be used autonomously and with the support of sexual health experts, contributing to close the sexual health care gap experienced by older adults, colorectal cancer survivors, and stroke survivors.

The strengths of this study include the inclusive, participatory, and multicountry design approach used in Anathema's development. This approach will ensure Anathema is culturally sensitive in the Netherlands, Austria, and Portugal, facilitating the program's acceptance and use in these countries. The fact that the program is inclusive and made available in English also enables the opportunity of conducting future research targeting other populations and countries. Regarding the study design,

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the multicentric feasibility RCT design to be used in the pilot phase is of utmost relevance, as it will provide information on Anathema's feasibility and preliminary efficacy, and increase the chances of the generalizability of the results. The assessment of 3 different service delivery models for Anathema in comparison with TAU is also an advantage, as it will provide data on their relevance and preliminary impact in the target populations, informing the design of future sexual health care services. Finally, the combination of the RCT design with the qualitative insights emerging from the posttest interviews will warrant deeper exploration of Anathema's acceptance and future use, facilitating its future implementation.

The potential limitations include challenges in the recruitment and retention of participants. The limited research conducted to assess the acceptability, feasibility, and efficacy of smartphone-delivered sexual health promotion programs in older adults, colorectal cancer survivors, and stroke survivors makes it difficult to estimate recruitment, retention, and adherence rates for Anathema. To overcome this limitation, a multicountry participatory design approach was used to design Anathema, and diversified recruitment strategies were defined (eg, local recruitment by clinical teams at each site, and advertisements of the studies in institutional newsletters, social networks, or newspapers).

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Data Availability

The data sets generated during and/or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

ACB and CMS conceptualized and designed the study. ALQG, RP, PV, and PN developed the sexual health promotion program and provided important feedback regarding the study design. CMS wrote the manuscript. ACB, ALQG, RP, PV, and PN revised the article for important intellectual content. ACB secured funding for this research. The authors alone are responsible for the views expressed in this article, and they do not necessarily represent the decisions, policy, or views of their affiliated institutions.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review report from the Active and Assisted Living Programme - AGE Platform Europe - European Commission (Brussels, Belgium).
[PDF File (Adobe PDF File), 61 KB - resprot_v12i1e46734_app1.pdf]

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Abbreviations

AAL: Active and Assisted Living
HRQoL: health-related quality of life
IPO-Porto: Instituto Português de Oncologia do Porto Francisco Gentil
RCT: randomized controlled trial
TAU: treatment as usual
WLC: waiting-list control

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Protocol

Ending Tobacco Use Through Interactive Tailored Messaging for Cambodian People With HIV (Project EndIT): Protocol for a Randomized Controlled Trial

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Abstract

Background: The prevalence of smoking remains high in many low- and middle-income countries (LMICs), including the Southeast Asian nation of Cambodia. Smoking is especially hazardous for people with HIV. In Cambodia, approximately 43%-65% of men with HIV and 3%-5% of women with HIV smoke cigarettes. Thus, there is a critical need for cost-effective smoking cessation interventions for Cambodian people with HIV. This paper describes the design, methods, and data analysis plans for a randomized controlled trial assessing the efficacy of a theory-based mobile health smoking cessation intervention in Cambodian people with HIV.

Objective: This 2-group randomized controlled trial compares the efficacy of a mobile health–based automated messaging (AM) intervention versus standard care (SC) in facilitating smoking cessation among Cambodian people with HIV.

Methods: Cambodian people with HIV who currently smoke and are receiving antiretroviral treatment (target, N=800) will be randomized to (1) SC or (2) the AM intervention. SC participants will receive brief advice to quit smoking, written self-help materials, nicotine patches, and will complete weekly app-delivered dietary assessments for 26 weeks. AM participants will receive all SC components (but will complete smoking-related weekly assessments instead of dietary assessments), in addition to a fully automated tailored messaging program driven by the weekly assessments to facilitate smoking cessation. In the Phase-Based Model of smoking cessation, the cessation process is partitioned into 4 phases: motivation, preparation (precessation),

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cessation (quit date to 2 weeks post quit), and maintenance (up to 6 months post quit). Our AM program targets processes within these phases, including increasing motivation to quit, enhancing self-efficacy, obtaining social support, skills to cope with nicotine withdrawal symptoms and stress, and skills to maintain abstinence. All participants will complete baseline and 3-, 6-, and 12-month in-person follow-up assessments. The primary outcome is biochemically confirmed abstinence at 12 months, with 3- and 6-month abstinence as secondary outcomes. Potential mediators and moderators underlying treatment effects will be explored, and cost-effectiveness will be assessed.

Results: This study was approved by all relevant domestic and international institutional and ethical review boards. Participant recruitment commenced in January 2023. Data collection is expected to conclude by the end of 2025.

Conclusions: By demonstrating the greater efficacy and cost-effectiveness of AM relative to SC, this study has the potential to transform HIV care in Cambodia and prevent tobacco-related diseases. Furthermore, it may be adapted for use in other Cambodian populations and in other low- and middle-income countries. Ultimately, the AM approach to smoking cessation could greatly improve public health in the developing world and beyond.

Trial Registration: ClinicalTrials.gov NCT05746442; https://clinicaltrials.gov/ct2/show/NCT05746442

International Registered Report Identifier (IRRID): PRR1-10.2196/48923

(JMIR Res Protoc 2023;12:e48923) doi:10.2196/48923

KEYWORDS

smoking cessation; HIV/AIDS; cost-effectiveness; low- and middle-income countries; Cambodia; Phase-Based Model; RCT; randomized controlled trial; mHealth

Introduction

Tobacco use remains the leading cause of preventable morbidity and mortality worldwide [1]. Although the prevalence of tobacco use has declined in high-income nations in recent decades, the prevalence of smoking remains strikingly high in many low- and middle-income countries (LMICs) [2]. In Cambodia, for example, national surveys have indicated that 33%-43% of adult men and 3% of adult women smoke cigarettes [3,4]. Thus, the development and evaluation of sustainable tobacco cessation interventions suitable for widespread implementation in Cambodia are pressing public health needs.

Certain special populations, such as people with HIV, are confronted with disproportionately high tobacco-related health risks. Data from high-income nations indicate that tobacco use represents a leading cause of mortality among people with HIV [5-10]. Nonetheless, there are few efficacious tobacco cessation interventions for people with HIV. The problem of tobacco use among people with HIV appears to be even more critical in Cambodia: available estimates indicate that 43%-65% of men with HIV and 3%-5% of women with HIV smoke cigarettes [11,12]. Although Cambodia has widespread coverage for antiretroviral treatment (ART), no known efforts have been made to provide tobacco treatment to ART recipients who smoke. Thus, complementing ART with efficacious tobacco cessation treatment offers tremendous potential to improve HIV care and prolong life for people with HIV.

This paper describes the design, methods, and analysis plans for an ongoing intervention trial with pharmacological and behavioral treatment components, including a fully automated, smartphone-delivered intervention. Mobile health (mHealth) interventions are proliferating in the United States, but efforts to use similar approaches in Cambodia are extremely limited. The World Health Organization (WHO) acknowledges that the use of mobile and wireless technologies for health promotion is cost-effective, scalable, and sustainable for the least developed countries [13]. In addition, text messaging interventions for smoking cessation have been shown to be effective [14,15], cost-effective [16], and very affordable for tobacco control globally [17-19].

We previously developed the mHealth-based intervention approach discussed in this paper and completed a pilot study with 50 Cambodian people with HIV who smoked and received care at an ART clinic. The results indicated that the biochemically confirmed, 7-day point prevalence abstinence rates at the 2-month follow-up were 40% in the group receiving the mHealth intervention versus 8% in the standard care (SC) control group (relative risk 5.0, 95% CI 1.2-20.5) [20]. This study will evaluate the long-term efficacy of this intervention with a fully powered sample size.

In this study, we are conducting a 2-group randomized controlled trial (RCT) to fully evaluate our mHealth-based automated messaging (AM) intervention versus an SC approach among Cambodian people with HIV who smoke. Specifically, we will assess the long-term (12 months) efficacy of AM, and we will conduct an economic evaluation to compare its cost-effectiveness to that of SC. We will also explore potential mediators and moderators underlying the associations between AM treatment and smoking abstinence (Multimedia Appendix 1).

Methods

Ethics Approval

Funding for this study was provided by the National Cancer Institute in 2021 (U01 CA261598-01). It was approved by Moffitt Cancer Center's institutional review board (IRB; Advarra), which was selected to serve as the single IRB of record for the research described in this protocol by all participating domestic institutions (#00000971), while the IRB of the Ministry of Health of Cambodia—the Cambodian

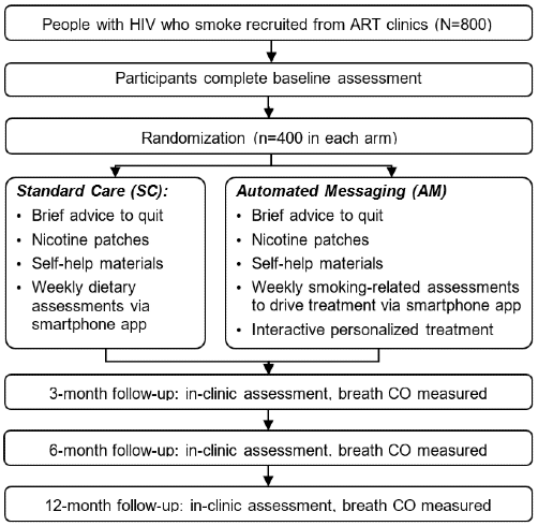
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National Ethics Committee for Health Research—approved the research conducted at sites in Cambodia (NECHR #092).

Study Design

We are using a 2-group RCT to compare the efficacy of 2 smoking cessation interventions: our already-developed smartphone-delivered AM intervention versus SC. Participants are people with HIV recruited through ART clinics in Phnom Penh. Following consent, participants will be randomly assigned to 1 of the 2 study groups: SC (n=400) or AM (n=400). Participants will be asked to complete in-clinic assessments at baseline, and at 3-, 6-, and 12 months following study enrollment (Figure 1). All participants also will complete brief weekly assessments via smartphone. All staff-participant interactions will be conducted to mitigate the potential spread of SARS-CoV-2 and other infections. Should COVID-19–related risks increase in Phnom Penh, we will adapt our procedures by conducting all assessments and follow-ups remotely.

Figure 1. Trial schema. CO: carbon monoxide.



Conceptual Framework for AM

Our AM intervention is based on the Phase-Based Model (PBM), a theoretical framework that is specific to smoking cessation [21]. The PBM partitions the cessation process into 4 phases: motivation, preparation (precessation), cessation (quit date to 2 weeks post quit), and maintenance (up to 6 months post quit); our project focuses on the 3 latter phases. The PBM helps to identify challenges and opportunities that smokers face at each phase, explains underlying phase-specific mechanisms, and facilitates the selection of intervention components and measures. Several putative mechanisms are relevant across phases and have been empirically shown to be reliably associated with long-term abstinence. These include withdrawal or craving, motivation to quit, positive or negative affect, coping with stress and urges, self-efficacy, and perceived support [21-25]. As such, the AM intervention specifically targets these mechanisms.

Participants and Eligibility

There are currently 12 ART clinics or hospitals in Phnom Penh that serve approximately 18,800 registered ART patients [26]. We will begin recruitment at sites that serve larger volumes of patients but may add additional clinic sites as needed to reach our accrual goals. Services provided include ART, ART adherence and risk-reduction counseling, nutrition education, and treatments for comorbidities other than tobacco use. Of the ART patients seen at these clinics or hospitals, >90% are of Khmer ethnicity, 49% of them are men, and 93% of them are aged ≥18 years [12,26,27]. The mean levels of education are seventh grade for men and fourth grade for women [28]. The mean duration of ART is 5.7 years. Registered patients at the clinics have periodic prescheduled appointments (about once per month for ART), further facilitating screening and tracking. Study inclusion criteria are: (1) aged ≥18 years; (2) HIV positive; (3) self-report of current combustible cigarette smoking (smoked ≥100 cigarettes in a lifetime and currently smoke ≥1 cigarette per day); (4) willing to set a quit date within 2 weeks of study enrollment; (5) able to provide written informed consent; and (6) able to read Khmer (score ≥4 points on the Rapid Estimate of Adult Literacy in Medicine—Short Form [29]). Exclusion criteria are (1) history of a medical condition that precludes the use of nicotine replacement therapy (NRT), (2) physician or clinician deemed ineligible to participate based on medical or psychiatric condition, or (3) enrolled in another cessation program or use of other cessation medications.

Baseline Assessment and Randomization

All eligible individuals will be invited to participate. Individuals interested in participating in the study will complete the informed consent process. Enrolled participants will be instructed to complete a tablet-delivered baseline computer-assisted self-interview (CASI), which is managed and delivered by an electronic data capture platform [30-32]. The use of an electronic data capture system that contains programmed logic checks and skip patterns enhances both accurate data collection across sites and timely and secure data transmission. Research staff will help participants complete the assessment if needed. The baseline assessment will take approximately 40 minutes to complete. Enrollees will be randomized to SC or AM via stratified randomization, with sex assigned at birth serving as the stratification variable. All participants will subsequently complete a brief training session

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on smartphone use and the smartphone app. Smartphones will be loaned to participants who need them. These procedures were followed in our pilot and were found to be feasible in the ART setting.

Intervention Conditions

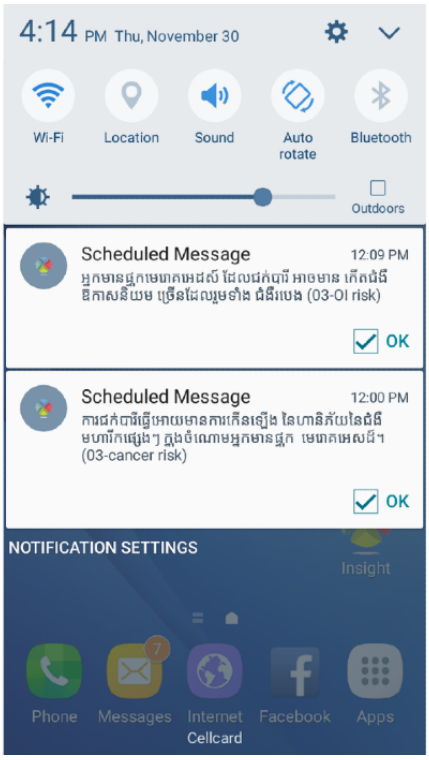
Standard Care

Participants randomized to SC receive brief advice to quit smoking delivered by trained research staff and self-help materials, including 2 fliers and a 32-page booklet. These self-help materials are from Khmer Quit Now, a national smoking cessation campaign in Cambodia, and are based on the WHO's "A guide for tobacco users to quit [33]." Participants also receive an 8-week supply of NRT in the form of nicotine patches, which is consistent with US Food and Drug Administration recommendations and has been found to double cessation rates in meta-analyses [34,35]. SC participants complete brief weekly smartphone assessments (4 items) about their diet for a 26-week period. The dietary assessments are included to approximately equate the 2 conditions on the number and frequency of assessments.

Automated Messaging

Participants in the AM group receive the SC components (with the exception of the dietary assessments) plus proactive personalized messages for smoking cessation. The AM content was adapted from the team's previous efforts and designed to tap the theoretical mechanisms described in the PBM (see Conceptual Framework for AM) [20,36,37]. That is, treatment content is designed to increase motivation, self-efficacy, use of coping skills, and social support and to reduce nicotine withdrawal symptoms and stress. The AM treatment begins immediately after enrollment and continues for a 26-week period. The Insight platform is used to manage and deliver the AM intervention and all weekly assessments [38]. The AM intervention approach allows for several levels of personalization for each participant, as it leverages the adaptive capabilities of the Insight platform. First, at baseline, participants are asked several questions about past quit attempts, preferred coping skills, and the presence or fear of specific health conditions. Messages tailored to these responses are delivered automatically throughout the treatment period. Second, there are different messages for different cessation phases to ensure that the AM intervention targets critical mechanisms of each phase. Phase identification is based on modified PBM definitions; specifically, preparation (enrollment to quit date), cessation (quit date to week 4 post quit date), and maintenance (weeks 4-26 post quit date) [39]. Third, participants are asked to complete brief (4-8 items) smartphone-delivered assessments during each week of the AM treatment course. Some questions vary depending on the phase (eg, current level of intrinsic motivation for preparation or maintenance phases) and other questions are asked in all phases (eg, smoking status in the past week and self-efficacy level). Intervention content (eg, types and frequencies of messages) is based on responses to these weekly assessments and participant phases. Our EndIT-Pilot results demonstrated that the app (Figure 2) worked very well, including being compatible with the 3 largest Cambodian cellular networks, properly delivering messages and weekly assessments, and reliably collecting and transferring data to our encrypted server [20].

Figure 2. Insight app user interface example.



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Measures

Overview

CASI assessments occur in-clinic at baseline and at 3, 6, and 12 months. Participants also complete brief, weekly assessments via smartphone for the first 6 months of the study. Table 1 summarizes study measures at each assessment.

Table 1. Study assessments.

Variable type and measure	Baseline	Weekly[a]	In-clinic follow-up (3, 6, and 12 months)
Descriptors or potential moderators			
Demographics; health literacy [40]	✓		✓[b]
Alcohol and drug use [41,42]	✓		✓
CD4 lymphocyte count, viral load, tuberculosis coinfection, COVID-19–related variables, other health outcomes	✓		✓
Dependence—Heaviness of smoking index [43]	✓		
Self-report measures of antiretroviral therapy adherence [44]	✓		✓
Adherence to treatment app			
Duration of phone on or off; numbers of messages or images or videos delivered, opened, and marked as viewed; numbers of weekly assessments opened and completed; data syncing frequencies	✓[c]	✓[c]	✓[c]
Phase-based model mechanisms			
Wisconsin Smoking Withdrawal Scale (WSWS-2) [45]	✓[a]		✓[b]
Reasons for quitting (intrinsic and extrinsic) [46]	✓		✓
Contemplation Ladder [47,48]	✓	✓	✓
Kessler Psychological Distress Scale (K6) [49]	✓	✓[b]	✓
Positive and negative affect schedule (I-PANAS-SF) [50]	✓	✓[b]	✓
Multidimensional Scale of Perceived Social Support [51]	✓		✓
Self-Efficacy (related to smoking cessation) [52]	✓	✓[b]	✓
Economic evaluation			
Five-level EQ-5D (EQ-5D-5L; for quality-adjusted life years calculations) [53]	✓		✓
Primary outcome			
Smoking status (includes nicotine replacement therapy adherence, number of quit attempts, days smoking or abstinent, and other products) [54]	✓	✓[b]	✓
Expired carbon monoxide [54]	✓		✓

[a]Delivered via smartphone app.

[b]Brief versions of the scales.

[c]Documented by digital date or time stamps in the smartphone app's activity log.

In-Clinic Assessments at Baseline, 3-, 6-, and 12-Month Follow-Ups

Three forms of data are collected at these time points: CASI, expired carbon monoxide (CO) assessed with a CO monitor (CoVita Breath CO) to verify smoking status biochemically, and medical record data. The CASI assessment is administered at baseline (requires approximately 40 minutes to complete) and at each in-clinic follow-up visit (requires approximately 20 minutes to complete). Medical records are used to collect participants' clinical information (with participants' consent), including most recent CD4 counts, viral loads, medication, tuberculosis diagnosis or treatment, and other HIV-related or health conditions. Currently, ART patients at the selected clinics have CD4 lymphocyte count and viral load tests every 3-6 months. However, if participants' medical records do not contain their CD4 lymphocyte count and viral load test results collected within the last 90 days, participants will be asked to provide a blood sample for these tests, following the current testing protocols at the ART clinics. At the final 12-month follow-up, we also will ask AM participants open-ended questions regarding usability, factors or features that helped them quit, barriers to cessation and how to overcome these barriers, and areas for improvement to the AM treatment program. Participants are compensated US $15 (~60,000 Cambodian riels) for each in-clinic visit.

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Brief Weekly Smartphone Assessments

Participants are asked to complete brief weekly assessments via smartphones for 6 months, delivered by the Insight app (University of Oklahoma). Participants in AM receive 4-8 questions as described in the Automated Messaging section. Although completion of these brief treatment-driving assessments could be conceptualized as part of the AM treatment, we will attempt to balance the effects of these weekly contacts between the treatment groups. Therefore, participants in SC are also asked to complete a brief 4-item weekly assessment via the app. However, questions for SC participants are about diet. Participants' responses are encrypted and stored on smartphones and synced to our secure server whenever a connection is active. Thus, our team has near real-time access to responses and we are able to track adherence carefully.

Primary Outcome

The primary outcome is smoking status 12 months post enrollment. Abstinence is defined as biochemically confirmed self-reported 7-day point prevalence abstinence with expired CO <6 ppm [54]. Secondary outcomes include 3- and 6-month biochemically confirmed abstinence. We will consider several other common outcomes, such as self-reported abstinence, length of abstinence, and number of quit attempts.

Data Analysis Plan

Aim 1: Conduct an RCT to Evaluate the Efficacy of AM for Cambodian People With HIV Who Smoke

H1: At the 12-Month Follow-Up, Smoking Abstinence Will Be Higher in the AM (vs SC) Group

The primary outcome is biochemically verified 7-day point prevalence abstinence at the 12-month follow-up. The primary abstinence analysis will be intention-to-treat, with patients who do not complete the follow-up assessments considered to be smokers; however, we will explore other approaches for dealing with missing data (see Missing Data and Dropouts below).

To estimate the effect of AM on abstinence rates while accounting for the potential clustering of participants recruited from multiple clinic sites, we will use generalized linear mixed models (GLMM) analyses in which intervention groups (AM vs SC) will be estimated as a fixed effect, while the clinic will be modeled as a random effect nested within the treatment condition. Specifically, log binomial mixed models will be used to estimate the relative risk of quitting in the AM (vs SC) group. Although groups should be similar in baseline characteristics due to randomization, we will explore models that control for any demographic or clinical variables that differ between groups at baseline. We will also use GLMM to examine changes in abstinence rates over time while accounting for relevant baseline covariates. Similar GLMM or methodology, as appropriate for each outcome variable, will be used to examine other smoking-related variables, such as continuous abstinence, prolonged abstinence, and quit attempts. Statistical analyses will be performed using SAS (version 9.4; SAS Institute, Inc).

Missing Data and Dropouts

Although treating participants lost to follow-up as "not abstinent" has been a widely used analytical strategy in smoking cessation studies, some researchers have pointed to potential problems with this "intent to treat" approach, especially when comparing treatment arms with differential dropout rates [55]. Thus, we will conduct sensitivity analyses to test for treatment differences assuming different missing data mechanisms. For example, we will consider a multiple imputation approach based on smoking-related patient characteristics at baseline as well as demographics to account for potential missing-at-random mechanisms. We also will explore pattern-mixture and selection models to account for potential (and likely) missing-not-at-random mechanisms [56]. Similar findings based on these sensitivity analyses will strengthen our study conclusions.

Aim 2: Conduct an Economic Evaluation to Compare the Cost-Effectiveness of the 2 Smoking Cessation Interventions (AM vs SC)

H2: AM Will Be More Cost-Effective Than SC

Information on costs and cost-effectiveness is especially important for decision makers in LMICs, as these countries are particularly resource constrained. Evidence of cost-effectiveness is critical for our partners in government agencies to implement and ultimately to scale up the AM program at ART clinics throughout Cambodia. To facilitate decision-making of stakeholders in the public sector, the cost-effectiveness analysis (CEA) will be conducted from the perspective of the governmental service providers.

Measures of Costs and Collection of Cost Data

For AM and SC, the costs associated with implementation will come from 4 sources: study personnel, capital costs, production of materials, and distribution of materials. If existing resources are used without charge (eg, office space or computers), we will estimate these costs, given that they would be required for implementation. We will not include the cost of the smartphones because once the efficacy of AM is established, implementation will capitalize on the wide availability of mobile devices in the community and will not involve the distribution of these devices.

Measures of Effectiveness

Two commonly used measures of effectiveness, number of quitters and years of life saved (YOLS) [57], will be used to compare with other CEAs of smoking cessation interventions published in the literature. The number of quitters in each arm will be extracted from the 12-month abstinence assessment. We will extrapolate from abstinence to YOLS using a published algorithm that models YOLS per quitter [58]. We will revise the algorithm using more current estimates of age-specific smoking-attributable deaths from tobacco [59], adjusting for reduction in survival for people with HIV. We also will include quality-adjusted life years, which will be calculated based on the five-level EQ-5D (EQ-5D-5L). The EQ-5D-5L is the latest version of the EQ-5D health–related quality of life questionnaire and has been translated into Khmer [53].

Analysis

We will summarize findings from the CEA in terms of the incremental cost-effectiveness ratio, calculated as the difference in mean costs between the AM and SC treatments divided by

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the difference in mean effectiveness between the 2. The incremental cost-effectiveness ratio estimates additional resources needed to achieve an increase in 1 unit of effectiveness and is compared with a commonly published threshold value, which is 3 times the gross domestic product per capita for LMICs according to WHO recommendations [60]. We will assess both short-term and long-term economic impacts of the interventions. To obtain the 95% CIs, we will apply nonparametric bootstrapping methods to the person-level data [61]. We will conduct 1-way sensitivity analyses to examine the impact of alternative measures of cost and outcomes or key assumptions. We will then apply the Bayesian approach to construct the cost-effectiveness acceptability curve and conduct probabilistic sensitivity analysis [62,63]. We will conduct the Bayesian analysis using WinBUGS (BUGS Project), with costs modeled as a gamma or lognormal distribution and abstinence as a binomial distribution [64].

Aim 3 (Exploratory): Explore Potential Mediators and Moderators Underlying the Associations Between Treatment Group and Abstinence

We will explore potential mediators and moderators underlying the associations between treatment group and abstinence, as informed by the PBM. We will compare the magnitude of the mediated effects of AM treatment on the outcome of abstinence. Potential mediators include NRT adherence, nicotine withdrawal, motivation, self-efficacy, social support, coping with stress, and positive or negative affect. We also will investigate moderators of the relationship between the treatment group and abstinence to determine the types of participants who may benefit most from AM treatment. We will explore biological sex, HIV stage (as measured by CD4 count and viral load), ART adherence, presence and treatments of common comorbidities (eg, tuberculosis), illicit substance use, and nicotine dependence level as possible moderators. Although we anticipate a small proportion of women in our study, we will make every effort to explore the potential moderating effect of biological sex on the association between treatment arm and abstinence.

Results

Participant recruitment commenced in January 2023, with all data expected to be collected by the end of 2025. Frequent data analyses to monitor participant performance will occur during the recruitment and follow-up periods, with final data analysis to occur after data collection concludes.

Discussion

This project capitalizes on a strong, collaborative partnership among researchers at Moffitt Cancer Center, University of Oklahoma Health Sciences Center, The University of Texas MD Anderson Cancer Center, and 3 national governmental agencies that are comprehensively responsible for HIV/AIDS control and care in Cambodia. The investigative team consists of US and Cambodian experts in tobacco, HIV, economic evaluation, mHealth, and health care administration. If our findings indicate that AM is efficacious and cost-effective, our collaboration with influential Cambodian governmental agencies will facilitate wide-scale implementation to HIV clinics across the country. Thus, the project has the potential to transform HIV care delivery throughout the country and to reduce tobacco-induced morbidity and mortality significantly.

Cigarette smoking among people with HIV represents a global public health problem. This issue is even more striking in Cambodia due to a high smoking prevalence in people with HIV and a lack of cessation treatment efforts for this population. Available data (ie, high smartphone ownership rates in Cambodia and high ART coverage) suggest that our approach, which involves recruiting participants from ART clinics and using smartphones to deliver a cessation intervention, represents an ideal and highly feasible way to address this public health problem. Existing data also suggest that Cambodians are receptive to mHealth interventions, and our promising data from the EndIT-Pilot support the feasibility, acceptability, and preliminary efficacy of our approach [20]. This project will provide valuable long-term efficacy data for the AM intervention in a large population of Cambodian people with HIV. Given AM's potential as a feasible, scalable, highly affordable, and cost-effective standalone intervention, the proposed work has the potential to transform HIV care delivery throughout Cambodia. Sustainability and widespread adoption potential are further enhanced by the direct involvement of Cambodian governmental health agencies. In addition, AM could potentially be integrated with other mHealth services for HIV/AIDS care, such as ART adherence and tuberculosis prevention or treatment. AM also has the potential to be broadly adapted for other populations in Cambodia and other LMICs to address the critical need for tobacco treatment. Finally, very little evidence to support the efficacy and cost-effectiveness of smartphone-based tobacco cessation treatment is available in LMICs [65], and it is largely unknown whether effective cessation interventions from high-income countries are transferable and applicable to LMICs. Therefore, our work will help to answer critical questions including what types of tobacco cessation interventions can be effectively introduced to LMICs and whether this type of mHealth intervention is more cost-effective than alternative treatments in settings with low-cost mobile phone services.

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Conflicts of Interest

MSB, DJV, and JIV are inventors of the Insight mHealth Platform, which was used to develop the app. They receive royalties related to its use. However, they did not receive royalties in this case.

Multimedia Appendix 1
Peer review reports from the National Cancer Institute Special Emphasis Panel on Tobacco Use and HIV in Low and Middle Income Countries.
[PDF File (Adobe PDF File), 136 KB - resprot_v12i1e48923_app1.pdf]

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Abbreviations

AM: automated messaging
ART: antiretroviral treatment
CASI: computer-assisted self-interview
CEA: cost-effectiveness analysis
CO: carbon monoxide
GLMM: generalized linear mixed model regression
IRB: institutional review board
LMICs: low- and middle-income countries
mHealth: mobile health
NRT: nicotine replacement therapy
PBM: Phase-Based Model
RCT: randomized controlled trial
SC: standard care
WHO: World Health Organization
YOLS: years of life saved

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Protocol

Evaluating an Innovative HIV Self-Testing Service With Web-Based, Real-Time Counseling Provided by an Artificial Intelligence Chatbot (HIVST-Chatbot) in Increasing HIV Self-Testing Use Among Chinese Men Who Have Sex With Men: Protocol for a Noninferiority Randomized Controlled Trial

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Abstract

Background: Counseling support for HIV self-testing (HIVST) users is essential to ensure support and linkage to care among men who have sex with men (MSM). An HIVST service with web-based real-time instruction, pretest, and posttest counseling provided by trained administrators (HIVST-OIC) was developed by previous projects. Although the HIVST-OIC was highly effective in increasing HIVST uptake and the proportion of HIVST users receiving counseling along with testing, it required intensive resources to implement and sustain. The service capacity of HIVST-OIC cannot meet the increasing demands of HIVST.

Objective: This randomized controlled trial primarily aims to establish whether HIVST-chatbot, an innovative HIVST service with web-based real-time instruction and counseling provided by a fully automated chatbot, would produce effects that are similar to HIVST-OIC in increasing HIVST uptake and the proportion of HIVST users receiving counseling alongside testing among MSM within a 6-month follow-up period.

Methods: A parallel-group, noninferiority randomized controlled trial will be conducted with Chinese-speaking MSM aged ≥18 years with access to live-chat applications. A total of 528 participants will be recruited through multiple sources, including outreach in gay venues, web-based advertisement, and peer referral. After completing the baseline telephone survey, participants will be randomized evenly into the intervention or control groups. Intervention group participants will watch a web-based video promoting HIVST-chatbot and receive a free HIVST kit. The chatbot will contact the participant to implement HIVST and provide standard-of-care, real-time pretest and posttest counseling and instructions on how to use the HIVST kit through WhatsApp. Control group participants will watch a web-based video promoting HIVST-OIC and receive a free HIVST kit in the same manner. Upon appointment, a trained testing administrator will implement HIVST and provide standard-of-care, real-time pretest and posttest counseling and instructions on how to use the HIVST kit through live-chat applications. All participants will complete a telephone follow-up survey 6 months after the baseline. The primary outcomes are HIVST uptake and the proportion of HIVST users receiving counseling support along with testing in the past 6 months, measured at month 6. Secondary outcomes include sexual risk behaviors and uptake of HIV testing other than HIVST during the follow-up period. Intention-to-treat analysis will be used.

Results: Recruitment and enrollment of participants started in April 2023.

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Conclusions: This study will generate important research and policy implications regarding chatbot use in HIVST services. If HIVST-chatbot is proven noninferior to HIVST-OIC, it can be easily integrated into existing HIVST services in Hong Kong, given its relatively low resource requirements for implementation and maintenance. HIVST-chatbot can potentially overcome the barriers to using HIVST. Therefore, the coverage of HIV testing, the level of support, and the linkage to care for MSM HIVST users will be increased.

Trial Registration: ClinicalTrial.gov NCT05796622; https://clinicaltrials.gov/ct2/show/NCT05796622

International Registered Report Identifier (IRRID): PRR1-10.2196/48447

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KEYWORDS

Chatbot; counseling; HIV self-testing; men who have sex with men; non-inferiority randomized controlled trial

Introduction

Background

Globally, the HIV epidemic among men who have sex with men (MSM) remains out of control [1]. High coverage of HIV testing among the at-risk population is the first and crucial step to achieving the 90-90-90 targets set by the joint United Nations Program on HIV/AIDS [2]. Therefore, international health authorities recommend that MSM take up HIV testing every 6 months [3,4]. However, despite the high risk of HIV infection among MSM in the Hong Kong Special Administrative Region of China (HIV prevalence: 6.54% in 2017), their HIV testing rate remained inadequate (65% in the past year) [5].

HIV self-testing (HIVST) could remove the obstacles of HIV testing faced by MSM, such as inconvenience and perceived stigma from service providers [6]. A systematic review and meta-analysis suggested that HIVST could significantly increase the frequency and coverage of HIV testing among MSM [7]. Therefore, the World Health Organization (WHO) strongly recommends that HIVST should be offered as an additional approach to existing HIV testing services [8]. MSM in Hong Kong mainly relied on facility-based HIV testing and counseling provided by community-based organizations (CBO) and governmental clinics [9]. During the COVID-19 pandemic, facility-based HIV testing services provided by CBOs and governmental clinics were suspended or closed in Hong Kong [10]. However, the availability of HIVST kits in Hong Kong was not affected by the pandemic. An increasing demand for HIVST among MSM was observed in Hong Kong [11].

Pretest and posttest counseling is essential for HIVST, facilitating linkage to care, and behavioral change among HIVST users. In standard-of-care HIV testing and counseling, the pretest counseling involves assessing the individual's risks, providing information about HIV testing, asserting the user's right to refuse the test, and informing the user about the possibility of beneficial disclosure of serostatus status, as well as providing preventive information and material [12]. Posttest counseling entails interpreting testing results, offering psychological support to individuals with positive results, facilitating beneficial disclosure of positive serostatus, and referring individuals for further care, treatment, and support services. Additionally, preventive information and material are provided for those with negative test results [12]. Despite the advantages of HIVST, HIVST users may skip pretest or posttest counseling. There are concerns about incorrect procedures, inadequate support for users, and potential issues related to the linkage of care [13]. A meta-analysis study examined that HIVST reduced linkage to care by 47% comparing facility-based HIV testing due to the lack of counseling support [14].

In previous projects, an evidence-based HIVST service was developed for MSM in Hong Kong, which included web-based promotion of HIVST, delivery of free HIVST kits, and provision of web-based, real-time instruction and standard-of-care pretest and posttest counseling through live chat application (HIVST-OIC) [15]. The HIVST-OIC is highly effective in increasing HIVST uptake and the proportion of HIVST users receiving counseling along with testing. A randomized controlled trial showed that after being offered HIVST-OIC, 87.9% of participants took up HIVST, and all HIVST users received counseling. Moreover, the HIVST-OIC was effective in reducing sexual risk behaviors among users. The Centers for Disease Control and Prevention listed HIVST-OIC as an evidence-based intervention and best practice [16]. However, there are issues during the implementation, as HIVST-OIC requires intensive resources. Therefore, it is difficult to increase the service capacity of HIVST-OIC, resulting in a significant gap in implementation.

A chatbot is a computerized program that can automatically select and provide different paths of intervention according to participants' responses. The chatbot can offer personalized, engaging, and on-demand health communication. With the advancement in artificial intelligence, a chatbot can learn from previous human-machine interactions to increase the accuracy and quality of future interactions [17]. A recent systematic review demonstrated the feasibility and effectiveness of chatbot in promoting healthy lifestyles, smoking cessation, treatment adherence, and substance misuse [18]. The chatbot is potentially useful for delivering real-time counseling to support HIVST users. To our knowledge, this approach is novel.

Objectives

This study aims to demonstrate whether an innovative HIVST service with web-based real-time instruction and counseling provided by a fully automated chatbot (HIVST-chatbot) is as efficacious, if not more efficacious, as HIVST-OIC in increasing HIVST uptake and the proportion of HIVST users receiving counseling alongside testing among MSM in Hong Kong.

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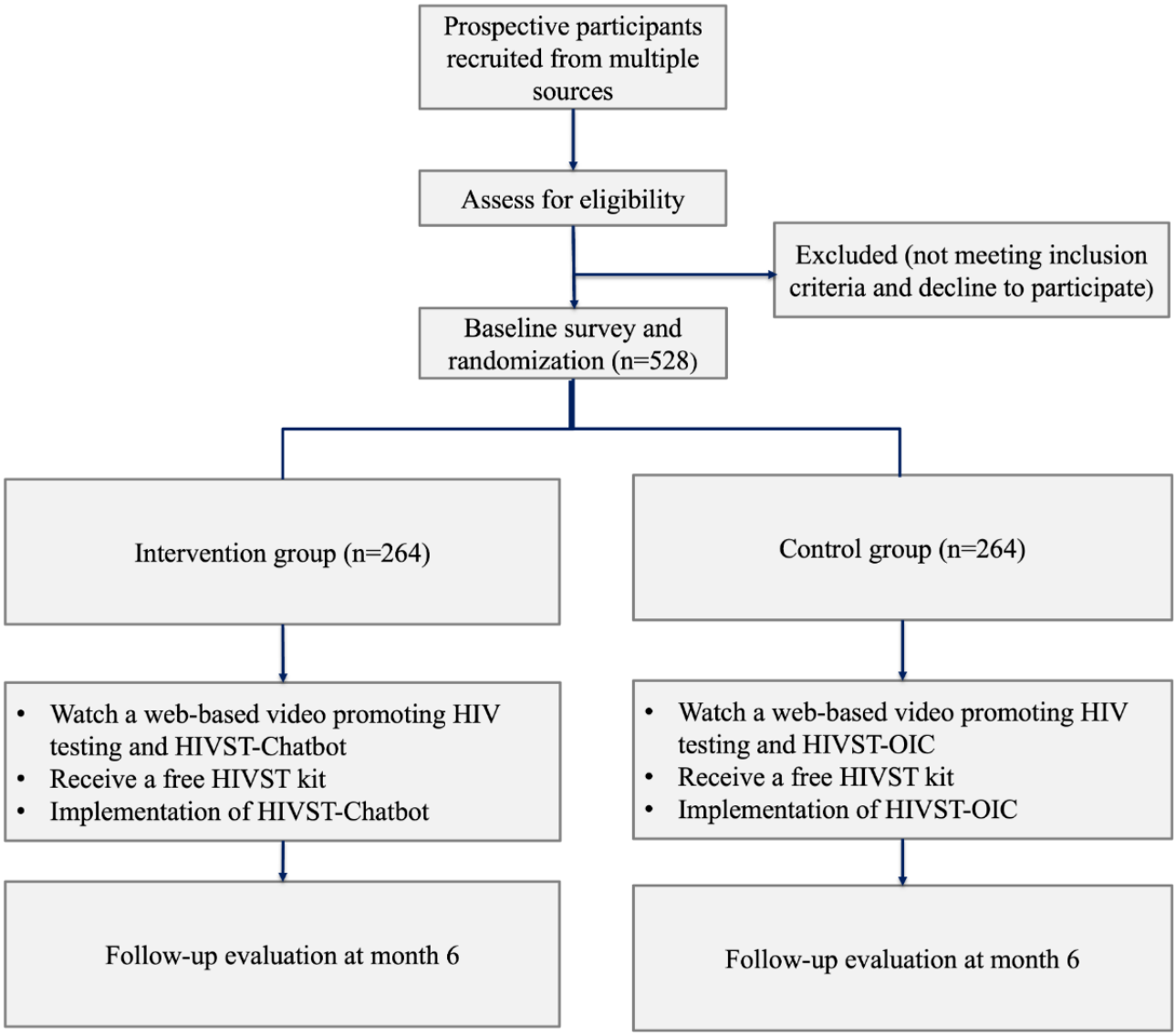
The primary objective is to establish whether HIVST-chatbot would produce effects similar to HIVST-OIC in increasing HIVST uptake and the proportion of HIVST users receiving counseling alongside testing within a 6-month follow-up period. We hypothesize that HIVST-chatbot would be statistically noninferior to HIVST-OIC in increasing HIVST uptake and the proportion of HIVST users receiving counseling alongside testing. The noninferiority margin is set as 10% (HIVST-chatbot is no worse than 10% less than that of the HIVST-OIC). The secondary objectives are to compare HIVST-chatbot with HIVST-OIC on the prevalence of condomless anal intercourse, multiple male sex partnerships, and uptake of HIV testing other than HIVST at month 6.

Methods

Study Design

A parallel-group, noninferiority randomized controlled trial will be conducted. A total of 528 participants are randomized 1:1 to either the intervention group (n=264) or the control group (n=264). We will promote and implement HIVST-chatbot and HIVST-OIC in the intervention group and control group, respectively. A telephone follow-up evaluation will be conducted 6 months after the baseline survey by blinded interviewers. The study was registered at ClinicalTrials.gov (NCT05796622). A flowchart diagram is shown in Figure 1.

Figure 1. Flowchart diagram for the noninferiority randomized controlled trial. HIVST: HIV self-testing; HIVST-OIC: HIV self-testing service with web-based real-time instruction, pretest and posttest counseling provided by trained administrators.



Participants and Recruitments

Inclusion criteria are (1) Hong Kong–based Chinese-speaking men aged at least 18 years; (2) anal intercourse with at least 1 man within the past 6 months; (3) willingness to provide contact information for follow-up at month 6; (4) having access to WhatsApp; and (5) not having the intention to leave Hong Kong for 1 month consecutively in the next 6 months. Those who have been diagnosed as HIV-positive will be excluded.

Participants will be recruited through multiple sources. Upon obtaining the approval of the owners, trained and experienced fieldworkers will approach prospective MSM participants in gay bars and saunas at different time slots during weekdays and weekends. They will brief prospective participants about the

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study details and give them an information sheet. The research team will also conduct web-based outreach by posting study information periodically as discussion topics on gay websites with the highest traffic in Hong Kong. If prospective participants are interested in this study, they can contact the research team through private messaging, WhatsApp, telephone, or email. Recruitment will be supplemented by peer referrals.

Ethics Approval

Participants will be guaranteed anonymity during the study, the right to quit at any time, and that refusal will have no consequences. Verbal instead of written informed consent will be obtained to allow participants to maintain anonymity. Field-workers will sign a form pledging that the participants have been fully informed about the study. Similar methods to obtain informed consent have been commonly used in interventional studies targeting MSM in Hong Kong [15,19-21]. Multiple forms of contact information will be obtained to make an appointment for a baseline telephone survey, which takes about 20 minutes to complete. Another telephone follow-up survey will be conducted 6 months after the completion of the baseline survey. A supermarket coupon (HK $50 [US $6.38]) will be mailed to an address provided by the participants upon completion of each survey. Ethics approval was obtained from the Survey and Behavioral Research Ethics Committee of the Chinese University of Hong Kong (SBRE-22-0488).

Sample Size Planning

The target sample size is 528 (n=264 per group) participants. Our previous study showed that about 90% of MSM used HIVST after exposure to HIVST-OIC promotion and implementation [15]. We conservatively assume that 80% of participants in the control group will take up HIVST during the project period. A noninferiority margin of between-group difference of this primary outcome is set at 10% (no worse than 10% less than that of the control group). A sample size of 198 per group will be sufficient to confer 80% power at the 1-sided significance level of .05 (PASS 11.0). Given the 25% dropout rate during the follow-up period [22], 264 participants per group (528 total) will be needed for the study.

The Baseline Survey and Random Allocation Process

Participants will be randomized evenly to either the intervention or control groups. Computer-generated random allocation codes will be produced and sealed in opaque envelopes by a research staff member without involvement in recruitment or baseline survey. One envelope will be drawn and opened by the fieldworkers. They will then inform the participant which group he is assigned to. Block randomization with a block size of 8 will be used.

The Control Group

Web-Based Promotion of HIVST-OIC

Participants will watch a 7-minute web-based video promoting HIV testing in general and HIVST-OIC developed by previous projects [15,20]. The web-based video is based on the constructs of perceived benefits and perceived barriers of the Health Belief Model [23]. The video has 2 parts. The first part is to promote HIV testing in general. A local MSM introduces the potential benefits of taking up HIV testing in general (eg, help to detect HIV infection earlier, increase trust between sex partners, and reduce psychological burdens) and the WHO recommendation for MSM with risk behaviors to take up HIV testing every 6 months. In the second part, the same MSM narratively discusses the benefits and barriers of HIVST-OIC, demonstrates its procedures, and emphasizes the availability of real-time web-based support.

Signing up for HIVST-OIC

After completing watching the web-based video, participants are asked to select their preferable HIVST kits (oral fluid-based or blood-based), choose a service model (comprehensive version with real-time instruction and pretest and posttest counseling or a simplified version with real-time posttest counseling only), and fill in their contact information and address to receive the HIVST kits. Participants can receive a free HIVST kit through rapid courier service, mail it in a plain envelope, or pick it up at collaborative CBO or the research office. Participants can make an appointment with trained HIV testing administrators to implement HIVST-OIC after receiving the HIVST kit. OraQuick in-home test kit (OraSure Technologies, Inc.; sensitivity: 91.7%; specificity: 99.9%) and BioSure HIV self-test kit (BioSure, Inc.; sensitivity: 99.7%; specificity: 99.9%) will be used in this study.

Implementation of HIVST-OIC

The implementation will follow the same procedures reported in previous studies [15,20]. Through live-chat applications (eg, Line, WhatsApp, and Skype), an experienced HIV testing administrator will guide the participants through self-test procedures on-screen and in real-time. Participants are guaranteed anonymity, and no taping will be made. Users may elect to refrain from displaying their faces on the screen. Standard-of-care pretest and posttest counseling will be provided if the user chooses the comprehensive version. The administrator will also explain how to use the HIVST kits and send the user a demonstration video if needed. The entire procedure of the comprehensive version takes about 60 minutes to complete, which is comparable to the time required for facility-based HIV testing and counseling. If the user prefers a simplified version, pretest counseling will be replaced by web-based pretest information (eg, window period of HIVST and types of sexual behaviors with a high risk of HIV transmission). Users can access the demonstration video and standard-of-care, real-time counseling. The simplified version will take about 20 minutes to complete. Users screened to be positive will be given immediate psychological support and explained about the need to take up free confirmatory HIV antibody testing offered by the Department of Health. If necessary, the collaborative CBO staff member will accompany them to the CBO or Department of Health.

The Intervention Group

Web-Based Promotion of HIVST-Chatbot

Participants in the intervention group will watch a web-based video promoting HIV testing in general and HIVST-chatbot. The first part of the web-based video promoting HIV testing generally is the same as the one for the control group. In the

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second part, the same MSM narratively discusses the advantages of HIVST-chatbot (no need to wait for an appointment, operates 24 hours a day, and artificial intelligence) and the availability of real-time support from chatbot and supporting staff (if users receive positive screening results). The video will also demonstrate the procedures of the HIVST-chatbot. Project staff will help the participants connect to the chatbot. Participants are guaranteed anonymity during the implementation.

Signing up for HIVST-Chatbot

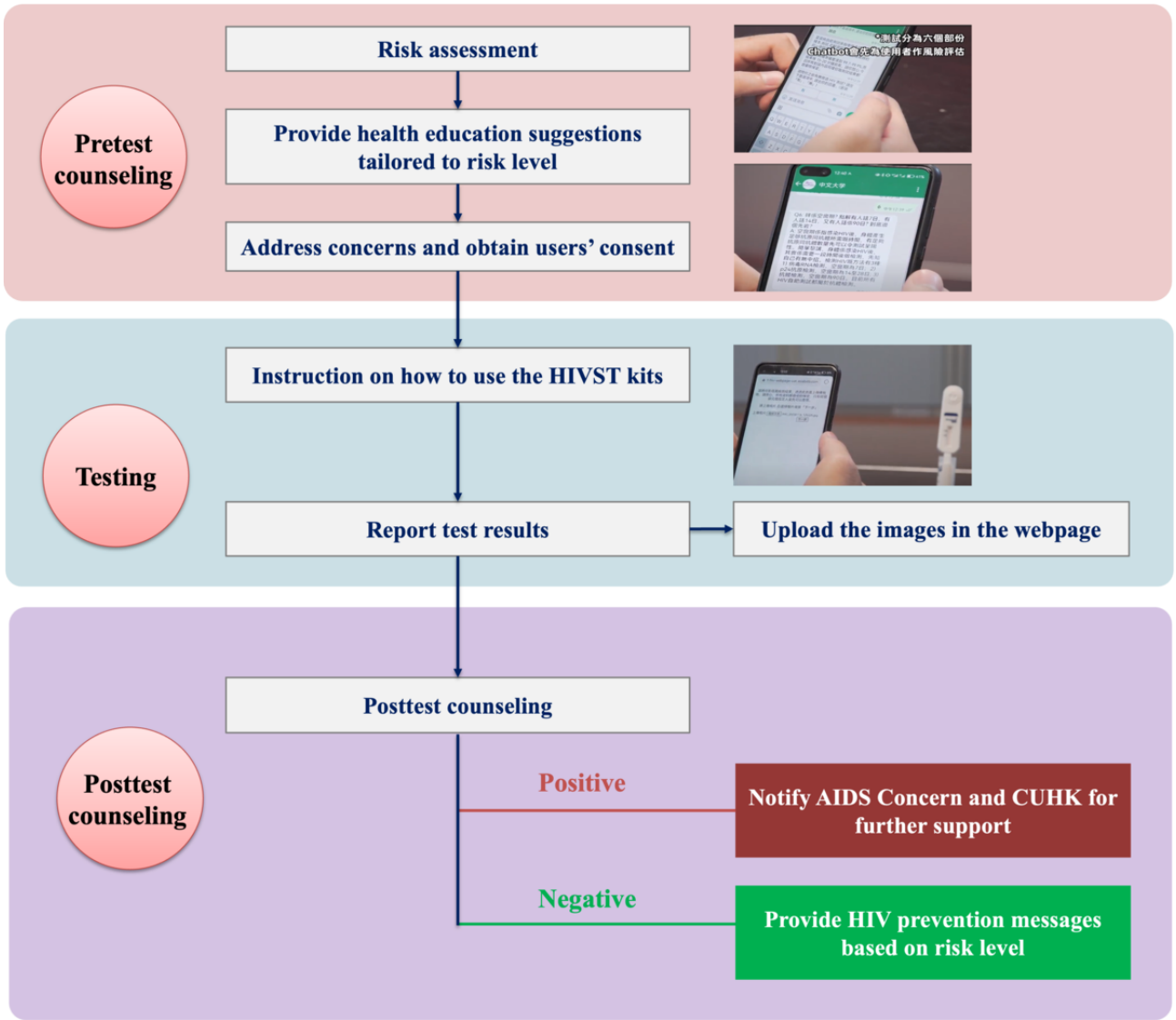
Participants will receive a free HIVST kit in the same manner. The chatbot will contact the participants to confirm receipt of the kits. Participants can get the chatbot to implement HIVST without a previous appointment.

Implementation of HIVST-Chatbot

Pretest Counseling

When users contact the chatbot for implementation, the chatbot will provide standard-of-care pretest and posttest counseling covering key components listed in the Quality Assurance Guideline on HIV Testing and Counseling Services in the format of text messages or videos [24]. The workflow of the HIVST-chatbot is presented in Figure 2.

Figure 2. The workflow of the HIVST-chatbot. CUHK: The Chinese University of Hong Kong; HIVST: HIV self-testing.



1. Risk assessment: The chatbot will ask some standard questions to assess users' HIV risk (eg, injective drug use, use of condoms and alcohol or drug during sexual behaviors, and use of preexposure prophylaxis) and show the response categories. After users complete the questions, the chatbot will interpret their responses and define their risk level. The questions and definition of risk level are identical to those used by facility-based HIV testing and counseling services in Hong Kong (Multimedia Appendix 1).
2. Providing health education advice tailored to risk level: The chatbot will inform users about their risk level and explain the rationale. For high-risk users, the chatbot will prepare them for potential positive results. It will explain the implication of positive screening results and follow-up procedures and emphasize that the staff of collaborative CBO will provide immediate support for users receiving positive testing results from 10 AM to 9 PM (Monday to Friday). These users are advised to perform HIVST within such a time frame. For users without high risk, advice on

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maintaining safe sex practices is provided. Users can skip parts (1) and (2). If they prefer to skip these parts, standard pretest information will be sent to them (eg, window period of HIVST or types of sexual behaviors with a high risk of HIV transmission).

3. Addressing concerns and obtaining consent for HIVST: Users can choose one or more references from a list of common concerns identified by literature review and interviews of local MSM and service providers. In case their problems are not included in the list, the participant can raise them verbally or in written text. The chatbot will interpret users' input, extract keywords, retrieve relevant information from the knowledge graph, and prepare a response in the text to the participants. Ultimately, the chatbot will ask whether users are ready to perform HIVST.

Instruction on How to Use the HIVST Kit

The chatbot will play a prerecorded web-based demonstration video showing the procedures of using an oral fluid-based or blood-based HIVST kit. Users can watch the demonstration video repeatedly. They can also skip it if they are familiar with the procedures.

Reporting Testing Results

The chatbot will show examples of positive, negative, and invalid results to help the users interpret them. Users will report their results by answering a multiple-choice question.

The chatbot will ask the users to take a photo of their testing result and upload it to a secure web page for verification.

Posttest Counseling

For users receiving negative testing results, the chatbot will explain that the user is not infected unless the test was taken within the window period, remind them about the risk of HIV infection, and provide advice for safe sex practices. Ultimately, the chatbot will emphasize the need for regular HIV testing.

For users receiving positive testing results, the chatbot will automatically notify a designated supporting staff from the collaborative CBO after obtaining users' consent. The supporting staff will follow up with the user as soon as possible. The chatbot will explain (1) this is a preliminary positive test result, (2) further confirmatory testing in the Department of Health is required, (3) a staff member from collaborative CBO is already notified and will follow up with them as soon as possible, and (4) emphasize that HIV treatment is very effective. Hotline numbers for 24-hour emotional support and the collaborative CBO will also be provided. Our project staff may accompany them to visit the collaborative CBO or the Department of Health if desired.

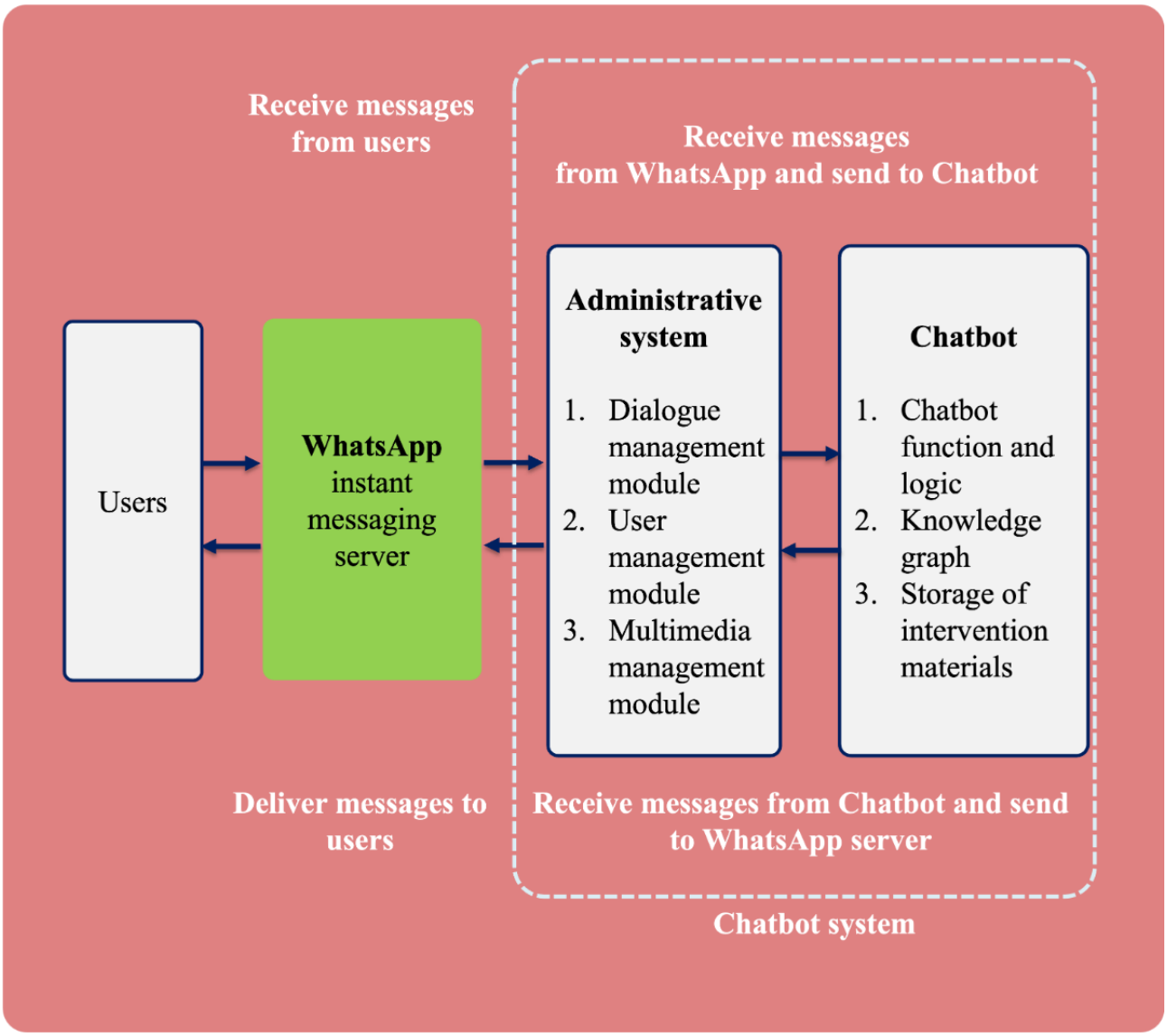
Development of the HIVST-Chatbot

The Architecture of the Chatbot System

We adopted the WhatsApp platform to implement the chatbot. The chatbot is integrated with WhatsApp through its public Web API services. Participants' messages are sent to WhatsApp's instant messaging server and a separately constructed chatbot system (an administrative system and the chatbot). The chatbot system processes and sends a message back to the WhatsApp instant messaging server. Finally, the users can view the message sent by the chatbot. The entire process spans less than a second without a sluggish feel for users. The architecture of the chatbot system is presented in Figure 3.

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Figure 3. Architecture of the chatbot system.



The chatbot system contains 3 modules:

1. Dialogue management module: The dialogue system records all conversations between users and the chatbot. The system can extract context information, such as basic statistics of users' activities and previous interactions between a user and the chatbot. The natural language processing module analyzes the text content of each message. Then, the message is forwarded to trigger specific actions based on preprogrammed rules. For example, when a user sends a message containing a specific keyword, the chatbot immediately responds with information that corresponds to that keyword. In addition, the module initiates new conversations based on the preprogrammed intervention plan.
2. User management module: This module records detailed information about user conversations. Administrators can link users' WhatsApp numbers with the chatbot and review the progress of the intervention delivery (eg, number of completed sessions or disconnection between users and the chatbot).
3. Multimedia management module: The chatbot system supports image uploading, sending, and updating through this module to allow image and video exchange.

Preparation of Knowledge Graph

To build a system that addresses various personal and relevant concerns related to HIV, HIV testing, and HIVST, we created a knowledge graph linking questions and responses. We conducted in-depth interviews with 10 local MSM to crowdsource concerns related to HIV, HIV testing, and HIVST. We also interviewed experienced HIV testing administrators, CBO workers, and experts in HIV prevention to obtain responses addressing these concerns. The knowledge graph will be used to set rules for the chatbot and train it to get familiar with and identify commonly encountered concerns or misinformation and how to address them through machine learning. The knowledge graph will evolve with more previous interactions during the intervention period.

Conversation Mechanism

1. The chatbot uses a mixture of techniques so that a dialogue is not merely rule-based, but it can also learn from a big

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pool of previous conversation patterns through machine learning. The chatbot resolves the recent conversation to create a plan for a suitable response. Relevant information is retrieved and used for the preparation of a reply. A persuasion template is selected in accordance with the current stance of the conversation and the perceived user characteristics by the chatbot. The pool of previous conversation patterns will grow bigger after extended usage, and the variety of responses will increase accordingly.

2. In case there is no relevant response to participants' input, the chatbot will respond by saying, "I am not confident about an answer to your question." The chatbot will suggest a new conversation topic after 3 off-topic inputs from the user.
3. In case the participants want to know more about 1 topic. The chatbot will respond differently within the knowledge graph to the same topic. Upon request, the chatbot can also repeat the response.
4. In case the conversation between the chatbot and the participants is interrupted. The chatbot will cancel participants' incomplete input and invite them to input again.
5. The chatbot will document previous conversations with the users and avoid responding repetitively to users' questions.

Pilot Testing and Refinement

We purposely recruited 30 MSM who were HIV-negative or unknown serostatus to use the HIVST-chatbot. With informed consent, the research team retrieved and reviewed users' interactions with the chatbot. Feedback was also collected from these users. The pilot study showed that the chatbot was running smoothly. Users were satisfied with the performance and interface of the chatbot.

Measurements

Primary Outcomes

The primary outcomes of this study are self-reported uptake of any HIVST at month 6 and the proportion of HIVST users self-reported having received counseling along with HIVST during the follow-up period. The chatbot will accurately document the number of HIVST-chatbot use, while HIV testing administrators will record the number of HIVST-OIC performed.

Secondary Outcomes

The secondary outcomes of this study are as follows:

1. Condomless anal intercourse with men and multiple male sex partnerships in the past 6 months measured at month 6.
2. Uptake of other types of HIV testing in the past 6 months measured at month 6. They are (1) HIV testing at CBOs in Hong Kong, (2) HIV testing at public hospitals or clinics in Hong Kong, (3) HIV testing at private hospitals or clinics in Hong Kong, (4) HIV testing at other organizations in Hong Kong, and (5) HIV testing in places other than Hong Kong.

Baseline Background Characteristics

Information on social demographics (eg, age, current relationship status, education level, and income), sexual orientation, history of HIV testing, COVID-19, and other sexually transmitted infections will be collected. In addition, participants are asked to report the use of preexposure prophylaxis and different HIV or sexually transmitted infection prevention services (receiving free condoms, peer education and pamphlets, and attending workshops).

Process Evaluation

At month 6, participants will be asked about their level of satisfaction with the promotion and implementation of HIVST-chatbot and HIVST-OIC.

Statistical Analysis

Intention-to-treat analysis will be performed. Multiple imputations will handle missing values at month 6. Markov Chain Monte Carlo method will be used to impute data with an arbitrary pattern of missing values, while monotone methods will be used to impute data having a monotone pattern of missing values. Predictors included baseline background characteristics and baseline values of these outcomes. The relative risk reduction, absolute risk reduction, and number needed to treat, and their 95% CIs will be calculated using Excel. The chi-square tests will inspect between-group balances of potential confounders at baseline. Adjustments will be made if any potential confounders show $P<.05$ in the comparisons. SPSS 26.0 for Windows (SPSS Inc) will be used for all analyses; statistical significance is set at the $P<.05$ level (1-sided).

Results

Study recruitment started in April 2023, and data collection is expected to be concluded in January 2024. No results are available as of manuscript preparation.

Discussion

The COVID-19 pandemic and its control measures (eg, lockdown, closure of business, and physical distancing) have direct and negative impacts on HIV testing service use among MSM, especially for facility-based HIV testing services [25-28]. Across countries, health authorities have been actively promoting HIVST to mitigate such negative impacts [29-31]. As a result, there was an increase in HIVST use among MSM [11]. Such growth may continue even in the postpandemic era. Therefore, ensuring sufficient support and linkage to care for the increasing number of MSM, HIVST users becomes more important. Although evidence-based HIVST services existed (eg, HIVST-OIC), most required intensive resources to implement and maintain. Such constraints limited their public health impacts. To our knowledge, this is the first attempt to apply an artificial intelligence chatbot to deliver real-time instruction and counseling support to HIVST users. This randomized controlled trial will compare the efficacy of the HIVST-chatbot with an evidence-based HIVST service, the HIVST-OIC, in increasing HIVST uptake and the proportion of HIVST users receiving counseling along with the testing. If HIVST-chatbot is proven noninferior to HIVST-OIC in improving HIVST uptake and coverage of counseling among users, it may address the existing HIVST service gaps. Since HIVST-chatbot is fully-automated and requires fewer resources

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to implement and maintain, it can be promoted and implemented by governmental organizations and CBOs in Hong Kong as an alternative approach to HIVST-OIC. The HIVST-chatbot has the potential to overcome the barriers to using HIVST (eg, concerns about lack of support and missing linkage to care), improve overall HIV testing coverage, and reduce the HIV burden among MSM.

Although the trial will yield essential insights for HIVST program planning and policy making, it has some limitations. First, the use of HIV testing other than HIVST-chatbot or HIVST-OIC is self-reported. Such responses may be over-reported due to social desirability. Second, similar to most interventional studies [15,19-21], participants will be recruited through convenient sampling. Cautions should be taken when generalizing the findings to MSM in Hong Kong. Third, collecting characteristics of MSM who refuse to participate in the study is difficult. Selection bias may exist.

In conclusion, this study will generate important research and policy implications regarding using chatbot in HIVST services. If HIVST-chatbot is proven noninferior to HIVST-OIC, it can be easily integrated into existing HIVST services in Hong Kong, given its relatively low resource requirement for implementation and maintenance. HIVST-chatbot holds the potential to overcome the barriers to using HIVST. Therefore, the coverage of HIV testing, the level of support, and the linkage to care for MSM HIVST users will be increased.

Acknowledgments

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Authors' Contributions

SC, QZ, CC, AC, PKHM, and ZW initiated the research plan and designed this protocol. SC, FY, YF, and ZW designed the measurements. SC, QZ, JC, FY, AC, and ZW developed the interventions. QZ, AC, PKHM, and ZW acquired the funding for this study. All authors edited the protocol and agreed with the final version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
The questions and definition of risk level are identical to those used by facility-based HIV testing and counseling services in Hong Kong.
[DOCX File , 52 KB - resprot_v12i1e48447_app1.docx]

Multimedia Appendix 2
AIDS Trust Fund approved letter with final peer-reviewed comments.
[PDF File (Adobe PDF File), 636 KB - resprot_v12i1e48447_app2.pdf]

Multimedia Appendix 3
Responses to peer-reviewed comments from AIDS Trust Fund.
[PDF File (Adobe PDF File), 230 KB - resprot_v12i1e48447_app3.pdf]

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Abbreviations

CBO: community-based organization
HIVST: HIV self-testing
HIVST-OIC: HIV self-testing service with web-based real-time instruction, pretest and posttest counseling provided by trained administrators
MSM: men who have sex with men
WHO: World Health Organization

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Protocol

A Trauma-Informed HIV Intervention (LinkPositively) to Improve HIV Care Among Black Women Affected by Interpersonal Violence: Protocol for a Pilot Randomized Controlled Trial

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Abstract

Background: Black women bear a disproportionate burden of HIV, accounting for nearly 60% of new diagnoses among US women. Black women living with HIV often experience mutually reinforcing epidemics, known as syndemics, including interpersonal violence and substance use. Syndemics are associated with decreased HIV care engagement and treatment adherence and worsening HIV outcomes. Few HIV services and resources are tailored to be culturally and gender-responsive and trauma informed for Black women living with HIV. Technology-based, psychoeducational, and peer navigation programs offer promising pathways to tailored HIV support and improved HIV care outcomes. Therefore, the web-based, trauma-informed intervention LinkPositively was developed in collaboration with Black women living with HIV to promote uptake of HIV care and ancillary support services.

Objective: This study primarily determines the feasibility and acceptability of the LinkPositively intervention among Black women living with HIV affected by interpersonal violence. The secondary aim is to examine the preliminary impact of the LinkPositively intervention on retention in HIV care, antiretroviral therapy adherence, and viral suppression while evaluating the role of mechanism of change variables (eg, social support) in the associations.

Methods: The LinkPositively trial is a pilot randomized controlled trial conducted in California, United States, among 80 adult Black women living with HIV who have experienced interpersonal violence. Core components of LinkPositively include one-on-one peer navigation with phone and SMS text message check-ins; 5 weekly one-on-one video sessions to build coping and care navigation skills; and a mobile app that contains a peer support social networking platform, an educational database with healthy living and self-care tips, a GPS-enabled HIV and ancillary care resource locator, and a medication self-monitoring and reminder system. Participants are randomly assigned to the intervention (n=40) or control (Ryan White standard of care; n=40) arm, with follow-up at 3 and 6 months. At each assessment, participants complete an interviewer-administered survey and submit hair samples for the assessment of HIV medication adherence. All research staff and investigators adhere to ethical principles and guidelines for conducting research activities. Data will be analyzed using generalized estimating equations.

Results: Final development and testing of the LinkPositively app were completed in July 2021. As of May 2023, we have screened 97 women for eligibility. Of the 97 women screened, 27 (28%) were eligible and have been enrolled in the study. The dissemination of preliminary results will occur in 2024.

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Conclusions: This trial will advance HIV prevention science by harnessing technology to promote engagement in HIV care while improving social support through peers and social networking—all while being trauma informed for Black women living with HIV with experiences of interpersonal violence. If shown to be feasible and acceptable, LinkPositively has the potential to improve HIV care outcomes among Black women, a marginalized key population.

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KEYWORDS

HIV; peer navigation; social networking; Black women; interpersonal violence; web application; randomized controlled trial; mobile phone

Introduction

Background

The United States has seen a reduction in HIV infections in recent years, yet Black women continue to bear a disproportionate burden of diagnoses [1-3]. In 2019, Black women comprised 13% of the US female population yet accounted for nearly 60% of new HIV diagnoses; by comparison, White women represented 62% of the female population but 22% of HIV diagnoses [4]. HIV incidence among Black women is 11 times that among White women (18.9 vs 1.8) [4]. Women living with HIV, in particular Black women, often experience HIV with mutually reinforcing epidemics known as syndemics. The substance use, violence, and HIV/AIDS syndemic is the overlapping and synergistic intersection of these conditions [5]; in addition, mental health coincides with the substance use, violence, and HIV/AIDS syndemic [6,7]. These mutually reinforcing conditions of violence, substance use, and adverse mental health among people living with HIV [6,7] are more prevalent among women than men [5,8-13]. Among women living with HIV, approximately 55% experience lifetime intimate partner violence (IPV) [14,15], 27% experience past-year IPV [16], and 67% experience lifetime interpersonal violence more broadly [17]. Black women generally face 35% higher lifetime IPV victimization than White women [18]. Women experiencing violence are more likely to experience adverse mental health [10,19], whereas women living with HIV have worse mental health outcomes than men living with HIV and women without HIV. Furthermore, women living with HIV experiencing IPV have worse mental health outcomes than those who do not experience IPV [19]. Black women living with HIV have 3-fold higher rates of prevalence of posttraumatic stress disorder (PTSD) and major depressive disorder compared with Black women without HIV regardless of substance use category [20]. Compared with women without HIV, women living with HIV have reported higher use of cigarettes, nonprescribed cannabis, cocaine, speed, and heroin in North American settings [21], and women living with HIV who have recently experienced violence have higher odds of using substances [22]. Together, these findings show that women living with HIV, especially Black women, are at a substantially increased risk of a variety of mental and physical health problems.

In addition to syndemic factors among women living with HIV, Black women continue to face worse HIV care outcomes than other people living with HIV, including non-Black women; these outcomes are exacerbated by syndemic experiences. Once diagnosed, Black women are significantly less likely than White women to be linked to care within 90 days of diagnosis [23], and once in care, only 56% of Black women are retained [23]. As a result, Black women are significantly less likely to be virally suppressed than White women [24,25]. Violence, substance use, and adverse mental health are associated with low or suboptimal antiretroviral therapy (ART) adherence, reduced viral suppression [10,14,15,17,22,26-29], and low retention in HIV care [30] among women living with HIV. Lifetime experiences of violence in particular are associated with an 8 times lower likelihood of being virally suppressed among women living with HIV compared with women not exposed to violence [31]. In studies that account for syndemic conditions among women living with HIV, more co-occurring conditions (IPV, substance abuse, and adverse mental health) was associated with worse ART adherence [32] and, among racial and ethnic minoritized women, reduced viral suppression [5].

Black women living with HIV lack services that are responsive to their syndemic needs, which likely contributes to suboptimal HIV outcomes. Syndemic experiences and the lack of trauma-informed care services may act as barriers to HIV care, complicating both the receipt of services logistically and the acceptability of services. People living with HIV with adverse mental health (PTSD and depression) have lower odds of retention in HIV care [30]. Furthermore, Black women living with HIV face sociostructural barriers to care (HIV stigma, medical mistrust, and unmet housing and transportation needs) at higher rates than HIV-negative and male HIV-positive individuals [33-35], affecting retention in care and ART adherence; racial and ethnic minoritized women are the most affected [34,36-42]. HIV stigma is the most noted barrier to care and ART adherence among women living with HIV [37,43-47]. Conversely, formal and informal social support networks may mitigate the effects of syndemic and sociostructural barriers on HIV care outcomes. Increased social support is associated with fewer depressive symptoms; less HIV stigma [48-50]; and improved HIV-related health symptoms [51], ART adherence [41,52-54], perceived ability to engage in HIV care [42], and HIV self-management [55].

Trauma-informed services offer a pathway to more acceptable care for syndemic-affected women living with HIV, particularly in the setting of peer navigation. Trauma-informed care is a strength-based approach that aims to meet the unique needs of trauma survivors. Trauma-informed care increases the

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acceptability and comfort of services while minimizing barriers to care. Although trauma-informed care has been studied and practiced in the context of addiction treatment, mental health, and health care, it has been less extensively practiced in terms of HIV prevention and treatment [56-61]. Peer navigators—medication-adherent role models with shared lived experiences with their clients—provide social support and modeling of engagement-supportive behaviors to their clients [62]. Peer navigators help build self-efficacy in patient-provider communication and decrease medical mistrust, offsetting the impact of syndemic factors affecting HIV care (eg, violence, substance use, and adverse mental health) [62]. Peer navigation for improving linkage to and retention in care among women living with HIV is feasible, acceptable, and efficacious in the United States and other countries [63-68]. Peer navigation can improve ART adherence [69,70] and viral suppression [63,71], although some studies have found no effect [72], perhaps because of the small samples or the lack of informal social support. The addition of informal social support may help reduce social isolation, build community, and share strategies for addressing barriers to ART adherence. Among women living with HIV, social support group participation with HIV-positive peers has demonstrated benefits related to mental health, relationships, and sociostructural barriers [73-76].

With increased internet access and smartphone ownership, technology-based interventions have become an increasingly feasible option for improving health [77] and demonstrate significant potential for trauma-informed interventions using peer navigation. Technology-based interventions related to HIV are primarily mobile app– or SMS text messaging–based and have been developed for women living with HIV who are outside the United States [78-81], older in the United States [82], and pregnant [83-85]; people living with HIV regardless of gender [86]; transgender women living with HIV [87,88]; and HIV prevention [89,90]. The results include decreased viral load and improved engagement in care and ART adherence [91-93]. Women report that technology-based interventions feel more confidential, lead to more efficient and perceived-safer care, and feel more empowering to women with a history of interpersonal violence than nontechnology interventions [94-98]. Overall, technology-based interventions among women living with HIV in the United States have been limited and, to our knowledge, nonexistent for Black women living with HIV or women who have experienced interpersonal violence, although most US women (91%) use the internet, including 78% of Black women [99]. Few of those that do exist have not considered the syndemic conditions and unique barriers faced by women living with HIV [100,101] despite interest in, advantages, and acceptability of technology-based interventions, particularly for increasing social support [102-105].

Given the unique needs and significant disparities faced by Black women living with HIV in the United States and the lack of services and interventions that are syndemically responsive and culturally tailored to Black women, we undertook the development of a trauma-informed HIV intervention for Black women living with HIV that uses a culturally and gender-tailored mobile app, LinkPositively, combined with one-on-one peer navigation.

Theoretical Foundations

LinkPositively is grounded in the theory of triadic influences and syndemic theory and informed by trauma-informed care as a derivative of trauma theory. The theory of triadic influence is a multilevel social cognitive theory that understands 3 streams of influence—individual, social, and structural—that act in combination to affect health behaviors [106]. This study considers individual-level influences, such as racial or ethnic minority identity and experiences of interpersonal violence, and indirect sociostructural influences, such as medical mistrust, HIV-related stigma, and limited access to resources. In consonance, LinkPositively was created under the framework of syndemic theory, which understands HIV as co-occurring and mutually exacerbating with other comorbidities in disadvantaged populations [107]. These synergistic conditions are influenced by the social, economic, environmental, and political settings in which a population exists [107]. Within the population of interest (Black women living with HIV who have experienced interpersonal violence), these other syndemic conditions or experiences include violence, mental health disorders, and substance use, which, in combination, negatively and synergistically affect HIV care outcomes. Finally, trauma-informed care is a service delivery model that aims to be responsive to the impacts of trauma by emphasizing physical, psychological, and emotional safety; empowerment; and healing for survivors of trauma and their care providers [108]. According to trauma theory, unprocessed trauma is stored as physiological reactions to circumstances that recall the initial trauma [109]; health care interactions in particular may elicit trauma responses [110]. Evidence from mental health, substance use, and social service settings finds that adopting trauma-informed care practices improves patient outcomes and enhances patient satisfaction and engagement with clinic staff [111]. Simultaneously, there have been calls to integrate trauma-informed care practices within HIV care settings [112,113].

Objectives

The primary aim of this study is to determine the feasibility and acceptability of the LinkPositively intervention and mobile app among Black women living with HIV affected by interpersonal violence. The secondary aim is to examine the preliminary impact of the LinkPositively intervention on retention in HIV care, ART adherence, and viral suppression while evaluating the role of mechanism of change variables (ie, social support, activation of social support networks, self-efficacy, and the use of ancillary support services) in the associations. Collectively, both aims serve as preparation for a large-scale R01 randomized controlled trial.

Methods

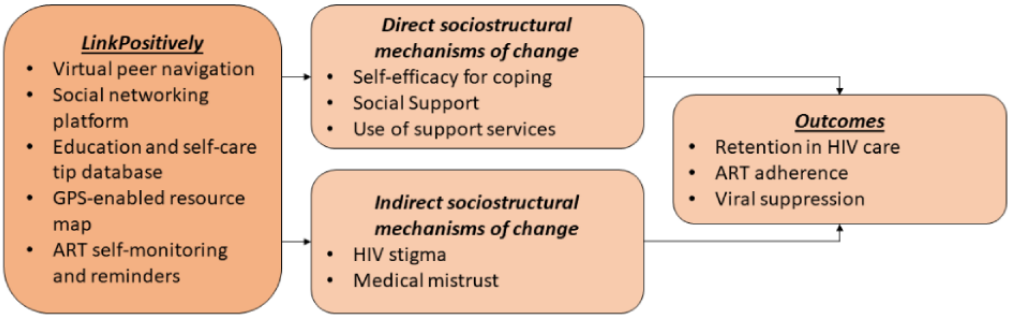
Study Design

The LinkPositively trial is a pilot randomized controlled trial of 80 Black women living with HIV who have experienced lifetime interpersonal violence, with 6 months of follow-up after enrollment. Women are randomized to the LinkPositively intervention (intervention arm; n=40) or Ryan White standard of care (control arm; n=40) groups. Survey and biological

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assessments occur at baseline and 3 and 6 months after randomization to evaluate improvement in primary and secondary outcomes. Feasibility and acceptability measures are assessed using a combination of self-reported surveys, intervention paradata, and study process measures (eg, retention rates). The primary outcomes are retention in HIV care, ART adherence, and viral suppression. Secondary outcomes are hypothesized direct and indirect mechanisms of change, including self-efficacy for coping, social support, the use of ancillary support services, HIV stigma, and medical mistrust (Figure 1).

Figure 1. LinkPositively conceptual model. ART: antiretroviral therapy.



Study Population

The inclusion criteria for LinkPositively are self-reported (1) self-identification as a woman; (2) Black or African American racial and ethnic background; (3) age of ≥18 years; (4) HIV-positive status; (5) current residence in the San Diego, Los Angeles, or Alameda counties in California, United States; (6) linked to HIV care but having fallen out of care; (7) lifetime experience of physical (ie, hitting, slapping, kicking, assault with a weapon, or threats thereof), sexual (ie, attempted, forced, or threatened sexual activities, including unwanted touching), or psychological (ie, yelling or insulting, controlling behavior, and fear of violence) abuse by a current or former partner or nonpartner (eg, relative, friend, or stranger); (8) ownership of a smartphone with internet-browsing capabilities; and (9) ability to speak English. Being out of care is defined as not having had a blood test while taking HIV medication for at least 3 months or within the past year, not having had a medical appointment with an HIV care provider, not having had an ART prescription filled, or not having had blood tests to monitor HIV (CD4 counts and HIV viral load). The exclusion criteria are (1) unwillingness to participate in the study and (2) cognitive impairment that would limit participation in study procedures. The study staff assess cognitive impairment through direct observation. Specifically, if during the consent process a participant appears to be experiencing paranoia or auditory hallucinations, has sporadic outbursts, or is not capable of comprehending the interview or materials, the participant is excluded from the trial.

Study Procedures

Recruitment and Screening

The recruitment methods for LinkPositively include 3 main approaches. First, we partnered with the San Diego Center for AIDS Research Health Equity Sociobehavioral Science Core to distribute flyers to community-based agencies. We also used the recruitment and retention subcommittee of the San Diego Center for AIDS Research Health Equity Sociobehavioral Science Core Community Advisory Board to promote and advertise the study. We partnered with local health care clinics and HIV service organizations within the community to passively recruit through flyer distribution. Los Angeles–based recruitment used the Los Angeles County Service Planning Area provider meetings; Commission on HIV caucus and work group meetings; and local community advisory board meetings, support groups, and education forums. Alameda County–based recruitment used the Collaborative Community Planning Council of the Oakland Transitional Grant Area and local HIV service agencies to disseminate study flyers. Second, we used social media platforms to maximize outreach and recruitment in the 3 California counties. Social media platforms included Facebook, Instagram, and Twitter. Paid advertisements, promotions, and web banner advertisements will be used to target populations based on demographic characteristics, including gender, age, race, ethnicity, and location of residence. Finally, we distributed advertisements, newspaper advertisements, and flyers at bus stops, libraries, transitional housing facilities, social service agencies, and businesses located in San Diego, Los Angeles, and Alameda County communities with at least 10% Black residents. Recruitment and screening for the study are ongoing to facilitate the development of a study cohort consisting of approximately 80 eligible women.

Enrollment and Randomization

Women interested in participating in LinkPositively provide consent to be screened and complete a screening survey that includes questions regarding age, gender, self-reported HIV status, HIV care status, and violence exposure history. The screening survey is self-administered or staff-administered depending on the preference of the potential participant and will be housed in REDCap (Research Electronic Data Capture; Vanderbilt University). Eligible participants are invited to enroll in LinkPositively and scheduled for an in-person or on the web (via Zoom [Zoom Video Communications]) baseline enrollment visit. At the baseline study visit, the participant provides documented informed consent and completes a 45-minute interviewer-administered, computer-assisted personal interview hosted on REDCap on topics including sociodemographic characteristics, HIV care, treatment history, substance use, mental health status, interpersonal violence, care interactions, medical mistrust, coping self-efficacy, social support, stigma, COVID-19, and technology use (Table 1). Participants also provide a hair sample in person or via mail to assess for

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tenofovir and emtricitabine concentrations as an objective measure of ART adherence. The hair sample collection kits include 1 piece of aluminum foil, 2 white adhesive labels, 2 alcohol swabs, 1 small freshness packet, and scissors. Hair sample collection involves the following steps: (1) cleaning the blades of a pair of scissors with an alcohol pad, (2) lifting up the top layer of hair from the occipital region of the scalp to isolate a small thatch of hair (approximately 100 fibers of hair) from underneath the top layer, (3) cutting the small hair sample as close to the scalp as possible, (4) keeping fingers on the part of the hair that was furthest away from the scalp and placing the hair sample down on an unfolded piece of tin foil, (5) placing a thin label over the end of the hair sample that was furthest away from the scalp, (6) refolding the foil over to completely enclose the hair and placing a study identification number label on the folded piece of foil, and (7) placing the folded piece of foil inside the plastic bag and sealing the bag. All hair samples are securely shipped to the University of California, San Francisco Hair Analytical Laboratory, where liquid chromatography or tandem mass spectrometry will be used to assess antiretroviral concentrations in hair samples over the past 3 months, requiring 3 cm of hair. Participants are compensated with US $25 upon the completion of the survey and US $25 upon the provision of the hair sample.

Following the completion of the baseline survey, participants are randomized at a 1:1 ratio into the LinkPositively intervention group or the control group, stratified by perpetrator of violent experience (intimate partner vs nonintimate partner). Randomization is conducted using a randomly permuted block randomization design by a study staff member with no participant contact. Participants are informed of their group assignment, and participants assigned to the LinkPositively intervention arm are shown how to download the LinkPositively app and given a demonstration of LinkPositively features. Follow-up assessments occur at the 3- and 6-month follow-up visits, requiring a survey and hair sample collection (Figure 2).

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Table 1. Exposure and outcome measures.

Measure category	Measures
Evaluation outcomes	
Feasibility	Number of participants recruited, number of participants enrolled, number of participants retained, and number of intervention group sessions completed
Acceptability	CSQ-8[a] and System Usability Scale [114]
Individual-level factors (survey)	
Sociodemographic characteristics	Age, education, employment, living situation, income, relationship status, household composition, medical insurance status, and food insecurity (6 items) [115]
HIV care and treatment history	Year first diagnosed with HIV, year they first started medical care for HIV, usual place for HIV treatment (yes or no), frequency of seeing an HIV care provider, period of intermittent care (yes or no), taking antiretroviral medication (yes or no), HIV medication adherence [116] (3 items), and barriers to HIV treatment since diagnosis [117] (14 items)
Interpersonal violence	Intimate partner violence (12 items), revised Conflict Tactics Scale (ever and since last visit) [118]; non–intimate partner violence (physical, sexual, or psychological abuse by a relative, friend, or stranger [ever and since last visit]); ACEs[b] (10 items); mental health coercion (3 items); substance use coercion (3 items); and DA-5[c] (5 items)
Co-occurring syndemic conditions (survey)	
Mental health	Depression (10 items), PHQ-9[d] [119]; PTSD[e] (9 items), NSESS[f]-PTSD [120]; anxiety (7 items), GAD-7[g] [121]; stressful life experiences (20 items), PCL-5[h] [122], and traumatic life events (17 items), LEC-5[i] [123]; resilience (10 items), PLHIV[j] Resilience Scale [124]; and suicidality (4 items), SBQ-R[k] [125]
Substance use	Alcohol use (10 items), AUDIT-10[l] [126], and drug use, NIDA[m]-modified ASSIST[n] 2.0 [127]
Direct sociostructural mechanisms of change measures (survey)	
Coping self-efficacy	Self-Efficacy Scale (CSE[o], 26 items) [128]
Social support	MMOS-SS[p] (20 items) [129]
Ancillary support use	Use and met need of ancillary support services (eg, transportation, housing, mental health care, domestic violence services, and substance use treatment)
Indirect sociostructural mechanisms of change measures (survey)	
HIV stigma	Chronic Illness Anticipated Stigma Scale (30 items) [130]
Medical mistrust	GBMMS[q] (12 items) [131]
COVID-19–specific PTSD	5 items, adapted PC-PTSD-5[r] [132]
Outcome measures	
Retention in HIV care	Having ≥2 laboratory tests (CD4[s] or VL[t]) dated at least 90 days apart [133]
ART[u] adherence	Self-reported 3-item measure, dichotomized (>90% adherent vs <90% adherent) [116]
ART adherence (objective measure)	Tenofovir and emtricitabine concentrations in hair sample [134]
Viral suppression	Undetectable or <200 copies of viral DNA per mL vs detectable or ≥200 copies of viral DNA per mL [135]

[a]CSQ-8: Client Satisfaction Questionnaire–8 item.

[b]ACE: adverse childhood experience.

[c]DA-5: Danger Assessment Short Form.

[d]PHQ-9: Patient Health Questionnaire–9 item.

[e]PTSD: posttraumatic stress disorder.

[f]NSESS: National Stressful Events Survey PTSD Short Scale.

[g]GAD-7: Generalized Anxiety Disorder–7.

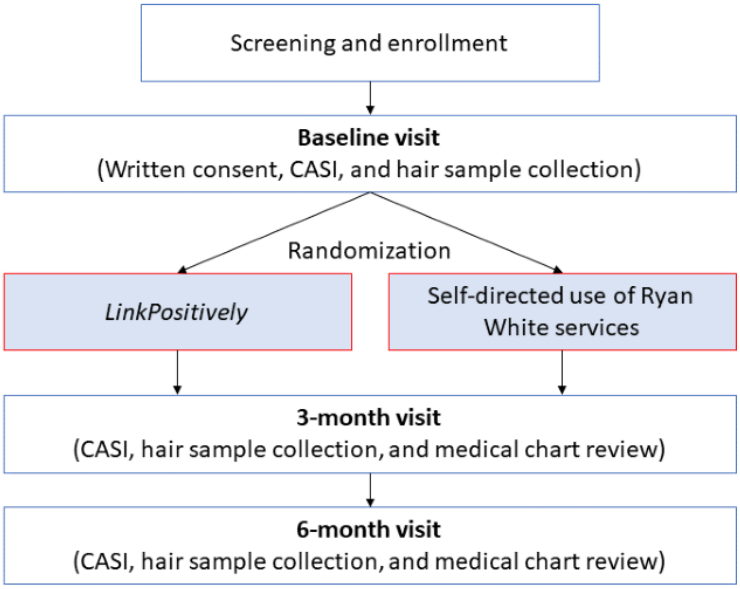
[h]PCL-5: Posttraumatic Stress Disorder Checklist- 5 Item.

[i]LEC-5: Lifetime Events Checklist DSM 5.

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[j]PLHIV: people living with HIV.
[k]SBQ-R: Suicidal Behaviors Questionnaire-Revised.
[l]AUDIT-10: Alcohol Use Disorders Identification Test-10 Items.
[m]NIDA: National Institute on Drug Abuse.
[n]ASSIST: Alcohol, Smoking and Substance Involvement Screening Test.
[o]CSE: Coping Self-Efficacy Scale.
[p]MMOS-SS: Modified Outcomes Study Social Support Survey.
[q]GBMMS: Group-Based Medical Mistrust Scale.
[r]PC-PTSD-5: Primary Care PTSD Screen for DSM-5 (PC-PTSD-5).
[s]CD4: cluster of differentiation 4.
[t]VL: Viral Load.
[u]ART: antiretroviral therapy.

Figure 2. Study flow. CASI: Computer Assisted Self-Interview.



Intervention Group

LinkPositively is a trauma-informed peer navigation intervention using a mobile-optimized web application that aims to improve retention in HIV care and ART adherence and promote reaching or maintaining viral suppression among Black women living with HIV who have experienced interpersonal violence. The development of the LinkPositively app with Black women living with HIV has been previously described [136]. In brief, the app comprises a social networking platform to facilitate connections among Black women living with HIV and information sharing, with the option to do so anonymously; an educational and self-care tip database; a self-monitoring and reminder system to promote ART adherence and other health behaviors; and a GPS-enabled resource locator for local and national HIV and ancillary care services (Table 2). Women assigned to the LinkPositively intervention group have access to all components of the LinkPositively app and one-on-one peer navigation. At the baseline visit, the women are introduced to the LinkPositively app. The study staff conduct onboarding, which involves training participants on how to download the app onto their smartphone, explaining the 5 components, and using each component, with an emphasis on contacting their assigned peer navigator. Within the first week of participants being assigned to this group, peer navigators schedule and complete a one-on-one video intake session with the participant. During this one-on-one intake session, the peer navigator conducts a thorough participant needs assessment to connect the participant to HIV medical care via local health clinics and identify other areas of need, services of need, and assisted referrals. These areas include but are not limited to domestic violence services, mental health care, substance abuse treatment, and housing and legal support. Peer navigators provide trauma-informed, intensive emotional and informational support, including guidance on accessing information (eg, agency name, address, website, and contact information) about referred services. Participants attend five 60-minute web-based one-on-one peer navigation sessions over a 5-week period, covering a variety of topics: building coping skills for syndemic conditions, activating social support networks, and addressing medical mistrust (Table 3). In addition, participants text or call their peer navigators during and after the 5-week period if they have questions or seek to debrief after sessions or appointments. In the back end of the web application, peer navigators enter case notes on peer navigation sessions and check-ins, set notifications and appointment reminders, and send their assigned participants direct messages that show up only on that participant's profile. Peer navigators can also view the women's responses in real time and data on medication and appointment outcomes to inform their upcoming session or check-in. In addition to

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videoconference or phone sessions and check-ins, participants receive automated daily medication reminder SMS text messages, scheduled appointment alerts, and access to daily postings in the education and self-care tip component of the app.

Table 2. LinkPositively app components, features, and mechanisms of change.

App element	Features	Hypothesized mechanism of change influenced
Profile page	• Option to customize avatar from a variety of preloaded options or upload photo[a] • Option to share information in the "about me" section • Option to customize profile page background using preloaded optionsa	N/A[b]
Social networking	• Ability to post text, images, or videos to a "timeline"[a] • Ability to react to content using emoticons • Ability to comment on others' postsa	• Social support • HIV stigma
Education and self-care tips	• Rotating tip featured daily on the timeline • Searchable database of tips categorized using tags • Integrated external resources	• Coping self-efficacy • Ancillary support use • HIV stigma • Medical mistrust
ART[c] self-monitoring and reminders	• Pre-established monitoring of ART adherence and mood • Ability to create customized reminders • Option to receive reminders at the time of their choosing • Option to receive reminders via in-app notifications or SMS text message • Ability to view responses to tracked activity in a past-month calendar depiction	• Coping self-efficacy
Resource locator	• Searchable database of services related to HIV and non-HIV medical and social support services • Up-to-date information on location, hours, and contact information • Information on insurance acceptance when available	• Coping self-efficacy • Ancillary support use • Medical mistrust

[a]Indicates features that may require *unlocking* through continued app use.

[b]N/A: not applicable.

[c]ART: antiretroviral therapy.

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Table 3. LinkPositively intervention content delivered via one-on-one peer navigation sessions.

Session number	Topic	Objectives
1	Emotional awareness	• Understanding how trauma and other co-occurring conditions (eg, substance use) affect emotions • Learn ways in which social environments influence how we experience emotions (social influences on our emotional experience exercise) • Introduce and practice labeling feeling states • Introduce and practice focused breathing
2	Emotional regulation and distress tolerance	• Introduce the benefits of emotion regulation (common unhealthy coping skills exercise and handout) • Learn the 3 ways in which we experience emotion (the 3 areas of emotion exercise or handout) • Explain why we tolerate unpleasant emotions and how to know whether to tolerate the unpleasant emotions or not • Learn how to assess the pros and cons of distress tolerance (pros and cons list) • Introduce different methods for healthy coping (with distress) with 3 ways in which we experience emotions (positive self-statements, pleasurable activities, and formal time-out)
3	Relationship patterns and activating social support networks	• Introduce interpersonal or relationship patterns (exercise—what are interpersonal patterns? The self-fulfilling prophecy) • Identify feelings and interpersonal or relationship patterns (how to identify your interpersonal patterns exercise and common interpersonal patterns exercise) • Learn what assertive communication and behavior are (exercise in defining assertive, nonassertive, and aggressive communication and behavior) • Understand how assertive behavior works in healthy relationships (healthy boundaries) • Learn how to make requests and ask for help clearly and in an assertive manner • Understand when and how to say “no” • Introduce basic personal rights (exercise and handout)
4	Interpersonal violence and the impact on existing sociostructural barriers	• Identify ways in which power and control dynamics, disclosure of violence, and interpersonal violence influence HIV stigma and medical mistrust • Explain the 3 types of power balances in relationships (exercise and handout) • Identify personal relationship patterns • Explore flexibility in relationships • Understand the role compassion and respect play in how we view ourselves and others
5	Medical mistrust and review	• Understand the relationship between discrimination and medical mistrust • Review conspiracy theories and HIV treatment • Learn skills for effective patient-provider communication • Review material covered in all 5 sessions

Control Group

Women assigned to the control arm are connected with and receive self-directed (not peer navigation–supported) treatment as usual at agencies and institutions in the San Diego, Los Angeles, or Alameda counties following the Ryan White HIV/AIDS Program standard of care (ie, referrals to physical, dental, and mental health care services; medical case management; and ancillary services [eg, alcohol/substance use recovery and family support]). Women who are not already receiving services and do not have other means of receiving services or are not under medical case management elsewhere are referred to care. Alternatively, women may request case management services via the Ryan White HIV/AIDS Program elsewhere in the counties.

Using the Ryan White standard of care, goals are set to create an individual care plan related to medical care, housing, financial, and other resources as needed. Referrals are made to appropriate services (eg, primary care, housing, benefits counseling, transportation, food, legal services, and support services) based on an intake interview. Women who require a higher level of care (eg, significant mental health concern, at risk, or falling out of care) and do not have other means of receiving services or are not under medical case management elsewhere may request case management services via the Ryan White HIV/AIDS Program.

Participants requiring medical case management have a case file that provides appropriate participant follow-up and tracking information. Case managers have in-person contact with all participants at least every 90 days to assess the further need for services. Either the participant or the case manager initiates a given contact. The case manager has in-person or phone contact with participants at least every 30 days to discuss changes and progress toward meeting the goals of the individual care plan and an in-person meeting with each participant at least once every 90 days. Participants are reassessed at least once every 120 days. It is important to note that the medical case management approach is self-guided versus intense peer

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navigation assistance, meaning that participants learn the responsibility to move toward autonomy in their HIV care.

Follow-Up

Participants enrolled in LinkPositively have 2 follow-up visits at 3 and 6 months after their baseline visit. Although follow-up visits occur virtually through Zoom, participants still follow the same activities from their baseline visit. Activities include a 45-minute computer-assisted follow-up survey and a self-collected hair sample. Participants are compensated with US $25 upon the completion of the survey and US $25 upon the provision of the hair sample.

Safety Protocols

Given that LinkPositively's focus is on women who have experienced interpersonal violence, we took additional measures to ensure the safety of participants in the study. This included the creation of a safety protocol, wherein all participants are screened for current IPV and risk of homicide by a current partner using the Danger Assessment [137] and are provided with violence-related resources, which are integrated both within the LinkPositively app and on the LinkPositively website. Furthermore, participants are asked about safety information when the study staff contacts them, such as the use of a different name or only contacting the participant through certain means or at certain times, and hair sample collection is conducted at a safe location of the participant's choosing. For participants who indicate current experiences of violence, the study team offers a warm handoff to violence services and follows up with the participant to ensure their safety. Finally, safety elements are integrated into the LinkPositively app itself, including an automatic log-out feature when the app is swiped away from and an ambiguous app icon and home screen that disclose no information about the purpose of the app and do not reference HIV. Study staff also monitor the social networking feed on the app to identify posts that suggest potential harm to the self or others. These posts are flagged, and a study staff member follows up with the participant, activating the safety protocol and reporting this as an adverse event to the University of California, San Diego (UCSD) Human Research Protection Program (HRPP). To date, no adverse events have been reported to the UCSD HRPP.

Ethics Approval, Informed Consent, and Data Privacy

All study procedures were reviewed and approved by the UCSD HRPP (UCSD HRPP project 191398), and a reliance agreement was executed for San Diego State University and Charles R. Drew University of Medicine and Science to rely upon the UCSD HRPP determination. Before engaging with research participants, all study staff members completed training in the ethical conduct of human participant research, data management and compliance, and the Health Insurance Portability and Accountability Act (HIPAA). All women enrolled in LinkPositively provide written informed consent and are asked to sign a HIPAA authorization form. This study was issued a certificate of confidentiality by the National Institutes of Health.

Data Management and Quality Assurance

In compliance with National Institute of Mental Health policies, LinkPositively operates under a data and safety monitoring plan, which details methods for secure data collection, management, and monitoring. Under the data and safety monitoring plan, all digital data collected are stored on a password-protected encrypted server, whereas physical copies of data are retained in a locked filing cabinet in a locked office within a restricted-access research building. Identifying information is stored separately from the study data, with study records associated via a participant identification number. Data for linkage between participant identification number and identifying information are stored in a HIPAA-compliant secure web application designed for participant management and tracking (Ripple Science). Study staff members are only provided with data access commensurate with their study role and specifically the lowest level of access needed. Access to study data is not granted until after the completion of full ethical training. Deidentified quantitative data are downloaded on a weekly basis by the study data manager. Hair samples are associated with participant identification numbers and stored in a locked cabinet within a locked office until they are batch shipped for analysis at the University of California, San Francisco. Following completion of the analyses, the results are transmitted deidentified via secure email to UCSD.

The study staff actively monitor adverse events and serious adverse events, which are reported immediately to the principal investigator and within 24 hours to the UCSD HRPP. Finally, study activities are monitored by a Data and Safety Monitoring Board (DSMB). The DSMB convenes twice annually, at which time the study team provides updates on study activities and the DSMB provides recommendations for participant safety and data security. The DSMB comprises (1) a professor of social work and licensed social worker with substantial experience in the development and implementation of interventions for gender-based violence and HIV, (2) a professor of disease prevention and health promotion and board-certified registered nurse with substantial research experience in health information use among people living with and at risk of HIV, and (3) a biostatistician with substantial experience in randomized controlled trials in public health research.

Analysis

Aim 1

The first aim is to determine the feasibility and acceptability of LinkPositively. We will assess the feasibility of the intervention by computing the percentage of participants retained at each follow-up visit and chi-square tests or Fisher exact tests to compare the intervention and control groups. Retention cutoff percentages will be used to determine the level of feasibility as follows: (1) ≥90%=strong feasibility, (2) 80% to 89%=acceptable feasibility, (3) 70% to 79%=modest feasibility with a need for improvement, and (4) <70%=unacceptable. We will assess the acceptability of the intervention by computing the percentage of participants endorsing a particular level of satisfaction on a Likert scale from questions on the Client Satisfaction Questionnaire–8 [138] and System Usability Scale [139]. We will obtain these percentages at the 3- and 6-month follow-up assessments. Responses from women in the intervention and control groups will be compared using 2-tailed *t* tests (for continuous acceptability measures) and chi-square

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tests (for dichotomous acceptability measures). We will also compute similar percentages based on responses from the peer navigators at the 6-month follow-up time point.

Aim 2

The second aim is to examine the preliminary impact of LinkPositively. Self-reported dichotomous outcomes of retention in HIV care, ART adherence, and viral suppression will be evaluated. Outcomes will be past–3-month measures assessed at each time point (3- and 6-month follow-ups). The primary independent variable will be intervention group. Chi-square tests will be used to test for significant differences in self-reported outcomes by intervention group. We will use generalized estimating equations to generate 3 independent repeated-measure logistic regressions to model retention in care, self-reported ART adherence, and viral suppression. We will also examine an objective biological outcome measure of ART adherence based on tenofovir and emtricitabine hair concentrations. We will use univariable random-intercept linear regression models to model tenofovir and emtricitabine hair concentrations, with the final model based on a generalized estimating equation repeated-measure linear regression model with a time variable (3 and 6 months). Aligned with the theory of triadic influence and syndemic theory, we will assess the impact of individual- (eg, sociodemographics, HIV treatment history, and social support), syndemic- (eg, PTSD and substance use), social- (eg, medical mistrust and HIV-related stigma), and structural-level (eg, unstable housing and insurance coverage for HIV services) factors on dependent variables. During model building, we will consider variables associated with outcome variables (univariate: $P<.10$; bivariate: $P<.10$). For the final models, adjusting for type-I error, the significance level will be set at $P<.05$.

Secondary analyses will be conducted among the 40 women randomized to the intervention group. We will estimate the association between the individual features of the LinkPositively app and retention in care, ART adherence, and viral suppression. Individual features of the LinkPositively app will include (1) the frequency of participant initiation of peer navigation through texting or calling the peer navigator, (2) number of messages sent and viewed to or by peers using the social networking platform, (3) frequency of viewing educational and self-care tips, (4) number of times the GPS-enabled resource locator was accessed, and (5) number of points earned through gamification features. Individual features of the LinkPositively app will be independent variables, and retention in care and ART adherence measures will be dependent variables. The regression models will follow those outlined for the primary analyses.

Results

LinkPositively was approved by the institutional review board in October 2019 and funded in December 2019. The LinkPositively app was designed and developed between February 2020 and January 2021. Beta testing and refinement of the app were completed in July 2021. Recruitment began in February 2022, with the goal of enrolling 3 participants per month. As of April 2023, we have screened 97 women for eligibility and enrolled 27 (28%) eligible participants. We anticipate the dissemination of preliminary results in early 2024.

Discussion

Anticipated Main Findings

LinkPositively is the first intervention that combines a tailored mobile app and peer navigation to address HIV care outcomes among Black women living with HIV who have a lifetime history of interpersonal violence. The anticipated main finding of this intervention study is that LinkPositively will be feasible and acceptable for Black women living with HIV. It is also anticipated that Black women living with HIV randomized to the LinkPositively arm will demonstrate improvements in retention in HIV care, ART adherence, and viral suppression compared with Black women living with HIV randomized to the control arm.

The use of a virtual intervention overcomes a number of structural- (eg, stigma) and individual-level (eg, access to transportation) barriers to intervention engagement. This is particularly important as our study population—Black women living with HIV—experience structural barriers (eg, medical mistrust and discrimination) to engagement with HIV health services [140,141]. In addition, social support provided by both the peer navigators and other study participants target interpersonal-level facilitators, reinforcing resilience and connectedness, which have been shown to be associated with improved HIV care outcomes. In addition, the peer navigators help disseminate and change behavioral norms that are conducive to achieving viral suppression. The integration of peer navigation, an evidence-based practice, may support further improvements in Black women's overall health and well-being outcomes beyond the HIV care continuum.

Future Research

If shown to be feasible and acceptable, LinkPositively has the potential to serve as an alternative for this marginalized, key population. We will test it further in a larger efficacy trial among a broader sample of Black women living with HIV. Although LinkPositively may not be accessible to all Black women living with HIV who experience interpersonal violence as some may not have access to a smartphone, it represents a critical avenue for intervention to improve HIV care among a large and growing group of women and has the potential for scale-up.

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Data Availability

Data sharing is not applicable to this paper as no data sets were generated or analyzed during this study.

Authors' Contributions

All the authors contributed to this paper. JKS was responsible for the conceptualization of the research, development of the methodology, investigation, provision of resources, writing of the original draft and review and editing, supervision, and funding acquisition. KMA was responsible for investigation, writing of the original draft and review and editing, visualization, project administration, and supervision. AFD was responsible for investigation, review and editing, and project administration. DMC was responsible for investigation, review and editing, supervision, and project administration. KT was responsible for development of the methodology, investigation, provision of resources, review and editing, and funding acquisition. KJH was responsible for the conceptualization of the research, development of the methodology, investigation, provision of resources, review and editing, and funding acquisition.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Grant peer review report.
[PDF File (Adobe PDF File), 179 KB - resprot_v12i1e46325_app1.pdf]

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Abbreviations

ART: antiretroviral therapy
DSMB: Data and Safety Monitoring Board
HIPAA: Health Insurance Portability and Accountability Act
HRPP: Human Research Protection Program
IPV: intimate partner violence
PTSD: posttraumatic stress disorder
REDCap: Research Electronic Data Capture
UCSD: University of California, San Diego

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Protocol

Feasibility of a Home-Based Cognitive-Physical Exercise Program in Patients With Chronic Obstructive Pulmonary Disease: Protocol for a Feasibility and Pilot Randomized Controlled Trial

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Abstract

Background: Chronic obstructive pulmonary disease (COPD) is a progressive condition associated with physical and cognitive impairments contributing to difficulty in performing activities of daily living (ADLs) that require dual tasking (eg, walking and talking). Despite evidence showing that cognitive decline occurs among patients with COPD and may contribute to functional limitations and decreased health-related quality of life (HRQL), pulmonary rehabilitation continues to focus mainly on physical training (ie, aerobic and strength exercises). An integrated cognitive and physical training program compared to physical training alone may be more effective in increasing dual-tasking ability among people living with COPD, leading to greater improvements in performance of ADLs and HRQL.

Objective: The aims of this study are to evaluate the feasibility of an 8-week randomized controlled trial of home-based, cognitive-physical training versus physical training for patients with moderate to severe COPD and derive preliminary estimates of cognitive-physical training intervention efficacy on measures of physical and cognitive function, dual task performance, ADLs, and HRQL.

Methods: A total of 24 participants with moderate to severe COPD will be recruited and randomized into cognitive-physical training or physical training. All participants will be prescribed an individualized home physical exercise program comprising 5 days of moderate-intensity aerobic exercise (30-50 minutes/session) and 2 days of whole-body strength training per week. The cognitive-physical training group will also perform cognitive training for approximately 60 minutes, 5 days per week via the BrainHQ platform (Posit Science Corporation). Participants will meet once weekly with an exercise professional (via

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videoconference) who will provide support by reviewing the progression of their training and addressing any queries. Feasibility will be assessed through the recruitment rate, program adherence, satisfaction, attrition, and safety. The intervention efficacy regarding dual task performance, physical function, ADLs, and HRQL will be evaluated at baseline and at 4 and 8 weeks. Descriptive statistics will be used to summarize intervention feasibility. Paired 2-tailed *t* tests and 2-tailed *t* tests will be used to compare the changes in the outcome measures over the 8-week study period within and between the 2 randomized groups, respectively.

Results: Enrollment started in January 2022. It is estimated that the enrollment period will be 24 months long, with data collection to be completed by December 2023.

Conclusions: A supervised home-based cognitive-physical training program may be an accessible intervention to improve dual-tasking ability in people living with COPD. Evaluating the feasibility and effect estimates is a critical first step to inform future clinical trials evaluating this approach and its effects on physical and cognitive function, ADL performance, and HRQL.

Trial Registration: ClinicalTrials.gov NCT05140226; https://clinicaltrials.gov/ct2/show/NCT05140226

International Registered Report Identifier (IRRID): DERR1-10.2196/48666

(JMIR Res Protoc 2023;12:e48666) doi:10.2196/48666

KEYWORDS

pulmonary disease; chronic obstructive; telerehabilitation; physical exercise; cognitive training; randomized controlled trial; pilot study

Introduction

Background

Chronic obstructive pulmonary disease (COPD) is a progressive respiratory condition characterized by chronic bronchitis and emphysema [1]. It is the third-leading cause of death worldwide [2] and is responsible for high levels of health care use because of frequent respiratory exacerbations [3]. Individuals with COPD experience significant airflow obstruction and dynamic hyperinflation of the lungs, leading to symptoms of dyspnea, sputum production, chronic cough, and fatigue [1]. Skeletal muscle dysfunction, comprising decreased muscular strength and endurance, is also a common consequence of COPD and is driven by a combination of several mechanisms, including muscle atrophy, altered fiber type, and impaired metabolism [4]. Collectively, these changes contribute to diminished exercise capacity, limitations in activities of daily living (ADLs), and reduced health-related quality of life (HRQL) among individuals with COPD [5].

Cognitive Impairment in COPD

A growing body of research has demonstrated the presence of limitations across several domains of cognition among individuals with COPD [6]. Decreases in attention, memory, and visual-motor processing have been commonly reported [6-8]. The underlying mechanisms of cognitive impairment among individuals with COPD are complex and have been attributed in part to neural tissue hypoxemia and systemic inflammation [9,10].

Recent studies have indicated that COPD is associated with impaired dual-tasking performance [11,12]. Dual tasking, the performance of 2 tasks simultaneously, is an important aspect of executive function and is often required for the performance of routine daily activities, such as walking and talking. The performance of a cognitive task (eg, spelling words backward) while carrying out a physical task (ie, usual-paced walking) can result in decrements in cognitive or physical performance (eg, walking speed or distance) owing to competing attentional demands. Dual task decrements (difference between dual and single task performance) are often more pronounced in those with existing cognitive impairments or neurological conditions compared with those without these disorders [13,14]. Indeed, increased dual task decrements for both motor [12,15] and cognitive [16] performance have been found among people with COPD compared with healthy individuals [17]. There is emerging evidence indicating that cognitive-motor dual task performance impairment among patients with COPD is related to alterations in markers of prefrontal cortex neural activity and inefficiency, which may impede the executive function needed to *plan one's day* [11,12,17]. Thus, combined cognitive-physical training may be a good strategy to improve neural efficiency in patients with COPD who may have a range of executive functional capacities. Cognitive training targeting attention, memory, executive functioning, and speed of processing when combined with physical exercise training may provide the neuroplasticity to derive synergistic benefits on the performance of ADLs and physical function [18-20].

Traditional Pulmonary Rehabilitation

Pulmonary rehabilitation is considered a primary management approach for moderate to severe COPD and has been shown to reduce dyspnea and increase exercise capacity, leading to improvements in daily function and HRQL among individuals with COPD [21]. To date, pulmonary rehabilitation strategies have typically focused on education (eg, medication management, breathing techniques, and stress reduction) and physical training (ie, aerobic and strength exercises) [21,22]. Currently, cognitive training is not included in most pulmonary rehabilitation programs despite evidence that cognitive impairments are common among individuals with COPD and are associated with greater functional limitations, decreased HRQL, and increased health care use in this population [8,23].

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Home-Based Pulmonary Rehabilitation

Several barriers limit engagement in pulmonary rehabilitation for people with COPD, including factors related to the environment (eg, travel and wait times), knowledge (eg, referral processes), and beliefs (eg, perceived benefits) [24]. Recently, accessibility has been further complicated by the COVID-19 pandemic. For these reasons, there is increasing interest in home-based pulmonary rehabilitation programs as an alternative strategy for COPD management compared with center-based pulmonary rehabilitation programs [25-27]. Several studies have demonstrated the safety and feasibility of remote telerehabilitation interventions for patients with COPD, with high levels of compliance with home training and no adverse events [28-30]. There is meta-analytic evidence from systematic reviews also indicating that the effects of home-based pulmonary rehabilitation interventions are similar to those of traditional outpatient programs for outcomes including dyspnea [26,27], exercise capacity [26,31], and HRQL [26,31], potentially offering increased accessibility to those with travel restrictions [32]. However, most studies on telerehabilitation for COPD have required study assessments to be conducted in person, and none have included remote assessment of functional testing, cognitive assessments, or dual task performance, a knowledge gap that this study hopes to address [27].

Study Purpose

The specific aims of this study are to evaluate the feasibility (ie, recruitment rate, program adherence, attrition, safety, and participant satisfaction) of an 8-week individualized, home-based cognitive-physical training program for patients with moderate to severe COPD and derive preliminary estimates of cognitive-physical training intervention efficacy on measures of cognitive and physical function, dual task performance, ADL, and HRQL. We hypothesize that it will be feasible to safely recruit patients with COPD into a home-based cognitive-physical training program with 75% adherence and high satisfaction ratings with the prescribed training. We also hypothesize that the cognitive-physical training group will demonstrate greater beneficial effects on cognitive function, dual task performance, ADL, and HRQL compared with the physical training group.

Methods

Design

This is a pilot randomized controlled trial (RCT) to assess the feasibility of a full-scale, adequately powered RCT evaluating a home-based combined cognitive-physical training program for patients with moderate to severe COPD. The study takes place at the University Health Network (UHN) in Toronto, Ontario, Canada, but has been expanded to include recruitment from community respirology clinics not affiliated with the UHN.

Ethics Approval and Informed Consent

Research ethics approval was obtained through the research ethics board of the UHN (study ID: 21-5336), and the study has been registered at ClinicalTrials.gov (NCT05140226). Informed consent will be obtained from participants before study enrollment.

Participants

The study sample will consist of older adults (aged ≥50 years) with a clinical and spirometric diagnosis of moderate to severe COPD (postbronchodilator forced expiratory volume in the first second [FEV_1]/forced vital capacity of <0.70 [or lower limit of normal of FEV1/forced vital capacity] and FEV_1=30%-79%). Participants will be required to have access to a reliable internet connection and be able to mobilize independently and safely with or without a walking aid. Exclusion criteria include the following: (1) current participation in supervised in-person or an internet-based pulmonary rehabilitation program; (2) COPD exacerbation in the previous 3 months to ensure clinical stability; (3) presence of cardiovascular, neurological, or musculoskeletal conditions that could interfere with the safe performance of study procedures (eg, unstable coronary artery disease, heart failure, stroke, myopathy, or moderate to severe arthritis); (4) severe cognitive impairment ascertained through chart review or self-report (eg, severe dementia or inability to perform ADLs independently); (5) medical instability (eg, hepatic dysfunction, metabolic abnormality, or active infection); (6) overt psychiatric disorder or substance abuse; (7) current use of home oxygen therapy; (8) insufficient English fluency to carry out testing and training; and (9) being listed for lung transplantation.

Recruitment and Screening

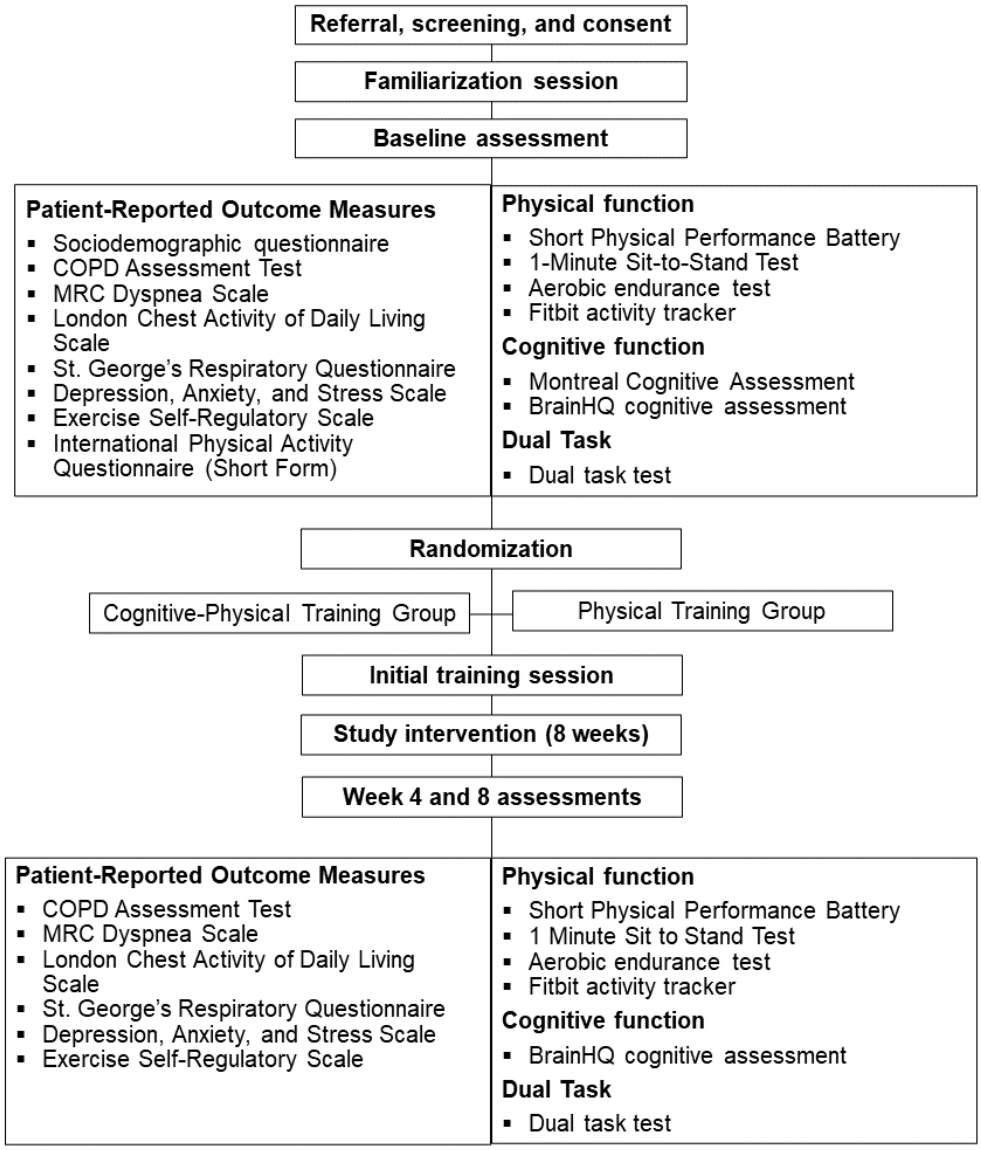
Participants will be recruited during routine visits to outpatient respirology clinics at UHN in Toronto, Ontario, Canada, and local respirology clinics. Clinic personnel within the circle of care will introduce the study to patients with COPD and ask if they are interested in participating. If interested, a member of the research team will then contact the potential participant to screen for eligibility criteria, review study procedures, and obtain informed consent. The study recruitment poster will also be provided to medical personnel at local respirology clinics who will introduce the study to patients with COPD and instruct them to contact the research team if they are interested in pursuing study participation.

Study Timeline

The study timeline is shown in Figure 1. After completing consent procedures, participants will receive a package by mail containing the following study equipment: Fitbit Charge 4 device (Fitbit Inc), foot peddler (VANGONA D2 pedal exerciser), pulse oximeter, resistance bands (Thera-Band), measuring tape, and exercise manual. They will also receive an email with instructions on how to access the internet-based appointment platform (Microsoft Teams; Microsoft Corp) on their devices. Following receipt of study materials, participants in both groups will be booked for a 45-minute videoconferencing familiarization session. During the familiarization session, participants will be introduced to the study equipment and software, their safety in performing remote physical testing will be assessed, and study assessment procedures will be explained. Furthermore, appropriate equipment setup for remote testing will be determined, and participants will have the opportunity to practice the physical assessment tests. After the familiarization session, participants will be booked for the *baseline assessment* session (1 hour) to complete the assessment measures described in the following sections.

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Figure 1. Study timeline. COPD: chronic obstructive pulmonary disease; MRC: Medical Research Council.



Randomization

After the baseline assessment, participants will be randomized to either the cognitive-physical training (intervention) group or the physical training (control) group using a 1:1 ratio. Randomization will be performed using shuffled opaque envelopes containing the group assignment. Given the pilot stage of this research and the nature of exercise interventions, group allocation will be known to the research team, exercise professionals, and study participants.

Intervention Groups

Summary

After randomization, participants in both groups will complete an initial training session (1 hour) to introduce the intervention. The initial training session will consist of a health and exercise history assessment, tailored exercise prescription, goal setting, and software account setup, as described in the following sections. Both groups will also receive weekly videoconferencing calls (30-60 minutes) from the study team via Microsoft Teams. Weekly sessions will involve a review of training and any adverse events, progression or adaptation of the program as needed, and troubleshooting of any difficulties encountered by the participant. Participants will also have the option of scheduling additional sessions with the study team during the week if further support is needed.

Physical Training Group

Overview

Participants in the physical training group will perform 8 weeks of home-based physical exercise training as per the current standard of care for pulmonary rehabilitation [22,33]. The physical training program was developed according to established guidelines for pulmonary rehabilitation [22,33] and includes both aerobic and strength training exercises that will be individually tailored to the specific needs and physical condition of each participant. Table 1 summarizes the physical exercise training program parameters.

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Table 1. Physical exercise training parameters.

Modality and frequency	Intensity	Time	Type	Progression
Aerobic: 5 days/week	• Moderate to vigorous (target Borg RPE[a] score of 4-6/10) • 60%-85% of symptom-limited maximum heart rate	• 30-50 minutes • Either continuous or interval training	• Foot peddler	• Gradual progression of training duration • Increase pedaling speed (revolutions/minute) or resistance • Increase target heart rate or RPE score
Strength: 2 days/week	• Target Borg RPE score of 4-6/10	• 6 exercises • 1-3 sets • 10-12 repetitions	• Resistance band exercises: band pull-aparts, seated bicep curls, seated rowing, and seated tricep kicks • Body weight exercises: chair sit-to-stand exercises and calf raises	• Resistance intensity will be increased when prescribed exercises can be completed without difficulty to maintain moderate exertion • Increase in resistance band tension • Increase in number of sets or repetitions

[a]RPE: Rating of Perceived Exertion.

Individualized progressive exercise prescriptions will be developed by an exercise professional and supported using a web application and mobile app (Physiotec) that allows for customizable exercise prescriptions with written instructions, video tutorials, and self-reported tracking of exercise completion. The exercise program will be reviewed, revised, and progressed as appropriate based on participants' needs during the weekly check-ins with the exercise professional. This will involve reviewing available data from Fitbit and self-report records from the participant, including pulse oximeter recordings.

Participants will be encouraged to include a warm-up and a cooldown period as part of their exercise training sessions. The warm-up will be a 5-minute routine consisting of mobility and breathing exercises to be implemented before starting physical activity. The cooldown at the end of each training session will comprise neck, shoulder, and leg stretches. See Table 2 for examples of warm-up and cooldown exercises.

Table 2. Summary of warm-up and cooldown exercises.

Exercise	Intensity	Time	Type
Warm-up (5 minutes)			
Breathing	• As tolerated • Gentle breathing exercises	• Approximately 3 minutes	• Pursed-lip breathing
Mobility	• Gentle mobility exercises as tolerated by the participants' range of motion while combining with the rhythm of breathing	• 5 exercises • 1 set of 10 repetitions	• Neck mobility (chin tuck and head to the sides) • Shoulder circles • Arms reach up and reach down (touch ankles) • Knee extension and flexion (performed while sitting in a chair)
Cool down (5 minutes)			
Stretching	• Gentle stretching exercises as tolerated by the participants' range of motion	• 3 exercises • 1 set of 2 repetitions for each exercise • Hold each exercise for 10 seconds	• Chest stretching in chair • Back stretching in chair • Leg stretching in chair

Aerobic Training

Aerobic training will consist of using a foot peddler (VANGONA D2 pedal exerciser) provided by the research team (Table 1). Participants will be asked to perform aerobic training 5 times per week for a minimum of 30 minutes (up to 50 minutes) at a moderate to vigorous intensity (level 4-6 out of 10 on the Borg Rating of Perceived Exertion [RPE] Scale). Aerobic exercise may be performed in intervals (eg, 5 minutes of pedaling and 2 minutes of rest) or completed in shorter bouts throughout the day if participants cannot tolerate 30 minutes continuously. Exercise duration and intensity will be adapted to the participants' level of dyspnea and fatigue. Aerobic training will progress under the guidance of the exercise professional by increasing duration, cycling speed, and resistance.

Strength Training

Strength training will be performed 2 times per week using resistance bands (provided by the research team), the participants' own body weight, and household items (eg, chairs).

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Participants will be prescribed 1 to 3 sets of 10 to 12 repetitions for 6 strength exercises targeting large muscle groups such as the chest, back, arms, shoulders, and legs. Exercises may include band pull-aparts, seated rowing, bicep curls, triceps extensions, sit-to-stand exercises, and calf raises. Specific exercises and the number of sets and repetitions will be tailored to suit the individual needs of each participant, with a target intensity level of 4 to 6 on the Borg RPE Scale. Strength training will be performed under the guidance of the exercise professional by increasing the number of sets or repetitions or by increasing the tension in the resistance bands.

Safety Precautions for Remote Training

Participants will be given a personalized exercise program supervised by a qualified exercise professional. The exercise professional will review important considerations for home exercise, such as maintaining an open training environment free from tripping hazards (eg, rugs, clutter, and pets), the suitability of exercise equipment setup, and appropriate exercise attire (eg, footwear). Before beginning the remote exercise sessions, the exercise professional will perform a safety check to determine the appropriateness of proceeding with testing or training. The safety check will involve an objective assessment of oxygen saturation, heart rate, and blood pressure (if available) and a subjective assessment of self-reported symptoms (eg, breathlessness, dizziness, and chest pain). The research team will also collect participants' home addresses, telephone numbers, and emergency contact information to be used in the event of a medical emergency during internet-based interactions.

Participants will be instructed to monitor their oxygen saturation (pulse oximeter), heart rate (pulse oximeter or Fitbit), and subjective level of exertion (Borg RPE Scale) and breathlessness (Borg Dyspnea Scale) while exercising using printed scales. They will be advised to lower their intensity level (ie, decrease cycling speed or resistance) if they reach a score of ≥7 on the Borg Dyspnea or RPE Scales, if their oxygen saturation drops to <85%, or if they experience any other symptoms (eg, light-headedness). They will be asked to track any adverse events using the training diary and encouraged to contact a member of the research team immediately upon noticing any adverse events. If participants experience chest pain or discomfort (uncomfortable feeling of pressure, pain, squeezing, or heaviness in the chest spreading to the shoulder, arms, neck, and back), they will be instructed to immediately stop exercising, rest, and seek emergency medical assistance if the symptoms persist beyond 5 minutes. The training program will be monitored by the exercise professional via weekly internet-based appointments involving a review of physiological exercise parameters (heart rate and oxygen saturation) from the Fitbit data and participant self-reported records. Participants will also be able to contact the exercise professional and study team at any time if questions or concerns arise.

If a participant communicates a medically concerning adverse event or contraindication to exercise (eg, cardiovascular event), the program will be suspended until medical clearance to resume the exercise program is obtained from the participant's physician and approved by the principal investigator. Participants who experience a COPD exacerbation during the study will be instructed to temporarily discontinue their training program. They will be reassessed by the principal investigator and exercise professional within 2 weeks for their ability to resume the study.

Cognitive-Physical Training Group

Overview

Participants in the cognitive-physical training group will perform 8 weeks of home-based web-based cognitive training in addition to physical exercise training.

Physical Exercise Training

Physical training, including aerobic and strength exercises identical to those in the physical training group, will be performed a minimum of 5 days per week, as described previously.

Cognitive Training

Cognitive training will be performed using the web-based BrainHQ training platform (Posit Science Corporation) [34]. Participants will be instructed to train 5 days per week with a target of 24 levels per session (approximately 60 minutes). Cognitive training may be completed on a desktop computer, laptop, or tablet. A tablet device will be provided to any participants without access to a personal device for training. A customized training focus has been designed for this study based on areas of cognition known to be affected by COPD: attention, memory, speed of processing, and executive function [6-8]. These cognitive domains will be targeted using the following BrainHQ exercises: Double Decision, Hawk Eye, Visual Sweeps, Eye for Detail, Mind Bender, and Target Tracker [35,36]. The BrainHQ platform is designed to have training difficulty continuously adjusted to be performed "at threshold" of 70% to 80% accuracy, meaning that exercises become easier or more difficult based on the individual's performance. All participants in the cognitive-physical training group will have a similar training session initially, but training parameters will become more individualized as users progress and the algorithm considers their individual performance history. Previous research indicates that the proposed training schedule (8 weeks, 40 hours total) is sufficient to elicit cognitive improvements [35,37,38].

Data Collection

Primary Outcomes

Overview

The primary outcomes for this study include the following indicators of intervention feasibility: recruitment rate, retention, adherence, safety, and satisfaction. See Table 3 for an overview of the feasibility outcomes.

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Table 3. Feasibility outcome measures.

Feasibility outcome	Assessment measure	Success criteria	Time point
Recruitment	Number of consented participants relative to the total number of eligible patients approached for consent	Recruitment rate of ≥30%	During study period
Retention	Number of participants who complete the final study assessment relative to the total number of participants enrolled and randomized	Retention rate of ≥80%	During study period
Adherence	Percentage of completion of physical and cognitive training intervention components according to training logs and BrainHQ records	Intervention adherence of ≥75%	During study period
Safety	Adverse events reported via exercise training logs and weekly check-in sessions	No study-related adverse events	During study period
Satisfaction	Participant satisfaction survey	≥80% reporting above-average or excellent satisfaction on a Likert scale	Weeks 1, 4, and 8

Recruitment

The recruitment rate will be defined as the percentage of consented patients relative to the total number of eligible patients who agreed to be approached by the study team for participation. Reasons for study participation and nonparticipation will also be collected. A recruitment rate of ≥30% has been established as our criterion to inform feasibility for a future study and help with modifications to recruitment for future studies.

Retention

Retention for the whole study and per group will be defined by the number of participants who complete the final study assessment compared with the number of participants enrolled and randomized. A retention rate of ≥80% (in each group) has been established as our criterion to determine feasibility for a future study.

Adherence

Adherence to the prescribed physical training and cognitive-physical training programs will be assessed via daily exercise training logs, the number of training levels completed in BrainHQ (displayed on a secure cloud-based group portal accessible by the study team), and weekly communications with participants. Adherence to the physical exercise training intervention will be expressed as the percentage of physical training days completed out of the total number of training days prescribed. Adherence to the cognitive training intervention will be expressed as (1) the number of cognitive training days completed out of the number of cognitive training days prescribed and (2) the number of cognitive training levels completed out of the total number of levels prescribed using the BrainHQ platform. Adherence to the interventions of ≥75% (ie, combination of physical training logs and cognitive training platform) is our criterion to determine feasibility for a future study.

Safety

Intervention safety will be monitored based on the occurrence and severity of adverse events. Participants will be instructed to log and report any side effects or adverse events during the intervention (ie, falls, injuries, and respiratory symptom worsening). Adverse events will also be reviewed by the exercise professional during weekly sessions.

Satisfaction

Participant satisfaction with the cognitive-physical training and physical training programs will be assessed at weeks 1, 4, and 8 using a Participant Evaluation Questionnaire developed for this study involving multiple-choice and open-ended questions. The results will be reviewed and analyzed by the study team at the end of the trial to determine overall satisfaction and any modifications required for future trials.

Secondary Outcomes

Overview

Effect size estimates will be evaluated using secondary outcome measures of physical and cognitive function, dual task performance, ADLs, and HRQL, as described in further detail in the following sections. These measures will be assessed at baseline and at 4 and 8 weeks after starting the intervention. See Table 4 for a summary of secondary outcome measures.

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Table 4. Secondary outcome measures by time point.

Outcome	Assessment measure	Time points
Characterization measures		
Sociodemographic information	• Sociodemographic questionnaire	• Baseline
Cognitive screening	• Montreal Cognitive Assessment Test	• Baseline
Disease impact	• COPD[a] Assessment Test	• Baseline, week 4, and week 8
Clinical characteristics	• Medical chart review	• During study period
Physical function		
Lower-body strength	• 1-Minute Sit-to-Stand Test	• Baseline, week 4, and week 8
Lower-body function	• Short Physical Performance Battery	• Baseline, week 4, and week 8
Aerobic endurance	• Foot peddler endurance test	• Baseline, week 4, and week 8
Cognitive performance	• BrainHQ assessment	• Baseline, week 4, and week 8
Dual-tasking performance	• Foot peddler dual task test	• Baseline, week 4, and week 8
Self-reported outcomes		
Dyspnea	• MRC[b] Dyspnea Scale • 18-item qualitative dyspnea scale • Borg Dyspnea and RPE[c] Scales	• Baseline, week 4, and week 8
Activities of daily living	• The London Chest Activity of Daily Living scale	• Baseline, week 4, and week 8
Health-related quality of life	• St. George's Respiratory Questionnaire	• Baseline, week 4, and week 8
Mood	• Depression, Anxiety, and Stress Scale (21 items)	• Baseline, week 4, and week 8
Exercise self-efficacy	• Exercise Self-Regulatory Efficacy Scale	• Baseline, week 4, and week 8
Physical activity		
Physical activity habits	• International Physical Activity Questionnaire–Short Form	• Baseline
Physical activity behaviors	• Fitbit activity tracker	• During study period
Health care use	• Medical chart review • Self-reported	• During study period and 1 year before study enrollment

[a]COPD: chronic obstructive pulmonary disease.

[b]MRC: Medical Research Council.

[c]RPE: Rating of Perceived Exertion.

Characterization Measures

Sociodemographic Information

Age, sex, ethnicity, employment status, educational level, and smoking history will be collected via chart review and self-report to characterize the sample and interpret findings from the cognitive assessments.

Montreal Cognitive Assessment

The Montreal Cognitive Assessment (MoCA) [39] is a 30-point screening test for mild cognitive impairment that has been previously applied in patients with COPD [12,40]. The MoCA specifically assesses short-term memory, visuospatial abilities, executive function, attention, concentration, working memory, language, and orientation to time and place. The MoCA will be administered only at the baseline assessment to help characterize the study population.

COPD Assessment Test

The COPD Assessment Test [41] is a short questionnaire for assessing and monitoring the impact of COPD. The COPD Assessment Test consists of 8 items that assess cough, the production of phlegm, chest tightness, breathlessness, activity limitation, confidence, sleep, and energy. Each item is rated on

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a 6-point scale, and the overall score ranges from 0 to 40, with a higher score indicating greater disease impact.

Clinical Characteristics

Clinical characteristics, including FEV_1; medications (eg, inhaled medications, opioids, and prednisone); baseline 6-minute walk distance; Body Mass, Obstruction, Dyspnea, and Exercise index; and exacerbation history, will be ascertained from chart review up to 1 year before study enrollment. We will also capture anthropometric measures and BMI from pulmonary function tests if available from routine clinical evaluations. Comorbidities in our study participants will be assessed using the Charlson Comorbidity Index and through chart review using a comprehensive comorbidity questionnaire previously applied by our group [42].

Physical Function

Lower-Body Strength

The 1-Minute Sit-to-Stand Test [43] will be used to evaluate lower-body strength. This test involves participants completing as many sit-to-stand rises from a chair as possible in 1 minute. Participants will be instructed to stand fully upright and then sit down again immediately without delay, with arms crossed at the chest to avoid the use of the arms to rise from the chair. The research team will guide participants in selecting an appropriate chair (approximate height of 46 cm) with a flat, noncushioned bottom and no armrests. Participants will be prompted to report their Borg Dyspnea and Borg Leg RPE scores before and after the test.

Lower-Body Function

The Short Physical Performance Battery [44] will be used to assess lower-extremity performance, including balance (ability to stand with feet side by side, semitandem, and tandem), gait (usual-paced walking speed over 4 meters), and chair stand (time to rise from a chair 5 times). The Short Physical Performance Battery score is a summation of the scores on the 3 tests, each scored from 0 to 4, with a maximal cumulative score of 12.

Aerobic Endurance

Aerobic endurance will be measured using a foot peddler test developed by our research group for this study. Participants will pedal for as long as they can up to 15 minutes at a set speed of 50 revolutions per minute and a resistance setting that allows them to carry on a conversation (approximately 3-4 on the Borg RPE Scale). This intensity level is intended to be challenging but not exhausting. The primary endurance measure will be the number of minutes of testing completed. The reason for test termination will also be recorded. Oxygen saturation, qualitative dyspnea descriptors, Borg Dyspnea score, and Borg Leg RPE score will be measured before and after endurance testing. The complete aerobic endurance testing protocol is described in Textbox 1.

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Textbox 1. Aerobic endurance foot peddler testing protocol.

Baseline measurements

- Oxygen saturation with pulse oximetry, qualitative dyspnea descriptors, Borg Leg Rating of Perceived Exertion score, and Borg Dyspnea score will be measured before testing.

Warm-up

- Participants will pedal for 1 minute at a self-selected speed as a warm-up in order to become familiar with the foot peddler.

Test period

- Participants will continue pedaling at a set speed of 50 revolutions/minute and a resistance setting that allows them to carry on a conversation (approximately 3-4 on the Borg Rating of Perceived Exertion Scale) for as long as they can up to a maximum of 15 minutes. Participants will be prompted every few minutes to monitor their heart rate and oxygen saturation using an oximeter and their Borg Dyspnea score. The test will be stopped based on any of the following stopping criteria:
  - 15 minutes have been completed.
  - Oxygen saturation drops to <85%.
  - Self-reported Borg Dyspnea score is >7.
  - The activity becomes unbearable (eg, severe leg pain or the participant is too tired to continue).
  - Heart rate reaches 85% of age-predicted maximum (calculated as 220 beats/minute–age).
  - Participant is unable to maintain a speed of 50 revolutions/minute.
  - The research team member decides to stop the test because of apparent breathlessness or discomfort of the participant.

Posttest measurements

- The reason for test termination will be recorded, and repeat measurements will be taken for oxygen saturation, qualitative dyspnea descriptors, Borg Leg Rating of Perceived Exertion score, and Borg Dyspnea score. We will also ascertain if participants have any additional comments regarding their test performance.

Cooldown

- Participants will be instructed to continue pedaling at a self-selected speed and resistance to cool down until heart rate drops to <110 beats/minute.

BrainHQ Cognitive Assessment

Cognitive performance will be evaluated via the BrainHQ assessment platform. A custom assessment battery modeled on the training exercises will be used, with a focus on evaluating changes in performance from training as a measure of target engagement [45]. These assessments were chosen in consultation with the scientific team at BrainHQ and coinvestigators with cognitive expertise (DG, RG, and JLC).

Dual Task Performance

Dual task performance will be evaluated through a dual task test on the foot peddler, as previously undertaken in other populations [46,47]. Participants will complete a motor, cognitive, and combined dual task (all of 1-minute duration) in random order: (1) the *cognitive task* involves spelling 5-letter words backward from a list of 100 words provided verbally (homonyms excluded), (2) the *motor task* involves pedaling on the foot peddler at a set speed of 50 revolutions per minute and a self-selected resistance corresponding to a moderate-intensity level allowing participants to hold a conversation (approximately level 4 on the Borg RPE Scale), and (3) the *dual task* involves spelling and pedaling at the same time. Participants will be instructed to prioritize both tasks equally. Spelling tasks (single and dual tasks) will be audio recorded using a Dictaphone to allow for precise scoring. The number of words correctly spelled backward and the distance covered while pedaling will be compared between the single and dual task conditions to calculate a dual task cost score for both the cognitive and physical performance tasks.

Patient-Reported Outcomes

Medical Research Council Dyspnea Scale

The Medical Research Council Dyspnea Scale [48] will be used to assess the degree of functional disability because of breathlessness. Participants will indicate the extent to which breathlessness limits their daily physical activities on a scale from 1 (only breathless with strenuous activity) to 5 (too breathless to leave the house or breathless when dressing or undressing).

ADL Outcomes

The London Chest Activity of Daily Living scale [49] will be used to assess limitations in performing ADLs because of dyspnea. It comprises 15 questions across 4 domains: self-care, domestic activities, physical activities, and leisure. Each question is rated on a scale from 0 to 5, with 5 representing the greatest dyspnea-related impairment. Total scores range from 0 to 75 points, with higher values indicating greater ADL limitations [50]. The London Chest Activity of Daily Living scale has been applied in patients with COPD with a minimally important difference of 4 points [49].

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HRQL Outcomes

The St. George's Respiratory Questionnaire [51] will be administered to measure the impact of COPD on overall health, daily life, and perceived well-being. The questionnaire comprises 50 items. Scores range from 0 to 100, with higher scores indicating worse HRQL. A minimally clinically important difference of 4 points has been identified in patients with COPD [52].

Mood

The Depression, Anxiety, and Stress Scale–21 [53] is a 21-item questionnaire that measures the emotional states of depression, anxiety, and stress. It has acceptable to excellent internal consistency and normative data for the COPD population [54]. Scores are categorized as normal, mild, moderate, severe, and extremely severe for each of the 3 domains.

Self-Efficacy to Exercise

The Exercise Self-Regulatory Efficacy Scale (Ex-SRES) [55] will be administered to measure exercise self-regulatory efficacy among participants. The Ex-SRES consists of 16 items asking participants to indicate the degree to which they are confident that they could continue to exercise regularly (3 times/week for 20 minutes) when faced with various barriers. Ratings are provided from 0% (not at all confident) to 100% (highly confident). The validity and reliability of the Ex-SRES have been demonstrated in individuals with COPD [55].

Physical Activity Levels

The *International Physical Activity Questionnaire–Short Form* [56] will be used to characterize baseline physical activity levels among participants. The International Physical Activity Questionnaire–Short Form consists of 7 questions that capture average time spent sitting, walking, and engaging in moderate and vigorous physical activity over the previous 7 days to provide an estimate of overall activity levels based on metabolic equivalent of task minutes per week.

During the 8-week study period, physical activity levels will be measured via a wrist-worn activity tracker (Fitbit Charge), which will capture daily step count, sedentary time, and number of active minutes (minutes of activity classified as "moderate" or "vigorous" intensity based on heart rate) [57].

Health Care Use

Health care use over the course of the 8-week intervention and 1 year before study enrollment will be assessed through chart review. The following information will be collected: COPD exacerbation history, history of falls, emergency department visits, admissions to hospital (reasons and length of hospital stay), and mortality during the study period.

Statistical Procedures

Sample Size

A sample size of 12 participants per group is considered appropriate for a pilot study to assess feasibility [58], accounting for an estimated attrition rate of approximately 20% in each group. Power calculations were not performed for the secondary outcomes as the primary study purpose is to assess effect estimates for further program development and evaluation in a future RCT.

Data Analysis

Descriptive statistics will be used to summarize recruitment and retention rates, program adherence, participant satisfaction, and safety in both groups. Means and 95% CIs will be reported for the secondary outcomes at baseline, 4 weeks, and 8 weeks within and between groups to derive effect estimates for analysis and sample size calculations for a subsequent larger-scale RCT. Paired 2-tailed *t* tests and 2-tailed *t* tests will be used to compare the changes in the secondary outcome measures over the 8-week study period within and between the 2 randomized groups, respectively. All participants will be included in the analyses based on the intention-to-treat principle according to their group allocation from randomization.

We will explore the contribution of age and sex to feasibility end points and secondary outcomes. Given the modest sample size and importance of age for both cognitive and physical function, we limited our inclusion criteria to the age of ≥50 years to ensure a more homogenous study population. Other important clinical factors such as BMI and medications will be included for descriptive purposes.

Data Quality and Management

Our research team is trained in the study processes, measurement protocols, and institutional requirements. We have received peer review comments from the Canadian Lung Association (Multimedia Appendix 1) and incorporated this feedback into the study protocol. Standard operating procedures are in place for all study procedures. The research team will make every effort to have participants complete all study elements, and incomplete or missing data will not be imputed. All participants will be closely supervised by the exercise professional, who will support adherence and accurate data collection.

As per national and institutional research guidelines, all participants will be given a unique study ID to be used in place of their name for all study data. Physical data collection forms and data collected from questionnaires will be kept in a cabinet in the principal investigator's office under lock and key. Electronic data will be stored on a password-protected research server. Once data collection is complete, deidentified data will be exported to statistical software for analysis.

Results

Recruitment began in January 2022. It is estimated that the study period will be 30 months long, with data collection to be completed by December 2023. Study results will be submitted for publication in the summer of 2024.

Discussion

Study Summary

COPD is associated with several physical and cognitive impairments contributing to limitations in daily activities that often involve the simultaneous performance of a physical (eg, walking) and cognitive (eg, talking) task, known as dual tasking.

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The benefits of pulmonary rehabilitation in reducing COPD symptoms and improving daily function are well established [21], and it is known to be feasible and effective when delivered remotely in the home environment via telehealth [26,27,31]. However, traditional pulmonary rehabilitation programs typically focus mainly on physical exercise training without addressing cognitive function despite evidence that many patients with COPD have some cognitive limitations, which can contribute to greater functional limitation, increased health care use, and decreased HRQL [6,23]. Patients with COPD with cognitive limitations are also at increased risk of noncompletion of pulmonary rehabilitation [59], suggesting that a better understanding of cognitive limitations and approaches to improve cognition may lead to better adherence and outcomes. However, to date, no studies have examined a pulmonary rehabilitation approach that specifically combines both physical and cognitive training. Therefore, this protocol describes a pilot RCT that is entirely internet based and home based and combines cognitive and physical training in patients with COPD with the aim of further improving daily function and HRQL beyond traditional pulmonary rehabilitation approaches.

Cognitive Training Mechanisms

Cortical activity is essential for all motor performance, ranging from complex activities to basic ADLs; thus, the benefits derived from cognitive training can be obtained even in those with normal cognition [60]. Cognitive training has been shown to be more effective in those completing a physical exercise intervention as the neural network is primed for neuroplasticity. Thus, cognitive training may be a complementary strategy in conjunction with physical exercise to improve dual tasking in patients with COPD, which is often required during routine daily activities (eg, talking or avoiding obstacles while walking). COPD is associated with impaired dual-tasking performance, manifested as changes in dual task gait properties, including reduced gait speed [12] and increased gait variability [15]. There is also evidence from our group that loss of neural automaticity may be an underlying mechanism contributing to slower gait speed among individuals with COPD [11]. Collectively, these changes suggest that cognitive limitations may arise from increased attentional demands and neural inefficiency, which may contribute to decreased cognitive and physical performance in COPD [17]. Although traditional pulmonary rehabilitation does not appear to improve dual task gait in patients with COPD [15], cognitive training is known to produce distinct benefits on dual task reaction time [61] and has been shown to independently improve measures of functional mobility among healthy older adults [62]. Therefore, the addition of cognitive training may help improve neural efficiency and attentional capacity in patients with COPD, leading to improvements in dual-tasking ability that may translate to better performance in daily activities and HRQL and reduction in the risk of falls.

Clinical practice guidelines established by several leading organizations recommend cognitive training as a strategy to decrease the risk of cognitive decline (World Health Organization; American Academy of Neurology; National Academies of Sciences, Engineering, and Medicine; and Agency for Healthcare Research and Quality) [63-66]. These recommendations were largely established based on strong scientific evidence in the form of meta-analyses showing both near and far transfer effects from cognitive training in older community-dwelling adults, those with mild cognitive impairment, and those with dementia [67-71]. BrainHQ by Posit Science is a computerized cognitive training platform offering game-based exercises that target the speed and accuracy of information processing across the domains of attention, memory, spatial navigation, executive function, and emotional processing. In the largest RCT on cognitive training to date involving 2832 healthy older adults, speed-of-processing training on BrainHQ was found to improve cognitive and functional performance to a greater extent than other forms of memory or reasoning training, which translated to a reduction in risk of impairments in daily activity performance and an increase in reported quality of life that remained at follow-up of 5 to 10 years [72]. BrainHQ training resulted in improved visual processing speed and accuracy, and these improvements were associated with improved balance and smaller decrements in dual task gait speed among older adults [73,74], which has important implications for patients with COPD who are at risk of falls [42]. To our knowledge, this study will be the first to explore BrainHQ cognitive training in a population of individuals with chronic lung disease.

Given the breadth of impairments associated with COPD and the complexity of routine daily activities, the rehabilitation approach described in this paper combining physical exercise with cognitive training targeting attention, memory, executive functioning, and speed of processing may offer the flexibility to further improve daily function and reduce the risk of falls in patients with COPD beyond physical training alone. Notably, the cognitive training modality to be implemented in this study is distinct from the proposed dual task outcome measure, supporting the potential transfer of gains to a variety of daily activities.

Strengths

There are several strengths to this study. The physical training program and assessments were specifically designed to support feasibility and safety in the home environment. All participants will be provided with exercise training equipment (foot peddler, resistance bands, Fitbit, and pulse oximeter), which will improve safety and accessibility and standardize physical training and assessments. This study is novel as it provides a new approach to remote assessments of aerobic endurance (ie, foot peddler), functional outcomes, and cognitive assessment and training as part of a home-based pulmonary rehabilitation program for patients with COPD [27]. Our protocol may optimize not only accessibility but also outcomes in home-based pulmonary rehabilitation programs. The use of commercially available software programs (Fitbit, Physiotec, and BrainHQ) supports the future clinical translation of this work as these and other similar programs may be used by clinicians and patients looking to integrate cognitive-physical training into pulmonary rehabilitation programs. Furthermore, the chosen cognitive training platform (BrainHQ) has the largest evidence base and, to our knowledge, is the only brain training program that meets all the National Academy of Medicine criteria for cognitive training [29,30]. Our specific cognitive training protocol was designed in consultation with neuropsychology and cognitive

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science experts to specifically target common areas of deficit among individuals with COPD.

Limitations

We also acknowledge that there are limitations to the design of this study. Given the small sample size, we will be unable to adjust the analyses for potential confounders such as medications (opiates, sedatives, or corticosteroids) or COPD exacerbations; however, these factors will be tracked throughout the study period to explore their influence on selected outcomes. This study will be conducted entirely remotely, and therefore, we are unable to prospectively measure specific tests of outcomes such as pulmonary function (ie, spirometry) or neural activity (ie, functional near-infrared spectroscopy). However, some of this information will be derived from chart review or will require future study. Furthermore, cognitive assessments will be completed independently at home, and differences in device or screen size (ie, computer vs tablet) may influence the results. Participants who do not have access to a suitable device will be provided with a tablet for the duration of the study. Owing to the nature of the training intervention and internet-based environment, blinding of participants and the exercise professional is not possible, thus creating a risk of bias. Furthermore, most of the physical training measures and intensity will be ascertained through self-report, which may not be as accurate as if they were captured electronically from the training devices.

Conclusions

A partly supervised, home-based, telehealth cognitive-physical training program may be an accessible intervention to improve cognitive function and further address dual-tasking abilities in people living with COPD. Evaluating the feasibility and effect estimates is a critical first step to inform future clinical trials evaluating this approach and its effects on physical and cognitive function, ADL performance, and HRQL.

Acknowledgments

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Authors' Contributions

DR and WDR conceived the study and participated in the design of the protocol and development of the intervention. DR, DSM, JLC, MBS, and WDR are the grant holders. SN and MIM helped with the coordination of the study under the direct supervision of DR. JS is responsible for the implementation of the study. DR, JS, and WDR helped draft this manuscript. DR, JS, ECP, SN, MIM, DSM, JLC, EH, RG, MHK, AL, DG, MBS, and WDR provided expert advice and reviewed the protocol. All the authors approved the final manuscript for submission.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review report from the Chronic Obstructive Pulmonary Disease Catalyst Grant Award.
[PDF File (Adobe PDF File), 258 KB - resprot_v12i1e48666_app1.pdf]

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Abbreviations

ADL: activity of daily living
COPD: chronic obstructive pulmonary disease
Ex-SRES: Exercise Self-Regulatory Efficacy Scale
FEV1: forced expiratory volume in the first second
HRQL: health-related quality of life
MoCA: Montreal Cognitive Assessment
RCT: randomized controlled trial
RPE: Rating of Perceived Exertion
UHN: University Health Network

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Protocol

Intravenous Magnesium: Prompt Use for Asthma in Children Treated in the Emergency Department (IMPACT-ED): Protocol for a Multicenter Pilot Randomized Controlled Trial

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Abstract

Background: Children managed for asthma in an emergency department (ED) may be less likely to be hospitalized if they receive intravenous magnesium sulfate (IVMg). Asthma guidelines recommend IVMg for severely sick children but note a lack of evidence to support this recommendation. All previous trials of IVMg in children with asthma have been too small to answer whether IVMg is effective and safe. A few major questions remain about IVMg. First, it has not been tested early in the course of ED treatment, when the impact on hospitalization would be greatest. Second, the clinical impact of hypotension, a known adverse effect of IVMg, has not been well characterized in previous research. Third, no trials have compared different IVMg doses or serial serum magnesium (total and ionized) concentrations to optimize dosing, so the most effective dose is unknown. A large, conclusive, randomized, placebo-controlled clinical trial of IVMg might be challenging due to the need to enroll and complete study procedures quickly, a lack of understanding of blood pressure changes after IVMg, and a lack of pharmacologic information to guide the optimal doses of IVMg to be tested. Therefore, a pilot study to inform the above gaps is warranted before conducting a definitive trial.

Objective: The objectives of this study are to (1) demonstrate the feasibility of enrolling children with severe acute asthma in the ED in a multicenter, randomized controlled trial of a placebo, low-dose IVMg, or high-dose IVMg; (2) demonstrate the feasibility of timely delivery of study medication, assessment of blood pressure, and evaluation of adverse events in a standardized protocol; and (3) externally validate a previously constructed pharmacokinetic model and develop a combined pharmacokinetic/pharmacodynamic model for IVMg using magnesium (total and ionized) serum concentrations and their correlation with measures of efficacy and safety.

Methods: This pilot trial tests procedures and gathers information to plan a definitive trial. The pilot trial will enroll as many as 90 children across 3 sites, randomize each child to 1 of 3 study arms, measure blood pressure frequently, and collect 3 blood samples from each participant with corresponding clinical asthma scores.

Results: The project was funded by the National Heart, Lung, and Blood Institute (1 R34HL152047-2) in March 2022. Enrollment began in September 2022, and 43 children have been enrolled as of April 2023. We will submit the results for publication in late 2023.

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Conclusions: The results of this study will guide the planning of a large, definitive, multicenter trial powered to evaluate if IVMg reduces hospitalization. Blood pressure measurements will inform a monitoring plan for the larger trial, and blood samples and asthma scores will be used to validate pharmacologic models to select the optimal dose of IVMg to be evaluated in the definitive trial.

Trial Registration: ClinicalTrials.gov NCT05166811; https://clinicaltrials.gov/ct2/show/NCT05166811

International Registered Report Identifier (IRRID): DERR1-10.2196/48302

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KEYWORDS

asthma; child; emergency service; feasibility studies; hospitalization; hypotension; magnesium; multicenter studies; randomized controlled trials

Introduction

Background

Asthma is the most common chronic illness in childhood and a leading cause of pediatric hospitalization, disability, and health care–related costs [1]. The current standard management of acute asthma in children is defined in guidelines published in 2007 by the National Heart, Lung, and Blood Institute (NHLBI) and includes inhaled bronchodilators (albuterol and ipratropium), systemic corticosteroids, oxygen, and further treatment depending on response [2]. Although these guidelines have been broadly implemented, hospitalization remains a common outcome for children with asthma after emergency department (ED) treatment, ranging from 13% to 50% of all asthma visits among pediatric EDs nationally [3].

Intravenous magnesium sulfate (IVMg) has been used to treat asthma for more than 70 years [4,5] and may reduce hospitalization in children with asthma. However, its specific role in treating pediatric acute asthma is still unclear [6]. NHLBI asthma guidelines suggest that clinicians consider a 20-minute infusion of IVMg in children or adults as an adjunct for life-threatening exacerbations, or for severe distress after an hour of initial therapy. These guidelines do not suggest a specific dose but rather provide a broad 3-fold dose range of 25-75 mg/kg. Conflicting evidence prevents a definitive recommendation or direction for clinical implementation [2]. In a review of care delivered to children with asthma over 6 years in 7 EDs, 5774 (25.7%) of 22,499 children hospitalized for asthma received IVMg in the ED [7]. A meta-analysis of previous small trials suggests that IVMg given in the ED may reduce hospitalization in children by 30% [8]. Applying a 30% reduction in hospitalization to the remaining hospitalized children who do not receive IVMg in the United States could potentially avoid 16,500 hospitalizations each year, each at an average cost of US $3600 [9], producing direct cost savings of US $65 million yearly in addition to avoiding indirect costs of missed school and work.

In this project, we are conducting a pilot trial that will address the following knowledge gaps needed to conduct a conclusive trial to assess the impact of IVMg on hospitalization.

First, previous trials evaluated IVMg for acute asthma only in children refractory to initial treatment. Though IVMg is currently infrequently used in clinical practice in the ED to prevent hospitalization [10], earlier administration could have a greater effect on this important outcome. Administration early in the treatment course would better align with the NHLBI recommendation that IVMg be considered after the first hour of treatment [2]. Only 1 previous trial of IVMg with hospitalization as an outcome attempted to enroll children on arrival to the ED [11]. Before a large trial can determine the effect of early administration of IVMg on hospitalization, protocols to support the administration in the first 90 minutes of treatment should be tested and refined in a pilot trial setting.

Second, the safety of IVMg has not been well characterized in previous trials. Earlier small trials reported no significant adverse events (AEs) after IVMg but included too few children to conclude adverse effects were rare. In a study of 100 children who received a single dose of 50 mg/kg in an ED, 11 had hypotension after IVMg, though only 7 received any intervention, limited to an intravenous (IV) fluid bolus with normalization of blood pressure [12]. In a multinational survey of ED physicians, 24% reported hesitancy about using IVMg in children because of the risk of hypotension [10]. Collection of safety outcomes in a trial environment, including data collected after discharge from the ED, will allow enhancement and refinement of safety monitoring procedures for the future trial.

Third, the optimal dosage of IVMg in pediatric acute asthma is unknown [8]. Our current pharmacologic understanding of IVMg is insufficient to define which doses should be tested in clinical trials to carefully strike a balance between avoiding potential adverse effects and exploring maximal clinical effect. To safely explore thresholds of efficacy and safety in a large trial, we must fill gaps in the pharmacologic understanding of IVMg. To define the optimal dose of IVMg, safety and efficacy outcomes must be correlated with serum concentrations of magnesium in children receiving a range of IVMg doses.

Informative pharmacodynamic (PD) analysis requires a marker of respiratory status that can be measured reliably and repeatedly in all patients. The use of spirometry as an inclusion criterion in most previous trials [13,14] excludes most older patients in severe respiratory distress and also excludes children 4 years and younger by design, as they can rarely cooperate sufficiently to perform adequate spirometry. The Pediatric Respiratory Assessment Measure (PRAM; Table 1) is a clinical respiratory score that has been validated in children to be predictive of hospitalization [15,16] and to show a change in respiratory status after a bronchodilator [17]. A respiratory score such as

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the PRAM is valuable because it allows repeated measurement in every patient, allows comparison of respiratory status between treatment arms, and can serve as a measure of respiratory status for PD modeling.

Table 1. Pediatric respiratory assessment measure.

Score	Suprasternal retractions	Scalene muscle contraction	Air entry	Wheezing	O_2 saturation, %
0	Absent	Absent	Normal	Absent	≥95
1	N/A[a]	N/A	Decreased at bases	Expiratory only	92-94
2	Present	Present	Widespread decrease	Inspiratory and expiratory	<92
3	N/A	N/A	Absent or minimal	Audible without stethoscope or silent chest with minimal air entry	N/A

[a]N/A: not applicable.

Objectives

The objectives of this study are to (1) demonstrate the feasibility of enrolling children in the ED with severe acute asthma in a multicenter, randomized controlled trial (RCT) of a placebo, low-dose IVMg, or high-dose IVMg; (2) demonstrate the feasibility of timely delivery of study medication to enrolled patients and assessment of blood pressure and associated AEs in a standardized protocol; and (3) externally validate a previously constructed pharmacokinetic (PK) model [18] and develop a combined PK/PD model for IVMg using magnesium (total and ionized) serum concentrations and their correlation with measures of efficacy (improvement in respiratory distress) and safety in children with severe acute asthma.

Methods

Study Overview

This pilot trial is a prospective double-blind, placebo-controlled trial of children 2-17 years of age with severe acute asthma. It was endorsed by the Pediatric Emergency Care Applied Research Network (PECARN) and is being conducted at 3 PECARN sites in Utah, Pennsylvania, and Ohio. The goal is to evaluate study procedures and gather the data necessary to plan a larger trial.

Study Population

Eligible participants are identified among children presenting to the ED for treatment of acute asthma. Specific criteria are listed in Textbox 1.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria:

- 2-17 years old
- Emergency Severity Index Triage acuity of 1 or 2
- Albuterol ordered to be administered in the emergency department (ED)
- A previous physician diagnosis of asthma confirmed by a licensed independent practitioner (ED attending, fellow physician, nurse practitioner, or physician assistant) in the ED who has spoken with the patient and family and reviewed the medical record
- Severe acute asthma, defined as a PRAM (Pediatric Respiratory Assessment Measure) score of 7 or greater as assessed by a treating physician at the time of screening using the study scoring instrument

Exclusion criteria:

- Positive pregnancy test in females of child-bearing potential (performed in all female potential participants 12 years and older) or known pregnancy (by a patient or parent report)
- Age-adjusted hypotension at presentation using age-based Pediatric Advanced Life Support parameters for systolic blood pressure in millimeters of mercury (children 1-10 years of age, systolic blood pressure (70 + 2×age in years) mm Hg; >10 years, systolic blood pressure <90 mm Hg) [19]
- Application of assisted ventilation before enrollment assessment (intubated, bilevel positive airway pressure, continuous positive airway pressure)
- Received IVMg within 24 hours before screening (by a parent, patient report, or medical record review)
- Enrollment assessment is 60 minutes or more after the start of ED treatment (start of first albuterol treatment)
- Previous enrollment in the same trial (by research staff review of trial records)
- Known severe renal impairment (by parent or patient report)

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Study Procedures

Overview

Descriptions of protocol procedures in this paper reflect protocol specifications and do not reflect whether protocol deviations have occurred. Significant protocol deviations will be reported in future publications.

Screening Schedule

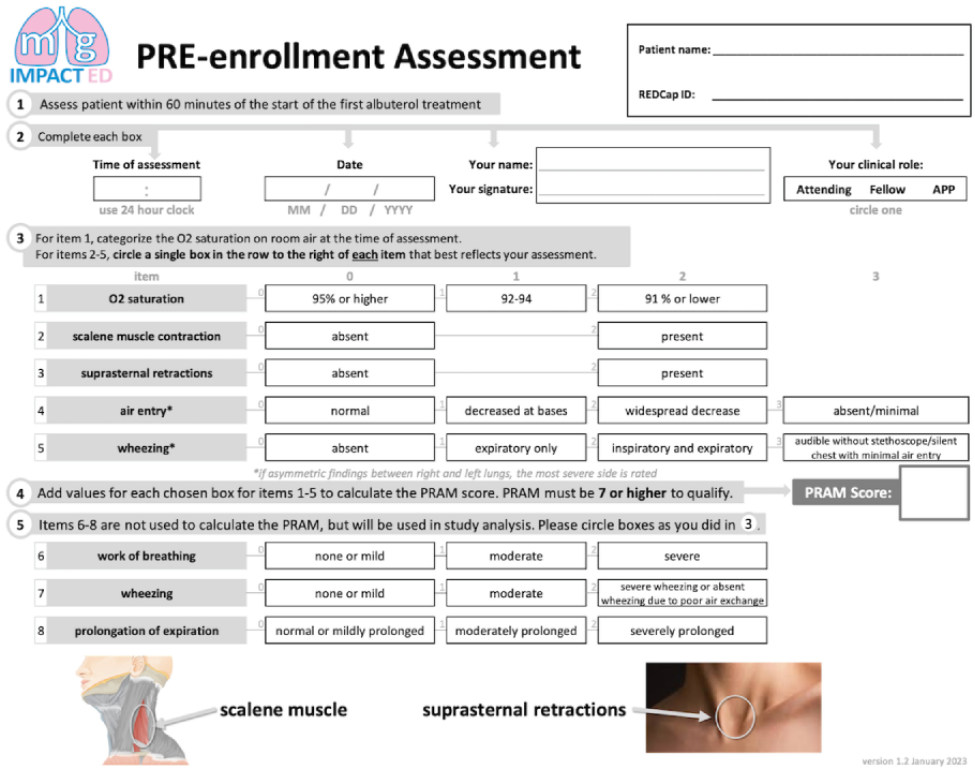
Research staff identifies children who present to the ED with acute asthma during screening hours maintained by each study site.

Screening and Enrollment

Research staff identifies children within the study age range who have physician orders to receive inhaled albuterol and are triaged at an Emergency Severity Index [20] acuity of 1 or 2. The research staff member approaches the treating physician to determine if the child is being treated for asthma, and if the child meets other inclusion criteria. The physician examines the child and completes an asthma scoring instrument that generates the PRAM score (Figure 1). If the PRAM is high enough, research staff review exclusions with the clinician, and if no exclusions apply, they introduce the study to the patient and family.

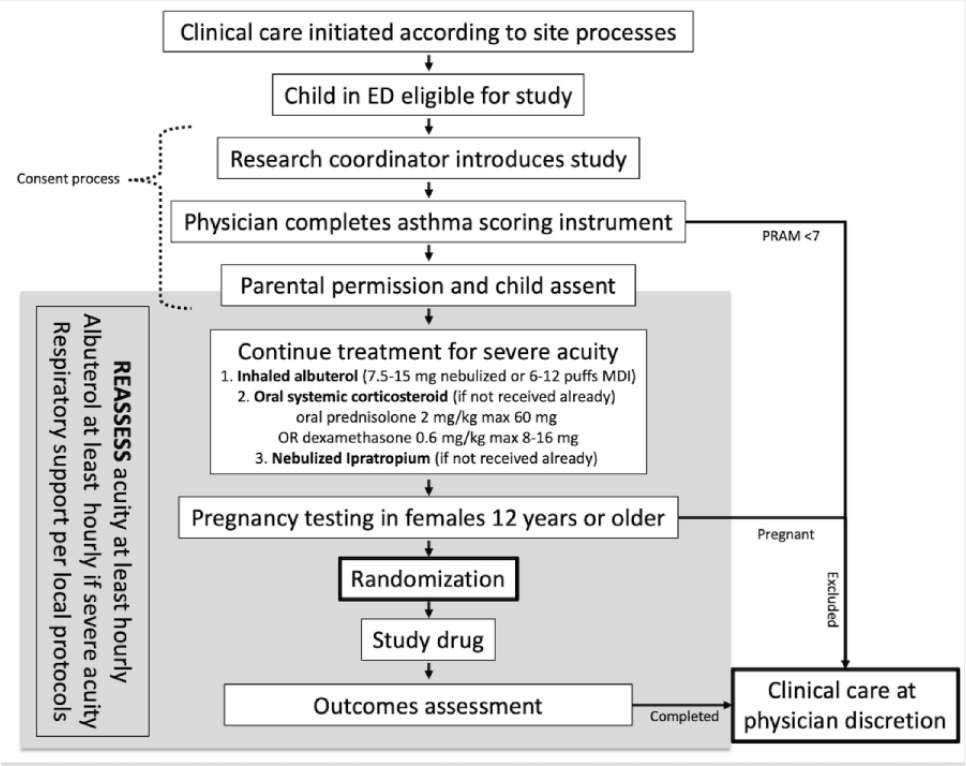
If the PRAM score is 7 or higher, the research staff approaches the family for consent (including parental permission for all children and child assent for children 7 years and older) and enrollment. Consent documents are prepared in Spanish and English, but patients whose primary language (or the language of their guardian) is not English or Spanish are included if a professional interpreter can communicate the content of consent documents to the family and discuss study consent. After consent is complete, the child receives standard asthma treatment according to the study protocol (Figure 2). After consent, females 12 years and older without a reported pregnancy provide a blood or urine sample for qualitative pregnancy testing and are excluded from receiving the study drug if positive. Clinical staff reports pregnancy results to patients and families following institutional policies and state regulations.

Figure 1. Preenrollment assessment including PRAM (Pediatric Respiratory Assessment Measure) score and items for pediatric asthma severity score [21].



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Figure 2. Study asthma treatment protocol. ED: emergency department; MDI: metered dose inhaler; PRAM: Pediatric Respiratory Assessment Measure.



Randomization

The investigational pharmacy at each institution prepares doses in a manner to maintain allocation concealment for all ED staff. A sequential randomization scheme with random-sized blocks stratified by each site was prepared in advance by a study statistician and entered into a Research Electronic Data Capture (REDCap) [22] database. After informed consent is completed, the physician requests the study drug from the pharmacy staff member, who then prepares and delivers the assigned dose for administration. The subject is considered enrolled when the earlier of 2 possible events occurs, that is, the REDCap randomization module is invoked to generate a randomization code for the patient, which code will then be relayed to the pharmacy, or the pharmacy dispenses a study drug dose based on the sequential randomization scheme. Nursing staff administers the dose regardless of the time since the initiation of treatment.

Study Drug Administration

Acquisition

The specific study agent used in this pilot trial is magnesium sulfate in water for injection, a sterile, nonpyrogenic solution of magnesium sulfate heptahydrate in water. The study agent is acquired by each hospital's research pharmacy from a common manufacturer as a solution of magnesium sulfate in water at 80 mg/mL. This agent is the commercially available preparation of IVMg and is shipped directly from the manufacturer to each study hospital pharmacy.

Preparation, Storage, and Labeling

Doses for each IVMg arm are prepared in an identical manner by drawing a specified volume of IVMg from the commercial container using a sterile technique and mixing it in a syringe or a polyvinylchloride container with a specified volume of sterile water. For the 50 mg/kg arm, this is accomplished by mixing 25 mL of IVMg (80 mg/mL) with 15 mL of sterile water for a final concentration of 50 mg/mL and a volume of 40 mL. For the 75 mg/kg arm, this is accomplished by mixing 37.5 mL of IVMg (80 mg/mL) with 2.5 mL of sterile water for a final concentration of 75 mg/mL and a volume of 40 mL. For the placebo arm, 40 mL of 0.9% sodium chloride solution are drawn into a polyvinylchloride container identical in appearance to the containers used for the IVMg arms.

Each prepared dose is labeled according to the sequential randomization scheme and stored according to the local pharmacy procedure. Either the pharmacist draws equivolumetric dosages (1 mL/kg, with maximum of 40 mL) from the prepared vials, or the pharmacist delivers the full dose to the bedside study team with instructions for the volume to be delivered.

Dosing Arms

Enrolled subjects are randomized to 1 of 3 arms:

1. IVMg 75 mg/kg arm: 75 mg/kg (maximum 3 gm, 40 mL) infused over 20 minutes through a peripheral IV catheter
2. IVMg 50 mg/kg arm: 50 mg/kg (maximum 2 gm, 40 mL) infused over 20 minutes through a peripheral IV catheter
3. Placebo arm: 1 mL/kg (maximum 40 ml) of normal saline over 20 minutes through a peripheral IV catheter

Dose Modification for Potential Toxicity

Clinicians are not to administer IVMg to enrolled subjects outside of the study protocol until study outcomes are determined 2 hours after the start of the infusion. The half-life of IVMg is approximately 2 hours [18]. Repeated-dose protocols

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in an intensive care unit setting that gave as much as 125 mg/kg IVMg to children with asthma over 2 hours produced no hypotension or other serious adverse effects [23]. Because of this margin of safety, open-label IVMg 50 mg/kg can be administered safely 2 hours after the study infusion under strict study monitoring protocols without the need for unblinding.

Unblinding Procedures

If a patient's asthma symptoms deteriorate before 2 hours, clinicians are instructed to assume that the subject received the highest dose of active study drug and that they can give IVMg at a dose as high as 50 mg/kg open-label as soon as 120 minutes after the start of initial study infusion without unblinding, which would result in a maximum of 125 mg/kg over 2 hours if the patient is in the 75 mg/kg arm. Other interventions are given as needed in response to the patient's condition. If unblinding is considered necessary, allocation information can be obtained from the site pharmacist, and unblinding is considered a study protocol violation.

Discontinuation of Study Drug

If hypotension is measured and perfusion is impaired (see Data Collection section), study infusion is stopped, clinicians give a 20 mL/kg bolus (maximum 1 L) of isotonic IV fluid and provide other interventions at the clinician's discretion. If perfusion is normal, study drug infusion is continued at the same rate.

Withdrawal From Study

Subjects are observed in the ED for a minimum of 2 hours after the start of study infusion unless they require transfer to the intensive care unit due to escalation of therapy. Parents can withdraw permission for their children to continue in the study at any time. If a parent or child chooses not to continue in the study during study infusion, the infusion of the study drug is stopped. All patients who withdraw are followed for AEs and other symptoms.

Data Collection

Baseline Data

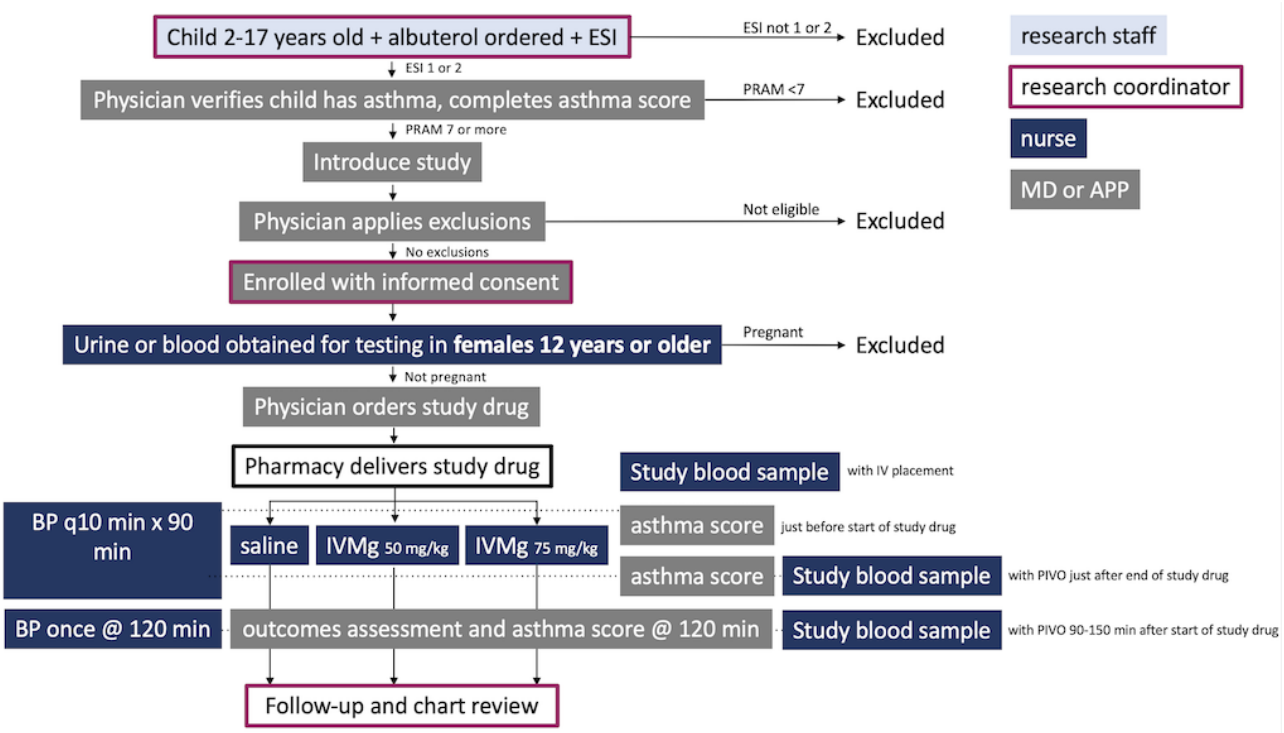
The research staff who approaches the patient for enrollment gathers baseline information from the child's parent or guardian, including age, sex, race, ethnicity, chronic asthma control status and medications, treatments received for the current illness before ED presentation, and chronic medical conditions. The research staff member also collects data from the treating ED team, including the following items:

- Scoring: The treating physician completes a clinical asthma scoring instrument that includes the components of the PRAM immediately before, 20-40 minutes after, and 2 hours after the start of study infusion.
- Blood samples: They are drawn by clinical staff through the IV before the start of study infusion, then through the IV using a PIVO blood-drawing device (BD Medical) 20-40 minutes and 90-150 minutes after the start of study infusion. When the blood draw is not possible using PIVO, blood is drawn through the existing peripheral IV if possible.
- Blood pressure: It is measured by the study staff using an automated device just before the start of study infusion (within 10 minutes before the start of infusion), every 10 minutes (±4 minutes) for 90 minutes following the start of infusion, and once more 2 hours (±10 minutes) after the start of study infusion.
- Perfusion: If age-adjusted hypotension is detected, a treating clinician, which could be the treating nurse, completes a standardized assessment of perfusion based on World Health Organization criteria [24]. This assessment is then reviewed with the research staff. If perfusion is impaired during study drug infusion, study drug infusion is stopped.
- Timing: The research staff records time points of screening, identification, consent, and randomization, as well as times of infusion and blood draws, using the nurse's documentation.
- Disposition: The research staff approaches the treating physician 2 hours after the start of study infusion and collects the stated disposition for the patient (hospitalization, discharge home, or uncertain), at which point study procedures are finished for the ED visit (see Figure 3).

Plasma is separated by centrifugation, transferred to a separate vial, stored at -80 C, and shipped to the study laboratory at the University of California, Davis

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Figure 3. Schedule of Activities. APP: Advanced Practice Provider; BP: blood pressure; ESI: Emergency Severity Index; IVMg: intravenous magnesium sulfate; MD: physician; PRAM: Pediatric Respiratory Assessment Measure.



Follow-Up Assessments

For patients discharged to home, study staff calls or texts the family in 12-48 hours and in 1 week (5-10 days) to determine if they returned to any ED, the outcomes of any return visit, and to assess for AEs. All data points initially recorded on paper forms are securely stored and then entered into a REDCap database created by the Emergency Medical Services for Children Data Center (EDC) at the University of Utah.

Medical Record Review

Study staff reviews the electronic medical records of all subjects 1 week after enrollment to determine the actual patient disposition and hospital course.

Instruments

The PRAM is outlined in Table 1 and section 3 of Figure 1.

Data Analysis

Specific Aim Analyses

Specific Aim 1

Demonstrate the feasibility of enrolling children in the ED with severe acute asthma in a multicenter RCT of a placebo, low-dose IVMg, or high-dose IVMg.

For the primary study hypothesis, we will identify, consent, and enroll 90 patients in 7 months or less. Our experience with previous trials within PECARN suggests a 7-month enrollment period is adequate to reach a stable rate of enrollment and demonstrate trial procedures. Because the future large RCT will need multiple sites for adequate enrollment, this pilot trial is testing trial procedures at 3 sites with various patient volumes, research infrastructures, and patient populations. Based on the projected 8% of asthma visits in the PECARN Registry that would qualify based on previous volumes at study sites, we anticipated that approximately 360 patients would qualify for the study during the 7-month study period, allowing for study completion even if only 25% of qualifying patients were enrolled. The study is expected to end once 90 patients are enrolled, even if this occurs in less than 7 months, but will not enroll for more than 9 months. An enrollment rate of 90 patients in 7 months for 3 sites would be sufficient to conduct a future trial powered to detect a difference in hospitalization, enrolling 800 patients in 23 months at 10 sites. A slower rate will prompt an adjustment of future trial length.

Specific Aim 2

Demonstrate the feasibility of timely delivery of study medication to enrolled patients and assessment of blood pressure and associated AEs in a standardized protocol.

Our first objective in this aim is to assess our ability to administer the study drug within 90 minutes after the start of asthma treatment. Timely delivery of study drug is considered feasible with current study procedures if 90% of study subjects received study medication within this time frame, giving time for study intervention to affect hospitalization and making hospitalization an outcome appropriate for the future trial. Delivery of study drug to less than 90% of study subjects indicates a need to further refine study procedures before the larger trial. We will optimize the delivery of study drug in the future trial by examining the impact of factors in the pilot trial that may influence study drug delivery. Factors associated with time to first study drug administration, administratively censored at 180 minutes, will be explored using Cox proportional hazards modeling. The Cox models are intended to identify features

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requiring additional planning to promote timely delivery rather than to find statistical significance.

Our second objective in this aim is to inform a safety monitoring plan for the future trial that is focused, clinically feasible, and effectively protects patient safety. We intensively monitor blood pressure (every 10 minutes) during the pilot trial for 90 minutes after the start of study drug infusion (see Data Collection section) and record all AEs from the time of randomization until the follow-up call approximately 1 week after enrollment. All serious, unexpected, and related AEs that are unresolved at the time of the patient's termination from the study or discharge from the hospital will be followed by the Clinical Center investigators until the events are resolved, the subject is lost to follow-up, the AE is otherwise explained or has stabilized, or 12 months have passed from the time of last study dose.

We consider the procedures of the pilot trial feasible for the larger trial if we can collect 90% or more of planned data points related to blood pressure. This collection rate would indicate that this data gathering does not pose an undue burden on the teams providing clinical care to study patients. We will use the degree to which data points are collected in coordination with the frequency and timing of blood pressure changes, the frequency and degree of age-adjusted hypotension and poor perfusion, interventions delivered to patients with measured hypotension, and other recorded adverse effects to devise a monitoring plan for the future trial that captures all AEs and is maximally feasible.

Specific Aim 3

Externally validate a previously constructed PK model and develop a combined PK/PD model for IVMg using magnesium (total and ionized) serum concentrations and their correlation with measures of efficacy (respiratory distress) and safety (adverse effects) in children with asthma.

We will use these data to validate a PK/PD model that will guide dosing for the large trial. Ideal external validation of our previous PK model requires blood samples from a minimum of 30 patients who receive IVMg at sites outside of the site used to derive the PK model [18]. For an enrollment of 90 subjects, we anticipate approximately 40 subjects to meet this criterion. Data from the samples collected in this study will be used to externally validate our previously developed population PK model and, if needed (ie, median prediction error >15% or <−15%; median absolute prediction error >30%, calculated as the median of the values obtained from equations 2 and 3 for all collected samples), update the model with this larger sample size. Concentration analysis, PK model validation, and updating our previous PK model (if needed) will use similar approaches as we have previously described [25]. Notably, this includes accounting for endogenous magnesium concentrations (Equation 1) assumed to be at steady-state before IVMg administration.



Once the PK model has been confirmed (or refined, if necessary), we will incorporate PRAM scores and other measures of respiratory distress to develop a population PK/PD model describing the relationship between IVMg systemic exposure and clinical response. Additionally, we seek to construct a PK/PD model describing the association between IVMg systemic exposure and AEs, including hypotension. PK/PD modeling will use NONMEM software (version 7.3, ICON Development Software). The first-order conditional estimation with the interaction method will be used throughout model building and evaluation. Model selection will be based on parsimony, objective function value (OFV), and visual diagnostic plots. Direct and indirect approaches to incorporating PD will be tested. After determining the base model, covariates will be tested for impact on PD using a forward inclusion (P<.05) and backward exclusion (P<.01) method. Covariates will be added to the model in a stepwise fashion and allowed to remain in the model if covariate inclusion decreases the OFV by at least 3.84 and its exclusion increases the OFV by at least 6.63. Once the final PK/PD model is determined, we will evaluate model accuracy and robustness through bootstrapping methods and visual predictive checks.

Dose-exposure response data simulated (1000 data sets) from the PK/PD model will be used to select doses used in the future large trial. Specifically, we will use the simulated data sets to determine the dose at which 10% of participants are expected to have adverse effects (ie, hypotension) and establish an upper limit of dosing for the future trial. Importantly, this analysis will allow us to evaluate the role of an upper dose limit (ie, the 2 or 3 gm maximum dose, regardless of patient weight) in preventing hypotension. Similarly, we will use the simulated PK and PD data to define doses expected to yield 20%, 40%, and 60% reductions in PRAM and hospitalization, respectively. We plan to target the use of these doses in the future study as the doses that are expected to maximally reduce hospitalization.

If we are unable to build a robust population PK/PD model using NONMEM, we will evaluate correlations between PK and PD using Pearson correlation analyses in GraphPad Prism version 6.05 (or later) software. In this scenario, the population PK model will be used to identify doses that generate simulated concentration data within the target therapeutic range established by the correlation analyses.

Per the PECARN Registry, approximately one-fourth of children receiving IVMg for asthma weigh more than 40 kg, the weight at which a 2 gm (50 mg/kg) or 3 gm (75 mg/kg) dose is reached. As a result of this maximum, children weighing more than 80 kg (low-dose arm) or 120 kg (high-dose arm) would implicitly have an intended dose less than 25 mg/kg IVMg, below the lower end of the range of doses in the guidelines. As a drug that exhibits first-order kinetics, delivering IVMg with an arbitrary maximum may reduce the benefit of the drug in a substantial portion of children. We will use the newly developed PD model and validated PK model to determine if patients above 40 kg have less improvement in clinical score and if any associations found are related to changes in serum values.

Sample Size Calculations and Statistical Power

Sample size for this pilot trial was driven by the first aim, which is to demonstrate the ability to enroll children severely ill with asthma in an RCT. The second aim is focused on the feasibility of study drug delivery and the collection of safety data, and the third aim is focused on pharmacologic modeling for dose

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estimation to be used in the large trial to follow this pilot trial. All 3 aims of the pilot trial are focused on generating data to inform the structure of the larger trial to follow, and accordingly, they do not have sample size calculations or associated calculations of statistical power.

Protection of Human Subjects

Ethics Approval

A single investigational review board (IRB) was used for this study. Study sites relied on the University of Utah IRB to act as the IRB of record (IRB #00104082). The EDC and each clinical center obtained IRB approval before participating in the study.

Risk Benefit Assessment

Asthma is a leading cause of hospitalization in children and incurs substantial costs for the health care system [1]. Previous trials of IVMg in children with asthma were too small to conclude whether IVMg can reduce hospitalization in children with asthma. To date, these small trials of IVMg in acute asthma have not been followed by larger, conclusive trials. Comparison to placebo in a large trial is needed to evaluate the effect of IVMg on hospitalization.

Risks of IVMg have been described in previous literature but not sufficiently to dismiss them as minor. This study will help ensure that monitoring for children enrolled in future trials is feasible and complete.

Considering the potential benefits and the anticipated risks, the research outlined in this proposal will provide important evidence to guide the care of children with asthma. By clarifying the efficacy, safety, and dose of IVMg for children with asthma, these results will influence the care provided to severely ill children with asthma nationally and globally through inclusion in NHLBI guidelines and other guidelines such as those developed by the Global Initiative for Asthma.

Population to Be Studied

The enrollment of patients in this trial is expected to reflect the population of children with severe acute asthma at each of the enrolling sites with respect to age, sex, race, and ethnicity.

Data and Safety Monitoring Plan

Data Safety Monitoring Board (DSMB)

Each clinician caring for a study patient had primary responsibility for the safety of the individual subjects under his or her care. A DSMB was established before the initiation of enrollment. The DSMB consisted of 3 members, 1 of whom had statistical expertise and 2 of whom had experience in emergency medicine. All individuals had experience in the conduct of randomized clinical trials and had no direct association with the clinical sites in the trial or other conflicts of interest that would interfere with their objectivity. We did not anticipate having sufficient interim data during the trial for the DSMB to reach conclusions regarding efficacy or safety, though safety data were considered in interim analysis. The DSMB is responsible for approval of the final study design, reviewing and analyzing the progress of the study, monitoring the safety of the study treatments (as outlined below), and reviewing reports of data quality. The DSMB met before the first site was activated for enrollment and again after approximately 30 subjects were enrolled. The DSMB, or study principal investigator (PI), had the power to request additional meetings. The DSMB has the power to halt the study if safety reasons exist.

Study-Specific AE definitions

Hypotension is defined as any systolic blood pressure (mm Hg) meeting the following age-specific norms [19]:

1. Children 1-10 years: <70 + (age in years × 2)
2. Children >10 years: <90

Measured hypotension without associated symptoms is categorized as a mild AE; the presence of symptoms is categorized appropriately based on the degree of impairment of activity.

A serious AE is defined as any experience that results in death, is life-threatening, results in prolongation of existing hospitalization, results in a permanent disability, results in congenital anomaly/birth defect, or any other event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

Investigational New Drug Application Information

Investigation of IVMg in this study is supported and supervised by the Food and Drug Administration (FDA) through Investigational New Drug Application No. 133781.

Study Training

A formal training program for investigators and research staff was held before the start of enrollment. The training covered regulatory topics, including applicable drug regulations and training in good clinical practice. The training provided in-depth explanations regarding study procedures, clinical care, AE reporting, data entry procedures, quality assurance, site monitoring, and the informed consent process. A manual of study operations was created and provided to each site investigator before the start of enrollment. The manual detailed specific information about the study procedures, regulatory information, safety reporting, and other necessary information. Updates and revisions to the manual were made available electronically. The EDC, in collaboration with the study PIs and clinical coinvestigator (MDJ, JJZ, and Dr Shihabuddin), was the main contact for study-related questions.

Before the start of enrollment, lead investigators and each site's research coordinator, along with EDC staff, met virtually or in person for a training session. Each site investigator instructed the ED physicians at their home institutions about the study procedures, provided training on the PRAM score, served as a local advocate and champion for the study, and answered questions as they arose. Throughout the study, the study investigators and research coordinators have at least monthly scheduled telephone conference calls or webinars for all study personnel and more frequent group communications, as necessary. BD Medical conducted training on the use of PIVO

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with blood-collection staff before subject enrollment at each site.

Monitoring of the research activities conducted during the pilot trial is supported by quality assurance visits conducted regularly by the nodal administrators of the involved PECARN sites, including regular assessment of support and funding for study effort and preparation for monitoring by the EDC and other data regulatory bodies, including the Food and Drug Administration. Each quality assurance visit is followed by a joint discussion with the site PI and study staff to define isolated, structural, or study-related barriers to study success.

Public Use Data Set

After subject enrollment and follow-up have been completed, the EDC will prepare a final study database for analysis. A releasable database will be produced and completely deidentified in accordance with the definitions provided in the Health Insurance Portability and Accountability Act (HIPAA). Namely, all identifiers specified in HIPAA will be recorded in a manner that will make it impossible to deduce or impute the specific identity of any patient. The database will not contain any institutional identifiers.

The EDC will also prepare a data dictionary that provides a concise definition of every data element included in the database. If specific data elements have idiosyncrasies that might affect interpretation or analysis, this will be discussed in the dictionary document. In accordance with policies determined by the investigators and funding sponsors, the releasable database will be provided to users in electronic form.

Results

The project was funded in March 2022, began enrollment in September 2022, will stop enrollment no later than the end of May 2023, and we expect to submit results for publication in late 2023.

Discussion

Overview

The study design for this pilot trial mirrors the design that we expect to use in the larger, conclusive trial. The future trial will be powered to evaluate the effect of bolus IVMg on hospitalization and will be conducted at more sites, while the pilot trial is designed to demonstrate feasibility and collect safety and pharmacologic data needed to optimize the design of the future trial. In this pilot trial, we seek to shift current research paradigms regarding the application of pharmacologic principles to pediatric clinical trials. More pharmacologic rigor in trials which include children would result in improved pharmacotherapy for children. In this project, we incorporated 3 key related innovations that improve our ability to integrate pharmacologic principles into the future large trial, and pediatric clinical trials in general.

First, we implement improved collection of study blood samples with less pain using a clinical device, which circumvents the need for repeated venipuncture for blood samples. Medication dosages used in children generally rely on prescribing data derived from adults, in small trials, or by group consensus [26]. Even when medications are tested in children in a trial, inadequate consideration of dosing is the most common reason a trial fails [27]. Defining appropriate pediatric doses within a trial requires repeated serum samples. Historically these samples were collected using repeat venipuncture to measure serum concentrations to inform PK models. This was how samples were collected during routine clinical care to inform the model we previously constructed using retrospective clinical data [18]. Pain and distress are the most common reasons for a child to reject participation in a trial, and children commonly experience pain and distress during venipuncture [28]. As a result, many studies do not collect the PK data needed to define dosing, and most previous trials of IVMg in children did not obtain serum samples. The 3 trials that obtained samples obtained only 2 per subject [13,14,29], insufficient for robust pharmacologic analysis or modeling. This current state of dose planning in trials involving children presents a pressing need to identify innovative strategies to collect serum samples from children while avoiding the pain and distress of venipuncture. The PIVO device is currently used clinically to facilitate repeat blood draws without repeat venipuncture, but it is not widely used in clinical research aside from a prospective study we conducted to validate our PK model [25]. As expected from our previous single-site study, we expect that use of the PIVO device at all sites in the pilot trial will reduce harm to children who participate in the trial, increase acceptability to children and parents (35/50, 70% of eligible children were enrolled in our previous study), and result in higher sample collection rates than expected with repeat venipuncture or drawing blood from the existing IV (29/35, 83% with 3 samples in our previous study using PIVO vs 97/308, 31% in previous PECARN studies).

Second, we incorporate trial optimization and dose finding in pediatric asthma guided by PK/PD modeling. Previous trials of IVMg in children with asthma in the ED did not use pharmacologic principles to select an optimal dose for evaluation. Though pharmacologic principles have been used to select dosages for many trials in children and adults, our application of PK and PD methods to the study of pediatric asthma in the ED is novel. Our team's preliminary studies in the ED demonstrated our ability to collect and analyze pharmacologic data, and we used these data to select doses for the pilot trial with maximal rigor. We will use the PIVO device to enable the collection of repeat serum samples, and we will use the data from our samples to integrate and refine our PK and PD models to optimize the doses we select for the future large conclusive trial.

Third, we evaluate early administration of intensive asthma treatment in a trial setting. Previous trials did not attempt to deliver the study drug to children with asthma early in the ED treatment. This reflects an outdated clinical paradigm of pediatric acute asthma treatment based on administering intensive treatments only when initial treatments have been ineffective. Though this is generally how care delivery is outlined in clinical guidelines published in 2007 [2], subsequent evidence supports the administration of continuous beta-agonists [30], steroids [31], and IVMg [32] *as early as possible for patients with severe illness*. Improving the timeliness of

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treatment delivery is a major focus of quality improvement in the ED care of children with asthma [33,34]. Early administration of intensive treatment to children with asthma in this project is a novel application of high-quality clinical care delivery in a trial setting.

Previous trials of IVMg are insufficient to guide the clinical use of IVMg. The equipoise needed to study the effect of IVMg versus placebo on hospitalization in a large clinical trial is illustrated by a combination of possible but uncertain clinical benefits for ill children, variation in clinical use, lack of consensus regarding clinical benefit, and evidence gaps from previous trials. IVMg is inexpensive, readily available, and widely used in current clinical settings, but it lacks evidence to guide its current use for children with asthma.

Limitations

A large trial in children severely ill with acute asthma, like other clinical trials in acutely ill children, is at risk of low patient accrual if not properly planned and conducted [26], including the risk that physicians may hesitate to enroll patients being randomized to either study therapy or placebo. With this trial, we will further the previous expertise of PECARN in conducting research on severely ill children. The trial outlined in this proposal represents a novel challenge for this network by requiring rapid enrollment after patient arrival, providing an opportunity to understand and manage these risks and challenges in the future trial.

Parental consent may be a barrier to enrollment, although consent in previous trials of children with acute respiratory illness conducted in PECARN has been obtained at rates of approximately 50% [35]. This pilot trial is structured to allow enrollment of our sample size during our 7-month study window even if only 25% of the estimated number of eligible patients consented and enrolled, though the number of patients eligible for enrollment could differ due to episodic variations in asthma illness that cannot be controlled or anticipated.

This pilot study anticipates 3 blood draws per patient: 1 with IV placement and 2 from the IV after infusion of study drug. Repeat blood draws from an IV avoid additional venipuncture but are at risk for failure or loss of the IV line, which would result in fewer than anticipated serum measurements. In a previous study of IV benzodiazepines conducted in PECARN [36], 64% (197/308) of patients successfully had multiple blood draws from a single IV (internal data). During preliminary study at 1 of the study sites [25], the PIVO vascular access device for IV blood draws allowed 2 consecutive blood draws from a peripheral IV in 90% of patients and 3 consecutive blood draws in 83%, which was adequate for trial procedures.

Conclusions

IVMg has the potential to improve the outcomes of ED treatment for children with severe acute asthma but requires further evaluation of its efficacy, safety, and optimal dosage in a robust pediatric trial setting. More broad and standardized use of IVMg, if effective, may reduce hospitalizations and related health care costs for children and would be cost-effective. An economic analysis of children with asthma at 2 hospitals concluded that the use of IVMg reduced costs by 28% and increased quality-adjusted life years [37]. If IVMg is found to not be effective in a well-powered clinical trial, its use could be appropriately guided and restricted by the trial's results, future investigations can focus on other therapies, and these findings should be included in institutional and national asthma guidelines. This pilot trial will provide important information to guide a larger, conclusive trial that can fully evaluate the effect of IVMg on hospitalization of children with severe acute asthma.

Acknowledgments

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Data Availability

Within 6 months of final patient contact and within 3 months of data lock, the data sets generated and analyzed during this study will be prepared by the EDC as a deidentified database accessible for public use [38].

Conflicts of Interest

None declared.

Multimedia Appendix 1
Most recent peer review of protocol by National Heart, Lung, and Blood Institute.

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[PDF File (Adobe PDF File), 142 KB - resprot_v12i1e48302_app1.pdf]

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Abbreviations

AE: adverse event
DSMB: Data Safety Monitoring Board
ED: emergency department
EDC: Emergency Medical Services for Children Data Center
HIPAA: Health Insurance Portability and Accountability Act
IRB: investigational review board
IV: intravenous
IVMg: intravenous magnesium sulfate
NHLBI: National Heart, Lung, and Blood Institute

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OFV: objective function value
PD: pharmacodynamic
PECARN: Pediatric Emergency Care Applied Research Network
PI: principal investigator
PK: pharmacokinetic
PRAM: Pediatric Respiratory Assessment Measure
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture

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Protocol

Effectiveness of a Community Empowerment Intervention to Improve Access to Pre-exposure Prophylaxis in Migrant Women Sex Workers: Protocol for a Mixed Methods Implementation Study

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Abstract

Background: The World Health Organization recommends pre-exposure prophylaxis (PrEP) for all populations at substantial risk of HIV infection. However, at-risk women very rarely use PrEP in France—this represents a critical issue among migrant women sex workers (MWSWs). Previous studies on PrEP use among women sex workers or migrants focused on individual or social determinants of motivation. However, operational studies in real-word settings using a holistic population approach to maximize PrEP adherence among MWSWs are lacking.

Objective: FASSETS (ie, "Favoriser l'Accès à la Santé Sexuelle des Travailleuses du Sexe"; English: "facilitate the access to Sexual Health in women sex workers") is a participative, multilevel, mixed methods study aiming to improve global knowledge of and access to sexual health care and PrEP among MWSWs through targeted empowerment strategies.

Methods: This study comprises several phases: (1) phase 1: an initial qualitative study combining semistructured interviews, informal interviews, and participative observations will be performed among MWSWs, local community nongovernmental organizations, and institutions providing sexual reproductive health services to identify the determinants of PrEP access among MWSWs and for respondent-driven sampling (RDS); (2) phase 2: the size of the hidden MWSW population is estimated in Marseille through capture-recapture (the RDS survey will serve as "recapture"); (3) phase 3: a longitudinal cohort will be formed through RDS to represent the MWSW population with a goal of 150 inclusions—this cohort will be followed up for 12 months, and sequential questionnaires exploring medical history; knowledge of sexual health, HIV, and sexually transmitted infections; migration route; and current living conditions will be administered at inclusion (month 0) and months 3, 6, and 12 to measure the following interventional phase's outcomes; and (4) phase 4: an interventional study with community empowerment actions

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about sexual health and PrEP will be conducted with community health workers; standardized questionnaires and semistructured interviews, observations, and focus groups will highlight MWSWs' experiences with empowerment resources, concerns about sexual health, and especially PrEP use or uptake, and we will evaluate whether and how community-adapted empowerment actions conducted by community health workers are effective in increasing access to sexual health, prevention and screening of sexually transmitted infections, and PrEP knowledge and access among MWSWs.

Results: Recruitment commenced on March 1, 2022. We estimate the follow-up period to end on September 30, 2023.

Conclusions: This multiphase study will provide robust evidence about the magnitude of the MWSW population in Marseille (the second largest town in France) and their current conditions of living, access to and knowledge of sexual health, and PrEP access. Using a mixed methods analysis, we will investigate whether individual and collective community health empowerment approaches can facilitate access to PrEP and its initiation, use, and adherence in this vulnerable population.

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KEYWORDS

community empowerment; sexual health; implementation science; migrants; women; sex workers; mixed methods; pre-exposure prophylaxis; PrEP; treatment; intervention; France; care; healthcare; health care; community

Introduction

In contrast to the population of men who have sex with men, where HIV incidence has decreased owing to pre-exposure prophylaxis (PrEP—taking antiretroviral drugs to prevent HIV infection), estimates of HIV incidence have not decreased in migrant populations in France and other European countries [1,2]. Indeed, the highest incidence of HIV infection has been currently reported in migrants in France [2]. Moreover, when living with HIV, migrants also tend to be diagnosed later than nonmigrants [3,4]. In this context, a recent French study has shown that a majority of migrants (58%) contracted HIV within 6 years after arrival [5], confirming previous results showing that migrants living with HIV in Europe frequently contracted the virus post migration [6-8]. In this French study, HIV acquisition after migration was linked to short or transactional partnerships and the lack of a residence permit [5]. These results highlight the economic and social determinants of HIV exposure in this population. Another study showed that in France, the majority of migrants do not know about PrEP as a tool for HIV prevention [9].

HIV prevalence among cis- or transgender women engaged in transactional sex (women sex workers [WSWs]) is substantially higher than that in similarly aged women worldwide [10,11]. Consequently, migrant WSWs (MWSWs) are at a particularly high risk of HIV infection, and progress toward the global target of HIV elimination will not be possible without interventions and programs aimed at them.

Previous studies on HIV prevention programs have specifically targeted WSWs, and PrEP has emerged as a potentially effective option for HIV prevention in this population, with most studies being performed in transitional countries [12]. PrEP is highly effective in reducing HIV incidence in this population with appropriate individual compliance [13]. Unfortunately, 2 PrEP trials among cisgender women in Africa were stopped early due to suboptimal adherence [14,15]. The subject of adherence and its determinants is of tremendous importance in this population [12]. As with HIV risk factors, determinants of PrEP use in WSWs arise from multiple social and biological factors [9,14,16]. MWSWs face structural factors associated with a precarious immigration status, migration, and occupation-related marginalization [11]. A systematic review among WSWs has stressed the need for comprehensive care in order to increase the use of and adherence to PrEP [12,17]. However, few studies have investigated how to implement community-based interventions to promote PrEP access and health equity within this vulnerable population [11]. Indeed, there is a need to develop interventions with a holistic approach, including specific clinics and social services [12,18]. Another key element is to implement a prevention intervention based on community empowerment, in which MWSWs take collective ownership of knowledge of and resources about sexual health [19].

In France, as in other European countries and the United States, women represent a minority of PrEP users (less than 3%) [20-22]. Marseille is France's second largest city and one of the poorest (with 200,000 people living with less than €1000 [US $1086.26] per month) located on the Mediterranean coast [23]. In 2018, overall 12% of Marseille's population (192,330 inhabitants) was born abroad and statistically considered a migrant population with 28% of them born in northern Africa and 14% of them born in sub-Saharan Africa [24]. These figures do not take into account undocumented migrants. Among 2197 people consulting for PrEP at the 10 medical centers for sexual health and prevention (managed by the departmental council of the Bouches du Rhône—an area of Marseilles and its suburbs) between 2016 and 2022, only 7 were MWSWs [25].

The objectives of the FASSETS (Favoriser l'Accès à la Santé Sexuelle des Travailleuses du Sexe) study are to (1) analyze the individual and structural determinants of the access to sexual health care and notably PrEP among MWSWs working in Marseille, (2) estimate the size of the MWSW population in Marseille, and (3) follow up with a representative cohort of 150 MWSWs to evaluate the effectiveness of a holistic approach based on community empowerment interventions targeting MWSWs to improve PrEP use.

For this purpose, we designed a mixed methods study comprising the following: (1) a study in the field with community health workers (CHWs) evaluating the determinants

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for the access to PrEP, (2) a capture-recapture method with respondent-driven sampling (RDS) to estimate the size and characteristics of a hidden and stigmatized population, (3) formation of a longitudinal cohort of MWSWs that will be followed up for 12 months, and (4) an intervention study involving CHWs to apply an empowerment strategy and evaluate its results with regard to the number of MWSWs taking PrEP at the end of the follow-up period.

Methods

Overview

Phase 1 of the FASSETS study is a qualitative multilevel evaluation of facilitators and barriers to PrEP access for MWSWs in Marseille, which will last 12 months before the intervention begins (Figure 1).

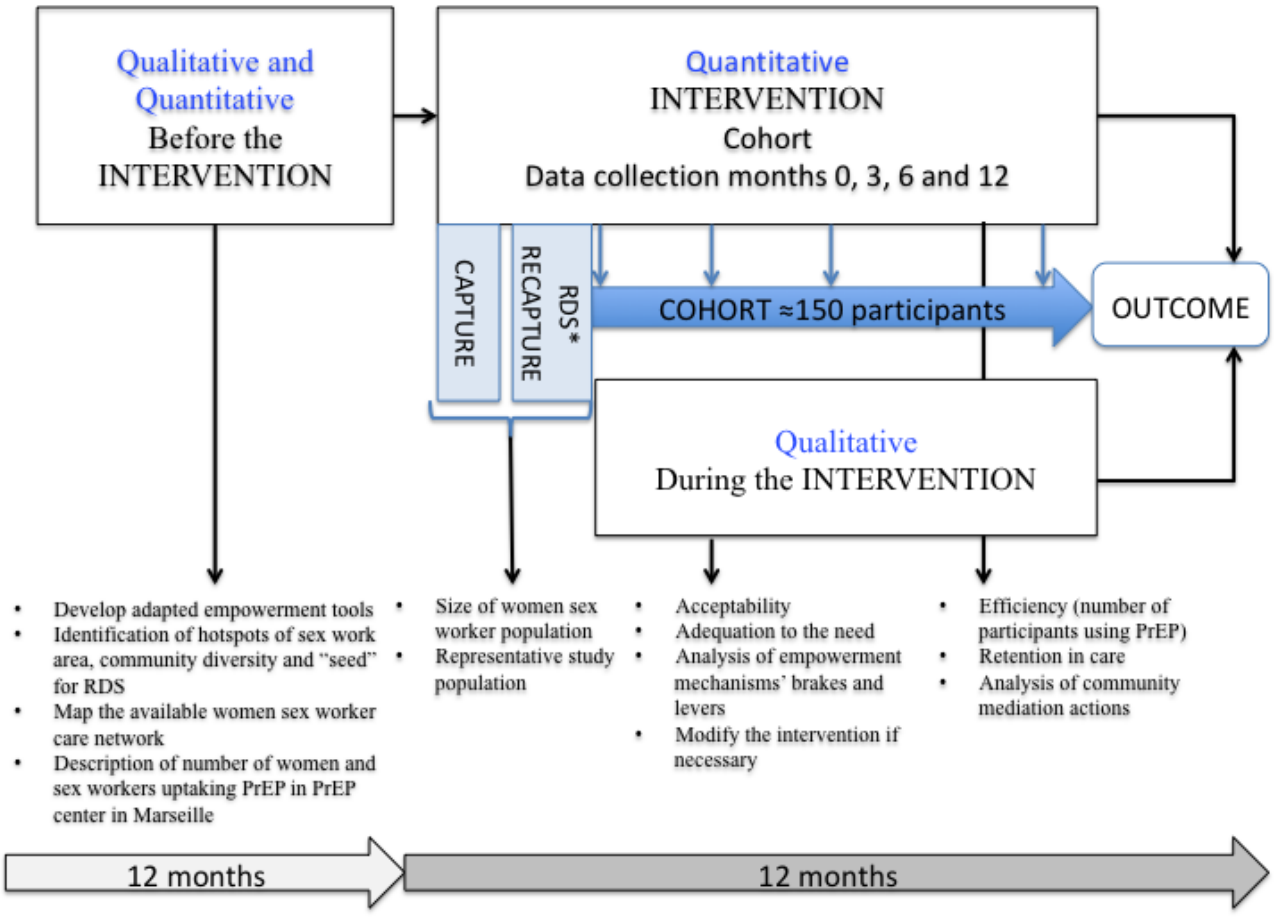
Phase 2 will be a capture-recapture study to evaluate the size of the MWSW population in Marseille (Figure 1).

Phase 3 will involve the formation and follow-up of a representative cohort of 150 MWSWs.

Phase 4 will be the community empowerment intervention by CHWs provided to the 150 MWSWs of the cohort recruited through RDS (Figure 1).

The intervention by CHWs will consist of facilitating knowledge and PrEP uptake but also more generally to facilitate access to health care and social services as needed, using an individual and longitudinal follow-up and collective empowerment actions.

Figure 1. Mixed methods model of intervention analysis. PrEP: pre-exposure prophylaxis; RDS: respondent-driven sampling.



Objectives of the Different Phases of the Study

Phase 1 will describe the determinants of PrEP uptake in MWSWs with a multilevel approach including individual, collective, and institutional analysis.

Phase 2 will determine the size of the MWSW population in Marseille.

Phase 3 will describe attitudes, knowledge, and practices of sexual and reproductive health (SRH) among MWSWs, health care pathways and mobility, testing for sexually transmitted infections, and prevalence and frequency of screening in the MWSW population at month 0 and their evolution during follow-up.

Phase 4's primary objective is to analyze access to PrEP and retention in care through a community empowerment follow-up of MWSWs. Secondary objectives will be to document individual and collective empowerment tools for MWSWs and to describe CHW interventions for MWSWs.

Key Outcomes for Each Phase of the Study

The key outcomes of phase 1 will be the analysis of the verbatim responses of MWSWs and institutional actors about the

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determinants of PrEP use, those of phase 2 will be the estimated number of MWSWs in Marseille, those of phase 3 will be the number of MWSWs included in the longitudinal study and quantitative analysis of the questionnaire data, and those of phase 4 will be the number of consultations for sexual health, access to rights, and PrEP uptake among MWSWs before and after the interventional phase.

Study Population

The FASSETS study will take place in Marseille, which is the second largest city in France, and a significant proportion of its population has precarious living conditions [26]. The FASSETS study was developed in collaboration with the nongovernmental organization (NGO) AIDES and a Nigerian community NGO for women (The Truth), which provides HIV prevention and testing services to MWSWs.

Phase 1: Qualitative Assessment

Qualitative data collection will be carried out separately with a trained qualitative researcher. Qualitative interviews will be conducted following semistructured interview guides in private with selected participants representative of the cohort, in focus groups, and in a multilevel assessment with doctors and social workers in the field. These interviews will be carried out to document the determinants for PrEP access in MWSWs.

Phase 2: Estimation of the Sample Size of the Hidden Population of MWSWs by Capture-Recapture

Population size estimation is a challenge because the MWSWs are hidden and difficult to reach. Hence, capture-recapture is recommended to estimate the size of the MWSW population in Marseille [27,28]. The estimation will be based on the following equation:

$$N=(n1\times n2)/m$$

where $n1$ is the number of MWSWs who received a token (capture), $n2$ is the number of MWSWs included in the RDS study (recapture), and m is the number of participants common to both groups (MWSWs with a token). Tokens (safety whistle: a little emergency whistle with a flashlight) will be distributed over a period of 15 days by the NGOs and institutions but also directly to the MWSW network. Indeed, distribution of safety whistles will serve as a first "capture" and the RDS survey will serve as "recapture." When participants visit the center for RDS enrollment, they will be asked if they had received a safety whistle; if they answer yes, the research team will ask them to identify the safety whistles from a group of photographs depicting different safety whistles. If the participants correctly identify the safety whistles from the photographs, they will be included as having received a safety whistle.

Phase 3: Representative Cohort Formation Through RDS and Follow-up

The inclusion criteria are being a cis- or transgender woman older than 18 years, self-reporting as having changed their sex for money or other resources during the past 12 months, having been born outside of France, living or working in the city of Marseille, and agreeing to participate in the study.

Numerous studies have demonstrated the effectiveness of RDS to engage adults in HIV research, particularly in stigmatized communities [29,30]. Initial RDS participants (ie, "seeds") will be recruited for the study to achieve good representativeness in terms of the type of community or nationality, sex work (eg, indoor, outdoor, via the internet), place of residence in Marseille, and gender (cis- or transgender women). The prior qualitative study will make it possible to clearly define the characteristics of representativeness. Approximately 150 participants are expected to be enrolled in the cohort. At the beginning, participants will be offered 3 coupons. Participants who meet the eligibility criteria will be provided with a food coupon worth €10 (US $10.86) for completing each part of inclusion and follow-up (at months 3, 6, and 12), and another food coupon worth €10 (US $10.86) for each eligible and participating peer recruited. In addition, FASSETS study participants will be given public transport tickets, free condoms, and lubricating gel.

Phase 4: FASSETS Community Empowerment Intervention and Follow-up Program

Empowerment Framework

There are many definitions of participant empowerment in the literature [31]. In this study, empowerment intervention will be defined as a process by which MWSWs take collective action to achieve the most effective SRH outcomes and address social and structural barriers to their health and human rights [32]. Most effective SRH effects have been defined in accordance with national and international guidelines [33,34]. The main outcomes are related to a decrease in the number of sexually transmitted infections, unintended pregnancy and abortion, sexual violence, and an increase in the access to comprehensive, good-quality information about sex and sexuality and the ability to access sexual health care. The main goal is to mainstream migrant health access to include people-centered health services. Community empowerment programs conducted in many countries to reduce HIV risk among WSWs have previously proven their effectiveness [35]. In order to evaluate empowerment, 5 specific principles will be used, including improvement, democratic participation, community knowledge, evidence-based strategies, and capacity building [36].

Participant and Public Involvement

CHWs and peer workers were involved in the design of the structures survey, with special attention paid to the terms and methods of communication used during participant interviews.

Participants will be involved in the intervention phase in the design of individual and collective empowerment actions. CHWs will be involved in the dissemination plans of this study by communicating in public conferences and workshops with local and nationwide actors in the field.

Community-Based Participatory Research

Community-based participatory research is an approach to research that involves a collective, reflective, and systematic study in which researcher and community stakeholders engage in all steps of the research process with the goal of improving practice [37]. This approach to research is recognized as particularly useful when working with populations that

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experience marginalization—as is the case for MWSWs—because it supports the sharing of control over individual and group health and social conditions [37,38]. The FASSETS study was initially developed around 2 community NGOs, AIDES and The Truth, which provide SRH community interventions for MWSWs. In accordance with community-based participatory research principles, this study will involve partnership building, regular exchange among partners and community NGOs, and experience sharing among the researchers, CHW staff, and the MWSW community. A community-based participatory research approach could mitigate the intersecting forms of marginalization faced by MWSWs. Indeed, a participatory approach is of particular relevance in health equity research, in which cultural and socioeconomic differences among the community, health care givers, and researchers potentially impede the identification of problems and discovery of their causes [39]. Partnering with the community will by no means eliminate this barrier during the evaluation but can enhance understanding and increase insight into the social and physical conditions as well as policy environments that are impacting the health of the community [39,40]. During the program and results dissemination, researchers, community participants, partner NGOs, and CHWs could also participate in increasing the use of social and health service usage by MWSWs and in advocacy to improve the overall living conditions of MWSWs.

Implementation Study

The term “implementation research” describes the scientific study of the process used in the implementation of an initiative as well as the contextual factors that affect these processes [41]. This study aims to address the factors affecting the implementation of PrEP among MWSWs (such as health literacy, poverty, access to health, or traditional beliefs), the processes of implementation themselves (proposal, distribution, and follow-up of PrEP), and the outcome of the implementation under study. Indeed, the FASSETS study should be aligned with MWSWs’ needs and respond to the particularities of different communities. The study will be conducted in a real-world setting and will consider context and other factors that influence implementation. A qualitative study will help understand and document the PrEP empowerment actions in the FASSETS cohort and to describe the community mediation implementation with its positive or negative impact on MWSWs and their needs.

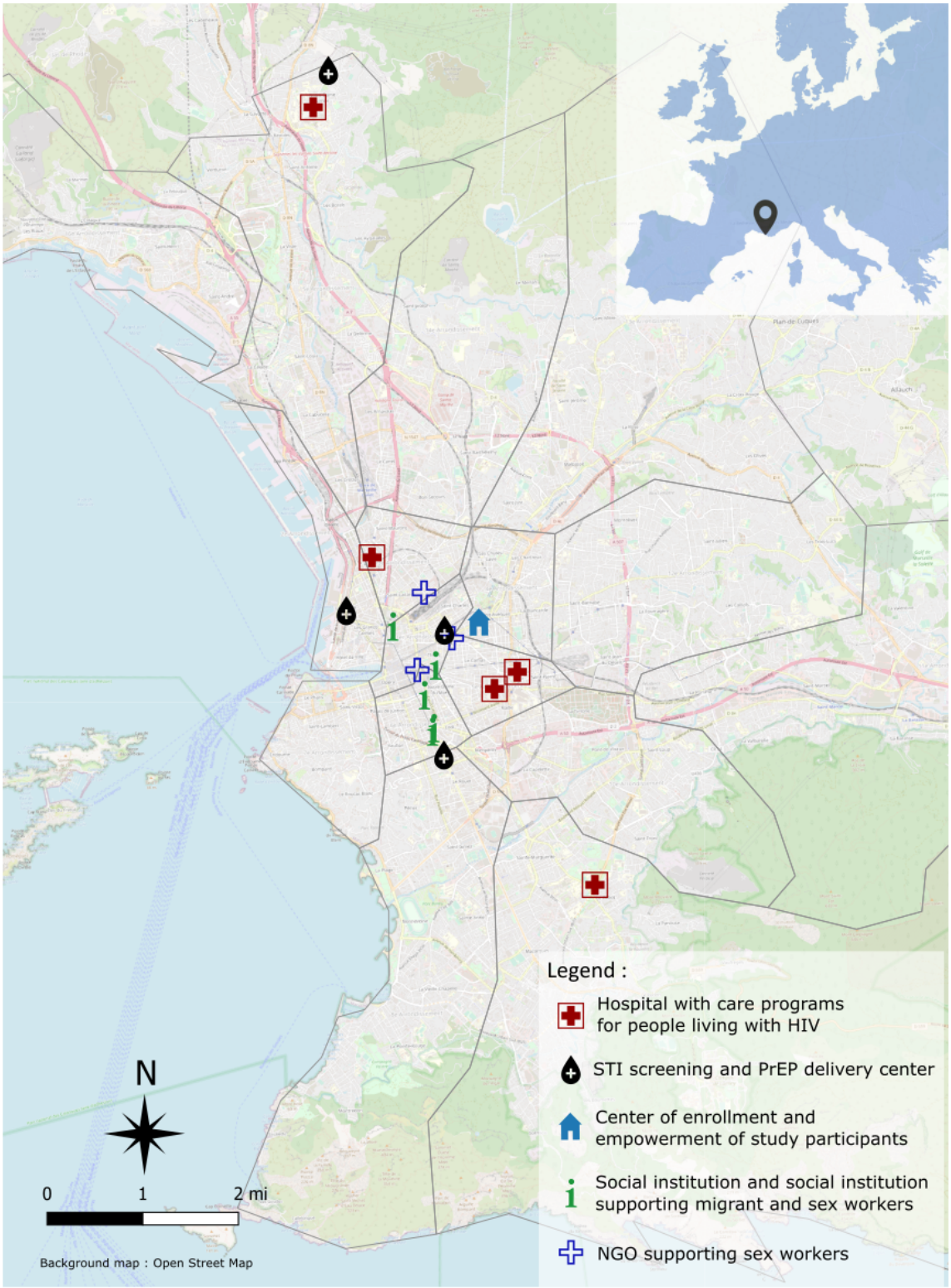
Field Implementation

The FASSETS intervention will take place at a center for enrollment and empowerment (Figure 2). The health care and social service network for MWSWs has already been mapped (Figure 2). Some NGOs and CHWs of the study are mobile and will visit some prostitution sites.

After inclusion, participants will be offered to be followed up at least every 3 months by CHWs, either in the mobile or fixed area, on the basis of their preference. Participants will also have access to health screening centers and other institutions or NGOs any time they need them, in addition to planned individual or collective meetings.

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Figure 2. Mapping of the sexual health and social care and support network for migrant sex workers in Marseille. PrEP: pre-exposure prophylaxis; NGO: nongovernmental organization; STI: sexually transmitted infection.



Training of Community Health Workers and Intervention Implementers

The CHWs will be members of the communities to which the recruited MWSWs belong. They will be able to improve recruitment, accurately monitor the correct understanding of the questionnaires, and conduct and ensure participation in empowerment, prevention, and screening interventions. They will provide information about PrEP and assist with care and follow-up for participants who wish to receive the treatment. They will be uniformly trained to conduct the survey using a structured interview. All actions (type, date, and public) taken by the CHWs with MWSW participants (eg, access to care, prevention, and assistance in accessing social insurance) will be also collected.

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The CHWs will be responsible for health education and individual and collective empowerment actions. They will receive rigorous prejob training and assessment, which include PrEP use and sexual health prevention and care, by caregivers (infectious disease physicians) and nationally recognized community-based NGOs working in the field of HIV prevention (including AIDES, Planning familial, and COREVIH [COordination REgionale de lute contre le Virus de l'Immunodéficience Humaine]). The training program will be conducted with the entire CHW group and will also include individualized follow-up. All CHWs will have a discussion platform via a social network to obtain real-time responses from physicians. Information or prevention tools, adapted to the MWSW populations, will be made available to the CHWs by the NGO's partners. Posttraining mentorship, supervision, and monitoring with regular training will take place every 3 months by the investigating physicians. CHWs' course evaluation feedback and posttraining monitoring visits will be provided by the study coordinator. Finally, a follow-up and psychological support will be set up to support the CHWs in their work with this vulnerable population.

Data Collection

Upon enrollment and at months 3, 6, and 12, participants will be asked to complete a structured survey administered by a CHW. The survey will include questions regarding network size for RDS weighting. These will include questions about the token given at the time of data capture. Individual data including sociodemographic characteristics; sexual practices; knowledge and behavior; HIV testing history; medical history; PrEP knowledge, adherence, and compliance; contraception; drug and alcohol use; mental health (including Perceived Stress Scale-10 scores); quality of life; literacy; social support; being subjected to racism; stigmatization or violence during the past 12 months; and mobility will be collected. Other more structural determinants will be collected as follows: residence permits, health insurance, housing conditions, and food security (Table 1). Indeed, such structural determinants are previously described to have a significant impact on health care access among sex workers [42]. The semistructured questionnaire will explore the barriers and levers to accessing PrEP among MWSWs. The instrument or interview guide will attempt to understand how PrEP fits into women's needs, care pathways, and mobility. Representation of MWSWs' PrEP uptake among caregivers and which mechanisms are (or are not) implemented by social institutions to facilitate access to prevention and care for MWSWs (Table 1).

Type, objective, and number of actions of mediation in terms of prevention, support, or access to health care or social services will be self-reported by CHWs.

CHWs will use encrypted and secure survey software to report the MWSWs' responses to the questionnaires and to monitor their actions of mediation. All electronic questionnaires will be forwarded to a database that is managed and hosted by SESSTIM (Inserm laboratory in Marseille). Each staff member will have a secure individual account.

Databases of all NGOs and institutional screening and PrEP centers of Marseille will be retrospectively analyzed to describe the HIV status and to assess PrEP characteristics among migrants and women in Marseille.

Table 1. Data collection tools and timing.

Method	Timing	Population	Data collected
Questionnaire	4 rounds: months 0, 3, 6, and 12	Randomized migrant woman sex worker cohort in Marseille	Sociodemographic data, knowledge of sexual health, results of tests for sexually transmitted diseases, medical treatment including pre-exposure prophylaxis (PrEP), retention time in care, health care pathway, residence permit, health insurance coverage, housing conditions, and food security
Questionnaire	Continuous	Community health workers	Type, number, and objective of actions
Semistructured interviews and focus groups	Continuous from September 2021 through January 2022	Migrant women sex workers	Perception of PrEP and sexual health, qualitative explanation of possible empowerment mechanisms, health needs, and care pathway
Semistructured interviews	Continuous from September 2021 through January 2022	Nongovernmental organizations (NGOs) and institutions in charge of the sexual health of sex workers in Marseille	Perception of PrEP and sexual health in migrant women sex workers, identification of available empowerment resources for migrant women, and health care offer
Observation	Continuous	NGOs and institutions in charge of the sexual health of sex workers and migrants in local and international territories	Social history of public sexual health strategies among migrant women sex workers

Data Analysis

Descriptive statistics will be applied to the characteristics of the survey population. Categorical variables will be reported as percentages and compared using the chi-square test (and the Fisher exact test for small numbers). Continuous variables will be expressed as mean (SD) or median (IQR) values, and compared using Student and Wilcoxon signed ranked tests in accordance with the variable distribution. A simple logistic regression analysis will be applied to select variables associated with the outcome, and all variables with a P value of <.10 will be entered into a multiple logistic regression model for each outcome. Statistical analysis will be performed using STATA

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(version 11.2; StataCorp), and statistical significance will be defined as a *P* value of ≤.05.

Survival analysis will be used to analyze cumulative retention in care for 12 months after the beginning of the intervention. Differences between survival curves will be assessed at month 12 using the Kaplan-Meier estimate (log-rank test).

Ethics Approval and Consent to Participate

The protocol received approval from French Ethics Committee in October 2021 (2021—A01746-35). Prior informed consent of the participants will be collected by a member of the research team before data collection. All the participants are free to withdraw from the study at any moment without incurring any penalties or consequences with regard to future care or services they might rightfully expect.

The study protocol has also been reviewed and approved by an independent peer review for funding by Sidaction.

Planned dissemination of study findings includes manuscript publication, conference presentations, and community dissemination (eg, community meetings and social network).

Results

Recruitment commenced on March 1, 2022. We estimate that the follow-up period will end on September 30, 2023.

Discussion

Anticipated Findings

Community empowerment interventions that aim to reduce the risk of HIV acquisition using PrEP among MWSWs are scarce worldwide. To our knowledge, this is the first intervention of its kind in Europe. Innovative and community-based approaches to bring MWSWs closer to health and social services are required. The findings from the FASSETS study will prove useful for tailoring PrEP use, proposing PrEP use to MWSWs and ensuring its adherence among them, and developing a sustainable community-based intervention.

One of the main challenges of this study is to take into account all the barriers to access to care in this vulnerable population and possibly the low prioritization of PrEP in light of their vital needs. Indeed, MWSWs have to deal with many structural factors such as the criminalization of their work, stigmatization, racism, or their precariousness [17,42]. This project, through a holistic approach based on the needs of the participants, aims to work on the issue of empowerment in a transversal approach. CHWs will be trained in sexual health prevention and will help the participants better access their rights and basic needs, especially those of housing, civic rights (eg, resident permit and social insurance), and access to food. Regarding the fight against stigmatization and racism, this study aims to set up a collective empowerment program with the help of CHWs for better consideration of their difficulties. Partner NGOs such as The Truth and AIDES will participate in advocacy in accordance with the difficulties encountered by the participants. Moreover, CHWs' actions have been previously described as having a social transformation impact [43].

The FASSETS intervention team has the capacity to provide cohort follow-up and individual and collective empowerment actions through partnerships with local organizations interested in connecting with the population of MWSWs. This team includes CHWs from multiple countries and cultures. FASSETS participants will have greater access to services, and health organizations may be able to reach a wider segment of the population to propose the use of PrEP.

FASSETS is a comprehensive, interdisciplinary, participatory study that combines clinical, epidemiological, and social sciences. Research questions are not limited to the participants and they take the health care network and implementing staff into consideration, notably with health mediation descriptions.

Limitations

Operational challenges are numerous and are linked to the relationship with MWSW communities and their perception of the intervention, mobility of the participants, stigmatization and racism that they could face from institutions, decrease in preventive actions, and modification of the type of sex work due to health measures or restrictions linked to the COVID-19 pandemic. Documenting all these logistic and operational aspects should enable gathering of crucial information regarding the potential transferability of the intervention.

Regarding the FASSETS methodology of evaluation, we were unable to use a control group or a stepped wedge method because of ethical problems (benefit to participate) and the difficulty to implement empowerment in a sequential and reproducible way. However, exhaustive local data from all screening and delivery PrEP centers in Marseille are available for investigators at the beginning and at the end of the study and will permit them to evaluate, through pre- and postintervention comparisons and those between participants and nonparticipants, the access and adherence to PrEP among MWSWs.

Conclusions

The FASSETS intervention aims to understand whether the implementation of a specific community accompaniment for MWSWs regarding PrEP use with an adapted follow-up and wide access to health care and social services are sufficient to improve the uptake of PrEP in this vulnerable population.

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Authors' Contributions

EM, FA, GI, MM, and CE designed the study. EM and CE wrote the first draft of the manuscript. EM, ER, and MH wrote the statistical analysis plan. EM and MH generated the figures. All authors contributed to reviewing, revising, and approving the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

CHW: community health worker
FASSETS: Favoriser l'Accès à la Santé Sexuelle des Travailleuses du Sexe
MWSW: migrant women sex worker
NGO: nongovernmental organization
PrEP: pre-exposure prophylaxis
RDS: respondent-driven sampling
SRH: sexual and reproductive health
WSW: woman sex worker

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Protocol

Efficacy of Cognitive Behavioral Therapy With Local Wisdom and Web-Based Counseling on Generalized Anxiety Disorders and Functional Gastrointestinal Disorders in Adolescent College Girls: Protocol for a Randomized Controlled Trial

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Abstract

Background: The high academic demands experienced by students will often have an impact on the quality of their mental and physical health. The most common health problems reported are gastrointestinal disorders. This condition tends to manifest in the emergence of generalized anxiety disorders (GADs) and reduces the quality of life and productivity. The population that experiences this disorder the most is female adolescents, and this condition occurs in both South African and Indonesian populations. The use of drugs, especially benzodiazepines, often causes psychological conditions as side effects. For this reason, it is necessary to have a solution in the form of a targeted and efficient approach to reduce psychological symptoms that arise from functional gastrointestinal disorders (FGIDs) in the form of anxiety.

Objective: The purpose of this study is to produce and implement a counseling intervention model to assist female students with GADs caused by FGID factors using an approach combining cognitive behavioral therapy (CBT), web-based counseling, and local wisdom in Indonesian and South African populations.

Methods: The research subjects will comprise 118 female adolescent students from Indonesia and 118 female adolescent students from South Africa, making a total sample of 236 participants, and the study will use a prospective, parallel randomized controlled trial design. The recruitment process will begin in July 2023, and the trial will begin in August 2023. The posttest assessment data gathering will take place by November 2023. Questionnaires that will be used in this study include the Functional Gastrointestinal Disorder Checklist (FGI-Checklist) to collect data related to FGIDs and the Generalized Anxiety Disorder 7-item (GAD-7) to measure the anxiety conditions experienced by respondents.

Results: By adopting the intention-to-treat principle, there will be significant mean changes in GAD scores and FGID scores after exposure to this combined approach in the Indonesian and South African populations. Implementing this comprehensive intervention will improve the students' psychological symptoms related to FGIDs and ultimately enhance their overall well-being.

Conclusions: This study will develop and implement a model of counseling intervention for female students with GADs obtained from FGIDs using a combination approach to CBT, web-based counseling, and local wisdom in both the Indonesian and South African populations. The trial findings will contribute to our understanding of the effects of CBT combined with local wisdom

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and web-based counseling approaches that mental health counselors can use to treat GAD-affected adolescent girls who have FGIDs.

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International Registered Report Identifier (IRRID): PRR1-10.2196/50316

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KEYWORDS

adolescent college girls; cognitive behavioral therapy; CBT; functional gastrointestinal disorders; FGIDs; generalized anxiety disorders; GADs; local wisdom; web-based counseling

Introduction

Background

Students experience various changes and challenges over the period of their studies. The high academic demands that students must meet and the tendency for weak control over health impact students' conditions [1,2]. Various mental health disorders also tend to increase during an individual's time as a student [3-5]. This condition tends to cause health problems and affects students' quality of life and mental condition. Disorders that appear commonly in students are functional gastrointestinal disorders (FGIDs) [6,7], which are characterized by abdominal pain, dysphagia, dyspepsia, diarrhea, constipation, bloating, and acute gastrointestinal (GI) disturbances [7-9]. Based on data from the Ministry of Health of the Republic of Indonesia in 2020, FGIDs are included in the list of 10 diseases that affect adolescents the most in Indonesia, with a prevalence of up to 40.85% [10]. FGIDs appear in conditions without an organic basis and are more likely to occur due to impaired communication between the brain and the gut. In other words, disturbances in digestive function are reciprocal. Individuals with FGIDs tend to experience anxiety disorders, while individuals with dominant anxiety conditions will experience digestive disorders [8,11-14]. Treating FGIDs based on the latest findings generally still relies on drug therapy, but this therapy tends to produce other side effects subsequently experienced by the patient [15]. In addition, FGID treatment, which essentially does not produce organic conditions, is time-consuming and expensive. In addition, the patient's anxiety condition often does not subside and worsens [13,16].

When viewed from a demographic perspective, anxiety disorders as a result of FGIDs are often experienced by the female population during their reproductive years [17,18]. It has been found in population-based case-control studies that women with FGIDs experience a more negative impact on their daily functioning than their male counterparts and other women without this condition [12]. In the South African population, 8% of the total population experienced this; in the KwaZulu-Natal province of South Africa, it was found that among 201 rural patients who presented with one type of FGID (functional dyspepsia), most patients (74.13%) [19] reported anxiety disorders. The impact is that if anxiety conditions and FGIDs are not handled properly, this will decrease students' productivity and quality of life. Generally, this impact will result in a decrease in students' opportunities for achievement and learning outcomes to the point of being unable to continue their studies [9,13,16,20]. Anxiety resulting from FGIDs also contributes significantly to the decline in quality of life. It impacts both the student's college life in terms of their learning, social, and personal lives, and the condition of their future career. Various attempts to alleviate this problem have been made but have not yielded significant results. Among others, a pharmacotherapeutic approach relieves anxiety symptoms that arise [15,21]. However, the use of drugs, especially benzodiazepines, often causes side effects on psychological conditions. For this reason, it is necessary to have a solution in the form of a targeted and efficient approach to reduce psychological symptoms that arise from FGIDs in the form of anxiety [22-41]. With a specific target on anxiety sufferers in the female population of student age, it is deemed appropriate to provide a cognitive behavioral therapy (CBT) approach combined with the implementation of web-based counseling and local wisdom. The advantage of this approach is that the assessment process can be carried out in a remote setting using web-based counseling technology developed in the author's previous research, then combined with an approach that has proven effective in conducting behavioral change therapy and emphasizes the implementation of local wisdom. In addition, the combination of these 3 elements will be able to spur positive changes in the anxiety experienced by female students with FGID conditions.

Objective

The purpose of this study is to produce and implement a counseling intervention model to assist female students with generalized anxiety disorders (GADs) caused by FGID factors using an approach combining CBT, web-based counseling, and local wisdom in Indonesian and South African populations.

Hypothesis

Based on the understanding that students face various challenges and changes during their university studies, including the high academic demands and potential impact on their health, particularly in terms of mental health, it is important to address these issues effectively. One common disorder among students is FGIDs, which not only affect their physical well-being but also have an impact on their quality of life and mental state. Additionally, anxiety disorders often coexist with FGIDs, further exacerbating the negative effects on students' overall well-being. Considering the prevalence of FGIDs and anxiety disorders among female students, it is crucial to develop an intervention model that combines CBT, web-based counseling, and local wisdom. Thus, this study hypothesizes that there will be significant mean changes in GAD scores and FGID scores after exposure to this combined approach in the Indonesian and South

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African populations. Implementing this comprehensive intervention is expected to improve the students' psychological symptoms related to FGIDs and ultimately enhance their overall well-being.

Methods

Research Design

This study is developmental research involving the systematic and conceptual design of a psychological treatment approach. The development model that will be used as the basis for this research activity is one adapted from the ADDIE (Analysis, Design, Development, Implementation, and Evaluation) model [42,43]. A prospective, parallel randomized controlled trial design involving pre- and posttesting of a treatment group and a control group will be used by the researchers [44]. At the end of a diagnostic interview conducted by the researchers, participants who are considered eligible for the study will be randomly assigned to 1 of 2 groups: the web-based CBT group or the usual care control group.

Research Subjects

The research subjects will consist of female adolescent students in Indonesia and South Africa (aged 15-17 years); 118 people from each country will be recruited from general practice or family medicine clinics as well as high schools within each study area to arrive at an overall sample of 236 participants for this study. An initial assessment will be conducted on 1000 potential participants (500 adolescent girls per country), who will be screened according to the research criteria so that a representative sample for the intervention may be obtained. The results of a recent study [45] found that 44.1% of participants were able to complete a CBT program using a web-based approach and that the average completion rate for the 12 sessions was 7.8 (65%). Therefore, we will take into account the attrition rate of 55.9% by including 55.9% extra participants in our initial sample for each group produced by the G*power (Heinrich-Heine-Universität Düsseldorf) sampling program [46]. To account for the potential effects of missed sessions in a standard web-based CBT program, as shown by recent research [45], 4.2 sessions (35%) will be added to the 12-session program, which will result in approximately 16 sessions (to be delivered over 4 months). Based on the G*power calculation, the required sample size is 38 participants per group (85% statistical power; medium effect size Cohen d=0.5; a priori probability level of 0.5) for a linear mixed model (LMM) analysis. Given the presumed attrition rate, we will recruit 59 participants per group in each country.

Randomization and Masking

This study will use a computer-generated random list obtained from Random Allocation Software [47] to randomize groups using a simple randomization technique by 2 biostatisticians (1 for each country) who are not part of the research team to ensure assignment concealment. Each country's research team is expected to have 59 research subjects in the treatment group and 59 research subjects in the control group, totaling 118 adolescent girl participants from each country. The group randomization process will be concealed from the study subjects. Thereafter, the researchers will notify subjects of their group membership through invitations to participate in the treatment intervention or usual care sessions.

Treatment Activities and Procedures

This research will be reported in line with the guidelines for the Consolidated Standards of Reporting Trials (CONSORT) [48]. The study was registered in a clinical trials registry before the recruitment of the first participant. A 16-session CBT manual incorporating web-based counseling techniques and principles and local wisdom approaches to the treatment of GAD among adolescent college girls with FGID symptoms will be developed by the research team for this study. The research team will adapt evidence-based techniques and procedures from existing CBT intervention manuals for GAD and FGID treatments with a focus on cultural components, traditions and values, and local wisdom, as well as web-based counseling techniques and processes, to address GAD and FGID symptoms among adolescent college girls. Each web-based session for the treatment group as well as the usual care session for the control group in each country (study site) is expected to last for 90 minutes each, once a week for 4 months. To assess the efficacy of CBT combined with local wisdom and web-based counseling approaches, we used the usual care as a comparison group. This study defines usual care as whichever treatment for GAD and FGIDs adolescents receive from their regular health care providers or therapists. This form of comparison group was selected to appraise the effects of CBT combined with local wisdom and web-based counseling approaches against the treatments that would normally be available without this intervention. The use of usual care as a comparison group also contributes to the viability of the trial since other clinicians are not required to be trained in a particular approach to comparator therapy. Due to this study's design, it is possible to compare the effects of CBT combined with local wisdom and web-based counseling methods with the usual practice in GAD treatment for adolescent girls with FGIDs. Three specialist raters in each country will evaluate the treatment's integrity. During the project, 2 postgraduate-level psychologists with a master's degree will serve as research assistants in each country. Two cognitive behavioral therapists with a doctorate in counseling psychology will provide the web-based CBT intervention for the treatment group, while the usual care intervention for the control group in each country will be provided by 2 CBT practitioners with doctorate degrees in psychology. The recruitment process will begin in July 2023, and the trial will begin in August 2023. The posttest assessment data gathering will be undertaken by November 2023. A summary of the treatment intervention is shown in Table 1.

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Table 1. Summary of the intervention components.

Sessions	Integrated web-based counseling with local wisdom CBT[a]
Initial assessment (session 1)	In the first session, the counselor and clients will engage in an initial assessment to identify the presenting issues and set goals for therapy. This assessment typically takes 1 session. This stage involve the use of a web-based assessment system.
Sessions 2-3	Psychoeducation (2 sessions): Over 2 sessions, the counselor provides educational materials and resources to the clients through text, videos, or web-based sources. The counselor explains the concepts of CBT, the connection between thoughts, feelings, and behaviors, and introduces the techniques and strategies that will be used in therapy.
Sessions 4-5	Identification of negative thought patterns (2 sessions): This process involves self-observation, reflection, and discussion, taking into account the perspective of cultural values and local wisdom. By incorporating cultural perspectives and values, the counselor aims to create a culturally sensitive and inclusive environment that respects the clients' cultural background. The exploration and identification of these patterns typically take 2 sessions, allowing sufficient time for the client to reflect and discuss their experiences within the context of their cultural beliefs and values.
Sessions 6-9	Restructuring negative thoughts (4 sessions): Once negative thought patterns are identified, the counselor and clients collaborate to restructure these thoughts and replace them with more realistic, balanced, and positive thoughts, integrating the principle of "nature as the master teacher" from Minangkabau culture in Indonesia. This process involves techniques such as realistic thinking, thought replacement, and asking challenging questions while drawing inspiration from nature's wisdom. By incorporating local wisdom, the counselor helps the clients develop a deeper understanding and connection with their cultural roots. In this respect, the Ubuntu counseling model as a local wisdom approach will be integrated to assist the South African adolescents during the treatment sessions since it involves integrating African culture into the therapeutic process in that it recognizes the relevance of culture to patient mental health and self-identity. Several group processes are emphasized in the Ubuntu counseling model, including communality, cooperation, and oneness among others. Several traditions and values are also intrinsic to the Ubuntu counseling model, and they determine how mental disorders are understood and treated in South Africa.
Sessions 10-13	Development of coping skills (4 sessions): The counselor assists the clients in developing healthier coping skills. This includes stress management strategies, relaxation techniques, problem-solving skills, and fostering adaptive thinking patterns. It typically takes 4 sessions to introduce and practice these skills.
Sessions 14-15	Assignments and exercises (2 sessions): Throughout therapy, the counselor assigns tasks and exercises for the clients to apply the concepts and skills learned in sessions to their daily lives. The counselor may review progress and provide feedback in 2 dedicated sessions for discussing and reviewing assignments.
Session 16	Monitoring and feedback (1 session): The counselor uses web-based monitoring tools, such as questionnaires or web-based daily journals, to track changes in the clients' thoughts, feelings, and behaviors. In 1 session, the counselor provides constructive feedback based on the information gathered and the progress made.

[a]CBT: cognitive behavioral therapy.

Inclusion and Exclusion Criteria

To be considered eligible, participants must (1) be between the ages of 15 and 17 years, (2) be experiencing moderate to severe GAD and FGID symptoms at baseline, (3) speak and understand English to a reasonable level, (4) be willing to take part in the web-based CBT program or attend the usual care program, (5) have been taking continuous doses of anxiety medications for at least two months before the commencement of the program, (6) have a smartphone or tablet device that is capable of running Whatsapp, Zoom, or the Konselo counseling app and have access to the internet, which is necessary to participate in the program sessions, and (7) demonstrate the ability to commit to the expectations of the trial. Some conditions will exclude participants from the study. This includes (1) participants who cannot answer questions in the assessment tools on their own with a reasonable degree of English, (2) participants affected by psychiatric or medical comorbidities that would severely impact their ability to participate or adhere to the program schedule, (3) persons who are currently receiving CBT treatment, (4) individuals who have practiced meditation regularly or previously, (5) a lack of internet access or the inability to use a device that is capable of connecting to the internet, and (6) inability to commit to the expectations of the trial. In each country, 2 postgraduate-level research assistants with a master's degree in psychology will be trained to screen prospective participants using these inclusion and exclusion criteria by telephone. On completion of the screening process and after it has been determined that participants are eligible for the study, they will be invited to complete a diagnostic interview with the research investigators in each study area to additionally validate their eligibility for the study. Participants will be reached by phone in line with the schedule of the program as soon as it has been determined that they are eligible to participate in the research study.

Outcome Measures

Questionnaires that will be used in this study include the Functional Gastrointestinal Disorder Checklist (FGI-Checklist) [49] to collect data related to FGIDs and the Generalized Anxiety Disorder 7-item (GAD-7) screening tool [50] to measure the anxiety conditions experienced by respondents.

The FGI-Checklist includes the 20 most common FGID symptoms, which encompass a series of symptoms across the GI tract [49]. Five subscales contribute to the total score of the FGI-Checklist, including abdominal and bowel syndrome (7 items; Cronbach α=.86), functional dyspepsia syndrome (5 items; Cronbach α=.87), reflux syndrome (4 items; Cronbach α=.80), esophageal syndrome (3 items; Cronbach α=.69), and nausea and vomiting syndrome (2 items; Cronbach α=.73).

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Several single items on the FGI-Checklist are used to ascertain the severity of global dyspeptic symptoms, abdominal symptoms, stool frequency, and stool form as per the Bristol stool scale. Thus, it is often seen as a comprehensive symptom assessment scale covering esophageal, epigastric, and abdominal symptoms. It is a self-administered outcome measure with a 7-day recall period [49]. Patients are required to rate the intensity of each symptom using 4 response options to indicate impairment in daily activities due to the symptom as follows: 0=none, 1=mild (not affecting daily activity), 2=moderate (some daily activities are affected), and 3=severe (almost all daily activities are affected). The FGI-Checklist total score, which ranges from 0 to 3, is calculated by averaging the scores of the 20 items. Patients with mild (monthly) to severe (weekly) symptoms can be identified with the FGI-Checklist. A higher score represents more severe symptoms [49].

It has been demonstrated that the GAD-7's internal consistency is excellent (Cronbach α=.92) and its test-retest reliability is adequate (intraclass correlation=0.83) [50]. The GAD-7 has a 4-point response scale ranging from 0 (not at all) to 3 (nearly every day). Scores between 0 and 4 indicate minimal GAD, 5 to 9 indicate mild GAD, 10 to 14 indicate moderate GAD, and 15 to 21 indicate severe GAD [50]. The GAD-7 also has a strong correlation with patients' mental health (r=0.75), social functioning (r=0.46), general perceptions of health (r=0.44), bodily pain (r=0.36), role functioning (r=0.33), and physical functioning (r=0.30) [50]. An invaluable feature of the GAD-7 is its ability to assess changes in anxiety symptoms severity over recent weeks (that is, over the previous 2 weeks).

Data Analyses

The analyses of the data in this study will include descriptive analysis, analysis of the coefficient of agreement between program raters (interrater reliability), and internal consistency analysis using Cronbach α and partial η^2 (effect size statistics). A sensitivity analysis will also be carried out to avert potential data dredging. The Mauchly sphericity test and Levene equality of variance test will be carried out to ensure that the assumptions of the chosen statistical test are met. LMM will be used to analyze the primary outcome measures statistically based on the principle of intention-to-treat to determine whether considerable changes have occurred over time [51]. By using LMM, participants with incomplete data will be included in the analyses so that treatment effects can be assessed over time (group time interaction) [51]. Using LMM, the treatment group, time, and interactions between the treatment group and time will be considered fixed factors; the covariance structure will be constructed in an unstructured manner. We will ascertain posttest outcomes in terms of mean changes in GAD-7 and FGI-Checklist scores from baseline to 4 months following the pretest. Complier-adjusted causal effect (CACE) analysis will be conducted based on the causal framework and estimation methods to account for variations in treatment effect due to variations in treatment adherence between the groups [51,52]. We will calculate CACE as the difference between the mean GAD-7 and FGI-Checklist scores of compliers in the treatment group as well as the control group. To be considered a complier, a participant must have attended 80% or more of the program sessions, which is a frequently used threshold [51,53]. A bootstrapping technique will be used to determine standard errors. Statistical analyses will be completed using R (R Core Team) to analyze the CACE data and SPSS (version 29; IBM Corp) for the rest of the analyses. P values of .05 or less will be considered statistically significant.

Ethics Approval

Each participant will be informed about their freedom to withdraw from the research project at any point in time without consequences. The research team will obtain web-based informed consent from the participating female adolescents, and their right to privacy will be respected. Parental consent will be sought. The project will be conducted in line with relevant ethical guidelines of the institutional review boards of the investigators; the research protocol has undergone ethical review approval (00402113712112520230227). Therefore, the project will comply with ethical research principles, including the issues of confidentiality, legality, professionalism, consent, privacy, and protection from harm. This research protocol has also been prospectively registered in the UMIN Clinical Trial Registry (UMIN000051386) on June 20, 2023.

Results

By adopting the intention-to-treat principle, there will be significant mean changes in GAD scores and FGID scores after exposure to this combined approach in the Indonesian and South African populations. Implementing this comprehensive intervention will improve the students' psychological symptoms related to FGIDs and ultimately enhance their overall well-being.

Discussion

Primary Findings

This study will aim to develop and implement a model of counseling intervention for female students with GAD obtained from FGIDs using a combination approach of CBT, web-based counseling, and local wisdom in Indonesian and South African populations. A substantial proportion of the South African population consists of adolescents, representing 17.4% of the population and accounting for 2.1% of the overall mortality rate [54]. Meanwhile, it is estimated that the Indonesian population consists of 46 million adolescents; this makes it vital for the nation to promote adolescents' health and well-being to fully take advantage of its demographic strength [55]. Adolescents are regarded as the potential workforce and contributors to national development and socioeconomic growth, which is why their health and well-being are paramount as they form a cornerstone of society [54]. However, the adolescent population may face some mental health challenges, such as GAD. Anxiety experienced by individuals (in this case, students) is closely related to the emergence of various health problems, especially digestive conditions [8,22-24]. This anxiety condition becomes psychopathological, which has a reasonably close and reciprocal correlation with the emergence of various GI problems. The problems most commonly experienced by students who experience anxiety are FGID symptoms, which are a group of disorders characterized by chronic GI symptoms (eg, abdominal

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pain, dysphagia, dyspepsia, diarrhea, constipation, and bloating) without any pathology that can be proven in conventional testing [25-27]. When individuals experience FGIDs, they tend to also experience anxiety reactions. This is so recurrent that it is challenging to stop the cycle of problems between psychological and physical disorders[28,29].

Previous studies have also revealed the relationship between psychological problems (especially anxiety) and FGIDs. This condition tends to be experienced in the form of dyspeptic disorders, with a correlation prevalence of 0.48 [30,31]. In addition, other studies show a strong relationship between FGIDs and major depressive episodes and GADs [56]. As a form of reciprocity, studies have shown that the incidence of psychological disorders in patients with FGIDs is significantly higher than in non-FGID patients; symptoms of FGIDs are strongly associated with mental health disorders, especially anxiety and depression [49,50]. Pathophysiological studies of FGIDs have shown that psychosocial factors can influence FGIDs by regulating processing pathways and decreasing visceral signaling in the brain [29,32]. Analyses of interventions for irritable bowel syndrome have shown that psychological interventions, including web-based CBT, could treat irritable bowel syndrome effectively in patients [56,57].

This study hypothesizes that there will be significant mean changes in GAD scores and FGID scores after exposure to this combined approach of CBT, web-based counseling, and local wisdom in the Indonesian and South African populations. So far, pharmacotherapy and psychological interventions have undertaken the management of anxiety that results in FGIDs, and vice versa [25,28]. These psychological interventions include psychotherapy, psychodrama, CBT, relaxation therapy, and hypnosis [33-36]. Psychological intervention refers to psychotherapeutic methods designed to change a person's cognition, perception, or behavior. Psychodynamic psychotherapy focuses on how maladaptive thoughts and behaviors occur [35,36]. The psychodynamics of interpersonal psychotherapy are more concerned with the relationship between therapist and patient. This method emphasizes that the therapist and patient form a robust, cooperative working alliance. Meanwhile, CBT aims to improve the quality of life by changing the patient's thoughts or patterns of thinking and behavior. Relaxation therapy allows the patient to experience the physical and mental pleasure that relaxation brings to correct the psychological and physiological dysfunction caused by tension [12,37,38]. Hypnotherapy is the use of hypnosis to treat patients and improve their condition. For this reason, it is necessary to have a new approach that uses collaborative and cross-approach concepts to get more effective and efficient results. Following previous research, there are empirical results regarding the impact of psychological interventions on reducing anxiety symptoms and improving pain due to FGID; there is still no single fixed model with a combination of approaches to reduce anxiety conditions effectively. In addition, existing research has not shown an in-depth evaluation process of research results in the adolescent population. This study uses a CBT approach that has proven useful for clients with maladaptive disorders such as stress and anxiety. The study also uses the web-based counseling intervention approach as a way to evaluate and supervise the progress of counseling and also uses the implementation of local wisdom. The therapeutic model of local wisdom is added to this study, considering that behavioral change is closely related to the cultural values it carries [39-41]. In this respect, the Ubuntu counseling model as a local wisdom approach will be integrated to assist the South African adolescents during the treatment sessions since it involves integrating African culture into the therapeutic process in that it recognizes the relevance of culture to patient mental health and self-identity [58]. This study uses cross-cultural analysis with very different cultures, namely Indonesian and South African cultures. The cross-cultural analysis will show whether the intervention can be applied to 2 different cultures with almost the same indications of anxiety in terms of symptoms and aggravating factors. The results of this study will contribute to the literature on GAD and FGID treatment by informing clinicians about the potential benefits of CBT combined with local wisdom and web-based counseling approaches for adolescent girls with FGIDs experiencing GAD. However, in this study, there are some potential limitations, including that the treatment pattern does not allow for the blinding of therapists, the possibility that participants may use other interventions or treatments while taking part in the study, and a sample size that may make it impossible to generalize the study results to a larger population and spot subtler effects. While participating in the trial, participants will be required to speak frankly about their medications and treatments. In addition, they will be required to notify the researchers about any modifications to their medication doses throughout the study. In this way, the results can be taken into account with respect to any confounding variables.

Conclusions

This study will develop a model counseling intervention for female students with GAD caused by FGID using a combination approach to CBT, web-based counseling, and local wisdom in Indonesian and South African populations. The study proposes that there will be significant mean changes in GAD scores and FGID scores after exposure to this combined approach of CBT, web-based counseling, and local wisdom in the Indonesian and South African populations. The use of drugs, especially benzodiazepines, often causes side effects on psychological conditions. Thus, it is necessary to have a solution in the form of a targeted and efficient approach to reduce psychological symptoms that arise from FGID in the form of anxiety. With a specific target of anxiety sufferers in the female population of student age, it is deemed appropriate to provide a CBT approach combined with the implementation of web-based counseling and local wisdom. The trial findings will contribute to our understanding of the effects of CBT combined with local wisdom and web-based counseling approaches that mental health counselors can use to treat GAD-affected adolescent girls with FGIDs.

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Data Availability

The data sets generated during or analyzed during this study will be made available from the corresponding author on reasonable request.

Authors' Contributions

ZA, CE, EY, FMY, and AWM conceived the study, contributed to the study design, and conducted literature searches and analyses. All authors contributed equally to the writing of the main manuscript text. All authors were responsible for the chosen methodology and reviewing of the final draft of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review by the World Class University International Collaborative Research Program, Universitas Negeri Padang.
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Abbreviations

CACE: complier-adjusted causal effect

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CBT: cognitive behavioral therapy
CONSORT: Consolidated Standards of Reporting Trials
FGI: functional gastrointestinal
FGI-Checklist: Functional Gastrointestinal Disorder Checklist
FGID: functional gastrointestinal disorder
GAD: generalized anxiety disorder
GAD-7: Generalized Anxiety Disorder 7-item
GI: gastrointestinal
LMM: linear mixed model

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Protocol

Using IT to Improve Outcomes for Children Living With Cancer (SyMon-SAYS): Protocol for a Single-Institution Waitlist Randomized Controlled Trial

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Abstract

Background: Children and adolescents with cancer may experience multiple disease- and treatment-related symptoms that negatively affect health-related quality of life. Routine symptom surveillance thus constitutes an important component of supportive care in pediatric oncology. The Symptom Monitoring and Systematic Assessment and Reporting System in Young Survivors (SyMon-SAYS) system will administer, score, interpret, and display the results of symptom assessments captured weekly using patient-reported outcomes presented via the electronic health record (EHR) portal between clinic visits in oncology ambulatory settings, when patients are likely to be more symptomatic. This study is testing a digital system for routine symptom surveillance that includes EHR-based reports to clinicians and alerts for severe symptoms.

Objective: In this randomized trial, we are examining the effects of the SyMon-SAYS system on perceived barriers to symptom management, self-efficacy, and symptom severity. Better self-management and timely clinical intervention to address symptoms promote adherence to treatment plans, strengthen child and parent self-efficacy, improve interactions between children, parents, and their clinical providers, and optimize clinical outcomes.

Methods: The SyMon-SAYS system is integrated into the EHR to streamline the presentation of symptom scores and delivery of alerts for severe symptoms to clinicians using EHR (Epic) messaging functionalities. Children (aged 8 to 17 years) complete the weekly symptom assessment and review the symptom report by logging into the patient portal (Epic MyChart). This single-institution waitlist randomized controlled trial is recruiting 200 children (aged 8-17 years) with cancer and their parents, guardians, or caregivers. Participating dyads are randomly assigned to receive the intervention over 16 weeks (Group A: 16-week SyMon-SAYS intervention; Group B: 8-week usual care and then an 8-week SyMon-SAYS intervention). Analyses will (1) evaluate the efficacy of SyMon-SAYS at week 8 and the maintenance of those effects at week 16; (2) evaluate factors associated with those efficacy outcomes, including contextual factors, adherence to the SyMon-SAYS intervention, demographic characteristics, and clinical factors; and (3) evaluate predictors of adherence to the SyMon-SAYS intervention and preference of SyMon-SAYS versus usual care.

Results: Data collection is currently in progress. We hypothesize that at 8 weeks, those receiving the SyMon-SAYS intervention will report decreased parent-perceived barriers to managing their children's symptoms, increased parent and child self-efficacy, decreased child symptom burden, and ultimately better child health-related quality of life, compared to waitlist controls. Feasibility,

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acceptability, and engagement from the perspectives of the children with cancer, their parents, and their clinicians will be examined using mixed methods.

Conclusions: We anticipate that this system will facilitate prompt identification of problematic symptoms. Additionally, we hypothesize that with the availability of graphical symptom reports over time, and timely provider responses, children or parents will become better informed and take an active role in managing their symptoms, which will further improve clinical outcomes.

Trial Registration: ClinicalTrials.gov NCT04789720; https://clinicaltrials.gov/study/NCT04789720

International Registered Report Identifier (IRRID): DERR1-10.2196/50993

(JMIR Res Protoc 2023;12:e50993) doi:10.2196/50993

KEYWORDS

pediatric, cancer; symptom monitoring; randomized controlled trial; protocol, electronic health record; health-related quality of life

Introduction

Background

Cancer can be distressing, in part, due to the unrelieved symptoms caused by aggressive therapy regimens implemented to treat the disease, which can last even after the completion of treatment [1]. Management of cancer-related symptoms in children has not kept pace with these advances in treatments. Children continue to experience distressing symptoms related to cancer and its treatment [2,3], as do childhood cancer survivors at all stages of survivorship. The unrelieved symptoms and side effects of often-aggressive cancer treatments can lead to poor psychosocial functioning and decreased health-related quality of life (HRQoL) for children with cancer and their families [4]. There is a need to improve child or family self-monitoring and self-management skills to better manage symptoms throughout the treatment continuum, from on-therapy to long-term survivorship, in order to provide timely intervention and lessen the adverse impacts of symptoms on HRQoL. Subsequently, it is recommended that children with cancer and their family should receive systematic assessments to identify their psychosocial health care needs [5].

Factors contributing to inadequate symptom management exist at the system, health care provider, and patient levels. Health care system barriers include the structure and organization of care, reimbursement, logistics, and resources [6,7]. Health care provider barriers include limited time available during a patient encounter [8], willingness to elicit information from patients [6,9], and challenges in obtaining systematic symptom assessment [10]. For very young patients, there is the added complexity regarding uncertainty about the accuracy of self-report. Patient-level barriers include failure to report symptoms to clinicians [11], desire to be a “good patient” to avoid conflict [12-14], concern over side effects of prescribed medications [12,15], and a perception that during cancer treatment symptoms are inevitable or untreatable [4]. A patient-centered approach to health care can minimize these barriers. Patient-related factors that facilitate self-management include: proactively seeking information and sharing their opinion about their self-management regimen with providers [16].

Improvements in the quality of communication between patients and health care providers can favorably affect symptom management, including improved information recall [17], satisfaction [18], overall HRQoL [19,20], and adherence to practitioners’ recommendations [21]. According to the IOM consensus report Cancer Care for the Whole Patient: Meeting Psychosocial Health Needs [22], inadequate communication and lack of patient involvement are particularly worrisome, as effective patient-clinician communication is linked to positive health outcomes. For patients and families, information is crucial to promote a sense of control, decrease emotional distress, support effective self-management, and eliminate disruptions to daily activities [23,24]. Research on adult oncology patients showed the average patient asks 5 or fewer questions during a 15-minute doctor’s office visit, with a high proportion asking no questions, suggesting that patients generally are not taking an active role in their care [25]. Previous literature suggests the clinician-patient relationship can be strengthened by the simple addition of a “prompt sheet,” encouraging patients to ask questions about treatment and prognosis; oncologists’ efforts to address the issues raised by the use of prompts promoted patient confidence to ask about prognosis, alleviated patient anxiety and reduced clinic visit length [26]. Yet, most literature examining interventions to strengthen patient-clinician communication about problematic issues has focused on adult patients and there has been limited research on children with cancer. Patients’ developmental ages are critical. Children’s less-developed verbal skills, along with parents’ and clinicians’ possibly conflicting communication styles and attitudes toward children, might prevent children from adequately communicating symptoms to providers [27]. Consequently, children are less likely than adults to discuss their symptoms with health care providers [28].

Health care delivery has shifted from inpatient to outpatient or home settings, leading investigators to focus on integrating technology into symptom monitoring and self-management support. The literature suggests that web-based symptom management programs in patients with pediatric cancer are feasible [29], may improve care, enhance patient and provider satisfaction, and lessen symptom burden, and generally do not increase provider time and effort. Tsimicalis et al [30] reviewed studies incorporating technology in pediatric oncology settings, identifying several benefits including surmounting logistical difficulties of distance, time, costs, and transport [31-34]; improving access to experienced and specialized health care professionals in rural and remote areas [35]; offering support

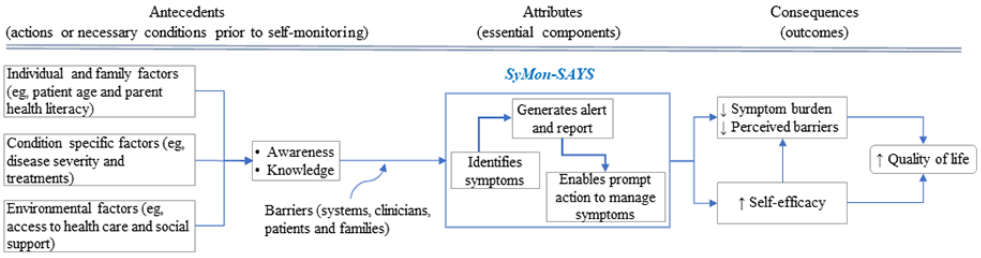
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after hours; and avoiding unplanned hospital visits [36]. The scope of research exploring electronic symptom surveillance systems in pediatric oncology has been constrained, primarily concentrating on palliative care [29] and hospitalized children [37]. Both do not capture symptoms that occurred between clinical visits. This study fills a gap in knowledge about the feasibility, acceptability, and effects on self-efficacy and symptom burden of measurement-based symptom care delivered via the electronic health record (EHR) and explores implementation challenges and strategies that will need to be addressed to refine this intervention for optimal efficacy and adoption. The aim of this manuscript is to outline the study protocol (version 4; February 17, 2023) for this waitlist randomized controlled trial.

Purpose

In this trial, we are testing the efficacy of 8 weeks of Symptom Monitoring and Systematic Assessment and Reporting System in Young Survivors (SyMon-SAYS), an EHR-based system for routine symptom surveillance with self-management support to children and parents or caregivers, reports to clinicians and alerts for severe symptoms. The conceptual model of the SyMon-SAYS intervention is shown in Figure 1; the model was modified from a self-monitoring model [38], our SyMon-SAYS pilot study [39], as well as from literature. “Self-monitoring” is defined as awareness of symptoms or bodily sensations that are enhanced through periodic measurements, recordings, and observations to provide information for improved self-management [38]. The interplay among awareness, measurement, and observations can enhance self-management by improving how individuals monitor their health. SyMon-SAYS is designed to capture 2 major attribute components: (1) increased awareness of symptoms, and (2) accurate measurement and recording of symptoms. Adherence to the SyMon-SAYS intervention (ie, completion of weekly reports of symptoms by patients and parents) is hypothesized to be influenced by contextual factors (child or family, condition-specific, environmental factors) as well as barriers and facilitators. Through technology-based monitoring and reporting, the SyMon-SAYS program facilitates self-monitoring of symptoms via systematic symptom assessments and graphic reports based on these assessments and facilitates self-management by directing patients or parents to web-based resources developed by clinicians for appropriate strategies to manage the symptoms identified by the assessment. The resources site can be accessed directly through MyChart. Because the SyMon-SAYS system is designed to help patients and parents track symptoms on a consistent basis, it aims to lessen perceived barriers to managing symptoms and symptom burden, enhance self-efficacy of patients and parents, and ultimately improve HRQoL [23,40-45].

Figure 1. SyMon-SAYS conceptual model modified based on the "Model of the concept of the the self-monitoring" by Wilde and Garvin [38]. SyMon-SAYS: Symptom Monitoring and Systematic Assessment and Reporting System in Young Survivors.



Objectives and Study Aims

Overview

In this single institution modified waitlist control randomized trial, 200 children (aged 8-17 years) with cancer and their parents will participate for 16 weeks (group A: 16-week SyMon-SAYS intervention; Group B: 8-week usual care and then 8-week SyMon-SAYS intervention). Our study is addressing the following specific aims.

Aim 1

Evaluate the efficacy of SyMon-SAYS after 8 weeks and its maintenance effects at week 16. We hypothesize that group A (vs group B) will report decreased parent-perceived barriers to managing their children’s symptoms, decreased child symptom burden, increased child and parent self-efficacy, and ultimately increased child HRQoL at week-8. We expect that these differences between Groups A and B will be narrowed at week 16 when Group B completes the 8-week SyMon-SAYS intervention.

Aim 2

Evaluate factors associated with aim 1’s efficacy outcomes, including but not limited to (1) contextual factors, (2) adherence to the SyMon-SAYS intervention, and (3) symptom communication between clinicians and children or families.

Aim 3

Evaluate predictors of adherence to the SyMon-SAYS intervention and preference of SyMon-SAYS versus usual care. We will identify predictors of adherence and model their association by using ordinal regressions. Preference of SyMon-SAYS versus usual care will be evaluated using responses from SyMon-SAYS program evaluation. This understanding will help to develop individualized symptom management approaches for better quality and outcomes of care in pediatric oncology ambulatory settings.

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Methods

Ethics Approval

This study was approved by the Institutional Review Boards of Northwestern University (STU00210598) and Ann & Robert Lurie Children's Hospital of Chicago (IRB 2019-3018). Lurie Children's maintains records of the authorization and reliance agreements. All subsequent modifications to the protocol will be submitted for review and approval by the Ann & Robert Lurie Children's Hospital of Chicago. This trial is registered in ClinicalTrials.gov (NCT04789720). The Data and Safety Monitoring Board (DSMB) of the study provides oversight for data and safety monitoring for this trial. The DSMB consists of 3 members outside of Northwestern University and Ann & Robert Lurie Children's Hospital of Chicago, who have extensive experience in research with clinical trials, patient-centered outcomes, and pediatric oncology. DSMB and the study teams meet annually to review the data and any adverse events that occurred.

Study Design and Setting

The study design is shown in Figure 2. To increase the utility and compliance of clinicians, children, and parents, the SyMon-SAYS system was built within the Ann and Robert H. Lurie Children's Hospital of Chicago (Lurie) EHR (Epic). Participants (parents and children) complete assessments using an iPad or a device with internet access at baseline, week-8, and week-16. They are randomly assigned to Group A (weeks 1-16: SyMon-SAYS intervention) or Group B (weeks 1-8: usual care; weeks 9-16: SyMon-SAYS intervention) after the baseline assessment. During the intervention weeks (either weeks 1-16 or weeks 9-16), participants complete a weekly symptom assessment wherever they have internet access using their MyChart patient portal, accessible via smartphone, tablet, or computer. The SyMon-SAYS intervention schema is shown in Figure 3.

Figure 2. Overall study design. SyMon-SAYS: Symptom Monitoring and Systematic Assessment and Reporting System in Young Survivors. Wk: week.

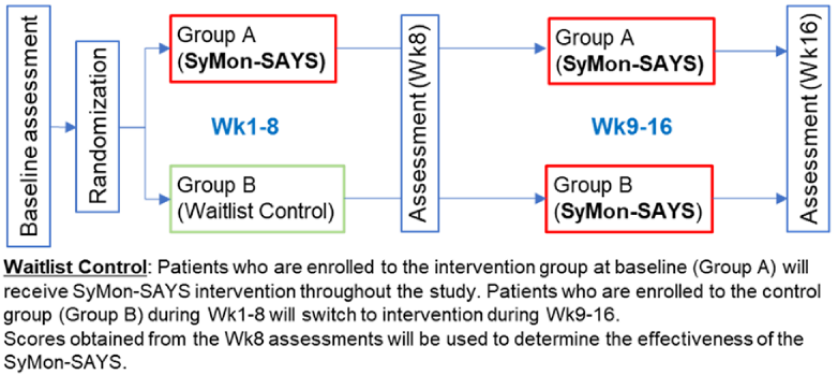
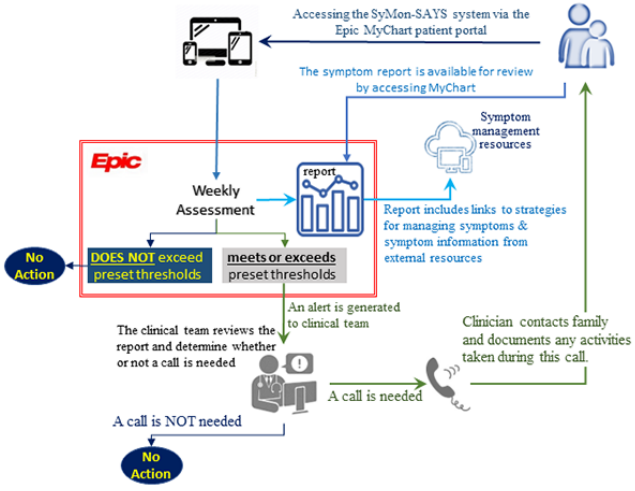


Figure 3. SyMon-SAYS intervention schema. SyMon-SAYS: Symptom Monitoring and Systematic Assessment and Reporting System in Young Survivors.



Participants

Overview

We are recruiting 200 children with cancer from hematology, oncology, and brain tumor clinics at Ann & Robert Lurie Children's Hospital, Chicago with an anticipated 20% attrition rate over a 16-week trial. In order to generalize our results to the entire pediatric cancer population and not exclude important patient subpopulations, we have broad inclusion criteria. Oncology clinical providers who treat participants are also enrolled in the study and provide informed consent as research participants per IRB's requirements at Lurie Children's Hospital. Our inclusion criteria are as follows.

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Patients

Eligible participants are those with a diagnosis of malignancy (including children with primary brain tumors), who are currently receiving cancer-directed therapy or are within 6 months of completing cancer-directed therapy, and who are between 8 and 17 years old at the time of enrollment, English-speaking, have sufficient cognitive and motor abilities to complete surveys via an electronic device (eg, smartphone, iPAD, etc) or computer, and able and willing to sign assent forms (for those between 12-17 years of age). No formal cognitive testing is conducted; eligibility based on cognitive status is determined by the judgment of their clinicians. Usage of any assistive device to complete the assessment is acceptable and will be documented.

Parents

A parent of eligible children (father, mother, or legal guardians) is eligible for the study if she or he demonstrates sufficient fluency in English or Spanish to understand and provide informed consent (either in clinic or via remote recruitment), agrees to complete assessments at all time points, and has sufficient cognitive and motor abilities to complete surveys via an electronic device (eg, smartphone, iPAD, etc) or computer. Only one parent per child participates in the study.

Clinicians

Eligible clinicians are oncology attending physicians, fellows, nurse practitioners, and nurses who treat participating children at Ann & Robert Lurie Children's Hospital.

Informed Consent Procedures

Study personnel explain the aims of the study, what is involved in study participation, and the potential risks and benefits of the study to the potential participants (children, their parents, and providers) so that they can make an informed decision as to whether they wish to participate. This explanation is done in plain, nonexculpatory language that is easy for parents, patients, and providers to understand. Additionally, all participants who are approached for participation in this study are informed that participation in this study is voluntary, and that a decision to not participate will not jeopardize or affect their medical care or their employment status (for clinical providers) in any way. They are informed that they are also free to discontinue participation at any time during the study with no adverse impact on their treatment, overall care, or employment status. Clinical provider participants are also be informed that their decision to participate or discontinue participation will not impact their employment status, and the data they provide during the course of their participation will be used for the purpose of this research study only and will not be made available to the institution or any managing or supervisory personnel (eg, for their merit reviews).

Risks and Ethical Issues

There are no known social or legal risks to subjects who participate in this study. Our experience with data collection using similar questions has indicated that few (less than 1% of over 15,000 participants over more than 20 years) are distressed by the content of the questions posed to them. Participants are advised that if they become upset by the questions, they will have the option to talk with a trained mental health professional. The principal investigator (PI) will be notified of all requests for consultation with a mental health professional.

There is a slight possibility that enhanced monitoring of symptoms could lead to an increase in anxiety. Yet our feasibility study showed that SyMon-SAYS significantly decreased children's anxiety levels at week-4 (P=.046; unpublished data). Furthermore, in this study, children's emotional distress (worry and sadness) are included in the weekly assessments and are monitored closely. As with all symptoms being monitored, an alert is generated when children's reports of worry or sadness meet or exceed the preestablished threshold. Clinicians are notified within 24 hours and take appropriate actions to respond to these symptom experiences. In addition, in consultation with the site clinical team, the study team reserves the right to withdraw any participant for whom there is concern that the intervention is having an adverse effect.

Measures to Protect Privacy and Confidentiality of Participants

Study personnel enroll patients and their parents and assign each patient and parent participant their unique ID code, which is used for identifying and tracking participants throughout the study. Parent codes are linked to corresponding patient (child or adolescent) codes. Clinician participants are recruited by the study team and are also assigned a unique ID code. All data collected from all participants are linked with this unique identifier and not the participants. Information of linking IDs to participants is saved as a separate password-protected file that only the PI and the study coordinator can access.

Sample Size Consideration

An effect size of at least 0.33 has been shown to be clinically meaningful in the measurement of PROs in patients with cancer [46,47]. An effect size of 0.45 is relevant when using cancer treatment satisfaction as an end point [48,49]. Therefore, effect sizes between 0.33-0.45 are expected and will represent clinically meaningful differences for the barriers and self-efficacy end points. We anticipate intervention effects will be maintained in Group A over 16 weeks, and comparisons between groups will be made using both week-8 and week-16 data. We have calculated statistical power to detect differences between the study arms at both weeks 8 and 16, taking into consideration attrition. First, we consider a simple 2-group comparison at the primary 8-week follow-up visit for each end point in aim 1. For this comparison, we calculated that a sample size of 180 (90 per group) will provide 80% power to detect effects of 0.42 for the primary comparisons at week 8. Considering effects at week 16, a sample size of 160 (80 per group) will provide 75% power to detect an effect size of 0.42 but would provide 80% power to detect an effect size of 0.45.

Based on our symptom monitoring studies with more than 100 patients with advanced cancer, fewer than 15% of patients dropped out of a 12-week study because of death, disease progression, ineligibility to continue (eg, transfer care or move), or unwillingness to continue study participation. The dropout rate was 9.5% (6/63) in the SyMon-SAYS pilot (8-week). We

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project a higher dropout rate (40/200, 20%) in the proposed 16-week study period, with approximately half of these dropouts (20/200, 10%) occurring by week 8. To accrue at least 180 patients who complete through week 8, which will provide adequate statistical power outlined above for the primary analyses, we plan to recruit 200 patients at baseline.

Randomization and Allocation

We will use a stratified block randomization approach. Participants are randomly assigned to Group A or B, stratified by gender, age, and cancer types. To achieve allocation concealment, the computer-based data management system (REDCap: Research Electronic Data Capture) assigns participants to 1 of 2 groups after the study enrollment procedures. Participants are informed of their group assignment (Group A or B) after the baseline assessment (see Table 1). Participants complete the weekly symptom checklist via Epic MyChart, a patient portal, during the intervention phase (Group A: weeks 1-16 or Group B: weeks 9-16). They are shown how to install the MyChart app on their smartphone and to access it on their personal computer or tablet. If they do not have a MyChart account, study personnel assist them in establishing one. The study team provides a smartphone during the study period if participants do not have one or are not willing to use their own device for the study.

Table 1. Study parameters that are completed at baseline, week 8, and week 16.

Study measure	Baseline (week 0)	Weeks 1-8	Week 8	Weeks 9-16	Week 16
Symptom severity item (1 item)[a]	P[b]	—[c]	—	—	—
Sociodemographic form	P	—	—	—	—
SyMon-SAYS[d] symptom checklist[e]	—	C[f]	—	C	—
Symptom management barriers questionnaire	P	—	P	—	P
PROMIS[g] HRQOL[h]	C (P)	—	C (P)	—	C (P)
NIH toolbox self-efficacy[i]	C	—	C	—	C
Health-LiTT[j]	P	—	—	—	—
Program evaluation (EXIT Survey)	—	—	—	—	P, M[k], C

[a]How much are you bothered by symptoms of your condition, or side effects of treatment ? (Not at all; A little; A lot)

[b]P: parent.

[c]Not available.

[d]SyMon-SAYS: symptom monitoring and systematic assessment and reporting system in young survivors.

[e]Symptoms included in this scale are tiredness, pain, insomnia, lack of appetite, worry, nausea, sadness, itch, and headache.

[f]C: Child; R: Research Assistant (ie, chart review).

[g]PROMIS: patient-reported outcome measurement information system.

[h]Health-related quality of life (HRQoL) Domains are: Depression, Anxiety, Anger, Fatigue, Mobility, Upper Extremity Function, Peer Relationships.

[i]NIH: national institutes of health.

[j]Health-LiTT: health literacy assessment using talking touchscreen technology short-form version, which can and will be administered without talking touchscreen technology in this study.

[k]M: MD and RN.

Study Implementation

Overview

All participants (Group A and B as shown in Figure 2) experience the intervention phase during the study—Group A during weeks 1-8 and weeks 9-16 and Group B during weeks 9-16 (see Figure 2). Hereafter, intervention phase participants will be referred to as “IP.” After enrollment, study personnel demonstrate how to complete baseline assessments using an iPad. Intervention participant (IP) participants are trained on accessing SyMon-SAYS using the Epic MyChart patient portal. IP participants are provided with a card containing their unique ID code and brief instructions for using the system. The card also contains the study personnel’s name and telephone number for any questions that might arise. IP participants are asked to choose a standard day of the week to access the system and complete their weekly symptom assessment. Parents of IP participants are informed that the study team will send a reminder to them 1 day prior to the chosen day regarding the upcoming assessment. IP participants are given a window of 1 business day before and 2 business days after their preferred day to access the system. IP participants complete the SyMon-SAYS symptom checklist (symptom items are available in Multimedia Appendix 1) every week for 8 weeks through Epic MyChart via mobile app, computer, or tablet. If IP participants do not access the system by midnight of the preferred day, study personnel contact the parent the following day (preferred day +1 business day) and remind them to complete the assessment or prompt their child to do so. If the participant does not access the system by midnight of the day following their preferred day, study personnel again attempt to contact the parent by phone (preferred day +2 business days) to remind them or prompt their child to access the system. Study personnel ascertains any issues that might be related to

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noncompliance (eg, hospitalization) during reminder calls. At weeks 8 and 16, all participants complete the measures listed in Table 1.

Symptom Clinical Intervention Triggers (Intervention Phase Only)

Children's symptom scores will be automatically monitored and reported to oncology care providers. When a child's symptom score exceeds the preset severity threshold (ie, scores 3 or higher), the system will generate an email alert through Epic messaging to the study team with the child's study ID. Upon receipt of an alert, the study coordinator will access the report in Epic and notify the child's treating team to determine whether a call is needed. If needed, the nurse will contact the parent within 1 business day to ascertain their child's current status (see Figure 3 for study schema). The nurse will document actions taken in Epic.

Symptom Monitoring Summary Report (Intervention Phase Only)

After children and parents complete the week 8 and week 16 assessments, study personnel print out symptom reports (Group A: week 8 and week 16; Group B: week 16 only) in clinic and deliver them to parents of IP participants and treating provider prior to their appointment (either week 8 or week 16). Parents are also encouraged to review the web-based version of the report by logging into MyChart prior to clinical visits. Clinicians in the child's care team are able to review this report in children's medical records, where it is stored along with other usual clinical data. These reports reflect children's cumulative symptom scores between baseline, week 8, and week 16 (Group A in Figure 2) or between week 8 to week 16 (Group B). Parents are encouraged to discuss the symptom reports with their child's treating clinicians.

Additionally, the study coordinator will inform children or parents during enrollment about the symptom management resources website that is linked directly to the symptom report in MyChart. This resource site was created by clinicians at Lurie Children's Hospital and the study team, which contain guidelines on managing symptoms at home and when to contact clinicians in a timely manner.

Study Outcomes

SyMon-SAYS Weekly Symptom Assessment

This checklist consists of 9 symptoms: tiredness, pain, insomnia, lack of appetite, worry, nausea, sadness, itch, and headache. These symptoms were selected by clinicians at Lurie Children's Hospital and referenced to our survey of 25 neuro-oncologists and nurses from October-December 2014 in which they were asked to name the top 3 symptoms to be listed on the report. Each symptom is measured by using 1 item with a 5-point rating scale. The SyMon-SAYS study team selected candidate items from existing instruments. Clinicians of Hematology, Oncology, Neuro-Oncology and Stem Cell Transplant Division, Lurie Children's Hospital reviewed candidate items and finalized items included in the symptom checklist. Final items were drawn or modified from Pediatric Patient-Reported Outcome Measurement Information System (PROMIS) Fatigue, Depressive Symptoms, Anxiety, and Sleep, PROMIS Pediatric Itch Questionnaire – Child, Pediatric Quality of Life in Neurological Disorders–Pain, Pediatric Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (Ped-PRO-CTCAE), Pediatric Functional Assessment of Anorexia/Cachexia Treatment, and Pediatric Functional Assessment of Cancer Therapy – Brain. Symptom Checklist items can be found in the Multimedia Appendix 1. Each item was measured by using a 5-point rating scale. An alert will be generated by SyMon-SAYS via Epic messaging when patients endorse a rating of 3 or higher.

Usability, Acceptability, and Engagement of the SyMon-SAYS Program

Feasibility, acceptability, and engagement will be evaluated using mixed methods across child-parent dyads and clinicians.

For the quantitative methodology, we will calculate the percentage of weekly symptom assessments that children complete, the number of weekly symptom scores that exceed a prior threshold to trigger alerts, as well as clinician documentation to symptom alerts in the EHR. In addition, a subset of participants (parent-child dyads) will be interviewed to obtain their feedback on the symptom report discussions with their clinician and their experience participating in the SyMon-SAYS study at the end of the intervention phase. Children and parents will be interviewed independently. Efforts will be made to balance gender (children and parents), ages (children), clinical variables of children as well as English- and Spanish-speaking participants (all children are English-speaking). Participants whose parents speak Spanish will be interviewed in Spanish.

At the completion of the study, clinicians, including attending physicians, fellows, advanced practice nurses and physician assistants, and registered nurses, will also be interviewed by either individual interviews (via telephone) or email survey to obtain their feedback on the symptom report, the study, and suggestions on how to make it more accessible and child friendly.

We plan to interview up to 30 parent-child dyads and up to 20 clinicians. The telephone interviews will be recorded for transcription and subsequent summary of feedback. Members of the study team will use selective qualitative analysis methods and an iterative coding process to identify common themes and develop coding rules to apply to interviewees' comments. The comments will then be compiled and summarized in frequency tables denoting the number of times certain responses emerge. Both frequency and the relative importance placed on the theme will be used to evaluate usability, acceptability, and engagement along with quantitative results.

Adherence to Intervention

The adherence to the SyMon-SAYS Intervention will be evaluated by using the percentage of dyads completing the assessments at all time-points, excluding those who are off-study or deceased.

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Measures Used for Primary and Secondary Outcomes

Modified Symptom Management Barriers Questionnaire

The modified Symptom Management Barriers Questionnaire (SMBQ) is a 23-item tool designed to assess the attitude (perceived barriers) of parents with children diagnosed with cancer toward the assessment and management of their child's symptoms. The SMBQ comprises items that encompass various recognized barriers to achieving effective symptom management. The original version of the SMBQ [9] items was devised with input from experts in symptom assessment and management and interviews with patients and their spouses. The study team made adjustments to the items to ensure their suitability for parents of children with cancer, such as replacing the pronoun "I" with "my child."

Pediatric PROMIS

Change in HRQoL over time will be analyzed by examining changes in the pediatric PROMIS measures. We will administer computerized adaptive tests (CATs) of the domains in the PROMIS Pediatric Profile [50]: (1) physical function-mobility, (2) physical function-upper extremity, (3) depressive symptoms, (4) anxiety, (5) anger, and (6) relationship with peers. The pediatric PROMIS offer good reliability across 2-3 standard deviations of the experiences of children 8-17 years old.

Self-Efficacy: NIH Toolbox Self-Efficacy

The National Institutes of Health (NIH) Toolbox initiative was developed to identify, create, and validate measures in the broad domains of cognitive function, emotional health, motor function, and sensory function [51,52]. Measures of self-efficacy, defined as a person's belief in their capacity to manage their functioning and have control over meaningful events, were developed within the emotional health domain. This measure is available for children aged 8-12 years, adolescents aged 13-17 years, and adults aged 18 years or older and is available as CAT. These measures demonstrated good psychometric properties; US general population norms are available. Patients and parents will complete age-appropriate CATs.

Statistical Analysis

Analysis for Aim 1: Evaluate Efficacy of SyMon-SAYS After 8 Weeks and its Maintenance Effects at Week 16

The coprimary outcomes of the study will be perceived symptom management barriers, child's and parent's self-efficacy, and child's anxiety and depression. Data obtained from baseline, week 8, and week 16 will be analyzed. The primary analysis of intervention efficacy will focus on differences in changes between Group A and Group B in perceived barriers to managing symptoms, self-efficacy and depression, and anxiety from baseline to week 8. We will fit mixed effects models for repeated measures. Barriers, child and parent self-efficacy, depression, and anxiety will each be examined separately as dependent variables in these models (ie, each with separate models). We also will explore the associations of demographic variables (eg, gender), individual factors (eg, health literacy), and clinical characteristics (eg, intensity of treatment) on primary outcomes. We will control for multiplicity among coprimary outcomes with the Benjamini-Hochberg [53] procedure.

Secondary outcomes are changes in other domains of HRQoL, including fatigue, mobility, and peer relationships, as well as symptom burden. We will use the same approach to changes in patients' PROMIS Fatigue, PROMIS Mobility, and PROMIS Peer Relationships will take the same approach as that described above for primary outcomes using mixed effects models. Regarding from baseline to week 8 (Group A) or from week 9 to week 16 (Group B) estimated by calculating the area under the curve (AUC) of each symptom score plotted over time for each participant. The AUC will be then divided by the total time to rescale back to the original units. We will calculate a *P* value for differences in AUC curves between arms with a Wilcoxon rank test.

We hypothesize that group A participants will report fewer perceived barriers, less symptom burden, better self-efficacy, and better HRQoL over phase 1 (weeks 1-8) and then either stay the same or continue to improve over phase 2 (weeks 9-16; exploratory end points), when they continue to receive the SyMon-SAYS intervention. Group B participants, on the other hand, are not expected to report significantly different scores from baseline to the end of phase 1 (ie, week 8) but are expected to report significantly improved outcomes at week 16 than the scores at the baseline.

Analysis for Aim 2: Evaluate Factors Associated With Aim 1 Efficacy Outcomes

For each of the Aim 1 outcomes, we will code individual patients as having improved or not improved by a clinically important threshold. Then, we will examine whether patient and parent contextual factors (eg, patient demographic variables, parent health literacy, and disease severity) are associated with improvement in each outcome (each modeled separately) using multivariable logistic regression models.

Analysis for Aim 3: Evaluate Predictors of Adherence to the SyMon-SAYS Intervention and Preference of SyMon-SAYS Versus Usual Care

We will estimate participants' adherence to SyMon-SAYS during the intervention phase (weeks 1-8 for Group A and weeks 9-16 for Group B), defined as percentage of dyads completing the assessments at all time-points. Preference for SyMon-SAYS versus usual care will be assessed using relevant items in the patient and parent EXIT evaluation survey. These item responses will be descriptively summarized with frequency distributions. Clinicians' perceptions of the acceptability and usefulness of SyMon-SAYS (Evaluation Form) will be similarly assessed by summarizing responses to survey items.

We will identify predictors of intervention adherence and preference using ordinal regression models using data from both groups' intervention phases (weeks 1-8 for group A, weeks 9-16 for group B). Based on number of weekly system assessments completed, patients will be classified as high adherence (completed 7 or 8 weekly assessments), intermediate adherence (completed 3-6 weekly assessments), or low adherence (completed 1 or 2 or fewer weekly assessments). Parent and patient contextual factors to be examined as predictors such as

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gender, age, race, parent education, and parent health literacy as well as clinical characteristics such as treatment types. Additionally, we will repeat the same analysis using data from week 9- week 16 from group A to explore whether the group membership (ie, high, intermediate, or low adherence) changed between phase 1 (baseline to week 8) and phase 2 (week 9-week 16) as well as predictors associated with the group membership.

Data Quality and Management

In order to ensure adequate numbers of patients with data for the primary end point analysis, we increased the sample size to account for 20% dropout. Prior to performing analyses, we will evaluate the amount, reasons, and patterns of missing data. We will compare the baseline characteristics of patients with and without complete data. If necessary, multiple imputations of weekly symptom data for secondary end points by chained equations will be used to impute missing data.

To be in compliance with NCI's established publications and data-sharing policy for projects that are funded as part of the Beau Biden Cancer Moonshot Initiative, we will create a data codebook that explains each variable in our databases. We will create deidentified databases in easily-readable formats (eg, tab-delimited) for the express purpose of data-sharing. Underlying primary data for the publications will be made broadly available through our Dataverse site [54]. We will make our publications immediately open access. Publication author eligibility guidelines will be followed. Electronic copies of publications will be deposited in PubMed Central with proper tagging of metadata to ensure web-based discoverability and accessibility within 4 weeks of acceptance by a journal.

Study Timeline

We plan to complete this study in 60 months, including startup (2 months), report development (3 months), assembling symptom management information from web-based resources (8 months), programming SyMon-SAYS (6 months), pilot testing the system, training study personnel, modifying the system based on pilot feedback (6 months), study implementation (36 months, including 16 weeks follow-up), data analysis and manuscript preparation (6 months). Recruitment began in April 2021 and is expected to be completed in Spring or Summer, 2024.

Results

This study has received approval from the institutional review boards of Northwestern University (STU00210598) and Ann & Robert Lurie Children's Hospital of Chicago (IRB 2019-3018). Recruitment began in April 2021 and is anticipated to be completed by Spring or Summer 2024. Following the completion of data collection and analysis, the results will be submitted for publication in a manuscript describing the updated trial results.

Discussion

SyMon-SAYS has several unique features that will significantly advance self-management through incorporating patient-reported symptom monitoring with IT. SyMon-SAYS is incorporated into the EHR to minimize clinic workflow disruption to clinicians and facilitate accessibility by parents and patients, thereby promoting adherence in children, parents and clinicians. Integrating PROs into the EHR has shown improved outcomes in adult patients with cancer [55]. Similar efforts in patients with pediatric cancer are still in their infancy with either focused on patients with pediatric cancer who were hospitalized [37] or were not incorporated into electronic medical records [56]. While SyMon-SAYS captures symptoms occurring between clinical visits. SyMon-SAYS produces user-friendly graphic symptom reports of scores displaying change over time that are presented to parents and clinicians. Parents (and clinicians) will be able to track patients' symptom levels over time, which can enhance their awareness of symptom variability, contribute to increased symptom and illness or disease knowledge, seek medical help in a timely manner, and promote their ability to prepare for communicating with the clinical team [57].

The study has some potential caveats that will need to be considered in interpreting the findings and should be addressed in future research. We considered several randomization strategies, including cluster randomization by physician versus individual-level randomization by patient-parent dyad. Due to the limited number of eligible physicians within a single institution, we deemed it best to randomize by patient despite the known limitations, the greatest of which is contamination. Although exposure to the intervention may influence physicians' discussion or management of their patients in the waitlist control (group B, weeks 1-8), they will not have access to symptom reports for their patients who have not yet crossed over from control to intervention. Given the potential for interinstitutional variability in functionalities to support routine symptom surveillance, we elected to conduct a single institution randomized phase 2 trial to detect an efficacy signal prior to moving to a pivotal phase 3 trial across multiple institutions if our findings demonstrate that the intervention is efficacious. This future trial would randomize by the clinic. We chose a waitlist control design primarily because it exposes Group B participants to both usual care and the SyMon-SAYS intervention, allowing them to state their preferred approach for symptom management. Instead of a cross-over design, we chose to have group A participants continue intervention during weeks 9-16 as it is not reasonable to discourage them from accessing reports and resources available in the Epic EHR that they are exposed to in weeks 1-8. Additionally, this approach allows us to evaluate the durability of the SyMon-SAYS intervention. This study will provide a better understanding of factors impacting patients' and parents' preferences, which can inform the development of individualized interventions to manage symptoms more effectively. We will review the frequency with which participants access web-based information resources. Group differences in frequencies of accessing information resources will not be evaluated during weeks 9-16, as there may be a sustained benefit from weeks 1-8. Thus, the primary comparisons will occur using data collected during the first 8 weeks.

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Conclusions

In conclusion, we believe that this randomized waitlist controlled trial of the SyMon-SAYS system will provide preliminary efficacy estimates, gauge feasibility and acceptability, identify predictors of engagement, and suggest strategies to strengthen adherence and adoption in subsequent trials of digital symptom monitoring and management tools in children with cancer across the disease continuum, from active therapy to long-term follow-up.

Acknowledgments

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Data Availability

Once the primary results are published, the underlying primary data for the publications will be made widely accessible through the Dataverse [58].

Conflicts of Interest

None declared.

Multimedia Appendix 1
Symptom monitoring and systematic assessment and reporting system in young survivors (SyMon-SAYS) weekly symptom checklist.
[DOCX File , 19 KB - resprot_v12i1e50993_app1.docx]

Multimedia Appendix 2
CONSORT e-HEALTH checklist (V 1.6.1).
[PDF File (Adobe PDF File), 1254 KB - resprot_v12i1e50993_app2.pdf]

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Abbreviations

AUC: area under the curve

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CAT: computerized adaptive test
DSMB: Data and Safety Monitoring Board
EHR: electronic health record
HRQoL: health-related quality of life
IP: intervention participant
NIH: National Institutes of Health
PI: principal investigator
Ped-PRO-CTCAE: pediatric patient-reported outcomes version of the common terminology criteria for adverse events
PROMIS: Pediatric Patient-Reported Outcome Measurement Information System
SyMon-SAYS: Symptom Monitoring and Systematic Assessment and Reporting System in Young Survivors

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Protocol

A Family-Based Mental Health Navigator Intervention for Youth in the Child Welfare System: Protocol for a Randomized Controlled Trial

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Abstract

Background: Youth in the child welfare system (child welfare–involved [CWI] youth) have high documented rates of mental health symptoms and experience significant disparities in mental health care services access and engagement. Adolescence is a developmental stage that confers increased likelihood of experiencing mental health symptoms and the emergence of disorders that can persist into adulthood. Despite a high documented need for evidence-based mental health services for CWI youth, coordination between child welfare and mental health service systems to increase access to care remains inadequate, and engagement in mental health services is low. Navigator models developed in the health care field to address challenges of service access, fragmentation, and continuity that affect the quality of care provide a promising approach to increase linkage to, and engagement in, mental health services for CWI youth. However, at present, there is no empirically supported mental health navigator model to address the unique and complex mental health needs of CWI youth and their families.

Objective: Using a randomized controlled trial, this study aims to develop and test a foster care family navigator (FCFN) model to improve mental health service outcomes for CWI adolescents (aged 12-17 years).

Methods: The navigator model leverages an in-person navigator and use of adjunctive digital health technology to engage with, and improve, care coordination, tracking, and monitoring of mental health service needs for CWI youth and families. In total, 80 caregiver-youth dyads will be randomized to receive either the FCFN intervention or standard of care (clinical case management services): 40 (50%) to FCFN and 40 (50%) to control. Qualitative exit interviews will inform the feasibility and acceptability of the services received during the 6-month period. The primary trial outcomes are mental health treatment initiation and engagement. Other pre- and postservice outcomes, such as proportion screened and time to screening, will also be evaluated. We hypothesize that youth receiving the FCFN intervention will have higher rates of mental health treatment initiation and engagement than youth receiving standard of care.

Results: We propose enrollment of 80 dyads by March 2024, final data collection by September 2024, and the publication of main findings in March 2025. After final data analysis and writing of the results, the resulting manuscripts will be submitted to journals for dissemination.

Conclusions: This study will be the first to produce empirically driven conclusions and recommendations for implementing a family mental health navigation model for CWI youth with long-standing and unaddressed disparities in behavioral health services

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access. The study findings have potential to have large-scale trial applicability and be feasible and acceptable for eventual system implementation and adoption.

Trial Registration: ClinicalTrials.gov NCT04506437; https://www.clinicaltrials.gov/study/NCT04506437

International Registered Report Identifier (IRRID): DERR1-10.2196/49999

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KEYWORDS

randomized clinical trial; foster care; child welfare–involved youth; navigator interventions; digital health technology; implementation science; community engagement

Introduction

Background

After a decade-long decline in the number of youth in placement outside of the home (ie, foster care) in the United States, the foster care caseload in most states rose between 2014 and 2019. The current foster care caseload exceeds 400,000 in the United States [1], with another approximately 165,000 youth receiving court-mandated services within their own homes [2]. Youth in out-of-home or foster care placement and those remaining in the home but are child welfare system and court involved are collectively referred to as *child welfare–involved (CWI)* and are considered some of the most underserved with respect to behavioral health care access in the United States. The COVID-19 pandemic has further increased the number of youth entering the child welfare system owing to having lost parents or caregivers from COVID-19–related death [3].

Rates of mental health symptoms and diagnoses in CWI youth are high, particularly among adolescents. The vast majority are referred to child welfare agencies because of child abuse or neglect [4], and, as a result of trauma experienced in their home of origin, the majority display mental health or behavioral health challenges [5]. According to the National Survey of Child and Adolescent Well-Being, much more than half of a national sample of youth in out-of-home care display behavioral or social competency problems [6], and studies that include smaller samples or regional samples suggest similar results [7,8]. Among 815 CWI youths aged 12 to 17 years, 43% reported at least 1 mental health concern, including attention-deficit/hyperactivity disorder (ADHD; 19%), suicidality (14%), anxiety (14%), depression (9%), and co-occurring substance use (23%) [9]. Youth in out-of-home care report higher rates of mental health problems than peers of a similar age [10,11]. Depending on the study, between 35% and 85% of all youth in out-of-home care experience a mental health condition [12], and youth in out-of-home care are 3 times more likely to be prescribed psychotropic medications for their mental health conditions [13].

Adolescence is a critical developmental period for the assessment, diagnosis, and treatment of mental health symptoms. Vulnerability to mental health disorders increases significantly in adolescence, and the emergence of disorders during this period (eg, early psychosis) increases the likelihood of persistence into adulthood [14]. Rates of depression escalate in adolescence, particularly among girls with extensive trauma histories (such as CWI youth) who are at substantially higher risk for poor mental health, substance use, and legal outcomes. Adolescence also encompasses unique factors associated with the transition to young adulthood (eg, for those aged 16-17 years), making it a highly vulnerable developmental stage for CWI youth [9]. Adolescents who are placed in out-of-home care face unique risks because chronic placement instability is the norm rather than the exception, particularly for older adolescents [15-17]. Studies demonstrate that youth with mental health difficulties are more likely to be moved from one placement to another, and these moves create or exacerbate mental health concerns [18,19]. These concerns are exacerbated for racial and ethnic minoritized youth [20] and reify ongoing and long-standing behavioral health disparities among CWI youth. Identifying adolescent mental health needs, matching these needs to appropriate services, and providing supports for mental health care access and linkage have great potential to resolve or offset challenges manifesting in adulthood.

Despite high need for evidence-based mental health services for CWI youth, ample evidence suggests that coordination between child welfare and mental health service systems is inadequate. Access to care for CWI youth is hampered by multiple system-level barriers, such as frequent change of placement as well as underreporting of mental health problems by foster parents, social workers, and physicians [13]. National survey data (n=3803) highlight a substantial gap between the identified need for and use of mental health services in child welfare populations, particularly among older youth: 66% of those aged 11 to 14 years have clinically significant mental health needs, yet only 26% use mental health services [21]. Data local to the site of the proposed project demonstrate critical gaps in mental health screening and full assessment, with only 28% of all youth assessed within 2 months of case opening, 45% by 3 months, and 69% by 6 months. Furthermore, by 12 months, 11% of youth had their case closed before ever receiving a mental health assessment [22].

The public health impact of gaps in mental health services delivery among CWI youth is significant. Untreated mental health concerns among CWI youth persist when they leave the out-of-home care system and transition to independence [23]. CWI youth are also likely to have dual (or *crossover*) involvement with the juvenile legal system [24], which can further exacerbate unmet services needs and disparities within this population. Persistent mental health concerns in this population can also contribute to placement instability [25] and re-entry into the child welfare and juvenile legal systems [26], which both compound mental health difficulties and strain public health systems and economies. Unaddressed mental health

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services needs also perpetuate racial and ethnic disparities in services access, engagement, and quality in this population, as well as perpetuate the root causes of these disparities (eg, systemic racism and discrimination), which have notable public health consequences. Data local to the site of the proposed project mirror national statistics, documenting the alarming overrepresentation of African American and Latinx youth in the child welfare system [21]: 36% of CWI youth aged 12 to 17 years are African American compared with 6.1% of the entire county population.

Navigator models (ie, the use of a navigator to support access to, and transition through, complex health care systems) provide a promising approach to increasing linkage to, and engagement in, mental health services for CWI youth with high rates of unaddressed mental health concerns. Navigator models have been successfully developed and deployed in other contexts (eg, cancer and HIV), with demonstrated improvements in service tailoring, linkage, and treatment retention [27]. A small number have also been developed for general adolescent populations with behavioral health needs (eg, the Family Navigation Project) [28]. However, existing mental health navigator models have not been empirically developed or tailored for system-involved (ie, child welfare or juvenile legal system) youth and families who have unique, complex multisystemic factors associated with mental health care needs and access.

Mobile health (mHealth) technology is gaining empirical support for improving adolescent mental health and behavioral health (eg, substance use) outcomes. Data suggest that SMS text messaging is a useful tool to improve youth attendance in outpatient mental health treatment [29] and can prevent adolescent substance use relapse [30]. A recent meta-analysis (n=14 studies) concluded that SMS text messaging technology is a promising substance use prevention strategy for adolescents and young adults [31], the majority of whom have access to, and regularly use, their mobile phones despite unique adolescent barriers to constant access and use (eg, service payment, continuous service, and no access while at school during the day). Our own work with community-supervised court-involved adolescents and their caregivers suggests that families and involved juvenile legal personnel and providers all heavily rely on digital and mHealth technology for communication and care coordination (eg, SMS text messaging, emailing, and social media instant messaging) [32].

Despite the promise and prevalence of mHealth technology, there is no systematic, empirically supported strategy leveraging mHealth to enhance family-based approaches to improving CWI youth mental health service use and outcomes. Studies show that only some caregivers are ready for electronic messaging support for health care [33] and that depending on caregiver race or ethnicity (eg, Latinx ethnicity), socioeconomic status (eg, low status) and age (eg, younger age), SMS text messaging may be more or less appealing as a tool for adolescent health care engagement [33,34]. Parent outreach via bidirectional SMS text messaging to enhance the uptake of adolescent vaccine and well care services improved these adolescent health outcomes [35], suggesting that a caregiver-level mHealth intervention may be effective in improving other adolescent health outcomes (eg, mental health). Caregivers of CWI youth have the additional context of juvenile legal system and child welfare system surveillance and involvement (eg, mandated youth treatment, sanctions-based approach to noncompliance, and information-sharing concerns) that might differentially affect their response to mental health navigator interventions, particularly those that incorporate mHealth for service tracking or monitoring. Given the high numbers of staff, providers, and systems that often operate separately and with minimal coordination to support CWI youth, mHealth has unique potential to improve communication between families and systems to support linkage to, and engagement in, mental health services.

Given the significant need for an empirically driven, timely, coordinated, and collaborative interagency response to addressing the mental health needs of CWI youth, the proposed project aims to develop and test an empirically derived navigator intervention that relies on interagency codevelopment and incorporates state-of-the-art mHealth technology to improve linkage to, and engagement in, mental health services among CWI youth. A randomized clinical trial (N=80 caregiver-youth dyads) comparing the navigator intervention with standard of care (clinical case management services) for CWI youth has the potential to have large-scale trial applicability and to be feasible and acceptable for eventual system implementation and adoption.

Study Objectives

This study will be the first to develop and test a foster care family navigator (FCFN) intervention for CWI youth that has the potential to significantly improve adolescent mental health disparities, particularly for racial and ethnic minoritized youth. The primary goal of the study is to assess the feasibility, acceptability, and preliminary impact of the FCFN intervention on the mental health services cascade of care (eg, screening, assessment, and treatment initiation) outcomes. Using a randomized controlled trial (RCT) design, we will randomize 80 families to receive either the FCFN intervention or standard of care (clinical case management services): 40 (50%) to FCFN and 40 (50%) to control. Qualitative exit interviews will inform the feasibility and acceptability of the services received during the 6-month period. Primary trial outcomes are mental health treatment initiation and engagement. Other pre- and postservice outcomes, such as proportion screened and time to screening, will also be evaluated.

Juvenile Justice Behavioral Health Services Cascade

The juvenile justice behavioral health services cascade, hereinafter referred to as the *cascade*, was recently developed (adapted from the HIV cascade of care models) [36] as part of the Juvenile Justice Translational Research on Interventions for Adolescents in the Legal System (JJ-TRIALS) study, a National Institute on Drug Abuse–funded, large-scale, multisite research and implementation science collaborative. JJ-TRIALS developed the *cascade* as a unifying framework for juvenile legal system and behavioral health partners to collectively (1) identify system-level substance use service strengths and needs along the continuum of care and (2) codevelop and test interventions to improve adolescent substance use service linkage and

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outcomes along the *cascade*. The *cascade* framework can also inform multiple interrelated research goals and be easily adapted for empirical application and testing with other youth populations (eg, foster care youth), systems (eg, child welfare system) and health (eg, mental health) outcomes [37] as in the proposed study. Figure 1 presents a hypothetical adapted *cascade* framework for CWI adolescent populations using the same cascade of care steps but modifying the involved systems (eg, from juvenile legal system to child welfare system). Table 1 presents step definitions (developed by the JJ-TRIALS group) adapted to CWI youth and system processes.

Figure 1. Example of juvenile justice behavioral health services cascade adapted for child welfare–involved (CWI) youth.

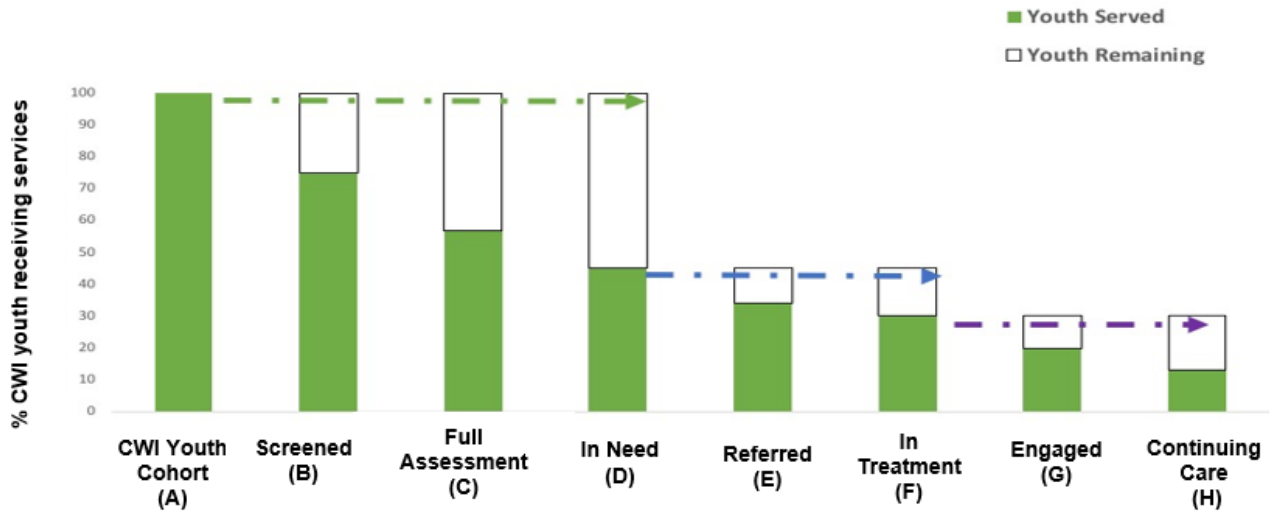


Table 1. Behavioral health services cascade definitions adapted for child welfare–involved youth and the foster care mental health (FCMH) system.

Step	Operational definition	Calculated proportion (based on step)
A. Child welfare referrals	Total number of referrals to FCMH over a designated period of time, less any youth already in treatment at that time	N/A[a]
B. Screened	Subset of FCMH referrals (A) with a screening date	B/A
C. Full clinical assessment	Subset of FCMH referrals (A) with a full clinical assessment (includes if follow-up to screening or other clinical assessment)	C/A
D. In need	Subset of FCMH referrals (A) with a need for mental health treatment based on screener, clinical assessment, or other sources of information	D/A
E. Referrals to treatment	Subset of those in need (D), referred by the child welfare or FCMH systems to mental health treatment	E/D
F. In treatment	Subset of those referred to treatment (E) who have a treatment start date	F/E
G. Engaged in care	Subset of those in treatment (F) who stay in treatment for at least 6 weeks (based on treatment discharge minus treatment start date)	G/F
H. Continuing care	Subset of those engaged in treatment (G) who are still receiving treatment after 90 days	H/G

[a]N/A: not applicable.

Digital Health Application (Chorus) and Approach

The FCFN intervention incorporates digital health technology grounded in participatory informatics (using the secure web-based Chorus platform [Chorus Innovations, Inc], which involved end users and navigators in app codevelopment as an inherent and critical component of successful navigation [38]). Chorus is an established digital health platform that provides the basis for a web application named Fostering Connections, which is accessible to a broad range of people (similar to visually creating slides in Microsoft PowerPoint) and includes interactive messaging and mobile web app capabilities [38]. Fostering Connections was adapted based on feedback from CWI families and stakeholders and is designed to support the navigation process across multiple dimensions by (1) supporting bidirectional SMS text messaging (and shared dashboards) to enhance communication between navigators and families, (2) including reminders for upcoming session and behavioral health services appointments, (3) storing navigation documents and resources, and (4) including surveys for completion by navigators. Thus, it is a proven and reliable system that will allow navigators to effectively opt in as well as communicate with, and engage, participants and other providers; in addition, it can be developed and tailored according to research study needs.

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Hypotheses

We hypothesize that youth receiving the FCFN intervention will have increased rates of mental health treatment initiation and engagement compared with youth receiving standard of care. We will also explore hypothesized mechanisms of intervention impact (eg, navigator satisfaction, youth treatment motivation, and perceived barriers to care) as well as potential moderators (eg, sex, race, ethnicity, and out-of-home placement status).

Methods

Study Design

Up to 5 FCFNs and 80 families (caregiver-youth dyads) will participate in the RCT to assess the preliminary impact of the FCFN intervention on mental health services use. CWI youth (in in-home or out-of-home placement) aged between 12 and 17 years as well as their caregivers will be referred for study participation at the point of referral from the child welfare system to a partnering mental health clinic (hereinafter referred to as the foster care mental health [FCMH] clinic) that specializes in serving foster care youth by linking them to specialty mental health services. Enrolled families will be randomized to either the FCFN intervention or standard of care.

Enrolled CWI youth and their caregivers will complete a computerized set of questionnaires (on a tablet device, mobile phone, PC, or laptop computer) at baseline, midintervention (1-month after baseline), and at 3 and 6 months after randomization.

The trial has been registered with ClinicalTrials.gov (NCT04506437).

Intervention Condition (FCFN)

Families (n=40) who are randomized to the FCFN intervention will complete six 60-minute intervention sessions in the first 2 to 3 months of the 6-month period. Sessions can be scheduled on a weekly or biweekly basis. The 6 sessions, described in Figure 2, are as follows: *Introduction to the navigator and navigation services*, *Specialty mental health services orientation*, *Clinical care team mapping*, *Barriers to care and stress management*, *Therapy expectations and stigma*, and *Values and motivation to engage in treatment*. The 6-month intervention period also includes brief check-ins with youth and caregivers, typically conducted through the Fostering Connections web application, by telephone and videoconferencing, depending on the preference and availability of families. The 6 intervention sessions will be audio recorded to separately assess for FCFN intervention fidelity by trained study staff (raters).

Figure 2. Session-by-session content.



Standard of Care (Clinical Case Management Services) Condition

Families (n=40) who are randomized to standard of care (comparison condition) will receive clinical case management services *as usual*, delivered by FCMH clinic case managers. The role of FCMH clinic case managers is to identify mental health treatment referral resources in the community that match current youth mental health service needs. FCMH clinic case managers facilitate direct referral to a community provider and then provide this information for the family to link to community-based care. FCMH clinic case managers do not typically meet with youth and their families directly but rather follow the existing FCMH clinic protocol of facilitating referrals and linkage via telephone and other communication with youth and their families and their FCMH clinic screening clinician.

Participants

FCMH Clinic Study Sample

Recruitment for the study commenced in August 2020 and will conclude by March 2024. Historically, the FCMH clinic has served an annual average of 100 unduplicated youth aged 12 to 17 years with mental health screening and other related services for those with medical necessity. The average length of time in the court dependency process is 6 months, but can be as long as 12 months in cases of family reunification, and up to 18 months in cases of permanency planning or transition-age youth.

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Youth who reach the age of 18 years while receiving FCMH services are eligible for, and continue to receive, services without disruption.

Racial, Ethnic, and Sex Considerations

FCMH clinic data from the 2017-2018 period suggest that the ethnic representation of youth will be approximately 29% Hispanic or Latinx and that the racial representation will be 29% African American, 3% American Indian or Alaska Native, 18% Asian or Pacific Islander, 14% European-American or White, 3% multiethnic, and 4% other. Of the FCMH clinic adolescent caseload, male adolescents represent approximately 41%, and female adolescents represent approximately 59%. African American and Latinx youth are disproportionately represented, given that, of the total population in the clinic's surrounding area, African Americans comprise only 6.1% and Latinx only 15.1%.

Behavioral Health Considerations

On the basis of FCMH clinic data from the 2017-2018 period, medical records identified the primary disorder diagnosis as 43% adjustment, 24% mood, 22% anxiety (including posttraumatic stress disorder [PTSD]), 7% behavioral (eg, oppositional), 1% psychosis, and 3% deferred.

Inclusion and Exclusion Criteria

Eligible participants will be youth aged between 12 and 17 years who have an active dependency petition with the local unified family court (newly filed or existing when the RCT commences), are referred to the FCMH clinic for services, have an involved caregiver or legal guardian who can consent and participate in the intervention, and whose family has mobile phone access. The exclusion criteria include youth and caregivers who are monolingual in languages other than English or Spanish, caregiver impairment that would preclude providing informed consent, and the lack of an available guardian for consent.

Recruitment and Consent

Study staff will be embedded in the FCMH clinic setting to introduce the study and procedures to eligible families at the time that families meet with FCMH clinic staff (eg, to complete the mental health screening). FCMH clinic staff will refer eligible families to meet with study staff. Interested youth and families will be separately assented or consented in a private place (FCMH clinic staff will not be involved). We will obtain a waiver of parental consent for referred youth.

Randomization

Participants will be randomized (using a computer-generated randomization tool) to either the FCFN intervention group (40/80, 50%) or the standard of care group (40/80, 50%) directly after consent and completion of the baseline assessment.

Ethics Approval

This study was approved by the institutional review board at the University of California San Francisco (268565) and was conducted in accordance with the ethical standards of the Helsinki Declaration.

Assessment Data Collection

Multiple sources of data will be collected, including electronic medical records (EMRs); mobile phone or web entry in the Fostering Connections web application; and self-reports from the FCFNs, youth, and caregivers (Textbox 1). Cascade mental health services–level data will be extracted from EMRs at baseline and at 1, 3, and 6 months for participants in both conditions. Assessments will be conducted via mobile phone or tablet device, depending on participant preference.

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Textbox 1. Study measures.

Identification (percentage of court cohort aged 12-17 years; electronic medical record [EMR])

- Percentage screened (Child and Adolescent Needs and Strengths [CANS; short form]), percentage assessed (CANS), and percentage in need
- Time to screening, full assessment, and determination of need (number of days)

Transition (percentage of those identified as in need; EMR)

- Percentage referred for treatment and percentage who initiated treatment
- Time to referral and initiation (number of days)

Retention (percentage of those referred for treatment; EMR)

- Engaged in care (≥6 weeks of attendance)
- Continuing care (number of total sessions completed)

Navigator background (foster care family navigator [FCFN])

- Age, race and ethnicity, education, training, and years in child welfare field

Number and types of contacts with navigator (Chorus platform, FCFN, youth, and caregivers)

- Video, SMS text messaging, in person, and telephone

FCFN intervention fidelity (FCFN)

- Developed as part of prior study procedures

Therapeutic Working Alliance (youth)

- Twelve-item Working Alliance Inventory [39], used in the Cannabis Youth Treatment Study [40], that assesses youth's perception of therapeutic alliance over time

Navigation Satisfaction Tool, Part I [41] (youth and caregivers)

- Twelve items that address client satisfaction with navigation services (eg, How satisfied are you with the navigator's ability to listen and understand your concerns? How satisfied are you with the frequency of contact with the navigator?)

Evidence-Based Practice Attitude Scale-50 (FCFN)

- A 50-item scale [42], developed and validated with mental health service providers, that assesses global attitudes toward the adoption of evidence-based practices

Barriers to Care Questionnaire (youth and caregivers)

- A 39-item scale (subscales of skills, marginalization, stigma, expectations, knowledge and beliefs, and pragmatics) [43] that assesses perceived barriers to child health care access; items are rated on the extent of the problem (ranging from 100 for "no problem" to 0 for "very big problem"), with higher scores indicating fewer barriers (items are at 5.7 grade reading level)

Motivation for Youth's Treatment Scale (youth and caregivers)

- A psychometrically valid 8-item scale [44] that youth and caregivers complete to measure intrinsic treatment motivation with the subscales of problem recognition and treatment readiness

Mobile health (mHealth) feasibility or satisfaction (Chorus platform, youth, and caregivers)

- Mobile phone type, mobile phone service interruptions, number of mobile phone numbers, most preferred types of SMS text messages, number of messages opened or read, and responses

Usability of mHealth intervention components or "system": System Usability Scale (SUS; FCFN, youth, and caregivers)

- A 10-item measure [45] widely used to evaluate web applications that has proven superior to other measures; the SUS yields a single number representing a composite measure of the overall usability of the system being studied, and scores will be compared with established norms for levels of usability; our goal is a score of 80 (top 10% of scores), which reflects excellent usability and is associated with recommending the product to a friend

Sociodemographics (EMR, youth, and caregivers)

- Race, ethnicity, sex, education, income, legal history, and placement type

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Pediatric Symptom Checklist (EMR, youth, and caregivers)

- A 35-item measure of child emotional and behavioral problems that has been identified as a feasible method for the early detection of mental health difficulties [46] and intervention outcomes measurement [47]; items are rated as "never present" (0), "sometimes present" (1), or "often present" (2), with the total (summed) score ranging from 0 to 70; for children and youth aged 6 to 18 years, the cutoff score is 28 (≥28=impaired)

University of California Los Angeles Posttraumatic Stress Disorder Reaction Index for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5; youth)

- An instrument that screens for exposure to traumatic events and the frequency of posttraumatic stress disorder symptom occurrence during the past month (ranging from 0=none of the time to 4=most of the time) [48]; items map directly onto DSM-5 intrusion, avoidance, and arousal criteria, whereas 2 additional items assess associated features (fear of recurrence and trauma-related guilt); scoring algorithms permit tabulation of the total score as well as B, C, and D subscale scores

Brief Symptom Inventory (caregivers)

- A 51-item measure of past week mental health symptoms [49]

Parent-Adolescent General Communication Scale (youth and caregivers)

- A scale that assesses positive and negative aspects of communication via 2 subscales (open family communication and problems in family communication) [50], with 5 items assessing the frequency of communication topics

Parental Monitoring Questionnaire (youth and caregivers)

- A 24-item measure of parental monitoring across 4 areas or subscales (parental knowledge, child disclosure, parental solicitation, and parental control), with higher scores indicating higher levels of monitoring domains [51]

Measures

Overview

Youth and caregivers in both conditions will each complete the electronic study assessment at baseline and at 1, 3, and 6 months (4 times in total). Unless it is specifically noted, all of the following measures will be collected from youth and caregivers across both conditions. FCFN navigator measures are also included.

Primary Outcome Measures

Cascade of Care Services

We will collect EMR data that will include (1) percentage screened (for mental health needs), percentage assessed (received full mental health assessment), and percentage in need (determined to meet medical necessity criteria for mental health services); (2) time to screening, full assessment, and determination of need (number of days); (3) percentage referred for mental health treatment as well as percentage who initiated treatment; (4) time to referral and initiation (number of days); (5) whether the youth engaged in treatment (whether they had ≥6 weeks of treatment attendance); (6) number of total mental health treatment sessions completed; (7) sociodemographics (to provide collateral EMR data on race and ethnicity, sex, education, income, legal history, and placement type); (8) Child and Adolescent Needs and Strengths (CANS) screener and full assessment (the number and descriptions of needs and strengths and based on the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition [DSM-5], diagnosis per the CANS rating and resources manual with regard to children and youth aged 5-18 years); and (9) Pediatric Symptom Checklist score (collected by the specialty mental health provider and entered into the EMR as part of standard clinical and billing practice).

Therapeutic Working Alliance

The 12-item Working Alliance Inventory (WAI) [39], which was used in the Cannabis Youth Treatment Study [40], assesses youth perception of therapeutic alliance over time.

Navigation Satisfaction Tool, Part I

The 12-item Navigation Satisfaction Tool (NAVSAT), Part I [41], addresses participant satisfaction with navigation services (eg, How satisfied are you with the navigator's ability to listen or understand your concerns? How satisfied are you with the frequency of contact with the navigator?)

Barriers to Care Questionnaire

This 39-item scale (subscales of skills, marginalization, stigma, expectations, knowledge and beliefs, and pragmatics) assesses perceived barriers to youth health care access [43]. Items are rated on the extent of the problem (ranging from 100 for "no problem" to 0 for "very big problem"). Higher scores indicate fewer barriers. The items are at 5.7 grade reading level, and thus youth can complete this questionnaire.

Motivation for Youth's Treatment Scale

This is a psychometrically valid 8-item scale that youth and caregivers complete to measure intrinsic treatment motivation with the subscales of problem recognition and treatment readiness [44].

System Usability Scale

The System Usability Scale (SUS) [52] is a 10-item measure that is widely used to evaluate web applications and has proven superior to other measures. The SUS yields a single number representing a composite measure of the overall usability of the system being studied [45]. The SUS scores will be compared with established norms for levels of usability. Our goal is to reach a score of 80, which is in the top 10% of scores, reflects excellent usability, and is associated with recommending the

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product to a friend (youth and caregivers; intervention group only).

Pediatric Symptom Checklist

This 35-item measure of child emotional and behavioral problems [46] is widely used in diverse pediatric primary care settings and has been identified as a feasible method for the early detection of mental health difficulties and intervention outcomes measurement [47]. Items are rated as "never present," "sometimes present," or "often present" and scored 0, 1, and 2, respectively. The total (summed) score ranges from 0 to 70; for children and youth aged 6 to 18 years, the cutoff score is 28 (≥28=impaired). We will collect this separately and in addition to available EMR Pediatric Symptom Checklist data to measure changes in symptoms over time (ie, for repeated measures).

Brief Symptom Inventory

This 51-item measure will be used to rate the extent to which parents have been bothered in the past week by their own mental health symptoms [49].

Texas Christian University Drug Screen 5

This 17-item measure assesses past 12-month quantity and frequency of alcohol and drug use and the perceived level of functioning and impairment associated with substance use (youth only) [53].

Parent-Adolescent General Communication Scale

This scale will assess the positive and negative aspects of general communication via 2 subscales (open family communication and problems in family communication) [50]. Five items assess the frequency of communication topics.

Parental Monitoring Questionnaire

This 24-item measure is designed to assess parental monitoring across 4 areas or subscales (parental knowledge, child disclosure, parental solicitation, and parental control) [51]. Higher scores indicate higher levels of monitoring domains.

Child and Adolescent Services Assessment

This assessment consists of a semistructured interview that obtains information about service use for mental health problems across multiple sectors (eg, juvenile legal system and schools) [54]. Information about the type of facility, the professional discipline of provider or providers, outpatient services, and out-of-home placements is obtained, and the measure has adequate reliability (intraclass correlation coefficient=0.74-0.76). We will categorize the length and nature of treatment received to increase the generalizability of our study results. We will also add items related to participants' arrest history.

University of California Los Angeles PTSD Reaction Index for DSM-5

This instrument is used to screen for exposure to traumatic events and assess the frequency of occurrence of PTSD symptoms in the past month [48]. We will use a modified version of this measure that will only ask about the total number of exposures to traumatic events and not the specific type of event or any details related to the event.

Sociodemographics

We will collect data on race, ethnicity, sex, education, income, legal history, and placement type.

Number and Types of Contacts

Data regarding the number and types of contacts between the FCFNs and youth and caregivers will be collected from the Fostering Connections web application (eg, total number of messages sent and received, number of messages read, content of the messages, and number of contacts with the FCFNs).

FCFN Feasibility, Acceptability, and Satisfaction: Evidence-Based Practice Attitude Scale-50

This 50-item scale was developed and validated with mental health service providers and assesses global attitudes toward the adoption of evidence-based practices [42].

FCFN Feasibility, Acceptability, and Satisfaction: FCFN Fidelity Forms

As part of intervention delivery, the FCFNs will rate the adherence to sessions (eg, activities completed and number of contacts) of youth and caregivers. The FCFNs will also complete their own feedback session forms after each of the six 60-minute sessions to document the occurrence of planned activities and content and the occurrence of additional activities (that might not have been part of the FCFN manualized intervention), as well as any aberrant events.

Exit Interviews With Youth and Caregivers

A subsample of 12 families or 24 participants (6 youths and 6 caregivers or 12 participants from each condition) will be invited to participate in an exit interview at the end of the 6-month intervention period to inform feasibility, acceptability, and satisfaction with the FCFN and standard of care (clinical case management services) conditions. Each participant will be offered a US $40 gift card (applicable to those who are allowed to receive it).

Exit Interviews With Foster Care Family Navigators

Up to 5 FCFNs will be invited to participate in an exit interview at the end of the pilot RCT study phase to provide more detailed feedback on their experiences of delivering the FCFN intervention and to inform future trials. Each participant will be offered a US $40 gift card (applicable to those who are allowed to receive it).

Statistical Analysis

Quantitative Analysis

Overview

Analyses will be conducted using SAS 9.4 (SAS Institute Inc) [55]. Preliminary analyses will include an examination of descriptive statistics and distributions. Scaled psychometric measures (eg, the Barriers to Care Questionnaire) will be scored according to established algorithms and internal consistency reliability examined. Item-level missing data will be minimized through the programming of surveys; multiple imputation (PROC MI) will be used for item-level missing data if missingness is random. A unified statistical framework—generalized linear mixed models (GLMMs; PROC

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GLIMMIX)—will be used for most analyses. These models account for the clustering of participants and for unit-level missing data.

Cascade Outcomes

GLMM analyses of dichotomous outcomes (screening, treatment initiation, etc) will include intervention (FCFN group vs control group) as a fixed between-participants effect. Cox regression analysis (PROC PHREG) will be used to compare the interventions on time-to-event outcomes (eg, time to assessment) using a shared frailty model that accounts for clustering within pods. The potential mediators and mechanisms of change, measured longitudinally (at baseline and at 1, 3, and 6 months) only for FCFN intervention participants, will be initially examined for intervention impact using GLMMs that include a repeated within-participants time effect. The majority of the mediators are scaled variables, anticipated to have normal distributions, but final models and link functions will be chosen based on observed distributions. It will not be possible to test mediation without data from the control group. Therefore, we will identify potential mediators to be studied in the future trial by first determining which potential mediators change between baseline and month 1 or month 3 and then examining whether month 1 or month 3 values and changes between baseline and month 1 or month 3 are associated with cascade outcomes.

Moderators

We will examine potential moderators (eg, sex, gender, race and ethnicity, and mental health symptoms) of intervention impact by adding the potential moderators one at a time, given the modest sample size, to the models used to examine cascade outcomes and mediators. Analyses of cascade outcomes will include moderator × intervention interactions, and analyses of mediators will include moderator × time interactions.

Qualitative Analysis

All individual interviews will be digitally recorded and transcribed verbatim. Interview facilitators will review the recording and write notes within 48 hours of each interview completion to construct an executive summary of the main discussion points and topics. Executive summaries have been used successfully in the work conducted by the principal investigator (MTS) to provide data quickly and provide evidence of whether discussion theme saturation is achieved. Key data from executive memos will be immediately entered into ATLAS.ti software (version 7; ATLAS.ti Scientific Software Development GmbH), and the results will be presented to the investigator team. After the completion of the executive summaries and development of the FCFN intervention content, interview data will be analyzed according to inductive thematic analysis methods. An initial codebook will be developed based on the interview guides and corresponding transcripts. To improve reliability and to ensure adequate intercoder agreement, one of the authors (ED) and a clinical research coordinator will compare coding patterns and refine the codebook until consensus is reached and then generate memos to highlight connections between codes and subcodes. Quotations from participants will be compiled and concepts and relationships pertinent to core themes developed. We will seek out and compare unique themes relevant to the analytic subgroups (eg, those based on age, sex, gender, race, and ethnicity) to capture important thematic group differences. Final codes and memos will be compared and combined into overarching themes and subthemes. Themes will be discussed, refined, and named for the final analysis. The principal investigator will provide guidance on coding and analysis at regular study meetings. ATLAS.ti software (version 7) will be used to facilitate the analyses.

Results

The study was funded by the National Institute of Mental Health on April 20, 2020. The trial is open and recruiting. We propose the enrollment of 80 dyads by March 2024 and final data collection by September 2024. After final data analysis and the writing of the results, the manuscripts will be submitted to appropriate journals for dissemination, with main findings published by March 2025.

Discussion

Summary

This study is a protocol for an RCT testing an empirically derived FCFN intervention with adjunctive digital health technology (the Fostering Connections web application) to support linkage to, and engagement in, mental health services among CWI youth. The FCFN intervention encompasses six 60-minute family-based intervention sessions designed to address barriers to, and build motivation for, engagement in outpatient community-based mental health services for CWI youth (aged 12-17 years). On the basis of prior literature on health navigator models delivered in community-based settings, we hypothesize that youth receiving the FCFN intervention will have higher rates of mental health treatment initiation and engagement than youth receiving FCMH clinic standard of care (clinical case management services).

The strengths of this study include the use of a randomized study design to maximize internal validity and scientific rigor as well as the use of empirically supported intervention models (ie, health navigation, family-based support, and motivational interviewing) that have been successfully implemented in community-based settings with diverse populations. The study also builds off prior community-engaged mixed methods work involving interagency collaboration, EMR data collection, and qualitative research (eg, system stakeholder interviews, youth and family interviews, focus groups, and direct observation) to develop and iteratively refine the FCFN intervention and study procedures to enhance scientific rigor and relevance. The study is also designed to maximize real-world implementation potential through the delivery of the FCFN intervention by existing staff at a community-based mental health clinic for CWI youth.

Potential limitations and design considerations include a partnering clinic that does not serve a sufficiently large sample size of CWI youth to be the sole site for the next phase of the large-scale trial. However, our investigators have existing research partnerships with other nearby large northern California counties that would allow us to expand and conduct large-scale FCFN intervention testing with other mental health clinics

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serving CWI youth using the same design approach as the pilot trial. Furthermore, sample size limitations may limit the current potential to analyze outcomes by those receiving the FCFN intervention as part of in-home services versus out-of-home placement and other demographic variables (eg, ethnoracial identity, gender, and socioeconomic status). Placement type and stability are important to consider in terms of intervention impact; thus, we will descriptively explore how outcomes may differ according to these variables to inform the future larger trial.

Conclusions

This study intends to move the field forward in several ways. First, it will extend a recently developed services continuum of care framework for legally involved youth with substance use (the juvenile justice behavioral health services cascade framework; JJ-TRIALS) and address the mental health service strengths, gaps, and needs of CWI youth, families, and systems. Second, the pilot trial design will provide an opportunity to engage community stakeholders and leverage existing staff resources for *real-world* intervention testing while also allowing for the measurement and observation of design feasibility and acceptability for a future large-scale hybrid 1 (efficacy or effectiveness) trial. Third and last, the incorporation of digital health tools will aid the navigation process (eg, tracking, care coordination, and communication) to ensure that CWI youth are receiving optimal care that navigators, outside providers, and other relevant CWI systems can measure. The inclusion of an established digital health platform (Chorus for the Fostering Connections web application) supports the navigation process by supporting bidirectional SMS text messaging, appointment reminders, and critical navigation document sharing to enhance communication across FCFNs and families. Taken together, such innovations will allow the study team to provide first-time empirically driven conclusions and recommendations related to the processes, strategies, and preliminary impact of a family mental health navigation model for CWI youth.

Acknowledgments

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Data Availability

Data sharing is not applicable to this study because no data sets have been generated or analyzed yet for the preparation of this protocol manuscript. After analysis and dissemination, data generated and analyzed in the randomized controlled trial will be available from the corresponding author upon reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review report by the Mental Health Services Research Committee of the National Institute of Mental Health.
[PDF File (Adobe PDF File), 133 KB - resprot_v12i1e49999_app1.pdf]

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Abbreviations

ADHD: attention-deficit/hyperactivity disorder
CANS: Child and Adolescent Needs and Strengths
CWI: child welfare–involved
DSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
EMR: electronic medical record
FCFN: foster care family navigator
FCMH: foster care mental health
GLMM: generalized linear mixed model
JJ-TRIALS: Juvenile Justice Translational Research on Interventions for Adolescents in the Legal System
mHealth: mobile health
NAVSAT: Navigation Satisfaction Tool
PTSD: posttraumatic stress disorder
RCT: randomized controlled trial
SUS: System Usability Scale
WAI: Working Alliance Inventory

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Protocol

A Model for Empowering Rural Solutions for Cervical Cancer Prevention (He Tapu Te Whare Tangata): Protocol for a Cluster Randomized Crossover Trial

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Abstract

Background: Māori are the Indigenous people of Aotearoa (New Zealand). Despite global acceptance that cervical cancer is almost entirely preventable through vaccination and screening, *wāhine* Māori (Māori women) are more likely to have cervical cancer and 2.5 times more likely to die from it than non-Māori women. Rural Māori residents diagnosed with cervical cancer have worse outcomes than urban residents. Living in rural Aotearoa means experiencing barriers to appropriate and timely health care, resulting from distance, the lack of community resourcing, and low prioritization of rural needs by the health system and government. These barriers are compounded by the current screening processes and referral pathways that create delays at each step. Screening for high-risk human papillomavirus (hrHPV) and point-of-care (POC) testing are scientific advances used globally to prevent cervical cancer.

Objective: This study aims to compare acceptability, feasibility, timeliness, referral to, and attendance for colposcopy following hrHPV detection between a community-controlled pathway and standard care.

Methods: This is a cluster randomized crossover trial, with 2 primary care practices (study sites) as clusters. Each site was randomized to implement either pathway 1 or 2, with crossover occurring at 15 months. Pathway 1 (community-controlled pathway) comprises HPV self-testing, 1-hour POC results, face-to-face information, support, and immediate referral to colposcopy for women with a positive test result. Pathway 2 (standard care) comprises HPV self-testing, laboratory analysis, usual results

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giving, information, support, and standard referral pathways for women with a positive test result. The primary outcome is the proportion of women with hrHPV-positive results having a colposcopy within 20 working days of the HPV test (national performance indicator). Qualitative research will analyze successes and challenges of both pathways from the perspectives of governance groups, clinical staff, women, and their family. This information will directly inform the new National Cervical Screening Program.

Results: In the first 15-month period, 743 eligible HPV self-tests were performed: 370 in pathway 1 with POC testing and 373 in pathway 2 with laboratory testing. The positivity rate for hrHPV was 7.3% (54/743). Data collection for the second period, qualitative interviews, and analyses are ongoing.

Conclusions: This Māori-centered study combines quantitative and qualitative research to compare 2 clinical pathways from detection of hrHPV to colposcopy. This protocol draws on rural community practices strengths, successfully engaging Māori from a *whānau ora* (family wellness) approach including *kanohi ki te kanohi* (face-to-face), *kaiāwhina* (nonclinical community health workers), and multiple venues for interventions. It will inform the theory and practice of rural models of the use of innovative technology, addressing Māori cervical cancer inequities and facilitating Māori wellness. The findings are anticipated to be applicable to other Indigenous and rural people in high-income countries.

Trial Registration: Australian New Zealand Clinical Trials Registry (ANZCTR) ACTRN12621000553875; https://anzctr.org.au/Trial/Registration/TrialReview.aspx?ACTRN=12621000553875

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KEYWORDS

uterine cervical neoplasms; cervical intraepithelial neoplasia; early detection of cancer; papillomavirus infections; New Zealand; self-testing; primary health care; Indigenous people; Māori; point-of-care systems; colposcopy; health equity

Introduction

Background

Māori are the Indigenous people of Aotearoa (New Zealand). *He Tapu Te Whare Tangata* reflects the veneration of *wāhine* Māori (Māori women) and people with cervices as sacred *whare tangata* (houses of humanity) from a Māori worldview [1]. The overall name of this project "He Tapu Te Whare Tangata—a model for empowering rural solutions" affirms the importance of women's right to best health.

Whānau (families) living in rural Aotearoa face barriers to appropriate and timely health care. This is a complex issue involving distance from main centers, the lack of community resourcing, and low prioritization of rural needs by the national health care system and government. Residents of rural areas have poorer health outcomes than those living in urban areas, and for Māori, who experience inequities in access to care, social determinants of health, and quality of care, this is accentuated [2-4]. To address these barriers, effective solutions for rural Aotearoa should involve both innovative technologies and community empowerment. Using the cervical cancer screening pathway, this partnership project pairs innovative technology with community control of the care pathway to reduce barriers to timely care.

Cervical cancer is one of the few cancers preventable through both vaccination and screening. Screening can detect precancer of the cervix that can be treated, halting the development of a potentially fatal outcome. *Wāhine* Māori are twice as likely to have cervical cancer and 2.5 times more likely to die from it than non-Māori women [5]. Māori living in rural areas diagnosed with cervical cancer have worse outcomes compared with urban residents [6]. These cancers disproportionately affect young *wāhine* Māori and are the second leading cause of cancer death for *wāhine* Māori aged 25-44 years [7,8]. These inequities are unacceptable and are caused by barriers to screening, diagnosis, and treatment [9].

Most cervical cancers occur in women who have not undergone screening or are screened less frequently [10]. The National Cervical Screening Program (NCSP) shows that the target level of 80% of *wāhine* Māori screened within the previous 3 years is not achieved in any region; once screened, there is a failure to achieve a timely diagnosis and treatment of abnormalities for *wāhine* Māori [9]. Fewer *wāhine* Māori have a colposcopy within an appropriate time frame following a high-grade abnormality when compared with non-Māori women. Furthermore, the proportion of women who had no record of any subsequent follow-up at 90 days is 4.4% for European women but 8.6% for *wāhine* Māori [11].

The current national screening approach for cervical cytology involves an invasive procedure using a speculum, which requires attending a clinic with associated transport and other costs. Cervical screening in rural Aotearoa is performed by the primary care nurse or physician, and the tests are sent to a centralized laboratory for analysis. The results are returned to the primary care clinician, who then notifies the patient. If the result is abnormal, the clinician writes a referral letter to a gynecologist requesting an appointment for a colposcopy. Hospital departments then control all further investigations and treatments. Delays can occur at each point, which in turn create barriers to access, timely diagnosis, and treatment [12].

Human papillomavirus (HPV) is the causative agent of cervical cancer. Infection with certain oncogenic (cancer forming) high-risk types of HPV cause changes in the cells of the cervix that can lead to cancer. Compared with cytology, HPV-based screening is a better test; it provides 60% to 70% greater protection against developing invasive cervical cancers [13,14].

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The World Health Organization recommends that all countries transition to HPV testing as the primary method for cervical screening [15-17]. It is also internationally recognized that a self-taken swab that uses molecular amplification testing platforms such as polymerase chain reaction is as effective in detecting high-risk HPV (hrHPV) as a clinician-taken sample [18,19].

The present cytology-based NCSP is changing to HPV primary testing this year [20]. HPV self-testing is an equitable tool for cervical screening. Increasing coverage with HPV self-testing will potentially contribute to a more equitable NCSP [20]. A recent randomized controlled trial found that offering an HPV self-test was almost 3 times more likely to result in a cervical screen for underscreened *wāhine* Māori compared with offer of conventional cervical cytology [21]. Qualitative research has shown that HPV self-testing is highly acceptable to *wāhine* Māori, although many who had a positive result felt that more information and support were needed to guide them through the colposcopy process [1,22].

Point-of-care (POC) technology enables on-site HPV testing of self-collected vaginal swabs. The Xpert HPV test by Cepheid has been clinically validated to detect infections with 14 hrHPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) that are likely to be associated with cervical disease (eg, cervical intraepithelial neoplasia 2+). The Xpert HPV test differentiates between HPV16 and HPV18/45, which are linked to approximately 70% of cervical cancers. The 14 hrHPV types assessed by the Xpert HPV test are associated with >90% of cervical cancers, as demonstrated in a recent Australian study [23]. The sensitivity and specificity of the Xpert HPV test are comparable with those of other well-established HPV central laboratory-based assays and fulfill the World Health Organization's criteria for use [19,24].

The research center Te Tātai Hauora O Hine (The National Centre for Women's Health Research Aotearoa, Victoria University of Wellington) was invited to partner with the Iwi (tribal) group Ngāti Pāhauwera Development Trust (NPDT) and Māori health provider Ngāti Porou Oranga (NPO, previously Ngāti Porou Hauora) to try a new clinical pathway for colposcopy using HPV self-taken vaginal swabs, POC testing, and direct referral to secondary services. In the early stages, Tipu Whaipua, a Wairoa-based community steering group formed through a prior research project with NPDT, helped inform the development of the design [25], which was guided by the principles of Ngāti Pāhauwera—*Pakatō i te ata, Pakatō i te ahiahi, Maure mahi Māuri ora* (planning for the future health and well-being of the people) and *Mahia nga māhi o Kahukura* (imagining and creating a better future).

NPO is a Māori primary health organization; it is the sole provider for a challenging geographic area, with a flourishing research and innovation program. The vision of the late Dr Paratene Ngata was "for Ngāti Porou Hauora to lead our own research, as a tikanga (traditional, customary way) and research-based centre of excellence for Hauora Māori" [26]. These principles provided the foundation for this research partnership and the resulting study, "He Tapu Te Whare Tangata—a model for empowering rural solutions."

This study combines a cluster crossover intervention trial with qualitative work to address inequities in the clinical care pathway to colposcopy for *wāhine* Māori in rural Aotearoa. This study pairs HPV self-testing with POC technology in a novel community-controlled cervical cancer prevention pathway. This easy-to-use technology with a 1-hour turnaround provides quick results for women *kanohi ki te kanohi* (face-to-face) and the ability to provide immediate woman-centered care, including information, *manaakitanga* (support), *whānau* (family) involvement, and shared decision-making. This, in turn, allows for immediate referral to colposcopy appointments for follow-up of positive tests.

Objectives

The objectives of this study are as follows: (1) to compare 2 pathways of care on the timeliness, referral to, and attendance for colposcopy following hrHPV detection (quantitative) and (2) to assess the acceptability and feasibility of the 2 cervical cancer prevention pathways (qualitative).

Methods

Overview

This is a cluster randomized crossover trial, with 2 primary care health practices (study sites) as clusters. Each site was randomized to implement either pathway 1 or pathway 2 in the first study period (15 months) and then crossing over to implement the other pathway in the second study period (15 months). The trial design is summarized in Figure 1.

Pathway 1 is HPV self-testing and POC results within 1 hour, with face-to-face information, support, and immediate referral to colposcopy for women with a positive test result for hrHPV—the community-controlled pathway.

Pathway 2 is HPV self-testing and laboratory analysis, followed by usual results giving, information and support, and standard referral pathways for women with a positive test result for hrHPV—the current standard pathway.

We hypothesize that pathway 1 will improve timely access to colposcopy compared with pathway 2.

We hypothesize that community control of the care pathways is acceptable and feasible for rural Māori communities.

This study is informed by the Kaupapa Māori inquiry paradigm. This paradigm sees being Māori as normal and challenges how Māori have been, and continue to be, constructed within a colonized worldview. It promotes a structural analysis of inequities for Māori, seeking to more fully understand people's lives and the systemic determinants of their health and wellness [27,28]. In this paradigm, Māori worldviews, ways of knowing, and *mātauranga* Māori (Māori knowledge) are seen as valid and legitimate.

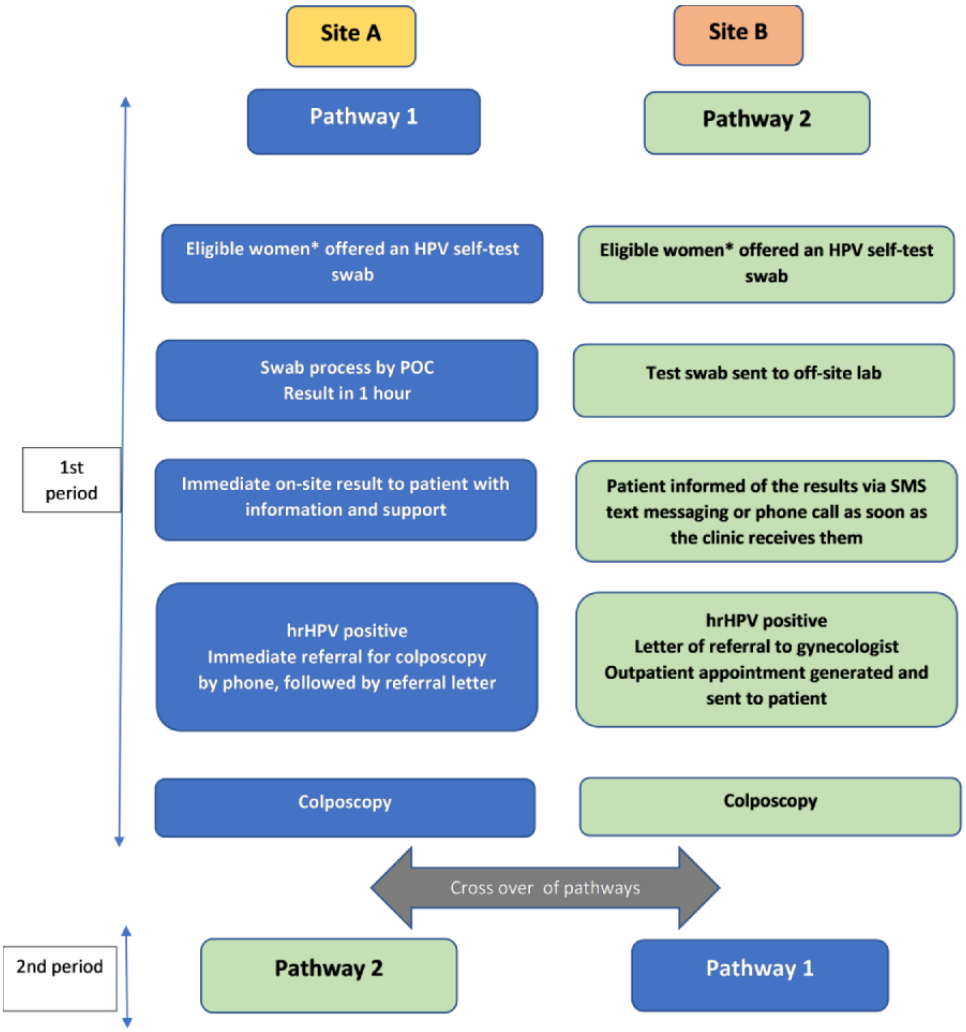
Non-Māori colleagues working collaboratively in a strengths-based approach are included in the team, which is Māori led [29]. With this Māori-centered approach led by *Kaumātua* (Māori elders and knowledge holders), we seek to combine multiple ways of knowing and seeing the world. Māori are involved at all levels, including protocol development,

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instigation, follow-up, and trialing of this innovative clinical care pathway [25]. Research practices reflect *tikanga* Māori (Māori customs), including the importance of place, relationships, and Māori self-determination [26,27].

The 2 rural North Island community primary health care practices are in Hawke's Bay and Tairāwhiti on the East Coast of the North Island of Aotearoa at sites A and B, respectively. These 2 primary health care providers serve a predominantly rural and Māori population. The Hawke's Bay practice is based in 1 health center in a rural town covering an area of approximately 4000 km^2. The Tairāwhiti practice includes 5 clinics situated in small rural communities, covering a coastline of >200 km.

Figure 1. He Tapu Te Whare Tangata—a model for empowering rural solutions: study design. HPV: human papillomavirus; hrHPV: high-risk human papillomavirus; POC: point-of-care. *Eligible women: women aged 24.5 to 69.9 years due or overdue for cervical cytology.



Outcomes

The primary outcome is the proportion of women having a colposcopy within 20 working days from the test, for those women with a positive test result for hrHPV.

Secondary outcomes are of those with a positive hrHPV test result:

- Proportion of women having a colposcopy within 40 working days of the test
- Proportion of women having a colposcopy within 20 working days of referral
- Proportion of women having a colposcopy within 40 working days of referral
- Time from test to colposcopy
- Time from referral to colposcopy
- Number of high-grade lesions (cervical intraepithelial neoplasia and carcinoma)
- Planned treatment for women with high-grade histology at colposcopy.

Secondary outcomes include of all women taking the HPV test:

- The proportion of women who test positive for hrHPV
- The proportion of women who test negative for hrHPV
- The proportion of women who have invalid results
- The proportions due for screening, underscreened, or never screened.

Qualitative outcomes are as follows:

- To explore and understand the successes and challenges of both pathways from the perspectives of the governance groups, clinical staff (nurses, doctors, *kaiāwhina* [nonclinical community health workers], and specialists),

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and women (including *whanau* or family supporters) at both sites
- To understand this new screening pathway to advise and inform a more culturally responsive NCSP.

On the basis of the percentage reported for *wāhine* Māori throughout Aotearoa, we estimated that 56.4% of women in the control arm will have a colposcopy within 20 working days following referral for a positive HPV test [30]. We aim to detect a 50% increase (relative risk 1.5) from 56.4% to 84% in the primary outcome for the intervention arm. A sample size of 80 women (n=40, 50% in each arm) in a 2-period, 2-cluster randomized crossover trial will provide 80% power at 2-sided α of .05 to detect a 50% increase in the intervention arm. With only 2 practices serving as the clusters, the sample size does not account for the cluster effect, which will be considered as a fixed effect in the final analysis.

The order of treatment for each practice has been randomly allocated by the study statistician using computer-generated random numbers. Using the eligible population list for each practice, the research team randomly allocated half of the under- or never-screened women to priority recruitment in the first study period and half to the second study period. This was done to reduce the potential bias from unequal recruitment of under- or never-screened women between the 2 study periods. The lists for priority recruitment were provided to the practices.

As this is a 2-period, 2-cluster randomized crossover trial, each practice acts as a comparator for the other practice during the trial period.

Blinding of participants and clinicians is not possible. The 2 trial statisticians will be unblinded and compile the data set and conduct the statistical analysis.

The inclusion criteria were women aged 24.5-69.9 years eligible for cervical screening in these 2 rural areas. In line with the current NCSP protocol, women can present for the first screen up to 6 months before their 25th birthday and be included. Women can present for screening up to 6 months before their due date and be included [31]. Women who are due for screening or who are underscreened (underscreened is defined as never screened or ≥4 years since last screening) are eligible.

Women with heavy bleeding at the time or those using a vaginal cream that might interfere with the test are asked to return at a later date. Women who opt for cervical cytology or whose general practitioner advises a speculum examination and cervical cytology can also participate in the study by taking an HPV self-taken (or clinician taken) swab first. Women who have symptoms such as abnormal bleeding can still be offered an HPV test, but they will also be seen and assessed by a general practitioner and may require assessment by secondary gynecology services despite a negative hrHPV test.

Primary care clinicians (physicians and nurses) and *kaiāwhina* at both sites received training from the research team on how to obtain informed consent from women. Training was conducted in person or via a video link. Trained clinicians or *kaiāwhina* obtain informed consent from women in both pathways for a copy of their HPV results (and if colposcopy is required, copies of histology results) to be sent to the researchers and the ordering health practitioner.

Women are also asked if they can be contacted later by a qualitative researcher for an interview on their experiences of the pathways (pathway 1 or 2, the HPV self-test, and overall process) and any subsequent follow-up. Other key stakeholders from general practice (management and staff) and the wider community have been identified and invited to participate in an interview.

Physicians, nurses, and *kaiāwhina* at both sites received an HPV update and information sharing session with the research team before recruitment started. These updates included the role of HPV in cervical cancer, the HPV self-test, the role of POC testing, how to obtain informed consent, how to instruct women on taking a self-taken swab, how to follow-up results, the role of the research team, and how the study will run. Training is augmented by regular ongoing contact between the research team, clinic staff, and managers.

All eligible women in both pathways are offered an HPV self-test. The participants receive verbal, written, and pictorial instructions from a physician, nurse, or *kaiāwhina* on how to self-collect a vaginal sample using a nylon-flocked swab (Copán FLOQswabs). Most sample collection takes place at the primary care practice, but some women self-collect the sample in their homes during a *kaiāwhina* visit or take one home from the clinic. Women in pathway 1 are provided information about POC testing. Women in both pathways who have positive HPV results are offered usual support to attend colposcopy. This includes petrol vouchers, transportation, and a support person to accompany them.

Intervention Description

Overview

The site randomized to pathway 1 for the first period nominated ≥2 primary care clinicians and *kaiāwhina* to be trained by qualified members of the research team in the operation and daily quality audit of the Cepheid GeneXpert IV instrument. POC training was overseen by the research team's molecular scientist in the week before recruitment began. This consisted of orientation and familiarization runs using contrived samples and official training directly from Cepheid via a video link. The technology is robust, but user training and support are vital. Only those holding a training certificate issued by Cepheid are authorized to run patient samples. Regular in-person, on-site POC updates run throughout the trial. User and instrument proficiency testing is built into the implementation process and conforms to the New Zealand Best Practice Guidelines for Point-of-Care Testing [32]. In addition, the research team and site clinicians involved in POC testing are participants in the Royal College of Pathologists of Australasia Quality Assurance Program [33]. The Cepheid GeneXpert IV instruments used in this study are loaned from the Australian Centre for the Prevention of Cervical Cancer.

A 2- to 4-week washout took place between the 2 study periods. The second site received the same training schedule on how to use the Cepheid GeneXpert IV instrument, and the instruments were transported, set up, and tested at the second study site.

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Pathway 1

Following self-collection, the vaginal sample is processed onsite by the Cepheid GeneXpert IV instrument, taking approximately 1 hour, and the result is documented in the patient management system (PMS). The intention is for women to receive the HPV test result in person onsite, as soon as the test result is available.

Women with hrHPV-positive results receive immediate on-site information about the result, its significance, the next steps, and support. An appointment for colposcopy is made straight away by a phone call to the appointment clerk at the hospital. This phone call is followed up with a referral letter from the referring primary care clinician.

Women with hrHPV-negative results are informed of the result and its significance and advised that they will not need screening for 5 years.

If a woman is unable to stay for an hour to receive her test result, her contact details are taken, and she is contacted as soon as the result is available.

Pathway 2

Following vaginal sample self-collection, the woman is asked how she would prefer to receive the result (by SMS text messaging, phone, or in person). The sample is then transported at room temperature to the diagnostic laboratory as part of the practice's routine laboratory collection. hrHPV genotyping is performed using the Roche Cobas 4800 system. This system detects 14 hrHPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) and provides a result which distinguishes types 16 and 18 from "other" high-risk types [34]. The use of dry vaginal swabs has been validated in international published studies, and the laboratory is undertaking this testing "off-label" [35,36]. The samples are disposed of in line with the standard pathology laboratory procedures. Test results are sent electronically (encrypted as other routine results) to the ordering primary care clinician and entered into the PMS, as cytology results would be.

Women with hrHPV-positive results are informed of the result and its significance by phone or in person. Information regarding the next steps and support are provided. The primary care clinician sends a referral letter to the colposcopy service at the hospital. The woman is triaged for a colposcopy appointment, and the appointment time is sent to the woman by mail, with or without phone follow-up.

Women with hrHPV-negative results are informed of the result and its significance and advised that they will not need screening for 5 years.

Data Collection and Analysis

Regular 3 monthly visits to the research sites are made by the members of the research team. These visits include updating the clinic staff on any amendments and audits of the PMS to ensure that the results are documented accurately and coded, given to women, and followed up appropriately. The research team's molecular scientist visits regularly to audit the POC instruments and sample testing process compliance. The practices have ownership of their data and all the results. Researchers are readily available via phone and email to support practices.

The ordering clinician and practices have the primary responsibility for follow-up. For clinical safety, the unblinded study statistician checks for colposcopy referrals and attendance. This is checked no sooner than 3 months from the hrHPV test date, so the primary outcome is not influenced but ensures that practices can contact any woman who has not yet attended a colposcopy appointment.

Follow-up colposcopy and treatment performed within the public health service are free for Aotearoa citizens and permanent residents. The new NCSP will start in September 2023, and the women in this trial will be registered with the new program appropriately.

Data collection and management are conducted as follows: copies of consent forms, POC test results, and laboratory results are provided to the research team by the study sites and used to track recruitment and monitor safety. Every 6 months, the colposcopy services provide data to the study statisticians: colposcopy attendance and date, colposcopy assessment and outcome, cytology result (if any) at colposcopy, histology, treatment plan, and any treatment provided. No other research team members have access to colposcopy data.

Each person using a health or disability support service in Aotearoa has a unique National Health Index (NHI) number [37]. The research team provides the NHI numbers of the participating women to the National Screening Unit to obtain cervical screening and clinical history at the start of the study period from the NCSP. The NHI number is also used to obtain ethnicity, the deprivation index (socioeconomic status), and age from the NHI data set.

The NHI number is replaced with a unique study code in all research data sets for analysis. No individuals will be identifiable in the reporting of study findings.

Study-specific source documents are maintained in locked file cabinets in locked rooms of Te Tātai Hauora o Hine, Victoria University, Wellington. Electronic data are stored on the secure Victoria University of Wellington server in restricted access folders and password-protected files. The data will be retained for 10 years and then destroyed securely.

Qualitative data collection is conducted as follows: up to 40 women who screen and test positive for HPV 16/18/"Other" (across both study sites and both pathways) and who indicate on their consent form that they are happy to be contacted for an interview will be approached by a *wāhine* Māori researcher. They are invited to take part in an interview at a time and location that suits them and are encouraged to bring any *whānau* (family) or other support. During the interview, they are provided a *koha* (gift) as a small token of appreciation for sharing their experiences and perspectives. Key informants from primary care (eg, clinical staff, nonclinical staff, and management), colposcopy services (eg, clinical and nonclinical staff, and management), and the wider community are invited to be interviewed, either individually or in small groups. Most interviews are conducted in person, but some may be conducted by telephone or Zoom (Zoom Video Communications)

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depending on COVID-19 precautions and participant preferences [37]. Informed consent is obtained before the interview commences. The researcher takes time to follow culturally appropriate rituals of encounter that help to create a comfortable and safe environment for the interview [38]. Interviews are semistructured around 4 discussion points that aim to elicit rich, nuanced qualitative data. Participants are asked about the acceptability of the screening pathway, perceived level of empowerment and decision-making in the pathway, preferences for screening services, and recommendations for future screening programs. Participants are encouraged to add or ask anything else at the end of the interview. The interviews are audio recorded and transcribed verbatim.

All statistical analyses will be performed using SAS (version 9.4; SAS Institute) and R (version 3.4.2; R Foundation for Statistical Computing). Analyses will be intention to treat and conducted at the individual participant level. All tests of significance are 2-tailed and at a 5% significance level throughout the analyses. Continuous variables will be compared with *t* tests or Mann-Whitney *U* tests, and categorical data will be compared using chi-square tests, as appropriate.

A generalized linear regression model with a binomial distribution will be used to analyze binary outcomes, a linear regression model will be used to analyze continuous outcomes, and the cluster design will be taken into account in the analyses. For the primary outcome, both unadjusted and adjusted analyses for potential covariates measured at baseline will be conducted (eg, deprivation index and age). Unadjusted and adjusted odds ratios will be reported with corresponding 95% CIs and associated *P* values. Relative risks will also be estimated using Poisson regression models with robust error estimates. For the primary outcome, participants with missing data will be assumed as not having a colposcopy within 20 working days. Sensitivity analyses will be conducted for the primary outcome to assess the robustness of the results, which will include per-protocol analyses (where participants with any protocol deviations will be excluded). Additional sensitivity analyses may be considered, such as the potential impact of COVID-19 restrictions or extreme weather events. Subgroup analyses will be conducted for ethnicity, screening history, HPV type, and symptoms (if the numbers are sufficient). Time to notification and time to colposcopy will be analyzed using Kaplan-Meier curves, log-rank tests, and Cox proportional hazard models.

Qualitative data will be analyzed thematically. This will involve reading and rereading the transcripts, coding sections of data inductively, and combining and rearranging the codes to create themes and subthemes [39]. NVivo12 (QSR International) qualitative data analysis software will be used to assist in the coding and theming of data. In reporting the themes, feedback from participants will be written about in a way that groups their talk about common issues and how these issues are interrelated.

Importantly, the governance of this project rests with NPDT and NPO, giving community control of leading-edge POC technology. The study coordinating center is National Centre for Women's Health Research Aotearoa and includes the roles of the principal investigator, project manager, investigators, research assistants, and Kaumātua. The study coordinating center is responsible for the day-to-day conduct of the trial and supports the practices to participate. This study is a multi-institutional, multidisciplinary, and international research collaboration. There are regular meetings once a week with the research team and once a month with the participating clinics. An external, independent data monitoring committee appointed by the Health Research Council of New Zealand was set up at the request of the research team and meets every 6 months to monitor safety and review recruitment progress and data completion. The National Centre for Women's Health Research Aotearoa regularly meets the Ministry of Health National Screening Unit to update on the study progress and inform the new NCSP.

Harm to the participants in this trial is very unlikely. In that event, women are eligible to apply for compensation from the national Accident Compensation Corporation, just as if they were injured in an accident, at work, or at home. This study uses the national Health and Disability Ethics Committee's (HDEC) definitions for serious adverse events, protocol deviations, and protocol violations. Events meeting these definitions are reported to the data monitoring committee and HDEC, along with the actions taken in response to any event.

Ethical Considerations

Ethics approval was granted on December 2, 2020, by the HDEC (Ref 20/NTB/311). All major protocol amendments are submitted to the HDEC for approval. Locality assessment authorization was granted by the Tairāwhiti District Health Board and Hawke's Bay District Health Board. Written informed consent is obtained from all participants.

Results

The first 7 months of the project was spent preparing for the trial (Table 1). Recruitment began in February 2021, and period 1 was completed on April 29, 2022. After a 3-week washout period, period 2 recruitment began on May 23, 2022. This protocol is version 3, dated February 2022. In the first period of 15 months, a total of 743 eligible HPV self-tests were conducted: 370 in pathway 1 with POC testing and 373 in pathway 2 with laboratory testing. The positivity rate for hrHPV was 7.3% (54/743) overall. This is within the globally recognized range of 6% to 15% [40]. The data collection for the second period is ongoing. Once data collection is completed, analysis will report the results for the primary and secondary outcomes. Qualitative data collection and interviews are near completion, and the analysis of themes is ongoing. We expect that final results and analysis will be published in late 2023.

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Table 1. He Tapu Te Whare Tangata—a model for empowering rural solutions: study timeline.

Task	July 2020 to February 2021	February 2021 to April 2022	May 2022 to July 2023	September 2023
Ethics applications	✓			
Iwi organization and practices consultation	✓			
Recruitment and training primary care practices	✓			
Randomization of sites to pathway 1 or 2		✓		
Intervention commenced		✓		
Data collection		✓		
Qualitative interviews		✓		
Regular progress meetings and visits		✓		
Crossover of pathways			✓	
Qualitative interviews continue			✓	
Analysis				✓
Write up				✓
Dissemination of findings				✓

Discussion

Principal Findings

This study combines a cluster crossover intervention trial with qualitative work to address inequities in the clinical care pathway to colposcopy for *wāhine* Māori in rural Aotearoa. This study pairs HPV self-testing with POC technology in a novel community-controlled cervical cancer prevention pathway. The 2 objectives are to compare the 2 pathways of care on the timeliness, referral to, and attendance for colposcopy following hrHPV detection and assess the acceptability and feasibility of the 2 cervical cancer prevention pathways. This protocol draws on the strengths of rural community practices that are successfully engaging Māori from a *whānau ora* (family wellness) approach.

It is known that POC technology is as good as other polymerase chain reaction platforms for testing hrHPV and that self-taken vaginal specimens are as good as clinically taken cervical specimens using these platforms [18,19,24]. There are studies examining POC HPV testing and clinical pathways in low-income countries, but to our knowledge, there is no literature on POC testing and the pathway to colposcopy for disadvantaged populations in high-income countries [41].

Strength and Limitations

The strengths of this study include that it is informed by a Kaupapa Māori inquiry paradigm. This study was a collaboration between community, Iwi (tribes), rural primary health care clinicians; secondary care gynecology services; and the research team. Health care workers were trained to use POC technology and supported with regular quality assurance. This will lead to the possibility of testing for and treating other common infections in remote or environmentally isolated regions.

The limitations of this study include the recruitment for this study during COVID-19 disruptions and lockdowns and severe flooding and damage to infrastructure due to Cyclone Gabrielle, which affected both research sites. There was a difference in the research sites, as one site had 1 large rural clinic and the other site had 5 small rural clinics; however, there will still be the ability for the analysis to compare each site with itself on each pathway.

Conclusions

The findings of this study will inform the theory and practice about rural models of the use of innovative technology, addressing Māori cervical cancer inequities and facilitating Māori wellness. Our goal is to enhance outcomes, which necessitates continuous consultation among our partnership (including researchers, community members, Iwi, and primary care providers) with various groups. Our priority for the dissemination of results will be firstly the community, Māori health organizations, and strategic organizations that have been part of the research process. Maintaining the link between academia and Māori communities is part of our commitment to ongoing consultation and dissemination. We have ongoing regular consultation with the National Screening Unit, with the goal that this community intervention, if successful, will directly inform future changes to the NCSP to prioritize Māori and lead to a program that meets the needs of Māori. It is expected that these impacts and solutions may be appropriate for other Indigenous and rural people in high-income countries.

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Acknowledgments

The authors would like to thank the primary care clinicians and staff at research sites and colposcopy teams at 2 district hospitals for their ongoing contribution to the study. The authors would also like to thank Frances King, the previous manager of Ngāti Porou Oranga, for her help and coordination of site visits, and Emma Tapp and Rebecca Lucas-Roxburgh at Medlab Central Limited for their advice and expertise. The study sponsor and Health Research Council of New Zealand (HRC) have no role in the study design; collection, management, analysis, and interpretation of data; writing of the report; or the decision to submit the report for publication. Neither the study sponsor nor the funder has ultimate authority over any of the abovementioned activities. This project received funding from HRC and the Health Delivery Research Project (grant 20/550).

Data Availability

All named investigators will have access to the final trial data set. This research aligns with the Te Mana Raraunga Principles of Data Sovereignty, which strictly govern Māori data use and sharing. Data requests with evidence that the proposed use addresses and upholds these principles may be sent to *He Tapu Te Whare Tangata*, rural empowering data manager [42], for consideration by the project data management and principal investigator.

Authors' Contributions

BL is the principal investigator and contributed to the conceptualization, study design, funding acquisition, methodology, project administration, resources, supervision, visualization, preparation of the original draft, and writing—review and editing. EJM contributed to the conceptualization, study design, data curation, funding acquisition, methodology, project administration, supervision, preparation of the original draft, and writing—review and editing. FS contributed to the conceptualization, data curation, funding acquisition, methodology, project administration, software, supervision, and writing—review and editing. JAS contributed to the conceptualization, project supervision of molecular science technology and training, methodology, resources, and writing—review and editing. AA contributed to the study design with expertise in qualitative methodology, investigation, data curation, funding acquisition, methodology, project administration for qualitative sections, formal analysis, and writing—review and editing. MG contributed to the data curation and management, statistical planning, funding acquisition, methodology, project administration, software, formal analysis, supervision, and writing—review and editing. VP is the study statistician and contributed to the data management, statistical planning, formal data analysis methodology, and writing. NKS contributed his expertise in qualitative methodology, investigation, data curation, formal analysis, and writing. BK contributed to the study design, community and rural primary care expertise, methodology, and writing. MT contributed to the study design, community and rural primary care expertise and consultation, methodology, writing, and review. HW provided community and rural primary care expertise and consultation, provided rural research expertise, and contributed to writing and review. MB and CSL provided Iwi community expertise and consultation and contributed to the study design, community and Iwi leadership and mentoring, methodology, writing, and review.

Conflicts of Interest

MS is an investigator on the Compass trial for which her organization, The Australian Centre for the Prevention of Cervical Cancer (ACPCC), has received kits and partial funding from Roche for the Compass trial. VCS Pathology has received funding from Copan for independent assessment of Copan products. VCS Pathology has also received Equipment or supplies from Abbott, AusDiagnostics, BD, Cepheid, Copan, Hologic, Microbiologics, MicroBix, NRL, Qiagen, Rovers, Roche, and Seegene for research purposes.

Multimedia Appendix 1
Peer reviewer #12 report for HRC.
[PDF File (Adobe PDF File), 106 KB - resprot_v12i1e51643_app1.pdf]

Multimedia Appendix 2
Peer reviewer #49 report for HRC.
[PDF File (Adobe PDF File), 105 KB - resprot_v12i1e51643_app2.pdf]

Multimedia Appendix 3
Peer reviewer #67 report for HRC.
[PDF File (Adobe PDF File), 105 KB - resprot_v12i1e51643_app3.pdf]

Multimedia Appendix 4
Peer reviewer #91 for HRC.
[PDF File (Adobe PDF File), 104 KB - resprot_v12i1e51643_app4.pdf]

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Abbreviations

HDEC: Health and Disability Ethics Committee
HPV: human papillomavirus
hrHPV: high-risk human papillomavirus
NCSP: National Cervical Screening Program
NHI: National Health Index
NPDT: Ngāti Pāhauwera Development Trust
NPO: Ngāti Porou Oranga
PMS: patient management system
POC: point-of-care

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Protocol

Effectiveness of Social Virtual Reality Training in Enhancing Social Interaction Skills in Children With Attention-Deficit/Hyperactivity Disorder: Protocol for a Three-Arm Pilot Randomized Controlled Trial

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Abstract

Background: Attention-deficit/hyperactivity disorder (ADHD) is one of the most common neurodevelopmental disorders among children. Children with ADHD have challenges in understanding social cues and behavioral problems when entering a social setting. Virtual reality (VR) has been applied to improve cognitive behaviors in children with ADHD. Previous studies have not adopted VR to improve social interaction competence and appropriateness in children with ADHD. VR offers a more effective alternative to therapeutic strategies for children with ADHD.

Objective: This study aims to examine the feasibility and effectiveness of social VR training in enhancing social interaction skills compared to traditional social skills training in children with ADHD. We hypothesize that participants in the social VR training group are likely to perform better on social interaction skills than those in the traditional social skills training group.

Methods: In this nonblinded, 3-arm randomized controlled trial (RCT), 90 participants with ADHD recruited from the community will be randomized 1:1:1 to the social VR intervention group, traditional social skills training group, or waitlist control group. The child psychiatrist will conduct assessments for each participant at baseline and after the intervention. The Social Skills Rating Scale–Parent will be used to assess the social interaction skills of the participants before and after the intervention. Participants in the social VR intervention group and traditional social skills training group will receive twelve 20-minute training sessions for 3 weeks. The participants in the waitlist control group will receive no training. The primary outcome measure is training acceptability and compliance. The secondary outcome measures are the child psychiatrist's assessment and the Social Skills Rating Scale–Parent before and after the intervention. Another outcome measure is the Behavior Rating Inventory of Executive Function and Attention. Differences in the scale scores will be examined using a *t* test and an *F* test.

Results: This study is set to commence in the fourth quarter of 2023. It is anticipated that participants in the social VR intervention group will exhibit superior social interaction skills than those in the traditional social skills training group.

Conclusions: To our knowledge, this RCT is the first study examining the feasibility and effectiveness of a social VR-based intervention for enhancing the social interaction skills of children with ADHD in Hong Kong. The VR-based social skills training is expected to provide a safer and more effective environment for children with ADHD to learn than the traditional approach. This study can lead to a full-scale RCT.

Trial Registration: ClinicalTrials.gov NCT05778526; https://clinicaltrials.gov/study/NCT05778526

International Registered Report Identifier (IRRID): PRR1-10.2196/48208

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KEYWORDS

attention-deficit/hyperactivity disorder; social interaction skills; executive functioning; emotional control; 3-arm randomized controlled trial; ADHD; attention deficit; hyperactive; hyperactivity; randomized; RCT; social interaction; social interactions; social skills; child; children; youth; pediatric; pediatrics; VR; virtual reality; childhood; neurodevelopmental

Introduction

Background

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common neurodevelopmental disorders frequently diagnosed in school-aged children. It is characterized by pervasive symptoms of inattention, hyperactivity, and impulsivity. There are 3 main types of ADHD: inattentive type, hyperactive-impulsive type, and combination type. ADHD impacts the children's emotions, behaviors, and ability to learn [1]. The hyperactivity and inattention levels of children with ADHD are noticeably higher than expected, causing distress or problems at home, at school, and with peers. The global prevalence rate of ADHD is about 5% to 7% [2]. According to the data from the Family Council in Hong Kong [3], there are 14,580 students with ADHD in Hong Kong, which is the second-highest number among the 9 types of special education needs.

Executive functions refer to a set of cognitive processes that enable an individual to plan, organize, manage, and execute a task, which includes working memory, cognitive flexibility, and inhibitory control [4]. Children with ADHD's executive functions can be delayed by up to 32% compared with typically developing peers [5]. Such delay can have tremendous impacts on the daily lives of individuals with ADHD [6]. For instance, inattention symptoms cause these children to have difficulty concentrating and listening to others, become distracted by the environment, and become overwhelmed [6]; hyperactivity symptoms cause high levels of distraction, sharing scattered thoughts, and excessive talking; impulsivity symptoms cause inappropriate initiation of conversations and becoming aggressive [4]. These children have relatively poor self-control, inhibitory control, emotion regulation, attention, and working memory [5]. Hence, children with ADHD have challenges in understanding social cues and behavioral problems when entering a social setting. They have difficulty comprehending some nonverbal expressions (body language, eye contact, and facial expressions) and spoken communication (pitch, speed, tone, and volume), making it difficult to listen to others and share their thoughts appropriately when interacting with them [7]. The social skill deficit causes it to become difficult to build friendships or even peer rejection [7]. To further avoid peer rejection, some of these children may avoid social interaction. Thus, it is critical to assist these children in developing appropriate social interaction skills.

ADHD has been associated with a wide range of detrimental impacts on those affected and imposes a severe financial burden on families and society [8,9]. The social problems faced by children with ADHD are associated with strained family relationships and social isolation from peers, which, in turn, can adversely affect emotional well-being, as some of them may experience both anxiety and depression [10]. Several studies reported that the economic burden of raising a child with ADHD was 5 to 6 times that on their counterparts, and the parents of children with ADHD tended to be fired and have low work efficiency [8,9,11]. Therefore, adequate and appropriate treatments should be provided to alleviate their behavioral issues and high health care costs. The commonly used social skills training tools among children with ADHD are traditional instructions, modeling, role-play activities, and behavior rehearsal [12]; however, these methods are limited to time and space and are short of real-life scenarios [13].

Virtual reality (VR) has emerged in plenty of domains as a promising tool for therapy and rehabilitation. Numerous studies adopted VR in improving cognitive behaviors in children with ADHD; however, the focuses of these studies were cognitive functioning in the context of daily living, attentional performance, and impulsivity [14-16]. None of these studies used VR to improve social interaction competence and appropriateness in children with ADHD. Furthermore, VR provides controllable immersive environments to engage children, sustain their attention, and allow them to effectively gain skills in a safer environment [17]. VR systems generally consist of a head-mounted display and screen so that the therapy can be conducted in a relatively low spatial limitation. Although no study has used VR to investigate social interaction skills in children with ADHD, previous studies have advocated the use of VR-based social skills training for children with autism spectrum disorder (ASD) [18-20]. Most of the studies about children with ASD also included some real-life scenarios—for example, classrooms, transportation, and supermarkets—in their social skills training program. This implies that children can develop social skills in a safe and controlled setting that can be designed in accordance with their needs [21]. VR can create different real environments for children to practice in repeatedly [21]. VR can provide instant feedback, which can help children recognize the appropriateness of their social interaction in practice [22]. The differences in social skills between children with ADHD and those with ASD are that the former are easily distracted, avoid or dislike concentrating on one thing, and are more likely to interrupt others when they are speaking, while the latter are less aware of others around them, overly attached to one object that they like, and find it difficult to give meaning to their speech [23]. Due to these discrepancies, the design of a social VR intervention in this study will be integrated with more instantaneous events, objects, and avatars in each scenario to improve the problem of distraction among children with ADHD. In addition, social VR, which allows more than 1 user to appear as avatars in a lifelike environment and connect with other users in real time, will be adopted in this study instead of VR to enhance engagement and interaction among children with ADHD.

Considering the prevalence and advantages of social VR, we plan to develop a social VR training program that contains 3 real-life scenarios and compare the effects of social VR training

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and traditional social skills training on social interaction skills, inhibitions, emotional control, behavioral and emotional difficulties, and conduct disorders for children with ADHD in Hong Kong receiving no training as a control.

Cultivating sufficient and appropriate social interaction skills for children with ADHD is a vital step to assist them in integrating into the community. VR technologies offer a more effective alternative to therapeutic strategies for children with ADHD. However, no previous study has adopted social VR to assess the competence and appropriateness of social interaction in children with ADHD, and no randomized controlled trial (RCT) has compared the effectiveness of social VR training and traditional social skills training on enhancing social interaction skills in children with ADHD. Traditional social skills training for children with ADHD lacks the provision of real-life scenarios and is limited by time and space. Social VR allowing real-time connection and interaction between patients and the virtual instructor has been absent in previous studies.

To fill these research gaps, we proposed conducting a 3-arm RCT to answer the research question of whether social VR training has higher effectiveness than traditional social skills training in enhancing the social interaction skills of children with ADHD in Hong Kong. The findings of this study are expected to unveil the clinical impacts and compliance and acceptability of social VR training for enhancing social interaction skills among children with ADHD.

Aims and Hypotheses

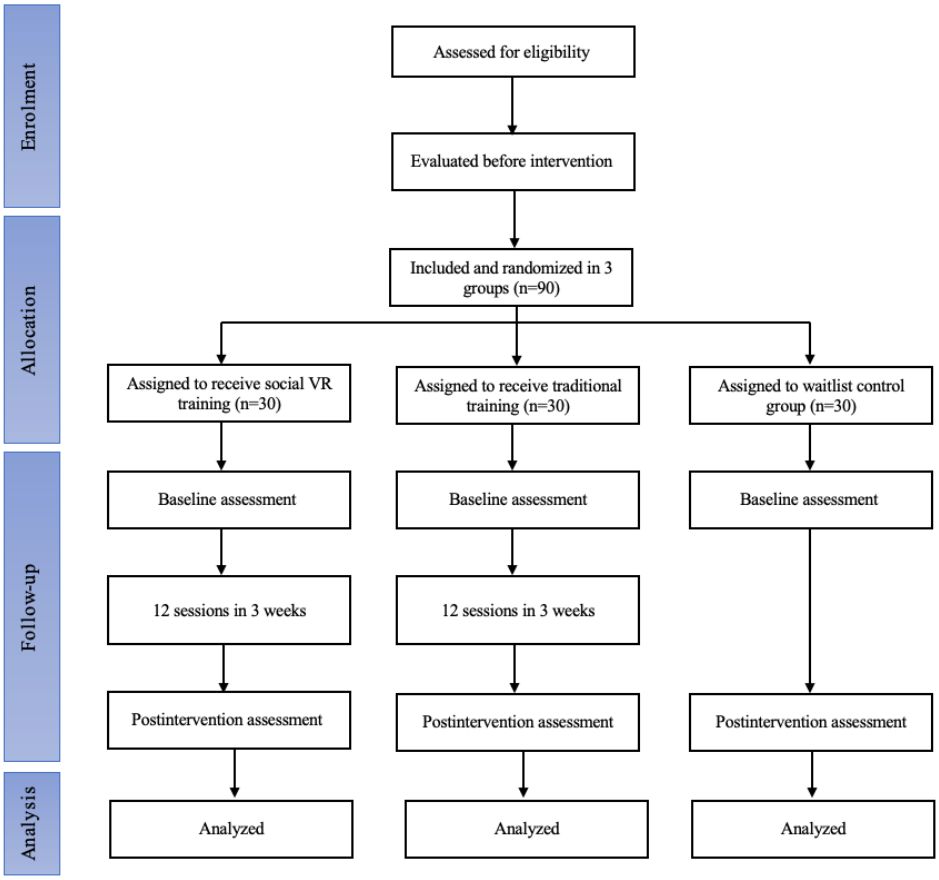
The study targets children diagnosed with ADHD and aims to (1) develop a social VR intervention, (2) investigate its effectiveness in improving the social skills of the children compared to traditional social skills training, and (3) evaluate the acceptability of and compliance with social VR training for enhancing social interaction skills. We hypothesize that participants in the social VR training group may perform better on social interaction skills than those in the traditional social skills training group. Participants in the waitlist control group are expected to show no change in social interaction skills compared with the 2 intervention groups.

Methods

Overview

This study will be a 3-arm RCT comparing the effects of a social VR intervention with those of traditional social skills training on social skills and executive functioning of children with ADHD. Participants in the social VR intervention group and those in the traditional social skills training group will receive 12 training sessions for 3 weeks (4 sessions per week), and those in the waitlist control group will be asked to retain their usual lifestyles for 3 weeks. The overall design of the study is illustrated in Figure 1.

Figure 1. Flowchart of the study.



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Participant Selection Criteria

Individuals who meet the inclusion criteria will be recruited. The criteria are as follows: (1) age between 6 and 12 years; (2) being ethnic Chinese; (3) residing in Hong Kong; (4) having received a diagnosis of ADHD by a Child Assessment Service in Hong Kong or via private practice; (5) being stable on pharmacological or psychological treatment (or both) for ADHD 8 weeks before baseline; (6) no initiation or change in pharmacological treatment for ADHD during the intervention period; (7) ability of the child and at least one of the child's parents or legal guardian to read Chinese and speak and listen to Cantonese; and (8) willingness to provide informed consent by both participants and one of their parents or legal guardian.

Exclusion criteria are as follows: (1) comorbid autism; (2) an estimated IQ lower than 85 (determined using the Wechsler Intelligence Scale for Children–Fourth Edition; Hong Kong); (3) ASD (previously diagnosed by health care professionals); (4) comorbid acute psychiatric disorder (previously diagnosed by health care professionals); (5) a comorbid severe physical disability (eg, blindness or deafness); and (6) having a learning disability in understanding and using spoken Chinese, calculating, and motor coordination.

Sample Size

Teare et al [24] and Whitehead et al [25] indicated that studies with a sample size of 20 participants per arm have at least 80% power and 90% confidence. A pilot study by van der Oord et al [26] involved 40 participants (20 in the control group and 20 in the intervention group) to examine the efficacy of computerized executive functioning remediation training with game elements in children with ADHD. The sample size of this pilot RCT is more than the recommended sample sizes and that of the published pilot studies; hence, a proposed sample size of 90 (30 per arm) could provide more reliable results. To obtain a statistical power of 90% at a significance level of .05 and assume that the maximum dropout rate is 50%, we aim to recruit 30 participants in the social VR group, 30 in the traditional social skills training group, and 30 in the waitlist control group (ie, a total of 90 participants).

Ethical Considerations

Ethical approval for the study has been obtained by the Human Subjects Ethics Application Review Committee of The Hong Kong Polytechnic University (HSEARS20221221003). Informed consent will be sought from the participants and their parents or legal guardians.

Procedure

Recruitment

Participants will be recruited from nonprofit organizations and community centers. The inclusion and exclusion criteria will be listed on the recruitment poster. Interested participants or parents who provide written informed consent will be further evaluated for inclusion and exclusion criteria by a clinical psychologist or a student with a master's degree in clinical psychology. Participants who meet the inclusion criteria will be invited to perform an IQ test at the university at baseline.

Randomization

Eligible participants will be randomized to the social VR group, traditional social skills training group, or waitlist control group. A computer-generated randomizer will be used to generate the random allocation list. Randomization will be undertaken by another research assistant not directly involved in the study. A number generated by the computer will be assigned to each eligible individual who will be randomly allocated to the 3 different groups based on the number. Parents or legal guardians will receive an email and a telephone call with a notification regarding allocation to groups 1-3.

Social VR Intervention

This social VR intervention is being developed to enhance the social interaction skills of children. The participants will wear a head-mounted display for the social VR intervention. Each session of the social VR intervention lasts for a maximum of 20 minutes to ensure that the participants focus on the intervention and to prevent causing any physical effect [27]. The duration will be adjusted depending on the emotions of the participants during the intervention. The social VR intervention will mainly help the participants enhance their social interaction skills and executive function. The intervention contains three real-life virtual scenarios, including (1) a classroom and playground, (2) mass transit railway, and (3) a supermarket and restaurant. One scenario will be adopted in each session. The sequences of the scenarios used in each session will be the same for all participants. During the social VR intervention, an research assistant will also appear as one avatar in the scenario to guide the participants to complete a series of tasks. Each intervention session will be conducted in a classroom independently for each participant.

Traditional Social Skills Training

An instructor with a background in education, psychology, or social work will teach the participants social interaction skills through traditional instructions and role-play activities. Four modules will be covered in the 3-week training: (1) how to introduce yourself and basic social skills, (2) how to listen to others, (3) how to share with others, and (4) learn to understand how people feel and how to empathize. These modules have been applied in many studies [12,28]. The content of this training will be as similar as possible to the social VR training. The training lasts 20 minutes, which depends on the participants' emotions. Each training session will be conducted in a classroom independently for each participant.

Waitlist Control Group

As in Beck et al's [29] study, the participants in this group will receive no training and they can participate in the social VR training after the intervention period. To ensure consistency in the experiment, the participants are not allowed to initiate or change their pharmacological treatment during the 3-week intervention period.

Outcomes Measures

Questionnaires

The parents or legal guardians of the participants will complete a structured questionnaire at baseline and immediately after the

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last session. Demographic information, including age, gender, medication, ADHD symptoms, and game experience will be recorded at baseline. The questionnaires include questions about social skills and executive functioning. The satisfaction of the participants and their parents or legal guardians with the training program will be assessed at week 3. VR sickness of the participants in the social VR group will be evaluated after each session. The clinical psychologist who evaluated the performance of the participants will be blinded to the treatment condition. The questionnaires will include the scales described in the following paragraphs.

Primary Outcome Measure: Assessment of Training Acceptability and Compliance

The attendance of the participants during the training will be recorded. To verify the validity of the findings, training-nonadherent participants will be excluded, which will be stated in the consent form. Absence in 3 or more training sessions will be considered nonadherence. The participants will be asked about their willingness to partake in this kind of training with a 7-point Likert scale question, which is used to reflect the acceptability of the intervention. The retention rate should be at least 85% according to a prior feasibility RCT [30].

Compliance with the training program will be evaluated by the communication log, in which the parents record their children's daily activity and emotions in the 3-week intervention period. The participants' parents will be reminded to attend the training by telephone in the first 4 training sessions and by WhatsApp, Signal, or WeChat in the fifth and eighth training sessions. No follow-up reminder will be provided in the remaining 4 sessions. These data will be used to evaluate their compliance.

Secondary Outcome Measures

Social Skills Rating Scale–Parent

The social skills of the children will be assessed using the Chinese-translated Social Skills Rating Scale–Parent (SSRS-P), which will be scored by the participants' parents before the first session and after the last session. This scale consists of 3 subscales, including self-control, assertiveness, and initiative and cooperation, with a total of 31 items. A 3-point Likert scale (never, sometimes, or often) is used to score. The SSRS-P is a validated instrument that has been commonly adopted in clinical trials of psychiatric and neurological disorders.

Child Psychiatrist's Assessment

One child psychiatrist will score the basic social skills of the participants in 15-minute tasks before the first session and after the last session to obtain an objective evaluation. The basic social skills assessment is adapted from the scale of Riggio [31]. Broken blinding is unavoidable in the child psychiatrist's assessment. To minimize unblinding bias during the assessment, each participant will be identified by a case number.

Behavior Rating Inventory of Executive Function

The Chinese-translated Behavior Rating Inventory of Executive Function (BRIEF), used to assess executive functioning in children, will be scored by the participants' parents before the first session and after the last session. The subscales of inhibitions (16 items) and emotional control (10 items) will be adopted in this study. A 3-point Likert scale (never, sometimes, or often) is used to score.

Satisfaction

Satisfaction is measured by a question rated with a 7-point Likert scale: "What grade would you give to this training program?" Both participants and parents or guardians have to answer the question.

Process Evaluation

Process evaluation of the training will be assessed by investigating (1) the recruitment rate, (2) participant completion, (3) side effects of training measured by participants' sickness or physical discomfort in the VR environment, and (4) safety assessment including adverse events and reasons for withdrawal.

- Recruitment rate: the recruitment rate is at least 48.5% of all referrals according to a prior feasibility study [32].
- Participant completion: participants attending at least 9 of the 12 (75%) sessions are considered to have completed the program [33].
- Simulator Sickness Questionnaire: the Simulator Sickness Questionnaire measures the motion sickness or physical discomfort of participants in a VR environment. Nine items will be measured, including discomfort, fatigue, headache, eyestrain, sweating, nausea, difficulty concentrating, blurred vision, and dizziness, with yes-or-no questions for each item.
- Assessment of safety: (1) adverse events: participants' parents or guardians will be asked, using open-ended questions, whether the participants experienced any adverse events during training. The severity and relationship of the adverse event to the intervention will be documented and investigated. (2) Reasons for withdrawal: when a participant withdraws before completing the study, the reasons for withdrawal will be recorded.

Statistical Analysis

All statistical analyses will be performed using SPSS software (version 26.0; IBM Corp) and are 2-sided with a level of significance of <.05. Demographic information of the participants will be summarized with frequency and percentage values for categorical variables. The continuous variables will be summarized with mean and SD values. The change from baseline to week 3 within each arm will be tested using *t* tests. To examine the between-group difference in measure outcomes from baseline to week 3, repeated analyses of covariance with adjustment of baseline characteristics will be conducted. To evaluate improvements during the intervention period among the 3 groups, *F* tests will be performed with primary and secondary outcome measures at the beginning of the first session and at the end of the last session. An intention-to-treat analysis will be performed. This analysis is considered the most appropriate approach to analyze RCT data by the highest-quality studies that have used the CONSORT (Consolidated Standards of Reporting Trials) standard [34].

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Results

Significant changes are expected to be noted in the mean values of the secondary outcomes, namely basic social skills as assessed by child psychologists, and social skills and executive functioning as assessed by parents, using the intention-to-treat principle. Conducting this pilot RCT will determine the feasibility and potential of social VR interventions in improving social interaction skills in children with ADHD.

Discussion

Anticipated Findings

To the best of our knowledge, this RCT is the first study examining the effectiveness of a social VR intervention for enhancing the social interaction skills of children with ADHD in Hong Kong. The study will contribute to evidence-based practice by testing the effectiveness of social VR training versus traditional social interaction skills training for children with ADHD. It may determine a causal relationship between social VR training and traditional social skills training on social interaction skills and executive functioning. The results of this study will provide clinical psychologists with an effective means to improve the social interaction skills of children with ADHD in Hong Kong. Social VR used in this study strengthens the attractiveness of the training and the interaction and communication between patients and guiders and the real-life situations. Considering their high availability and accessibility, the cost and time of developing the social VR programs would be worthwhile if they could be promoted among more children with ADHD to enhance their social interaction skills with limited human resources. In addition, these findings will facilitate the development of a social VR training program that is customized for children with ADHD in Hong Kong, resulting in the improvement of these children's social skills and psychological well-being; this will be beneficial in integrating them into society. There is potential for the government to set up an accreditation scheme to enhance the social VR training to cater to the children with special education needs in various settings, including special schools, integrated schools, community centers, and social support groups.

Conclusions

This pilot RCT has the potential to enhance the understanding of the feasibility and effectiveness of using social VR to improve social skills in children with ADHD. This will help determine whether the use of social VR is acceptable for children with ADHD and understand which approach (ie, social VR or traditional social skills training) is most likely to achieve better outcomes. It will also determine the feasibility of a larger trial.

Acknowledgments

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Authors' Contributions

KPW and JQ conceptualized the intervention. Both authors read and made comments on the previous drafts of the manuscript and have approved the final manuscript for publication.

Conflicts of Interest

None declared.

Multimedia Appendix 1
External peer review report.
[PDF File (Adobe PDF File), 108 KB - resprot_v12i1e48208_app1.pdf]

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Abbreviations

ADHD: attention-deficit/hyperactivity disorder
ASD: autism spectrum disorder
BRIEF: Behavior Rating Inventory of Executive Function
CONSORT: Consolidated Standards of Reporting Trials
RCT: randomized controlled trial
SSRS-P: Social Skills Rating Scale–Parent
VR: virtual reality

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Protocol

A Complex mHealth Coaching Intervention to Prevent Overweight, Obesity, and Diabetes in High-Risk Women in Antenatal Care: Protocol for a Hybrid Type 2 Effectiveness-Implementation Study

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Abstract

Background: Women with overweight and obesity are at higher risk of developing complications in pregnancy such as gestational diabetes and longer-term chronic conditions. Research concerning health behavior change interventions during pregnancy and postpartum shows promising effects, but implementation into routine services is sparsely investigated. Most interventions focus on the antenatal or postpartum life stages, failing to meet the needs of women. IMPACT DIABETES Bump2Baby is a multicenter project across 4 high-income countries developed to test the implementation of an antenatal and postpartum evidence-based mobile health (mHealth) coaching intervention called Bump2Baby and Me (B2B&Me) designed to sit alongside usual care in the perinatal period.

Objective: We aim to explore the feasibility and implementation of the B2B&Me intervention and investigate the effectiveness of this intervention in women at risk of gestational diabetes.

Methods: IMPACT DIABETES Bump2Baby is a hybrid type 2 effectiveness-implementation study, which integrates an evidence-based mHealth coaching app that includes personalized health behavior change coaching provided by health care professionals alongside antenatal care from the first antenatal visit to 12 months postpartum. The mHealth app offers the possibility of synchronous calls, asynchronous contact (including coach-participant text and video messaging exchanges tailored to the participant's needs), and ongoing access to an extensive library of bespoke intervention materials. Participants will interact

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asynchronously with their health coach throughout the intervention via the app. This randomized controlled trial across 4 clinical sites within Ireland, the United Kingdom, Spain, and Australia will recruit 800 women in early pregnancy to evaluate the effectiveness on postpartum weight. The Exploration, Preparation, Implementation, and Sustainment implementation framework is the theoretical underpinning of the study. The implementation evaluation will be assessed at the individual, hospital staff, and broader community levels using the Reach, Effectiveness, Adoption, Implementation, Maintenance (RE-AIM) framework. Data sources for the RE-AIM evaluation will include app and platform analytics, screening and training records, participant medical records, key informant interviews, participant and partner exit interviews, cost data, study questionnaires, staff surveys, and blood sample analyses.

Results: The study was approved and registered with the Australian New Zealand Clinical Trials Registry on November 19, 2020. Recruitment commenced on February 9, 2021, and data collection is ongoing. Publication of the results is expected in 2024.

Conclusions: This is the first hybrid effectiveness-implementation study of an 18-month mHealth coaching intervention in at-risk women that we are aware of. As research aims to move toward real-world implementable solutions, it is critical that hybrid studies are conducted. The data from this large multicenter study will be useful in planning the potential implementation and scale-up of evidence-based perinatal health behavior change interventions.

Trial Registration: Australian New Zealand Clinical Trials Registry ACTRN12620001240932; https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=380020&isReview=true

International Registered Report Identifier (IRRID): DERR1-10.2196/51431

(JMIR Res Protoc 2023;12:e51431) doi:10.2196/51431

KEYWORDS

hybrid type 2 effectiveness-implementation; gestational diabetes; obesity; mHealth; mobile health; health behavior change; pregnancy; postpartum; weight management; health coaching; maternal health

Introduction

Overweight and obesity are growing worldwide health concerns. For women in their reproductive years, this brings an increased risk of serious pregnancy complications such as preeclampsia, gestational diabetes mellitus (GDM), cesarean delivery, and stillbirth [1,2]. Obesity in pregnancy impacts offspring health with higher rates of congenital anomaly, large for gestational age, childhood obesity [3-5], gut microbiota dysbiosis, behavioral problems, or altered brain functioning, among others [6]. GDM is one of the most common pregnancy complications impacting approximately 1 in 7 pregnancies worldwide [7], with immediate and long-term health impacts for both mother and baby [8-10]. Excessive gestational weight gain (GWG) increases the risk of developing GDM and independently increases child obesity risk [2,11] and a woman's risk of obesity, heart disease, and type 2 diabetes (T2DM). GWG is frequently retained after birth and compounded by interpregnancy weight gain with a cycle of increasing weight through the reproductive years [12,13].

Pregnancy is a key time point to intervene and yield a benefit for both mother and child [12]. Meta-analyses show that behavioral interventions during pregnancy provide cost-effective support for optimizing GWG, GDM prevention and treatment, T2DM conversion prevention, and postnatal weight retention [14-16]. Meta-analyses have also identified that antenatal behavioral interventions are associated with reduced GDM and emergency cesarean delivery, and as a result the US Preventative Task Force now recommends implementing them [17]. Interventions to reduce postpartum weight retention are challenging to deliver but offer health benefits [18] with individual participant meta-analysis data showing that decreasing prepregnancy or early pregnancy maternal BMI reduces childhood obesity [11]. Current evidence, therefore, supports the efficacy of antenatal, postpartum, and interpregnancy health behavior change interventions in diet and physical activity during pregnancy and postpartum for improving maternal and child outcomes. Key evidence gaps include that studies typically focus on intervening during either the antenatal or postpartum period but not both and that studies tend to be short in duration (6 months is the average duration), which is known to be less effective at supporting sustained health behavior change [19-21]. Importantly, a large research translation gap exists around achieving adequate population penetration, participation, and implementation at scale with efficacious prevention interventions [19,20,22,23]. Limited studies have explored intervention implementation aspects beyond highly controlled clinical trials [19,23].

While the implementation of health behavior change interventions is recommended at a population level, identifying women at higher risk of adverse outcomes for targeted intervention is likely to yield improved health and economic benefits. This includes identifying women at risk of developing GDM through risk factor screening [24,25] and recognizing higher risks in different BMI groups with variable GWG guidelines [26]. However, few studies have focused on implementing these approaches with large variations in guidelines [27] and limited uptake in practice [8], which fails to identify pregnant women who would benefit from intervention. Postpartum and interpregnancy reach, penetration, and participation are all key barriers to both efficacy and implementation, and evidence is not yet strong enough to recommend population-level scale-up. Few studies have engaged women in pregnancy to optimize reach and participation in the face of competing family demands and less contact with the

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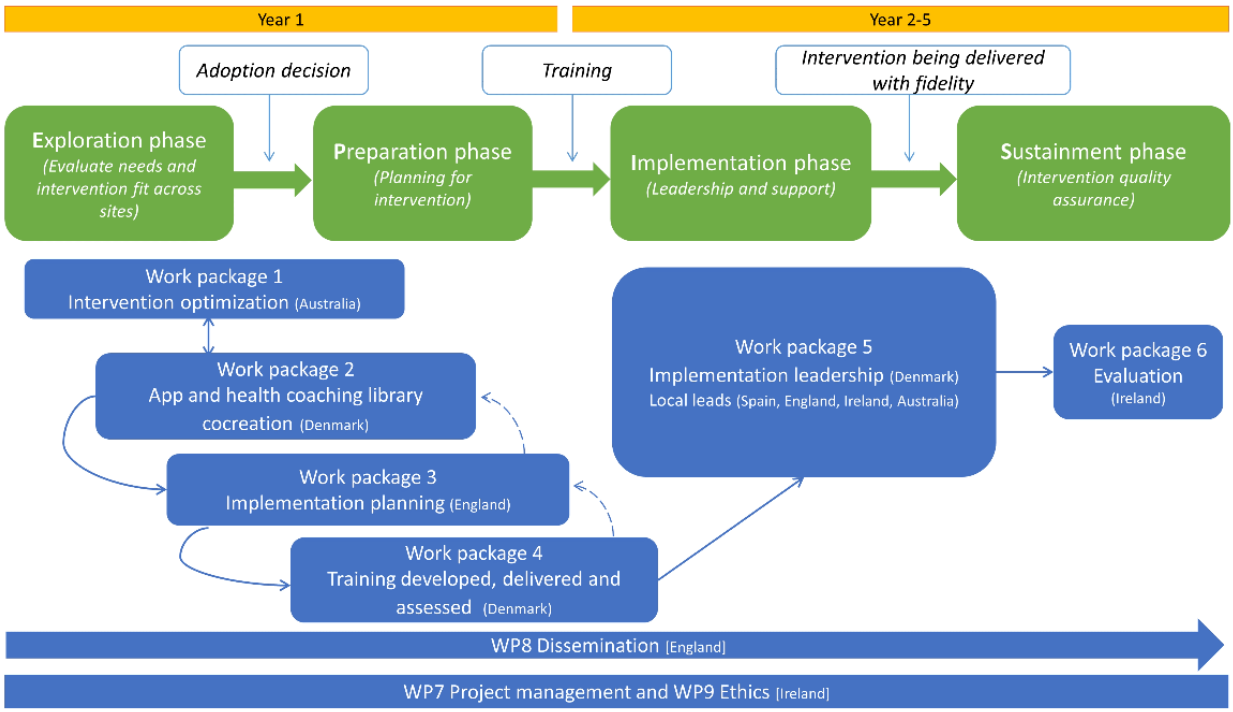
health system [28]. Again, implementation research in the real world that addresses these barriers is vital to inform population-level strategies and future roll-out and scale-up.

Methods

Context

IMPACT DIABETES Bump2Baby (IDB2B) is a 5-year European Union and Australian research innovation project looking to demonstrate the implementation of an evidence-based system of care for the prevention of T2DM, overweight, and obesity in women at risk of GDM (Figure 1). It is designed to be delivered in the antenatal setting of 3 European countries (Ireland, England, and Spain) and Australia. Within IDB2B, the Bump2Baby and Me (B2B&Me) health behavior change intervention was designed during formative work and will be subject to a randomized controlled trial (RCT) to test the integration of screening for at-risk women, the mobile health (mHealth) app, and personalized health coaching in pregnancy through to 12-month postpartum. The detailed B2B&Me RCT protocol is published elsewhere [29], with the focus here being on the implementation protocol. The formative work included the selection of the GDM risk screening tool. The Monash tool [30] was selected as it incorporated overweight and obesity, it was shown to have reasonable accuracy, it was based on the best available evidence, and it was validated internationally [31]. The B2B&Me intervention design was also closely informed by robust evidence from pregnancy including systematic synthesis of the evidence on health behavior change interventions in pregnancy [15,19] and postpartum [18,20,32] to identify key intervention and implementation components required in our intervention study design. The B2B&Me intervention design was also closely informed by robust evidence from pregnancy [33,34] or postpartum [35,36] low-intensity, theoretically underpinned, and low-cost interventions led by the international authorship team. These health behavior change interventions [33-36] were systematically deconstructed and reconfigured considering the systematic synthesis and the Behaviour Change Wheel Framework [37] to develop the B2B&Me intervention. The intervention was designed to be delivered using mHealth, which enables remote delivery via an app and personalized remote health coaching during pregnancy and postpartum, and to run in parallel to standard health service provision. The design of the health coaching via a health care professional and optimized health behavior change content in the app was focused on supporting a meaningful coaching relationship with the woman at the center of B2B&Me.

Figure 1. The Exploration, Preparation, Implementation, and Sustainment framework applied to the IMPACT DIABETES Bump2Baby project (2020-2024).



Aims

The overarching aim of IDB2B is to contribute to the prevention of maternal and child overweight, obesity, T2DM, and other noncommunicable diseases. It seeks to achieve this through a hybrid type 2 effectiveness-implementation study that combines evidence-based antenatal and postpartum health behavior change interventions into a single seamless support program (B2B&Me) that optimizes health outcomes for the mother and baby and contributes to the prevention of T2DM and adverse long-term programming effects in the offspring. The primary efficacy outcome of the B2B&Me trial will be reduced postpartum weight gain and secondary health outcomes include the health of the mother and child. The secondary implementation aims are to explore the fidelity of health coaching training, delivery, and receipt; the feasibility of the B2B&Me implementation strategy through a process evaluation; and the intervention's

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reach, cost-effectiveness, adoption, implementation, and maintenance.

Study Design

This is a type 2 hybrid effectiveness-implementation study. Type 2 hybrid designs have a "dual focus on the clinical intervention and implementation-related factors" with a clear implementation strategy that is deemed plausible in the real world [38]. Here, implementation factors may be secondary outcomes or coprimary ones [39]. We plan to study the effectiveness of the intervention using the B2B&Me RCT data as the primary outcome. We will evaluate the implementation process using the Reach, Effectiveness, Adoption, Implementation, Maintenance (RE-AIM) framework [40] to examine the reach, efficacy, adoption, implementation, and maintenance as secondary outcomes.

Health System Context

The health care systems in Ireland, England, Spain, and Australia are similar. They use a government-supported system where universal free care is provided to all eligible citizens and residents. The private health system is funded by individuals and subsidizes the costs of private care and provides greater choice in where health care is provided (public, private, or semiprivate). IDB2B was located within public care systems, and Figure 1 describes the work packages that formed the project.

Framework

The Exploration, Preparation, Implementation, and Sustainment (EPIS) framework was used to scaffold IDB2B [41,42]. The framework was developed out of the public sector and allied health services systems in America and has 4 main implementation process phases (exploration, preparation, implementation, and sustainment) with outer and inner organizational contexts and factors identified [41]. EPIS also includes innovation factors that relate to newly implemented intervention characteristics and bridging factors that explore the interplay between inner and outer contexts [41]. The exploration phase for IDB2B will involve evaluating current needs to ensure the intervention fits across system levels, organization levels, and staff and recipient levels through key informant interviews, site-level surveys, and systematic reviews. The preparation phase involved planning for the B2B&Me intervention through staff training, usual care service mapping, and awareness raising. The implementation and sustainment phases will be assessed using the RE-AIM framework [40], which measures results along the dimensions of reach, effectiveness, adoption, implementation fidelity, and maintenance.

Study Sites and Eligibility Criteria

IDB2B delivered the B2B&Me RCT in a single maternity health service site within Ireland, Spain, England, and Australia, and the usual care provided in each one is described in Table 1. The Monash GDM screening tool will be used to screen women at all sites attending antenatal care in their first trimester [30]. Women scoring ≥3 are eligible to enroll. The IDB2B study population will include women of reproductive age 18 years or older and attending their service for maternity care in the study sites that meet the B2B&Me eligibility criteria [29]. Key informant interviews will be conducted with senior staff involved in the delivery of antenatal services at each site. The interviews will also be conducted with the research teams and health coaches involved in delivering B2B&Me at each site. General hospital staff will be approached to participate in site-level surveys. All staff within the sites will be eligible to participate in the site-level surveys and the key informant interviews.

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Table 1. Description of 2021-2022 usual maternity care across the 4 clinical sites involved in the Bump2Baby and Me randomized controlled trial in women at risk of gestational diabetes (2021-2023).

	National Maternity Hospital, Dublin, Ireland	Southmead Hospital, North Bristol NHS Trust, Bristol, United Kingdom	San Cecilio University Hospital, Granada, Spain	Monash Medical Centre, Monash Health, Melbourne, Australia
Service	Urban; maternity, gynecological, neonatology, and reproductive care provided; Dublin and North Wicklow communities serviced; 194 inpatient beds	Urban; adult care including maternity services provided; Bristol, South Gloucestershire, and North Somerset communities serviced; 996 inpatient beds	Urban; adult care including maternity services provided; Granada communities serviced; 547 inpatient beds	Urban; adult care including maternity services provided; greater Melbourne residents serviced; 640 inpatient beds
Staff, n	930	12,000	3200	4000
Babies delivered, n	7855	6000+	2265	3800
Number diagnosed with GDM[a], n	774	~600 [43]	68-204	760
Rates of high BMI in pregnancy (≥25 kg/m^2) (%)	43.5	50.2 [44]	43.2	51 [45]
Notification of pregnancy	Women notify hospital	A community midwife is notified first and then transferred to the hospital	Women notify hospital	Women notify hospital
Models of care available	Midwife-led, medical team-led, or specialist care	Midwife-led, medical team-led, or specialist care	Midwife-led, medical team-led, or specialist care	Midwife, collaborative (midwife and medical team), specialty, shared (affiliated community provider and hospital), or medical team-led specialist care
Universal screening for GDM and test performed	No—HSE[b] guidelines followed [46], 2-step 50 g GCT[c] followed by 100 g 3-hour GTT[d]	No—NICE[e] guidelines followed [47], 75 g 2-hour GTT	Yes—SEGO[f] and GEDE[g] guidelines followed [48,49], 100 g 3-hour GTT	Yes—ADIPS[h] group guidelines followed [50], 75 g 2-hour GTT
GDM diagnostic criteria	Fasting ≥5.3 mmol/L, 1-hour ≥10.0 mmol/L, 2-hour ≥8.6 mmol/L, 3-hour ≥7.8 mmol/L; 2 out of range values needed for diagnosis	Fasting ≥7.0 mmol/L, 2-hour ≥7.8 mmol/L; 1 out of range l value needed for diagnosis	Fasting ≥5.8 mmol/L, 1-hour ≥10.6 mmol/L, 2-hour ≥9.2 mmol/L, 3-hour 8.1 mmol/L; 2 out of range value needed for diagnosis	WHO[i] (2013) ≥5.1 mmol/L fasting, ≥10.0 mmol/L 1-hour, ≥8.5 mmol/L 2-hour; 1 out of range value needed for diagnosis
Care pathway for high BMI	BMIs >25, access to group healthy eating and physical activity health behavior change education program	Nil	Nil	Limited—women with BMIs >35 may have access to group healthy eating and physical activity health behavior change education program
Care pathway for GDM	A multidisciplinary team provides support with diet and physical activity being the primary intervention followed by metformin or insulin management	A multidisciplinary team provides support with diet and physical activity being the primary intervention followed by medication or insulin management	Multidisciplinary team provides support with diet and physical activity being the primary intervention followed by medication or insulin management	Multidisciplinary team provides support with diet and physical activity being the primary intervention followed by medication or insulin management
Postdischarge care	Public health nurse–delivered, visits recommended—72 hours after discharge, 2 weeks, 6 weeks, 2 months, 3 months, 4 months, 6 months, 9 months, and 12 months	Health visitor or midwife delivered, visits recommended—within 72 hours after birth, 1-2 weeks, 6-8 weeks, and 9-12 months	Maternal and child health nurse delivered, visits at 1-2 weeks and 3 and 12 months after birth	Maternal and child health nurse delivered, visits recommended—home visit after birth, 2 weeks, 4 weeks, 8 weeks, 4 months, 8 months, and 1 year

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	National Maternity Hospital, Dublin, Ireland	Southmead Hospital, North Bristol NHS Trust, Bristol, United Kingdom	San Cecilio University Hospital, Granada, Spain	Monash Medical Centre, Monash Health, Melbourne, Australia
Postpartum GDM care recommended	General practice normal location for 6- to 12-week postpartum glucose tolerance test, annual diabetes screening with preconception planning [46]	General practice normal location for 6- to 13-week postpartum fasting plasma glucose test or glycated hemoglobin if after 13 weeks postpartum, annual diabetes screening with preconception planning [47]	General practice normal location for 6- to 8-week postpartum oral glucose tolerance test, annual diabetes screening with preconception planning [49]	General practice for their 6- to 12-week postpartum glucose tolerance test and regular diabetes screening is recommended [50]

[a]GDM: gestational diabetes mellitus.

[b]HSE: Health Service Executive.

[c]GCT: glucose challenge test.

[d]GTT: glucose tolerance test.

[e]NICE: National Institute of Clinical Excellence.

[f]SEGO: Sociedad Española de Ginecología y Obstetricia.

[g]GEDE: Grupo Español de Diabetes y Embarazo.

[h]ADIPS: Australian Diabetes In Pregnancy Study.

[i]WHO: World Health Organization.

Intervention

While the intervention is described elsewhere [29], briefly, it consists of a hybrid model that consisted of a smartphone app (Liva Healthcare provider) and linked health care professional health coaching (Figure 2). The health behavior change techniques within the intervention combine 3 frameworks that share a core person-centered philosophy to guide the structure of the program delivery and integration of behavior change techniques and relational techniques, these being social cognitive theory [51], the reciprocal triad of causation [51], self-determination theory [52], and the transtheoretical model of behavior change [53]. The health coaches will be allied health care professionals with an interest or training in midwifery and maternal and child health. They will receive 5 days of training prior to engaging with participants. The health coaching training will be a mixture of pedagogical approaches, including direct instruction, modeling, skills practice, and problem-solving, all supported by self-directed learning and self-reflection, outside of the formal 5-day program. Liva Healthcare has an existing internal quality development and assurance program where team leaders conduct regular supervision meetings with coaches. These sessions are frequent for new coaches until they demonstrate the expected coaching competencies based on systematic observation of coaching data. Hereafter, the frequency decreases over time to quarterly supervision sessions. Women will commence the intervention in their early pregnancy and will be offered a personalized baseline session where they meet their health coach during a synchronous web-based video call lasting 45-60 minutes. During this session, coaches establish a relationship with each woman, support them to set some initial health goals, and instruct them on the use of the smartphone app. The app offers the possibility of synchronous calls, asynchronous contact (which includes text and video messaging exchanges between the coach and participant tailored to the woman's needs), and ongoing access to an extensive library of materials developed specifically for the intervention (Figure 3). The women will interact asynchronously with their health coach throughout the intervention via the smartphone app. The health coach will have access to a dashboard that allows them to provide asynchronous, continuous coaching across a large volume of women. During pregnancy, the asynchronous interactions occur once a week for the first 4 weeks and then biweekly until birth, resulting in a total of 14 contacts. If the woman is diagnosed with GDM (typically 24-26 weeks of gestation), an additional 15-minute synchronous video call will be included as well as additional educational material on GDM. The health coaching content during pregnancy centers on diet and physical activity for a healthy pregnancy, it also includes emotional aspects, breastfeeding preparation, expectations for delivery, and so forth. For the postpartum period, a synchronous call is scheduled for 6-8 weeks after delivery to re-engage participants in the coaching program, to have a delivery debrief with the coach, and to set new goals tailored to the postpartum period. This is followed by 1 weekly and 22 biweekly asynchronous contacts. The postpartum health coaching content centered on diet and physical activity for the woman and child including infant feeding and active play. Participants can spread out the timing of any contacts to suit their needs. The smartphone app collects detailed analytics on the woman's time spent in the app, number of resources accessed, type and amount of goals set, goal progress, communications with health coaches (number of coach messages accessed and responded to), communications with peers within the app, and self-monitoring data (steps, activity, and diet).

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Figure 2. Overview of the Bump2Baby and Me (B2B&Me) randomized controlled trial in women at risk of developing gestational diabetes (2021-2023). GDM: gestational diabetes; T2DM: type 2 diabetes.

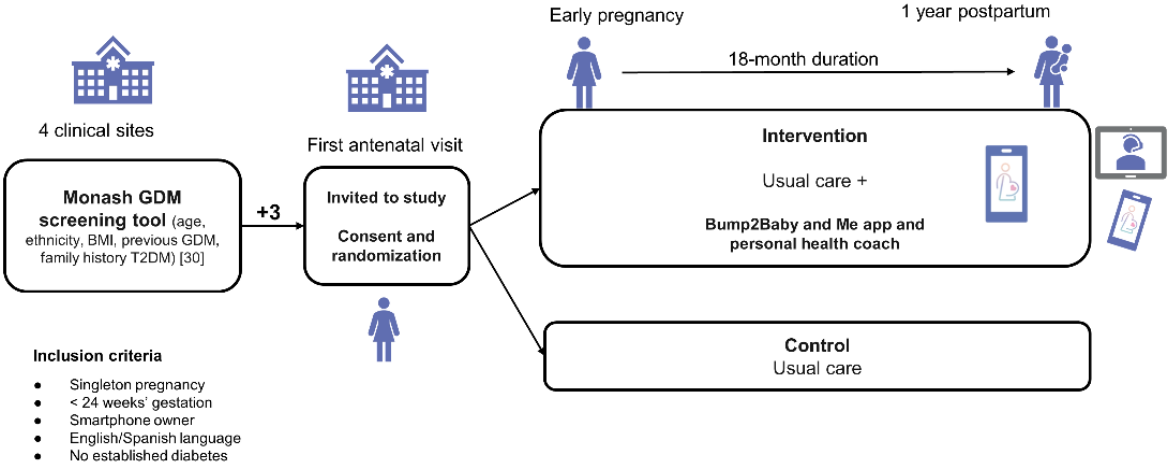
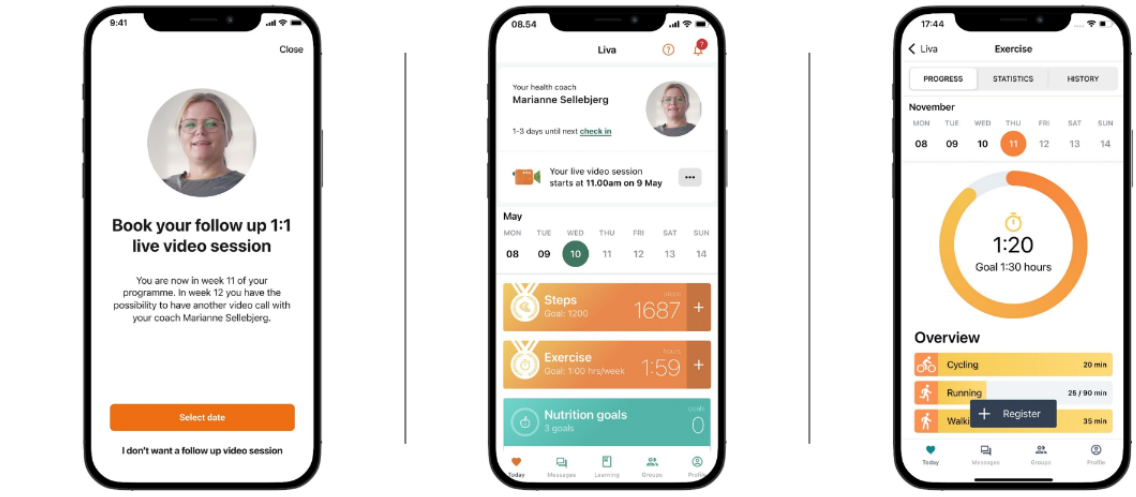


Figure 3. Screenshots of the mobile health coaching app Bump2Baby and Me.



Data Collection

Overview

Table 2 demonstrates the RE-AIM evaluation framework for the IDB2B project. Each evaluation item is described in greater detail.

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Table 2. Evaluation framework for IMPACT DIABETES Bump2Baby project (2020-2024) that incorporates the Bump2Baby and Me randomized controlled trial across 4 countries in women at risk of developing gestational diabetes.

RE-AIM[a] dimension and definition	Indicator	Data sources
Reach		
Penetration and participation in B2B&Me[b]	• % women screened and randomized out of hospital population (penetration) • % women eligible agreeing to participate in the trial (trial participation)	Screening records in IDB2B[c] database
	• % women completing minimum health coaching sessions (health coaching participation) • App and platform analytics for intervention women (mHealth[d] engagement)	Liva Healthcare app and platform analytics
	• Characteristics of participants by each site compared with the hospital population (representativeness)	Screening records in IDB2B database and hospital annual reports
Effectiveness		
B2B&Me impact on outcomes	• Change in BMI at 12 months postpartum • % women with any complications recorded • Change in BMI at delivery • % women diagnosed with GDM[e] • % women delivered via each mode of birth • Placenta weight recorded (g) • Infant birth weight (g), length (cm), and head circumference (cm) • Duration of breastfeeding • Change in physical activity/diet/sleep/quality of life/depression/blood glucose and lipid levels at 12 months postpartum • Infant growth pattern and neurodevelopment during the first year of life	B2B&Me questionnaires and blood sample analysis
	• % women scoring ≥3 on Monash Gestational Diabetes Risk Scoring Tool out of a total number of women screened (gestational diabetes "at-risk" prevalence)	Screening records in the IDB2B database
Adoption		
Site and individual level willingness to initiate B2B&Me	Site adoption: • Number of site training sessions delivered • Attitudes and engagement assessment of key informants and general staff	• IDB2B database • Key informant interviews and general staff questionnaires
	Health coach adoption: • Number of health coach training sessions delivered • % retention of health coaches	Liva Healthcare platform data and IDB2B database
Implementation		
Fidelity of B2B&Me to protocol and uptake of the intervention	Health coaching fidelity: • Health coaching fidelity index scores for each health coach • % women who receive a minimum number of health coaching sessions • Health coach training testing scoring • % women who record goals as part of health coaching • Maintenance of health behavior change goals achieved	Liva Healthcare app and platform analytics
	Program fidelity: • % scheduled visits completed • Number of protocol adaptations and rationale for changes	IDB2B database, exit interviews with participants and partners (where available to participate)

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RE-AIM[a] dimension and definition	Indicator	Data sources
	Implementation challenges: • Exploratory findings developed through key informant interviews, focus groups, and RCT[f] working group minutes	IDB2B database, exit interviews with participants and partners (where available to participate)
	Health economic evaluation: • Total intervention cost • Integrated cost-effectiveness	Cost of intervention components Intervention effectiveness for primary outcome
Maintenance		
Extent to which B2B&Me has the potential for long-term effects	• Potential for future implementation across key informants and women	Semistructured interviews

[a]RE-AIM: Reach, Effectiveness, Adoption, Implementation, and Maintenance.

[b]B2B&Me: Bump2Baby and Me.

[c]IDB2B: IMPACT DIABETES Bump2Baby project.

[d]mHealth: mobile health.

[e]GDM: gestational diabetes mellitus.

[f]RCT: randomized controlled trial.

Reach

Reach includes data on penetration, which is how many in the service were eligible and how many of those engaged and were recruited. Participation relates to adherence and dropout. The reach measures will be collected from the absolute screening numbers for each site and recording reasons for declining or ineligibility, participation records, app analytics, and health coaching completion data. This will yield data on the proportion and representativeness of individuals who are willing to participate in the intervention. We will apply a novel trial recruitment process, whereby individuals initially express interest in participation before randomization. Once randomized, participants will be provided with an arm-specific information sheet and consent form. Thus, participants know what intervention they are signing up to and this provides some estimate of intervention reach, which is not available from a standard consenting process.

Effectiveness

A detailed description of the data collection for the effectiveness evaluation is available in the RCT protocol publication [29]. The maternal and child data will be collected in the IDB2B database, which is purpose built and allows for secure web-based data entry for both participants and research staff with the ability to audit record entries and changes over time. All biological samples collected will be processed on site and frozen to −80 °C before shipping to Dublin for analysis. Screening data including Monash GDM risk tool scores and medical records for GDM diagnosis will be further explored to understand how effective the GDM screening tool was in predicting GDM diagnosis.

Adoption

The adoption data will explore the proportion and representativeness of the setting and intervention agents willing to initiate the intervention. All quantitative data collected during the intervention will be at the site level and entered into the IDB2B database by research staff when transcription has occurred. The adoption measures will be collected using a short anonymous digital and paper attitudinal survey of hospital staff at clinical sites. All hospital staff will be invited to participate from senior management to administrative staff. The validated survey [54] asks for the staff's opinions on screening women to provide a diet and physical activity intervention and weight management to women at high risk of developing GDM. The survey will be circulated to staff at the start and end of the project. The responses will be analyzed comparing baseline views to those collected at the end of the project to provide insight into the readiness of the inner context to uptake the intervention and whether it was normalized in the longer term. This aligns with the EPIS framework preparation and sustainment phases measurement. Additional qualitative data will be collected by conducting stakeholder interviews with maternity services staff in leadership positions to explore adoption as well as other RE-AIM aspects. Longitudinal interviews of key stakeholders such as clinical nurse managers at each clinical site will be carried out during the project, aiming for quarterly. These semistructured interviews will assess the local context and environment to measure what is happening within the hospital clinics and services that might impact the intervention and how well it fits with the current routine care.

Implementation

Data collected on implementation fidelity measures will come from health coach training sessions, health coaching analytics collected within the app, attendance records for meetings, and participant visits and logs for all documentation changes and reasons. The health coaching training will include training on the smartphone app and coach dashboard; an introduction specific to the trial, insights into the participant journey; both synchronous and asynchronous consultation frameworks; qualitative coaching aspects; and the management of critical time points like disengagement, relapse, and medical escalation.

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The training will address housekeeping and content review procedures, followed by an activity checklist and 2 initial consultation role-play exercises with feedback sessions as well as dedicated time for questions and answers. After the health coach training, each coach will complete a checklist of tasks within the app and platform and complete a practice baseline synchronous call with another experienced health coach. The health coach qualitative supervision framework assists the Liva supervisor in assessing 9 key competencies across the coaching journey. The supervisor evaluates each competency, which is scored individually, to ensure that all relevant competencies are covered in a repeatable fashion. When evaluating competency, the supervisor reviews a minimum of 3 participants using the app and 5-8 if the health coach is new to the role. Of these, the supervisor reviews 4-5 videos or interventions. While carrying out an evaluation of competency, the supervisor can allocate a 0, 1, and −1 or an N/A to each competency in the supervision framework. A score of −1 is assigned when a coach is not achieving the requirements of the competency, or when the supervisor assesses that there are significant improvements to be made. A score of 0 is assigned when a coach infrequently achieves the requirements of the competency or when the supervisor assesses that there are improvements to be made. A score of 1 is assigned when a coach fulfills the requirements of the competency or when the supervisor assesses that there are minimal insignificant improvements to be done. An "N/A" score is assigned when the area in question is not relevant or not possible to assess on this occasion. In completing the framework, a total score is calculated automatically. This score is a quantitative measure to assist the supervisor. After a supervision has taken place, the supervisor delivers feedback to the coach. This score will be evaluated alongside the fidelity index that was developed for the initial synchronous coaching sessions with independent specialist input. This fidelity index identified 18 health coaching techniques that need to be delivered in the initial health coaching session. The index assesses the use of relational techniques used to build a constructive empathic working alliance between the coaches and the study participants, and specific behavior change techniques used to facilitate individuals achieving their health goals.

The health coaching analytics include data relating to the number of participants coached, coach capacity, percentage contacts delivered on schedule, retention rate, demographics, goals set by participants, and coach rating by Liva supervisor. Women and their partners will have exit interviews at the end of the project with research staff. Health coaches will participate in focus groups following the active intervention completion in all sites. The exit interviews and focus groups will be semistructured and follow topic guides with prompts to provide a deeper understanding of implementation measures. The focus group and interview topic guides were informed by the EPIS framework, predominantly the implementation and sustainment aspects. The interviews and focus groups will be conducted by an experienced qualitative researcher independent of the maternity service. The recording of interviews and focus groups will be conducted using a digital audio recorder. The transcription will be conducted by trained staff, and all transcripts will be independently checked for accuracy before anonymization.

Maintenance

Participant-level maintenance of behavior change will be measured by goals achieved within the smartphone app. The adherence, retention, and loss to follow-up of participants in the mHealth coaching and the trial will inform future delivery. The cost information on the intervention delivery will be collected by participant questionnaires at 3 monthly intervals postpartum and from medical records for pregnancy data. The measures that will be collected from medical records include birth outcomes, length of hospital stay, admission to neonatal intensive care unit, and medications. The postpartum questionnaire will collect data on childcare use to support health behavior change and costs associated with health care professional visits. The health service's interest in delivering the screening tool in usual care will be explored using key informant interviews at the trial completion.

Data Analysis

Reach

The representativeness of the participants will be assessed within each site and barriers and enablers to participation will be explored using participant exit interviews.

Effectiveness

We will assess the RCT impact on the intervention's prespecified primary and secondary outcomes [29]. The reach evaluation penetration data will support the prevalence analysis of women at higher risk of developing GDM.

Adoption

We will use process data to assess site and health coach adoption. Additional surveys and key informant interviews will be conducted over the course of the intervention to inform other aspects of the adoption. The interview transcripts will be analyzed inductively using reflexive thematic analysis [55] and deductively using normalization process theory [56] to explore this aspect.

Implementation

We will assess the fidelity of the health coaching delivery and the program. The fidelity of delivery will be assessed separately for synchronous coaching and asynchronous interactions. For the synchronous coaching, these will be digitally recorded. These recordings will then be reviewed, and each health coaching technique identified and timed. This will then be compared with the specified techniques to be used from the Health Coaching Manual and used to generate an index of congruency. For the asynchronous coaching, we will code the Health Coaching techniques used in each coaching message. This will then be used to generate a technique profile aggregated for each individual from all interactions and aggregated for each coach. We will also do an exploratory analysis of the key informant interviews and focus groups using thematic analysis to identify implementation challenges. The key informant interviews and focus groups will take a variety of key stakeholder perspectives including hospital staff, health coaches, and the participants. They are informed by the EPIS framework. These data will be complemented by the RCT working group meeting minutes, which ran monthly for the duration of the

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project and detailed implementation challenges from the perspective of the trial.

Cost-effectiveness analysis (CEA) is a well-founded and widely used method within health economics, where the costs and outcomes of a specific intervention are compared to an alternative (normally usual care). The CEA produces an incremental cost-effectiveness ratio (ICER). This ratio is compared to established willingness to pay thresholds and to similar interventions to evaluate the cost-effectiveness and comparative effectiveness of the studied intervention. The CEA explained in this analysis plan will be used to evaluate the costs and health outcomes of the IDB2B intervention compared to usual care. The results from the analysis will serve as a foundation for health care policy makers in the decision-making surrounding the implementation of the intervention.

The 2 main health outcomes for the economic evaluation are health-related quality of life measured using the quality-adjusted life year (QALY) approach and BMI 12-month postpartum. QALYs are a summary health outcome measure routinely used for economic evaluation integrating quantity or time and quality of life into a single index. QALYs will be calculated based on responses from the EuroQol 5 dimensions long (EQ-5D-L) questionnaire, and country-specific value sets will be applied. Effects (QALYs and BMI) for the economic evaluation will be measured at the individual level over an observation period corresponding to the trial follow-up time of individual patients. The cost-effectiveness analyses will be performed from both a health sector perspective and a societal perspective. Cost categories for the economic evaluation from a health sector perspective include the value of all health care consumption, pharmaceuticals, and the cost of the intervention itself. The CEA from a societal perspective entails incorporating indirect costs, that is, productivity losses due to short-term and long-term sickness (sick leave). Information on the usage of health services will be collected at the individual level for all patients enrolled in the trial. These services will be captured from the electronic case report forms maintained by IDB2B clinical sites. If a patient visits health providers that are not one of the trial centers, the number of diagnostic and treatment procedures will be obtained based on self-reporting by patients. Valuation of the resources identified and measured will be done using country-specific diagnosis-related group tariffs. Comparing treatment effects and costs between 2 alternatives results in an ICER, which is calculated as follows:



where C^{IDB2B} and C^{UC} are the mean costs among patients in the IDB2B and usual care arms, while E^{DB2B} and E^{UC} are the mean effects (QALYs or BMI).

Depending on the effect measure chosen, the ICER expresses the additional costs per unit decrease in BMI or per QALY gained if IDB2B is used by pregnant women at risk of GDM. Concluding whether the intervention or the comparator is the cost-effective alternative depends on the societal willingness to pay (for a specific country), that is, if the ICER is below the willingness-to-pay threshold the intervention will be regarded as cost-effective. The evaluation will follow the Consolidated Health Economic Evaluation Reporting Standards (CHEERS). The analysis will pool data from all countries as well as conduct country-specific estimates with a comparative analysis of the health system and contextual factors affecting cost-effectiveness across countries. To estimate the long-term cost-effectiveness of the IDB2B intervention, a Markov cohort model will be used.

Maintenance

The future potential implementation of the B2B&Me program will be explored through semistructured interviews with key informants and participants from each participating site. The interview transcripts will be analyzed inductively using reflexive thematic analysis [55] and deductively using normalization process theory [56] to explore this aspect. The impact of the lengthy health coaching duration will also be explored as the 18 months of coaching is novel within this field.

Ethics Approval

The National Maternity Hospital Human Research and Ethics Committee was the primary approval site (EC18.2020) with approvals from University College Dublin HREC-Sciences (LS-E-20-150-OReilly), Junta de Andalucía Comités de Ética de la Investigación con Medicamentos/Comité Ético de Investigación Provincial de Granada (2087-M1-22), Monash Health Human Research Ethics Committee (RES-20-0000-892A), and NHS Health Research Authority and Health and Care Research Wales (21/WA/0022).

Results

Recruitment commenced on February 9, 2021, and data collection is currently ongoing. Publication of the results is expected during 2024.

Discussion

At the end of this 5-year project, we aim to assess the effectiveness and implementation of a complex intervention aligned with maternity services for women at high risk of developing GDM. It is clear that structured diet and physical activity interventions in antenatal care are associated with improved maternal outcomes, such as less GWG [19] and T2DM prevention, and that the capacity to implement such interventions in antenatal care settings is limited. There is a great need to conduct more pragmatic implementation research to generate learnings that could benefit the broader antenatal and postnatal care settings [18,19] and develop interventions that transcend pregnancy into the longer postpartum period in at-risk groups. The communication gap between maternity service and primary care is a well-known challenge for GDM management [22] but also wider continuity of care.

While the evaluation of the B2B&Me's mHealth coaching intervention effectiveness will be valuable, the implementation process assessment will make an important contribution as well. The duration of the health coaching particularly through the mHealth platform is novel, with the average duration being 6 months [57]. The type 2 hybrid effectiveness-implementation study design was selected because both aspects are

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complementary for evaluating this complex implementation project. The effectiveness evaluation takes a best-practice approach using an RCT. An important future implementation consideration of the design was the decision to ensure the data required to screen for eligibility were collected within routine care at the first antenatal visit for all 4 countries. This will facilitate the screening being potentially embedded within usual care as opposed to other risk factor screening tools that use biochemical or nonroutine tests [58,59]. The RE-AIM framework evaluation will yield valuable data that are important for the adoption of the intervention, if proven to be efficacious, and support wider implementation learnings.

IDB2B is not without limitations. The use of an RCT design brings with it the known issues with recruitment of those with potentially different demographics to the wider maternity population and the process of seeking consent will inherently curtain reach. We will measure the penetration of the study population as a means of looking further into this potential limitation, but we will likely not be able to control it. In the analysis of the implementation, it is likely that variation across countries will be a factor that will affect our data. We are planning to measure and potentially account for socioeconomic and ethnic variability among the women participating, but we cannot account for these factors among other stakeholders. This study cannot account for changes in the standard of care provided in primary care for reasons such as the COVID-19 pandemic. Any changes that occurred within the 4 maternity services' usual care should be accounted for within the longitudinal stakeholder interviews.

The project has the potential to provide a high-quality implementation assessment of a complex mHealth coaching intervention across multiple maternity services and the postpartum period. The IDB2B project has the potential for more general usage as an mHealth coaching platform beyond the B2B&Me RCT in the control and prevention of GDM and the long-term consequences for the mother and the offspring, if found to be effective. We expect that the results of this evaluation will yield important findings that will potentially support the improved health of women and children over the first 1000 days and beyond.

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Data Availability

Data can be made available upon reasonable request to the corresponding author.

Authors' Contributions

SLOR is the principal investigator who proposed the original study concept and led the protocol development. SLOR developed the first draft of the manuscript. All other authors contributed to the development of the concept and the final study design. All authors have been involved in revising the manuscript, have given final approval of the version to be published, and agree to be accountable for all aspects of the work. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Grant peer review report IMPACT DIABETES B2B_ESR
[PDF File (Adobe PDF File), 195 KB - resprot_v12i1e51431_app1.pdf]

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Abbreviations

B2B&Me: Bump 2 Baby and Me
CEA: cost-effectiveness analysis
CHEERS: Consolidated Health Economic Evaluation Reporting Standards
EPIS: exploration, preparation, implementation, and sustainment framework

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EQ-5D-L: EuroQol 5 dimensions long
GDM: gestational diabetes
GWG: gestational weight gain
ICER: incremental cost-effectiveness ratio
IDB2B: Impact Diabetes Bump2Baby
mHealth: mobile health
QALY: quality-adjusted life year
RCT: randomized controlled trial
RE-AIM: Reach, Effectiveness, Adoption, Implementation Fidelity, and Maintenance framework
T2DM: type 2 diabetes

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Protocol

Evaluating the Feasibility and Acceptability of a Digital Pre-Exposure Prophylaxis Navigation and Activation Intervention for Racially and Ethnically Diverse Sexual and Gender Minority Youth (PrEPresent): Protocol for a Pilot Randomized Controlled Trial

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Abstract

Background: To end the HIV epidemic by 2030, we must double down on efforts to tailor prevention interventions to both young men who have sex with men and transgender and nonbinary youth. There is an urgent need for interventions that specifically focus on pre-exposure prophylaxis (PrEP) uptake in sexual and gender minority youth (SGMY) populations. There are several factors that impact the ability of SGMY to successfully engage in the HIV prevention continuum, including uptake of PrEP. Patient activation, having the knowledge, skills, and self-efficacy to manage one's health, is an important indicator of willingness and ability to manage one's own health and care autonomously. Patient navigation also plays an important role in helping SGMY access PrEP and PrEP care, as navigators help guide patients through the health care system, set up medical appointments, and get financial, legal, and social support.

Objective: This study aims to evaluate the feasibility and acceptability of a digital PrEP navigation and activation intervention among a racially and ethnically diverse sample of SGMY living in the Los Angeles area.

Methods: In phase 1, we will conduct formative research to inform the development of PrEPresent using qualitative data from key informant interviews involving PrEP care providers and navigators and working groups with SGMY. In phase 2, we will complete 2 rounds of usability testing of PrEPresent with 8-10 SGMY assessing both the intervention content and mobile health delivery platform to ensure features are usable and content is understood. In phase 3, we will conduct a pilot randomized controlled trial to evaluate the feasibility and acceptability of PrEPresent. We will randomize, 1:1, a racially and ethnically diverse sample of 150 SGMY aged 16-26 years living in the Los Angeles area and follow participants for 6 months.

Results: Phase 1 (formative work) was completed in April 2021. Usability testing was completed in December 2021. As of June 2023, 148 participants have been enrolled into the PrEPresent pilot randomized controlled trial (phase 3). Enrollment is expected to be completed in July 2023, with final results anticipated in December 2023.

Conclusions: The PrEPresent intervention aims to bridge the gaps in PrEP eligibility and PrEP uptake among racially and ethnically diverse SGMY. By facilitating the delivery of PrEP navigation and focusing on improving patient activation, the PrEPresent intervention has the potential to positively impact the PrEP uptake cascade in the HIV care continuum as well as serve as a model for the tailoring of PrEP interventions based on behavior-based qualifications for PrEP instead of generalized gender-based eligibility.

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International Registered Report Identifier (IRRID): DERR1-10.2196/50866

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KEYWORDS

PrEP; mobile health; LGBTQ; transgender; adolescent; mobile phone

Introduction

Background

Because young men who have sex with men (YMSM) account for the vast majority of new HIV infections each year, HIV-prevention research has prioritized this population [1,2]. Among Black men who have sex with men newly diagnosed with HIV in 2017, 34% were between the ages of 13 and 24 years and 41% were between the ages of 25 and 35 years [3]. Rates of new infections among Latino YMSM are similarly alarming—while overall rates of HIV infection among this population declined from 2005 to 2014, new infections among 13-24 year old Latino YMSM increased by 87% [4]. Less is known about the engagement of transgender, nonbinary, and other gender nonconforming youth within the HIV care continuum.

Transgender and nonbinary identities are growing, especially among youth, at a fast rate. In a 2022 US Centers for Disease Control and Prevention (CDC) summary, it was estimated that over 1.6 million members of the US population identify as transgender people (0.5% of the population), and about 300,000 youth (1.4%) identify as transgender people [5]. Of these estimates, 38.5% are transgender women, 35.9% are transgender men, and 25.6% are gender nonconforming. In a 2021 lesbian, gay, bisexual, transgender, and queer (LGBTQ) sampling study of the United States, it was estimated that about 11% of LGBTQ adults identify as nonbinary. This percentage was approximated to just over 1 million nonbinary people (aged 18-60 years) living in the United States at the time of the report [6].

Emerging studies are examining the HIV incidence among transgender and nonbinary people. In a 2019 cohort study of 1608 transgender women, 42% of participants tested positive for HIV. In total, 82% of participants reported they had been tested in the last 12 months, and 96% reported being tested in their lifetime [7]. According to a 2018 analysis of care among transgender men living with HIV from 2009 to 2014, 69% of respondents had undetectable viral loads but only 40% reported HIV or sexually transmitted infection (STI) prevention counseling by a health care professional [8]. In a recent report of new HIV infections among transgender people, sexual contact exposure accounted for 90% of infections in transgender women, 73% of transgender men, and 82% of infections within an "additional gender identity" category [9], highlighting the importance of extending HIV-related interventions to all individuals based on their risk factors for HIV transmission as opposed to gender identity.

If we are to end the HIV epidemic by 2030, we must double down on efforts to tailor prevention interventions to both YMSM and transgender and nonbinary youth, hereafter referred to as sexual and gender minority youth (SGMY), especially youth of color. Pre-exposure prophylaxis (PrEP) uptake has remained exceedingly low among SGMY [10-12]. While there is now substantial evidence demonstrating that YMSM have high levels of PrEP awareness [13,14], very few have ever used PrEP. Strauss et al [14] found that 68% of YMSM recruited from 3 cities (Atlanta, Chicago, and New York City) reported awareness of PrEP; however, only 9% reported having ever used PrEP. The Healthy Young Men's Cohort Study of Black and Latino YMSM has shown that while 90% of YMSM are aware of PrEP and 86% are eligible for PrEP (using CDC criteria), only 23% have ever been prescribed PrEP and just 8% report currently using PrEP [15]. In a 2017 national digital study of transmasculine individuals, 24.2% of participants met criteria for PrEP eligibility based on behavior in the last 6 months. Of those eligible, only 64.9% had received a HIV test in the last year, 33.9% reviewed PrEP information from their provider, and only 10.9% were currently taking PrEP [16]. Within the Transgender Youth of Color Cohort Study, 67% of nonbinary youth assigned female at birth and 65% of transgender men reported condomless sexual interactions in the last 6 months. Despite these rates of condomless sex within the cohort, only 8% had taken PrEP in their lifetime and 3% of participants reported actively taking PrEP [17]. This underscores the urgent need for interventions that specifically focus on PrEP uptake within SGMY populations.

There are several factors that impact one's ability to successfully engage in the HIV prevention continuum, including uptake of PrEP. For example, individual factors such as illicit drug use and depression have been found to create disparities to accessing HIV prevention services [18-20]. In addition, sociocultural and structural determinants, such as inadequate access to health care, mistrust of health care providers, food insecurity, and residential instability, have also been found to serve as barriers to both HIV prevention and PrEP uptake [13,21,22].

In one study of young sexual minority men (n=492), only 14% reported having ever used PrEP; barriers to PrEP uptake included concerns about paying for PrEP and talking to one's provider about sexual behaviors [23]. PrEP-related stigma has also been found to be a significant barrier to PrEP use among YMSM, including negative stereotypes about PrEP users [24-26]. Concerns about needing to use PrEP daily and possible side effects have also been found to serve as barriers to PrEP uptake. Additional factors inhibit transgender and nonbinary people from accessing PrEP [27]. In focus groups conducted with transgender men in San Francisco, barriers around lack of PrEP knowledge, financial concerns, finding a transcompetent doctor, and discussing sexual matters with providers emerged as key themes, mirroring barriers faced by young sexual minority cisgender men [28].

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Patient activation, having the knowledge, skills, and self-efficacy to manage one's health, is considered to be an important indicator of the willingness and ability to manage one's own health and care autonomously [29,30]. Recent studies have found patient activation can significantly increase adherence and improve health-related outcomes [31-35]. Numerous studies have demonstrated that patients who are more activated in their care are also more likely to enact preventive behaviors, such as having regular checkups, screenings, and immunizations. Furthermore, research demonstrates that training individuals on how to ask questions and giving them the support to do so increases their participation in their own care and increases their activation levels [36]. A patient activation intervention may be ideally suited for use with SGMY, particularly if the goal is to activate them to become more engaged in their health, their use of health care and HIV prevention services, and PrEP uptake.

Patient navigation could also play an important role in helping SGMY access PrEP and PrEP care. Navigators help guide patients through the health care system and help patients set up medical appointments and get financial, legal, and social support. They may also help patients communicate with their health care providers. Often, patient navigators provide emotional support and help individuals access services to address their basic needs (eg, residential stability, food security, transportation, and language interpretation services) [37,38]. Innovative approaches to PrEP navigation, such as digital delivery using a mobile health (mHealth) app or digital platform, could help youth access care. Although numerous mHealth platforms now exist or are being developed, few are customized for inclusive use by SGMY or have been designed specifically for PrEP uptake. The PrEPresent app adapts an existing mHealth platform, developed by and for SGMY, and uses it to facilitate the delivery of PrEP navigation, increase knowledge about HIV and PrEP, increase intention to use PrEP, reduce PrEP stigma, and increase patient activation.

Theoretical Framework for Intervention

PrEPresent is a PrEP navigation, activation, and support intervention that builds upon the patient activation theory, which is rooted in concepts of self-efficacy and locus of control [39-41], and in the transtheoretical model of change [42]. This model refers to "the individual's knowledge, skills, and confidence in managing [their] own health and care" [43]. Patient activation theory describes an incremental process that patients undergo when becoming protagonists of their care management [44]. Building on this theory, we developed an intervention that is specifically targeted to increase PrEP uptake. Through both the mHealth platform itself and through interactions with PrEP navigators, participants are provided with developmentally appropriate information to (1) increase their self-awareness of their risk for HIV, (2) increase their awareness and knowledge about PrEP, and (3) address PrEP misperceptions and stigma. PrEP navigators also activate participants by increasing their PrEP self-efficacy and helping them develop strategies to address structural barriers related to PrEP uptake, such as obtaining insurance, finding an LGBTQ- and youth-friendly PrEP provider, obtaining transportation, finding a convenient pharmacy, obtaining and refilling PrEP prescriptions, paying for PrEP, developing a routine and reminders for taking a daily pill, and scheduling follow-up clinic visits.

Aims and Objectives

This study aims to (1) conduct formative research to inform the development of PrEPresent using qualitative data from key informant interviews involving PrEP care providers and navigators and working groups with SGMY, (2) complete 2 rounds of usability testing of PrEPresent with 8-10 SGMY assessing both the intervention content and mHealth delivery platform to ensure features are usable and content is understood, and (3) evaluate the feasibility and acceptability of PrEPresent within a racially and ethnically diverse sample of 150 SGMY aged 16-26 years living in the Los Angeles area.

Methods

Ethics Approval

The research and ethics described in this study have been reviewed and approved by the institutional review board of Children's Hospital Los Angeles (CHLA-20-00596). A certificate of confidentiality was obtained from the National Institutes of Health, and a waiver of parental consent has been obtained for participants aged 18 years or younger. This study is registered at ClinicalTrials.gov (NCT05281393).

Phase 1: Formative Research

To inform the development of PrEPresent, we will conduct 2 sets of formative research activities (phase 1A and phase 1B). During phase 1A, we will conduct qualitative interviews lasting 60-minutes with 15 PrEP providers and PrEP navigators serving SGMY. Participants will receive US $35 to complete an interview and will be employed at health care or community-based organizations located in Los Angeles County, at least 18 years old, and of all genders. During phase 1B, we will form 2 working groups, each with 6-10 racially and ethnically diverse SGMY. Participants will meet via chat or videoconference on a weekly basis for a total of 4 weeks and each session will last 2 hours. Participants will be compensated US $50 for each session they attend and will receive an additional US $50 for active participation across the groups. Active participation includes attendance, contributing to session discussions, and participating in session activities. Participants will be (1) aged between 16 and 26 years; (2) cisgender male, transgender people, gender nonconforming, or identify differently from the gender picked for them at birth; (3) gay, bisexual, or some other same-sex identity, or report having had sex with anyone with a penis during the previous 12 months; (4) White or Caucasian, Black or African American, Latinx, Asian-Pacific Islander, Indigenous, Native American or multiracial; (5) living in the Los Angeles metro area; (6) have daily access to an iOS or Android smartphone or tablet with internet access; and (7) know their HIV status and be HIV-negative at time of enrollment.

We will engage participants in guided discussions on a variety of topics, including (1) general discussion around health and where participants access health information; (2) experiences discussing sexual health, sexual identity, sexuality, and gender with health care providers; (3) knowledge, attitudes, and beliefs

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about PrEP; (4) a PrEP journey activity (ie, use of a digital board game activity to facilitate discussion about the steps young LGBTQ people need to get and stay on PrEP and to develop possible app features and resources that will facilitate this); (5) how participants use mobile phone apps in their daily lives; (6) an app tracking activity (ie, each participant downloads an activity tracking app and reports back on what they like and dislike about the app, and how it could be improved); and (7) specific app features, such as avatars, badges, and discussion forums.

Phase 2: Usability Testing

Following initial development of the PrEPresent digital platform, we will conduct usability testing with 8-10 racially and ethnically diverse SGMY. Study participants will participate in 1 digital focus group to download and review the app, 1 digital (chat or videoconference) session with our live PrEP Navigator (the "PrEPresentative"), and a one-on-one exit interview to provide feedback on the app. Participants will also be asked to complete pre- and posttest surveys to assess app experience and general usability. Participants will be compensated US $40 for each digital session they attend.

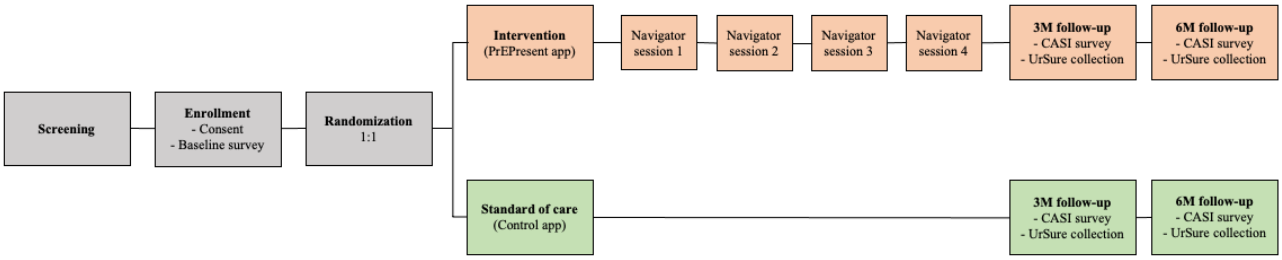
During the digital focus group, which will last 60-90 minutes, we will prompt participants for feedback in the following categories: understanding of features, overall impressions of the relevance of the intervention, and additional content or features that might be added to increase their likelihood of use. Then, participants will be instructed to use the app over a 2-week period and to schedule a 30-minute meeting with the PrEPresentative. PrEPresentative sessions will occur via chat or videoconference and will use the app's scheduling and meeting features. These sessions will assess the feasibility of the newly developed features and provide an opportunity to gather feedback about the PrEPresentative role. The one-on-one exit interview will occur approximately 3 weeks after the digital focus group. This will allow participants time to use the app, generate feedback, and meet with the PrEPresentative. The interview, which will last 30-45 minutes, will include questions regarding overall intervention satisfaction, technical functionality and performance, and specific questions about each feature available in the app (medication tracker, resources, goal setting, forums, PrEPresentative, activities, badges, and avatars). Pre- and posttest surveys will be administered before downloading the app and after the 2-week testing period (but before the exit interviews to reduce response bias). Participants will meet the same eligibility criteria as outlined for phase 1B of the study (see above).

Phase 3: Pilot Randomized Controlled Trial

Design

The pilot randomized controlled trial (RCT) to evaluate intervention feasibility and acceptability will enroll up to 150 SGMY living in Los Angeles County, California, who will be randomized 1:1 to either the intervention (PrEPresent app) or control (information-only app) arms. The active intervention period is from 0 to 3 months and participants will complete study visits at baseline, 3, and 6 months (see Figure 1).

Figure 1. PrEPresent pilot randomized controlled trial study schema. 3M: 3 months; 6M: 6 months; CASI: computer-assisted self-interview.



Participants

Participants will be (1) aged 16-26 years; (2) cisgender male, transgender people, gender nonconforming, or identify differently from their gender picked for them at birth; (3) gay, bisexual, or some other same-sex identity, or report having had sex with anyone with a penis during the previous 12 months; (4) White or Caucasian, Black or African American, Hispanic or Latino or Latinx, or multiracial with one of these identities; (5) living in the Los Angeles metro area; (6) have daily access to an iOS or Android smartphone or tablet with internet access; (7) report having insertive or receptive sex in the previous 6 months or report a positive STI result in the previous 6 months; (8) not currently on PrEP and have no plan to start or restart PrEP in the following 7 days; and (9) not currently enrolled in another HIV prevention study.

Prospective participants will be considered ineligible if they are non-English speaking, living with HIV, or if they participated in phase 1 or phase 2 study activities.

Recruitment

Individuals will be recruited from multiple in-person and digital sources. First, study staff will contact potentially eligible youth from 2 existing longitudinal cohorts (Healthy Young Men's Cohort and the Transgender Youth of Color Cohort Study) who consented to being contacted about future research opportunities to assess their interest in and eligibility for PrEPresent. Staff will also use venue-based methods (eg, tabling events, referral from health or social service agencies) via flyers. Digital recruitment will include targeted advertisements on popular social media sites (eg, Facebook and Instagram). Potential participants recruited in any of the aforementioned ways will be directed to the study screening survey hosted on Qualtrics (Qualtrics Inc), a Health Insurance Portability and Accountability Act (HIPAA)–compliant digital software program. After reviewing a brief description of the study and providing consent to be screened, potential participants will complete the brief screening survey and provide contact information for follow-up use. Eligible SGMY will be invited

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to an initial in-person or digital visit in which staff will describe the study, confirm eligibility, obtain informed consent, sign a HIPAA release, and complete a baseline assessment. Youth who self-report living with HIV while reviewing eligibility criteria will be linked to care.

Randomization

Participants who meet eligibility criteria, consent to participation in the study, and complete the baseline survey will be randomized in a 1:1 ratio to the control or intervention arm using a prespecified randomization sequence that is reviewed by the study statistician. Randomization will not be stratified.

Intervention Arm

Participants assigned to the intervention will be asked to download the PrEPresent app and will be given a guided tour of the app and its main features (Table 1). Participants will be encouraged to schedule their first navigation session with the PrEPresentative and to use the app's other features on a regular basis.

The PrEPresent platform will include live chat topics for the PrEP navigator, a repository of motivational text messages covering a range of identified barriers and facilitators to PrEP uptake, a curriculum for the PrEP navigator's videoconferencing sessions, and a library of media and informational content to address identified gaps in PrEP knowledge, strategies, and skills. The app also includes an anonymous forum to facilitate peer-to-peer exchange, interactive activities, and a direct portal to engage in one-on-one interactions with the PrEPresentative either through text or video.

Participants randomized to the intervention arm will receive up to 4 sessions with the PrEPresentative over the 3-month intervention period (Table 2). Sessions will occur approximately 1 month apart, with session 1 beginning from the date of enrollment. Sessions will be scheduled via the PrEPresent app and can be scheduled, based on participant choice, via one of three ways: (1) text via app, (2) phone call, and (3) HIPAA-compliant videoconferencing (WebEx). During these sessions, the PrEPresentative will begin developing a tailored plan to link participants to PrEP care screening, HIV or STI testing, or prescriptions for PrEP. The PrEPresentative will also work with participants to increase patient activation (self-advocacy, self-efficacy, and motivation), help them identify a pharmacy to fill prescriptions, if necessary, help them pay for prescriptions (eg, insurance enrollment), and help develop practical, individualized behavioral strategies to support adherence. The PrEPresentative will check in via chat or videoconference at least weekly with participants to (1) ensure their needs continue to be met, and (2) provide reminders and prompts to ensure adherence to PrEP. The PrEPresentative will also use the mHealth platform to deliver motivational text messages, monitor PrEP follow-up visits, and monitor prescription refills. Participants can respond to these messages or engage in text messaging via the intervention app using the secure 2-way communication portal.

Table 1. Overview of PrEPresent app intervention features.

App feature	Description
Health tracker	Medication and habit tracking allows users to visualize patterns in their adherence, self-monitor, and receive feedback for improvement.
Forum	Users can participate in forum discussions and polls to foster community support and peer-to-peer sharing within the app.
Resources	Provides educational content across a range of health topics.
Activities	Supports app engagement and behavior change through information and skill-building.
Goals	Pushes tailored content through a curriculum that keeps users on target with health and wellness goals. Provides milestones, tasks, tips, connections, and journal opportunities related to participant's goals.
Appointments	Connects users to a PrEP navigator to support them along their PrEP journey. Users can request times from available time slots, as well as a preferred method of contact (phone, text, or video).
Ask the expert	Subject matter experts answer anonymously submitted health and wellness questions from users. Questions and answers are visible to all participants to promote shared knowledge and connection to resources.
Avatar customization	Supports ongoing engagement by unlocking new accessories the more users engage with the app.
Care locator	Directory of local services specific to their need. Covers physical health, mental health, legal support, housing resources, and more.
Badges	Users can earn badges for actions taken within the app. Rewards engagement and participation in the study.

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Table 2. Overview of PrEPresentative sessions.

Session	Time point	Delivery window	Topics
1	BL[a]	Days 0-14	Building rapport, introduction to intervention, overview of PrEPresentative role, PrEP[b] motivation, and needs assessment.
2	1 month	Days 15-44	Developing tailored linkage to PrEP plans, adherence strategies (as needed), and supporting ongoing patient activation.
3	2 months	Days 45-74	Reviewing progress, follow-up and adjustments to tailored linkage to PrEP plans, adherence strategies (as needed), and supporting ongoing patient activation.
4	3 months	Days 75-104	Reviewing progress, intervention off-boarding (transition), reinforcement of adherence strategies (as needed), and maintenance of patient activation.
Check-ins	Weekly	Day determined at initial visit	Ensure needs continue to be met, provide reminders and prompts for linkage to PrEP care, medication refills, and adherence.

[a]BL: baseline.

[b]PrEP: pre-exposure prophylaxis.

Standard of Care Arm

Participants randomized to the standard of care arm will be given access to an information-only version of the PrEPresent app that only includes the library of media and informational resources regarding PrEP. These participants will not have access to the PrEPresentative sessions or other enhanced features of the app. Standard of care participants will be encouraged to use the control app on a regular basis.

Follow-Up Visits and Retention

At 3 and 6 months after enrollment, participants will be asked to complete a survey assessment and UrSure (UrSure Inc) at-home test kit to measure PrEP uptake. Study staff will contact participants prior to their target date using the participant's preferred contact method indicated at baseline. Additional reminders will be provided via email, text, and phone call on and after the target date as needed to ensure completion of study visit procedures. Staff may leave messages (voicemails) for participants who consented to this at baseline.

Incentives

Participants will be compensated for completion of surveys at baseline and 3 and 6 months (US $50 each) and urine specimens at 3 and 6 months (US $20 each). If participants successfully complete all survey assessments and specimen collections, they will receive an additional US $50 bonus. Control arm participants can receive up to US $240, while intervention participants could receive up to US $280, as they will be asked to complete a brief satisfaction survey after each of their 4 PrEPresentative sessions (US $10 each).

Data Collection

At the time of enrollment, baseline surveys will be administered, while follow-up surveys will be administered 3- and 6-months postenrollment. Urine specimen results will be collected at 3- and 6-months postenrollment.

Primary Outcome Measures

We will assess the feasibility and acceptability of the patient navigation and mHealth platform aspects of the PrEPresent intervention. We will define patient navigation feasibility as at least half of intervention participants attending on average at least 2 sessions over the 3-month intervention period and mHealth platform feasibility as at least half of intervention participants using the platform on average at least 2 times per week over the 3-month intervention period. Patient navigation acceptability will be defined as a mean postnavigation satisfaction survey score of 4 or higher and mHealth platform acceptability as a score of greater than 70 using the 10-item System Usability Scale [45,46].

Secondary Outcome Measures

Preliminary efficacy of the PrEPresent intervention will include PrEP uptake measured using self-report PrEP use scales at the 3- and 6-month timepoints. Additionally, biological specimens using the UrSure point-of-care rapid urine test of tenofovir will be used. Potential mediators and moderators of the PrEPresent intervention, including PrEP self-efficacy, PrEP stigma, barriers to PrEP use, and patient activation will be assessed via 3- and 6-month surveys.

Statistical Analysis

Univariate statistics (eg, SD, range, and value) will be used to describe the study sample as well as values of the trial measures detailed above. Bivariate analyses will examine relationships among variables of interest. We will also produce summary scores and scales for constructs of interest (eg, System Usability Scale). Scale scores will be created as means or sums of unweighted composite scores depending on original item types.

To assess intervention feasibility and acceptability, we will summarize related data as means and proportions, with the 95% CI, by assessment period. Pre- to postintervention changes will be evaluated with generalized linear mixed models; a subject-level random intercept will be specified. Estimates of changes at each postintervention assessment will be calculated, along with the 95% CI.

We will follow steps for mediation analysis using nonparametric bootstrapping to assess indirect (mediated) effects and determine the CI [47,48]. Both the direct (unmediated) and indirect (mediated) effects of the intervention on each outcome of interest will be estimated and tested. Moderators (eg, racial and ethnic group) will be evaluated in these models, estimating and

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testing for differences in intervention effects across groups or other specified subgroups.

Results

Phase 1 (formative work) began January 2021 and was completed April 2021. Usability testing began November 2021 and was completed December 2021. Institutional review board approval for the phase 3 (the pilot RCT) was granted in May 2022 and data collection began the same month. As of June 2023, 148 participants have been enrolled into the PrEPresent pilot RCT. Enrollment is expected to be completed in July 2023, with final results anticipated in December 2023.

Discussion

Overview

PrEPresent is a mHealth intervention that will address evidence-based barriers to engagement in PrEP care for SGMY in Los Angeles, California. The intervention is innovative in that its eligibility criteria are not strictly based on gender but prioritize populations engaging in sexual behaviors that qualify individuals for PrEP usage per CDC guidelines. PrEPresent leads with a patient activation strategy to encourage self-advocacy, self-efficacy, and motivation in accessing care within the HIV care continuum, particularly within sexual and gender minority populations who face medical stigma and structural disadvantages to engagement in affirming health care. The PrEPresentative, or patient navigator, will also use motivational interviewing techniques to address additional barriers such as HIV stigma, sexual wellness education, insurance and provider navigation, transportation, and housing difficulties.

Limitations

During the creation of the PrEPresent intervention, care was taken to conduct formative research with PrEP providers and navigators in the Los Angeles areas to understand barriers and activators to uptake within a local landscape. This research is limited in its generalizability due to its centralization within a major metropolitan city and due to the location-specific resources available surrounding HIV-related care. Both California as a state and Los Angeles as a county offer universal health care coverage and have prioritized PrEP uptake and access within their HIV prevention efforts.

Participant eligibility criteria for the project included meeting the CDC qualifications for PrEP prescription. It is possible that fluctuations in participant sexual activity due to different factors may impact their willingness to uptake PrEP. A limitation of the current protocol is that PrEP uptake is only measured over a period of 6 months. Additional education and guidance throughout the intervention period may have longer-reaching impacts on PrEP willingness and use beyond this timeline.

Additionally, while efforts were made to include youth in formative research with expansive genders, ethnic identities, and experiences to inform tailored, affirming, and engaging app content, there may be population-specific areas that were not addressed among the resources available within the app.

Conclusions

The PrEPresent intervention aims bridge the gaps in PrEP eligibility and PrEP uptake among racially and ethnically diverse SGMY. By facilitating the delivery of PrEP navigation and focusing on improving patient activation, the PrEPresent intervention has the potential to positively impact the PrEP uptake cascade within the HIV care continuum as well as serve as a model for the tailoring of PrEP interventions based on behavior-based qualifications for PrEP instead of generalized gender-based eligibility.

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Data Availability

The data sets generated and analyzed during this study will be available from the corresponding author upon reasonable request.

Conflicts of Interest

None declared.

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Multimedia Appendix 1
Peer-review report from HIBI, HIV/AIDS Intra- and Inter-personal Determinants and Behavioral Interventions Study Section (USA).
[PDF File (Adobe PDF File), 160 KB - resprot_v12i1e50866_app1.pdf]

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Abbreviations

CDC: US Centers for Disease Control and Prevention
HIPAA: Health Insurance Portability and Accountability Act
LGBTQ: lesbian, gay, bisexual, transgender, and queer
mHealth: mobile health
PrEP: pre-exposure prophylaxis
RCT: randomized controlled trial
SGMY: sexual and gender minority youth
STI: sexually transmitted infection
YMSM: young men who have sex with men

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Protocol

Optimizing a Technology-Based Body and Mind Intervention to Prevent Falls and Reduce Health Disparities in Low-Income Populations: Protocol for a Clustered Randomized Controlled Trial

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Abstract

Background: The lack of health care coverage, low education, low motivation, and inconvenience remain barriers to participating in fall prevention programs, especially among low-income older adults. Low-income status also contributes to negative aging self-perceptions and is associated with a high perceived barrier to care. Existing fall prevention intervention technologies do not enable participants and practitioners to interact and collaborate, even with technologies that bring viable strategies to maintain independence, prevent disability, and increase access to quality care. Research is also limited on the use of technology to enhance motivation and help individuals align their perception with physiological fall risk. We developed a novel, 8-week Physio-Feedback Exercise Program (PEER), which includes (1) technology-based physio-feedback using a real-time portable innovative technology—the BTrackS Balance Tracking System, which is reliable and affordable, allows for home testing, and provides feedback and tracks balance progression; (2) cognitive reframing using the fall risk appraisal matrix; and (3) peer-led exercises focusing on balance, strength training, and incorporating exercises into daily activities.

Objective: This study consists of 3 aims. Aim 1 is to examine the effects of the technology-based PEER intervention on fall risk, dynamic balance, and accelerometer-based physical activity (PA). Aim 2 is to examine the effects of the PEER intervention on fall risk appraisal shifting and negative self-perceptions of aging. Aim 3 is to explore participants' experiences with the PEER intervention and potential barriers to accessing and adopting the technology-based PEER intervention to inform future research.

Methods: This is an intention-to-treat, single-blinded, parallel, 2-arm clustered randomized controlled trial study. We will collect data from 340 low-income older adults at baseline (T1) and measure outcomes after program completion (T2) and follow-up at 3 months (T3) and 6 months (T4). Participants will be enrolled if they meet all the following inclusion criteria: aged ≥60 years, cognitively intact, and able to stand without assistance. Exclusion criteria were as follows: a medical condition precluding exercise or PA, currently receiving treatment from a rehabilitation facility, plan to move within 1 year, hospitalized >3 times in the past 12 months, and does not speak English or Spanish.

Results: As of August 2023, the enrollment of participants is ongoing.

Conclusions: This study addresses the public health problem by optimizing a customized, technology-driven approach that can operate in low-resource environments with unlimited users to prevent falls and reduce health disparities in low-income older adults. The PEER is a novel intervention that combines concepts of physio-feedback, cognitive reframing, and peer-led exercise by motivating a shift in self-estimation of fall risk to align with physiological fall risk to improve balance, PA, and negative aging self-perception.

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International Registered Report Identifier (IRRID): DERR1-10.2196/51899

(JMIR Res Protoc 2023;12:e51899) doi:10.2196/51899

KEYWORDS

fall prevention; fear of falling; low income; older adults; exercise; technology

Introduction

Background

In 2020, there were 37.2 million people living in poverty in the United States, approximately 3.3 million more than in 2019 [1]. Every 19 minutes, an American individual dies from a fall, and every 11 seconds, an older individual is treated in an emergency department for a fall [2]. Falls and fear of falling (FOF) are significantly higher in racially diverse low-income older adults than in the general older population [3-5]. There is an association between poverty, fall injury, and mortality, resulting in health disparities [6,7]. Falls cause 95% of hip fractures, 40% of admissions to facility-based care, and 40% of fall victims to lose mobility and independence [8]. In 2018, the direct costs of fatal falls were >US $754 million, and nonfatal falls were US $50 billion, but only US $9 billion was paid by Medicaid [9]. As the number of low-income older adults increases sharply and inequalities continue to grow, this is now a widely recognized problem that requires urgent and significant action [10]. The lack of health care coverage, low education, low motivation, and inconvenience remain barriers to participating in fall prevention programs [11,12]. Low-income status contributes to negative aging self-perceptions [13] and is associated with a high perceived barrier to care [14]. A higher level of concern over falling and FOF were more prevalent in low-income older adults and functional independence in daily activities [12]. Low-income status is independently associated with FOF, which induces activity restriction [15] and functional decline [16]. People who live in low-income communities are less likely to engage in physical activity (PA) [17-19]. The lack of PA is related to falls and poor quality of life [20,21].

Addressing maladaptive fall risk appraisal (FRA) can be challenging owing to self-report bias and cognitive deficit. We developed an *FRA matrix*, a graphical grid categorizing perception (levels of FOF) and body function (level of balance) into four groups: (1) rational FRA (low FOF and normal balance), (2) incongruent FRA (low FOF despite poor balance), (3) irrational FRA (high FOF despite normal balance), and (4) congruent FRA (high FOF and poor balance) [22,23]. On the basis of our previous works [24-26] and other studies [27], approximately 64% to 79% of older adults had maladaptive FRA. Older adults in maladaptive FRA groups were 2 to 3 times more likely to fall than those in adaptive FRA [24,25]. Those with irrational FRA serve as a barrier, creating a high FOF that inhibits low-income older adults from staying physically active. High FOF restricts mobility and daily activities and increases fall risk [28], with chronic FOF predicting an increased risk of functional decline [16]. Individuals with FOF overestimated their gait performance and showed deficits in motor imagery of gait [29]. They may not exhibit increased FOF and subsequently fall if they accurately appraise their physical abilities [27]. Evidence, including our data, indicates that an intervention program must help older adults reframe FRA and maintain PA [27,30]. We found that the FRA matrix is associated with moderate to vigorous PA (MVPA), Centers for Disease Control and Prevention (CDC) fall risk score, self-reported strength and flexibility, difficulty walking several city blocks, and left-hand average handgrip strength [31].

Older adults with FOF overestimated their gait performance and showed deficits in motor imagery of gait [29]. Older adults may exhibit less FOF and subsequently fall if they accurately appraise their physical abilities [27]. In addition, maladaptive FRA can result in activity withdrawal, decline in physical and cognitive abilities, and increased social isolation [23]. Therefore, adaptive FRA is a key component of activity participation and maintenance of self-reliance [32]. Several types of interventions focus on reducing FOF [33-41]; however, some degree of FOF can increase conscious awareness and reduce fall risk by encouraging individuals to avoid exposure to unnecessary risks [42]. Low-income older adults with better-perceived physical health may experience less FOF [43].

In addition, existing fall prevention intervention technologies do not enable participants and practitioners to interact and collaborate [44] even with technologies that bring viable strategies to maintain independence, prevent disability, and increase access to quality care. Acceptability, privacy issues, technology costs, implementation costs, and barriers have rarely been addressed [44]. Research is also limited on the use of technology to enhance motivation and help individuals align their perception with physiological fall risk [45]. Offering additional advantages, technology-based exercise interventions have good adherence and may provide a sustainable method of promoting PA and preventing falls [45,46].

We developed a novel, 8-week Physio-Feedback Exercise Program (PEER) [32], which includes (1) technology-based physio-feedback using a real-time portable innovative technology—the BTrackS Balance Tracking System (BBS), which is reliable [47,48] and affordable, allows for home testing, provides feedback, and tracks balance progression; (2) cognitive reframing [49] using the FRA matrix; and (3) peer-led exercises [50] focusing on balance, strength training, and incorporating exercises into daily activities. Our pilot study supports the feasibility and acceptability of using BBS technology in low-income communities to screen individuals with maladaptive FRA. It also supports using the results to tailor interventions to improve PA and reduce falls [31,51,52]. The findings highlight reducing sedentary time to help shift from irrational to rational groups and increasing MVPA time to help shift from congruent and irrational to rational FRA groups. We found a significant

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difference in sedentary time between the rational and irrational groups (P=.04). This indicates that if a person exhibits high FOF despite their normal balance (irrational), they tend to be more sedentary compared with people with low FOF and normal balance (rational). Importantly, we showed that the FRA matrix and 4-group quadrant design (irrational, incongruent, congruent, and rational) allows stratified analysis, which provides a more efficient overall fall risk assessment, which has rarely been reported in the literature.

Aims and Hypotheses

Aim 1 is to examine the effects of the technology-based PEER intervention on fall risk, dynamic balance, and accelerometer-based PA.

The hypotheses are as follows:

- *H 1.1:* The PEER group will reduce the fall risk compared with the control group.
- *H 1.2:* The PEER group will improve the dynamic balance compared with the control group.
- *H 1.3:* The PEER group will improve accelerometer-based PA compared with the control group.

Aim 2 is to examine the effects of the PEER intervention on FRA shifting and negative self-perceptions of aging.

The hypotheses are as follows:

- *H 2.1:* The PEER group will have a more adaptive shifting compared with the control group.
- *H 2.2:* The PEER group will have a more positive shift in their perceptions of aging compared with the control group.

Aim 3 is to explore participants' experiences with the PEER intervention and potential barriers to access and adoption of the technology-based PEER intervention to inform future research. A purposive sample of 30 participants from the PEER group will participate in semistructured one-on-one interviews to explore their perceptions of barriers to access and adoption of technology and intervention.

Methods

Study Design

This is an intention-to-treat, single-blind, parallel, 2-arm clustered randomized controlled trial study. We will collect data at baseline (T1) and measure outcomes after program completion (T2) and follow-up at 3 months (T3) and 6 months (T4) to test our hypotheses. We include a retention period of 6 months to determine whether fall risk, dynamic balance, PA, altered maladaptive FRA (FRA shifting), and negative self-perceptions of aging are maintained without ongoing intervention. This study is registered on ClinicalTrials.gov (NCT05778604).

Settings

The intervention will be offered in low-income, independent living communities, units, and apartments in Orlando, Florida. Florida has a large aging population with drastically different income levels and degrees of socioeconomic status [53]. The diversity of potential participants is also high, as Florida's population is approximately 17% African American, 3% Asian, 26% Hispanic or Latinx, and 54% non-Hispanic White [54].

Study Participants

A sample of 340 participants will be enrolled if they meet all the following inclusion criteria:(1) aged ≥60 years, (2) cognitively intact based on Mini-Mental State Examination score ≥24 [55], and (3) able to stand without assistance. Exclusion criteria were as follows: (1) a medical condition precluding exercise and PA, such as feeling pressure when performing PA; (2) currently receiving treatment from a rehabilitation facility; (3) plan to move within 1 year; (4) hospitalized >3 times in the past 12 months; and (5) does not speak English or Spanish.

Power Analysis and Sample Size

The sample size estimate was based on the primary outcomes of fall risk (CDC fall risk score) and PA (normalized MVPA) for aim 1 and the secondary outcome of FRA shifting (BBS score) for aim 2. The difference in the normalized mean MVPA between the PEER group (mean 3.67, SD 2.54) and the control group (mean 5.38, SD 2.68) and the difference in the fall risk score between the PEER group (mean 2.72, SD=3.23) and the control group (mean 2.21, SD=2.06) are considered markers of PA and fall risk, respectively. Considering a clinically relevant normalized difference in MVPA of 1.7 (SD 2.60) and a fall risk score difference of 0.50 (SD 2.56), the medium effect size Cohen d=0.25, intraclass correlation (ICC) of 0.8, and a significance level of are used for the calculation of the sample size. A sample size of 120 participants per arm is needed to reach 80% statistical power to detect the difference between the PEER and control groups on repeated measures of normalized MVPA. A sample size of 120 participants per arm is needed to reach 80% statistical power to detect the difference between the PEER and control groups on repeated measures of normalized MVPA.

In addition, the sample size was also based on the following: (1) at least 3 sites per arm; (2) an initial hypothesis that at least 10% (34/340) of the irrational, incongruent, and congruent FRA would shift to rational FRA after PEER completion; (3) an approximate study adherence rate of 80% [56], and (4) an estimated study dropout rate of approximately 40% (136/340) over time. Therefore, the sample size was increased from 120 to 170 per arm, resulting in a total of 340 participants. On the basis of our pilot study [26], we estimate that approximately 60% (204/340) of the low-income older adults will meet all inclusion and exclusion criteria and will be interested in participating in this study. We estimate that a minimum of 567 low-income older adults will be screened to identify 340 low-income older adults for enrollment, and approximately 240 low-income older adults (120 per arm) are needed to complete the study. Given the sample size of 120 per arm, a significance level of P=.05, and 80% power, considering a clinically relevant BBS mean score difference of 8 (SD 12), the effect size Cohen d=0.36 can be achieved to compare the intervention effect based on secondary outcomes.

Recruitment, Randomization, and Procedures

Research sites will be recruited through a partnership with local communities, personal contacts, referrals, and phone calls. The

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unit of randomization is an independent living senior community, which is defined as a company-owned facility with a design for low-income independent adults aged ≥55 years and without health care services provided on campus. Research sites will be selected based on the prespecified criteria, including the number of residents, geographic proximity (urban vs suburban), and ability to implement the intervention. We plan to recruit 6 sites (3 intervention sites and 3 control sites). Collectively, approximately 10 sites and 800 low-income individuals are available for screening, and we can add sites, as they are abundant in the area. The participating sites will be randomized to either the intervention or control group in a 1:1 ratio. RX (coinvestigator and statistician) will use a computerized pseudorandom number generator to determine the randomization order in advance. The project director (PD) will reveal the randomization of the sites before the study [57]. Following randomization, we will recruit participants using standard strategies, including placing flyers on information boards and participating in open-house sessions or health fairs for face-to-face recruitment. Participants will also be recruited from their units by email. We will screen participants by a phone call to determine their initial eligibility, and those eligible will be invited for the baseline assessment. The research staff will explain the study and complete the consent process. The PEER intervention sites will be required to select 6 to 7 volunteers called *peer coaches* (PCs) to lead the exercise group, and the PCs will be eligible if they report having a regular PA routine or having an educational background in health care; are aged >55 years; can read, write, and understand English and Spanish; and are committed to delivering the protocol for 8 weeks. JS (coinvestigator) and the principal investigator (PI) will provide two, 3-hour sessions to train the PCs in balance and strength training, safety in the exercise, and participant motivation in collaboration with a successful PC from our pilot study. Each PC will be matched to 8 to 10 low-income older adults in the PEER group according to the place of residence and will supervise low-income older adults in groups while they are engaged in group exercises. This procedure was successful in our pilot study.

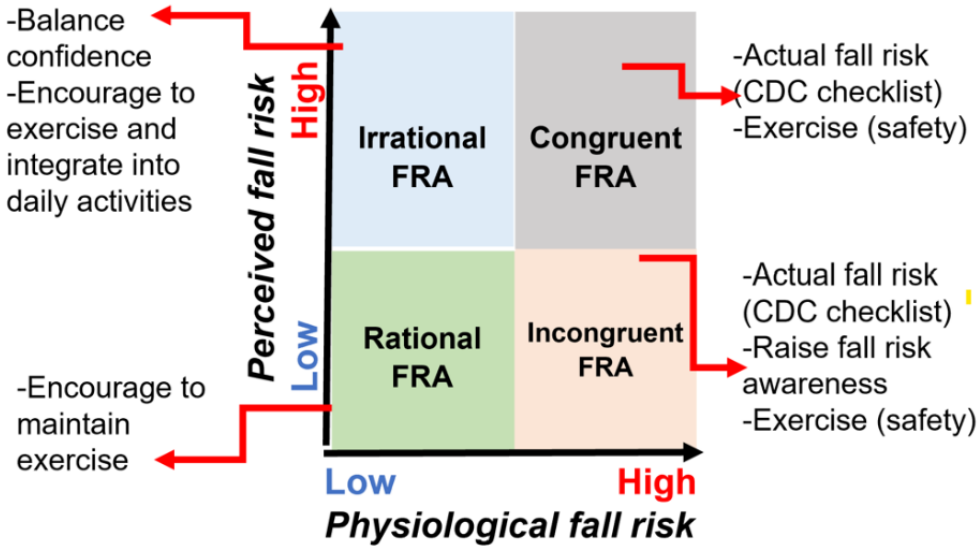
Intervention

The PEER consists of 3 components with 3 steps.

Step 1: Technology-Based Physio-Feedback

The research assistant (RA) presents the BTrackS software (Balance Tracking Systems, Inc) to display the participant's BBS scores with interpretations and then categorizes the participants into 4 groups (irrational, incongruent, congruent, and rational) according to the FRA matrix and plots the position in 1 of the 4 quadrants on the FRA matrix chart (Figure 1). The RA will provide physio-feedback to the participants at baseline (T1) and after program completion (T2).

Figure 1. Technology-based physio-feedback. CDC: Centers for Disease Control and Prevention; FRA: fall risk appraisal.



Step 2: Cognitive Reframing

Cognitive reframing will be based on the FRA matrix. We will present the FRA matrix, and activities will be tailored based on the quadrant that the participant fits (Figure 1):

- *Quadrant 1* (irrational): focus on increasing balance confidence and maintaining exercise.
- *Quadrant 2* (incongruent): focus on individual fall risk factors from the CDC fall risk checklist, enhance fall risk awareness, and participate in the exercise.
- *Quadrant 3* (congruent): focus on individual fall risk factors from the CDC fall checklist and participate in the exercise.
- *Quadrant 4* (rational): encourage to maintain exercise.

Step 3: Peer-Led Exercises

Peer-led exercises focus on balance, strength training, and incorporating exercises into daily activities. A trained PC will lead the group-based exercises for 60 minutes (8-10 per group). Exercise training includes 4 sets of warm-ups, strength for the upper and lower body, balance (standing and moving), and stretching of the upper and lower body. Our training sessions follow the guidelines established by the American College of Sports Medicine, which take into account the frequency, intensity, time, and type of exercise recommended for each individual level of progression. These levels are classified as beginner, intermediate, and advanced [58,59]. On the basis of these guidelines, a duration of 91 to 120 minutes of exercise

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per week is the most effective in improving overall balance performance [60]. Therefore, the dose of exercise that will be tested in the PEER group is 120 minutes for 8 weeks (60 min/wk for group exercise led by the peer and at least 30 min twice a wk for individual exercise). We will offer a booklet with exercise instructions in both English and Spanish, featuring illustrations to guide users through each exercise set. The booklet contains a diverse range of exercises that can be easily incorporated into daily routines, such as cooking. The participants will be instructed to keep a weekly log of their exercise activities, noting the type and duration of each activity they performed at home.

Treatment Fidelity and Monitoring

The PI and PD will oversee the treatment fidelity and monitoring plan. We will use a modified Treatment Fidelity Assessment Tool based on National Institutes of Health's Behavioral Change Consortium treatment fidelity research [61]. In total, 5% (17/340) of the intervention sessions will be randomly observed by the PI using the modified Treatment Fidelity Assessment Tool, including treatment design, training, delivery of treatment, receipt of treatment, and enactment of treatment skills [61,62]. It is evaluated on a 3-point scale (1=present, 2=absent but should be present, and 3=not applicable). Problems identified, including deviation from the protocol, will be discussed with the research team, assessors, and interventionists biweekly. Retraining will be provided if adherence is <90%. A continual process evaluation plan will be used in this study. The plan is based on the guidelines of the Medical Research Council framework [63], which includes three components: (1) implementation, (2) mechanisms of impact, and (3) contextual factors. The implementation of the PEER intervention will be evaluated based on fidelity (whether the PEER was delivered as intended), completeness (quantity of the PEER implemented), adaptation (alterations made), and reach (characteristics of the population reached). The mechanisms of impact (how the delivered PEER produced change) and contextual factors (how context affects implementation and outcomes) will be assessed in this study. Adherence to the PEER intervention will be monitored by phone calls by a PC. Adverse events will be monitored throughout the study period. Low-income older adults will be instructed to contact RAs, the PI, or the PD if they have falls, near falls, or a change in status that led to medical attention. Contact will be recorded by the RAs. The low-income older adults will be asked to identify reasons for adherence as well as nonadherence. A project logbook, registration checklists, participant records, and self-reports will be used to collect these data.

End Points

The intervention will be delivered per protocol until 1 of the following end points is met (whichever occurs first): (1) unable to participate in PEER activities (eg, exercise), (2) past 8 weeks of enrollment, and (3) other exclusion criteria are met (eg, severe cognitive problems).

Control Group

The control group or enhanced usual care will receive an information pamphlet about falls (English or Spanish version) developed by the CDC Stopping Elderly Accidents, Deaths, and Injuries–Older Adult Fall Prevention. These pamphlets provide details on fall risk, ways to prevent falls, how to check for safety, postural hypotension, chair rise exercise, what they can do to avoid falls, ensure safety, and manage postural hypotension [2]. The control group will be encouraged to discuss fall prevention with their primary care provider and continue their regular activities for 6 months. They will be offered the PEER intervention when the study concludes. They will receive monthly phone calls from the RA to record a monthly fall incidence log.

Outcome Measures and Data Collection

Primary Outcome Measures

Fall Risk

Fall risk will be assessed using the CDC's Stopping Elderly Accidents, Deaths, and Injuries fall risk checklist. It consists of 12 statements related to physical and psychological fall risk factors, with responses of either yes or no. If a person scores ≥4 points, it suggests that there is a risk of falling [2]. The sensitivity of this checklist for discriminating fallers and predicting future fallers among community-dwelling older adults is 73% to 80% [64].

Dynamic Balance

Dynamic balance will be assessed using the "Timed Up and Go" (TUG) and "Sit to Stand" (STS) tests suggested by the CDC [2] and the American Geriatric Society [65]. It is important to conduct >1 balance test, as some participants may be identified as at risk on one and not another [64]. The TUG test is a commonly used method for evaluating functional mobility and predicting the risk of falling [66,67]. The TUG test has been validated among older adults in the community [68]. The TUG test has been proven to be effective in assessing older adults at risk of falling, with a sensitivity and specificity of 87% [69]. The STS is reliable for various populations [70,71]. For the TUG test, participants will stand up from a standard armchair, walk at a normal pace for 3 m, return, and sit down again [72]. Participants who complete the TUG test in <12 seconds will be classified as having a low fall risk [73]. Then they will complete the STS. To begin, the participant should sit in the center of the chair, crossing their hands at the wrists and placing them on the opposite shoulder. They should keep their feet flat on the floor, their back straight, and their arms against their chest. Then, they should repeat the motion of standing up and sitting back down for 30 seconds. The results will be scored based on their age and sex as suggested by the CDC [2].

PA Measures

PA participants will have their activity levels monitored using ActiGraph GT9X Link wireless activity monitors for 7 consecutive days. These devices, which are triaxial accelerometers, will be worn on the nondominant wrist by all participants. The GT9X Link has a sample rate of 30-100 Hz and a dynamic range of ±8G. It also has a rechargeable battery that lasts up to 14 days and can store up to 4 GB of data for 180 days. Information is collected every minute. A sensor checks if the device is being worn or not. The GT9X Link gives accurate 24-hour measurements of PA, such as steps taken, energy expended, intensity, and the user's position. Measuring

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PA through accelerometry is a reliable method (ICC=0.98), especially when assessing free-living individuals [74]. It has been validated through comparison with measurements of direct observation, energy expenditure, and sedentary behavior [75,76].

Secondary Outcome Measures

FRA Shifting

FRA shifting consists of (1) maladaptive shifting, which is moving from the rational quadrant into any other quadrant, and (2) adaptive shifting, which is moving from irrational, incongruent, or congruent into the rational quadrant [77]. We use the FRA matrix, a graphical grid categorizing levels of FOF (mind) and levels of balance (body) into four quadrants [22,23]: (1) *rational:* low FOF (short Falls Efficacy Scale-International [FES-I] ≤10) and normal balance (BBS ≤30), (2) *incongruent:* low FOF (short FES-I≤10) despite poor balance (BBS>30), (3) *irrational:* high FOF (short FES-I>10) despite normal balance (BBS≤30), and (4) *congruent:* high FOF (short FES-I>10) and poor balance (BBS>30).

Levels of FOF

Levels of FOF will be assessed using the short FES-I. It is a 7-item self-report questionnaire (English and Spanish version) that provides information on the level of concern about falls for a range of activities of daily living [78]. On a 4-point Likert scale, low-income older adults will be asked to rate their concerns about the possibility of falling when performing 7 activities such as dressing. The scores range from 7 to 28 [79]. Higher total FES-I scores indicate higher FOF [78]. Scores of 7 to 10 indicate low concern about falling, whereas scores of 11 to 28 indicate high concern about falling [80,81]. The short FES-I has been validated in community-dwelling older adults [80]. Cronbach α=.97 and ICC=0.979 among older adults [82].

Levels of Balance

Levels of balance will be assessed using the BBS. During the BBS, a piece of sturdy furniture or a standard walker will be placed within the participant's reach to reduce the risk that FOF will contaminate performance and enable even frail people to participate. Individuals will stand as still as possible on the BTrackS Balance force plate with their hands on the hips and eyes closed [83]. After the test, there are three results: (1) baseline, postbaseline, and percentage of changes; (2) comparison with sex and age group; and (3) levels of fall risk. In comparison with the age group, the software uses the BBS Normative Database to compare the individual with others in their age group. The BBS score is dependent on age and sex but not body size so that the percentile rankings can be determined across various age groups and for men and women separately [84]. A scale from 0 to 100 represents the percentile ranking of the BBS. A score of 0 to 30 indicates a low fall risk (normal balance) [84].

Negative Self-Perceptions

Negative self-perceptions will be measured using the Brief Aging Perceptions Questionnaire, which consists of 17 items [84]. In the proposed study, we will calculate an overall negative perception score (range 17-85, as in the study by Fawsitt et al [85] and Freeman et al [86]) by summing all negative scales after reverse scoring positive subscales. In our pilot study (N=48), this measure's Cronbach α was .64.

Additional Measures of Interest

Social Determinants of Health

Social determinants of health from the PhenX tool kit include protocols related to demographics or participants' characteristics including age, sex, education, history of falls, the number of comorbidities, access to health services, health literacy, and access to health technology [87].

Depression

Depression will be measured using the Patient Health Questionnaire-9. The Patient Health Questionnaire-9 (English and Spanish) is a valid and reliable tool for screening depression in older adults [88,89]. It has high internal consistency (Cronbach α=.89) [88,89]. Participants will score how often each symptom (eg, feeling tired) was present within the last 2 weeks. The total scores range from 0 to 27, with scores ≥10 indicating moderate depression [88].

Anxiety

Anxiety will be measured using the Geriatric Anxiety Inventory-Short form, which consists of 5 items, investigates 3 dimensions of anxiety (somatic, cognitive, and affective), and is rated on a 4-point Likert scale, ranging from 0 (not at all) to 3 (all the time) [90-92]. It has adequate internal consistency and validity for screening anxiety in older adults [93].

Incidence of Falls

We will measure the number of falls and near falls. A *fall* is defined as an unexpected event in which an individual comes to rest on the ground, floor, or a lower level. An *injurious fall* is defined as hospitalization for or receipt of outpatient care because of a fall [94,95]. A *near fall* is a stumble event or loss of balance that would result in a fall if sufficient recovery mechanisms were not activated. At least 2 compensatory mechanisms (eg, unplanned movement of the arms, legs, and trunk tilt) should be activated [96]. The number of falls and near falls will be assessed using a monthly fall log by low-income older adults and follow-up phone calls by RAs.

Exercise Adherence

A weekly exercise log is designed from our pilot work to record activity including the types and duration of exercise that low-income older adults performs at home. A weekly exercise log will be handed to the PC at the group exercise in the week after.

Data Collection

Demographic data (eg, age, sex, living status, and education level), perceived general health, self-report of vision, medication use, urinary incontinence, and the number of falls in the past 6 months will be assessed at baseline to provide context about low-income older adults. A trained RA will perform all baseline and follow-up assessments and will be blinded to the group assignment. Low-income older adults will be instructed not to inform assessors of their group status. All questionnaires and tests (except the PA test) take approximately 60 to 90 minutes

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to complete, and no risks or discomfort were associated with the balance and PA tests in our pilot studies.

Data Management and Integrity

Data files will be built on a password-protected computer using REDCap (Research Electronic Data Capture; Vanderbilt University), which will be housed on a secure university server [97,98]. RX (coinvestigator) and RAs will be responsible for data cleaning and will teach the data entry system to the study team members who will be recording data in REDCap. Following an initial audit, the data will be double entered, and files will be matched to verify the accuracy of the data for the first 5 participants, after which a random 5% (17/340) of the total sample will be double checked periodically throughout the study. The data will be systematically examined for out-of-range values and inconsistencies. We anticipate no more than 5% missing values on any 1 item, as data will be collected in person on site and via phone calls. Missing data will be identified and obtained during follow-up interviews or with follow-up contact with participants. We will create an audit trail to identify and correct issues, protect participants' privacy, ensure confidentiality, and maintain data integrity [99]. If causes of error other than random variation are identified, we will modify or adjust our procedures and train team members as needed.

Data Analysis

We will collect demographic information from the participants for the study. We will compare baseline variables, such as essential participant characteristics, primary, and secondary end points, to summarize the differences between the 2 groups at the start of the study (T1). For the analysis of categorical data and continuous data, the chi-square test and 2-tailed *t* test will be used. We use R (version 4.1.2; R Foundation) for data analyses, with a significance level of P=.05.

Aim 1 is to examine the effects of the technology-based PEER intervention on fall risk, dynamic balance, and accelerometer-based PA.

The hypotheses are as follows:

- *H 1.1*: The PEER group will reduce the fall risk compared with the control group.
- *H 1.2*: The PEER group will improve the dynamic balance compared with the control group.
- *H 1.3*: The PEER group will improve accelerometer-based PA compared with the control group.

Data will be analyzed according to the intention-to-treat principle [100]. We will model the fall risk, dynamic balance, and accelerometer-based PA as longitudinal outcomes consisting of 4 measurements (baseline or T1, after program completion or T2, follow-up at 3 months or T3, and follow-up at 6 months or T4) using the longitudinal linear mixed model (LMM) [101]. The LMM allows all low-income older adults and their available data to be included in the analysis, even for unequal group sample sizes, and the group heterogeneity can be addressed in the variance structure of random effects. It is hypothesized that the PEER group will show improvement in all outcome measures over time. To test hypothesis *1.1*, between-arm differences for fall risk scores, the likelihood ratio test (LRT) [101] associated with LMM will be used from all follow-up assessment visits. Similarly, the LRTs will be used to test hypotheses *1.2* and *1.3* for between-arm differences for dynamic balance and PA, respectively. The CDC-recommended scoring scheme will be adopted to process fall risk, TUG, and STS data [102]. For example, the average score of the number of STS repetitions a person can complete is based on different age and sex groups [102].

Raw acceleration data from ActiGraph will be downloaded and converted to ".csv" files using ActiLife 6 Software (version 6.13.4; ActiGraph LLC). PA data will be processed using the R package *GGIR* (version 2.4-0). *GGIR* R package used to process multiday raw accelerometer data for PA research [103] includes (1) auto-calibration of acceleration signals according to local gravity [104], (2) detection of nonwear time, and (3) calculation of the average magnitude of dynamic acceleration corrected for gravity (ie, Euclidean Norm Minus One) over 5-second epochs and expressed in milli-gravitational units (mg) [105]. Nonwear time and sustained abnormally high accelerations will be imputed using the default settings [105]. The Euclidean Norm Minus One cut-off points will be used to estimate the total time spent in sedentary behavior, light intensity PA, and MVPA in participants.

For missing data treatment, the missing values will be imputed using the method of multiple imputations [106]. The maximum number of missing values within a scale will be based on the guidelines provided by the scale developers or based on a limit of 25% missing values. In the first analysis, all low-income older adults will be included according to their original group assignment [100]. Participants in the PEER group who completed at least 5 of the 8 group-based sessions will be included in the per-protocol analysis. Although every attempt will be made to ensure that low-income older adults complete all assessments, there may be some participant attrition over time. The missing data mechanism is assumed to be missing at random. The dropout patterns or missing data rates for the 2 arms will be examined to assess the differences. When possible, the models should be modified to account for relevant factors such as age, sex, general health perception, and the number of falls in the 6 months leading up to the baseline. To determine the impact of the PEER intervention during follow-up evaluations, the group-by-time interaction term will be incorporated into the model. Effect sizes (Cohen *d*) [107,108] will be calculated based on the estimated means and the pooled SD.

Aim 2 is to examine the effects of the intervention on FRA shifting and negative self-perceptions of aging.

The hypotheses are as follows:

- *H 2.1*: The PEER group will have a more adaptive shifting compared with the control group.
- *H 2.2*: The PEER group will have a more positive shift in their perceptions of aging compared with the control group.

To test hypothesis *2.1* (FRA shifting), the 4 FRA quadrants will be determined by grid coordinates based on 2 continuous level measures (BBS and short FES-I scores). We will classify shifting into 2 types: maladaptive and adaptive shifting.

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Adaptive shifting is moving from irrational, incongruent, or congruent to rational. The outcome is a percentage of low-income older adults with baseline (T1) in irrational, incongruent, or congruent quadrants who end up in the rational quadrant after program completion (T2). Maladaptive shifting is a movement from rational to any other quadrant, and the percentage of low-income older adults will be calculated. After program completion (T2), the baseline FRA categories (T1) may remain the same or shift to a different FRA category. We will form a 4×4 contingency table for the 4 FRA categories at each follow-up time point (T3 and T4) to summarize the shifts. The standard 4×4 table analysis will be performed to examine the FRA shifting, either using a chi-square test or exact test, depending on the actual counts observed in the 4×4 table. The BBS and short FES-I scores will be collected in 4 planned visit time points (T1, T2, T3, and T3). We will use the Generalized Linear Mixed Model (GLMM) to analyze these 2 end points for assessing the difference between the PEER intervention and control arms on the shift of FRA categories [109]. Our longitudinal data on the PEER effects of different types of shifting on low-income older adults will contain repeated binary measures of the shifting status over time. The binomial GLMM with the logic link will allow us to assess the difference between the 2 arms in FRA shifting, and the associated LRT [101] will be used to test hypothesis *2.1* if a significant adaptive shifting is detected in the PEER group compared with the control group. The GLMM can address the group heterogeneity by specifying the corresponding covariance structure in random effect terms.

To test hypothesis *2.2*, positive shift in their perceptions of aging, the longitudinal mixed model analysis of variance will be used to test the effects of the intervention by comparing the PEER group with the control group from all follow-up assessment visits. Measurements, such as the negative self-perceptions of aging, can be incorporated into the GLMM model to investigate their potential role as mediators of FRA shifting and examine the effects of the intervention.

Aim 3 is to explore participants' experiences with the intervention and potential barriers to access and adoption of the technology-based PEER intervention to inform future research.

Rationale

A qualitative approach will allow us to explore the complex, multilevel pathways through how the PEER intervention affect at individual and peer-group levels. We may also identify barriers to successful FRA adaptation and barriers to access and adoption of the technology-based intervention that cannot be identified in quantitative data but will be important to consider in the future. Interviews with participants will provide insights into the variability across settings and implementation factors that will be instructive for program and policy planning. Importantly, interviews will amplify the voices of low-income individuals who traditionally hold less power in program planning [110].

Design and Sample

We will use in-depth, one-on-one, semistructured interviews with up to 30 participants from the PEER after the completion of the intervention (T2). Semistructured interviews will help ensure that key concepts are addressed while allowing flexibility to adjust and rearrange questions to maximize interview flow and useful data collected. Theoretical sampling will help us gain the perceptions we need in terms of demographic and experiential variation [111,112]. We will sample until saturation of themes and content has occurred. The interviews (30-40 minutes) will be conducted by a trained interviewer either in person or by phone or web conferencing and will be audio recorded. The COREQ (Consolidated Criteria for Reporting Qualitative Research) [113,114] will be used during all phases of the process to optimize quality.

Interview Guide

The National Institute on Minority Health and Health Disparities research framework [115] will help inform the development of the interview guide and focus on the (1) three domains of influence (biological, behavioral, and sociocultural) and (2) two levels of influence (individual and peer groups) that are most relevant to participant experiences and intervention evaluation. Interview questions will focus on their experience of participating in the PEER intervention, acceptability of PEER, potential barriers to accessing and adopting PEER in the community, and recommendations for future work. Consistent with the standard qualitative methodology, interview guides will be pilot-tested and adjusted based on findings from early interviews [116].

Analysis

Data will be analyzed based on the analytic process of interpretive description, which is used to develop findings for clinical practice [117,118]. VL (coinvestigator) and the PI will generate initial codes focusing on participants' experiences with PEER and will meet to establish consensus on the coding and using the NVivo software (version 12; QSR International) to aid in sorting and organizing the data. Consistent with the interpretive description, we will maintain an open stance toward coding to understand participant experiences [118]. Coding will continue until no new information is forthcoming from the data and the categories appear "saturated" [112]. Field notes will be coded to aid data interpretations and provide context, as they will contain interviewers' impressions and observations during the interviews [111]. We will collate codes into themes, review them for their fit to the data, and categorize and label themes. We will conduct initial analyses on all data as soon as they are collected to allow for theoretical adjustments to the questions and guide sampling strategies for future interviews.

Domains of Quality

We will enhance quality via the following strategies:

- Maximal variation in sampling by ensuring variability on the factors that likely influence participants' experience (age and context). We will enhance the credibility of the data and seek out a range of responses to the PEER, both positive and negative.
- Throughout the study, we will document all the methodological decisions and the reasoning behind them to maintain an accurate audit trail and ensure interpretive rigor [111].

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- After identifying general themes and subthemes in the qualitative data analysis process, the entire research team will review and discuss a summary through peer debriefing [119].
- We will encourage team members who are not directly involved in the analysis to provide feedback and ask critical questions about the methods, decisions, and interpretation.
- Inference transferability will provide a description of the participants to allow for transferability of findings to similar settings, contexts, and people [120].

Ethical Considerations

The Institutional Review Board of the University of Central Florida granted ethics approval for this study (protocol STUDY00003206) on October 14, 2022. All participants will receive information before participation.

Results

As of August 2023, the enrollment of participants is ongoing.

Discussion

Principal Findings

Our developed PEER intervention is focused on providing physio-feedback using technology, promoting cognitive reframing, enhancing peer-led exercises, and incorporating exercises into daily activities. We aimed to examine the effectiveness of the technology-based PEER intervention on 3 primary outcomes (fall risk, dynamic balance, and accelerometer-based PA) and 2 secondary outcomes (FRA shifting and negative self-perceptions of aging). We hypothesized that the PEER group will reduce the fall risk, improve the dynamic balance, and improve accelerometer-based PA compared with the control group.

Our pilot study found that the PEER intervention (n=19) had a significant reduction in the CDC fall risk score from preintervention to postintervention (effect size Cohen *d*=0.6; *P*=.02) [32]. We also found that the PEER group had significant improvement in the TUG (*P*=.001; Cohen *d*=1.0) and STS (*P*<.001; Cohen *d*=0.95) tests [32]. In addition, in a pilot study [77], 11% of participants in the PEER group (n=19) had adaptive shifting compared with none in the control group (n=22). Up to 32% of the participants in the control group had maladaptive shifting compared with only 5.3% in the PEER group [77].

Existing fall prevention intervention technologies do not enable participants and practitioners to interact and collaborate [44] even with technologies that bring viable strategies to maintain PA, prevent disability, and increase access to quality care. The physio-feedback using portable technology is a vital component of the PEER intervention for screening fall risk at home or in their communities and initiating a fall risk communication between older adults, their caregivers, and practitioners. The physio-feedback and cognitive reframing strategies improve older adults' competence by aligning their physiological fall risk with FOF or body and mind and increasing their fall risk awareness [116]. Few studies focused on improving PA in socioeconomically disadvantaged groups [121] despite recommendations for action on the social determinants of health for improving PA. Regular PA improved quality of life and reduced fall risk and mortality [122]; however, a lack of motivation to participate in PA is a crucial barrier. The peer-led exercises with peer coaching strategies may help build a connection and increase the motivation to participate in PA for older adults [50].

Future Implications

This study addresses the public health problem by optimizing a technology-driven, tailored approach that can operate in low-resource environments with unlimited users to prevent falls and reduce health disparities in low-income older adults. It also supports using the results to tailor interventions to improve PA and reduce falls [31,51,52]. If effective, this intervention can provide an innovative, scalable, and accessible model for fall prevention in diverse and underserved populations. The use of a noninvasive technology that does not require special training and can operate in low-resource environments may scale up the intervention for low-income communities. The BBS can be used for fall risk assessment, tailored interventions, and tracking the changes in balance performance. Technology-based physio-feedback regarding balance has a positive effect on balance confidence and task selection, which could help reframe unrealistic perceptions and lead to healthy behaviors. This study is conducted by an interdisciplinary team and collaborates with community-based and public health organizations, which will ensure the research is relevant, contextually appropriate, and will ultimately be translated into real-world settings.

Limitations, Potential Challenges, and Alternatives

There are several limitations and potential challenges including (1) recruitment and retention, (2) respondent burden, (3) staffing, and (4) lack of skills to use BBS technology.

Recruitment and Retention

Although the recruitment and retention of low-income older adults in randomized controlled trial studies is often challenging, our tailored strategies will address these issues by ensuring that our bilingual RAs are well trained, providing information in English and Spanish versions, and using a straightforward data collection process.

Respondent Burden

During the intervention, the PCs and RAs will complete a weekly exercise log and monthly fall or near falls logs. After the 8-week intervention, the only data to be collected monthly from participants will be the fall logs. These were used successfully in our pilot study; we found no falls and 2 near falls in the PEER group.

Staffing

Our staffing plan ensures coverage by study personnel for 8 weeks of the intervention and the 3- and 6-month follow-up assessment.

Lack of Skills to Use BBS Technology

This study does not expect low-income older adults to test themselves using the BBS. We will train an RA at each site to run the test.

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Conclusions

More than half of all older adults have maladaptive FRA, leading to reduced PA and a corresponding increased risk of falls. This study focuses on fall interventions tailored to low-income older adults who have a mismatch between physiological fall risk (body) and perceived fall risk (mind). The PEER is a novel intervention that combines concepts of physio-feedback, cognitive reframing, and peer-led exercise by motivating a shift in self-estimation of fall risk to align with physiological fall risk to improve balance, PA, and negative aging self-perception that no one has studied before. The major strength of this study is the use of a noninvasive technology that does not require special training and can operate in low-resource environments with unlimited users. The PEER intervention can be implemented on a large scale in community settings. Such an approach may reach older individuals at risk who do not participate in or are not referred to standardized conventional training programs to help them prevent falls and reduce health disparities.

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Data Availability

The data sets generated during this study are available from the corresponding author upon reasonable request.

Authors' Contributions

LT, RX, JHP, NL, VL, and JS contributed to the study conceptualization, design, and data analysis. LT wrote the original draft, and RX, JHP, NL, VL, and JS contributed to a substantial revision of the original draft. All authors have agreed on the final version of this manuscript.

Conflicts of Interest

None declared.

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Abbreviations

BBS: BTrackS Balance Tracking System
CDC: Centers for Disease Control and Prevention
COREQ: Consolidated Criteria for Reporting Qualitative Research
FES-I: Falls Efficacy Scale-International
FOF: fear of falling
FRA: fall risk appraisalGLMM: Generalized Linear Mixed Model

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ICC: intraclass correlation
LMM: linear mixed model
LRT: likelihood ratio test
MVPA: moderate to vigorous physical activity
PA: physical activity
PC: peer coach
PD: project director
PEER: Physio-Feedback Exercise Program
PI: principal investigator
RA: research assistant
REDCap: Research Electronic Data Capture
STS: Sit to Stand
TUG: Timed Up and Go

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Protocol

Assessment of the SmartJournal Intervention for Improved Oral Care in Nursing Homes: Protocol for a Cluster Randomized Controlled Trial

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Abstract

Background: Poor oral health is common in nursing home residents, and health care professionals report numerous barriers when it comes to the provision of oral care for care-dependent older adults, such as a lack of oral health knowledge and skills, care-resistant behaviors in residents, lack of adequate oral care routines, insufficient systems for documentation of issues related to oral health, a high workload, and unclear responsibilities. An intervention, SmartJournal, has been developed to assist health personnel in preserving older patients' oral health. SmartJournal is a digital tool with three components: (1) documentation of oral hygiene routines; (2) monthly oral health assessment; and (3) education on geriatric oral care. An updated framework for research on complex interventions has been used to guide the various phases in the development of this intervention. This study focuses on the evaluation phase.

Objective: We aim to assess (1) the effectiveness of SmartJournal use in enhancing nursing home caregivers' capability, opportunity, motivation, and routines related to oral care; and (2) whether SmartJournal use results in improved oral health for nursing home residents.

Methods: We will use a cluster randomized controlled trial to assess impacts of SmartJournal use as specified under study objectives. Nursing homes located in Rogaland, Norway, will be recruited and randomly assigned to an intervention and a control group. The intervention group will be provided with tablets containing SmartJournal and support from research staff, while the control group will continue with existing oral care routines. Both groups will receive oral hygiene packages. The intervention will last for 12 weeks. Measurements will be performed in both groups at baseline, 3 months, and 9 months and include (1) a survey assessing caregivers' capability, opportunity, motivation, and routines related to oral care; and (2) assessment of oral health status in residents using mucosal-plaque score as a primary outcome measure. Analyses will include descriptive statistics and statistical techniques to look for changes and differences in the study variables within and between the intervention and control groups throughout the study period. Associations between study variables will also be investigated.

Results: Recruitment of nursing homes for the intervention and control groups was completed in February 2023. Recruitment of individual participants (ie, nursing home residents and caregivers) is ongoing, and baseline measurements are being performed consecutively. Results are expected to be ready for analyses in fall 2024.

Conclusions: We aim to assess the effects of SmartJournal use on oral care and oral health in nursing homes. Results from this work may inform further development and implementation of SmartJournal and similar digital tools aiming to enhance health care services offered to care-dependent people. Finally, SmartJournal may have potential as a learning tool in educational programs for nurses and other health care professionals.

Trial Registration: ClinicalTrials.gov NCT05724043; https://clinicaltrials.gov/study/NCT05724043

International Registered Report Identifier (IRRID): DERR1-10.2196/46926

(JMIR Res Protoc 2023;12:e46926) doi:10.2196/46926

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KEYWORDS

cluster randomized controlled trial; digital tool; gerodontology; intervention; nursing homes; oral health

Introduction

Background

Poor oral health is common in frail and care-dependent older adults and includes tooth loss, poor oral hygiene, a high prevalence of dental caries and periodontal disease, defective dental prostheses, hyposalivation, and various oral lesions caused by misfitting dentures or precancerous or cancerous states [1,2]. Alarmingly, oral health is shown to be the most neglected area in Norwegian nursing homes [3], and oral health care is the first task to be downgraded due to a lack of resources [4]. A study by Willumsen et al [5] indicated that more than 40% of Norwegian nursing home residents have unacceptable oral hygiene. Neglect of oral health, resulting in poor oral hygiene, may cause infections and inflammation both locally and systemically. Oral infections have been associated with systemic conditions such as atherosclerosis [6,7], diabetes [8], and aspiration pneumonia [9,10]. Aspiration pneumonia is a highly mortal disease, and a review by Sjøgren et al [11] estimated that 10% of all deaths from pneumonia in nursing homes could have been prevented with improved oral hygiene. Moreover, chewing difficulties as a result of poor dental status have been associated with altered dietary habits, malnutrition, and cognitive decline [2]. Yet, the oral health of care-dependent older adults does not receive the necessary attention [12]. A few decades ago, most older adults were denture wearers. Today, an increasing number of older adults keep their natural teeth, often in combination with complex fixed or removable prostheses [13]. While dentures are easy to manage, more complex prosthetic devices can pose a challenge with regard to handling and cleaning [14]. Thus, the care-dependent older adults have to rely on caregivers to maintain satisfactory oral health [15]. In Norway, nursing home residents (and other care-dependent people) have a statutory right to good oral hygiene and necessary dental treatment [16]. Health personnel are responsible for preserving these rights through daily oral hygiene routines and referral to dental professionals when needed. Research from Sweden and Denmark has shown that about 80% of nursing home residents need assistance with daily oral hygiene practices [15,17]. Thus, it is disturbing that health care professionals report numerous barriers when it comes to the provision of adequate oral care assistance. The most frequently reported barriers are lack of knowledge and skills [18] and care-resistant behaviors (CRB), in particular among patients with dementia [18,19]. A study by Willumsen et al [5] showed that more than 50% of Norwegian nursing home residents with dementia refuse oral care assistance. In cases of frequent CRB, daily oral care may be postponed repeatedly, resulting in poor oral hygiene and an increased risk of oral and systemic infections. Other reported barriers include a lack of adequate oral care routines, a lack of systems for documentation of issues related to oral health [20,21], a high workload, and unclear responsibilities [19].

Various tools have been developed to assist health personnel in providing oral care to older adults. One example is “oral care cards” with illustrated instructions about how to carry out daily oral hygiene routines with individual patients. Another example is “signature lists” to document daily oral care. These tools may function well but have some shortcomings. While oral care cards do not allow for documentation of oral health issues, signature lists do not contain information on individual needs. Moreover, text-based diagnostic tools such as the Revised Oral Assessment Guide (ROAG) [22] and the Oral Health Assessment Tool [23], have been developed to assist caregivers in recognizing oral conditions. However, research indicates that these tools may not be well suited for nondental professionals [24,25]. Other limitations of the above-mentioned tools are that they lack procedures for documentation of deviance related to oral health and that none of them include strategies for handling CRB.

The SmartJournal Intervention

As a response to the shortcomings of existing tools and to overcome reported barriers to the provision of adequate oral care in nursing homes, an intervention tailored to nursing staff has been developed by researchers at the Oral Health Centre of Expertise Rogaland, Norway, in close collaboration with innovative research and development institutions and dental and health care professionals. An updated framework for research on complex interventions, developed jointly by the United Kingdom’s Medical Research Council and the National Institute for Health Research [26], has been used to guide the various phases of intervention development: an innovation phase (completed), a feasibility study (completed), and an evaluation study (recruitment is ongoing). An overview of the phases is presented in Table 1. This study focuses on the evaluation phase.

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Table 1. SmartJournal study overview describing aims, methods, and participants for each phase of the study.

Phase	Aims	Methods	Participants
Phase 1: innovation (completed)	Develop an intervention (digital tool) to reduce or overcome barriers related to oral care in nursing homes (theoretical basis: the COM-B[a] model [27]).	• Step 1: collaborative innovation based on current literature, meetings, and workshops with stakeholders resulted in the SmartJournal prototype. • Step 2: initial, small-scale functionality tests with the test panel. • Step 3: refinement of the tool based on results from functionality tests.	• Step 1: practitioners and researchers within dentistry, geriatric nursing, health education, eHealth, and the development of digital learning tools. • Step 2: health personnel (n=11) recruited from nursing homes in Rogaland, Norway. • Step 3: researchers and engineers.
Phase 2: feasibility study (completed)	Investigate health personnel's acceptance of and experiences with the SmartJournal prototype in a nursing home setting.	• Real-life testing of the SmartJournal prototype in nursing homes. • Design: mixed methods, cross-sectional study • Qualitative data: thematic analysis of data from semi-structured interviews. • Quantitative data: statistical analysis of data from survey questionnaires.	• Health personnel were recruited from 3 nursing homes in Rogaland, Norway. • Semistructured interviews (n=11). • Survey questionnaire (n=86).
Phase 3: evaluation study (in progress)	Evaluate the effectiveness of SmartJournal use on: (1) caregivers' capability, opportunity, motivation, and routines related to oral care; and (2) residents' oral health (theoretical basis: the COM-B model [27]).	• Step 1: Further refinement of the tool based on results from phase 2. Functionality tests with different test panels. • Step 2: 12-week intervention with measurements at baseline, 3 months, and 9 months. • Design: Cluster-randomized controlled trial with nursing homes randomly assigned to intervention (SmartJournal use and support) and control group (continue with existing oral care routines). • Measures: a survey questionnaire assessing caregivers' capability, opportunity, motivation, and routines related to oral care. Clinical assessment of residents' oral health: MPS[b] [17] and tooth count [28].	• Step 1: refinement of the tool, researchers, and engineers. • Functionality tests: panels of auxiliary nursing students (n=70) and master students in innovation and knowledge development (n=20). • Step 2: a total of 12 nursing homes in Rogaland, Norway: 6 in the intervention and control groups, respectively. Power analyses suggest 360 residents (n=180 in each group). All eligible caregivers are invited to participate.

[a]COM-B: capability, opportunity, motivation model of behavior.

[b]MPS: mucosal-plaque score.

The intervention addresses key behavioral components as postulated by the capability, opportunity, motivation model of behavior (COM-B) [27]. According to the COM-B model, there must be sufficient capability (C), opportunity (O), and motivation (M) present for a given behavior to occur. Hence, this intervention seeks to facilitate oral care in nursing homes by providing strategies to improve caregivers' capability, opportunity, and motivation for this task. The intervention is constructed as an interactive and easy-to-use app for tablet named SmartJournal. SmartJournal consists of 3 modules. Module 1, "registration of oral hygiene routines," offers a system for simple checkbox registration of daily oral hygiene routines (ie, whether they have been performed or not). It also includes an open text field for additional comments if relevant (eg, reasons for not performing oral hygiene routines or strategies used to reduce CRB in the patient). This straightforward registration ensures documentation of oral hygiene routines and deviations related to such routines, keeping health personnel informed about potential oral hygiene issues for individual patients. Module 2, "monthly oral health assessment," offers a system for monitoring the patient's oral health status through monthly check-ups. In this component, the principles of the text-based tool ROAG are transformed into an image-based, interactive learning and assessment tool. As for ROAG, conditions for 6 oral sites (lips, mucous membranes, tongue, gingiva, teeth, and prosthetic devices, including all forms of removable dentures and fixed prosthodontics) are graded as follows: grade 1=healthy or normal condition, no need for measures; grade 2=pathology, need for measures at a "local level" (ie, at the nursing home, delivered by nursing home personnel); and grade 3=advanced pathology, need for measures delivered by dental professionals (in the nursing home if feasible, at a dental clinic if necessary). SmartJournal contains several validated example pictures for each grade for all 6 oral sites. This part of the tool is also checkbox-based to limit health personnel's workload related to documentation. Upon completion of the monthly oral health assessment, health personnel receive a summary report with suggestions for tailored preventive or curative measures to be initiated, thus reducing the risk of deteriorated oral health in the patients. Module 3, "electronic learning (e-learning)," offers an easily accessible knowledge base that includes information on geriatric oral health, standard equipment and procedures for daily oral hygiene routines in patients with natural teeth and various prosthetic devices, and oral care for patients with special care needs (including patients with swallowing difficulties, bedridden patients, and patients on palliative care). It also includes detailed information on scientifically documented strategies that may

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be used to approach patients with dementia who refuse oral care assistance. These strategies are adapted from the interventions Managing Oral Hygiene Using Threat Reduction [29,30] and Mouth Care Without a Battle [31]. The content in this part of the tool is illustrated with photos and figures and includes a video with recommendations on how to handle situations where patients refuse oral care assistance. The acceptability of the SmartJournal prototype has been tested in a feasibility study. Preliminary results from this study indicate that SmartJournal is well accepted among its users. According to survey data collected from caregivers employed at 3 nursing homes in Rogaland, Norway (n=86), 72% (62/86) reported that SmartJournal is a useful tool, 94% (81/86) reported that it is easy to use, and 69% (59/86) reported that they would like to use a refined version of the tool in the future. Further results from the feasibility study will be published elsewhere.

Further Improvement of the SmartJournal

Recently, the SmartJournal prototype has been further improved and adapted to the nursing home setting. Since user involvement is a central feature in the development of interventions [32], this improvement was guided by results obtained from the feasibility study (ie, information acquired from meetings, qualitative interviews, and survey questionnaires). The improved version has been subjected to 2 functionality tests in a controlled laboratory environment. These tests were performed by the Norwegian Smart Care Cluster, a national and international collaboration arena for companies, municipalities, hospitals, public organizations, user organizations, academia, research and development institutions, and investors that works to develop sustainable health solutions for the future [33]. Insights gained through the tests have been used for additional, minor adjustments to the tool, which is now ready to be tested in the evaluation study described in the following sections.

Aims and Objectives

Since SmartJournal seems to be well accepted among its potential users, this study aims to evaluate the impacts of its use. More specifically, the objectives of the current research are to assess (1) the effectiveness of SmartJournal use in enhancing nursing home caregivers' capability, opportunity, motivation, and routines related to oral care tasks and (2) whether SmartJournal use may result in improved oral health for nursing home residents.

Methods

Design

A pragmatic cluster randomized controlled trial [34] will be used to assess the effects of SmartJournal use as specified under study objectives. Public nursing homes located in the southern part of Rogaland, Norway, will be recruited and randomly assigned to an intervention group and a control group. Institutions housing long-term residents will be included, while institutions with primarily short-term residents, institutions already following a specific protocol for oral care, or institutions participating in other comprehensive interventions are excluded (Textbox 1). Nursing homes in the intervention group will be provided with smart tablets containing SmartJournal and user support (a help desk) by research staff employed at the Oral Health Centre of Expertise Rogaland, while nursing homes in the control group will continue with existing oral care routines. Both groups will receive oral hygiene packages, including toothbrushes for permanent teeth and prosthetic devices, dental floss, interdental brushes, toothpaste, and inspection mirrors, to make sure that oral hygiene equipment is easily accessible for all participants. Nursing homes and individual participants will not receive information about who is included in the intervention and control groups, respectively. They will only receive information that is relevant to their participation. The chosen study design (a cluster randomized controlled trial) facilitates this masking by reducing the possibility of contamination between the groups. The intervention will last for 12 weeks. Measurements will be performed at baseline, 3 months, and 9 months.

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Textbox 1. Inclusion and exclusion criteria for the SmartJournal evaluation study.

Inclusion criteria

- Nursing homes
  - Located in Rogaland, Norway
  - Long-term facilities
- Residents
  - Long-term residents (ie, residents with the nursing home as their permanent address)
  - Residents with and without dementia who can undergo oral examination
- Caregivers
  - All types of nursing staff (nurses, auxiliary nurses, students)
  - Full-time and part-time staff

Exclusion criteria

- Nursing homes
  - Specialized nursing homes (eg, psychiatry and substance abuse)
  - Short-term facilities (eg, rehabilitation and respite care)
  - Nursing homes already following a specific protocol for oral care or those participating in other comprehensive interventions
- Residents
  - Short-term residents
  - Critically ill and terminal patients receiving palliative care
- Caregivers
  - Staff with purely administrative tasks (eg, heads of institutions)

Participants and Procedures

Strategies used for recruitment of individual participants (caregivers and residents) and procedures for delivery of the intervention will be similar to those used in the feasibility study since they proved to be successful. Resource groups, comprised of heads of wards and selected nursing staff, will be established at each of the included nursing homes. Meetings will be scheduled to adapt the delivery of the project to each individual institution's resources and facilities, and members of the resource groups will be assigned the task of recruiting individual participants. Written informed consent will be requested for both residents and caregivers to be enrolled in the study. Nursing home residents constitute a vulnerable group in which many individuals may have reduced decision-making capacity. For these individuals, deputy consent will be obtained from their next of kin. Residents receiving end-of-life palliative care are excluded (Textbox 1). Both full-time and part-time nursing staff will be included. Health personnel with purely administrative tasks (ie, heads of institutions) are excluded (Textbox 1). Following recruitment of participants and baseline measurements, nursing homes in the intervention group will be provided with SmartJournal toolboxes and packages with oral hygiene equipment, while nursing homes in the control group will receive oral hygiene equipment packages only. The SmartJournal toolboxes include smart tablets with SmartJournal installed, antibacterial touchscreen wipes, flashlights for monthly oral inspections, an instruction video, an instruction book, and SmartJournal information posters. The oral hygiene equipment packages include toothbrushes for permanent teeth and prosthetic devices, dental floss, interdental brushes, toothpaste, and inspection mirrors. Training, follow-up, and technical support for SmartJournal users will be provided by project staff employed at the Oral Health Centre of Expertise Rogaland.

Measurements

The effectiveness of SmartJournal in enhancing nursing home caregivers' capability, opportunity, motivation, and routines related to oral care tasks will be measured by a survey questionnaire capturing components of the COM-B model [27]. Caregivers in both the intervention group and the control group will be asked to fill out the survey questionnaire three times: at baseline, 3 months, and 9 months.

The effects of SmartJournal use on nursing home residents' oral health will be assessed by low-invasive oral inspections using the mucosal-plaque score (MPS) [17] as a primary outcome measure. MPS is comprised of a 4-point plaque score (PS) and a 4-point mucosal score (MS). PS=1: no visible plaque; PS=2: plaque is barely visible; PS=3: moderate amount of plaque; and PS=4: large amount of plaque almost covering the whole surface of teeth. MS=1: normal mucosa; MS=2: mild inflammation;

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MS=3: medium inflammation; and MS=4: strong inflammation. For both scores, if in doubt between 1 and 2, dental personnel are instructed to score 1. If in doubt between 3 and 4, they are instructed to score 4. The MPS index is designed to evaluate oral health and oral hygiene in groups of individuals. This makes it a suitable index to be used when conditions are not optimal to assess the patient's oral health. In a nursing home setting, dental personnel have limited equipment and poor lighting compared to an ordinary dental clinic setting. Therefore, using an index designed to be applied outside a dental clinic setting is feasible in this context. Moreover, the number of natural teeth will be counted and used as an additional outcome measure. The number of natural teeth is a frequently used measure of oral health in older adults since it is associated with nutritional status, general health, and quality of life [28]. Residents in both the intervention group and the control group will have MPS assessed and teeth counted three times: at baseline, 3 months, and 9 months. All clinical assessments will be performed by dental professionals employed at the Oral Health Centre of Expertise Rogaland, Norway. Calibration has been undertaken to ensure the reliability of the clinical measurements.

Additionally, patient journal data shown to be associated with oral health (ie, sociodemographics, medical conditions, and prescribed medication) will be retrieved and used to describe the study sample. These data will also be included as covariates in statistical analyses investigating factors associated with oral health among residents included in this study.

Power Calculations and Estimation of Sample Size

Experiences from the feasibility study show that resident participation may pose a challenge due to the high rates of morbidity, mortality, and CRB in this part of the population. The estimation of sample size is largely reproduced from Overgaard et al [35], who also used MPS as a primary outcome variable in their study on oral health in nursing home residents. Overgaard et al [35] based their power calculations on reductions in MPS ≥2 from 60% to 15%, as reported by Hede et al [17]. Like Overgaard et al [35], we assume α=.5, a power of 80%, a 33% dropout rate due to the residents' frailty, and a median resident time of 2 years. A medical statistician has been consulted to further adapt the calculations to this study's setting (taking into account the number of eligible nursing homes and residents in the southern part of Rogaland), recommending the inclusion of 12 nursing homes each with 30 residents who opted for oral health assessments. Thus, a total of 360 residents will be included for oral health assessments, 180 in the intervention and control groups, respectively. All eligible caregivers in the 12 included nursing homes will be invited to take part in the survey capturing components of the COM-B model as described in the Measurements section. Experiences from the feasibility study indicate that this broad inclusion strategy, along with assigning the recruitment task to members of the institutions' resource groups, fosters a sense of community regarding project participation. This may, in turn, motivate institutions and individual participants to remain part of the project throughout the study period.

Data Analyses

The statistical software package SPSS (IBM) will be used for data analyses. These analyses will include descriptive statistics (to describe the samples) and statistical techniques to look for changes and differences in the study variables within and between the intervention group and the control group throughout the project period, for example, 2-tailed *t* tests and ANOVA tests. We hypothesize that SmartJournal use will lead to favorable changes in variable scores in the intervention group as compared to the control group. In caregivers, it will lead to increased scores on the measured COM-B components (survey data), and in residents, it will lead to improved oral health as measured by improved MPS and, possibly, fewer natural teeth lost. Additionally, regression analysis may be used to investigate associations between study variables while adjusting for potential covariates (eg, age, gender, ethnic origin, educational level, medical conditions, and prescribed medication).

Ethics Approval

This study is approved by the Norwegian Regional Committee for Medical and Health Research Ethics (REK 2022/472796). The SmartJournal intervention aims to assist nondental care providers with preserving nursing home residents' statutory right to good oral hygiene and necessary dental treatment. Respect for the individual's intrinsic value, self-determination, and situation pervades the development and anticipated use of the tool. The project is guided by the intentions of the Declaration of Helsinki and ethical guidelines provided by the Norwegian National Research Ethics Committees. Informed consent will be obtained from nursing home caregivers and residents before data collection. Consent forms are designed in accordance with the templates for information material provided by Sikt, the Norwegian Agency for Shared Services in Education and Research, and the Regional Committees for Medical and Health Research Ethics. Nursing home residents constitute a vulnerable group in which many individuals may have reduced decision-making capacity and, thereby, difficulties giving free and informed consent to being participants in research. However, since the overall aim of the SmartJournal intervention is to assist health personnel with preserving oral health in this particular group, it is essential to include them in the research. Therefore, if residents have reduced decision-making capacity, deputy consent will be obtained from their next of kin.

Data registered in SmartJournal (ie, data for residents included in the intervention group) will be transferred to a research database at the University of Stavanger. At the SmartJournal login website, health personnel are asked to enter three codes: one code for the nursing home, one (personal) caregiver code, and one (personal) resident code. The codes for caregivers and residents will be listed in an identification key that is only available to authorized project staff. At the end of the project, data will be deidentified, and it will not be possible for anyone to link any information to individual participants. Data obtained from questionnaires, clinical assessments (MPS, number of teeth), and patient journals are registered with the same individual codes as data registered in SmartJournal, which makes it possible to link data obtained from all sources. Extractions from the University of Stavanger database and data from

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questionnaires will be stored in a highly secured data system at the Oral Health Centre of Expertise Rogaland. Only authorized project staff will have access to the data.

Results

Recruitment of nursing homes for the intervention and control groups was completed in February 2023. Recruitment of individual participants (ie, nursing home residents and caregivers) is ongoing, and baseline measurements will be performed consecutively. Results from measurements at all time points (ie, baseline, 3 months, and 9 months) are expected to be ready for analyses in fall 2024.

Discussion

Principal Considerations

Poor oral health in care-dependent older adults is a substantial public health problem, as it is associated with reduced general health and quality of life in this growing part of the population [1,2,6]. Research has revealed that oral health is the most neglected area in Norwegian nursing homes [3], resulting in unacceptable oral hygiene in large proportions of nursing home residents [5]. As described in the Background section, numerous barriers to adequate oral care in nursing homes have been reported, including a lack of knowledge and skills among nursing staff, CRB in patients with dementia, a lack of adequate oral care routines and systems for documentation of oral care issues, a high workload, and unclear responsibilities [18-21]. Thus, there is an urgent need for interventions that can improve oral care and oral health among care-dependent older adults. Previous tools developed to assist health personnel in providing oral care to frail older adults have shortcomings, and some of them are not well suited for nondental professionals [24,25]. The SmartJournal intervention was developed to overcome these challenges, following principles of responsible research and innovation in terms of stakeholder involvement, acceptability, functionality testing, and quality testing, with continuous attention to issues related to ethics and sustainability in this study's context [36].

Strengths and Limitations

Among the strengths of this study is the application of an established framework for research on complex interventions [26], including theory such as the COM-B model [27], to guide intervention development, testing, and analyses. Another strength is that the study includes data from several different sources and modes of data collection, that is, caregivers' responses to survey questionnaires, SmartJournal registrations on oral care routines, patients' oral health status (ie, clinical outcome measures), and selected data from patient journals. Thus, the "common methods problem" is reduced compared to situations where only one data source is available. However, this study also has some limitations that have to be mentioned. The self-report measures used to assess caregivers' capability, opportunity, motivation, and routines related to oral care may be subjected to bias related to recall, introspective ability (ie, participants may not be able to assess themselves accurately), interpretation of questionnaire items, socially desirable responding (ie, the tendency to answer questions in a manner that will be viewed favorably by others), and sampling (ie, people who complete the questionnaire are the sort of people who are inclined to complete a questionnaire) [37]. There is also a risk of getting a low response rate from caregivers due to the general lack of time and high workload among health personnel [38].

Conclusions and Dissemination

This study aims to assess the effects of SmartJournal use on oral care and oral health in nursing homes. Results from this work may be used to inform the continued development and implementation of the SmartJournal intervention in nursing homes and other caring facilities, including in-home care. Similarly, the findings may inform the development and implementation of other digital tools aiming to enhance health care services offered to care-dependent people. Moreover, since oral health knowledge and skills seem to be inadequate for nondental health care professionals, SmartJournal may have potential as a learning tool in educational programs for nurses and other health care professionals. Results from the study will be published in high-impact academic journals and other relevant channels of dissemination, including academic and practitioners' conferences and various public media.

Peer Review

Multimedia Appendix 1 contains the peer review report by the Regional Research Funds Rogaland, Norway.

Time Schedule

The study is scheduled between February 1, 2023, and December 31, 2025 (Table 2).

Table 2. Anticipated time schedule and research activities for the SmartJournal evaluation study.

Activities	Period
Recruitment and baseline measurements (T0)	First quarter of 2023 to second quarter of 2023
Intervention[a]	Second quarter of 2023 to fourth quarter of 2023
Measurements at 3 months (T1)[a]	Fourth quarter of 2023 to first quarter of 2024
Measurements at 9 months (T2)[a]	First quarter of 2024 to third quarter of 2024
Analyses and dissemination	Fourth quarter of 2024 to fourth quarter of 2025

[a]The intervention will last for 12 weeks. Since the start date may vary between the included nursing homes, a 12-month period is scheduled to perform the intervention and measurements at T0, T1, and T2.

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Acknowledgments

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The initial phases of the SmartJournal project (ie, development of the prototype and the feasibility study) were funded by the Regional Research Funds Vest (project ID 291051/2018) and the Oral Health Centre of Expertise Rogaland, Norway. The evaluation study is funded by the Regional Research Funds Rogaland, Norway (project ID 332666/2022).

Data Availability

The data sets generated and/or analyzed during this study are not publicly available due to the sensitive nature of the information, and because participants' consents for public data sharing were not obtained.

Authors' Contributions

VHB and KSH contributed to development and pretesting of the SmartJournal intervention. KSH gave input to on-site procedures. ELM designed and performed the feasibility study. ELM and VHB designed the evaluation study. ELM drafted the manuscript, which was critically reviewed by VHB and KSH. The final manuscript was approved by all authors.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review report by the Regional Research Funds Rogaland, Norway (Hovedprosjekt Regionalt forskningsfond Rogaland - vedtaksbrev - 332666).
[PDF File (Adobe PDF File), 256 KB - resprot_v12i1e46926_app1.pdf]

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Abbreviations

COM-B: capability, opportunity, motivation model of behavior
CRB: care-resistant behavior
e-learning: electronic learning
MPS: mucosal-plaque score
MS: mucosal score
PS: plaque score
ROAG: Revised Oral Assessment Guide

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Protocol

The DrinksRation Smartphone App for Modifying Alcohol Use Behaviors in UK Military Service Personnel at Risk of Alcohol-Related Harm: Protocol for a Randomized Controlled Trial

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Abstract

Background: Consumption of alcohol is synonymous with military populations, and studies have shown that serving personnel drink more than age- and sex-matched civilian populations. While ingrained in the military culture, excessive alcohol use is associated with increased rates of disciplinary issues, sickness absence, and loss of productivity, as well as contributing to a burden of acute and chronic health problems. Alcohol brief interventions can reduce alcohol use in civilian populations, but there is a paucity of evidence relating to the effectiveness of similar interventions in military populations. The DrinksRation smartphone app was designed to have a basis in behavior change technique theory and focuses on providing interactive behavioral prompts tailored to a military population. It has previously been shown to be effective in a help-seeking veteran population.

Objective: The primary aim of the Military DrinksRation randomized controlled trial study is to determine whether it is similarly effective in a serving military population.

Methods: We compare the effectiveness of the DrinksRation smartphone app with treatment as usual for personnel identified at risk of alcohol-related harm using the Military DrinksRation study that is a 2-arm, single-blind, 1:1 randomized controlled trial of the UK Armed Forces population. It is hypothesized that the DrinksRation app will be more efficacious at reducing alcohol consumption compared to treatment as usual. Recruitment will be predominantly from routine, periodic dental inspections all service personnel regularly undertake, supplemented by recruitment from military-targeted media messaging. The primary outcome is the change in alcohol units consumed per week between baseline and day 84, measured using the timeline follow-back method. Secondary outcome measures are a change in the Alcohol Use Disorders Identification Test score, a change in the quality of life assessment, and a change in drinking motivations and app usability (intervention arm only) between baseline and day 84. A final data collection at 168 days will assess the persistence of any changes over a longer duration.

Results: The study is expected to open in August 2023 and aims to enroll 728 participants to allow for a study sample size requirement of 218 per arm and a 40% attrition rate. It is expected to take up to 12 months to complete. The results will be published in 2024.

Conclusions: The Military DrinksRation study will assess the efficacy of the smartphone app on changing alcohol use behaviors in service personnel. If a positive effect is shown, the UK Defence Medical Services would have an effective, evidence-based tool to use as part of an alcohol management clinical pathway, thereby providing better support for military personnel at risk of harm from alcohol drinking.

Trial Registration: ISRCTN Registry 42646;. https://doi.org/10.1186/ISRCTN14977034

International Registered Report Identifier (IRRID): PRR1-10.2196/49918

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(JMIR Res Protoc 2023;12:e49918) doi:10.2196/49918

KEYWORDS

alcohol drinking; alcohol brief intervention; digital intervention; military

Introduction

Overview

Consumption of alcohol is highly prevalent in the United Kingdom, with 65% of men and 50% of women reporting having consumed an alcohol-containing drink in the past week [1]. Consumption in the general population has steadily risen since the 1950s, with the most significant increase among women [2,3]. Exploration of drinking trends across the United Kingdom suggests that there has been an overall small reduction in intake in recent years. However, this is due to moderate reductions in the prevalence of drinking (from 70% to 60%) and alcohol intake in young men aged 16-24 years [2]. This reduction masks a 3 unit per week increase in alcohol intake and an increase in the prevalence of drinking by women. While there has been a reduction in the number of drinkers and the amount consumed by the 16-24-year-old age group, they are the group most likely to binge drink, a trend that transfers into the military population. A large cross-sectional study demonstrated that UK military personnel consume alcohol at rates higher than age- and sex-matched civilian personnel [4]. Military personnel are additionally more likely to drink excessively [4,5]. This binge pattern is attributed to the populations being "young single individuals [who] are less likely to have children and other domestic responsibilities that make heavy drinking less frequent or possible" [4] and the military culture of communal risk-taking [5].

Alcohol's negative effects are wide-ranging and associated with harm to health, accidents, criminality, social disruption, and poor occupational outcomes [1]. For those aged 15-49 years in England, alcohol misuse is the single largest risk factor for ill health and premature death [3]. UK defense data suggest that 59% of military personnel are at risk of alcohol-related harm, which is higher than the general population (42%) [6]. Alcohol was linked to, or the cause of, almost 5% of aeromedical evacuations between 2018 and 2019, and the number of personnel with an alcohol abuse or misuse read code in their primary care clinical notes increased from 457 to 584 between November 2017 and April 2019 [6]. From a health perspective, alcohol is implicated in much of the mental health burden within defense primary health care (DPHC) and complicates other health-related activity through interactions with medication, treatments, and direct exacerbation of symptoms [6,7].

Alcohol is implicated in military disciplinary issues [8,9] and occupationally, alcohol misuse is associated with a loss of productivity, in a dose-dependent manner, through increased rates of sickness absence and presenteeism [3,5]. The occupational impacts of alcohol on the military are more extensive than in the civilian workforce due to the nature of military employment [4,5]. Recognizing the impact that alcohol has on the effectiveness of military personnel, there are various strategies aimed at reducing their alcohol use. Personnel aged 30 years or younger have mandatory alcohol lectures that highlight the harmful effects of excessive consumption and disciplinary issues complicated by alcohol attracting more significant punishment [10].

National guidance recommends alcohol brief interventions (ABIs) for patients identified as consuming alcohol at hazardous or harmful levels [11]. An ABI is "a simple intervention aimed at individuals who are at risk through drinking above the guidelines but are not typically seeking help for an alcohol problem" [12]. All UK Armed Forces (AF) personnel are screened for risky drinking behaviors using the Alcohol Use Disorders Identification Test for Consumption (AUDIT-C) [13] at periodic dental inspections (PDIs). A "brief intervention" is given to personnel who record a score of 4 or more (men) or 3 or more (women). There is concern, however, that recent apparent reductions in alcohol intake reflect reporting bias rather than an actual reduction in the AUDIT-C score. An intentionally low misrepresentation of actual intake would avoid the individual being given an ABI or offered a referral to the general practitioner [14] and avoid any associated concerns about the career impact of being identified as being at risk of harm from drinking.

Existing evidence for the effectiveness of ABIs appears robust, with an extensive Cochrane review determining they can reduce alcohol consumption by 2 standard drinks per week after a year [15]. However, this defined an ABI as "a conversation comprising 5 or fewer sessions of brief advice or brief lifestyle counseling and a total duration of less than 60 minutes" [15]. This exceeds the time available for opportunistic ABIs within DPHC consultations. The Cochrane review also excluded digital interventions, which are intuitively of huge relevance in a young, digital native population such as the AF. Face-to-face interventions may be effective, but not if they are not accessed by a digital generation [16-18]. A narrative review of 10 studies involving military personnel and veterans found that web-based interventions may be of benefit [19]. There remains a paucity of evidence available for the effectiveness of ABIs on military populations, or indeed, for which aspects of behavior change theory are effective in a population with rigid command structures and regulations.

The primary purpose of the DrinksRation randomized controlled trial (RCT) study is to determine whether similar effectiveness is found in a serving military population.

Military DrinksRation (MDR) Study Aim

DrinksRation is a military-focused smartphone app that has been shown to be effective in reducing alcohol consumption in a veteran, help-seeking population [20]. The primary purpose of this RCT is to determine whether the DrinksRation app has similar effectiveness in a serving, non–help-seeking military population. An effective app could support or integrate into the defense alcohol management pathways and provide support to service personnel while they wait for specialist intervention from defense community mental health services. Additionally,

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if the links between drinking behaviors and social and health outcomes are better understood, there is scope for future policy design to target the precipitating factors leading to a more positive and healthy life.

Methods

Ethical Considerations

This study was approved in September 2023 by the Ministry of Defence Research Ethics Committee (MODREC; registration number: 2154/MODREC/22) and registered as a clinical trial with the International Standard Randomised Controlled Trial (ISRCT) number registry (submission number: 42646). Any amendments to the protocol will be registered with ISRCT and approved by MODREC.

Study Design

The MDR study is a 2-arm, single-blind, 1:1 RCT of the UK AF population comparing the effectiveness of the DrinksRation smartphone app with treatment as usual (TAU) for those at risk of alcohol-related harm. It is hypothesized that the DrinksRation app will be more efficacious at reducing alcohol consumption compared to TAU.

Study Sample

A protocol for the veterans' RCT of the DrinksRation app calculated a sample size of 37 participants in each arm to achieve significance and a target of 620 invitations to cover nonparticipation and attrition [17]. Assessing the sample size for a serving (nonveteran), non–help-seeking population, an effect size of 4 units of alcohol per week, and a mean consumption of 30.5 (SD 14.9) units/week were used. Consumption is based on a large systematic review of face-to-face ABIs [21]. The mean change of 4 units is based on a change of 2 units detected in a systematic review for the general population [21]; 7 units detected in a previous DrinksRation study [16]; and 4 units being used in the help-seeking veteran RCT [17]. The sample size was calculated as 218 per arm. The study will aim to recruit 728 participants to allow for a 40% attrition rate. Defense statistics state that 59% of the serving AF population are at risk of alcohol-related harm [6]. This equates to approximately 7250 personnel per month having a PDI and being eligible for the study.

Recruitment

Potential participants for the MDR study will be currently serving UK AF personnel identified through PDIs and self-identification following study publicity. All 148,000 serving military personnel are offered PDI at least annually. Before the PDI, all personnel are asked to complete an AUDIT-C screening tool. Those scoring at increasing risk of alcohol-related harm to health (≥5) are given an alcohol brief intervention by the dental staff, which consists of a single brief discussion around the risks of drinking lasting 2-3 minutes. Those scoring in the higher risk group (8-10) or suggesting possible dependence (11-12) are offered a referral from the dentist to a general practitioner for follow-up.

The trial will be publicized through service-specific communications, social media, and recruitment posters displayed across the UK defense estate. Additionally, potential participants will be identified through service-specific communication, including links and QR codes to the study website promoted through single service information pathways and on the defense intranet. MyNavy and similar apps within the defense gateway will also be used to announce the trial and direct potential participants to the study website. Military-focused social media, such as #MilTwitter and AF-specific Facebook groups, will be asked to promote the study and host links to the study website. Posters with a short link and QR code for the study website will also be displayed in areas of high footfall in large establishments.

All potential participants will be screened for eligibility using a web-based AUDIT-C tool [13] on Research Electronic Data Capture (REDCap) [22]. Those scoring ≤4 will not be eligible for the DrinksRation RCT. Personnel scoring ≥5 will be given an ABI either in the form of the standard defense guidance on reducing alcohol use or by the dental staff as per usual management. Personnel will then be directed to the participant information sheet (PIS), eligibility criteria, and web-based consent form on REDCap.

Participants will be included in the study if they are currently serving UK AF; have an Android or iOS smartphone and are willing or able to download the DrinksRation app; report an AUDIT-C score of ≥5; and provide a telephone number or email address for participant safety purposes.

Participants will be excluded if they are unwilling or unable to download the DrinksRation app or if they scored ≤4 on AUDIT-C. There will be no exclusion on the grounds of harmful drinking identified by AUDIT-C screening.

There are no age or sex restrictions on participation beyond those of the military population. Specifically, personnel aged 18 years or younger are not excluded from the MDR study, as they form a small proportion of the UK military population. While the purchase of alcohol by those aged 18 years or younger is illegal, consumption by underage personnel does happen, and age does not proffer any immunity against potentially harmful drinking behaviors [23]. Indeed, living with people who are drinking alcohol increases the likelihood of a child drinking (odds ratio 3.6 for children living with 3 or more drinkers) [3].

After consenting to inclusion in the study and the collection of baseline demographics, participants will be randomized to the intervention group or TAU group using the embedded REDCap randomization module.

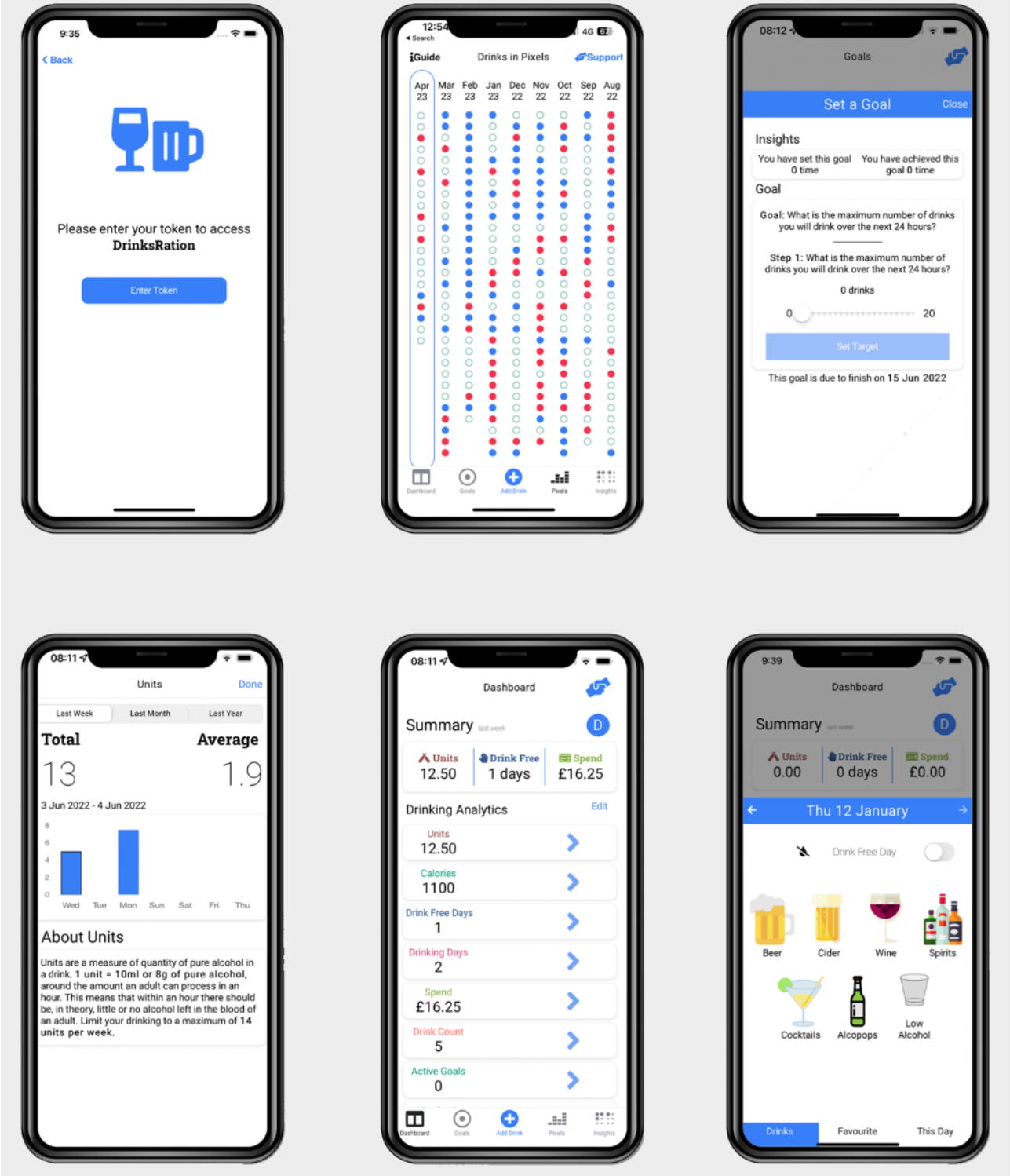
Intervention

Participants randomized to the intervention arm of the RCT will be sent an email link to the DrinksRation app with a unique reference code to enable data linkage between REDCap and DrinksRation. The app's function, theoretical basis, and supporting evidence are fully described elsewhere [16,20,24]. Images of the app and its functionality are shown in Figure 1. After downloading the app, on first use, participants will be prompted to complete baseline assessment surveys. App usage and further surveys were then presented by the app with push notifications to the participant, highlighting the need for completion. Participants will be asked to use the app for a

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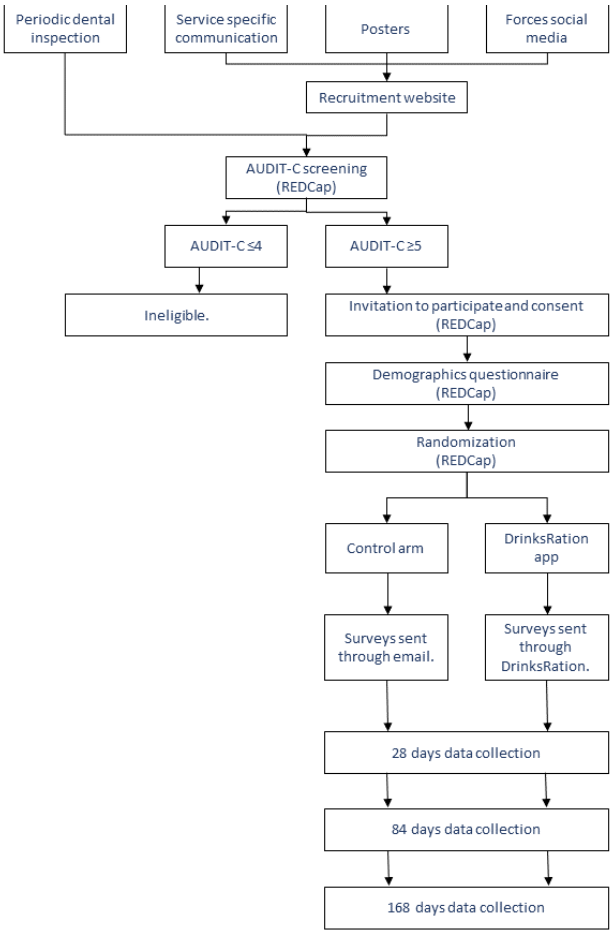
minimum of 28 days. Participant flow through the study is shown in Figure 2.

Figure 1. Military DrinksRation randomized controlled trial: smartphone app screenshots.



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Figure 2. Study flow diagram. Primary and secondary outcomes are assessed at day 84, with outcomes reassessed at day 168 in order to understand the longer-term benefits of the intervention. AUDIT-C: Alcohol Use Disorders Identification Test for Consumption; REDCap: Research Electronic Data Capture.



Control

Participants randomized to the control arm will receive baseline assessment and all further surveys through email with the same periodicity as the intervention group. The control group will be asked to complete the surveys and will be given access to the DrinksRation app at the end of the study period. Noncompletion of surveys will prompt an automated push notification (intervention arm) or email (control arm) reminder after 24 hours. The structural difference between the arms was considered unavoidable due to the difficulty of creating a sham digital psychological intervention [25]. If a pared-down "dumb" version of the app were offered to the control arm, then it would be difficult to determine whether any effect was due to the visibility of the app or interaction with the app. A previous study of the DrinksRation app showed a large attrition rate in the control arm when participants were given a dumb version of the app [20].

Randomization and Blinding

Participants will be randomized using the in-built randomization module of the REDCap program. This module automatically allocates participants to either the DrinksRation app or the TAU group based on a randomization table generated on the internet using the Sealed Envelope website [26]. Two participant blocks in a 1:1 ratio will be used. Randomization will be stratified by sex because it has previously been shown that alcohol use in the UK military is different between the sexes [4]. The randomization module will be programmed by the study independent medical officer (IMO), who is not blinded to the allocations in order to enact the safety protocols if required. The researchers had no visibility of programming, and role-based access to REDCap prevented access to any identifiable information or allocation for the research team. There was no contact between researchers and participants at any stage of the trial.

Participants were blinded to the intervention as they were told that the research involved them completing various surveys about drinking behaviors, health, and well-being. The study IMO will not be blinded to allocation and will have data access rights allowing him to link the participant reference codes to personal identifiers in case of any adverse events.

Measures

The primary outcome measure is a change in alcohol units consumed per week between baseline and day 84, as measured by the timeline follow-back method [27]. Secondary outcomes are a change in the Alcohol Use Disorders Identification Test (AUDIT) score, a change in the quality of life assessment, and a change in drinking motivations and app useability. While the DrinksRation intervention aims to reduce alcohol intake at 84 days, a final data collection at 168 days will assess any persistent benefits.

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Data will be collected through a selection of surveys pushed to the participants in line with the periodicity detailed in Table 1.

The study instruments are all validated for the general population and are detailed in Table 1. The alcohol and mental health symptomatology surveys were included in the veteran's trial. The MDR trial additionally includes surveys for drinking motivations (Drinking Motives Questionnaire 9-item tool [DMQ-R]), recent life events (Recent Life Events Questionnaire [RLE-Q]), gambling motives (Gambling Motivations Questionnaire [GMQ-9]), and domestic abuse and sexual assault (National Crime Survey for England and Wales). These behaviors have been associated with both alcohol consumption [3] and a military population [40,41]. A tertiary outcome of the MDR study is to assess the correlation of these issues with alcohol use within the military population. This information does not contribute to the assessment of the app's effectiveness, but it is valuable information for UK defense policy makers.

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Table 1. Summary of measures and data collection time points.

Measure	Total questions	Day 0	Day 0-1	Day 3	Day 7	Day 28	Day 84	Day 168
Demographics	18	✓						
AUDIT-C[a] [13]	3	✓						
Participation information and consent	N/A[b]	✓						
Alcohol use (AUDIT[c]) [28]	10		✓			✓	✓	✓
Alcohol intake (TLFB[d]) [27]	N/A		✓			✓	✓	✓
Resource allocation (YAACQ[e]) [29]	24		✓				✓	✓
Readiness to change ruler	1		✓					
Self-efficacy ruler	1		✓					
Depression (PHQ-2[f]) [30]	2		✓			✓		
Anxiety (GAD-2[g]) [31]	2		✓			✓		
International trauma questionnaire for PTSD[h] (PC-PTSD-5[i]) [32]	5		✓			✓		
World Health Organization Quality of Life-BREF[j] (WHOQOL-BREF) [33]	27			✓		✓	✓	✓
Loneliness (De Jong Gierveld) [34]	11			✓		✓		
Drinking motivations (DMQ-R[k]) [35][l]	20			✓			✓	
Recent life events (RLE-Q[m]) [36][l]	21			✓				
Gambling motives (GMQ-9[n]) [37][l]	9				✓			
Domestic abuse (NCSE&W[o]) [38][l]	30				✓			
Sexual assault (NCSE&W) [38][l]	13				✓			
mHealth App Usability Questionnaire (MAUQ) [39]	16					✓		
Approximate time to answer (min)[p]	—[q]	10	13	15	9	20	15	15

[a]AUDIT-C: Alcohol Use Disorders Identification Test for Consumption.

[b]N/A: not applicable.

[c]AUDIT: Alcohol Use Disorders Identification Test.

[d]TLFB: timeline follow-back.

[e]YAACQ: Young Adult Alcohol Consequences Questionnaire.

[f]PHQ-2: Patient Health Questionnaire 2-item tool.

[g]GAD-2: Generalized Anxiety Disorder 2-item tool.

[h]PTSD: posttraumatic stress disorder.

[i]PC-PTSD-5: Primary Care-Posttraumatic Stress Disorder 5-item screening tool.

[j]BREF: Best Available Technique Reference Document.

[k]DMQ-R: Drinking Motives Questionnaire 9-item tool.

[l]Not included in veterans' DrinksRation study.

[m]RLE-Q: Recent Life Events Questionnaire.

[n]GMQ-9: Gambling Motivations Questionnaire.

[o]NCSE&W: National Crime Survey for England and Wales.

[p]Allowing 10 seconds per question, rounded up and with additional comfort time added.

[q]Not available.

Statistical and Analysis Plan

The MDR study is based on a recently completed study of veterans, which was sponsored by the Forces in Mind Trust. Analysis will therefore be undertaken in accordance with the published protocol for that study [16,20]. There will be no interim analysis. The threshold for significance will be P=.05. Effect sizes will be reported.

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Descriptive statistics (eg, demographics and response rate) and independent sample *t* tests and chi-square tests will be carried out to explore and identify potential differences between the intervention and control arms at follow-up. An intention-to-treat method will be used for primary outcome analysis, such that those who are lost to follow-up will be retained in the primary analysis. Multiple imputations will be performed to estimate missing data, where appropriate. The primary outcome analysis will examine whether there is a statistically significant difference between the intervention and control arms on change in self-reported timeline follow-back UK units consumed. Repeated-measures mixed modeling analyses will be conducted to examine the primary hypothesis that those randomized to receive the DrinksRation app will report a greater reduction in alcohol consumption compared with control participants from baseline to 3-month follow-up (day 84).

For the secondary outcomes, changes in the AUDIT score and World Health Organization Quality of Life- Best Available Technique Reference Document (WHOQOL-BREF) computed quality of adjusted life years will be assessed using repeated-measures mixed modeling. These analyses will be repeated to assess changes between baseline and follow-up and will serve as a secondary outcome to assess the long-term impact of the intervention on participants [17]. Tertiary outcomes will be assessed for correlation with alcohol consumption and will be reported separately to the RCT outcome.

The study will be reported in line with the CONSORT (Consolidated Standards of Reporting Trials) [42] criteria for RCTs and the Template for Intervention Description and Replication guide [43]. The study was designed in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement [44].

Data Management and Confidentiality

All study data will be captured and held electronically within REDCap or the DrinksRation app, depending on the participant arm. There is no physical paperwork and no requirement for any. Consent forms are held electronically within REDCap. Data will be processed and stored in line with the General Data Protection Regulation (GDPR) Article 6 (1.e) “processing is necessary for the performance of a task carried out in the public interest or in the exercise of official authority vested in the controller” [45]. DrinksRation app data are stored on Google-managed, UK-based servers contracted by the King’s Centre for Military Health Research (KCMHR). All other study data are held within the defense medical services REDCap servers at the University of Birmingham.

Data Monitoring

A data monitoring committee is not necessary because the intervention is well-defined and not considered to be a risk to participants [46]. Prompts to complete surveys will be sent to participants through the app (intervention arm) or by email (control arm). A reminder notification will be sent if surveys are not completed within 24 hours. There is no further follow-up for missing data. Missing data do not impact further survey prompts being sent; all participants will receive notification when the next survey is due in accordance with Table 1. No additional plan to promote participant retention is required because the app evaluation needs to consider natural attrition rates and adherence to app usage.

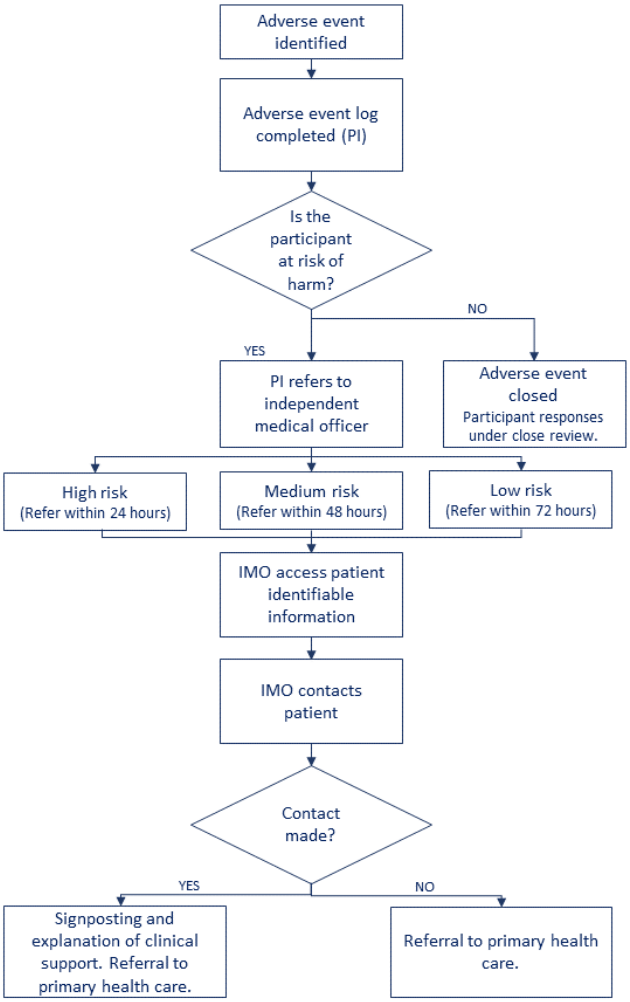
Adverse Events

The investigators will review the data weekly to identify any potential adverse events. As per the veteran’s DrinksRation study, an adverse event is defined as a participant either consuming more than 25 units of alcohol in a 24-hour period or giving survey responses suggesting a significant mental health problem [17]. Additionally, participants can register an adverse event or problem by contacting the researchers through the study email address or website.

If an adverse event is identified, the principal investigator (PI) will review the available data for the participant, and if there are concerns, the PI will inform the IMO. The IMO will have access to the patient identifiable information and will contact the patient to facilitate referral to primary care if required and assess suitability to continue in the trial. Figure 3 details the adverse event management plan. All adverse events will be recorded in a risk event log held within the REDCap research database.

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Figure 3. Adverse events management plan showing the unblinded role of the independent medical officer (IMO) in order to address potential harms. PI: principal investigator.



Study Consent and Withdrawal

Consent will be managed on the internet through REDCap; immediately after AUDIT-C screening, potential participants are shown the PIS and study consent form. Consent is captured electronically within the REDCap platform. Participants who want time to think about participation or to ask questions can do so by using the option to "save and return later," therefore allowing participants to consider their participation at their leisure. The study website hosts a "frequently asked questions" document and a contact email address for the PI. Staff in dental centers will be given a standard briefing about the study and asked to direct further questions to the investigators through the study email address. Participants will be informed that their data will be used primarily for the purposes of the MDR study. However, if results indicate that further studies are beneficial for the military community, the data may be further processed to extend the scope of the research in the field of alcohol behavior change. If this is deemed beneficial, then participants will be informed before the compatible processing occurs.

No payment for participation will be made to ensure that payment does not impact app usage rates. Any participant who sustains harm as a direct result of the study can apply for compensation under the Ministry of Defence's No-Fault Compensation Scheme. Details of the scheme will be available to participants with the PIS. The DrinksRation app has been designed and built by KCMHR, is published with open-source coding, and is free to download. It does not provide financial benefit. The PI is employed by the Royal Navy, and academic fees associated with this study are paid for by defense; however, defense has had no influence over the content or design of this trial.

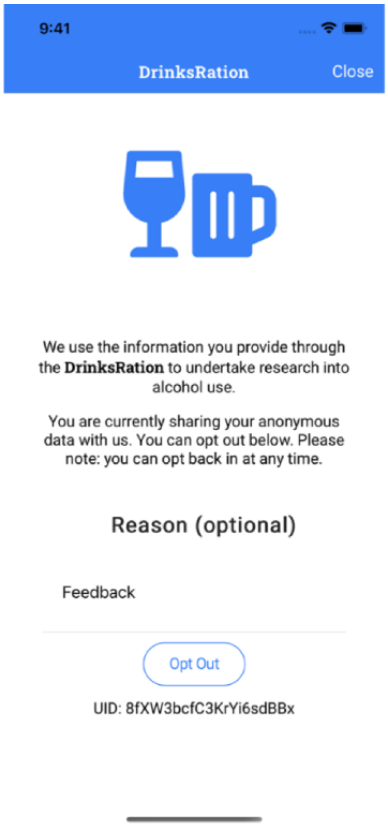
All the data gathered will be written up as part of the thesis submitted for an MD (Research) in Psychological Medicine Research at King's College London. Results will be published with open access in line with best practices [47]. Authorship will be as per this paper. Additionally, an "executive summary" will be written to facilitate access to findings by nonresearchers across defense. Participants wanting to be informed of the study outcomes will be emailed the summary and a link to any published article. Findings will be fed back to key stakeholders within defense.

Participants are able to withdraw from the study at any point up to the point when the data capture is extracted for analysis. At this point, the data will be grouped, and it will no longer be possible to select individual data. Withdrawal from the intervention arm is managed entirely from within the DrinksRation app. Participants visit the "Settings" tab, and the

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option to withdraw is visible (see Figure 4 below). To withdraw from the control arm, participants will need to email the PI, either directly or through the study website. Withdrawing participants are given the option to delete the data already collected or allow the research team to use this data.

Figure 4. Participant withdrawal screen, which includes the ability to delete the account or withdraw from the study.



Results

Recruitment will commence in August 2023 and be completed by October 2023. Results are expected by autumn 2023.

Discussion

The existing evidence for brief interventions in alcohol behavior management is robust, with several large systematic reviews published in this area [15,19,21,48,49]. The types of brief interventions used in these reviews are varied and often resource-intensive, with many of the included interventions not aligning with the National Institute of Health and Care Excellence guidelines. These face-to-face interventions have a place in an evidence-based alcohol management strategy but come with a training burden and a requirement for a significant uplift in primary care appointments in order to address the high levels of potentially hazardous drinking in the AF population. This considerably limits their practicality because they exceed the time available within standard primary health care appointments of 10-15 minutes. Digital interventions have been developed to address this issue and have also been shown to have an effect [50]. There are 2 systematic reviews of digital alcohol interventions identified on NHS Evidence [50,51]. They report that digital interventions can reduce alcohol consumption. The larger Cochrane review reports that brief interventions are responsible for alcohol reductions of 22.8 (95% CI 15.4-30.3) g of alcohol per week compared to no intervention [50], approximately 2 standard drinks per week. The smaller review included observational and experimental study types and so quantitative synthesis was not undertaken. A digital solution may be desirable to a digital native population [18] and confers resource advantages over face-to-face interventions. Fundamentally, face-to-face interventions may be effective, but they also may not be accessed by the digital generation, which forms the majority of the current serving AF population [16-18].

The UK AF population also has a relationship with alcohol that differs from that of the general public [5], and there is no existing evidence for the use of brief interventions within the UK AF. A single systematic review including UK AF personnel and veterans was found, but the heterogeneity and risk of bias within the included studies precluded a meta-analysis. The data and narrative synthesis showed that digital interventions may be effective in this mixed population [19]. Interestingly, a statistically significant reduction in binge drinking (mean difference –0.24, 95% CI –0.35 to –0.13 binges/week) [50] was seen with digital interventions, which is not seen in face-to-face interventions (mean difference –0.08, 95% CI –0.28 to 0.12 binges/week) [21]. The finding of effect in terms of binge drinking also makes digital interventions especially beneficial to the AF population [52,53].

The DrinksRation app fulfills the requirement for the intervention to be delivered within available time resources in DPHC and has been shown to be effective in a small-scale study of veterans [16,54]. However, there are some significant

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demographic differences between the serving and veteran populations, namely the age profile. A third of veterans are aged 80 years or older; half are aged 65 years or older; and less than 10% are aged 30 years or younger [55]; compared to just under half of the serving AF population being 30 years old or younger [56]. This study will determine whether the DrinksRation app is effective at changing the alcohol use behavior in this younger, serving AF population and, for the first time, provide defense medical services with an evidence-based alcohol intervention designed for military personnel.

Data Availability

The data sets generated during this study are not publicly available in line with Ministry of Defence research policies but are available from the corresponding author on reasonable request.

Conflicts of Interest

DL is a Reservist in the UK Armed Forces. This work has been undertaken as part of his civilian employment. KK is employed by the Royal Navy. This work has not been reviewed or amended by the chain of Command. NF is part funded by a grant from the UK Ministry of Defence and is a trustee (non-paid) of a UK charity supporting the wellbeing of service personnel, veterans and their families.

Multimedia Appendix 1
Defence Medical Services Research Steering Group- Endorsement Letter-Dec 20.
[PDF File (Adobe PDF File), 35 KB - resprot_v12i1e49918_app1.pdf]

Multimedia Appendix 2
Peer Review comments from Defence Medical Services Research Steering Group Sep 20.
[PDF File (Adobe PDF File), 84 KB - resprot_v12i1e49918_app2.pdf]

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Abbreviations

ABI: alcohol brief intervention
AF: Armed Forces

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AUDIT: Alcohol Use Disorders Identification Test
AUDIT-C: Alcohol Use Disorders Identification Test for Consumption
CONSORT: Consolidated Standards of Reporting Trials
DMQ-R: Drinking Motives Questionnaire 9-item tool
DPHC: defense primary health care
GDPR: General Data Protection Regulation
GMQ-9: Gambling Motivations Questionnaire
IMO: independent medical officer
ISRCT: International Standard Randomised Controlled Trial
KCMHR: King's Centre for Military Health Research
MDR: Military DrinksRation
MODREC: Ministry of Defence Research Ethics Committee
PDI: periodic dental inspection
PI: principal investigator
PIS: participant information sheet
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
RLE-Q: Recent Life Events Questionnaire
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
TAU: treatment as usual
WHOQOL-BREF: World Health Organization Quality of Life- Best Available Technique Reference Document

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Protocol

Mindfulness-Based App to Reduce Stress in Caregivers of Persons With Alzheimer Disease and Related Dementias: Protocol for a Single-Blind Feasibility Proof-of-Concept Randomized Controlled Trial

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Abstract

Background: Informal caregivers (ie, individuals who provide assistance to a known person with health or functional needs, often unpaid) experience high levels of stress. Caregiver stress is associated with negative outcomes for both caregivers and care recipients. Mindfulness-based interventions (MBIs) show promise for improving stress, emotional distress, and sleep disturbance in caregivers of persons with Alzheimer disease and related dementias (ADRD). Commercially available mobile mindfulness apps can deliver MBIs to caregivers of persons with ADRD in a feasible and cost-effective manner.

Objective: We are conducting a single-blind feasibility proof-of-concept randomized controlled trial (RCT; National Institutes of Health [NIH] stage 1B) comparing 2 free mobile apps: the active intervention Healthy Minds Program (HMP) with within-app text tailored for addressing stress among caregivers of persons with ADRD, versus Wellness App (WA), a time- and dose-matched educational control also tailored for caregivers of persons with ADRD.

Methods: We aim to recruit 80 geographically diverse and stressed caregivers of persons with ADRD. Interested caregivers use a link or QR code on a recruitment flyer to complete a web-based eligibility screener. Research assistants conduct enrollment phone calls, during which participants provide informed consent digitally. After participants complete baseline surveys, we randomize them to the mindfulness-based intervention (HMP) or educational control podcast app (WA) and instruct them to listen to prescribed content for 10 minutes per day (70 minutes per week) for 12 weeks. Caregivers are blinded to intervention versus control. The study team checks adherence weekly and contacts participants to promote adherence as needed. Participants complete web-based self-report measures at baseline, posttest, and follow-up; weekly process measures are also completed. Primary outcomes are a priori set feasibility benchmarks. Secondary outcomes are stress, emotional distress, sleep disturbance, caregiver burden, mindfulness, awareness, connection, insight, and purpose. We will calculate 1-sided 95% CI to assess feasibility benchmarks. Effect sizes of change in outcomes will be used to examine the proof of concept.

Results: Recruitment started on February 20, 2023. We have enrolled 27 caregivers (HMP: n=14; WA: n=13) as of June 2023. Funding began in August 2022, and we plan to finish enrollment by December 2023. Data analysis is expected to begin in May 2024 when all follow-ups are complete; publication of findings will follow.

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Conclusions: Through this trial, we aim to establish feasibility benchmarks for HMP and WA, as well as establish a proof of concept that HMP improves stress (primary quantitative outcome), emotional distress, sleep, and mindfulness more than WA. Results will inform a future efficacy trial (NIH stage II). HMP has the potential to be a cost-effective solution to reduce stress in caregivers of persons with ADRD, benefiting caregiver health and quality of care as well as patient care.

Trial Registration: ClinicalTrials.gov NCT05732038; https://clinicaltrials.gov/study/NCT05732038

International Registered Report Identifier (IRRID): DERR1-10.2196/50108

(JMIR Res Protoc 2023;12:e50108) doi:10.2196/50108

KEYWORDS

caregiver; dementia; mindfulness; mobile app; protocol; randomized controlled trial

Introduction

Background

More than 1 in 5 Americans (ie, approximately 53 million) are informal caregivers [1]. These individuals provide assistance to known persons with physical, mental, or cognitive illness or disability, often unpaid [2]. Almost half of caregivers who provide help to older adults care for someone with Alzheimer disease or related dementias (ADRD) [3]. Caregivers have been dubbed "the hidden patients" because the negative physical and mental health consequences of caregiving are often underrecognized and undertreated [4]. Nearly 60% of caregivers of persons with ADRD experience high levels of psychological stress, and more than 1 in 3 caregivers of persons with ADRD report that their health has deteriorated due to caregiving responsibilities [5]. Some key sources of caregiver stress include ongoing worry about their loved one's health, concerns about whether they are doing the caregiving job well, challenges navigating regular life in addition to caregiving responsibilities, concerns about the impact of caregiving on their own health, social isolation, and financial strain [6,7]. High caregiver stress is associated with mental health concerns [8], sleep difficulties [9], and an increased risk for morbidity and mortality [10]. In previous studies, 42%-55% of caregivers reported looking for feasible and effective stress management interventions [11]; yet this population often has limited time for outpatient psychotherapy. Given the negative consequences of caregiver stress on the health and well-being of both caregivers and care recipients, decreasing caregiver stress in an accessible delivery format is a public health concern.

Mindfulness-based interventions (MBIs) show promise as an efficacious nonpharmacological treatment to reduce caregiver stress [2]. Mindfulness meditation is defined as paying attention on purpose, in the present moment, nonjudgmentally [12,13]. Practicing mindfulness is thought to help individuals cultivate acceptance and inner peace, regardless of challenging life circumstances [14-16]. Across many populations, the practice of mindfulness meditation is associated with decreased stress [17,18], improved emotional functioning [19,20], and improved sleep [21,22]. Several recent systematic reviews have supported the effectiveness of MBIs for improving stress, emotional functioning, and sleep in caregivers, including caregivers of persons with ADRD [2,14,17,18,21,23-27].

Although research has established the benefits of MBIs for caregivers, the prevailing models of delivery of these interventions fall short for several reasons. First, many of these programs are conducted in person [28], which is sometimes not feasible for caregivers' schedules (eg, needing respite for care recipients) [7]. Second, even when programs have been delivered remotely, these often follow a synchronous format (ie, caregivers must attend remotely at the same time each week), which is challenging given the unpredictability of caregiving responsibilities. Third, traditional programs typically demand substantial amounts of continuous time that caregivers are unable to commit (eg, a traditional mindfulness-based stress reduction program involves 8 weekly 2.5- to 3.5-hour-long sessions as well as 45 minutes of prescribed practice per day) [29]. Fourth, traditional programs require trained providers who are often costly, are not usually covered by insurance, and are not always readily available [30-32]. More feasible, scalable, and cost-effective solutions are needed to deliver MBIs to caregivers.

Mobile mindfulness apps may be uniquely positioned to address the aforementioned barriers by allowing caregivers to practice meditation on their own schedule at little or no cost. The majority of caregivers own a smartphone and regularly use mobile apps [33]. Additionally, adults aged 50 years or older, who represent a sizable portion of caregivers of persons with ADRD, are the fastest-rising users of smartphone technology in the past decade [34]. In qualitative studies, caregivers express interest in using mobile apps for stress management and health information [35] including to learn mindfulness meditation for stress management [36-39]. To the best of our knowledge, there are no consumer-based mobile apps with proven efficacy in decreasing stress, emotional distress, and sleep difficulties among caregivers of persons with ADRD [40]. Although mindfulness-based mobile apps show promise for helping caregivers of persons with ADRD decrease stress, emotional distress, and sleep difficulties, additional research is needed to establish feasibility and efficacy before widespread dissemination.

Healthy Minds Program (HMP) is a mindfulness-based mobile app that may be well suited for use with caregivers of persons with ADRD for several reasons. First, HMP is unique because it teaches mindfulness skills grounded in theory [41] with empirical support [42-44]. Having a theoretical underpinning is important because it allows the app to be a vehicle for the delivery of evidence-based mindfulness skills. Second, previous research has shown that HMP reduced emotional distress and burnout in firefighters [44]; improved psychological distress, stress, social connectedness, and mindfulness in adults [43];

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and reduced stress and increased mindfulness, self-compassion, and human flourishing in medical students [42]. Third, HMP is free of charge, which increases its reach especially among caregivers who often experience financial burdens because of their role. Fourth, HMP has customizable features (eg, a diverse set of voices to choose from) that have the potential to increase acceptability across race, ethnicity, and gender. Finally, HMP supports content tailoring to include on-screen language and scenarios that are relevant for caregivers of persons with ADRD.

Here, we will be conducting a National Institutes of Health (NIH) stage 1B trial (NCT05732038) comparing HMP with a time- and dose-matched educational control app, Wellness App (WA). Our team tailored the content of both apps to highlight case scenarios specific to caregivers of persons with ADRD. Both interventions (HMP and WA) consist of 12 weeks of guided listening for 10 minutes per day. Participants complete outcome measures at baseline, posttest, and follow-up (2 months after posttest), as well as weekly process measures.

Objectives

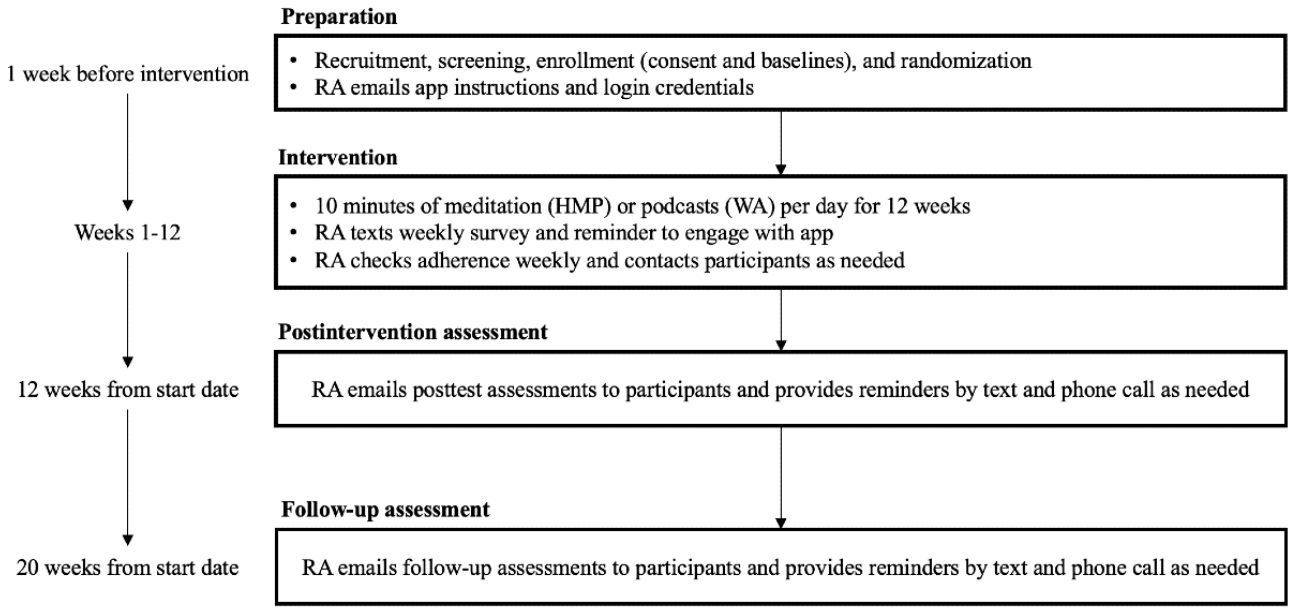
The purpose of this paper is to describe the protocol and status of our ongoing single-blind feasibility proof-of-concept randomized controlled trial (RCT) of HMP versus WA in caregivers of persons with ADRD. Our primary hypothesis is that HMP and WA will meet a priori feasibility markers (ie, acceptance and demand benchmarks). Our secondary hypothesis is that participation in HMP will be associated with a greater decrease in caregiver stress (primary quantitative outcome), emotional distress, sleep dysfunction, and caregiver burden, and a greater increase in mindfulness, awareness, connection, insight, and purpose (secondary quantitative outcomes) compared with WA, and improvement will be sustained through the 20-week follow-up. Results will directly inform an NIH stage 2 fully powered RCT of HMP versus WA.

Methods

Study Design and Setting

This NIH stage 1B, single-blind, feasibility, proof-of-concept RCT is testing HMP versus WA (time- and dose-matched control) in caregivers of persons with ADRD. Data collection is underway (started in February 2023; n=27 caregivers as of June 2023). We plan to recruit 80 caregivers of persons with ADRD reporting elevated levels of stress. Our institutional review board approved this study (2022P001601). Figure 1 provides an overview of the study design and timeline.

Figure 1. Study design and timeline. HMP: Healthy Minds Program; RA: research assistant; WA: Wellness App.



Inclusion and Exclusion Criteria

Table 1 presents the study inclusion and exclusion criteria and rationale. These eligibility criteria were informed by previous MBI studies with caregivers, including those of persons with ADRD [2,14,17,18,21,23-27], as well as a previous study with caregivers funded by the NIH (NCT00177489). The criteria are meant to be as inclusive as possible to maximize generalizability by allowing individuals who self-identify as caregivers to participate rather than requiring a certain number of hours spent caregiving, specific responsibilities, or other criteria.

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Table 1. Study inclusion and exclusion criteria and rationale.

Criteria	Rationale
Inclusion	
Age 18 years or older	Most caregivers are adults; study procedures are formulated for adults only
English fluency and literacy	Measures, instructions, and app are in English
Meeting criteria for being a caregiver (ie, family or friend of a care recipient who provides care not through an agency) [2]	Population
Perceived Stress Scale (4 items) version ≥6 [45]	Population; ensure that the intervention is needed (not all caregivers experience caregiver stress)
Willing to be randomized	Necessary for scientific rigor
Care recipient must be rated >1 on the Functional Assessment Staging Tool [46]	Population; ensure that caregivers have a threshold of caregiving tasks
Exclusion	
Any planned change in psychotropic pharmacologic treatment for the duration of the study	Treatment confound
Use of any consumer-based mindfulness meditation app for more than 60 minutes per month in the past 6 months	Treatment confound
Current participation in a meditation program (eg, mindfulness-based stress reduction, mindfulness-based cognitive therapy, etc)	Treatment confound
Major illness anticipated to worsen dramatically or require surgery in the next 20 weeks (study duration)	Treatment confound
Active treatment for cancer (chemotherapy or radiation)	Treatment confound
Imminent placement of care recipient in a nursing home or with another caregiver (within 4 months)	Treatment confound
Involvement in another clinical trial for caregivers	Treatment confound
For participants aged 65 years and older: Short Portable Mental Status Questionnaire: ≥4 errors [47]	Validity and feasibility

Recruitment and Screening

For this trial, we are focused on recruiting geographically, racially, and ethnically diverse informal caregivers to ensure generalizability. We have established partnerships with a variety of organizations dedicated to supporting caregivers and care recipients (eg, National Alliance of Caregiving and Boston Ministerial Alliance) that share our recruitment materials (eg, flyer) on social media and listservs. Additionally, we directly contact caregivers from our previous nonclinical trial studies that indicated interest in learning about additional research opportunities. Interested caregivers use a link or QR code on flyers, social media ads, and email blasts to fill out a web-based eligibility questionnaire through REDCap (Research Electronic Data Capture; Vanderbilt University) [48]. Caregivers who want more information on the study can contact the research assistant (RA) before completing the screening in REDCap. Ineligible caregivers receive an on-screen message at the end of the screening in REDCap notifying them of their ineligibility along with a link to a resource sheet. For participants who meet initial eligibility criteria, a final survey page appears where they confirm their interest in participating and provide suitable times for a 20- to 30-minute enrollment phone call. During this call, the RA administers the Short Portable Mental Status Questionnaire (SPMSQ; for those over the age of 65 years) [47] and the Functional Assessment Staging Tool (FAST) [46] to finalize eligibility criteria.

Ensuring Validity of Participant Data by Avoiding "Imposter" Participants

Previous research has shown that remote studies have an increased risk of enrolling "imposter" participants (ie, participants who misrepresent themselves to appear eligible for a study) [49,50]. In a web-based study using MTurk (a crowdsourcing service), Hydock [49] found that more than 12% of participants falsified their identities "for the chance of financial gain." To address this concern, our team has identified "red flags" that suggest that a participant is misrepresenting their identity and requires additional attention and screening, including (1) large volumes of back-to-back inquiries following a similar format (eg, all emails are firstnamelastname ####@gmail.com), (2) spelling mistakes and grammatical errors, (3) incorrect or inconsistent survey responses (eg, one participant wrote they heard about this study on Craigslist), (4) providing out-of-service or Google Voice (Google LLC) numbers (the use of Google Voice numbers has been cited as a commonality among many imposter participants [51]), (5) poor sound quality during phone calls, and (6) exaggerated or illogical statements during phone calls (eg, stating, "I take my father with advanced dementia to the gym and we work out together"). These are not exclusion criteria but rather indicate to the research team that

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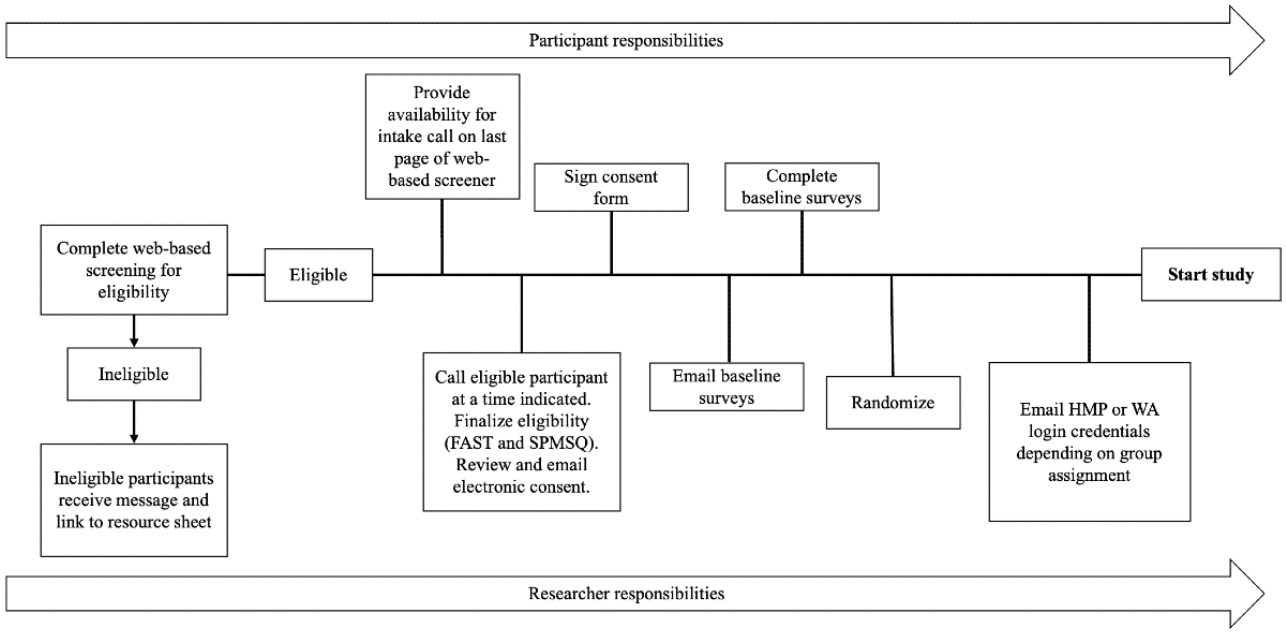
it is possible that the inquiry about the study was made by a potential imposter participant.

Our team has developed a protocol to prevent imposter participants from enrolling. First, when participants inquire about the study on public-facing platforms (eg, "Rally," a web-based platform for advertising research studies across our hospital system), we call them before sending the link to the screening survey. This has been cited in other studies as a strategy to eliminate imposter participants [51]. Second, we have used a "three-strike" system. Once a potential participant has displayed 3 red flags (described above), they are no longer considered eligible for this study. We move these participants to the "suspected imposter" section of our log and do not continue contact attempts; we have noticed that the more we engage with potential imposter participants, the more false inquiries we receive. Third, we do not provide compensation for the completion of baseline assessments; instead, our compensation is divided up between posttest and follow-up, which discourages imposter participants who might enroll for the baseline compensation and then drop out. So far, we have identified 44 suspected imposter participants (approximately 36%) out of the 123 inquiries we have received. We acknowledge that these procedures have the potential to exclude eligible participants (ie, false negatives); however, as a team, we agreed to prioritize the integrity of the data for this small-scale feasibility RCT.

Enrollment

If participants are deemed eligible during the enrollment call, the RA reviews the consent form, answers any questions, and assists the participant with signing the consent form by electronic consent on REDCap. Once the consent form has been signed, the RA emails baseline surveys to the participant through REDCap. Study staff randomize the participants after baseline completion. Our senior biostatistician programmed randomization into REDCap and stratified by gender (given that caregivers tend to be women) [1]. The RA emails the participant instructions to download and login to their assigned app (HMP or WA). To protect participant confidentiality, the study team creates accounts with study-specific login email addresses (eg, mghstridestudy+1@gmail.com and mghstridestudy+2@gmail.com) so there are no personal identifiers (eg, email, name, and date of birth) associated with participants' accounts. The spreadsheet containing login information and the corresponding participant's information is stored in a secure, password-protected database. After receiving instructions and login information, participants have the option of scheduling a phone call or Zoom (Zoom Video Communications) meeting with the RA to assist with setting up their app. Figure 2 summarizes the recruitment and enrollment procedures.

Figure 2. Recruitment and enrollment procedures. FAST: Functional Assessment Staging Tool; HMP: Healthy Minds Program; SPMSQ: Short Portable Mental Status Questionnaire; WA: Wellness App.



Treatment Conditions

Participants in both treatment conditions (HMP or WA) listen to prescribed guided listening on a mobile app for at least ten minutes per day (70 minutes per week) for 12 weeks. Participants download their assigned app through the Google Play (Google LLC) or Apple App (Apple Inc) Store, and participants are blinded to the condition (ie, intervention or control). Participants can complete their daily listening at any time of day. Both apps suggest a specific ordering of the audio clips, but participants can choose to listen to any audio content within the app based on their preferences—the only requirement is that they listen for at least 10 minutes per day. Participants are encouraged to turn on "push notifications" to remind them to do their daily listening, but this is not mandatory. Both apps allow participants to view their daily listening history and mark which content has already been listened to.

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Healthy Minds Program

Full details on the HMP app can be found on the web at Healthy Minds Innovations [52]. In summary, HMP is a self-guided meditation app that includes training in mindfulness through the 4 "pillars" of mental training: awareness, insight, connection, and purpose. Guided listening in each pillar trains listeners to be more focused and self-aware in the present moment (awareness), develop skills to strengthen compassionate connection with others (connection), learn about how a person's thoughts affect their emotions (insight), and stay more grounded in one's values and principles (purpose) [41,52]. Each pillar contains guided listening consisting of brief lessons labeled "learn" and meditations labeled "practice." Participants are asked to complete at least 10 minutes of "practice" each day (meditations can be set for 5, 10, 15, 20, or 30 minutes) and are encouraged to listen to the "learn" content in conjunction with their practices. Participants have the choice to make any meditation "sitting" or "active" and can also select the speaker of each meditation, allowing for racial, ethnic, and gender diversity of the speaker. Our multidisciplinary team tailored the HMP app text that introduces and describes the mindfulness exercises to include language, case-based scenarios, and stressors that are common among caregivers of persons with ADRD (eg, gratitude for positive aspects of caregiving).

Wellness App

WA is an investigator-developed time- and dose-matched control that offers daily caregiver-related guided listening consisting of knowledge-based podcasts for the 12-week intervention. If podcasts are longer than 10 minutes, caregivers are instructed to spread the listening out over multiple days to ensure that they are only listening for 10 minutes per day. All podcasts were individually selected by the study team to ensure that their content was relevant for caregivers of persons with ADRD. Examples of topics include "money and the unique needs of the older caregiver" and "how dementia affects sleep cycles." Study staff also listened to ensure that no skills related to mindfulness or meditation were taught in any podcast to remove potential confounds. On the basis of feedback from 13 WA participants, we reviewed participant ratings of podcast quality and updated content to best meet the needs of participants in the control. For example, we replaced "overly negative" or "boring" content with more uplifting stories or engaging podcasts. The app has successfully been used as a control in multiple previous studies testing app-based meditation interventions [53,54].

Strategies for Adherence

Regardless of group, participants are sent a text message each Monday of the intervention reminding them to listen to their daily content for at least ten minutes per day (ie, 70 minutes per week). This text message also includes a brief weekly survey with process measures (Textbox 1). Study staff members download and review participants' listening data each Thursday. If a participant does not listen to at least 75% of their recommended listening in the past week (ie, <52.5 total minutes), a study staff member texts the participant a visual (ie, a "meme") reminder catered toward their treatment condition (Multimedia Appendix 1). If participants do not consent to "meme" reminders, they receive a text message catered to their treatment condition instead (Multimedia Appendix 2). Participants who do not consent to receive text messages receive all reminders and surveys through email. If a participant does not listen to at least 75% of their recommended listening for 2 consecutive weeks, a study staff member calls this participant to troubleshoot potential barriers to adherence. Participants are also offered a monetary incentive for participating in the study (ie, US $20 for completing their posttest assessment and US $30 for completing their follow-up assessment, for a total of US $50).

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Textbox 1. Secondary outcomes.

Demographics (pretest)

- Age; gender; biological sex; sexual orientation; race; ethnicity; educational level; employment status; occupation; income; marital status; housing situation; languages spoken; health insurance status; zip code; importance of religion or faith; mental health history; current psychotropic and pain medication intake; overall physical health status; number of individuals to provide informal caregiving to; patient's diagnoses; relationship to patient; duration of caregiving; number of hours of caregiving per week; and whether caregiver is living with patient

Outcome measures (pretest, posttest, and follow-up)

- Perceived Stress Scale-10 [55,56]: assesses perceived stress using a 5-point Likert scale
- Hospital Anxiety and Depression Scale [57]: 14-item measure to assess symptoms of emotional distress (anxiety and depression)
- Patient-Reported Outcomes Measurement Information Systems (PROMIS) Sleep Disturbance Short Form [58]: 8 items assessing sleep
- Applied Mindfulness Process Scale [59]: assesses mindfulness in 3 domains: decentering, positive emotion regulation, and negative emotion regulation
- Caregiver Reaction Scale [60]: assesses caregiver burden. We are administering the following subscales: role entrapment (4 items); role overload (4 items); mastery as a caregiver (4 items); self-mastery (4 items); workplace productivity (5 items)
- Healthy Minds Index [61]: a 17-item measure based on the Healthy Minds Program framework that assesses awareness, connection, insight, and purpose

Process measures (weekly)

- Emotional Distress Thermometer: scale (0-10) to assess how caregivers rate their level of distress each week: "During the past week, how would you rate your emotional distress on a scale from 0 to 10? (0=not at all; 10=extremely emotionally distressed)"
- Sleep Thermometer: scale (0-10) to assess how caregivers rate their quality of sleep: "During the past week, how would you rate your quality of sleep on a scale from 0 to 10? (0=extremely low quality; 10=extremely high quality)"
- Mindfulness Thermometer: scale (0-10) to assess how caregivers rate their level of mindfulness each week: "During the past week, how would you rate your mindfulness on a scale from 0 to 10? (0=not at all; 10=extremely mindful)"
- Stress Thermometer: scale (0-10) to assess how caregivers rate their level of stress each week: "During the past week, how would you rate your stress on a scale from 0 to 10? (0=not at all; 10=extremely stressed)"

Other measures (post)

- Modified Patient Global Impression of Change [62]: a 1-item questionnaire to assess the extent to which caregivers perceive the intervention's improved functioning and symptoms: "Do you think your ability to manage stress associated with caring for your loved one with dementia is now improved, about the same, or worse, as compared to before your participation in this program?"
- Perceptions of daily meditations and podcast: we will assess caregivers' perceptions of their app prescription by asking, "Do you think that the amount of prescribed app content was: too little, just enough, too much?"
- Perceptions of emails and text reminders: we will assess caregivers' perceptions of email and text message reminders by asking, "Do you think that the amount of emails/texts you received was: too little, just enough, too much?"
- Perceptions of the overall study: we will assess caregivers' perceptions of the study by asking, "Do you have any feedback about your experience in this program (content of the program, content of the text message reminders, etc) that you would like to share?"
- Perceptions of prompts and contacts in low adherence situations: We will assess caregivers' perceptions of the number of prompts and contact in situations where they were not adhering to their practice by asking, "Do you think that the amount of prompts you received when you struggled with your practice was: too little, just enough, too much?"

Feasibility Markers

Table 2 outlines the a priori set benchmarks and criteria that are consistent with guidelines for early feasibility studies [63]. We will assess the feasibility (acceptability and demand markers) of both mobile app treatment conditions and participants' perceptions of their involvement in the study.

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Table 2. Primary outcomes.

Benchmarks and markers	Description	Criteria
Acceptability benchmarks		
Feasibility of recruitment	We will assess the number of caregivers enrolled from the number of caregivers who were eligible	80 caregivers will be recruited in 6 months; ≥70% of eligible caregivers will enroll
Treatment satisfaction	We will use the Client Satisfaction Questionnaire [64] to assess caregivers' satisfaction with the intervention	At least 70% of caregivers will have scores on the Client Satisfaction Scale over and above the midpoint in both the HMP[a] and WA[b] groups
Credibility and expectancy	We will use the Credibility and Expectancy Questionnaire [65] to assess caregivers' perceptions that the treatment will work after learning about the study.	At least 70% of caregivers will have scores on the Credibility and Expectancy Scale above the midpoint in both the HMP and WA groups.
Demand benchmarks		
Adherence to treatment	We will assess data from the HMP app and the WA to measure adherence to the intervention and the control conditions	≥70% of caregivers will complete ≥75% of weekly prescribed minutes
Dropout	We will assess the number of caregivers who complete the study from the number of caregivers who started the study	>70% of caregivers who start the study will complete posttest assessments; ≤30% attrition
Data collection benchmarks		
Feasibility of weekly REDCap[c] measures	We will assess the feasibility of the weekly REDCap measures sent to patients	≥70% caregivers will answer ≥75% of weekly REDCap measures
Feasibility of quantitative measures	We will assess the feasibility of the quantitative measures sent to caregivers at baseline, postintervention, and follow-up	No questionnaires fully missing in ≥25% caregivers

[a]HMP: Healthy Minds Program.

[b]WA: Wellness App.

[c]REDCap: Research Electronic Data Capture

Quantitative Assessments

The self-report measures and assessment domains were selected consistent with the purpose of the study [66]. Demographics are measured pretest, outcome measures are given during the main assessment points (pretest, posttest, and follow-up), and process measures are administered weekly. Textbox 1 provides a brief description of all self-reported assessments.

Data Analysis

We will assess the acceptability and demand of the intervention in line with Bowen and colleagues' standards for feasibility studies and components of the Behavioral Change Consortium's Treatment Fidelity model [63,67]. Specifically, we will assess the acceptability, credibility, satisfaction, and perceived appropriateness and usefulness of the daily prescribed app content. Benchmarks and measurements for each feasibility construct are listed in Table 2. One-sided 95% CI will be calculated for each proportion to evaluate feasibility benchmarks. Depending on the nature of the estimate or comparison, exact binomial tests, Fisher exact tests, 2-tailed *t* tests, or correlations may be used to summarize the data and test for statistical significance. HMP and WA user data (ie, what content users listened to, when, and for how long) are collected automatically from users.

Consistent with guidelines for early feasibility studies, our analysis will not assess efficacy, as we are not powered to do so [68]. However, we will estimate between-group differences in changes from baseline to posttest (12 weeks) to follow-up (20 weeks) as proof of concept that the intervention shows promise with the intended population [63]. Variance components and effect sizes will be estimated for each outcome. We will use variance estimates from repeated-measures analysis of data on Perceived Stress Scale-10 to guide the design and power calculations for a future trial testing efficacy [69,70]. We will compute the effect sizes of change in these scores to cautiously guide future work. Proof of concept will be demonstrated if the decrease in caregiver stress (Perceived Stress Scale-10, the primary outcome in future trials) in the intervention group from baseline to posttest is greater than in the WA group, with at least small to moderate effect sizes favoring HMP (between-group test of superiority).

Results

The trial is ongoing. As of June 2023, we had enrolled 27 caregivers (14 HMP and 13 WA). We aim to recruit 80 caregivers in total. Table 3 details the select demographics of enrolled participants.

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Table 3. Demographics for enrolled participants.

Variable	Participants, n (%)
Gender	
Women	24 (89)
Men	3 (11)
Sexual orientation	
Heterosexual	26 (96)
Lesbian	1 (4)
Race	
White	24 (89)
Black or African American	2 (7)
More than 1 race	1 (4)
Ethnicity	
Not Hispanic or Latino or Latina	27 (100)
Income (US $)	
Chose not to answer	4 (15)
15,000-29,000	3 (11)
30,000-49,000	2 (7)
50,000-69,000	1 (4)
70,000-99,000	9 (33)
>100,000	8 (30)
Relationship to care recipient	
Adult child (caring for parent)	12 (44)
Spouse	11 (41)
Friend or nonkin	2 (7)
Sibling	1 (4)
Other	1 (4)

Discussion

Scientific Contribution

The intervention at present is catered to caregivers' interest in using mobile apps for stress management and health information [35] including learning mindfulness meditation for stress management [36-39]. This modality addresses barriers to caregiver participation (eg, in-person, synchronous format, time commitment, and cost) for a more feasible, scalable, and cost-effective intervention to reduce stress among this high-need population. The HMP app adapted for caregivers of persons with ADRD seeks to address this clinical gap by testing a no-cost mobile app to reduce stress, emotional distress, and sleep difficulties [40]. This protocol describes an entirely remote, single-blind feasibility, proof-of-concept RCT of HMP versus a time- and dose-matched educational control (WA) in stressed caregivers of persons with ADRD. Our protocol also introduces novel strategies for addressing concerns in mobile app–based RCTs with caregivers, including a protocol for managing "imposter" participants and using "memes" for promoting adherence and engagement.

Limitations

There are important limitations to note. First, our initial recruitment efforts have yielded limited diversity in terms of enrolling caregivers from racial and ethnic minoritized (89% White, 100% non-Hispanic) as well as sexual and gender minoritized backgrounds (96% heterosexual, 100% cisgender). We are now modifying recruitment efforts to attempt to recruit a more representative sample (eg, sharing recruitment flyers with community organizations that serve minoritized older adults and caregivers, and developing Instagram advertisements that target geographically diverse populations). Second, we are delivering this program to English-speaking caregivers only. In the future, we hope to offer HMP in different languages. Third, the fully remote nature of the study increases the likelihood of enrolling imposter participants that are not truly caregivers of persons with ADRD but rather seek to participate for financial benefits; see the Methods section for a detailed plan of how we are addressing this issue. Lastly, it is possible that participants may be unblinded if they carry out web searches about our research.

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Conclusions

In summary, we are currently testing the feasibility and proof of concept of HMP versus a time- and dose-matched health education control (WA). Between February and June 2023, we had 27 caregivers enrolled, and we aim to recruit 80 caregivers in total. At the conclusion of this trial, we will examine whether HMP and WA meet feasibility (acceptability and demand) benchmarks, as well as if HMP demonstrates proof of concept in improving stress, emotional distress, sleep, and mindfulness above WA in stressed caregivers of persons with ADRD. Our findings will inform a future, fully powered RCT of HMP versus WA. This work has the potential to pave the way for feasible, scalable, and cost-effective interventions for caregivers of persons with ADRD.

Acknowledgments

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Data Availability

The data sets generated during this study are not publicly available due to the ongoing nature of the trial but will be available from the corresponding author on reasonable request upon conclusion of the study.

Conflicts of Interest

RGT is the senior director of measures and research at Healthy Minds Innovations.

Multimedia Appendix 1
Visual (ie, “meme”) reminders for low-adherence situations.
[DOCX File , 1219 KB - resprot_v12i1e50108_app1.docx]

Multimedia Appendix 2
Engaging text message reminders for low-adherence situations.
[DOCX File , 16 KB - resprot_v12i1e50108_app2.docx]

Multimedia Appendix 3
Peer-review reports from Clinical Management in General Care Settings Study Section, Healthcare Delivery and Methodologies Integrated Review Group, Center for Scientific Review, CMGC, NIH (USA).
[PDF File (Adobe PDF File), 145 KB - resprot_v12i1e50108_app3.pdf]

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Abbreviations

ADRD: Alzheimer disease and related dementias
FAST: Functional Assessment Staging Tool
HMP: Healthy Minds Program
MBI: mindfulness-based intervention
NIH: National Institutes of Health
RA: research assistant
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
SPMSQ: Short Portable Mental Status Questionnaire
WA: Wellness App

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Protocol

Objectively Quantifying Pediatric Psychiatric Severity Using Artificial Intelligence, Voice Recognition Technology, and Universal Emotions: Pilot Study for Artificial Intelligence-Enabled Innovation to Address Youth Mental Health Crisis

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Abstract

Background: Providing Psychotherapy, particularly for youth, is a pressing challenge in the health care system. Traditional methods are resource-intensive, and there is a need for objective benchmarks to guide therapeutic interventions. Automated emotion detection from speech, using artificial intelligence, presents an emerging approach to address these challenges. Speech can carry vital information about emotional states, which can be used to improve mental health care services, especially when the person is suffering.

Objective: This study aims to develop and evaluate automated methods for detecting the intensity of emotions (anger, fear, sadness, and happiness) in audio recordings of patients' speech. We also demonstrate the viability of deploying the models. Our model was validated in a previous publication by Alemu et al with limited voice samples. This follow-up study used significantly more voice samples to validate the previous model.

Methods: We used audio recordings of patients, specifically children with high adverse childhood experience (ACE) scores; the average ACE score was 5 or higher, at the highest risk for chronic disease and social or emotional problems; only 1 in 6 have a score of 4 or above. The patients' structured voice sample was collected by reading a fixed script. In total, 4 highly trained therapists classified audio segments based on a scoring process of 4 emotions and their intensity levels for each of the 4 different emotions. We experimented with various preprocessing methods, including denoising, voice-activity detection, and diarization. Additionally, we explored various model architectures, including convolutional neural networks (CNNs) and transformers. We trained emotion-specific transformer-based models and a generalized CNN-based model to predict emotion intensities.

Results: The emotion-specific transformer-based model achieved a test-set precision and recall of 86% and 79%, respectively, for binary emotional intensity classification (high or low). In contrast, the CNN-based model, generalized to predict the intensity of 4 different emotions, achieved test-set precision and recall of 83% for each.

Conclusions: Automated emotion detection from patients' speech using artificial intelligence models is found to be feasible, leading to a high level of accuracy. The transformer-based model exhibited better performance in emotion-specific detection, while the CNN-based model showed promise in generalized emotion detection. These models can serve as valuable decision-support tools for pediatricians and mental health providers to triage youth to appropriate levels of mental health care services.

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KEYWORDS

pediatric; trauma; voice AI; machine learning; mental health; predictive modeling; artificial intelligence; social determinants of health; speech-recognition; adverse childhood experiences; trauma and emotional distress; voice marker; speech biomarker; pediatrics; at-risk youth

Introduction

Background

The mental health care delivery system of care for youth is in crisis. The suicide rate for youths aged 10 to 24 years increased by 62% between 2007 and 2021 [1]. There is a shortage of trained mental health professionals, especially in low- and middle-income countries and communities, having less than one mental health professional per 10,000 people [2]. Training professionals and therapists require comprehensive effort to develop the appropriate levels of clinical skills equal to the trauma-based severe mental health issues in these communities. Conventional training methods, which typically involve long durations of apprenticeship and supervision, are often resource-intensive. The current system struggles to meet the growing demand for mental health services, especially for pediatric patients and youths [3]. Furthermore, evaluating the effectiveness of therapy remains challenging, as mental health conditions are often complex and multifaceted, and current evaluation methods primarily rely on subjective assessments [4].

The use of artificial intelligence (AI) in emotion detection from audio recordings is an emerging approach to address these challenges. Studies have shown that speech carries rich information beyond words, including vital emotional cues and biomarkers associated with mental health conditions [5]. This helps in measuring the effectiveness of therapy and identifying patients in high-risk environments, thus enabling timely interventions. Such quantifying emotions also aids in the optimal allocation of resources by preventing unnecessary treatments [6].

In this paper, we present the development of a deep learning model that classifies emotions using a 15- to 90-second voice sample collected as part of a counseling session. Our study focuses on audio recordings of children with significant psychiatric symptoms partly related to high adverse childhood experience (ACE) scores reading a fixed script. In total, 4 highly trained therapists classified audio segments based on 1 of the 4 emotion intensity levels (none, low, medium, and high) for each of the 4 emotions (anger, fear, happiness, and sadness). The paper reports the development and training of the machine learning (ML) models and discusses the implications of our findings for the broader landscape of mental health care.

As surveyed by Koolagudi and Rao [7], speech emotion recognition (SER) is a prevalent area of research with numerous classification models, feature extractors, and publicly available data sets. However, there are many limitations in the current body of research. Many corpus of speech data are focused on recognizing actor-simulated speech emotion, which contains much higher emotional intensities than what is found in ordinary speech. Additionally, many research results are based on data sets with a limited number of speakers. For example, the IEMOCAP data set [8] is frequently used in literature for SER tasks. However, it comprises actor-simulated emotional utterances from only 10 different speakers. It is also noteworthy that classification of the intensity of emotion found in speech is much more limited. The RAVDESS data set is one of a few publicly available data sets containing actor-simulated audio recordings labeled with emotion intensity (either low or high) [9]. The data sets found in the literature are also very short in duration. The audio clips in IEMOCAP and RAVDESS are both segmented at the utterance level, such that one audio clip only contains a handful of spoken words and is usually only 1-2 seconds in duration.

Numerous model architectures have been used for SER tasks. Zhang et al [10] developed a fully convolutional network (FCN) to classify the emotion type from audio recordings in the IEMOCAP data set [8]. They used an Alexnet-based [11] convolutional neural network (CNN) for feature extraction and a soft-attention–based classifier, resulting in a class-weighted accuracy of around 68%. This approach was appealing to us due to its insensitivity to input length the FCN is able to handle inputs of different sizes without the need to crop or divide inputs into multiple segments.

Participants

Participants were recruited from 3 mental health care centers that focused primarily on children and adolescents from low-income communities. The participants receive mental health services paid for by Medicaid, the Children's Health Institute Program, and the Department of Children and Family Services. The participants are children aged 5-18 years and those referred for behavioral health services through schools, DJJ, and child protective agencies.

Methods

Data Exploration and Processing

The data set used for this project was gathered as part of the National Science Foundation Small Business Innovation Research Phase I and Phase II study. It encompassed 1055 audio recordings obtained during therapy sessions with children who are receiving mental health services and who have been diagnosed with at least 1 DSM (Diagnostic and Statistical Manual of Mental Disorders) condition. The recordings focused on the children reading scripted passages, though the textual content itself was not a central aspect of the project. Each audio recording was meticulously annotated with an emotional

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intensity level (none, low, medium, or high) for 4 emotions, namely anger, fear, sadness, and happiness. To ensure robustness, 4 different labelers were involved in this annotation process for each recording, and the attribution of each labeler was recorded.

Throughout the exploratory phase, several noteworthy observations were made regarding the data. One key finding was that meaningful disagreements among the labelers were evident due to multiple labelers providing annotations for most recordings. Additionally, the recordings exhibited a degree of noise, with varying background noise levels, the occasional presence of multiple speakers (such as the therapist themselves), and instances where the speaker sounded distant from the recording device. Moreover, the duration of the recordings varied significantly, ranging from as short as 2 seconds to over 6 minutes. Though the majority fell within the 30-90 seconds range, this presented a notable difference compared to typical data sets found in the existing literature.

A contributing factor to these challenges can be attributed to the data collection process, which took place in the natural environments of the patients, such as their schools or homes. While this approach offers valuable insights, it also introduced certain complexities that needed to be addressed during data processing and analysis.

Data Preprocessing

Label Disagreement

Various methodologies were used to address the discrepancies among labelers in handling emotion intensities. First, we transitioned from a 4-class classification to a binary classification, distinguishing between low and high emotion intensities. To achieve this, we combined the categories “none” and “low” to represent the binary class 0, and similarly, we grouped “medium” and “high” for the binary class. Additionally, we trained 2 distinct types of models: one where the mode predictions across the 4 labelers served as the “ground truth,” and another where we developed individual models for each labeler. This approach allowed us to explore different perspectives and optimize model performance.

Denoising

As stated earlier, some of the voice samples were noisy despite the therapist’s effort to manage the background noise. Although some of the models used have noise resistance capabilities, it was often not sufficient for the models to achieve good results. Therefore, data set denoising had to be carried out. In recent years, neural network denoising has become the state-of-the-art approach to solving speech denoising. Therefore, one of the latest works [3] from Facebook was applied. It uses Demucs architecture, which was originally developed for the task of music source separation [12].

Voice Activity Detection

The data set’s recordings include extended periods of silence and background noise with no speech. When training models, especially those with attention layers, using extensive portions of audio from silent regions leads to less effective results, and the training process takes longer. This issue is partly influenced by participants experiencing severe symptoms of depression or anxiety, requiring substantial support to finish the reading tasks.

To address this, we conducted an experiment where we applied a voice activity detection (VAD) algorithm to identify and remove sections of the audio files where no active speaker was present. For this purpose, we used Silero models to extract these voice fragments [13].

Diarization

Another issue with the data set is the presence of various voices besides those of children, such as therapists asking questions, among others. The inclusion of these additional voices can lead the model to focus on irrelevant parts of the input data, resulting in poorer performance. To address this problem, we conducted experiments involving a diarization algorithm to process the data, retaining only the segments with children’s voices. Diarization models, however, cannot definitively identify child speakers. Nevertheless, in recordings where strangers speak, children’s voices generally dominate in terms of time, making it possible to distinguish and isolate them. It is important to mention that certain recordings experienced high levels of noise, leading to instances where the diarization algorithm detected 3 or more speakers, particularly in shorter audio recordings. Consequently, we decided to filter out such instances from our data set.

Modeling

Fully Convolutional Networks

In recent years, FCNs have emerged as a favored method for speech-emotion recognition due to their modest parameter count and ability to handle variable-length inputs. In this study, we developed FCN models based on the work of [10].

To begin, we computed the Mel spectrogram, which captures both frequency and intensity variations in the audio clip over time, representing it as a single image per recording. The advantage of using FCNs is that they can directly process these variable-length images without the need for resizing or cropping. Longer audio clips produce larger spectrograms, but the FCN efficiently handles them.

Subsequently, the image was fed through a CNN to extract meaningful features from the spectrogram, facilitating emotion intensity classification. Like how individual consonant and vowel sounds can be discerned from inspecting the spectrogram, we posit that comparable features exist for emotion intensity identification.

Finally, the outputs of the CNN are passed through one or more parallel output blocks, each comprising a 1×1 convolution step followed by a global-average pooling layer. This step reduces the dimensionality to the number of emotion intensity classes, independent of the input size. Consequently, classification is achieved without the need for dense layers with fixed dimensions.

We performed fine-tuning on 2 pretrained CNN backbones: Alexnet [11] and Googlenet [14]. Both these architectures are well-known CNNs that were pretrained on ImageNet and have been widely used for various image classification tasks [15,16].

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We chose Alexnet for its compact size and previous success in similar speech-emotion recognition tasks in the literature. On the other hand, Googlenet was selected for its use of "inception blocks," which we believed might offer advantages with its convolutional filters of different sizes. To adapt these pretrained networks, we worked with their Pytorch implementations.

Our experimentation explored 2 output layer structures: "single-head" and "multi-head." The models with a single output block enabled the prediction of emotion intensity for one specific emotion, while the multi-head model consisted of 4 separate output blocks, one for each emotion. Although a multi-head model would be more convenient, we aimed to investigate whether there were any performance differences in learning features for classifying a single emotion compared to learning features that could classify all 4 emotions simultaneously.

Speechbrain

All models described earlier require a Mel spectrogram as an input. However, this speech representation has disadvantages, such as loss of information, complexity, etc. It also requires additional model capacity to be trained to extract useful information for each specific task. That is why, in recent times, self-supervised models for speech processing have gained a lot of attention. As can be deduced by its name, these models are trained in a self-supervised fashion like popular Natural Language Processing models such as BERT. The most popular ones are Hubert [17] and Wav2Vec 2.0 [18]. Both models have convolution layers in the beginning and Transformer layers after the convolution layers. The high-level pipeline is similar: the model accepts raw input audio and is trained to predict the cluster number for each audio chunk.

There are, however, some cluster refinement differences between the models. This enables them to extract phoneme-like structures in audio data and helps to extract more useful information, especially for speech-processing tasks. It is important to note that the model has some denoising capabilities by design, as this pipeline resembles the one used to train Automatic speech recognition models. The major difference is that instead of phonemes, we have cluster numbers. These types of models are implemented in a framework called Speech-the brain. In this work, we used architecture Wav2Vec 2.0. To apply this model to our task, its' architecture needed to be slightly modified and fine-tuned. We added a final head as a multilayer perceptron layer after the transformer modules. The model was trained in the usual classification problem manner with MSE loss. The gradient was backpropagated to all Wav2Vec2.0 layers. Each model was trained for 30 epochs. The multilayer perceptron layer has 2 outputs, and the model is trained to differentiate whether an emotion appears in the input or not. The setup with classifying all emotions at once was also attempted but gave poor results compared to a binary classifier.

Ethical Considerations

The study received ethical board approval (protocol #21-TQIN-101) for a multisite pilot involving children and adolescents. We will receive written and informed consent from participants. The activities for patients enrolled in the study include data collected using multiple surveys and a voice sample. The surveys include structured and unstructured voice samples based on a reading selected by the research team. The ethical board approves all the study contents.

Data Collection

ThinkQuality, TQI's Phone App, was used to collect voice samples from youth receiving mental health and family preservation services at the point of care. The data collection process includes concurrently administering a scientifically validated survey. The patient's emotional disorder severity is confirmed based on the scores of the Symptoms and Functioning Severity Scale (SFSS), ACE, and Patient Health Questionnaire-9 (PHQ-9), the patient's diagnosis, and other clinical information from the patient's treatment history. For every voice sample collected, the pilot has a diagnosis or multiple, current procedural terminology code, and the therapist's clinical input. These data serve to categorize voice sample data into distinct categories and train voice-based ML algorithms to distinguish children in need and at high risk. The innovation is focused on families with low socioeconomic status, in which ACEs are common.

Data are collected by therapists (n=35). An Android mobile app collects speech samples, SFSS, PHQ-9, and ACE scale responses. Each therapist receives a 3 to 5-hour in-person training about app installation and access, data (SFSS, voice sample) collection using the app, compliance and parameters, the process of the reward program, communication, and real-time technical support. Data are collected from patients during mental health or other family-based intervention visits weekly or biweekly, based on the intensity of the psychiatric symptoms. Visits occur in a suitable (private) location at home (including foster and group homes) or school as part of a state's commitment to reduce barriers to services and easily access services. Data are collected partially web-based during the service shift secondary to the COVID-19 pandemic.

To elicit speech for recording and analysis, patients are asked to choose from a subset of readings. Patients' reading is recorded for up to 90 seconds—a clock feature in the app signals when the time is up. In general, if the child's reading label is like the grade, the reading could be completed in less than 50 seconds. Voice samples are stored in a separate deidentified database, allowing 3 to 4 psychologists to label the voice sample independently. SFSS, PHQ-9, and ACE responses are collected using the same app. The app scores the surveys immediately and makes the results available to the therapist to share with their patients if it is clinically appropriate; real-time data availability is intended to close the gap in transparency, accountability, and family engagement.

Results

Overview

The primary goal of this research was to investigate diverse data preprocessing and modeling approaches in order to identify fruitful opportunities. As a result, significant dedication was put into testing various combinations within our suggested methodology to discover promising options. To facilitate this process, we extensively used the experiment tracking platform

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called Biases. It enabled us to store training results and test metrics, and save potential model candidates for future deployment on the web app. While most models underwent 10 epochs of training with a learning rate of 5e-5, a few were terminated earlier due to the validation loss plateauing without any additional performance gains.

Evaluation Metrics

The evaluation process for the FCN models involved computing metrics using a 15% hold-out test set. Conversely, for the speech brain-based models, metrics were computed using a 10% hold-out test set. Since the task at hand was a binary classification problem, we used precision and recall as our evaluation metrics. The primary objective was to identify a model capable of accurately detecting high intensity of emotion within audio files while keeping false positives to a minimum.

Denoising

First, the denoising effects were evaluated by initially applying a pretrained denoiser model to the unmodified source audio files as a preprocessing step. Subsequently, 3 pairs of models were trained, each corresponding to 1 of 3 emotions (anger, fear, and sadness). Each pair included 1 model trained on the original audio files and another model trained on the audio files with the denoiser applied.

To maintain consistency, only the labels from a single labeler (Labeler 1) were used, given their extensive number of labeled samples. Additionally, a similar pair was trained using the model with all 4 emotion heads. The results of these experiments can be found in Table 1.

The outcomes revealed that denoising alone led to a slight improvement in the Anger emotion, but resulted in a marginal or more significant performance decrease for the FCN model in the other emotions. Moreover, the FCN model equipped with 4 output heads exhibited worse performance when denoising was added.

Table 1. Fully convolutional network model results with and without denoiser for audio samples labeled by Labeler 1.

Emotion and denoise	Precision	Recall
Anger		
No	0.612	0.513
Yes	0.656	0.667
Fear		
No	0.741	0.769
Yes	0.717	0.756
Sadness		
No	0.801	0.801
Yes	0.667	0.737
All 4		
No	0.833	0.833
Yes	0.806	0.801

VAD

The impact of VAD on the results was analyzed through a series of experiments. Initially, the unmodified source audio files underwent preprocessing with a pretrained VAD model. In total, 3 sets of emotion-specific models were then trained, both with and without the application of VAD. Additionally, a model with all 4 emotion heads was trained using VAD. The outcomes are presented in Table 2. It was observed that applying VAD led to negligible or marginal enhancements in the single-emotion FCN models' performance while causing a decline in the performance of the 4-emotion FCN model.

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Table 2. Fully convolutional network model results with and without VAD[a] for audio samples labeled by Labeler 1.

Emotion and VAD	Precision	Recall
Anger		
No	0.612	0.513
Yes	0.627	0.609
Fear		
No	0.741	0.769
Yes	0.729	0.763
Sadness		
No	0.801	0.801
Yes	0.808	0.808
All 4		
No	0.833	0.833
Yes	0.814	0.793

[a]VAD: voice activity detection.

Denoising+VAD

The effects of preprocessing with both the denoiser and VAD were similarly compared. In this case, the unmodified source audio files first had the denoiser applied, followed by VAD. Then, the same 3 pairs of models, one per emotion, were trained, as well as the pair using all 4 emotion heads. The results are shown in Table 3.

The effects of preprocessing with the denoiser and VAD were also compared against a baseline using only VAD (rather than a baseline without any preprocessing). This set of models was trained using the speech brain-based model. The results are shown in Table 4. As we can see, in some cases, denoising boosts the quality, but in some cases, it decreases quality. In cases where quality decreased, the primary cause was extremely noisy data, and the denoiser overcompensated.

Table 3. Fully convolutional network model results with and without both denoiser and VAD[a] combined for audio samples labeled by Labeler 1.

Emotion and denoise+VAD	Precision	Recall
Anger		
No	0.612	0.513
Yes	0.651	0.550
Fear		
No	0.741	0.769
Yes	0.761	0.776
Sadness		
No	0.801	0.801
Yes	0.711	0.756
All 4		
No	0.833	0.833
Yes	0.803	0.792

[a]VAD: voice activity detection.

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Table 4. Speechbrain model results with and without denoiser for audio samples with voice activity detection applied and labeled by Labeler 1.

Emotion and denoise	Precision	Recall
Anger		
No	0.777	0.734
Yes	0.783	0.765
Fear		
No	0.811	0.82
Yes	0.812	0.845
Sadness		
No	0.781	0.81
Yes	0.863	0.794

Denoising+VAD+Diarization

Experiments with diarization were also conducted. It can be observed that for a particular labeler, a slight decrease in performance occurred, which indicates overwork. The results are shown in Table S5 in Multimedia Appendix 1.

Alexnet Versus Googlenet

Another comparison we were interested in is how different CNN architectures performed on this data set. Alexnet and Googlenet are both powerful backbones used in similar image recognition tasks. To compare the two, we trained 2 models—1 pair with only a single prediction head (for the fear emotion) while the other pair had 4 prediction heads, 1 for each emotion. These models were trained without any preprocessing steps applied to the audio files. Unfortunately, not many experiments could be run on this combination due to the long training time required for Googlenet (10-15 times slower than Alexnet). Overall, Googlenet performed worse in both cases than Alexnet. Part of this could be attributed to a much trickier training process for Googlenet—it was difficult to dial the learning rate to prevent the model from over-fitting after only 1-2 epochs. The results are shown in Table S6 in Multimedia Appendix 2.

Single- and Multi-Head Models

In our study, we conducted a comparison between models equipped with single and multiple output heads. To achieve this, we trained a model using 4 output heads to predict emotion intensity for 4 emotions. This training used data from a single labeler. Subsequently, we used the same labeled data to train 4 separate models, each with only 1 output head dedicated to predicting a specific emotion. Both Labeler 1 and Labeler 3 data sets were used for this purpose.

Although direct comparison of the results proved challenging, they provided valuable insights. The model with multiple output heads demonstrated reasonable performance and merits further exploration. It is possible that optimizing the model with multiple emotion heads simultaneously may lead to intermediate features that are more generalized, enhancing the prediction of various emotions. For detailed results, please refer to Table S7 in Multimedia Appendix 3.

One Model per Emotion

In the preceding sections, the focus was solely on models trained with data from individual speakers. However, it is more practical to use 1 model per emotion during the inference process. To explore this approach, several experiments were conducted, and the outcomes are presented in Table S8 in Multimedia Appendix 4. For these experiments, all 3 preprocessing techniques (denoising, VAD, and diarization) were applied.

The results obtained from this approach were not as promising as those achieved with separate labelers, mainly due to the lack of consensus among data labelers. This was further confirmed by computing the Krippendorf coefficient for various subsets of labelers, as shown in Table S1 in Multimedia Appendix 5. The majority of combinations yielded results close to zero, indicating a significant lack of agreement among speakers. However, it is worth noting that for the emotion “sadness,” some combinations did achieve a score of 0.45, which is considered acceptable.

FCN Versus Speechbrain

It may also be useful to compare the differences in model architectures. For this experiment, models were trained on a per-labeler, per-emotion basis using both the Alexnet-based FCN model and the Speechbrain model. The preprocessing was consistent in this comparison, with both models using the data set with denoising and VAD applied. Attention-based models like Wav2vec 2.0 can determine temporal relationships, dependencies, and correlations that are not linked with a local aspect like CNN or sequential like an RNN. The wav2vec 2.0 model can capture long-term temporal dependencies from time stamp complexity. Since the audio files contain multiple emotions and are quite long, this explains why wav2vec 2.0 outperforms the FCN-based model. The results are shown in Table 5.

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Table 5. Comparing FCN[a] and Speechbrain models using data with denoiser, and voice activity detection applied.

Labeler and emotion	Precision (FCN)	Precision (Speechbrain)	Recall (FCN)	Recall (Speechbrain)
Labeler 1				
Anger	0.651	0.782	0.660	0.765
Fear	0.761	0.811	0.776	0.844
Sadness	0.711	0.862	0.756	0.794
Labeler 3				
Anger	0.670	0.818	0.690	0.823
Fear	0.715	0.811	0.671	0.785
Sadness	0.723	0.845	0.723	0.846
Labeler 2				
Anger	0.934	0.832	0.966	0.832
Fear	0.677	0.853	0.685	0.853
Sadness	0.684	0.885	0.685	0.882
Labeler 4				
Anger	0.742	0.837	0.739	0.842
Fear	0.658	0.781	0.640	0.755
Sadness	0.841	0.835	0.802	0.763

[a]FCN: fully convolutional network.

Discussion

Principal Findings

In this study, we developed a deep learning model to classify emotions from voice samples collected during the psychotherapy session. Audio recordings from a clinical population have been considered a critical step in leveraging AI-driven tools for mental health care. These models can serve as valuable decision-support tools for pediatricians and mental health providers to triage youth to appropriate levels of mental health care services. The ability to accurately quantify emotional states can potentially improve disparities in treatment outcomes, especially for youth from low-income communities and marginalized communities. Our model demonstrated proficiency in predicting therapists' intensity-based labels for different emotions.

There are several implications and potential applications of this proposed model. First, the ability to objectively measure emotional states could complement therapists' subjective assessments, leading to more precise and data-driven clinical decision-making in therapeutic interventions. In addition, quantifying emotions can contribute to streamlining resource allocation in mental health care, ensuring that individuals in critical need receive timely attention; the crisis in youth mental health and projected shortage of qualified mental health providers may require AI-driven solutions to effectively manage resources by focusing on the neediest.

However, the implementation of such models should regard ethical considerations and adoption. Patient privacy and data security must be ensured. Moreover, as AI can significantly augment the capabilities of professionals, it should not be introduced as a replacement for human connection, which is at the root of effective psychotherapeutic endeavors; instead, it should be used as a supporting tool that enhances therapists' abilities to make informed decisions.

Limitations

The study presents several limitations. The quality of speech data, including background noise and speech disorders, continues to affect the accuracy and reliability of the ML model. Second, the sample population may not be representative of the greater US population, limiting the generalizability of findings; participants have at least 1 DSM diagnosis. There are very limited voice samples of happiness. Finally, legal and regulatory considerations, including privacy rules and compliance with regulations, must be reviewed based on the state and jurisdictions and may limit the use of the algorithm. The latter must be considered to protect participants and ensure the lawful use of data [19].

Implication and Future Work

We discovered that many of our models, including our best one, hit some kind of predictive ceiling. We believe data quality may be the limiting factor in this case. Since the data labels apply to long audio segments, information density is relatively low. It is difficult to know whether a specific utterance in a long recording caused a labeler to label the audio anger as high or if the overall tone of the speaker throughout the recording indicated a high anger level. One valuable area for future work would be to break down the audio clips into smaller chunks, perhaps even to the sentence or utterance level. Having more granular labels would enable their data scientists to incorporate commonly used data sets found in literature as additional training samples. We have started breaking down the length of

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the audio to 15 seconds and labeling them; accordingly, we plan to publish the result of this process.

Another area of potential future work is to work on model interpretability. Tools like saliency maps are commonly used in vision problems to understand better the features extracted at intermediate model layers. Trying similar techniques to help diagnose the current model limitations would be interesting. Perhaps this could be extended to reconstructing the relevant audio segments from the salient portions of the spectrogram and see if the labelers agree with what the model picks up on.

Conclusions

The children and adolescent system of care remains volatile despite the end of the COVID-19 pandemic that precipitated the current crisis; rural and intercity locations have taken the brunt of symptom severity and lack of access. The integration of digital mental health innovations is crucial in addressing the ongoing mental health crisis; these technologies need to fit into the existing workflow of medical providers and therapists. Speech-based digital biomarkers that can be collected quickly via a user-friendly interface hold promise for identifying emotional distress and functional impairments in this population. This study is one such technology that contributes to the broader digital health transformation and paves the way for proactive and collaborative mental health care services to improve treatment outcomes and reduce disparities for individuals from low-income communities and marginalized groups.

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Data Availability

Data sharing is not applicable to this study as no data sets were generated or analyzed during this study. Preliminary work was completed using a public data set, and the data set is cited in the paper.

Conflicts of Interest

YA is the Founder and Chief Executive Officer of the National Science Foundation awardee company and the principal investigator for the National Science Foundation Small Business Innovation Research Phase I grant. The company has also received an award from the Google Black Founders Fund which partially funded this research. The company was also awarded a patent for this technology (serial number 17/550,544) a year and a half after this study.

Multimedia Appendix 1
Speechbrain model results with and without diarization for audio samples labeled by Labeler 1.
[DOCX File , 16 KB - resprot_v12i1e51912_app1.docx]

Multimedia Appendix 2
Fully convolutional network model results comparing Alexnet and Googlenet for audio samples labeled by Labeler 1.
[DOCX File , 16 KB - resprot_v12i1e51912_app2.docx]

Multimedia Appendix 3
Fully convolutional network model results comparing Single and Multiple output heads for Labeler 1 and Labeler 3.
[DOCX File , 17 KB - resprot_v12i1e51912_app3.docx]

Multimedia Appendix 4
Speechbrain model results for aggregated labels.
[DOCX File , 16 KB - resprot_v12i1e51912_app4.docx]

Multimedia Appendix 5
Krippendorf metrics for all combinations of labelers.
[DOCX File , 17 KB - resprot_v12i1e51912_app5.docx]

Multimedia Appendix 6
Peer review reports.
[PDF File (Adobe PDF File), 18 KB - resprot_v12i1e51912_app6.pdf]

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Abbreviations

ACE: adverse childhood experience
AI: artificial intelligence
CNN: convolutional neural network
DSM: Diagnostic and Statistical Manual of Mental Disorders
FCN: fully convolutional network
ML: machine learning
PHQ-9: Patient Health Questionnaire-9

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SER: speech emotion recognition
SFSS: Symptoms and Functioning Severity Scale
VAD: voice activity detection

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Protocol

The Web-Based Pain-at-Work Toolkit With Telephone Support for Employees With Chronic or Persistent Pain: Protocol for a Cluster Randomized Feasibility Trial

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Abstract

Background: Chronic or persistent pain affects one's ability to work or be productive at work, generating high societal and economic burden. However, the provision of work-related advice and support for people with chronic pain is variable or lacking. The Pain-at-Work (PAW) Toolkit was cocreated with people who live with pain, health care professionals, and employers. It aims to increase knowledge about employee rights and how to access support for managing a painful chronic condition in the workplace and provides advice on lifestyle behaviors that facilitate the management of chronic pain.

Objective: We aimed to establish the feasibility of conducting a definitive cluster randomized controlled trial comparing access to the PAW Toolkit and telephone support calls from an occupational therapist (PAW) with treatment as usual (ie, standard support from their employer). Our primary outcomes are establishing parameters of feasibility, acceptability, usability, and safety of this digital workplace health intervention. We will assess the candidate primary and secondary outcomes' feasibility and test research processes for a definitive trial.

Methods: This is an open-label, parallel 2-arm pragmatic feasibility cluster randomized controlled trial with exploratory health economics analysis and a nested qualitative interview study. We aim to recruit 120 participants from at least 8 workplace clusters (any type, >10 employees) in England. The recruitment of workplaces occurs via personal approach, and the recruitment of individual participants is web based. Eligible participants are vocationally active adults aged ≥18 years with internet access and self-reporting chronic pain interfering with their ability to undertake or enjoy productive work. A restricted 1:1 cluster-level randomization is used to allocate employment settings to PAW or treatment as usual; participants are unblinded to group allocation. Following site- and individual-level consent, participants complete a web-based baseline survey (time 0), including measures of work capacity, health and well-being, and health care resource use. Follow-up is performed at 3 months (time 1) and 6 months (time 2). Feasibility outcomes relate to recruitment; intervention fidelity (eg, delivery, reach, uptake, and engagement); retention; and follow-up. Qualitative evaluation (time 2) is mapped to the Capability, Opportunity, Motivation–Behavior model and will

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explore intervention acceptability to employees and employers, along with individual and contextual factors influencing the delivery and uptake of the intervention.

Results: Ethics approval was obtained in March 2023. Trial recruitment began in June 2023.

Conclusions: The PAW Toolkit is the first evidence-based digital health intervention aimed at supporting the self-management of chronic or persistent pain at work. This study will inform the design of a definitive trial, including sample size estimation, approaches to cluster site identification, primary and secondary outcomes' selection, and the final health economic model. Findings will inform approaches for the future delivery of this digital health intervention.

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KEYWORDS

eHealth; chronic pain; disability; workplace; randomized controlled trial; feasibility

Introduction

Background

In the United Kingdom, chronic or persistent pain affects approximately one-third to one-half of the population [1,2]. This figure is predicted to increase largely owing to an aging population [1-3]. Chronic pain poses a high societal and economic burden [4,5]. In England, the direct medical costs of chronic pain amount to approximately £580 million (US $707.6 million), including the total prescription of analgesic medication and pain-related primary care appointments [6]. The broader economic costs to individuals with chronic pain, their employers, and society are substantial because of the costs of health and social care, productivity losses, sickness absenteeism, and early retirement [7,8], estimated to be over £100 billion (US $122 billion) annually [7]. People living with chronic pain report significant impacts on physical and mental health [9] and lower quality of life than the general population and patients with other long-term conditions [10]. The COVID-19 pandemic has increased the overall burden of chronic pain worldwide through the emergence of newly diagnosed conditions and by exacerbating existing conditions or their risk factors [11-13].

The importance of promoting and improving the way in which people self-manage chronic pain conditions is advocated in clinical guidelines [14]. Self-management interventions can be effective in improving pain, mental health, and health-related quality of life outcomes [15]. However, self-management interventions for chronic pain often focus on specific conditions or pain types (eg, *back pain* [16-20], *chronic musculoskeletal conditions* [21,22], *arthritis* [18,23], *chronic orofacial pain* [24], and *cancer pain* [25]). This potentially excludes a broader spectrum of chronic primary or secondary pain conditions (as in Korwisi et al [14]) and individuals who experience pain but lack a medical diagnosis or do not access health care services.

Studies on the management of chronic pain commonly focus only on medical, physical, or psychological strategies for pain management, whereas very few studies have reported on work-related impacts, strategies, or outcomes [26]. However, interventions focused on changes at work for people with chronic conditions (eg, to working conditions, work environment, and work organization) may enhance work participation across a range of chronic diseases [27]. Chronic pain affects people's ability to be productive at work, be fulfilled at work, or remain in the active workforce [9,28-30] and leads to social inequalities (eg, *disability pay gap*). Retaining vocationally active adults in the workforce is important for reducing health and social inequalities because employment is inversely related to pain severity [31] and worklessness is associated with poorer physical and mental health [8,32,33], social exclusion [34], and all-cause mortality [35].

In clinical services, access to work-related advice (eg, occupational therapy) for people with chronic pain is highly variable and influenced by many factors such as referrals, provider availability, and resources [36]. Occupational therapists (OTs) work within health care and occupational health settings, providing interventions for pain management and return to or staying at work, but access to OTs is limited [37].

Researcher-led interventions targeting work-related outcomes are promising (eg, *vocational rehabilitation* [38,39]), but such studies tend to focus on specific conditions (eg, arthritis) and recruit participants from clinical settings (eg, rheumatology clinics), excluding people with other chronic pain conditions and those who are self-managing their condition outside of health care services.

Similar to self-management interventions, workplace-delivered interventions for the management of chronic pain also tend to focus on specific conditions (eg, *back pain* [40-45], *neck pain* [46-48], *shoulder pain* [49,50], and *musculoskeletal conditions* [51-54]); target specific occupational groups or job types (eg, *workers with physically demanding work* [52] or *nurses* [43]); or focus on specific types of intervention (eg, *exercise or physical activity* [41,42,51,55], *physical conditioning* [44], *rehabilitation interventions* [45,56], *ergonomic interventions* [57,58], and *return-to-work or retention interventions* [59-64]). Therefore, many workplace-delivered interventions will not reach the wider population of adults with chronic pain (with or without a formal diagnosis) or the wider spectrum of occupational groups. In addition, the narrow focus of existing interventions means that people with chronic pain need to access information and support from multiple places and may not know where and how to access it.

In practice, employers do not routinely provide support for and advice to employees with chronic pain conditions [65], and the

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provision of education and supportive materials for employees with chronic pain is therefore inconsistent or lacking across organizations and sectors. Only 30% to 34% of the UK workforce has access to specialized occupational health care [66]; a more recent estimate of 51% with access [67] was argued to be vastly overestimated [68]. Even when occupational health services are available, some occupational health professionals are not necessarily knowledgeable about chronic pain [69].

Digital approaches to the delivery of self-management are gaining popularity. Immersive technologies such as mobile health (the use of mobile phones and other wireless technology) and eHealth (the use of information and communication technology to support health and health care) have been used to provide pain therapy, education, symptom monitoring, lifestyle advice, health coaching, and cognitive behavioral therapy via virtual reality, mobile apps, or web-delivered programs in adults with diverse pain conditions [70-86]. Such interventions are primarily focused on improving pain, functional disability, or psychological outcomes but do not address barriers to work, facilitators of work ability, or pain self-management in the context of work, and work-related outcomes are often not measured.

In summary, there is a clear need for workplace interventions aimed at building the knowledge, skills, and confidence of vocationally active adults to effectively self-manage their condition at work (eg, through help seeking, adjusting job roles or physical environments, accessing support, and healthy lifestyle behaviors). Intervention is required that delivers comprehensive advice and support across a range of self-management areas, which is suitable for employees with any type of chronic pain working in any type of employment setting. Digital solutions are a potentially low-cost and scalable approach for the delivery of health interventions [87]. They have wide geographic reach and offer flexibility to the end user, which is increasingly valuable in the context of changes in job roles, work patterns, and locations (eg, hybrid or remote working) that have escalated in recent years [88,89].

The Pain-at-Work (PAW) Toolkit is the first accessible digital resource [65,90] designed to support people with chronic or persistent pain in self-managing their condition at work. It is designed to be relevant to any vocationally active adult with chronic pain in any organization type, size, or sector. The PAW Toolkit offers evidence-based advice about chronic or persistent pain, disability rights, work capacity, pain self-management strategies, and signposting to support. The design of the PAW Toolkit considers known enablers and barriers to engagement in digital interventions for people with chronic pain (eg, flexibility for access, inclusivity for people with disabilities, and low technological skill requirement). This intervention has been cocreated, pilot-tested, and evaluated with employees from public, private, and third sector organizations across the United Kingdom, and the comprehensive development processes are described elsewhere [65]. The feasibility and acceptability of the PAW Toolkit across employment sectors and different organization sizes and types, and the feasibility of testing the PAW Toolkit within a trial is yet to be determined.

This study is an important next step toward establishing the effectiveness and cost-effectiveness of the PAW Toolkit as a workplace intervention to support employees with chronic pain. Ultimately, the PAW Toolkit could contribute to reducing social inequalities (ie, *disability pay gap*) and the overall health, societal, and economic burden of chronic pain.

Aims and Objectives

The overall aim of the study is to determine the feasibility of conducting a definitive cluster randomized controlled trial (cRCT) on the effectiveness and cost-effectiveness of the PAW Toolkit with telephone support for vocationally active adults with chronic or persistent pain.

To achieve this, the objectives are as follows:

1. To measure feasibility outcomes to assess whether it would be possible to recruit to a definitive trial (recruitment and retention)
2. To test the feasibility of reaching different employee groups (eg, age, gender, ethnicity, and job role or type), sectors (eg, public, private, and third), and organizational types (eg, small to medium or large enterprises)
3. To explore whether participants and employers find the intervention and trial design acceptable
4. To obtain an estimate of the intracluster correlation coefficient to inform the future sample size calculation for the main trial
5. To collect a range of outcome measures to help identify the most appropriate primary outcome for a definitive trial
6. To assess the feasibility of capturing health economic data in a future trial
7. To design a future trial and implementation plan

Methods

Trial Design

This study is an open-label, 2-arm multicenter pragmatic cluster randomized controlled feasibility trial of the PAW Toolkit compared with a no-intervention control group in working adults with chronic or persistent pain. Both groups will continue to receive treatment as usual (TAU; ie, standard support from their employer). The analysis will be performed on an intention-to-treat basis. The feasibility trial included an exploratory health economics evaluation and a nested qualitative interview study. The study aligns with the Medical Research Council framework for developing and testing complex interventions [91] and will be conducted in accordance with the CONSORT (Consolidated Standards of Reporting Trials) extension to randomized pilot and feasibility trials [92]. The protocol was developed using the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines [93].

Ethical Considerations

The University of Nottingham Faculty of Medicine and Health Sciences Research Ethics Committee granted ethics approval on March 31, 2023 (Faculty of Medicine and Health Sciences 237-0323). The trial was prospectively registered on May 1, 2023 (ClinicalTrials.gov NCT05838677).

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Patient and Public Involvement

Our extensive preparatory work to inform the PAW Toolkit development (n=472) was a rigorous collaborative participatory process involving surveys with employees (n=274) and employers (n=107), a stakeholder workshop (n=27), and expert peer review (n=40) [65]. Content was cocreated with "Burning Nights" (a pain charity in the United Kingdom), people living with chronic pain, health care professionals, occupational health and trade union advisers, and employers. Our trial protocol was discussed with 6 members of the patient and public involvement groups at 2 national pain centers. People with lived experience of chronic pain are represented in our trial management group, trial steering group, and trial advisory group. This paper is coauthored by the chair of The Patient Voices Committee of the British Pain Society.

Eligibility Criteria

Settings

Organizations are eligible if they are located in England, are from any sector (public, private, or third), and have ≥10 employees (small: 10-49 workers; medium: 50-249 workers; or large: >250 workers). At least 8 organizations will be recruited as the unit of randomization.

Participants

Participants are eligible if they are working-age adults (employees), are aged 18 years and older, have self-reported chronic pain interfering with their ability to undertake or enjoy productive work, can comprehend English language, and are able to provide informed consent. We will include employees of any age, gender, nationality, ethnicity, income level, occupation (eg, manual or office based, low or high skilled, and low or high income), or employment status (eg, full or part time, permanent, contracted or subcontracted, volunteer, and gig workers). We use the term "employee" in this protocol to cover any type of worker. Organizations are excluded if they are outside England or are micro-organizations with fewer than 10 employees. Participants are excluded if they do not identify as having chronic pain, are unemployed at the time of recruitment, or are unable to provide informed consent. Employees with an inability to comprehend written English are excluded because it is a requirement to provide informed consent and understand the current PAW Toolkit materials. Although access to the internet is a prerequisite to engage in the study (to be able to use the intervention and complete data collection surveys), we will record the number of participants requiring telephone support for survey completion or challenges with intervention use as a proxy indicator of computer literacy.

Sample Size

A formal sample size calculation is not required for feasibility studies, although based on prior studies with a similar design [94-96], our aim is to recruit 120 employees from at least 8 organizations. Given the variability in organization size, if 120 employees are not recruited from 8 organizations, additional organizations may be recruited. Owing to the variability in the number of employees agreeing to participate in individual organizations, the total number of employees may exceed 120.

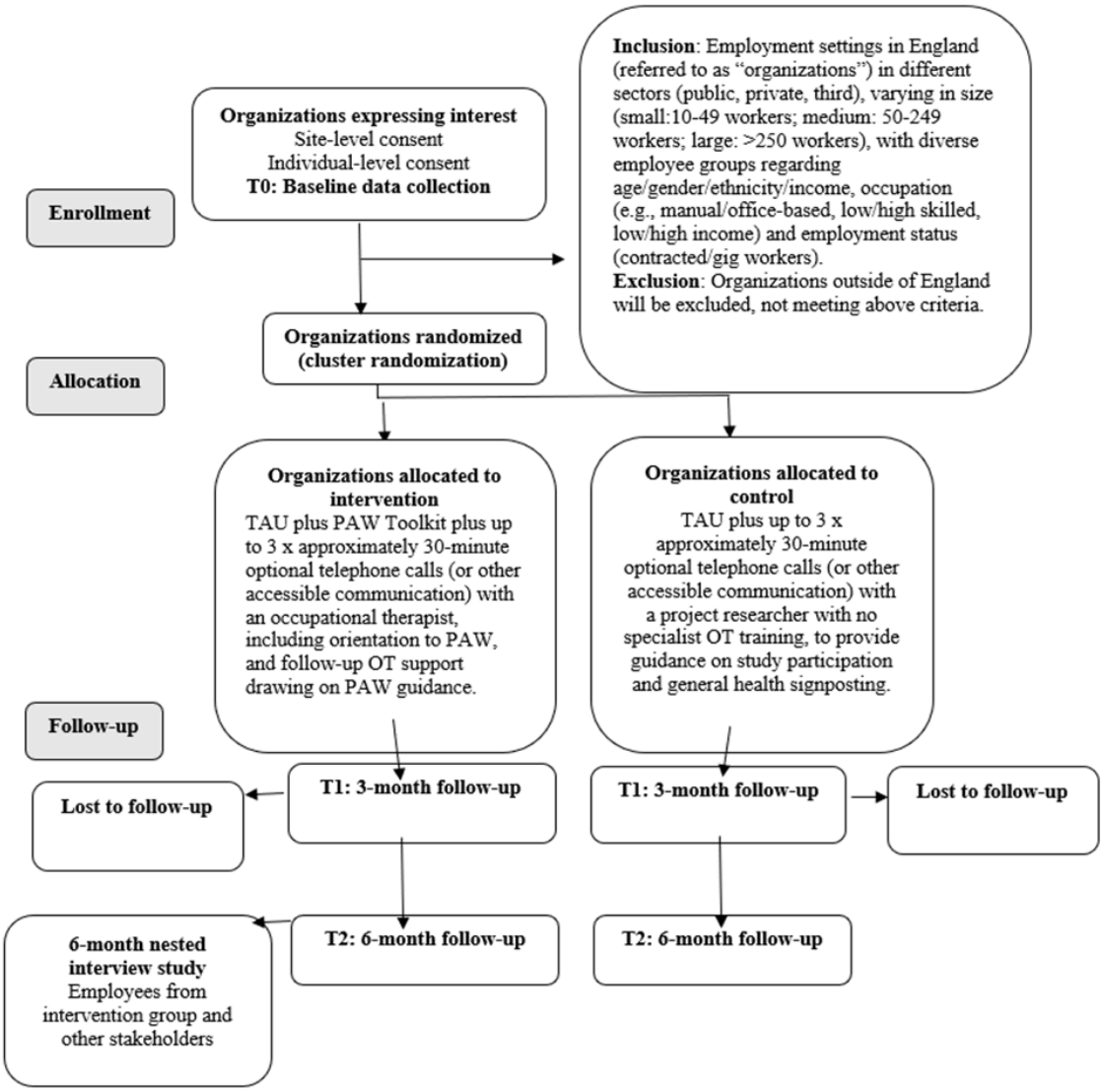
Study Procedure

Overview

The recruitment of organizations (cluster sites) and employees (participants) will be undertaken by the study researcher on a rolling basis. Each participant will be involved for approximately a 6-month duration for the feasibility trial, comprising a 6-month intervention period (baseline to final follow-up). In a subsample, qualitative interviews will be conducted at 6 months and within 8 weeks of the study end. The participant's journey through the study is shown in the CONSORT flow diagram in Figure 1. Participants will remain free to withdraw from the trial at any time without giving reasons and without prejudicing their employment or health care and will be provided with a contact point where they may obtain further information about the trial.

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Figure 1. CONSORT (Consolidated Standards of Reporting Trials) participant flow diagram. TAU refers to services and provisions provided as routine practice by the participating organization. OT: occupational therapy; PAW: Pain-at-Work; TAU: treatment as usual; T0: time 0 (baseline); T1: time 1 (3 months); T2: time 2 (6 months).



Recruitment of Organizations

Organizations in England will be identified in several ways by promoting information about the study via employer professional networks and platforms (eg, Building People), learned societies and professional organizations (eg, as identified on GOV.UK [97]), and social media (eg, LinkedIn and X [formerly known as Twitter]). Eligible organizations will be sent a formal invitation to participate by email containing a weblink to a study information sheet and consent form, and reminders will be sent to nonresponders. They will have the opportunity to discuss the study (eg, by telephone or videoconferencing) with a member of the project team. Once organizations volunteer to participate, the researcher will review the organization against the eligibility criteria to confirm that the organization meets the entry criteria. Web-based informed consent is obtained from the employer representative ("gatekeeper"). Information about the organization (eg, type, size, sector, and number of employers) will be collected by the researcher via email, telephone, or videoconference call. Gatekeepers will then be asked to provide information about the study to their employees by whichever method is appropriate for their organization. Employers' routes to providing study information to their employees will be recorded. As this is a feasibility study, strategies to incentivize organizations to participate may be added if uptake is low.

Recruitment of Participants

Employees receive information about the study from their employers (eg, email or other employer-selected routes). Employees will self-determine whether they meet the eligibility criteria as the presence of chronic or persistent pain conditions may only be known to individuals. Those who wish to participate in the study will independently access the study information via a weblink that they will receive via email, provide their consent, and complete baseline measures via a web-based data collection form. Employees will receive an email confirmation of their participation and be assigned a unique identifier. Participants will be able to contact the project researcher (by email, telephone, or videoconferencing) with any queries related to their participation in the trial or to access support with completion of the web-based surveys.

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Stopping Guidelines

Employees will be made aware that they can withdraw their consent at any time during the trial without it affecting their employment. If a participant chooses to leave the study prematurely, the primary reason for discontinuation will be determined and recorded if possible. Participants who have withdrawn will not be replaced. They will be made aware (via the information sheet and consent form) that should they withdraw, the data collected to date cannot be erased and may still be used in the final analysis. In the unlikely event that an organization withdraws participation after randomization, the organization will not be replaced. The organization will be made aware that the data collected on the organization and employees at that organization to date cannot be erased and may still be used in the final analysis. Participants will be advised that their organization has withdrawn.

Randomization

Organizations are randomized by the study statistician to either (1) active control group or (2) the PAW Toolkit with telephone support. Cluster randomization (rather than individual randomization) is required because of the nature of the intervention and risk of contamination between intervention and control participants working in the same organization. Organizations are randomized into the intervention or control group using an allocation ratio of 1:1. As this is an eHealth intervention, the researcher and participants will not be blinded to group allocation.

Interventions

Active Control Group

Participants will not receive the PAW Toolkit but continue to receive TAU from their employer. The nature of TAU will be recorded as part of the feasibility study. Depending on the employing organization, TAU may consist of but is not limited to any combination of the following: occupational health, counseling, line manager support, and signposting to education about factors that may have positive or negative effects on chronic pain. To help minimize the possibility of outcomes being influenced simply by the additional contact time offered to participants in the intervention group (ie, social support provided by additional telephone calls or contacts), this is an active control group. In this study, active control means that participants can access up to 3 opt-in nonspecialist telephone calls from a researcher for general discussion (eg, their participation in the study), by means of providing a comparable level of social contact that is unrelated to the intervention.

PAW Toolkit

Intervention participants will receive TAU and the web-based PAW Toolkit. The PAW Toolkit is designed to be relevant to any employee with chronic pain in any organization type, size, or sector. PAW offers evidence-based advice on chronic or persistent pain, disability rights, work capacity, pain self-management strategies, and signposting to support. It is based on a theory of change: "Providing employees with access to the PAW Toolkit will increase knowledge about employee rights, how to access support for managing a painful chronic condition in the workplace, and lifestyle behaviours that facilitate the management of chronic or persistent pain. This in turn will lead to improved self-management of pain at work. The ultimate aim is to improve outcomes for individuals (self-efficacy, work ability, job perceptions, health, and wellbeing) and organisations (presenteeism, absenteeism)" [65].

The PAW Toolkit is authored by the lead author (HB) and colleagues (Sarah Greaves, Sarah Somerset, and VA-F) [90]. External peer review was undertaken from January to February 2023 to ensure that the materials were current, and minor updates were completed in April 2023. It is free to access, and participants will not be paid to access it during the trial. The front page includes logos for the institutions that developed the intervention and funded its development, including a university, a pain charity, and a research council. The toolkit is based on direct instruction (information and advice) and experiential learning (advice being acted on by the end user). No training is required to use the PAW Toolkit. Individuals involved in the development processes (eg, stakeholder consultation, peer review, and technical support, as reported in the study by Blake et al [65]) are named in the PAW Toolkit. The pages contain brief text, images, multimedia (ie, video clips), and hyperlinks.

The PAW Toolkit is accessed via a weblink [90]. Each organization participating in the trial will receive a unique link from the study participants recruited from their site. Technical support is available throughout the trial to resolve any arising technical issues. The delivery of the toolkit is asynchronous (ie, not prescheduled and flexible access at a time to suit the end user). Although the PAW Toolkit may be used as a stand-alone intervention, in this feasibility trial, the delivery is supported by up to 3 opt-in OT telephone appointments (approximately 30 min of contact time each) or other accessible communication if requested by a participant, such as SMS text messaging. OT support involves orientation to the PAW Toolkit, individually tailored advice, signposting, and behavioral strategies for managing pain at work, which are aligned with the PAW Toolkit content. Content headings are shown in Figure 2. The sections and contents of the PAW Toolkit are described in Multimedia Appendix 1 [65]. The TIDieR (Template for Intervention Description and Replication) checklist and guide [98] is used to describe the intervention and use parameters (ie, dose, frequency, and duration) in Multimedia Appendix 2.

The intervention draws on the principles of persuasive system design [99] (Figure 3). Detailed mapping of the PAW Toolkit intervention and feasibility trial to the persuasive systems design is described in Multimedia Appendix 3.

Evaluation of the intervention will draw on the Technology Acceptance Model [100] and behavior change theory (Behavior Change Wheel and Capability, Opportunity, Motivation–Behavior [COM-B] model [101]).

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Figure 2. Pain-at-Work (PAW) Toolkit sections.



Figure 3. Persuasive system design.



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SMS Text Message Reminders

Participants in both the control and intervention groups will receive SMS text message reminders delivered through an automated system because SMS text messages can improve responses to web-based data collection surveys [102]. For intervention participants only, messages will include reminders to access the PAW Toolkit and OT support, as SMS text message reminders can increase the uptake of health interventions [103]. Message content will be informed by the COM-B model [101], an approach used previously for SMS text messaging aligned with workplace health intervention [104]. The content, frequency, and duration of messages will be determined through patient and public involvement consultation, message peer review, and prior research.

Study Outcomes

Outcomes are separated into (1) those that determine the feasibility and acceptability of a large definitive trial, (2) employer outcomes, and (3) participant-reported outcome measures (PROMs) to inform the choice of the primary outcome for the definitive trial. Outcomes will be measured at baseline (time 0: T0), 3 months (time 1: T1), and 6 months (time 2: T2). Items from the Checklist for Reporting Results of Internet E-Surveys (CHERRIES) [105] will be applied when reporting the findings from our web-based surveys. Multimedia Appendices 4 and 5 provide details of all feasibility and acceptability (Multimedia Appendix 4), employer- and participant-reported (Multimedia Appendix 5) data collection measures, and timeframes.

Employer-Reported Data

At the time of recruitment, details about the employment setting (Multimedia Appendix 5) will be collected from the organization representative ("gatekeeper"). This will document the sector, organization type, and size; number of staff; role of the "gatekeeper" employee representative; views toward workplace culture at the organization; and description of TAU in terms of existing provisions to support staff with long-term health conditions. Sickness absence data will be requested from the organization's records, with consent from the participants at T0, T1, and T2.

PROMs Data

Overview

PROMs (Multimedia Appendix 5) are self-assessed using web-based questionnaires, which include logos for the lead institution (university) and trial funder (charity). Closed, web-based measures will be collected using the Jisc web-based surveys at T0, T1, and T2. To help minimize attrition, participants completing surveys at all 3 time points from both groups will have the opportunity to opt into a prize draw to receive a £250 (US $305) high street shopping voucher. Participants will provide sociodemographic data (ie, age, gender, ethnicity, income, and education); health data (ie, pain conditions, present numeric pain rating scale [0-10], comorbidities, and medications); employment characteristics (eg, employment status, occupation, hours worked, and job features); sector; size and type of employing organization; assessment of their perception of organization culture; and the TAU services or support they have accessed via their employer. TAU may consist of but is not limited to any combination of the following: occupational health, counseling, line manager support, and signposting to education about factors that may have positive or negative effects on chronic pain.

PROMs are collected via a web-based survey at T0, T1, and T2 to measure the changes between time points, as presented in the following sections.

Work-Related PROMs

The Work Limitations Questionnaire-25 [106] is used as a measure of work presenteeism, that is, the "degree to which health problems interfere with specific aspects of job performance and the productivity impact of these work limitations" [107]. The scale demonstrates high reliability and validity in employee populations with chronic conditions [106-108].

The Work Productivity and Activity Impairment Questionnaire: General Health V2.0 [109] is used to measure absenteeism, presenteeism, work productivity loss, and activity impairment during the past 7 days. The validity, reliability, and responsiveness of the scale have been demonstrated in adults with chronic conditions [110-112].

The Work Ability Index Item 1 [113] is used to measure work ability (ie, how well an employee is able to perform their work). Validity and reliability have been demonstrated in employee populations [114].

The Work Self-Efficacy Scale [115] is used to measure employees' perceptions of their capability to manage specific work domains. The scale demonstrates good psychometric properties [116].

Single global items will be used to measure job satisfaction [117] and job stressfulness [118]. These items have established reliability and validity [117,118] and have been used in other employee populations [119]. Turnover intentions will be assessed using a single global item used in a web-based survey with an employee population adapted from [117] and used in [119].

Social support in the workplace will be measured using the Demand Control Support Questionnaire Social Support Subscale [120]. The scale has been shown to be valid and reliable in workplace samples [120].

Psychological and Health-Related Quality of Life PROMs

Depression symptoms will be measured using the Patient Health Questionnaire [121]. The scale has established validity as a screening tool for major depression [122,123].

Anxiety will be assessed using the General Anxiety Disorder Scale [124,125]. The scale has established reliability and validity [124,126,127], including in employee samples [123,128].

Health-related quality of life will be measured using EQ-5D-5L [129]. The scale has been shown to be reliable and valid for use in people with chronic conditions [130,131].

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Health Resource Use

Exploratory health economics data capture will be informed by previously published guidance produced by a coauthor (PM) on designing and undertaking a health economics study of digital health interventions [132]. A health care resource use questionnaire will be tested to measure completion rates for items of resource use, such as frequency of use of secondary and primary care, social care, private health care, and medications. Items are adapted from health economics data capture in previous research with pain populations [133,134].

Technology Adoption PROMs

At T1, the intervention group will complete the questions related to technology adoption. Items were developed by the study team and mapped to the Technology Acceptance Model [100] to measure perceived knowledge, perceived ease of use, perceived understandability, attitudes, and behavior related to the intervention. This will provide data to assess whether and how participants engaged with this digital health intervention and provide insights into the likely impacts of this engagement.

Data Analysis

The analysis will primarily be descriptive in line with the aims of a feasibility study. This will include estimates of recruitment and retention rates and descriptive statistics for baseline and follow-up outcome measures. For PROMs, we will undertake a dummy-run analysis presenting total scores (T0 and T1) and change from T0 to T2 (adjusting for baseline). Differences between arms may be presented with 95% CIs, where appropriate. Health economic measures (TAU costs, health care resource use costs comprising medicine use, primary care consultations, hospital stays, and outpatient visits for reasons related to chronic pain, anxiety, or depression) and quality of life measurement using EQ-5D-5L will be presented as unadjusted mean (SD) and median (IQR) values. Regression-based adjusted costs and EQ-5D-5L utility values will also be calculated, with baseline cost, quality of life values, treatment group, PAW Toolkit engagement (time spent), work absence, and respondent demographics as covariates. The percentage of missing data per resource use item and EQ-5D-5L dimension will also be presented. This analysis, along with a framework analysis of patients' views on the relevance of PROMs to self-management of their chronic pain condition (captured as a part of the questionnaires and nested interviews), will guide the choice of relevant PROMs for use in a definitive trial of the PAW Toolkit.

Nested Qualitative Interview Study

At T2, we will conduct semistructured individual interviews with up to 40 stakeholders from intervention sites to explore the views of employees who received the intervention and key stakeholders that employees identify as involved in their support (eg, line managers, company owners, human resources, occupational health, or trade union). Participants will be purposively selected to reflect diverse views from across self-identified employee groups (eg, age, gender, ethnicity, and job type), sectors, organization size, and type. The eligibility criteria for the nested interview study are (1) working for an organization participating in the trial and selected for participation in the nested interview study (employees) and (2) employed in a role providing management or support for employees in a participating organization (stakeholders). The interviews will be held by telephone or videoconferencing (eg, Teams [Microsoft Corporation]) at a mutually convenient time and will be audio recorded with consent. The recordings will be transcribed in full and anonymized. We expect the interviews to last approximately 45 to 60 minutes.

Questions will be developed using a framework for qualitative research in feasibility randomized controlled trials [135,136] and reviewed by people with lived experiences of pain. Interviews will ascertain participants' views about the feasibility and acceptability of the intervention, trial processes and outcome measures, and any perceived changes in individual or organizational outcomes. Employee questions are mapped to the COM-B model [101] to explore influencers of capability, opportunity, and motivation to self-manage their condition at work (including knowledge, attitudes, and confidence).

Employees and other stakeholders will provide informed consent via a web-based consent form. Verbal consent will be audio recorded before the interview. The qualitative researchers undertaking the interviews will provide information to the participants, explain the study, and obtain consent. It will be explained to the potential participant that entry into the study is entirely voluntary and that their employment will not be affected by their decision. Using framework analysis [137], we will explore barriers to or facilitators of engagement with or use of the intervention and recommendations for future implementation.

Results

We received funding from the Nuffield Foundation and Versus Arthritis, and the project started in March 2023. The trial was opened for recruitment in June 2023. The goal is to recruit approximately 8 organizations and 120 eligible participants (approximately 60 in each arm). As of August 11, 2023, three organizations have been recruited and randomized. The trial is currently in the recruitment phase. Data collection is expected to be completed by August 2024. Data analysis will begin once all the data have been obtained, following the established plan.

Discussion

Overview

The aim of this study is to determine the feasibility of conducting a definitive cRCT on the effectiveness and cost-effectiveness of the PAW Toolkit with telephone support for vocationally active adults with chronic or persistent pain. The ultimate aim is to retain vocationally active adults in the workforce, which is important for reducing health and social inequalities. This feasibility trial will ascertain whether it is possible to recruit and retain organizations and eligible participants in a cluster randomized trial and provide insights into the feasibility of reaching different types of organization (of diverse sizes, types, and sectors) and employees (of diverse occupational and demographic groups). The data will determine whether the intervention and trial processes are acceptable to

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employers and employees. The knowledge gained from the study will inform the design of a definitive trial, including sample size estimation, approaches to cluster site identification, selection of primary and secondary outcomes, and the final health economic model. This trial will ascertain how the PAW Toolkit can be best optimized in future research and implementation in real-world employment settings.

Our study addresses the limitations of prior studies on (1) self-management of chronic conditions, (2) workplace-delivered interventions for the management of chronic pain, and (3) studies that target work-related outcomes. Through this trial, we provide an intervention that delivers comprehensive advice and support across a range of self-management areas, which is suitable for employees with any type of chronic pain working in any type of employment setting.

Limitations

We are unable to collect data from employees who do not participate in the trial. Workplace research presents challenges in terms of recruitment and high risk of attrition [138]. However, we have also included strategies intended to maximize uptake and retention.

Conclusions

The PAW Toolkit is the first evidence-based digital health intervention aimed at supporting the self-management of chronic or persistent pain at work in vocationally active adults. The PAW feasibility trial will provide novel evidence on the feasibility of a cRCT evaluation of this digital intervention to support vocationally active adults at work, who are living with chronic or persistent pain.

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Authors' Contributions

HB conceived the study and HB and VA-F developed the intervention. HB, EW, PM, GT, DM, DAW, and KW-B contributed to the study design and secured funding for this research. HB and WJC secured the ethics approval. JH provided therapist advice. AF provided technical support for the intervention amendments. HB drafted the manuscript with input from WJC. All authors have read and approved the final version of the manuscript.

Conflicts of Interest

HB reports grant support from Gilead Sciences, Inc., Midlands Engine (Midlands Health and Productivity Pilot), and The Productivity Institute outside of this study. KW-B and JH report personal fees from the Nuffield Foundation Oliver Bird Fund and Versus Arthritis to support their input to the study. DM reports grant support from Pfizer and Eli Lilly outside this study. DAW reports grant support from Pfizer, Eli Lilly, GlaxoSmithKline, UCB, and Orion Pharma outside of this study. All other authors declare no other conflicts of interest.

Multimedia Appendix 1
Pain-at-Work Toolkit sections and content.
[DOCX File , 14 KB - resprot_v12i1e51474_app1.docx]

Multimedia Appendix 2
Application of the TIDieR (Template for Intervention Description and Replication) checklist to the intervention.
[DOCX File , 20 KB - resprot_v12i1e51474_app2.docx]

Multimedia Appendix 3
Mapping the Pain-at-Work Toolkit intervention and feasibility trial to persuasive systems design.
[DOCX File , 17 KB - resprot_v12i1e51474_app3.docx]

Multimedia Appendix 4
Feasibility and acceptability measures.
[DOCX File , 16 KB - resprot_v12i1e51474_app4.docx]

Multimedia Appendix 5

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Employer- and participant-reported outcomes.
[DOCX File , 29 KB - resprot_v12i1e51474_app5.docx]

Multimedia Appendix 6
Peer-review report by the Nuffield Foundation's Oliver Bird Fund and Versus Arthritis.
[PDF File (Adobe PDF File), 83 KB - resprot_v12i1e51474_app6.pdf]

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Abbreviations

CHERRIES: Checklist for Reporting Results of Internet E-Surveys
COM-B: Capability, Opportunity, Motivation–Behavior
CONSORT: Consolidated Standards of Reporting Trials
cRCT: cluster randomized controlled trial
OT: occupational therapist
PAW: Pain-at-Work
PROM: participant-reported outcome measure
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
TAU: treatment as usual
TIDieR: Template for Intervention Description and Replication

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Protocol

The Influence of Branched-Chain Amino Acid Supplementation on Fatigue and Tryptophan Metabolism After Acute and Chronic Exercise in Older Adults: Protocol for a Pilot Randomized Controlled Trial

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Abstract

Background: Fatigue is a strong predictor of negative health outcomes in older adults. Kynurenine, a metabolite of tryptophan, is strongly associated with fatigue. Reductions in fatigue are observed with exercise; however, exercise training does not completely alleviate symptoms. Branched-chain amino acids (BCAAs) have been shown to have advantageous effects on exercise performance and compete with kynurenine for transport into the central nervous system. Thus, the combination of BCAA and exercise may exert synergized effects of mental and physical fatigue. Therefore, we hypothesize that BCAA added to exercise will shift kynurenine metabolism toward enhanced synthesis of kynurenic acid, thereby reducing fatigue.

Objective: This randomized, double-blind, placebo-controlled trial aims to compare the effects of acute (approximately 45 min) and chronic (8 wk) exercise with and without BCAA supplementation on mental and physical fatigue and assess whether the hypothesized outcomes are modulated by changes in kynurenine metabolism in 30 older adults (n=15, 50% per group).

Methods: Older adults (aged 60-80 y) who do not exercise >2 days per week and self-report fatigue (≥3 on a scale of 1-10) will be recruited. Participants will be randomized to either the exercise+BCAA group or exercise+placebo group. Participants will engage in high-volume, moderate-intensity, whole-body exercise training (aerobic and resistance exercise; either in-person or web-based sessions) 3 times per week for 8 weeks. In addition, participants will consume daily either 100 mg/kg body weight of BCAA (2:1:1 leucine:isoleucine:valine) or placebo (maltodextrin) throughout the 8-week intervention. BCAA and placebo powders will be identical in color and dissolved in 400 mL of water and 2.5 g of a calorie-free water flavor enhancer. Muscle biopsies will be collected before and after the intervention after a 12-hour fast to examine changes in the biomarkers of tryptophan metabolism and inflammation. Our primary outcomes include changes in mental and physical fatigue and metabolism after the 8-week exercise training between the 2 groups. Mental and physical fatigue will be measured before and after the intervention. Mental fatigue will be subjectively assessed through the completion of validated questionnaires. Physical fatigue will be measured by isometric handgrip, 1-repetition maximum, chair rise, 400-meter walk, and cardiopulmonary exercise tests.

Results: The study was funded in March 2022, with an anticipated projected data collection period lasting from January 2023 through December 2023.

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Conclusions: The discovery that kynurenine concentrations are associated with fatigue and are responsive to BCAA supplementation during exercise training could have important implications for the development of future interventions, both lifestyle and pharmacologic, to treat fatigue in older adults.

Trial Registration: ClinicalTrials.gov NCT05484661; https://www.clinicaltrials.gov/study/NCT05484661

International Registered Report Identifier (IRRID): DERR1-10.2196/52199

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KEYWORDS

branched-chain amino acids; kynurenine; fatigue; older adults; exercise

Introduction

Background

The prevalence rate of self-reported mental and physical fatigue among older adults is at least 25% in primary care settings [1]. Mental fatigue refers to a decrease in cognitive resources, whereas physical fatigue refers to the inability of muscles to maintain optimal performance. Studies suggest that mental fatigue may be present before the onset of disability and morbidity [2] and has been reported by older adults to be a main reason for activity restriction and poor compliance with exercise interventions [3]. Although prior studies show that both mental and physical fatigue are associated with low-grade inflammation [4], more research is needed to pinpoint specific biological pathways to connect chronic inflammation to fatigue-associated health declines.

One pathway that may play an integral role in fatigue progression is that of the essential amino acid tryptophan. Normally, 90% to 95% of tryptophan is metabolized along the kynurenine pathway in the liver. Inflammation upregulates kynurenine pathway enzymes outside the liver, causing intracellular and circulating kynurenine or oxidative kynurenine metabolite concentrations to rise. The accumulation of kynurenine and its oxidative metabolites are strongly associated with physical fatigue, including weaker grip strength and slower walking speed [5]. Furthermore, they can readily cross into the central nervous system (CNS) and underlie the behavioral and cognitive impairments caused by inflammation [6].

Evidence in animal models suggests that reductions in physical fatigue often observed with exercise training are mediated by skeletal muscle peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α), inducing a shift of kynurenine to kynurenic acid [7,8]. This is catalyzed by kynurenine aminotransferase (KAT) enzymes, which prevent the oxidative metabolism of kynurenine as well as its entry into the CNS; this may have an influence on mental fatigue. We have shown that reductions in skeletal muscle inflammation are associated with reductions in mental and physical fatigue after exercise training [9]; however, a recent study in older adults also found that exercise training significantly increased skeletal muscle PGC-1α gene expression and KAT isoforms by nearly 2-fold [10]. These data suggest that the tryptophan metabolism pathway may play an integral role in regulating mental and physical fatigue after exercise.

Exhaustive exercise results in the branched-chain amino acids (BCAAs; leucine, isoleucine, and valine) being taken up by the skeletal muscle, leading to reductions in the plasma concentration. In the past 2 decades, numerous studies have shown the advantageous effects of BCAA supplementation on acute and chronic exercise performance, including improvements in time to exhaustion and strength [11,12]. Furthermore, studies in animal models suggest that BCAAs decrease the transport of tryptophan and its metabolites into the CNS because BCAAs and tryptophan compete for the same carrier system. In addition, it has been shown that the depletion of plasma BCAAs after dialysis is highly associated with mental fatigue [13]. In animal models, BCAAs attenuate changes in skeletal muscle PGC-1α caused by acute exercise by approximately 50% [14]. Although currently unexplored, these data suggest that when combined with exercise, BCAA supplementation may have the ability to modify mental and physical fatigue by modulating the tryptophan pathway.

Objectives

This pilot study will examine the influence of systemic and skeletal muscle tryptophan metabolism on mental and physical fatigue after exercise training with and without BCAA supplementation in fatigued older adults. Our central hypothesis is that 8 weeks of daily BCAA supplementation added to 3-times-per-week exercise training will increase systemic and skeletal muscle expression of KAT, shifting kynurenine metabolism toward the enhanced synthesis of kynurenic acid, thereby reducing mental and physical fatigue.

Methods

Study Design and Overview

We propose a randomized, double-blind, placebo-controlled pilot study. The study protocol follows the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines [15]. Any deviations from the protocol, breaches of confidentiality, and adverse events will be reported to the institutional review board (IRB) and data safety monitoring board (DSMB) according to local policies. In addition, the DSMB will evaluate study materials and review the collected data to ensure data security, integrity, and quality assurance. The study is registered with ClinicalTrials.gov (NCT05484661). As shown in Textbox 1, the experimental design involves 5 phases, completed over 3 to 4 months. In phase 1, we will recruit, screen, and enroll 30 participants (n=15, 50% per group). In phase 2, all participants will undergo baseline testing (described in the following subsections). In phase 3, participants will be randomly assigned to the exercise+placebo group or exercise+BCAA group, and we will test the acute effects of

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BCAA intake on fatigue and changes in the biomarkers of tryptophan metabolism and inflammation through a blood draw that will be performed after a 12-hour fast and 30 minutes after consuming either BCAA or a placebo. Phase 1 to 3 data will be collected at the Sam and Ann Barshop Institute for Longevity and Aging Studies of the University of Texas Health Science Center at San Antonio. Study phase 4 is the intervention and will consist of exercise training 3 times per week over 8 weeks with or without daily BCAA intake. To test the chronic effects of fatigue, participants will repeat all phase-2 tests at the end of the intervention (phase 5). Intervention staff and participants will be blinded to supplement allocation. Participants will receive either the BCAA or a placebo, both in powder form. Only study team members without direct participant interaction will know supplement allocation.

Textbox 1. Study design and timeline.

Week –4 (phase 1)

- Recruitment
- Screening
- Enrollment (n=30)
- Consent

Week –2 (phase 2)

- Baseline tests and assessments
- Strength and endurance
- Blood draws
- Anthropometrics
- Muscle biopsies
- Questionnaires

Week 0 (phase 3)

- Randomization (1:1)
- Acute fatigue test

Week 1 (phase 4)

- Exercise+branched-chain amino acid group (n=15)
- Exercise+placebo group (n=15)
- 8-wk intervention

Week 9 (phase 5)

- Postintervention assessments (repeat assessments outlined in phase 2)

Phase 1: Participant Recruitment, Screening, and Enrollment

Participants and Inclusion and Exclusion Criteria

The study will recruit a total of 30 community-dwelling older adults from the San Antonio, Texas, area. The inclusion criteria are as follows: (1) fatigue (participants self-reporting ≥3 on a 1-10 scale), (2) aged 60 to 80 years, (3) lack of menses for at least 1 year for women, (4) BMI 20 to 40 kg/m^2, and (5) untrained with regard to structured exercises training (≤2 times/wk). The exclusion criteria are as follows: (1) taking an anticoagulant medication (ie, heparin, apixaban, or rivaroxaban); (2) allergic to lidocaine; (3) neurologic, musculoskeletal, or other condition that limits the participant's ability to complete study physical assessments; (4) active inflammatory, autoimmune, infectious, hepatic renal, gastrointestinal, malignant, or psychiatric disease; (5) cognitive impairment (Montreal Cognitive Assessment [MoCA] score <21); (6) consuming a special diet or protein or CAA supplements; and (7) uncontrolled depression (Center for Epidemiologic Studies Depression Scale [CES-D] score ≥16).

Recruitment

Recruitment methods may include electronic medical record and approved registry queries, posting study flyers at medical offices or senior centers, community engagement activities, and newspaper or web-based advertisements (including social media). Telephone prescreening before the clinic screening visit will be used to ensure that potential participants meet the inclusion and exclusion criteria for enrollment. Those who qualify preliminarily will be scheduled for a full in-clinic evaluation and will be sent an advance copy of the consent form.

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Screening

We will conduct an in-clinic evaluation consisting of a medical history; physical examination; resting, seated blood pressure; weight; height; and electrocardiogram. A fasting blood profile for lipids as well as liver, renal, and hematological function will be performed.

Enrollment

Participants will be enrolled if they provide informed consent and pass all required screening assessments.

Phase 2: Baseline Assessment Measures

Participants will complete questionnaires related to their mental fatigue, depression, quality of life, and physical fatigue (they will be asked to perform tests of strength and endurance; Textbox 2). In addition, participants will have blood draws and muscle biopsies to assess markers of inflammation or immune status, quantify amino acid and metabolite levels, and examine changes in muscle gene expression and intracellular signaling pathways (ie, PGC-1α and KAT).

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Textbox 2. Baseline and postintervention assessment measures.

Laboratory tests

- Blood draw: plasma, serum, and whole blood will be collected for the assessment of thyroid-stimulating hormone, complete blood count, and a comprehensive metabolic panel with liver function tests and lipid profile. Plasma will be processed for the quantitative assessment of branched-chain amino acids and kynurenine metabolites using liquid chromatography–mass spectrometry, whereas plasma C-reactive protein, interleukin-6, interleukin-1β, and tumor necrosis factor-α will be measured by enzyme-linked immunosorbent assay (ELISA). Immune function (immunoreactivity) will be measured in diluted whole blood stimulated in vitro with 0-1000 ng/mL lipopolysaccharide (LPS) or 0-1000 ng/mL dexamethasone in the presence of 100 ng/mL LPS. Secreted cytokines will be measured by ELISA.
- Skeletal muscle biopsy: vastus lateralis muscle biopsies of the dominant leg will be obtained with a Bergström needle with local anesthesia by a credentialed clinician after a 10- to 12-h fast. Muscle tissue will quantitate local inflammation and tryptophan metabolism markers.

Anthropometric measurements

- BMI: weight (kg) will be measured on a standard physician's scale at baseline and after the intervention without shoes and with light clothing. Standing height (cm) will be measured using a stadiometer at screening. BMI will be calculated as weight (kg)/height (m^2).
- Waist and hip circumference: minimum and maximum waist and hip circumference will be measured with a tape measure. Measurements will be taken by trained personnel and will follow the World Health Organization guidelines.
- Body composition: whole-body dual-energy x-ray absorptiometry will be performed to measure lean and fat body mass and to examine the effect of the intervention on body composition [10,16]. In participants who are overweight where portions of the body fall outside the scan area, a half-body scan of the right side is carried out and a contralateral estimated performed [17].

Quantitative assessments

- Energy intake and expenditure
- Automated Self-Administered 24-Hour Dietary Assessment (ASA24): this validated web-based tool developed by the National Cancer Institute that enables multiple, automatically coded, and self-administered 24-h diet recalls will be used to calculate energy intake. The ASA24 will be used to calculate the Healthy Eating Index (HEI). HEI scores range from 0 to 100, with higher scores indicating better adherence to the Dietary Guidelines for Americans [18,19].
- Activity monitor (ActiGraph): ActiGraph GT9X Link accelerometers will be used to monitor total daily activity energy expenditure (kcal/d). Participants will wear an accelerometer around the right hip continuously for 7 d, except when sleeping, bathing, or swimming. In addition, participants will subjectively log their activity on the days that the accelerometer is worn.
- Short HEI (sHEI): The sHEI will be used to measure diet quality and assess how well dietary patterns align with the key recommendations of the Dietary Guidelines for Americans [20].
- Patient-Reported Outcomes Measurement Information System: this 57-item validated questionnaire will be used to evaluate and monitor 7 health domains (depression, anxiety, physical function, pain, sleep, fatigue, and social health) in adults [21].
- Mental fatigue (self-report measures)
  - Fatigue Assessment Scale: this 10-item validated fatigue measure scale will be used to evaluate the severity of fatigue and its impact on daily living [22].
  - Center for Epidemiologic Studies Depression Scale (CES-D): this 20-item screening test will be used to assess depression and depressive disorder. The CES-D measures symptoms defined by the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition for a major depressive episode [23].
  - Minnesota Leisure Time Physical Activity Questionnaire (MLTQ): this validated questionnaire will be used to measure physical activity (duration and frequency) and energy expenditure during leisure time physical activity [24].
  - Insomnia Severity Index: this 7-item questionnaire will be used to assess the nature, severity, and impact of insomnia and monitor treatment response in adults [25].
  - Visual analog scale: this validated psychometric measuring instrument will be used to measure global pain, fatigue, and quality of life, with scores for each measure ranging from 0 to 100 mm and higher scores indicating greater intensity of pain, tiredness, and fatigue as well as better quality of life [26,27].
- Physical fatigue (strength and endurance)
  - Isometric handgrip: handgrip strength of both arms will be assessed using a handheld dynamometer. Measures will be taken in triplicate to take the average of the 3 measures [28].
  - Strength: Knee extension and chest press strength will be measured by a standardized 1-repetition maximum (1-RM) protocol that includes 4 to 6 trials with rest periods. Muscle endurance will be assessed by asking the participant to perform repetitions of the leg extension and chest press exercises at 60% 1-RM to volitional fatigue, with the number of repetitions recorded [29].
  - Chair rise: the chair rise test will be used to assess functional lower extremity strength. Chair stand number will be recorded as the number of chair stands completed as quickly as possible in 30 s with arms folded across the chest [30]. Assessment will be administered following the Stopping Elderly Accidents, Deaths, & Injuries protocol developed by the Centers for Disease Control and Prevention. Furthermore, the amount of time (s) required to sit and stand 5 times in succession will be recorded [31].

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- Cardiopulmonary exercise test (CPET): a resting electrocardiogram (ECG) and blood pressure reading will be collected before the test. Open circuit spirometry will be performed during a CPET using a customized protocol to evaluate the cardiopulmonary response (ie, peak oxygen uptake [VO2peak] and ventilatory threshold) to strenuous exertion under clinical supervision and continuous vital sign and ECG monitoring according to the participant's tolerance, perceived exertion, and gait stability. The test will be reviewed and participants cleared to participate by a research clinician [32].
- 400-meter walk: the 400-meter walk test will used to measure walking ability and endurance [33]. The total time (s) taken to complete 400 m, maximal heart rate, and perceived exertion (rated on a scale ranging from 0 to 10, with 10 indicating maximum intensity) will be assessed.

- Frailty: frailty will be classified using the Fried phenotype criteria [34]: (1) self-reported unintentional weight loss of ≥10 lb (≥4.5 kg) in the past year, (2) self-reported exhaustion, (3) low energy expenditure measured using the MLTQ to assess physical activity (duration and frequency), (4) weakness measured via grip strength using a handheld dynamometer in the dominant hand, and (5) slow walking speed measured by 10-foot walk test. A frailty score will be calculated as the number (0-5) of frailty characteristics present. Those with ≥3 of these 5 characteristics are categorized as frail, those with 1 or 2 are categorized as prefrail, and those with none are categorized as nonfrail [35].

Phase 3: Randomization

Participants will be randomized 1:1 to the exercise+placebo group or exercise+BCAA group. At this visit, participants will have resting vital signs assessed and 10- to 12-hour fasting blood draw performed. After the fasting blood draw, participants will consume (blinded) either 100 mg/kg of the BCAA or the maltodextrin (depending upon group allocation) and then will rest for 30 minutes. Immediately after the 30-minute rest, a 400-meter walk will be completed (as outlined in Textbox 2). A second blood draw will be performed within 3 to 5 minutes of completing the 400-meter walk.

Phase 4: Exercise+Placebo or Exercise+BCAA Intervention

Exercise

Participants will attend in-person or web-based exercise sessions 3 times per week for 8 weeks. The exercise training protocol is designed to provide a high-volume, moderate-intensity, whole-body stimulus. The exercise will be prescribed by an exercise physiologist via provided heart rate (HR) monitors. Aerobic exercise training will start conservatively with a goal of 30 minutes total duration at 40% to 50% of maximal HR reserve determined according to the formula developed by Karvonen et al [36]:

$$\text{Training HR} = \%(\text{HRmax} - \text{HRrest}) + \text{HRrest} \quad \textbf{(1)}$$

HRmax is defined as peak HR assessed during a peak cardiopulmonary exercise test (described in Textbox 2). Aerobic exercise will advance weekly, as tolerated, to a goal of 75% to 85% of HR reserve for 30 minutes. In addition, participants will perform resistance exercise using TheraBands. They will perform the chest press, knee extension, leg curl, row, and bicep curl (15 repetitions for 2 sets and to exhaustion on the third set) for 5 major muscle groups. Resistance will be gradually increased to account for strength gains when participants are able to complete 20 repetitions on the third set.

BCAA or Placebo

Overview

This study will use over-the-counter dietary supplement powders. The BCAA supplement is manufactured and distributed by Naked Nutrition. One scoop (5 g) contains 2500 mg of L-leucine, 1250 mg of L-isoleucine, and 1250 mg of L-valine and sunflower lecithin. The placebo (maltodextrin) is manufactured and distributed by Nutricost. One scoop (15 g) contains 14 g of a complex carbohydrate (maltodextrin).

Labeling and Distribution of BCAA and Placebo Supplementation

Following double-blinded procedures, the study team will receive the BCAA or placebo supplements in prepackaged containers for the use of individual participants from the on-site clinical pharmacy. The pharmacy will maintain inventory; ensure appropriate temperature control; label each individual participant container with study and participant ID; and be responsible for storage, inventory, and destruction, following pharmacy protocol.

BCAA and Placebo Consumption

Participants will be randomly assigned to 8 weeks of BCAA or placebo supplementation. Participants will be instructed to consume either 7 to 10 g (100 mg/kg body weight) of BCAA supplement or placebo daily. The powders, identical in color, will be distributed in a double-blind fashion and dissolved in 400 mL of water and 2.5 g of a calorie-free water flavor enhancer (ie, Crystal Light). The supplement to be consumed on nonexercise days will be in prepackaged containers and provided to participants along with water flavor enhancers on a weekly basis. On nonexercise days, participants will be instructed to take the supplement between 9 AM and 10 AM each day and to log each intake on a provided spreadsheet. On exercise days, the supplement will be consumed immediately after finishing exercise training while being monitored by study staff. The distribution and consumption of the supplement will be logged by study staff. In addition, participants will be asked about supplement intake at every exercise session to track compliance. The assessment of side effects will be performed at every exercise session.

Phase 5: Postintervention Measures

After the intervention, participants will repeat all baseline (phase 2) assessment measures and qualitative assessments (Textbox 2).

Outcomes and Analysis

An important goal of statistical analyses is to determine effect sizes to make certain that future studies evolving from the current work are adequately powered. Although data do not exist to provide more precise effect sizes for this experiment, based upon previous studies [37], a mean decrease of 0.64 (SD

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0.19) µmol/L in kynurenine concentration was observed after exercise training. The anticipated additive effect of BCAA supplementation is 0.25 µmol/L. Assuming an SD of 0.25 µmol/L, 12 participants per group are necessary to achieve at least 80% power with a significance level of 5%. To allow for a 20% dropout rate, we will recruit a total of 30 participants with the intent of having 24 complete the study.

In light of the small sample size, 2 separate independent samples 2-tailed *t* tests will be used for each outcome measure (ie, mental fatigue and physical fatigue) to compare changes between the BCAA and placebo groups: (1) before and after phase 3 acute exercise (400-meter walk acute fatigue test) and (2) before and after chronic (8-wk changes from phase 2 to phase 5) exercise training. We will use intention-to-treat principles per CONSORT (Consolidated Standards of Reporting Trials) guidelines to avoid the effects of attrition, which may break the random assignment to the treatment groups in a study. All statistical tests will be 2-sided and unadjusted for multiple comparisons.

Participant Safety and Minimizing Potential Risk

Overview

The risks from participating in the research study are mild to moderate and involve some slight temporary discomforts. Procedures that involve a degree of risk include completing the questionnaires, exercise training, functional assessment, BCAA or placebo supplementation (maltodextrin), muscle biopsy, blood draws, and dual-energy x-ray absorptiometry (DXA) scans. Halting the study will be at the discretion of the study clinical staff and DSMB. There is no known risk of stopping the study supplements early or abruptly.

Questionnaires

The questionnaires are time consuming but pose minimal risk.

Exercise Training and Functional Assessments

The physical activity requirement for this study is associated with shortness of breath, muscle soreness, and strains, along with the risk of cardiovascular complications such as chest pain, heart attack, or sudden death. To offset this minimal risk, all participants will undergo prescreening with medical examinations before exercise. In addition, an exercise physiologist or other medical professional will be present for all exercise sessions. There is also a minimal risk of falling during the fatigue assessment walking tests. A standby aide will always be present, and sufficient periods or rest will be provided to minimize risk.

Supplementation

The risks from consuming the BCAA and maltodextrin are expected to be minimal and may include gastrointestinal distress, such as cramps and gas. Participants will be monitored at each exercise session, and any unanticipated or serious side effects will be reported immediately to the study clinical staff, IRB, and DSMB.

Muscle Biopsy

Mild to moderate discomfort is likely but not serious and may include a sensation of pressure or thumping, cramping, pain, soreness, and bleeding. The pain is typically mild to moderate and lasts 5 to 10 seconds. The pain usually stops when the needle is removed but muscle soreness could last for a few days. Ice packs are applied to the biopsy site to minimize discomfort.

Blood Draw

The risks associated with blood sampling include discomfort, bruising, swelling, fainting, and possible infection at the site of sampling. This is minimized by having skilled professionals perform the blood draw.

DXA Scans

Participants will be exposed to a minor dose of ionizing radiation (total 0.6 mrem/scan) during the DXA scans at phase 2 and phase 5 [16], which is well below the dose of a standard chest x-ray (10 mrem; United States Environmental Protection Agency Radiation Sources and Doses [38]).

Data Management

All research records created will be held strictly confidential. A study number rather than the participant's name will be used on study records whenever possible. Electronic data will be password protected and placed on the secure local area network (REDCap [Research Electronic Data Capture; Vanderbilt University]; hosted at the University of Texas Health Science Center San Antonio]). Randomization codes will be created at random and kept electronically by a study team member not directly involved with participants (ie, the statistician). We anticipate that blinding will only be broken before the completion of the study if requested by the DSMB owing to safety concerns. Unblinding before study completion will be reported to the IRB and DSMB.

Ethical Considerations

The study was approved by the local IRB (University of Texas Health Science Center at San Antonio; 20220493H) in accordance with the ethical standards of the responsible committees on human experimentation and the Declaration of Helsinki. Eligible participants will have the study explained and an in-person IRB-approved informed consent will be obtained from each participant. Participants may choose to leave or opt out the study at any time during the study without penalty or loss of benefits they are entitled. All data and biospecimens will be deidentified. Participants will receive US $50.00 compensation after completion of the 2 testing phases (phase 2 and phase 5) for a total of US $100.00 for completion of the entire study.

Dissemination

The results of this study will be made available to health care professionals and the public through the National Library of Medicine PubMed Central website within 1 year after the date of publication. In addition, the findings of this study will be presented at scientific meetings. The study investigators will be responsible for writing all publications and will not use the services of professional writers.

Results

The study was funded in March 2022, with a projected data collection period lasting from January 2023 through December

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2023. The screening and enrollment of participants for phase 1 began in December 2022. Data collection began in January 2023 and is projected to be completed at the end of November 2023. As of August 2023, a total of 24 participants have been recruited and enrolled in the study. Data analysis and results are aimed to be published in early 2024.

Discussion

Summary

The purpose of this study is to examine whether the addition of a BCAA to acute and chronic exercise can reduce mental and physical fatigue using a pilot randomized, double-blind, placebo-controlled trial. This study will also address whether clinical outcomes are modulated by changes in circulating and skeletal muscle tryptophan metabolism because this may identify potential targets for future investigation. We anticipate that 8 weeks of a BCAA added to exercise will increase the expression of KAT, shifting kynurenine metabolism toward the enhanced synthesis of kynurenic acid, thereby reducing fatigue.

Fatigue is one of the most common idiopathic complaints in older adults [39], with up to 50% of older adults aged 65 years [40] and 75% of those aged >85 years [41] self-reporting symptoms. Studies show that both mental fatigue and physical fatigue are associated with accelerated decline in physical function and cognition [42], which are strong predictors for the loss of independence in community-dwelling older adults [43]. Although fatigue can significantly affect an individual's quality of life, social well-being, and livelihood [44], its etiology remains unknown, and effective treatment strategies remain elusive.

Tryptophan is the precursor of serotonin and kynurenine, and accumulating evidence suggests that kynurenine metabolic pathways are associated with mental and physical fatigue [45]. A recent study demonstrated that the uptake of peripheral kynurenine into the brain of mice increased kynurenic acid production and induced mental fatigue [45]. This supports previous evidence that has shown that the ingestion of tryptophan by humans can also induce fatigue [45,46]. These data suggest that the tryptophan metabolism pathway may play an integral role in regulating mental and physical fatigue.

Exercise has been associated as a low-cost strategy for improving symptoms linked to fatigue [47]; however, symptoms are not eliminated. A recent randomized controlled trial has shown that exercise training can reduce the incidence of moderate to severe mental and physical fatigue by 30% to 60%; however, 82% of the participants continued to report mild fatigue after the intervention [9]. Animal models suggest that the reduction of fatigue from exercise is mediated by skeletal muscle PGC-1α, which shifts tryptophan metabolism [9] and therefore may influence fatigue. A recent study in older adults found that exercise training significantly increased skeletal muscle PGC-1α gene expression [10]. In addition, it has been shown that sedentary fatigued older adults had decreased concentration and suppression of PGC-1α in muscle tissue compared with nonfatigued older adults [48].

BCAAs play a critical role in the regulation of multiple physiological functions, including nutrient metabolism, energy homeostasis, immunity, intestinal health, protein synthesis, and aging [49]. Evidence suggests that BCAA supplementation can be beneficial during exercise, with studies showing improved ratings of perceived exertions and mental performance [49,50]. The consumption of BCAAs causes a rapid increase in serum concentration and competes with tryptophan for entry into the CNS [51]. In addition, BCAAs have been shown to attenuate changes in skeletal muscle PGC-1α caused by exercise [11,12]. Although currently unexplored, data suggest that, when combined with exercise, BCAA supplementation may have the ability to modify mental and physical fatigue by modulating the tryptophan pathway. Therefore, this study will fill a knowledge gap by determining whether changes in tryptophan metabolism occur after exercise with and without BCAA supplementation and relate to reductions in mental and physical fatigue, because this may identify potential targets for future lifestyle and pharmacologic investigation.

The identification of BCAA plus exercise as being superior to exercise alone could have clinical implications for older adults to improve cardiometabolic and functional risk. By reducing fatigue, older adults may be able to engage in longer periods of physical activity, thereby reducing weight gain common to older adults and improving the mental and physical quality of life.

Limitations

A randomized controlled trial is generally accepted as the gold standard for investigating causal relationships between an intervention and outcomes; however, despite its strength, this study design has potential limitations that should be considered. The small sample size increases the possibility of a type II error, which decreases the power of the comparison. In addition, the potential for heterogeneity between the intervention and control groups could result in false-positive results [52]. The use of self-report measures for some clinical outcomes limits any conclusion from being drawn about cause and effect and limits the generalizability of the results. Furthermore, participants could have low adherence to the study protocol although study has been designed to mitigate risk.

Future Direction

This pilot will provide preliminary evidence for larger grant applications to examine the combined effects of BCAA supplementation and exercise on mental and physical fatigue. In addition, based on the findings from this project, future clinical studies may address how other nutrient-rich foods or supplements or weight loss could further alter the response to BCAA and exercise. Furthermore, there are numerous other important clinical outcomes related to fatigue that could be examined as influenced by BCAA and exercise (ie, muscle quality, fall risk, and cognitive functioning). The discovery that kynurenine concentrations are associated with fatigue and are responsive to BCAA supplementation during exercise training could have important implications for the development of future interventions, both lifestyle and pharmacologic, to treat fatigue in older adults.

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Conclusions

Through BCAA supplementation during exercise, the clinical research proposed herein has the potential to provide insight into whether BCAA supplementation can effectively reduce mental and physical fatigue when combined with acute and chronic exercise and whether these improvements are related to alterations in tryptophan metabolism in fatigued older adults. This could have important implications for prescribing exercise in older adults and the development of future interventions, both lifestyle and pharmacologic, to treat fatigue in older adults.

Acknowledgments

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Data Availability

A deidentified final data set underlying all publications resulting from the proposed research will be shared on request pursuant to a data use agreement, appropriately limiting the use of the data set and prohibiting the recipient from identifying or reidentifying (or taking steps to identify or reidentify) any individual whose data are included in the data set.

Authors' Contributions

RNR, JCOC, and MCS wrote the initial draft of the manuscript. All authors have reviewed and edited the manuscript. All authors have approved the manuscript for publication.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review report from the National Institute on Aging (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 83 KB - resprot_v12i1e52199_app1.pdf]

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Abbreviations

BCAA: branched-chain amino acid

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CES-D: Center for Epidemiologic Studies Depression Scale
CNS: central nervous system
CONSORT: Consolidated Standards of Reporting Trials
DSMB: data safety monitoring board
DXA: dual-energy x-ray absorptiometry
HR: heart rate
IRB: institutional review board
KAT: kynurenine aminotransferase
MoCA: Montreal Cognitive Assessment
PGC-1α: peroxisome proliferator-activated receptor γ coactivator 1α
REDCap: Research Electronic Data Capture
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Protocol

Sleep Treatment Education Program for Young Adult Cancer Survivors (STEP-YA): Protocol for an Efficacy Trial

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Abstract

Background: Young adult cancer survivors (YACS) are at elevated risk for chronic insomnia, even years after completing treatment. In addition to potential health consequences, insomnia can interrupt social, educational, and vocational development just as they are trying to "make up" for time lost to cancer. Cognitive behavioral therapy for insomnia (CBTI) is recommended as first-line treatment for insomnia but remains largely unavailable to YACS due to several barriers (ie, shortage of trained providers, geographic limitations, financial limitations). Traditional CBTI has not been adapted to meet YACS' unique developmental and circadian challenges. To improve availability of effective behavioral insomnia treatment for this population, we developed the Sleep Treatment Education Program for Young Adult Cancer Survivors (STEP-YA), a low-intensity educational intervention delivered virtually online.

Objective: In this phase 2 "proof of concept" trial, primary aims are to test the efficacy of STEP-YA to improve insomnia symptoms and mood in YACS and assess the utility of individualized coaching to improve treatment effects. A secondary aim will explore participant variables associated with clinically significant response to STEP-YA.

Methods: This 2-arm randomized prospective trial will enroll 74 off-treatment YACS aged 20 years to 39 years with clinically significant insomnia. Each participant completes the STEP-YA intervention in a 1-on-1 synchronous online session led by a trained interventionist following a structured outline. The 90-minute intervention presents educational information on the development of insomnia after cancer and offers specific suggestions for improving insomnia symptoms. During the session, participants review the suggestions and develop a personalized sleep action plan for implementing them. After the session, participants are randomized to either the coaching condition, in which they receive 2 telephone coaching sessions, or the no-coaching condition, which offers no subsequent coaching. The Insomnia Severity Index (ISI) and the Profile of Mood States: Short Form (POMS-SF) are assessed at baseline and 4 and 8 weeks postintervention.

Results: Enrollment began in November 2022, with 28 participants currently enrolled. We anticipate recruitment will be completed in 2024. The primary endpoint is a change in ISI score from baseline to 8 weeks postintervention. The secondary endpoint is change in mood symptoms (POMS-SF) from baseline to 8 weeks postintervention. Change scores will be treated as continuous variables. Primary analyses will use ANOVA methods. A within-subjects analysis will examine if the STEP-YA intervention is associated with significant changes in insomnia and mood over time. A 2-way ANOVA will be used to evaluate the utility of coaching sessions to improve treatment effects.

Conclusions: Chronic insomnia has significant negative effects on YACS' medical, educational, and psychological functioning. STEP-YA aims to address their needs; study results will determine if the intervention warrants future effectiveness and dissemination studies and if individualized coaching is necessary for adequate treatment response.

Trial Registration: ClinicalTrials.gov NCT05358951: https://clinicaltrials.gov/study/NCT05358951

International Registered Report Identifier (IRRID): DERR1-10.2196/52315

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(JMIR Res Protoc 2023;12:e52315) doi:10.2196/52315

KEYWORDS

insomnia; cancer survivors; young adults; protocol; coaching; mood

Introduction

Background

Because cancer disrupts their physical, emotional, and social development during a critical period in their life, young adult cancer survivors (YACS) are particularly vulnerable to treatment late effects, including insomnia [1-8]. Insomnia is commonly mistakenly viewed by patients and providers "as a temporary reaction to the cancer diagnosis or treatment" [9], with few long-term consequences. However, insomnia frequently develops into a debilitating chronic condition. As many as 1 in 4 YACS experience significant insomnia many years after cancer treatment has ended [5-7,10]. Chronic insomnia is associated with significant health problems in the general population, including heart disease, obesity, hypertension, diabetes, depression, and anxiety [11-20]. Because of their medical history, YACS are already vulnerable to many of these health conditions, making access to effective insomnia treatment critically important to their overall health [21-23].

Cognitive behavioral therapy for insomnia (CBTI) is a well-established and empirically supported treatment. CBTI is the recommended first-line treatment by the American Academy of Sleep Medicine and American Colleges of Physicians for insomnia disorder in adults [24,25]. Multiple randomized trials have demonstrated CBTI is the most effective long-term insomnia treatment, even compared with pharmacotherapy [26-28]. A review of CBTI for cancer survivors similarly concluded it "provides significant, lasting improvement" [29].

Unfortunately, CBTI is largely unavailable to the growing population of YACS who need it [30,31]. To make CBTI widely available to YACS, several barriers need to be resolved, including the shortage of trained CBTI providers [32,33], the patient burden of standard CBTI regimens [34-36], and the lack of CBTI interventions specifically targeting the needs of YACS. Moreover, as YACS' access to effective insomnia care is limited by geography and other factors [30,31,33,37-39], it is imperative CBTI be made more accessible to them in their communities.

To address these challenges and deliver effective insomnia treatment to YACS, we developed the Sleep Treatment Education Program for Young Adult Cancer Survivors (STEP-YA). STEP-YA is a brief, low-intensity intervention presenting core elements of CBTI in an online educational format. Delivered in a 90-minute, 1-on-1, instructor-led session, STEP-YA educates YACS about causes of insomnia after cancer, including developmental, social, and health factors affecting YACS, and introduces them to CBTI principles and methods. During the synchronous (live) online session, survivors review their current sleep habits and consider alternative strategies consistent with CBTI recommendations. The standard elements of CBTI are presented in STEP-YA but with modifications previously shown to maintain efficacy while reducing treatment demands [40]. Additionally, information particularly salient to the experience of YACS was added, including information about how cancer diagnosis and treatment impact sleep and how to deal with young adult stressors (ie, fear of missing out, disconnecting). Following a self-management approach, the instructor provides guided behavioral planning, encouraging survivors to develop an individualized sleep action plan they will implement after the session.

Objectives

The STEP-YA intervention is designed to address barriers to insomnia treatment for YACS because it is brief, low-cost, low-burden, and targets their specific needs and experiences. Delivered virtually, STEP-YA is available to YACS when and where they need it, without requiring travel to a specialized insomnia treatment site. As a self-management intervention, STEP-YA supports YACS' autonomy by helping them make informed choices to manage their own insomnia [41], without taking the prescriptive stance commonly found in behavioral therapies. The efficacy of STEP-YA is currently being evaluated in a clinical trial described here. The primary aims of the study are to (1) test the hypothesis that STEP-YA improves insomnia symptoms (primary outcome) and mood (secondary outcome) in YACS and (2) determine if improvement in these outcomes is superior in the coaching condition compared with the noncoaching condition. A secondary aim of the study is to explore participant variables associated with clinically significant response to the STEP-YA intervention.

Methods

Study Design

Guided by the Obesity-Related Behavioral Intervention Trials (ORBIT) model for development and early testing of behavioral interventions [42-44], the STEP-YA intervention is being evaluated in an early-stage (phase 2A) randomized clinical trial. Participants are randomized (1:1) to receive the STEP-YA intervention either (1) alone (noncoaching condition) or (2) with the addition of 2 remote coaching sessions (coaching condition). STEP-YA sessions are delivered online via live videoconference. Outcomes are assessed at baseline and again 4 weeks and 8 weeks postbaseline. Participants are off-treatment YACS recruited from treatment centers, advocacy groups, and social media, and will complete all study activities remotely.

Ethics Approval

Prior to study activation and participant enrollment, the study protocol was approved by the Dana-Farber/Harvard Cancer Center Institutional Review Board (Protocol 21-613).

Participants

Participants will be 74 off-treatment YACS aged 20 years to 39 years. To be eligible for enrollment, YACS were diagnosed with cancer (excluding nonmelanoma skin cancer) at least 1

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year prior, have received no cancer therapy (excluding chemoprevention) in the prior 4 months, and have no additional cancer therapy planned. Additionally, participants must be able to read and write in English and have significant insomnia as evidenced by an Insomnia Severity Index (ISI) ≥12 [45]. YACS who have specific conditions, medications, or past insomnia treatments that may affect their sleep or response to STEP-YA are excluded; these inclusion and exclusion criteria are detailed in Table 1.

Table 1. Study inclusion and exclusion criteria.

Category	Criteria	Rationale
Inclusion criteria		
General	• Age 20 years to 39 years • Able to read and write in English	Enroll off-treatment YACS[a] able to participate in the intervention currently available only in English
Health issues	• History of a cancer diagnosis (except nonmelanoma skin cancer) ≥1 year prior • No active cancer therapy (excluding chemoprevention) in the past 4 months and no further therapy planned	Enroll off-treatment YACS able to participate in the intervention currently available only in English
Sleep problems	• Significant insomnia, as evidenced by an Insomnia Severity Index (ISI) score ≥12	To test this intervention with individuals with clinically significant insomnia
Exclusion criteria		
General	• Any impairment (hearing, visual, cognitive) that interferes with the ability to complete all study measures independently	Exclude individuals not able to independently complete the study procedures
Health issues	• Diagnosed with bipolar disorder • Report being diagnosed with a seizure disorder or having experienced a seizure in the past 12 months	Exclude individuals for whom behavioral treatment for insomnia may require modification due to medical conditions
Sleep problems	• Intention to adjust (decrease or increase) use of any prescribed or over-the-counter medications taken to decrease insomnia during the study period • Survivors who report being diagnosed with sleep apnea who are not receiving recommended medical treatment for their sleep apnea • Survivors who report suspected sleep apnea who have not completed an evaluation by a sleep specialist • Survivors who report their usual bedtime is not between 5 PM and 5 AM • Employment that involves irregular sleep patterns, such as shift work or frequent long-distance travel across time zones, or employment in a position that could impact public safety	Exclude individuals whose sleep symptoms may require significant modifications in behavioral treatment for their insomnia
Prior insomnia treatment	• Prior participation in a research study that provided an educational or behavioral intervention for insomnia • Prior participation in a behavioral treatment or patient education program for insomnia delivered at the study site • Participation in behavioral or educational interventions for insomnia in the 2 years prior to enrollment (including synchronous and asynchronous online insomnia programs)	Enroll only participants naïve to the insomnia educational programs and behavioral treatments

[a]YACS: young adult cancer survivors.

Recruitment

Recruitment materials and procedures are designed to allow YACS to self-refer to the study. These materials include a brief informational video, study information sheet, outreach letters and emails, informational postcards, and brief study descriptions suitable for posting on patient-facing materials distributed by patient support and advocacy groups. All materials provide phone, email, and web contact information for YACS interested in learning more about the study. Examples of these can be seen on the study website [46].

To distribute these materials to potentially eligible YACS, several methods are used. At our cancer center, recruitment postcards are placed in patient waiting areas, and study information appears on hospital screens presenting information and notices to patients. Clinical providers are informed of the study and given recruitment information and materials. In several cases, providers have granted permission to send recruitment letters directly to their eligible patients. Programs that serve supportive care needs at the center are also asked to include study information in their newsletters, emails, or social media posts. Following similar procedures, recruitment information and materials have been shared with providers at several other cancer centers in the United States. Outside of cancer centers, these materials are also posted on research portals, posted on social media sites (ie, Facebook, Instagram,

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Reddit), and provided to patient advocacy and support groups (regionally and nationally) for distribution to their members.

Procedures

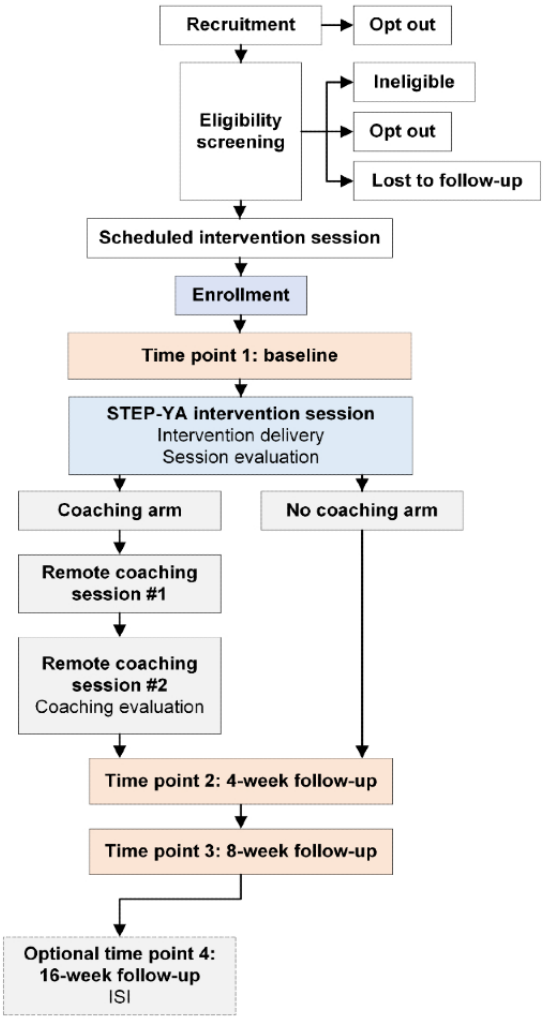
Screening and Scheduling

YACS who contact the study team are provided with information about the study including the study information sheet, which provides details of the study aims and procedures. Questions about the study are answered through email or telephone contact. Survivors who are interested in participating are offered the opportunity to schedule a screening meeting via videoconference. In this meeting, survivors can ask any additional questions and complete the eligibility screening, which is conducted by a research assistant. Eligible YACS are then invited to schedule an intervention session, while ineligible survivors are provided with resources [47] for finding help for insomnia. Any questions or concerns about eligibility are referred to the study's principal investigator (CJR) for clarification and eligibility determination.

Intervention Session

In the intervention session, eligible participants complete the consent procedure and a baseline survey before receiving the STEP-YA intervention (Figure 1). Following the intervention, participants are randomized to either the coaching or noncoaching condition, and follow-up contacts are scheduled.

Figure 1. Participant study flow chart for the Sleep Treatment Education Program for Young Adult Cancer Survivors (STEP-YA) study. ISI: Insomnia Severity Index.



Consent Process

YACS who are screened for eligibility more than 2 weeks prior are rescreened for eligibility. Potential participants are provided with a study information sheet, which contains all the elements of informed consent. The interventionist reviews this study information and answers any questions the potential participant may have. Individuals who wish to enroll in the study are then asked to provide verbal consent to the interventionist, who documents this in the study record. This study has been approved for a Waiver of Documentation of Informed Consent, as it is a minimal risk study involving no procedures for which signed consent is generally required outside of the research context.

Baseline Survey

After consenting, participants complete a baseline survey. Study staff guide participants in completing the survey using the Qualtrics web-based survey platform [48]. Participants enter data directly into the system, and the study staff do not collect data from participants.

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STEP-YA Intervention Delivery

STEP-YA is delivered in a single, 90-minute synchronous videoconference session using HIPAA-compliant Zoom technology [49-51] licensed to our cancer center. Interventionists with graduate-level training in psychology, social work, or a closely aligned discipline are trained and supervised by psychologists with CBTI expertise to deliver the STEP-YA intervention. The interventionist delivers STEP-YA in a 1-on-1 session using a slide deck of 47 slides and following a structured outline. During the session, the participant can see and hear the presenter, view the presentation slides, and ask questions. To support participants in developing and implementing their sleep action plan, take-home materials including a copy of the presentation slides and the sleep action plan template are provided by email. The presentation begins with educational information on the problem of insomnia after cancer and the 3-P model of insomnia by Speilman and colleagues [52], before presenting specific suggestions for improving sleep in YACS. These suggestions are based on the CBTI components of sleep hygiene, stimulus control, and cognitive restructuring [29,35,53-55]. To aid comprehension, this material is presented in 4 sections addressing (1) lifestyle issues (eg, benefits of exercise and limiting alcohol), (2) sleep environment (eg, importance of a dark, quiet bedroom; avoiding bed for nonsleep activities), (3) sleep timing (eg, regular wake time, sleep ritual), and (4) managing expectations and challenges (eg, sleep worry, physical symptoms, social pressures). For each suggestion, the underlying rationale and potential benefits are presented. Both the look and content of the STEP-YA material are targeted to appeal to YACS. For example, text describing the benefits of exercise is accompanied by photos of young adults engaged in traditional and contemporary exercises, (eg, yoga, spin class), and the description of the effects of caffeine includes photos of products YACS commonly consume (eg, energy drinks, green tea, sodas, coffee drinks). In section 4, examples of the social, developmental, and health challenges that YACS may encounter are noted, along with suggestions for managing them. These include living spaces shared with roommates or parents, social pressures, “fear of missing out,” and a tendency toward a delayed sleep phase common in young adults, as well as physical health symptoms (eg, pain or hot flashes). At the conclusion of each section (eg, lifestyle), the participant is asked to review the suggestions in the section and complete their sleep action plan template with the interventionist to record their current sleep practices and behavioral changes they intend to make. Action plans of this kind are central to self-management education [41] and have been shown to increase successful behavior change [56,57]. To close the session, the presenter offers examples of STEP-YA suggestions implemented in a daily routine and asks the participant to review and revise their sleep action plan, including anticipating challenges and planning strategies to manage them.

Randomization and Follow-Up

After receiving the STEP-YA intervention, participants are randomized using Sealed Envelope [58], a commercially available online software application for randomizing patients into clinical trials. Participants are randomized (1:1) to either (1) STEP-YA alone (noncoaching condition) or (2) STEP-YA with the addition of 2 remote coaching sessions (coaching condition). In order to ensure the 2 arms of the study are balanced by age group, randomization, with a block size of 4, is stratified by those aged 20 years to 29 years versus those aged 30 years to 39 years. Participants are informed of whether they have been randomized to receive the coaching sessions, then they are scheduled for their next telephone contact with the study (Figure 1). Coaching condition participants are scheduled for the first coaching session, and noncoaching participants are scheduled for their 4-week follow-up call. Additionally, participants are asked to provide preferences for all future study contact and correspondence (eg, phone, email, text, mail).

Baseline Session Evaluation

At the end of the intervention session, all participants are asked to complete a satisfaction form evaluating their experience with the intervention session. Participants receive a link to a questionnaire on which they report on ease of use and acceptability, satisfaction, and credibility of the session. To promote completion of the questionnaire, participants are encouraged to complete it while still in the intervention session but can choose to complete it later. Participants receive a US $10 gift card upon completion of this evaluation.

Postintervention Follow-Up

Coaching Sessions

Participants randomized to the coaching condition receive 2 individualized remote coaching sessions conducted via phone call: 1 a week following the STEP-YA session and again 2 weeks following their STEP-YA session. Optimal timing for coaching sessions is 7 days and 14 days after the STEP-YA session but may be scheduled between 5 days and 23 days after the STEP-YA session with at least 5 days between coaching sessions. Paraprofessional coaches (ie, research assistants) trained and supervised by psychologists with CBTI expertise follow a structured coaching outline. In the sessions, designed to last approximately 30 minutes, coaches ask participants to review their progress and challenges implementing their personal sleep action plan. Coaches offer support and encouragement and may refer participants to the take-home materials to help answer questions and reinforce program goals and suggestions. Following principles of self-care management and previous coaching interventions successful with cancer survivors [59-63], coaching sessions are not prescriptive but support YACS to use self-management skills, including decision-making, goal setting, self-assessment, and problem-solving, to help them implement their individual sleep action plan. Administrative data on coaching session duration and sessions missed, interrupted, or rescheduled are collected.

Outcome Data Collection

At 4 weeks and 8 weeks postbaseline, study staff recontact participants by telephone at previously scheduled times, ask them to enter follow-up data directly into Qualtrics, and provide technical assistance if needed. Participants who cannot complete the full assessment at that time due to time constraints are asked to complete the 7-item ISI (primary outcome measure) verbally, and their responses are collected; they are then asked to complete the full questionnaire at their earliest convenience.

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Participants receive emailed reminders in advance of each phone call. At the 4-week call, participants schedule a phone call for the 8-week assessment. Upon completion of the 4 and 8-week assessments, participants receive a US $25 gift card. At the time of their 8-week follow-up phone call, participants are asked if they would be willing to complete an optional assessment 2 months later. Participants who agree receive a Qualtrics link to the 7-item ISI 16 weeks after the intervention session by email. This takes approximately 1 minute to 2 minutes to complete, and participants do not receive an incentive for this optional assessment. The link is sent again 1 week later for nonresponders, but participants receive no additional reminders.

Intervention Training and Supervision

STEP-YA Intervention

Interventionist trainees familiarize themselves with the STEP-YA protocol and participant-facing STEP-YA materials and discuss these materials with the principal investigator. They are asked to closely review the STEP-YA presentation slides and the structured outline detailing how each slide should be presented to participants before reviewing audiotaped, videotaped, and transcribed STEP-YA sessions. When possible, and with the consent of a participant, trainees attend at least 1 live intervention session to observe STEP-YA administration. Following the session, the interventionist answers any questions the trainee might have and demonstrates postsession procedures. After completing these steps, trainees deliver the STEP-YA intervention in mock interviews with a research assistant (≥2 interviews) and an experienced interventionist (≥1 interview) playing the role of a study participant. Mock sessions are transcribed, scored for fidelity, and reviewed by the principal investigator. Interventionists are approved to conduct STEP-YA sessions with study participants after reliably demonstrating the ability to follow the structured outline for each slide of the STEP-YA presentation in a final mock interview. All interventionists record and transcribe an intervention session (recording only themselves, not the participant) after every 5 to 10 participants. These transcriptions are scored for fidelity and discussed with the principal investigator to ensure adherence to the STEP-YA intervention outline and to reduce deviation between interventionists.

Coaching

Paraprofessionals are trained as STEP-YA coaches using a coaching session outline and semistructured script. Coach trainees listen to a minimum of 3 live coaching sessions conducted by an experienced coach and discuss the flow of the script based on participants' reports of sleep action plan challenges and successes. Trainees then conduct 2 audiotaped mock coaching sessions with an experienced coach or psychologist with CBTI experience acting as a participant and receive feedback on the content of the sessions. Finally, trainees conduct at least 2 live sessions with study participants accompanied in the session by an experienced coach serving as a session co-leader. With approval of the principal investigator (CJR), coaches are then able to conduct their own sessions with study participants.

Measures

Outcomes for the trial are change in insomnia symptoms as measured by the ISI (primary) and change in mood symptoms as measured by the Profile of Mood States Short form (POMS-SF; secondary) [64]. In addition to these scales, measures of demographic and health variables are included, as are measures of participant experience and satisfaction with the intervention. Details of all measures and time points they are given are included in Table 2.

Table 2. Study measures.

Measure	Baseline	Coaching session #2	4-week follow-up	8-week follow-up	Optional 16-week follow-up
Demographic information	X	—[a]	—	—	—
Medical information	X	—	—	—	—
Morningness-Eveningness Questionnaire (MEQ)	X	—	—	—	—
SF-12 Item: Health Rating	X	—	X	X	—
Pain thermometer	X	—	X	X	—
Insomnia Severity Index (ISI)	X	—	X	X	X
Profile of Mood States: Short Form (POMS-SF)	X	—	X	X	—
Session evaluation	X	—	—	—	—
Telehealth Usability Questionnaire	X	—	—	—	—
Coaching evaluation	—	X	—	—	—
Sleep treatment change	—	—	X	X	—

[a]Not measured at this time point.

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Statistical Analysis

Endpoints

This is a randomized 2-arm trial evaluating the STEP-YA intervention when delivered with and without a supplementary remote coaching session. The primary endpoint is the change in ISI score from baseline to 8 weeks postintervention. The secondary endpoint is the change in mood symptoms on the POMS-SF from baseline to 8 weeks postintervention. Change scores will be treated as continuous variables, and primary analyses will use analysis of variance methods. Cohen *d* will be used to quantify within-group effect sizes, and Hedges *g* adjustment will estimate between-group effect sizes. Data collected at the 4-week postintervention assessment will be analyzed using similar methods for descriptive and exploratory purposes.

Missing Data

Participants are randomized after completing a baseline assessment so complete baseline data are assured. Primary analysis will be an intent-to-treat analysis of randomized participants. Based on experience using similar data collection methods, we anticipate minimal missing data (<10%). If needed, we will use multiple imputation to account for missing data. Potential factors in the imputation model include baseline sleep and mood variables. Sensitivity analysis will be used to evaluate the potential impact of imputation on results.

Results

Primary and Secondary Outcomes

Aim 1 of the study will be addressed using a within-subjects analysis including all participants to determine if the STEP-YA intervention is associated with significant changes in outcome measures (insomnia and mood) over time. Aim 2 will be addressed using 2-way analysis of variance with 1 between-subjects factor (coaching vs noncoaching) and 1 within-subjects factor (time) and an interaction term.

To address the secondary exploratory aim, logistic regression analysis will be used to identify participant factors associated with a clinically significant response to the STEP-YA intervention. Analyses will attempt to identify demographic and sleep factors (eg, age, severity of insomnia symptoms) associated with a reduction of ISI scores ≥6 points at 8 weeks. Variables identified in univariate analysis (P<.10) will be entered into a multivariable model estimating STEP-YA response from baseline variables. Analyses will explore these relationships separately in the 2 study arms; pooled analyses including participants across arms will be conducted if univariate analyses indicate the relationships of predictors and outcome are consistent.

Sample Size and Statistical Power for the Primary Outcome

To meet study aims, we require 64 participants with evaluable data but will enroll 74 as a hedge against attrition. Our prior single-session educational interventions have demonstrated large effects on insomnia symptoms of d≥1.00; the study is conservatively powered to detect an effect size of .52 (primary aim). With sample size of 64 (32 per arm), the study will have 80% power to detect an effect of this size within each arm (α=.05). To compare the relative improvement in the primary endpoint between arms, 64 subjects will have 80% power to detect a difference of d=0.62 between arms (α=.05, 1-sided).

Timeline

Enrollment began in November 2022. As of September 2023, 30 participants had been enrolled. We anticipate recruitment will be completed in 2024.

Discussion

Overview

STEP-YA was developed to meet YACS' need for effective behavioral insomnia treatment by addressing the low completion rates and lack of access to care common to standard CBTI treatment [30,37,65] and by targeting developmental, social, and health factors that affect their sleep. As a low-intensity intervention, STEP-YA is not intended to completely replace intensive CBTI treatment, which some YACS likely require. Rather, by meeting the needs of the majority of YACS for whom standard insomnia treatments are not appealing, not needed, or currently not available, STEP-YA aims to reduce treatment barriers and avoid potential overtreatment. Though adapted from 2 previously tested brief behavioral interventions for insomnia with cancer survivors [40,66], STEP-YA is a novel intervention as yet unsupported by clinical testing. As recommended in the ORBIT model for development and testing of novel behavioral interventions [42-44], this trial will provide the first empirical evidence evaluating the efficacy of STEP-YA. Study results will help determine whether evidence of efficacy is sufficient to warrant future trials of the existing STEP-YA intervention and aid in the design of future trials investigating its clinical effectiveness in clinical practice. Additionally, results will help to identify subgroups of YACS most likely to benefit from STEP-YA and help to determine whether individualized coaching or other efforts to further optimize the intervention are warranted. We anticipate that data supporting the efficacy of STEP-YA would lead to Phase 3 efficacy trials of STEP-YA in larger and more diverse populations. In addition, positive trial results would also support implementation research into the potential to deliver STEP-YA in small groups and in collaboration with existing survivor advocacy and support groups, which could increase access to insomnia treatment for YACS.

Limitations and Strengths

Conceptualized within the ORBIT model, this early (stage 2a) trial is designed with a limited scope; it is not intended to conclusively evaluate the efficacy of STEP-YA but to determine if preliminary evidence supporting "proof of concept" for STEP-YA is sufficient to warrant continued efficacy research. As such, the trial design has several notable limitations. Without a control group, study results cannot evaluate how much the observed trial effects are due to natural changes over time or nonspecific effects associated with trial participation. With a modest sample size of English-speaking participants, data on how demographic, cultural, and other participant variables

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moderate the effects of the intervention will be limited. Similarly, the study will not be able to shed light on any long-term effects of the intervention for participants beyond the 8 and 16-week time points.

Despite these limitations, the trial is well-positioned to provide new and clinically relevant information regarding insomnia interventions for YACS. STEP-YA represents a significant innovation in behavioral insomnia treatment for YACS by delivering a self-management intervention that is less demanding than standard CBTI and attends to YACS specific concerns. In addition, by using nonclinician interventionists to deliver the intervention synchronously online, it aims to overcome logistical barriers and increase access while avoiding uptake and adherence challenges common to asynchronous insomnia interventions [38,67-70]. Investigating the efficacy of this approach is critical for evaluating the potential utility of the STEP-YA intervention and for the potential of applying these intervention methods to address other behavioral needs in this vulnerable population.

Conclusion

It is well known that behavioral treatment significantly reduces insomnia symptoms but only for those who can access it, which most YACS cannot [30,31]. Our work aims to provide YACS access to empirically supported behavioral insomnia treatment by developing and testing a brief, low-intensity intervention that addresses their needs and interests and can be delivered to them wherever they have internet access. If shown to be effective, this approach has the potential to greatly improve access to the growing population of YACS whose health and quality-of-life are affected by insomnia.

Acknowledgments

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Data Availability

The data sets generated and analyzed during this trial will be available from the corresponding author on reasonable request following completion of the trial and publication of the main outcomes.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Funding information.
[PDF File (Adobe PDF File), 145 KB - resprot_v12i1e52315_app1.pdf]

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Abbreviations

CBTI: cognitive behavioral therapy for insomnia
ISI: Insomnia Severity Index
ORBIT: Obesity-Related Behavioral Intervention Trials
POMS-SF: Profile of Mood States: Short Form
STEP-YA: Sleep Treatment Education Program for Young Adult Cancer Survivors
YACS: young adult cancer survivors

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Protocol

Design and Rationale of Cytokine Filtration in Lung Transplantation (GLUSorb): Protocol for a Multicenter Clinical Randomized Controlled Trial

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Abstract

Background: Lung transplantation (LTx) is the only treatment option for end-stage lung disease. Despite improvements, primary graft dysfunction (PGD) remains the leading cause of early mortality and precipitates chronic lung allograft dysfunction, the main factor in late mortality after LTx. PGD develops within the first 72 hours and impairs the oxygenation capacity of the lung, measured as partial pressure of oxygen (PaO_2)/fraction of inspired oxygen (FiO_2). Increasing the PaO_2/FiO_2 ratio is thus critical and has an impact on survival. There is a general lack of effective treatments for PGD. When a transplanted lung is not accepted by the immune system in the recipient, a systemic inflammatory response starts where cytokines play a critical role in initiating, amplifying, and maintaining the inflammation leading to PGD. Cytokine filtration can remove these cytokines from the circulation, thus reducing inflammation. In a proof-of-concept preclinical porcine model of LTx, cytokine filtration improved oxygenation and decreased PGD. In a feasibility study, we successfully treated patients undergoing LTx with cytokine filtration (ClinicalTrials.gov; NCT05242289).

Objective: The purpose of this clinical trial is to demonstrate the superiority of cytokine filtration in improving LTx outcome, based on its effects on oxygenation ratio, plasma levels of inflammatory markers, PGD incidence and severity, lung function, kidney function, survival, and quality of life compared with standard treatment with no cytokine filtration.

Methods: This study is a Swedish national interventional randomized controlled trial involving 116 patients. Its primary objective is to investigate the potential benefits of cytokine filtration when used in conjunction with LTx. Specifically, this study aims to determine whether the application of cytokine filtration, administered for a duration of 12 hours within the initial 24 hours following a LTx procedure, can lead to improved patient outcomes. This study seeks to assess various aspects of patient recovery and overall health to ascertain the potential positive impact of this intervention on the posttransplantation course.

Results: The process of patient recruitment for this study is scheduled to commence subsequent to a site initiation visit, which was slated to take place on August 28, 2023. The primary outcome measure that will be assessed in this research endeavor is the oxygenation ratio, a metric denoted as the highest PaO_2/FiO_2 ratio achieved by patients within a 72-hour timeframe following their LTx procedure.

Conclusions: We propose that cytokine filtration could enhance the overall outcomes of LTx. Our hypothesis suggests potential improvements in LTx outcome and patient care.

Trial Registration: ClinicalTrials.gov NCT05526950; https://www.clinicaltrials.gov/study/NCT05526950

International Registered Report Identifier (IRRID): PRR1-10.2196/52553

(JMIR Res Protoc 2023;12:e52553) doi:10.2196/52553

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KEYWORDS

lung transplantation; cytokine filtration; primary graft dysfunction; chronic lung allograft dysfunction; randomized controlled clinical trial

Introduction

Lung transplantation (LTx) remains the standard option for treating patients with irreversible end-stage pulmonary disease [1]. Of all transplanted organs, the mean 5-year survival is the lowest following LTx [2]. The high mortality is highly associated with primary graft dysfunction (PGD), which arises in the first 72 hours after LTx and can lead to chronic lung allograft dysfunction (CLAD) within the first 3-5 years [3]. The cumulative incidence of these 2 conditions is between 40% and 80%. The fear of PGD leads to a low use rate of donated lungs, with only 20% of donated lungs being used [4].

PGD is reflected in the oxygenation capacity of the lung, measured as the ratio of the partial pressure of oxygen (PaO_2) to the fraction of inspired oxygen (FiO_2), which decreases with increasing PGD severity [2]. PGD is diagnosed according to International Society for Heart and Lung Transplantation guidelines [5] if the PaO_2/FiO_2 ratio drops below 300 and radiographic infiltrates are present in the lungs, consistent with pulmonary edema. Consequently, increasing the PaO_2/FiO_2 ratio following LTx is critical and may directly impact survival.

There is a general lack of effective treatments for both PGD and CLAD. When a transplanted lung is not accepted by the immune system in the recipient, a systemic inflammatory response starts where cytokines play a critical role in initiating, amplifying, and maintaining the inflammation leading to PGD [6]. Cytokine filtration can remove these cytokines from the circulation, thus reducing inflammation. Cytokine filtration devices have been shown in vitro and in vivo during orthotopic heart transplantation and kidney transplantation to target and reduce levels of medium– and low–molecular-weight molecules, such as cytokines, pathogen-associated molecular pattern molecules, and damage-associated molecular patterns [7-9]. Other than our feasibility study (ClinicalTrials.gov; NCT05242289) and a case series using extracorporeal cytokine adsorption therapy as rescue after LTx [10], this tool has not been applied to human LTx.

In this study, we want to test whether cytokine filtration improves outcome if administered in conjunction with LTx, for 12 hours in the first 24 hours following the procedure.

Methods

Study Design

The SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist was used when writing this report [11]. This report is based on protocol version GLUSorb-CIP-V1 dated March 4, 2023. All items from the World Health Organization's trial registration data set are found at ClinicalTrials.gov (NCT05526950).

Intervention

The CytoSorb Device (CytoSorb) is a single-use, polymer-based adsorption system for the dialysis of physiological fluids in extracorporeal therapies. It consists of a cartridge, containing a cross-linked divinylbenzene polymer that can be connected to various extracorporeal circuits. Blood is pumped through the CytoSorb cartridge and then returned to the body. The beads bind to a wide range of inflammatory mediators, including cytokines and chemokines. The device has been used in several trials, mostly for cardiac surgery patients [12-17]. The device is Conformité Européene–marked and is to be used within its intended use and indication and according to the manufacturer's instructions.

The CytoSorb device will be connected for 12 consecutive or nonconsecutive hours within the first 24 hours after the end of the surgery. As participants will be in the intensive care unit during this time, adherence to intervention protocol will be the responsibility of the attending physician and perfusionist. The device may be disconnected and reconnected as necessary for the care of the patient, for example during extubation or mobilization. The participant may also be removed from a clinical investigation by the treating physician, and the intervention discontinued if they find that this is in the best interest of the participant. All other concomitant care and interventions will be according to clinical standard procedures for LTx in Sweden.

Purpose of the Clinical Investigation

The purpose of this clinical trial is to demonstrate the superiority of cytokine filtration in improving LTx outcome, based on its effects on oxygenation ratio, plasma levels of inflammatory markers, PGD incidence and severity, lung function, kidney function, survival, and quality of life (QOL) compared with standard treatment with no cytokine filtration.

Study Design and Setting

The investigation is a randomized, parallel group, Swedish national multicenter superiority trial comparing cytokine filtration following LTx to standard treatment with no cytokine filtration. A comparator device will not be used in the control group as there is currently no clinically accepted alternative to achieve cytokine removal from the blood, and thus, the control group will only receive standard LTx treatment. The trial sponsor is Region Skåne and SL is the sponsor representative.

Inclusion Criteria

The participant must meet the following inclusion criterion:

- Eligibility to undergo double LTx at either trial site (Skane University Hospital or Sahlgrenska University Hospital) [18].

Exclusion Criteria

The participant must not meet any of the following exclusion criteria:

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- Age <18 years
- Previous organ transplantation
- Presence of any conditions at the time of surgery that require immunosuppressive therapy. Immunosuppressive therapy is defined as:
  - Cyclosporine, tacrolimus, everolimus, or sirolimus—minimum 1 month of treatment prior to transplantation and active treatment at the time of transplantation.
  - Any form of antibody-based treatment that is known for having an immunomodulatory effect taken up to 1 week before transplantation.
- Nonconsent

Patients fulfilling the inclusion criterion and none of the exclusion criteria as shown will be randomized to 1 of the 2 groups. Enrollment will continue until the required sample size is achieved or until the interim analysis.

Any substantial modifications to the protocol after this study begins will be duly communicated to them.

Clinical Investigation Objectives

Primary Objective

The primary objective is to determine whether cytokine reduction by cytokine filtration leads to improved oxygenation in patients undergoing LTx.

Secondary Objective

The secondary objective is to determine whether cytokine reduction by cytokine filtration improves levels of plasma inflammatory markers (including cytokines), lung infiltrates and oedema, arterial blood gas measures, incidence and severity of PGD, need for norepinephrine, mortality, lung diffusion capacity, spirometry measures, acute rejection episodes, chest computed tomography (CT) findings, CLAD, kidney function, and QOL in patients undergoing LTx.

Safety Objective

The safety objective is to determine the number of adverse events and plasma levels of immunosuppressant drugs following cytokine filtration in patients undergoing LTx.

Exploratory Objective

The exploratory objective is the collection of lung tissue, blood, bronchoalveolar lavage fluid samples and, when available, explanted tissue from recipients for future exploratory analyses of cytokines and immune cells in patients undergoing LTx with and without cytokine filtration.

Study Population

This study's population will consist of a representative group (n=116) of patients with de novo double lung transplants in Sweden who fulfill the requirements according to the inclusion and exclusion criteria stated above.

Outcomes

Primary Performance End Point

The primary end point is the oxygenation ratio, defined as the highest PaO_2/FiO_2 ratio within 72 hours after LTx.

Secondary Performance End Points

The secondary end points are (1) plasma levels of inflammatory markers: interleukin (IL)-10, IL-1β, soluble IL-2 receptor, IL-6, IL-8, and tumor necrosis factor α before and immediately after transplantation and at 6, 12, 24, 48, and 72 hours after transplantation and C-reactive protein and white blood cells before and immediately after transplantation and at day 1, 2, and 3 after transplantation; (2) infiltrates and oedema measured by chest x-ray or CT scan of the thorax at day 1, 2, and 3 after transplantation; (3) highest daily arterial blood gas measurements recorded on day 1, 2, and 3 after transplantation, as a measure of lung function; (4) PGD severity as evaluated per standard clinical procedures using a rating scale from 0 to 3 on day 1, 2, and 3 after transplantation, as a measure of lung function; (5) presence of any grade of PGD on day 1, 2, and 3 after transplantation, as a measure of lung function; (6) total dose of norepinephrine administered in the first 72 hours; (7) mortality up to 48 months after transplantation; (8) lung diffusion capacity, measured by carbon monoxide diffusion, at 6, 12, 24, and 48 months after transplantation, as a measure of lung function; (9) forced expiratory volume, forced vital capacity, and total lung capacity measured by spirometry at 1, 3, 6, 12, 24, and 48 months after transplantation, as a measure of lung function; (10) occurrence of any acute rejection episodes (clinically treated and/or biopsy verified) up to 48 months after transplantation, as a measure of lung function; (11) chest CT findings at 1, 3, 6, 12, 24, 36, and 48 months after transplantation; (12) the presence of any CLAD and CLAD subtypes up to 48 months after transplantation, as a measure of lung function; (13) kidney function evaluated by measurement of serum creatinine levels; calculated glomerular filtration rate and need for renal replacement therapy on day 1, 2, and 3 and at 1, 3, 6, 9, 12, 24, and 48 months after transplantation; urea levels on day 1, 2, and 3 after transplantation; and iohexol-clearance at 3, 6, 9, 12, 24, 36, and 48 months after transplantation; and (14) QOL evaluated by the 36-Item Short Form Health Survey at 24 and 48 months after transplantation.

Safety End Points

The safety end points are adverse events, serious adverse events (SAEs), and plasma levels of immunosuppressant drugs (cyclosporine, tacrolimus, everolimus, or sirolimus) in the first 72 hours after transplantation.

Exploratory End Points

The exploratory end points are the collection of a portion of routinely collected transplanted lung tissue by transbronchial biopsy and bronchoalveolar lavage fluid (at least at 1, 3, and 12 mo, with additional time points if clinically indicated), collection of explanted recipient lung tissue, and collection of blood samples (at least before transplantation; immediately after transplantation; 6, 12, 24, 48, and 72 h; 1 and 2 wk; and 1, 3, 6, 9, 12, 24, 36, and 48 mo after transplantation, with additional

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time points if clinically indicated) in a biobank for future exploratory analyses. Sample collection protocols will be detailed in a separate standard operating procedure.

Methodology

Medical Chart Review

The following data will be collected from medical charts at specified timepoints: background variables (demographics, comorbidities, therapies, and perioperative data), FiO_2 measurements (baseline and 0-72 h after transplantation, adjusted for ventilation), arterial blood gas measurements (baseline and d 1-3 after transplantation), radiological assessments (infiltrates and edema at d 1-3), PGD severity (d 1-3 using a 0-3 scale), total norepinephrine dosage (first 72 h), lung carbon monoxide diffusion capacity (baseline, 6, 12, 24, and 48 mo), spirometry (forced expiratory volume, forced vital capacity, total lung capacity at 1, 3, 6, 12, 24, and 48 mo), chest CT findings (1, 3, 6, 12, 24, 36, and 48 mo), CLAD assessment (presence and subtype up to 48 mo), renal function (serum creatinine, glomerular filtration rate, need for renal replacement therapy at specified intervals), urea levels (d 1-3), iohexol clearance (3, 6, 9, 12, 24, 36, and 48 mo), mortality data (up to 48 mo), acute rejection episodes (occurrence and type up to 48 mo), immunosuppressant levels (first 72 h), adverse events, and SAEs.

Follow-Up Questionnaires

QOL will be evaluated at 24 and 48 months after transplantation by designated follow-up assessors who are trained in the administration of the questionnaire. QOL scores will be collected using the Short Form Health Survey questionnaire, which assesses QOL and severity of disease for various chronic conditions [19].

Clinical Assessment

Data from assessments and visits will be obtained from the medical records. All data must be supported by the patient's medical records, that is, source documentation, and subsequently stored in an electronic case record form (eCRF).

Safety Assessment

The investigators will report all SAEs and device deficiencies to the sponsor no later than 3 calendar days after they become aware of the event. The sponsor will report to the Swedish Medical Products Agency all of the following reportable events: (1) any SAE that has a causal relationship with the investigational device, the comparator or the investigation procedure, or where such causal relationship is reasonably possible; (2) any device deficiency that might have led to a SAE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate; and (3) any new findings in relation to any event referred to above. Foreseeable adverse events related to LTx will not be reported [20-26].

Data Safety Monitoring Board

Safety reviews and oversight will be under the direction of a Data Safety Monitoring Board (DSMB). The DSMB will be composed of a statistician and 2 physicians (with knowledge in the therapeutic area) who otherwise are not involved in the clinical investigation and are independent from the sponsor, without any competing interests. The DSMB shall be blinded in their safety assessments but can request to unblind the analysis in case of safety concerns. The DSMB will also carry out the interim analysis of the primary outcome variable described in the statistical analysis section. The clinical investigation can be terminated if the DSMB determines that the number of adverse events in the intervention group is unacceptable.

Blinding

The physicians, perfusionists, and nurses administering the treatment will not be blinded. Thus, unblinding for these parties is not possible. Outcome assessors for long-term follow-up visits after 1 month will be blinded. Statisticians carrying out the analyses after the end of this study will be blinded. In the case of termination of the clinical investigation, the statisticians will only be unblinded after all analyses are complete, regardless of whether this study is terminated on time or prematurely.

Statistical Considerations

Analysis Population

An intention-to-treat (ITT) analysis population will comprise all patients who have been randomized and who have reached the intervention period (the 24 h immediately after the end of LTx surgery), the so-called modified ITT. Patients who were randomized but did not undergo LTx surgery, who died during surgery, or who did not reach the intervention period for any reason will not be included in this population. Analyses based on this population (modified ITT) will group patients according to the treatment they were randomized to receive, regardless of the actual treatment received. We do not expect missing data for the primary outcome variables. Any missing data will be handled as recommended by Jakobsen et al [27].

Descriptive Statistics

Normally distributed continuous data will be presented as the mean (SD) and 95% CIs. Nonnormally distributed continuous data will be presented as the median, IQR, and 95% CIs. Categorical and binary data will be presented as a percentage with CIs, and as absolute numbers. Ordered categorical variables will be presented as the median, IQR, and 95% CIs.

Statistical Design, Method, and Analytical Procedures

All statistical analyses will be performed by an independent statistician. Treatment allocation will remain concealed during the initial analysis, with the 2 groups labelled as "group A" and "group B," ensuring a blinded statistical analysis. All statistical tests will be 2-sided. The distribution of continuous variables will be determined by visual inspection of histograms and quantile-quantile plots. The primary outcome will be based on the mean highest PaO_2/FiO_2 ratio within the first 72 hours (a continuous variable). Differences between treatment groups in the mean highest PaO_2/FiO_2 ratio within the first 72 hours will be compared using a multivariate linear regression model adjusted for, at minimum, the stratification variables (site, age, and gender). Continuous variables, ordered categorical variables, and binary variables measured over time will be compared using

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mixed models for repeated measures. The distribution of the data will be checked using quantile-quantile plots, and if the data are skewed, then a generalized linear mixed effects model with the appropriate distribution will be used. A random intercept will be applied at the patient level. We will check model assumptions for each model. Kaplan-Meier survival analysis will be performed for mortality data up to 48 months after transplantation. Median QOL scores from each instrument (ordinal variables) will be compared using the Mann-Whitney *U* test at each time point. Subgroups for analysis shall be described in detail in the statistical analysis plan.

Level of Significance and Power

In the interim analysis (described below), the DSMB will use Pocock stopping boundaries ($P<.03$). Therefore, the 2-sided α value in the final analysis will be $P=.03$. We will use a power of 0.8 (80%).

Sample Size

The power calculation, performed using GPower 3.1 (AdvanSci Research Solutions), is based on superiority analysis assumptions for the primary end point (improved oxygenation ratio, defined as the highest PaO_2/FiO_2 ratio measured within 72 h after LTx). Based on data from a cohort of patients undergoing LTx from Skåne University Hospital in Lund from 2011 to 2020, we estimate that the mean PaO_2/FiO_2 value in the control group will be approximately 300 (SD 100) mm Hg and that values will be normally distributed. We estimate that the average PaO_2/FiO_2 value will be 60 (SD 100) mm Hg higher (effect size) in the treatment group compared with the control group.

The sample size was calculated using a 2-tailed *t* test to compare the PaO_2/FiO_2 values in the treatment versus control groups. We will require 52 participants in each group to achieve the power and α level detailed above. We will add 10% of the required sample size to account for possible dropouts, withdrawal of consent, or mortality in the first 72 hours. Thus, we aim to recruit 58 patients in each group to a total of 116 participants. With this number of participants, we estimate that all secondary outcome variables will have a power of at least 80% at an α level of .05.

Expected Dropout Rates

Based on clinical experience, perioperative and postoperative mortality within the first 72 hours after transplantation is expected to be low. The sample size estimation has been adjusted to account for possible losses due to dropouts. Long-term follow-up visits will coincide with standard visits, and thus we do not expect many dropouts during the long-term follow-up.

Interim Analysis

The DSMB will perform an interim analysis of the primary outcome after at least 30 participants for each group have undergone LTx and reached the intervention period and the 72-hour time point has been passed for the 30th participant in each group. The DSMB will use Pocock stopping boundaries ($P<.03$) as the statistical limit to guide its recommendations regarding early termination of the trial on the basis of rejecting the null hypothesis. If the *P* value for the primary outcome is below .03 at the interim analysis, then a decision will be taken by the trial management team to either stop the trial early or to continue recruitment. This has been accounted for in the sample size calculation above, and no additional adjustments for multiple testing are necessary.

Randomization

An allocation sequence will be created in advance by an independent statistician and linked to a digital randomization module in the eCRF. As each patient is included by the investigator, the next number in the sequence will be revealed and the patient will be assigned to the intervention indicated therein. Randomization is performed using a web-based system (REDCap; Research Electronic Data Capture; Vanderbilt University) and patients are randomized in a 1:1 ratio to 1 of the 2 groups. Randomization will be done using random permuted blocks of varying size, stratified by site, gender, and age.

Replacement

Participants who withdraw or are withdrawn from this study or who are lost to follow-up will not be replaced. If a participant's transplantation surgery is cancelled or rescheduled after they are randomized (they will keep the randomization number if later transplanted), new participants will continue to be randomized until the target number of participants has completed their transplantation surgery.

Site Monitoring

This study will be monitored by an independent monitor before this study begins, during this study's conduct, and after this study has been completed, to ensure study conduct in accordance with the clinical investigation plan, accuracy of entries in the eCRF, adherence to the protocol and Good Clinical Practice (GCP), and progress of enrollment. Monitoring standards will be followed and all checks of the consistency of the source data with the eCRFs will be performed according to the monitoring plan.

Data Management and Data Collection

Forum Söder, a nonprofit organization associated with Lund University and Skåne University Hospital, is contracted for planning and execution of data management activities. Data collected from the patients' medical records, in paper data logs, and from QOL questionnaires will be transferred into an eCRF in the data capture tool REDCap. Automatic validation programs check for data discrepancies in the eCRFs, and by generating appropriate error messages, allow for modification or verification of the entered data by the investigator staff before being saved in the database.

Database Management and Quality Control

The monitor will review the eCRFs entered by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Electronic data capture systems will undergo extensive user acceptance testing before they are implemented to ensure that they are verified and validated. To ensure the system is secured, REDCap is located on Windows server 2012 R2 standard, with

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a firewall. Individual log-in with a 2-factor authentication is maintained. The server is backed-up every night. The sponsor, investigators, statisticians, and trial management team will have access to the final data set.

Procedures to Protect Participant Confidentiality

REDCap is compliant with GCP standards and fulfils criteria for handling patient data according to Swedish legislation on management of personal data and the General Data Protection Regulation of the European Union. Patients will be pseudonymized through assignment of a study ID number in the database and the code will be safely stored at each site.

Ethical Considerations

The protocol received approval from Swedish Ethics Committee in September 2022 (registration [daybook] 2022-04567-01) and by the Swedish Medical Products Agency in April 2023 (registration [daybook] 5.1- 2023-23105). Any substantial modifications to the protocol after this study begins will be duly communicated to them. Prior informed consent of the participants regarding participation in the trial and collection of biological specimens will be collected by a trained member of the research team before data collection. All the participants are free to withdraw from this study at any moment without incurring any penalties or consequences with regard to future care or services they might rightfully expect. This study plan has also been reviewed and approved by an independent peer review for funding by the Swedish Research Council (registration [daybook] 2022-00319). Written informed consent will be obtained before any study-related procedures are implemented. This study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH-GCP and applicable local regulatory requirements. This study was registered at ClinicalTrial.gov (NCT05526950; September 2, 2022)

Ancillary and Posttrial Care

At the end of this study, participants will continue to receive whatever care is deemed necessary by their physician, regardless of their assigned intervention.

Dissemination Policy

The sponsor shall prepare a publicly available clinical investigation report in accordance with regulation (European Union) 2017/745 within 1 year after the end of this study. Planned dissemination of study findings includes paper publication, conference presentations, and community dissemination (eg, community meetings and social network). Professional medical writers may be contracted for preparation of the clinical trial report and publications. There are no plans to make the full protocol, participant-level data set, or statistical code publicly available.

Results

The recruitment of patients started after a monitor site initiation visit on August 28, 2023. The enrollment is expected to last 3.5 years. The collective rate of LTx at the 2 sites together is expected to be 40-60 patients per year. Since the inclusion criterion is very broad (all patients who are eligible for double LTx in Sweden), we only expect about 1-4 patients per year to be noneligible for this study. Thus, we expect to recruit 30-50 participants per year, making this enrollment time feasible. Long-term follow-up after the end of the investigation is expected to last 4 additional years from the final enrollment. Thus, the investigation and postinvestigation follow-up together are expected to last 7.25 years.

Discussion

Overview

Intolerance to a new lung, which leads to PGD, begins already during transplantation and is driven by intense inflammation caused by circulating cytokines [6]. Cytokine filtration can remove the cytokines that lead to intolerance and subsequent PGD from the circulation, thus reducing inflammation, and could therefore improve outcomes in LTx. However, the effectiveness of the CytoSorb device in LTx has yet to be established. Other than our feasibility study (NCT05242289) and a smaller case series that was rescued with extracorporeal cytokine adsorption therapy following LTx [10], this tool has not been applied to human LTx by any clinic within our network or in any trials that are registered at ClinicalTrials.gov or other registries. Therefore, this clinical investigation is justified and relevant as it will establish the effectiveness of cytokine reduction by cytokine filtration using the CytoSorb device in improving lung function following LTx, an area where there is a high unmet need. The clinical investigation is designed to evaluate whether the investigational device is suitable for the purposes and populations for which it is intended within LTx, namely for removal of cytokines in these patients.

Following LTx, the anticipated clinical benefits of cytokine filtration using the CytoSorb device in LTx are reduced severity and incidence of PGD, improved lung function, improved kidney function, improved hemodynamic stability, and reduced mortality.

In a preclinical study of LTx carried out by Ghaidan et al [28], pigs were randomized 1:1 to undergo LTx with or without cytokine filtration with the CytoSorb device during the first postoperative period and followed for 3 days after transplantation. Cytokine filtration significantly improved lung function, evidenced by increased PaO_2/FiO_2 ratio, and reduced the incidence of histologically confirmed PGD. Treated animals also had lower levels of inflammatory biomarkers in plasma and bronchial alveolar lavage fluid, lower levels of lymphocytes, neutrophils, and total white blood cells; required less inotropic support; and experienced greater lactate clearance postoperatively.

The mechanisms driving PGD are still not fully comprehended, just as the mechanisms of action behind how the CytoSorb device could improve PGD remain not fully understood. Elevated levels of neutrophil extracellular traps (NETs) have been identified in cases of PGD, underscoring the significance of approaches aimed at mitigating their presence [29,30]. While the precise mechanisms underlying PGD are still not fully elucidated, its association with heightened incidences of both

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acute and chronic rejection underscores the urgency for the development of proactive interventions [3].

We have recently completed a successful clinical feasibility study of cytokine filtration in conjunction with LTx using a similar protocol as described in this application (ClinicalTrials.gov; NCT05242289). The results from the first 4 randomized patients were published as a brief communication [31]. Treated patients exhibited diminished levels of circulating nucleosomes, as a marker of reduced circulating NETs, and remained free from both PGD and histopathological indications of acute rejection at both 1- and 3-months after transplant. In contrast, patients who did not undergo cytokine adsorption experienced higher levels of circulating nucleosomes, PGD of grades 1 and 3, as well as histopathological signs of acute rejection. Incorporating CytoSorb during transplantation could potentially foster a reduced systemic inflammatory response characterized by lower NET levels, consequently providing support for graft acceptance. We are currently working on finalizing all analyses in the feasibility study. To this point, no adverse events have been reported (unpublished work).

Limitations

Participant-related factors that may compromise the outcome or interpretation of results include baseline characteristics, demographics, lifestyle, and concomitant medications. Participant-related factors will be mitigated by randomization, exclusion criteria, and stratification by gender and age. Multivariate analyses will be used to adjust for the effect of any differences in demographic characteristics and concomitant medication use between the groups.

Site- and procedure-related factors that may compromise the outcome or interpretation of results include minor local differences in clinical procedures. Site-related factors will be mitigated by stratification of randomization by site to ensure equal numbers of patients are randomized to each intervention at each site. Subgroup analyses will be used to examine the effect of any differences between sites.

Conclusions

The investigation is a randomized, parallel-group, Swedish national multicenter superiority trial that compares cytokine filtration following LTx to standard treatment without cytokine filtration. This study aims to investigate the effects of cytokine filtration in conjunction with LTx. This treatment is administered for 12 hours within the first 24 hours following LTx with the goal of improving outcomes. It is hypothesized that cytokine filtration will lead to improvements in lung transplant outcome, enhance lung transplant care, and increase overall survival.

Acknowledgments

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Data Availability

The data sets generated or analyzed during this study are available from the corresponding author on reasonable request.

Conflicts of Interest

SL (sponsor representative) declares a speaker's bureau with CytoSorbents. Unrelated to the current study, JM discloses an unrestricted grant from Boehringer Ingelheim and consulting fees from Boehringer Ingelheim, Astra Zeneca, GlaxoSmithKline, Takeda pharma, Vicore Pharma, and Mallinckrodt. LL receives consultancy fees from XVIVO Perfusion AB. GD received an institutional research grant for an investigator-initiated ScanCLAD study (ClinicalTrialsGov number NCT02936505), an Abbott institutional research grant regarding a destination therapy study on LVAD (the SweVAD study, ClinicalTrialsGov number NCT02936505), and an institutional research grant for an industry-initiated study on organ preservation (NIHP trial). GD is also a board member of XVIVO. Publication funding was provided by the Swedish Research Council. Open access funding was provided by Lund University.

Multimedia Appendix 1
Peer-review report by the Swedish Research Council.
[PDF File (Adobe PDF File), 76 KB - resprot_v12i1e52553_app1.pdf]

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Abbreviations

CLAD: chronic lung allograft dysfunction
CT: computed tomography
DSMB: Data Safety Monitoring Board
eCRF: electronic case record form
FiO2: fraction of inspired oxygen
GCP: Good Clinical Practice
IL: interleukin
ITT: intention-to-treat
LTx: lung transplantation
NET: neutrophil extracellular trap
PaO2: partial pressure of oxygen
PGD: primary graft dysfunction
QOL: quality of life
REDCap: Research Electronic Data Capture
SAE: serious adverse event
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Protocol

Mobile Phone Technology for Preventing HIV and Related Youth Health Problems, Sexual Health, Mental Health, and Substance Use Problems in Southwest Uganda (Youth Health SMS): Protocol for a Pilot Randomized Controlled Trial

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Related Article:

This is a corrected version. See correction statement: https://www.researchprotocols.org/2024/1/e55725

Abstract

Background: East and Southern Africa have the highest HIV incidence and prevalence in the world, with adolescents and young adults being at the greatest risk. Despite effective combination prevention tools, including the recently available pre-exposure prophylaxis (PrEP), HIV incidence among adolescents and young adults in Uganda remains high, and PrEP use remains low. Mental health and substance use (behavioral health) play a role in sexual behavior and decision-making, contributing to an increase in the risk for acquiring HIV. Interventions that target multiple HIV risk factors, including sexual and mental health and problematic substance use, are crucial to ending the HIV epidemic. Yet few interventions addressing HIV related health disparities and comorbidities among adolescents and young adults in East and Southern Africa currently exist.

Objective: This study aims to evaluate the acceptability and feasibility of Kirabo, an SMS text message intervention informed by the information, motivation, and behavior model and to be disseminated through secondary schools. The study will gather preliminary estimates of Kirabo's effectiveness in increasing HIV testing and linking users to mental health counselors.

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Methods: We identified Mobile 4 Reproductive Health for adaptation using the assessment, decision, administration, production, topical experts, integration, training, testing (ADAPT-ITT) framework. Mobile 4 Reproductive Health is an evidence-based automated 2-way SMS text messaging and interactive voice response platform that offers sexual and reproductive health information and links users to HIV clinics in East Africa. Through ADAPT-ITT we refined our approach and created Kirabo, an SMS text message–based intervention for linking adolescents and young adults to health services, including HIV testing and mental health counseling. We will conduct a 2-arm randomized controlled trial in Masaka, Uganda. Adolescents (N=200) will be recruited from local schools. Baseline sociodemographic characteristics, HIV test history, and behavioral health symptoms will be assessed. We will evaluate acceptability and feasibility using surveys, interviews, and mobile phone data. The preliminary efficacy of Kirabo in increasing HIV testing and linking users to mental health counselors will be evaluated immediately after the intervention and at the 3-month follow-up. We will also assess the intervention's impact on self-efficacy in testing for HIV, adopting PrEP, and contacting a mental health counselor.

Results: Intervention adaptation began in 2019. A pretest was conducted in 2021. The randomized controlled trial, including usability and feasibility assessments and effectiveness measurements, commenced in August 2023.

Conclusions: Kirabo is a tool that assists in the efforts to end the HIV epidemic by targeting the health disparities and comorbidities among adolescents in Uganda. The intervention includes local HIV clinic information, PrEP information, and behavioral health screening, with referrals as needed. Increasing access to prevention strategies and mitigating factors that make adolescents and young adults susceptible to HIV acquisition can contribute to global efforts to end the HIV epidemic.

Trial Registration: ClinicalTrials.gov NCT05130151; https://clinicaltrials.gov/study/NCT05130151

International Registered Report Identifier (IRRID): DERR1-10.2196/49352

(JMIR Res Protoc 2023;12:e49352) doi:10.2196/49352

KEYWORDS

adolescence; PrEP; pre-exposure prophylaxis; HIV; mental health; substance use; sexual health; mobile phones; randomized controlled trial; adaptation; Uganda

Introduction

Background

Globally, adolescents and young adults aged 10 to 24 years represent approximately 30% of people living with HIV. East and Southern Africa (ESA) have the highest HIV incidence in the world, with adolescents and young adults being at the greatest risk [1-3]. AIDS is the leading cause of death for adolescents and young adults in the region and the second leading cause of death for adolescents and young adults worldwide [4,5]. Despite combination prevention efforts, including pre-exposure prophylaxis (PrEP) [6], HIV incidence among adolescents and young adults remains high [1], and PrEP use remains low [7]. Further, in part owing to the lack of access to information and services related to mobility, the uptake of antiretroviral therapy among adolescents and young adults in Uganda living with HIV is considerably lower than that among adults in Uganda living with HIV [8-10].

Mental health and substance use affect decisions regarding sexual and reproductive health (SRH) and can increase the risk for acquiring HIV infection [11-13]. It is estimated that mental illness contributes to an estimated 4- to 10-fold increase in the risk for acquiring HIV [14-17]. In Uganda, alcohol is the primary substance used, and the country has one of the highest per capita alcohol consumption rates in ESA [18,19]. Thus, in the proposed protocol, we primarily focus on alcohol consumption. It is widely recognized that designing interventions for addressing multiple HIV risk factors, including sexual and mental health and problematic substance use, is crucial to ending the HIV epidemic, yet few such interventions currently exist for adolescents and young adults in ESA [20]. Integrating screening for mental health and alcohol use problems with appropriate referral mechanisms into existing SRH interventions may be a feasible first step toward addressing this gap.

In Uganda, household mobile phone ownership has risen dramatically over the last 15 years, from approximately 10% in 2004 to 74% in 2020, yet few people own smartphones [21,22], with a similar pattern in the specific region of study [23,24]. SMS text messages can be sent or received using any mobile phone, and SMS text messaging is the most widespread means of communication in ESA [25,26]. Systematic reviews have indicated that SMS text messaging is a feasible and acceptable method for delivering health interventions [27] focused on substance use [28], mental health [29], and HIV prevention and care [30,31]. Mobile phone–based HIV interventions in ESA are well represented in the literature. However, most mobile phone–based interventions that focus on mental health and substance use have been implemented in Europe and the United States [27-29].

This Study

This study focuses on adolescents aged 15 to 19 years who are in secondary school in the greater Masaka region of Uganda. This is a critical developmental time for intervention, as many adolescents within this age range begin to leave school, search for work, and engage in sex and are thus at an increased risk for HIV infection [32-36]. This is also the age when, if at risk, symptoms of mental disorders typically emerge [37-40]. Consequently, this stage of adolescence is a critical time for preventive interventions, and our preliminary qualitative work shows the importance of mobile phones for finding sexual partners and the as-yet-underused potential for mobile phones

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to promote health [23]. As noted earlier, mental health and alcohol abuse are associated with an increased risk for HIV infection. Thus, screening adolescents with mental health or alcohol use problems and linking them to counselors may help address these factors and reduce the risk for HIV infection. We identified the local mental health partner StrongMinds (authors CO, CT, CN, and VM). StrongMinds is an international nongovernmental organization in Uganda that offers free evidence-based, telehealth-based group interpersonal therapy [41-47].

Through our formative work described in the subsequent section, we used the ADAPT-ITT (assessment, decision, administration, production, topical experts, integration, training, testing) [48] framework to adapt and update a mobile phone–based SRH intervention. Our adapted intervention, named Kirabo, is also informed by the information, motivation, and behavior (IMB) model [49] and uses automated SMS text messaging to link adolescents to HIV testing and mental health counselors. Through the proposed research, we will evaluate the feasibility and acceptability of Kirabo and generate the preliminary estimates of Kirabo's efficacy in HIV testing. Adolescents today rely heavily on mobile phones for information and services; therefore, we believe that the proposed intervention could be applied and adapted across ESA and potentially in other underresourced settings [21,50,51].

Methods

Formative Work

We used the ADAPT-ITT [48] framework (Table 1) to adapt an existing evidence-based SRH mobile phone intervention, Mobile 4 Reproductive Health (m4RH), originally designed by FHI 360 [52-55]. Through our formative work, including discussions with our in-country research team (RK, OIN, and PN), we named our adapted intervention *Kirabo*, a Luganda-language gender neutral name that means "gift." In the subsequent section, a detailed description of the adaptation process is provided, including our summary of prior findings and context, a description of the Kirabo pretest, and the proposed design of our randomized controlled trial (RCT) pilot study. Researchers at the HIV Center for Clinical and Behavioral Studies at the New York State Psychiatric Institute (NYSPI) and Columbia University (CU), in collaboration with researchers at the Ugandan office of the International Center for Child Health and Development (ICHAD) at the University of Washington in St Louis, conducted this formative work. Study participants were recruited from secondary schools in southwest Uganda, one of the regions hardest hit by HIV [1]. This region is bordered by Lake Victoria. Most of the population (80%) lives in rural communities and engages in small-scale agriculture. Most of the population (75%) is aged under 30 years [56], and the Ugandan government policy supports HIV testing and PrEP for adolescents, whom they have designated a *priority population* [6]. In the region of study, HIV clinics provide free HIV testing, PrEP, and antiretroviral treatment, although the uptake of these services among adolescents and young adults is persistently low and HIV incidence has remained high [1,6,7,57].

Table 1. ADAPT-ITT[a] phases.

Phase	Methodology
1. Assessment (formative)	• Analyses of quantitative and qualitative secondary data
2. Decision	• Publish formative findings • Submit IRB[b] protocol
3. Administration	• Administer pretest in Uganda (24 adolescents and young adults)
4. Production	• Produce mobile phone–based EBI[c] draft 1
5. Topical experts	• Identify and review "product" with experts
6. Integration	• Integrate expert input to create pilot-ready EBI
7. Training	• Train staff to implement EBI draft 2
8. Testing and evaluation	• Pilot study • Initiate evaluation • Mixed methods: interviews, pre-post surveys, and mobile phone data

[a]ADAPT-ITT: assessment, decision, administration, production, topical experts, integration, training, testing.

[b]IRB: institutional review board.

[c]EBI: evidence-based intervention.

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Phases 1 and 2: Assessment and Decision

Overview

We first conducted formative work that involved secondary data analysis of both quantitative and qualitative data to assess how mobile phones may be associated with health risks and may also present opportunities for intervention [23,58,59]. Through our longitudinal analyses among youths in southern Uganda, we found that for adolescents and young adults, mobile phone ownership was associated with social and health behaviors; adolescents and young adults who owned phones were more likely to have multiple and concurrent sexual partners, and adolescent and young adult men who owned phones were more likely to be circumcised [23,24,34,58]. Furthermore, our mixed methods analysis demonstrated how mobile phones were a key tool that adolescents and young adults used to make social and economic connections. In qualitative interviews, adolescents and young adults also expressed an unmet need for mobile phones to provide health information [23]. Adolescents and young adults in southern Uganda are highly mobile, as structural factors, such as the lack of available employment, force adolescents and young adults to move after they leave school and search for work [34]. Mobility makes it difficult to track adolescents and young adults for recommended health care services [8], and mobility is also associated with a greater risk of HIV infection [32-34]. Thus, mobile phones present an opportunity to reach adolescents and young adults with high mobility [25,26,34,50]. We identified m4RH as a candidate for adaptation. m4RH is an evidence-based [52-55] automated 2-way SMS text messaging and interactive voice response (IVR) platform that offers SRH information and links users to HIV clinics in East Africa [52-55]. IVR is an automated technology that allows incoming callers to access information via a voice response system of prerecorded messages. Communicating via the platform is free in Uganda and across East Africa owing to existing agreements between FHI 360, which designed the original m4RH platform, and the regional mobile phone service provider Airtel. However, m4RH was not specifically tailored to adolescents, and it did not include PrEP information, nor did it include any behavioral health elements.

The IMB Model

The IMB model [49] guided our design of new content for the adapted intervention. The IMB model posits that information (in this project, communicated through interactive SMS text messages), motivational factors, and behavioral skills (measured through self-efficacy and intentions) influence the adoption of a new behavior (HIV testing, PrEP uptake, and mental health counseling). Our adapted SMS text messages, beyond communicating basic facts, were organized through narratives, which appealed to emotions, imagination, and value systems [60-63]. Narrative components influence how people think, behave, and develop lasting health-related behaviors and, therefore, influence both information and motivational factors. In the IMB model, *motivational factors* include *positive outcome expectancies*, for example, starting PrEP will enable me to achieve future goals by protecting me from getting HIV; *negative outcome expectancies* are undesirable consequences (eg, HIV infection). Motivational factors that may be enhanced by engaging with the mobile phone platform include *perceived risk*; perceptions of *peer norms*, that is, whether a new behavior is perceived positively or negatively by important referents, such as partners, other women, or family; and *barriers to and facilitators* of adopting preventive behaviors. The IMB model also highlights the importance of increasing *behavioral skills* and a sense of self-efficacy in adopting prevention practices and persisting despite barriers. In short, self-efficacy is a person's confidence in their ability and skills to perform a behavior [64]. We posit that SMS text messaging via the platform will increase adolescents' self-efficacy by providing them with simple and direct information (including information about HIV prevention skills, clinic location and contact numbers, and information about behavioral health counselors), thus promoting their belief that they can perform the target behavior successfully (eg, going to the clinic and taking an HIV test).

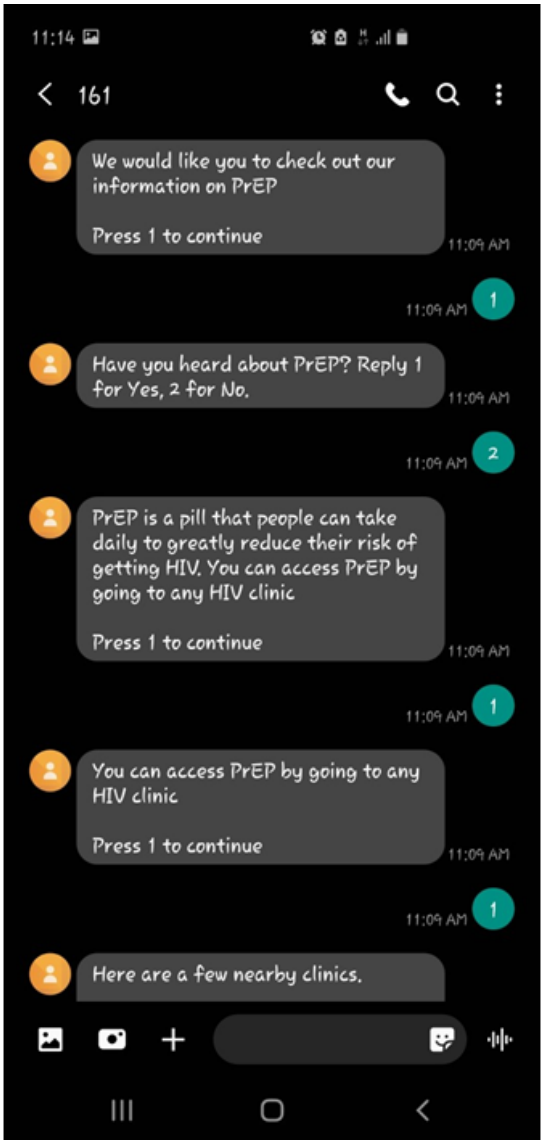
Three Main Modifications

In Kirabo, we made the following three main modifications to the existing m4RH approach:

1. In prior work, m4RH was disseminated via radio and magazine advertisements and at family planning clinics [52,53,55,65]. To ensure that we reach the target population of adolescents for Kirabo, we partnered with local schools and will disseminate Kirabo at the schools or via SMS text messages. Our researchers will deliver an IMB-informed oral script, describing Kirabo in person at local schools and further disseminating Kirabo via flyers.
2. When m4RH was designed, PrEP was not available in sub-Saharan Africa. Thus, in Kirabo, we added and updated the existing m4RH HIV prevention menu to include the current information on PrEP and the location of local clinics. To create PrEP messages, we used text from the Centers for Disease Control and Prevention's (CDC) informational materials and published qualitative research studies [66-68]. Figure 1 displays an example of PrEP messages from Kirabo, with the numbers indicating user responses and menu selections. In Figure 1, Kirabo asks the adolescent the following question: "have you heard of PrEP? Reply 1 for Yes, 2 for No." The adolescent then replies "2," indicating that they had not previously heard of PrEP and thus triggering Kirabo to begin to describe PrEP. Furthermore, we added additional details, such as local landmarks, directions, and contact numbers for local HIV clinics. As part of this formative work, we contacted 6 HIV clinics in the southern Ugandan region. Of the 6 clinics, 5 confirmed that they were currently able to prescribe PrEP to adolescents according to the national guidelines and had ample PrEP medication in supply [69]. The clinic location and contact information were included in the adapted intervention.
3. Finally, because we know that mental health is critical to HIV prevention efforts, in Kirabo, we additionally focus on behavioral health. Adolescents will complete screeners, which are then used to tailor the SMS text messages they receive.

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Figure 1. Pre-exposure prophylaxis (PrEP) messages.



For mental health, we will measure depression using the 4-item Patient Health Questionnaire (PHQ-4), which includes the first 2 questions of the 9-item Patient Health Questionnaire (PHQ-9) [70] and the first 2 questions of the 7-item Generalized Anxiety Disorder Questionnaire (GAD)-7 for assessing anxiety [71]. For example, question 1 of the PHQ reads, “over the last two weeks, how often have you had little interest or pleasure in doing things?” Possible responses range from “not at all (0)” to “nearly every day (3).” Individuals who score ≥1 on the first 2 questions of the PHQ-9 or GAD-7 will be directed to complete the full measure. If the respondents score 0 on the first 2 questions of these measures, the system will respond with a brief message thanking them for their time. To be cautious and consistent with StrongMinds’ approach, we will use a cutoff point of 8 on the PHQ-9 to determine a referral to a StrongMinds counselor. Additional information regarding these measures is provided in Table 2.

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Table 2. Additional information regarding measures and their times of collection.

Construct	Measures	Time
Behavioral, mental health, and alcohol use measures		
Demographics	Items developed for previous Suubi studies [72-74], including age, sex, parents' occupation, household size, orphanhood status, primary caregiver, and community of origin	Baseline
COVID-19 experiences	CASPE[a] (adapted from Suubi+Adherence [74] and the study by Ladouceur [75])	Baseline
HIV testing	Self-report of HIV test (yes/no; past year [at baseline], during the study period [immediately after the intervention], and past 3 months [at follow-up]) confirmed with proof of results from the clinic using measures and procedures adapted from Suubi studies [72-74]	Baseline, immediately after the intervention, and 3-month follow-up
Intention to test for HIV	Questions adapted from a study of secondary school students in Uganda [76]	Baseline, immediately after the intervention, and 3-month follow-up
Self-efficacy	Questions adapted from a study with secondary school students in Uganda [76] and a study with high school students in the United States [77], including questions regarding self-efficacy in testing for HIV, trying PrEP[b], using condoms consistently, contacting a behavioral health counselor	Baseline, immediately after the intervention, and 3-month follow-up
Current HIV prevention strategies	This measure includes items developed for previous Suubi studies [72,73] in Uganda (in addition to a question regarding PrEP; range 5-25; 5 question items; α=.70), for example, "I think it is very important to use condoms every time one has sex," "as a teenager I think AIDS is a threat to my health," and "I think all people my age who have sex should use condoms." Scores range from 4: strongly agree; 3: somewhat agree; 2: somewhat disagree; to 1: strongly disagree.	Baseline, immediately after the intervention, and 3-month follow-up
HIV-related knowledge	This measure includes items from previous Suubi studies [72,73] in Uganda; this measure includes 13 items about HIV infection and prevention mechanisms (range 0-16; 16 question items; α=.83), for example, "HIV can be passed by an infected person even though that person is not feeling sick." Possible scores are 1: true; 2: false; and 3: don't know or 1: not sure; 2: unsafe; and 3: safe.	Baseline, immediately after the intervention, and 3-month follow-up
Sexual risk behaviors	This measure includes items from previous Suubi studies [72,73] in Uganda (range: 5-25; 5 question items; α=.76), for example, "I believe it's OK to have sex without protection with someone you know." Scores range from 1: never; 2: sometimes; 3: about half of the time; 4: most of the time; to 5: always.	Baseline, immediately after the intervention, and 3-month follow-up
PrEP knowledge	Adapted 13-item true-false questionnaire on PrEP knowledge [78,79] including questions such as "PrEP is a pill you can take to prevent HIV" and "PrEP is only for people who are HIV negative"	Baseline, immediately after the intervention, and 3-month follow-up
Depressive symptomatology	PHQ-9[c] [70], a standardized 9-item self-report instrument used to assess depression, is used. Participants rate the frequency of their symptoms over the past 2 weeks. Items are rated on a 4-point scale, ranging from 0 (not at all) to 3 (nearly every day), and scale scores range from 0 to 27. PHQ-9 scores of 5 to 9 represent minimal to mild depression and 10 to 20 represent moderate to severe depression. A score ≥10 has a sensitivity of 88% and a specificity of 88% for major depression.	Baseline and immediately after the intervention

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Construct	Measures	Time
Anxiety	GAD-7[d] [71], is a standardized instrument that asks participants to rate their symptoms over the past 2 weeks on a 4-point scale ranging from 0 (not at all) to 3 (nearly every day), is used. Overall scores for the GAD-7 range from 0 to 21. At a cutoff point of 10 (indicative of clinically significant symptoms), the sensitivity and specificity of the scale equal 89% and 82%, respectively. The GAD-7 has a Cronbach α of.92, indicating good internal consistency, and an intraclass correlation of 0.83, indicating good procedural validity.	Baseline and immediately after the intervention
Alcohol use disorder screen	AUDIT-C[e] [80,81], a 3-item screener excerpted from the full standardized 10-item AUDIT tool for assessing hazardous alcohol consumption, is used. Items are scored on a 5-point scale for a possible score of 0 to 12. The higher the score, the higher the risk of hazardous alcohol consumption. AUDIT-C scores of ≥4 in men and ≥3 in women are considered positive for hazardous alcohol consumption.	Baseline and immediately after the intervention
Reported (and confirmed) sessions with mental health counselor	Self-report and local school and clinic records	Baseline and immediately after the intervention
Peer messaging	Self-report of messages shared with peers	Baseline and immediately after the intervention
Technological, feasibility, and acceptability measures		
Survey of acceptability	This measure, adapted from CyberSenga [82] (a mobile health HIV study with youths in Uganda), is a 12-item survey with a Likert scale of 1 to 3 (disagree, somewhat agree, and strongly agree).	Immediately after the intervention
Number of messages viewed	Retrieved via user database consistent with previous m4RH evaluations [54]	Continuous
Type of messages (regarding sexual health, mental health, and alcohol use)	Retrieved via user database consistent with previous m4RH evaluations [54]	Continuous
Mental health and alcohol use screens completed (AUDIT, GAD-7, and PHQ-9)	Retrieved via user database	Continuous
HIV clinic locator (number of times used)	Retrieved via user database	Continuous
Feasibility	Enrollment of recruited adolescents	Immediately after the intervention

[a]CASPE: COVID-19 Adolescent Symptom & Psychological Experience Questionnaire.

[b]PrEP: pre-exposure prophylaxis.

[c]PHQ-9: 9-item Patient Health Questionnaire.

[d]AUDIT-C: Alcohol Use Disorders Identification Test–Consumption.

[e]GAD-7: 7-item Generalized Anxiety Disorder Questionnaire.

Similarly, the GAD-7 [71] will be used to screen and measure the severity of generalized anxiety symptoms among participants. Through Kirabo, we will administer the first 2 questions of the GAD-7. Table 2 provides additional information regarding this measure. To be cautious and consistent with StrongMinds' approach, we will use a cutoff point of 8 to determine a referral to a StrongMinds counselor.

The 3-item Alcohol Use Disorders Identification Test–Consumption (AUDIT-C) [80] will be used to measure hazardous alcohol use (Table 2). Similar brief measures have been used and validated globally, specifically in East Africa and Uganda [18,83-89]. To improve user experience and consistent with the prior work described subsequently, screener length will be determined by an adolescent's response to initial questions. Table 2 provides additional details regarding the AUDIT-C [90].

In our initial version of Kirabo, if an adolescent screened positive for symptoms of depression, anxiety, or hazardous alcohol use, the adolescent was provided with the contact number of our mental health partner StrongMinds.

Phases 3 and 4: Administration of Pretest and Production

The ICHAD has research relationships with 70 secondary schools in the region, and a well-established protocol for recruitment is described subsequently. The field research team (RK, OIN, and PN) worked primarily out of the ICHAD offices in Masaka, Uganda. ICHAD researchers distributed flyers to

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students and staff, noting that adolescents aged 15 to 19 years may be eligible to participate. Research team members with no relationship with students conducted the recruitment. Further, students did not receive any class credit or extra credit for participating. Students were compensated for their time at rates consistent with the ICHAD policies and in accordance with Ugandan and US ethics board guidance. Adolescents were compensated 8500 Uganda shillings (US $2.25) for participating in the mobile phone–based portion of the research, and adolescents who joined the focus groups were offered an additional 20,000 Uganda shillings (US $5.30). Teachers were not informed about which students were contacted and consented/assented to participate. We will use similar procedures to recruit for the RCT described subsequently. That said, if the current COVID-19 protocols or other factors result in the school not currently being in session, a head teacher may provide researchers with a list of students who have expressed interest and meet the age eligibility for a final screen by the research team.

To conduct the pretest, we recruited 24 adolescents (aged 15 to 19 years) from 2 secondary schools in southern Uganda. Over a 1-week period, the adolescents were prompted via a daily automated SMS text message, amounting to 5 prompts per week, to interact with Kirabo. We tested the following three different methods of contacting Kirabo: (1) through IVR by dialing 161, (2) through unstructured supplementary service data (USSD) by dialing *161#, or (3) through SMS text messaging by texting "Hi" to 161. IVR allows callers to access prerecorded messages through speech recognition. USSD is similar to SMS text messaging, except that the messages disappear after a texting session. Only adolescents with phone numbers registered in our study could access the messages.

Our daily automated SMS text messages described how the system could be accessed via IVR by dialing 161 or via SMS text messaging by sending "Hi" to 161. On each day of the 5-day pretest, our automated messages encouraged the adolescents to interact with a different component of the platform. Day 1 focused on HIV testing, day 2 focused on PrEP, day 3 focused on mental health, day 4 focused on alcohol use, and day 5 focused on HIV testing again. To select an option, the user should reply with a text using a keyword or code from the provided menu, for example, "press 2 for PrEP information." The platform then automatically responds with a text or an IVR message. Adolescents could choose to interact with Kirabo in English or Luganda, the most commonly spoken local language in the region. Adolescents were advised to use their phones outside school hours, and no adolescents reported conflicts with parents or school staff regarding their use of phones in our pretest. Figure 1 shows an example of how an adolescent could move through the PrEP messages.

During the 5-day pretest, of the 24 adolescents, 22 (92%) accessed Kirabo at least once. In total, adolescents accessed Kirabo 339 times: 145 (42.8%) times through USSD, 83 (24.5%) times through SMS text messaging, and 111 (32.7%) times through IVR. SMS text messaging had the highest rate of message category completion (meaning that an adolescent viewed and responded to all messages; see Figure 1 for a PrEP example), with 83% (69/83) of the access attempts successfully running from beginning to end, compared with 58% (82/145) for USSD and 61% (68/111) for IVR.

Of the 24 adolescents, 22 (92%) completed the behavioral health screeners. The PHQ-9 scores ranged from 0 to 17 (mean 3.99, SD 3.85), and 5 (21%) adolescents scored ≥10 and thus screened positive for clinically significant symptoms of depression. Among the 24 adolescents, 1 (4%) screened positive for suicidal ideation. Our project coordinator followed up with this adolescent and, as dictated by our emergency protocol, used the Columbia Suicide Severity Rating Scale (C-SSRS) [91] to assess suicide risk. The adolescent described that they no longer experienced suicidal ideation. The project director determined that the participant was at moderate risk and then linked the adolescent to an ICHAD mental health counselor for further evaluation and support.

The GAD-7 scores ranged from 0 to 15 (mean 4.39, SD 3.77), and of the 24 participants, 5 (21%) scored ≥10 and thus screened positive for clinically significant symptoms of anxiety. In total, 3 (12%) adolescents screened positive for both symptoms of anxiety and depression. No adolescents screened positive on the AUDIT scale, with scores ranging from 0 to 4 (mean 0.5, SD 1.01).

In focus groups with 19 (79%) of the 24 adolescents, 10 (53%) preferred SMS text messaging and 9 (47%) preferred USSD, noting that SMS text messages arrived more quickly and could be revisited because they were saved on the phone. A female student aged 15 years said, "if the messages are saved, it can help me to seek clarification of what I haven't understood. I can review those messages for me to understand them well." None of the adolescents preferred IVR, which had the most reported issues. The adolescents explained that IVR calls frequently dropped mid-call owing to poor phone service. This would require an adolescent to call back and start at the beginning of the menus. Not surprisingly, the adolescents expressed frustration when describing this process. In addition, although using IVR was free, some adolescents assumed that calling the IVR system would cost them money. Furthermore, adolescents were hesitant to call StrongMinds counselors because they did not want to incur charges. Some adolescents noted that receiving messages after chores in the morning was preferable, whereas the majority preferred to receive messages after school and in the evening.

With regard to HIV prevention, most adolescents reflected that Kirabo helped them learn about PrEP and the health centers where they could access HIV services. As one of the adolescents succinctly explained, "it [Kirabo] is good because most of us have not been knowing what PrEP is." Another adolescent added, "the messages I liked most were those regarding PrEP. I got more clarification about PrEP because I only knew about a tablet that you take to prevent yourself from getting infected with HIV, but I didn't know its name." A third adolescent described how Kirabo "directed us to the nearest health facilities where a person can easily access HIV testing and PrEP services." These excerpts and the broader focus group discussions align with prior work showing an unmet need for mobile health HIV prevention interventions for adolescents in the region [23].

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Phases 5 to 6: Consultation With Topical Experts and Integration

In addition to weekly meetings where author 1 discussed and designed the intervention and modifications with coauthors 2, 3, and 4, the first iteration of Kirabo was presented to a group of topical experts as part of an HIV Implementation Science and Inter-Centers for AIDS Research (CFAR) Fellowship program (2022-2023; P30AI094189). In the culminating session of this 9-month training program, author 1 presented pretest findings to 30 trainees (graduate students, postdoctoral fellows, and early career faculty) and 5 faculty mentors in person (Drs Sheree Schwartz, Stefan Beral, Patrick Sullivan, and JD Smith). This presentation was given in Baltimore, Maryland, on April 5, 2022. One of the audience members suggested that given the potentially sensitive nature of the messages, we should send a preliminary greeting message with no sexual or mental health content. Another point of discussion was to consider using a shorter follow-up period of 3months as opposed to the initially planned 6 months. Comments on the presentation in combination with our pretest findings led us to make the following three key changes to Kirabo in the proposed RCT:

1. Most adolescents preferred SMS text messaging. Thus, to streamline our delivery, recruitment, and evaluation, we decided to focus on SMS text messaging in this pilot RCT. In addition, to protect privacy, we added an initial message to be sent on each day of the intervention period that asked, “is this a good time to chat?” By contrast, the initial prompt from the pilot test immediately introduced the topic of the day (HIV testing, mood, etc). If adolescents respond with “yes,” then they would be sent the follow-up message that introduces the topic of the week. If adolescents respond with “no,” they would be sent a message that says, “ok thanks, write back with yes when you are free and available.”
2. In the pretest, adolescents who screened positive for symptoms of depression, anxiety, or hazardous alcohol were provided with the contact number of the general StrongMinds counselor. As described earlier, adolescents expressed concern that they would incur charges by calling StrongMinds counselors. Therefore, we revised our methods (including language in our consent forms), and in the RCT, we will provide a daily update to StrongMinds counselors with a list of contact numbers of adolescents who screened positive for symptoms of depression, anxiety, or hazardous alcohol use.
3. On the basis of our initial focus group discussions and our presentation at the HIV Implementation Science Fellowship, we expect that a 3-month follow-up will be sufficient to determine feasibility and accessibility. In addition, a shorter follow-up period will limit the possibility of unforeseen historical or COVID-19–related interruptions.

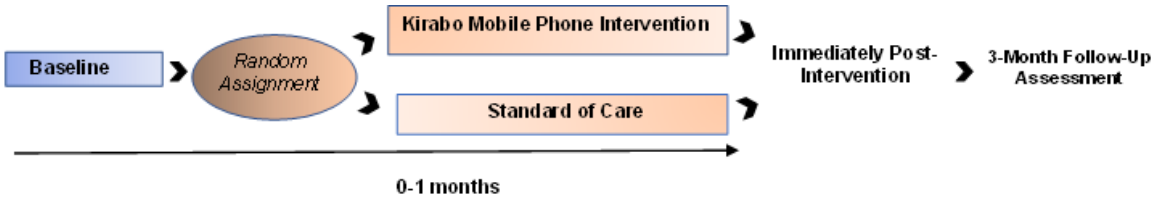
Phases 7 to 8: Training and RCT Pilot Study

Procedures

We plan to conduct a 2-arm, randomized controlled study via mobile phones among adolescents in the greater Masaka region of Uganda. We will compare Kirabo to an inactive control and evaluate whether adolescents who interacted with Kirabo had higher rates of self-reported HIV testing (yes/no; verified with the HIV clinic when possible) immediately after the intervention and at the 3-month follow-up assessment. Secondary outcomes include differences in condom use, PrEP knowledge, PrEP uptake for eligible patients, HIV-related knowledge and sexual risk behaviors, and antiretroviral treatment uptake for eligible patients. Exploratory aims include the number of participants who screen positive for symptoms of depression, anxiety, and hazardous alcohol use and the proportion of confirmed linkages to mental health counseling.

Adolescents (aged 15-19 years) in the greater Masaka region in southern Uganda who own a mobile phone will be eligible for the trial. Adolescents will be involved in the trial for approximately 5 weeks with a 3-month follow-up assessment (Figure 2). After informed assent and parental permission, the baseline assessment, and confirmation of eligibility, adolescents will be randomly assigned to the Kirabo intervention group or standard of care group. Randomization will be performed in a 1:1 ratio and stratified by gender and school (to minimize contamination) with a block size of 10. We anticipate recruiting students from 20 schools. The treatment assignments will be generated using a pseudorandom number generator. An electronic list of IDs, access codes, and credentials will be provided securely to the sites.

Figure 2. Timeline of participant involvement and measures.



Accessing Kirabo

Twice per week over the 5-week study period, Kirabo will send enrolled adolescents an SMS text message encouraging them to interact with our system. As noted earlier in the pretest, adolescents in the RCT can access Kirabo by sending the SMS text message “Hi” to #161 to initiate an interaction with Kirabo in English or Luganda. In the pretest, adolescents did not report any conflict with parents or school staff regarding their use of a mobile phone to interact with Kirabo.

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Measures

Overview

To evaluate the intervention's impact, there will be 3 main assessment time points: baseline, immediately after the intervention, and 3-month follow-up. Table 2 provides a full list of measures. The primary outcome will be self-reported HIV testing, confirmed by HIV clinic records when possible. We will also measure the uptake of HIV prevention strategies (PrEP uptake and condom use) and, although we expect this to be a rare occurrence, the initiation of antiretroviral treatment. For adolescents who screen positive for behavioral health problems, we will confirm self-reports of linking to mental health care with a StrongMinds counselor.

Many of the measures have already been used, pretested, and made culturally appropriate to the Ugandan context in past studies [92,93], including current HIV prevention strategies and HIV-related knowledge. New measures, such as PrEP knowledge, will be adjusted according to the established ICHAD procedures. Specifically, to assess the uptake of HIV prevention strategies, we will compare presurvey and postsurvey scores from the current HIV prevention strategy measures that have been previously used in this region of Uganda with adolescents (Table 2) [72,73]. For questions measuring sensitive behaviors (ie, sexual risks), we will use audio computer-assisted self-interviews so that the participants may take the survey themselves on a minilaptop.

Behavioral Health Screeners via Mobile Phone

As in the pretest, behavioral health screeners will be delivered via adolescents' mobile phones and automatically scored by Kirabo. In addition, we will use the same measures of behavioral health in the baseline and 3-month follow-up battery.

Acceptability and Feasibility Measures

All adolescents in the intervention will complete the 15-item acceptability survey adapted from prior mental, sexual, and reproductive health work among adolescents in Uganda [94]. To further evaluate feasibility, we will use paradata and text count measures previously used by FHI 360 (Table 2) [54].

In addition to the quantitative measures included in Table 2, immediately after the intervention, we will conduct 30 key informant interviews (KIIs) with participants in the intervention group. The KII guide draws from the Consolidated Framework for Implementation Research (CFIR) [95,96], with a focus on the intervention characteristics and the outer setting, and will be adapted from our pretest KII guide. For example, through our pretest and subsequent focus groups, we identified the necessary changes to our intervention based on adolescents' descriptions of outer-setting barriers. Specifically, adolescents reported that they often experienced intermittent mobile phone service. Our earlier version of the mobile phone intervention that included IVR required callers to restart at the initial message each time they called in. Adolescents in our focus groups expressed that restarting the IVR each time a call dropped was cumbersome and frustrating. By contrast, adolescents found that SMS text messaging could be resumed wherever they had left off when their service resumed. Adolescents overwhelmingly selected SMS text messaging as their preferred means of interacting with Kirabo. Acceptability questions will probe adolescents' comfort with content and delivery methods. All adolescents in the intervention will complete the 15-item acceptability survey adapted from prior mental, sexual, and reproductive health work among adolescents in Uganda [94]. To further evaluate feasibility, we will use paradata and text count measures previously used by FHI 360 (Table 2) [54].

Statistical Analysis

Primary and Secondary Outcomes and Analysis

Summary statistics will be used to describe all metrics and compare them between the students receiving Kirabo and those in usual care at baseline, 1-month postintervention assessment, and the final 3-month follow-up assessment. Means and SDs will be used for continuous outcomes, followed by box plots, and frequency tables will be used for binary and categorical metrics. The primary analysis of this RCT will test whether postintervention HIV testing rates among the adolescents who interacted with Kirabo are significantly higher than those who received standard of care. We will use a generalized linear mixed model to determine statistical significance. In the model, the outcome is the binary indicator of whether an adolescent received an HIV test during or immediately after the intervention. We will also examine the differences between the model at the 3-month follow-up. The main predictor is the intervention assignment (Kirabo or usual care). The school will be included in the model as the random effect to adjust for within-school correlations. We will apply similar analyses to investigate the impact of Kirabo on the secondary outcomes.

Depending on the nature of the outcome, we will use different link functions in the generalized linear mixed model. We will use the identity link for continuous outcomes, the logistic link for binary outcomes, and the log function for ordinal outcomes. For incidence/frequency outcomes, a log function with adjustment for exposure time will be used. We will formally test whether the students in the 2 intervention groups have comparable baseline characteristics, including demographic factors, moderators, and variables measuring potential mechanisms of action (Table 2). If any of these variables are significantly different at baseline, they will be included in the model to adjust for their potential confounding effects.

Acceptability Power Analyses

The primary purpose of this pilot RCT is to determine whether Kirabo is acceptable (>70% of adolescents "agree" or "completely agree" with 70% of acceptability measure items) and feasible (enrollment >75%) in this setting. The 100 participants in the Kirabo arm will provide 80% power to detect the proportion of participants who meet the acceptability agreement threshold as significantly greater than 70% if the observed proportion of participants who meet this threshold is at least 83.5%.

Feasibility

The 100 participants in the Kirabo arm will provide 80% power to detect enrollment greater than 75% if the observed enrollment is at least 87.3%. These calculations assume a 1-sided

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significance level of 5%. In addition, we will calculate summary statistics of the technological variables to describe feasibility, including paradata (eg, number of adolescents who ever contacted Kirabo out of the total sample and messages and types of messages viewed), and to assess behavioral health, we will divide the number of counselor calls attempted by the number of counselor calls completed. These measures will objectively show whether adolescents were able to use Kirabo.

Effectiveness Power Analysis

There is limited information on the impact of SMS text message–based interventions on increasing HIV testing among adolescents in rural Uganda. We expect that the baseline 12-month HIV testing rate among adolescents aged 15 to 19 years will be 26% [97]. With 200 students (intervention: n=100, 50%; standard of care: n=100, 50%) from 10 schools, we have 80% power to detect an average postintervention HIV test rate of ≥46% at the significance level of.05.

Handling of Missing Data

If more than 10% of the observations are missing, we will use multiple imputation strategy to accommodate missing data, followed by sensitivity analysis. The inclusion of cases with partial data is an important step because the intention-to-treat approach is planned to be the main analytic strategy for the primary aim of generating preliminary estimates of Kirabo's efficacy. If the statistical or clinical significance of treatment effects appears to differ depending on how missing data are addressed in the analyses, such findings will be reported.

Primary End Point Analysis for the Pilot RCT

We will recruit 200 students who own mobile phones and randomize them in a 1:1 ratio into intervention and control groups. The variables of focus are listed in Table 2. The primary end point is the binary indicator of whether there is an increase in HIV testing following the intervention. Chi-square tests will be used to determine whether intervention participants were more likely to take an HIV test in the past month. We will then build a logistic model to estimate intervention efficiency while adjusting for baseline characteristics, including baseline HIV prevention strategies, HIV knowledge, sexual risk behaviors, depression, anxiety, alcohol use, and demographics. The same analysis will be applied to the 6-month postintervention follow-up to determine the long-term effects of the intervention. These estimated parameters allow reliable estimates of sample size, power, and detectable effects for the subsequent study.

Secondary End Point Analysis

We will evaluate the change in behavioral health status and PrEP knowledge before and after the intervention and construct 95% CIs. Generalized linear mixed effect models will be used to reassess the intervention effect on these measurements while adjusting for the baseline characteristics age, gender, and other demographics. Finally, the same analysis will be applied to the 3-month postintervention follow-up measures to determine the long-term effects of the intervention. These estimated parameters allow reliable estimates of sample size, power, and detectable effects for the subsequent study.

Mixed Methods Implementation Analysis

We will use mixed methods, including systematic coding informed by CFIR [95,96], surveys, and paradata, to identify the specific elements of Kirabo that we hypothesize will be predictive of successful implementation [98]. This approach will inform the evaluation of the complex processes that motivate adolescents in underresourced settings to seek care. We will transform qualitative data into quantitative data for adolescent responses pertaining to the variables that IMB and CFIR dictate will be predictive of implementation outcomes. For instance, we will focus on constructs in adolescent KII responses that relate to perceived risks and benefits of care for mental health and alcohol use problems. In addition, for specific constructs, we will incorporate technological data, qualitative data, and referral to care data. We will then link users' actual paradata from their texts (eg, the number of intervention messages viewed) with our adapted m4RH program to their KII responses, survey responses on the perceptions of risk behavior before and after the intervention, and service-seeking rates. This approach will offer a deeper and complex understanding of the ways in which adolescents' beliefs impact their decision to seek care.

Ethical Considerations

The research staff obtained written informed consent from adolescents aged ≥18 years and personal assent and permission from adult parents/guardians for adolescents aged <18 years before study enrollment. The consent processes for adults and children were performed separately to avoid coercion. Both consent and assent forms were translated into Luganda (the most widely spoken local language in the study region) and back-translated into English to ensure consistency. Both the assent and consent processes were conducted verbally in Luganda, given that some caregivers and adolescents were illiterate. The study team received training on Good Clinical Practice (GCP) so that sensitive research activities could be handled appropriately. In addition, all interviewers completed the Collaborative Institutional Training Initiative (CITI) certificate and National Institutes of Health (NIH) certificate for the protection of research participants. All study procedures were approved by the NYSPI Institutional Review Board (IRB), the home institution of the principal investigator (PI), and the in-country local ethics board of the Uganda Virus Research Institute (UVRI; reference number GC/127/835). The ethics protocol was also reviewed and approved by the Uganda National Council for Science and Technology (UNCST; reference number SS969ES). This study was registered at ClinicalTrials.gov (NCT05130151).

Adverse Events and Safety Monitoring

The study will maintain records of adverse events and any referrals for counseling as well as copies of the consent and assent forms. All records will be maintained in a locked filing cabinet at the ICHAD Uganda field office and will be accessible only to the research team. The PI will be responsible for data security and record keeping. The data sets used for analysis will not contain any identifying information, specifically the names and addresses of the participants.

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The HIV Center for Clinical and Behavioral Studies has a Performance and Safety Monitoring Board (PSMB) that consists of an independent group of experts. Currently, the members are Stephen Morin (chair), Joseph Hogan, Patricia Marshall, and Timothy Wilkin. The members of the PSMB serve in an individual capacity and provide their expertise and recommendations for studies involving human participants. The primary responsibilities of the PSMB are to (1) periodically review and evaluate the accumulated study data for participant safety; study conduct and progress; and, when appropriate, efficacy and (2) make recommendations concerning the continuation, modification, or termination of studies. The PSMB considers study-specific data as well as relevant background knowledge about the disease, test agent, or patient population under study. The PSMB has defined deliberative processes, including event triggers that would call for an unscheduled review, stopping procedures that are consistent with the protocol, unmasking (unblinding), and voting procedures. The event triggers include serious adverse events. The PSMB is also responsible for maintaining the confidentiality of its internal discussions and activities as well as the contents of reports provided to it. On November 9, 2022, Kirabo was presented to the PSMB. At that time, the PSMB had no concerns regarding the performance, monitoring, or safety of the study and recommended the continuation of the study as planned.

All study personnel based in Uganda will be trained in identifying indicators of conditions that may jeopardize the welfare of participants and the limits of confidentiality. This training, conducted by author FS and research staff, focuses on possible scenarios and key questions used to assess risk. Interview staff are trained to err on the side of caution and told to contact the project coordinator and the Masaka diocese in charge of schools, both of whom are always available, via telephone, in the event of the need to break confidentiality owing to an instance of mandatory reporting. Under the guidance of author FS, author OIN, and the parish priest, research staff are trained either to contact the police to ensure the safety of participants or, if appropriate, to have emergency personnel take the adolescent to the nearest hospital.

Adverse events will be reported according to a project protocol. In addition to the PSMB, described earlier, for this study, the PI (PK), the author FS, the project coordinator (author OIN, based in Uganda), and the parish priest (also based in Uganda) will oversee the safety and monitoring of adverse events. This group is expected to meet in person 3 to 4 times per year and will have weekly conference calls. In case of an adverse event, staff will inform the in-country project coordinator and the parish priest immediately and then the US-based PI within 24 hours (with substantial efforts made to also inform the PI immediately) of the occurrence of a possible unanticipated adverse event. Any occurrence of a possible unanticipated adverse event will be immediately reported and brought to the attention of the NYSPI IRB along with the UVRI Research Ethics Board and Ugandan National Council of Science and Technology IRB. The IRBs and PSMB will determine whether it is appropriate to stop the study protocol temporarily or will provide suggestions and modifications for the study procedures. Possible modifications may include adding new risks to the consent form and reconsenting all study participants.

Kirabo aims at HIV prevention and screening for mental health and alcohol use problems. Preliminary outcome data will be examined monthly by the PI (PK) and authors OIN, FS, JSS, and CAM. If preliminary outcome data indicate a harmful impact of the study on the participants (the adolescents), the NYSPI IRB, as well as the Uganda National Council of Science and Technology, will be notified, and it is possible that the study will be discontinued immediately. However, we do not anticipate any negative effects of participation at this time, as much of the proposed intervention is publicly available through m4RH without adverse events. In addition, findings from earlier studies guiding this application suggest an association with positive outcomes, such as increased knowledge of family planning approaches.

Data Management, Study Oversight, and Monitoring

Human participant protection and data safety are of utmost priority. The primary risk in this study is loss of confidentiality, and there is a possible risk of psychological discomfort or distress arising from the personal and potentially sensitive nature of the information elicited during interviews or intervention sessions. The level and probability of experiencing such risks are minimal, and the monitoring plan described in this paper is commensurate with these risks. All procedures and measures were approved by the UVRI Research Ethics Board and the UNCST as well as the IRBs at the NYSPI and CU and the HIV Center for Clinical and Behavioral Studies PSMB. In addition, the Kirabo intervention was also presented to and approved by the Ugandan Ministry of Health.

Results

Study recruitment commenced in August 2023 (N=200). Data collection and analysis are expected to be concluded by 2025, respectively. At the time of manuscript submission, no data had been analyzed. This trial was registered with ClinicalTrials.gov (NCT05130151), where the results are expected to be published from 2024 to 2025.

Discussion

Principal Findings

Kirabo begins to address the National Institute of Health Office of AIDS Research high priority area of reducing HIV incidence by targeting health disparities and comorbidities, as they challenge the efforts to end the epidemic. The first step in this direction is to promote HIV testing and increase mental health and alcohol use problem screening and linkage to counselors for adolescents and young adults who are symptomatic in regions with a high HIV seroprevalence and limited resources. As described in this protocol, we used the ADAPT-ITT [48] framework to adapt an existing evidence-based mobile phone–delivered sexual health program [54,65,99]. Through this process, including a pretest, we created Kirabo, a pathbreaking approach to link adolescents and young adults to local HIV clinics, PrEP, and mental health and alcohol use problem screening, with referral as needed.

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Our pretest results were promising and suggest that it is possible to use school-based recruitment, and the IMB model [49] informed mobile phone SMS text messaging to integrate HIV prevention strategies and mental health care for adolescents and young adults in rural Uganda. The larger population included in our upcoming pilot RCT will provide a clearer understanding of the broad challenges that may impact feasibility and acceptability as well as initial estimates of the intervention effect size.

Mobile phones present an opportunity for contacting, providing information, and motivating adolescents and young adults to seek HIV and mental health care. Although not a panacea, mobile phones have been used for HIV-related sexual health and substance use interventions [100-103] and hold promise for adolescents and young adults who have limited access to the few and frequently overburdened mental health professionals in the region [104,105], specifically in Uganda [18,106,107]. A systematic review of digital innovations for HIV care and prevention noted the need for increased research tailored to context and population to reduce risky behaviors [30]. Furthermore, a review of mobile phone–based interventions in low- and middle-income countries found that they are feasible and improve both HIV and other sexually transmitted infection prevention and care [99]. Notably, a recent systematic review and meta-analysis of digital interventions for common mental disorders in low- and middle-income countries did not include a single study conducted in Africa [108]. The review authors called for future studies “to proactively tackle these challenges and prioritize evaluating digital interventions in low-income countries, especially in Africa, considering its rapidly growing population and potential” [108]. This RCT for evaluating a digital mental health intervention, Kirabo, in Uganda and other recent [109] and ongoing protocols [110] across the continent begin to address this disparity in research.

Limitations

There are some limitations to this protocol. The scope of activity and budget preclude a larger sample size to conduct a full analysis of intervention effectiveness and assess mediators and moderators. Additional studies will be needed to examine whether Kirabo could be implemented on a regional or national level. Further, the technological limitations in the region [23] prevent us from proposing a more interactive digital intervention. Another limitation is that the current protocol will be conducted over a relatively short period (5 weeks of intervention). Additional work could examine whether Kirabo was available for a year or longer and how the linkage to care might fluctuate as adolescents and young adults pass through developmental transitions, which could involve changes in their sexual relationships or potential levels of stress and need for counseling.

Despite these limitations, this protocol will provide preliminary estimates of Kirabo’s efficacy as a tool for promoting linkage to current HIV prevention and behavioral health care for adolescents and young adults who are susceptible to HIV. These preliminary data will serve as the basis for a larger R01 hybrid effectiveness trial [111,112], with the potential to use more advanced technology if it becomes available. This larger-scale trial would include a sufficient sample size to conduct a rigorous analysis of mediators and moderators and a longer-term follow-up to assess the impact of the mobile phone–based intervention on preventing HIV infection by promoting HIV prevention strategies and increasing linkage to care for sexual health, mental health, and alcohol use problems. Digital interventions such as Kirabo may increase access to effective biomedical HIV prevention (PrEP) and begin to address the disparities in access to behavioral health care for adolescents and young adults in Africa. Increasing access to prevention strategies and reducing factors that make adolescents and young adults susceptible to HIV acquisition can contribute to global efforts to end the HIV epidemic.

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Data Availability

The quantitative data sets generated during this study will be made available in the National Institute of Mental Health (NIMH) Data Archive repository [113].

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Authors' Contributions

With support and guidance from mentors JSS, CAM, and GW and advisers FS, YW, MY, and LWC, PK conceptualized and received funding for this study and led and supervised all aspects of study implementation. PK drafted the manuscript. PK, RK, OIN, CAM, FS, GW, YW, MY, CO, CT, CN, VM, LWC, and JSS reviewed and edited the manuscript. RK, OIN, PN, and FS supervised study implementation in the field. All authors reviewed the final draft of the manuscript for intellectual property.

Conflicts of Interest

None declared.

Multimedia Appendix 1
National Institute of Health study section Summary Statement.
[PDF File (Adobe PDF File), 147 KB - resprot_v12i1e49352_app1.pdf]

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Abbreviations

ADAPT-ITT: assessment, decision, administration, production, topical experts, integration, training, testing
AUDIT-C: Alcohol Use Disorders Identification Test–Consumption
CDC: Centers for Disease Control and Prevention
CFAR: Centers for AIDS Research
CFIR: Consolidated Framework for Implementation Research
CITI: Collaborative Institutional Training Initiative
C-SSRS: Columbia Suicide Severity Rating Scale
CU: Columbia University
ESA: East and Southern Africa
GAD-7: 7-item Generalized Anxiety Disorder Questionnaire
GCP: Good Clinical Practice
ICHAD: International Center for Child Health and Development
IMB: information, motivation, and behavior
IRB: institutional review board
IVR: interactive voice response
KII: key informant interview

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m4RH: Mobile 4 Reproductive Health
NIH: National Institutes of Health
NYSPI: New York State Psychiatric Institute
PHQ-4: 4-item Patient Health Questionnaire
PHQ-9: 9-item Patient Health Questionnaire
PI: principal investigator
PrEP: pre-exposure prophylaxis
PSMB: Performance and Safety Monitoring Board
RCT: randomized controlled trial
SRH: sexual and reproductive health
UNCST: Uganda National Council for Science and Technology
USSD: unstructured supplementary service data
UVRI: Uganda Virus Research Institute

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Protocol

Digital Therapeutic Intervention for Women in the UK Armed Forces Who Consume Alcohol at a Hazardous or Harmful Level: Protocol for a Randomized Controlled Trial

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Abstract

Background: Alcohol misuse is common in the United Kingdom Armed Forces (UKAF), with prevalence significantly higher than in the general population. To date, digital health initiatives to support alcohol misuse have focused on male individuals, who represent approximately 89% of the UKAF. However, female veterans drink disproportionally more than female members of the public.

Objective: This 2-arm participant-blinded (single-blinded) confirmatory randomized controlled trial (RCT) aims to assess the efficacy of a brief alcohol intervention (DrinksRation) in reducing weekly self-reported alcohol consumption between baseline and a 3-month follow-up (day 84) among women who have served in the UKAF.

Methods: In this 2-arm single-blinded RCT, a smartphone app that includes interactive user-focused features tailored toward the needs of female veterans and designed to enhance participants' motivations to reduce the amount of alcohol they consume is compared with the UK Chief Medical Officer guidance on alcohol consumption. The trial will be conducted among women who have served at least 1 day of paid service in the UKAF. Recruitment, consent, and data collection will be carried out automatically through the DrinksRation app or the BeAlcoholSmart platform. The primary outcome is change in self-reported weekly alcohol consumption between baseline (day 0) and the 3-month follow-up (day 84) measured using the Timeline Follow Back for alcohol consumption. The secondary outcome is the change in the Alcohol Use Disorders Identification Test score measured at baseline and 3-month follow-up between the control and intervention groups. The process evaluation measures include (1) app use and (2) usability ratings as measured by the mHealth App Usability Questionnaire.

Results: RCT recruitment will begin in January 2024 and last for 5 months. We aim to complete all data collection, including interviews, by May 2024.

Conclusions: This study will assess whether a smartphone app tailored to the needs of women who have served in the UKAF is efficacious in reducing self-reported alcohol consumption. If successful, the digital therapeutics platform could be used not only to support women who have served in the UKAF but also for other conditions and disorders.

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Trial Registration: ClinicalTrials.gov NCT05970484; https://www.clinicaltrials.gov/study/NCT05970484
International Registered Report Identifier (IRRID): PRR1-10.2196/51531

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KEYWORDS

mental health; digital health; DrinksRation; women; woman; United Kingdom; Armed Forces; alcohol; randomized controlled trial; RCT; controlled trials; study protocol; alcohol misuse; smartphone app; mobile app; mobile health; mHealth; veterans; women veterans; mobile phone; digital therapeutic

Introduction

Background

There are 2.5 million military veterans in the United Kingdom (defined by the British government as those who have served in the military for at least 1 paid day), of whom 11% are estimated to identify as female [1]. Female veterans have served in the United Kingdom Armed Forces (UKAF) for >100 years. Although their valuable contribution has been recognized by successive governments and improved military culture. However, with evolving service requirements, they have had a significant impact on the health and well-being of many female veterans [2,3]. Nevertheless, there is a dearth of evidence on the impact of alcohol use on female veterans' health.

The limited existing evidence suggests that female veterans' alcohol use is increasing and that they are significantly more likely to report symptoms of hazardous drinking than female civilians [4]. Increased rates of hazardous drinking were also observed by Palmer et al [5], who found that half of the female veterans (389/779, 49.9%) were misusing alcohol at a hazardous or higher level, which is considered harmful to their health [5]. To place this into context, the UK Chief Medical Officer recommends that people do not regularly drink >14 units per week to keep health risks from drinking alcohol to a low level.

Alcohol misuse often co-occurs with common mental health disorders, including posttraumatic stress disorder (PTSD), anxiety, or depression, and alcohol is frequently used as a coping mechanism [2]. Common mental health disorders are more common in female than male veterans [4]. Research has also shown that female veterans face barriers to accessing mental health support, often owing to misusing alcohol [6,7]. Ultimately, although female veterans drink less than male veterans, their rates of hazardous drinking are higher than those of the general population, putting them at increased risk of poorer health.

The impact of alcohol misuse among female veterans on the wider society (eg, health care use, productivity, and welfare) is unknown. In England, heavy drinking (deemed as drinking >14 units of alcohol/wk) is estimated to cost the National Health Service (NHS) £3.5 billion per year (US $3.9 billion; 3.6% of its annual budget) [8] and is more common in people with mental health difficulties [9]. As female veterans drink more than their civilian counterparts, the relative costs are likely to be even higher. Innovative solutions are urgently required.

In recent years, there has been a growing treatment gap in the United Kingdom, with patients waiting longer for treatment and support for alcohol misuse. To overcome this gap, we developed the DrinksRation platform [10], an automated brief digital intervention designed to support help-seeking veterans in managing and reducing the amount of alcohol they drink [11-14]. DrinksRation is unique in that the app content is tailored using behavior change techniques (BCTs) to promote positive changes in behavior. DrinksRation is the only app targeting alcohol misuse in the UKAF community. It is designed to (1) overcome geographic limitations, (2) use wearable technology (eg, Fitbit and Apple Watch) to inform decision-making and personalization, (3) avoid the stigma associated with receiving help in person, and (4) provide convenience because users can use the app as they prefer (discreetly or openly). The app is freely available on the Apple App Store and Google Play Store. The app has received support and endorsement from Combat Stress and is currently being trialed among serving personnel [15]. DrinksRation is supported by a robust evidence base, including a randomized controlled trial (RCT) that demonstrated that the app is efficacious in reducing alcohol consumption [12].

The DrinksRation app was developed to support veterans who have sought help for a mental health problem and was not designed with potential gender differences in mind. A recent viewpoint highlighted a critical need for feminist intersectionality in digital health to incorporate the unique needs of female individuals [16]. Digital health technologies can bolster gender equality through providing increased access to health care, empowering decision-making about one's health data, overcoming the specific barriers facing female veterans, and reducing the burden on health care systems [17-19].

Objectives

This project aims to tailor the DrinksRation app to reflect the specific needs of female veterans and evaluate these changes using a confirmatory RCT. It is hypothesized that a refined version of DrinksRation will be efficacious at reducing self-reported weekly alcohol consumption between baseline and the 3-month follow-up (day 84) among female veterans who drink at a hazardous or harmful level.

Methods

Ethical Considerations

This study was approved by the ethics committee of King's College London (LRS/DP-22/23-36879). The study has been registered prospectively on ClinicalTrials.gov (NCT05970484). After completing outcome questionnaires (day 84) at the primary end point (day 84), participants will receive a US $25 (£20 GBP) Love2Shop voucher. There will be no cash alternative

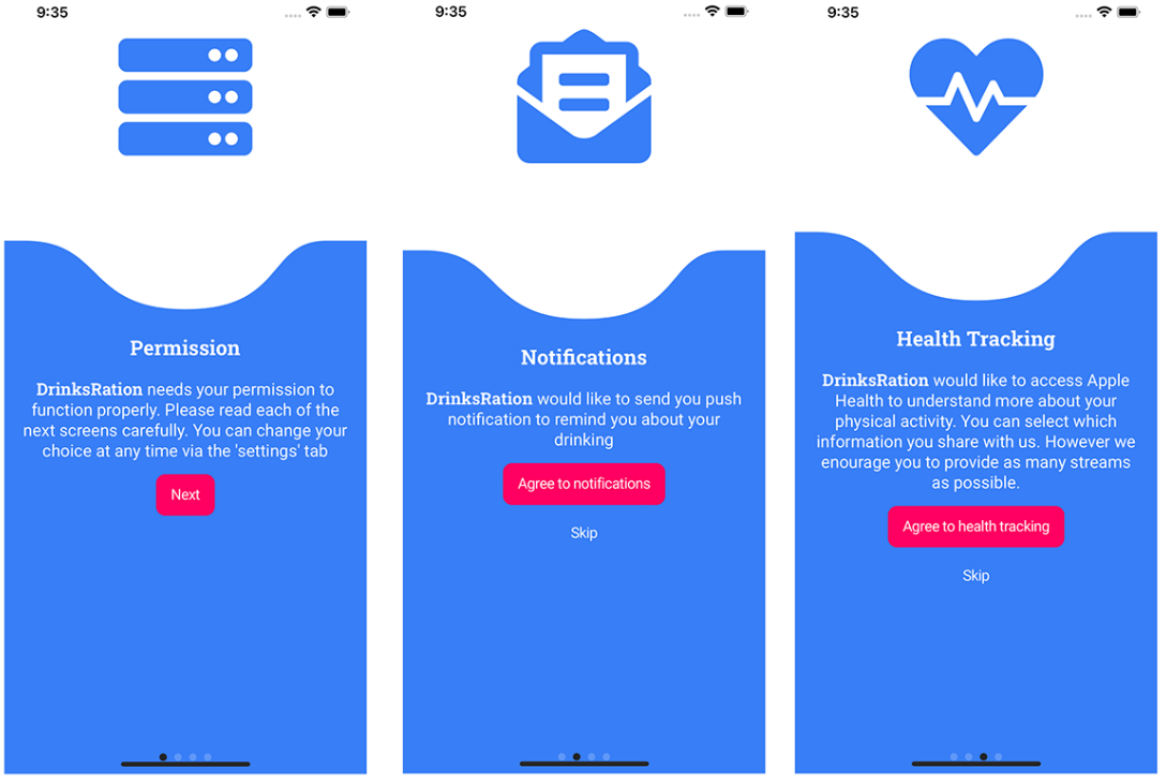
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offered to participants. We will seek informed consent from all participants via the eligibility and consent survey before the collection of any personal data. For participants in the intervention arm, we will additionally ask for specific on-device permissions to enable the full functionality of the DrinksRation app (eg, to receive push notifications or share health tracking data; refer to the example screenshots presented in Figure 1). Participants can change these optional permissions at any time via the settings page of the app.

Participants will be informed via the participant information sheet that they can withdraw from the study or withdraw from data collection at any time. For participants who withdraw from the study, we will (1) attempt to collect follow-up information if they agree to continued data collection and (2) retain their existing data if they agree to their use. Alternatively, withdrawn participants can delete their study data by contacting the research team. Participants in the control arm will need to withdraw by contacting the research team, whereas those in the intervention arm can withdraw via the app.

If participants in the intervention arm withdraw, they will be asked to delete the intervention app and denied further access. All data, including those from withdrawn participants, except for those who make a request for their data to be deleted, will be included in the final analysis.

Figure 1. Consent flow screenshot examples presented to all study participants.



Study Design

Overview

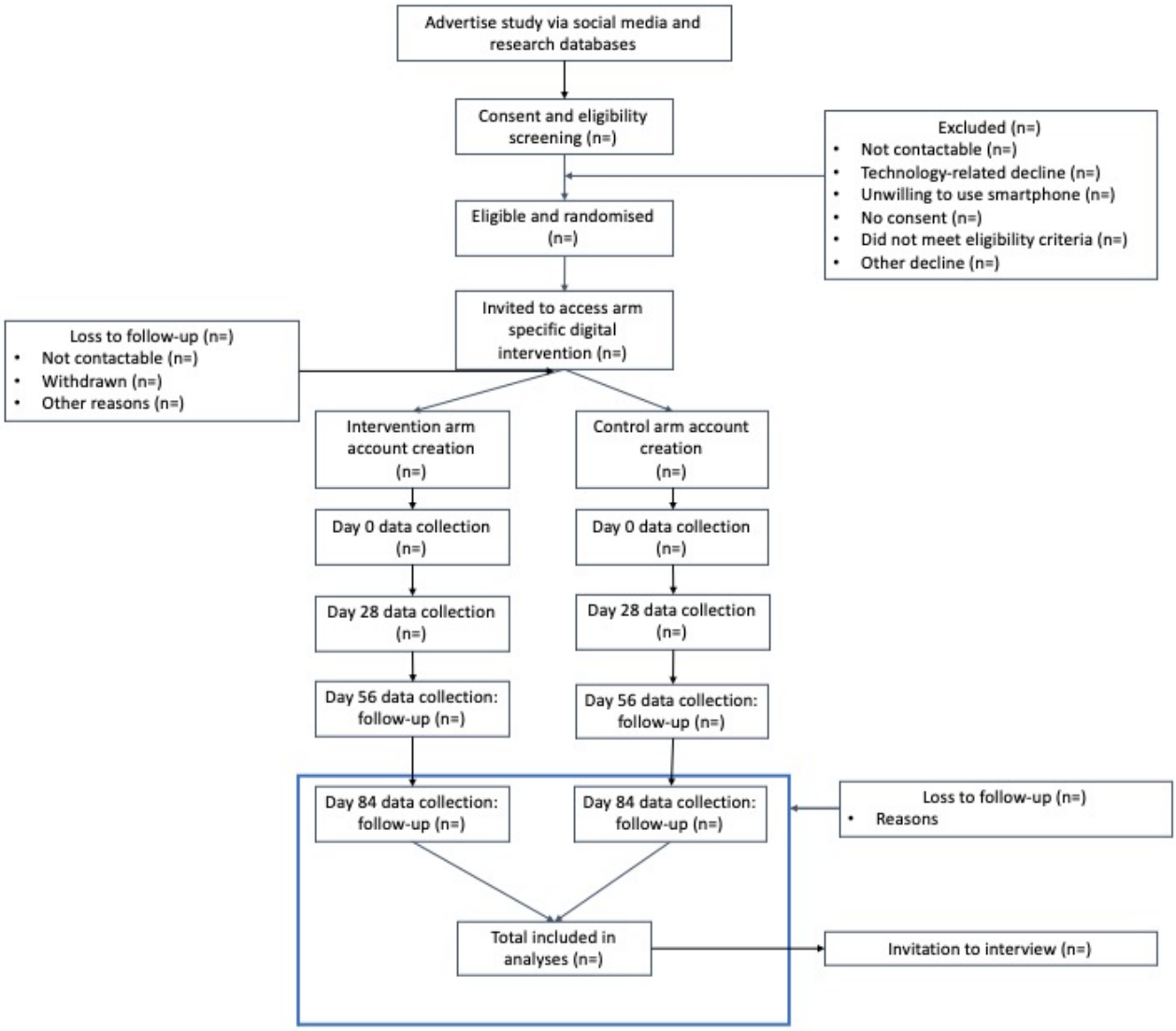
This is a 2-arm participant-blinded (single-blinded) confirmatory RCT comparing the DrinksRation smartphone app (intervention arm) with a progressive web application (PWA) presenting NHS-focused drinking advice (named *BeAlcoholSmart*; control arm). The DrinksRation app provides individualized normative advice with features designed to enhance participant motivation, interactive feedback, self-efficacy in modifying their alcohol consumption, and personalized gender-specific messaging. We hypothesize that the intervention arm will be efficacious in reducing alcohol consumption compared with the control arm.

Both the control and intervention arms will be delivered digitally. Participants in the control arm will be given access only to a PWA that comprises a calculator for calculating alcohol units consumed over the previous week, generic public health guidance [20], and weekly reminders to use the calculator (refer to the *Control Arm* subsection for details). Participants in the intervention arm will be given access to the full enhanced DrinksRation app, which includes a range of theoretically driven features and behavioral change messaging (discussed further in the *Intervention Arm* subsection). We have designed this study so that the control arm resembles the intervention arm (eg, an app delivered digitally and usable on a smartphone) but lacks the active ingredients present in the DrinksRation intervention arm (eg, a drinks diary, interactive drinking feedback, and goal setting). This approach was selected to ensure consistency between the arms (both groups receive a digital intervention) and to facilitate participant blinding to treatment assignment.

Participants in both arms will be asked to use the digital interventions for 12 weeks (the intervention period; 84 days). Figure 2 presents the study flow and data collection points.

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Figure 2. Study flow diagram. Primary outcome is assessed at day 84.



Intervention Arm

The DrinksRation (formerly called *InDEx* [13,14,21]) app was developed following the Medical Research Council's guidelines for developing and evaluating complex interventions and using a co-design methodology. It was developed by the King's Centre for Military Health Research (King's College London) and Lancaster University with support from experts in smartphone app development, epidemiology, addiction psychiatry, and military mental health. The app is designed to support veterans drinking at a hazardous or harmful level by providing bespoke advice and support.

The app seeks to enhance participants' motivation and self-efficacy in modifying their alcohol consumption using BCTs presented via the in-app content (Multimedia Appendix 1) and through messages sent to participants. The iterative development process, theoretical framework, feasibility trial, pilot, and RCT are reported elsewhere [11-14,21]. Briefly, DrinksRation was developed and tested with 5 core modules (Textbox 1; refer to Figure 3 for example screenshots).

The app is compatible with all modern iOS- and Android-supported devices. Participants in the intervention arm will complete all questionnaires via the app, including additional questionnaires on their mood and general mental health, which are used to personalize the app content and push notifications. Participants will receive push notifications every few hours on the day that each questionnaire is due to prompt the completion of unanswered questions.

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Textbox 1. Core modules of the DrinksRation app.

Account management

- Participants can modify personal information (eg, first name and mobile phone number) and app parameters (eg, automatic log out, data-sharing permission, and withdrawing from the study).

Questionnaire and individualized normative feedback

- This feature captures the participant's responses to a set of questions and aggregates the responses to produce personalized feedback on drinking behaviors.

Self-monitoring and feedback

- This feature records alcohol consumption by participants and provides a range of visual illustrations (eg, charts, figures, and text) to allow for the monitoring of consumption. Furthermore, the participant can select visual metrics relevant to their interest (eg, calories, cost, and exercise required).

Goals (setting and review)

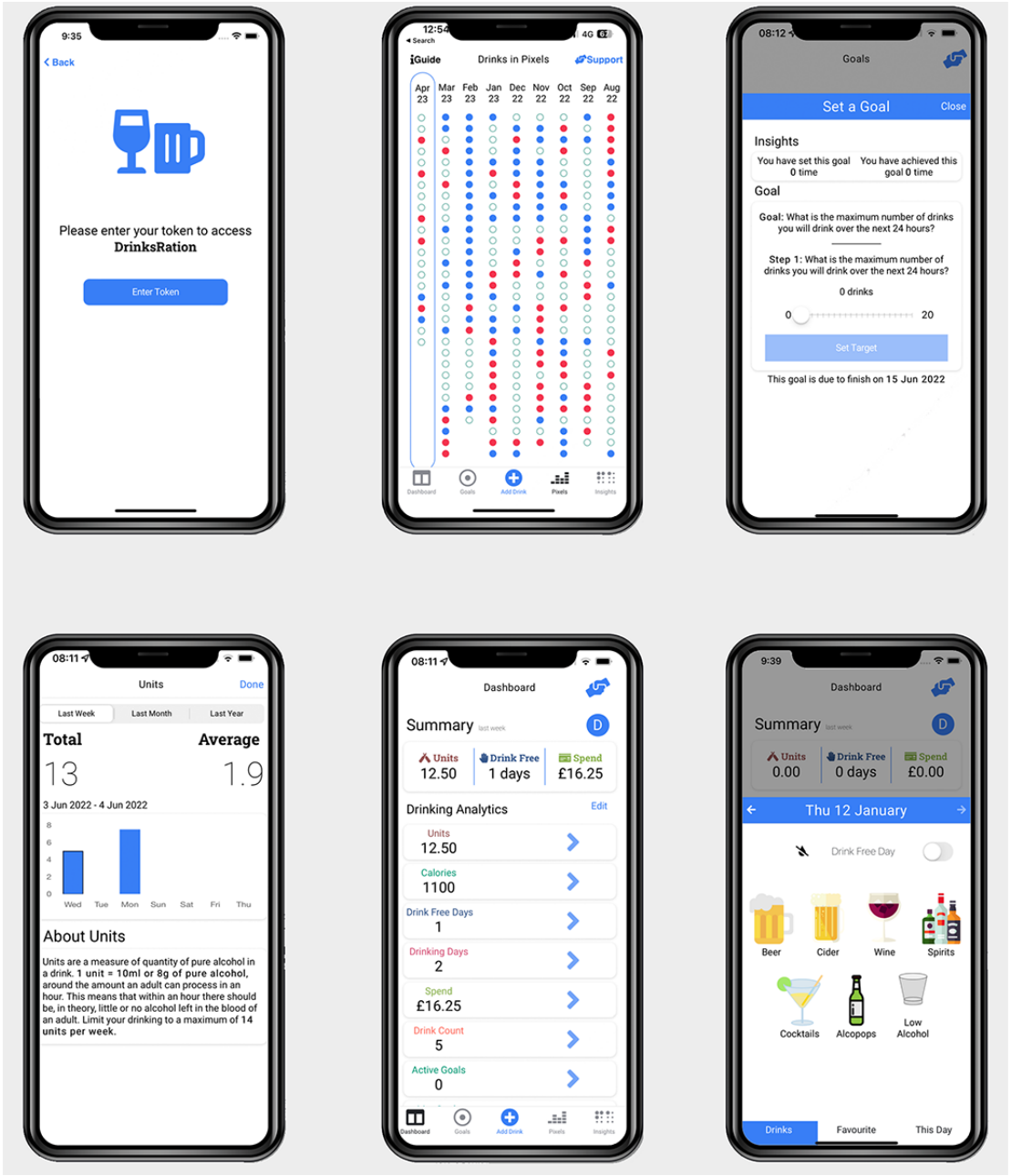
- Participants can set goal or goals based on the implementation intentions (if and then) [22] methodology; visual feedback provides feedback on progress toward achieving the goal or goals set.

Personalized messaging

- Participants are sent tailored messages via push notification, which provide prompts to use the drinks diary, suggest alternative behaviors, and provide feedback on goals.

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Figure 3. Example screenshots of the DrinksRation app.



Control Arm

The control arm will receive access to the BeAlcoholSmart PWA. A PWA is a website that looks and behaves like a smartphone app. The PWA can take advantage of smartphone features such as push notifications and haptics without requiring the participant to download it via an app store. The BeAlcoholSmart PWA will be accessible to participants in the control arm via a unique link. The app will contain a 7-day alcohol unit calculator and generic public health guidance on safe drinking [20]. Participants will also receive reminders via email prompting them to consult the guidance provided as part of the BeAlcoholSmart PWA. Control participants will be invited to complete all questionnaires via Qualtrics (Qualtrics International Inc), with an email reminder being sent when they are due.

Participant Co-Design

This study will evaluate an adapted version of the DrinksRation app that caters to the specific needs of female veterans. To ensure that any adaptations and new features are suitable for the target population, we will undertake participatory research—following the guidelines provided in the study by Bell and Pahl [23]—in the form of co-design and cocreation via a patient advisory board (PAB) and a stakeholder advisory board (SAB). The PAB will include those with lived experience of military service, whereas the SAB will include stakeholders and those representing the target population, such as charities treating alcohol misuse. PAB and SAB members will be recruited via our existing networks and communication channels.

We aim to recruit up to 5 members on both the PAB and SAB. Before undertaking any data collection, we will hold 2 roundtable discussions to collect input on the (1) development

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of app content, (2) refinement of existing app content, (3) development of new app features, and (4) suitability of tailored messaging.

In addition to PAB and SAB discussions, we will also ask members of the PAB to provide iterative feedback on updates to the DrinksRation app, study protocol, and study findings. Furthermore, we will hold a PAB and SAB meeting every quarter to provide updates on the study progress and to promote research awareness. PAB members will receive a US $13 (£10 GBP) digital Love2Shop voucher for each video session they attend. It is important to note that PAB members will not be allowed to participate in the RCT.

Eligibility Criteria

The eligibility criteria are provided in Textbox 2.

Textbox 2. Inclusion and exclusion criteria.

Inclusion criteria

- Aged ≥18 years
- Identify as female (self-reported sex)
- Live in the United Kingdom
- Consume ≥15 UK units (approximately 150 g) of alcohol/wk as measured using Timeline Follow Back for alcohol consumption [24] at baseline (day 0; the choice of a minimum threshold of 15 UK units of alcohol/wk reflects scientific research and UK national guidelines that indicate that regular drinking of >15 units/wk carries increased health risks [25])
- Are veterans of the United Kingdom Armed Forces (UKAF), defined as per UK definitions as having completed at least 1 day of paid employment in the UKAF (verified by self-report at eligibility screening)
- Have downloaded the mobile app onto an iOS or Android smartphone

Exclusion criterion

- Do not own a smartphone

Sample Size Calculation

A power calculation was performed based on previously reported data from the DrinksRation RCT [12]. With 148 participants (n=74, 50% per arm), we will have at least 80% power to detect a difference in alcohol consumption of 3 units (approximately 30 g of alcohol/wk) between the intervention and control arms at the 84-day follow-up assessment. This calculation assumes an SD of 5.6 units, an attrition rate of 40% by day 84, a correlation between successive follow-up assessments of 0.7, and an α of 5%.

We have chosen a minimum difference of 3 units based on treatment effects observed in similar studies [26-28] and in reductions observed in the DrinksRation feasibility trial [11] and the confirmatory RCT among help-seeking veterans [12], which found reductions at 28 days of 22 units between the arms. We have chosen a smaller minimum difference of 3 units, recognizing that treatment effects for brief interventions reduce over time and that the target population for this study is not a help-seeking population.

Recruitment

Participants will be recruited via an existing research cohort [26] and social media [29] following published recruitment strategies [29,30]. The research cohort will comprise participants from the King's Centre for Military Health Research health and well-being longitudinal cohort study [26], and participants will be sent an email inviting them to take part. We will also seek to recruit participants via paid promotional advertisements on social media (eg, Twitter, Facebook, and Instagram) with a link enabling potential participants to complete the eligibility and consent survey.

Potential participants who respond to the email invitation or social media advertisements will be sent an email containing an explanation of the study, a link to the participant information sheet, and an invitation to complete the eligibility and consent survey (Multimedia Appendix 2). Eligible participants will then be randomized (refer to the Randomization and Blinding subsection) and sent instructions on accessing the BeAlcoholSmart or DrinksRation app using a unique QR code. Once they have accessed the platform, they can register an account and complete the baseline questionnaire (day 0).

Randomization and Blinding

Randomization will be conducted automatically when a token code is generated alongside a unique proxy identifier (managed by researcher GW). At this point, participants are automatically randomized to receive the control or intervention arm and are blinded. The randomization procedure is carried out automatically via a randomization algorithm with no human involvement except to provide a proxy identifier. As allocations are generated dynamically, it is not possible to view future allocations. Researchers DL and GW will be unblinded to treatment allocation to enable the management of the BeAlcoholSmart and DrinksRation platforms as well as participant recruitment and retention, whereas researcher EC will be unblinded to treatment allocation to prepare statistical reports. Researchers DL and EC will not be involved in any participant engagement or recruitment. All other members of the study team will be blinded to treatment allocation.

Messaging: Push Notifications and Email Messaging

Participants in the intervention arm (DrinksRation) will receive personalized push notifications to prompt them to use the drinks diary, engage with the app, and complete outcome measures,

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as well as to suggest alternative behaviors, provide feedback on goals, and promote a healthy lifestyle. We will use a bank of 180 messages developed previously [13], informed by the Health Action Process Approach framework and targeting specific BCTs.

DrinksRation uses baseline and weekly questionnaires to inform participant messaging and provide an individualized participant-centric approach. Baseline measurements are used to identify suitable messages, and as a participant engages with DrinksRation, regular measurements, including questionnaires (baseline and weekly questionnaires) and the drinks diary, are used to reflect current behavior and attitude. The notifications cover a wide range of topics to target beliefs and motivations with the primary aim of increasing the participant's awareness of their drinking habits and behaviors. The notifications are divided into 3 categories: tailored (personalized to drinking habits as well as baseline and weekly questionnaires), tailored and triggered (tailored to baseline and contiguous measurements and a specific event occurring), and targeted (generic; sent on specific days to highlight inactivity, to remind participants to complete a questionnaire, or to alert participants to a new feature).

The system automatically decides when a message should be sent.

For the control arm (BeAlcoholSmart), participants will only receive notifications (via email) when they join the platform and when outcome measures are due. The welcome email will contain information on how to use the BeAlcoholSmart platform and when future notifications will be sent. The questionnaire emails will include a reminder to consult the BeAlcoholSmart platform and complete a questionnaire. No other notifications will be sent.

Study Instruments

Overview

A summary of measures and data collection time points in this study is presented in Table 1.

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Table 1. Summary of measures and data collection time points (days 0, 7, 14, 21, 28, 56 and 84).

Measure (Multimedia Appendix 3)	Days after randomization													
	0		7		14		21		28		56		84 (primary end point)	
	I[a]	C[b]	I	C	I	C	I	C	I	C	I	C	I	C
Questionnaires														
Informed consent or consents	✓	✓												
Sociodemographics	✓	✓												
Depression (PHQ-2[c]) [31]	✓	✓	✓		✓		✓		✓		✓	✓	✓	✓
Anxiety (GAD-2[d]) [32]	✓	✓	✓		✓		✓		✓		✓	✓	✓	✓
ITQ-PTSD[e] [33]	✓	✓							✓	✓	✓	✓	✓	✓
Readiness-to-Change Ruler [34]	✓	✓							✓	✓	✓	✓	✓	✓
Self-Efficacy Ruler [34]	✓	✓							✓	✓	✓	✓	✓	
AUDIT[f] [35]	✓	✓							✓	✓	✓	✓	✓	
EQ-5D-5L [36]	✓	✓							✓	✓	✓	✓	✓	✓
7-d TLFB[g] for alcohol consumption [24]	✓	✓							✓	✓	✓	✓	✓	✓
Adverse event reporting									✓	✓	✓	✓	✓	✓
Usability evaluation														
Qualitative interviews[h]													✓	✓
MAUQ[i] [37]									✓	✓	✓	✓	✓	✓
Remote data collection (continuous)														
Wearable sensors[j]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Smartphone sensors[j]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

[a]I: intervention arm data collected via app.

[b]C: control arm data collected via Qualtrics (Qualtrics International Inc) through BeAlcoholSmart platform.

[c]PHQ-2: Patient Health Questionnaire-2.

[d]GAD-2: Generalized Anxiety Disorder-2.

[e]ITQ-PTSD: International Trauma Questionnaire for Posttraumatic Stress Disorder.

[f]AUDIT: Alcohol Use Disorders Identification Test.

[g]TLFB: Timeline Follow Back.

[h]A total of 10 participants will be invited to participate in a qualitative interview after day 84.

[i]MAUQ: mHealth App Usability Questionnaire.

[j]Additional participant consent is required.

Baseline Measures

After they have downloaded the respective platforms, participants will be asked to complete a baseline questionnaire to assess physical and mental health, readiness to change, self-efficacy, health status, and sociodemographics (eg, age, gender, ethnicity, employment status, and occupation). The questionnaire set is available in Multimedia Appendix 3, and the schedule is presented in Table 1.

Outcome Measures

The primary outcome in this study is self-reported alcohol consumption measured by the 7-day Timeline Follow Back for alcohol consumption. At baseline (day 0) and 28, 56, and 84 days after randomization, participants will be asked to report the number and types of drinks that they consumed in each of the previous 7 days via DrinksRation or BeAlcoholSmart. Using standard unit measurements (Multimedia Appendix 4), we will calculate weekly alcohol consumption for baseline and each follow-up by summing the number of units assigned to each drink. To maximize the completion of the primary outcome at each follow-up, participants will first be asked to complete the primary outcome measure before completing the rest of the questionnaire. The secondary outcome is the change in the Alcohol Use Disorders Identification Test score, measured at

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baseline (day 0) and day 84 follow-up between the control and intervention groups.

Usability

We will examine the usability of the DrinksRation and BeAlcoholSmart platforms using the mHealth App Usability Questionnaire [37] at day 28. Questionnaire responses will be aggregated into (1) overall usability, (2) ease of use, (3) interface and satisfaction, and (4) usefulness. The results will be summarized with means and SDs.

Qualitative Interviews

A random sample of 10 participants from the intervention arm will be invited to participate in a debrief session with the research assistant (RA; researcher GW) at the end of the intervention period. The 60-minute interview will address the participants' experiences of using the DrinksRation app, their views on its acceptability and usability, and what further modifications could be made to improve their experiences of using the app. Interviews will be conducted on the web (via Microsoft Teams or Zoom [Zoom Video Communications, Inc]), and transcripts will be generated and used for analysis. A thematic analysis approach will be used. The findings from the qualitative interviews will be reported separately from the main trial results. Any participant who completes the day 84 outcome measure will receive a US $13 (£10 GBP) Love2Shop voucher as a gesture of goodwill.

Adverse Events

It is not expected that participation in this study will lead to an increase in alcohol consumption or any untoward or unintended consequence. In this study, we have defined 4 categories of risk events (Textbox 3).

Adverse events and serious adverse events will be monitored throughout the intervention period via (1) direct contact between participants to the research team; and (2) a questionnaire presented to participants via the app on days 28, 54, and 84 after randomization. All reported events will be reviewed by a clinician (researcher DM), who, where required, will contact participants to perform a clinical interview and risk assessment. If concerns remain, a signposting booklet to relevant charities will be provided to the participants. The study RA will remove potentially unblinding information before sending it to the study clinician. The study clinician or the RA may register an adverse event based on the definitions outlined in Textbox 3.

Textbox 3. Categories of risk events.

Adverse event

- Any untoward medical occurrence in a trial participant that does not necessarily have a causal relationship with this treatment (eg, consuming >25 units of alcohol in a 24-h period).

Adverse reaction

- Any untoward and unintended medical occurrence in a trial participant that is related to the intervention (eg, reaction to a questionnaire).

Unexpected adverse reaction

- An adverse reaction where the nature and severity of the reaction are inconsistent with the information known about the study.

Serious adverse event, serious adverse reaction, or unexpected serious adverse reaction

- Any adverse event, adverse reaction, or unexpected adverse medical event reaction that (1) results in death, (2) is life threatening or requires immediate safeguarding, (3) requires hospitalization or prolongs existing hospitalization, or (4) results in persistent or significant disability or incapacity.

Project Management Group

Project oversight will be provided by a project management group (PMG). The PMG will be chaired by the principal investigator and attended by all coinvestigators. The PMG will meet every quarter and will be responsible for all aspects of project management, including (1) monitoring the delivery of the scientific results needed to progress the study; (2) monitoring the study against the schedule and act if required; (3) monitoring the study against agreed milestones and the identification of risks to achieving milestones as well as solutions for managing risks and issue resolution; (4) providing access to appropriate resources necessary for project progression, including internal and outsourced resources and the management of these resources; and (5) regular review of a blinded report from the study clinician about adverse and serious adverse events (ie, total numbers pooled across arms).

PMG members will be blinded to treatment allocation.

Executive Steering Committee

An executive steering committee will oversee safety requirements and make recommendations to the PMG. This committee will consist of an independent chair and the study clinician. The committee will receive regular reports from the trial statistician (researcher EC) and the RA on risk and appraise study functions. Concerns and recommendations will be raised with the principal investigator and discussed at PMG meetings.

Protocol Amendments

Protocol amendments will be discussed and approved by the PMG as well as the PAB and minuted. They will be reported in subsequent closed reports (eg, prepared by the unblinded trial statistician). Any approved amendments will be submitted to the King's College London ethics committee for approval and published on the Open Science Framework.

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Statistical Analysis

We will describe participant characteristics using appropriate summary statistics (eg, frequency and percentage for categorical items and mean and SD or median and IQR for continuous items).

We will analyze the primary outcome using a linear mixed effect model. The outcome will be the 3 repeated outcome assessments (collected on days 28, 56, and 84). The model will include (1) the baseline measure of the outcome (day 0); (2) a dummy variable indicating treatment allocation (0=control arm and 1=intervention arm); (3) time, measured as weeks since baseline; (4) a treatment × time interaction; and (5) baseline characteristics associated with missingness. The model will additionally include a participant random intercept to account for repeated assessments clustered within individual participants and an unstructured residual covariance matrix. The mixed model will use all available information, retaining participants with at least 1 follow-up assessment, to improve efficiency. Treatment effects (adjusted between-group mean differences in alcohol units) will be estimated from the model for each follow-up separately. Cohen *d* effect sizes at 28, 56, and 84 days will be calculated as the adjusted mean difference divided by the sample SD of the outcome at baseline. The threshold for statistical significance is $P<.05$.

The intention-to-treat analyses will include all participants who complete at least 1 follow-up assessment (day 28, day 56, or day 84).

Analyses will be conducted using Stata (StataCorp LLC) or R statistical software (R Foundation for Statistical Computing).

Process Evaluation

We will examine process evaluation measures as a proxy for app use. These will be reported in three categories: (1) app use based on app analytics data provided by Google Analytics, (2) drinking analytics based on server interactions, and (3) notifications sent by the server. Where appropriate, these will be summarized as either median with IQR or mean with SD.

Access to Study Data

All study data will be made available in an anonymized format alongside any source code via the Open Science Framework. There are no contractual agreements that limit access to, or the sharing of, data.

Data Management

Data collected in this study will be stored on Google Firebase servers located in the United Kingdom, with audited and copied in real time to Google BigQuery data storage to ensure data integrity. Access to these systems is protected using Google authentication and a zero-trust modal. Upon completion of the study, data will be extracted from the Google Firebase servers and Google BigQuery and compared for assurance and data quality.

During active data collection, the research team (DL and GW) will monitor incoming data to ensure that each platform functions correctly. The research team will not contact participants outside of automatic messaging unless they reach out to the research team with queries (managed by GW; eg, with technical issues concerning how to perform a task or if risk alerts are triggered).

Results

RCT recruitment will begin in January 2024 and last for 5 months. We aim to complete all data collection, including interviews, by May 2024. The results of this study will be communicated via publication, lay articles disseminated via stakeholders and collaborators, and a participant newsletter.

The study will be reported following the TIDieR (Template for Intervention Description and Replication) [38] checklist as well as the CONSORT (Consolidated Standards of Reporting Trials) [39] and CONSORT-EHEALTH (Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth) [40] checklists.

Discussion

Summary

This project aims to tailor the DrinksRation app to reflect the specific needs of female veterans and evaluate these changes using a confirmatory RCT. We hypothesize that a refined version of DrinksRation will be efficacious at reducing self-reported weekly alcohol consumption among female veterans who drink at a hazardous or harmful level. Alcohol misuse is a persistent problem in the UKAF, with estimates forecasting that >50% of those who have left the UKAF meet the criteria for hazardous alcohol use. This is almost double that of the general population [41] and higher in female veterans. Innovative digital interventions can be used to great effect to meet this growing demand for support and treatment for alcohol misuse [42,43].

Currently, there are no smartphone-based alcohol interventions targeting female veterans of the UKAF to reduce alcohol misuse. Therefore, we propose to refine DrinksRation—a theory-driven and user-centered smartphone app—to address this gap for female veterans. Although DrinksRation has been tested in a largely male population, there has been little focus on female veterans. This study protocol describes the design of an RCT to determine the efficacy of DrinksRation among a female veteran population.

The Ministry of Defence Research Ethics Committee and the National Institute for Health and Care Research have identified female veterans as an underserved group regarding support and treatment for alcohol misuse. This is often due to medical services targeting male counterparts, failing to target specific female barriers to care, and a general lack of awareness of female motivations for drinking [17,18,44]. Given the limited evidence to date, there is an urgent need for innovation to support female veterans.

A key strength of this study protocol is the collaboration among the charitable sector, stakeholders, academia, and the UKAF, enabling the development and public release of DrinksRation. A further strength includes remote delivery via a smartphone to overcome issues related to availability or geographic

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limitations for participants. Furthermore, DrinksRation is unique in that it uses personalized push notifications to promote positive changes in behavior among participants [45]. This ensures longer-term engagement and adherence. DrinksRation can also be used on any iOS and Android device released in the last 7 years. However, owing to personalization, the app requires an active data connection to function.

This study will not be without challenges, the first of which concerns our ability to recruit and retain a sufficient number of female veterans to power our analysis. This is due to a known issue: many of those who have alcohol-related problems are reluctant to seek help to ameliorate their problems. We planned our recruitment approach following best practice and our prior experiences in recruitment to mitigate this issue. Furthermore, the app has been designed to promote its active use, with frequent reminders, which is expected to promote adherence to the app. Second, we expect that some participants may encounter technical issues related to the app (eg, unable to log drinks or receive notifications) or the mobile device. To mitigate potential technical or mobile device issues, we have undertaken extensive testing across a range of popular mobile devices, and we will allow participants to provide in-app feedback that will be regularly monitored by the research team. Third, participants may reduce engagement or disengage in the control arm because BeAlcoholSmart is a static service. We will mitigate this by promoting its use to participants and ensuring that all information and data are presented appropriately. Finally, we acknowledge that our sample comprises participants who may be undergoing active treatment. To mitigate this risk, we will measure and describe the number of participants in each arm already receiving treatment for alcohol.

Open Access Statement

For the purposes of open access, the author has applied a Creative Commons attribution (CC BY) license to any accepted author manuscript version arising from this submission.

Conclusions

If this study is successful, the DrinksRation platform along with its refined features could be used not only to support women who have served in the UKAF but also for other conditions and disorders.

Acknowledgments

This study has been funded by the Office for Veterans' Affairs (OVA). Combat Stress, a national charity in the United Kingdom that provides clinical mental health services to veterans, has provided sponsorship to the DrinksRation app to cover computing costs. NTF is partly funded by the UK Ministry of Defence. SD and DL have received funding from the OVA Veterans Health Innovation Fund. The views expressed are those of the authors and not necessarily those of the Forces in Mind Trust, the National Health Service, the UK Ministry of Defence, or the OVA.

Data Availability

Data and code syntax arising from the randomized controlled trial will be made available via the Open Science Framework.

Authors' Contributions

DL, EC, NTF, LG, and DM conceptualized the study. GW, DL, EC, NTF, LG, and DM were responsible for the methodology. DL and GW were responsible for the software. DL, EC, NTF, LG, and DM wrote the original draft. DL, EC, NTF, KK, AS, LG, and DM reviewed and edited the draft. DL and EC supervised the study. GW and DL were responsible for project administration. DL, EC, NTF, LG, and DM were responsible for funding acquisition.

Conflicts of Interest

DM is a trustee of the Forces in Mind Trust and is employed by Combat Stress. NTF sits on the independent group advising on the release of patient data at National Health Service Digital and is also a trustee of a military-related charity. KK and AS are full-time member of the UK Armed Forces. DL is a reservist in the UK Armed Forces; this work has been undertaken as part of his civilian employment. SD is a member of the Office for Veterans' Affairs (OVA) Academic Advisory Board and sits on the Forces in Mind Trust Mental Health Steering Group. All other authors declare no other conflicts of interest.

Multimedia Appendix 1
Behavior change technique assignment to each DrinksRation component.
[DOCX File , 30 KB - resprot_v12i1e51531_app1.docx]

Multimedia Appendix 2
Eligibility and consent questionnaire.
[DOCX File , 29 KB - resprot_v12i1e51531_app2.docx]

Multimedia Appendix 3
Questionnaire set.

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[DOCX File , 38 KB - resprot_v12i1e51531_app3.docx]

Multimedia Appendix 4
Drinks menu alcohol unit assignment.
[DOCX File , 28 KB - resprot_v12i1e51531_app4.docx]

Multimedia Appendix 5
Peer-review report by the Cabinet Office – Office for Veterans Affairs – UK Government.
[PDF File (Adobe PDF File), 287 KB - resprot_v12i1e51531_app5.pdf]

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Abbreviations

BCT: behavior change technique
CONSORT: Consolidated Standards of Reporting Trials
CONSORT-EHEALTH: Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth
NHS: National Health Service
PAB: patient advisory board
PMG: project management group
PTSD: posttraumatic stress disorder
PWA: progressive web application
RA: research assistant
RCT: randomized controlled trial
SAB: stakeholder advisory board
TIDieR: Template for Intervention Description and Replication
UKAF: United Kingdom Armed Forces

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Protocol

Relapse Prevention Therapy for Problem Gaming or Internet Gaming Disorder in Swedish Child and Youth Psychiatric Clinics: Protocol for a Randomized Controlled Trial

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Abstract

Background: Although gaming is a common arena where children socialize, an increasing number of children are exhibiting signs of problem gaming or internet gaming disorder. An important factor to the development of problem gaming is parent-child relationships. A cognitive behavioral therapy–based form of treatment, labeled relapse prevention, has been developed as a treatment for child and adolescent problem gaming or internet gaming disorder. However, no study has evaluated the effect of this treatment among Swedish children and youth nor the role of the parent-child relationships in this treatment.

Objective: This study aims (1) to evaluate a relapse prevention treatment for patients showing signs of problem gaming or internet gaming disorder recruited from child and youth psychiatric clinics and (2) to test whether the quality of parent-child relationships plays a role in the effect of relapse prevention treatment and vice versa—whether the relapse prevention treatment has a spillover effect on the quality of parent-child relationships. Moreover, we explore the carer's attitudes about parent-child relationships and child gaming, as well as experiences of the treatment among the children, their carers, and the clinicians who carried out the treatment.

Methods: This study is a 2-arm, parallel-group, early-stage randomized controlled trial with embedded qualitative components. Children aged 12-18 years who meet the criteria for problem gaming or internet gaming disorder will be randomized in a 1:1 ratio to either intervention (relapse prevention treatment) or control (treatment as usual), with a total of 160 (80 + 80) participants. The primary outcomes are measures of gaming and gambling behavior before and after intervention, and the secondary outcomes include child ratings of parent-child communication and family functioning. The study is supplemented with a qualitative component with semistructured interviews to capture participants' and clinicians' experiences of the relapse prevention, as well as attitudes about parent-child relationships and parenting needs in carers whose children completed the treatment.

Results: The trial started in January 2022 and is expected to end in December 2023. The first results are expected in March 2023.

Conclusions: This study will be the first randomized controlled trial evaluating relapse prevention as a treatment for child and adolescent problem gaming and internet gaming disorder in Sweden. Since problem behaviors in children interact with the family context, investigating parent-child relationships adjacent to the treatment of child problem gaming and internet gaming disorder is an important strength of the study. Further, different parties, ie, children, carers, and clinicians, will be directly or indirectly

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involved in the evaluation of the treatment, providing more knowledge of the treatment and its effect. Limitations include comorbidity in children with problem gaming and internet gaming disorder and challenges with the recruitment of participants.

Trial Registration: ClinicalTrials.gov NCT05506384 (retrospectively registered); https://clinicaltrials.gov/ct2/show/NCT05506384

International Registered Report Identifier (IRRID): DERR1-10.2196/44318

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KEYWORDS

problem gaming; internet gaming disorder; parent-child relationship; randomized controlled trial; relapse prevention; psychiatry; psychology; treatment

Introduction

Background

In 2013, internet gaming disorder, a syndrome of dysfunctional gaming behaviors that result in distress and affect personal, social, and educational functioning, was included in the appendix of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) [1] as a disorder that needed further research. Although the prevalence of internet gaming disorder is generally low, an increasing number of children who play digital games exhibit problematic gaming behaviors [2], which often result in dysfunctional social behaviors and mental health problems [3]. Delivering high-quality treatment for children with internet gaming disorder is key. This protocol describes a Swedish research project in which we will implement and evaluate an intervention labeled relapse prevention among children at Swedish child and youth psychiatry clinics.

Gaming, or playing offline or online digital games, has received a lot of attention from researchers and professionals in recent years. In Sweden, 68% of Swedish 13-16–year-old children and 55% of 17-18–year-old adolescents play computer games every day [4]. Gaming has become a common everyday arena where children and young people interact and socialize with others. Although some research suggests that gaming could be associated with more positive psychological outcomes, such as a stronger sense of belonging [5] and higher intelligence [6], other studies indicate that gaming can be linked to poor developmental outcomes such as physical and mental illness in adolescence [3]. Indeed, a small proportion of those who play digital games show a problematic development trajectory, similar to that of substance addiction, which is one of the reasons for including internet gaming disorder as an addiction diagnosis in the DSM-5 [1]. The diagnosis is phrased as "a persistent and recurrent use of the Internet to engage in games, often with other players, leading to clinically significant impairment or distress as indicated by five (or more) of the following criteria in a 12-month period: Preoccupation with gaming, withdrawal symptoms when gaming is taken away or not possible (sadness, anxiety, irritability), giving up other activities or continuing to game despite problems" [1]. Although the prevalence of problem gaming and internet gaming disorder in Swedish children and adolescents is to date unknown, a large European study with 12,938 children of 14-17 years of age reports that 5.1% exhibit problem gaming behaviors by fulfilling up to 4 criteria for internet gaming disorder, whereas 1.6% meet all the criteria for internet gaming disorder [7]. As many digital games are aimed at children, whose cognitive development means they are not always well equipped to deal with the instant gratification of most computer games [8], it is expected that problem gaming among children and adolescents will rise.

A development in the clinical management of the more well-established diagnosis of gambling addiction involving money [9,10] has brought attention to the possible association or co-occurrence of gambling, digital gambling, and problem gaming [11], not least given the development of in-game features such as loot boxes, ie, game-related purchases with a chance-based outcome. Moreover, earlier studies suggest that important correlates to child and adolescent problem gaming are male gender [12], neuropsychiatric disorder [13], difficulties with cognitive regulation [14], and substance use [15]. In addition, as parent-child relationships play an important role in child development [16], relationship features such as parent-child bonds and parent-child communication seem to be critical in terms of the development of problem gaming and internet gaming disorder [17]. Children with close parent-child bonds and open parent-child communication could more easily be offered and accept support from their parents, which subsequently could help them control their gaming behaviors. These factors need to be acknowledged both in routine practice as well as in the development of treatment for children and adolescents with problem gaming or internet gaming disorder.

To date, there is no gold standard treatment for children and adolescents with internet gaming disorder. Cognitive behavioral therapy (CBT) is, however, often identified as a first-line treatment for problem gaming, offering patients help with recognizing triggers and cues for gaming, and for understanding and controlling their gaming behaviors [18]. A CBT-based form of treatment, relapse prevention [19,20], has been developed as a treatment for child and adolescent problem gaming and internet gaming disorder. The relapse prevention program, which includes 3 to 8 sessions, has a motivational and relapse-prevention approach [19] where the therapist explores the target, ie, the problem behavior of the individual. Such program is traditionally used as a tertiary (or indicated) intervention strategy, meaning that such preventive effort is used to alleviate the impact of an ongoing problem and to prevent more complications. Relapse prevention treatment is often provided in outpatient clinics, for reducing the likelihood of relapsing into addiction and substance abuse. It is considered among the most effective preventive efforts for substance addiction [20] and works by teaching the individual to identify both internal and external cues to prevent future relapses in

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similar situations. We hypothesize that by targeting these mechanisms, the treatment could also be effective in treating children and adolescents with problem gaming and internet gaming disorder, because of the similarities of these behavioral addictions to substance addiction.

The effect of an intervention such as relapse prevention could, however, be dependent on the general quality of parent-child relationships and interactions between parents and their adolescent children, such that adolescents with strong family bonds and open parent-child communication would be likely to have more promising outcomes than adolescents with poor family bonds and communication. In that sense, the parent-child relationship could be an important moderator for the effectiveness of an intervention. In addition, given that adolescent development happens in interaction with their environment, such as family and more specifically parents [16], it is also possible that an intervention aimed at adolescents would also have a spillover effect on their environments where parent-child relationships are included. In that sense, not only would the individual benefit from such an effort, but the entire family would as well. Although such ideas seem compelling, they have not been tested in a context of gaming or relapse prevention.

Aim and Objectives

The aim of the study is twofold: (1) to evaluate a relapse prevention treatment for patients with problem gaming and internet gaming disorder recruited from child and youth psychiatry clinics across southern Sweden (Region Skåne) and (2) to test whether the quality of parent-child relationships plays a role for the effect of relapse prevention treatment and vice versa—whether the relapse prevention treatment has a spillover effect on the quality of parent-child relationships.

The specific objectives are to:

1. Undertake an internal pilot to assess the recruitment and feasibility of delivering the treatment in a child and youth psychiatric clinic.
2. Conduct a randomized control trial (RCT) to determine the effectiveness of relapse prevention on child and adolescent problem gaming and internet gaming disorder.
3. Examine the moderating role of the parent-child relationship, including parent-child bonds and communication on the effect of relapse prevention on child and adolescent problem gaming and internet gaming disorder.
4. Investigate the effect of completed relapse prevention treatment on parent-child relationships
5. Introduce a qualitative component to address:
    - The subjective experiences of relapse prevention treatment among children and adolescents who took part in the program and their view of problematic gaming
    - Perceived attitudes about parent-child relationships and parenting needs in carers whose children accomplished the relapse prevention treatment
    - The feasibility of the treatment among clinicians who delivered the program

Methods

Design

This study is a 2-arm, parallel-group, early-stage RCT with embedded qualitative components. The internal pilot will determine the recruitment and feasibility of the treatment. The recruitment start date is January 1, 2022, and the end date is December 30, 2022.

Recruitment and Eligibility

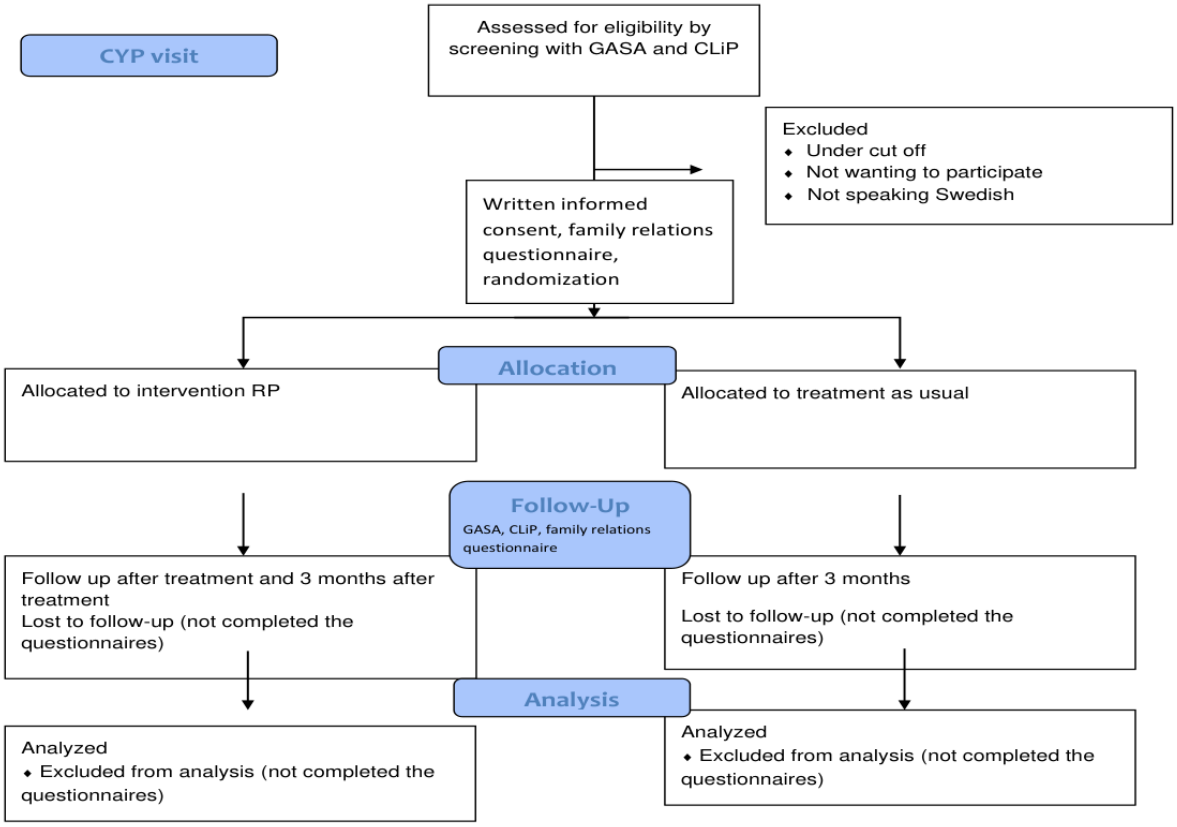
The trial and the recruitment will be carried out in several outpatient child and youth psychiatric clinics in Region Skåne in southern Sweden. As part of routine practice, all children (ages 12-18 years) coming for their first visit to 4 child and youth psychiatric units in Region Skåne will be screened for gaming or gambling behaviors. Children will be eligible to be included in the trial if they are aged 12-18 years and referred to outpatient child and youth psychiatric clinics in Region Skåne, meet criteria for problem gaming and internet gaming disorder, and have capacity to provide written informed consent. Children below the age of 15 years need to have their caregivers' consent. Children will be excluded if they do not speak Swedish. The clinicians who meet children during their first visit to the child and youth psychiatric unit will inform and invite the eligible children to participate in the study.

Randomization

Participants will be randomized in a 1:1 ratio to either intervention or control. The study will include a total of 160 participants, applying a random allocation sequence using the "chit method" by preparing 160 chits of paper indicating either control or treatment [21]. Each patient will be allocated to a condition (control or treatment), and the chit will not be replaced if the patient drops out of the study. The allocation to treatment and control arms may thus be uneven at certain times during the trial, but the end result of randomization will result in an equal distribution between control and treatment. It will not be possible to blind participants, clinicians, or supervising researchers to randomization allocation. The control group will receive "treatment as usual" at their home clinic. For an overview of recruitment and randomization, see the flow diagram in Figure 1.

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Figure 1. Flow diagram. CYP: Child and Youth Psychiatric Clinic; CLiP: Control, Lying, and Preoccupation; GASA; Game Addiction Scale for Adolescents; RP: relapse prevention.



Intervention

There is at this time a lack of consensus regarding treatment methods for problem gaming [22], in part due to a lack of clinical research [23]. However, together with 4 experienced psychologists in the field, we developed a manual drawing on previous knowledge in the field of addiction and the field of child and adolescent psychiatric treatment. Relapse prevention for alcohol and substance abuse was used as a theoretical underpinning [20] to develop a manual with 2 aspects in mind: adapting the blurbs and examples for children and adolescents—in part by including a fictionalized adolescent when demonstrating the theme of the particular session; and by structuring the sessions so that they could be easily adapted to fit the participant's primary problem behavior—gaming or gambling. Patients who meet the criteria for disordered gambling or gaming (according to tentative criteria from the DSM-5) will be offered the opportunity to participate in a relapse preventive treatment intervention at their local clinic or where applicable at an adjacent clinic. The treatment will be administered in an individual format and consist of 7 to 9 sessions of 45 minutes over a period of 7 to 9 weeks. The treatment will be offered to participants both in person and via video link to facilitate participation for children and adolescents living further away from the participating clinics.

The treatment consists of three parts: (1) setting goals, (2) understanding and identifying high-risk situations and problem behaviors, and (3) consolidating the new activity schedule and identifying future high-risk behaviors. The first part is focused on examining the patient's undesirable behavior, his/her motivation for change, and establishing goals with the treatment (this part primarily draws on motivational interviewing). This part of the treatment therefore varies between 1 to 3 sessions as participants may have different levels of motivation for changing their primary problem behavior, which is why some participants may require 1 or 2 extra sessions at the start of the treatment. The second part (drawing more from traditional CBT techniques) consists of exploring problematic situations using functional analysis; identifying high-risk situations and events, emotions, and cognitions that induce the problematic gaming behavior or result in a relapse; and managing game time with activity scheduling and practicing problem-solving skills. The final part consists of recognizing early warning signals that may indicate that the primary problem behavior is more likely to occur and consolidating the parts of the treatment that have been the most helpful in maintaining the new activity schedule.

Clinicians (psychiatrists and psychologists) with training in CBT will beforehand be educated in relapse prevention and will throughout the treatment be supervised by a clinician with vast experience of treating adults with gambling and gaming addictions.

Sample Size

Patients who have agreed to participate in the treatment study will be randomized in a 1: 1 ratio between intervention and control group. In our power calculation, we estimated that 40% in the intervention group and 20% in the control group will see improvement through the treatment offered in different groups, and after this treatment fall under the cutoff for problem gaming. With these figures, 160 (80 + 80) patients must be included in

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the treatment study for us to be able to demonstrate a significant difference with sufficient power. Given the large number of patients in pediatric and youth psychiatry in the region and the likely high incidence of problem behaviors in the population, we believe it is possible to reach this number of participants in the study.

Ethics Approval

The study was reviewed and approved by the Swedish Ethical Review Authority (Ref 2019-04797, December 13, 2019). Subsequent amendments have been approved (Ref 2021-05592-01, January 3, 2021; Ref 2022-01289-02, March 15, 2022).

Informed Consent

After eligibility is confirmed, written and verbal information about the study will be provided to all participants according to the Swedish Act concerning the Ethical Review of Research Involving Humans (SFS 2003:460). All patients, their carers, and clinicians who verbally agree to take part in the project will be provided with a consent form enabling them to provide written consent. For patients below the age of 15 years, a carer's written consent will be needed for their children to take part in the study. All participants will be informed that their partaking in the study is voluntary; their data would be handled with strict confidentiality; results will be reported on a group level, which means that individual participants will not be identifiable; and they are free to withdraw from the study at any time without reporting a reason for withdrawal. Please see Multimedia Appendix 1 for details. The trial intervention is similar to other clinical practices offered in child and youth psychiatric clinics, which is why we consider the risks with the trial as minimal.

Measures and Data Collection

Background information, including gender, age, housing situation, and diagnosis, as well as primary outcome measures assessing gaming and gambling problems, will be collected via the platform "Blå appen" ("Blue application" in Swedish). Blå appen is a digital platform developed by the child and youth outpatient department in Region Skåne, distributing and summarizing online self-rated questionnaires. It is used throughout Swedish child and youth psychiatry to facilitate the usage of self-rated questionnaires to patients. The secondary outcome measures, including parent-child communication and connectedness and family climate, will be administered in paper format after the child has provided consent to the study. Because the secondary outcomes measures assess general parent-child interactions, specific questions about gaming will also be added. The patients who consent to the RCT will rate their gaming and gambling activity as well as their parent-child relationships before and after the treatment. The "treatment at usual" arm will do the rating of gaming and gambling activity as well as their parent-child relationships at the inclusion and 3 months after the inclusion to the study. The following primary outcome measures will be used:

- The Game Addiction Scale for Adolescents [24] applies to gaming behavior during the previous 6 months based on 7 items. Each question covers one criterion in the DSM-5, answered on a 5-point Likert scale ranging from 1 (never) to 5 (very often) and should according to the developer be counted as endorsed when rated 3 or higher.
- The Diagnostic Screen for Gambling Problems–Control, Lying, and Preoccupation (NODS-CLiP) [25] is the shorter form of the NODS [26], which assesses gambling problems. NODS yield a score ranging from 0 to 10, corresponding to the DSM-4 criteria for gambling, where a score of 5 or more qualifies as pathological, a score of 3-4 corresponds to the subclinical syndrome of problem gambling, and scores of 1-2 corresponds to an "at-risk" status. NODS-CLiP comprises the 3 NODS items that best describe problem gambling, with 3 NODS questions pertaining to loss of Control, Lying, and Preoccupation—the "CLiP."

The following secondary, somewhat adapted, outcome measures will be used:

- Parent-child communication [27] includes six subscales: (1) parent knowledge of child activities (eg, "Do your parents know how much time you spend on gaming?"); (2) parent control (eg, "How often do your parents set rules about your gaming activities?"); (3) parent solicitousness (eg, "How often do your parents ask you about your gaming activities?"); (4) child disclosure (eg, "Do you tell your parents about your gaming activities?"); (5) child secrecy (eg, "Do you hide a lot from your parents in terms of your gaming activities?"); and (6) child feelings of being overly controlled (eg, "Do you think your parents want to know too much about your gaming activities?"). Items are rated on a 5-point Likert scale ranging from 1 (often) to 5 (never).
- Family climate [28] includes 2 subscales, family cohesion and conflict. Although family cohesion assesses the bonds between family members (eg, "In my family, we help and support each other"), family conflict assesses the conflicts between family members (eg, "In my family we often fight with each other"). Items are rated on a 4-point scale, ranging from 1 (not true at all) to 4 (very true).

Data Management

Personal and identifiable data will be collected from patients. Data will be kept confidential and managed in accordance with the Data Protection Act, General Data Protection Regulation policies and Swedish Act concerning the Ethical Review of Research Involving Humans (SFS 2003:460). Data will be held on services located within the Region Skåne databases, stored and secured both physically (in locked cabinets designed for the purpose) and electronically (behind firewalls), and be accessible to the study team only.

Statistical Analysis

Preliminary analyses will be conducted with regression analyses, paired sample *t* tests and ANOVAs. Analyses of pre- to postintervention change will be based on probability modeling using both unadjusted and adjusted models with 95% CIs. Appropriate interaction terms will be included to test subgroup differences in the models [29]. Analyses will be performed in Mplus [30].

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Qualitative Component

In addition to the RCT, the study will be supplemented with a qualitative component with semistructured individual interviews in order to capture participants' and clinicians' experiences of the treatment, as well as attitudes about parent-child relationships and parenting needs in carers whose children completed the relapse prevention treatment. Specifically, the interviews with the children will focus on the children's meaning-making of problem gaming, their experiences of the treatment, as well as their reflections on parent-child relationships before and after treatment. The interviews with the clinicians will focus on the clinicians' experiences of carrying out the treatment, as well as their understanding of problem gaming. Finally, the interviews with the carers will focus on carers' attitudes in terms of parent-child relationships before and after treatment of the child, as well as their reflections on potential parenting support needs in terms of their child's gaming.

All interviews will be conducted by staff with knowledge of qualitative interview methodology. Each interview template will be pilot-tested prior to data collection. The respondents will be offered participation through a physical or digital interview. After the collection phase, the generated data will be analyzed with the help of thematic analysis based on the recommendations by Braun and Clarke [31].

Dissemination

Findings from the study will be published in peer-reviewed journals and presented at local, national, and international conferences; workshops with key stakeholders; and interviews, pods, seminars, and lectures with general audiences. Results will also be reported to the funders.

The trial was retrospectively registered on ClinicalTrials.gov (NCT05506384; date of registration: April 13, 2022) due to administrative overload.

Results

The trial started in January 2022 and is expected to end in December 2023. The first results are expected in March 2023.

Discussion

Expected Findings

In this research project, we will evaluate relapse prevention as a treatment for children and youth (aged 12-18 years) showing signs of problem gaming and internet gaming disorder. In addition, we will also test the role of parent-child relationships for the effects of treatment and include a qualitative component involving interviews with children, carers, and clinicians in order to gain a deeper understanding of the treatment and its anticipated effects.

CBT-based forms of treatment, such as relapse prevention [19,20], typically used as a treatment for substance addiction [20], has been adapted to the treatment of child and youth problem gaming and internet gaming disorder. The goal of the treatment is to help the individual to identify both internal and external cues to prevent future relapses in similar situations. More specifically, the relapse prevention treatment is thought to help children to recognize triggers and cues for gaming, as well as to understand and control their gaming behaviors. Therefore, we hypothesize that by targeting these mechanisms, the treatment could be effective in treating children and adolescents with problem gaming and internet gaming disorder. As children are a part of a family system [16], it is likely that aspects of parent-child relationship, such as communication and emotional bonds, would have impact on child gaming behaviors [17]. Acknowledging parent-child relationships as being an important factor for child behavioral development, we hypothesize that the quality of parent-child relationships will play role for the effect of the treatment in a sense that the treatment will be more efficient for children reporting stronger parent-child bonds and communication. In addition, as children and parents interact in a dynamic manner [16], we also expect that the treatment will have spillover effect on parent-child relationships. We also have exploratory components to the projects. As previous research on user acceptability and satisfaction with relapse prevention as a treatment for problem gaming and internet gaming disorder is lacking, we explore how children and their carers, as well as clinicians who carried out the treatment, experience relapse prevention as a treatment for problem gaming and internet gaming disorder among children and youth. In addition, we also explore carers' attitudes in terms of parent-child relationships before and after treatment of the child, as well as their reflections on potential parenting support needs in terms of their child's gaming.

Limitations and Strengths

There are however some limitations to the study. The trial is not blinded, which may have an impact on both the patients' behavior as well as clinicians' practices. On the other hand, blinding does not necessarily ensure internal or external validity of the results [32], which is why we consider this limitation minor. As neuropsychiatric disorder is one of the major risk factors in problem gaming and internet gaming disorder [13], we expect that many of the patients included in the trial with be diagnosed with a neuropsychiatric disorder. This could be a potential limitation of the trial as the effect of the treatment may be affected by comorbidity in children with problem gaming or internet gaming disorder. Another possible limitation is the difficulty with recruiting patients as well as the potential dropout. Many children who game may not be aware of the problems that their gaming is imposing on their everyday lives, which is why they may not be likely to seek help or accept the given support. In addition, they may not be motivated to be engaged in the treatment. Therefore, we offer motivational sessions in the beginning of the treatment. Despite these limitations, there are several strengths to be noted. To our knowledge, this is the first RCT study testing the effect of relapse prevention on child and adolescent problem gaming and internet gaming disorder. As an increasing number of children engage in gaming [4,24], for some children, this activity may include significant problems [6,22] that would need attention from the clinics. Evaluating the efforts made by the clinics may provide more knowledge of the treatment of problem gaming in children. As problem behaviors in children interact with the

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family context, investigating parent-child relationships adjacent to the treatment of child problem gaming or internet gaming disorder is another important strength of the study. Further, this study includes a qualitative component involving different parties directly or indirectly involved in the treatment, ie, children, carers, and clinicians. Interviews with children, carers, and clinicians may help gaining knowledge of how the treatment is perceived by the individual who is directly involved in the treatment, the adults who take part in the child's life on a daily basis, as well as the clinicians who are important stakeholders of the treatment.

Conclusion

To conclude, in this project, we will evaluate relapse prevention as a treatment for children and youth (aged 12-18 years) showing signs of problem gaming and internet gaming disorder. The treatment will be evaluated in an RCT. The measures will include gaming frequency and gaming experiences, as well as perceived parent-child relationships and parent-child communication in order to understand the possible of role of parent-child relationship for the effect of the treatment. In addition, the study will also include a qualitative component involving interviews with children, carers, and clinicians in order to gain a deeper understanding of the treatment and its anticipated effects, as well as the parenting support needs the carers express. The results of the project will inform the development of practices in child and youth psychiatric clinics, putting focus on both children and their carers as important stakeholders in the practices.

Acknowledgments

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Data Availability

The data sets generated and/or analyzed during the current study are not publicly available because this study's ethical review does not allow for study data to be in a public repository. Requests to access the datasets should be addressed to ECK or SK.

Authors' Contributions

ECK, SK, SG, FA, and AH designed the trial and, together with IE and MW, contributed to the qualitative component, recruitment, and data collection. SK drafted the protocol. All authors read and approved the final manuscript. All authors have agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflicts of Interest

None declared.

Editorial Notice

This randomized study was only retrospectively registered, due to administrative overload. The editor granted an exception from ICMJE rules mandating prospective registration of randomized trials because the risk of bias appears low and the study was considered formative, guiding the development of the application. However, readers are advised to carefully assess the validity of any potential explicit or implicit claims related to primary outcomes or effectiveness, as retrospective registration does not prevent authors from changing their outcome measures retrospectively.

Multimedia Appendix 1
Information letters and consent forms.
[PDF File (Adobe PDF File), 541 KB - resprot_v12i1e44318_app1.pdf]

Multimedia Appendix 2
Peer review report by Swedish Research Council for Health, Working Life and Welfare / Forskningsrådet för hälsa, arbetsliv och välfärd - FORTE (Stockholm, Sweden).
[PDF File (Adobe PDF File), 413 KB - resprot_v12i1e44318_app2.pdf]

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Abbreviations

CBT: cognitive behavioral therapy
DSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
NODS-CLiP: The Diagnostic Screen for Gambling Problems–Control, Lying, and Preoccupation
RCT: randomized controlled trial

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Protocol

Effects of Aerobic Exercise on Cardiorespiratory Fitness, Cardiovascular Risk Factors, and Patient-Reported Outcomes in Long-Term Breast Cancer Survivors: Protocol for a Randomized Controlled Trial

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Related Article:

This is a corrected version. See correction statement: https://www.researchprotocols.org/2023/1/e54462/

Abstract

Background: Anthracycline-based chemotherapy has been mainstay of adjuvant breast cancer therapy for decades. Although effective, anthracyclines place long-term breast cancer survivors at risk of late effects, such as reduced cardiorespiratory fitness and increased risk of cardiovascular disease. Previous research has shown beneficial effects of exercise training on cardiorespiratory fitness, but the effects of exercise on limiting factors for cardiorespiratory fitness, cardiovascular risk factors, and patient-reported outcomes in long-term survivors are less clear. Whether previous exposure to breast cancer therapy modulates the effects of exercise is also unknown.

Objective: The primary aim of the CAUSE (Cardiovascular Survivors Exercise) trial is to examine the effect of aerobic exercise on cardiorespiratory fitness in anthracycline-treated long-term breast cancer survivors. Secondary aims are to examine effects of exercise training on limiting factors for cardiorespiratory fitness, cardiovascular risk factors, and patient-reported outcomes, and to compare baseline values and effects of exercise training between similar-aged women with and those without prior breast cancer. A third aim is to examine the 24-month postintervention effects of aerobic exercise on primary and secondary outcomes.

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Methods: The CAUSE trial is a 2-armed randomized controlled trial, where 140 long-term breast cancer survivors, 8-12 years post diagnosis, are assigned to a 5-month nonlinear aerobic exercise program with 3 weekly sessions or to standard care. Seventy similar-aged women with no history of cancer will undergo the same exercise program. Cardiorespiratory fitness measured as peak oxygen consumption (VO_{2peak}), limiting factors for VO_{2peak} (eg, cardiac function, pulmonary function, hemoglobin mass, blood volume, and skeletal muscle characteristics), cardiovascular risk factors (eg, hypertension, diabetes, dyslipidemia, obesity, physical activity level, and smoking status), and patient-reported outcomes (eg, body image, fatigue, mental health, and health-related quality of life) will be assessed at baseline, post intervention, and 24 months post intervention.

Results: A total of 209 patients were included from October 2020 to August 2022, and postintervention assessments were completed in January 2023. The 24-month follow-up will be completed in February 2025.

Conclusions: The findings from the CAUSE trial will provide novel scientific understanding of the potential benefits of exercise training in long-term breast cancer survivors.

Trial Registration: ClinicalTrials.gov NCT04307407; https://clinicaltrials.gov/ct2/show/NCT04307407

International Registered Report Identifier (IRRID): DERR1-10.2196/45244

(JMIR Res Protoc 2023;12:e45244) doi:10.2196/45244

KEYWORDS

breast cancer; cardiooncology; cardiorespiratory fitness; exercise medicine

Introduction

Background

Due to advances in diagnostics and treatment, the 5-year survival rate for early breast cancer has surpassed 90% in the Western world, and the number of breast cancer survivors (BCSs) is steadily increasing. Long-term BCS (ie, living beyond 5 years after diagnosis) are at increased risk of several late effects, such as increased risk of cardiovascular disease (CVD) and incidence cardiovascular (CV) risk factors (eg, obesity, hypertension, and dyslipidemia) [1,2].

Cardiotoxicity is a well-recognized adverse effect of anthracycline therapy, which has been a key component of breast cancer therapy for decades. Anthracycline treatment can induce myocardial damage [3,4] and lead to irreversible left ventricular dysfunction and heart failure [5]. Although the incidence of manifested anthracycline-induced cardiotoxicity after breast cancer treatment is approximately 2%-5% [6,7], the incidence of subclinical left ventricular dysfunction may be significantly higher [8].

Previous studies have demonstrated impaired cardiorespiratory fitness (CRF) in BCSs [9,10]. CRF is an integrative measure of global cardiopulmonary and skeletal muscle function assessed as peak oxygen consumption (VO_{2peak}). Reduced CRF is not only an expression of impaired physical functional capacity but is also associated with a greater risk of CVD [11,12]. Cardiac output, pulmonary function, blood oxygen carrying capacity, and peripheral arteriovenous oxygen extraction capacity are physiological determinants of CRF, also termed as limiting factors for CRF. Given the systemic effect of chemotherapy, anthracycline-induced late effects may not be limited to cardiotoxicity, but likely affects the entire cardiopulmonary-muscle axis [13]. In line with this perspective, studies have reported reduced microvessel density, impaired mitochondrial function, and reduced skeletal muscle cell size during anthracycline treatment of breast cancer [14]. To our knowledge, no study has investigated if such adverse effects are present in long-term BCS.

BCS may also face psychosocial late effects, including body image concerns, increased levels of mental distress [15], and chronic fatigue [16,17], potentially negatively affecting their work life and reducing their health-related quality of life (HRQoL) [18,19].

Aerobic exercise has shown to improve CRF in cancer survivors [20], but knowledge on the effects of aerobic exercise on limiting factors for CRF is sparse. To the best of our knowledge, there are no existing data on the effects of exercise training on cardiac morphology and function after anthracycline exposure in long-term cancer survivors.

In nononcological settings, higher levels of physical activity are associated with a dramatic reduction in CVD risk [21]. Studies evaluating such effects among cancer survivors are limited [22]. Adams et al [23] reported improved vascular function and CRF and lower low-density lipoprotein and high-sensitivity C-reactive protein after 12 weeks of supervised high intensity aerobic exercise in survivors of testicular cancer, and similar data on BCS are missing. Finally, exercise training has also been shown to improve mental distress and fatigue [24], and improve HRQoL [25,26] in patients with cancer, but research has mainly been conducted during or shortly after treatment.

Aims and Hypothesis

The primary aim of this study is to examine the effect of aerobic exercise on CRF in anthracycline-treated long-term BCS compared to standard care. Secondary aims are to examine the effects of exercise training on limiting factors for CRF, CV risk factors, and health-related patient-reported outcomes (PROMs) compared to standard care, and to compare baseline values and effects of exercise training between BCS and similar-aged women without prior cancer. Tertiary aims are to investigate long-term effects of the intervention on CRF, CV risk factors, and health-related outcomes 24 months post intervention. We hypothesize that aerobic exercise will improve CRF.

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Methods

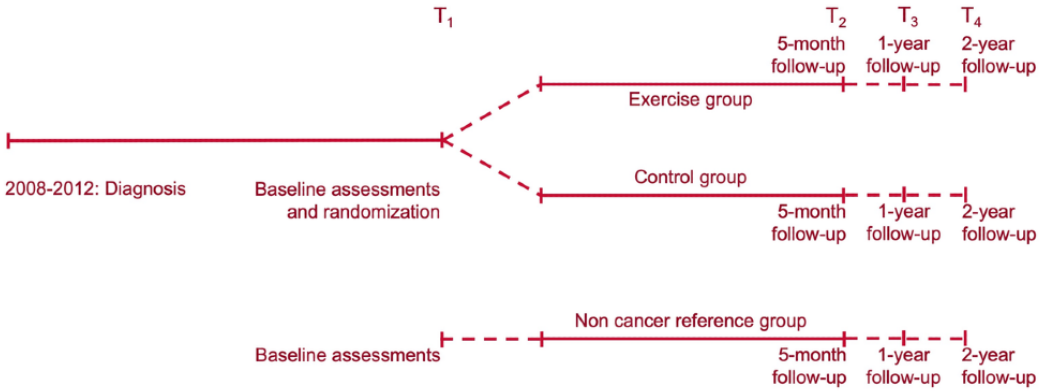
Ethics Approval

The CAUSE (Cardiovascular Survivors Exercise) trial is conducted according to the Helsinki Declaration, and all study participants will sign informed consent before any study-related procedures. The study is approved by the Regional Committees for Medical and Health Research Ethics (2019/1318) and is preregistered on clinicaltrials.gov (NCT04307407).

Design

The CAUSE trial is a 2-armed, phase II randomized controlled trial that compares aerobic exercise (exercise group) to standard care (control group) in BCS. A third group comprising similar-aged women with no previous cancer diagnosis is also included (noncancer reference group). The exercise group and the noncancer reference group undergoes the same aerobic exercise program. The overall study design is outlined in Figure 1.

Figure 1. Study outline. Participants in the exercise group, control group, and noncancer reference group undergoes assessments at baseline (T1), after 5 months (post intervention) (T2), and 1 and 2 years post intervention (T3 and T4).



Participants

BCS Group

BCS are invited to participate if diagnosed with human epidermal growth factor receptor 2–negative breast cancer stage I-III between 2008 and 2012 (ie, 8-14 years after diagnosis), aged 60 years or younger at the time of diagnosis, and received the anthracycline epirubicin as part of their adjuvant therapy. All eligibility criteria are listed in Textbox 1.

Textbox 1. Eligibility criteria for breast cancer survivors in the CAUSE (Cardiovascular Survivors Exercise) trial.

Inclusion criteria:

- Adjuvant treatment with epirubicin
- Breast cancer diagnosis between 2008 and 2012
- Exercises ≤90 minutes per week
- Physicians' approval of participation

Exclusion criteria:

- Stage IV breast cancer at diagnosis
- Treatment with trastuzumab
- Recurrence of breast cancer
- Presence of other malignancies (except for basal cell carcinomas)
- Former major cardiac surgery
- Presence of a pacemaker
- Chronic atrial fibrillation
- Recent or uncontrolled cardiovascular disease
- Any physical or mental condition restricting adherence to study procedures (by self-evaluation)

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Noncancer Reference Group

Participants in the noncancer reference group are women without a history of cancer who otherwise meet the eligibility criteria listed in Textbox 1.

Recruitment

Women who were diagnosed with breast cancer stage I-III between 2008 and 2012, and live within reasonable distance from Oslo, are identified from the Cancer Registry of Norway. An invitation with study information is sent by mail to all candidates. Thereafter, the study personnel contact the candidates by phone to screen for eligibility and provide additional information. Candidates who meet the eligibility criteria and are willing to participate are then invited to baseline assessments.

Participants for the noncancer reference group are recruited in 2 steps. First, BCS randomized to the exercise group are encouraged to invite a similar-aged friend or relative to participate in the noncancer reference group. The remaining participants in the noncancer reference group are recruited through advertisements in news media and through appropriate social media channels. Interested candidates who meet the eligibility criteria are included.

Randomization

BCS are block randomized with a 1:1 allocation ratio to the exercise group or to the control group. Due to the strict eligibility criteria, no additional stratification factors are included. A random sequence of study IDs was made by a random number generator prior to inclusion of the first participant. The allocation sequence is concealed from the study personnel involved in baseline assessment until the baseline assessments are completed.

Assessments

Overview

Study outcomes, assessment methods, and assessment times are summarized in Table 1 and described in detail below. Primary outcome is CRF assessed by VO_{2peak}. Secondary outcomes are limiting factors for VO_{2peak}, CV risk factors, and PROMs. To evaluate long-term effects of the intervention, primary and secondary outcomes are assessed at 24 months (T_4) postintervention. Some PROMs are also assessed at 12 months (T_3) postintervention.

All participants are screened by a cardiologist before the assessments. Presence of possible contraindications to exercise training will be evaluated according to the guidelines from the American College of Sports Medicine. [27].

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Table 1. Outcomes, assessments, and time point of assessments in the CAUSE (Cardiovascular Survivors Exercise) trial.

Domain and outcomes	Assessment method	Time point of assessment
Primary outcome: cardiorespiratory fitness		
Peak oxygen consumption	Treadmill cardiopulmonary exercise test	T_1, T_2, T_4
Secondary outcomes		
Limiting factors for cardiorespiratory fitness		
Cardiac function		
Cardiac dimensions	Echocardiography	T_1, T_2, T_4
LV[a] and RV[b] systolic function	Echocardiography	T_1, T_2, T_4
LV diastolic function	Echocardiography	T_1, T_2, T_4
NT-proBNP[c]	Blood sample	T_1, T_2, T_4
Blood oxygen transport capacity		
Hemoglobin mass	Carbon monoxide rebreathing method	T_1, T_2, T_4
Hemoglobin concentration and blood volume	Venous blood sample and carbon monoxide rebreathing method	T_1, T_2, T_4
Skeletal muscle characteristics		
Fiber size	Immunohistochemistry	T_1, T_2, T_4
Fiber composition	Immunohistochemistry	T_1, T_2, T_4
Capillaries per fiber	Immunohistochemistry	T_1, T_2, T_4
Mitochondrial proteins	Western blotting	T_1, T_2, T_4
Proteins involved in β-oxidation	Western blotting	T_1, T_2, T_4
Gene expression	Methylome wide arrays	T_1, T_2, T_4
Pulmonary function		
Forced vital capacity	Spirometry	T_1, T_2, T_4
Forced expiratory volume in 1 second	Spirometry	T_1, T_2, T_4
Ventilatory capacity	Estimated from FEV_1[d] x 40 or MVV[e]	T_1, T_2, T_4
DLco[f] for carbon monoxide	DLco test	T_1, T_2, T_4
DLco/alveolar volume	DLco test	T_1, T_2, T_4
Total Lung Capacity-$_{SB}$	DLco test	T_1, T_2, T_4
Cardiovascular risk factors		
Hypertension		
Blood pressure	Electronic sphygmomanometer	T_1, T_2, T_4
Metabolic dysfunction		
Fasted glucose, HbA_{1c}[g], insulin	Blood sample	T_1, T_2, T_4
Lipids	Blood sample	T_1, T_2, T_4
High-sensitivity C-reactive protein	Blood sample	T_1, T_2, T_4
Obesity		
BMI	Scale and stadiometer	T_1, T_2, T_4
Lean body mass	Dual x-ray absorptiometry	T_1, T_2, T_4
Fat body mass	Dual x-ray absorptiometry	T_1, T_2, T_4

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Domain and outcomes	Assessment method	Time point of assessment
Unhealthy lifestyle		
Level of physical activity	ActiGraph GT3X+	T_1, T_2, T_4
Smoking status	HUNT-4[h]	T_1, T_2, T_4
Patient-reported outcomes		
Lifestyle		
Physical activity and Exercise training	HUNT-4 and GLTEQ[i] [28]	T_1, T_2, T_4
Diet	HUNT-4	T_1, T_2, T_3, T_4
Sleep habits	Modified HUNT-4	T_1, T_2, T_4[j]
Work aspects	WAI[k]	T_1, T_2, T_4
Health, QoL[l] and late effects		
Comorbidity	Modified HUNT-4	T_1, T_2, T_4
HRQoL[m]	EORTC[n] QLQ[o]-C30 [29]	T_1, T_2, T_4
QoL and Vitality	SWLS[p] [30] SVS[q] [31]	T_1, T_2, T_4
Breast cancer–specific symptoms and complaints[r]	EORTC QLQ-BR23 [32]	T_1, T_2, T_4
Neuropathy	SCIN[s] [33]	T_1, T_2, T_4
Fatigue	Chalder FQ[t] [34]	T_1, T_2, T_4
Anxiety Depression symptoms	GAD[u]7 [35] PHQ[v]9 [36]	T_1, T_2, T_4
Fear of recurrence	ASC[w] [37]	T_1, T_2, T_3, T_4
Training motivation and mastery		
Training motivation	BREQ[x] 2 [38]	T_1, T_2, T_4[j]
Exercise competence	PCS[y] [39]	T_1, T_2, T_4

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Domain and outcomes	Assessment method	Time point of assessment
Training need satisfaction[z]	BPNES[aa] [40]	T_1, T_2, T_4[j]

[a]LV: left ventricular.
[b]RV: right ventricular.
[c]NT-proBNP: N-terminal fragment of brain natriuretic peptide.
[d]FEV_1: forced expiratory volume in 1 second.
[e]MVV: maximal voluntary ventilation.
[f]DLco: diffusion capacity of the lung for carbon monoxide.
[g]HbA_{1c}: glycated hemoglobin.
[h]HUNT-4: The Trøndelag Health.
[i]GLTEQ: Godin leisure time exercise questionnaire.
[j]4 and 12 weeks post T_1.
[k]WAI: Work Ability Index.
[l]QoL: quality of life.
[m]HRQoL: health-related quality of life.
[n]EORTC: European Organization for Research and Treatment of Cancer.
[o]QLQ: quality of life questionnaire.
[p]SWLS: satisfaction with life scale.
[q]SVS: subjective vitality scale.
[r]Body image, sexuality, lymphoedema, and pain.
[s]SCIN: scale for chemotherapy-induced long-term neurotoxicity.
[t]FQ: fatigue questionnaire.
[u]GAD: generalized anxiety disorder.
[v]PHQ: patient health questionnaire.
[w]ASC: assessment of survivors concerns.
[x]BREQ-2: Behavioral Regulation in Exercise Questionnaire-2.
[y]PCS: perceived competence scale.
[z]Exercise groups only.
[aa]BPNES: Basic Need Satisfaction in Exercise Scale.

Primary Outcome

CRF

VO_{2peak} is assessed by an incremental treadmill cardiopulmonary exercise test (CPET) using a modified Balke protocol (RL2700E, Rodby) [41]. The participants are briefly familiarized to treadmill walking prior to the test. The test is continued until voluntary exhaustion despite encouragement by the test leaders. Continuous expired gases are measured breath-by-breath using a gas and volume calibrated metabolic chart (Oxycon Pro, Jaeger GmbH). The highest volume of oxygen consumed across a 30-second period is registered as VO_{2peak}. All exercise tests will be supervised by an exercise physiologist and observed by a cardiologist, following standard clinical guidelines [42].

Secondary Outcomes

Limiting Factors for CRF

The following limiting factors for CRF were will be considered:

- Cardiac function: cardiac morphology and function will be assessed by resting transthoracic echocardiography using Vivid E9 (GE Vingmed). Standard 2D parasternal and apical views are acquired in the end-expiratory phase with participants in the supine left lateral position. Apical 3D recordings will be obtained by stitching together minimum 4 consecutive heart cycles. In addition, left ventricular outflow tract velocity time integral will be obtained immediately after the CPET to estimate maximal stroke volume and cardiac output. Images will be subsequently analyzed offline on EchoPac version 202 (GE Vingmed). Echocardiographic outcomes (listed in Table 1) are measured as recommended by American Society of Echocardiography and European Society of Cardiology [43]. Left ventricular myocardial work will be estimated by a noninvasive method using pressure-strain loop analysis [44].
- Pulmonary function: ventilatory function will be assessed by maximal expiratory flow volume loops (MasterScreen Pneumo Jäger) [45]. The best forced expiratory volume in 1 second and forced vital capacity after 3 acceptable trials will be recorded. Ventilatory capacity, for calculation of breathing reserve during CPET, will be measured by a Maximum Voluntary Ventilation test while breathing as hard and fast as possible for 10 seconds in standing position. Best of 2 maximal attempts will be recorded. The diffusion capacity of the lung for carbon monoxide (DLco) will be measured using the single-breath method, adjusted for serum hemoglobin levels. The average of 2 satisfying

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attempts will be evaluated for DLco, DLco/alveolar volume (carbon monoxide transfer coefficient), and total lung capacity. All measurements are in accordance with guidelines from The European Respiratory Society/American Thoracic Society [45,46]. The Global Lung Function Initiative reference equations are used, and the outcomes are expressed as absolute values, percent predicted, and *z* scores [47-49].

- Blood oxygen transport capacity: hemoglobin mass will be measured using a carbon monoxide (CO) rebreathing method [50]. First, the participant will be seated for 10 minutes, before capillary blood sampling in two 125-µL preheparinized tubes (Clinitubes; Radiometer). Thereafter, the participant will inhale a bolus of 1 mL/kg body weight of chemically pure CO (AGA Norge) administered via a spirometer (Blood tec GmbH). In a closed circuit, the CO will be rebreathed for 2 minutes together with 3 L of pure oxygen (AGA Norge). Two capillary fingertip blood samples will be collected, 6 and 8 minutes following the administration of CO. All blood samples will be immediately analyzed in duplicate for percent carboxyhemoglobin (ABL80 CO-OX FLEX, Radiometer). Hemoglobin mass will be calculated by dilution of CO in blood with correction for loss of CO to myoglobin (0.3% of the administered CO per minute). Blood volume, plasma volume, and red cell volume will be calculated from hemoglobin mass using venous hemoglobin and venous hematocrit.
- Skeletal muscle characteristics: muscle biopsies will be obtained from vastus lateralis muscle by the Bergström Needle-biopsy technique according to standard procedures established in our laboratory [51]. Muscle fiber size and composition and capillary density will be assessed via immunohistochemistry. The content of mitochondrial proteins and proteins involved in β-oxidation is assessed by western blotting [51]. A subgroup of the muscle biopsies will be processed for RNA and DNA extraction. Methylome wide arrays (eg, 850,000 CpG sites, Infinium Methylation EPIC BeadChip arrays, Illumina, or genome-wide bisulfite sequencing) and transcriptome technology (eg, U133 plus 2.0 array or Claricom S HT Human Array or RNA sequencing) will be applied to assess the expression of epigenetically regulated genes.

CV Risk Factors

Resting blood pressure will be measured by an electronic sphygmomanometer (Welch Allyn ProBP 2400) in supine position after echocardiography. Biomarkers listed in Table 1 will be analyzed in accordance with established procedures at Fürst Laboratories from blood samples obtained in a fasted state. Height and weight will be measured by the same scale and stadiometer at all time points (SECA 213). Absolute and relative content of fat mass and lean body mass will be assessed by whole-body dual x-ray absorptiometry (Lunar iDXA, GE Healthcare) in a fasted state. Daily level of physical activity will be measured by accelerometers, using ActiGraph model GT3X+ (ActiGraph LLC). Participants will be instructed to wear accelerometers on the right hip for 7 consecutive days after completion of baseline assessments and during the last week of the intervention period. Smoking status will be recorded.

Patient-Reported Outcomes

An overview of the PROMs is presented in Table 1. Sociodemographic variables including marital status, number of children living at home, and education level will be recorded using the same or modified questions from the HUNT-4 (The Trøndelag Health) study [52]. Lifestyle variables include physical activity and exercise measured by questions from HUNT-4 study and Godin Leisure Time Exercise Questionnaire [28], and information on diet, tobacco, alcohol, and sleep habits will be measured by the same or modified questions from the HUNT-4 study. Work aspects will be measured as in the HUNT-4 study and by the Work Ability Index (Finnish Institute of Occupational Health. Work Ability Index, 2006). Information on comorbidities, HRQoL, and general and breast cancer–specific late effects will be measured using a modified version of that used in the HUNT-4 study, the European Organization for Research and Treatment of Cancer Quality of Life Questionnaires (EORTC QLQ C-30 and EORTC QLQ BR-28), including the breast cancer module [29], and the Satisfaction With Life Scale [30,32]. Neuropathy will be assessed by the scale for chemotherapy-induced long-term neurotoxicity [33], fatigue by the Chalder Fatigue Questionnaire [34], vitality by the Subjective Vitality Scale [31], anxiety by Generalized Anxiety Disorder 7 items [35], and depressive symptoms by a modified version of the Patient Health Questionnaire-9 [36]. Fear of recurrence is measured by Assessment of Survivors Concerns questionnaire [37].

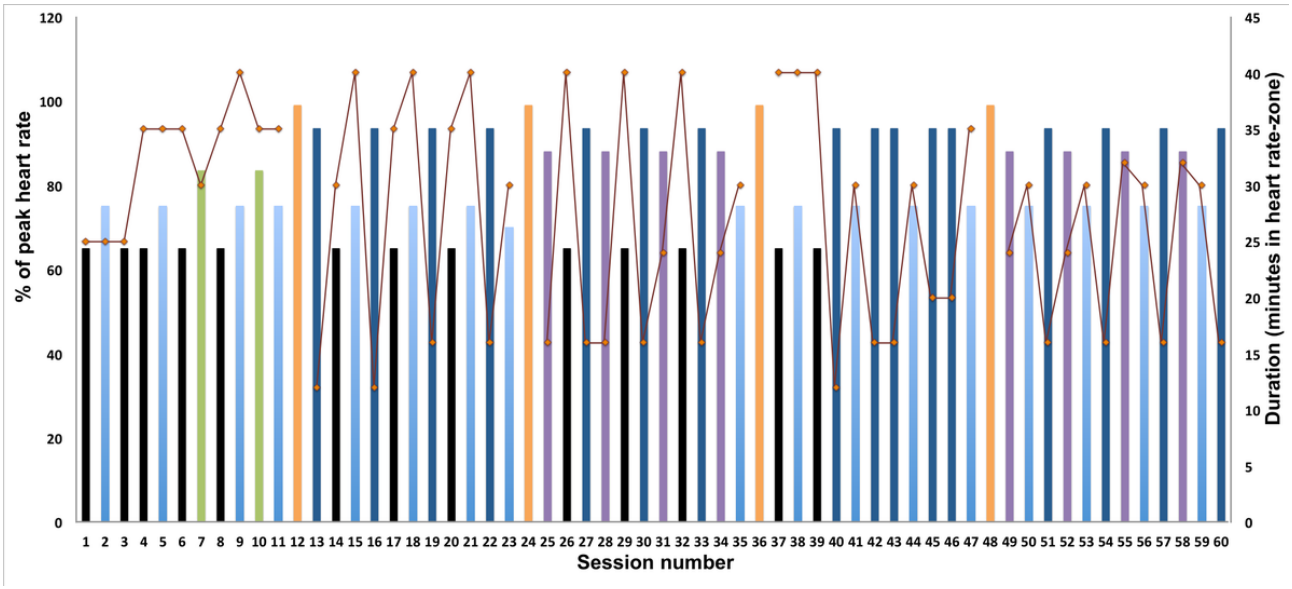
Motivation for exercise will be measured by the Behavioral Regulation in Exercise Questionnaire-2 [38] and sense of exercise mastery by Perceived Competence Scale [39]. In the exercise group only, experience with the instructor and exercise program will be measured by the short version of the Health Care Climate Questionnaire [53] and Basic Need Satisfaction in Exercise Scale [40].

Intervention

The intervention duration is 5 months. Participants in the exercise group perform 3 weekly aerobic exercise sessions aimed at increasing CRF. The exercise plan includes both continuous sessions, with low to moderate exercise intensities, as well as interval sessions performed at higher intensities. The intensity and duration of each individual session and sequencing of the different sessions are outlined in Figure 2. Importantly, the sessions will be scheduled so that the weekly amount of exercise is progressively increased across the intervention period, both in intensity and duration [54]. The preferred exercise modality is inclined treadmill walking or running. The exercise prescription is individually tailored to each participant based on their CPET result.

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Figure 2. Exercise prescription outline. Bars represents the exercise intensity (% of peak heart rate) at a given exercise session, and the dotted line represents the duration (minutes) at the prescribed exercise intensity in a given session.



In Figure 2, the intensity of each session is depicted by the colored bars as a percentage of the mean peak heart rate (HR_{peak}) for the session. "Black sessions" are performed at 65% of HR_{peak} for 25-40 minutes (n=13), "light blue sessions" are performed at 75% of HR_{peak} for 30 minutes (n=17), and "green sessions" are performed at 83.5% of HR_{peak} for 30 minutes (n=2). "Dark blue sessions" are performed as three to five 4-minute intervals at 93.5% of HR_{peak} with 3 minutes active rest (brisk walking) between intervals (n=16), and "purple sessions" are performed as two to four 8-minute intervals at 88% of HR_{peak} with 4 minutes active rest (brisk walking) between intervals (n=8). Orange bars represent sessions where the CPET exercise protocol is repeated and are conducted every fourth week (n=4). The treadmill speed and grade at voluntary exhaustion at the CPET protocol sessions will be recorded and used to monitor and report training progression throughout the intervention.

All exercise sessions will be supervised by an instructor at the participant's local gym. The instructors make sure that the planned exercise sessions are performed and adjust the sessions if necessary. They will also register any deviation from the exercise prescription and report the reason for any adjustment following metrics suggested by Nilsen et al [55]. Adverse events will be reported to the study staff. To increase exercise adherence and educate the instructors, the instructors will be encouraged to undergo a series of web-based seminars. They will be introduced to the rationale for the study, behavior change principles, and how to identify facilitators and barriers to exercise.

BCS randomized to the control group will be encouraged to maintain their current activity level at the time of randomization.

Statistical Analysis

The sample size calculation was based on the primary outcome VO_{2peak}, using a mean change of 3.6 (SD 7.2) mL/kg/minute, from a comparable intervention by Adams et al [23]. With a significance level of 5% and a power of 90% (to compensate for using published results from a single study in our sample size calculation), 63 BCS are needed in each group. To allow for a dropout rate of 7 participants (10%), a total of 70 BCS are included in each group. The same number of participants are included in the reference group. The primary and secondary outcomes are analyzed by generalized linear mixed models. Baseline outcomes in women with and without previous cancer are compared by a 2-sample *t* test.

Results

The inclusion started in October 2020 and was completed in August 2022. A total of 209 participants were included and postintervention assessments (T_2) were completed in January 2023. The 24-month follow-up (T_4) will be completed in February 2025.

Discussion

Exercise training has previously been shown to improve CRF [20], but there is a paucity of studies investigating the effects of exercise training on other CVD risk factors following cancer treatment [22]. The CAUSE-trial will provide a novel understanding of the potential of exercise training to improve CRF, CV risk profile, and self-reported health-related outcomes in long-term BCS. Since impaired CRF has been reported in cancer survivors [9,10], it is pivotal to understand how previous exposure to cancer treatment modulates the effects of exercise. We hypothesize that previous exposure to cancer treatment, even 10 years ago, would have an impact on the expected results from exercise training. This study will expand on the current literature by thoroughly evaluating exercise effects across the entire cardiopulmonary-muscle axis, and by including an exercise group without a history of cancer. This allows us to directly compare baseline levels and intervention effects between women previously exposed to cancer therapy and unexposed women, and to identify potential bottlenecks to physiological adaptation to exercise training.

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As with CRF, the positive effects of exercise training on several PROMs have been reported previously, but the existing literature is mainly limited to effects of exercise training during or shortly after cancer treatment. This is concerning, since approximately 30% of BCS still report chronic fatigue up to 10 years after completing treatment. Results from exercise training performed during or immediately after cancer treatment cannot necessarily be extrapolated to long-term survivors as the mechanisms behind chronic fatigue might differ from the more acute complaints. Although positive effects of exercise training on quality of life already have been demonstrated, less is known about the impact of exercise on other late effects in long-term BCS, such as mental distress, disturbed body image, pain, and sexual health challenges.

One of the major strengths of this study is the solid multidisciplinary constellation of the research group. Our group includes sports physiologists, cardiologists, oncologists, and behavioral scientists. This is also reflected by the list of study outcomes (Table 1) ranging from cardiopulmonary function to skeletal muscle cell function and morphology, and quality of life. Combined with a well-monitored, individually tailored exercise intervention, inclusion of a noncancer reference group, large study cohorts, and longtime follow-up, this will allow for exploring interactions across disciplines.

Our study design has some potential limitations. As with any lifestyle intervention study, we risk recruiting the most motivated and physically active participants, which may compromise the external validity of our results. We aim to reduce this risk of selection bias by recruiting BCS through the Cancer Registry of Norway rather than through media advertisements. Importantly, we use similar exclusion criteria for physical activity levels between cancer survivors and the reference groups, which enable us to identify any modifying effects of previous cancer treatment. Unfortunately, this study lacks completely blinded assessors. As an effort to reduce the influence of known group allocation, assessors will not know the baseline values of participants prior to the postintervention CPET. Furthermore, study staff will use similar feedback and encouragement during all tests. As in all clinical trials, poor intervention adherence and dropouts are major concerns. We attempt to counteract this by using instructors trained in motivational feedback. The knowledge acquired from this study will help to inform future cancer care guidelines.

Acknowledgments

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Data Availability

The data sets generated during and analyzed during the current study are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review report from the Norwegian Cancer Society's Krafttak mot kreft 2018 / Norwegian Cancer Society.
[PDF File (Adobe PDF File), 15 KB - resprot_v12i1e45244_app1.pdf]

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Abbreviations

BCS: breast cancer survivor
CAUSE: Cardiovascular Survivors Exercise
CO: carbon monoxide
CPET: cardiopulmonary exercise test
CRF: cardiorespiratory fitness
CV: cardiovascular
CVD: cardiovascular disease
DLco: diffusion capacity of the lung for carbon monoxide
HR_{peak}: peak heart rate
HRQoL: health-related quality of life
HUNT-4: The Trøndelag Health
PROM: health-related patient-reported outcome
VO_{2peak}: peak oxygen consumption

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Protocol

Examination of Web-Based Single-Session Growth Mindset Interventions for Reducing Adolescent Anxiety: Study Protocol of a 3-Arm Cluster Randomized Controlled Trial

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Abstract

Background: Anxiety disorders are the most common mental disorders worldwide. In Hong Kong, 7% of adolescents are diagnosed with anxiety disorders, and 1 in every 4 secondary school students reports clinical-level anxiety symptoms. However, 65% of them do not access services. Long waitlists in public services, the high cost of private services, or the fear of being stigmatized can hinder service access. The high prevalence of anxiety and low intervention uptake indicate a pressing need to develop timely, scalable, and potent interventions suitable for adolescents. Single-session interventions (SSIs) have the potential to be scalable interventions for diagnosable or subclinical psychopathology in adolescents. Providing precise and context-adapted intervention is the key to achieving intervention efficacy.

Objective: This study aims to compare the effectiveness of three SSIs: single-session intervention of growth mindset on negative emotions (SIGMA), SSI of growth mindset of personality (SSI-GP), and active control, in reducing adolescent anxiety.

Methods: Adolescents (N=549, ages 12-16 years) from secondary schools will be randomized to 1 of 3 intervention conditions: the SIGMA, SSI-GP, or active control. The implementation of each intervention is approximately 45 minutes in length. Adolescent participants will report anxiety symptoms (primary outcome), perceived control, hopelessness, attitude toward help-seeking, and psychological well-being at preintervention, the 2-week follow-up, and the 8-week follow-up. A pilot test has confirmed the feasibility and acceptability of SIGMA among adolescents. We hypothesized that SIGMA and SSI-GP will result in a larger reduction in anxiety symptoms than the control intervention during the posttest and 8-week follow-up period. We also predict that SIGMA will have a more significant effect than SSI-GP. We will use the intention-to-treat principle and linear regression-based maximum likelihood multilevel models for data analysis.

Results: This study will be conducted from December 2022 to December 2023, with results expected to be available in January 2024.

Conclusions: This protocol introduces the implementation content and strategies of growth mindset SSIs (consists of 2 forms: SIGMA and SSI-GP) among school students. The study will provide evidence on the efficacy of different growth mindset SSIs for adolescent anxiety. It will also establish implementation strategies for self-administrative SSIs among school students, which can serve as a pioneer implementation of a scalable and self-accessible brief intervention to improve the well-being of young people.

Trial Registration: ClinicalTrials.gov NCT05027880; https://clinicaltrials.gov/ct2/show/NCT05027880

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KEYWORDS

growth mindset; fixed mindset; mental health; secondary school students, brief intervention, belief-in-change

Introduction

Background

Anxiety is one of the leading causes of illness and disability among adolescents aged 10-19 years [1]. In the past decade, Hong Kong recorded a 6.9% prevalence rate of anxiety disorders with severe impairment [2], and 25% of youths were experiencing high subclinical anxiety symptoms in a 3-month period and required a clinical intervention [3]. Based on the prevalence and local youth population data [4], it can be roughly estimated that in Hong Kong there are 85,000 secondary students requiring help and intervention for their anxiety symptoms.

However, an estimated 65% of individuals with general anxiety disorders in Hong Kong do not access mental health services [5]. The median waiting time between the onset of symptoms and receiving public child and adolescent psychiatric service is 58 weeks, and the cost of seeking private treatment is reported HK$3000 (US $385) per monthly consultation, which means that many families have no choice but to wait for public services [6]. Lengthy waitlists or costly clinic-based treatments provided by highly trained mental health professionals may be difficult to disseminate on a broad scale. This traditional setting makes access to service more difficult in special circumstances, such as during the COVID-19 pandemic [7]. Moreover, adolescents with mental health symptoms are particularly vulnerable to stigma and discrimination and may not actively seek school-based interventions [8]. Even among youth who do access care, most drop out prematurely, completing just over 3 therapy sessions on average [9]. There is clearly a need to develop briefer, scalable, nonstigmatizing, and youth-friendly interventions for adolescents with general anxiety symptoms.

Single-session interventions (SSIs) are promising to be scalable, accessible, and cost-effective for youth's mental health needs. SSIs refer to structured programs that intentionally involve only 1 visit or encounter with a clinic, provider, or program [10]. SSIs may serve as stand-alone or adjunctive clinical services. Emerging evidence supports the efficacy of SSIs in reducing and preventing youth's mental health symptoms. For example, Schleider and Weisz [11] found that growth mindset SSIs led to more significant improvement in youth depression and perceived behavioral control in a 9-month follow-up than in active control. They also found that enhancing belief-in-change of personality-enhanced treatment access for adolescent depression [12], but recorded nonsignificant changes in general anxiety, social anxiety, and conduct problems [13].

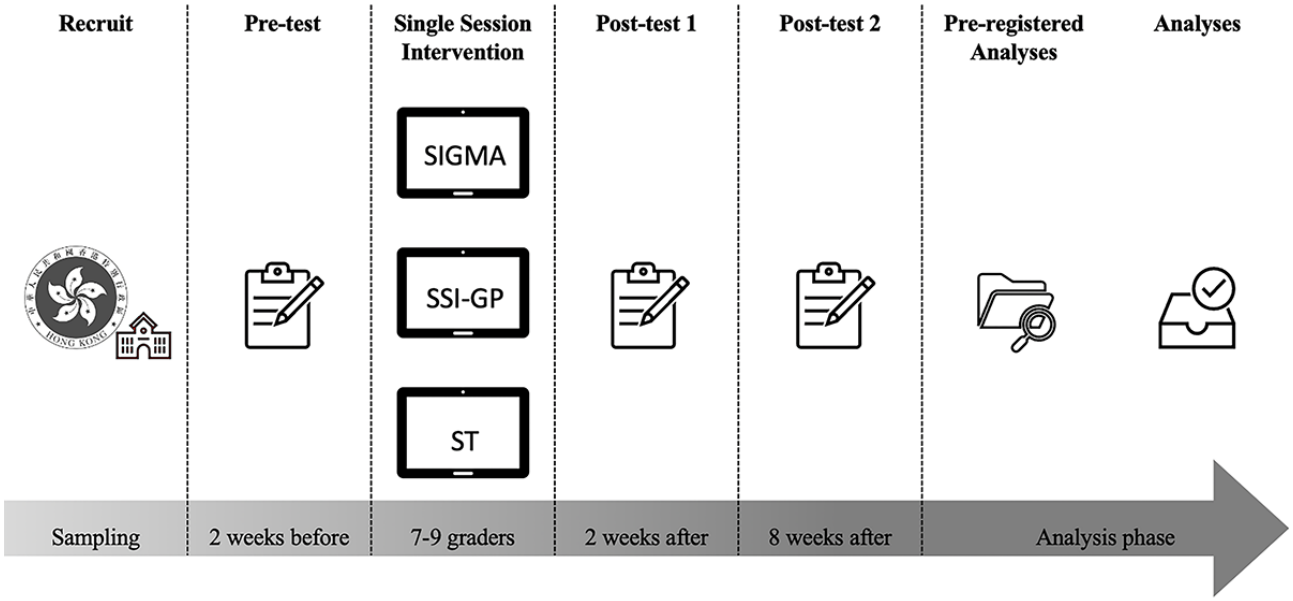
A brief intervention can be effective if the intervention precisely addresses the underlying psychological process that contributes to the social or psychological problems [14]. Walton [14] and Wilson [15] underscore the importance of precise intervention and adaptive context to secure the potency of brief interventions. Brief interventions targeted to remove specific psychological barriers and produce recursive dynamics will affect long-term outcomes. Thus, the effectiveness of SSI is highly related to the implementation content (what to intervene) and strategies (how to implement). However, the existing SSIs vary in the effect size of effectiveness. Examining psychological mechanisms that address mental health more precisely and designing and implementing the intervention carefully will improve the efficacy of growth mindset SSIs.

This proposal aims to develop and examine the efficacy and effectiveness of growth mindset SSIs for adolescent anxiety in the Chinese context. It will advance the extant literature by implementing and comparing different domains of growth mindset and developing implementation strategies for SSI among Chinese adolescents. The existing growth mindset SSIs teach adolescents the growth mindset of personality (SSI-GP), which means the person can change. However, the effectiveness of SSIs for reducing anxiety was not as significant as reducing depression. Recently, Zhu et al [16,17] found the fixed mindset of negative emotions closely associated with adolescent depression and anxiety. Therefore, an intervention promoting growth mindsets of negative emotions may be a more precise factor in alleviating the worry and anxiety of adolescents, but it is not examined yet. Thus, this protocol presents our newly developed intervention: the single-session intervention for growth mindset on negative emotions (SIGMA) and compares its effectiveness with the SSI-GP and an active control.

The SIGMA, which aims to instill the belief that negative emotions can change, may address the need for a scalable intervention for reducing anxiety. It has 3 unique features. First, it is a mechanism-targeted intervention with a carefully constructed and theoretically precise program that directly addresses the belief of suffering symptoms. Therefore, it may also advance the existing growth mindset SSI in reducing worry about symptoms and increasing perceived control and hope. Second, SIGMA can be developmentally adapted and culturally adapted for adolescents. It will be particularly suitable for secondary school students with general anxiety due to the engaging nature of web-based interventions, videos, peer sharing, and nonstigmatizing feature. Third, the brevity and flexible format could make it attractive to those who might not otherwise access care, and for whom a targeted, "light touch" intervention might be just enough. Given the large need-to-access gap among youths, we propose this 3-arm randomized controlled trial to provide evidence on the effectiveness of SIMGA and compare it against the existing growth mindset intervention (SSI-GP) and support theory as an active control. See Figure 1 for the research design.

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Figure 1. Design of the 3-arm randomized controlled trial. SIGMA: single-session intervention of growth mindset for anxiety; SSI-GP: single-session intervention of growth mindset of personality; ST: support therapy.



Aims and Objectives

The overarching goal of this study is to build the most effective implementation strategy of web-based growth mindset SSIs for reducing adolescent anxiety.

The primary objective of the proposed study is to evaluate the effectiveness of a SIGMA on reducing general anxiety symptoms in secondary school students. By using a 3-arm randomized control trial, we will compare the effectiveness of SIGMA to the SSI using growth mindset of personality (SSI-GP) and an active control condition using support therapy (ST).

The secondary objective is to compare the effectiveness of the aforementioned programs on secondary outcomes, including reducing hopelessness and increasing perceived control over emotions, attitude toward help-seeking, and psychological well-being.

There are 3 study hypotheses: (1) SIGMA and SSI-GP are more effective than the active control using ST in the primary outcomes, reducing general anxiety symptoms, and secondary outcomes, reducing hopelessness, enhancing perceived control, increasing positive attitude to help-seeking, and enhancing psychological well-being; (2) SIGMA is more effective than SSI-GP in the above primary and seconday outcomes; and (3) the effectiveness of SIGMA is greater in participants with higher motivation for change than in those with low to no motivation.

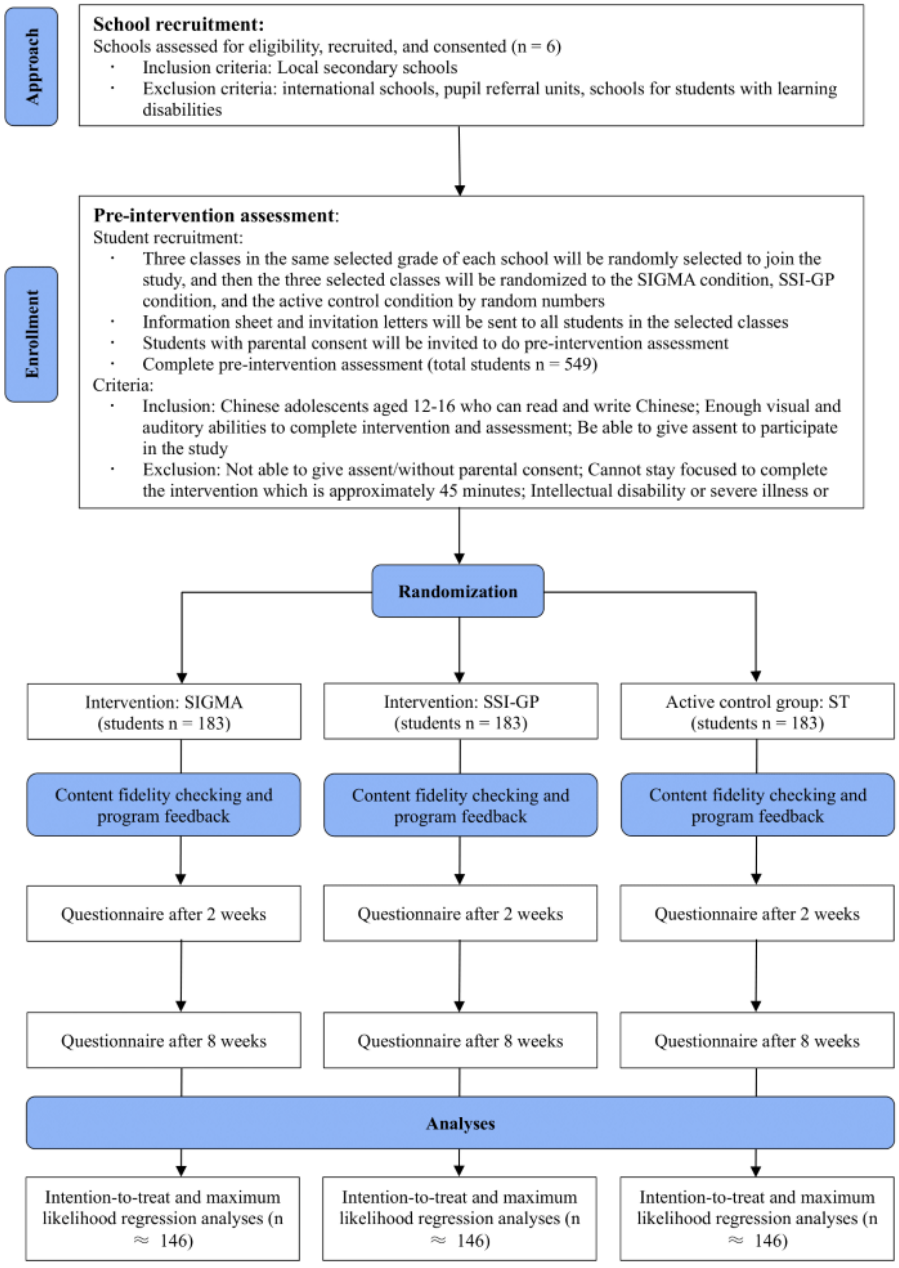
Methods

Research Design

This study will use a cluster-randomized control trial design. A conceptual model is provided in Figure 1. The intervention protocol will be pre-registered before data collection in ClinicalTrials.gov (ref: NCT05027880), and strictly follow the CONSORT (Consolidated Standards of Reporting Trials) guidelines [18,19]. At least 3 classes in the same grade of the participating school will be randomized (using computer-generated random numbers) into the (1) SIGMA group, (2) SSI-GP group, and (3) ST group (active control condition group), which will provide ST intervention at the same time. All participants will receive regular interventions in school. Three repeated assessments of the measures will be conducted for the 3 groups simultaneously at (1) baseline, (2) 2-week postintervention, and (3) 8-week postintervention (Figure 2). The cluster randomization at the classroom level can balance the risk of contamination between the intervention and active control groups and the school heterogeneity due to the school culture, schedule, and management.

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Figure 2. CONSORT (Consolidated Standards of Reporting Trials) diagram reflecting the flow of participants through this study. SIGMA: single-session intervention of growth mindset for anxiety; SSI-GP: single-session intervention of growth mindset of personality; ST: support therapy.



Sample Size Determination

To make sure the sample size is big enough to test the hypotheses, a small to medium effect size (Cohen *d*=0.33) is used based on prior research [11], power set at 0.80, and α set at .05. A final sample size of 438 (146 per arm) is required. With reference to the attrition rate of our previous studies in a school setting, which is less than 20%, there is a requirement to recruit 549 participants at the baseline (183 per arm).

Participant Eligibility and Randomized Control Process

Eligible participants (aged 12-16 years) in grades 7-9 will be recruited from 6 secondary schools through cluster randomized sampling. The inclusion criteria will include (1) ages between 12 and 16 years, (2) Chinese youth who can read and write Chinese, (3) enough visual and auditory abilities to complete the intervention and assessment, and (4) ability to give assent to participate in the study.

Exclusion criteria will include (1) no parental consent; (2) inability to stay focused to complete the intervention, which is approximately 45 minutes; and (3) intellectual disability or severe illness or pain that would lead to significant bias in students' health and mental health situation. Eligible participants will not be screened for their anxiety symptoms; thus, this study will comprehensively examine the efficacy of the interventions for students with mild, moderate, and severe levels of anxiety.

The school and student recruitment process will include the following steps. First, we will send research invitations to schools chosen randomly from the school list. Invitations will stop when 6 schools agree to participate. At least 3 classes in the same selected grade of each school will be randomly selected

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to join the study, and then the 3 selected classes will be randomized to the SIGMA condition, SSI-GP condition, and the active control condition by random numbers. All students in those classes will be invited to participate and the final participation depends on parental consent and students' assent. Based on prior trials in local schools, about 60% of students are likely to agree to participate with parental consent. Thus, approximately 90 students will be recruited from each school.

After consenting, students will be asked to complete a battery of questionnaires (detailed below) via the Qualtrics survey system. The students in 1 class will be in the same intervention conditions. The interventions will be conducted separately for each group in the school activity rooms with sufficient computers or tablets and headphones. All intervention activities are self-administered and delivered in a web-based format. The principal investigator and well-trained research assistants will stay in the intervention rooms to provide guidance and help if needed. All groups in 1 school will be conducted concurrently or within 2 weeks to reduce the influence of the time factor.

Implementation Content

SIGMA

The SIGMA intervention group will adapt the SSI-GP protocol in two ways: (1) by introducing the growth mindset of emotions rather than personality and (2) by providing an experiential process of negative emotion change. SIGMA also consists of five components: (1) an introduction to emotions and the brain for conveying a scientific understanding of emotion and growth mindset of negative emotions; (2) stories and testimonials from high school–aged youths who described their beliefs that people's negative emotion states (eg, anxiety, depression, and stress) are malleable, and how these mindsets influence their coping with anxiety; (3) emotion changing experience induced by short videos; (4) common questions and misconceptions about growth mindset; and (5) self-persuasion writing exercises in which the participants write notes to younger students about the growth mindset of emotion. Table 1 presents the key elements of the interventions. For participants at each school who belong to the SIGMA group, we will randomly select half of them to give them booster messages with core intervention content every 2 weeks between the 2-week posttest and the 2-month follow-up survey, that is, a total of 5 weekly booster messages will be sent to half of the participants of the intervention group, which will help us determine the most effective way of implementing the intervention.

Table 1. Intervention elements.

Intervention elements	SIGMA[a] (45 minutes)	SSI-GP[b] (45 minutes)	ST[c] (45 minutes)
Science knowledge about neural plasticity of the brain	✓ Growth mindset of negative emotions	✓ Growth mindset of personality	Nil Science videos about emotions
Stories and testimonials from high school-aged youths	✓ Focused on emotion changing experience	✓ Focused on personality change	✓ Focused on emotion sharing
Experiential exercises	✓ Emotion coping strategies	Nil	Nil
Self-persuasion writing exercises	✓ Focused on the malleability of negative emotion	✓ Focused on the malleability of personality	✓ Focused on sharing emotion to close others

[a]SIGMA: single-session intervention of growth mindset on negative emotions.

[b]SSI-GP: single-session intervention growth mindset of personality.

[c]ST: support therapy.

A pilot test among 13 secondary students (ages from 15 to 17 years) was conducted to confirm the feasibility and acceptability of the intervention in a small sample of the targeted population. The intervention lasted around 45 minutes and could be finished in one school class session.

SSI-GP

SSI-GP intervention group will use the intervention protocol of project personality [20]. We will translate it into Chinese by 2 bilingual native English and Chinese speakers and make adaptations to the local education context. The key potent elements of SSI-GP consist of five components [15,21,22]: (1) an introduction to the brain about the potential of neuroplasticity and behavioral change; (2) written testimonials from older, high school–aged youths of their belief in change of personality; (3) additional vignettes written by older youths about how growth mindset of personality helped them succeed following setbacks; (4) overview of common questions and misconceptions about growth mindset; and (5) an exercise of writing notes to younger students about the malleability of people's personality traits.

Active Control Group: ST

The control condition will be a structurally similar web-based session of supportive therapy. The goals of supportive therapy are to encourage the client to identify and express feelings and to share their emotions—both positive and negative—with close others. The ST group does not teach or emphasize specific skills or beliefs. The active control group includes the same number

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of activities as the SIGMA and SSI-GP interventions. Also, to mirror the intervention groups as closely as possible, supportive therapy will include vignettes written by similar school-aged youths, who describe times when they benefited from sharing their feelings with friends or family members.

Implementation Strategies

As the SSIs in this study are all self-administer web-based interventions, we adopt 5 strategies to ensure the interventions are understandable, relevant, acceptable, engaging, and effective. These strategies will also help promote context sensitivity among school students in the Chinese context.

First, we form a youth advisory group to make sure the intervention content is understandable and relevant to students' life. The group includes 2 secondary school students of the targeted age group, 2 school social workers, and 2 university students. For example, the testimonials of anxiety situations and coping should be context-adaptive, and the introduction of scientific knowledge should be in plain language and easy to understand. The youth advisory group includes students from the target population, school social workers and counselors, and local university students. We seek their feedback and suggestions during the development and the pilot test of the study to further improve the intervention.

Second, we adopt the philosophy of solution-focused brief therapy. We do not focus on the problem but seek future-oriented solutions relevant to daily living. These techniques can help engage the participants to make the intervention relevant and can ensure the intervention is solution-focused rather than problem-focused.

Third, we integrate "design art and computing science" to make the intervention engaging; for example, we design animation icons and design videos, and use clickers in the self-administrative intervention to maintain the focus of the participants.

Fourth, we empower student participants to act as "helpers" or "experts" by framing the participants as active contributors in the improvement of the intervention and by asking them to provide support to peers [10,11]. This design aligns with adolescents' desire for respect [22].

Fifth, to ensure the intervention will be conducted in a standardized surrounding, the intervention will be conducted in activity rooms in each school. Around 12 to 20 student participants with parental consent will be invited to participate in the intervention as a group under the support and administration of well-trained research assistants. We also monitor the time spent on each part of the presentation with computing programming techniques. Participants with too long and too short duration time (usually above 2 SDs) in 1 section will be double-checked on their participation effectiveness, and biased data will be eliminated.

Data Collection and Management

Assessments will be conducted by a blinded researcher trained in using the instruments. Self-rated scales will be completed by the participants under guidance. All the measures have been pilot-tested, and the questionnaires take about 20 minutes to be completed. Two attention-checking items will be included in the surveys of each time point for careless responding screening (eg, "Please choose *Strongly Agree* for this item"). Only those who answer both attention-checking items correctly each time will be included in the final data analysis [23]. As the literature has shown motivation playing pivotal roles in people's behavioral change, we will also add 2 items at the beginning of the survey at baseline to assess participation motivation of our participants with a 6-point Likert scale, asking about their motivation to participate in this program and improve their emotion regulation ability, respectively.

Content Fidelity Checking

Mindsets of Negative Emotions

The validated Chinese version 12-item Mindset of Depression, Anxiety and Stress Scale will be used to assess participants' belief in change of negative emotion states, that is, depression, anxiety, and stress [16]. The sample items are "When you have a certain level of depression, you really cannot do much to change it"; "To be honest, people cannot really change how anxious they are"; and "No matter how hard people try, they cannot really change the level of stress that they have."

Each item scores on a 6-point Likert scale; a higher score means a more fixed mindset of negative emotions (Cronbach α=.94). There are 3 subscales: depression mindset, anxiety mindset, and stress mindset, containing 4 items in each subscale. The Cronbach α of 3 subscales are .91, .89, and .90, respectively [16].

Mindset of Personality

Three items of implicit theory of personality [24,25] will be used to measure the belief in change of personality on a 6-point Likert scale from 1 (*strongly disagree*) to 6 (*strongly agree*). A higher score means a more fixed mindset. The sample item is "People can do things differently, but the important parts of who they are can't really be changed." The Cronbach $\alpha$was .85.

Intervention Feedback Scale

It is developed based on the theoretical framework of acceptability (TFA), which consists of 7 component constructs including affective attitude, burden, intervention coherence, perceived effectiveness, opportunity costs, self-efficacy, and ethicality [26]. Except for a general acceptability item, 6 items for the 6 components of TFA except for ethicality and 4 items including 2 open-ended written feedback items in regards to the impression of the intervention from the well-validated Program Feedback Scale [27] will also be integrated to assess the acceptability of the intervention. Among the final scale, except the open-ended item, the other 10 items will be assessed on a 5-point scale, such as "How acceptable was the intervention to you?" ("1=Completely unacceptable" to "5=Completely unacceptable").

Motivation to Apply Things Learnt From the Program

Right after the intervention, we will ask participants after this program the extent to which they would like to apply the intervention content and the extent to which they would like to improve their emotion regulation on a 6-point Likert scale.

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Primary Outcome

Anxiety symptoms measured by the Generalized Anxiety Disorder-7 (GAD-7) [28,29] are the primary outcome. The GAD-7 scale includes 7 items that assess whether anxiety symptoms have bothered the individual in the previous 2 weeks, ranging the frequency from 0 (*not at all*) to 3 (*nearly every day*). Example items were "Feeling nervous, anxious, or on edge" and "Not being able to stop or control worrying." GAD-7 is the self-rating scale and effectively reflects symptom severity in adolescents; it is highly correlated with clinician-administered ratings of anxiety symptoms. It is brief and suitable for self-report study [30]. The Cronbach α was .93 [31].

Secondary Outcomes

Perceived Control

The Anxiety Control Questionnaire-Emotion Control [32] is a 15-item questionnaire that measures how much perceived control participants have over their anxiety. It is 1 of the 3 validated subscales of the anxiety control questionnaire and contains 4 items (eg, *I am able to control my level of anxiety*) rated from 0 to 5. The scale has a well-validated factor structure in a nonclinically selected sample, is strongly associated with anxiety and depression symptoms, and has demonstrated good internal consistency in previous investigations. The Cronbach α was .73.

Hopelessness

The 4-item helplessness subscale of the Demoralization Scale [33] will be used to measure the participants' faith in the future. Each item scores on a 5-point Likert scale, and the mean of all 4 items is taken to measure the hopelessness, with a higher score meaning a correspondingly higher level of hopelessness. An example item is "I feel hopeless." The Cronbach α of the Chinese version of this helplessness subscale was .72 [34].

Attitude Toward Seeking Help

We use 2 items from the Attitude toward Seeking Counselling Help Assessment [32,33], participants' understanding of counseling and attitudes toward seeking counseling help. An example item is "If I believed I was having a mental breakdown, my first inclination would be to get professional attention." The Cronbach α was .72 [34]. We develop a brief scale including 2 items to assess participants' help-seeking behavior. The 2 items are "when I encounter difficulties, I will not ask help from teachers" and "when I encounter difficulties, I will not ask help from social workers/counsellors." This scale will be rated on a 6-point Likert scale from 1 (very untrue of me) to 6 (*very true of me*).

Psychological Well-being

The short version Warwick-Edinburgh Mental Well-being Scale (WEMWBS-14) [35,36] will be used to measure the extent to which participants generally experience well-being states. The WEMWBS includes 14 items, scoring on 5-point Likert scale, the average of all 14 items indicates the well-being of the participants. The sample item is "I have been feeling optimistic about the future," and the Cronbach α was .93.

Covariates

Sociodemographic information consists of a range of participant characteristics and is measured at the baseline to examine variability between the groups such as gender, age, grade, ethnicity, and socioeconomic status.

Data Analysis

An intention-to-treat analysis will be conducted for any missing data. Two-level analyses will be used to account for cluster randomization [37]. To examine the effects of the interventions, multilevel regression will be used to test the group effect, time effect, and their interaction effect on outcome measures. Additionally, we will calculate effect sizes using estimated marginal means; these effect sizes compare mean gain scores (Cohen *d*), reflecting changes in each outcome from baseline to 2 follow-ups for youths receiving the mindset versus active control interventions. The effect sizes will also be compared between participants in the intervention group who receive booster messages and those who do not. A *P* value of <.05 will be considered statistically significant, and SPSS version 26 (IBM Corp) will be used for all statistical analyses.

Ethics Approval

The study has obtained research ethics approval from the institutional review board of the principal investigator's university (HSEARS20201004001-01). This trial was preregistered at ClinicalTrials.gov (NCT05027880). Participation will be voluntary. Informed written consent or digital consent will be obtained from parents and participants. We will remind the participants that they have the right to terminate the intervention or omit any questionnaire questions and assure the confidentiality of their answers. We will also provide additional information for referral services to the student participants. Students are also invited to indicate if they need further support from school social workers or counselors in the postintervention questionnaire. With the participant's assent, we will refer the participant to the school caring professionals. All identifiable information will be removed, and codes will replace names to ensure privacy. All personally identifiable data will be locked up and destroyed 3 years after the study ends. Participants' data will not be identifiable in any publication or reporting.

Results

Recruitment will start in December 2022, and data collection is expected to end in 2023. Results are expected to be available in January 2024. We also intend to make the publications available in 2024. The findings of this trial will be presented as well at conferences. We will only report aggregated group data, and no personal information will be leaked.

Discussion

Overview

We anticipate that SIGMA, which highlights that emotion states are changeable, will significantly enhance the growth mindset of emotion and reduce general anxiety symptoms and secondary outcomes compared to SSI-GP and the active control. However,

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the effect size will be small because single-session self-help interventions are low-dosage interventions. SSI-GP is hypothesized to have better outcomes than the active control group. The half with booster messages in the SIGMA group will have better outcomes than the half without boosters, especially in the 8-week follow-up.

To date, this will be one of the few randomized controlled trials to apply a single-session growth mindset intervention to reduce anxiety. As focusing on the key aspects and using effective ways to make changes are the key mechanism of effective SSI, addressing the key aspects that can secure changes is essential for designing SSIs. This 3-arm randomized controlled trial will help elucidate the mechanisms of change in adolescent anxiety symptoms: believing that negative emotion can change (SIGMA), believing that personality can change (SSI-GP), or receiving support (active control). This proposed study will find the potent core element of brief intervention in helping youth with anxiety.

This study will also be a pioneer study examining the self-administered web-based intervention among Chinese adolescents. There is a paucity of research in the Chinese context on effective implementation strategies for self-administrative SSI. As the effect size of SSI varies from small to medium in extant interventions, the dedicated design and careful implementation matter in the efficacy of the study. This study will provide a clear protocol of implementation content and strategies, which will be helpful for the future use and development of SSIs.

This project has theoretical, practical, and clinical contributions. Examining the efficacy of the notion of malleability of negative emotion on youth anxiety will advance the understanding of the impact of implicit theory and mental health symptoms. The easy-access self-help program will enable adolescents with anxiety symptoms to access timely help, and reduce the risk of deterioration of anxiety symptoms and development of comorbid mental health problems before adolescents can access therapy provided by a trained therapist or psychiatrist. If proven effective, SIGMA will benefit a proportion of youths who would otherwise go without service entirely. It can also benefit youth on the waitlist for psychiatric services by invoking intrinsic motivation and avoiding hesitance to get treatment. It can also serve as a complement to multisession psychosocial treatments. This project may provide a generalizable model for the development and implementation of SSI among youth people in the Chinese context.

Limitations

There are limitations that need to be considered. First, as this study does not exclude individuals based on the severity of their anxiety symptoms, the efficacy of the interventions to reduce anxiety symptoms of students without anxiety or with low levels of anxiety may not be significant and thus affects the statistical significance on the whole. However, the proposed intervention can be inclusive to youths with a diverse range of anxiety problems and offers a unique opportunity to study the differentiated impacts with subgroup analyses. We expect the secondary outcomes will have significant changes after the intervention, even for those with low-level anxiety symptoms. Second, there is no waitlist control group as all 3 groups are implemented with specific interventions, with even the control group receiving ST (active control). In this study, we aim to compare the effects of different interventions with specific strategies. However, the setting of a waitlist control group will help in better understanding the effect of interventions overall.

Conclusions

This study presents the evidence-based implementation of web-based single-session growth mindset interventions for student anxiety and compares the efficacy of SSIs using growth mindsets on negative emotions and growth mindsets on personality. Our study will provide an example of the implementation of SSIs among the Chinese adolescents and will help to develop easy-access, low-cost, and scalable interventions for mental health promotion among young people.

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Data Availability

Data are not publicly available but can be obtained via contacting the corresponding author.

Authors' Contributions

SZ conceived this evaluation study initially and drafted the first draft of the grant proposal. ST and KLC provided comments for the randomized control trial design and the grant proposal. PL contributed to the data analysis plan. QC provided comments for web-based intervention implementation. JS provided comments from psychiatric profession. SZ developed all aspects of the proposal and manuscript related to the implementation of intervention and data collection. All authors edited and approved the final manuscript.

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Conflicts of Interest

None declared.

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Abbreviations

CONSORT: Consolidated Standards of Reporting Trials
GAD-7: Generalized Anxiety Disorder-7
SIGMA: single-session intervention of growth mindset on negative emotions
SSI: single-session intervention
SSI-GP: single-session intervention of growth mindset of personality
ST: support therapy
TFA: theoretical framework of acceptability
WEMWBS: Warwick-Edinburgh Mental Well-being Scale

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Protocol

Parent Experiences of Child Loss and End-of-Life Care in a Pediatric Intensive Care Unit: Protocol for a Qualitative Study

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Abstract

Background: Death of a child in the pediatric intensive care unit is a rare event that can occur after failed cardiopulmonary resuscitation efforts, after a brain death diagnosis, or after a decision to limit therapeutic efforts. Nevertheless, even in the case of children with terminal and progressive illnesses, death is a crisis that comes as a surprise to parents and is perceived as unexpected. In the final stage of a child's life, health care staff play a key role in sharing feelings and experiences with the family and in supporting them throughout the process in order to facilitate the grieving process.

Objective: The aim of this study is to explore the experiences of parents whose children have died in a pediatric intensive care unit.

Methods: To address the study aims, a qualitative phenomenological study based on the van Manen proposal will be carried out. The study will be conducted in the pediatric intensive care unit of a tertiary care hospital. The study population will be parents or guardians (older than 18 years) of children who have died in the unit at least 6 months prior to potential participation in the study. Purposive sampling will be used to ensure sample diversity in relation to experiential variables. Families will be initially contacted by letter sent alongside the standard letter of condolences from the hospital, and then recruited in a subsequent telephone call. The sample size will be determined by data saturation. In-depth interviews will be conducted individually or in pairs. Parents will decide when, how, and where to conduct the interviews, which will be transcribed verbatim and examined using thematic discourse analysis.

Results: This study was awarded a grant in December 2020 and was approved by the Medical and Health Research Ethics Committee on December 21, 2020. Data collection started in April 2021, and the results are expected to be published in 2023.

Conclusions: This project is intended to maintain, strengthen, and build on a particular line of research on end-of-life care with a focus on effective coping, spiritual well-being, and the adaptive grieving process. The results will contribute to establishing action guidelines that are both based on the discourses of parents who have experienced the death of a child and geared toward high-quality end-of-life care through dignified death and adaptive grief management.

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KEYWORDS

hospice and palliative care nursing; intensive care units; pediatric; patient-centered care; family nursing; death; qualitative research

Introduction

Child and adolescent death caused by noncurable diseases is still a present reality despite developments in pediatric medicine [1]. According to the World Health Organization data [2], 6,073,010 children under the age of 14 years died in 2019 around the world, leaving an intense, lasting impact on their families.

Death produces anxiety, distress, depression, and fear, especially when the deceased is a child. As children exhibit different characteristics from adults, the approach to palliative and

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end-of-life care for these patients and their families should also be different. The primary objective is to ease suffering through proper symptom control, psychological, social, and spiritual support, and preparation for death and grieving. The maladjustment process that occurs within the family is particularly relevant, as it complicates the acceptance of their loss. The sorrow arising from this loss, coupled with the ongoing decline in the structure and function of the family unit, makes it difficult to develop coping strategies and worsens the experience of grief. Even in the case of children with terminal and progressive illnesses who experience life-threatening events, death is a crisis that comes as a surprise to parents and is perceived as unexpected [3].

In pediatric end-of-life care [4], it is widely accepted that the family's experiences in the hospital can have a significant long-term impact on memories and the grieving process [5]. There is therefore an important incentive to improve the quality of care provided in these circumstances, both to improve patient experience as well as to support the impending grief of families. Meert et al [6] identified a high incidence of complicated grief symptoms in parents whose children had died in the pediatric intensive care unit (PICU). In their study, they note that these symptoms lessen between 6 and 18 months after the child's death, although not for all parents. In light of the above, we believe it is relevant to investigate the experiences of the families of children who have died in the PICU to better discern the actions of health care workers; how to provide the family with the most appropriate resources needed to ease their grieving process; how to foster a supportive atmosphere and a dignified death; and to assess whether the care provided by health care workers is satisfactory.

Over the last decade, pediatric care has seen improvements in the care of critically ill children, most notably, the adoption of the family-centered care (FCC) model. This model is based on the premise that parents are the people who know their children best [7] and should therefore be included in the caring relationship, as their involvement improves patient outcomes. The definition of FCC encompasses 4 fundamental concepts: respect and dignity; information sharing; participation in care and decision-making; and collaboration between patients, families, and the health care team. In addition to the physical benefits for patients, when parents are involved in their children's daily care by playing an active role in the care team, emotional and psychological aspects improve through effective coping.

Death of a child in the PICU is a rare event that can occur after failed cardiopulmonary resuscitation (CPR) efforts, after a brain death diagnosis, or after a decision to limit therapeutic efforts (LTE). According to data provided by the MOMUCIP study [8], which explores the causes of death in PICUs, the most frequent cause of death was after a decision to LTE (n=151, 50.7% of all cases, widely ranging between 19.2% and 64.6% depending on the hospital), followed by indicated but failed CPR (n=114, 33.8%), and brain death (n=52, 15.4%). The main reason for LTE was failure to provide CPR for cardiac arrest (n=45%), followed by withdrawal of mechanical ventilation (n=48, 31.5%), and administration of vasoactive drugs (n=33, 21.6%).

Technological advances have increased the ability to provide support in very critical situations. However, life does eventually come to a natural end, and the continuation of therapeutic interventions is not always suitable, sometimes raising the question of whether continuing treatment is in the child's best interest. If the decision is made to withdraw life-support therapy, the main focus then shifts from an interventionist approach (aimed at sustaining life) to an approach aimed more at providing as much comfort and emotional support as possible to the child and their family. In the final stage of a child's life in PICUs, health care staff play a key role in sharing feelings and experiences with the family and in supporting them throughout the process. Providing high-quality end-of-life care for patients and their families eases suffering through appropriate decision-making and symptom management, which helps to facilitate the grieving process.

In relation to the available evidence, Mitchell and Dale [9] highlight the importance of providing anticipatory care for patients with life-limiting illnesses by planning care in advance together with the family to let them make decisions based on clear information and to avoid unnecessary interventions. Regarding the planning and implementation of palliative care in intensive care units, it is neonatal units that have made the most progress in this area and where the vast majority of scientific evidence is available. As early as 2002, Catlin and Carter [10] established the key elements necessary for an effective approach to palliative care, forming the basis for numerous subsequent studies and protocols, serving as an example of a high-quality practical guide [11].

Recent studies address a range of issues, including evaluating the implementation of a care program in neonatal intensive care units (NICUs) [12]; the benefits of implementing interventions that focus on early symptom management; the possibility of planning interdisciplinary meetings to discuss issues such as end-of-life care (ie, anticipating complications and treatment options or not starting treatment or resuscitative measures); and the promotion of joint decision-making for neonates with severe and incurable illnesses (ie, morbidity and mortality associated with the condition). These studies also emphasize the need to train nurses in palliative and end-of-life care, as lack of training is one of the barriers that may be encountered [13] when preempting symptom recognition in the child and their family and when attempting to improve nursing care and support. The literature also stresses the need to continue new lines of research involving health care workers who care for children with conditions requiring palliative and end-of-life care and for their families [14]. The creation of clinical practice guidelines where palliative and curative approaches coexist and where the timing of their transition is established is also of vital importance, as there is ample evidence of the benefits of palliative care in PICUs and NICUs. However, the number of publications successfully reporting such benefits through protocols and care programs is scarce [11].

All of the above brings to the forefront the fundamental roles that nurses play in end-of-life care [15]. This is further accentuated in intensive care environments and even more so in the pediatrics branch, in the case of FCC. The role of the nursing professional takes on greater importance when it comes

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to supporting the patient and their family at the end of the patient's life. This is due to the therapeutic relationship based on trust and support that is established between them, which improves the family's ability to cope. Similarly, several nursing theories and models throughout history have considered palliative care as a significant part of nursing functions [16], creating a framework for action of its own. According to Wu and Volker, the Humanistic Nursing Theory approaches the field of palliative care through the lens of the bond created between the nurse and the patient, seeking to provide patient comfort, encourage decision-making, and maintain dignity [15].

There is also a major pillar of nursing that illustrates the importance of nurses in end-of-life care—the nursing care process (NCP). This, together with the North American Nursing Diagnosis Association taxonomy, allows specific nursing diagnoses directly related to palliative care to be identified, for example, risk for maladaptive grieving (00302), maladaptive grieving (00301), and readiness for enhanced grieving (00285) [17,18]. Through the NCP, and based on standardized language, nurses carry out interventions specific to their discipline (Nursing Interventions Classification) such as active listening, anxiety reduction, coping enhancement, and dying care, which give them a sufficient degree of autonomy when it comes to achieving measurable outcomes (Nursing Outcomes Classification) [19], which in turn contribute to the resolution of patient problems.

For these reasons, the general aim of this study was to explore the experiences of parents of children who have died in the PICU. In addition, the specific aims of this study were the following: to explore parents' perceptions of their capacity for self-determination and active participation in the process of caring for their child at the end of their life; to identify needs perceived by parents when saying goodbye to their deceased child; and to identify limitations regarding family support as perceived by parents and strategies for improvement.

Methods

Design

The project will be based on the constructivist paradigm, and a qualitative phenomenological study will be carried out according to the van Manen methodological proposal. According to this author, phenomenological research is the study of life experiences, of the lifeworld and everyday life (which constitutes the prereflective experience), the nonconceptualized or noncategorized experience [20]. In keeping with the above, an interpretative phenomenological or hermeneutic approach will be taken, as it provides an understanding that there is no single reality but multiple realities [21], which depend on the subjective interpretations of the individuals who experience a given phenomenon, the life stage that they are at when that phenomenon occurs, the place they are in, and their interactions with the people around them) [22].

We propose an intersubjective approach to the study phenomenon, which means seeking to gain access to the multiple interpretations of reality through the subjectivities of the families who have experienced first-hand the loss of a child in the PICU while at the same time recognizing the active participation of researchers themselves in the research process [21,22].

Study Setting

The study will be conducted in the PICU at the Gregorio Marañón General University Hospital in Madrid, Spain. This is a multipurpose unit that provides clinical care for critically ill children and coordinates and supports other hospital services in the prevention and treatment of life-threatening situations, as well as in the care of complex technology–dependent patients. It has an intensive care and an intermediate care hospitalization area with a total of 17 beds and an occupancy rate of 70%-80%.

The reasons for admission of PICU users, according to their clinical records, were as follows: heart conditions or postoperative cardiac surgery (23%); respiratory (30.4%), hemodynamic (14.2%), hemato-oncological (3.5%), neurological, gastrointestinal (2.9%), or renal problems (2.7%); multitrauma (5.9%); and infection or acute sepsis (6.5%), transplant (3.9%), and so forth. During the last 3 years (2018-2020), an average of 385 children were admitted to the PICU per year, with a mortality rate of 4.6%, 1.9%, and 2.9%, respectively. The most frequent causes of death were limitation of therapeutic efforts, multiorgan failure, and brain death [23].

Participants

The study population will include parents or guardians, older than 18 years, of children who have died in the PICU at least 6 months prior to their potential participation in the study [9], who are able to communicate verbally or in writing, and who voluntarily agree to participate in the study. Participants will be assured that their participation and the subsequent interview will not put them at any emotional or psychological risk.

In relation to the grieving process, the literature consulted recommends different time periods for inviting families to participate, ranging from 4 [24] to 12 months [25] after the death of their child. However, each family's circumstances will be assessed during the phone interview, ensuring that all stages of grief have been overcome successfully, and avoiding significant dates such as birthdays and anniversaries.

All persons whose participation in the study may put them at risk of emotional instability, such as parents who are going through pathological or complicated grief, will be excluded [26].

Purposive sampling [27] will be used to ensure sample diversity regarding experiential variables. These variables will be determined by the research team's consultation of available evidence and prior experiential knowledge (Multimedia Appendix 1) and attempts will be made to ensure access to varied, meaningful, and competing narratives. In more advanced stages of the research process, a decision will be made to follow either a theoretical sampling method that includes new variables or experiential criteria, which emerge from the analysis.

For the recruitment of families, together with the institutional letter of condolences sent by the unit, they will be asked in writing about the possibility of participating in the study. In a later telephone call, the project will be explained to them in

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greater depth, any doubts or questions will be addressed and compliance with the inclusion criteria will be assessed.

The final sample size will be driven by data saturation, that is, the occurrence of redundant and repeated information [27]. This stage of the research will end when a solid set of primary protocol materials (interviews, observations, and notes) has been collected and described and there are enough data to perform a comprehensive categorization or classification which, in turn, can inform sound analysis, interpretation, and theorization, leading to valuable results [28].

However, after consulting the available literature, it is estimated, in terms of time and budget planning, that data saturation can be achieved after a total of between 10 [9,25] and 25 parent interviews. These sample sizes are taken as a reference, but results will depend on the interviewer's expertise, the richness of participant discourse, and the analyst's ability to see beyond the data (or the analyst's theoretical sensitivity), among other aspects [29].

Data Collection

In-depth individual or paired interviews will be conducted according to each family's preferences (paired interviews allow family practices to be analyzed and shared family realities to be co-constructed) [30]. The interview is a technical instrument that is very much in tune with theoretical hermeneutic phenomenology, as it is intended to explore and collect experiential narrative material and to be the vehicle for investigating the meaning of that experience. Given the sensitive nature of the topic, a script for the semistructured interviews will help the interviewer to focus on the most relevant aspects of the experience while ensuring that emotional vulnerability is carefully managed [20]. Although the interview script is not meant to be a closed framework, it does allow for some control over the most emotionally sensitive areas and the routes to reach them if the participant is not prepared.

Based on the general and specific study objectives and taking the researchers' experiences into consideration, carefully worded dynamic interview questions have been drafted in order of the most general to the most specific, and from the least sensitive to the most sensitive (Multimedia Appendix 2). The script will be flexible in nature and will evolve according to the fieldwork and the needs arising from it. The information gathered and topics emerging from this information will refocus the approach and the collection of additional new data [28].

The families who agree to participate will decide when, how, and where they want to be interviewed: in person, with different locations available (travel expenses will be covered), or remotely, by videoconference or telephone. These will be audio-recorded. The recordings will be kept for up to 1 year after the publication of the study results in case further analysis is required. They will then be deleted.

While the interviews are being conducted, through close observation [29], the data obtained from nonverbal communication will be recorded in a field notebook. This is how, according to van Manen [32], we come as close as possible to the participant's lifeworld, so that we can grasp the meaning of that person's particular experience. This register can help to contextualize the families' discourses and to understand how the death of a child in the PICU impacts their parents in greater depth. Participant files will also be created where sociodemographic, clinical (reason for admission, time spent in the PICU, date, and cause of death), and relational data will be collected to help understand and contextualize their discourses. Some data will be retrievable from their clinical records, while others will have to be completed during the interviews.

Data Analysis

The van Manen hermeneutic approach [32] will be used for the qualitative analysis of the data. The interviews will be transcribed verbatim, and a thematic discourse analysis will be performed by identifying the themes that give meaning to the text and the experience. The themes are interpreted as the significance of the experience itself—attributing meaning and significance to the phenomenon at hand in an attempt to understand it, in such a way that each theme describes a different facet of the experience being faced. As themes emerge, an attempt will be made to capture the thematic status networks in more phenomenologically sensitive paragraphs by making reflective-theoretical notes (memoing) that will result in a creative hermeneutic process [20].

Subsequently, the themes that will inform the phenomenological description will be established: since not all the meanings that we find when reflecting on a phenomenon or lived experience are unique to that phenomenon or experience, this means that the key themes will be identified. To this end, we will identify the main qualities of each of the themes that are quintessential to that phenomenon.

For coding, the support software ATLAS-ti (Estudiantes; L-BFB-FEC, individual license) will be used for structuring the analysis and storage of data. This program will facilitate the identification of codes, the creation of the first themes for analysis, and the initial exploration of all written documents arising from the interviews for the study of qualitative data [33].

During the analysis process, the results will be cross-checked and compared with those of similar studies to verify how they emerge from different perspectives or broader theoretical frameworks and to better explain what the study really means. Comparing and contrasting emerging theoretical proposals with those of other researchers will lead to greater integration and enrichment of the study area's body of knowledge [28]. This comparison will lead to the reformulation, restructuring, extension, or refinement of previous theoretical constructs. The constant comparative method is a way of generating theory from the comparative and systematic analysis of data [34]. In order to synthesize the final findings, efforts will be made to integrate all the themes into a coherent and logical whole, with evocative meaning.

Ethical Considerations

Parents' principle of autonomy [35] will be preserved by signing the informed consent form after reading an information sheet that will be provided to them, containing the rationale for the project, a brief explanation of the study, who is involved, and the risks and benefits associated with their participation.

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Permission will be requested from participants to be audio-recorded. All participant questions will be answered before signing the informed consent form. They will choose to participate without any pressure or coercion. Informed consent will be written using the informed consent form designed for this purpose and approved by both ethics committees.

All interviews will be attributed codes, eliminating any personal details of the informants. Confidentiality will be preserved throughout the study, and the safety of participants will be ensured at all times, bearing in mind that the study is sensitive in nature [36]. The project was approved by the Clinical Research Ethics Committee at the Gregorio Marañón Hospital (CuidFin_Enf1; January 12, 2021), as well as by the Research Ethics Committee at the Autonomous University of Madrid, Spain (CEI-121-2451; February 11, 2022).

Rigor

To ensure the internal validity of the project (credibility and accuracy), the following will be used: several forms of triangulation [22] of data collection techniques from interviewers and analysts; audit strategies, for example, member checking [37] or feedback from participants and the "critical friend" strategy [38] or feedback from critical experts); and thorough descriptions of the research process and methodological decision-making.

With regard to external validity (transferability), a detailed description of the characteristics of the participants and the study setting will be provided in order to contextualize the findings and assess the relevance of the gathered evidence for application in other clinical settings.

In addition, auditability will be ensured so that other researchers wishing to conduct the same research based on the data from this study will reach the same or similar conclusions. To this end, all documents and a complete record of all decisions made and ideas put forward shall be made available.

Results

The project was funded in December 2020 and started in April 2021. By December 2022, a total of 19 participants had registered, and the first themes of the analysis were beginning to emerge. These emerging themes are informing further rounds of interviews. Recruitment is expected to be completed in February 2023, reaching thematic saturation, with results to be published in mid-2023.

Discussion

The future results will provide a basis for establishing action guidelines based on the experiences of parents who have suffered the death of a child in the PICU. This is intended to ensure the provision of high-quality end-of-life care that helps patients to die a dignified death and parents to better manage their grief. A review of the literature found numerous studies conducted in NICUs, but only few studies involving PICUs may serve as a reference for future lines of research.

Due to the COVID-19 pandemic, the number of children admitted to the unit has been lower (with a consequent decrease in deaths). This raises the need to recruit participants retrospectively by including parents with children who have died since 2019 in the study population. Initially, a pilot study will be conducted with particularly approachable and cooperative families to decide on the questions that will make up the interview script, as well as the most appropriate time and channel for contacting families.

A potential limitation in the execution of the study is the language barrier, as the PICU at the Gregorio Marañón University Hospital is a leading cardiology unit where admitted patients (and their families) are not fluent in Spanish. Another limitation may be linked to the impact that their child's death may have on parent participation in the study.

End-of-life care is one of the main objectives of health care. Taking an in-depth look at this issue is an opportunity to improve health care delivery and the humanization of care, to help families to manage their grief and to foster a climate conducive to a dignified death. This project is intended to maintain, strengthen, and build on a particular line of research on end-of-life care in order to contribute to care excellence in the psychosocial and spiritual dimensions by focusing on effective coping, spiritual well-being, and the adaptive grieving process.

Acknowledgments

We would like to express our heartfelt gratitude to all the parents who have shared their experiences with us in the hope that families going through a similar experience in the future will receive the excellent care they need. We would also like to thank Elena Peña, Alberto Sánchez, Rosa Blanca Ortiz, and Dr Jesús López-Herce (working in the PICU at the Gregorio Marañón Hospital) for their collaboration in data collection and future participation in subsequent analyses.

Data Availability

The data sets used and analyzed during this study are available from the corresponding author on reasonable request.

Conflicts of Interest

The researchers declare that they have no conflict of interest that could affect their proposed ideas or the undertaking of the present research study. The research protocol has been funded by the Intramural Nursing Programme of the Biomedical Research Foundation at the Gregorio Marañón Hospital in Madrid, with a contribution of €5000 (US $5465.85; document attached). The

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role of the funding institution is to promote, manage, and develop nursing research at the hospital. The funding institution is not a commercial institution, but a research foundation (Biomedical Research Foundation at the Gregorio Marañón Hospital [39]). The project award has been peer-reviewed. The funding institution exercises its functions and competencies without incurring conflicts of interest with the development of the project and its future results.

Multimedia Appendix 1
Experiential characteristics.
[DOCX File , 13 KB - resprot_v12i1e43756_app1.docx]

Multimedia Appendix 2
Interview guide.
[DOCX File , 15 KB - resprot_v12i1e43756_app2.docx]

Multimedia Appendix 3
Peer review report by Programa Intramural de Impulso a la I+D+i - Fundación para la Investigación Biomédica del Hospital Gregorio Marañón (FIBHGM) - Instituto de Investigación Sanitaria Gregorio Marañón (IiSGM) (Madrid, Spain).
[PDF File (Adobe PDF File), 471 KB - resprot_v12i1e43756_app3.pdf]

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Abbreviations

CPR: cardiopulmonary resuscitation
FCC: family-centered care
LTE: limit therapeutic efforts
NCP: nursing care process
NICU: neonatal intensive care unit
PICU: pediatric intensive care unit

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Protocol

The Efficacy of Trunk Bracing With an Instrumented Corrective Exercise on Spinal Deformity, Pulmonary Function, Trunk Muscle Endurance, and Quality of Life in Adolescent Idiopathic Scoliosis: Protocol for a Parallel Groups Clinical Study

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Abstract

Background: Adolescent idiopathic scoliosis is a 3D spine distortion with an unidentified etiology. It results in noticeable trunk deformity, decreased muscle strength and endurance at the trunk, changes in chest volume, breathing issues, and ultimately a decline in the quality of life. Trunk bracing and corrective exercises make up most of the treatment of patients with scoliosis when their deformity is between 20° and 45°, and they have not yet attained skeletal maturity. Evidence suggests that spinal deformity in people with scoliosis may result from improper motor control. Automatic response training is an exercise therapy technique that can modify the pattern of trunk muscle control for supporting the spinal column in normal alignment. An apparatus called a cantilever device is required for this type of exercise, which facilitates training at home. In spite of research showing the benefit of braces and therapeutic exercise in adolescents with scoliosis, less emphasis has been given to the impact of home-based training, especially when this intervention is paired with braces.

Objective: We aim to compare the efficacy of bracing and a conventional exercise program to a combination treatment that includes trunk bracing and exercises with a cantilever device performed at home on the degree of spine curvature, pulmonary function, trunk muscular endurance, and quality of life.

Methods: This study was a 2-arms parallel-group clinical study. A total of 16 adolescents with idiopathic scoliosis and single lumbar and thoracolumbar curves of 20°-45° were recruited and randomly assigned into 2 groups. Group A received a combination of trunk bracing and exercise using an instrument known as a “cantilever.” Group B (controls) received trunk bracing and a conventional exercise program (without a tool). The study outcomes were the Cobb angle of the scoliotic curve, pulmonary function, the endurance of the trunk muscles, and quality of life. The study outcomes were measured at 2 time points: before the intervention (T1) and 12 weeks following the start of the intervention (T2; at this time, the intervention period has been completed). Multivariate analysis of variance was used to test between- and within-group differences.

Results: Recruitment for this study began in fall 2022 and is expected to be completed by the end of summer 2023.

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Conclusions: We studied the efficacy of a combined trunk bracing program and postural response exercises using a cantilever device in treating adolescent idiopathic scoliosis and compared it with trunk bracing and conventional home exercises. Exercises performed at home using a cantilever device are anticipated to raise the endurance of trunk muscles, which will help reduce trunk deformity, enhance pulmonary function, and improve the quality of life of participants.

Trial Registration: Iranian Registry of Clinical Trials IRCT20220330054371N1; https://www.irct.ir/trial/62811

International Registered Report Identifier (IRRID): PRR1-10.2196/43265

(JMIR Res Protoc 2023;12:e43265) doi:10.2196/43265

KEYWORDS

home exercise; orthotic device; quality of life; scoliosis

Introduction

Adolescent idiopathic scoliosis (AIS) is a 3D spine deformity with an unknown etiology [1]. It is stated that 0.47%-5.2% of people aged between 11 and 18 years have an AIS [2]. Typical side effects of scoliosis include apparent trunk deformities, pulmonary restriction, muscular weakness, activity limitations, and a decline in health-related quality of life [3,4]. The current treatment goals for AIS include preventing the progression of the deformity, resolving the scoliosis curve, and improving quality of life [5]. Treatment options for AIS vary depending on the degree of spinal curvature and skeletal growth [1]. Physiotherapy, exercise, and monitoring techniques are often used with patients with curves less than 20°, especially those with substantial remaining skeletal growth [6]. Trunk bracing and exercises are prescribed for curves between 20° and 45° to promote soft tissue flexibility and enhance the functions of muscles that support the trunk [6,7]. Surgical correction is a typical treatment for curves greater than 45° [6].

A major concern with AIS is the loss of motor control, which can manifest as asymmetrical or weak muscles [8]. Also, abnormal breathing patterns are observed in those with AIS, which can exacerbate the scoliosis deformity [7,9]. People with scoliosis frequently have less strength and endurance in their trunk muscles than people without the condition [10]. Therefore, exercise therapy is often regarded as the cornerstone of recommended treatment for AIS [11].

Trunk bracing is the most prevalent nonoperative method for preventing curve progression in mild to moderate AIS (ranging from 20° to 45° Cobb angles) [12]. Evidence suggests that the effectiveness varies with different brace types [13]. Rigid braces have shown superior effects in preventing curve progression than nonrigid braces [13,14]. The external corrective forces delivered via a rigid brace reduce asymmetric spine loading and thereby prevent asymmetric growth [15]. The rigid bracing can limit the user's physical activity, resulting in a loss of muscular strength and endurance over time [16,17]. The long-term use of a stiff brace may impede rib cage expansion and decrease lung capacity [18,19]. The study agrees that using selective exercise can compensate for the adverse effects of rigid trunk bracing on muscular and respiratory functions [16,20-22]. Activation of the muscles involved in spinal stabilization can be beneficial in reducing the risk of treatment failure in AIS [23]. Providing expanding chambers in conjunction with pressure zones is a feature of innovative brace designs like the Cheneau that help to activate muscles inside the brace [24].

Scoliosis treatment guidelines recommend home exercise as an adjunct to brace therapy [22]. Physical training enhances the effects of the brace by increasing muscular strength and endurance and removing the drawbacks of trunk bracing as a single treatment [21,25]. Moreover, exercise reduces the curve's progression and improves pulmonary function and the quality of life of people with AIS [21]. Recent ideas on conservative scoliosis therapy suggest that therapeutic exercise should be specifically tailored to modify the motor control of the spine [21]. It has been substantiated that the brain and spine do not communicate effectively in AIS [21,26]. The incorrect perception of gravity could affect muscle tone and cause spinal curvatures [26]. Postural response training is thought to improve the activation of spinal muscles and balance the body against external forces [5,21,26]. An apparatus known as a "cantilever" is typically needed for postural response training to apply external forces to the body during repeated exercise [26]. According to prior research, there is little study on the efficiency of combination brace and exercise therapy in AIS [13,22]. Furthermore, a thorough search of the literature by the authors also discovered that no prior research has yet evaluated the effectiveness of postural response training paired with trunk bracing. This study compares the efficacy of combination bracing and conventional exercise with combined bracing and postural response training. It has been hypothesized that postural control training will improve the functioning of the spine's muscles, which will help to straighten the spine, increase chest space, enhance respiratory function, and eventually enhance an individual's quality of life.

Methods

Study Design

This prospective study was a 2-armed, participant-blinded, randomized controlled trial (intervention vs control group) performed to investigate the objectives. The study procedure was reported using the TIDieR (Template for Intervention Description and Replication) checklist and associated guidelines. The Intervention Description and Replication checklist outlines a consistent method for meticulously recording information and enables authors to define treatments precisely in their research [27]. The CONSORT (Consolidated Standards of Reporting Trials) checklist was used to report data effectively in a clinical trial [28].

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Setting

Participants were consecutively recruited from individuals with AIS, Risser sign 0-2, and Cobb curvature 20°-45°, and were referred to a spine specialist (author AA) for their first evaluation in the Orthopedic Clinic at Al-Zahra Hospital in Isfahan, Iran.

Sample Size

A total of 16 adolescents with single lumbar and thoracolumbar curves of 20°-45° and idiopathic scoliosis were recruited for the study. Based on the findings of an earlier study, the ideal sample size was calculated [29]. The Cobb angle was reported as 24.26° (SD 1.96°) for the intervention group and 26.59° (SD 3.57°) for the control group, respectively [29]. We calculated the sample size using G*power software (version 3.1.9.4, Universität Düsseldorf) and determined that 7 subjects in each trial arm would provide 60% power once α was set at .1. We also considered a 10% overall dropout rate (eg, lost to follow-up). Consequently, we aimed to recruit 16 individuals (8 in each study arm).

Participants

A simple (convenient) sampling method was used to recruit the AIS individuals with single lumbar and thoracolumbar curves of 20°-45° at the orthopedic clinic. Physical assessments and spine x-rays taken by an orthopedic specialist were used to confirm the diagnosis of AIS [30]. The following are the inclusion requirements of the study: Risser sign (0-2) [31], a single moderate scoliosis curve (20°-45°) in the lumbar or thoracolumbar regions [32], physical and mental capacity to use braces and exercise equipment [33], the absence of AIS treatment in the preceding year [34], and physician approval to take part in the study. The exclusion criteria are as follows: deformities in the lower extremities [35]; having neuromuscular conditions like cerebral palsy, spina bifida, muscular dystrophy, congenital myopathy, and any other illness that prevents them from exercising [33]; and people with any history of surgery, trauma, fractures, or other spine injuries [33,35]. The parent of each eligible participant signed an informed consent form before the study. Participants were allowed to withdraw from the study at any time.

Assignment, Randomization, and Blinding (Masking) Procedures

After verification of eligibility, participants were randomly assigned to one of 2 groups: (1) the intervention group (combined brace and home-based exercise aid; n=8) or (2) the control group (brace and scoliosis exercise program at home; n=8). Block randomization was used, 4 blocks with a block size of 4, to achieve balance in allocating participants to study arms [36]. The assessor uses Random Allocation Software for the randomization process (version 1.0) [37]. This study is single-blinded, so the measurement of the curve angle was undertaken by blinded assessors. The assessors measured the curve angle without being aware of the group assignment or individual information.

Adverse Events and Dropouts

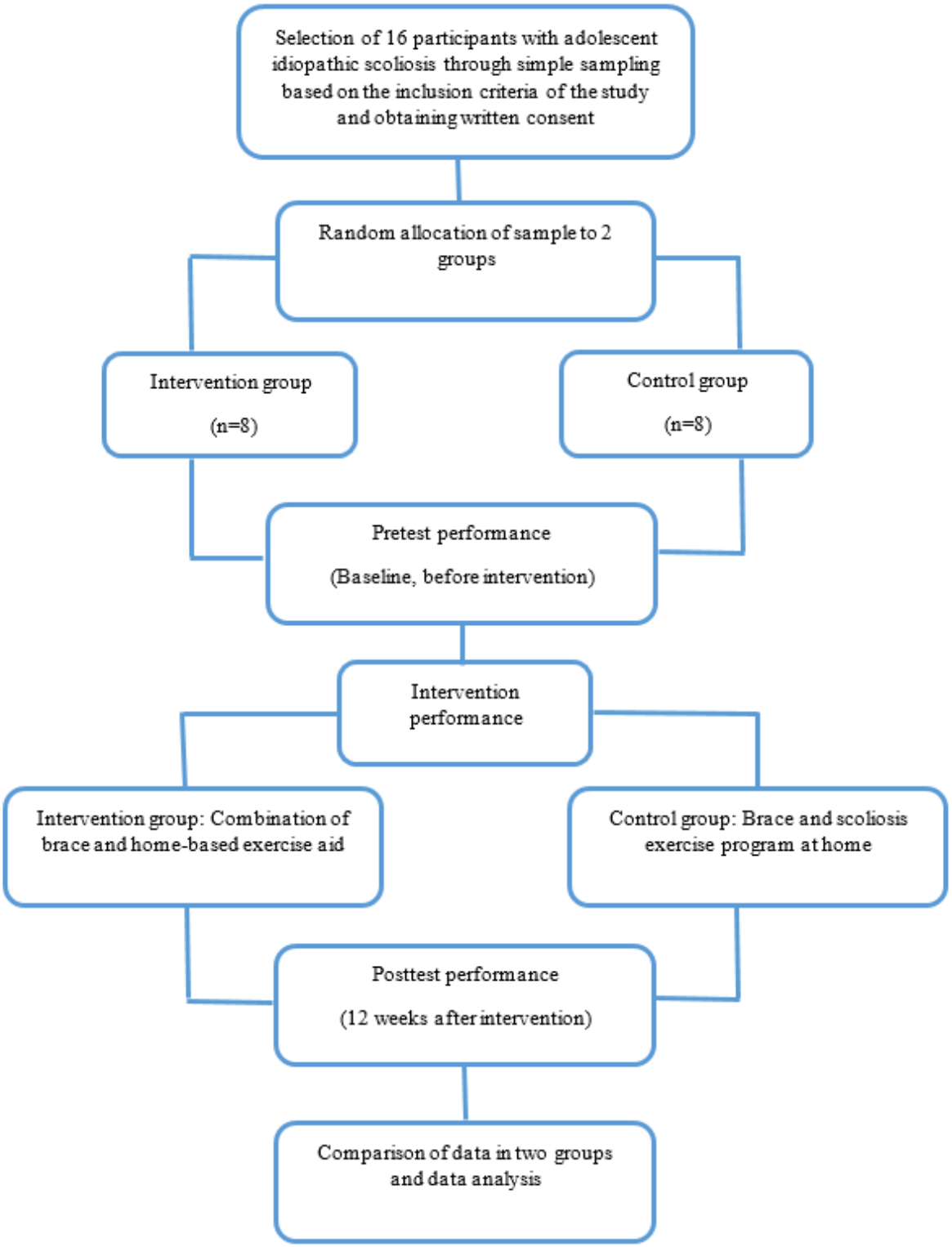
Adverse events were acknowledged and documented throughout the study to ensure participant safety. The final report summarized adverse event information, including the date and the participant's experience. The details of research participants who dropped out were recorded. Furthermore, the causes of dropout, including COVID-19 symptoms, loss of follow-up, and illness, were disclosed.

Study Arms and Content

There were 2 study arms. For the intervention group, the first arm received a combination of brace and home-based postural response training. For the control group, the second arm received a brace and a traditional scoliosis exercise program at home. The outcomes include Cobb's angle of curvature, pulmonary function, the endurance of the trunk muscles, and quality of life index. The study outcomes were measured at 2 time points: baseline, before the intervention (pretest), and 12 weeks after the intervention began [38] (posttest; at this time, the intervention period has been completed). Figure 1 presents the study process.

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Figure 1. The study flowchart for the randomized controlled trial.



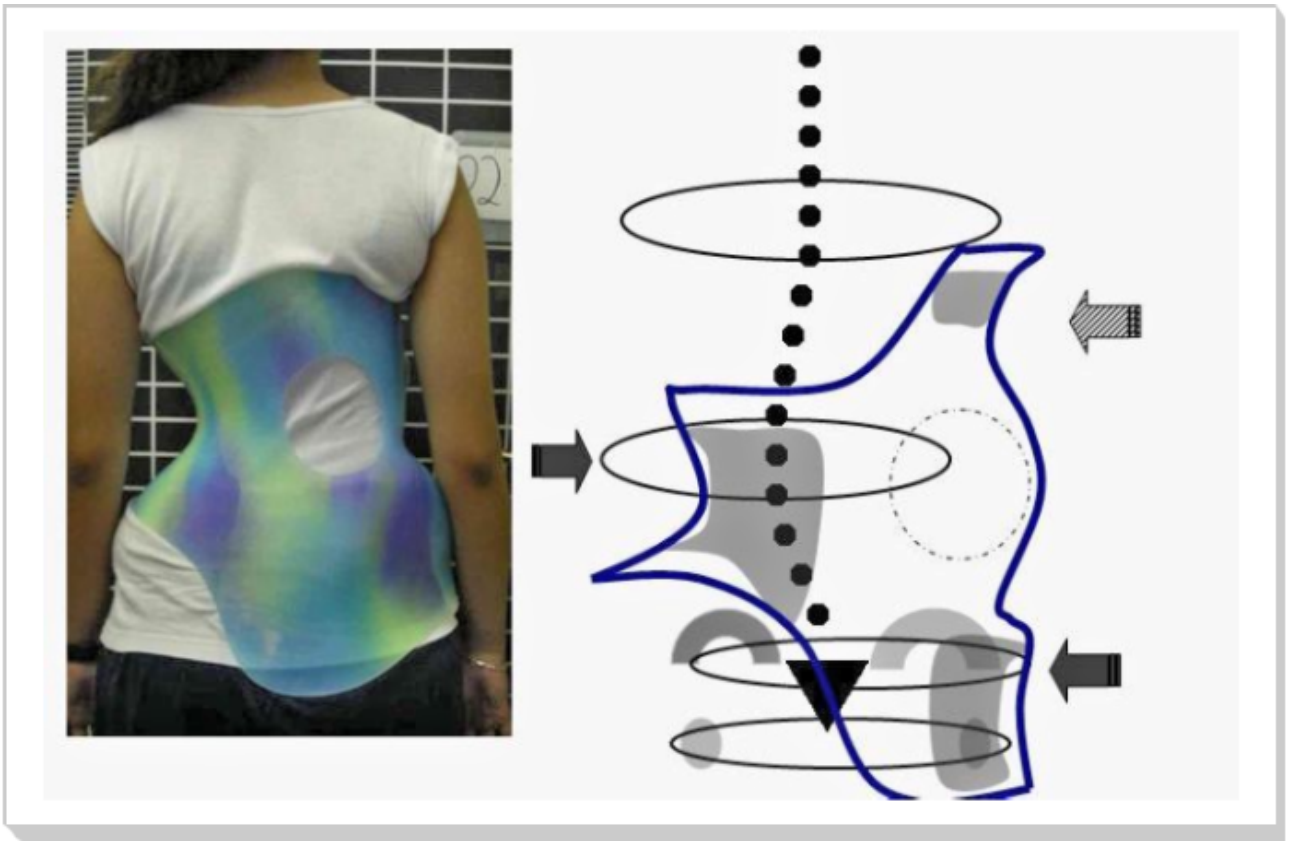
Intervention

Cheneau Brace

Cheneau is a rigid trunk brace used to treat AIS [24]. This thoracolumbosacral brace is made of polypropylene with an anterior opening (Figure 2). The Cheneau brace applies pressure on the convexity of the curve and shifts the spine to the normal alignment. The brace walls allow the overcorrection of the curvature; thereby, the user can perform in-brace muscle contraction and therapeutic exercise [24,39]. In this study, all braces are single lumbar and thoracolumbar, also called E1 and E2, respectively [40]. The E-type Cheneau braces for single lumbar or thoracolumbar curves (Figure 2) are custom-molded orthoses that were fabricated by a qualified orthotist. The brace users were instructed how to wear it and asked to wear it full-time during the trial course.

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Figure 2. The E-type Cheneau brace for a single lumbar-thoracolumbar curve pattern [40].

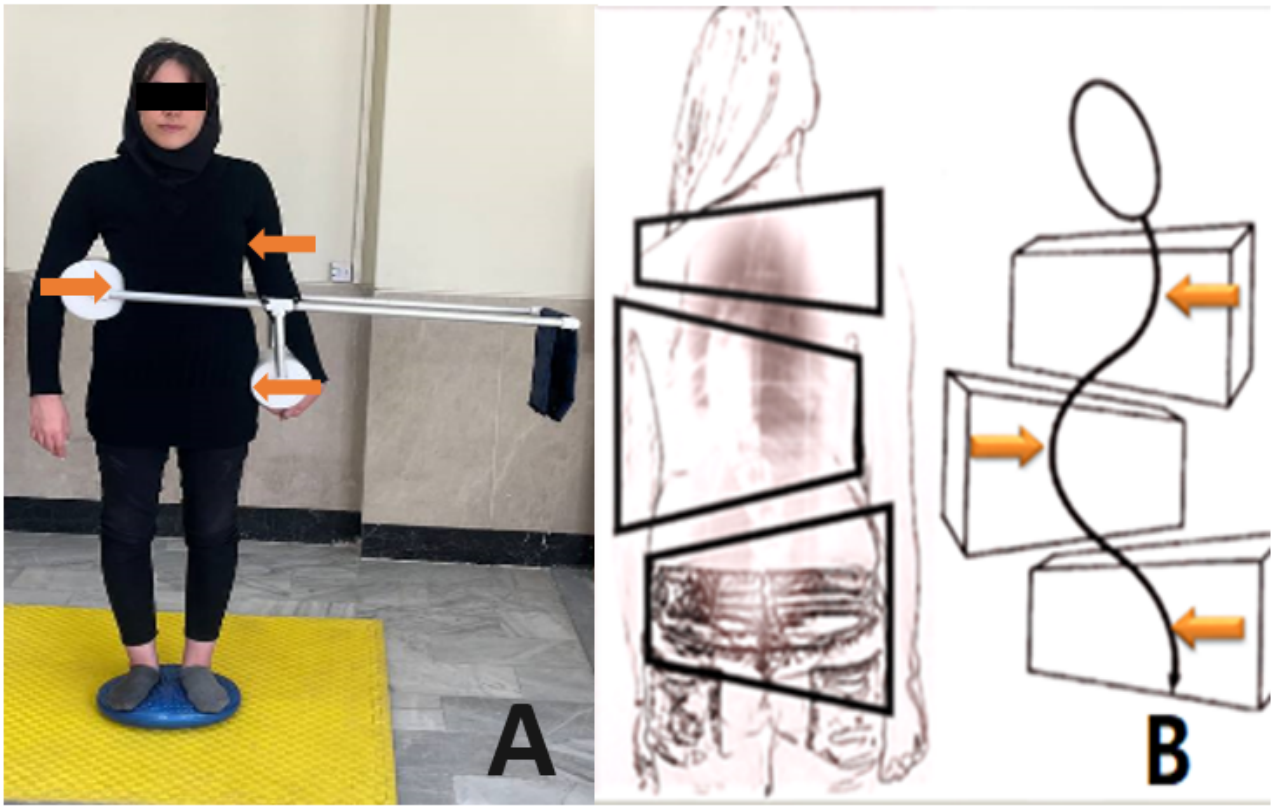


Cantilever Device

In this study, postural response training for individuals with AIS was carried out using a torso trainer device known as the "cantilever" (Figure 3). The cantilever device increases the mechanical advantage of the corrective forces applied to the trunk for curve correction [26]. The 3 pressure points that make up the system's correcting mechanism (Figure 3A) provide transverse force to the spine in order to reduce deformity [26]. Each cantilever device was customized by an orthotist to fit the size of each unique user and has a robust tubular structure (as shown in Figure 3A). Low-density polyurethane was used for the device's pads. The thoracic pad of the device was fitted on the convex side of the deformity, while the lumbar pad is located between the lower ribs and the iliac crest. To enhance the resistance during an incremental training program, up to 4-pound weights can be applied at the end of the lever.

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Figure 3. (A) The cantilever device and (B) the 3-point system for correction of deformity [41].



Postural Response Training

This exercise is to modify the activity pattern of the muscles to stabilize the spine. It has been reported that response training could enhance the role of proprioceptive feedback in detecting spinal misalignment [26]. Therefore, postural response training is expected to help regulate the appropriate muscle activity in people with AIS [26,42]. There are 3 phases in each session for postural response [42] as outlined in Textbox 1.

Textbox 1. Three phases of postural response training.

- Participants will first attempt to slide their hand down their outside leg, on the convex side of the curvature while standing. After holding this flexed position for 15 seconds, they will return to the starting position. Participants will complete this workout 20 times with a 15-second break between each repetition.
- Participants will carefully put on the cantilever device during the second phase, placing the pressure pads where the therapist had instructed them and adjusting the length of the levers and the weight distribution. Then participants will stand on a vestibular disk and attempt to adjust their spine toward the convexity of the curve by using a cantilever device so that the weight hanging on the device is at the horizontal level. After holding this level position for 15 seconds, they will return to the starting position and rest for 15 seconds. Participants will perform this workout 10 times, followed by a 5-minute break. This process will be repeated 4 times so that the total training time of the second phase lasts 40 minutes.
- In the last stage, the participants kneel on the floor with their buttocks resting on the heels and stretch their arms as far forward as they can. They hold this posture for 15 seconds.

Conventional Scoliosis Exercise

The exercise outlined in Textbox 2 was instructed to each participant and carried out under a physiotherapist's supervision. These exercises are designed based on the literature on exercise for AIS [43,44].

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Textbox 2. Steps of conventional scoliosis exercise.

- The participant will face backward on a chair. Sitting far back, they hold hands on the back of the chair, elbows sideways and upwards. The knee on the convex side will be held further back for pelvic derotation. The head and trunk will lean to the convex side.
- The participant is in side-lying on the concave side with the arm stretched underneath the head.
- The participant kneels on the floor with thighs vertical and arms extended forward in a V-position, then brings the upper chest toward the floor.
- The participant will place on all 4 limbs. The participant performs a breathing exercise and simultaneously rotates the trunk to correct the scoliotic curve.
- The participant will be placed in the lateral side-lying position so that the concave side faces the floor. The elbow will be bent, and the arm will support body's weight. The participant then tries to lift the pelvis and correct the spinal curve.
- Participants will sit on a chair with their backs on the wall. Participants will keep their feet together, arms stretched, elbows straight, and hands touching the wall from behind. They lean forward with their trunk as far as possible, without losing the contact between their hands and the wall.

Outcome Measures

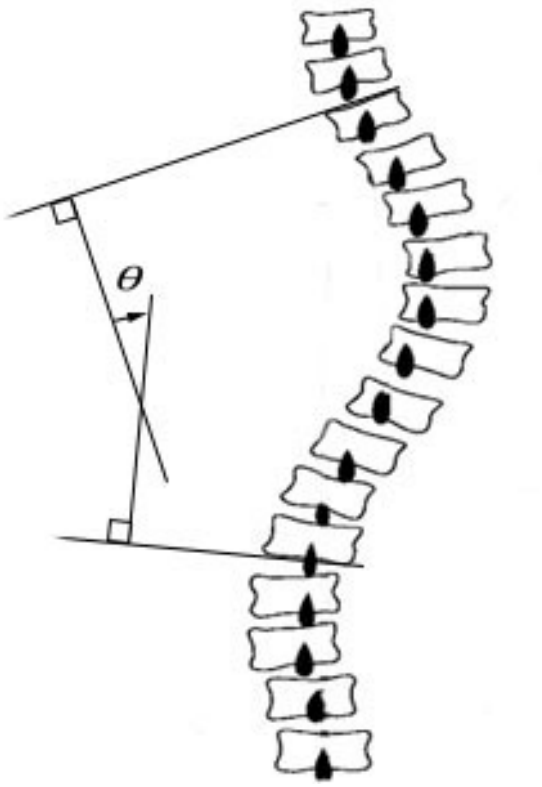
The study outcome measures were calculated throughout the course of 2 sessions. All tests were conducted with a certified orthotic practitioner before intervention (baseline) and after 12 weeks of follow-up required to complete the intervention (posttest).

Primary Outcome Measures

Spinal Deformity

The lateral deviation of the spine in the frontal plane was measured using the Cobb angle. This method is the gold standard for correctly identifying, assessing, and predicting the progression of the scoliosis curve [30,45]. An orthopedic specialist manually measured the Cobb angle using an anteroposterior spine x-ray. The Cobb angle was measured by drawing an end-point line at the upper and lower end of the scoliosis vertebrae. The Cobb angle (Figure 4) is the intersection of the 2 vertical lines drawn on each end-point line [30].

Figure 4. Measurement of the Cobb angle (ϕ).



Secondary Outcome Measures

Pulmonary Function

A digital spirometer (HI-301, Chestgraph, Japan) was used to evaluate pulmonary function. The spirometer was used to measure the following parameters: forced vital capacity, peak expiratory flow, forced expiratory volume in 1 second, vital capacity expiratory, vital capacity inspiratory, total lung capacity, and vital capacity. The participants were instructed to take off the brace at least 2 hours before the test. Spirometry is conducted while the patient is seated in a chair [46]. Each

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participant was asked to do a regular inspiration first. The participants took a deep exhalation after the mouthpiece of the gadget was put in his mouth. The experiment ended once the participant has had a deep inspiration, a deep expiration, and a deep inspiration. Care was taken during the test to keep the mouth and the device's input together. The time between her inspiration and exhalation should not be broken, and a thorough exhalation should continue for at least 6 seconds [46]. This test was measured 3 times, and the average values were reported for data analysis. Each participant was given 2 minutes of resting time between trials. All tests were administered at the same time during the day in a quiet location, and participants were asked to refrain from engaging in strenuous exercise prior to testing.

The Trunk Muscles' Endurance

The lumbar trunk muscle endurance test was used to measure trunk flexor and extensor endurance, while the side-bridge test measured lateral trunk flexor endurance.

The next assessment was carried out to evaluate the patient's flexor muscle endurance [47]. Each participant was instructed to lie on a flat surface in the supine position and elevate their lower limbs off the ground while maintaining a 90° flexion angle in both the hip and knee joints. Then participant strives to remove both scapulae from the flat surface by maintaining maximal neck flexion as their arms are positioned crosswise on their chest (Figure 5). The patient was instructed to lie prone on a flat surface, elevate the sternum from the surface, and maintain maximal neck flexion to test the patient's trunk extensor muscle endurance [47]. To lessen lumbar lordosis, a cushion was positioned beneath the lower abdomen (Figure 6).

Next, the participants were requested to lie on their lateral side to assess the strength of the lateral muscles in the trunk. The individual rises the upper body and pelvis straight from the surface, while the forearm and leg bear the body's weight (Figure 7). The participant keeps this position as long as possible, and the examiner records the time before the pelvic drops [48]. This test was repeated for the opposite side, and a 5-minute rest was given between 2 trials [48].

Figure 5. Endurance test of trunk flexor muscles.



Figure 6. Endurance test of trunk extensor muscles.



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Figure 7. Endurance test of trunk lateral flexor muscles.



Quality of Life

Quality of life was measured using the Persian version of the Italian Spine Youth Quality of life [49]. This questionnaire has good validity and reliability (intraclass correlation coefficient ≥0.7) to use for people with AIS [49]. This questionnaire includes 13 spinal health–related questions and was filled out by each participant. The responses to each question were quantified based on a 3-point rating scale (0-2) with 3 possible replies (never, sometimes, often). The quality of life ranged from 0 to 26, with 0 being the best quality of life [50].

Demographic and Clinical Data

Age; weight; height; BMI; and the type, location, degree, and magnitude of the scoliosis curve as well as the Risser sign, were prospectively gathered and noted on report forms.

Data Analysis

Analysis of covariance was used to compare how well each treatment influenced the outcomes of the study. Trunk bracing with postural response training versus bracing with regular exercise is the independent variable, and the dependent variables are study outcomes recorded after the exercise protocols were completed. In these statistical analyses, the covariant is the baseline measurement of the research results among the individuals. The preliminary statistics were carried out to ensure that the assumptions of normality, linearity, homogeneity of variances, homogeneity of regression slopes, and accurate measurement of covariates are not violated. Statistical analyses were conducted using the SPSS (version 19; IBM Corp). The level of significance was set at .05 for all tests.

Ethics Approval

The Isfahan University of Medical Sciences Regional Ethics Committee approved the study protocol (IR.MUI.NUREMA.REC.1401.025). Then, the research protocol was registered in the Iranian Registry of Clinical Trials on May 9, 2022 (IRCT20220330054371N1).

Results

Recruitment for this study began in fall 2022 and is expected to be completed by the end of summer 2023.

Discussion

Overview

It is well acknowledged that expected scoliosis consequences include dysfunction of motor control, which could demonstrate asymmetrical or weak muscles [8], less muscular strength and endurance [10], and abnormal breathing patterns [7,9]. Consequently, exercise therapy and conditioning are consistently indicated as a necessary element of AIS treatments [11].

Trunk bracing is the most popular nonoperative technique to prevent curve progression in mild to moderate AIS (from 20° to 45° Cobb angle) [12]. Evidence, however, indicates that rigid bracing might restrict a user's physical activity, which can lead to a loss of muscle strength and endurance [17]. Besides, rigid trunk bracing could impede rib cage expansion and reduce lung capacity [19]. Exercise can mitigate the negative impact of rigid trunk bracing on muscular and respiratory functions [20-22]. The study agrees that specific exercise can counteract the adverse effects of rigid trunk bracing on the respiratory and muscular functioning of people with AIS [20,21].

Therapeutic exercise appears necessary as part of conservative scoliosis treatment focusing on changing the spine's alignment control [21]. An incorrect perception of gravity can affect muscle tone and cause spinal curvatures [26]. Postural response training aims to change how one feels gravity and how active one's trunk muscles are. Future research is necessary because there is little research that supports the effectiveness of this approach.

Strengths and Limitations

The study's most noteworthy strength is the combination of trunk bracing and exercise in the treatment of AIS. There is limited research on the benefits of trunk bracing with exercise therapy [13,22]. The Cheneau brace and postural response

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training were developed using an active strategy for curvature correction [26]. According to this strategy, individuals with AIS should practice aggressively using their trunk muscles to keep their spine in a normal alignment [44]. Compliance with the intervention may be one of the most significant difficulties in the present study. Through phone calls or SMS text messages, authors strived to keep track of each participant's commitment to brace wearing and exercise and record that information in the logbook.

Acknowledgments

The authors gratefully acknowledge the research deputy of Isfahan University of Medical Sciences for supporting this study.

Data Availability

The data sets generated or analyzed during this study are available from the corresponding author upon reasonable request.

Authors' Contributions

All authors contributed substantially to the conception and design and drafted the paper. Eligibility criteria of participants was confirmed under the supervision of AA and ZR completed data collection and analysis with guidance from ES-D and FB All authors reviewed and revised the paper for important intellectual content and approved the final version.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review report from Isfahan University of Medical Sciences - Vice Chancellery for Research and Technology (Isfahan, Iran).
[PDF File (Adobe PDF File), 171 KB - resprot_v12i1e43265_app1.pdf]

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Abbreviations

AIS: adolescent idiopathic scoliosis.
CONSORT: Consolidated Standards of Reporting Trials
TIDieR: Template for Intervention Description and Replication

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Protocol

Criteria for Advanced Prosthetic Foot Prescription: Rationale, Design, and Protocol for a Multisite, Randomized Controlled Trial

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Abstract

Background: The prescription of prosthetic ankle-foot devices is often based on the professional judgment of the limb loss care team or limited evidentiary research. Current prosthetic research efforts have focused on the design and development of prosthetic devices rather than on understanding which devices are the most appropriate to prescribe. This investigation will evaluate biomechanical, functional, and subjective outcome measures to help determine the optimal prescription parameters of prosthetic ankle-foot devices.

Objective: This study aims to develop evidence-based guidelines for limb loss care teams for the appropriate prescription of commercially available prosthetic ankle-foot devices to improve function and satisfaction.

Methods: This investigation will be a multisite, randomized, crossover clinical trial targeting the enrollment of 100 participants. Participants will use 3 different types of prosthetic devices (energy storing and returning, articulating, and powered) in random order. Participants will be fitted and trained with each device and then separately use each device for a 1-week acclimation period. Following each 1-week acclimation period, participants will be evaluated using several functional measures and subjective surveys. A random subset of participants (30/100, 30%) will also undergo full-body gait analysis, following each 1-week acclimation period, to collect biomechanical data during level ground and incline and decline walking. After all individual device evaluations, participants will be given all 3 prostheses concurrently for 4 weeks of home and community use to capture user preference. Activity monitoring and a guided interview will be used to determine overall user preference.

Results: The study was funded in August 2017, and data collection began in 2018. Data collection is expected to be completed before July 2023. Initial dissemination of results is expected to occur in the winter of 2023.

Conclusions: By identifying biomechanical, functional, and subjective outcomes that are sensitive to differences in prosthetic ankle-foot devices, a benchmark of evidence can be developed to guide effective prosthetic prescription.

Trial Registration: ClinicalTrials.gov NCT03505983; https://clinicaltrials.gov/ct2/show/NCT03505983

International Registered Report Identifier (IRRID): DERR1-10.2196/45612

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KEYWORDS

limb loss; amputation; prosthetic prescription; prosthetic ankle-foot devices; lower extremity

Introduction

Background

More than 1700 service members have experienced combat-related limb loss since the beginning of Operation Iraqi Freedom, Operation Enduring Freedom, and Operation New Dawn [1,2]. Most of these service members are now veterans, and 95% of veterans with limb loss from these conflicts use the Veterans Affairs (VA) Healthcare System within 5 years of separation from active duty [3]. VA has a responsibility to serve this unique population for their lifetime and provide care to an additional 41,000 veterans who have lower limb loss at levels proximal to the ankle [3]. At VA, most major limb amputations have resulted from the increase in aging veterans with dysvascular disease and diabetes mellitus [4]. For those receiving prosthetic ankle-foot devices, providers within the limb loss care teams have >100 commercial devices available for prescription [5]. Unfortunately, there are limited evidence-based guidelines available to aid clinicians in prescribing appropriate componentry. As such, prescription tends to be governed largely by professional judgment of the limb loss care team or available research, which tends to be noncommittal or lacks the guidance required for clinical practice [6].

Clinical Consensus for Prosthetic Prescription

As prosthetic ankle-foot devices have evolved over the last 2 decades, clinical prescription has remained a complex and challenging process. Comparative studies have been contradictory or noncommittal, which makes evidence-based prescription difficult for clinicians. In 2004, a Cochrane review was conducted to determine whether a clear clinical consensus on prescription criteria could be determined for various prosthetic ankle-foot devices for individuals with lower limb loss [7]. Review of 23 trials concluded that there was insufficient evidence from high-quality comparative studies to develop or establish criteria for the prescription of prosthetic ankle-foot devices. In 2005, Hafner [8] evaluated clinical prescription and the use of prosthetic ankle-foot mechanisms in the literature, again concluding that the available studies had limited applicability for clinical decision-making. The author suggested that future studies that aim to develop guidelines to prescribe prosthetic devices should include a large sample size and standardize the devices based on shared characteristics or mechanical behaviors. In 2012, Schaffalitzky et al [9] gathered expert opinions on the most important outcomes, predictors, and facilitators of lower limb prosthetic prescription and use. The investigators and an expert panel of 21 service providers and users identified 13 outcomes, 19 predictors, and 34 facilitator factors that can contribute to an evidence base for optimal prosthetic prescription. While highlighting the importance of a comprehensive evaluation, including physical, psychosocial, and environmental outcomes, a universal solution was not identified for optimal prosthetic prescription; however, it is unclear whether all users would benefit from a universal prescriptive solution [9]. Finally, a Cochrane review in 2018, which aimed to investigate the evidence from randomized controlled trials of individuals with lower limb loss, found that the scientific literature did not provide sufficient high-quality evidence to allow strong conclusions about the effectiveness of prosthetic intervention [10]; however, many nonrandomized controlled studies were excluded from the analysis.

Prosthetic Ankle-Foot Device Categories

Despite the lack of scientific guidelines for appropriate prosthetic prescription, energy storing and returning (ESR) ankle-foot devices are the current gold standard for prescription within VA and the Department of Defense (DoD). Individuals with transtibial limb loss using ESR devices have demonstrated faster walking speeds and reduced cost of energy during ambulation compared with those using traditional prosthetic device options, such as the solid ankle cushion heel and stationary attachment flexible endoskeletal feet [11]. Similarly, the use of ESR devices has been shown to improve elastic response [12], reduce the requisite activation for propulsory muscles [13], and improve stair ascent initiation by reducing the time of initial double-limb support [14]. Although there are various types of ESR devices with distinct mechanical features, there remains insufficient evidence to support the prescription of specific prosthetic ankle-foot devices within this overarching classification [15-17]. Moreover, discrete parameters derived from common kinetic and kinematic biomechanical analyses often lack statistically significant differences between these ESR devices [8].

More advanced ESR devices are also commercially available, including passive hydraulic or microprocessor-controlled articulating ESR (ART) ankle-foot devices. Although ART ankle-foot devices have been typically reported to decrease energy return in individuals with transtibial limb loss, there is recent evidence suggesting that current devices can improve ambulation on level ground and on inclines and stairs [15]. For example, De Asha et al [18,19] described improved progression of the center of pressure in a prosthetic ankle-foot device with a hydraulic ankle compared with devices with a fixed attachment in a population of individuals with lower limb loss. Portnoy et al [20] found decreased load at heel strike when using an ESR hydraulic ankle-foot device compared with a conventional ESR device. Fradet et al [21] reported that a microprocessor-controlled ankle-foot device set to adaptive ankle mode improved kinematics during ramp ascent compared with the same device when set in neutral angle mode. This evidence suggests that individuals with lower limb loss who negotiate specific environments may benefit from an ART device.

Commercially available ESR ankle-foot devices with active (ie, powered) plantarflexion have potential biomechanical benefits for the user beyond that of the ESR or ART ankle-foot options.

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Empower (Ottobock Inc), the only commercially available powered ESR ankle-foot device, functions to replicate the dynamic contractile tissues of the gastrocnemius-soleus complex in individuals with lower limb loss [22,23]. This powered prosthetic ankle-foot device has the ability to normalize ankle power, which can potentially reduce kinetic asymmetries that lead to musculoskeletal imbalances, thus improving physical function [22,24]. Grabowski and D'Andrea [25] noted that individuals with transtibial limb loss had a reduction in peak resultant forces and knee adduction moments in the unaffected limb during level ground walking when using a powered ESR device (iWalk BiOM) versus a passive ESR device. These reductions could potentially limit the risk of secondary musculoskeletal comorbidities, which are common in this population [26].

Despite the noted advances in prosthetic technology, research efforts so far have largely focused on the design and development of prosthetic technology, rather than on understanding which devices are most optimal to be prescribed for individuals with lower limb loss. Moreover, many studies are limited by small sample sizes, the nonstandardization of device characteristics, and the use of outdated components, which collectively reduce the direct applicability of scientific evidence to clinical decision-making [8]. Through a multicentered clinical trial with a large sample size (N=100), standardized categories of prosthetic ankle-foot characteristics, and the evaluation of outcomes both within laboratory and community-based settings, this research investigation will comprehensively evaluate biomechanical, functional, and subjective outcome measures to help aid in determining optimal prescription parameters of prosthetic ankle-foot devices. Health care, according to comparative effectiveness research, is under constant pressure to become more efficient and effective, while reducing overall cost. The lack of evidence-based scientific guidelines to support lower extremity prosthetic prescription is a critical inefficiency. By identifying biomechanical, functional, and subjective outcomes that are sensitive to differences in prosthetic ankle-foot devices, a benchmark of evidence can be developed to guide effective prosthetic prescription.

Study Objectives

The overarching goal of this investigation is to generate data that offer new knowledge that can be used to improve current clinical practice guidelines and develop new prescription algorithms for prosthetic ankle-foot devices. This information will lead to clinical prescriptions that facilitate the achievement of maximal functional ability and user satisfaction. Criteria will be developed to assist the limb loss care teams in prescribing appropriate, advanced prosthetic ankle-foot devices based on patient-specific needs and goals, in addition to the individual's current physical abilities. Therefore, the purpose of this investigation is to develop the criteria for prosthetic ankle-foot prescription for veterans and service members with transtibial limb loss. The objectives of this investigation are as follows:

1. To determine the appropriate functional and biomechanical outcome measures to support the prescription of a type or category of prosthetic ankle-foot device for veterans or service members with transtibial limb loss
2. To correlate patient goals and subjective measures with objective data to determine the appropriate prosthetic ankle-foot category that will facilitate the greatest overall function for the user
3. To develop criteria for the appropriate prescription of nonarticulating ESR, ART, and powered plantarflexion ESR ankle-foot devices

Methods

Study Overview

This investigation will be a prospective, multicenter study, including 4 sites: Veterans Affairs New York Harbor Healthcare System (VANYHHS), Veterans Affairs Puget Sound Healthcare System, James A Haley Veterans' Hospital (JAHVH), and Walter Reed National Military Medical Center (WRNMMC). Enrollment began in 2018, and data collection is expected to be completed in 2023. A total of 100 participants will be enrolled from the 4 sites. Briefly, participants will use 3 different types of prosthetic ankle-foot devices (refer to device categorization in the following sections) with duplicate sockets. Participants will be fitted and trained with each device and then separately use each ankle-foot device for a 1-week acclimation period. Participants will only use the assigned study device for each acclimation period. Although previously reported acclimation periods for lower extremity prosthetic device studies have ranged from minutes to months depending on componentry [27-30], this study will use a 1-week acclimation period to balance the time that participants need to adjust to the features of each ankle-foot device with the overall duration of their participation. To augment the acclimation period, device-specific training will be provided to ensure that participants meet a minimum standard of performance. Following each 1-week acclimation period, participants will be evaluated in the laboratory using several functional and subjective measures. Furthermore, a subset of participants (30/100, 30%) will be randomly chosen to undergo a full gait analysis to collect biomechanical data during level ground and incline and decline walking using each ankle-foot device. Following the 3-week data collection period, participants will be given all 3 prostheses at the same time for 30 days to use at home and in their community. Step activity monitoring during home-based and community-based use and a final guided interview will be used to determine overall user preference.

Participants

In total, 100 individuals with unilateral transtibial limb loss will be recruited for this investigation. Inclusion and exclusion criteria are presented in Textbox 1. All participants will consent to participate before any study activity.

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Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Veteran, service member, or civilian with unilateral transtibial limb loss
- Uses a prosthesis with a well-fitting socket for a minimum of 1 month
- Must achieve at least modified independence score on the Functional Independence Measure for the 2 mobility items (locomotion and stairs)
- Aged >18 years
- Current use of an energy storing and returning device
- Has a minimum clearance to accommodate all devices

Exclusion criteria

- Active wounds, ulcers, or substantial musculoskeletal comorbidities on the intact limb that would impair the ability to participate in all functional outcome measures
- Any comorbidity that results in rapid limb volume changes (eg, end-stage renal disease with dialysis)
- A poorly fitting socket
- Cognitive deficits or mental health pathology limiting an individual's ability to fully participate in the investigation
- Unable or unwilling to comply with all study visits
- Women who are pregnant or who plan to become pregnant during study activities, determined via self-report
- Body mass greater than product capacity

Ethics Approval and Informed Consent

This study was approved by the following institutional review boards (IRBs): Veterans Affairs New York Harbor Healthcare System IRB (protocol ID 1603); University of South Florida IRB (IRB study Pro00030555), which is the IRB of record for James A Haley Veterans' Hospital; Walter Reed National Military Medical Center IRB (protocol ID WRNMMC-2017-0103); and Veterans Affairs Puget Sound Healthcare System IRB (protocol ID 01587). The oversight and protection of human participants was also approved by the US Army Medical Research and Development Command Office of Human Research Oversight (E04076). All participants will provide informed consent before participating in any study activity.

Ankle-Foot Categorization

In accordance with recommendations from previous literature to standardize the categorization of devices according to specific features [8], the prosthetic ankle-foot devices included in this investigation were systematically selected and categorized at the time of study initiation by a diverse panel of experts in the limb loss field, including prosthetists, physiatrists, biomechanists, physical therapists, and limb loss researchers. The panel considered device structure, componentry, function, and biomechanical properties to create ankle-foot device categories. On the basis of the criteria developed by the expert panel for each group, all ankle-foot devices included in this investigation were placed into one of the following three categories:

1. ESR (nonarticulating)—This group includes any qualifying nonarticulating ESR ankle-foot device that is commercially available. As per the inclusion criteria, participants will use their current device for this category. There are >100 commercially available devices that fit the criteria for this category [5].
2. Active plantarflexion ESR (PWR)—This group will include all commercially available ESR ankle-foot devices with active plantarflexion. Currently, Empower (Ottobock Inc) is the only device classified into the PWR group. No new devices that meet the criteria for the PWR group will be included in this investigation after the commencement of active enrollment. However, it is not anticipated that any future powered device will come to the market during active enrollment.
3. ART—This group includes all current, commercially available options in the K3 Medicare Functional Classification System category that have an articulating ankle and ESR properties. Overall, 14 devices that met the criteria were identified at the time of study initiation (Table 1). No new devices that meet the criteria for the ART group will be included in this investigation after the commencement of active enrollment. If any ART device is replaced by the manufacturer with a new generation during active enrollment, the study expert panel will determine whether the new generation can be considered as a replacement device (if not fundamentally distinct). If the new generation of ART device is considered to be fundamentally different from the study ART device by the expert panel, it will not be included as a study device, to reduce confounding variables during analysis. However, the current generation of ART device used in the investigation will be configured to match patient specifications for any future participant who is assigned that ART device.

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Table 1. Articulating energy storing and returning ankle-foot devices included in the study.

Manufacturer	Device
Blatchford	Echelon
Blatchford	EchelonVT
Blatchford	Elan
Fillauer	Motion Foot
Proteor	Kinnex
Proteor	Kinterra
Ossur	Proprio
Ossur	Flex-Foot Balance
Ossur	Proflex Pivot
Hosmer	Raize
College Park	Odyssey K3
College Park	Trustep
College Park	Tribute
College Park	Venture

Justification for Inclusion of Commercially Available ESR Ankle-Foot Devices

ESR Group

Many nonarticulating ESR prosthetic ankle-foot devices have different mechanical features (eg, torsion and vertical shock) that provide for specific Healthcare Common Procedure Coding System classifications, as descried in the *Prosthetic Foot Project* conducted by the American Orthotic and Prosthetic Association [31]. Although subtle mechanical differences may exist between these ankle-foot devices, studies so far have not shown any significant differences in functional outcomes between different nonarticulating ESR ankle-foot devices [32]. More specifically, published literature often reports contradictory results regarding biomechanics and function during level ground ambulation, stair negotiation, and incline and decline ambulation using these ESR ankle-foot devices [15]. Clinical consensus has also shown that patients may have individual preferences for specific nonarticulating ESR ankle-foot devices, but there is no current metric to predict this. Limiting the investigation to one or just a few nonarticulating ESR ankle-foot devices would limit the generalizability of the findings to the overall group of ESR ankle-foot devices. In addition, most patients who ultimately enroll in this investigation often have the opportunity to trial many different ankle-foot devices as part of their standard clinical care, given that prescription is not driven by reimbursement rates within VA and the DoD. For example, the limb loss care teams at VA and the DoD are not required to abide by the Medicare Functional Classification System for prosthetic prescription and can prescribe any device deemed clinically beneficial for veterans and service members. Therefore, the ESR ankle-foot device the participant enrolls with may be their foot of preference within the overall nonarticulating ESR category. Furthermore, prosthetic devices frequently change, update, or can even be taken off the market for another generation of device. Limiting the ESR ankle-foot devices may also risk not investigating the current or future prescription trends in the limb loss care clinics at all 4 study sites.

ART Group

The ART group includes mechanical and microprocessor-controlled prosthetic ankle-foot devices with ESR properties. These ART devices have different ankle ranges of motion, which vary from 9° to 50°. It has been reported that the average range of motion for a healthy individual with an intact lower limb is 20° to 40° of ankle plantarflexion and dorsiflexion [33]. As such, there is no published research so far regarding the ideal ankle range of motion for individuals with transtibial limb loss; thus, all commercially available ART devices that meet the study specifications will be included (Table 1). Although there are studies comparing these ART devices with solid ankle cushion heel and nonarticulating ESR ankle-foot devices, there are no current studies suggesting any differences among the devices within this group and their effect on functional performance.

PWR Group

Criteria for this group include the following: commercially available, articulating, and provides plantarflexion energy during terminal stance at a rate that is greater than the total energy absorbed (ie, >100%). These criteria are currently only satisfied by Empower (Ottobock Inc).

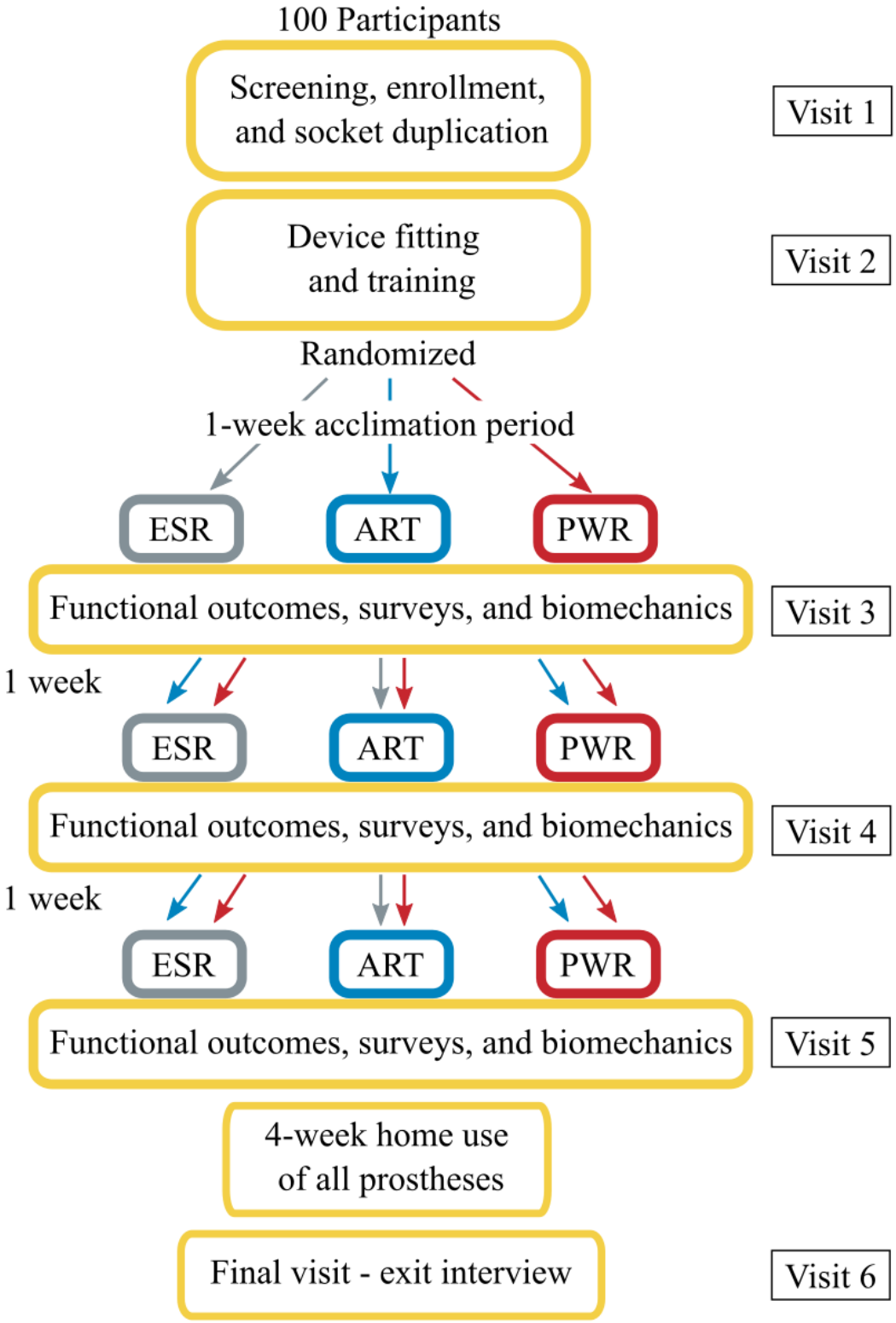
Internal analysis within all groups will be conducted at the completion of this investigation to substantiate or rebut these groupings and to determine whether there are outliers that should be classified differently for future studies.

Research Protocol

The flowchart in Figure 1 outlines the protocol procedures for each participant in this investigation. The following sections describe each participant visit.

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Figure 1. Flowchart of participant protocol visits. ART: articulating energy storing and returning; ESR: energy storing and returning; PWR: active plantarflexion energy storing and returning.



Visit 1—Screening, Consent, Enrollment, and Prosthetic Socket Assessment

Participants (N=100) will be recruited from the rehabilitation and prosthetics clinics at each site. The principal investigator, site–principal investigator, research assistant, research physical therapist, or study prosthetist will meet with interested patients to discuss the investigation and obtain informed consent. Once informed consent has been obtained, participants will be screened according to the inclusion and exclusion criteria and enrolled. Demographic information will be collected, including age, sex, race, ethnicity, height, weight, limb loss etiology, employment, marital status, living situation, and time since transtibial limb loss. A baseline pain measurement using a visual analog scale (VAS) of 0 (no pain) to 100 (worst possible pain) will be performed at the first visit. Fit and comfort of each

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participant's existing socket will be evaluated by the study prosthetist using standardized prosthetic guidelines. Once fit and comfort are confirmed, the study prosthetist will create a mold using plaster of Paris or alginate to fabricate 2 additional, identical prosthetic sockets. All sockets will be centrally fabricated at VANYHHS. Identical materials and prosthetic componentry used in the participant's current socket will be used to create each additional socket to eliminate any variance in perceived weight or socket flexibility. Each additional socket will be aligned with a designated ankle-foot device according to the manufacturer's specifications by the study prosthetist.

Randomization of Ankle-Foot Device Selection and Order of Evaluation

The ankle-foot devices for each participant and the order in which they will be evaluated will be block randomized using a computer-generated algorithm that randomly selects from all available devices and then assigns the order. The randomization will be performed before study enrollment, so that each combination of device order is used an equal number of times. Investigators who process and evaluate the data will be blinded to the data. Owing to the distinct differences between prosthetic ankle-foot devices, the participants and study prosthetists cannot be blinded to which foot is assigned.

Visit 2—Static Fitting, Dynamic Fitting, and Prosthetic Alignment

Participants will return to the prosthetic clinic for fitting of the definitive sockets and prostheses by the study prosthetist. Another subjective pain VAS measurement will be performed at the beginning of the fitting visit, before the participant returns home with an ankle-foot device. All prostheses will initially be bench aligned based on the manufacturer's specifications for a static fitting. After successful static fitting is achieved, the dynamic alignment of each prosthesis will occur. The participant will separately ambulate with each of the prostheses, and adjustments will be made to the alignment, as needed, to achieve an optimal gait pattern, as determined by the study prosthetist and physical therapist. Dynamic fitting may require multiple visits, and participants will progress to the next part of the study protocol after an appropriate dynamic alignment has been established.

Device-Specific Training to Meet a Minimum Standard of Performance

After appropriate fit and alignment of each prosthesis has been established using each ankle-foot device, all participants (100/100, 100%) will undergo device-specific training by a qualified clinician to meet a minimum standard of functional performance. Overall, 2 aspects of the Functional Independence Measure will be evaluated: the ability to walk over level ground and the ability to ascend and descend stairs. To advance in the study, the participant must score 6 (modified independence) or 7 (complete independence) on the Functional Independence Measure. If the participant fails to achieve this outcome, guided rehabilitation to enhance the participant's use of their ankle-foot device will be provided until they are able to meet the minimum standard of performance. The process of device-specific training may require multiple visits. When the minimum standard of performance is met, participants will return home with the first randomized ankle-foot device for a 1-week acclimation period.

Description of the Physical Therapy Plan If the Minimum Standard of Performance Is Not Met

Participants who do not meet the minimum standard of performance using a study ankle-foot device will complete a series of physical therapy training sessions lasting 30 to 45 minutes each during the training period, completing 2 sessions per week, on average. Sessions 1 and 2 will specifically focus on education, strengthening through therapeutic exercises, and early neuromuscular re-education. A home exercise program will be initiated with the participant during the initial sessions and progressed along with the program. Sessions 3 and 4 will include gait training on level surfaces. Sessions 5 and 6 will include continued progression in all areas, including multidirectional training for both neuromuscular re-education and gait. Training will conclude with sessions 7 and 8, during which the previously taught skills will be further challenged and mastered. In addition, advanced gait skills, such as ambulation on stairs and ramps, will be covered. If a participant is unable to meet the minimum standard of performance after receiving physical therapy, they will be unenrolled from the study, as determined by the study physical therapist.

Visits 3 to 5—Functional Assessment of ESR, ART, and PWR Ankle-Foot Devices

Visit 3 will begin after the 1-week acclimation period while using the first assigned ankle-foot device. Participants will complete the VAS pain scale and then a battery of outcome measures and surveys (outlined in the following sections). In addition, during visit 3, a subset of participants will also be randomized to undergo biomechanical gait analysis while using the first prosthesis (described in the following sections). Once visit 3 is completed, the participant will receive the second prosthesis according to the established randomization schedule, and the initial prosthesis will be returned to the study prosthetist. The participant will again complete a 1-week acclimation period. During visit 4, the participant will undergo the same pain scale and battery of outcome measures and surveys. The same subset of participants will also undergo biomechanical gait analysis using the second prosthesis. The third prosthesis will be issued at the end of visit 4, and the second prosthesis will be returned to the study prosthetist. Participants will receive the same 1-week acclimation and will complete the same pain scale and battery of outcome measures and surveys during visit 5. In addition, the same subset of participants will undergo biomechanical gait analysis while using the third prosthesis. For visits 3 to 5, a visit window of –2 to +2 days will be implemented.

Functional and Subjective Outcome Measures

The functional and subjective outcome measures were selected to optimize relevance to the participant population, providers, and health care systems. These measures are commonly used in prosthetic clinics and represent critical information in the functional and subjective domains needed to develop guidelines for prescription. Following the completion of the investigation, the selected outcome measures will be statistically analyzed to

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determine which measures are the most sensitive to changes in device type. The battery of functional outcome measures and subjective surveys collected after each acclimation period will be administered by a local research team member. Functional outcome measures include the 6-Minute Walk Test, Timed-Up-and-Go, Four Square Step Test, Amputee Mobility Predictor, Stair Assessment Index, and Hill Assessment Index. Surveys include the Prosthesis Evaluation Questionnaire, Short Form-12, and Orthotics and Prosthetics Users Survey. These measures are described in Textbox 2.

Textbox 2. Measures included in the study.

6-Minute Walk Test (6MWT)

- 6MWT measures the distance an individual can walk in 6 minutes without help or encouragement. The 6MWT is a valid and reliable metric that correlates with physical function and functional capacity [34] and has good interrater and intrarater reliability in individuals with lower limb loss [34].

Timed-Up-and-Go (TUG)

- TUG measures the time taken by an individual to stand up from a standard armchair, walk 10 feet, turn, walk back to the chair, and sit down. The TUG is both reliable and valid in individuals with lower limb loss [35]. In addition, the TUG has also been used as a measure to determine risk of falling [36] and correlates well with other measures of physical functioning [37].

Four Square Step Test

- Four Square Step Test is a high-order, complex task assessing dynamic balance and has been validated for use in individuals with lower limb loss [38,39].

Amputee Mobility Predictor

- Amputee Mobility Predictor is a 21-item instrument designed to measure basic prosthetic mobility of individuals with lower limb loss [40].

Hill Assessment Index

- Hill Assessment Index is a rated, qualitative scale on how an individual with lower limb loss negotiates up and down an incline [41]. This will be performed on a standardized ramp (rise-to-run ratio of 1:6) with a minimum length of 4.9 m to allow for sufficient number of steps to be taken by the participant.

Stair Assessment Index

- Stair Assessment Index is a rated, qualitative scale for stair negotiation for individuals with lower limb loss [41]. This assessment will be performed while participants ambulate on at least 4 steps that are compliant with the Americans with Disabilities Act (17 cm high, 28 cm long, and 91 cm wide).

Prosthesis Evaluation Questionnaire (PEQ)

- PEQ is self-report, visual analog scale–style questionnaire for individuals with lower limb loss who use a prosthesis. It is used to evaluate the prosthesis and life with the prosthesis. It consists of 82 items with 9 functional domain scales, including ambulation, residual limb health, utility, appearance, sounds, frustration, perceived response, social burden, and well-being. The PEQ also contains items beyond the subscales, including satisfaction, pain, transfers, prosthetic care, self-efficacy, and importance [42].

Short Form-12

- Short Form-12 is a non–disease-specific survey that can be used to measure the relationship between physical and mental health functioning and the social determinants of health [43].

Orthotics and Prosthetics Users Survey

- Orthotics and Prosthetics Users Survey is a set of self-report instruments that assess functional status, quality of life, and satisfaction with prosthetic devices and services that can be used in prosthetic clinics [44].

Visit 6—Home-Based and Community-Based Assessment

After the completion of visits 1 to 5, participants will return home with all 3 prostheses for a period of 30 days, to assess performance and preference during home-based and community-based conditions. All 3 prostheses will be fitted with a Modus Health StepWatch 3 (Modus Health LLC), which is a research-grade instrument for long-term assessment of ambulatory activity during day-to-day life [45,46]. Capturing prosthetic performance while navigating home-based and community-based environments is a key piece of information that is yet to be effectively used in the prescription process [47]. Activity monitoring devices, such as the Modus Health StepWatch 3 used in this investigation, offer the potential to capture this critical information owing to their accuracy for those ambulating with a prosthesis [48]. Participants will also complete an activity log to document their daily activities to allow for correlation between the prosthesis used and activity. Participants are free to use each prosthesis as they choose. Ankle-foot device preference will be based upon total activity time for each prosthesis. Following 30 days of home-based and

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community-based use, participants will return to the prosthetic clinic to complete a closeout, guided interview to assess subjective preferences. A visit window of –5 to +5 days will be implemented for the final visit.

Biomechanical Analysis

In addition to completing the functional and subjective outcome measures during visits 3 to 5, a subset of 30% (30/100) of the participants will also undergo gait analysis during these visits. Biomechanical gait analysis will include kinetic and kinematic evaluation of level ground walking at 3 speeds and kinematic evaluation of incline and decline ambulation at a self-selected speed. The purpose of these sessions is to collect joint angles, forces, torques, and powers while participants use each ankle-foot device.

Gait Laboratory Instrumentation

Gait analysis will be performed at the Veterans Integrated Service Network 2 Biomechanics Research for the Advancement of Veteran Outcomes Laboratory at VANYHHS, the Biomechanics Laboratory at WRNMMC, and the Rehabilitation and Biomechanics Laboratory at JAHVH. The Veterans Integrated Service Network 2 Biomechanics Research for the Advancement of Veteran Outcomes Laboratory is a 1440-square foot space comprising an 11-camera motion capture system (Qualisys Inc) with 4 multiaxis force platforms (AMTI Inc). At WRNMMC, the Biomechanics Laboratory is an 1800-square foot space comprising an 18-camera motion capture system (Qualisys Inc) and 6 multiaxis force platforms (AMTI Inc). At JAHVH, the Rehabilitation and Biomechanics Laboratory is equipped with a 12-camera motion capture system (Vicon Inc) and 4 multiaxis force platforms (AMTI Inc). The systems track the positions of passive reflective markers at a rate of 120 Hz, and force platforms sample ground reaction forces at a rate of 1200 Hz. Visual3D software (C-Motion Inc) will be used for analysis of 3D motion capture data.

Collection of Reliable Gait Data Among Laboratories

A previous interlab reliability study was conducted among gait laboratories at the 3 military treatment facilities, which demonstrated that despite differences in marker configurations, camera systems, and examiners among the sites, reliable gait data were collected across the 3 gait laboratories [49]. A key to similarity among sites was the use of identical anatomical segment definitions for the respective gait models. To reduce variability during data collection, the 3 laboratories in this investigation will implement the key recommendations of the interlab reliability study, including the use of identical anatomical segment definitions. In addition, all 3 sites will use identical marker sets, and a single examiner at each site will conduct postprocessing of the respective data.

Kinematic and Kinetic Data Capture

Gait analysis will be performed after each acclimation period during visits 3 to 5. Each participant will be provided biomechanically neutral shoes that offer neither supinatory nor pronatory control. A custom, full-body passive reflective marker set will be placed on each participant, which tracks each segment independently, allowing for the accurate measurement of movements. A total of 78 markers will be placed or digitized on the head, trunk, pelvis, and extremities in the following locations: bilaterally over the positions of the medial and lateral ankle malleoli; lateral and medial condyles of the femur; tibial tuberosity; fibula head; first, third, and fifth metatarsals; anterior superior iliac spine; posterior superior iliac spine; calcaneus; lateral of the calcaneus; jugular notch; xiphoid process; spinous process of the seventh cervical vertebrae and tenth thoracic vertebrae; acromioclavicular joints; right and left scapulae; medial and lateral epicondyles of the humerus; styloid process of the radius and ulna; forearm; third metacarpal; and 4 markers on the head. Marker placements for the prosthetic limb will be matched to those of the intact leg or on centers of rotation. The cluster technique will be used to minimize the surface-to-bone displacements for the thigh-mounted, shank-mounted, and upper arm–mounted markers [50]. As such, tracking clusters will be placed bilaterally on the thigh, shank (tibial crest), and upper arm. Functional joints will also be calculated for the intact ankle and bilaterally for the knees and hips [51].

Data Collection Procedure

During each experimental session, participants will walk at 3 speeds across a 4-m instrumented walkway until 5 acceptable trials for each foot are completed. Trials will be considered acceptable when a foot makes full contact with a force platform. As kinetic outcome measures are speed dependent, participants will ambulate at 3 separate, controlled speeds: 1, 1.3, and 1.5 m/s. These speeds were selected to represent slow, moderate, and fast walking speeds for individuals with lower limb loss. The order of speeds will be randomized for each participant for each data collection visit. Auditory feedback will be provided to the participant by the study team to ensure that all participants walk at the targeted speed (–5% to +5%). Participants will be asked to repeat the walking trials until 5 acceptable trials for each foot at each speed are collected.

Incline and Decline Ambulation

Participants in this subset will also perform ramp ascent and descent to collect kinematic data during ramp ambulation. This will be performed on a standardized ramp (rise-to-run ratio of 1:6) with a minimum length of 4.9 m to allow for sufficient number of steps to be taken by the participant. Participants will be instructed to ambulate at a comfortable, self-selected walking speed. This will include 5 trials ascending and 5 trials descending the ramp.

Data Analysis

The reflective marker positions will be digitized using motion tracking software. A 15-segment (head, trunk, pelvis, bilateral upper and lower arms, hands, thighs, shanks, and feet) rigid body model will be created based on the skin-mounted markers and functional joints. Local coordinate systems for each segment will be defined using the International Society of Biomechanics recommendations [52,53]. The data of acceptable walking trials of each participant at each speed will be processed using Visual3D. Marker data will be filtered with a 6-Hz Butterworth low-pass filter. Raw analog data will be filtered using a second-order low-pass Butterworth filter with a 25-Hz cutoff frequency. Visual3D will be used to calculate temporal-spatial values, walking speed, and lower extremity kinematics and

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kinetics. Inverse dynamic analysis will be applied to the kinematics of the biomechanical model and to the location, magnitude, and direction of ground reaction forces acting on the foot to calculate lower extremity joint torques and powers, including ankle, knee, and hip power of the biological and prosthetic limbs during stance and the frontal plane knee moments for the unaffected limb of participants (30/100, 30%). The resultant ground reaction force will be calculated as the magnitude of the ground reaction force vector. Several parameters, including temporal-spatial variables (eg, step lengths, stance and swing times, cadence, and stride length); peak angles; segment ranges of motion, moments, and powers for the ankles, knees, and hips during each phase of gait; and other biomechanical parameters (eg, external adduction moment rate, impulse external knee adduction moment, peak vertical ground reaction force, and peak resultant ground reaction force) will be measured and statistically compared across all conditions. Means, maximum and minimum values, ranges of motion, SEs, and coefficients of variation will be computed for the values attained per gait cycle over each trial and for each set of trials.

Statistical Analysis

Across the study population, outcomes will be assessed using descriptive statistics (ie, means and SEs) and compared between each ankle-foot device category. Inferential statistics for ordinal data will be conducted with a repeated-measures Friedman test (α=.05) and a Dunn post hoc test at 95% CI. To identify which measures are the most sensitive to changes in ankle-foot device type, a linear mixed effects model will be used. Separate models will be run for each type of measure (ie, subjective, functional, and biomechanical), and measures that have a significant association with device type in the presence of adjusting or control variables will be determined. In the case of significance, pair-wise comparisons will be tested for significance using linear contrasts with Tukey Honestly Significant Difference or by applying Bonferroni correction. The performance of each device in each test will be ranked, and the arithmetic mode will be used to determine which device is the most suitable for each participant. Adjusting or control variables in the model will include weight, height, etiology, time since limb loss, sex, race, functional level, and current ankle-foot device.

Development of Prediction Model

To develop evidence-based guidelines for the prescription of prosthetic ankle-foot devices, the goal of this investigation is to determine which factors and outcomes are the most predictive of optimal performance to meet patient goals. To do this, initial analyses will consist of bivariate cross-tabulations, performed using chi-square analyses. Variable selection for the multivariate model will be informed by these bivariate findings. Logistic regression will then be performed with participants' preference of prosthesis regressed on each of several domains (eg, functional levels and outcomes, activity levels, and biomechanical parameters). The models will simultaneously control for multiple variables, and overall model predictive value will be assessed using the C-statistic. Domain-specific models (based on bivariate findings) and 1 parsimonious stepwise logistic regression model combining the domains will be created to determine whether each distinct component predicts optimal prescription outcome. Each domain-specific model will control for the identified confounding factors. The individual variables of each domain will be used as fixed predictors. Finally, stepwise multiple regression will be used to determine the factors and outcomes that represent the best predictors, which will be conducted through a series of domain-specific, forward regression models. The significant variables in the forward selection models will then be placed in a backward regression model. Significant variables from the backward regression will be considered as the strongest predictive factors and used to develop prosthetic prescription guidelines.

Sample Size Determination and Power Analysis

Sample size determination was based on power analysis of several biomechanical, subjective, and functional measures collected during pilot investigations (Table 2). Assuming an α error rate of 5% and using within-group SDs determined from the pilot investigations, power is provided for selected parameters for a sample size of 100 participants for functional and subjective outcomes and a sample size of 30 for biomechanical parameters.

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Table 2. Sample size determination and power analysis of selected parameters.

Parameters	Difference, mean (SD)	Power (N=100; subset of 30/100, 30%, where appropriate), %
Biomechanical parameters		
Ankle range of motion (°)	2.9 (3)	95.3
Ankle peak plantarflexion (°)	3.2 (3.6)	91.1
Peak ankle power (W/kg)	1.7 (0.7)	99.9
Effective foot length ratio	0.9 (0.06)	99.2
Instantaneous radius of curvature (cm)	7.3 (9.2)	81.7
Subjective outcome measures		
PEQ[a]—satisfaction	13.6 (12.4)	98.7
PEQ—frustration	15.9 (24.7)	68.6
PEQ—utility	8.4 (8.8)	95.5
Functional outcome measures		
Steps at high activity (%)	9 (13.1)	74.4
6-minute walk distance (m)	60 (61)	96.3

[a]PEQ: Prosthesis Evaluation Questionnaire.

Results

The study was funded in August 2017, and data collection began in 2018. Data collection is expected to be completed before July 2023. Data analysis of the full data set is expected to begin after final data collection. Initial dissemination of results is expected in the winter of 2023, with subsequent publication of secondary analyses in 2024.

Discussion

Expected Outcomes and Anticipated Principal Findings

The expected outcomes of this investigation are to generate data that offer new knowledge that can be used to develop new prescription algorithms for prosthetic ankle-foot devices to improve the current clinical practice guidelines. This information will lead to clinical prescriptions that facilitate the achievement of maximal functional ability and user satisfaction for individuals with lower limb loss. Specifically, this study will help to determine the appropriate functional and biomechanical measures to support the prescription of prosthetic ankle-foot devices; correlate patient goals and subjective measures with objective data to determine the optimal prosthetic ankle-foot category to facilitate the greatest overall function for the user; and finally, develop the criteria for the appropriate prescription of nonarticulating ESR, ART, and powered plantarflexion ESR ankle-foot devices.

VA and the DoD have historically been leaders in the early adoption of advanced prosthetic technology for the clinical care of veterans and service members with limb loss. Despite the recent (and ongoing) evolution of lower limb prosthetic technology and the large number of commercially available devices, there are limited guidelines to aid the limb loss care team in prescribing appropriate prosthetic technology to achieve optimal functional ability. With the expectation of continued active lifestyles for veterans and service members with limb loss, the absence of effective, evidence-based interventions not only limits near-term outcomes but likely also increases the susceptibility for secondary physical conditions and degenerative changes over the long term. Furthermore, projected trends indicate that the overall number of amputations will increase dramatically, largely attributable to the aging population and the number of people living with dysvascular disease and diabetes [4]. As the aging veteran population advances in these diseases, this will become a major quality-of-life concern for VA, and effective outcome-based clinical practice will be necessary to decrease long-term disability and provide high quality of life. Therefore, it is the goal of this proposal to develop evidence-based lower limb prosthetic prescription guidelines for the achievement of maximal functional ability and patient satisfaction. Following the completion of this research project, the biomechanical, functional, and subjective parameters that are the most indicative in yielding the most successful and appropriate ankle-foot device prescription will have been determined. Thus, the evidence-based outcomes obtained from this research investigation can be appropriately translated into clinical practice and drive the future of clinical care and research. As future technology develops and becomes available, this protocol will help to establish the methodological framework necessary to aid in the appropriate clinical prescription of prosthetic ankle-foot devices.

Dissemination Plan

It is expected that the outcomes and results of this investigation can become an influential source of evidence-based health care practice for prosthetic prescription that can also be incorporated in lower extremity clinical practice guidelines. Disseminating the results of this study within the DoD, VA, and civilian health care systems will be critical in changing clinical practice to affect the quality of life of individuals with transtibial limb loss. First, both VA and the DoD are integrated networks that leverage various modalities to enable the dissemination and adoption of best practices among different disciplines.

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Specifically for limb loss care teams, the DoD and VA Extremity Trauma and Amputation Center of Excellence leads efforts to enhance the health care of veterans and service members. Participation in the Extremity Trauma and Amputation Center of Excellence webinar series will be an excellent opportunity to present the results of this study. The webinars reach a multidisciplinary group of clinicians, scientists, researchers, and other members of the limb loss care team. This webinar series contains presentations that are broadcast and available across the entire DoD and VA health care network and occurs every other month. This forum provides an excellent platform to present the results of this study to a large, diverse audience of researchers and health care professionals in the field of limb loss care. By disseminating our results to leaders and clinicians in the field of limb loss care, we can directly influence the care provided to veterans and service members with limb loss.

To reach stakeholders in the civilian health care systems, we aim to communicate the importance of the results of this study through leading peer-reviewed publications in scientific journals and presentations at professional conferences that target clinical providers (eg, Gait and Clinical Movement Analysis Society conference, American Society of Biomechanics conference, and Military Health System Research Symposium) and by sharing our data through large data repositories.

Finally, in addition to providing a wide distribution of results through peer-reviewed publications, outcomes will be disseminated to industry leaders for improvement of their products. The DoD and VA have supported similar efforts across the prosthetics industry. Specific, relevant results provided to industry leaders can help in the evolution of lower extremity prosthetic components, which will then lead to improved devices for veterans and service members.

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Disclaimer

The views expressed in this paper are those of the authors and do not necessarily reflect the official policy of the Departments of the Air Force, Army, Navy, Defense, and Veterans Affairs or the US Government. The identification of specific products or scientific instrumentation is considered as an integral part of the scientific endeavor and does not constitute endorsement or implied endorsement on the part of the author, Department of Veterans Affairs, Department of Defense, or any component agency.

Data Availability

All data for this manuscript are included in this published paper. Final results will be available via a publicly available data repository.

Authors' Contributions

JTM participated in conceptualization of the study, methodology development, data collection, writing and editing of the manuscript, project administration, supervision of the project and staff, and funding acquisition. BDH participated in methodology development, project administration, supervision of the project and staff, writing and editing of the manuscript, and data collection. CLD participated in methodology development, review and editing of the manuscript, and funding acquisition. ALP participated in conceptualization of the study, methodology development, data collection, review and editing of the manuscript, and funding acquisition. SLP participated in methodology development, supervision of the project and staff, project administration, data collection, and review and editing of the manuscript. JTH participated in methodology development, project administration, supervision of the project and staff, data collection, and review and editing of the manuscript. ANS participated in data collection and review and editing of the manuscript. MJH was a major contributor to the project administration, data collection, and review

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and editing of the manuscript. JMC participated in methodology development, data collection, review and editing of the manuscript. LMN participated in conceptualization of the study, funding acquisition, and review and editing of the manuscript. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review report by the US Army Medical Research and Materiel Command - Congressionally Directed Medical Research Programs - 2015 Orthotics and Prosthetics Outcomes Research Program - Prosthetics Outcomes Research Award (USA).
[PDF File (Adobe PDF File), 134 KB - resprot_v12i1e45612_app1.pdf]

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Abbreviations

ART: articulating energy storing and returning
DoD: Department of Defense
ESR: energy storing and returning
IRB: institutional review board
JAHVH: James A Haley Veterans' Hospital
PWR: active plantarflexion energy storing and returning
VA: Veterans Affairs
VANYHHS: Veterans Affairs New York Harbor Healthcare System
VAS: visual analog scale
WRNMMC: Walter Reed National Military Medical Center

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Protocol

Personal Health Libraries for People Returning From Incarceration: Protocol for a Qualitative Study

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Abstract

Background: Individuals released from carceral facilities have high rates of hospitalization and death, especially in the weeks immediately after their return to community settings. During this transitional process, individuals leaving incarceration are expected to engage with multiple providers working in separate, complex systems, including health care clinics, social service agencies, community-based organizations, and probation and parole services. This navigation is often complicated by individuals' physical and mental health, literacy and fluency, and socioeconomic status. Personal health information technology, which can help people access and organize their health information, could improve the transition from carceral systems to the community and mitigate health risks upon release. Yet, personal health information technologies have not been designed to meet the needs and preferences of this population nor tested for acceptability or use.

Objective: The objective of our study is to develop a mobile app to create personal health libraries for individuals returning from incarceration to help bridge the transition from carceral settings to community living.

Methods: Participants were recruited through Transitions Clinic Network clinic encounters and professional networking with justice-involved organizations. We used qualitative research methods to assess the facilitators and barriers to developing and using personal health information technology for individuals returning from incarceration. We conducted individual interviews with people just released from carceral facilities (n=~20) and providers (n=~10) from the local community and carceral facilities involved with the transition for returning community members. We used rigorous rapid qualitative analysis to generate thematic output characterizing the unique circumstances impacting the development and use of personal health information technology for individuals returning from incarceration and to identify content and features for the mobile app based on the preferences and needs of our participants.

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Results: As of February 2023, we have completed 27 qualitative interviews with individuals recently released from carceral systems (n=20) and stakeholders (n=7) who support justice-involved individuals from various organizations in the community.

Conclusions: We anticipate that the study will characterize the experiences of people transitioning from prison and jails to community settings; describe the information, technology resources, and needs upon reentry to the community; and create potential pathways for fostering engagement with personal health information technology.

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KEYWORDS

carceral settings; personal health information technology; qualitative research; systemic oppression; transition from incarceration

Introduction

In a typical year, more than 10 million people cycle in and out of prisons and jails. Incarcerated individuals predominantly come from racial and ethnic minority groups and are of low-income status [1]. Those with a history of incarceration have chronic medical conditions—such as diabetes, hypertension, hepatitis C, depression, and substance use disorders—higher than the general population [2-6]. Upon release, these individuals bear high risks of death and hospitalization from preventable conditions [2,7-9]. Medicare beneficiaries recently released from correctional facilities have higher hospitalization rates and an increased risk of mortality compared with the general population [10,11]. A Washington state study found that individuals recently released from prison had a 2-fold increase in the risk of mortality in the year after release compared to the general population [7].

During incarceration, people reside in a highly controlled environment with constitutionally guaranteed access to health care services and little or no autonomy or opportunity to gain skills in self-management of medications, exercise, or diet [12,13]. This lack of autonomy may adversely affect an individual's ability to manage their health upon release [12-14]. In total, 40% of individuals are diagnosed with a new chronic condition while incarcerated and do not have any experience managing that illness in a community setting [15]. Many individuals are released from carceral settings without any discharge planning and have no information on their health records, their medications, or their recent lab results [16]. Improving health outcomes in this population is further complicated given the immediacy of people's social needs and legal obligations, including securing housing, food, and employment, as well as meeting the mandates of community supervision. After incarceration, people have an increased rate of homelessness, and incarceration leads to increased housing vulnerability due to loss of housing during incarceration, decreased eligibility for employment and public housing, and disrupted community ties [17]. In addition, more than 90% of formerly incarcerated persons meet the United States Department of Agriculture criteria for food insecurity [18]. Although many individuals have at least 1 chronic medical condition on release, 80% are released without health insurance or having a primary care provider [19,20]. Meeting these needs requires individuals just released from incarceration to engage with many different health, social, and legal entities to organize and manage their information.

Personal health information technologies are untapped resources that could facilitate improved access and organization of information, especially in the period after release. In addition, personal health information technologies increase patient engagement in health and self-efficacy efforts by organizing health information, improving communication with providers, and coordinating care. Research on personal health information technologies has mostly focused on patient portals (electronic personal health records tethered to institutional electronic health records), which has helped improve adherence to medications and quality measures for chronic conditions [21-25]. Yet, research has demonstrated this one-size-fits-all approach to designing personal health information technologies has resulted in low utilization of patient portals and barriers to use among racial and ethnic minority groups, people with low socioeconomic status, and people with limited health literacy [22,26,27]. In addition to low utilization and the challenges with use, patient portals do not have the desired functionality to aggregate information between different health systems and other organizations, like community-based social service organizations and carceral health facilities. Furthermore, the existing personal health information technologies that are not tied to an electronic health record aggregate information across multiple different sources but do not have features that address health literacy, concerns of privacy and security, and other barriers to technology use [28-30]. Existing personal health information technology, such as personal health libraries, has not been designed to meet the needs and preferences of people recently released from incarceration, which is critical for its acceptance and use [11,31]. Incorporating input from intended users and knowledge of their technology use and behaviors can help diminish potential intervention-generated inequalities [32,33]. The objective of this study is to explore the facilitators and barriers to using personal health information technology with formerly incarcerated persons and other community stakeholders. This study will inform the design, development, and usability testing of personal health libraries created for people with histories of incarceration to facilitate their transition from carceral to community settings.

Methods

Study Design, Study Setting, and Participants

We will use qualitative methods and conduct semistructured interviews with people just released from jails or prisons (anticipated n=20) and community and correctional stakeholders (anticipated n=10) to understand the individual, organization,

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and systemic factors that shape people's access to health and technology supports after release from incarceration. The following study protocol was reviewed and approved by the Yale University Human Subjects Research Committee Institutional Review Board (200028862). The research will be conducted in partnership with a primary-care clinic that cares for people who have chronic health conditions and histories of incarceration. The clinic, located in the northeastern United States, is part of the Transitions Clinic Network (TCN), a national network of primary-care clinics that integrates community health workers (CHWs) who have lived experience of incarceration into clinical teams [3,15]. Additionally, the TCN clinic has collaborations with local organizations that support individuals released from correctional settings. We will create an advisory board for this project that includes clinicians and service providers who care for people with a history of incarceration, CHWs with a history of incarceration, and correctional system administrators. The advisory board will provide overarching feedback on study design, data collection, and data analysis.

Recruitment and Interviewing of Formerly Incarcerated Individuals

One team member (MS), who is a CHW in the clinic, will recruit potential participants through TCN clinic encounters and professional networking with justice-involved organizations. To be eligible for this interview, patients need to be at least 18 years old, carry a diagnosis of at least 1 chronic disease (eg, diabetes, heart disease, kidney disease, arthritis), be English-speaking, and have been released from jail or prison within the past year.

Recruitment and Interviewing of Stakeholders

Team members (MF, MCB, MS, KW) will use professional networks and snowball sampling to recruit stakeholder participants from social service agencies, community organizations, and carceral facilities. To be eligible for this portion, participants need to have direct experience working with people who have recently been released from incarceration.

All interested and eligible people will be given study-informed consent forms with detailed information about the purpose of the study, their rights as research participants, and contact information for further questions. A team member will schedule in-person interviews in physical or web-based spaces that are convenient for participants. All participants, both formerly incarcerated individuals and community stakeholders, will receive a US $50 gift card at the end of the interview in appreciation for their time.

Data Collection

The team developed 2 interview guides using the constructs of the technology acceptance model and input from stakeholders who are part of the TCN professional network (see Multimedia Appendices 1 and 2 for interview guides) [34,35]. The interview guide for people just released from incarceration includes questions about participants' experiences with technology, information-seeking behavior, and needs during their transition from incarceration to the community. Questions include:

- What experiences did you have with technology before incarceration? During incarceration?
- Describe some of the initial things you needed to figure out when you were released.
- How do you figure out what to do next?
- How do you organize your information?

Participants will also be asked to give feedback on wireframe models of a personal health library and share examples of information they would like to track or manage within a digital app, such as their identification card or address of residency prescription medications, or applications for education, employment, or financial assistance.

The stakeholder interview guide seeks to obtain information about technology access and information-seeking behaviors from a service provider perspective. Questions include:

- What kind of information do you collect and store on individuals who are in or just released from correctional settings?
- What type of information do you want to help you with your ability to promote health for the individuals you work with?
- What are your concerns about clients using technology to access their health information?

The team will iteratively refine both interview guides throughout data collection to incorporate emergent ideas into future interviews.

Three researchers will serve as interviewers for the study: 2 are experienced qualitative researchers (MF, MCB) while the third will be trained as part of the larger grant aims (MS). All interviews will be audio-recorded and professionally transcribed. Identifying information will be removed from the transcript to preserve participant confidentiality.

Data Analysis

Four team members (MF, MCB, MS, KW), including the 3 interviewers, will serve on the analytic team. This structure will support a closeness with the data and a collaborative analytic process [36]. The team members' experiences are professionally and personally diverse and span more than 10 years in the care of structurally marginalized populations, including expertise in justice research (MF), social work research (MCB), community health work and community advocacy (MS), medicine and community-engaged informatics (KW). They will use a rapid qualitative analysis to efficiently process and distribute data to the larger study team [37,38], so that the findings are incorporated into the user-centered design and software development process. The analytic team will develop a template to organize the salient findings from each individual interview [38]. The template contains sections describing each participant's experiences with preparation for release from incarceration, perspectives on priorities for people after they are released from incarceration, and the type of information sought, shared, and used during the transition process from carceral settings to the community.

The analysts will complete summaries for each interview independently, with at least 2 analysts assigned to each

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transcript. They will then convene as a group to discuss their work and further explore the data through questions and comparisons with other study interviews, field experiences, and research findings. The team will record their progress, including ongoing thematic analysis through memoing and visualizations [39,40]. All written (transcripts, summaries, memos) and graphic (visualizations) data will be uploaded to Dedoose (version 9.0.17; Socio-cultural Research Consultants, LLC) for data storage, sharing, and retrieval. The summaries and visualizations will be sent to the larger research team to inform the ongoing design and development of a personal health library for individuals transitioning from carceral settings. The summary template includes a section that will be used to develop a qualitative codebook that can be applied to all transcripts for further analysis. This coding process will also facilitate the retrieval of aggregated, deidentified data for future study needs [41,42].

Following rapid qualitative analysis, the team will conduct interpretation sessions (led by TM) and develop an affinity diagram [43]. By creating an affinity diagram, the team can take the large amounts of data gathered during the interviews and organize them into groups or themes based on their relationships. The benefit of creating the affinity diagram is that it can reveal common issues and themes across all users and help to identify key requirements for developing the personal health library app. The purpose of the interpretation session is to turn the data gathered from the interviews into draft models for design. The study results will be disseminated to study participants and the advisory board for reflection and feedback.

Ethics Approval

The institutional review board at Yale School of Medicine approved the study and all participants gave informed consent (2000028862).

Results

As of February 2023, we have completed 27 interviews with people just released from carceral systems (n=20) and stakeholders (n=7). The data analysis derived from the interviews will inform the development of user requirements, identify facilitators and barriers to personal health library use with our population of interest, capture emergent needs and priorities during the transition process from correctional to community settings, and build a comprehensive codebook for further analysis. The interviews with people with a recent history of incarceration have elucidated a wide range of social and health services that they interact with upon release, such as identity verification and obtainment of identity documentation, 211 services (information and referral service organization in Connecticut servicing individuals with utility assistance, food, housing, child care, after school programs, elder care, and crisis intervention), the Department of Social Services that delivers and funds a wide range of programs and services as Connecticut's multifaceted health and human services agency, and the Department of Mental Health and Addiction Services, whose purpose is to promote and administer comprehensive, recovery-oriented services in the areas of mental health treatment and substance abuse prevention and treatment throughout Connecticut [44-46]. We are purposively sampling to recruit more female participants with recent histories of incarceration, as well as stakeholders affiliated with specific areas of need.

Discussion

Anticipated Findings

People recently released from carceral settings face a unique set of challenges when they return to the community [47]. They may face challenges with meeting their basic needs, such as being unhoused, unemployed, and food insecure, in addition to challenges maintaining their health and well-being when entering back into the community from prison or jail. In this transition back to the community, personal health libraries may be the bridge that facilitates access to information about community resources as well as facilitate the organization and preparation of personal health information, emergency contacts, community providers, and employment opportunities. From our qualitative analysis, we will have a rich understanding of the experiences of those previously imprisoned and their perspectives on the use of technology, their concern for security and safety use with technology, how they organize information that is important to them, and specifically how technology may or may not be leveraged for their personal health needs. In addition, by leveraging a participatory design process, the findings produced by this study will result in a nuanced understanding of the facilitators and barriers to the design, development, and utilization of personal health information technologies among people returning to the community from carceral settings. These findings from the interviews and the participatory design process may lead to increased personal health engagement through technology use.

Conclusion

Millions of individuals leave jails and prisons each year, and in this transition, many experience poor health outcomes. Personal health information technologies, which are currently underutilized, may positively impact their health by improving individual self-efficacy and by facilitating communication between the health system and social service providers, and control of information by patients themselves. To improve transitions of care from carceral to the community health system, we need to have targeted and feasible solutions to capitalize on the benefits of personal health information technologies.

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Data Availability

The data sets generated during and analyzed during the current study are not publicly available due to ongoing data collection from participants but may be made available from the corresponding author on reasonable request.

Conflicts of Interest

TM is a member of the Clinical Diversity Advisory Board at Woebot Health as well as the Digital Wellbeing Advisory Board at Peer Health Exchange. TM is also the associate editor of the *Journal of Medical Internet Research*. KW also receives research funding from Genentech, Inc. Woebot Health, Peer Health Exchange, and Genentech, Inc were not involved in the writing of this paper or the decision to submit it for publication. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Multimedia Appendix 1
Interview guide for stakeholders.
[DOCX File , 19 KB - resprot_v12i1e44748_app1.docx]

Multimedia Appendix 2
Interview guide for formerly incarcerated persons.
[DOCX File , 20 KB - resprot_v12i1e44748_app2.docx]

Multimedia Appendix 3
Peer-review reports from the Biomedical Informatics, Library and Data Sciences Review Committee - National Library of Medicine (National Institutes of Health, USA).
[DOCX File , 28 KB - resprot_v12i1e44748_app3.docx]

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Abbreviations

CHW: community health worker
TCN-CT: Transitions Clinic Network, Connecticut

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Protocol

Comprehensive Acute Kidney Injury Survivor Care: Protocol for the Randomized Acute Kidney Injury in Care Transitions Pilot Trial

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Abstract

Background: Innovative care models are needed to address gaps in kidney care follow-up among acute kidney injury (AKI) survivors. We developed the multidisciplinary AKI in Care Transitions (ACT) program, which embeds post-AKI care in patients' primary care clinic.

Objective: The objective of this randomized pilot trial is to test the feasibility and acceptability of the ACT program and study protocol, including recruitment and retention, procedures, and outcome measures.

Methods: The study will be conducted at Mayo Clinic in Rochester, Minnesota, a tertiary care center with a local primary care practice. Individuals who are included have stage 3 AKI during their hospitalization, do not require dialysis at discharge, have a local primary care provider, and are discharged to their home. Patients unable or unwilling to provide informed consent and recipients of any transplant within 100 days of enrollment are excluded. Consented patients are randomized to receive the intervention (ie, ACT program) or usual care. The ACT program intervention includes predischarge kidney health education from nurses and coordinated postdischarge laboratory monitoring (serum creatinine and urine protein assessment) and follow-up with a primary care provider and pharmacist within 14 days. The usual care group receives no specific study-related intervention, and any aspects of AKI care are at the direction of the treating team. This study will examine the feasibility of the ACT program, including recruitment, randomization and retention in a trial setting, and intervention fidelity. The feasibility and acceptability of participating in the ACT program will also be examined in qualitative interviews with patients and staff and through surveys. Qualitative interviews will be deductively and inductively coded and themes compared across data types. Observations of clinical encounters will be examined for discussion and care plans related to kidney health. Descriptive analyses will summarize quantitative measures of the feasibility and acceptability of ACT. Participants' knowledge about kidney health, quality of life, and process outcomes (eg, type and timing of laboratory assessments) will be described for both groups. Clinical outcomes (eg, unplanned rehospitalization) up to 12 months will be compared with Cox proportional hazards models.

Results: This study received funding from the Agency for Health Care Research and Quality on April 21, 2021, and was approved by the Institutional Review Board on December 14, 2021. As of March 14, 2023, seventeen participants each have been enrolled in the intervention and usual care groups.

Conclusions: Feasible and generalizable AKI survivor care delivery models are needed to improve care processes and health outcomes. This pilot trial will test the ACT program, which uses a multidisciplinary model focused on primary care to address this gap.

Trial Registration: ClinicalTrials.gov NCT05184894; https://www.clinicaltrials.gov/ct2/show/NCT05184894

International Registered Report Identifier (IRRID): DERR1-10.2196/48109

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KEYWORDS

acute kidney injury; acute renal failure; care transitions; chronic kidney disease; nephrologists; randomized controlled trials

Introduction

Acute kidney injury (AKI) affects nearly 20% of hospitalized patients. It is associated with a 6.5-fold higher mortality, a 3.5-day longer length of stay, and US $5 billion in annual hospital costs in the United States. Chronic kidney disease (CKD) develops in 15%-30% of AKI survivors and 49% are readmitted to the hospital within 1 year. These complications decrease patients' quality of life and strain health care resources. This significant risk of poor outcomes can be partially attributed to gaps in kidney-focused care and education during transitions. One study found that 30% of AKI survivors failed to receive basic laboratory and clinical follow-up of kidney health after discharge and that avoidable nephrotoxin exposure during this period independently increased the risk for chronic kidney disease [1,2]. Another study showed that laboratory monitoring of serum creatinine and urine protein, which is recommended as best practice, was only done in 54% and 14%, respectively, of AKI survivors at 6 months [3]. These care gaps place patients at risk for exposure to potentially modifiable determinants of long-term complications, such as nephrotoxins. A large population-based cohort study showed that 74% of AKI survivors received 1 or more nephrotoxins at hospital discharge. This was associated with a 1.4-fold increase in risk for new or worsening CKD and compounded 1.13-fold with each additional nephrotoxin [2].

Survivorship programs facilitating the transition from inpatient to outpatient care have improved clinical and patient-centered outcomes in patients with complex care needs, such as cancer and critical illness survivors [4-7]. Though experience with AKI survivor care transition programs is limited, the most frequently proposed model is a dedicated nephrologist-led clinic to deliver core components of best practices for post-AKI care. These have been associated with improved patient kidney health knowledge and process outcomes, such as timely serum creatinine monitoring after discharge [8,9]. Despite promising results in initial reports, concerns exist about scalability, acceptability of patients, and generalizability to rural and low-income populations where specialty nephrology care is often unavailable [10,11]. Patients are typically seen more than 1 month after discharge, increasing the risk for nephrotoxin exposure and loss of follow-up. Additionally, specialty consultation may not be needed for all patients and may introduce additional fragmentation of care, costs, and treatment burden. Nephrologists have called for the integration of other disciplines to enhance AKI survivor care delivery capacity [12], including primary care providers (PCP) to evaluate laboratory tests and perform a kidney function assessment early in the postdischarge period [13].

To address these concerns, we developed the multidisciplinary AKI in Care Transitions (ACT) program, which embeds post-AKI care in the patient's medical home, primary care. The bundled intervention includes (1) the use of an electronic health record (EHR) alert to identify high-risk AKI survivors, (2) education and care coordination from nurses in nephrology before discharge, and (3) a posthospital visit with a PCP and a pharmacist within 14 days after discharge. Nephrology referral is coordinated based on the needs and preferences of the patient, inpatient care providers, and the patient's PCP. Pilot testing revealed higher 14- and 30-day cumulative incidence of laboratory and provider follow-up in ACT program participants compared to those receiving usual care. In addition, participants who received kidney health education improved their understanding of AKI and its consequences.

This pilot trial aims to test the feasibility of study procedures for a future hybrid effectiveness and implementation trial, including patients' willingness to be enrolled and randomized, participant retention, and chosen outcome measures. We will also assess the feasibility and acceptability of participation in the ACT program and identify determinants of successful implementation into routine clinical care.

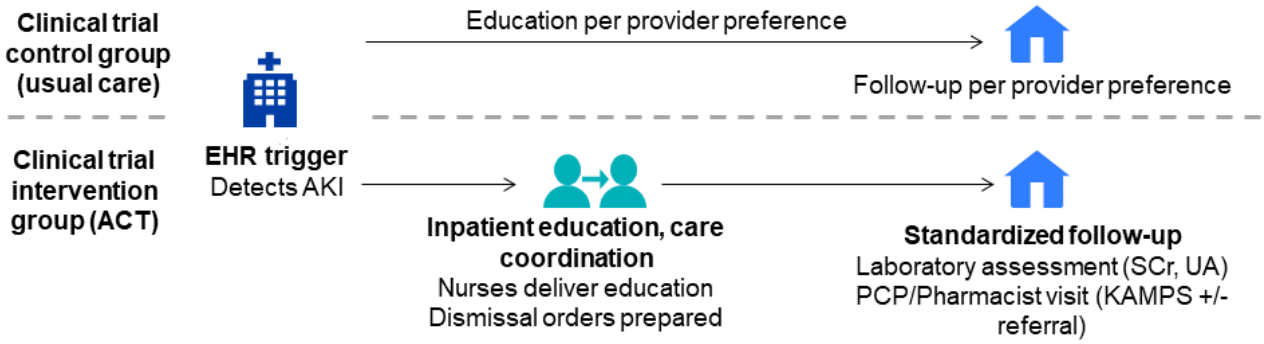
Methods

Overview

In preparation for a future large-scale clinical trial to test the effectiveness and implementation of the ACT program for improving care quality and outcomes, this study will evaluate the feasibility and acceptability for patients and staff (aim 1) and gather preliminary effectiveness data (aim 2). To accomplish these aims, we will conduct a pilot randomized trial using a convergent mixed methods approach (Figure 1). We will use the Consolidated Framework for Implementation Research (CFIR) [14] to systematically assess potential barriers and facilitators (ie, determinants) that influence implementation outcomes.

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Figure 1. Overall study design. ACT: acute kidney injury in care transitions; AKI: acute kidney injury; EHR: electronic health record; KAMPS: kidney health follow-up framework (Textbox 1); PCP: primary care providers; SCr: serum creatinine; UA: urinalysis.



Ethics Approval

The study was reviewed and approved by the Mayo Clinic Institutional Review Board (21-011055) on December 14, 2021, and was registered at ClinicalTrials.gov (NCT05184894). This study will employ a Data Safety and Monitoring Plan to monitor participant safety, data completeness and adherence to study protocol, data integrity, participant privacy, data confidentiality, and study documentation.

Setting and Participants

This pilot trial was conducted at Mayo Clinic, an academic medical center in Rochester, Minnesota. Mayo Clinic is an integrated health care delivery system delivering primary and specialty care to local, regional, national, and international patients. Mayo Clinic primary care practices provide comprehensive primary care to approximately 150,000 empaneled patients —local area residents, Mayo Clinic employees and their dependents—cared for at 7 full-service clinical sites and 2 express care sites in Rochester and surrounding counties. It employs a team-based care model that includes physicians, advanced practice providers (nurse practitioners and physician assistants), nurses, and embedded clinical pharmacists who consult with patients independently or in collaboration with the PCP. At Mayo Clinic, no formal dedicated AKI-survivor clinic exists.

Mayo Clinic Rochester Hospital has 5 inpatient nephrology consultation services that include nurse educators whose primary role is educating hospitalized patients discharged on dialysis. Patients can be referred for nephrologist follow-up in a Rochester clinic by inpatient care teams, including the nephrology consult services, or any other inpatient or outpatient provider.

Patient participants for the ACT trial are identified using an EHR screening alert, a validated electronic AKI surveillance tool that uses serum creatinine and urine output to detect AKI [15]. Eligible individuals have stage 3 AKI (severe) based on consensus criteria [16] during their hospitalization, a PCP at Mayo Clinic in Rochester, do not need dialysis at discharge, and are not discharged to hospice. Patients who are unable to participate (eg, clinician-documented dementia in the EHR or with limited English proficiency) or who do not provide informed consent are excluded. Recipients of any transplant or acute cellular therapy within 100 days of enrollment are also excluded. Eligibility is determined using the EHR screening alert and through manual chart review by a study team member. Individuals may only be enrolled in the trial one time. Remuneration is not provided to any participant.

Patient participants in the intervention group and staff involved in delivering components of the ACT program are invited to participate in semistructured interviews or observations of ACT program interactions (eg, patient education, provider visit) to explore the feasibility and acceptability of the ACT program. Participants are sampled on key factors (eg, age, urban or rural geographic location, and ACT program role) to facilitate the selection of information-rich cases while capturing major variations based on patient factors or staff background or experience.

Patients provide written informed consent for trial enrollment and indicate whether they consent to be contacted for an interview and/or have their visit observed. Oral consent is obtained from clinicians before participating in interviews or observations. Clinicians are approached for oral consent at the first study encounter they are involved in. This consent carries forward for all subsequent encounters (eg, with other patients). Observations are performed using video and audio recordings. At any time once enrolled, including during the visit, a patient or clinician may withdraw their consent for participation in the trial, observations, or an interview. Declining participation in 1 aspect of the trial does not preclude ongoing participation in others.

Study Groups

Participant Identification

A study team member contacts potential patient participants before discharge to obtain written informed consent for the trial. Patients are approached approximately 48-72 hours before the estimated discharge date. Participants are randomized 1:1 to either the control or intervention group. Individuals are randomly allocated equally to the intervention or control groups using a permuted block design with varying block sizes between 2 and 4. The study statistician set up the randomization scheme and provided numbered envelopes to the study coordinator with the randomly assigned group enclosed. After completing the

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informed consent, the study coordinator opens the envelope and discloses the group allocation to participants.

Intervention Group

Participants in the intervention group receive a care bundle inclusive of education, care coordination, and postdischarge follow-up. Before discharge, participants receive a consultation from nephrology nurse educators. These nurses provide kidney health education, as previously described [17], which is tailored to the patient's needs. To ensure consistency, nurses aim to achieve understanding using teach-back questions. Scheduling coordinators place orders for postdischarge laboratory tests (serum creatinine and urine study for protein assessment) and outpatient visits with a PCP and a pharmacist for signature by the primary inpatient service before discharge. Laboratory and provider visits are ideally scheduled within 14 days of discharge [4]. PCP and pharmacist encounters can occur in person or through video (PCP or pharmacist visits) or telephone (pharmacist visits only). Structured around the KAMPS framework (Textbox 1 [18, 19]), the PCP and pharmacist provide patient education, medication reconciliation, and disease state management with specialist referral as needed.

Textbox 1. KAMPS framework for components of kidney follow-up care [18,19].

Framework

- K: Kidney function assessment with laboratory testing
- A: Awareness and education
- M: Medication reconciliation and review
- P: Individualized blood pressure monitoring
- S: Sick day education

It is expected as part of standard care that the PCP and pharmacist review the range of care needs for the patient in the transitional period, including, but not limited to AKI. Pharmacists discuss recommendations with the provider in person, if possible, or through secure message. Clinical decision support tools have been developed and embedded in the EHR [17], including descriptions of the KAMPS framework domains and links to additional kidney care resources through a proprietary medical knowledge system [20]. Orders for outpatient nephrology follow-up, if indicated, may be placed by the inpatient care teams or the PCP. Participants in this group are also invited to participate in semistructured interviews.

Control Group

Participants receive no specific study-related intervention. AKI identification, patient education, and follow-up care are at the discretion of the primary treating team. It is customary for these patients to receive some degree of laboratory monitoring and clinical follow-up in the postdischarge period, but for this group, timing and components are not standardized. Care providers have access to the same educational materials for providers and patients as in the intervention group.

Data Collection

Overview

Individuals that consent to participate will be captured in the REDCap system. Those found to be ineligible or eligible but declining participation will be captured in a recruitment tracking log. If spontaneously offered, reasons for declining participation will be recorded, but these will not be deliberately probed due to regulatory limitations. The Mayo Clinic Unified Data Platform will be used to abstract electronically available data. The Unified Data Platform is an aggregated data resource inclusive of current and legacy EHR and administrative billing data across the Mayo Clinic enterprise. Other sources of data include interviews and direct observations of clinical encounters. An overview of the data collection plan is outlined in Table 1.

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Table 1. Summary of study measures and assessment timing.

Element	Source	Hospital admission	Randomized	Hospital discharge	Study follow-up visit (ACT[a] patients only)	30 days	90 days	1 year
Sociodemographic factors, comorbidities	UDP[b]	✓						
Attributes of hospitalization and AKI[c] episode	UDP			✓				
Medication use	UDP	✓		✓		✓		
Brief health literacy screen	Patient self-report		✓					
mKiKS[d]	Patient self-report		✓			✓		
PROMIS 10	Patient self-report		✓			✓		
Was it worth it?	Patient self-report					✓[e]		
Encounter observation	Audio or video-recording				✓[e]			
Qualitative interviews	Patient or staff self-report					✓[e,f]		
MAKE[g], unplanned ED[h] visit, rehospitalization	UDP						✓	
CKD[i] or death	UDP							✓
Kidney laboratory assessments, outpatient visits	UDP						✓	

[a]ACT: AKI in Care Transitions.

[b]UDP: Unified Data Platform, source for quantitative data collection unless otherwise specified.

[c]AKI: acute kidney injury.

[d]mKiKS: modified Kidney Knowledge Survey.

[e]Intervention patients or clinicians only.

[f]Staff participating in interviews will complete the Feasibility of Intervention Measure and Acceptability of Intervention Measure surveys [21].

[g]MAKE: major adverse kidney event.

[h]ED: emergency department.

[i]CKD: chronic kidney disease.

Quantitative Data

Data will be abstracted from the Mayo Clinic UDP on patient demographics, comorbidities, attributes of the hospitalization, details about the episode of AKI and the degree of kidney function recovery by discharge, follow-up processes of care (laboratory assessments and visits), and clinical outcomes. Health literacy is evaluated in all participants at baseline using the Brief Health Literacy Screen (Multimedia Appendix 1) [22]. Select medication data will be collected at baseline (preadmission based on the documented medication list in the EHR), discharge, and 30-day follow-up. This will include the use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, sodium-glucose cotransporter 2 inhibitors, metformin, glucagon-like peptide 1 receptor antagonists, sulfonylureas, insulin, loop diuretics, thiazide diuretics, statins, aspirin, and nonsteroidal anti-inflammatory drugs. The total number of medications at discharge will be evaluated. Using previously described methods, we will review pharmacist documentation of medication discrepancies and drug therapy problems for any patient completing a pharmacist visit [4]. Drug therapy problems will be categorized as pertaining to effectiveness, indication, safety, or adherence and relationship to renoprotective or nephrotoxic medications (Textbox 2). Drug therapy problems will be assessed and categorized by a single pharmacist with 11 years of experience and advanced credentialing as a medication management services pharmacist specializing in primary care.

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Textbox 2. Medications classified as nephrotoxic or renoprotective. Medication data will be collected at baseline (ie, preadmission medications), hospital discharge, and 30-day outpatient follow-up.

Nephrotoxic medications

- Antivirals: Acyclovir, ganciclovir, tenofovir, valacyclovir, foscarnet
- Antibiotics: Aminoglycosides, ciprofloxacin, colistimethate, nafcillin, oxacillin, penicillin, polymyxin, rifampin, trimethoprim/sulfamethoxazole, vancomycin (intravenous product only), piperacillin/tazobactam, ticarcillin or clavulanate
- Immunosuppressants: tacrolimus, sirolimus, cyclosporine
- Chemotherapeutics: Carboplatin, cisplatin, cyclophosphamide, ifosfamide, imatinib, irinotecan, gemcitabine, ibrutinib, oxaliplatin, lenalidomide, melphalan, sorafenib, temozolomide, topotecan, methotrexate (>20 mg/week)
- Other: Amphotericin B, lithium, mesalamine, pamidronate, sulfasalazine, topiramate, zonisamide, zoledronic acid, proton pump inhibitors, nonsteroidal anti-inflammatory drugs (includes aspirin doses >325 mg/day)

Renoprotective medications

- Angiotensin-converting enzyme inhibitors
- Angiotensin receptor blockers
- Sodium-glucose cotransporter 2 inhibitors
- GLP-1 receptor agonists

Qualitative Data

Interviews will be conducted by a female study team member with expertise in qualitative methods (DMF) who has no prior relationship with participants. Interviews begin with a brief description of the ACT program, the study's goals, and information about informed consent, which is documented. CFIR domains informed the creation of 1 semistructured interview guide for patients and 1 for staff (Multimedia Appendix 1), where questions are tailored to each role (eg, PCP, pharmacist, and scheduling coordinator). Interviewees will be asked to describe their experiences with the ACT program and their sense of the outcomes. Interviews will be conducted over the phone and recorded and transcribed with permission. Transcripts will be reviewed by 2 additional study team members and content experts (HPM and EFB), with the refinement of the interview guide as needed.

Two study team members, including 1 with training in qualitative methods (HPM), will review observations to assess the impact of the ACT interventions on the clinical encounter. Reviewers will watch the video (when available) or read the transcripts of the encounter. Using an observation template for field notes, encounters will be primarily evaluated for the 5 elements of KAMPS framework (Textbox 1) [19,23]. The duration spent on each KAMPS framework element and discussion about kidney health (relative to other conditions) will be cataloged. Reviewers will record whether they observed the clinician using the ACT clinical decision support tools or any print or electronic materials about AKI or kidney health. Occasions where kidney health is discussed will be cataloged as clinician-initiated or patient-initiated.

Study team members will use freeform field notes throughout the study to document notable observations during interactions with patient and staff participants (eg, participating patients failing to recall study enrollment or their episode of AKI).

Outcomes

Feasibility, Fidelity, and Acceptability

To assess the feasibility of patients' willingness to be enrolled and randomized, we will evaluate the number of patients screened, approached for consent, and randomized during the study time frame (intention-to-treat group). Intervention fidelity will be measured by the proportion of participants in the intervention group who complete the nurse education, laboratory testing, pharmacist visit, and PCP visit (per-protocol group). For those who do not complete the full ACT intervention, we will characterize the attrition (eg, inability to deliver education during hospitalization, inability to schedule postdismissal visits, and patient did not complete the postdismissal visits), which reflects the feasibility of incorporating the ACT program into routine transitional care. We will also evaluate the proportion of participants in the ACT group where clinicians interfaced with clinical decision support alerts using electronic audit trails. Staff participating in interviews will complete the Feasibility of Intervention Measure and Acceptability of Intervention Measure surveys, validated tools to measure implementation outcomes [21]. Acceptability of the ACT program will also be determined through patient completion of the "Was it worth it?" survey at follow-up (Multimedia Appendix 1) [24], qualitative interviews with consenting staff and patients, and observations of the clinical encounter.

Patient Knowledge and Quality of Life

We will evaluate patient knowledge about AKI measured with an adaptation of the Kidney Knowledge Survey (modified KiKS; mKiKS). mKIKS assesses participants' objective knowledge about AKI causes, risk factors, and management [25]. Unanswered questions (missing data) on the mKiKS are assigned a score of 0, and the total score is used for comparisons (Multimedia Appendix 1). Quality of life will be assessed using the PROMIS Global 10 tool v1.2 (Multimedia Appendix 1). Patient-reported outcomes will be collected in person or over the phone by a study team member.

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Process and Clinical Outcomes

Participants will be followed for 1 year post discharge or until death or loss of follow-up within that time frame. Process outcomes include kidney laboratory assessments and their timing, clinician visits (eg, with the PCP, pharmacist, and nephrologist), visit type, and timing (in-person vs telemedicine or web-based). At 90 days, clinical outcomes for assessment include major adverse kidney event, emergency department visits, or unplanned rehospitalization. Incidence of de novo or progressive chronic kidney disease or death up to 12 months after discharge will be documented. The number of identified nephrotoxic or renoprotective medications, medication discrepancies, and drug therapy problems will be described.

Data Analysis

Quantitative Data

To describe the feasibility of ACT and generate preliminary estimates of the effect on patient-reported and clinical outcomes, descriptive analyses will be conducted in three groups: (1) the intention-to-treat population (anyone randomized), (2) the per-protocol population (randomized patients who receive all components of the study intervention), and (3) the complete follow-up population (the per-protocol population with follow-up patient-reported outcomes at 30±7 days). Baseline characteristics will be described with means (SDs) and counts and percentages. Comparisons will use the *t* test for continuous data and the chi-square test for categorical data. Any baseline imbalances ($P<.05$) will be explored as a possible factor to adjust for when the outcome measures are analyzed. Clinical outcomes up to 12 months will be compared with Cox proportional hazards models.

AKI knowledge will be described between groups with the mean mKiKS score. Model imputation will be used for patients with incomplete follow-up. Mean between-group differences in the total baseline and follow-up scores will be compared using the *t* test or nonparametric Mann-Whitney *U* test. An exploratory multivariable linear regression model will be fit with group assignment as the independent predictor of interest, mean follow-up knowledge scores as the dependent variable, and baseline scores as a covariate. Other variables to be considered will include age, sex, baseline health literacy, and baseline comorbidities, specifically CKD.

Qualitative Data

Interview transcripts will be uploaded to NVivo, software that assists in qualitative data organization and analysis. Five interview transcripts will be reviewed by 2 qualitative methods experts (DMF and JMG) and 2 content experts (HPM and EFB) to develop an initial codebook, which will be iteratively refined as it is applied to all interview data by 2 independent coders (DMF and HPM). Codes will be deductive (informed by CFIR domains) and inductive (identification of emerging concepts) and used in a framework analysis conducted by experts in qualitative methods (DMF and JMG) and post-AKI care (HPM and EFB). Themes will be developed through discussion and consensus and compared to ensure they capture the full range and depth of interview data. Themes will be compared between data types (eg, staff roles) and assessed for areas of complementarity (eg, domains describing interrelated factors), concordance, and discordance.

Twenty percent of the recorded encounters will be reviewed independently and in duplicate by 2 study team members. Concordance between individuals in assigned ratings of the 5 elements of the KAMPS framework will be evaluated. If greater than 0.8, reviewers will be considered concordant, and 1 study team member will evaluate the remaining encounters. If concordance is not met, an additional 20% of the included encounters will be evaluated in duplicate.

Data Integration

Quantitative data on feasibility and acceptability will be supported by qualitative data and integrated using an embedding approach. Herein, findings from qualitative interviews will supplement results by providing rich data on patient and staff experiences and perspectives on participating in the ACT program. Data will be integrated at the conclusion of the trial. Divergence (ie, inconsistent or conflicting findings) will be examined through refined data analysis and reconciliation, where results are reviewed with a deliberate focus on understanding inconsistencies. Results will be reported using a weaving narrative and joint display tables.

Sample Size

Pilot data estimates that approximately 1-2 patients per week will be identified with the EHR trigger, of which 70% will be eligible, agree to participate in the trial, and have evaluable outcomes data. We will assess the feasibility of study recruitment and randomization and the chosen outcome measures through comparison with these estimates. We project that a sample size of 25 patients per group is needed to assess the feasibility and acceptability of participating in the ACT intervention. Thus, we aim to enroll 50 total patients during an 18-month study time frame.

Results

This study received funding from the Agency for Healthcare Research and Quality on April 21, 2021. Institutional Review Board approval and study commencement were delayed due to unavoidable challenges associated with the COVID-19 pandemic. Following Institutional Review Board approval on December 14, 2021, the first participant was enrolled on January 24, 2022. As of March 14, 2023, seventeen participants each have been enrolled in the intervention and usual care group (total 34).

Discussion

Overview

Nephrologists have called for integrating other disciplines to enhance AKI survivor care delivery capacity [12]. Nephrologists and PCPs support early laboratory monitoring and kidney function assessment in primary care, and PCP follow-up is considered a cornerstone of care continuity [13]. PCPs have a preexisting rapport with patients and caregivers, familiarity with all the patient's medical conditions, and insights into both clinical and nonclinical factors affecting a patient's health and

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health care. They may also provide less expensive and more accessible care for the health system [5]. As part of comprehensive primary care, the contribution of other allied health team members to care delivery is a recognized facilitator of high-quality, patient-centered care [19,26]. Nurses delivering kidney health education and coordinating post-AKI care have improved patient participation [9] and kidney health knowledge [27]. Likewise, pharmacists are uniquely qualified to complete a detailed medication reconciliation and identify medication therapy problems during the dynamic arc of kidney function recovery [28]. Pharmacist-PCP collaboration can reduce hospital readmission and the potential for medication harm compared to care with a PCP alone [4,29]. Despite widespread support for a multidisciplinary approach to post-AKI care, there is a paucity of data describing the incorporation of nonnephrologists into health care delivery models. The ACT program is poised to address common barriers faced by AKI survivors transitioning from the hospital to home through a patient-centered approach integrated in primary care.

Limitations of the proposed study must be acknowledged. The primary outcome of the trial is feasibility and acceptability, thus the sample size is modest. The data will be collected to gather preliminary estimates on clinical outcomes to inform a future trial, but this study is not expected to provide definitive insight into clinical outcomes. All participants will receive primary care in the same region as the tertiary care center where they are hospitalized for AKI, and all sites use a shared EHR. Although this minimizes the likelihood of missing follow-up data, it is unknown how these findings may translate to patients receiving primary care at a greater distance or in practices that do not share an EHR with the discharging hospital.

Conclusion

The ACT program uses a multidisciplinary, coordinated care transition model to enhance kidney health, knowledge, and safety in high-risk patients with existing gaps in care quality. Results from this trial will indicate the feasibility of recruitment and retention, study procedures, chosen outcomes, and the acceptability of the ACT program to patients and staff participants. In addition, this will determine the suitability of the ACT program for further large-scale testing, with the ultimate goal of improving patient and provider experience and outcomes.

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Data Availability

Source data may be made available upon reasonable request.

Authors' Contributions

All authors take responsibility for the trial protocol and provided critical manuscript revision.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Instruments and guides.
[PDF File (Adobe PDF File), 305 KB - resprot_v12i1e48109_app1.pdf]

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Abbreviations

ACT: Acute Kidney Injury in Care Transitions
AKI: acute kidney injury
CFIR: Consolidated Framework for Implementation Research
CKD: chronic kidney disease
EHR: electronic health record
mKiKS: modified Kidney Knowledge Survey
PCP: primary care provider

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Protocol

Voluntary Medical Male Circumcision and Incident HIV Infection Among Men Who Have Sex With Men in China (The CoM Study): Protocol for a Randomized Controlled Trial

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Abstract

Background: Systematic reviews and meta-analyses based on observational studies have shown voluntary medical male circumcision (VMMC) may reduce HIV risk among men who have sex with men (MSM). There is a lack of randomized controlled trial (RCT) data assessing the efficacy of VMMC.

Objective: The primary objective of this study is to assess the efficacy of VMMC for preventing HIV acquisition among MSM who primarily engage in insertive anal sex.

Methods: A multicenter RCT will be conducted among MSM in 8 cities in China. Eligible participants are men aged 18-49 years who self-report ≥2 male sex partners in the past 6 months, predominantly practice insertive anal sex, and are willing to undergo circumcision. Interested men who satisfy inclusion criteria will be tested for HIV 1 month before enrollment and at enrollment, and only those who are HIV negative will be enrolled. At baseline, all enrolled participants will be asked to report sociodemographic characteristics and sexual behaviors; provide a blood sample for HIV, syphilis, and herpes simplex virus type 2 testing; and provide a penile swab for human papillomavirus testing. Participants will be randomly assigned to the intervention or control group. Those in the intervention group will receive VMMC and undergo a web-based weekly follow-up assessment of postsurgery healing for 6 consecutive weeks. All participants will be tested for HIV at 3-, 6-, 9-, and 12-month follow-ups. All participants will also be asked to report sexual behaviors and undergo repeat herpes simplex virus type 2 and human papillomavirus testing at 6- and 12-month follow-ups. The primary end point is HIV seroconversion. Secondary end points are

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the safety and satisfaction with VMMC and the changes in sexual behaviors after VMMC. The grouped censored data will be analyzed by intention-to-treat approach.

Results: Recruitment for the RCT began in August 2020 and continued through July 2022. Data collection is expected to be completed by July 2023, and full data analysis is going to be completed by September 2023.

Conclusions: This study will be the first RCT to assess the efficacy of VMMC in preventing HIV infection among MSM. Results from this trial will provide preliminary evidence for the potential efficacy of VMMC to reduce incident HIV infection among MSM.

Trial Registration: Chinese Clinical Trial Registry ChiCTR2000039436; https://www.chictr.org.cn/showproj.html?proj=63369

International Registered Report Identifier (IRRID): DERR1-10.2196/47160

(JMIR Res Protoc 2023;12:e47160) doi:10.2196/47160

KEYWORDS

voluntary medical male circumcision; HIV; men who have sex with men; randomized controlled trial; China

Introduction

Overview

Men who have sex with men (MSM) are at high risk for HIV infection. Evidence-based HIV preventive measures for MSM include behavioral interventions (eg, condom use) and biomedical interventions (eg, preexposure prophylaxis [PrEP] and postexposure prophylaxis [PEP]). Condoms are highly effective in preventing HIV transmission, but the prevalence of condomless sex remains high among MSM [1,2]. HIV PrEP reduces risk of HIV infection, but uptake among MSM is limited [3]. The effectiveness of HIV PEP is constrained by lack of awareness, limited availability of PEP services, and poor adherence to medications and clinic follow-ups, particularly in resource-limited settings [4-6]. Innovative, effective, and acceptable HIV prevention measures are needed to complement and expand existing prevention strategies among MSM.

Voluntary medical male circumcision (VMMC) may protect men from HIV infection by reducing mucosal surface area and the concentration of HIV target cells in the penis [7,8]. Three large randomized controlled trials (RCTs) in Africa found that VMMC reduced the risk of HIV infection by 50%-60% among heterosexual men [9-11]. Debate remains on whether VMMC can effectively prevent HIV acquisition among MSM. Two systematic reviews and meta-analyses in 2008 and 2011 [12,13] showed that there was no statistically significant association between VMMC and HIV acquisition among MSM. However, new evidence has emerged over the past 10 years. A 2018 meta-analysis found that VMMC may reduce risk of HIV infection by 20% among MSM [14]. Similarly, a 2019 systematic review and meta-analysis of 67 observational studies [15] reported that VMMC was associated with a 23% lower odds of HIV infection among MSM overall and 42% lower odds of HIV among MSM in low- and middle-income countries. Furthermore, VMMC was associated with a 16% lower odds of herpes simplex virus and a 29% lower odds of penile human papillomavirus (HPV) infection among MSM living with HIV [15]. Another systematic review in 2019 [16] found VMMC was associated with 7% and 38% lower odds of HIV infection among MSM overall and MSM in Asia and Africa, respectively. These systematic reviews found that no previous RCTs have evaluated the impact of circumcision on HIV acquisition among MSM. Interventional trials are needed to confirm the findings of previous observational studies.

Sexual position preference may have a significant impact on the efficacy of VMMC to reduce HIV infection among MSM. Men who practice insertive anal sex may benefit more from VMMC than those who practice receptive anal sex. Subanalysis in a 2019 systematic review and meta-analysis [15] found that MSM who primarily engage in insertive anal sex had a 56% lower odds of HIV infection, a stronger association compared to what was found among MSM overall. In China, 70% of MSM practice either exclusively insertive anal sex or both insertive and receptive anal sex [17,18]. Thus, VMMC has the potential to become an important HIV prevention option for most MSM in China.

Only 15.3% of MSM in China have undergone circumcision [19]. This proportion is lower than the global average of 37%-39% [20]. Mainstream social conventions and religious practice in China are neutral on circumcision, neither promoting nor forbidding the procedure. Implementing a VMMC intervention in China should not be significantly hindered by Chinese traditions or cultural values. Other potentially effective interventions, such as PrEP, are still in promotion phase in China, which is impeded by high cost, low accessibility, and stigma among MSM [21,22]. As for consistent condom use, the rate of its use among MSM remains relatively low, approximately 50% [23,24]. Hence, it is essential to determine an alternative HIV prevention strategy in China. Given the high proportion of Chinese MSM who are uncircumcised and the need for alternative HIV prevention strategies in China, it is theoretically feasible to conduct an RCT to evaluate the efficacy of VMMC to reduce incident HIV infection among MSM in China. This RCT could provide valuable information to inform HIV prevention policy as well as future mathematical models and additional clinical trials of VMMC.

Objectives

The primary objective of this study is to assess the efficacy of VMMC for preventing HIV acquisition among MSM who primarily engage in insertive anal sex. The secondary objectives are to assess (1) the safety of and satisfaction with surgical VMMC among MSM; (2) changes in reported sexual risk behaviors after circumcision among MSM; and (3) the efficacy

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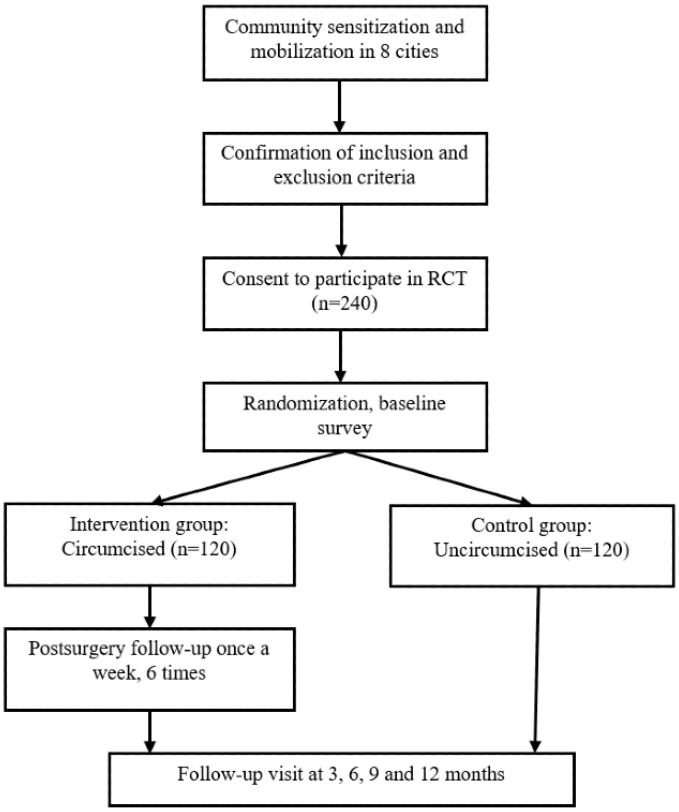
of VMMC for preventing sexually transmitted infections (STIs), including herpes simplex virus type 2 (HSV-2), syphilis, and penile HPV among MSM. Our hypothesis is that VMMC could reduce the risk of HIV infection among MSM.

Methods

Study Design

This is a multicenter RCT to evaluate the efficacy of VMMC on incident HIV infection among MSM in China over a 12-month follow-up period (Figure 1).

Figure 1. The flow chat of the CoM (circumcision of men who have sex with men) Study. RCT: randomized controlled trial.



Study Setting

The VMMC and incident HIV infection among MSM in China (circumcision of men who have sex with men [CoM] Study) will be conducted in 8 cities in Mainland China: Beijing, Tianjin, Qingdao, Chongqing, Shenzhen, Guangzhou, Foshan, and Luzhou (Table 1).

This study began on August 1, 2020, and is scheduled to be completed by September 31, 2023. The study has 3 phases: eligibility screening, enrollment, and follow-up (Table 2).

Table 1. Study sites of the CoM (circumcision of men who have sex with men) Study.

City and province	Study site	Nature of study site
Beijing	Beijing You'an Hospital, Capital Medical University	Tertiary hospital
Tianjin	Tianjin Centers for Disease Control and Prevention	Provincial CDC[a]
Qingdao, Shangdong	Qingtong Volunteer Service Center for HIV/AIDS Prevention	NGO[b]
Guangzhou, Guangdong	Guangzhou Zhitong Public Service Center	NGO
Shenzhen, Guangdong	Shenzhen Rainbow 258 Center for Men	NGO
Foshan, Guangdong	Foshan Pengyou Care and Rescue Center for AIDS Prevention	NGO
Chongqing	AIDS/STD[c] Control and Prevention Institute, Chongqing CDC	Provincial CDC
Luzhou, Sichuan	Luzhou Red Ribbon Heart Association	NGO

[a]CDC: centers for disease control and prevention.

[b]NGO: nongovernmental organization.

[c]STD: sexually transmitted disease.

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Table 2. Schedule of events of the CoM (circumcision of men who have sex with men) study.

Events	Eligibility screening	Enrollment	Follow-up			
	Month 1	Month 0 (baseline)	Month 3	Month 6	Month 9	Month 12
Recruitment and enrollment						
Screening questionnaire	√					
One-on-one consultation	√					
Watching enrollment videos	√					
Informed consent		√				
Assignment of study group		√				
Intervention[a]		√				
Assessments						
HIV rapid testing	√	√	√	√	√	√
Baseline questionnaire		√				
Follow-up questionnaire				√		√
STIs screening[b]		√		√		√

[a]For participants in the intervention group, they will be formally enrolled after completing the circumcision. There is a maximum waiting period of 3 months for surgery and a 6-week postoperative recovery period before formal follow-up phase. For participants in the control group, they will remain uncircumcised at enrollment and follow-up, and they will enter the formal follow-up phase after completing the enrollment and baseline questionnaire.

[b]STIs include herpes simplex virus type 2, syphilis, and penile human papillomavirus.

Interventions

VMMC is the intervention to be evaluated in this study. Men in the intervention group will undergo VMMC within 3 months of randomization, and they could choose one of 2 types of circumcision (disposable circumcision stapler surgery and conventional surgical procedure), while those in the control group will remain uncircumcised during the follow-up. All men will be followed for 12 months.

Study Outcomes

The primary outcome is HIV incidence, comparing the intervention and control groups. Secondary outcomes are the safety and satisfaction with VMMC; changes in sexual behaviors after VMMC will also be evaluated. The penile HPV incidence, clearance, and persistent infection; HSV-2 incidence; and syphilis incidence are compared in both groups.

Eligibility Criteria

Individuals who meet all of the following criteria are eligible for enrolment in the CoM Study: (1) aged 18-49 years; (2) assigned male sex at birth; (3) ≥2 male sex partners and ≥10 episodes of anal sex in the past 6 months; (4) practiced insertive role in ≥7 of the last 10 episodes of anal sex with male sex partners; (5) HIV negative; (6) has foreskin that covers over half the glans when the penis is not erectile; (7) is willing to undergo VMMC; (8) resides in the city where a study site is located and has no plan to relocate in the next 12 months; (9) is willing to provide a blood sample and exfoliated penile swabs to test for HIV, HSV-2, syphilis, and HPV; and (10) is able to provide informed consent. Men who are already circumcised or enrolled in other biomedical HIV intervention studies will be excluded. Men who have been diagnosed with a bleeding disorder or have other medical contraindications to VMMC will also be excluded.

Patient and Public Involvement

There was collaboration with MSM community–based organizations staff who were not involved in the study, to ensure study processes were well integrated into these settings. Patients were not involved in the design of the study.

Participant Recruitment and Enrollment

As the distribution of our target population unknown and MSM in China are a hard-to-reach population, we will use convenience sampling and snowball sampling to recruit participants. A public account on WeChat (a multi-purpose instant messaging app developed by Tencent, with over 1 billion active monthly users) will be used to communicate with participants. Recruitment, enrollment, provision of health education, and participant follow-up will be accomplished through WeChat. This RCT will also recruit and enroll potential participants in collaboration with local MSM community–based organizations by using their organizational WeChat accounts and in-person outreach activities. An offline survey will be carried out at MSM community–based organizations and the department of dermatology at participating hospitals.

A QR code which links to an online screening questionnaire will be included in recruitment materials. Recruitment materials will include paper materials (eg, posters, folding pages, table tent cards, and business cards) and video materials (ie, a 2-minute enrollment video with a brief introduction and a 15-minute enrollment video with detailed information). Paper and video materials will include summaries of the following: (1) current state of research on efficacy of VMMC to prevent HIV infection; (2) potential benefits of VMMC; and (3) potential

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risks of VMMC. Potential participants will be invited to scan the QR code included in these paper or video materials and then complete a web-based screening questionnaire with preprogramed logic to assess eligibility.

Eligible men will be invited to participate in this study. Men who agree to participate will receive a face-to-face introduction to the CoM Study by a trained investigator at the study site. Questions about the study will be answered by these investigators during these introductions. For men who are willing to undergo VMMC, HIV rapid testing will be conducted 1 month before enrollment and at enrollment.

Randomization and Follow-Up

Eligible men will be randomized using a 1:1 allocation ratio to the intervention and control groups. Randomization lists for each study site have been pregenerated by researchers. Each envelope with a unique number will be assigned for 1 allocation sequence, into which a card with grouping information will be put before sealing. Trained investigators at each study site will assign an envelope to each participant according to the order of the participant's arrival. Participants cannot be blinded due to the nature of the intervention. After randomization, trained researchers will provide HIV prevention counseling to participants in both groups, including promotion of consistent condom use and regular HIV testing.

Participants randomized to the intervention group will be encouraged to complete VMMC within 1 week of enrollment. Time to VMMC can be extended up to 3 months after enrollment on a case-by-case basis. We recommend participants to undergo VMMC at a secondary or higher-level medical center of their own choice. Although the clinical VMMC activities are not part of study procedures, a research assistant would accompany the participants to the hospital to undergo the circumcision. This trial will provide a surgical subsidy of CNY 1000 (US $160). If participants do not complete VMMC within 1 month of enrollment, a text message reminder will be sent. The surgeon will check the condition of the foreskin of participants before the operation to determine if surgery is necessary. Men in the intervention group will be advised to abstain from sex for 6 weeks after undergoing VMMC, and the 12-month follow-up period will begin after this 6-week period of abstinence. If men resume sexual behaviors earlier than 6 weeks after VMMC, then the 12-month follow-up period will begin at the time of their first sexual encounter after VMMC.

Men randomized to the control group will complete the baseline survey after enrollment. The 12-month follow-up period for the control group will begin immediately after completing the baseline survey. At the end of the 12-month follow up period, men in the control group will be offered a CNY 1000 (US $160) subsidy to undergo VMMC.

Study Measures

The baseline and follow-up surveys will collect information on sociodemographic characteristics (including age, ethnic, educational background, marital status, and monthly individual income) and sexual behaviors (including the number of male and female sex partners, frequency of vaginal or anal sex, condom use, and HIV-positive sex partners) for all enrollment participants. Follow-up surveys will be completed at 6- and 12-month follow-ups. Men randomized to receive VMMC will also be asked to complete weekly follow-up surveys for 6 weeks after VMMC to monitor for postsurgical complications, including pain, poor surgical site wound healing or infection, and premature resumption of sexual behaviors. If an adverse event is reported, trained investigators will contact participants and provide advice on whether further clinical evaluation is needed.

Fingertip blood drop samples will be collected at baseline as well as 3-, 6-, 9- and 12-month follow-ups and tested for HIV using an HIV rapid test. Venous blood samples collected at baseline as well as 6- and 12-month follow-ups will be tested for HIV, syphilis, and HSV-2. Penile swab samples will be collected at baseline as well as 6- and 12-month follow-ups and tested for HPV.

HIV rapid testing will detect antibodies against HIV-specific antigens using a solid-phase immunochromatographic assay (SD Bioline HIV/Syphilis Duo test; Standard Diagnostics Inc), and these assays will be performed at study sites. Venous blood samples will be tested for HIV using a chemiluminescent microparticle immunoassay (Anti-HIV CLIA Microparticles; Autobio Diagnostics Co) performed at Guangzhou Hybribio Medical Laboratory Limited. If a participant's sample is found to have a positive result for HIV, we will recollect a venous blood sample from that participant and perform a confirmatory Western blot test at the local Centers for Disease Control and Prevention. Except for HIV, laboratory assays will be applied for syphilis, HSV-2, and HPV test. HPV DNA testing and genotyping was performed using the 37 HPV GenoArray Diagnostic Kit (Hybribio; Chaozhou, China). Syphilis serological tests will be performed using tolulized red unheated serum test and treponema pallidum particle assay. Detection of HSV-2 immunoglobulin G and HSV-2 immunoglobulin M in blood samples are based on a chemiluminescent microparticle immunoassay. Participants who test positive for pathogens or antibodies will be offered STI counseling and referred to a hospital for treatment.

Participation Incentives and Follow-Up Reminders

Web-based educational materials on sexual health will be regularly posted for all participants to read via WeChat by the CoM Study's official WeChat account. Short voluntary quizzes will be included at the end of each posted educational material, and participants who complete these quizzes will receive a CNY 2 or CNY 5 (US $0.3 or US $0.8) reimbursement. Each participant will also receive a CNY 50 (US $8) reimbursement each time they complete a questionnaire and provide a blood sample for HIV and STI testing. Participants who complete the surgery according to the study procedures will receive CNY 1000 (US $160) surgery subsidy. In addition, participants will receive an additional CNY 500 (US $80) subsidy after completing all required follow-up surveys as well as HIV and STI testing.

Reminders to complete follow-up surveys will be sent to all enrolled men via WeChat. If follow-up surveys are not completed on time, investigators will contact enrolled participants with additional reminders each week for up to 5

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weeks to encourage participation and minimize loss to follow-up.

Data Collection and Management

All data will be collected using Wenjuanxing (Ranxing Information Technology Co, Ltd [25]), a web-based questionnaire platform. Several quality-control questions will be included in the study questionnaires, and the consistency of answers will be examined by trained investigators. Information concerning identification, eligibility, baseline surveys, intervention, and follow-up surveys will be recorded in case record form. Adverse events will also be recorded. Identity information will be collected for allowance distribution purpose only, which will not be used for statistical analysis or intended for information leakage. Only study staff will be able access the study database, which will be protected with a unique log-in password that will be updated monthly to maximize data safety. The data safety monitoring committee (DSMC) of the CoM Study will be comprised of 2 statisticians, 2 clinicians, and key study investigators. The DSMC will supervise procedures, including data quality control, data integrity, data security, data sharing, and data analysis. All investigators have completed standard operating procedure training and data management training.

Sample Size

The sample size is calculated based on the supposed protective rate of circumcision. Studies have shown that HIV incidence among MSM was 12.5/100 person-years in Chongqing [26], 15.5/100 [27] and 10.3/100 person-years [28] in Shenyang, and 15.6/100 person-years in 8 cities in China [29]. Considering participants in the CoM Study predominantly practiced insertive anal sex, consequently with lower HIV infection risk compared with those who primarily practiced receptive role, and that the effect of VMMC may be higher among men who primarily or exclusively practice the insertive anal intercourse than MSM overall, we suppose HIV incidence among MSM to be 10/100 person-years and protective rate of circumcision to be 80%, and thus, HIV incidence would be 2/100 person-years in the intervention group. A target sample size of 240 (120 in each group) is set to achieve 80% power at 1-sided α=.10, with 10% lost to follow-up.

Statistical Analysis

All data will be analyzed based on the principle of intention to treat. We will assess the type of missing data and assess attrition effects by testing whether there are systematic differences between dropouts and nondropouts. Key baseline characteristics will be examined between the intervention and control groups to ensure they are balanced; if not, subsequent analyses will assess whether these characteristics are confounding factors of the intervention.

For continuous variables, we will calculate means and SDs, and means will be compared with 2-sample *t* tests or Mann-Whitney tests. For categorical variables, proportions will be compared with chi-square tests or Fisher exact tests. In addition, we assume that HIV status at the end of follow-ups is grouped censored data and suitable for exponential, proportional hazards model with constant baseline hazard. Therefore, differences between the intervention and the control groups will be identified with a Poisson regression model, which includes observed covariates (ie, HIV risk behaviors, such as condom use, number of sexual partners, frequency of insertive anal sex, and HIV-positive sexual partners as well as demographic variables, such as age, education level, and income). Incidence rates will be calculated for each outcome in the 2 groups. Moreover, the incidence rate ratios and their 95% CIs will be estimated using the Poisson regression model. For all the outcome variables, including the primary (ie, HIV incidence) and secondary (ie, penile HPV incidence, clearance and persistent infection, HSV-2 incidence, and syphilis incidence) outcomes of interest, the aforementioned analyses will be repeated across all the visits (ie, 6- and 12-months follow-ups).

The changes in sexual behaviors after VMMC over time between the intervention and the control groups will be compared with the generalized estimating equations. For outcomes of VMMC safety and satisfaction among circumcised MSM, we will perform the same statistical description and comparative analyses described as above.

A 2-sided *P* value lower than .05 will be used to infer statistically significant difference. All the statistical analyses will be performed with R software (version 4.2.1; R Core Team).

Ethics Approval

This study has obtained ethics approval from Ethical Review Committee for Biomedical Research of School of Public Health (Shenzhen), Sun Yat-sen University (SYSU-PHS-2020041) and Ethics Committee of Beijing Youan Hospital, Capital Medical University (2020-049). All participants will provide written consent prior to taking part in the study.

Results

Participant recruitment began in August 2020 and continued through July 2022. We expect that follow-up phase and data collection will be completed by July 2023, and primary data analyses will be completed by September 2023. The study findings will be submitted for presentation at relevant international conferences and for publication in a peer-reviewed journal.

Discussion

Principal Findings

The CoM Study is an RCT to evaluate the efficacy of VMMC to prevent incident HIV infection among MSM in China. MSM who primarily practice insertive anal sex and are willing to undergo VMMC will be recruited using promotional materials disseminated through web-based platforms and community-based organizations. Participants will be randomly assigned to receive or not receive VMMC and then will be followed for a 12-month period to assess incident HIV infection. As an RCT with limited observed person-years, priority will be given to MSM with high-risk sexual behaviors. Follow-up for MSM randomized to receive VMMC will start after a 6-week postsurgical follow-up period to ensure men in the intervention and control groups have comparable opportunity to acquire HIV

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after enrollment. HIV testing will be conducted every 3 months; it helps to detect acute HIV infection. Findings from this trial will provide preliminary RCT evidence on whether VMMC can effectively prevent HIV among MSM.

Limitations

The CoM Study will have several limitations. First, because the 8 study sites are located in different parts of Mainland China, we cannot ensure that VMMC will be performed in a uniform manner for all men randomized to the intervention group. We will provide men in the intervention group with a list of hospitals that provide standard VMMC services. But men will be able to choose a hospital at their own discretion. Second, MSM who undergo VMMC may experience surgical site complications, particularly when they resume insertive anal sex. Men who have recently undergone VMMC may therefore chose to avoid insertive anal sex. This may increase their frequency of receptive anal sex, and thereby, increase their risk of HIV infection. At enrollment, participants will be provided with detailed sexual health consultations to reduce sexual intercourse during abstinence. Third, sexual health behaviors will be assessed by self-report, and therefore, may be affected by recall and social desirability biases.

Conclusions

To achieve the sustainable development goal of ending the AIDS epidemic as a public health threat by 2030, more viable HIV prevention strategies are urgently needed. The CoM Study proposes VMMC as an intervention and assesses its preliminary efficacy to prevent incident HIV among MSM. Results from this study are expected to offer reliable data in supporting the development of mathematical models, which aim to estimate the effect of VMMC on HIV risk reduction among MSM under various conditions and assumptions.

Acknowledgments

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Data Availability

The data sets used and analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

HZ is the principal investigator of this study and obtained grant funding. HZ, YG, TY, and HZQ conceived the study. YG, WZ, YS, LY, Y Zhan, YFL, YL, ZG, Y Zhou, ZL, and TF participated in the development of the study protocols. BS, ZZ, JD, G Wang, XC, LO, GS, Y Zhou, AL, YY, G Wu, and MY will supervise recruitment and follow-up at study sites. All authors contributed to the intellectual content of the manuscript and the development of the trial protocol, and they have read and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

CoM: circumcision of men who have sex with men
DSMC: data safety monitoring committee
HPV: human papillomavirus
HSV-2: herpes simplex virus type 2
MSM: men who have sex with men
PEP: postexposure prophylaxis
PrEP: preexposure prophylaxis
RCT: randomized controlled trial
STD: sexually transmitted disease
STI: sexually transmitted infection
VMMC: voluntary medical male circumcision

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Protocol

Testing the Efficacy of a Scalable Telephone-Delivered Guided Imagery Tobacco Cessation Treatment: Protocol for a Randomized Clinical Trial

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Abstract

Background: Tobacco use continues to be a leading preventable cause of death and disease in the United States, accounting for >480,000 deaths each year. Although treatments for tobacco use are effective for many, there is substantial variability in outcomes, and these approaches are not effective for all individuals seeking to quit smoking cigarettes. New, effective therapeutic approaches are needed to meet the preferences of people who want to stop smoking. Guided imagery (GI) is a mind-body technique that involves the guided visualization of specific mental images, which is enhanced with other sensory modalities and emotions. Preliminary evidence provides initial support for the use of GI as a treatment for cigarette smoking. Meta-analyses have shown that standard treatment for cigarette smoking delivered over the telephone via quitlines is effective. A telephone-based intervention that uses GI might provide another effective treatment option and increase the reach and effectiveness of quitlines.

Objective: This study aims to test the efficacy of *Be Smoke Free*, a telephone-delivered GI treatment for smoking cessation.

Methods: This multisite randomized clinical trial (RCT) will compare a novel telephone-delivered GI tobacco cessation treatment with a standard evidence-based behavioral treatment. The study will be conducted over 5 years. In phase 1, we refined protocols and procedures for the New York State and West Virginia sites for use in the RCT. During phase 2, we will conduct an RCT with 1200 participants: 600 (50%) recruited via quitlines and 600 (50%) recruited via population-based methods. Participants will be randomly assigned to either the GI condition or the behavioral condition; both treatments will be delivered by trained study coaches located at the University of Arizona. Assessments will be conducted at baseline and 3 and 6 months after enrollment by University of Arizona research staff. The primary outcome will be self-reported 30-day point prevalence abstinence 6 months after enrollment. Secondary outcomes include biochemically verified 7-day point prevalence abstinence 6 months after enrollment.

Results: Recruitment in West Virginia and New York began in October 2022. As of March 31, 2023, a total of 242 participants had been enrolled. Follow-up assessments began in November 2022. As of March 31, 2023, of the 118 eligible participants, 97 (82.2%) had completed the 3-month assessment, and 93% (26/28) of eligible participants had completed the 6-month assessment. Biochemical verification and qualitative interviews began in April 2023. Recruitment will continue through 2025 and follow-up assessments through 2026. Primary results are expected to be published in 2027.

Conclusions: The *Be Smoke Free* study is a first-of-its-kind RCT that incorporates GI into telephone-based tobacco cessation treatment. If successful, *Be Smoke Free* will have substantial benefits for the long-term health of people who use tobacco across the United States.

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International Registered Report Identifier (IRRID): PRR1-10.2196/48898

(JMIR Res Protoc 2023;12:e48898) doi:10.2196/48898

KEYWORDS

tobacco; smoking; treatment; integrative health; guided imagery; behavior change; telephone; mobile phone

Introduction

Background

Tobacco use continues to be a leading preventable cause of death and disease in the United States, accounting for >480,000 deaths each year, including 41,000 deaths from secondhand smoke exposure [1,2]. The annual economic cost of tobacco use in the United States was US $332 billion in 2014 and increases every year [2,3]. Moreover, tobacco use aligns with other systemic health inequities in the United States [1,4]. The prevalence of tobacco use among Medicaid beneficiaries and individuals of lower socioeconomic status is nearly twice that among the general population [1,4]. Importantly, however, tobacco cessation results in a nearly universal improvement in health.

Although evidence-based treatments for tobacco use are effective for many, there are multiple limitations, including a substantial variability in outcomes and limited reach. Current evidence-based approaches are not effective for every individual seeking to stop smoking [2,5]. Quitlines have made standard cognitive behavioral treatment widely accessible, but they reach fewer than 1% of the individuals who smoke cigarettes annually. In addition, evidence suggests that at least some of the individuals who smoke do not wish to engage in *standard* cognitive behavioral treatment and would prefer a more holistic or integrative approach (ie, combining complementary or alternative and standard treatments) [6-9]. New therapeutic approaches are needed to attract, engage, and retain individual tobacco users in treatment for smoking cessation and ultimately increase the number of individuals who achieve long-term abstinence from tobacco use.

A large proportion of the American population uses integrative health approaches, including mind-body techniques, in addition to, or instead of, conventional treatment [5]. Guided imagery (GI) is a mind-body technique that involves the visualization of mental images. GI is an alternative way to develop effective strategies to quit smoking, such as developing awareness and directing attention to one's thoughts, feelings, situational cues or triggers, and urges. GI can effectively assist individuals to quit or reduce smoking [6-8]. A randomized controlled trial (RCT) with 779 adult smokers compared the use of bupropion versus brief psychotherapy that included GI intended to enhance self-management, decidedness, assertiveness, self-determination, and self-assurance [8]. Intent-to-treat analysis showed 12-month abstinence rates of 39.1% and 12.3% for the psychotherapy and bupropion groups, respectively [8]. In another RCT, 33 adults were taught mindfulness and GI and encouraged to practice at home [9]. The results showed that home practice predicted reduced cigarette use over 4 weeks [9]. In a pilot RCT, a GI program for smoking cessation was found to be feasible and improved intermediate abstinence measures [10]. In a small trial that compared education and counseling with education and counseling plus GI training, abstinence rates were 12% and 26%, respectively [7]. Finally, our teams' preliminary evidence provides strong support for the use of GI for smoking cessation [11,12]. These findings support the potential efficacy of GI for smoking cessation. In addition, we are proposing to deliver a GI intervention in a low-cost highly scalable way (ie, by telephone). To date, no studies have established the efficacy of an integrative GI tobacco cessation treatment delivered by telephone.

Several meta-analytic reviews have shown that proactive telephone-based tobacco cessation services are an effective way to deliver treatment for tobacco dependence [13-15]. Telephone quitlines are efficient, centralized, and a highly scalable way for individuals to access tobacco treatment in all 50 states plus the District of Columbia, Guam, and Puerto Rico. Quitlines are the largest tobacco treatment network in the United States [16,17]. Researchers have demonstrated the cost-effectiveness of telephone quitlines in the United States and Europe over the past 25 years [3,13,15,18]. However, quitlines have limited reach into the population of people who use tobacco in the United States. According to a recent study, most US quitlines reach only 1.1% of this population [19]. This situation has prompted many state sponsors to try to improve their reach by increasing the types of evidence-based treatment offered to tobacco users. Evidence-based integrative treatment approaches that are appealing to those individuals not interested in standard behavioral approaches may increase the reach and effectiveness of quitlines. Using telephone technology enables access to a wide range of people who smoke because it does not rely on having an internet connection or competence in using more advanced technology. According to a 2019 survey [20], about 96% of Americans own a mobile phone of some kind; thus, our intervention is highly accessible and scalable.

Objectives

The objective of this RCT is to test the efficacy of *Be Smoke Free*, a telephone-delivered integrative GI treatment for smoking cessation compared with a standard, evidence-based behavioral treatment. The specific aims and hypotheses of the study are described in the following subsections.

Aim 1

We will test the efficacy of a telephone-delivered integrative GI tobacco cessation treatment versus an evidence-based behavioral treatment on self-reported 30-day abstinence 6 months after enrollment (T2). Secondary outcomes are self-reported and biochemically verified 7-day point prevalence smoking abstinence at T2.

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Hypothesis 1

Participants in the GI condition (GIC) will demonstrate 10% higher quit rates than those in the behavioral condition (BC).

Aim 2

We will conduct dose-response analyses on the effect of GIC adherence (measured by self-reported minutes of intervention use per week, the number of times GI skills practiced per week, the number of sessions attended, and coach-rated participant engagement in sessions) on abstinence at 6 months. We will also examine effects of the GIC and BC on tobacco use for those participants who do not report abstinence at 6 months.

Hypothesis 2A

GIC participants who are more adherent to the intervention will have higher rates of abstinence.

Hypothesis 2B

GIC and BC participants who do not report abstinence will report statistically significant reductions in tobacco use.

Aim 3

We will conduct subgroup analyses of moderators (eg, recruitment method, location, sex, race and ethnicity, and the level of tobacco dependence) on tobacco cessation outcomes at 6 months and explore subgroup differences in participants using a mixed methods approach (eg, surveys and in-depth interviews).

Project Impact

The project has the potential for high overall impact. Should this approach become readily available to quitlines as an evidence-based treatment, it will provide a sustainable and powerful alternative to the traditional treatment options available throughout the United States. There have been few innovations in quitline treatment. Thus, increasing the treatment options might also serve to increase the reach of quitlines into the tobacco-using population.

Methods

Overview

This 5-year, 2-group RCT will test the efficacy of the integrative GI treatment versus an evidence-based behavioral treatment. Participants will be recruited from 3 states (Arizona, New York State, and West Virginia). We will randomize 1200 participants to either the GIC or the BC: 600 (50%) participants will be recruited through the quitlines (n=200, 33.3%, per quitline) and 600 (50%) through population-based methods (eg, social media, earned media, local organizations, and health care providers) to ensure that we obtain a representative sample of people who smoke. Assessments will occur at baseline (T0), 3 months after enrollment (T1), and T2. The research team will deliver the GIC and BC protocols, coordinate and conduct all assessments, and perform all data analyses at the University of Arizona. The primary outcome will be self-reported 30-day abstinence at T2. Secondary outcomes will be self-reported and biochemically verified (expired carbon monoxide [CO]) 7-day point prevalence abstinence at 6 months.

This study is being conducted in 2 phases: during phase 1, we refined protocols and procedures for the New York State and West Virginia sites for use in the RCT. During phase 2, we are conducting the RCT.

Phase 1: Revisions to Protocols and Procedures

We worked with our collaborating quitlines to revise procedures for recruitment, screening, data transfer, and reporting for half of our sample. Each of our participating sites provides different services and uses different procedures for screening callers. This required us to tailor our study recruitment, screening protocols, and procedures for each site. We also worked with each quitline to identify existing networks (eg, health departments and community organizations) to add to our population-based recruitment methods for each state. In addition, we tailored the methods for transferring participant data from each quitline to our project staff in a Health Insurance Portability and Accountability Act (HIPAA)–compliant and secure manner. Finally, we worked with each site to determine the process for providing regular reports on client contacts and tracking callers transferred to study staff. Noneligible callers who are transferred by project staff to our study will be transferred back to their respective quitlines so that they may return for quitline services before study completion. We worked with staff at each site to learn about their unique structures and tailor all study processes and materials to fit both the needs of the quitline and our study. Half of our sample will be recruited through the quitlines.

We will use population-based methods (eg, social media paid advertising, earned media, and community contacts) for the other half of the sample. The materials and methods created during the feasibility trial were designed for use in Arizona [21]. Therefore, they were modified for use in the other states participating in this study. These states serve different demographics of tobacco users who may also need to be reached in different ways (eg, rural vs urban and print vs web based). We worked with our collaborators in each state to identify changes that needed to be made to the text and graphics in our recruitment advertisements and materials (eg, wording and images for advertisements placed on social media and different photographs representing tobacco users in each state for use in print materials). We convened a community advisory board (CAB) that included key informants from each state (eg, members of community health organizations identified by our collaborators) to obtain information using semistructured questionnaires. Interviews or group interviews were recorded and transcribed. The study team analyzed the comments and developed a plan for refining the recruitment methods and materials for each state.

In consultation with our collaborating quitlines, we made minor refinements to our study protocols and corresponding participant materials to address the specific needs of people who use tobacco in different states; for example, although all participants will identify their primary tobacco use as cigarette smoking, a proportion will also use other tobacco products (eg, e-cigarettes or vaping products and smokeless tobacco). The use of these other tobacco products varies widely by state. The prevalence of smokeless tobacco use is very low in Arizona but much higher in West Virginia (2.8% vs 8.9%, respectively) [22]. Therefore,

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we have included additional information in the protocols to address secondary smokeless tobacco use. On the basis of the information and feedback we received from each participating site, we made final changes to our protocols, which were programmed into REDCap (Research Electronic Data Capture; Vanderbilt University). Using REDCap allows our coaches to consistently deliver the protocol for each condition across participants and collect data on each session. For this RCT, we used the same REDCap system developed under the feasibility trial.

On the basis of changes to the study protocols, we made corresponding refinements to the coach training program and coach materials. Information was added regarding regional differences in smoking and other tobacco use patterns, culturally responsive counseling for specific racial and ethnic groups, issues specific to rural versus urban tobacco users, and other state-specific differences that the coaches may encounter when working with participants across our participating states.

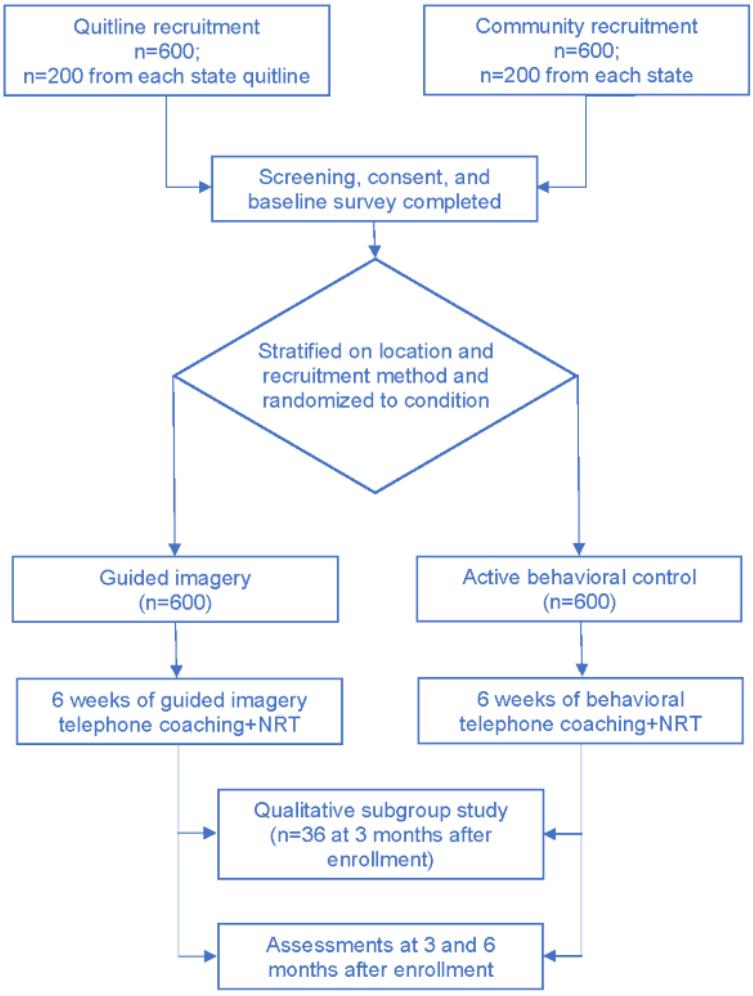
We hired 4 coaches (2 for each condition) to deliver one of the study protocols at the University of Arizona. The training of the intervention coaches included a 2-part workshop, individual and group exercises designed to provide practical experience that resulted in competency to deliver the protocols and achieve a positive therapeutic alliance, and ongoing supervision designed to solve problems and maintain implementation fidelity. The workshops for both conditions involved the cognitive and motivational underpinnings of each program. The BC workshop focused solely on behavioral strategies for motivating and assisting tobacco users to quit and the use of nicotine replacement therapy for minimizing withdrawal symptoms. The GIC workshop included all content in the BC workshop plus the use of GI, including how to create vivid and evocative GI scripts and record them as audio files for participants assigned to this condition.

Phase 2: RCT

Study Design

This 2-group RCT will test the efficacy of the integrative GIC versus the evidence-based BC. Participants will be recruited from 3 states (Arizona, New York State, and West Virginia). We will randomize 1200 participants to either the GIC or the BC. Of these 1200 participants, 600 (50%) will be recruited through the quitlines (n=200, 33.3%, per quitline) and 600 (50%) through population-based methods (eg, social media, earned media, local organizations, and health care providers) to ensure that we obtain a representative sample of smokers (Figure 1). Assessments will occur at T0, T1, and T2. The research team will deliver the intervention and control protocols, coordinate and conduct all assessments, and perform all data analyses at the University of Arizona.

Figure 1. Study design. NRT: nicotine replacement therapy.



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RCT Protocol

The study protocol was adapted from our existing protocol [12,23]. Participant recruitment occurs during years 2 to 4 of the project, after coaches are trained and competent in the GIC and BC protocols. All screening, enrollment, and treatment activities are conducted by telephone, email, and SMS text message by research staff at the University of Arizona.

Recruitment occurs through quitlines and population-based activities. Quitline staff prescreen potential participants and describe the study to callers. Quitline staff collect eligible and interested callers' contact information, including their telephone number, and transfer these data to project staff located at the University of Arizona. For population-based activities, potential participants recruited through population-based methods contact project staff.

For both recruitment methods, project staff contact interested callers within 1 business day. Project staff provide a detailed description of the study. Callers who are interested in participating are screened again for eligibility by project staff. Staff then consent eligible callers and administer the T0 survey or send survey links (REDCap) by SMS text message or email to participants who choose to complete the forms themselves. Those participants who complete the T0 survey are randomly assigned to the GIC or the BC via REDCap. Noneligible or noninterested callers are transferred back to their state quitline. Randomized callers are contacted by their study coach within 2 business days. Once callers complete their first session, they are considered enrolled participants in the study. All coaches are located at the University of Arizona. Participants in each condition receive 6 sessions, lasting from 10 to 60 minutes, depending on the condition and session topic.

All session activities and interactions with participants are managed and recorded in REDCap. Coach competencies and protocol fidelity are routinely monitored by the investigators. Process data (ie, coach notes and in-depth interviews) will be collected during the 6-week program and at T1.

Participants are assessed via REDCap or telephone (for nonresponders) at T1 and T2 by project staff. A subsample of participants (36/1200, 3%) will be recruited to participate in surveys and in-depth interviews to explore subgroup differences in intervention use, response, and satisfaction. Participants will receive up to US $100 (in gift cards) for their efforts: US $10 for completing the T0 assessment, US $15 for the 3-month assessment, US $25 for the 6-month assessment, and US $50 for the biochemical verification. Participants chosen for the qualitative interviews will receive a US $25 gift card.

Participant Recruitment, Eligibility, Enrollment, and Randomization

Recruitment Methods

Participants are recruited from two populations: (1) individuals who contact one of our collaborating quitlines; or (2) individuals who smoke in Arizona, New York State, or West Virginia. Different recruitment methods will be used to recruit participants from each population. For the quitline population, we monitor quitline recruitment—an increase or decrease in the number of days per week that we recruit based on the volume of incoming calls. For population-based recruitment, we send out press releases describing the study, post on social media sites, network with our contacts in each state, and place paid advertisements, as needed. We monitor recruitment weekly and make adjustments to recruitment procedures to ensure that we are meeting our recruitment goals. We do not foresee any problems recruiting our sample according to the timeline. However, we have an additional 3 months in which we can extend our recruitment period if needed.

Eligibility Criteria

The inclusion criteria are as follows: primary tobacco use is smoking; smoke daily for the last 30 days; aged at least 18 years; speak English; have a smartphone with SMS text messaging; do not take antipsychotic medications or experience symptoms of psychosis; have not received quitline coaching for the previous 12 months; agree to telephone coaching and SMS text message reminders; can download an mp3 or mp4 file; live in Arizona, New York State, or West Virginia; no current use of any tobacco cessation program or medication; and only 1 participant per household.

Enrollment

Potential participants are screened by trained study staff over the telephone or via REDCap. Eligible participants complete the T0 survey and informed consent over the telephone or on REDCap. Participants download the consent form from REDCap or request that study staff send them a hard copy. Study staff send condition-specific program materials to randomized participants. Ineligible callers are transferred back to the quitline in their state of residence using a *warm handoff* (ie, study staff call the quitline, talk to enrollment staff, and then transfer the caller directly to the quitline enrollment staff) or a HIPAA-compliant electronic process (eg, encrypted email).

Randomization

Participants are stratified by state and method of recruitment (ie, quitline or community) and then randomized automatically in REDCap using a randomization table created by the study biostatistician. Statistical software was used to create a randomized-block allocation to the GIC or the BC, stratified by recruitment method and location.

Measures

Overview

All measures and the time points at which they are administered are displayed in Table 1. All these measures have been used in our previous work [11,12,23-25].

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Table 1. Measures by time point for both conditions.

	T0[a]	T1[b]	T2[c]
Demographics	✓		
Tobacco use	✓	✓	✓
Dependence	✓	✓	✓
Cravings	✓	✓	✓
Self-efficacy	✓	✓	✓
Expectancy and credibility	✓	✓	✓
VVIQ[d]	✓	✓	✓
Biochemical verification (expired CO[e])			✓
Consumer satisfaction		✓	
Sociotechnical outcomes		✓	

[a]T0: baseline.

[b]T1: 3 months after enrollment.

[c]T2: 6 months after enrollment.

[d]VVIQ: Vividness of Visual Imagery Questionnaire.

[e]CO: carbon monoxide.

Demographics

At T0, we will collect sex, age, race and ethnicity, level of education, insurance, marital status, smokeless tobacco use, cannabis use, chronic health conditions, and prior use of guided mental imagery.

Tobacco Use

At T0, T1, and T2, we will collect tobacco use status using a series of questions that have been standardized and used in previous studies [25-27] and the level of dependence using the Fagerström Tolerance Nicotine Dependence Scale [28].

Self-Efficacy for Quitting

We will measure self-efficacy for quitting smoking with an abbreviated version of the Condiotte and Lichtenstein Confidence Questionnaire [29].

Cravings

All participants will be asked to rate their experience with withdrawal symptoms and cravings using the Nicotine Dependence Syndrome Scale [30] at each follow-up assessment.

Expectancies and Credibility

We will include items adapted from the Borkovec and Nau Treatment Credibility Scale [31] and used in our completed GI mobile app study to measure expectancies and perceived credibility of GI for smoking cessation [11,23]. We will also adapt this measure to assess for expectancies and perceived credibility of the behavioral program used in the BC.

Consumer Satisfaction Measure

At T1, participants will complete a consumer satisfaction survey that we have used in our previous research [25,32] and consists of up to 11 items (using a 5-point Likert scale), measuring overall satisfaction with the program in each study condition, perceived usefulness and relevance of the information, likeability, the level of interest, and the ease of use, as well as whether they would recommend the program to others.

Intervention Adherence

Adherence will be measured by a composite of self-reported minutes of intervention use per week, the number of times skills practiced per week, the number of sessions attended, and coach-rated participant engagement in sessions.

Imagery Vividness and Sociotechnical and Ethical Outcomes

At T0, T1, and T2, we will assess participants' perceptions about the effectiveness of GI for tobacco cessation and their vividness of visual imagery using the Vividness of Visual Imagery Questionnaire, which we have adapted to include images of smoking [33]. At T1, we will examine participants' use of GI during the RCT and their perception of the GI program's *fit* in their lives through semistructured in-depth interviews [34,35].

Biochemical Verification of Tobacco Abstinence

All participants who self-report 7-day abstinence at the 6-month assessment will be selected for biochemical verification. We will (1) use enhanced collection procedures, including contact with participants via telephone before the assessment and via video call during the assessment if participants request assistance; (2) provide an iCO Smokerlyzer expired CO monitor (Bedfont Scientific Limited) to each participant who reports abstinence, a procedure that has been used successfully in previous remote collection studies and has high accuracy [36-38]; and (3) provide an incentive of US $50 for the completion of the biochemical assessment.

Biomarkers

Expired CO will be measured among smokers using iCO Smokerlyzer personal CO monitors. A monitor will be sent to each participant who reports abstinence at the 6-month follow-up assessment. Each participant will exhale into the monitor

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according to instructions. Readings are measured in parts per million. A cutoff of <6 parts per million is recommended [39]. The results will be transmitted electronically to the research team.

Collection Procedures

Project staff will contact participants who report abstinence at the 6-month assessment via SMS text message, telephone, or email to schedule a HIPAA-compliant encrypted video call during which biochemical verification will be completed. On the scheduled day of assessment, project staff will verify the participant's identity through the confirmation of their name and face from a photograph ID. During this session, project staff will provide step-by-step instructions for completing biochemical verification.

Outcomes

Our primary outcome is self-reported 30-day abstinence as measured at the 6-month assessment. Secondary outcomes include self-reported 7-day abstinence as well as biochemically verified 7-day abstinence at the 6-month assessment and, for nonquitters, cigarettes smoked per day.

We will also examine the effect of adherence to the GI on cessation outcomes, conduct subgroup analyses of moderators (eg, recruitment method, location, sex, race and ethnicity, and level of dependence) on tobacco cessation outcomes at 6 months, and use a mixed methods approach (eg, surveys and in-depth interviews) to explore subgroup differences in GI adherence and cessation outcomes.

Qualitative Subgroup Study

Subsample participants (36/1200, 3%) will be recruited after a preliminary analysis of the T1 data and based on the following criteria: recruitment method, location, sex, race and ethnicity, and abstinence status. After a quantitative analysis of the subgroups, the team will identify 36 participants through purposive sampling (eg, identifying participants who were recruited through community methods). Only those participants who indicate an interest in participating in in-depth interviews at T1 will be invited to participate in in-depth interviews via telephone, email, or SMS text message. One-hour telephone interviews will be conducted by a member of the study team, who will use a semistructured interview guide to explore the following aspects: program use during the RCT (eg, how did the technology they used influence completion of coaching calls?), their perceptions of program effectiveness for tobacco cessation (eg, how does GI work to help them stop smoking?), and their perception of the program's *fit* in their lives (eg, how does GI integrate or not integrate with their lifestyle?).

Power and Sample Size

A sample size of 1200 participants would yield 90% power to detect a difference in smoking cessation rates between the arms of 10%, assuming a control arm cessation rate of 0.30, a 20% dropout, and a noncontinuity-corrected chi-square test at a 2-tailed significance level of 5%. We believe that 10% is a clinically significant difference with positive public health implications. Although the control arm had a higher cessation rate in our pilot study (50%) [19], we believe that this rate was unusually high. Furthermore, the rates were self-report, not biochemically verified, which are estimated to be 10% to 50% lower [39]. It was also high compared with quitline cessation rates, which are closer to 30% to 40% [15,40].

This sample size also yields 90% power to detect small-to-medium standardized effect sizes for continuous secondary outcomes of Cohen d=0.28, using a Bonferroni correction to account for multiplicity (20 tests), assuming a 2-sided 2-sample t test. Aim 3 will investigate effect modification, which requires approximately 4 times the sample size (or, equivalently, results in a larger detectable effect size) [41]. Assuming that a subgroup of interest makes up 50% of the sample, we have 90% power to detect a difference in cessation rates of 0.141 and 80% to 90% power to detect standardized effect sizes of 0.26 to 0.30, assuming no multiple testing correction. We recognize that the inputs to these calculations are estimates only.

Table 2 displays a sensitivity analysis, showing power for control arm cessation rates of 0.20 and 0.40, dropout rates of 20% to 40% (typical range for cessation trials), and differences of 0.10 to 0.15, showing ample power for different scenarios. These power calculations are conservative; simulation studies demonstrate that mixed effects models (the proposed analyses [Data Analysis subsection]) yield more power than chi-square and t tests [42,43].

Table 2. Sensitivity analysis (N=1200).

Dropouts, n[a]	Cessation rate: 0.20		Cessation rate: 0.40	
	Detectable difference: 0.10	Detectable difference: 0.15	Detectable difference: 0.10	Detectable difference: 0.15
240	0.95	0.99	0.88	0.99
360	0.92	0.99	0.83	0.99
480	0.87	0.99	0.77	0.98

[a]Dropout rate: 20% (n=240); 30% (n=360); 40% (n=480).

Data Analysis

Overview

This is a 2-arm parallel RCT where the primary outcome is self-reported 30-day abstinence at 6 months. Questionnaires will be scored according to developer instructions. In the case of missing items, where developers do not have explicit instructions, we will use a half-mean imputation rule, as outlined in Bell et al [44]. All analyses will be adjusted for the randomization stratification. The primary analysis will use a

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significance level of .05; other tests will use a Bonferroni correction for multiple comparisons to control the overall type I error at 5%. Demographics, including sex, will be described with means, SDs, ranges, and frequencies or proportions and explored as correlates for successful tobacco outcomes using appropriate regression models.

Aim 1

We will test the efficacy of a telephone-delivered GI tobacco cessation treatment versus an evidence-based behavioral treatment on self-reported 30-day abstinence from smoking at T2. Secondary outcomes include self-reported and biochemically verified 7-day point prevalence abstinence at T2.

Hypothesis 1

Participants in the GIC will have 10% higher quit rates than those in the BC.

Generalized linear mixed models with a binomial distribution and a logit link will be used to model smoking outcomes. Time will be used categorically to avoid model misspecification, and the indicators for the stratified variables (ie, location and recruitment method) will be included in the models as covariates to control for the study design variables. Comparisons between the intervention and control groups at 3 and 6 months will be carried out using contrasts within these models. Mixed models are robust to missing outcome data (with respect to bias) and consistent with an intention-to-treat analysis; in addition, they yield more power than chi-square and *t* tests [42,43,45-47]. Secondary outcomes measured over time, including self-reported abstinence, nicotine dependence, self-efficacy, and cravings, will also be analyzed with mixed models (linear for continuous outcomes and generalized linear with a logistic link for binary). Biochemically verified abstinence at 6 months will be analyzed with a logit regression model. Unadjusted and adjusted models will be fitted, with adjusted models including key covariates such as expectancy. Sensitivity analyses with respect to missing data will be undertaken if missing data rates for the primary outcome are >10% at the 6-month follow-up. Multiple imputation by chained equations using data that are associated with missingness, the outcome, or both will be included in the imputation model [16]. We will compare T0 characteristics of participants who drop out with those of participants with complete data.

Aim 2

We will conduct dose-response analyses on the effect of GIC adherence (measured by self-reported minutes of intervention use per week, the number of times GI skills practiced per week, the number of sessions attended, and coach-rated participant engagement in sessions) on abstinence at 6 months. We will also examine effects of the GIC and the BC on tobacco use for those participants who do not report abstinence at 6 months.

Hypothesis 2A

GIC participants who are more adherent will have higher rates of abstinence at 6 months.

Hypothesis 2B

Participants not reporting abstinence will report statistically significant reductions in tobacco use.

We will investigate a dose-response effect of intervention engagement using logistic regression for cessation at 6 months and linear regression for dependence, self-efficacy, and so on, with adherence. Mediation models using a causal framework will also be used [17]. We will compare self-reported tobacco use levels in GI participants who have not quit at 6 months with the control group using regression models and also investigate their changes from T0 use. Consumer satisfaction will be described with summary statistics.

Aim 3

We will conduct subgroup analyses of moderators (eg, recruitment method, location, sex, race and ethnicity, and the level of dependence) on tobacco cessation outcomes at 6 months and assess participants using a mixed methods approach (eg, surveys and in-depth interviews) for exploring subgroup differences.

Logistic regression models will be used to investigate effect modification of the intervention effect on abstinence at 6 months by various moderators. These regression models will include interaction terms, and if statistically significant, a stratified (by moderator) analysis will be performed and reported.

Qualitative interviews will be recorded, transcribed, and consensus coded for themes by 2 coders to guarantee intercoder reliability [48,49]. The team will document variation in the subgroups' reported program use during the RCT, including perceptions of the program's effectiveness and ease of use.

Project Timeline

This project will occur in 2 phases over 5 years. In phase 1 (year 1), we worked with our collaborators in New York State and West Virginia to tailor our protocols and procedures to their quitlines, refine our recruitment methods to each state's smokers, refine all study (participant) materials to ensure that the demographics of each state are represented, and update our training materials to include state-specific data and issues that may be relevant to specific participant populations. We hired and trained all coaches to competency and user-tested all our systems and procedures. In phase 2, we will conduct the RCT. Recruitment, enrollment, T0 assessments, and the delivery of the intervention will occur during years 2 to 4. Follow-up assessments will occur during years 2 to 5, with data analyses and dissemination of the findings in year 5.

Ethics Approval, Informed Consent, Data Protection, and Participation

This study has been reviewed and approved by the University of Arizona institutional review board (2103633455; principal investigator [PI]: JG). All participants complete an informed consent document either through REDCap or on the telephone with trained study staff. Potential participants may ask questions of study staff before signing the consent document. The consent document describes the study, expectations, risks, and benefits of study participation. All study data are housed in REDCap and University of Arizona Box Health. Both systems are encrypted and HIPAA compliant. Only trained study staff have access to participant data, and data are restricted to study staff by role on the project. Participants may receive up to US $125

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for participating in all study activities. Participants receive US $10 for completing the T0 survey, US $15 for completing the 3-month survey, and US $25 for completing the 6-month survey. All participants who report 7-day abstinence at the 6-month assessment are asked to complete an expired CO test to biochemically verify abstinence. Participants who complete biochemical verification receive US $50. Some participants will be selected based on their responses to the 3-month survey and invited to participate in a semistructured interview. Participants who complete this interview will receive US $25.

Results

The *Be Smoke Free* study was funded in September 2021 (National Center for Complementary and Integrative Health, R01AT011500; PI: JG). Recruitment started in August 2022, with a staggered start. The West Virginia and New York State quitlines and community recruitment were all active as of October 2022. As of March 31, 2023, a total of 242 participants had been enrolled in the study, surpassing our accrual goal of 240. The Arizona Smokers' Helpline (ASHLine) contract was transferred to another vendor, and we lost this as a recruitment site. The New York State and West Virginia quitlines each agreed to recruit an additional 100 participants to compensate for the loss of 200 Arizona quitline participants.

Follow-up assessments began in November 2022. As of March 31, 2023, of the 118 participants who were eligible for the 3-month assessment, 97 (82.2%) completed the assessment, and 93% (26/28) of participants eligible for the 6-month assessment had completed it. Because of technical difficulties with the hardware and software, biochemical verification began in April 2023. Qualitative interviews began in April 2023. Recruitment will continue through 2025 and follow-up assessments through 2026. Primary results are expected to be published in 2027.

Discussion

Overview

Phase 1 of the study was conducted between October 1, 2021, and July 30, 2022, and completed successfully. The study team met weekly and updated the design, content, and formatting of the intervention quit booklets that were created for the pilot study. We also created recruitment materials, including digital and print media, featuring images representing various communities. We recruited 8 stakeholders from 3 states to form a CAB. We held general and state-specific CAB meetings to obtain feedback on recruitment and intervention materials, as well as recruitment plans and methods. We also updated and refined coach training materials, revised data collection materials from the pilot study, and created new data collection materials. We developed protocols for screening, contact attempts, biochemical verification, and other data collection procedures and programmed and tested them all in the REDCap database. We developed procedures for recording and storing coaching calls using new Zoom (Zoom Video Communications, Inc) technology and hired and trained 4 quit coaches and all research staff. We received institutional review board approval for all human participants study procedures and registered the study with ClinicalTrials.gov.

We began phase 2, conducting the RCT, in July 2022. We have experienced both challenges and successes in the first 6 months of the RCT. To date, we have recruited participants through the West Virginia and New York State quitlines and via study social media posts and posts from community partners in Arizona, New York State, and West Virginia. We designed and sent recruitment postcards to former New York State quitline clients, used display ads on Meta sites, advertised on radio stations in New York State and Arizona, and distributed rack cards and flyers to our CAB members and other contacts in the community (eg, physicians' offices). We recruited our first participant in Arizona in July 2022, then opened recruitment in West Virginia in August 2022, and in New York State in September 2022. In September 2022, the ASHLine contract was transferred from the University of Arizona to National Jewish Health, and the Arizona Department of Health Services declined to collaborate on the rest of the study. The New York State Smokers' Quitline agreed to increase recruitment to compensate for the loss of the ASHLine.

Potential participants who were referred by a quitline or found out about the study from community-based methods were contacted via telephone calls, emails, and SMS text messages and screened by study staff. Potential participants who met the eligibility criteria completed consent and T0 assessments on the web in REDCap and were randomized to 1 of 2 study conditions.

Randomized participants who scheduled and completed the first study visit (session 1) were considered *enrolled participants* in the study.

To ensure that we are meeting our goals and maintaining fidelity of all procedures, we review enrollment and recruitment progress at weekly study team meetings, monitor intervention fidelity in REDCap, and review call recordings on a monthly basis. Any discrepancies in fidelity are immediately corrected, and study personnel receive weekly feedback. Coaches attend individual monthly supervision sessions with the PI.

We are currently retaining >80% of the sample at 3 months and >75% at 6 months. This is similar to our pilot study [12] and compares favorably with other studies that are conducted entirely remotely [50]. If participants miss some data collection visits or drop out from the study after session 1, partial data will be captured for them. As indicated previously, mixed effects models will be used to model smoking outcomes. Mixed effects models have an inherent way to handle ignorable missing data mechanisms (ie, missing completely at random and missing at random), which can be accounted for based on the observed data. In addition, extensive efforts will also be made to maximize retention as well as minimize missing data, and reasons for dropping out and missing data will be recorded. If the missing data mechanism is suspected to be nonignorable (ie, missing not at random), a multiple imputation–based sensitivity analysis approach [51] will be used to evaluate the impact of missing data mechanisms on the intervention effect, where the sensitivity analysis parameter controls the missing mechanism, and the multiply imputed data will be analyzed using standard methods based on the established rules in Rubin [52] that account for uncertainty owing to missingness.

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Limitations

We experienced several challenges during the first year of the RCT. First, we lost one of our quitline partners. Despite many attempts to replace the ASHLine, we were unable to do so. Both the New York State and West Virginia quitlines agreed to compensate for our loss of the ASHLine. However, West Virginia experienced a drop-off in call volume and staffing shortages. Therefore, the New York State Smokers' Quitline increased their recruitment to maintain accrual goals. Although the demographics of New York State are different from those of Arizona, we will continue to conduct community recruitment from Arizona so that we can examine treatment outcomes by state.

Second, the social media advertising and earned media (eg, interviews with news outlets) strategies were not as successful as in our pilot study. Therefore, we attempted to recruit using radio advertising. However, radio advertising was not effective either. We have engaged a recruiting firm to assist with community recruitment in Arizona. Despite these setbacks, we have consistently maintained our accrual goals. If needed, we have built in an additional 3 months in year 5 for continued recruitment.

Third, biochemical verification has been difficult for many participants because of inexperience using technology. Although study staff schedule Zoom sessions to *walk participants through* the data collection procedure, many of the participants find it difficult or impossible to complete the expired CO test. Therefore, self-reported 30-day abstinence is our primary outcome, and we will also examine 7-day self-reported and biochemically validated abstinence.

Finally, because the intervention is conducted entirely remotely with no person contact, we experience high attrition between randomization and the first treatment session. Therefore, we classify people as participants only after they have scheduled and completed their first treatment session, and all metrics regarding outcomes are reported for enrolled participants. Participants do not know to which condition they have been randomized until the first session. Therefore, we do not expect differential attrition before session 1 to cause bias while evaluating the intervention effects. Even if the differential attrition rate is not expected to relate to the intervention conditions, an inverse probability of attrition weighting approach [53] will be used to handle differential attrition rates and account for potential bias if attrition is indeed selective.

Conclusions

The *Be Smoke Free* study is a first-of-its-kind RCT that incorporates GI into telephone-based tobacco cessation treatment. This study uses rigorous, transparent, and reproducible methods. The study protocols are based on strong theoretical frameworks and empirical evidence. We use best practices to address challenges in large studies with remote program delivery and data collection, well-established measures to reduce errors associated with self-report, successful recruitment and retention methods to reduce selection and nonresponse biases, and both intent-to-treat analysis and other methods to handle missing data.

Delivering a GI tobacco cessation intervention via telephone is a highly scalable novel integrative approach that may appeal to a broad range of smokers and increase the use of evidence-based tobacco treatment quitlines. This rigorous research has the potential for high overall impact. If successful, the *Be Smoke Free* program will have substantial benefits for the long-term health of people who use tobacco across the United States.

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Data Availability

Data from this study will be made available after the outcome paper is published or 6 months after the end of the study, whichever comes first.

Conflicts of Interest

None declared.

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Abbreviations

ASHLine: Arizona Smokers' Helpline
BC: behavioral condition
CAB: community advisory board
CO: carbon monoxide
GI: guided imagery
GIC: guided imagery condition
HIPAA: Health Insurance Portability and Accountability Act
PI: principal investigator
RCT: randomized clinical trial
REDCap: Research Electronic Data Capture
T0: baseline
T1: 3 months after enrollment
T2: 6 months after enrollment

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Protocol

Measuring the Potential Effects of Mirror Therapy Added to the Gold Standard Facial Neuromuscular Retraining in Patients With Chronic Peripheral Facial Palsy: Protocol for a Randomized Controlled Trial

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Abstract

Background: Facial neuromuscular retraining (fNMR) is a noninvasive physical therapy widely used to treat peripheral facial palsies. It consists of different intervention methods that aim to reduce the debilitating sequelae of the disease. Recently, the use of mirror therapy in the acute facial palsy and postsurgical rehabilitation contexts has shown promising results, suggesting its use as an adjunct to fNMR in treating patients with later stages of paralysis, such as the paretic, early, or chronic synkinetic.

Objective: The main aim of this study is to compare the efficacy of an added mirror therapy component with fNMR in patients with peripheral facial palsy (PFP) sequelae in 3 different stages. The specific objectives of this study are to measure the effects of combined therapy compared to fNMR alone on (1) participants' facial symmetry and synkinesis, (2) quality of life and psychological aspects of the participants, (3) motivation and treatment adherence, and (4) different stages of facial palsies.

Methods: This study is a randomized controlled trial that compares the effect of fNMR combined with mirror therapy (experimental group: n=45) with fNMR alone (control group: n=45) in 90 patients with peripheral facial palsy presenting with sequelae 3-12 months after onset. Both groups will receive 6 months of rehabilitation training. Facial symmetry and synkinesis; participants' quality of life; and their psychological factors, motivation, and compliance will be assessed at baseline (T0), 3 months (T1), 6 months (T2), and 12 months (T3) postintervention. Outcome measures are (1) changes in facial symmetry and synkinesis assessed with facial grading tools, (2) quality of life changes with patient questionnaires, and (3) therapy motivation with a standardized scale, as well as adherence to treatment with metadata. Changes in facial symmetry and synkinesis will be judged by 3 assessors blinded to group assignment. Mixed models and Kruskal-Wallis, chi-square, and multilevel analyses will be conducted according to the appropriate variable type.

Results: Inclusion will start in 2024 and is anticipated to be completed in 2027. The 12-month follow-up will be completed with the last patient in 2028. We expect patients included in this study to experience improvement in facial symmetry, synkinesis, and quality of life, regardless of group assignments. A potential benefit of mirror therapy for facial symmetry and synkinesis could be noted for patients in the paretic phase. We hypothesize better motivation and adherence to treatment for the mirror therapy group.

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Conclusions: The results of this trial may provide new guidelines for PFP rehabilitation with patients dealing with long-term sequelae. It also fills the need for robust evidence-based data in behavioral facial rehabilitation.

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KEYWORDS

facial rehabilitation; neuromuscular retraining; mirror therapy; facial paralysis; synkinesis; palsy; rehabilitation; neuromuscular; paralysis; palsies; physical therapy; physiotherapy

Introduction

Background

Peripheral facial palsy (PFP) with sequelae is a debilitating condition that can significantly impact a patient's quality of life due to functional, social, and psychological factors [1]. Facial asymmetry and the inability to express emotions and smile adequately can make communication challenging, leading to high levels of social problems, frustration, anxiety, and depression [1]. In nonflaccid facial palsy, patients may have hyperkinesis, muscle contracture, and synkinesis, which can affect normal activities such as drinking, eating, and articulating and can cause embarrassment and, in some cases, facial pain [2,3]. Therefore, providing adequate interventions to help patients deal with these issues is essential. Physical therapy is a type of nonsurgical treatment shown to help manage the sequelae previously mentioned in patients with nonflaccid chronic peripheral facial palsy [4]. Optimal facial rehabilitation modalities could also differ depending on the stage of nonflaccid PFP [5]. Although there are no generally accepted guidelines for the different stages, some authors define the paretic phase as recovery from 3 to 6 months after onset, while the early synkinetic phase would be defined as 6 to 9 months after onset [5,6]. The chronic synkinetic phase would begin at 9 months after onset, as defined by Beurskens et al [7].

Facial Neuromuscular Retraining

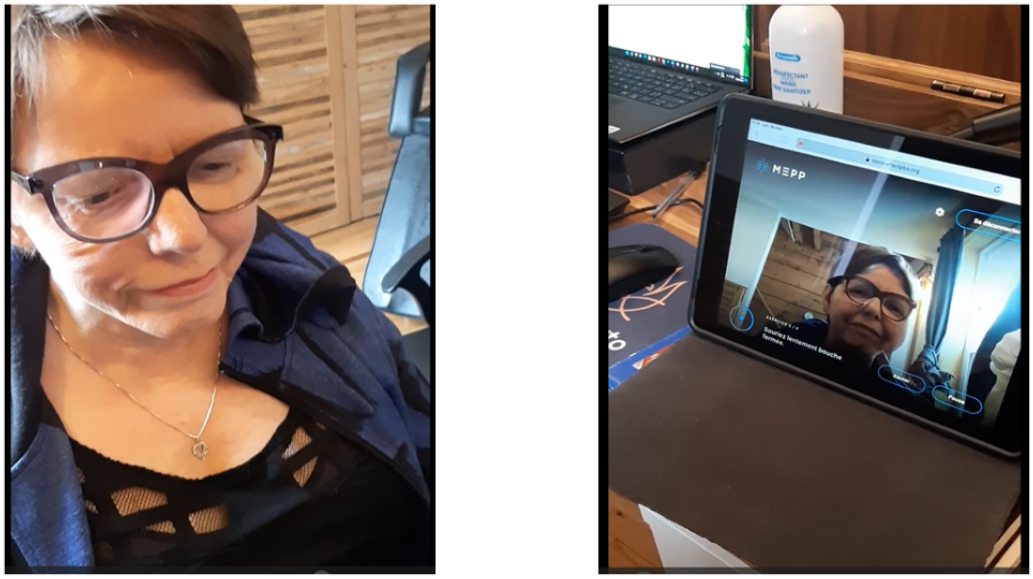
Mime therapy [8,9] and facial neuromuscular retraining (fNMR) [10] are 2 rehabilitation techniques for managing facial palsy sequelae that stand out in the literature [11]. Mime therapy consists of facial massage and specific facial retraining to coordinate both hemifaces by using emotional cues to express a particular facial movement or by starting to use a specific muscle to create an expression [8]. Similarly, fNMR consists of relearning motor patterns to improve facial movements through conscious, consistent, and slow selective activation of facial muscles using individualized training programs made by qualified facial therapists [12]. This therapy aims to normalize facial muscle functions by inhibiting synkinetic contractions and improving resting tone altered by contractures [13]. In the literature, these 2 therapies have recently merged into one called fNMR, which combines techniques such as soft tissue massage, biofeedback, education, relaxation, and selective movement retraining [14]. fNMR is considered a well-supported approach that has been studied in many cohort studies [14].

Mirror Therapy in Facial Rehabilitation

Mirror therapy is a form of motor therapy that involves placing a mirror in the patient's midsagittal plane, reflecting the unaffected limb or body part onto the affected one, creating the illusion of normal movements on the absent or affected side [15]. It is based on the brain's ability to undergo cortical reorganization [15]. The first clinically reported effects of mirror therapy were pain reduction in arm amputees and alleviation of hemiparesis [16]. Since then, this therapy has been used in other contexts, including facial rehabilitation and uses specific computer software to replicate the unaffected side over the affected side [17] (Figure 1).

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Figure 1. Representation of the setting with mirror therapy for facial rehabilitation. (A) Patient sits in front of the computer with a webcam. (B) Visual biofeedback of modified face.



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A recent study investigated the effects of mirror therapy over 3 months on 32 patients diagnosed with facial nerve palsy less than 12 months after acoustic neuroma resection surgery [17]. The control group received traditional rehabilitation with mime therapy, while the experimental group had to perform an additional weekly session of mirror therapy using specific software and motor imagery exercises with different emotions or gestures. Both groups were evaluated for facial symmetry using the House-Brackmann Facial Nerve Grading system [18], Sunnybrook [19], and Facial Clinimetric Evaluation (FACE) [20]. Although every subject demonstrated improvement in facial symmetry, the experimental group showed significantly better results than the control group for House-Brackmann scores and quality of life. In a recent case report, mirror therapy and motor imagery were used with a small group of patients (n=5) with chronic facial palsy to reduce synkinesis, which resulted in the reduced muscular activity of synkinetic muscles with mirror therapy [21].

A recent longitudinal study recruited patients with Bell palsy within 14 days of onset and followed them for 1 year [22,23]. The control group received only basic counseling in their rehabilitation, while the experimental group followed a new protocol called the Mirror Effect Plus Protocol (MEPP), which was mainly based on mirror therapy [24] and motor imagery [25]. One year after onset, significant results included less synkinesis development, increased facial symmetry, and improved self-reported quality of life in the experimental group [23]. Although the MEPP shows interesting results in patients with Bell palsy when initiated in the acute phase, to our knowledge, there is very limited evidence for mirror therapy as an effective treatment tool for patients presenting with long-standing peripheral facial paralysis from different etiologies.

Expected Effects of Rehabilitation Techniques

Based on the work of Diels and Beurskens [14], fNMR is expected to improve facial symmetry and reduce synkinesis in long-standing facial palsy. Increased resting tone on the patient's affected side often creates muscle tightness or contractures, leading to decreased range of motion, alteration of facial expressions, and patient discomfort. Therefore, soft tissue mobilization and specific facial manipulations can reduce such tightness and increase facial symmetry at rest [14]. To inhibit synkinesis, the therapy seeks to recognize abnormal movement patterns and uses different strategies to reduce them while activating desired facial muscles [5]. Patients must be instructed to perform slow, small, and controlled facial expressions or movements. As the patient's control improves and the synkinesis movements remain suppressed, the range of motion, facial function, and symmetry are believed to improve [14]. As proprioceptive input is absent in facial muscles, fNMR uses different education and biofeedback strategies, such as surface electromyography and touch, to help patients focus on the right muscle contraction. Although successful results have been demonstrated in the past with patients in the chronic phase, more randomized controlled trials are required to assess its efficacy [4]. It has been noted that when traditional mirrors are used in practice sessions as biofeedback, the mismatch between the motor command and the visual feedback associated with the affected side might result in maladaptive muscle hyperactivity and compensation, which is counterproductive with fNMR [26,27]. In this context, adding mirror therapy during practice is an interesting idea because it might avoid such discrepancies between motor command and sensory input [23]. However, the potential added value of mirror therapy for long-standing facial palsies remains to be proven.

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Study Aims

There is a growing interest in exploring the effect of adding mirror therapy as a biofeedback tool in fNMR, particularly in patients with peripheral facial palsy dealing with sequelae 3-12 months after onset. Therefore, the general aim of this protocol is to compare the potential effects of adjunctive mirror therapy with the gold standard fNMR on facial function and rehabilitation in nonflaccid facial paralysis. The specific objectives of this study are (1) to measure the effects of combined therapy compared to fNMR alone on participants' facial symmetry and facial synkinesis, (2) to measure the effects of combined therapy versus fNMR alone on the quality of life and psychological aspects of the participants, and (3) to measure the effects of combined therapy versus fNMR alone on motivation and treatment adherence.

Methods

Eligibility Criteria

To be included in the study, patients must be 18 years or older, experiencing their first PFP, be from 3 months to 12 months after onset, and must have a score 4 or 5 on Facial Nerve Grading System 2.0 (FNGS 2.0) [28]. In addition, they must have sufficient cognitive status, measured by a cutoff score of 23 on the Montreal Cognitive Assessment [29,30], and present with no active mental health diagnosis. They should also not present with a history of neurologic diseases affecting facial function. Patients with concomitant therapies or botulinum toxin type A injections, presenting with bilateral palsies or with medically uncontrolled metabolic diseases, will be excluded from the study. Access to an internet connection and basic computer literacy will also be verified as eligibility criteria.

Recruitment and Compensation

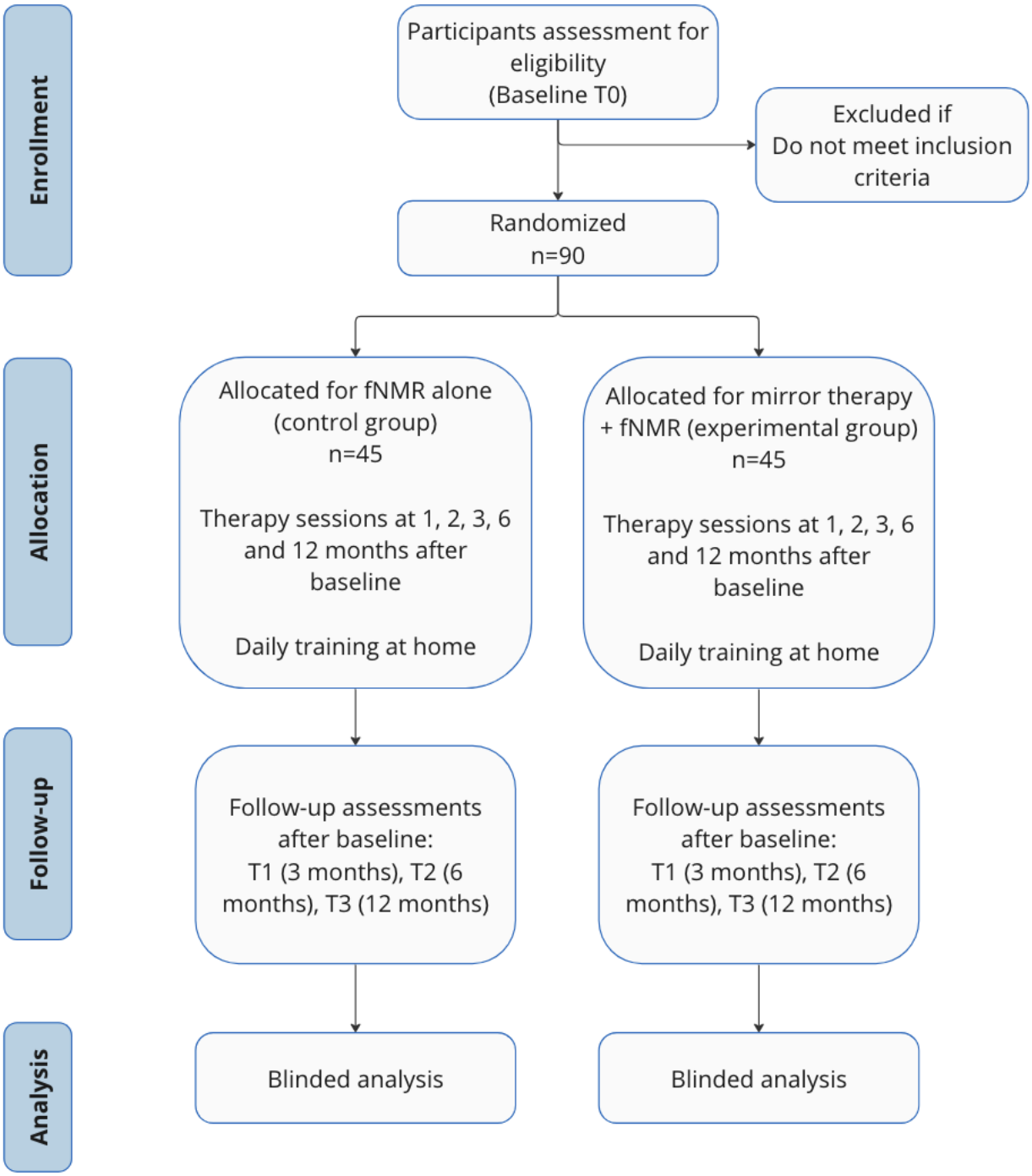
As determined, thanks to a power calculation measure based on Martineau et al [22] to reach a power of 0.8 with a size effect of 0.6 and an α of .005, 90 patients with peripheral facial palsy of diverse etiologies in the paretic (n=30), early synkinetic (n=30), or chronic synkinetic phase (n=30) will be recruited to the study. They will then be randomized into 2 groups, mirror therapy plus fNMR or fNMR alone, by computerized block randomization. No compensation or incentive is planned to be provided at this time. Recruitment is planned to be conducted in 3 tertiary care centers (hospitals) in Canada, England, and Belgium (Hôpital Maisonneuve-Rosemont, Queen Victoria Hospital, and Sint-Augustinus GZA Hospital, respectively). A telehealth option will be available for the participants via institutionally secured platforms.

Study Procedures

This trial will compare the effect of mirror therapy in addition to gold standard fNMR (experimental group) over fNMR alone (control group) in patients with peripheral facial palsy dealing with sequelae 3-12 months after onset. During 6 therapy sessions (Textbox 1), all patients will benefit from standardized education on facial anatomy and physiology, eye care, and management of facial dysfunction (eg, eating, drinking, speaking, and nonverbal communication), as well as from rehabilitation to increase symmetry and decrease synkinesis, specific to their needs. These sessions will be provided by speech-language, physical, or occupational therapists, all certified by their respective professional corporation. In addition, a minimum of 5 years of expertise in facial palsy training is required to be included in the study. These clinicians will also perform the different study measurements, but 3 judges (also experts in facial therapy but blinded to therapy allocation) will then analyze the data. The mirror therapy group will also receive modified visual feedback during facial retraining, along with appropriate instructions about its use. In parallel, patients will be prescribed daily specific at-home rehabilitation depending on the nature of their group. Patients in the combined group (mirror therapy plus fNMR) will do their therapy at home with the MEPP 2.0 app [31], while patients in the fNMR group alone will do their therapy at home with the Physitrack app [32]. Figure 2 presents the overall study design.

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Figure 2. Overall study design. Participants in the control group and in the experimental group are assessed at baseline (T0), 3 months postintervention (T1), 6 months postintervention (T2), and 12 months postintervention (T3). fNMR: facial neuromuscular retraining.



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Textbox 1. Frequency and length of appointment.

- Sessions
  - Session 1 (1 hour to 1 hour and 30 minutes) for initial assessment and start of management.
  - Session 2 (1 hour) 1 month after session 1.
  - Session 3 (1 hour) 1 month after session 2.
  - Session 4 (1 hour) generally 1-2 months after session 3.
  - Session 5 (1 hour) is generally 3 months after session 4.
  - Session 6 (1 hour) final session generally 6 months after session 5, then discharge to continue independently.
- The total treatment course will last 12 months.
- 2-3 sessions of 10 to 15 minutes of daily home rehabilitation are expected to be done by the patients from baseline until 12 months.

Measures

For data collection, each measure will be taken at baseline, 3 months, 6 months, and 1-year postintervention. Evaluation sessions will be recorded, allowing 3 independent evaluators to blindly assess the objective outcome measures. The final assessment (T3) will measure the training retention of participants following therapy sessions.

Facial Function Assessment Tools: Symmetry and Synkinesis

Different tools will be used to measure the effects of combined therapy compared to fNMR alone on facial symmetry and synkinesis of the participants. First, Emotrics [33], a designed open-source machine learning algorithm, will enable objective facial metrics for patients with facial paralysis. The algorithm uploads a front-view picture of the patient's face into the program. Then, it automatically places 68 facial landmarks and computes a set of facial metrics relevant to facial palsies, such as palpebral fissure width, smile excursion, and smile and brow symmetry. Second, the FNGS 2.0 [28] and Sunnybrook Facial Grading Scale [19] will be used by 3 independent blinded evaluators to assess facial symmetry at rest, voluntary facial movement, and synkinesis. The FNGS 2.0, also called the modified House-Brackmann scale, is a scale where 4 regions of the face are assessed and scored into different categories depending on the degree of movements and synkinesis presence [34]. It generates a final score between 4 and 24 and converts it into one of the original House-Brackmann categories ranging from I (normal function) to VI (total paralysis). In other words, it incorporates synkinesis scoring and regional scoring to the original validated House-Brackmann scale [28]. As described by Vrabec et al [28], this revised scale presents high inter- and intraobserver agreement with the original scale while providing additional information. On the other hand, the Sunnybrook Facial Grading Scale uses a continuous scale of 0% (total facial paralysis) to 100% (normal facial function and symmetry). This scale has been chosen because of its high sensitivity to changes induced by the intervention [34].

Patient-Related Outcome Measures: Quality of Life

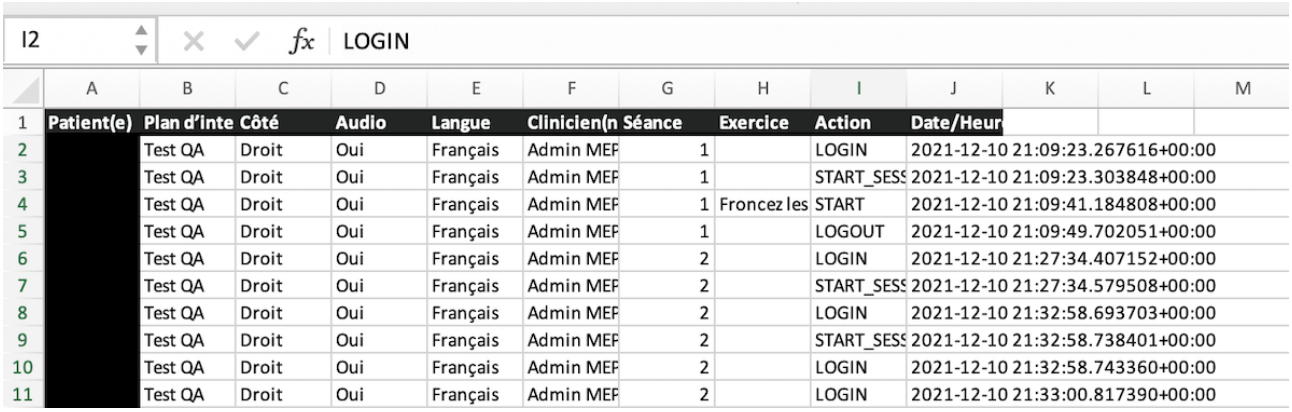
To measure the effects of combined therapy compared to fNMR alone on the quality of life and psychological issues of the participants, different patient-related outcome measures will be used including the FACE [20] and the Facial Disability Index (FDI) [6]. The FACE assesses 6 main domains: facial comfort, facial movement, oral function, lacrimal control, eye comfort, and social function through 15 questions. Overall, facial function depends on a score previously calculated that ranges from 0 (worst) to 100 (best) [20]. It has been previously demonstrated that FACE effectively discriminates the normal functional state of a person who does not have facial palsy from the state of a person have the disease [20]. Furthermore, the FACE can be used in different clinical contexts, such as assessing the evolution of patients' facial palsy handicaps from distinct etiologies and reporting changes in patients' perceptions of social and functional plans [20]. Kahn et al [20] performed an exhaustive process to validate the instrument, which is internationally used for its validity, sensitivity, specificity, and reliability [35]. On the other hand, the FDI has 10 questions that assess 2 domains: physical and social function. Social function scores from 0 (worst) to 100 (best), while physical function scores from −25 (worst) to 100 (best) [6]. Its validity and reliability have been demonstrated by VanSwearingen and Brach [6]. While the FACE scale provides more domains, it lacks measures about specific functional information, such as speech, which is why the use of FDI could be complementary [36].

Motivation and Adherence to Treatment

To measure the effects of combined therapy compared to fNMR alone on the rehabilitation process of the participants and motivation to treatment, the intrinsic motivation inventory [37] will be used. This multidimensional tool has been developed to assess participants' intrinsic motivation toward specific activities in laboratory experiments. Interest or enjoyment, perceived competence, effort, pressure or tension, usefulness, perceived choice, and relatedness of a task are all assessed while the participant performs a specific task. The scale has been validated in several contexts [37,38]. Patients' compliance to treatment will be assessed through intrinsic features of both websites that record metadata every time the participant logs in. These features allow therapists to see if the patient completed their rehabilitation program as recommended. Figure 3 shows an example of the metadata that the MEPP website can generate on an Excel (Microsoft Corp) sheet about compliance with treatment.

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Figure 3. Example of metadata about compliance with the Mirror Effect Plus Protocol website.



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2		Test QA	Droit	Oui	Français	Admin MEP	1		LOGIN	2021-12-10 21:09:23.267616+00:00			
3		Test QA	Droit	Oui	Français	Admin MEP	1		START_SESS	2021-12-10 21:09:23.303848+00:00			
4		Test QA	Droit	Oui	Français	Admin MEP	1	Fronce z les	START	2021-12-10 21:09:41.184808+00:00			
5		Test QA	Droit	Oui	Français	Admin MEP	1		LOGOUT	2021-12-10 21:09:49.702051+00:00			
6		Test QA	Droit	Oui	Français	Admin MEP	2		LOGIN	2021-12-10 21:27:34.407152+00:00			
7		Test QA	Droit	Oui	Français	Admin MEP	2		START_SESS	2021-12-10 21:27:34.579508+00:00			
8		Test QA	Droit	Oui	Français	Admin MEP	2		LOGIN	2021-12-10 21:32:58.693703+00:00			
9		Test QA	Droit	Oui	Français	Admin MEP	2		START_SESS	2021-12-10 21:32:58.738401+00:00			
10		Test QA	Droit	Oui	Français	Admin MEP	2		LOGIN	2021-12-10 21:32:58.743360+00:00			
11		Test QA	Droit	Oui	Français	Admin MEP	2		LOGIN	2021-12-10 21:33:00.817390+00:00			

Statistical Analysis

As mentioned, a power calculation was done based on a previous study [23] for the primary outcome (changes from baseline to 6 months). Every measure of facial symmetry and synkinesis will be judged by 3 assessors, blinded to group assignment. Intraclass correlation coefficients will be calculated to ensure interrater reliability, and the resulting means of the assessors' findings will be used for further statistical analysis. We will first gather descriptive statistics to provide summary data. Then, for continuous variables (Emotrics measurements, Sunnybrook global score, FNGS 2.0 global scores, FACE score, FDI, and intrinsic motivation inventory), a mixed model analysis with patients as random variables and time+group assignment as fixed variables will be considered, with auto-regressive covariance structure, given the structure of the time points for the assessments. Comparison between the timing of recruitment after PFP onset (3-6 months after onset vs 6-9 months vs 9-12 months) and outcomes at T2 and T3 will be specifically measured using multilevel analysis. Kruskal-Wallis analyses will be considered for ordinal variables (synkinesis subscores, symmetry subscores, and motivation subscores). Finally, chi-square analysis will be considered for dichotomous variables (adherence yes or no). Data will be encoded with Excel sheets, and SPSS (IBM Corp) will probably be used for statistical analysis.

Ethical Considerations

Ethics approval will be sought by January 2024 for an international and multicentric randomized control trial involving tertiary care centers in Canada, the United Kingdom, and Belgium. Only participants who are adults and able to consent will be recruited for this study. This study presents minimal risks for participants, as only behavioral therapy will be provided in the study procedures: there will be no use of approved or unapproved drugs, biologics, food, or dietary supplements. This study does not evaluate the safety or effectiveness of a device. No protected health information will be collected or placed into electronic medical records. No compensation or incentive is planned to be provided at this time.

Data Management Plan

All data will be collected in an electronic format. In the unanticipated event that data cannot be collected electronically, the same information will be collected via pen and paper, transferred to Excel, and the paper format will be destroyed at the earliest opportunity. All collected data will be strictly confidential, within the limits established by law, and a numerical code will identify each participant. Data will be recorded in the cloud of the University of Montreal, specially developed for research purposes, and only the team members will have access. Furthermore, all data will be conserved, for a minimum period of 7 years, after which they will be destroyed. None of the potential scientific publications or communications related to the study will contain participant-identifiable information. The researchers and the research assistants will only consult data. No facial recordings or sensitive or medical information will be held on the websites used in the study. Only the name, email address, and information about the affected side of the facial palsy (for duplication of the unaffected side purpose) and preference about sound level (with or without sound) will appear. Moreover, both websites use the latest versions of tools and information components, such as long time support, which offer support and security updates regularly, and a specialized technical team will ensure security updates and support for maximal security.

Results

The inclusion will start in late 2024, and data collection is anticipated to be completed over 3 years by 2027. Therefore, the last patient will have their final follow-up (T3) in 2028. Data analysis will be completed in 2028-2029. The results will be published in 2030.

Discussion

Main Study Findings

The primary objective of this protocol is to compare the potential effects of adjunctive mirror therapy with the gold standard fNMR for facial function and rehabilitation in cases of nonflaccid facial paralysis. In particular, this study aims to evaluate the impact of combined therapy versus fNMR alone on participants' facial symmetry, facial synkinesis, quality of life, motivation, and treatment adherence.

Comparison With Prior Work and Scientific Value of This Work

A recent Delphi study has confirmed the significance of fNMR and mime therapy in treating patients with various types of

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peripheral facial paralysis [39]. While mirror therapy was not unanimously agreed upon for inclusion at that time, subsequent data published after the study indicated that mirror therapy, when initiated a few days after the onset (10-14 days) of Bell palsy, had notable benefits. These benefits included a significant improvement in facial symmetry, quality of life, and a reduction in the development of synkinesis [23]. Similar positive outcomes have also been observed in patients with facial palsy after acoustic neuroma resection and in those who underwent lengthening temporalis myoplasty surgery [17,24]. However, despite these findings, there is a dearth of research examining the potential effects of mirror therapy in patients with peripheral facial palsy experiencing delayed recovery and sequelae at least 3 months after the onset, compared to more traditional therapies like fNMR.

Irrespective of the etiology and group allocation (fNMR vs mirror therapy), our hypothesis posits that all patients with peripheral facial palsy enrolled in this study will experience improvements in facial symmetry, synkinesis, and quality of life [11,23,40]. Drawing on previous studies [23,41] and considering that mirror therapy appears most beneficial when initiated early, we anticipate mirror therapy to have greater benefits for patients in the paretic phase (3-6 months after onset), particularly in terms of restoring facial symmetry. Patients presenting with synkinesis at the time of recruitment should experience a decrease in synkinesis in the fNMR group, as indicated by several previous studies [4,5,7,13,14]. Similarly, a decrease in synkinesis is expected in the mirror therapy group, but no significant differences between the 2 groups are anticipated. Moreover, in line with previous findings [5,23], we expect both the fNMR and mirror therapy groups to demonstrate improvements in self-reported quality-of-life measures. Additionally, motivation is crucial in achieving positive therapy outcomes [42] and will be specifically assessed in this study. The hypothesis of greater motivation with mirror therapy is based on a previous study where patients reported that performing facial exercises while viewing a symmetrical face aided them as it represented their desired goal [41]. On the contrary, some patients may experience emotional responses when confronted with a face they perceive as “lost” due to facial paralysis.

Finally, we anticipate that patients in the mirror therapy group will exhibit better treatment adherence compared to those undergoing fNMR alone. Adherence to facial retraining has been shown to be influenced by various factors, including time constraints due to other daily activities and accessibility to the training facilities [43]. Facial therapists often overestimate their patients’ commitment to the facial rehabilitation process, with data indicating that only 30% of patients fully comply [43]. Nonadherence to therapy can impact treatment outcomes, highlighting the importance of measuring adherence in this study. Objective measures of adherence using metadata will be used, providing strength compared to relying solely on subjective measures of compliance. Subjective measures of compliance (such as patient questioning) may be influenced by patients’ memory or perceptions [44]. Furthermore, the postpandemic shift toward telehealth for service delivery may facilitate adherence [44]. In this study, we will document whether participants received care via telehealth and examine whether this factor appears to influence compliance.

Strengths and Limitations

The primary strength of this protocol lies in its international multicentric collaboration, which will facilitate the examination of a substantial number of participants representing diverse etiologies of peripheral facial nerve palsy (n=90, with 45 patients per group). The randomized controlled trial design used in this study allows for assessing the potential additional benefits of incorporating mirror therapy into the rehabilitation of PFP. This investigation has the potential to contribute to an evidence-based approach for clinicians involved in the care of these patients.

However, the study design does have certain limitations. First, it is not feasible to blind both the patients and treating clinicians to the assigned conditions, which could introduce bias in terms of motivation and perception of treatment efficacy. To mitigate these risks, blinded judges will be involved in assessing participants, and therapists will use a standardized feedback approach in both therapy sessions and assessments. Additionally, using Emotrics will allow for more objective facial metrics at each assessment time point [33,45]. Second, the inclusion of paretic patients in the study poses a potential confounding factor due to the occurrence of spontaneous recovery in certain cases of facial palsy [3]. However, the large number of participants and their enrollment at least 3 months after the onset of symptoms should help mitigate potential biases. It is worth noting that in Bell palsy, the most common cause of PFP, approximately 70% of patients experience full recovery within 3 months of onset [3]. The advantage of including patients across such a broad timeframe (3-12 months after onset) is to recruit a cohort that is as representative as possible of the clinical reality of facial rehabilitation in different countries.

Conclusions

By comparing treatment modalities such as fNMR and mirror therapy within the scope of this international study, clinicians can gain valuable insights into effective approaches for addressing specific facial sequelae in patients. Understanding which modalities may be more effective at different stages of PFP is important for the field. Moreover, this study has the potential to shed light on the impact of motivation and treatment adherence on treatment outcomes.

Acknowledgments

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Data Availability

Data sets gathered in this study are planned to be deposited in the publicly available repository of Montreal University (Borealis Data).

Authors' Contributions

FD contributed to study design, literature reviewing, protocol writing, and revising, CN contributed to study design and revising the manuscript, LD contributed to study design and revising the manuscript, SM contributed to study design, literature reviewing, protocol writing, and revising, and SM received the funding obtained by Direction des Affaires Internationales de l'Université de Montréal.

Conflicts of Interest

None declared.

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Abbreviations

FACE: Facial Clinimetric Evaluation
FDI: Facial Disability Index
FNGS 2.0: Facial Nerve Grading System 2.0
fNMR: facial neuromuscular retraining
MEPP: Mirror Effect Plus Protocol
PFP: peripheral facial palsy

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Protocol

HIV-Response Intergenerational Participation Intervention Among Black Men in Ontario, Canada: Protocol for a Pilot Intervention Study

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Abstract

Background: Black men and their communities are more affected by HIV. Although they constitute less than 5% of the Ontarian population, they accounted for 26% of new HIV diagnoses in 2015, nearly half of which (48.6%) were attributed to heterosexual contact. HIV stigma and discrimination reinforce African, Caribbean, and Black men's HIV vulnerability by creating unsafe environments that deter them from testing and disclosure, resulting in isolation, depression, delayed diagnosis and linkage to treatment and care, and poor health outcomes. In response to these challenges, intergenerational strategies were identified from previous community-based participatory studies as best practices to reduce HIV vulnerabilities and promote resilience among heterosexual Black men and communities. The proposed intervention is premised on this recommendation of intergenerational intervention.

Objective: The overarching objective is to engage heterosexual Black men and communities in cocreating a community centered, culturally safe intergenerational intervention to reduce HIV vulnerabilities and related health disparities.

Methods: We will engage 12 diverse community stakeholders in Ontario, inclusive of heterosexual Black men, in 8 weekly sessions to evaluate existing evidence of effective HIV health literacy interventions, identify essential and relevant aspects, and work collaboratively to co-design the HIV-Response Intergenerational Participation (HIP) intervention for use with Black men and communities. Next, we will recruit 24 self-identified heterosexual Black men aged 18-29, 29-49, and ≥50 years. We will pilot and evaluate the HIP intervention with 24 heterosexual Black men from these 3 age groups (split as 2 events: a total of 12 participants in person in Toronto and 12 participants on the web in Windsor, London, and Ottawa). We will use the data obtained along with questionnaires from validated scales and focus groups to evaluate the effectiveness of HIP. The data will include HIV knowledge, perceived stigma toward people living with HIV, acceptance and uptake of HIV testing, preexposure prophylaxis (PrEP), postexposure prophylaxis (PEP), and condom use. We will also collect data related to perceptions about system-level factors such as discrimination, socially misconstrued masculine identity, etc. Quantitative analysis will essentially be a univariate descriptive analysis. We will use thematic analysis to highlight the results of the focus group discussions. Finally, we will disseminate the evaluation results and engage researchers, leaders, Black men, and communities to expand the project team and scale up the intervention in Ontario and across Canada.

Results: Implementation commences by May 2023, and by September 2023, we should have produced, among others, an evidence-informed HIP intervention that can be adapted for use by heterosexual Black men and communities beyond Ontario.

Conclusions: The pilot intervention will strengthen critical health literacy and build resilience against HIV through intergenerational dialogue among heterosexual Black men of all ages.

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KEYWORDS

community-based participatory project; heterosexual Black men; HIV response; intergenerational participation; intervention

Introduction

Background

Black men and communities are disproportionately affected by HIV through heterosexual exposure than other racialized groups in Canada [1-3]. While Black people make up only 5% of the Ontarian population, they accounted for 26% of new HIV diagnoses in 2015, with nearly half (48.6%) attributed to heterosexual contact [4-6]. Black men remain vulnerable to HIV due to structural inequities, including the lack of access to culturally safe programs that provide them opportunities to dialogue about their vulnerabilities and cocreate solutions [7-9]. Systemic factors such as institutional discrimination, poor representation of Black populations in health care decision-making, a lack of accessible information in relevant languages, and a lack of culturally safe health services constitute barriers to effective HIV responses [10-13]. Furthermore, HIV stigma and discrimination hinder them from testing and disclosure, thereby increasing their vulnerabilities, social isolation, depression, delays in HIV testing, diagnosis, linkage to treatment or care, and poor health outcomes [14,15]. HIV stigma also reinforces community denial, undermines HIV prevention efforts, impedes the provision of accessible community care, and prevents access to HIV information [16,17].

In 2020, the weSpeak team undertook a community consultation on best practices to reduce HIV vulnerabilities among heterosexual Black men and communities. They engaged 60 heterosexual Black men in Ontario through *group concept mapping* [18,19]. Data analysis of the 123 statements generated by the participants showed that the actionable cluster *"individual and family level HIV prevention"* was ranked highest among all the go-zone statements in both the scores of importance (4.06/5.0) and feasibility (3.61/5.0). Furthermore, detailed reviews of the statements within this cluster indicated the need for older generations to meaningfully engage the younger generations within families and in communities to promote cultural pride, collective resilience, and positive action to reduce HIV vulnerabilities. The priority of developing intergenerational programs and safe spaces for heterosexual Black men to engage in culturally safe dialogue and action was also supported by findings from the qualitative phase of weSpeak where over 200 heterosexual Black men and service providers were engaged in focus groups and individuals interviews in 2019 [20-24]. Emerging from these interviews was the call by participants to use an intergenerational approach to engage heterosexual Black men, families, and community stakeholders to raise awareness about HIV prevention and increase connections to HIV care as a community priority.

Evidence from intervention research undertaken in the United States also shows that parent-, family-, and community-engaged HIV prevention programs are effective (eg, the *Collaborative HIV Prevention and Adolescent Mental Health Project*) [25-27]. Intergenerational interventions such as youth-adult partnerships and parent-youth connections have been shown to build connection, improve youth efficacy, increase capacities for engagement, and increase responsibility at individual and systemic levels. They spur social-level benefits such as adult support, encouragement, shared trust, shared experience, and knowledge, and these in turn, further produce individual level outcomes of self-efficacy, self-esteem, and self-confidence. The cycle continues with individual outcomes leading to more social outcomes, such as positive peers, and a system-level outcome, for example, education of others [28-31]. Hence, models that support parent-youth and intergenerational dialogue and connections are promising for HIV-related intervention [32].

Objectives

In this proposed study, we will draw on existing literature and local evidence [17,20-24] to engage heterosexual Black men and communities to co-design the HIV-Response Intergenerational Participation (HIP) intervention. Based on the recommendations from weSpeak concept mapping, intergenerational connection is conceptualized beyond individual families to include social connections across different generations of heterosexual Black men and leaders in Black communities. The overarching goal of the study is to promote literacy on HIV prevention (eg, condom use, preexposure prophylaxis [PrEP], postexposure prophylaxis [PEP], safer sex negotiation, partner communication), testing (eg, access, point-of-care testing, and self-testing), and linkage to care. The specific objectives are to:

1. Advance critical HIV health literacy among heterosexual Black men and communities.
2. Engage heterosexual Black men, community leaders, and stakeholders in co-designing the HIP intervention to reduce HIV vulnerabilities and promote community resilience.
3. Pilot the HIP intervention with heterosexual Black men of diverse ages and assess its acceptability, feasibility, and effectiveness.
4. Apply study results to refine the HIP intervention for potential scale-up in Ontario and Canada.

Theoretical Framework

The project is underpinned by the principles of health equity, community empowerment, and meaningful engagement [33,34]. We will use a community-based participatory research (CBPR) approach to promote *critical health literacy* among heterosexual Black men and communities [35]. Critical health literacy refers to "the degree to which people are able to access, understand, appraise, and communicate information to engage with the demands of different health contexts in order to promote and maintain good health across the course of life" [36]. Early conceptualization of health literacy mainly focused on *functional health literacy skills*, that is, individuals' ability to obtain relevant health information to assess their health risks and engage in relevant health behaviors. Over the years, health

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literacy has evolved to include *interactive health literacy skills*, that is, individuals' ability to extract information from different sources to make health decisions and interact with service providers with confidence; and *critical health literacy skills*, that is, individuals' ability to analyze health information to gain a critical understanding of health in the context of social, economic, and environmental determinants and engage in organized efforts to advocate for health equity [37,38]. Critical health literacy has also led to more attention being placed on the roles and responsibilities of health providers and health organizations in providing accessible, culturally safe, and inclusive health information and resources. In using an intergenerational approach to build critical health literacy, heterosexual Black men will be able to tap into community wisdom from key stakeholders (eg, Black men living with HIV, Black knowledge holders, and Black activists for health). A co-designed intervention based on lived experiences and community wisdom will promote collective self-determination among heterosexual Black men and increase community literacy on HIV prevention and care. Guided by *a CBPR approach*, we will apply meaningful engagement strategies throughout the study. We will set up a project advisory committee (PAC) comprising 6-8 Black leaders from the youth, heterosexual Black men living with HIV, LGBTQ+ (lesbian, gay, bisexual, transgender, and queer/questioning), faith, and social justice sectors. The PAC will advise the team on cultural relevance and inclusion, research design and processes, community connections, data interpretation, and knowledge dissemination. Using CBPR, we will build equitable collaborative partnerships that promote meaningful involvement of people, organizations, and communities to increase collective self-determination in Black health, enhance HIV prevention, and improve health outcomes in heterosexual Black men and communities [14-17]. The processes will empower heterosexual Black men and the community to gain a critical understanding of the interpersonal and structural determinants of HIV vulnerabilities and codevelop strategies to address HIV-related health disparities experienced by heterosexual Black men and communities.

Methods

The proposed project consists of 4 interconnected components that work in tandem to engage heterosexual Black men and communities in knowledge uptake and cocreate a culturally safe intergenerational HIV literacy intervention.

Component One: Engaging Heterosexual Black Men in Knowledge Interpretation and Uptake (Objectives 1 and 2)

Overview

The objective of Component One is to apply an integrative approach to engage heterosexual Black men in knowledge interpretation and uptake to inform the development of the HIP intervention. We will recruit 12 self-identified heterosexual Black men with diverse lived experiences. Participation criteria include being aged 18 years or older; being HIV-positive, HIV-negative, or having an unknown HIV status; engagement in faith, arts, media, health or social care, education, or social justice sectors; being interested in codeveloping culturally safe and accessible HIV health literacy intervention for heterosexual Black men and communities; and being available to take part in 2 series of 4 co-design workgroup sessions. To achieve our objective of developing an intergenerational HIP intervention, we will specifically recruit heterosexual Black men from 3 age groups: 18 to 29 years; 30 to 49 years; and 50 years or older. We will engage participants in 4 weekly sessions on critical interpretation of evidence [20-24] to create a shared understanding of HIV vulnerabilities of heterosexual Black men at multiple levels: intrapersonal, interpersonal, organizational, and policy levels. The shared critical understanding gained through the following 4 sessions will be used to inform the co-design of the HIP intervention in Component Two.

Session 1: Social Identities of Heterosexual Black Men and HIV Vulnerabilities

In this session, we will present existing evidence on how heterosexual Black men negotiate their racialized masculine identities and social positions (race or ethnicity, age groups, socioeconomic status, education, employment, relationship status, etc) through practices that may protect them from HIV and put them at increased risk of HIV. We will then engage participants to identify real-world and culturally relevant strategies to address these issues.

Session 2: Structural Determinants of HIV Vulnerabilities of Heterosexual Black Men

In this session, we will present existing evidence on how structural determinants and public policies impact the HIV vulnerabilities of heterosexual Black men through inaccessibility to HIV services and other health and social care resources, socioeconomic resources, and adequate health care access (access to employment, stigma, and discrimination, etc). We will then engage participants to identify real-world and culturally relevant strategies to address these issues.

Session 3: Gaps in HIV Response and Cascade of HIV Care Affecting Heterosexual Black Men and Communities

In this session, we will present local evidence on existing heterosexual Black men's experiences in accessing HIV prevention, testing, and care in Ontario. In addition, we will invite 3 heterosexual Black men panel speakers with lived experiences to share their insights about gaps in HIV response. We will then engage participants to identify strategies to address these issues.

Session 4: Critical HIV-Related Health Literacy for Change

In this session, we will engage participants in learning and critically examining the 3 levels of critical health literacy: (1) functional health literacy skills, that is, heterosexual Black men's ability to obtain relevant and accurate information on HIV prevention (eg, transmission, condom use, PrEP, and PEP; treatment as prevention; undetectable=untransmissible, etc) and connection to care (eg, HIV testing, early diagnosis, and treatment and care) to guide their actions and behaviors; (2) interactive health literacy skills, that is, heterosexual Black men's ability to extract information from different sources (eg,

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evidence on social determinants of HIV vulnerabilities, Black pride as a protective factor, social support and resilience, etc) to make HIV related sexual and health decisions, and to interact with service providers with confidence to meet their health needs; and (3) critical health literacy, that is, heterosexual Black men's ability to analyze population health information (eg, proportion of HIV infections among heterosexual Black men compared to other groups; impact of gender discourses on sexual practices) to gain a critical understanding of HIV vulnerabilities in the context of social, economic, and environmental determinants, and to engage in organized efforts to advocate for health equity. We will hire an intervention specialist to work closely with the study team and participants in Component One to ensure that critical information and key elements for co-design are documented and applied in Component Two. Results from Component One will be presented to the PAC for feedback and discussion to inform Component Two.

Component Two: Co-design of HIP Intervention (Objectives 1 and 2)

The aim of this component is to apply the results from Component One to develop the HIP intervention and to seek community feedback on the intervention before pilot testing it in Component Three. We will engage the same 12 participants from Component One in the co-design of the HIP intervention. Participants who are not able to continue due to time constraints or other reasons will be replaced by new participants with detailed preparation based on the results of Component One. There will be *4 sessions* of the HIP intervention co-design:

1. In *session 1*, participants will collaborate to define the intervention objectives and outcome indicators.
2. In *session 2*, participants will identify the contents, learning activities, and required resources.
3. In *session 3*, participants will identify evaluation measurements (tools and indicators). After session 3, the team will work closely with the intervention specialist to construct the HIP intervention based on results and recommendations from participants. This semifinal HIP intervention will be presented to the PAC for feedback.
4. In *session 4*, participants will critically review the HIP intervention and collaborate to finalize HIP. The expected outputs of Component Two include 4-6 intervention modules with a facilitation manual, participant worksheets, experiential learning resources, and community engagement strategies. The HIP intervention modules will be designed based on the 3 levels of critical health literacy, as described above. In addition, we will produce a training toolkit for HIP champions with clear training objectives, theoretical concepts, demonstration videos, and implementation fidelity checklists to ensure that the intervention is implemented consistently.

Component Three: Piloting the HIP Intervention and Evaluation (Objective 3)

Piloting

In Component Three, we will pilot the HIP intervention co-designed by participants in Components Two and Three. We will engage 2 groups of 12 heterosexual Black men (N=24): a total of 12 participants for in-person piloting in Toronto and another 12 participants for virtual piloting from all sites (a total of 3 per site). Based on our team's previous experience in intervention research, we anticipate that the HIP intervention will consist of 6 half-day sessions or eight 2-hour sessions (a total of 16-18 hours). Participation criteria include being self-identified as heterosexual Black men; being aged 18 years or older; being interested in HIV literacy and becoming an HIV prevention champion among heterosexual Black men and communities; and being available to take part in 16-18 hours of colearning in group sessions. To achieve our objective of implementing an intergenerational HIP intervention, we will specifically recruit heterosexual Black men from 3 age groups: 18 to 29 years, 30 to 49 years, and 50 years or older to engage in the HIP intervention. The HIP sessions will be cofacilitated by EBE and JPW in person and RA and PNB on the web. Piloting HIP as both an in-person and a web-based intervention will enable us to gain important insights for future scale-up. For example, the web-based format will enable us to engage heterosexual Black men across regions and increase access to participation among heterosexual Black men living in smaller communities.

Evaluation

All participants will be asked to complete a presurvey with sociodemographic information and questions on their knowledge of HIV transmission and prevention, community resources on HIV responses for heterosexual Black men and communities, structural determinants of HIV, stigma attitude, HIV testing behaviors, levels of community engagement, and readiness for HIV championship in Black communities. We will also invite participants to complete a survey at immediate-, post-, and 8-week post-HIP intervention to evaluate the effectiveness of HIP at all 3 levels of critical HIV health literacy. Depending on the final design of HIP, some of the relevant scales may include the HIV Knowledge Questionnaire [39], the adapted Social Capital Scale [40], the Multidimensional Inventory of Black Identity (MIBI) [41], and the Scale of Stigmatizing Attitudes Toward People Living with HIV (SAT-PLWHA-S) [42,43]. In addition, we will collect postsession feedback forms at each training session to assess participants' self-report of satisfaction, knowledge gained, and confidence in specific skills. Insights gained from the postsession feedback will be used to refine and improve HIP for future scale-up.

Data Analysis

Because the survey is for a small-sized sample (N=24), quantitative analysis will essentially be a univariate descriptive analysis with frequencies, percentages, and central tendencies (mean, median, mode, and range). We will use Braun and Clarke's [44] 6-step framework to conduct thematic analysis of the qualitative data from focus groups.

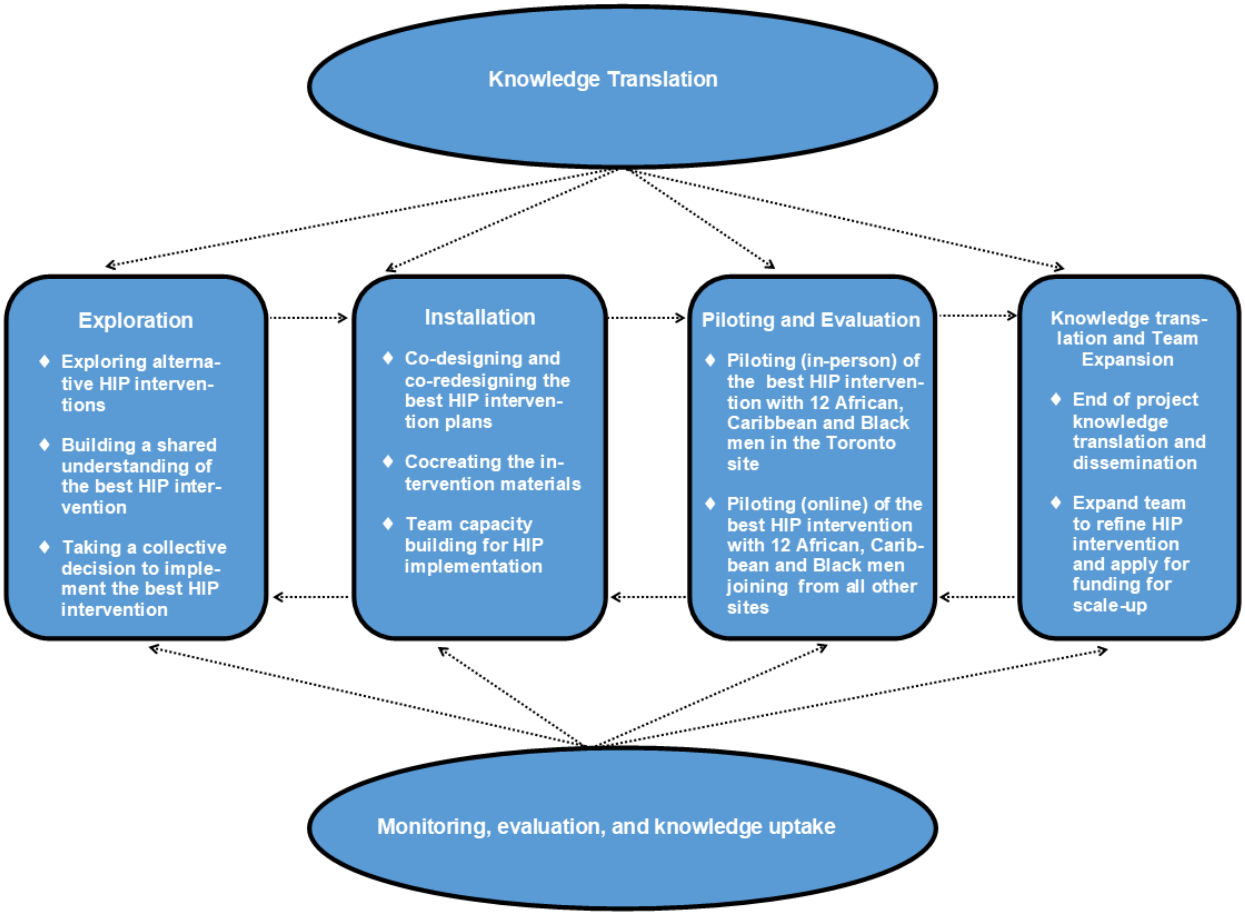
Component Four: End-of-Grant Knowledge Translation and Evidence Uptake (Objectives 1 and 4)

In addition to the knowledge translation activities integrated throughout phases 1-3, we will be engaged in end-of-grant knowledge translation in 2 ways. First, we will expand our

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existing research team to engage additional community partners, interdisciplinary researchers, and knowledge users to form a new team to refine and scale up the HIP intervention for use across Ontario and Canada. Second, we will engage community partners and collaborators to coproduce and disseminate culturally inclusive, accessible, and audience-specific knowledge translation products (eg, infographics, e-posters, community reports, conference presentations, peer-reviewed publications, community forums to demonstrate HIP intervention activities, webinars, and social media postings). Figure 1 summarizes the interconnected relationships of all 4 study components [45].

Figure 1. Adapted Fixen's interconnected phases of implementation in HIP Project. HIP: HIV-response intergenerational participation.



Informed Consent

Participants who meet the inclusion criteria and express interest in participating will receive a consent form with detailed information describing the purpose of the study, the data collection process, anticipated risks and benefits, and the process of maintaining confidentiality. The consent will have principal investigator's contact information for participants to reach out to if they have questions or are seeking additional information about the study. Participants will be given a week to review the consent form to enable them to make an informed decision whether they want to participate. As an ongoing process, we will continually seek consent from participants during the implementation of each component of the project.

Team Expertise and Resources

Our interdisciplinary team consists of HIV researchers, service providers, community organizations, faith organizations, and heterosexual Black men. The team consists of researchers of diverse career stages (full professors, associate professors, assistant professors, postdoctoral fellows, research coordinators, and research assistants). The research team brings extensive relevant experience in HIV community-based research, knowledge mobilization, translating research evidence into community-based interventions, intergenerational intervention, heterosexual Black men studies, equity-based health research, etc. The team also includes community collaborators and partners, with capacities to contribute to project advisory, knowledge translation, and the design, delivery, and scaling up of the pilot intervention.

Potential Limitations and Strengths

We recognize 2 potential challenges in carrying out this research. First, as a catalyst project, we are testing out novel ideas over a 12-month period. To ensure that we achieve our objectives, we will establish an implementation plan with clear time lines and deliverables. We will also work closely with our knowledge users and collaborators to ensure successful community engagement. Second, our research activities require participants to engage in a series of 4-6 group sessions. We anticipate that some participants may withdraw due to other competing demands. We will overrecruit, that is, a total of 12 participants per group instead of 8-10 to ensure sustainable participation. In addition, we will design our group activities

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in ways that promote enthusiasm and commitment, which our team has achieved in previous studies.

Ethics Approval

This study was reviewed and approved by the University of Toronto HIV Research Ethics Review Board (RIS Protocol #44285), the Toronto Metropolitan University Research Ethics Board (REB 2023-099), and the University of Ottawa Research Ethics Board.

Results

This is a funded 1-year project with a funding start date of September 2022. Due to the time lag for research ethics approval, data collection is proposed to commence in July 2023, with an expected project end date of March 2024. To date, recruitment has been limited to 12 members of the PAC who are providing insights into the project planning activities. Actual recruitment of participants will commence in July 2023 prior to data collection. We expect that our innovative, action-oriented project will produce numerous deliverables, including (1) documentation of effective processes to engage heterosexual Black men and community stakeholders in co-designing the HIP intervention; (2) knowledge and insights gained from piloting and evaluating the HIP intervention; (3) an evidence-informed HIP intervention that can be adapted for use by heterosexual Black men and communities beyond Ontario; (4) accessible knowledge translation products for community members as well as researchers and policy makers; and (5) an expanded team to refine HIP and secure resources to scale-up HIP across Ontario and Canada. We also anticipate many positive outcomes. At the individual level, the expected outcomes include increased capacity among heterosexual Black men to acquire accurate knowledge on HIV prevention and increased understanding of the structural influences on Black masculinities and sexualities; apply knowledge to guide their sexual practices and help-seeking behaviors; and gain increased skills in communicating their needs for HIV resources to service providers. At the collective level, we anticipate increased engagement and collaboration among heterosexual Black men, families, and communities to promote open dialogue about sexualities, HIV prevention and care, cultural pride, and collective resilience. There will also be increased capacity among heterosexual Black men and communities to advocate for a culturally inclusive HIV response and equitable access to related care and resources [46,47].

Discussion

The HIP is an innovative project that recognizes that heterosexual Black men's vulnerability and resilience are not an individualized phenomenon but a function of the social system in which they live. Based on this fact, HIP proposes to apply the collaborative efforts of heterosexual Black men themselves and members of their social system (leaders, service providers, intervention specialists, decision makers, and policy makers, community-based research experts, women, local businesses, the LGBTQ community, people living with HIV, etc) to co-design a culturally safe intervention. The pilot intervention will strengthen critical health literacy and build resilience against HIV vulnerabilities through intergenerational dialogue among heterosexual Black men of all ages without reinforcing any preexisting stereotype and discrimination against any other group in their social system.

Acknowledgments

The study is supported by Canadian Institute of Health Research (CIHR) catalyst grant (CDE-184602) and is being administered by Ontario HIV Treatment Network. The authors acknowledge the contributions of the Project Advisory Committee through their commitment to the planning of meetings at setup.

Data Availability

The anonymized and encrypted data generated by the study will be stored on a secure institutional repository for a period of 5 years for the purpose of conducting secondary analysis by researchers upon reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review report by HIV/AIDS Community-Based Research - General Stream (Merged) (CIHR/IRSC, Canada).
[PDF File (Adobe PDF File), 40 KB - resprot_v12i1e48829_app1.pdf]

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Abbreviations

CBPR: community-based participatory research
HIP: HIV-response intergenerational participation
LGBTQ+: lesbian, gay, bisexual, transgender, and queer/questioning
MIBI: Multidimensional Inventory of Black Identity
PAC: project advisory committee
PEP: post-exposure prophylaxis
PrEP: pre-exposure prophylaxis
SAT-PLWHA-S: Scale of Stigmatizing Attitudes Toward People Living with HIV

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Protocol

The Senior Companion Program Plus for African American Caregivers of Persons With Alzheimer Disease and Related Dementias: Protocol for a Randomized Controlled Trial

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Abstract

Background: Alzheimer disease and related dementias (ADRD) pose significant challenges as chronic health conditions in the United States. Additionally, there are notable disparities in the diagnosis and prevalence of ADRD among diverse populations. Specifically, African American populations have a higher risk of developing late-onset ADRD than White people, and missed diagnoses of ADRD are more common among older African American populations than older White populations. These disparities also impact African American ADRD family caregivers.

Objective: The overall goal of this project is to develop a culturally informed, lay provider psychoeducational intervention named Senior Companion Program Plus (SCP Plus), which is specifically designed for African American ADRD caregivers and is potentially accessible, affordable, and sustainable.

Methods: In the proposed explanatory sequential mixed methods study, a randomized controlled trial will be used that includes 114 African American family caregivers of a relative with ADRD who will participate in the 3-month SCP Plus program.

Results: The study was funded on September 15, 2018, by the National Institutes of Health (1R15AG058182-01A1). Data collection began on May 16, 2019, but due to COVID-19 restrictions, ended 12 months into the planned 27-month recruitment period on March 31, 2023. The study was completed in June 30, 2023, and currently the results are being analyzed.

Conclusions: The SCP Plus offers promise as an intervention that utilizes an existing platform for the delivery of a lay provider intervention and offers a novel approach for addressing gaps in accessible, community-based support for caregivers of people with ADRD.

Trial Registration: ClinicalTrials.gov NCT03602391; https://classic.clinicaltrials.gov/ct2/show/NCT03602391

International Registered Report Identifier (IRRID): RR1-10.2196/49679

(JMIR Res Protoc 2023;12:e49679) doi:10.2196/49679

KEYWORDS

Alzheimer disease; dementia; lay provider; senior companion; volunteer; intervention; culturally informed; African American; family caregivers

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Introduction

Background

Approximately 6.7 million Americans aged 65 years and older are currently impacted by Alzheimer disease and related dementias (ADRD) [1]. Given that age is a key risk factor for ADRD and the number of older Americans continues to grow, it is expected that cases of ADRD will also increase [1]. ADRD is a disease marked by profound disability and dependence that worsen over time. Informal family caregivers provide most of the care to persons with ADRD, and they are at greater risk for negative physical and psychosocial outcomes when compared to noncaregivers or other types of caregivers [2].

Several intervention strategies have been implemented and evaluated to alleviate stressors and other negative outcomes among dementia family caregivers. In particular, research suggests that psychoeducational interventions may positively impact caregiver well-being, including burden [3], perceived health [4], and mental health [5,6]. While most psychoeducational interventions use trained interventionists, [7,8] peer-led interventions have demonstrated considerable promise. For example, research suggests that peer-led interventions may enhance family caregivers' social support and help with the management of chronic conditions [9-11]. Additionally, the translation potential of peer-led programs is further enhanced because of the use of lay providers rather than trained interventionists.

African American ADRD Caregivers

Based on demographic projections, the African American older population will grow to nearly 11% of the older adult population in the United States by 2050 [12]. Compared to White people, African Americans are about 2 times more likely to develop ADRD [1] and may live longer with ADRD than other races [13]. However, there are disparities in how ADRD is diagnosed and treated among African American older adults. For example, research suggests that missed diagnoses of ADRD occur more often among older African American adults than among Whites [14].

These disparities also affect African American ADRD family caregivers. Among this group, outcomes related to caregiver burden are mixed. For example, as reported by Brewster et al [15], a study presented by McLennon [16] indicated low scores on the Zarit Burden Scale [17] in African American ADRD family caregivers of persons with moderate-to-severe ADRD. However, the qualitative findings suggested that ADRD family caregivers experienced several challenges related to finances, safety concerns such as wandering, and providing physical care. Similarly, Brewster and colleagues [15] reported that in a mixed methods study of African American ADRD family caregivers conducted by Moss et al, participants scored relatively high on measures of quality of life but qualitatively reported stress and negative aspects related to caregiving [18]. Although psychosocial interventions for caregivers of persons with ADRD have shown promise, more research on culturally relevant interventions for African American ADRD caregivers is needed.

The Senior Companion Program

The Senior Companion Program (SCP) is one of 3 core programs funded by AmeriCorps.The SCP focuses on lower-income older adult volunteers providing assistance and friendship to other older adults who need support with daily living tasks [19]. SCP volunteers must be "at least 55 years of age or older and be capable of serving the frail elderly or adults who have one or more physical, emotional, or mental health limitations and are in need of assistance to achieve and maintain their highest level of independent living" [20]. Senior companions (SCs) serve as volunteers for 5 to 40 hours per week and receive modest hourly stipends [20]. Their typical tasks include providing assistance with meal preparation, offering medication reminders, accompanying their care recipient (CR) to social activities and medical appointments, and providing respite to family caregivers [20].

The Senior Companion Program Plus

Despite the benefits of the services provided by the SCP, many ADRD caregivers still report significant stress, as the SCP does not currently include a unique service to address caregiver stress/burden for ADRD caregivers [21]. Augmenting the SCP with ADRD-specific training is ideal as it extends the typical services of the SCP by providing psychoeducation to address the stress and burden that ADRD family caregivers continue to experience.

The Senior Companion Program Plus (SCP Plus) is the proposed intervention adapted from the work of Morano and King [22]. However, the SCP Plus differs from that work by training lay providers (ie, SCs) rather than clinical experts to deliver the intervention to increase its accessibility and translational potential. In the pilot study of the SCP Plus [21,23], the research team held focus groups with African American SCs to refine the work of Morano and King [22] and to adapt their intervention for use with the SCP. The SCP Plus trains SCs as lay provider "interventionists" to deliver a 9-week in-home psychoeducational intervention with African American ADRD caregivers. The SCP Plus includes 9 educational modules that cover topics on education, safety, strategies for challenging behaviors, communication, coping, finding purpose/meaning in caregiving, and community-based services (for an overview of each module, see Fields et al [23]).

The SCP Plus includes 12 hours of training for the SCs over 2 days and reviews the essential components of the intervention. Following this training, SCs deliver 1 module of the SCP Plus to the African American dementia caregivers during a weekly 60-minute meeting in the caregivers' or CRs' homes over a 3-month period (for a total of 9 hours). Based on the success of a pilot study of the SCP Plus [21,23], the proposed project will expand the program to 3 US states to conduct a randomized evaluation of efficacy.

For this proposed study, the revised sociocultural stress and coping model [24,25] provides the conceptual framework to examine caregiver burden, along with how cultural values affect the coping style, social support, and well-being of ADRD caregivers. This study's aims and hypotheses are listed in Textbox 1.

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Textbox 1. Study aims and hypotheses.

- Aim 1: We will examine the specific effects of the Senior Companion Program Plus (SCP Plus) to increase knowledge about Alzheimer disease, reduce caregiver burden and stress, and increase caregiver well-being after the SCP Plus intervention.
- Hypothesis 1: Participants will indicate clinically significant and statistically significant (P<.05) reductions in caregiver burden/stress and increased caregiver well-being at 3 months and a 6-month postintervention interval.
- Aim 2: We will examine the specific effects of the SCP Plus to improve caregiver coping skills.
- Hypothesis 2: Participants will indicate statistically significant (P<.05) improvements in coping skills associated with dementia caregiving.
- Aim 3: We will analyze the specific effects of the SCP Plus to increase caregiver satisfaction with social support (eg, received support, satisfaction with support, social support network, and negative interactions).
- Hypothesis 3: Participants will indicate statistically significant (P<.05) increases in social support.
- Aim 4: We will explore and interpret the statistical results obtained in the first quantitative phase to help explain why participants who scored in the lower and upper quartiles on caregiver burden/stress were or were not impacted by the usefulness of the intervention.

Methods

Study Design

The proposed study is a randomized control trial that will assess the effects of SCP Plus on African American dementia caregiver stress and burden, coping skills, and social support. An explanatory sequential mixed methods design [26] will be utilized, involving collecting quantitative data first and then analyzing the data to identify subsamples of participants who reported the greatest and least change in caregiver stress/burden. Among individuals in the SCP group with the highest quartile (n=14, 25%) and lowest quartile (n=14, 25%) of change, we will conduct follow-up qualitative interviews to capture the details of their situation and present a more comprehensive analysis that leverages the strengths of both methods. We propose a 3-year study. The study will take place in collaboration with SCP at sites in Texas, Louisiana, and Arkansas with approximately 114 SC-caregiver dyads. Half of the sample will receive services as usual (SAU) without the SCP Plus intervention. The control group will be randomly selected after baseline screening of all family caregivers, and all measures will be collected blind to the group condition. To further prevent selection bias, statistical techniques such as mixed factorial analysis of covariance (ANCOVA) will be conducted to adjust for covariate imbalance during data analysis.

Participants and Setting

Power analyses performed with G*Power software (version 3.1.9) indicated that a total of 114 participants are required to address our primary research objective using a mixed factorial ANOVA of our primary study outcome—caregiver burden. This sample size estimate was based on a small effect size (f=.12) and a 2-tailed alpha of .05 and a beta of .20. This effect size estimate was generated from our pilot data, which indicated a mean change in caregiver burden of 2.82.

Study participants will be the SC-caregiver dyads that include the SCs (n=114) recruited from the state-wide agencies with SCP as well as the African American caregivers (n=114) of older adults with ADRD who are currently enrolled in a Senior Companion Program in Texas, Arkansas, or Louisiana. Each dyad consists of 1 SC matched with 1 caregiver. To be eligible for this study, SCs must be (1) currently participating in the SCP and (2) currently providing respite services to the caregivers. As per the requirements of the SCP, SCs must be "55 years of age or older, be determined by a physical examination to be capable of serving the frail elderly, and be able to provide such service without detriment to either themselves or the clients served" [20]. For caregivers that receive services from the SCs, they must be (1) self-identified as African American, (2) 21 years of age and older, (3) providing unpaid care for an older adult with ADRD, and (4) cognitively intact as measured by a 6-item screener [27]. CRs with ADRD must have a physician diagnosis of ADRD and live at home in the community. Caregivers who are involved in another caregiver psychosocial intervention study or have an acute illness that would prevent them from participating for at least 6 months will not be eligible.

Study Procedures

Randomization

The SCP directors at each site will first help identify the potential SC-caregiver dyads who meet the inclusion criteria. The identified potential participants will then be randomly selected, and the research team will contact them afterward. Participant dyads who are interested in participating in the study will be guided through the informed consent process, administered a baseline survey via phone, and randomized to one of two groups: (1) the SCP Plus group that will receive the intervention plus SAU and (2) the control group that only receives SAU as part of the SC Program. SAU includes providing respite care for the family caregiver and personal care and light housekeeping/meal preparation for the person with dementia.

Data Collection

Quantitative data will be collected at preintervention, postintervention, and at the 6-month postintervention follow-up. The research team will then analyze the quantitative data at 3 time points to assess the effectiveness of the intervention and identify caregivers who reported the greatest and least change in caregiver stress/burden. Individuals in the highest and lowest quartiles of change in stress/burden will be recruited for follow-up interviews to understand their results in more depth through a qualitative study analysis.

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SAU Program

For SAU, SCs volunteer with frail, low-income older adults approximately 20 hours a week. SCs' tasks include helping older adults with ADRD by accompanying them to health care professional appointments, accompanying them to recreation/social activity/senior centers; providing assistance with ambulation and mobility; dressing, grooming, and feeding; reading, writing letters/forms; light cleaning; light meal preparation; monitoring for safety; peer support/companionship; and general caregiver respite. As part of the SCP, all SCs receive 40 hours of training from their agency, which includes topics such as program and agency policies, code of conduct, and a criminal background check.

SCP Plus

SCs randomly assigned to the SCP Plus will receive the 12-hour training. Two members of the research team will conduct all the SCP Plus training in person at each site. The training protocol was developed to affirm and build on the SCs' existing knowledge and skills related to ADRD caregiving [23]. The SCP Plus training will be delivered in person in a group format that includes both didactic approaches and role-play experiences. The SCP Plus training will last 2 days (6 hours per day). To ensure treatment fidelity related to the training, manuals and protocols for the training were created before the onset of this study. The training material will be audio recorded and reviewed by the research team using a checklist to quantify adherence to the training program.

SCP Plus is based on a dementia caregiver program [22] and adapted by Fields and colleagues [21,23]. ADRD caregivers whose SCs are randomly assigned to the intervention group will receive the SCP Plus intervention. The SCP Plus intervention will be delivered face-to-face by the SC who is a part of the SC-caregiver dyad. The intervention involves 9 in-home psychoeducational sessions over a 3-month period with 1 session per week.

Every week for 9 weeks, the SC-caregiver dyad will meet for 1 hour in the home of the CR (ie, the person with dementia). This allows the SC to maintain their duties while still participating in the SCP Plus program. It also allows the ADRD caregiver to receive intervention in the home setting of the person with dementia. Each week, the SC will deliver 1 module from the SCP Plus. "Icebreaker" questions will be included at the beginning of each module to answer any questions that the ADRD may have from the previous module and to facilitate a time for informal, supportive communication between the SC and the ADRD caregiver. At the end of each module, the SC will ask the ADRD caregiver to reflect on the content of the module, which will be written down in the form of brief notes by the SC. The inclusion of incentives (ie, retail gift cards) will be used to reduce caregiver attrition.

Measurements

The outcome evaluation will include measures of caregivers' stress and burden, knowledge of ADRD, coping skills, social support and activity, caregiver appraisal, caregiver physical health, and cultural justifications for caregiving. Standardized measures will be used to assess these outcome variables. The study by Xu and colleagues [28] contains an illustration of how these measures are mapped onto the conceptual model for this study.

The sociodemographic characteristics of the caregivers and their CRs will be collected at baseline, including age, gender, education, length of caregiving relationship, self-rated health [29], and number of hours spent in caregiving. Information about CRs' activities of daily living (ADL) and instrumental activities of daily living (IADL) that require help from caregivers will also be collected [30]. The Global Deterioration Scale [31] will be used to measure the severity of dementia of the person with ADRD. The frequency and duration of weekly contact with the SC will also be collected from the agency timesheets.

Dementia Caregiver burden and stress will be measured by the Zarit Burden Interview (ZBI) [17]. The ZBI was developed to measure the burden experienced by caregivers of persons with dementia living in the community [32]. The ZBI has 22 items measured with a 5-point Likert scale ranging from (never) to 4 (nearly always). Total sum scores range from 0 to 88, with higher scores indicating higher levels of distress. Studies have shown that ZBI has good validity and reliability among various minority dementia caregivers [33], particularly African American caregivers [34].

Knowledge of ADRD will be measured by the Knowledge of Dementia (KAD) scale [35]. KAD consists of 4 subscales concerning the (1) epidemiology and etiology of ADRD, (2) perceived effectiveness of different and currently available treatments, (3) beliefs regarding the perceived threat of ADRD for oneself, and (4) how respondents learned about the disease. KAD has shown good reliability and validity in assessing attitudes and beliefs regarding ADRD among dementia caregivers of different ethnic minorities [36].

Coping skills will be measured by the Brief Coping Orientation to Problems Experienced (COPE) subscales and religiosity coping. The Brief COPE questionnaire consists of 28 items measuring the ways/strategies caregivers have been coping with the stress in their life with a 4-point scale ranging from 1 ("I have not been doing this at all") to 4 ("I have been doing this a lot"). This scale has shown good validity and reliability in caregivers of persons with dementia [37]. Religiosity coping will be examined with the short form of the Brief Religious Coping (RCOPE) scale to measure the positive and negative aspects of religious coping [38]. All items are measured on a 4-point scale ranging from 0 ("a great deal") to 3 ("not at all"). This measure has shown good validity and internal consistency among racially and ethnically diverse populations of ADRD caregivers [33], including African American participants [39].

Social support will be measured with 13 items from four domains: (1) received support [40,41], (2) satisfaction with support [41,42], (3) social support network [43], and (5) negative interactions [41]. Social support networks will be measured by a modified Lubben Social Network Scale [43] that uses 3 items on a 6-point scale (none, 1, 2, 3 or 4, 5 to 8, and 9 or more). All other items have a 4-point scale that ranges from 0 (never) to 3 (very often) [44]. Social support measures have been proven to

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be valid and reliable with ethnic minority dementia caregivers [39], including African American dementia caregivers [39].

Caregiver appraisal will be measured with two components: (1) appraisal of problem behaviors and (2) appraisal of benefits. For an appraisal of problem behaviors, a modified version of the Revised Memory and Behavior Problems Checklist (RMBPC) [45] will be used to ask caregivers whether CRs' problems occurred during the past week (yes or no). If the answer is yes, caregivers will then be asked to rate how much the problem "bothered or upset" them on a 5-point Likert scale ranging from 0 (not at all) to 4 (extremely). RMBPC has been shown in the literature to be a valid and reliable measure for different ethnic minority caregivers [46], especially African American caregivers [47]. For appraisals of benefits from caregiving, the Positive Aspects of Caregiving (PAC) scale will be assessed [48]. The PAC has 9 statements about the caregiver's mental affective state regarding their caregiving experience. Each statement begins with "Providing help to the care recipient has…" followed by specific items (eg, made me feel useful, enabled me to appreciate life more). Each statement is rated on a 5-point Likert scale ranging from 1 (disagree a lot) to 5 (agree a lot). Studies show that the PAC is a valid and reliable measure for different ethnic minority dementia caregivers [33] and especially useful for African American dementia caregivers [49].

Caregiver well-being will be measured by the 12-Item Short-Form Health Survey (SF-12) [50] and the 16-item short version of the Caregiver Well-Being Scale (CWBS-ShortVersion). The SF-12 is a frequently used screening scale used to measure physical and mental health outcomes. It asks participants about their health, how they feel, and how well they can complete their usual daily activities. It has been shown to be a valid and reliable measure with African American older adults [51]. The CWBS-ShortVersion was developed to help family caregivers, clinicians, and researchers to identify areas of caregiver strength and areas in which additional support is needed. All 16 items will be measured by a 5-point scale ranging from 1 (rarely) to 5 (usually). The CWBS-ShortVersion has good content and construct validity regardless of the ethnicity of the caregivers [52].

Cultural justifications for caregiving will be measured by the Cultural Justifications for Caregiving Scale (CJCS) [53]. The CJCS consists of 10 items designed to assess caregivers' cultural reasons and expectations in providing care. Each item is measured using a 4-point Likert scale ranging from 1 (strongly disagree) to 4 (strongly agree). Summed scores range from 10 to 40, with higher scores indicating stronger cultural reasons for giving care. Study results have shown this scales' good reliability and validity score with African American caregivers [54].

Qualitative Questions

The second qualitative phase will explore and interpret the statistical results obtained in the first quantitative phase. The interview protocol will include a semistructured interview guide to explore domains of difference (eg, perceptions of treatment, level of engagement, and intervention processes).

Data Analysis

Quantitative Data Analysis

After the data are collected and entered into statistical software, the data quality will be carefully reviewed and then checked both automatically and manually. These review processes include checking the coding of observations, responses, and out-of-range values in SPSS software (IBM Corp), adding variable and value labels where appropriate, checking completeness or any errors of data entry, double-checking any errors in statistical analyses, and correcting errors made during transcriptions. In addition, data will be reviewed for risk of disclosure of research participants' identities, for sensitive data, and for private information to ensure confidentiality. Since all the key concepts in the proposed study are measured with standard scales, reliability tests for each scale and test-retest reliability across the 3 surveys will be conducted. Summed scores will be calculated for each of the standard scales.

Any random missing data, such as those due to random mistakes in data collection and entry, and are not related to research staff or patient noncompliance, will be submitted to maximum likelihood estimation procedures to estimate those missing values. Maximum likelihood estimation for random missing data is a common and accepted procedure for missing data estimation [55,56].

We will apply an intent-to-treat analytic approach to the study data. Fisher exact tests, Pearson chi-square tests, and independent sample *t* tests will be computed to test for group differences that may be attributable to caregiver variables such as gender, age, ethnicity, clinical site, length of caregiving relationship, and number of hours spent in caregiving. If the groups significantly differ on any of these variables, the variable will be incorporated into the following analyses as a covariate, thereby controlling for potential influences that the covariate may have on the dependent variables. As noted in the statistical literature, large power gains can be achieved by including correlated stationary covariates in ANCOVA, ordinary least squares regression, and Cox proportional hazards regression [57]. Moreover, if at the culmination of this study, our sample sizes are unequal in the treatment groups and our outcome data are nonnormal, we will follow through with appropriate statistical corrections where necessary.

Mixed factorial ANCOVAs will be computed to compare the SCP Plus and SAU over time on caregiver burden (ZBI), beliefs about dementia (KAD), coping (Brief COPE), social support, caregiver appraisal, well-being (CWBS-ShortVersion), and cultural expectations (CJCS). The covariates will be any significant variable yielded from the univariate analyses, and the dependent variable will be the scores at the pretest, posttest, and 6-month follow-up periods. Moreover, 95% CIs will be computed for each adjusted mean difference. The study alpha will be set at .05, with no adjustments for multiple comparisons due to the preliminary nature of this study and the increased risk of type 2 errors as a result of alpha adjustment [58]

Qualitative Data Analysis

Qualitative interviews will be recorded digitally, transcribed, and analyzed using conventional content analysis [59]. A

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constant comparative approach [60] will be used to explore similarities and differences in participants who did and did not benefit from the SCP Plus. Multiple strategies will be utilized to address rigor and credibility including peer debriefing and an audit trail.

Ethics Approval

The study protocol was approved by the Institutional Review Board of the University of Texas at Arlington (2017-0431 on 9/30/2018). It will be conducted following the Declaration of Helsinki.

Results

This study was funded on September 15, 2018, by the National Institutes of Health (1R15AG058182-01A1). Data collection began on May 16, 2019, and ended on March 31, 2023. The study was completed in June 30, 2023, and currently the results are being analyzed.

The study participants are SC-caregiver dyads. Due to COVID-19 social distancing requirements, data collections were halted in March 2020, 12 months into the planned 27-month recruitment period. The final sample size for the proposed study consisted of 20 dyads at baseline, and only 11 CGs completed the posttest and follow-up test. There were no missing data, so imputation was not necessary.

For the SCs in the 3 sites (N=20), all of them were female with a median age of 71 (range 58-80) years. Over one-third were either widowed or divorced (n=8, 40%). In terms of educational status, half (n=10, 50%) of the SCs were high school graduates or below. All SCs reported attending a religious service at least once per month. The participating SCs had taken care of their current CR with ADRD for a median of 4.5 (range 1-15) years and provided a median of 30 (range 6-40) hours weekly for their CRs. The majority (n=17, 85%) of the SCs felt very confident or confident in providing care to their clients with ADRD. Half (n=10, 50%) of them reported difficulty in paying for their basic needs (ie, financial strain). In general, the SCs had moderate levels of self-rated health (median 3). They helped their CRs with ADL (median 2.5, range 0-6) and IADL (median 7.5, range 4-8).

For the caregiver participants, the 20 CGs were a median age of 60.5 (41-80) years. The majority were female (n=17, 85%), married (n=11, 55%), and lived with their CR (n=16, 80%) for a median of 3 (range 0-48) years. The majority (n=15, 75%) of the CGs worked outside of the home, 45% (n=9) were employed full-time, and 35% (n=7) had to reduce their working hours to take care of the CRs. The CGs reported that spirituality was important (median 3.5, range 1-4). They also regularly attended religious services (median 3, range 1-5) and often prayed or mediated (median 5, range 1-5). The majority (n=13, 65%) of the CGs were children of the CRs. They had been taking care of their CRs for a median of 5 (range 1-26) years and provided a median of 12 (range 2-24) hours of care daily. The majority of CGs used formal services “several times a week” (n=16, 80%) and were “satisfied” or “strongly satisfied” (n=18, 90%) with the services received. The CGs had moderate self-rated health (median 3, range 1-5). They reported their CRs’ general health as low (median 1.5, range 1-4) and their memory issues as a median of 25 (range 10-49).

For other results, please see Xu and colleagues [28].

Discussion

Expected Findings

SCP Plus offers an innovative approach to using a peer-led psychoeducational intervention for caregivers of persons with ADRD. Given that the SCP is a national program, there is potential for sustainability and cost-effectiveness. SCP Plus will advance the scientific knowledge about how African American ADRD caregivers can build coping skills and protective factors through engagement with lay health care providers such as SCs. The implementation of the SCP Plus will increase insight into the sociocultural experiences of dementia caregivers and enhance the ability of community-based providers to meet the unique needs of minority caregiver populations.

Limitations

Due to the risks and feasibility of conducting an in-person intervention with SCs and ADRD caregivers during COVID-19, data collection for the intervention was suspended in March 2020. For a full description of the study limitations, see Xu et al [28].

Comparison With Prior Work

During the past 30 years, the development and evaluation of ADRD caregiver interventions have focused on providing information, skills building and psychoeducation, psychosocial support, and respite to families [61]. Although many ADRD caregiving interventions have demonstrated efficacy, these programs are inaccessible to the majority of family caregivers; for these reasons, current efforts have focused on translating interventions into clinical or community-based settings to evaluate the relevance of study outcomes for key stakeholders [62,63]. However, it remains unknown whether existing dementia caregiver interventions are culturally relevant to African American dementia caregivers [62].

Conclusions

The proposed project is aligned with the National Alzheimer’s Project Act [64] to better address the needs of persons with ADRD and their family caregivers. In particular, SCP Plus is aligned with three NAPA recommendations: (1) ensuring that family and unpaid caregivers have the support that they need; (2) ensuring representation and diversity in ADRD research; and (3) researching evidence-based interventions for ADRD care support. Finally, the implementation of SCP Plus will increase knowledge about how ADRD caregivers from minority populations can build coping skills and protective factors through engagement with lay health care providers such as SCs.

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Acknowledgments

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Data Availability

This research does not use a publicly available data set.

Authors' Contributions

NLF, LX, ICW, JEG, and DJC contributed to the conceptualization, methodology, writing, reviewing, editing, and funding acquisition. LX contributed to the software. NLF, LX, ICW, and JEG contributed to the validation and writing of the original draft. NLF, LX, and DJC contributed to the formal analysis and data curation. NLF, LX, and ICW contributed to the investigation. NLF and LX contributed to the resources, supervision, and project administration.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review reports from the Center for Scientific Review Special Emphasis Panel, Nursing and Related Clinical Sciences, National Institutes of Health (USA).
[PDF File (Adobe PDF File), 174 KB - resprot_v12i1e49679_app1.pdf]

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Abbreviations

ADL: activities of daily living
ADRD: Alzheimer disease and related dementia
ANCOVA: analysis of covariance
CJCS: Cultural Justifications for Caregiving Scale
COPE: Coping Orientation to Problems Experienced
CR: care recipient
CWBS-ShortVersion: Short Version of the Caregiver Well-Being Scale
IADL: instrumental activities of daily living
KAD: Knowledge of Dementia
PAC: Positive Aspects of Caregiving
RCOPE: Brief Religious Coping
RMBPC: Revised Memory and Behavior Problems Checklist
SAU: services as usual
SC: Senior companion
SCP Plus: Senior Companion Program Plus
SCP: Senior Companion Program
SF-12: 12-Item Short-Form Health Survey
ZBI: Zarit Burden Interview

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Protocol

Examining Feasibility, Acceptability, and Preliminary Outcomes of a Culturally Adapted Evidence-Based Postpartum Depression Preventive Intervention for Women in Doha, Qatar: Protocol for a Randomized Controlled Trial

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Abstract

Background: Postpartum depression and anxiety are the 2 most common perinatal mental health disorders, with prevalence rates higher among women living in the Middle East than in most Western countries. The negative outcomes associated with postpartum depression and anxiety are profound and include less responsive parenting and compromised infant and young child development. Although interventions exist to prevent postpartum depression and anxiety, to date, there have been no studies that have attempted to prevent postpartum depression or anxiety among Arabic-speaking women in the Middle East, including Qatar.

Objective: The purpose of this study is to conduct a randomized controlled trial (RCT) of an evidence-based postpartum depression preventive intervention—Mothers and Babies (MB)—culturally adapted for use with Arabic-speaking women in Doha, Qatar. MB is guided by a cognitive behavioral therapy framework that focuses on increasing pleasant activities, promoting healthy thought patterns, and increasing the type and frequency of personal contacts. MB is tailored to specific needs and issues related to pregnancy and the postpartum period.

Methods: A multidisciplinary and multiethnic investigator team adapted MB to promote cultural and contextual fit for Arabic-speaking women. Intervention concepts were reviewed to ensure core content would be understood by Arabic-speaking women in Qatar. Subsequently, images, activities, and examples in the intervention manuals were adapted, as needed, to make the content more relevant to Arab culture. To deliver the adapted intervention, 30 Arabic-speaking individuals with mental health backgrounds were trained. The adapted intervention was subsequently pilot-tested with 10 pregnant women receiving prenatal care at Sidra Hospital in Doha. We are now conducting an RCT to examine the effectiveness of the adapted intervention. We plan to enroll 210 pregnant individuals who are Arabic-speaking, with 1:1 randomization to the MB intervention or usual prenatal care. Among the enrolled participants, a stratified subsample of 40 pregnant women with diabetes is being recruited. Data collection will take place at baseline and a 6-month follow-up. The primary outcomes are depressive and anxiety symptoms and perceived stress. Diabetes self-care is the exploratory outcome for the subsample of individuals with diabetes. Intervention implementation will be assessed via client and provider surveys during and after intervention delivery. Power and sample size were calculated using a 2-sided 5% effort rate and assumed analyses on the individual level, accounting for attrition of 20%.

Results: The cultural adaptation and pilot study of the adapted MB intervention are completed. A total of 157 women have been enrolled in the RCT as of March 31, 2023.

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Conclusions: This study is highly innovative, as it is the first study to our knowledge to examine the effectiveness of an evidence-based postpartum depression preventive intervention in the Middle East. Limitations include a single follow-up time point and a small subsample of individuals with diabetes.

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International Registered Report Identifier (IRRID): DERR1-10.2196/11623

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KEYWORDS

postpartum depression; intervention; prevention; cultural adaptation; Arabic

Introduction

Perinatal mental health (PMH) disorders are common and have significant impacts on women, their infants, families, and communities [1,2]. Postpartum depression and postpartum anxiety are the 2 most common PMH disorders [3,4]. Systematic reviews have found a pooled prevalence of 15.5% across studies conducted in high-income countries [5], while systematic reviews of studies conducted in low- and middle-income countries found a higher pooled prevalence of 24.7% [6]. Among low- and middle-income countries, the highest prevalence rates were found in the Middle East and North Africa. Studies conducted in Qatar have found postpartum depression prevalence rates ranging from 18.6% to 27.3% [7,8].

An array of efficacious interventions exist that prevent postpartum depression [9,10], with several of these interventions demonstrating effectiveness in improving anxiety symptoms given the comorbidity with postpartum depression [11]. One intervention that has demonstrated efficacy in reducing depressive and anxiety symptoms and preventing the onset of new cases of postpartum depression is the Mothers and Babies (MB) course [12-15]. MB is a manualized intervention guided by a cognitive behavioral therapy (CBT) framework. CBT is characterized by a focus on (1) increasing pleasant activities, (2) focusing on one's thoughts, and (3) the type and frequency of personal contacts (ie, social support). MB contains a module in each of these 3 areas. The content of MB is tailored to specific needs and issues related to pregnancy and the postpartum period.

Despite the prevalence rate of postpartum depression exceeding those found in Western countries and the availability of interventions effective in preventing postpartum depression, to date, there have been no intervention studies that have attempted to prevent postpartum depression among Arab women in the Middle East and North Africa region, including Qatar. The overarching goal of this study is to examine the feasibility, acceptability, and outcomes associated with MB delivered to women in Doha, Qatar. However, because MB was developed and previously examined when delivered to Western pregnant women, cultural adaptation was required before rigorous testing of the intervention in Qatar. The specific aims of this study are:

1. To adapt MB for use with Arab Arabic-speaking women in Qatar. Cultural and contextual adaptations were undertaken by a multidisciplinary and multiethnic research team.
2. To conduct a small pilot study (n=10) that examines the acceptability, appropriateness, and feasibility of the adapted MB intervention when delivered to Arab Arabic-speaking women in Qatar. Pilot study findings are used to make final revisions to intervention and research protocols.
3. To conduct a randomized controlled trial (RCT; n=210) to determine the effectiveness of the adapted MB intervention on depressive symptoms, anxiety symptoms, and perceived stress among Arab Arabic-speaking women in Qatar. Our primary hypothesis is that women receiving the adapted MB intervention will exhibit greater reductions in depressive symptoms, anxiety symptoms, and perceived stress compared to women not receiving the intervention.

A subaim is to recruit a stratified random sample of 40 women with diabetes (n=20 control group; n=20 MB intervention) and examine intervention effects on mental health outcomes as well as diabetes self-management.

Methods

Ethics Approval

The study procedures described below have been approved by the institutional review boards of Sidra Medicine (2019-0004) and Northwestern University (STU00211149).

Study Participants, Recruitment or Retention, and Informed Consent

A total of 210 women will be recruited. Women will be recruited from the prenatal care clinic at Sidra Medicine in Doha, Qatar. Women >18 years of age receiving prenatal care at Sidra Medicine—a women's and children's hospital—who are <28 weeks' gestation at the time of study enrollment, are of Arab origin, and speak Arabic fluently will be eligible. Women meeting these criteria will be approached by Arabic-speaking research assistants while they are waiting for their prenatal health care appointment. Research assistants will administer the Edinburgh Postnatal Depression Scale (EPDS) [16] and the Generalized Anxiety Disorder-7 (GAD-7) item version [17]. To be eligible for the study, participants must score between 7 and 12 on the EPDS or 10-15 on the GAD-7, symptom ranges that are both indicative of mild to moderate symptoms of depression and anxiety, respectively. Participants who endorse a past history of major depression will also be eligible, while individuals endorsing current treatment for depression will be excluded given this study's focus on the prevention of postpartum depression and anxiety. Other exclusion criteria have been minimized; however, women who self-reported receiving mental health treatment or having a serious mental health condition will also be excluded, as this may preclude

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women from regularly attending intervention sessions. Once eligibility is determined, the Arabic-speaking research assistant will introduce the study, answer any questions, and obtain signed informed consent from the participant.

Recruitment procedures emphasize the importance of participating in all MB sessions (for intervention participants) and remaining in the study through the 6-month follow-up assessment. The research team obtains ample tracking information at baseline, which includes the participant's name, email address, home and cell phone numbers, and mailing address. The research team uploads contact information about each participant's preferred mode of communication (eg, phone and text) at the time of recruitment.

Randomization Procedures and Intervention Conditions

Randomization Procedures

Stratified permuted block randomization with blocks of sizes 2 and 4 will be used to randomize consenting women into the control arm or the intervention arm in a one-to-one fashion. The stratification will be based on the diabetic status of the woman. The randomization will be done by a statistician who is not involved in recruiting patients. A randomized list was created by the biostatistician, which was later uploaded to Research Electronic Data Capture (REDCap; Vanderbilt University) [18,19], a web-based software package for data management. This allows for the lack of human involvement on the part of the research team in the assignment of a participant to a group. It also allows for the on-the-spot assignment of participants into either the control or intervention groups.

Control Arm

Women randomized to the control arm will receive standard prenatal care delivered at Sidra Medicine.

Intervention Arm

Women randomized to the intervention arm will receive the culturally adapted MB intervention. MB consists of 12 sessions, each designed to last 15-20 minutes. The first 2 sessions provide (1) an understanding of the emotional and physical outcomes associated with stress, including concerns related to parent-child interaction, (2) strategies to notice one's mood, and (3) an overview of how the remaining CBT content can help minimize stress levels. Sessions 3-5 focus on the CBT module of Pleasant Activities, while sessions 6-8 focus on Thoughts, and sessions 9-11 focus on Contact with Others. Session 12 is a course wrap-up and graduation. Intervention sessions provide concrete skills participants can use—for example, developing lists of pleasurable activities and strategizing how to overcome obstacles to engage in those activities. At the end of each session, a short personal project is provided to participants to encourage skill practice prior to the next session. Intervention sessions are delivered in-person, by phone, or via telehealth (Zoom and Microsoft Teams) by a mental health professional trained in MB. Sessions are intended to be delivered weekly or every other week, with flexibility given to deliver sessions at the same time to facilitate the timely completion of the intervention. Incentives will be provided to participants after completing each MB module to encourage their continued intervention participation. Additional content was added to selected sessions for the diabetic subgroup. This content was intended to draw links between the core MB cognitive-behavioral skills and diabetes management and self-care. For example, content that indicates how exercise and a healthy diet—aspects that are important for diabetes management—are also related to mental health, as both interventions have a positive effect on mental and emotional well-being, was added.

Interventionist Training

Interventionist training in MB was provided by the senior author (SDT) and first author (SRA). Training was a 1-day in-person training conducted at Sidra Medicine. The first part of the training covered the conceptual underpinnings of MB (eg, its cognitive-behavioral framework), a brief history of previous implementation of MB, instruction on the format of the MB instructor manual, and discussion of implementation logistics. The second part of the training reviewed each of the 12 MB sessions from start to finish. Training was interactive, with opportunities for discussion and modeling the communication of material by the trainers. Training also involved group activities, where training attendees practiced delivering curriculum material and received feedback on strengths and areas needing improvement from the trainer and other training participants. We trained 30 individuals who met the following criteria: (1) employed as a nurse or health care professional or received graduate training in psychology; (2) were aged 18 years or older; and (3) had at least a bachelor's degree in nursing or psychology, or equivalent mental health counseling training, experience, or certification. All trained individuals were fluent in Arabic.

Data Collection Procedures and Study Assessments

The RCT includes 2 data collection time points—baseline and 6-month follow-up. We will attempt to collect 6-month assessments for intervention participants regardless of their engagement with the intervention. Participants will receive a remuneration of US $40 after completing each survey. Baseline and follow-up data will be collected and managed using REDCap. Women who do not choose to complete REDCap assessments will be contacted by phone by the research assistant to complete the assessment by phone or in person.

This study's primary outcomes are a reduction in depressive symptoms, anxiety symptoms, and perceived stress. Secondary outcomes are closely linked with core MB content; secondary outcomes include behavioral activation, social support, mood regulation, decentering of thoughts, and MB skill use. The outcome associated with our exploratory aim is diabetes self-care. All measures have been validated in Arabic.

We will also assess various aspects of intervention implementation. We will conduct client surveys at the end of each MB module to assess clients' perceptions of intervention acceptability and satisfaction. Each survey lasts 2-3 minutes and asks 3 questions pertaining to enjoyment with MB material, understanding of MB material, and anticipated use of MB material. Six months after a facilitator begins MB delivery with a client, the facilitator will receive a REDCap survey to report

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on the extent to which they covered all topics within an MB session (on average) and the extent to which clients were engaged in the MB material during intervention sessions.

Safety and Data Monitoring

For any woman who endorses the suicidality question on the EPDS screener with a response that they think about suicide "quite often" or "sometimes," the research assistant conducting the EPDS will escort the client to the outpatient mental health clinic, ensuring that the client is seen by a clinician. The clinicians in the Sidra Medicine outpatient clinic are trained to determine whether the client is in danger of harming herself or others and will determine the necessary steps to ensure the safety of the study participant. Regarding data monitoring, the study team will develop a series of data status and quality reports via an automated task, which study staff will review each week. These reports will focus primarily on reviewing missing data from collected assessments, accrual and retention, adverse events, and the number of women endorsing suicidal ideation.

Statistical Analysis

A flowchart will be constructed based on the CONSORT (Consolidated Standards of Reporting Trials) guidance to show the number of recruited, excluded, lost to follow-up, and analyzed participants. Descriptive statistics will be used to summarize baseline characteristics overall and by study arm. As appropriate, mean (SD) and frequency (proportions) will be used to summarize continuous and categorical variables, respectively. Median (IQR) will be used in cases of skewed or nonnormal distributions. Analyses will use normal theory methodology as appropriate, and in cases of violations of assumptions, transformations or nonparametric analyses may be used. We will use SPSS (version 27; IBM Inc) to perform all analyses.

Analyses will be done using the intent-to-treat principle and will compare the 3 primary outcomes between study arms using the independent 2-tailed *t* test (or the Wilcoxon rank sum test in cases where outcomes were highly skewed). The analyses above will be repeated using univariate linear regression to be able to adjust later for any imbalances in baseline characteristics between the study arms and the baseline values of the primary outcomes. Additional analyses will include fitting multivariate linear regression models for each of the 3 main outcomes to assess the effectiveness of the intervention while adjusting for the baseline value of the outcome and any observed imbalances in participants between the 2 study arms. Unadjusted and adjusted mean differences in the primary outcomes between the 2 study arms will be presented along with their standard deviations and *P* values. For the primary outcomes, missing data at 6 months will be imputed using the average of the patients in that group or other methods such as multiple imputation by chained equations, and the primary analyses will be repeated as a sensitivity analysis. Secondary outcomes will be analyzed by comparing study arms using the chi-squared test (or Fisher exact test if expected cell counts are below 5) for categorical outcomes and the independent 2-tailed *t* test (or Wilcoxon rank sum test for highly skewed data) for numeric outcomes. Compliance with the intervention will be assessed by counting the number of intervention sessions received.

Power and Sample Size Calculations

With 105 participants recruited per study arm and an estimated attrition of 20%, the study will be able to detect an effect size of 0.5 in any of the 3 primary outcomes using the independent 2-tailed *t* test with a power of 80% and a significance level of .017.

Results

This study is in progress. We have completed the cultural adaptation of MB as well as the pilot study of the adapted MB intervention. Recruitment for the RCT began in February 2022.

Cultural Adaptation of MB

A multidisciplinary Arabic-speaking research team comprised of psychologists, psychiatrists, obstetricians, endocrinologists, and nurses led the adaptation process. This research team was of different Arab backgrounds, with ethnic backgrounds represented including Qataris, Egyptians, Sudanese, Omani, and Palestinians. This combination of different ethnic backgrounds helped tailor MB to ensure a diversity of Arab cultures. The research team worked from the MB facilitator and participant manuals and reviewed them to first ensure that core intervention concepts would be understood by Arab-origin, Arabic-speaking women in Qatar. Additionally, images, activities, and examples found in the manuals were reviewed and adapted, as needed, to render the content more relevant and appropriate to Arab culture. For example, mindfulness sessions were adapted to include an Islamic and spiritual perspective to introduce the mindfulness sessions to the client (eg, how to improve the relationship with God, which can help in daily life and how to practice culturally informed mindfulness practices). Examples of pleasant activities that clients could engage in were modified to include culturally appropriate examples (eg, reading from the Quran and visiting family) and address contextual differences in activities (eg, removing examples of window shopping and gardening) that are not typically performed by Arab women in Qatar.

Pilot Study of Adapted MB

A byproduct of this project is deepening the capacity of mental health professionals in Qatar to address mental health with their perinatal clients. As such, 29 individuals fluent in Arabic were trained on the adapted MB manuals. The individuals included graduate students from the Doha Institute for Graduate Studies' new master's in psychology program, medical students from Weill Cornell Medicine in Qatar, PMH nurses from Hamad Medical Corporation and Primary Health Care Cooperation, and nurses from Sidra Medicine. The nomination of these trainees was performed based on their medical backgrounds, prior experience with CBT, and availability to deliver the intervention during the time frame of the research study. Training was led by the 2 multiple principal investigators (SRA and SDT). Training occurred over a full day and introduced trainees to the MB intervention's core concepts and implementation considerations. Subsequently, each intervention session was reviewed with key considerations highlighted by the trainers. Emphasis was placed on highlighting places in the curriculum where adaptations were made to promote cultural

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and contextual fit. A second training was held for 14 of the individuals who completed the first training and indicated an interest in facilitating MB intervention sessions. This second training provided these 14 individuals with details on the study's intervention and research procedures (eg, facilitator responsibilities, patient recruitment process). Training was delivered in both Arabic and English.

For the pilot study, 4 of these facilitators delivered the MB intervention to 10 pregnant individuals. The average number of sessions received was 7.0 (out of 12), and 4 individuals completed all 12 sessions. Baseline assessments were conducted to pilot procedures and measures to be used in the RCT. Client and facilitator feedback was used to modify study procedures and slightly adapt the intervention content.

RCT Recruitment

Recruitment for the RCT began in February 2022 and is expected to be completed by December 2023. As of March 31, 2023, a total of 259 pregnant women had been consented and screened for eligibility. Of those screened, 157 were eligible and enrolled in the study.

Discussion

This study has several notable strengths and innovations. It is the first study to our knowledge that examines the effectiveness of a postpartum depression preventive intervention with Arab women in the Middle East, including Qatar. Given the higher prevalence of postpartum depression among women in the Middle East [6], interventions aimed at preventing and treating postpartum depression need to be examined in this context. The intervention tested in this study is an adapted version of an evidence-based postpartum depression preventive intervention—MB. Several RCTs of MB have demonstrated its effectiveness in preventing postpartum depression in diverse perinatal populations in the United States. However, given the significant cultural differences between the United States and Qatar, we engaged in a process of culturally adapting the intervention before testing its effectiveness with Arab-origin, Arabic-speaking women in Qatar. This cultural adaptation is another strength of this study, as a multidisciplinary team of researchers and clinicians from different Arab backgrounds engaged in an intensive process of reviewing and adapting the MB facilitator and participant manuals to ensure their cultural and contextual fit.

Our recruitment of a stratified subsample of diabetic women enhances the potential impact of this project. It is well established that stress during pregnancy has an impact on blood glucose control [20]. Pregnant women with diabetes who receive MB are likely to exhibit reduced stress levels by learning the cognitive, behavioral, and stress management techniques taught through the intervention. As a result, we anticipate that we will observe better diabetes self-management.

Because each MB session lasts only about 20 minutes, sessions can be delivered during an existing health care visit (eg, while waiting for a prenatal care appointment). MB is also highly flexible, allowing for intervention delivery in person, by phone, or via telehealth (eg, Zoom, Microsoft Teams). The use of non-face-to-face interventions may be of particular benefit to women who struggle to attend prenatal appointments—for example, if women do not feel well, have a child who is unwell, or have difficulty accessing transportation or childcare. The use of phone or telehealth approaches allows for the intervention to be more easily delivered during very hot weather or during Ramadan—important contextual considerations for interventions delivered to women in Qatar and the Middle East.

This study is not without limitations. Although the adaptation of MB was conducted to promote cultural and contextual fit, caution will need to be used in generalizing findings beyond the sample recruited from one medical center in Doha. Our 6-month follow-up time point is also limited in its ability to examine sustained intervention effects as well as the impact of the intervention on parenting or parent-child attachment outcomes. Although the diabetic subsample is innovative, our sample size is limited for this exploratory aim.

Pregnancy and the early postpartum period are times of increased risk of mental health disorders—particularly depression and anxiety—that impact not only maternal and fetal well-being and functioning but also mother-infant attachment, parenting practices, and infant development. These time periods are opportune times for mental health interventions given that women access health care more frequently and families are often more motivated to engage in health-promoting activities to promote positive outcomes for their children. This study has the potential to add to the evidence base on postpartum depression preventive interventions broadly and will also be the first of its kind to do so among exclusively Arab women in the Middle East.

Acknowledgments

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Data Availability

The data sets generated or analyzed during this study are available from the corresponding author upon reasonable request.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review report by the National Priorities Research Program, Qatar National Research Fund (Qatar).
[PDF File (Adobe PDF File), 121 KB - resprot_v12i1e11623_app1.pdf]

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Abbreviations

CBT: cognitive behavioral therapy
CONSORT: Consolidated Standards of Reporting Trials
EPDS: Edinburgh Postnatal Depression Scale
GAD-7: Generalized Anxiety Disorder-7
MB: Mothers and Babies
PMH: perinatal mental health
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture

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Protocol

Strengthening Mental Health and Resilience Through Schools: Protocol for a Participatory Design Project

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Abstract

Background: Mental health problems are a main contributor to the global burden of disease in children and young people within urban environments. In response, the potential of both school- and sport-based mental health promotion interventions has been advocated. However, there exists limited insights into how sport-based interventions can be integrated within school environment. Moreover, there is a need to consider children and young people's specific needs, challenges, and motivations when designing novel mental health promotion interventions.

Objective: The Strengthening Mental Health and Resilience Through Schools (SMARTS) project aims to co-design an evidence-informed school-sport-based mental health promotion program. Specific objectives include (1) co-designing a multicomponent program, integrating sport sessions with class-based sessions, and complementing with educational modules for teachers and parents; (2) exploring how the mental health program can be implemented most effectively within the Brussels school system; and (3) conducting preliminary process and outcome testing of the program.

Methods: A participatory design framework will be adopted to develop the program. This framework involves end users throughout the entire study process, from problem identification to intervention delivery and evaluation, while at the same time ensuring program development remains directly informed by the available scientific evidence.

Results: Participant recruitment will commence in September 2023. The full project will be completed by March 2027.

Conclusions: With this intervention, we aim to provide a direct contribution to the promotion of children and young people's mental health within the Brussels school context. At a broader level, conducting and documenting this large participatory design project can, hopefully, inspire other researchers to tailor their mental health programs to specific populations.

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children; physical activity; psychological symptoms; sport; well-being; youth

Introduction

Overview

Mental health problems form one of the main contributors to the global burden of disease among young people. The first onset of most mental disorders typically occurs in childhood or early adolescence [1], with children and young people between the ages of 13 and 15 years being most at risk for first onset of psychological symptoms and distress. According to the World Health Organization [2], 1 in 7 children and young people is experiencing a mental disorder (eg, depression or anxiety), and suicide forms the fourth leading cause of death among this age group. Moreover, evidence suggests that up to 20% of

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school-going youth have engaged in nonsuicidal self-injury (NSSI) at least once [3]. NSSI forms a particularly relevant marker of mental health, as it is one of the strongest predictors of suicide [4] and is associated with a variety of other negative mental health outcomes in children and young people, including anxiety, depression, and personality disorders [5]. The mental health of children and young people also forms a particularly relevant and major social-urban challenge, as evidence suggests that mental health problems are more prevalent within metropolitan contexts compared to rural settings [6,7]. In Belgium, for example, inhabitants from the Brussels capital region tend to report significantly lower perceived well-being and higher prevalence rates of mental disorders, suicide attempts, and use of psychopharmacological medication compared to regional or national averages [8]. Moreover, the mental health of children and young people within urban settings has increasingly come to the forefront during the COVID-19 pandemic. Evidence suggests that the pandemic, as well as isolation and loneliness as a consequence of lockdown measures, have led to a considerable increase in symptoms of depression and anxiety in young people [9,10]. Even post the COVID-19 pandemic, the rates of psychological symptoms seem to remain remarkably high. Overall, the impact of mental health problems on young people is profound, as individuals experiencing psychological distress are particularly vulnerable to social exclusion, discrimination, stigma, educational difficulties, risk-taking behaviors, physical ill-health, and human rights violations [2].

These sobering facts highlight the need for evidence-informed mental health interventions for children and young people within urban settings. The World Health Organization [11] defines good mental health as "a state of well-being that enables people to cope with the stresses of life, to realize their abilities, to learn and work well, and to contribute to their communities. Mental health is an integral component of health and well-being and is more than the absence of mental disorders." This definition supports a 2-factor model of mental health [12], which distinguishes positive subjective well-being and psychopathology as 2 related but essentially distinct dimensions of mental health [11-14].

Concerning psychopathology, there is a clear need for preventive and early intervention programs to complement traditional clinical care. This is particularly important as many children and young people never seek out professional care [15]. In Belgium, for example, data indicate that up to 41% of adolescents who are experiencing severe mental health problems never receive professional treatment [8]. Moreover, even when professional treatment is reached, this typically does not occur until several years after the initial onset of mental disorders [1]. Finally, from a practical perspective, the increased recognition and prevalence of mental health problems in children and young people has severely strained the available health care system, leading to often month-long waiting lists for clinical mental health care. At the same time, the 2-factor model recognizes that mental health reflects more than merely the absence of mental disease or ill-health. Interventions may therefore equally consider a mental health promotion approach [12], focusing on children and young people's ability to achieve developmentally appropriate tasks and enhance their self-esteem, mastery, resilience, social inclusion, and well-being [16,17]. As such, mental health promotion forms an "important component of the mental health intervention spectrum, which can serve as a foundation for the prevention and treatment of mental disorders" [16].

Existing mental health interventions for children and young people have commonly been delivered through school-based programs. School environments offer a unique opportunity to integrate mental health interventions within existing school structures, thereby reaching a far greater group of potentially at-risk children and young people compared to more traditional health care services [18]. In Flanders, for example, the government supports school-based health prevention primarily through activities that are rooted in the strategic plan "De Vlaming Leeft Gezonder in 2025." The idea is to strive for an integrated policy ("Health in all policies") that is reflected in important life domains (so-called "settings," among other educational settings). A growing body of evidence indeed suggests that such school-based programs can be effective in promoting mental health and well-being [19-21], as well as preventing specific psychological symptoms such as NSSI and suicidality [22,23], although a better theoretical understanding of program outcomes and ways of sustaining them remains necessary. This is particularly important given recent suggestions that, in certain cases, universal school-based interventions may not only be ineffective in promoting mental health but even actively cause harm to children and young people [24].

In addition to school-based initiatives, there has been increasing interest in the potential of sport and physical activity to promote mental health in young people. There exists strong evidence indicating the positive effects of physical activity in and of itself on the mental health and well-being of children and young people [25,26]. When used purposefully and deliberately, sport can also form an important vehicle for positive youth development [27]. The notion of positive youth development closely connects with mental health promotion, as it reflects a strength-based approach aimed at providing optimal developmental experiences to enable individuals to lead healthy, satisfying, and productive lives, both as a youth and later in life [28]. Additionally, sport can provide a "hook" to grab children and young people who would otherwise not find their way to traditional help-seeking pathways (eg, men and people of minority ethnic backgrounds) [29]. In particular within major urban areas, sport has the potential to reach and engage underprivileged, difficult-to-reach and at-risk populations, and has been posited as a cornerstone for inclusive and comprehensive social and well-being policies [30].

Despite the potential of sport-based interventions, there still exists a lack of research into the use of sport as a vehicle to promote mental health in young people, and existing initiatives often lack a clear theoretical or evidence base [31]. Moreover, existing programs have mostly been limited to organized sport contexts. To date, only a single study has developed a school-based mental health program that aims to integrate and complement physical activity sessions with traditional classroom-based sessions [32]. Although insightful, this

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intervention was developed in the United Kingdom as a response to specific challenges in their local communities. As such, it is unclear to what extent this intervention is transferable to the Brussels context. Moreover, the intervention specifically targeted pupils with a diagnosed mental illness rather than providing a broad mental health promotion intervention targeting the entire pupil population [32].

In sum, there is a timely and important need to develop and test novel evidence-informed mental health promotion programs for children and young people within the Brussels urban setting. The context of Brussels is unique as it is highly polarized geographically, economically, and socially, with a large youth population of minority ethnic background and lower socioeconomic status [33]. These factors have been associated with increased mental health stigma and form crucial barriers toward seeking and accessing traditional forms of mental health care [34]. To address such issues, a mental health promotion program integrating class-based sessions with sport sessions may offer considerable potential. To maximize impact, such a program would be best designed as a multicomponent intervention [18,19], offering multiple intervention components targeting both the promotion of subjective well-being (eg, strengthening resilience and promoting mental health literacy [MHL]) and the prevention of key psychological symptoms (eg, NSSI prevention) [12]. Moreover, interventions may also benefit from adopting a multilevel approach, by engaging multiple stakeholders (eg, parents and teachers) around the individual [2,18]. Such a holistic "whole-school" approach focuses on leveraging social and environmental influences to promote positive mental health in adolescents. At the same time, to be effective and sustainable, interventions need to account for the complexity of each target context and carefully tailor intervention components to the needs, challenges, motivations, and key competencies of the program's end users [18].

Moving Toward a Citizen Science Approach

Although school-based mental health programs have been around for over 3 decades, the majority of these interventions have been developed in the United States. In their review of the literature, Kuosmanen et al [18] noted that interventions tend to show less consistent positive results when they are directly transferred to other countries or contexts. Both cultural and contextual factors play a crucial role in determining a program's impact, and one may, therefore, question to which end existing programs are applicable to handle specific local challenges [18]. Moreover, there seems to exist a "science-to-practice gap" in implementing such preventive mental health interventions [18]. Despite promising results, many large-scale randomized controlled trials of school-based mental health programs have proven difficult to sustain and upscale within "real-world" settings [20] and scholars have noted high levels of attrition within such programs [21]. All in all, these issues highlight the need for interventions to be carefully designed in function of the needs and challenges of the end users within their specific cultural and geographical context and, at the same time, be engaging and motivating to ensure end users are willing to start (and continue participating in) the program. In other words, there is a need to move from discrete intervention packages to creating sustainable implementation structures and climates [18].

Citizen science, or more specifically, a participatory design approach, might, therefore, be particularly suited to tailor a mental health program to the specific needs, challenges, and motivations of children and young people within the Brussels urban context. Participatory design "offers an evolving set of critical, conceptual, and practical tools to support the active participation of users in the design of different systems, services, and products" [35]. As such, interventions are designed from the perspective of the end user and actively involve them as co-designers. Such participatory research, promoting community participation, is particularly important to address "wicked problems," wherein different stakeholders may hold disagreements regarding the interpretation of the problem and the science behind it, as well as conflicting values, goals, and life experiences [36]. As such, addressing these problems cannot be achieved by relying solely on interdisciplinary, expert-driven approaches. Concerning the design of mental health programs, participatory design forms an active affirmation of young people's rights to define their own mental health goals and be involved in their own mental health care [35]. Benefits of adopting a participatory design approach toward developing a mental health program can include addressing stigma in intervention end users, involving populations who are otherwise hard to reach within traditional mental health care (eg, young men with minority ethnic background), creating a "shared language" between researchers and participants, and ultimately improving the likelihood of the program being used in the applied field [35]. Participatory design is also particularly suited to develop an intervention that is evidence-informed and, at the same time, engaging for children and young people. Similar participatory design approaches are currently being implemented to develop evidence-informed mental health interventions in other populations, including sexual and gender minority youth [37] and young people with schizophrenia [38].

Research Objectives

Given the state-of-the-art presented above, the current Strengthening Mental Health and Resilience Through Schools (SMARTS) project aims to co-design a comprehensive, novel, evidence-informed school-sport-based mental health promotion program, developed with, and tailored for children and young people (aged 13-15 years) within the Brussels urban context. The specific objectives set out in this project include (1) co-designing a multicomponent (ie, MHL, strengthening resilience, prevention of NSSI and suicidality, and other psychological symptoms) mental health program for pupils, integrating sport sessions with class-based sessions, and complemented with educational modules for teachers and parents; (2) exploring how the mental health program can be implemented most effectively within the Brussels school system; and (3) conducting preliminary process and outcome testing of the entire mental health program.

To achieve these objectives, a participatory design approach will be central to the project. This participatory design will be informed by the framework set out by Hagen et al [35]. The central principles within this guiding framework are (1) the

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involvement of young people as active participants throughout the entire research process; (2) the active contribution of young people in idea generation and program design; and (3) the continuous evaluation of the program from the perspective of young people in terms of relevance, meaningfulness, and engagement.

Underpinning Intervention Principles

The SMARTS intervention components will be informed by several underpinning, evidence-informed principles, and theories. These principles will provide structure and help shape the participatory design process.

MHL Framework

MHL is defined as "understanding how to obtain and maintain positive mental health, understanding mental disorders and their treatments, decreasing stigma related to mental disorders, and enhancing help-seeking efficacy" [39]. It includes knowledge of preventive strategies, the ability to recognize warning signals for mental health problems, awareness of help-seeking options, and first aid skills to help others who are struggling with mental health problems. A lack of MHL has been associated with increased stigma and poor symptom recognition and serves as a barrier toward help-seeking behaviors [15]. As such, developing MHL in young people and their main "helpers" (eg, parents and teachers) has been recognized as a key component for preventive and early intervention programs [40].

Psychological Resilience

Resilience is commonly defined as the capacity to withstand or quickly recover from stressors [41]. It entails a dynamic process of adaptation wherein individuals learn to draw on their personal and environmental resources to maintain mental health under stressful life circumstances. Within the SMARTS project, the focus on resilience reflects a strength-based approach with an emphasis on stress and emotion regulation skills as well as the capacity to build and draw upon social support networks [42].

Onset Prevention of Psychological Symptoms

Promoting MHL and resilience may also be complemented with interventions aimed at preventing the onset of psychological symptoms, such as NSSI. A meta-analysis by Fox et al [43] has demonstrated the insignificant effects of interventions that focus on reducing or preventing NSSI as a stand-alone intervention. However, a recent pilot study investigated the differences between a general in-classroom mental health prevention program called "Happyles" and a school-based prevention program called "HappylesPLUS" which also targeted NSSI by adding a 1-hour NSSI-focused psychoeducation module [23]. The extra module focuses on key variables that impact the onset of mental health problems in general and NSSI specifically, such as the impact of social media on mental health, negative body images, and peer stigmatization. Both groups reported a reduced likelihood of engaging in NSSI in the future 6 weeks after receiving the program in comparison to before receiving the program. Results also indicated increased emotional awareness in both groups. However, analysis of the qualitative data led to the indication that "HappylesPlus" may have direct benefits for some students with lived experience (eg, an increase in help-seeking behavior for NSSI) [23]. Building on this pilot project, the SMARTS project will equally include an NSSI-focused psychoeducational module within the intervention and will broaden its scope to include other prevalent mental health problems in the Brussels region, such as suicidality and addiction.

Sport-for-Development

Sport is often considered a vehicle for the promotion of desirable social and psychological outcomes. For example, with regard to mental health, sport can be a context to promote both MHL and resilience [29,44]. However, sport-for-development scholars have noted that beliefs surrounding the developmental potential of sport in and of itself are often naive, idealistic, and based on limited empirical support [45]. It is crucial to carefully consider the context and conditions under which sport might contribute to such desirable psychological outcomes. Within this project, we therefore focus on a sport plus approach, defined as interventions "in which sports are adapted and often augmented with parallel programs in order to maximize their potential to achieve developmental objectives" [45]. Within such a sport-plus approach, we will critically examine how sports activities can be shaped, adapted, and augmented to maximize the potential to achieve the envisioned outcomes, rather than solely relying on the supposed direct impact of sport and physical activity in and of themselves on children and young people's mental health [25,26].

Methods

Overview

As stated, this study will use the participatory design framework presented by Hagen et al [35], as illustrated in Table 1. This framework identifies 6 research stages that provide a structured approach to involving end users throughout the entire study process, from problem identification to intervention delivery and evaluation, while at the same time ensuring program development remains directly informed by the available scientific evidence.

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Table 1. Overview of the study stages.

	WP 1[a]		WP 2[b]		WP 3[c]	WP 4[d]
	IDENTIFY	DEFINE	POSITION	CONCEPT	CREATE	USE
Aim of the study stage	Identify the problem from the perspective of the end users	Define the problem space and objectives within them	Understand how the intervention needs to be positioned in order to have the envisioned impact	Identify, generate, and evaluate concepts that represent what the intervention needs	Evolve, build, and refine an intervention that is useful and usable	Deliver, use, and evaluate the intervention based on the experiences of the end users
Methods to enable active participant involvement	WP 1 focus group interviews with pupils, teachers, and parents	WP 1 focus group interviews with pupils, teachers, and parents	WP 2 co-design workshops with pupils, teachers, and parents	WP 2 co-design workshops with pupils, teachers, and parents	WP 3 pilot study with detailed process evaluation by intervention end users	WP 4 implementation and detailed process and outcome evaluation by intervention end users
Evidence-informed research activities	Consultations with experts and review of epidemiological data	Scoping review of risk factors and resources for adolescent mental health	Consultations with experts and review of behavior change theories underpinning mental health interventions	Consultations with experts to establish relevant process, impact, and outcome indicators	Build and test (qualitative and quantitative) data collection battery	Group-controlled quasi-experimental study

[a]WP 1: work package 1.

[b]WP 2: work package 2.

[c]WP 3: work package 3.

[d]WP 4: work package 4.

Participants

Pupils

For the first 4 research stages (IDENTIFY, DEFINE, POSITION, and CONCEPT) we will recruit approximately 60 high-school pupils enrolled within the Brussels school context (aged 12-15 years). Within this sample, we will strive for a relatively heterogeneous group, recruiting participants from different schools, different education levels, different ethnic backgrounds, and with a balanced gender distribution. Within the CREATE research stage, we will sample an additional 40 pupils, representing 2 different classes. These classes will be purposefully selected from different schools to complete a pilot study of the proposed intervention. Finally, for the final research stage (USE), 300 participants will be recruited to complete the intervention, with another 300 pupils acting as matched controls. Pupils will be recruited from different schools, different educational levels, and different ethnic and socioeconomic backgrounds. The total number of participants within the USE phase is sufficient to ensure enough power for the planned statistical analyses and takes into account an attrition rate of 30%.

Teachers

For the first 4 research stages (IDENTIFY, DEFINE, POSITION, and CONCEPT), we will recruit approximately 24 high-school teachers. Within this sample, we will purposefully sample those teachers who will be involved in later stages of the delivery of the intervention. Specific attention will also be paid to involve physical education teachers. Within the CREATE research stage, we will sample 15 teachers to participate in the pilot study, representing 2 different schools. Finally, for the final research stage (USE) 50 teachers will be recruited from different schools to participate in the educational module for teachers.

Parents

For the first 4 research stages (IDENTIFY, DEFINE, POSITION, and CONCEPT) we will recruit approximately 24 parents of children enrolled within the Brussels school context. Within this sample, we will strive for a relatively heterogeneous group, recruiting parents of children from different schools, different education levels, different ethnic backgrounds, and with a balanced gender distribution. Within the CREATE research stage, we will sample 15 parents to participate in the pilot study, representing parents of pupils from 2 different schools. Finally, for the final research stage (USE) 50 parents will be recruited from different schools to participate in the educational module for parents.

Experts

For the IDENTIFY, POSITION, and CONCEPT research stages, an interdisciplinary group of applied and academic experts will be involved to help shape the evidence-informed intervention. We expect approximately 16 experts to be involved within the project's life span. These experts will be recruited based on their specific expertise and applied experience within the project topic and setting and through the different project partners. These experts will consist of the following:

1. 4 school directors and 4 "zorgcoördinators" (care coordinators) from different schools within the Brussels region;
2. 2 school counseling consultants from different schools within the Brussels region;
3. 2 government prevention advisors with specific expertise in mental health and well-being;

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4. 4 academic experts with specific expertise in mental health and well-being and (clinical) sport psychology.

Procedures

Based on the project design outlined above (see Table 1), 4 main work packages are proposed. Each of the work packages is described separately below.

Work Package 1

The first work package will encompass the IDENTIFY and DEFINE research stages. Key activities and milestones within this work package include the following:

1. Focus group interviews with pupils, teachers, and parents: focus groups will be conducted to (1) understand the problem from the perspective of the end users and (2) help define objectives to address this given problem.
2. Consultations with experts: consultations will be conducted to understand the problem from the perspective of applied and academic experts.
3. Scoping review of the literature: a scoping review will be conducted to (1) evaluate epidemiological evidence and (2) identify risk factors and resources for adolescent mental health.

Work Package 2

The second work package will encompass the POSITION and CONCEPT research stages. Key activities and milestones within this work package include the following:

1. Co-design workshops with pupils, teachers, and parents: co-design workshops will be conducted to understand how the intervention needs to be positioned from the perspective of the end user and generate intervention content.
2. Review of behavior change theories: a brief literature review will be conducted on leading behavior change theories that can aid in the design of engaging, evidence-informed intervention content.
3. Consultations with experts: consultations with experts will be conducted to establish key indicators to evaluate the intervention process, impact, and outcome based on content developed during the co-design workshops.

Work Package 3

The third work package will encompass the CREATE research stage. Key activities and milestones within this work package include the following:

1. Pilot study with detailed process evaluation by intervention end users; a detailed pilot study will be conducted to test the intervention with a small sample of end users.
2. Build, test, and finalize data collection battery (quantitative and qualitative); a battery will be developed and tested during the pilot study based on the established indicators for intervention process, impact, and outcome (see WP 4).

Work Package 4

The fourth work package will encompass the USE research stage. Key activities and milestones within this work package include the following:

1. Implementation of a group-controlled quasi-experimental intervention: a quasi-experimental intervention will be conducted, randomly allocating participants at group level (ie, class) to either experimental or control conditions. The experimental condition will receive the intervention over a 6-month period, whereas the control group will serve as a "usual care" control group. Additionally, a selected sample of teachers and parents of pupils within the experimental group will be provided with the complementary educational modules.
2. Pretest, posttest, and 3-month follow-up (quantitative and qualitative) evaluations; a 3-wave data collection design will be adopted to collect both qualitative and quantitative data on the intervention process, impact, and outcome. These include pretest, posttest, and 3-month follow-up data collection points.

Data Collection

Throughout the project, a mixed methods approach to data collection will be adopted. Qualitative data will be collected primarily through focus group interviews and co-design workshops. Each focus group and co-design workshop will be both audio- and video-recorded. Audio recordings will be transcribed verbatim, and transcriptions will be used for further analysis. Video recordings can be used to clarify the context of certain statements or to ascertain group dynamics within the interviews or workshops that cannot be discerned through audio alone.

Quantitative data will also be collected to evaluate program outcomes during the CREATE and USE research stages. In line with our participatory design approach, the determination of the most relevant project outcomes and the development of a corresponding test battery to assess these outcomes will be based on a co-design process during the project life span. As such, we have purposefully not determined an a priori set of outcome measures. However, an indicative set of outcome measures includes the following:

1. subjective well-being, as measured using the World Health Organization-Five Well-Being Index (WHO-5) [46];
2. psychological distress, as assessed using the Kessler Psychological Distress Scale [47];
3. mental health stigma, as assessed using the Peer Mental Health Stigma Scale [48];
4. help-seeking intentions, as measured by the Attitudes Toward Seeking Professional Psychological Help Scale-Short Form [49]; and
5. emotion regulations, as measured by the Difficulties in Emotion Regulation Scale [50].

Data Analysis

Qualitative data will primarily be analyzed using reflexive thematic analysis. Reflexive thematic analysis is particularly suited to gain sense and meaning from participants' lived experiences while at the same time recognizing the subjectivity of human experience and emphasizing that meaning-making from this experience is the result of a process of cocreation between the participant and the researcher [51]. To support our co-design principles and involve participants as active

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contributors throughout all phases of the analysis process, member reflections will also be used. Member reflections are structured opportunities for participants to provide feedback and reflection on tentative qualitative analysis, not as a way to verify the truthfulness of the analysis but rather as a way to generate novel insights and data [52].

Within the USE research stage, analysis of the main outcome measures will be calculated using a mixed-model ANOVA including 2 groups (mental health program vs control group) and measures at 3 time points (pre, post, and 3-month follow-up). Missing data will be dealt with by using appropriate methods.

Ethical Considerations

Institutional ethics approval has been requested and will be obtained for the SMARTS project. All participants will provide active, informed consent before their participation. For the participating children and young people, informed consent will also be obtained from a parent or legal guardian. The informed consent forms and participant information sheets are currently also under review by the institutional ethics board. Given the sensitive nature of the topic, the information sheets will include contact details from the researcher as well as several currently available mental health resources, should the participants feel the need for support following their participation in the study. All data collected throughout the project will be pseudonymized and stored for a duration of 10 years within a secure data repository following the completion of the project.

Results

Funding for the SMARTS project was approved in January 2023. Upon obtaining ethics approval, participant recruitment for the first research phase will commence in September 2023. The full project will be completed by March 2027.

Discussion

Children and young people living within urban environments form a particularly at-risk population for mental health problems [2]. School-based mental health programs have, therefore, often been proposed as key interventions to target this population [19-21]. Additionally, sports have also been proposed as a context for mental health promotion programs, as well as a "hook" to attract children and young people to such programs [32]. Nevertheless, there currently exists a "science-to-practice gap" in the implementation of mental health promotion programs for children and young people [18], with existing interventions often proving difficult to sustain and upscale to broader settings. One potential solution to this issue might lie in the use of participatory design approaches, focusing on the active involvement of intervention end users (ie, children and young people) as co-designers throughout all phases of intervention development. The SMARTS project, thus, aims to develop an intervention that is evidence-informed and, at the same time, engaging for children and young people, through the adoption of a rigorous participatory design approach [35].

To achieve this objective, the SMARTS project will co-design and evaluate a comprehensive evidence-informed school-based mental health promotion program, integrating sport sessions with class-based sessions, complemented with educational modules for teachers and parents. This intervention is targeted at school-going children and young people aged 13-15 years. This particular age range was chosen as it coincides with the typical age during which children and young people are at risk for first onset of psychological symptoms and distress [1]. The mental health promotion program will integrate principles based on MHL [39], psychological resilience [41], existing school-based programs to prevent psychological symptoms [23], and insights from the sport-for-development literature [45]. To develop the program, the rigorous participatory design framework presented by Hagen et al [35] will be adopted. Through several consecutive research stages, the SMARTS project will (1) co-design the multicomponent program, (2) explore how the intervention can be implemented most effectively within the Brussels school system, and (3) conduct preliminary process and outcome testing of the full mental health promotion program. A key challenge when conducting such a participatory design project lies in the recruitment and activation of all relevant stakeholders within the co-design process. However, this can be mitigated as the SMARTS consortium, which includes local school organizations, will play an active role in both participant recruitment and the design and implementation of the eventual organization.

With this intervention, we aim to provide a direct contribution to the promotion of children and young people's mental health within the Brussels school context. This is particularly relevant as children and young people within the Brussels urban context tend to report higher prevalence rates of mental disorders, compared to regional or national averages [8]. In part, this may be attributed to increased mental health stigma, as well as experienced social and economic barriers toward traditional mental health care. At a broader level, we hope that conducting and documenting large participatory design projects like SMARTS can inspire and guide other researchers to tailor mental health interventions to specific at-risk populations.

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The authors would like to express their gratitude to all partner organizations involved in the SMARTS project, including the GO! Scholengroep Brussel, CLB Brussel, and Gezond Leven. We would also like to explicitly thank Anja De Neve and Elke De Ridder for their contributions to the conceptualization and design of the project. Finally, we would like to thank the Citizen Science Contact Point of the Vrije Universiteit Brussel for their practical support in the organization of the SMARTS project. Funding for the SMARTS project was provided through the "Bijzonder Onderzoeksfonds" (BOF) of the Vrije Universiteit Brussel (grant OZR4051).

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Data Availability

Data gathered during the SMARTS project will be stored in a restricted-access data repository. These can be made available upon reasonable request to the authors.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review report from VUB Research (Brussels, Belgium).
[PDF File (Adobe PDF File), 145 KB - resprot_v12i1e49670_app1.pdf]

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Abbreviations

MHL: mental health literacy
NSSI: nonsuicidal self-injury
SMARTS: Strengthening Mental Health and Resilience Through Schools

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Protocol

Improving the Quality of Postpartum Care in Ghana: Protocol for a Parallel Randomized Controlled Trial

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Abstract

Background: Although the postpartum period poses substantial risks and can result in significant maternal morbidity and mortality, postpartum care of the mother receives much less attention in transitional countries.

Objective: We describe the protocol for a randomized controlled trial to implement and evaluate a postpartum care delivery model titled Focused-PPC (Focused Postpartum Care).

Methods: Focused-PPC is an integrated group postpartum care model that meets the clinical care, education, and support needs of mothers up to 1 year after birth. The Focused-PPC intervention is a parallel randomized controlled trial with a total of 192 postpartum women at 4 health centers in Tamale, Ghana. Participants will be randomized into 1 of 2 trial arms at a 1:1 allocation ratio: (1) the control arm, which receives the standard postnatal care currently delivered in health facilities, or (2) the intervention arm, which receives the Focused-PPC model of care. Women enrolled in the intervention arm will receive postpartum clinical assessments and education for the first 6 weeks and will continue to receive education, measures of vital signs, and peer support for 12 months post partum during child welfare visits. Led by trained midwives, each postpartum group in the intervention arm will meet at 1-2 weeks, 6 weeks, and monthly thereafter for up to 1 year post partum, following the Ghana Health Service postnatal care schedule.

Results: The Focused-PPC guide, data collection tools, and audiovisual education materials were successfully developed and translated into the local language. We have enrolled and conducted baseline surveys for 192 women (sample size met) in the Focused-PPC trial who have been randomized into intervention and control arms. We have established a total of 12 Focused-PPC groups in the intervention arm, 3 groups from each site, all of which have sessions underway.

Conclusions: Focused-PPC has the potential to change the postpartum care delivery model in Ghana and other countries in sub-Saharan Africa and beyond.

Trial Registration: ClinicalTrials.gov NCT05280951; https://clinicaltrials.gov/study/NCT05280951

International Registered Report Identifier (IRRID): DERR1-10.2196/47519

(JMIR Res Protoc 2023;12:e47519) doi:10.2196/47519

KEYWORDS

postpartum care; postnatal care; maternal mortality; Ghana; randomized controlled trial; protocol

Introduction

Maternal mortality is a major global health challenge, defined as the death of a woman while, or up to 42 days after, termination of pregnancy, related to the pregnancy itself and not by accidental causes [1]. Around the world, about 810 women die every day from preventable causes related to pregnancy and childbirth [1]. Most maternal deaths are preventable, yet sub-Saharan Africa continues to be impacted disproportionately compared to the rest of the globe, accounting for two-thirds (66%) of all maternal mortality worldwide [1].

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Ghana has a particularly high maternal mortality ratio of 308 deaths per 100,000 live births, compared to a maternal mortality ratio of 211 globally and only 11 in high-income countries [1]. Most of these deaths occur during the postpartum period, the period following birth, as compared to during pregnancy or labor and delivery [2].

In terms of health care provision, the postpartum period receives much less attention than pregnancy or childbirth. However, the period after birth still poses substantial risk to mothers and can result in significant maternal morbidity and mortality [1]. The median national coverage of routine postnatal visits for the mother stands at 71%, which is still significantly behind global targets for 2025, with some nations demonstrating coverage as low as 44% [3]. The World Health Organization (WHO) recommendations for postpartum care include continuous care in a health care facility for up to 24 hours and further postpartum clinical examinations at 48-72 hours, 7-14 days, and 6 weeks after birth [4]. These recommendations also state that postpartum clinical examinations should include assessments of vital signs, vaginal bleeding or discharge, uterine contraction, fundal height, urine void, and breast tenderness [4]. However, within developing countries, recommended postpartum clinical assessments are not consistently provided to women at recommended time points [5,6]. For instance, among women delivering in health facilities in Malawi, over half reported a lack of postpartum clinical assessments, including blood pressure checks, temperature checks, abdominal examinations, vaginal examinations, and breast examinations [5].

Mortality is worsened by a lack of access to appropriate postpartum care. Postpartum complications are frequently unforeseen and necessitate an immediate reaction, making quality care essential for the health and survival of the mother after birth. For instance, postpartum hemorrhage can be fatal within a matter of hours without prompt treatment [7]. Sufficient postpartum care enables medical professionals to quickly recognize and address complications as they arise [8]. Postpartum care also provides the opportunity for health care providers to meet the social and health needs of women and to encourage women to adopt evidence-based postpartum practices at home. As maternal self-care typically occurs at home after birth, it is essential that mothers are empowered with proper knowledge to mitigate their health risks after birth [4].

Within the postpartum period, obstetric complications are the primary cause of direct maternal deaths worldwide [2]. Complications such as hemorrhage, hypertension, and sepsis account for 62.4% of maternal deaths in sub-Saharan Africa [9]. Each of these complications has identifiable warning signs that, if noticed early, are likely to result in improved maternal outcomes. Therefore, ensuring knowledge of warning signs of complications is a key strategy in improving women's complication readiness and reducing deaths resulting from delays in seeking care [10]. If a mother has adequate knowledge of warning signs, she is far more likely to promptly recognize symptoms and seek timely postpartum care. However, several studies have reported that postpartum women in transitional countries experience inadequate knowledge of postpartum warning signs of complications [11-14]. Furthermore, midwives working in Tamale, Ghana, have self-reported inadequate knowledge and skill sets to adequately educate patients about all detrimental postpartum complications and how to manage those complications [15,16].

Comprehensive patient education is a widely established, low-cost intervention effective in improving health outcomes [17-19]. Patient education addressing postpartum recovery and potential complications that may happen after birth has significant potential to improve postpartum health outcomes among women in Ghana. Women are expected to manage their postpartum recovery following discharge from the hospital, meaning that all women are expected to recognize potential complications and seek timely emergency care accordingly from 48 hours after birth and beyond [20]. Therefore, it is crucial to ensure that all women, regardless of their risk factors, are educated regarding the early warning signs of potential complications and when symptoms necessitate care-seeking. Maternal morbidity and mortality can be reduced through the provision of quality education administered by health care providers [21].

From our experience working in the setting, there is a lack of integrated postpartum care that incorporates recommended clinical assessments, education, and support for women after birth. Our intervention, entitled Focused Postpartum Care (Focused-PPC), fills this gap through the provision of comprehensive postpartum clinical care, targeted education, and peer support for women in Ghana. A shift toward standardized care simultaneously addressing the needs of both the mother and the baby has significant potential to reduce maternal morbidity and mortality in this setting. In this paper, we describe the protocol for a randomized controlled trial in Tamale, Ghana. The aim of our study is to implement and evaluate Focused-PPC in a parallel randomized controlled trial with 192 postpartum women at 4 health centers in Tamale, Ghana.

Methods

Study Design

This is a parallel randomized controlled trial with balanced randomization (1:1) conducted in 4 health centers in Sagnarigu municipality, Tamale, Ghana. An overview of the study design can be found in Textbox 1.

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Textbox 1. Study design.

- Recruitment of potential participants
- Enrollment of eligible participants
- Informed consent and baseline survey
- Random assignment into intervention and control groups:
  - Kanvilli: 48 participants (intervention: n=24 [3 groups of 8]; control: n=24)
  - Choggu: 48 participants (intervention: n=24 [3 groups of 8]; control: n=24)
  - Kalpohin: 48 participants (intervention: n=24 [3 groups of 8]; control: n=24)
  - Bagabaga: 48 participants (intervention: n=24 [3 groups of 8]; control: n=24)
- Focused Postpartum Care (Focused-PPC; intervention arm)
  - Focused-PPC care
  - Focus group discussions at end
- Standard postnatal care (control arm)
  - Usual care
  - Not applicable
- Interviewer administered surveys at certain time points (see Table 1) for both arms

Table 1. Outcomes and evaluation.

Variables	Measurement	Baseline	1-2 weeks	6 weeks	3 months	6 months	12 months
Independent variables and potential covariates	Demographic questions, Obstetric history questions, Readiness for Hospital Discharge Scale – New Mother Form	✓					
Knowledge of postbirth warning signs	Investigator developed questions based on common postbirth complications	✓	✓		✓	✓	
Postpartum health behaviors	Specific questions assessing health behaviors will be tailored to the time frame post partum. Will include attendance to visits		✓	✓	✓	✓	✓
Postpartum health status	Edinburgh Postnatal Depression Scale, Perceived Stress Scale, Questions on complications experienced and other questions on health status as appropriate to the time frame after delivery, Measures of blood pressure, temperature, pulse, and weight	✓	✓	✓	✓	✓	✓
Feasibility, acceptability, and satisfaction	Focus groups with midwives and each group of participants in Focused-PPC[a] intervention arm using focus group discussion guide						At exit

[a]Focused-PPC: Focused Postpartum Care.

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Setting

The study will be conducted in Sagnarigu municipality, Tamale, which is located in the Northern region of Ghana. The public health sector in this area is run by the Ghana Health Service (GHS) and constitutes the most commonly accessed health facilities. The study will be conducted at 4 GHS health centers. The health centers are: Choggu Health Center, Kanvilli Health Center, Bagabaga Health Center, and Kalpohin Health Center.

Participants and Recruitment

Participants who are 18 years of age or older will be recruited in their third trimester while attending antenatal care visits in the health centers. Project assistants employed in each health center will conduct face-to-face recruitment using a script. The script describes the study, its eligibility criteria, and its voluntary nature. Typically, women arrive at the antenatal care visit and wait until it is their turn to enter the consulting room. Recruitment will occur during this wait time. When eligible patients agree to participate, they will provide their name and contact information for follow-up. Eligible and interested participants will also be provided with the project contact information and project assistant number to call or text at delivery, and project assistants will also follow up with women. Participants will be enrolled in the research study after delivery. Eligibility criteria at enrollment include being currently admitted to the postnatal ward, having had a live birth, having a newborn not in the neonatal intensive care unit, being able to speak and understand English or Dagbani, and having the capacity to provide informed consent. Since the intervention arm requires participants to have given birth within the same week or 2, randomization into the intervention arm (Focused-PPC) and control arm (usual care) will occur after each woman has given birth.

Sample Size

To establish an appropriate sample size, a power analysis was conducted using G*Power (Erdfelder, Faul, and Buchner) [22,23]. The experimental design has 4 total health centers. Individuals at every health center will be randomly assigned to an intervention arm, keeping in mind that the intervention arm needs to be in multiples of 8 at a time and that intervention groups are equal in size. Baseline characteristics are not expected to affect the outcome. In G*Power, the power analysis was run with 2 groups (the control arm and the intervention arm), which were then split up into 8-equal sized subgroups (health center A intervention, health center A control, ..., health center D intervention, health center D control). The model included 3 time points for measurements. The correlation among repeated measures that varied for a range of values from 0.05 (representing nearly uncorrelated measurements) to 0.3 (representing moderately correlated measurements) was considered. The desired power was always set to 0.8, and the nominal type I error was set to .05. A range of Cohen (1988) effect sizes was evaluated, from 0.10 (very small) up to 0.25 (a medium effect size). The outcome, the mean knowledge of postbirth warning signs, is a continuous variable. This was accomplished by varying the intervention arm's mean knowledge level. Based on previous study data, 1.9 was used as the control sample's mean knowledge score, and 1.4 was used as the SD within groups. For the intervention sample, a range of values for the mean knowledge score was tested, from 2.2 (which equates to a 0.1 effect size) to 2.65 (equating to a 0.25 effect size). The control arm and the intervention arm were assumed to have the same SD.

Under optimal conditions, where the correlation among repeated measures is minimal at 0.05 with a medium effect size of 0.25, a total sample size of 64 (16 individuals split into 1 intervention and 1 control group per clinic) is required [24]. Whereas under the worst assumed conditions (a small effect size of 0.10 and any correlation among repeated measures), a total sample size of 512 (128 individuals per clinic split into 16 intervention and 16 control groups) would be necessary. Assuming we want to detect a Cohen f of 0.15 with any size correlation up to 0.3 among repeated measures and no attrition, the recommended sample size is 192 (with 48 individuals split up into 3 intervention and 3 control groups per clinic).

Randomization

Project assistants will meet with eligible participants after birth, at discharge, in a designated private spot at the health facility, where they will obtain consent and complete the baseline survey. After the baseline survey, participant allocation will be 1:1 for equal intervention and control sizes. Allocation will be completed according to a computer-generated list of random numbers, allocating group sizes of 8. The allocation will be generated by a data scientist on the research team. The data scientist will provide participant allocations (intervention arm or control arm) to the project team. Participants in the intervention arm will also receive a group allocation (allocated in groups of 8). Intervention arm group participants will then be contacted to begin their group postpartum care. There will be no blinding, as the study team will know which women are in the intervention arm (receiving Focused-PPC) and the control arm (receiving usual care).

Group Conditions

Control Arm

Women in the control arm will receive standard postnatal care currently practiced in their respective health centers. This involves attending visits at the health center within 14 days after birth, at 6 weeks, and monthly thereafter up to 1 year. Currently, the GHS recommends beginning postnatal care immediately after birth, with the mother and baby receiving care within 14 days and at 6 weeks. After 6 weeks, the mother attends monthly child welfare clinic visits with the baby for up to 12 months.

Intervention Arm

Overview

Each Focused-PPC group in the intervention arm will consist of 8 postpartum women who will meet at 1-2 weeks, 6 weeks, and monthly thereafter for up to 1 year post partum, following the GHS postnatal care schedule. All Focused-PPC group sessions follow a guide developed by the research team with content derived from evidence-based guidelines, reviewed by experts, and approved by the GHS. These group sessions consist of two components: (1) 15-minute individual clinical assessments and counseling for each mother performed by

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midwives and (2) a 1-hour-long group education session and peer support led by midwives. Each Focused-PPC session will be led by 2 trained and registered midwives from each health center, who will provide both clinical care and education and support as needed. In addition, each group session will be supported by a project assistant, who will be responsible for collecting research data. Focused-PPC will be implemented in addition to newborn care.

Postpartum Clinical Assessments

The clinical care component of the intervention follows the recommended clinical assessments by the GHS and the WHO and includes assessment of vital signs, fundal assessment, vaginal bleeding or discharge assessment, incision assessment, and a breast examination. After the 6-week postpartum time point, only vital signs are measured at each session. In sub-Saharan Africa, over 60% of maternal deaths occur within the vulnerable first year after birth [2]. Since maternal deaths extend far beyond the traditional 6-week time frame, it is important that quality clinical care extend to 1 after birth. Focused-PPC provides regular contact with and monitoring by a midwife for up to a year following birth.

Postpartum Education

The content of Focused-PPC education will focus on the unique needs of postpartum women based on the time frame after delivery. Educational resources will be developed by the research team and an expert panel to apply to different time points throughout the postpartum period and to address the complex needs of postpartum mothers while conforming to the regulations and practices of the GHS. Educational content will then be converted into audiovisual resources, which will be used by midwives to present information during Focused-PPC sessions. Education content will cover the following topics: what to expect for normal postdelivery recovery, self-care, potential postpartum complications and danger signs, risk factors, food and nutrition, breastfeeding, mental health, social support, family planning, menstrual cycles, and interconception care.

Postpartum Peer Support

Women in Focused-PPC groups will engage in peer support by discussing issues relevant to them. Group prenatal care models have been shown to improve both pregnancy outcomes and maternal satisfaction with care [25-27]. In the postpartum period, group treatment and peer support programs have been shown to improve postpartum depression and prevent postpartum depression [28-31].

Intervention Fidelity

The Focused-PPC intervention will be maintained and monitored through fidelity checklists that are specific to each time point at which a session is held. These checklists will be completed by project assistants and midwives at every session. Additionally, video recordings will be recorded during Focused-PPC sessions at the initial sessions, midpoint sessions, and final sessions. Project assistants will also file session reports that address participant actions and discussions and other session details.

Data Collection or Measures

In addition to the baseline survey, all participants will be given surveys at 1-2 weeks, 6 weeks, 3 months, 6 months, and 12 months from baseline. All surveys will be interviewer-administered by the project assistants and completed electronically via tablets using a secure database system. Strict procedures will be followed to protect participants' confidentiality. We also plan to evaluate the feasibility, acceptability, and satisfaction of Focused-PPC. Focus Group Discussions will be conducted with the midwives who implemented Focused-PPC and with each group of participants enrolled in the Focused-PPC intervention arm after their 12-month sessions.

Independent variables and potential covariates will be measured through demographic and obstetric history questions and the Dagbani Readiness for Hospital Discharge Scale-New Mother Form (RHDS-NM). The RHDS-NM is a 22-item instrument that includes a self-reported rating scale with item scores ranging from 0 to 10 and possible scale scores ranging from 0 to 220 [32]. Higher scores indicate greater readiness for hospital discharge. The RHDS-NM, designed for use within English-speaking populations, was translated into Dagbani and adapted for use in Tamale. The Dagbani version of the RHDS-NM has demonstrated excellent reliability (Cronbach α=.94) and measures postpartum mothers' perceptions of readiness for discharge through examination of their personal status, knowledge, coping ability, and expected support [33].

The primary outcome is knowledge of postbirth warning signs, measured through questions developed based on an evidence-based assessment of the most common postbirth complications. The secondary outcome is postpartum health behaviors, including specific questions assessing health behaviors tailored to the specific time frame postpartum. Other descriptive outcomes include postpartum health status, which will include measures of postpartum depression, stress, complications experienced, vital signs, and other questions on health status as appropriate to the time frame after delivery. Postpartum depression is measured through the Edinburgh Postnatal Depression Scale (EPDS), a self-report screening tool commonly used in perinatal settings [34,35]. The EPDS consists of 10 items assessing women's depressive symptoms over the past week. The EPDS has a maximum score of 30, with higher scores indicating higher frequency and increased severity of depressive symptoms. Stress is measured through the Perceived Stress Scale (PSS), a 10-item scale assessing women's stress levels over the last month [36]. The PSS evaluates a woman's perceptions of unpredictability, lack of control, and overloading in her life, with a higher score indicating higher levels of perceived stress. The feasibility and acceptability of the intervention will be measured using end-project focus group discussion data obtained from midwives and participants in the intervention arm. Outcomes and time points of data collection can be found in Table 1.

Analysis Plan

Differences in outcomes between the intervention and control arms will be assessed. We expect that the intervention arm will have higher knowledge of postbirth warning signs than the

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control arm at every time point measured and that the intervention arm will have a larger increase in knowledge of postbirth warning signs between time points. We expect postpartum health behaviors to be different between the intervention and control arms.

All data will be reviewed for completeness and transferred to STATA (StataCorp) statistical software for analyses [37]. The primary variable of interest is knowledge of postbirth warning signs, measured on 4 occasions. The baseline measurement of knowledge of postbirth warning signs will be used in an initial *t* test to confirm that there is no difference in knowledge between the intervention and control arms before the study to validate the randomization procedure. We will model and test the difference between intervention and control arm knowledge of postbirth warning signs at each time point, and knowledge between time points will be assessed using a repeated measures multivariate ANOVA (MANOVA) with a time and treatment interaction as the primary analysis controlling for baseline demographic variables. For the intervention arm, follow-up secondary analyses will measure the change in postpartum health status, postpartum health behaviors, and clinical assessment data over time using repeated measures MANOVA. Ancillary analyses to be run between the intervention and control arms include a proportion test for the patient's readiness for hospital discharge. Additionally, an evaluation of feasibility, acceptability, and satisfaction will be summarized for inclusion when discussing the cost or benefit of the intervention.

Using intent-to-treat, participants providing data at baseline and first check-in will be included. Missing data (eg, due to attrition) will be accounted for using multiple imputations via the mice package in R (R Core Team) [38]. Sensitivity to missing data will be assessed by comparing multiple imputations to complete case analyses.

Ethics Approval

The Informed Consent process and all other study procedures were reviewed and approved by the University of Notre Dame institutional review board (protocol 21-06-6662). Additionally, in-country ethical approval was obtained from the Navrongo Health Research Center institutional review board (App/Focused-PPC/7/2021). Approval to conduct the study has also been obtained from both the regional and district levels of the GHS. All project team members have current human subject training. Informed consent will be obtained from all participants.

Results

In the first 6 months of the project, we will complete start-up activities inclusive of inception meetings with GHS representatives at the district and regional levels, developing training guides and Focused-PPC education content, training project staff, and developing data collection tools. In the next 6 months of the project, we will recruit and enroll participants, begin Focused-PPC intervention sessions, and complete data collection. Focused-PPC intervention sessions and data collection will continue in year 2 of the project. End-line focus group discussions will be conducted with project participants and midwives when groups have completed their final intervention sessions at 12 weeks.

Ethical approval was successfully obtained from the Navrongo Health Research Center, and the appropriate approvals were obtained from the GHS. The Focused-PPC Guide (education and session guide) was successfully developed with input from GHS and evidence-based resources and underwent multiple levels of expert review to produce the final guide. All team members, midwives, and project assistants have been trained in the study protocol. Measures for data collection were successfully translated into Dagbani (the local language), and audiovisual resources for the sessions were developed and translated into Dagbani. Clinical trial registration is completed at ClinicalTrials.gov (NCT05280951).

We have enrolled and conducted baseline surveys for 192 women (sample size met) in the Focused-PPC trial who have been randomized into intervention and control arms. We have established a total of 12 Focused-PPC groups in the intervention arm, 3 groups from each site, all of which have sessions underway. Midwives are successfully conducting Focused-PPC sessions using the study's established guide and protocol. The Focused-PPC intervention is maintained and monitored through fidelity checklists, which are specific to each time point and completed by project assistants and midwives at every session. Project assistants are also documenting sessions through photos, videos, and session reports, addressing participant actions, discussions, and collaboration.

Discussion

Principal Findings

The purpose of this study is to implement and evaluate a postpartum care model entitled Focused-PPC in a parallel randomized controlled trial with 192 postpartum women at 4 health centers in Tamale, Ghana. Focused-PPC sessions are underway in all participating health facilities. The primary outcome is knowledge of post-birth warning signs. We expect that the Focused-PPC group will have higher knowledge of post-birth warning signs than the control group at every time point measured and that the Focused-PPC group will have a larger increase in knowledge of postbirth warning signs between time points. We are also measuring postpartum health behaviors such as eating a healthy diet, uptake of family planning, breastfeeding, and so on. We expect that more participants in the Focused-PPC groups will eat a balanced diet most days of the week and uptake family planning compared to participants in the control groups. Additionally, we also expect mental health outcomes such as positive depression screens to be significantly lower over time in the Focused-PPC group compared to the control group. Other descriptive outcomes include postpartum health status, and we expect to capture and treat blood pressure cases during the course of the study.

Challenges Encountered

A major hurdle the team faced early in the intervention, which impacted the scheduled engagements with the leadership of GHS, was the application and subsequent acquisition of institutional review board clearance from the Navrongo Health

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Research Center. The clearance was obtained after about 3 months of waiting time, and implementation could not commence unless proof of clearance was presented to the leadership of GHS in the Northern Region for permission to be given for the team to commence implementation. Delays in reviewing the Focused-PPC guide also contributed to a later than expected start of recruitment. The guide went through multiple levels of review, and reviews took longer at each stage than had been planned. In addition, the project team faced some difficulties finding context-specific audiovisual content to be used as supporting aids during the FPPC sessions. Finding and creating context-specific teaching aids took longer than expected. There have been no protocol modifications to the study so far.

We are consistently monitoring and improving upon data collection as necessary. For instance, following issues with inconsistent participant tracking numbers, our data scientist was able to install a mechanism into our survey software that double-checks each tracking number and will not allow remaining data to be documented until this has been addressed. We have also implemented solutions to address accidental missed data by alerting project assistants in real time if important information is missing, allowing them to review entered surveys before submission, and getting an email confirmation immediately after submitting a survey. Our monitoring efforts on this front have led to more accurate and comprehensive data so far and also improved the process of recording data for our project assistants. Furthermore, we have held monthly meetings with the project team, including all members from both the United States and Ghana. These meetings have helped substantially in prioritizing the goals of the trial and have allowed us to properly deal with obstacles as they arise.

Anticipated Limitations

Due to the nature of the study described in this protocol, the intervention is not blinded. There may be a potential for contamination since the midwives implementing the study are used in the health centers. However, since the study is not blinded, different midwives provide care and education to women during postpartum visits if they are in the control group to minimize contamination. In addition, the study is being conducted in one municipality in Tamale, so generalizability will be limited. We hope to conduct a larger study in the future. Given that the team in Ghana has worked in the setting since 2009 and has an established relationship with the health centers and women in the communities, we do not anticipate major recruitment difficulties. However, retention of participants and some participants missing scheduled sessions may be a challenge. We will engage participants and call them individually to remind them of upcoming sessions. We will ensure that midwives recap sessions are comprehensive enough to ensure knowledge transfer to those who missed previous sessions.

Dissemination Plan

To ensure that the results of this research impact practice and maximize the benefit to women, we will target multiple audiences with our research findings. These include health care providers, community service providers, nonprofit organizations, policy makers, the public, academia, and pregnant and postpartum women. We will prepare, print, and share information notes about the project and its findings and share these among key stakeholders. We will also produce a 5-minute video documentary of the project that demonstrates what was done at each stage of the project and the ultimate outcomes. This project's video documentary would be widely disseminated through various web-based and offline platforms. Our dissemination plan includes (1) peer-reviewed manuscripts, (2) peer-reviewed presentations at prestigious conferences, (3) presentations to stakeholders, (4) media releases, blog or website posts, (5) technical and research reports, and (6) presentations to postpartum women at the study facilities during postnatal care gatherings as well as community dissemination.

Conclusions

This project will be the first of its kind to implement an integrated and comprehensive group postpartum care delivery model in Ghana, focused on the care of the mother in addition to the baby. Focused-PPC has the potential to change the postpartum care delivery model in Ghana and other countries in sub-Saharan Africa and beyond. Results from this implementation will be used to further refine and scale up the Focused-PPC model of postpartum care.

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Data Availability

The data sets generated during or analyzed during this study are available from the corresponding author on reasonable request.

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Conflicts of Interest

None declared.

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Abbreviations

EPDS: Edinburgh Postnatal Depression Scale
Focused-PPC: Focused Postpartum Care
GHS: Ghana Health Service
MANOVA: multivariate ANOVA
PSS: Perceived Stress Scale
RHDS-NM: Readiness for Hospital Discharge Scale – New Mother Form
WHO: World Health Organization

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Protocol

Reminiscence and Digital Storytelling to Improve the Social and Emotional Well-Being of Older Adults With Alzheimer's Disease and Related Dementias: Protocol for a Mixed Methods Study Design and a Randomized Controlled Trial

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Abstract

Background: Increasing attention is being given to the growing concerns about social isolation, loneliness, and compromised emotional well-being experienced by young adults and older individuals affected by Alzheimer disease and related dementias (ADRD). Studies suggest that reminiscence strategies combined with an intergenerational approach may yield significant social and mental health benefits for participants. Experts also recommended the production of a digital life story book as part of reminiscence. Reminiscence is typically implemented by trained professionals (eg, social workers and nurses); however, there has been growing interest in using trained volunteers owing to staffing shortages and the costs associated with reminiscence programs.

Objective: The proposed study will develop and test how reminiscence offered by trained young adult volunteers using a digital storytelling platform may help older adults with ADRD to improve their social and emotional well-being.

Methods: The proposed project will conduct a randomized controlled trial to assess the effects of the intervention. The older and young adult participants will be randomly assigned to the intervention (reminiscence based) or control groups and then be randomly matched within each group. Data will be collected at baseline before the intervention, in the middle of the intervention, at end of the intervention, and at 3 months after the intervention. An explanatory sequential mixed methods design will be used to take advantage of the strengths of both quantitative and qualitative methods. The quantitative data from surveys will be entered into SPSS and analyzed using covariate-adjusted linear mixed models for repeated measures to compare the intervention and control groups over time on the major outcomes of participants. Conventional content analysis of qualitative interviews will be conducted using data analysis software.

Results: The project was modified to a telephone-based intervention owing to the COVID-19 pandemic. Data collection started in 2020 and ended in 2022. In total, 103 dyads were matched at the beginning of the intervention. Of the 103 dyads, 90 (87.4%) dyads completed the midtest survey and 64 (62.1%) dyads completed the whole intervention and the posttest survey. Although we are still cleaning and finalizing data analyses, the preliminary results from both quantitative and qualitative data showed promising results of this intergenerational reminiscence approach that benefits both the older adults who have cognitive impairments and the young adult participants.

Conclusions: Intergenerational reminiscence provided by young adult college student offers promising benefits for both the younger and older generations. Future studies may consider scaling up this pilot into a trackable, replicable model that includes more participants with diverse background (eg, public vs private college students and older adults from other agencies) to test the effectiveness of this intervention for older adults with ADRD.

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KEYWORDS

Alzheimer's disease and related dementias; ADRD; digital storytelling; DST; intergenerational reminiscence; older adult; young adult; randomized controlled trial

Introduction

Background

The projected number of individuals aged ≥65 years living with Alzheimer disease and related dementias (ADRD) is expected to reach 7.1 million by 2025, marking a 22% increase from the current figure of 5.8 million older adults affected [1]. Unless significant advancements in medical research lead to preventive measures, treatments, or cures for ADRD, these statistics are projected to escalate to 13.8 million by 2050 [1]. In addition to memory loss, difficulties in daily functioning, and behavioral symptoms, ADRD profoundly affects the social and emotional well-being of those living with the condition.

Most older adults with ADRD live in the community, and many of these individuals live alone [1,2]. There is growing concern about social isolation and loneliness among people with ADRD, particularly as both have been widely linked to poor physical health outcomes and compromised quality of life and well-being [3]. Studies suggest that people with ADRD are at great risk for social withdrawal, social isolation, and loneliness [4]. Individuals with ADRD also tend to have few close friends, which may negatively affect their quality of life [5]. In addition, ADRD is associated with increased risk of depression; anxiety; and other negative emotional well-being outcomes [6], including decreased resiliency, which may prevent individuals from recovering from life's challenges [7,8]. Although there are no interventions to prevent or cure ADRD, there is a pressing need to address and understand the social and emotional well-being of people with the disease.

However, people of all ages may experience social isolation and loneliness. The younger generation has various sources that caused their loneliness. It has been reported that Generation Z (aged 18-22 years) is the loneliest generation and claims to be in worse health than older generations [9]. Overall, 7 out of 10 respondents feel alone (73%), shy (72%), or that no one really understands them well (71%) [9]. In the workplace, they also feel abandoned by their coworkers when under pressure at work (42%), alienated by their coworkers (40%), emotionally distant from the people they work with (54%), and disconnected from others at work (55%) [9]. Moreover, young adults were reported to experience heightened levels of loneliness and mental health challenges during the COVID-19 pandemic [10]. Neglecting the issue of social isolation and loneliness can have detrimental effects on both the mental and physical well-being of individuals, as evidenced by studies such as that by Mushtaq et al [11]. Therefore, it is crucial to develop programs or interventions that aim at preventing or addressing loneliness, so that physical and mental health of young and older adults is maintained.

Reminiscence Approach

Reminiscence has been identified as a potentially effective intervention strategy for alleviating depression [12-14] and in promoting social and emotional well-being for older adults [15]. Reminiscence typically involves a discussion of past activities, events, and experiences aided by the use of familiar items and objects such as photographs and music [16]. Reminiscence work with people with ADRD is viewed as a psychosocial intervention with a credible evidence base [17]. There is also evidence suggesting that individual reminiscence work that involves a life review and subsequent production of a life story book is associated with improvements in the well-being of people with ADRD [18].

Intergenerational Reminiscence Approach

Studies suggest that reminiscence combined with an intergenerational approach may yield significant social and mental health benefits for young and older adults. Through intergenerational reminiscence, older people may pass on their life experiences and life lessons to younger generations [19,20], and the sharing of autobiographical memories has both social and psychological functions [21]. Previous studies also assert that the use of an intergenerational approach is an effective strategy for promoting positive social and mental health in later life, such as reducing social isolation or loneliness [22]. Establishing intergenerational contact and fostering relationships between older individuals and young adults serve as effective measures to prevent the formation of stereotypes or negative attitudes and to challenge and dispel existing ones [23,24]. In addition, intergenerational programming can enable the younger generation to develop meaningful connections with older adults [23].

Reminiscence is typically implemented by trained professionals (eg, social workers and nurses); however, there has been growing interest in using trained volunteers owing to staffing shortages and the costs associated with reminiscence programs [25]. As part of the efforts to use volunteers rather than professionals, the concept of joining young volunteers and older generations together for intergenerational reminiscence has emerged as a promising area of research. So far, the work of Chung [25] and Gaggioli et al [26] are the only peer-reviewed studies implementing intergenerational reminiscence with young volunteers. Although several benefits were reported for both generations in these 2 studies, the small size of the sample and absence of a control condition limited the study results. The findings underscore the need for more studies related to intergenerational reminiscence that include young adult

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volunteers, as this approach may potentially offer a more sustainable and cost-effective intervention for implementation in community-based settings. Thus, more studies are needed to better understand and rigorously measure this approach to intergenerational reminiscence interventions, particularly for older adults with ADRD.

Reminiscence and Digital Storytelling

There are previous studies of reminiscence work that endorse the use of a life story book that are pertinent to the proposed study [18,25]. Recent studies recommend the production of a digital life story book [17] as part of reminiscence. Digital storytelling (DST) is a technology that uses a 2- to 5-minute audio-visual clip combining text, images, music, photographs, voice-over narration, and other audio [27]. Psychological well-being benefits of DST for the general population have been reported in a systematic review [28]. Previous studies also demonstrate the benefits of DST for people with ADRD [29,30]. Studies of intergenerational DST, which combines DST and intergenerational programming, reported positive outcomes including reciprocal relationships, empathy, connection, and confronting agism [31]. However, few studies combined a reminiscence approach and DST or intergenerational DST. Thus, this study is the first one to develop and test how intergenerational reminiscence using a DST platform may help older adults with ADRD and young adults to improve their social and emotional well-being.

College Student Involvement

The proposed study will include young adult volunteers recruited from University of Texas at Arlington (UTA), a large and diverse institution of higher education. The rationale for including undergraduate and graduate students in the proposed study is that the positive impact of intergenerational learning experiences on students' academic and personal development is well documented [32]. Previous studies support the value of intergenerational activities in postsecondary education; provide evidence of benefits, reciprocity, and empowerment outcomes [33]; and suggest that these learning experiences may better prepare undergraduate and graduate students for future work with older adults [31]. Studies further suggest that intergenerational learning experiences that involve interactions with people with ADRD also result in positive gains in academic learning and attitude toward older adults among college students [34]. By connecting young adult volunteers with older adults through interactions during the proposed intervention and preintervention training, this proposed study aims to have a positive influence on attitudes toward aging and knowledge about ADRD. Furthermore, with rapidly changing demographics in the United States, there is an urgent need to combat the stereotypes and negative attitudes toward aging and agism and discrimination of older adults that often exists among younger populations [35].

Studies suggest that intergenerational reminiscence is promising for individuals with ADRD; however, these studies are limited by small sample sizes and less rigorous study designs. A recent systematic review of reminiscence therapy provided in the Cochrane Library specifically recommends large-scale, randomized controlled trials that include a life story book component for people with ADRD [17]. Although a few studies have attempted to use young volunteers as part of small-scale intergenerational reminiscence studies [25,26], the use of undergraduate and graduate students is unexamined so far.

Aims and Research Questions

Overview

To fill the abovementioned research gaps, the proposed study aims to develop and evaluate the feasibility and effectiveness of an intergenerational reminiscence approach in improving the social and emotional well-being of older adults with ADRD. The intervention is guided by continuity theory [36], which posits that the reminiscence process guides individuals to adjust and adapt to changes that occur in their lives. Moreover, a continuity theory approach to reminiscence may also facilitate a strong sense of self [37] and has been recently used in other reminiscence interventions [38]. On the basis of literature and the continuity theory, it is hypothesized that the framework of reminiscence combined with an intergenerational approach and DST will help to improve the social and emotional well-being of both generations and help strengthen or build resilience in older adults with ADRD. Specifically, the study addresses 5 goals.

Goal 1—To Quantitatively Test the Effectiveness of This Intervention in Improving the Social Well-Being of Older Adults With ADRD and Young Adults

The objectives are to (1) provide a 10-session intervention with reminiscence and DST to older adults by trained young adult volunteers and (2) test whether older or young adults report significant improvement in quality of life or decline in loneliness after the intervention. Hypotheses include the following: (1) older participants in the intervention group will have high levels of quality of life in the middle of and after the intervention compared with their pretest scores and compared with those in the control group and (2) young and older participants in the intervention group will have low levels of loneliness in the middle of and after the intervention compared with their pretest scores and compared with those in the control group.

Goal 2—To Quantitatively Test the Effectiveness of This Intervention in Improving the Emotional Well-Being of Older Adults With ADRD

The objectives are to (1) provide a 10-session intervention with reminiscence and DST to older adults by trained young adult volunteers and (2) test whether older adults report significant changes in affect or resilience after the intervention. Hypotheses include the following: (1) older participants in the intervention group will have high positive affect (PA) and low negative affect (NA) in the middle of and after the intervention compared with their pretest scores and compared with those in control group and (2) older participants in the intervention group will have high resilience scores in the middle of and after the intervention compared with their pretest scores and compared with those in control group.

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Goal 3—To Quantitatively Test Attitudes Toward Aging Among the Young Adult Volunteers

The objectives are to (1) offer opportunities for trained young adult volunteers to engage with older adults in the 10-session intervention and (2) test changes in their attitudes toward aging after the intervention using surveys. Hypotheses include the following: (1) young adult volunteers in the intervention group will have more positive attitudes toward aging after the intervention compared with that before the intervention and (2) young adult volunteers in the intervention group will have more positive attitude toward aging after the intervention compared with those in the control group.

Goal 4—To Quantitatively Test Knowledge and Awareness About ADRD Disease Among the Young Adult Volunteers

The objectives are to (1) offer a 3-hour training to the young adult volunteers before the intervention starts, which covers the biological aspects of ADRD and how to communicate and connect interpersonally to people with ADRD, and (2) test changes in their reported knowledge and awareness about ADRD using surveys. Hypotheses include the following: (1) young adult volunteers in the intervention group will report more knowledge and awareness about ADRD disease after the intervention compared with their pretest scores and (2) young adult volunteers in the intervention group will report more knowledge and awareness about ADRD disease compared with those in the control group after the intervention.

Goal 5—To Qualitatively Evaluate the Usefulness of This Intervention From the Perspectives of the Dyads

The objectives are to (1) explore and interpret the statistical results obtained in goals 1 and 2 through individual interviews with older adults who report the greatest and least changes in well-being; (2) explore and interpret the statistical results obtained in goals 3 and 4 through individual interviews with young adult volunteers who report the greatest and least changes in attitudes toward aging; and (3) examine dyad participants' perceptions about the intervention in terms of its quality, benefits, and usefulness.

Methods

Study Design

The proposed project will conduct a randomized controlled trial to assess the effects of the intergenerational reminiscence approach with DST on the social and emotional well-being of older adults with ADRD. An explanatory sequential mixed methods design [39] will be used, which first involves collecting quantitative data and analyzing the data to identify subsamples of participants who report the greatest and least changes and then conducting qualitative interview with these subsamples. Half (46/92, 50%) of the dyad sample will receive the reminiscence DST intervention, and the other half (46/92, 50%) of the sample will receive a regular social visit from young adult volunteers without the intervention. Dyads will be randomly assigned to either the intervention or control group after baseline screening of all participants and, subsequently, randomly matched within each group. To further prevent selection bias, statistical techniques such as covariate-adjusted linear mixed models will be used to adjust for covariate imbalance during data analysis.

A total of 92 dyads are required to test the effectiveness of the intervention in this proposed study (refer to power analysis in the *Sample and Recruitment Plan* section). We will recruit participants on a rolling basis until we recruit 92 dyads. At least one-fourth (23/92, 25%) of the total sample of older adults and young adult volunteers will be recruited before they are randomly matched. Upon signing the consent form, participants will be given the chance to engage in the study. They will be provided with guidance throughout the informed consent process and will subsequently undergo a baseline survey in which all measures will be collected blind to group conditions.

The first group will receive the intervention (X), which includes reminiscence and DST components provided by the young adult volunteers, whereas the second group will serve as the sham control group, which will include social visits calls by the young adult volunteers and an unstructured, nondigital recording (eg, scrapbook or journal) of the social visits. To account for the potential influence of attention and social interactions stemming from the intervention, the control activity is intentionally designed to offer comparable social contacts. This ensures that any observed improvements in participants cannot solely be attributed to the intervention itself. The features of the intervention and sham protocols are the same, except that participants in the intervention group will participate in structured reminiscence and DST, whereas those assigned to the control group will be facilitated to do otherwise. Similar to the study by Lai et al [40], the sham protocol will include talking about overall issues related to wellness in later life (eg, diet and health, social activities, and family relationships) and creating a wellness scrapbook or journal.

As shown in Figure 1, data will be collected at baseline before the intervention, in the middle of the intervention, at the end of the intervention, and at 3 months after the intervention. The design of this study is depicted in scientific notation.

Figure 1. Data collection overview. G1: first group; G2: second group; O1: before the intervention; O2: middle of the intervention; O3: end of the intervention; O4: 3 months after the intervention; X: intervention.

$$\begin{array}{cccccc} G_1 & O_1 & X & O_2 & O_3 & O_4 \\ G_2 & O_1 & \text{Sham} & O_2 & O_3 & O_4 \end{array}$$

Sampling and Recruitment Plan

Power analyses performed using G*Power 3.1.9 indicated that a total of 92 dyads (or 184 participants) are required to address our study objectives using a linear mixed model. This sample size estimate was based on a small effect size (*f*=0.22), a significance level of α=.05, β of .20, anticipated *r* over time of

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0.30, and 5% attrition rate based on the findings of Chung [25], for 2-tailed tests.

Participants in this study will be community-dwelling older adults and undergraduate and graduate students (ie, young adult volunteers) enrolled at UTA. The eligibility criteria of the older adult participants include individuals who (1) are aged ≥65 years; (2) have cognitive impairment measured by the Ascertain Dementia 8 (AD8) [41]; (3) have decisional capacity as measured by the University of California, San Diego Brief Assessment of Capacity to Consent (UBACC) [42]; (4) are not participating in any other research protocol currently; and (5) can speak and understand English. The exclusion criteria for older adults are (1) participating in another trial, (2) having health issues that prevent them from participating in the study for 3 months, and (3) inability to commit to being available for the full 10 weeks of the intervention.

The older adult participants will be recruited through Tarrant County Meals On Wheels (MOW), which is a partner agency of the Area Agency on Aging of Tarrant County. Eligibility criteria to enroll in Tarrant County MOW is that a person must be homebound and have no one to help them on a regular basis. The Area Agency on Aging is very committed to expanding services and supports to people with ADRD, as many MOW clients with ADRD are living alone in Tarrant County. Moreover, studies suggest the need for additional research in the area of loneliness among clients using MOW [43]. Participant recruitment will begin with case managers and other MOW staff using their client database system to search for clients with ADRD who meet the study criteria. Next, case managers will contact potential study participants and then ask for permission to share their telephone number with a member of the UTA research team. The principal investigators (PIs) and graduate research assistants (GRAs) will follow-up with all the potential participants provided by MOW.

The young adult volunteers will include undergraduate or graduate students from UTA. The inclusion criteria for the young adult volunteers are the following: (1) aged 18 to 30 years, (2) currently enrolled as a student at UTA, and (3) can commit to be available for the full 10 weeks of the intervention. Young adult volunteers who have health issues or limited availability that prevent them from participating for the entire 10 weeks of the intervention will be excluded from the study. The study will be widely advertised across the UTA campus through avenues such as different student organizations, departmental social media accounts, departmental websites, and the offices of campus partners (eg, student health services, career services, campus recreation, and undergraduate honor program). Other recruitment efforts will include posting flyers across the campus, emailing student listserves, social media, advertising on television monitors located in buildings across campus, and classroom visits.

Procedure

Before the intervention starts, the young adult volunteers in the intervention group and control group will be offered a mandatory separate group training through Microsoft Teams. Training for young adult volunteers in the intervention group will last 3 hours and be offered by LX, NLF, KMD, and BAT. Students will be provided with hard and electronic copies of the training materials. As part of the training, LX will cover an overview of the study and the intervention protocol, project timelines, responsibilities of the young adult volunteers, roles of the research personnel, and importance of human participants' protection in the research activities. KMD will provide training related to ADRD, communication skills with older adults with ADRD, and how to deal with unexpected behavior or emotional symptoms of older adults during the intervention. NLF will cover how to communicate with older adults with ADRD. BAT will provide an overview of DST and details about DST techniques and demonstrate strategies for successful DST. Similarly, training for the young adult volunteers in the control group will be approximately 1 hour in duration and will cover human participants' protection; study procedure (social visits); and explanation of the unstructured, nondigital record of the social visits. The trainings will be audio recorded and later analyzed for fidelity.

Subsequently, participants will participate in this telephone-based intervention. In this study, the young adult volunteers (in both the intervention and control groups) will talk with older adults through telephone calls each week for 10 weeks with the same process described in the following sections. Older adults in the intervention group will receive 10 sessions of life review with the trained young adult volunteers (1-1.5 hours each week for 10 weeks). During weeks 1 to 6, a life history interview will be conducted with different themes in each week: major turning points in life (W1), family history (W2), life or career accomplishments (W3), history of love and hate (W4), stress experiences (W5), and meaning and purpose of life (W6). Guidelines for conducting a life history interview will be prepared for the young adult volunteers based on the work of Watt and Cappeliez [44]. The implementation outline will encompass integrative and instrumental reminiscence techniques that aim to foster self-acceptance, conflict resolution, reconciliation, sense of purpose and self-value, recollection of effective coping strategies used in the past, and leveraging past experiences to address current challenges. After each session, the young adult volunteer will write a 1-page summary and reflect about the interview to help prepare for the subsequent DST in the later weeks. During weeks 7 to 10, the dyads will develop the DST together using tablets already owned by the UTA School of Social Work. The contents of sessions 7 to 10 will be structured as outline or script; plan and storyboard (W7); film and record (W8); evaluate, integrate, and finalize (W9); and publish or share (W10). It is acceptable if no filming or video aspect of the DST is conducted. Audio-based DST without video recording is still common, as it captures the voices that give life to the photos [27]. Photos obtained from the internet or the participants may be used as part of the DST to accompany the audio. For example, photos of the individual's hometown, familiar places (ie, parks), familiar vacation locations (ie, monuments and historical markers), and so on, will help augment the voice recordings.

Older adults in the control group will have general social visit conversation with the young adult volunteers, and the content of weeks 1 to 6 will be based on general topics related to wellness in later life, instead of structured reminiscence

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guidelines. The topics of weekly social conversation are diet and health (W1), exercise or activity and health (W2), emotions and health (W3), religious or spiritual practices and health (W4), family or friend relationships and health (W5), and social activities or engagement and health (W6). For weeks 7 to 10, instead of DST, the young adult volunteer will work with the older adult to create an unstructured, nondigital record of the social visit related to wellness in later life (eg, wellness scrapbook or journal).

Every effort will be made to minimize risks by closely monitoring participants' mood during weekly fidelity treatment checks. Weekly calls with the dyads in both the intervention and control groups will be conducted by the research team to closely monitor the participants' mood and to serve as a fidelity check. These calls will include questions related to the study protocol (eg, topics covered, time spent, and challenges that occurred) and questions related to the well-being of participants (eg, How are you feeling? Do you need anything from the research team? and Are you experiencing any challenges?). If a study participant experiences emotional distress during the study, a clinical social worker and registered nurse practitioner, who are members of the research team, will offer consultation, and if necessary, they may refer study participants to additional services through the local Area Agency on Aging. Finally, individual retraining will be provided to the young adult volunteers in the case of problems with treatment fidelity.

To prevent contamination, the importance of confidentiality will be emphasized to participants in the intervention group at the beginning of the study. Participants (especially the young adult volunteers) in intervention group will be asked not to share the protocol with the participants in the control group for the duration of the study to minimize contamination. To further prevent contamination, the research team will check in with young adult participants in the intervention group 3 times (3 weeks, 6 weeks, and 9 weeks after the intervention starts) via telephone to ensure that no information has been shared with participants in the control group. Furthermore, young adult participants in the control group will also be asked 3 times during the study period whether they received any information related to the reminiscence and DST content, and this will be documented by the research team. In addition, substantial contamination can be tolerated within the usual individual randomized trial [45]. Finally, if contamination occurs, any documentation of hearing about or implementing reminiscence in the control group will be included as a covariate in the study analyses.

After the intervention, qualitative interviews with subsamples in the intervention group will be conducted. For the individuals in the highest 10% and lowest 10% of changes based on survey tests, we will conduct follow-up qualitative interviews to capture the details of their situations and present a more robust analysis, taking advantage of the strengths of both methods. The interview will last for 45 to 60 minutes and will be conducted by research teams through telephone calls.

Measurement

Overview

The primary outcomes of the study will be the social and emotional well-being of older adults, and the secondary outcomes will be the benefits to the young adult volunteers. Social well-being will be measured by quality of life and loneliness, whereas emotional well-being will be measured by affects (positive and negative) and resilience. Regarding social well-being, quality of life is a relatively global and stable phenomenon that comprehensively measures people's psychosocial well-being [46]. Recent studies suggest that loneliness, which represents the negative subjective experience of the inadequacy of social relationships, is a factor in evolutionary fitness across the life span [47] and is a good indicator of social well-being [48]. Regarding emotional well-being, PA and NA have been used as general dimensions to describe affective, emotional components of subjective well-being [49]. Resilience, as an important indicator of emotional well-being, assesses one's ability to bounce back from or adapt to stressful situations or crises, such as having been diagnosed with ADRD [10,11]. Young adult volunteers will be asked about their attitude toward aging and knowledge and awareness about the ADRD disease. Demographic information about each dyad, such as age, sex, education, self-reported health, and so on, will also be collected in the pretest survey. A pilot test will be conducted on 3 volunteer dyads using assessment tools to evaluate participants' possible overload impacts. In accordance with the input provided by pilot participants, the research team will review and make necessary modifications to the measurement selections within the initial 6 months of the project (preparation stage).

Primary Outcome Measurements for Older Adults

Quality of life of older adults in this study will be measured using Quality of Life–Alzheimer's Disease (QoL-AD) [50]. The QoL-AD questionnaire consists of 13 items that cover various aspects including physical health, energy levels, mood, living situation, memory, family relationships, marital status, friendships, self-perception, ability to perform daily chores, engagement in enjoyable activities, financial situation, and overall life satisfaction. The higher the QoL-AD score, the better is the quality of life. Self-rating QoL-AD will be used, which had showed high reliability and validity [51,52].

Loneliness among older participants will be measured using the De Jong Gierveld Loneliness Scale [53]. This 6-item scale measures both emotional and social loneliness. This instrument has undergone validation in numerous countries, with validation studies encompassing various sexes and age groups and specifically including older adults. High scores indicate great loneliness. Reliability coefficients for both subscales were 0.81 to 0.85 [54].

The measurement of PA and NA in older adults will be conducted using the widely used Positive and Negative Affect Schedule (PANAS) [55]. PANAS assesses the respondent's emotional state by inquiring about 10 positive and 10 negative emotions using a 5-point scale ranging from "Very slightly or not at all" to "Extremely." This scale has demonstrated strong

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psychometric properties, with Cronbach α of .88 for PA and .87 for NA. Furthermore, PANAS has been validated across various cultures and languages worldwide, consistently exhibiting robust psychometric properties in multiple studies [49,56]. Total scores will be calculated for PA and NA, with high scores indicating more PA and NA, respectively.

The resilience of older adults will be measured using the Brief Resilience Scale [57]. The Brief Resilience Scale is recognized as one of the top and extensively endorsed resilience scales and recommended by Windle et al [58]. Extensive literature supports its high reliability and validity, as demonstrated by studies conducted by Smith et al [57,59]. A total of 6 items will be asked, and responses for each item ranges from 1 (*low resilience*) to 5 (*high resilience*). After reverse coding 3 items, total scores will be calculated for final analysis, with high score indicating more resilience.

Secondary Outcome Measurements for Young Adults

To measure the loneliness among young adult participants, we will use the De Jong Gierveld Loneliness Scale [53], following the same methodology used for measuring loneliness among older adults, as mentioned previously.

The Alzheimer's Disease Knowledge Scale (ADKS) [60] will be used for the young adult volunteers. The ADKS is a comprehensive instrument consisting of a 30-item true or false scale. It can be completed in approximately 5 to 10 minutes and covers a wide range of domains, including risk factors, assessment and diagnosis, symptoms, disease progression, impact on daily life, caregiving, and treatment and management. Initial findings indicate that the ADKS exhibits satisfactory reliability, including test-retest and internal consistency and validity, including content, predictive, concurrent, and convergent validity. These results have been reported in studies conducted by Carpenter et al [60] and Spector et al [61]. Total scores will be calculated for final analysis, with high score indicating more knowledge.

To assess the young adult volunteers' attitudes toward aging, the Fraboni Scale of Agism (FSA) will be used. The FSA, initially developed by Fraboni et al [62] and subsequently revised by Rupp et al [63], consists of 29 statements. Participants will rate their agreement on a 4-point Likert scale, ranging from 1 (*strongly disagree*) to 4 (*strongly agree*). The FSA has been widely used among college students and has demonstrated strong internal consistency and robust validity in previous studies [64,65]. Total scores will be calculated for final analysis, with high scores indicating more agism.

In addition, a 20-item questionnaire [25] will be developed to collect feedback from the young adult volunteers, covering (1) intervention preparation and organization, (2) intervention format and workload, and (3) perceived gains. Each item is rated on a 5-point scale (1=*strongly disagree* to 5=*strongly agree*), and the higher the score, the more positive the perception about the intervention.

Other Outcomes

Follow-up qualitative interviews will be conducted to explore participants' overall experience with and perceptions about the intervention. On the basis of the results from the survey, we will select older and young adult participants who have the highest and lowest levels of changes in the outcomes for further qualitative interviews (10 dyads in total). Each generation's experiences, perspectives, challenges, and suggestions regarding this intervention will be asked during these in-depth interviews.

Data Collection Plan

Data will be collected at baseline, midpoint, end of the intervention, and 3 months after the intervention by telephone. A total of 3 GRAs will be trained to collect the data. Training on the assessment battery and interview techniques will be provided by PIs to GRAs. For the quantitative survey, after training, interrater reliability checks will be performed by 1 PI on pilot interviews of team members and participants (3 older adults and 3 college students not included in the final sample size), based on audiotaped interviews. For the qualitative interviews, training related to conducting interviews will be provided to GRAs, such as talking less and listening more, how to build rapport with the respondents, and how to handle unexpected emotions of participants. The GRAs will also pilot-test their qualitative interviewing skills based on role-plays with the research team. GRAs will have weekly supervision meeting with the PIs regarding participant recruitment and follow-up and survey assessments.

Several strategies will be used to track clients during the study and to minimize attrition. At the baseline and at each subsequent interview, participants will be asked to provide the names of 2 people who may know where they are if the researcher has difficulty in contacting them. We will also have the older participants' MOW case managers as a backup point of contact. We will adopt the strategies of minimizing attrition in longitudinal studies [66], which results in 90% follow-up. These strategies (ie, getting several contacts, getting emails, reminder letters, and thank you letters) have proved to be useful in previous community-based studies conducted by the research team.

For individual missing responses on multiitem scales, we will compute scale scores by summing the available item scores as long as at least 80% of the item responses are available [67]. Missing data at the variable level will be handled through maximum likelihood imputation [67]. A concern with longitudinal research is that data are not missing randomly owing to systematic dropout. We will conduct attrition analyses to identify any factors systematically related to dropout and, if found, control for these effects in subsequent analyses. Any missing data that are random in nature, such as those that occur owing to random mistakes in data collection or entry and are not related to research staff or patient noncompliance, will be submitted to maximum likelihood estimation procedures to estimate those missing values. Maximum likelihood estimation for random missing data is a common and accepted procedure for missing data estimation [68,69]. If specific patterns of missing data are identified, we will further address missing values with multiple imputation. Multiple imputation will maximize accurate statistical inferences and allow for valid statistical inferences by appropriately accounting for the uncertainty caused by missing data [68,69].

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Statistical Analysis

After data are collected and entered into the statistical software, data quality will be carefully reviewed and then checked both automatically and manually. The review processes involved in data management encompass several steps. These include cross-checking the coding of observations or responses and identifying out-of-range values; ensuring data completeness; adding variable and value labels as needed; verifying random samples of digital data against the original data; implementing double entry of data; conducting statistical analyses such as determining the frequencies, means, and ranges to identify errors and unusual values; and rectifying any errors made during transcription. In addition, data will be thoroughly reviewed to address concerns related to the protection of human participants and confidentiality. This includes assessing the risk of potential disclosure of research participants' identities, safeguarding sensitive information, and preserving the privacy of the collected data. As all the key concepts in the proposed study are measured using standard scales, reliability tests for each scale and test-retest reliability across the 4 surveys will be conducted.

For quantitative data analyses, descriptive analyses will first be conducted to provide the overall means and frequencies of key outcome variables for both older and young participants in the intervention and control groups. Fisher exact tests, Pearson chi-square tests, and independent samples *t* tests (2-tailed) will be computed to test for group differences that may be attributable to participants, such as age, sex, education level, income, and health conditions. If the groups significantly differ on any of these variables, the variable will be incorporated into the following analyses as a covariate, thereby controlling for potential influences that the covariate may have on the dependent variables. Moreover, in the event that at the culmination of this study, our sample sizes are unequal in the treatment groups or our outcome data are nonnormal, we will follow through with appropriate statistical corrections where necessary. Covariate-adjusted linear mixed models for repeated measures will be performed to compare the intervention and control groups over time for the major outcomes of older adults and young adult volunteers. The covariate will be any significant variable yielded from the univariate analyses, and the dependent variable will be the scores before the intervention, in the middle of the intervention, at the end of the intervention, and at 3-month follow-up. In this study, 95% CIs will be computed for each adjusted mean difference. The study α will be set to .05, with no adjustments for multiple comparisons owing to the preliminary nature of this study and the increased risk of type-2 error as a result of α adjustment [70].

Several different combinations of statistical results are possible. The results may indicate that the intervention and control groups significantly differ in outcomes among the older participants and the young adult volunteers. Another possibility is that differences may be discovered for one age group but not the others. Outcome measures may significantly change over time for none of the groups, some groups, or all groups. Another possibility is that the pattern of change over time for one group may not replicate in another group. This possibility, which would be identified via a significant interaction in linear mixed models, would require post hoc testing to investigate the nature of changes over time. In this case, groups will be isolated, and patterns of change will be identified via linear mixed models for repeated measures (with no between-participants factors). *For the qualitative data analysis*, the process will involve digitally recording and transcribing the qualitative interviews, followed by using conventional content analysis, as outlined by Hsieh and Shannon [71]. The research team, including LX and NLF, along with the research assistants, will independently code the data, forming the foundation for an initial coding framework. Subsequently, the researchers will convene to compare and establish consensus on the coding outcomes. Pertinent excerpts from the transcripts will be extracted and reorganized based on thematic relevance. The constant comparison process, as described by Glaser and Strauss [72], will be used to explore similarities and differences among participants who did and those who did not benefit from the intervention, generating subthemes within the broad topics. This comparative approach will enhance consistency and broaden the dimensions and comprehensiveness of each code. Eventually, the codes will be synthesized or combined into overarching recurrent themes. During the analysis stage, themes, research notes, and field notes will be reviewed using thematic charts. Multiple strategies, including peer debriefing, will be implemented to address potential investigator bias and enhance the study's credibility. Maintaining comprehensive documentation will also ensure that an audit trail is available for future reference.

Data Management and Participants' Safety

The research team will be the sole individuals with knowledge about and access to the names of both the older and young participants. Although certain demographic information, such as age, sex, and racial and ethnic background, may be recorded, the questionnaires will not contain any participant identifiers such as date of birth or address. The preintervention and postintervention questionnaires will also be devoid of participant identifiers. To ensure confidentiality, participant names will be deidentified, with each individual assigned a unique study identifier or number. All data files will be securely stored in encrypted, password-protected folders on laptops provided by UTA. These laptops will also have encryption in accordance with the guidelines set by the UTA Office of Information Technology. Participant privacy will be diligently safeguarded, and records containing names and other identifiable information will be stored separately from the interviews, using password-protected, encrypted files on UTA-issued laptops. The PI (LX) and the UTA institutional review board (IRB) will bear the responsibility of ensuring participant safety and the attainment of the study's scientific objectives. The research team possesses previous experience in organizing and managing clinical trials, including implementing data safety monitoring measures for interventions.

All the older adults and young adult volunteers will provide informed consent before participating in the study. Potential participants will be informed that refusal to consent to the study or withdrawing from the study will have no effect on the services that they currently receive or might receive through UTA (ie, young adult volunteers) or through MOW or the Area Agency on Aging (ie, older adults). Participants who provide informed

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consent will be contacted for baseline measurement and then randomized to 1 of the 2 treatment groups. The protocol and consent forms will be approved by the UTA IRB before conducting any study procedures. Student members of the research team will receive training regarding procedures required to obtain informed consent.

Human participants' risk related to the study is minimal. The study carries potential risks related to the identification of depression or anxiety, as participants may become aware of their symptoms during the intervention sessions. This heightened awareness could lead to the recognition of distressing thoughts. In addition, there is a risk associated with the process of recalling past memories, as it may evoke difficult or emotional experiences for participants. Every effort will be made to minimize risks by closely monitoring the participants' mood during weekly fidelity treatment checks. In the event that a study participant experiences emotional distress during the study, KMD, a registered nurse and gerontological nurse practitioner, along with NLF, a licensed clinical social worker, will be responsible for providing the necessary support and counseling to address the participant's emotional well-being. They will also be available as needed for referral to the resources through the local Area Agency on Aging for the older adults and university services for the young adult volunteers, as needed.

Ethics Approval

The study was approved by the UTA IRB on March 25, 2021 (2021-0206).

Results

The study was funded in January 2021. Data collection started in May 2021 and ended in mid-2022. In total, 103 dyads were matched at the beginning of the intervention. Of the 103 dyads, 90 (87.4%) dyads completed the midtest survey and 64 (62.1%) dyads completed the posttest survey. Although a total of 92 dyads were planned to test the effectiveness of the intervention in this proposed study, the post hoc power analyses performed using G*Power 3.1.9 indicated that 64 dyads will yield sufficient power to test the interaction between groups over time (power=0.95), the changes over time (power=0.95), and the differences between the groups (power=0.71). These parameters are based on a small anticipated effect size (f=0.22), α=0.05, two-tailed, with measures correlated at r=0.30.

We also collected qualitative interview data for this study with selected dyads in the intervention group (8/27, 30%). Weekly reflection page from UTA student participants, weekly fidelity check forms, final digital story books, and final scrapbooks were also saved for future data analyses. We are currently engaged in data cleaning and analysis for both quantitative and qualitative data. One manuscript has already been published [73], and we anticipate publishing several more manuscripts reporting the results within the next 1-2 years.

Discussion

Principal Findings

The aim of this study is to develop and implement a 10-session intervention that combines reminiscence and DST techniques and foster connections between young adult college students and older adults with ADRD in a community setting. Through the collection of qualitative and quantitative data, this study seeks to evaluate the intervention's potential efficacy in enhancing the social and emotional well-being of young and older adults and in improving the knowledge about ADRD and attitudes of young adults toward aging. By focusing on reminiscence and life review content, integrating DST technology, and including older adults with cognitive impairment, this study will contribute valuable and current data to address the existing research gaps.

Considering the multitude of psychological and mental health challenges experienced by older adults with ADRD, this study holds academic significance. By focusing on the social and emotional well-being of this population, the aim is to enhance their overall life satisfaction, positive emotions, and sense of purpose, factors that contribute to resilience and quick recovery from adversities linked to dementia diagnosis. Furthermore, this study adopts an innovative approach that combines the beneficial practice of reminiscence or life review facilitated by a DST product, alongside an intergenerational perspective, which also aims to address the social well-being (loneliness) issues of young adults. By engaging young adults as interventionists, this strategy empowers them to gain insights into older adults with ADRD, while reshaping their perspectives about aging. It also taps into their enthusiasm as volunteers, addressing staffing shortages and reducing expenses linked to professional interventionists. Consequently, it establishes a sustainable and economically viable intervention approach that is well suited for community-based environments. In addition, this study aims to address the limitations identified in previous studies, such as small sample sizes and the absence of a control condition.

Limitations

A limitation of this study is its lack of representativeness. The older adult participants in this study only include MOW clients who generally have low income and are homebound. The young adult college students come from 1 public university in Dallas-Fort Worth area. Thus, the study has limited representativeness that cannot extend to other community-dwelling older adults and college students from other universities. Moreover, this study only focuses on the Dallas-Fort Worth area and thus, its results cannot be generalized to other cities, states, or regions. Future studies may consider scaling up this pilot into a trackable, replicable model in multiple sites to test the effectiveness of this intervention for older adults with ADRD. In addition, this protocol is proposed for in-person interactions between young and older generations. Owing to the risks and feasibility of conducting an in-person intervention during the COVID-19 pandemic, this project has to be tailored to telephone-based approach. Future study may

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consider comparing the effectiveness of interventions between in-person meeting versus telephone-based approach.

Conclusions

Intergenerational reminiscence program that connects older adults with ADRD with young adult college student volunteers offers promising benefits for both younger and older generations in improving their social and emotional well-being. Future studies may consider scaling up this pilot into a trackable, replicable model that includes more participants with diverse background (eg, public vs private college and older adults from other agencies) to test the effectiveness of this intervention for the benefits of older adults with dementia and young adults.

Acknowledgments

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Data Availability

The data sets generated and analyzed during this study are available from the corresponding author upon reasonable request.

Authors' Contributions

LX, NLF, KMD, and BAT were involved in conceptualization; LX, NLF, KMD, and DJC contributed to the methodology; LX and NLF were involved in validation, investigation, resources, supervision, and project administration; LX, NLF, and DJC conducted the formal analysis; and LX was involved in data curation. All authors were involved in preparing, reviewing, and editing the original draft of the manuscript and in funding acquisition. All authors have read and approved the published version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review comments from the Retirement Research Foundation for Aging.
[PDF File (Adobe PDF File), 179 KB - resprot_v12i1e49752_app1.pdf]

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Abbreviations

ADKS: Alzheimer’s Disease Knowledge Scale
ADRD: Alzheimer’s disease and related dementia
DST: digital storytelling
FSA: Fraboni Scale of Agism
GRA: graduate research assistant
IRB: institutional review board
MOW: Meals On Wheels
NA: negative affect
PA: positive affect
PANAS: Positive and Negative Affect Schedule
PI: principal investigator
QoL-AD: Quality of Life–Alzheimer’s Disease
UTA: University of Texas at Arlington

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Protocol

The Effectiveness of Video-Based Game Exercise Therapy Applications in Pes Planus Rehabilitation: Protocol for a Randomized Controlled Trial

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Abstract

Background: Pes planus is one of the most common foot deformities. Although there are many studies on the effectiveness of various exercise methods in pes planus rehabilitation, the number of studies on video-based game exercise therapy applications is very limited.

Objective: This study aims to evaluate the effectiveness of 2 video-based game exercise therapies and structured exercise practices in pes planus rehabilitation.

Methods: This study is a 3-arm, parallel-group, single-blinded randomized controlled trial. The study will include 69 patients with flexible pes planus aged between 18 and 25 years who attend the orthopedics and traumatology clinic and meet the inclusion criteria. The primary outcomes are measures of navicular drop and pedobarographic analysis before and after the intervention, and the secondary outcomes include balance, femoral anteversion, and lower extremity muscle strength. Participants will be evaluated with a navicular drop test for medial longitudinal arch height, a pedobarographic analysis system for plantar pressure analysis, a Craig test for femoral anteversion, the Becure Balance System for balance measurement, and a myometer device for lower extremity muscle strength measurement. Participants will be randomly assigned to a structured exercise group, an exergame group, or a serious game group according to their order of arrival. The structured exercise group will use a short foot exercise, a towel-picking exercise, and various walking and balance exercises. Patients in the serious play group will play the lower extremity games in the Becure Balance System. Patients in the exergame group will play balance games on the Nintendo Wii game console. All participants will participate in 18 exercise sessions (3 days a week for 6 weeks). After the treatment, the initial measurements will be repeated.

Results: The study started in January 2023. It is expected to be completed in June 2024.

Conclusions: This study will be the first randomized controlled study to evaluate the effectiveness of 2 different video-based game exercise therapy applications in pes planus rehabilitation. Through this study, the use of video-based game exercise therapy in pes planus rehabilitation, together with the developing technology, will be a guide. In addition, a new exercise protocol, including serious game exercises, will be added to the literature. In the future, it is expected that our study on the development of different game systems, especially for the ankle, will provide pioneering feedback.

Trial Registration: ClinicalTrials.gov NCT05679219; https://clinicaltrials.gov/study/NCT05679219

International Registered Report Identifier (IRRID): DERR1-10.2196/51772

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(JMIR Res Protoc 2023;12:e51772) doi:10.2196/51772

KEYWORDS

exergame; pes planus; rehabilitation; serious game; video-based game therapy

Introduction

Pes planus, one of the most common foot deformities in all age groups, is defined as the condition where the medial longitudinal arch (MLA) chronically loses its height [1]. The most significant problem with pes planus is excessive pronation during load-bearing activities. Increased pronation of the subtalar joint causes the tibia to remain in internal rotation (IR) longer than usual during walking. For this reason, valgus stress occurs in the knees and IR increases in the hips. Anterior tilt is seen in the pelvis, increasing lumbar lordosis [2-5]. Complaints of pain, fatigue, and weakness while walking and standing may also accompany the symptoms [6]. Previous studies show that pes planus affects the mobility of the MLA, increases stress on the foot, and causes impaired load distribution; it also causes posterior tibial tendon failure, patellofemoral pain syndrome, and compensatory hip internal rotation. These have been reported to negatively affect performance and balance [7-10].

Pes planus deformity can be seen together with pain, instability, and various functional limitations, or it can be mild. However, the biomechanical changes caused by the deformity may increase over the years and cause clinical symptoms and functional problems. Therefore, even if pes planus is asymptomatic in young adults, it should be treated considering the problems it may cause in the future. Treatment can be surgical or conservative, depending on symptoms and clinical assessment. Conservative treatment options include activity modifications, analgesic drugs, physiotherapy, and orthotics. The physiotherapy program includes intrinsic foot exercises, stretching, strengthening and balance exercises for the ankle and lower extremity muscles, and video-based game exercise (VBGE) programs. The literature on rehabilitation of pes planus includes studies on the effects of exercise practices on the MLA, foot biomechanics, and balance [11-18].

Pes planus is a pathology that requires long-term rehabilitation. Considering the secondary pathologies that the deformity may cause, rehabilitation protocols that have high participation from an early period are needed. This makes VBGE treatments, which are becoming increasingly widespread in rehabilitation with the development of technology, come to mind. The literature describes VBGE treatments as exergames, serious games, and rehabilitative games.

Exergames are the therapeutic application of commercially developed video games in an exercise form. Exergame applications use game systems such as the Wii (Nintendo Inc), Xbox Kinect (Microsoft Corp), and PlayStation Move (Sony Inc), which were produced for entertainment purposes and are frequently used in rehabilitation. [19,20]. It has been reported that lower extremity games for the Xbox applied for 12 sessions in patients with flexible pes planus improved balance and navicular drop [12]. Serious games are games developed for rehabilitation rather than entertainment purposes. These games are developed specifically for a certain disease group or disease symptoms. Thus, they aim to provide rehabilitation by increasing active participation in therapy with higher motivation. One of the systems developed for this purpose is the Becure system, formerly known as Fizyosoft. The Becure system has software that can integrate with the Wii Balance Board. Studies in the literature show that Becure games lead to positive results in different disease groups [21-25]. However, there has been no study conducted with serious games for pes planus.

Today, the rapid development of technology and patients' search for new treatments have made it necessary to add these technologies to the rehabilitation process. There are many studies in the literature on VBGE therapy in different patient groups. However, there is a lack of literature regarding VBGE therapy in individuals with flexible pes planus. There is only one study, which used the Xbox Kinect [12]. Thus, we aim to compare the effects of different exercise protocols on functional parameters in pes planus rehabilitation. Also, our study will contribute to the literature by being the first study to compare Wii-based exergame protocols and Wii-based serious game exercise protocols.

Methods

Participants

The number of cases to be included in the study was determined by G*Power (version 3.0.10; Universitat Düsseldorf). Navicular drop test results from the study by Yıldırım Şahan et al [12] were taken as a reference. For α=.05 (error), 1–β=95% (power), and f=0.49 (effect size), we determined that it would be necessary to include a total of 69 people, with 23 in each group.

Participants will be recruited among individuals aged 18 to 25 years who attend the Medipol Mega University Hospital Orthopedics and Traumatology Department. The study will include 69 individuals who volunteer to participate and meet the inclusion criteria. The inclusion criteria were a navicular drop of more than 10 mm, flexible pes planus, and no previous use of insoles or exercise therapy. At the same time, since excess weight can affect pes planus, only individuals with a BMI within the range of 18 to 24.9 kg/m^2 will be included. Individuals with orthopedic or neurological problem affecting the lower extremities and balance, a history of surgery or trauma in the last 6 months, diabetes, pregnancy, or visual or auditory problems will also be excluded from the study.

Ethical Considerations

The study was approved by the Istanbul Medipol University Non-Interventional Clinical Research Ethics Committee (E-10840098-772.02-7170; November 28, 2022). The Declaration of Helsinki will guide the study. After eligibility is confirmed, written and verbal information about the study will be provided to all participants. Then, participants will sign a written informed consent form stating that they agree to

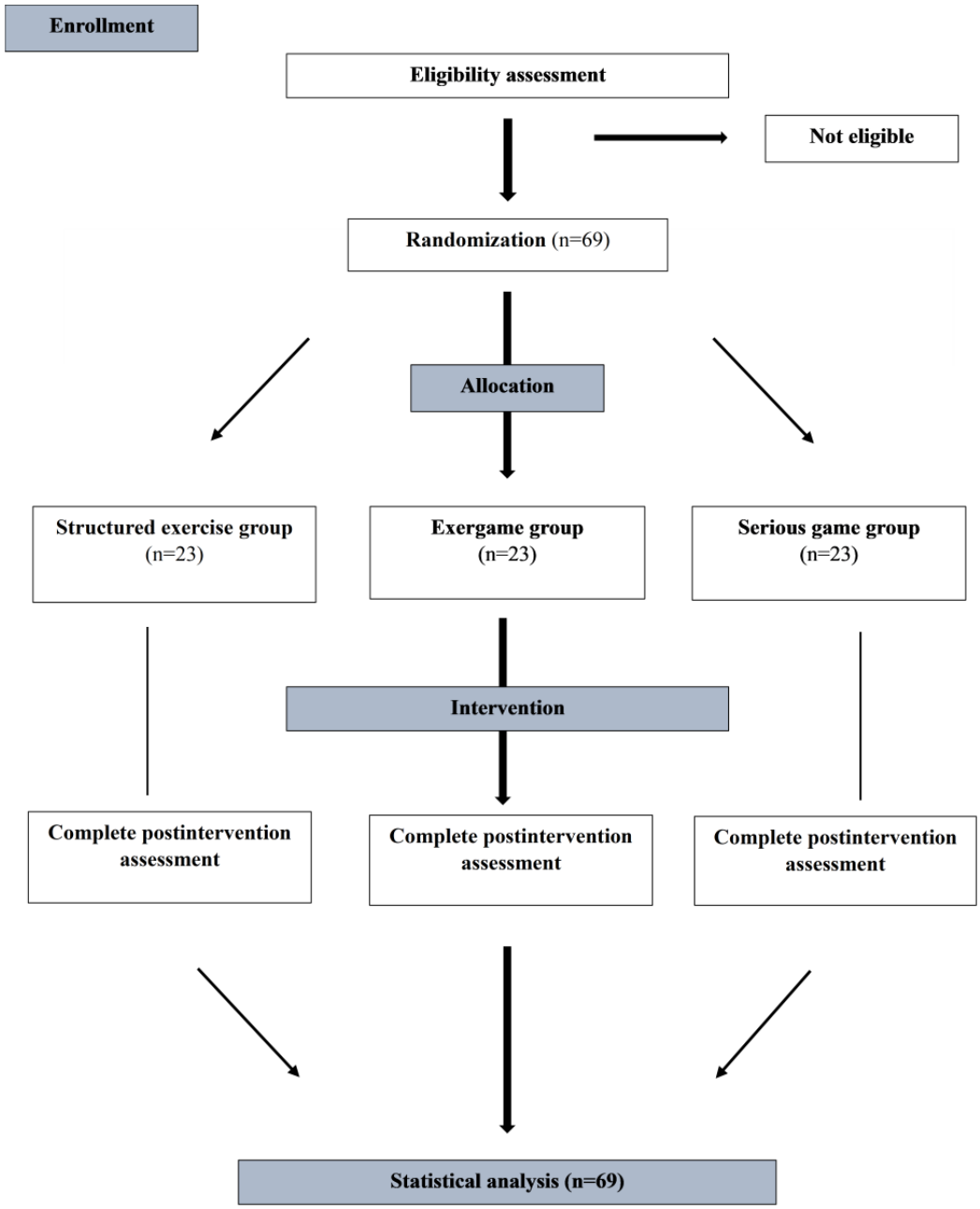
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participate in the research. The informed consent form also states that participation in the study is free and voluntary. No additional fees will be charged to the participants, and no payment will be made. The personal data and identity information of the participants will be kept confidential. Participants have the right to withdraw from the study at any time. The data will be used purely to contribute to science without any profit motive. At the same time, the data can be statistically analyzed without secondary approval when necessary. The trial intervention is similar to other clinical practices, so we consider that risks from the trial are minimal.

Study Design

This study has been registered with ClinicalTrials.gov (NCT05679219). It is a 3-arm, parallel-group, single-blinded randomized controlled trial. The study will be carried out in Istanbul Medipol University Physiotherapy Laboratory. A permit has been obtained from the institution. The demographic characteristics of the participants (eg, age, height, weight, diseases) will be recorded. Participants will be divided into 3 groups using a simple randomization method according to the order of arrival (1:1:1) with a web-based randomizer [26]. Participants do not know which exercise group they will be included in, nor will they know the differences between the exercises. The participants and the therapist who made the assessments were blinded. The flow chart of the study is shown in Figure 1.

Figure 1. Study flow diagram.



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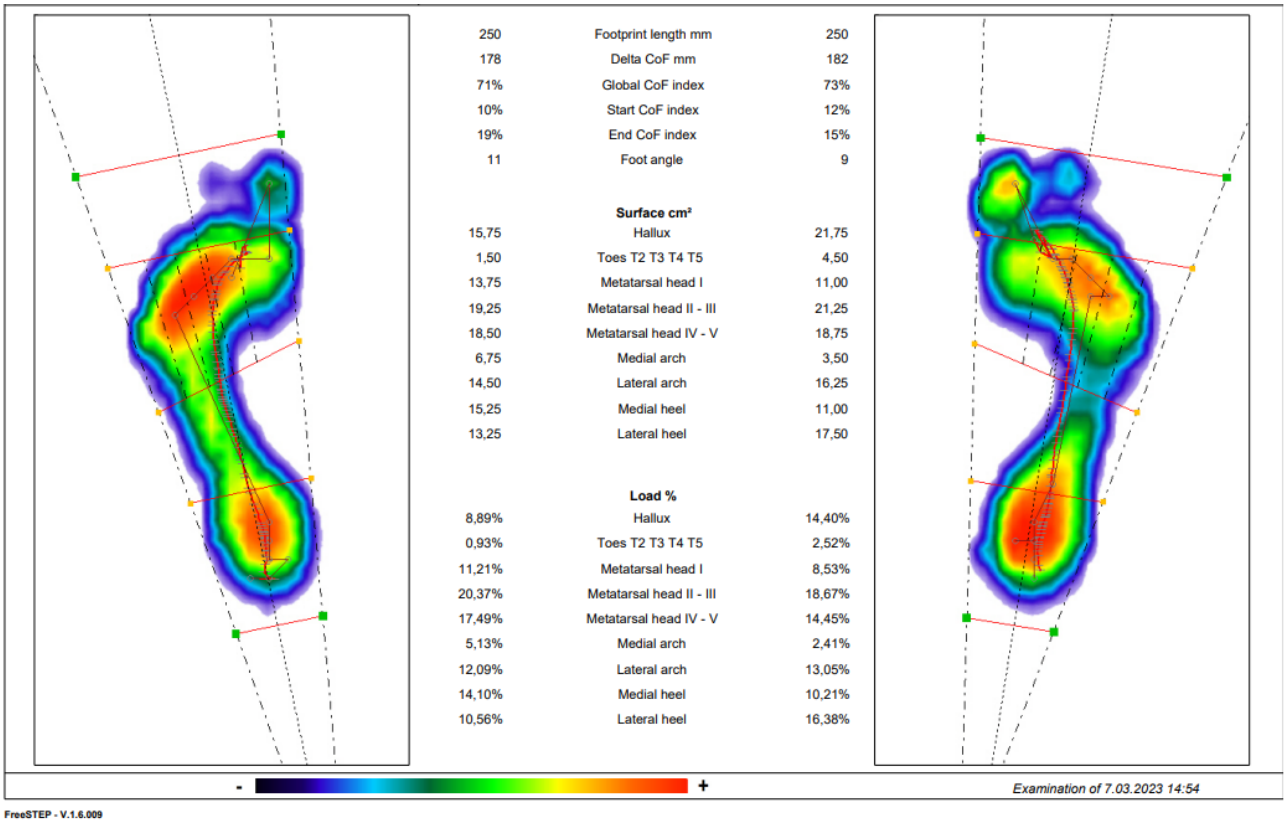
Outcome Measures

The primary outcome measures are navicular drop and the results of a pedobarographic analysis, and the secondary outcomes include balance, femoral anteversion, and lower extremity muscle strength. Participants will be evaluated before and after treatment. Measurements will be taken by an experienced therapist, who will not be the same therapist as the one who performs the exercises. The therapist performing the measurements will create the random allocation order, enroll the participants, and assign the participants to the interventions.

Pedobarographic Analysis

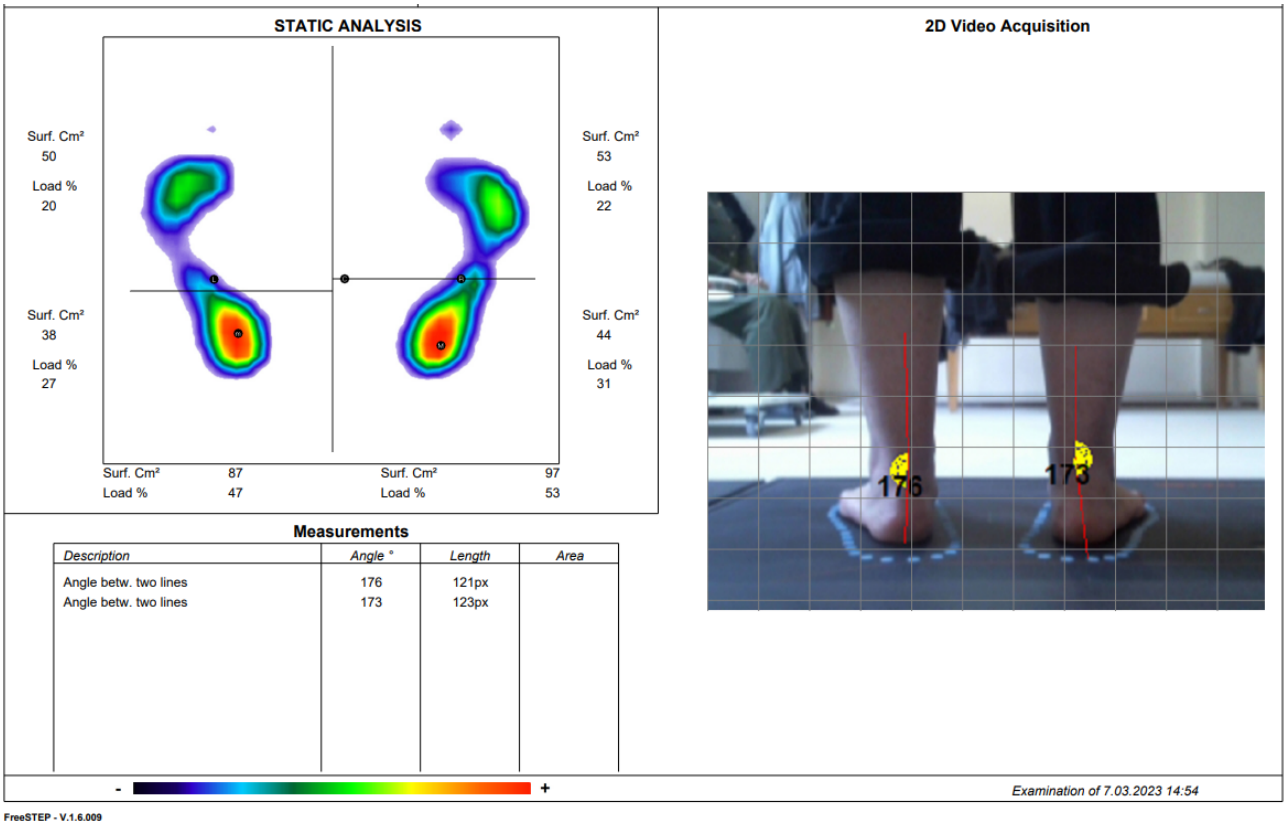
The pedobarographic analysis will be done in 2 steps, statically and dynamically, with the Sensor Medica Maxi brand device (Sensormedica). Static analysis data will be recorded while standing upright. Dynamic analysis data will be recorded while walking on the platform 6 times. Data such as ankle valgus angle, medial arch, lateral arch, medial heel, lateral heel surface area (cm²), and load (%) will be recorded. Plantar pressure analyses will be determined through FreeStep (version 1.6.009; Sensormedica), which is compatible with the device (Figures 2 and 3) [27].

Figure 2. Screenshot of pedobarographic analysis (dynamic analysis). CoF: center of foot.



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Figure 3. Screenshot of pedobarographic analysis (static analysis). Betw: between; px: pixel; Surf: surface.



Navicular Drop

The navicular drop test will determine the severity of pes planus. A navicular drop greater than 10 mm is an inclusion criterion. To determine the result of the exercises, the measurements will be repeated and compared to determine whether they have decreased [28].

Femoral Anteversion

The femoral anteversion angle will be evaluated with the Craig test. The participant will lie prone with the knees flexed to 90 degrees. In this position, the participant will be asked to rotate their lower extremities internally. The resulting angle will be measured with a goniometer [29].

Flexibility

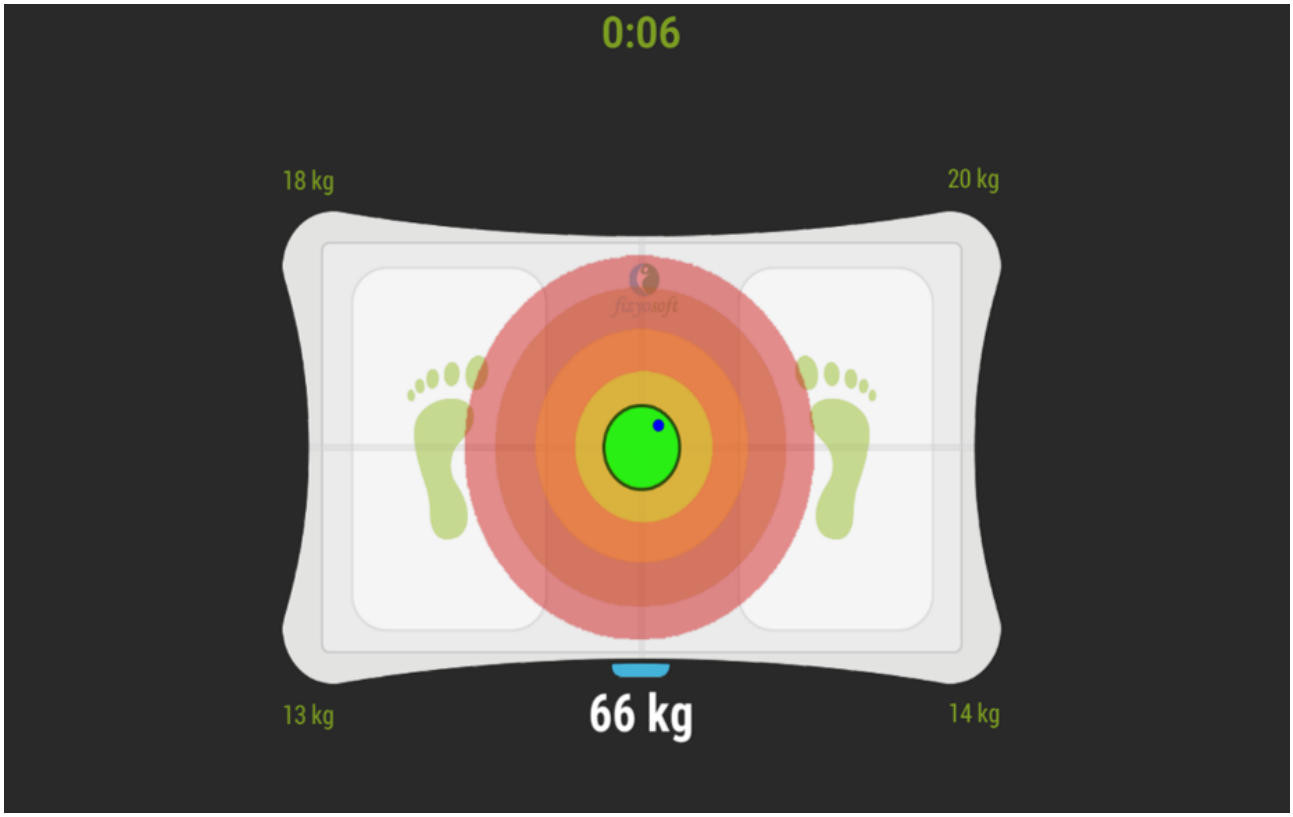
Flexibility will be evaluated with the Jack test [30]. The test is positive if MLA is formed by passive extension of the first toe. This test is one of the most important indicators that the pes planus deformity is flexible and that the foot shape can be altered with exercise.

Balance

Balance measurements will be evaluated with the Becure Balance System (Becureglobal). A validity and reliability study of the Balance Board balance device, which is integrated with Becure, was conducted by Tarakcı et al [24]. In this context, measurements of individuals with their eyes open or closed on both feet or a single foot will be taken (Figure 4). The system reports the oscillation in centimeters to stay balanced during the measurements [24]. A decrease in oscillation after treatment is interpreted as improvement.

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Figure 4. Example of balance measurement.



Muscle Strength

Participants' muscle strength in the lower extremity dorsiflexor, plantar flexor, inverter, evertor, knee flexor, knee extensor, and hip flexor muscle groups will be measured with a Lafayette myometer device (Pelican 1150 Case; Pelican Products). Results will be recorded in newtons [31].

Intervention

Participants will be treated by a specialist physiotherapist 3 days a week for 6 weeks for a total of 18 sessions of 40 minutes each. The same therapist will follow the exercises of all 3 groups.

Structured Pes Planus Exercise Group

In this group, exercises will include a short foot exercise, towel curl, walking (toe, heel, tandem), eccentric gastro soleus stretching, object picking with toes, and balancing on 1 leg (Figure 5). The primary purpose of the exercises is to increase the MLA, especially by contracting the foot intrinsic muscles, and simultaneously to improve balance. Walking exercises will be performed for 10 meters over 10 rounds, while other exercises will be performed with 30 repetitions for both feet; the entire session will be 40 minutes. The first 2 sessions with the participants will be face-to-face with the therapist. Then, an email with photos and videos of the exercises will be sent. The remaining sessions will be performed online (mobile-based) and supervised by the therapist every 3 sessions.

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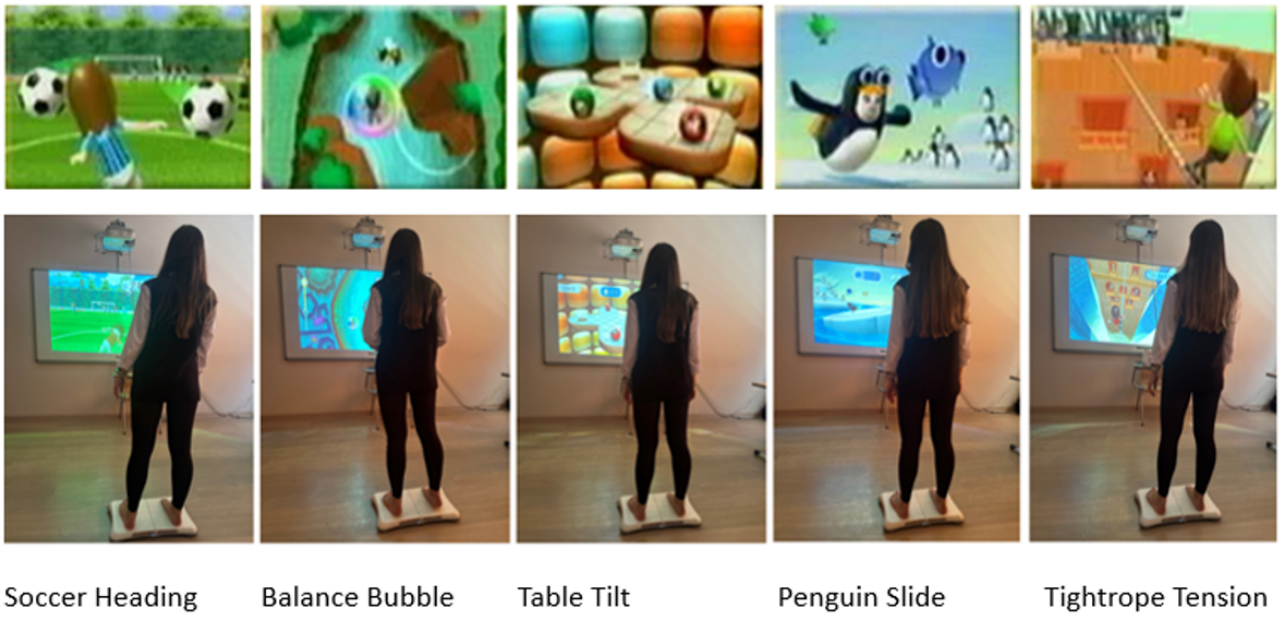
Figure 5. Structured pes planus exercises.



Wii-Based Exergame Group

Balance games for the Wii game console, which is frequently used for different disease groups in the literature, will be played by this group. In this context, 5 games will be played for a total of 40 minutes (8 minutes playtime each) under the supervision of a specialist physiotherapist (Figure 6). It will be noted that the person should not transfer weight to the medial part of the foot.

Figure 6. Wii-based exergame game screens and gameplay.



In the Soccer Heading game, weight transfer to the right and left is required to catch balls coming out of the goal. The more balls caught, the higher the score. It is necessary to avoid objects other than the ball in order not to lose points.

In the Balance Bubble game, it is necessary to transfer weight to the forward, right, and left in order to move forward without hitting the surface of a river. In order to advance quickly, it is necessary to put weight on the tips of the toes. This position is essential in increasing the MLA by causing the contraction of the foot's intrinsic muscles. The aim is to complete the stage as quickly as possible.

In the Table Tilt game, it is necessary to transfer weight in 4 directions to hit balls into gaps in a target. After all the balls pass through the gap, the level is passed. There are 9 levels in total. As the levels progress, the game becomes more complex, and the number of balls that need to be passed through the gaps increases. It is necessary to put weight on the tip of the toe during anterior weight transfer.

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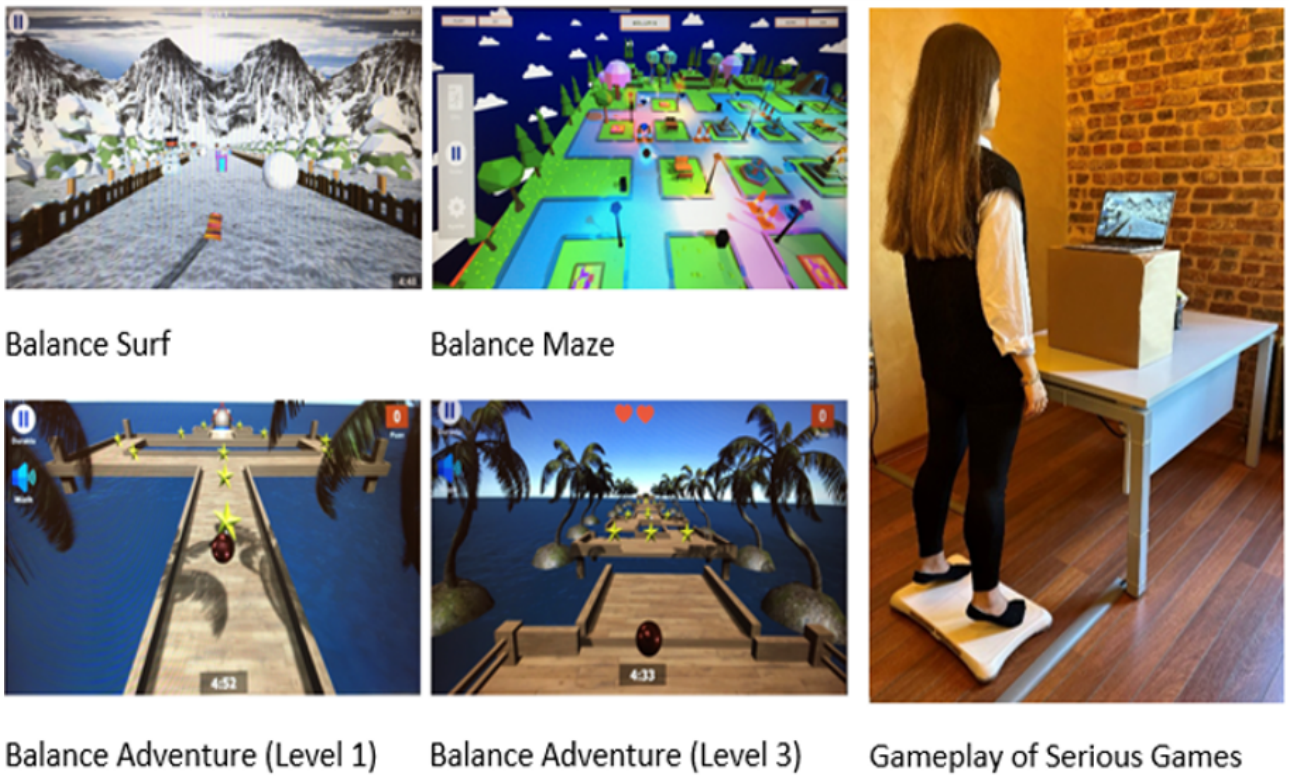
In the Penguin Slide game, the aim is to catch a fish without falling into the water over a glacier and collect points. The game includes transferring weight from right to left. The aim is to complete the game by catching all the fish as soon as possible.

In the Tightrope Tension game, weight transfer must be done rhythmically to the right and left to complete the game. The aim is to reach the goal by walking along the rope as quickly as possible.

Wii-Based Serious Game Group

This group will play the games in the Becure Balance System. Three games considered suitable for the participants will be played under the supervision of an expert physiotherapist for 40 minutes in each session (Figure 7). It will be noted if a participant should not transfer weight to the medial part of the foot.

Figure 7. Wii-based serious game screens and gameplay.



Balance Adventure is a game that involves transferring weight in 4 directions. There are 3 different levels, from easy to complex. At level 1, the aim is to reach the exit by collecting all the stars. In level 3, the aim is to collect the stars on a moving surface and advance the ball without dropping it. Each participant will play level 1 of the game for 5 minutes for warm-up and level 3 for 10 minutes; they will play for the highest target score and use the most-forward weight transfer mode. Selecting the forward weight transfer mode requires placing more weight on the front of the foot in order to advance the target. It is necessary to put weight on the tip of the toe. Thus, the foot's intrinsic muscles are more active.

The Balance Surf game is played with right to left and forward weight transfer. The aim of the game is to gain points by directing the surfboard on the screen, collecting stars and gift package objects. Speed parameters can be determined automatically and manually. Each participant will play the game for 15 minutes at level 8, the balanced weight transfer mode, with manual speed adjustment. In automatic mode, transferring weight toward the tips of the toes does not affect the progression speed. However, in manual-speed mode, the more weight the participant moves forward, the faster they move. Progress stops if the participant stands straight without moving weight to the front. This position requires the person to play the game by rising more on their toes. This is designed to make the foot's intrinsic muscles more active and increase the MLA.

Balance Maze is played with anterior to posterior and lateral balance movements. There are 5 levels. As the levels progress, the maze floor that is moved becomes larger, and the number of stars to collect increases. At the same time, the number of obstacles on the playing field increases. The game must be finished by collecting all the stars. Level 4 and level 5 will be played for 5 minutes each for all participants.

Statistics

Data will be statically analyzed using SPSS (version 25.0; IBM Corp). Normality tests (visual and analytical) will be applied. Descriptive statistics will be expressed as arithmetic means with SDs. After obtaining the results of the normality evaluation, analyses will be carried out with tests suitable for the distribution of the groups. Statistical analyses will be interpreted according to the significance level of $P<.05$.

Results

The study was approved by the ethics committee on November 28, 2022. The study was funded by Tübitak on April 19, 2023.

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From this date, cases started to be included in the study. So far, the treatment has been completed for an average of 7 patients per group. Data will be analyzed when all subjects scheduled to participate have completed treatment. The study is expected to be completed in June 2024.

Discussion

This study evaluates the effectiveness of 2 VBGE applications (an exergame and a serious game) and structured exercise applications on functional parameters in pes planus rehabilitation. In this context, the effects of exercise protocols on functional parameters such as navicular drop, muscle strength, balance, and plantar pressure will be evaluated. All 3 exercise protocols are expected to yield positive results on functional parameters. It has been reported in the literature that exercises for lower extremity muscle groups provide improvement in functional parameters.

Lynn et al [8] compared the short foot exercise and towel curl exercise, which were repeated 100 times per day for 4 weeks; they determined that the short foot exercise led to greater improvement in dynamic balance. Kim and Kim [14] compared the effects of the short foot exercise and insoles applied 3 days a week for 5 weeks in individuals with flexible pes planus. They reported that short foot exercises led to greater improvement in navicular drop and dynamic balance.

Ravichandran et al [16] compared the effects of concentric and eccentric tibialis posterior strengthening exercises in individuals aged 18 to 25 years with flexible pes planus. Like our study, the participants used exercises such as resistant dorsiflexion, plantar flexion and inversion, towel curls, and toe-tip elevation. They determined that both concentric and eccentric exercises improved navicular drop equally. Goo et al [11] evaluated the relationship between navicular drop and muscle activation during walking with 2 exercise protocols assigned to individuals with pes planus. They assigned abductor hallucis strengthening exercises combined with gluteus maximus strengthening exercises to one group and abductor hallucis strengthening exercises to the other. They reported that gluteus maximus strengthening exercises were important in recovering navicular drop and providing a typical gait pattern. Engkananuwat et al [32] evaluated the effects of performing gluteus medius strengthening exercises in addition to foot exercises in individuals with flexible pes planus. For 4 weeks, one group performed the short foot exercise and the other group performed a hip-strengthening exercise in addition to the foot exercise. The authors found that hip exercises added to the foot exercise; they determined that it was more effective in reducing medial plantar pressure, static balance, and navicular drop data. The exercise protocols in our study are similar to the studies in the literature.

The biomechanics of the foot directly affect the whole body's posture and gait. Considering the studies in the literature, it is not sufficient to only strengthen the intrinsic foot muscles in pes planus rehabilitation. Strengthening the other lower extremity muscles is also very important. In parallel with the literature, we will assign strengthening exercises for all lower extremity muscles in all 3 groups in our study.

In recent years, VBGE therapy applications have been used frequently in orthopedic rehabilitation, in accord with patients' search for new treatments and the development of technology. There are studies showing that video-based exercise applications lead to positive results in different patient groups [19-25]. However, there are insufficient studies on these applications for pes planus rehabilitation. There is only one study in cases with pes planus. Yıldırım Şahan et al [12] divided 40 patients with flexible pes planus into 2 groups and compared the effects of Microsoft Xbox Kinect lower extremity games and short foot exercises performed 3 days a week for 4 weeks. They found a significant improvement in both groups' navicular drop and balance data after treatment. They reported that VBGE was an effective exercise method in patients with pes planus. However, the study's limitations were a limited number of participants, a short duration of treatment (12 sessions), and a lack of objective evaluation methods.

Compared to the study by Yıldırım Şahan et al [12], we used a relatively longer session duration (18 sessions), included a large number of cases, and used only objective evaluation methods, thereby increasing the importance of our study. However, it is known that games for the Nintendo Wii game console (exergames) and the Becure Balance system (serious games) are designed to improve the overall body balance. Therefore, it is unclear to what extent exercises for the intrinsic and extrinsic muscles of the feet are included in the content of both video-based games. They are likely to have similar potential effects. This situation can be considered as a limitation of our study. But at the same time, thanks to our study, the effectiveness of these games in the rehabilitation of pes planus will be determined, and the ground will be prepared for the development of specific games for the treatment of foot and ankle pathologies in the future.

Our study will contribute to the literature, as it is the first to compare Nintendo Wii games and Wii-based serious game protocols for pes planus rehabilitation. At the same time, it will determine whether video-based game exercise applications are superior to structured exercise applications. We aim to determine which exercises are superior with the most objective methods. The use of VBGE therapy for the rehabilitation of pes planus will be a guiding principle. Also, this study will introduce a new exercise protocol that includes serious game exercises to the literature. In the future, we expect that our study on the development of different game systems, especially for the ankle, will be a pioneer in providing feedback.

Acknowledgments

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Data Availability

The data sets generated during and/or analyzed during this study are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
CONSORT-EHEALTH checklist (V 1.6.1).
[PDF File (Adobe PDF File), 1164 KB - resprot_v12i1e51772_app1.pdf]

Multimedia Appendix 2
Peer-reviewer report from Turkish Scientific and Technological Research Institution.
[PDF File (Adobe PDF File), 404 KB - resprot_v12i1e51772_app2.pdf]

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Abbreviations

IR: internal rotation
MLA: medial longitudinal arch
VBGE: video-based game exercise

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Protocol

A Hospital-Wide Open-Label Cluster Crossover Pragmatic Comparative Effectiveness Randomized Trial Comparing Normal Saline to Ringer's Lactate: Protocol and Statistical Analysis Plan of The FLUID Trial

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Abstract

Background: Normal saline (NS) and Ringer's lactate (RL) are the most common crystalloids given to hospitalized patients. Despite concern about possible harm associated with NS (eg, hyperchloremic metabolic acidosis, impaired kidney function, and death), few large multicenter randomized trials focused on critically ill patients have compared these fluids. Uncertainty exists about the effects of these fluids on clinically important outcomes across all hospitalized patients.

Objective: The FLUID trial is a pragmatic, multicenter, 2×2 cluster crossover comparative effectiveness randomized trial that aims to evaluate the effectiveness of a hospital-wide policy that stocks either NS or RL as the main crystalloid fluid in 16 hospitals across Ontario, Canada.

Methods: All hospitalized adult and pediatric patients (anticipated sample size 144,000 patients) with an incident admission to the hospital over the course of each study period will be included. Either NS or RL will be preferentially stocked throughout the hospital for 12 weeks before crossing to the alternate fluid for the subsequent 12 weeks. The primary outcome is a composite of death and hospital readmission within 90 days of hospitalization. Secondary outcomes include death, hospital readmission, dialysis, reoperation, postoperative reintubation, length of hospital stay, emergency department visits, and discharge to a facility

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other than home. All outcomes will be obtained from health administrative data, eliminating the need for individual case reports. The primary analysis will use cluster-level summaries to estimate cluster-average treatment effects.

Results: The statistical analysis plan has been prepared "a priori" in advance of receipt of the trial data set from ICES and any analyses.

Conclusions: We describe the protocol and statistical analysis plan for the evaluation of primary and secondary outcomes for the FLUID trial.

Trial Registration: ClinicalTrials.gov NCT04512950; https://classic.clinicaltrials.gov/ct2/show/NCT04512950

International Registered Report Identifier (IRRID): DERR1-10.2196/51783

(JMIR Res Protoc 2023;12:e51783) doi:10.2196/51783

KEYWORDS

statistical analysis plan; fluid therapy; normal saline; Ringer's lactate; cluster randomized trial; pragmatic; comparative effectiveness

Introduction

Crystalloid resuscitation fluids, including normal saline (NS) and Ringer's lactate (RL), are among the most common interventions administered in hospitalized patients [1,2]. These fluids may be used as a life-saving measure to re-establish hemodynamic stability, replace fluid losses, and maintain intravascular volume.

In observational studies, NS has been associated with acute renal injury as compared to RL and other balanced crystalloid fluids, hypothesized to be due to higher chloride concentration and resultant metabolic acidosis that can occur with NS administration [3-5]. However, RL and other balanced crystalloid fluids with buffers have the potential to cause metabolic alkalosis [6,7] and theoretically, cause arrhythmias, tetany, coma, and seizures [8-10]. The lactate in RL may accumulate in the setting of liver failure and may influence clinical diagnoses and clinical decision-making [11-13]. Moreover, RL has a lower osmolarity in comparison to NS; when administered rapidly in large volumes, RL theoretically reduces plasma osmolarity and increases the risk of edema formation [14], which raises potential concern for patients with cerebral edema.

In total, 2 large single-center multiple crossover trials conducted in the intensive care unit (ICU) and the emergency department (ED) among patients who did not require admission to the ICU, found that balanced crystalloid fluids as compared to NS were associated with lower major adverse kidney events at 30 days, which is a composite outcome of mortality, new renal replacement therapy, or persistent renal dysfunction [2,15]. In contrast, 2 large multicenter randomized trials (Balanced Solution versus Saline in Intensive Care Study [BASICS]; Plasma-Lyte 148 versus Saline [PLUS]) [16,17] examined the efficacy of NS as compared to a balanced crystalloid (RL and Plasma-Lyte 148 respectively) on the primary outcome 90-day mortality. Neither of these trials detected differences in 90-day mortality. In BASICS, the mortality rate was 22% versus 21.8%; and in PLUS, mortality was 27.2% versus 26.4% in patients receiving NS and RL, respectively. Renal function did not differ between the fluid groups in either trial, although the PLUS trial was stopped early due to recruitment challenges and insufficient funding during the pandemic. In a systematic review of 35,884 participants in 13 critical care trials published before January 2022, there were no detectable differences in renal function. In low-risk-of-bias trials, there was no significant difference in mortality for the NS as compared to the balanced crystalloid group (28.2% and 27.9% respectively; Relative Risk 0.96, 95% CI 0.91-1.01), nor renal function [15-28]. However, the authors concluded that there is a high probability that balanced crystalloids reduce death since the CIs ranged from a 9% relative reduction to a 1% relative increase in death.

Crystalloid fluids are administered to the majority of patients admitted to the hospital and continued throughout their hospital stay. To address ongoing uncertainty on this topic, and address this evidence gap about fluid administered outside the ED and ICU, we designed a cluster randomized crossover trial. Our objective was to compare a hospital-wide strategy to preferentially stock NS or RL as the main crystalloid resuscitation fluid, aiming to have all admitted patients receive the allocated crystalloid from the time they enter hospital to hospital discharge, evaluating the primary composite outcome of death or readmission to hospital in the first 90 days. The design of the FLUID trial is novel because it involves a pragmatic cluster randomized crossover design, a waiver of patient informed consent to include all hospitalized patients, hospital-based randomization, and the use of routinely collected electronic health administrative data for the description of baseline characteristics and all study outcomes. FLUID will generate data at low risk of bias, providing key evidence about the consequences of crystalloid fluid on clinically important outcomes, and informing patient care and health care policy. It will also provide insight into a novel approach to the conduct of large pragmatic clinical trials.

This manuscript describes the protocol and statistical analysis plan for the evaluation of primary and secondary outcomes for the FLUID trial.

Methods

Overview

The protocol and feasibility results for the FLUID pilot trial have been published [29,30]. The 4 pilot sites will be included in the analysis of the large trial as only feasibility outcomes have been previously reported and no major protocol changes were necessary following the pilot trial. The structure of this protocol and statistical analysis plan (version 1.0; March 29,

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2023) follows the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) Guidelines [31] (see Multimedia Appendix 1 and Table 1) and Guidelines for the Content of Statistical Analysis Plans in Clinical Trials (see Multimedia Appendix 2) [32]. The reporting of the trial results will follow the CONSORT (Consolidated Standards of Reporting Trials) Statement's extension for Cluster Trials [33] and Randomized Crossover Trials [34], as applicable.

Table 1. SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) table.

Study period									
Preallocation			Postallocation						
Time point	Enrollment ($-t_1$)	Allocation (0)	Run-in (1 week)	Period 1 (12 weeks)	Wash-out (2 weeks)	Run-in (1 week)	Period 2 (12 weeks)	Wash-out (2 weeks)	Close-out
Enrollment									
Eligibility screen	✓								
Allocation		✓							
Interventions									
Fluid A				✓			✓		
Fluid B				✓			✓		
Assessments									
Demographics	✓								
Case mix group	✓								
Type of surgical admission	✓								
Surgical subgroup	✓								
Severity of illness	✓								
Comorbidities	✓								
Primary outcome									✓
Secondary outcomes									✓

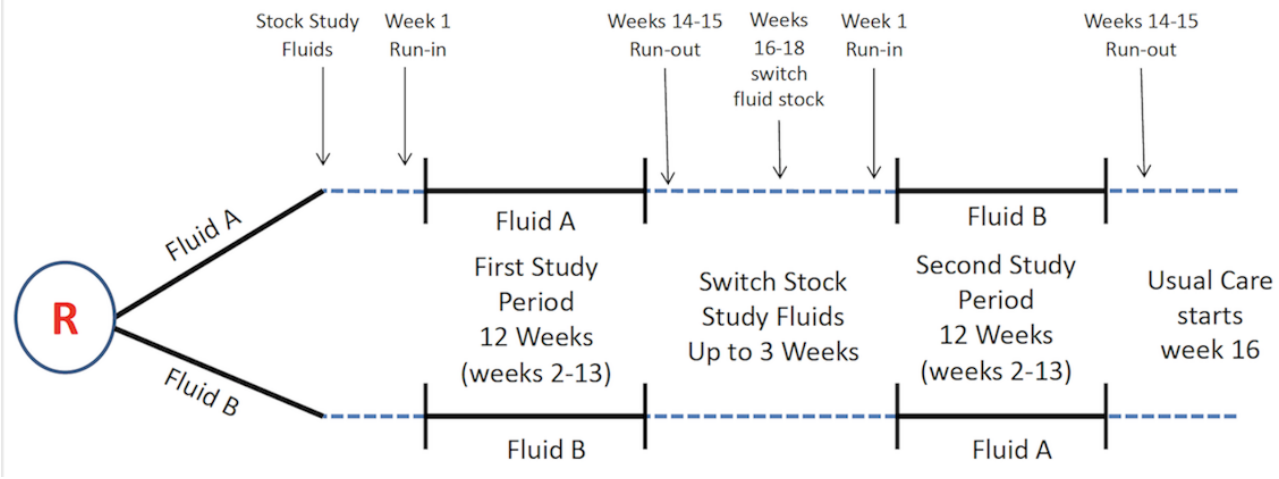
Trial Design

The study is a pragmatic, multicenter, 2×2 cluster crossover comparative effectiveness randomized trial. A completed PRECIS-2 table and wheel have been attached as Table S1 and Figure S1 in Multimedia Appendix 3. We defined clusters as hospital sites, allocated to one of two sequences in a 1:1 ratio. The interventions are a hospital-wide strategy of stocking predominantly NS (control) or RL (treatment) throughout the hospital. FLUID is an open-label trial as the cost of blinding the fluids is infeasible and prohibitively costly; this design is in keeping with a real-world evaluation of NS and RL whereby research is integrated into clinical care.

FLUID has two 15-week study periods. For each study period, week 1 will serve as a run-in, weeks 2-13 (12 weeks) as the study period during which all patients with index admissions to the study hospital will be included for analysis. Weeks 14 and 15 are the run-out period during which time the study fluid remains stocked in the hospital for use by patients admitted during weeks 2-13; however, new patients admitted during weeks 14 and 15 will not contribute to the analysis. After the 2-week run-out period, sites will have 1 week to switch out the study fluid and cross over to the period 2 study fluid. See Figure 1.

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Figure 1. FLUID trial study design.



Trial Population

Cluster Screening and Eligibility

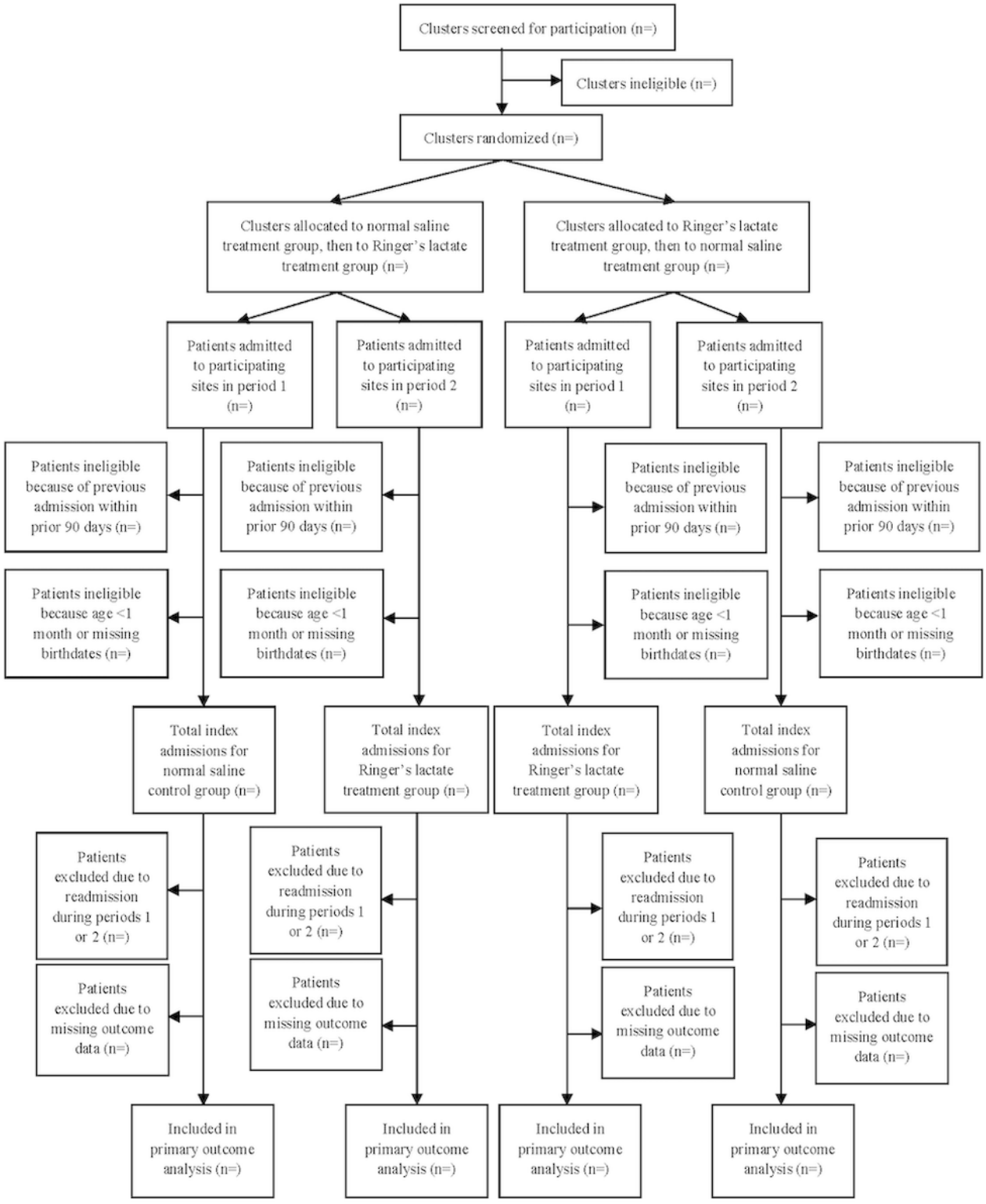
Inclusion criteria for participating clusters include (1) level II or III ICU capacity [35] and (2) the admission of at least 6000 patients per year to hospital. A list of included study sites will be included in the main trial report.

Patient Screening and Eligibility

All admitted patients to participating study sites for the first time (index hospital admission) over the duration of the study period will be included under a waiver of informed consent obtained from the research ethics committee; only neonatal patients (age <1 month) will be excluded as RL is not recommended for use in this population [36]. Patients readmitted to the hospital during study periods 1 or 2 and patients admitted during the run-in or run-out study periods will also be excluded. An index admission is defined as a patient admission with no prior hospital admission in the previous 90 days. CONSORT flow diagram of participant recruitment is presented in Figure 2.

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Figure 2. CONSORT (Consolidated Standards of Reporting Trials) flow diagram for participants.



Randomization

The order of treatment allocation for each hospital site (cluster) will be randomly assigned using computer-generated random numbers, using a permuted block design of length 2, at the coordinating center. The allocation sequence will be prepared by a statistician not familiar with the participating sites, which will be randomized in a 1:1 ratio. Half of the sites will be allocated to sequence 1 and begin the trial with NS as the control, while the other half will be allocated to sequence 2 and begin the trial with RL as the treatment. Each site will cross over to the other fluid after the 12-week study period. To control for period effects, while balancing logistical considerations, randomization will proceed in batches of 4 sites. The allocation sequence will be maintained on a password-protected computer and concealed from investigators until the next batch of sites have been enrolled and are ready to receive their allocation.

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Approach to Safety

No serious adverse events were reported to the coordinating center during the 4-center pilot trial. A Data and Safety Monitoring Committee conducted a review of the data from the 4-center pilot trial, reporting no reason to suspect harm resulting from either fluid. For the main trial, participating hospitals monitor serious adverse events via routinely scheduled meetings of safety committees or morbidity and mortality rounds. Site Principal Investigators report to the coordinating center any serious adverse event occurrence related to study fluid administration.

Sample Size

A total of 16 hospital sites (including the 4 pilot sites) will yield data on approximately 144,000 hospital admissions. It required 12 sites in a 2-period cluster crossover trial over 6 months to achieve 80% power with a 2-sided α of 0.05 to detect a minimum clinically important absolute difference of 1% in the primary outcome in favor of RL, assuming a proportion of 0.16 in the NS condition, a within-period intracluster correlation coefficient of 0.006, a cluster autocorrelation coefficient of 0.95, and an average of 1500 patients per hospital per month [37]. These estimates were calculated from available routinely collected data for January 1 to December 31, 2013, for all eligible hospitals across the province of Ontario, Canada. Our calculations account for nonadherence based on pilot data (94% adherence NS, 80% RL). We added 2 clusters as an approximate small sample correction [38] and a further 2 to account for cluster size variation [38], for a final sample size of 16 sites.

Interim Analysis and Stopping Guidance

As a risk to participants in FLUID is minimal, and given the delayed availability of data from the Ontario provincial health administrative databases needed for outcome assessment, no interim analyses are planned in the FLUID trial.

Adherence and Protocol Deviations

Protocol adherence will not be measured at the individual patient level. Adherence will be measured according to the aggregate use of the study fluid throughout the hospitals using the hospital inventory system. Adherence will be monitored at 2-week intervals over the study period and reported according to each study group across all participating hospitals, combined and according to major fluid user groups in specific settings (ED, surgery, medicine, operating room, ICU, postoperative assessment unit, and obstetrics). Overall adherence will be defined as the total use of the allocated study fluid divided by the total combined use of NS and RL.

Participant Withdrawal

We will not be collecting individual patient-level data, as all data will be collected through the ICES provincial database. As informed consent is not being sought, only clinically available data are being analyzed, and no unique research data are being collected, participants cannot withdraw from the study.

Participant Follow-Up

We anticipate near 100% follow-up since all clinical data and outcome measures from participating sites in Ontario will be available at ICES, except for a very small number of patients who leave the province of Ontario within 90 days after enrollment.

Data Sources

Data will be obtained and housed using Ontario's population-based health administrative databases at ICES. ICES is an independent, nonprofit research institute whose legal status under Ontario's health information privacy laws allows the collection and analysis of health care and demographic data. The data sets identified in Table 2 were linked using unique identifiers and analyzed at ICES.

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Table 2. ICES data sources.

Database	Acronyms
Registered Persons Database	RPDB
Discharge Abstract Database	DAD
Ontario Mental Health Reporting System	OMHRS
National Ambulatory Care Reporting System	NACRS
Ontario Health Insurance Plan	OHIP
Same Day Surgery	SDS
Ontario Drug Benefit	ODP
OHIP lab claims	All OHIP billings have a fee code beginning with "L"
OHIP physician billings	N/A[a]
Home Care Database	OACCAC[b] HCD
Complex and Continuing Care	CCRS
National Rehabilitation System	NRS
Continuing Care Reporting System	CCRS
Family Health Organization or Family Health Network Capitation	FHO or FHN
Long term care	N/A
National Ambulatory Care Reporting System visits to hospital outpatients clinics and dialysis clinics	NACRS
National Ambulatory Care Reporting System visits to cancer clinics	NACRS
New Drug Funding Plan chemotherapy drugs	NDFP
Assistive Device program	ADP

[a]N/A: not applicable.

[b]OACCAC: Ontario Association of Community Care Access Centres.

Timing of Final Analysis

All follow-up and data collection for patients at the participating sites will be captured by ICES. The approach to analysis will be supervised by the study statistician and principal investigator; however, the final analysis will be conducted by an independent statistician not involved as a coinvestigator in the FLUID trial.

Statistical Principles

Analytical Framework

All study outcomes will be tested for superiority.

CIs and P Values

All statistical tests will be 2-sided and performed using a 5% significance level. We will report all CIs as 95% and 2-sided. Results will be expressed as absolute differences produced by analyses described below.

Analysis Populations

Our primary analysis will use the intention-to-treat approach and will include all enrolled patients in the treatment groups to which their cluster was randomized at the time of the index hospitalization. Because true fluid exposure status is not recorded in administrative databases, all admitted patients will be included in the analysis, regardless of actual fluid administration.

Outcome Definitions

Primary Outcome

The primary outcome is a composite of death or readmission to the hospital within 90 days of the index hospitalization. All-cause death will be obtained at a patient level using the Registered Persons Database, while hospital readmission will be measured from Discharge Abstract Database (DAD). Cluster randomized trials can address 2 types of estimands: the participant-average or the cluster-average treatment effect [39]. The former estimates the effect of an intervention for an average participant, whereas the latter estimates the effect for an average cluster. In the FLUID trial, intervention exposure will be unknown at the individual patient-level and the primary study objective is to inform a decision by the health system stakeholder; thus, the primary estimand in the FLUID trial is the cluster-average treatment effect. It is known that cluster-average and participant-average treatment effects will differ when cluster sizes are informative, meaning that either the outcomes or treatment effects vary with cluster size. In the FLUID trial, it is possible that treatment effects will vary between larger or smaller hospitals, and thus, informative cluster sizes cannot be ruled out. The statistical analysis plan was therefore formulated to yield an unbiased estimate for the cluster-average treatment effect in the presence of informative cluster sizes.

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Secondary Outcomes

The secondary outcomes are 90-day death, hospital readmission within 90 days of the index hospitalization, and requirement for new dialysis within 90 days; and for surgical patients, requirement for reoperation, postoperative reintubation in the postoperative assessment unit, ED visits within 90 days, hospital length of stay, and discharge to facility other than home. All secondary outcomes will be obtained at the patient level from DAD and National Ambulatory Care Reporting System.

Tertiary Outcomes

The tertiary outcomes relate to the health economic analyses and include the incremental cost per one death averted and incremental cost per one quality-adjusted life year (QALY) gained.

Analysis Methods

Descriptive Analyses

Baseline data will be collected and summarized as means and SDs for continuous variables or counts and percentages for categorical variables as shown in Table 3. We will summarize outcome data as cluster-period frequencies and proportions for dichotomous primary and secondary outcomes and medians with IQRs for the length of stay. Outcome data will be reported by the treatment group.

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Table 3. Baseline characteristics.

Characteristic	Total # index admissions	Normal saline	Ringer's lactate
Sex, female, n (%)			
Age (years), mean (SD)			
Age group, n (%)			
1 month to 18 years			
>18 to 65 years			
>65 to 80 years			
>80 years			
Case mix group, n (%)			
Medicine			
Surgery			
Pregnancy and childbirth			
Mental health			
Type of surgical admission, n (%)			
Elective			
Urgent			
Surgical admission<24 hours			
Surgical subgroups			
General			
Thoracic			
Cardiac			
Vascular			
Orthopedic			
Obstetrical			
Gynecological			
Ear or Nose or Throat			
Plastic			
Urological			
Neurosurgery			
Trauma			
Other			
Severity of illness, n (%)			
Admission to ICU[a]			
Infection Alone and Infection and Organ Dysfunction			
Infection Alone and Infection and Organ Dysfunction and ICU admission			
Trauma ISS[b] ≥12, n (%)			
Trauma ISS≥12+ICU			
Traumatic brain injury, n (%)			
Traumatic brain injury+ICU			
Comorbidities			
Elixhauser Comorbidity Score, mean (SD)			
Elixhauser Comorbidities, n (%)			

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Characteristic	Total # index admissions	Normal saline	Ringer's lactate
Diabetes, complicated			
Hypertension, uncomplicated, and complicated			
Cardiac arrhythmias			
Solid tumor without metastasis			
Fluid and electrolyte disorders			
Diabetes, uncomplicated			
Congestive heart failure			
Metastatic cancer			
Chronic pulmonary disease			
Other neurological disorders			
Peripheral vascular disorders			
Coagulopathy			
Valvular disease			
Obesity			
Renal failure			
Paralysis			
Liver disease			
Alcohol abuse			
Pulmonary circulation disorders			
Depression			
Deficiency anemia			
Lymphoma			
Drug abuse			
Rheumatoid arthritis or collagen vascular diseases			
Hypothyroidism			
Weight loss			
Psychoses			
Blood loss anemia			
Peptic ulcer disease excluding bleeding			
AIDS or HIV			

[a]ICU: intensive care unit.

[b]ISS: injury severity score.

Primary Analyses of the Primary and Secondary Outcomes

All analyses will be conducted according to recommendations for cluster randomized crossover trials, accounting for clustering to ensure correct type I error rates and CIs [38,40]. In the case of a small number of clusters, mixed-effects regression and generalized estimating equation approaches are known to not perform well; analysis for FLUID will, therefore, be performed using cluster-level summaries. This method is known to perform well even with a very small number of clusters. Equal weight will be given to each cluster to obtain unbiased estimates for the cluster-average treatment effect. To implement the cluster-level method, binary outcomes will be expressed as proportions in each cluster-period and the differences (proportion under RL minus proportion under NS will be calculated for each cluster. These differences will then be analyzed using an unweighted linear regression model as described by Turner et al [41]. The t-distribution with degrees of freedom equal to the number of clusters minus 2 will be used. The intervention effect will be expressed as an absolute difference with 95% CI. To improve precision, the primary analysis will account for the following patient risk factors as fixed effect covariates: age, sex, comorbidity index, type of hospital admission (medicine, surgery, pregnancy and childbirth, and mental health), and admissions to ICU, using the 2-stage method recommended by Hayes and Moulton [42]. Patient age will be modeled using a restricted cubic spline to allow for the possibility of a nonlinear association. Mean imputation within

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hospitals will be used for missing baseline covariates. The same approach and covariates will be used for primary and secondary outcomes. The 2-stage method will be implemented as follows: (1) a multivariable regression model (logistic regression for binary outcomes and linear regression for length of stay) with the baseline characteristics as covariates but excluding the treatment and cluster indicators will be fit to the individual patient data in period 1 and period 2. Length of stay will be log-transformed prior to analysis. We will use each regression model to obtain predicted probabilities for each binary outcome and predicted length of stay for each patient. (2) For binary outcomes, we will calculate the expected number of events by summing the predicted probabilities across all patients in that cluster period; for length of stay, we will obtain the expected mean length of stay by averaging across all patients in that cluster period. (3) We will obtain residuals for binary outcomes by calculating the observed number of events minus the expected number of events divided by the number of patients in the cluster, and for length of stay by calculating the observed mean minus the expected mean. To estimate the treatment effect, the cluster-level method described above will then be applied to the residuals. Estimated intracluster correlation coefficients will also be reported [33]. The data presentation is indicated in Table 4.

Table 4. Study outcomes.

	Normal saline (control; n=XXX)	Ringer's lactate (treatment; n=XXX)	Absolute difference (95% CI)	*P* value
Primary outcome, n (%)				
Composite of death and hospital readmission within 90 days of index admission				
Secondary outcomes, n (%)				
Death within 90 days of index admission				
Readmission to the hospital within 90 days of index admission				
New dialysis within 90 days of index admission				
Requirement for postoperative intubation in the postoperative assessment unit				
Requirement for reoperation within 90 days of index admission				
ED[a] visit within 90 days within 90 days of index admission				
Hospital length of stay, median (IQR)				
Discharge to a facility other than home				

[a]ED: emergency department.

Subgroup Analyses

The primary outcome will be analyzed within the following subgroups of patients who are at a higher risk for exposure to fluids and with greater risk profiles and or severity of illness than other patients. These include age (<18, 18 to ≤65, 66 to ≤80, and >80 years); sex; type of hospital admission (medical, surgical, pregnancy and childbirth, mental health); elective and urgent or emergent surgical admissions, surgical admissions <24 hours, surgical subgroups (as described in Table 3); admission to ICU, infection alone and infection and organ dysfunction, infection alone and infection and organ dysfunction and ICU admission, trauma with injury severity score (ISS) ≥12, trauma with ISS=12 and ICU admission, traumatic brain injury, traumatic brain injury and ICU admission, and comorbidity index (Elixhauser) [43]. These subgroup analyses will be implemented without covariate adjustment and using the cluster-level summary method as described for the primary and secondary outcomes but applied to subgroup differences within each cluster. Results will be presented using forest plots.

Sensitivity Analyses

Testing for carryover effects will not be carried out as the risks of carryover were minimized in the design by allowing for a wash-out period to allow most patients admitted in the first period to complete their hospitalization before the hospital crosses over and by only considering index hospitalizations.

Sensitivity analyses for primary and secondary outcomes will exclude patients who are extremely unlikely to receive the study fluids (direct hospital admissions to psychiatry), those who are otherwise healthy (patients who have vaginal and cesarean births and elective surgical admissions <24 hours), and those who may have been exposed to both types of study fluids (lengths of stay spanning both FLUID study periods).

Cost-Effectiveness Analyses

We will conduct a cost-effectiveness analysis of RL and NS from the perspective of the Canadian public health care payer using a hybrid decision tree and Markov models. A decision tree with a 90-day time horizon will be used to determine the effects of each fluid on mortality, requirement for dialysis, and health system costs. Baseline characteristics will be based on

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the concurrent trial. Surviving patients will enter a Markov component of the model [44] in which outcomes and costs will be modeled in annual cycles for the remainder of the patient's lifespan. Based on close consultations with coinvestigators, the model structure will incorporate the long-term consequences of fluid therapy; potential health stats may include dialysis-free, dialysis, and death. In each Markov cycle patients could remain in their existing health state, progress to the more severe state, or die. Transition probabilities between health states will be obtained from the concurrent trial and utility values will be derived from the published literature. Direct health care costs, such as physician costs and dialysis costs, will be derived from provincial health administrative data available at ICES and from publicly available sources in Canada.

The model outcomes will include incremental cost per one death averted and incremental cost per one QALY gained. An annual discount rate of 1.5% will be applied to both costs and health outcomes, as recommended by Canada's economic evaluation guideline [45]. Scenario analyses will be conducted to assess the impact of structural uncertainty and the uncertainty associated with model assumptions on cost-effectiveness results. The model will be fully probabilistic and address parameter uncertainty.

Missing Data

The prevalence of missing data is expected to be minimal as outcomes will be obtained from ICES. Nevertheless, missing data for each outcome will be summarized by the treatment group. If substantial missingness is observed (>10%), sensitivity to missing data will be examined under a range of missing-not-at-random scenarios by assuming first that all patients with missing outcomes had the event of interest and then that all patients with missing outcomes did not have the event of interest.

Statistical Software

The statistical analyses will be performed with SAS (version 9.4; SAS Institute) and R (R Foundation for Statistical Computing).

Dissemination of Findings

Guided by a theory and evidence-informed dissemination planning guide [46], the plan will be guided by the dissemination objective, knowledge of user audiences, dissemination strategies targeted to the audience, and the expertise required to deliver the strategies and required resources. Knowledge user audiences will certainly include health policy leads, health system managers, clinicians, patients and caregivers, and researchers. Depending on the magnitude, strength, and nature of the findings, the dissemination goals could range from increasing awareness of the findings by interested parties to influencing hospital policy and physician prescribing practices at the provincial, national, and international levels. To reach researchers and clinicians, we plan rapid open access publication of our study results in a high-impact journal. We will hold webinars to present and discuss our study results with hospital administrators and clinicians in Ontario. We will reach out to local and provincial social media and traditional media to inform the public, patients, and caregivers about our study findings. If RL is found to be superior to NS, then we will have a particular dissemination focus on health policy and decision-makers to encourage the switch to use these fluids in Ontario hospitals. Finally, we will communicate and present our study findings to the Council of Academic Hospitals of Ontario and plan to host meetings targeted toward health policy decision-makers and high-level hospital administrators (chief executive officers) around the province of Ontario.

Ethical Considerations

The FLUID Trial was approved at all participating sites through Clinical Trials Ontario (#0778) and the Queensway Carleton Hospital Research Ethics Board (#16-05). Waivers of patient consent were obtained to receive the study intervention and for data collection from ICES, as the risks of study participation are minimal, and requiring informed consent would render the study infeasible.

Results

At the time of this submission, a total of 7 centers have completed recruitment into FLUID. The statistical analysis plan has been prepared "a priori" in advance of receipt of the trial data set from ICES and any analyses.

Discussion

The results of this trial will determine whether a hospital-wide policy of stocking predominantly NS versus RL reduces the composite of death and readmission to hospital, as well as other adverse secondary outcomes. We provide a detailed statistical analysis plan which will reduce the risk of data-driven approaches and biased interpretation and increase the transparency of our analyses and results.

There are several challenges related to the design and conduct of the large FLUID trial. These include a risk of study fluid contamination due to a lack of awareness of FLUID, noncompliance to the study protocol, and carryover due to the crossover design. Hence, our team first conducted the FLUID pilot trial in advance of the large trial with the aim of evaluating strategies to address these challenges [29]. In the pilot study, we developed extensive center-specific communication plans for multiple stakeholder groups (eg, chief executive officers, hospital administrators, clinical managers, physicians, nurses, trainees, and logistical services) for implementation in the large trial. To maximize compliance with the study fluid, we implemented (1) an automatic substitution order during the trial study periods for both paper and electronic orders with an override if the treating physician indicates "no substitution" in the physicians' orders, (2) the hospital ward shelves were stocked with at least 80% study fluid for the duration of the study periods, (3) bright signage prominently placed where NS and RL are stored to help remind nurses about the automatic substitution, and (4) to have the other resuscitation crystalloid fluid available only in small quantities on the clinical shelves. The risk of carryover (effect of study fluid on patients included in study period 1 carrying over to study period 2) is minimized as the vast majority of patients will be different in each study period. The median length of hospital stay is 2 days (10th and

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90th percentile 1 and 5.2 days; data derived from FLUID-eligible sites using ICES data); the majority of administered crystalloid resuscitation fluids occur during the first few days of hospital admission; and only index admissions will be included. Furthermore, a 2-week run-out between study period 1 and the end of study period 2 will minimize the occurrence of patients being exposed to 2 different kinds of fluids during the same hospitalization.

Conclusions

We describe the protocol and statistical analysis plan for the evaluation of primary and secondary outcomes for the FLUID trial. FLUID will determine whether RL as compared with NS reduces death or requirement for hospital readmission by an absolute difference of 1%. In contrast to trials that have generated evidence in specific populations with fluid interventions limited to geographic locations in the hospital (ICU, ED), the results of FLUID will apply broadly to patients who are admitted throughout the hospital. As such, FLUID will provide important evidence-based guidance at the hospital and system level as to what fluids could be predominantly stocked for use throughout the hospital and the associated health care resources required for such supply.

The results of FLUID will help define clinical practice for physicians who care for patients admitted to the hospital regardless of whether differences between the 2 fluid groups in the proposed clinical outcomes are found. The question of the selection of optimal crystalloid fluid is, as evidenced by contemporaneous studies on this theme, an international one, and the results of FLUID will impact hospital management practices around the world. Should FLUID reveal a difference in clinical outcomes for patients, reflected in lives saved and hospital admissions avoided, then one fluid will become the dominant fluid stocked in centers; it may also result in significant savings to the health care system through bulk purchasing of one type of fluid. If no differences are found, then the less expensive crystalloid fluid may become the dominant fluid stocked in centers.

Acknowledgments

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Data Availability

The data sets generated or analyzed during this study will not be publicly available as this trial used exclusively health administrative data provided by ICES in the province of Ontario, Canada. The data sets generated and analyzed during the study are not publicly available to protect study participant privacy.

Authors' Contributions

JFS drafted the manuscript for this paper in close collaboration with LAM, MT, TM, and YO. All authors made substantial contributions to the development of the manuscript and approved the final version of the manuscript. LAM, MT, and DAF are the principal coinvestigators. MT is the senior statistician. YO is the trial statistician.

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT Checklist.
[DOCX File , 39 KB - resprot_v12i1e51783_app1.docx]

Multimedia Appendix 2
Statistical Analysis Plan (SAP) Checklist.
[DOCX File , 26 KB - resprot_v12i1e51783_app2.docx]

Multimedia Appendix 3
PRECIS-2 Table and Wheel.
[DOCX File , 153 KB - resprot_v12i1e51783_app3.docx]

Multimedia Appendix 4
CIHR Peer-review Report.

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[PDF File (Adobe PDF File), 21 KB - resprot_v12i1e51783_app4.pdf]

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Abbreviations

BASICS: Balanced Solution versus Saline in Intensive Care Study
CONSORT: Consolidated Standards of Reporting Trials
DAD: Discharge Abstract Database
ED: emergency department
ICU: intensive care unit
ISS: injury severity score
NS: normal saline
PLUS: Plasma-Lyte 148 versus Saline
QALY: quality-adjusted life year
RL: Ringer's Lactate
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Protocol

Immunological Responses of Arsenicum album 30CH to Combat COVID-19: Protocol for a Double-Blind, Randomized, Placebo-Controlled Clinical Trial in the Pathanamthitta District of Kerala

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Abstract

Background: COVID-19 is a recent major public health concern caused by the SARS-CoV-2 virus, with approximately 44.6 million COVID-19–positive cases and 530,000 deaths in India (as of February 1, 2023). The COVID-19 vaccination drive in India was initiated in January 2021; however, an effective preventive strategy with high efficacy and immunological safety remains elusive.

Objective: The aim of this study is to assess the immunogenic responses of *Arsenicum album* 30CH (AA30CH) as COVID-19 prophylaxis, including assessment of immunological markers, innate and acquired immune responses, COVID-19 symptoms, and its associated antibody responses.

Methods: This randomized controlled clinical trial (RCT) will include two parallel comparator groups of AA30CH and placebo with an allocation ratio of 1:1 conducted in the Pathanamthitta district of Kerala, India. The placebo or AA30CH will be administered in three intervention schedules and blood samples will be collected before and after each of the intervention schedules. Based on the inclusion and exclusion criteria, 112 participants per arm (with an expected dropout of 20%) will be screened. Immunogenic responses will be evaluated by determining the antigen density and modulation in immunological markers and lymphocyte subsets CD3, CD4, CD8, CD24, CD27, CD38, CD4 interferon-γ, CD4 CD17, CD4 CD25 (activated T lymphocytes), T cells, B cells, dendritic cells (mature and immature), and natural killer cells on days 1, 5, 23,27, 45, 49, and 66. The innate and acquired immune responses will also be evaluated by a real-time reverse-transcriptase polymerase chain reaction (RT-PCR) array profiler (84-gene set) before and after the study interventions. The toxicity status of AA30CH in study participants will be evaluated through hepatic, renal, and hematological parameters and peripheral smears on days 1, 5, 23, 27, 45, 49, and 66. The number of participants developing COVID-19–like symptoms per National Centre for Disease Control guidelines and the number of participants testing positive for COVID-19 in RT-PCR during follow-ups in any of the three intervention schedules will be identified. Moreover, a subgroup analysis will be used to assess the COVID-19 antibody responses between vaccinated and unvaccinated participants.

Results: This RCT protocol has been approved by various committees and funded by the Central Council for Research in Homoeopathy, Ministry of Ayush, Government of India. The project has been implemented in collaboration with the Department of Homoeopathy, Government of Kerala. The RCT was rolled out on January 25, 2023, and enrollment was completed April 3, 2023. The immunological assays will be conducted at the Department of Biotechnology-Translational Health Science and Technology Institute, Faridabad, India.

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Conclusions: This study will represent the first evaluation of the immunological efficacy and safety of AA30CH in an RCT, which may significantly impact the use of homeopathy as an evidence-based medicine approach.

Trial Registration: Clinical Trials Registry-India CTRI/2022/08/045089; https://tinyurl.com/mryrpkvk

International Registered Report Identifier (IRRID): DERR1-10.2196/48479

(JMIR Res Protoc 2023;12:e48479) doi:10.2196/48479

KEYWORDS

COVID-19; Arsenicum album 30CH; randomized controlled trial; Pathanamthitta; immunology

Introduction

COVID-19 infection caused by SARS-CoV-2 is a recent major public health burden leading to clusters of mild to moderate respiratory illnesses. COVID-19 became a pandemic affecting more than 200 countries worldwide owing to its high infectivity [1,2]. COVID-19 infection is accompanied by an aggressive inflammatory response that releases several proinflammatory cytokines [3,4]. The host immune response to the SARS-CoV-2 virus is hyperactive, resulting in an excessive inflammatory reaction [5]. The incubation period of COVID-19 was reported to be 2-14 days [6,7]. It is currently believed that SARS-CoV-2 is most likely of zoonotic origin [8-10] and transmits from person to person by infected droplets, with more severe infections mainly found in older people and those suffering from comorbidities [11,12].

The World Health Organization (WHO) dashboard of COVID-19 reported approximately 753,479,439 confirmed cases of COVID-19, including 6,812,798 confirmed deaths (as of January 31, 2023) globally. The United States has been declared the country with the highest number of cases, followed by China, India, France, Germany, Brazil, Japan, the Republic of Korea, Italy, the United Kingdom, the Russian Federation, Turkey, and Spain, respectively (as of January 31, 2023) [13]. As per official reports of the Government of India, the country reported 44,682,895 COVID-19–positive cases with 530,740 deaths as of February 1, 2023. The Indian states of Maharashtra and Kerala reported the highest number of cases. Maximum deaths were reported in the second wave of COVID-19, which peaked in May 2021 [14]. The Government of India initiated the COVID-19 vaccination drive in January 2021. Nevertheless, an effective preventive measure needs to be identified with evidence of breakthrough infections and reduced protection against the Delta variant of SARS-CoV-2.

Several therapeutic strategies and clinical evaluations are ongoing to combat SARS-CoV-2 infection; however, no effective treatment has been developed with immunological safety. The WHO initiated a large global, randomized clinical study on four therapies (remdesivir, hydroxychloroquine, lopinavir/ritonavir, and interferon [IFN] therapy), showing that all four therapies had little or no influence on overall mortality, ventilation initiation, or hospital stay for hospitalized patients [15]. Furthermore, the usage of antibiotics in patients with COVID-19 raises the risk of harmful consequences such as antibiotic resistance [16,17].

Homeopathy has been vital in preventing epidemics, especially before modern sanitation, antibiotics, and vaccinations [18]. Homeopathy has also displayed effectiveness in combating many outbreaks in its history of 200 years, such as scarlet fever in 1799 [19], leptospirosis in 2007 [20], and dengue fever in 2018 [21,22]. Homeopathy has also been successfully documented in the medical literature for both the treatment and prophylactic use of flu-like epidemics such as the “Spanish” flu of 1918 [23], “Asian” flu of 1951 [24], and H_1N_1 influenza pandemic of 2009-2010 [25]. The homeopathic formulation *Arsenicum album* 30CH (AA30CH) was previously reported to be effective in various respiratory diseases such as swine flu, influenza-like illness, and other respiratory illnesses [25-29]. In one study, *Arsenicum album*, as one of the constituents of 7X-24X complex, exhibited nuclear factor-κB hyperactivity according to reduced expression of the reporter gene in green fluorescent protein-transfected HT29 cells and also reduced the release of tumor necrosis factor-α in macrophages [30]. Due to the looming threat of the COVID-19 pandemic and the lack of effective treatments, alternative preventive strategies need to be established.

During the pandemic, AA30CH was advised as a preventative medicine for COVID-19 by the Ministry of Ayush, Government of India, toward the end of January 2020 [31]. A subsequent advisory issued by the Ministry of Ayush on March 6, 2020, also mentions the immunomodulatory action of AA30CH [32]. However, the exact role of AA30CH in innate immunity against COVID-19 was not fully understood. The observation that individuals with underlying diseases are more susceptible to severe illness than healthy people or young children is mainly attributed to the low efficacy of the innate immune response [33]. Therefore, the aim of this study is to investigate the cellular pathways related to innate and adaptive responses to AA30CH using flow cytometry–based immunological assays and gene expression analysis of 84 vital genes with a real-time reverse transcription-polymerase chain reaction (RT-PCR) array profiler. This PCR array profiler includes genes related to the interleukin-1 receptor (IL-1R) and Toll-like receptor (TLR) signaling pathways, including IL-1R and TLR genes involved in the sensing of pathogens. Genes related to host defense are also represented in this array, including the acute-phase response, complement activation, the inflammatory response, and the antiviral humoral response.

Moreover, gene expression profiling of human natural killer (NK) cell responses will also be investigated. This randomized controlled clinical trial (RCT) is being conducted by the Central Council for Research in Homoeopathy (CCRH), an apex research body under the Ministry of Ayush, Government of India, in the Pathanamthitta district of Kerala state, in close collaboration with the District Medical Office (under the

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Department of Homoeopathy, Government of Kerala) after signing an agreement with the Government of Kerala. The CCRH also signed a Memorandum of Understanding with the Department of Biotechnology-Translational Health Science and Technology Institute (DBT-THSTI), Faridabad, a Coalition for Epidemic Preparedness Initiative–approved laboratory facility under the Government of India for conducting the immunological assays as part of the primary objective of the study.

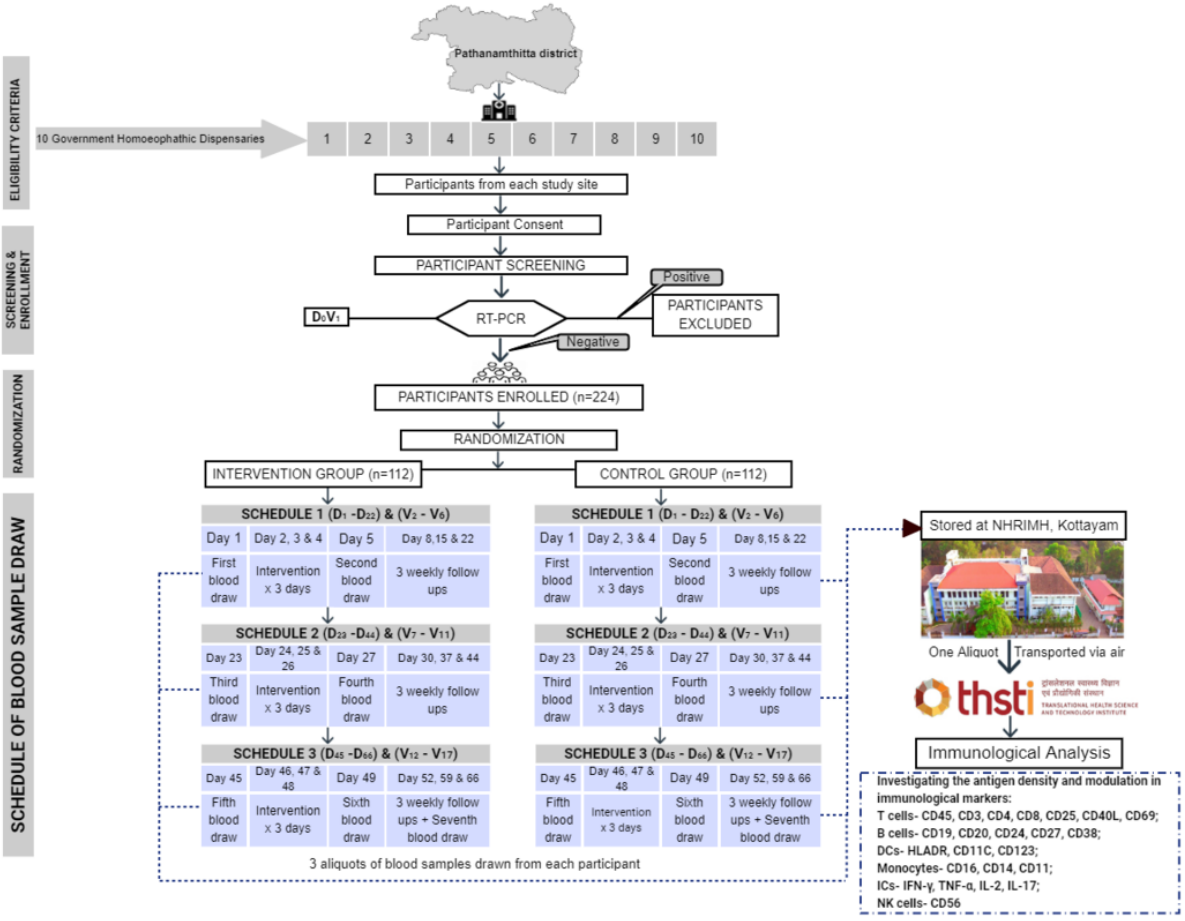
The primary objectives of the study are to elucidate the immunogenic responses of AA30CH in COVID-19 prophylaxis by determining the antigen density and identifying the variation in immunological markers and lymphocyte subsets CD3, CD4, CD8, CD24, CD27, CD-38, CD4 IFN-γ, CD4 CD17, CD4 CD25 (activated T lymphocytes), T cells, B cells, dendritic cells (DCs; mature and immature), and NK cells; and to estimate the innate and acquired immune responses by real-time RT-PCR array analysis (see Multimedia Appendix 1). The secondary objectives of the study are the toxicological evaluation in study participants who took either a placebo or AA30CH, limited to hepatic, renal, and hematological parameters, by conducting liver function tests (LFTs), renal function tests (RFTs), complete blood count (CBC), and peripheral smear; to identify the number of participants developing COVID-19–like symptoms as per National Centre for Disease Control (NCDC) guidelines during follow-ups in any of the three intervention schedules; to identify the number of participants testing positive for COVID-19 in RT-PCR during follow-ups in any of the three intervention schedules; and to determine the COVID-19 antibody responses between vaccinated and unvaccinated participants.

Methods

Study Design

This clinical trial is designed as a randomized, double-blind, placebo-controlled clinical study with two parallel comparator arms of AA30CH and placebo, using an allocation ratio of 1:1. The participants will be enrolled and randomized only after two phases of initial screening (screenings I and II), followed by three schedules of intervention and follow-ups in the intervention phase of 66 days. The flow chart of the study design is represented in Figure 1. The protocol is reported following the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2013 guidelines.

Figure 1. Flow diagram of the screening and randomization of the participants. D: day; DC: dendritic cell; IFN: interferon; IL: interleukin; NK: natural killer; NHRIMH: National Homoeopathy Research Institute in Mental Health; RT-PCR: reverse transcription-polymerase chain reaction; TNF: tumor necrosis factor; V: visit.



Study Setting

This RCT will be implemented in the 10 government homeopathic dispensaries/hospitals located in 10 different panchayats of the state of Kerala in India, identified by the District Medical Officer (Pathanamthitta District), Department of Homoeopathy, Government of Kerala, based on the higher incidence of COVID-19 and elevated test positivity rate (TPR).

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These identified study sites are: (1) Government Homoeopathic Dispensary, Elanthoor panchayat; (2) Government Homoeopathic Dispensary, Naranganam panchayat; (3) Government Homoeopathic Dispensary, Kulanada panchayat; (4) Government Homoeopathic Dispensary, Pandalam panchayat; (5) Government Homoeopathic Dispensary, Ezhamkulam panchayat; (6) Government Homoeopathic Dispensary, Puthusserimala Ranni panchayat; (7) Government Homoeopathic Dispensary, Mezhuveli panchayat; (8) Ayush Primary Health Centre Homoeopathy (under National Health Mission, Government of India), Ranni Angadi panchayat; (9) Government Homoeopathic Dispensary, Ayush Health and Wellness Center, Kuttappuzha panchayat; and (10) Government Homoeopathic Hospital, Kottanad panchayat. The National Homoeopathy Research Institute in Mental Health (NHRIMH), located in the Kottayam district of Kerala state under the CCRH, Government of India, is designated as the facilitating institute of the study with prior approvals, and two nodal site principal investigators (PIs) and supporting team will operate from the NHRIMH during the RCT. The PI will form monitoring teams who will visit the 10 study sites on all blood draws and on intervention days of the trial and report to the competent authorities in real time.

Eligibility Criteria

Inclusion Criteria

Apparently healthy male and female participants, aged 18-60 years, residents of the Pathanamthitta district of Kerala, with negative COVID-19 RT-PCR test reports at least 48 hours before the first day of the intervention, and those who have not taken *Arsenicum album* medicine in any homeopathic potencies in the past 4 months will be included in the study; both COVID-19 vaccinated and unvaccinated participants will be eligible for inclusion.

Exclusion Criteria

Participants with a positive COVID-19 RT-PCR test report at least 48 hours before the first day of the intervention; those with history of severe viral diseases in the past 3 months, such as herpes zoster, dengue, chikungunya, and chicken pox; those having a history of chronic respiratory ailments with shortness of breath as a recurring symptom; and those taking concomitant medications such as immunosuppressants, hormonal therapies, or Ayush therapies for chronic ailments will be excluded from the study.

Sample Size

The study is aimed at evaluating the immunologic responses of AA30CH. The study is based on earlier encouraging leads provided through community studies on the role of AA30CH in preventing COVID-19. Several parameters are in consideration for the evaluation of immunogenic responses. With regard to the computation of sample size, based on the literature and expert opinions, it is proposed to consider some limited immunologic parameters that are more relevant. Owing to the scarce availability of literature, it would be quite challenging to hypothesize the assumption. Assuming a type 1 error of 5% and a power of 80%, it was estimated that there would be 93 participants each in the intervention and control groups, with a total of 186 participants. This could be escalated based on attrition due to loss in follow-up. If this loss to follow-up is considered at 20%, a total of 112 participants have to be enrolled in each group, with a total sample of 224 that would need to be recruited for the study.

Randomization and Blinding

The study participants will be recruited from 10 preidentified study sites in the Pathanamthitta district of Kerala. Recruitment will be achieved according to the study inclusion criteria and based on the initial and final screening. The participants will be allocated to either intervention or placebo groups as per the randomization sequence generated using PASS 2021 (v21.03) software. Prenumbered or coded identical containers will be used for allocation concealment. The PI at CCRH headquarters will be involved in the sequence generation process and allocation concealment procedure. The PI will label the interventions as per the randomization codes, which will be handed over to the site PIs. The site PIs will enroll participants and randomly assign participants to interventions. The trial participants and the site PIs assigning participants to interventions will be blinded. To ensure blinding quality, the packaging for both the intervention and placebo will be identical in shape, color, size, taste, and odor. The unblinding will be done only at the end of the study by the PI at CCRH headquarters. If the participants reported severe adverse events (SAEs) during the trial, unblinding may be performed per Data and Safety Monitoring Board (DSMB) or ethical committee recommendations. The reason for urgent unblinding should be well-documented.

Pretrial Preparation

The selection of 10 homeopathic dispensaries was based on the COVID-19 incidences and TPR in the Pathanamthitta district. The CCRH conducted a preliminary short survey to identify these 10 sites. Following Central Ethics Committee approval, the clinical trial was registered in the Clinical Trials Registry-India (CTRI) under registration number CTRI/2022/08/045089 (August 30, 2022). An Indian Council of Medical Research–approved and National Accreditation Board for Testing and Calibration Laboratories–accredited laboratory was engaged for RT-PCR screening, hematology, clinical biochemistry, and peripheral blood mononuclear cells (PBMCs) isolation. The isolated PBMC samples for conducting immunological assays will be stored in a –80°C freezer located at the central laboratory facility in the facilitating institute of the RCT. The isolated PBMC samples will be transported to the DBT-THSTI in batches for the immunological assays. The blood samples collected from the study participants will also be used to evaluate the safety profile of the drug, mainly in terms of hematology parameters, liver function, and renal function. Training will be administered to the laboratory staff for the procedures of PBMC isolation. A mock drill will also be conducted at one of the study sites to identify the practical difficulties encountered during the screening, participant recruitment, sample collection, and storage procedures (no participant recruitment will be allowed with the mock drill). All site PIs in the 10 sites will be included in the mock drill for the practical demonstration of handling the samples and to

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streamline the logistics involved in the sample transportation and PBMC isolation procedures until storage in the –80°C freezer. Detailed standard operating procedures for the procedures and data collection, case record forms (CRFs), and screening forms were designed and printed as individual booklets.

Screening and Enrollment

All the participants will be voluntarily invited to the study and then required to sign an informed consent form containing information on the regulatory authorities and related procedures, including initial RT-PCR screening, laboratory screening, and subsequent randomization after enrollment. The RT-PCR test will screen the participants fulfilling the eligibility criteria for an ongoing COVID-19 infection. If the RT-PCR test result is found to be negative for COVID-19, the participant will be investigated for an initial (baseline) LFT, RFT, CBC, and peripheral blood smear as part of the second screening for any abnormal parameters. Those with borderline elevated or normal values will be enrolled in the trial, followed by randomization. Screened participants with positive RT-PCR reports for COVID-19 will be notified to the local health authorities. Their health status will be telephonically monitored during quarantine or hospital stay by the site PI. Each study site will maintain a log register that records all details of the screened participants and the reason(s) for exclusion. Enrolled participants will then be randomized and allocated to the intervention or the placebo arm as per the generated randomization sequence using PASS software version 21.03.

Assessment, Data Analysis, and Manuscript Preparation

The laboratory parameters recorded during the seven blood draws of each participant will be analyzed for any statistically significant changes using appropriate statistical tests. The PBMCs isolated during the seven blood draws and stored in the –80°C freezer will be transported as air freight in liquid nitrogen tankers to DBT-THSTI, Faridabad, for immunological assays and data analysis. The interim reports will be confidentially submitted to the designated DSMB, internal committees of CCRH, and Ministry of Ayush, Government of India, on availability as per requirements. Manuscripts with the study findings will be prepared and submitted to Scopus-indexed peer-reviewed journals. Patents pertaining to this RCT will be filed as per the directions of the Ministry of Ayush, Government of India.

Dropout, Withdrawal, and Suspension Criteria

Dropout Criteria

Participants who develop SAEs will be withdrawn from the RCT after reporting to the Institutional Ethics Committee. Participants who develop concomitant diseases of viral origin during the trial that would affect the efficacy and safety assessment intervention, participants with poor compliance, those changing the intervention or adding therapy prohibited under the study for any reason, breaking the double-blind setting of the clinical trial, and those found to have any serious violations of the inclusion/exclusion criteria after enrollment will be withdrawn from the study.

Voluntary Withdrawal of Participants

The participant can become unwilling/unable to continue in the RCT and request the site PI to withdraw them from the RCT; other participants who stop visiting even after prompt reminders by the site PI will be withdrawn from the study. Every participant can withdraw from the trial anytime for any reason and without prejudice. Any participant who withdraws from the trial shall undergo a complete final examination, if possible, or at least a last telephonic interview at the time of withdrawal from the study about the state of their health by the investigator, and if necessary, from the point of view of drug safety and the validity of study results. The reason for the withdrawal will be recorded in the Participant Off Study form of the CRF.

Conditions for Trial Suspension

If any SAE occurs during the study, the trial will be terminated immediately as per recommendations of the DSMB and Ethics Committee. If there is a major error in the trial or a serious protocol deviation during implementation, which would make it difficult to evaluate the drug efficacy and safety, the trial will be stopped. The trial will also be terminated if the funding agency or collaborating institution requests to stop the trial or if the regulatory authority cancels the trial. The Council is entitled to terminate the trial prematurely at any time for medical and/or organizational reasons. This decision will generally be made based on the recommendations of the Scientific Advisory Board, CCRH, New Delhi, or the Director of Homoeopathy, Government of Kerala.

Intervention Procedure

Preparation of Study Intervention and Placebo Materials

AA30CH will be prepared at Dr Willmar Schwabe India Pvt Ltd, Noida, Uttar Pradesh, India (a licensed homeopathic drugs manufacturing company complying with Good Manufacturing Practice standards in India) as per the Homoeopathic Pharmacopoeia of India standards, using the active component of *Arsenicum album* in a fine powder mixed with glycerin, purified water, and pharmaceutical-grade ethanol following standard homeopathic drug manufacturing protocols approved by drug licensing authorities in India. The placebo (30CH) will be identically prepared using only glycerin, purified water, and pharmaceutical-grade ethanol, without the medicinal active component (*Arsenicum album*).

Interventions in Each Group

Following the second screening, participants with normal or borderline elevated values will be allocated to intervention and placebo arms as per the randomization sequence generated using the software PASS 2021 (v21.03). The intervention period for both groups consists of three schedules of 21 days each, with a total trial period of 66 days, including intervention, blood sample collection before and after the intervention, and three weekly telephonic follow-ups in each of the schedules. The sealed bottles of AA30CH and placebo 30CH dilutions will be opened at the in-house pharmacy of NHRIMH, Kottayam, under the supervision of the PI and the pharmacy in charge. Following standard pharmacy practice, these dilutions will further be used (approximately nine drops) for medicating one-grain lactose/sucrose (inert nonmedicated) tablets. Participants will

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be administered either the homeopathic medicine AA30CH or placebo as per the randomization sequence in three doses of single tablets orally for each of the 3 consecutive days of the 21-day schedule. Each of the three intervention schedules will be preceded and followed by a blood draw of the participants. The administered dose will be recorded in the Drug Dispensation Log of the CRF.

Criteria for Discontinuing or Modifying Allocated Interventions

All participants shall be advised to telephonically inform the site PI if they develop symptoms similar to COVID-19 infection. If any participant reports symptoms, the intervention shall be stopped, and if testing positive for COVID-19 in RT-PCR, the local health authorities will be informed by the site PI. Study participants shall be advised to take the treatment of their choice from the dispensary at the study site through teleconsultation or from other medical facilities nearby. In case of requirement, the study participants will also be provided support through an already allocated medical health insurance policy (valid for 1 year) for their hospitalizations or other related treatments. They shall be under observation in this study until their recovery from the symptoms and may report any events that may be an SAE. The site PI will record the days to recovery, disease stage, and severity of symptoms, among other clinical data. The details of treatment and progress will be acquired from family members or the participants themselves, which may be recorded in the follow-up and participant study forms in the CRF. A COVID-19–positive status with the intervention or placebo will be considered as the study endpoint for participants with a positive test result on RT-PCR.

Strategies to Improve Adherence to Intervention Protocols and Procedures for Monitoring Adherence

The participants must visit the study site for the 3 days of the intervention at each schedule. To ensure compliance, the independent dispenser will only administer the medicine and placebo to the participants at the prescribed dosage. The intervention procedure will be under the supervision of the site PI to ensure adherence. Any deviation in these procedures will be recorded in the Deviation/Unanticipated Problem Tracking Log of the CRF. Participants will be under observation of the site PI at the study site for at least 1 hour to monitor for any immediate drug-related adverse effects, which will be recorded and informed to the PI. If the participant feels any discomfort, they will be medically examined by the site PI. Vital parameters such as heart rate, respiratory rate, and blood pressure will be monitored and recorded. In case of any SAE, the participant will be referred to a tertiary-care facility after receiving appropriate first aid at the site by the site PI. The DSMB and Ethics Committee will be duly informed about these events. Blood samples will be drawn and stored 1 day before and after 3 days of the intervention and on the last day of the study by the designated laboratory involved in sample collection and storage. During each visit, participants will be compensated for travel from their home to the study site and provided with protein-based refreshments to minimize their difficulty at each visit to the study site, thereby improving adherence.

Relevant Concomitant Care and Interventions Permitted or Prohibited During the Trial

Any medical problem a participant faces during the trial period will be informed to and managed by the site PI of the study site appropriately and documented and reported to the PI. The administration of vaccinations is not permitted during the study duration as it would interfere with the study results. If a participant is taking immunosuppressants, hormonal therapies, or any other Ayush therapies for chronic ailments, they will be considered a dropout. If the participant reports the intake of any other concomitant medications not specified in the exclusion criteria, the same may be documented in the Concomitant Medication Log of the CRF.

Outcome Measures

The primary outcome measures of the study are the estimation of antigen density and modulation in immunological markers (CD3, CD4, CD8, CD24, CD27, CD38, CD4 IFN-γ, CD4 CD17, CD4 CD25 [activated T lymphocytes], T cells, B cells, DCs [mature and immature], and NK cells) observed from the blood sample drawn 1 day before and after 3 days of the intervention (ie, on days 1, 5, 23,27, 45, and 49) and at the end of the study (day 66), along with the innate and acquired immune responses from the blood sample drawn on days 1, 23, 45, and 66 of the study interventions.

The secondary outcome measures of the study are to evaluate the toxicity status of study participants who have taken AA30CH or placebo based on hepatic, renal, and hematological parameters and peripheral smears 1 day before and after 3 days of the intervention (ie, on days 1, 5, 23, 27, 45, and 49) and at the end of the study (day 66); the number of participants developing COVID-19–like symptoms as per NCDC guidelines during follow-ups in any of the three intervention schedules; and the number of participants with COVID-19–like symptoms who test positive for RT-PCR during follow-ups in any of the three intervention schedules.

Participant Timeline

The study consists of three schedules of 21 days each. Each participant will have seven blood draw visits (V2, V6, V7, V11, V12, V16, and V17) during the study period. The blood samples will be drawn for conducting LFTs, RFTs, CBC, and peripheral smears 1 day before and after 3 days of the intervention (ie, on days 1, 5, 23, 27, 45, and 49) and at the end of the study (day 66) (Table 1, Figure 2).

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Table 1. Participant visits (V) for the three schedules with the telephonic follow-up (T) timeline.

Procedures	Baseline		Schedule 1				Schedule 2				Schedule 3			
	V0	V1	V2	V3-V5	V6	T1-T3	V7	V8-V10	V11	T1-T3	V12	V13-15	V16	T1, T2, V17
Consent	✓													
RT-PCR[a] test		✓												
Enrollment, randomization, and first intervention				✓[b]										
Blood sample collection for immunological assays (PBMCs[c]), innate and acquired immune responses, LFT[d], RFT[e], CBC[f], peripheral smear			✓		✓		✓		✓		✓		✓	✓
Intervention (AA30CH[g] or placebo)				✓				✓				✓		
Follow-ups						✓				✓				✓

[a]RT-PCR: reverse transcription-polymerase chain reaction.

[b]At V3 only.

[c]PBMC: peripheral blood mononuclear cell.

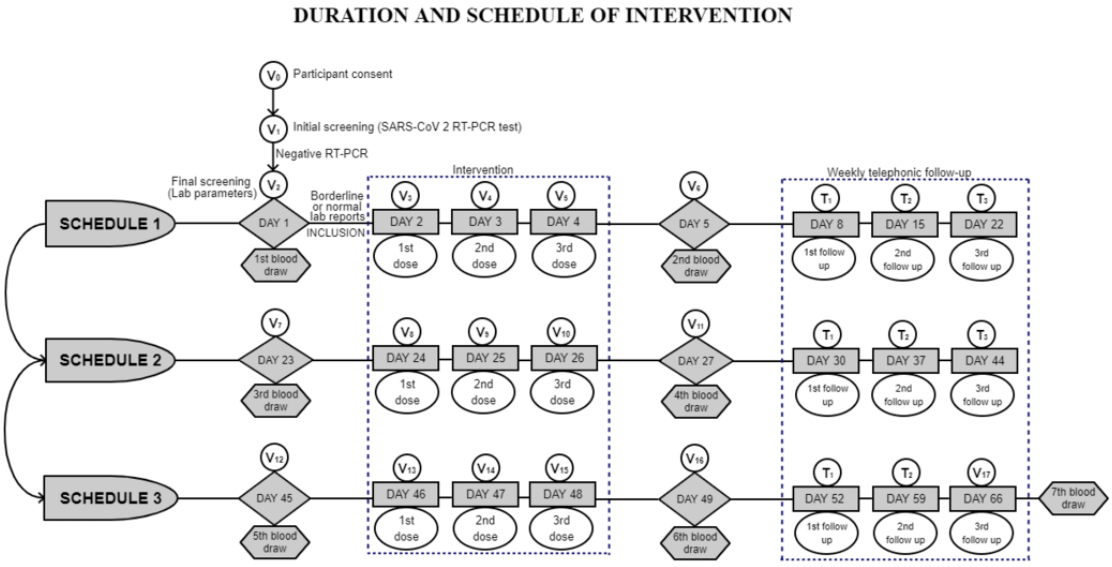
[d]LFT: liver function test.

[e]RFT: renal function test.

[f]CBC: complete blood count.

[g]AA30CH: *Arsenicum album* 30CH.

Figure 2. Flow diagram of three schedules of intervention (21 days each). RT-PCR: reverse transcription-polymerase chain reaction; T: telephonic follow-up; V: visit.



Adverse Events

Any SAE that occurs during and after the study period and is possibly considered due to the study intervention or participation will be recorded and reported immediately to the concerned ethical committee and DSMB.

Data Monitoring and Management

The PI will monitor the study regularly, and site visits/online meetings will be held periodically on intervention and blood draw days. The PI will allocate adequate time for such monitoring activities and ensure that the monitor or other compliance or quality assurance reviewer can access all the study-related documents and study-related facilities (eg, pharmacy, diagnostic laboratory). The original records of participants (including CRFs, consent forms, follow-up forms, and laboratory reports) will be maintained at the study site by the site PI. These records will be reviewed during the scheduled monitoring visits by the PI to ensure compliance. The site PI will be responsible for the completeness and accuracy of the study materials and the nodal site PIs will check these during their visits to the study sites. Any observations/corrective

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measures required will be duly communicated to the site PIs for compliance. These records will be sent to the PI at CCRH headquarters after the completion of the study or as per the requirement of the study. The data of the laboratory parameters that indicate the safety aspects of the drug will be evaluated at the end of each of the three schedules. They will be presented/submitted to the DSMB for their recommendations. The data will be analyzed after completion of the study.

Statistical Analysis

Data analysis will be performed following the intention-to-treat/per-protocol method. The safety and immunological parameters will be analyzed at each of the seven time points and comparisons will be made between the subjects and groups. Additional analyses (eg, subgroup analyses according to age, sex, and perceived risk categories) will also be performed based on the evolving trends from the analysis. A trial statistician will be engaged for the statistical analysis of the clinical trial.

Ethics Considerations

Research Ethics Approval

The Scientific Advisory Board and the Central Ethics Committee of the CCRH have approved the study protocol and the amendments (6-2/2020-2L/CCRH/Tech./27thEC/4656; August 16, 2022). The study will be conducted in accordance with the Declaration of Helsinki and the standards of Good Clinical Practice in India. CCRH will provide insurance cover in the trial for the said study duration, according to the terms finalized under clinical trial cover with the identified insurance firm.

Protocol Amendments

The investigator has to meet the study requirements as specified in the protocol. Protocol amendments are possible only in exceptional cases (eg, where the health or well-being of the participant is affected) and only after approval by the Ethics Committee. Every amendment must be justified in writing and signed by all those concerned. Every amendment will be notified to the CTRI. Circulating protocols will be numbered and their distribution list will be maintained. The PI will update all circulating protocols by adding the amendment.

Informed Consent

Individuals above the age of 18 years will be considered eligible for consent. The site PI will obtain voluntary consent from the participants before the screening test after explaining the study. The participants will be provided with the Participant Information Sheet describing the study details and will voluntarily sign the consent form if they agree to take the intervention. The site PI must also countersign the consent form at each study site.

Confidentiality

The investigator will inform the participants that all trial results recorded will be treated in strict confidence. During documentation and analysis, the participants will only be identified by their subject code and unique identifier number. In contrast, the name of the participant and any personal data of the participants will be stored as per data protection regulations.

Dissemination Policy

The investigators will communicate trial results to participants, health care professionals, the public, and other relevant groups (via publication, reporting in results databases, or other data-sharing arrangements) after the completion of the study. However, no information based on unjustified claims or the findings of interim analysis would be communicated in any form.

Auditing and Inspecting

The PI will permit study-related monitoring, audits, and inspections by the DSMB constituted for the study, Ethical Committee, or government regulatory bodies and make available all study-related documents (eg, source documents, regulatory documents, data collection instruments, study data). The PI will also ensure the capability to inspect applicable study-related facilities (eg, pharmacy, diagnostic laboratory).

Results

The CCRH, Ministry of Ayush, Government of India, funded the project in September 2022. Further, collaborations with the Department of Homoeopathy, Government of Kerala, were initiated, and the study was rolled out on January 25, 2023. As of April 3, 2023, the enrollment has been completed and the immunological assays will be conducted at DBT-THSTI, Faridabad, India.

Discussion

The COVID-19 pandemic has become widespread worldwide and severely impacted the human population. Vaccination efforts have increased exponentially in the past 2 years to protect the vulnerable population, mainly through emergency clearances. According to the vaccine study literature, adverse effects have always been part of mass vaccination strategies across the globe. According to the WHO, in the case of side effects of inactivated virus–based vaccines, the most common local and systemic adverse reactions are injection site reactions, fatigue, fever, headache, and allergic dermatitis, which are self-limiting [34,35]. With the emerging evidence of breakthrough infections and reduced protection against the Delta variant of SARS-CoV-2, an effective preventive therapeutic strategy still needs to be identified.

During the COVID-19 pandemic, the homeopathic medicine AA30CH was widely distributed to the 10.6 million Indian population as a prophylactic. The data obtained from 580,000 individuals were analyzed to conclude that preventive consumption significantly reduced the risk of contracting COVID-19 in high-risk groups [26]. A prospective parallel cluster cohort study conducted by Nayak et al [28] reported the protective effect of AA30CH against laboratory-confirmed COVID-19 cases of 74.40%. Interestingly, this study also reported AA30CH treatment as an adjunct to standard treatment in COVID-19 patients [28]; however, the current protocol is the first investigation exploring the immunological efficacy and

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safety of AA30CH in an RCT. Different aspects in clinical trials with homeopathic drugs were previously explored, where the prominence of placebo-controlled RCTs in homeopathy was critically reviewed [1]. The medications used in those RCTs of homeopathy were mostly prepared as per the guidelines laid out in pharmacopoeia of the respective countries; however, several recommendations in the design and conduct of trials on homeopathic medicinal products were recently discussed [2]. In a previously published RCT in homeopathy conducted in France, the intervention was prepared according to the French National Pharmacopoeia standards, where the placebo was identical pillules containing only unmedicated pharmaceutical-grade ethanol [3]. The preparation for both the intervention and placebo in this study will be similar to that adopted in previous studies; however, we will adhere to the standards mentioned in the Homoeopathic Pharmacopoeia of India.

Several previous studies evaluated the immunological responses to COVID-19 infection and the efficacy of vaccine candidates [36,37]. The strategies toward these immunologic responses to develop candidate vaccines were vastly explained [38,39]. Immunological considerations to develop vaccine candidates were reported [40]; however, no such system was established for any alternative system of medicines, especially for homeopathy. This study intends to explicitly reveal the protective effect of AA30CH against COVID-19 by investigating the possible immune mechanisms that might play a role in its prophylactic action. The current protocol represents the first such evaluation, including immunological phenotyping; determining the antigen density; and identifying the variation in immunological markers and lymphocyte subsets CD3, CD4, CD8, CD24, CD27, CD-38, CD4 IFN-γ, CD4 CD17, CD4 CD25 (activated T lymphocytes), T cells, B cells, DCs (mature and immature), and NK cells.

The current protocol also investigates the expression analysis of 84 vital genes of interest related to the cellular pathways associated with innate and adaptive immune responses. This will be studied in detail using a well-established RT-PCR array profiler previously used for several other viruses [41-45]. The array selected for this study includes genes related to the IL-1R and TLR signaling pathways and genes involved in the sensing of pathogens. Genes related to the host defense response are also represented on this array, including the acute-phase response, complement activation, inflammatory responses, and antiviral humoral response. NK cells are reported to be vital to lyse virus-infected cells, thereby controlling the viral infection and cellular damage [38]. This protocol also aims to investigate the expression profiles of vital genes involved in the human NK cell responses, which may further reveal the possible effect of AA30CH on viral sensing and neutralization.

As mainly overseeing the primary objective of immunological efficacy and safety of AA30CH, this study also aims to assess the safety of AA30CH in terms of the results of LFTs, RFTs, CBCs, and peripheral smears between the intervention and placebo groups. Previously, the acute and subacute toxicity of AA30CH were investigated in an animal model and no adverse events or organ-related toxic effects were reported [46]. This study would also evaluate these findings in an RCT, which may support establishing the safety profile of AA30CH that could further open new vistas of research for an effective prophylactic therapy against SARS-CoV2 infection.

The timely, detailed investigation of the immunopharmacology of drug candidates is challenging [47,48]. In searching for therapeutic strategies against the COVID-19 pandemic, these essential investigations may be limited to a preliminary analysis or primary data obtained due to the pressing priority. Based on the objectives, our study is limited to the immunological responses of AA30CH against COVID-19 in healthy individuals; however, when AA30CH is mass distributed in an ongoing COVID-19 transmissible zone, a detailed investigation on the prevalence of COVID-19 incidence may provide more insights into its prophylactic efficacy.

In conclusion, the current RCT primarily emphasizes the immunological efficacy of AA30CH as a COVID-19 prophylaxis. Secondarily, the hematologic, hepatic, and renal toxicity evaluation of AA30CH would provide a comprehensive understanding of its use in healthy individuals; however, further directions on these parameters in comorbid conditions still need investigation.

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Data Availability Statement

No data are associated with the protocol. The details of the protocol can also be accessed from the Clinical Trials Registry-India.

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Authors' Contributions

Conceptualization: PAS and GPS; methodology: PAS and GPS; software: PAS, LK, and JVS; validation: PAS; formal analysis: PAS and GPS; investigation: PAS and GPS; resources: SPA and GPS; data curation: PAS and RTSK; writing: PAS and GPS; writing-review and editing: PAS, LK, JVS, DB, RTSK, and GPS; visualization: PAS and GPS; supervision: GPS, RTSK, KCM, and SK; project administration: PAS, RTSK, KCM, and SK; funding acquisition: PAS and RTSK. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Reverse transcription-polymerase chain reaction array gene list.
[PDF File (Adobe PDF File), 37 KB - resprot_v12i1e48479_app1.pdf]

Multimedia Appendix 2
Peer-review reports from Central Council for Research in Homeopathy.
[PDF File (Adobe PDF File), 3041 KB - resprot_v12i1e48479_app2.pdf]

Multimedia Appendix 3
Peer-review reports from Central Council for Research in Homeopathy.
[PDF File (Adobe PDF File), 2939 KB - resprot_v12i1e48479_app3.pdf]

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Abbreviations

AA30CH: Arsenicum album 30CH
CBC: complete blood count
CCRH: Central Council for Research in Homoeopathy
CRF: case record form
CTRI: Clinical Trials Registry-India
DBT-THSTI: Department of Biotechnology, Translational Health Science and Technology Institute
DC: dendritic cell
DSMB: Data and Safety Monitoring Board
IFN: interferon
IL-1R: interleukin 1 receptor
LFT: liver function test
NCDC: National Centre for Disease Control
NHRIMH: National Homoeopathy Research Institute in Mental Health
NK: natural killer
PBMC: peripheral blood mononuclear cell
PI: principal investigator
RCT: randomized controlled trial
RFT: renal function test
RT-PCR: reverse transcription-polymerase chain reaction
SAE: severe adverse event
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
TLR: Toll-like receptor

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TPR: test positivity rate
WHO: World Health Organization

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Protocol

A Neuro-Influence Experiment to Evaluate the Persuasiveness of Pre-Exposure Prophylaxis Promotion Messages Among Men Who Have Sex With Men: Protocol for a Randomized Controlled Trial

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Abstract

Background: Pre-exposure prophylaxis (PrEP) is recommended by the US Centers for Disease Control and Prevention, but behavioral factors limit uptake, especially among men who have sex with men. A better understanding of how humans cognitively process information may inform health message development to promote PrEP uptake.

Objective: This paper is informed by the neuroscience of persuasion and influence and describes the protocol of a neuro-influence experiment using functional near-infrared spectroscopy (fNIRS) to evaluate the persuasiveness of PrEP promotion messages among men who have sex with men in Baltimore, Maryland.

Methods: We will conduct a randomized controlled trial using fNIRS to measure brain activation among 60 participants viewing PrEP promotion messages either developed through a crowdsourcing open contest implemented by the study team or developed with a traditional social marketing approach. We will evaluate the effectiveness of PrEP promotion messages by assessing brain activation in the regions associated with persuasion and changes in PrEP willingness, behavioral intention, initiation, and action between the 2 groups.

Results: This study is funded by the National Institutes of Health (National Institute of Mental Health: R34MH116725). Participant recruitment and data collection were completed in October 2023. The first results are expected to be submitted for publication in 2024.

Conclusions: In addition to providing insight into the effectiveness of PrEP promotion messages, this study will examine the feasibility, acceptability, and utility of neuroimaging techniques to evaluate PrEP promotion messages for high-risk men who have sex with men. The findings can also demonstrate the utility of fNIRS as a tool for preproduct testing of health campaigns and enable the public health community to deliver more effective messages to improve health outcomes.

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KEYWORDS

HIV; men who have sex with men; neuroimaging; persuasion; PrEP; pre-exposure prophylaxis

Introduction

Background

Pre-exposure prophylaxis (PrEP) is a highly effective HIV prevention drug for decreasing new infections [1]. There has been an increased effort to identify effective health communication strategies for increasing awareness, acceptability, and uptake of PrEP among those most at risk for HIV transmission as an HIV primary prevention tool [2]. Pretesting the effectiveness of health communication materials before large-scale implementation is highly beneficial given the significant expenditures associated with the implementation of a large-scale campaign [3]. However, some research suggests that using traditional methods to select public health campaign messages, such as self-reports, may not always be the best way to predict population-level behavioral change [4,5].

A better understanding of how humans cognitively process information may inform the selection of persuasive messages that are more likely to change attitudes and behaviors. A core foundation of many persuasion theories is that a message must connect to and resonate with an individual's preexisting beliefs, values, and identity. Social judgment theory [6], for example, posits that all individuals have latitudes of acceptance around different attitudes—that is, alternate points of view they are willing to accept. Messages that fall outside this zone, into an individual's latitude of rejection, will elicit counterarguments and will be rejected. Cognitive dissonance theory [7] offers additional insight into this process: individuals will be more likely to adopt messages that are consonant with, or can be incorporated into, their existing beliefs, values, and identity, and more likely to reject messages that are dissonant. Thus, messages that are too discrepant may result in no effect, at best, and a boomerang effect, at worst.

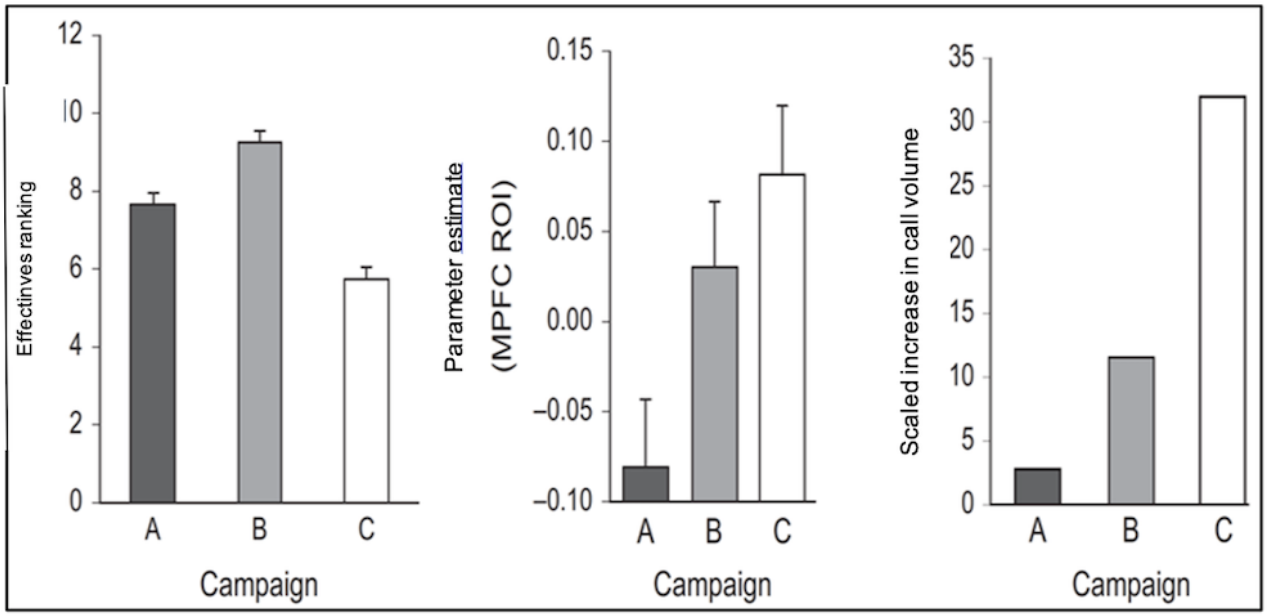
Empirical data on neural correlates of persuasion suggest that neuroscience may be significantly more reliable than traditional methods for understanding persuasion and behavior change [5,8,9]. A systematic review identified 20 studies that provided evidence of persuasive processing and outcomes of health communication messages using neurocognitive measures across different health behaviors (eg, smoking, sun safety, and narcotic substances), message types (eg, text-based phrases, video, and audio), and cultural groups [10].

The Neurocognitive Persuasion Model [11] identifies key brain regions associated with influence and persuasion. Accordingly, successful persuasion is associated with brain activity in the medial prefrontal cortex (MPFC) [6,12-14], through a process of self-integration, that is, increased brain activity for messages and cues that are successfully integrated with one's self-concept [15]. In a population-level study [5], individuals viewed 3 tobacco cessation advertisements (A, B, and C) and were then asked to rank the effectiveness of the advertisements for helping them quit smoking on a scale of 1 to 10 (the left graph in Figure 1). The center graph in Figure 1 shows the average brain activity within the MPFC for those individuals viewing the advertisements, measured by functional magnetic resonance imaging (fMRI). To measure the population-level effectiveness of each advertisement, a 1-800 quitline call volume was assessed the month after each campaign aired. The right graph in Figure 1 shows the call volume after each advertisement was aired. Results indicated that the MPFC activity provides a stronger correlation to the real-world effectiveness of different advertising campaigns at the population level than self-report in this study, suggesting that neural response is a more reliable correlate of behavior change than self-reported perceived effectiveness.

In recent years, technological advances in the field of neuroscience have allowed us to study the structure of the brain and its functioning from a previously unknown approach. Functional near-infrared spectroscopy (fNIRS) is a noninvasive tool to measure key neural processes associated with influence and persuasion. fNIRS is particularly attractive for studying the neuroscience of persuasion and influence because most regions of the brain associated with this process are in the frontal cortex and accessible through fNIRS. The lower cost and greater portability of fNIRS make it a more cost-effective tool than fMRI, thus allowing scalability. In this study, we will use fNIRS to measure MPFC as the region most commonly predictive of individual- and population-level behavior change in past studies. There have been multiple studies that have used fNIRS measurements of MPFC to predict a person's preferences [16,17]. To the best of our knowledge, there has been no published study using fNIRS in sexual health research or among highly marginalized populations.

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Figure 1. Comparison of self-report (left) and neural response (center) to tobacco cessation advertisements against effectiveness measure (right). MPFC: medial prefrontal cortex; ROI: region of interest.



Objectives

Informed by the neuroscience of persuasion and influence, this paper aims to describe the protocol of a neuro-influence experiment using fNIRS to compare the effectiveness of 2 sets of PrEP promotion messages, one developed through a crowdsourcing open contest the study team implemented [18] and another developed through a traditional social marketing approach. Open contests, a form of crowdsourcing, involve a large number of community members in developing, vetting, and implementing solutions to public health problems in the form of a contest [19]. In our study, 79 PrEP promotion messages were submitted by community members, and then the top 4 entries were selected by 155 community votes in Baltimore. We expect the messages developed through open contests to be highly relevant to the community because open contests explicitly incorporate local knowledge, culture, and style by directly involving a large number of community members [20].

We hypothesize that individuals viewing PrEP promotion messages developed through crowdsourcing open contests will show higher brain activation in the MPFC regions than those viewing messages developed by a social marketing approach. We further hypothesize that brain activation in the MPFC regions will be significantly more correlated with PrEP behavioral intention, initiation, and action than self-reported message effectiveness.

Methods

Overview

We will conduct a randomized controlled trial using fNIRS to measure brain activation in MPFC among 60 participants. The key inclusion criteria for the participants are as follows: (1) 18 years or older, (2) biological male sex at birth, (3) never taken PrEP, and (4) being eligible for taking PrEP [21]. Participants will be recruited by community partners in Baltimore, Maryland, from a range of settings, including venue-based outreach (community-based organizations and health clinics) and word-of-mouth referral.

Participants will be randomly assigned to view 4 PrEP promotion messages developed through an open contest the study team implemented [18] or PrEP campaign messages developed with a traditional social marketing approach. We will compare brain activities between the 2 groups and follow up with participants in 30 days to assess any behavioral change.

Study Procedure

After being screened eligible and providing written consent, each participant will be assigned a study ID and complete a baseline survey programmed in Qualtrics. Then we will make an appointment for an in-person experimental visit, roughly a week after completing the baseline survey. During the experimental visit, participants will be randomized to one of two conditions: (1) the top 4 messages developed through an open contest (ie, the intervention group) or (2) a total of 4 PrEP campaign messages developed with a traditional social marketing approach (ie, the control group). The participant's assigned condition will be recorded in a logbook. Block random assignment (in batches of 10) will be used to keep the sizes of the 2 groups similar. The order in which the groups are assigned in each block is randomized and determined by a computer algorithm. This process is repeated for consecutive blocks of study participants until all participants are randomized.

After the randomization, a research assistant will take the participant to a private room. The research assistant will measure and fit the participant's head for the fNIRS headband, which is connected to an NIRSport2 (NIRx) [22]. NIRSport2 is a portable fNIRS device to measure the neural response as participants view 4 messages on a computer screen. Once participants are fitted with the headband, the signal quality will be checked. The

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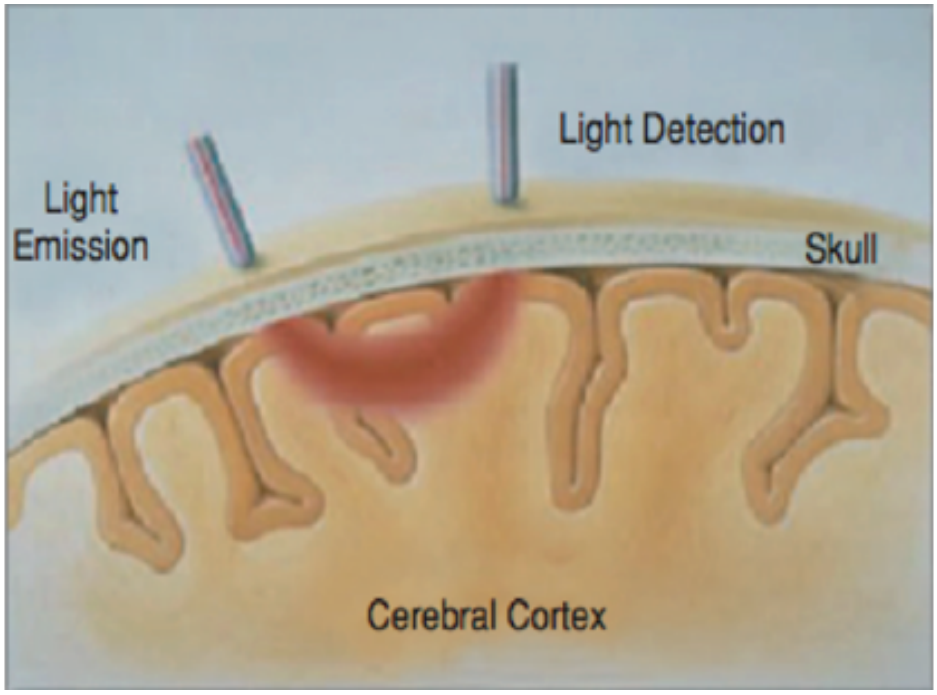
lights in the room will be turned off during testing to limit ambient light. A black shower cap will be placed over the participant's head to further limit any potential ambient light, and the research assistant will verify signal quality again. The LED emitter and detector on the headband will measure brain activity when participants view messages. Participants in each group will view 4 messages programmed in PsychoPy [23] on a computer screen while brain activity will be recorded. Each message appears on the screen for 10 seconds, and there are 10 seconds of resting time between messages. Messages are ordered randomly, and we did not find any ordering effect in our previous study [11]. After reviewing all messages, participants will answer questions on self-efficacy (individual's beliefs about their ability to follow through on a given behavior) and willingness and behavioral intention to use PrEP (see the "Measures" section). Semistructured questions on the acceptability of fNIRS will also be asked. All participants will complete a 2-week follow-up call to assess PrEP behavioral outcomes.

Measures

Brain activity

fNIRS detects the ratio of oxygenated hemoglobin (O2HB) to deoxygenated hemoglobin (HHB) based on its optical properties, with higher ratios indicating greater neural activity. Neural tissues are relatively transparent to light in the near-infrared range between 700 nm and 1000 nm, and O2HB and HHB reflect distinct wavelengths in this range. By modulating light at different wavelengths, emitting the light on the skin-exposed areas of the cranium, and detecting that light, fNIRS measures the blood oxygenation level–dependent signal like fMRI. Because the photons reflected from neural tissue follow a reliable "banana-shaped" path, photodetectors can be used to measure this on the scalp (see Figure 2). By measuring the amount of absorbed light directed at the neural tissue, we can measure the amount of O2HB and HHB present in a region of the brain at a given time and draw inferences about the level of neural activity.

Figure 2. Functional near-infrared spectroscopy measurement of cerebral cortex.



PrEP-Related Beliefs, Willingness, Behavioral Intention, and Behavior

All questions will be asked to participants at baseline (only to individuals aware of PrEP), at the second visit after reviewing all messages, and at the 30-day follow-up, except questions on PrEP action and initiation, which will only be asked at the 30-day follow-up. Self-efficacy [24] is assessed on a 5-point Likert scale ranging from "strongly disagree" to "strongly agree" to rate their agreement with the statement "I feel confident I could take PrEP as prescribed." Willingness is assessed by asking participants, "Suppose that PrEP is at least 90% effective in preventing HIV when taken daily. How likely would you be to take PrEP if it were available for free?" with responses ranging from "I would definitely take it" to "I would definitely not take it" [25]. We will assess behavioral intentions to actually begin PrEP based on a real-world situation [25]. To do this, participants will be asked, "PrEP is currently available with a prescription from your doctor and research has shown that a majority of insurance companies cover most or all of the costs of PrEP. Do you plan to begin PrEP?" Response options range from "yes, I will definitely begin taking PrEP" to "no, I definitely will not begin taking PrEP." Those participants who indicate they intend to take PrEP will also be asked a follow-up question regarding how soon they plan to begin taking PrEP. PrEP action and initiation will be assessed by asking, "Have you spoken with a provider about PrEP during the past 30 days?" and "Have you started taking PrEP during the past 30 days?" [25].

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Message-Related Measures

All questions will be asked after participants finish reviewing each message during the second visit. Perceived effectiveness will be measured using a validated scale [26]. Participants will be asked, on a 5-point Likert scale ranging from "strongly disagree" to "strongly agree," to rate their agreement that the message is believable, new, unconvincing, and important to them; helps them feel confident about using PrEP; would help their friends use PrEP; and puts thoughts in their mind about using PrEP and how much they agree or disagree with the message.

Acceptability of fNIRS

Participants will be asked to provide feedback on their experience with fNIRS, including questions: (1) "Do you feel comfortable wearing the cap?" with responses ranging from "extremely comfortable" to "not comfortable at all." (2) "Do you feel the size of the cap is too small, a good size, or too big?" (3) "How do you feel about a machine reading your brain activity?" with responses ranging from "extremely comfortable" to "not comfortable at all." (4) "How likely are you to participate in another study using the same type of machine in the future?" with responses ranging from "I would definitely take it" to "I would definitely not take it."

Baseline Socioeconomic and Behavioral Factors

We will collect baseline data on age, the highest level of education attained, living situation, employment status, relationship status, biological sex at birth, gender, sexual identity, sources and amount of personal and household income, health insurance status, usual health care, and sexual behavior in the past 90 days.

Data Analysis

We will conduct a descriptive analysis of the acceptability of fNIRS. The primary aim of data analyses is to assess the effectiveness of PrEP promotion messages developed through an open contest by assessing brain activation in the MPFC regions and changes in PrEP willingness, behavioral intention, initiation, and action between participants in the intervention group and those in the control group. We will compare (1) the level of neural activity in MPFC, (2) the increase in willingness and behavioral intention to take PrEP between baseline and 30-day follow-up, and (3) PrEP action and initiation at 30-day follow-up between participants in the 2 groups. A secondary aim is to evaluate the neural correlates of behavioral change.

Neural time series data will be captured for 23 brain regions in the prefrontal cortex. The time series signals will be averaged for each stimulus duration and for each 30-second rest period in between stimuli. These block averages will in turn be averaged across participants from the 2 groups. The level of brain activation for the intervention group compared with the control group will be evaluated using a pairwise comparison. For the binary outcome measures, that is, the increase in willingness and behavioral intention to take PrEP and PrEP action and initiation, we will first compare proportions by groups separately for each measurement period using standard bivariate analytic techniques such as Spearman rank-order correlations, odds ratios, and the Fisher exact test. Then we will use generalized linear mixed models (GLMM) to evaluate the effectiveness of messages developed through an open contest. GLMM permits us to measure the fixed effect of the messages developed through an open contest on neural activity, willingness, and behavioral intention to take PrEP, and PrEP action and initiation while allowing a random effect that accounts for within-person correlation. Given the binary nature of 2 primary outcomes, we will specify a logit link function for our GLMM models. Comparisons of the characteristics of participants who are lost to follow-up to those who are evaluated will be conducted to assess for systematic patterns that could influence results.

Self-reported effectiveness for individual messages will be averaged to compute self-reported message effectiveness for each group. We first examine the overall ordering of (1) self-reported message effectiveness by group assessed by mean ratings, (2) neural activity by group assessed by mean MPFC parameter estimate, and (3) PrEP action and initiation by group assessed by proportion of participants reporting taking PrEP action and initiation during 30-day follow-up. We next use a chi-square test to compare the proportion of individuals who produce each possible ranking with what would be expected by chance (1/6). Finally, we will confirm the reliability of the proportion-based predictions using weighted Kendall tau [27].

Ethical Considerations

The study protocol has been approved by an institutional review board (Study ID: Pro2022000225). Screening for participant eligibility will be conducted in person or on the web after verbal consent. Once screened, eligible individuals will review the written consent and consent if they agree to participate in the study. Each participant will be assigned a study ID. Participants will receive US $15 for completing the baseline survey, US $60 for completing the experimental visit, and US $10 for completing the follow-up call.

Results

This study is funded by the National Institutes of Health (National Institute of Mental Health: R34MH116725). Participant recruitment and data collection were completed in October 2023. The first results are expected to be submitted for publication in 2024.

Discussion

Findings from the study will improve the scientific understanding of health communication in HIV prevention and treatment efforts. PrEP promotion messages identified as most persuasive with fNIRS will serve as a template for future contests with a focus on visual images (eg, color photographs, black-and-white photographs, and videos less than 1 minute) and distribution networks (eg, men who have sex with men social media networks, in-person men who have sex with men businesses, and in-person men who have sex with men social networks). The findings can also demonstrate the utility of fNIRS as a tool for preproduct testing of health campaigns and enable the public health community to deliver more effective messages to improve health outcomes.

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We are well aware of the limitations of relying exclusively on small-scale pilots to determine whether messages developed through an open contest approach are more persuasive, namely that sizable standard errors are associated with effect sizes due to the small sample size. However, we are primarily interested in exploring the pattern of results for any evidence of support for the effectiveness of PrEP messages developed through the open contest on the primary outcomes. Effect size estimates determined through this study will be essential in the design of a larger and fully powered efficacy study that tests intervention effects on PrEP uptake.

In summary, the findings of this proposed study will transform the design, evaluation, and implementation of HIV campaigns, potentially bringing new ideas for local health departments and community-based organizations to develop more impactful PrEP campaigns.

Acknowledgments

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Data Availability

Data sharing is not applicable to this article as no data sets were analyzed during this study.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review report by the National Institutes of Health, USA.
[PDF File (Adobe PDF File), 62 KB - resprot_v12i1e52546_app1.pdf]

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Abbreviations

fMRI: functional magnetic resonance imaging
fNIRS: functional near-infrared spectroscopy
GLMM: generalized linear mixed models
HHB: deoxygenated hemoglobin
MPFC: medial prefrontal cortex
O2HB: oxygenated hemoglobin
PrEP: pre-exposure prophylaxis

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Protocol

Effectiveness and Safety of Different Estradiol Regimens in Transgender Women (TREAT Study): Protocol for a Randomized Controlled Trial

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Abstract

Background: Current guidelines for gender-affirming hormone therapy (GAHT) for transgender women are mostly based on clinical experience from experts in the field and treatments used on postmenopausal women. While care is currently provided with the best available evidence, there is a critical gap in knowledge about the safest and most effective estradiol routes of administration for GAHT in transgender women; this statement is supported by the World Professional Association for Transgender Health on their *Standards of Care for the Health of Transgender and Gender Diverse People, version 8*. Furthermore, the reported rates of cardiometabolic adverse events in transgender women highlight the importance of investigating changes in lipoproteins, glucose, and insulin sensitivity, among other markers while receiving GAHT.

Objective: This study aims to evaluate the degree of testosterone suppression achieved at 1, 6, and 12 months in treatment-naive transgender women when randomized to GAHT with estradiol and spironolactone as antiandrogens. As a secondary aim, this study will assess the treatment effect on metabolic and coagulation factors from baseline to 6 and 12 months after initiating GAHT.

Methods: This is a prospective pilot, open-label, randomized clinical trial conducted at an adult transgender clinic in a tertiary medical center. The 3 treatment arms include once-daily sublingual 17-β estradiol, twice-daily sublingual 17-β estradiol, and transdermal 17-β estradiol. All participants received spironolactone as an antiandrogen. Transgender women aged 18 to 45 years who are being evaluated for the initiation of GAHT with 17-β estradiol and did not have a history of coagulopathy, cigarette smoking, liver disease, dyslipidemia requiring treatment, or use of gonadotropin-releasing hormone agonist were eligible to enroll. The main outcome is the total testosterone suppression at 1 and 6 months after the initiation of GAHT, and the secondary outcome is to assess treatment effect in a lipid panel; homeostatic model assessment for insulin resistance; coagulation factors II, IX, and

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XI; Von Willebrand factor; activated protein C resistance; protein C; and protein S at baseline, 6 months, and 12 months after therapy is initiated.

Results: This study was funded in March 2022, and enrollment concluded in August 2022. It was concluded in July 2023, and currently, the results are being analyzed for publication.

Conclusions: The Transgender Estradiol Affirming Therapy (TREAT) study offers a rigorous and reproducible approach to answer important questions regarding GAHT in transgender women, specifically, the most effective 17-β estradiol regimen to suppress testosterone levels to 50 ng/dL, as currently recommended.

Trial Registration: ClinicalTrials.gov NCT05010707; https://clinicaltrials.gov/study/NCT05010707

International Registered Report Identifier (IRRID): DERR1-10.2196/53092

(JMIR Res Protoc 2023;12:e53092) doi:10.2196/53092

KEYWORDS

transgender research; transgender health; clinical trial; estrogen; transwomen

Introduction

Transgender individuals experience discordance between their self-identified gender and biological birth sex [1-3]. Some transgender individuals experience gender dysphoria, which the *Diagnostic and Statistical Manual of Mental Disorders* defines as clinically significant distress or impairment in social, occupational, or other key areas of functioning. Increasing numbers of adolescents seek care at gender identity centers in Western countries [4,5].

Studies using short self-reports of gender identity and its variants suggest that 0.17% to 1.3% of adolescents and young adults identify as transgender [6]. Even using the conservative estimate of 0.3%, the number of people living in the United States who identify as transgender is nearly 1 million [7]. Given the widespread acknowledgment of the health care needs of this population, priority should be given to those actions that will ensure timely access to appropriate care. Such action includes coverage of transition care and a requirement to ensure safe, effective, appropriate, and sensitive care in health centers [8-10].

Transgender women seek gender-affirming hormone therapy (GAHT) to reach physical features consistent with their gender identity [11-13]. The goal of GAHT for transgender women is to achieve feminine features and maintain estradiol levels within the normal woman range while suppressing endogenous testosterone [11]. The current approach to GAHT is not uniform and is used off-label for this indication. It also depends on the cost of the regional health care system and availability of estrogens and antiandrogens.

A typical regimen includes estrogen to provide feminizing effects in conjunction with therapy to block testosterone (antiandrogens or gonadotropin-releasing hormone analogs) [14]. The currently preferred estrogen formulation that can be provided in tablets, patches, and injections is 17-β estradiol, and spironolactone is the most prescribed antiandrogen in the United States.

Studies have demonstrated that transgender individuals on hormone therapy have higher rates of adverse cardiovascular events (myocardial infarction, venous thromboembolism, and ischemic stroke), highlighting the importance of investigating surrogate markers such as changes in lipoproteins, estrone, glucose, and insulin-sensitivity based on the estrogen preparation used during GAHT [8,15-21].

Both the World Professional Association for Transgender Health and the Endocrine Society have created transgender-specific guidelines that serve as a framework for providers caring for gender minority patients [9,22]. These guidelines are primarily based on clinical experience from experts, and guidelines for estrogen therapy in transgender women are loosely based on treatments for postmenopausal women [1]. Therefore, stronger evidence is needed to guide clinicians on best clinical practices for this population, as stated in the *Standards of Care for the Health of Transgender and Gender Diverse People, version 8*: "Determining the safest and most efficacious estrogen compound and route of administration for transgender people is an important topic" [9,22,23].

For this proposed study, we aimed to evaluate the degree of testosterone suppression and treatment-related changes in metabolic and coagulation factors in transgender woman patients undergoing randomized GAHT for a period of 12 months. Participants were randomized to once-daily sublingual 17-β estradiol, twice-daily sublingual 17-β estradiol, or transdermal 17-β estradiol, using spironolactone as an antiandrogen in all 3 treatment arms.

We chose to look at once versus twice-daily sublingual 17-β estradiol to evaluate if there is a difference in the level of suppression of gonadotrophins based on 1 larger peak serum level of estradiol versus 2 peaks. To date, no studies have looked at the effects of estradiol pulses (once vs twice) on suppression of the hypothalamic or pituitary axis.

Methods

Overview

This prospective pilot, open-label, randomized clinical trial compares the testosterone-suppressing effects of 3 commonly used 17-β estradiol regimens in transgender woman adults initiating GAHT. The 17-β estradiol regimens used in this trial include once-daily sublingual 17-β estradiol, twice-daily sublingual 17-β estradiol, and transdermal 17-β estradiol patch.

The primary end point is testosterone suppression from baseline to 1 and 6 months with secondary evaluation of treatment-related

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changes in lipid panel; homeostatic model assessment for insulin resistance; coagulation factors II, IX, and XI; Von Willebrand factor; activated protein C resistance; protein C; and protein S at baseline, 6 months, and 12 months after therapy is initiated.

The study took place at the Washington University Transgender Center. Patients aged 18 to 45 years who were being evaluated for the initiation of GAHT with 17-β estradiol and did not have a history of coagulopathy, cigarette smoking, liver disease, dyslipidemia requiring treatment, or use of gonadotropin-releasing hormone agonist were eligible to enroll. Initially, the study was limited to those aged 18-30 years and with BMI <30 kg/m^2, but these were later removed to increase the population available to screen and participate in the study.

Power analyses indicated that 12 participants per group would provide 80% power to detect differences in total testosterone between groups when the true difference between groups is 230 ng/dL. The type I error probability is .05.

We will use a likelihood-based mixed-effects model to separately evaluate the effects of time and treatment assignment on serum testosterone, estradiol, and estrone from baseline to 1 and 6 months after initiation of medications.

We will also use a likelihood-based mixed-effects model to separately evaluate the effects of time and treatment on metabolic and coagulation factors from baseline to 6 and 12 months after the initiation of treatment. We will also determine if there is any correlation between estradiol and estrone levels with coagulation factors as suggested by other studies.

Ethical Considerations

The Washington University in St. Louis Institutional Review Board approved the study protocol (IRB# 202104092) in May 2021, which was executed in accordance with the Declaration of Helsinki. Participants received financial compensation for their time and costs associated with participation in the study ($30 per visit).

Study Procedures

Participants who met eligibility criteria and provided informed consent were randomized 1:1:1 to either once-daily sublingual 17-β estradiol, twice-daily sublingual 17-β estradiol, or a transdermal 17-β estradiol patch. All participants received spironolactone as an antiandrogen. The dosing protocol is shown in Table 1.

Table 1. Dosing regimen per treatment group.

Medication	Once-daily sublingual	Twice-daily sublingual	Transdermal
17-β estradiol	• Starting dose: 2 mg once a day • Increase by 2 mg/day	• Starting dose: 1 mg twice daily • Increase by 2 mg/day	• Starting dose: 100 mcg/24 h • Increase by 100 mcg/24 h
Spironolactone	• Starting dose: 50 mg daily • Increase by 50 mg/day • Maximum dose: 200 mg/day	• Starting dose: 50 mg daily • Increase by 50 mg/day • Maximum dose: 200 mg/day	• Starting dose: 50 mg daily • Increase by 50 mg/day • Maximum dose: 200 mg/day

Initial evaluation included a comprehensive medical history, physical examination, and baseline laboratory testing. During the initial visit, patients were randomized and started on spironolactone and 17-β estradiol based on their treatment group assignment. The initial evaluation was completed in conjunction with the treating endocrinologist with follow-up conducted by the study investigator.

Once participants started their GAHT treatment assignment, they underwent a titration phase in which the hormone profile including estradiol, total testosterone, estrone, and basic metabolic panel was assessed every 4 weeks until total testosterone was less than 50 mg/dL. If the total testosterone is above goal, 17-β estradiol and spironolactone doses were adjusted based on their group dosing regimens as depicted in Table 1.

Anthropometric measurements and metabolic and coagulation factors were obtained at baseline, 24 weeks, and 52 weeks (Table 2). Blood testing was conducted before their morning dose for participants randomized to sublingual 17-β estradiol or the morning when the transdermal 17-β estradiol patch is due for replacement.

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Table 2. Study visits and laboratory testing.

Laboratory testing	Baseline	Titration phase	6 months	12 months
Anthropometric measurements				
Weight	✓		✓	✓
Height	✓		✓	✓
BMI	✓		✓	✓
Waist circumference	✓		✓	✓
Blood pressure	✓		✓	✓
Hormone profile				
Total testosterone	✓	✓	✓	✓
Estradiol	✓	✓	✓	✓
Estrone	✓	✓	✓	✓
Basic metabolic panel	✓	✓	✓	✓
Liver function panel	✓		✓	✓
Metabolic parameters				
Fasting serum glucose	✓		✓	✓
Fasting total insulin	✓		✓	✓
Fasting lipid panel	✓		✓	✓
Coagulation factors				
Factor II activity	✓		✓	✓
Factor IX activity	✓		✓	✓
Factor XI activity	✓		✓	✓
Von Willebrand Factor Antigen	✓		✓	✓
Activated protein C resistance (APCR)	✓		✓	✓
Protein C activity	✓		✓	✓
Free protein S antigen	✓		✓	✓

Results

This study was funded in March 2022, and enrollment concluded in August 2022. It was concluded in July 2023, and currently, the results are being analyzed for publication.

Discussion

Expected Findings

The Transgender Estradiol Affirming Therapy (TREAT) study offers a rigorous and reproducible approach to answer important questions regarding the GAHT in transgender women. Specifically, the study will determine if significant differences in testosterone suppression between once-daily, twice-daily, or transdermal 17-β estradiol exist.

This study will also provide insights into metabolic and coagulation changes in transgender women on GAHT with sublingual and transdermal 17-β estradiol and spironolactone as antiandrogens. These outcomes, with the GAHT used in this study, have not been explored in prior studies.

In addition, this study will provide insights into the best strategies and most reliable methods to inform the design of future, fully powered randomized clinical trials.

Limitations

Due to a lack of uniformity on the current prescription patterns for GAHT, we decided to conduct this study using the most common regimens prescribed in our clinical setting with no prior studies describing their effects on metabolic and coagulation factors. Hence, it may not be representative of other approaches to GAHT in transgender women, including estradiol valerate or cypionate, which were not included in the study.

Conclusions

The proposed study addresses areas of research that have been determined as important by the most recent World Professional Association for *Standards of Care for the Health of Transgender and Gender Diverse People, version 8*, including the most effective estrogen regimen (route of administration and dosing schedule), while providing insights on metabolic and coagulation factor changes with concurrent use of spironolactone, which has not been explored previously. Furthermore, this study

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provides insight into methodology and statistics that will inform larger clinical trials.

Acknowledgments

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Authors' Contributions

SC, GN, TB, and MF contributed to the conceptualization, methodology, statistical analysis, reviewing, and editing protocol. DM, TG, and ZG contributed to the study administration. CH and KW assisted with patient recruitment and reviewed and edited the paper.

Conflicts of Interest

MF declares equity ownership in Proclara Biosciences and consulting for Global Blood Therapeutics. CH is a consultant for Teladoc Health.

Multimedia Appendix 1
Peer reviewe report from Washington University Institute of Clinical and Translational Sciences.
[PDF File (Adobe PDF File), 181 KB - resprot_v12i1e53092_app1.pdf]

Multimedia Appendix 2
CONSORT checklist.
[DOC File , 219 KB - resprot_v12i1e53092_app2.doc]

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Abbreviations

GAHT: gender-affirming hormone therapy
TREAT: Transgender Estradiol Affirming Therapy

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Protocol

Correlation Between Serum and Urine Biomarkers and the Intensity of Acute Radiation Cystitis in Patients Treated With Radiation Therapy for Localized Prostate Cancer: Protocol for the Radiotoxicity Bladder Biomarkers (RABBIO) Study

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Abstract

Background: Despite improvements in radiation techniques, pelvic radiotherapy is responsible for acute and delayed bladder adverse events, defined as radiation cystitis. The initial symptoms of bladder injury secondary to pelvic irradiation are likely to occur during treatment or within 3 months of radiotherapy in approximately 50% of irradiated patients, and have a significant impact on their quality of life. The pathophysiology of radiation cystitis is not well understood, particularly because of the risk of complications associated with access to bladder tissue after irradiation, which limits our ability to study this process and develop treatments.

Objective: It is an original study combining digital data collection to monitor patients' symptoms and biological markers during irradiation. The main objective of our study is to evaluate the correlation of biological biomarkers with the intensity of acute radiation cystitis and the quality of life of patients, assessed with the digital telemonitoring platform Cureety.

Methods: Patients with intermediate-risk localized prostate cancer who are eligible for localized radiotherapy will be included. Inflammatory biomarkers will be analyzed in urine and blood samples before the start of radiotherapy and at weeks 4, 12, and 48 of irradiation, through quantitative methods such as a multiplex Luminex assay, flow cytometry, and enzyme-linked immunosorbent assay. We will also characterize the patients' gut and urine microbiota composition using 16S ribosomal RNA sequencing technology. Between sample collection visits, patients will complete various questionnaires related to radiation cystitis symptoms (using the International Prostate Symptom Score), adverse events, and quality of life (using the Functional Assessment of Cancer Therapy–Prostate questionnaire), using the Cureety digital remote monitoring platform. Upon receipt of the questionnaires, an algorithm will process the information and classify patients in accordance with the severity of symptoms and adverse events reported on the basis of Common Terminology Criteria for Adverse Events and International Prostate Symptom Score standards. This will allow us to correlate levels of urinary, blood, and fecal biomarkers with the severity of acute radiation cystitis symptoms and patient-reported quality of life.

Results: The study started in March 2022. We estimate a recruitment period of approximately 18 months, and the final results are expected in 2024.

Conclusions: This prospective study is the first to explore the overexpression of inflammatory proteins in fluid biopsies from patients with symptoms of acute radiation cystitis. In addition, the 1-year follow-up after treatment will allow us to predict which

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patients are at risk of late radiation cystitis and to refer them for radioprotective treatment. The results of this study will allow us to develop strategies to limit radiation damage to the bladder and improve the quality of life of patients.

Trial Registration: ClinicalTrials.gov NCT05246774; https://clinicaltrials.gov/ct2/show/NCT05246774?term=NCT05246774

International Registered Report Identifier (IRRID): DERR1-10.2196/38362

(JMIR Res Protoc 2023;12:e38362) doi:10.2196/38362

KEYWORDS

radiation cystitis; radiotoxicity; urine; bladder; serum; quality of life; remote monitoring; biomarker; prostate; cancer; immunosorbent; urology; cytometry; protocol; telehealth; telemedicine; health platform; online platform; monitor; digital health; radiotherapy; radiation; risk; inflammation; inflammatory; sequencing; biopsy; biopsies; gene expression; protein; microbiology; cystitis; microbe; microbiota; RNA; proteomics; assay; algorithm; oncology; radiology; radiation therapy; prostate cancer; diagnostic; quality of life

Introduction

Background and Rationale

Prostate cancer is the leading cancer diagnosed in men in France, with 50,400 new cases and 8100 deaths in 2018. Improved diagnostic strategies and therapeutic management have led to a 3.7% reduction in mortality between 2010 and 2018, and the survival rate is 93% at 5 years and 80% at 10 years [1], resulting in improved overall survival. However, treatment-related adverse events can be significant and have an impact on adherence to treatment, frequency of hospitalization and associated costs, as well as on the health-related quality of life of patients [2].

Radiation therapy (including conventional radiation therapy, stereotactic body radiation therapy, and brachytherapy) is an important therapeutic technique in the management of pelvic cancers, including prostate cancer [3,4]. Despite improvements in radiation techniques, pelvic radiotherapy remains responsible for a number of acute and late bladder adverse events—these symptoms are grouped under “radiation cystitis.” In France, late radiation cystitis affects 9000 to 18,000 patients per year [5].

Early symptoms of radiation cystitis may occur during treatment and up to 3 months after the end of radiotherapy, with an estimated all grade incidence of nearly 50% after pelvic irradiation [5]. These side effects are characterized by frequent and urgent urination during day- and nighttime, a burning sensation during urination (irritative symptoms), and pain. Difficulty in urinating (obstructive symptoms) or, more rarely, blood in the urine (hematuria) may also be present [6]. More rarely, in 5%-10% of cases, complications appear later (more than 6 months after radiotherapy), whether or not they were preceded by early signs [5,7]. Late lesions involve blood vessel damage and fibrosis of the bladder wall, which may progress chronically and lead to bladder atrophy and even retraction in the most extreme cases [5]. Clinical signs vary depending on the dominant clinical form: cystalgia, pollakiuria, bladder hyperactivity, and isolated mictional disorders. In a classic clinical scenario, recurrent hematuria is a predominant symptom, occurring in abundance and with variable frequency, which can potentially progress to urinary retention with bladder clotting. The chronic and recurrent nature of hemorrhagic cystitis often has a considerable impact on the quality of life of patients. The most severe forms can lead to clot formation and acute urinary retention, which can be life threatening [5,7].

Although some factors have been identified, such as the dose received, fractionation and, comorbidities (eg, diabetes and tobacco smoking), the pathophysiology of radiation cystitis remains poorly studied, particularly because of the risks of complications arising from access to the bladder tissue post irradiation, thus limiting our knowledge of and therapies targeting this process.

The Role of Immunity in the Pathomechanism of Radiation-Induced Injury

Immunity plays an important role in the mechanism of radiation-induced toxicity or inflammation [8,9]. During the repair process of radiation-induced injuries, inflammatory cells (macrophages, neutrophils, and lymphocytes) are recruited to the site of injury, which may contribute to late inflammatory tissue diseases through a continuous mechanism involving inflammation, hypoxia, and fibrosis [10]. The balance between M1 and M2 macrophages plays a central role in the fibrotic process, with a polarization toward M1 macrophages in a fibrotic situation [11,12]. Functional tests measuring the apoptosis of $CD4^+$ and $CD8^+$ T lymphocytes after irradiation found a significant association between these apoptotic lymphocytes and the risk of occurrence of late genitourinary toxicity [13].

The interstitial cystitis model is similar to the radiation cystitis model in terms of not only collagen accumulation but also symptoms. Patients with interstitial cystitis have very severe genitourinary pain, and many are diagnosed with depression and anxiety. A positive correlation between elevated urinary proinflammatory cytokines (interleukin [IL] 4 and macrophage-derived chemokines) and the severity of interstitial cystitis has been reported [14,15].

Role of the Microbiota in the Pathomechanism of Radiation-Induced Lesions

Evidence of the protection of microbial communities, especially in the gastrointestinal tract, has led to investigations of the role of the human microbiota in patient health and well-being [16,17].

Radiation therapy to the prostate causes a disruption in the composition of the microbiota, which may promote gastrointestinal toxicities through altered gut barrier function

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and inflammation [18,19]. It has been shown that the gut microbiota of patients with pelvic cancers who have had radiotherapy is less diverse than that of patients who have not been irradiated [18]. Wang et al [19,20] reported that pelvic radiotherapy is associated with dysbiosis characterized by a decrease in α-diversity in favor of β-diversity. In order to reduce the digestive disorders induced by pelvic radiotherapy, an approach based on fiber supplementation in patients (partially hydrolyzed guar gum) has proven to be effective in reducing diarrhea induced by radiotherapy and has allowed the improvement of the bacterial load of the microbiota while improving nutritional status and the quality of life of patients with cancer [21]. However, the numbers considered in Bull et al's [21] study were limited. Another study [22] also considered fecal microbiota transfer as a therapeutic solution to slow the spread of radiation-related symptoms—this approach showed encouraging signals for reducing the symptoms of hematuria and diarrhea.

Biomarkers based on the urinary microbiota may represent new diagnostic, prognostic, and therapeutic tools for functional disorders of the lower urinary tract. It has been shown that the urinary microbiota of patients with interstitial cystitis is less diverse than that of patients without these symptoms [20].

To date, no study has evaluated the modification of the urinary microbiota in patients with radiation cystitis. A better understanding of the impact of the urinary microbiota on the etiopathogenesis of urological disorders may help optimize medical management.

It is also important to note that the microbiota of different organs are linked. It is known that the gut microbiota is capable of changing its microbial composition, and these changes can affect the urinary microbiota [21].

Main Objective

The main objective of this study is to determine inflammatory and remodeling markers involved in the occurrence of early (<3 months) radiation cystitis in patients with localized prostate cancer.

Secondary Objectives

Our secondary objectives are to determine biological markers of the severity of early radiation cystitis and to describe changes in urinary and fecal microbiota in accordance with the severity of early radiation cystitis.

Exploratory Objectives

Our exploratory objectives are to describe the biological markers of severity of late radiation cystitis (>6 months) and to describe the lipidome and metabolome changes in accordance with the precocity of radiation cystitis.

Methods

Study Design

The Radiotoxicity Bladder Biomarkers (RABBIO) study is an interventional, prospective, single-arm, exploratory study aimed to identify factors potentially related to radiation-induced bladder toxicity in patients with localized prostate cancer treated with radiotherapy. This study will be conducted at the Bégin Military Teaching Hospital (Saint-Mandé, France).

Ethical Considerations

The study has been validated by national ethics committees (unique protocol ID number 2021-A03196-35; favorable opinion of the South Mediterranean Committee for the Protection of Persons I 03/02/2022) and the French Data Protection Agency. The study is registered on ClinicalTrials.gov (NCT05246774). The survey complies with the tenets of the Declaration of Helsinki. All patients will be informed that the data collected may be used for research purposes, and will be asked to provide their written consent.

Patient Population

The eligibility criteria for the RABBIO study are listed in Textbox 1.

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Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria:

- Collection of signed informed consent forms prior to participation in the study
- Patients are aged ≥18 years at the time of selection
- Histologically confirmed adenocarcinoma of the prostate is present
- Localized adenocarcinoma of the prostate according to the D'Amico classification is present
- Patients are eligible for external radiotherapy or brachytherapy
- Patients are affiliated to a social security scheme
- Patients are able to communicate well, understand, and comply with the requirements of the study according to the physician investigator
- Patient has a smartphone or computer to use the Cureety platform

Exclusion criteria:

- Patients have advanced or metastatic prostate cancer
- Patients are receiving preirradiation hormone therapy
- Patients have bladder or urethral cancer or a history of cancer
- Previous urinary tract surgery (bladder augmentation or cystectomy)
- Patients are participating in an interventional clinical study
- Patients have a history of pelvic irradiation

Participants' Calendar

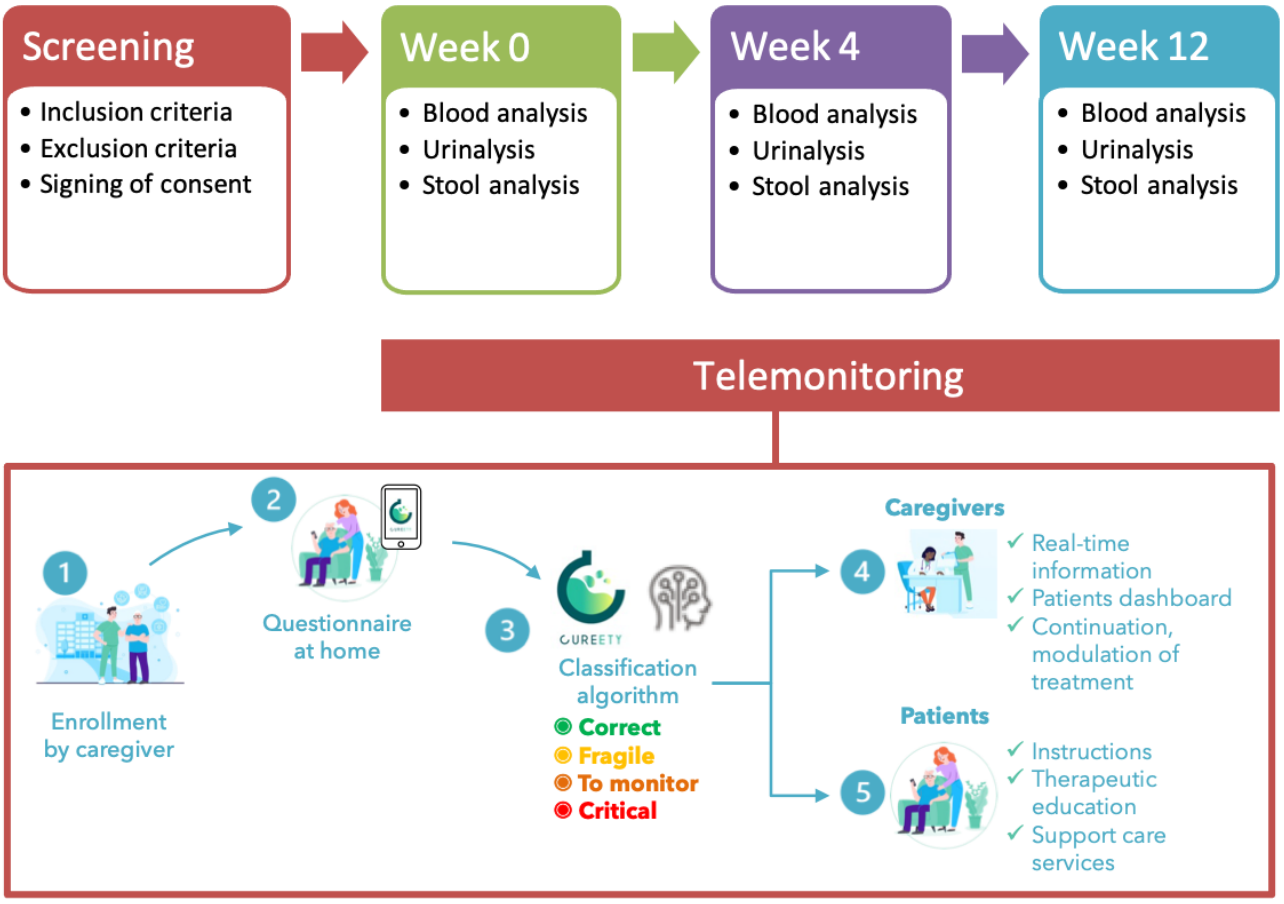
Early symptoms of radiation cystitis are likely to occur during treatment or within 3 months of radiotherapy in approximately half of the patients [7]. Therefore, we decided to follow the early manifestations of radiation-induced bladder toxicity for 3 months (weeks 1 to 12) and to attempt to identify biomarkers that are potentially related to acute radiation cystitis symptomatology.

Late manifestations of bladder damage secondary to pelvic irradiation may occur after a minimum of 3 months or even several years after the end of irradiation [4,6]. It has been established that the average delay in the occurrence of these complications is 2 years [6]. However, the pathophysiological changes between the end of radiation and the occurrence of late complications are not known. In this study, we aim to, as an exploratory objective, determine biomarkers that may be predictive of late radiation cystitis by quantifying biomarkers at week 52.

The design of RABBIO study is shown in Figure 1.

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Figure 1. Study design.



Data Collection

Clinical Data

Demographics and Disease Characteristics

Demographic data and cancer characteristics (localized or biologically relapsed prostate cancer, stage of disease, radiation regimen, concomitant treatments, and comorbidities) of the patients will be collected.

Clinical Examination

Clinical examination at each visit will include performance index (performance status), weight, blood pressure, heart rate, and oxygen saturation.

Monitoring of Radiotherapy Adverse Events and Patient-Reported Quality of Life Using the Cureety Platform

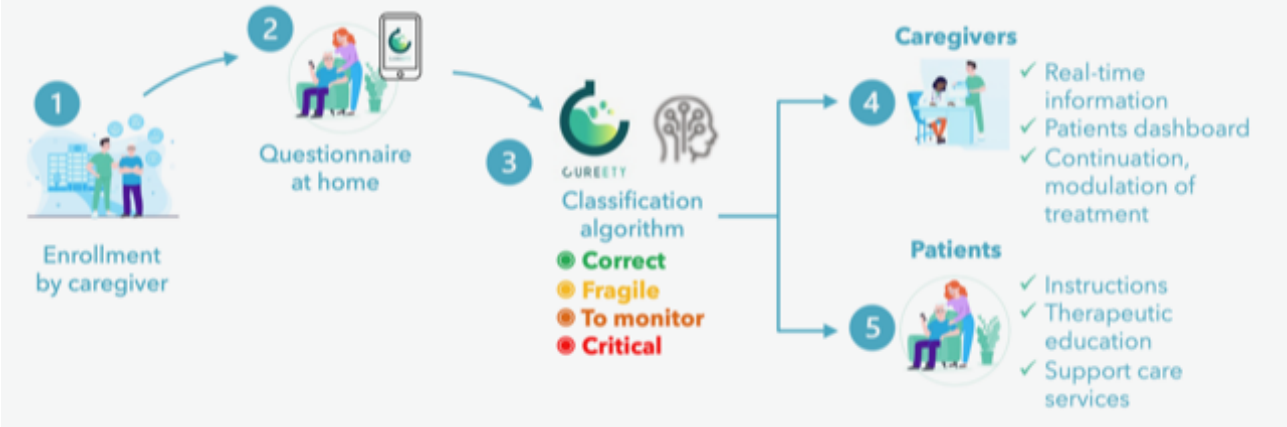
The Cureety platform will allow remote monitoring of urinary symptoms reported by patients in accordance with the CTCAE (Common Terminology Criteria for Adverse Events) guidelines [22] (Multimedia Appendix 1).

Patients will complete the Pelvic Radiation Adverse Events Questionnaire at the inclusion visit, then once a week for 3 months (weeks 1 to 12), and then at the end-of-study visit (week 52). The questionnaire includes the following items: fatigue, nausea or vomiting, pain, hematuria, frequency of urination (pollakiuria), urinary burning, diarrhea, fecal incontinence, urinary leakage, blood in the stool (rectorrhagia), constipation, weight loss, and dysuria.

On receipt of the questionnaires on the adverse effects of radiation, an artificial intelligence algorithm will classify patients into 1 of 4 states: correct condition (green), fragile state (yellow), condition to monitor (orange), and critical condition (red; Figure 2). The patient will receive therapeutic advice depending on the severity of the symptoms. If the patient's condition changes to orange (watch) or red (critical), rapid management of the patient will be activated by the health care team (Figure 2).

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Figure 2. Monitoring of radiotherapy adverse events and patient-reported quality of life using the Cureety app.



International Prostate Symptom Score

The International Prostate Symptom Score (IPSS) [23] is a structured, validated, self-administered questionnaire that assesses lower urinary tract voiding disorders. The questions cover the following items: incomplete emptying of the bladder, frequency of micturition, intermittent micturition (stopping and restarting the stream), urgent micturition (feeling of "urgency"), weak stream, effort to urinate (forcing or pushing), and nocturia (Multimedia Appendix 1).

The Functional Assessment of Cancer Therapy–Prostate Questionnaire

The Functional Assessment of Cancer Therapy–Prostate (FACT-P) questionnaire [24] is a prostate cancer–specific, self-administered questionnaire that assesses weight loss, appetite, pain, physical comfort, urinary, and sexual and bowel function in 12 items. The score ranges from 0 to 156, with higher scores reflecting a better quality of life.

The International Physical Activity Questionnaire

The International Physical Activity Questionnaire (IPAQ) [25] is a 7-item questionnaire that assesses overall physical activity and sedentary time over the past 7 days. The questionnaire assesses intense or moderate walking activity, as well as time spent sitting (sedentary), whether during leisure activities, at work, in daily life, or during transport. The questionnaire classifies the subject in accordance with 3 levels of activity: inactive, moderate, and high [25].

The IPSS, FACT-P and IPAQ questionnaires will be completed by the patient via the Cureety platform at inclusion and at the visits at weeks 4, 12, and 52.

Biological Data

Overview

Nearly 2 dozen studies have defined urinary biomarkers indicative of visceral disorders. Three main categories of markers have been studied: proteins involved in epithelial cell growth, mediators of inflammation, and neurotrophins. All marker levels were significantly altered in patients with interstitial cystitis, but antiproliferative factor, epidermal growth factor, and heparin-binding epidermal growth factor were the markers with the most promising results [26,27]. For radiation cystitis, the 2 studies by Zwaans et al [9,28] are the only ones to report elevated urinary levels of plasminogen activator inhibitor 1, the matrix metalloproteinases tissue inhibitor of matrix metalloproteinase 1 and 2, hepatocyte growth factor, VEGF-A, and placental growth factor. Based on the biomarkers reported in the literature, we chose to assess variations in the expression of 33 serum and urine biomarkers [9,28].

Biomarkers of urinary and intestinal microbiota may be prognostic of radiation-induced functional disorders [18-20]. Thus, we chose to assess changes in the composition of the urinary and fecal microbiota before, during, and after radiotherapy.

Physical activity, as determined on the basis of muscle contraction and the oxygen consumption it generates, can induce changes in the gut microbiota profile, helping to explain the health benefits of exercise. Researchers have identified differences in the composition of the gut microbiota of elite athletes in comparison with those of sedentary individuals [29]. A recent study has shown that the composition of the microbiota also differs in accordance with the sport practiced [30].

The collected samples will be analyzed for circulating biomarkers and microbiota composition.

Inflammatory and Remodeling Biomarkers

Overall, 6 mL of blood and 5 mL of urine per patient per visit will be used for the analysis of the following 33 biomarkers: inflammatory biomarkers (including macrophage migration inhibitory factor; cytokines IL-1α, IL-1β, IL-4, IL-6, IL-7, IL-8, IL-10, IL-13, and IL-17α; macrophagic inflammatory protein 1α; TNF-α; vascular cell adhesion molecule 1; intercellular adhesion molecule 1; chemotactic cytokines including monocyte chemoattractant protein 1 and 3 and regulated on activation, normal T-expressed, and secreted; the C-X-C motif chemokine ligand 10; the M1:M2 macrophage ratio; $CD4^+$ and $CD8^+$ T cells; and CRP) and biomarkers of remodeling (including plasminogen activator inhibitor 1, metalloproteinases such as matrix metalloproteinase 9, matrix metalloproteinase inhibitors including tissue inhibitor of matrix metalloproteinase 1 and 2, hepatocyte growth factor, placental growth factor, VEGF, epidermal growth factor, heparin-binding epidermal growth factor, nerve tissue growth factor, and glycoprotein GP51).

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Urinary and Fecal Microbiota

The advent of molecular biology and high-throughput sequencing has revealed the diversity of urinary and fecal microbiota and led to a better understanding of these ecosystems. Over the past 2 decades, shotgun metagenomic and 16S ribosomal RNA sequencing approaches have been widely used to determine the composition of these microbiota.

Lipidome and Metabolome

This involves the analysis of metabolites (small molecules) and lipids in the blood and urine before, during, and after radiation therapy. The identity and quantity of the different metabolites and lipids depend on several factors such as available nutrients, environmental stimuli, or physiological state. Metabolome and lipidome analyses help elucidate the influence of radiotherapy on the expressed phenotype and metabolism of the patient. A GC 7890B gas chromatography system (Agilent) coupled to a MS 7010 triple quadrupole mass spectrometer will help identify lipid and metabolic proinflammatory mediator profiles in the serum and urine of patients.

Statistical Analysis

As this is a pilot exploratory study, the sample size was not based on a statistical argument. As the variability and evolution of biomarkers over time and the history of the disease are not known, and in order to explore the links between biomarkers and the occurrence of radiation cystitis, based on the hypothesis that half of the patients initially included will develop cystitis, a sample size of 60 individuals—including 30 individuals with cystitis and 30 individuals without cystitis—seems acceptable. Statistical analysis will be carried out using SAS (version 9.4; SAS Institute Inc) and R (The R Foundation) [31].

Basic statistics will be used for continuous variables n, missing n (if applicable), mean, type of deviation, median, first and third quartiles, and minimum and maximum values, and for categorical variables, we will use frequency and percentage values.

The type I error (α, 2-sided) will be 5%. The type II error (β) will be 20%; that is, a power (1-β) of 80% will be considered.

End Points and Evaluation

The primary end point will indicate variations in the expression of the 33 inflammatory and remodeling biomarkers assessed using the MILLIPLEX MAP technique for the analysis of circulating markers and flow cytometry for the analysis of the immune population at the 4th and 12th weeks after the start of irradiation.

The secondary endpoints will indicate symptoms and the severity of early radiation cystitis through electronic reporting of patient-reported outcomes–CTCAE self-assessment questionnaires at inclusion and once a week during weeks 1 to 12. We will also be interested in voiding disorders, quality of life, and physical activity assessed using the IPSS, FACT-P, and IPAQ self-assessment questionnaires at inclusion and at weeks 4 and 12. Furthermore, we will characterize the composition of the urinary and fecal microbiota via 16S ribosomal RNA sequencing at baseline and at weeks 4 and 12. Finally, we shall explore the eligibility criteria, and then at week 52, the symptoms and severity of cystitis will be assessed through electronic reporting of patient-reported outcomes–CTCAE self-assessment questionnaires, and voiding disorders, quality of life, and physical activity will be assessed with the IPSS, FACT-P, and IPAQ self-assessment questionnaires, and then the composition of the urinary and fecal microbiota will be characterized through 16S ribosomal RNA sequencing. We will analyze serum and urine lipidome and metabolomes at weeks 4, 12, and 52.

Results

The RAABIO study started in March 2022. It is an original study combining digital data collection to monitor patients' symptoms and biological markers during irradiation. We estimate a recruitment period of approximately 18 months. The final results are expected in 2024.

Discussion

The quality of life of long-surviving patients is a goal of their care. Minimizing the impact of our treatments remains very challenging. This study is expected to improve our knowledge of the pathophysiology of radiation cystitis and its impact on the quality of life of our patients.

Radiation cystitis—which is characterized by hematuria, inflammation, and partly by fibrosis—has a strong impact on the daily life of our patients. Telemonitoring allows the recording of patients' experiences and the assessment of the impact of side effects on his quality of life. Collecting data from the patient (patient-reported outcomes) help to correct the discrepancy in the severity of the side effects when reported by the clinician or by the patient. Remote monitoring has been shown to provide high-quality care and has the potential to significantly improve patient care.

An increasing number of pathologies or their treatments, including radiation therapy of the prostate, now report alterations of the host-microbiome symbiosis [32,33]. In addition to remote monitoring patients' experiences, disorders involving the gastrointestinal area could be assessed by monitoring host-microbiome interactions using wireless ingestible capsules technologies as described recently by Miley et al [34]. These emerging technologies could be useful in tailoring daily treatments and helping patients reduce the side effects of radiation.

This prospective study is the first to explore the overexpression of inflammatory proteins in fluid biopsies from patients with symptoms of acute radiation cystitis. In addition, the 1-year follow-up after treatment will allow us to predict which patients are at risk of late radiation cystitis and to guide them toward radioprotective treatment. The RABBIO study will provide a better understanding of the pathophysiology of radiation-induced cystitis, along with data on the kinetics of these biomarkers. The results of this study will allow us to develop strategies to limit radiation damage to the bladder and improve the quality of life of patients.

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Data Availability

The data sets generated or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

All authors contributed to the design of the work, the acquisition, analysis and interpretation of the data, and approved the submitted version. They have agreed to be personally responsible for their own contributions.

Conflicts of Interest

None declared.

Multimedia Appendix 1
The Common Terminology Criteria for Adverse Events (version 5.0) questionnaire for classification of noninfectious cystitis and the International Prostate Symptom Score for the severity of prostate cancer symptoms.
[DOCX File , 15 KB - resprot_v12i1e38362_app1.docx]

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Abbreviations

CTCAE: Common Terminology Criteria for Adverse Events
FACT-P: Functional Assessment of Cancer Therapy–Prostate
IL: interleukin
IPAQ: International Physical Activity Questionnaire
IPSS: International Prostate Symptom Score
RABBIO: Radiotoxicity Bladder Biomarkers

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Protocol

Examining the Individual Response to a Low-Sodium Diet in Patients with Hypertension: Protocol for a Pilot Randomized Controlled Trial

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Abstract

Background: Excessive dietary sodium intake is an independent risk factor for hypertension and cardiovascular disease (CVD). Despite the large body of evidence concerning the effects of dietary interventions on blood pressure (BP) and CVD outcomes, trials have often reported low adherence to decreased sodium intake, likely due in part to heterogeneous BP responses. To address the challenges, recent clinical findings suggested a precise and personalized dietary approach that seeks to deliver more preventive and practical dietary advice than the "one-size-fits-all" guidelines and weighs the personal risk of developing specific diseases.

Objective: The purpose of this pilot randomized controlled trial was to test the feasibility and preliminary efficacy of integrating the use of mobile technology and metabolomics with a low-sodium diet intervention in patients with hypertension to develop personalized low-sodium diet programs. Additionally, the study will examine the associations of urine metabolites with urinary sodium levels and BP control based on the hypothesis that targeted urine metabolites. In this report, we describe the design and protocol of the pilot trial.

Methods: A total of 40 patients with hypertension will be randomly assigned to either a 8-week low-sodium diet group (n=20) or a standard care group (n=20). Each week, intervention participants went through individual sessions with an interventionist via videoconferencing to discuss low-sodium diet regimens, patients' food choices, and BP tracks on mobile apps. The control group followed their usual care for hypertension management. All participants in both groups monitored diet and BP using mobile apps for 8 weeks. A 24-hour urinary sodium excretion for the estimation of dietary sodium intake, systolic, and diastolic BPs were measured at the baseline and at 8 weeks. The primary outcomes of this study include the feasibility of conducting a randomized controlled trial (RCT) by reporting recruitment, retention, and completion statistics. The preliminary effects of intervention will be tested by a generalized estimating equation model.

Results: This pilot RCT study was approved by the institutional review board at the University of Texas Health San Antonio in January 2021. The first participant was enrolled in April 2021, and currently, 26 participants were enrolled. All data collection is expected to conclude by March 2023, with data analysis and study results ready for reporting by December 2023. Findings from this pilot RCT will further guide the team in planning a future large-scale study.

Conclusions: The findings of this proposed study will establish a comprehensive knowledge base for future research and development of personalized dietary interventions to promote adherence to dietary strategies and self-management of chronic disease using the Precision Health approach for millions of Americans who are struggling with uncontrolled hypertension.

Trial Registration: ClinicalTrials.gov NCT04764253; https://clinicaltrials.gov/ct2/show/NCT04764253

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International Registered Report Identifier (IRRID): DERR1-10.2196/39058

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KEYWORDS

adherence to low-sodium diet intervention; adherence; metabolite profile; salt sensitivity; digital self-monitoring; hypertension; salt; blood pressure; sodium; diet; metabolite; nutrition; metabolomics; precision medicine; personalized; personalization; RCT; randomized controlled trial; genetics; genomics; chronic disease; chronic condition; urinary; dietary; dietary sodium; hypertensive patient; cardiovascular disease

Introduction

Excessive dietary sodium intake is an independent risk factor for hypertension and cardiovascular disease (CVD). CVD is the leading cause of death in the United States. Risk factors for CVD include obesity, diabetes, and hypertension. Nutritional practices are a critical component in the prevention of CVD [1,2]. It is well documented that excess sodium intake can lead to hypertension, the primary risk factor for CVD [3]. Indeed, among all risk factors for CVD, elevated intake of sodium alone was ranked the 11th most important [4]. The scale of this problem resulted in calls for dietary sodium reduction to be considered a public health priority. Sodium intake is included in the top 5 priority actions for chronic disease control [5]. Despite this effort, daily dietary sodium intake among Americans chronically exceeds recommendations (2300 mg per day).

Numerous clinical trials demonstrated that a low-sodium diet reduces the risk of cardiovascular outcomes, including the incidence of hypertension, stroke, and cardiovascular morbidities [6-8]. Most recently, a systematic review and meta-analyses demonstrated that lowering sodium intake significantly reduced resting systolic blood pressure (BP) by 3.39 mm Hg and resting diastolic BP by 1.54 mm Hg [9]. When sodium intake was < 2 g/day versus ≥ 2 g/day, systolic BP was reduced by 3.47 mm Hg and diastolic BP by 1.81 mm Hg [9]. These changes seem small but are significant.

Prior dietary interventions successfully reduced sodium intake, but adherence to these dietary strategies is difficult to maintain [10,11]. This issue is likely due in part to the heterogeneity of BP responses to alterations in dietary sodium intake. In addition to examining group average BP responses to sodium intake, BPs of some—but not all—individuals fall with reduction in sodium intake, leading to the concept of intraindividual variability in BP response to a low-sodium diet [11-14]. Because there is considerable intraindividual random daily variation in BP without a change in sodium intake, both individual and intraindividual random variations in BP must be considered [15]. This proposed pilot study aims to address these challenges and investigate whether a low-sodium diet would induce changes in metabolic profiling and reflect intraindividual variability in response to a low-sodium diet among patients with hypertension, and also measure the association with reduced BP.

In recent years, precision health is often described in relationship to precision medicine, an emerging approach for disease treatment and prevention that accounts for intraindividual variability in genes, environment, and lifestyle [16]. Precision or personalized nutrition focuses on ways to deliver tailored dietary recommendations to promote and maintain health and prevent disease [17]. However, this field is in its infancy and currently has limited clinical applicability to CVD.

Metabolomics can measure the full profile of small-molecule metabolites in biofluids and provide a comprehensive picture of a person's overall dietary intake [18]. Diet encompasses a complex set of intercorrelated exposures, and self-reported tools are prone to random and systematic errors [18]. Although several biomarkers that measure nutrient intake have been identified, objective measurement of the overall dietary pattern remains elusive. Metabolite profiling accounts for intrinsic variability in metabolism by measuring downstream components or metabolic products of foods and, therefore, may more accurately measure true exposure than the traditional methods that measure individual food intake [18]. Although a few studies [19,20] identified metabolites associated with sodium intake, little research addresses metabolic phenotyping in relation to a low-sodium diet. This project aims to examine the variance in metabolite profiling caused by a low-sodium diet while controlling for covariates such as age and gender and provide the preliminary findings that estimate the variance of a modifiable factor (a low-sodium diet) in BP control.

Salt sensitivity (SS) as a preceding factor for individual BP response to a low-sodium diet can be tested with a genetic approach. SS is influenced by many factors, including genetics, age, gender, race or ethnicity, BMI, and diet [20,21]. The most robust method for assessing SS is through modifying dietary sodium intake using a crossover study design where a 5-7–day intervention period is given for a normal, low, and high dietary sodium intake level [22,23]. When a change in BP is not observed despite changes in sodium chloride intake, the individual is classified as salt resistant. Validated rapid tests or diagnostic markers to identify SS of BP in clinical practice were not available until now. In the most recent published study, which used data from the Genetic Epidemiology Network of Salt Sensitivity, GNAI2 single-nucleotide polymorphisms (SNPs) were positively associated with SS independently of subject sex or age [24]. Examining SS in BP using a genetic approach will enhance the identification of individuals at high risk for developing hypertension and would also benefit from a low-sodium diet.

Mobile apps that monitor food intake have the potential to improve eating habits and promote healthy diets. Although most popular apps are intended to monitor calorie intake to promote weight loss, they could also be used to monitor specific nutrient concerns such as dietary levels of sodium or monitor adherence to therapeutic dietary plans. One pilot study using a smartphone

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app showed that the change in the predicted 24-hour sodium excretion significantly differed between groups using an app versus a group recording intake in a journal (mean change −838, SD 1093 and 236, SD 1333 mg, respectively) [25]. Thus, further research is needed to explore whether mobile apps facilitate the real-time assessment of dietary intake as a means to improve self-managing dietary behavior using more precise monitoring [26].In conclusion, despite the benefits of low-sodium diet programs for reducing high BP and improving CVD outcomes in patients with hypertension, much of the existing empirical support for low-sodium diet programs are based on the evidence from a one-size-fits-all approach and has not accounted for individual responses to diet modification. Using a precision nutrition approach, we can address these gaps by providing more personalized interventions that may enhance adherence to a low-sodium diet and improve sustainability for individuals with hypertension. However, research developing and implementing a personalized low-sodium diet for patients with hypertension is limited, and more foundational evidence is needed.

Methods

Study Design and Overview

We are currently conducting a randomized controlled trial to test the feasibility of integrating the use of mobile technology and metabolomics with a low-sodium diet program compared to standard care (control). We will randomly assign 20 participants with hypertension to each group (N=40) to the intervention or the control group. The intervention is 8 weeks long and we will measure adherence and BP outcomes as the primary end points.

Ethical Considerations

This study is approved by the University of Texas (UT) Health Science Center at San Antonio's Institutional Review Board (#HSC20200054H). All databases containing personal data will be encrypted to minimize the risk of a breach. In addition, all the servers where data are stored will be encrypted and require a one-time password to be made available for analysis. Participants who completed the baseline visit and follow-up visit received US $60 of ClinCards per institutional policy as compensation for their time.

Specific Aims and Hypotheses

The aims of this clinical trial are to (1) determine the feasibility and preliminary efficacy of delivering a low-sodium diet intervention focused on changes in metabolomic profiling and reduction of urinary sodium level and BP in patients with hypertension; (2) examine the associations of urine metabolites with urinary sodium levels and BP control based on the hypothesis that targeted urine metabolites will have significant associations with urinary sodium level and differences in systolic BP (SBP) and diastolic BP (DBP).

Study Setting

The UT Health San Antonio School of Nursing will serve as the coordinating center for this study. Eligible participants will be recruited from primary care centers at UT health physicians. Data will be collected in the UT Health San Antonio School of Nursing.

Sample

Sample Size Justification and Power

This is a pilot study and will be inherently underpowered; therefore, quantitative outcomes will be interpreted only as feasibility and pilot data. A sample size of 40 subjects will provide an adequate sample size [27] to calculate meaningful CIs for our estimates of feasibility and preliminary effects. With this sample size, we expect to have sufficient diversity of input on the intervention components to plan refinements for a larger intervention trial.

Inclusion and Exclusion Criteria

To examine the underlying mechanism of intraindividual response to a low-sodium diet, a randomized, controlled study will be conducted in a sample of 40 patients with hypertension aged >40 years. Children are thought to have minimal levels of high BP; therefore, we will only recruit adults. Participants will be asked to own their own smartphone for using mobile apps during the study. Our exclusion criteria are clinic BP of <140 mm Hg; estimated glomerular filtration rate of <15 mL/min/1.73 m^2 or on dialysis; history of organ transplantation; cardiovascular event, procedure or hospitalization for unstable angina/chronic heart failure within last 6 months; life expectancy of <1 year or a cancer diagnosis and treatment within the past 1 year that, in the judgment of clinical study staff, would compromise participant's ability to comply with the protocol and complete the trial; active alcohol or substance abuse within the last 12 months; residence in a nursing home; diagnosis of dementia, treatment with medications for dementia; and unwilling or unable to participate in either of the interventions.

Measures

After obtaining informed consent, we will begin collecting baseline data and schedule the 8-week study visit. The summary of variables, measures, and time of evaluation is presented in Table 1.

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Table 1. Factors, variables, measures, and time data collected.

Factors and variables	Measures	Time data collected
Individual characteristics		
Age	Years	Baseline
Sex	Male and female	Baseline
BMI	Weight and height	Baseline and 8 weeks
Physiological factors		
Metabolite profile	24-hour urinary sample	Baseline and 8 weeks
Salt sensitivity gene	Single-nucleotide polymorphism genotyping	Baseline
Feasibility measures		
Retention rate	Number of subjects that came to the follow-up visit	Over 8 weeks
Attendance at education sessions	Number of education sessions attended on the internet	Over 8 weeks
Adherence to dietary sodium intake monitoring	Logging a meal in the app/manual	Over 8 weeks
Adherence to in-home blood pressure monitoring	Logging BP using BP monitor device	Over 8 weeks
Outcomes		
Blood pressure	WelchAllyn Vital Signs Monitor	Baseline and 8 weeks
Sodium intake	24-hour urinary sodium excretion	Baseline and 8 weeks

Individual Characteristics

Age and sex will be self-reported. BMI will be calculated using height and weight measurements and obtained with an Accu-Hite wall mounted stadiometer and a Withings electronic scale, respectively.

Physiological Factors

Metabolite profile will be measured by using targeted capillary electrophoresis/mass spectrometry (CE/MS) for 48 amino metabolites from 24-hour urine samples collected at baseline and at 8 weeks.

The SS gene will be screened using targeted genotyping. The targeted gene under investigation will be GNAI2 SNPs, which are positively associated with SS independently of sex and age. The primary SNPs investigated will be rs10510755, rs9852677, rs2282751, rs4547694, and rs2298952 identified from the HapMap and 1000Genomes projects to capture 100% of the genetic variation in GNAI2 using the Affymetrix Genome Wide-Human SNP Array AFFY_6.0.

Feasibility Measures

Four feasibility measures will be used to help elucidate our understanding of using a low-sodium diet intervention with mobile technology and metabolomics to measure intervention compliance intervention and protocol adherence.

Retention rate is the percentage of subjects who attended the 8 weeks post intervention. Attendance to education sessions will be measured by the number of 8-week education sessions attended within intervention group.

We will measure adherence to dietary sodium intake monitoring with the Fitbit companion mobile dietary app. The Fitbit app is intended as an intervention tool to enhance self-monitoring and promote adherence, not as a reliable assessment tool for dietary sodium intake (the 24-hour urinary samples will be used for this purpose). Each subject will register and assigned a unique ID in the platform developed by the Center on Smart and Connected Health Technologies at UT Health San Antonio. Each Fitbit account will be linked to his or her unique ID through this platform. Subjects will be instructed to record food intake in real time. Adherence to sodium intake monitoring is measured by calculating the percentage of days a participant logs at least 1000 kcal his or her meals in the dietary app.

Adherence to in-home BP monitoring is the percentage of days a subject uses the BP monitoring device (Omron 7 Series Upper Arm BP Monitor) to log BP. It has a range of 0 to 299 mm Hg for BP and 40 to 180 beats per minute for heart rate. The cuff is inflated with an electric pump and deflated with a pressure release valve. SBP, DBP, and heart rate are displayed on the LCD screen after each measurement. The device can also display a symbol on the screen, indicating an irregular heartbeat detected during measurement of SBP and DBP. Each subject will register for an Omron app account, which will be linked to their Connected Health platform unique ID. We will provide instructions on how to measure BP while in a sitting position and transfer the BP data to Omron mobile app using the BP monitoring device.

Outcomes

BP will be measured with the Vital Signs Monitor 300 Series model (WelchAllyn) at baseline and 8-week follow-up appointments. The midsection circumference of the dominant upper arm will be measured with a tape measure [28], and the proper sized cuff will be selected accordingly. SBP and DBP will be measured in the dominant arm twice with a 2-minute rest period between measures [29]; the 2 measures will be averaged. Sodium intake will be measured using a 24-hour urinary sodium excretion (mg excreted/day) test collected at baseline and at 8 weeks post intervention.

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Procedures

Recruitment

Recruitment began in April 2021. After obtaining approval from the institutional review board, subjects will be informed about the study via (1) UT Health San Antonio internal IT systems (ie, email and clinical trials website), (2) using Epic system to identify potentially eligible patients and send MyChart invitations, (3) study brochures posted at the primary care centers, and (4) word of mouth. For interested potential subjects, the principal investigator arranged a convenient time for consent process and screening for eligibility.

Informed Consent, Screening, and Randomization

After explaining the study's purpose, procedures, and potential benefits and risks in greater detail, we will obtain informed consent and screen BP (Table 2). For those meeting all criteria, we will arrange a convenient date and time for data collection in the Biobehavioral Research Laboratory. To prevent subject attrition, we will send appointment reminders 1 day prior to the scheduled visit. We will randomly assign the subjects into 1 of 2 groups using block randomization to balance sample sizes across groups [30].

Table 2. Procedures.

Variables	Screening (30 minutes)	Pretest (60 minutes)	Intervention (8 weeks)	Posttest (30 minutes)
Information session	N/A[a]	• A low-sodium diet intervention • Using wireless, wearable, and a mobile app • 24-hour urine collection	N/A	N/A
Self-report	• Age • Informed consent	N/A	• Dietary sodium intake • In-home blood pressure monitoring	N/A
Noninvasive measure	• Blood pressure	• Height and weight • Blood pressure • 24-hour urinary excretion	N/A	• Height and weight • Blood pressure • 24-hour urinary excretion
Blood collection	N/A	• Salt sensitivity gene	N/A	N/A

[a]N/A: not applicable.

Baseline Data Collection

After measuring height and weight, BP will be measured twice with a 2-minute rest period between the measurements. Next, we will draw 4.0 mL of blood by venipuncture. The research team will provide a low-sodium diet intervention tutorial and hold an information session to explain the mobile app, Fitbit wristband, and the in-home BP monitoring system. Subjects will be instructed to create user accounts for each device and receive hands-on training for dietary sodium intake and BP level self-monitoring using the Fitbit and wireless device. We also will provide participants with a designated helpline number for technical support. We will issue a designated container and instructions for 24-hour urinary collection. Subjects will be asked to note the start time in a written log and discard the first urine, then collect all urine over the next 24 hours, noting the time and amount excreted for each collection in the written log. Stored urine will not require refrigeration. In total, 4.0 mL of peripheral blood will be drawn into an anticoagulant tube during baseline visit. The anticoagulant tube will be centrifuged at 4000 rpm at 4 °C for 10 minutes. The Illumina Infinium system will be used for high-throughput genotyping of SNPs using microarrays. The 24-hour urine sample will be analyzed using the targeted capillary electrophoresis/mass spectrometry method for 48 amino metabolites.

Group Conditions

The intervention consists of 8 educational sessions (45 minutes each) delivered via a videoconferencing program and accessed through personal computer or smartphone at participants' preferred time. In the control condition, 20 subjects will receive their routine medical and nursing care for hypertension and take medications as prescribed. In both groups, over the 8-week intervention, participants will be allowed in digital self-monitoring using Fitbit, its companion app, and wireless BP monitor (Table 3).

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Table 3. Major content of intervention sessions.

Session	Content
1. Getting started and blood pressure overview	• Introduction to the program • Education about blood pressure and hypertension • Discussion of symptoms and complications for uncontrolled hypertension
2. A low-sodium diet and digital self-monitoring	• Education about a low-sodium diet in hypertension • Discussion of the importance of digital self-monitoring of diet and taking blood pressure at home
3. Gradual dietary sodium reduction	• Education about the rationale for gradual adaptation strategy, physical gradual adaptation process in taste buds, and psychological adaptation process • Setting up weekly goals in gradual adaptation
4. Strategies to overcome barriers to adhere to a low-sodium diet	• Education about individual's barriers to adhere to a low-sodium diet including cooking, eating out at restaurants, grocery shopping, salt substitutes or seasonings, fast food choice, and menu development
5. Food labels and sodium	• Education about reading food labels and nutrition facts • Facts about salt and sodium, and tips for how to lead a low-sodium life • Revisiting the gradual sodium reduction goal
6. Serving sizes and portion control	• Discussion about serving sizes, portion control, and the plate method • Reviewing the gradual sodium reduction goal
7. Meal planning, shopping, and eating out	• Discussion of planning for meals and tips for shopping and eating out • Checking in on goal progress
8. Planning for lasting change	• Review of overall program content • Discussion of what worked with a low-sodium diet adherence • Planning for lasting change activity

Follow-up Data Collection

After completion of the intervention, the PI will ask all participants to measure BMI, BP, and collect a 24-hour urine sample to measure sodium excretion in the same manner as the baseline.

Data Analytic Plan

Data analysis will be performed with SAS (version 9.4; SAS Institute) and R (version 4.1+; RStudio, Inc). Baseline demographic information will be summarized using descriptive statistics. Continuous variables will be summarized with means and SDs. Categorical variables will be summarized with counts, proportions, and medians (IQR). The distribution of all variables will be examined before any analysis, using appropriate statistical tests like the Shapiro test for normality checking. If the assumption of normality is not met, equivalent nonparametric approaches or data transformation will be used; for instance, log transformation can be conducted to the metabolomics profile before standardized to unit variance and zero mean. The multiple testing problem will be accounted for using Bonferroni correction or the Benjamini-Hochberg procedure: for example, the false discovery rate will be controlled when testing multiple urinary metabolites. All testing will be 2-sided, and a P value of .05 will be used as the family-wise significance level. If needed, statistical analysis will also be conducted after controlling for age, sex, and BMI.

Aim 1

Using both pre- and posttest data, we will assess feasibility by measuring (1) the percentage of subjects present at the 8-week follow-up, (2) the number of education sessions attended on the internet (intervention group), (3) the percentage of days subjects logged meals using a mobile dietary app; and (4) the percentage of days subjects logged in-home BP measurements with the BP monitoring device. We will test the preliminary effect of a low-sodium diet on the outcome variables using a generalized estimating equation model to account for the repeated measures over 8 weeks, which includes fixed effects of time (baseline and 8 weeks) and study arm (intervention or control), an interaction term for time by arm, and other covariates such as age. The interaction term will be tested to assess whether the changes from baseline differ by groups.

Aim 2

Using pretest data, a random forest [31] using R (version 4.2.0) will be used to identify associations between 48 amino metabolites, BP phenotypes (including SBP or DBP), and 24-hour urinary excretion to predict the classification of study subjects. For urinary metabolites nominated by the random forest analysis, we will use generalized linear model to generate P values and false discovery rate to correct for testing multiple urinary metabolites using the Benjamini-Hochberg procedure.

Results

To date, interventionist training is completed. The first participant was enrolled in April 2021, and currently, 26 participants were enrolled. All data collection is expected to conclude by March 2023, with data analysis and study results ready for reporting by December 2023. The findings from this

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pilot randomized controlled trial (RCT) will further guide the team in planning a future large-scale study.

Discussion

Findings and Implications

This report describes the protocol and design of a pilot RCT of a low-sodium diet intervention leveraging digital self-monitoring of daily diet and BP among patients with hypertension. We hypothesize that excessive sodium intake in individuals with hypertension can be modified with nutritional advice in addition to real-time diet and BP tracking and daily trends. Participants in the intervention group are anticipated to have a greater reduction in dietary sodium intake and BP than those in the control group. This study is the first attempt to develop a rigorously designed, low-sodium diet intervention to enhance metabolite response and dietary adherence for this vulnerable population. In addition, by examining metabolites to BP response and outcomes to a low-sodium diet, the findings of this study may establish a comprehensive knowledge base for future research and the development of precise and personalized nutrition regimens for high-risk individuals who are vulnerable to the negative effects of sodium on BP control based on genetic phenotypes and metabolite profiles. The findings of this proposed study will establish a comprehensive knowledge base for future research and development of personalized dietary interventions to promote adherence to dietary strategies and self-management of chronic disease using the Precision Health approach for millions of Americans who are struggling with uncontrolled hypertension.

Strengths and Limitations

First, this study is a pilot randomized trial, the sample size is relatively small, and we are not adequately powered to detect statistical significances between groups. Second, study recruitment and retention will likely be the most challenging aspect, given the multiple web-based lessons and self-monitoring activities. We will monitor recruitment monthly, and if lagging, will expand recruitment clinics. We will also encourage enrollment by compensating participants with a US $30 gift card for completing each visit. We will use multiple strategies (eg, being flexible for scheduling appointments and sending motivational messages) to address and reduce dropout. By providing flexibility, we are successfully maintaining the enrollment of participants in the current pilot study over 8 weeks without dropout. Finally, potential confounding factors were not analyzed: randomization should address differences in other factors that may affect BP, such as physical activity, sleep, and comorbidity. These factors will be measured in a larger study.

Nonetheless, this study represents an initial step to examine the metabolite responses to integrating the use of mobile technology and metabolomics with a low-sodium diet intervention in patients with hypertension to develop personalized low-sodium diet programs. If the results are promising, this may serve as an important milestone in considering how to develop and implement personalized low-sodium diet interventions in millions of Americans who struggling with uncontrolled hypertension. The findings from this study will also serve as the foundation for a large full-scale RCT to test the program in a broad population.

Acknowledgments

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Data Availability

The data sets generated or analyzed during this study are available from the corresponding author upon reasonable request.

Conflicts of Interest

None declared.

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Abbreviations

BP: blood pressure
CE: capillary electrophoresis
CVD: cardiovascular disease
DBP: diastolic blood pressure
MS: mass spectrometry
RCT: randomized controlled trial
SBP: systolic blood pressure
SNP: single-nucleotide polymorphism
SS: salt sensitivity
UT: University of Texas

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Protocol

The Independent Walking for Brain Health Intervention for Older Adults: Protocol for a Pilot Randomized Controlled Trial

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Abstract

Background: Extensive research suggests that physical activity (PA) is important for brain and cognitive health and may help to delay or prevent Alzheimer's disease and related dementias. Most PA interventions designed to improve brain health in older adults have been conducted in laboratory, gym, or group settings that require extensive resources and travel to the study site or group sessions. Research is needed to develop novel interventions that leverage mobile health (mHealth) technologies to help older adults increase their engagement in PA in free-living environments, reducing participant burden and increasing generalizability of research findings. Moreover, promoting engagement in moderate-to-vigorous PA (MVPA) may be most beneficial to brain health; thus, using mHealth to help older adults increase time spent in MVPA in free-living environments may help to offset the burden of Alzheimer's disease and related dementias and improve quality of life in older age.

Objective: We developed a novel PA intervention that leverages mHealth to help older adults achieve more minutes of MVPA independently. This pilot study was a 12-week randomized controlled trial to investigate the feasibility of providing just-in-time (JIT) feedback about PA intensity during free-living exercise sessions to help older adults meet current PA recommendations (150 minutes per week of MVPA).

Methods: Participants were eligible if they were cognitively healthy English speakers aged between 65 and 80 years without major cardiovascular, neurologic, or mental health conditions; could ambulate independently; and undergo magnetic resonance imaging. Enrollment occurred from October 2017 to March 2020. Participants randomized to the PA condition received an individualized exercise prescription and an mHealth device that provided heart rate–based JIT feedback on PA intensity, allowing them to adjust their behavior in real time to maintain MVPA during exercise sessions. Participants assigned to the healthy aging education condition received a reading prescription consisting of healthy aging topics and completed weekly quizzes based on the materials.

Results: In total, 44 participants were randomized to the intervention. A follow-up manuscript will describe the results of the intervention as well as discuss screening, recruitment, adverse events, and participants' opinions regarding their participation in the intervention.

Conclusions: The long-term goal of this intervention is to better understand how MVPA affects brain and cognitive health in the real world and extend laboratory findings to everyday life. This pilot randomized controlled trial was conducted to determine

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the feasibility of using JIT heart rate zone feedback to help older adults independently increase time spent in MVPA while collecting data on the plausible mechanisms of change (frontal and medial temporal cerebral blood flow and cardiorespiratory fitness) that may affect cognition (memory and executive function) to help refine a planned stage 2 behavioral trial.

Trial Registration: ClinicalTrials.gov NCT03058146; https://clinicaltrials.gov/ct2/show/NCT03058146

International Registered Report Identifier (IRRID): DERR1-10.2196/42980

(JMIR Res Protoc 2023;12:e42980) doi:10.2196/42980

KEYWORDS

older adults; seniors; real world; real time; digital health; feasibility; brain perfusion; cognition; adaptive intervention; exercise; clinical trial; mechanisms

Introduction

Background

It is projected that Alzheimer's disease and related dementias (ADRD) diagnoses in people aged ≥65 years will increase by 22% from 2020 to 2025 [1]. Given the lack of effective treatments for ADRD, interventions that focus on healthy lifestyle choices to prevent cognitive decline and bolster brain health are important. In this regard, the evidence suggests that the modifiable lifestyle factors most strongly associated with ADRD risk include midlife obesity, physical inactivity, and low education [2] and that approximately 21% of Alzheimer's disease cases in the United States are thought to be attributable to physical inactivity [3]. Importantly, up to 40% of dementia cases could be prevented by management of modifiable risk factors, including physical inactivity [4]. Moreover, strong evidence links physical activity (PA) with a reduction in age-related cognitive decline and dementia risk [4-6]. For example, higher PA is associated with 14% lower risk of dementia when compared with those with lower levels of PA [7], whereas, compared with sedentary individuals, even low-to-moderate PA has been associated with a 35% reduction of risk for cognitive decline [8]. Despite this, just 46% and 32.3% of individuals aged 65 to 74 years and ≥75 years, respectively, met the 2008 Physical Activity Guidelines for Americans [9], and 29.4% of people aged ≥65 years reported performing no PA other than their job in the past 30 days in 2020 [10]. The 2018 Physical Activity Guidelines for Americans issued by the US Department of Health and Human Services recommend that older adults achieve at least 150-300 minutes per week of moderate-intensity PA or 75-150 minutes per week of vigorous-intensity PA, perform muscle-strengthening activities on ≥2 days per week, do balance training, and “move more and sit less” throughout the day [11,12]. Traditionally, the cognitive and ADRD-preventing benefits of PA have been more strongly linked to changes in moderate-to-vigorous PA (MVPA) [13] that can lead to improvements in cardiorespiratory fitness [14,15]. As such, interventions that target MVPA are needed to help older adults achieve current PA guidelines and prevent ADRD in late life.

It should be noted that most interventions that investigate how changes in MVPA affect cognition and brain health have been conducted in controlled settings or under supervised conditions. These interventions are difficult to implement on a large scale and are less generalizable than those conducted in a person’s natural environment. Research is needed to develop novel interventions to help older adults increase their engagement in MVPA in free-living environments. Notably, mobile health (mHealth) technology (eg, smartwatches and heart rate trackers) can help fill this gap and extend laboratory findings to the real world by helping older adults achieve PA recommendations independently, reaching more individuals, and potentially increasing adoption and adherence [16,17].

To maximize the efficacy of mHealth interventions, there is a need for these technologies to offer adaptive and just-in-time (JIT) feedback to help individuals change their behavior in real time [18,19], as well as provide social support to help promote behavior change [20]. For example, leveraging heart rate tracking to provide JIT support about PA intensity in real time during an exercise session can cue individuals to change their walking pace accordingly and spend more time in MVPA during an exercise bout. This JIT support can also help with self-monitoring, which is an important component of successful mHealth PA interventions [20]. Although mHealth use may at times be challenging for some older adults, there is low-to-moderate evidence that mHealth interventions may help to increase PA in older adults in the short term [20], and research supports the effectiveness of mHealth approaches in those aged ≥50 years [21]. Similarly, tracking with mHealth devices has been shown to enhance the positive effect of PA levels on satisfaction with physical fitness [22], and older adults find that mHealth devices that provide JIT feedback can help them to walk faster during free-living exercise sessions [23]. Overall, research suggests that mHealth can facilitate behavior change in older age [24-26].

Objectives

The Independent Walking for Brain Health study was a 12-week small pilot randomized controlled trial (RCT) conducted to determine the feasibility of using JIT heart rate–based feedback to help older adults independently meet PA recommendations of 150 minutes of MVPA per week [12,27], while collecting data on the plausible mechanisms of change (frontal and medial temporal cerebral blood flow [CBF] and cardiorespiratory fitness) that may affect cognition (memory and executive function) to help refine a planned stage 2 behavioral trial. We hypothesized that the heart rate–based JIT feedback would help older adults to increase the time they spent in MVPA during free-living exercise sessions [23]. The long-term goal of this intervention is to better understand how MVPA affects brain and cognitive health in the real world and extend laboratory findings to everyday life. Participants randomized to the PA

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condition (PAC) were provided with personalized walking prescriptions, weekly performance summary emails, goal setting, and regular telephone calls from study staff to review achievements and revise goals if needed. JIT mHealth strategies included immediate haptic and visual alerts when the participants deviated from their individualized heart rate target zone during an exercise session. Participants in the healthy aging education condition (HAEC) received a reading prescription and answered quizzes based on the materials. We collected accelerometer data, cardiorespiratory fitness data, brain imaging data, and cognitive performance data to evaluate the feasibility of the study procedures, as well as daily-level heart rate data from the mHealth device that participants used to record their exercise sessions. This protocol paper describes the Independent Walking for Brain Health pilot RCT.

Methods

Study Procedures

The Independent Walking for Brain Health study was a 12-week free-living pilot RCT to determine the feasibility of using JIT heart rate–based feedback to help older adults independently meet PA recommendations of 150 minutes of MVPA per week. Participants who met the inclusion criteria (described in the next section) were randomly assigned to the PAC or HAEC and were provided with either a walking prescription or a reading prescription, respectively. All aspects of the intervention took place remotely, aside from the measurement visits, which were conducted at the University of California San Diego at baseline, 6 weeks, and 12 weeks. More details about each component of the intervention and the measures collected are described in the sections that follow. Table 1 shows the assessments collected and the time interval in which they were administered. Figure 1 depicts the study flow and procedures.

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Table 1. Measures administered and schedule of administration.

Measure	Phone screen	Baseline	6 weeks	12 weeks	Continuous
Demographic and medical history					
Basic demographics	✓				
Self-reported physical activity	✓				
Eligibility criteria	✓	✓			
Physician's clearance	✓				
Framingham Stroke Risk Profile		✓			
Blood pressure, heart rate, weight, and height		✓		✓	
mHealth[a] heart rate tracking					✓
Cognition					
Telephone interview for cognitive status	✓				
Mattis Dementia Rating Scale		✓			
Rey Auditory Verbal Learning Test		✓	✓	✓	
Trail-Making Test		✓	✓	✓	
Stroop Color Word Interference Test		✓	✓	✓	
Verbal Fluency		✓	✓	✓	
WMS-R[b] Logical Memory I and II		✓	✓	✓	
NIH[c] Toolbox Cognition Battery		✓	✓	✓	
Accelerometer measurement (7 days)		✓	✓	✓	
Submaximal GXT[d] treadmill test		✓		✓	
Brain magnetic resonance imaging		✓		✓	
Apolipoprotein E genotype				✓	
Questionnaires					
Geriatric Depression Scale		✓	✓	✓	
Sedentary Behavior Questionnaire		✓	✓	✓	
Everyday Cognition Questionnaire		✓	✓	✓	
Subjective Cognitive Decline Questionnaire		✓	✓	✓	
PROMIS[e] Anxiety		✓	✓	✓	
PROMIS Depression		✓	✓	✓	
PROMIS Social Sat DSA[f]		✓	✓	✓	
Exit survey				✓	

[a]mHealth: mobile health.

[b]WMS-R: Wechsler Memory Scale, revised version.

[c]NIH: National Institutes of Health.

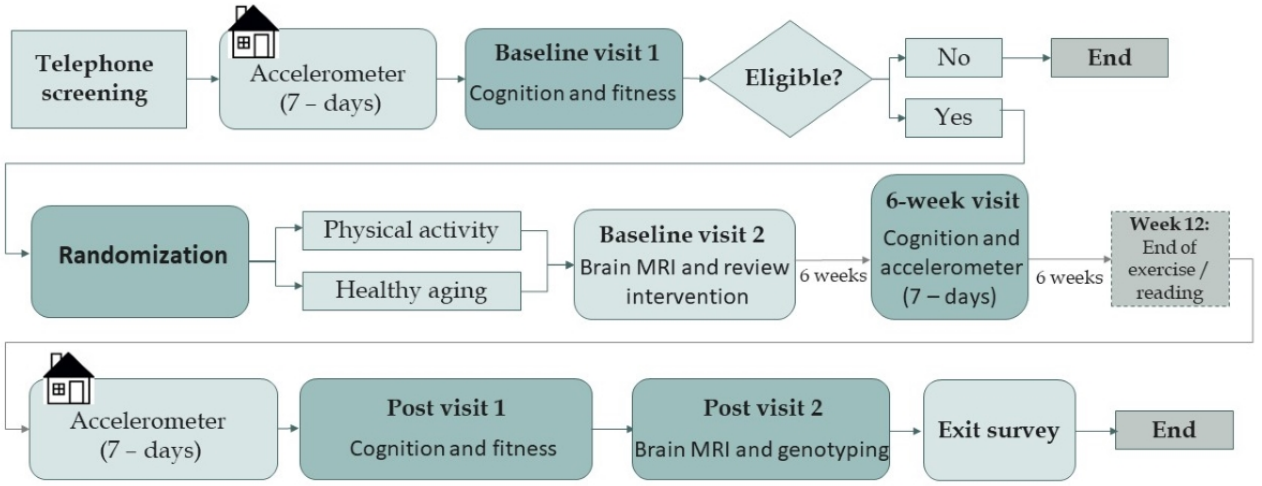
[d]GXT: graded exercise testing.

[e]PROMIS: Patient-Reported Outcomes Measurement Information System.

[f]Social Sat DSA: Satisfaction with Participation in Discretionary Social Activities.

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Figure 1. Study flow. MRI: magnetic resonance imaging.



Participant Recruitment and Inclusion Criteria

Participants were recruited from ongoing studies at the Wellness Initiative for Senior Enrichment laboratory at the University of California San Diego and the Shiley-Marcos Alzheimer's Disease Research Center, as well as from ResearchMatch [28], flyers, community engagement talks (ie, talks at retirement communities, senior centers, libraries, and health fairs) and by word of mouth. All participants were enrolled between October 2017 and March 2020, at which time study recruitment was terminated because of the COVID-19 pandemic.

All potential participants were prescreened via telephone to determine basic eligibility, which included (1) age between 65 and 80 years, (2) able to obtain a signed physician's clearance for participating in PA, (3) English speaking, (4) not meeting the current PA recommendations of 150 minutes of MVPA per week (via self-report), (5) not reporting contraindications for magnetic resonance imaging (MRI), and (6) able to ambulate independently. Participants were excluded if they had (1) objective evidence of cognitive impairment during the telephone screen (scores ≤34 on the modified Telephone Interview for Cognitive Status [29]) or during baseline (first in-person visit) neuropsychological testing (performance >1 SD below demographically adjusted norms on at least 2 measures within the same cognitive domain [30]); (2) history of head injury involving loss of consciousness within the past 6 months; (3) major neurological disorders (eg, dementia, multiple sclerosis, or epilepsy); (4) chronic major psychiatric disorders (eg, schizophrenia or bipolar disorder); (5) history of major vascular events (eg, myocardial infarction or stroke); (6) history of diabetes; (7) history of falls in the last year resulting in hospitalization; and (8) unstable or severe medical problems (eg, uncontrolled heart failure or hypertension, pulmonary disease with hypoxia or hypercapnia, significant liver problems, or renal failure), treatment of cancer (other than nonmelanoma skin cancer) in the past 2 years, or were HIV positive.

Ethics Approval

All study procedures were reviewed and approved by the institutional review board of the University of California, San Diego (IRB #151278), and abided by the declaration of Helsinki. Written informed consent was gathered from all participants after a thorough discussion of the risks and benefits of participating in the program. All data were deidentified and maintained in a Health Insurance Portability and Accountability Act–compliant server (Research Electronic Data Capture [REDCap]; Vanderbilt University). All participants were compensated up to US $200 for participating in the in-person study visits.

Study Design

The Independent Walking for Brain Health pilot study was a 12-week RCT designed to test the feasibility of using an mHealth device to assist older adults independently achieve recommended PA guidelines (≥150 minutes per week of MVPA) in their free-living environments. Only the participants randomized to the PAC received an individualized exercise prescription and a commercially available mHealth device that provided heart rate–based JIT feedback regarding PA intensity during exercise sessions. Those assigned to the HAEC received a reading prescription about healthy aging topics and completed weekly quizzes based on the materials. More details are provided in the following sections.

Randomization Procedures

We planned to recruit 60 older adults to be randomized to the HAEC (n=30, 50%) or PAC (n=30, 50%). Because of the COVID-19 pandemic, only 44 participants were randomized before study termination, with 23 (52%) in the HAEC and 21 (48%) in the PAC. Stratified blocked randomization was used to ensure a similar balance of age (block 0: 65-72 years and block 1: 73-80 years) and sex (block 0: male and block 1: female) between the intervention conditions (block 0: HAEC and block 1: PAC). The randomization table was generated by an independent statistician and uploaded to the REDCap database. Participants were randomized to the PAC or HAEC after completing their first baseline visit to ensure that they met our cognitive testing inclusion criteria and were able to safely perform the cardiorespiratory fitness test. Participants who did not meet our cognitive testing inclusion criteria or did not pass the treadmill test were withdrawn from the study before randomization (Figure 1). Randomization was performed by the REDCap database using the randomization schedule randomly created by the statistician. Given the pilot nature of

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the study, the principal investigator (PI) and measurement staff were not blinded to the participants' assigned condition.

Intervention Arms

PAC Description

The main goal of the PAC was to use the mHealth device as a *coach* to provide JIT support to prompt real-time changes in PA intensity to maintain MVPA. Participants received individualized walking prescriptions based on heart rate targets equivalent to MVPA obtained from submaximal graded exercise testing (GXT) at baseline. As such, each participant's heart rate target for the MVPA prescription was different based on their GXT performance (described in the Measures section). The individualized exercise prescriptions were built to gradually increase the intensity of PA and the number of minutes spent in MVPA to 150 per week. Refer to Table 2 for an example of the exercise prescription. Although the prescriptions were based on walking, participants were encouraged to perform any purposeful activity that increased their heart rate above their individualized minimum target equivalent to MVPA. Participants who did not meet the weekly number of MVPA minutes in the prescription during a given week were encouraged to increase MVPA by 10 minutes the following week. The exercise prescription also included prompts for performing strength and flexibility exercises weekly (ankle circles, toe lifts, partial stands, knee flexion and extension, and wrist, shoulder, calf, and shin stretches) accompanied by pictures and descriptions to guide participants on how to perform these exercises safely at home. As our focus was on increasing MVPA, we did not track progress or engagement in the strength and flexibility exercises.

Table 2. Exercise prescription. Prescribed number of minutes per week within each intensity level.

Intervention week	Slow minutes	Moderate minutes	Fast minutes	MVPA[a] (moderate+fast) minutes	All active minutes per week
1	50	20	0	20	70
2	60	20	10	30	90
3	30	40	15	55	85
4	0	70	15	85	85
5	0	90	30	120	120
6	30	60	35	95	125
7	0	100	35	135	135
8	30	100	25	125	155
9	0	110	35	145	145
10	0	115	35	150	150
11	0	125	35	160	160
12	0	125	35	160	160

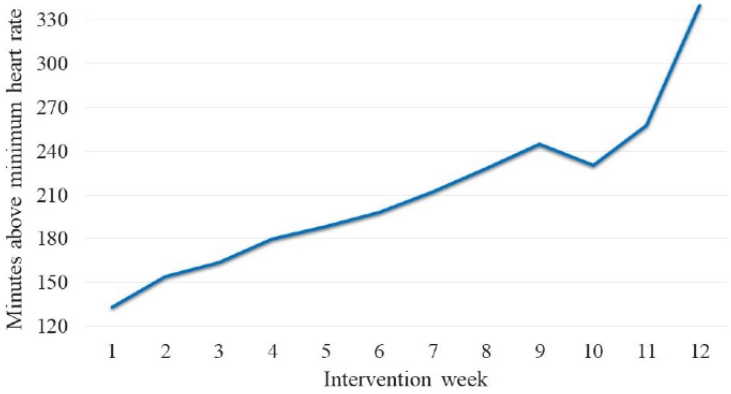
[a]MVPA: moderate-to-vigorous physical activity.

During the randomization visit, participants in the PAC received their individualized walking prescriptions, the mHealth device, and a folder containing readings about PA, safety, and troubleshooting the mHealth device, as well as important contact information and a detailed schedule of upcoming telephone calls and in-person appointments. Participants were also coached on how to use the mHealth device and respond to the JIT feedback during a walking session with study staff. Participants received a weekly personalized email summarizing the number of minutes spent in MVPA for that week (Figure 2), which also delineated their MVPA goal for the following week. Weekly telephone calls from study staff (ZZZ, the PI, who is a licensed clinical neuropsychologist) lasted 10 to 15 minutes and were conducted during the first month, followed by biweekly calls during months 2 and 3. The telephone calls focused on reviewing the minutes of MVPA achieved, identifying challenges to engaging in exercise, revising goals as needed, and checking on each participant's safety.

At home, the mHealth device tracked participant heart rate during each exercise session, providing JIT haptic and visual feedback in real time (blue=below zone, green=in zone, and red=above zone) when they deviated from their prescribed heart rate target zone. This allowed them to correct their walking pace or exercise intensity in real time. Participants were encouraged to exercise above their minimum heart rate equivalent to MVPA, but they were not discouraged from going above their target zone if they felt it was safe to do so. Minute-by-minute heart rate data gathered from the mHealth device was saved to the device and later synced with the corresponding app and emailed to the study team on a regular basis. This helped with accountability and tracking by the study team to provide weekly feedback about progress via emails and telephone calls. Participants' perspectives about using the mHealth device in this study have been described elsewhere [23].

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Figure 2. Example progress graph emailed weekly to participants in the physical activity condition to review moderate-to-vigorous physical activity goals and set new goals for the following week. The y-axis shows the number of minutes the participant spent above their minimum moderate-to-vigorous physical activity heart rate target for each week based on tracking from the mobile health device. The x-axis depicts the treatment week.



HAEC Description

Participants assigned to the HAEC received a reading prescription that equated the time spent reading study materials to the time those in the PAC spent engaging in PA (approximately 2.5 hours per week). The reading prescription consisted of 50 short or bulleted chapters to be completed over 12 weeks on topics that included retirement, quality of life, talking to your physician, bladder health, pain, preventing falls, legal and financial planning, heart health, nutrition, stress management, and humor. There were 4 to 5 chapters (the number of chapters varied based on chapter length) emailed to participants every week, which they could read at their own pace. Participants received a weekly quiz via REDCap that required them to answer 3 to 5 questions about each chapter to measure adherence to the reading prescription. Participants received weekly telephone calls from study staff during the first month, followed by biweekly calls during months 2 and 3. The purpose of the telephone calls, which lasted 5 to 10 minutes, was for the participants to receive equal amounts of attention from study staff between the conditions as well as for the study staff to answer any questions related to the materials and check on the participant's health status. All the chapters were prepared by the investigative team using materials freely available from the National Institute on Aging and Alzheimer's Association websites among other reputable sources. Textbox 1 lists the reading prescription topics assigned per month.

Textbox 1. Reading prescription topics assigned to participants in the healthy aging education condition.

Month and topics
1. Retirement, driving, immunizations, health care, prostate and bladder health, pain, memory, eye health, medications, heart health, disability, taste, smell, frontotemporal disorders, quality of life, and talking to your physician
2. Mental health, dementia, preventing falls, antiaging tips, leukemia, disease prevention, hearing loss, arthritis and osteoporosis, legal and financial planning, mild cognitive impairment, Alzheimer's disease, lifestyle and longevity, sexual health, high blood pressure, Alzheimer's disease caregiving, and humor
3. Heart disease, stress management, gum disease, alternative medicine, headaches and migraines, diabetes, myocardial infarction, nutrition, preventive medicine, skin care and aging, sleep and aging, social media, stroke, constipation, hydration, food for thought, and happiness in the home and the community

Measures

Cognitive Testing

In a quiet room with a trained study staff member, participants completed the Mattis Dementia Rating Scale [31]; the National Institutes of Health (NIH) Toolbox Cognition Battery [32] (including the optional Oral Symbol Digit Test); the Rey Auditory Verbal Learning Test (RAVLT) [33]; the Golden version of the Stroop Color Word Interference Test [34]; the Wechsler Memory Scale-revised Logical Memory I and II [35]; Trail-Making Test parts A and B [36]; and verbal fluency tests (FAS Test [assessment of phonemic fluency by requesting an individual to orally produce as many words as possible that begin with the letters F, A, and S within 1 minute] and animal naming) [37]. As executive and memory functions are most responsive to exercise in intervention trials with older adults [14], we created executive and memory composite scores by converting raw scores into *z* scores based on the entire sample, and then averaging across *z* scores for the following tests:

- Executive composite scores: Trail-Making Test part B minus Trail-Making Test part A (scores were reversed before averaging to reflect higher scores=better performance), Stroop Color Word Trial, and verbal fluency FAS Test
- Memory composite scores: Wechsler Memory Scale-revised Logical Memory I and II; RAVLT trials 1 to 5, trial 6 (short-delay free recall), and RAVLT delayed recall

We picked these measures because they have previously been reported in the PA intervention literature and have been shown to change as a function of exercise [14].

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PA Measurement

PA was measured using triaxial accelerometers (GT3X; ActiGraph, LLC) for 7 consecutive days [38,39]. Participants were instructed to wear the accelerometer on a belt on their hip during waking hours for a minimum of 12 hours per day. They were also instructed not to change their regular activities. To ensure compliance, all participants received 2 telephone calls from study staff (on days 2 and 5 of the monitoring period). Participant data were considered valid only if they had accumulated a minimum of 600 minutes of accelerometer wear per day and a minimum of 3000 total minutes of wear spread across at least 4 valid days. Data were processed using ActiLife software (version 6.0; ActiGraph, LLC). Using the low-frequency extension option thought to be most appropriate for older adults [40], data were aggregated to 60-second epochs so that published cut points could be applied. Consistent with standard practice, sedentary time was defined as time spent at <100 counts per minute and MVPA as ≥1952 counts per minute [41]. Minutes within each intensity level were then averaged across days worn, reflecting the average time in minutes per day spent at each intensity level.

Cardiorespiratory Fitness Measurement and Heart Rate Target Zones for the Exercise Prescription

Cardiorespiratory fitness was measured via submaximal GXT protocol at baseline and at 12 weeks. During the treadmill test, heart rate was plotted against the workload and its corresponding estimated VO_2 [42], and VO_2 max was estimated plotting the slope of the line to estimated maximal heart rate (calculated using the formula 220–age). A 1-minute warm-up at 2 mph (3.2 km/h) was used to familiarize participants with the treadmill and give them time to adjust to walking without holding the handrails. After the warm-up, the speed was increased to 2.5 mph (4 km/h) at 0% grade, equivalent to 2.9 metabolic equivalents (METs), which is just below the threshold for moderate-intensity exercise. This stage lasted 3 minutes to ensure that steady state was achieved. The speed was then increased to 3 mph (4.8 km/h) at 0% grade, equivalent to 3.3 METs, which is just above moderate-intensity exercise. This stage lasted 5 minutes. One-minute stages with grade increments of 1.5% (0.62 METs) per stage continued until the participant's heart rate reached volitional fatigue. Heart rate was monitored continuously using a Polar heart rate monitor (Polar FT4 or similar; Polar Electro) throughout the test and for at least 5 minutes of recovery. Blood pressure was recorded for the first 3 stages of exercise and every minute during recovery, at which time participants continued walking at a very slow pace (1 mph; 1.6 km/h) for 2 minutes, followed by 3 minutes of sitting recovery with light foot tapping to prevent venous pooling.

The heart rates measured during the final 10 seconds of minutes 7 and 9 of the GXT were used to determine heart rate target zones for the exercise prescription.

These heart rate measurement times occurred during stage 3 (3 mph; 4.8 km/h) at which participants are estimated to be working at a level equivalent to 3.3 METS, a threshold slightly higher than the minimum level to be considered *moderate* activity. Minutes 7 and 9 of the total protocol were chosen because of the likelihood that participants would have reached *steady state* after ≥3 minutes at that workload. Steady state is the point at which the heart's work is equal to the workload and is unlikely to change with increased exercise duration. For exercise prescription purposes, the 2 heart rate values gathered during minutes 7 and 9 of the total protocol were averaged if the difference was ≤3 beats per minute, and the greater of the 2 heart rates was used if the difference was >3 beats per minute. Participants were asked to refrain from consuming caffeine or other stimulants on the day of their test.

For this pilot RCT, we were interested in examining the plausible mechanisms by which changes in MVPA may affect cognition, including changes in cardiorespiratory fitness. We defined changes in cardiorespiratory fitness as the total time to 85% of estimated maximal heart rate (with an exception made for participants taking β-blockers, as described later in this paragraph) and changes in rate-pressure product (RPP), which is the product of heart rate and systolic blood pressure divided by 100 measured toward the end of each of the first 3 stages of exercise. RPP is an indirect assessment of cardiac workload. A decrease in RPP for a given amount of aerobic work often signifies an improvement in cardiac function [43]. Individuals taking β-blockers were asked to exercise to a workload corresponding to 80% of their age-predicted maximal heart rate. This precaution accounts for the approximately 5% reduction in heart rate observed with taking β-blockers and allowed the research team to provide scaled exercise prescriptions.

Brain MRI Measurement and Processing

MRI data were acquired on a GE Discovery MR750 3.0T (General Electric Company) whole body system with a body transmit coil and an 8-channel receive-only head coil at the University of California, San Diego Center for Functional MRI. The structural brain sequence consisted of a high-resolution T1-weighted fast spoiled gradient echo (3DFSPGR) scan for anatomy and registration purposes: 172 1-mm contiguous sagittal slices, field of view=25 cm, repetition time (TR)=8 ms, echo time (TE)=3.1 ms, flip angle=12°, inversion time=600 ms, 256 × 192 matrix, bandwidth=31.25 kHz, frequency direction=S-I, NEX=1, and scan time=8:13 minutes. CBF was quantified with a 2D pseudocontinuous arterial spin labeling (ASL) MRI sequence: TR=4500 ms, TE=3.2 ms, field of view=24 cm, labeling duration=1800 ms, postlabeling delay=2000 ms, with a single-shot spiral acquisition and a total scan time of 4:30 minutes plus a 40.5-second calibration scan. The calibration scan was acquired immediately after the ASL scan using a spiral readout with TR=4.5 seconds and TE=3.2 ms with 8 dummy radiofrequency pulses (amplitude set to 0) to generate a 36-second delay followed by a 90-degree radiofrequency pulse in the last repetition interval to generate proton density–weighted contrast. Field map scans were collected for offline field map correction to minimize signal bunching and dropouts in the frontal or medial temporal lobes.

T1-weighted anatomical images were processed using FreeSurfer software (version 6.0). Briefly, images underwent skull stripping, B1 bias field correction, segmentation of gray matter and white matter, reconstruction of cortical surface models, and parcellation and labeling of regions on the cortical surface, as well as segmentation and labeling of subcortical

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structures [44]. FreeSurfer was also used to generate intracranial volume. ASL data were processed using the Cerebral Blood Flow Biomedical Informatics Research Network (CBFBIRN) [45] pipeline established by the University of California, San Diego Center for Functional MRI. CBFBIRN uses a combination of custom MATLAB (The MathWorks, Inc) [46] routines and various Analysis of Functional NeuroImages [47] and FMRIB Software Library [48] functions to quantify CBF and adjust for partial volume effects. MATLAB was used to form a mean ASL image from the average difference of the control and tag images. Voxelwise CBF calibration was performed using the proton-density image to convert the ASL difference signal into physiological units (mL/100 g/min). Slice-timing delays were also accounted for, making the postlabeling delay slice specific. Skull stripping of the high-resolution T1-weighted image was performed using the Analysis of Functional NeuroImages 3dSkullStrip function. Tissue segmentation was performed using the FMRIB Software Library Automated Segmentation Tool algorithm to define cerebrospinal fluid, gray matter, and white matter regions. The high-resolution T1-weighted image and partial volume segmentations were registered to ASL space. A linear regression method was used to correct for partial volume effects and ensure that CBF values were not influenced by decreased perfusion in the white matter or increased volume of cerebrospinal fluid [49], with a 5 × 5 regression kernel to obtain corrected gray matter CBF measurements. Each participant's partial volume–corrected quantified CBF map (in units of mL/100 g tissue/min) was downloaded to a local server. Voxels with negative intensities were replaced with 0. FreeSurfer was used to generate a priori anatomical regions of interest for the CBF data. Briefly, for each participant, the FreeSurfer-formatted T1-weighted brain volume was registered to the ASL CBF-aligned T1-weighted anatomical image (the latter was derived as part of the CBFBIRN pipeline). The resulting coregistration matrix was used to align the FreeSurfer aparc+aseg segmentation volume to the ASL CBF-aligned T1-weighted image. The CBF-aligned FreeSurfer volumes were visually inspected to ensure proper alignment and were then downsampled to the resolution of the CBF ASL image. Mean CBF was then extracted for FreeSurfer regions of interest. For this pilot RCT, we were interested in examining the plausible mechanisms by which changes in MVPA may affect cognition, including changes in total gray matter CBF, frontal lobe CBF (mean of superior frontal, rostral and caudal middle frontal, pars opercularis, pars triangularis, pars orbitalis, lateral and medial orbitofrontal, precentral, paracentral, and frontal pole CBF), and medial temporal lobe CBF (mean of entorhinal, parahippocampal, and hippocampal CBF).

Apolipoprotein E Measurement

Saliva samples were collected using the Isohelix SK-2S DNA buccal swab kit (Cell Projects Ltd) to provide information regarding genetic risk for Alzheimer's disease. Genotype for apolipoprotein E was determined by real-time analysis of single nucleotide polymorphism using TaqMan technology (Life Technologies). The real-time analysis was performed using validated TaqMan assays on a CFX96 Touch Real-Time Polymerase Chain Reaction Detection System (Bio-Rad Laboratories, Inc) according to the manufacturer's instructions. Analysis was performed using Bio-Rad CFX Manager software.

Monitoring Adverse Events and Data Safety and Monitoring Plan

All adverse events were carefully monitored via telephone contact with participants throughout the trial and were reported to the institutional review board of the University of California, San Diego, and the National Institute on Aging program official according to NIH guidelines. A data safety and monitoring plan was developed for this study focusing on close monitoring by the PI (ZZZ) and research staff, in conjunction with oversight from a safety officer (AAM, a practicing geriatrician). A future publication of the pilot trial's results will report all adverse events.

Data Management and Quality Control

All study staff completed NIH-required human research participants training as well as thorough training by the study PI (ZZZ) on how to perform telephone screenings, administer and score the cognitive tests, and interact with participants, as well as on ethical aspects of clinical trials research and safe data monitoring practices. All cognitive testing data were double scored by 2 different staff members and entered into the REDCap database, which was also double-checked for accuracy. Accelerometer and cardiorespiratory fitness data were collected by professionals at the University of California, San Diego Exercise and Physical Activity Resource Center, which specializes in collecting these measurements with highly trained exercise physiologists. All brain imaging data were collected and analyzed by highly trained study personnel, including the PI. Study protocols were strictly followed to ensure scientific rigor and allow for reproducibility.

Results

Enrollment for this study began in October 2017 and was terminated early in March 2020 as a result of the COVID-19 pandemic. In total, 44 participants were randomized to the intervention, with 21 (48%) in the PAC and 23 (52%) in the HAEC. In keeping with the CONSORT (Consolidated Standards of Reporting Trials) guidelines for pilot and feasibility trials [50,51], the results from this pilot intervention will focus on discussing the feasibility of the JIT mHealth alerts to increase MVPA, presenting estimates of variability in response to the outcome and plausible mechanisms, presenting recruitment and retention numbers and challenges, discussing adherence by study condition, discussing adverse events, discussing the ability to implement the intervention or lessons learned, and summarizing the participants' opinions regarding the intervention. The results, which will be reported in a separate manuscript, will inform the optimization of a planned stage 2 behavioral intervention trial to help maintain cognitive function through increases in MVPA using mHealth.

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Discussion

Overview

This protocol paper describes the Independent Walking for Brain Health pilot RCT. The study was an innovative mHealth trial to determine the feasibility of using heart rate–based JIT feedback to help older adults maintain MVPA during free-living exercise sessions. This pilot trial also explored the mechanisms, namely changes in CBF and cardiorespiratory fitness, by which increasing MVPA via JIT alerts may influence cognitive function. Between October 2017 and March 2020, a total of 44 participants were randomized to the intervention, with 21 (48%) in the PAC and 23 (52%) in the HAEC. A follow-up manuscript will describe the results of the pilot intervention.

The literature shows that MVPA, performed under supervised conditions (in the laboratory, gym, or supervised by a trainer) is important for maintaining brain health [52-55] and can boost cognitive performance in older age [56-59]. However, there is a lack of interventions that leverage mHealth to help older adults increase their engagement in MVPA independently, which would generalize study findings to the real world and remove some of the barriers to performing PA (eg, travel to the gym and monetary constraints). This pilot RCT is the first step in the refinement of a future stage 2 behavioral trial to help older adults achieve and maintain MVPA independently to help support their cognition and brain health. The findings from this pilot RCT will help inform the larger trial and refine the plausible mechanisms of change, as well as determine whether JIT heart rate–based feedback can help older adults to increase time spent in MVPA independently.

Limitations

The pilot study includes the following limitations:

1. A short intervention time (12 weeks), which is not sufficient to observe changes in cognitive function [60]. Future mHealth interventions should be of longer duration.
2. The mHealth device used in this study was not specifically designed for older adults. Future trials should use devices that have been tested with older adults to increase the likelihood of adherence to, and acceptability of, the intervention.
3. Importantly, this trial focused on promoting only MVPA because evidence suggests that MVPA is needed to maintain brain health and perhaps prevent ADRD [13]. That said, we did encourage participants to perform stretching and toning exercises twice per week (and provided them with related materials) to follow the current PA guidelines.
4. Most recently, dementia prevention interventions have followed a multimodal approach, targeting several lifestyle factors such as diet, sleep, and cognitive training along with PA [61-67]. This study is limited in targeting only MVPA as a tool to promote brain health; however, data gathered from this study will be useful to determine whether using JIT heart rate–based feedback via mHealth successfully increases MVPA in free-living environments, which could be implemented in future multimodal interventions.

Conclusions

In conclusion, the findings from this pilot RCT can inform future mHealth interventions that target MVPA to promote brain and cognitive health in older age and will help us to determine the utility of using JIT heart rate–based feedback to help maintain MVPA in free-living environments. Although more research is needed to determine the efficacy of JIT interventions to improve PA in older age, these interventions have the potential to be a powerful tool to help older adults lead healthier lifestyles [18,19,68]. Healthy lifestyles that include higher levels of MVPA are promising to ameliorate the burden of ADRD on the health care system and patients and their families, as well as improve the quality of life of older adults [4,63,69].

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Conflicts of Interest

MWB receives royalties from Oxford University Press. The authors have no further interests to declare.

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Abbreviations

ADRD: Alzheimer's disease and related dementias
ASL: arterial spin labeling
CBF: cerebral blood flow
CBFBIRN: Cerebral Blood Flow Biomedical Informatics Research Network
CONSORT: Consolidated Standards of Reporting Trials
FAS Test: assessment of phonemic fluency by requesting an individual to orally produce as many words as possible that begin with the letters F, A, and S within 1 minute
GXT: graded exercise testing
HAEC: healthy aging education condition
JIT: just-in-time
MET: metabolic equivalent
mHealth: mobile health
MRI: magnetic resonance imaging
MVPA: moderate-to-vigorous physical activity
NIH: National Institutes of Health
PA: physical activity
PAC: physical activity condition
PI: principal investigator
RAVLT: Rey Auditory Verbal Learning Test
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
RPP: rate-pressure product
TE: echo time
TR: repetition time

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Protocol

Using a Safety Planning Mobile App to Address Suicidality in Young People Attending Community Mental Health Services in Ireland: Protocol for a Pilot Randomized Controlled Trial

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Abstract

Background: Over 700,000 people die by suicide annually, making it the fourth leading cause of death among those aged 15-29 years globally. Safety planning is recommended best practice when individuals at risk of suicide present to health services. A safety plan, developed in collaboration with a health care practitioner, details the steps to be taken in an emotional crisis. SafePlan, a safety planning mobile app, was designed to support young people experiencing suicidal thoughts and behaviors and to record their plan in a way that is accessible immediately and in situ.

Objective: The aim of this study is to assess the feasibility and acceptability of the SafePlan mobile app for patients experiencing suicidal thoughts and behaviors and their clinicians within Irish community mental health services, examine the feasibility of study procedures for both patients and clinicians, and determine if the SafePlan condition yields superior outcomes when compared with the control condition.

Methods: A total of 80 participants aged 16-35 years accessing Irish mental health services will be randomized (1:1) to receive the SafePlan app plus treatment as usual or treatment as usual plus a paper-based safety plan. The feasibility and acceptability of the SafePlan app and study procedures will be evaluated using both qualitative and quantitative methodologies. The primary outcomes are feasibility outcomes and include the acceptability of the app to participants and clinicians, the feasibility of delivery in this setting, recruitment, retention, and app use. The feasibility and acceptability of the following measures in a full randomized controlled trial will also be assessed: the Beck Scale for Suicide Ideation, Columbia Suicide Severity Rating Scale, Coping Self-Efficacy Scale, Interpersonal Needs Questionnaire, and Client Service Receipt Inventory. A repeated measures design with outcome data collected at baseline, post intervention (8 weeks), and at 6-month follow-up will be used to compare changes in suicidal ideation for the intervention condition relative to the waitlist control condition. A cost-outcome description will also be

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undertaken. Thematic analyses will be used to analyze the qualitative data gathered through semistructured interviews with patients and clinicians.

Results: As of January 2023, funding and ethics approval have been acquired, and clinician champions across mental health service sites have been established. Data collection is expected to commence by April 2023. The submission of completed manuscript is expected by April 2025.

Conclusions: The framework for Decision-making after Pilot and feasibility Trials will inform the decision to progress to a full trial. The results will inform patients, researchers, clinicians, and health services of the feasibility and acceptability of the SafePlan app in community mental health services. The findings will have implications for further research and policy regarding the broader integration of safety planning apps.

Trial Registration: OSF Registries osf.io/3y54m; https://osf.io/3y54m

International Registered Report Identifier (IRRID): PRR1-10.2196/44205

(JMIR Res Protoc 2023;12:e44205) doi:10.2196/44205

KEYWORDS

suicide prevention; mobile health; mHealth; safety planning; SafePlan; mobile phone

Introduction

Background

More than 700,000 people die by suicide every year, representing the fourth leading cause of death among 15-29-year-olds globally in 2019 [1]. In Ireland, provisional figures indicate that 340 individuals died by suicide in 2020 [2]. Approximately one-third of people who die by suicide have been in contact with mental health services in the year before their death, and approximately 1 in 5 had contact with a health professional in the month before their death [3]. Suicide prevention guidelines recommend safety planning interventions alongside follow-up treatment by mental health services for those presenting to health services at risk of suicide [4]. However, the decision to implement safety planning in practice can be influenced more by clinicians' beliefs about their efficacy than by empirical research [5]. The transient nature of suicidal ideation [6] may challenge the feasibility of paper-based plans and suggests the need for alternative modalities.

Suicide Risk Factors

Suicidal behavior remains extremely difficult even for experienced clinicians to predict [7], leading researchers to focus their efforts on brief interventions designed for those at immediate risk [8]. A meta-analysis of 50 years of research in the area indicated that our predictive ability has not improved in that time and called for a shift from a focus on risk factors to machine learning–based risk algorithms [9]. The application of machine learning to large data sets may offer a means of better understanding the complex processes proposed by prominent theorists in the area [10,11]. Reflective of these research findings, recent clinical best practice guidelines recommend against the use of suicide risk assessment measures to predict future suicide or repeated self-harm in young people [12] and point to the importance of comprehensive psychosocial assessment and the development of a collaboratively developed and accessible safety plan.

Safety Planning Intervention

The safety planning intervention (SPI) developed by Stanley and Brown [13] is a collaborative safety plan developed with a trained practitioner and recorded using a paper-based document. It is a brief structured intervention widely used in health systems and is often cited as the best practice in the treatment of patients with a high risk of suicide [14]. SPI is a key component across multiple treatment approaches targeting suicidal behavior, such as collaborative assessment and management of suicidality and cognitive behavioral therapy for suicide prevention. A safety plan outlines the steps to take in an emotional crisis and includes the identification of personalized warning signs, internal coping skills, people and places that provide distraction, people to contact for support, and contact details to use in a crisis. A cohort comparison trial of patients in the emergency department in US veteran hospitals presenting with suicidality found that SPI and phone follow-up significantly reduced suicidal behaviors and increased treatment engagement [13]. A recent systematic review of the effectiveness of SPI for adults experiencing suicide-related distress indicated improvements in suicidality (ideation, behaviors, and death), suicide-related outcomes (depression and hopelessness), and treatment outcomes (hospitalization) [15].

Safety Planning Mobile Apps

Recording a safety plan on a mobile app may further enhance accessibility. The use of mobile devices by individuals at risk of suicide has been recommended by the World Health Organization [16]. The delivery of suicide prevention interventions through mobile health (mHealth) apps provides many opportunities when individuals need help the most [17]. SPI has been shown to be adaptable in its modality (digital or paper based) [15]. Further research is needed to better understand the extent to which using apps as an add-on to the treatment of patients with suicidal tendencies is feasible for clinicians and patients themselves. The MYPLAN safety planning app is undergoing clinical trial (ClinicalTrial.gov NCT02877316), and the Continuous Assessment for Suicide Prevention And Research study aims to implement a Dutch translation of the MYPLAN app alongside a self-monitoring app for suicidal patients in the Netherlands [18]. Researchers recently reported on the feasibility of using smartphone apps as treatment components for outpatients with depression and suicidal tendencies and found that mobile safety planning (using

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the BackUp app) was acceptable and usable for this group; however, the integration of apps into routine treatment needs to be further explored [19]. Indeed, researchers attest that effective interventions for suicidality do exist, but many patients do not receive them because implementation efforts tend to be time limited and unsystematic [20].

Integrating mHealth in Mental Health Services

This protocol is underpinned by the research team's previous research on the experiences of mental health professionals involved in integrating mHealth technology into existing mental health services [21]. The potential benefits of using mobile apps identified by mental health professionals include increased accessibility, increased engagement with young people, and the convenience and feasibility of a client using a mobile app during a crisis [21]. Many of the benefits identified in previous research are consistent with those asserted by mental health professionals in previous research [22]. A concern identified by professionals included the potential for the technology to be used instead of face-to-face services. Such findings are in line with previous research [23], suggesting that although professionals acknowledge their possible benefits and cost-effectiveness, health care providers are conservative about integrating mHealth technologies into everyday practice.

Mental health professionals identified the following barriers to adoption: lack of trust in the technology (privacy and confidentiality) and in the health care organization, training needs, policy guidance requirements, technical support requirements, and the need for further research. This mirrors the systematic review findings of the app literature, calling for further research before such technology is recommended or prescribed [24]. The benefits identified included the needs addressed by this technology to increase accessibility, enhance engagement, enhance the efficacy and generalization of skills acquired outside of the clinic setting, and the potential for individualized data collection to enhance treatment [24]. Similar enablers have been cited by mental health professionals in previous research [23].

Engaging Young People

The use of mobile apps to record and store one's safety plan may be particularly useful in supporting young people experiencing suicidal thoughts and behaviors, often simultaneously experiencing a transition to adulthood and to adult-focused services. The onset of many psychopathologies has been shown to coincide with the transition age [25,26]. Approximately 75% of all psychiatric disorders in adults start before the age of 24 years, and 50% of all psychiatric disorders start before the age of 14 years. However, there is discord in the pattern of increased risk of psychopathology in young people and mental health service use. Clinicians have previously identified the potential benefits of mobile app use in promoting engagement among young people with mental health services [21]. Approximately 64% of adolescents reported using apps to manage their mental health symptoms [27]. Indeed, 59% of health and fitness app users are aged between 18 and 34 years, indicating a higher level of engagement in health apps within this age group [28].

Methodological Considerations

This trial is informed by a systematic review examining the effectiveness of mHealth technology tools in reducing suicide-specific outcomes, along with the review protocol [29,30]. This systematic review identified 7 studies that met the inclusion criteria. A total of 4 published articles that reported on the effectiveness of the following mobile phone apps were included: iBobbly [31], Virtual Hope Box [32], BlueIce [33], and Therapeutic Evaluative Conditioning [34]. The results demonstrated some positive impacts for individuals at an elevated risk of suicide or nonsuicidal self-injurious behaviors, including reductions in depression, psychological distress, and self-harm and increases in coping self-efficacy. However, none of the evaluated apps demonstrated the ability to significantly decrease suicidal ideation when compared with a control condition.

A significant limitation identified across all studies pertained to the heterogeneity of outcomes. Studies focused on differing suicide outcomes such as suicidal ideation as opposed to suicidal behaviors and often used differing outcome measures (ie, Beck Suicidal Intent Scale, Columbia Suicide Severity Rating Scale [C-SSRS], and Suicidal Ideation Attributes Scale). This hampered the extent to which the data could be compared and generalized. Another methodological issue is the practice of excluding individuals experiencing current suicidal thoughts or behaviors from participation. Importing empirically supported treatments for depression may not be appropriate because the trials in which efficacy was established excluded individuals who engage in suicidal behavior By embedding the trial within secondary-level mental health services, individuals at risk of suicide can participate safely while accessing mental health treatment. This methodological change is designed to reduce sample bias, enhance generalizability, and inform implementation research [20]. The evidence available indicates that suicide prevention mobile apps lead to reductions in depression, psychological distress, and self-harm in those at elevated risk of suicide or self-harm [29]. However, the pace of suicide prevention app development needs to be matched by scientifically rigorous research and the use of clinically valid methodologies that inform broader implementation of existing mental health services.

SafePlan

SafePlan is a safety planning mobile app designed to be used as an adjunct to therapy for individuals experiencing suicidal thoughts and behaviors who access mental health services. The SafePlan app was designed and developed following significant stakeholder engagement and cocreation with young people, clinicians, suicide prevention researchers, suicide prevention policy developers, computer scientists, and human-computer interaction specialists. The SafePlan design process is described in detail elsewhere [35]. In addition to the capacity to develop and record a collaborative safety plan on the app, it also supports the completion of dialectical behavior therapy (DBT) diary cards, which was deemed appropriate. This feature was included on the advice of clinicians who noted that individuals who complete a safety plan as part of their treatment may also engage in DBT. The integration of DBT diary cards [36] can be enabled

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in the app's clinical settings, in consultation with a mental health care professional, for patients who are engaged in this form of intervention. Consistent with research evaluating the Virtual Hopebox [32], the app also supports the inclusion and display of personalized Reasons for Living, such as photos, text, and videos, in visibly prominent places within the app.

This study details the first feasibility trial of the SafePlan mobile app within mental health services. Current Medical Research Council (MRC) guidance on complex interventions [37] advocates pilot trials and feasibility studies as part of a phased approach to the development, testing, and evaluation of health care interventions.

Study Objectives

The study objectives are as follows: (1) examine the feasibility and acceptability of the SafePlan app as an adjunct to therapy for patients (aged 16-35 years) accessing secondary-level Irish mental health services and their clinicians; (2) assess the feasibility of the study procedures for both clinicians and patients within secondary-level mental health services; (3) determine the sample size required for a full randomized controlled trial (RCT) by collecting suicide outcome data at baseline, post intervention, and at 6-month follow-up; (4) determine whether the SafePlan app condition yields superior outcomes on the outcomes of suicidal ideation, suicidal behavior, and nonsuicidal self-injurious behavior at 6-month follow-up and post treatment when compared with the control condition; and (5) complete an economic analysis of the intervention.

Research Question

> *Is the SafePlan app, along with the proposed outcome measures, feasible and acceptable to patients aged 16-35 years at risk of suicide and their clinicians, in secondary-level mental health services in Ireland?*

The feasibility and acceptability of using the following outcome measures in a full RCT will be assessed: the Beck Scale for Suicide Ideation (BSSI), C-SSRS, Coping Self-Efficacy Scale (CSES), Interpersonal Needs Questionnaire (INQ), and Client Service Receipt Inventory (CSRI) [38-42].

Data will be collected at baseline, post intervention, and at 6-month follow-up to determine whether the SafePlan app yielded superior outcomes on primary outcomes of suicidal ideation, suicidal behavior, and nonsuicidal self-injurious behavior when compared with the control group.

- Participants: A total of 80 patients aged 16-35 years accessing secondary-level mental health services who present with current suicidal ideation, nonsuicidal self-injurious behavior, or a previous suicide attempt will be randomized to the SafePlan or control condition.
- Intervention: SafePlan is a safety planning mobile app informed by the paper-based SPI by Brown and Stanley [13]. Participants in the SafePlan condition will use the SafePlan app to record their safety plan in consultation with their mental health professional over an 8-week period as an adjunct to usual treatment.
- Comparison: The control group will receive treatment as usual (TAU) supplemented with the paper-based safety plan by Brown and Stanley [13] completed with their mental health professional.
- Outcome: The primary outcomes are feasibility outcomes and include the acceptability of the app to participants and clinicians, feasibility of delivery in this setting, recruitment, retention, and app use. Data collected on measures of suicidal ideation; suicidal behavior; and nonsuicidal self-injurious behavior at baseline, post intervention (8 weeks), and at 6-month follow-up will be used to compare changes in outcomes for the SafePlan condition relative to the control condition. A cost-outcome description will also be undertaken. Thematic analyses will be used to analyze the qualitative data gathered through semistructured interviews with patients and clinicians.

Methods

Design

The SafePlan study is a pilot RCT of SafePlan, a mobile-based safety planning app. A parallel group randomized design will be used with 1:1 patient allocation to the 2 treatment arms. In the control condition, participants will receive TAU supplemented with a paper-based safety plan. In the intervention condition, participants will use the SafePlan app to record their safety plan in consultation with their mental health professional, in addition to routine treatment. In both conditions, participants will receive appropriate care through their mental health team for an elevated risk of suicide throughout the study. Quantitative data will be collected at baseline, post intervention (8 weeks), and at 6-month follow-up (from baseline), with an additional safety check assessment at 4 weeks in both conditions.

Participants

Participants will include patients aged 16-35 years who are currently accessing secondary-level mental health services (child and adolescent mental health services [CAMHS] or adult mental health Services [AMHS]). Participants who present with current suicidal ideation, nonsuicidal self-injurious behavior in the previous 6 months, or a previous self-reported suicide attempt will be recruited across 2 community health care organizations. Participants will be assessed by members of their mental health team, will be accessing treatment with an assigned key therapist for the entire duration of the intervention, and will provide appropriate consent (for participants aged 16-18 years, parental consent is also required). Key workers will inform potential participants who meet the eligibility criteria (Textbox 1) and for whom a SPI is clinically indicated. Participants' psychiatric diagnoses will be recorded, but it will not be a cause for exclusion, as suicidality occurs across diagnostic categories.

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Textbox 1. Participant inclusion and exclusion criteria.

Inclusion criteria

- Aged 16-35 years
- Presenting with current suicidal ideation, nonsuicidal self-injurious behavior in the last 6 months, or having a lifetime history of a self-reported suicide attempt
- Currently accessing Health Service Executive community mental health services (child and adolescent mental health services or adult mental health services)
- Have been allocated a key clinician to work with the participant for the duration of the intervention
- The key clinician or treating team identify that a safety plan is clinically indicated
- They were proficient in English to allow the provision of informed consent and the completion of measures in English
- Use a smartphone and can download the SafePlan app

Exclusion criteria

- Indicates no suicidal ideation, nonsuicidal self-injurious behavior, or previous suicide attempts
- Are medically unfit for interview
- Are not actively engaged with mental health services
- Are unable to provide informed consent
- Are outside of the specified age range
- Level of English is not sufficient to complete outcome measures in English
- Do not have access to a smartphone

Clinicians

Clinicians involved in providing the intervention in both arms will be mental health service professionals and members of the patient's multidisciplinary team who have undergone specialist training in addressing suicidality in clinical practice and the implementation of safety planning and who have completed the SafePlan technical orientation and training session. Data regarding the type of treatment received will be collected across both groups from the person's clinical file (number of face-to-face contacts, therapeutic approach used, profession of the key clinician, and prescribed medications) and the CSRI [42].

Sample Size

There is no established gold standard for calculating the sample size for a feasibility study, as the purpose of the study determines the sample size justification. In a systematic assessment of sample sizes in pilot and feasibility trials, Billingham et al [43] reported a median sample size of 36 participants, ranging from 10 to 300 participants. The aim of the SafePlan trial is to evaluate the feasibility of using the app as an adjunct to treatment. According to the clinician's and service manager's advice, a sample of 60 patients would be eligible for recruitment. With an expected 25% (20/80) dropout rate [43], a sample of 80 patients appeared adequate for the purposes of this study. Therefore, we will aim to recruit 80 patients from mental health services in Health Service Executive (HSE) West and Mid-West.

Setting

Participants will be recruited from community mental health services across 2 Irish community health care organizations. Participants will complete the baseline, postintervention, and follow-up measures in their mental health service setting. The orientation to the SafePlan intervention will be conducted face-to-face in the participant's service. The control condition participants will also be introduced to paper-based safety planning face-to-face and in their service. Semistructured interviews will be conducted in the participants' service and in the clinician's workplace. Interviews exploring the intervention process may also be conducted by phone, depending on participant's preferences and other safety considerations. Where face-to-face data collection is not possible owing to health concerns or other unforeseen circumstances, measures may be completed remotely. In such instances, the researcher will communicate with the participant's key worker and members of the treating team, following the call to ensure that any information relevant to the participant's safety is communicated to their treating team.

Procedures

Mental health service multidisciplinary teams across both health care areas will be informed of the study and made aware of the inclusion and exclusion criteria. Team members will be asked to identify patients who are eligible to participate and for whom a safety plan is clinically indicated. Mental health service professionals will inform potential participants about the study and invite them to meet the researcher. If the patient agrees, the researcher will approach the patient, provide them with a participant information sheet, and answer any questions they may have. If the patient agrees, informed consent will be obtained by the researcher. In consenting to participate, participants will also agree to the researcher accessing their medical file notes. Information on the semistructured interviews and fidelity assessment will also be provided, and consent to

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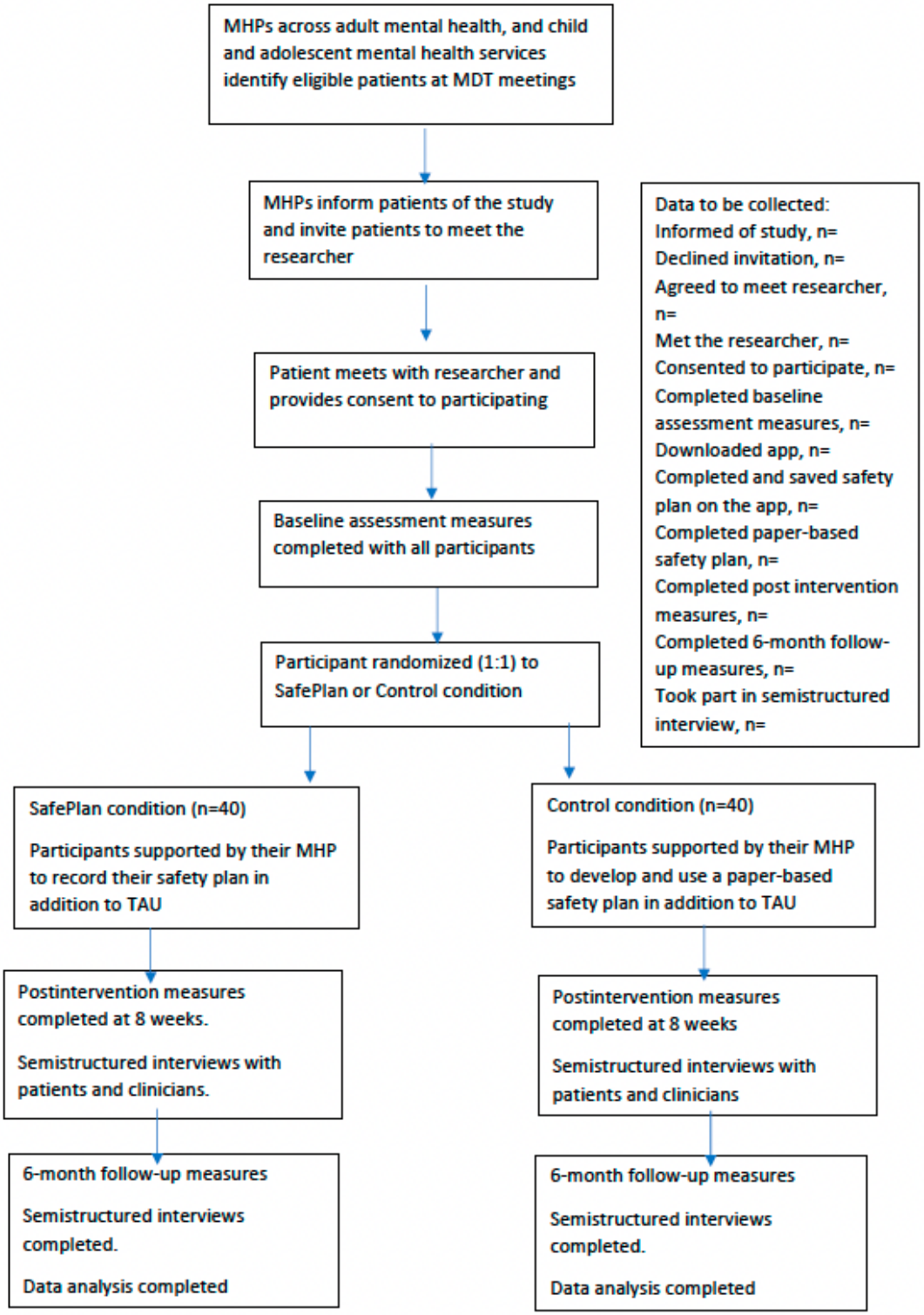
future contact for this purpose will be sought. Clinicians across both community health organizations will be invited to participate in semistructured interviews to discuss their experiences of delivering the intervention.

Previously established clinician champions at each site will promote recruitment within their own teams and at weekly team meetings. Doctorate in clinical psychology students, in fulfillment of their clinical research experience and under the supervision of the principal investigator, will also support data collection across sites.

Baseline assessment measures will be administered to eligible participants who have consented to participate. Following the baseline assessment, participants will be randomized (1:1) to either the SafePlan or control condition.

An overview of the study procedures is provided in Figure 1.

Figure 1. Overview of SafePlan protocol. MDT: multidisciplinary team; MHP: mental health professional; TAU: treatment as usual.



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Randomization

Randomization of participants will occur with equal probability for both groups. Participants will be stratified based on the suicide outcomes reported using the C-SSRS (Suicidal ideation/Non Suicidal Self Injurious Behavior/Suicide Attempt). Randomization will be carried out by a clinician using the sealed envelope randomization package.

Blinding

Neither the participant nor the researcher will know the treatment arm allocation while the initial study measures are being completed. Participants will receive either the SafePlan as an adjunct to TAU or TAU supplemented with a paper-based safety plan. After randomization, both the participant and researcher will be unblinded to the participant's allocation, which is unavoidable given the nature of the study.

Before starting the SafePlan intervention, all participants will receive a 15-minute training session on how to use the app, including downloading and password protection settings. Measures will be taken face-to-face at baseline, post intervention (8 weeks), and at 6-month follow-up. In addition to accessing TAU, phone-based check-ins will be conducted at week 4 for all participants. Participants will, therefore, have face-to-face or telephone contact with the clinician researcher at baseline assessment, 4 weeks (check-in), 8 weeks (post intervention), and 6-month follow-up. The control group participants will receive the same schedule of contacts and assessment measures.

SafePlan Condition

The SafePlan mobile app is available to download for free and is accessed at no cost to participants. SafePlan enables participants to record their safety plan, developed with a clinician, and store it on the app to facilitate access and use outside of the clinic. Participants assigned to the SafePlan condition will meet the researcher for instructions on downloading and using the app on their personal smartphones and subsequently meet their key clinician to guide individual use of the app for safety planning. Participants will be guided by the researcher and subsequently their clinician to use SafePlan to record their safety plan in the clinic and implement the plan outside the clinic. Both patients and clinicians will be encouraged to refer to the SafePlan app during their appointments over the 8-week course of the intervention period. The SafePlan app will be used as an adjunct to treatment and will be implemented in parallel with routine community mental health care.

Control Condition

Participants assigned to the control condition will similarly meet the researcher following enrollment for orientation to paper-based safety planning and subsequently meet their clinician to guide individualized safety planning using the safety planning template by Brown and Stanley [12]. As with the SafePlan condition, participants in the control group will be guided by the researcher and subsequently by their clinician to develop and record a safety plan using the paper-based safety plan template by Brown and Stanley [12]. Both patients and clinicians will be encouraged to refer to the paper-based safety plan during their appointments over the 8-week course of the intervention period. A paper-based safety plan will be used in addition to routine community mental health care.

Data Collection

Feasibility

Feasibility is defined as the extent to which the app can be successfully used by patients attending community mental health services and by their clinician as components of standard treatment. Feasibility will be assessed in terms of recording a safety plan on the app, in-session app use, and app use over the course of treatment (as reported by patients and clinicians). Quantitative data from patients will be collected at baseline, post intervention (8 weeks), and at 6-month follow-up; qualitative data from patients and clinicians will be collected through semistructured interviews. Table 1 presents the study data collection timelines. Psychometric measures will be administered at multiple time points to identify possible differences in the outcomes over the course of the study.

Feasibility outcomes will include the acceptability of the intervention to participants and clinicians, feasibility of delivery in this setting, recruitment, retention, and app use. Quantitative data on the number of potential patients who were approached and who declined, who were not eligible, and who were retained will be recorded and presented in the Consolidated Standards of Reporting Trials diagram for the study.

This study will be conducted in line with the MRC guidelines on the evaluation of complex interventions [37], with data collected via quantitative and qualitative methods.

Participants who consent to be contacted for the qualitative element of the study will be invited to participate in a one-to-one interview about their experiences of the intervention and of study procedures. The interviews will be conducted face-to-face at the university or health service site, and where necessary, participants will be given the additional option of a telephone interview. In the case of telephone interviews, verbal consent will be audio-recorded at the beginning of the interview.

Mental health professionals (n=12) directly involved in participants' care and in delivering the intervention (eg, CAMHS/AMHS multidisciplinary team members) will be invited to participate in the semistructured interviews. Interviews will focus on the feasibility of the intervention and the acceptability of the study and intervention procedures, including experienced or perceived barriers and facilitators, intervention "fit" within the setting, and suggestions for improvement.

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Table 1. Study data collection timelines.

	Demographic information	Clinical file data	Client Service Receipt Inventory	Columbia Suicide Severity Rating Scale	Beck Scale for Suicide Ideation	Interpersonal Needs Questionnaire	Coping Self-Efficacy Scale	Safety plan completion	App use (self-report)	Paper plan use (self-report)
Baseline SafePlan condition	✓	✓	✓	✓	✓	✓	✓			
Baseline control condition	✓	✓	✓	✓	✓	✓	✓			
4-week check-in SafePlan condition				✓				✓	✓	
4-week check-in control condition				✓				✓		✓
8-week SafePlan condition			✓	✓	✓	✓	✓	✓	✓	
8-week control condition			✓	✓	✓	✓	✓	✓		✓
6-month SafePlan condition			✓	✓	✓	✓	✓		✓	
6-month control condition			✓	✓	✓	✓	✓			✓

Outcome Measure Feasibility

Participants will be asked to complete several questionnaires with the researcher to assess the feasibility and acceptability of using these questionnaires in a full trial. The questionnaires to be completed during the trial are detailed below (an additional check-in at 4 weeks will include further administration of the C-SSRS [38]).

The BSSI [39], the proposed primary outcome for a full trial, will be administered at baseline, post intervention (8 weeks), and at 6-month follow-up to assess the feasibility of this measure in collecting suicide outcome data at multiple time points. The data collected using the BSSI will be used to calculate the sample size required for a full trial. The scale has been used as a tool for screening for the presence or absence of suicidal ideation and, more recently, as a brief measure of change in suicidal thoughts and ideation over time. This scale has high internal reliability and concurrent validity [39].

The C-SSRS is a 20-item semistructured brief and valid tool used to assess suicide risk including suicidal ideation, suicidal behaviors, previous attempts, and preparatory behaviors [38].

The CSES has shown reliability and validity in a mental health service population and can be used to assess changes in coping ability over time [40]. The Cronbach α coefficients of the factors 1, 2, and 3 and the whole CSES-Vietnamese version were at acceptable levels (.91, .86, .75, and .93, respectively).

The INQ is a 15-item measure of perceived burdensomeness and thwarted belongingness, with items rated on a 7-point Likert-type scale [41].

The CSRI is a measure used in mental health service evaluation to capture information about the use of services. The following domains will be captured within this study: general practitioner (GP) consultations, outpatient visits, use of hospital services for physical or mental health problems, mental health helpline contacts, and psychiatrist or social worker or psychologist contacts [42].

The remaining data to be gathered at 8 weeks will include the self-rated helpfulness, benefit, ease of use, likelihood of continued use, and likelihood of recommending the SafePlan app to others.

Demographic Data

Participants will be asked to provide consent to share clinical data and will have demographic data collected at enrollment. This will include participant age, sex, relationship status, highest level of educational attainment, employment status, type of service (AMHS or CAMHS), and geographic service area (Community Health Organisation 1 & 2). Clinical data collected from the participant's file will include details of current

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psychiatric diagnoses, current treatment plan (including medication if relevant), key clinician profession, and information in relation to previous suicidality to supplement participant self-report (suicidal ideation, nonsuicidal self-injurious behavior, and previous suicide attempt). Information regarding previous suicide risk or behavior is necessary to support patient safety and to inform factors that may be considered potential moderators or mediators in a full trial. A description of treatment received in both the TAU and the SafePlan conditions will be captured using the CSRI and clinical file data.

Data Sharing

At baseline, participants will be asked to consent to the researcher accessing their mental health clinical file; the researcher accessing details of the participant's emergency contact or key clinician, consultant psychiatrist, and GP and sharing clinically important information with those individuals to maintain patient safety as necessary during the trial; and the collection of data post intervention and at 6-month follow-up.

Participants in the SafePlan condition will hold their own data on their device until they choose to show it to their mental health professional when they attend the clinic in person. Their data are not automatically shared or monitored, and this is communicated to participants both upon enrollment in the study and through the terms and conditions presented when downloading the app.

A separate participant information and consent form has been developed for use with mental health professionals who will partake in semistructured interviews focusing on the feasibility and acceptability of the intervention and study procedures. All interview data will be anonymized in the final report.

Qualitative Interviews

Qualitative interviews will be conducted with patients (SafePlan group, n=12; control group, n=12) and clinicians (n=12) involved in delivering the intervention to assess the feasibility of the intervention and study procedures. The participants and their clinicians will be informed of the qualitative component of the trial during the consent process. Participants will be invited to attend a semistructured interview following the completion of the 8-week intervention. Semistructured interview topic guides will be used. Interviews will seek to better understand participants' experience of the SafePlan intervention and of the study procedures and to identify barriers to engagement with the intervention. Researchers will also seek to interview participants in the control condition (n=12) to better understand their experiences of TAU, paper-based safety planning, potential contamination, and the acceptability of study procedures.

Ethics Approval

This study was approved by the University Hospital Limerick Research Ethics Board in October 2021 (REC Ref: 055/2021). This study was preregistered through the Open Science Framework.

Consent

The researcher will follow the SafePlan Standard Operating Procedure to take appropriate action to maintain participant safety throughout. In accordance with the HSE CAMHS Operational Guidelines [44] and local HSE policy and as stated in the study information sheet, this may include contacting the participant's key clinician, consultant psychiatrist, GP, and emergency contact or contacting emergency services.

Participants will be identified by members of their mental health team and will be accessing treatment with an assigned key therapist for the entire duration of the intervention. Clinicians will identify potential participants for whom a safety plan is clinically indicated and will provide them with further information about the trial. Participants who wish to participate will be approached by the researcher, and informed consent will be obtained. In the case of those aged <18 years, assent will be required from the young person, and parental or legal guardian signed consent will be obtained before the person can proceed to enrolling in the study. All participants will be informed of their right to refuse to participate and their right to withdraw from the study.

In consenting to participate, the participants will also agree to the researcher accessing their clinical file. Information on the semistructured interviews and the fidelity assessment will also be provided, and consent to future contact for these purposes will be sought.

Data collected during the administration of the outcome measure will be shared with the participant's key clinician to support participant safety. The researcher and any personnel involved in the study will receive standardized training in addressing suicidality in line with the Irish HSE National Office for Suicide Prevention Education and Training Plan 2021-2022 [45]. Baseline, outcome, and follow-up assessments will be conducted (unless otherwise required by the participant) in the participant's mental health clinic and face-to-face to ensure optimum clinical support in situ. It is hoped that the semistructured interviews will provide further information on any potential adverse effects of data collection.

The SafePlan study will be conducted in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice standards, which is an international minimum quality standard for the ethical and scientific conduct of clinical research [46]. Safety planning is an established suicide prevention intervention that has been found to reduce the recurrence of suicidal behaviors [15]. Therefore, although the information arising from that intervention will be recorded differently, participants across conditions will receive an evidence-based intervention that is considered good practice alongside TAU. One group will store this information on a paper-based safety plan template, and the other group will store the information on their SafePlan app.

Fidelity Assessment

The MRC guidelines [37] on complex interventions strongly recommend the inclusion of fidelity assessment to explain discrepancies between expected and observed outcomes, to understand how context influences outcomes, to clarify causal mechanisms, and to provide insights to aid implementation.

Treatment fidelity assessment will include the following:

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1. Documentation of key clinician's behavior, including attendance at the SafePlan orientation and training session, completion and filing of paper-based safety plan (control condition), and development of an interactive safety plan and recording this plan using the SafePlan app (intervention condition).
2. A checklist based on the 6 core steps outlined in the safety planning template by Brown and Stanley [13] will be used to assess the extent to which key components of safety planning are addressed by clinicians in both conditions.
3. A sample (16/80, 20% approximately) of participant intervention sessions will be attended by the researcher, and the checklist will be completed to further assess the fidelity of the plan by Brown and Stanley [13].

Health Economics

A cost-outcome description will be undertaken. Data on costs will be collected on resource use related to intervention delivery (staff costs, training, and intervention materials) and patient resource use in terms of the broader health service. The CSRI will be used at baseline, 8 weeks, and 6-month follow-up to capture information regarding the use of health and social care services, such as GP consultations, outpatient visits, use of hospital services for physical or mental health problems, and social worker contacts.

The cost of providing the intervention will be calculated based on the average time taken to carry out the intervention and the hourly cost of employing the mental health professional involved. The hourly employment rate of a mental health professional at the midpoint of the salary scale will be calculated based on the available health service salary scale [47]. This will be revised upwards to account for employer-related costs and overheads, based on guidance for conducting an economic analysis within the Irish health care system [48]. Following estimation of the cost of carrying out the intervention, net cost benefit and cost-benefit ratio for providing the service will be calculated.

Data Analysis

Quantitative Data Analysis

Descriptions of recruitment rates, attrition, retention, and reported app use will be summarized. The baseline characteristics of both groups will be summarized (age, diagnosis, and treatment details). Descriptive statistics will be used to examine the uptake of the app (reported in-session app use, reported app use outside the clinic, completion of a safety plan using the app, and use of modified exponential moving average features). Data from all other measures completed at baseline, post intervention, and at 6-month follow-up (C-SSRS, INQ, Emotion Regulation Questionnaire, and Client Receipt Inventory) will be summarized.

The proposed primary outcome measure to be used in a further definitive trial—BSSI—will be summarized by a randomized group. Analyses will be conducted according to the intention-to-treat principle, using available measurements from all participants and according to their allocated groups. Missing data will be accommodated based on all available information using maximum likelihood estimation. We will examine between-group differences in BSSI scores from baseline to post intervention (8 weeks). To further explore preliminary efficacy, we will evaluate within-group changes from baseline to post intervention for each condition separately and then for both groups combined. Finally, within each condition separately, we will explore the potential maintenance of intervention benefits with a repeated measures ANOVA, including the 3 data collection time points (baseline, 8 weeks, and 6 months).

Qualitative Data Analysis

Qualitative data from interviews with study participants and clinicians will be analyzed via thematic analysis using the approach by Braun and Clark [49]. Data collection will continue until data saturation is reached. In total, 25% (9/36) of the interviews will be double coded to ensure reliability. Disagreements will be resolved by discussion.

There are specific ethical challenges when conducting qualitative research. As there may be potential for distress, the team developed a research protocol that provides contact details of appropriate additional support if needed. It is important to maintain confidentiality and pseudoanonymity. Informed consent is an ongoing process that continues after obtaining written consent [50]. The team will be cognizant of this throughout the project.

McGrath and Nilsson [51] outlined the challenges in qualitative data sharing. However, transparency and rigor are critical. We will use some of the strategies outlined by McGrath and Nilsson [51], which include outlining procedures for data sharing when obtaining informed consent, data minimization, and pseudonymization.

Tsai et al [52] advocated that "coding queries may offer greater anonymity compared with full transcripts because statements are grouped by theme rather than by study participant." They further support this process as preferable to sharing full transcripts. In this research, qualitative analysis will be managed using NVivo (version 12; QSR International) qualitative analysis software [53]. This will provide a clear audit trial and permit the execution of coding and matrix queries to ensure transparency.

Progression From Feasibility to Full Trial

Shanyinde et al [54] reported 14 issues that needed to be evaluated in feasibility studies or pilot trials. "A process for Decision-making after Pilot and feasibility Trials" (ADePT) by Bugge and Williams [55] examines the "methodological issues" identified in a feasibility study that may hinder or facilitate progression to a definitive trial. ADePT permits an examination of the evidence from the feasibility study and the degree to which "methodological issues, " such as recruitment, retention, adherence, and acceptability of the intervention, among others, have been successful. From the feasibility study findings, ADePT provides a framework to decide whether there should be an amendment to the intervention, context of its delivery, and confirmed trial design before embarking on a full trial. This study will use the ADePT 14-point reporting framework of methodological issues and decision tools to evaluate whether the feasibility study has achieved its objectives and to identify

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the need for intervention, clinical context, and trial design modification.

Results

As of January 2023, funding has been approved, ethics approval has been received, and clinician champions across mental health service sites have been established. Service-wide Suicide Prevention and Self-harm Mitigation Training has been completed with clinicians with the support of the National Office for Suicide Prevention. The process of research personnel recruitment has commenced. Data collection is expected to commence when personnel are in post (estimated April 2023). The projected date of submission of completed manuscript is April 2025.

Discussion

Principal Findings

This study will provide clinically valid data on the feasibility and acceptability of the SafePlan app as an adjunct to therapy for patients (aged 16-35 years) accessing community mental health services and their clinicians. It is hypothesized that patients and clinicians will find the app both feasible and acceptable and that important barriers and enablers to its use within Irish community mental health services will be identified. Data regarding the feasibility of the study procedures for both patients and clinicians will inform the decision to progress to a full trial. This is the first study to examine the feasibility of the SafePlan app and accompanying trial study procedures. Suicide outcome data collected at baseline, post intervention, and at 6-month follow-up will inform the sample size required for a full RCT. These data will also help determine whether the SafePlan app condition yields superior outcomes on standardized measures of suicidal ideation, suicidal behavior, and nonsuicidal self-injurious behavior at 6-month follow-up and post treatment when compared with the control condition. It is hypothesized that the SafePlan app condition will yield superior outcomes when compared with the control condition.

Safety planning interventions offer an evidence-based means of addressing suicidality in at-risk individuals [14]. A meta-analysis of safety planning–type interventions (SPTIs) for suicide prevention found that the relative risk of suicidal behavior among patients who received an SPTI compared with a control condition was 0.570 (95% CI 0.408-0.795; *P*=.001; number needed to treat: 55). The results support the use of SPTIs to help prevent suicidal behavior and the inclusion of SPTIs in clinical guidelines for suicide prevention [14]. SafePlan moves beyond the recording of safety plans using paper-based templates to record and store the plan, developed with a health care professional, on a mobile app. The results of this study will inform further research and the integration of safety planning apps within mental health services.

SafePlan is distinctly different from the mobile apps currently being trialed with this population [19,31,32]. Previous and ongoing trials used a safety planning app and a separate ecological momentary assessment app in parallel. Trial authors note “the next step would be to combine mobile safety-planning and self-monitoring apps” [19]. SafePlan delivers this by providing a means of recording behaviors that patients can discuss with their mental health professional at their next clinic appointment. The findings of this study will, therefore, provide provisional data on the feasibility and acceptability of this next-generation safety planning app in community mental health services.

Previous research has focused on the use of safety planning interventions in hospital settings and as a stand-alone intervention [13]. However, safety planning is also an important treatment component of community mental health services for those presenting with suicidal ideation and behaviors. This study adds to the existing research by focusing on the feasibility of using such technology within such services.

Limitations

A potential limitation of the study procedure is that the participants will be unblinded to the type of intervention once they have been assigned to either condition. This is unavoidable, given the distinct nature of each condition (paper based vs app based). However, both the participants and researchers will be unaware of the treatment condition while the baseline measures are being completed.

As data are not automatically shared by the app with the clinician on an ongoing basis, the researcher will depend on the participant attending follow-up appointments and choosing to share their data at that time. It may be the case that useful data will be lost because of attrition, particularly at 6-month follow-up. This may be particularly relevant to understanding the experiences of participants who discontinued using the app. However, the data-sharing procedures were designed to respect and protect participant data. All participants were informed of the procedures before they consented to participate. It is hoped that the inclusion of semistructured interviews with both patients and their clinicians will help address this potential limitation.

Conclusions

Health care policy nationally and internationally [56,57] proposes the need for integrated care facilitated by innovations in digital health. The use of mobile devices by individuals at risk of suicide has been recommended by the World Health Organization [16]. The SafePlan app was designed to support individuals in completing and recording an evidence-based safety plan with their clinician. This protocol outlines the first feasibility and acceptability trial of the SafePlan App and the related study procedures. The trial adds to the existing research conducted in hospital settings by examining the feasibility of this safety planning mobile app within community mental health services. The findings may have implications for patients, clinicians, health services, and policy makers regarding the integration of safety planning mobile apps more generally and may inform future research in mHealth and suicide prevention.

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Acknowledgments

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Data Availability

Deidentified aggregate data sets generated during or analyzed during this study may be made available from the corresponding author upon reasonable request and provided data sharing is in accordance with the study's ethics approval, the study's data protection impact statement, and general data protection regulations.

Conflicts of Interest

None declared.

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Abbreviations

ADePT: Decision-making after Pilot and feasibility Trials
AMHS: adult mental health services
BSSI: Beck Scale for Suicide Ideation
CAMHS: child and adolescent mental health services
CSES: Coping Self-Efficacy Scale
CSRI: Client Service Receipt Inventory
C-SSRS: Columbia Suicide Severity Rating Scale
DBT: dialectical behavior therapy
GP: general practitioner

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HSE: Health Service Executive
INQ: Interpersonal Needs Questionnaire
mHealth: mobile health
MRC: Medical Research Council
RCT: randomized controlled trial
SPI: safety planning intervention
SPTI: safety planning–type intervention
TAU: treatment as usual

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Protocol

An Intervention to Increase Condom Use Among Users of Sexually Transmitted Infection Self-sampling Websites (Wrapped): Protocol for a Randomized Controlled Feasibility Trial

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Abstract

Background: Reducing the rates of sexually transmitted infections (STIs) among young people is a public health priority. The best way to avoid STIs from penetrative sex is to use a condom, but young people report inconsistent use. A missed opportunity to intervene to increase condom use is when young people access self-sampling kits for STIs through the internet. The potential of this opportunity is enhanced by the increasing numbers of young people being tested through this route every year in England. Hence, in a cocreation by young people, stakeholders, and researchers, Wrapped was developed—a fully automated, multicomponent, and interactive digital behavior change intervention developed for users of STI self-sampling websites, who are aged 16-24 years.

Objective: This paper is a protocol for a feasibility randomized controlled trial (fRCT). The fRCT seeks to establish whether it is feasible to run a randomized controlled trial to test the effectiveness and cost-effectiveness of Wrapped. Wrapped aims to reduce the incidence of STIs through increasing correct and consistent use of condoms among users of STI self-sampling websites, who are aged 16-24 years.

Methods: A 2-arm parallel-group randomized fRCT of Wrapped plus usual care, compared to usual care only (basic information on STIs and condom use), with a nested qualitative study. A minimum of 230 participants (aged 16-24 years) are recruited from an existing chlamydia self-sampling website. Participants are randomized into 1 of 2 parallel groups (1:1 allocation). Primary outcomes are the percentage of users recruited to the fRCT and the percentage of randomized participants who return a chlamydia self-sampling kit at month 12. Additionally, besides chlamydia positivity based on biological samples, surveys at baseline, month 3, month 6, and month 12, are used to assess condom use attitude, behavioral capability, self-efficacy, and intention, along with details of any partnered sexual activity and condom use, and health economic data. Nested qualitative interviews with trial participants are used to gain insight into the factors affecting recruitment and attrition.

Results: Recruitment to the fRCT began in March 2021 and was completed in October 2021. Data collection was completed in December 2022.

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Conclusions: This feasibility study will provide data to inform the design of a future-definitive trial. This work is timely given a rapid rise in the use of internet testing for STIs and the sustained high levels of STIs among young people.

Trial Registration: ISRCTN Registry ISRCTN17478654; http://www.isrctn.com/ISRCTN17478654

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KEYWORDS

adolescent; condom use; digital health; eHealth; feasibility randomized controlled trial; sexual health; sexually transmitted infections; STIs; self-testing; young people

Introduction

Background and Rationale

Sexually transmitted infection (STI) diagnoses in England have been persistently high over the past decade [1]. Although the most recent annual data show a 32% reduction in STI diagnoses, down from a 10-year high of 467,096 in 2019 to 307,901 in 2020, this likely reflects a temporary shift brought about by the COVID-19 pandemic, which placed restrictions on public behavior and reduced access to STI testing [1,2]. Young people continue to carry a high burden of infection, with 46% of all new diagnoses among 15- to 24-year-olds [1]. Furthermore, women, those of Black ethnicity, those living in the most deprived areas, and men who have sex with men, remain disproportionately affected [1]. Among young people, chlamydia continues to be the most prevalent STI [1]. Rates of chlamydia among 15- to 24-year-olds have been high but stable over recent years, whereas increases have been observed for other STIs, such as gonorrhea and syphilis [2]. The removal of COVID-19 restrictions and an increase in testing availability will likely bring with it a return to prepandemic levels of STI diagnoses and as such, sexual health continues to be a public health concern [1]. Untreated STIs can lead to serious health consequences, such as pelvic inflammatory disease, ectopic pregnancy, and infertility, which have a significant impact on health and quality of life [3]. The estimated annual cost to the National Health Service (NHS) of STI treatment is £620 (US $762.6) million [4]. The best way to avoid STIs from penetrative sex is to use a condom [5], but young people report inconsistent use [6,7].

Although condom use is the cornerstone of STI prevention, STI testing is important for treatment and to prevent onward transmission. There have been notable changes in the landscape of STI testing within England since 2017. In the period between 2017 and 2019, against a backdrop of increasing testing overall, there was a shift toward the use of internet services, and away from other nonspecialist services [8]. Between 2018 and 2019, while the number of tests carried out by specialist sexual health services (eg, genitourinary medicine services) remained relatively stable, those carried out by nonspecialist services (excluding internet testing), such as pharmacies, general practice, and community-based settings, decreased by 9%, and those by internet services increased by 69% [8]. This trend reflects recent year-on-year increases, with internet testing accounting for 4% of all testing in 2017, 13% in 2018, and 19% in 2019 [8]. The global COVID-19 pandemic has further served to accelerate the move in this direction across Europe [9,10]. In England, despite there being a reduction of 30% in expected levels of chlamydia testing in 2020, a 2-fold increase in internet testing was observed, with approximately 40% of all chlamydia testing being processed through the internet in 2020 [1]. Whether internet testing remains at these elevated levels or begins to adjust back toward those observed prepandemic, remains to be seen. Regardless, internet testing is now an established and significant route to STI diagnosis and treatment within England.

Evidence indicates that STI self-sampling websites are effective at reaching higher prevalence groups; chlamydia positivity is comparable to that of other nonspecialist services [8], and they attract equivalent numbers of males and females, and those from across the spectrum of deprivation (E Hollis, unpublished data, 2017). Repeated use of internet testing services is however common, with chlamydia positivity remaining high for those that retest (E Hollis, unpublished data, 2017), suggesting that testing online does not reliably translate into future individual prevention efforts. Furthermore, while information on STIs and contraceptive methods is typically found on self-sampling websites, this is insufficient for behavior change [11], and inconsistent with Public Health England guidance to provide those at elevated risk of STIs with preventative intervention [12]. As such, self-sampling websites provide an important but currently missed opportunity to intervene with a priority group.

In 2016-2017, with the support of Medical Research Council Public Health Intervention Development funding and in line with Medical Research Council guidance on the development of complex interventions [13], Wrapped was cocreated by young people, stakeholders, and researchers [14]. Wrapped is a fully automated, multicomponent, and interactive digital intervention developed for the users of STI self-sampling websites aged 16-24 years. It aims to reduce the incidence of future STIs by increasing correct and consistent use of condoms for penetrative sex. The users of STI self-sampling websites can be signposted to Wrapped upon order of an STI self-sampling kit (through a hyperlink). Content is tailored, with between 1 and 6 different components allocated to users in accordance with their self-identified barriers to condom use. These barriers reflect important behavioral determinants of condom use identified through existing meta-analyses [15-18], namely condom use attitudes (particularly beliefs around pleasure, enjoyment, and spontaneity), condom availability, and behavioral capability and self-efficacy for condom use and communication.

In 2019, funding was awarded by the National Institute for Health and Care Research Public Health Research program to determine whether it is feasible to run a randomized controlled

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trial (RCT) to test the effectiveness and cost-effectiveness of Wrapped. This paper presents the protocol for this feasibility randomized controlled trial (fRCT).

Aim and Objectives

The aim of this study is to assess whether and how it is possible to carry out a future definitive RCT to evaluate the effectiveness and cost-effectiveness of Wrapped plus usual care, in comparison to usual care only.

The primary objectives are to estimate the following parameters for planning a definitive RCT:

1. The rate of recruitment of eligible participants.
2. The rate of participant follow-up for the definitive RCT primary outcome measure (chlamydia positivity at 12 months measured using biological samples).

The secondary objectives are as follows:

1. Estimate the rate of participant follow-up for the definitive RCT secondary outcome measure chlamydia cumulative incidence.
2. Identify whether the level of deprivation of the final sample is representative of web-based STI self-sampling users.
3. Identify whether differential retention occurs across groups (gender, ethnicity, sexual identity, deprivation, randomized groups, and chlamydia diagnosis at baseline).
4. Measure chlamydia positivity at 12 months in the intervention and control groups (to support sample size calculation for the definitive RCT).
5. Identify the rate of attrition at 3 months, 6 months, and 12 months, and ways of minimizing this.
6. Determine the feasibility and participant acceptability of all primary and secondary outcome measures (including health economic measures).
7. Identify which recruitment messages result in the highest rate of recruitment.
8. Identify and remove the intervention "friction points" (using web analytics data) to minimize attrition and maximize the future intervention dose.
9. Identify costs and resource use associated with the intervention for health care services and users (to inform the design of the definitive RCT and the future economic evaluation).
10. Measure contamination of intervention effect in the control group.
11. Identify possible adverse effects of the intervention, for example, participants' inadvertent disclosure that they are testing for an STI or increase in consumption of pornography.

Study Design

A 2-arm parallel group fRCT of Wrapped plus usual care compared to usual care alone with a nested qualitative study.

Methods

Please refer to Multimedia Appendix 1 for a visual representation of the study design, recruitment process, and timing of measures based on the Consolidated Standards of Reporting Trials (CONSORT) extension for pilot and feasibility trials [19].

Study Population and Setting

Recruitment, intervention delivery, and data collection are conducted entirely on the internet. Participants will be recruited from an existing chlamydia self-sampling website (freetest.me [20]). Freetest.me provides a web-based chlamydia testing service to local authority areas across England (typically subcontracted to and administered through NHS trusts) and is free at the point of use. For the purposes of this study, users of freetest.me residing in 1 of 4 local authority areas will be invited to participate.

Eligibility Criteria

The inclusion and exclusion criteria are outlined in Textbox 1.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria:

- Aged 16-24 years.
- Living in a local authority area participating in the study.

Exclusion criteria:

- No internet access.
- Sexual activity does not typically include penetrative sex (penis in vagina or anus).

Participant Timeline

Table 1 gives an overview of participant activities and timing.

To recompense for time spent in completing activities, participants will receive payment in the form of vouchers (see Multimedia Appendix 2 for the schedule of payments).

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Table 1. Participant activities across the duration of the study.

Activity	M0[a]	M3[b]	M6[c]	M12[d]
Read participant information	✓			
Complete consent	✓			
Complete survey	✓	✓	✓	✓
Self-report chlamydia test result	✓			
Complete chlamydia self-sample		✓		✓

[a]M0: month 0.

[b]M3: month 3.

[c]M6: month 6.

[d]M12: month 12.

Recruitment

A study invitation will be placed on the "thank you" page of the freetest.me website displayed to users after they have placed an order for a chlamydia self-sampling kit. Every 2 weeks, the advert will change to emphasize a different value proposition (see Multimedia Appendix 3 for the list of adverts). A hyperlink within the advert will take users to Research Electronic Data Capture (REDCap), a secure data capture and management platform, for participant information and consent (see Multimedia Appendix 4 for a copy of the participant information and consent form). Each individual's freetest.me order number will be appended to the URL. This order number will be captured by REDCap enabling the research team to ensure that each participant is a unique and genuine user of freetest.me.

Survey Completion (Months 0, 3, 6, and 12)

REDCap is being used to monitor and manage all survey data collected as part of this study. Surveys will be conducted at baseline (month 0 [M0]), month 3 (M3), month 6 (M6), and month 12 (M12) and used to collect data on condom use attitude, behavioral capability, self-efficacy, and intention, along with details of any partnered sexual activity and condom use that has occurred in the previous 3-month period. The surveys will also be used to measure the experience of partner resistance to condom use and to collect health economic data. There are between 63 and 76 core items per survey (depending on time point), with data largely being collected using fixed response items and Likert scales (see Multimedia Appendix 5 for survey items). The baseline survey will additionally collect participant's contact details to enable communication with participants regarding the completion of follow-up surveys, and basic demographic data. The M3 survey will also be used to collect self-reported data on participant engagement with the intervention.

Completion of the baseline survey is scheduled immediately after consent is provided. All other survey completion will be triggered by email. Participants who do not complete the survey will be sent up to 3 reminders (delivered by SMS text message). Subsequently, if no response is received, 1 email and 1 telephone call will be made to prompt completion. During the telephone call, participants will be given the option to verbally respond to a reduced set of survey questions. Finally, if there is still no response, a paper-based version of the survey will be posted out with a stamped addressed return envelope. Those who have not provided any data 20 days after the initial survey is sent out will be classed as nonresponder. Surveys will continue to be sent to nonresponders (as well as chlamydia tests—see below) at subsequent time points unless a participant asks to be withdrawn from the study.

Chlamydia Testing (M0, M3, and M12)

Chlamydia tests will be processed by freetest.me at M0, M3, and M12. The chlamydia test at M0 is triggered by participants when they order a self-sampling kit through the freetest.me website immediately before receiving the study invite (see "recruitment" above). Participants will be asked to self-report their result, and any treatment received if applicable, through SMS text message. A single SMS text message reminder will be sent to participants who do not respond. Those who have not provided this data 4 weeks after the SMS text message contact is made will be classed as nonresponders.

The chlamydia tests at M3 and M12 will be processed differently to that at M0. For this purpose, chlamydia self-sampling kits will be sent directly from the study team to participants. One week before posting the kits, participants will be sent an SMS text message asking them to confirm or amend their postal address. The kits that participants receive at M3 and M12 will contain the usual user instructions to collect the sample and return by Freepost to freetest.me for processing. Participants will be sent 3 SMS text message reminders to complete the test kit. If the test kit still has not been returned after this point, 1 phone call will be made to prompt return. Those who have not returned their kit 30 days after it is posted out will be classed as a nonresponder. Participants who have a positive test result at M0, M3, or M12 will receive 1 item within SMS text message survey 2 weeks post results to record whether their infection has been treated or not. If treatment is incomplete, or the participant does not respond, they will be sent 1 reminder SMS text message to obtain this information. Each local NHS trust will be informed of any positive cases (for participants residing in their local authority area) so that they can provide appropriate treatment and follow-up.

Randomization

Randomization of participants to trial groups in a ratio of 1:1, is fully automated, and fully concealed within REDCap software, and will take place following completion of the M0

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survey. Before randomization of each participant, the research team will manually check that each individual is unique, by cross-checking their identifying information (name, email address, postal address, mobile phone number, and freetest.me order number) with participants already within the sample. They will also check that the participant has answered the baseline survey with reasonable care (ie, no evidence of random responding or completion under the expected minimum time). Those not meeting these criteria will not be randomized. Participants will be blind to group allocation and the research team will be unable to influence any aspect of this procedure. The randomization list will be generated by the study statistician who will monitor randomization on a weekly basis during active recruitment to ensure that the algorithm is being correctly applied. Randomization will be at the individual level as control group contamination is not anticipated (although this will be monitored to determine the suitability of this approach for the definitive trial). Stratification across groups, using randomly permuted blocks (ethnicity, sexual identity, deprivation) will be performed to balance participants across the trial arms.

Intervention Access, Content, and Tracking

Participants will be individually randomized within the stratifications into 1 of 2 groups: usual care or Wrapped plus usual care (see "Wrapped website" and "comparator website" below for further details on the respective interventions). Participants will be directed to their allocated intervention following randomization through a hyperlink. All participants will be free to interact as much or as little with the respective materials; participants will be emailed the hyperlink to enable repeat visits. An email reminder to visit the intervention will be sent to all participants who have not done so 2 weeks after first access is provided.

Wrapped Website

See Multimedia Appendix 6 for the intervention logic model which presents the theoretical model and an outline of intervention components. Newby et al [14] have provided a detailed description of intervention content reported in line with Template for Intervention Description and Replication guidance and have provided screenshots, images of intervention materials, and example videos.

Comparator Website

Usual care is the comparator. Existing STI self-sampling websites typically provide only basic information on STIs and condom use to their users [21]. To replicate this level of health promotion, and to provide an equivalent "intervention" experience for those in the control group, a stand-alone WordPress website presenting comparable basic information has been created [22]. The same basic information is also provided on the Wrapped website.

Analytics Data

Participant access to and engagement with their allocated website will be tracked. There is no minimum acceptable level of engagement—all participants will be allowed to continue in the trial regardless of their level of interaction with the material. Tracking will occur in the background (with each participant's explicit consent) to ensure that it is unobtrusive. Data will be collected within the Wrapped website itself using an analytics package called Matomo, a secure open-source platform [23] (see Multimedia Appendix 7 for details on what will be measured). Analytics data will be used to calculate intervention dose received and to identify any fixable "friction points" in the user journey that may adversely affect usability.

Primary Outcome Measures

Primary outcome measures are as follows:

1. The percentage of freetest.me users recruited to the feasibility RCT.
   This will be assessed as the number of participants randomized out of those using freetest.me in the 4 local authority areas, that is, all those exposed to the recruitment advert.
2. The percentage of randomized participants with a valid primary outcome measure. This will be assessed as the percentage of randomized participants who provide a chlamydia test result at M12.

Secondary Outcome Measures

Secondary outcome measures are as follows:

1. Percentage of randomized participants with outcome data required to measure cumulative incidence of chlamydia (measured using M3 and M12 chlamydia self-sample, and the relevant item within M3, M6 and M12 surveys).
2. The distribution of Index of Multiple Deprivation quintile among users of freetest.me over the 3-month recruitment period, compared to that of the final sample, within each of the 4 recruitment areas.
3. The number of randomized participants with a valid primary outcome measure at M12 by group (gender, ethnicity, sexual identity, deprivation, randomized groups, and chlamydia diagnosis at baseline).
4. The number of randomized participants testing positive for chlamydia at M12 in the intervention and the control group.
5. Attrition curves comparing the percentage of valid participants in the trial at randomization, M3, M6, and M12 plotted for the intervention and control arms (dropout attrition).
6. Completeness of data from outcome measures that would be needed in a definitive trial (ie, self-report of chlamydia result at baseline, results from biological samples, demographic information, self-report of condom use and chlamydia infection, and data needed for cost-effectiveness and cost-utility analyses).
7. The percentage of freetest.me users randomized following each of the different recruitment messages employed.
8. The percentage of valid participants in the 2 arms that do not achieve predetermined intervention "goals" (ie, do not follow instructions within each component of the Wrapped website to their culmination, for example, ordering a sample pack, or watching a suggested video), and the bounce rate for home and content pages.
9. Completeness of data on costs and resource use that would be needed for the economic evaluation in the definitive RCT.

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10. Proportion of participants in the control group who report (at M12) any exposure to Wrapped.
11. The total number of adverse events reported during the course of the study (inadvertent disclosure that sexually active or testing for STI if overseen using Wrapped, initiation or change in the consumption of pornography, or other).

Sample Size

At least 60 participants per arm are recommended to allow proportions to be estimated with good precision [24]. This is inflated to allow for an estimated 25% nonreturn of initial chlamydia self-test sample (based on freetest.me statistics; 60/0.75=80) and a further estimated 30% dropout over the course of the feasibility trial (a conservative estimate based on 19% dropout achieved in Free et al [25] sexual health feasibility RCT (80/0.7=114 per arm). Based on this, the total sample size required for the present fRCT has been calculated as 230 participants.

Progression Criteria

The following criteria will be used to inform progression to a full trial:

1. The proportion of freetest.me users recruited to the feasibility trial is sufficient to obtain the sample size required for the definitive RCT (sample size for the definitive RCT will be determined using data from multiple sources, including chlamydia positivity in the control group of the present fRCT and national level data on chlamydia positivity among young people testing for STIs through the internet (used to estimate the level of chlamydia positivity in the target population), expert opinion on what would be a clinically meaningful reduction in chlamydia positivity for the target population, typical effect sizes achieved in comparable studies, and the size of the available sampling pool for the future RCT).
2. A total of 60% (138/230) of participants (those randomized) followed up for the definitive RCT primary outcome measure at M12
3. Index of Multiple Deprivation quintile distribution for the final sample is comparable to that of individuals in the sampling pool (freetest.me users in the partner local authority areas).
4. Adverse events are judged as sufficiently infrequent and/or serious to cause concern.

The progression decision will be determined by the independent Study Steering Committee (SSC), in conjunction with the Data Monitoring and Ethics Committee, based on achievement of all the above criteria, or convincing evidence that any 1 criterion is amenable for necessary improvement.

Ethical Considerations

Ethical approval was obtained from the NHS East Midlands—Leicester Central Research Ethics Committee (reference 20/EM/0275) and the trial was registered with the ISRCTN (ISRCTN17478654). To participate, all individuals will be required to provide informed consent. All participants will receive a £65 (US $79.95) payment in the form of vouchers to recompense for time spent completing the research activities. All research data will be deidentified before analysis and reporting.

Data Management and Analysis

Data Management

All trial data will be collected in REDCap, a secure data management program hosted on a university server. REDCap will create a unique ID for each participant at the point of consent. All activity will be associated with this unique ID, enabling data across time points to be easily and accurately linked. Analytics data will be stored within Matomo and the Wrapped website, also linked to the unique ID. Only the research team will have access to data stored on REDCap, Matomo, and the Wrapped website. At the end of data collection, all data captured through these platforms will be exported to a password-protected folder for analysis purposes. Only the research team will have access to this folder. Consent data will be separated from all other data (research data) through storage in 2 separate folders. For the research data, at the point of export, all identifying data will be removed and the remaining data linked using the unique participant ID before cleaning. Once the research team agrees that all data is present and complete, all data present in REDCap, Matomo, and the Wrapped website will be permanently deleted. Research data will remain in the password-protected folder until analysis is complete after which it will be deleted. Consent data will be kept for 6 years before deletion. In line with the funder's requirements, a copy of the raw anonymized research data will be deposited within the University of Hertfordshire Research Archive (UHRA [26]) and made available indefinitely on an open-access basis.

Statistical Analysis

Researchers performing the analysis (KN, KB, LJ, and SB) will be blinded to participant allocation. Quantitative data will be analyzed descriptively. Measures of location and dispersion, including means and SDs, medians and IQRs, and number and percent for categorical variables, will be used to describe the data at baseline and at each follow-up time point. CIs will be calculated and presented as appropriate. All analyses will be performed using SPSS (version 28; IBM Corp). As with the raw data, the syntaxes used for analysis and the output generated will also be deposited within the UHRA and made available indefinitely on an open-access basis.

Nested Qualitative Study

A nested qualitative study will be conducted during the fRCT. The aims of this study will be to explore participant's views and experiences of the Wrapped intervention, experience of trial procedures and materials, and perceptions of whether and how the intervention has changed their condom use beliefs or behavior.

Approximately 30 individuals (number to be determined by data saturation) participating in the fRCT will be invited to take part. All participants will receive a £20 (US $24.6) voucher in recognition of their time. Participants will be asked at baseline (single question in survey) whether they are willing to take part

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in a semistructured telephone or video call interview and if so, to provide suitable contact details.

Participants will be purposively selected to create a varied sample representing different demographic criteria, completers and noncompleters from both trial arms, those with varying levels of intervention engagement, and those thought to have experienced specific events that could influence dropout. Selected individuals will be contacted and directed to a new project page on REDCap where they will be asked to provide informed consent to take part in this additional aspect of the study.

Interviews will last up to 1 hour and will be fully transcribed before analysis. Framework analysis [27] will be used to analyze the data.

At the end of each interview, a second aspect of the qualitative study will be discussed with the participants. This is interviewing sexual partners to better understand any changes in condom use decision-making in light of the intervention. After the interview, an email invitation will be sent to the participant which they can choose to forward to their partner if they wish. It will then be up to the sexual partner to contact the research team if they want to participate. They will be given the option to email or telephone the research team if they have any questions, or simply to follow a hyperlink straight to the relevant project page on REDCap. Here, they will be required to provide informed consent to take part in the study. All data will be collected, processed, and analyzed as described above for primary interviewees. Each individual who participates will be given a £20 (US $24.6) voucher in recognition of their time.

Patient and Public Involvement

A patient and public involvement (PPI) group will be formed for this study. Members will be existing users of web-based STI self-sampling services. The research team will work with the PPI group to determine the different value propositions included in the study advertisements; determine strategies for effective retention of participants (eg, the level and timing of voucher payments provided, communication methods, and tone of messaging); draft the participant information and consent statements for the fRCT and nested qualitative study to ensure that they are clear and easy to understand; iteratively test the surveys before their use to maximize content validity, readability, clarity, and comprehensiveness; review fRCT findings and reflect on changes that should be made to recruitment and retention strategies before a definitive trial; and two members of the PPI group will also support the monitoring of the fRCT by serving as members of the SSC.

Research Governance Risks, and Dissemination

Monitoring

An independent SSC and Data Monitoring and Ethics Committee will be convened to provide oversight and ensure adherence to standards of best practice. Institutional sponsorship is required. A clinical trial unit will provide trial management and statistical oversight.

Risks, Support, and Safeguarding

Participating in the fRCT has limited risk associated with it for participants. As a result of participation in the fRCT, some people may attempt to use condoms and fail, if for example, their sexual partner responds negatively to their request to use a condom or there are condom-use errors, and this may have some negative psychological impacts in the short-term. Both the Wrapped and the comparator website will contain links to sources to help and support on topics of sex and relationships, including condom use and intimate partner violence. All participants will be provided with a debrief email at the end of their participation in the trial (at M12). Surveys at all time points will include items that measure sexual well-being. Responses may indicate that a participant was or is the victim of sexual coercion or abuse. Participants aged 18 years and over who indicate this will be signposted to appropriate sources of support by email and offered, at their request, to receive support from a university safeguarding officer. Alternatively, if a participant younger than 18 years indicates coercion or abuse, the study safeguarding procedure will be initiated. Under these circumstances, the confidentiality agreement with the participant will end, and the information provided will be passed to their local NHS trust sexual health service so that they can support them in line with existing protocols. Data-sharing agreements will be in place with these trusts to enable this action to be performed. The relevant individual will not be able to refuse this referral process, but they will be informed that this is happening. All participants are informed of this safeguarding procedure within the participant information and are required to agree to this at consent. A reminder of this process is also stated alongside the relevant questions within each survey. Participants will also be asked to disclose their experience of adverse events within M3, M6, and M12 surveys. These events could be as follows: (1) inadvertent disclosure to another person that the participant is sexually active or testing for an STI as a result of them being overseen using Wrapped, (2) initiation or change in the consumption of pornography by the participant, and (3) other. If an event is disclosed, the circumstances will be discussed by the research team who will seek advice from the sponsor, ethics committee, and/or steering committee, if required before determining the most appropriate course of action.

Participation in the nested qualitative study is low risk. Participants will be asked about their experiences of condom use before and after the intervention. It is possible that some participants may find these types of questions uncomfortable. The nature of the study is clearly outlined in the participant information and participants are made aware that they can withdraw at any time, as well as choosing not to answer any question that they are uncomfortable with. Debriefing information will be emailed to all secondary participants (sexual partners of participants in the fRCT) after the interview; primary participants will receive this on completion of the fRCT.

Consent

Informed consent will be taken on the internet through REDCap (separately for the fRCT and the nested qualitative study). Participants must agree to all statements before being allowed

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to proceed. Participants who do not agree will be thanked for their interest and routed out of the project; no data will be collected (see Multimedia Appendix 4 for a copy of the consent form).

Confidentiality

Individuals' decision to take part and all their data will be treated as confidential. All data will be stored securely, and access restricted to the research team. At the point of consent, a unique identifier will be assigned, and all data linked using this. At download, personal identifying information will be removed from the data set. The only data preserved after the end of the study will be consent data (kept for 6 years) and the anonymized data set, held in a research archive indefinitely.

Dissemination

During the study, progress will be communicated to stakeholders through a project website and linked Twitter account. At end of the study, findings will be disseminated to the public through a written and video lay summary. Findings will be communicated to the academic community through conference presentations and publications in an open-access journal.

Results

Recruitment to the fRCT began in March 2021 and was completed in October 2021. Approximately half of all participants have reached the M12 time point (study end) to date. Data collection was completed in December 2022.

Discussion

Overview

This fRCT is designed to assess whether and how it is possible to carry out a future definitive RCT to evaluate the effectiveness and cost-effectiveness of an intervention to increase condom use among young people. The rapid increase in use of web-based STI self-sampling services, accelerated by the COVID-19 pandemic, means that young people are increasingly required to self-manage their own sexual health screening. This, along with persistently high rates of STIs among this age group, makes the provision of behavior change support in this web-based context imperative.

Strengths and Limitations

This fRCT employs the proposed design and methods that would be used in a full RCT. This will enable the research team to develop, assess, and optimize all the systems and procedures required to run the full trial before time and resource commitments are allocated. Furthermore, the study has been setup to inform important aspects of this future trial, such as which advertisements results in the highest recruitment rate? Are there any friction points within the intervention content that may contribute to dropout? Could the tone, content, or frequency of communication with participants be improved? Should the progression criteria for this feasibility fRCT be satisfactorily met, the research team will refine intervention content and study procedures in line with this to further enhance participant recruitment and retention, and study efficiency.

As this is an fRCT, the study is being conducted on a much smaller scale than a future trial. Some technical aspects of the study that are manageable at this stage will likely need to be revised. In the present study, for example, the research team are reporting positive chlamydia test results (arising from M3 and M12 testing) to each relevant trust which is time-consuming and represents an avoidable data protection risk. An alternative would be for this information to be passed directly to the trusts by the self-sampling service provider. In the future-full trial, the team would seek to overcome such technical issues.

The unusual context in which this fRCT is being run should be acknowledged. The COVID-19 pandemic has affected sexual health services and sexual behavior in ways that could not have been imagined at the time this study was conceived. When recruitment to the fRCT was initiated, restrictions on public behavior imposed to control the spread of infection were still in place but were lifted approximately 3 months later. The impact of the environment at that time on STI testing and diagnoses will not be known until the release of annual STI data in Autumn 2022. Although an increase in the use of internet testing will serve to increase the size of the sampling pool drawn upon for this study, thus potentially accelerating recruitment, it should not impact upon the recruitment rate, as this is merely a reflection of the rate at which those who see the advert are converted into participants. It should, however, be acknowledged that the pandemic is likely to have both positively and negatively impacted on people's time and/or willingness to engage in research, factors which for some will also have changed with changing restrictions and may serve to influence study recruitment and retention. It is also important to consider whether changes in sexual risk behavior during this time could lead to fewer cases of chlamydia being identified in the present study than anticipated. This concern is, however, not supported by community surveys, which indicate that a substantial proportion of people continued to engage in at-risk behavior during 2020 [28-30], and the most recent STI data which shows that among those seeking internet testing, chlamydia positivity was comparable between 2019 (23,426/284,050, 8.2%) and 2020 (33,294/381,744, 8.7%) [1].

Acknowledgments

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Data Availability

A copy of the raw anonymized research data, the syntaxes used for analysis, and the output generated, will be deposited within the University of Hertfordshire Research Archive (UHRA; accessible via https://uhra.herts.ac.uk) and made available indefinitely on an open access basis.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Wrapped CONSORT Diagram.
[DOC File , 75 KB - resprot_v12i1e43645_app1.doc]

Multimedia Appendix 2
Schedule of voucher payments.
[DOC File , 14 KB - resprot_v12i1e43645_app2.doc]

Multimedia Appendix 3
Advert schedule.
[DOC File , 20 KB - resprot_v12i1e43645_app3.doc]

Multimedia Appendix 4
Participant information and consent.
[DOC File , 90 KB - resprot_v12i1e43645_app4.doc]

Multimedia Appendix 5
Survey items.
[DOC File , 137 KB - resprot_v12i1e43645_app5.doc]

Multimedia Appendix 6
Intervention logic model.
[PPTX File , 6858 KB - resprot_v12i1e43645_app6.pptx]

Multimedia Appendix 7
Analytics data measurements.
[DOC File , 14 KB - resprot_v12i1e43645_app7.doc]

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Abbreviations

CONSORT: Consolidated Standards of Reporting Trials

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fRCT: feasibility randomized controlled trial
NHS: National Health Service
PPI: patient and public involvement
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
SSC: Study Steering Committee
STI: sexually transmitted infection
UHRA: University of Hertfordshire Research Archive

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Protocol

Assessing a Sleep Interviewing Chatbot to Improve Subjective and Objective Sleep: Protocol for an Observational Feasibility Study

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Abstract

Background: Sleep disorders are common among the aging population and people with neurodegenerative diseases. Sleep disorders have a strong bidirectional relationship with neurodegenerative diseases, where they accelerate and worsen one another. Although one-to-one individual cognitive behavioral interventions (conducted in-person or on the internet) have shown promise for significant improvements in sleep efficiency among adults, many may experience difficulties accessing interventions with sleep specialists, psychiatrists, or psychologists. Therefore, delivering sleep intervention through an automated chatbot platform may be an effective strategy to increase the accessibility and reach of sleep disorder intervention among the aging population and people with neurodegenerative diseases.

Objective: This work aims to (1) determine the feasibility and usability of an automated chatbot (named MotivSleep) that conducts sleep interviews to encourage the aging population to report behaviors that may affect their sleep, followed by providing personalized recommendations for better sleep based on participants' self-reported behaviors; (2) assess the self-reported sleep assessment changes before, during, and after using our automated sleep disturbance intervention chatbot; (3) assess the changes in objective sleep assessment recorded by a sleep tracking device before, during, and after using the automated chatbot MotivSleep.

Methods: We will recruit 30 older adult participants from West London for this pilot study. Each participant will have a sleep analyzer installed under their mattress. This contactless sleep monitoring device passively records movements, heart rate, and breathing rate while participants are in bed. In addition, each participant will use our proposed chatbot MotivSleep, accessible on WhatsApp, to describe their sleep and behaviors related to their sleep and receive personalized recommendations for better sleep tailored to their specific reasons for disrupted sleep. We will analyze questionnaire responses before and after the study to assess their perception of our proposed chatbot; questionnaire responses before, during, and after the study to assess their subjective sleep quality changes; and sleep parameters recorded by the sleep analyzer throughout the study to assess their objective sleep quality changes.

Results: Recruitment will begin in May 2023 through UK Dementia Research Institute Care Research and Technology Centre organized community outreach. Data collection will run from May 2023 until December 2023. We hypothesize that participants will perceive our proposed chatbot as intelligent and trustworthy; we also hypothesize that our proposed chatbot can help improve participants' subjective and objective sleep assessment throughout the study.

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Conclusions: The MotivSleep automated chatbot has the potential to provide additional care to older adults who wish to improve their sleep in more accessible and less costly ways than conventional face-to-face therapy.

International Registered Report Identifier (IRRID): PRR1-10.2196/45752

(JMIR Res Protoc 2023;12:e45752) doi:10.2196/45752

KEYWORDS

automated chatbot; behavior analysis; conversational agents; older adults; sleep disorders; sleep interview

Introduction

Overview

Evidence exists for a bidirectional relationship between sleep disorders in the aging population and people with neurodegenerative disease [1-3]. Specifically, between 40% and 70% of the older population report difficulties in sleep onset or maintenance and insomnia symptoms [4-6], which increase their risk of developing neurodegenerative disorders. Similarly, there is a high prevalence of sleep disorders, such as sleep apnea and circadian rhythm disorders, among people with neurodegenerative disorders [7-10], where sleep disorders can accelerate cognitive decline [11,12]. Moreover, neurodegenerative disorders affect not only patients but their entire households, especially the primary carer. Indeed, studies [13-16] have shown that approximately two-thirds of older adult caregivers have some form of sleep disturbance. Thus, early intervention of sleep disorders among older adults can improve their quality of life, reduce their risk of developing neurodegenerative disorders, and prevent further complications among household members.

Researchers have conducted clinical trials using cognitive behavioral therapy [17-19] and motivational interviews [20-22] to improve sleep quality among older people, people with neurodegenerative disorders, and their carers. However, one-to-one individual therapies (in-person or remote) and face-to-face group therapies may be costly and difficult to access.

Several digital insomnia tracking and treatment systems [23,24] have been developed and evaluated. For example, Zaslavsky et al [22] developed a mobile health (mHealth) monitoring and self-management app. mHealth monitors sleep quality through the wearable Fitbit Charge 2 and automatically sends text messages that provide weekly information and motivational feedback. Zaslavsky et al [22] showed that their proposed mobile app mHealth, combined with motivational interviews conducted by telephone, can significantly improve participants' self-reported sleep quality after 19 weeks of participation. In addition, Aji et al [23] showed that a self-reporting mobile app (SleepFix), connected to a wearable sleep-tracking device, can encourage users' engagement with the app's self-reporting functionality in a pilot randomized controlled trial.

However, these studies only combine digital sleep quality monitoring with a digital self-reporting mechanism or periodic text messages to encourage users to engage in sleep quality reporting, good sleep habits, and routine. They do not engage in conversations that may further encourage information sharing and behavioral changes. To engage more actively with users, Rick et al [24] proposed a Telegram-based chatbot, SleepBot, that dynamically enquires about users' sleep information based on preprogrammed questions. Aarts et al [25] proposed a chatbot Snoozy for children aged 8-12 years with sleep difficulties, which asks children how their sleep was, the reasons for it if they slept poorly, and what behavioral methods they have tried to help with their sleep. Aarts et al [25] showed that a chatbot could help collect subjective reports from children over sustained period instead of traditional diaries.

In this feasibility study, we propose a sleep intervention chatbot design named MotivSleep. Our proposed MotivSleep first triages participants' sleep based on information gathered from a contactless sleep-tracking analyzer. Then, MotivSleep starts conducting sleep interviews only when the sleep analyzer identifies a bad night's sleep. The automatic sleep interview asks participants about any potential adverse factors that might have affected their sleep the night before, prior to using this information to provide personalized recommendations for better sleep (ie, healthy habits that you can practice during the day to help you get a good night's sleep) [26] and encouraging them to maintain good sleep habits.

Design Engineering Process

This work is built upon automated and manual monitoring and care procedures followed by the Care Research and Technology Center (CRT), part of the UK Dementia Research Institute (UK DRI). The design of our proposed MotivSleep chatbot involved an advisory group with patients and health care professionals from its conception, following the identified key characteristics in developing human-centered care technologies [27]. Specifically, carers, health professionals, occupational therapists, sleep specialists, chatbot researchers, and designers have come together in 2 workshops where the needs and values of the stakeholders were discussed [28]. We also requested input from the advisory board, conducted interviews with people living with dementia and their carers, conducted patient and public involvement and engagement sessions with healthy older adults, and surveyed results to develop initial dialogue plans that can conduct sleep interviews through chatbot.

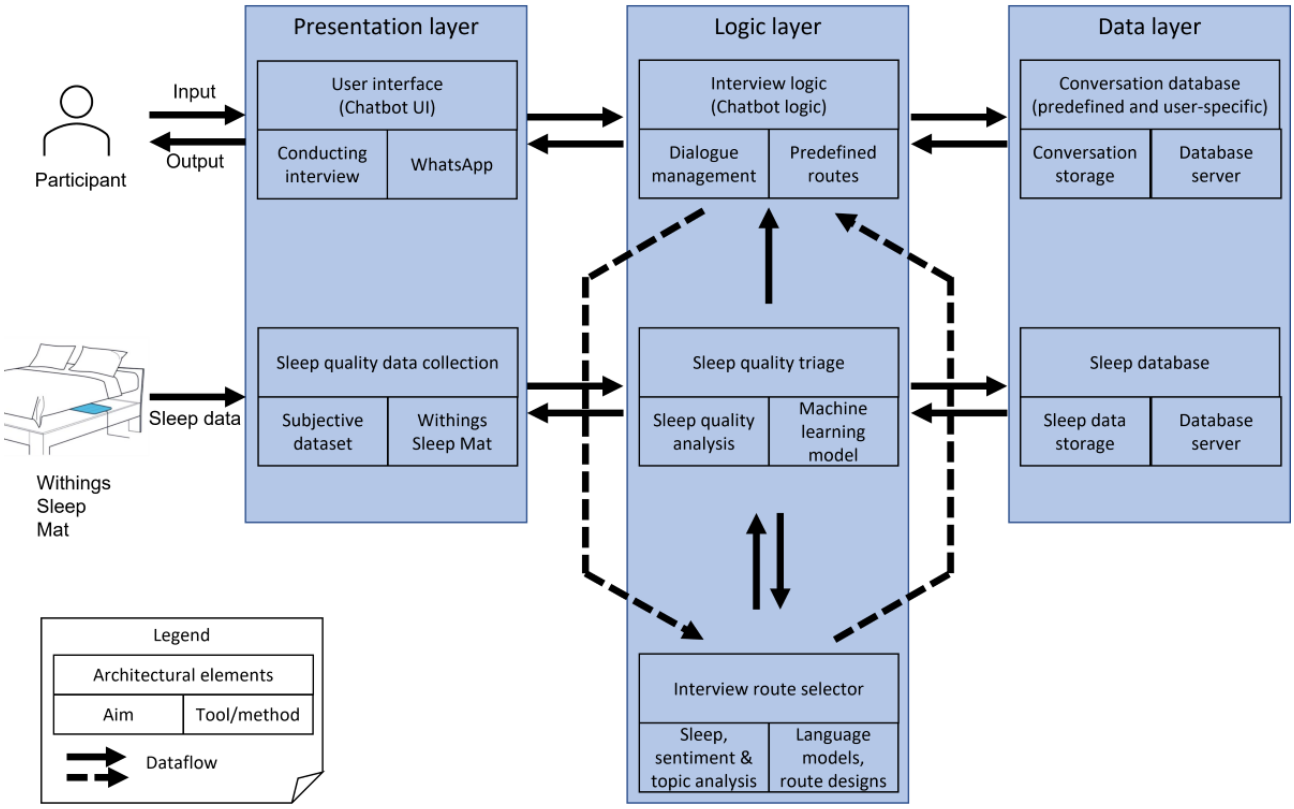
Based on information and advice from the groups mentioned above, we built a sleep management chatbot integrated with WhatsApp. This internationally available messaging platform provides instant text and voice messaging services through the American company Meta Platforms. To access the proposed MotivSleep chatbot, we will gather the participants' phone numbers and add them to the MotivSleep database, where messages will be sent out automatically at the user's preferred time, potentially daily. Additionally, we will use the Withings sleep analyzer, a commercially available contactless device, to

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monitor and track participants' objective sleep parameters. The sleep analyzer can be installed under the participant's mattress, and the information gathered can be accessed through an API. The Withings sleep analyzer is chosen due to its passive recording ability (ie, it does not need recharging or adjustments once installed) and previous collaboration between UK DRI and Withings that provides easy integration. Additionally, the Withings sleep analyzer has been evaluated and showed comparable results to actigraphy and polysomnography based sleep assessment, in older people [29]. In this study, we will analyze participants' sleep data to monitor the participants' objective sleep parameters based on respiration, heart rate, snoring, and apnea episodes. This analysis triggers the conversation stage of our proposed MotivSleep chatbot.

The chatbot component of our proposed MotivSleep chatbot will automatically start a conversation with the user at least twice a week, on Wednesdays and Saturdays, to prevent data scarcity and ensure we collect data from all participants. In addition to the previously mentioned 2 days, the chatbot will start the conversation when the server detects anomalous sleep patterns from the participant's data. Other than on these occasions, MotivSleep will not start the conversation to avoid too many repetitive requests for information from participants. Furthermore, participants can trigger the chatbot at any time by initiating the chat (ie, by sending "Hi MotivSleep" to the chatbot). The architecture of MotivSleep is shown in Figure 1 and is based on the Distinguish Business Logic from ML Model pattern [30].

Figure 1. The architecture of the proposed MotivSleep chatbot. UI: user interface.



Specifically, MotivSleep consists of 3 layers: a presentation layer, a logic layer, and a data layer, as follows:

1. The presentation layer provides a user interface to conduct interviews where participants interact with MotivSleep delivered through WhatsApp. Backend structures allow MotivSleep to acquire sleep data from the Withings sleep analyzer.
2. The logic layer that provides the chatbot logic to manage the chatbot dialogue based on predefined dialogue routes, a sleep assessments triage module that analyzes participants' sleep assessments using pretrained machine learning models, and an interview route selector that selects conversation paths based on sentiment analysis and topic modeling using machine learning models.
3. The data layer that provides data storage for participants' conversation history and sleep data gathered from the Withings sleep analyzer.

Chatbot Features

The participants will interact with the WhatsApp chatbot and have a Withings sleep analyzer installed to track their sleep. Our system's backend server is connected to the Withings sleep analyzer database. The sleep monitoring data is accessible through the designed triage mode and the chatbot feature, with which the participants can interact. Specifically, MotivSleep accesses participants' sleep-tracking data in the morning and triages their objective parameters. The triage will result in three signals, as follows:

1. Red: an anomalous night with significant differences from the usual (ie, gathered 2 weeks before the start of the chatbot engagement) patterns is detected. Specifically, this relates to participants' bedtime, wake-up time, the number of times they leave the bed during the night, and the duration of snoring time.

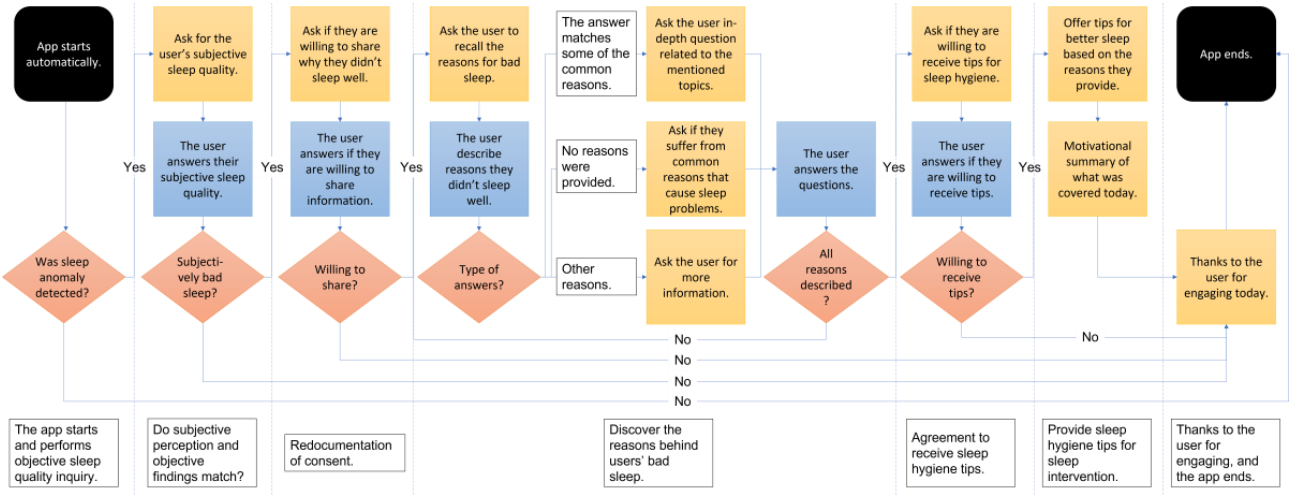
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2. Yellow: when the model detects ongoing problems in their sleep.
3. Green: when there are no significant differences in sleep patterns or other existing sleep problems.

The MotivSleep chatbot follows a dialogue route with multiple branches, which may end or continue the conversation. Figure 2 shows the dialogue design of our chatbot. Specifically, our chatbot is designed with seven stages, as follows:

1. The objective sleep assessment: sleep quality is highly challenging to assess, with a range of potential models for data fusion from the internet of things devices. In the context of our study, we will initiate analyses of the objective sleep assessment using measures provided by the installed Withings sleep analyzer. Specifically, MotivSleep starts at a predefined time each day and calculates the sleep quality using the sleep tracking device. If the triage result is red or yellow, MotivSleep will continue to the next stage to start the chatbot and engage with the participant; otherwise, MotivSleep will not send the initial text message and will quit automatically. We note that the UK DRI CRT has ongoing work in sleep quality evaluation using the Withings sleep analyzer, which could be incorporated into the study for comparison when available.
2. The subjective sleep assessment: MotivSleep chatbot activates the interview through WhatsApp and asks the participant, "Did you sleep well last night?" This stage helps MotivSleep confirm with the participant if they had a bad night's sleep. If the participant denies having had a bad sleep, our chatbot will go to stage 7, wishing them a good day and quitting. However, if the participant confirms that they have had a bad night, the chatbot will continue to ask the next question.
3. Redocumentation of consent: the chatbot will briefly remind the participant about the study, ask them for their consent to participate in the current interactions, and provide insights into their poor sleep. If they do not consent, the chatbot will go to stage 7, where we thank them for their engagement, and the chat ends; otherwise, the chatbot will continue to the next stage.
4. The information-seeking stage: in this stage, the chatbot will ask the participant for reasons that might explain why they did not sleep well the previous night. This open question seeks insights into participant's behaviors before and during their sleep that may have contributed to a bad night's sleep. Answers to this question are collected and analyzed, and the analysis result will prompt the following three types of further questions:
   i. In-depth questions related to predefined specific reasons that cause their poor sleep. These questions will be triggered if we identify predefined reasons from the participant's answers;
   ii. Multiple-choice questions consist of potential reasons that might cause poor sleep. These questions will be asked if the participant answers that they do not know why they had a poor sleep;
   iii. Similar questions to the previously asked question (ie, why did you sleep poorly?) until they confirm there is no more information to add. These questions will be asked if the reasons the participant provided early are not one of the predefined reasons.
5. Agreement to receive personalized recommendations for better sleep: in this stage, the chatbot will ask the participant whether they want to hear personalized recommendations for better sleep. If they disagree, the chatbot will go to stage 7, where we thank them for their engagement, and the chat ends; otherwise, the chatbot will continue to the next stage.
6. Provide personalized recommendations for better sleep: in this stage, we provide specific recommendations to the participant based on the information gathered during stage 4. Furthermore, we provide a motivational summary of what was covered today, including their reasons for poor sleep and recommendations for better sleep.
7. The end of the conversation: in this stage, we thank the participant for the engagement, wish them a good day, and end the conversation. To further motivate the participants, the chatbot also praises the participant if some of the repeated behaviors negatively affecting their sleep were not mentioned in this interaction.

Figure 2. Chatbot dialogue design. Note that the black ovals denote the start and the end of the skill, the yellow rectangles denote the dialogue by the chatbot, and the blue rectangles and the blue diamond denote the participants' inputs. The orange diamonds denote the diverging options.



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This chatbot aims to perform knowledge transfer, that is, using the information gathered from the fourth stage to provide personalized recommendations for better sleep in the sixth stage, thus transferring knowledge on better sleep to the participants.

Research Questions

The MotivSleep chatbot used in this feasibility study has been co-designed with patients, carers, and other health professionals. Together, we identified the following research questions:

1. *RQ1* Is our proposed MotivSleep chatbot accessible to participants, and how feasible is it to engage the participants with interviews using MotivSleep? We focus on assessing the feasibility and usability of our proposed MotivSleep, by measuring the number of turns and time spent chatting with the skill per engagement. Moreover, we assess MotivSleep's accessibility by asking participants to rate their willingness to promote the chatbot using the net promoter score (NPS) [31] question in the exit questionnaire. Finally, we assess the participants' perception of the chatbot by asking participants to complete the Godspeed Perceived Intelligence subscale (GPIS) [32] and Trust Perception Scale-Human Robot Interactions (TPS) [33] questionnaires.
2. *RQ2* Can our proposed MotivSleep chatbot help improve participants' subjective sleep assessment? We aim to evaluate the participants' self-reported sleep assessment to analyze if the proposed MotivSleep helps participants to subjectively sleep better through the completion of the Epworth sleepiness scale (ESS) [34], Insomnia Severity Index (ISI) [35], modified Pittsburgh sleep quality index (PSQI) [36], and the single-item sleep quality scale (SQS) [37], conducted at the beginning, the end, and every 2 weeks throughout the study.
3. *RQ3* Can our proposed MotivSleep chatbot help improve participants' sleep, measured using the Withings sleep analyzer? We aim to analyze participants' objective sleep assessments using sleep recordings gathered by Withing sleep analyzer throughout the study.

Methods

Overview

Once reviewed by the Imperial College Research Ethics Committee, we will recruit 30 healthy older adults (aged 65-90 years) in 3 cohorts through the UK DRI CRT community outreach group community outreach in West London. Participants will have access to the conversational agent through WhatsApp chat. We estimate that the average conversation will take less than 10 minutes. Each participant will also have access to the Withings sleep analyzer provided by the research group.

A poststudy questionnaire consisting of the GPIS, TPS, and NPS will be completed when the participant finishes the study. We analyze participants' answers to assess the participants' opinions on the proposed MotivSleep chatbot's intelligence, trustfulness, and participants' satisfaction with MotivSleep, to answer RQ1. Additionally, all participants will complete the ESS, ISI, modified PSQI, and SQS questionnaires before the start, fortnightly during the study, and at the end of the study. We analyze the answers to these questions to investigate RQ2.

The first cohort of 10 participants will use both the Withings sleep analyzer for 6 weeks (the first 2 weeks aims to establish baseline sleep assessments without the usage of MotivSleep) and the WhatsApp chatbot for 4 weeks, with WhatsApp message reminders to encourage WhatsApp chatbot engagement sent out fortnightly (ie, twice for the first cohort of 10 participants). The first batch of participants' feedback and engagement measures will inform a new iteration of improvements.

The second cohort of 10 participants and the third cohort of 10 participants will use the WhatsApp chatbot for 8 weeks and 12 weeks and the Withings sleep analyzer for 10 weeks and 14 weeks, respectively. Participants will be reminded fortnightly (ie, 4 times for the second cohort participants and 6 times for the third cohort participants) to encourage participation with the WhatsApp chatbot when activated. After each cohort, participants' technical feedback will be addressed by improving the software.

The feasibility study will have a single experiment condition that includes three types of features:

1. A sleep tracking device (ie, Withings sleep analyzer) and sleep analysis model.
2. A chatbot (ie, MotivSleep) hosted on WhatsApp that conducts sleep interviews. The dialogue is designed to understand the reason behind participants' sleep problems, provide personalized recommendations for better sleep, and support behavior changes to improve their sleep assessments.
3. WhatsApp messages that encourage interaction with MotivSleep.

We will measure three classes of outcome variables as follows:

1. Assess the feasibility and usability of our proposed chatbot MotivSleep (RQ1)—the number of interactions in each MotivSleep conversation and time spent chatting with MotivSleep, and the poststudy questionnaire consisting of NPS, GPIS, and TPS.
2. Assess the subjectively perceived sleep assessments (before, during, and after the study) (RQ2)—ESS, ISI, PSQI, and SQS questionnaires.
3. Assess the objectively measured sleep assessments (before, during, and after the study) (RQ3)—obtained from the Withings sleep analyzer and analyze using the Withings provided sleep analysis models.

Recruitment

This study will be conducted in 3 batches. Participants in all 3 batches will be healthy older adults with no neurodegenerative disease. The participants will be recruited through the UK DRI CRT community outreach group in West London. The recruitment process follows the recommendations and requirements laid out in the UK National Institute for Health and Care Research Clinical Research Network policy, based on the inclusion and exclusion criteria. Specifically, Participants should be aged between 65 and 90 years, able to communicate fluently in English, experiencing sleep problems and wanting

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to improve their sleep, willing to install a Withings sleep analyzer and use the WhatsApp chatbot and have access to high-speed wireless internet connection at home, and able to provide informed consent. The exclusion criteria include the following: (1) people with unstable mental states, including severe depression, severe psychosis, agitation, and anxiety; (2) people with severe sensory impairment; (3) people who have active suicidal thoughts; (4) people who are receiving treatment for terminal illnesses.

Participants will be compensated for their time and inconvenience with £25 (US $31.15) per 2 weeks for participation, that is, for filling out the prestudy informed consent and questionnaires before, during, and after the study and engaging with the chatbot. The questionnaires will be provided on Qualtrics, separately to the chatbot, and sent to the participants as WhatsApp messages. Additionally, our team will teach the participants to complete the questionnaire using their smartphones before the study on an in-person visit when they sign the consent form. The subsequent questionnaires during the study will be sent to their mobile as WhatsApp messages.

A total of 30 individuals will be recruited in 3 cohorts. In total, we aim to include 18% of individuals who self-identify as members of a minority ethnic group to ensure alignment with the UK population [38] and avoid exclusion. Only approved phone numbers (of people who have consented to the study) can interact with the chatbot.

Data Management

WhatsApp messages are automatically encrypted, so conversations are private and cannot be accessed by Meta (the mother company of WhatsApp).

We will create 2 databases in Microsoft Azure, where both databases are only accessible through designated virtue private network connections, which are available only to the app and the researchers. We will use the Research Data Storage (RDS) managed by the Imperial College London to host the data sets after obtaining them through Azure. RDS is only available to researchers within the project through university-hosted Virtual Private Network connections.

Specifically, we will first pseudoanonymize each user by assigning them an automatically generated user ID and storing this information in a secure Azure database. MotivSleep then automatically stores the transcripts anonymously in a second secure database. Both databases are hosted on Azure before being transferred to RDS. After moving both user information and transcripts to RDS, they will be permanently deleted from the Azure databases. There will be 2 copies of sleep tracking data, that is, Withings will store 1 copy, and the RDS will store another copy. Responses to the questionnaires will be stored in Qualtrics servers.

According to the Imperial College data retention policy, the data will be retained for at least 12 years.

Analysis Plan

We aim to analyze the following four types of data:

1. The dialogue transcripts: dialogue transcripts can help us understand how much time participants spend talking to the chatbot, what sleep behaviors each participant exhibits, and how often these behaviors appear when troublesome sleep patterns are detected.
2. The answers to the GPIS and TPS questionnaires: these answers help us to understand how participants perceive our proposed chatbot MotivSleep, in terms of usability, feasibility, intelligence, and trustfulness.
3. The answers to the ESS, ISI, modified PSQI, and SQS questionnaires before, during, and after the study help us analyze participants' subjective views of their sleep assessments and provide insights into their perceived sleep changes over time.
4. The sleep data tracked by the sleep tracking device Withings sleep analyzer: Sleep tracking helps us monitor participants' objective sleep assessment changes over time, measured by the tracking devices unrelated to participants' subjective feeling of their sleep.

Ethical Considerations

The study will be submitted to the Imperial College Research Ethics Committee at Imperial College London, London, United Kingdom. All participants will be provided with an information sheet detailing the aim and rationale for the research; inclusion and exclusion criteria; what will happen if they agree to take part; any risks of taking part in the study; clarification of the process for ensuring anonymity and confidentiality, including any limits to confidentiality; what information will be held about them and who will have access to it; possible benefits; and plans for project report. All participants will then be required to sign the informed consent form before participating in the study. Additionally, all participants' identifiable data will first be anonymized. The identifiable and anonymized data will be stored in separate secure cloud-based databases (Azure PostgreSQL server) before being transferred to Research Data Store. Finally, each participant will be compensated £25 (US $31.15) per 2 weeks for their participation.

Results

The planning and development of this study started in August 2022. We have since developed the chatbot MotivSleep. The chatbot's design is being evaluated by carers, health care professionals, and occupational therapists and will be updated after their evaluation. The first cohort of participation recruitment will start in May 2023, the second cohort will begin in June 2023, and the third cohort will start in August 2023. The anticipated study completion date is December 2023.

In this study, we aim to test three hypotheses as follows:

1. First, we hypothesize that participants will perceive our chatbot as intelligent and trustworthy and are satisfied with our proposed MotivSleep.
2. We also hypothesize that our proposed chatbot MotivSleep can improve participants' subjective sleep assessment over their usage of the chatbot based on collected using ESS, ISI, PSQI, and SQS questionnaires and their objective sleep quality based on the Withing sleep analyzer.

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3. Finally, we hypothesize that participants' objective sleep assessment will improve, measured by the Withings sleep analyzer.

Discussion

Principal Findings

Sleep disturbances are commonly observed among older people, with and without neurodegenerative disorders, and among carers for people with neurodegenerative disorders. This study will provide critical evidence pertaining to the feasibility and acceptability of the proposed chatbot MotivSleep, hosted on WhatsApp, which aims to conduct automatic sleep interviews and provide personalized recommendations for better sleep that may improve their sleep. Specifically, we evaluate the participants' perceived usability and feasibility of the chatbot, changes in participants' subjective sleep assessment before, during, and after the study, and changes in participants' objective sleep assessment measured by the sleep tracking device Withings sleep analyzer.

This paper describes the protocol used in the MotivSleep study. To the best of our knowledge, no other studies have focused on developing an automated chatbot for older people with problematic sleep or conducting automated sleep interviews. The MotivSleep study aims to shed light on the feasibility of using a chatbot to conduct interviews for a prolonged period of time. Furthermore, the intervention and protocol were designed to be more accessible and simpler than frequent in-person assessment or intervention sessions. This allows future deployment to older adults with mobility issues or within hard-to-reach communities.

Limitations

Our study requires participants to use 2 devices (a Withings sleep analyzer and a smartphone to access WhatsApp) and complete web-based questionnaires. As such, older people unfamiliar with or unwilling to use these devices might self-exclude. However, successful findings from this study could be leveraged to revise further to allow for more accessible options on the technological design for a broader audience and users. Additionally, excluding participants with diagnosed life-threatening illnesses and severe mental health problems is a limitation. However, for this preliminary study, such exclusion is warranted to ensure that participants are medically stable and not reporting severe clinical symptoms that would require a higher level of care, which a digital chatbot cannot help treat.

Furthermore, we acknowledge the small number of participants in this feasibility study. Thus, we do not expect to find significant differences with respect to gender or age. However, the proposed sample size aligns with previous research on the number of participants needed to assess usability and feasibility.

Conclusions

To conclude, the MotivSleep study is innovative in using an automated chatbot to conduct sleep interviews for older people who wish to improve their sleep. Evidence of its feasibility and acceptability will facilitate a larger trial. Participants perceived changes and sleep tracking devices' recorded changes will provide early evidence of its effectiveness. Moreover, the MotivSleep chatbot has the potential to be deployed by a large number of people due to its automated nature. This can offer older people access to supportive care that is more easily accessible and more affordable than face-to-face therapy with sleep experts.

Acknowledgments

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Data Availability

The sleep anomaly detection model is developed based on sleep records from more than 3.6 million nightly summaries from 13,671 individuals from the general population who use the Withings sleep analyzer, which is unavailable to the community due to the Withings Company's policy. However, based on the ethics approval, dialogue data will be made available upon request to support scientific transparency.

Conflicts of Interest

None declared.

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Abbreviations

CRT: Care Research and Technology Center
ESS: Epworth sleepiness scale
GPIS: Godspeed Perceived Intelligence subscale
ISI: Insomnia Severity Index
mHealth: mobile health
NPS: Net Promoter Score
PSQI: Pittsburgh sleep quality index
RDS: Research Data Storage
SQS: single-item sleep quality scale
TPS: Trust Perception Scale
UK DRI: UK Dementia Research Institute

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Protocol

A Virtual Reality–Assisted Cognitive Behavioral Therapy for and With Inuit in Québec: Protocol for a Proof-of-Concept Randomized Controlled Trial

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Abstract

Background: Emotion regulation is an ability related to psychological well-being; when dysregulated, individuals may have psychiatric symptoms and maladapted physiological responses. Virtual reality–assisted cognitive behavioral therapy (VR-CBT) is an effective psychotherapy to target and strengthen emotion regulation; however, it currently lacks cultural sensitivity and can be improved by adapting it to the cultural context of service users. During previous participatory research, we co-designed a culturally adapted cognitive behavioral therapy (CBT) manual and 2 virtual reality (VR) environments to function as a complement to therapy (VR-CBT) for Inuit who would like to access psychotherapy. Emotion regulation skill building will occur in virtual environments that have interactive components such as heart rate biofeedback.

Objective: We describe a protocol for a proof-of-concept 2-arm randomized controlled trial (RCT) with Inuit (n=40) in Québec. The primary aims of this research are to investigate the feasibility, benefits, and challenges of the culturally adapted VR-CBT intervention versus an established VR self-management that is available commercially. We will also investigate self-rated mental well-being and objective psychophysiological measures. Finally, we will use proof-of-concept data to identify suitable primary outcome measures, conduct power calculations in a larger trial for efficacy, and collect information about preferences for on-site or at-home treatment.

Methods: Trial participants will be randomly assigned to an active condition or active control condition in a 1:1 ratio. Inuit aged 14 to 60 years will receive a culturally adapted and therapist-guided VR-CBT with biofeedback or a VR relaxation program with nonpersonalized guided components over a 10-week period. We will collect pre- and posttreatment measures of emotion regulation and biweekly assessments over the treatment and at 3-month follow-up. The primary outcome will be measured by the Difficulties in Emotion Regulation Scale (DERS-16) and a novel psychophysiological reactivity paradigm. Secondary measures include psychological symptoms and well-being via rating scales (eg, anxiety or depressive symptoms).

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Results: As this is the prospective registration of an RCT protocol, we do not yet report any results from the trial. Funding was confirmed in January 2020, and recruitment is expected to start in March 2023 and is set to finish in August 2025. The expected results are to be published in spring 2026.

Conclusions: The proposed study responds to the community's desire for accessible and appropriate resources for psychological well-being, as it was developed in active collaboration with the Inuit community in Québec. We will test feasibility and acceptance by comparing a culturally adapted, on-site psychotherapy with a commercial self-management program while incorporating novel technology and measurement in the area of Indigenous health. We also aim to fulfill the needs for RCT evidence of culturally adapted psychotherapies that are lacking in Canada.

Trial Registration: International Standard Randomized Controlled Trial Number (ISRCTN) 21831510; https://www.isrctn.com/ISRCTN21831510

International Registered Report Identifier (IRRID): PRR1-10.2196/40236

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KEYWORDS

Inuit health; randomized controlled trial; emotion regulation; virtual reality; cognitive behavioral therapy; co-design; biofeedback; cultural adaptation; Indigenous

Introduction

Emotion Regulation and Mental Health

Emotion regulation is a set of skills and competencies that individuals have to a variable extent: strong emotion regulation skills can facilitate mental health. When those skills are dysregulated, the difficulties related to emotion regulation are implicated in various psychological complaints and disorders [1]. Biosignals such as heart rate, skin conductance, and diastolic blood pressure response are also phenotypical in populations with difficulties in emotion regulation, indicating multiple levels of involvement in the health of individuals [2]. Some psychotherapies exert to large effect, decreasing dysregulation and increasing the ability to regulate emotions [3-6]. Improvements in emotion regulation during psychotherapy are associated with decreases in anxiety, depression, substance use, and other psychopathologies [7]. Moreover, emotion regulation is robustly and longitudinally associated with psychological resilience [8] and associated with life satisfaction, positive affect, and other well-being indicators with a small to moderate effect size [9].

Enhancing Emotion Regulation Interventions With Virtual Reality and Biofeedback

Virtual reality (VR)–assisted mental health interventions effectively increase mental well-being, including building the ability to regulate emotions [10-12]. VR is an interactive, computer-generated, 3D world of images, videos, and sounds delivered through a VR headset system. Combined with the efficacy of cognitive behavioral therapy (CBT), v*irtual reality–assisted cognitive behavioral therapy (VR-CBT)* has several therapeutic advantages, including increased interactivity of the therapy and patient participation. Immersive visuals can create a holistic approach to therapy with mind-body exercises (eg, biofeedback integrated with VR). Therapists can present clients with enhanced skill-building scenarios and modulate elements in the environment for the personal needs of the client. For instance, the varying intensity of the exposure can be shown to the client through visual aids that reflect their physiological states [13]. *Biofeedback* is a process of rapidly demonstrating physiological metrics to an individual, sometimes with the goal of changing thoughts, behaviors, or physiology [14].

Integrating Inuit Culture, Community Needs, and Technology

In addition to therapeutic advantages, combining VR and CBT presents a unique opportunity for the advancement of cultural sensitivity in treatment. Up to 60% of Inuit live in urban centers, and many experience adversities in health [15]. Inuit residing in urban centers reported only fair or poor access to health care [16], and in Montreal, Indigenous peoples reported trauma, anxiety, and depression to be some of their primary concerns to be addressed [17]. The increased mental health risks and lack of culturally sensitive resources for First Nations, Métis, and Inuit are part of the complex consequences of ongoing settler colonialism. The mental health impacts of colonialism can be intergenerational, with adverse impacts documented into the second and possibly third generations [18,19]. The Indigenous historical and intergenerational trauma also stresses the importance of development and research with the aim of increasing the knowledge base toward strengthening resilience of the communities and their members.

Because of its relatively low cost, flexibility, and immersion, VR has been used in Indigenous contexts, such as in art, storytelling, culture, language, and transferring cultural heritage [20-23]. There is interest in digital technology solutions for Indigenous health and mental well-being; however, most follow a format of conventional psychotherapy via telemedicine [21,24]. VR could offer opportunities for access to mental health care resources for populations affected by health inequities, delivering specialized content at a low cost and in many locations.

Co-design and Collaboration With Inuit in Québec

VR-CBT

To expand access to mental well-being resources for Inuit in Québec, we will evaluate the efficacy of 2 emotion regulation–based VR interventions in a proof-of-concept randomized controlled trial (RCT). Our team developed the VR-CBT with experts in psychotherapy, VR, and Inuit health

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and culture, including an Inuit advisory committee. The advisory committee was composed of Inuit and non-Inuit individuals, health and social services providers, and Inuit representational organizations. The advisory committee included both women and men. We consulted Inuit representational organizations before embarking on this project with the aim of naming research priorities and building a collaboration toward those goals. We then collaborated to culturally adapt the study procedures and materials. The process of culturally adapting the treatment manual and other materials will be described further in Gomez Cardona et al, *in preparation*.

VR for Mental Well-Being: Self-management

Another application that is part of the study is Calm Place—a commercial VR program previously developed by Mimerse that involves guided relaxation and meditation techniques. The application has been used in clinical settings and is rooted in nature's effects on well-being [25]. This intervention was chosen in consultation with the advisory committee based on the unacceptability of the waitlist or nonactive controls and similar therapeutic goals (eg, emotion regulation through guided activities).

Research Aims

The primary aims of this proof-of-concept RCT are to investigate the feasibility, benefits, and challenges of a culturally adapted VR intervention versus an established VR self-management program. We will assess the feasibility and validity of psychophysiological measures as objective outcomes of the interventions. In addition, we estimate the effect size of each treatment through between-group and within-group measures of emotion regulation, mental well-being, and difficulties in mental well-being (anxiety, depression, and posttraumatic stress disorder) with a longitudinal follow-up.

We work in a novel area in the literature, providing a VR intervention for an Indigenous population with a specifically therapeutic aim [24]. In addition, we will use both objective and subjective outcome measures—a novel but robust approach [2]. This novel psychophysiological approach has been validated in healthy individuals in our laboratory (Seon et al, in preparation).

Methods

Design

The study design is a 2-arm proof-of-concept RCT co-designed with an Inuit advisory committee. The first treatment arm (A) is a 10-week VR-CBT. An active control treatment with minimal attention; the second treatment arm (B) will be using Calm Place as a 10-week self-management. There will be no crossover between conditions, and we will use a 1:1 ratio randomization procedure. The protocol is described in accordance with the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines for interventional trials and is detailed in Multimedia Appendix 1. Ultimately, the goal of the study is to establish the initial feasibility of the VR-CBT and the technologies used and to identify the best measures for initial efficacy.

Setting

This trial will take place at an outpatient psychiatric institute in Québec, Canada.

Participants

Sampling

Our primary *inclusion criteria* are that the participants must (1) self-identify as Inuk, (2) live in the city where the study is taking place, (3) be aged between 14 and 60 years of age, and (4) be proficient in English or French.

With exclusion criteria, we confirm safety and best fit with the study necessitating VR and psychophysiological equipment use. We exclude those who do not identify as Inuk, youth aged <14 years, and adults aged >60 years, as well as individuals who do not tolerate VR headset and study sensors. We exclude individuals with a self-reported history of psychosis or schizophrenia, with current substance abuse as measured by screens (score >8 on the Alcohol Use Disorders Identification Test C (AUDIT-C) or >3 on the Drug Abuse Screen Test), or with any change in psychoactive medications 4 weeks before screening. In addition, we exclude individuals with physical conditions that might cause risks during VR use (ie, history of cardiac condition or epilepsy). There are no exclusions based on other concomitant care.

Meeting the diagnostic criteria for any specific disorder, verified history of trauma, or trauma symptoms was not part of our inclusion and exclusion criteria, given our focus on cultural sensitivity, our chosen skills-building approach in the therapy manual, and the shared history of trauma by community members.

Sample Size

There is, to our knowledge, no estimate of the effect size of emotion regulation–based VR interventions among Indigenous populations, and this proof-of-concept study will be necessary for accurate estimation of power in future trials. As described in the previous section, mental health risks among Indigenous and Inuit populations differ from those among the general population, which emphasizes the need for this proof-of-concept study specifically in this population for power calculations in future work. However, a previous VR intervention for anxiety disorders among a general population sample had an estimated effect size of g=0.78 (medium) compared with minimal-attention controls and g=0.90 (large) with no-treatment controls [26,27]. To attain statistical power >90% with an alpha of $P<.5$, the sample size of n=20 in the active treatment group and n=20 in the active control group is sufficient for generalized linear models with a similar effect size (power=0.97; $df=38$; $P=.05$).

Procedure

Recruitment

The research team will recruit participants who are potentially willing to participate in either of the 2 arms of the trial. Recruitment methods will include word of mouth, flyers, and posts on social media, websites, and Montreal neighborhoods. First contacts with potential participants will involve informing them about the study and screening for initial eligibility criteria

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(eg, aged 14-60 years, having no acute medical or psychological risks, etc). First contacts will be done to further explain the study protocol and evaluate the eligibility criteria with potential participants. This can occur over the phone, via secure email, or in person. Our eligibility criteria include screening for suicide risk and higher scores on alcohol and drug measures. This screening will occur in person during the first visit to enroll in the study or via telephone. Once eligibility and interest in the study are established either in person or via telephone, the participants can proceed to the informed consent process with our team (in person).

Randomization and Masking

After receiving informed consent for participation, a research assistant will use a computerized randomization generator to randomly assign participants in a simple 1:1 ratio (VR-CBT or Calm Place). Before randomization, we will show participants the treatment rationales, explaining the 2 possible study groups. They will report their preference for either treatment in a forced-choice question, rate their preference for each treatment on a scale from 1 to 10, and provide comments on why they selected this choice. This information is collected to inform future larger trials and clinical services. The treatment cannot be supplied blinded to the content. However, as the measurements are self-reports and objective measurements, we do not use blinded outcome evaluation. Once random assignments are decided, they will be kept hidden from researchers and research assistants until the participants begin the trial.

Ten-week VR Interventions

Culturally Adapted VR-CBT as the Active Condition

The culturally adapted therapy is a manualized CBT with an emotion regulation focus. The VR-CBT therapy will take place in a clinical setting and will consist of traditional therapeutic processing complemented by therapist-guided training in a VR environment. The main therapeutic strategies are stress inoculation and guided mastery with biofeedback components. Our group developed 2 VR environments (SB UQO [Université du Québec en Outaouais] cyberpsychology laboratory)—one for safe practice and the other for challenging emotion regulation skills. The first, called Snowy Place, is a snowy tundra that mimics the arctic life well known to Inuit. In developing Snowy Place, the Inuit advisory committee believed that this would be a comforting environment. The second is a small environment with many people and no children (small stressors), where the environment and elements (eg, social and situational) demand emotion regulation skills. The participant will train learned emotion regulation skills using these environments under the guidance of a psychotherapist. The VR-CBT can have interactive components where partial avatars (eg, hands of the participant) and preprogrammed avatars (eg, static or acting people in the room) are present. Multimedia Appendix 1 provides a detailed overview of the CBT therapist manual, including a session-by-session overview.

Calm Place as the Active Control

During the use of the VR application, the Calm Place user may see flowing water, mountains, and tree cover; a tropical atoll with sand, palm trees, and the ocean; or an arctic scene with large pines, snow cover, and large stones. In Calm Place, each virtual environment offers applications [25,28], such as visual breathing aids, time and weather cycles, and meditation voice overs, with the guidance of the VR program. Here, the guidance on relaxation is nonpersonalized and is based on the selections of the user within the VR environment. Thus, though participants' weekly choices regarding prevalence and duration of use are self-managed and done from their home, this intervention involves guided programming for guidance. The self-management program—Calm Place—does not have any avatar, social-interactive, or personalized components. The research team will contact these minimal-attention control participants weekly to check whether they use the application and to verify their safety.

Translation

A professional translator translated each of the self-reported measures that did not have the existing French versions. For comparability, given the small sample size, the surveys will be administered in either English or French for data collection, and the language controlled for in statistical analysis. However, each psychometric measure was translated to Inuktitut to complement the understanding of English and French surveys.

Data Collection

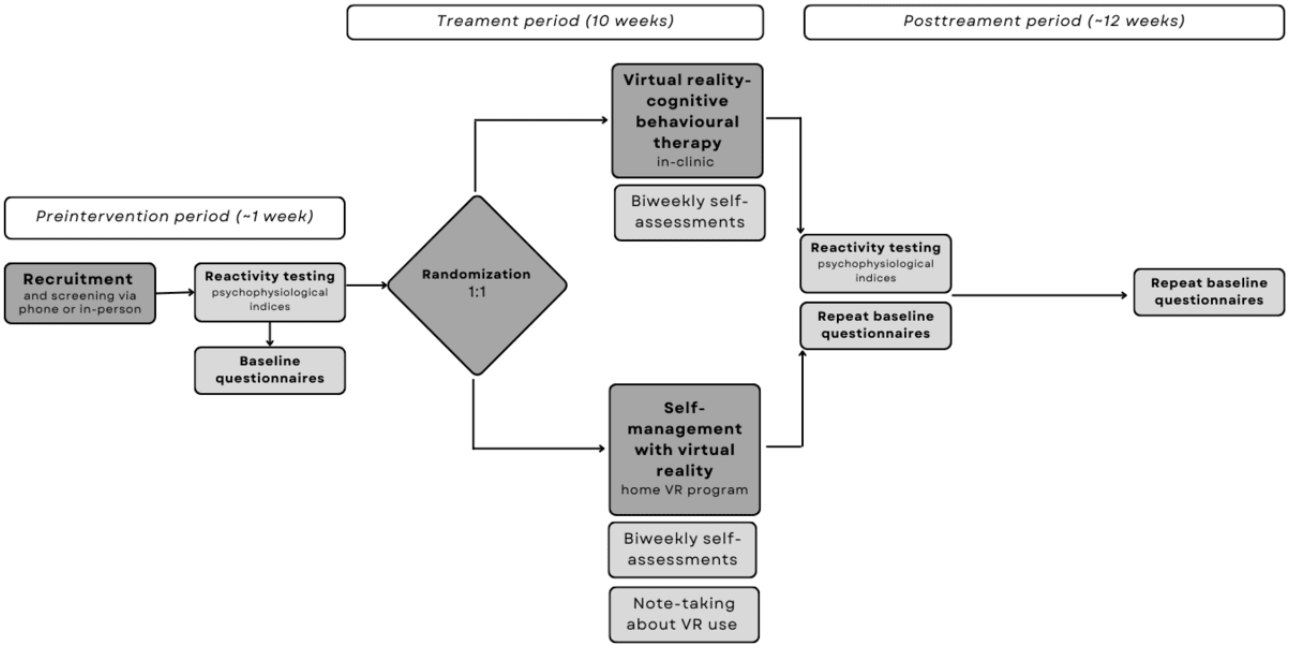
Week 0: Screening, Consent, and Randomization

Before their participation, participants will be fully informed by research assistants about their role in the study and treatment options; if willing to participate in either of the treatments, adults or guardians will sign an informed consent form (study procedures in Figure 1). The number of participants rejecting one or another treatment and thus excluded from the actual trial will be registered for evaluation of acceptance. Initial visits will involve checking eligibility and preference for treatment. We then randomly assign participants to one of the 2 VR interventions—Calm Place or VR-CBT—for a maximum of 10 weeks.

The participant study procedures from recruitment until the end of participation include a baseline measurement, a 10-week intervention period, and follow-up.

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Figure 1. Flow of proof-of-concept study. VR: virtual reality.



Week 0: Baseline Measurement of Subjective and Objective Outcomes

At the first evaluation done in the days before the intervention, we evaluate the baseline subjective and objective measurements. Data will be collected and stored with REDCap (Research Electronic Data Capture) data collection software (Vanderbilt University), protecting the confidentiality of patients with research IDs. We will collect data on participants' rest and stress psychophysiology during a 1-hour reactivity testing paradigm, where VR exposure will evoke relaxation (forest walk) or moderate stress (height exposure). Baseline measures include the Difficulties in Emotion Regulation Scale (DERS)-16 [29]; Clinical Outcome Routine Evaluation-Outcome Measure (CORE-OM) and Clinical Outcome Routine Evaluation- 10 item (CORE-10) [30,31]; Warwick-Edinburg Mental Well-being Scale (WEMWBS) [32,33]; Generalized Anxiety Disorder 7-item (GAD-7) [34]; Primary Care Screen for Posttraumatic Stress Disorder for Diagnostic and Statistical Manual 5 version (PC-PTSD-5) [35]; Patient Health Questionnaire 9-item (PHQ-9) [36]; visual analog scales for anxiety, emotional arousal, and emotional valence [37-40]; DAST-10 [41]; AUDIT-C [42]; and Severity of Dependence Scale for Cannabis (SDS-C) [43]. We will measure blood pressure using a calibrated, Health Canada–approved device. Figures 1 and 2 show the study flow diagram.

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Figure 2. SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) flow table. VR: virtual reality, VR-CBT: virtual reality–assisted cognitive behavioral therapy.

	Study Period								
	Enrolment	Allocation	Postallocation					Close-out	
Time point	- t_1	0	t_1	t_2	t_3	t_4	t_5	t_6	t_7
Enrolment:									
Eligibility screen	X								
Informed consent	X								
Baseline measurement		X							
Allocation		X							
Interventions:									
VR-CBT			←	—	—	—	→		
Self-management VR			←	—	—	—	→		
Assessments:									
Psychophysiology		X					X	X	
Emotion regulation, symptoms, and wellbeing		X	X	X	X	X	X	X	X
Safety and feasibility			X	X	X	X	X	X	X
Preference		X							

Weeks 1 to 10: Intervention Period and Weekly Questionnaires

During the intervention period, we will send participants biweekly questionnaires. In their final visit, participants will repeat the procedures from the first visits (visits 1 and 2). Participants will receive a small financial compensation (gift card) for each visit.

Week 10 to 11: Repeat Measure of Subjective and Objective Measurements

Once the intervention is complete, participants repeat the questionnaires and the reactivity testing paradigm from week zero to provide a second measurement.

Week 22: Postintervention Follow-up

Twelve weeks after their final visit, we will follow up with the participants on all baseline questionnaires.

Materials

To support the delivery of the interventions and the corresponding collection of data during the trial, a sensor management system and web-based clinician portal were developed in collaboration with the National Research Council Canada (DJ and CP). The sensor management system facilitates the connection and initialization of the biofeedback sensor, eVu TPS (Thought Technology Ltd) as well as the streaming of data to the web portal. The web portal allows the management of participant sessions as well as live and postsession biofeedback data visualization. The raw biofeedback data (in CSV format) are also available through the portal to study coordinators and clinicians for postprocessing and analysis.

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Measures

Primary Outcome Measures

DERS-16 Scores

The DERS-16 is a short, valid measure of emotion regulation [29,44]. Participants rate their ability to accept and be aware of their emotions, direct themselves toward their goals, control their impulses, access regulation strategies, and have emotional clarity [45]. The DERS's psychometric properties are favorable, having moderate to very strong internal consistency (α=.69-.97) and strong retest reliability (*r*=0.88; ρI=0.85) [29, 46-49]. Correlating with anxiety, depression, stress, borderline traits, and more, the DERS-16 has good construct validity [29,47,50]. Although consistent across demographics and culturally adapted for some groups, the scale is not yet adapted for any Indigenous groups [48,51]. The full DERS is translated into French and validated [52]. Although there are no formal cutoff scores for the DERS, the English scale achieves moderate diagnostic accuracy (area under the curve [AUC]) among emotional disorders and nonsuicidal self-injury populations [53-55], and it is sensitive to changes following treatment [56-60].

Visual Analog Scales: Anxiety, Emotional Arousal, Emotional Valence

Participants will respond to the Visual Analog Scale (VAS)-Anxiety (VAS-A), Visual Analog Scale-Emotional Arousal (VAS-EA), and Visual Analog Scale-Emotional Valence (VAS-EV) during reactivity testing. These items have favorable properties, including construct validity and sensitivity [37-40].

Objective Measures

The participants will undergo a psychophysiological reactivity testing paradigm. This will be repeated after the end of the VR intervention for those who completed a minimum of 7 and a maximum of 10 sessions of therapy as soon as possible after the final session. We will collect and measure several metrics, including heart rate, blood volume pulse, skin conductance, blood pressure, and accelerometer data. Participants first respond to baseline subjective arousal, emotional arousal, and VAS-EV. We then begin collecting psychophysiological data with a portable finger sensor, covered with a piece of cloth for light sensitivity, by attaching it to the participant's nondominant index finger. They fill out a survey, including several symptom scales as described during this approximately 15-minute period, and have their blood pressure taken with an ambulatory blood pressure machine. We also record a no-task seated baseline recording of sensor data for 3 minutes. Then, participants will familiarize themselves with VR in a forest walk environment with no tasks other than to walk and explore (5.5 minutes), with minimal interaction with the research team. In the next segment, participants walk a VR plank exposing them to the heights below for 5.5 minutes (instructed to walk back and forth, with no interaction). If the exercise is too challenging (eg, participant distress at a tolerable level), participants remain in the environment without walking for 2 minutes or withdraw completely (eg, intolerable distress) from the exercise. Finally, participants re-enter the same VR environment, this time with a floor rather than a plank beneath them and walk (3 minutes). The last segment is a 10-minute seated rest period. After each segment, participants report using the same visual analog scales.

Secondary Outcome Measures

PC-PTSD-5 Scores

On a scale of 5 items, the PC-PTSD-5 first verifies trauma exposure and then evaluates the presence of the 4 symptom clusters of PTSD [35]. The 5 items include symptoms such as arousal, re-experiencing, avoidance, and negative cognitions and mood. The scale has strong test-retest reliability (*r*=0.83) and is associated with important clinical variables such as suicide [35,61]. With a cutoff score of 3, the PC-PTSD-5 has strong diagnostic accuracy (AUC=0.941) [35]. The scale was translated by the Clinical Psychology and Psychotherapy Unit of the Bielefeld University into French [62].

WEMWBS Scores

The WEMWBS with both its 14-and short 7-item versions, measures holistic aspects of well-being. The dimensions include eudemonic aspects, hedonic aspects, psychological functioning, and subjective well-being [32,33]. Positive mental health provides an independent factor for functionality in the presence or absence of a mental illness. This scale has favorable psychometric properties. Using the WEMWBS, we can calculate mental health costs and quality-adjusted life-years [63,64]. In a study of Indigenous Australians, the Short-Form WEMWBS achieved an internal consistency of α=.69 to .88 [65]. The WEMWBS has also been evaluated in various minority and cultural groups [66].

GAD-7 Scores

The GAD-7 [34] is a validated self-report scale that measures anxiety presence and severity [67]. Among outpatients with anxiety and mood disorders, the GAD-7 is a reliable (*P*=.85) and sensitive (79.5%) measure with a cutoff score of 10 [68]. The GAD-7 scores have been categorized into mild, moderate, and severe anxiety, with cutoffs of 5, 10, and 15 [34,68]. Among Indigenous students in Canada, the GAD-7 achieved an internal consistency of α=.86 and correlated strongly with related constructs [69]. The scale was translated and validated in French [70].

PHQ-9 Scores

The PHQ-9 is a depression severity measure based on the Diagnostic and Statistical Manual Version IV [36]. In a meta-analysis of the scale's psychometric properties, the PHQ-9 achieved optimal sensitivity and specificity with a cutoff score of 10 [71]. Among Indigenous North Americans, the scale's psychometric properties were favorable, with an internal consistency of α=.94 [72].

CORE-OM, 10-Item Version

The CORE is widely used as an outcome measure in psychotherapy and has several versions, including the CORE-OM and the 10-item version CORE-10 [30,31]. The CORE-OM and CORE-10 are screening measures for psychological distress, including items for well-being, psychological symptoms, functioning, and risk. The CORE-OM has excellent internal consistency in clinical samples (α=.94) and for each of its subscales (α=.75-.94); it also has good

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test-retest reliability (*P*=.83) [73]. The CORE-10 with a cutoff score of 11 differentiated between clinical and nonclinical general samples with a sensitivity of .85. Its internal consistency was α=.90, and it had a reliable change index of 6 points [30]. The widely accepted French translation had validity results forthcoming from the University of Toulouse [74].

Feasibility: Attrition and Adherence

We will collect data about the feasibility of the treatment in the form of weekly use data (Calm Place group) and study attrition and adherence to treatment (VR-CBT group). These metrics will be assessed by the number of treatment sessions attended, completion of treatment, percentage of sessions attended, number of patients who dropped out, and when possible, reasons for dropping out, comments and notes on feasibility in diary responses, the time spent using the program, and consistency in using the program over 10 weeks. Treatment completers for VR-CBT will be defined as individuals who attend 7 out of 10 sessions, and for Calm Place, 7 reported sessions over 10 weeks. Dropouts for VR-CBT are defined as individuals missing 2 consecutive sessions of therapy without rescheduling (no-show). Noncompleters are individuals who complete <7 sessions (but attend at least 1). In the case participants are judged by the research team as *at risk* (eg, psychologically), they may also be withdrawn from the study.

Safety: AUDIT-C, DAST-10, and SDS-C

During the treatment period, we also want to confirm that the VR-CBT is a safe pretreatment and want to observe a potential increase in the use of alcohol and drugs during the therapy. This will be done using presession evaluations with AUDIT-C, DAST, and SDS-C with a 1-week time frame. The AUDIT-C assesses alcohol consumption and drinking behaviors using 3 items [42]. The full AUDIT with 10 items has been translated and validated. Both the English and French versions of AUDIT have favorable psychometric properties, including high sensitivity and specificity (approximately 90%), and this also concerns the AUDIT-C [75-77].

The DAST is a 10-item validated self-report scale that will be used to screen for and assess drug use over the previous 12 months [41,78]. Typically, the DAST-10 achieves a sensitivity of 41% to 95% and a specificity of 68% to 99%, depending on the population and diagnostic information used [78]. No information is yet available about the validity of the French translation of the DAST.

The SDS-C[43] consists of 5 items with good internal reliability and discriminant validity, with a cutoff score of 4 [79]. No information is yet available about the validity of the French translation of the Severity of Dependence Scale [80].

Data Analysis

Analyses for Rating Scales

Expecting nonnormally distributed data in a small human sample, we will conduct nonparametric tests and generate descriptive and comparative statistics to detect between-group differences for the 2 conditions, VR-CBT (A) and Active Control VR program (B), using R Statistical and Computing Software (R Core Team). We will use generalized mixed linear models to compare the 2 conditions using scores on DERS-16 across several time points (pre- and posttreatment as well as biweekly and bimonthly time points). In addition, we will describe changes in mood, anxiety, and trauma symptoms for the 2 conditions (pre- and posttreatment, as well as biweekly and bimonthly time points). The data collection for time points varies based on the administration instructions for each scale (weekly, biweekly, monthly, etc). Cohen *d* or nonparametric tests will calculate the effect size between the 2 conditions.

Objective Psychophysiology Data Analyses

To accurately identify peaks and not simply gradual increases in skin conductance observed over time, we will filter skin conductance data with a threshold value of 0.04 µS and average over 5 seconds [81,82]. As our study involves movement in a VR space in addition to exposure to a potential stress-inducing situation, we will filter the data with a lower limit of 40 bpm and an upper limit of 200 bpm [83]. Heart rate will also be averaged over 5 seconds. Following averaging, we will use open-source filters for preprocessing the data; then, the psychophysiological data will be processed with existing packages in MATLAB and Python. To correlate the DERS-16 and secondary outcome measures (CORE, WEMWBS, GAD-7, PHQ-9, and PC-PTSD-5) with psychophysiological data, we will employ nonparametric regression analyses in R Statistical and Computing Software. In addition, we will explore preliminary cutoff sum scores for therapeutic response by plotting receiver operating characteristic curves and conducting AUC analyses. We will also compare baseline to postintervention (second baseline) changes in psychophysiology using regression models. Cohen *d* or nonparametric tests will calculate the effect size between groups A and B.

Ethical Approval

The protocol was approved by the Research Ethics Board of the Centre Integré de Santé et Services Sociaux de l'Ouest de l'Ile (IUSMD 21-52), and it follows the standards of the World Health Organization's Helsinki Declaration 1975, revised in 2013. Approval for the protocol was granted by the Douglas Mental Health University Institute Ethics Review Board (IUSMD 21-52). In accordance with Tri-Council Policy Statement 2 and guidelines by the Inuit Tapiriit Kanatami and Nunavut Research Institute, the consent process involves both community and individual consent [84,85]. First, we consulted Inuit representational organizations and co-designed with community members. Before participation, we will obtain written, informed consent from all participants, their parent or guardian, or oral consent. Data will be collected and stored with REDCap data collection software, protecting the confidentiality of patients with research IDs. All publications resulting from the research will maintain confidentiality requirements by deidentifying any data. Participants will receive a small financial compensation (gift card) for each hour of in-person participation and surveys (approximately CAD $15 [US $11] per hour).

Data Dissemination Plan

Respect for Inuit Ethical Standards

This research recognizes community protocols and the holistic approach to health and wellness in many Indigenous cultures.

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By doing that, we respect the ethics framework in Indigenous contexts, composed of principles of respect for persons and concern for Equity and Reciprocity [84]. We seek to follow and respect the principles outlined by Inuit communities in the Tri-Council Policy Statement 2 and the National Inuit Strategy on Research and the Negotiating Research Relationships with Inuit Communities guide [85,86]. These guidelines can apply to Inuit, First Nations, and Métis communities and provide structure for privacy, intellectual property, data custody, and secondary use of data. In adherence to these values, respect for people is necessary, and this is achieved through free, informed, and continued consent of the Inuit community and individual research participants [87]. We also aim toward, "research that is efficacious, impactful, and meaningful to Inuit" [85] in aligning with Inuit research priorities through consultation with representational organizations and the formation of an advisory committee. We strive to bolster social equity through the creation of materials that will belong to the Inuit community.

Maximized Participation of the Inuit Community

All results of this research will be validated by the community members and representational organizations and returned to them. We will communicate the final results and a report of the study to all those who participated in it and to the community organizations that would be interested. All publications resulting from the research will maintain the requirements of confidentiality and where they approve, will mention the contribution of everyone involved. The rights of coauthors of Indigenous contributors will be recognized. In any publication derived from this project, participants' geographical localization will be mentioned as well as the Indigenous group they belong to (Inuit in Québec). This identification of participants as a group will be disclosed but not their personal information.

Inuit Ownership of VR Manual and Environments

The rights and permissions to use the treatment manual and VR environments belong to the Inuit community, although they are attached and available in this document. As the main intention of all products of this study is to benefit the Inuit community in Québec, the materials will not be commercialized; however, authors should be consulted before use (to be approved by the Inuit community). Any use of study materials should acknowledge the role of the advisory committee (Inuit community) in developing them and should only be used with express permission (contact SB to initiate this process).

Results

As this is the prospective registration of an RCT protocol, we do not yet report any results from the trial. This study has been registered prospectively and is available on the web [88] (registration number ISRCTN21831510). Funding was confirmed in January 2020, recruitment is expected to start in March 2023, and is set to finish in August 2025. Expected results to be published in spring 2026.

Any major changes to the protocol will be submitted and approved by our research ethics board, documented on the trial registration platform, and justified in future publication.

Discussion

Summary of Objectives

This proof-of-concept study is necessary to respond to the following main concerns: (1) the limited availability of culturally acceptable versions of otherwise validated treatments [89], (2) limited number of RCTs on culturally adapted psychotherapies in Canada, and 3) the use of self-management as an active comparator. This protocol, which compares VR-CBT and Calm Place as self-management, responds to the community's desire for culturally safe and efficient therapeutic treatments and scientific needs for further investigation into the need and efficacy of culturally adapted treatments. The Inuit community in Montreal co-designed this project with the research team based on their desire for a resilience-based mental health resource.

Gaps in Research on Culturally Adapted Interventions

Previous evidence of increased acceptability and increased adherence of culturally adapted treatments, with a comparable efficacy to conventional psychotherapy and pharmacological interventions, is promising [90-92]. A recent systematic review of 14 studies conducted in Canada involving culturally adapted mental health treatments concluded that most interventions reduced anxiety, depression, and suicidality among First Nations, Métis, and Inuit [93]. Nevertheless, none of the 14 studies included an RCT, with most RCT evidence for culturally adapted interventions so far being conducted in the United States, low-and middle-income countries, or among refugee populations [90-93]. Furthermore, previous reports have mainly focused on clinic-based treatments or inactive controls. Although our study is randomized, we do ask about preferences between the active treatment and active control treatment and will record the number of participants excluded after accepting only one of the treatments. This will give some indication of the initial perceptions of the acceptability of the treatments.

Implications of VR With Culturally Adapted Therapies

As technology-assisted psychotherapies advance, VR-CBT or self-management with VR may become complementary options for Indigenous health. In addition to the possibilities of remote treatment (or telemedicine), VR-CBT combines a transdiagnostic and effective treatment modality with potentially improved control and immersion into therapy [1,7]. For instance, therapists can track real-time psychophysiological responses to therapeutic challenges through biofeedback [13]. The client can participate in the therapy in any environment judged most appropriate by the therapist and client to enhance access to treatment. Lastly, Inuit in Nunavik—the northern part of Québec—often experience inconvenience and financial and emotional devastation when attempting to seek care for a health concern, as they may have to travel away from their family to the southern part of the province [94]. We explore several health technologies in the RCT, and future work includes continuing remote therapy.

Strengths and Limitations

The process of cultural adaptation of psychotherapy was conducted to increase acceptance. The advisory committee

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recommended study inclusion based on sociocultural background, not trauma symptoms, to improve the cultural safety of the trial. Accordingly, inclusion is based on subjective motivation for improved mental health rather than any categorical diagnosis or subjective or objective need for treatment. In addition, the content of the psychotherapy was modified to confirm safety, according to the comments from the advisory committee. These modifications include reducing exposure and distress-producing exercises and removing the homework normally part of the therapy. A limitation is that these changes may challenge the odds of a psychotherapeutic response.

In our study protocol, we included an active control group, noting the vulnerability of the study population; this may lead to reduced between-group effects. However, only the active treatment is culturally adapted and guided by a psychotherapist, which could improve attendance and thus long-term efficacy in the active treatment group. We will observe the impact of the setting as compared with the content on acceptance while asking for the preference for therapist-guided or self-management treatment. This proof-of-concept RCT will inform us about the potential challenges or limitations of the study protocol, and we can characterize the best outcome measures and calculate power for the further efficacy trial. We consider the scientific risks acceptable, given the extreme imbalance between the need and availability for access to valid and safe treatments.

Conclusions

The proposed study responds to the community's desire for accessible and appropriate resources for psychological well-being, as it was developed in active collaboration with the Inuit community in Québec. We will observe preference for therapist-guided, at-clinic treatment, or at-home self-management and compare the acceptance and feasibility of a culturally adapted, VR-assisted psychotherapy with a commercial self-management program in VR. We incorporate novel technology in providing treatment and in objective outcome measurement in the area of Indigenous health. We also aim to fulfill the needs for RCTs to test the efficacy of culturally adapted psychotherapies.

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Data Availability

The final trial data set will be accessible to the researchers of this project. The data generated from this study are not publicly available to respect the privacy and confidentiality of participants (who are a small group that is potentially more identifiable) but are available from the corresponding author on reasonable request. The initial version of the portal (backend) that was provided to Douglas Research Institute at the beginning of the project is owned by NRC, ownership of the developments and integrations for the specific work is determined by the IP policy of Douglas Research Institute. The rights to benefit from and permissions to use the treatment manual and VR environments belong to the Inuit community, although they are attached and available in this document.

Authors' Contributions

OL is the primary investigator who confirmed the funding, conceived the study, and led the project development and planning. LGC coordinated cultural safety and co-design. SP, JO, EPR, CS, and M Lalonde, among others, comprised the advisory group; only consenting AG members were included as co-authors. SP, JO, EPR, CS, M Lalonde, OL, LGC and SB co-designed the content of the Virtual Reality–Assisted Cognitive Behavioral Therapy. SB led the design of the treatment manual and technical design of the VR environment based on the AG comments. DJ and CP (National Research Council of Canada, NRC) were in response of the creation of the therapist portal. SB, DJ, and CP were responsible for the integration of the portal, sensor data, and visual biofeedback in the VR environment. EPR followed cultural safety during the integration phase. NM, MK, MY, M Lashley, LGC, DJ, CP, QS, SB, and OL contributed to the design and development of the trial protocol, with comments from the advisory group. QS and OL authored the first version of the manuscript. All authors read and approved the final manuscript.

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Conflicts of Interest

SB is president and a shareholder of Cliniques et Développement In Virtuo, a university spin-off that uses virtual reality as part of its clinical services and distributed virtual environments. The terms of these arrangements have been reviewed and approved by the Université du Québec en Outaouais in accordance with its conflict-of-interest policies. The remaining authors report no financial relationships with commercial interests.

Multimedia Appendix 1
The appendix contains the treatment manual for psychotherapists (for use contact S.B).
[PDF File (Adobe PDF File), 2241 KB - resprot_v12i1e40236_app1.pdf]

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Abbreviations

AUC: area under the curve
AUDIT: Alcohol Use Disorders Identification Test
CBT: cognitive behavioral therapy
CORE: clinical outcomes in routine evaluation
DAST: Drug Abuse Screening Test
DERS: Difficulties in Emotion Regulation Scale
GAD-7: Generalized Anxiety Disorder 7-item
PC-PTSD-5: Primary Care Screen for Post-Traumatic Stress Disorder Diagnostic and Statistical Manual 5 version
PHQ-9: Patient Health Questionnaire 9-item
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
SDS-C: Severity of Dependence Scale for Cannabis
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
VR: virtual reality
VR-CBT: virtual reality–assisted cognitive behavioral therapy
WEMWBS: Warwick-Edinburg Mental Well-Being Scale.

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Protocol

Delivering a Home-Based Exercise Program to Youth With Osteogenesis Imperfecta: Protocol for a Comparative-Approach Study

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Abstract

Background: Osteogenesis imperfecta (OI) is a rare bone fragility disorder associated with muscle weakness. Individuals with OI may therefore benefit from exercise interventions aiming to improve muscle and bone strength. Given the rarity of OI, many patients do not have access to exercise specialists who are familiar with the disorder. As such, telemedicine, the provision of health care through technology to provide care at a distance, may be well suited for this population.

Objective: The main objectives are (1) to investigate the feasibility and cost-effectiveness of 2 telemedicine approaches for the delivery of an exercise intervention for youth with OI and (2) to assess the impact of the exercise intervention on muscle function and cardiopulmonary fitness in youth with OI.

Methods: Patients with OI type I (the mildest form of OI; n=12, aged 12-16 years) from a pediatric orthopedic tertiary hospital will be randomized to receive a 12-week remote exercise intervention in either (1) a supervised group (n=6), monitored every session, or (2) a follow-up group (n=6), receiving monthly progress update appointments. Participants will undergo the following pre- and postintervention evaluations: sit-to-stand test, push-up test, sit-up test, single-legged balance test, and a heel-rise test. Both groups will be given the same 12-week exercise regimen, which includes cardiovascular, resistance, and flexibility training. For each exercise training session involving the supervised group, a kinesiologist will provide instructions to participants through live video sessions using a teleconferencing application. On the other hand, the follow-up group will discuss their progress with the kinesiologist every 4 weeks over a teleconferencing video call. Feasibility will be assessed by recruitment, adherence, and completion rates. A cost-effectiveness analysis of both approaches will be computed. Changes in muscle function and cardiopulmonary fitness will be examined between the 2 groups, pre- and postintervention.

Results: It is anticipated that the supervised group will have higher adherence and completion rates compared to the follow-up group, which may be associated with greater physiological benefits; however, it may not be as cost-effective compared to the follow-up approach.

Conclusions: By determining the most feasible telemedicine approach, this study may serve as a basis for providing increased access to specialized adjunct therapies for individuals with rare disorders.

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KEYWORDS

adherence; cost-effectiveness; exercise; osteogenesis imperfecta; telemedicine

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Introduction

Osteogenesis imperfecta (OI) is a rare congenital disorder characterized by bone fragility occurring in approximately 1 in every 10,000 individuals [1]. OI is typically caused by a dominant mutation in 1 of the 2 genes that code for the alpha chains in collagen type I, *COL1A1* and *COL1A2* [1]. The Sillence clinical classification of OI is divided into 4 phenotypic groups, with type I being the mildest and most frequently diagnosed [1,2]. OI type I comprises individuals with bone fragility and those whose stature falls within or close to normal limits [2,3]. While bone fragility is the leading characteristic of OI, we have shown that children and adolescents with OI type I have lower peak muscle force and muscle size compared to age- and sex-matched controls [4,5]. Given the positive relationship between muscle force and bone strength, muscle function deficits are likely to contribute to bone mass deficits in youth with OI [4-6].

For both healthy children and children with OI type I, exercise has been shown to be an effective method for improving cardiopulmonary fitness, as well as muscle strength [7,8]. Therefore, given the previously mentioned muscle deficits in children and adolescents with OI [4,5], individuals with OI type I may be more likely to benefit to a greater extent from this adjunct therapy, in addition to the typical mainstay of treatment, which includes rehabilitation programs, bisphosphonate therapy, and orthopedic surgery [9]. However, given the rarity of the disorder, many patients have challenges accessing exercise specialists who are familiar with the treatment of OI; thus, patients often seek or receive care from specialized tertiary hospitals. Attending both regular exercise training interventions in addition to frequent therapeutic visits at tertiary care centers may present a barrier for many patients, as specialized hospitals are often located in large urban areas, which can be far from patients' homes.

Telemedicine is a method for the remote delivery of professional health services at a distance by linking clinicians and patients through information technology [10,11]. Lambert et al [12] used a telemedicine approach for the delivery of a 16-week home exercise program for pediatric acute lymphoblastic leukemia survivors. This supervised telemedicine approach was shown to be feasible, as the results demonstrated a mean adherence rate of 89% and a completion rate of 75% [12]. In contrast, Gagnon et al [13] used a follow-up telemedicine approach for the delivery of a 12-week home exercise program for youth with arthrogryposis multiplex congenita, where clinicians conducted follow-ups with study participants every 3 weeks. The results showed a 68% adherence rate and a 64% completion rate, which was sufficient for most study participants to achieve their goals [13]. As the recent literature demonstrates, the follow-up approach may be less effective as it led to a lower completion rate [12,13]. However, additional clinician time cost associated with the supervised approach may exceed the increase in benefits associated with constant supervision.

There remains a gap in the literature with respect to the comparison between supervised and follow-up telemedicine approaches and the associated cost-effectiveness of both approaches. Hence, the aim of this study is to evaluate the feasibility and cost-effectiveness of 2 telemedicine approaches (supervised vs follow-up) for the delivery of a home exercise program. The secondary aim of the study is to investigate the effectiveness of the home-based exercise program on muscle function and cardiopulmonary fitness in youth with OI type I. Given the aims of this study, it is hypothesized that participants in the supervised group will have higher adherence and completion rates compared to the follow-up group, which will be further associated with greater increases in muscle strength and cardiopulmonary fitness from the exercise intervention. However, the additional intervention delivery time required for the supervised group may make it less cost-effective compared to the follow-up approach.

Methods

Study Design

This pilot study examines the feasibility of delivering an exercise intervention to a pediatric and youth population with OI by means of telemedicine. Study participants will be randomized into 1 of 2 telemedicine approach groups: (1) the supervised group and (2) the follow-up group. Given the COVID-19 pandemic, this protocol was designed to be conducted remotely, including the assessments. Therefore, simple clinical tests rather than hospital-based evaluations, which require cutting-edge technology, were favored.

Participant Eligibility

Individuals with a diagnosis of OI type I based on clinical evaluation and genetic mutation who are followed at a tertiary pediatric orthopedic hospital, ranging in age from 12 to 16 years, will be invited to participate in this study. Inclusion criteria encompass (1) confirmed genetic mutation in *COL1A1* or *COL1A2* genes; (2) medical approbation to initiate an exercise program by the patient's treating physician; (3) the ability to communicate in either English or French; and (4) the availability of the internet, a webcam, and a microphone. The exclusion criteria include (1) fractures of long bones in the lower or upper limbs within the past 12 months, (2) fractures of the spine within the past 12 months, (3) lower and upper limb long bone or spinal surgery within the past 12 months, and (4) location outside of the province of Quebec due to professional license restrictions.

Ethical Considerations

Study approval was granted by McGill University's Faculty of Medicine and Health Sciences Institutional Review Board (A01-M01-17A). Informed consent forms will be provided for participants aged 14 years and older. Any participant younger than 14 years will be asked to sign an assent form. Additionally, for those younger than 14 years, parents or caregivers will be required to sign a parental consent form as per Quebec's provincial regulations. Individuals who meet the study inclusion criteria and agree to participate in the research study will be deidentified and assigned a study ID number. Direct subject identifiers will be stored as key codes and kept separate from the study data set. Patient's medical record number, date of birth, and corresponding study ID number will be saved in a password-protected file that will be stored on a hospital

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computer in the office of the principal investigator. The key code will be the only link that reidentifies the study participant to their health information; all other patient data will be deidentified. All study records will be retained and stored in the principal investigator's office for 7 years. Study participants will not receive compensation for their participation.

Recruitment

A total of 12 patients with OI type I will be recruited at a tertiary orthopedic hospital. Given that this study will be conducted remotely, patients who meet the study eligibility criteria will be contacted by the study coordinator over the phone. Those who are interested in participating will receive a follow-up email from the study coordinator with the appropriate consent or assent form, providing them with more information regarding their participation. Based on participant's preference, consent or assent forms will be either emailed or mailed to their place of residence. To ensure privacy, all emails from the study coordinator will be sent encrypted. Study participants will be randomized into either (1) the supervised group or (2) the follow-up group. Study personnel will produce a block randomization list using a random number generating software, which will be sent to the principal investigator. Each randomized number will be written on piece of paper and placed in an envelope. Once a study participant is enrolled, a hospital employee who is not involved in the study will select one of the envelopes and deliver it to the study personnel, who will assign the study participant to the specified group.

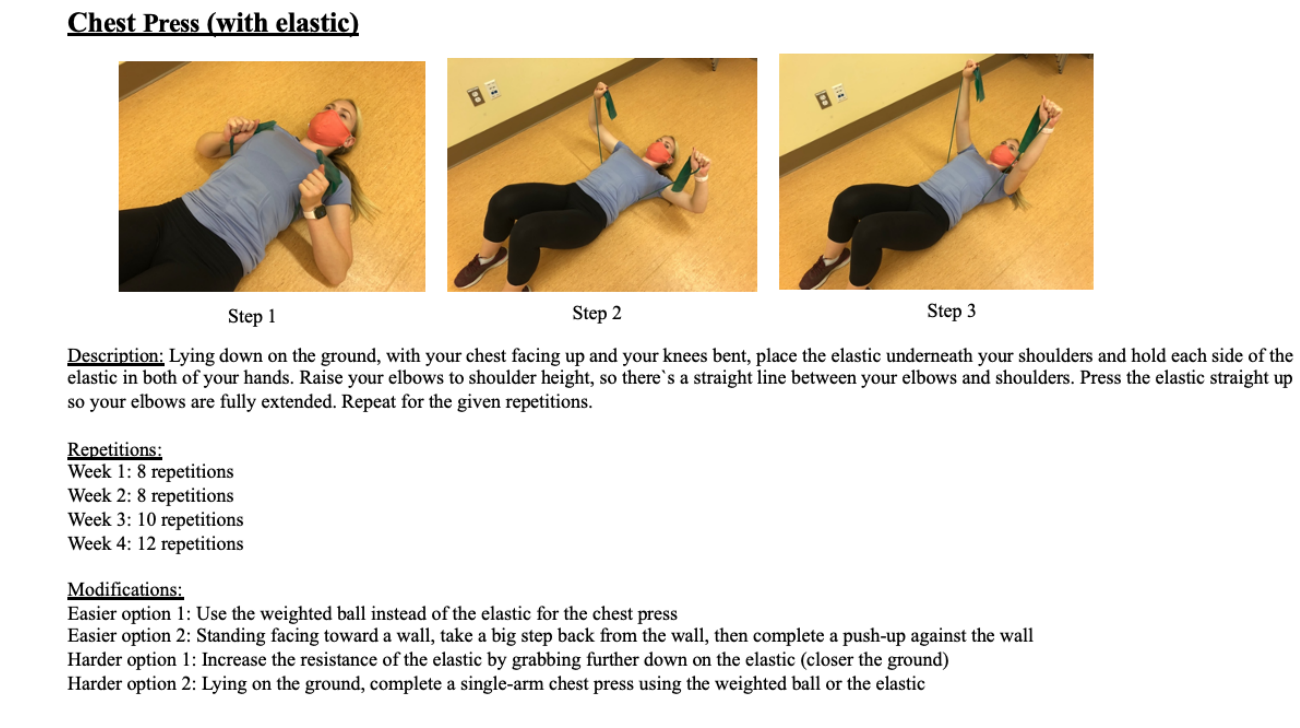
Evaluations and Intervention

Overview

The duration of the study is 16 weeks: 12 weeks for the intervention and 2 weeks at the beginning and end for evaluations. All participants will be given an exercise program to be completed at home. Both groups will use the teleconferencing application Microsoft Teams (version 1.3.00.28, Microsoft Corp). The supervised group will be monitored every session, while the follow-up group will receive feedback every 4 weeks.

Previous to the intervention, participants will be provided with initial testing and tutorials on the telemedicine application (Microsoft Teams) and the activity and heart rate monitor (Polar A370 watch; Polar Electro). Participants will be mailed the required equipment, such as the Polar A370 activity monitor (Polar watch), a 5-pound exercise ball, and a resistance band. All attempts possible have been made to ensure this study uses a minimal amount of equipment in order to reach a larger population that may have limited access to resources while also ensuring no sacrifices are made to the overall quality of the study. Both video and written instructions in English and French will be available to participants throughout the study. Instructions for the following will be included: telemedicine connections, completion of questionnaires, and Polar watch details (Bluetooth and USB connections, charging, and data transfer). Additionally, all study participants will have access to the 12-week exercise plan throughout the entire study. The exercise plan includes an illustration, video, and written description of each exercise, as well as 2 easier and 2 more difficult modifications for each movement (Figure 1). The exercise plan comprises 6 warm-up exercises, 7 to 8 exercises that will be repeated 3 times, and 5 cool-down stretches.

Figure 1. Home-exercise program instructions.



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Evaluations

Overview

To assess the impact of the 12-week exercise program, a comparison of pre- and postintervention evaluations will take place (Table 1). The pre- and postintervention evaluations will be recorded on Microsoft Teams in order to better assess and compare participants' progress before and after the intervention. Throughout the evaluations, study personnel will ask participants to have a parent or caregiver supervising nearby. During the pre- and postintervention evaluations, participants will be asked to complete the following three Patient-Reported Outcomes Measurement Information System (PROMIS) questionnaires: (1) Mobility Short Form, (2) Pain Interference Short Form, and (3) Physical Activity Short Form. Previous research has shown that PROMIS questionnaires have been successfully validated and are clinically feasible for a pediatric population [14]. These questionnaires will establish a baseline indicator for participant's pain, mobility, and physical activity levels previous to the intervention. Participant's pre- and postintervention questionnaires will be compared to determine what changes, if any, were realized by the participant.

Table 1. Pre- and postintervention evaluation tests.

Test	Assessment	Parameter
Sit-to-stand test	Cardiopulmonary fitness and lower body muscular strength	Heart rate (beats per minute) and total number of repetitions performed
Single-legged balance test	Visual and proprioceptive inputs	Time (seconds)
Push-up test	Upper body muscular endurance	Total number of repetitions performed
Sit-up test	Abdominal strength	Total number of repetitions performed
Heel-rise test	Lower body muscular endurance	Time (seconds)

Sit-to-Stand Test

The sit-to-stand test assesses cardiopulmonary fitness and lower body muscle strength [15,16]. The participant will sit down and stand up from a chair with their hands on their hips as many times as possible within 1 minute. The participant's heart rate (in beats per minute) will be taken immediately before, during, and after the test, which will be measured on the Polar A370 heart rate monitor. The number of repetitions completed will be recorded at the end of the test and expressed in absolute value [16]. Additionally, the number of completed repetitions will be expressed as the product of body weight to provide an index of total work (repetitions × weight in kg) [16,17].

Single-Legged Balance Test

Postural control will be assessed with 2 visual conditions: eyes open and eyes closed. The participant will stand on 1 leg with their arms crossed over their chest for up to 45 seconds. The participant will complete both visual conditions on each foot. Throughout the test, study personnel will ask the participant's parents or caregivers to stand close by for support in case the participant loses their balance. The duration of time the participant can maintain their balance under each condition will be collected [7].

Push-Up Test

The push-up test assesses upper-body muscular endurance of the chest, shoulders, and arms. The participant will perform as many consecutive push-ups as they can with no time limit. The test will be stopped if the participant is unable to maintain proper technique over 2 consecutive repetitions. Following the Canadian Society of Exercise Physiology, Physical Activity Training for Health (CSEP-PATH) guidelines, female participants will use their knees as their pivot point, whereas male participants will use their toes as their pivot point [7].

Sit-Up Test

The sit-up test will evaluate abdominal strength. The participant will complete as many sit-ups as they can within 1 minute. The participant will rise to a seated position from lying down with their knees bent and their arms crossed over their chest [7].

Heel-Rise Test

The heel-rise test evaluates muscular endurance of the lower limbs [18]. The participant will complete 2 trials of raising their heels 20 times in a row, as fast as possible, with their arms crossed over their chest. Participants will be given a rest period of 2 minutes between the 2 trials. Ankle plantar flexor strength is scored from 0 to 5, based on the number of heel rises the participant is able to complete [18].

Exercise Intervention

The exercise intervention will begin with 35 minutes twice a week, including a warmup and cooldown, each 5 minutes in duration. Every 4 weeks, the training will intensify in either duration of exercise or number of sessions per week, which is required to stimulate physiological adaptation and enhance improvement [7]. For the duration of the intervention, a kinesiologist (human movement specialist) will provide training and supervision to participants in the supervised group at home through live video sessions. Participants in the supervised group will be separated into 2 groups of 3 participants. For the follow-up group, the kinesiologist will meet with participants individually every 4 weeks to review their progress, preview the next month's exercise plan, and address any concerns or challenges the participants may have. The exercise program timelines for both groups are outlined below (Figures 2 and 3).

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Figure 2. Summary of the 12-week home exercise program for the supervised group. PROMIS: Patient-Reported Outcomes Measurement Information System.

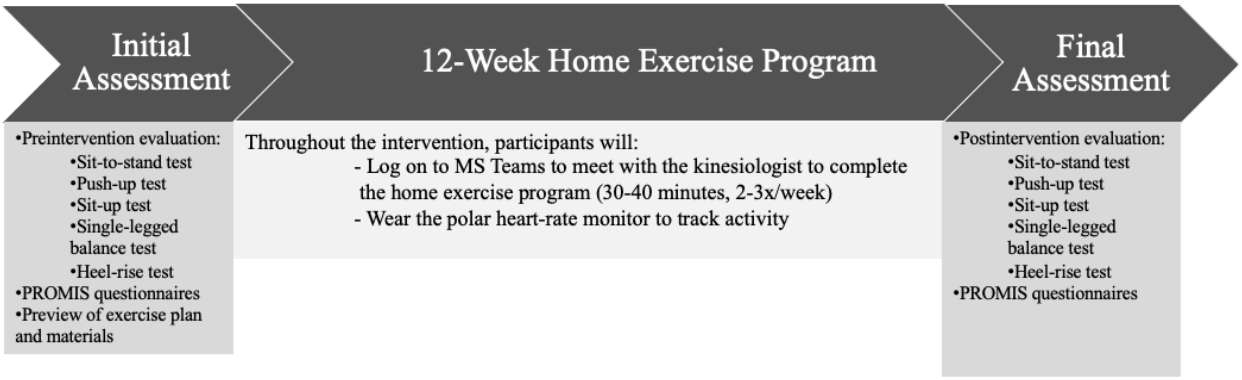
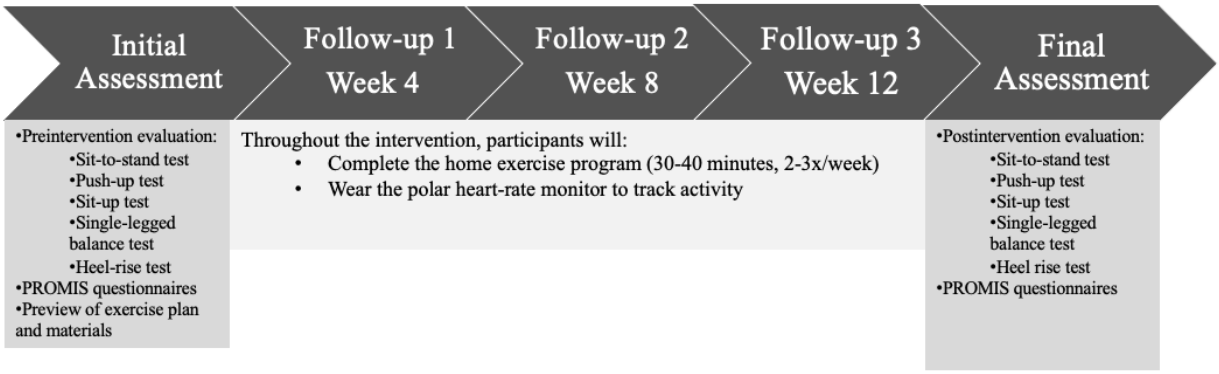


Figure 3. Summary of the 12-week home exercise program for the follow-up group.



Measurement

Feasibility

In determining the feasibility of the telemedicine approaches for the delivery of an exercise intervention, recruitment, adherence, and completion rates will be measured. Recruitment rate will be calculated by dividing the study sample by the total number of contacted potential participants [19]. Adherence rate is defined as the percentage of the exercise intervention sessions completed per participant [20]. To monitor participants' adherence to the exercise intervention, data exported from the activity monitor (Polar watch) will be recorded by study personnel on an activity log for all participants in both groups. Finally, completion rate is defined as the number of participants that completed the exercise intervention as a percentage of the overall number of participants that began the intervention [20].

Cost

To determine the cost comparison between the 2 groups, the number of hours spent by the kinesiologist delivering the exercise intervention to the supervised group will be recorded and compared to the number of hours spent with participants in the follow-up group. The kinesiologist will be paid a rate which is commensurate with their previous experience as well as a wage that aligns with the rate of pay for a kinesiologist in the market in which this study is conducted. The equipment costs (Microsoft Teams, Polar heart rate monitor, resistance band, and weighted exercise ball) will be reported and included in the calculations. When drawing cost comparisons for the 2 approaches, the supervised approach is a group approach, whereas the follow-up approach is an individualized approach. Therefore, a direct comparison between the 2 approaches presents a challenge. Nevertheless, to mitigate the difference in group and individualized approaches, the cost comparison for both the supervised and follow-up groups will be computed and presented as a cost per participant.

Cost-Effectiveness

To compare the cost-effectiveness of the 2 telemedicine approaches, a bottom-up approach will be used, a method for the assessment of each resource required to provide health care and assigning the related costs accordingly [21,22]. For both the supervised and follow-up groups, the mean performance outcome for each of the 5 preintervention evaluation tests will be computed. These means are then compared within their group (supervised or follow-up) to a mean for the same 5 postintervention evaluations, determining the mean outcome (increase or decrease) for each of the 5 tests. These mean outcomes will then be compared to the total cost of each telemedicine approach to determine the cost (on a per-unit basis) of the health outcome. Doing so allows for the assessment of not only which telemedicine approach has a higher cost overall, but most importantly, the per-unit cost of the health outcome for the supervised and follow-up groups. This provides a more accurate comparison, with respect to financial costs, of the 2 methods.

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Statistical Analysis

As this is a feasibility study, the testing procedure will be assessed rather than only focusing on the potential outcomes of the intervention. To determine the optimal clinical practice of telemedicine for an exercise intervention, recruitment, adherence, and completion rates of 2 randomized groups (supervised and follow-up approaches) will be investigated. Descriptive statistics will be presented as means and SDs. Based on previous research on home-based exercise interventions [23], the adherence rate will be assessed with a set threshold of 80%. A Wilcoxon rank sum test will be used to evaluate the adherence rate and compare both telemedicine approaches. Whereas both recruitment and completion rates will be compared using descriptive statistics and assessed with a set threshold of 50%. To measure the change in outcome parameters of participants' muscle strength and cardiopulmonary fitness, pre- and postintervention evaluation results will be assessed with a Friedman ANOVA. A Kruskal-Wallis test will be used to determine the differences in outcome parameter changes between the 2 groups (supervised and follow-up groups).

To assess the cost-effectiveness of the 2 telemedicine approaches, a cost-effectiveness plane and an incremental cost-effectiveness ratio will be computed. The incremental cost and incremental effect will be plotted on a cost-effectiveness plane, where the horizontal axis will represent the incremental cost and the vertical axis will represent the incremental effect [24,25]. The costs and clinical outcomes for both telemedicine groups will be plotted on the plane, which will visually demonstrate the additional cost per unit of health gain for each telemedicine approach. To calculate the incremental cost-effectiveness ratio, the difference in costs will be divided by the difference in mean performance outcomes between the supervised and follow-up groups.

Finally, as OI is classified as a rare disorder [1], analyses will be carried out with a significance level (α) of 0.10 [26]. Statistical analyses will be conducted using the statistical analysis software SPSS, version 25 (SPSS Inc).

Results

As the costs associated with both telemedicine approaches can be estimated, the anticipated cost comparison and breakdown of each approach are summarized below (Table 2 and Textbox 1).

Table 2. Estimated cost comparison per telemedicine approach.

Cost estimations	Supervised group, CAD $ (US $)	Follow-up group, CAD $ (US $)
Kinesiologist		
Per group	2700 (2006)	1620 (1204)
Per participant	450 (334)	270 (201)
Equipment		
Per group	1646 (1223)	1646 (1223)
Per participant	274 (204)	274 (204)
Microsoft Teams		
Per group	74 (55)	74 (55)
Per participant	12 (9)	12 (9)
Total group cost estimation	4420 (3284)	3340 (2482)
Total per participant cost estimation	736 (547)	556 (414)

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Textbox 1. Estimated cost comparison breakdown per telemedicine approach.

Kinesiologist

- Evaluations
  - 2 hours (preintervention evaluation)+2 hours (postintervention evaluation)×6 participants=24 hours
- Intervention
  - Estimated time required for the supervised approach (8 hours [month 1]+12 hours [month 2]+18 hours [month 3])×2 (number of groups)=76 hours 24 hours (evaluations)+76 hours (intervention)=100 hours Total: 100 hours (total hours)×CAD $27 (US $20) (hourly rate)=CAD $2700 (US $2006)
  - Estimated time required for the follow-up approach (2 hours [month 1]+2 hours [month 2]+2 hours [month 3])×6 (number of participants)=36 hours 24 hours (evaluations)+36 hours (intervention)=60 hours Total: 60 hours (total hours)×CAD $27 (US $20) (hourly rate)=CAD $1620 (US $1204)

Equipment

- Per participant: CAD $8.30 (US $6.17) (resistance band)+CAD $258.75 (US $192.26) (polar watch)+CAD $7.23 (US $5.37) (weighted ball)=CAD $274.28 (US $203.80)
- Per approach: CAD $274.28 (US $203.80) ×6 (number of participants)=CAD $1646 (US $1223)

Microsoft Teams

- Per approach: CAD $18.40 (US $13.67) (monthly subscription fee)×4 (number of months)=CAD $74 (US $55)

Discussion

Overview

The aim of this study is to evaluate the feasibility of 2 telemedicine approaches for the delivery of a home-based exercise program and determine the most cost-effective approach. The secondary aim of the study is to investigate the effect of a home-based exercise program on muscle function and cardiopulmonary fitness in youth with OI type I. Given the aims of the study, it is hypothesized that the supervised group will have higher adherence and completion rates compared to the follow-up group, and therefore, the physiological benefits will be greater in the supervised group than the follow-up group due to additional benefits from constant supervision. However, the follow-up group will receive individual attention in contrast to the supervised group, in which the specialist will work with groups of 3 patients. Direct comparison of patient performance in the supervised and follow-up groups will allow us to identify which telemedicine approach is more cost-effective and efficient for the delivery of an exercise program to OI pediatric patients.

Greater adherence rates can be associated with benefits such as increased positive reinforcement, improved exercise techniques, and higher self-efficacy [12]. Furthermore, direct supervision is associated with a greater overall volume of exercise achieved and potentially more efficient training, as with this approach, clinicians have the ability to adjust exercises in real time to prevent injury or pain [12]. However, in the follow-up approach, there is schedule flexibility, as participants can perform the intervention sessions when it's most convenient to them. As well, participants may develop autonomy by completing these sessions independently, which in the long term may lead to long-lasting physical activity as individuals feel more confident in their abilities to exercise on their own. Whereas participants in the supervised group rely on study personnel for instruction and motivation and may not develop the same level of autonomy as individuals in the follow-up group. Although there are several health benefits associated with direct supervision, these advantages may not outweigh the increased cost associated with this approach. Thus, the insight gained from this study into the level of participant supervision necessary for a telemedicine approach to be effective will satisfy the current gap in literature. The results pertaining to the feasibility and cost-effectiveness of both the supervised and follow-up telemedicine approaches will provide clinicians with fundamental knowledge regarding which approach is most feasible for the remote delivery of care to a pediatric and youth population.

To date, little is known about the potential effectiveness of exercise for children and adolescents with OI. Previous research has shown that children and adolescents with OI type I experience muscle weakness in addition to bone fragility [4]. Consequently, this muscle weakness may contribute to bone fragility elicited by the genetic mutation in the *COL1A1* or *COL1A2* genes [5]. Given the severe bone fragility in patients with OI and the strong positive relationship between muscle force and bone strength, therapies aiming to improve muscle force may lead to an increase in bone strength [5]. The results of this study will shed light on the physiological response to exercise in children and adolescents with OI. Takken et al [27] evaluated cardiopulmonary fitness and muscle strength in children and adolescents with OI type I and determined that cardiopulmonary exercise tolerance and muscle strength were significantly reduced in patients with OI. To the best of our knowledge, Van Brussel et al [8] is the only published study which demonstrated significant improvements in both aerobic capacity and muscle force and reduced fatigue levels in children and adolescents with OI type I and type IV following a 12-week supervised exercise program. On the contrary, from 2 different OI mice models, results from Tauer et al [28] and Gremminger et al [29] showed very mild improvements in muscle force and

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tolerance to fatigue following long-term (multiple weeks) exercise training, suggesting that in OI, there may be a decreased physiological response to exercise. Results from the proposed study will further build upon Van Brussel et al [8], providing insight into the frequency and intensity of the stimulus required to trigger physiological improvements following a 12-week exercise program for youth with OI type I.

Limitations

The limitations of this study are the technical difficulties associated with telemedicine that may arise for both study personnel and participants, such as a poor internet connection, which may lead to low-quality, incomplete, or missed training sessions for those in the supervised group. For the follow-up group, a limitation to consider is the potential that participants will not wear the heart rate monitor during the sessions, as there will not be any direct supervision to provide reminders. This would lead to missed training data, limiting the quantity of data available for comparison between the 2 groups. Although this study was designed primarily to assess the feasibility of delivering a home-based exercise intervention through telemedicine, the data collected regarding the potential change in muscle function and cardiopulmonary fitness and the small sample size of only 12 participants may limit the ability to draw any strong conclusions. As well, given the narrow age range, the results of this study are not a predictor of younger or older patient populations; therefore, a larger-scale study would be beneficial. However, given the paucity of data regarding the physiological response to exercise in youth with OI, preliminary data will provide the basis for a larger intervention study. Additionally, as OI is primarily characterized by bone fragility, given this study's remote delivery methods, it is not possible to assess the skeletal response to the 12-week exercise program. Thus, to build upon this study and given the skeletal deficits associated with OI, future research should investigate the impact of an exercise program on bone mineral content in individuals with OI. Recent research from Sinkam et al [30] demonstrated reduced mechanical tendon properties in a dominant severe OI mouse model. Given these results and the fact that tendons are typically rich in collagen type I, in addition to investigating skeletal parameters, researchers should evaluate the physiological response of tendons in OI from an exercise intervention.

The completion of a 12-week exercise program may present a challenge for some participants, especially during the final 4 weeks of the exercise intervention when the number of sessions increases to 3 times per week. To mitigate this potential concern, study participants in the supervised group will have the flexibility of completing missed training sessions on their own schedule and therefore have access to the exercise plan with detailed instructions, images, and videos of each exercise. Whereas participants in the follow-up group are given the flexibility of completing the training sessions when convenient to the individual rather than a rigid weekly schedule.

Conclusion

Telemedicine provides health care professionals with the opportunity to deliver consistent care to individuals with rare disorders, such as OI, who may have previously been unable to obtain access to such treatments. Given that the COVID-19 pandemic has imposed great challenges in the delivery of health care, this study will provide beneficial insight into the feasibility and cost-effectiveness of remote health care delivery methods. If this study is successful, guidelines and recommendations may emerge, providing individuals with OI with a higher level of targeted care geared toward increasing their quality of life. Finally, the results of this study may be advantageous for the treatment of other rare disorders, furthering the possibility to provide access to care to a far greater patient population.

Acknowledgments

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Data Availability

Data sharing does not apply to this study as this is a protocol paper; no data sets were generated or analyzed at this point.

Authors' Contributions

GP, MG, SK, FR, and LNV designed the protocol. GP, MG, and LNV established and wrote the initial protocol and obtained funding for this study. GP wrote the manuscript. MG, SK, FR, and LNV revised the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

CSEP-PATH: Canadian Society of Exercise Physiology, Physical Activity Training for Health
OI: osteogenesis imperfecta
PROMIS: Patient-Reported Outcomes Measurement Information System

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Protocol

A Text Messaging Intervention for Priming the Affective Rewards of Exercise in Adults: Protocol for a Microrandomized Trial

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Abstract

Background: Physical activity is a critical target for health interventions, but effective interventions remain elusive. A growing body of work suggests that interventions targeting affective attitudes toward physical activity may be more effective for sustaining activity long term than those that rely on cognitive constructs alone, such as goal setting and self-monitoring. Anticipated affective response in particular is a promising target for intervention.

Objective: We will evaluate the efficacy of an SMS text messaging intervention that manipulates anticipated affective response to exercise to promote physical activity. We hypothesize that reminding users of a positive postexercise affective state before their planned exercise sessions will increase their calories burned during this exercise session. We will deploy 2 forms of affective SMS text messages to explore the design space: low-reflection messages written by participants for themselves and high-reflection prompts that require users to reflect and respond. We will also explore the effect of the intervention on affective attitudes toward exercise.

Methods: A total of 120 individuals will be enrolled in a 9-week microrandomized trial testing affective messages that remind users about feeling good after exercise (40% probability), control reminders (30% probability), or no message (30% probability). Two types of affective SMS text messages will be deployed: one requiring a response and the other in a read-only format. Participants will write the read-only messages themselves to ensure that the messages accurately reflect the participants' anticipated postexercise affective state. Affective attitudes toward exercise and intrinsic motivation for exercise will be measured at the beginning and end of the study. The weighted and centered least squares method will be used to analyze the effect of delivering the intervention versus not on calories burned over 4 hours around the time of the planned activity, measured by the Apple Watch. Secondary analyses will include the effect of the intervention on step count and active minutes, as well as an investigation of the effects of the intervention on affective attitudes toward exercise and intrinsic motivation for exercise. Participants will be interviewed to gain qualitative insights into intervention impact and acceptability.

Results: Enrollment began in May 2023, with 57 participants enrolled at the end of July 2023. We anticipate enrolling 120 participants.

Conclusions: This study will provide early evidence about the effect of a repeated manipulation of anticipated affective response to exercise. The use of 2 different types of messages will yield insight into optimal design strategies for improving affective attitudes toward exercise.

Trial Registration: ClinicalTrials.gov NCT05582369; https://classic.clinicaltrials.gov/ct2/show/NCT05582369

International Registered Report Identifier (IRRID): PRR1-10.2196/46560

(JMIR Res Protoc 2023;12:e46560) doi:10.2196/46560

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KEYWORDS

mobile health; mHealth interventions; physical activity; affective attitudes; mobile phone

Introduction

Background

Exercising is crucial for maintaining and improving health and fitness and is linked to improvements in both physical and mental health [1,2]. However, only 53% of Americans [3] meet the recommended threshold of 150 active minutes a week [4], and only 23% meet guidelines for both muscle strengthening and aerobic exercise [3], creating a critical need for effective interventions to help Americans exercise. Health researchers have explored ways to leverage technologies such as smartphones and wearables to meet this need, devising interventions that use displays, messages, and other technological channels to encourage physical activity [5]. Reviews of this extensive body of work have found that mobile interventions hold promise [6,7], with a correlation between engagement with the mobile health (mHealth) intervention and efficacy [7]. However, the effects of mHealth interventions on physical activity thus far have often been relatively modest [5,8], when they are effective at all [9,10]. In addition, effects generally do not last long term [11].

Most existing mHealth interventions use a limited set of strategies to encourage physical activity [12,13]. In particular, many interventions rely on goals- and self-efficacy–related strategies, such as supporting goal setting and self-monitoring, providing feedback on performance [5,8], offering rewards [14], and providing some form of social support [8]. However, this range of approaches is relatively narrow compared with a full taxonomy of behavior change techniques [15]. One review found that only 39 out of 93 techniques were used across all top physical activity mobile apps [12]. One potential avenue for improving the efficacy of physical activity mHealth interventions is to devise interventions that expand the range of the targeted mechanisms of behavior change, for example, by developing affective interventions.

The Potential of Affective Interventions for Physical Activity

Interventions that specifically target affect (eg, by using emotion-related behavior change techniques [16]) have the potential to improve the performance of behavior change mHealth apps. Affect is a challenging target for behavior change apps, in part because the relationship between exercise and affect is not straightforward. First, researchers have described a wide variety of separate constructs related to affect [17], including how an individual feels in the moment (incidental affect), their conscious or unconscious assessments of the pleasantness of exercise (affective attitudes and affective associations, respectively), how an individual feels as a result of performing target behavior (affective response), and other aspects of emotional experience [17,18]. Different models of behavior change link these individual constructs differently to health behavior (eg, by listing affect as a component of more general attitudes that factor into behavioral intention [19] or as individual constructs that affect motivation through a variety of conscious and nonconscious processes [17,20-24]). Second, the effect of exercise on individual affective constructs itself varies greatly; for instance, the intensity of exercise has been shown to have an impact on incidental affect during exercise: gentle physical activity is associated with more positive affect, and vigorous exercise is generally associated with a negative affective shift [25].

Despite these complexities, affective constructs are a promising target for intervention. A growing body of work is demonstrating that affective constructs are meaningful predictors of exercise behavior [21]; for instance, positive nonconscious affective evaluations of exercise are associated with higher exercise volume [21] and play a role in both conscious and nonconscious processes regarding exercise behavior [26]. The effect of differences in affective attitudes to exercise can be powerful: 1 study found a 38-minute weekly increase in exercise for every increase of 1 unit on the Feeling Scale (a scale used to measure affective valence [27]) at the 6-month mark of an aerobic exercise program and a 41-minute increase at 12 months [28]. Affective assessments of exercise are even more impactful than other determinants such as self-efficacy [21,29], and 1 study found that sending affectively framed messages yielded more exercise behavior than cognitively framed messages [30].

One affective construct that holds potential for influencing physical activity is *anticipated affective response*, or how an individual expects that a target behavior will make them feel [17]. Generally, affect takes a negative shift during vigorous exercise but rebounds immediately afterward [25]. Much evidence has associated exercise with positive affective states or, at minimum, recovered affective states afterward, starting immediately after exercise and lasting for as long as a day afterward [25,31]. Although the evidence concerning the relationship of positive postexercise affect with exercise intention is somewhat mixed, and there is need for more research on affective responses to exercise to understand individual variation and guard against biased results [32,33], there is some evidence that positive postexercise affect influences affective attitudes toward exercise [34], which themselves are linked to improved exercise behavior [21,34]. Moreover, *anticipated* positive affective response has been positively associated with exercise intention [35] and behavior [17,18], and *priming* people to expect to feel good after exercise has been shown to increase positive affect over the course of exercise [36], postexercise affect [35,36], and exercise intention [35]. The manipulations thus far of anticipated positive postexercise affect have not consistently resulted in increased exercise behavior [35,36], but priming interventions that trigger increased mental elaboration have been associated with more positive postexercise affect [35], suggesting that how a priming intervention is designed may influence its effectiveness. This finding echoes the findings in human-computer interaction literature that reflection at key stages can affect physical activity behavior [37] and suggests that work is needed to understand what forms of interventions can be most effective.

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Text Messaging Physical Activity Interventions

One relatively common form of intervention is SMS text messaging. With >95% of American adults owning a mobile phone capable of sending and receiving SMS text messages [38], SMS text messaging interventions are broadly accessible and can reach more populations than interventions that rely on smartphones [39]. SMS text messages may make up stand-alone interventions or act as components in a larger intervention [39]. Reviews of SMS text messaging interventions for physical activity have encouragingly found positive effects in reducing weight and promoting physical activity [39,40], although evidence is more ambiguous for specific populations [39,41]. Importantly, the efficacy of SMS text messaging interventions rests in part on their content [30] and tailoring, as well as other characteristics [39].

Study Contribution

In this study, we will conduct a microrandomized trial [42] (trial registration: ClinicalTrials.gov NCT05582369) to evaluate the effect of a stand-alone SMS text messaging intervention designed to manipulate anticipated postexercise affect to increase exercise behavior. Microrandomization is an efficient trial design that enables causal inference with relatively small samples [42,43]. The primary objective is to determine whether manipulating postexercise affect before planned exercise increases calories burned over the 4-hour period when individuals planned to exercise. Our study extends prior research by examining the influence of anticipated postexercise affect not only on exercise intentions but also on actual exercise behavior. The study will contribute empirical findings on the effect of manipulating anticipated postexercise affect on exercise duration and intensity, actual postexercise affect, and other measures of affective attitudes toward exercise, as well as qualitative findings about how such interventions should be designed.

Methods

We will conduct a 9-week microrandomized trial of an SMS text messaging intervention to make the affective rewards of exercise salient before planned exercise, recruiting adults from the general American population who have an Apple Watch and an iPhone. The field deployment will be followed by interviews to learn about participant experiences with the intervention.

Intervention Description

The intervention consists of SMS text messages about feeling good *after* exercise, which are sent to participants *before* they exercise to manipulate anticipated postexercise affect. There are 2 types of affective intervention messages: high-reflection messages and low-reflection messages (Table 1). High-reflection prompts ask participants to think about and write down, in the reply message, topics related to feeling good after exercise. Low-reflection SMS text messages do not require a response. They contain messages that participants will write themselves at the time of study enrollment, using fill-in-the-blank templates. The research team will review these messages at the time of enrollment to ensure that they are topical. The fill-in-the-blank templates were developed through a series of pilots on Amazon's Mechanical Turk, a website that enables paid crowdworkers to complete web-based tasks. The final set consistently generated topical responses from Mechanical Turk respondents. Out of 18 messages (n=9, 50% high-reflection prompts and n=9, 50% low-reflection prompts, enough for participants to complete the study without repeated messages), participants will receive a randomized subset. Having 2 types of SMS text messages will both generate variety for participants and allow us to explore differences in participant experience resulting from different interaction mechanisms; although both are highly personalized, high-reflection messages provoke reflection and mental elaboration in the moment. In other works, mental elaboration or reflection in written form at different planning or pre-exercise stages has been associated with improved postexercise affect [35] and increased step counts [37].

Table 1. Primary intervention message types and examples.

Message type	Participant involvement	Example messages
High-reflection messages	Researcher generated; participant response via texting required	• What's your favorite thing about the way exercise makes you feel afterwards? • What positive feelings do you want to experience after exercise today? Name three. • When was the last time you did some exercise outside? Tell us what it was and one good feeling you felt afterwards.
Low-reflection messages (templates)	Participant generated based on researcher-created fill-in-the-blank templates; no response required	• Exercise can be its own reward, because _____ makes you feel _____ afterwards. (Fill in the first blank with something you enjoy about exercise. Fill in the second blank with a good feeling that you get from exercise) • Working your body makes you feel _____ after you exercise. (Fill in the blank with a good feeling you get from exercise) • Exercise makes you feel _____ afterwards, because ____. (Fill in the first blank with a good feeling that you get from exercise. Fill in the second blank with a reason exercise makes you feel good)

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Study Procedures

Microrandomized Trial

To investigate the effect of the intervention, we will conduct a 9-week microrandomized trial. Participants will complete self-report assessments at enrollment and at the study close. During the 9-week deployment, participants will be randomized twice a week, before planned exercise sessions, to receive an affective intervention message (40% probability), a simple reminder message (30% probability), or no message (30% probability). The study design and measurement points are illustrated in Figure 1 and Table 2. Instruments are listed by study phase in Textbox 1, and specific measures are detailed in Table 3.

Figure 1. Randomization procedure.

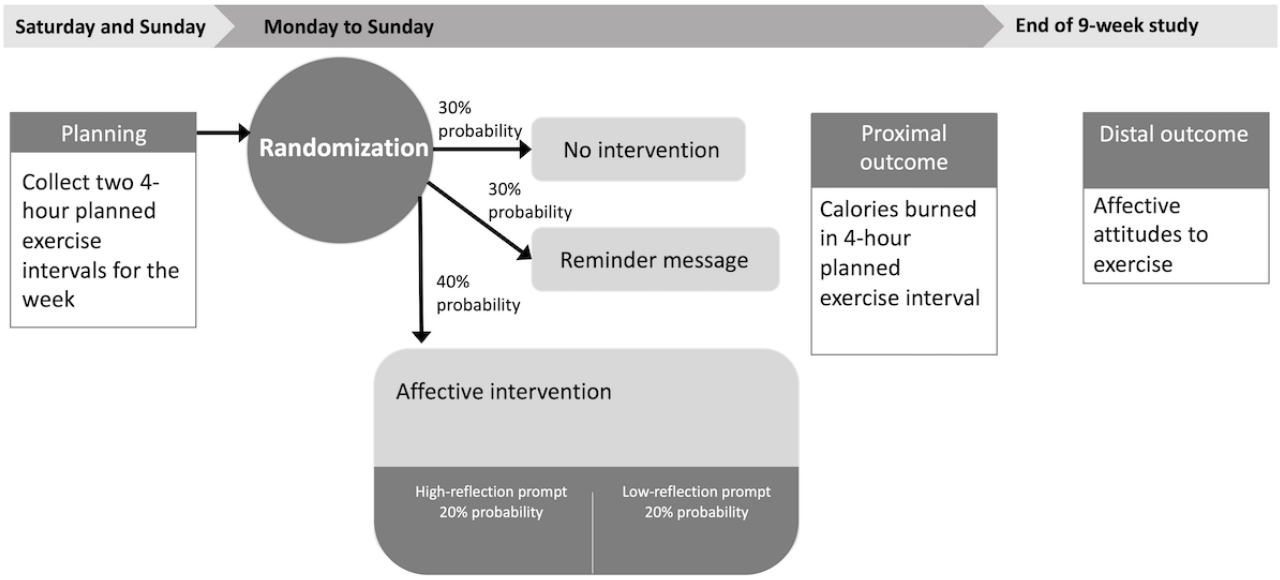


Table 2. Participant activities and measures by study phase.

Study phase	Participant activities	Measures
Enrollment	• Complete low-reflection prompt	• Affective Measures • SRQ-E[a] • PACES-8[b]
Trial period: 9 wk[c]	• Plan 2 exercise sessions/wk • Receive and read study SMS text messages • Respond to high-reflection prompts via texting • Wear Apple Watch • Report exercise afterward	• Planning Questionnaire • Exercise Self-Report Questionnaire
Study close	• Closing Questionnaire	• Affective Measures • SRQ-E • PACES-8
Optional interviews	• Answer questions about experience with the intervention	• N/A[d]

[a]SRQ-E: Exercise Self-Regulation Questionnaire.

[b]PACES-8: Physical Activity Enjoyment Scale.

[c]Affective intervention messages: 40% probability, reminder messages: 30% probability, and no message: 30% probability.

[d]N/A: not applicable.

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Textbox 1. Measures used by study phase.

Enrollment

- Consent and enrollment questionnaire (contains affective items)
- Exercise Self-Regulation Questionnaire (SRQ-E)
- Physical Activity Enjoyment Scale (PACES-8)

Microrandomized trial (9 wk)

- Planning questionnaire (a version with a question about anticipated postexercise affective state for the next exercise session included will be sent once halfway through study)
- Exercise self-report questionnaire
- Sensor data collection

Exit

- Closing questionnaire (contains affective items)
- SRQ-E
- PACES-8

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Table 3. Specific measures used in the study.

Specific measure or topic; number of times measured during the study	Questionnaires	Items; answer options
Pre- and postintervention measures		
SRQ-E[a] [44,45]; 2	Consent and enrollment, closing	• Refer to the SRQ-E [44]
PACES-8[b] [46]; 2	Consent and enrollment, closing	• Refer to the PACES-8 [46]
Baseline activity (self-report); 1	Consent and enrollment	• How many days a week do you typically exercise? By exercise, we mean moderate or intense physical activity that lasts for at least 20 minutes (e.g. a brisk 20 minute walk, yoga, running, swimming, etc.); 1 to ≥6
General affective attitude; 2	Consent and enrollment, closing	• How much do you like or dislike exercising?; 7-point scale ranging from I hate exercising to I love exercising
Affective association; 2	Consent and enrollment, closing	• When considering exercise, I feel...; 7-point scale ranging from sad to happy
Anticipated regret (adapted from the study by Conner et al [47]); 2	Consent and enrollment, closing	• If I were not to exercise this week, I would regret it; 7-point scale ranging from very unlikely to very likely
Anticipated pride (adapted from the study by Conner et al [47]); 2	Consent and enrollment, closing	• If I were to exercise this week, I would feel better; 7-point scale ranging from very unlikely to very likely
General during-exercise affect; 2	Consent and enrollment, closing	• While you are doing exercise, how do you typically feel?; free text • Rate how good or bad you typically feel while you are doing exercise; Feeling Scale [27]
General postexercise affect; 2	Consent and enrollment, closing	• After you finish exercising, how do you typically feel?; free text • Rate how good or bad you typically feel after exercising; Feeling Scale [27]
Planned exercise information		
Planned exercise activity; 9	Planning Questionnaire	• What exercise do you plan to do on [day]? Please tell us the activity you plan to do; free text • Please tell us roughly how long you plan to do your activity on [day]; free text
Planned exercise intensity; 9	Planning Questionnaire	Please rate what you expect your overall level of exertion during your planned activity will be. This feeling should reflect how heavy and strenuous you expect the exercise to feel, combining all sensations and feelings of physical stress, effort, and fatigue. Focus on what you expect your total feeling of exertion will be, not any one specific factor?; 10-point scale ranging from 1=*rest* (no exertion at all) to 10=*maximal effort* (I was completely exhausted and it felt almost impossible to keep going)
Exercise self-report information (after every planned exercise session)		
Exercise self-report; 18	Exercise self-report questionnaire	• Did you do any exercise today?; Yes, No • (conditional) Was the exercise you did today the same as what you originally planned, or different?; Exactly what I had planned; Different from what I had planned; I'm not sure, I can't remember what I planned • (conditional) What exercise did you do today?; free text • (conditional) Please let us know why exercise didn't fit into your day today • (conditional) How did the exercise you did differ from what you had planned?; Pushed myself harder; Scaled back my activity; Did the activity in a different place or with different company; Did a different activity; Did the activity at a very different time than I had planned; Other difference

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Specific measure or topic; number of times measured during the study	Questionnaires	Items; answer options
Exercise exertion; 18	Exercise self-report questionnaire	• Thinking back on your physical activity session today, rate your overall level of exertion during it. This feeling should reflect how heavy and strenuous the exercise felt to you, combining all sensations and feelings of physical stress, effort, and fatigue. Focus on your total feeling of exertion, not any one specific factor; 10-point scale ranging from 1=rest (no exertion at all) to 10=maximal effort (I was completely exhausted and it felt almost impossible to keep going)
Affect during exercise (recollected); 18	Exercise self-report questionnaire	• While you were doing your exercise session today, how did you feel overall?; free text • Rate how good or bad you felt overall while you were doing your exercise; Feeling Scale [27]
Postexercise affect (recollected); 18	Exercise self-report questionnaire	• After you did your exercise session today, how did you feel overall?; free text • Rate how good or bad you felt after your exercise session; Feeling Scale [27]
Anticipated postexercise affect (next session); 19	Exercise self-report questionnaire and planning questionnaire (with baseline questions)	• How do you expect to feel after your next exercise session? Select the number that best represents how good or bad you expect to feel; Feeling Scale [27]
Unplanned exercise; 18	Exercise self-report questionnaire	• Have you done any unplanned exercise since your last planned exercise session (not today's)?; Yes, No, This was my first planned exercise session for this study • (conditional) What was the unplanned exercise you did?; free text

[a]SRQ-E: Exercise Self-Regulation Questionnaire.

[b]PACES-8: Physical Activity Enjoyment Scale.

Study Procedures Overview

At enrollment, we will ask participants to write their low-reflection prompts and to self-report demographic and baseline activity–level information. In addition, we will assess participants' anticipated affect for exercise, their affective association with exercise, and their overall enjoyment of exercise. On top of these measures, we will ask participants to complete the Exercise Self-Regulation Questionnaire [44,45] to measure their intrinsic motivation for exercise and the Physical Activity Enjoyment Scale (PACES-8) [46] to measure their enjoyment of exercise.

For the next 9 weeks, at the start of each week, participants will be asked to list 2 time intervals during which they plan to exercise in the coming week. At the start of each planned exercise time interval, participants will be randomized to receive an affective SMS text message (intervention), a control reminder message, or no message, and at the end of the day, they will be asked to report their actual exercise details (refer to *Exercise Data: Sensor and Self-Report Data* section). Thus, each participant will be randomized to receive an intervention, a control reminder message, or no message 2 times each week.

At the close of the 9-week period, participants will be sent a closing questionnaire that contains questions about their experience with the intervention, all items from the Exercise Self-Regulation Questionnaire and the PACES-8, and the same questions about affect related to exercise that were assessed at baseline.

After the 9-week study period, a subset of participants will be interviewed to gather in-depth data about their experience with the intervention and their perceptions of its impact on their attitudes toward exercise and on exercise behavior. We plan to stratify our interview sample based on participant characteristics such as exercise frequency and participant responses to the closing questionnaire, low-reflection sentences, and responses to high-reflection prompts.

Intervention Delivery

Microrandomized trials are designed around *decision points*—times when it may be appropriate and helpful to provide an intervention [42]. As the intervention in this study operates by increasing the salience of postexercise affective rewards, the intervention is likely to be most helpful when participants have an opportunity to exercise but have not yet exercised. To determine these times, participants will complete a planning questionnaire each weekend where they will specify 2 time intervals during which they intend to exercise in the coming week. Participants are asked to give a day and a 4-hour interval (eg, Thursday, 4-8 PM) during which they intend to exercise. We define an intervention decision point as the start of this interval (eg, Thursday, 4 PM). The 4-hour range was selected to be wide enough to give users some flexibility to accommodate small fluctuations in their schedules but narrow enough to still offer a targeted interval to measure outcomes without the addition of too many sources of noise. The planning questionnaire will be sent on Saturdays and again on Sundays and Monday evenings if not yet completed for the week. Participants who do not complete the questionnaire by the end

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of the day on Monday will not be sent any additional messages for the week.

The planning questionnaire will ask participants both when they intend to exercise and what exercise they plan to do. Participants can do any kind of exercise, as long as their session is at least 20 minutes long and is of moderate or greater intensity. Note that participants may exercise more frequently than twice a week, but only 2 of these sessions—those scheduled through the planning questionnaire—will determine the intervention decision points. Additional, unplanned exercise sessions will be assessed through sensor data and the exercise self-report questionnaire (refer to the *Exercise Data: Sensor and Self-Report Data* section).

The planning questionnaire will be delivered on a weekly, rather than daily, basis to minimize user burden and lower the risk of participant dropout. As the questionnaire requires participants to plan ahead, there is some chance that participants' plans will change and that they will not exercise at their planned times. If participants change their plans for exercise after sending the planning questionnaire, the intervention may not reach them when they are truly receptive to it. However, the microrandomization of intervention delivery should balance this inaccuracy in delivery across conditions so that the observed effect of the intervention should not be biased in either direction, although it may be attenuated. In addition, the exercise self-report questionnaire, as well as Apple Watch data, will help in detecting whether participants actually exercised during their planned times (refer to *Exercise Data: Sensor and Self-Report Data* section).

Reminder Message

The planning questionnaire enables the delivery of the affective intervention messages, but, as a form of implementation intention, it could influence behavior in its own right [48,49]. Specifically, the affective messages may work as reminders of previously made plans, which have been shown to improve the effectiveness of planning [50,51]. We control for these effects by including a reminder message whose delivery will be randomized along with that of the affective intervention messages. The reminder message simply reminds participants to fill out the exercise day questionnaire. As in the case of the affective intervention messages, reminder messages will be sent at the start of the planned exercise interval.

Randomization During the 9-Week Trial

Randomization Overview

For each planned exercise interval, participants will be randomly assigned to receive an affective intervention message (40% probability), a reminder message (30% probability), or no message (30% probability; Figure 1). If participants are randomized to receive an affective intervention message, they will be further randomly assigned to receive either a high-reflection message or a low-reflection message with equal probability (ie, 20% each). For each participant, as there will be 9 high-reflection messages and 9 low-reflection messages to choose from, the message to be sent will be chosen from the appropriate set randomly without replacement so that participants will not receive the same message twice.

Randomization Procedure

As the number of decision points is known in advance (2 sessions/wk, or 18 decision points), we can construct randomized treatment sequences of length 18 for each of the 120 participants. These will be consistent with the 18 decision points per person. Before the start of the project, we created 120 randomization schedules to account for the required sample size, allowing for dropouts. Each schedule consists of a sequence of 18 numbers. To ensure that we achieved the right condition balance across participants, we drew these numbers randomly from a uniform number distribution, then placed them randomly into a hundred 18-number sequences. From the numbers that were randomly selected, we assigned the bottom 30% to the control condition, the next 30% to the reminder condition, and the top 40% to the high- or low-reflection affective message conditions. The result is a randomized sequence of condition assignments for the duration of the study, independent of the time and date of planned exercise sessions (refer to Multimedia Appendix 1 for an example randomization schedule). Across all randomization schedules but not within schedules, the conditions are balanced such that 30% of the planned exercise sessions are assigned to control, 30% to the reminder message condition, and 40% to an affective message condition. We then carried out a second round of randomization on the affective message condition sessions to determine which messages would be sent (eg, high-reflection message 1 and low-reflection message 2). As participants will create a set number of low-reflection messages based on fill-in-the-blank templates, we can randomize message selection before message creation. When a participant enrolls, they will be assigned to a randomization schedule. The actual time and date at which each message is sent will be based on the participants' responses to the planning questionnaires each week.

Text Message Delivery

SMS text messages will be delivered through an SMS text messaging service that enables scheduled sending. Low-reflection prompts, high-reflection prompts, reminder messages, and reminders to wear the Apple Watch and fill out the planning questionnaire will not be personalized with participants' names or other identifiers (however, for low-reflection prompts, each participant will receive only the messages that they themselves wrote). SMS text messages will be sent from the same mobile phone number each time so that participants recognize it as coming from the study team. The participants' responses to high-reflection prompts will be received by the same SMS text messaging service and associated with their mobile phone number so that their responses can be tracked and analyzed.

Measures

Study data will include activity data as measured by Apple Watch (primary outcome) and self-report, questionnaires about affect and exercise, and video chat or telephone interview data about participant experience with the intervention. Questionnaires will be hosted on the Qualtrics platform and sent to participants via SMS text message.

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Primary Outcome

The primary outcome for the microrandomized trial will be *calories burned*, as assessed by the Apple Watch, over the planned 4-hour exercise periods scheduled through the planning questionnaire. Apple Watch data will be collected through the MyDataHelps platform (CareEvolution, LLC), a secure platform for the collection of sensor (Apple Watch and Fitbit) and self-report data in health research. Participants will install the MyDataHelps app on their mobile phone. As calories burned can be reported by Apple Watch in discontinuous intervals, we will sum the calories burned over the 4-hour planned exercise period. When the intervals of reported calorie data cross the 4-hour planned exercise period boundary, we will assume that the calories burned are equally distributed across the reported interval and include only these calories in the 4-hour planned exercise period. Although Apple Watch's calories burned measurement has moderate rather than high correlation with other energy expenditure measures [52], calories burned were selected as the primary outcome measure because it enables us to assess participants' engagement in a greater variety of exercises compared with a more restrictive measure, such as steps. In this study, participants are instructed to perform any moderate to vigorous exercise they choose and to tell us what they plan to do in the planning questionnaire. Other data (described in the next subsection) will provide secondary records of the exercise performed for secondary analyses.

Exercise Data: Sensor and Self-Report Data

In addition to exercise being assessed via calories burned, it will also be assessed through several additional Apple Watch metrics, including active minutes, steps, and standing time. These metrics will also be collected through the MyDataHelps mobile app. As with calories burned, we will analyze step data and active minutes in the 4-hour planned exercise period.

On the days that participants plan to exercise, they will be asked to complete an exercise self-report questionnaire in the evening asking whether they exercised that day and, if so, how their activity compared with what they had planned; for example, was it shorter or longer in duration than they had planned? Participants will further be asked about their perceived exertion and affective state during and after exercise and, as a manipulation check, whether they received and read an SMS text message from the study team before exercise. If participants say they did not exercise, they will be asked why.

Affect Measures

The exercise self-report questionnaire will ask participants about their affective states during and after exercise, as well as expected postexercise affect for the next exercise session. In addition, at 3 points in the study (baseline, the 3-week check-in, and the end of the study), participants will be asked questions about their affective attitudes toward, during, and after exercise (Table 3).

Participant Experience

A closing survey will ask participants about their subjective perceptions of different aspects of the intervention. In addition, interviews will allow us to explore participant experience with the intervention and their perceptions of its impact on their behavior and attitudes.

Participants

US residents with an iPhone and Apple Watch who are aged at least 18 years and have not been medically advised against physical activity are eligible to participate. Participants will be recruited through web-based channels such as email lists and relevant internet forums. They will be informed about the study and will give consent through a web-based questionnaire.

Sample Size and Power

Sample size was calculated according to the methods published by Liao et al [43]. A microrandomized trial is an efficient trial design that enables causal inference with relatively small samples [42,43]. For this study, proximal treatment effect was estimated at 0.2, significance set at .05, and power set to 0.9. To power our study for the primary analysis (refer to the next subsection)—a contrast between no message and affective messages—availability was set to 0.7 to exclude reminder messages that are randomized at 30% probability. Given these assumptions, 89 participants are needed. We intend to recruit up to 120, allowing for dropouts.

Data Analyses

Primary Analysis

Our primary interest is the average effect of the affective message intervention across time on calories burned during the planned exercise periods compared with no message being sent. To assess this effect, we will use the centered and weighted least squares method, a standard approach for analyzing microrandomized trial data that allows for robust causal inferences about treatment effects [53] and accounts for correlations in longitudinal data by nesting outcomes within participants. The covariates in our analysis will include time in study, the prior week's proximal outcome, self-reported baseline activity levels, age, and gender.

Secondary and Exploratory Analyses

Additional analyses of the microrandomized trial data will investigate the time trend of the effect of affective messages (ie, the change in the effect of the affective messages over the duration of the study), the contrast between affective messages and reminder messages, and separate over-time and time-trend effects of low-reflection and high-reflection messages. In addition, we will investigate the intervention's effect on other outcomes, such as step count and active minutes for the 4-hour planned exercise interval, as collected from the participants' Apple Watches. These analyses, as in the case of the primary analysis, will all be conducted using the centered and weighted least squares method.

In addition to the microrandomized trial analyses, we will conduct a number of exploratory analyses of the affective measure data. We will examine potential changes in the anticipated postexercise affect by investigating changes in pre- and postintervention ratings on the Feeling Scale [27]. Exploratory analyses will include an investigation of changes in other affective measures used and the role of potential moderating factors such as baseline activity level, planned

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exercise intensity, and exercise intensity on postexercise affective state predictions. In addition to these quantitative analyses, we will thematically analyze interview data in accordance with the principles described in the study by Braun and Clarke [54]. After transcribing the interviews, we will use an iterative inductive approach to explore themes in the data around participants' underlying needs and the impact the intervention had on their lives. We will triangulate interview responses with observed participant behavior and responses to the closing questionnaire to get a full picture of participant experience with the intervention and insight into appropriate outcome metrics for future iterations.

Missingness

Missing data are likely to occur because participants forget to wear their watch or respond to questionnaires. We will send weekly reminders to participants to wear their Apple Watches. For missing wearable and questionnaire data, we will explore whether any observed variables can be used to explain missingness and include these variables in analyses.

Ethics Approval

This study has been approved by the University of Michigan institutional review board (HUM#00190301).

Informed Consent and Participation

Informed consent will be obtained through a web-based questionnaire; after filling out an eligibility screener survey, eligible participants will be directed to a separate informed consent questionnaire containing information about the study and contact information for the research team. Although some participant identifiers such as name and mobile phone number must be collected to deliver the intervention and participant incentives, these data will be stored on password-protected servers, and data will be deidentified for analysis. All identifying data will be destroyed by the end of December 2024. Participants will be compensated for their participation with Amazon gift cards. Participants will be given US $10 Amazon gift cards on enrollment and another US $20 Amazon gift card on completion of the study. Participants will additionally be entered into raffles for additional gift cards with every study questionnaire they complete, and they will be given an additional US $10 Amazon gift card if they are interviewed, up to a maximum of US $95 in Amazon gift cards.

Results

Enrollment began in May 2023, with 57 enrolled by the end of July 2023. The results will be published after data collection is complete.

Discussion

Implications and Limitations

Researchers have increasingly highlighted the potential of affective and nonconscious motivators to influence exercise behavior [21,55]. Past work has demonstrated the ability of the manipulations of expected postexercise affect to have an impact on during-exercise affect, postexercise affect, and behavioral intention to exercise [35,36]. Our study investigates the impact of repeating that manipulation in a format that is at once highly personalized and highly scalable and that can be carried forward through time at key decision points for exercise behavior. In addition, we extend prior work by examining the impact of the manipulations of expectations of postexercise affect not only on behavioral intentions but also on actual exercise behavior. The findings will elucidate the influence of this intervention over time on both immediate exercise behavior and overall affective attitudes toward exercise. Given recent findings that affective attitudes toward exercise on a particular day have an impact on exercise behavior over and above affective attitudes toward exercise in general [56], there is high potential for an mHealth intervention manipulating affective attitudes in the moment to influence physical activity. As our study design includes qualitative data, we will also gain insight into participants' *experience* with the intervention, yielding findings that can shape the design of other systems and uncover unforeseen complications.

Although researchers are increasingly exploring interventions that target affective judgments about physical activity, the emotional consequences of physical activity remain an underused target [57]. Studies that have used SMS text messages that are either ambiguously [58] or explicitly [59] about postbehavior affective states have found affective messaging to be a critical part of effective interventions for such behaviors as physical activity [58] and even water consumption [59]. However, more work is needed to demonstrate the efficacy of interventions in changing both affective attitudes and resultant behavior. Although this study does use some planning- and self-monitoring–related techniques (planning exercise and self-reporting on the consequences, in addition to requiring possession and use of an Apple Watch that also provides feedback on physical activity), our focus is on the manipulation of salience and beliefs about emotional consequences [15]. Our study represents an early test of an intervention targeting these constructs, and our analyses will investigate the impact of messaging that manipulates affective constructs over and above any potential influences of planning and self-monitoring contained in the study.

The findings from this study will shed more light on which directions are profitable to explore within the complex landscape of affective interventions; for instance, if our intervention is effective at changing both attitudes and behavior, further research will be needed to explore the longevity of this effect. By contrast, an observed movement in only 1 of these domains could point toward the need to explore different design techniques to influence anticipated postexercise affect (eg, by investigating whether timing, modality, or accompaniment with other affective interventions helps us to leverage this intervention target to effect behavior change).

Our study has several limitations. A key limitation is that the intervention decision points rely on participants' understanding on the weekend of when they would be able to exercise in the coming week. Given the messiness of life, participants' plans or ability to execute these plans may change. Although this dependence on predicted ability to be active is suboptimal, microrandomization should help to ensure that the circumstances

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that may derail exercise plans will be balanced across the experimental conditions and thus will not bias the estimates of treatment effects. Furthermore, any intervention that is likely to work in the real world will need to be able to deal with a noisy, hard-to-predict environment of people's day-to-day lives. As such, any potential effects that we see in this study may be conservative estimates of the potential of this type of intervention because future work could substantially improve the timing with which such prompts are delivered.

A second limitation of our study is power with relation to the *form* of affective messaging. Although we have 2 types of affective messages, we will lack power to rigorously assess differences in the effect of each type. However, interviews will help to bridge this gap because the participants' testimony will give us a rich depiction of their experience with each type of affective message.

Our findings will also be constrained by the limitations of the Apple Watch. Our primary outcome is calories burned; as noted previously, we have selected this measure because the calories burned metric captures a greater variety of exercise types than step count, but our findings will be limited by the ability of the Apple Watch to measure calories burned with precision and accuracy [52]. In addition, not even calories burned can capture every activity. Early Apple Watch models are not waterproof, and even later models that can capture most aquatic activities cannot be used for activities such as diving. These limitations mean that some activities cannot be captured by Apple Watch sensors. However, participants will be able to report them in a questionnaire, enabling us to identify when the sensor data are not reliable.

Conclusions

Despite the difficulty of promoting physical activity, researchers continue to try new tactics because physical activity is so critical for public health. This study will yield initial evidence about the potential of affective interventions based on anticipated affect to support exercise behavior and will do so based on an intervention that is lightweight, scalable, and can be highly personalized to each individual.

Acknowledgments

The authors thank Dr Alexander Muratov for his help in creating the randomization schedules.

Data Availability

The data sets generated during this study will be available from openICPSR, a service of the Inter-university Consortium for Political and Social Research, after they have been deidentified.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Example randomization schedule.
[XLSX File (Microsoft Excel File), 18 KB - resprot_v12i1e46560_app1.xlsx]

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Abbreviations

mHealth: mobile health
PACES-8: Physical Activity Enjoyment Scale

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Protocol

A Tailored mHealth Intervention for Improving Antenatal Care Seeking and Health Behavioral Determinants During Pregnancy Among Adolescent Girls and Young Women in South Africa: Development and Protocol for a Pilot Randomized Controlled Trial

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Abstract

Background: South Africa, a middle-income country, has an adolescent fertility rate far higher than that of high-income countries. Adolescent girls and young women have an increased risk of pregnancy-related complications and lower antenatal appointment attendance rates than older adult pregnant women. Mobile health (mHealth) interventions to improve health behaviors among pregnant adolescent girls and young women in low- and middle-income countries are scarce.

Objective: This paper describes the development and components of an mHealth intervention to improve antenatal appointment attendance and health behavioral determinants among pregnant adolescent girls and young women in South Africa and details the protocol for a pilot randomized controlled trial that evaluated the intervention's efficacy and user acceptability.

Methods: The intervention, Teen MomConnect, sent tailored motivational behavior change and behavioral reinforcement SMS text messages to participants about antenatal appointment keeping and pregnancy behaviors. The delivery methodology of the intervention was adapted from MomConnect, an mHealth education program for pregnant women in South Africa that has nationwide coverage. In addition, participants received a face-to-face motivational interviewing session delivered by a trained research assistant. Pregnant adolescent girls and young women aged 13 to 20 years were recruited from health facilities and community networks. Participants were randomized into the control group that received the standard MomConnect health SMS text messages or the experimental group that received the Teen MomConnect intervention. Participants completed a baseline questionnaire upon enrollment in the study and a follow-up questionnaire after the end of their pregnancy. The questionnaires assessed demographic characteristics, pregnancy behaviors, and the psychosocial determinants of antenatal appointment attendance (knowledge, attitudes, social support, risk perceptions, self-efficacy, intention, and action planning). Feasibility was assessed using descriptive analyses of acceptability, study implementation processes, and perceived satisfaction with the intervention. The number of appointments attended was obtained from the participants' clinic records. Appointment attendance was compared between the control and experimental groups, as were awareness of HIV status and the psychosocial determinants of antenatal appointment attendance.

Results: Participant recruitment was conducted from May 2018 to December 2018, and the questionnaire-based data collection was completed by December 2019. Overall, 412 participants were enrolled.

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Conclusions: This paper describes the Teen MomConnect intervention to improve antenatal appointment attendance and pregnancy health behaviors among adolescent girls and young women. The results on the intervention's preliminary efficacy and user acceptability will inform policy makers and health program officers on how tailored, age-appropriate, and motivational health behavior messages can be delivered via mobile phone to pregnant adolescent girls and young women.

Trial Registration: Pan African Clinical Trial Registry (PACTR) PACTR201912734889796; https://pactr.samrc.ac.za/TrialDisplay.aspx?TrialID=9565

International Registered Report Identifier (IRRID): DERR1-10.2196/43654

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KEYWORDS

antenatal care; adolescent girls and young women; AGYW; adolescent pregnancy; mobile health; mHealth; tailoring; motivational interviewing; South Africa; mobile phone

Introduction

Background

South Africa's adolescent fertility rate of 68 births per 1000 girls aged 15 to 19 years is more than quadruple that of high-income countries [1]. Adolescent girls and young women have an increased risk of pregnancy-related complications, including low birth weight, eclampsia, and preterm birth, compared with older women [2-6]. Furthermore, maternal and infant mortality rates are higher in adolescents than in adult women [5,7]. Pregnant adolescents also face problems such as iron deficiency, inadequate nutrition, and higher engagement in tobacco smoking and alcohol and substance use [4] and have more psychological and social needs than older women [4,8].

The adolescent Institutional Maternal Mortality Ratio in South Africa was 76.9 deaths per 100,000 live births in 2014 to 2016 [9]. The Confidential Enquiries into Maternal Deaths found that almost three-quarters of the deaths among adolescent mothers were from factors such as non–pregnancy-related infections (including HIV or AIDS-related infections, tuberculosis, or pneumonia), hypertension, obstetric hemorrhage, and medical and surgical disorders [9].

Maternal health and pregnancy outcomes among adolescent girls and young women can be improved through appropriate antenatal care (ANC) and practicing healthy behaviors during pregnancy. Behaviors that are recommended for a healthy pregnancy include following a healthy diet; practicing physical activity; taking nutrient and folate supplements; practicing oral hygiene; managing preexisting conditions; and avoiding the use of tobacco, alcohol, and illicit substances [10]. Notably, pregnant adolescents often have poor diet quality, inadequate nutritional knowledge [11], and less knowledge of danger signs [12]. These adolescents typically have less knowledge of what to expect and how to appropriately care for themselves during pregnancy [13,14]. Furthermore, environments of lower socioeconomic status hamper the ability to practice healthy pregnancy behaviors. This is relevant as teenage pregnancies in South Africa are more prevalent in areas of lower socioeconomic status [15].

Early initiation and routine attendance to ANC allows for the prevention, early detection, and management of risk factors and pregnancy-related complications and for the provision of pregnancy-related health promotion [16]. In South Africa, where basic ANC is available at public health facilities at no cost, 77% of pregnant adolescents attend the recommended requisite of at least 4 ANC visits [17]. Studies indicate lower ANC attendance and late ANC booking among adolescents and very young women in South Africa than older women [18,19].

Mobile health (mHealth) interventions are increasingly being used to provide educational, motivational, and behavioral content for a range of issues such as smoking cessation, weight loss, and mental and sexual health [20-23]. SMS text messaging has been previously shown to positively influence the uptake of antenatal visits among pregnant women in low- and middle-income countries (LMICs) [24]. SMS text messaging has the ability to reach large populations with no costs incurred by the recipients. The high mobile phone access in South Africa, a middle-income country, provides opportunities for mHealth behavior change programs to reach large numbers of people and improve health behaviors. Currently, 92% of South Africans own a mobile phone [25], with youth being significant contributors to the mobile phone market. As early as 2012, approximately 70% of high school learners reported having their own mobile phone [26].

The MomConnect program [27], launched by the South African National Department of Health in 2014, is one of the largest mHealth programs worldwide. MomConnect uses mobile phones to register pregnancies in a central database and sends SMS text messages containing maternal health information to pregnant women in the language of their choice throughout the course of their pregnancy until 1 year after giving birth. MomConnect messages are based on maternal health SMS text messages from the Mobile Alliance for Maternal Action in South Africa [28]. Pregnant women are routinely assisted in registering on MomConnect when they attend ANC at health facilities. Between August 2014 and April 2017, over 1.1 million women were successfully registered to MomConnect, corresponding to approximately half of the women attending ANC and 60% of those attending ANC that own a mobile phone [29]. Nearly one-third of registrations occur by the end of the first trimester of pregnancy [29].

Given that the MomConnect messages were designed more for adult pregnant women, we posited that it might be beneficial to adapt the message content for adolescent girls and young women. In light of this, a review of MomConnect registrations found that the odds of opting out of MomConnect were higher

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for younger women, that is, those aged <25 years [29], thus suggesting a need for retaining younger audiences. In addition, MomConnect sends a fixed set of messages based on the stage of pregnancy. A growing number of mHealth interventions provide tailored messages whereby participants receive content that is matched to a sociodemographic, motivational, behavioral, or personality attribute [30,31]. Therefore, messages that are cognitively, language, age, and context appropriate; motivational in nature; and tailored to the behaviors, attitudes, and health status of pregnant adolescent girls and young women may have the potential to increase uptake of content and induce greater behavior change.

Objectives

There are currently few mHealth studies on interventions that are specifically targeted at improving health behaviors among pregnant adolescent girls and young women in LMICs [32]. Their behavioral, cognitive, and motivational needs and position in society are distinctly different from those of adult women. Therefore, this study sought to develop a mobile-based intervention targeting pregnant adolescent girls and young women. It adapts the MomConnect methodology. It includes motivational behavior change and behavioral reinforcement messages aimed at improving ANC attendance and its psychosocial determinants during pregnancy, as well as tailored message feedback on behavioral and psychosocial determinants. The intervention, titled Teen MomConnect, would be embedded in an SMS text messaging–based system similar to that of MomConnect. An additional component of the Teen MomConnect intervention is a motivational interviewing (MI) face-to-face counseling session delivered by research assistants. This paper describes the development and components of the intervention as well as the protocol for the pilot 2-arm randomized controlled trial (RCT) to evaluate the intervention's preliminary efficacy and user acceptability.

Methods

Development Process

Messaging Content

Formative qualitative research with pregnant adolescents, a review of maternal health education resources, and a review of the existing MomConnect messages provided extensive data that were collectively used to develop and refine the Teen MomConnect intervention messages.

First, key behavioral domains were identified to be included. A multidisciplinary team of researchers in behavioral science, health communication, maternal health, and mHealth and individuals from the technical implementing partner of the MomConnect program reviewed the messages in the existing MomConnect program to categorize them into behavioral domains. To further refine the list of behaviors that place young mothers at risk to be relevant to South African pregnant adolescents, existing maternal health education materials such as the Western Cape Department of Health "Caring for mothers, Caring for you" maternity health education booklet, maternity care guidelines in South Africa, and a review of the literature were used. The data gathered from this work resulted in the selection of 13 behavioral domains for the intervention messages, which are listed in Textbox 1. Health communication specialists from the research team drafted a few examples of intervention messages from each of these behavioral domains and their determinants that were to be pretested.

Textbox 1. List of behavioral domains for the intervention messages.

- Alcohol
- Appointment keeping
- Attitude toward pregnancy
- Clinic attendance
- General health information
- Illegal drugs
- Nutrition
- Self-care and hygiene
- Smoking
- Social stigma
- Social support
- Sexually transmitted diseases
- Tuberculosis

The formative qualitative research with pregnant adolescent girls and young women comprised 4 individual in-depth interviews and 4 mini focus group discussions of between 2 and 5 participants among a sample of 19 pregnant adolescent girls and young women aged 13 to 19 years who attended ANC services in Cape Town, South Africa [33]. The interviews and focus groups investigated experiences with ANC attendance, perceptions of MomConnect, determinants of appointment attendance, and the environmental and social context of participants. In addition, participants were asked to provide feedback on the initial Teen MomConnect sample messages that were drafted by the research team. The findings from the

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qualitative research informed the fine-tuning of the messages and the development of new messages. The following paragraphs provide a detailed description of the data gathered and how they were used for the creation of the messages.

Feedback from the participants on the MomConnect program in general was that MomConnect provided valuable information about the baby's development at various stages of pregnancy. The participants valued that the messages communicated directives to attend appointments, practice healthy behaviors, and prepare for labor admission. They found that being able to read the SMS text messages and make sense of them in their own time was more helpful than being told the information all at once at the health facility. Some participants reported that several MomConnect messages contained information that was not applicable to everyone or that they already knew. They expressed the need for language that is simple, concise, and appropriate for young people and suggested including teenage slang to be more understandable. Participants requested more specific information, such as the kind of food to eat rather than generic advice to eat healthily. The need for information on labor, labor signs, hygiene practices, high blood pressure, and the consequences of not exercising was expressed. Some participants reported that they would like to be checked up on regularly to ensure that they were receiving the messages after registering. The feedback indicated an overall need for a more personalized or tailored messaging approach.

Feedback on the Teen MomConnect draft messages was that participants appreciated the specific and practical examples of behaviors and healthy foods provided within the draft messages. They welcomed message content on topics that they were unaware of, such as explanations of why practicing behaviors such as exercise was important. They reported that some messages provided examples that were impractical in their environments, such as exercise activities that were costly or unavailable in their residential areas. Participants suggested including messages that reminded them of their appointment dates. Findings from the focus groups on factors contributing to antenatal appointment attendance and the social context of participants also informed the development and refinement of the intervention messages.

Stakeholder meetings held with professional officers from the Western Cape Department of Health provided further insights into experiences with the MomConnect program, adolescent access to basic ANC services, local health facility operations, and the recruitment of pregnant adolescent girls and young women from the facilities. This information was used to contextualize the proposed intervention content.

Following the stakeholder meetings and the qualitative research findings on experiences with MomConnect and on the perceptions of the Teen MomConnect draft messages, a full set of SMS text messages was developed. The content and tailoring of the messages were based on techniques for tailoring health communication messages used in previous studies [30,31,34] and were grounded in self-determination theory [35]. Therefore, the messages applied an autonomy-supported tone to foster autonomous motivation for behavior change [35]. As such, the messages used phrases such as "consider to," "you can choose to," or "have you been able to" instead of authoritative or definitive phrases such as "you should." Reflective statements and questions rather than commands were often used, such as "What can you do to remind yourself next time?" for participants who forgot to attend their last appointment. The self-determination theory components of enhancing competence and relatedness were incorporated into the message content by providing practical information on behavioral barriers (eg, "giving up [smoking] even now can still have positive effects for you and your baby") and using language that was supportive, respectful, and relatable. The messages were restricted to 160 characters to comply with the required length of an SMS text message. The messages were developed in English and translated and back translated into isiXhosa and Afrikaans. The translated messages were checked to ensure that they maintained the tone and intent of the original messages.

The final message library comprised 66 messages in English, Afrikaans, and isiXhosa and covered the 13 behavioral domains. The messages were tailored by pregnancy week and the week in which the participant joined the intervention program (join week). The logic flow allowed users who had missed messages from earlier pregnancy weeks to be sent relevant *catch-up messages* with the content they missed. There were 48 static or 1-way messages that did not require the user to respond and 18 "two-way" tailored message sets that asked the user a question. The 2-way messages allowed participants to respond by typing a letter corresponding to their response option. The user would receive a tailored feedback message depending on their response to the question. For example, the question assessing smoking asked the following—"During the past month (30 days), on how many days did you smoke cigarettes?"—with the following options: "a. 0," "b. 1 to 15," and "c. 15 to 30." If the participant answered "a," then they would receive the following message: "Well done! By not smoking during pregnancy you will have much lower chances of having a low birth-weight." If they answered "b" or "c" or did not respond to the question, they would receive the following message: "Quitting smoking can be hard but it is one of the most important things you can do for a healthy pregnancy and healthy delivery." Therefore, the logic flow was designed to send a customized response even when the user did not respond to the message. In this way, the intervention would allow each user to receive a unique set of messages based on their pregnancy week and responses to questions. With regard to appointment attendance behavior, the logic flow applied iterative tailoring for 2-way messages on appointment attendance. These included appointment reminders every 4 weeks for those who did and did not know their appointment dates, checkups of whether the appointments were actually attended, and tailored feedback addressing various reasons for not attending each appointment. For affirmative responses to 2-way messages on engaging in smoking, alcohol use, and drug use, users would receive tailored follow-up messages every 4 weeks motivating them to stop these behaviors. Examples of messages on appointment attendance and smoking behavior and their logic flows and timing are presented in Multimedia Appendix 1, whereas brief example messages of the remaining 11 message domains are presented in Table 1.

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The MomConnect program used an open-source SMS text messaging platform to distribute the messages, and user registrations occurred via Unstructured Supplementary Service Data (USSD). USSD is a communication protocol for mobile phones to communicate with mobile network operators' computers [29]. The Teen MomConnect intervention messages were delivered via SMS text messages using the same technology platform and user registration process as MomConnect to facilitate comparability. Although a smartphone app was considered to deliver the intervention, SMS text messages were chosen as many adolescents and young people did not have access to a smartphone and an app would incur data costs to users. The intervention messages and the corresponding coding and logic flows were integrated into the technology platform used to implement MomConnect.

Table 1. Extract of SMS text messages.

Message domain	Message	Type
Alcohol	It can be hard to give up drinking but it is one of the most important things you can do for a healthy pregnancy and healthy delivery.	Tailored response to consuming alcohol in the past month
Attitude toward pregnancy	We understand pregnancy can be stressful. Many girls feel the same! You can talk to someone you trust about your feelings, or come to a clinic for support.	Tailored response to feeling stressed about their pregnancy
Clinic attendance	Regular check ups at the clinic will ensure that you and your baby stay healthy. Consider attending all your scheduled clinic appointments.	Static
General health information	Your baby's lungs are starting to develop and its heart beat can be heard.	Static
Illegal drugs	Have you been able to give up hard drugs since you knew that you were pregnant? Reply with a or b. a. Yes b. No	Tailored question
Nutrition	Including iron-rich food like eggs, beans, green vegetables and meat will ensure that your baby develops normally.	Static
Self-care and hygiene	Proper hygiene is important to prevent you from getting sick. Regularly wash your hands with soap, especially before eating and after going to the toilet.	Static
Social stigma	Not everyone is kind to young mothers. We know some people may judge you. Talk to someone you trust, or you can speak to a counsellor at the clinic.	Static
Social support	Emotional support can help with moms' mental and physical health. Think about who you can trust and talk to during this time.	Tailored response to preference for emotional support over informational support
STDs[a]	Finding out about your HIV status can help to make sure you and your baby receive the right medicine on time. You can choose to do an HIV test at your clinic.	Tailored response to unknown HIV status
Tuberculosis	Getting treated can reduce the risk to you and your baby. If you don't have medicines, talk to your health care worker.	Tailored response to positive tuberculosis test

[a]STD: sexually transmitted disease.

Development of the MI Content

The "Difficulty by Motivation" matrix for behaviors and interventions [36] guided the decision to supplement the messaging component with MI. Although tailored messaging can help change behaviors such as attending an appointment, complex behaviors where individuals show higher resistance to changing and require greater motivation and competence to change, such as sustained appointment adherence and substance abuse, often require more intense and interpersonal interventions such as MI. MI [37,38] is an evidence-based, patient-centered style of counseling that has been used in a range of health behavioral interventions in adolescents and adults. MI has been successful in improving health behaviors in pregnant women [39]. The aim of the MI session was to motivate and encourage the participants to attend ANC appointments and improve their health behaviors during pregnancy. MI differs from other types of counseling in that, instead of providing information and directive advice, the participants are encouraged to reflect on and express their own reasons for and against change and how their current behavior affects their life and family goals or core values and explore possible options for making change. Ambivalence and resistance are explored before moving toward action. The development of the MI content was informed by the key themes that emerged from the formative qualitative interviews previously conducted with pregnant adolescent girls and young women; focus group interviews conducted with health care workers and with research assistants who worked with the participants; and an analysis of the behaviors, social norms, and attitudes reported in the baseline questionnaire. The key themes of appointment keeping, substance use, HIV and tuberculosis testing, medication adherence, nutrition, and overall healthy pregnancy behaviors formed the basis of the MI content. The session was tailored to the participants to be relevant to their specific behaviors and questions. The MI sessions were first intended to be conducted by health care workers at the facilities. However, discussions with the facility staff revealed

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that they could not accommodate delivering these sessions into their already heavy workloads. Research assistants were then identified to conduct the sessions with the participants. The research assistants attended a training workshop facilitated by an expert counselor in MI. The training session taught reflective listening, asking open-ended questions, formulating affirmations, reflective listening, promoting change talk, and developing an action plan to improve behaviors identified as problematic. The research assistants were taught how to balance the expression of empathy with the need to build room for change. One face-to-face MI session was to be delivered by a research assistant during the participants' pregnancies.

Study Design

The aims of the study were to evaluate the feasibility of the Teen MomConnect intervention and test its preliminary efficacy on antenatal appointment attendance, health behaviors, and psychosocial mediators.

A pilot 2-arm RCT was conducted. Participants were randomized into the intervention or experimental group that received the Teen MomConnect intervention or the control group that received the standard MomConnect mobile messaging. This study was registered in the Pan African Clinical Trial Registry as trial PACTR201912734889796. This study was conducted in Cape Town in the Western Cape province of South Africa from April 2018 to December 2019. Cape Town is predominantly urban, and 9.5% of its 67,485 in-facility deliveries are among adolescents [40]. In the Western Cape province, 29% of pregnant women present late for their first antenatal appointment, that is, beyond 20 weeks of pregnancy. The overall Institutional Maternal Mortality Ratio in the Western Cape is approximately 50 deaths per 100,000 live births, which is lower than the national average. The Western Cape has the second highest provincial percentage of low–birth weight babies (17.3%) and the lowest provincial proportion of stillbirths (16.6%) [41]. In addition, substance use during pregnancy is high in Cape Town, where 9% of women attending ANC use illicit drugs and one-fifth consume alcohol during pregnancy [42].

A sample of 200 (100 participants/group) was decided upon for the pilot RCT. With this sample, it was determined that there would be sufficient power (≥0.80) to detect a Cohen *d* effect size of ≥0.40. This equates to a difference of 0.52 visits between groups at posttest measurement. This assumes a posttest mean of 4.1 (SD 1.3) visits in the intervention group and 3.58 (SD 1.3) visits in the control group (Cohen $d = 0.52 / 1.3 = 0.40$). Owing to the high expected attrition rate in adolescent longitudinal studies and the fact that participants with missing contact details and pregnancy characteristics would be excluded from registration to the mobile intervention, it was decided to recruit as many participants as possible for the baseline survey.

Participants

In South Africa, pregnant girls and women receive ANC and maternity services at outpatient clinics, community health centers, or midwife obstetric units (MOUs) within the primary health care system, which serves over 70% of the population. Pregnant adolescent girls and young women aged 13 to 20 years who had access to a mobile phone were eligible to be recruited to participate in the study. The Western Cape Department of Health provided information on priority communities and clinics where youth pregnancy rates were high and provided guidance on recruitment procedures. On the basis of these discussions, 16 community facilities that provided ANC (comprising public health clinics, community health centers, and MOUs) were identified for recruitment. The facilities were located in 4 of the 8 health subdistricts in Cape Town: Cape Town Eastern, Cape Town Northern, Mitchells Plain, and Tygerberg. Participants were recruited while attending ANC at these facilities. The research team discussed recruitment and data collection activities with the facility managers. Research assistants introduced the study to attendees in the antenatal service waiting areas. In some cases, facility staff referred the research assistants to potential participants. Participants were also recruited from communities via social networks. The research assistants explained the study to potential participants in their language of choice. The research assistants were fluent in English and either Afrikaans or isiXhosa, which are the 3 predominant languages spoken in Cape Town.

The study initially aimed to recruit participants who were up to 24 weeks pregnant to maximize their exposure to the messaging content over the duration of their pregnancies. However, a considerable number of pregnant adolescent girls and young women were beyond 24 weeks when approached during recruitment. Therefore, it was decided to recruit all pregnant adolescent girls and young women.

Recruitment Procedure

A total of 20 trained research assistants conducted recruitment and data collection activities. Recruited participants received information sheets that described the objectives, benefits, and potential risks of the study; the dissemination of findings; the privacy and confidentiality of the study; and their right to withdraw from the study at any time. The participants were asked to complete a consent form (for participants aged ≥18 years) or assent form (for participants aged <18 years) before being enrolled in the study. In addition, parental consent forms were required for participants aged <18 years. Consenting individuals completed a self-administered baseline questionnaire on an electronic tablet or mobile phone. Baseline questionnaire completion was facilitated by the research assistants. In a few cases in which the participant was not comfortable with completing the questionnaire themselves, the research assistant administered the questionnaire. The questionnaire took approximately an hour to complete. Participants received a US $3 incentive for questionnaire completion.

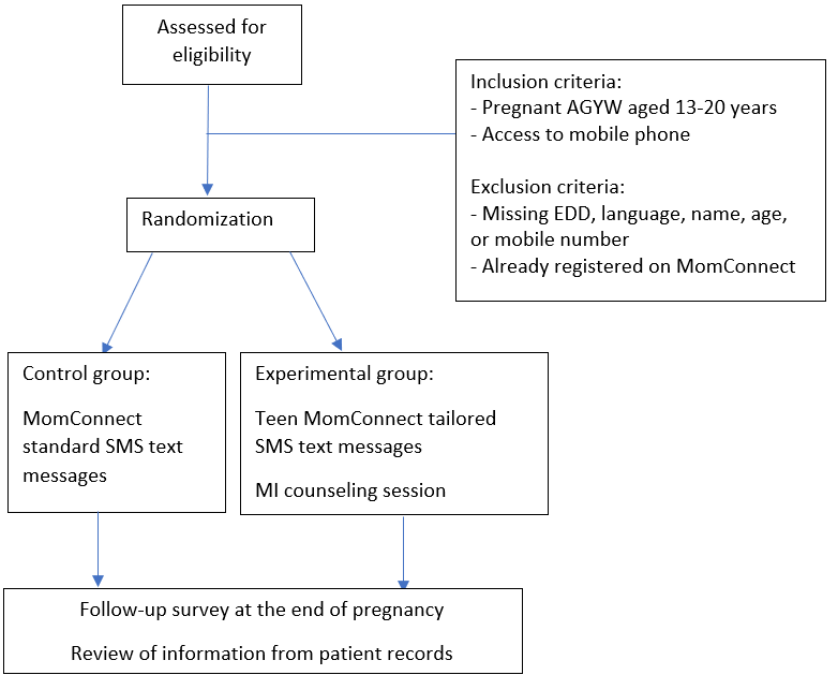
User registration to receive the MomConnect and Teen MomConnect messages required information to be entered on the name, mobile phone number, age, language, and expected date of delivery (EDD) of users. These variables, as well as the estimated last menstrual date (LMD) and current enrollment in MomConnect, were extracted from the baseline data. In the few cases in which the participant did not have their own mobile phone, they were advised to enter into the baseline survey the mobile phone number of someone whom they lived with and whose mobile phone they could use to access the messages sent

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during the study. The EDD was required as messages are dependent on pregnancy week. In cases in which the EDD was missing, an estimate was calculated using the reported LMD. In cases in which both dates were missing, the participant was contacted telephonically several times to try to obtain either their EDD or LMD. The language was asked to assess the language in which participants would receive their messages. The options were English, Afrikaans, and isiXhosa. Participants were excluded from enrollment in the intervention study if one or more of their EDD, language, name, age, and mobile phone number was missing or if they were already registered on MomConnect.

Participants were then randomized to the experimental or control group using simple randomization (Figure 1). The study was blinded for participants as they were not told which group they were entered into. Participants were registered on the respective Teen MomConnect and MomConnect messaging programs in weekly or biweekly batches. The control group, which was registered in the MomConnect messaging program, received the MomConnect standard messages according to their pregnancy week and join week. The experimental group participants, who were registered in the Teen MomConnect messaging program, received the messages from the Teen MomConnect SMS text message library based on their pregnancy week, join week, and responses to the tailored questions. In addition, the experimental Teen MomConnect group were to receive 1 face-to-face behavioral counseling group session using MI administered by a trained research assistant.

Figure 1. Diagram of the study procedure. AGYW: adolescent girls and young women; EDD: expected date of delivery; MI: motivational interviewing.



The research assistants contacted participants from September 2018 to December 2018 to schedule MI sessions at times that were convenient for them. Preliminary interview sessions revealed that some participants did not answer their phones, many scheduled sessions but did not attend them, many could not make time to attend a session because of school and other commitments, and it was difficult to allocate participants to times when all group members were available. Therefore, based on the ascertained limited availability of participants between enrollment into the study and the end of their pregnancy, it was decided to conduct motivational interviews with participants until 30% of the sample had received an interview session. Interview sessions could be conducted one-on-one or in groups of up to 5 people. Participants received an incentive of US $6 for attending a session.

Once the EDD had passed, participants in both the experimental and control groups were programmed to receive the standard postpartum messages that users receive in the MomConnect program. Participants were contacted a week after their EDD had passed to schedule voluntary completion of the follow-up questionnaire. Participants who had an abortion, miscarriage, or stillbirth were also contacted. As with the baseline questionnaire, participants completed the follow-up questionnaire on an electronic device facilitated by the research assistants, and they received a US $3 incentive. Electronic administration of both the baseline and follow-up surveys was facilitated using the Qualtrics electronic survey tool (Qualtrics International Inc) [43].

Ethics Approval

The Research Ethics Committee of the Human Sciences Research Council (REC 2/17/08/16) granted ethics approval for this study. Permissions were obtained from the Western Cape Provincial Government and the Department of Health to conduct research within the communities' public health clinics and MOUs.

Measurement Instruments

Data were gathered from the baseline and follow-up questionnaires and from a review of patient clinical records at the facilities.

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Questionnaires

Questionnaire development was informed by the reasoned action approach [44] and the Integrated Behavior Change Model (I-Change Model) [45], as well as a literature review on the psychosocial and socioeconomic factors associated with antenatal appointment attendance and health risk behaviors among young pregnant women.

The baseline questionnaire (Multimedia Appendix 2) assessed demographic characteristics; previous pregnancies; attitudes about the pregnancy; mental health status; knowledge of HIV and tuberculosis; HIV and tuberculosis testing; pregnancy risk behaviors (smoking, alcohol use, and illicit drug use); exposure to violence and harassment; perceptions regarding healthy pregnancy behaviors; knowledge regarding appointment attendance; risk perceptions; social support; peer norms; peer, partner, and family attitudes regarding appointment attendance; and participant attitudes, self-efficacy, action planning, and intention toward attending antenatal appointments.

The items on perceptions of healthy pregnancy behaviors, risk perceptions, social support, peer norms, attitudes, self-efficacy, action planning, and intention were all measured on a 4- or 5-point Likert scale, with responses ranging from *strongly disagree* to *strongly agree*.

Perceptions of healthy pregnancy behaviors included items on dietary behavior, nutrient intake, and physical activity. The perception statements were extracted from maternity health information booklets, including the Western Cape Department of Health "Caring for mothers, Caring for you" booklet. Exposure to violence was measured using 13 items on the lifetime frequency of exposure to violence or harassment from relatives, partners, teachers, or health care workers. The questions were adapted from the work by Reddy et al [26]. Knowledge of antenatal appointment attendance was measured using 16 statements informed by maternity booklets. Construction of the attitude, self-efficacy, peer norm, and intention items was based on the reasoned action approach by Fishbein and Ajzen [44], and the action planning, risk perception, and social support items were informed by the I-Change Model [45]. Risk perceptions referred to the perceived implications of not attending or missing antenatal appointments and the risks of pregnancy complications. Social support for attending ANC referred to the encouragement received from family, friends, and partners or boyfriends to attend appointments.

The follow-up questionnaire included the same items as the baseline questionnaire and additional items assessing the outcome of the pregnancy. In addition, evaluation questions were included in the follow-up questionnaire that assessed the participants' experiences with the SMS text messages and the motivational interview content, overall satisfaction with the study, and experiences with the research assistants. Specifically, 21 items evaluated the messaging component by measuring comprehension, tone, appropriateness, and content of the messages; the perceived degree to which the messages motivated behavior change; the frequency of receiving the messages; and whether participants were able to respond to the messages. The items evaluating the MI were administered to those who reported attending a session. A total of 17 items assessed the perceived degree to which the MI session motivated behavior change, with responses on a 5-point Likert scale.

Review of Patient Records

Patient records were accessed from the facilities where the participants were attending ANC or where they gave birth. The patient folder contains the maternity case booklet and other related files, in which facility personnel record information from the patient's antenatal visits, during labor, and after giving birth. Research assistants and the research team captured the following information from the maternity case booklet and its related files: clinical measures such as blood pressure at antenatal visits, dates of antenatal visits by pregnancy week, HIV and sexually transmitted disease testing, clinical measures from the labor process, and birth weight of the infant. The total number of antenatal visits was obtained from the recorded dates of antenatal visits by pregnancy week.

Primary and Secondary Outcomes

The primary outcome variables for feasibility were the perceived satisfaction and user acceptability of the intervention, whereas the outcome variable for assessing initial preliminary efficacy was the number of antenatal appointments attended. The number of antenatal appointments attended was obtained from the patient records at the facility. A secondary approach was to code the number of antenatal appointments attended into a binary variable for <4 versus ≥4 visits to calculate the proportion of participants who attended the requisite of at least 4 appointments during pregnancy [17]. Secondary outcomes were awareness of HIV status, psychosocial determinants of antenatal appointment attendance (knowledge, risk perceptions, attitudes, self-efficacy, intentions, and action planning), perceptions of healthy pregnancy behaviors, number of intervention messages responded to, and variables evaluating the recruitment and study implementation processes.

Statistical Analysis

Analyses will be conducted using SPSS (version 27.0; IBM Corp). Variables on perceived satisfaction with and acceptability of the Teen MomConnect messages and MI sessions in the evaluation section of the follow-up questionnaire as well as the number of messages responded to and MI attendance will be used for descriptive analyses to evaluate how the Teen MomConnect intervention was implemented and received. The outcomes of antenatal appointment attendance and its psychosocial determinants in the experimental (Teen MomConnect) and control (MomConnect) groups will be analyzed using linear regression for continuous outcomes and logistic regression for binary outcomes (including the outcome of percentage that attended ≥4 antenatal sessions) at follow-up. Covariates include age, race, previous pregnancies, school attendance, pregnancy week at enrollment, and exposure to MI. For outcomes related to knowledge, risk perceptions, attitudes, self-efficacy, intentions, and action planning scores that were measured at both baseline and follow-up, the change in mean values between baseline and follow-up in the experimental and control groups will be analyzed using analysis of covariance [46]. For each of these outcomes, moderation effects for race,

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gestational age at enrollment, socioeconomic status, age, and number of previous pregnancies will be tested with interaction terms in the regression models.

Data Management, Confidentiality, and Privacy Protection

The data from Qualtrics were protected by log-in ID and password. The server that stored data on message sends and responses was password protected. The data were sent to the statistician and principal investigator upon study completion. The consent forms are kept in a locked storeroom.

Quality Assurance

Practical training on recruitment and data collection procedures, with refresher sessions, was provided to the research assistants throughout the study to ensure its validity and accuracy. The baseline and follow-up data collected were checked for possible errors an average of every 2 weeks. The research assistants encouraged participants to ask questions about any concerns they had with the study. The research team monitored the study to oversee its progress. The research assistants provided feedback to the project manager 3 to 4 times per week on the study progress and any barriers encountered.

Results

Recruitment of participants was conducted from May 2018 to December 2018. A total of 412 eligible participants were enrolled in this trial (Table 2). The participant characteristics did not differ significantly between the experimental and control groups, with the exception of average gestational week (control group: 23.1, SD 7.69; experimental group: 20.8, SD 6.76; P=.002). The mean age was 18.0 (SD 1.56) years; 36.2% (149/412) were attending an educational institution, 75.4% (307/407) lived in formal dwellings, 59.6% (242/406) reported household shortages of important items, and 10.9% (45/412) had been pregnant before. Of the 412 enrolled participants, 256 (62.1%) completed the follow-up questionnaire. Patient records were able to be retrieved for 54.4% (224/412) of the participants. Results on the preliminary efficacy and acceptability of the intervention will be disseminated via publications and conference proceedings throughout 2023.

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Table 2. Characteristics of the sample at baseline (n=412)[a].

	Control (n=219)	Intervention (n=193)	Total sample	*P* value[b]
Age (years), mean (SD)	18.1 (1.49)	17.9 (1.64)	18.0 (1.56)	.21
Gestational age (weeks), mean (SD)	23.1 (7.69)	20.8 (6.76)	22.0 (7.35)	.002
Racial group[c,d], n (%)				.29
Black African	59 (27.2)	64 (33.2)	123 (30)	
Coloured	157 (72.4)	128 (66.3)	285 (69.5)	
Other	1 (0.5)	1 (0.5)	2 (0.5)	
Attending an educational institution, n (%)				.29
Do not attend educational institution	145 (66.2)	118 (61.1)	263 (63.8)	
Attend educational institution	74 (33.8)	75 (38.9)	149 (36.2)	
Dwelling type[e], n (%)				.79
Informal	54 (25.1)	46 (24)	100 (24.6)	
Formal	161 (74.9)	146 (76)	307 (75.4)	
Self-perceived cost of living[f], n (%)				.12
Food and clothes shortage	41 (19.2)	51 (26.6)	92 (22.7)	
Shortage of other important things	78 (36.5)	72 (37.5)	150 (36.9)	
Have important basics	95 (44.4)	69 (35.9)	164 (40.4)	
Had been pregnant before, n (%)				.73
Yes	25 (11.4)	20 (10.4)	45 (10.9)	
No	194 (88.6)	173 (89.6)	367 (89.1)	

[a]Counts do not always sum to 412 due to missing observations for some variables.

[b]Testing the difference in estimates between the control and intervention groups using chi-square tests for categorical variables and 2-tailed *t* tests for continuous variables.

[c]Control group: n=217; total sample: n=410.

[d]Race was self-reported by participants. Racial categories provided in the questionnaire were according to Statistics South Africa's standard population groups: Black African, Coloured, White, and Indian. The White and Indian categories were collapsed for analysis due to small sample sizes. Race was reported not with the intention of reifying sociocultural constructs but rather to study ongoing health disparities across groups.

[e]Control group: n=215; intervention group: n=192; total sample: n=407.

[f]Control group: n=214; intervention group: n=192; total sample: n=406.

Discussion

Synopsis

This paper describes the development of the Teen MomConnect intervention and the protocol for the pilot RCT to measure its feasibility and preliminary efficacy. The intervention aimed to improve antenatal appointment attendance among pregnant adolescent girls and young women using tailored 2-way messaging and MI. The results of the pilot study will inform policy makers and health program officers on how tailored, age-appropriate, and motivational health behavior messages can be delivered via mobile phone to large numbers of young people. The intervention expands the messaging content of the MomConnect program, which already has high coverage, to be relevant to youth. If the intervention shows promising results (eg, in terms of feasibility), it can be tested in a formal, fully powered trial. The findings will also show how the intervention was implemented and inform how it can be improved in the future.

Implementational Challenges

This study is subject to some foreseen implementational challenges. mHealth interventions often have high dropout rates, especially among young people. This study aimed to mitigate this by allowing for oversampling of baseline participants. This study will assess retention between baseline and follow-up, and the evaluation can inform retention strategies in future mHealth studies with adolescents. Second, many individuals in South Africa frequently change their mobile phone numbers, and this is expected to be common among adolescents and young adults. Studies on the MomConnect program found that messages were not delivered to a large number of users, which was attributed to users having changed their phone numbers [28]. This study was subject to the same problems. Future mHealth programs, particularly those designed for adolescents, can use smartphone apps rather than SMS text messaging–based systems. Nevertheless, SMS text messages were the most practical delivery option for this study as they facilitated comparison with the MomConnect SMS text message delivery and SMS

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text messages can reach all mobile phone users regardless of whether they have a smartphone and have no added costs to the user. This is particularly relevant in LMICs such as South Africa that experience challenges with mobile data costs, speed, and coverage [47]. Third, capturing information on the number of appointments attended is subject to the availability and ease of accessibility of the patient health records and the accuracy with which this information is captured by personnel at the facility. Therefore, the research team included questions on whether the participants attended all their appointments in the follow-up questionnaire. This question, although subject to self-report bias, can be used to supplement the analyses of appointment attendance.

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Data Availability

The data sets generated and analyzed during this study are available from the corresponding author upon reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Extract of SMS text messages on smoking and appointment keeping and the logic for tailoring and timing of delivery.
[DOCX File , 18 KB - resprot_v12i1e43654_app1.docx]

Multimedia Appendix 2
Baseline questionnaire.
[PDF File (Adobe PDF File), 415 KB - resprot_v12i1e43654_app2.pdf]

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Abbreviations

ANC: antenatal care
EDD: expected date of delivery
LMD: last menstrual date
LMICs: low- and middle-income countries
mHealth: mobile health
MI: motivational interviewing
MOU: midwife obstetric unit
RCT: randomized controlled trial
USSD: Unstructured Supplementary Service Data

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Protocol

MASI, a Smartphone App to Improve Treatment Adherence Among South African Adolescents and Young Adults With HIV: Protocol for a Pilot Randomized Controlled Trial

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Abstract

Background: Adolescents and young adults with HIV repeatedly demonstrate low rates of antiretroviral therapy (ART) adherence as well as low rates of viral suppression. Digital health interventions are a promising way to engage adolescents and young adults with HIV to support ART adherence. However, few digital health interventions have been developed and tested with adolescents and young adults in countries like South Africa, where the HIV burden among adolescents and young adults is greatest. *Masakhane Siphucule Impilo Yethu* (MASI; Xhosa for “Let's empower each other and improve our health”) is a comprehensive ART adherence-supporting app for South African adolescents and young adults with HIV. It was culturally adapted using the HealthMpowerment platform.

Objective: The aim of this paper is to describe the protocol for a pilot randomized controlled trial examining the feasibility, acceptability, and preliminary efficacy of MASI on self-reported ART adherence and social support.

Methods: We will enroll 50 adolescents and young adults with HIV ages 15-21 years. Participants will be recruited from public ART clinics linked to a large government-funded teaching hospital in Cape Town, South Africa. Participants will be randomized 1:1 into either the intervention arm receiving a full version of MASI or the control arm receiving an information-only version of the app (n=25 per arm). Participants will be asked to engage with MASI daily for 6 months. All participants will complete baseline and follow-up assessments at 3 and 6 months.

Results: Study screening began in May 2022 and the first participant was enrolled on June 21, 2022. As of June 12, 2023, 81 participants have completed screeners, and 36 eligible participants have been enrolled in the pilot randomized controlled trial. Recruitment is anticipated to last through August 31, 2023, with study activities anticipated through February 29, 2024.

Conclusions: There is an urgent need for innovative interventions to improve ART adherence among adolescents and young adults in settings like South Africa. If found to be feasible and acceptable, MASI could be implemented with adolescents and young adults with HIV in other parts of the country.

Trial Registration: ClinicalTrials.gov NCT04661878; https://clinicaltrials.gov/ct2/show/study/NCT04661878

International Registered Report Identifier (IRRID): DERR1-10.2196/47137

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(JMIR Res Protoc 2023;12:e47137) doi:10.2196/47137

KEYWORDS

HIV; adherence; mHealth; digital health; smartphone; adolescents and young adults; youths; South Africa; social support; randomized; controlled trial; pilot; antiretroviral therapy; sexually transmitted; app; apps; mobile phone

Introduction

Background

Adolescents and young adults with HIV represent a large and growing proportion of people living with HIV globally [1]. Despite considerable progress in prevention and treatment, adolescents and young adults lag behind other age groups with respect to UNAID's 95-95-95 targets for testing and treatment outcomes [2,3]. Consistent adherence to effective antiretroviral therapy (ART) is needed to suppress HIV viral load to undetectable levels, resulting in improved health outcomes and eliminating transmission [4]. Unfortunately, adolescents and young adults repeatedly demonstrate low rates of ART adherence as well as low rates of viral suppression, with estimates of viral suppression ranging from 47% to 59% [3,5]. Adolescents and young adults with HIV face a variety of barriers to ART adherence, including patient-level factors (eg, stigma, misconceptions, secrecy, treatment fatigue, forgetfulness, and lack of self-efficacy), caregiver-related factors (lack of assistance or support), and health system-related factors (eg, inconvenient clinic times) [6]. Given their developmental stage, adolescents are particularly sensitive to contextual influences, such as a lack of social support, and experience greater distress due to social exclusion [7,8].

Over 70% of adolescents and young adults with HIV live in Eastern and Southern Africa, with South Africa accounting for 22% of all adolescents and young adults with HIV globally [1]. Despite having the greatest HIV burden, interventions designed to support ART adherence and care engagement among adolescents and young adults in settings like South Africa remain limited [9-11]. A systematic review of interventions to improve adherence among adolescents and young adults conducted in 2015 identified no studies implemented in Eastern or Southern Africa [9]. A more recent review of interventions published between 2015 and 2019 identified 7 studies conducted in Eastern or Southern Africa [12]. While this is an encouraging increase, and additional trials are underway [13-15], there remains an urgent need for innovative interventions to improve ART adherence within this important population.

Digital health interventions are a promising way to engage adolescents and young adults with HIV to support ART adherence, given their increasing access to and interest in mobile technology [16,17]. Digital health interventions can be used to target multiple factors influencing a behavior (eg, knowledge, attitudes, skills, social support, and norms), which makes them well-suited to address a complex behavior like ART adherence. They can also be used to support web-based communities with the potential to reduce social isolation and loneliness while providing participants with emotional and informational social support [18,19]. Mobile phone access in South Africa was 95% as of 2018, and an estimated 91% of all phones in the country are smartphones [20,21]. Data from South Africa show that smartphone ownership is higher among young people [22], who consistently express more interest in adopting technology, making digital health interventions targeting adolescents and young adults feasible and potentially scalable in this setting.

Despite their promise, few digital health interventions to date have been developed and tested with adolescents and young adults in Eastern or Southern Africa. Among those that have been evaluated, basic applications such as SMS text messaging and phone calls have been the most common [23]. The findings of such SMS text messaging–delivered interventions have been mixed [24], highlighting the limitations of addressing only 1 adherence challenge (eg, forgetfulness), and underscoring the potential of incorporating multiple behavior change techniques (BCTs) to comprehensively address the varied adherence barriers experienced by adolescents and young adults.

To address these gaps, we developed *Masakhane Siphucule Impilo Yethu* (MASI; Xhosa for "Let's empower each other and improve our health"), an ART adherence-supporting app for South African adolescents and young adults with HIV, based on formative research in Cape Town, South Africa [25]. MASI was culturally adapted using our team's evidence-based HealthMpowerment (HMP) platform. HMP was built upon years of human-centered design and research [26-29] and has demonstrated improvements in HIV risk behaviors, HIV care engagement, and stigma among youths in the United States [29,30]. The HMP platform is built to support use in low-resource settings like South Africa; it includes offline support to allow use without internet access and allows participants to customize data use, which is important when wireless coverage is limited and data use fees apply.

Objectives

The goal of this study is to conduct a pilot randomized controlled trial (RCT) of MASI with 50 adolescents and young adults with HIV, ages 15-21 years, to (1) assess its feasibility and acceptability and (2) explore preliminary effects on ART adherence and social support. This study's protocol is guided by the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines [31], and the CONSORT (Consolidated Standards of Reporting Trials) reporting guidelines for pilot and feasibility trials [32].

MASI Intervention

MASI Mobile App Overview

MASI is a comprehensive intervention designed to promote ART adherence and foster social support using a strengths-based approach. MASI was adapted through formative research with South African adolescents and young adults with HIV, including in-depth interviews with 15 adolescents and subsequent beta testing with 12 adolescents [25]. The interviews, conducted between January and March 2021, addressed participants' health-related challenges and unmet needs to inform the

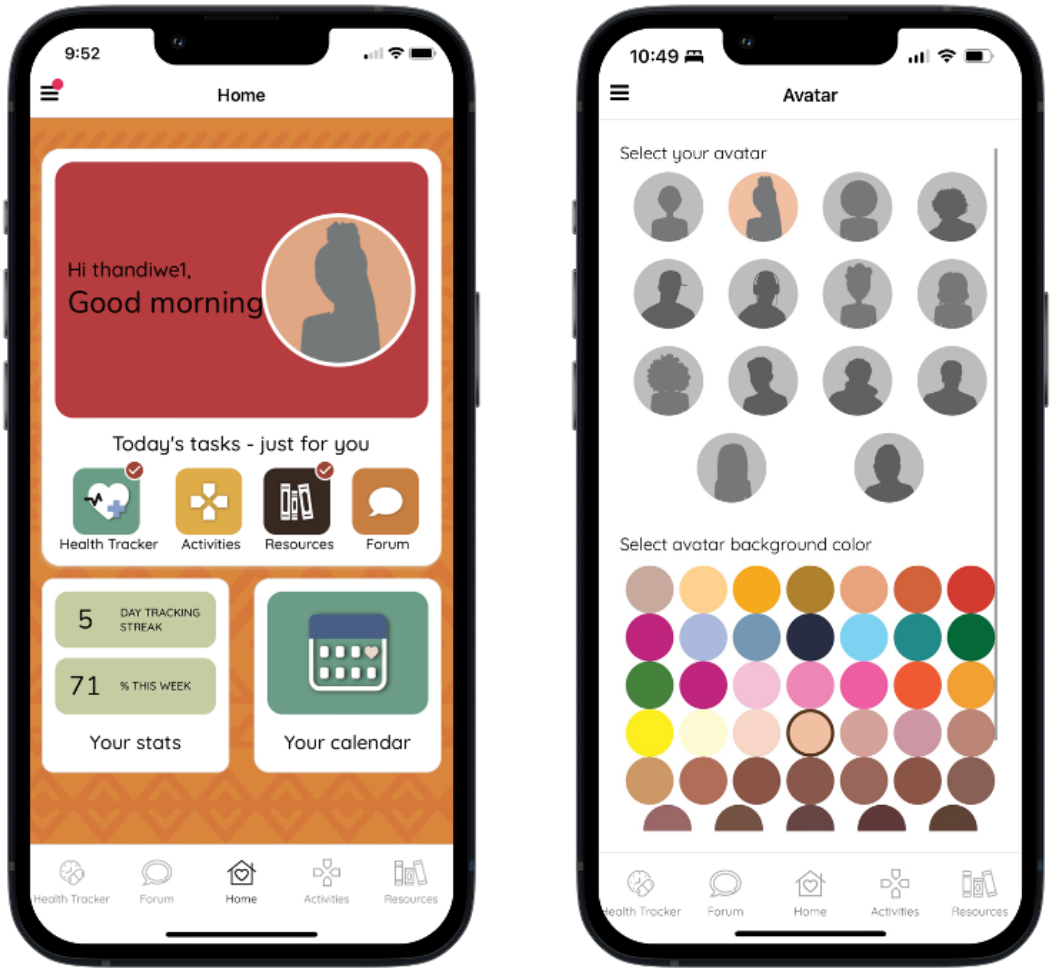
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adaptation process and the development of tailored content to meet their needs. The majority of participants also described their preference for having content in English rather than Xhosa, the predominant home language of our study participants, noting the simplicity of English and the increased comfort with the language among youths [25].

After adaptation, MASI was beta tested with 12 adolescents with HIV between September and December 2021. Beta testing supported the feasibility of using MASI on participants' devices and identified no major technical issues [33]. Our mixed methods analysis of participant paradata (ie, back-end app use metrics [34]) and in-depth interview transcripts after beta testing found MASI to be functional, usable, and highly desirable [35]. Modifications to MASI were made prior to the pilot trial based on findings from beta testing, including the addition of new resources and activities, modifications to the app programing to promote ease of navigation, and a plan for posting new content in the app at the start of the pilot RCT to encourage participant engagement (eg, icebreakers and polls).

The MASI mobile app is available for Android and iOS and smartphones from either Google Play or the Apple App Store; access to the app requires a code provided by the research study. Users select a username and password and are encouraged to pick a username that does not contain any identifying information so that they can remain anonymous to other app users. Users also customize an avatar, which is displayed on the home page, along with time-specific greetings (Figure 1). The home page also includes a list of "Today's tasks" related to 4 of the main app features: Health Tracker, Activities, Resources, and Forum. The Activities and Resources button takes participants to a prespecified activity or resource for the day. Once completed, the home screen displays a red check mark on the feature's button in the "Today's tasks" section.

Figure 1. *Masakhane Siphucule Impilo Yethu* home screen and avatar customization options.



MASI Mobile App Features

Core MASI features are described in Table 1, with their associated BCTs. The BCTs were identified using a taxonomy developed by Michie et al [36], which classified 93 hierarchically clustered techniques (clustered within 16 groups).

The MASI Health Tracker (Figure 2) prompts users to add details about their HIV medications (eg, frequency and time of day), and then allows users to pick a customized, tailored reminder to be sent by the app as a push notification at the selected time. If a user clicks on the reminder, they can track their adherence. If a user indicates that they missed a pill, they are prompted to provide a reason, and the app provides tips on how to overcome that challenge in the future. Users can also track other health behaviors and statistics, including meals, mood, and alcohol consumption. They can view graphs and visuals of their tracked health behaviors over time.

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The MASI Forum (Figure 3) allows participants to interact with other MASI users and peer mentors by starting or adding to existing discussion posts. Users can upload images, videos, or links and can favorite posts and follow other users. Research staff, including peer mentors from the clinic who have been hired to support our MASI users, monitor and add to forum posts or create their own icebreaker posts to encourage dialogue.

The Ask the Expert feature (Figure 4) allows users to submit questions that are answered by a doctor or counselor, sourcing credible information. Questions are posted anonymously, and responses are visible to all participants. Responses from the expert often link to further resources within the app related to the topic of interest.

The Activities feature (Figure 5) offers engaging activities covering a range of health-related and lifestyle topics. Example activities include quizzes that test knowledge on a subject and provide instant feedback and explanations of the answers. Goal-setting activities allow for the users to identify action steps they want to take toward a goal and receive tips on improving selected behaviors. Other activity types include self-assessments or fill-it-in activities that allow for users to reflect on a prompt and enter in responses, such as identifying motivations for staying in HIV care.

The MASI Resource feature (Figure 6) provides access to multimedia resources and information on various health topics. There are over 140 articles and videos, with new content added to the resource center as it is developed. All content has been developed or adapted to the South African setting, including links to local websites or resources for more information and support. Resource topics include healthy living, love and relationships, living with HIV, all about sex, life skills, prevention, and creating change. Many of the resources contain links to other articles related to the topics, or to a relevant activity, such as a quiz to test their knowledge or a goal-setting activity.

The MASI app also includes elements of gamification, such as badges (Figure 7) that are awarded to participants based on their app use. For example, users are awarded the “Book Worm” badge after reading 10 articles and earn the “Unshakable” badge once they report that they have taken their medication 30 times.

Table 1. MASI[a] core features and associated behavior change techniques.

MASI feature	Description of feature	Behavior change techniques [36]
Health Tracker	• Tracking available for ART[b] adherence and other health-related behaviors and statistics, including meals, mood, financial stress, smoking, alcohol, drugs, sex life, CD4[c] count, and viral load. • Customizable reminders sent via notifications, with recommended text generated to connect taking medication with the timing of other daily behaviors (eg, brushing teeth). • Feedback based on entered data to encourage behavior change.	• Prompts or cues • Feedback on behavior • Self-monitoring of behavior • Self-monitoring of outcomes of behavior • Habit formation
Forum	• Forum threads can include images, YouTube videos, or text. • Users can start or contribute to existing forum threads or “like” or “favorite” posts. • MASI peer mentors and staff monitor the forum and add posts, including polls, to boost engagement.	• Social support (unspecified) • Social support (emotional) • Role-modeling • Social comparison
Resources	• Multimedia resources and information on health and wellness, stigma, resilience, and life skills. • Information about consequences of various HIV-related behaviors (eg, disclosure and ART adherence). • Resources inclusive of various learning styles and health literacy levels. • Resource articles link to care locator with up-to-date local resources available.	• Instruction on how to perform behavior • Information about health consequences
Activities	• Activities include risk assessments, quizzes, goal setting, sorting, and matching.	• Goal setting (behavior) • Goal setting (outcome)
Ask the Expert	• Direct connection to a health care provider who answers questions submitted within the app.	• Credible source
Game-based elements	• Badges awarded for prespecified targets (eg, 30 min using MASI). • Avatars represent MASI users and can be swapped out for various colors and silhouettes.	

[a]MASI: *Masakhane Siphucule Impilo Yethu*.

[b]ART: antiretroviral therapy.

[c]CD4: cluster of differentiation 4.

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Figure 2. Home screen displaying reminder push notification and Health Tracker, highlighting feedback provided on antiretroviral therapy adherence behavior.

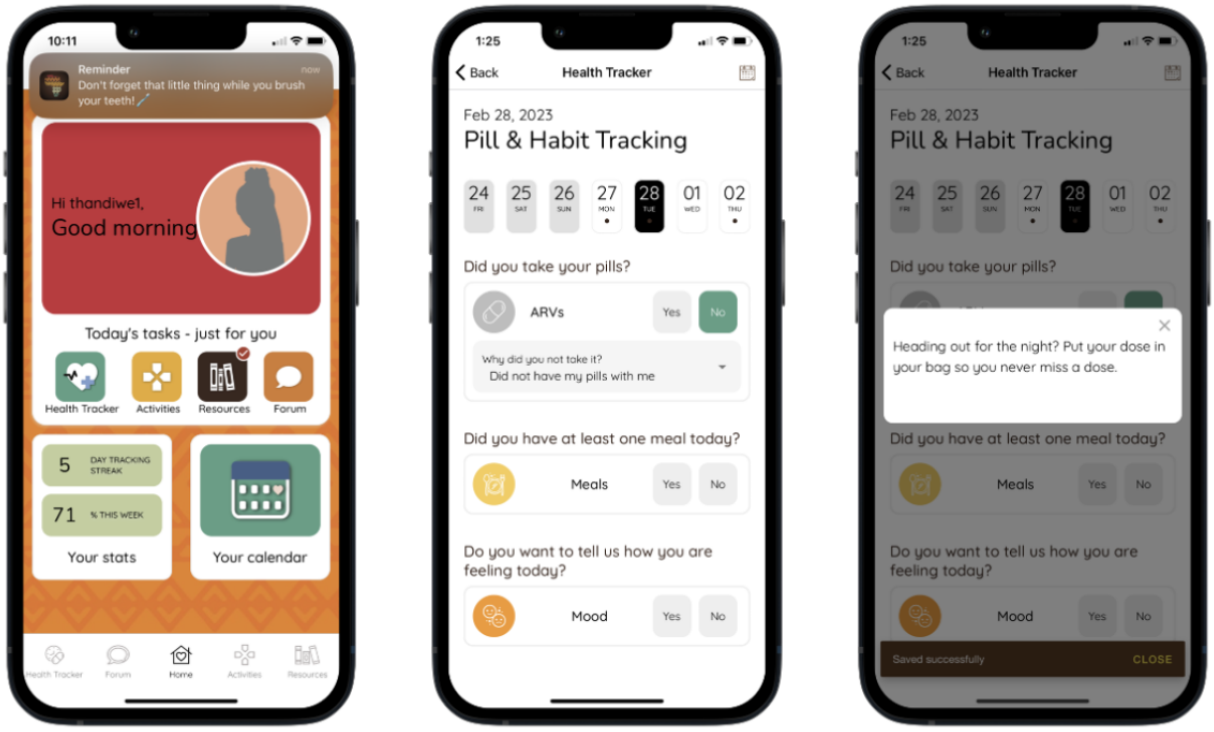
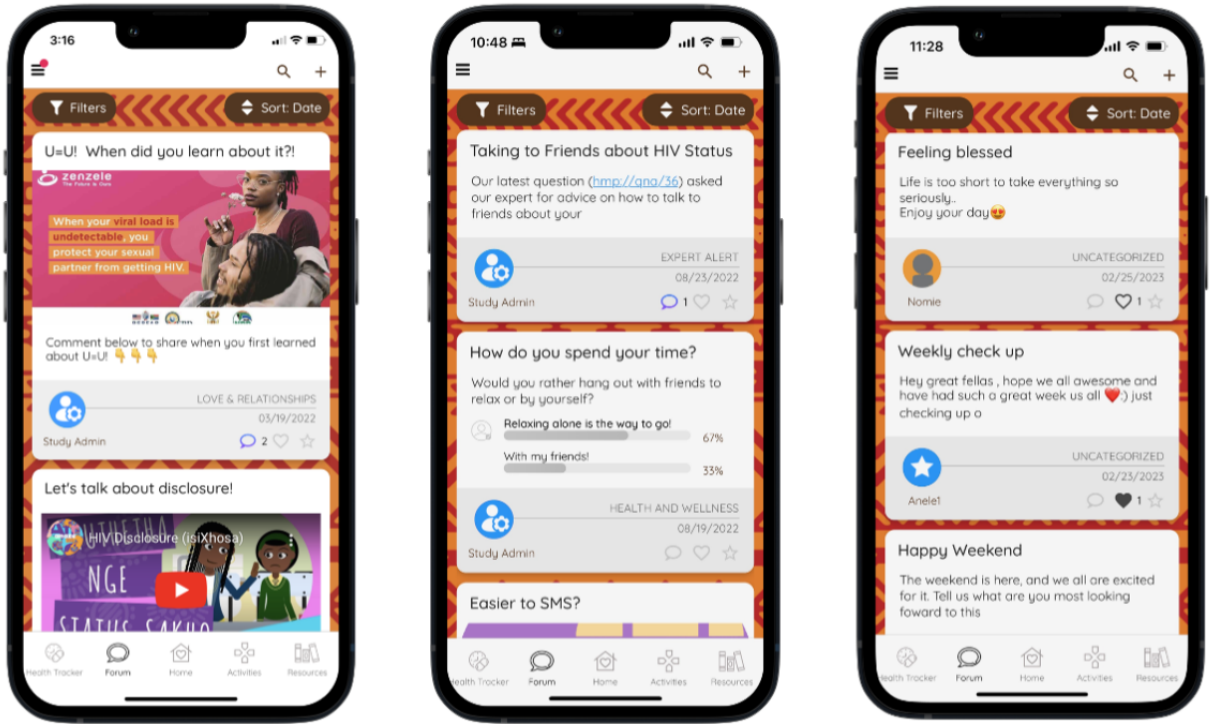


Figure 3. Forum displaying images, YouTube videos, polls created by study staff, and posts by study participants and peer mentors.



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Figure 4. Ask the Expert feature, displaying submitted questions and preview of answer.

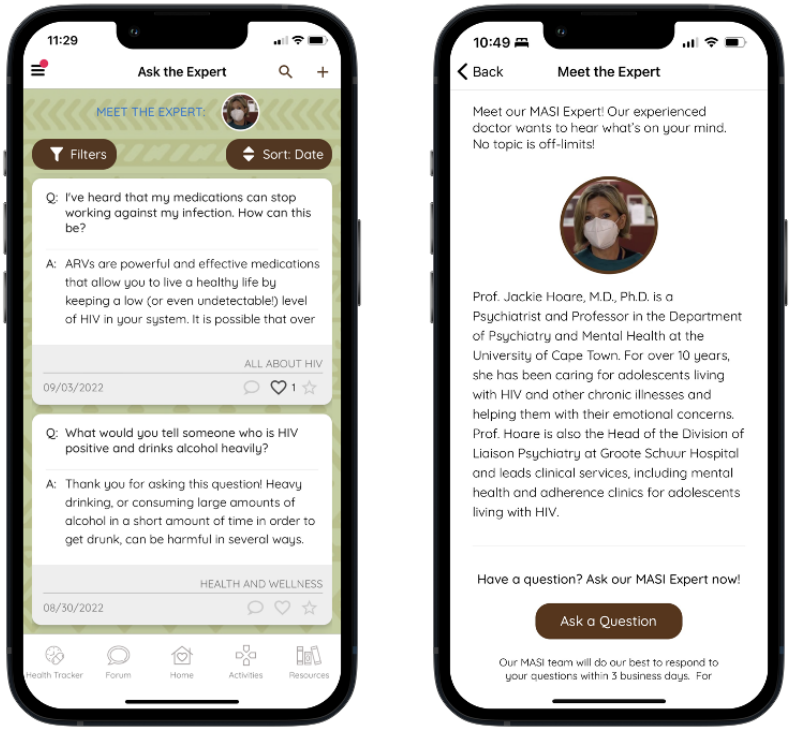
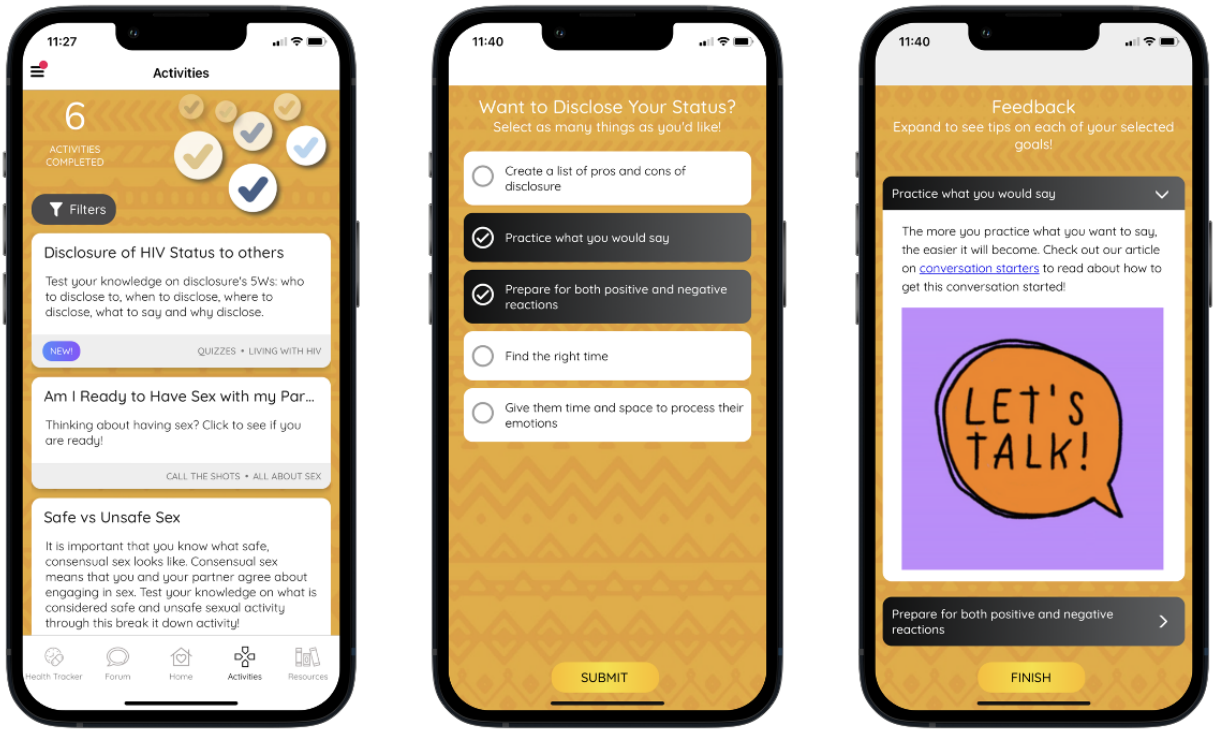


Figure 5. Activities landing page and example of disclosure goal-setting activity.



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Figure 6. Resources landing page, example of articles within a subtopic, and example article.

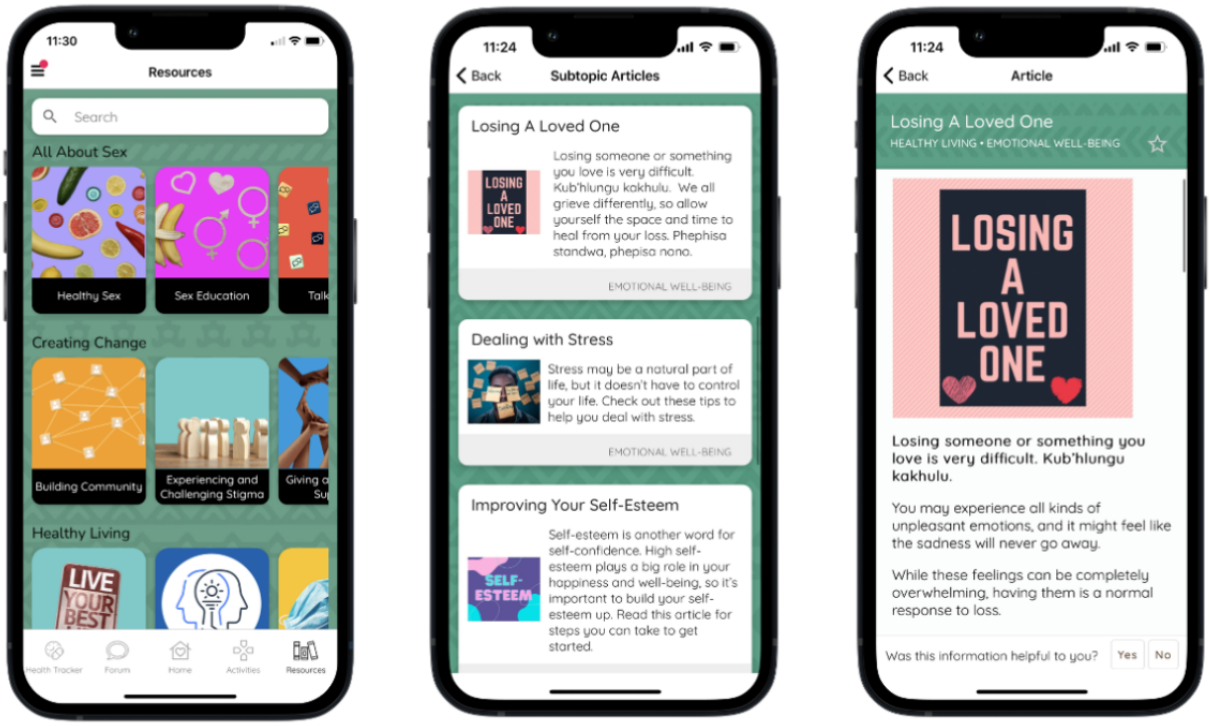


Figure 7. Notification for receipt of "Unshakable" badge and screen of all badges.



MASI Peer Mentors

Our study will hire at least 2 part-time MASI peer mentors to provide support to MASI users. Peer mentors will be between the ages of 18 and 29 years with a track record of good adherence to ART and HIV care engagement, strong communication skills, and demonstrated leadership qualities. We will hire individuals who have been trained to serve as in-person peer mentors and facilitate in-person support groups at local ART clinics. MASI peer mentors will be trained on how to use the app, and they will be asked to interact with MASI intervention participants through the forum feature. Their role will be to post icebreakers, respond or react to participant posts, share their own personal experiences to relate to participants, and help generate ideas for new content.

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MASI Content Library

The MASI Content Library is a compilation of the materials shared on the MASI app via the administrative portal, including multimedia resources and activities, "Ask the Expert" questions and responses, and forum posts. It also includes materials to support this content, such as a catalog of images and GIFs to be used in forum posts, articles, and activities.

Content is developed and curated from multiple sources, including the HMP Content Library and web-based resources designed for South African adolescents and young adults (eg, Amaze animated videos on sexual health topics adapted by Marie Stopes International for use in South Africa [37]). All content is adapted and reviewed by the South African research team to ensure cultural relevance, age appropriateness, and accuracy of listed local resources (eg, where to access pre-exposure prophylaxis locally).

The initial content available on the app at the start of the pilot RCT covers a wide variety of topics related to HIV, general health, safe sex, and lifestyle. Additional content will be generated and added to the app in response to participant interests, input from peer mentors, and emerging topics in the news. Topics for additional content will be identified by reviewing Forum posts and Ask the Expert questions for topics of interest, examining the app-generated paradata for content searches by users, and asking participants for feedback during data collection. This process was modeled during our beta testing phase, during which resources related to sexual and gender diversity were developed and added to MASI in response to a participant's searches for resources and a question to experts about same-gender-loving relationships.

MASI Admin Portal

The MASI administrative (admin) portal is a web platform that allows study administrators to manage the content on the MASI app, manage participant access to the app, and review paradata generated by participants' app use. All content that is live on the app is housed in the admin portal, which allows for links across features and content (eg, links within an article to additional resources or related activities). When a participant asks a question to the expert on the app, the response can be drafted and posted within the admin portal to appear on the app, and this study's team can add a forum post alerting participants of a new question. The admin portal allows for scheduling of posts so that content can be developed in advance and released at ideal times. This study's team can also manage notifications that participants receive in-app or via SMS text messaging, which includes notifications about new articles, responses to participant forum posts or messages, or encouragement to log in if users have been away from the app for a few days.

The data analytics feature of the admin portal allows this study's team to run ad hoc queries examining the paradata for quick feedback on app use [34,38]. User data will help inform the development of new content tailored to user's interests or preferences by identifying gaps in content or topics and activity types with a high level of user engagement.

Methods

Study Design

This study is a pilot RCT that will enroll 50 adolescents and young adults with HIV. Participants will be stratified by self-reported sex assigned at birth and randomized 1:1 (n=25 per arm) into 2 parallel arms: the intervention arm receiving a full version of MASI or the control arm receiving an information-only version of the app. Participants will be asked to engage with MASI daily for 6 months.

Study Setting

This study takes place in Cape Town, South Africa. In South Africa, HIV prevalence is significantly higher among Black Africans compared to other racial groups. These racial disparities are rooted in structural and contextual inequalities, including the legacy of apartheid policies that produced economic and health advances for those classified as White [39].

Participants will be recruited from public ART clinics linked to a large tertiary government-funded teaching hospital in Cape Town. As a tertiary hospital, it offers a standard of care to all patients, who are admitted to the facility through referrals from primary and secondary health care facilities. In addition, it offers specialized pediatric and adolescent ART services with a qualified and experienced team of clinicians such as psychiatrists, psychologists, nurses, and HIV lay counselors.

Participants

Participants will be eligible for this study if they meet the following eligibility criteria: (1) they are aged ≥15 years and ≤21 years, (2) they know their HIV status (screened participants who do not know their HIV status will receive information on free voluntary HIV counseling and testing services), (3) they are living with HIV, (4) they have been prescribed medication to treat HIV, (5) they are not attending school for learners with special needs (eg, School of Skills) and have not repeated a grade in school more than once (this is to increase the likelihood that adolescents have the decisional capacity to provide informed consent to participate in this study and to reduce the risk of the research activities causing confusion among participants with diminished capacity or cognitive impairment), (6) they have a smartphone that can download apps, (7) they feel comfortable using an app with content in English, (8) they have no plan to move outside of Cape Town in the next 6 months, (9) they have not previously participated in the MASI beta testing phase of our study, and (10) they are able to successfully install the MASI app on their smartphone.

Procedures

Recruitment and Screening

Participants will be recruited at ART clinics in Cape Town, South Africa. Peer mentors will work with clinic nurses to identify potential participants in clinic waiting rooms to share details about this study, assess their interest in learning more, and collect their contact info for screening. We will also recruit participants from other research studies who have provided consent to be contacted for future research.

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Potential participants will be screened by phone after providing verbal consent to see if they meet the eligibility criteria for this study. Participants who meet these criteria will be invited for an in-person appointment. After completing the informed consent or assent process (including consent from an adult caregiver for participants between 15 and 17 years of age), this study's team will confirm that the participant is able to successfully install the MASI app on their smartphone. Screening data will be entered electronically by the interviewer using Research Electronic Data Capture (REDCap), a secure, web-based application hosted at Duke University [40]. REDCap will also be used to track the status of potential participants, including documenting reasons for declining participation and ineligibility.

Baseline Data Collection

Eligible participants will complete a baseline assessment, an interviewer-administered survey with data entered electronically by the interviewer using REDCap. REDCap provides an intuitive interface for validated data entry, audit trails for tracking data manipulation and exporting, and automated export procedures for data downloads to common statistical packages. For survey questions with a higher potential for social desirability bias (eg, sexual behavior and study feedback), participants will be offered the opportunity to self-enter data into REDCap. The assessment items will be displayed on the screen in both English and Xhosa, the most commonly spoken home language among our study participants [33], and assessments will be conducted by bilingual interviewers.

Randomization

After completing the baseline assessment questions, participants will be randomized at a 1:1 ratio to the intervention condition (full MASI app) or control condition (information-only version of MASI). In total, 25 participants will be assigned to each condition and participants will be stratified by self-reported sex at birth. Randomization will be revealed by this study's interviewer using the REDCap Randomization Module, which uses a computer-generated allocation sequence created in Excel and uploaded to the module prior to the start of the trial. This study's interviewers will be unaware of this study condition prior to allocation. Participants will not be blinded to their allocation, as all participants will become aware of the full MASI features during the informed consent process.

Experimental Conditions

Intervention

Participants randomized to the intervention condition will receive access to the full MASI app, including all its features (ie, Health Tracker, Forum, Ask the Expert, Activities, and Resources). Through the Forum feature, participants will be able to interact anonymously with the other intervention participants, along with peer mentors and study staff.

This intervention is intended to supplement existing clinical care, so it will not impact access to routine medical care.

Control

Participants randomized to the control condition will receive access to an information-only version of MASI. Control participants will have access only to the Resources feature (Figure 8). An information-only version of MASI was chosen as the comparator given recommendations from the local study team, the need to download MASI to confirm the final eligibility requirement of this study, and the benefit of equalizing contact with participants to check-in on app access and provide smartphone data.

Figure 8. Home screen for users in the information-only control group.



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Onboarding

Once participants have been allocated to their condition, a research assistant will help them set up their profile and username. Participants will be advised to pick a username that does not include their real name, email address, or other social media account names. The research assistant will then walk the participant through the MASI features and demonstrate how to navigate the app and how to contact this study's staff if needed. Participants will be asked to log into the app daily and will be given 1 GB of smartphone data each month to support their app use.

Follow-Up Assessments

Participants will complete assessments at 3 and 6 months after enrollment; follow-up assessments will aim to be scheduled as close to the 3 or 6 month date as possible but may occur within 4 weeks before or after the target dates to accommodate participant scheduling (eg, holidays and school breaks). Follow-up assessments will be administered in the same way as the baseline assessment, using REDCap data collection software. Assessments will include a few open-ended questions to give participants the opportunity to share feedback on things they liked about MASI, note any challenges experienced, or explain periods of lost access to the app (eg, lost phone and forgot password). In the event that it is not possible to conduct in-person data collection, follow-up assessments prioritizing main study outcomes may be conducted by phone.

Participant Tracking and Retention

Research staff will inquire about preferred and acceptable methods of communication, including alternative contacts if participants cannot be reached on a primary phone number. Participants will be contacted each month to send a 1-GB data top-up to support their app use. At this time, study staff will confirm if the participant still has access to their phone and the MASI app and will document any shared reasons for app nonuse. Study staff will also help troubleshoot any app-related technical challenges encountered.

To promote participant retention, research staff will emphasize the importance of attending all assessment appointments. Ahead of the 3- and 6-month study visits, research staff will arrange for a registered transportation company to collect participants (and accompanying adults, if aged 18 years or younger) in their area of residence and bring them to the research site for assessments. We will reschedule appointments as needed and will follow-up with participants who miss appointments.

Reimbursement

Participants will receive R250 (approximately US $14.50) at each visit. Participants (and their adult caregivers, if applicable) will also be given refreshments, including a snack and a drink.

App Access After Conclusion of Study

Participants will consent to 6 months of app access. After 6 months, the app will display a message informing the participant that they have completed this study and no longer have access to the app. The message will thank participants for their participation and encourage them to share any additional feedback by contacting our study team. Content generated by participants (eg, forum posts and Ask the Expert questions), will still be visible to other users on the app after their access ends. The decision to end access to the app was made due to our ethical obligations to monitor and be responsive to content from active users and the nature of on-going data generated from app use.

Outcomes

Primary outcome measures include intervention feasibility measures recorded by app backend paradata (the number of days participants log into the app, the total time participants spend using the app, and the number of days participants log medications using the app) and intervention acceptability (mean composite score from the adapted System Usability Scale [41,42]) at 3- and 6-month follow-ups.

Secondary outcome measures include adherence to ART (30-day recall of missed doses) and perceived social support using the adapted Medical Outcomes Study Social Support Survey scale [43,44] at 3- and 6-month follow-up.

All other measures are exploratory and include HIV/AIDS knowledge and stigma. HIV/AIDS knowledge will be measured using a scale adapted from a United States Agency for International Development toolkit for transition of care for adolescents with HIV [45] and a scale measuring HIV treatment knowledge in context of treatment as prevention [46]. Stigma will also be measured with the Adolescents Living with HIV Stigma Scale, which includes internalized stigma (5 items), anticipated stigma (2 items), and enacted HIV stigma (3 items) [44,47,48]. We will also measure various psychological and behavioral covariates as well as demographic characteristics. HIV disclosure and disclosure intentions will be measured using items previously used with adolescents living with HIV [49]. Disclosure concerns will be measured using 2 items from the HIV Stigma Scale for children [50]. Anxiety will be measured with the General Anxiety Disorder scale [51]. Depression will be measured with the Patient Health Questionnaire-9 [51]. Social isolation will be measured using the National Institutes of Health Toolbox Loneliness Scale (for ages 8-17 years) [49]. Resilience will be measured using the Connor-Davidson Resilience Scale 10 [52]. Demographic information collected will include age, sex assigned at birth and current gender identity [53], population group, and home language. Participants will also self-report if they were born with HIV.

Primary and secondary outcomes are described in Textbox 1 along with potential covariates and proxy outcomes of interest. To the extent possible, outcome measures were selected based on their prior use with adolescents and young adults with HIV in South Africa. Measures without existing Xhosa translations were translated from English into Xhosa and then back-translated, with team discussion to determine the best translation for items. Items will be displayed on the REDCap data collection screen in both English and Xhosa.

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Textbox 1. Pilot randomized controlled trial primary and secondary outcomes.

Primary outcomes

- Intervention feasibility:
  - Number of days participants log in to the app as recorded by app backend paradata (3 and 6 months).
  - Total time participants spend using the app (minutes), as recorded by app backend paradata (3 and 6 months).
  - Number of days participants log medications using the app as recorded by app backend paradata (3 and 6 months).
- Intervention acceptability:
  - Average score of an adapted version of the system usability scale [41,42]. Total possible range: 0-100. Higher score indicates higher usability and helpfulness (better outcome). Average System Usability Scale score >68 (average for digital health apps [54]) will be considered acceptable (3 and 6 months).

Secondary outcomes

- Adherence to antiretroviral therapy:
  - Self-reported number of missed antiretroviral therapy doses in the past 30 days (3 months and 6 months).
- Perceived social support:
  - Adapted version of the Medical Outcomes Study Social Support Survey [43,44], which measures 4 domains of social support: emotional or informational support, tangible support, affectionate support, and positive social interaction. Total possible range: 12-48. Higher score indicates higher social support (better outcome; 3 months and 6 months).

Statistical Analysis

This study will enroll 50 adolescents and young adults with HIV into this study (25 males and 25 females based on self-reported sex assigned at birth). This study's sample size (N=50) was selected to be large enough to reasonably evaluate the feasibility and acceptability of MASI while balancing budgetary constraints [55].

Descriptive summaries will be computed for all study outcomes with continuous variables summarized with means and SD (or medians with IQR in the case of skewed distribution) and categorical variables summarized with counts and proportions. Outcomes will be summarized, stratified by treatment group, at each available study time point.

As a pilot study with a primary focus on feasibility and acceptability, the examination of MASI's preliminary efficacy will be exploratory. To explore MASI's preliminary efficacy on ART adherence and social support at 3 and 6 months, we will use linear mixed models to compare outcomes among participants randomized to MASI compared versus the information-only control at each time point. Log transformed outcomes and alternative modeling approaches such as Poisson and negative binomial will be considered in the event that assumptions for the linear model are violated. All models will include a fixed effect for sex assigned at birth (stratification variable) and a random intercept term to account for correlation in the response due to repeated measures within study participants over time. A random slope for participant will also be considered, as will the covariance structure of the errors (eg, exchangeable and autoregressive). Distribution of residuals will be examined to confirm that modeling assumptions are met. Because sample size is small (this study is not powered to detect clinically meaningful effect sizes) and the regression analyses are exploratory in nature, inference will focus on the size and direction of the total treatment effects rather than statistical significance.

Additional exploratory analyses will examine MASI's effects over time on HIV/AIDS knowledge and stigma using methods similar to those used for adherence and social support outcomes. We will also conduct descriptive analyses examining trends and patterns in user engagement with various components of the MASI interface over time.

Monitoring

This study's procedures have been determined to be low-risk, and we do not anticipate any adverse events as a result of study participation. While a data monitoring committee is not needed for this study, the research team will meet regularly to report on study progress and monitor compliance to this study and ethics protocols.

Our team has developed a set of standard operating procedures (SOP) for various scenarios that includes instructions for following up in response to concerns about participant distress, child abuse, sexual assault, underage sex, violence toward others, and suicidal ideation. Study staff are trained to identify situations of concern, including monitoring posts on the MASI app and participant comments or behavior during in-person study activities. Our data collection surveys include 2 items that assess for suicidal ideation [48,56] (ie, endorsement of "thoughts that you would be better off dead or of hurting yourself in some way" and feelings that one "would rather die than live with HIV"). If either item is endorsed, a message will be displayed to the interviewer at the end of the assessment to remind them to initiate the SOP. The SOP includes appropriate follow-up steps and procedures for situations where reporting to outside

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authorities is required by South African law (eg, mandatory reporting of child abuse).

Ethics Approval

This study has been approved by the ethical review boards at the University of Cape Town (Ref 600/2020) and Duke University Health System (Pro00103309). The ethical review boards will meet annually to review the trial progress and conduct throughout the trial period. The trial is registered at ClinicalTrials.gov (NCT04661878).

Results

Study screening via phone calls began in May 2022 and the first participant was enrolled on June 21, 2022. As of June 12, 2023, 81 participants had completed screeners, and 56 participants were considered preliminarily eligible for this study. Of these, 38 attended an in-person visit to confirm eligibility (including successful installation of the MASI app) and complete the baseline survey.

In total, 36 participants have been enrolled, have completed baseline, and have been randomized to a study arm. Further, 25 participants have completed a 3-month follow-up survey (100% retention rate to date), and 15 participants have completed a 6-month follow-up survey (79% retention rate to date).

Recruitment is anticipated to last through August 31, 2023, to reach the target enrollment of 50 participants, with study activities anticipated through February 29, 2024, and results available in 2024.

Discussion

Principal Findings

There is an urgent need for innovative interventions to improve ART adherence among adolescents and young adults in settings like South Africa. Digital health interventions are a promising approach allowing for adaptation and customization to unique needs and interests, widespread reach and scalability, and discreet use. They also allow for the integration of multiple strategies to elicit behavior change, promote connection, and support well-being. As access to technology and device ownership becomes more widespread, particularly in low- and middle-income countries, a “new type of digital divide” is emerging, characterized by inequities in access to high-quality web-based opportunities and experiences [57]; in this setting, it is argued that the “most vulnerable youths” also have the most to gain from technological interventions, yet are often the least supported by digital interventions. MASI seeks to address this gap by creating a platform tailored to the needs of adolescents and young adults in Cape Town, South Africa.

MASI is a comprehensive adherence-promoting app adapted for the South African setting that capitalizes on opportunities presented by mobile health (mHealth) platforms. MASI includes multiple BCTs to address the various complex barriers to adherence experienced by adolescents and young adults. Other studies have found that interventions with more BCTs are more effective than those with a limited amount of BCTs [23,58]. The multiple BCTs are integrated into a variety of features within the MASI app that allows users to explore and use features that are most helpful and desirable to them. The collection and analysis of app-generated paradata, in combination with survey data, will allow our team to explore participants’ use of MASI across features and lend insight into what features or BCTs may be most effective or enjoyed by participants.

The comprehensiveness and customizability of MASI are possible because it is built using HMP, an existing platform originally built to support youths in the United States [26,28]. Building mHealth interventions on existing platforms has numerous benefits, including technological sophistication and increased potential for scalability. By building MASI using an existing platform, rather than developing a mobile app from scratch, we benefited from more rapid development, substantial cost savings, and achieved a more sophisticated technological product than we would have otherwise. The use of the HMP platform also allows for the lessons learned from this RCT to be more readily applied to other interventions using the HMP platform, or the potential adaptation of MASI to meet the needs of other populations. If found to be feasible and acceptable, MASI could be implemented with adolescents and young adults in other parts of South Africa.

Limitations

Our team acknowledges limitations in our study design related to a small sample size and therefore limited power to establish the efficacy of MASI. However, the sample size is appropriate for a pilot study focused on feasibility and acceptability as primary outcomes. The follow-up time for this pilot RCT is also limited to 6 months, which will not allow us to establish the feasibility or acceptability of a longer-term intervention.

Although smartphone ownership is widespread among South African youths, not all adolescents and young adults with HIV will be eligible for our study, as participants will be required to have a smartphone to be eligible. Restricting this study to adolescents and young adults who have a smartphone will impact the generalizability of the findings. We also recognize that excluding adolescents and young adults without smartphones may deepen existing inequities and leave out individuals with limited access to resources and social support. Furthermore, participants may lose access to their devices during the course of this study, which may impact study outcomes. Future research is needed to examine best practices for reducing technology-related barriers to participation in the research process.

ART adherence will be analyzed using a self-reported adherence outcome. Self-reported adherence measures may be impacted by social desirability bias, which could lead to measurement error for the adherence outcome. Data from this pilot RCT will be used to inform a fully powered future trial that will also include biomarker data such as viral load.

Finally, it is possible that participants randomized to the intervention arm may discuss or show MASI to participants randomized to the control condition. We do not expect such contamination to be frequent, but we will measure contamination to better understand the extent to which it occurs.

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Data Availability

Data sharing is not applicable to this paper as no data sets were generated or analyzed during this study.

Authors' Contributions

MIM was the principal investigator for this study and conceived and designed this study with significant contributions from LBH-W, JH, KEM, and ETK. BM and MM were involved in the early implementation of this study, adaptation of the protocol to the local context, and continuing implementation of the protocol. THW and MA-M contributed to the implementation and refinement of this study's protocol. JRE and AP contributed to the statistical analysis plan. All authors critically reviewed each draft of the paper and approved the final version publication.

Conflicts of Interest

None declared.

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Abbreviations

ART: antiretroviral therapy
BCT: behavior change technique
CONSORT: Consolidated Standards of Reporting Trials
HMP: HealthMpowerment
MASI: *Masakhane Siphucule Impilo Yethu*
mHealth: mobile health
NIH: National Institutes of Health
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
SOP: standard operating procedure
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Protocol

Refocusing of Attention on Positive Events Using Monitoring-Based Feedback and Microinterventions for Patients With Chronic Musculoskeletal Pain in the PerPAIN Randomized Controlled Trial: Protocol for a Microrandomized Trial

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Abstract

Background: Chronic musculoskeletal pain (CMSP) affects between 13% and 47% of the population, with a global growth rate of 20.3% within the last 15 years, suggesting that there is a high need for effective treatments. Pain diaries have long been a common tool in nonpharmacological pain treatment for monitoring and providing feedback on patients' symptoms in daily life. More recently, positive refocusing techniques have come to be used, promoting pain-free episodes and positive outcomes rather than focusing on managing the pain.

Objective: This study aims to evaluate the feasibility (ie, acceptability, intervention adherence, and fidelity) and initial signals of efficacy of the PerPAIN app, an ecological momentary intervention for patients with CMSP. The app comprises digitalized monitoring using the experience sampling method (ESM) and feedback. In addition, the patients receive 3 microinterventions targeted at refocusing of attention on positive events.

Methods: In a microrandomized trial, we will recruit 35 patients with CMSP who will be offered the app for 12 weeks. Participants will be prompted to fill out 4 ESM monitoring questionnaires a day assessing information on their current context and the proximal outcome variables: absence of pain, positive mood, and subjective activity. Participants will be randomized daily and weekly to receive no feedback, verbal feedback, or visual feedback on proximal outcomes assessed by the ESM. In addition, the app will encourage participants to complete 3 microinterventions based on positive psychology and cognitive behavioral therapy techniques. These microinterventions are prompts to report joyful moments and everyday successes or to plan pleasant activities. After

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familiarizing themselves with each microintervention individually, participants will be randomized daily to receive 1 of the 3 exercises or none. We will assess whether the 2 feedback types and the 3 microinterventions increase proximal outcomes at the following time point. The microrandomized trial is part of the PerPAIN randomized controlled trial (German Clinical Trials Register DRKS00022792) investigating a personalized treatment approach to enhance treatment outcomes in CMSP.

Results: Approval was granted by the Ethics Committee II of the University of Heidelberg on August 4, 2020. Recruitment for the microrandomized trial began in May 2021 and is ongoing at the time of submission. By October 10, 2022, a total of 24 participants had been enrolled in the microrandomized trial.

Conclusions: This trial will provide evidence on the feasibility of the PerPAIN app and the initial signals of efficacy of the different intervention components. In the next step, the intervention would need to be further refined and investigated in a definitive trial. This ecological momentary intervention presents a potential method for offering low-level accessible treatment to a wide range of people, which could have substantial implications for public health by reducing disease burden of chronic pain in the population.

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KEYWORDS

experience sampling method; ESM; ecological momentary intervention; EMI; microrandomized trial; mobile health; mHealth; positive intervention; complex intervention; mobile phone

Introduction

Background

Musculoskeletal pain is defined as chronic if it exceeds a time frame of 3 months or recurs for >3 months [1]. Chronic musculoskeletal pain (CMSP) is estimated to affect between 13% and 47% of the population worldwide (eg, in the European Union [2], the United States [3], Canada [4], Australia [5], and low- to middle-income countries [6,7]). The global disease burden caused by CMSP has been increasing by 20.3% in the last 15 years [8]. Therefore, from a public health perspective, there is an urgent need for accessible and effective treatments. To determine the etiology and treatment of chronic pain, it is now widely suggested that a biopsychosocial model be followed [1,9,10]. CMSP is associated with a range of symptoms and disorders, mainly comorbid depression and anxiety [11-17], as well as low self-esteem [18-20], attention to and fear of pain [21,22], and avoidance behaviors [23-25]. Therefore, targeting psychological and behavioral aspects can be effective in treating chronic pain [26,27].

Diary methods including the experience sampling method (ESM) [28,29], where participants are prompted to answer several questionnaires per day during their daily life, have become common for monitoring psychological and somatic symptoms, yielding sufficient response compliance across health conditions and age groups [30]. Pain diaries, specifically paper or electronic versions, have proven high satisfaction, feasibility, and compliance for patients with CMSP, providing good psychometric properties [31-34]. However, using ESM pain diaries that remind participants to rate their level of pain once or several times per day [35] or provide personalized feedback [36] may hold restrictions, as this may promote attention to pain, that is, hypervigilance [37] or attentional bias [38-40], which in turn may even increase pain intensity [41]. This is why it has been suggested to focus on positive psychological processes [42] that may broaden attentional focus to positive aspects in life [43,44] and away from pain.

Similarly, positive interventions may be a strategy to promote a focus on resources and resilience [42,45,46]. Previous studies have shown that positive interventions that aim to increase awareness of positive aspects of life can improve pain intensity and catastrophizing, happiness, positive affect, depression, and anxiety [47-49]. In addition, targeting psychological aspects and comorbidities of chronic pain, cognitive behavioral therapy for low self-esteem has been shown to increase self-esteem, psychological functioning, and depression in populations with transdiagnostic psychiatric disorders [50,51]. Behavioral activation or activity scheduling aimed at increasing positive activities and experiences has shown a large meta-analytic effect in the treatment of depression [52] and first positive evidence in the treatment of chronic pain [53,54].

Following recent advances in digital technology, mobile health (mHealth) approaches such as ecological momentary interventions (EMIs) that deliver psychological treatment components in daily life [55,56] can be a promising way to provide early, low-level, accessible, and scalable treatment [57,58]. As EMIs are provided via mobile phone apps, they may help overcome barriers that can arise for interventions delivered in the clinical setting [28,55,59]. Several studies have shown that app-based approaches are feasible and can be effective in the treatment of chronic pain [60-62]. Furthermore, when patients with chronic pain are offered digitalized monitoring and feedback, they are willing to accept less frequent physician consultations [63].

Within the PerPAIN consortium investigating whether personalized allocation to psychological treatment approaches can enhance treatment effects in CMSP [64], we developed the PerPAIN app. The PerPAIN app targets positive refocusing of attention to positive events using digitalized monitoring, feedback, and microinterventions in daily life. Thus, the PerPAIN app is a complex intervention comprising several intervention components delivered at varying time points.

To evaluate behavioral interventions that comprise multiple intervention components, Collins et al [65] introduced a new

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approach, that is, the multiphase optimization strategy (MOST) [65,66]. In addition to the preparation and evaluation phases of an intervention, MOST introduces an optimization phase in which individual intervention components can be evaluated separately according to predefined optimization criteria [65,66]. This information can then be used to optimize the intervention as a whole to proceed to the evaluation phase [65,66].

Objective

In this paper, we describe an optimization trial to evaluate the intervention components of the PerPAIN app in line with MOST [65,66]. Specifically, we designed a microrandomized trial, an experimental research design developed to evaluate and optimize mHealth interventions (for a comprehensive introduction, see Qian et al [67]). By repeatedly randomizing individuals to different forms of an intervention component (ie, within-person randomization), this research design allows the investigation of the immediate effects of intervention components on repeatedly measured proximal outcomes [68], as opposed to distal outcomes measured once at the end of treatment or follow-up. In this microrandomized trial, we aim to (1) establish the feasibility for conducting a microrandomized trial in patients with CMSP (based on acceptability, satisfaction, compliance, adherence, and fidelity of delivering the intervention) and (2) investigate initial signals of efficacy of the feedback component (ie, daily and weekly feedback presented as texts or graphs) and the exercises delivered in microinterventions (namely, the journal of joyful moments, the positive data log, and the activity planner) on the proximal outcomes.

To this end, we hypothesize that feasibility criteria for conducting a microrandomized trial evaluating the PerPAIN app in patients with CMSP will be met (hypothesis 1).

Second, we hypothesize that within participants, momentary absence of pain (candidate primary proximal outcome) after providing feedback (as text or graph) at the end of a training day on which participants reported at least medium (ie, ≥4) absence of pain, positive mood, or subjective activity will, on average across time, be higher compared with time points when no feedback was provided on such days (within-person control condition; hypothesis 2).

Third, we hypothesize that within participants, momentary (a) positive mood and (b) subjective activity (candidate secondary proximal outcomes) after providing feedback (as text or graph) at the end of a training day on which participants reported at least medium (ie, ≥4) absence of pain, positive mood, or subjective activity will, on average across time, be higher compared with time points when no feedback was provided on such days (within-person control condition; hypothesis 3a and 3b).

Finally, we hypothesize that within participants, momentary (a) absence of pain, (b) positive mood, and (c) subjective activity after delivering a microintervention (ie, journal of joyful moments, positive data log, or daily activity planner) at an individually predefined time point will, on average across time, be higher compared with comparable time points on days on which no microintervention was delivered (within-person control condition; hypothesis 4a, 4b, and 4c).

We will also explore differences between the 2 types of feedback presentation and 3 types of microinterventions in terms of efficacy and time trends across the 12-week intervention period. In this paper, we describe the PerPAIN app and its intervention components in detail as well as the microrandomized trial implemented to investigate the feasibility and initial signals of efficacy. For a description of the clinical trial that this microrandomized trial is embedded in, we refer to the protocol by Beiner et al [64].

Methods

Procedure, Study Design, and Randomization

A total of 35 patients with CMSP will be recruited to undergo the PerPAIN mobile training, an mHealth app targeted at refocusing of attention on positive events, comprising digitalized monitoring using the ESM, personalized feedback, and EMIs. During a one-on-one structured briefing session, the participants will receive the study app preinstalled on a study smartphone. A trained member of the study team will explain the basic functionalities of the device and app to the participant and answer any potential questions before the participant takes the device into their daily life. The app sends different types of prompts each day for 12 weeks, including monitoring questionnaires, feedback presentations, and microinterventions. Answering all prompts requires approximately 15 minutes per day. A trained member of the study team checks in with the participants up to 6 times to answer any potential questions. The app follows a microrandomized design to evaluate the intervention components (see Multimedia Appendix 1 for a visualization). The training follows a fixed schedule across 12 weeks and entails 4 types of randomization procedures, resulting in a total of t=143 decision points, that is, time points when automated randomization of an intervention component takes place in the backend of the app. First, every evening during the 12 weeks (84 decision points), participants will receive microrandomized daily feedback (text vs graph vs none). Second, at the end of each training week (12 decision points), the participants receive microrandomized weekly feedback (text vs graph vs none). Third, in the second half of the training, the exercises participants are prompted to do as microinterventions are randomized (journal of joyful moments vs positive data log vs daily activity planner vs none) every day for 6 weeks (42 decision points). Fourth, starting from week 8, the weekly activity planner is randomized (on vs off) each week for the remaining 5 weeks (5 decision points). The ESM monitoring questionnaires prompted 5 times per day to serve as proximal outcome assessments. This microrandomized trial is nested in and carried out as part of the PerPAIN trial (see the protocol by Beiner et al [64] for a detailed description of this study, adhering to the Standard Protocol Items: Recommendations for Interventional Trials 2013 checklist [69]).

Participants

For this microrandomized trial, we aim to recruit adult patients (aged ≥18 years) experiencing CMSP for >3 months as a symptom of nonspecific chronic back pain, osteoarthritis, fibromyalgia syndrome, or rheumatoid arthritis. Participants must be able to see and use a mobile phone (including visual

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aids). Exclusion criteria include insufficient or unclear treatment of the underlying disease; severe visual impairment or inability to use a mobile phone; application for retirement or pension pending; ongoing psychotherapy; and severe physical, psychiatric, or neurological comorbidity (see the protocol by Beiner et al [64] for more details). Participants will be recruited primarily via an outpatient pain clinic.

PerPAIN App

Overview

The PerPAIN app is a stand-alone, app-based, self-help training with a total duration of 12 weeks, entailing 3 core components. First, it uses the ESM to monitor participants' momentary absence of pain, positive mood, subjective activity, and context several times a day in a positive pain diary (ie, monitoring). Second, the app provides personalized feedback to the participants on the basis of the monitoring data. Third, short exercises based on the principles of cognitive behavioral psychotherapy and positive psychology are provided, which are both taught and implemented within the daily life context (ie, microinterventions). Among these components, gamification elements are used to potentially increase compliance and user engagement.

Monitoring and Feedback

The ESM will be used to collect entries for a positive pain diary. The app will prompt participants to answer 4 monitoring questionnaires per day scheduled at semirandom time points within set blocks of time during their waking hours to record their momentary experiences and context. The ESM variables, that is, sleep quality, trust in the intervention, absence of pain, positive mood, and subjective activity, as well as appraisals of momentary and daily context, are rated on a 7-point scale. The monitoring questionnaire consists of 16 to 21 items (depending on the type of prompt and branching rules; see Multimedia Appendix 2 for a full list of items).

The PerPAIN app uses the monitoring data to provide feedback on the three main ESM monitoring and outcome variables: (1) absence of pain, (2) positive mood, and (3) subjective activity. We implemented three types of feedback: (1) immediate feedback presented directly after a monitoring questionnaire, (2) daily feedback presented after the last monitoring questionnaire of the day, and (3) weekly feedback presented after each week of monitoring. In accordance with our aim of refocusing of attention on positive events, immediate and daily feedback is only provided if it qualifies as *positive*. Therefore, immediate and daily feedback on each variable is only displayed if the (mean) score exceeds a predefined threshold of 4, that is, the center of the 7-point scale.

Immediate feedback is designed as a type of gamification. After the participant completes filling out the monitoring questionnaire, the conditions for providing positive feedback are checked. Whenever a variable is ≥4, meaning the participant is considered to be pain-free, in a good mood, or active, feedback is displayed at the end of the questionnaire, that is, the participant collects a pain-free, feel-good, or activity point, respectively (Multimedia Appendix 3).

Daily feedback is made available to the participant in a separate prompt after the last random monitoring questionnaire of the day. Before triggering a prompt for daily feedback, a server checks the conditions for providing positive feedback. Whenever the daily mean score of at least 1 of the 3 main ESM variables is ≥4, daily feedback is generated. If, at the same time, one of the other mean scores is <4, feedback for this variable is masked out. For example, if the mean scores of positive mood and subjective activity are both 5 and the mean score of absence of pain is 2, daily feedback is generated, but no value is presented for the absence of pain. Whenever daily feedback is available, a stratified randomization procedure is applied to determine the type of feedback presentation (1:1:1). Feedback is either presented as a bar chart or as a short text, or, in a control condition, no daily feedback is provided. Immediately after the feedback prompt, a monitoring questionnaire containing only the questions regarding the main ESM outcome variables is presented to assess proximal, that is, immediate effects of the daily feedback component.

Weekly feedback is made available to the participant in a separate notification after each week of monitoring, that is, in the morning of every 7th day at the earliest possible time for the app to interact with the participant. Unlike daily feedback, weekly feedback is always provided without any restrictions concerning the mean scores of the variables, that is, values <4 are also displayed, as this matches most accurately a paper-pencil positive pain diary that was piloted before this study. Again, a stratified randomization procedure is applied to set the type of feedback presentation (1:1:1). Weekly feedback is either presented as a bar chart or a short text (Multimedia Appendix 3), or, in a control condition, no weekly feedback is provided. Immediately after the feedback prompt, a monitoring questionnaire containing only the questions regarding the main ESM outcome variables is presented to assess the proximal effects of the weekly feedback component.

Microinterventions

In addition to the monitoring and feedback components, the PerPAIN app incorporates the principles of EMI. Specifically, it entails 3 exercises implemented as microinterventions alternating across the 12-week training period (Figure 1). In the first half of the training, participants are prompted to complete 1 exercise presented as a microintervention per week. As previously used in an EMI targeted at ecological translation of principles of compassion-focused therapy to daily life [70], the app will offer enhancing, consolidating, and interactive microinterventions. Initially, each exercise is introduced to the participant in an introduction block at the beginning of a new week (ie, enhancing). Once familiar with the microintervention, the participants set the time they wish to be prompted to complete the exercise once a day in a separate notification (ie, consolidation). In addition, if indicated by the participants' answers on a monitoring questionnaire, an exercise is prompted interactively. In the second half of the training, starting from week 7, consolidating and interactive microinterventions alternate each day according to the randomization procedure described in the *Procedure*, *Study Design*, *and Randomization* section.

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The journal of joyful moments is based on a positive intervention called the "3 good things" intervention [71]. In a continuously growing list structured like a diary, participants collect moments that were happy or joyful for them; things that made them smile; or, in general, made them feel good. The aim of this technique is to draw attention to positive things that happen in daily life, increase well-being, and decrease feelings of depression [71]. Participants can make a new entry ("Please note your joyful moment") once per day at the consolidation prompt, manually whenever they wish to make an entry, or during a monitoring prompt whenever they are likely to have experienced a joyful moment, according to their answers in a monitoring questionnaire. For this purpose, the following conditions were defined: (1) the participant indicates that they are in a good mood, that is, ≥4; (2) the participant indicates that their absence of pain is high, that is, ≥4; and (3) the participant indicates a high level of activity, that is, ≥4 (Multimedia Appendix 4). Once the enhancing exercise is completed, the participant can (in all following training weeks) make an entry in the journal and look at the growing list of joyful moments from the home screen of the app (Multimedia Appendix 5).

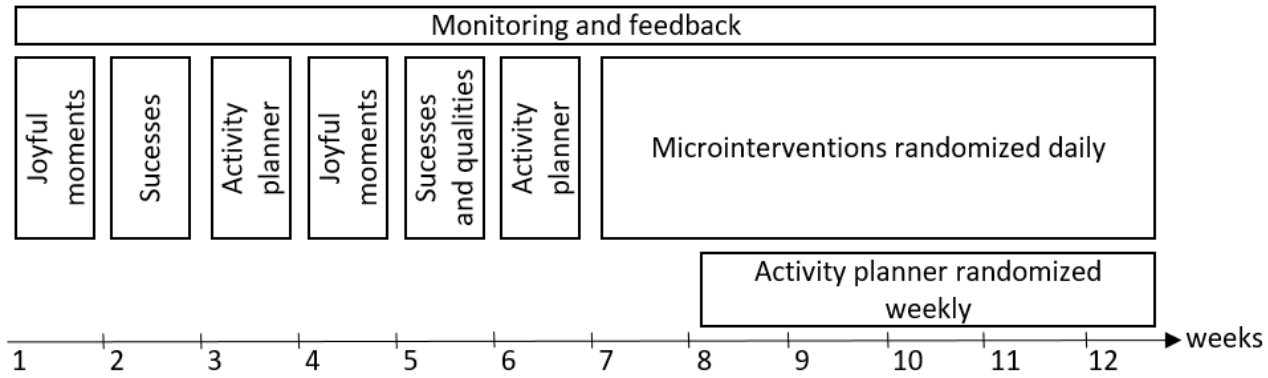
The positive data log is based on an intervention manual developed to increase self-esteem [72]. The aim of a positive data log is to help correct information-processing errors [73]. The microintervention consists of two parts: (1) collecting small successes during daily life and (2) inferring positive qualities of oneself from the list of successes. When this microintervention is first introduced in week 2, participants collect small or large successes they have experienced in their daily life in a diary. A success can be anything positive or successful the participant does, everything they do well, and anything that they made progress with or put effort into. The aim of this technique is to draw attention to one's own small or big successes in daily life to build self-efficacy and confidence instead of focusing on things that go wrong [72]. Participants can make a new entry ("Please note your success") (1) once per day at the consolidation prompt, (2) manually whenever they wish to make an entry, or (3) during a monitoring prompt whenever they are likely to have had a success according to their answers in a monitoring questionnaire or whenever they do not feel well and will likely benefit from redirecting their attention to something positive. For this purpose, the following conditions were defined: (1) the participant indicates that they have experienced a positive event, (2) the participant indicates that they are at work, school, or university to uncover work-, school-, or university-related successes, and (3) the participant indicates that they are in a bad mood or in pain (Multimedia Appendix 4).

In week 5 of the training, when this microintervention is repeated (Figure 1), the section on positive qualities is added to the positive data log. After collecting several successes in their daily life, that is, observable behavior, participants are guided to infer positive qualities that underlie those successful behaviors by answering the question "What qualities does a person have that shows these behaviors?" Thus, participants start a second list with their own positive qualities. Each time the participant makes an entry into their positive data log, they are invited to add a positive quality. Once the enhancing of each part of the exercise is completed, the participant can (in all following training weeks) make an entry to the positive data log and look at the growing list of successes and positive qualities from the home screen of the app (Multimedia Appendix 5).

The activity planner is based on a manual for behavioral activation [74], a behavioral therapy technique used in the treatment of depression [75] and chronic pain [76]. In behavioral activation, pleasant activities are systematically increased to change corresponding cognitions. In an introductory block, the participant is educated about the interdependence between pleasant activities and positive thoughts and feelings (Multimedia Appendix 5). The participant then creates their own activity plan for the week in a guided process. From a list of activities from different life domains, that is, sociability, hobbies and free time activities, sports and physical activities, culture and education, nature and gardening, and self-care and delight, the participant is invited to choose 3 activities or insert activities they would like to do in the following week. After choosing each activity, the participant is instructed to define the number of times they would like to do the activity. This step is based on the idea that progress toward specific goals can be monitored easily and can therefore be more motivating [74]. During the activity week, the participant can monitor their progress with their planned activities. Each morning, the participant receives a notification reminding them of their planned activities. Optionally, they can plan an additional activity for the upcoming day only (ie, daily activity planner). Participants can make a new entry ("Please tick off all activities you have done today") once per day at the consolidation prompt or manually by entering the activity planner from the home screen of the app. On the last consolidation prompt of the activity week, the planned and actual frequencies of each activity are presented to the participant, and they can indicate whether they have achieved, exceeded, or not accomplished their goal. The achievement or exceedance of goals is rewarded using the gamification elements described in the *Gamification* section.

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Figure 1. Timeline of the PerPAIN training intervention components.



Gamification

Gamification is a concept that integrates game elements into nongame contexts. It builds on the engaging and motivating potential of games [77]. In mHealth, gamification elements can be used to increase compliance and shape and reward desired behaviors [78]. After downloading an mHealth app, user engagement can vary greatly (eg, see the study by Rahman et al [79]), which is why it is a common objective of researchers to design apps to optimally support engagement [80]. In the PerPAIN app, we implemented three gamification elements aimed at increasing compliance and providing rewards: (1) an overall training score, (2) immediate feedback designed as points, and (3) a progress bar. The overall training score increases whenever the participant answers a prompt or makes an entry (Multimedia Appendix 3). Hence, this gamification element is aimed at increasing users' overall engagement with the app. In the overall introduction to the app as well as the enhancing blocks introducing the microinterventions, the participant is informed which actions lead to an increase in the training score (eg, answering a monitoring prompt, making an entry in the journal of joyful moments, or achieving an activity goal). After a monitoring prompt, the participant can receive 3 types of points (ie, pain-free, feel-good, and activity points), whenever the values of the 3 scales were ≥4. These points are collected throughout the training and mainly serve as positive feedback but may also reinforce behaviors that lead to reporting higher values of absence of pain, positive mood, or subjective activity in the monitoring questionnaire. The overall user advancement is presented to the participant on a summary page that includes a progress bar displaying progression throughout the training using an icon of a person walking on a path of 12 tiles representing the 12 training weeks. This gamification element aims to increase the transparency and completion rates of the training.

Measures

We will assess the feasibility of delivering the smartphone training and the effects of intervention components.

Feasibility Measures

In line with previous research on the feasibility of delivering EMIs [70,81,82], feasibility measures will include acceptability, intervention adherence, and fidelity. Acceptability will be assessed in a debriefing questionnaire rating satisfaction with the intervention, ease of use, accessibility, and comprehensiveness [70,81,82]. In addition, we will use the user version of the mobile app rating scale [83] to assess the subjective quality of the app. Adherence to the mobile training will be operationalized by the completion rates of the intervention components (ie, mean number of monitoring questionnaires, consolidating or interactive tasks completed/wk, and [mean] number of feedback prompts answered). As a core feature of the PerPAIN training is the delivery of intervention components in daily life, that is, in varying contexts, aiming to support a positive attention focus while reducing transfer effects, we will measure fidelity by the variety of contexts in which participants engage with the app and the proportion of participants who still use the app at the end of the 12-week training period. To establish levels of feasibility, we will classify our feasibility outcomes using a traffic light system into 3 categories, that is, green=feasibility fully established, yellow=feasibility established with a need for modification of the study procedures, and red=feasibility not established [70] (Table 1).

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Table 1. Feasibility criteria of delivering the PerPAIN training.

Category	Acceptability	Adherence	Fidelity
Red (feasibility not established)	Low satisfaction in the debriefing questionnaire (ie, mean satisfaction rating of ≤3 on a 7-point scale) and the uMARS[a] (ie, mean subjective quality rating of ≤2 on a 5-point scale)	Poor compliance to the monitoring and feedback component (≥60% of the participants answering on average <50% of the questionnaires/d and ≥60% of the participants viewing their provided feedback on average less than once/wk) and EMI[b] tasks (ie, mean number of consolidating or interactive EMI tasks completed/wk is <0.8)	Poor use of the app overall (≥60% of the participants using the app for <3 wk) and poor variability of intervention contexts (≥60% of the participants using the app in 1 context exclusively, as measured by the "current activity" item)
Yellow (feasibility established but study procedures need modifying)	Fair satisfaction in the debriefing questionnaire (ie, mean satisfaction rating of >3 on a 7-point scale) and the uMARS (ie, mean subjective quality rating of >2 on a 5-point scale)	Fair compliance to the monitoring and feedback component (≥60% of the participants answering on average at least 50% of the questionnaires and ≥60% of the participants viewing their provided feedback on average at least once/wk) and EMI tasks (ie, mean number of consolidating or interactive EMI tasks completed/wk is ≥0.8)	Fair use of the app overall (≥60% of the participants using the app for ≥3 wk) and fair variability of intervention contexts (≥60% of the participants using the app in at least 2 contexts, as measured by the "current activity" item)
Green (feasibility fully established)	Moderate to high satisfaction in the debriefing questionnaire (ie, mean satisfaction rating of >4 on a 7-point scale) and the uMARS (ie, mean subjective quality rating of >3 on a 5-point scale)	Moderate to strong compliance to the monitoring and feedback component (≥80% of the participants answering at least 50% of the questionnaires and ≥80% of the participants viewing their provided feedback on average at least once/wk) and EMI tasks (ie, mean number of consolidating or interactive EMI tasks completed/wk ≥1)	Moderate to high use of the app overall (≥80% of the participants using the app for ≥ 6 wk) and moderate to high variability of intervention contexts (≥80% of the participants using the app in at least 2 contexts, as measured by the "current activity" item)

[a]uMARS: user version of the mobile application rating scale.

[b]EMI: ecological momentary intervention.

Candidate Primary Outcome

The candidate primary outcome of the microrandomized trial is the proximal measure of the absence of pain assessed in the monitoring questionnaires. Specifically, we will investigate the immediate effect of the daily feedback component on the absence of pain rating measured on a 7-point scale in the monitoring questionnaire presented either directly after daily feedback was displayed or in a separate prompt without feedback being displayed (control condition), depending on the microrandomization (Multimedia Appendix 1).

Candidate Secondary Outcomes

The 2 candidate secondary outcomes of the microrandomized trial are the proximal measures of positive mood and subjective activity assessed on a 7-point scale in the monitoring questionnaires. As for the candidate primary outcome, we will use the ratings given in the monitoring questionnaire presented either directly after daily feedback was displayed or in a separate prompt without feedback being displayed (control condition), depending on the microrandomization.

Time-Fixed Covariates

In line with the PerPAIN study [64], we will use the treatment condition (personalized vs nonpersonalized treatment allocation), gender, and baseline pain severity (as measured by the German version of the Multidimensional Pain Inventory [84]) as covariates in all models.

Sample Size

This microrandomized trial forms part of the PerPAIN randomized controlled trial [64]. Given that we expect to include 35 participants in this microrandomized trial, we performed power analysis for microrandomized trials [85] to determine the effect sizes we will be able to detect in the given study setup with sufficient power of at least 80% testing at α=.05 (for a description of the tool, see Seewald et al [86]).

Regarding the daily feedback component with 1 decision time point for a total of 84 days, we will be able to detect an average proximal treatment effect of 0.16 with a power of 80.4% and a sample size of 35, assuming that at least 1 ESM variable is >4 (therefore, available for feedback) on every second day of the study (ie, availability parameter of 0.5). Regarding the microinterventions with 1 decision time point for a total of 42 days, we will be able to detect an average proximal treatment effect of 0.18 with a power of 80.8%, a sample size of 35, and an availability parameter of 1, as microinterventions will be prompted every day without any restrictions. Intervention components randomized weekly (weekly feedback and weekly activity planner) do not produce sufficient power to be tested for proximal treatment effects in this study.

Assessment of Safety in the Microrandomized Trial

Throughout participation in this microrandomized trial, we will monitor any serious adverse events, such as serious incidents resulting in death or hospitalization, and adverse events (see the protocol by Beiner et al [64] for more details). Furthermore, we will record any potential adverse device effects and technical problems reported by participants, such as crashing of the app or bugs. Whenever possible, we will fix technical problems immediately and introduce a new version of the app for future participants using the app.

Statistical Analysis

To address hypothesis 1, we will use descriptive statistics and 95% CIs as appropriate to evaluate the feasibility of delivering

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the PerPAIN training in line with the predefined feasibility criteria described in Table 1.

To test initial signals of efficacy on candidate primary and secondary proximal outcomes, we will use the weighted and centered least squares estimator to estimate the causal excursion effect of the daily feedback component [87,88]. To investigate whether there is an overall effect (ie, on average across time) of daily feedback on our candidate primary proximal outcome momentary absence of pain (hypothesis 2), we will calculate the weighted and centered least squares estimator by specifying a generalized estimation equation with absence of pain in the subsequent monitoring questionnaire as the proximal outcome, with a treatment indicator specifying whether daily feedback was delivered (=1) or not (=0), including 84 decision points, that is, once every day for 12 weeks. As feedback is only delivered whenever the daily average of one of the main outcome variables was >4, we will create a new variable *good_day* (1=at least 1 outcome is >4 and 0=no outcome is >4) serving as an availability indicator in the equation. The analysis will be controlled for time-fixed covariates. To address hypotheses 3a and 3b, we will repeat this procedure using our candidate secondary proximal outcomes: (a) momentary positive mood and (b) momentary subjective activity at the subsequent monitoring questionnaire as the proximal outcome. In the next step, to explore the effect of different feedback types individually (ie, as text or graph), we will include 1 treatment indicator for each type of feedback. Furthermore, we will explore whether there is a time trend in the effects of daily feedback by including a variable *training_day* counting the days in the study (with the value 0 on the first day).

To investigate the immediate effects of the microinterventions, we will use momentary absence of pain, positive mood, and subjective activity rated on a 7-point scale in the next monitoring questionnaire prompted after the predefined consolidation time, unless the consolidation prompt was the last prompt of the day, to avoid overnight effects. To determine whether there is an overall effect, that is, on average across time, of the microinterventions (hypotheses 4a, 4b, and 4c), we will specify 3 generalized estimation equations with a treatment indicator specifying whether a microintervention was delivered at the individually predefined consolidation time on that day (=1) or not (=0), that is, control condition, using each outcome: (a) momentary absence of pain, (b) momentary positive mood, and (c) momentary subjective activity at the subsequent prompt as a proximal outcome, including 42 treatment occasions, that is, once every day between week 7 and 12. There will be no availability indicator, and time-fixed covariates will be included. We will then include 1 treatment indicator for each type of intervention to investigate the effects of the 3 microinterventions individually (ie, journal of joyful moments, positive data log, and daily activity planner) and explore the time trend in the effects of the microinterventions by including the *training_day* indicator. Data analysts will be blinded to the treatment indicators.

Results

The Ethics Committee II of the University of Heidelberg approved this study (2020-579N) on August 4, 2020. At the time of submission of this protocol (October 10, 2022), we are working with trial protocol version 6 (October 6, 2021). The outcome assessments are ongoing. The first enrollment in this microrandomized trial was conducted in November 2021. As of October 10, 2022 (the date of submission), 24 participants were enrolled in the microrandomized trial, and 13 participants completed the training. Data will not be accessed for interim analysis before the completion of all outcome assessments. The last assessment for the last participant is scheduled for July 2023, and we expect the results to be published in early 2024.

Discussion

Extending the widely used method of symptom monitoring using pain diaries, we will investigate the feasibility and initial signals of efficacy of a newly developed self-help app targeted at refocusing of attention to positive events with different intervention components based on principles of EMI. EMIs offer the great advantage of delivering intervention components in various contexts in daily life [28,55-59]. EMIs are frequently implemented as hybrid interventions [70,81,82] or stand-alone interventions, such as the PerPAIN app. Owing to the microrandomized design, we will be able to evaluate individual intervention components separately to optimize the intervention as a whole and proceed to the evaluation phase in line with MOST [65,66]. The results of this optimization trial will show whether delivering an app-based self-help training with different intervention components is feasible. Furthermore, we will investigate its acceptability, satisfaction, compliance, adherence, and fidelity in a population of patients with CMSP. The results of this trial promise first insights into the potential proximal effects of delivering daily feedback and prompting microinterventions to improve the absence of pain and increase positive mood and subjective activity. The results of this trial may suggest ways to optimize these intervention components. For instance, the results may point toward 1 type of feedback presentation (eg, as a graph) or microintervention (eg, activity planner) having greater initial effects than another. Alternatively, there may be initial evidence of a time trend across the 12 weeks of the training, which could inform the setup of future studies.

If this trial is successful, the next step will be to proceed to a confirmatory trial with a larger sample powered to detect the expected effect sizes established in this trial.

However, for the interpretation of the results of this study, it should be considered that the effect sizes that will be established may be diminished because of the design of the PerPAIN study this microrandomized trial is nested in. As a result of the randomization procedure to investigate a personalized treatment approach (see the protocol by Beiner et al [64]), 50% (17/35) of the participants in this microrandomized trial will be allocated to participate in the PerPAIN training according to a personalized treatment allocation procedure, whereas the other half will be allocated to the PerPAIN training against the personalization approach.

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Positive psychological approaches seem to be promising for the treatment of CMSP [42,45-49]. Therefore, investigating how these approaches can be implemented using mHealth technologies is an important step in tackling the global disease burden caused by CMSP. Overall, EMIs using microinterventions offer a great opportunity to provide low-level treatment in the context of daily life, thereby overcoming barriers to interventions delivered in the clinical context [55-57,59]. After positive scientific evaluation, this type of treatment promises significant public health impact as it is scalable to a large population of patients with CMSP, which may ensure continuity of care and reduce on-site consultations [63].

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Visualization of the microrandomized design.
[DOCX File , 154 KB - resprot_v12i1e43376_app1.docx]

Multimedia Appendix 2
Full list of the monitoring items.
[DOCX File , 19 KB - resprot_v12i1e43376_app2.docx]

Multimedia Appendix 3
Examples of immediate (left) and daily (middle) feedback and gamification (right) in the PerPAIN app.
[DOCX File , 114 KB - resprot_v12i1e43376_app3.docx]

Multimedia Appendix 4
Conditions for interactive microinterventions prompted within a monitoring questionnaire.
[DOCX File , 17 KB - resprot_v12i1e43376_app4.docx]

Multimedia Appendix 5
Examples of microinterventions in the PerPAIN app (from left to right: journal of joyful moments, positive data log, and activity planner).
[DOCX File , 172 KB - resprot_v12i1e43376_app5.docx]

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Abbreviations

CMSP: chronic musculoskeletal pain
EMI: ecological momentary intervention
ESM: experience sampling method
mHealth: mobile health
MOST: multiphase optimization strategy

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Protocol

mHealth Intervention for Vietnamese Living With Diabetes: Protocol for a Stepped Wedge Pilot Study

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Abstract

Background: Evidence indicates participation in a diabetes self-management education and support program improves self-care behaviors and hemoglobin A_{1c}. Language and cultural differences may be barriers to program participation resulting in ineffective self-management, but these factors can be addressed with appropriate interventions. Given the high health care costs associated with diabetes complications, we developed a multicomponent, culturally tailored Self-Management Mobile Health Intervention for US Vietnamese With Diabetes (SMart-D).

Objective: This study aims to evaluate the SMart-D intervention's feasibility, acceptability, and effectiveness with intentions to scale up the intervention in the future. This mixed methods study incorporates the Reach, Effectiveness, Adoption, Implementation, Maintenance framework to evaluate the intervention.

Methods: This stepped wedge randomized controlled pilot study will be conducted over 2 years in collaboration with primary care clinics. Eligible participants are patients with type 2 diabetes who are receiving health care from participating clinics. Clinics will be randomly assigned to an implementation date and will begin with patients enrolling in the control period while receiving standard care, then cross over to the intervention period where patients receive standard care plus the SMart-D intervention for over 12 weeks. Focus groups or interviews will be conducted with clinicians and patients after study completion. Qualitative data will be analyzed using NVivo. Outcomes on self-care behavior changes will be measured with the Summary of Diabetes Self-Care Activities scale and clinical changes will be measured using laboratory tests. A generalized linear mixed-effect model will be used to compute time effect, clustering effect, and the interaction of the control and intervention periods using SAS (version 9.4; SAS Institute).

Results: We hypothesize that (1) at least 50% (n=5) of eligible clinics and 50% (n=40) of eligible patients who are invited will participate, and at least 70% (n=56) of patients will complete the program, and (2) patients who receive the intervention will have improved self-care behaviors and clinical test results with at least 75% (n=60) of the patients maintaining improved outcomes at follow-up visits compared with baseline, and participants will verbalize that the intervention is feasible and acceptable. As of August 2023, we enrolled 10 clinics and 60 patients. Baseline data results will be available by the end of 2023 and outcome data will be published in 2025.

Conclusions: This is the first Vietnamese diabetes self-management education and support intervention that leverages mobile health technology to address the barriers of language and culture differences through collaboration with primary care clinics. This study will provide a better understanding of the implementation process, demonstrate the potential effectiveness of the intervention, accelerate the pace of moving evidence-based interventions to practice among the US Vietnamese population, and potentially provide a replicable implementation model that can be culturally adapted to other non-English speaking ethnic minorities.

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KEYWORDS

Vietnamese; type 2 diabetes; diabetes self-management; mobile health technology; intervention study; stepped wedge design; mobile health; intervention; mobile app; digital health; diabetes; self-management; awareness; mhealth; implementation

Introduction

Diabetes is a leading cause of death in the US Vietnamese population [1]. The term US Vietnamese will be used hereafter to indicate Vietnamese individuals living in the United States. Members of racial and ethnic minority groups are at an increased risk for developing type 2 diabetes (T2D) and experiencing complications from this disease [2]. After being diagnosed with T2D, individuals face many physical, emotional, and social challenges including the need to know about the strict diet and medication regimen and necessary lifestyle changes [3].

Nutrition is often the focus of self-management among US Vietnamese with diabetes, and little focus is placed on medication, blood glucose monitoring, risk reduction behaviors, or personal strategies for health promotion [4-6]. Self-management and health behaviors are influenced by cultural beliefs, practices, and availability of resources [7]. Ineffective self-management can lead to complications and increased health care costs. Glycemic control can reduce the risks of diabetes complications, but few resources are available to educate and support self-management among US Vietnamese. Despite the capability of improving health behaviors with evidence-based interventions, efforts to adapt and disseminate linguistic and culturally appropriate diabetes self-management education and support (DSMES) are lacking among this group.

Nguyen and Edwards [6] reported that linguistic and cultural differences as well as transportation issues are the main barriers to participating in existing DSMES programs among study participants. Many US Vietnamese living with T2D receive information from family, friends, and others diagnosed with diabetes for knowledge and decision-making around self-care [6]. Without formal DSMES, knowledge gained from informal education may negatively influence self-care behaviors. Low diabetes literacy hindered effective disease self-management, which is a striking finding among the participants that was revealed in every interview [6]. A needs assessment survey identified the community's desire and need for formal diabetes education and support to be offered in the Vietnamese language in Oklahoma [8]. Studies showed that having limited English proficiency reduced the ability of study participants to obtain appropriate information to manage chronic conditions, such as heart disease and diabetes [9,10].

The 2022 National Standards for Diabetes Self-Management Education and Support [11] emphasized the need to provide services that embrace cultural differences, address social determinants of health, and use technological engagement platforms and systems. These National Standards cited strong evidence supporting DSMES delivery through digital, telehealth, telephone, SMS text messaging, and web-based or mobile phone app [11].

Nguyen et al [12] conducted a systematic review of intervention studies focused on improving health behaviors and health care services using mobile technology among the Vietnamese population and found the main device used was mobile phones. These devices were used for patient remote monitoring, assessment, or counseling for health behavior change through SMS text messaging, internet access, email, and videos. SMS text messaging was most frequently used as the primary intervention, which is consistent with many studies that have evaluated the usage of mobile health (mHealth) to support lifestyle and health behavior changes in other populations [13-16]. Using SMS text messaging to provide health education and monitor chronic diseases was feasible and acceptable mainly due to the low cost and easy operation of SMS text messaging [12]. However, the feasibility and acceptability of SMS text messaging to provide education and support among US Vietnamese patients is unknown and thus the aim of this study's protocol.

In response to the burden of diabetes and the need to afford an opportunity for US Vietnamese with T2D an intervention that meets the National Standards [11], this Self-Management Mobile Health Intervention for US Vietnamese With Diabetes (SMart-D) study protocol will provide linguistically and culturally relevant diabetes education, health behavior change support, and emotional support through secure mHealth technology to help patients understand the disease process and gain skills to manage their condition. This protocol aims to describe a pilot study to test the acceptability and feasibility of the SMart-D intervention, determine the effectiveness, and assess its sustainability using the Reach, Effectiveness, Adoption, Implementation, Maintenance (RE-AIM) framework to measure outcomes. Focus groups or individual interviews will be conducted at program completion to assess intervention acceptability and participant experiences as well as perceived barriers to sustaining the behavior change.

Methods

Study Design

This study is a stepped wedge randomized controlled pilot study to implement a multicomponent intervention among US Vietnamese with T2D. The stepped wedge design allows the practical staggering of intervention delivery while enabling all participants to receive it. The intervention, incorporating both synchronous and asynchronous components over 12 weeks, is based on the patient empowerment and Health Belief Model and intends to target the unique needs of Vietnamese-speaking patients. Participants will receive a print booklet covering

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self-management strategies, daily mHealth SMS text messaging to promote self-care and enhance self-efficacy, and weekly nurse calls to coach and provide support for self-management goals. Offering these ongoing contacts will help to motivate participants to follow the care plan and engage in better self-management.

After the 12-week intervention, participants will opt to accept or decline a low dose of 1 monthly SMS text message and 1 monthly nurse call alternating biweekly for the next 9 months. This study will evaluate pre- and postintervention measures at 3, 6, 9, and 12 months from baseline. This framework will allow a comparison of outcomes between the standard care and intervention period as well as between baseline and follow-up data. To ensure the high quality of this pilot, this study will follow the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2013 checklist [17,18].

Intervention Components

The intervention has 3 components: print materials, mHealth SMS text messages, and nurse coaching telephone calls. Print education materials and follow-up telephone calls have been shown to be incrementally effective on their own [19-23]. Combining these components along with mHealth SMS text messaging may achieve a more significant effect. All 3 intervention components were assessed for usage and usability by piloting the components with 2 nurses and 4 Vietnamese individuals with T2D. Modifications to the intervention components were made based on the participants' feedback.

All participants will receive a copy of printed materials entitled Small Change, Big Impact for People with Diabetes, which covers 8 chapters focusing on patient-centered strategies and incorporating cultural foods and practices. The content focuses on the day-to-day activities of living with diabetes with respect for the US Vietnamese individual's life experiences helping participants (1) understand diabetes, (2) monitor blood glucose, (3) stay physically active, (4) cope with the diagnosis, (5) make healthy food choices, (6) understand Eastern and Western medications, (7) manage hypo- or hyperglycemia, and (8) prevent diabetes complications. The education content incorporates the Association of Diabetes Care and Education Specialists framework [24] and materials developed by the Centers for Disease Control and Prevention [25] diabetes resources and were adapted for cultural relevancy. All printed materials are available in Vietnamese and English language, side-by-side, to help participants learn the terminologies to communicate with their providers.

An mHealth SMS text message will be used to deliver educational content in the Vietnamese language via video, audio, and SMS text messages based on a schedule when specific criteria are met. The prerecorded videos are embedded in the SMS text messages and feature a registered dietician consulting with participants on developing a healthy eating plan that incorporates Vietnamese food and a pharmacist demonstrating insulin injection and self-monitoring of glucose. The secure mHealth platform will enhance both accurate, timely data collection across sites and ensure secure data transmission. During the 12-week intervention at least 1 message will be sent daily; up to 6 messages may be sent depending on the participants' responses. If a participant does not respond to messages for 7 consecutive days, the coach nurse will assess any technical issues during the routine weekly calls. After the 12-week intervention, messages will be sent at a lower dose once monthly for the remaining follow-up period to allow continuing engagement with participants as they desire.

Participants will have a telephone coaching call with a Vietnamese-speaking nurse once per week during the 12-week intervention period. The day and time of these phone calls will be arranged between the participant and the nurse. Every week, participants will be encouraged to set one or more goals related to the scheduled lesson. During these coaching calls, the nurse will follow a script and use a motivational interviewing approach [26,27] to review participants' goals and identify barriers, review status on self-management strategies, help participants build a capacity to problem solve, improve self-efficacy, and support health behavioral change. The use of a motivational interviewing approach by the coach nurse will encourage each participant's intrinsic motivation to engage in self-care, change health behaviors, and improve their glycemic control [28]. Using a checklist, the nurse will document the content of each call and emphasize key educational topics including discussion of weekly goal attainment, discussion of barriers if the goal is not met, setting of goals for next week's lesson, and provision of the opportunity to obtain personalized feedback if participants experience any challenges, and address concerns.

Patient and Public Involvement in Intervention Development

The SMart-D intervention was developed with substantial engagement with the Vietnamese community of Oklahoma, including leaders of the Asian District Cultural Association, faith-based leaders, health care professionals, and people with T2D. This 23-member group served as an advisory board for over a 1-year period and highlighted the need to develop a feasible and appropriate study design as well as the need to incorporate language and culture-relevant information [29]. By incorporating the Health Belief Model, this SMart-D intervention emphasized the need to reduce diabetes complication risks and motivated participants to take into account the central concept of risk, thus encouraging health behavior change [30]. Accordingly, both Vietnamese language and cultural practices are strong components of this intervention, and using the stepped wedge design allowed all consented participants to receive the intervention. In addition, the intervention was preliminarily tested with a group of targeted individuals prior to implementation to ensure the usage and usability of the education content and method of delivery. After this study is completed, reports will be made available to clinics and patients in the form of a newsletter as well as a scheduled in-person seminar where the research team will describe findings with each individual clinic.

Study Procedures

Inclusion or Exclusion Criteria

There are 2 levels of inclusion and exclusion: clinics and patients. Clinics are eligible if they currently serve more than 5 US Vietnamese adults diagnosed with T2D. T2D patients who

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identify as Vietnamese adults and receive health care at a participating primary care clinic will be eligible. Patients must be 18 years of age or older, diagnosed with T2D, able to provide verbal or written consent in English or Vietnamese, able to speak or read Vietnamese, and possess or have access to a mobile phone.

The exclusion criteria at the clinic level are those clinics that currently serve fewer than 5 US Vietnamese patients with T2D. At the patient level, individuals younger than 18 years of age, individuals visiting the United States as tourists, those with cognitive impairment, those unable to provide consent in English or Vietnamese, and pregnant women are excluded as pregnancy affects diabetes care differently at each trimester [11]. Patients will be terminated early if they become pregnant or explicitly refuse to have blood drawn as ordered by their physicians.

Clinic Recruitment and Consent Process

Primary care clinics will be identified according to the geographical area in which many US Vietnamese patients receive health care services. Prior to recruiting clinics of large health care systems, permission will be sought from the responsible administrators and medical directors. Independent and privately owned clinics will receive an invitation letter describing this study and its aims. Clinics that respond to the invitation will be assessed for eligibility by the principal investigator (PI). Clinics that do not respond to the initial mailed letter within 2 weeks will be contacted by email or phone.

Once the clinics are determined to be eligible, the PI will contact the office manager and the health care provider to ask for approval for the clinics to participate and obtain consent from these individuals. Next, the PI will set up 2 sessions of 1 hour briefing about this study and 1 hour training with clinic staff. Then participating clinics will identify and refer interested patients with a diagnosis of T2D via telephone contact or email.

Patient Recruitment and Consent Process

This study will recruit 80 patients from 10 clinics, approximately 8 patients from each clinic. We expect to have approximately 5 to 6 patients complete this study from each clinic giving a 70% (n=56) study completion rate. The power calculation was conducted by using the linear mixed effect modeling of the R (R Foundation for Statistical Computing) package "*swdpwr*," which gives power of 0.95 for the alternative hypothesis treatment effect change of 0.005 (2-sided type I error 0.05). The recruitment strategy includes a letter and flyer to be sent by the clinics with the research team's contact information. Study information will be provided to those who reach out to a research team member with their interest and an opt-out contact will be applied after 3 days of receiving the letter. A member of the research team will arrange a time to meet with eligible patients to discuss the option to participate in this study, complete the informed consent procedure, complete this study's screener, and enroll them in this study if the individual is both eligible and interested. All patients will have the option of completing the consent and confidentiality forms in English or Vietnamese language. Upon full study enrollment, a member of the research team will collect baseline data.

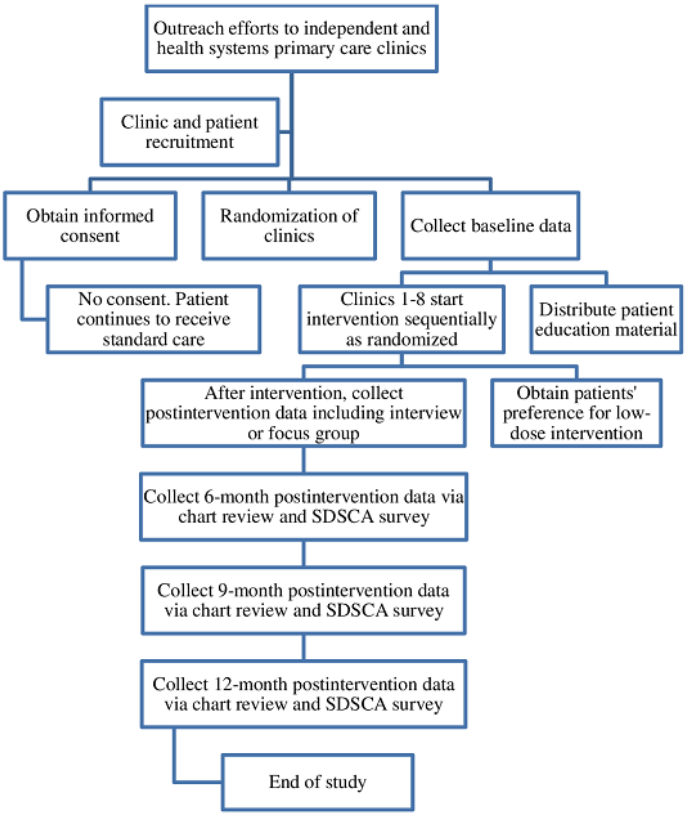
Randomization

Because individual randomization is not feasible due to potential contamination of the intervention for control participants, this study will use a programmatic roll-out in a stepwise fashion where each clinic that is not yet receiving the intervention will function as a control. Another reason for the selection of a stepped wedge design is that the measurement of outcomes is at the clinic level and individual patient level. Randomization of the intervention sequence will be conducted at the level of the clinics with computer-generated assignment using SAS (version 9.4; SAS Institute) by a statistician blinded to the identity of the clinics and not involved in the intervention delivery. The clinics will be randomized from 1 through 10 and will be allocated a date of implementation which will be concealed until interventions are assigned. Clinics will be informed that the order of allocation to the intervention will be unknown in advance of randomization.

During the initial control period, no clinic will be exposed to the intervention. Subsequently, at each 3-month interval, 1 clinic will transition from the control to the intervention period. This staggered schedule will allow for optimal training, implementation, and supervision of clinic staff. The process will continue until all 10 clinics have crossed over to receive the intervention. Figure 1 illustrates this study's procedures.

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Figure 1. Study procedures for a randomized clinical trial in collaboration with primary care clinics. SDSCA: summary of diabetes self-care activities.



Data Collection

At enrollment, participants will complete the self-report demographic information survey, which will include age, gender, years of residence in the United States, and clinical information about their current treatment regimen to characterize the sample. For baseline data, participants will also complete the validated Summary of Diabetes Self-Care Activities (SDSCA) scale to measure self-care behaviors. The SDSCA scale, available in both English and Vietnamese languages, measures the participant's management of diabetes in the last 7 days regarding diet, physical activity and exercise, blood glucose testing, foot care, and smoking. Participants answer 11 questions by indicating the number of days the behavior was followed in the past 7 days (0-7 days). In addition to self-reported behaviors, lab test results including triglyceride, low-density lipoprotein, high-density lipoprotein, hemoglobin A_{1c}, and clinical assessments including BMI, blood pressure, and weight will be collected from their medical chart and entered into Research Electronic Data Capture (Vanderbilt University), a secure database. This information will be collected again at completion of the 12-week program and at 6 months, 9 months, and 12 months from baseline. Table 1 describes the timing of data collection and evaluation plan by the RE-AIM framework.

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Table 1. Data collection and evaluation plan using RE-AIM[a] framework: assessment objectives, data, instruments, and timeline.

RE-AIM domain	Method	Baseline	Follow-ups (months after baseline)			
			3	6	9	12
Demographic patient information	Paper questionnaire	✓	N/A[b]	N/A	N/A	N/A
Clinic or facility information	Paper questionnaire	✓	N/A	N/A	N/A	N/A
Reach: absolute number and characteristics of those participating in the intervention						
Percentage of eligible patients who respond to texts and nurse calls at least 1 week of program	mHealth[c] data and field notes	✓	N/A	N/A	N/A	N/A
Differential characteristics between participating and nonparticipating patients	Clinic data and field notes	✓	N/A	N/A	N/A	N/A
Barriers and facilitators to reach	Focus groups or interviews	✓	N/A	N/A	N/A	N/A
Effectiveness: modification in self-care behavior and improvement in biological markers						
Changes in SDSCA[d] scale	Paper questionnaire	✓	✓	✓	✓	✓
Changes in triglyceride, LDL[e], HDL[f], HbA_{1c}[g], BMI, BP[h], weight	Clinical assessment and lab results	✓	✓	✓	✓	✓
Percentage of patients enrolled at end of study period	Enrollment data	✓	✓	✓	✓	✓
Adoption: intervention adoption at clinic and patient level						
Percentage of eligible clinic sites who participated	Enrollment data	✓	N/A	N/A	N/A	N/A
Barriers and facilitators to adoption	Focus groups or interviews	✓	N/A	N/A	N/A	N/A
Implementation: key features of program delivery						
Fidelity to the protocol	mHealth data and field notes	✓	✓	✓	✓	✓
Barriers and facilitators to implementation (feasibility and acceptability)	Focus groups or interviews	✓	✓	N/A	N/A	N/A
Maintenance: extent of clinics sustaining the program and patients maintaining improved outcomes						
Sustainability of intervention at each site through end of study period	Focus groups or interviews	✓	✓	✓	✓	✓
Sustainability of improved outcomes through the end of the study period	Clinical assessments and lab results	✓	✓	✓	✓	✓

[a]RE-AIM: Reach, Effectiveness, Adoption, Implementation, Maintenance.

[b]N/A: not applicable.

[c]mHealth: mobile health.

[d]SDSCA: summary of diabetes self-care activities.

[e]LDL: low-density lipoprotein.

[f]HDL: high-density lipoprotein.

[g]HbA_{1c}: glycated hemoglobin.

[h]BP: blood pressure.

Outcome Measures

The primary outcomes are the degree of reach, effectiveness, adoption, implementation, and maintenance measured by using the RE-AIM framework [31]. Reach is the ability to recruit patients and will be determined by assessing the number of people who received an invitation over the number of those who may be eligible to participate in the same clinic. Data sources include the number of invitations and the number of eligible patients seeking care at the clinic. Adoption will be measured by the proportion of clinicians who used the program and the number of patients who participate in the intervention by assessing the number of enrolled participants over the number of those invited, 3 months after the initiation of the intervention. Program implementation will be assessed by conducting a focus group or interview with the clinicians and patients separately at each clinic to gather feedback. Differences and similarities will be compared within and across clinics to identify emerging themes. Barriers and facilitators to program adoption by clinics will also be identified. See Table 2 for postintervention focus group or interview questions.

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Table 2. Postintervention focus group or interview questions for participants.

Measures	Interview questions
Acceptability	• How would you describe your experience of taking part in this tailored DSMES[a] program? • What aspect of the program did you like the most? What was your favorite session? • Suppose a friend of yours was diagnosed with diabetes and came to you for advice. What would you tell them about this DSMES program?
Process of change	• What did you learn from this program? • How has your perspective of living with diabetes changed since completing the program? • What differences have you noticed in your life as a result of taking part in this DSMES program?
Barriers	• What kind of difficulties did you experience taking part in this DSMES program?
Improvement	• What did you least like about the program? What do you think could be improved about this DSMES program?
Implementing change	• How often do you practice the self-care behaviors such as following a healthy eating plan, testing your blood sugar, caring for your foot, etc. learned from this program?

[a]DSMES: diabetes self-management education and support.

The secondary outcomes are self-reported changes in behaviors and clinical test results, which will be compared to determine intervention maintenance and effectiveness. Repeated outcome measures will be assessed at 5 points in time. The translated and validated SDSCA revised scale [32] will be used to measure behavioral changes and assess 5 topics: diet, physical activity and exercise, blood glucose testing, foot care, and smoking. The average interitem correlations within scales were high (mean r=0.47) with the exception of specific diet; test-retest correlations were moderate (mean r=0.40). Correlations with other measures of diet and exercise generally supported the validity of the SDSCA subscales (mean r=0.23). Triglyceride, low-density lipoprotein, high-density lipoprotein, hemoglobin A_{1c}, BMI, weight, and blood pressure will be used to measure clinical changes, which will be obtained from the participants' medical records. Participants will be monitored for an additional 9 months via chart reviews and self-report using the SDSCA scale to determine whether any improvements observed at completion of the intervention will still be evident.

Data Analysis

To evaluate the first hypothesis, descriptive statistics will be used to analyze the acceptability and feasibility of the intervention, which include the proportion of individuals who met the criteria, proportion of eligible participants who agreed to participate, the proportion of mHealth responses completed, and attrition rate at follow-up periods. A linear regression model will be used to examine the association of response rate and attrition rate with other predictors. To evaluate the second hypothesis, continuous variables will be calculated using descriptive statistics including quantiles, mean, and SD. To examine the association of continuous outcome variables and other predictors, a linear mixed effect model will be used to examine time effects, clustering effects, and the interaction of the two. Transformation of outcome variables will be conducted to normalize the nonnormal distributions. To examine the association of categorical outcome variables and other predictors, a generalized linear mixed effect model will be used to examine time effects, clustering effects, and the interaction of the two. In order to handle missing values, sequential multiple imputation will be performed before the analysis. SAS (version 9.4; SAS Institute) will be used for statistical analysis.

To analyze qualitative data from the focus groups and interviews, field notes will be transcribed for coding and analysis. Focus groups and interviews conducted in Vietnamese will be translated into English by the research assistant and verified by the PI before coding and analyzing thematically. Prior to analyzing the transcripts, the researchers will read the transcripts at least twice and compare them with the field notes to ensure accuracy and completeness. Selected transcripts will be reviewed by an experienced qualitative researcher to compare the consistency in developing a coding schema. The NVivo (Lumivero) software will be used to manage and analyze qualitative data.

Intervention Fidelity

The intervention uses 3 fidelity checks to ensure that participants have received the intended information. First, the mHealth SMS text messages will be distributed automatically. Second, progress will be monitored and followed up with participants who abruptly stop reading or responding to our SMS text messages. Third, the nurse coaching call sessions will be monitored randomly by the PI, who will make note of any deviations and will provide further training for the nurse. These fidelity assessments are structured to ensure the intervention is implemented as intended during the delivery process.

Ethics Approval

Ethical approval has been granted by the University of Oklahoma Health Sciences Center institutional review board on October 25, 2022 (IRB#14700). Permission from the large health systems and each clinic has also been granted. The SMart-D intervention involves research with an ethnic minority and understudied population. To ensure the needs of this population are met, the research team has led a prior project with members of this community who contributed to the design, development, and implementation of this study. Ethical procedures include steps for continuation of health education

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for participants after study completion by coordinating with local health departments to refer participants to the existing and structured Total Wellness program of Oklahoma. Baseline data and lessons learned will be presented at conferences, and study outcomes will be published in scientific journals. Study results will also be communicated to relevant health care professionals and to the US Vietnamese community through lectures, posters, and pamphlets.

Results

Planning for the SMart-D study began in January 2022, clinic recruitment began October 28, 2022, and patient recruitment began November 4, 2022. Data collection of outcome measures will be completed in 2024. This study was funded during July 2022 to June 2024. As of August 24, 2023, 10 clinics and 60 patients were enrolled in this study. The results are expected to be available by 2025 and will demonstrate intervention acceptability, feasibility, effectiveness, and sustainability.

Discussion

This study is driven by two hypotheses: (1) at least 50% (n=5) of eligible clinics and 50% (n=40) of eligible patients who are invited will participate, and at least 70% (n=56) of patients will complete the program, and (2) patients who receive the intervention will have improved self-care behaviors and improved clinical test results with at least 75% (n=60) of the patients maintaining improved outcomes at follow-up visits compared with baseline, and participants will verbalize that the intervention is feasible and acceptable. This protocol was designed with an interprofessional research group that has many strengths. An overall strength is the stepped wedge design, which allows participating clinics to be randomized with an opportunity for all consented patients to participate in the intervention. The staggering of clinic implementation allows the research team to train clinic staff and monitor potential implementation issues. The mixed method and longitudinal design provide insights into long-term outcomes over time.

Another strength of this protocol is this is the first Vietnamese DSMES intervention to be implemented in collaboration with primary care clinics that leverages mHealth technology to address the barriers of language and cultural differences. Vietnamese-speaking individuals have few opportunities to participate in health-related randomized clinical trials. This protocol allows that opportunity because it is offered in the Vietnamese language to promote self-determination and independence, and improve self-management strategies.

Further, 1 limitation of the stepped wedge design is that patients of clinics that were randomized for implementation later will have to wait months before receiving the intervention. This waiting period may reduce engagement with the researchers and may increase attrition rates. Another limitation is the repeated measurements of questionnaires and clinical tests may lead to a higher respondent burden on patients and clinic staff.

In conclusion, this study will improve understanding of the implementation process, demonstrate the potential effectiveness of the intervention, accelerate the pace of moving evidence-based interventions to practice among the Vietnamese population, and potentially provide a replicable implementation model that can be culturally tailored to other non-English speaking ethnic minorities. Furthermore, successful study results may be implemented across other localities and states and across both primary care and specialty clinics.

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Data Availability

Data sharing is not applicable to this paper, no data sets were analyzed during the development of this protocol. To support scientific transparency, we will publish deidentified data and additional supporting files in the main paper.

Authors' Contributions

AN wrote the first draft. ZN led in the dissemination and implementation of the research design. TB and MB led in the mobile health design and implementation. SC wrote the statistical analysis plan. VE and KD completed the final paper revision. All authors contributed to this study's design and critical review and revision of this paper. All authors read and approved the final version.

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Conflicts of Interest

MB is the primary inventor of the Insight mHealth platform, the platform used to create the smartphone application described in this paper. MB receives royalties when investigators outside of the University of Oklahoma use this platform. However, since the lead investigators are at the University of Oklahoma, MB did not receive any royalties in this case.

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Abbreviations

DSMES: diabetes self-management education and support
mHealth: mobile health
PI: Principle investigator
RE-AIM: Reach, Effectiveness, Adoption, Implementation, Maintenance
SDSCA: Summary of Diabetes Self-Care Activities
SMart-D: Self-Management mobile health Intervention for US Vietnamese with Diabetes
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
T2D: type 2 diabetes

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Protocol

Motivational Enhancement Interventions to Increase Pre-Exposure Prophylaxis Use in Sexual Minority Men Who Use Stimulants: Protocol for a Pilot Sequential Multiple Assignment Randomized Trial

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Abstract

Background: Although pre-exposure prophylaxis (PrEP) could substantially mitigate HIV risk, sexual minority men who use stimulants commonly experience difficulties with engaging in PrEP clinical services. Motivational interviewing (MI) and contingency management (CM) reduce substance use and condomless anal sex (CAS) in this population, but these motivational enhancement interventions require modifications to promote engagement along the PrEP care continuum.

Objective: PrEP Readiness Interventions for Supporting Motivation (PRISM) is a pilot sequential multiple assignment randomized trial testing the feasibility, acceptability, and preliminary effectiveness of distinct combinations of telehealth MI and CM in 70 cisgender sexual minority men who use stimulants that are not currently taking PrEP.

Methods: A national sample was recruited via social networking applications to complete a baseline assessment and mail-in HIV testing. Those with nonreactive HIV results were randomized to receive either (1) a 2-session MI intervention focusing on PrEP use (session 1) and concomitant stimulant use or CAS (session 2) or (2) a CM intervention with financial incentives for documented evidence of PrEP clinical evaluation by a medical provider (US $50) and filling a PrEP prescription (US $50). At the 3-month follow-up assessment, participants who reported they had not filled a prescription for PrEP were randomized a second time to either (1) *switch* to a second-stage intervention (ie, MI+CM or CM+MI) or (2) *continue* with assessments only. Outcomes for both responders and nonresponders were reassessed at a 6-month follow-up. The primary outcome is documented evidence of filling a PrEP prescription over 6 months. Self-reported secondary outcomes include PrEP clinical evaluation by a medical provider, stimulant use, and CAS. Qualitative exit interviews were conducted with a subgroup of responders and nonresponders to characterize their experiences with the MI and CM interventions.

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Results: Implementation of PRISM underscores challenges in reaching sexual minority men who use stimulants to optimize HIV prevention efforts. Approximately 1 in 10 (104/1060) eligible participants have enrolled. Of the 104 who enrolled, 87 (84%) completed mail-in HIV testing. We delivered 5 preliminary HIV-positive results, including posttest counseling with referrals to confirmatory testing.

Conclusions: Lessons learned from PRISM underscore the central importance of a flexible, participant-centered approach to support the engagement of sexual minority men who use stimulants. Leveraging telehealth platforms to deliver motivational enhancement interventions also expanded their reach and potential public health impact with this high-priority population. Further research is needed to determine the effectiveness of telehealth MI and CM for supporting PrEP use in sexual minority men who use stimulants.

Trial Registration: ClinicalTrials.gov NCT04205487; https://clinicaltrials.gov/study/NCT04205487

International Registered Report Identifier (IRRID): DERR1-10.2196/48459

(JMIR Res Protoc 2023;12:e48459) doi:10.2196/48459

KEYWORDS

cocaine; contingency management; methamphetamine; motivational interviewing; pre-exposure prophylaxis; intervention; men; stimulant; condom; HIV testing; prevention; HIV; effectiveness; telehealth; motivation

Introduction

Sexual minority men continue to account for more than two-thirds of new HIV infections in the United States [1-4], and it is estimated that 70% of seroconversions in this population occur during receptive condomless anal sex (CAS) [5-7]. Consequently, expanded efforts are needed to optimize the benefits of pre-exposure prophylaxis (PrEP) among sexual minority men at greatest risk for HIV. The Centers for Disease Control and Prevention [2,8] has estimated that 1 in 6 sexual minority men will acquire HIV in their lifetime, including half of Black sexual minority men and one-quarter of Latino sexual minority men. Over and above these profound racial disparities, there is a resurgent epidemic of methamphetamine use among sexual minority men that is disproportionately affecting Black and Latino sexual minority men [9-12]. Although methamphetamine use appeared to decline somewhat after significant public health attention in the early- and mid-2000s [13,14], it is again on the rise [13,15-19]. For over two decades, methamphetamine and other stimulant use has been identified as a prominent driver of the HIV/AIDS epidemic in sexual minority men that is associated with engagement in CAS [20,21], altered rectal immune function [22,23], and faster rates of HIV seroconversion [24-26]. The public health impact of stimulant use is evidenced by recent findings from a cohort of sexual and gender minorities who have sex with men, where 1 in 3 new HIV infections were among those reporting methamphetamine use [26].

Sexual minority men who use stimulants experience substantial barriers to navigating HIV prevention services that undermine the clinical and public health benefits of PrEP. This is evidenced by findings from one study, where sexual minority men who use methamphetamine had 5-fold greater odds of repeat prescription for postexposure prophylaxis and a 3-fold greater rate of HIV seroconversion [27]. This underscores the clear benefits of supporting the entry or re-entry of sexual minority men who use stimulants into the PrEP care continuum. Although some studies found that sexual minority men who use substances report concerns about their hypothetical ability to adhere to PrEP [28,29], actual PrEP use among sexual minority men who use substances such as methamphetamine and amyl nitrites (ie, poppers) appears to be comparable to or greater than their peers who do not use substances [30-38]. At the same time, there is growing evidence that sexual minority men who use stimulants and other substances can experience difficulties achieving prevention-effective levels of daily oral PrEP adherence [33,39,40] that may serve as early indicators of greater risk for disengagement from PrEP care and discontinuing PrEP [41-43]. For example, those engaging in heavy cocaine use have nearly 3-fold greater odds of disengagement from PrEP care compared to nonusers [41]. Taken together, there is a clear need for scalable interventions to promote the entry or re-entry of sexual minority men who use stimulants into the PrEP care continuum.

The effectiveness of motivational interviewing (MI) and contingency management (CM) interventions are supported by decades of clinical research in people with substance use disorders [44], and these are the only interventions that are efficacious for reducing both substance use and CAS in sexual minority men [45-49]. MI is an evidence-based counseling intervention targeting *intrinsic motivation* for health behavior change [50]. CM targets *extrinsic motivation* by providing tangible incentives as positive reinforcement for performing health behaviors [51], and it has also been successfully used to promote HIV-related health behavior change in people who use substances [52-57]. Interestingly, findings from one meta-analysis of the substance use disorder treatment literature indicate that MI achieves small but durable outcomes, while CM leads to moderate short-term outcomes [58]. PrEP Readiness Interventions for Supporting Motivation (PRISM) addresses an important gap by testing sequentially delivered MI and CM interventions for promoting entry or re-entry into the PrEP care continuum.

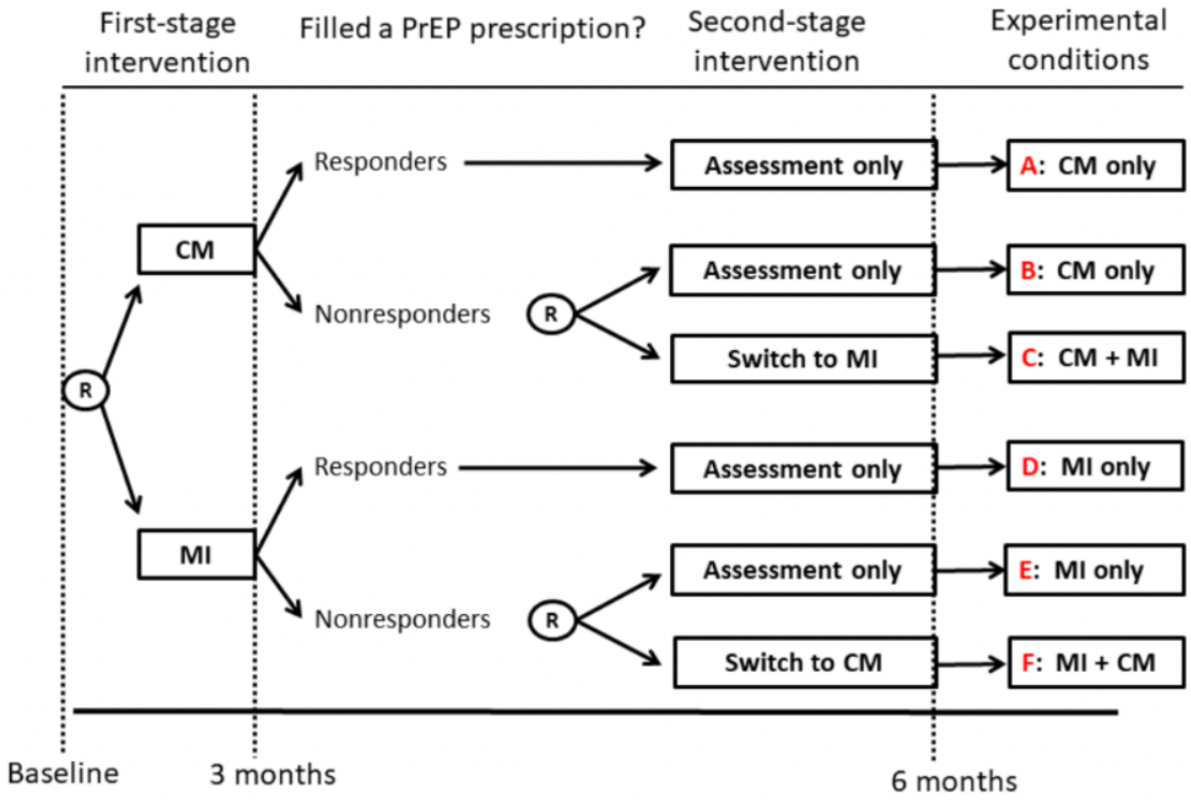
Cognitive evaluation theory proposes that motivational processes are arranged hierarchically such that the extrinsic rewards for behavior change provided during CM could paradoxically undermine intrinsic motivation in some circumstances [59]. In cognitive evaluation theory, higher-order needs for autonomy and self-determination govern the regulation of intrinsic motivation and self-efficacy, both of which could be partially

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undermined by CM incentives. This underscores the need for clinical research to test if there are distinct combinations of MI and CM that optimize durable PrEP use while decreasing stimulant use and CAS among sexual minority men.

This paper describes the protocol for a pilot sequential multiple assignment randomized trial (SMART [60]) testing the feasibility, acceptability, and preliminary effectiveness of the PRISM telehealth motivational enhancement interventions. The primary outcome is documented evidence of filling a PrEP prescription over 6 months. As shown in Figure 1, using sequential randomization procedures allowed for a comparison of 2 first-stage interventions: MI versus CM (randomized 1:1 after baseline). Then, among those who did not fill a PrEP prescription after 3 months (ie, nonresponders), we conducted a second randomization to *switch* to a second-stage intervention (ie, MI+CM and CM+MI) versus *continue* with assessments only (also randomized 1:1 for those not on PrEP at 3 months). Because CM has been shown to yield moderate short-term effects, we hypothesize that a greater proportion of those randomized to receive CM as the first-stage intervention will have filled a PrEP prescription and report being evaluated for PrEP by a medical provider over 6 months. Because MI also targets concomitant HIV risk behaviors, we hypothesize that those randomized to receive it as the first-stage intervention will show greater reductions in self-reported stimulant use and CAS over 6 months. Finally, among nonresponders, we hypothesize that participants randomized to *switch* to a second-stage intervention (ie, CM+MI and MI+CM) will have greater improvements in the primary and secondary outcomes compared to those who *continue* with assessments only.

Figure 1. Pilot SMART of the PRISM telehealth motivational enhancement interventions to facilitate entry or re-entry into the PrEP care continuum. CM: contingency management; MI: motivational interviewing; PrEP: pre-exposure prophylaxis; PRISM: PrEP Readiness Interventions for Supporting Motivation; SMART: sequential multiple assignment randomized trial.



Methods

Study Design

This pilot SMART randomized 70 HIV-negative sexual minority men who use stimulants (ie, methamphetamine, powder cocaine, or crack cocaine) that are not currently taking PrEP, and completion of the final follow-up assessments is anticipated in July 2023. Participants were recruited via social networking applications across the United States. Interested individuals were directed to a web-based screener that assessed the following inclusion criteria: (1) 18 years of age or older; (2) identified as a cisgender man; (3) reported anal sex with a man (past 6 months); (4) reported using methamphetamine, powder cocaine, or crack cocaine in the past 3 months; (5) HIV-negative or unknown serostatus; (6) met Centers for Disease Control and Prevention criteria for PrEP eligibility [61]; and (7) not currently prescribed PrEP. PrEP eligibility was operationalized as any CAS regardless of partner type or any sexually transmitted infection (past 6 months).

Research Team

Master's and doctoral-level staff were trained in assessment administration, randomization, and intervention activities. Ongoing oversight and safety monitoring were provided by the principal investigators. Fidelity monitoring and group supervision for staff delivering MI sessions were overseen by a licensed psychologist who is a member of the Motivational Interviewing Network of Trainers. Follow-up assessments were conducted by staff who were blinded to intervention conditions.

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One team member with graduate-level training in qualitative methods conducted qualitative exit interviews with participants.

Ethical Considerations

All procedures for this pilot SMART were approved by the University of Miami Institutional Review Board (UM IRB Study ID: MODCR00000105) with a reliance agreement from the City University of New York Graduate School of Public Health. All participants completed an informed consent before study enrollment. All pilot SMART activities were conducted using Zoom (Zoom Video Communications, Inc), which emerged as a flexible response to the COVID-19 pandemic and represents a scalable platform for reaching the broader population of sexual minority men who use stimulants with the PRISM telehealth motivational enhancement interventions. Potentially eligible participants were invited to an enrollment visit that included informed consent for the first 3 months of the pilot SMART and a baseline assessment via Zoom. Those who completed the enrollment visit received a US $50 Amazon gift card, Venmo, or Zelle cash application payment. In total, participants could make up to US $335 over the course of the pilot SMART, depending on the interventions they received. Information regarding the payment for each study activity is included in the paper where relevant. All data were stored on a Food and Drug Administration and Health Insurance Portability and Accountability Act–compliant University of Miami server, and all electronic files containing identifiable information were password-protected with access limited to institutional review board–approved study staff only.

Sequential Informed Consent

At baseline, participants provided informed consent for the first 3 months of the pilot SMART with trained staff. This consent described the first-stage randomization to MI versus CM as well as the 3-month follow-up assessment. We used sequential informed consent procedures to ensure that participants did not plan to delay filling a PrEP prescription to be eligible for the second-stage randomization and the possibility of additional incentives (eg, those initially randomized to MI would delay filling a PrEP prescription to have another chance to receive CM financial incentives). After the 3-month follow-up assessment, participants completed a second informed consent that described procedures for the second-stage randomization of nonresponders, the 6-month follow-up assessment, and qualitative exit interviews. The follow-up assessments at 3 and 6 months were completed by an independent assessor who had not previously delivered MI or CM to participants. Participants were sent a link to the self-report measures to complete on their own, and they received a US $50 Amazon gift card or cash application payment for completing each assessment.

Mail-In HIV Testing

After the baseline assessment, participants were sent a testing kit to collect a saliva sample with an OraSure HIV-1 (LOT 6691354; OraSure Technologies, Inc) testing device, with instructions on how to take the test and a prepaid return envelope to the HIV testing laboratory. Participants received a US $25 Amazon gift card or cash application payment for mailing this sample to a laboratory for HIV testing [62,63]. Participants who did not complete HIV home testing or those with reactive HIV test results were excluded prior to randomization. Participants with reactive HIV test results were provided with posttest counseling and assisted in connecting with local confirmatory testing [64].

Pilot SMART Procedures

As shown in Figure 1, participants who provided a saliva sample that was nonreactive for HIV were randomized to a first-stage intervention: (1) a 2-session MI intervention or (2) a CM where they received up to US $100 in financial incentives for taking the first step toward starting or restarting PrEP. Randomization at baseline was stratified as a function of whether participants have previously taken PrEP with the randomization schemes created in SAS (version 9.4; SAS Institute Inc) by the data manager using randomly permuted block sizes of 2, 4, and 6. The randomization schemes were administered using REDCap (Research Electronic Data Capture; Vanderbilt University) and were not viewable by staff until the moment of randomization for each participant. Randomization probabilities at each stage were 1:1. Immediately following randomization, participants received their first MI session or a brief introduction to the financial incentives they could earn during the 3-month CM period. All participants received a US $20 Amazon gift card or cash application payment for attending this first-stage randomization visit. After 3 months, participants who reported that they have not filled a PrEP prescription in the prior 3 months are classified as nonresponders. Nonresponders were randomized a second time (no stratification) to either (1) *switch* to a second-stage intervention (MI+CM or CM+MI) or (2) *continue* with assessments only. Finally, responders and nonresponders completed a final follow-up assessment at 6 months to measure the primary and secondary outcomes. Participants received a US $50 Amazon gift card or cash application payment for completing each follow-up assessment at 3 and 6 months.

MI Intervention

The 2-session MI intervention simultaneously targeted PrEP use (session 1) as well as co-occurring substance use and CAS (session 2). Each session was delivered approximately 1 week apart via Zoom, and participants received a US $20 Amazon gift card or cash application payment at each session. Participants had up to 3 months to complete both MI sessions.

Session 1 focused extensively on enhancing intrinsic motivation for starting or restarting PrEP. To begin, participants were invited to tell the facilitator a bit about themselves and describe what they know about PrEP. Using elicit-provide-elicit techniques, the facilitator provided relevant information to address any gaps in knowledge about PrEP. This included topics like the effectiveness and safety of PrEP, prevention effective adherence levels for sexual minority men, different oral dosing strategies (eg, 2-1-1), navigating PrEP care, and the availability of financial support for those without insurance. Then, participants were invited to describe their thoughts and feelings about the possibility of starting PrEP with selective reinforcement of change talk by the facilitator. Using the *change ruler*, participants rated on a scale of 1 to 10 how important it is for them to see a medical provider to learn more about PrEP.

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The facilitator used this to elicit change talk by asking participants why they did not pick a lower number (eg, "Why did you pick a 3 and not a 1?"). Next, the facilitator engaged participants in the *roadmap exercise*, where the decision regarding whether to start PrEP was presented as a fork in the road. Participants were asked to consider what life might look like in 1-2 years if they did not start PrEP and then if they chose to start PrEP. The session ended with a summary, and participants were encouraged to examine what (if any) steps they were ready to take toward starting or restarting PrEP. Those who were actively planning to start or restart PrEP were asked to elaborate on the timeline and examine any potential barriers they might encounter in accessing PrEP care.

At the beginning of session 2, participants were asked to describe their current thoughts and feelings about starting or restarting PrEP. The facilitator selectively reinforced change talk and answered any questions participants might have about navigating PrEP care. Next, participants were introduced to the focus of session 2, concomitant stimulant use, and CAS. Participants were presented with a menu of options that reflect possible topics for the session including (1) change how I use stimulants, (2) start substance use treatment, (3) attend a self-help group, (4) abstain from stimulants, (5) fewer sex partners, (6) less sex on stimulants, (7) use condoms, and (8) get tested for HIV regularly. Participants were encouraged to identify a topic of focus for the session that they wanted to discuss at greater length. Our approach to addressing stimulant use and CAS embraces the philosophy of harm reduction such that participants were not required to be ready, willing, or able to abstain from stimulant use or use condoms every time during anal sex [65]. Instead, the facilitator assisted participants with exploring a range of possible behavior change targets such as reducing the frequency of stimulant use, changing the mode of stimulant administration (eg, snorting instead of smoking), and using condoms during receptive anal sex with casual partners. Once a behavior change target was identified, participants were encouraged to elaborate on it to reinforce change talk. Using the *change ruler*, participants rated on a scale of 1 to 10 how important it is for them to make this change. The facilitator used this to elicit change talk by asking participants why they did not pick a lower number (eg, "Why did you pick a 3 and not a 1?"). Next, the facilitator engaged the participant in the *roadmap exercise*, where the decision regarding whether to make this change was presented as a fork in the road. Participants were asked to consider what life might look like in 1-2 years if they did not make a change and then if they chose to change. The session ended with a summary, and participants were encouraged to examine what steps (if any) they were ready to take toward change. Those who were actively planning to make a change in their behavior were asked to elaborate on the timeline and examine any potential barriers they might encounter.

CM Intervention

Facilitators provided a brief overview of the CM protocol and encouraged participants to ask any questions they may have about how to access PrEP in their community. Facilitators provided tailored referrals for local PrEP services [66] and web-based PrEP providers. Participants were provided financial incentives as positive reinforcement for 2 key behaviors that are crucial to PrEP care continuum entry or re-entry. First, participants received a US $50 incentive for documented evidence of completing a medical visit for PrEP clinical evaluation that includes HIV testing. Documentation can include either a note from a medical provider indicating that the participant was seen for a PrEP evaluation or laboratory results consistent with PrEP clinical evaluation (eg, HIV testing and kidney function). Second, participants who provided evidence that they filled a recent PrEP prescription for Truvada or Descovy matched to their photo identification (eg, photo of the medication bottle), received an additional US $50 incentive. Participants on Apretude as injectable PrEP were asked to provide documentation from their provider or medical record demonstrating that they received an injection to obtain the US $50 incentive. Because filling a PrEP prescription requires participants to receive a PrEP clinical evaluation by a medical provider, those who had not previously received US $50 for a PrEP clinical evaluation received US $100 when they provided evidence they filled a PrEP prescription. To provide timely positive reinforcement for these behaviors, incentives were provided via remote payment applications (eg, Venmo and Zelle) within 2 business days.

Fidelity Monitoring

The procedures for monitoring the fidelity of the CM and MI intervention protocols were as follows: (1) detailed curriculum manuals for each intervention, (2) intensive training in delivering MI and CM, (3) incorporation of mock training sessions to ensure staff meet performance criteria for delivery, (4) facilitator checklists, and (5) audio taping of sessions. Audio recordings of facilitator sessions were reviewed to assess adherence to the protocol, delivery, interpersonal skills, facilitator or participant rapport, and session flow. Fidelity monitoring was also crucial to mitigate the risk of contamination (eg, possible delivery of MI counseling during CM). The first 3 participants for each staff member (MI and CM) were reviewed immediately. Staff members also participated in ongoing individual and group supervisions. Fidelity ratings of MI sessions used the MI treatment integrity protocol [67], which is the gold standard approach for monitoring the fidelity of MI. MI treatment integrity scores review 4 global categories (cultivating change talk, softening sustain talk, partnership, and empathy) and are based on a Likert-scale from 1 (low) to 5 (high) [68].

Primary Outcome

The primary outcome is verified evidence that a participant filled a PrEP prescription (ie, photo of a recently filled medication bottle) over the 6-month follow-up. For participants who did not provide evidence of a PrEP prescription as part of CM, those who reported taking PrEP were subsequently notified that they could receive an additional US $20 incentive for providing evidence of a recent PrEP prescription. We chose to implement this strategy to mitigate differential assessment of the primary outcome due to CM incentives. Participants were offered the US $20 incentive for providing evidence only after they self-reported recently filling a PrEP prescription so that it did not function as a CM incentive.

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Secondary Outcomes

Participants completed self-report measures over the 6-month follow-up to assess several secondary outcomes that are described briefly below.

PrEP Clinical Evaluation

Participants were asked to indicate if they attended an appointment with a medical provider about starting PrEP in the past 3 months. Those who indicated they attended any medical appointment about starting PrEP over the 6-month follow-up were classified as completing PrEP clinical evaluation.

Stimulant Use Severity

The World Health Organization Alcohol, Smoking, and Substance Involvement Screening Test is a validated self-report measure of substance use [69,70]. We plan to examine changes in the amphetamine-type stimulant and cocaine use composite scores, which measure the severity of symptoms for stimulant use disorders. Where participants reported using multiple stimulants at a given time point, the highest mean score was selected. We will also examine changes in clinically validated cut-points for moderate and severe stimulant use disorders using the Alcohol, Smoking, and Substance Involvement Screening Test (mild=0-3; moderate=4-26; and severe=27 or greater). Again, where participants are using multiple stimulants at a given time point, the cocaine or amphetamine-type stimulant use score that reflects higher severity was selected.

Receptive and Insertive CAS

Participants were asked to separately indicate the number of men with whom they had receptive or insertive anal sex "without a condom at least part of the time" in the past 3 months. If participants reported having CAS partners, they were asked to separately indicate the number of receptive and insertive CAS partners who were taking PrEP or were HIV-positive undetectable to examine the extent to which participants are biomed sorting [71].

PrEP Intentions

A 3-item PrEP intentions scale assessed intentions to complete certain PrEP-related behaviors within the next 3 months (eg, "During the next 3 months, I will talk to a health care provider about PrEP."). Responses were rated on a 4-point scale from definitely will not do (1) to definitely will (4) with higher scores indicating stronger intentions to use PrEP [72].

PrEP Self-Efficacy

An 8-item scale assessed how difficult participants viewed behavior skills related to PrEP use (eg, "How difficult would it be for you to talk openly and honestly with a doctor about your sexual behaviors?"). Participants rated their responses on a 4-point scale ranging from very hard to do (1) to very easy to do (4) with higher ratings indicating greater self-efficacy for PrEP use [72].

PrEP Attitudes

A 5-item scale assessed attitudes toward PrEP use (eg, "PrEP is effective at preventing HIV.") [72]. Participants rated response options on a 5-point scale ranging from strongly disagree (1) to strongly agree (5) with higher scores indicating more positive attitudes toward PrEP use.

PrEP Stigma

This 5-item scale assessed stigmatizing notions around PrEP use (eg, "People who take PrEP are promiscuous.") [72]. Participants rated response options on a 5-point scale ranging from strongly disagree (1) to strongly agree (5) with higher scores indicating more stigmatizing views about PrEP [72].

Intent-to-Treat Analyses

Using logistic regression, we will examine the intent-to-treat effects of first-stage randomization (ie, MI vs CM) on (1) any documented evidence of filling a PrEP prescription (primary outcome) over the 6-month follow-up and (2) any self-reported PrEP clinical evaluation by a medical provider over the 6-month follow-up. These logistic regression analyses will test our primary hypothesis that it is better to start with CM versus MI. Intent-to-treat analyses of secondary outcomes involving longitudinal trajectories of continuous measures will be tested using multilevel random coefficient models (ie, hierarchical linear modeling). These analyses will test our secondary hypotheses that those randomized to receive MI as a first-stage intervention will display a greater decrease in stimulant use severity and number of CAS partners over 6 months. Finally, exploratory analyses using the methods described earlier will be conducted among nonresponders only. We hypothesize that nonresponders randomized to *switch* to a second-stage intervention (ie, CM+MI and MI+CM) will have greater improvements in the primary and secondary outcomes compared to those who *continue* with assessments only.

Power Analysis

Recent statistical modeling clearly demonstrates that it is inappropriate to use effect size estimates from a pilot trial for establishing effectiveness or informing subsequent power analyses [73]. Thus, the most appropriate focus of a pilot is to examine issues relevant to feasibility and acceptability, which do not require adequate statistical power. At the same time, we will examine the preliminary intent-to-treat effects of starting with MI versus CM in this pilot SMART. With 70 randomized participants, α=.05 (2-tailed), power=0.80, and 75% retention at 6 months, minimum detectable standardized mean differences for continuous outcomes ranged from 0.53 to 0.79 for within-subjects correlations r ranging from 0.10 to 0.80. For binary outcomes, using the same inputs as above plus small, medium, and large base rates of 10%, 25%, and 50%, respectively, raw proportion differences for r=0.10 ranged from 21% to 25% (standardized difference=0.55); and for r=0.80, the corresponding raw proportion differences ranged from 34% to 38% (standardized difference=0.80). Statistical power estimates following the second-stage randomization are dependent on the nonresponse rate.

Qualitative Exit Interviews

After the 6-month follow-up assessment, participants were purposively selected for a qualitative exit interview examining their experiences with the PRISM telehealth motivational enhancement interventions received. Participants were purposively selected for in-depth qualitative interviews based

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on whether they were responders (n=10) or nonresponders (n=10) after 6 months. Participants invited to complete an in-depth qualitative interview received a US $50 Amazon gift card or cash application payment.

Interviews were conducted by a member of the study team that has not previously interacted with the participants at any point in the trial. Interviews were approximately 60 minutes. The interviewer completed ongoing training and supervision in qualitative methods and the pilot SMART objectives. The semistructured interview guide was tailored based on the responder status (responder at stage 1, responder at stage 2, or nonresponder at 6 months). Topics included likes and dislikes of PRISM telehealth interventions, views on the adequacy of study incentives, thoughts about PrEP, interest in injectable PrEP, and barriers and facilitators to PrEP uptake and adherence.

Qualitative Analyses

Interviews were audio recorded on Zoom with the participants' consent and transcribed verbatim. The transcripts are reviewed for accuracy and quality assurance. A general inductive approach [74] will be used to analyze themes relating to the acceptability and feasibility of the PRISM interventions. Codes will be derived inductively starting with a thorough reading of the transcripts and identification of relevant information expressed by participants. An initial codebook will be developed by the primary data analyst after a comprehensive reading of all transcripts. Next, a random sample of 5 interviews will be selected for a second data analyst to code for interrater agreement. The 2 researchers will review and discuss any discrepancies in the coding, emergent themes, and the need for refined definitions. The researchers will accept all codes where there is agreement and come to a consensus for areas of nonagreement based on their discussions; they will revise the codebook and recode the transcripts based on the revised codebook. Next, a second random sample of 5 interviews will be selected to determine interrater agreement. When the analysts reach an interrater agreement of 85%-90% in the second round of coding, the transcript codes will be finalized [75]. Agreement is defined as whether identical codes are applied to the selected text by both coders. Once interrater agreement is reached, all interviews will be coded by either one of the two analysts based on the final codebook following established guidelines for determining coding saturation [76].

Results

Recruitment of participants via social networking applications reached a large pool of potentially eligible participants. Although 7800 people completed the web-based screener, the large number of screeners completed yielded 1060 (14%) potential participants. Of those who screened eligible, 104 (10%) participants completed a Zoom enrollment visit. As shown in Figure 1, 87 (84%) enrolled participants provided a saliva sample for mail-in HIV testing. Notably, we identified 5 (6%) new HIV infections, and these men were provided with posttest counseling as well as referrals to confirmatory testing. Of the 82 participants with a nonreactive HIV result, 70 (85%) were randomized to a stage 1 intervention in the pilot SMART.

There were no significant differences between enrolled and nonenrolled groups in race or ethnicity, age, and type of stimulants used. As shown in Table 1, 46 (44%) of enrolled participants were ethnic minorities with an average age of 38.5 (SD 8.9) years. Most enrolled participants reported only methamphetamine use in the last 3 months (n=65, 63%), followed by couse of methamphetamine and powder or crack cocaine (n=23, 22%), and then only powder or crack cocaine use in the last 3 months (n=16, 15%). Although enrolled participants were more likely to know about "on-demand PrEP" or "event-based dosing" as an alternative to daily oral PrEP, nearly three-fourths of enrolled and nonenrolled participants expressed interest in this dosing strategy.

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Table 1. Comparison of eligible participants who enrolled versus those who did not enroll (N=1060).[a]

	Enrolled (n=104)	Not enrolled (n=956)	*P* value
Age (years), mean (SD)	38.5 (89)	38.1 (10.1)	.69
Stimulant use (past 3 months), n (%)			.76
Powder or crack cocaine only	16 (15.4)	141 (14.8)	
Methamphetamine only	65 (62.5)	630 (65.9)	
Powder or crack cocaine and methamphetamine	23 (22.1)	185 (19.4)	
Interested in on-demand PrEP[b], n (%)	77 (74.0)	714 (74.7)	.89
On-demand PrEP is a good prevention choice for me, n (%)	74 (71.2)	671 (70.3)	.85
It would be difficult for me to use on-demand PrEP, n (%)	9 (8.7)	101 (10.6)	.54
Race or ethnicity, n (%)			.08
Black or African American	16 (15.4)	76 (8.1)	
White	58 (55.8)	548 (58.1)	
Hispanic or Latino	21 (20.2)	212 (22.5)	
Other ethnic minority	9 (8.7)	108 (11.4)	
HIV status, n (%)			.30
HIV-negative	84 (80.8)	729 (76.3)	
Unknown	20 (19.2)	227 (23.7)	
Diagnosed with a STI[c] (past 6 months), n (%)	17 (16.4)	114 (12.0)	.20
Any sex exchange for money or drugs, n (%)	29 (28.4)	303 (31.9)	.47
Aware of on-demand PrEP, n (%)	73 (70.2)	575 (60.2)	.047
Previously used on-demand PrEP, n (%)	4 (3.9)	25 (2.6)	.52[d]

[a]A pooled *t* test was used to compare means across both groups for the continuous characteristic, age.

[b]PrEP: pre-exposure prophylaxis.

[c]STI: sexually transmitted infection.

[d]Chi-square test of proportions was used for all categorical characteristics except for this value, where Fisher exact test was used.

Discussion

Implementation of the pilot SMART of the PRISM telehealth motivational enhancement interventions highlights the challenges associated with launching and sustaining a national recruitment campaign to achieve our target sample size. Additionally, the onset of the COVID-19 pandemic necessitated delivery of the PRISM motivational interventions using a telehealth platform. Participant enrollment, scheduling, and completing intervention activities via telehealth as well as mail-in HIV testing efforts afforded the research team various successes, challenges, and lessons learned.

Enrolling potentially eligible participants proved to be more difficult than anticipated such that only 1 in 10 who screened eligible enrolled in the pilot SMART. This reflects the challenges in optimizing HIV prevention with sexual minority men who use stimulants, a high-priority population that is often difficult to access because many are not actively seeking services. Despite the challenges we experienced in enrolling potentially eligible participants, there were no significant differences between enrolled and nonenrolled groups in race or ethnicity, age, and type of stimulants used. Enrolled participants appear to be generally representative of the broader population of sexual minority men who use stimulants that we screened from social networking applications. Future randomized controlled trials will likely require a substantial investment of time and resources for national recruitment campaigns to examine the effectiveness of the PRISM telehealth motivational enhancement interventions.

Throughout the pilot SMART, we developed and refined strategies to support the engagement of potentially eligible participants through SMS text messages and other communications that emphasized the nonjudgmental, flexible, and participant-centered approach of our team. We devoted substantial resources to enrolling participants with multiple contacts to facilitate scheduling and often multiple missed enrollment visits. Many eligible participants did not respond to multiple attempts to contact them via text; for those who did respond, our staff reported approximately two-thirds no-show rate for scheduled Zoom enrollment visits. PRISM staff implemented procedures regarding appointment reminders that included nonjudgmental language regarding follow-ups for missed appointments (eg, “Sorry we missed each other today. Happy to reschedule for another time.”) and encouraged participants to re-establish contact. This is consistent with

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findings from previous studies using social media to recruit sexual minority men most vulnerable to HIV acquisition [63,77] as well as SMS text messages to enhance engagement and retention [78].

The inclusion of HIV testing provided additional successes and challenges for our staff. Staff time was required to assemble and mail HIV testing kits, resending kits as needed, as well as time spent texting reminders to participants to return their saliva specimens. Throughout implementation of the pilot SMART, we refined standard operating procedures for ensuring timely completion of mail-in HIV testing and delivery of reactive HIV results. Although mail-in HIV testing with a US $25 incentive was feasible and acceptable in this pilot SMART, conducting rapid HIV self-testing during the enrollment visit over Zoom would have removed operational barriers to completing HIV testing as a prerequisite for randomization. There were routine delays of approximately 6 weeks in receiving HIV test results from the laboratory. Because nonreactive HIV results were required prior to the randomization visit, these delays may have contributed to the attrition of some otherwise eligible participants during this waiting period.

With the onset of the COVID-19 pandemic in 2020, our team revised the pilot SMART protocol to focus on the telehealth delivery of MI and CM to national sample. Instead of in-person, local sessions, we were able to enroll sexual minority men who use stimulants from over 30 states. Recruiting a national sample also expanded the reach of the pilot SMART to test the potential benefits of delivering telehealth motivational interventions in geographic regions with varying degrees of structural stigma toward sexual minority men and different levels of access to PrEP clinical services. As some of our participants were located in rural areas, many did not have a PrEP provider available within a reasonable traveling distance. This required referrals for web-based PrEP delivery options that were the only source of PrEP access for some participants. Randomized controlled trials are needed to determine whether and how geographic region moderates the effectiveness of telehealth motivational enhancement interventions with this high-priority population.

Although the development and implementation of this pilot SMART have been successful in many ways, we do recognize some limitations. First, the sample size is underpowered because our primary focus was to estimate the feasibility and acceptability of PRISM telehealth motivational interventions. A larger trial is needed to determine the effectiveness of distinct combinations of CM and MI for PrEP use as well as concomitant changes in substance use and CAS. Implementation of mail-in HIV testing also presented some challenges, including delays in the provision of saliva samples and laboratory wait times. Future research should determine the feasibility and acceptability of at-home rapid HIV testing with posttest counseling over Zoom.

Development and implementation of the pilot SMART of the PRISM telehealth motivational enhancement interventions for sexual minority men who use stimulants have afforded our team many successes and learning experiences. Our focus on modification of the MI and CM intervention protocols for telehealth delivery during the COVID-19 pandemic expanded their reach and potential public health impact. We also gained experience with implementing a national recruitment campaign that will guide appropriate resource allocation in subsequent randomized controlled trials. Implementing a waiting period prior to randomization did not meaningfully diminish our randomization rate and highlighted the operational efficiencies of leveraging rapid HIV testing that could be used in subsequent randomized controlled trials. We anticipate dissemination of estimates of feasibility, acceptability, and preliminary effectiveness from the pilot SMART with findings from qualitative exit interviews in the coming year. Lessons learned from this pilot SMART will guide more definitive trials of behavioral interventions to optimize success along the PrEP care continuum with this high-priority population of sexual minority men who use stimulants.

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Data Availability

The data sets generated during or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

LDE served as project manager and led the writing of the paper. CG and AWC served as project principal investigators and were major contributors to the writing of the paper. RV served as intervention staff and contributed to the writing of the paper. JM served as motivational interviewing trainer and supervisor and contributed to the writing of the paper. SD served as data manager and data analyst for the paper. OV, NO, EC, SC, and MV served as trial staff and editors. SDL served as the scientific advisor for the trial and met with recently diagnosed participants to answer their questions about HIV treatment. INS served as a content expert in sequential multiple assignment randomized trial methods. All authors read and approved the final paper.

Conflicts of Interest

SDL received research support from Gilead Sciences and Merck.

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Abbreviations

CAS: condomless anal sex
CM: contingency management
MI: motivational interviewing
PrEP: pre-exposure prophylaxis
PRISM: PrEP Readiness Interventions for Supporting Motivation
REDCap: Research Electronic Data Capture
SMART: sequential multiple assignment randomized trial

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Protocol

A Trauma-Informed, Geospatially Aware, Just-in-Time Adaptive mHealth Intervention to Support Effective Coping Skills Among People Living With HIV in New Orleans: Development and Protocol for a Pilot Randomized Controlled Trial

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Abstract

Background: In 2020, Greater New Orleans, Louisiana, was home to 7048 people living with HIV—1083 per 100,000 residents, 2.85 times the US national rate. With Louisiana routinely ranked last in indexes of health equity, violent crime rates in Orleans Parish quintupling national averages, and in-care New Orleans people living with HIV surviving twice the US average of adverse childhood experiences, accessible, trauma-focused, evidence-based interventions (EBIs) for violence-affected people living with HIV are urgently needed.

Objective: To meet this need, we adapted *Living in the Face of Trauma*, a well-established EBI tailored for people living with HIV, into *NOLA GEM*, a just-in-time adaptive mobile health (mHealth) intervention. This study aimed to culturally tailor and refine the NOLA GEM app and assess its acceptability; feasibility; and preliminary efficacy on care engagement, medication adherence, viral suppression, and mental well-being among in-care people living with HIV in Greater New Orleans.

Methods: The development of NOLA GEM entailed identifying real-time tailoring variables via a geographic ecological momentary assessment (GEMA) study (n=49; aim 1) and place-based and user-centered tailoring, responsive to the unique cultural contexts of HIV survivorship in New Orleans, via formative interviews (n=12; aim 2). The iOS- and Android-enabled NOLA GEM app leverages twice-daily GEMA prompts to offer just-in-time, in-app recommendations for effective coping skills practice and app-delivered *Living in the Face of Trauma* session content. For aim 3, the pilot trial will enroll an analytic sample of 60 New Orleans people living with HIV individually randomized to parallel NOLA GEM (intervention) or GEMA-alone (control) arms at a 1:1 allocation for a 21-day period. Acceptability and feasibility will be assessed via enrollment, attrition, active daily use through paradata metrics, and prevalidated usability measures. At the postassessment time point, primary end points will be assessed via a range of well-validated, domain-specific scales. Care engagement and viral suppression will be assessed via past missed appointments and self-reported viral load at 30 and 90 days, respectively, and through well-demonstrated adherence self-efficacy measures.

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Results: Aims 1 and 2 have been achieved, NOLA GEM is in Beta, and all aim-3 methods have been reviewed and approved by the institutional review board of Tulane University. Recruitment was launched in July 2023, with a target date for follow-up assessment completion in December 2023.

Conclusions: By leveraging user-centered development and embracing principles that elevate the lived expertise of New Orleans people living with HIV, mHealth-adapted EBIs can reflect community wisdom on posttraumatic resilience. Sustainable adoption of the NOLA GEM app and a promising early efficacy profile will support the feasibility of a future fully powered clinical trial and potential translation to new underserved settings in service of holistic survivorship and well-being of people living with HIV.

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KEYWORDS

mobile health; mHealth; HIV; traumatic stress; posttraumatic growth; coping; geospatial; just-in-time adaptive intervention; JITAI; just-in-time; posttraumatic; medication adherence; mental well-being; viral suppression; coping; development; design; acceptability; feasibility; mobile phone

Introduction

Background

Trauma, violence, and survivorship are often closely intertwined for people living with HIV [1-4]. Among people living with HIV, posttraumatic stress disorder (PTSD) prevalence has been estimated at 28% worldwide [5]. Women living with HIV endure PTSD at rates as high as 35% (nearly 10 times the estimated national prevalence among adults in the United States) [5,6], with up to 97.1% reporting lifetime trauma histories in clinic-based samples [7], including cumulative adverse childhood experiences [8,9]. Early-life adversities are often compounded by syndemic food insecurity [10,11]; poverty [12]; and chronic prolonged exposure to relational, sexual [1,2,13,14], and community violence [15], particularly among Black people living with HIV, who are diagnosed at 22 to 33 times the rate of White American individuals [16]. Among seropositive young Black men who have sex with men enrolled in the Chicago-based Project nGage, which studied personalized social support as facilitator of antiretroviral therapy (ART) adherence, 40% had a close friend or relative die in violent circumstances; most had endured secondhand violence exposure—hearing gunshots (78%) and witnessing a physical assault (59%) [17]. Indeed, the syndemic effects of chronic violence exposure are often multiplicative, compounding, and disruptive to HIV continuum of care (CoC) maintenance, particularly among Black people living with HIV and men who have sex with men [18].

The daily toll of survivorship (regardless of formal PTSD diagnosis) is considerable for violence-affected people living with HIV [18]. Somatoform symptoms, including headaches, muscle ache, sexual discomfort, and fatigue, lacking “organic” etiology [19,20], can affect people living with HIV with trauma histories [5,21]. Continuous community violence, even endured vicariously, can represent a chronic environmental stressor, leading to self-isolation, collapse of social support networks [18], and persistent avoidance of trauma-related settings [1,5,18]; these can include clinical care sites for people living with HIV [1,4], with implications for dropout from the HIV CoC and reluctance to engage in clinic-based social support [8]. Approximately half (48% [22]) of people living with HIV in multisite samples show diagnosable substance use disorder (SUD), the foremost predictor of poor CoC retention [23]. SUD can represent a form of maladaptive coping, which is especially burdensome for violence-affected people living with HIV. In clinic-based samples, high PTSD symptom burden can increase the likelihood of opioid misuse (adjusted odds ratio 1.55, 95% CI 1.31-1.83); hazardous alcohol use (adjusted odds ratio 1.28, 95% CI 0.07-1.52) [24]; and, among New Orleans people living with HIV, membership in heavy-drinking alcohol use typologies [25]. Comorbid PTSD, depressive symptoms, and SUD interact to drive sexual transmission risk behaviors and derail CoC milestones [13,23], incurring risk of individual virologic rebound and immunologic dysfunction [26-28] and endangering population-level, treatment-as-prevention goals [29]. These entanglements of violence, traumatic stress, and biobehavioral sequelae suggest the need for closely tailored, trauma-informed interventions to support both proximal psychosocial and distal CoC goals for violence-affected people living with HIV remains acute.

Among the limited range of trialed interventions that target people living with HIV–specific violence exposure, trauma symptoms, and related sequelae [2,30] in service of CoC and adherence end points, *active, effective (also known as adaptive) coping* has emerged as a key mechanism of action able to mediate intraindividual pathways from lifetime, violence-induced traumatic stress to SUD and sexual risk [1,2,4] and facilitate posttraumatic growth [31,32]. The 15-session group intervention *Living in the Face of Trauma* (LIFT) is exemplary of such an approach [9,33]. LIFT, and the specific coping skills it aims to impart, is grounded in the cognitive theory of stress and coping (CTSC) [33,34]. The CTSC, in translation to an intervention model, recognizes 2 types of coping: “problem-focused” coping—strategies that aim to change or proactively manage a stressor (recognizing it as *changeable*)—and “emotion-focused” coping—strategies that aim to exert control over an emotional reaction to a stressor (acknowledging that it is *unchangeable*) [35]. Examples of the former include structured problem-solving skills, whereas the latter can include techniques such as cognitive restructuring, a technique to challenge and dismantle automatic thoughts such as dwelling on single negative details, which can undermine

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self-efficacy and self-esteem [33]. LIFT, notably, is not a PTSD treatment [33]. Among violence-affected people living with HIV, these adaptive coping strategies are meant to reduce the burden of posttraumatic stress, interrupting automatic recourse to maladaptive strategies such as hazardous alcohol use and, by extension, mitigating forward HIV transmission risk behaviors such as ART nonadherence and CoC dropout [8,13,23,33,34].

In an early randomized controlled trial (RCT) among mostly Black (68.6%) people living with HIV with histories of childhood sexual abuse, 40% of whom surpassed Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, diagnostic thresholds for PTSD, LIFT demonstrated clinically significant improvements in intrusive symptom burden [34] and reduction in avoidant coping styles and traumatic stress symptoms longitudinally [36]. A theoretically grounded, Centers for Disease Control and Prevention "Best Evidence"–designated intervention [37], LIFT has been adapted to meet the needs of South African women living with HIV [38] exhibiting exceedingly high (≤76.6%) sexual abuse prevalence, leading to statistically significant reductions in avoidance and hyperarousal symptoms of PTSD and improved ART adherence motivations at the 3-month follow-up in exploratory outcome analyses. However, a group session component was poorly attended, a challenge that the investigators attributed to participant concerns about privacy, stigma, and transportation logistics [39]. The preliminary short-term success of this adaptation, *Improving AIDS Care after Trauma*, points to the "innovation adaptability" of LIFT [40] and to the attunement of its core components to the needs of people living with HIV across high-incidence, resource-constrained settings.

Orleans and Jefferson Parishes, which constitute the New Orleans metropolitan area, Louisiana, were home to 7048 people living with HIV in 2020, a rate of 1083 per 100,000 population—2.85 times the US national rate [41]. With the second highest 2019 Gini coefficient (0.6) in the United States [42] and Louisiana routinely ranked last in national indexes of health care and income equality [43], the New Orleans 2019 murder rate (30.7 per 100,000) was 5 times the national average [44]. Contemporary findings from the *New Orleans Alcohol Use in HIV* study show that an in-care cohort of New Orleans people living with HIV survived an average of 3.5 adverse childhood experiences (vs 1.6 nationally) [45], with 21.2% obtaining high (>3/5) PTSD scores on the *Primary Care PTSD Screen for the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)* [46]. Disparate exposure to high-density alcohol outlet environments is conducive to harmful SUD-consistent consumption patterns and depressive symptoms among New Orleans people living with HIV [45], reinforcing previous research implicating place-based drivers of CoC dropout [47,48]. In short, Greater New Orleans presents a setting in which syndemic HIV, traumatic stress, and violence exposure burden may be amenable to accessible coping skills interventions tailored for people living with HIV.

Study Objectives

This study aims to develop, pilot, and refine *NOLA GEM*, a smartphone-delivered LIFT adaptation informed by within-person geographic ecological momentary assessment (GEMA) data on time-variant stressors and symptom profiles among violence-affected people living with HIV in New Orleans [49]. Mobile health (mHealth) and internet-delivered interventions that activate evidence-based, trauma-informed psychotherapies have shown promise in enacting clinically significant PTSD improvement [50,51], with a 2018 Cochrane review pointing toward opportunities to bolster the evidence base and calling for closer attention to mechanisms of change [52]. The benefits of mHealth in advancing CoC milestones are well established [53,54], although innovations in cultural and contextual tailoring are urgently needed to ensure sustainability [55-57]. These benefits can be augmented by in-app geospatial awareness, building on prior work that leverages GPS to (for example) alert mHealth users to the proximity of HIV and sexual and reproductive health clinics [58,59] or, in contrast, use real-time GPS coordinates to (1) describe routine activity paths and (2) apply this geospatial awareness at a hyperlocal level to address the potential of spatial-environmental stressors to evoke traumatic stress and drive CoC churn and, alternatively, identify restorative spaces to reduce stress. By developing NOLA GEM, we engage these opportunities to advance the field; meet the needs of New Orleans people living with HIV [41,45,46]; and address the nonlinear, holistic nature of traumatic stress [1,2,4,8] by delivering effective coping skills education and reinforcement in real time [33].

We will engage these objectives via the following specific aims:

1. *Aim 1*: conduct GEMA with violence-affected people living with HIV to (1) describe activity spaces associated with CoC and (2) assess potential mediated pathways through mood, mental health, substance use, trauma cognitions, and coping to inform novel intervention targets.
2. *Aim 2*: develop NOLA GEM, an mHealth LIFT adaptation, incorporating GEMA-informed mediators of well-being tailored for New Orleans people living with HIV.
3. *Aim 3*: test the feasibility, acceptability, and preliminary efficacy of the NOLA GEM app against GEMA alone on primary CoC (care engagement, ART adherence, and viral suppression) and secondary mental well-being end points.

Throughout, we use "NOLA GEM" to refer exclusively to the app that was developed in aim 2 to record GEMA data and deliver adapted LIFT intervention content.

Methods

Overview

NOLA GEM was developed through a multiphase National Institute on Alcohol Abuse and Alcoholism–funded pilot (R34AA028961) applying GEMA (*aim 1*)- and in-depth interview (*aim 2*)–derived insights to adapt LIFT to a just-in-time adaptive mHealth modality [60,61]. Aim 1 was launched in March 2021 and closed out in September 2021 (although aim 1 eventually recruited a sample of 89, owing to scheduling constraints, a subset of 49 informed intervention development). Aim-2 interviews were conducted in March 2022 and April 2022. This study protocol recounts the concurrent triangulated aim-1 and aim-2 analyses, their findings, and the consequent development of NOLA GEM and describes the

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design and conduct of the acceptability, feasibility, and preliminary efficacy (*aim 3*) trial. Throughout, we adhered to the SPIRIT (Standard Protocol Items: Recommendation for Interventional Trials) guidelines [62] as modified for pilot and feasibility trials [63].

Aim 1: GEMA

Overview

A GEMA approach triangulates conventional ecological momentary assessment (EMA) methods, in which repeated assessments of participants' cognitions, affect, behaviors, and biomarkers (eg, salivary cortisol [64]) are taken at multiple daily intervals, contextualized by GPS coordinates [49,65]. Through GEMA, recall bias is mitigated, and naturalistic spatiotemporal influences on individual health can be inferred [65]. It is particularly well suited for detecting context-specific environmental stressors and facilitators of individual resilience [66,67]. Using GEMA, aim 1 intended to describe *activity spaces*, the spatial configurations in which routine events occur with characteristic rhythms [68,69] associated with durable within-person patterns (both risk markers and risk buffers) of adherence and care among people living with HIV in New Orleans. Particular attention was paid to detecting potential mediated pathways via mood, mental health, substance use and misuse, trauma cognitions, coping skills, and domain-general self-efficacy variables, indicating the potential to operationalize these constructs as intervention touch points or proximal outcomes [70,71].

A small observational pilot of the GEMA method was reported by Theall et al [66]. Detailed methods and full (N=89) aim-1 GEMA findings are forthcoming.

Study Setting

As a nested, microlongitudinal study, aim 1 recruited and used the baseline and medical record data of a subset of participants already enrolled in the New Orleans area longitudinal *New Orleans Alcohol Use in HIV* cohort study [72,73]. This parent study recruited through the HIV outpatient clinic of a large university-affiliated medical center at which approximately 50% of New Orleans people living with HIV receive care.

Participants and Procedures

Inclusion criteria for the parent study (N=365) included age of ≥18 years, documented HIV serostatus, and being in care at an HIV specialty clinic; any patient experiencing an acute illness within the previous 6 weeks, acute intoxication, or pregnancy was excluded, with the option to participate once the then-acute medical issue was resolved. Enrolling a longitudinal cohort, the *New Orleans Alcohol Use in HIV* study's primary aims are to advance clinically actionable knowledge on the biological mechanisms and socioenvironmental drivers of HIV- and alcohol-related comorbidities [72,73]. Details of the parent study protocol are available in Appendix 1 of the study by Welsh et al [72]. For the sake of aim-2 intervention development, aim 1 recruited people living with HIV (n=49; a limited subsample because of scheduling delays incurred during the recovery from 2021 Hurricane Ida) on ART who either self-reported a personal history of violence or lived in a high-violence neighborhood in the parent study. These "either/or" multilevel eligibility criteria were formulated pragmatically to ensure sufficient statistical power. History of violence criteria included reporting childhood physical or sexual abuse or physical assault as an adult or endorsing moderate to high stress because of neighborhood crime and family or relational violence. Living in a high-violence neighborhood was defined as the respondent's residential Census tract having violent crime rates at or above the 75th percentile for violent crime rates for tracts within Orleans Parish. According to these criteria, 96% (47/49) of the sample indicated an individual personal history of violence exposure, with 4% (2/49) endorsing tract-level violence exposure exclusively. Parent study participants who met the inclusion criteria were contacted initially by phone after randomizing the order in which outreach was conducted. If interested, they were asked to schedule a 1-hour dedicated baseline appointment at which informed consent procedures were undertaken, a baseline assessment was conducted using REDCap (Research Electronic Data Capture; Vanderbilt University) [74], the daily diary EMA measures were reviewed for comprehension, and a GPS app was installed on participants' smartphones. Eligible people living with HIV who did not possess a smartphone were provided one by study staff. Once enrolled, daily diary and geospatial tracking data were collected for each individual over a continuous 14-day daily diary survey period.

The 49 aim-1 participants whose GEMA responses informed intervention development recounted a range of lifetime violence exposures at baseline: 24 (49%) recounted childhood domestic violence, 18 (37%) recounted childhood sexual assault, 26 (53%) recounted physical assault in adulthood, 20 (41%) recounted current crime and violence exposures, and 9 (18%) recounted current intrafamilial violence. Screener responses suggested a range of potential mental health challenges: of the 49 participants, 13 (27%) had borderline or clinical PTSD as defined by the DSM-5, a total of 19 (39%) had borderline or clinical anxiety, and 12 (24%) had borderline or clinical depression. ART nonadherence was reported by 28 (57%). The broader sociodemographic attributes of aim-1 participants are presented in Table 1.

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Table 1. Aim-1 participant (n=49) sociodemographic attributes.

Characteristics	Values
Age (years), mean (SD)	57.06 (9.59)
Years living with HIV, mean (SD)[a]	23.00 (9.41)
Sex assigned at birth, n (%)[b]	
Female	16 (33)
Male	33 (67)
Racial and ethnic identity, n (%)	
Black or African American, non-Hispanic	40 (82)
Native Hawaiian and Pacific Islander, non-Hispanic	1 (2)
White non-Hispanic	5 (10)
White Hispanic	2 (4)
Sexual identity, n (%)	
Heterosexual or straight	28 (57)
Gay or lesbian	11 (22)
Bisexual	7 (14)
Missing	3 (6)
Household income (US $) in the past year at BL[c], n (%)	
<20,000	39 (80)
20,000-39,999	9 (18)
40,000-59,999	0 (0)
60,000-84,999	0 (0)
≥85,000	1 (2)
Housing at BL, n (%)	
Single-family dwelling	45 (92)
HIV-specific group facility	1 (2)
Homeless or shelter	3 (6)
Homeless (lifetime), n (%)	22 (45)
Incarcerated (lifetime), n (%)	25 (51)

[a]Computed by subtracting the year of HIV diagnosis in the medical records from the present year (2022); 13 participants lacked a recorded year of diagnosis.

[b]In line with the 2-step approach to ascertaining transgender identity in sociomedical research [75], a "current gender" item is included in the follow-up assessments presently underway.

[c]BL: baseline.

Daily Diaries

The daily diary measures, which operationalized the EMA aspect of aim 1, assessed a range of intrapsychic constructs, behaviors, and environmental stressors, combining brief prevalidated scales with novel study-specific measures. Participants were prompted by SMS text message and asked to complete the daily diary measures within a 3-hour window 3 times daily: 8 AM to 11 AM, 1 PM to 4 PM, and 7 PM to 10 PM Central Time Zone. Qualtrics (Qualtrics International, Inc) hosted the survey measures and administered the preprogrammed SMS text message prompts [76].

The daily diary measures for aim 1, with sample items, is shown in Multimedia Appendix 1.

Geospatial Tracking

At aim-1 baseline appointments, participants were guided through the installation of Actsoft Encore GPS-tracking app [77]. Throughout each individual's 14-day daily diary survey period, Encore captured longitudinal and latitudinal coordinates at 1-minute intervals when moving and 1-hour intervals when stationary (for aim 3, the NOLA GEM app itself will deliver daily diaries and record geospatial trajectories). GPS data were stored on a password-protected cloud server. Participant GPS data were then transformed into activity paths at 50-, 100-, and 200-meter buffers using Python (Python Software Foundation)

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[78]. Environmental exposures were assessed through the creation of activity paths and interceptions with the 3 buffer sizes. Both static and dynamic environmental exposures were captured. Static data included, for example, annual rates per US Census tract level of exposure such as alcohol outlet density, community violent crime rate, poverty, and concentrated disadvantage. Dynamic data included time-stamped data linked to daily GPS points, including time-incident violent and nonviolent 9-1-1 calls to service data points and police stop-and-frisk calls. Activity path data were then aggregated to be merged with daily diary data for triangulation.

Aim-1 Formative Insights

In the course of exploratory and interim analyses of baseline and daily diary data, a range of environmental stressors with salience to the everyday lives of New Orleans area people living with HIV emerged. The study's original objective was to understand how local spatial exposure and daily experiences may serve as determinants of traumatic stress or retraumatization connected to downstream maladaptive coping behaviors such as alcohol use and consequent patterns of ART nonadherence [79,80]. Our preliminary analyses did not find associations between outcomes related to alcohol use and daily mood across activity path–based spatial alcohol and violence exposure. These null results necessitated a departure from the original aim-1 goal of building generalizable place-based exposures as just-in-time adaptive intervention (JITAI) inputs into the NOLA GEM app. As such, tailoring variables, and the daily diary items through which they were captured in aim 1, were selected based on their overall prevalence at baseline, capturing past and cumulative experiences and associations with key outcomes within individuals on a given day among aim-1 participants. In recognition of the irreducibly idiographic nature of spatial traumatic stress determinants evidenced in this study, an individually customizable geofencing solution was built into the eventual NOLA GEM app (detailed in the *NOLA GEM App* section).

These stressors, with relevant statistics illustrating the rationale for their inclusion as JITAI tailoring variables, are provided in Table 2.

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Table 2. NOLA GEM app just-in-time adaptive intervention tailoring variables—description and rationale.

Stressor	Rationale	Sample item or items[a]
Mental health challenges	• 51.22% endorsed "somewhat" or "very" stressful mental health challenges (past 30 days)[b]	• In the past 30 days, how stressful were the following events? You can say "Not Applicable" if you did not experience this event. • Worried about my mental health (not at all, somewhat, a lot)

Financial challenges	• Within individuals on a given day, more financial stress positively predicted[c]:
	  • Mental health worries: β=1.12, SE 0.36
	• Individuals who had greater financial stress over 14 days also had greater[c]:
	  • PTSD[d] symptom burden: β=1.4, SE 0.44
	  • Pain symptom burden: β=2.6, SE 1.24
		• The next few questions ask about difficult events you might have experienced today. Please mark all that you experienced today:
		  • Financial stress
		  • Had a problem with money (yes, no)
		  • Worried about running out of food (yes, no)
		  • Worried about paying rent or getting evicted (yes, no)

Violence: direct	• 57.32% experienced IPV[e] • 31.71% experienced sexual assault (lifetime)[b]	• IPV was measured using the Composite Abuse Scale (Revised)–Short Form [81]. • The following are a couple of difficult or stressful things that sometimes happen to people either in relationships or not. These things can happen with someone you know, like a caregiver or partner, or someone you don't know well like a stranger or acquaintance. • Sexual assault: rape, attempted rape, made to perform any type of sexual act through force or threat of harm (never happened, happened but not in the past 12 months, happened in the past 12 months)
Violence: indirect	• 37.80% heard gunfire • 17.07% experienced or witnessed police violence or intimidation • 14.63% witnessed robbery, assault, or verbal threats (past 30 days)[b]	• In the past 30 days, how stressful were the following events? You can say "Not Applicable" if you did not experience this event. • Heard gunfire (not, somewhat, very stressful) • Experienced or saw police violence or intimidation (not, somewhat, very stressful) • Saw someone get robbed, injured, or threatened (not, somewhat, very stressful)
Violence: posttraumatic stress	• >82.98% experienced ≥1 PTSD symptom (14-day aim-1 study period)c	• How much were you bothered by avoiding thoughts, activities, or feelings about difficult life events that have happened to you? (not at all, a little bit, moderately, extremely; scale adapted from Erwin et al [82])

Social support deprivation	• Within individuals on a given day, reporting no social support predicted[c]:
	  • Mental health worries: β=1.66, SE 0.58
	  • Negative affect: β=.69, SE 0.23
	• Individuals who reported less social support over 14 days also reported more[c]:
	  • PTSD symptoms: β=10.74; SE 2.5
		• The next few questions ask about difficult events you might have experienced today. Please mark all that you experienced today (checklist):
		  • Didn't feel supported by friends/family (yes, no)

Social support deprivation	• Within individuals on a given day, reporting an argument predicted[c]:
	  • PTSD symptoms: β=.97, SE 0.31
	  • Negative affect: β=.59, SE 0.21
		• The next few questions ask about difficult events you might have experienced today. Please mark all that you experienced today (checklist):
		  • Had an argument with a friend, family member, or romantic partner (yes, no)

Internalized HIV stigma	• Within individuals on a given day, more negative feelings regarding HIV were positively associated with[c]:
	  • Mental health worries: β=1.05, SE 0.36
	  • PTSD symptom burden: β=.25, SE 0.15
	  • Negative affect: β=.31, SE 0.07[c]
		• Since last night/your last diary entry, how have you felt about your HIV status? Check all that apply (checklist):
		  • Ashamed (yes, no)
		  • Stressed (yes, no)
		  • Not as good as other people (yes, no)

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[a]All aim-1 daily diary items are provided in Multimedia Appendix 1.

[b]Captured at baseline.

[c]Captured via daily diary.

[d]PTSD: posttraumatic stress disorder.

[e]IPV: intimate partner violence.

Aim 2: Intervention Adaptation

Overview

Although GEMA can undergird rich, sophisticated statistical insights on the activity spaces of New Orleans people living with HIV, an overreliance on the "technocratic thrust" of decontextualized mathematical modeling risks overlooking the lived expertise of longtime New Orleanian survivors, with implications for external validity specifically [83,84] and epistemic justice, which is broadly defined as affording appropriate credibility to the knowledge- and sense-making practices of structurally marginalized groups such as people living with HIV [80,85]. As such, aim 2 recruited a subcohort of people living with HIV (n=12) enrolled in aim 1 to contribute their insights on stress, coping, and survivorship via in-depth interviews. This phase aimed to adapt LIFT in a manner that (1) activated the unique, uniquely powerful value propositions of mHealth [51,53,54,86] and (2) interlocked GEMA-derived intervention touch points with the core components of an extant evidence-based intervention (EBI) logic [33,34,36-39] while (3) recognizing the singular cultural and historical context of HIV survivorship in contemporary New Orleans. As such, aim 2 embraced principles of *design justice*, which call for a nonhierarchical, nonexploitative stance toward engaging the lived expertise of local communities [87] while leveraging the pragmatic, product-focused toolkit of *Lean User Experience*, which emphasizes an accelerated, iterative build-measure-learn approach to software development [88].

By invoking principles of epistemic and design justice, we aimed, in practice, to learn about and integrate community perspectives, needs, and especially strengths into the functionality of NOLA GEM [89]. This resulted in JITAI tailoring variables closely attuned to the needs of—and intervention content and proximal outcomes that reliably tap into the inductively derived strengths of—longtime violence-affected HIV survivors in New Orleans as "socially embedded, socially situated" community members [90]. In line with Jaworski et al [91] and Maestre et al [92], we synthesized mixed methods–derived insights in a manner calibrated to (1) appreciate local, culturally congruent nuances in our constructs of interest; (2) understand the precise conditions in which digital tools are used (and not used) among New Orleans people living with HIV; and (3) foreground coping focally and emotional well-being broadly as determinants of distal biomedical outcomes such as virologic control while calling on an extant EBI [33,34,36-39]. This approach is in line with core design justice principles, specifically design intentions committed to healing, sustainment, and empowerment; the catalyzation of people living with HIV end users' lived expertise with formal design techniques; and, in particular, embracing "what is already working," both via an adaptation of a demonstrated EBI and by incorporating aim-2 participants' own drivers of survivorship and resilience while respecting users' personal beliefs and local knowledge [87].

LIFT Intervention

Overarchingly, LIFT activates the CTSC, relying on that theory's distinction between problem- and emotion-focused coping [33-35]. Through this lens, a range of adjunctive coping skillsets is taught, practiced, and discussed by group members in the course of a LIFT implementation in the field. These include breathing awareness and retraining, mindfulness meditation, journaling and distinguishing problem- versus emotion-focused and adaptive versus maladaptive coping styles, setting attainable personal goals, and surmounting common trauma cognitions (eg, all-or-nothing thinking). Theoretically grounded details of their precise trauma-informed mechanisms of action are provided by Sikkema et al [9,34,36] and in the *LIFT Manual* (hereafter, the *Manual*) [33]. The essentials of integrating each skillset into a LIFT participant's daily life are reinforced through a range of skillset-specific handouts (eg, "Handout 4: Guidelines for Journal Writing"). The content of the NOLA GEM app was adapted by combining the *Manual*'s facilitator notes, sample (facilitator) scripts, and handouts [33]. In resituating the provision of this skill-building content from an in-person sequential group modality to a smartphone-delivered just-in-time modality, we envisioned use cases in which, for instance, the stress of hearing gunshots in the morning could be ameliorated via real-time access to breathing awareness or journaling (both emotion-focused coping skills per the CTSC [35]), interrupting the possibility of resorting to maladaptive coping strategies such as alcohol misuse.

JITAI Approach

A JITAI provides individually tailored intervention content precisely when needed, typically by tapping into the key affordances of smartphone-based models of delivery. Key elements of a JITAI include decision points, the time points at which the precise provision of intervention content is decided; tailoring variables, the data inputs that determine the nature of the intervention content offered; and decision rules, which embed the logics of tailoring variables at each prespecified decision point [60,61]. The end points of a JITAI logic are *proximal* (or short-term) outcomes, typically mediators of an intervention's ultimate *distal* outcomes [60]. JITAIs have been reliably demonstrated to drive significant improvements across behavioral health domains in pretest-posttest trials and against waitlist, inert, and active controls [93].

Semistructured Interviews

To attain a balanced age distribution, aim 2 planned, initially, to recruit 5 to 10 participants from two studies: (1) the parent *New Orleans Alcohol Use in HIV* cohort (age range 18-65 years [72,73]), whose participants' ages were concentrated in middle adulthood (median 50, IQR 41-56 years), and (2) the adolescent and young adult–focused Adolescent Medicine Trials Network

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for HIV/AIDS Interventions cohort (age range 12-24 years [94]; aim 2 planned to recruit participants aged ≥18 years exclusively). Ultimately, we were only able to enroll participants (n=12; mean age 57.83, SD 10.12 years; 58.33% Black and 75% male) from the parent longitudinal study [72]. Interviews ranged from 34 minutes, 31 seconds to 1 hour, 32 minutes, 18 seconds in length. Participants were given the option of a Zoom (Zoom Video Communications)-conducted [95] versus an in-person interview; 2 preferred Zoom. Adherent to the Tulane University Health Sciences Center COVID-19 control protocols then in place, all participants were required to bring proof of vaccination. Interviewers, who conducted the interviews in pairs, and participants remained masked at all times. Data collection proceeded subsequent to a verbal informed consent script.

The sociodemographic attributes of the aim-2 participants are shown in Table 3.

Table 3. Aim-2 participant (n=12) sociodemographic attributes.

Characteristics	Values
Age (years), mean (SD)	57.83 (10.12)
Years living with HIV, mean (SD)[a]	26 (7.93)
Sex assigned at birth, n (%)[b]	
Female	3 (25)
Male	9 (75)
Racial and ethnic identity, n (%)	
Black or African American, non-Hispanic	7 (58)
Native Hawaiian and Pacific Islander, non-Hispanic	0 (0)
White non-Hispanic	4 (33)
White Hispanic	1 (8)
Sexual identity, n (%)	
Heterosexual or straight	5 (42)
Gay or lesbian	5 (42)
Bisexual	2 (17)
Household income (US $) in the past year at BL[c], n (%)	
<20,000	8 (67)
20,000-39,999	2 (17)
40,000-59,999	1 (8)
60,000-84,999	0 (0)
≥85,000	1 (8)
Housing at BL, n (%)	
Single-family dwelling	9 (75)
HIV-specific group facility	2 (17)
Homeless or shelter	1 (8)
Homeless (lifetime), n (%)	7 (58)
Incarcerated (lifetime), n (%)	6 (50)

[a]Computed by subtracting the year of HIV diagnosis in the medical records from the present year (2022); 2 participants lacked a recorded year of diagnosis.

[b]In line with the 2-step approach to ascertaining transgender identity in sociomedical research [75], a "current gender" item is included in the follow-up assessments presently underway.

[c]BL: baseline.

Interviews were semistructured in format and mixed methods interpretivist in orientation [83]. Initially, participants were prompted to designate how helpful they would find the skillsets offered by LIFT and a range of potential mHealth modalities (eg, SMS text messages or games) on a 4-point forced-choice Likert-type scale. The aim-2 sample was LIFT naive; the particular coping skillsets were introduced via brief interviewer-administered synopses (eg, "When managing daily stress related to life with HIV, how helpful would you find breathing retraining or finding different ways to breathe?"), with scripted in-depth definitions abstracted from the *Manual* available as needed (eg, "The way we breathe can affect the

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way we feel. Daily stress and anxiety can change the way we breathe and keep us feeling stressed. Breathing retraining describes ways we can adjust our breathing to help us relax when managing everyday stress"). Unstructured probes reflecting interviewees' own language wherever possible elicited further detail on within-person patterns of successful coping grounded in the lived experiences of violence-affected people living with HIV in New Orleans. In addition, participants were asked to describe stress-inducing and reliably calming places and personal histories of violence, spirituality, relationships, drugs, and alcohol. A series of items grounded in design justice principles [87] prompted participants to reflect on the idiographic influences of their gender, ethnoracial and cultural heritage, and ability or disability on (1) their preferred stress management techniques and (2) the ways in which they interact with and selectively disengage from digital technologies. Each interview culminated in an adapted think-aloud exercise calling upon tenets of human-centered design [96,97] in which participants were reminded of the LIFT skillsets and mHealth modalities that they had previously considered "helpful" or "very helpful" and of particular stressors that they had characterized as "able to throw [their] whole day's plans off track," incite drug and alcohol misuse, or disrupt ART adherence. Aiming to encourage creative leaps [96] while eliciting context-specific JITAI dynamics rooted within the life worlds of New Orleans people living with HIV, participants were asked to narrativize precisely how their preferred LIFT skillsets would aid their coping through their most acute stressors, with impromptu probes (whenever possible) articulating details of their ideal mode of smartphone-based delivery. All interviews were audio recorded using a Sony ICD-PX470 digital voice recorder and transcribed verbatim.

Aim-2 Analysis

The qualitative analyses were subdivided into two phases, each with a dedicated intervention adaptation purpose:

1. A rapid inductive analysis dedicated to identifying *contender proximal outcomes*, a JITAI-specific construct that describes measurable potential mediators on the causal pathway to attaining *distal* (ie, our primary) outcomes.
2. A coding reliability thematic analysis dedicated to identifying survivorship and resilience themes, which would guide the adaptation of manualized LIFT worksheets into in-app NOLA GEM content responsive to the experiences of violence-affected New Orleanian people living with HIV. These themes were not operationalized as potential mediators but, rather, served to prioritize elements of the *Manual* to retain in the necessarily briefer NOLA GEM multimedia content.

The app development timeline necessitated this subdivision. Programming operationalized contender proximal outcomes as "SkillCheck" quizzes (described later in this paragraph) was an early, urgent development milestone, whereas in-app content adaptation could occur on a more generous, investigator-initiated schedule. The analytic procedure of the first phase of aim 2 relied, first, on a variant of rigorous and accelerated data reduction, a rapid matrix analysis technique [98]. Coders (n=7) condensed each interview into its richest, most salient excerpts using matrices in Microsoft Excel (Microsoft Corp) [99]. Independently, each coder inductively developed first-cycle ("open" in grounded theory terminology) descriptive, process, and in vivo codes [100]. Concurrently, each coder, consistent with a causation coding approach [100], identified contender proximal JITAI outcomes—inductively derived potential mediators of the NOLA GEM intervention's predetermined distal outcomes [60,61]. The first author (SJS), in collaboration with LVH, synthesized these initial codes and contender proximal outcomes into second-cycle ("axial") codes. These contender proximal outcomes were then preliminarily operationalized as "SkillCheck" quizzes, which would be provided to end users upon completion of prespecified units of intervention content (a process that is detailed in the *Intervention Design* section).

Subsequently, in the analysis in the second phase of aim 2, the second-cycle coding schema and complete interview data set were migrated to Dedoose (SocioCultural Research Consultants) [101]. In Dedoose, 3 coders, accompanied by the first author (SJS), pilot coded randomly selected full transcripts masked to each other's coding applications, resolved coding discrepancies, and refined the final codebook in conference until a pooled intercoder reliability of κ=0.78 was achieved [102]. After obtaining acceptable intercoder reliability, the balance of transcripts was coded independently (KS, LVH, and MBS).

Aim-2 Formative Insights

A total of 10 contender proximal outcomes were detected through the rapid matrix analyses in the first phase of aim 2. These constructs and the SkillCheck items used to operationalize them as potential mediators are provided in Textbox 1.

Building on the insights from the first phase of aim 2, refined survivorship and resilience themes, with 2 nested subthemes, were detected across the inductive analyses in the second phase of aim 2. Methodologically, we generated second-cycle pattern codes, formatted as process codes, which rely on gerunds to (consistent with dynamic JITAI logics [60]) "imply actions intertwined with the dynamics of time" [100]. The complete set of themes, subthemes, definitions, and illustrative excerpts is provided in Table 4.

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Textbox 1. Formative results of the first phase of aim 2—proximal outcomes and SkillChecks. All response options were 4-point forced-choice Likert scales ("strongly agree" to "strongly disagree") in format. Although the phrase Please rate your agreement with the following statement recurs in each SkillCheck, we omitted it from subsequent textbox examples to avoid needless duplication.

Strengthened grounding skills

- "Grounding" refers to focusing on our own bodies, how they occupy time and space, to reclaim our minds from unpleasant thoughts or feelings.
- *Please rate your agreement with the following statement*: This skill helped me: *build grounding into my everyday life*.

Strengthened healthy routines

- Healthy routines that reflect our authentic selves, interests, and practical wisdom can keep our minds occupied and self-care needs met.
- This skill helped me: *build healthy routines into my everyday life*.

Strengthened positive social bonds

- Having a few go-to people in our lives ready to listen and support us through a rough day is essential to our well-being.
- This skill helped me: *take steps toward building a supportive social circle into my everyday life*.

Strengthened awareness of spatial triggers

- Certain parts of the city—certain neighborhoods, corners, bars, or parks—can cause sudden painful memories or unpleasant feelings.
- This skill helped me: *think through certain spaces and places that can trigger my stress*.

Strengthened redirect skills

- "Redirecting" refers to recognizing the unhelpful or hurtful places where our thoughts may be taking us and conscientiously steering our minds in a more meaningful, productive direction.
- This skill helped me: *redirect away from negative coping strategies that arise in everyday life*.

Strengthened insights on self-management capacity

- Being honest with ourselves about the stressful situations that we can handle versus the situations we cannot keeps us out of situations that may compromise healthy decision-making.
- This skill helped me: *better understand the situations I can handle versus those I cannot*.

Strengthened comfort with survivorship disclosures

- It can take great strength to disclose our HIV survivorship, even if it emerges as a source of inner strength or a point of fellowship.
- This skill helped me: *ease stress and build my comfort around disclosing my HIV survivorship*.

Strengthened help-seeking capacity

- It can take self-honesty to admit when we need help sometimes, and reaching out to others when in need can be even harder.
- This skill helped me: *build my comfort in reaching out to others when I need help*.

Strengthened forgiveness skills

- It can take wisdom to let go of resentment, forgiving ourselves and others for past decisions that may have been hurtful or mistaken.
- This skill helped me: *build my ability to forgive myself and others*.

Strengthened insights on spirituality and well-being

- Deeper understandings of the mind, the soul, spirituality, and meditation often guide us away from unpleasant thoughts and feelings whether we consider ourselves religious or not.
- This skill helped me: *connect my inner life with my own day-to-day well-being*.

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Table 4. Formative results of the second phase of aim 2—themes, definitions, and illustrative excerpts.

Theme	Definition	Example[a]
Accepting and adapting	Captures any instances in which participants describe accepting difficult or nonoptimal life circumstances, typically through processes of self-reflection or recognition of the limits of control over one's life and its trajectory	"I'm the kind of person that can adapt to really anything. I would have maybe a little hissy fit at first, but I do cope with change well. And I just move on because that's really all you can do in life." [Participant M; Black male individual[b]; aged 42 years[c]]
Accepting and adapting (*self-reflecting*[d])	Captures specific, explicit mentions of the self-reflective processes that facilitate accepting and adapting	"I have made some mistakes, but that's history. They've been paid for, squashed. But you can reflect on that. It's like, 'Mm-hmm [affirmative].' Just, you move on. Be happy about what you do, where you're at. That's the way I look at it." [Participant R; White male individual; aged 63 years]
Affirming shared experience	Subsumes any mentions of forging social bonds regarding shared histories or experiences in common, often emphasizing learning and problem-solving	"Sometimes you just want to be by yourself and think things out. But sometimes, it's also very helpful because you talk with somebody and you're realizing, they have the same situation, and they do something that might help them and you're open to try something else and maybe might help you." [Participant H; White female individual; aged 54 years]
Cultivating spirituality	Captures any mention of the role of self-evolved, personal, idiographic modes of spirituality as preferred or relied-upon modes of coping; spiritual aspect must be explicit	"Well, I pray all the time. Not all the time, but frequently all day long. Just to stay calm. Help me stay calm. Not that I'm stressed out much, but [prayer] help me not get a tone." [Participant F; White male individual; aged 65 years]
Embracing routine	Subsumes mentions of carrying out repeated, cadenced tasks or rituals to occupy the mind and body, typically emphasizing the stress mitigation aspect thereof	"I get up every morning and I clean my whole neighborhood stores up, the laundromat. They don't pay me. I just walk and do it. And they've just been a routine all my life." [Participant U; Black female individual; aged 70 years]
Enacting boundaries	Subsumes acknowledgments that restricting or eliminating contact with select individuals is protective of emotional, spiritual, and physical well-being; relational-interpersonal aspect must be explicit	"Just the idea of waking up being among the living, had something to do to pay attention other than being 'round people with bad influence, making you do something that you regret doing, or make your regret doing something they want you to do [to] satisfy them...why should I make myself miserable just to be your friend, knowing I'm going to pay for it?" [Participant I; Black male individual; aged 58 years]
Finding fellowship	Captures any mention of community as continuity and community as facilitating coping; includes faith communities, organized religion, and social bonds formed therein	"The rest of my relationships and the relationships in my life, they add bits and pieces to help my mental health basically, like talking to friends and when I need to vent, venting to my sisters...Like, 'Hey, I got an issue. Hey, how would you do this, or let me bounce this off of you so I can understand where I'm coming from,' or something like that." [Participant Z; Black male individual; aged 39 years]
Regulating impulses	Subsumes mentions of conscientiously recognizing, confronting, minimizing, or extinguishing impulsive urges and behaviors	"I've experienced violence twice. I witnessed it on somebody else, and I made cognitive decisions that my partner is not going to have to deal with what my friend was dealing with his partner. And my coping mechanism is silence. Just silence. I just, rather than pop off and say things you regret later, I'll just shut down." [Participant E; White male individual; aged 67 years]
Regulating impulses (*rejecting substances*)	Subsumes instances of impulse regulation specifically, explicitly related to overcoming hazardous alcohol and drug use behaviors	"Because I used to use drugs about four years ago. Alcohol too. When I got rid of that, because when I got into my spirituals, I took away the alcohol and the desire for drug." [Participant O; Black male individual; aged 60 years]
Self-soothing	Captures any instances in which healthy, adaptive activities chosen or routinely undertaken to minimize stress and exposure to stressors are described	"Pray. Little deep breaths, calm myself down, talk to myself 'Calm down, don't don't let it get to you.' Give myself my own little pep talk. Calm down, whatever. And just go and hang out with my grandkids and that's destressed right there." [Participant H; White female individual; aged 54 years]
Staying situationally aware	Captures any mention of vigilance with regard to one's surroundings, often emphasizing the potential for violence (inclusive of law enforcement–enacted violence); spatial aspect must be explicit	"Well, [participating in GEMA] brought me to the point to be more observative...that really made me pay attention. Is you in drug free zone? Is it easy to get alcohol? Is it easy to get drug? And when I read those things, that made me alert not to go to those places because I know if I go around some of these places...I smell trouble." [Participant I; Black male individual; aged 58 years]

[a]Excerpts have been edited lightly for conciseness.

[b]Assigned sex.

[c]Age at time of interview.

[d]Italicization denotes subthemes.

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Intervention Design

Lean user experience (UX) recognizes the challenge of user-centered outcomes losing focus over the course of complex, multistakeholder technology development cycles—a challenge that is intensified when faced with extant, theoretically grounded EBI logics [33,34]. As such, we called on Lean UX techniques to integrate the full gamut of formative insights cultivated across aims 1 and 2, counteracting the (interrelated) possibilities of stakeholder misalignment or theoretical fragmentation [103] (as an added strength of this approach, Lean UX exists in tandem with the Agile workflows adopted by most contemporary software developers [88]).

Specifically, using the Miro whiteboarding platform [104], we assembled a feature hypothesis chart and conducted a design workshop in which the formative research undertaken to date was organized according to a JITAI-consistent intervention logic [60,61,91]. *Hypothesis* in this context refers to an easily communicable single-sentence association between a user outcome; a software feature; and (in terms by Mohr et al [105]) the usage aims and elements of a behavioral intervention technology logic, whereby each element is positioned as a column header in the feature hypothesis chart. The workshop, facilitated by the first author (SJS) in June 2022, formulated feature hypotheses accordingly: "We will achieve [*distal outcome*] if user can overcome [*environmental stressor* (derived from Aim I descriptives)], operationalized via [*daily diary input* (selected from among Aim I measures)], to attain [*contender proximal outcome* (derived from aim-2 rapid matrix analyses)], by mastering [*LIFT coping skillset* (abstracted from the *Manual*)], in a manner informed by [*survivorship and resilience themes* (derived from Aim IIb thematic analysis)], delivered through [*mHealth multimedia modality*]." All faculty investigators and interviewers (serving as end-user advocates) were present. A mocked-up feature hypothesis chart is shown in Figure 1 [88,104].

Subsequently, these JITAI logics were refined into user story maps, a user experience research technique that uses simple but summative flow diagrams to portray complex in-app interactions and contingencies [88]. An illustrative excerpt of the user story maps that we provided to our developers, Crowdbotics, is shown in Figure 2 (hosted in full resolution [106]).

The complete user story maps, encompassing all possible daily diary–coping skills recommendation–SkillCheck sequences, are provided in Multimedia Appendix 2 (which can be downloaded in full resolution [107]).

Figure 1. (A) Mocked-up feature hypothesis chart displaying column heads representing each element of a theoretically grounded, culturally tailored just-in-time adaptive intervention (JITAI) and (B) a sample JITAI logic tying together formative insights derived from aims 1 and 2. The format was adapted from Gothelf and Seiden, and the graphic was created in Miro. DD: daily diary; LIFT: Living in the Face of Trauma; mHealth: mobile health.

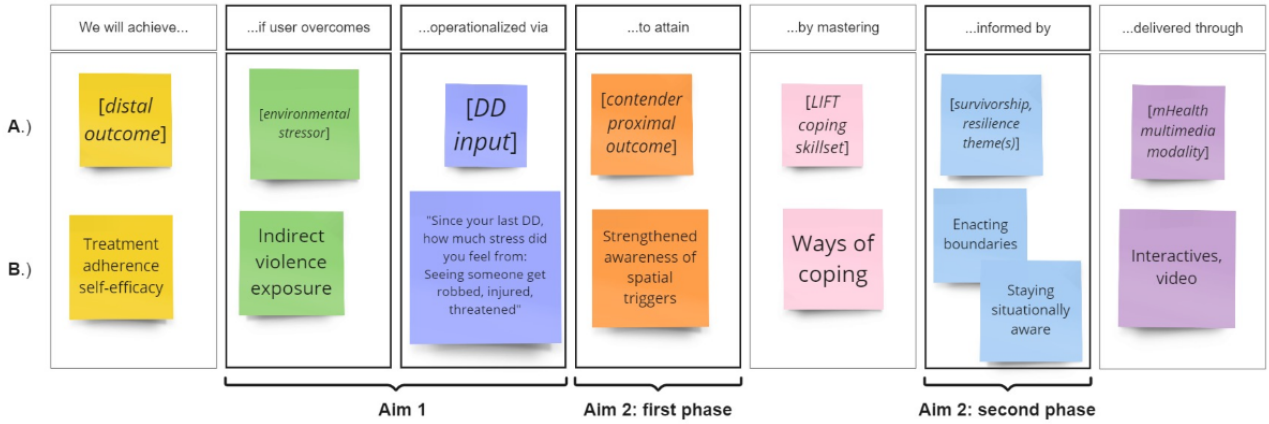
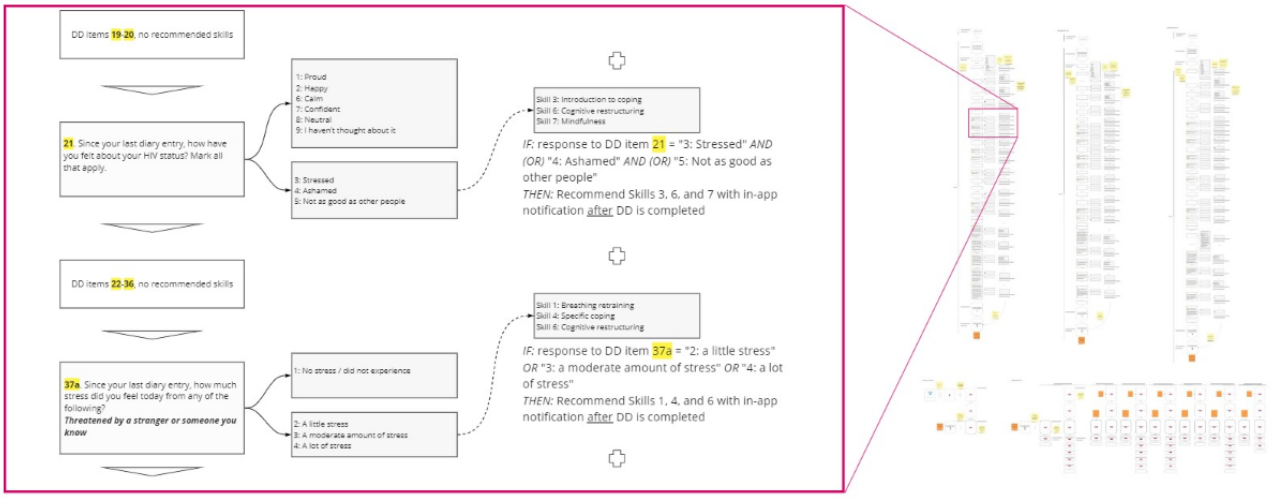


Figure 2. Selected user story map illustrating just-in-time adaptive intervention logic. DD: daily diary.



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NOLA GEM App

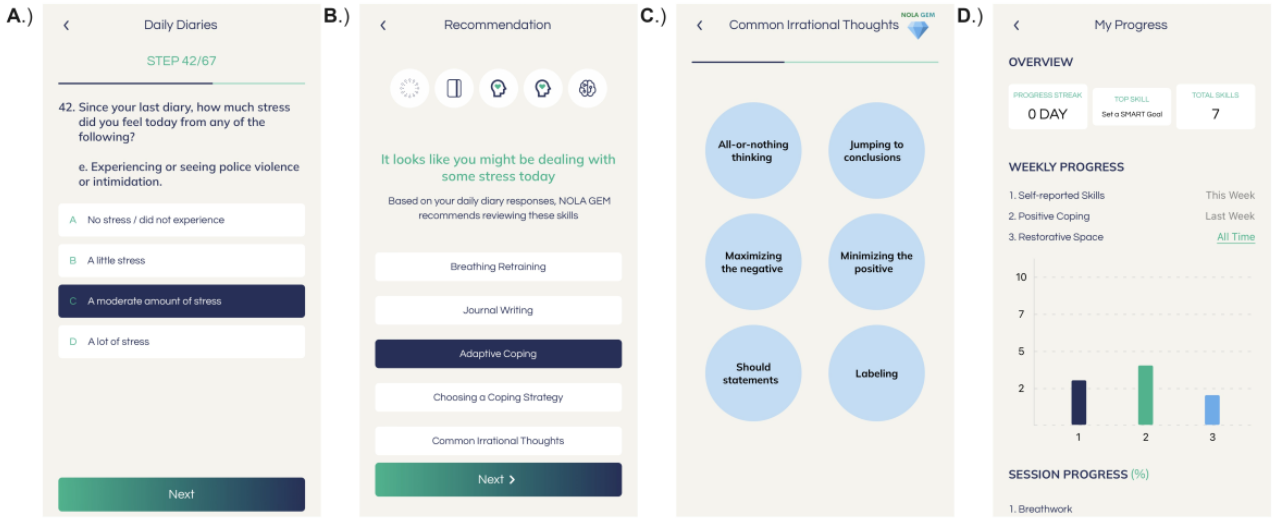
Fundamental to a JITAI adaptation is the determination of (1) tailoring variables; (2) the timely provision of appropriate intervention content, mapped to a plausible contender proximal outcome, at each predefined threshold of a tailoring variable; and (3) clear, succinct, programmable logics defining the mechanisms of (1) and (2) [60,61]. NOLA GEM incorporates a subset of aim-1 daily diary inputs as tailoring variables. On the basis of aim-1 findings, the constructs and environmental stressors that will initialize the NOLA GEM app's JITAI logics are mental health challenges; financial problems; *direct* violence experienced firsthand, such as an assault (with a built-in emergency response management protocol, if warranted); *indirect* violence, witnessed or overheard; *past* violence, resurfaced in the form of intrusive thoughts, memories, or trauma cognitions [82]; interpersonal discord or lack of social support; HIV-related stigma; alcohol-related craving and coping; and a general stress measure, the triggering of which will offer the end user a selection of all LIFT skills.

These stressors are operationalized via the daily diary measures piloted initially in aim 1. If the end user indicates an acute stressor during a daily diary beyond a prespecified cutoff value, they receive an in-app notification after completion of the daily diary inviting them to open a recommended LIFT skill. Should multiple postthreshold stressors be endorsed, the user is given the option to select their preferred LIFT skill. The microcopy of these messages is uniformly strengths-based, encouraging, and nonpathologizing (eg, "It looks like you might be dealing with some stress today. Based on your daily diary responses, NOLA GEM recommends reviewing these skills"). Embedded hyperlinks will automatically launch the recommended LIFT session if a user chooses to. Aiming to minimize "interaction cost," or the cognitive load associated with navigating a user interface [108,109], multifaceted interactivity was largely eschewed in favor of brief, "snackable" content [110] in which practical skills are foregrounded, available in text and audio formats. Each session encapsulates the CTSC-based strategies taught by the manualized LIFT intervention [33,35]. NOLA GEM users are not required to complete each skill within a single session. Upon completion at a user-directed pace, end users are presented with single-item "SkillChecks," which assess the degree to which each LIFT skillset was successfully imparted by the app and operationalize the proximal outcome to which the LIFT session and tailoring variable were mapped on the feature hypothesis chart using dedicated items in a Likert-type format. Structuring SkillChecks in this fashion further reduces interaction costs and permits both knowledge delivery and proximal outcomes to be examined as potentially distinct mediators of distal outcomes in aim 3.

In addition, supplanting the originally envisioned generalized geospatial JITAI triggers [79], NOLA GEM users, during onboarding to the app, can leverage a geofencing feature to prespecify areas or locations that reliably evince stress. With such geofencing established, entering the prespecified area will activate an SMS text message prompt ("It looks like you may be in a stressful place") recommending each user's favored LIFT coping skills. In addition, foregrounding resilience, an option to prespecify a place that end users associate with personal restorativeness is included.

Illustrative screenshots of the NOLA GEM user interface are provided in Figure 3 (hosted in full resolution [111]).

Figure 3. Illustrative screenshots of the NOLA GEM user interface. (A) sample daily diary item, (B) sample just-in-time adaptive intervention prompt, (C) Living in the Face of Trauma skill content, (D) "My Progress" tracker.



Aim 3: Acceptability, Feasibility, and Preliminary Efficacy

Trial Design

The pilot trial will be a single-blind parallel superiority trial assessing NOLA GEM (treatment arm) against GEMA alone (control arm) for a period of 21 days, allocated at a 1:1 ratio. In contrast to aim 1, the NOLA GEM app is capable of delivering SMS text message–linked daily diaries and recording GPS coordinates without recourse to third-party software. The GEMA-alone control was chosen to control for any intervention effects of recording daily mood, experiences, and other psychosocial variables as some research has demonstrated improvements in outcomes such as PTSD, depressive symptoms,

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and emotional awareness in participants recording their experiences using EMA methods [112-115] (aim-2 interviewees, unprompted, disclosed similar enhancements in self-awareness during their experience as aim-1 participants). This design establishes a high-resolution comparator to NOLA GEM, capturing GEMA data across both trial arms while potentially isolating the effects of JITAI-based momentary provision of LIFT content as a hypothesized mechanism of action.

Screening

The aim-3 inclusion criteria are equivalent to those of aims 1 and 2, although both HIV outpatient clinic–based as well as community-based recruitment strategies will be used, inviting people living with HIV across the New Orleans metropolitan area to learn about the study through flyers and screening in real time via a QR code. Once the code is scanned, users will be brought to a Qualtrics survey that will ask basic demographic questions to facilitate quota sampling, history of living with HIV, current ART medications, and past violence exposure, which will be assessed via the *Adverse Childhood Experiences Questionnaire* and US Department of Veterans Affairs National Center for PTSD *Life Events Checklist for DSM-5* [116].

An option to screen by phone, with a research assistant manually inputting each potential participant's screener responses, will also be available. Once individuals are determined to meet the eligibility criteria, they will be called to set up an intake appointment.

Sample Size Considerations

The target sample size is approximately 100, which will accommodate an anticipated ≥10% attrition rate based on previous experience enrolling local violence-affected in-care people living with HIV, for an optimal analytic sample of 60 (30 per arm).

Study Settings

Participants will be recruited using flyers from several clinics and community locations in New Orleans that offer services to people living with HIV. Many of the community sites provide linkage to care by guiding people through insurance eligibility, appointments, and medication access. Two of these community sites were founded to provide services specifically to Black and African American women living with HIV. The clinic sites are federally qualified health centers that provide a range of care; however, we are working specifically with their HIV prevention and care teams.

By and large, aim 3 will comprise a digital trial subsequent to NOLA GEM onboarding. Screeners will be completed either on the participants' phones or by calling research staff. Once participants are screened, intake appointments will take place either over Zoom or at private clinical facilities within the Tulane University School of Public Health and Tropical Medicine. All further aspects of the study will take place on the NOLA GEM app or over the phone.

Participants and Procedures

With eligibility determined, participants will be randomized, and a baseline appointment will be scheduled. Quota sampling will ensure a ≥50% female, 50% aged >40 years and 50% aged <40 years, and ≥75% Black sample, reflecting the unique drivers and PTSD symptom constellations endured by women and Black Americans while also reflecting New Orleans people living with HIV demographics.

At baseline, informed consent will be obtained, and an in-person or Zoom assessment will be administered by the research staff. The NOLA GEM app (through which participants can be assigned to either treatment or control user types via an integrated back end) will be installed on participants' smartphones from the Crowdbotics-hosted Apple App Store or Google Play Store, and a detailed onboarding will be conducted by research staff to ensure uniform comprehension of the app's features, the nature of GEMA, and the wording of daily diary items. Although participants will be instructed on the expectations, functional affordances, and user expectations specific to their trial arm, they will be blinded to their explicit treatment versus control assignment.

Smartphones

An iPhone SE smartphone will be provided to participants without access to a personal smartphone. Devices will be provided to participants with a scheduled return date. Once returned, iPhones will be sanitized and recharged, and all device histories (calls, browser, and SMS text message) will be cleared. If participants do not return the study-provided iPhone and become unreachable, they will be considered dropped from the study.

Data Collection and Management

The study app is Health Insurance Portability and Accountability Act (HIPAA) compliant and will transmit daily diary and GPS data to a Crowdbotics-hosted administrator panel, also HIPAA compliant, eschewing sensitive, identifiable data storage on participants' personal devices. GPS data collection will occur continuously, recording latitudinal and longitudinal points at 1-minute intervals. In both arms, participants will be prompted twice each day by SMS text message to complete their daily diary items within a 3-hour window (9 AM-noon and 6 PM-9 PM) whenever ready and able to find privacy.

The aim-3 daily diary items are shown in Multimedia Appendix 3.

Throughout the conduct of the aim-3 trial, data will be securely stored on REDCap, and data sets that are downloaded for analysis will be stored on secure Tulane-hosted Box cloud servers. NOLA GEM user-level paradata, including daily diary responses, will be downloaded from the HIPAA-compliant Crowdbotics-hosted administrator panel, manually cleaned, and transformed into a standard "wide" data format in which each row corresponds to a unique participant using dedicated R scripts (R Foundation for Statistical Computing).

Data Safety Monitoring

All data collected will be monitored weekly by the research staff to ensure the privacy and confidentiality of the participants. General quality assurance checks will also be run on the data during and after collection. Any adverse events or unanticipated problems will be reported immediately to the institutional review board. To ensure the confidentiality of the data, each participant

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is assigned a unique identifier that will not be linked to any identifying information. Any technology used (Zoom, Qualtrics, NOLA GEM app, or REDCap) is HIPAA secure. All SMS text message–delivered reminders sent to participants during the research period will be generic and will have no specific content in case participants wish to keep their participation private.

Intervention Arm

Intervention arm participants will be provided access to the SMS text message prompts; daily diary interface; a resource list that covers local health care, housing, domestic violence, family, and mental health services; a "My Progress" screen where they can track elements of their interaction with the app; and the full suite of LIFT sessions, skills, and SkillChecks. Following the submission of each daily diary, the study app will recommend specific LIFT content based on participants' particular patterns of momentary stressors. In addition, participants can access all content in their own time.

Control Arm (GEMA Alone)

Control arm participants will have access to the SMS text message and daily diary functions exclusively plus the resource list provided to treatment arm participants.

Primary Outcomes

Primary, distal outcome measures will be assessed at the immediate postintervention time point (within 1 week of completing the 21-day intervention period) and the 30- and 90-day follow-up assessments, as specified in the following sections.

Acceptability, Feasibility, and Usability

JITAI-specific proximal outcomes have been summarized previously. The aim-3 distal outcomes and their precise operationalization are outlined in this section.

Feasibility and acceptability will be assessed after participation in the 21-day trial period. Feasibility will be operationalized via screening and enrollment rates; completion rates of daily diaries; and paradata describing within-person patterns of use, including JITAI-triggered prompts [61,117]. Acceptability will be operationalized as follows. Intervention arm participants will complete the *User Experience Questionnaire* (short version), with ratings of the NOLA GEM app's pragmatic and hedonic quality User Experience Questionnaire domains assessed against available benchmarks [118]. The single-item *Net Promoter Score* will ask about participants' likelihood to recommend NOLA GEM on a 0 to 10 scale [119]. Both measures will be administered at the immediate postintervention assessment.

Attrition rates will also be recorded, and those who drop out of the study will receive a set of questions exploring motivations for discontinuation wherever possible.

CoC Milestones

Primary outcomes, representing recognized HIV CoC milestones [1,21,23], will be operationalized as follows via a postassessment survey.

Care Engagement

Past-30-day outpatient retention will be assessed using the 12-item *HIV Treatment Adherence Self-Efficacy Scale*. A well-validated measure, the HIV Treatment Adherence Self-Efficacy Scale recognizes care engagement as a holistic, psychosocially, and environmentally contingent construct, with particular attention to personal routine [120]. In addition, participants will self-report the percentage of appointments they missed in the past 90 days at their 90-day follow-up assessment.

ART Adherence

The capacity to maintain ART regimens will be assessed using a novel single-item visual analog scale (VAS) [72]. The VAS asks participants to estimate the percentage of their medication that they have taken in the past 30 days. Details of the VAS format and development are provided by Giordano et al [121]. In addition, daily diary measures operationalizing use of and feelings toward ART medication will be administered over the 21-day trial period (eg, "Did you have difficulty fitting your HIV treatment into your daily routine yesterday [Yes/No]"). These measures are provided in full in Multimedia Appendix 3.

Viral Suppression

Virologic control will be assessed via a self-report item asking participants whether their most recent HIV viral load test result was <50 copies/mL at the 90-day follow-up assessment. This item is adapted from the study by Carter et al [122].

Secondary Outcomes

Mental Well-Being

Diverse domains of psychosocial and emotional well-being will be assessed among all aim-3 participants.

PTSD Assessment

At 30 days after baseline, the *PTSD Checklist for DSM-5*, a 20-item self-report measure that assesses the presence and acuity of *DSM-5* PTSD symptoms, will assess traumatic stress burden for participants [123]. Considered an acceptable means of provisional diagnosis, the PTSD Checklist for DSM-5 has demonstrated psychometric soundness and acceptable continuity between Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, and *DSM-5* PTSD conceptualizations [124]. In addition, a range of daily diary measures (detailed in Multimedia Appendix 3) will record daily fluctuations in posttraumatic stress symptom acuity.

Anxiety and Depression

At 30 days after baseline, the 14-item *Hospital Anxiety and Depression Scale* will assess the presence and severity of anxiety and depression symptoms. Fielded and assessed for decades [125], the Hospital Anxiety and Depression Scale is shown to possess acceptable construct validity and internal consistency among clinical samples [126]. In addition, a mood checklist is administered via the daily diaries prompting participants to mark all moods they have experienced in the interim since their last daily diary (eg, "excited," "relaxed," or "scared"; Multimedia Appendix 3).

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Effective Coping

At 30 days after baseline, the Brief *Coping Orientation to Problems Experienced* and *Coping Self-Efficacy Scale* will measure participants' recourse to adaptive versus maladaptive styles of coping [127]. Translated into French, Spanish, Malay, and Russian and fielded successfully among broadly heterogeneous populations, the Brief Coping Orientation to Problems Experienced consistently evidences acceptable psychometric properties, although its internal factor structure remains contested [128]. The Coping Self-Efficacy Scale also demonstrates good reliability and validity, including among samples of in-care people living with HIV [129]. Via a checklist, coping strategies ("getting emotional support from others" and "criticizing myself") will be logged in the aim-3 daily diaries (Multimedia Appendix 3).

Hazardous Substance Use

At 30 days after baseline, the 3-item *Alcohol Use Disorders Identification Test*, a valid instrument for detecting heavy, potentially unhealthy alcohol use patterns [130], will be applied to that end in aim 3. The "Alcohol/Drugs" section of the widely used *Addiction Severity Index* will assess the effects of participants' alcohol and drug use across key domains of daily functioning [131]. Dedicated daily diary items will also prompt participants to describe patterns of alcohol and drug use since "last night" (morning daily diary) or "your last daily diary" (afternoon daily diary; Multimedia Appendix 3).

Domain–General Stress

Finally, at 30 days after baseline, the *Perceived Stress Scale–4* will measure situational subjective stress among aim-3 participants [132]. In addition, a 24-item aim 1–generated novel daily stressor severity checklist operationalizing a wide array of potential sources of stress arousal (eg, community and police violence, intrafamilial strife, and employment challenges) will assess multidomain stress experienced by aim-3 participants at the 30-day follow-up relative to their baseline stress burden.

Analytic Approach

Consistent with aim 1, aim-3 data will be cleaned and saved in SAS data files (SAS Institute), with extensive consistency checks conducted at all levels of data [66]. At the completion of each check, the data will be added to the existing database for analysis. GPS data will be stored on a password-protected server and constructed into activity paths, replicating the aim-1 approach [66].

Preliminarily, descriptive and crude bivariate associations between variables of interest will be generated. Daily diary completion rates and agreement with aggregate retrospective survey data for comparable measures will be calculated. Data reduction techniques, mitigating the high volume and dimensionality of GEMA-derived data, will include the creation of composite indexes of cumulative risk, with exploratory factor analysis, assessment of internal consistency, and Bonferroni correction applied as warranted.

Aim-3 analyses of preliminary efficacy will include analysis of each day-to-day distal outcome as a continuous variable as well as average exposures across the total intervention period. We will explore potential transformations to approach normality on key response variables [133]. Linear mixed-effects models will relate day-level outcomes to day-level indexes of cumulative risk and protective exposure derived originally from aim 1, adjusted for baseline values [134]. Random effects will be included to account for within-subject series correlations. Control variables will be modeled as fixed effects.

Ethics Approval

All methods and materials were reviewed and approved by the Biomedical and Social Behavioral Institutional Review Boards of Tulane University (aim 1: 860463; aim 2: 2021-1220; and aim 3: 2022-1861).

Results

Aim 1, enrolling 89 people living with HIV, was completed in September 2022. Aim 2, informed by a pilot aim-1 sample of 49 participants and a subset of 12 interviewees, was completed with the handover of the NOLA GEM app to investigators in April 2022. NOLA GEM is available to aim-3 participants as a native iOS and Android app hosted in the Apple App Store and Google Play Store, respectively. The app's onboarding and sign-on flow accommodates both intervention (treatment arm) and GEMA-only (control arm) account credentials. Ethics approval was obtained, and recruitment subsequently began, in July 2023. We anticipate that all follow-up appointments will be completed by February 2024, with the final results ready for dissemination by May 2024. The results will be disseminated to key stakeholders via scientific conferences, peer-reviewed academic journals, and Tulane University social media channels. Ultimately, as an R34-supported project, the longer-term objective is to "prune" underused or preliminarily inefficacious JITAI logics to refine a parsimonious NOLA GEM theory of change, consequently supporting an application for National Institutes of Health support for a full-scale RCT.

Discussion

Summary

This study aims to advance knowledge on temporally fluctuant and place-based stressors endured by people living with HIV in New Orleans and assess the acceptability, feasibility, and preliminary efficacy of NOLA GEM, a JITAI-consistent mHealth intervention responsive to these stressors. Key to the significance of NOLA GEM is its capacity to capture and intervene in real time on a holistic range of time-variant psychosocial and behavioral variables [10,15,21,60,61] alongside crucial neighborhood-level factors known to affect CoC outcomes and well-being among people living with HIV [11,12,23,44-48], particularly violence-affected people living with HIV [1,4,7,15]. To our knowledge, NOLA GEM is the first smartphone-delivered, trauma-informed intervention tailored for people living with HIV. As such, it will leverage a well-demonstrated EBI [33,34,36-39]; previous research supporting cognitive behavioral touch points for intervention among people living with HIV with trauma histories [135-137]; and the confidentiality, discretion, and real-time accessibility of mHealth [54,86]. Through the latter strengths in particular,

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we hope to address participant privacy and in-person group attendance concerns that may have stemmed the uptake and, possibly by extension, the longer-term efficacy of *Improving AIDS Care after Trauma* [39], the LIFT adaptation preceding NOLA GEM [38].

Notably, the mean ages of aim-1 and aim-2 participants were 57 and 58 years, respectively. This skew toward older adulthood relative to the intended user base of many people living with HIV–tailored mHealth interventions [138] may have influenced the design of NOLA GEM. Since 2014, smartphone adoption has accelerated among older adults, reaching 86% among adults aged >50 years and 62% among adults aged >70 years [139]. With motivation (both intrinsic and extrinsic) and proper feedback and support, mHealth and eHealth tools can find success among older adults [140], including older people living with HIV who, for example, engaged with the features of the *PositiveLinks* platform in a significantly more dedicated, sustained manner than younger (aged <50 years) users [141]. Success among this user base relies on a baseline degree of digital readiness [140], which is itself often contingent on device familiarity—a strength of NOLA GEM, which leverages common SMS text message and native app functional affordances, distinct from, for example, a wearable actigraphy sensor. Though some aim-2 participants attached their preferred coping techniques to their age (accepting and adapting: "You're getting older and you can't do anything about it. Just accept it and let move on" [participant F]), few, when prompted, described personal traits such as age or disability influencing their personal technology use. Post hoc, open-ended usability interviewing conducted during or shortly after intervention offboarding will allow us to examine the role of participant age (among both younger and older adults) qualitatively within the specific context of the NOLA GEM user experience.

Overarchingly, our objective is to introduce an innovative model of adaptive coping support in a periurban US Gulf South context characterized by elevated rates of HIV prevalence [41], poverty and economic inequality [42,43], and violent crime [44], reinforcing a focus on traditional HIV CoC end points with precision-tailored support for person-centered proximal outcomes grounded in the lived experience of local people living with HIV.

Limitations

As a small-scale pilot trial, aim 3 is subject to a number of inherent limitations. First, and by design [142], it is underpowered to examine efficacy in a formal hypothesis-driven manner. Mediation analyses of proximal outcomes will necessarily be exploratory in nature and inform the causal pathway hypotheses for the planned RCT. Although the selection of control conditions for mHealth trials remains an area of active investigation and debate [143], a passive GEMA-alone control may inflate preliminary estimates of NOLA GEM (incorporating GEMA+LIFT coping skills) efficacy on primary outcomes, an issue that is potentially exacerbated by the small sample size [144]. Adaptations of complex, sequential, and multicomponent group interventions risk dismantling key mechanisms of action that undergird effectiveness in their original contexts [33,34,101]. Adaptation to mHealth across HIV science remains a highly active but often methodologically impromptu area [145]. Pragmatic considerations required us to deprecate certain components of LIFT as originally manualized [33] and demonstrated to reduce traumatic stress [34,36]. Group cohesion and dedicated in-person facilitation of the group member disclosure and support processes define the LIFT intervention trajectory, which is sequenced across 15 sessions [33]. We abstracted the CTSC-based strategies built into NOLA GEM from their original, in-person, session-by-session framework to activate the "just-in-time" aspect of a JITAI adaptation while mitigating ethical concerns that, if faced with an acute stressor, a NOLA GEM user would be denied the best-suited coping support if they had not yet reached the appropriate session had a strictly linear intervention model been retained. Similarly, although a peer-to-peer support forum or social media–style feature [146,147] in which users could interact pseudonymously was briefly considered, lacking active human (vs algorithmic) content moderation, such a space could become consumed with off-topic, inane, or even outrage-inducing user-generated content and external media [86,148]. In addition, by recruiting people living with HIV who were either violence-affected individually or lived in a high-violence neighborhood, a degree of heterogeneity in needs was introduced into the aim-1 and aim-2 samples, which may have swayed the formative insights—and, by extension, intervention design—derived from the *New Orleans Alcohol Use in HIV* study subsamples. Although violence exposure at the within-person and neighborhood levels is associated with distinct sequelae among people living with HIV, it is our intention that the multitude of possible NOLA GEM user journeys can offer the necessary support to a wide range of personal violence histories. By nature, an acceptability and feasibility trial will provide insights on many of these concerns, whereas merged paradata and GEMA data will permit high-resolution analyses of users' engagement with and navigation of NOLA GEM [149].

Conclusions

Aligning user-centered development practices with principles that elevate the lived expertise of people living with HIV, mHealth-adapted EBIs can sustain well-specified theories of change while leveraging the affordances of mobile technologies. The results of the aim-3 trial will generate needed evidence concerning the value of such a locally tailored JITAI approach while pointing toward opportunities to improve upon the initial release of NOLA GEM in anticipation of a fully powered RCT offering definitive evidence of the potential of mHealth-delivered effective coping support that operationalizes the self-knowledge of communities of end users.

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Acknowledgments

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Data Availability

Deidentified aim-1 data are deposited and deidentified aim-3 data will be deposited upon completion of the pilot trial on the National Institute on Alcohol Abuse and Alcoholism Data Archive of the National Institute of Mental Health Data Archive [150].

Conflicts of Interest

SJS was a paid advisor to Waverider, which builds customizable cognitive behavioral therapy–dialectical behavior therapy eHealth tools, for the duration of this work. All other authors declare no other conflicts of interest.

Multimedia Appendix 1
Aim-1 daily diary measures—domains and operationalization.
[PDF File (Adobe PDF File), 315 KB - resprot_v12i1e47151_app1.pdf]

Multimedia Appendix 2
Complete NOLA GEM just-in-time adaptive intervention user story maps.
[PDF File (Adobe PDF File), 1105 KB - resprot_v12i1e47151_app2.pdf]

Multimedia Appendix 3
Aim-3 daily diary measures—domains and operationalization.
[PDF File (Adobe PDF File), 297 KB - resprot_v12i1e47151_app3.pdf]

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Abbreviations

ART: antiretroviral therapy
CoC: continuum of care
CTSC: cognitive theory of stress and coping
DSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
EBI: evidence-based intervention
EMA: ecological momentary assessment
GEMA: geographic ecological momentary assessment
HIPAA: Health Insurance Portability and Accountability Act
JITAI: just-in-time adaptive intervention
LIFT: Living in the Face of Trauma
mHealth: mobile health
PTSD: posttraumatic stress disorder
UX: user experience
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
SPIRIT: Standard Protocol Items: Recommendation for Interventional Trials
SUD: substance use disorder
VAS: visual analog scale

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Protocol

Digital Training Program for Line Managers (Managing Minds at Work): Protocol for a Feasibility Pilot Cluster Randomized Controlled Trial

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Abstract

Background: Mental health problems affect 1 in 6 workers annually and are one of the leading causes of sickness absence, with stress, anxiety, and depression being responsible for half of all working days lost in the United Kingdom. Primary interventions with a preventative focus are widely acknowledged as the priority for workplace mental health interventions. Line managers hold a primary role in preventing poor mental health within the workplace and, therefore, need to be equipped with the skills and knowledge to effectively carry out this role. However, most previous intervention studies have directly focused on increasing line managers' understanding and awareness of mental health rather than giving them the skills and competencies to take a proactive preventative approach in how they manage and design work. The Managing Minds at Work (MMW) digital training intervention was collaboratively designed to address this gap. The intervention aims to increase line managers' knowledge and confidence in preventing work-related stress and promoting mental health at work. It consists of 5 modules providing evidence-based interactive content on looking after your mental health, designing and managing work to promote mental well-being, management competencies that prevent work-related stress, developing a psychologically safe workplace, and having conversations about mental health at work.

Objective: The primary aim of this study is to pilot and feasibility test MMW, a digital training intervention for line managers.

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Methods: We use a cluster randomized controlled trial design consisting of 2 arms, the intervention arm and a 3-month waitlist control, in this multicenter feasibility pilot study. Line managers in the intervention arm will complete a baseline questionnaire at screening, immediately post intervention (approximately 6 weeks after baseline), and at 3- and 6-month follow-ups. Line managers in the control arm will complete an initial baseline questionnaire, repeated after 3 months on the waitlist. They will then be granted access to the MMW intervention, following which they will complete the questionnaire post intervention. The direct reports of the line managers in both arms of the trial will also be invited to take part by completing questionnaires at baseline and follow-up. As a feasibility pilot study, a formal sample size is not required. A minimum of 8 clusters (randomized into 2 groups of 4) will be sought to inform a future trial from work organizations of different types and sectors.

Results: Recruitment for the study closed in January 2022. Overall, 24 organizations and 224 line managers have been recruited. Data analysis was finished in August 2023.

Conclusions: The results from this feasibility study will provide insight into the usability and acceptability of the MMW intervention and its potential for improving line manager outcomes and those of their direct reports. These results will inform the development of subsequent trials.

Trial Registration: ClinicalTrials.gov NCT05154019; https://clinicaltrials.gov/study/NCT05154019

International Registered Report Identifier (IRRID): DERR1-10.2196/48758

(JMIR Res Protoc 2023;12:e48758) doi:10.2196/48758

KEYWORDS

acceptability; anxiety; burnout; cluster randomised control trial; depression; digital training; feasibility; intervention; intervention; managers; mental health; stress; usability; work; workplace

Introduction

Background

Common mental health problems (eg, stress, anxiety, and depression) were estimated to account for the majority of days lost due to work-related ill health in the United Kingdom in the year 2021 to 2022 (7.0 million and 7.3 million, respectively) [1]. The annual cost of absenteeism, presenteeism, and turnover associated with mental ill health in the United Kingdom has increased by a quarter since 2019 and is now estimated to be £53-£56 (US $67.51-$71.33) billion [2]. Despite these costs, many employers are unaware of the actions they could take to support their employees' mental health and of the potential return on investment of workplace mental health and well-being practices. Recent estimates suggest a return, on average, of £5.30 (US $6.75) for every £1 (US $1.27) invested [2].

There are 3 main categories of interventions that aim to mitigate the impact of poor mental health in the workplace. Primary interventions are preventative in focus and aim to remove or minimize work stressors (eg, excessive job demands, time pressure, and bullying at work) associated with work-related stress and poor mental health at work. Primary prevention involves changing the way that work is designed and managed to reduce the risks to employees' work-related stress and mental health. Secondary interventions target the identification of employees already experiencing work-related stress and poor mental health through raising awareness and knowledge of common mental health symptoms and associated workplace behaviors, such as problems concentrating, feeling uptight, distressed, and fatigued [3], and aim to provide the skills and resources to bolster coping for those employees affected. Finally, tertiary interventions aim to provide treatment of symptoms, for example, return-to-work programs, employee assistant programs, occupational therapy, and medical stress interventions [3], to minimize any effects of poor mental health at work and support the return-to-work and retention of an employee. While employers should incorporate all 3 types of intervention, a primary preventative approach is widely acknowledged as the priority [4-6].

Line managers have a key role in the operationalization and impact of such preventative approaches in the workplace. They play a vital role in designing jobs, managing work tasks and workload, treating employees with respect and clarity, creating a work environment that is supportive and psychologically safe, and encouraging open and honest conversations about mental well-being at work [7]. However, line managers need to be equipped with appropriate skills and knowledge to effectively fulfill this role.

Limited mental health or stress prevention training interventions targeting line managers exist, with only a small number using a randomized trial methodology to evaluate their impact [8-10]. These intervention studies have demonstrated effectiveness in improving line managers' knowledge of mental health [8], their skills in communicating about mental health and related resources [9], their confidence in creating a mentally healthy workplace [11], and lowered sickness absence of the employees they supervise [10]. Most of these line manager training packages have focused exclusively on increasing their awareness and knowledge of mental health at work and providing guidance on how to support and signpost employees who are already experiencing poor mental health. However, few line manager training interventions exist that aim to improve the behavioral competencies and skills of managers in preventing work-related stress and promoting mental health at work.

Equipping line managers to enable primary preventative approaches is a critical next step. Stansfeld et al's [12] study assessed the effectiveness of an evidence-based e-learning package that aimed to improve line managers' competencies in preventing work-related stress [13,14]. However, this study only used employee-related outcome measures of psychological

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distress and sickness absence, which remained unchanged, and did not examine changes in line managers' confidence, knowledge, or behavior.

This study takes a preventative approach by training line managers but broadens the content of the training beyond that of Stansfeld et al's [12] intervention to include multiple components (based on evidence and theory-driven) on the causes of work-related stress and poor mental health at work. The development of the MMW digital learning intervention is fully described in Blake et al's paper [15].

In terms of the outcome measures studied in trials to date, most studies have used primary outcomes relating to line managers (such as changes in their confidence and knowledge about mental health), which are closely linked to the content and purpose of the training. A small number of studies have explored employee outcomes such as well-being and sickness absence [12], employee distress [11], employees' perceptions of changes in their manager's behavior [9,11], and employees' use of resources available [9]. This study will build on the methods adopted by others to consider the feasibility of collecting data on the outcomes more closely related to digital training for line managers as well as outcomes related to employees, specifically their well-being and productivity.

The delivery of the training for line managers in previous trials has largely been based on face-to-face sessions [8-10] although 2 studies used web-based delivery [11,12]. With a rapid increase in the use of web-based workplace training due to the COVID-19 pandemic, the use of e-learning and digital training packages has been embraced by many employers as a way of offering more flexible learning to employees [16] and is advocated to be cost-effective as a delivery method [17]. Furthermore, providing more control to individual learners may increase motivation for, and satisfaction with, learning [18,19]. Therefore, the evaluation of digital learning and training resources has relevance in the modern workplace, and studies are needed that explore their use and acceptance by learners when related to workplace mental health. This study will primarily use qualitative data to explore the usability and acceptability of the digital mode of training and how this could be further enhanced to increase engagement and support the transfer of learning into practice.

Study Aims and Objectives

Aims

This study is part of a larger research program, the Mental Health and Productivity Pilot (MHPP) which is funded by Midlands Engine [20]. The broader aims of the MHPP program are (1) to reduce the impact of poor mental health in the workplace and barriers to employability and productivity; (2) to reduce stigma around workplace mental health; and (3) to deliver evidence-based, locally relevant, tested, and sustainable workplace programs to suit the needs of employers and employees.

This study describes a pilot and feasibility trial of a digital intervention with interactive training materials delivered on the internet to line managers (ClinicalTrials.gov NCT05154019). The intervention aims to increase managers' confidence, knowledge, and behavioral competencies to prevent work-related stress and promote mental health at work among the people they manage. The MMW training for line managers includes existing evidence-based resources that support line managers in reducing work-related stress and developing a workplace that actively promotes and supports the mental health and well-being of the people they manage (their direct reports). This study aims to determine the feasibility of a full cluster randomized controlled trial (RCT), testing the effectiveness of the MMW training on improving line managers' outcomes (confidence, knowledge, and behavior) and direct report outcomes (well-being, perceptions of line manager behaviors, and sickness absence).

Objectives

To assess the feasibility of a full trial of the MMW intervention, our specific objectives are to test:

1. The potential for uptake within small, medium, and large organizations by identifying and monitoring the:
   - willingness of employers to register interest in participating in the trial and allow line managers to take part in the trial;
   - recruitment and retention rates of line managers in the trial; and
   - recruitment and retention of managers' direct reports.
2. The perceived suitability and effectiveness of the MMW intervention for line manager training by determining the:
   - acceptability, usability, and utility of the training among line managers and stakeholders within the participating organizations;
   - potential for improving line managers' confidence (primary outcome), knowledge, and behaviors (secondary outcomes) to inform the planning of a larger trial;
   - potential for improving direct report outcomes (well-being, absence, and self-reported productivity) by assessing changes to inform the planning of a larger trial; and
   - barriers and facilitators to the intervention implementation and effectiveness.
3. The data collection methods for primary and secondary outcome measures are to:
   - inform key parameters for a larger trial relating to sample size and clustering.

How these research objectives map onto the data collection methods and measures is depicted below (Table 1).

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Table 1. Mapping of research objectives onto data collection methods and measures.

Research objective	Method of data collection	Data source or measure
Willingness of organizations to take part in trial	• Study records • Interviews with stakeholders	• % conversion from interest to participating • Qualitative data
Acceptability of waitlist control	• Interviews with stakeholders • Researcher diaries	• Qualitative data
Willingness to allow access to organizational level data on absence	• Interviews with stakeholders • Researcher diaries	• Qualitative data
Recruitment of line managers	• Study records	• % eligible line managers who consent
Retention of line managers	• Web-based survey data	• % consenting managers who complete follow-up
Recruitment of managers' direct reports	• Study records	• % eligible direct reports who consent
Retention of managers' direct reports	• Web-based survey data	• % consenting direct reports who complete follow-up
Acceptability, usability, and utility of the intervention	• Interviews with managers and stakeholders • End of module feedback from line managers	• Qualitative data • Qualitative feedback and quantitative data: fidelity delivery and engagement, implementation qualities [21]
Barriers and facilitators to the intervention implementation and effectiveness	• Interviews with line managers and stakeholders • End of module feedback from line managers	• Qualitative data • Qualitative feedback
Improvement in line manager confidence	• Web-based survey	• Confidence to create a mentally healthy workplace [11,22]
Improvement in line manager mental health knowledge	• Web-based survey	• Mental Health Knowledge Scale [23] • Mental Health Literacy in the Workplace [24]
Improvements in line manager ratings of their managerial behavior	• Web-based survey	• Management Competency Indicator Tool-manager version [13]
Improvement in direct reports' well-being	• Web-based survey	• Warwick-Edinburgh Mental Well-Being Scale 14-item [25]
Improvements in ratings of manager behavior	• Web-based survey	• Management Competency Indicator Tool-employee version [13]
Improvement in direct reports' sickness absence and productivity	• Organizational records • Self-reports	• Sickness absence rates • Productivity rating

Methods

Ethics Approval

The study will be conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki, 1996; the Principles of Good Clinical Practice; and the UK Department of Health Policy Framework for Health and Social Care, 2017. Ethics approval has been granted by the University of Nottingham's Faculty of Medicine and Health Sciences Ethics Committee (Ref. FMHS 299-0621, with amendment approved June 6, 2022). No recruitment, data collection, or intervention delivery will take place before ethical approval is in place. Informed consent will be collected for each participant in the study, following the provision of detailed information about the study. This will emphasize that participation in the study is entirely voluntary, and participants are free to withdraw at any time. Participants will not be compensated for taking part in the study. All data are to be stored securely in password-protected storage with any identifiers removed in adherence to the General Data Protection Regulations (GDPR, 2018). Any quotes from interview participants used in reports and articles will be anonymized.

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Design

This feasibility pilot study is a multisite, 2-armed cluster RCT taking place in work organizations of different sizes and sectors across the Midlands area of England. The organizations are the units of randomization (the clusters), with data collected from individual line managers (the participants) and the direct reports who are supervised by managers within those organizations. If large, multisite organizations are recruited for the study, we will consider the option of using an internal control group within that organization if there is a low risk of contamination between the intervention arm and control arm within that large organization. The data collection schedule for the study is summarized below for the intervention arm (Table 2) and the control arm (Table 3). A repeated measures design will be adopted, whereby participating line managers in the intervention arm will complete web-based questionnaires at baseline, on completion of the MMW training (approximately 6 weeks after baseline), and at 3- and 6-month follow-up periods after baseline. A 3-month waitlist control group will be used with participating line managers. They will be asked to complete web-based questionnaires at baseline, 3-month follow-up (before starting the intervention), and after completion of the training (6 months after baseline).

Table 2. Data collection schedule for the intervention arm.

	Baseline survey	Postintervention survey (approximately 6 weeks after baseline)	3 months after the baseline follow-up survey	6 months after the baseline follow-up survey	Process evaluation interviews
Intervention arm					
Managers	✓	✓	✓	✓	✓
Direct reports	✓		✓	✓	
Stakeholders					✓

Table 3. Data collection schedule for the control arm.

	Baseline survey	Preintervention survey (3 months after baseline)	Postintervention follow-up survey (6 months after baseline)	Process evaluation interviews
Control arm				
Managers	✓	✓	✓	
Direct reports	✓	✓	✓	
Stakeholders				✓

Setting

The study setting will be any organization with line managers and their direct reports within the Midlands area of the United Kingdom.

Sample Size

A minimum of 8 clusters (randomized into 2 groups of 4) will be sought to inform a future trial, as recommended for pilot clinical trials [26]. We will aim to recruit 30 line managers for each arm as per guidance for feasibility trials [27].

Recruitment

Organizations

Participating organizations will be recruited through the communication channels (Twitter, newsletters, and website) related to the wider MHPP program. A flyer advertising the study will inform organizations about the aims of the study and ask them to register their interest in participating through a web-based form. Organizations that register their interest will receive a follow-up phone call from a study researcher to provide further information about the study. We will identify the "gatekeeper," the person within the organization who will support the implementation of the study within that organization by facilitating communication with line managers and promoting the study within the organization. We will share study details, including program content and randomization. Organizations may want to provide the intervention to managers within certain departments or divisions or at certain levels of seniority within their organization. These options will be discussed as part of the organization's recruitment for the study to identify whether all managers or specific groups of managers will be approached for participation in the study. Once agreed upon in principle, we will request written informed organizational consent at the site level for the research.

Line Managers and Direct Reports

Managers within the participating organizations will be approached to participate in the study through a poster or flyer about the study, which will be shared with them by the gatekeeper within the organization. Line managers who express interest in taking part will be given information about the study and asked to provide written informed consent before participating in the study. To take part in the study, line managers must be aged 18 years or older (no maximum age but must be employed with managerial responsibilities); have direct managerial or supervision responsibility for 3 or more staff; have a work computer or mobile phone and email address with which to access the training and receive reminders; and be able to provide informed consent. Line managers will be excluded from the study if they are due to retire or be made redundant in

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the next 6 months or have undertaken work-based training on mental health at work within the past 6 months.

To assess any changes in outcomes of line managers' direct reports, all participating managers will be asked to share details of the study with their direct reports to invite them to also participate in a web-based survey at at baseline, 3-month and 6-month follow up. Participant information sheets and consent forms will be provided on the internet before these surveys are completed. Direct reports will not have any access to the training intervention itself.

All participant information sheets and consent forms will be in English. As the intervention we are testing will only be delivered in English, it will not be possible to include non-English speakers in this feasibility and pilot study. It will be explained to all potential participants that entry into the study is entirely voluntary and that they can withdraw from the study at any time without negative repercussions.

Allocation to Intervention

Organizations (clusters) will be randomly assigned (1:1) to either the intervention or waiting list control group using a web-based random sequence generator [28]. This allocation will be stratified to ensure a spread of different sizes of organizations within the intervention and control arms. Where the organization is sufficiently large to have distinct departments, divisions, or units with minimal risk of contamination between them, we will randomly assign 2 of these different departments, divisions, or units to either intervention or waiting list control using the same approach.

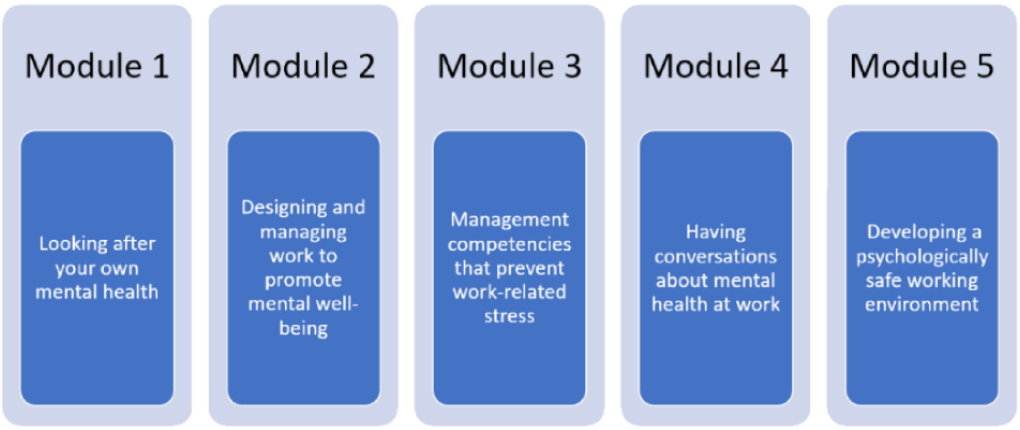
The research team and participants will not be blinded to the outcome of randomization due to practical reasons (ie, sending reminder emails to participating managers). The lead researcher will enroll participating organizations and line managers and will assign organizations (clusters) to the intervention or control arm.

The MMW Intervention

Developing the MMW Intervention

The intervention was co-designed with stakeholders to ensure it addresses employer needs and supports the engagement of participating organizations. The intervention development process was guided by Agile Science approaches as used in 2 previously published studies by Blake and colleagues [29] and fully described in Blake et al's study [15]. Stakeholder consultation and review was an iterative process, allowing for continuous delivery and a resource-efficient approach to training development. See Figure 1 for an overview of the MMW content. The MMW intervention materials were developed with considerable input from a range of stakeholders, including academic experts, learning and development experts, well-being managers, organizational representatives, and line managers. The MMW intervention is described throughout as a digital training course, and the modules therewithin refer to the various stages of this training.

Figure 1. Overview of the content of the Managing Minds at Work modules.



The MMW Training Intervention

The intervention is a digital, interactive training course delivered on the internet that includes evidence-based material, guidance, and practical exercises. It will be made accessible to participants through a secure website using a personal computer, laptop, tablet, or mobile phone. Although larger screen devices (eg, personal computer or standard laptop) are recommended to maximize readability. Individual usernames and passwords will be provided to each participating line manager to gain access to the training. The training materials are presented using a web-based, interactive, and multimedia software called Xerte [30]. The training material includes evidence-based guidance, interactive tasks with opportunities for reflection, short videos, embedded links, and downloadable checklists (an in-depth overview of the modules, using the TiDiER [Template for Intervention Description and Replication] checklist, is described in the MMW intervention development paper) checklist [15]. The training covers 5 topic areas, presented as a series of independent, stand-alone modules:

- Module 1: looking after your own mental health
- Module 2: designing and managing work to promote mental well-being
- Module 3: management competencies that prevent work-related stress
- Module 4: developing a psychologically safe workplace
- Module 5: having conversations about mental health at work

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Each module is designed to take between 20 and 30 minutes to complete. Participants will be permitted by their employer to complete the training within their work hours. The training is self-led, so each participant can progress through each module at their own pace and at a time that suits them. At the start of the intervention, a suggested schedule will be provided to each participant, whereby line managers are encouraged to schedule and complete 1 module per week. Reminder emails will be sent to participants on a weekly basis to encourage engagement and completion of that week's module.

Organizations (clusters) will communicate with line managers (either all line managers or those in selected divisions, departments, or levels of seniority) about the intervention and study. Managers in the intervention arm will be invited to register for the training and start it right away. Managers in the control arm will be invited to register for the training and start it after a 3-month wait.

Outcome Measures

Trial Feasibility and Acceptability-Related Outcomes

To address objectives 1a, 1b, 1c, 2a, and 2d, we will collect data on the following to assess the feasibility of a trial and acceptability of the intervention:

1. Number of employers registering interest in participating in the study
2. Number of employers consenting to take part in the study (minimum of 8 organizations recruited within a 6-month period)
3. Number of line managers sent information about the study
4. Recruitment of line managers into the study in both the intervention and control arms, and retention of those recruited through the follow-up points to completion in the intervention and control arms (70% at 3 months and 50% at 6 months)
5. Recruitment and retention of line managers' direct reports
6. Line manager views on the acceptability, usability, and utility of the intervention through postmodule feedback forms and end-of-study interviews
7. Stakeholders' views on the acceptability, usability, and utility of the intervention through interviews
8. Possible barriers and facilitators to the intervention implementation and effectiveness through interviews with line managers and stakeholders.

Research-Related Primary and Secondary Outcomes

In relation to objectives 2b, 2c, and 3a, we will collect the following data to assess the potential for improving line manager and direct report outcomes and inform the planning of a larger trial. The primary outcome we will assess is line managers' confidence in creating a mentally healthy workplace [11,22,31]. The secondary outcomes will be line managers' mental health knowledge [23]; line managers' workplace mental health literacy [24]; line managers' self-rating of behavior (Stress Management Competency Indicator Tool [SMCIT]–manager version) [13]; line managers' psychological well-being (Warwick-Edinburgh Mental Well-Being Scale [WEMWBS]) [25]; direct reports' psychological well-being (WEMWBS) [25]; direct reports' rating of line manager behavior (SMCIT-employee version) [13]; direct reports' sickness absence (organizational records); and direct reports' productivity (self-reported).

Data Collection Procedure in Intervention Arm

In the intervention arm, line managers will be invited to complete the digital training. Participants will be encouraged to complete the modules in succession, from introduction through to modules 1 to 5, aiming to complete a module a week. The training program should, therefore, be completed in 6 weeks. Data will be collected as per Table 2, at baseline, on completion of the MMW training (approximately 6 weeks after baseline), and at 3- and 6-month follow-up periods from baseline. Line managers' direct reports will be invited to take part in the study to determine whether they notice any change in their line manager's behavior or whether their own mental health outcomes are affected by the line manager training. Line managers' direct reports will therefore be invited to complete web-based questionnaires at baseline when the line manager starts the training, and 3 and 6 months later. Where available, data will also be collected from organizational records on the sickness absence levels of employees managed by the participating line managers.

Data Collection Procedure in Control Arm

Line managers in the organizations within the control arm will receive the intervention after a 3-month wait and will complete web-based questionnaires at baseline, just before the start of the training (3 months after baseline), and after completing the training (ie, approximately 6 months after baseline). Line managers' direct reports will be invited to complete web-based questionnaires at baseline, 3 and 6 months later. Where available, data will also be collected from organizational records on the sickness absence levels of employees managed by the participating line managers.

Measures for Line Managers (Intervention and Control)

The web-based questionnaire will contain the following items (Table 4). Demographics (including age, gender, number of years as a manager, and number of direct reports) were collected at baseline only.

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Table 4. Summary of assessments.

Activity or measure	Enrollment	Baseline	On completion of intervention (approximately 6 weeks after baseline; intervention arm only)	3 months post baseline	6 months after baseline
Obtain enrollment data	✓				
Provide username and password	✓				
Web-based consent		✓			
Manager only					
Demographics		✓			
Confidence to create a mentally healthy workplace		✓	✓	✓	✓
Mental Health Knowledge		✓	✓	✓	✓
Workplace Mental Health Literacy		✓	✓	✓	✓
Management Competency Indicator Tool-manager version		✓	✓	✓	✓
WEMWBS[a] 14		✓	✓	✓	✓
Direct reports only					
Demographics		✓			
WEMWBS[a] 14		✓		✓	✓
Management Competency Indicator Tool-employee version		✓		✓	✓
Self-reported Productivity Rating		✓		✓	✓

[a]WEMWBS: Warwick-Edinburgh Mental Well-Being Scale.

Line managers' confidence to create a psychologically healthy workplace will be quantified by a self-report measure used previously by Gayed et al [11,22] by modifying a previously published supervisor scale [31]. This measure includes 6 workplace scenarios (eg, "creating a work environment that prevents and reduces stress within my team"), which require line managers to rate their confidence on a scale of 1 ("not very confident") to 5 ("very confident"). The items are summed to create a composite score with a range of 6 to 30, with higher scores indicative of more in creating a mentally healthy workplace.

The mental health knowledge schedule (MAKS) [23] will be used to measure the line manager's mental health. It is a 6-item measure consisting of 6 key areas, such as help-seeking, recognition, support, employment, treatment, and recovery. MAKS is measured on a 5-point Likert scale ranging from 1 ("strongly disagree") to 5 ("strongly agree"). Items are summed to create a composite score ranging from 6 to 30, with higher scores indicating better knowledge of mental health.

Workplace Mental Health Literacy [24] aims to measure line managers' workplace literacy. It consists of 16 items, 4 vignettes featuring various manifestations of mental ill health within the workplace, and parallel questions exploring 4 dimensions of mental health literacy. These items are rated on a 5-point Likert scale ranging from 1 ("very low") to 5 ("very high"). A higher score represents better workplace health literacy (range 16-80).

The SMCIT [13] measures management competencies surrounding the prevention and management of work-related stress. This measure consists of 36 items examining 4 key competencies: "managing emotions and having integrity," "managing and communicating existing and future work," "managing the individual within the team," and "reasoning and managing difficult situations." Items are measured on a scale of 1 ("strongly disagree") to 5 ("strongly agree"). Each subscale is summed together, with higher scores indicating higher levels of competency. The measure has a version for both line managers (manager version) and employees (employee version), with the same content adjusted to suit the audience.

The WEMWBS [25] aims to quantify both line managers' and employees' psychological well-being over time. This measure consists of 14 items asking participants to rate a series of statements (eg, "I have been feeling useful") on a scale of 1 ("none of the time") to 5 ("all the time"). Summed scores range from 14 to 70 with higher scores representing better mental well-being.

After each of the training modules has been completed, participating managers will also be asked to complete a web-based feedback form, giving quantitative and qualitative feedback on the module. This will include questions on fidelity delivery and engagement with the training module [29]; questions on implementation qualities [29]; and open questions about how long the module took them to complete, which aspects of the module they found most useful, what they plan to change in their managerial practice, and how the module could be improved.

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Measures for Direct Reports (Intervention and Control)

Overview

On registering for the training, all participating line managers in both the intervention and control arms will be asked to send an invitation to participate in a web-based survey to their direct reports. The purpose of this is to assess whether completion of the training by line managers affects their direct reports' perception of line managers' behavior or the mental health and sickness absence outcomes of direct reports. The web-based survey for direct reports will contain the following items: demographics (age, gender, and number of years in the organization) collected at baseline only, WEMWBS 14-item [25], SMCIT-employee version [13], and a single-item self-reported productivity rating.

The web-based survey for direct reports at follow-up will contain the same items (as above) with the addition of open-response questions about any changes to how they are managed or their line manager's behavior.

Organizational Sickness Absence Records

We will collect information from the organizations regarding the sickness absence records of those the participating line managers directly manage. Preintervention data will cover the 6 months before the intervention starts. Postintervention data will cover the 6 months after intervention completion. All organizational absence records will be anonymized at source before being securely transferred to the research team.

Data Analysis

Statistical analysis will produce summary statistics to assess the parameters for a full trial. Missing data will be imputed using multiple imputations. SPSS (version 26; IBM Corp) will be used for statistical analysis. As this is a pilot trial, no emphasis will be put on the *P* values for any inferential statistical tests conducted. The primary analysis will use an intent-to-treat approach with repeated measures. Differences between the intervention and waiting list control groups at follow-up will be examined against baseline. The pilot data will provide information on the parameters needed for a realistic sample size calculation (mean, SD, and treatment effects of the primary outcome for the 2 arms) for a future main cluster RCT.

Economic Measures

We will consider the feasibility of collecting data on costs and savings from the perspective of the employer. The costs considered will be the working hours lost to complete training during working hours, and, in turn, the cost or saving of any change in sickness absence rate over the follow-up will be calculated based on the median hourly wage (£15.6 [US $19.87] per hour) [32] of employees in the United Kingdom.

Process Evaluation

Overview

A qualitative process evaluation will run alongside the pilot trial to explore the experience of the intervention with line managers and other stakeholders (eg, human resource managers and well-being coordinators) within participating organizations; assess the acceptability, usability, and utility of the intervention; and identify barriers and facilitators to implementation. Semistructured interviews will be used to collect the data to inform the process evaluation. In addition, module feedback forms will be completed by line managers after each of the 5 modules in the training course to allow more specific feedback relating to each module, including any changes in their managerial practice that participants are planning to make as a result of completing each module.

For the process evaluation interview study, participants will be invited to take part in interviews after the 6-month follow-up. Interviews will take place with (1) line managers in the intervention arm and (2) stakeholders in both the intervention and control arms.

Interviews will be conducted face-to-face, by video call, or by telephone at the participant's preference and arranged at a mutually convenient time and location. The interview schedule will cover the following research questions and topics: acceptability, usability, and utility of the intervention; changes the line manager has introduced since undertaking the training; barriers and facilitators to the intervention implementation and effectiveness; and suggested improvements to the intervention. The interviews with stakeholders will cover the following research questions and topics: barriers and facilitators to taking part in the study; acceptability of the waitlist control condition (control arm only); acceptability, usability, and utility of the intervention; and barriers and facilitators to the intervention implementation and effectiveness. For stakeholders, the gatekeeper for each participating organization (intervention and control arms) will be asked to email an invitation to participate in an interview to all relevant stakeholders within their organization (eg, human resource managers, well-being managers, learning and development managers, and trade union representatives). Principles of data saturation will be used to guide the final sample size, but as a guideline, we would expect there to be interviews with approximately 20 line managers and 1-2 stakeholders per participating organization. All interviews and analyses will be conducted by members of the research team (CB, BV, and LT). Interviews will be guided by the interview schedules and audio recorded where consent is given. Digital audio files will be transcribed and fully anonymized.

Data Analysis

The qualitative data collected will be analyzed using thematic analysis [33,34] guided by the principles of framework analysis [35,36]. The Consolidated Framework for Implementation Research [37] and the Technology Acceptance Model [38,39] will be used to provide overarching frameworks for the qualitative analysis.

Study Management

The study management group will be the research team based at the University of Nottingham and Nottinghamshire Healthcare National Health Service Foundation Trust's Institute of Mental Health. A wider advisory group will include researchers from other UK universities who are part of the wider MHPP team and who will meet monthly to monitor progress. All data will

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be managed according to the GDPR, anonymized as soon as possible, and kept securely on a database that can only be accessed by the research team.

The study duration will be 24 months, with participating organizations starting to be enrolled in June 2021, and the study will cease at the end of May 2023.

Criteria for Terminating the Study

The study may be stopped as a result of a formal or informal interim analysis and based on overwhelming evidence of efficacy or inefficacy, major safety concerns, new information, or issues with study conduct (eg, poor recruitment and loss of resources). The study may be stopped at a single site as a result of a formal or informal interim analysis and based on major safety concerns at that site, new information, or issues with study conduct at that site (eg, poor recruitment and loss of resources).

Results

Recruitment for the study opened in September 2021 and closed in January 2022. A total of 24 organizations have consented to take part in the study, and 224 line managers have been recruited within these organizations. Data analysis was finished in August 2023, and we aim to publish the results later in 2024.

Discussion

This protocol describes a feasibility trial that aims to assess the recruitment and retention rates for the study; the acceptability, usability, and utility of the MMW digital training intervention; the potential for improving outcomes for line managers and their direct reports; and the barriers and facilitators to the intervention implementation and effectiveness. This type of intervention fills an important gap as its primary focus is on the prevention of poor mental health at work through the design and management of work in a way that has been shown to promote mental well-being and prevent stress. Line managers have a critical role in this regard, and the initial testing of a digital intervention that is able to engage and be used effectively by line managers in a range of contexts is an important development. The results from this pilot and feasibility study will be a first step in informing the development of subsequent trials for MMW by providing insight into the usability and acceptability of the MMW digital training in a range of employment contexts and some initial indications of change in outcome variables for line managers and their direct reports.

We acknowledge that there are some limitations to the design to be adopted in this study. The intervention has been designed as general and relevant to line managers and supervisors across all sectors and contexts. Recruiting line managers from a wide variety of organizational contexts and sectors introduces a range of potential factors that could affect the delivery of the intervention (eg, work demands, reducing the time available to complete the intervention, and a lack of support from senior managers for mental health interventions), which could in turn affect the acceptability and usability of the results. However, the planned process evaluation interview data should help us identify some specific contextual factors that act as barriers to the intervention being accessed and used by participants. The use of a waitlist control group has been chosen to allow us to recruit more organizations and line managers into the pilot feasibility trial by offering the intervention to all participants by the end of the study. This design is often used in organization or workforce intervention studies due to the complexities of engaging businesses and public sector organizations in research and the ethics of ensuring control participants have the opportunity to potentially benefit from the intervention [40-42]. However, this is a limitation as it introduces possible biases. For example, we cannot rule out contamination of the waitlist control group. All organizations, both those allocated to the intervention and those in the waitlist control, were informed by the research team about the active components of the intervention to obtain organizational consent to participate in the study. Blinding organizations to their allocation to the intervention or waitlist control was not possible, as the research team had to explain the timing of the intervention delivery to the organizational stakeholders. To try to mitigate this, the research team ensured that organizations did not know who else was taking part in the study to avoid further contamination between sites. While we acknowledge the advantages of using single- and double-blinded designs to reduce such bias, this needs to be balanced with the pragmatism of conducting research in businesses and public sector environments.

Acknowledgments

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Data Availability

The data sets generated during the study will be made available from the corresponding authors upon reasonable request.

Authors' Contributions

LT, JH, and HB conceived and designed the study. All authors are coinvestigators and helped to develop and refine the study design. JH developed the quantitative statistical analysis plan. LT, JH, HB, BV, CB, JY, and FM contributed to developing the intervention components. AF created the first draft of the manuscript. All listed authors read and approved the final manuscript.

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Conflicts of Interest

None declared.

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Abbreviations

GDPR: General Data Protection Regulations

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MAKS: mental health knowledge schedule
MHPP: Mental Health and Productivity Pilots
MMW: Managing Minds at Work
RCT: randomized controlled trial
SMCIT: Stress Management Competency Indicator Tool
TiDiER: Template for Intervention Description and Replication
WEMWBS: Warwick-Edinburgh Mental Well-Being Scale

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Protocol

Feasibility and Effectiveness of a Personalized Home-Based Motor-Cognitive Training Program in Community-Dwelling Older Adults: Protocol for a Pragmatic Pilot Randomized Controlled Trial

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Abstract

Background: Exergame-based motor-cognitive training in older adults has been associated with improvements in physical, cognitive, and psychological functioning. The novel Cocare system (Dividat GmbH), developed through a user-centered design process, allows motor-cognitive training in a telerehabilitation setting. It includes (1) a stationary stepping platform for supervised exergame training (Dividat Senso; Dividat GmbH), (2) a home-based version (Dividat Senso Flex, which is a rollable pressure-sensitive mat; Dividat GmbH), (3) an assessment system (including motor-cognitive tests), and (4) a rehabilitation cockpit for remote training supervision and management.

Objective: The aim of this study is to test the feasibility and effectiveness of this novel training system.

Methods: A total of 180 older adults from Switzerland, Italy, and Cyprus aged ≥60 years with a prescription for rehabilitation are randomly allocated to an intervention group or a control group. Both groups continue with their usual care, whereas participants in the intervention group additionally perform a 2-week supervised exergame training program at rehabilitation centers, followed by a 10-week home training program under remote supervision. The assessment system is used to indicate the start level of each participant, and, in both intervention periods, standardized progression rules are applied. The measures of feasibility include adherence, attrition, exergame enjoyment, willingness to perform such a training program, and the number and types of help requests. Effectiveness is assessed in terms of cognitive and physical functioning, balance confidence, and quality of life.

Results: Data collection started in February 2023 and is ongoing. Final measurements are expected to be performed in January 2024.

Conclusions: Owing to the user-centered design approach, the Cocare system is expected to be user-friendly and offers several novel features to cover the whole continuum of care. This pragmatic trial will provide valuable information regarding final necessary adaptations and subsequent implementation efforts.

Trial Registration: ClinicalTrials.gov NCT05751551; https://www.clinicaltrials.gov/study/NCT05751551

International Registered Report Identifier (IRRID): DERR1-10.2196/49377

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(JMIR Res Protoc 2023;12:e49377) doi:10.2196/49377

KEYWORDS

telerehabilitation; home-based; eHealth; exergaming; older adults; motor-cognitive training; feasibility; pragmatic trial

Introduction

Background and Rationale

A steep growth in the number of people aged ≥60 years is expected by the end of the 21st century [1]. Age-related declines in physical and cognitive functioning and the associated adverse outcomes, such as restricted mobility, cognitive impairment, and falls, ultimately result in a decrease in the quality of life of older adults. Therefore, the term "active and healthy aging" (AHA) [2] is becoming increasingly important in policy frameworks worldwide.

A common strategy to promote healthy aging is to engage in physical activity. Previous research has shown that physical activity has a number of positive effects on physical and psychological health outcomes as well as on cognition in older adults [3-5]. Furthermore, it has been demonstrated that older adults benefit similarly from cognitive training programs targeting various cognitive functions such as memory, executive functions, attention, visuospatial skills, and information processing speed [6].

Given the comprehensive positive effects of physical activity and cognitive training, it has been suggested that a combination of both might be promising. Indeed, previous studies have revealed that simultaneous motor and cognitive training may be equally effective as, or even more effective than, separate or sequential training of both functions [7-13]. In fact, simultaneous motor-cognitive training can lead to improvements in physical functions such as balance [14-16], aspects of gait (eg, gait initiation) [17], and movement quality [18] as well as in cognitive functions such as executive control and processing speed [19,20], exercise enjoyment [21], decreased depressive symptoms, and an increased mental health–related quality of life [22].

However, several issues are limiting the success of such training programs; for instance, because most physical and cognitive training programs are provided face-to-face, accessibility is a major concern for older adults owing to potential mobility limitations, transportation issues, or a lack of facilities in their nearby community. Furthermore, demographic changes are increasing the need for long-term care and treatment [23] and pose financial, time, and personnel challenges to health care systems. As a result, training interventions can often not be provided for long enough durations, thus preventing patients classified as geriatric from reaching their full recovery potential and from leading an active and healthy lifestyle [24].

A solution to the aforementioned obstacles is offered by information and communication technologies, which can support the provision of care through telerehabilitation. Telerehabilitation is a broad term and can be defined as the remote provision of rehabilitation services [25]. Such a transfer of postacute rehabilitation to the home setting potentially offers a cost-effective solution to meet the increased demands on health care services, may solve the problem of accessibility, and can therefore play a key role in AHA. In addition, telerehabilitation is especially important during lockdown periods, such as those experienced during the recent COVID-19 pandemic.

Exergames are a promising option to provide telerehabilitation by means of simultaneous motor-cognitive training. They can be described as interactive whole-body movement game-based training approaches that efficiently connect motor and cognitive tasks [10]. This is the basic idea of the Cocare system (Dividat GmbH), a novel multicomponent exergame-based telerehabilitation system, including a stationary (Dividat Senso; Dividat GmbH) as well as a portable (Dividat Senso Flex; Dividat GmbH) exergame hardware device, an assessment system, and a digital training management system—the so-called rehabilitation cockpit. A more detailed description of the system can be found in the study by Seinsche et al [26].

Interventions with the Cocare system can be defined as complex interventions considering "the number of components involved; the range of behaviors targeted;...the number of groups, settings, or levels targeted; or the permitted level of flexibility of the intervention or its components" [27]. Implementation-based complex intervention research is primarily focusing on how to develop interventions that are implementable, cost-effective, and transferable to real-world settings and across different contexts [27,28]. Thereby, complex intervention research comprises four phases: (1) development of the intervention, (2) testing its feasibility, (3) evaluating the intervention, and (4) implementation of the intervention. In each phase, a major core element is the engagement of appropriate stakeholders, including those who will deliver and use the intervention [27,28]. Following this framework for the design and evaluation of complex interventions, the Cocare project was initiated to develop and validate the Cocare system applying an iterative user-centered design process to constantly refine the components of, and interventions with, the Cocare system. Previously, a focus group study was conducted to identify primary (older adults) and secondary (health care professionals) end-users' needs and requirements regarding an exergame-based telerehabilitation system in general as well as the Cocare system specifically [26]. On the basis of the results, the Cocare system was adapted before being tested in a usability study that examined the perceived usefulness as well as the ease of use, acceptability, and enjoyment of the training approach [29]. In this usability study, the Cocare system received good acceptance by primary and secondary end users, with the primary end users indicating high enjoyment while playing the exergames. However, barriers such as difficulties in understanding certain assessment and game instructions were mentioned as well. After repeated adjustments, phases 2 and 3 of complex intervention research are now targeted (ie, testing the system's feasibility and conducting a preliminary evaluation of its effectiveness).

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Objectives

The objectives of this study are (1) to test the feasibility of a personalized exergame-based motor-cognitive telerehabilitation training approach using the Cocare system in older adults with a prescription for rehabilitation (inpatient or outpatient) and (2) to obtain first insights into the effects of this training approach on cognitive and motor functions, balance confidence, and quality of life.

Methods

Trial Design

To be useful for decision makers, complex intervention research should take into consideration the complexity based on the intervention's components as well as on its interaction with the context in which it is being implemented [27], which is why a pragmatic design approach was chosen. Thus, this study is conducted as an international pragmatic pilot randomized controlled trial (RCT) with 2 arms (parallel groups). The SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2013 checklist was used for the reporting of this pragmatic RCT [30]; however, the item order has been modified slightly for good comprehensibility of our study procedures.

Ethical Considerations

The study protocol was approved by all local ethical committees, including the Cantonal ethics committee in Zurich, Switzerland (2022-01746); the Don Carlo Gnocchi Foundation ethics committee in Italy (06_16/12/2022); and the Cyprus National Bioethics Committee (ΕΕΒΚ ΕΠ 2021 51). It has been registered at ClinicalTrials.gov (NCT05751551). Any amendments of the protocol are noted, and substantial changes will be reported to the ethics committees. All interested participants receive an information sheet and a consent form describing the study and providing sufficient information for the participant to make a decision regarding study participation. A team member (ie, the principal investigator or other investigators involved) arranges a personal meeting with the prospective participants and informs them again about all study procedures, benefits, risks, and their rights regarding study participation. Afterward, the consent form is signed by both—the participant and the investigator—before the participant undertakes any study procedure. The informed consent process is documented in REDCap (Research Electronic Data Capture; Vanderbilt University).

Participants

Study Setting

This study is an international multicenter RCT, involving an intervention group (IG) and a control group (CG), conducted in three countries or trial sites: (1) Switzerland (ETH Zurich in collaboration with VAMED Rehabilitation Center Zurich Seefeld, Zurich), (2) Italy (Don Carlo Gnocchi Foundation, Milan), and (3) Cyprus (Materia Group, Nicosia). Each trial site follows detailed standard operating procedures that have been developed before the study start for each step of the study, including recruitment, measurements, intervention, and data management.

Eligibility Criteria

Interested participants are screened for eligibility via telephone and in person. The inclusion criteria are (1) aged ≥60 years (2) a prescription for rehabilitation (as inpatient or outpatient) within the past 6 months, (3) Mini-Mental State Examination (MMSE) score ≥24, (4) physically able to independently stand for at least 2 minutes, (5) able to give informed consent, (6) internet access at home, and (7) availability of a television or a large screen at home.

The exclusion criteria are (1) permanently living in a nursing home, (2) mobility limitations or comorbidities impairing the ability to perform a step-based motor-cognitive training program, (3) cognitive limitations or comorbidities impairing the ability to perform a step-based motor-cognitive training program, (4) severe sensory impairments, (5) previous or acute major psychiatric illness (eg, schizophrenia, bipolar disorder, and recurrent major depression episodes), (6) a history of drug or alcohol abuse, (7) terminal illness, (8) participation in another clinical trial, and (9) absence from home of >2 weeks during the study period.

Intervention

Overview

The study comprises two intervention periods: (1) a 2-week supervised exergame-based intervention period at the rehabilitation center and (2) a home-based exercise intervention period of 10 weeks (a total of 12 wk considering a maximum permitted interruption of 2 wk). The first period serves as the supervised familiarization of the participants with the training approach before continuing training in their homes without direct supervision. The second period starts with the study investigators visiting the participants at home to provide guidance and safety instructions for the training program and to set up the system. After 5 weeks of home-based training, the study investigators visit IG participants again for major adaptations in the training plan. For the second half of this intervention period (week 6-week 10), a new selection of games is implemented to create sufficient variety and thus minimize boredom. In addition, participants in both groups receive biweekly telephone calls by a study investigator to collect data about their usual care as well as daily physical and cognitive activities and to ask about the perceived level of training difficulty. Adherence to, and performance in, the training sessions are supervised remotely using the rehabilitation cockpit, which also serves for remote training management or progression setup.

Description of the Training Device and the Motor-Cognitive Intervention

The device that delivers the exergame training at the clinic is the Dividat Senso, which is a stepping platform with 5 pressure-sensitive plates connected to a screen on which the stimuli of the exergames appear. The exergames are played by taking steps in 4 directions (front, back, left, and right) or body weight shifting. This approach has been shown to be feasible for motor-cognitive training in older adults and has proven effective in improving various motor and cognitive outcomes [14,31-33]. For the home-based training program, Dividat Senso

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Flex (a portable version of the Dividat Senso hardware) is used. This is a foldable pressure-sensitive mat that is also connected to a television or screen. The Senso Flex system allows the same functionalities as the stationary Senso system. The motor-cognitive training with the game software targets different cognitive functions, such as attention, executive functions, and memory, and visuospatial functions as well as balance and strength.

Before starting the first intervention period, a series of physical and cognitive assessments are conducted to evaluate the participants' functional status and to create individual training plans. In both intervention periods, participants are instructed to train 3 times per week for 20 minutes, but they are allowed to divide total training volume (3 × 20 = 60 min) into more training sessions or to merge training sessions (eg, 2 × 30 = 60 min) if they wish. A training plan consisting of 15 levels of difficulty for each trained function (cognition, balance, and endurance) has been created with the levels progressing in terms of (1) choice of more difficult games and (2) increasing game duration. The initial training level is determined based on each participant's functional status.

Subsequently, training progression and personalization are carried out based on three factors: (1) a progression algorithm integrated into the software adapting the level of difficulty in each game in real time, (2) an objective progression criterion (performance plateau, defined as <5% performance increase from 1 week to the other [34]), and (3) a subjective rating of the level of difficulty by the participants based on the Borg Ratings of Perceived Exertion Scale [35] indicating whether a game was too exhausting or too easy. If, in the context of progression, new games are implemented in the training plan, the participants are informed accordingly by written messages sent via the rehabilitation cockpit.

With our training plan, we aim to follow the findings of previous systematic reviews that suggest that to be effective, a combined motor-cognitive training approach should be applied for a minimum of 8 weeks, 2 to 4 times a week, and should be based on tailored intensity monitoring and progression [10,11,36].

Usual Care and Choice of Comparator

Both IG and CG participants continue their usual care throughout the study. In pragmatic trials, usual care is difficult to define and could theoretically include a large range of interventions [37]. It could be argued that CG participants should receive 1 specific predefined treatment, but "patients in usual care control group should be confronted with the heterogeneity of treatments available in real, daily practice, rather than receiving a treatment chosen by the researchers" [37]. For this reason, we aim to administer the content of the usual care programs as precisely as possible through training logs.

Criteria for Discontinuing or Modifying Allocated Interventions

The criteria for which a participant is withdrawn from the study are (1) the withdrawal of informed consent, (2) acute hospitalization, (3) the occurrence of events or diseases listed in the exclusion criteria, and (4) the occurrence of any intervention-related major safety issues. In case of the last-named criterion, the study will be discontinued.

Strategies to Improve Adherence to Interventions

During the home-based training period, regular telephone calls (4 times) and personal visits (2 times) are made, which are expected to improve the participants' adherence. In addition, written motivational and feedback messages can be sent to the participants via the rehabilitation cockpit.

Relevant Concomitant Care Permitted or Prohibited During the Trial

There is no relevant concomitant care or intervention that is specifically permitted or prohibited during the intervention.

Outcomes and Outcome Measures

Primary Outcome

The primary outcome of this study is the feasibility of a home-based exergame training program with the Senso Flex in older adults. Thus, we follow the phases defined in the updated framework for developing and evaluating complex interventions commissioned jointly by the Medical Research Council and the National Institute for Health Research and recommended for the development of complex interventions [27]. For this purpose, we assess adherence, attrition, and perceived enjoyment in IG participants (Table 1).

The adherence rate is determined by calculating the duration of completed training sessions as percentages of the recommended duration of training. Furthermore, the attrition rate in both groups is calculated as the percentage of dropouts during study participation.

Perceived enjoyment while playing the exergames is measured with the Exergame Enjoyment Questionnaire, developed to assess enjoyment of the physical activity aspect in exergames together with enjoyment of the gaming elements [38]. The questionnaire comprises 20 items that are rated on a 5-point Likert scale, resulting in a minimum possible score of 20 and maximum possible score of 100. Considering the results of previous literature [38] and of a preliminary study testing the usability of this motor-cognitive training approach [29], an average Exergame Enjoyment Questionnaire score of 70 points (out of 100) can be deemed as *acceptable*.

However, the criteria for trial success are solely based on adherence and attrition rate measures. A 70% adherence rate was defined as being "adherent to the training program" [46,47]. According to a systematic review [47], an attrition rate of ≤10% is *acceptable* for RCTs. However, because this study is a pragmatic RCT, we deem an attrition rate of ≤20% as *acceptable*.

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Table 1. Outcomes, outcome measures, and time points.

Category and outcome	Assessment	Assessment time point
Primary outcomes		
Feasibility		
Adherence	Adherence rate	IP 2[a]
Perceived enjoyment	EEQ[b] [38]	T3[c]
Attrition	Number of dropouts	Whole study period
Secondary outcomes		
Feasibility		
Subjective workload	NASA-TLX[d] [39]	T3
Willingness to continue home-based exergame training	Single question	T3
Cognition		
Psychomotor speed	Reaction time test	T2[e] and T3
Selective attention	Go-no-go test [40]	T2 and T3
Cognitive flexibility	Flexibility test [40]	T2 and T3
Information processing	Flexibility test [40]	T2 and T3
Balance		
Static balance	Tandem Romberg test [41]	T2 and T3
Dynamic balance	Coordinated stability test	T2 and T3
Functional balance	Timed up-and-go dual task [42]	T2 and T3
Dual task	Timed up-and-go dual task [42]	T2 and T3
Strength		
Mobility	Timed up-and-go dual task [42]	T2 and T3
Leg power	30-s chair-stand test [43]	T2 and T3
Psychological factors		
Balance confidence	ABC[f] Scale [44]	T2 and T3
Quality of life and satisfaction with health	Two questions	T2 and T3
Other outcomes		
Usual care		
Usual care and daily physical and cognitive activities	Self-made questionnaire	Whole study period
Training		
Training time (IG[g])	—[h]	IP 2
Demographics		
Age, sex, years of education, living situation, body weight and height, reason for therapy prescription, and number of falls	Questionnaire	T1[i]
Comorbidities	Charlson Comorbidity Index [45]	T1

[a]IP 2: intervention period 2 (home-based exercise intervention period of 10 wk).

[b]EEQ: Exergame Enjoyment Questionnaire.

[c]T3: after the intervention.

[d]NASA-TLX: National Aeronautics and Space Administration Task Load Index.

[e]T2: before IP 2.

[f]ABC: Activities-Specific Balance Confidence.

[g]IG: intervention group.

[h]Training time is automatically recorded by the system and presented in the rehabilitation cockpit.

[i]T1: at study entry.

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Secondary Outcomes

Overview

Several other feasibility measures are assessed as secondary outcomes (Table 1). The National Aeronautics and Space Administration Task Load Index [39] is used to assess the subjective workload during exergaming. It consists of 6 subscales: mental demand, physical demand, temporal demand, performance, effort, and frustration. Each subscale is rated on a 20-point Likert scale ranging from 0=very low to 20=very high. The raw National Aeronautics and Space Administration Task Load Index scores are calculated by multiplying each subscore by 5.

In addition, after the intervention, participants will be asked about their willingness to continue a similar home-based exergame training program after the end of the study (as a proxy for training satisfaction), and agreement will be determined on a 5-point Likert scale. Finally, during the whole home-based intervention period, the number and types of additional instructions as well as help instructions are noted.

Furthermore, a series of physical and cognitive functions as well as balance confidence are assessed before and after the home-based intervention as secondary outcomes to obtain first indications regarding the effectiveness of the home-based exergame intervention (Table 1).

Cognitive Assessments

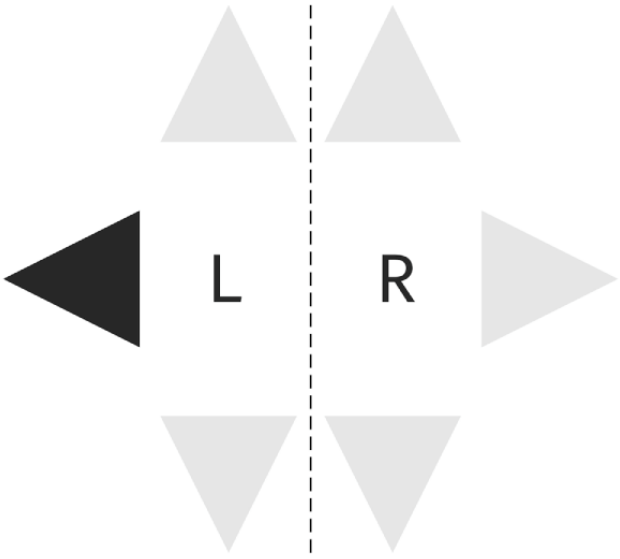
The cognitive assessments are mainly based on the standardized and validated *Test for Attentional Performance* (TAP) developed by Zimmermann and Fimm [40], a collection of reaction time tasks with tasks consisting of “simple and easily distinguishable stimuli that the patients react to by a simple motor response” [48], and are conducted using the Dividat Senso.

The reaction time test measures psychomotor speed. Six triangles are presented on the display. When a triangle turns dark, the participants are asked to react as fast as possible by taking a step in the corresponding direction (Figure 1). The arrows also indicate with which foot the step must be taken. The average reaction time (ms) and errors will be included in the analysis of effectiveness.

The go-no-go test was developed based on the go-no-go test from the TAP assessment battery [40] and measures selective attention and inhibition. More precisely, it evaluates the ability to suppress a response in the presence of irrelevant stimuli as well as the response latency during stimulus selection. Participants are asked to react as fast as possible when a cross (x) is presented on the screen. However, in case the stimulus is a plus sign (+), they must remain still (Figure 2). The average reaction time (ms) will be included in the analysis of effectiveness, and errors will be described descriptively.

The flexibility test is based on the flexibility test from the TAP battery [40] and aims to assess the flexibility of focused attention. Participants are instructed to react by taking a step toward the rounded figure and then toward the angular figure in an alternating manner (Figure 3). The average reaction time (ms) and errors will be included in the analysis of effectiveness.

Figure 1. Reaction time test.



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Figure 2. Go-no-go test.

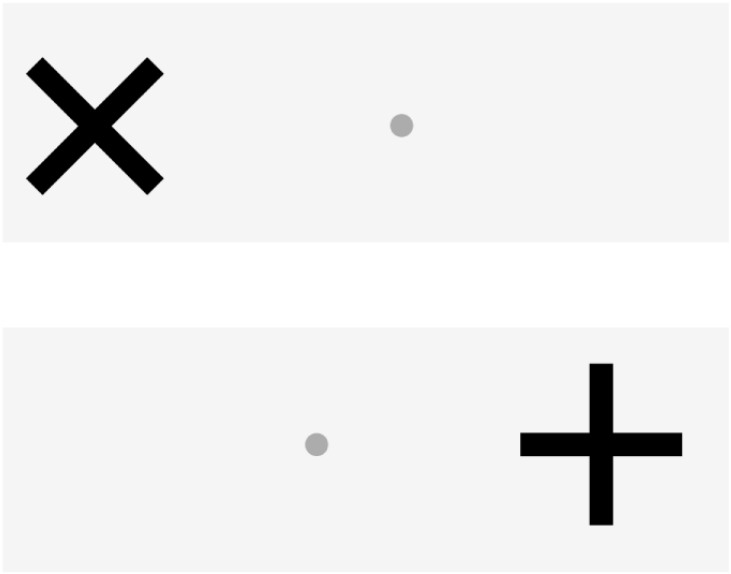
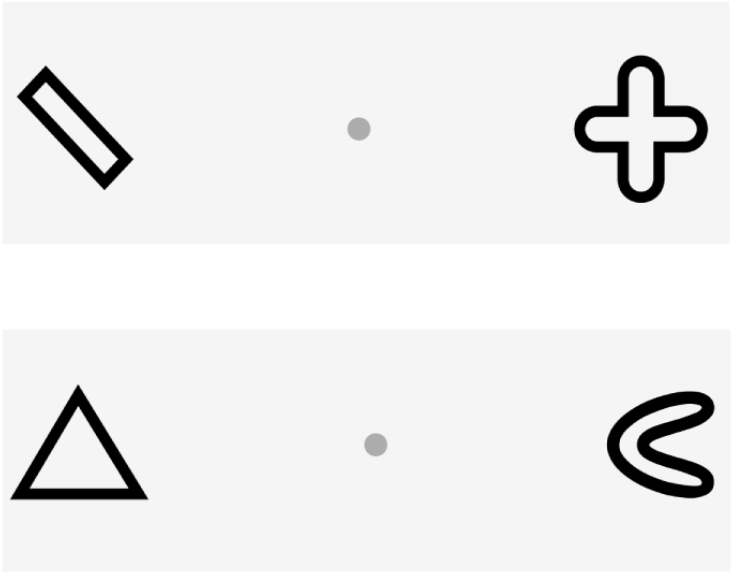


Figure 3. Flexibility test.



Balance

The sway test is based on the Romberg test [49,50] and is conducted on the Senso. The participants are instructed to stand as still as possible for 30 seconds. Meanwhile, postural sway, which is the movement of the center of pressure, will be recorded. The sway path length (mm) will be used for further analyses.

The coordinated stability test serves to measure dynamic balance. At the beginning, the participants are instructed to stand with their feet hip width apart on the middle plate and keep their arms crossed in front of their chest for the entire duration of the assessment. The task is then to follow a figure shown on the screen by shifting their center of pressure without lifting their feet. The output metrics, which will be included in the analysis of effectiveness, are the difference from the ideal path (mm) and the completeness of the path (percentage).

The timed up-and-go test [42] is a measure of mobility and functional balance and requires the participant to “rise from a standard armchair, walk to a line on the floor 3 meters away, turn, return, and sit down again” [42]. The timed up-and-go dual task (DT) complements this motor task (as the primary task) with a secondary task—here a cognitive task. For the cognitive task, participants are instructed to count backward from 90, subtracting 7 successively. This simultaneous execution of motor and cognitive tasks reflects real-life conditions better, considering the fact that in older adults, gait is not only a motor activity but also involves cognitive demands [51]. Two attempts without DT and 2 attempts with cognitive DT are conducted. In both cases, the time until the patient is fully seated again is recorded, and the best attempts are used for further analysis. DT cost is calculated by determining the percentage at which the secondary task interfered with the test performance:

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DTC [%] = 100 × (DT score − simple task score) / simple task score **(1)**

where "DTC" is the DT cost [52].

Leg Power

The 30-second chair-stand test [43] is used to assess lower limb power and short-term endurance. The participants start seated on a chair; after a countdown, they must stand up straight and sit down again as many times as possible within a time frame of 30 seconds. Meanwhile, the number of times the patient fully stands up from a seated position is counted.

Balance Confidence

The Activities-Specific Balance Confidence Scale measures the fall-associated self-efficacy of a person in different activities and situations (eg, stair climbing and walking on icy pavements). The scale is able to detect the loss of balance confidence in highly functioning older adults too [44].

Quality of Life

Participants are asked to rate their overall quality of life and satisfaction with their health. Both assessments use a 5-point Likert scale (ranging from 1=very poor or very dissatisfied to 5=very good or very satisfied).

Other Outcomes

In addition, every 2 weeks, all participants are queried by a study investigator regarding the dose (frequency and time) and content (intensity and type) of their usual care as well as their daily cognitive and physical activities, and the training times of the IG participants are collected.

At baseline, the following demographic information is collected to describe the study population: age, sex, years of education, living situation (living with another person or alone), body weight and height, reason for therapy prescription, number of falls, and comorbidities (Charlson Comorbidity Index) [45].

Assessment Time Points and Duration

Assessments are performed in a standardized order at study entry (T1), before intervention period 2 (T2), and after the intervention (T3; Tables 1 and 2). Depending on group allocation, the T1 assessment takes 30 to 60 minutes and mainly serves to collect demographic data, randomize participants, and, in the case of IG participants, assess the functional status to subsequently create their training plan. The T2 and T3 assessments represent pre- and postintervention measurements for the evaluation of the home-based intervention's effectiveness. Both measurements take approximately 90 minutes to complete.

Table 2. Schedule of interventions and assessments.

Study phase	Information and screening; phone call and study center[a]	Inclusion and baseline (T1); study center[a]	Intervention period 1; study center	Measurements before intervention period 2 (T2); study center	Intervention period 2; home setting[a]	Postintervention measurements (T3); study center
Oral and written information	✓	✓				
Eligibility criteria	✓	✓				
Written consent		✓				
Baseline factors		✓				
Primary outcomes					✓ (IG[b] only)	✓ (IG only)
Secondary outcomes				✓	✓ (IG only)	✓
Intervention			✓ (IG only)		✓ (IG only)	
Other outcomes: training time			✓ (IG only)		✓ (IG only)	
Other outcomes: usual care			✓		✓	

[a]Mode and location.

[b]IG: intervention group.

Participant Timeline

Overview

Table 2 displays the time schedule of enrollment, interventions, and measurements for IG and CG participants, as well as the respective data collected at each time point.

Sample Size

An intended sample size of 180 is based on recommendations from Whitehead et al [53], who stated that, in pilot clinical trials, for an extra small standardized effect size (≤0.1) and 90% power, 75 participants per group are required. We are expecting a 20% dropout rate, which is why we aim to recruit 90 participants per group; thus, in total, 180 participants (n=60, 33% at each trial site).

Recruitment

In Switzerland, participants are recruited through VAMED Rehabilitation Centre Zürich Seefeld, through an advertisement in the University of the Third Age of the University of Zurich, through announcements to various senior centers and organizations, and through university newsletters. Furthermore, participants of previous studies on older adults are contacted. Participants in Italy are recruited via convenience sampling, and in Cyprus, older adults who are members of existing networks are contacted, and collaborations with multifunctional

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centers for older adults are used. Besides, an open invitation to the general public has been published.

Assignment of Interventions

Sequence Generation, Allocation Concealment, and Implementation

Participants are randomly allocated to either the IG or the CG with a 1:1 allocation ratio using permuted block randomization to avoid group size imbalances as well as allocation predictability. Blocks of 4, 6, and 8 were randomly generated. The allocation list was created with the web-based randomization tool Sealed Envelope [54] and uploaded on REDCap by a study investigator not involved in the enrollment, assessment, and randomization of participants. Randomization is then run in REDCap after baseline assessments. This allows a careful allocation concealment, and the investigators responsible for recruitment and baseline assessments are unaware of the group to which a participant will be allocated.

Blinding

Given the nature of a pragmatic RCT, neither the investigators nor the participants are blinded. The investigators will be responsible for supervising the interventions as well as for conducting the measurements, and participants cannot be blinded because the CG participants do not receive any intervention (other than usual care).

Data Management and Analysis

Data Management

All investigators received theoretical and practical trainings about all study procedures, including data collection and entry. Besides, written instructions have been created to ensure standardized conduction and reproducibility of the study protocol. These trainings were documented noting date, training time point, trainer name, trainee names, and training content.

All data of all study participants are kept strictly confidential. Data are coded, and the key remains password protected in a secure network folder.

REDCap, an electronic data capture system that meets the requirements of Good Clinical Practice, is used for electronic data entry. To ensure data quality, ranges for data values have been prespecified in REDCap, which will give a warning sign if the entered data lie outside these ranges. In addition, all data entered are double-checked by an investigator not involved in specific data collection who then confirms data accuracy with their signature.

Statistical Analysis

Baseline data of IG and CG participants will be compared with independent, 2-tailed *t* tests to validate the comparability of the 2 groups. The feasibility measures will be analyzed in a descriptive way. Besides, qualitative reports will be created based on the notes of the investigators regarding the kind of help requests and additional instructions, as well as other observations.

A generalized linear mixed model will be built to analyze changes in the measures of effectiveness for the IG participants compared with the CG participants (time × group interaction to indicate whether change differs between the groups). Thus, the explanatory variables include time (T2 and T3), group (IG or CG), and the interaction between time and group. To estimate the size and direction of effects, effect sizes (Pearson correlation coefficient *r*) and CIs will be calculated [55].

Per-protocol analysis will be conducted including data of only those participants who underwent the whole study procedure, with a training adherence of at least 70% of the training at home.

In case of missing data, a missing value imputation method will be used.

Monitoring

Overview

An internal monitoring visit was conducted at ETH Zurich before the inclusion of the first participants. Further monitoring visits will be conducted after the inclusion of the first participants, throughout the whole study period to track the study progress, and at closeout, which will ensure data quality and the early detection of possible mistakes. Moreover, the clinical trial unit of the Don Carlo Gnocchi Foundation as well as the chief scientist of Materia are monitoring this study. Furthermore, there are regular meetings with the whole study team for the principal investigator to check on and manage the accuracy of the study procedures at all trial sites.

Adverse Event Reporting and Harms

In case of an adverse event, we will investigate whether it was caused by the study intervention. Furthermore, a severity assessment of the event as mild, moderate, or severe will be made. If necessary, a report will be sent to the local ethics committees.

Auditing

The ethics committees may conduct a quality assurance audit of this study.

Dissemination Plan

The study results will be disseminated to academic groups and the public through publications, conference presentations, and social media.

Results

Data collection started in February 2023 and is still ongoing. As of May 2023, we enrolled 77 participants. Final measurements are expected to be performed in January 2024, and results are expected to be published in spring 2024.

Discussion

Study Rationale

This pragmatic RCT will provide new knowledge on the feasibility and effectiveness of an exergame-based telerehabilitation program in older adults.

Despite the promising results of previous studies investigating telerehabilitation and exergames in older adults, the feasibility and effectiveness of a combination of both have not yet been

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sufficiently demonstrated. Furthermore, the combined provision of both approaches (motor-cognitive training) performed in a home setting and independently by older adults is another novel, underexplored, and fertile research area tapped by this study. To the best of our knowledge, previous research has either investigated telerehabilitation approaches that rely on the consecutive conduction of motor and cognitive training [56], or, in the case of approaches that rely on exergames, these have often limited their focus to specific populations (eg, survivors of stroke [57-60]; patients with Parkinson disease [61,62]; and older adults with cognitive impairment [63], subsyndromal depression [22], or lower limb amputation [64]) or healthy older adults [65-67]. However, exergame-based telerehabilitation should be feasible and effective in a broader population of both healthy and recovering older adults. It should especially target those without long-term access to traditional rehabilitation interventions and should accompany them to full recovery.

For this reason, and given the nature of a pragmatic RCT, in this study, the inclusion and exclusion criteria are formulated in a rather broad way to analyze the feasibility of a motor-cognitive telerehabilitation intervention in a diverse population of older adults to mirror or reflect real-life conditions and usual clinical practice as best as possible. Therefore, only participants who are clearly unable to perform a step-based motor-cognitive training program owing to physical and cognitive limitations must be excluded (another reason for exclusion: they cannot be regarded as future targets of such intervention approaches).

Concerning the study design, pragmatic RCTs have a limited internal validity, but they provide real-world evidence as well as generalizability to many real-world settings and therefore high external validity. Thus, they are “becoming a major tool in the evaluation of complex interventions and services” [68].

Conclusions

The Cocare system is complex and innovative in terms of 4 aspects. First, it includes an assessment system comprising cognitive as well as physical assessments that are based on the validated TAP battery [40]. Second, it introduces in a home environment an exergame-based training approach that has previously been proven to be effective in inpatient rehabilitation of patients classified as geriatric [31]. This seems promising, given decreasing access to conventional supervised interventions owing to the demographic change. Third, the training program can constantly be monitored and managed by health care professionals who can also communicate with the participants directly through the system (eg, send them motivational or feedback messages). Finally, and most importantly, the system has been developed in an iterative user-centered design process, which previous system developers have failed to do [69,70]. Thus, after being adapted based on a focus group study and a usability study, the Cocare system is ready to enter phases 2 and 3 of complex intervention research, and an acceptable feasibility and effectiveness can be expected.

Acknowledgments

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Data Availability

Pending approval by the responsible local ethics committees, all data will be publicly available on Zenodo. Otherwise, data will be available to researchers upon reasonable request.

Authors' Contributions

JS was responsible for conceptualization, methodology, data curation, formal analysis, and writing the original draft. EG was responsible for conceptualization, methodology, supervision, and writing the original draft. EDdB was responsible for the trial sponsor, methodology, and cosupervision. IC, MF, SI, SM, FR, and ES were responsible for methodology, data curation, and reviewing and editing the manuscript. All authors revised the manuscript and approved the version submitted for publication and agree to be accountable for all aspects of the work.

Conflicts of Interest

EDdB was a cofounder of Dividat GmbH, the spin-off company that created and developed the Cocare system. However, no revenue was paid (or promised to be paid) directly to EDdB or his institution. All other authors declare no other conflicts of interest.

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Abbreviations

AHA: active and healthy aging
CG: control group
DT: dual task
IG: intervention group
MMSE: Mini-Mental State Examination
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
TAP: Test for Attentional Performance

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Protocol

Short-Wavelength Light–Blocking Filters and Oral Melatonin Administration in Patients With Retinitis Pigmentosa: Protocol for a Randomized Controlled Trial

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Abstract

Background: The medical community is beginning to recognize that retinitis pigmentosa (RP), due to its disabling progression, eventually leads to a reduction in the patient´s quality of life, a direct economic impact, and an increase in the burden on the health care system. There is no curative treatment for the origin of the disease, and most of the current interventions fail in reducing the associated negative psychological states, such as anxiety and depression, which lead to increased variability of vision and pose a continuous threat to the patient's independence.

Objective: The aim of this study is to assess the effect of oral melatonin (OM) administration alone and combined with short-wavelength light (SWL)–blocking filters on patients with RP and test their effectiveness in improving the level of stress and sleep problems in many of these patients.

Methods: We have developed a low-cost therapy protocol for patients with RP with sleep disorders and negative psychological stress. Patients will be randomized to receive a combined intervention with SWL-blocking filters and OM, SWL-blocking filters alone, or OM alone. There will also be a nonintervention arm as a control group. This study will be conducted across 2 retinal units in patients with RP with sleep disorders and high perceived stress and anxiety score reports. Patients will be assessed in the preintervention period, weekly during the 4 weeks of intervention, and then at 6 months postintervention. The primary outcomes are the differences in changes from baseline to postintervention in hormone release (α-amylase, cortisol, and melatonin) and sleep quality, as measured with the visual analog scale. Secondary outcome measures include clinical macular changes, as measured with optical coherence tomography and optical coherence tomography angiography; retinal function, as measured using the visual field and best-corrected visual acuity; sleep data collected from personal wearables; and several patient-reported variables, such as self-recorded sleep diaries, quality of life, perceived stress, and functional status.

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Results: This project is still a study protocol and has not yet started. Bibliographic research for information for its justification began in 2020, and this working group is currently seeking start-up funding. As soon as we have the necessary means, we will proceed with the registration and organization prior to the preliminary phase.

Conclusions: In this feasibility randomized clinical controlled trial, we will compare the effects of SWL blocking alone, administration of OM alone, and a combined intervention with both in patients with RP. We present this study so that it may be replicated and incorporated into future studies at other institutions, as well as applied to additional inherited retinal dystrophies. The goal of presenting this protocol is to aid recent efforts in reducing the impact of sleeping disorders and other psychological disorders on the quality of life in patients with RP and recovering their self-autonomy. In addition, the results of this study will represent a significant step toward developing a novel low-cost therapy for patients with RP and validating a novel therapeutic target.

International Registered Report Identifier (IRRID): PRR1-10.2196/49196

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KEYWORDS

retinitis pigmentosa; oral melatonin; short-wavelength light; intrinsically photosensitive retinal ganglion cells; ipGC; retinal dystrophy; quality of life; rare eye disease; eye disease; burden; health care system; intervention; treatment; vision loss; psychological stress; sleep disorder; eye; retina; cornea; lens; glaucoma; cataract

Introduction

Background and Rationale

Retinitis pigmentosa (RP) is the most frequent form of inherited retinal dystrophy (IRD) and the main cause of hereditary blindness, with more than 1.5 million patients affected worldwide and a prevalence of 1:4000 people [1]. The term was coined by Donders in 1857 [2] and compounds a group of heterogeneous diseases characterized by a progressive degeneration of photoreceptors, starting with rods and eventually affecting cones as well. This is the mechanism responsible for the progressive loss of vision function [3].

RP can have bilateral or, less frequently, unilateral involvement and can occur isolated or as part of a syndrome [1,4,5]. It is caused by more than 3000 mutations in over 70 genes, creating a wide heterogeneity among patients with RP [6].

RP affects mainly the outer retina, but in the final stages of the disease, atrophy and damage ultimately affect the inner retina, including retinal ganglion cells [7]. Intrinsically photosensitive retinal ganglion cells (ipGCs) constitute a special type of photoreceptors within the retina that contain the melanopsin photopigment [8,9]. Although they represent less than 10% of the total ganglion cells, they play a key role in regulating the pupillary reflex, circadian photoentrainment, mood, and diverse cognitive functions [9-16]. Alterations in circadian rhythms, partially dependent on ipGC integrity, have been previously reported in different ocular diseases and blindness [17-22]. These patients usually do not properly receive light signals that ordinarily synchronize their internal circadian clock to the 24-hour day, causing sleep-wake cycle abnormalities and recurring blocks of days with severe insomnia and excessive daytime sleepiness [21]. This circadian clock impairment could ultimately affect the quality of life due to sleep disorders and could also involve cardiovascular problems or emotional disorders or trigger or accelerate the pathology progression in neurodegenerative diseases [7,23,24].

The few therapeutic options for patients with RP currently available in daily clinical practice just retard disease progression and are limited. There is no therapy nowadays that restores vision, so the prognosis is poor [3]. Because of the chronic nature of this disease and its disabling progression, there has been great interest in the development of new strategies to help patients cope with the social and psychological impacts of blindness.

Among nonpharmacological strategies aimed at slowing down the degenerating process are those that are based on light protection. Some pieces of evidence indicate that some hereditary pigmentary retinopathies are partly light dependent [25,26]. Violet (400-440 nm) and blue (440-500 nm) light constitute the lower wavelength of the visible spectrum, which carries the highest amount of energy per photon [27]. The possible role of short-wavelength light (SWL) in the photochemical damage to retinal tissue and retinal pigment epithelium (RPE) cells has been studied, with high-energy SWL (415-455 nm) being the most harmful to the eye (the second type of phototoxicity or blue-light hazard) [28-30]. Blue-violet light could cause oxygen-dependent retinal injury, acting on specific chromophores, and *N*-retinylidene-*N*-retinylethanolamine (A2E) is considered the most important target molecule. Reactive oxygen species (ROS) initiate the activity of cysteine-dependent proteases, ultimately leading to apoptosis and cell death [28,31-34]. Mitochondria from photoreceptors, retinal ganglion cells, and RPE cells are the main targets of blue light–associated oxygen free radicals [35-37]. Moreover, photophobia, a common unpleasant symptom in patients with RP, has been described to be caused primarily by SWL in its interaction with S-cones from the retina [38]. In addition, in experimental RP models, limiting SWL exposure by the application of optical filters has been demonstrated to slow retinal degeneration [39].

However, some studies have shown that longer blue wavelengths of the visible spectrum (465-495 nm) are essential for the circadian rhythm, pupillary reaction, color discrimination, and night vision [7,23,24,40-43]. Numerous studies have demonstrated their close association to circadian rhythm regulation, alertness, memory, and cognition [44,45]. Therefore, blue-light exposure could regulate the secretion of melatonin

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in the pineal gland through the retinal–suprachiasmatic nucleus (SCN)–pineal axis, modulating cortisol expression through the hypothalamic–pituitary–adrenal (HPA) axis or the autonomous nervous system [7,23,24,44]. These responses are driven primarily by intrinsically photosensitive retinal ganglion cells (ipGCs), which are more sensitive to 480 nm SWL and remain functional in late stages of the disease [7]. In contrast, melatonin suppression has a peak sensitivity of roughly 460 nm in humans, the same spectrum that has been shown to reset the circadian pacemaker and directly enhance alertness [46].

In consequence, evening SWL exposure in daily life may affect sleep, hormone release, and the circadian rhythm in patients with RP. In fact, it has been reported that wearing SWL-blocking glasses that virtually eliminate SWL is effective in improving sleep, the circadian rhythm, and mood. Three randomized controlled trials (RCTs) have demonstrated that SWL-blocking glasses bring about significant improvement in sleep quality in participants with insomnia [42,43,47].

Among pharmacological interventions, the trophic and antioxidant effects of vitamins or nutritional supplements have been evaluated in patients with RP to demonstrate a protective action on cone death [48-50]. Accumulating evidence indicates that melatonin therapy is a promising approach in the treatment of various ocular degenerative disorders (eg, age-related macular degeneration, diabetic retinopathy, and RP) since it can exert a protective effect against damage to RPE cells evoked by ROS, but it has also been reported to increase ROS-induced damage to photoreceptors and RPE cells [51-55].

Melatonin is an endogenous hormone that has been implicated in a variety of biological processes, including antioxidant, anti-inflammatory, and neuroprotective activities [56,57]. Melatonin is released from the pineal gland in a circadian fashion, which is controlled by the SCN. However, many other tissues and organs also synthesize melatonin. In the retina, it is mainly synthesized by photoreceptors and is involved in the modulation of neuronal activities. Its circadian production results in a high concentration at night and a low level during the day, although its amount is small compared to its pineal counterpart [7,51,58].

Oxidative damage has been proposed to be an important contributor to cone death in RP, and antioxidants may prevent cone damage in RP by reacting with free radicals produced during light absorption [59]. Melatonin behaves like synthetic mitochondria-targeted antioxidants, which are concentrated in the mitochondria at relatively high levels [51,58]. It exerts its antioxidant actions in the eye via several mechanisms, including direct ROS scavenging, stimulating antioxidant enzymes, improving the functioning of the mitochondrial electron transport chain (ETC), reducing the extent of electron leakage from the mitochondrial complexes, and improving the efficacy of other antioxidants. As mentioned before, mitochondria from photoreceptors, retinal ganglion cells, and RPE cells are the main targets of ROS produced by the ETC, and thus, melatonin may prevent mitochondrial damage in patients with RP [7,51,58,60,61].

However, it has also been demonstrated that daily administration of appropriately timed melatonin can synchronize the circadian clock [62-66] in patients with sleep disorders; its use is even recommended by the Standards of Practice Committee of the American Academy of Sleep Medicine [67]. The phase-shifting effects of melatonin are essentially opposite to those of light. It can phase-shift the endogenous circadian clock and, in the absence of light, entrain the sleep-wake and neuroendocrine rhythms (cortisol) [61]. Therefore, it is likely that OM may also be effective in sleep and circadian rhythm management in patients with RP. However, to the best of our knowledge, no previous RCT has investigated the potential additive benefits of adjunctive SWL-blocking glasses plus OM in improving sleep, perceived stress, and the circadian rhythm in patients with RP.

The aim of this study is to assess the efficacy of OM combined with SWL-blocking filters in patients with RP who have sleep disorders and stress compared to any intervention alone or no intervention. We hypothesized that both interventions would improve their sleep quality, reduce their perceived stress levels, and shift their circadian rhythm to morningness.

Need for a Trial (Innovation Aspect)

RP is the commonest of inherited retinal disorders, with a great economic impact and poor associated quality of life [68]. In addition, there is a lack of standard treatment with a good level of efficacy data, which brings a fruitful opportunity to add new knowledge and pursue evidence-based interventions.

The innovation in this study is based on a noninvasive approach—SWL-blocking filters combined with OM. This treatment protocol might represent a better option for patients with RP, especially those with moderate or severe RP, who present with greater functional disability, glare symptoms, and variations in cortisol, salivary α-amylase (sAA), and melatonin levels.

Although a few trials have assessed the efficacy of different vitamins and melatonin in visual and sleep pattern anomalies in patients diagnosed with RP, none of them used a similar combined therapy and even fewer focused on variations in cortisol, sAA, and melatonin levels or determined the impact of these interventions on psychological factors. This study aims to fill this gap in the literature by enhancing the level of evidence with a double-blind RCT that evaluates the benefits that OM combined with SWL-blocking filters may bring to patients with moderate or severe RP.

Significance/Impact of the Study

RP is accompanied by significant disability, greater dependency, and a decrease in the health-related quality of life, with increased rates of admission to institutional facilities [68-70]. It is also considered a public health issue and a primary cause of headaches, sleep disturbances, and increased rates of depression [71]. Patients with RP also face difficulties in performing daily activities and increased risk of cardiovascular, metabolic, and psychiatric disorders [68-70]. Productivity losses for patients with visual impairment are likely to be amplified in patients with RP because of the early age at onset, vision challenges at school, and loss of visual function without some type of rehabilitation during prime working years [68-70].

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The annual cost of adult vision problems for the National Health Service (NHS) is around US $51.4 billion. Among adults with retinal diseases, the annual total health care costs were estimated to be US $7317 higher per patient with RP, increasing the community costs by around 2.5 times because of the number of years of blindness experienced [72].

SWL-blocking filters and OM have been playing an important role in the treatment of several kinds of retinal conditions and sleep disabilities [42,43,47,60,61,73]. Unlike other expensive treatments for sleep disorders, anxiety, and depression, SWL-blocking filters or OM may provide effective control of the human circadian clock through changes in the HPA axis or the retinal–SCN–pineal axis, which could be positively correlated with improvement in the quality of life and visual function disability.

Some studies suggest a multidisciplinary treatment program that includes specialists from different areas of expertise [74]. This program provides a combination of drug treatment and SWL-blocking filters with an adequate assessment of the grade of severity (via clinical assessment) and biochemical stress (by analyzing biomarkers) and determines the impact of psychological factors on patients with RP. It could be considered a good alternative for patients with moderate and severe RP who have not benefited from expensive therapies (eg, bionic eye or genetic therapy) individually. Therefore, in this study, we suggest mimicking a multidisciplinary treatment by combining treatments and analyzing the impact of biochemical and psychological factors on anxiety and sleep disability.

Choice of Comparators

To date, therapeutic approaches for RP are restricted to slowing down the degenerative process; treating ocular complications, such as cataracts and macular edema; and helping patients cope with the social and psychological impacts of blindness. In addition, the evidence from RCTs on the visual protective effects of vitamins and nutritional supplementations in patients with RP is limited and in some cases contradictory. Moreover, as mentioned before, few studies on the effects of blocking SWL on visual discrimination capacity in patients with RP have been reported. In addition, in clinical practice, there is insufficient experience to recommend the use of optical absorbing filters, since their potential effects on regulating the human internal circadian (24-hour) clock in patients with RP are yet unknown.

For this reason, the intervention groups will consist of SWL blocking alone (SWL group), OM therapy alone (OM group), and SWL blocking plus OM therapy (SWL+OM group) in order to determine whether there is any summative effect. No intervention has been chosen for comparison to avoid performance bias and other biases related to loss of blinding in the trial. Therefore, as several treatments have been proposed to slow down the degenerative process and the current evidence from their results is still limited, no intervention as the control group is justified for this study.

Methods

Overview

This parallel-group RCT will be performed at a single institution, which is a tertiary referral hospital with an affiliated research institute (Institute of Applied Ophthalmobiology [IOBA], University of Valladolid). The retinal units in both institutions are highly specialized to manage inherited retinal dystrophies and other related retinal eye diseases. Additionally, the IOBA has a clinical trial unit that could help with the local ethical requirements for running a clinical trial and any oversight or external auditing of data that is needed.

There will be 4 parallel groups of patients. Recruitment will be facilitated by a local foundation for patients with retinitis pigmentosa called the Retina Castilla y León (ReCYL) and will be tightly supervised by an ophthalmologist with specialization in retinal degenerations. Figure 1 provides a summary of the clinical pathways.

A draft intervention protocol will be developed for each group, covering preintervention, intervention, postintervention, and discharge settings based on the literature. A steering committee comprising ophthalmologists, opticians, nurses, psychologists, and the research team will be created to develop these protocols. Additionally, 2 ophthalmology residents will be included. Finally, 1 patient with RP, who is the current president of the Federation of Inherited Retinal Dystrophies' Associations, will be included in the steering committee. The steering committee members are experts in their respective fields and have used the existing literature (summarized in the *Background and Rationale* section) to inform the inclusion of the different interventions in the protocols. The draft intervention protocols are presented in Table 1. Although the choice of each intervention in these protocols will be informed by the literature [7,28,30,36,51,57,67,75-82] and expert consensus of the steering committee, the study will assess the efficacy of combined interventions in sleep disorders and stress control in a large group of patients with RP. Before the intervention period, all patients will be asked to complete sleep diaries for 2 weeks. In addition, patients in the intervention groups (SWL, OM, SWL+OM) must complete them during the intervention period (30 days). Patients from the SWL and SWL+OM groups will wear SWL-restricting goggles in bright-light conditions and when using light-emitting diode (LED) electronic devices for the 30 days of intervention. Patients from the OM and SWL+OM groups will take 3 pills of Circadin 2 mg (OM) every evening at 10:00 P.M. with a margin of 30 minutes before and after.

A preintervention time of 1.5 years will be necessary for recruitment, informed consent, eligibility screening, and baseline data collection. Next, patients will be randomized to 4 groups in a 1:1 ratio. The treatment groups will include SWL with or without the use of OM. The control group will include patients who are eligible for the study but not willing to be randomized to an intervention sleep and stress management pathway. When the intervention phase (4 weeks) is over, all patients will be followed up for 6 months via standard monitoring. Figure 2 provides a summary of the RCT timeline.

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Figure 1. Flow diagram illustrating the study protocol. At the allocation to interventions, the number of patients who receive the intervention will be registered, as well as those who do not receive it (together with the reason it was not applied) and those who get lost in the follow-up or discontinue the intervention. In addition, unbearable side effects and SUSARs would be appropriately notified and registered. e: patients excluded; r: randomized patients; RP: retinitis pigmentosa; SUSAR: suspected unexpected serious adverse reaction; SWL: short-wavelength light; VA: visual acuity.

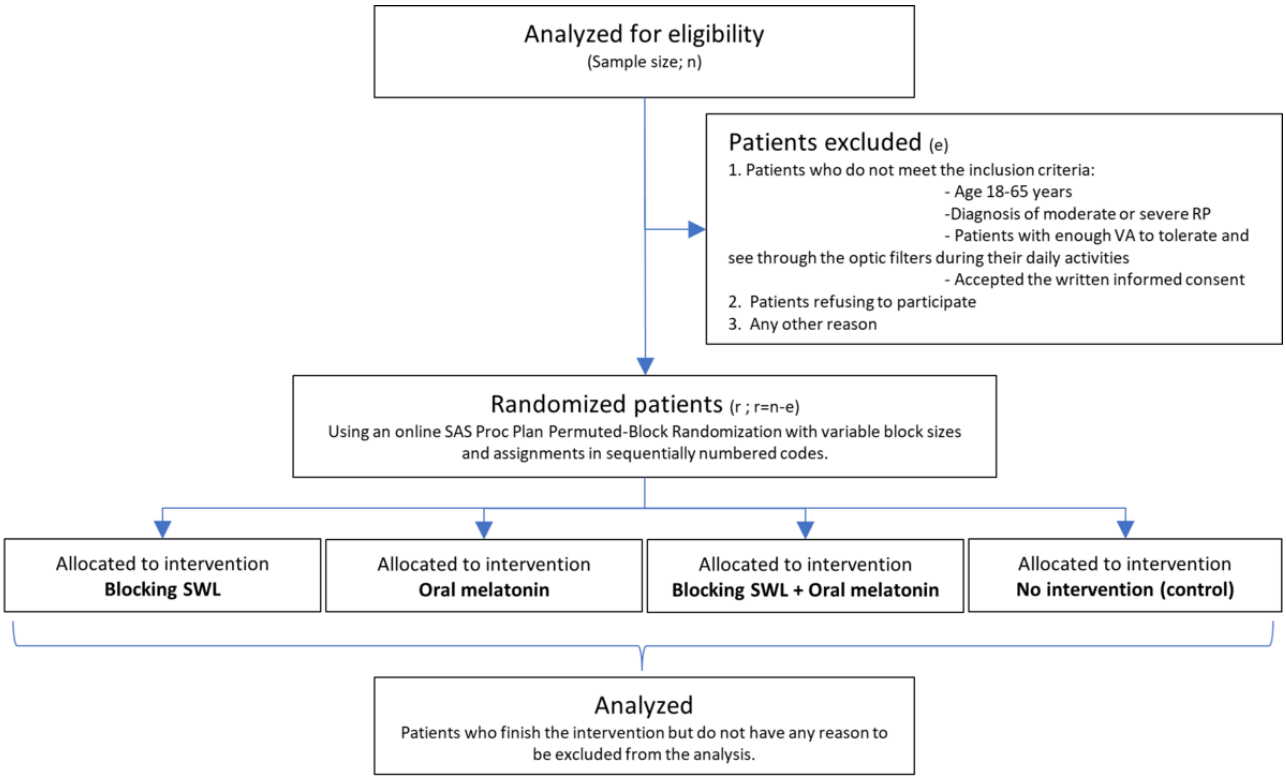


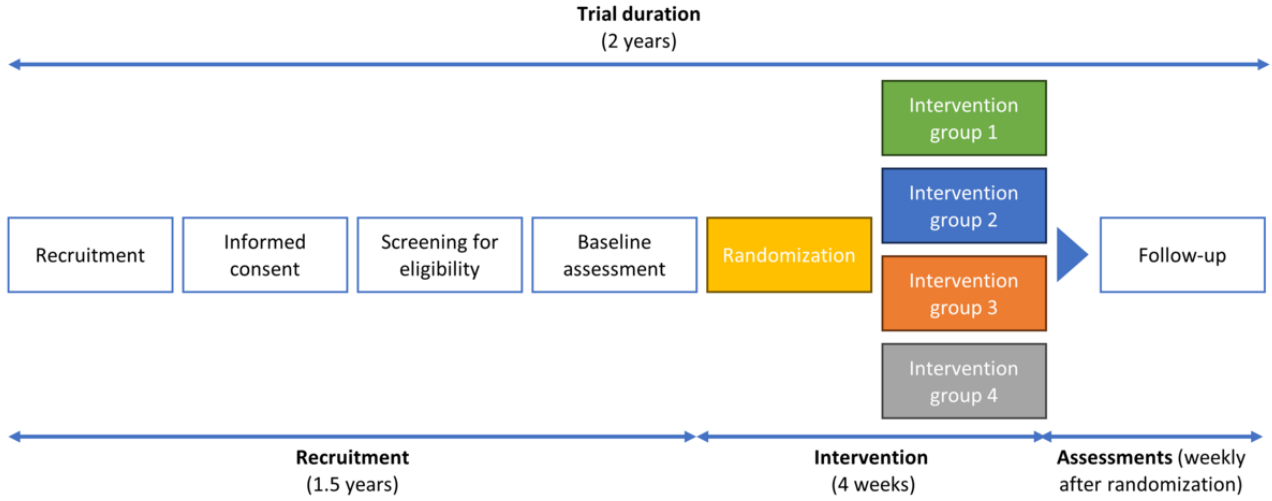
Table 1. Protocols of the intervention.

Group	Preintervention period (2 weeks)	Intervention period (30 days)
SWL[a]: optical SWL filters	Sleep diary	Sleep diary, goggles
OM[b]	Sleep diary	Sleep diary, OM
SWL+OM: optical SWL filters and OM	Sleep diary	Sleep diary, goggles, OM
Control: no intervention	Sleep diary	None

[a]SWL: short-wavelength light.

[b]OM: oral melatonin.

Figure 2. RCT timeline. RCT: randomized controlled trial.



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Study Population

The study population will comprise patients aged 18-65 years with a history of moderate or severe RP with a grading severity scale score of >1 point according to Iftikhar et al's [83] scoring criteria. Eligible patients who provide written informed consent will be randomized to 1 of the 4 study groups. Outcomes will be assessed at multiple time points: at baseline in the preintervention period; then at 1, 2, 3, and 4 weeks of the intervention period; and then at 6 months postintervention.

Patient Selection, Recruitment, Randomization, and Blinding

Eligibility

Eligibility will be determined based on the inclusion and exclusion criteria listed in Table 2. Eligible participants will be identified after initial evaluation by a staff ophthalmologist, determined to satisfy 1 of the qualifying procedures, and approached for informed consent by the ophthalmologist and research staff. At this time, patients will watch an introductory video explaining the purpose of the clinical trial. The physician also will lead an in-depth preintervention discussion explaining each approach to stress and sleep disability (SWL and OM vs control) and postintervention expectations. If patients decline to participate in the RCT, they will be presented with the option of enrolling in the control group (no intervention). There will be no restrictions on patient care due to enrollment in the study.

Table 2. Inclusion and exclusion criteria at screening.

Inclusion criteria	Exclusion criteria
• Age 18-65 years, from ReCYL[a] • Diagnosis of moderate or severe RP[b] (grading severity scale score>1 point) • Visual function enough to tolerate and see through the optic filters during daily activities • Written informed consent provided	• Underwent any ocular surgery within the previous 6 months • Involvement in any other ongoing clinical trial • Pregnancy and lactation or under hormonal treatment • Allergy or hypersensitivity to melatonin • Previous or current therapy with melatonin • Autoimmune diseases • NSAID[c] and others anti-inflammatory drug treatment • Psychiatric disorders or under any psychotropic medication

[a]ReCYL: Retina Castilla y León.

[b]RP: retinitis pigmentosa.

[c]NSAID: nonsteroidal anti-inflammatory drug.

Recruitment

Screening Visit

Patients will undergo an initial screening visit that includes a semistructured interview, a series of questionnaires, a complete ophthalmic examination, and laboratory assessment. Eligible patients will be provided with a verbal description of the trial and presented with a comprehensible informed consent form.

Semistructured Interview

All patients will undergo a semistructured interview to collect medical (signs and symptoms, personal and family records, coexisting pathology, previous or current medication, etc), demographic (age, gender, ethnicity, etc), socioeconomic (relationship status, educational attainment, employment status, etc), and lifestyle (physical exercise, consumption of drugs, use of hair dyes, BMI, etc) data.

Ophthalmic Examination

All patients will undergo a complete ophthalmological examination, which will include the best-corrected visual acuity (BCVA) with the Early Treatment of Diabetic Retinopathy Study (ETDRS) letter score, a slit lamp examination, intraocular pressure measurement, fundoscopy, contrast sensitivity with a CSV-1000 chart (Vectorvision), and a glare test with the MonPack 3 device (Metrovision).

Ancillary Tests

Visual field impairment (VFI) will be assessed using a Humphrey 750i visual field analyzer (Carl Zeiss) and the central 30-2 SITA fast strategy protocol. Only tests that met the criteria (low [<20%], false positive, false negative, and fixation loss parameters) were evaluated [84].

Optical coherence tomography (OCT) images, assessing the central retinal thickness (CRT), macular ganglion cell–inner plexiform layer (GCIPL) thickness, and retinal nerve fiber layer (RNFL), will be performed using Cirrus HD-OCT 5000 with AngioPlex OCT-A (Carl Zeiss Meditec V.10.0) and cube scans. Only images with a signal strength of >6 with no movement artifact will be included in the study.

Two consecutive optical coherence tomography angiography (OCTA) images will be obtained by a single skilled examiner. A foveal centered scan area of a 3×3 mm^2 pattern will be used, and all scans will be analyzed using en face OCTA images generated automatically with the optical coherence tomography microangiography (OMAG) algorithm in Angioplex software (ZEISS). The foveal avascular zone (FAZ) area will be manually outlined and expressed as square millimeters.

The vascular density (VD) will be measured automatically by the software, which will quantify the VD of a local region of tissue according to the ETDRS subfields. We will analyze the VD of each ETDRS sector, the inner ring, and the full area in

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3×3 mm^2 rings and exclude OCTA images with a signal strength of <7 [12].

The axial length will be calculated using an IOLMaster 500 optical biometer (Carl Zeiss Meditec) to be used as a correcting variable in the analysis, if necessary.

Questionnaires and Diaries

The State-Trait Anxiety Inventory (STAI), the Epworth Sleepiness Scale (ESS), the Pittsburgh Sleep Quality Index (PSQI) questionnaires and a sleep diary will be used to ask patients about their level of sleep quality, perceived stress, and anxiety.

Sleep Diary

During the 2-week period before trial commencement and the 4-week period of the intervention, patients will fill a daily self-recorded sleep diary at home. The sleep diary will record parameters such as bedtime, wake time, sleep onset, and sleep offset time.

State-Trait Anxiety Inventory

STAI is designed to assess the degree of state and trait anxiety in research participants (in this study, patients with moderate and severe RP) and takes about 10 minutes to complete. It is a reliable, valid, and responsive questionnaire consisting of 20 items for assessing state anxiety and 20 for trait anxiety. Higher scores (maximum score of 40) are positively correlated with higher levels of anxiety [85]. To evaluate the magnitude of any treatment effect, the minimum clinically important difference (MCID) will be regarded as a 30% reduction from baseline [86]. This magnitude represents a "small" effect in the behavioral sciences.

Epworth Sleepiness Scale and Pittsburgh Sleep Quality Index

The ESS and the PSQI are both sleep quality questionnaires. The ESS is widely used in the field of sleep medicine as a subjective measure of a patient's sleepiness. The overall score ranges from 0 to 24. The scale estimates whether the patient is experiencing excessive sleepiness that possibly requires medical attention [87]. The PSQI is a self-reporting questionnaire that assesses sleep quality over a 1-month time interval. The global PSQI score is calculated by adding the 7 component scores, providing an overall score ranging from 0 to 21, where lower scores denote a healthier sleep quality [88].

As determination of the MCID in the sleep quality questionnaires remains controversial, with no consensus on methodology, we will estimate the minimum clinically important improvement in the ESS and PSQI to lie between −2 and −3 for this trial [88-92].

Laboratory Assessment

All patients will undergo a salivary and hair draw to confirm eligibility. Sample collection will be carried out between 9:00 A.M. and noon to minimize potential errors associated with diurnal variations in neuroendocrine parameters. Samples will be collected in the same room, and temperature and humidity will be recorded. After collection, samples will be frozen at –20 °C until analysis. When analyzing results, in female subjects, menstrual cycle phases will be considered.

Salivary α-Amylase, Cortisol, and Melatonin levels

Salivary samples will be collected by patients using the passive secretion drooling method. Two samples of saliva from each patient will be collected in 24 hours. At least 1 mL is required for analysis. The putative salivary indicators will be assayed with enzyme-linked immunosorbent assay (ELISA): cortisol (DRG Salivary Cortisol ELISA, DRG Instruments GmbH) and melatonin (DRG Instruments GmbH). Salivary α-amylase (sAA) will be determined with an α-amylase kit (Salimetrics) [93].

Cortisol Levels in Hair Samples

Three single 3-cm-long locks of hair will be collected from each patient to measure hair cortisol levels in a 3-month period (assuming an average growth rate of 1 cm per month). After collection, each hair sample will be wrapped in aluminum foil to protect it from light and humidity until analysis. The cortisol level in each sample will be measured using the Cortisol Hair ELISA kit (Alpco Diagnostics) with phosphate-buffered saline (PBS) at pH 8.0.

Randomization

All patients who provide written informed consent for participation and meet the eligibility criteria will be randomized and assigned using the online SAS Proc Plan permuted-block randomization with variable block sizes and assignments in sequentially numbered codes provided by the central randomization service on its website [94]. The randomization code will not be released until the patient has been recruited into the trial after baseline measurements have been completed.

An administrative assistant not otherwise involved in the study will provide the next treatment code in the sequence and will record the assignment in a confidential log.

Blinding

In our double-blinded trial, the principal investigator and statistician will be blinded to treatment allocation. Staff responsible for recruitment and grading severity will not be allowed to receive information about the group allocation. Raters will not be present during the lab analysis. Randomization will be conducted by the central randomization service to keep the principal investigator and statistician blind to the data management and study condition.

In the event of a SUSAR (suspected unexpected serious adverse reaction), if requested by the Data Safety Monitoring Committee (DSMC), or if a medical emergency occurs where knowledge of the blinded treatment is necessary, unblinding will be performed independently of the group allocation. The reporting of all SUSARs needs to be expedited.

Intervention

All patients will be provided with a leaflet with clear instructions at the baseline visit, and they will be asked to follow the guidelines throughout the 4-week follow-up period.

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Optical Filters for Blocking SWL

Patients will be provided with SWL-restricting goggles to wear during the daytime, in indoor bright-light conditions, and when using LED electronic devices in order to prevent the suppression of melatonin for at least 30 days. Optical filters will allow selective exclusion of less than 480-nm-wide wavelengths, while maintaining relatively good contrast sensitivity and a visual light transmittance of 70%-75% [95].

Oral Melatonin (6 mg)

Patients will be asked to intake a 6 mg melatonin dose orally once a day for 30 days in the evening (22:00 P.M. with a margin of 30 minutes before and after) to activate its sleep-promoting effects approximately 2 hours after intake, avoiding fatigue and sleepiness during the daytime [96-99].

Although the chosen dose is safe to obtain the desired effect, patients will be prompted to report any possible side effects, if present, during the intervention period [79,81,82,100]. If they experience unbearable side effects, they will have to discontinue the OM intervention. If they wish, they can participate in the SWL-blocking intervention and will be evaluated over the 4-week follow-up period.

SWL Blocking + Oral Melatonin (6 mg)

Participants in this combination arm will receive both interventions—filter goggles and OM—at the same time under the same conditions as the SWL and OM groups and for the same 30-day period.

No Intervention

The purpose of this arm is to serve as the procedural control, so patients in this group will be asked to fill their sleep diaries at home only for the first 2-week period after trial commencement. They will be chosen as comparator to avoid performance bias and other biases related to loss of binding in the trial.

Adherence

Adherence monitoring will be performed to find new strategies to avoid attrition during the study and to look for unexpected problems that may prevent patients from attending the sessions. Patients will receive weekly phone calls to confirm appointments and obtain educational instructions about the study protocols to reassure them of the importance of adherence. Upon discharge, patients will be provided with instructions to contact their physician for unacceptable levels of sleep disability or perceived stress to receive an outpatient prescription of antianxiety medications and lifestyle techniques. Additionally, if a patient deviates from the intervention protocol assigned to them, they will not be considered a study failure. Instead, we will continue to follow the patient through study completion and continue to track patient-reported outcomes.

Data Collection and Outcome Measures

Baseline Assessments and Frequency of Follow-Up Assessments

A full list of assessments obtained at each time point is summarized in Table 3.

We will obtain baseline assessments during each patient's screening visit. These measures will include, but will be not limited to, demographics, comorbidities, subjective sleep quality and perceived stress rating, ophthalmic and laboratory outcomes, and patient-reported outcomes specific to the planned intervention.

Initial follow-up assessments will be obtained at 1, 2, 3, and 4 weeks after the start of the intervention. Patients will also be asked to return for postintervention follow-up visits 6 months after the intervention. These visits will be scheduled at the beginning of the study. Patients unable to attend any in-person visit will be asked to at least provide all subjective patient-reported outcomes over the phone or via an electronic survey for that visit in order to facilitate retention and optimal follow-up.

Sleep quality level, laboratory outcomes, ophthalmic clinical outcomes, questionnaire patient-reported outcomes, and potential complications will be gathered during these visits.

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Table 3. Assessments and follow-up.

Clinical and laboratory event	V_{-1}[a] (–4 weeks)	V_0 (0 weeks)	V_1 (1 weeks)	V_2 (2 weeks)	V_3 (3 weeks)	V_4 (4 weeks)	V_F (6 months)
Screening	✓[b]	—[c]	—	—	—	—	—
Clinical	—	✓	—	—	—	✓	✓
Physical examination	—	✓	—	—	—	✓	✓
Salivary sample collection	—	✓	✓	✓	✓	✓	—
Hair sample collection	—	✓	—	—	—	✓	—
STAI[d] questionnaire	—	✓	—	—	—	✓	—
ESS[e] and PSQI[f] questionnaires	—	✓	—	—	—	✓	—
Inclusion criteria	✓	—	—	—	—	—	—

[a]V: visit; V_{-1}, screening visit, when inclusion and exclusion criteria will be checked; V_0, visit to assess baseline characteristics; V_1-V_4, visits during the intervention period (every week); and V_F, final visit after 6-month follow-up.

[b]✓: applicable.

[c]Not applicable.

[d]STAI: State-Trait Anxiety Inventory.

[e]ESS: Epworth Sleepiness Scale.

[f]PSQI: Pittsburgh Sleep Quality Index.

Primary Outcome Measures

The primary outcomes are the differences in changes from baseline to postintervention in hormone release (sAA, cortisol, and melatonin levels in salivary and hair samples) and sleep quality, as measured by the ESS and the PSQI.

Intra-Assay Variations

To evaluate the reproducibility of each salivary and hair biomarker, the within-subject standard deviation (Sw) will be calculated by obtaining the square root of the sum of the within-subject variance and the error variance estimated in a linear random-effects model. The mean intra-assay coefficients (ICCs) will be determined for each biomarker and interpreted as follows: 0 (SD 0.2), poor agreement; 0.3 (SD 0.4), fair agreement; 0.5 (SD 0.6), moderate agreement; 0.7 (SD 0.8), strong agreement; and >0.8, almost perfect agreement.

Secondary Outcome Measures

Secondary outcome measures include any clinical macular changes or retinal function measured with the ETDRS scale, CSV-1000 chart, and ancillary tests, such as the VFI, OCT, and OCTA. In addition, several patient-reported variables, such as self-recorded sleep diaries, perceived stress, and functional status will be recorded.

Covariates and Confounders

Several variables will be measured as potential covariates, including preintervention sleep quality scores, concomitant procedures, medical comorbidities, alcohol use, antianxiety medications or other nonprescribed medications used to help with insomnia and anxiety relief, tobacco use, and nonsteroidal anti-inflammatory drug (NSAID) and others anti-inflammatory drug treatment. In addition, basic demographic information will be obtained.

Ethical Considerations

The protocol was reviewed by the local Institutional Review Board of the East Health Area of Valladolid (CASVE 21-520) and will be registered with ClinicalTrials when a start date is decided.

Informed consent will be obtained from each patient in the preintervention period, which must be signed, thumb-imprinted, or recorded by the patient and collected by a coached research assistant, when necessary.

Privacy and confidentiality will be guaranteed for each patient, and the study will be conducted in accordance with the principles of the Declaration of Helsinki.

Data Management, Analysis, and Additional Information

Data Management

In the clinical trial, data handling will be managed by a third-party agency. The investigators, patients, and clinical staff rating or applying therapies will not have access to information until the data analysis is completed by predetermined statisticians. They will also not be aware of the allocation of patients in the trial. Data entry into the virtual system will also be managed by the third-party agency.

Patients' information will be encrypted in a virtual database, secured, and password-protected. Only the data monitoring committee (DCM) will have access during the trial. Data coding will begin at randomization; SAS will generate an alphanumeric code for each block. An ID number will be assigned to each patient. If a major adverse effect occurs, it will be identified by the ID number.

The software will record any changes made by any person involved in the functioning of the program. The user ID will identify people who make any changes to the system, and this

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information will be used for the purpose of auditing the trial. During a regulatory audit, the auditors can verify any changes that occur in the system and data. All data will be regularly backed up to a password-secured database.

Data Monitoring

The DCM will comprise a data manager, a database programmer/designer, a medical coder, a clinical data coordinator, a quality control associate, and a data entry associate. A member of the DCM can have 1 or more duties. The DCM will be established according to the Spanish Agency of Medicines and Medical Devices (AEMPS) rules. According to Royal Decree 1090/2015, of December 4, the AEMPS is the regulatory authority responsible for clinical trial oversight, approval, and inspections in Spain and is attached to the Ministry of Health. The Institutional Ethics Committee will review and approve the clinical trial applications prior to the AEMPS initiating its review and approval process.

Data monitoring will take place in a pre-established room, with easy access to data, inside the institution but not in the same room where the trial is performed.

Interim Analysis

The clinical trial will have 4 major evaluation time points of interventions, that is, every week after V_0 and 4 weeks and 6 months postintervention. In each visit for application of the intervention, the patient's personal diary will be reviewed by the clinical staff. They have the responsibility to notify the DMC about eventual minor or major adverse effects.

Adverse events will be recorded from the start of stimulation through the end of the study. All adverse events regardless of attribution to OM and any unexpected adverse event due to the optical filters will be recorded using standard adverse event forms. Adverse events will be measured in several areas: seriousness, severity, length of duration, and any causal relationship, if any, with the intervention. Serious adverse events will be defined as those that are life threatening/disabling, require hospitalization, or result in death.

Patients who develop any adverse effect will be followed up. The DCM will have unblinded access to all patient data and will discuss the adverse events at a meeting. The decision of allowing a patient to withdraw from the study will be made by a majority consent of 50% or more.

Statistical Analysis

Sample Size Calculation

A sample size estimation of 48 patients (n=12, 25%, per group) was calculated for a target power of 80% and considering an α (probability of rejecting a true null hypothesis) of 5% and an actual power of 80.02%. Cohen d was 1.2 [101]. Due to the possible overestimation of the effect size in pilot studies, an effect size of 0.6 (medium-high) was chosen for this study. We calculated a total sample size of 60 participants (a total of 15, 25%, patients per group), adding approximately 20% (3 more patients per group than before) to manage possible dropouts [102-105].

Statistics

A linear mixed effect regression model will be applied to compare intervention arms against the control at baseline and stimulated measures for the HPA axis or the retinal–SCN–pineal axis comprising cortisol, melatonin, and sAA [106]. Baseline characteristics of patients from each group will be compared applying independent *t* tests, 2-way repeated-measures ANOVA, and the Fisher exact test. To grade the RP severity (by quantifying clinical features, the ETDRS score, and visual field deviation) and the primary outcomes, we will consider both to be continuous variables and apply a multiple linear regression model. For secondary outcomes, normally distributed variables will be statistically assessed via parametric tests, such as the *t* test or ANOVA, while nonnormal distributed variables will be assessed with nonparametric tests, such as the chi-square test or the Fisher exact test and the Mann–Whitney U test. A chi-square or Fisher test will be performed to compare STAI, PSQI, and ESS scores among groups.

Statistical associations between covariates and outcomes will be evaluated using the appropriate statistical methodology, as previously described. Multivariable linear regression models will be appropriately fitted to continuous data based on the distributions of those data. Multiple logistic regression models will be fitted for all dichotomous outcome variables. Appropriate variable selection methods and model fit statistics will be used to determine the best-fitting model to determine the effects of treatment after adjusting for significant effects of covariates.

Finally, any protocol amendment will be first submitted to the Institutional Review Board for approval. If the amendment changes anything about what is reported

on ClinicalTrials, then the study's registration on ClinicalTrials will be updated accordingly.

Modification/Discontinuation

If patients experience unbearable side effects related to melatonin, they must leave their intervention group. If they wish, they can continue participating in the study as part of the SWL group being evaluated over the 4-week follow-up period. To reflect these changes at the end of the study, an intention-to-treat analysis will be conducted.

Missing Data

Dropouts and missing facts are known as missing data. A dropout rate of 5%-10% is expected based on recent OM clinical trials [99,107]. An intention-to-treat analysis, regardless of the treatment administered, will be carried out for every primary and secondary endpoint. A preprotocol analysis will also be conducted with those who complete the trial, since secondary outcomes could be more affected by uncensored withdrawals. Both analyses must be favorable for the intervention to be considered better than standard. To deal with missing data, imputation techniques will be applied.

Dissemination

Once the study enters the data reporting phase, the data sets used and analyzed during the study will be available from the corresponding author upon reasonable request. The protocol and results will be released on the ClinicalTrials website, as

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required upon study completion. Final study results will be published in a peer-reviewed, PubMed-indexed journal to reach health care professionals. The authors will also seek to present the study findings at relevant ophthalmic subspecialty society meetings. The Federación de Asociaciones de Retinosis Pigmentosa de España (FARPE) website will describe this project. Final findings and results will be published on this website for the general public, as well as disseminated through the FARPE social networking channels.

Results

This work is a clinical trial protocol that has not yet been launched. The bibliographic research for information for its justification began in 2020, and this working group is currently seeking start-up funding. As soon as we have the necessary means, we will proceed with the registration and organization prior to the preliminary phase.

Discussion

Summary of Findings

The aim of the implementation of this clinical trial is to find an innovative strategy that allows a holistic approach for patients with RP, focusing on slowing down the progression of the disease, if possible, and improving their quality of life, especially their mood problems as well as their sleep-wake rhythm disorders.

The use of optical filters blocking SWL in the daylight was chosen as an intervention because of its nature as a noninvasive strategy as well as its protective potential against retinal neurodegeneration and melatonin suppression, both of which are relevant in these patients.

One of the main known sources of blue light is sunlight, but the widespread use of high-brightness lights with LED technology had made an increasing contribution in the past decade. A significant part of the LED emission spectrum peaks at 450 nm, within the wavelength range of blue light. Thus, with the increasing popularity of blue-rich LED-blacklight display devices, such as smartphones and tablets, computer screens, and other commonly used devices, our eyes are exposed to more blue light than they were in the past [28,36,75,108].

In addition, shorter-wavelength blue light has been reported to play a pivotal role in glare disability, especially in patients with retinal dystrophies [38,76]. Photophobia occurs because RPE cells appear to be defective with regard to absorbing light and because a lack of photoreceptors makes the adaptation to different lighting levels difficult [38,76]. Several studies have shown that patients with RP present higher values of intraocular scattering and, therefore, a decreased visual discrimination capacity in comparison to healthy people [77,109-111].

However, although excessive blue light is theoretically harmful, some studies have shown that longer blue wavelengths of the visible spectrum (465-495 nm) are essential for the circadian rhythm, pupillary reaction, color discrimination, and night vision [7,23,24,40-43]. Therefore, optical SWL filters may offer interesting advantages in having a positive effect on the visual discrimination capacity and decreasing glare disability in patients with RP. Finally, they could also help in circadian rhythm regulation and modulate the spectral transmittance of SWL, protecting injured eyes from potential additional photochemical damage.

We have selected melatonin as an intervention because of its close relationship with and involvement in the regulation of circadian cycles and its antioxidant and anti-inflammatory potential.

Melatonin's functions are either receptor dependent or receptor independent. The former includes circadian rhythm control and sleep regulation. There is a considerable body of evidence of melatonin regulating sleep in various sleep disorders [7,62-66]. In fact, melatonin appears as one of the most effective drugs for treating circadian rhythm sleep-wake disorders [67]. Aging, the presence of certain diseases (eg, primary degeneration of the autonomous nervous system and diabetic neuropathy, some types of neoplasms, Alzheimer disease), and certain drugs (eg, β-blockers, clonidine, naloxone, and NSAIDs) abolish the nocturnal production of melatonin and are associated with impaired sleep [7,61,79,81].

Melatonin acts via its own receptors (MT1, MT2) present at the SCN, which are members of the G protein–linked receptor family [61]. The phase-shifting effects of melatonin are essentially opposite to those of light. In humans, its sleep-promoting effects become significant about 2 hours after intake, similar to the physiological sequence at night. However, administration of melatonin during the daytime (when its endogenous levels are minimal) results in induction of fatigue and sleepiness in humans [79,81].

Thus, melatonin administration appears to be one of the most promising approaches, with long-term benefits, for circadian rhythm sleep disorders because it simultaneously treats sleep and wake state problems and, in addition, synchronizes other bodily rhythms so as to maintain the body's internal temporal order and prevent internal desynchronization [67,79,81].

Although the receptor-independent functions of melatonin include the detoxification of ROS and other reactive molecules, the antioxidant action of melatonin can also be expressed by increasing the efficacy in preventing oxidative DNA damage [7,51,58,60,61].

In addition to its pleiotropic actions, melatonin possesses an advantage over other possible candidates due to its amphiphilic character, which enables it to enter any fluid, cells, or subcellular structures, including mitochondria. Conversely, melatonin exhibits poor pharmacokinetic properties (eg, limited oral bioavailability and short plasma half-life) and low subtype receptor selectivity [79,81]. The effective doses reported are between 0.5 and 10 mg without a clear dose-response relationship (Multimedia Appendix 1). This mainly reflects the large interindividual variability in melatonin bioavailability, which is well known in the published literature and is attributed to differences in first-pass metabolism (Multimedia Appendix 1).

The acute toxicity of melatonin, as seen in both animal and human studies, is extremely low [82]. Melatonin may cause

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minor adverse effects, such as headache, insomnia, rash, diarrhea, and nightmares [82]. In animals, a lethal dose for 50% of the subjects (LD50) could not be established; even 800 mg/kg body weight (high dose) was not lethal [100]. Studies on human subjects given varying doses of melatonin (1-6.6 g/day) for 30-45 days and followed with an elaborate battery of biochemical tests to detect potential toxicity have concluded that in addition to drowsiness, all findings were normal at the end of the test period [79,81,82].

In the same line as the previous Spanish RCT (EudraCT no: 2012-002436-82) with OM and patients with RP, we have considered that 6 mg of OM for 30-40 days will be a safe dose to reach the desired effects without causing side effects in our target population. In general, a dose between 0.2 and 10 mg has been considered a safe starting dose in most of the previous studies with OM [67,79,81,82].

Accumulating evidence indicates that melatonin has a protective effect against various ocular disorders, such as uveitis, diabetic retinopathy, glaucoma, and even optic neuritis, through different mechanisms of action [60,61,73,112-115]. The multifaceted role of melatonin in neuroprotection might imply that melatonin may possess the capacity to attenuate the harmful effects that occur in degenerative retinal diseases, such as RP. Daily administration of melatonin has been shown to delay the photoreceptor apoptotic loss in RP mice [53,116]. This evidence supports that a clinical trial using melatonin to at least delay cell loss in RP in humans might be beneficial. In this context, a Spanish RCT (EudraCT no: 2012-002436-82) with 6 mg of OM and patients with RP is ongoing. Thus, therapeutic treatments of eye diseases using melatonin alone or in combination with other strategies deserve serious investigation.

The possibility of synergy between the 2 strategies stems from the common point between them—their involvement in circadian rhythms. Glucocorticoid hormones, particularly cortisol, participate in the body's homeostasis and stress responses and follow a circadian rhythm, exhibiting a predictable peak in the morning, with a typically sharp elevation 30 minutes to an hour after awakening [117-119], although one that is apparently more complex than the melatonin rhythm.

The sAA enzyme has been used as a marker for the sympathetic nervous system response [118,120,121] and, like cortisol, has been shown to respond to psychosocial stress [118]. As with melatonin and cortisol, sAA production exhibits a regular circadian pattern [118]. Under normal, steady-state conditions, high levels of cortisol tend to be associated with low levels of sAA and vice versa.

Synthesis of melatonin is affected by SWL, whereas cortisol production and sAA levels are modulated by both short- and long-wavelength light. Since light is a well-known stimulus for suppressing the synthesis of the hormone melatonin at night, it was considered important for this study to also understand how blocking SWL in bright-light conditions may prevent the suppression of melatonin, which could affect perceived stress, sleep quality, and the quality of life of patients with RP.

Limitations

The limitations that may be encountered in the application of this clinical trial are likely to be related to the large phenotypic and genotypic variability found among patients with RP; the difficulties in recruiting patients who meet the eligibility criteria, especially those with enough visual acuity that allows them to use the filters; and the subjective nature of the results of the questionnaires. However, this could be overcome by a good baseline study that allows for proper analysis that considers possible confounding variables. However, a sleep-monitoring device could be used, such as second-generation multisensory sleep trackers, but their price would increase the cost of the study and there is still no validated device for this purpose, so for the time being, they have not been included in the study protocol [122].

Conclusion

Preservation of vision in retinal degeneration is one of the priorities of the World Health Organization Vision 2020 program. Clinical trials of melatonin in the context of controlling RP, for example, warrant serious consideration. Furthermore, positive results of such studies would not only benefit patients with various ocular disorders but also be particularly helpful in countries where the treatments are expensive and not easily accessible.

This protocol for a double-blind RCT aims to shed light on the benefits that OM combined with SWL-blocking filters might have for patients with moderate or severe RP in terms of disease progression and quality of life. The goal is that this protocol be replicated for future studies, applied to additional inherited retinal dystrophies, and potentially incorporated into clinical practice. Should this study demonstrate the superiority of the combined intervention versus no intervention, its findings may also help reduce the impact of sleeping disorders and negative psychological disorders on the quality of life of patients with RP and help them recover their self-autonomy.

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Data Availability

All data sets generated and analyzed during this study are included in this published paper and Multimedia Appendix 1. Once the study enters the data reporting phase, the data sets will be available from the corresponding author upon reasonable request.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Supplementary table with all existing randomized controlled trials registered at ClinicalTrials.gov to date using oral melatonin.
[PDF File (Adobe PDF File), 470 KB - resprot_v12i1e49196_app1.pdf]

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Abbreviations

AEMPS: Spanish Agency of Medicines and Medical Devices
DCM: data monitoring committee
ELISA: enzyme-linked immunosorbent assay
ESS: Epworth Sleepiness Scale
ETC: electron transport chain
ETDRS: Early Treatment Diabetic Retinopathy Study
FARPE: Federación de Asociaciones de Retinosis Pigmentosa de España
HPA: hypothalamic–pituitary–adrenal
IOBA: Institute of Applied Ophthalmobiology
ipGC: intrinsically photosensitive retinal ganglion cell
LED: light-emitting diode
MCID: minimum clinically important difference
NSAID: nonsteroidal anti-inflammatory drug
OCT: optical coherence tomography
OCTA: optical coherence tomography angiography
OM: oral melatonin
PSQI: Pittsburgh Sleep Quality Index
RCT: randomized controlled trial
ReCYL: Retina Castilla y León
ROS: reactive oxygen species
RP: retinitis pigmentosa
RPE: retinal pigment epithelium
sAA: salivary α-amylase
SCN: suprachiasmatic nucleus
STAI: State-Trait Anxiety Inventory
SUSAR: suspected unexpected serious adverse reaction
SWL: short-wavelength light
VD: vascular density
VFI: visual field impairment

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Protocol

Evaluation of a Cannabis Harm Reduction Intervention for People With First-Episode Psychosis: Protocol for a Pilot Multicentric Randomized Trial

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Abstract

Background: Cannabis use is highly prevalent in young people with first-episode psychosis (FEP). Most report cannabis use and are often diagnosed with a cannabis use disorder upon admission to specialized services for psychosis. Cannabis use in this population is associated with worse clinical and psychosocial outcomes, rendering it an important clinical target. Despite this,

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few cannabis-specific interventions have been developed for FEP and empirically evaluated through randomized controlled trials. Most evaluated interventions have targeted cannabis abstinence, with limited efficacy, but none have centered on harm reduction outcomes for people with FEP who use cannabis. Early intervention services (EIS), the standard of care for FEP, have not successfully addressed problematic cannabis use in people with FEP either. Clinical trials are needed to explore the potential of harm reduction strategies, although these should be preceded by robust pilot studies to establish optimal design and approaches.

Objective: Recognizing the need for harm reduction strategies for individuals with FEP who use cannabis and based on research on patients' preferences supporting harm reduction interventions, we developed a mobile app–based cannabis harm reduction intervention for this population. This intervention is called Cannabis Harm–reducing Application to Manage Practices Safely (CHAMPS). Here, we describe the protocol for a multicenter, 2-arm, parallel group, randomized pilot trial evaluating the acceptability of CHAMPS for people with FEP who use cannabis and the feasibility of conducting a full-scale trial in this population using CHAMPS. The impact on key clinical outcomes will also be explored.

Methods: This pilot trial aims to recruit 100 young people with FEP using cannabis from 6 Canadian EIS clinics. Participants will be randomized in a 1:1 ratio to CHAMPS+EIS or EIS-only. CHAMPS acceptability will be assessed using completion rates for the intervention arm. Trial feasibility will be assessed using a retention rate for randomized participants. Secondary outcomes will explore tendencies of change in the use of protective behavioral strategies and in motivation to change strategies. Exploratory outcomes include cannabis use–related problems, other substance use, the severity of dependence, psychotic symptoms, and health care service use.

Results: Recruitment began in December 2021. Data collection and analysis are expected to be completed in early 2024. Study results describing CHAMPS acceptability and trial feasibility will then be submitted for publication in a peer-reviewed journal.

Conclusions: CHAMPS uniquely combines evidence-based approaches, patient perspectives, and mobile health technology to support harm reduction in people with FEP who use cannabis. Attaining adequate acceptability and feasibility through this trial may justify further exploration of harm reduction tools, particularly within the context of conducting a larger-scale randomized controlled trial. This pilot trial has the potential to advance knowledge for researchers and clinicians regarding a feasible and user-acceptable research design in the cannabis and early psychosis fields.

Trial Registration: ClinicalTrials.gov NCT04968275, https://clinicaltrials.gov/ct2/show/NCT04968275

International Registered Report Identifier (IRRID): DERR1-10.2196/53094

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KEYWORDS

cannabis, psychosis, harm reduction, pilot, mobile health; psychological intervention; mHealth; young adult; schizophrenia; motivational interviewing; intervention; RCT; randomized; controlled trial; controlled trials; multi-centric; young people; clinical trials; feasibility; perspectives; perspective; evidence-based

Introduction

Background

Cannabis use is widespread in young people with psychosis, with 60% of young people with first-episode psychosis (FEP) reporting cannabis use at admission into specialized mental health services such as early intervention services (EIS) [1]. Compared to individuals with FEP not using cannabis, people with co-occurring cannabis use are susceptible to worse short- and long-term clinical and mental health outcomes, including persistent psychotic symptoms, more frequent relapses and hospitalizations, and worse psychosocial functioning [1-7]. Given the increased risk of worsened prognosis, it is necessary to deploy evidence-based interventions that target problematic cannabis use (including cannabis use disorder [CUD]) in people with FEP. However, relatively few cannabis-specific interventions have been developed for and tested in people having FEP and those studied have mainly focused on achieving abstinence, showing overall limited efficacy [8-10]. A minority of individuals will recover from CUD without any cannabis-specific treatments [11], and only about half of people with FEP will recover from CUD within 2 years of regular EIS treatment [1]. For many individuals who continue to use cannabis, including those who do not wish to participate in cannabis cessation interventions, more research is needed to determine effective therapeutic options that can reduce potential cannabis use–related harms.

In response to this challenge, there is a growing interest in innovative harm reduction interventions to help individuals with FEP and persistent cannabis use [12-14]. Cannabis harm reduction is an approach that has been endorsed in public health or government reports, as well as by clinicians and young people using cannabis [15-19]. Harm reduction in a drug use context shifts the focus away from the all-or-nothing goal of abstinence and instead focuses on improving the health or quality of life of individuals by targeting the reduction of harmful drug–related consequences [20]. Harm reduction approaches often leverage motivational interviewing techniques to augment motivation to change drug use habits [20]. Motivation to change use habits reportedly represents a major barrier to successful cannabis intervention implementation for young adults with FEP [18]. Harm reduction approaches, especially when using motivational interviewing, may thus be well suited as an alternative to people who are ambivalent or reluctant to reduce their cannabis use but who may be ready to modify their cannabis use practices. Examples of such modifications might include reducing the

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number of times they use cannabis before work to avoid work problems, avoiding cannabis use while using other substances to reduce compounded deleterious physical or mental health harms, and so forth.

Although used to address problems related to other substances for many years [20], harm reduction initiatives for cannabis are only just emerging [21-23]; few trials (in nonclinical populations [24]) have evaluated their effectiveness, but initial findings are promising. However, there are, so far, no cannabis harm reduction interventions that have been specifically designed and evaluated for people with FEP who use cannabis [8]. This population is characterized by distinct clinical features, such as impaired attention and memory, and cognitive deficits [25], which must be considered when designing or recommending interventions. More research is needed to evaluate whether harm reduction interventions could benefit people with FEP and continued cannabis use, who are at risk of experiencing related harms.

Study Aims

Our team developed a novel harm reduction intervention for individuals with FEP who are interested in reducing their cannabis use–related harms, called the Cannabis Harm–reducing Application to Manage Practices Safely (CHAMPS), which is delivered through a smartphone app. The development of CHAMPS was informed by related projects in cannabis use and psychosis conducted by our team [8,18,26] and co-designed in collaboration with clinicians, patient-partners, and experts in cannabis and psychosis (see intervention description in the Study Arms section). To our knowledge, the CHAMPS intervention represents the first psychosocial mobile health intervention aiming to reduce cannabis use–related harms in people with FEP. Our team is also currently working on a psychosocial mobile health intervention that addresses CUD in people with FEP and focuses on decreasing cannabis use or cessation [27].

Due to the paucity of cannabis harm reduction research in this population, a preliminary assessment of trial feasibility and intervention acceptability as well as an initial assessment of key clinical outcomes were necessary before conducting a large-scale randomized controlled trial (RCT) of CHAMPS [28]. As EIS represent the mainstay of treatment for FEP [29], we opted to evaluate this novel intervention as an adjunctive clinical tool to existing services. We will thus evaluate CHAMPS+EIS versus EIS-only in a multicenter, 2-arm, parallel group, open-label, randomized pilot study. The primary objectives of our study are to assess whether it is feasible to conduct a future RCT of the CHAMPS intervention in people with FEP who use cannabis and want to modify their cannabis behaviors and determine if CHAMPS is an acceptable intervention for this population. Secondary objectives aim to descriptively determine whether CHAMPS+EIS influences the use of protective behavioral strategies (PBS) and motivation to change PBS, compared to EIS only, in young people with psychosis who use cannabis. Exploratory objectives aim to descriptively estimate the effect of the intervention arm on cannabis-related problems, quality of life, cannabis and other substance use, severity of dependence, psychotic symptoms, and health care service use. We hypothesize that CHAMPS will be acceptable to those randomized to the CHAMPS+EIS intervention arm and that the pilot trial will demonstrate adequate feasibility, with a minimum trial retention rate of 60%.

Methods

Participants and Recruitment

This study will involve 100 young adults (50 per arm) who meet the study's eligibility criteria. Briefly, the inclusion criteria are having a diagnosis of psychosis, being 18 to 35 years old, having recent cannabis use, and being treated at an EIS (see Textbox 1 for detailed inclusion and exclusion criteria). Participants will continue their usual pharmacological and psychosocial interventions offered at the EIS, including taking any medication prescribed for their psychosis or other health concerns while participating in this study; these will be recorded in the patient study file.

If the CHAMPS intervention is considered clinically relevant for a potential participant, a clinician approaches this person, briefly explains the intervention, and asks about any interest in meeting the research team to learn more about the trial. If the person agrees, the referring psychiatrist or clinician collects screening and medical eligibility information. In other words, participant recruitment will use purposive sampling. The research staff then schedules a full screening visit, where eligibility is confirmed, and informed consent is obtained from interested participants (Figure 1; Multimedia Appendices 1 and 2). For study visits conducted via telepsychiatry, e-consent and verification of comprehension are documented using the Research Electronic Data Capture (REDCap; Vanderbilt University) web-based data entry system [30].

Clinicians will assist participants as needed, as they download the CHAMPS app from the Apple Store or the Google Play Store. If potential participants do not own a smartphone, the research staff will loan them a smartphone for the study duration. All participants will receive a compensation of CAD $30 (US $22.14) for participating at each visit (eg, screening, baseline, and follow-up assessment visits), with a maximum of CAD $150 (US $110.69) per participant. In addition, participants randomized to the EIS-only arm are offered CHAMPS access after their trial completion; these data will not be collected for research purposes.

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Textbox 1. Inclusion and exclusion criteria for participants and recruitment sites.

Inclusion criteria

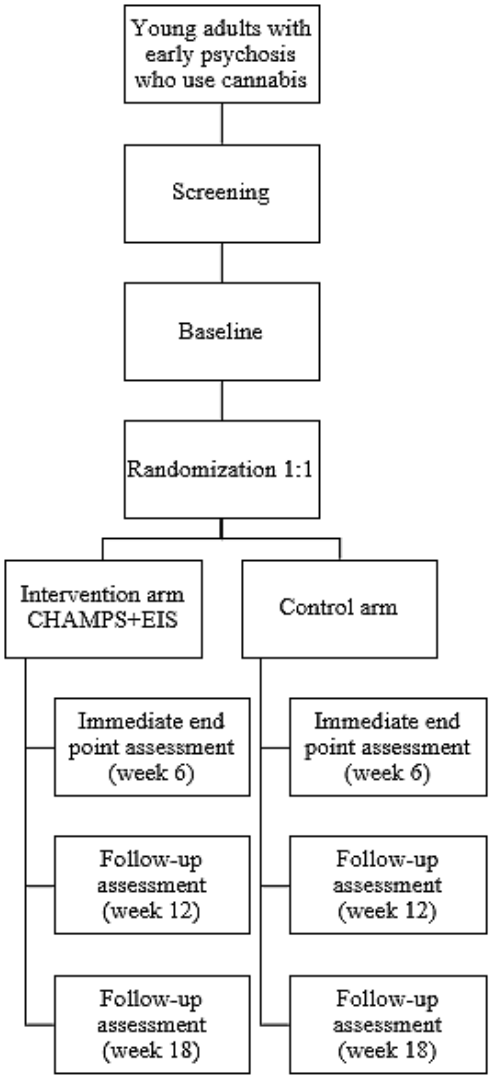
- Participants
  - Young adults (18 to 35 years of age)
  - Diagnosis of a psychotic disorder (including primary psychotic disorders, mood disorders with psychotic features, substance-induced psychosis, etc)
  - Receiving care for psychosis at early intervention services for at least 2 months
  - Recent cannabis use (in the last 30 days)
  - Interest in changing cannabis-related practices
  - Provide informed consent
  - Comply with study procedures
  - Read French or English
- Recruitment sites
  - Specialized early intervention services for the treatment of people with early-phase psychosis
  - Demonstrate capacity to provide early intervention services for psychosis
  - Agree to offer Cannabis Harm–reducing Application to Manage Practices Safely alongside early intervention services
  - Have sufficient patients to achieve enrollment targets
  - Have a sufficient psychiatrist and clinician availability and acceptance of the study to refer patients
  - Adhere to trial procedures

Exclusion criteria for participants

- Participation in another cannabis-focused intervention or treatment
- Currently seeks cannabis use disorder treatment

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Figure 1. Study flowchart. CHAMPS: Cannabis Harm-reducing Application to Manage Practices Safely; EIS: early intervention service.



The lead site is located at the Centre Hospitalier de l'Université de Montréal (CHUM). Recruitment takes place at 6 EIS clinics in Nova Scotia and Quebec, Canada, which have varying clinical and sociogeographical contexts. See Textbox 1 for inclusion criteria for EIS. Each local site has a similar structure that includes clinicians (eg, case workers and psychiatrists), research staff, a research coordinator, and site principal investigators (PIs). With the assistance of local site PIs, our research team conducts a project presentation for clinicians working with this population at collaborating sites. Clinicians who are available to recruit and can adhere to CHAMPS trial procedures and requirements recruit participants for this study. Local site investigators responsible for local study oversight are invited as study coauthors. Clinicians contribute to recruitment and support using the CHAMPS app. Research staff and coordinators contribute to data collection, assist with recruitment, and conduct follow-up assessments. Local site PIs oversee research ethics board processes, recruitment, staff training, and coordination with the lead site. The lead site additionally oversees any potential study implementation challenges, ensures the quality of the data collection and databases, and monitors study progress.

Randomization and Blinding

Participants are randomized in a 1:1 ratio to either arm (EIS-only and EIS+CHAMPS). Randomization is stratified by sex and CUD status using random permuted blocks. The CHUM Center for Integration and Analysis of Medical Data generates the allocation sequence. Access to the randomization code is strictly controlled by the data management team. Individual participant codes can be broken without unblinding the sequence allocation of other participants. Due to the nature of the intervention, clinicians and research staff collecting data cannot be blinded; however, the research staff conducting data analysis are blinded to group assignment. Participants are not able to switch arm assignments.

Study Arms

EIS-only (ie, "Control") offers EIS to all participants as per the standard of care at participating sites. Many EIS international and national guidelines are available and typically followed by these programs [31-33]. Most EIS offer similar services, including integrated treatments such as psychopharmacology and psychosocial interventions (eg, case management, family interventions, cognitive behavioral therapy, motivational interviewing, vocational recovery interventions, and outreach

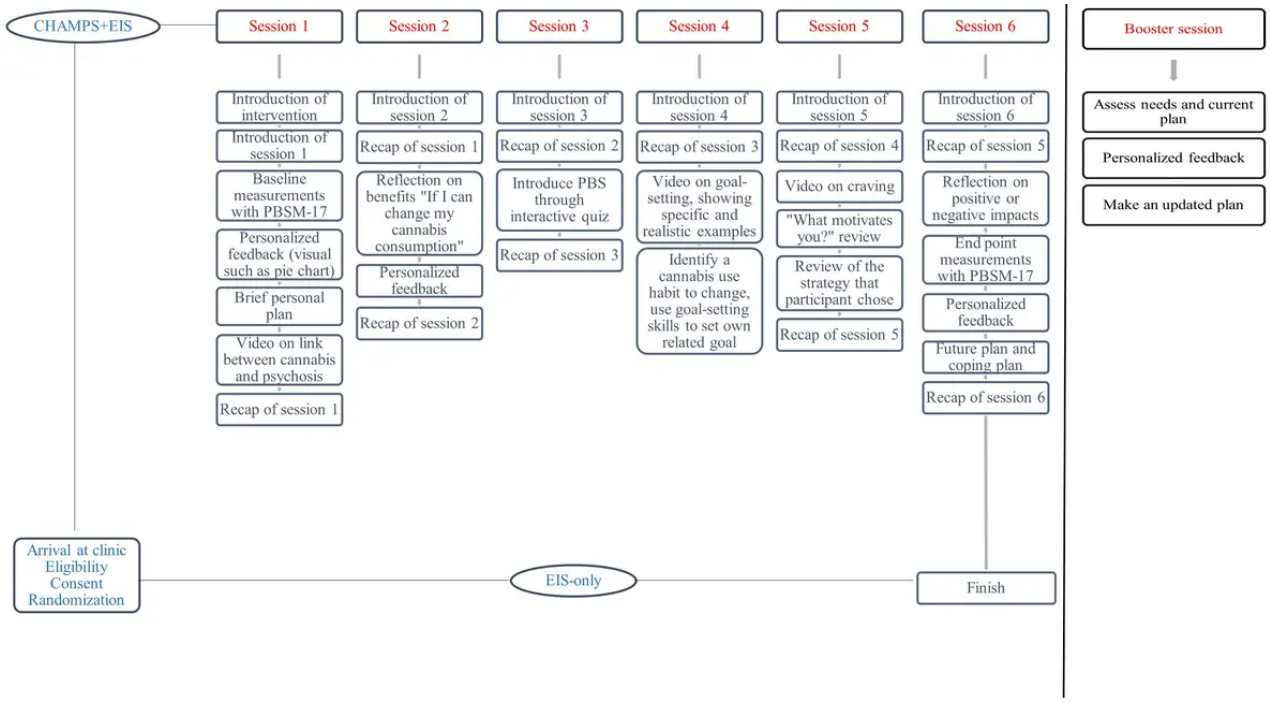
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interventions) [29]. Regarding substance use services, a survey found that the majority of English-speaking Canadian EIS reported offering informal and general substance use services to patients (eg, individual psychoeducation), and only 12% reported offering cannabis-specific formal interventions [34]. A similar survey of 28 of 33 EIS in Quebec found that only 16 of 28 EIS offered group or individual substance use services [35]. The Quebec EIS framework explicitly states that substance use is important to address, ideally using motivational interviewing and cognitive behavioral strategies, although no formal harm reduction–focused interventions are recommended [33]. Practices may differ between EIS across Canada; we can expect at least some EIS to offer an unstructured, nonspecific, informal substance use intervention. Most EIS use a case management model, where a clinician takes the central role of treating a patient [29]. Any visits and services offered (eg, in person or via teleconsultation) at EIS will be considered "usual care."

CHAMPS+EIS (ie, "Intervention") arm offers participants access to EIS usual care in addition to the CHAMPS intervention. CHAMPS is a psychosocial intervention that aims to promote positive behavioral changes and a reduction of cannabis use–related harms, using motivational interviewing, psychoeducation, skills training, and personalized feedback strategies. CHAMPS is self-guided and delivered through a smartphone app; this delivery mode was guided by previous studies signaling an acceptability of and preference for technology-based interventions [36,37]. The CHAMPS protocol recommends accompanying clinicians to provide support using CHAMPS if participants request it as well as to encourage its use. If the participant consents, accompanying clinicians can also access the participant dashboard, which shows high-level app data, such as how many modules they have completed, as well as participant responses in the CHAMPS intervention (eg, goals they have set during module 4, reasons for changing cannabis use stated in module 2). No additional participant data will be shared with accompanying clinicians.

There are 6 modules in the intervention and a booster session module 4 weeks after the last module (see Figure 2). Each module is expected to take up to 15-20 minutes to complete. In essence, CHAMPS informs participants about cannabis use and its effects on people with FEP, offers strategies to reduce related harms (inspired by harm reduction tools), and guides participants to set their own cannabis harm reduction-related goals to help improve their well-being. Suggested goals can target participants' physical or mental well-being, social relationships, or even cannabis use itself; however, no goal will be imposed, and participants will decide which goals they would like to work on. Table 1 provides a detailed description of each module, and Textbox 2 provides examples of harm reduction strategies and goals from CHAMPS.

Figure 2. CHAMPS intervention detailed description. CHAMPS: Cannabis Harm-reducing Application to Manage Practices Safely; EIS: early intervention service.



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Table 1. Detailed CHAMPS[a] module descriptions.

Week	Module	Description
1	Module 1	Measures baseline cannabis protective behavioral strategies (PBS[b]) and automatically provides participants with personalized feedback on their cannabis practices, as well as suggestions on what cannabis practices they could improve
2	Module 2	Explores what is important to participants and the possible benefits of adopting safer cannabis use strategies
3	Module 3	Exposes participants to various evidence-based cannabis PBS using interactive psychoeducational techniques
4	Module 4	Introduces participants to goal setting and asks them to set their own cannabis-focused goals, which they can immediately implement in their lives
5	Module 5	Helps participants reflect on their goal progress and offers help to the participant in either revising their current goal or adopting a new goal
6	Module 6	Reassesses cannabis PBS and encourages participants to continue improving their cannabis practices
10	Booster session	Four weeks postintervention, participants will receive a booster session, also lasting between 15 and 20 minutes. The purpose of this booster session will be to review the main components of the intervention, remind participants of what they explored about their cannabis use as well as goal setting during the intervention, and revise it as needed

[a]CHAMPS: Cannabis Harm-reducing Application to Manage Practices Safely.

[b]PBS: protective behavioral strategies.

Textbox 2. CHAMPS harm reduction strategies and sample goals.

Limit the amount of cannabis you smoke in one sitting

"I will put a quarter of the amount of cannabis I usually put in my joints for a prespecified period of time."

Avoid mixing cannabis with other drugs

"I will avoid using alcohol and cannabis at same time during a pre-specified period of time"

Avoid using cannabis to help cope with emotions such as sadness, depression, anxiety, and fear

"Instead of using cannabis, I will practice using alternate and healthier coping strategies (eg, trying a new sport, calling a friend) the next time I feel negative emotions"

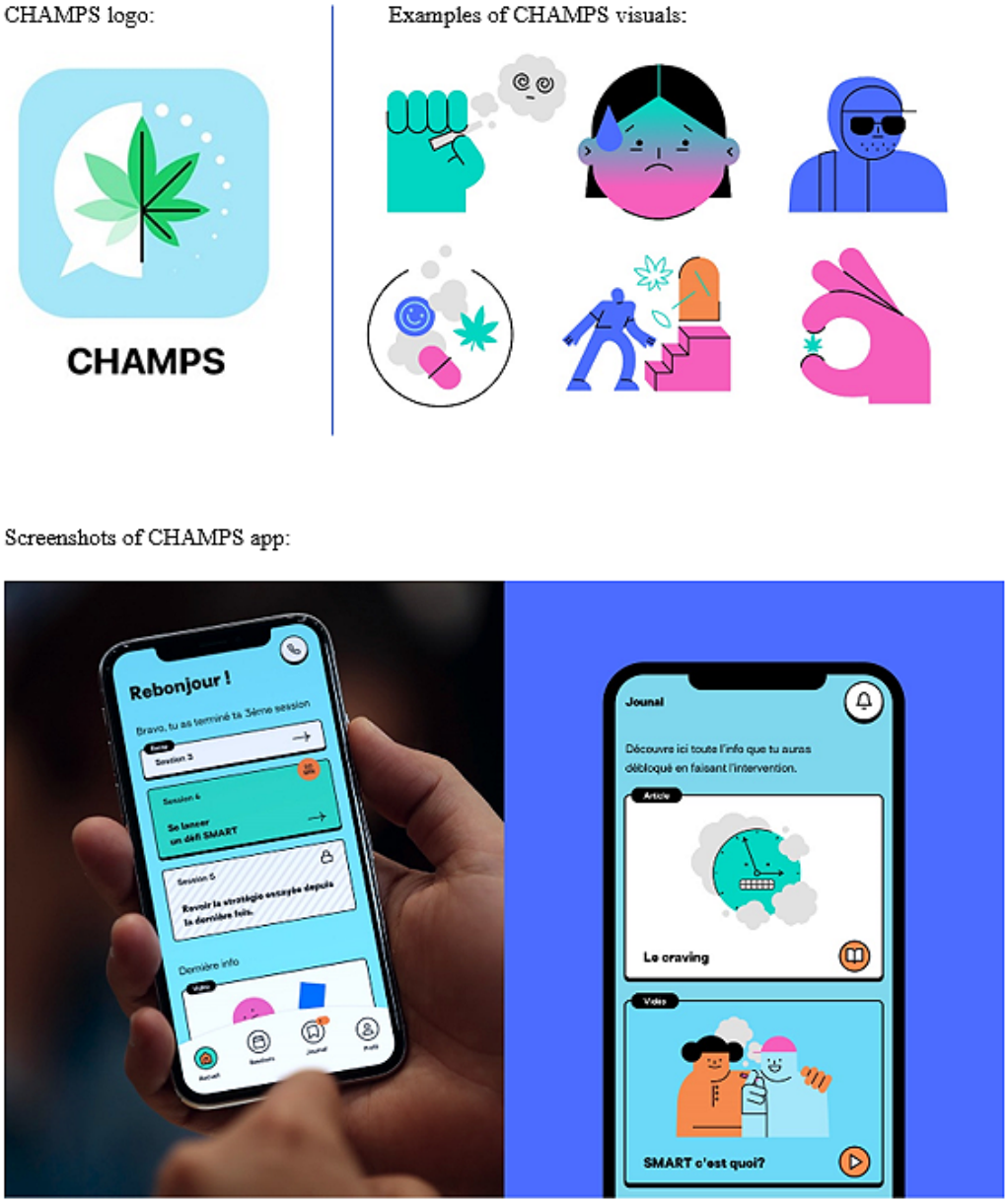
CHAMPS Intervention Development

The CHAMPS intervention was inspired by the Behavioral Change Wheel theoretical framework, which has been used to design behavioral interventions in various settings including for young people at ultra-high risk for psychosis [38,39]. The CHAMPS intervention uses the following behavior change techniques detailed in this framework: feedback on behavior, brief action planning, modeling of behavior, reflection of health, social and environmental consequences, instructions on how to perform a behavior and behavioral experiments, review behavioral goals, and behavioral rehearsal and practice. The findings of our qualitative study outlining barriers and facilitators in a variety of cannabis-focused interventions according to young adults with FEP who use cannabis and to accompanying clinicians also helped guide the CHAMPS intervention development [18]. This study supported the use of harm reduction for people who used cannabis and lacked motivation for more intensive cannabis-focused treatments and reported openness to technology-based interventions, citing potential benefits such as quicker intervention access for patients, decreased clinician workload, and so forth. The modalities of CHAMPS were informed by our preference study for cannabis harm reduction interventions, which surveyed 89 young adults with FEP using cannabis. This survey, which featured a quantitative discrete choice experiment design, found that respondents significantly preferred interventions with shorter durations and sessions, technology-based interventions, and brief booster sessions (personal communication by SC-M and DJ-A, September 2023 on patient preference survey results; associated manuscript submitted for publication).

The design of CHAMPS used a participatory approach, where people with lived experience were integrated into different facets of the study. We created the CHAMPS patient advisory committee comprising young individuals who used cannabis, had FEP, and attended EIS. This committee consulted on and helped co-design CHAMPS. For example, this committee contributed to the selection of the visuals we used, the tones and language of our CHAMPS content, the phrasing, the frequency and content of add-ons such as notifications, and so forth (see Figure 3 for examples of CHAMPS app visuals). Some patient-partners were also involved in the content creation, as they coproduced video testimonials of their experience with changing their cannabis use habits. Additionally, 1 patient-partner was involved in knowledge dissemination related to this project, copresenting on the protocol at a scientific conference and detailing the involvement of the patient advisory committee.

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Figure 3. Examples of CHAMPS app. CHAMPS: Cannabis Harm-reducing Application to Manage Practices Safely.



Outcomes and Data Collection

Participant Characteristics

Sociodemographic data are collected at baseline using a questionnaire on sociodemographic outcomes that include gender identity, sex, ethnicity, educational attainment, vocational status (eg, employment), income, and housing status.

Primary Outcomes

The feasibility of conducting a future RCT will be determined through the trial's retention rate. The retention rate will be calculated by dividing the number of participants who completed all end point assessments (week 6) by the number of total randomized participants at baseline. As discussed, there are so far no other harm reduction–oriented studies in this population to guide our study design. Therefore, to establish an adequate minimum retention rate, we looked at related trials of (1) psychosocial mobile health interventions in populations with psychotic disorders, which had retention rates ranging from 76% to 100% [40-43] and (2) RCTs of face-to-face cannabis interventions for people with FEP, which had retention rates ranging from 52% to 96% [44-47]. The mobile health intervention trials either did not include comparison groups, did not focus specifically on individuals with FEP who used cannabis, or did not evaluate cannabis-focused interventions. The face-to-face interventions all focused on cannabis use in people with psychosis, but the delivery method precluded generalization to our trial. Given our intervention characteristics, we expect our retention rate will be on the lower end of these spectrums. We believe a 75% retention rate is a conservative estimate, but we are setting the minimum threshold for retention rate at 60%, which we believe represents a clinically important retention rate for our population.

Acceptability of the CHAMPS intervention will be assessed using the CHAMPS completion rate. This rate will be calculated by dividing the number of participants who completed at least

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the first 4 modules of CHAMPS by the number of total participants randomized to CHAMPS. We selected this completion threshold as the first 4 modules represent the core of the intervention, exposing participants to psychoeducation, motivational interviewing, personalized feedback, and skills training.

Secondary Outcomes

The efficacy of CHAMPS will be described by examining the change in participants' use of PBS, using the Short Form Protective Behavioral Strategies-Marijuana measure [21]. This is a 17-item self-report measure that includes evidence-based strategies that promote safer cannabis experiences. The marginal reliability of the short-form measure is high (0.93) [21].

The efficacy of CHAMPS will also be estimated by measuring the change in participants' motivation to change PBS, which is assessed using the Readiness to Change Questionnaire (RCQ) modified for cannabis use [48,49]. The RCQ is a 12-item clinician-administered measure based on Prochaska and DiClemente stages-of-change model and assesses 3 stages of change: precontemplation, contemplation, and action [49]. The internal consistency is satisfactory; the 3 stages of change scales have acceptable internal consistency, ranging from Cronbach α=.73 to α=.85 [48].

Exploratory Outcomes

Cannabis use–related physical, psychological, social, and functioning problems will be assessed using the Marijuana Problems Scale, a 19-item self-report instrument that measures changes in problems related to cannabis use over time [50,51].

Cannabis and other drug use in the past 2 weeks will be assessed using the Timeline Follow-back. This tool has high test-retest reliability and has been validated using other measures of drug-related problems or in clinical populations [52,53]. This tool has previously been used in a trial of people with psychosis who use cannabis [54]. This tool assesses the self-reported days of cannabis use per week, as well as the type of cannabis products, quantity, and dose or concentration of cannabinoids. The main end point for this outcome will be the number of days per week of cannabis use. The frequency of other drug use in the past 2 weeks will also be assessed using this tool.

Psychotic symptoms will be measured using the Positive and Negative Syndrome Scale-6, which is easily administered and has good psychometric properties [55,56]. The scale consists of 6 items: delusions, conceptual disorganization, hallucinatory behavior, blunted affect, passive or apathetic social withdrawal and lack of spontaneity, and flow of conversation.

Severity of cannabis dependence will be measured using the Severity of Dependence Scale [57]. This is a short, easily self-administered instrument developed to provide a brief measure of the psychological aspects of dependence experienced by users of various types of illicit drugs. It is a measure of compulsive use. This scale has good internal consistency (Cronbach α ranging from .80 to .90) [57,58] and has previously been used in trials with people with FEP [5,59].

Health service use data are collected via participant self-report and are confirmed as needed through patient medical record abstraction and contact with the clinician, gathering information on the total number of past-month emergency visits and days of hospitalization.

Data relating to the reception of EIS, CHAMPS usage data, and participant satisfaction will be used to complement data on CHAMPS acceptability and trial feasibility. We collect data on participants referred, screened, considered eligible, recruited, and consented; participants who initiated the intervention; and participants who completed baseline assessments. We will calculate the control group completion rate by dividing the total participants randomized to the control group by the number of participants who, at week 12, are still participating in EIS treatment.

Understanding of CHAMPS acceptability by study participants will be complemented by an evaluation of participant satisfaction with CHAMPS, using the Client Satisfaction Questionnaire-I, which is a modified version of the Client Satisfaction Questionnaire-8 and which measures global satisfaction with a web-based intervention [60]. This measure has an adequate internal consistency, as represented by Cronbach α=.93 for the 8-item scale [60,61]. Those randomized to EIS-only will receive the Client Satisfaction Questionnaire-8 and accompanying instructions to evaluate the cannabis-related treatment components of EIS using this questionnaire.

Data Collection and Management

Participation in the trial lasts up to 22 weeks, including up to 4 weeks between screening and randomization, 6 weeks of active CHAMPS intervention (immediate end point assessment), a booster session 4 weeks after the end of active CHAMPS intervention, and follow-up assessments conducted at weeks 12 and 18 (Table 2). Assessments are conducted either in person, over the phone, or using videoconferencing platforms. Communication and contact can be done digitally, over the telephone, or during in-person visits (only if confidentiality can be strictly maintained). All interactions are recorded in the patient study file. Furthermore, sites track participant interactions and collect information on recruitment, ineligibility reasons, and nonparticipation reasons. The research team uses these data to refine the recruitment strategy during the trial if needed.

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Table 2. Schedule of assessments.

Assessment name	Time point										
	Screening visit (week-4-2)	Baseline (W-2-W0)	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 10	Week 12	Week 18
Screening form	✓										
Informed consent form	✓										
Locator form	✓							✓		✓	
Demographic questionnaire		✓									
Social Provision Scale-10		✓									
Readiness to Change Questionnaire		✓						✓		✓	✓
Marijuana Problems scale		✓						✓		✓	✓
Timeline Follow-back		✓						✓		✓	✓
Positive and Negative Syndrome Scale		✓						✓		✓	✓
Severity of Dependence Scale		✓						✓		✓	✓
Health care use		✓						✓		✓	✓
Randomization		✓									
Protective Behavioral Strategies—Marijuana		✓						✓		✓	✓
Client Satisfaction Questionnaire								✓		✓	
Adverse events								✓		✓	✓
Intervention and services form								✓		✓	✓

Data are entered into REDCap by site research staff or directly by the participant (through the CHAMPS app). The data dictionary will be built on REDCap and will be available upon request to the corresponding author. Final data quality assurance checks will be conducted by the data management team, and the study database will be locked, prohibiting further modification. The REDCap system was developed and implemented by the Center for Integration and Analysis of Medical Data to ensure that guidelines and regulations surrounding the use of computerized systems in clinical trials are upheld.

Participants are attributed a unique numeric study identifier to anonymize data, and data are password-protected on computerized databases and kept strictly confidential. Records are accessible only to research staff. Intervention arm participants are provided with detailed information regarding their data usage and protection (Multimedia Appendix 3). The final analysis data set will be kept on the secure server at the CHUM in Montreal, Québec, for 10 years, in line with *Fonds de la recherche en santé du Quebec* and CHUM research ethics board requirements.

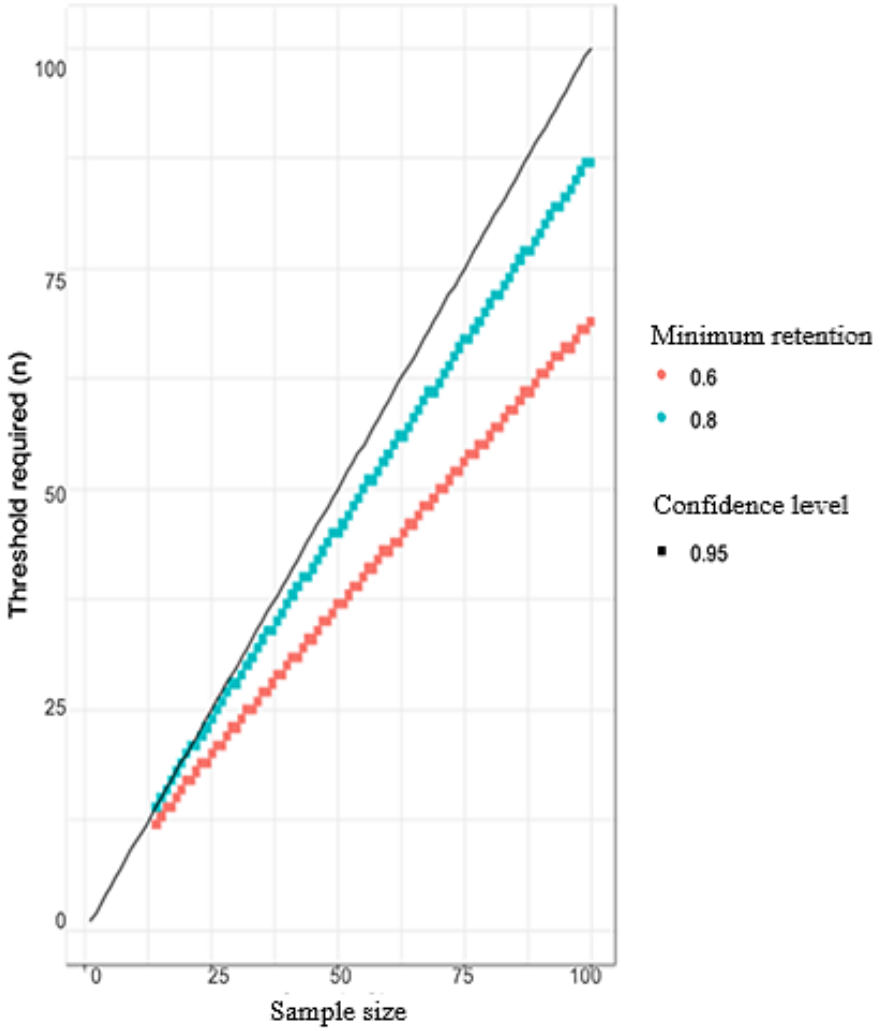
An independent data and safety monitoring board examines accumulating data to ensure the protection of participants' safety during the study. This board determines whether there is ground for trial continuation; evidence that study procedures require modifications; or whether the trial should be halted for participant safety, intervention efficacy issues, or inadequate trial performance reasons.

Sample Size

The sample size for pilot trials is typically not driven by power calculations but rather by convenience or precision estimates [62], both of which we used to inform our sample size. Using a precision-based approach, we estimated the number of participants we would need to retain in this trial to detect with 95% confidence the true retention rate for a future trial. As aforementioned, based on related literature and our current context, we deemed 60% a clinically significant retention rate for this trial [40-43]. As seen in Figure 4, if we recruit 100 participants and retain at least 69 participants at the end of the study, we would have 95% confidence that the true (ie, population-level) retention rate is above 60%. Regarding convenience, our existing partnerships with Canadian EIS clinics and experience recruiting relatively large samples from this population [63] lead us to believe that recruiting 100 eligible individuals is feasible for this trial.

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Figure 4. Diagram of trial retention rates.



Statistical Analysis

We will be analyzing primary outcomes using univariate analyses. The trial retention rate will be measured in terms of the percentage of randomized individuals retained in the intervention at end point assessment and will include a 1-sided 95% confidence interval to estimate the lower bound of the retention rate. CHAMPS acceptability will be reported using univariate analysis. We will also conduct exploratory analyses to test whether belonging to either study arm influenced EIS completion rates.

To describe sociodemographic and clinical variables at baseline, trial parameter data, and secondary and exploratory outcomes, we will conduct univariate analyses. We will use multivariable statistical methods to explore the following outcomes: participant satisfaction, use of cannabis PBS, and motivation to change cannabis PBS. To compare satisfaction between groups, we will use a hierarchical linear regression. The first regression model will insert the intervention arm as the independent study variable; the second model will insert other covariates. We will also conduct a hierarchical linear regression exploring the use of cannabis PBS over time as the outcome; the first regression model will insert study arms as the independent variable, and the second model will insert baseline PBS scores and other relevant covariates. To look at motivation to change, analyses will be done as with cannabis PBS, using hierarchical models that look at RCQ scores as the outcome and control for RCQ scores at baseline.

In multivariable models, we will include sites as random effects and will include certain covariates of interest that differ at baseline. These covariates may include age, sex, gender, study site, education status, employment, housing status, social support, and baseline clinical characteristics including cannabis use and CUD severity. Sensitivity analyses will explore key outcomes in subgroups of participants (eg, location-based subgroups), as well as the use of different thresholds to determine whether participants have completed CHAMPS.

Missing data will be handled issuing guidance of the missing data treatment for each instrument. The proposed analyses will include all participants with at least 1 nonmissing visit. Our analysis plan includes both intention-to-treat and per-protocol analyses.

Ethical Considerations

Ethical approval for the proposed study was obtained from the CHUM research ethics board (#20.433). Prior to initiating the study, local approval to conduct the study at each respective location was also obtained. This study will be conducted in accordance with the ethical principles outlined in the Declaration

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of Helsinki, the International Conference on Harmonization Good Clinical Practice Guidelines, and all other applicable regulatory requirements. This pilot trial protocol was developed in accordance with the extension of the Consolidated Standards of Reporting Trials statement for randomized pilot or feasibility trials [64] (Multimedia Appendix 4).

Site PIs will ensure that the trial is conducted according to good clinical practice guidelines and may perform quality assurance audits for protocol compliance. The local research ethics board may inspect research records for verification of data, compliance with federal, provincial, and local guidelines on human participant research and to assess participant safety. Adverse events reported by the participant will be recorded electronically by study staff and reported to the site PI, study nurse, and study clinician for assessment and referral as appropriate. Site PIs will review each adverse event and assess the possible relatedness of any adverse event to the study intervention or other study procedures. Each of the sites has established practices for managing medical and psychiatric emergencies, and the study staff will use these procedures.

Results

Enrollment took place from December 2021 to June 2023. Data collection and analysis are expected to be completed by early 2024, and study results will be submitted for publication in peer-reviewed scientific journals thereafter. For participants who opt to receive the results, we will apply various knowledge transfer tools (eg, health cards, summaries with charts and graphics, video clips accessible on the web or through social media) in English and French to effectively translate our findings. Furthermore, we will leverage our networks to relay study findings in a format that is tailored to this population. We have designed an ancillary qualitative study that will explore CHAMPS pilot trial participants' and accompanying clinicians' experiences regarding the CHAMPS intervention and its implementation in EIS. This ancillary study will serve to further understand the barriers and facilitators of CHAMPS and its implementation and can inform future trials of similar interventions.

Discussion

Principal Findings

This mobile health and harm reduction intervention is the first of its kind to be evaluated in the context of reducing cannabis use–related harms for this population. We consider that CHAMPS was strengthened by its unique development process, using preference research to shape the intervention and involving individuals with lived experience as CHAMPS coproducers. Despite potential barriers to coproduction research, such as a high turnover rate of clinicians or researchers and stigma toward patients [65], our patient-partners anecdotally reported that the coproduction process was successful in building healthy relationships between coresearchers and patient-partners and provided opportunities for personal growth. Feedback from our co-researchers also highlighted the benefits, including the production of a well-informed intervention that valued the knowledge of all contributors.

Another strength of this pilot trial is its rigorous and carefully crafted design, considering the limited literature on cannabis use–related harm reduction in people experiencing FEP and the use of mobile health technology in this context. The CHAMPS trial design, as a multicenter, randomized pilot study, will enable rigorous assessment of the feasibility of running a full-scale RCT with CHAMPS and of the acceptability of the CHAMPS intervention for this population. Furthermore, we are collecting data exploring how CHAMPS may potentially influence harm-related outcomes. The results of this pilot trial and its ancillary qualitative study may offer valuable insights for future trials assessing similar psychosocial interventions.

Mobile health interventions like CHAMPS may contribute to the alleviation of strained health care systems by improving accessibility for participants and providing an independent tool to aid clinicians in delivering optimal care to their patients [66]. Surveys and personal communication by SC-M and DJ-A on September 2023 on patient preference survey results (associated manuscript submitted for publication) demonstrate the theoretical acceptability of and preference for mobile health interventions to target CUD or cannabis use by people with FEP [36,37]. However, the implementation of a novel mobile health intervention or concerns around data confidentiality may hinder the potential acceptability of this intervention. More research piloting the use of new technologies, such as CHAMPS, to address existing mental health challenges in individuals with FEP needs to be undertaken before recommending these initiatives in clinical contexts.

Limitations

The present trial has limitations and may face a variety of possible challenges. Previous data suggest that continued cannabis use predicts persistently poor treatment adherence for people with psychosis [67]; if such patterns also translate to psychosocial intervention adherence, then this may lead to retention challenges for our trial. We are recruiting participants from Quebec and Nova Scotia provinces, which differ in their sociocultural and clinical contexts from each other and other provinces. To explore the potential impact of these differences, we will be doing sensitivity analyses to explore possible site-specific effects on outcomes. On the other hand, our potentially heterogeneous sample may provide researchers with insights regarding the effectiveness of CHAMPS in multiple real-world contexts, facilitating generalization to other settings. The context-specific adaptations that occurred as a result of the ongoing COVID-19 pandemic (eg, transitioning to telehealth services) and which our participants may have experienced may influence the results of our study. For example, tightening restrictions may have resulted in less frequent in-person clinical consultations. These tightened restrictions may also have particularly impacted people with psychosis, who are likely to be single and have limited social networks [68], and resulted in higher levels of isolation and emotional distress for certain participants. It is possible that these changing regulations and societal restrictions may have influenced the reception, effectiveness, satisfaction, or other related outcomes of our intervention and EIS. The role of this particular context must be considered during our analyses and may limit the generalizability of our study findings. Finally, while we

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consulted the literature to determine best practices for data protection and confidentiality strategies while designing CHAMPS, concerns around data protection and privacy have previously been a hindrance to the acceptance of mental health–related apps [66]. It is thus still possible that we will face confidentiality and privacy issues or that risk perception by participants may impact our capacity to recruit and engage them in the intervention.

Conclusions

CHAMPS uniquely combines evidence-based approaches, harm reduction strategies, patient perspectives, and mobile health technology to address cannabis use–related harms in young people with FEP and persistent cannabis use, potentially addressing an unmet need in this population. Our study findings have the potential to advance knowledge in the cannabis and psychosis fields. To gain a better understanding of harm reduction interventions, future research should prioritize conducting robust, large-scale RCTs. Preliminary studies, like the present pilot trial, are urgently required to refine optimal design and approaches for these interventions.

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Authors' Contributions

SC-M wrote the initial manuscript draft, tables, and figures. SC-M, AA-B, JC, DC, SD, BF, PL-T, TL, SL, CO-P, M-AR, OT, PT, MV, AW, and DJ-A contributed to the study conceptualization, critically reviewed, and edited the manuscript. AA-B, DC, SD, TL, SL, CO-P, M-AR, PT, MV, and DJ-A contributed to the data acquisition. DJ-A obtained funding and supervised the study’s development and conduct. All authors approved the manuscript.

Conflicts of Interest

BF has held research grants and contracts in the areas of substance use, health, and policy from public funding and government-related agency (ie, public only) organizations and has consulted as a scientific expert with such entities in different countries. DJ-A received investigational products (2022-23) from Cardiol Therapeutics for a clinical trial funded by the Quebec Ministry of Health and Social Services. DJ-A received study materials from Cardiol Therapeutics and Exka for clinical trials funded by Quebec government.

Multimedia Appendix 1
Example informed consent form.
[DOCX File , 37 KB - resprot_v12i1e53094_app1.docx]

Multimedia Appendix 2
CHAMPS screening form.
[DOCX File , 36 KB - resprot_v12i1e53094_app2.docx]

Multimedia Appendix 3
CHAMPS data privacy statement.
[DOCX File , 45 KB - resprot_v12i1e53094_app3.docx]

Multimedia Appendix 4
CONSORT checklist for pilot or feasibility trial [65].
[DOCX File , 30 KB - resprot_v12i1e53094_app4.docx]

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Abbreviations

CHAMPS: Cannabis Harm-reducing Application to Manage Practices Safely
CHUM: Centre Hospitalier de l'Université de Montréal
CUD: cannabis use disorder
EIS: early intervention service
FEP: first-episode psychosis
PBS: protective behavioral strategy
PI: principal investigator
RCQ: Readiness to Change questionnaire
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture

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Protocol

Ohnut Versus a Waitlist Control for the Self-management of Endometriosis-Associated Deep Dyspareunia: Protocol for a Pilot Randomized Controlled Trial

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Abstract

Background: Endometriosis-associated deep dyspareunia is associated with reduced sexual quality of life, lower self-esteem, and impaired sexual function.

Objective: The primary objective is to assess the acceptability of a phallus length reducer (brand name: Ohnut [OhnutCo]), which is a buffer worn over the penis or a penetrating object to reduce endometriosis-associated deep dyspareunia, and the feasibility of a definitive randomized controlled trial (RCT). The secondary objective is to obtain estimates of the effectiveness of the buffer. An embedded substudy will explore the acceptability and the preliminary validity and reliability of a vaginal insert for the self-assessment of deep dyspareunia.

Methods: Ours is an investigator-initiated, 2-arm RCT. We will recruit 40 patient participants with diagnosed endometriosis between the ages of 19 and 49 years, as well as their sexual partners. The participating couples will be randomized in a 1:1 ratio into the experimental arm or the waitlist control arm. The length of the study period will be 10 weeks, during which time all participants will record deep dyspareunia severity following each episode of sexual intercourse. In weeks 1 to 4, all patient participants will record deep dyspareunia severity at each sexual encounter. In weeks 5 to 10, participants in the experimental arm will use the buffer during vaginal penetration; participants in the waitlist control arm will continue engaging in vaginal penetration as usual. Participants will complete questionnaires for assessing measures of anxiety, depression, and sexual function at baseline, at 4 weeks, and at 10 weeks. In the substudy, patient participants will self-assess dyspareunia by using a vaginal insert on 2 occasions, at least 1 week apart. The primary outcomes—the acceptability and feasibility of the buffer—will be assessed with descriptive statistics, and the secondary outcome—phallus length reducer effectiveness—will be assessed by using an analysis of covariance–based approach. For the vaginal insert, we will assess acceptability, test-retest reliability, and convergent validity via correlation analyses comparing the use of the insert to clinical examination in terms of dyspareunia assessment outcomes.

Results: Our pilot will provide initial data on the acceptability and effectiveness of the buffer and the feasibility of the study methodology. The results from our study are expected to be submitted for publication by the spring of 2023. As of September 2021, we have consented 31 couples into the study.

Conclusions: Our study will provide preliminary evidence for the self-assessment and management of endometriosis-associated deep dyspareunia. The findings will inform the decision to proceed to a definitive RCT.

Trial Registration: ClinicalTrials.gov NCT04370444; https://clinicaltrials.gov/ct2/show/NCT04370444

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KEYWORDS

endometriosis; dyspareunia; randomized controlled trial; self-management; pilot project; pilot study; women's health; pain; gynecology; gynecologist; sexual health; sexual medicine

Introduction

Endometriosis is the presence of endometrial-like glands and stromata that abnormally grow outside the uterus [1]. This disease affects approximately 1 in 10 women and can cause various types of pain, including dysmenorrhea; chronic pelvic pain; and deep dyspareunia, which is defined as pain with deep vaginal penetration [1,2]. Deep dyspareunia is often neglected due to its intimate nature and reservations among both patients and clinicians in discussing sexual health [3,4]. People with endometriosis and deep dyspareunia have been shown to have significantly reduced sexual quality of life [5], lower self-esteem [6], and impaired sexual function [7]. Qualitative research has shown that many people with deep dyspareunia feel guilty about their pain and often continue to engage in penetrative activity even when the pain is severe [6].

Endometriosis-associated deep dyspareunia is multifactorial and can result from the endometriotic lesions themselves and other factors, such as myofascial pelvic pain and central nervous system sensitization [1,2,8]. A subset of patients do not experience improvements in deep dyspareunia after standard care, such as hormonal or surgical interventions for endometriosis [7-11], indicating an important need for self-management approaches. One self-management option is a phallus length reducer (PLR; brand name: Ohnut [OhnutCo])—a buffer that is worn externally over the penis or a penetrating object to reduce the depth of penetration [9]. Conceptually, this should reduce deep dyspareunia by limiting contact with deep pelvic structures; however, this intervention has not been empirically tested.

The assessment of deep dyspareunia for clinical and research purposes is challenging; pelvic examination in the clinical context may not reliably reflect sexual activities, particularly for patients who have experienced trauma [12], while questionnaire-based measurement is limited by recall bias that may be exacerbated for patients who have become abstinent as a result of dyspareunia. A study that investigated superficial dyspareunia among people with vulvodynia found that the Tampon Test—a self-administered test involving the insertion and removal of a tampon—was reliable and demonstrated good construct validity [13]. The study showed 95% adherence, providing evidence that participants found the test to be an acceptable method of assessing superficial dyspareunia [13]. Similarly, the self-assessment of endometriosis-associated deep dyspareunia by using a vaginal insert may be an acceptable, ecologically valid approach to assessing this symptom.

In our pilot randomized controlled trial (RCT) protocol, the primary objective is to assess the acceptability of a PLR and the feasibility of a definitive RCT. The secondary objective is to obtain estimates of the effectiveness of the PLR, which will be compared to those of a waitlist control for reducing endometriosis-associated deep dyspareunia. An embedded substudy will explore the acceptability, reliability, and preliminary validity if a vaginal insert for the self-assessment of deep dyspareunia.

Methods

Trial Design

Our study is a pilot study of a parallel-group, 1:1 RCT of the PLR, which will be compared to a waitlist control. An embedded substudy will investigate the use of a vaginal insert (brand name: Soul Source Rigid Plastic Vaginal Dilator Size #P1 [Soul Source Therapeutic Devices Inc]) [14] for the self-assessment of deep dyspareunia.

This protocol was developed by using the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist [15], the CONSORT (Consolidated Standards of Reporting Trials) extension for randomized pilot and feasibility trials [16], and published guidance for the reporting of protocols of pilot and feasibility trials [17]. This protocol describes the study rationale, proposed methods, organization, and ethical considerations.

Study Setting

The study is being conducted at a tertiary care center for endometriosis within a large urban center in western Canada. Our research team manages a prospective patient registry called *Endometriosis and Pelvic Pain Interdisciplinary Cohort* (EPPIC; ClinicalTrials.gov trial number: NCT02911090) [18]. Baseline data collected in EPPIC are derived from patient-reported questionnaires and clinician-reported data from clinic consultations. The variables that are included in this prospective registry have been described previously [18]. New or rereferral patients at the center are invited to participate in the registry and can consent to being contacted about further research. In our study, all procedures will be conducted by the participants at home.

Eligibility Criteria

Eligible patient participants will be new or rereferred patients in EPPIC who attended a clinic visit between January 1, 2018, and December 31, 2020; those who consented to being contacted for future research; and those who have a history of surgically confirmed endometriosis. Details of the inclusion and exclusion criteria are listed in Textbox 1.

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Textbox 1. Inclusion and exclusion criteria for the patient participants and their partners.

Patient participants

- Inclusion criteria
  - 19 to 49 years of age
  - Birth-assigned female
  - Monogamous sexual relationship
  - Sexually active or not currently sexually active due to deep dyspareunia
  - Self-reported deep dyspareunia score of ≥4 (out of 10)
  - Sexual partner who consents to participating in the study
  - Willing to engage in penetrative sex at least once during the duration of the study
- Exclusion criteria
  - Self-reported superficial dyspareunia score of ≥4 (out of 10; this is a potentially confounding variable, as the phallus length reducer is not expected to affect introital pain)
  - Severe anxiety or depression symptoms in the last 2 weeks (Generalized Anxiety Disorder-7 or Patient Health Questionnaire-9 score of ≥15)
  - Confirmed "yes" to question "In the last 2 weeks, have you had intense fear/anxiety in anticipation of, during or as a result of vaginal intercourse?"
  - Current use of a phallus length reducer
  - Inability to complete English-language questionnaires

Partners

- Inclusion criteria
  - 19 years of age or older
  - Any sex and gender
- Exclusion criteria
  - Current use of a phallus length reducer
  - Inability to complete English-language questionnaires

Sample Size

A sample size for a pilot study is often recommended to be at least 12 per group [19]. Given potential dropout and the uncertainty around the variance in acceptability, we will aim to recruit 20 participants and their sexual partners per group (ie, 40 couples or 80 total study participants).

Recruitment

Individuals will be selected from a list of potential participants and will be telephoned and emailed about the study by a study coordinator. Interested individuals will be asked a series of screening questions to confirm that they meet the eligibility criteria. An important inclusion criterion listed in Textbox 1 is that participants must have a self-reported deep dyspareunia score of ≥4 (out of 10). This criterion was established to exclude patients who may have undergone surgery or other interventions that reduced deep dyspareunia symptoms. If the inclusion criteria are met and no exclusions are identified, patient participants and their partners will be emailed the consent form to review. The study coordinator will then review the consent forms with both the patient participants and their partners in a second telephone call and address any questions that the patient participants or their partners may have. Participants will give their consent to participate electronically, using an e-consent form.

Interventions

The PLR (brand name: Ohnut) is made of a Food and Drug Administration–approved body- and skin-safe polymer blend. The blend is a thermo-set material that does not contain bisphenol A, phthalates, and latex and can be used with either silicone lubrication or water-based lubrication [20]. The PLR is a buffer that is worn externally over the penis or a penetrating object to limit the depth of penetration.

The vaginal insert is made of polyurethane and is stable from −40 to 70 °C. It will be self-inserted by the patient participants to self-assess the tenderness of pelvic structures implicated in deep dyspareunia that are typically assessed by a clinician during a pelvic examination. This is a novel, off-label use of the device.

To support the use of the vaginal insert and PLR, the study team developed patient-centered study booklets, which include instructions for the use of each tool (Multimedia Appendix 1).

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The instructions were developed with a gynecologist specialized in the assessment of dyspareunia, a pelvic floor physiotherapist with expertise in guiding patients to use vaginal inserts, and a clinical psychologist with experience in coaching patients and their partners to integrate the PLR in penetration. A medical illustrator was engaged to create diagrams for guiding the use of the vaginal insert.

Outcomes

Primary Outcomes

The primary outcomes are the acceptability of the PLR and the feasibility of study methods. Details of the specific outcomes are listed in Textbox 2.

Textbox 2. Primary outcomes of the feasibility and acceptability of the phallus length reducer (PLR).

Outcomes and explanations

- Response: the number of individuals who responded divided by the total number of individuals contacted
- Refusal: the number of individuals who refuse to participate divided by the number of individuals who responded
- Screen fail: the number of individuals who did not meet the inclusion criteria divided by the number of individuals who responded
- Recruitment rate: the number of participants enrolled divided by the length of the recruitment period (months)
- Retention: the number of participants who complete the study divided by the number of participants enrolled
- Adherence: the number of sexual events completed with the PLR divided by the total number of sexual events reported
- PLR acceptability: a 34-item, built-for-purpose questionnaire (adapted from a previously published measure for assessing the acceptability of female condoms [21]), with a response scale ranging from 1 to 5, will be completed by participants in the experimental arm in week 10 (Multimedia Appendix 1)

Secondary Outcomes

The secondary outcome is the effectiveness of the PLR, which will be determined by comparing changes in outcomes reported from week 4 to week 10 by patient participants in the experimental arm to those reported by participants in the control arm. Details of these outcomes are listed in Textbox 3.

Textbox 3. Secondary outcomes of the effectiveness of the phallus length reducer.

Outcomes and explanations

- Deep dyspareunia: an 11-point numeric rating scale, wherein 0 corresponds to no pain and 10 corresponds to the worst pain, will be used to measure deep dyspareunia intensity (using an item previously published by our team [18]); mean dyspareunia scores from weeks 1 to 4 will be compared with those from weeks 5 to 10 in the control and experimental arms
- Sexual function: total score on the Female Sexual Function Index, a 19-item self-report measure that captures information on sexual desire, arousal, lubrication, orgasm, satisfaction, and pain over the past 4 weeks [22]
- Sexual distress: total score on the Female Sexual Distress Scale-Revised, a 13-item self-report measure that captures sex-related personal distress over the past 4 weeks [23]
- Anxiety: total score on the Generalized Anxiety Disorder-7, a 7-item questionnaire validated for monitoring the severity of general anxiety [24]
- Depression: total score on the Patient Health Questionnaire-9, a 9-item questionnaire validated for monitoring the severity of depression [25]

Substudy Outcomes

The substudy will explore the acceptability and the preliminary convergent validity and test-retest reliability of a vaginal insert for the self-assessment of deep dyspareunia. The vaginal insert acceptability substudy outcome is based on an 18-item, built-for-purpose questionnaire adapted from a previously published measure for assessing the acceptability of female condoms [21] on a response scale ranging from 1 to 5. This questionnaire will be completed by all patient participants by week 4 (Multimedia Appendix 1).

Participants will use the vaginal insert to palpate various pelvic organs and structures (ie, to palpate the bladder anteriorly, the pelvic floor laterally, the pouch of Douglas posteriorly, and the cervix at the apex of the vagina) that have been previously associated with deep dyspareunia [26], and they will indicate whether they feel pain (“yes” or “no”) and the severity of the pain (11-point numeric rating scale wherein 0 corresponds to no pain and 10 corresponds to the worst pain). The number of tender sites for each participant will be calculated based on the self-reported number of tender anatomic sites that the participants identify when using the insert. Data on clinically assessed tenderness (“yes” or “no”) for each participant were previously collected through digital pain mapping, which was completed by a clinician. Data for clinically assessed tenderness are stored in EPPIC. These pain-related variables will be used to assess the convergent validity and test-retest reliability of the vaginal insert.

Assignment of Interventions

The study coordinator will use a REDCap (Research Electronic Data Capture; Vanderbilt University) extension package called *randomization* to randomly assign consented participants in a 1:1 ratio to 1 of 2 study arms; the experimental PLR arm will receive the PLR, and the waitlist control arm will receive the

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PLR once the study has concluded. Both arms will receive the vaginal insert for the substudy.

Participant Timeline

Throughout the study, all participants will continue concurrent endometriosis treatments and treatments for other conditions as usual. At the start of the study, both arms will complete baseline demographic, psychological, and sexual function questionnaires. In weeks 1 to 4 of the study, patient participants in both arms will engage in sexual activity as usual and be asked to record a daily diary of all sexual events and the severity of deep dyspareunia (score: range 0-10). Psychological and sexual function questionnaires will be repeated at the end of week 4. In week 5, participants in the experimental arm will receive and begin to use the PLR. Participants in the waitlist control arm will not receive the PLR and will continue to record deep dyspareunia severity at each sexual encounter. At the end of week 10, all patient participants will repeat the psychological and sexual function questionnaires, and participants in the experimental arm will indicate the acceptability of the PLR. At the conclusion of the study period, participants in the waitlist control arm will receive the PLR.

For the substudy, during weeks 1 to 4, all patient participants will self-assess deep dyspareunia by using the vaginal insert on weeks 2 and 3 of their menstrual cycle or on another two occasions (1 week apart) in the absence of regular bleeding. At the end of week 4, all patient participants will indicate the acceptability of the vaginal insert. The participant timeline is depicted in Table 1.

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Table 1. Schedule of interventions and assessments.

Groups and activities	Weeks 1 to 4			Weeks 5 to 10	
	Start of study	Vaginal insert self-assessment	Midstudy questionnaire	Experimental period	End of study
Group 1 (PLR[a] group)					
Patients					
Informed consent	✓				
Demographics form	✓				
Study diary	✓	✓	✓	✓	✓
Vaginal insert self-assessment (twice)		✓			
Receive and use PLR				✓	
Questionnaires					
FSFI[b]	✓		✓		✓
FSDS[c]	✓		✓		✓
PHQ-9[d]	✓		✓		✓
GAD-7[e]	✓		✓		✓
Vaginal insert feedback form			✓		
PLR feedback form					✓
Partners					
Informed consent	✓				
Demographics form	✓				
PLR feedback form					✓
Group 2 (control group)					
Patients					
Informed consent	✓				
Demographics form	✓				
Study diary	✓	✓	✓	✓	✓
Vaginal insert self-assessment (twice)		✓			
Continue sex as usual				✓	
Receive PLR					✓
Questionnaires					
FSFI	✓		✓		✓
FSDS	✓		✓		✓
PHQ-9	✓		✓		✓
GAD-7	✓		✓		✓
Vaginal insert feedback form			✓		
Partners					
Informed consent	✓				
Demographics form	✓				

[a]PLR: phallus length reducer.

[b]FSFI: Female Sexual Function Index.

[c]FSDS: Female Sexual Distress Scale.

[d]PHQ-9: Patient Health Questionnaire-9.

[e]GAD-7: Generalized Anxiety Disorder-7.

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Confidentiality

The list of potential participants is password protected and stored on a secure server at the study site, and it will only be available to select members of the research team. Upon enrollment to the study, each participant will be given a unique study ID number that does not correlate to any personally identifying information. All reports, data collection sheets, and administrative forms will be identified by this number to maintain confidentiality. This ID number can only be decrypted by a password-protected linking file, which is stored separately on the secure server at the study site; similarly, it will only be available to select members of the research team.

Data Management

Study materials, such as the instruction booklet, the daily diaries, and the PLR, will be mailed to the participants, depending on their study arm allocation. The study coordinator will follow up with each participant to collect the daily diaries of the control and intervention group participants upon the completion of the study. We will not blind the research team to the study arm allocations. Once the participants have completed the study, a research team member will extract the data from the daily diaries and upload the data onto a Microsoft Excel (Microsoft Corporation) sheet. The data will be stored on a secure server at the study site, and they will only be available to select members of the research team. Details of the data management procedures can be found in the study's research ethics board application, which can be provided upon request. We do not anticipate any adverse events with the use of the PLR, and as such, we will not need a data monitoring committee. If any adverse events occur, the participants can record them in the daily diary, and they will have the contact information of the study team to debrief such cases.

Statistical Methods

Descriptive statistics for demographic data and outcome variables will be presented by using means and SDs for continuous variables that are normally distributed, medians and IQRs for continuous variables that are not normally distributed, and frequency tables for the categorical variables of each study arm and the whole sample. Baseline measures will be compared to assess balance between the two arms, using Fisher exact tests for categorical variables and Kruskal-Wallis tests for continuous variables. With regard to our analytic approach for missing data.

Acceptability of the PLR and Vaginal Insert

For the PLR and vaginal insert, an overall acceptability index will be calculated by summing the acceptability questionnaire item responses and dividing the sum by the total possible score. The index will be characterized by using means and SDs, and individual items will be reported by using medians and IQRs. For the PLR, results that are stratified by participant type (patient or partner) will be reported.

Effectiveness of Using a PLR to Reduce Deep Dyspareunia

For the experimental and waitlist control arms, the difference in deep dyspareunia scores from week 4 to week 10 between the two arms will be assessed by using an analysis of covariance (ANCOVA)–based approach [27]. We will compare mean scores from weeks 5 to 10 between the two arms, using preintervention (weeks 1-4) mean scores as covariates in the model. Similar ANCOVA modeling will be used for the Female Sexual Distress Scale-Revised, Female Sexual Function Index, Generalized Anxiety Disorder-7, and Patient Health Questionnaire-9 scores. If the assumptions of the ANCOVA model are not met by the data set, then we will consider conducting other appropriate statistical analyses, such as the ANOVA-based approach, 2-tailed *t* tests, linear regression modeling, and nonparametric approaches for the ANCOVA model.

Validity and Reliability of the Vaginal Insert for the Self-assessment of Deep Dyspareunia

Tenderness at each pelvic anatomic site, as assessed via the vaginal insert test, as well as the highest score across all anatomic locations, will be correlated with the mean deep dyspareunia score, highest deep dyspareunia score, and lowest deep dyspareunia score. The self-assessed tenderness scores will be correlated with self-reported deep dyspareunia scores, using the Spearman rank correlation test. Participants without sexual events during weeks 1 to 4 will be compared to participants with ≥1 sexual event.

The results of assessments of tenderness ("yes" or "no") from the most recently performed clinical pelvic examinations, if applicable (these data are collected in EPPIC), will be correlated with self-assessed tenderness, as measured with the vaginal insert (score: range 0-10), by using a 2-tailed *t* test or Mann-Whitney *U* test.

To evaluate test-retest reliability, self-assessed tenderness scores for each anatomic site from the first assessment will be correlated with self-assessed tenderness scores from the second assessment to determine if the two sets of vaginal insert data are reproducible over time. This will be done by using scores (0-10) to calculate the intraclass correlation coefficient, as well as by categorizing tenderness ("yes" or "no") and using the McNemar test.

With regard to our analytic approach for missing data, if the maximum amount of missingness in any variable is <5%, we will exclude cases with missing data via pairwise exclusion. Otherwise, if the maximum amount of missingness is >5%, multiple imputation via chained equations will be used to impute the missing values. Results from imputed data sets will be pooled to provide final results.

Ethics Approval

The research presented in this protocol was approved by the Children's and Women's Research Ethics Board of the University of British Columbia (approval number: H19-00294). The study is also registered on ClinicalTrials.gov (trial number: NCT04370444). Any subsequent modifications to the study protocol will be reviewed by the Research Ethics Board of the University of British Columbia for approval, submitted to ClinicalTrials.gov, and communicated to the study participants.

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Results

The results from our study are expected to be submitted for publication by the spring of 2023. As of September 2021, we have recruited 31 couples into the study.

Discussion

Deep dyspareunia affects approximately 50% of people with endometriosis and has significant impacts on their sexual and mental health [5-7]. One gap in the care of endometriosis-associated deep dyspareunia is the lack of evidence-based self-management tools. A second gap is the lack of validated self-assessment tools that patients can use for objective measurements of deep dyspareunia that can supplement patient-reported outcomes of pain severity. In this protocol, we propose a pilot RCT for evaluating the feasibility and acceptability of, and obtaining estimates of effectiveness for, a PLR (brand name: Ohnut), which is a buffer that limits the depth of penetration and can be used as a self-management tool for deep dyspareunia. Embedded in our pilot RCT is a substudy that will evaluate a vaginal insert for objectively self-assessing anatomic sites associated with deep dyspareunia.

Potential feasibility issues pertain to the recruitment rate, retention, and adherence. Both the PLR and vaginal insert will be used in vaginal penetrative activities. The vaginal insert will be used on 2 occasions (in order to test reproducibility), and the PLR will be used during sexual encounters involving vaginal penetration over 6 weeks. Moreover, pain scores will be prospectively recorded for each sexual encounter during the 6 weeks. These intensive procedures and prospective data collection activities may reduce the recruitment rate, retention, and adherence. Acceptability issues may include impacts on the sexual function of the partners and how the placement of the PLR on the penis or a penetrating object affects the sexual response cycles of the participants. We also aim to estimate the potential effectiveness of the PLR in reducing deep dyspareunia by comparing it to a waitlist control.

The strengths of the protocol include having a randomized design, taking prospective pain measurements at each sexual encounter, and supplementing the trial by embedding the vaginal insert as a potential novel self-assessment tool. One limitation of the protocol is that it is not placebo controlled; however, it would be difficult to design a placebo for the PLR. Another limitation is that we will be comparing the vaginal insert to clinical examinations that are done at entry into the registry, which may be conducted several months before enrollment into the trial. In a future study, a pelvic examination can also be performed at recruitment. Furthermore, a limitation of the pilot trial is that we will not control for variables like age and BMI, which are potential confounders that may affect the use of the vaginal insert or PLR.

In summary, the PLR may be a noninvasive self-management tool for people with endometriosis-associated deep dyspareunia. The results of our pilot RCT will inform a future full-scale RCT of both the PLR and the vaginal insert test. The results from our study will be reported in peer-reviewed journals, in conference presentations, and to the study participants and the public through plain-language knowledge translation strategies. Ultimately, these innovations will contribute to the body of work on the rigorous investigation and evidence-based management of endometriosis-associated deep dyspareunia.

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Data Availability

We do not have institutional ethics approval to publicly share the data sets in our study.

Authors' Contributions

Authors NLO, KJW and PJY are cosenior authors for this manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Instructions for the control group and intervention group, as well as the acceptability questionnaires for the phallus length reducer and vaginal insert.
[DOCX File , 1818 KB - resprot_v12i1e39834_app1.docx]

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Abbreviations

ANCOVA: analysis of covariance
CONSORT: Consolidated Standards of Reporting Trials
EPPIC: Endometriosis and Pelvic Pain Interdisciplinary Cohort
PLR: phallus length reducer
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Protocol

Comparing Implementation Strategies for an Evidence-Based Weight Management Program Delivered in Community Mental Health Programs: Protocol for a Pilot Randomized Controlled Trial

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Abstract

Background: Among people with serious mental illness (SMI), obesity contributes to increased cardiovascular disease (CVD) risk. The Achieving Healthy Lifestyles in Psychiatric Rehabilitation (ACHIEVE) randomized controlled trial (RCT) demonstrated that a behavioral intervention tailored to the needs of individuals with SMI results in clinically significant weight loss. While the research team delivered the ACHIEVE intervention in the trial, community mental health program staff are needed to deliver sessions to make scale-up feasible. Therefore, we adapted the ACHIEVE-Dissemination (ACHIEVE-D) curriculum to ease adoption and implementation in this setting. Designing and testing of implementation strategies is now needed to understand how to support ACHIEVE-D delivery by community mental health program staff coaches.

Objective: This study aims to conduct a pilot trial evaluating standard and enhanced implementation interventions to support the delivery of ACHIEVE-D in community mental health programs by examining effects on staff coaches' knowledge, self-efficacy, and delivery fidelity of the curriculum. We will also examine the effects on outcomes among individuals with SMI taking part in the curriculum.

Methods: The trial will be a cluster-randomized, 2-arm parallel pilot RCT comparing standard and enhanced implementation intervention at 6 months within community mental health programs. We will randomly assign programs to either the standard or enhanced implementation interventions. The standard intervention will combine multimodal training for coaches (real-time initial training via videoconference, ongoing virtual training, and web-based avatar-assisted motivational interviewing practice) with organizational strategy meetings to garner leadership support for implementation. The enhanced intervention will include all standard strategies, and the coaches will receive performance coaching. At each program, we will enroll staff to participate as coaches and clients with SMI to participate in the curriculum. Coaches will deliver the ACHIEVE-D curriculum to the clients with SMI. Primary outcomes will be coaches' knowledge, self-efficacy, and fidelity to the ACHIEVE-D curriculum. We will also examine the acceptability, feasibility, and appropriateness of ACHIEVE-D and the implementation strategies. Secondary outcomes among individuals with SMI will be weight and self-reported lifestyle behaviors.

Results: Data collection started in March 2021, with completion estimated in March 2023. We recruited 9 sites and a total of 20 staff coaches and 72 clients with SMI. The expected start of data analyses will occur in March 2023, with primary results submitted for publication in April 2023.

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Conclusions: Community mental health programs may be an ideal setting for implementing an evidence-based weight management curriculum for individuals with SMI. This pilot study will contribute knowledge about implementation strategies to support the community-based delivery of such programs, which may inform future research that definitively tests the implementation and dissemination of behavioral weight management programs.

Trial Registration: ClinicalTrials.gov NCT03454997; https://clinicaltrials.gov/ct2/show/NCT03454997

International Registered Report Identifier (IRRID): DERR1-10.2196/45802

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KEYWORDS

community mental health services; weight reduction programs; mental disorders; implementation science; mental health; randomized controlled trial; obesity; behavioral intervention; weight loss; strategy; community; weight; body mass index; BMI; obesity; mental illness; mental health; cardiovascular disease; psychiatric rehabilitation; RCT; coach; electronic coach

Introduction

The prevalence of obesity is significantly elevated in people with serious mental illness (SMI) [1,2]. Obesity is a leading cause of preventable death in this population, both directly through its effects on cardiovascular disease (CVD) and indirectly by contributing to other CVD risk factors [3-6]. In general populations, behavioral weight loss interventions have been demonstrated to improve CVD risk by reducing blood pressure and glucose, as well as improving lipid profiles [7]. However, behavioral interventions targeting changes in diet, exercise, and weight loss need to be tailored to the particular needs of people with SMI, such as memory impairment and limited executive function [8,9]. The National Institute of Mental Health (NIMH)–funded Achieving Healthy Lifestyles in Psychiatric Rehabilitation (ACHIEVE) randomized controlled trial (RCT) tested a behavioral weight-loss intervention for individuals with SMI who attended community-based psychiatric rehabilitation programs [10]. The ACHIEVE RCT demonstrated clinically and statistically significant weight loss [11]. ACHIEVE included group and individual weight-management sessions and group exercise sessions, which were led by trained study interventionists. Given the obesity epidemic in persons with SMI, there is an urgent need to disseminate ACHIEVE.

We posited that the ACHIEVE intervention might be ideal for dissemination by training and supporting community mental health program staff to deliver the sessions [12]. In the ACHIEVE RCT, the interventionists were study staff that received substantial onboarding and ongoing in-person training, as well as performance feedback with particular emphasis on motivational interviewing (MI) skills [10,11]. Time and other logistical constraints prevent community mental health program staff from participating in such intensive training. By leveraging novel strategies that incorporate advances in training and feedback modalities (eg, web-based training and web-based training environments), we could train community mental health program staff to facilitate the real-world implementation of the ACHIEVE program. We used the enhanced Replicating Effective Programs (REP) Framework for translating evidence-based interventions into community settings [13,14]. This model has 4 stages: preconditions, preimplementation, implementation, and maintenance. Preconditions identify needs, effective interventions, and implementation barriers to draft an intervention package. Preimplementation adapts and pilot tests implementation strategies for the community. Implementation focuses on training, support, evaluation, and refinement. Maintenance supports sustained implementation and dissemination.

We completed the REP preconditions stage for ACHIEVE by adapting the intervention to facilitate implementation by community mental health program staff while retaining core elements [15]. We modified the schedule and format to support efficient, staff-led delivery but retained the core messages and behavioral strategies. We previously evaluated this adapted curriculum in a proof-of-concept study at a community mental health program (NCT03999892) [16], which informed further refinements based on feedback from staff observers and participating individuals with SMI. Table 1 outlines this modified weight management curriculum, ACHIEVE-Dissemination (ACHIEVE-D), which will be used in the REP preimplementation stage.

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Table 1. Overview of the ACHIEVE-Dissemination curriculum adapted for delivery by community mental health program staff.

	ACHIEVE-Dissemination curriculum[a]
Duration	• 6 months
Group sessions	
1 group type	• Multipurpose group weight management and exercise: 45-minute class, 3 times a week with weigh-ins (17 minutes of weight management, 20 minutes of moderate intensity exercise, and 8 minutes for weigh in)
Individual sessions	• None
Total time	• ~540 minutes per month
Delivery modality of components	• Weight management: led by staff member assisted with short videos and facilitator guide • Exercise: video-assisted
Facilitators	• Trained staff member and peer leader
Behavioral messages	
6 messages	• Weight loss success • No sugar drinks • No junk food • Eat smart portions • Eat more vegetables • Putting it all together
Goal	• 5-lb weight loss in 6 months[b] • (tailored to individual)

[a]ACHIEVE: Achieving Healthy Lifestyles in Psychiatric Rehabilitation trial.

[b]Goal of a 5-lb weight loss at 6 months was based on results from the ACHIEVE trial [11] and adult obesity guidelines [7].

We describe the protocol for a pilot RCT comparing standard and enhanced implementation interventions that train and support community mental health program staff as coaches delivering the ACHIEVE-D weight management curriculum. This study represents our REP's preimplementation stage. Our primary outcomes will be knowledge, self-efficacy, and delivery fidelity to the ACHIEVE-D curriculum among staff coaches. Both implementation interventions will include multimodal staff training and organizational strategy meetings. The staff coaches in the enhanced intervention will also receive performance coaching. We hypothesize that both implementation interventions will lead to increased knowledge of the ACHIEVE-D curriculum, self-efficacy for delivering the program, and fidelity for ACHIEVE-D delivery and that the enhanced intervention will have improved outcomes as compared to the standard intervention. To prepare for REP implementation and dissemination stages, we will use a mixed methods approach to examine acceptability, appropriateness, and feasibility, as well as compare differences in implementation and process measures to guide further refinements of both the ACHIEVE-D curriculum and implementation interventions. Secondarily, we will examine outcomes among individuals with SMI who participate in the curriculum, in particular self-reported lifestyle behaviors and measured weight.

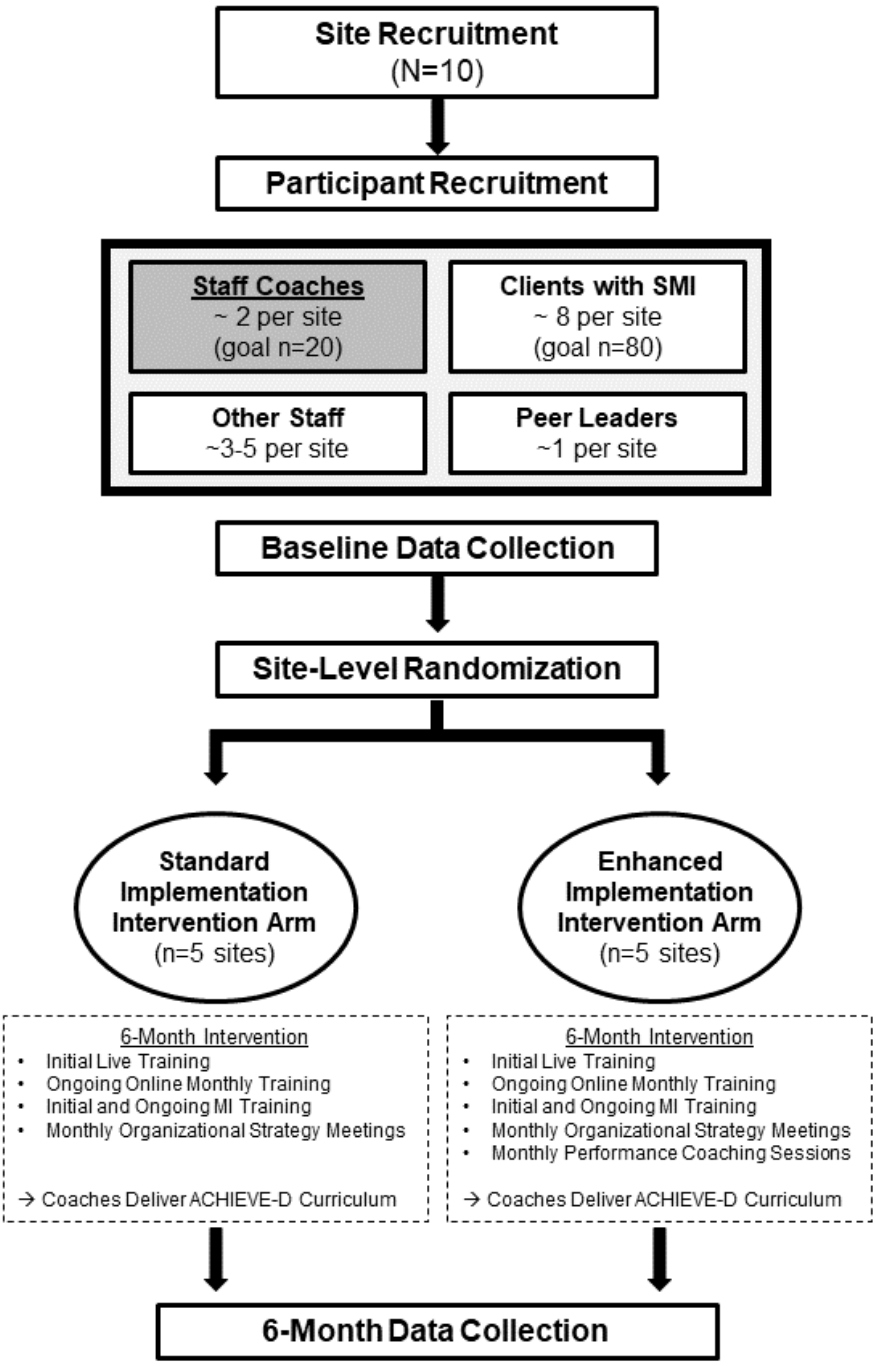
Methods

Study Design

The design will be a cluster-randomized, 2-arm parallel pilot RCT comparing standard and enhanced implementation intervention at 6 months within community mental health programs. We will aim to randomly assign 10 programs in Maryland to either the standard or enhanced implementation intervention arms. Figure 1 provides an overview of the study. Multimedia Appendix 1 contains the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist for RCTs [17].

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Figure 1. Overview of the study design. This diagram shows the planned study steps in this pilot randomized controlled trial. The gray shaded box indicates our primary study participant group who will take part in the implementation interventions. ACHIEVE-D: Achieving Healthy Lifestyles in Psychiatric Rehabilitation-Dissemination; SMI: serious mental illness.



Overview of the ACHIEVE-D Curriculum

The ACHIEVE-D program is a 6-month curriculum comprised of structured group sessions incorporating behavioral weight management lessons along with group exercise. Groups will last approximately 45-60 minutes and occur at least once a week. Groups may be delivered in person or remotely. Table 1 outlines the components of the ACHIEVE-D curriculum, and Multimedia Appendix 2 includes a detailed description of the ACHIEVE-D curriculum. The curriculum has been previously tested in other studies [11,16]. As such, this study will focus on testing implementation interventions to support the delivery of the curriculum by community mental health program staff.

Site Eligibility Criteria

We will aim to recruit 10 community mental health programs as study sites. Site inclusion criteria include (1) an adult psychiatric rehabilitation program (PRP) within Maryland, (2) a willingness for at least 2 staff to be trained as coaches and implement the ACHIEVE-D curriculum, (3) a willingness for leaders and staff to participate in monthly organizational strategy meetings, and (4) the anticipated ability to recruit clients with SMI to participate. Site leadership will indicate their agreement

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to fulfill these criteria with study staff and complete a reliance agreement for the study with the Johns Hopkins Institutional Review Board. At each site, we will recruit participants from three different study populations: (1) staff to serve as coaches; (2) clients with SMI to take part in the curriculum; and (3) other staff and peer leaders—we describe the eligibility criteria, recruitment, and measures separately for each group of study participants in the sections below.

Coaches

Eligibility and Recruitment

To be included, the person must be ≥18 years old, staff at an enrolled PRP, and willing to complete all training activities, deliver all components of the ACHIEVE-D curriculum, and complete data collection procedures. We will exclude staff that plans on leaving their position or taking a leave of absence from the program. Site leadership will identify potential staff to serve as coaches, and the research team will approach these individuals to discuss the study and obtain a waiver of documentation of consent. We will aim to recruit 20 coaches (at least 2 per site).

Measures

Table 2 describes the assessment schedule for the primary outcomes and implementation measures for coaches. Multimedia Appendix 3 describes other measures that we plan to collect among coaches. The following will be the primary outcome and implementation measures for coaches.

Table 2. Assessment schedule for coaches: primary outcomes and implementation measures.

	Baseline	Follow-up		
		During	6M[a]	Post[b]
Primary Outcomes				
ACHIEVE-D[c] Curriculum Weight Management Knowledge	✓		✓	
ACHIEVE-D Curriculum Exercise Knowledge	✓		✓	
ACHIEVE-D Curriculum Self-Efficacy	✓		✓	
ACHIEVE-D Fidelity		✓		
Implementation Measures				
Acceptability of training	✓		✓	
Feasibility of training	✓		✓	
Appropriateness of training	✓		✓	
Motivation for implementation	✓		✓	
Implementation climate	✓			
Focus groups or interviews	2		✓	✓

[a]M: month.

[b]Postperiod will be approximately 6 months after completion of the intervention.

[c]ACHIEVE-D: Achieving Healthy Lifestyles in Psychiatric Rehabilitation-Dissemination.

Primary Outcomes

ACHIEVE-D Curriculum Knowledge, Self-Efficacy, and Fidelity

We will assess knowledge about key curricular elements using 2 measures at baseline and 6 months: a 22-item ACHIEVE-D Curriculum Weight Management Knowledge measure and a 16-item ACHIEVE-D Curriculum Exercise Knowledge measure. The research team created these questions using the best practices recommended by the National Board of Medical Examiners for item writing [18]. We will assess self-efficacy to deliver key curricular elements at baseline and 6 months using a 31-item ACHIEVE-D Curriculum Self-Efficacy measure. The research team used principles from confidence rulers in creating this measure [19], where participants rate their confidence to deliver each element on a 10-point scale. To determine fidelity, each coach will video-record their delivery of an ACHIEVE-D group session once a month. Two research team members will view each recording and use the ACHIEVE-D Curriculum Fidelity rating tool to assess performance on key elements. The research team created this tool to evaluate how a coach implements key ACHIEVE-D curriculum elements, including a counseling style consistent with MI techniques (eg, open-ended questions and affirmations) [20], within each segment (before the session, group exercise, weigh-in, focus on weight loss, role model video, commitment to high-impact behavior). Each item will be scored as absent (0) or present (2) or on a 3-point scale of absent (0), below expectations (1), or meets expectations (2). Quarterly meetings will be conducted to ensure alignment between coders. Table 3 displays example items from instruments used for the primary outcomes.

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Table 3. Samples of included items in primary outcome measures.

Primary outcomes	Sample questionnaire items
ACHIEVE-D[a] Curriculum Weight Management Knowledge	
Example 1	• An evidence-based weight loss program includes which of the following? • Uses solid scientific evidence to drive recommendations[b] • Promises results that sound too good to be true • Has evidence from personal testimonials about weight loss success • Don't know
Example 2	• Jessica is taking part in ACHIEVE. She wants to say "no" to junk foods, but needs help identifying foods that she eats that are considered junk foods. Which of the following things that she eats would be considered a junk food in the ACHIEVE program? • Orange slices • Chocolate bars[b] • Cheese • Don't know
ACHIEVE-D Curriculum Exercise Knowledge	
Example 1	• What should you do if a client has arthritis in their knees and cannot keep up with the class choreography? • Tell the client with the arthritis that they must do a different exercise move • Choose slower music for the entire class so that all clients can keep up • Remind all clients that they can choose a lower intensity[b] • Don't know
Example 2	• Joy is 45 year old woman with obesity. She is sedentary (does not exercise). If Joy starts going for a 20 minute brisk walk every morning, she will: • Start losing weight • Will not lose weight, because exercise doesn't help with weight loss • May not lose weight, but will get benefit from exercising[b] • Don't know
ACHIEVE-D Curriculum Self-Efficacy[c]	
Example 1	Use a leader's guide along with any other needed materials, props, visual aids, videos, or lesson presentations for the class.
Example 2	Communicate with clients how their diet, activity and other behaviors aligns with weight change.
ACHIEVE-D Curriculum Fidelity[d]	
Example 1	• Asks about success with high impact behavior. • 0: Does not ask participants about progress on high impact behavior • 1: Asks some participants about progress on high impact behavior • 2: Asks all participants about progress on high impact behavior
Example 2	• Ensures session remains focused on main topic as per leaders guide. • 0: Did not focus on the main topics in the leaders guide for this module • 1: Some topic elements covered, but a major deviation from a main topic occurred • 2: All topic elements covered with minor acceptable deviations

[a]ACHIEVE-D: Achieving Healthy Lifestyles in Psychiatric Rehabilitation-Dissemination.

[b]Indicates correct responses. Complete measures are available from the authors upon request.

[c]Participants indicate how confident they are that they can currently perform the listed task during a behavioral weight loss program for a group of adults with serious mental illness.

[d]All items have a numerical value, and we will sum key items to create a composite score.

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Implementation Measures

We will determine the perceived acceptability, feasibility, and appropriateness of the implementation interventions (eg, coach training) and the ACHIEVE-D curriculum. We adapted these assessments from previously validated measures [21]. We will also assess motivation and implementation climate using adapted, validated instruments [22,23]. At 6 months, we will conduct focus groups with staff coaches to elicit feedback on the following: acceptability, appropriateness, and feasibility of the implementation intervention and ACHIEVE-D curriculum; barriers to implementation; strategies to overcome barriers; and suggestions for further refinement. We will conduct a second series of focus groups or interviews at each site approximately 6 months after the conclusion of the intervention to determine whether and how the ACHIEVE-D curriculum was sustained and the challenges experienced.

Clients With SMI

Eligibility and Recruitment

Clients with SMI will participate in the ACHIEVE-D weight management program delivered by the staff coaches. To be included, the person must be ≥18 years old, a client with SMI at an enrolled PRP, BMI ≥25 kg/m^2 (ie, overweight or greater), and willing to make lifestyle changes to lose weight and participate in all ACHIEVE-D activities at least once a week. We will exclude individuals with contraindications to losing weight (eg, history of anorexia, liver failure, and pregnancy), who have conditions that require medically supervised weight loss (eg, myocardial infarction in the last 6 months and insulin-dependent diabetes mellitus), who plan to pursue other obesity treatments (eg, antiobesity medication and bariatric surgery), who plan to leave the PRP or move out of the geographic area within 12 months, or who are unwilling to complete all data collection procedures. Staff at each site will identify potential clients to participate who may meet the eligibility criteria; the research team will approach these individuals, on a first-come, first-served basis, to discuss the study, screen individuals, and obtain a waiver of documentation of consent. We will aim to recruit 80 clients with SMI (~8 per site).

Measures

Table 4 describes the assessment schedule for individuals with SMI. Multimedia Appendix 3 describes other measures that we plan to collect among individuals with SMI. In other studies, we have successfully used all selected measures among individuals with SMI. Similar to our prior studies, study staff will be available to assist clients with SMI complete measures, if needed. The following will be the secondary outcome and process measures for individuals with SMI.

Table 4. Assessment schedule for individuals with serious mental illness: secondary outcomes and process measures.

	Baseline	Follow-up	
		During	6M[a]
Secondary outcomes			
Weight[b]	✓		✓
CARDIA[c]/EARLY[d] Q[e]—sedentary behavior	✓		✓
Block Dietary Fat Q	✓		✓
Block Dietary Fruit or Vegetable Q	✓		✓
EARLY Eating Away from Home Q	✓		✓
EARLY SSB[f] Consumption Q	✓		✓
Process measures			
Consumer Satisfaction and Helpfulness Q			✓
Attendance		✓	
Participation in group session		✓	

[a]M: month.

[b]If weight measurement cannot be done in person, due to COVID-19 restrictions, participants will self-measure weight on a scale that the study provides to them.

[c]CARDIA: Coronary Artery Risk Development in Young Adults.

[d]EARLY: Early Adult Reduction of Weight through Lifestyle Intervention.

[e]Q: questionnaire.

[f]SSB: sugar-sweetened beverage.

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Secondary Outcomes

Weight and Lifestyle Behaviors

Study staff will measure weight to the nearest 0.1 lb. on a high-quality digital scale with participants wearing light indoor clothes without shoes at baseline and 6 months. We will assess several lifestyle behaviors at baseline and 6 months. Study staff will administer the Coronary Artery Risk Development in Young Adults (CARDIA)–Early Adult Reduction of Weight through Lifestyle Intervention (EARLY) sedentary behavior questionnaire [24]. For diet, we will administer the block fat, fruit, vegetable, and fiber screener questionnaires [25,26]. We will also administer the EARLY eating away from home and sugar-sweetened beverage questionnaires [27,28]. These measures have been recommended by the National Institutes of Health Accumulating Data to Optimally Predict Obesity Treatment (ADOPT) Core Measures for Obesity Studies [29].

Process Measures

We will adapt prior measures to assess the helpfulness of the behavioral weight loss intervention component [30] and satisfaction with the ACHIEVE-D curriculum and staff coaches [31]. We will collect attendance and participation information for each enrolled client.

Other Staff: Eligibility, Recruitment, and Measures

We will recruit 2 groups of other staff: program leaders (ie, program directors or coach supervisors) and general staff members. Program leaders will participate in monthly organizational strategy meetings with the coaches. General staff members will not participate in training or meetings. To be eligible as other staff, the person must be ≥18 years old, staff at an enrolled PRP, and willing to complete data collection procedures. After site leadership facilitates contact with other staff, the research team will approach these individuals to discuss the study and obtain a waiver of documentation of consent. All other staff will complete baseline demographics as well as motivation for implementation and implementation climate [22,23] measures at the baseline and 6-month follow-up. Program leaders will be in the aforementioned end-of-study focus groups with the coaches.

Peer Leaders: Eligibility, Recruitment, and Measures

When possible, we will recruit a peer leader for each site. To be eligible, the individual must be a person with SMI who is ≥18 years and interested in helping staff coaches with the ACHIEVE-D curriculum. Staff at each site will identify potential clients to participate as peer leaders; the research team will approach these individuals to discuss the study and obtain a waiver of documentation of consent. The study will proceed at sites without peer leader support if no candidates are identified. Peer leaders will participate in the following: training with the staff coaches, assisting staff coaches in the delivery of the ACHIEVE-D curriculum to clients, modeling behavior by participating in group exercises, and completing data collection (same measures as coaches except for ACHIEVE-D curriculum fidelity).

Implementation Interventions

Overview

The study team's prior research and experience with ACHIEVE informed our selection of components that will comprise the implementation interventions for the standard and enhanced arms. Both arms will use multimodal training in combination with organizational strategy meetings with site leadership to support the implementation of the ACHIEVE-D group sessions. In the enhanced arm, staff coaches will also receive performance coaching from research team members with expertise in weight management and MI.

Multimodal Coach Training—Both Arms

Table 5 provides an overview of all coach training that will be conducted by the research team during the 6-month intervention period. Multimodal training will include real-time initial training via videoconference, ongoing monthly virtual training, and web-based avatar-assisted MI practice for coaches [32,33]. This training approach will provide interactive opportunities for coaches to practice the skills needed to implement the ACHIEVE-D curriculum—a more effective strategy than didactic education [34]. All coaches will receive initial training in real-time delivered via videoconferencing (approximately 14 hours in total). The initial training will include an introduction to MI, highlighting the effectiveness of this counseling style for weight management. Ongoing monthly training will be offered through a digital platform with the goal of orienting coaches to upcoming content (less than 30 minutes per month). The coaches will also have access to a web-based avatar module to review and practice MI techniques when discussing weight management with a simulated client avatar. The research team developed this module in partnership with a health care simulation company. Coaches will receive reminders to complete the monthly web-based training and avatar modules.

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Table 5. Overview of ACHIEVE-Dissemination trainings for coaches.

Type and training components	Approximate length
Initial training (synchronous, videoconference, and research team–delivered)	
Overview of the ACHIEVE[a] program and introduction to behavior change for weight loss	2 hours
Components of an ACHIEVE group and observing research staff deliver a group lesson	2 hours
Introduction to Module 1: Weight Loss Success	45 minutes
Weight management practice session	60 minutes
MI[b] techniques for weight loss	4 hours
Common challenges that may come up when running a weight loss group and how to address them	60 minutes
Exercise in the ACHIEVE program	20-60 minutes
Introduction to Module 2: Say No to Sugar Drinks	50 minutes
Resources for implementing the ACHIEVE program	20 minutes
Overview of performance coaching	40 minutes
Ongoing training (asynchronous, digital, and self-paced)	
Didactic training for each core and seasonal module with real-world examples of how to deliver the content in groups	15-20 minutes per month
Avatar simulations to practice using motivational interviewing skills when discussing weight management with a consumer	15 minutes per month

[a]ACHIEVE: Achieving Healthy Lifestyles in Psychiatric Rehabilitation.

[b]MI: motivational interviewing.

Organizational Strategy Meetings—Both Arms

Programs targeting frontline staff, like ACHIEVE-D, are more effective when supplemented with implementation interventions that successfully engage organization leaders [35]. Therefore, to enhance curriculum uptake and increase engagement from site leadership [36], we will hold monthly organizational strategy meetings (30-60 minutes each month). Research team members, coaches, and site supervisors or leadership will be encouraged to attend. These meetings will support the development, adoption, and sustainment of organizational strategies needed for implementation and provide opportunities to problem-solve barriers encountered (eg, changing the class schedule to maximize attendance).

Performance Coaching—Enhanced Arm Only

At sites randomized to the enhanced intervention arm, coaches will take part in monthly performance coaching. Performance coaching is an implementation strategy where coaches "learn by doing" and receive feedback on their ACHIEVE-D delivery [37]. Performance coaching may be particularly beneficial when evidence-based practice is new to the implementers, as is the case with ACHIEVE-D [38-40]. The performance coach will be a research team member with extensive knowledge of the ACHIEVE-D curriculum, behavioral weight loss, and MI. Each month, the performance coach and staff coach will meet to review the staff coach's monthly video-recorded group session (see the video recording described in coach measures above). The performance coach will share their evaluation of the video, identifying areas of strength, opportunities for improvement, and a performance improvement plan (1.5 hours each month). Performance coaching feedback will be grounded in evidence-based behavioral weight loss principles and core ACHIEVE-D messages, mirror a MI style, and promote skill development and high-fidelity curriculum delivery. Of note, the study staffs who deliver performance coaching will be different from the study staff rating the video-recorded sessions for fidelity.

Pilot Trial Sample Size

This pilot trial will provide useful information on protocol feasibility and parameter estimates for designing a future confirmatory trial but will not necessarily be powered to detect differences in outcomes. With 5 sites per arm and 2 coaches per site, we will have 80% power to detect large changes in effect size in our primary coach-level outcomes from baseline to 6 months between arms (1.5-1.6 in units of outcome SD). We assume an intracluster correlation coefficient of 0.05-0.2 and a within-coach correlation of 0.5 between outcomes at baseline and 6 months, using a 2-sided alpha of .05.

Randomization and Blinding

Following recruitment and baseline data collection, sites will be randomized to the standard or enhanced arm. The randomization sequence will be generated in the block size of 2 using computer software by the trial biostatistician, and assignments will be delivered to the eligible sites by the research coordinator. Due to the nature of the intervention, both staff coaches and some research team members will be aware of the assignment. For our primary outcomes of knowledge and self-efficacy, staff coaches will self-complete specific questionnaires, which may reduce the risk of bias. For our primary outcome of fidelity, study team members who rate the video-recorded sessions will be masked to study arm assignment, which may also reduce the risk of bias. Individuals with SMI

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taking part in the curriculum and other staff will not be aware of the assignment.

Statistical Analysis

Quantitative Analyses

We will assess the effects of the implementation intervention on coaches' knowledge, self-efficacy, and fidelity to the ACHIEVE-D curriculum, as well as client outcomes, using generalized linear mixed-effects models under the intent-to-treat approach. The mean models will include a binary intervention group indicator, time indicators, and intervention-by-time interaction terms. The time indicator coefficients estimate time-specific mean outcome changes in the standard arm, and the interaction coefficients estimate the between-arm differences of time-specific outcome changes from the baseline. The linear combination of these time-specific coefficients captures the time-specific mean outcome changes in the enhanced arm. Site differences will be assumed to follow a normally distributed random effect, while an unstructured variance-covariance matrix will be used for the repeated outcome measurements over time within individuals. For our implementation measures, we will use descriptive statistics to analyze survey measures of perceptions of acceptability, feasibility, and appropriateness of the implementation intervention and ACHIEVE-D curriculum. Point estimates and corresponding 95% confidence intervals will be obtained.

Qualitative Analyses

Focus groups will be audio- or video-recorded, and recordings will be transcribed. Given that we are seeking to understand experiences across sites and participants, we will use thematic analysis [41,42], which can serve as a standalone analytic method. We will use a 6-step process, which includes data familiarization, initial code generation, searching for themes (ie, repeated patterns), reviewing themes, defining or naming themes, and producing a report. The first 3 steps will be conducted by 2 research team members, and the larger research team will be involved in the final steps.

Ethics Approval

The Johns Hopkins University School of Medicine Institutional Review Board approved this study (IRB00247344). Consent will be obtained from all participants using a waiver of documentation of consent.

Results

This trial was funded by an ALACRITY center grant from the NIMH (funding started in August 2018). We started recruitment and data collection in March 2021. We estimate all data collection will be completed in March 2023. We recruited 9 sites and a total of 20 staff coaches and 72 clients with SMI. We expect to start data analyses in March 2023, with primary results submitted for publication in April 2023. We will also communicate the results with participating sites after the study through a presentation with leadership or a report.

Discussion

Principal Findings

Addressing inequities in CVD risk among persons with SMI is needed to meet current public health objectives of improving cardiovascular health for all persons [43]. Given the prevalence of obesity among adults with SMI and its associated increased CVD risk, it is critical to implement effective behavioral weight loss interventions tailored to this population in real-world settings. The ACHIEVE trial demonstrated the efficacy and safety of such a behavioral weight loss intervention [11], which has been translated into the ACHIEVE-D weight management curriculum appropriate for delivery by community mental health center staff [16]. We are applying the Enhanced Replicating Effective Programs Framework to increase the acceptability and feasibility of implementing the ACHIEVE-D curriculum in community settings [13,14]. In this pilot trial, we will compare an enhanced implementation intervention to a standard intervention on community mental health program staff coaches' knowledge, self-efficacy, and fidelity to the ACHIEVE-D curriculum.

We will use a mixed methods approach [44], where the design will be primarily quantitative with a sequential supplementary qualitative component among staff coaches. The quantitative component will determine whether the staff coaching approach is a feasible one, while the qualitative component will be key to understanding staff experiences as coaches and leadership experiences with having ACHIEVE-D at their site. We anticipate that we will identify patterns of facilitators and barriers common across staff and sites through the focus groups, and we will use these findings to guide further refinements in the ACHIEVE-D curriculum and implementation interventions.

There are several potential strengths in this study. We are training community mental health program staff to deliver the curriculum, which may have numerous advantages when considering dissemination. Staff members already have an established rapport with clients, which may be helpful when addressing sensitive topics such as weight. The ACHIEVE-D curriculum is a turnkey product with coach guides and videos for staff to use, which may minimize work burden and increase confidence in providing safe, evidence-based recommendations to clients. In addition, we created an adapted and abbreviated strategy for remotely delivered training to program staff, which may address potential time and logistical constraints [12]. Asynchronous web-based training will be brief, which may enhance coach uptake and completion of this training as this approach meets the needs of staff with competing priorities. Since training alone is often insufficient to adopt new interventions [45-48], this trial will incorporate organizational strategy meetings to engage leadership and test the addition of performance coaching in the enhanced arm. Finally, we anticipate recruiting diverse program staff with varying years of experience, education, and profession (eg, counselors and nurses) and diverse organizations with varying staffing models, geographic locations (eg, urban, suburban, and rural), and delivery models (eg, in-person and remote). This diversity may provide novel lessons relevant for dissemination. Overall, these

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strengths may help support testing of future REP stages of implementation and maintenance of the ACHIEVE-D curriculum in community mental health settings through a hybrid effectiveness-implementation trial approach [49].

Limitations

Our pilot trial will have limitations and challenges. Our study sites will be limited to community mental health programs in Maryland, specifically psychiatric rehabilitation programs. Other states may not offer such programming, and billing practices may differ, which may limit generalizability. This trial may be impacted by the high staff turnover rates that are common in community mental health programs. In anticipation of this challenge, we plan to recruit at least 2 staff coaches for each site and have the flexibility to train replacement coaches if needed. This study is a pilot trial, and as such, our sample size is small. The COVID-19 pandemic will present several challenges, as this trial will be recruiting and conducting the study during this period. First, community mental health program staff turnover may be even higher, which may negatively impact staff engagement in the study due to increased workload. Second, PRP may experience changes related to COVID-19 restrictions, such as format (in-person versus remote) and the number of clients permitted on-site. These factors may affect delivery and client attendance at ACHIEVE-D sessions. Third, sites might experience closures due to COVID-19, which would result in gaps in ACHIEVE-D delivery. As consistency and repetition are key elements for clients with SMI, such gaps may affect client engagement and participation, as well as weight and behavioral outcomes. Finally, we will be unable to blind coach participants or interventionists to study arm allocation due to the nature of the intervention in this pilot trial; however, we will mask the study assignment of study team members to determine fidelity. Future studies should consider blinding data collectors and analysts to study arm allocation.

Conclusions

This trial aims to provide key information on implementation strategies to increase community mental health program staff coaches' knowledge, self-efficacy, and fidelity to deliver the ACHIEVE-D weight management curriculum for persons with SMI. Our results may inform future research that definitively tests the implementation and dissemination of behavioral weight management programs. Unless effective weight management interventions are disseminated into real-world settings, obesity and CVD disparities among persons with SMI will likely persist.

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Data Availability

Data sharing is not applicable to this paper as no data sets were generated or analyzed during this study. Future data collected as part of the study described in this protocol will be made available from the corresponding author upon reasonable request.

Conflicts of Interest

KG serves as the medical director for the American Board of Obesity Medicine, has a research grant from Novo Nordisk, and is a paid consultant to Eli Lilly. All other authors declare that they have no competing interests.

Multimedia Appendix 1
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist and figures.
[DOCX File , 65 KB - resprot_v12i1e45802_app1.docx]

Multimedia Appendix 2
Detailed information about Achieving Healthy Lifestyles in Psychiatric Rehabilitation-Dissemination (ACHIEVE-D) curriculum.
[DOCX File , 33 KB - resprot_v12i1e45802_app2.docx]

Multimedia Appendix 3
Other planned measures for coaches and individuals with serious mental illness.
[DOCX File , 35 KB - resprot_v12i1e45802_app3.docx]

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Abbreviations

ACHIEVE: Achieving Healthy Lifestyles in Psychiatric Rehabilitation
ACHIEVE-D: Achieving Healthy Lifestyles in Psychiatric Rehabilitation-Dissemination
CVD: cardiovascular disease
MI: motivational interviewing
PRP: psychiatric rehabilitation program
RCT: randomized controlled trial
REP: replicating effective programs
SMI: serious mental illness

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Protocol

A Series of Remote Melatonin Supplement Interventions for Poor Sleep: Protocol for a Feasibility Pilot Study for a Series of Personalized (N-of-1) Trials

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Abstract

Background: Poor sleep, defined as short-duration or poor-quality sleep, is a frequently reported condition with many deleterious effects including poorer cognitive functioning, increased accidents, and poorer health. Melatonin has been shown to be an efficacious treatment to manage symptoms of poor sleep. However, the treatment effects of melatonin on sleep can vary greatly between participants. Personalized, or N-of-1, trial designs represent a method for identifying the best treatment for individual participants. Although using N-of-1 trials of melatonin to treat poor sleep is possible, the feasibility, acceptability, and effectiveness of N-of-1 trials using melatonin are unknown. Using the National Institutes of Health Stage Model for Behavioral Intervention Development, a stage IB (intervention refinement, modification, and adaptation and pilot testing) design appeared to be needed to address these feasibility questions.

Objective: This trial series evaluates the feasibility, acceptability, and effectiveness of a series of personalized interventions for remote delivery of melatonin dose (3 and 0.5 mg) versus placebo supplements for self-reported poor sleep among 60 participants. The goal of this study is to provide valuable information about implementing remote N-of-1 randomized controlled trials to improve poor sleep.

Methods: Participants will complete a 2-week baseline followed by six 2-week alternating intervention periods of 3 mg of melatonin, 0.5 mg of melatonin, and placebo. Participants will be randomly assigned to 2 intervention orders. The feasibility and acceptability of the personalized trial approach will be determined with participants' ratings of usability and satisfaction with the remote, personalized intervention delivery system. The effectiveness of the intervention will be measured using participants' self-reported sleep quality and duration and Fitbit tracker–measured sleep duration and efficiency. Additional measures will include ecological momentary assessment measures of fatigue, stress, pain, mood, concentration, and confidence as well as measures of participant adherence to the intervention, use of the Fitbit tracker, and survey data collection.

Results: As of the submission of this protocol, recruitment for this National Institutes of Health stage IB personalized trial series is approximately 78.3% complete (47/60). We expect recruitment and data collection to be finalized by June 2023.

Conclusions: Evaluating the feasibility, acceptability, and effectiveness of a series of personalized interventions of melatonin will address the longer term aim of this program of research—is integrating N-of-1 trials useful patient care? The personalized trial series results will be published in a peer-reviewed journal and will follow the CONSORT (Consolidated Standards of

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Reporting Trials) extension for N-of-1 trials (CENT 2015) reporting guidelines. This trial series was approved by the Northwell Health institutional review board.

Trial Registration: ClinicalTrials.gov NCT05349188; https://www.clinicaltrials.gov/study/NCT05349188

International Registered Report Identifier (IRRID): DERR1-10.2196/45313

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KEYWORDS

feasibility; insomnia; melatonin; N-of-1; personalized trial; personalized; placebo; poor sleep; sleep duration; sleep quality; supplements; virtual

Introduction

Sleep health is understood to be a multidimensional construct influenced by dimensions such as duration, satisfaction, timing, efficiency, and alertness, and it is a partially subjective experience that should be assessed in the context of the individual. In recent years [1], the prevalence of self-reported difficulty sleeping has increased, and population studies have shown increasing trends toward shorter sleep duration [2]. A recent study of US workers found the prevalence of short sleep duration to be 37.6% and associated poor sleep quality to be 19.2% [3]. Deleterious effects of poor sleep include a heightened stress response; pain; depression; anxiety; and deficits in cognition, memory, and performance [4]. Short sleep duration or poor-quality sleep is also associated with health outcomes including obesity [5], diabetes [6], hypertension [7], cardiovascular disease [7], higher productivity loss [8], reduced quality of life [9], depression [9], and mortality [8]. The causes of poor sleep, defined by short sleep duration and the commonly associated poor-quality sleep [10], can be complex and diverse. These include personal factors such as sex, mental health status, and BMI [8]. Lifestyle factors such as smoking, poor diet, and low physical activity (less than 120 minutes) also predict short sleep duration [8]. Further, environmental factors including financial concerns, children, marital status, irregular work hours, and a long commute can also influence sleep quality and duration. Finally, discrete sleep disorders such as obstructive sleep apnea, insomnia, and restless leg syndrome may also affect sleep [11]. The complex etiology of sleep duration and quality means that not all individuals suffering from poor sleep have comparable presentations. The widespread and increasing nature of poor sleep and the gravity of its effects support the need for innovative treatments. Furthermore, the diversity of factors contributing to poor sleep warrants treatment that accounts for individual differences among participants. Poor sleep has been determined as high priority for a personalized trial approach by previously interviewed clinicians and patients [12].

Exogenous melatonin supplements are widely used to treat insomnia and sleep disorders as well as to adjust altered sleep schedules related to jet lag [13]. Doses of melatonin available over the counter range from 0.3 mg to a maximum of 10 mg, but they typically fall within the range of 0.3 to 3 mg [14]. Because melatonin is naturally occurring within the brain and external food sources such as fish, eggs, milk, nuts, and seeds [15], it is considered a dietary supplement, therefore warranting less regulation before distribution than a typical drug [16]. As such, research evaluating the efficacy of melatonin across populations is still developing. However, various clinical trials have been conducted demonstrating the efficacy of exogenous melatonin in treating sleep disorders regardless of the etiology of the disorder [17-20].

Functionally, endogenous melatonin secretion is governed by the suprachiasmatic nucleus (SCN) of the hypothalamus, which is the primary circadian pacemaker in mammals [21]. In addition to its endogenous activity, the SCN responds to retinal light exposure to help regulate circadian rhythms, which impact significant processes relevant to survival, including sleep, wake, appetite, mood, hormone secretions, and behaviors. During the daytime, the SCN, reinforced by external light patterns, activates processes that maintain wakefulness, attention, and cognitive capacity. Melatonin, secreted by the pineal gland primarily during darkness or nighttime in response to a signal from the SCN, is thought to facilitate sleep in part by inhibiting processes associated with wakefulness [21]. Therefore, exogenous melatonin supplements are thought to promote increased sleep duration by signaling to melatonin receptors that day has, in fact, shifted into night [22]. As such, melatonin has been found to be particularly useful in facilitating sleep initiation and increased sleep duration for individuals with disrupted circadian rhythms resulting from, for example, overnight shift work, jet lag, or sleep-wake disorders [23]. Melatonin has also been indicated in improving sleep efficacy and daytime sleepiness in healthy volunteers [24].

Importantly, clinical trials of melatonin therapy for sleep have found that not all participants benefit equally from treatment with melatonin. Several meta-analyses assessing the efficacy of melatonin therapy found evidence for significant heterogeneity in the effectiveness of melatonin interventions, particularly for outcomes including sleep onset latency, total sleep duration, and sleep efficiency [25,26]. Furthermore, the authors of a recent systematic review assessing melatonin's effect on these sleep dimensions across 23 clinical trials identified significant between-study heterogeneity, which they attributed to differences in participant health status [27]. Participants with respiratory diseases, metabolic disorders, and sleep disorders saw greater sleep improvement from melatonin therapy than participants with a variety of other health concerns, including mental disorders, neurodegenerative diseases, and breast cancer [27]. Authors across meta-analytic publications additionally cite concerns regarding the heterogeneity of treatment dosage between studies; without consistent dosage information, the authors could not draw robust conclusions regarding overall treatment efficacy or minimum and maximum dosage recommendations for different populations [26,28].

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These findings suggest that not all participants benefit equally from treatment with melatonin.

Because of this variability in treatment provision and response, participants taking melatonin may benefit from a personalized (N-of-1) trial approach [29,30]. Personalized trials are a research approach that helps participants to select which treatments work best for them individually. Participants in a personalized N-of-1 trial receive a multiple crossover trial with continuous collection of objective outcome data throughout the trial. Interventions are delivered in alternating time periods of treatment, alternative treatment, and placebo therapies, usually in randomized blocks [31,32]. At the completion of the personalized trial, the effect of each intervention is evaluated and the trial participants are able to select which intervention works best for them. Personalized trials are designed to provide patients with high-integrity, evidence-based information uniquely relevant to the outcomes and values important to them so they may identify efficacious treatments [33]. Despite the potential of personalized trials, N-of-1 personalized designs are not often used in clinical practice [31,34-36]. In surveys that examined attitudes about personalized trials, hesitancy to engage in personalized N-of-1 trials was attributed to the cost and effort required for implementation [31,34,36].

In the context of melatonin therapy, personalized trials would elucidate gaps in previous research by helping to identify the optimal melatonin treatment for participants despite a variety of demographic, health-related, and environmental factors. However, given prior issues with implementing personalized N-of-1 trials, it is important to evaluate the feasibility of this type of intervention for feasibility and acceptability from a participant perspective and the effectiveness of melatonin delivered in a personalized N-of-1 trial. On the basis of guidelines in the National Institutes of Health Stage Model for Behavioral Intervention Development [37], we will conduct a stage IB (ie, intervention refinement, modification, and adaptation and pilot testing) design trial to address these feasibility questions.

This study evaluates the feasibility, acceptability, and effectiveness of a series of personalized interventions for remote delivery of higher dose melatonin at 3 mg, lower dose melatonin at 0.5 mg, and a placebo supplement in 60 participants with self-reported poor sleep. By using new wearable technologies (such as Fitbit devices), commercially available supplements (such as melatonin produced by Pure Encapsulations), and commercially available medication adherence devices (such as Nomi by SMRxT), the current protocol allows for remote assessment of outcomes and thereby also continuous data collection. Further, remote delivery of the intervention allows each participant to receive the intervention and be assessed for poor sleep in their own home with limited disruption. Results from this study will determine whether remote delivery of these interventions is feasible and acceptable for participants with self-reported poor sleep and will allow clinicians to identify whether remote delivery of melatonin can effectively allow patients to manage their sleep.

Methods

Study Design

The study is a series of 60 randomized personalized N-of-1 trials examining the effects of 3 mg of melatonin and 0.5 mg of melatonin versus placebo for poor sleep. The intervention will be delivered remotely to participants residing in the United States over the course of 14 weeks. Participants will be provided with a Fitbit Charge 5 device, all necessary supplements, and 3 Nomi by SMRxT medication adherence devices. Nomi by SMRxT is a smart pill bottle that monitors medication-taking behavior in real time to collect adherence data without active participant input (see Figure 1).

Figure 1. The Nomi pill bottle by SMRxT.



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The first 2 weeks of the study will be a baseline assessment period. Participants will not take any melatonin or placebo pills during this time. During baseline assessment, each study participant will be asked to both engage in their usual methods of managing sleep and wear their Fitbit device at all times, including during sleep. Participants will also be asked via SMS text messaging to rate an ecological momentary assessment (EMA) of their fatigue, pain, concentration, stress, mood, and confidence at 3 random times throughout the day. Each morning, participants will answer a survey questionnaire assessing their sleep quality from the previous night. Every other Sunday evening, participants will complete a longer survey measure asking them to reflect on their sleep quality over the past 2 weeks. Participants will be encouraged to wear their Fitbit devices day and night, asked to sync their device with the Fitbit application on their phone at least every 2 days, and asked to charge their Fitbit device at least every 4 days.

After successfully completing the baseline period, participants will be randomized into 2 arms with six 2-week intervention blocks of 3 mg of melatonin, 0.5 mg of melatonin, or placebo pills. During the intervention, participants will be discouraged from taking additional melatonin or using other sleep treatments outside those provided during the study. Within 3 months of the end of the 14-week trial, each participant will be provided with a report containing their analyzed data and asked to complete a satisfaction survey. After the satisfaction survey is completed, study coordinators will reach out to each participant to interview them about their experience with the personalized trial. Study recruitment began in April 2022, and the study completion is anticipated to occur by June 2023.

Study Population

Participants in this study will be volunteer subjects from across several states within the United States. This will include the approximately 77,000 employees of the Northwell Health System [38]. Digital recruitment of potential participants will include email blasts and advertisements in newsletters circulated to the Northwell Health team member population. To expand beyond the Northwell Health system, recruitment will also target web and social media; Facebook and Google ads for the study will be published in users' web feeds and searches. Additionally, web posts to communities on platforms such as Reddit, Craigslist, and LinkedIn will also be used to appeal to individuals with sleep issues. With 93% of US adults reporting using the internet, 69% reporting ever using Facebook, and 18% reporting using Reddit, use of digital recruitment methods significantly broadens the potential span of our outreach [39].

All potential participants will be required to self-identify as having a minimum threshold of poor sleep for at least 4 weeks using the Insomnia Symptom Questionnaire (ISQ). Poor sleep for this study was defined by self-reported difficulty in falling asleep, staying asleep, and feeling refreshed by sleeping 4 to 7 times per week for a period of at least 4 weeks. Participants must also report 1 or more sleep symptoms that bother them "quite a bit" or "extremely." Potential sleep symptoms on the ISQ include disrupted work, irritability, and feeling fatigued. An example of the ISQ measure used to assess sleep disruption can be found in Multimedia Appendix 1. Because of the high prevalence of poor sleep [3] and wide reach of our recruitment methods [39], we anticipate a large pool of potential participants from which to recruit.

Recruitment and Consent

Participants for this study will be recruited via advertising and social media posting on Facebook, Instagram, Google, Craigslist, LinkedIn, and Reddit. Posting and advertisement will comprise multiple formats of information (including videos, images, and text posts). Additional recruitment methods will include Northwell Health team member email listserves, word of mouth, recruitment emails to individuals who previously expressed interest in personalized trials, and the Northwell Health Clinical Trials Listing.

Interested individuals who respond to any of the above recruitment methods will be directed to an digital information screen with details about the pilot study and asked to complete screening measures containing questions regarding study inclusion and exclusion criteria (Textbox 1). This information will be reviewed by study staff to determine participant eligibility before consent. If a potential participant is deemed ineligible or is wait-listed due to high demand, study staff will reach out to the participant to notify them within 2 business days. Upon completion of screening, eligible individuals will be provided with a link to an electronic consent form and a short video explaining details of the study protocol and consent form. If individuals wish to speak with a staff member regarding details of the study or consent, they will be offered a 30-minute informational phone call with study staff to review key points within the consent form and any questions the potential participant has about the study. A study staff member will confirm the scheduled time for this call with the participant within 2 business days. After the phone call, the study staff will send the eligible participant a message containing the electronic consent form, the explanatory video, and a 4-question screening measure assessing participant understanding of the protocol and consent process.

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Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Aged ≥18 years
- Fluent in English
- Able to take melatonin and a placebo
- Self-report of poor sleep symptoms using the Insomnia Symptom Questionnaire
- Own and can regularly access a smartphone capable of receiving SMS text messages
- Owns and can regularly access an email account
- Lives in the United States
- Agrees to adhere to lifestyle considerations including wearing a Fitbit device day and night and potentially adapting their current melatonin routine to fit the protocol throughout the study duration

Exclusion criteria

- Aged <18 years
- Pregnant or breastfeeding
- Diagnosed with depression, seasonal affective disorder, schizophrenia, autoimmune disease, or asthma
- Take monoamine oxidase inhibitors or corticosteroids
- Diagnosed with low blood pressure
- Clinically diagnosed with a sleep disorder (eg, narcolepsy, circadian rhythm sleep-wake disorders, periodic limb movement disorder, restless leg syndrome, obstructive sleep apnea, etc)
- Deemed unable to complete the study protocol due to cognitive impairment, severe medical or mental illness, or active or prior substance abuse
- Participate in shift work (evening/night shifts, early morning shifts, rotating shifts, etc)
- Frequently travel across time zones (eg, pilots or flight attendants)
- Receive specialty mental health care for insomnia (eg, cognitive behavioral therapy for insomnia and medications for insomnia)
- Advised by a doctor or health care provider that taking melatonin is unsafe
- Do not own or cannot regularly access a smartphone capable of receiving SMS text messages
- Do not possess or cannot regularly access an email account
- Lives outside of the United States
- Scheduled for planned surgery within 6 months from the study start date

Persons who are eligible to participate after screening and who opt out of the educational phone call will receive a message from study staff containing an electronic copy of the consent form and an explanatory video. These potential participants will also receive the same 4-question screening measure to assess their understanding of the consent form and study protocol.

Consent will be obtained electronically. Participants will receive a copy of the institutional review board (IRB)–approved consent form, a copy of their signed consent form, and a copy of their signed HIPAA (Health Insurance Portability and Accountability Act) authorization form via an encrypted message. Signed consent and HIPAA authorization forms will be stored electronically on a HIPAA-compliant, Northwell Health–approved shared drive accessible only to the IRB-approved study staff. The example study consent form can be found in Multimedia Appendix 2.

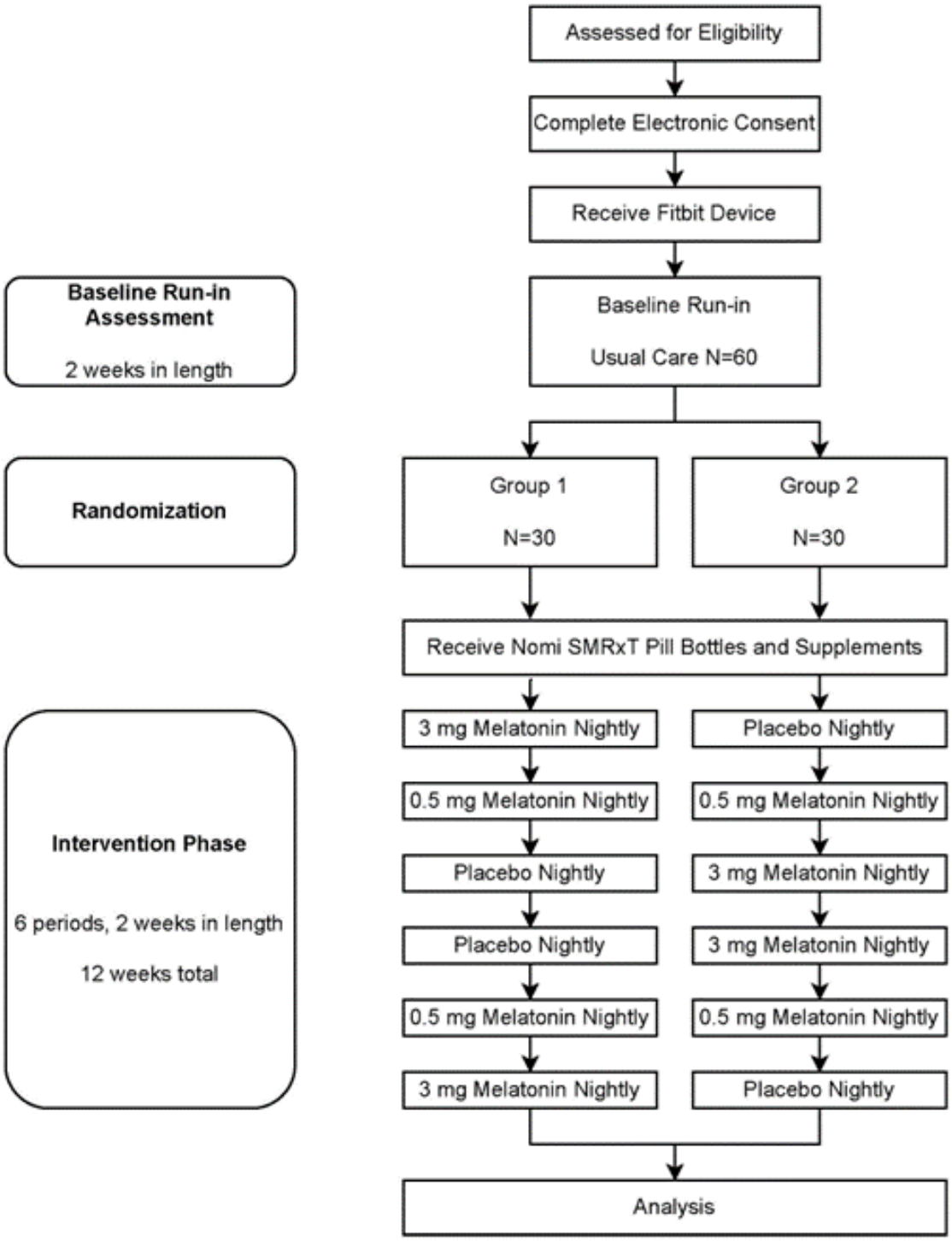
After consent, participants will be able to choose a study start date during their enrollment process from a provided list of dates. No more than 20 potential participants will begin their baseline period on the same day. Study enrollment will continue until 60 participants have been randomized after the baseline assessment.

Assignment of Interventions

Each treatment was assigned a letter with A=3 mg of melatonin, B=0.5 mg of melatonin, and C=placebo. Of those participants who are enrolled in the study, approximately 30 will be randomized by the study statistician to receive the protocol in the following order of 2-week treatment periods: 3 mg of melatonin, 0.5 mg of melatonin, placebo, placebo, 0.5 mg of melatonin, 3 mg of melatonin (ABCCBA). Approximately 30 more participants will be randomized in the following order of 2-week treatment periods: placebo, 0.5 mg of melatonin, 3 mg of melatonin, 3 mg of melatonin, 0.5 mg of melatonin, placebo (CBAABC). This randomization pattern can be viewed in the participant time line in Figure 2.

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Figure 2. Participant Timeline.



Interventions

Once a participant successfully completes baseline and is randomized into the study, they will be mailed 3 Nomi pill bottles (see Figure 1). Each bottle will contain 28 pills of 3 mg of melatonin, 0.5 mg of melatonin, or placebo labeled “A,” “B,” or “C.” The doses of 3 and 0.5 mg of melatonin were selected to compare high and low doses of melatonin, respectively. Previous studies have classified doses of 0.3 to 1 mg as low doses of melatonin, which may still be effective [40]. Higher doses of melatonin (ranging between 2 mg and 6 mg) have been found to be effective for treating sleep disruption [41,42]. In this study, 3 and 0.5 mg of melatonin were selected because they are provided by the manufacturer, and color- and size-matched placebos are available. Both the 3 and 0.5 mg of melatonin pills are presented in the same type of capsule (ie, same size and appearance) but with different concentrations of melatonin. The placebo pill is an identical capsule filled with

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a glucose solution. The melatonin and placebo doses provided for this study are prepared by Pure Encapsulations LLC, a National Sanitation Foundation Good Manufacturing Practices–registered laboratory that exceeds United States Pharmacopeia standards for supplement manufacturing. This laboratory has a 50-year history of producing products for clinical research [43-45]. Participants will receive a treatment schedule that indicates which pill bottle of medications is assigned to each week of the intervention. During intervention weeks, participants will receive nightly SMS text message reminders an hour before their self-reported bedtime, instructing them to take a pill from their assigned pill bottle depending on where they are in the randomization time line. Participants will be asked to refrain from taking additional melatonin for the duration of the study. During all treatment periods, participants will be asked to wear the Fitbit device 24 hours a day and answer up to 5 survey measures sent to them via SMS text messaging daily.

Participant Time Line

Figure 2 illustrates the participant time line.

Adherence

During the baseline period, the study team will assess participant adherence to the protocol. Adherence will be evaluated using the Fitbit tracker and survey completion. Participants wearing the Fitbit for 12 or more hours per day, including at least 180 minutes of sleep time, will be defined as adherent [46,47]. During the 14 days of the baseline period, participants who do not achieve a minimum of 80% adherence to Fitbit tracker wear and study measures (including EMA and survey measures) will be withdrawn from the study before randomization. Those participants with 80% adherence or higher by the final day of the baseline period will be randomized to the intervention phase. To encourage adherence, participants will be provided with short educational videos and protocol reminders via SMS text messaging, and they will be encouraged to contact study staff with concerns by phone, email, or secure portal message.

Participant Report

Participants who complete the intervention portion of the trial will have generated a 15-page personalized report summarizing their trial results and showing the impact of 3 mg of melatonin, 0.5 mg of melatonin, and placebo on their Fitbit-recorded sleep duration. The goal of the report is to display participants' sleep duration averaged across each study intervention with the goal of helping participants to select which treatment works best for them. The participant report also presents summaries and results for other sleep- and wellness-related outcomes that are both Fitbit-recorded (such as sleep efficiency, average time spent in sleep stages, and average number of steps) and self-reported (such as daily sleep quality and EMA fatigue). This report is not to be interpreted as medical advice. Participants are encouraged to seek a medical professional's opinion if they have any questions or concerns about the data displayed in their report. A similar version of the participant report in a series of personalized trials for chronic lower back pain is described and displayed in further detail elsewhere [48].

Results for the participant report are generated by comparing the effectiveness of 3 mg of melatonin and 0.5 mg of melatonin relative to placebo for each of the outcomes measured in the study. The participant report contains information about the magnitude of the difference for each outcome between each treatment period. Participants will be provided information about whether the difference was statistically significant (defined as $\alpha \leq .05$) in generalized least-squares (GLS) regression analyses. They will also be provided with estimates of their adherence to the intervention, Fitbit device, and survey measures.

After automated generation by the study data team, each participant report will be individually reviewed for accuracy, consistency, and comprehensibility by several study team members before delivering the report to the participant as a printable PDF file via a secure web portal. Personalized participant reports will be delivered to the participants within 3 months of their intervention completion, and they will be given the option to review their report along with a study team member. Participants will have an opportunity to provide their feedback on their report in the satisfaction survey and follow-up study interview.

Patient and Public Involvement Statement

Pilot data with participants and internal use testing were used to help determine which medication adherence device to select for this trial. We did not directly involve participants in any other elements of the design of this trial.

Ethics Approval

This study underwent ethics review and was approved by the Northwell Health IRB (IRB #21-0239). All amendments to the protocol will be submitted for approval to the ethics committee and Northwell Health IRB.

Data Monitoring

A Data and Safety Monitoring Board (DSMB) will be assigned to periodically assess for participant safety, scientific integrity, and the trial's progress. This DSMB will include 4 members who will have varying areas of scientific expertise including statistics and medicine. The DSMB conduct periodic reviews of study data for accuracy, completeness, and timeliness of submission. The study DSMB will also assess for evidence of potential harms, including adverse treatment events and loss of confidentiality. Following these reviews, the DSMB will be responsible for making recommendations regarding the continuation, modification, and termination of the project in reports provided to the study principal investigator. Regular collaboration between the study team and the DSMB will ensure access to study data for monitoring and regulatory inspection.

Treatment Adverse Events

Melatonin poses a low risk of physical harm to subjects, as it has a very low side effect profile and limited evidence of habituation and tolerance. A 2015 review on the safety of melatonin supplements indicated that only mild side effects were reported in various short-term studies that involved adults, surgical patients, and critically ill patients [49]. Some of the mild side effects that were reported in the studies included

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headache, dizziness, nausea, and sleepiness [49]. Less common side effects include short-lasting feelings of depression, mild tremor, mild anxiety, abdominal cramps, irritability, reduced alertness, confusion or disorientation, and abnormally low blood pressure. The chances that participants could experience these side effects during the trial are low given the duration and dosing proposed for this research [50]. Participants document any side effects they experience that may be related to the supplements to the study team daily in the morning survey. Participants are informed that they may discontinue supplement dosing at any point during the trial.

The exclusion criteria for this study were used to prevent participants who are at greater risk of harm from participating in the study. Protocol adherence is monitored throughout the trial, and participant re-education is conducted as needed.

Loss of Confidentiality or Privacy

A risk that may be incurred by participating in the trial is a loss of privacy or confidentiality. The participant is made aware of all the data collected and the companies and devices employed to collect the data via the consent process. All identifying information of participants is stored in a secure, password-protected, Northwell Health–approved, HIPAA-complaint database, and personal and identifying information is not stored on any devices used in the study. Using the devices employed in this trial as part of this study as compared with using the devices as a consumer presents no additional risk. Once participants complete their study involvement, identifying information will be destroyed. All research team members with access to identifiable and deidentified data are trained and included on the IRB submission for approval. Regular meetings will occur with the principal investigator and other study team members to ensure protocol adherence and data accuracy.

Costs

This pilot study is funded by the National Institutes for Health (R01LM012836). All study-related equipment, devices, procedures, melatonin, and placebo supplements will be provided to participants at no cost, and participant insurance will not be billed. This study uses SMS text messaging to deliver notifications, reminders, and study questionnaires, which may include standard message and data rates from the participants' wireless carrier. Study participants will not be compensated for any costs related to data usage or sending or receiving SMS text messages by the study or by members of the study team.

Compensation

After completing all components of the study (ie, successful completion of a research team–approved intervention period, submission of a satisfaction survey, and returning the Nomi devices), study participants will be mailed a US$ 100 payment card (ClinCard). Additionally, as a thanks to study participants for their participation, they will be allowed to keep their Fitbit Charge 5 (a value of US$ 150.00).

Primary Outcome

The primary outcomes of this study will be feasibility as measured by the mean usability score evaluated using the 10-item System Usability Scale (SUS) [51] and acceptability as measured by an 18-item satisfaction survey. The SUS is a validated questionnaire that asks users to score each item on a Likert scale from "strongly disagree" (1) to "strongly agree" (5) [52,53]. Individual item scores are multiplied by 2.5 and summed to generate a total score ranging from 0 to 100, with higher scores indicating a greater level of usability. This measure has been used and validated in multiple contexts [52,53]. The SUS will be presented to the participants as addressing the ease of use, complexity, and consistency of the personalized trial system as a whole. Satisfaction will be measured using a 6-item satisfaction survey. The survey will assess participant satisfaction with elements of the trial, including explanatory resources, the Fitbit device, the personalized trial design, survey assessment measures, and the participant report. Participants will be asked to rate their satisfaction on a scale of 1 ("not very satisfied") to 5 ("very satisfied").

The satisfaction survey will also include a 7-item series of questions regarding the participant's experience in the personalized trial as a whole. Satisfaction with aspects of the trial including the onboarding process and ease of trial adoption will be rated on a scale of 1 ("strongly disagree") to 5 ("strongly agree"). Finally, satisfaction with the personalized report will be assessed through 5 questions on a scale of 1 ("strongly disagree") to 5 ("strongly agree").

Secondary Outcomes

The secondary outcomes in this study will include Fitbit device–recorded nightly sleep duration, self-reported sleep quality using a modified version of the Consensus Sleep Diary (CSD), EMA self-reported fatigue ratings, EMA self-reported pain ratings, adherence to use of the Fitbit device, and adherence to each of the interventions (3 mg of melatonin, 0.5 mg of melatonin, and placebo).

Nightly sleep duration and daily steps will be assessed using non–Near Field Communication, Fitbit Charge 5 devices. During baseline assessment (2 weeks) and all intervention weeks (12 weeks), participants will be asked to wear their Fitbit device each day and night (for a total of 14 weeks overall). All enrolled participants will be provided with a Fitbit device and Fitbit account that the research team has created with no identifying information for use in the study. A file linking the Fitbit account identifier to the study participant will be housed in a Northwell Health–approved drive to store protected health information. It will be accessible solely to members of the study team listed in the IRB application. Participant Fitbit data will be retrieved using N1Thrive and Fitabase, both secure web portals. Participants' study Fitbit accounts will be linked to an identification number in the N1Thrive and Fitabase systems. No identifying information will be stored in the Fitabase data set. Fitabase and N1Thrive will stop tracking participant Fitbit data at the end of the trial. As an added security measure, participants will be instructed to remove the Fitbit study account from their smartphone device to keep the Fitbit.

The CSD is a daily instrument used to assess and track intervention effects on sleep symptoms, quality, and satisfaction [54]. Three versions of the CSD were originally put out by its authors: the core CSD containing 9 items, an expanded morning

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version with optional additional items to be completed upon arising, and an expanded evening version with separate morning and evening items to be optionally completed. This study uses a modified version of the core CSD, asking participants about perceived sleep quality (via a Likert scale), sleep onset latency, the time at which the participant believes sleep onset occurred, duration of nighttime awakenings, final rise time, and a multiple-selection question asking if any of 10 (or an optional "other" selection) listed factors directly impacted the participant's sleep. The CSD will be sent to participants within an hour of their self-reported wake time each day of the study to assess and monitor patient-reported outcomes regarding sleep quality throughout each intervention period of the trial. Data observed through the CSD will be reported back to participants via the personalized participant report.

Daily self-reported fatigue and pain ratings will be assessed via EMA using a measure adapted from the Numeric Pain Rating Scale [55]. These assessment measures are single-item assessments administered 3 times daily via SMS text messaging asking participants to rate their fatigue and pain in the current moment on a scale of 0 to 10. The timing of the SMS text messages will be randomized between a participant's self-reported wake and sleep times. For fatigue, ratings of 0 indicate no feeling of fatigue, with scores of 1 to 3, 4 to 6, 7 to 9, and 10 respectively indicating a little, somewhat, quite a bit, and very much feeling fatigued. Interpretations of scores remain the same for pain. EMAs are collected daily via surveys using the secure study platform N1Thrive, a Northwell Health–approved and HIPAA-compliant system used for patient engagement and collecting and storing research data. A workflow was constructed for this study to include automated messaging pathways delivered via SMS text messaging directly to the participant's smartphone via the platform.

Participant adherence to the intervention and time of melatonin or placebo use will be measured using the Nomi smart pill bottle. The Nomi system includes a smart bottle that is designed to look just like a typical prescription pill bottle. The bottle comes equipped with a sensor that measures patient adherence using weight, time, movement, and temperature. The data are then made available to health care providers via a cellular connection to the SMRxT cloud. Below the sensor is a light that flashes when it recognizes that a dose has been taken, the device's battery is low, or the device is unable to connect to the network. From the digital Nomi dashboard, study team members will remotely assign treatments to patients, create treatment schedules, and monitor medication usage. No patient information or identifying data will be stored on the device or within the Nomi adherence dashboard—only unique study IDs will be used to collect data. The bottle serial number and the unique study ID will be linked to subjects in REDCap, a secure data management system managed only by research staff. The Nomi system will also be integrated with the study platform to deliver automated SMS text message reminders in cases of deviation from assigned supplement dosing.

Exploratory Outcomes

The exploratory outcomes in this trial will include self-reported sleep disturbance measured using the Insomnia Severity Index (ISI), participant self-reported side effects, EMA self-reported pain ratings, EMA self-reported mood ratings, EMA self-reported concentration ratings, and EMA self-reported confidence ratings. We will also measure participant adherence to survey measures and EMA assessment measures. The ISI is a brief patient-reported outcome insomnia instrument assessing the severity of nighttime insomnia and related daytime impairment [56]. It comprises 7 items, each scored using a 5-point Likert scale, which summate to a total score. Lower ratings on the scale equate to less disturbance (0=no problem) and higher ratings of more disturbance (4=very severe). This overall score can function as a diagnostic of the severity of clinically significant insomnia or subclinical sleep disturbances. The ISI will be sent to participants as a biweekly survey every other Sunday evening (ie, at the end of baseline and the end of each intervention block), and it will ask them to reflect on their sleep disturbance symptoms for the past 2 weeks (or the past study block). This instrument will therefore be the key data point to solicit participants' self-reported sleep disturbance on a retrospective basis for an intervention period as a whole. ISI data will be reported back to the participants in the participant report.

Patient self-reported side effects will be assessed daily using a survey measure. EMA measures of stress, mood, confidence, and concentration will be assessed in using single-item assessments administered 3 times daily via SMS text messaging asking participants to rate how they feel in the current moment on a scale of 0 to 10. Delivery and assessment of these measures will be identical to the methods used for EMA fatigue and pain described above. Participant adherence to survey measures (including the sleep diary and ISI) and EMA check-in measures will also be tracked.

Results

Recruitment Status

As of the submission of this protocol, recruitment for this pilot is approximately 78.3% (47/60). We expect recruitment and data collection to be finalized by June of 2023.

Sample Size Calculation

The sample size of 60 participants was chosen to ensure a sufficient number to obtain a preliminary assessment of the feasibility of this series of personalized trials of melatonin therapy for sleep. The feasibility for this study is determined using scores from the SUS, which is administered at the completion of the trial. With 60 participants receiving the intervention and use of a single sample binomial test with α set to 2.5% significance, we will have approximately 90% power if 70% of participants complete the trial. With 60 randomized participants—and an expected trial completion rate of 70%—we anticipate SUS data to be available in approximately 42 participants, thus giving a standard error no greater than 8% in estimating the rate of SUS ≥85, an exceptional level of usability [57]. Individual participant responses will be reported so that individual-level heterogeneity can be assessed and evaluated [58].

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Primary Analysis

The primary analysis will be based on usability ratings submitted by all enrolled participants (n=60) on the SUS. These usability ratings will be summarized using descriptive statistics including means, medians, SDs, and IQRs and visualized via a histogram. If the trial receives a score of 70 or greater, it will be judged to have "acceptable" levels of feasibility, whereas scores of 80 or greater are interpreted as "excellent" [57]. The SUS has been used and validated for use in multiple programs and trials [52,53].

We will also analyze participant self-reported levels of satisfaction. Self-reported satisfaction levels will be reported for each component of the trial (eg, interventions and design) using means and SDs. Participant responses to each satisfaction item will also be depicted graphically to show the distribution of participant responses from "not very satisfied" to "very satisfied." This satisfaction measure has previously been used to evaluate acceptability of personalized trials [47].

Secondary Analyses

Means and SDs for Fitbit device–recorded nightly sleep duration, self-reported sleep quality using a modified version of the CSD, EMA self-reported fatigue ratings, and EMA self-reported pain ratings will be reported for the baseline assessment period (2 weeks) and each intervention period (6 blocks of 2 weeks) and depicted graphically. Proportion of days adherent to the Fitbit device and adherence to the intervention will be reported using mean proportions and SDs for the study overall. We will also calculate mean and SD values for each secondary outcome across intervention periods for 3 mg, 0.5 mg, and placebo. For example, we will sum all outcome measures for both the 2-week intervention periods to derive an overall mean value for the 3 mg melatonin period. The same process will be followed for the 0.5 mg melatonin and placebo periods. As the timing of melatonin doses may influence the effect of melatonin on sleep [59-61], the time of dose relative to sleep onset will be examined in sensitivity analyses.

Finally, the effects of each intervention (3 mg of melatonin, 0.5 mg of melatonin, and placebo) on the secondary outcomes will be examined using generalized linear mixed models with an autoregressive, AR(1), model. This model accounts for possible autocorrelation and linear trends between fatigue ratings across time. We will consider week as a linear term and factor in the mixed model to explore the nonlinear time effects of each treatment. This will generate estimates of each intervention on each of the secondary outcomes for the overall sample. In addition, we will conduct analyses to evaluate the effects of each intervention on the secondary outcomes at the level of the individual participant. Using GLS analyses with an AR(1) model, we will be able to generate estimates of the effect for each intervention for each participant for each of the secondary outcomes. This level of individual-level analyses is essential for personalized trials.

Exploratory Analyses

Exploratory outcome measures, including ISI, participant self-reported side effects, EMA self-reported pain ratings, EMA self-reported mood ratings, EMA self-reported concentration ratings, and EMA self-reported confidence ratings, will be reported using means and SDs overall and by the study period. Similar to analyses of secondary outcomes, the effects of each intervention on the exploratory outcomes will be evaluated with generalized linear mixed model analyses using autoregressive models in the overall sample and with GLS analyses using autoregressive models with individual participants. Exploratory adherence measures (adherence to surveys and EMA measures) will be represented using proportions for the overall study and by the study period. Comparisons between the 2 treatment orders (ABCCBA and CBAABC) will also be conducted to identify potential confounding effects due to treatment order.

Discussion

This study represents an advancement in the process of developing feasible, acceptable, and effective personalized interventions for a variety of health conditions. Widespread use of personalized N-of-1 designs has been hampered by difficulties in the feasibility of creating them, with many researchers and clinicians feeling that personalized N-of-1 trials are not the worth the effort needed to conduct them [62]. In assessing the feasibility and acceptability of our developing personalized N-of-1 platform, which has been previously implemented to treat chronic lower back pain [47] and fatigue [46], we hope to continue refining a programmatic template for using personalized N-of-1 designs for other health conditions and other interventions. Further, we hope the use of digital enrollment, consent, intervention delivery, and outcome assessment will make personalized N-of-1 trials more feasible in research and clinical practice.

Potential limitations for the current trial include potential issues with representativeness of the participant sample and with doses of melatonin selected in the trial. Although our recruitment efforts are directed to identify a diverse sample for enrollment in the current trial, inaccurate sampling of participants with disrupted sleep is possible. For example, using digital recruitment methods may oversample individuals who have disrupted sleep due to excess internet usage time or exposure to blue light. For evaluations of effectiveness, this is not a concern since the goal of a personalized N-of-1 trial is to assess treatment effectiveness in each individual participant. However, the primary goal of this trial is to evaluate the feasibility and acceptability of personalized trials for poor sleep. Failing to recruit a representative sample of participants with poor sleep may limit our conclusions regarding the feasibility and acceptability of personalized N-of-1 trials of melatonin for sleep. In addition, individual participants may respond more optimally to other doses of melatonin than those examined in the current trial (namely 0.5 and 3 mg). Although these doses are representative of lower and higher doses of melatonin used in previous sleep interventions, assuming that some individuals may respond optimally to higher doses of melatonin (eg, 6 mg) or to doses not examined in the current trial (eg, 1 mg) is reasonable. In addition, some research suggests that depending on how melatonin supplements are prepared, the dose within each supplement may also vary [63]. Further, it is possible that dose duration may influence findings, as longer duration melatonin treatments have been associated with increased sleep

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duration [25]. For example, a participant may have responded better to a longer duration (eg, a 4-week block of melatonin rather than a 2-week block). However, the current goal of this trial is to identify the feasibility and acceptability of personalized N-of-1 designs rather than to select the ideal treatment for each individual participant. Another potential limitation for the current trial is the lack of information about participants' habitual melatonin levels before beginning the trial. Prior research suggests that individuals with lower endogenous melatonin secretion may benefit more from receiving melatonin replacement [64]. Therefore, the cause of participants' self-reported poor sleep may not be influenced by melatonin.

Despite these potential limitations, this trial represents a significant step forward in the design of digital, remote, personalized trials. If it is found to be feasible and acceptable among individuals dealing with poor sleep, revision of the design of the intervention to evaluate alternative formulations of the current treatment (such as longer dose durations or different strength doses of melatonin) or multiple alternative treatments (such as behavioral interventions for sleep hygiene and exercise) in comparison to melatonin is possible. Further, if these personalized trials are found to be feasible as prior series of trials have been [47], we will be able adapt the platform used in this intervention for other health conditions and hopefully integrate personalized N-of-1 trials into clinical practice.

Acknowledgments

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Data Availability

Data archives containing the raw study data and data dictionaries for this study are available on the Open Science Framework platform [65].

Dissemination

The trial results will be published in a peer-reviewed journal. All publications resulting from this series of personalized trials will follow the CONSORT extension for N-of-1 trials (CENT 2015) reporting guidelines [66]. Trial results will be reported to study collaborators and participants after study completion.

Authors' Contributions

KWD, SD, AS, and Y-KC contributed to the development of the trial idea. KWD, SD, AP, JR, DM, and Y-KC contributed to the development of the trial protocol. MJB drafted the manuscript and all authors contributed to its revision and gave final approval. TC and Y-KC provided statistical expertise.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Insomnia Symptom Questionnaire.
[DOCX File , 36 KB - resprot_v12i1e45313_app1.docx]

Multimedia Appendix 2
Study Consent Form.
[DOCX File , 79 KB - resprot_v12i1e45313_app2.docx]

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Abbreviations

CSD: Consensus Sleep Diary
DSMB: Data and Safety Monitoring Board
EMA: ecological momentary assessment
GLS: generalized least squares
HIPAA: Health Insurance Portability and Accountability Act
IRB: institutional review board
ISI: Insomnia Severity Index
ISQ: Insomnia Symptom Questionnaire
SCN: suprachiasmatic nucleus
SUS: System Usability Scale

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Protocol

The Efficacy and Feasibility of an Interoceptive Exposure Technique for Preventing the Transition From Subacute to Chronic Back Pain by Altering the Emotional Response to Pain: Protocol for a Pilot Randomized Controlled Trial

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Abstract

Background: Psychological factors such as stress, anxiety, mood, emotions, cognitive functioning, and pain behavior are relevant to the onset of pain and its continuation in the transition to chronic conditions. Subacute low back pain (LBP), a precursor to chronic LBP, is particularly poorly understood, and its relationships with psychological factors are understudied.

Objective: We will conduct a study aiming to prevent the chronicity of subacute LBP by altering the emotional response to pain using an interoceptive exposure technique (IET). Considering the recent increase in knowledge about psychological risk factors, as well as recent findings in cognitive neuroscience regarding emotional and cognitive background factors in the LBP chronicity process, efforts should be made to discover effective preventive methods.

Methods: We present a novel method aiming to prevent the transition from subacute to chronic back pain by altering the emotional response to pain using an IET. In this pilot randomized controlled trial, participants who are at a higher risk of LBP chronification due to the presence of a biomarker (ie, functional connectivity between the medial prefrontal cortex and nucleus accumbens) will be randomly assigned to the IET intervention group or control group A (treatment as usual). Participants who do not present with the biomarker will be assigned to control group B (treatment as usual) to assess how well this biomarker predicts the chronification of subacute LBP in this study population. Questionnaires measuring the pain experience and psychological distress will be used before the intervention, after the intervention (at 3 months), and at the 12-month follow-up.

Results: This research project will combine 2 novel methods: a biomarker as the inclusion criterion and an IET as the intervention. The comparative study design enables evaluation of the efficacy of the IET, as well as replication of the biomarker's validity as a possible clinical screening method.

Conclusions: If found to be useful, the IET would offer a cost-effective and reasonable way to develop treatment for acute and subacute back pain conditions. Potential benefits include increased pain management and quality of life for the individual patient with the addition of a potentially useful functional pain management method at the societal level.

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KEYWORDS

biomarkers; functional connectivity; interoceptive exposure; low back pain; prevention; subacute

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Introduction

Overview

As low back pain (LBP) has been shown to be highly prevalent and hence a major problem throughout the world, preventing LBP from becoming chronic can be considered a major challenge in pain medicine [1]. LBP prevalence rates between 3.9% and 20.3% have been reported [2], with the highest prevalence among female individuals and those aged between 40 and 80 years [3].

Although LBP episodes and associated disability usually improve within weeks, pain and disability typically continue, and recurrences are common [4]. The predictive power of biomarkers for chronic LBP has so far proven to be insufficient [5]. Risk factors for LBP may be genetic, acquired, or due to an individual's interaction with the environment [6]. In a review of prospective studies, Linton [7] concluded that psychological variables such as stress, distress, anxiety, mood, emotions, cognitive functioning, and pain behavior were relevant to the onset of pain and its continuation in the transition to chronic conditions. The transition from acute localized LBP into chronic widespread LBP has shown relationships with the progression of both peripheral and central sensitization [8]. Furthermore, patients with chronic LBP might develop maladaptive behavioral strategies [9].

Recent brain imaging studies have further supported the role of emotional factors in the LBP chronification process, revealing mental factors influencing pain conditions [10]. Even in acute pain states, emotional factors seem to directly influence neural pain processing, as shown in the brain imaging study by Orenius et al [11], in which a valence-independent emotion interacted with the pain processing in the secondary somatosensory cortex. Functional and emotional nonadjustment factors have been identified in the acute LBP chronification process [12], with emotional nonadjustment relating to helplessness and hopelessness. Furthermore, chronification does not simply implicate the presence of enduring pain symptoms; it signifies a complex process associated with alterations in cortical structure and function. Vachon-Presseau et al [13] emphasized the importance of the emotional brain (ie, the cortico-limbic system) in the modulation of acute pain and in the prediction and amplification of chronic pain. A functional magnetic resonance imaging (fMRI) study showed that chronification of LBP shifts brain representation from nociceptive to emotional neural circuits [14]. These findings indicate the pivotal role that the neural structures involved in emotional learning play in the chronification of back pain [15]. Furthermore, the strength of synchronicity (ie, functional connectivity) between the medial prefrontal cortex (mPFC) and nucleus accumbens (NAc) was predictive (with >80% accuracy) of individuals who would subsequently transition from subacute pain to chronicity at a 1-year follow-up [15].

Neuroimaging studies have shown that cognitive behavioral therapy can change anxiety-related dysfunctions (phobia, traumatic stress, obsessive-compulsive disorder, and panic) of the nervous system [16]. Brain regions associated with attention, interoception, and sensory processing, including the prefrontal cortex and right anterior insula, are thicker in meditation participants than in matched controls, with the thickness of 2 regions correlating with meditation experience [17]. It has also been shown that mindfulness-based stress reduction techniques (a subcategory of cognitive behavioral therapy) produce macroscopic cortical plasticity in the adult human brain, demonstrating a dynamic relationship between behavioral state and cerebral anatomy [18]. Stress reduction correlated with structural changes in the amygdala after an 8-week mindfulness-based stress reduction intervention, demonstrating an association between neuroplastic changes and corresponding improvements in a psychological state variable [19]. An anatomical likelihood estimation meta-analysis showed that 8 brain regions were consistently altered in meditators, including areas key to meta-awareness, exteroceptive and interoceptive body awareness, memory consolidation and reconsolidation, self-regulation and emotion regulation, and intra- and interhemispheric communication [20]. Therefore, psychological interventions can produce both objective structural changes and alterations in the neural processing of emotions.

The treatment of chronic LBP has not primarily focused on removing an underlying organic disease but rather, within a biopsychosocial framework, on identifying the underlying mechanisms driving the disorder and thus enabling treatment to favorably influence the outcome [21]. Psychological methods targeting therapeutic processes relate to attention, cognition, emotions (including emotion regulation), and overt pain behaviors [22]. Despite a growing knowledge of relevant background factors in the transition from acute to chronic LBP [23], insight into preventive psychological methods applicable to subacute (4-12 weeks) LBP, a precursor to chronic LBP, is still particularly scarce. Insufficient theoretical guidance and integration in the design, selection, and delivery of methods that precisely target known dysfunctional behavioral processes have been presented as plausible shortcomings [24]. A recent systematic review showed that psychological interventions aiming to prevent chronification of subacute LBP had an insignificant preventive impact on pain measures [25].

Aims and Objectives

There is a shortage of studies on interventions to prevent the chronicity of subacute back pain [25]. Considering the recent increase in knowledge about psychological risk factors, as well as recent findings in cognitive neuroscience regarding emotional and cognitive background factors in the LBP chronicity process, efforts should be made to discover effective preventive methods. Therefore, we will conduct a study aiming to prevent the chronicity of subacute LBP by altering the emotional response to pain using an interoceptive exposure technique (IET).

The aims of this study are as follows:

1. A pilot study will address the efficacy and feasibility of IET in preventing the chronicity of subacute pain. Participants who are found to have a higher risk of pain chronification due to the presence of a biomarker (functional mPFC-NAc synchronicity) will be randomized to the intervention group (n=7) or control group A (n=7; treatment as usual). To assess how well this biomarker predicts LBP chronification, participants who are not found to have the

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biomarker will be assigned to control group B (treatment as usual) without a defined number of participants.

2. A full-scale study (intervention group: n=20; control group: n=20) will address the efficacy and feasibility of the IET in the prevention of subacute LBP chronicity with the same parameters as in the pilot study.

Methods

Participant Selection and Sampling Strategy

All participant recruitment will take place through the pain clinic at the Orton Orthopaedic Hospital and another private occupational health center. All study participants will be outpatients at the pain clinic and the private occupational health center. They are working-aged Finnish citizens who speak Finnish as their first or second language. A health care professional will diagnose the participants' back pain and assess them based on the inclusion and exclusion criteria.

The inclusion criteria approximately correspond to those of Baliki et al [15]: pain intensity >40/100 on the numeric rating scale (NRS) [26] and back pain duration <16 weeks. Deviating from the abovementioned criteria, we limit the pain duration time more precisely (ie, to 4-10 weeks) to enable commencement of the IET before exceeding the valid 12-week time limit for pain chronicity. Additionally, it will be implied that participants experience at least occasional back pain when lying on their backs. Exclusion criteria resemble those of Baliki et al [15]: other chronic painful conditions, systemic disease, history of head injury, psychiatric diseases, or more than mild depression (score >19), as defined by Beck Depression Inventory-II (BDI-II) [27]. As an addition, exclusion criteria also include self-reported earlier diagnosed prolonged LBP episodes and longer sick leaves due to LBP.

A health care professional (physician or physiotherapist) will ask patients with subacute back pain if they are willing to participate in the study. When a patient is willing to participate, the research secretary will contact the patient and check that he or she meets the research criteria. Then, the health care professional will provide the patient with information about the study procedure and deliver the information and a consent form to the patient, who will sign the consent document. The patient will be told that he or she has the right to stop his or her participation at any time without having to explain the reason. The participant, accompanied by the research secretary, will undergo an fMRI scan and fill out the questionnaires. The feedback from the lumbar magnetic resonance imaging (MRI) will be given to the participants by the clinician. If necessary, proper further examinations and treatments will be provided, and the participants will be excluded from the study.

Neuroimaging and Data Acquisition

All participants will undergo an fMRI measurement at the Advanced Magnetic Imaging Centre, Aalto University, Espoo, Finland, to determine if they meet the criteria for the biomarker (mPFC-NAc synchronicity), according to the study by Baliki et al [28]. The fMRI is done only in the initial stage, and no post-IET measurement is done to demonstrate possible effects on the biomarker.

The fMRI data will be collected with a 3T Magnetom Skyra whole-body scanner (Siemens Healthineers) and a standard 32-channel head coil. Anatomical T1 magnetization prepared–rapid gradient echo images will be acquired with the following parameters: orientation=sagittal; repetition time (TR)=2530 ms, time to echo (TE)=33 ms; 176 slices, slice thickness=1 mm, gap=50%; phase encoding direction=A-P; field of view=256 mm; and flip angle=7°.

Next, fMRI images will be acquired with a T2* weighted echo planar imaging sequence with the following parameters: orientation=transversal; TR=1570 ms, TE = 30 ms; 38 interleaved slices with no gap, slice thickness=3 mm; phase encoding direction=R-L; field of view=220 mm; flip angle=70°; base resolution=74; and 400 time points/volumes. A total of 4 dummy scans will be acquired for signal stabilization.

We will collect 1 anatomic MRI and 1 fMRI series for each participant. Throughout the fMRI acquisition, the participants will be asked to rate their LBP on a sliding cursor from "no pain" to "worst imaginable pain" (0-10). Participants will be given the following instructions (in Finnish): "Continuously rate the intensity of your low back pain. Indicate the intensity of your low back pain and changes in it by adjusting the cursor to the location corresponding to the intensity of your pain." Participants will give their answer with a handheld 2-button device. Participants' answers will not be recorded.

Functional Connectivity Analysis and Participant Grouping

The functional mPFC-NAc connectivity of each participant will be analyzed with data processing assistant for resting-state fMRI [29]. Slice timing correction will be performed using the first acquired slice (slice number 2) as the reference slice. Images will be realigned, and normalization will be completed using a new segment and the diffeomorphic anatomical registration through exponentiated lie (DARTEL) algebra algorithm [30]. Images will be smoothed by DARTEL using a Gaussian kernel of full width at a half-maximum of 5 mm. Nuisance covariate regression will be performed with the Friston 24-parameter model. White matter signals and cerebrospinal fluid signals will be used as covariates. A 0.01 to 0.1 Hz filter will be applied. The functional region of interests, defined according to the criteria of Baliki et al [28], are spheres with a 10-mm radius. Talairach seed coordinates for the mPFC (x=2, y=52, z=–2) and right NAc (x=10, y=12, z=–8) will be transformed into Montreal Neurological Institute coordinates before calculating mPFC-NAc synchronicity. Participants with $z(r) \geq 0.25$ will be classified as having an increased risk for LBP chronification.

Participants who are found to have a higher risk of pain chronification due to the presence of a biomarker (mPFC-NAc synchronicity) will be randomized to the intervention group (IET) or control group A (treatment as usual). To assess how well this biomarker predicts the chronification of LBP, participants who are not found to have the biomarker will be assigned to control group B (treatment as usual).

Participants who fit the inclusion criteria (based on fMRI) will undergo a lumbar spine MRI examination (1.5 Tesla) to rule out specific causes of the low back symptoms (ie, tumors,

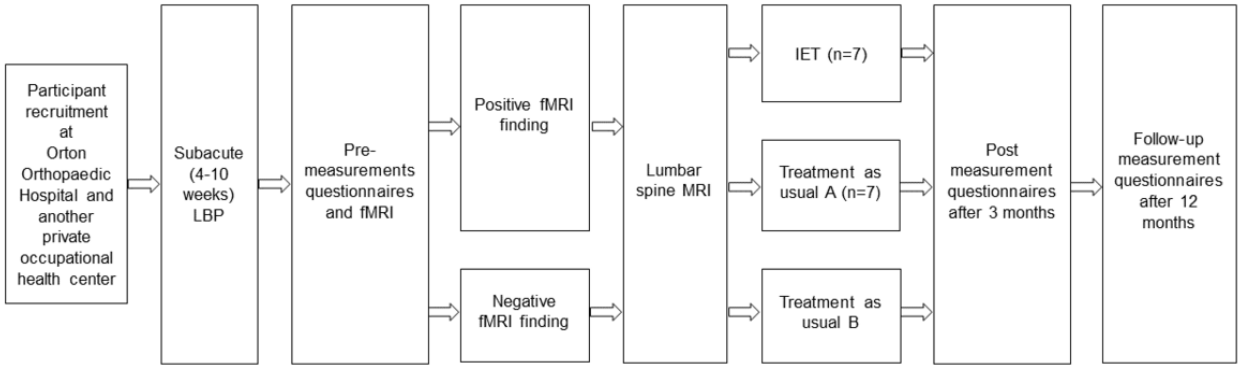
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evidence of ankylosing spondylitis) or other conditions requiring special attention. Furthermore, the lumbar MRI ensures the homogeneity of the study population. The feedback from the MRI examination will be given to the participants by the clinician briefly in the style of "no specific causes or special factors to be taken into account," after which the participants will participate according to the protocol. If necessary, proper further examinations and treatments will be provided, and the participants will be excluded from the study.

Study Procedure

The study procedure is outlined in Figure 1. All participants will complete the study questionnaires before the fMRI, 3 months after completing the IET, and 12 months after the fMRI. Questionnaires will be presented in paper form. Post-IET questionnaires will be sent to participants by paper mail. Questionnaires will be pseudonymized.

Figure 1. The study procedure. fMRI: functional magnetic resonance imaging; IET: interoceptive exposure technique; LBP: low back pain; MRI: magnetic resonance imaging.



Participants at risk for LBP chronification will be classified and categorized within 48 hours after fMRI. High-risk participants will be further pseudo-randomized into the intervention (IET) or control group (A), whereas low-risk participants will form the treatment-as-usual group (B). Participants will be provided with group-specific instructions on the remaining study procedures by email and telephone. Participants in the intervention group will begin practicing the IET within a week after neuroimaging.

Study Setting

The IET to be used in this study is a modified version of the IET used by Flink et al [31]. The original Swedish version used in the original study was translated into Finnish with small adjustments to the IET without departing from the structure and scope of the original exercise. At the beginning of the study procedure, the participants will be given brief information about the IET. The participants will access the IET through a web-based platform secured by a personal password and a username. The platform can be accessed on a mobile phone or a home computer with internet access. The participants will then be told to perform the 8 minutes and 26 seconds–long IET exercise 3 times a week (Monday, Wednesday, and Friday) in as serene a setting as possible. During the IET, the participants will be asked to relax and calmly focus their attention on the sensation of pain. They will be told to focus on the pain with an open and nonjudgmental attitude and to feel the pain as much as possible without trying to change it or block it. If their attention wanders from the pain, they will be asked to return their focus to the pain sensation. The web-based exercise platform will keep track of the participant's activity. Platform visits and the time spent committing to the IET will be recorded. In this way, the research team can contact the participant if he or she is not logging on to the platform or if the IET is not carried out completely. The participant will be reached by phone to investigate the problem with attendance. If the participant misses 3 consecutive training sessions (ie, 1 week's training), he or she will be excluded from the study. The IET intervention is designed to take 12 weeks. The IET exercise (in Finnish) is presented in Multimedia Appendix 1.

Outcome Assessment and Measurements

The questionnaires used in the study will address conditions of pain experience and psychological distress. All measures are standardized and commonly used in pain research.

For all visits, participants will complete the short form of the Finnish version of the McGill Pain Questionnaire (MPQ), abbreviated as the FPQ [32]. The main component of the MPQ consists of 12 sensory and 4 affective descriptors, which are used to compute the sensory and affective scores, respectively. Radiculopathy scores are quantified from pain locations, which patients shade in with pencil on the MPQ form 15. Depression scores are assessed using the BDI-II [27]. All questionnaires will be given on the same day before brain scanning. The questionnaires are presented in Textbox 1.

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Textbox 1. Behavioral measures and corresponding questionnaires to be used in the study, with abbreviations in brackets.

Measures and corresponding questionnaires

- Pain intensity: Numeric Rating Scale (NRS) [26]
- Pain experience: the Finnish Version of the McGill Pain Questionnaire (FPQ) [32]
- Pain-related anxiety: Pain Anxiety Symptoms Scale (PASS-20) [33]
- Anxiety symptoms: State-Trait Anxiety Inventory (STAI) [34]
- Fear of movement: Tampa Scale of Kinesiophobia (TSK) [35]
- Depression: Beck Depression Inventory-II (BDI-II) [27]

Pain intensity will be estimated with the numeric rating scale (NRS), with a pain intensity ranging from "no pain" to "worst pain" (1-10) according to the conventional use of the NRS [26]. The subjective unpleasantness will be measured analogously on the NRS, ranging from "not unpleasant" to "extremely unpleasant." The primary outcome will be pain intensity on the NRS. Secondary outcomes will be pain experience [32], pain-related anxiety [33], state and trait anxiety [34], fear of movement [35], and depressive symptoms [27] (Textbox 1).

Data Collection and Statistical Analysis

Data will be obtained before the fMRI, 3 months after completing the IET, and 12 months after the fMRI. Data will be compared between the groups (IET vs treatment as usual in control groups A and B). The data will be analyzed using a repeated-measures analysis (mixed models).

Ethics Approval

This study has obtained ethical approval from the ethical committee at Helsinki and Uusimaa Health District (HUS/2435/2017). Good research ethics practices will be maintained in the study according to the Declaration of Helsinki.

There will be no inclusion of vulnerable groups (ie, children, prisoners, individuals with mental disorders). No participant reimbursement will be provided to prevent economic factors from impacting the recruitment process. No specific physical health risks can be seen to be involved in participating in the study. Participants will be physically checked with a handheld metal detector before entering the scanner. However, the procedure could cause slight stress for participants and might even provoke pain. The fMRI and MRI procedures could cause some distress for some participants. The IET training might test participants' motivation.

Anonymity and confidentiality will be ensured by using numerical codes for the participants. Only the research group members will know the participants' names. Data protection and storage security will be ensured by storing the participant information and questionnaires in a locked cabinet at Orton. Data will be stored behind electronic passwords securely on Orton's server.

For the duration of the fMRI measurements, all participants will have patient insurance against possible injuries.

Results

This research project will consist of a pilot randomized controlled trial in which 2 novel methods will be combined: a biomarker as the inclusion criterion and an IET as the intervention. The comparative study design enables evaluation of the efficacy of the IET as well as replication of the biomarker's validity as a possible clinical screening method. This study will yield valuable new information about both the neural processes driving pain to chronicity and a specific and promising intervention to modulate that process.

As of September 2023, we have not enrolled any participants.

Discussion

Principal Findings

The principal finding will be pain intensity. Secondary findings will be pain experience, pain-related anxiety, state and trait anxiety, fear of movement, and depressive symptoms.

Strengths and Limitations

This study will combine neuroscience and psychology in a novel and innovative way. The study's strengths will be precise diagnostic criteria, objective selection criteria with measurement methods, and behavioral metrics that have been found to be reliable. Furthermore, the comparative design with 3 groups can be considered a strength.

The small number of participants in the pilot phase can be considered a weakness, as can the completion of the IET at home without objective supervision, which could become a possible source of error.

Study Significance and Feasibility

The first step of this project was to write a systematic review. It was registered with PROSPERO (Prospective Register of Systematic Reviews; CRD42019053580) and published in 2022 [25]. This study has also been registered at ClinicalTrials.gov (NCT05450263). We have (adjusted to our research design) followed the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials)-2013 recommendations for clinical trial protocols and related documents [36].

This study will yield valuable new information about both the neural processes driving pain to chronicity and a specific and promising intervention to modulate that process. In addition,

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this study will offer new insight into the use of mindfulness meditation in pain management. If found to be useful, the IET would offer a cost-effective and reasonable way to develop treatment for back pain. The potential benefits are improved pain management and quality of life for the individual patient, with the addition of a potentially useful functional pain management method at the societal level.

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Data Availability

The data sets generated during and/or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

All authors made substantial contributions to the conception or design of the study; the acquisition, analysis, or interpretation of data for the study; the drafting or critical revision of the manuscript for important intellectual content; final approval of the version to be published; and agreement to be accountable for all aspects of the study in ensuring that questions related to the accuracy or integrity of any part of the study are appropriately investigated and resolved.

Conflicts of Interest

None declared.

Multimedia Appendix 1
The interoceptive exposure training (IET) in Finnish.
[PDF File (Adobe PDF File), 19 KB - resprot_v12i1e45701_app1.pdf]

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Abbreviations

BDI-II: Beck Depression Inventory-II
DARTEL: diffeomorphic anatomical registration through exponentiated lie
fMRI: functional magnetic resonance imaging
FPQ: Finnish version of the McGill Pain Questionnaire
HUS: Helsinki and Uusimaa Health District
IET: interoceptive exposure technique
LBP: low back pain
mPFC: medial prefrontal cortex
MPQ: McGill Pain Questionnaire
NAc: nucleus accumbens
NRS: numeric rating scale
PROSPERO: Prospective Register of Systematic Reviews
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
TE: time to echo
TR: repetition time

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Protocol

Model Clinic to Increase Preventive Screenings Among Patients With Physical Disabilities: Protocol for a Mixed Methods Intervention Pilot Study

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Abstract

Background: People with physical disabilities often experience premature multimorbidity and adverse health events. A tailored primary care approach for this vulnerable population that also accounts for social and functional risk factors could promote healthier aging and more equitable health care.

Objective: This project will evaluate the implementation of a health program designed for people with physical disabilities. The proposed evaluation result is to generate the first best-practice protocol focused specifically on developing primary care to help reduce preventable causes of morbidity and improve functioning among people with physical disabilities.

Methods: We will design and implement a pilot health program for people with physical disabilities at a primary care clinic within Michigan Medicine. The health program for people with physical disabilities will be an integrated intervention involving a tailored best practice alert designed to prompt family medicine providers to screen and monitor for common, preventable health conditions. The program will also collect social and functional status information to determine the patient's need for further care coordination and support. Adult participants from this clinic with identified physical disabilities will be targeted for potential enrollment. To create a quasi-experimental setting, a separate departmental clinic will serve as a control site for comparison purposes. A quantitative analysis to estimate the treatment effect of implementing this health program will be conducted using a difference-in-differences approach. Outcomes of interest will include the use of preventative services (eg, hemoglobin A_{1c} for diabetes screening), social work assistance, and emergency and hospital services. These data will be extracted from electronic health records. Time-invariant covariates, particularly sociodemographic covariates, will be included in the models. A qualitative analysis of patient and health care provider interviews will also be completed to assess the effect of the health program. Patient Health Questionnaire-9 and Generalized Anxiety Disorder 7-item scores will be assessed to both screen for depression and anxiety as well as explore program impacts related to addressing health and functioning needs related to physical disabilities in a primary care setting. These will be summarized through descriptive analyses.

Results: This study was funded in September 2018, data collection started in September 2021, and data collection is expected to be concluded in September 2023.

Conclusions: This study is a mixed methods evaluation of the effectiveness of an integrated health program designed for people with physical disabilities, based on a quasi-experimental comparison between an intervention and a control clinic site. The intervention will be considered successful if it leads to improvements in greater use of screening and monitoring for preventable health conditions, increased social worker referrals to assist with health and functioning needs, and improvements in emergency and hospital-based services. The findings will help inform best practices for people with physical disabilities in a primary care setting.

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KEYWORDS

clinical decision support; electronic health records; mixed methods; people with physical disabilities; primary care

Introduction

People with disabilities make up approximately 26% (54 million) of the adult population in the United States [1]. Among this population, the most common disabilities are those that impact mobility [1]. Premature multimorbidity and adverse health events are more common among people with physical disabilities compared with the population norm [2-5]. Research shows that healthy aging is strongly influenced by patients' social, behavioral, and environmental variables [6-8]. However, patients' information on social and functional status factors is not systematically collected in health care, and therefore, these factors are not considered in medical decision-making aiming to promote healthy aging among this priority population.

There is evidence that primary care generates the largest ability to reduce illness and premature death, as well as providing more equitable health care in populations [9], yet little is known on how this can be achieved effectively for people with physical disabilities [10,11]. The Centers for Disease Control and Prevention (CDC), following the Forman-Hoffman et al [12] report, has provided suggested recommendations to address the existing gaps for individuals with disabilities. These actions include (1) providing a system in which people with physical disabilities at risk for adverse health events, including premature death, can be identified to proactively provide the care and social services that may be needed; (2) tailoring health care services, including health education and prevention, for people with physical disabilities whose needs differ from people without a disability [9]; (3) improving the inclusion of behavioral health interventions for people with physical disabilities; and (4) providing care management for people with physical disabilities by health care staff trained to work with this population [12].

This study aims to explore how care for people with physical disabilities can be fostered and improved through the implementation and comprehensive evaluation of a pilot integrated health program, which will include social support services. To do this, we will (1) design, pilot, and evaluate an accessible, integrated health program for people with physical disabilities at a primary care clinic within Michigan Medicine (ie, Briarwood Family Medicine), scalable for other integrated health centers, and (2) assess how the systematic collection of social and functional status information and use of this information by care managers may reduce adverse health events and improve the social and functional status of people with physical disabilities. Ultimately, our goal is to develop a protocol that provides guidance to other primary care clinics in need of improving the delivery of health care to people with physical disabilities. To our knowledge, this would be the first tailored best practice advisory (BPA) and health care-initiated social intervention designed for people with physical disabilities.

Methods

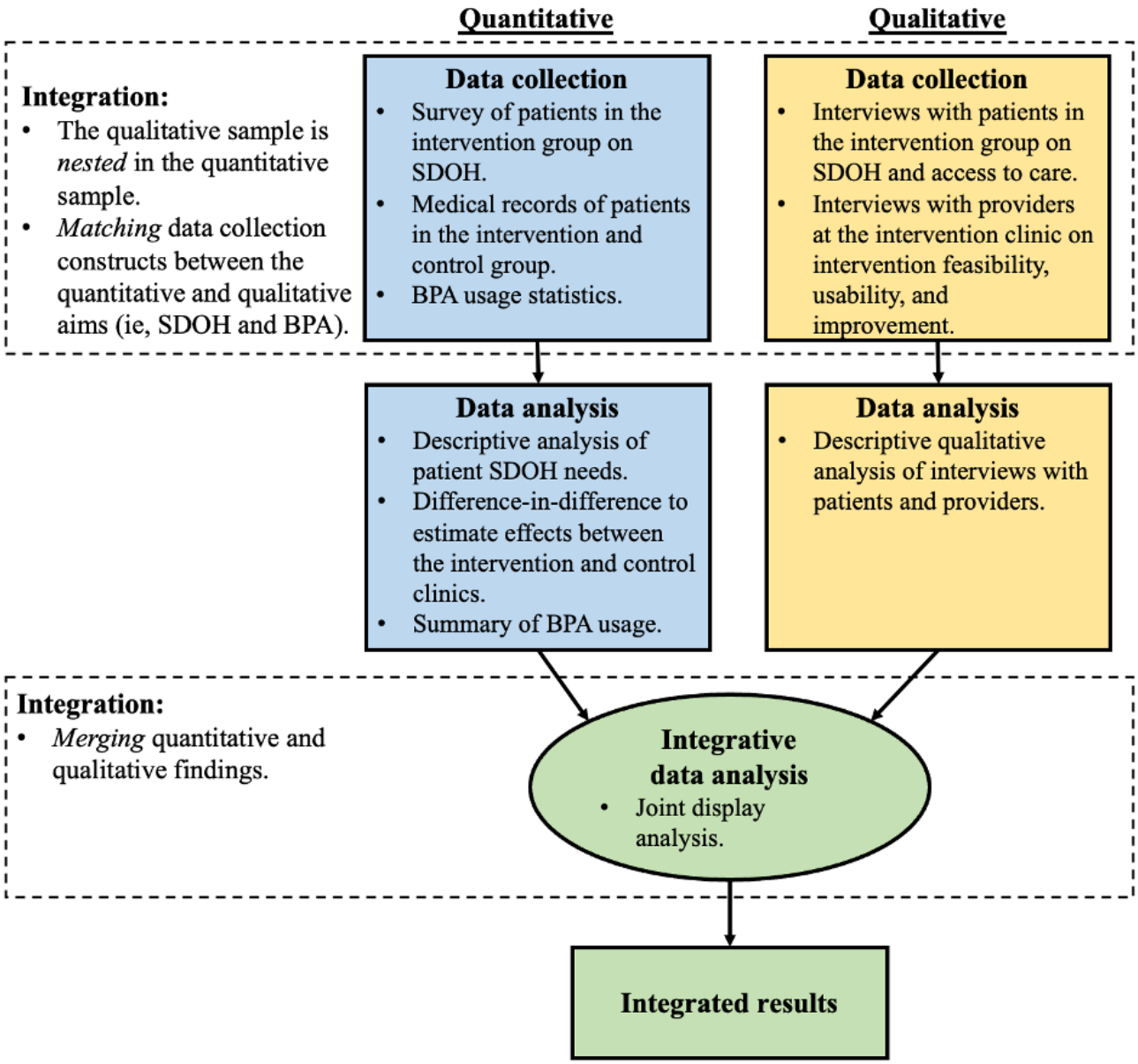
Study Design

Overview

This is a pilot intervention study using a convergent mixed methods design. For the quantitative analysis, we will use a quasi-experimental approach, enrolling participants from an intervention site into an integrated health program and using a control site with patients not enrolled in such a program for comparison purposes. Both the intervention and control sites will be separate ambulatory care clinics managed by Michigan Medicine's Department of Family Medicine. Both sites are located in Southeast Michigan. We will use qualitative methods to better understand social determinants of health among the patient cohort, as well as the perspectives of health care providers on the feasibility and usability of the proposed intervention. An overview of the study design is shown in Figure 1.

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Figure 1. Overview of the pilot intervention study of an integrated care clinic for patients with physical disabilities. BPA: best practice advisory; SDOH: social determinants of health.



Intervention

The intervention is based on the paradigm of integrated health programs, which are designed to improve collaboration among primary care providers, social workers, and behavioral health specialists. The co-location of these health professionals at the same clinic allows for higher levels of patient care collaboration; for example, through primary care providers regularly having regular consultations with clinical social workers. This collaboration parallels institution-wide efforts at Michigan Medicine to improve service delivery and integrate medical, social, and behavioral health in a single clinic. This model has been successfully implemented to address significant behavioral health gaps for deaf and hard-of-hearing patients in the Michigan Medicine Family Medicine clinics [13,14].

The intervention has multiple components: (1) development and implementation of an electronic health record (EHR)–based alert to improve preventive screenings among people with physical disabilities; (2) training of providers on how to improve care for people with physical disabilities; and (3) inclusion of a specialized social worker with disability health training.

Clinical Decision Support Alert

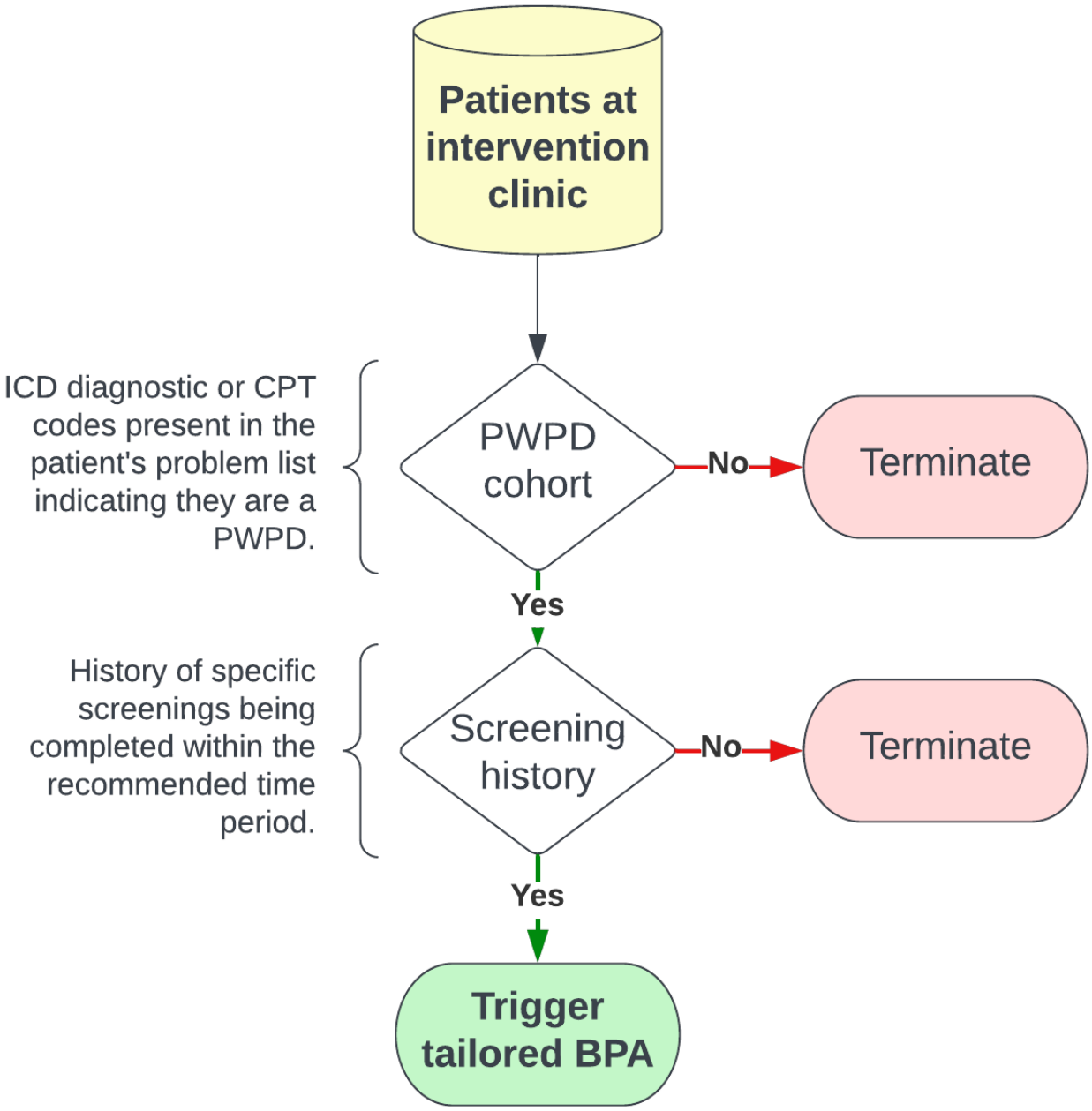
We will use tailored BPAs in the EHR to provide clinical decision support to primary care providers of people with physical disabilities. This was based on a previously completed study using BPA that increased the rate of hearing screenings and audiology referrals at primary care clinics [15]. BPAs are a type of clinical decision support tool available in Michigan Medicine's Epic medical record software called MiChart. BPAs are activated in a patient's medical record when a patient meets eligibility criteria based on factors including diagnostic codes, procedure codes, quality indicators, or laboratory results. BPAs can be used by health care providers to more efficiently order or be reminded about screenings or immunizations. These tools can also aid in documenting medical decision-making. When this BPA is activated, the primary care provider will be

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prompted to engage the patient to determine the applicability of the BPA by selecting one of the recommended actions or dismissing the alert.

The BPA for this intervention is designed to prompt preventive and screening services for which there are well-documented disparities for people with physical disabilities [16-18]: hemoglobin A_{1c}, bone density DEXA scan, lipid panel, laboratory panels (eg, basic metabolic panel), renal ultrasound, referral to a nutritionist, and referral to a specialized social worker with disability health training. A description of the BPA trigger conditions is available in Figure 2.

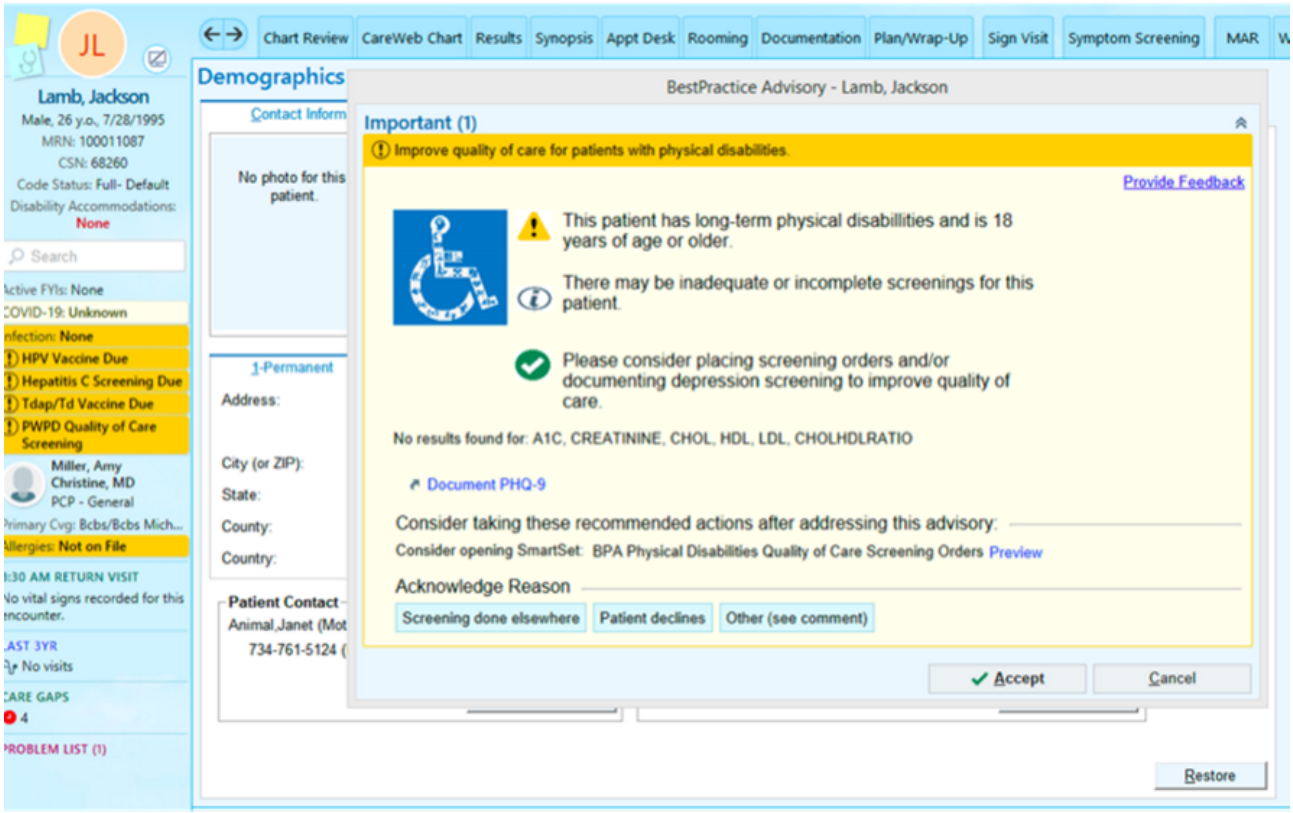
Figure 2. Flowchart of best practice advisory (BPA) activation triggers to improve preventive care for people with physical disabilities (PWPD). CPT: Current Procedural Terminology; ICD: International Classification of Disease.



When the BPA is activated for a specific patient, the alert will appear in their medical record in a yellow alert box on the main screen, along with the patient summary (left column; Figure 3). This alert remains active until it is acted on or dismissed by the provider. Available actions are “act on any of the suggested alerts,” “dismiss with an explanation” (eg, patient declines or already completed elsewhere), and “ignore.” Based on the provider’s recommendation and discussion with the patient, the provider can accept the SmartSet proposed by the BPA. The BPA will be pilot-tested by an Epic programming analyst with Michigan Medicine, TGJ, and MM before activation.

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Figure 3. Screenshot of the best practice advisory to improve preventive care for people with physical disabilities (mock patient).



Provider Training and Communication

Primary care providers at the intervention clinic will be initially trained in intervention design to help reduce preventable causes of morbidity and improve functioning among people with physical disabilities. This training will be done before the implementation of the intervention and will be led by a family medicine clinician-scientist who is an expert in disability health. In addition, throughout the intervention, the research team will meet with the clinic director and other providers to communicate feedback and updates about the intervention.

Social Worker

Social work theory posits that an individual's health may be influenced by organic processes as well as by psychosocial factors in the environment [19]. Therefore, social workers at Michigan Medicine have historically been well integrated with clinics [14], providing case management services, advocacy, care management for maintenance of chronic health conditions, psychotherapy, and additional social support. The social worker for this intervention will work closely with the intervention clinic's primary care providers to provide additional support in addressing the health, behavioral, functional, and social needs of people with physical disabilities. Patients without any current identified needs will be monitored for any changes with annual BPA prompts.

Patients to be contacted by the social worker will be identified in two ways. Survey participants will complete the seven-item Generalized Anxiety Disorder Scale (GAD-7) and the Patient Health Questionnaire-9 (PHQ-9; Multimedia Appendix 1). The social worker will contact those who indicate moderate to severe anxiety or depression and assess the patient's need for mental health resources and psychotherapy. A MiChart referral to social work will be created and prepopulated with the following common reasons for referral: caregiver support; durable medical equipment and community referrals; grief and loss; guardianship and advance directives; home modifications; long-term planning; mental health and substance abuse concerns; safety concerns; violence and abuse; and other (with a comment field). Social work interventions will mostly be completed by phone.

Patient Cohort

People with physical disabilities will be identified using the International Classification of Disease, Ninth Revision (ICD-9) and International Classification of Disease, Tenth Revision (ICD-10) diagnostic and procedure codes from patients' problem lists in MiChart (Multimedia Appendix 2). The patient cohort at the intervention clinic will be patients who are identified as people with physical disabilities and who are patients at the intervention clinic (Briarwood Family Medicine). To create a quasi-experimental setting for our intervention, another primary care clinic in the same department will serve as a control clinic (Dexter Family Medicine).

Eligibility Criteria

All patients with identified physical disabilities, aged 18 years and older, will trigger the BPA. Using conservative estimates (eg, ICD-9 and ICD-10 codes with strongly associated physical disabilities in Multimedia Appendix 2), we identified 284 patients who were seen in the past 12 months before BPA implementation at the intervention clinic. The characteristics of the patients that were seen in the past 12 months at the intervention clinic were 166 (58.4%) female, 51 (18%) Black,

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57 (20.1%) Medicaid insured, and 137 (48.2%) Medicare insured. A similar number of people with physical disabilities is anticipated to be identified in the control clinic.

Data Sources

Overview

This study will use multiple quantitative and qualitative data sources. The alignment of variables and constructs between quantitative and qualitative aims is provided in Textbox 1.

Textbox 1. Quantitative and qualitative data sources and related variables and constructs.

Michigan Medicine electronic health record

- General patient demographics
- Best practice advisory usage

Patient questionnaire

- General patient demographics
- Social needs
- Activities of daily living
- Depression and anxiety

Patient in-depth interviews

- General facilitators and barriers to accessing primary care
- Patient-provider communication
- Social needs

Provider in-depth interviews

- Implementation factors related to using the best practice advisory

Michigan Medicine Electric Medical Record (MiChart)

We will download structured clinical data, patient demographics, health care visits, diagnoses, procedures, laboratory orders, and results using the data warehouse at Michigan Medicine. We will also be able to capture the specific use of the BPAs for each patient. Textbox 2 summarizes the important domains that we will use in our analyses. Further, we will use an existing search algorithm [20] in the Electronic Medical Record Search Engine [21], to work with free-text and unstructured clinical documents in electronic medical records in order to identify influential social factors.

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Textbox 2. Patient-related domains and variables in structured electronic medical record.

Sociodemographic

- Age
- Race and ethnicity
- Insurance and payor category
- Disadvantage and affluence index (derived from National Neighborhood Data Archive [21])

Most common comorbidities

- Driven based on International Classification of Diseases (Ninth Revision before October 2015 or Tenth Revision after October 2015) coding algorithms for Elixhauser comorbidities (29 conditions) from inpatient, outpatient, or emergency visits during the previous 12 months

Medication count

- 1-5
- 6-10
- 11-20
- >20

Use of agents

- Antithrombics
- Chemotherapeutics
- Hypoglycemics
- Insulins
- Narcotics
- Opioids, etc

Abnormal biomarkers

- High-density lipoprotein
- Hemoglobin A_{1c}
- Lactate dehydrogenase, etc

Patient Questionnaire

A short questionnaire (“Partners in Health”) will be prospectively collected from people with physical disabilities who meet our inclusion criteria at the time of the BPA implementation. The collected data are related to basic social needs (eg, ability to pay and social and family support; Multimedia Appendix 1).

Patient In-Depth Interviews

To understand barriers and facilitators to accessing primary health care among people with physical disabilities, we will recruit people with physical disabilities who complete the aforementioned patient questionnaire and consent to being recontacted for a one-hour interview. The interview will be semistructured, guided by an interview guide (Multimedia Appendix 3), and implemented by the intervention social worker (LC) or mixed methods methodologist (TGJ).

Provider In-Depth Interviews

Provider interviews will be conducted to understand usability, feasibility, and implementation constructs related to the use of the BPA alert. The interview guide (Multimedia Appendix 4) is informed by the Consolidated Framework of Implementation Research (CFIR) [22]. These interviews will be conducted by MM, a family medicine clinician-scientist, to aid in establishing rapport and trust.

Quantitative Analysis

Preliminary Analyses

Before being analyzed, the data will be explored to identify any missingness, which will be handled appropriately (eg, using imputation techniques or keeping complete cases only), based on its extent, impact on the sample size, and missing data pattern.

The characteristics of patients in the intervention group will be summarized using descriptive statistics. We will compare the characteristics of the intervention clinic with those of the control clinic and test for relevant associations using Student's *t* test or Wilcoxon signed-rank test for continuous variables and chi-square or Fisher exact tests for categorical variables as appropriate.

If this preliminary exploration of the full sample shows a lack of balance between the groups, we will apply inverse propensity

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weighting to calculate a weight defined as the inverse probability of observing the given sample [23-25].

To verify the comparability of the intervention and the control sites, which is a key requirement for our quantitative intervention effectiveness analysis, we will also analyze data on the main outcomes of interest dating back to three years before the launch of the intervention.

In addition, preliminary analyses will also include summarizing the patient questionnaire data, mental health scores (GAD-7 and PHQ-9 overall scores), and BPA usage data. The questionnaire data will be described and may be merged with EHRs to be further used in qualitative analyses. The BPA usage data analysis will be used to investigate the (1) provider type acting on the BPA, (2) type of appointment when the BPA is firing, and (3) what actions were taken with respect to the BPA order.

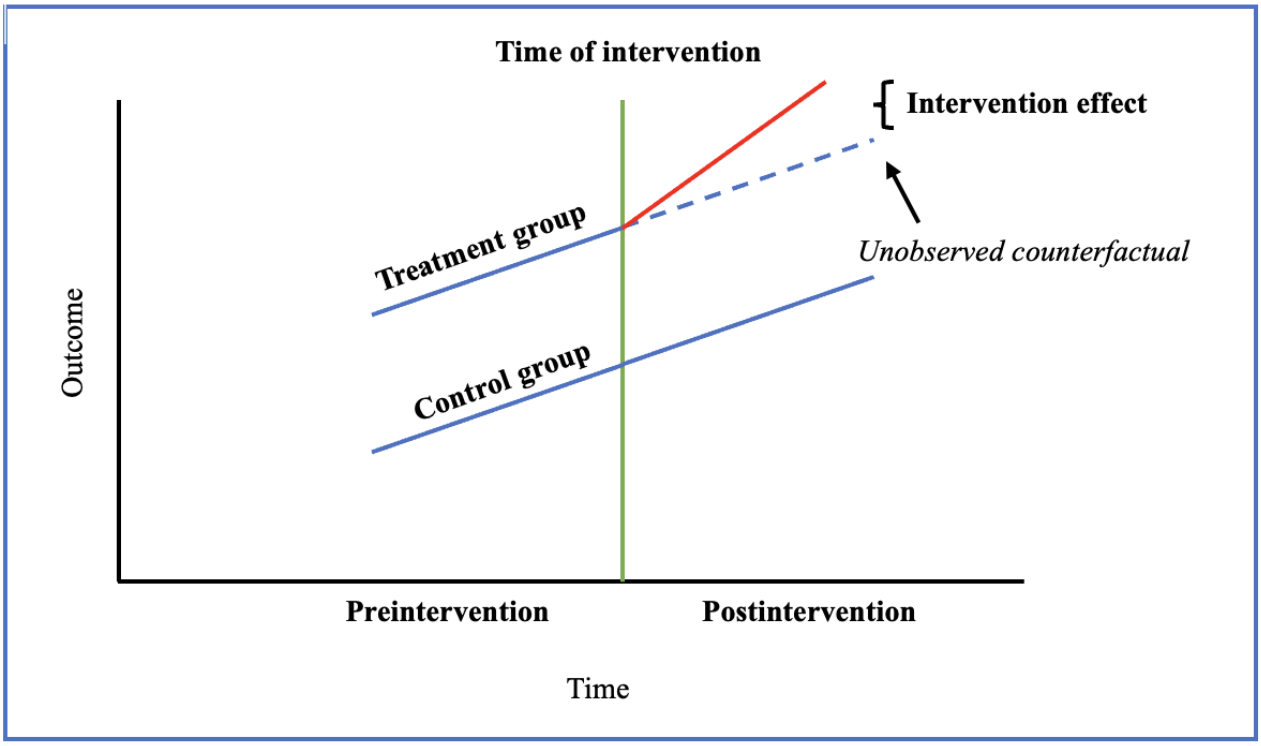
Difference-in-Differences (DD) Intervention Effectiveness Analysis

The primary health–based outcomes assessed will be used for preventative services (eg, diabetes and lipid screening rates and hemoglobin A_{1c}) and the number of emergency room or hospital visits. The primary behavioral outcomes will be based on the changes in the PHQ-9 and GAD-7 overall scores before and after the intervention (after one month).

In order to evaluate the effect of the integrated health program on these outcomes, we model these outcomes using a DD approach [26]. DD is a statistical technique applied to longitudinal data that attempts to find a causal effect between an intervention and a control group in a quasi-experimental setting before and after a certain intervention is implemented. It assumes that, if the groups were similar based on observable characteristics and preintervention trends, any differences between them with respect to the outcomes of interest can be attributed to the intervention itself, rather than to systematic, preexisting differences. The average change in the outcome in each group is compared to estimate an average intervention effect for the intervention group (known as the average treatment effect for the treated).

The key assumption DD relies on is, thus, the presence of parallel trends; in the absence of the intervention, the treatment and control groups would continue to follow analogous trends with respect to the outcomes of interest. The postintervention, parallel trend in the intervention group would be an unobserved counterfactual path. Additionally, in the context of DD, particular attention to meeting the stable unit treatment value assumption is also required; the composition of treatment and control groups should remain stable over time to avoid spillover effects [9]. Figure 4 provides a simple graphical representation of the intervention effect and the parallel trend assumption.

Figure 4. Graphical representation of difference-in-differences approach's intervention effect and parallel trend assumption.



In the simple case of 2 time periods (1 pre- and 1 postintervention period), DD involves building a regression model with the following key predictors: a binary time covariate (before and after the intervention), a binary intervention covariate (treatment and control group), an interaction term between the 2 variables (ie, the DD estimator), and any time-varying covariates that may affect the outcome's trend over the observed time period without being themselves affected

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by the intervention. Table S1 in Multimedia Appendix 5 outlines the list of outcomes and related models.

All statistical analyses will be performed using the software RStudio [27].

Qualitative Data Analysis

Qualitative data will be collected from the semistructured interviews with people with physical disabilities and primary care providers at the intervention clinic. Interviews will be audio-recorded to facilitate transcription by a Health Insurance Portability and Accountability Act (HIPAA)–compliant transcription service. Transcriptions will be imported into MAXQDA 2022 (Verbi Software) to conduct qualitative analysis.

The research team will code patient and provider interviews separately, as the codes that are developed will be different; provider interview questions are based on an implementation framework, while the patient interview questions are focused on quality of life and clinic access. The overarching qualitative strategy that will be used in this study is the qualitative description, as described by Sandelowski [28,29]. In qualitative description, the researchers seek to keep the analysis closely grounded in the participants' words while also using theory and conceptual models as appropriate.

A preliminary codebook will be developed through multiple members of the research team open-coding the same transcript from each group and meeting to discuss coding decisions. This process encourages a collaborative process of developing codes and code definitions across multiple coders who will independently code the transcripts. In addition, transcripts from the provider group will be coded using codes aligned with the CFIR [22]. Additional codes may be added to the codebook as the analysis progresses; in this case, the qualitative analysis team will meet to discuss the appropriateness of developing a new code, the name of the code, and its definition. Previous transcripts will be rereviewed to ensure the same codebook is applied to each transcript. Throughout the analysis, coders will be encouraged to memo transcripts with overarching thoughts, theme development, and other analytic insights [30].

Themes will be developed after the coding is complete. The research team will review the developed memos, code segments, and code relations, in addition to "focusing strategies" as described by Saldana [30]. For example, we will use the "touch test" to ensure that the developed themes are conceptually relevant and not just a description of a code.

Ethical Considerations

This study was approved by the University of Michigan institutional review board (HUM00189835). The project was given an exemption from the institutional review board because the information obtained from the survey is recorded in such a manner that the identity of the survey participants cannot readily be ascertained. The consent form included a statement that deidentified participant information may be shared in publications or for research purposes. There was a hybrid informed consent process. Paper consent forms and surveys were sent to all potential participants, which could be returned through an included envelope. Participants were also given the option to complete an electronic consent form and survey through Research Electronic Data Capture (REDCap). An incentive of US $2 cash was included with the mailed paper survey. Interview participants were given a gift card worth US $10 for their participation.

Results

The BPA was activated in the intervention clinic's EHR on September 16, 2021. The research team has had monthly meetings with the clinical director and the Department of Family Medicine's Director of Medical Informatics since implementation. The intervention patient cohort was sent the survey on May 5, 2022, and data collection for this source was completed on November 1, 2022.

Questionnaire data, including anxiety and depression overall scores (ie, GAD-7 and PHQ-9), and basic needs access (ie, "Partners in Health"; Multimedia Appendix 1), as well as BPA usage data, will be explored through descriptive statistics in the fall of 2023. Preliminary analyses to test assumptions about the comparability of the intervention and the control clinics will be conducted in late 2023 using data from the EHR, provided by the Michigan Medicine Data Office for Clinical and Translational Research. Interviews with people with physical disabilities were completed in December 2022, and formal data analysis will begin in the fall of 2023. During the spring and summer of 2023, we will meet with health care providers at the intervention clinic to conduct the semistructured interviews.

The results from our quantitative and qualitative analyses will be combined using mixed methods integrative data analysis [31,32]. These integrated results will be used to advance knowledge of best practices in the area of primary care and well-being for people with physical disabilities and pave the way for a more comprehensive and equitable approach to care for people with physical disabilities. Our findings will be submitted for publication in peer-reviewed journals once the study is completed.

Discussion

Overview

The quantitative results from the primary aim of this study, which is to measure the effectiveness of a pilot model clinic designed for people with physical disabilities, will advance knowledge on best practices for caring for a population that is disenfranchised in health care. Supplementing the primary findings with the aid of qualitative methods, our secondary focus on social support will allow us to explore the full extent of the role that an integrative approach can have in improving the health and well-being of people with physical disabilities. The integration of different data points will help determine if the intervention can be successfully implemented into a primary care setting. Second, it will help inform whether the intervention leads to (1) an improved use of tailored screening and monitoring needed for this population; (2) an increased social worker referral to assist with health and functioning needs related to their physical disabilities; and (3) reduced preventable

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causes of morbidity and improved functioning among people with physical disabilities. Thus, the merit of a combined quantitative and qualitative approach in the particular context of researching and improving care for people with physical disabilities is that together these methodologies will allow us to explore both the measurable, physical impact of an integrated approach to care for people with physical disabilities and the less measurable, nuanced social, behavioral, and environmental factors, which are better captured in questionnaires and interview settings than chart abstraction.

The mixed methods findings of this study will be used to improve the proposed clinical model and identify further opportunities to develop a comprehensive protocol for primary care clinics to improve the care of people with physical disabilities. In line with previous literature observing the key impact of primary care and of people with physical disabilities' social, behavioral, and environmental factors on the health of people with physical disabilities [9], our uniquely integrated intervention has the potential to significantly advance care and preventive practices for people with physical disabilities. Integrated findings will also be used to improve the BPA. This protocol will also provide a framework for the actions recommended by the CDC to address the existing health care gaps for individuals with disabilities. The overarching clinical model, with recommended improvements, may be tested in future clinical trials.

Some of the major strengths that we anticipate for this study are the presence of a similar number of eligible patients with physical disabilities in the intervention and control sites, the sites being part of the same health group and based in the same geographic area, which facilitates comparisons and monitoring to prevent spillover effects, and the presence of all health professionals involved in the integrated health program within each site, which enables close collaboration during the implementation period.

Despite the considerable benefit of the knowledge gained from this study and the noted strengths, this study presents some possible limitations. DD, the main approach adopted to test intervention effectiveness, will allow us to estimate a causal effect only if its assumptions are satisfied. The assumptions that could represent the biggest threat to validity in our case are low between-group similarity, parallel trends preintervention, and stable group composition pre-post intervention (including, ideally, during the follow-up period). If required, we will attempt to address a lack of balance with respect to the covariates of interest through inverse propensity weighting and any potential failure to meet other DD assumptions by adopting alternative modeling methodologies.

In addition, the sample size in the qualitative aim is a potential risk. Adequate sample size, prolonged engagement, and participant trust are pivotal to ensuring the credibility of results [33]. To help address these factors, medical providers will be interviewed by a medical provider (MM), while interviews with patients will be conducted by a trained clinical social worker (LC) and a community-engaged, mixed methods research methodologist (TGJ).

Finally, because this is a pilot study, we are limiting its implementation to one intervention and one control site. While having more sites would provide us with a larger sample size and a stronger claim for external validity, trialing the intervention on a smaller, local scale will allow us to follow the program closely and develop it optimally, with the aim of expanding its scope in the future and working on a more extensive analysis.

Overall, this study will integrate findings from multiple data sources to best assess the feasibility and potential effectiveness of the proposed model clinic for primary care tailored to people with physical disabilities. Our findings will inform health care services for people with physical disabilities and lead to a more equitable paradigm with respect to primary care for people with physical disabilities.

Conclusions

Currently, there are no formal guidelines to ensure that people with physical disabilities, a particularly vulnerable population, receive appropriate, tailored care for their needs and susceptibility to premature multimorbidity and adverse health events. This is aggravated by the lack of available data on the social and functional context (known factors that contribute to healthy aging) of people with physical disabilities. Research that links all these aspects and tests effective solutions that can be feasibly scaled is crucial to changing this and establishing best practices. The results and protocol generated from this quasi-experimental study aim at achieving this in a robust manner, providing a contribution to the literature as well as making an impact on the national health system.

Acknowledgments

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Data Availability

The data sets currently being generated or analyzed during this study will first be curated and anonymized through the assistance of the data archive staff at the University of Michigan's Inter-university Consortium for Political and Social Research. Once this is completed, this will be made publicly available.

Authors' Contributions

BP contributed to the methodology, software, validation, visualization, and writing. TGJ contributed to the investigation, methodology, and writing. EM and MM contributed to the conceptualization, methodology, and writing. LC, AS, and RH contributed to the writing. All contributed to the critical revision of the paper and the final approval of the submitted version.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Patient Questionnaire.
[DOCX File , 71 KB - resprot_v12i1e50105_app1.docx]

Multimedia Appendix 2
Diagnostic and Procedure Codes to Identify Patient Cohort.
[DOCX File , 14 KB - resprot_v12i1e50105_app2.docx]

Multimedia Appendix 3
Patients with Physical Disabilities Interview Guide.
[DOCX File , 17 KB - resprot_v12i1e50105_app3.docx]

Multimedia Appendix 4
Provider Interview Questions.
[DOCX File , 14 KB - resprot_v12i1e50105_app4.docx]

Multimedia Appendix 5
Outcomes and models for the intervention effectiveness analysis.
[DOCX File , 15 KB - resprot_v12i1e50105_app5.docx]

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Abbreviations

BPA: best practice advisory
CDC: Centers for Disease Control and Prevention

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CFIR: Consolidated Framework for Implementation Research
DD: difference-in-differences
EHR: electronic health record
GAD-7: 7-item Generalized Anxiety Disorder Scale
HIPAA: Health Insurance Portability and Accountability Act
ICD-10: International Classification of Disease, Tenth Revision
ICD-9: International Classification of Disease, Ninth Revision
PHQ-9: Patient Health Questionnaire-9
REDCap: Research Electronic Data Capture

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Protocol

A Silver Fluoride Intervention to Improve Oral Health Trajectories of Young Indigenous Australians: Protocol for a Cluster Randomized Controlled Trial

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Abstract

Background: Indigenous Australian children and adolescents experience profound levels of preventable dental disease. The application of silver fluoride (AgF) to active dental caries is a noninvasive alternative to traditional dental treatment approaches. There is particular utility among Indigenous children and young people with dental fear, who may not have access to timely or culturally safe dental service provisions.

Objective: The aims of this study are to: (1) assess levels of active dental caries among Indigenous children and young people in 6 Australian states and territories; (2) determine if an AgF intervention reduces levels of active disease over 12-24 months; (3) measure the impact of improved oral health on social and emotional well-being (SEWB) and oral health-related quality of life; and (4) calculate the cost-effectiveness of implementing such an initiative.

Methods: The study will use a 2-arm, parallel cluster randomized controlled trial design. Approximately 1140 Indigenous children and youth aged between 2 and 18 years will be recruited. Each state or territory will have 2 clusters. The intervention group will receive the AgF intervention at the start of the study, with the delayed intervention group receiving the AgF intervention 12 months after study commencement. The primary outcome will be the arrest of active carious lesions, with arrested caries defined as nonpenetration by a dental probe. Secondary outcomes will include SEWB, oral health-related quality of life, and dental anxiety, with covariates including dental behaviors (brushing and dental visits). Effectiveness measures for the economic evaluation will include the number of children and young people managed in primary oral health care without the need for specialist referral, changes in SEWB, the numbers and types of treatments provided, and caries increments.

Results: Participant recruitment will commence in May 2023. The first results are expected to be submitted for publication 1 year after a 24-month follow-up.

Conclusions: Our findings have the potential to change the way in which active dental disease among Indigenous children and young people can be managed through the inclusion of specifically tailored AgF applications to improve dental health and SEWB delivered by Indigenous health care workers. Desired impacts include cost savings on expensive dental treatments; improved SEWB, nutrition, social, and learning outcomes; and improved quality of life for both children and young people and their caregivers and the broader Indigenous community. The AgF application could be easily implemented into the training program of Indigenous health workers and yield critical information in the management armamentarium of health and well-being recommendations for Australia's First Peoples.

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KEYWORDS

clinical trial; community; dental caries; Indigenous Australian; intervention; silver fluoride intervention

Introduction

Young Indigenous Australian Oral Health

Indigenous Australian children and adolescents experience profound levels of preventable dental disease [1]. These have an impact on Indigenous children's and young people's ability to eat, speak, socialize, and learn. It is a leading cause of child malnutrition, poor quality of life, and nonoptimal social and emotional well-being (SEWB) [2]. Trajectories of dental disease among Indigenous children and adolescents are increasing at a rate far greater than for non-Indigenous children and adolescents, with severe cases requiring care under a hospital-based general anesthetic [3]. Poor oral health in childhood is the leading cause of poor oral health in adulthood [4] and has associations with other systemic conditions, including diabetes, cardiovascular disease, and chronic kidney disease [5].

Dental Treatment Under General Anesthesia

Provision of dental care to young children can pose many challenges because of their emotional and physical development and lack of cooperation in the dental chair. The issues are multiplied for Indigenous children in rural and remote locations, where access to dental care is severely limited. Hospital-based treatment under general anesthesia is becoming an increasingly used mode of dental care for Indigenous children, with Australian Institute of Health and Welfare statistics showing that the rate of Indigenous Australian child admissions for dental treatment is twice that of non-Indigenous children [6]. However, dental treatment under general anesthesia does not prevent the occurrence of new dental decay, with children frequently readmitted for hospital-based dental general anesthesia after initial treatment [7]. Recent reports also suggest that oral rehabilitation under general anesthesia does little to alleviate dental fear or change noncooperative behavior and may, in fact, heighten these characteristics [8,9]. Moreover, comprehensive dental care under general anesthesia is not without risk, including the potential for long-term adverse neurodevelopmental effects [10-12]. Dental general anesthetics are extremely expensive for the taxpayer, the Australian health care system, and the community more broadly, and require considerable time and financial investments from carers (to transport the child to the hospital, stay overnight, ensure fasting before the operation, etc). The estimated mean cost of dental general anesthetics for Indigenous children is substantially higher than the cost of care for non-Indigenous children [10]. Treatment and preventive approaches that can be undertaken in Indigenous primary care settings to reduce the number of Indigenous children undergoing dental general anesthetics are thus urgently required.

Interventions to Improve Indigenous Children's Oral Health

In the past decade, there have been 4 published interventions aimed at reducing the burden of dental caries among Indigenous Australian children. Slade and colleagues [13] conducted a cluster randomized controlled trial of a dental health program that included the application of fluoride varnish to the teeth of Indigenous children aged between 18 and 47 months and dental education in 30 remote communities in the Northern territory. Although the study team reported reduced experience of dental disease among the intervention group compared with the control group, overall levels of dental disease at 2-year follow-up were extremely high, with 94% of children having experienced caries. Jamieson et al [14] conducted an early childhood caries intervention among Indigenous children and their families in South Australia, commencing during pregnancy and when children were aged 6, 12, and 18 months old. The intervention comprised dental care during pregnancy, fluoride varnish application to the teeth of children, anticipatory guidance, and motivational interviewing. At 5-year follow-up, children in the immediate intervention group had significantly less decay than those in the delayed intervention group (who received intervention at ages 2 to 3 years), but 47% of children still had experience of dental disease (Jamieson et al [14]). Smith et al [15] tested the effectiveness of a dental education program among young Indigenous children and their families from 8 Aboriginal Community Controlled Health Organizations (ACCHOs) in New South Wales. They reported that children in the education program had fewer dental caries at age 30 months than a comparator group drawn from the community, but the study did not follow standard randomization processes, meaning the conclusions are weakened (Smith et al [15]). Roberts-Thomson et al [16] used a silver fluoride (AgF) intervention among remote-dwelling Indigenous children and reported that children exposed to the intervention had less dental pain, dental extractions, use of antibiotics for dental infections, and fillings than children not exposed to the intervention. AgF was reportedly well accepted, easy to use, and at least as effective as conventional dental care (fillings and extractions). There were limitations, however, including a lack of robust randomization, only 2 trial sites included, only primary molar teeth included, a large loss to follow-up, and outcome measures not including specific assessments of dental caries or any patient-reported outcome measures such as oral health-related quality of life (OHRQoL), SEWB, and dental anxiety. As such, it has not been able to influence policy. A study that has more rigor (ie, is properly randomized), has a larger number of study sites (ie, more power in a statistical sense), uses explicit measures of dental caries (such as tooth surfaces with active dental decay), includes all present teeth, and comprehensively measures changes to SEWB, quality of life, and anxiety is urgently needed. Only then can we realistically expect policy

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changes, with the ultimate goal being to introduce the treatment for adults as well.

What is Silver Fluoride and How Does it Prevent Dental Caries?

AgF is a cariostatic agent clinically applied to manage active dental caries to prevent further progression of disease. The fluid comprises 2 key therapeutic ingredients: silver and fluoride. The fluoride helps replenish the fluoride reservoir in the enamel (the outermost surface of the tooth) to ensure a robust crystalline structure and to promote the remineralization of carious lesions. Formulations of AgF at 38% present the highest concentration of fluoride (44,800 ppm F) among the available remineralizing agents—nearly twice the concentration of professionally applied fluoride varnish (22,600 ppm F) [17]. The silver acts as an antimicrobial agent, altering the composition of cariogenic biofilm within the dentine tubules of treated lesions (Sulyanto et al [18]). In contact with decalcified dentine, AgF forms insoluble silver microwires that block dentine tubules and contribute to the increased hardness of tissues [19]. AgF also has an inhibitory effect on matrix metalloproteinases involved in the degradation of collagen [20]. Unlike other modes of treatment for active dental caries, AgF may be applied by nondentally qualified staff, meaning the cost-benefit ratio is substantial [21]. Although it has been around for at least fifty years, the uptake of AgF has been limited because, under the old formulation, the active ingredient (silver) stained decalcified soft dentine black. However, the application of a potassium iodide solution immediately after the placement of AgF has been reported to reduce staining and improve aesthetic outcomes [22,23]. The World Health Organization has recently included AgF on the list of essential medicines for children [24].

Why is Economic Evaluation Important?

In Australia, the Pharmaceutical Benefit Advisory Committee and Medical Services Advisory Committee require evidence of cost effectiveness for their reimbursement decisions. As such, it is important to conduct an economic evaluation for any health intervention to ensure financial sustainability in addition to clinical effectiveness. Moreover, to convince state and federal health services to sustain the funding of a new health intervention, it is imperative to prove the cost-effectiveness of the program. In the broader scientific community, there is now an expectation that clinical trials evaluating medicines and procedures should additionally assess the economic value of such interventions [25]. This expectation reflects both interest in economic information for new technologies and the regulatory and reimbursement regimes that require evidence of economic value along with clinical efficacy before implementing policy change. Nowhere is this more critical than in the field of young Indigenous Australian dental care. Indigenous Australians experience a disproportionate burden of disease, which translates into a 30% higher cost of health care delivery per capita for Indigenous populations compared to the general population [26]. Any demonstration of the cost-effectiveness of a dental care intervention over standard care is going to be of benefit to not only Indigenous children receiving the intervention but also to taxpayers contributing to the health care budget. To the best of our knowledge, there have been few evaluations of the cost-effectiveness of child dental caries interventions. The only one within the Indigenous child dental space was evaluated by Kularatna et al [27], with economic evaluations of dental health interventions per se being scarce.

Most ACCHOs in regional and remote locations in Australia are unable to provide dental care, yet they recognize that these services are critically important [28]. AgF can be applied by nondental personnel in home environments with minimal cost and equipment. This means AgF implementation, uptake, and cultural acceptability are superior to many other expensive health service models delivered by non-Indigenous staff.

The aims of this study are to (1) assess levels of active dental caries among Indigenous children and young people in 6 Australian states and territories; (2) determine if an AgF intervention reduces levels of active disease over 12-24 months; (3) measure the impact of improved oral health on SEWB and OHRQoL; and (4) calculate the cost-effectiveness of implementing such an initiative.

Methods

Overview

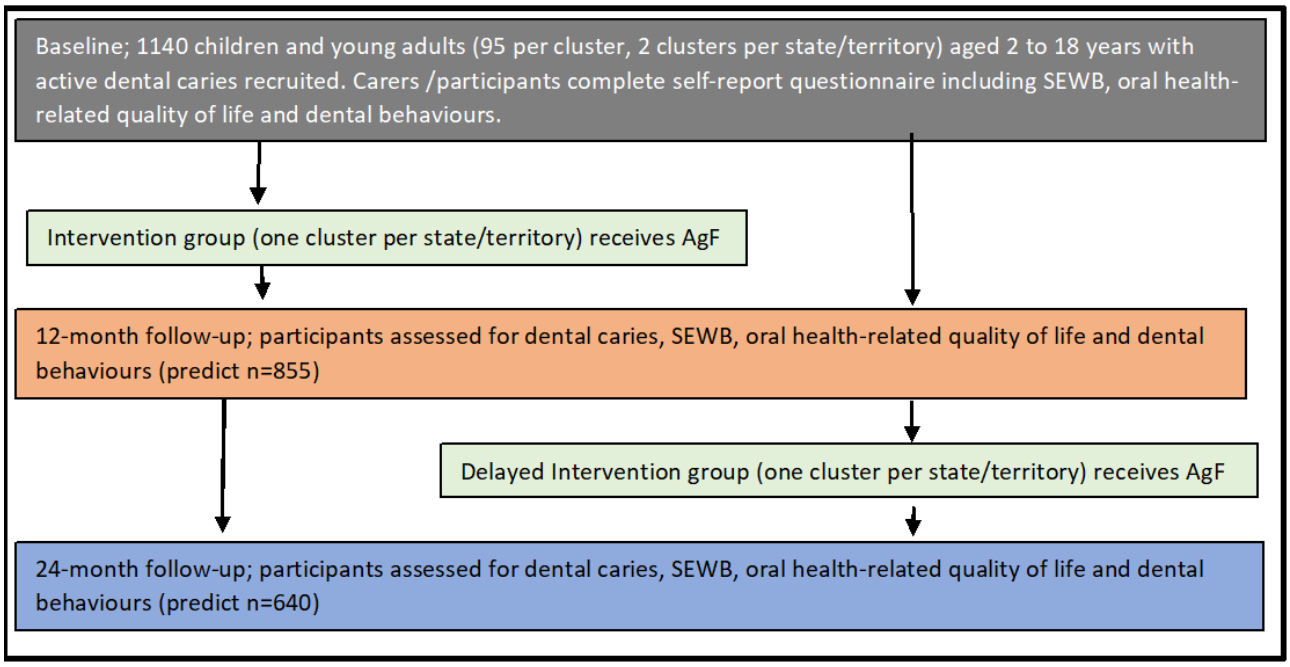
This is an Indigenous-led project conducted in partnership with ACCHOs across 6 states or territories in Australia. Meaningful and respectful engagement with ACCHOs ensures Indigenous self-determination and culturally appropriate research practices for the context of each Indigenous community throughout all stages of the study.

Study Design

The study will use a 2-arm, parallel, matched-paired cluster randomized controlled trial design with 2 study sites (clusters) in each partnering state and territory (Figure 1). The intervention group will receive the AgF intervention at the start of the study, with the delayed intervention group receiving the AgF intervention 12 months after study commencement.

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Figure 1. Study plan schema. AgF: silver fluoride; SEWB: social and emotional well-being.



Inclusion Criteria

Indigenous children and young adults aged between 2 and 18 years with active carious lesions (nonpulpally involved) in the primary or permanent dentition residing in selected study clusters will be eligible. Caregivers or participants who are unable to provide written informed consent, participants with a history of allergy to silver, or those presenting oral ulceration will be excluded. At the tooth level, symptomatic or pulpally involved teeth (pulp exposure, presence of an abscess or fistula, obvious discoloration indicative of pulp necrosis, or premature hypermobility) will be excluded from receiving the intervention.

Randomization

The randomization schedule will be developed by biostatisticians at the Australian Research Centre for Population Oral Health, who will not be involved in the trial, using a computer-generated block-randomized algorithm. The random allocation will be 1:1 per state and territory; that is, 1 cluster per state or territory will be randomly allocated as the intervention site, leaving the other cluster to be the delayed intervention site. Randomization will be done before baseline fieldwork. Field staff will have no access to the randomization algorithm, thus allowing the randomization process to be audited.

Participant Recruitment

We will adopt recruitment strategies that have been successfully applied in our wide body of research with Indigenous communities across Australia and that build upon the extensive community consultation processes that have already been undertaken for the proposed study. We will employ local Indigenous people as research assistants to continue to facilitate community engagement and participant recruitment. These research assistants will, in turn, be guided by senior Indigenous project officers. All participants at baseline will receive a clinical dental examination by a calibrated dental examiner, with participants aged 15 years or older or caregivers asked to complete a baseline questionnaire containing items on SEWB, oral health-related quality of life, dental behaviors, and sociodemographic characteristics. Participants in the delayed intervention cluster will be able to access standard dental care during the first 12 months of the study at their own volition.

Reimbursement for Time

As per our standard procedures for participants involved in health research projects, all participants will receive an Aus $20 (US $15) gift voucher as a reimbursement for their time at both the initial recruitment and 12- and 24-month follow-ups. Each participant will additionally receive a sample bag of oral and general health-related items at baseline, including fluoridated toothpaste and toothbrushes.

Intervention

After cleaning teeth with dry gauze and drying the cavities with cotton pellets, dentally qualified research officers will apply 38% AgF (Riva Star Aqua Step 1, Southern Dental Industries Ltd) to sites of active caries in the primary and permanent dentition using a microbrush applicator and keeping the solution in contact with the lesion for 60 seconds. No attempts will be made to remove soft dentine. Potassium iodide (Riva Star Aqua Step 2, Sothern Dental Industries Ltd) will be applied immediately after Riva Star Aqua Step 1 until the white precipitate is clear, signaling that all free silver ions have reacted with the potassium iodide. Petroleum jelly will be applied to the lips and gingival mucosa to avoid direct contact of AgF with soft tissues. Participants will be instructed to refrain from drinking, eating, or rinsing their mouths for at least thirty minutes. A single AgF application will occur at the baseline visit for the immediate intervention clusters and at the 12-month follow-up for the delayed intervention clusters. Any participants requiring additional dental treatment at the baseline, 12-month,

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or 24-month follow-ups will be referred for standard dental care to the local dental service provider.

Outcomes

The primary outcome will be the arrest of carious lesions in the dentition, with arrested caries defined as nonpenetration by a dental probe. Secondary outcomes will include SEWB, OHRQoL, dental anxiety, and dental behaviors. A SEWB measure has been developed by our team based on community consultation, item polling, and a theoretical framework that identified six core SEWB domains for Indigenous Australian youths: (1) feeling empowered; (2) feeling strong in my body; (3) feeling loved and safe; (4) feeling resilient; (5) feeling strong in my mind; and (6) feeling strong in my identity. OHRQoL will be assessed using the Caries Impacts and Experiences Questionnaire [29], which we have validated and successfully implemented in other studies involving Indigenous Australian children [30]. Dental anxiety will be assessed using the Child Dental Anxiety and Scale [31], modified to capture anxiety from adolescent participants, which we have also validated and implemented in studies involving Indigenous children [30]. Behaviors will be assessed using items from the 2012-2014 National Child Oral Health Survey [1]. These will include participant age when commenced tooth brushing, tooth brushing frequency, use of fluoride toothpaste, last time participant saw an oral health care provider, usual reason for participant to visit an oral health care provider, and consumption of sugar-sweetened beverages and foods.

Effectiveness measures for the economic evaluation will include the number of children and young people managed in primary oral health care without the need for specialist referral, changes in SEWB, the numbers and types of treatments provided, and caries increments. A cost-utility analysis will be undertaken using the recently developed dental caries utility index for adolescents [32] and ECOHIS-4D to measure the utility values of the health states experienced by children and young people [33].

Oral Epidemiological Examinations

Caries experience will be collected through standardized oral epidemiological examinations by calibrated dental examiners. Didactic and clinical training for the examination teams will be conducted before baseline data collection, with refresher sessions provided during the fieldwork phase. Examinations will be in participants' homes, ACCHOs, schools, or wherever the caregiver, child, or young person feels most comfortable. All examiners will be tested in the field against the senior trainer to estimate interexaminer reliability. Intraclass correlation coefficients for caries assessment scores will be used to assess reliability.

Sample Size Calculation

Based on the literature, in which approximately 81% of carious lesions were estimated to have been arrested with AgF [34], the community intracluster correlation was calculated as 0.09. Using these parameters at 80% power, α=.05, and 12 clusters available (6 clusters per treatment arm), the estimated sample size required is 320 in each arm. Allowing for a 25% loss to follow-up each year, the estimated sample size is 570 per arm, or 95 children and adolescents per cluster (rounded up). Sample size estimations were undertaken on STATA 15 (StataCorp) using the commands for cluster randomized trials for proportions of caries arrest.

Data Analysis

The trial has been registered in the Australian and New Zealand Clinical Trials Registry (ACTRN12622001066774p). All analysis will be reported according to CONSORT (Consolidated Standards of Reporting Trials) guidelines. Data analysis will use intention-to-treat approaches, with standard imputation measures used to manage missing data. The analysis plan for each aim is as follows.

Aim 1 (severity of dental disease in young Indigenous Australians): the severity of dental disease will be calculated using the decayed, missing, and filled tooth surface index (dmfs/DMFS) for the primary and permanent dentition. The 2014-2016 National Child Oral Health Survey will enable comparison with both general and Indigenous population-level estimates [1]. General analysis will comprise the chi-square and 1-tailed Student *t* tests within the study sample and a nonoverlapping 95% CI when comparing with population estimates.

Aim 2 (changes in dental disease following AgF intervention): the trial will be analyzed on an intention-to-treat basis according to group allocation. Generalized linear mixed models will be performed to determine differences in the primary outcome (arrest in dental caries) between the 2 groups and over time when the outcome is continuous. For binary outcomes, general estimating equations with the log binomial family will be used [35].

Aim 3 (economic evaluation of the intervention): the cost-effectiveness of the intervention will be estimated using standard approaches from a health provider perspective. Effectiveness measures will include quality of life and utility indicators. A literature review will inform long-term cost savings to the health system by improving Indigenous children's and young people's experiences of dental disease. The usual method of determining the cost effectiveness of a health intervention is by estimating the incremental cost effectiveness ratio, the ratio between the incremental cost and the incremental outcome. Incremental cost is the cost difference between the intervention and usual care, while incremental outcome is the outcome difference between the intervention and usual care. The economic evaluation will compare any incremental costs of the intervention (costs accrued in the intervention arm compared to those in the delayed intervention arm) to the full list of incremental primary and secondary outcome endpoints, all expressed in their natural units of measurement. Costs will be measured from activity data with pathway analysis to fully specify all activities in both the immediate and delayed intervention arms. Resource use will be obtained from research and provider records. Measured resource use will be valued using both existing estimates of the costs of each unit of resource use from market prices and the Medicare fee rates. Intervention costs will exclude research project costs. Standard discounting will be applied to both costs and outcomes, with uncertainty in these data subjected to sensitivity analyses.

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Ethical Considerations

Ethics approval (number 04-22-1013) has been obtained from the Aboriginal Health Council of South Australia Human Research Ethics Committee, the University of Adelaide Human Research Ethics Committee, the Human Research Ethics Committee of the Northern Territory Department of Health and Menzies School of Health Research, the Far North Queensland Human Research Ethics Committee, the Aboriginal Health and Medical Research Council of New South Wales Human Research Ethics Committee, the Australian Institute of Aboriginal and Torres Strait Islander Studies Human Research Ethics Committee, and the Western Australian Aboriginal Health Ethics Committee. Before being recruited, all participants will be required to sign an informed consent form, which includes consent for the authors to publish the findings in the peer-reviewed scientific literature. All authors are named investigators on the project; they all contributed to the intellectual input of the study design and in writing this protocol.

Results

Participant recruitment for this study commenced in May 2023, and up until September 2023, around 540 children and young adults have been recruited. We anticipate the first results to be submitted for publication 2 years following initial recruitment.

Discussion

What are the Views of the Indigenous Community About the Study?

Feedback from multiple Indigenous participants in our current studies reveals that poor access to dental services is a key barrier to achieving optimal health. Many participants should be in the prime of their lives, yet ongoing concerns about their oral health are impacting important life decisions (eg, shame about poor oral health prevented one from singing in a television documentary, while embarrassment about bad breath prevented another from attending a job interview). These inequities begin in early childhood, with Indigenous children as young as 2 years old in some communities requiring all teeth to be removed under a hospital-based general anesthetic because of advanced dental decay.

Why is This Study Important?

Despite the unacceptable poor oral health experienced by many Indigenous children and young people in regional and remote locations, there have been few interventions developed using culturally safe methodologies for improving oral health using low-cost approaches that are non–resource-intensive. Consequently, the management arsenal available to reduce the incidence of active dental decay among Indigenous children and young people that does not involve extensive restorative care (needles, drilling, and filling) is limited. The proposed study will investigate a novel use (AgF) for a potentially widely available public health service with which every health professional can become familiar. Currently, AgF is the only nonsurgical therapeutic option for the management of active dental caries. Our results may provide evidence for decision makers to make informed resource allocations in Indigenous oral health, which impacts both SEWB and health-related quality of life. This is especially necessary in the ACCHO sector.

Strengths and Limitations

This study will test the hypothesis that Indigenous children and young people in 6 Australian states and territories can be provided with appropriate dental care in local Indigenous settings using the AgF approach without specialist intervention and avoiding the need for treatment under hospital-based general anesthesia. This study has six major strengths: (1) it will evaluate the and severity of dental disease in Indigenous children and young people in 6 states and territories; (2) it will test the efficacy of a simple and culturally safe AgF initiative, which could be easily implemented into the training program of Indigenous Health Workers to be included in their remit of care; (3) we will have capacity to comprehensively assess the cost-effectiveness of the intervention, meaning uptake into clinical guidelines will be much swifter than if no cost-effective analysis was undertaken; (4) the intervention will likely lead to SEWB improvements in Indigenous children and young people; an important strategic priority given current commitments to improving child health and well-being, with the Australian Government launching, in October 2021, the world's first National Children's Mental Health and Well-Being Strategy [36]; (5) we have engaged and consulted considerably with participating ACCHOs, using their feedback to shape the research questions and; (6) our researchers are world-class experts in their respective specialties and have experience working with Indigenous child and adolescent populations. Limitations include operationalizing a national-level trial while COVID-19 is still present and assessing active dental caries by clinical examination only (no use of radiographs). Conducting a clinical trial in challenging contexts and following the cultural protocols of local Indigenous communities prevents us from blinding study participants.

In conclusion, our findings have the potential to change the way in which the oral health of Indigenous children and young people is managed, with desired impacts including cost savings on expensive dental treatments, improved SEWB, nutrition, social, and learning outcomes, and improved quality of life for both children and young people and their caregivers and the broader Indigenous community. This study addresses priorities raised in the National Aboriginal and Torres Strait Islander Health Plan 2013-2023 [37], particularly in regard to increasing understanding of Indigenous health issues at a community level, improving public health measures that address Indigenous health, and facilitating the collection of Indigenous health data.

Acknowledgments

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Conflicts of Interest

None declared.

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Abbreviations

ACCHO: Aboriginal Community Controlled Health Organization
AgF: silver fluoride
CONSORT: Consolidated Standards of Reporting Trials
dmfs/DMFS: decayed, missing, and filled tooth surface index
OHRQoL: oral health-related quality of life
SEWB: social and emotional well-being

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Protocol

A Brief Digital Screening and Intervention Tool for Parental and Adolescent Tobacco and Electronic Cigarette Use in Pediatric Medical Care in Canada: Protocol for a Pilot Randomized Controlled Trial

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Abstract

Background: Though rates of tobacco smoking have decreased consistently over the past 3 decades, cigarette use remains the top preventable cause of premature death in North America. The Clinical Effort Against Secondhand Smoke Exposure (CEASE) is a medical clinic-based intervention that systematically screens parents for tobacco use and offers them direct access to evidence-based smoking cessation services. While the effectiveness of CEASE for parents who smoke has already been demonstrated in the United States, the CEASE model has not yet been tested in Canada, among parents who use e-cigarettes, or among adolescents who use cigarettes and e-cigarettes.

Objective: We aim to demonstrate the feasibility and evaluate the preliminary effectiveness of the CEASE program for parental smoking cessation and its adapted version for adolescent smoking cessation and adolescent and parental vaping cessation.

Methods: We will approach parents or guardians of children aged between 0 and 17 years, as well as adolescent patients aged between 14 and 17 years, from a tertiary care pediatric hospital in Montreal, Quebec, Canada, for participation in this single-blinded, pilot randomized controlled trial. Eligible participants are those who report using tobacco cigarettes or e-cigarettes at least once in the last 7 days and present to an outpatient pediatric clinic for a scheduled appointment. Our recruitment target is 100 participants: 50 parents or guardians of children aged 17 years or younger, and 50 adolescents aged between 14 and 17 years. The feasibility of implementation of the CEASE model will be measured by recruitment and retention rates for all 4 participant groups (stratified as follows: parents who use cigarettes, parents who use e-cigarettes exclusively, adolescents who use cigarettes, and adolescents who use e-cigarettes exclusively). Parent and adolescent participants within each group are randomized to the intervention and control groups using a 1:1 ratio through a computer-generated randomization list. Preliminary effectiveness outcomes include self-reported smoking and e-cigarette cessation, use of cessation resources, changes in smoking and e-cigarette use, motivation to quit, and quit attempts among participants. Participants complete electronic questionnaires on a tablet in the clinic at baseline as well as electronic follow-up questionnaires at 1, 3, and 6 months. Individuals reporting successful quit attempts are invited to provide a urine sample for cotinine testing to biochemically confirm quit. Analyses include descriptive statistics as well as exploratory trajectory analyses of smoking, e-cigarette use, and motivation to quit.

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Results: Research activities began in June 2022. Participant enrollment and data collection began in February 2023 and are expected to be completed in 15 months.

Conclusions: There is a strong need for effective and cost-effective smoking and vaping cessation interventions for parents and adolescents. If successful, this study will help inform the preparation of a fully powered randomized controlled trial of CEASE in Canada in these populations.

Trial Registration: Clinicaltrials.gov NCT05366790; https://www.clinicaltrials.gov/study/NCT05366790

International Registered Report Identifier (IRRID): DERR1-10.2196/47978

(JMIR Res Protoc 2023;12:e47978) doi:10.2196/47978

KEYWORDS

adolescents; cessation; e-cigarettes; parents; pediatric clinic; screening; tobacco

Introduction

Tobacco use is the single greatest preventable cause of morbidity and mortality in Canada, accounting for 48,000 deaths and CAD $16.2 billion (US $11.9 billion) in attributable health-related costs annually [1,2]. Smoking is a significant risk factor for multiple cancers [3] as well as cardiovascular diseases [4], thus shortening the life expectancy of smokers who initiate during adolescence by more than 10 years [4]. Despite parental smoking being an important risk factor for child initiation of tobacco (children of parents who smoke have 4-fold greater odds of becoming smokers when compared with children of nonsmoking parents) as well as for the development of several illnesses, such as bronchiolitis, asthma exacerbations, and pneumonia [5], about 15% of Canadian children are still exposed to household secondhand smoke [6]. Parents are thus an important target for smoking cessation interventions to improve their own health and protect that of their children and future generations. Given that 90% of smokers start smoking before the age of 18 years [7], adolescence represents a critical period to intervene in the fight against smoking [8].

Smoking among adolescents and young adults remains common despite rates decreasing over the past 3 decades, and adolescent use of nicotine-containing e-cigarettes (hereafter referred to as e-cigarettes) has shown a worrying increase over the past 10 years [9]. Most adults who use e-cigarettes (e-cigarette use is referred to interchangeably with vaping) do not have a history of tobacco use; however, once vaping has been initiated, the risk of subsequent tobacco, alcohol, and drug use increases [9]. Commonly used e-cigarettes usually contain high concentrations of nicotine, and while potentially effective for adult smoking cessation [10], they are not effective for youth smoking cessation and should not be recommended in this population [11].

In 2019, more than half of smokers in Canada (57.9%) reported seriously considering quitting in the next 6 months, and 26.9% were considering doing so in the next month [12]. Similarly, the majority of adults and adolescents who use e-cigarettes report that they intend to quit vaping [13,14]. Individuals trying to quit without behavioral support or smoking cessation medication (eg, nicotine replacement therapy [NRT]) can face great challenges due to nicotine's addictive nature and severe psychological and physical withdrawal symptoms [3]. Several evidence-based smoking cessation interventions exist, including behavioral and pharmacological treatments that can be used alone or in combination [15], which greatly increase the odds of successfully quitting [16], and even more so when behavioral and pharmacological (NRT) interventions are combined [17]. Behavioral support traditionally refers to counseling; however, newer modalities, such as SMS text messages and app-based interventions, have shown promise [16] and would provide individuals with personalized, accessible behavioral support in quitting at low to no cost.

Health care providers can enhance the success of quit attempts by offering assistance and facilitating access to smoking cessation interventions [18]. Through their regular contact with families, pediatric health care providers are in a unique position to assist parents and adolescents in quitting smoking and vaping. However, studies and clinical experience show that pediatric health care providers rarely capitalize on this opportunity [19]. Lack of time, lower perceived priority of smoking or e-cigarette cessation relative to other care, fear of upsetting families, and lack of perceived efficacy are among the reasons why this type of intervention is rarely provided [20]. Digital preappointment screening questionnaires to identify individuals who smoke or vape and connect them with existing resources are a promising avenue to deliver cessation interventions in pediatric clinics [21]. This approach is well-accepted by patients and health care providers [21].

The Clinical Effort Against Secondhand Smoke Exposure (CEASE) intervention is an effective and cost-effective medical clinic-based intervention that systematically screens parents for tobacco use and offers them direct access to evidence-based smoking cessation services [22,23]. The model has been studied in the United States with promising results. A cluster randomized trial showed a 3.7% decrease in smoking prevalence between the intervention and control groups over a 2-year observation period (2.7% decrease in smoking rates in the intervention group vs 1.1% increase in the control group; difference –3.7%, 95% CI –6.3% to –1.2%; [23]). Cost-effectiveness data from Drouin et al [22] also showed that the incremental cost per quit (among adult participants who smoked) was US $1132 compared with usual care, a much lower figure than other clinical care-based smoking cessation interventions.

The primary objectives of this pilot randomized controlled trial of CEASE are to demonstrate the feasibility and preliminary effectiveness of CEASE for adults who smoke tobacco and its adapted version for parents with e-cigarette use and adolescents

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with cigarette and e-cigarette use in Canada. This pilot trial seeks to accomplish the following three aims: (1) evaluate the feasibility and effectiveness of the CEASE model in the Canadian setting, which differs from the United States in pediatricians' scope of practice, financial incentives for physicians, and insurance coverage for NRT [24]; (2) address the gaps in knowledge regarding vaping cessation, for which many professional societies recommend using similar cessation tactics, strategies, and resources as with regular tobacco cigarettes [11,25]; and (3) validate the feasibility of recruiting participants in proposed sites of care (hospital-based pediatric clinics) and obtaining data on quit interest and intent in this population.

This pilot randomized controlled trial of CEASE in Canada aims to answer these questions by recruiting parent and adolescent participants from hospital-based pediatric clinics and randomizing them to the CEASE program or usual care.

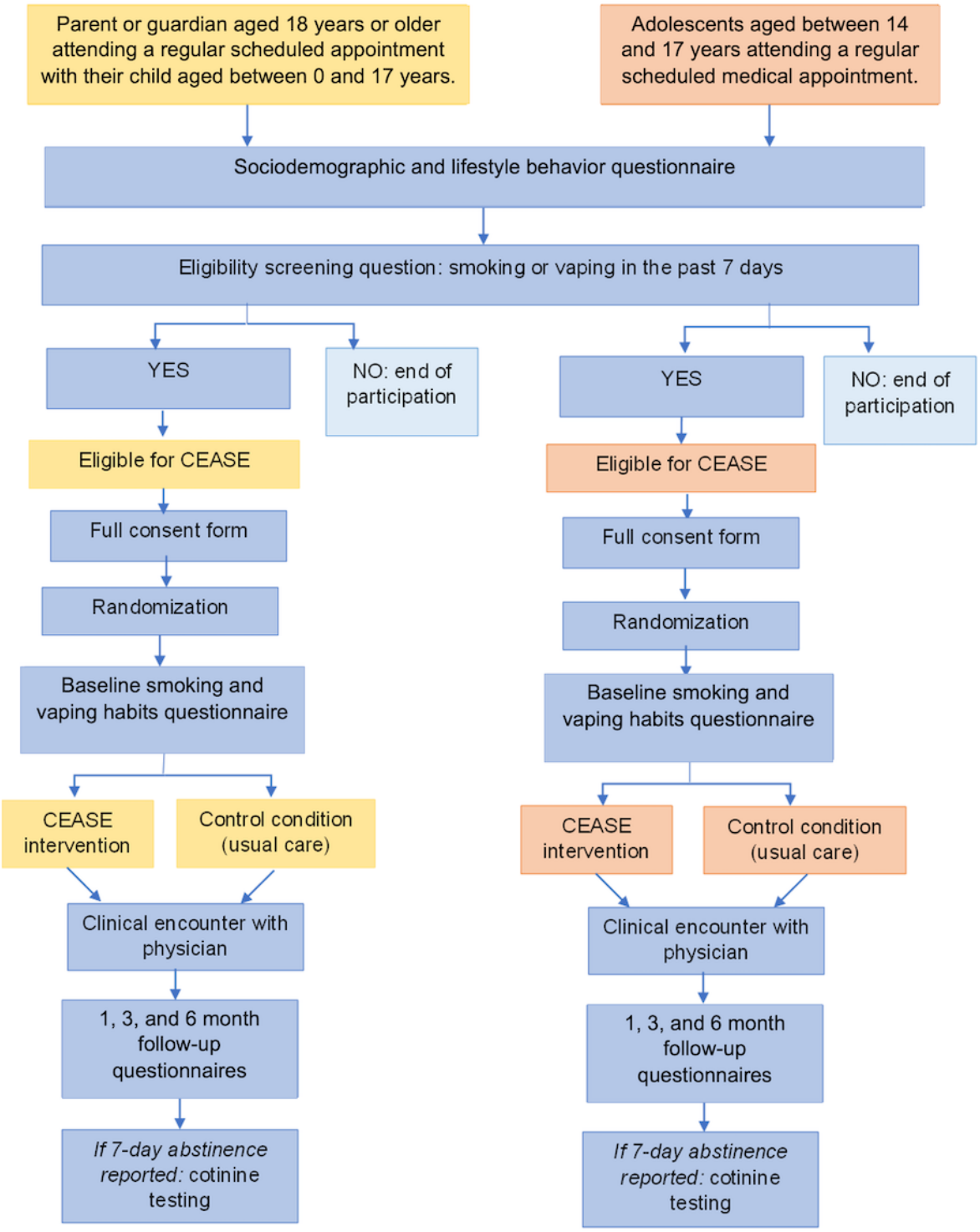
Methods

Study Design, Setting, and Participants

This is a single-center, pragmatic, single-blind, pilot randomized controlled trial comparing the CEASE intervention to usual care (control condition). Participants will be recruited over a 9-month period and followed for 6 months (15-month study period). Figure 1 shows the study flow diagram. This study is being conducted in various clinics within the Sainte-Justine University Hospital Centre, (Montreal, Quebec, Canada), including the general pediatrics clinic, the adolescent medicine clinic, and the orthopedics and sports medicine clinics.

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Figure 1. Study flow diagram illustrating participant trajectory through study of a brief digital screening and intervention tool for parental and adolescent tobacco and electronic cigarette use. CEASE: Clinical Effort Against Secondhand Smoke Exposure.



The recruitment target is 100 individuals who report using tobacco or e-cigarettes (either tobacco or e-cigarettes alone, or both tobacco and e-cigarettes) in the 7 days before responding to the study questionnaire. A minimum of 50 parents and 50 adolescents will be recruited.

The study will be reported according to the Strengthening the Reporting of Observational Studies in Epidemiology Statement: Guidelines for Reporting Observational Studies [26].

Recruitment

The appointment schedules of participating clinics will be reviewed the week before by the research team, and a recruitment schedule will be made according to the clinical volume of each clinic to maximize the number of potential patients approached. At the time of registration for their scheduled appointment, parents or legal guardians (hereafter referred to as parents) of children aged between 0 and 17 years

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as well as adolescents aged between 14 and 17 years are approached by a research assistant in the clinic waiting room to complete the screening survey on an electronic tablet. The survey is preceded by an abbreviated consent form. This approach is similar to that which was successfully used in CEASE studies in pediatric primary care in the United States [23]. Parents and adolescents are asked sociodemographic, smoking, and e-cigarette screening questions (see "Inclusion and Exclusion Criteria" section). Participants who respond "yes" to at least 1 of the 2 screening questions are invited to participate in the CEASE pilot study and have access to the full consent form. These forms are available in the Multimedia Appendix 1. During the entire study period, research assistants keep a detailed recruitment log, including information on participant screening, eligibility, recruitment, randomization, and retention in the study.

Inclusion and Exclusion Criteria

Inclusion Criteria

Parents of children aged between 0 and 17 years who smoke cigarettes or use nicotine-containing e-cigarettes. Users are defined as those who answer "yes" to at least 1 of the 2 screening questions: (1) Have you smoked a single cigarette, even a puff, in the past 7 days? (smoking), and (2) Have you used an e-cigarette or vaping device containing nicotine, even a puff, in the past 7 days? (vaping).

Parents are eligible if (1) they are aged 18 years or older, (2) their child is aged between 0 and 17 years, (3) they are attending a regular scheduled medical appointment, and (4) they are sufficiently proficient in either French or English to be able to read and answer a written questionnaire. Informed consent is obtained before data collection.

Adolescent users are defined as those who answer "yes" to at least 1 of the above screening questions.

Adolescents are eligible if they are aged between 14 and 17 years, meet the aforementioned 3rd and 4th criteria, and have provided informed consent (in Québec, adolescents aged 14 years can provide consent).

Exclusion Criteria

Adolescents whose parents (if present) are not agreeable to their participation and families presenting to the clinic for an urgent medical issue will be excluded.

In each age category, a total of 2 participant groups are formed: "smokers," defined as all users reporting past 7-day use of traditional combustible cigarettes, with or without e-cigarette use, and "e-cigarette-only users," who report exclusive use of e-cigarettes. E-cigarettes include any electronic nicotine delivery systems, for example, vape pens, e-pens, e-cigars, e-pipes, or vaporizers containing nicotine. This division was created on the basis that the CEASE model has only been tested in individuals who report cigarette use (with or without e-cigarette use) but has not yet been tested in individuals using exclusively e-cigarettes [22].

Intervention

The CEASE Intervention

The CEASE intervention is an evidence-based parental smoking cessation intervention delivered in pediatric practices, leveraging existing health care and community resources [23]. In this project, CEASE is delivered through electronic tablets in pediatric clinic waiting rooms. It integrates evidence-informed tobacco (cigarette) and vaping (e-cigarette) product use screening and cessation assistance into routine visits to pediatric clinics. This workflow, used by Winickoff et al [19] in the United States, requires less than 10 minutes to complete, does not disrupt clinic flow, can be sustained over a 2-year period, and is acceptable to families and health care providers. CEASE is based on the 5As (ask about smoking, advise to quit, assess readiness to quit, assist with a quit plan, and arrange follow-up) model of smoking cessation. Given that CEASE is a 1-time intervention, "arrange" is removed, and the fourth step "assist" is divided into 2 parts: (1) providing behavioral support (in-person, phone, SMS text message, or app quit support) and (2) providing pharmacological support (access to NRT). Specifically, CEASE includes the following steps:

1. Ask (routine, systematic identification of smokers and e-cigarette users)
2. Advise (brief motivational intervention)
3. Assess (self-assessment of readiness and quitting preferences)
4. Assist (support to quit for those interested)
    - Behavioral support
    - Pharmacological support (NRT)

Ask: Routine, Systematic Identification of Smokers and E-Cigarette Users

Families with a scheduled appointment are approached by a research assistant and prescreened for eligibility using a brief anonymous survey on the secure REDCap (Research Electronic Data Capture; Vanderbilt University) platform. Eligible participants are randomized to either (1) the intervention (CEASE) or (2) the control (usual care condition).

Advise: Brief Motivational Intervention

Brief motivational interventions have been shown to improve quit rates and may include goal setting, setting a quit date, secondhand smoke education (shown to increase acceptance of services), and enlisting social support. After collecting data on participant smoking and vaping behaviors (a baseline questionnaire delivered through an electronic tablet), CEASE will automatically include brief motivational messages describing the main short- and long-term health benefits of smoking cessation to increase participant engagement and acceptance of services [23].

Assess: Self-Assessment of Readiness and Quitting Preferences

Next, participants are invited to indicate whether they are interested in trying behavioral (eg, in-person, phone, SMS text message, or app-based) or pharmacological (ie, NRT) interventions to help them quit or cut down.

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Assist: Support to Quit for Those Interested—Behavioral Support

In-person or phone quit line support is offered through the government-funded and evidence-based smoking cessation internet platform "J'Arrête (I Quit Now)," provided by the Conseil Québécois sur le Tabac et la Santé (CQTS). Interested individuals can sign up for cessation services directly on the website [27]; study participants have the opportunity to do so directly on the electronic tablet. The Canadian Cancer Society's (CCS) Short Messages Against Tobacco [28], available from the J'Arrête (I Quit Now) website, is also presented as an option for participants who are interested in receiving SMS text messaging support to help them quit. Participants are offered to sign up to the "J'Arrête (I Quit Now)" web-based app, which provides a platform for the creation and realization of their smoking quit plan, as well as a dashboard to track their progress, trophies, tricks, and a variety of exercises to help overcome smoking cravings. In the week following the completion of the baseline questionnaire, interested participants receive an email or SMS text message reminder with information on how to access the behavioral resources they selected. All in-person, web-based, and SMS text messaging services are available in French and English for both adults and adolescents who smoke and use e-cigarettes. After signifying their interest in signing up for either of these services, participants are asked to consent to their information being transferred to the CCS or to the CQTS, which may contact them in the future and offer them additional smoking or vaping cessation resources.

Assist: Support to Quit for Those Interested—Pharmacological Support

CEASE automatically generates a written recommendation for NRT [23], to be discussed with a community pharmacist, including for those cutting down to quit as recommended in the latest national and international guidelines [29]. Since the best practice for NRT is to provide both a long- (ie, patch) and short-acting form (eg, gums or lozenges), a recommendation for 2 forms of NRT is automatically populated and printed in the clinic, provided to the participant, and sent to the participant by email. Given that pharmacists can now prescribe NRT in Quebec, the recommendation is written as detailed instructions for the pharmacist to prescribe NRT for a period of 3 months (the time period covered by public medical insurance in Quebec) and adjust the dosage based on the participant's reported use of tobacco or e-cigarettes. Study investigators remain available to support community pharmacists as needed.

The role of the provider in this intervention is adjunctive and not necessary to trigger intervention delivery. As such, CEASE is a standalone intervention and can take place without any provider involvement.

Control Condition

The control condition is care as is usually delivered in participating clinics. Current practice at those sites does not currently include routine provision of assistance for parental nor adolescent smoking and e-cigarette cessation (eg, referral to quit lines and NRT prescription). Participants in the control conditions will complete the same questionnaire as those in the intervention group; however, they will not be presented with a list of resources at the end of the questionnaire. While completing the final 6-month follow-up questionnaire, participants in the control group will be offered the option to receive a 1-time direct linkage to CEASE smoking and vaping cessation resources (behavioral supports and NRT recommendation).

Data Collection and Compensation

After consenting to the study, participants are asked to fill out a baseline questionnaire on an electronic tablet. Participants randomized to the intervention group have the option of receiving direct access to the CEASE evidence-informed cessation resources (if interested) after completing their questionnaire, while those randomized to the control group are only offered access to these resources at the end of the 6-month follow-up period (see "Control Condition" section). Participants in both groups are followed for 6 months following recruitment, with data collection at 1, 3, and 6 months (and the possibility of obtaining direct access to evidence-informed resources at each time point, if interested, for participants in the intervention group). Data collection tools (questionnaires) are available upon reasonable request to the corresponding author. Participant confidentiality is protected by limiting the collection of identifying information to an email address and phone number; date of birth, name, or participant address will not be collected. All data are stored on the secure web-based REDCap platform and in study logs on the Sainte-Justine University Hospital Centre server without participant-identifying information. Only the study investigators will have access to this data set at the end of the study period.

At each time point, participants are contacted by the study team by email, phone, or SMS text message (based on their preference) with a notification to complete the follow-up survey through REDCap, a secure web-based platform. If participants declare an abstinence of 7 days or more and consent to undergoing urine cotinine testing, they are contacted to arrange for biochemical confirmation of smoking cessation (cotinine testing) [30]. Data for confirmatory smoking or vaping cessation testing (urinary cotinine testing results) is sent directly to the study coordinator (to maintain investigator blinding) using a secure web-based portal. Participants will be called by research assistants and sent reminder emails or SMS text messages (based on their preference) to bolster the completion of follow-up questionnaires. They will receive CAD $10 (US $7.31) in compensation for each survey completed and an additional CAD $20 (US $14.62) per urine sample provided for cotinine testing.

Recruitment is expected to last a period of 9 months, with an additional 6 months required for follow-up with all recruited participants to complete data collection. The data analysis will begin with the end of recruitment and is expected to be completed in the 9 months following the final participant follow-up, for a total of a 24-month study period.

Allocation

This study aims to recruit an equal number of parent and adolescent users. Parent and adolescent participants are randomized to the intervention and control groups using a 1:1

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ratio. Parent and adolescent participants are stratified into 2 subgroups: those who smoke traditional combustible cigarettes (with or without e-cigarette use) and those who report exclusive use of e-cigarettes. A computer-generated randomization list created by a biostatistician external to the study team is used to randomize participants within each group.

Blinding

This is a single-blinded study in which investigators will be blinded to the participant's group allocation, and data analysis is blinded, but participants and research assistants remain unblinded. Pediatricians may decide to discuss smoking and vaping with families as part of their usual care, and participants may mention the CEASE intervention during the encounter with the provider. As such, participants and physicians will not be blinded. Participant data is anonymized using individual participant codes. No participant identifiers (eg, birth date and hospital number) are included in the database.

Outcomes

The capacity of CEASE to provide cessation assistance for parental and adolescent smoking and e-cigarette use is assessed using a series of outcomes detailed in Tables 1 and 2. Table 1 includes all clinic-level outcomes, while Table 2 includes all patient-level outcomes. Each table includes details and a summary of each outcome measure, their operational definition, as well as the suggested time line for data collection and feasibility threshold when applicable. Outcomes were based on Winickoff's previous experience conducting CEASE feasibility and effectiveness trials in the United States [23].

Feasibility thresholds of 50% of potential participants screened for eligibility, 15% clinic-level smoking and vaping prevalence, 20% enrollment rate, and 3 participants (total) recruited per week (at least 6 parents and 6 adolescents recruited per month; primary outcome for this study) have been set (Table 1). Given an average of 250 patients seen per week across all 4 clinic recruitment sites, we anticipate that these thresholds will allow for 100 participants to be recruited over 36 weeks (9 months). Similarly, a feasibility threshold for baseline and follow-up questionnaire completion has been set at 90% and 80%, respectively, as shown in Table 2.

Data are obtained directly from participants through baseline and follow-up questionnaires, as well as from recruitment logs, biochemical assay results, and key informant interviews with clinic staff (eg, clinical nurse, front desk staff, and medical director) to inform about the potential impacts of the study on clinic flow. The key informant semistructured interview template is presented in Multimedia Appendix 2.

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Table 1. Clinic-level outcomes of a pilot randomized controlled trial evaluating the feasibility and preliminary effectiveness in Canadian pediatric clinics of a brief digital screening and intervention tool for parental and adolescent tobacco and electronic cigarette use.

Outcome	Operational definition and details of measure	Timeline	Data collection	Feasibility threshold
Recruitment				
Clinic flow	Number of potential participants (parent and adolescent) per month for each clinic	Throughout	Recruitment log	N/A[a]
Proportion screened	Proportion of potential participants screened for eligibility	Throughout	Recruitment log	>50%
Clinic-level smoking and vaping prevalence	Self-reported smoking and vaping rates among parents and adolescents screened	Throughout	Recruitment log	>15%
Eligibility rate	Number of eligible parents and adolescents per month for each clinic	Throughout	Recruitment log	N/A
Enrollment percentage	Proportion of eligible participants approached who are enrolled	Throughout	Recruitment log	>20%
Reason for declining	Reasons for declining participation in the study	Throughout	Recruitment log	N/A
Recruitment rate (primary outcome)	Total number of participants recruited per month (parents and adolescents)	Throughout	Recruitment log	>3 participants, total, per week; >6 adolescents and >6 parents per month
Feasibility of the intervention				
Interest in smoking or vaping cessation	Proportion of eligible participants per category (parents and adolescents) who declare interest in smoking or vaping cessation	End of study	Baseline and follow-up questionnaires	>5%
Interest in smoking or vaping cessation services	Proportion of eligible participants (parents and adolescents) who want to be connected with smoking or vaping cessation services (quit lines, etc)	End of study	Baseline and follow-up questionnaires	>5%
Interest in obtaining NRT[b]	Proportion of eligible participants in each category who want to receive NRT	End of study	Baseline and follow-up questionnaires	>5%
Impact on clinic workflow				
Clinic staff evaluation	Key informant semistructured interview template (Multimedia Appendix 2) based on a number of references, including the CFIR[c] interview guide [31] and RE-AIM[d] [32]	End of study	Key informant interviews	N/A
Patient flow	Pre- and postrecruitment average weekly and monthly patient volumes in each clinic	End of study	Key informant interviews	<10% change

[a]N/A: not applicable.

[b]NRT: nicotine replacement therapy.

[c]CFIR: Consolidated Framework for Implementation Research.

[d]RE-AIM: Reach, Effectiveness, Adoption, Implementation, and Maintenance.

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Table 2. Participant-level outcomes of a pilot randomized controlled trial evaluating the feasibility and preliminary effectiveness in Canadian pediatric clinics of a brief digital screening and intervention tool for parental and adolescent tobacco and electronic cigarette use.

Outcome	Operational definition and details of measure	Timeline				Data collection	Feasibility threshold
		Baseline	1 month	3 months	6 months		
Protocol fidelity							
Baseline questionnaire completion	Proportion of participants who complete the baseline questionnaire out of randomized participants (REDCap[a] survey)	✓				Baseline questionnaire	≥90%
Access to web-based resources	Proportion of participants who want to be connected to the web-based resources who report access these resources (self-report)	✓	✓	✓	✓	Baseline and follow-up questionnaires	N/A[b]
Access to quit lines (phone, or SMS text messaging support)	Proportion of interested participants who received a communication from the quit lines (self-report)		✓	✓	✓	Baseline and follow-up questionnaires	N/A
Access to NRT[c]	Proportion of participants who want to receive NRT who receive a report receiving a formal written recommendation or prescription for NRT	✓	✓	✓	✓	Baseline and follow-up questionnaires	N/A
NRT use	Proportion of participants who have used NRT (self-report)		✓	✓	✓	Baseline and follow-up questionnaires	N/A
Study retention							
Participant retention	Proportion of randomized participants that could be contacted (initiation of REDCap survey, phone, or email contact) at follow-up		✓	✓	✓	Follow-up questionnaires	≥80%
Smoking and vaping status	Availability of self-reported smoking and vaping status for randomized participants		✓	✓	✓	Follow-up questionnaires	≥80%
Completion of data at follow-up	Complete survey data available for randomized participants		✓	✓	✓	Follow-up questionnaires	≥60%
Cotinine testing	Availability of cotinine testing results		✓	✓	✓	Web-based portal	N/A

[a]REDCap: Research Electronic Data Capture.

[b]N/A: not applicable.

[c]NRT: nicotine replacement therapy.

Power Calculations

The most recent Statistics Canada data show prevalence rates for daily or occasional smoking that are higher among males (17.3%) than females (12.3%), though this gap is narrowing [33]. In Québec, where the study is conducted, smoking prevalence is slightly higher (17.0%) than the Canadian average (14.8%) [33]. Among adults, especially adults aged older than 25 years, smoking rates remain significantly higher than vaping rates, as only 3.2% of adults aged older than 25 years report past-month use of a vaping device, and a significant proportion of adult e-cigarette users report dual use of cigarettes and vaping devices [34].

The latest provincial statistics report an 18% vaping prevalence among youth aged between 15 and 17 years [35] in Quebec, which is 4.5 times higher than the smoking prevalence (4%) in this age group, though the majority of adolescents who smoke also report past use of an electronic cigarette [34].

Considering recent epidemiological trends, a conservative 15% prevalence estimate is expected for the combined use of cigarettes and vaping devices among both parents and adolescents, resulting in a potential participant pool of approximately 1 in 7 parents or adolescents presenting to the clinic. With average clinic volumes of 250 patients per week and the screening and enrollment rates mentioned above, we anticipate attaining targeted recruitment rates of 3 participants per week.

To estimate the retention rate, using a sample size of 50 participants per age group (parents and adolescents) will allow for a 95% CI within 15% of the estimate obtained. As such, if a study completion rate of 60% is observed, the 95% CI would be 44.2%-75.8%. Other research groups have reported

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challenges in recruiting teenagers for vaping cessation research studies [36]. As such, recruitment and retention rates are expected to differ between adult and adolescent participants; enrolling 50 parents and 50 adolescents for this pilot study will provide the 2 participation rate estimates.

Analyses

Clinic-level outcomes will be evaluated using descriptive statistics (recruitment and feasibility) and qualitatively (key informant interviews). Participant-level outcomes will also be evaluated using descriptive statistics, both overall and stratified by participant type (parents vs adolescents), nicotine product used (cigarettes with or without vaping vs vaping only), and clinic where recruitment occurred. Recruitment outcomes will be compared by participant gender. Given that this is a pilot trial with insufficient power to formally test the effectiveness of CEASE, exploratory analyses comparing smoking and vaping cessation, use of cessation resources, and motivation to quit smoking and vaping between intervention and control participants will be performed to identify potential trends and signals of effectiveness in all 4 participant groups.

Ethical Considerations

This study was reviewed and approved by the Institutional Review Board of the Sainte-Justine University Hospital Research Centre (2023-4237) and has been registered on ClinicalTrials.gov (NCT05366790). Any modifications or deviations from the protocol or adverse events will be recorded in the study logs on REDCap and reported immediately (within 48 hours) to the Institutional Review Board of the Sainte-Justine University Hospital Research Centre.

Results

This study obtained funding in April 2022. Research activities for this study began in June 2022. Participant enrollment and data collection began in February 2023 and are expected to be completed in 9 months (October 2023). As of September 30, 2023, a total of 115 participants—61 parents and 54 adolescents—have been recruited and have completed all baseline data. Data analysis will begin once all participants have been recruited and follow-up measures (1, 3, and 6-month follow-up) are in progress. The primary results of this study are expected to be available in the first months of 2025.

Discussion

Potential

This is the first study to test the feasibility and preliminary effectiveness of the CEASE intervention in Canada, as well as with adolescents and individuals with exclusive e-cigarette use. If shown feasible by reaching the feasibility recruitment threshold of 6 parent and 6 adolescent participants per month, this study could allow for the planning of a full-scale randomized controlled trial testing CEASE's effectiveness in Canada in these populations.

Strengths and Limitations

This study includes several strengths. First, it builds on the CEASE intervention, which has previously been demonstrated to be effective and cost-effective. Second, the electronic format of the screening and intervention will facilitate the integration of the tool in clinic workflow without any required intervention from clinical staff and will help with scale-up to additional sites. Finally, the study leverages existing cigarette and e-cigarette cessation resources, foregoing the need for additional costs for resource development. This also means that those resources can evolve and improve over time without affecting the design or feasibility of the study.

This study has certain limitations. Given the pilot nature of the study and the small sample size, this study does not have the statistical power to evaluate the effectiveness of the CEASE intervention. This study is also being conducted exclusively in an urban tertiary care hospital, which may not be reflective of pediatric clinics in community hospitals or other primary care clinics. Nonetheless, as recruitment is taking place in both general pediatric and adolescent medicine clinics as well as several specialized pediatric clinics, it allows for testing of the CEASE model in a diverse parent and adolescent patient group. Given this diversity of participants and recruitment clinics within a single center, we elected to randomize at the participant level rather than following the cluster-randomization protocol previously used to evaluate CEASE [23]. This decision does, however, pose a risk of contamination, wherein participants in the control group learn of the intervention and choose to seek out these publicly available smoking cessation resources themselves. While this may result in a decreased effect size of "The Clinical Effort Against Secondhand Smoke Exposure–Canada" (CanCEASE) in this study, all participants are offered access to these resources at the end of the study period, and the CanCEASE questionnaire itself may prompt individuals wishing to quit smoking or vaping to seek out these publicly available resources themselves during the study. Furthermore, cluster randomization would have been impractical in the context of this pilot study, as a larger sample size is required.

Logical next steps for our work will be to consider expanding CEASE recruitment to other clinic settings, including primary and secondary care clinics as well as rural settings, and conducting a full-scale cluster randomized controlled trial.

Conclusions

Cigarette smoking and nicotine vaping remain highly prevalent among parents and adolescents. Pediatric clinics represent an underutilized opportunity for the promotion of healthy lifestyle behaviors. This study tests the feasibility and preliminary effectiveness of a simple approach to smoking and vaping cessation. If successful, it could pave the way for a large-scale randomized controlled trial testing the effectiveness of this approach for adolescents and parents who smoke and vape in a Canadian setting. It also has the potential to inform clinicians and researchers about preferred cessation tools for parents and adolescents who use cigarettes and e-cigarettes, which remains an understudied area.

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It is anticipated, based on previous implementation of CEASE in the United States, that CEASE will be feasible, as determined by a satisfactory recruitment rate as well as high proportions of participants interested in cessation, referral to cessation services, and NRT. As such, the data obtained through this study will help inform the design and implementation of a fully powered randomized controlled trial of CEASE in Canada.

Acknowledgments

This study is supported by a bridge grant from the Canadian Institutes of Health Research (CIHR). OD and NC are supported by Clinician Scholar Awards from the Fonds de recherche du Québec-Santé. MPS is supported by a Junior 2 Clinician Scholar Award from the Fonds de recherche du Québec-Santé.

These funding sources had no role in the design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results.

Data Availability

The data sets generated during and/or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

NC and OD conceived of the study and study design and prepared the initial study protocol. TP and AAS implemented the study design. TP managed study data and adherence to protocol. MPS and JO provided statistical expertise; JPW oversaw study design and provided guidance in study oversight. ED is conducting the primary statistical analysis. All authors contributed to the refinement of the study protocol and approved the final manuscript.

Conflicts of Interest

JPW has served as an expert witness in litigation against the tobacco industry.

Multimedia Appendix 1
Consent form (English) for participation in a randomized-controlled pilot trial evaluating the feasibility and preliminary effectiveness in Canadian pediatric clinics of a brief digital screening and intervention tool for parental and adolescent tobacco and electronic cigarette use.
[DOCX File , 130 KB - resprot_v12i1e47978_app1.docx]

Multimedia Appendix 2
Key informant interviews.
[DOCX File , 32 KB - resprot_v12i1e47978_app2.docx]

Multimedia Appendix 3
Peer Review Reports from the Canadian Institutes of Health Research (CIHR).
[PDF File (Adobe PDF File), 178 KB - resprot_v12i1e47978_app3.pdf]

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Abbreviations

CanCEASE: The Clinical Effort Against Secondhand Smoke Exposure–Canada
CCS: Canadian Cancer Society
CEASE: Clinical Effort Against Secondhand Smoke Exposure
CQTS: Conseil Québécois sur le Tabac et la Santé
NRT: nicotine replacement therapy
REDCap: Research Electronic Data Capture

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Protocol

Management of Pain and Cachexia in Pancreatic Cancer: Protocol for Two Systematic Reviews, Network Meta-Analysis, Surveys, and Focus Groups

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Abstract

Background: Approximately 75% of people with pancreatic cancer experience pain, and >50% of them have cachexia (weakness and wasting of the body). However, there is considerable uncertainty regarding the management of these distressing symptoms.

Objective: Our primary objectives are to compare the relative benefits and harms of different interventions for pain in people with unresectable pancreatic cancer and for prevention and treatment of cachexia due to pancreatic cancer, through systematic reviews and network meta-analysis. Our secondary objectives are to develop an evidence-based clinical care pathway to manage pain and prevent and treat cachexia in people with pancreatic cancer through surveys and focus groups involving patients, carers, and health care professionals.

Methods: We will perform 2 systematic reviews of the literature related to pain and cachexia in people with pancreatic cancer using searches from Cochrane Library, MEDLINE, Embase, Science Citation Index, and trial registries. Two researchers will independently screen for eligibility and identify randomized controlled trials (no language or publication status restriction), comparing interventions for pain or cachexia based on full-texts for articles shortlisted during screening. We will assess risk of bias in the trials using the Cochrane risk of bias tool (version 2.0) and obtain data related to baseline prognostic characteristics, potential effect modifiers and outcome data related to overall survival, health-related quality of life, treatment-related complications, and resource utilisation. We aim to conduct network meta-analysis on outcomes with multiple treatment comparisons where possible, otherwise, meta-analysis with direct comparisons, or narrative synthesis. We will perform various subgroup and sensitivity analyses. Using information obtained from both systematic reviews, we will conduct 2 surveys: one directed to patients or carers to assess acceptability of interventions, and the other to health care professionals to assess feasibility of delivery in the National Health Service. Four mixed focus groups will be conducted to evaluate findings and foster consensus in the development of the care pathway.

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Results: Funding was awarded from April 2022 (NIHR202727). Both systematic review protocols were prospectively registered on PROSPERO in May 2022. Formal searches began thereafter. Approval by the University College London Research Ethics Committee (23563/001) was received in December 2022. Data collection began in January 2023; data analysis will begin in May 2023 (completion expected by October 2023).

Conclusions: This study will comprehensively encompass major interventions for management of pain in people with unresectable pancreatic cancer, and prevention and treatment of cachexia in people with pancreatic cancer. Key stakeholders will facilitate the development of an evidence-based care pathway, ensuring both acceptability and feasibility. The project ends in April 2024 and published results are expected within 12 months of completion. We aim to present the findings through patient group websites, conferences, and publications, irrespective of the findings, in a peer-reviewed journal.

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KEYWORDS

cachexia; pain relief; palliative care; pancreatic cancer; quality of life; systematic review

Introduction

What Is the Problem Being Addressed?

In the United Kingdom, 11,700 people were diagnosed and 10,000 people died from pancreatic cancer in 2020 [1]. The incidence of pancreatic cancer is increasing in the United Kingdom and in many other countries worldwide [2-9]. If the trend continues, it is likely to become the third-most common cause of cancer death in the United Kingdom by 2030 [10]. Surgical resection remains the only treatment with the potential for long-term survival and cure. However, only about 10% to 20% (n=~61,203) of patients are suitable for resection [8,11-13]. In people who do not undergo resection, the main options are chemotherapy, chemoradiotherapy, and treatment of symptoms [13-18]. The major symptoms related to pancreatic cancer, particularly in those with unresectable cancers, are pain, cachexia, and jaundice. In this work, we will be looking at the evidence for the management of pain and cachexia.

Pain

Pancreatic cancer can cause severe pain. It is estimated that 70% to 80% of people with pancreatic cancer seek medical help for the treatment of abdominal or back pain [19,20]. The 2 major mechanisms of pain are pancreatic ductal obstruction and pancreatic neuropathy (increased activation of pain nerve fibers) [20]. The main treatment options evaluated for pancreatic cancer pain include nonopioid analgesics such as nonsteroidal anti-inflammatory drugs (NSAIDs), opioid analgesics such as morphine, corticosteroids, neuropathic pain medications such as gabapentin or pregabalin, palliative radiotherapy, thoracoscopic splanchnicectomy (severing the splanchnic nerves), celiac plexus nerve blocks or neurolysis, and other treatments include pancreatic duct stenting, acupuncture, and hypnosis [20-24]. Review 1 is a systematic review focusing on the benefits and harms of the different pain control strategies in people with unresectable pancreatic cancer. There are no previous network meta-analyses (NMA) on the topic. Head-to-head comparison systematic reviews included comparison of celiac plexus nerve block plus analgesics with analgesics alone [23,25,26] and videothoracoscopic splanchnicectomy [27], stereotactic radiotherapy [28], various ablative therapies [29], kanglaite (Chinese medicine) in addition to chemoradiotherapy versus chemoradiotherapy alone [30]. The current clinical guidelines on the management of pain in pancreatic cancer are based on the World Health Organization's 3-step ladder for cancer pain [31]. The National Institute of Health and Care Excellence (NICE) suggests nonpharmacological treatments such as coeliac plexus blocks when the pharmacological treatment fails or is unacceptable because of adverse events [32], a recommendation that has been questioned [21]. The NICE acknowledged the uncertainty in the recommendation [32].

Cachexia

Cancer cachexia is a multifactorial syndrome defined by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment [33]. An estimated 55% to 85% (n=~170) of people with pancreatic cancer have cachexia [34,35]. The major proposed mechanism for cachexia of pancreatic cancer is decreased appetite, decreased production and increased lysis of lipids, increased protein lysis, decreased liver function, fat malabsorption, and decreased muscle mass due to increased cytokines and tumor-derived factors [34,36,37]. Mechanical intestinal obstruction due to the cancer, pancreatic exocrine insufficiency, and nutritional deficiency because of the combination of the above factors are other potential mechanisms [34,36,37]. Interventions evaluated for the prevention and treatment of cachexia include pancreatic enzyme replacements, increased calorie intake, ketogenic diet, amino acid supplementation, nutritional supplements, appetite stimulants, corticosteroids, NSAIDs, progesterone analogues such as megestrol acetate, cytokine inhibitors such as melatonin, omega-3 fatty acids, and exercises to improve muscle mass [37-39]. Review 2 is a systematic review of the prevention and treatment of cachexia in people with pancreatic cancer. There are no previous NMAs on the topic. The existing systematic reviews on the topic are different from this study because of the types of studies included [40,41], types of interventions included [40-42], risk of bias assessment [40-42], and the type of outcome measures studied [40-42]. The NICE guideline on pancreatic cancer does not recommend anything specific for cachexia [32]; however, only nutritional interventions (for cachexia) were evaluated.

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Why Is This Research Important to Patients and Health and Care Services?

Increased pain decreases the health-related quality of life [43]. Cancer cachexia can lead to decreased health-related quality of life and may increase treatment complications, health care costs, and deaths [44]. Low performance status due to cachexia may preclude patients receiving more toxic but effective treatments such as the combination chemotherapy FOLFIRINOX [45]. The research questions included in this study are among the top 10 research priorities of the James-Lind Alliance Priority Setting Partnership on pancreatic cancer therapy involving people with pancreatic cancer in Germany, their carers, and clinicians treating them [46,47], that is, "How can the best treatment for each individual patient with pancreatic cancer be identified?" and "Does nutrition influence the survival or quality of life of patients with pancreatic cancer?" Furthermore, the use of evidence-based clinical care pathways in the National Health Service (NHS) helps to streamline care and avoid health care inequities and therefore would be beneficial for the management of pain and cachexia in people with pancreatic cancer.

Aims and Objectives

The overarching aim of this study is to answer the following research question: "What is the best treatment and NHS care pathway to decrease pain and cachexia and improve health-related quality of life in people with pancreatic cancer?"

The primary objectives include the following:

- To compare the benefits and harms of different treatments for pancreatic cancer pain through network meta-analyses, and to generate rankings of the different treatments according to their safety and efficacy.
- To compare the benefits and harms of different interventions in the prevention and treatment of pancreatic cancer cachexia through a systematic review (and meta-analysis when possible).

The secondary objectives include the following:

- To identify the gaps in the existing research that cause uncertainty in decision-making (based on the systematic review and NMA).
- To develop an evidence-based pathway for the management of pain and for the prevention and treatment of cachexia (using evidence collected as part of primary objectives), through surveys and focus group discussions with patients, carers, and NHS clinicians.

Methods

The bulk of the study is contained within work package 1, in which we will complete 2 comprehensive systematic reviews and meta-analyses on the management of pain and cachexia in pancreatic cancer. Work package 2 forms a smaller part of the overall study, yet it will involve surveys and focus groups of patients, carers, and health care professionals, leading to the development of a proposed evidence-based clinical care pathway for the management of pain and cachexia in people with pancreatic cancer.

Work Package 1: Systematic Reviews and NMA

We will perform two systematic reviews:

- Management of pain in people with unresectable pancreatic cancer: a systematic review of randomized controlled trials and NMA (review 1).
- Prevention and treatment of cachexia in people with pancreatic cancer: a systematic review of randomized controlled trials (review 2).

We will register the protocols in PROSPERO (International Prospective Register of Systematic Reviews) and conduct and report the systematic review according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement and its extension for NMA [48,49] (Table 1).

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Table 1. Eligibility criteria for systematic reviews.

	Review 1	Review 2
Title	Management of pain in people with unresectable pancreatic cancer	Prevention and treatment of cachexia in people with pancreatic cancer
Type of studies	All randomized controlled trials regardless of the publication status, year of publication, and language of publication	All randomized controlled trials regardless of the publication status, year of publication, and language of publication
Setting	Primary, secondary, tertiary, or community care	Primary, secondary, tertiary, or community care
Types of participants	People with unresectable pancreatic cancer	People with pancreatic cancer regardless of whether the tumor was resectable or not
Types of interventions		
	NSAIDs,[a] opioid analgesics, neuropathic pain medications, thoracoscopic splanchnicectomy, celiac plexus blocks or neurolysis, splanchnic nerve blocks or neurolysis, radiotherapy, pancreatic duct stenting, acupuncture, and hypnosis	Pancreatic enzyme replacements, increased calorie intake, ketogenic diet, amino acid supplementation, nutritional supplements (oral or parenteral), appetite stimulants, corticosteroids, NSAIDs, progesterone analogues, cytokine inhibitors, omega-3 fatty acids, and exercises to improve muscle mass
	Within each review, the above interventions will be considered if used either alone or in combination with other interventions listed and compared with another intervention (or combination of interventions) listed above.	Within each review, the above interventions will be considered if used either alone or in combination with other interventions listed and compared with another intervention (or combination of interventions) listed above.

[a]NSAIDs: nonsteroidal anti-inflammatory drugs.

Outcomes

The choice of outcomes is based on the Core Set of Patient-Reported Outcomes in Pancreatic Cancer (ie COPRAC) study that involved patients with pancreatic cancer and health care professionals involved in their care [50]. We will collect all outcomes at 3 time points: until 3 months from randomization or intervention, 3 to 12 months from randomization or intervention, and beyond 12 months.

The primary outcomes include the following:

1. Overall health-related quality of life (any validated scale)
2. Pain (however defined by authors) (this will be secondary outcome for review 2)
3. Cachexia (however defined by authors) (this will be secondary outcome for review 1)

The secondary outcomes include the following:

1. Consumption of analgesics (drug, quantity, and frequency) (review 1 only)
2. Change in body weight (total amount and percentage of body weight) (review 2 only)
3. Death from any cause (all-cause mortality)
4. General health (any validated scale)
5. Physical ability (any validated scale)
6. Ability to work and do usual activities (however defined by authors)
7. Satisfaction with services and care organization (any validated scale)
8. Relationship with partner and family (any validated scale)
9. Serious adverse events (ICH-GCP [51] or any other definitions used by authors)
10. Number of hospital attendances and hospital admissions
11. The total length of hospital stays (planned admissions related to all components of treatments and admissions related to observation or treatment of complications)

Search Strategy

The following electronic databases will be searched to retrieve all eligible studies: The Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library; MEDLINE (OvidSP); Embase (OvidSP); and Science Citation Index Expanded (Web of Knowledge); Conference Proceedings, from inception to date of search using free text and controlled vocabulary terms; ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform [52], which searches various trial registers, including ISRCTN and ClinicalTrials.gov. The search strategies are provided on the web-based published study registration records on PROSPERO (CRD42022333239 and CRD42022333241).

Additionally, we will search the references of the identified trials and the existing recent major systematic reviews on the topics to identify additional trials for inclusion. We will also contact the study authors to identify further trials and obtain aggregate data from unpublished studies.

Data Collection and Management

Selection of Studies

Two review authors will independently identify trials for inclusion by screening the titles and abstracts and make the final selection for inclusion based on the full-text articles (after translation if required) selected during screening. We will resolve any discrepancies through discussion and arbitration. The process will be documented to enable the completion of the PRISMA flowchart.

Data Collection

Two review authors will independently extract the following data using a prepiloted data extraction form:

1. Intervention and control details (including who delivers it, dose, how long and how frequently it is delivered, and compliance as appropriate)

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2. Outcome definition, scale, and data
3. Data on potential effect modifiers: both reviews: age, performance status; review 2: presence of pancreatic exocrine insufficiency; resectable versus unresectable pancreatic cancer
4. Length of follow-up
5. Information to assess risk of bias
6. Other data include year and language of publication, country and setting, ethnicity of participants, recruitment period, and inclusion and exclusion criteria.

Assessment of Bias

We will use the Cochrane risk of bias tool version 2.0 to assess the risk of bias in the included randomized controlled trials [53]. We will assess reporting bias by the completeness of search.

Meta-analysis of Clinical Effectiveness

Measures of Treatment Effect

For binary outcomes, we will calculate the odds ratio with 95% credible interval (CrI). For continuous outcomes, we will calculate the mean difference (if trials used same scale) or standardized mean difference (if trials used different scales) with 95% CrI. For count outcomes, we will calculate the rate ratio with 95% CrI. For time-to-event data, we will calculate hazard ratio with 95% CrI.

Data Synthesis

We will conduct NMA on all outcomes with multiple treatment comparisons wherever possible. We will obtain a network plot to understand the network geometry and ensure that the trials are connected by interventions. We will report only the direct pairwise meta-analysis for comparisons that are not connected to the network. We will summarize the population and methodological characteristics of the trials included in the NMA in a table based on pairwise comparisons and ensure that the transitivity assumption is reasonable. If there are concerns about the transitivity assumption, we will perform only direct comparisons. We will conduct a Bayesian NMA by using the Markov chain Monte Carlo method in OpenBUGS 3.2.3 as per the guidance from the NICE Decision Support Unit (NICE DSU) documents using study-level data and appropriate likelihood, and link functions [54]. We will calculate the additive main effects, 2-way interaction, and the full-interaction models [55] to capture the effect of a component, interactions between the components and the overall effect of a combination of components. We will use the model fit to guide the selection of the model to be reported, when we perform a component NMA. We will use the standard of care as the reference group.

We will perform a fixed-effect model and random-effects model for the NMA, and report the more conservative model. The codes that we use for the analysis will account for the correlation between the effect sizes from the studies with more than 2 groups [54]. We will use a hierarchical Bayesian model using "vague" priors and 3 different sets of initial values (to ensure convergence of values), using the codes provided by NICE DSU. We will estimate the probability that each intervention ranks at one of the possible positions by using the NICE DSU codes. We will obtain the surface under the cumulative ranking curve (cumulative probability) and rankogram [56,57].

Presentation of Results

We will present the effect estimates with 95% CrI for each pairwise comparison calculated from the direct comparisons and NMA. We will also present rankograms and surface under the cumulative ranking curve [58,59]. We will present "Summary of Findings" tables for each of the primary and secondary outcomes using the methods described by the GRADE Working Group for presenting the Summary of Findings for NMA [60].

Dealing With Missing Data

In the first instance, we will endeavor to contact trial investigators to obtain missing data. We will perform an intention-to-treat analysis, whenever possible [61]; otherwise, we will use the data available to us. We will conduct best-worst case and worst-best case scenario analyses as sensitivity analyses for binary outcomes, whenever possible. For continuous outcomes, we will impute the mean and SD from median and *P* values according to the guidance in the Cochrane Handbook if the data seem to be normally distributed [62].

Alternatives to Meta-analysis

For outcomes where meta-analysis is not possible (eg, where the data were not normally distributed), we will present the studies in a table and report the median and quartiles of the differences. When it is inappropriate to perform a meta-analysis because of major differences in the types of participants included in the studies, we will summarize the information in a table and perform only a narrative synthesis. For the narrative synthesis, we will present the results systematically by the comparisons for each outcome and will report the findings according to "Synthesis Without Meta-analysis" guidelines [63].

Assessment and Investigation of Heterogeneity and Inconsistency

Heterogeneity

We will assess clinical and methodological heterogeneity by carefully examining the characteristics and design of the included trials. The potential sources of clinical heterogeneity include age, performance status, presence of pancreatic exocrine insufficiency; resectable versus unresectable pancreatic cancer, baseline risk (may be related to when the trial was conducted reflecting improvement in supportive care), variations in the intervention, different definitions used for outcomes, different scales used for assessment of outcomes, and period of follow-up.

We may encounter a diverse range of outcome measures, that is, for pain and health-related quality of life, using different scales. To account for this we will convert the available data into standardized mean difference and the SE that can be directly used in the NMA applying the standard WinBUGS codes available from the NICE DSU documents [54], that is, we will use the codes for combining "treatment differences." We may also encounter cases in which pain may be reported as "pain response" in some trials, but reported as continuous outcomes in other trials. In these cases, we will convert the available data

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into standardized mean difference using the methods provided in the Cochrane Handbook (version 6.3, Section 10.6) [62] for the conversion of odds ratio to standardized mean difference (and its SE). Once converted into standardized mean difference, this can be used in the same way as above in the NMA. We will consider this variation in the way that outcomes are reported as a source of heterogeneity and address this by meta-regression and subgroup analysis, as appropriate.

Investigation of Heterogeneity

We will assess statistical heterogeneity by comparing the results of the fixed-effect model meta-analysis and the random-effects model meta-analysis, between-study variance, and by calculating NMA-specific I^2 [64]. If we identify substantial, clinical, methodological, or statistical heterogeneity, we will explore and address the heterogeneity in subgroup analysis and meta-regression by using the methods and codes described in the NICE DSU documents [65].

Inconsistency

We will evaluate the plausibility of transitivity assumption by looking at the inclusion and exclusion criteria in the studies and limit the NMA to a subset of trials, where transitivity assumption is reasonable.

We will assess inconsistency (statistical evidence of the violation of transitivity assumption) by fitting both an inconsistency model and a consistency model. We will use the inconsistency models employed in the NICE DSU manual [59], as we will use a common between-study SD. In addition, we will use the design-by-treatment full interaction model and inconsistency factor plots to assess inconsistency [56,66]. If there was evidence of inconsistency, we will identify areas in the network where substantial inconsistency might be present in terms of clinical and methodological diversities between trials and, when appropriate, limit NMA to a more compatible subset of trials.

Sensitivity Analysis

In addition to the best–worst case scenario and worst–best case scenario sensitivity analyses mentioned above, we will also perform a sensitivity analysis excluding the trials in which mean or SD or both were imputed and use different imputed SDs.

Work Package 2: Development of the Clinical Care Pathway

The information from work package 1 (both systematic reviews and NMA) will be supplemented by surveys and focus group discussions involving patients, carers, and health care professionals. We aim to engage these key stakeholders in a discussion about the acceptability and feasibility of interventions toward developing an evidence-based clinical care pathway for the management of pain and cachexia in pancreatic cancer.

Surveys

Two web-based surveys will be performed: one directed to patients or carers and the other to health care professionals. Both surveys will address pain and cachexia symptoms in turn and will precede the focus group discussions. Both surveys will include a question asking respondents whether they would be willing to participate in a focus group to further discuss the acceptability and feasibility of the different treatments toward the development of a care pathway for pancreatic cancer pain and cachexia. In this way, we will recruit members for the subsequent focus group discussions. The surveys will be hosted via a web-based survey platform using REDCap software. We will also offer a word-processing version, as well as paper surveys with stamped return envelopes, to increase participation. There will be an appropriate mix of closed questions to allow for quantitative analysis and open questions enabling free-text, qualitative responses. The survey templates are available from the researchers upon request. We will use the Checklist for Reporting Results of Internet E-Surveys (CHERRIES) when formally reporting the results of the surveys for publication [67].

First Survey

For the sample frame, people with pancreatic cancer and their carers are identified through the Pancreatic Cancer UK patient network.

We expect approximately 50 responses for this survey. Although we recognize the importance of gaining views directly from people with pancreatic cancer, we have included carers due to the nature of this severe illness meaning people with pancreatic cancer and symptoms of the pan and cachexia may be too unwell to answer for themselves, and thus carers could provide valuable insights and views on behalf of people with pancreatic cancer.

The first survey aims to direct the focus group discussions toward deciding on the acceptability of the interventions (identified from the systematic reviews). We will provide the details of the procedure (what the procedure involves in plain language), and the effectiveness and complications of the procedures (again in plain language). Patients and carers will be asked to rank the treatments in the order of their preference or acceptability, according to how acceptable or tolerable they consider the treatment to be. We will summarize the acceptability (after stratification by symptom) in bar charts and pie charts.

Second Survey

For the sampling frame, health care professionals in NHS are identified through the Pancreatic Cancer UK clinical network.

We will also use the National Cancer Research Institute Upper Gastrointestinal Group (Pancreatic cancer Workstream) to publicize and increase the outreach of the survey. We expect around 50 responses for this web-based survey.

The purpose of the second survey will be to help inform the focus group discussions to understand the feasibility of performing the above interventions (identified in the systematic reviews) in the NHS and where best to deliver the intervention (ie, community, primary care, secondary care, specialist centers, hospice, etc). Health care professionals will be asked to score each intervention on a scale of 1 to 10, according to how feasible or realistic they consider for it to be delivered in NHS. We will summarize the feasibility of the treatments (after stratification by the category of the health care professional) in bar charts and pie charts.

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Focus Group Discussions

We will conduct focus group discussions involving patients, their carers, and health care professionals to develop a care pathway using the information from the systematic reviews (work package 1) and the surveys described above. Having a rich, mixed focus group (50% patients and carers and 50% health care professionals) will enable all participants to discuss their respective opinions and comments regarding the acceptability and feasibility of treatments, thereby enabling a consensus to be reached.

We will present the evidence from the systematic reviews and meta-analysis, and acceptability of treatments for each of pain and cachexia in two ways:

- ordered by the number of people who ranked an intervention as the most acceptable treatment
- ordered by their weighted ranking score using weights applied in reverse, for example, if there were 5 interventions, the most acceptable intervention will get a weight of 5, the second most acceptable intervention a weight of 4, the third most acceptable intervention a weight of 3, and so on.

Similarly, we will then present the feasibility of treatments in the NHS for each of pain and cachexia in 2 ways:

- ordered by the number of people who ranked an intervention as the most feasible treatment
- ordered by the average feasibility score.

After the presentation of the results of the surveys, the focus group will begin in-depth discussions to review the findings. The focus group discussions will focus around areas of contention—that is, interventions that are acceptable to patients but not very feasible to deliver in NHS or vice versa, or interventions that are highly acceptable but limited efficacy is found in the systematic review. Additionally, further discussions will take place regarding the most appropriate site of delivery of interventions. The templates for the focus group discussions are available from the researchers on request. We anticipate 2 focus group discussions (involving 8 to 12 participants each) covering each symptom (ie, 2 focus groups for pain interventions and 2 focus groups for cachexia interventions). Each round will be iterative, in that findings from the first focus groups in each symptomology will feed into each of the second focus group discussions. Each focus group's meeting is expected to last from 60 to 90 minutes. We plan to conduct the focus group meetings in-person; however, we have the flexibility to conduct the meetings on the web via Microsoft Teams or using a hybrid model, if preferable for participants. We will record all focus group discussions and use General Data Protection Regulation–compliant transcription services for transcribing the discussions for analysis. The transcript will not contain any identifiable participant details.

The focus group discussions will be analyzed using the Framework method [68], using a preliminary logic model developed following Phase 1 of the study to inform the development of the analytical framework. This logic model will describe the theory underlying a potential care pathway for the management of pain and cachexia and will use a Situation (*pain, cachexia*)–Inputs (*resources*)–Outputs (*activities*)–Mechanism –Outcomes (*short and longer terms*) configuration [69,70]. The focus group data will be coded and mapped onto this framework and further themes and subthemes will be developed and used to modify the logic model as required. Regular research team discussions will be held to ensure that the coding scheme reflects the data. We will use the Standards for Reporting Qualitative Research when formally reporting the results of the focus group discussions for publication [71].

We anticipate the development of a proposed care pathway in further iterative communications among the research team and relevant additional health care professionals (depending upon the intervention) identified through National Cancer Research Institute Upper Gastrointestinal Group (Pancreatic cancer Workstream), thus reaching a final agreement via email or teleconferences.

Patient and Public Involvement

The research team includes a patient representative who was involved in the preparation of the grant project proposal and determined that this research was important to patients. The patient representative will be part of the research oversight committee for the project and will help to facilitate the focus group discussions.

Ethics Approval

This study was approved by the University College London Research Ethics Committee (Ethics number: 23563/001).

Results

The funding for this study has been awarded from April 2022 to April 2024. The actual project start date occurred on schedule in April 2022. Immediately, prior to any study selection or formal searches, both systematic review protocols were prospectively registered publicly on the PROSPERO database in May 2022, along with the formal search strategies (CRD42022333239 and CRD42022333241). Formal searches and subsequent study screening began shortly thereafter. Data collection began in January 2023. Ethical approval (with regard to the surveys and focus groups pertaining to the second part of the project) was received in December 2022, and hence the full project protocol was prepared for publication in January 2023. Data collection began in January 2023 and data analysis is due to begin in May 2023 (expected to be completed by October 2023). Surveys and focus groups will run thereafter. The project ends in April 2024 and results are expected to be published within 12 months of project completion.

Discussion

Strengths and Limitations of This Study

This study will provide comprehensive coverage of all the major interventions for the management of pain in people with pancreatic cancer not suitable for pancreatic resection, and for the prevention and treatment of cachexia in people with pancreatic cancer regardless of whether they are suitable for pancreatic resection. It will also be the first time for network meta-analysis to be used for the systematic review on the

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management of pain in people with unresectable pancreatic cancer, which has several advantages in terms of evaluating multiple treatment comparisons, and enabling calculation of additive main effects, 2-way interactions, and the full interaction models, which allow us to find out if there are any interactions between different combinations of treatments. However, the main limitation of the study is that sufficient outcome data may not be available from the randomized trials to enable network meta-analysis to be performed.

Nevertheless, this study will identify the gaps in the existing research that cause uncertainty in decision-making in the management of pain and cachexia in people with pancreatic cancer. A further strength is that the study will consult key stakeholders in the development of an evidence-based care pathway for pain and cachexia in pancreatic cancer, ensuring acceptability for patients and carers and feasibility for delivery in the NHS.

Dissemination

The team will disseminate the findings of the research through patients group websites, social media groups, conferences, and publish the findings in peer-reviewed journals.

Acknowledgments

The authors used the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols checklist when writing their report [72]. This work is funded by the National Institute for Health and Care Research (NIHR) Research for Patient Benefit Programme (Project Ref: NIHR202727). This protocol is based on the grant application that was submitted, peer-reviewed, and accepted by the funder; however, the funder was not involved in the preparation of this manuscript. The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.

Data Availability

For the systematic reviews in work package 1, all the data will be available from the published report. Regarding data generated from the surveys and focus group discussions in work package 2, we will provide summary data only, in line with the data management plan that was ethically approved.

Authors' Contributions

DAR and KG wrote the manuscript. The manuscript was critically revised by EW, CM, YK, SP, APS, EP, JS, MHG, and BD. DAR is the guarantor of this manuscript.

Conflicts of Interest

KG is the co-lead applicant for the grant from NIHR which provides funding for this report. Their promotions and salary depend upon peer reviewed journal publications. The clinical practice of the clinicians in the project (DAR) may be altered by the findings of the review.

Multimedia Appendix 1
Peer review reports.
[PDF File (Adobe PDF File), 464 KB - resprot_v12i1e46335_app1.pdf]

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Abbreviations

CHERRIES: Checklist for Reporting Results of Internet E-Surveys

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CrI: credible interval
NHS: National Health Service
NICE DSU: National Institute of Health and Care Excellence Decision Support Unit
NMA: network meta-analysis
NSAIDs: nonsteroidal anti-inflammatory drugs
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO: International Prospective Register of Systematic Reviews

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Protocol

Risk of Bias Mitigation for Vulnerable and Diverse Groups in Community-Based Primary Health Care Artificial Intelligence Models: Protocol for a Rapid Review

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Abstract

Background: The current literature identifies several potential benefits of artificial intelligence models for populations' health and health care systems' efficiency. However, there is a lack of understanding on how the risk of bias is considered in the development of primary health care and community health service artificial intelligence algorithms and to what extent they perpetuate or introduce potential biases toward groups that could be considered vulnerable in terms of their characteristics. To the best of our knowledge, no reviews are currently available to identify relevant methods to assess the risk of bias in these algorithms. The primary research question of this review is which strategies can assess the risk of bias in primary health care algorithms toward vulnerable or diverse groups?

Objective: This review aims to identify relevant methods to assess the risk of bias toward vulnerable or diverse groups in the development or deployment of algorithms in community-based primary health care and mitigation interventions deployed to promote and increase equity, diversity, and inclusion. This review looks at what attempts to mitigate bias have been documented and which vulnerable or diverse groups have been considered.

Methods: A rapid systematic review of the scientific literature will be conducted. In November 2022, an information specialist developed a specific search strategy based on the main concepts of our primary review question in 4 relevant databases in the last 5 years. We completed the search strategy in December 2022, and 1022 sources were identified. Since February 2023, two reviewers independently screened the titles and abstracts on the Covidence systematic review software. Conflicts are solved through consensus and discussion with a senior researcher. We include all studies on methods developed or tested to assess the risk of bias in algorithms that are relevant in community-based primary health care.

Results: In early May 2023, almost 47% (479/1022) of the titles and abstracts have been screened. We completed this first stage in May 2023. In June and July 2023, two reviewers will independently apply the same criteria to full texts, and all exclusion motives will be recorded. Data from selected studies will be extracted using a validated grid in August and analyzed in September 2023. Results will be presented using structured qualitative narrative summaries and submitted for publication by the end of 2023.

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Conclusions: The approach to identifying methods and target populations of this review is primarily qualitative. However, we will consider a meta-analysis if quantitative data and results are sufficient. This review will develop structured qualitative summaries of strategies to mitigate bias toward vulnerable populations and diverse groups in artificial intelligence models. This could be useful to researchers and other stakeholders to identify potential sources of bias in algorithms and try to reduce or eliminate them.

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KEYWORDS

health equity; health disparity; algorithms; artificial intelligence; primary care; rapid review; systematic review

Introduction

Background

There is growing interest in artificial intelligence (AI) in medical research and clinical practice. Judicious use of algorithms could potentially improve the quality of care and accessibility to health services [1,2]. AI in health care is mostly used for training supervised models on previously collected data [1,3]. Some health specialties benefit from these tools that allow the application of AI models safely with a controlled risk of bias. For instance, the use of AI in medical imaging allows an improvement in the detection of some anomalies [4,5], and initiatives in radiology seem to improve efficiency and health outcomes [6]. Similarly, AI models could potentially have a positive impact on populations in vulnerable situations who access the health care system through primary care [1,7]. Unfortunately, AI remains poorly integrated into primary and community health services [8].

A potential use and implementation of AI models in the primary health care context could be in citizen portals by promoting health-oriented behaviors and preventing the onset of chronic diseases [8]. As elsewhere in Canada and worldwide, such portals are currently implemented in some electronic medical records in the province of Québec and serve as an interface between clinicians and patients [9]. These portals can provide access to laboratory results, reports of health questionnaires, or communication with health care professionals.

Citizen portals with integrated AI could lead to virtual assistance throughout the health care system or in situations where vulnerable populations do not have direct and rapid access to physicians' advice (eg, remote, isolated, vulnerable, and stigmatized populations) [1,2]. However, since these AI models are deployed in communities and vulnerable populations are concerned, there are risks of biases affecting patient care quality and safety, and their sources must be explored and identified prior to implementation [10]. We need to take a specific interest in medical and ethical parameters to ensure user quality and safety, as these models may be biased especially by ethnicity, sex, or gender [11-14]. Moreover, inequitable access to resources and recommendations could potentially put some users at risk [10].

Community-Based Primary Health Care

As defined by the Canadian Institutes of Health Research, community-based primary health care (CBPHC) "covers the broad range of primary prevention (including public health) and primary care services within the community, including health promotion and disease prevention; the diagnosis, treatment, and management of chronic and episodic illness; rehabilitation support; and end of life care" [15]. The current literature identifies several potential benefits of AI to develop and integrate clinical tools for population health, care team well-being, and efficiency of the CBPHC system [1,16-18]. Integration of AI technologies into CBPHC could help in many ways especially "to help people to get the care (including prevention) they need" [15]. However, there is a lack of understanding on how the risk of bias is considered in the development of these AI models and to what extent they perpetuate or introduce potential biases toward groups that could be considered vulnerable in terms of their characteristics (eg, sex, gender identity, sexual orientation, race, ethnicity, socioeconomic status) [16,19]. In response to this concern, the US Food and Drug Administration recently "calls for efforts to develop a methodology to develop devices to be well suited for a racially and ethnically diverse patient population" [1,16].

In a recent scoping review with the objective to "assess the nature and extent of the body of research on AI to primary care," the authors concluded that AI "is at an early stage of maturity (...) and more evaluation studies are needed" [7]. To the best of our knowledge, no reviews are available on methods to assess risk of bias and health inequity in primary care algorithms. We recently found a scoping review protocol aiming "to summarize the extent to which AI systems in primary care examine the inherent bias toward or against vulnerable populations and appraise how these systems have mitigated the impact of such biases during their development" [20]. Unless we are mistaken, the results of this protocol have not yet been published, and we still lack an overview of bias mitigation interventions and the characterization of groups and subgroups to which they are applied in CBPHC.

The aim of this rapid qualitative systematic review is to identify relevant methods (eg, frameworks, tools, checklists) for a risk of bias assessment for vulnerable or diverse groups in the development or deployment of algorithms in CBPHC and identify mitigation strategies deployed to promote and increase equity, diversity, and inclusion in CBPHC algorithms.

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Review Questions

The research questions are:

- Which strategies have been suggested for consideration when assessing the risk of bias in CBPHC algorithms toward vulnerable or diverse groups?
- What methods assessed the risk of bias for vulnerable and diverse groups in CBPHC algorithm applications?
- Which mitigation interventions are deployed and (if applicable) what are the quantitative results?

Methods

Overview

This protocol follows the Cochrane Collaboration guidance for rapid reviews [21] and the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) guidelines [22,23]. PRISMA-P guidelines recommend the use of PICO (Participant, Intervention, Comparator, and Outcome) to frame the review question and develop a search strategy [22,23]. However, other options are available depending on the review objective. For a scoping review, the Joanna Briggs Institute recommends the PCC (Population or Participant, Concept, and Context) search framework [24]. Although we are not in a scoping review process, the PCC search framework [25] seems more appropriate and consistent with our open-ended qualitative research question (Table 1).

Table 1. PCC (Population or Participant, Concept, and Context) framework used for the search strategy[a].

PCC elements	Definition (per JBI Reviewer's Manual Ch 11)	PCC elements applied in this review
Population	"Important characteristics of participants, including age and other qualifying criteria" (11.2.4)	Any vulnerable populations or diverse groups
Concept	"The core concept examined by the scoping review should be clearly articulated to guide the scope and breadth of the inquiry. This may include details that pertain to elements that would be detailed in a standard systematic review, such as the 'interventions' and/or 'phenomena of interest' and/or 'outcomes'" (11.2.4)	Strategies or methods to assess risk of bias in algorithms (artificial intelligence)
Context	"May include...cultural factors such as geographic location and/or specific racial or gender-based interests. In some cases, context may also encompass details about the specific setting."	Community-based primary health care

[a]PCC framework [25]. Topic: risk of bias assessment methods developed/used in community-based primary health care algorithms. Primary review question: Which strategies can assess the risk of bias in community-based primary health care algorithms toward vulnerable or diversity groups?

Search Strategy

In November 2022, an information specialist developed a search strategy based on the main concepts of our primary review question and adapted it to the most relevant databases (PubMed, CINAHL, Web of Science, and PsychINFO). We used five relevant articles to test the sensitivity, and the search covered the last 5 years (2017-2022) aligned with the concept's emergence time frame. The database search strategies can be found in Multimedia Appendix 1.

Data Collection

We include all studies on methods developed or tested to assess risk of bias in algorithms that are relevant in CBPHC. In December 2022, all citations were exported to the web-based collaborative tool Covidence (Veritas Health Innovation) [26] where 581 duplicates were removed by the automated function. Since February 2023, two reviewers have independently screened the titles and abstracts of the identified records (N=1022) and assessed the inclusion and exclusion criteria (Table 2). Conflicts on study selection are resolved by consensus, and the opinion of a senior researcher is sought if required. At the full-text assessment step, two reviewers (and the information specialist if required) will search and obtain all the full texts of the selected references, and they will import the PDF files into Covidence.

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Table 2. Inclusion and exclusion criteria.

PCC[a] elements [25]	Inclusion criteria	Exclusion criteria
Population	• Any vulnerable populations or diverse groups targeted by CBPHC[b] interventions	• Any populations targeted by hospital or specialized care interventions
Concept	• All the methods, tools, recommendations, or any intervention used to assess the risk of bias in CBPHC algorithms • All mitigation strategies deployed to promote and increase equity, diversity, and inclusion in CBPHC algorithms	• Methods or interventions not CBPHC related • CBPHC interventions that do not include any algorithm/AI[c] system
Context	• Include all the CBPHC algorithms (AI) applications that can perpetuate/introduce potential biases toward groups that could be considered as vulnerable in terms of their characteristics	• Algorithms used by primary health care providers for support in administrative tasks and for operational aspects, rather than for clinical decisions

[a]PCC: Population or Participant, Concept, and Context.

[b]CBPHC: community-based primary health care.

[c]AI: artificial intelligence.

Data Extraction

Team members will complete the extraction on a structured prespecified grid in Covidence, and the data will be reviewed and pretested by the research team. We will extract descriptive data (title, year of publication, authors, country), study type (published, study design), and population data (populations targeted by the intervention, number of participants). Characteristics of populations will be mainly extracted to our prespecified grid according to the PROGRESS (place of residence, race/ethnicity/culture/language, occupation, gender/sex, religion, education, socioeconomic status, and social capital) framework [27]. This framework addresses "health inequalities and unfair differences in disease burden," and these characteristics "that stratify health opportunities and outcomes" are "place of residence, race/ethnicity/culture/language, occupation, gender/sex, religion, education, socioeconomic status, and social capital" [27]. We will add to that list the "Plus" in the acronym PROGRESS-Plus, referring to the "1) personal characteristics associated with discrimination (e.g. age, disability) 2) features of relationships (e.g. smoking parents, excluded from school) 3) time-dependent relationships (e.g. leaving the hospital, respite care, other instances where a person may be temporarily at a disadvantage)" [28].

We will also extract concept data: identification and characteristics of the assessment method used/developed; identification and characteristics of the algorithm, including purpose (eg, diagnosis- or prognosis-related, used for disease detection or surveillance), type (eg, machine learning, natural language processing, expert systems), and any other available detail (eg, input information/parameters, outcomes); and context data, including details about the specific settings (ie, identification of potential biases for vulnerable or diverse groups) and the results of the intervention (eg, bias mitigation data).

Quality Assessment

We will appraise the quality of empirical studies included based on experiment, observation, or simulation (randomized controlled trial, quasi–randomized controlled trial, prospective cohort study, pre-post study, observational study, mixed methods study, qualitative study) by applying the Mixed Methods Appraisal Tool (MMAT) [29].

Data Synthesis

We will synthesize data using structured narrative summaries around our main concept/context and provide a list of available methods. The development process and main features of the methods (eg, potential sources of bias/items covered, signaling questions, differences and similarities, strengths and weaknesses) will be described. Furthermore, we will present mitigation strategies deployed with these methods (eg, algorithm parameter adjustments, mitigation or elimination of bias).

Ethics Approval

We obtained approval by the Ethics board of the "Comité d'éthique de la recherche sectoriel en Santé des Populations et Première Ligne du CIUSSS de la Capitale-Nationale" for the Protecting and Engaging Vulnerable Populations in the Development of Predictive Models in Primary Health Care for Inclusive, Diverse and Equitable AI (PREMIA) project (#2023-2726).

Results

We completed the search strategy in December 2022, when 1022 sources were identified and 581 duplicates were removed by the automated function of Covidence. In early May 2023, a total of 479 out of 1022 (46.9%) titles and abstracts have been screened. This first screening step was completed in May 2023. In June and July 2023, two reviewers will independently apply the same inclusion and exclusion criteria to full texts. Data from the selected studies will be extracted using a validated grid in August 2023. The quality of studies will be appraised along with the data extraction by applying the MMAT [29] in August 2023. Data will be analyzed in September 2023, and the results will be presented using structured qualitative narrative summaries. We plan to complete this review and submit a final manuscript by the end of 2023.

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Discussion

Principal Findings

We anticipate structured narrative summaries of identified bias mitigation methods would be useful to researchers, data scientists, ethicists, and other CBPHC providers. We also anticipate that identification and documentation of these methods would be particularly relevant for multidisciplinary teams: "AI initiatives should have two main goals: they should be designed and utilized in a manner that does not create or maintain health disparities currently experienced by vulnerable groups, and they should address and remove existing health disparities" [1]. We hypothesize that giving methods and tools to multidisciplinary teams, with the participation of vulnerable populations in the entire process, would be useful to achieve inclusive AI when applied to health. We also expect that few studies will present quantitative bias mitigation data and results. Nevertheless, we will present these data in qualitative structured summaries.

Comparison to Prior Work

Other reviews generally focused on a few specific population characteristics. In a recent study on hospital readmission rates, the authors focused on racial and socioeconomic status biases in algorithms due to an increased risk in these groups [19]. In another example, the authors explored the source of age-related bias in AI systems [30]. There are many other "subgroups or unprotected groups" that can be considered to address "health inequalities and unfair differences in disease burden" [31]. We expect that our focus on primary health care will offer a different insight and that the PROGRESS-Plus framework will be helpful to identify potential interventions to mitigate health inequalities [27,28]. We anticipate listing and describing which vulnerable or diverse groups are considered (and which could be considered).

Strengths and Limitations

The main strength of our review is that we are applying an equity lens [27,28] to describe mitigation strategies in primary health care AI models. However, this review has three main limitations. First, its rapid nature implies that we limit our search to the last 5 years and to 4 databases only. Some relevant studies might not be included. However, given the recent interest in AI in primary care, this is unlikely. Second, we will consider all types of health conditions and various types of populations, which could bring important heterogeneity in the results and limit the possibility of synthesizing this information. Finally, applying the findings of this review to existing AI-based algorithms could present challenges because of the different contexts and populations in which they were developed.

Future Directions and Dissemination Plan

This rapid review is the first step of the larger PREMIA project. This work will be presented to key stakeholders, and we will conduct qualitative data collection to identify and evaluate biases in one AI model. Giving a voice to diverse groups [32,33] at the development or deployment stages of CBPHC AI-based algorithms could have a substantial impact on this review. Recommendations will be implemented into tools able to guide developers, researchers, and decision makers on strategies to reduce the risk of bias in AI primary health care programs and services, with the objective to protect vulnerable groups and not further exacerbate inequalities.

Conclusion

Identifying methods developed and deployed to mitigate biases toward vulnerable populations is needed to develop equitable primary health care. AI models can have many benefits for patients, but factors that stratify health opportunities and outcomes need to be addressed to mitigate inequalities toward members of vulnerable or diverse groups. To our knowledge, no reviews are currently available to identify risk of bias mitigation strategies in CBPHC AI algorithms. This rapid review will contribute to providing comprehensive structured narrative summaries of risk of bias assessment methods. This knowledge could be useful to CBPHC researchers and other stakeholders to identify potential sources of bias in AI algorithm development and eventually try to reduce or eliminate them.

Acknowledgments

The Protecting and Engaging Vulnerable Populations in the Development of Predictive Models in Primary Health Care for Inclusive, Diverse and Equitable AI (PREMIA) project is funded by the International Observatory on the Societal Impacts of AI and Digital Technology (OBVIA).

Data Availability

The database search strategy data is available in Multimedia Appendix 1. All data generated or analyzed during this study (including the PRISMA [Preferred Reporting Items for Systematic Reviews and Meta-Analyses] flow diagram) will be included in the results manuscript submission as multimedia appendix files. Databases created in the data extraction process can be provided upon reasonable request.

Authors' Contributions

MS is the corresponding author and guarantor of the review. MPG is the leader of Predictive Models in Primary Health Care for Inclusive, Diverse and Equitable AI (PREMIA) project administration and funding acquisition. All authors, except SO and FB, contributed to the whole PREMIA project design. MS and MPG equally contributed to the design, methodology, and review of

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this protocol. SO wrote the initial manuscript, and FB developed the specific search strategy. CR and VC reviewed the initial manuscript and submitted suggestions and modifications. All authors reviewed and approved this manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
The search strategies for each database.
[DOCX File , 25 KB - resprot_v12i1e46684_app1.docx]

Multimedia Appendix 2
Peer-review reports from the l'Observatoire international sur les impacts sociétaux de l'IA et du numérique (OBVIA) / International Observatory on the Societal Impacts of AI and Digital Technology (Quebec, Canada).
[PDF File (Adobe PDF File), 99 KB - resprot_v12i1e46684_app2.pdf]

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Abbreviations

AI: artificial intelligence
CBPHC: community-based primary health care
MMAT: Mixed Methods Appraisal Tool
PCC: Population or Participant, Concept, and Context
PICO: Participant, Intervention, Comparator, and Outcome
PREMIA: Protecting and Engaging Vulnerable Populations in the Development of Predictive Models in Primary Health Care for Inclusive, Diverse and Equitable AI
PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols
PROGRESS: place of residence, race/ethnicity/culture/language, occupation, gender/sex, religion, education, socioeconomic status, and social capital

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Protocol

Clinical Integration of Digital Patient-Reported Outcome Measures in Primary Health Care for Chronic Disease Management: Protocol for a Systematic Review

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Abstract

Background: Health measurement guides policies and health care decisions are necessary to describe and attain the quintuple aim of improving patient experience, population health, care team well-being, health care costs, and equity. In the primary care setting, patient-reported outcome measurement allows outcome comparisons within and across settings and helps improve the clinical management of patients. However, these digital patient-reported outcome measures (PROMs) are still not adapted to the clinical context of primary health care, which is an indication of the complexity of integrating these tools in this context. We must then gather evidence of their impact on chronic disease management in primary health care and understand the characteristics of effective implementation.

Objective: We will conduct a systematic review to identify and assess the impact of electronic PROMs (ePROMs) implementation in primary health care for chronic disease management. Our specific objectives are to (1) determine the impact of ePROMs in primary health care for chronic disease management and (2) compare and contrast characteristics of effective ePROMs' implementation strategies.

Methods: We will conduct a systematic review of the literature in accordance with the guidelines of the Cochrane Methods Group and in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines for its reporting. A specific search strategy was developed for relevant databases to identify studies. Two reviewers will independently apply the inclusion criteria using full texts and will extract the data. We will use a 2-phase sequential mixed methods synthesis design by conducting a qualitative synthesis first, and use its results to perform a quantitative synthesis.

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Results: This study was initiated in June 2022 by assembling the research team and the knowledge transfer committee. The preliminary search strategy will be developed and completed in September 2022. The main search strategy, data collection, study selection, and application of inclusion criteria were completed between October and December 2022.

Conclusions: Results from this review will help support implementation efforts to accelerate innovations and digital adoption for primary health care and will be relevant for improving clinical management of chronic diseases and health care services and policies.

Trial Registration: PROSPERO International Prospective Register of Systematic Reviews CRD42022333513; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=333513

International Registered Report Identifier (IRRID): DERR1-10.2196/48155

(JMIR Res Protoc 2023;12:e48155) doi:10.2196/48155

KEYWORDS

systematic review; patient-reported outcome measure; primary healthcare; health care; implementation science

Introduction

Primary health care is essential, comprehensive, and universally available to a community [1]. For most of the Canadian population, primary health care represents the first contact with the health care system, and in 2016, overall, 88.5% of the Canadian population had access to a family physician attached to a primary health care service [2]. Mostly managed in primary health care, chronic diseases affect 3 out of 5 Canadian adults, significantly impacting their quality of life, and account for approximately 80% of disability and 70% of deaths in Canada [3]. Primary health care management of chronic diseases remains a challenge at the core of the health care system.

Health measurement guides policies and health care decisions and is necessary to describe and attain the quintuple aim of improving patient experience, population health, care team well-being, health care costs, and equity [4]. In the primary care setting, health measurement allows outcome comparisons within and across settings and helps improve the clinical management of patients [4,5]. However, for these outcomes to be informative, researchers, key stakeholders, clinicians, and patients must codevelop a measurement framework integrating the perspectives of end users [5,6] and for outcome measurement to deliver on the promise of addressing the quintuple aim [5].

Patient-reported outcome measures (PROMs) are health reports of patients' conditions, capturing their perception of their own health, without clinician input [5]. PROMs enable patients to report on their quality of life, daily functioning, symptoms, and other aspects of their health and well-being [5]. A body of evidence shows that effective use of PROMs in the clinical context reduces consultation time [7], improves patient-provider communication [8], identifies patient needs and allows for a patient-centered practice [9], decreases symptom severity, increases survival, and decreases emergency department visits [10,11].

The development of integrated digital solutions to care pathways is essential for PROMs to have a clinical impact [8,12,13]. It has been reaffirmed in the 2021-2026 Canadian Institutes for Health Research's strategic plan that researchers must accelerate digital transformation of health care systems for efficient health measurement and data analysis [4]. Electronic PROMs (ePROMs) can bring several benefits to the use of pen-and-paper PROMs: higher motivation to complete the task of self-reporting, lower rates of missing data and errors, improved chronology on historical patients' data [14], remote and quick data collection, integrated data analysis, and availability of reports for care teams [15].

However, ePROMs are still not adapted to the clinical context of primary health care, which is an indication of the complexity of integrating these tools in this context [16,17]. The effectiveness of including ePROMs in routine clinical care has been studied in contexts of specialized care among homogenous patient groups based on diagnoses such as cancer [18-24]. Whereas successful ePROMs implementation in Canada has been noted (eg, Cancer Care Alberta), unfortunately, there are additional implementation challenges specific to primary health care, including the heterogeneity of the patient population [25]. There are also significant disparities among patients regarding their ability to understand and use digital tools [26]. The development of ePROMs is expected to increase the existing digital divide and reduce the ability to self-report outcomes among certain populations [26]. Understanding the extent to which ePROMs provide outcomes for clinicians and patients and prioritize the adaptation of additional ePROMs in this context is critical to present exhaustive evidence of what works and how to implement ePROMs in primary health care. Consequently, to address these abovementioned critical needs and challenges, we must gather evidence of the impact of ePROMs on chronic disease management in primary health care and understand the characteristics of effective implementation.

With the goal of accelerating the integration of ePROMs to optimize the delivery of primary health care and bring about rapid and meaningful benefits to patients, we will conduct a systematic review to identify and assess the impact of ePROMs implementation in primary health care for chronic disease management.

Our objectives are to (1) determine the impact of ePROMs in primary health care for chronic disease management and (2) compare and contrast the characteristics of effective ePROMs implementation strategies. We expect that our results will directly contribute to providing decision makers with high-quality, timely, accessible, and relevant evidence to inform policies and practices.

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Methods

We will conduct a systematic review of the literature in accordance with the guidelines of the Cochrane Methods Group and in compliance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines for its reporting [27,28]. We have registered the study protocol to the PROSPERO systematic review registry (CRD42022333513) [29].

Conceptual Underpinnings

This review will be grounded in the integrated knowledge translation approach to pursue its objectives [30]. According to this approach, knowledge users (KUs) will be involved in all aspects of the research process to enhance its relevance and usability in practice. The Strategy for Patient-Oriented Research framework for patient engagement will be used to complete integrated knowledge translation in promoting a respectful climate between researchers and KUs, including decision makers and patient partners [31].

Synthesis Questions

The following questions will be addressed: (1) what are the outcomes of ePROMs in primary health care in chronic disease management? (2) What are the effective strategies to implement ePROMs in primary health care? (3) What are the challenges, barriers, and facilitators to successful implementation of ePROMs in primary health care?

Eligibility Criteria

We will address all types of evidence matching the Population, Intervention, Comparison, Outcomes, and Setting/context criteria [28]. *Participants* include all studies reporting on the implementation of an ePROM among adults for chronic disease management. We have no restrictions regarding the *Interventions/phenomena of interest*; we will include all types of implementations, theoretical models, structures or PROMs. We have no restrictions regarding the *Comparator*; we will consider all outcomes reported in the studies. We will seek outcomes related to patients, caregivers, health care providers, policy makers, barriers, facilitators, acceptability, feasibility, adoption, fidelity, morbidity, mortality, quality of life, satisfaction, cost and cost-effectiveness. Regarding *Setting*, we will only include studies taking place in primary health care settings in any geographical setting and extract information regarding implementation. All types of studies will be included (ie, those using qualitative, quantitative, and mixed methods), which were published in French, English, or Spanish.

Search Strategy

We will develop the search strategy under the leadership and guidance of an experienced information specialist (FB). An iterative process of revision by the research team members and a revision by another experienced information specialist will be carried out (per the PRESS [Peer Review of Electronic Search Strategies] checklist) [32]. All relevant comments will be integrated in the final version of the search strategy. Specific search strategies will be formulated for the following databases: Cochrane Database of Systematic Reviews, MEDLINE (Ovid), CINAHL (EBSCO), Embase, PsycINFO (Ovid), Web of Science, and ProQuest Dissertations & Theses. Considering the recent nature of the topic, a time limit of 20 years will be applied to the search strategies. No restriction on language will be applied. We will develop and include a gray literature search strategy. We will perform an internet search in the following sources and search engines: Google, Google Scholar, Canadian Evaluation Society, EuroScan, OpenGrey, Grey Literature Report, GreyNet, and Grey Matters. Since innovation implementations are often conducted by government entities or large health care systems, we will search within the websites of key governmental agencies (eg, US Agency for Healthcare Research and Quality's studies on health care systems [eg, Kaiser Permanente]). Furthermore, we will perform backward citation searches of included studies and recent literature reviews for additional relevant references.

Data Collection and Screening

We will export all citations in the web-based collaboration tool Covidence, where duplicated entries will be removed with the automation function [33]. Titles and abstracts will be screened independently by pairs of reviewers. A pilot testing to validate the screening process will be completed on 5% of a random sample of all studies. Variability in reviewer assessment will be documented using the Cohen κ statistic [34]. Ambiguous or incomplete abstracts will be retained to be reviewed in full and additional information could be obtained from the authors. We will search and obtain all the full texts of the selected references and will import the PDF files in Covidence. Pairs of reviewers will independently apply the inclusion criteria using the full texts following a pilot testing using the process outlined above. At any moment in the overall screening process, a third reviewer will help resolve any discrepancy. All the reasons for exclusion will be recorded in Covidence. A PRISMA flowchart will be used to describe study identification, screening, inclusions, and exclusions [35].

Data Extraction and Appraisal

We will codevelop the extraction form with all KUs and team members to ensure that we are capturing relevant information (ie, what matters the most for them). Pairs of reviewers will independently complete data extraction following a pilot testing (see above). We will extract descriptive data (title, year of publication, authors, funding, conflicts of interests, and country), study types (published or gray literature), methodological data (design, sample size, measure constructs, and name of the instrument), setting data (clinical setting, type health professionals, and patient population), implementation data (description of implementation activities, facilitators, and barriers), outcomes (patient health, providers workflow, and cost), and outcome types (qualitative and quantitative). The quality of the included studies will be evaluated using the mixed methods appraisal tool [36]—a tool adapted to systematic reviews synthesizing data from qualitative, quantitative, and mixed methods studies.

Data Synthesis

We will use the RE-AIM (reach, effectiveness, adoption, implementation, maintenance/sustainability) framework as a

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data analysis framework. The RE-AIM framework has been developed to evaluate the public health impacts of interventions and has been used in systematic reviews to help structure the assessment of the different implementation factors at play in complex contexts and settings [37,38]. This framework includes 5 dimensions: reach (how willing the targeted population is to participate in the intervention; ie, ePROMs), efficacy (what is the impact of the intervention on outcomes?), adoption (can this be adopted by new groups with ease and minimal changes?), implementation (what are the special issues and barriers?), and maintenance (can the intervention be maintained and its impact sustained?). The use of the RE-AIM framework will enable us to provide an overview of the parameters strengthening (review questions 2 and 3) the efficiency (review question 1) of ePROMs' integration in primary health care and its impact on outcomes associated with the quintuple aim.

We will use a 2-phase sequential mixed methods synthesis design (ie, conduct a qualitative synthesis) and use its results to perform a quantitative synthesis [39]. In phase 1 (qualitative), we will use a thematic synthesis procedure [40] wherein we will summarize and describe methods and approaches designed to implement and integrate ePROMs in primary care. The qualitative data synthesis will produce structured narrative summaries of main themes of data in accordance with the RE-AIM framework. In phase 2 (quantitative), for each phase 1 theme, we will synthesize quantitative data with study subgroups centered around the theme in a descriptive manner when statistics and calculation methods are available. We will summarize study characteristics and methodological differences and similarities to highlight the following points: strengths and weaknesses of each implementation method, main outcomes of implementation, main conclusions regarding the relationship between methods and outcomes, main resources used and their impacts, and whether any trade-offs are described and their effect on the results of the study. If data are available in the primary studies, sex and gender similarities and differences (eg, adoption and satisfaction) will be included in our synthesis. The diversity in team expertise, clinical background, and gender will contribute to the orientation of the synthesis and choices that could lead to inclusive recommendations for clinical choices and policies. This study will also follow the Canadian Institutes for Health Research's SAGER (Sex and Gender Equity in Research) for study design and reporting of the results. If needed, we will also provide training in sex and gender equity for the trainees and the patient partners on the team [41].

Results

The study was initiated in June 2022 by assembling the research team and the knowledge transfer committee. The preliminary search strategy was developed and completed in September 2022. The main search strategy, data collection, study selection, and application of inclusion criteria were completed between October and December 2022. Data analysis will be completed and reports, briefs, and papers will be written from January to September 2023. The knowledge translation committee meets throughout the study period, once every 2 months, but more actively, from January to March 2023.

Discussion

In order to not only impact but also document the extent of success toward the abovementioned quintuple aim, health measurements must include patients' self-evaluation of health, well-being, and behaviors that contribute to care quality, service comparability, provider performance, patient engagement, and general patient status. Effective implementation of relevant ePROMs in primary health care is necessary to orient chronic disease management that is patient-centered and personalized in a contemporary and modern context of care. This study aims to synthesize the learning from using ePROMs in primary health care organizations. This information will be useful in supporting the adoption of PROMs in clinical settings. Optimal implementation of PROMs in primary health care would improve perceived relevance and adoption by health care providers and patients. Results from this review will orient the delivery, accountability, effective implementation, and contextualized usefulness of PROMs for the implementation of ePROMs in clinical settings. Optimal implementation of ePROMs in primary health care would improve perceived relevance and adoption by health care providers and patients. Results from this review will orient the delivery, accountability, effective implementation, and contextualized usefulness of PROMs. The patient-centered approach facilitated by PROM use will greatly improve health equity for populations needing a personalized care approach of primary health care.

Results from this review will help support implementation efforts to accelerate innovations and digital adoption for primary health care and will be relevant for improving clinical management of chronic diseases, health care services, and policies. Efficient ePROM implementation has a direct impact on the quintuple aim of improving patient experience, improving health, improving health professionals experience, improving care value, and advancing health equity.

Data Availability

The data sets generated during and/or analyzed during this study are available from the corresponding author on reasonable request.

Conflicts of Interest

NB is the director of scientific affairs for the electronic medical records provider Omni-Med.Com Inc.

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Multimedia Appendix 1
Peer-review report.
[PDF File (Adobe PDF File), 419 KB - resprot_v12i1e48155_app1.pdf]

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Abbreviations

ePROM: electronic patient-reported outcome measure
KU: knowledge user
PRESS: Peer Review of Electronic Search Strategies

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PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROM: patient-reported outcome measure
RE-AIM: reach, effectiveness, adoption, implementation, maintenance/sustainability
SAGER: Sex and Gender Equity in Research

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Clinical Integration of Digital Patient-Reported Outcome Measures in Primary Health Care for Chronic Disease Management: Protocol for a Systematic Review
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Protocol

Determinants of Adolescent Sexual and Reproductive Health in Sub-Saharan Africa: Protocol for an Umbrella Review

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Abstract

Background: Adolescents are a large proportion of the population in sub-Saharan Africa and face multiple risks to their health and well-being. Prior systematic reviews have focused on specific adolescent sexual and reproductive health outcomes such as teen pregnancies, HIV/AIDS, and sexually transmitted diseases. A comprehensive synthesis of the influential factors that shape different aspects of adolescent sexual and reproductive health can inform health policy and program development for this important segment of the population.

Objective: This paper presents the protocol for an umbrella review that aims to synthesize the existing knowledge in the literature on the associations among individual, family, and societal factors and sexual and reproductive health outcomes among adolescents in sub-Saharan Africa.

Methods: We will include systematic reviews that identify factors associated with sexual and reproductive health outcomes among adolescents, 10-19 years of age, in sub-Saharan Africa. Reviews can include quantitative and qualitative primary studies with or without meta-analysis. Academic and gray literature searches will identify reviews from PubMed, Scopus, CINAHL, Cochrane Database of Systematic Reviews, ProQuest, Google, and Google Scholar. Two reviewers (MZG and KO) will independently carry out title, abstract, and full text screening, assess methodological quality, and extract data. We will assess the methodological quality of the included studies using the Joanna Briggs Institute standard forms. The review will present findings in narrative form and in tables and will follow PRISMA (the Preferred Reporting Items for Systematic Reviews and Meta-Analyses) reporting guidelines.

Results: A preliminary search in April 2023 found 1351 articles to be screened.

Conclusions: This umbrella review will permit a comprehensive and high-level understanding of the various factors that influence adolescent sexual and reproductive health in sub-Saharan Africa.

Trial Registration: PROSPERO International Prospective Register of Systematic Reviews CRD42023394512; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=394512

International Registered Report Identifier (IRRID): DERR1-10.2196/51278

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KEYWORDS

adolescents; youth; sexual health; reproductive health; sexually transmitted infections; pregnancy; sub-Saharan Africa

Introduction

Adolescence is the transition phase between childhood and adulthood that serves as a window of opportunity for development and growth. Different exposures help adolescents establish patterns of behaviors related to diet, physical activity, substance use, and sexual activity. These behaviors and influences, especially related to adolescent sexual and reproductive health (ASRH), can either protect or put at risk their health and the health of others around them now and in

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the future [1]. During the past 25 years, following the International Conference on Population and Development in Cairo (Egypt), there has been improvement in ASRH outcomes globally [2]. However, progress is unequal between and within countries and in different regions, such as Sub-Saharan Africa [3]. Adolescent girls in sub-Saharan Africa face an elevated risk of early marriage [4], teenage pregnancies [5], and exposure to unsafe abortions [6], leading to a high rate of maternal deaths among this group [7]. Lack of knowledge about safe sexual and reproductive behaviors and practices [8,9] exposes adolescents to HIV and sexually transmitted infections [10]. The risks are higher among rural girls who are poor and uneducated [4]. Multifaceted barriers at the individual, family, community, service, and policy levels still impede ASRH policies and programs in the provision of comprehensive information and services to adolescents [11-13]. Attitudes of peers, parents, family members, and service providers influence adolescents' access to ASRH information and services [14]. In many settings, discussion about ASRH and the use of related services, especially by unmarried adolescents, is stigmatized.

To improve ASRH and address inequalities, policy makers and planners need to set priorities based on robust evidence. Historically, statistics about adolescents have often been merged with children or adults even in national databases [15,16]. There has been a steady growth in published evidence, including systematic reviews, about ASRH in sub-Saharan Africa. However, studies and reviews focus on specific ASRH outcomes (such as the use of contraceptives [17], teen pregnancies [18,19], transactional sex [20], HIV/AIDS [21], and other sexually transmitted diseases [STDs]) or interventions [22]. There remains a need for a comprehensive and overarching review of factors associated with the range of ASRH outcomes. In our search of the 3 main systematic review registries (the PROSPERO [International Prospective Register of Systematic Review], Joanna Briggs Institute Systematic Review Register, and Open Science Framework Registries), we did not find any umbrella review registered on this topic.

This umbrella review will identify and summarize evidence on the factors associated with the range of ASRH outcomes in sub-Saharan Africa. The aim is to identify and synthesize existing knowledge on the associations between individual, family, and societal factors and ASRH outcomes. The research questions are (1) what are the overlapping and unique factors associated with a broad range of ASRH outcomes (including teen pregnancies, transactional sex, sexual abuse, gender violence, HIV/AIDS, and other STDs)? (2) What are the research gaps in the literature around ASRH in sub-Saharan Africa? The intention is to cover a wide range of ASRH outcomes, using previously synthesized evidence in systematic reviews. The review will form part of the evidence considered in a larger study to co-design strategies to promote and protect ASRH in Bauchi State, Nigeria [23].

Methods

Study Design

The umbrella review [24] will examine the documented associations between ASRH outcomes including teen pregnancy, transactional sex, sexual abuse, gender violence, HIV/AIDS, and various STDs, and individual, family, and societal factors. There are many preexisting reviews of factors related to specific ASRH outcomes; we will not conduct a review of primary studies. The unit of search and data analysis will be systematic and scoping reviews, with or without meta-analyses [25]. By using an umbrella review approach, we can cover a wide range of ASRH outcomes. An umbrella review will permit a more comprehensive and higher-level analysis of the various factors that influence ASRH in sub-Saharan Africa. We seek to synthesize the available evidence about factors associated with each ASRH outcome. We will examine whether the results and conclusions of individual reviews of factors related to specific ASRH outcomes are consistent or contradictory. This review will provide an overarching view of current knowledge about the multifaceted issue of ASRH and will identify research gaps in the literature.

Search Strategy

A comprehensive search strategy included both peer-reviewed articles and gray literature. We searched for peer-reviewed articles in PubMed, Scopus, CINAHL, and Cochrane Database of Systematic Reviews on April 11, 2023. The search matrix included a combination of controlled vocabulary and keywords to represent reviews, adolescents, sexual and reproductive health outcomes, and sub-Saharan Africa. We used a similar search matrix in the gray literature database ProQuest to search for relevant theses or dissertations. The gray literature search also used the Google and Google Scholar search engines with the search terms such as adolescent sexual reproductive Africa review. We included the first 10 search results from Google and Google Scholar in the initial screening. The initial searches considered published articles and gray literature irrespective of date of publication.

Eligibility Criteria

The review will include systematic and scoping reviews of both quantitative and qualitative primary studies, with or without meta-analyses. All included reviews must describe a reproducible and systematic search strategy, well-defined inclusion and exclusion criteria and outcome, and risk of bias assessment of included primary articles. We will include academic and gray literature in English or French, irrespective of the date of publication. The population of interest is adolescents, 10-19 years of age, in sub-Saharan Africa. This includes studies irrespective of gender, place of residence (urban and rural demographics), and educational attainment (students and out-of-school youth). We will include reviews that include children, adults, or countries outside of sub-Saharan Africa if they present disaggregated data on youth (10-19 years of age) and sub-Saharan Africa. We will exclude studies of specific subpopulations, such as athletes or orphans. Textbox 1 describes the inclusion and exclusion criteria for this umbrella review.

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Textbox 1. Inclusion and exclusion criteria for an umbrella review of factors related to adolescent sexual and reproductive health in sub-Saharan Africa.

Inclusion criteria

- Reviews published in peer-reviewed journals, thesis manuscripts, and reports
- All reviews irrespective of date of publication and date range of search
- Articles written in English or French
- Quantitative and qualitative reviews. Scoping and systematic reviews, with or without meta-analyses. Reviews must include a reproducible and systematic search strategy, well-defined inclusion and exclusion criteria and outcome, and risk of bias assessment of included primary articles
- The review should include male and female adolescents, 10-19 years of age, or present disaggregated data for adolescents
- The review should include studies from sub-Saharan Africa or present disaggregated data from a country or countries in sub-Saharan Africa
- The domain under investigation is adolescent sexual and reproductive health. Adolescent sexual and reproductive health outcomes include issues around teen pregnancy, transactional sex, gender violence, sexual abuse, and the transmission of HIV and other sexually transmitted diseases. This review will consider any outcome that the authors explicitly state is related to adolescent sexual and reproductive health

Exclusion criteria

- Blogs, websites, and conference papers
- Reviews without a systematic and reproducible methodology for article identification, such as well-defined eligibility criteria and outcome of interest
- Reviews that do not provide the list of included primary studies
- Reviews concerned with specific populations such as adolescent athletes or patients

Outcome

The primary domain of interest is outcomes related to ASRH. ASRH refers to more than the absence of disease. It also includes the physical, mental, and social well-being of adolescents such as the ability to access sexual health services, the prevention of unintended pregnancies, safe abortion, the prevention of STDs including HIV/AIDS, and all forms of sexual violence and coercion. This umbrella review will consider any outcome that has been explicitly defined by the authors as being related to ASRH. All included reviews will describe the individual, family, or societal factors associated with an ASRH outcome. Reviews may include studies of interventions to address ASRH outcomes such as school-based sex education initiatives, behavior change interventions, programs, and policies.

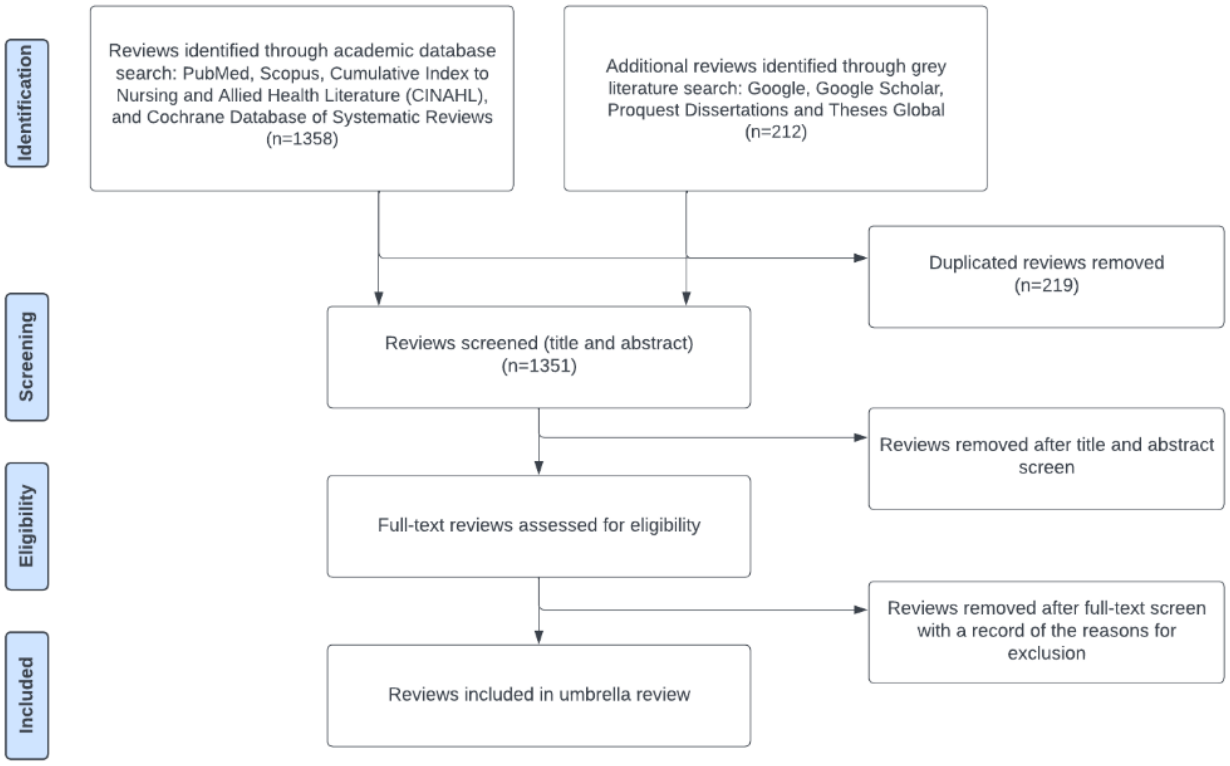
Study Selection

We will combine reviews identified in the academic and gray literature searches and remove duplicates. Two reviewers (MZG and KO) will independently screen all articles. In the first round of study selection, 2 reviewers (MZG and KO) will independently read titles and abstracts and select potentially eligible articles. They will discuss and resolve disagreements on selection, with articles retained if there is no agreement.

In the second round of study selection, 2 reviewers (MZG and KO) will screen full-text articles of the remaining reviews from the first round, according to the eligibility criteria described above. The 2 reviewers will agree on whether to include or exclude each article and on the primary reason for exclusion. They will discuss and resolve disagreements, if necessary involving a third reviewer (AC). The study selection process is depicted in Figure 1.

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Figure 1. Flow diagram illustrating the study selection process of review articles in an umbrella review of the determinants of adolescent sexual and reproductive health in sub-Saharan Africa.



Data Extraction

Reviewers will extract data from eligible articles with the use of a systematic review management software called Covidence (Veritas Health Innovation Ltd). The research team will develop a data extraction template to capture the items such as study information, study participants' characteristics, characteristics of included primary studies, how the ASRH outcomes of interest are defined, factors associated with the outcomes of interest, and intervention models used (if relevant) and their influence on ASRH outcome. Factors under consideration include but are not limited to age, sex, marital status, schooling level, employment status, wealth, religion, knowledge about ASRH-related topics, age of sexual initiation, various behaviors such as the use of contraception or engagement in transactional sex, rural versus urban dwelling, parental care and communication, parental education, media influence, gender and cultural norms, and policies. For each included article, 2 reviewers (MZG and KO) will independently complete an extraction template, documenting all responses in Covidence. A third reviewer (AC) will resolve any disagreements about data extraction.

We will assess the methodological quality of the included articles using the Joanna Briggs Institute Critical Appraisal Checklist for Systematic Reviews and Research Syntheses, which covers both quantitative and qualitative research. Two reviewers will conduct the assessments independently and in pairs, and a third reviewer will resolve disagreements. The umbrella review will report the findings of the risk of bias assessment.

Data Synthesis

The umbrella review will present a narrative synthesis of a range of ASRH outcomes and their associated factors. We will not attempt a meta-analysis of quantitative findings. We will organize the data by ASRH outcome—including pregnancy, HIV/AIDS transmission, intimate partner violence, and others—and synthesize the factors that have been explored in systematic reviews for each outcome. The review will also present subgroup analyses about associations of factors such as sex, age, school attendance, and rural versus urban dwelling with ASRH in sub-Saharan Africa.

Ethical Considerations

This protocol follows the PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols) guidelines [26]. The review is registered with PROSPERO (CRD42023394512). The review will exclusively use data from secondary sources and will not involve interactions with human subjects. Ethical clearance is not required. The findings will form part of the evidence to be discussed in a larger project to co-design strategies for improving ASRH in Bauchi State, Nigeria. The research team will also disseminate findings in conference presentations and publications.

Results

The initial academic and gray literature search started in April 2023 and has resulted in a total of 1358 and 212 articles, respectively. After the removal of duplicates, 1351 articles remain to be screened. We expect to publish the review findings before the end of 2023.

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Discussion

Summary

This is the first umbrella review within the sub-Saharan African context to assess comprehensively ASRH outcomes and the factors associated with them. By systematically reviewing both academic and grey literature, we aim to identify, synthesize, and critically evaluate existing research evidence on factors related to ASRH outcomes within the region. Existing systematic reviews focus on specific aspects of ASRH, but these are often intertwined so a broad overview across different outcomes is timely. By synthesizing the findings from multiple systematic reviews, this review will identify gaps in the existing evidence base. This can guide future research to fill these gaps.

The literature about ASRH in sub-Saharan Africa is diverse and complex, covering a range of outcomes, associated factors, and interventions. Many systematic reviews have synthesized the literature relating to different outcomes; our preliminary search strategy resulted in 1351 articles to be screened. An umbrella review is timely to synthesize existing systematic reviews and meta-analyses and will provide a comprehensive overview of the available evidence. Sub-Saharan Africa has limited human and financial resources. An umbrella review can guide the efficient allocation of scarce resources by identifying the most robust and relevant evidence, minimizing duplication of effort, and identifying areas where further research or interventions are needed.

Anticipated limitations of this review include the diversity and varying quality of the included reviews. We will consider the quality of the included reviews in our interpretation of the findings of our umbrella review. Another limitation is the potential overlap of original articles between the reviews included within our umbrella review. Ignoring potential overlap might lead umbrella reviews to overstate certain results and conclusions. We will identify overlaps in our synthesis report.

Conclusions

This umbrella review of factors related to ASRH outcomes in sub-Saharan Africa is timely. It will provide a comprehensive overview of the landscape of studies on ASRH outcomes and potential determinants in sub-Saharan Africa. It will identify gaps in the evidence base and guide future research on the topic.

Acknowledgments

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Data Availability

Data sharing is not applicable to this paper as no data sets were generated or analyzed during this study.

Authors' Contributions

All authors contributed to and approved the final manuscript. MZG and KO performed the initial systematic literature searches and drafted the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review reports.
[PDF File (Adobe PDF File), 78 KB - resprot_v12i1e51278_app1.pdf]

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Abbreviations

ASRH: adolescent sexual and reproductive health
PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol
PROSPERO: International Prospective Register of Systematic Review
STD: sexually transmitted disease

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Protocol

A Metasynthesis and Meta-analysis of the Impact and Diagnostic Safety of COVID-19 Symptom Agnostic Rapid Testing in Low- and Middle-Income Countries: Protocol for a Systematic Review

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Abstract

Background: Amid all public health measures to contain COVID-19, the most challenging has been how to break the transmission chain. This has been even more challenging in low- and middle-income countries (LMICs). A public health emergency warrants a public health perspective, which comes down to prevention. Rapid mass testing has been advocated throughout the pandemic as a way to promptly deal with asymptomatic infections, but its usefulness in LMICs is yet to be fully understood.

Objective: The study objectives of this paper are to (1) investigate the impact of the different rapid mass testing options for SARS-CoV-2 that have been delivered at point of care in LMICs and (2) evaluate the diagnostic safety (accuracy) of rapid mass testing for SARS-CoV-2 in LMICs.

Methods: This review will systematically search records in PubMed, EBSCOhost, Cochrane library, Global Index Medicus COVID-19 Register, and Scopus. Records will be managed using Mendeley reference manager and SWIFT-Review. Risk of bias for randomized controlled trials will be assessed using the RoB 2 assessment tool, while nonrandomized interventions will be assessed using the tool developed by the Evidence Project. A narrative approach will be used to synthesize data under the first objective, and either a meta-analysis or synthesis without meta-analysis for the second objective. Tables, figures, and textual descriptions will be used to present findings. The overall body of evidence for the first objective will be assessed using the Grading of Recommendations Assessment, Development, and Evaluation–Confidence in the Evidence from Reviews of Qualitative research (GRADE-CERQual) approach, and for the second objective using GRADE.

Results: The screening of records has been finalized. We hope to finalize the synthesis by the end of February 2023 and to prepare the manuscript for publication by April 2023. The study will be reported in accordance with standard guidelines for the reporting of systematic reviews. Review results will be disseminated through conferences and their peer-reviewed publication in a relevant journal.

Conclusions: This review highlights the role of a preventive approach in infection control using rapid mass testing. It also flags the overriding need to involve users and providers in the evaluation of such tests in the settings for which they are intended. This will be the first review to the best of our knowledge to generate both qualitative and quantitative evidence regarding rapid mass testing specific to LMICs.

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KEYWORDS

SARS-CoV-2; 2019-nCoV; rapid test; diagnostic accuracy; meta-analysis; metasynthesis; COVID-19; low- and middle-income countries

Introduction

Background

The real challenge of COVID-19 containment is to break the transmission chain by preventing individuals from getting infected and preventing those infected from transmitting to others [1]. The gold standard of COVID-19 containment has shifted to mass vaccination, with the belief that vaccines will break the chain of transmission. It is reported that current vaccines are close to 100% effective in reducing hospitalizations and deaths [2]. These significant efficacy results from conducted studies may however be limited given that these are just 2 of the endpoints of vaccine effectiveness. In reality, the effectiveness of available vaccines in preventing *infections* is yet to be fully understood in many countries. The duration of immunity of current vaccines is also a critical yet unanswered question [3]. It becomes even more challenging to measure the above endpoints amid emerging new variants [4-8] since this requires constant knowledge renewal on viral genomic epidemiology [9]. New variants of SARS-CoV-2, including B.1.1.7, B.1.351, and P.1, have been reported in the United Kingdom, South Africa, and Brazil, respectively. The emergence of these new variants—when the global economy is yet to recover from the devastating effects of the previous variants still in circulation—is particularly challenging. More so, the fact that these new variants of concern [10,11] are not only more transmissible but appear to be more asymptomatic and resistant to polymerase chain reaction detection, flags the overriding importance of waiting time in the detection of those infected. Transmissibility of the virus appears to vary by context as factors reported to determine transmission include the capacity for the virus to replicate, the exhibition of symptoms (cough), and the individual associated environmental factors (including behavior) [12].

It is reported that a major factor that can contribute to up to 50% of infected persons being overlooked during symptom screening is the inability to detect the virus during the asymptomatic stage by programs designed to diagnose cases when the disease is quite advanced [13]. Apart from a group of people who deliberately might not declare they have symptoms, the first 2 days of the 12-day infectious period of the virus, during which infected persons do not show any symptoms, remain an important proportion in the transmission mechanism of a deadly disease. The inability to effectively manage the transmission mechanism in low- and middle-income countries (LMICs) due to limited resources prompts the need for low-cost rapid tests in these countries. While some remain skeptical about the diagnostic safety and effectiveness of rapid tests [14,15], others believe that the currently available rapid tests are equally accurate enough in detecting some of the new variants [16-18]. The current evidence of what these different tests are and their diagnostic safety [19] within the context of LMIC is limited. In addition, standard guidelines for their use [20,21] seldom exist in these settings, making their effective deployment more challenging.

Key questions to ask when planning to identify infections promptly include, among others, the following: (1) When to test? (2) Where to test? (3) When to get the results? (4) How safe? and (5) How regular? As the global economy learns to cope with the more silent new variant infections, it is apparent that low-cost regular rapid mass testing might assume an important role [22,23], but their diagnostic safety [24] may be an issue particularly in LMICs. According to a 2020 report by the World Bank, low-income countries are those with a gross national income per capita of ≤US $1045, and middle-income countries are those with a gross national income per capita of US $1046 to US $12,695 [25]. About 500 million tests have been estimated to be needed in LMICs in 2021 [26], and the adoption of low-cost rapid tests might lead to up to 50% cost savings [27,28]; however, their fitness for purpose in these countries is yet to be fully understood. This study seeks to systematically review the evidence-based rapid mass testing options for SARS-CoV-2 that can be delivered at point of care in LMICs.

Specific Objectives

The specific objectives of this study are as follows: (1) to investigate the impact of the different rapid mass testing options for SARS-CoV-2 that have been delivered at point of care in LMICs and (2) to evaluate the diagnostic accuracy of rapid mass testing for SARS-CoV-2 in LMICs.

Research Questions

Given that our review was geared toward going beyond a quantitative evidence synthesis, the research questions were framed following the Perspective, Setting, Phenomenon, Environment, Comparison, Timing, and Findings (PerSPEcTiF) framework to incorporate the (1) setting, (2) time, and (3) place [29] for objective 1, and using the population, intervention, comparison, outcome (PICO) approach for objective 2 [30].

Objective 1

From a preventive health perspective in a LMIC, what do rapid tests for SARS-CoV-2—in an environment of limited resources with silent transmissions from infection up until diagnosis—mean to patients, health personnel, and the general public?

Objective 2

What is the diagnostic accuracy of near-the-patient rapid mass testing options for SARS-CoV-2 implemented, irrespective of symptoms in LMICs?

Methods

Study Design

This is a systematic review of both qualitative and quantitative evidence synthesis. A qualitative approach will take the form

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of a metasynthesis while the quantitative approach will take the form of a meta-analysis.

Eligibility Criteria

Searched records will be screened using the inclusion and exclusion criteria. Given the important role played by both contextual variables and time in the detection of SARS-CoV-2 to break the transmission chain, we believed that rapid mass testing interventions were complex ones [31], not only following a systems approach but underpinned by both contextual variability and time scale [29]. The eligibility criteria for the first objective follows the PerSPEcTiF framework, while that for the second objective follows the PICO framework, as seen in Table 1.

Table 1. Inclusion and exclusion criteria.

Objective	Inclusion	Exclusion
Objective 1 (PerSPEcTiF[a])		
Perspective	Preventive care [32,33] and public health [21,34] perspective	Diseased population
Setting	Point of care or near the patient [35,36], including GP[b] surgeries; physician offices; community (population); walk-in or drive-through testing sites; primary care centers; nursing; and long-term care facilities, hospital wards, clinics, prisons, pharmacies, schools, workplaces, sports centers, and border testing sites	Lab-based testing
Phenomenon	Non–lab-based rapid and point of care test [37]; they are highly accessible, applied irrespective of symptoms, easily transported, and inexpensive, and should provide results in 1 visit [38].	Serology tests, lab-based tests, and non–point of care tests
Environment	In low- and middle-income countries [25]	High-income countries
Comparison	N/A[c]	N/A
Timing	Time during which infection remains asymptomatic; results delivered in 1 visit	Time of diagnosis includes symptoms; if time to results is more than 24 hours
Findings	Impact of rapid tests including the knowledge, attitude, and perception of patients, health care providers, and the public	Studies not evaluating the impact of rapid tests on the public
Objective 2 (PICO[d])		
Participants	Asymptomatic patients with COVID-19 and close contacts of index cases	COVID-19 or symptomatic patients
Intervention	Rapid antigen and point-of-care tests	Lab-based tests
Comparison	Lab-based reverse transcription–polymerase chain reaction [39-41]; the test could miss up to 30%-40% of infections [42,43]	Tests other than reverse transcription polymerase chain reactions
Outcome	Diagnostic test accuracy	Nondiagnostic test accuracy studies
Other		
Studies	Qualitative and mixed methods studies for objective 1; RCTs[e], non-RCTs, and cross-sectional cohort studies for objective 2	Longitudinal cohort, case-control, case-control cross-sectional, and all prognostic and predictive DTA[f] studies

[a]PerSPEcTiF: Perspective, Setting, Phenomenon, Environment, Comparison, Timing, and Findings.

[b]GP: general practitioner.

[c]N/A: not applicable.

[d]PICO: population, intervention, comparison, outcome.

[e]RCT: randomized controlled trials.

[f]DTA: diagnostic test accuracy.

Information Sourcing

Electronic Databases

The literature search will be performed in PubMed, EBSCOhost (CINAHL Plus), Global Index Medicus COVID-19 register, Cochrane (library and COVID-19 register), and Scopus. Gray literature from MedRxiv, BioRxiv, AiXiv, and other preprint servers will be ensured through the inclusion of the Global Index Medicus database. No restriction will be set on language. The search for records will follow the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) [44]. A PRISMA flow diagram will be used to present the workflow of how studies were included.

Manual Search

The search for useful articles will be conducted in Google scholar using the keywords of included articles, for objective 1, and the Cochrane COVID-19 Study Register for objective 2.

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We will also search manually through professional networks and other sources.

Citation Search

We hope to locate useful studies through the reference list of identified records by searching them online using their digital object identifiers in Crossref, DOI resolver, or through the journals in which they were published. Articles will also be identified through the reference list of suitable systematic reviews in the Cochrane Special Collections for COVID-19 Infection Control and Prevention.

Alerts and Generic Sources

Wherever necessary and possible, we will (1) set up email alerts in the electronic databases searched, (2) screen the citation manager's generic suggestions as well as those from databases, and (3) screen database suggestions for similar articles.

Search Strategy

Electronic Search Terms

Search terms will include "Qualitative"[Mesh], "Qualitative Study"[tiab], "Mixed-method"[tiab], "Interview"[Mesh], "Attitude"[Mesh], "Knowledge[Mesh]", "Practice"[Mesh], "KAP"[tiab], "Acceptance"[Mesh], "Public Perception"[tiab], "Public Acceptance"[tiab], "Public Attitude"[tiab], "Compliance"[Mesh], "Adherence"[Mesh], "Qualitative Research"[Mesh], "Explor*"[tiab], "COVID-19 Testing"[Mesh], "COVID-19 Nucleic Acid Testing "[Mesh], "Rapid Diagnostic Testing"[tiab], "Lateral Flow Tests"[tiab], "Nucleic Acid Testing"[Mesh], "Rapid test"[Mesh], Lateral Flow[tiab], "Mass Testing"[Mesh], "Mass Screening"[Mesh], "Diagnostic Test"[tiab], "Diagnostic Performance"[tiab], "Test Accuracy"[tiab], Test Performance"[tiab], "Universal Testing"[Mesh], "Universal Screening"[Mesh], "Point-of-Care Testing"[Mesh], "Point-of-Care"[tiab], "Point-of-Care Screening"[Mesh], "POC Testing"[Mesh], "Community Testing"[tiab], "Asymptomatic Infections"[Mesh], "Asymptomatic"[tiab], "Carrier State"[Mesh], "Asymptomatic Diseases"[Mesh], "COVID-19"[Mesh], "SARS-CoV-2"[Mesh], "2019-nCoV"[Mesh], "SARS-CoV-2 Variants"[Mesh], "VOC"[Mesh], "SARS-CoV-2 Variants"[Supplementary Concept], "RT-PCR"[tiab], "PCR"[Mesh], and "Molecular"[tiab]

Electronic Search Strategy

Records will be searched in databases highlighted under the electronic databases subsection. A date limit will be applied using electronic filters of search engines and set to 2020 and beyond. Searches will constantly be updated throughout the research period. A detailed search strategy in PubMed can be found in the study protocol [45]. The search strategy for each database can be seen in Table 2.

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Table 2. Search strategy for each database.

Database and query order	Search query
PubMed	
#1	((((((((((((((((((((“Qualitative”[tiab]) OR (“Qualitative Study”[tiab])) OR (“Mixed-method”[tiab])) OR (“Mixed Method”[tiab])) OR (“Interview”[tiab])) OR (“Attitude”[MeSH])) OR (“Knowledge”[MeSH])) OR (“Practice”[tiab])) OR (“health personnel*”[tiab])) OR (“KAP”[tiab])) OR (“Acceptance”[tiab])) OR (“public acceptance”[tiab])) OR (“public perception”[tiab])) OR (“public attitude*”[tiab])) OR (“Compliance”[MeSH])) OR (“Patient Compliance”[MeSH])) OR (“Adherence”[tiab])) OR (“Patient adherence”[tiab])) OR (“Qualitative research”[MeSH])) OR (Explor*[tiab])) OR (“Health Knowledge, Attitudes, Practice”[MeSH])) OR (“Attitude of health personnel”[MeSH])
#2	((((((((((“Point-of-Care Testing”[Mesh]) OR (“Point-of-Care”[tiab])) OR (“Point-of-Care Test*”[tiab])) OR (“Point-of-Care Detect*”[tiab])) OR (“Point-of-Care Screen*”[tiab])) OR (“Rapid Diagnostic Test*”[tiab])) OR (“Lateral Flow*”[tiab])) OR (“Mass Test*”[tiab])) OR (“Mass Screen*”[tiab])) OR (“Universal Test*”[tiab] OR “Universal Screen*”[tiab])) OR (“Rapid Test*”[tiab])
#3	((“COVID-19 Testing”[Mesh]) OR (“COVID-19 testing”[tiab])) OR (“SARS-CoV-2 Testing”[tiab])
#4	((((“SARS-CoV-2”[Mesh] OR (“COVID-19 Nucleic Acid Testing”[Mesh]) OR (“COVID-19 Nucleic Acid Testing”[tiab])) OR (“SARS-CoV-2 Nucleic Acid Testing”[tiab])) OR (“SARS-CoV-2 Nucleic Acid Detection”[tiab])) OR “SARS-CoV-2 variants” [Supplementary Concept])
#5	#3 OR #4
#6	(“PCR”[tiab]) OR (“RT-PCR”[tiab])
#7	((((“Asymptomatic Infections”[Mesh]) OR (“Asymptomatic Infections”[tiab])) OR (“Asymptomatic”[tiab])) OR (“Asymptomatic Diseases”[tiab])) OR (“Carrier State”[tiab]) OR (“Carrier”[tiab])
#8	#1 AND #2 AND #5 AND #7
#9	#5 AND #6 AND #7
#10	#6 AND #7
#11	((((((((((“Point-of-Care Testing”[Mesh]) OR (“Point-of-Care”[tiab])) OR (“Point-of-Care Test*”[tiab])) OR (“Point-of-Care Detect*”[tiab])) OR (“Point-of-Care Screen*”[tiab])) OR (“Rapid Diagnostic Test*”[tiab])) OR (“Lateral Flow*”[tiab])) OR (“Mass Test*”[tiab])) OR (“Mass Screen*”[tiab])) OR (“Universal Test*”[tiab] OR “Universal Screen*”[tiab])) OR (“Rapid Test*”[tiab]) AND (((“Test accuracy”[tiab]) OR (“Test performance”[tiab])) OR (“Diagnostic accuracy”[tiab])) OR (“Diagnostic performance”[tiab])
#12	#9 AND #11
#13	#10 AND #11
#14	#8 OR #12
#15	#12 OR 13
#16	#8 OR #15
Cochrane	
#1	“Diagnostic” OR “Diagnostic test” OR “Diagnostic accuracy” OR “Diagnostic performance” OR “Test accuracy” in Title Abstract Keyword AND Mass test* OR Universal test* OR Universal screen* OR Point-of-care test* OR Rapid test* OR “PoC test*” OR Point-of-care* OR “Point-of-care test” OR “lateral flow” OR “lateral flow test” OR community test* in Title Abstract Keyword AND “Asymptomatic carrier” OR “Asymptomatic” OR SARS-CoV-2 OR “SARS-CoV-2 transmission” OR “Asymptomatic transmission” in Title Abstract Keyword AND “Qualitative study” OR Qualitative OR Mixed-method OR interview OR Acceptance OR Knowledge OR Attitude OR Practice OR Perspective OR Perception OR Adherence OR “Public acceptance” OR “Public perception” OR “Public attitude” OR “Public adherence” in Title Abstract Keyword - (Word variations have been searched)
#2	“Diagnostic” OR “Diagnostic test” OR “Diagnostic accuracy” OR “Diagnostic performance” OR “Test accuracy” in Title Abstract Keyword AND Mass test* OR Universal test* OR Universal screen* OR Point-of-care test* OR Rapid test* OR Point-of-care* OR “Point-of-care test” OR “lateral flow” OR “lateral flow test” OR community test* in Title Abstract Keyword AND “RT PCR” OR RT-PCR OR “RT PCR test*” OR “RT-PCR analys*” OR “Molecular” in Title Abstract Keyword AND “Asymptomatic carrier” OR “Asymptomatic” OR SARS-CoV-2 OR “SARS-CoV-2 transmission” OR “Asymptomatic transmission” in Title Abstract Keyword - (Word variations have been searched)
#3	#3= #1 OR #2
EBSCOhost	

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Database and query order	Search query
#1	AB (covid-19 or coronavirus or 2019-ncov or sars-cov-2 or cov-19 or pandemic or 2019 novel coronavirus or coronavirus disease) AND AB (rapid testing or antigene test or lateral flow test or mass test or universal test or mass screen or universal screen or point of care testing or poc or poct) AND AB (qualitative research or qualitative study or qualitative methods or interview or ethnographic or phenomenological)
#2	AB (point of care testing or poc or poct) OR AB mass screen* OR AB universal test* OR AB universal screen* OR AB lateral flow* OR AB rapid test* AND AB turnaround time AND AB diagnostic accuracy
#3	AB (covid-19 or coronavirus or 2019-ncov or sars-cov-2 or cov-19) AND AB asymptomatic covid-19 NOT AB immune* NOT AB antibod* NOT AB immunoassay* NOT AB serolog* NOT AB seroprevalence NOT AB influenza NOT animal*
#4	AB RT-PCR AND AB Asymptomatic*
#5	S2 AND S3 AND S4
#6	S1 OR S5
Global Index Medicus	
#1	tw:((tw:(rapid test* OR lateral flow* OR point-of-care test* OR poc test* OR antigene test)) AND (tw:(covid-19 asymptomatic OR asymptomatic*)))
#2	tw:((tw:(mass test*)) OR (tw:(universal screen*)) OR (tw:(universal test*)) OR (tw:(rapid test*)) OR (tw:(lateral flow*)) OR (tw:(point-of-care test*)) OR (tw:(poc test*)))
#3	tw:((tw:(rt-pcr*)) AND (tw:(test accuracy OR test performance OR diagnostic accuracy OR diagnostic performance)))
#4	tw:((tw:(covid-19 asymptomatic)) OR (tw:(asymptomatic*)))
#5	#2 AND #3 AND #4
#6	#1 OR #5
Scopus	
#1	(TITLE-ABS-KEY (covid-19 OR coronavirus OR 2019-ncov OR sars-cov-2 OR “novel coronavirus”) AND TITLE-ABS-KEY (“rapid test*” OR “antigene test*” OR “lateral flow test*” OR “lateral flow” OR “mass test*” OR “universal test*” OR “point of care test*” OR “point-of-care”) AND TITLE-ABS-KEY (qualitative* OR mixed-method OR interview* OR perspective* OR knowledge OR attitude* OR practice OR perception OR “public perspective*” OR acceptance OR “public attitude”))
#2	(TITLE-ABS-KEY (rapid AND test*) OR TITLE-ABS-KEY (lateral AND flow*) OR TITLE-ABS-KEY (mass AND test*) OR TITLE-ABS-KEY (universal AND test*) OR TITLE-ABS-KEY (point-of-care AND test*) OR TITLE-ABS-KEY (“point of care”))
#3	(TITLE-ABS-KEY (covid-19) OR TITLE-ABS-KEY (sars-cov-2) OR TITLE-ABS-KEY (2019-ncov) AND TITLE-ABS-KEY (asymptomatic*))
#4	(TITLE-ABS-KEY (rt-pcr* OR rt-pcr AND test*) AND TITLE-ABS-KEY (test AND accuracy OR diagnostic AND accuracy OR diagnostic AND performance))
#5	#2 AND #3 AND #4
#6	#1 OR #5

Search Peer Review

Search terms will be performed and verified by a second person to ensure search reproducibility. Both results were then compared, and any differences were resolved by modifying and rerunning the searches.

Study Records

Data Management

Mendeley reference manager (Elsevier) and SWIFT-Review (Sciome) will be used to manage search records. SWIFT-Review workbench will be used to deduplicate, screen records, and code [46]. Data analysis will be conducted with the help of the SWIFT-Review and Stata package (Stata Corp).

Screening Process

We will start by identifying and removing duplicates in the first phase followed by the screening of titles and abstracts in the second phase, following the outlined inclusion and exclusion criteria. Screening of titles and abstracts will be conducted by 2 independent reviewers (PK and KA) while a third reviewer will serve as an arbitrator. If necessary, full articles will be read should it not be possible to screen records by title or abstract alone. The unavailability of full text will lead to exclusion.

Data Extraction

Data extraction for the first objective will be performed by the author leading the protocol development (MM) using SWIFT-Review. This will be done with the help of the SWIFT-Review Tag Browser and manually applied tags. Two reviewers (PK and KA) will independently extract data for the second objective using a customized data extraction template

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for RCTs and non-RCTs) [47]. The data form which can be accessed in Multimedia Appendix 1 aligns with the Methodological Expectations of Cochrane Intervention Reviews (MECIR) [48].

Management of References

A reference management software (Mendeley reference manager) will be used to manage records both for citations and for the generation of bibliography.

Data Items

Data items to be extracted will include study title, year, author, country, study objective, conflicts of interest, funding, study design, population (age, sex, and ethnicity), setting, sample size, eligibility criteria, type of test, the time interval between the index and reference tests, the sample collected, statistical analysis, test status, time to results (turnaround time), test accuracy, and study limitations.

Outcomes and Prioritization

The outcome of interest for the first objective is the test impact (patients, health personnel, and the general public). The outcome of the intervention for the second objective based on PICO is the status of SARS-CoV-2/COVID-19, which involves how well the test can identify those with the target condition and reject those without the conditions. Studies comparing the index and reference tests regarding the above will be prioritized.

Risk-of-Bias Assessment

The assessment of the risk of bias of included studies will be conducted using the most relevant tools and based on study design [49]. Randomized controlled trials will be assessed using the revised version of the Cochrane Risk of Bias (RoB 2) assessment tool [50,51]. The items for risk-of-bias assessment using the RoB 2 tool will be organized into 5 domains including (1) bias due to randomization, (2) bias due to deviation from intended intervention, (3) bias due to missing data, (4) bias arising from outcome measurements, and (5) bias in the selection of reported results. Studies will be categorized into "low," "some concerns," and "high" for randomized controlled trials, as shown in Table S1 of Multimedia Appendix 2. Nonrandomized intervention studies will be assessed using the 8-item tool developed by the Evidence Project, suitable for a variety of study designs [52]. This tool assesses the risk of bias under 3 domains, including (1) study design, (2) representation of participants, and (3) comparison group of equivalence. Following the view not to attribute a summary risk-of-bias score for studies evaluated using the Evidence Project tool [52], the risk of bias of nonrandomized studies will be reported based on Table S2 of Multimedia Appendix 2.

Metabias

Publication bias will be reduced through the inclusion of gray literature [53,54]. Additionally, in the event of a meta-analysis, publication bias will be assessed by inspecting the funnel plot. Any indication of missing data through funnel plot asymmetry will be adjusted using the "trim and fill" approach [55]. A positive difference between the corrected and uncorrected diagnostic accuracy values will be indicative of an overestimation of diagnostic accuracy due to missing data.

Data Synthesis

Synthesis Procedure

Our synthesis approach for objective 1 to a greater part will take the form of a narrative synthesis [56,57]. Other studies have been found to use a similar method [58-61]. This will help maintain the contextual nature of the different mass testing options that will emanate from the literature. We will perform a meta-analysis for the second objective. We also anticipate possible heterogeneity in study design, study population, setting, and type of test, which may not make it possible to do a meta-analysis, in which case we will perform a synthesis without meta-analysis. Given the role played by context and system setup, we hope to capture both the quantitative and qualitative nature of diagnostic test studies.

Synthesis Framework

For outcomes under objective 1, the synthesis will follow four elements regarding the implementation of rapid mass testing, including (1) theoretical modeling, (2) preliminary synthesis (3), data interrelatedness, and (4) synthesis robustness [56]. Each of the aforementioned elements will be assessed using the most appropriate technique. An interpretative technique will be used to develop a theory about mass testing in relation to the outcomes of interest. The preliminary synthesis will be done using tabulation, textual description, clustering, and data translation. The relationship between data will be assessed using conceptual triangulation, case description, visual representation, and methodological triangulation. We will do a narrative synthesis to describe the outcomes of interest and other contextual factors. The synthesis robustness will be assessed through a critical reflection on the synthesis performed.

Concerning objective 2, we will perform a meta-analysis using the bivariate hierarchical logistic regression [62,63] in Stata, should there be a reasonable number of similar studies with the possibility of generating 2 x 2 tables. This multilevel model considers the correlation between sensitivity and specificity as well as variations in test performance between studies. If this is not possible, we will use positive and negative outcome events to pool event rates. We will inspect heterogeneity through direct observation of CIs on forest plots, where possible, and other graphs, as well as interstudy variability. The 95% CI binomial exact test will be used to report sensitivities and specificities for tests with single studies.

Data Presentation

The review findings will be presented using tables, figures, and case descriptions. Risk-of-bias assessment visualizations will be conducted using the robvis web application [64] where possible. Included studies will be organized by point-of-care setting using table rows and by study design, sample size, population, index test, index and reference tests interval, the sample collected, target gene, turnaround time, and accuracy, using table columns. Case summaries regarding outcomes of interest for the first objective (impact on patients, personnel, and the general public) will be summarized and presented according to the World Bank's classification of countries by income for 2021-2022 [65]. Evidence of effect under the second objective will be presented using forest plots where possible.

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Quality of Evidence

The search strategy will follow the PRISMA search guidelines [66]. The quality of database search will be improved by searching beyond Medical Subject Headings (MeSH) terms by including "AND" and "OR" strings to the MeSH terms. Retained studies will be assessed for risk of bias using the most appropriate guidelines and checklists. The overall body of qualitative evidence in the first objective will be assessed using a critical reflection as highlighted [56], and the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) Confidence in the Evidence from Reviews of Qualitative research (GRADE-CERQual) [67]. If applicable, the GRADE will be used to assess the overall body of evidence regarding objective 2 [68,69]. This will consider the risk-of-bias assessments, precision in reported results, consistency, directness, and publication bias.

Ethics and Dissemination

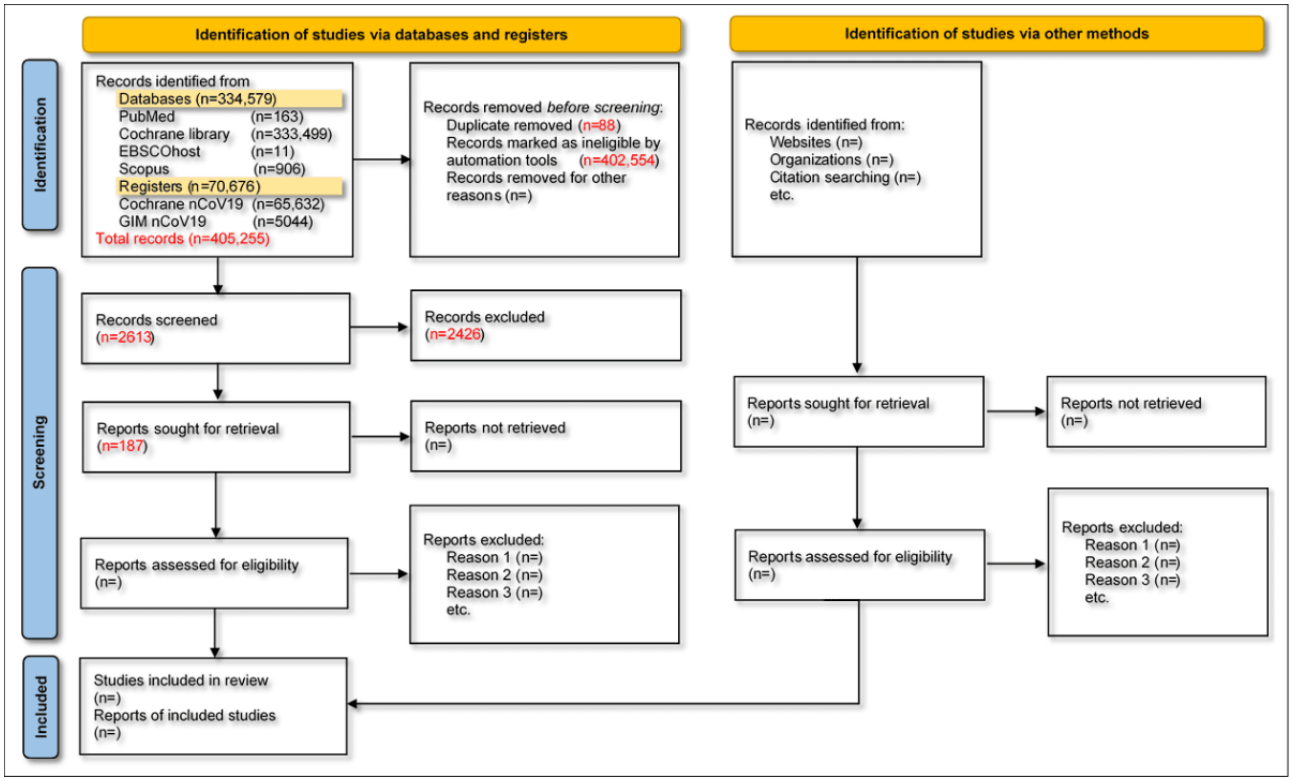
This study does not warrant any ethical approval. This protocol has been registered with the International Prospective Register of Systematic Reviews (PROSPERO; CRD42022283776) [45], in line with the standards for undertaking systematic reviews. Review results will be disseminated through conferences and their peer-reviewed publication in a relevant journal.

Results

This protocol will be in line with the PRISMA protocol checklist [66]. We do not expect to have a reasonably high number of studies for rapid tests performed at point of care in LMICs in this review. Should this be the case, the results will be reported as 2 separate reviews and published in a relevant journal, as it might be unlikely to summarize all results in 1 report that robustly addresses both research questions. Following the above, the results of this review will be reported per (1) RAMESES (Realist and Metanarrative Evidence Syntheses: Evolving Standards) publication standards for meta-narrative reviews [70] regarding objective 1 and (2) the PRISMA checklist [71] or the Synthesis Without Meta-analysis in systematic reviews checklist [72], in the event that a meta-analysis was not possible, regarding objective 2.

The second round of screening has been finalized. Figure 1 shows the search results from the different databases. We hope to finalize the synthesis by the end of February 2023 and to prepare the manuscript by April 2023.

Figure 1. Preliminary PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram. GIM: Global Index Medicus; nCoV19: COVID-19.



Discussion

Summary

This protocol is based on the diagnostic usefulness and safety of rapid diagnostic tests in LMICs. A point-of-care test is one that can be delivered at the point of sample collection or near the patient, with results made available almost immediately. By "near the patient," we refer to settings as specified by the Centers for Disease Control and Prevention [36] and the Medicines and Healthcare products Regulatory Agency [73]. A range of rapid tests esteemed to be useful in surveillance has been reported in the literature [18,74,75], broadly categorized into diagnostic, screening, and public health surveillance tests [76]. Moreover, 36 lateral flow devices believed to have the minimum performance requirements have been published by

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the UK government [37]. Their usefulness is however yet to be fully understood within the context of LMICs.

Comparison With Prior Work

A search for reviews evaluating rapid point-of-care test against the gold standard on asymptomatic carriers in Cochrane library found 3 reviews [38,77,78]. Only 1 of the reviews [38] evaluated the diagnostic accuracy of rapid diagnostic tests. The review concluded that evidence for the testing of asymptomatic carriers was limited and highlighted the overriding need for the evaluation of rapid tests in the settings for which they are intended. This review will be the first, to the best of our knowledge, to address this knowledge gap in LMICs from a public health perspective.

Although rapid mass testing programs came under serious criticism early in the pandemic [79-82], it is still obvious that the symptom-based testing alone is not comprehensive enough as it failed to bring the virus under control prior to the approval of vaccines; this is partly because even the gold standard reverse-transcription polymerase chain reaction test is also prone to false negatives [83]. One possible way of ensuring that people are detected as soon as they become infected is by making a rapid mass testing regime available at point of care and service points [84].

Strengths and Limitations

This protocol presents many strengths starting with its registration with PROSPERO. It is the first protocol that seeks to investigate both qualitative and quantitative evidence regarding the diagnostic safety of rapid mass tests in LMICs. The protocol's specific objectives, search strategy, and reporting are all in line with the guidelines for the undertaking of systematic reviews.

Conclusions

This review highlights the role of context in infection prevention and control using rapid mass testing. It flags the overriding need to involve users and providers in the evaluation of such tests in the settings for which they are intended. This will be the first review, to the best of our knowledge, to generate both qualitative and quantitative evidence regarding rapid mass testing specific to LMICs.

Acknowledgments

MM is an independent researcher. He can be reached at Alumni Relations, London School of Hygiene & Tropical Medicine.

Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during the current study.

Authors' Contributions

MM developed and registered the protocol and generated the first draft of the manuscript. PK and KA pilot-tested the data collection form. The manuscript was reviewed and approved by all authors.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Data extraction form.
[DOCX File , 44 KB - resprot_v12i1e41132_app1.docx]

Multimedia Appendix 2
Risk-of-bias assessment tools.
[DOCX File , 25 KB - resprot_v12i1e41132_app2.docx]

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Abbreviations

CERQual: Confidence in the Evidence from Reviews of Qualitative research
GRADE: Grading of Recommendations Assessment, Development, and Evaluation
LMIC: low- and middle-income country
MeSH: Medical Subject Headings
PerSPEcTiF: Perspective, Setting, Phenomenon, Environment, Comparison, Timing, and Findings
PICO: population, intervention, comparison, outcome
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analysis
PROSPERO: International Prospective Register of Systematic Reviews
RAMESES: Realist and Metanarrative Evidence Syntheses: Evolving Standards

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Protocol

The Effectiveness of Internet-Based Cognitive Behavioral Therapy as a Preventive Intervention in the Workplace to Improve Work Engagement and Psychological Outcomes: Protocol for a Systematic Review and Meta-analysis

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Abstract

Background: Mental health has become an increasingly significant issue in the workplace. Non–health care workers are experiencing increased levels of psychological symptoms in their workplaces, especially during the COVID-19 pandemic, which limited social interactions and health service access. These conditions have a negative effect on employees' mental health and may also be associated with work-related outcomes, such as reduced levels of work engagement. Cognitive behavioral therapy (CBT) is one of the most effective methods used for treating workers with mental illness and preventing work-related psychological outcomes. The delivery of internet-based CBT (iCBT) has been established as a result of both technological improvements that have influenced health promotion and prevention components, and limited social contact and health service access.

Objective: The purpose of this systematic review is to synthesize the best available evidence concerning the preventive effect of iCBT on employees.

Methods: A systematic search will be conducted across 12 electronic databases, including a hand search for main journals and reference lists. Randomized controlled trials testing the effects of iCBT on psychological outcomes and work engagement among employees will be eligible. Initial keywords will cover the concepts of employees, workers, non–health care personnel, internet-based, web-based, eHealth cognitive behavioral interventions, stress, depression, anxiety, and work engagement, and then a full search strategy will be developed. Following titles, abstracts and the full text will be screened for assessment against the inclusion criteria for the review. Search results will be fully reported and presented per Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Two independent reviewers will screen and extract data, appraise methodological quality using the Cochrane risk-of-bias assessment tool, and assess overall quality of evidence with the Grading of Recommendations Assessment, Development, and Evaluation approach. A random effects meta-analysis and standardized mean differences using review manager software will be applied to synthesize the effect of iCBT based on similar outcomes.

Results: This protocol was registered in the International Prospective Register of Systematic Reviews in March 2022 and is now an ongoing process. The data will be analyzed in August 2022, and the review process should be completed by December 2022. All included studies will be synthesized and presented to demonstrate the effectiveness of iCBT in decreasing psychological distress and optimizing work engagement outcomes among employees.

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Conclusions: According to the findings of this study, iCBT therapies will be used to promote mental health concerns such as depressive symptoms, anxiety, psychological distress, stress, insomnia, and resilience among non–health care professionals. In addition, the results will be used to ensure the policy related to reducing psychological distress and optimizing work engagement in the workplace.

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KEYWORDS

systematic review; internet-based; cognitive behavioral therapy; work engagement; psychological outcomes; employees; workplace; web-based; occupational health; mental health; stress; depression; anxiety; eHealth; digital health

Introduction

Background

The extended COVID-19 pandemic has had an impact on the mental health of both health care workers and non–health care personnel [1]. Previous research has found a significant frequency of depression (34.6%), anxiety (42.3%), and psychological distress (65.1%) among workers during the COVID-19 pandemic [2]. This means that psychological distress has turned out to be more noticeable among employees in the workplace [3] during the COVID-19 pandemic. Psychological distress is the unique, uncomfortable, emotional state experienced by an individual in response to a specific stressor or demand that results in harm, either temporary or permanent, to the person [4]. Employees in various workplaces commonly face stress, anxiety, depression, attention-deficit/hyperactivity disorder, and bipolar illnesses. The symptoms indicate psychological distress involving insomnia, fatigue, difficulty concentrating, etc [5]. Long working periods, inappropriate salaries, job stress, an unhealthy working environment, and several risk factors in the workplace could also have a serious impact on one's mental health [6].

Previous systematic reviews have found that psychological distress such as stress, depression, and anxiety have been endured by a large number of employees around the world [3,5]. Those symptoms could prompt weakened prosperity such as sleep problems, fatigue, burnout, and manifest diseases including the consequence of work engagement outcomes. This not only impacts individuals' psychological well-being and reduces their capacity [6-8] but also leads to a financial burden on companies and governments [3,9]. Work engagement is also an important point among employees because it is linked to job performance and productivity. Work engagement is defined as a good, satisfying state of mind related to work that is characterized by vitality, dedication, and immersion [10]. Work engagement has been related to significant individual and organizational outcomes [11].

To minimize these consequences, a greater understanding of interventions that facilitate the improvement of psychological problems among employees is essential for protecting and promoting the mental health of workers during the prolonged COVID-19 pandemic [1,8,12].

Cognitive Behavioral Therapy Intervention

Cognitive behavioral therapy (CBT) is one of the most effective interventions to not only treat mental illnesses [13] but also prevent work-related psychological outcomes [14,15]. Internet-based CBT (iCBT) is a form of psychotherapy based on CBT principles, which is delivered through the internet by an individual or software that is not physically present with the client [13]. The delivery of iCBT was developed because of today's advanced technology, which has impacted everyday life, including aspects of health promotion and prevention, as well as providing an advantage during the COVID-19 crisis, which limited social interaction and health service access. Internet-delivered programs are named differently as *online interventions*, *web-based interventions*, *e-therapy*, *eHealth*, and *computerized cognitive behavioral therapy* [16]. In recent years, iCBT interventions have yielded techniques, which have been developed and tested in different forms for mental problems including depression and anxiety [13,17-19].

Rationale for Performing a Systematic Review

Previous systematic reviews have suggested that group iCBT interventions enhanced work performance among mental health workers [20]; reduced stress, anxiety, and depression among health personnel [21]; and reduced subsequent sickness-related absenteeism from work among adults with common mental disorders [14]. In addition, several researchers have examined the effectiveness of iCBT in improving outcomes for people with chronic illnesses and chronic mental disorders [18,19,22]. However, all of these existing reviews focused on health personnel and persons with mental health disorders and thus results may not be generalized to healthy workers and non–health care workers. Furthermore, most reviews used anxiety, depression, and insomnia as psychological outcomes but overlooked other work-related variables such as work engagement. Consequently, a comprehensive review and meta-analysis investigating the effectiveness of iCBT interventions on these outcomes among healthy workers is necessary.

A preliminary search of the Cochrane Database of Systematic Reviews, The JBI Database of Systematic Reviews and Implementation Reports, and the previous registration of an ongoing study in International Prospective Register of Systematic Reviews (PROSPERO) found no recent systematic reviews on this topic in progress. Therefore, the aim of this systematic review and meta-analysis is to evaluate the efficacy

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of iCBT as a preventive intervention on work engagement and psychological outcomes for nonclinical workers.

Review Objective and Question

An objective of this systematic review is to synthesize the best available evidence concerning the preventive effect of iCBT on employees. Review questions are as follows: (1) in comparison to controls, what is the preventive effect of iCBT in improving psychological outcomes (including stress, anxiety, depression, insomnia, and resilience) among healthy non–health care employees? (2) In comparison to controls, do iCBT interventions, as preventive interventions, enhance work engagement among healthy non–health care employees?

Methods

The proposed systematic review will be conducted in accordance with the Cochrane Handbook for Systematic Reviews of Interventions [23].

Protocol Registration

A summary of the protocol and supplemental data were registered in PROSPERO (CRD42022320589) [24] to provide a methodological outline of this systematic review and meta-analysis.

Eligibility Criteria

Study Selection

This systematic review will admit studies that (1) involved participants who were healthy non–health care workers of any sociocultural background, such as office workers, military personnel, and teachers; (2) examined programs using iCBT or iCBT with co-interventions; and (3) included our primary outcomes, including psychological distress, depression, stress, anxiety, insomnia, and resilience, and examined our secondary outcome—work engagement. Due to logistic issues, we considered studies reported in English without any year restriction.

Exclusion criteria for this systematic review are studies that (1) involved participants who were health care professionals and those with mental disorders or physical illnesses who were different in context from non–health care workers, and (2) tested only face-to-face CBT.

Intervention

For this review, the iCBT program, as a preventive intervention, is defined as a psychotherapy program based on CBT principles such as cognitive restructuring, behavioral activation, and behavioral experiments, delivered via the internet, remotely, or through mobile-based platforms in an individual or group formats. This is in accordance with the aim of this review, which is to test the effectiveness of the core method of iCBT interventions on psychological distresses and work engagement outcomes.

Comparator

This review will consider studies that compare intervention groups with no intervention controls, active controls, placebo controls, and usual-care groups.

Outcomes

The studies that evaluate the effect of iCBT on any aspect of psychological outcomes including depression, stress, anxiety, insomnia, and resilience will be considered primary outcomes. This review will also consider studies of the effect on work engagement, which is operationalized as a good, satisfying state of mind associated with work, characterized by vitality, dedication, and immersion as a secondary outcome.

Types of Studies

This review will consider only randomized controlled trials. Studies reported in English will be included without any year restriction.

Information Sources

The 6 electronic databases to search published studies include PubMed, CINAHL, Embase, Ovid, MEDLINE, Scopus, and IEEE Xplore. Ongoing clinical trials will be searched in the clinical trial registry. Sources of unpublished studies or gray literature to be searched include Google Scholar, ProQuest Dissertations, and Theses Global and Ethos. The date when each database will be last searched is May 2022.

Search Strategies

The search strategy targets published and unpublished studies. The Peer Review of Electronic Search Strategies checklist [25] will be used in the search strategy. An initial limited search of PubMed will be undertaken to identify articles on the topic. Initial keywords will cover the PICO framework [26], which includes *participants* (employees, workers, and non–health care personnel), *intervention* (internet-based, web-based, and eHealth cognitive behavioral interventions), and *outcomes* (such as depression, anxiety, and work engagement; Multimedia Appendix 1). Boolean and proximity operators will be used to combine the search terms. Subsequently, the text words contained in the titles and abstracts of relevant articles, and the index terms used to describe the articles were used to develop a full search strategy for CINAHL, Embase, Ovid, MEDLINE, and Scopus. The search strategy, including all identified keywords and index terms, will be adapted for each included database and information source. A librarian will be consulted to ensure the comprehensiveness of the search strategy. The reference list of all included sources of evidence will be screened for additional studies. A hand search for the main journal such as the *Journal of Occupational Health*, the Journal *of* Occupational Health Psychology, and the Journal of Medical Internet Research will be also conducted.

Study Selection

Keywords and Medical Subject Headings terms (ie, *Internet-based cognitive behavioral therapy program* AND *Employees*) were piloted on PubMed. Following the search, all identified citations will be collated and uploaded into EndNote version 9 [27,28], and duplicates will be removed. Titles and abstracts will then be screened by 2 independent reviewers for assessment against the inclusion criteria for the review. The full text of selected articles will be assessed in detail against the inclusion criteria by 2 independent reviewers. Reasons for exclusion of sources of evidence in the full text that do not meet

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the inclusion criteria will be recorded. Any disagreements that arise between the reviewers at each stage of the selection process will be resolved through discussion or with an additional reviewer. The results of the search will be reported in full in the final systematic review and presented in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram [29].

Assessment of Methodological Quality

A pilot test with 6 studies will be undertaken to guarantee consistency between the 2 reviewers responsible for the selection and data extraction process. Then, 2 independent reviewers will assess each eligible study for methodological quality prior to inclusion in the review, using the Cochrane risk-of-bias tool for randomized trials [30]. Potential biases in studies may include a selection bias, performance bias, detection bias, attrition bias, and selective report bias. Each domain will be rated as "Yes," "No," or "Unclear." All included studies will be processed in the next phase regardless of risk-of-bias scores. The study authors will be contacted to obtain information if needed.

The overall quality of evidence will be assessed using the Grading of Recommendations Assessment, Development and Evaluation method. Findings for each outcome will be rated as high, moderate, low, or very low quality. Items include study design, risk of bias, imprecision, inconsistency, indirectness, and publication bias. Any disagreements that arise between the reviewers will be resolved through discussion or with other reviewers.

Data Extraction

Data will be extracted from studies included in the review by 2 independent reviewers. A pilot test will be conducted on 6 studies to ascertain agreement between the reviewers. The data extracted will include specific details about the populations, interventions, comparison, outcomes, findings, and measurement of significance to the review objective. Any disagreements that arise between the reviewers will be resolved through discussion or with a third reviewer. Authors of papers will be contacted to request missing or additional data, where required.

Data Synthesis and Presentation

Outcomes will be analyzed as continuous and dichotomous outcomes whenever possible. Meta-analyses will be performed using the random effects model for outcomes using Review Manager (RevMan) [31] computer software. For continuous outcomes, the standardized mean difference and 95% CIs for the means will be calculated. A P value of less than .05 will indicate statistical significance for the overall effect. Heterogeneity of effect sizes across studies will be determined by significant chi-square values and an I^2 value of >60%. Subgroup analyses will be performed [32]. A Funnel plot will be used to examine publication bias if there are 10 or more studies included in the meta-analysis. An asymmetry funnel plot will substantiate the presence of publication bias. A meta-analysis will be conducted with studies that report on the same outcomes.

Results

This study was supported by the Department of Public Health Nursing, Faculty of Public Health, Mahidol University, Thailand, in January 2022. This systematic review protocol was started in February 2022 and registered in PROSPERO in March 2022. As of August 2022, the data were analyzed, and the final report of the review were completed at the end of December 2022.

The characteristics of the included studies and the description of iCBT interventions will be summarized. The findings from the meta-analysis will show and describe the ability of iCBT to change psychological distress and work engagement outcomes among employees. When quantitative synthesis is not possible, a narrative synthesis of the results will be used.

Discussion

Here we provide a short summary of the main findings related to the aim and hypothesis of this review. The discussion will be motivated by the fact that the iCBT intervention will benefit selected outcomes based on the existing pool effect size of all included studies and how they add new findings to these fields. In addition, here we shall explain why the effective iCBT interventions yielded the results that they did and how they would be supported by the current evidence and comparison to prior work.

There will be strengths and limitations to this review. In contrast to previous reviews, we will concentrate on healthy non–health care workers. The new evidence of preventive psychological and work engagement outcomes is to be included in our review. Only randomized controlled trials were included in the study because they are regarded as the most suitable research designs.

The meta-analysis will be carried out in order to pool the effect size among individual studies for each outcome. This result could predict the evidence supporting the use of iCBT interventions in clinical practice. The limitations to this review will be explained in terms of the possibilities for future research, such as the generalizability of the findings, confirming further results, and clarifying more outcomes in future research.

The findings from this review will provide evidence for clinical and policy implications that internet delivery has the potential to improve the benefits of CBT in terms of reducing psychological consequences and increasing work engagement level. This conclusion will be used to assist in making decisions regarding implementing iCBT techniques as a preventive intervention for healthy non–health care employees in clinical practice, such as the variety of program characteristics, including content and duration, which will be examined for use in enhancing employee outcomes. The efficacy of iCBT will also be used to improve the negative impacts of psychological conditions and support high levels of work engagement in the workplace.

According to the findings of this study, iCBT therapies will become a strategy for promoting mental health issues among healthy non–health care workers, such as depressive symptoms,

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anxiety, psychological distress, stress, insomnia, and resilience. The summary of this review will also support future decision-making regarding the adoption of an internet-based intervention to reduce psychological discomfort among employees. Importantly, the findings will be used to ensure workplace policies that aim to alleviate the negative impacts of psychological conditions.

Acknowledgments

This study was supported by the Department of Public Health Nursing, Faculty of Public Health, Mahidol University, Thailand.

Authors' Contributions

WL, PB, and PKY conceived the initial concept for the review. All authors revised and approved the protocol, which was developed by WL. WL and PB will carry out the search strategy, screening, extraction, and analysis of the included studies. WL will draft the final manuscript of this systematic review with contributions and approval from all authors.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Summary of systematic search strategies.
[PDF File (Adobe PDF File), 54 KB - resprot_v12i1e38597_app1.pdf]

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Abbreviations

CBT: cognitive behavioral therapy
iCBT: internet-based cognitive behavioral therapy
PROSPERO: International Prospective Register of Systematic Reviews

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Protocol

Artificial Intelligence and Precision Health Through Lenses of Ethics and Social Determinants of Health: Protocol for a State-of-the-Art Literature Review

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Abstract

Background: Precision health is a rapidly developing field, largely driven by the development of artificial intelligence (AI)–related solutions. AI facilitates complex analysis of numerous health data risk assessment, early detection of disease, and initiation of timely preventative health interventions that can be highly tailored to the individual. Despite such promise, ethical concerns arising from the rapid development and use of AI-related technologies have led to development of national and international frameworks to address responsible use of AI.

Objective: We aimed to address research gaps and provide new knowledge regarding (1) examples of existing AI applications and what role they play regarding precision health, (2) what salient features can be used to categorize them, (3) what evidence exists for their effects on precision health outcomes, (4) how do these AI applications comply with established ethical and responsible framework, and (5) how these AI applications address equity and social determinants of health (SDOH).

Methods: This protocol delineates a state-of-the-art literature review of novel AI-based applications in precision health. Published and unpublished studies were retrieved from 6 electronic databases. Articles included in this study were from the inception of the databases to January 2023. The review will encompass applications that use AI as a primary or supporting system or method when primarily applied for precision health purposes in human populations. It includes any geographical location or setting, including the internet, community-based, and acute or clinical settings, reporting clinical, behavioral, and psychosocial outcomes, including detection-, diagnosis-, promotion-, prevention-, management-, and treatment-related outcomes.

Results: This is step 1 toward a full state-of-the-art literature review with data analyses, results, and discussion of findings, which will also be published. The anticipated consequences on equity from the perspective of SDOH will be analyzed. Keyword cluster relationships and analyses will be visualized to indicate which research foci are leading the development of the field and where research gaps exist. Results will be presented based on the data analysis plan that includes primary analyses, visualization of sources, and secondary analyses. Implications for future research and person-centered public health will be discussed.

Conclusions: Results from the review will potentially guide the continued development of AI applications, future research in reducing the knowledge gaps, and improvement of practice related to precision health. New insights regarding examples of existing AI applications, their salient features, their role regarding precision health, and the existing evidence that exists for their effects on precision health outcomes will be demonstrated. Additionally, a demonstration of how existing AI applications address equity and SDOH and comply with established ethical and responsible frameworks will be provided.

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KEYWORDS

artificial intelligence; clinical outcome; detection; diagnosis; diagnostic; disease management; ethical framework; ethical; ethics; health outcome; health promotion; literature review; patient centered; person centered; precision health; precision medicine; prevention; review methodology; search strategy; social determinant

Introduction

Overview

Precision health is described as the ability to assess disease risks at an individual level, detect early preclinical conditions, and initiate preventive strategies [1]. Precision health refers to personalized health care based on a person's unique genetic, genomic, or omics composition within the context of lifestyle, social, economic, cultural, and environmental influences to help individuals achieve well-being and optimal health [2]. As a field of research, it is still being delineated in relation to other fields such as precision medicine [3], while at the same time giving rise to other research concepts that it may actually encompass, such as precision public health [4]. In this manner, the scope of precision health is broader than that of precision medicine, by including strategies for health promotion and disease prevention that occur outside the setting of health care institutions, which can be widely adopted [5]. Thus, precision health strives to match promotion, prevention, diagnostic, and treatment interventions with genetic, biological, environmental, and social and behavioral determinants of health in a more person-centered manner [6]. Precision health, in a nutshell, entails shifting the focus from treatment to promoting health and preventing the onset of diseases.

Precision health, an evolution of precision medicine, combines genetic and genomic sequence, protein, metabolite, and microbiome information collectively known as "omics" with lifestyle, social, economic, cultural, and environmental factors [1].

Precision health applications often combine more than one data source to assess risks and diagnose and initiate preventative interventions, including biological, genetic, environmental, social, and lifestyle-related measurements or observations. Although combining clinical- and community-based health data sources has not yet been established as necessary to fall within the realm of precision health, the field does provide the theoretical basis to amalgamate precision medicine and the social determinants of health (SDOH) [7] within the same interventions. This ambitious approach to health includes dynamic linkages between the research and practice of medicine, economics, population health, and public health [6].

Digital technologies such as artificial intelligence (AI) are playing an increasing role in precision health. AI systems are partially or wholly autonomous machine-based systems that can, using statistical and mathematical modeling techniques for a given set of human-defined objectives, make predictions, recommendations, or decisions influencing real or digital environments [8]. A recent review has identified few studies on machine learning techniques that promote behavioral changes and physical or mental health [9]. AI-based health technologies are rapidly entering the precision health domain outside the clinical setting. Examples of such technologies include screening and early detection devices and applications, health tracking applications, and mobile devices that support healthy living and improve chronic diseases management. In many cases, such technologies are integrated into devices where precision health was not the primary function or purpose. This may affect both the reliability and accuracy of, but also access to, precision health strategies. Some scholars have highlighted the potential of AI-based interventions in integrating the SDOH and precision medicine to improve overall population health [6,10].

With the prevalence and rapid development of health AI applications, the World Health Organization (WHO) has released a set of guiding principles for the ethical use and governance of AI in health [11]. Per the WHO guidelines, emphasis should be on (1) protecting autonomy; (2) promoting human well-being, human safety, and the public interest; (3) ensuring transparency, explainability, and intelligibility; (4) fostering responsibility and accountability; (5) ensuring inclusiveness and equity; and (6) being responsive and sustainable during its deployment. These guidelines thereby address a recent discussion of AI's bias [12] and other challenges [13] to its use in health applications. The source of such bias and related challenges may be largely related to a long-entrenched health research focus on specific socioeconomic and demographic populations. A recent review further demonstrated that only 20% of studies include individuals from socioeconomically disadvantaged backgrounds [14]. There is, therefore, considerable risk for bias which should be clearly considered in AI algorithms that steer precision health interventions.

The Organisation for Economic Co-operation and Development has also published 5 complementary values--based principles for the responsible stewardship of trustworthy AI [8]. Three Organisation for Economic Co-operation and Development countries' health regulatory agencies further elaborated upon these values by providing a common set of machine learning best practices for medical device development [15]. A potential challenge with value-based ethical frameworks is their openness to interpretation and lack of enforceability. Health AI technologies' rapid development and focus on individualization may also affect the longevity and scope of guidance for their application, suggesting a need for more tailored assessment than current standards [16], if not stricter regulations. The European Union (EU) Commission has also proposed a legal framework for trustworthy AI based on EU values and fundamental rights

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[17], stressing human-centrism, trust, safety and compliance with the law, and fundamental rights.

Several state-of-the-art reviews have been conducted for a broad array of AI-based applications in precision medicine [18], including oncological treatment [19], cardiovascular imaging [20,21], and optimization of clinical workflows [22]. However, similar, timely reviews of AI-based applications within the broader context of precision health are not yet available, and the types and categories of such applications are largely undefined. One summary of state-of-the-art consumer health informatics and education was conducted in 2018 [23] to elucidate opportunities, challenges, and practical implications of AI in these applications, stating that direction and evidence on the benefits of AI to individuals' health were lacking. Since then, the global AI in health care market size is projected to grow from US $8.23 billion in 2020 to US $194.14 billion in 2030, growing at a rate of 38.1% [24].

Review Questions and Objectives

We plan to conduct a state-of-the-art literature review to address research gaps and reduce the knowledge gap regarding novel AI-based applications in precision health. The research questions guiding the review are as follows:

- What novel AI-based applications exist that target precision health and what is their role?
- How are AI-based applications categorized?
- What evidence exists for the effects of AI application on precision health outcomes?
- How do AI-based applications account for ethical and responsible AI principles according to the recent WHO and other guidelines, and if so, how are they operationalized?
- How do AI-based applications for precision health address socioeconomic determinants of health?

The objectives for the review are therefore:

- to identify and categorize novel precision health-related AI applications reported in both scientific and gray literature,
- to summarize the most recent evidence demonstrating effects of AI-based interventions in contributing to precision health outcomes,
- to identify evidence for compliance of AI-based applications in precision health with the WHO principles for ethical AI according to the WHO [11], and
- to assess how AI-based applications for precision health affect health equity in relation to socioeconomic determinants of health [25].

Methods

Overview

This article outlines the protocol for an original state-of-the-art review that will be undertaken and reported according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [26]. State-of-the-art reviews address more current matters and the most current literature in contrast to other kinds of reviews, offering new perspectives on the issue in focus and highlight areas in need of further research [27,28].

The review will encompass applications that use AI as a primary or supporting system or method when primarily applied for precision health purposes in human populations. Any geographical location or setting, including web-based, community-based, and acute, or clinical settings will be included, reporting clinical, behavioral, and psychosocial outcomes, including detection-, diagnosis-, promotion-, prevention-, management-, and treatment-related outcomes. Primary empirical research studies published in scientific or gray literature in the English language will be included for all dates prior to onset of searches.

Textbox 1 describes the planned eligibility criteria for the review based on population, intervention, contexts, and types of studies or evidence.

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Textbox 1. Eligibility criteria for the planned state-of-the-art review.

Inclusion criteria

- Human participants of any age, health status, residence and background; and their samples, material, or data related to their health

  *Note: The use of samples, material, or data falls within the inclusion criteria. Fictional or fabricated material will be included as long as the trained models are validated for external previously unseen real populations.*N
- Applications that use artificial intelligence (AI) as a primary or supporting system or method, when primarily applied [1] for precision health purposes
- Any geographical location or setting, including web-based, community-based, acute, or clinical settings
- Clinical, behavioral, and psychosocial outcomes, including detection-, diagnosis-, promotion-, prevention-, management-, and treatment-related outcomes
- Primary empirical research studies published in scientific or gray literature (see information sources)
- English language for scientific and gray literature; those that can be obtained as full texts or reports
- All dates prior to the onset of searches

Exclusion criteria

- Any participants, samples, material, or data not obtained or derived from humans
- AI-based systems or methods that are primarily applied for other reasons, even if they indirectly affect precision health outcomes

  Note: An example of an excluded intervention would be an AI-based application for tailored marketing of services or products, which affects the users' psychological or well-being status.
- Economic or organizational outcomes (eg, cost-effectiveness or organizational efficiency studies)
- Qualitative, nonempirical studies, editorial or opinion pieces, or reviews
- All other languages; articles that cannot be obtained as full texts or reports

Information Sources

Scientific database searches will be conducted from all dates prior to the onset of searches in Medline (EBSCOHost), CINAHL Plus (EBSCOHost), APA PsycInfo (EBSCOHost), Scopus [29], Web of Science [30], IEEE [31], and Cochrane Central Registry of Controlled Trials [32].

Searches in gray literature, or "that which is produced on all levels of government, academics, business and industry in print and electronic formats, but which is not controlled by commercial publishers, i.e., where publishing is not the primary activity of the producing body" [33], will be conducted. The purpose of the gray literature searches is to identify ongoing or completed studies that are not available in the commercial scientific literature databases. Links to such studies may also be found in device registries. The following gray literature sources will therefore be searched:

- Study registries and registers of medical devices:
  - WHO ICTRP [34]
  - ClinicalTrials.gov [35]
  - FDA list of approved AI-enabled medical devices [36]
  - EU EUDAMED register [37]
  - International Health Technology Assessment Database [38]
  - arXiv (stat.ML, cs.AI, cs.LG) [39]
  - medRxiv [40]
- Multidisciplinary gray literature databases:
  - OAlste [41]
  - Bielefeld Academic Search Engine [42]
  - Dissertations and thesis databases:
  - Dissertations and Theses A&I (ProQuest)
  - Open Access Theses and Dissertations [43]
  - DART-Europé [44]
- Web search engines:
  - Google scholar [45]

Search Strategy

The preliminary search terms and number of retrieved documents are provided in Table 1. The full review will include both free-text and controlled vocabulary, and the search terms will be adapted for each database. The search terms related to the intervention precision health through AI will be divided into 2 blocks. Proximity operators will be used, where possible, to increase the chance of finding relevant references. Searches of gray literature will be simplified to individual terms if required. No date limit will be applied.

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Table 1. Example of the search strategy in Medline (EbscoHost, October 17, 2022)

Search #	Search blocks	Retrieved documents, n
1	TI ((genomic* OR precis* OR personali* OR individuali* OR stratif* OR tailo* OR adapt* OR custom* OR predictive) N2 health*) OR AB ((genomic* OR precis* OR personali* OR individuali* OR stratif* OR tailo* OR adapt* OR custom* OR predictive) N2 health*)	18,454
2	(TI "Artificial Intelligence" OR AB "Artificial Intelligence") OR (TI "machine learning" OR AB "machine learning") OR (TI "deep learning" OR AB "deep learning")	104,534
3	(MH "Artificial Intelligence+")	156,342
4	2 OR 3	208,639
5	4 AND 1	571
Limiters	Narrow by Language: English	566

A larger alteration concerning the search block relating to AI is applied based on the recent publication [46]. However, due to complexity, databases such as IEEE and Cochrane Trials are excluded. Yin et al [46] argue that AI is a broadly encompassing term and includes specific AI techniques, such as neural networks, support vector machines, decision trees, and natural language processing. Yet, such studies are highly likely to use "artificial intelligence" or "machine learning" in abstracts or keywords [47].

The final search terms and eligibility criteria (Textbox 1) will be designed to capture a range of precision health research. The search strings are presented in Table 1.

Data Management Plan

All identified records will be entered into EndNote (Version X20, Clarivate Analytics) and duplicates will be removed. Remaining records will then be entered into and managed within the Covidence systematic review software (Veritas Health Innovation Ltd) for the remaining review process.

The PRISMA guidelines for reporting of systematic reviews [27] will be followed. Three researchers will conduct the review process in 4 steps:

1. Initial screening: the titles, keywords, and in some cases abstracts of the obtained records will be screened for relevance by 2 reviewers independently in duplicate and voted upon for relevance for further review. Consensus will result in inclusion or exclusion, with conflicts resolved by a third researcher.
2. Full-text screening: the full text for all studies proceeding to this step will be obtained and read independently by 2 reviewers, who will vote upon inclusion in the next step. Consensus will result in inclusion or exclusion, with conflicts resolved by the third researcher.
3. Citation searching: the cited references for, and citations of, any studies included after the full-text screening step will be searched in the same manner as the source articles, and then follow the steps preceding this in the review process.
4. Data extraction: essential information regarding the study aim, design, conduct, population, intervention, and outcomes, as well as results data for relevant outcomes, will be extracted from each included study by 2 reviewers independently. Consensus will result in the inclusion of the extracted data in the review's summary of findings, with conflicts resolved through dialogue or, failing consensus thereafter, by the third researcher.

Quality Assessment of AI Interventions

Due to the diversity and heterogeneity of existing AI techniques, significant biases are likely to occur, making it difficult to interpret the results and implement these models in practice [48]. AI-based models rely substantially on data, quality, quantity, and type of data to ensure high algorithmic accuracy. Additionally, studies related to AI interventions require high methodological quality and rigorous standards of outcome reporting and representative study participants.

Thus, Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) will be used to validate the quality of studies in the review [49]. The QUADAS-2 tool includes 4 domains covering flow and timing, reference, standard, and patient selection. Each domain is evaluated for biases and assessed for applicability.

Framework for SDOH

There is no universal standardized method for categorizing SDOH. For example, the WHO's conceptual framework includes micro-, meso-, and macrolevel measures [50]. SDOH is further defined by the Centers for Disease Control and Prevention as "conditions in the environments in which people are born, live, learn, work, play, worship, and age that affect a wide range of health, functioning, and quality-of-life outcomes and risks" [51]. Thus, SDOH falls into 5 key categories: health care access and quality, education access and quality, social and community context, economic stability and the neighborhood, and the built environment.

For this review, the framework for SDOH will be based on the sociocultural environment within the framework for digital health equity. This includes social determinants that include downstream and upstream factors at the individual, interpersonal, community, and societal levels [52].

Ethics and Dissemination

This study will not involve human participants and their primary data or unpublished secondary data, thus ethical approval is not required. Findings of the state-of-the-art review will be disseminated through publication in an open-access scientific journal as well as through research networks and journalistic media.

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Patient and Public Involvement

The primary and secondary analyses will be presented to representatives of multiple stakeholder groups, including users or patients, professionals, and public purchasers (if relevant). Their input will then be solicited to assist in the secondary analyses regarding anticipated impact and consequences on equity and the SDOH.

Results

Overview

This article is step 1 toward a full state-of-the-art literature review with data analyses, results and discussion of findings which will also be published.

The anticipated consequences on equity from the perspective of SDOH will be analyzed. Keyword cluster relationships and data analyses will be visualized to indicate which research foci are leading the development of the field and where research gaps exist. Results will be presented based on the data analysis plan that include primary analyses, visualization of sources, and secondary analyses. Results from this review will potentially guide continued application and development of AI applications and pinpoint agenda for future research to reduce the knowledge gaps and improve practice related to precision health. New insights regarding examples of existing AI applications, their categorization and role regarding precision health, and the existing evidence for their effects on precision health outcomes will be demonstrated. Additionally, how existing AI-based applications account for ethical and responsible AI principles and address socioeconomic determinants of health will be analyzed.

Primary Analyses

The main statistics in each study relevant to the aims of the review will be reported as well as grouped across studies by target population (eg, older individuals, risk groups, disease state), channel (eg, device, software, or app), setting (eg, home or primary care), area of focus (eg, detection and treatment), and outcome (clinical, behavioral, and psychosocial). Depending on the statistical reporting of the studies, which is often less rigorous in gray literature, further synthesis may be conducted. As this is not a systematic review, the strength of the cumulative body of evidence will not be assessed.

Secondary Analyses

The compliance of the precision health AI interventions or applications with the WHO principles for ethical AI [11] will be assessed and analyzed on quantitative (number of principles) and qualitative (degree or veracity of fulfilment of principles) levels. The anticipated consequences on equity from the perspective of SDOH will be analyzed.

Discussion

Overview

This article is step 1 toward a full state-of-the-art literature review with data analyses, results, and discussion of findings, which will also be published.

Keyword cluster relationships and data analyses will be visualized to indicate which research foci are leading the development of the field and where research gaps exist. Results will be presented based on the data analysis plan that include primary analyses, visualization of sources, and secondary analyses. Results from this review will potentially guide continued application and development of AI applications and pinpoint agenda for future research to reduce the knowledge gaps and improve practice related to precision health. New insights regarding examples of existing AI applications, their categorization, and role regarding precision health and the existing evidence for their effects on precision health outcomes will be demonstrated. Additionally, how existing AI-based applications account for ethical and responsible AI principles and address socioeconomic determinants of health will be analyzed.

This protocol is step 1 in the full state-of-the-art review that intend to provide insights on the evidence-based novel AI applications that promote precision health and how these applications comply with the WHO principles for the ethical use and how they affect health equity in relation to socioeconomic determinants of health.

As per our knowledge, this will be the first review addressing and precision health through lenses of ethics and SDOH. As an example of the search we conducted, search strategy in Medline (EbscoHost, October 17, 2022) indicated a total of 566 retrieved documents. Updated searches will be conducted in the full review.

Primary analyses will include main statistics in each study relevant to the aims of the review as well as grouped across studies by target population, setting, area of focus, and outcome. Visualization of sources will include mapping the existing literature on the use of AI in precision health and will help illustrate what precision health-related AI applications exist.

Secondary analyses will include compliance of the precision health AI interventions or applications with the WHO principles for ethical AI and consequences on equity. Due to the diversity and heterogeneity of existing AI techniques, and the significant biases that are likely to occur, QUADAS-2 will be used to validate quality of studies in the review [49]. This will enable interpretation of the results from the review and address implementation of AI models in practice [48].

Conclusions

This protocol will guide the development of the full review article. Results will potentially guide continued development of AI applications, future research in reducing the knowledge gaps, and improve practice related to precision health. New insights regarding examples of existing AI applications, their categorization and their role regarding precision health, and the existing evidence exists for their effects on precision health outcomes will be demonstrated. Additionally, demonstration of how existing AI applications address equity and SDOH and comply with established ethical and responsible framework will be provided.

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Implications for future research and person-centered public health will be discussed in the full review in the light of strengths and limitations.

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Authors' Contributions

SWA conceived the project and conceptualized the research idea and is the guarantor of the review. SLS performed the literature search. MXR performed data extraction and data analysis. All authors contributed to the conceptualization and the drafting of this work. Inspirations were collected from previous reviews. All authors approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

AI: artificial intelligence
EU: European Union
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QUADAS-2: Quality Assessment of Diagnostic Accuracy Studies 2
SDOH: social determinants of health
WHO: World Health Organization

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Protocol

The Need to Prioritize Model-Updating Processes in Clinical Artificial Intelligence (AI) Models: Protocol for a Scoping Review

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Abstract

Background: With an increase in the number of artificial intelligence (AI) and machine learning (ML) algorithms available for clinical settings, appropriate model updating and implementation of updates are imperative to ensure applicability, reproducibility, and patient safety.

Objective: The objective of this scoping review was to evaluate and assess the model-updating practices of AI and ML clinical models that are used in direct patient-provider clinical decision-making.

Methods: We used the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist and the PRISMA-P protocol guidance in addition to a modified CHARMS (Checklist for Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modelling Studies) checklist to conduct this scoping review. A comprehensive medical literature search of databases, including Embase, MEDLINE, PsycINFO, Cochrane, Scopus, and Web of Science, was conducted to identify AI and ML algorithms that would impact clinical decision-making at the level of direct patient care. Our primary end point is the rate at which model updating is recommended by published algorithms; we will also conduct an assessment of study quality and risk of bias in all publications reviewed. In addition, we will evaluate the rate at which published algorithms include ethnic and gender demographic distribution information in their training data as a secondary end point.

Results: Our initial literature search yielded approximately 13,693 articles, with approximately 7810 articles to consider for full reviews among our team of 7 reviewers. We plan to complete the review process and disseminate the results by spring of 2023.

Conclusions: Although AI and ML applications in health care have the potential to improve patient care by reducing errors between measurement and model output, currently there exists more hype than hope because of the lack of proper external validation of these models. We expect to find that the AI and ML model-updating methods are proxies for model applicability and generalizability on implementation. Our findings will add to the field by determining the degree to which published models meet the criteria for clinical validity, real-life implementation, and best practices to optimize model development, and in so doing, reduce the overpromise and underachievement of the contemporary model development process.

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KEYWORDS

model updating; model calibration; artificial intelligence; machine learning; direct clinical care

Introduction

Background

The ubiquitous application of artificial intelligence (AI) and machine learning (ML) algorithms in health care delivery has increased [1]. Investments in clinical AI and ML algorithms are based on their perceived potential to improve health care quality [1]. These algorithms can automate insights directly from data without using standard computer programming [2]. In addition, they can analyze large data sets with high dimensionality to yield insights and predictions on complex associations without prior assumptions from traditional statistical methods, differentiating AI and ML models from other statistical techniques (interference statistics, classical prediction models, and hypothesis testing) [3,4]. Generally, 2 methods of learning from data exist in AI and ML: supervised and unsupervised learning. Supervised learning involves making predictions based on a set of prespecified input, references, and output variables, whereas unsupervised learning is used to draw inferences from data sets consisting of input data without labeled responses [5].

There has been a paradigm shift in health care stakeholders' goals of quality improvement in recent years, with an emphasis on achieving better outcomes at lower costs, while improving the efficiency of care delivery and prioritizing personalized care [6]. This change, resulting in the use of AI and ML algorithms, has also been driven by regulators and payers demanding high-value care rather than volume-based care, as well as the changing role of patients as consumers [7]. In addition, the unprecedented abundance of data with the advent of electronic health records (EHRs) and other direct consumer wearables allows the application of data-heavy clinical models [8].

Despite these perceived potentials, AI and ML algorithm performance degrades over time, particularly because of model calibration (calibration drift), which refers to the accuracy of risk estimates in terms of agreement between the predicted risks of events and their actual observed frequencies [9]. Calibration drift arises as a consequence of deploying a model in a dynamic environment, with the resulting difference between the population or setting in which the model was trained and that in which it was implemented [10].

Degradation of a model over time can also occur within the same health care system where it was derived [11]. Among other factors, there is a tendency toward a systematic data shift when a model is successfully deployed [12,13]. The downstream characteristics of data change owing to differences in the distribution of outcomes in a prognostic model as users respond to the model prediction. The more effective a predictive model is to improve outcomes, the faster the model will likely degrade [14].

Because of the sensitive nature of patient-level algorithm predictions, consistency and accuracy are critical. Therefore, an appropriate model-updating process is essential across the lifetime of the model [15]. Model updating aims to improve the performance of an existing model by adjusting (recalibrating) its parameters and predictors, either within the same clinical environment in which the model was developed or within an external environment [15,16]. The best practice is to update a clinical model rather than abandon the model, build another, or repeat the selection of predictors, which leads to a loss of the previous scientific information captured [11,17].

The existence of multiple models for the same clinical scenario without model-updating methods declared ab initio leaves clinicians uncertain of which model is appropriate to use, potentially resulting in adverse consequences for patient care [17]. For example, there are more than 80 models for the prognosis of stroke [18], more than 20 models predicting intensive care unit stay after cardiac surgery [19], more than 100 published algorithms for prognosis after neurotrauma [20], and over 50 models to predict outcomes after breast cancer [21].

Peculiarities and Challenges of Model Updating in the Health Care Environment

The health care model updating process faces unique challenges owing to the health care sector's dynamic clinical, environmental, and regulatory ecosystem [22]. Therefore, it is imperative to consider all these issues from the early stages of clinical model development to ensure consistency and accuracy over time [1,23].

Subtle population demographic changes, in addition to changes in health care access and the heterogeneity of health insurance coverage (health disparity), can also deteriorate a model's future output [1,24]. Changes in best practice clinical guidelines, in addition to variations in practice preferences across different health care providers, can also be a source of data shift, resulting in suboptimal model output [1,15,25-29].

Health centers often update or change information systems and digital health tools such as imaging software and EHRs. Models that are not updated based on the data output of new information systems will be suboptimal [1]. In addition, there is a constant change in clinical nomenclature and disease coding, which can also affect the output [23].

The health care regulatory landscape is constantly evolving as well [30,31]. The enactment of the Affordable Care Act, which was associated with many sweeping reforms to health care delivery and redefining value in health care delivery, rendered previous standards of care invaluable [31]. As such, a model built based on those standards will likely be suboptimal.

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Issues Regarding Health Care Model Input Data

Learning artifacts or bias specific to the sites where training data sets were produced or because of the nature of the data set itself can ultimately result in a data set shift and model degradation over time [1]. Most AI tools are developed based on the nuances of specific local health care workflows and the data they generate. For example, consider an algorithm developed to predict sepsis based on a patient's lactate level. The algorithm will learn to correlate the physician's lactate orders with a high possibility of sepsis. However, model quality would be reduced if there were a policy change requiring more frequent ordering of lactate tests.

Model validation in these circumstances shows reduced performance, as the learned pattern does not generalize across sites and circumstances [24,32]. In addition, there is systemic bias in the geographic distribution of patient cohorts, as algorithms trained on US data were disproportionately trained on patients from just 3 states (New York, California, and Massachusetts) [33].

Label and causality leakage phenomena occur when the model's prediction target is directly or indirectly present in the training data set, rendering the model prediction irrelevant [34]. An example is a model developed to predict hospital mortality in patients admitted to the intensive care unit. An AI model trained naively on all data will learn to correlate extubating and turning off the ventilator with the death of a patient and ultimately produce a near-perfect predictive performance yet with absolutely no clinical utility [34]. Causality leakage in the clinical model can occur in a situation whereby a clinician orders a test based on a high index of suspicion of a clinical outcome that the algorithm is meant to predict; the algorithm then uses the test to generate an alert that results in an action [35].

Overview of Model Updating Methods in Health Care

There are several methods that address the data shift required to update models [1,16,17,23,36]. Although extensive details of these methods are beyond the scope of our analysis, we have highlighted the most important methods here [16,17,23,36]. The least complex method involves adjusting the model intercept to a different prevalence or incidence rate according to the new population (assuming risk factors still confer the same level of risk). Another option is adjusting the population prevalence rate and adding a single adjustment to all risk factors in the model. One or more risk factor relationships may also need to be adjusted, given the changes in relationships over time. A more drastic method involves adjusting both the prevalence and the coefficients and adding new risk factors into the model.

The last option involves refitting the entire model based on a new data sample, either alone or in combination with the addition of new potential risk factors (essentially remodeling the problem from scratch on a new sample). The best options typically depend on the time from initial model development to the time sample sizes are updated [23]. With larger samples or longer time periods since the initial fitting, ideal updates usually involve the prevalence updating option or refitting the model based on the updated sample. With small samples, it is generally advised that no updates are made. With shorter periods of time since the last update, it is generally recommended that the prevalence be updated.

Time and Frequency of Model Updating

A few approaches exist to guide the timing and frequency of model updating, each with its own advantages and limitations. Real-time calibration drift detection and updating is usually the most computationally intensive approach; however, real-time detection provides users with the peace of mind that their models are accurate at the time of use without requiring manual steps [23]. A similar approach is incremental updating, in which models are updated based on new instances as they become available [16,23]. This approach is computationally extensive and requires the same infrastructure to automatically provide near-real-time updates automatically. Fixed and batch updating at specified intervals is another option, with models evaluated and updated at specific intervals; however, if the frequency of the update is not ideal, model drift issues may exist before the update [16,23].

Study Objectives

Our main study objective is to evaluate model updating in AI and ML clinical models and assess model updating practices used in direct patient-provider clinical decision-making. Previously published reviews have established that most clinical AI and ML models do not conduct external validation of their models [5]. In addition, phases of model development pertaining to applicability and reproducibility (model updating, impact assessment, and implementation) have received less attention in the scientific literature [37]. Clinical model-updating processes seek to prevent model deterioration with adverse consequences, such as inaccuracy or lack of practicality in clinical settings; model updating can also impact generalizability and reproducibility [37]. The model-updating processes of clinical algorithms must be determined proactively from the time of initial model development [32,37] to ensure patient safety and quality of care. Understanding the degree to which model updating is prioritized will help inform the validation of future models and guide the modification of best practices in model development.

Our intentions are as follows:

1. To determine if the process of clinical model updating is mentioned or prioritized in the reviewed published clinical AI studies used to support direct patient-provider clinical decision-making.
2. To determine if AI and ML studies in the literature include demographic data and if there are significant geographic distributions of models whose investigators recommended model-updating procedures in their publications.
3. To test correlations between the quality of published AI clinical models and prioritization of the model-updating process.

Methods

Eligibility Criteria: Inclusion and Exclusion

This study protocol is for a scoping review. Our original protocol was developed based on the PRISMA (Preferred Reporting

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Items for Systematic Reviews and Meta-Analyses) Protocols [38].

Inclusion Criteria and Rationale

Only AI and ML studies that involve clinically predictive or prognostic modeling used to support specific clinical decisions by medical providers for or against intervention for direct patient care will be included. In addition, only human studies with algorithms applied to organic and emotional and behavioral health domains used directly in addressing clinical problems (by supporting patient-provider decision-making) will be included. Examples of algorithms we will include are those predicting outcomes that affect clinical decisions and treatment (mortality and morbidity and predicting length of hospital stay) and those predicting complications and health improvement.

Algorithms comparing diagnostic modalities and tools with the possibility of affecting clinical decisions also fall under our inclusion criteria. We will include both observational and experimental studies regardless of study methods, as there is a dearth of randomized controlled trials (RCTs) in AI and ML studies owing to the novelty of AI applications in health care [39].

Supervised ML methods, including both classification and regression methods, will also be included. Most supervised predictive model outputs directly impact decisions at the point of use, unlike unsupervised or clustering and semisupervised methods, mostly to generate insights for a predictive problem [40]. Studies will be included without geographic or regional preferences. All studies that were published from March 2018 until March 2021 will be reviewed (Textbox 1).

Textbox 1. Inclusion criteria.

- Inclusion criteria and definition
  - Only artificial intelligence and machine learning studies that involve clinically predictive or prognostic modeling: Diagnostic prediction models calculate an individual's risk of having an illness, whereas prognostic prediction models calculate the risk of certain health conditions that could occur in the future.
  - Study outcome and outcome measures format: Only human studies with algorithms and outcomes in organic and emotional or behavioral health domains. All study outcome measures format will be included as follows: continuous, binary, ordinal, multinominal, and time-to-event.
  - Supervised machine learning technique: Only articles with supervised learning methods will be included, with methods such as regression, ensemble, and decision trees.
  - Study design and data source: Any experimental or observational study that meets our inclusion criteria will be included. These include randomized controlled trials, prospective and retrospective cohorts, case-control studies, and case-cohort studies. All data sources are permitted, including data registries and electronic health record data.
  - Predictors: Articles that use at least two predictor variables in their model development will be included.

Exclusion Criteria

Health care AI models that do not use clinical domains as a primary end point (studies of health care operations, finance, billing, and inventory management) will be excluded.

AI and ML studies whose predictions may not directly support provider-patient clinical decision-making, including the following, will also be excluded.

- Studies of population-based estimates only (incidences, prevalence, and others)
- Patient or provider satisfaction with care
- Studies designed to improve diagnostic tools, such as imaging and genomics
- Imaging biosignal studies that do not directly impact clinical decision-making
- Studies that evaluate health care system quality indicators

Unsupervised and semisupervised learning and clustering studies will also be excluded, as most data mining and unsupervised learning models are used to generate insights into a problem or identify predictive modeling problems [40]. Reviews, articles, commentaries, letters to the editor, conference abstracts, and commentary articles without algorithms will also be excluded.

We will exclude models embedded in proprietary software where the specific ML methods used are not specified. Failure to meet any of the above eligibility criteria will result in exclusion from the review (Textbox 2).

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Textbox 2. Exclusion criteria.

- Exclusion criteria and definition
  - Health care artificial intelligence studies that do not involve clinical domains as the primary end point: Studies of health care operations, finance and billing, and inventory managements. These do not fall primarily under patient treatment and care.
  - Purpose and potential of study not directly supporting provider-patient clinical decision-making: Studies that may not impact direct provider decision-making at the point of care, such as population-based estimates only (incidences and prevalence), those designed to improve diagnostic tools, and those that evaluate health care system quality indicators.
  - Unsupervised learning and clustering studies: Those that mostly are used to generate insight into a problem or identify predictive modeling problems.
  - Nonexperimental articles and proprietary models: Reviews, articles, commentaries, letters to the editor, abstracts, commentaries without algorithms, and models embedded in a proprietary software whereby the specific machine learning methods used are not specified.
  - Genomics and advanced genetic algorithms: These articles are usually based on very high dimensional data and unsupervised methods, which are beyond the scope of our analysis.
  - Pathological specimen and image signal studies: Pathological specimen studies mostly seek to improve accuracy at the level of the clinical pathologist. Image signals studies are mostly used to improve the accuracy of an imaging instrument rather than provide a basis for preferred clinical outcomes.

Information Sources

A comprehensive literature search will be conducted using the following databases: Ovid Embase, Ovid MEDLINE, Ovid PsycINFO, Web of Science Core Collection, Scopus, and the Cochrane Library. Searches will be limited to articles published from January 1, 2018, to December 31, 2021.

Search Strategy

The search strategy for each database was developed by a medical librarian (SW) in concert with the rest of the team. Each search strategy used a combination of keywords and subject headings related to ML, predictive algorithms, medical diseases and disorders, and study design (Multimedia Appendix 1).

Statistical Analysis

Data Management

All search results will be imported into Covidence software for deduplication and screening [41]. Covidence facilitates a blind review process, and results from multiple databases can be imported, deduplicated, and screened for eligibility. Following the title and abstract screening phase, the full text of all included abstracts will be gathered and imported. Covidence will create a PRISMA flowchart and facilitate the data extraction and quality appraisal phases [42].

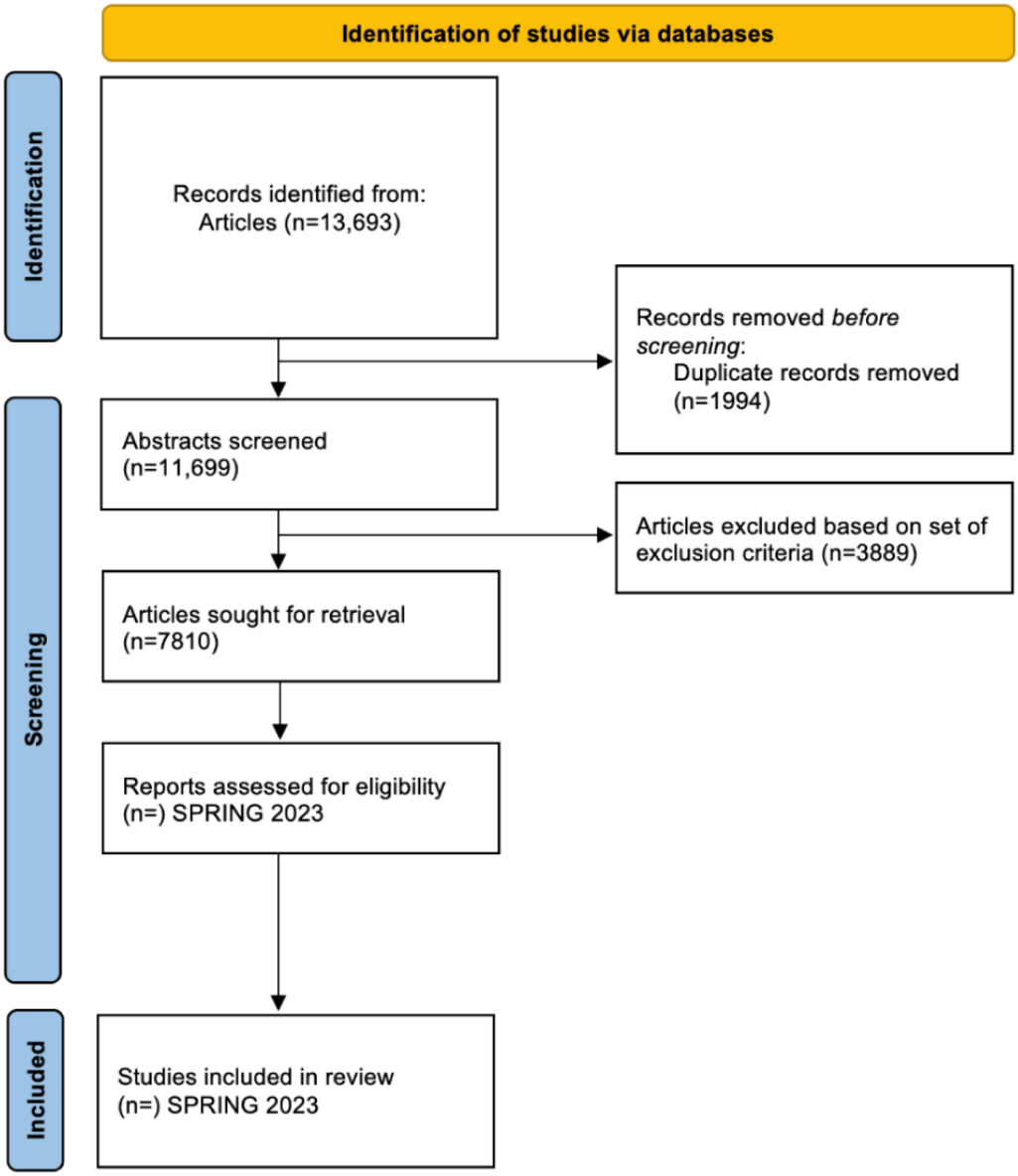
Selection Process

Two reviewers will use the Covidence software to independently screen the title and abstract of each article and the full text of all included abstracts. A third-party independent reviewer will resolve disparities. The screening process will be documented and presented using the PRISMA flow diagram like the flowchart in progress in Figure 1.

Before title and abstract screening, the review team will meet to screen a random sample of 50 records to validate the inclusion and exclusion criteria.

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Figure 1. PRISMA flow chart.



Data Collection Process

Variables collected from each eligible study will be guided by the CHARMS (Checklist for Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modelling Studies) [43] and PRISMA checklists [42].

Data Items

Data items will reflect the objective of our study, which is the need to prioritize clinical model updating as an integral part of validating published medical algorithms. Therefore, our data items will pertain to generalizability and applicability.

We will collect general study information, such as the title; first author; year of publication; clinical setting, such as academic, nonacademic, vendor, and governmental agency; disease system of the study; aim of the algorithm (predictive vs prognostic); type of algorithm (traditional ML vs neural network or deep learning); and geographic region. We will also collect data on study type and model type (research vs production model) as well as model-updating methods.

Our preliminary search on geographic clusters of AI adoption and model implementation revealed that AI and ML adoption is mostly clustered in the United States, Canada, the United Kingdom, Australia, the European Union, China, Taiwan, and Israel [44,45]. As these regions account for most of the clinical models created, we will use another category of “Other” to capture models developed in other geographic regions. We will also collect information about the data sources such as EHRs, open registry or open sources, and closed registry or proprietary databases.

In the *Methods* section, we will abstract the data relating to the assessment of study quality (Table 1). Data on handling missing data will also be abstracted, such as sample size, well-defined primary outcomes, and predictors. We will also abstract data on the study limitations considered in the Discussion section of the article in review.

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Table 1. Checklist for Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modelling Studies.

Domains and key items	General	Applicability	Risk of bias
Source of data			
Source of data (cohort, case-control, randomized trial participants, or registry data)		✓	✓
Participants			
Participant eligibility and recruitment methods (consecutive participants, location, number of centers, setting, and inclusion and exclusion criteria)	✓	✓	
Participant descriptions	✓	✓	
Details of treatment received, if relevant		✓	✓
Study dates	✓	✓	
Outcome to be predicted			
Definition and methods for outcome measurements		✓	✓
Determine if the same outcome definition and method for measurement was used in all patients			✓
Type of outcome (single or combined end points)	✓	✓	
Determine if the outcome was assessed without knowledge of candidate predictors (blinded)			✓
Determine if candidate predictors were part of the outcome (in panel or consensus diagnosis)			✓
Time of outcome occurrence or summary of duration of follow-up		✓	
Candidate Predictors (or Index Test)			
Number and type of predictors (demographics, patient history, physical examination, additional testing, and disease characteristics)	✓		
Definition and method for measuring candidate predictors		✓	✓
Timing of predictor measurement (patient presentation, diagnosis, and treatment initiation)		✓	
Determine if predictors were assessed blinded for outcome and for each other (if relevant)			✓
Handling predictors in the modeling (continuous, linear, and nonlinear transformation or categorized)			✓
Sample size			
Number of participants and number of outcomes or events	✓		
Number of outcomes or events in relation to the number of candidate predictors (events per variable)			✓
Missing data			
Number of participants with any missing values (including predictors and outcomes)	✓		✓
Number of participants with missing data for each predictor			✓
Handling of missing data (complete case analysis, imputation, or other methods)			✓
Model development			
Modeling methods (logistics, survival, neural networks, or machine learning techniques)	✓		
Modeling assumptions satisfied			✓
Method for selecting predictors for inclusion in multivariable modeling (all candidate predictors and preselection based on unadjusted association with the outcome)			✓
Methods for selecting predictors during multivariable modeling (full model approach backward or forward selection) and criteria used (*P* value and Akaike Information Criterion)			✓
Shrinkage of predictor weights or regression coefficients (no shrinkage, uniform shrinkage, and penalized estimation)		✓	✓
Model performance			
Calibration (calibration plots, calibration slope, and Hosmer-Lemeshow test) and discrimination (*C*-statistic, *D*-statistic, and log-rank) measures with CIs		✓	
Classification measures (sensitivity, specificity, predictive values, and net reclassification improvement) and whether a priori cut points were used			✓
Model evaluation			

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Domains and key items	General	Applicability	Risk of bias
Method used for testing model performance: development data set only (random split of data, resampling methods, bootstrap or cross-validation, or none) or separate external validation (temporal, geographic, different settings, and different investigators)			✓
In case of poor validation, whether the model was adjusted or updated (intercept recalibrated, predictor effects adjusted, or new predictors added)		✓	✓
Results			
Final and other multivariable models (basic, extended, and simplified) presented, including predictor weights or regression coefficients, intercept, baseline survival, and model performance measures (with SEs or CIs)	✓	✓	
Any alternative presentation of the final prediction models (sum score, nomogram, score chart, and predictions for a specific risk subgroup with performance)	✓	✓	
Comparison of the distribution of predictors (including missing data) for development and validation data sets			✓
Interpretation and discussion			
Interpretation of presented models (confirmatory, model useful for practice vs exploratory, and more research needed)	✓	✓	
Comparison with other studies, discussion of generalizability, strengths, and limitations	✓	✓	

Evaluation Outcomes

Primary Outcome

The primary outcome of this scoping review is the percentage of published algorithms that prioritize model-updating methods (model updating is considered prioritized if it is part of the algorithm protocol). We also identify articles that mention model updating but do not apply it to algorithm protocols.

Secondary Outcomes

We will also identify any correlations between prioritizing model updating and geographic region, and quality of studies, as well as temporal correlation and correlation by setting of model development. In addition, we will assess how frequently EHRs are used for model development, given the high incidence of inaccuracies in EHR data [46-48].

As a secondary end point, we will capture the incidence of models reporting the demographic breakdown of their data (ethnic background and gender); this is of particular importance owing to potential societal harm and resulting AI and ML algorithm setbacks because of the use of nonrepresentative data [49].

Quality of Studies and Risk of Bias Assessment

Owing to the overemphasis on model technical validity at the expense of downstream clinical validity in published algorithms, a clinical model that has acceptable, technically valid prediction results during model development with favorable statistical indexes, such as area under the curve, does not automatically translate to model effectiveness when deployed in real-life clinical scenarios [1,50-52]. Rather than the in-depth technical validity of model results, our evaluation of individual model quality will assess a model's ability to attain high real-life clinical validity for generalizability. Our goal is to focus on established factors and best practices that indicate a study's applicability and low risk of bias to ensure generalizability beyond the model's technical output as follows [52-54]:

- Applicability: the extent to which the study fits within the inclusion and exclusion criteria of the review
- Risk of bias: the extent to which any flaws in the study lead to overly optimistic estimates of predictive performance measures (CHARMS article)
- Generalizability: the degree to which the study results are relevant to the larger population
- Reproducibility: the ability to duplicate the study using the same methods used in the original study

Checklist/Evaluation Tools for Study Quality Assessment

Best practices recommend adequate reporting of model development to ensure reproducibility and applicability of models in real clinical settings [2]. To evaluate the quality of reporting of the reviewed published models, we used an adaptation of a verified tool available for model quality assessment [43]. The CHARMS is an 11-item checklist, with each item created to assess the model study on the domains of risk of bias and applicability (Table 1). The checklist is a comprehensive guide created from a combination of 8 other published guides that include both criteria to ascertain applicability and reproducibility with implications for patient safety, as well as technical validity of a model's results, some of which are beyond the scope of our review.

We created our quality assessment tool by extracting the criteria that are more specific to applicability and reproducibility analysis and that have a potential impact on patient safety and quality of care at the level of clinical model deployment, which resulted in our 6-item checklist for study quality assessment (Table 2). A total of 5 items out of our 6-item checklist were adapted from the CHARMS checklist; our last criteria, the model development checklist standard, was obtained from literature review best practices for model development.

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Table 2. Quality of studies and risk of bias assessment.

Assessment criteria	Maximum score (stars)
Study design and missing data	
Study design	
RCTs[a]	(**)
Other sources and designs; cohorts, registries, convenient sampling	(*)
Handling of missing data	(*)
Outcome	
Primary outcome is well defined	(*)
Model testing and evaluation methods	
Separate external validation data; geographical, temporal, and population	(**)
Same development data used for validation; random split and reassembly (bootstrap and cross-validation)	(*)
Model updating method	
Yes	(**)
Model interpretation and applicability concerns	
Strengths and weaknesses of model (reproducibility, applicability, or risk of bias)	(*)
Model reporting and development standard	
Best practice standard for model development and reporting defined; examples of standards: CONSORT-AI[b], SPIRIT-AI[c], DECIDE-AI[d], NEUR-UPS ML[e], TRIPOD-ML[f], PROBAST-ML[g], and STROBE[h]	(*)

[a]RCT: randomized controlled trial.

[b]CONSORT-AI: Consolidated Standards of Reporting Trials-Artificial Intelligence.

[c]SPIRIT-AI: Standard Protocol Items: Recommendation for Interventional Trials- Artificial Intelligence.

[d]DECIDE-AI: Developmental and Exploratory Clinical Investigation of a Decision-Support System Driven by Artificial Intelligence.

[e]NEUR-UPS ML: Neural Informational Processing System in Machine learning.

[f]TRIPOD-ML: Transparent Reporting of a Multivariable Prediction Model of Individual Prognosis Or Diagnosis-Machine Learning.

[g]PROBAST-ML: Prediction model Risk Of Bias Assessment Tool- Machine Learning.

[h]STROBE: The Strengthening the Reporting of Observational Studies in Epidemiology.

Rationale for Checklist Items

Checklist Items Adapted From the CHARMS Checklist: Study Design and Data Source for Model Development

The data used to develop the algorithm may be sourced from retrospective and prospective cohorts including RCTs and cross-sectional studies. In addition, there is a proliferation of sourcing model data from registries, databases, and EHRs. Although RCTs are considered the gold standard, they also have shortcomings similar to all other methods. Although RCTs are designed to reduce biased outcomes, their findings can lead to impaired generalizability of outcomes in real-life clinical scenarios owing to the rigid eligibility criteria of study participants [43]. Data sources for model development are critical for the predictive accuracy, applicability, and reproducibility of any algorithm [11,12,43,50,51].

- Outcomes: the lack of well-defined study outcomes increases risk of bias and adversely affects model reproducibility in real-life clinical scenarios [43]. For example, 40% of cancer prognostic model studies were found to have poorly defined outcomes [55]. For our quality assessment, a well-defined outcome is considered to occur when the definition and measurement of the outcome events or target disease clearly correspond to the outcome definition of the study objective [43].
- Model testing and evaluation methods: model validation is the process of quantifying model performance in other individuals beyond the training and testing data set used to develop the model [56]. Whenever the predictive performance of a model is estimated using the same data set that was used to develop the model, it is referred to as "apparent performance" [43]. Regardless of which modeling technique is used, apparent performance tends to be biased, as it can overestimate performance relative to the performance of other individuals. It is very important that all models be evaluated in an independent data set (external validation) before deployment [55]. Externally validated models (either temporal or geographic validation) provided the best insights into the usefulness of the model for other individuals, centers or settings, and regions. Several reviews have shown that external validation studies are generally uncommon [5,20,57,58], as most studies are only internally validated by a random split sample of the data into development and validation samples [5]. Because of the higher impact of external validation on model applicability in real-life clinical scenarios, we prioritize these models in

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our checklist by allocating 2 stars to any study with externally validated models (Table 1)

- Model updating method recommendation: in the event that an existing model shows poor performance when evaluated in other settings (geographic or temporal), it is best practice to adjust, update, or recalibrate the original model to increase performance [43], as there are well-established methods to achieve successful model updating. It is also best practice that the potential techniques for updating a model on external deployment can be identified before deployment [1,32]. The primary outcome of our review is the proactive determination of possible model-updating methods. As such, we will prioritize any study that proactively suggests a model-updating method as part of its study method by scoring it as 2 stars.
- Model interpretation and generalizability concerns: best practice guidelines for reporting medical studies recommend discussing strengths, weaknesses, and future challenges with regard to the generalizability of the studies [59-61]. For models, these studies should therefore provide insight into the model's applicability, usefulness, and intended users [43]. This discussion also serves as a basis for comparison with other studies. Therefore, our quality checklist will include a score (1 star) for a study that mentions the strengths and weaknesses of their model in the Discussion section.

Other CHARMS Checklist Items

The remaining 6 items in CHARMS were excluded from our assessment tool because they were already considered during the initial screening stage of our review process (participant characteristics and predictors). We also excluded items that focused on technical assessment, as that is beyond the scope of our study objective of real-life clinical applicability (technical process of model development, model performance, results, and sample size). Although the checklist still needs to be validated, our adapted checklist captures the essence of our review.

Checklist Items Based on a Literature Review of Best Practices of Clinical Model Studies: Model Development Reporting Standards

The best practice standards for reporting primary prognostic and predictive model studies exist in the literature [62] and include SPIRIT-AI (Standard Protocol Items: Recommendation for Interventional Trials- Artificial Intelligence), CONSORT-AI (Consolidated Standards of Reporting Trials-Artificial Intelligence), TRIPOD (Transparent Reporting of a Multivariable Prediction Model of Individual Prognosis Or Diagnosis), REMARK (Reporting Recommendations for Tumour Marker Prognostic Studies), and GRIPS (Genetic Risk Prediction Studies) [63-67]. Adhering to these guidelines may ensure study reproducibility and could improve future real-life applications [62,63,68]. Despite the availability of these guidelines, there is poor overall quality of reporting in many published AI models [53,62,68,69]. Therefore, we have included declaring a reporting standard as part of our checklist (reporting standard scores will receive 1 star).

For each checklist item fulfilled by the study reviewed, studies will be scored with 1 or 2 stars as described above, with a maximum score of 10 stars each.

Data Synthesis

After extracting data from the manuscripts, we will conduct a narrative synthesis. Data will be summarized using descriptive statistics, figures, and tables for visualization. Categorical data will be presented through numbers and percentages. The distribution of continuous data such as sample size and the number of predictors will be assessed and described using means and SDs for normally distributed data using median and 25th and 75th percentiles for nonnormally distributed data. The results will be characterized by study design, outcomes, service delivery type, ML techniques, and model-updating properties.

Ethics Approval

On August 13, 2021, our systematic review protocol was registered with the International PROSPERO (Prospective Register of Systematic Reviews) CRD42021245470 [70]. Our protocol was developed based on the PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols) 2015 statement [38]. Our study does not require an ethics committee review because our research does not directly involve human subject data and it will be conducted on publicly available data from published articles.

Results

So far, we have conducted a literature search of the specified databases. We are now in the title and abstract screening phase. Our initial literature search yielded 13,693 articles; after removing duplicates, we obtained approximately 11,699 articles. We identified approximately 7810 articles for full article review among the 8 reviewers (Figure 1). We hope to complete the review process and disseminate the review results by spring of 2023.

Discussion

Principal Findings

AI and ML applications in health care are significantly increasing at an estimated 40% compounded annual growth rate [71]. Most models are proliferating because of their perceived potential for increased quality of health care at the point of care by providing real-time clinical decision support, early warning sign systems, clinical documentation, improved administrative workflow, medical device automation, and better imaging analysis [2,71,72]. Their implementation has the potential to move the needle from a reactive to a proactive approach, focusing on health management rather than disease treatment [71]. Despite this potential, there is a lack of adequate external validation and real-life assessment of the applicability of these models [5,36], which can adversely affect the generalizability of clinical models at the point of implementation [5,73]. There is also concern regarding algorithmic bias and worsening health inequity.

Owing to the complex nature of health care environments, clinical algorithms tend to deteriorate over time. Considering

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the constantly evolving nature of medical practice in response to new technology, epidemiology, and social phenomena, it appears we will always be chasing a moving target with regard to outcome prediction using an algorithm [72]. Therefore, the relevance of clinical data as predictor factors decays with a half-life of only 4 months [74]. This decay phenomenon reinforces the need for model-updating methods that can adapt to evolving data from the inception of model development [74]. Although there are proposed methods for model updating in the literature [23], a lack of inclusion of these methods in published algorithms can impair a model's applicability and reproducibility. This review aims to highlight and raise awareness of these issues to encourage model developers to improve their protocols.

Limitations

Interpretation of our review should bear some limitations in mind. First, AI and ML implementations in health care are relatively novel and lack standardization across different regions and clinical specialty domains. Although we established our literature search strategy (Multimedia Appendix 1), this lack of standards can impact the scope and sensitivity of our search and render the reproducibility of our review challenging. While the terms "AI" and "ML" are included in our search, terms used to describe models and modeling are not standardized, and therefore, it is possible that our strategy will not capture possible emerging or lesser-known terms. In addition, our search included only English language publications, and, as such, we cannot generalize our findings to publications in other languages. In addition, we did not include book chapters, theses, short papers, editorials, non–peer-reviewed reports, or conference abstracts. Another factor to consider in the interpretation of our results is that the studies we reviewed were published during the global COVID-19 pandemic. The impact of the pandemic on the nature and type of AI and ML studies published during this time is unknown.

Conclusions

In this scoping systematic review, we will review published AI and ML algorithms across all clinical fields and geographic regions to determine how frequently model-updating methods are suggested in published studies. We believe that the AI and ML model-updating methods offered in published models are a proxy for a model's generalizability and implementation reproducibility. We aim to determine the geographic distribution of published models that prioritize model-updating methods and if any correlations exist between the quality of the model reported and the suggested model-updating method. Owing to the faulty evaluation of real-life generalizability and reproducibility of AI systems, recent studies have shown that health care AI and ML performance may be overly optimistic [72]. Although AI and ML applications in health care have potential, some have argued that AI and ML is presently riding atop the peak of "inflated expectations" [72]. We aim to ascertain the degree to which published model results include ethnic and gender demographic data in the light of well-established algorithmic bias in health care.

Our findings will add to the literature on model clinical validation and real-life implementation and help improve best practices for model development by prioritizing updating. We will conduct the scoping review with the hope of moving the needle of contemporary model development away from the peak of "inflated expectations" [72] to the nadir of enlightened reality.

Authors' Contributions

All authors contributed to manuscript writing, revision, data abstraction, and search strategy. In addition, SW formulated and modified the search strategy.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Complete search strategy.
[PDF File (Adobe PDF File), 60 KB - resprot_v12i1e37685_app1.pdf]

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Abbreviations

AI: artificial intelligence
CHARMS: Checklist for Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modelling Studies
CONSORT-AI: Consolidated Standards of Reporting Trials-Artificial Intelligence
EHR: electronic health record
GRIPS: Genetic Risk Prediction Studies
ML: machine learning
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols
PROSPERO: Prospective Register of Systematic Reviews
RCT: randomized controlled trial
REMARK: Reporting Recommendations for Tumour Marker Prognostic Studies
SPIRIT-AI: Standard Protocol Items: Recommendation for Interventional Trials- Artificial Intelligence
TRIPOD: Transparent Reporting of a Multivariable Prediction Model of Individual Prognosis Or Diagnosis

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Protocol

Design Principles in mHealth Interventions for Sustainable Health Behavior Changes: Protocol for a Systematic Review

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Abstract

Background: In recent years, mHealth has increasingly been used to deliver behavioral interventions for disease prevention and self-management. Computing power in mHealth tools can provide unique functions beyond conventional interventions in provisioning personalized behavior change recommendations and delivering them in real time, supported by dialogue systems. However, design principles to incorporate these features in mHealth interventions have not been systematically evaluated.

Objective: The goal of this review is to identify best practices for the design of mHealth interventions targeting diet, physical activity, and sedentary behavior. We aim to identify and summarize the design characteristics of current mHealth tools with a focus on the following features: (1) personalization, (2) real-time functions, and (3) deliverable resources.

Methods: We will conduct a systematic search of electronic databases, including MEDLINE, CINAHL, Embase, PsycINFO, and Web of Science for studies published since 2010. First, we will use keywords that combine mHealth, interventions, chronic disease prevention, and self-management. Second, we will use keywords that cover diet, physical activity, and sedentary behavior. Literature found in the first and second steps will be combined. Finally, we will use keywords for personalization and real-time functions to limit the results to interventions that have reported these design features. We expect to perform narrative syntheses for each of the 3 target design features. Study quality will be evaluated using the Risk of Bias 2 assessment tool.

Results: We have conducted a preliminary search of existing systematic reviews and review protocols on mHealth-supported behavior change interventions. We have identified several reviews that aimed to evaluate the efficacy of mHealth behavior change interventions in a range of populations, evaluate methodologies for assessing mHealth behavior change randomized trials, and assess the diversity of behavior change techniques and theories in mHealth interventions. However, syntheses on the unique features of mHealth intervention design are absent in the literature.

Conclusions: Our findings will provide a basis for developing best practices for designing mHealth tools for sustainable behavior change.

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KEYWORDS

behavior change; intervention; mHealth; personalization; dialogue; mobile health; mobile app; self-management

Introduction

One of the most significant achievements in human health in the past century was the extension of life expectancy from 45 to >75 years, resulting in an expanding, aging global population [1]. Concurrently, lifestyles have changed with industrialization, inducing dramatic shifts in the global disease burden, which is now dominated by chronic diseases [2,3]. Globally, the leading modifiable risk factors for chronic diseases are poor diet, alcohol consumption, smoking, and a lack of physical activity [4]. More importantly, these lifestyle behaviors are also modifiable factors for chronic disease management [5]. Hence, sustaining healthy lifestyle behaviors has been recommended by the World Cancer Research Fund [6], the International Society of Hypertension [7], the International Diabetes Federation [8], and many others [9-12].

Since the 1950s, the harm of smoking has been embedded in medical training with policy support to promote smoking cessation [13]. Coupled with individual behavior change strategies, smoking rates have seen a continuous decline since the 1960s [14]. In sharp contrast, the inclusion of diet and physical activity as topics in medical training was only initiated as recently as the 21st century [15-18]. Unique to quitting smoking, which removes one behavior, initiating and maintaining healthy dietary patterns and an active lifestyle (ie, reducing sedentary behavior and increasing physical activity) requires sustained behavior changes throughout life. Therefore, responsibility for these behaviors ultimately falls on patients, who must self-manage their chronic diseases in the long term, even with the availability of system and policy supports [19].

Theory-based behavior change interventions are highly efficacious in controlled experiments. Multiple behavior change theories have been tested in selected populations (eg, the Theory of Planned Behavior and the Social Cognitive Theory), targeting individual knowledge and cognitive and affective determinants of behavior. To reduce the complexity of using multiple theories, the Theoretical Domains Framework was developed in 2005 by bringing together 33 models of behavior change [20]. In 2011, the Behaviour Change Wheel was created as a causal "behavior system" to guide intervention design through mapping Theoretical Domains Framework–based behavior determinants to the Behaviour Change Technique Taxonomy [21].

Despite high efficacy in experimental settings, the real-world application of behavior theories has had limited effectiveness at the population level in achieving sustainable changes in diet, physical activity, and sedentary behavior [22,23]. For models that emphasize the interaction between individuals and the environment within a social system (eg, the Ecological Model), environmental influences and policy context often become the primary target [24], risking disparities within population subgroups (ie, by creating urban-rural disparities). Human behavior is dynamic, and sustained behavior change following interventions is dependent on the individual's ability to adopt and continuously use behavior change techniques [25-27]. Intervention fidelity (ie, the delivery-receipt-enactment chain) is the key process measure of the mechanism linking intervention to outcome [28]. The process of enactment is the most sensitive to potential breakdowns in the delivery-receipt-enactment chain, occurring when individual-level factors and contextual resources are not properly aligned to support enactment [25]. Hence, real-time personalized interventions are desired to improve self-enactment and fidelity by facilitating the continuous alignment of individual and contextual factors.

The growing computing capabilities of mobile phones have enabled us to monitor and deliver health metrics continuously in real time [29,30]. Therefore, mobile health (mHealth) has the potential to enable personalized, real-time feedback and monitoring of targeted behaviors. The term "mHealth" describes the practice of medicine and public health supported by mobile devices [31]. The World Health Organization has recommended mHealth as a key health promotion strategy to improve global health across low- to middle- and high-income countries [32]. In recent years, mHealth has increasingly been used as a method in behavioral research for disease prevention and self-management through supporting positive changes in diet, physical activity, and sedentary behavior [33].

It is important to note that technology-enabled mHealth tools are twofold, including the active ingredients of behavior change interventions as the intervention content and the mHealth tools themselves as the intervention delivery strategy [34]. The computational power (ie, how fast a system can process data and perform a computational task) of mHealth tools can provide unique functions compared to conventional interventions, such as providing personalized behavior change recommendations and delivering them in real time with the support of dialogue systems. It is also worth noting that mHealth interventions differ from in-person interventions in the resources they deliver. For instance, mHealth interventions may deliver behavior change techniques as an end product with virtual resources [35], whereas conventional interventions may be able to deliver direct physical resources, such as in-person group interventions, exercise equipment, or access to facilities [36]. However, design principles for mHealth interventions to incorporate personalization, real-time functions, and deliverable resources have not been systematically evaluated.

The goal of this review is to identify best practices for the design of mHealth interventions targeting diet, physical activity, and sedentary behavior changes for chronic disease prevention and self-management. We aim to review and identify specific designs in current mHealth tools that feature personalization, real-time functions, and deliverable resources. Our findings will provide a basis for developing best practice guidelines for designing mHealth tools targeting sustained behavioral change.

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Methods

Prospective Registration and Reporting Guidelines

This systematic review has been registered with PROSPERO (CRD42021261078), an international database of prospectively registered systematic reviews. Conduct of this review will be guided by the 2022 updated PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [37].

Eligibility Criteria

We will focus on randomized controlled trials that have reported using mHealth tools for interventions targeting diet, physical activity, or sedentary behavior for chronic disease prevention or management purposes among adults aged 18 years or older. The inclusion criteria are as follows: (1) the study must include a behavior change intervention for chronic disease prevention and self-management; (2) the mHealth tool must include a personalization feature (eg, personalized intervention content and dose, delivery process, or feedback) or a real-time feature (eg, real-time behavioral monitoring or a dialogue system); (3) the behavior change need not have been the primary aim of the study or the primary outcome measure of the study, but a specific measure of behavior change must be reported; (4) a deliverable resource does not have to have been included in the mHealth intervention, although we will review and summarize deliverable resources (eg, virtual social support, access to facilities, diet recipes, or exercise videos) in the mHealth tool; (5) the study must be peer-reviewed and must also have an English abstract, even if it is written in a different language. We will screen non-English abstracts for inclusion and leverage international colleagues for full-text screening and data extraction.

Information Sources

Two reviewers will independently search electronic databases, including MEDLINE, CINAHL, Embase, PsycINFO, and Web of Science, for studies published since 2010 that report findings from mHealth interventions. The year 2010 was chosen because it was when several national and international health organizations identified mHealth as a health promotion strategy with funding opportunities [32,38].

Search Strategy

We will use keywords for mHealth, behavior change, interventions, and self-management and combine them using the “AND” term (Multimedia Appendix 1). Literature found with the search will discuss mHealth interventions targeting lifestyle behavior changes for chronic disease prevention and self-management. Next, we will use keywords for diet, physical activity, and sedentary behavior to limit the search to mHealth interventions targeting these behaviors. Finally, we will use keywords for personalization and real-time functions, respectively, to limit the identified interventions to ones that have reported these design features.

Selection Process

The search strategy will be applied to all databases and aggregated in Endnote reference management software (Clarivate LLC). One reviewer will remove obviously irrelevant references by screening the titles and abstracts, with a 5% sample of these decisions being verified by another reviewer. All remaining abstracts will be assessed for inclusion by one reviewer, with all those selected for exclusion being checked by the other reviewers before final exclusion. The full text of all remaining studies will be obtained and assessed independently for inclusion by 2 reviewers, with any discrepancies resolved in discussion with a third reviewer. The process of study selection will be reported in PRISMA flow diagrams [37] and the reasons for exclusion will be noted. Reference lists of the included studies will also be reviewed to further identify relevant studies.

Data Collection Process

The lead reviewer will develop a data extraction form. Two reviewers will independently pilot the data extraction form on 5 studies. Extracted data will be reviewed by the entire review team to refine the data extraction form. At the commencement of data extraction, 2 reviewers will each extract the data from half of the included studies and perform a cross-check to verify the extracted data. Any discrepancies will be recorded and resolved by discussion.

Data Items

The following data will be extracted for each included study: first author name, year of publication, journal, country, setting, and objective; study design and content of the mHealth intervention (ie, the targeted behavior, behavior change theory used, personalization features, real-time functions, and deliverable resources); procedures for defining, recruiting, and sampling from the intervention and control groups; characteristics and sample size of the study population; frequency and duration of follow-up; definition and measures of behavior change; reference group in any statistical modeling and results of any statistical tests reported; and subgroup analyses or any evidence relating to effects on other health outcomes.

Study Risk of Bias Assessment

Study quality will be assessed using the Risk of Bias 2 assessment tool, an update to the original Cochrane risk of bias tool [39]. The Risk of Bias 2 tool evaluates the following domains in randomized controlled trials: randomization process, deviations from the intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Two reviewers will assess study quality independently, and their assessments will be compared for agreement, with any discrepancies resolved in discussion with a third reviewer.

Synthesis Methods

Based on our knowledge and findings from an initial search, we expect substantial heterogeneity in the mHealth interventions across the targeted chronic conditions, targeted behavior (ie, diet, physical activity, and sedentary behavior), reported outcomes, and methods (ie, frameworks and technologies) to achieve personalization, real-time functions, and deliverable resources. Hence, meta-analysis is unlikely to be feasible or appropriate. Therefore, we will perform narrative syntheses following the Reporting Guidelines of Synthesis Without

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Meta-Analyses [40] guideline for each of the 3 design features of interest.

We will first present detailed descriptions of the included studies in both narrative and tabular formats. This description table will focus on reporting the year of publication, country, setting, study objectives, population, mHealth intervention, comparison group, and outcome measures. Next, the included mHealth interventions will be further evaluated for 3 key design features based on the targeted behavior (ie, diet, physical activity, or sedentary behavior): personalization, real-time functions, and deliverable resources. The study team will develop a separate table for each targeted behavior to map the personalization (ie, personalized intervention content and dose, delivery process, and feedback), real-time functions (ie, the inclusion of technologies to support real-time behavior monitoring and a dialogue system), and deliverable resources (ie, social support, access to facilities, diet recipes, and exercise videos). Finally, the effectiveness of the included mHealth interventions will be presented by showing their unique features, that is, features that they do not share with usual care or nonintervention. A narrative synthesis of the included mHealth interventions will be presented together with an evaluation of study quality (ie, the risk of bias assessment) to provide context for the study findings and support confidence in our evaluation of the state of the field.

Although we anticipate a low likelihood of quantitative synthesis, meta-analyses for outcomes that include a sufficient number of studies will be considered if deemed feasible. We will provide statistical descriptions for behavior change related to the mHealth intervention for specific targeted behaviors and design features, such as personalization and real-time functions. We will estimate the summary effect size and its 95% CI through both fixed and random effects models. Between-study association will be estimated using the I^2 metric; values of 50% are indicative of high heterogeneity, while values above 75% suggest very high heterogeneity [41]. Whenever necessary, we will calculate the evidence of small-study effects (ie, whether small studies have inflated effect sizes compared to larger ones). To this end, we will use the regression asymmetry test developed by Egger and colleagues [42]. A P value of .10 with more conservative effects in large studies in random-effects meta-analyses is considered indicative of a small-study effect.

Results

As of November 10, 2022, we have completed our database search and have begun searching by hand. After removing 607 duplicates, the initial search yielded 2961 studies; the review team will screen the titles, abstracts and full texts. We aim to complete the review by March 2023.

Discussion

This systematic review will provide a comprehensive overview of the literature to better understand the design of mHealth tools and their unique features, such as support for personalization, real-time functions, and deliverable resources, in interventions targeting diet, physical activity, and sedentary behavior. The main contribution of our review will be an understanding of the current methods and technologies used in mHealth interventions. Any amendments or modifications made to the protocol will be reported in the final paper.

Lifestyles and environments have changed in modern society with industrialization, inducing dramatic shifts in the global disease burden, which is now dominated by chronic diseases [43]. As such, now more than ever, we must face the consequences of the massive societal burden of chronic diseases. Importantly, lifestyle behaviors are both a major cause of chronic diseases and the key to effective management of chronic diseases [44]. Therefore, it is critical to develop tools to support positive changes in lifestyle behaviors and to support individuals in adopting environmental resources for sustainable behavior change. To this end, mHealth tools offer promising avenues to deliver personalized interventions in real time, powered by technology and computing capacity. The coverage rate of mobile technology worldwide increased from 87% to 95% from 2011 to 2012 and is expected to rise to 96% by 2026 [45]. However, best practices for designing mHealth tools to support positive behavior change are unclear.

We have conducted a preliminary search for existing systematic reviews and review protocols on mHealth-supported behavior change interventions. We identified several reviews that aimed to evaluate the efficacy of mHealth behavior change interventions in a range of populations [46-48], evaluate methodologies for assessing mHealth behavior change randomized trials [49], and assess the diversity of behavior change techniques and theories in mHealth interventions [35,48]. However, syntheses of features unique to mHealth intervention design, including personalization, real-time functions, and deliverable resources, are lacking in the literature.

Based on the synthesized data, the key outcomes of our review will be (1) identifying gaps in the existing literature and (2) informing future research to improve the design of mHealth interventions and incorporate their unique features to support sustainable behavior change. These findings will be summarized and reported in a peer-reviewed journal.

Data Availability

The data sets generated during and/or analyzed during the current study will be made available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

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Multimedia Appendix 1
Search syntax.
[DOCX File , 15 KB - resprot_v12i1e39093_app1.docx]

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Abbreviations

mHealth: mobile health
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

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Protocol

The Use of Patient-Generated Health Data From Consumer-Grade Mobile Devices in Clinical Workflows: Protocol for a Systematic Review

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Abstract

Background: With the rapid advancement of mobile technology, the scope of mobile health (mHealth) has expanded to include consumer-grade devices such as smartphones and wearable sensors. These solutions have typically been used for fitness purposes; however, due to their ubiquitous capabilities for data collection, they have the potential to bridge information gaps and supplement data from clinical visits. Patient-generated health data (PGHD) can be derived from mHealth solutions and be used by health care professionals (HCPs) as complementary tools in the care process, yet their integration into clinical workflows presents a myriad of challenges. PGHD might be a new and unfamiliar source of information for most HCPs, and the majority of mHealth solutions have not been designed to be used by HCPs as active reviewers. As mHealth solutions become more available and attractive to patients, HCPs may see an increase in the influx of data and related inquiries from their patients. This mismatch in expectations can result in disruptions to clinical workflows and negatively impact patient-clinician relationships. For PGHD to be integrated into clinical workflows, its use should be proven beneficial for both patients and HCPs. However, so far, only limited research has been done on the concrete experiences of HCPs as active reviewers of PGHD from consumer-grade mobile devices.

Objective: We aimed to systematically guide the review of existing literature to identify what types of PGHD from consumer-grade mobile devices are currently being used by HCPs as complementary tools in the care process.

Methods: The PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) 2015 was followed for the design of the search, selection, and data synthesis processes. Electronic searches will be done on PubMed, ACM Digital Library, IEEE Xplore, and Scopus.

Results: Preliminary searches have been conducted, and previous related systematic and scoping reviews have been found and evaluated. The review is expected to be completed in February 2023.

Conclusions: This protocol will guide the review of existing literature on the use of PGHD produced by consumer-grade mobile devices. Although there have been previous reviews related to this topic, our proposed approach seeks to understand the specific opinions and experiences of different types of HCPs who are already using PGHD in their clinical practice and the motives for deeming these data useful and worth reviewing. Depending on the studies that will be included, there may be an opportunity to provide a wider understanding of what types of HCPs trust PGHD, despite the possible challenges that its use might convey, potentially contributing with the knowledge to support the design strategies of mHealth tools that could be integrated into clinical workflows.

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KEYWORDS

patient-generated health data; mobile health; mHealth; health care professional; mobile technology; health self-management; smartphone; mobile phone; condition; care; intervention; support; control; clinical; literature; data; devices; review; meta-analysis; PubMed; Scopus; integration; electronic; treatment

Introduction

Background

Mobile health (mHealth) refers to the use of mobile technology to obtain data pertinent to wellness and disease diagnosis, prevention, and management [1]. With the rapid advancement of mobile technology in the last decade, the scope of mHealth has expanded to include consumer-grade devices, such as smartphones and wearable sensors, which allow for convenient access to health apps [2], motion sensing, as well as physiological and biochemical tracking. The certification of medical-grade mobile devices is based on clinical evidence, often needing years to bring a device to the market [3]; however, consumer-grade devices are evolving at a more rapid pace, and although they are typically used for fitness purposes, their capabilities for data collection are opening possibilities for their use in the medical sphere as well [4]. Ubiquitous health data collection can theoretically make it possible to monitor and intervene whenever and wherever acute and chronic medical conditions occur [1].

The data created, recorded, and gathered by and from patients, using mHealth tools such as smartphones and wearable devices, are known as patient-generated health data (PGHD) [5]. The PGHD derived from mHealth solutions has the potential to bridge information gaps and supplement data from clinical visits by providing a rich picture of a patient's daily behaviors, environment, lifestyle, and biometric data outside of the clinic.

In the past, mHealth solutions have been mostly designed for general wellness purposes; in recent years, mHealth interventions targeting specific health conditions have been increasing [6]. Likewise, the body of evidence that proves the potential value of mHealth is growing [7]; however, there seems to be only limited evidence of its efficacy [8]. Furthermore, the strength and quality of clinical evidence have been identified as factors that impact the adoption of mHealth tools by health care professionals (HCPs). Although the adoption of HCPs seems to be one of the most influential factors regarding the success of mHealth tools [7], there has not been much research on the role HCPs are expected to play in the implementation process of mHealth tools [3,9].

The use of mHealth tools by patients enables access to electronic PGHD by HCPs; however, access does not equate to active use. Furthermore, the integration of PGHD into clinical workflows presents a myriad of challenges, including data security and privacy, data standardization, difficult and time-consuming interpretation, and interoperability, among others [5,10].

In regular clinical workflows, patients often interact with HCPs with different medical specialities, who might have different approaches and goals when collecting data from their patients, depending on their role in the care process. A scoping review by Nittas et al [9] identified that there are 2 roles that HCPs can take when integrating PGHD into the care process: the supporter and the reviewer. In the supporter role, the HCP mostly motivates patients and oversees the use of PGHD. In the reviewer role, the HCP analyzes PGHD to personalize advice, conduct remote monitoring, and complement medical data [9]. PGHD can encompass diverse data sets that come from both passive sensing (through mobile and wearable devices) and active sensing (through mHealth apps) [1]; therefore, PGHD might be a new and unfamiliar source of information for most HCPs [11]. Considering that the reviewing tasks imply a more active stance from HCPs, it is reasonable to assume that not all of them might be interested or confident in becoming PGHD reviewers.

mHealth solutions are becoming increasingly available and attractive to patients, with many integrating mHealth apps and tracking devices into their everyday life as ways to improve their health and well-being [12]. A recent scoping review identified 31 studies that evaluated mHealth interventions for self-management of chronic conditions [3], of which over a third required or encouraged patients to share data with their health care providers. However, only 2 of those studies described mHealth solutions that were meant to be used by HCPs as active reviewers. This sort of mismatch in expectations from patients and HCPs can result in disruptions to existing clinical workflows and negatively impact patient-clinician relationships [13].

For PGHD to be effectively integrated into clinical workflows as a complementary tool to bridge information gaps and supplement data from clinical visits, their use should prove beneficial for both patients and HCPs. However, so far, little research has been done on the concrete experience of HCPs as active reviewers of PGHD from consumer-grade mHealth solutions.

Objectives

The main objective of our review will be to systematically analyze existing literature to try to identify the profile of HCPs who are using PGHD from consumer-grade mobile devices as complementary tools for their clinical practices.

The secondary objective will include the identification of the types of PGHD, produced by consumer-grade mobile devices and mHealth apps, that HCPs might deem useful and worth reviewing.

To attain these objectives the research questions to be addressed by the review are as follows:

- How are the PGHD from consumer-grade mobile devices used by HCPs in the clinical workflow?
- Which types of HCPs are actively reviewing PGHD in their clinical practice?
- What kind of PGHD from consumer-grade devices do HCPs find useful?

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Methods

Design

For the design of this protocol, the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) 2015 [14] was followed. For the design of the search, selection, and synthesis processes, the guidelines for performing systematic literature reviews in software engineering [15] were also consulted.

For the review design, we will use a convergent design for systematic mixed studies reviews [16]. The systematic review will adhere to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement [17].

Search Strategy

Eligible studies will be identified through comprehensive literature searches conducted in the bibliographical databases that focus on health and biomedicine, information technology domains, or encompass journal articles and conference proceedings from multiple disciplines. The selected sources are PubMed, ACM Digital Library (including the ACM Guide to Computing Literature), IEEE Xplore, and Scopus. The advanced search methodologies and limitations of each source were revised in advance to standardize the final search terms and resulting search string, which will be used in all sources without alterations to maintain consistency.

The search strategy was constructed iteratively to ensure that relevant articles were more likely to be identified. After a pilot search in PubMed, it was deemed that the searches should be delimited by 3 key topics: “patient-generated health data,” “health personnel,” and “mobile technologies.” Considering that the key aspects of this review will be more relevant to the medical context than to the technological context, the Medical Subject Headings will be used to search for literature.

Terms comparable to “patient-generated health data,” “health personnel,” and “mobile technologies” were added to the search string using AND operators. To avoid overlooking relevant articles by excluding terms and to prevent retrieving an excessive number of irrelevant results, exact phrases were used with some of the terms. To identify the most appropriate phrases, trial searches were performed in Google Scholar, using possible variations identified in the literature. The final search string was validated by a research librarian from the University of Oulu (Table 1).

Additional filters will be used in all sources to limit the results to articles published in scientific peer-reviewed journals or conferences, written in English, with a publication date between January 2013 and May 2022, and with topics related to medical disciplines or the field of information technologies.

Once the electronic searches have been completed, a supplementary hand search of studies will be performed within previous systematic literature reviews and scoping reviews related to the topic PGHD that were identified in the pilot searches.

Table 1. Search string to be used in the electronic searches.

Concept	Search string	Definition
“Patient-generated health data”	“Patient-generated health data” OR “patient health data” OR “patients health data” OR “patient-generated data” OR “person-generated data” OR “person-generated health data” OR “patient-reported data” OR “patient self-reported data” OR “patients self-reported data” OR “patient-generated clinical data” OR “patient-generated medical data” OR “self-reported patient data” OR “self-generated patient data” OR “personal health data” OR “mHealth patient data” OR “patient collected data” OR “patient-collected health data” OR “self-collected health data” AND	MeSH[a] terms introduced in 2018 to refer to health-related data created, recorded, or gathered (outside of clinical settings) by patients, family members, or caregivers to help address a health concern [18].
“Health personnel”	“Health personnel” OR “care professionals” OR “medical professionals” OR “health care professionals” OR “health professionals” OR ”health care providers” OR “health providers” OR “medical providers” OR “health care worker” OR “health care workers” OR “health care worker” OR “health care workers” OR practitioners OR specialists OR clinicians OR doctors OR nurses OR physicians OR physiotherapists OR “clinical team” OR “clinical staff“ OR “medical staff” OR “medical team” AND	MeSH terms in use since 1992 to refer to people working in the provision of health services, whether as individual practitioners or employees of health institutions and programs [19].
“Mobile technologies”	“Mobile technolog*” OR “mobile phone” OR “mobile device” OR “mobile phones” OR “mobile devices” OR “smart device” OR smartphone OR smartwatch OR “smart ring” OR “smart device” OR “smart devices” OR wearable* OR “health tracker” OR “activity tracker” OR “fitness tracker” OR “mobile app*” OR “health app*” OR “mobile health intervention” OR “mHealth intervention” OR “mobile health solution” OR “mHealth solution” OR “mHealth solutions” OR “mobile health tool” OR “mHealth technology”	These terms commonly refer to internet-enabled devices like smartphones, tablets, and smartwatches. These are the latest in a progression that includes two-way pagers, notebook computers, mobile telephones, GPS navigation devices, and more [20].

[a]MeSH: Medical Subject Heading.

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Inclusion Criteria

Types of Studies

Primary studies will be included irrespective of their design. Both qualitative and quantitative research findings from the selected studies will be integrated, with the use of qualitative data transformation technique methods [21]. Eligible studies will include clinical trials, nonrandomized controlled trials, cross-sectional studies, longitudinal studies, observational studies, case studies, and other types of qualitative studies. The studies must have been published in peer-reviewed scientific journals and conferences.

Types of Participants

The review will focus on the experiences of HCPs who have already used PGHD in their clinical practice, as part of standalone mHealth interventions, by personal initiative, or for any other reasons. The type of HCP is not being limited to specific medical specialities as long as the participants can be recognized as health care workers who are interacting directly with patients.

Types of Technology

The review will focus on mHealth solutions that allow for patient data to be collected outside of clinical settings by patients, using mobile apps or commercial mobile devices such as smartphones or tablets and wearable devices like smartwatches, smart rings, fitness bands, chest straps, and other wearable health trackers.

The current mobile and wearable technologies started to become more available to consumers at the beginning of the last decade. As of 2013, only a few mHealth interventions that aimed at assessing the impact of native apps for smartphones had been reported in the literature, all of which had been created only for research purposes and were not yet available in public app stores [2]; therefore, our search will be limited to articles published since 2013.

Exclusion Criteria

- The articles that explicitly indicate they are study protocols, scoping reviews, and systematic literature reviews will automatically be excluded.
- Studies on interventions based on SMS, chats, social media interactions, phone calls, or another type of two-way communications as the main method for data collection will not be included; we did not consider them to be mHealth solutions, as they are targeted for communication in general and require additional time and effort from HCPs not only to review data but also to maintain the communication between appointments.
- Studies based on interventions that required the use of specialized medical-grade devices that are not designed to be worn or meant to be used as mobile trackers will not be included.
- Studies related to nonelectronic PGHD.

Data Collection and Analysis

Selection of Studies

After the electronic search in all sources and the supplementary hand search of systematic reviews are finalized, the resulting articles will be imported into Covidence (Veritas Health Innovation) to conduct the screening process. Covidence will automatically identify duplicates and allows for multiple reviewers to perform the screening and selection process in a consensual manner.

The initial screening will be limited to the titles and abstracts. This part of the process will be done independently by 2 reviewers to reduce bias. Both reviewers in charge of this stage have a background in computer science and previous research experience with mHealth and PGHD. Before starting the screening process, the reviewers will complete a joint exercise to validate the reviewing methodology and ensure that both reviewers understand the inclusion and exclusion criteria correctly.

Once the reviewers have a preliminary list of candidate studies to be included, they will proceed with the full-text screening of those articles.

During the full-text screening, reviewers will also try to identify if multiple papers could be based on the same study. In this case, both reviewers will revise the possibly duplicated articles and decide, based on author names, study descriptions, and sample characteristics. In the case of duplications, the most recent article would be preferred; however, the final decision should be agreed upon by both reviewers, considering which papers better fits the inclusion criteria.

In case of disagreement in either the initial screening or during the full-text screening, both reviewers will discuss the reasons for disagreement. In case the disagreement persists, a third reviewer will act as an arbitrator and will review the article to decide whether or not the article should be included. The disagreements will be documented, and the reason for the final inclusion or exclusion will be recorded.

The search and screening results will be reported using a PRISMA flow diagram.

Data Extraction

The key information of the included articles will be extracted using the Data Extraction Form function offered in Covidence. The extraction task will be completed by the 2 initial reviewers and 2 additional reviewers, all of whom have previous research experience with the topics related to this review.

Each article will be assigned randomly to 2 reviewers. Each reviewer will extract the data independently and the data extracted by both reviewers will be compared using Covidence. In the case of differences in the extracted data, a consensus will be reached between the 2 primary reviewers. In the case of differences that could not be agreed upon by the 2 primary reviewers, the conflicting data will be discussed by the 4 reviewers to reach a consensus.

The data extraction form will assist in the extraction of relevant information from the selected studies, following the template

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in Table 2. The main author will pilot the extraction of 5 articles, using the proposed extraction form, to identify possible adjustments that could be required before the data extraction process starts with the reviewing team.

In the case of papers that do not report complete descriptions of the intervention, outcomes, or other information relevant to this research, the article author will be contacted via email to ask for complementary information.

Table 2. Basic template of the data extraction form.

Item	Characteristics
Article general information	• Year of publication • Author(s)' name(s) • Country of origin
Characteristics of the study	• Objectives • Main findings
Research methods	• Sampling method • Sample size • Data collection method
Information about participants	• Profession or medical specialty • Main motivation of HCPs[a] to use PGHD[b]
Context of PGHD use	• Conditions being treated • Mobile technology used • Type of PGHD collected • The mechanism for PGHD visualization

[a]HCP: health care professional.

[b]PGHD: patient-generated health data.

Studies' Quality Assessment

The quality of included studies will be assessed in parallel to the data extraction process, using a quality assessment form that will be included in Covidence, following the checklist to assess the quality of studies proposed by Kitchenham [15].

Data Synthesis

The included studies might comprise qualitative and quantitative data that will need to be transformed into a qualitative format and be synthesized through narrative synthesis. For this, we will be using a descriptive narrative form with an appropriate table format. The extracted data will be organized in the table by type of technology, type of condition, type of participants, and type of data being collected or used to identify any interesting findings, trends, relationships, and limitations that can assist in addressing the proposed review questions.

A data coding strategy is suggested for the analysis. NVivo (QSR International) will be used to assist in the data coding strategy. The codes will be defined in accordance with the research objectives of the review. The strategy will be piloted with 5 studies, and any necessary changes to the strategy will be made and later reported in the full review.

Results

As of May 2022, preliminary searches have been done to refine the search strategy and assess the availability of studies on our research topic. Previous related systematic and scoping reviews have been found and evaluated. Systematic searches, data extraction, data synthesis, analysis, and the writing of the systematic review document are expected to be completed by February 2023.

Discussion

Expected Outcomes

The proposed systematic review will report on the use of PGHD produced by consumer-grade mobile technology, as complementary tools for HCPs in the clinical workflow. Considering that most research related to this topic has been done under controlled conditions, our interest lies in identifying the characteristics of PGHD that foster its use by HCPs. We assume these characteristics might comprise aspects such as the type of clinical activities where PGHD from consumer-grade devices could be useful and the particular characteristics of HCPs who are willingly using PGHD due to the realization of PGHD benefits to complement their current practices.

Previous research on PGHD has explored its effect on patient-clinician relationships [13], its use in clinical practices [11], and its use to facilitate prevention and health promotion [9]. Nevertheless, after examining these reviews, we have identified 3 determinant aspects for our review that will report on research gaps that previous reviews have not addressed in detail. The first aspect is that previous reviews did not limit their research to PGHD collected outside of the clinic but also included other types of PGHD as patient-reported outcomes collected during appointments with HCPs [13]. Second, the types of mobile technologies from which PGHD has been produced have not been limited to consumer-grade mobile or wearable devices but have also included medical-grade devices [9,11,13], which tend to be more accurate and more widely

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accepted in the medical field. The last differentiating aspect is that previous research has not focused on understanding the specific experiences of HCPs who are already performing the role of PGHD reviewers to support their patients' care but mostly on their expectations as potential users or in a predominantly supportive role.

The use of PGHD is a relatively new trend, and its relevance might be different across countries, medical specialities, or clinical settings. Depending on the studies that will be included in this review, there may be an opportunity to provide a wider understanding of what types of HCPs trust PGHD from consumer-grade mobile solutions despite the potential challenges that its use might convey. We are interested in understanding why and how they have decided to use this type of data, assuming this knowledge could contribute to the design strategies of mHealth tools that could be integrated into clinical workflows.

Limitations

Some limitations to the design of this review include the exclusion of papers not written in English and considering only papers that explicitly mention PGHD (or its possible variations). PGHD is a relatively new definition, and it could be possible that some relevant papers on mHealth interventions might not explicitly address PGHD using that specific term but instead could have used other terms not included in our search string.

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Authors' Contributions

SGM developed the research questions; designed the review, search, and selection strategies; and contributed meaningfully to the drafting and editing. MI aided in the development of the study methods and contributed meaningfully to the drafting and editing and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

HCP: health care professional
mHealth: mobile health
PGHD: patient-generated health data
PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols
PRISMA: Preferred Reporting Items for Systematic Review and Meta-Analyses

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Protocol

Impact of the COVID-19 Pandemic on Health, Well-being, and Quality of Work-Life Outcomes Among Direct Care Nursing Staff Working in Nursing Home Settings: Protocol for a Systematic Review

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Abstract

Background: Increased workload, lack of resources, fear of infection, and the suffering and loss of residents have placed a significant emotional burden on regulated and unregulated direct care nursing staff (eg, registered nurses, licensed practical nurses, and care aides) in nursing homes (residential long-term care homes). Psychological distress and burnout related to COVID-19 have been cited among direct care staff within nursing homes. Studies have also emphasized the resilience of direct care staff, who, despite the significant challenges created by the pandemic, remained committed to providing quality care. To date, only one nursing home–specific review has synthesized evidence from 15 studies conducted early in the pandemic, which reported anxiety, posttraumatic stress disorder, and depression among direct care staff.

Objective: The objectives of this systematic review are to (1) synthesize all empirical evidence on the impact of the COVID-19 pandemic on direct care staffs' mental health, physical health, and work-life outcomes; (2) identify specific risks and protective factors; and (3) examine the effect of strategies or interventions that have been developed to improve these outcomes.

Methods: We will include all study designs reporting objective or subjective measurements of direct care staffs' mental health, physical health, and quality of work-life in nursing home settings during the COVID-19 pandemic (January 2020 onward). We will search multiple databases (MEDLINE, CINAHL, Embase, Scopus, and PsycINFO) and gray literature sources with no language restrictions. Two authors will independently screen, assess data quality, and extract data for synthesis. Given the heterogeneity in research designs, we will use multiple data synthesis methods that are suitable for quantitative and qualitative studies.

Results: As of December 2022, full text screening has been completed and data extraction is underway. The expected completion date is June 30, 2023.

Conclusions: This systematic review will uncover gaps in current knowledge, increase our understanding of the disparate findings to date, identify risks and factors that protect against the sustained effects of the pandemic, and elucidate the feasibility and effects of interventions to support the mental health, physical health, and quality of work-life of frontline nursing staff. This study will inform future research exploring how the health care system can be more proactive in improving quality of work-life and supporting the health and psychological needs of frontline staff amid extreme stressors such as the pandemic and within the wider context of prepandemic conditions.

Trial Registration: PROSPERO CRD42021248420; https://tinyurl.com/4djk7rpm

International Registered Report Identifier (IRRID): DERR1-10.2196/40390

(JMIR Res Protoc 2023;12:e40390) doi:10.2196/40390

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KEYWORDS

care aide; COVID-19 pandemic; direct care; frontline staff; mental health; nurse; nursing home; physical health; residential long-term care; work-life

Introduction

Overview

The COVID-19 pandemic has exposed nursing home (residential long-term care home) residents and staff to a diverse set of challenges affecting their physical, psychological, and social well-being [1,2]. Evidence from the 2003 severe acute respiratory syndrome outbreak and emerging COVID-19 studies suggest that there will be global phenomena such as increased anxiety, depression, and trauma experienced by health care workers, which will likely have long-term impacts [3-9]. An analysis conducted in February 2021 of national data sets for 22 countries reported that nursing home deaths accounted for 41% of the total COVID-19 deaths (9%-64%) [10]. Concerted action to address the needs of staff working in nursing homes is needed to prevent and manage the impact of COVID-19 [11]. Therefore, a systematic review to synthesize all empirical evidence on the effects of COVID-19 on regulated and unregulated frontline nursing staff (registered nurses [RNs], licensed practical nurses [LPNs], and care aides) working in nursing homes is warranted.

Background

Frontline nursing staff (RNs, LPNs, and care aides) working in nursing homes routinely experience challenges that are known to have negative effects on work-life. Prior to the COVID-19 pandemic, both regulated and unregulated direct care staff (RNs, LPNs, and care aides) experienced higher levels of burnout and mental health issues than the general population and difficulties meeting the daily care needs of residents [1,12-14]. Most nursing home residents have Alzheimer disease or another age-related dementia (~90% have cognitive impairment), multiple chronic diseases, recurrent medical problems, and complex emotional and social needs. The increasing complexity and dependency of resident populations, in the absence of commensurate resources, has led to unmanageable workloads for nursing home staff [12].

In the context of a COVID-19 outbreak, witnessing extreme suffering and the loss of residents with whom staff had long-term relationships has led to emotional exhaustion, which is a component of burnout [15]. Frontline nursing staff have also been subjected to substantial pressure from health authorities, who have introduced additional infection control and monitoring measures; from family members [16] who are concerned about residents' well-being; and from the public and media. Despite a general acknowledgment that the challenges observed during the COVID-19 crisis in nursing home settings, particularly those that have contributed to severe resident outcomes, are symptoms of more systemic issues [1], the media has highly scrutinized nursing home staff. Additionally, nursing home staff have received little recognition for caring for persons infected with COVID-19 compared to hospital staff [16-18].

Prior Work

Emerging evidence from nursing home settings across regions has generally reported higher rates of mental health symptoms, somatic symptoms, burnout, and reduced quality of work-life [15,19-21]. One study reported 71.3% (211/296) of the respondents had medium to high emotional exhaustion, and 64.2% (190/296) of the respondents had medium to high depersonalization [19]. The current and anticipated need for psychological or psychiatric support was 21.6% (64/296) and 41.0% (141/296), respectively [19]. Reports of job satisfaction vary. Two studies reported worsened job satisfaction [20,21], one of which compared nursing home staff data from COVID-19 to data from 2013 and noted an increase in burnout syndromes. In contrast, Blanco-Donoso and colleagues [15] found that 98.2% (329/335) of the participants agreed or totally agreed with the single item—*I feel satisfied to be able to help people*.

A descriptive study among Spanish nursing home staff reported 71% (149/210) of respondents had clinical stress, 29% (n=61) had clinical insomnia, and rates of clinical depression and anxiety were 49% (n=102) and 59% (n=124), respectively [16]. Riello and colleagues [22] found 44% (471/1071) of respondents passed the set threshold for moderate to severe anxiety and 44% (471/1071) of respondents passed the set threshold for moderate to severe symptoms of posttraumatic stress disorder (PTSD) [22]. A high risk of suicidality was found in 25% (10/40) of participants working in 2 nursing homes in Italy [23]. Previous COVID-19 infection was associated with a higher risk of suicidality [23].

Other studies examining individual and organizational risks and protective factors of mental health and work-life outcomes identified several modifiable and nonmodifiable characteristics. Factors influencing the rates and severity of mental health symptoms include access to personal protective equipment [15,22,24], professional support in the workplace [15,21,25], safety guidelines [24], psychological support [24], changes to work activities [25], increased workload [15,21], and direct contact with patients or colleagues who are COVID-19 positive [14,15,22]. Other factors increasing the risk of adverse outcomes include younger age [26], female sex [22,26], less education [22,26], and less work experience [26]. Shift workers, such as frontline nursing staff, have also been found to have higher rates of somatic symptoms [24]. Staff resilience has been associated with lower rates of anxiety, depression, insomnia, and stress [26].

Several reviews have been conducted during the COVID-19 pandemic in general health care worker populations. To date, however, only one review conducted by Gray and colleagues has synthesized a portion of the nursing home-specific evidence from 14 studies published between March 2020 and March 2021. This review reported a high prevalence of anxiety, PTSD, and depression among direct care staff in nursing home settings based on quantitative studies [27]. The synthesis of qualitative studies suggested various personal experiences among nursing

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home care staff, including psychological and mental health concerns, feeling undervalued and abandoned, fear of contagion, poor working conditions, lack of skills and knowledge, and support and the positive impacts of COVID-19 [27].

The number of studies on the impact of COVID-19 on nursing home staff has rapidly accumulated since the publication of Gray's [27] review. An updated review is warranted to capture emerging studies and, most importantly, the enduring effects of COVID-19 as a sustained extreme stressor and potential effective interventions. This review is an important first step toward supporting the mental health of frontline staff during and after the COVID‐19 crisis and during other disease epidemics and pandemics. This is important for the health and well‐being of individual health care staff as well as nursing home residents.

Objective

The purpose of this systematic review is to synthesize the empirical evidence on the effects of COVID-19 on frontline nursing staff who provide direct resident care, which includes RNs, LPNs, registered psychiatric nurses, and health care aides (HCAs), also called personal support workers (PSWs), direct care assistants, or nursing assistants, who worked in nursing homes during the COVID-19 pandemic. This systematic review will combine and synthesizes both quantitative and qualitative evidence. Its specific objectives are as follows: (1) to assess the impact of the COVID-19 pandemic on mental health (eg, stress, distress, depression, anxiety, PTSD, well-being, and somatic symptoms) and work-life outcomes (eg, burnout, job satisfaction, responsive behaviors directed toward staff, moral injury, distress, and working short-staffed) of frontline nursing staff (regulated and unregulated) working in nursing home settings (residential long-term care home); (2) to identify specific risks and protective factors; and (3) to examine the types and feasibility of strategies or interventions that have been developed to improve the outcomes of interest.

Methods

Protocol Registration

This protocol is reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) checklist (Multimedia Appendix 1) [28,29]. This protocol is registered with PROSPERO (CRD42021248420). Any amendments to this study protocol will be documented and filed with PROSPERO.

Eligibility Criteria

All empirical study designs reporting the outcomes of interest for frontline nursing staff (regulated and unregulated) working in a nursing home setting and providing direct care during the COVID-19 pandemic will be considered for inclusion, without restriction on publication language. Articles published in languages other than English will be translated by authorized translators. We will exclude review articles; however, original studies included in reviews will be sourced and screened for inclusion. Articles that do not report primary study results, such as editorials, commentaries, opinion papers, theoretical papers or discussions, and anecdotal evidence will also be excluded.

Population

Overview

Frontline nursing staff (regulated and unregulated) engage in direct contact with the resident (eg, physically providing care, administering medications, assisting with activities of daily living, providing social and emotional support, and assessing or developing care plans). In general, unregulated staff have a scope of employment defined by their job description rather than a scope of practice and are accountable to their employer. In contrast, regulated staff are governed by legislation, have legally defined scope of practice, and are answerable to an external nursing regulator that sets standards of practice and monitors the quality of care provided [30]. In contrast to synthesizing evidence on multiple workforce groups or settings, our review will investigate in detail the evidence available for frontline nursing staff to provide a comprehensive synthesis of a broader range of outcomes.

Inclusion Criteria

Frontline nursing staff include RNs, LPNs, registered psychiatric nurses, and HCAs, who are also called PSWs, direct care assistants, and nursing assistants. Studies may include other participant groups; however, they will limit data to only the subgroup of frontline nursing staff.

Exclusion Criteria

Nursing staff not providing direct care services (eg, management and administrative staff) will be excluded. Studies reporting on the outcomes of interest among frontline nursing staff exclusively from the perspective of a third-party informant, such as management (non–self-reported outcomes), will be excluded.

Concept

Overview

We will study the effects of the COVID-19 pandemic as an extreme, sustained stressor on health and work-life outcomes among frontline nursing staff working in nursing homes. For this study, exposure to the COVID-19 pandemic is not limited to nursing homes with confirmed cases of COVID-19.

Inclusion Criteria

These criteria include studies reporting mental health, physical health, or work-life outcomes among frontline nursing staff during the COVID-19 pandemic (after January 2020).

Exclusion Criteria

These criteria include studies examining the impact of infectious diseases other than the current COVID-19 pandemic on health and work-life outcomes among frontline nursing staff.

Context

Overview

According to the World Health Organization, nursing homes are responsible for the maintenance of well-being in older adults with a significant loss of functioning [31]. In this review, we define a nursing home (residential long-term care home) as a facility that provides living accommodations and 24-hour care

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services [32]. Direct care provided in nursing home settings ranges from health care services by regulated health care workers (eg, RNs and LPNs) to personal care provided by unregulated health care workers (eg, HCAs and PSWs) such as assisting with meals and bathing [32]. Studies will not be limited to settings with confirmed staff or resident cases of COVID-19.

Inclusion Criteria

These criteria include studies conducted after January 2020 in nursing home settings (eg, long-term care, residential care, and aged care) regardless of the country of origin. We will include studies in which there is a mix of different settings and will limit data to only the subgroup of nursing home staff when possible. If this is not possible, we will include the mixed data and explore how the inclusion affects the results by completing sensitivity analyses.

Exclusion Criteria

Studies conducted exclusively in nonnursing home settings will be excluded.

Outcomes and Effects of Interest

Mental Health Outcomes

There is a wide range of mental health–related symptoms frontline nursing staff may experience [33]. Outcomes considered critical to this review include measures of mental health and well-being as these are anticipated to be highly impacted due to the conditions of COVID-19. Mental health describes an individual's emotional and psychosocial well-being; it is defined by the World Health Organization as a state of well-being determined by interconnected social, psychosocial, and biological factors [34]. In this review, measures of mental health include but are not limited to experiences or symptoms of stress, distress, depression, anxiety, PTSD, and well-being.

Physical Health Outcomes

Physical health outcomes include somatic symptoms (eg, headache, insomnia, and emotional exhaustion). Since mental health is interrelated with somatic symptoms [34], all reported physical health outcomes and experiences will be included.

Work-Life Outcomes

Work-life outcomes include but are not limited to experiences or symptoms of burnout, job satisfaction, work engagement, responsive behaviors directed toward staff, moral distress, moral injury, and working short-staffed.

Risks and Protective Factors

We will extract all identified risks and protective factors affecting nursing home staff mental health and work-life outcomes. A risk factor is a condition, characteristic, or behavior that increases the risk of disease or injury [35]. Risk factors that can negatively impact mental health and work-life outcomes include increased workload, negative colleague and management relationships, lack of personal protective equipment, poor pandemic response planning, short staffing, staff turnover, extended work hours or mandatory overtime, and inability to take time off.

In contrast, protective factors are conditions, characteristics, or behaviors that improve well-being [35]. Resilience has been identified as an important protective factor that reflects the ability to cope with the negative effects of stress or adversity [1]. Additional examples of protective factors are an adequate supply of personal protective equipment, staff access to mental health resources, proper communication between staff and management, and paid sick days.

Type and Feasibility of Strategies or Interventions

Examples of interventions include workplace‐based psychological support strategies (peer support networks, employee wellness programs, psychological first aid, flexible schedules, regular information updates, and additional training), additional psychological support (guided and nonguided strategies, such as web-based therapy, web-based well-being and sleep apps, journaling, relaxation techniques, mediation and mindfulness programs, yoga, and coherent breathing), and interventions promoting or supporting healthy lifestyle and self‐care: eating, sleeping, exercising, following a routine, avoiding excess social media, staying in touch with family and friends, and doing things that are enjoyable [36,37].

Search Strategy

A preliminary search of PubMed, Cochrane Library, Google Scholar (pages 1-10) and PROSPERO was conducted to ensure that no similar review is underway. The index terms and text words contained in the titles and abstracts of relevant papers were used to develop a full search strategy in consultation with a university health sciences librarian. We will conduct the search using combinations and synonyms of the core concept keywords for "COVID-19 pandemic," "direct care staff," "frontline staff," and "nursing home." We will search MEDLINE, CINAHL, Embase, Scopus, and PsycINFO databases, as well as sources of gray literature. These will include health discipline colleges and associations (eg, Registered Nurses Association of Ontario) and relevant conference programs (eg, Gerontological Society of America Annual Conference).

Additional sources of data will be identified by reviewing reference lists of relevant publications and reports, and contacting authors of relevant publications and reports to clarify published and seek unpublished information. The search strategy, including all identified keywords and index terms, will be adapted for each included database and information source. If reviews are identified, the citation list will be screened to ensure all relevant studies are included. To ensure all emerging intervention studies are included in our synthesis, we will repeat our search prior to publication. The results of the search will be reported in full and presented in a PRISMA flow diagram [28]. The search strategy is shown in Multimedia Appendix 2.

Data Collection and Analysis

Identifying Relevant Literature

Screening will be undertaken using Covidence, a web-based citation software program, that facilitates web-based collaboration and blinding of reviewers during screening activities. All team members will receive training on the application of Covidence prior to screening. Two team members

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independently, using a 2-step process, will assess the results of the published and gray literature searches. In level 1, all records will be assessed against the following three screening questions: (1) Is the record a primary empirical study? (2) Is the study conducted in a nursing home (residential long-term care home) setting during the COVID-19 pandemic? (3) Does the study assess outcomes among frontline nursing staff that address the impact of the COVID-19 pandemic? All potentially relevant records, as well as those that do not contain enough information to determine eligibility, will be retained.

In level 2 screening, the full text of all retained records will be obtained and assessed for inclusion against the screening questions and inclusion criteria. Pilot testing, including the calculation of interrater agreement, will be completed at each stage of screening against the inclusion criteria for the review. All discrepancies will be resolved by consensus and, where necessary, by consulting a third senior team member. Reasons for exclusion will be documented. In situations where there are multiple reports (publications) for the same study that do not report additional outcomes or results, we will include the initial publication.

Data Extraction

We have adapted data extraction templates that were successfully used in past systematic reviews by the research team [38-40]. Using a small sample of eligible studies from the preliminary search, our study team worked collaboratively to establish and pilot-test the data extraction tool used for the review (Multimedia Appendix 3). The study team convened to compare the data extraction results from 2 reviewers and discuss the inconsistency that might stem from unclarity in the data extraction instructions and issues associated with the application of the tool. The discussions led to further modification and finalization of the tool. Google Forms will be used for the data extraction process so that reviewers can assess independently, and the results can be easily exported and compared.

Methodological Quality

Two reviewers will independently assess the quality of each included study using the Joanna Briggs Institute Quality Appraisal Forms (Checklist for Randomized Controlled Trials, Checklist for Quasi-Experimental Studies, Checklist for Cohort Studies, Checklist for Case-Control Studies, Checklist for Case Series, Checklist for Prevalence Studies, Checklist for Analytical Cross-Sectional Studies, Checklist for Qualitative Research) [41] and the Mixed Methods Appraisal Tool, version 2018 [42]. Disagreements will be resolved through consensus and, if necessary, by consulting a third senior team member. For intervention studies, the research team will investigate if protocols have been published. When available, the protocols will be compared to the final publication to assess the presence of reporting bias. Appraisal results will be summarized narratively. Given the emergent nature of the topic and the descriptive focus of this review, we will not exclude studies based on quality.

Data Synthesis

We will use a parallel-results convergent design to synthesize both quantitative and qualitative evidence. According to the typology of synthesis designs for synthesizing qualitative and quantitative evidence developed by Hong and colleagues, a parallel-results convergent design analyzes and presents qualitative and quantitative evidence separately. The integration occurs during the interpretation of results in the Discussion section [43]. Data synthesis will be conducted separately for each objective. Quantitative studies will be stratified by outcome of interest or intervention and analyzed accordingly. If 3 or more studies investigate the same outcome using comparable methods, we will conduct statistical synthesis (meta-analysis). Details of the statistical models, methods and effect estimates, and measures of statistical heterogeneity will be reported. Where statistical pooling is not possible, findings will be presented in a narrative form, including tables and figures to aid in data presentation. For qualitative studies, careful comparisons will be made between the studies included in the synthesis to identify concepts and themes that are common or similar across the studies.

Mental Health, Physical Health, and Work-Life Outcomes

For the included quantitative studies, we will summarize and map outcomes of interest and the instruments used to measure the outcome (eg, established valid instruments and self-developed instruments). We will group the findings of included quantitative studies that reported the same outcome into main categories of outcomes and report the prevalence of the outcomes by presenting the original scores of instruments and cutoffs. Using narrative synthesis, we will report what is known about the impact of the COVID-19 pandemic on frontline nursing staffs' work-life and mental health outcomes as well as how these outcomes have been examined. Narrative content analysis will be used to synthesize staffs' experiences of mental health and work-life outcomes and generate themes (with representative quotes). This will allow us to identify associations between the COVID-19 pandemic and outcomes that may not have been quantitatively investigated. More details are provided in Multimedia Appendix 4.

Risks and Protective Factors

A narrative description of patterns derived from the findings will be used to understand the risks and protective factors that influence the experiences of frontline nursing staff. This will involve grouping studies by focus, methods, and outcomes to make comparisons between them. Synthesis will include calculating the proportion of quantitative studies that report significant results by factor (eg, the percent of studies that report peer support is a significant protective factor or that lack of peer support is a significant risk factor). The proportion of qualitative studies that describe significant factors (risk or protective) will also be reported.

Type and Feasibility of Strategies or Interventions

We anticipate a limited number of randomized controlled trials in this field and heterogeneity in study designs, interventions, and outcome measures. Accordingly, a quantitative synthesis of intervention effects may not be possible. In this regard, we will narratively synthesize the types of interventions developed or tested (psychological interventions and individual, group, or

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organizational-level intervention), the phase of the study (eg, feasibility study, pilot study, efficacy trial, and effectiveness trial), study design, and study findings.

Subgroups and Sensitivity Considerations

Where 3 or more studies investigate the same outcome using comparable methods, we will conduct subgroup analyses to determine whether results differ by (1) quality rating, (2) settings included in the study (multisetting vs nursing home only), and (3) the use of different measures of the same outcome. Gray et al [27] found evidence of worse outcomes among females and nurses when compared to other workforce groups [12,22,44]. If results indicate that other subgroups (eg, socioeconomically disadvantaged persons, racial or ethnic minorities, and unregulated staff) are disproportionately affected and there is an adequate number of studies with similar methods and outcomes representing each subgroup, we will conduct additional subgroup analyses. Comparison across or within countries may also be possible as emerging studies include large representative samples from over 20 countries, with the largest proportions from the United States, Canada, Spain, and the United Kingdom.

Review Quality

This review will be conducted in accordance with Cochrane's principles for systematic reviews [45], with adaptations for observational and qualitative study designs, which are frequently used in studies of staff mental health and quality of work-life outcomes. We will follow the PRISMA statement [46], a checklist of 27 essential items for transparent reporting of systematic reviews (Multimedia Appendix 1). We will also use the AMSTAR-2 tool, a 16-item checklist (developed as a quality appraisal tool for systematic reviews) to ensure our review meets quality standards and to avert any possible deficiencies in the conduct and reporting of our review [47].

Ethics Approval

Ethical approval is not required as this project does not involve primary data collection.

Results

Overview

This study was funded in 2021. As of December 2022, full-text screening is complete and data extraction is underway. The expected completion date is June 30, 2023. Our preliminary search identified approximately 10 studies published in 2020, over 40 studies in 2021, and approximately 15 studies published in the first 4 weeks of 2022 that meet our eligibility criteria. These are primarily observational studies; however, 4 intervention studies, including 1 randomized controlled trial conducted in nursing homes, were identified. Most studies sampled frontline staff from nursing homes only; however, a portion include staff from multiple settings (eg, hospital, home care, and intensive care).

Dissemination

Findings will be disseminated through conference presentations and publication in a peer-reviewed journal. Additionally, we will produce a plain-language summary of the findings for informing users on what is known on this topic and recommendations for use in practice. Any amendments made to this protocol when conducting the study will be outlined in PROSPERO and reported in the final manuscript.

Discussion

Overview

To date, there have been numerous COVID-19 studies of the impact on frontline nursing home staff with varied methods and, in some cases, disparate findings—leaving knowledge users with uncertainty. Therefore, a robust evaluation is required to gain a broader understanding of the impact of the sustained effects of COVID-19 on the nursing home workforce. This systematic review will uncover gaps in current knowledge to inform future research exploring how nursing homes can be more proactive in supporting the health and psychological needs of frontline nursing staff amid extreme stressors such as the pandemic and within the wider context of prepandemic conditions.

Summary

Findings from the preliminary search suggest that nursing home workers have worse mental health outcomes than staff working in other health care settings [6]. Studies comparing outcomes by service setting (eg, nursing home, hospital, and primary care) report higher rates in one or more of clinical depression, anxiety, stress, PTSD, and insomnia among nursing home staff [12,14,44,48]. One study found that nursing home staffs' risk of extended sick leave (<3 weeks) was almost 2-fold higher, while groups working in other health care had no elevated risk of sickness absence due to COVID-19 [49]. For frontline staff working in nursing homes, preexisting stressors may partially explain the increased risk of developing negative mental and physical health symptoms due to pandemic-related work conditions [12,16,50].

We identified 4 heterogeneous intervention studies in nursing home settings [36,51-54]. The first study aimed to prove the feasibility and effectiveness of treating anxiety and depressive symptoms among nurses who were highly mobilized during the acute phase of COVID-19 using a web-based (remote) Eye Movement Desensitization and Reprocessing (EMDR) protocol [36]. The authors concluded that web-based EMDR was both feasible and effective [36]. However, this study did not include a control group and all participants had received prior EMDR treatments from the therapist who provided the study intervention. This limits the ability to draw conclusions on the effectiveness of the EMDR protocol [36]. The second study was a randomized control trial that examined the effectiveness of self-help plus in reducing anxiety and posttraumatic symptomatology [51]. No difference in self-reported anxiety or posttraumatic symptomatology was found postintervention [51]. The third study used a mixed methods approach to evaluate the effectiveness of a web-based education program delivering just-in-time learning and best practices to improve staff confidence and comfort level when working with residents who were at risk, confirmed, or suspected of having COVID-19 [52]. The results indicated that the intervention effectively delivered

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time-sensitive information and best practices to support nursing home staff [52]. Lastly, Lathren and colleagues [53] explored the feasibility and effects of self-compassion training for certified nursing assistants working in nursing homes (n=34). Self-compassion training was found to be feasible and beneficial for the stressors that certified nursing assistants experienced during the COVID-19 pandemic [53].

Strengths and Limitations

While there is significant interest in this topic, a preliminary search of the literature indicates that there is limited research available specifically focused on nursing home settings. Our inclusion of all designs will ensure that we provide the best evidence possible on the effects of the COVID-19 pandemic on frontline nursing staffs' mental health and work-life outcomes that are protective and those that increase risk, as well as the effects of interventions to limit negative outcomes.

Second, the heterogeneity between study designs, outcomes of interest, and how these are measured may limit our ability to statistically compare results. Therefore, our analysis will include descriptive analysis, which will synthesize all available and potentially actionable evidence. We will also conduct a subgroup analysis if sufficient data are available to compare results when different measures are used to capture the same outcomes.

A third potential challenge we may face is that an insufficient number of intervention studies will be captured based on the timing of this review. The search will be repeated before synthesis to ensure all available intervention studies are included. Finally, as with all reviews, misinterpretation of the original research or data extraction errors is possible. To minimize this risk, 2 team members will independently engage in these activities, and discrepancies will be discussed to reach consensus. Should we encounter unforeseen circumstances where we need to deviate from our protocol, we will document and report the change in the completed review.

Conclusions

Systematic reviews have a central place in informing decision-making from the level of individual patient care to health care policy makers [45,54]. To better understand the impact of the COVID-19 pandemic on frontline nursing staff health and work-life outcomes, identify the risks and protective factors, and determine which interventions are feasible and effective, a comprehensive synthesis of all existing evidence is needed. To date, there have been numerous COVID-19 studies related to its impact on frontline nursing home staff with varied methods and disparate findings, leaving knowledge users with uncertainty. This systematic review will inform the interpretation of the disparate findings to date and uncover gaps in current knowledge; doing so will guide future research exploring how the health care system can be more proactive in improving quality of work-life and supporting the health and psychological needs of frontline staff amid extreme stressors such as the pandemic and within the wider context of prepandemic conditions. Future research may examine specific interventions and policies to support nursing home staffs' well-being, ultimately promoting better work-life and optimizing nursing home staffs' ability to provide optimal quality of care to residents.

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Data Availability

No data sets were generated or analyzed during the development of this protocol. We will include all data generated or analyzed during the systematic review in the published manuscript (and its Multimedia Appendices). CAE will have full access to all data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis and synthesis.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA Checklist.
[PDF File (Adobe PDF File), 109 KB - resprot_v12i1e40390_app1.pdf]

Multimedia Appendix 2
Exemplar Search Strategy.
[DOCX File , 19 KB - resprot_v12i1e40390_app2.docx]

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Multimedia Appendix 3
Data Extraction Termplate.
[DOCX File , 19 KB - resprot_v12i1e40390_app3.docx]

Multimedia Appendix 4
Exemplar Measures of Mental Health and Work-life Outcomes.
[DOCX File , 18 KB - resprot_v12i1e40390_app4.docx]

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Abbreviations

EMDR: Eye Movement Desensitization and Reprocessing
HCA: health care aide
LPN: licensed practical nurse
PSW: personal support worker
PTSD: posttraumatic stress disorder
RN: registered nurse

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Protocol

Characteristics of Occupational Therapy Interventions for Community-Dwelling Adults With Anxiety: Protocol for a Scoping Review

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Abstract

Background: Anxiety is linked to decreased life quality and well-being. Living with an anxiety disorder results in higher personal and societal financial expenditure. Occupational therapists work with people living with anxiety in a variety of settings. A preliminary database search was conducted, and no current or underway systematic or scoping reviews on the topic were identified. Developing an overview of studies of occupational therapy interventions for people with anxiety is a necessary first step to understanding the existing knowledge and to increase the impact of future interventions. This scoping review will build on the findings of a previously conducted systematic review.

Objective: This scoping review will identify the following: (1) what occupational therapy interventions exist for adults with anxiety and (2) the intervention characteristics including outcomes used and impact observed.

Methods: This protocol was reviewed by an occupational therapist as part of a patient and public involvement consultation. The review will consider all studies and publications of occupational therapy that include community-dwelling adults with a diagnosis of anxiety who are aged 18 years and older and diagnosed with an anxiety disorder (Diagnostic and Statistical Manual of Mental Disorders [DSM-5-TR] criteria). Databases to be searched are MEDLINE, CINAHL, Cochrane Library, Science Direct, PsycArticles, Psychology & Behavioural Sciences Collection, Embase, PubMed, TRIP, Proquest, Social Care Online, JBI EBP database, OpenGrey, and OALster. Titles and abstracts will be screened against the inclusion criteria using Rayyan Qatar Computing Research Institute. Potentially relevant studies will be retrieved in full and assessed against the inclusion criteria. Articles published in English will be included. No date limiters will be used. Study selection will be completed by 2 independent reviewers. Data will be extracted using a data extraction tool.

Results: Data will be charted using the Template for Intervention Description and Replication (TIDieR) checklist in alignment with the review objectives. The scoping review will be reported in accordance with the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols statement.

Conclusions: This scoping review will produce valuable information about community-based interventions used to improve participation, life quality, and well-being for adults with anxiety to support the development of occupational therapy interventions.

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The findings will be disseminated through professional and National Health Service bodies, employer organizations, conferences, and research articles. The findings will be of value to health care professionals and researchers working to improve the lives of people living with anxiety.

Trial Registration: Open Science Framework DOI 10.17605/OSF.IO/JS549; https://osf.io/js549/

International Registered Report Identifier (IRRID): DERR1-10.2196/41230

(JMIR Res Protoc 2023;12:e41230) doi:10.2196/41230

KEYWORDS

occupational therapy; anxiety; adult; health; activities of daily living; therapy; intervention; community; life quality; well-being; quality of life; support; development; research

Introduction

Background

Anxiety and stress-related disorders, conditions that involve excessive fear or worry about a current or anticipated future event, are the ninth-highest global cause of disability [1]. Anxiety disorders are highly persistent over a person's lifetime and are associated with elevated levels of disability, reduced quality of life, and decreased participation [2]. Living with an anxiety disorder results in higher personal and societal financial expenditure. For example, in the United Kingdom, the mean annual care costs for people living with anxiety are £71 million (US $84.2 million) [3]. In the United States, this figure is approximately US $52 billion [4].

Anxiety disorders, no matter the type or origin of the disorder, have a profound influence on an individual's ability to participate in their chosen activities in daily life to a level with which they are satisfied [5]. The stress associated with anxiety disorders reduces energy and the motivation to complete activities of daily living [6] and is linked to both resilience and occupational adaptivity, that is, any adjustment or behavior change in response to the demands of living [7]. Focusing on the biochemical or cognitive aspects of anxiety as part of a health intervention may not necessarily contribute to an improvement in an individual's participation in life activities. Additionally, poor functioning can continue after full or partial recovery from an anxiety disorder due to the longitudinal impact of psychosocial impairment, suggesting that participation in daily life appears to be independent of symptoms of anxiety [8]. It is also known that participation and functioning are a greater predictor of health care usage and cost than the severity of either anxiety or depressive symptoms [9]. These findings point to a need to identify the characteristics of interventions that focus on how individuals with anxiety participate in daily activities, as this will contribute to the development of more targeted and effective interventions in the future. Furthermore, interventions that are targeted more appropriately may potentially be more cost-effective [10].

The stories of those living with anxiety disorders emphasizes the impact that this condition has on people's everyday lives. This includes the effect that anxiety has on social relationships and feelings of shame and embarrassment:

> *I go to the bathroom and when I come back he says "where have you been?" I've been to the toilet. "You have been a long time." So trying to hide… (the attacks). He thinks it's stupid. It makes you feel ashamed.* [11]

The experience of anxiety is a complex phenomenon that affects people across cultures. In a study of adults living with anxiety in Iran, the participants explained the experience as "*it is like I am in a cage*" and fearing being both rejected or neglected by others, such as being mocked or losing popularity [11]. In the United Kingdom, some have explained the experience of anxiety and its impact as "*My head says I'm under attack and physically I feel like I'm under attack"* and "*it has prevented me from doing a lot of things*" [12]. This range of experiences further reinforces the need to explore the characteristics of interventions for people.

Occupational therapists have historically worked with people experiencing anxiety in a variety of settings. In a systematic review and narrative synthesis of occupational therapy interventions for people with anxiety disorders, Fox et al [13] were unable to make a judgment on overall clinical effectiveness due to the heterogeneity of the identified studies. As it was an effectiveness review, the authors highlighted the potential for replicability of the interventions in future research and as treatments, the characteristics of the identified studies, and their interventions were not charted in detail. It is also unclear if the authors adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement for reporting a systematic review, which the limits replicability and transparency of their review. In their conclusion, Fox et al [13] highlight that future research should report on the impact of occupational therapy interventions for people living with anxiety. The proposed scoping review seeks to further the authors' findings [13] by updating the search and exploring and understanding the current landscape of intervention characteristics of the interventions identified to aid the development of future interventions and research. A search of the CINAHL database has identified that studies have been conducted since 2019 that would add to the data.

The identification of potential intervention characteristics is crucial to the development of new complex interventions (those interventions with several interacting components) [14]. If too little time is spent on identifying characteristics in the early stage of the complex intervention development cycle, this may result in a flawed intervention that is lacking in clinical and cost-effectiveness [14]. Furthermore, identifying the characteristics of previous occupational therapy studies will benefit the design and future evaluation of new interventions

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by examining how the research is conducted and identifying knowledge gaps [14,15]. This approach aligns with the development stage of the "development-evaluation-implementation process" for complex interventions as outlined by the Medical Research Council [15]. Adopting this approach will help to ensure that future interventions have a better chance of being effective when evaluated and of implementation, that is, being adopted in real-world settings [14].

A preliminary search of MEDLINE, the Cochrane Database of Systematic Reviews, and *JBI Evidence Synthesis* was conducted, and no current or underway systematic reviews or scoping reviews on the topic were identified. Thus, the objective of this scoping review is to examine the range and characteristics of occupational therapy interventions that have been reported to improve the participation, quality of life, and well-being of community-dwelling adults living with anxiety. This scoping review will create a map of community-based interventions used to improve participation, quality of life, and well-being for adults with anxiety. It is hoped that the findings of the review will support the development of occupational therapy interventions to empower people to live well with their condition by improving their quality of life, mood, and participation in meaningful occupations.

Review Questions

What Occupational Therapy Interventions Exist Globally for Adults With Anxiety?

Specifically, this review will collect and chart data to address the following subquestions: (1) what are the characteristics of the occupational therapy interventions identified? (2) What are the outcome measures used to evaluate the occupational therapy interventions identified? (3) What was the reported impact of occupational therapy interventions for adults with anxiety? (4) What are the implications for practice and future research of the occupational therapy interventions identified?

Methods

Study Design

The proposed scoping review will be conducted in accordance with the Joanna Briggs Institute (JBI) methodology for scoping reviews [16]. This scoping review protocol is registered on the Open Science Framework [17] and will be reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) statement [18]. This scoping review protocol will be conducted using the JBI guidelines for scoping reviews to ensure a systematic methodology that can be replicated [16]. The planned review will be reported in line with the PRISMA Extension for scoping reviews [19].

Eligibility Criteria

Participants

The review will consider studies of occupational therapy that (1) include adults with a diagnosis of anxiety who are aged 18 years and older and are resident in their own home or a care setting and (2) include diagnoses such as generalized anxiety disorder, panic disorder, and anxiety disorder not otherwise specified as defined by DSM-5-TR (or earlier versions) criteria. Studies for exclusion will be those with people without a confirmed diagnosis of an anxiety disorder, those concerning pharmacological interventions, researches focused on diagnostics, researches focused on stress or stress-related disorders.

Concept

The concept being mapped within this scoping review will be occupational therapy interventions used to support the participation, well-being, and quality of life of people living with anxiety. The terms anxiety and stress are often used interchangeably in research. As a result, these terms require clarification. Bystritsky and Kronemyer [20] explain that stress tends to be an external stimulus arising from the environment. Alternatively, Hallion and Ruscio [21] describe anxiety as a persistent internal feeling of fear and worry that is intrusive in daily life. Clarifying these definitions suggests that it is more appropriate to focus solely on anxiety in this scoping review, rather than a combination of terms.

Occupation is viewed as the performance of chosen daily life tasks that provide desirable levels of pleasure, productivity, and restoration [22]. Examples of meaningful occupations may include (but is not exclusive to) walking in nature, interacting with the community (eg, leisure groups), or going to work (paid and unpaid). Occupational therapy interventions can be characterized as occupation based or occupation focused [22]. Occupation-based interventions therapeutically use the individual's participation in a chosen meaningful occupation in the context as it would unfold in that person's everyday life, for example, running, working, cooking, and as the method for evaluation. Occupation-focused interventions focus on training the specific skills required for the successful performance of an individual's chosen occupation, for example, the provision of compensatory or adaptive equipment or teaching alternative strategies during a personal care occupation such as toileting [22]. Interventions that are focused on changing a person's basal physiology are neither occupation based nor occupation focused.

The specific items of interest are the characteristics, outcome measures, impact, and implications for the practice of the identified interventions. Participation can be defined as the ability of a person to meaningfully engage and be satisfied with their activities of daily life and has been identified by the World Health Organization as essential to health [23,24]. For the purposes of this review, all types of occupational therapy interventions that support participation in meaningful occupation as the method for evaluation and intervention will be included. All modes of delivery will be incorporated, and any dosage or frequency of intervention will be considered. Examples of types of interventions include self-management, social support, and psychosocial interventions and their variants, and examples of modes of delivery include support groups, one-to-one sessions, telehealth, and digital delivery models.

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Context

This scoping review will consider studies that specifically include community-based occupational therapy interventions in all countries for adults living with anxiety. This could include people with anxiety living in their own homes or other care settings.

Types of Sources

This scoping review will consider both experimental and quasi-experimental study designs including randomized controlled trials, nonrandomized controlled trials, before and after studies, and interrupted time-series studies. In addition, analytical observational studies including prospective and retrospective cohort studies, case-control studies, and analytical cross-sectional studies will be considered for inclusion. This review will also consider descriptive observational study designs including case series, individual case reports, and descriptive cross-sectional studies for inclusion.

Qualitative studies will also be considered that focus on qualitative data including, but not limited to, designs such as phenomenology, grounded theory, ethnography, qualitative description, action research, and feminist research. In addition, systematic reviews that meet the inclusion criteria will also be considered, depending on the research question. Text and opinion papers will also be considered for inclusion in this scoping review.

Review Team

The review is being conducted by a team comprised of a National Institute for Health and Care Research Clinical Doctoral Research Fellow (CL), academics (KB, IS, and JM), and an information specialist (MS).

Patient and Public Involvement

The scoping review protocol has been reviewed by an occupational therapist (AP) with experience of working in a community setting.

Search Strategy

The search strategy will aim to locate both published and unpublished studies. An initial limited search of MEDLINE, CINAHL, and PsycINFO was undertaken to identify articles on the topic. The text words contained in the titles and abstracts of relevant articles, and the index terms used to describe the articles were used to develop a full search strategy for PubMed, MEDLINE, CINAHL, JBI EBP database, PLoS, Social Care Online, The Cochrane Library, Science Direct, Embase, PsycArticles, Psychology & Behavioural Sciences Collection, TRIP database, OpenGrey, OALster, and ProQuest Dissertations & Theses (see Multimedia Appendix 1). The search strategy, including all identified keywords and index terms, will be adapted for each included database and information source. The reference list of all included sources of evidence will be screened for additional studies. The searches will be conducted by MS and CL.

Studies published in English will be included, as the resources for translation are not available, and no date limiters will be used.

Study or Source of Evidence Selection

Following the search, all identified citations will be collated and uploaded into the bibliographic citation management system, EndNote 20.2.1 (Clarivate Analytics), and duplicates removed [25]. The citations will be transferred to Rayyan Qatar Computing Research Institute to manage the screening process [26]. Following a pilot test, titles and abstracts will then be screened by two or more independent reviewers (CL and KB) for assessment against the inclusion criteria for the review. Potentially relevant sources will be retrieved in full, and their citation details imported into the JBI System for the Unified Management, Assessment, and Review of Information [27]. The full text of selected citations will be assessed in detail against the inclusion criteria by 2 independent reviewers (CL and KB). The reasons for the exclusion of sources of evidence at full text that do not meet the inclusion criteria will be recorded and reported in the scoping review. Any disagreements that arise between the reviewers at each stage of the selection process will be resolved through discussion, or with an additional reviewer (JM or IS). The results of the search and the study inclusion process will be reported in full in the final scoping review and presented in a Preferred Reporting Items for Systematic Reviews and Meta-analyses extension for scoping review (PRISMA-ScR) flow diagram [19].

Data Extraction

A data extraction form is provided (see Multimedia Appendix 2). The Template for Intervention Description and Replication (TIDieR) checklist will be used for data extraction [28]. This internationally recognized checklist for describing interventions will enable a systematic description of the interventions and their characteristics in sufficient detail to allow future replication (if required). Data will be extracted from papers included in the scoping review by 1 reviewer (CL) using the TIDieR checklist. A second reviewer (KB) will check the extracted data. The data extraction process will first be piloted by the 2 reviewers initially on 3 papers to ensure that TIDieR checklist is used consistently. The data extracted, in line with the TIDieR checklist items, will include specific details about the intervention rationale, materials, procedures, provider, delivery mode, location, dosage, modifications, and fidelity. Any disagreements that arise between the reviewers will be resolved through discussion, or with an additional reviewer. If appropriate, the authors of papers will be contacted to request missing or additional data, where required.

Ethical Considerations

Since the scoping review methodology consists of reviewing and collecting data from publicly accessible material, this study does not require ethical approval.

Results

The extracted data will be charted in tabular form using the TIDieR checklist [28]. A narrative summary will accompany the charted results and will describe how the results relate to the review's objective and question. The results will be presented following the TIDieR format and the main conceptual categories used in the extraction too, as well as gaps in the

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literature. These will be presented in relation to the question of this scoping review.

Discussion

This scoping review will produce a map of the current body of research and community-based occupational therapy interventions that are used to improve participation, quality of life, and well-being of adults living with anxiety by building on the findings of a previously published systematic review [13].

To the best of our knowledge, this is the first scoping review to map the characteristics of community-based occupational therapy interventions for community-dwelling adults living with anxiety. The comprehensive information about the characteristics of such interventions, such as the outcome measures used and impact, will make an important contribution to the development of new occupational therapy interventions and future research. Identifying the characteristics and components of currently used interventions and published research is useful in optimizing the clinical and cost-effectiveness of future treatments and studies [14]. As anxiety is a global health issue, these findings will be of interest not only to clinicians and researchers in the United Kingdom but also to those in the international community working in this area.

As with any review, there are several limitations to conducting the proposed scoping review. While a rigorous identification and inclusion strategy has been outlined, there remains a risk that some data which may have provided further insights are inadvertently omitted. This risk is enhanced by the challenges of searching gray literature. In addition, as scoping reviews explore the breadth of a topic and not the depth, the reviewers cannot comment on the quality of the studies included in the scoping review. The proposed scoping review will synthesize the study limitations and findings as reported by the included literature. A methodological appraisal of the included studies will not be performed. Thus, the limitations and findings reported in the proposed review are not necessarily exhaustive or interrogated beyond the peer-review process of the published article. Finally, restricting the search strategy to articles only published in English means that articles that would be eligible for inclusion have the potential to be missed.

The review authors will use the findings of this scoping review to contribute to the co-production of a new complex intervention to help people with Parkinson to live well with anxiety, embedded within the UK National Health Service. Similarly, these findings will be of value to a wider audience of health care professionals and researchers involved in service development or research projects that aim to improve the lives of people living with anxiety.

Acknowledgments

The authors would like to thank Anna Paisey for her contributions to the development of this protocol.

Data Availability

All data relevant to the study are included in the article or uploaded as supplementary information.

Authors' Contributions

The design of the protocol was conducted by CL, IS, MS, JM, and KB. The drafting of the manuscript was done CL, IS, and KB. CL, IS, JM, and KB approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search strategy.
[DOCX File , 15 KB - resprot_v12i1e41230_app1.docx]

Multimedia Appendix 2
Data extraction instrument (TIDieR) [28].
[DOCX File , 15 KB - resprot_v12i1e41230_app2.docx]

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Abbreviations

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols
PRISMA-ScR: Preferred Reporting Items for Systematic Review and Meta-Analyses Extension for Scoping Reviews
JBI: Joanna Briggs Institute
TIDieR: template for intervention description and replication

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Protocol

Promoting Self-management and Patient Activation Through eHealth: Protocol for a Systematic Literature Review and Meta-analysis

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Abstract

Background: Major advances in different cancer treatment modalities have been made, and people are now living longer with cancer. However, patients with cancer experience a range of physical and psychological symptoms during and beyond cancer treatment. New models of care are needed to combat this rising challenge. A growing body of evidence supports the effectiveness of eHealth interventions in the delivery of supportive care to people living with the complexities of chronic health conditions. However, reviews on the effects of eHealth interventions are scarce in the field of cancer-supportive care, particularly for interventions with the aim of empowering patients to manage cancer treatment–related symptoms. For this reason, this protocol has been developed to guide a systematic review and meta-analysis to assess the effectiveness of eHealth interventions for supporting patients with cancer in managing cancer-related symptoms.

Objective: This systematic review with meta-analysis is conducted with the aim of identifying eHealth-based self-management intervention studies for adult patients with cancer and evaluating the efficacy of eHealth-based self-management tools and platforms in order to synthesize the empirical evidence on self-management and patient activation through eHealth.

Methods: A systematic review with meta-analysis and methodological critique of randomized controlled trials is conducted following Cochrane Collaboration methods. Multiple data sources are used to identify all potential research sources for inclusion in the systematic review: (1) electronic databases such as MEDLINE, (2) forward reference searching, and (3) gray literature. The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines for conducting the review were followed. The PICOS (Population, Interventions, Comparators, Outcomes, and Study Design) framework is used to identify relevant studies.

Results: The literature search yielded 10,202 publications. The title and abstract screening were completed in May 2022. Data will be summarized, and if possible, meta-analyses will be performed. It is expected to finalize this review by Winter 2023.

Conclusions: The results of this systematic review will provide the latest data on leveraging eHealth interventions and offering effective and sustainable eHealth care, both of which have the potential to improve quality and efficiency in cancer-related symptoms.

Trial Registration: PROSPERO 325582; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=325582

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International Registered Report Identifier (IRRID): DERR1-10.2196/38758

(JMIR Res Protoc 2023;12:e38758) doi:10.2196/38758

KEYWORDS

digital health; cancer supportive care; cancer-related symptoms; self-efficacy; supported self-management

Introduction

The incidence of cancer is rising, and it is estimated that by 2040, globally, more than 28 million people will experience cancer as new cancer cases [1]. It is expected that nearly half of Canadians will develop cancer in their lifetimes [2]. The main goal of a cancer treatment program is to cure or considerably prolong the life of patients and to ensure the best possible quality of life for cancer survivors [3]. Major advances in different cancer treatment modalities (ie, surgery, chemotherapy, radiotherapy, hormonal therapy, and biological response modifiers) have been made, and people are now living longer with cancer than they were in the past [3-5]. However, patients with cancer experience from a range of physical and psychological symptoms during their cancer journey. These symptoms are either directly related to the adverse effects of cancer or arise from the different types of treatments and may range from mild and temporary to severe, chronic, and life-threatening [6]. Moreover, symptoms impact daily physical function and can lead to or exacerbate psychological distress and worse health-related quality of life [7,8].

Globally, there is recognition that patients benefit from being actively engaged in their own health [9]. Active engagement of patients is considered critical to minimize the consequences of disease in daily living, support a better quality of life [10], and reduce health care costs [9].

eHealth interventions could potentially enhance the clinical, organizational, and relational aspects of care by integrating patient databases for individualized treatment and real-time decision support. Moreover, it has been reported that electronic technology, by identifying decision support, care coordination, and continuity of care, could improve cancer care delivery [11]. This approach can empower patients to manage their symptoms, improve patient-professional interactions, prevent unplanned hospital admissions, and reduce health care costs [12,13]. Additionally, for nurses, working with innovations such as mobile health (mHealth) in practice is becoming essential as it may facilitate the provision of quality care [14].

Even though there is empirical evidence that substantiates the role of eHealth interventions in the delivery of supportive care to people living with the complexities of chronic health conditions [15-19], the effects of eHealth interventions specifically designed for supporting patients with cancer to manage cancer-related symptoms and the effects on outcomes, that is, symptom burden, are less clear [20,21].

Reviews on the effects of eHealth interventions are scarce in the field of cancer supportive care, particularly for interventions to increase patient activation and empower patients to self-manage cancer-related symptoms. There is substantial evidence that patients who have the appropriate information and skills are more likely to engage actively in their care and effectively manage the consequences of treatment, including their physical and psychological symptoms [13,22]. Furthermore, information on how these interventions were planned and carried out and who benefited from these approaches is still required [23].

We propose to conduct a systematic review with meta-analysis and methodological critique of the literature to answer the following PICO (Population, Intervention, Comparison, Outcomes) research question: What is the efficacy in cancer populations (population: any phase of cancer, treatment, survivorship, palliative, and end of life care) of eHealth interventions (intervention) compared to usual care or other active intervention (comparison) on symptom severity, psychological distress, self-management behaviors, health outcomes, and health use (emergency department use, unplanned visits to the health care provider, hospitalization, patient activation, and patient empowerment; outcomes).

This review aims to explore usage and effectiveness of eHealth interventions designed to support patients with cancer in managing cancer-related symptoms and the effects on outcomes. The findings could inform and promote evidence-informed oncology practice for eHealth interventions targeted at cancer and advance science in the field.

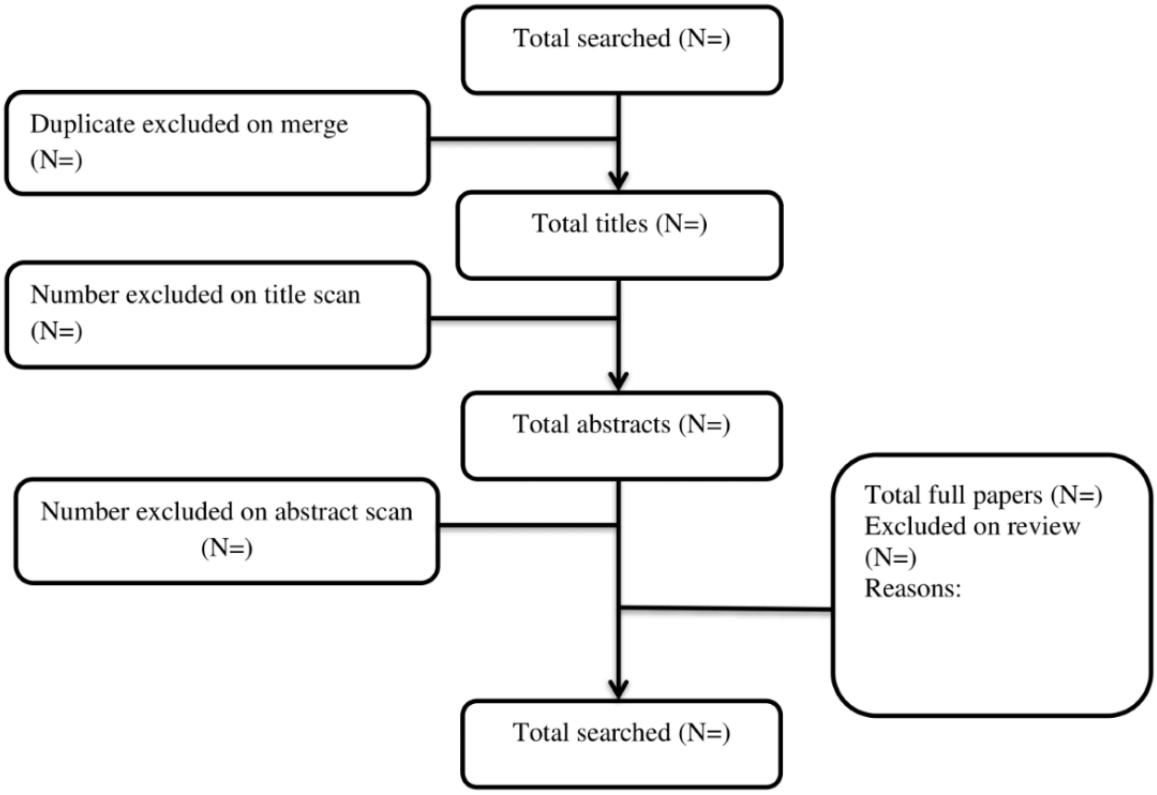
Methods

Overview

This systematic review to identify randomized controlled trials (RCTs) and meta-analyses follows methods as specified by the Cochrane Collaboration [24] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (see Figure 1) [25]. A broad search to identify trial evidence for eHealth interventions to empower cancer patients to manage their symptoms, increase patient activation, and improve patient-professional interactions will be conducted. We posed the following specific research questions.

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Figure 1. CONSORT (Consolidated Standards of Reporting Trials) chart: self-management and patient activation through eHealth review.



Primary Research Question

Are eHealth interventions (or programs) effective in reducing the physical or psychological effects of cancer and its treatment or improving other health outcomes (ie, function, health-related quality of life, health use, or costs) compared with usual care or other active treatment?

Secondary Research Questions

Does effectiveness (effect sizes [ESs]) of eHealth interventions (or programs) differ by patient or disease characteristics (age, race or ethnicity, education, cancer type, stage or phase in trajectory, treatment modality, or other antecedent personality variables such as optimism or trait anxiety), that is, effect modifiers?

Does effectiveness (ESs) of eHealth interventions (or programs) differ based on intervention design (delivery setting) or methods (eHealth-based self-management tools and platforms), training and qualities of the interventionist, intervention components, length of the intervention, or other potential mediators, that is, adherence to the intervention?

Literature Search Strategy

The search strategy was developed with assistance from a library information specialist. A computerized search of electronic databases will be conducted from January 2000 until January 2022 as follows: The Cochrane Central Registry of Controlled Trials (CENTRAL), Cochrane Library and Trials Registry and the Database of Abstracts of Reviews of Effectiveness (DARE), MEDLINE (2000 to January 2022), Embase (2000 to January 2022), CINAHL (2000 to January 2022), PSYCHINFO (2000 to January 2022), and CancerLit (2000 to January 2022). In addition, the gray literature databases, EAGLE (2000 to January 2022), openSIGLE (2000 to January 2022), and PsychEXTRA (2000 to January 2022) will be searched. The reasons for limiting the literature search from 2000 onwards are the development of internet technology and the use of internet-based support programs in the delivery of supportive care over the past 22 years [26].

Search Terms

The search for eligible studies will include search terms: self-manage* or “self-manage*” or self-car* or “self-care*”, behave* or cognitive* or train* or instruct* or patient education or “patient education” or “management plan*” or “management program* (AND) ehealth* or mHealth* or “mobile Health*” or Telehealth* (AND) terms for neoplasms, cancers, or cancer symptoms (fatigue, nausea or vomiting, pain, depression, anxiety, insomnia) and sensitive search terms for identifying randomized trials as subject headings specified by Cochrane [27]. The initial search strategy will be developed in MEDLINE (Multimedia Appendix 1) and will be adapted for all other databases.

Types of Studies

Eligible studies will be identified based on the inclusion or exclusion criteria described below.

Inclusion Criteria

The following inclusion criteria were used:

- RCTs, quasi-randomized, or controlled clinical trials with an intervention group and a comparison patient group (receiving another intervention or standard care)

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- Interventions using eHealth technology (web-based interventions, mHealth, etc)
- Interventions targeted at improving self-management or patient activation in managing physical symptoms or psychological distress
- Include one of the following outcomes: physical health status or symptoms, psychological health status or psychological symptoms or health distress, quality of life
- Comparisons were made with usual care or another active intervention
- Adults (18 years or older) at any stage or type of cancer

Exclusion Criteria

The following exclusion criteria were used:

- Studies without an eHealth intervention in the self-management of cancer
- Studies that did not include usual care controls or active intervention controls
- Studies published in non-English language
- Interventions that do not include a formal analysis of effects or use valid instruments

Types of Outcome Measures

Primary Outcomes

We will be studying the following primary outcomes:

- Self-reported measures of physical health status or symptoms on valid and reliable scales
- Self-reported measures for psychological health status or symptoms, that is, depression or anxiety
- Quality of life or functioning is measured with valid and reliable scales

Secondary Outcomes

We will be studying the following secondary outcomes:

- Patient characteristics, including demographic and clinical data, and the intervention (intervention type, delivery, and intervention components)
- Participant's withdrawal from the studies
- Subjective and objective measures of physical function or disability
- Symptom limitations or interference
- Healthcare utilization (hospital admissions, emergency department use, urgent visits to the family physician), and other health care or social costs

Selection of Studies

Studies will be selected using Covidence software based on a review of the title, keywords, and abstract and coded using the following criteria: (1) include: an RCT, with a focus on cancer patient activation or self-management; (2) exclude: no self-management focus. Selecting studies includes these steps: (1) using a reference management software to merge search results and remove duplicates; (2) examine all titles initially to remove articles that are clearly not eHealth, followed by an abstract review (if there is any uncertainty, the abstract is included for a full text review); and (3) retrieve the full study reports and assess compliance with eligibility criteria independently by 2 reviewers. Agreement will be examined using interrater agreement (<75 nonagreement); disagreements will be resolved by consensus or in consultation with a third reviewer. Authors| will clarify study eligibility criteria or missing data results if necessary. Interventions with more than 1 article will also be retrieved and reviewed to complement the data abstraction and quality assessment of the study (Multimedia Appendix 2).

Data Abstraction and Management

Data will be abstracted using a data abstraction form developed for the review based on Cochrane methods. Data abstraction is independently assessed by 2 reviewers with reliability of coding assessed by computing Kappa, or percentage agreement, for categorical data and the intraclass correlation for continuous data. If any aspect of the study design and conduct is unclear, the study authors will be contacted to complete data abstraction. Two other review authors will check a random sample of the abstractions. Disagreements will be resolved by discussion, with arbitration by a third author if necessary, following an independent review of the study report in question. The data abstraction form will be pretested on a minimum of 5 studies. The abstracted data will include categories as per Cochrane: (1) source and setting; (2) methods; (3) participants; (4) experimental interventions (extent to which specific intervention components delivered as described [adherence]; number, length, and frequency of implementation of intervention components; and characteristics of the interventionists); (5) control treatment; (6) analysis; (7) adverse events; (8) outcome measures; (9) results; (10) conclusions of study authors; and (11) miscellaneous, that is, funding sources.

Assessment of Study Quality

A quality assessment will be performed by 2 review authors and checked by another author. A methodological quality assessment of studies will be conducted based on an adapted version of the Cochrane Collaboration Back Review Group criteria [28], which were previously used in other systematic reviews of internet-based interventions [29,30]. The Cochrane criteria was modified to better suit the type of examined studies: specification of eligibility criteria, randomized groups, treatment allocation concealed, groups similar at baseline, explicit description of interventions, description of compliance, description of dropout and comparison with completers, long-term follow-up (>3 months after postintervention assessment), timing of outcome assessment comparable, sample size described with power calculation, intention-to-treat analyses, and point estimates and measures of variability. The quality score could range from 0 to 12 points. For each study, all criteria will be scored as yes, no, or unclear, resulting in a maximum quality score of 12. In line with other researchers [29-31], studies obtaining at least two-thirds of the total score (ie, ≥8 points) will be considered high quality. Studies scoring 4 to 7 points will be rated as moderate quality, and studies scoring lower than 4 points will be rated as low quality.

Authors will be contacted with 2 reminders to complete missing data. Reviewers will be blinded to the authors of study reports. For each of these potential sources of bias, a judgment of yes (low risk of bias), no (high risk of bias), or unclear is assigned to each study (number of yeses is the single score or study). A

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summary table of the risk of bias across studies will be developed for reporting purposes.

Data Analysis and ES Calculation

Outcomes will be analyzed as continuous or dichotomous variables depending on data reporting using standard statistical techniques. For continuous data (ie, symptom severity), a standardized mean difference with 95% CIs will be calculated as appropriate to facilitate comparison between intervention and controls with correction for differences in the direction of the scale. If reported as medians with ranges, means and SDs will be calculated [32]. For dichotomous outcomes, a relative risk ratio with 95% CIs is calculated.

Assessment of Heterogeneity

As per Cochrane, clinical heterogeneity (variability in the participants, interventions, and outcomes) [33,34] will be examined using the "I" squared statistic [35]. Random effects meta-analysis will be used if heterogeneity across studies cannot be explained; otherwise, a fixed-effects model will be used [33,36].

Subgroup Analysis

The following subgroup analysis will be conducted if the number of studies available for the analysis is adequate (10 studies for each characteristic modeled by participant characteristics and intervention components) as described below and based on the research questions posed:

1. Study intervention characteristics: The potential effect modifiers examined may include the characteristics of the intervention (length of follow-up, use of a number of components emphasized).
2. Study participant characteristics: Subgroup analysis will be conducted for disease stage (early and advanced), sex (male, female), and disease subtype, as some types of cancer may be associated with higher mortality.

Measurement of Treatment Effects and ES Calculation

A summary of findings table will be completed to synthesize the reporting of common primary outcomes: physical effects (function and symptoms), psychological effects (depression, anxiety, and health distress), and secondary outcomes (quality of life, health care use, and satisfaction) using the GRADEpro software. ES computations will be calculated using Hedges *g*. [37]. Where *g* cannot be computed directly from means and SDs based on the source paper, it will be computed indirectly from the available test statistics, for example, t, based on Rosenthal [38]. The estimates of *g* will be corrected for small-sample bias [37]. Given that outcomes could be differentially effective over different dimensions, particularly for symptoms, separate analyses for comparison, that is, physical symptoms (pain, fatigue, nausea or vomiting, insomnia), psychological symptoms (depression, anxiety, health distress), and separately for quality of life and use of health care services, will be conducted. For studies where a primary outcome is possible for the main analysis, this will require the identification of a primary outcome.

Sensitivity Analysis

A sensitivity analysis will be conducted to evaluate the robustness of the meta-analysis, that is, the effects of methodological quality on study outcomes, by assessing for associations between individual items in the methodological quality checklist and the study outcomes. When data can be pooled, sensitivity analysis will be conducted by pooling the "yes" versus "no" responses to risk. When the data cannot be pooled, the sensitivity analysis will be performed using a chi-square analysis as per Cochrane.

Results

The literature search and data collection started in October 2017, after making a work plan to design and run the systematic search strategies in databases and the timeframe for delivery of the search results with the Library and Information Services within the University Health Network. However, to provide a comprehensive snapshot of knowledge since the time of incorporation of data from studies identified during the first search, a second literature search was conducted in February 2022 to ensure new studies were included and increase the validity of the review. The literature search yielded a total of 10,202 publications. Data will be summarized, and if possible, meta-analyses will be performed to evaluate the effectiveness of eHealth interventions on the outcomes. Results are expected to be published in winter 2023.

Discussion

Recent literature has highlighted the utility of eHealth interventions with promising outcomes in cancer care, although mixed and inconclusive results were also presented [39]. The main contributions to this review will be the following: the use and effectiveness of eHealth interventions for supporting patients with cancer in managing cancer-related symptoms; identifying the key implications for better design, integration, and implementation that may have important effects on intervention outcomes; and a discussion, based on the data synthesized, on current gaps and limitations to inform better research toward all phases of development and evaluation of these interventions. Therefore, we will provide essential information for developing and implementing these interventions into clinical practice by providing recommendations based on the current best available evidence. The evaluation of the interventions might be limited by explicitly reporting the interventions. Any modifications or revisions made to the protocol will be presented in the final reports.

Acknowledgments

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Conflicts of Interest

MB has served an advisory role to Merck, Bristol-Myeers Squib, Novartis, GSK, Sun Pharma, Pfizer, Immunocore, Medison, IDEAYA, Instil Bio, and IOVANCE. He has received grant funding from Merck, Takara Bio, and Novartis. He has served on a safety review committee for Adaptimmune and GSK. He has received financial support for lectures from Merck, BMS, Novartis, Sanofi, and Pfizer.

Multimedia Appendix 1
Ovid MEDLINE search history.
[DOCX File , 35 KB - resprot_v12i1e38758_app1.docx]

Multimedia Appendix 2
Data abstraction form.
[DOCX File , 26 KB - resprot_v12i1e38758_app2.docx]

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Abbreviations

ES: effect size
mHealth: mobile health
RCT: randomized controlled trial

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Protocol

The Effects of Online Self-management Interventions for Patients With Mood Disorders: Protocol for a Systematic Review and Meta-analysis

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Abstract

Background: Self-management has become important as a complementary approach to the recovery of patients with mood disorders, and the need for a remote intervention program has been revealed in relation to the COVID-19 pandemic.

Objective: The aim of this review is to systematically review the studies for evidence on the effects of online self-management interventions based on cognitive behavioral therapy or psychoeducation for patients with mood disorders and to verify the statistical significance of the effectiveness of the interventions.

Methods: A comprehensive literature search will be conducted using a search strategy in nine electronic bibliographic databases and will include all randomized controlled trial studies conducted up through December 2021. In addition, unpublished dissertations will be reviewed to minimize publication bias and to include a wider range of research. All steps in selecting the final studies to be included in the review will be performed independently by two researchers, and any discrepancies will be resolved through discussion.

Results: Institutional review board approval was not required because this study was not conducted on people. Systematic literature searches, data extraction, narrative synthesis, meta-analysis, and final writing of the systematic review and meta-analysis are expected to be completed by 2023.

Conclusions: This systematic review will provide a rationale for the development of web-based or online self-management interventions for the recovery of patients with mood disorders and will be used as a clinically meaningful reference in terms of mental health management.

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KEYWORDS

self-management; mood disorders; online interventions; systematic review; intervention program; cognitive behavioral therapy; psychoeducation; electronic database; development; mental health

Introduction

Mood disorders are emotional disturbances that can be divided into depressive disorders and bipolar disorders [1]. Depressive disorder is a disease experienced by more than 300 million people worldwide, with 13.4% of women and 8.3% of men with the disability according to the World Health Organization [2]. Bipolar disorder, which is classified as a mood disorder along with depressive disorder, affects about 2% of the world's population and is the 10th most common disease in young adults [3,4]. For all ages, depressive disorder is the third most common

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disease that leads to living with a disability, and the prevalence of major depressive disorder has been significantly increasing over the years [5]. The prevalence of bipolar disorder is also rapidly increasing year after year, and in general, bipolar disorder takes an average of 5 to 10 years from the time the disease occurs to an accurate diagnosis [6,7]. Despite effective treatment, 40% of those diagnosed with bipolar disorder experience frequent recurrence, with 20%-40% of those diagnosed with major depressive disorder experiencing recurrence within one year of recovery. This suggests that mood disorders are likely to be chronic [8].

Self-management is an individual's ability to manage the symptoms, treatment, physical and psychosocial consequences, and lifestyle changes inherent in living with a chronic condition. Promoting self-management prevents recurrence based on an understanding of one's disease, and it is becoming important as a complementary approach to optimizing recovery from mood disorders and improving quality of life [9,10]. Self-management of mental illness can be used as a primary low-intensity intervention, especially in individuals with mild to moderate symptoms, supplementing usual clinical therapies such as drugs and psychotherapy [11]. Among the psychosocial treatments corresponding to low-intensity interventions, cognitive behavioral therapy (CBT) or psychoeducation is particularly effective in improving the psychosocial functioning, treatment adherence, and clinical course of patients with depression [12]. CBT, one of the most studied types of depression prevention intervention, is considered an effective treatment type for adults with treatment-resistant depression by reducing depressive symptoms [13,14].

The demand for and necessity of online-based interventions are increasing due to the recent influence of the COVID-19 pandemic. Recently, as the cost for health care clients increases and mental illness patients face resource limitations due to delayed treatment time, several studies have shown that computer-based or internet-based treatments are as effective as face-to-face psychotherapy in treating mood disorders [15-19]. Online-based treatment is more cost-effective than face-to-face treatment in many aspects, and it has the advantage of facilitating learning and retention because the patient has easy access to the program. In addition, the patient's treatment progress and results can be monitored immediately, enabling prompt intervention before a crisis occurs [19].

Although the need for self-management for patients with mood disorders and the importance of online-based intervention is increasing, there is a lack of articles that have conducted systematic reviews of the literature on this topic. Therefore, to establish a theoretical basis, we will integrate the research results of online interventions based on either CBT or psychoeducation for mood disorders in a comprehensive perspective through a systematic review of the literature. Furthermore, we will verify the effect of the intervention through a meta-analysis.

Methods

This protocol is reported in line with the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) statements [20], and the systematic review will be conducted and reported in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement [21]. The systematic review protocol was registered under CRD42022299474 in PROSPERO.

Identification of the Search Question

What is the evidence that online-based interventions to enhance self-management for people with mood disorders improve clinical and health outcomes?

Search Strategy

The search strategy will be conducted by the researchers using an electronic database and search engine. A comprehensive literature search written in English will be conducted in five bibliographic databases, including PubMed, Embase, PsycINFO, CINAHL, and CENTRAL. A comprehensive literature search written in Korean will be conducted in the Research Information Sharing Service (RISS) and KoreaMED. The search will be limited to peer-reviewed journal articles available in English and Korean published until December 2021. In this study, gray literature will also be included in the review to minimize publication bias. The gray literature will be searched using Google Scholar, ProQuest Dissertations & Theses Global, and RISS.

In developing an initial search strategy based on PubMed, we adopted not only MeSH (Medical Subject Headings) terms but also synonyms and analogues as free-text terms and combined them with appropriate Boolean operators. The search strategy will be reviewed by a librarian with extensive experience in searching databases. Search strategies developed based on PubMed will be syntactically adjusted when applied to other databases. The search string will be searched using various terms such as Textbox 1. All search results will be imported from EndNote (Clarivate), a citation management software, and will be managed by researchers.

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Textbox 1. Search strategy (PubMed).

1. "bipolar disorder"[MeSH Terms] OR "mania"[MeSH Terms] OR ("depressive disorder"[MeSH Terms] OR "depression"[MeSH Terms]) OR "depressive disorder"[MeSH Terms] OR "mood disorders"[MeSH Terms] OR "cyclothymic disorder"[MeSH Terms] OR "bipolar*" OR "manic*"[Title/Abstract] OR "mania*" OR "hypomani*" OR "depressi*" OR "melancholia*" OR "involutional psychos*" OR ("involutional"[All Fields] AND "paraphrenia*") OR "dysthymi*" OR "mood disorder*" OR "affective disorder*" OR "cyclothymi*"
2. "internet based intervention"[MeSH Terms] OR "internet"[MeSH Terms] OR "therapy, computer assisted"[MeSH Terms] OR "computer assisted instruction"[MeSH Terms] OR "computers, handheld"[MeSH Terms] OR "cell phone"[MeSH Terms] OR "mobile applications"[MeSH Terms] OR "smartphone"[MeSH Terms] OR "telemedicine"[MeSH Terms] OR "web browser"[MeSH Terms] OR "online systems"[MeSH Terms] OR "electronic mail"[MeSH Terms] OR "digital technology"[MeSH Terms] OR "internet*" OR "web" OR "computer*" OR "online*" OR "on line*" OR "mobile*" OR "tele monitor*" OR "telemonitor*" OR "e health*" OR "ehealth*" OR "tele health*" OR "telehealth*" OR "m health*" OR "mhealth*" OR "wireless*" OR "tablet*" OR "blackberr*" OR "android*" OR "ipad*" OR "podcast*" OR "ipod*" OR "iphone*" OR "cellphone*" OR "smart phone*" OR "smartphone*" OR "cell phone*" OR "cellular tele*" OR "app" OR "personal digital assist*" OR "pocket pc*" OR "cyber*" OR "e learn*" OR "elearn*" OR "network*" OR "electronic mail*" OR "email*" OR "e mail*" OR "digital technolog*" OR "digital electronic*"
3. "self management"[MeSH Terms] OR "self care"[MeSH Terms] OR "self manag*" OR "self care*" OR "self help*" OR "self chang*" OR "self train*" OR "self guid*" OR "self unguid*" OR "self therap*" OR "self support*" OR "self direct*" OR "self monitor*" OR "self instruct*" OR "self promot*" OR "self educat*" OR "self program*" OR "self teach*" OR "self learn*" OR "self assist*" OR "self health*" OR "self participa*" OR "self treat*" OR "self admin*" OR "self intervention*"
4. "randomized controlled trial"[Publication Type] OR "random allocation"[MeSH Terms] OR "random*" OR "randomized controlled trial*" OR "random assignment*" OR "random allocation*" OR "RCT"
5. 1 AND 2 AND 3 AND 4

Eligibility Criteria

Studies will be included if they were conducted on adults older than 18 years, assessed those who have been diagnosed with depressive disorder or bipolar and related disorders, or who meet the diagnostic criteria. Studies will also be included if they performed online-based self-management interventions based on CBT or psychoeducation, provided sufficient information to calculate the effect size, and were conducted as a randomized controlled trial. Studies will be excluded if they were preliminary studies with no control/comparison group, performed online-based self-management interventions as part of another intervention or in combination with another intervention, or do not give access to the full text. Specifically, studies will be selected according to PICOS (Participants, Interventions, Comparisons, Outcomes, and Study Design), which is presented below.

Participants

The participants in the systematic review will be adults 18 years or older who have been diagnosed with or meet the diagnostic criteria for depressive disorders or bipolar and related disorders. Specifically, depressive disorders include major depressive disorder, persistent depressive disorder, and disruptive mood dysregulation. Bipolar and related disorders include bipolar I disorder, bipolar II disorder, and cyclothymic disorder.

Interventions

In the systematic review, we will include interventions provided in online or mobile form based on CBT or psychoeducation. Interventions should be aimed at promoting self-management in patients with mood disorders. Studies in which interventions were conducted in conjunction with or as part of other interventions will be excluded because the effectiveness of the intervention cannot be independently evaluated.

Comparisons

The comparison groups will be adults 18 years or older with a diagnosis of depressive disorder or bipolar and related disorders who received the following interventions: wait-list control, treatment as usual, face-to-face self-management interventions, and online self-management interventions that are not based on CBT and psychoeducation.

Outcomes

The primary outcomes of interest in this review will be treatment efficacy demonstrated through changes in scores for manic or depressive symptoms and quality of life. The secondary outcomes of interest will be the improvement of social functioning confirmed through the degree of change in social relationship and adaptation scores, as well as the feasibility and acceptability of the intervention calculated by the dropout rates.

Study Design

The study design to be included in the systematic review will be a randomized controlled trial with access to the full text. In addition, unpublished dissertations will be included in the review to minimize the risk of publication bias.

Study Selection

All steps will be carried out independently by two authors with strict application of specific qualification criteria. Studies will be assessed by having their eligibility considered by the first author and then revised by the second author. Disagreement will be resolved through discussion. Studies retrieved from the databases listed above using a search strategy will be stored in EndNote, and then, duplicate studies will be removed through manual review by the authors and an automatic function of EndNote. A primary screening will be conducted by two authors independently, where the studies with titles and abstracts indicating that they do not meet the eligibility criteria will be removed. If at least one author identifies that a study is likely to meet the eligibility criteria, the study will not be excluded

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from the full-text screening. A full-text screening to select studies for final inclusion in this review will follow, which will be conducted independently by the authors. If there is disagreement at this step, the study will be reviewed and discussed together to decide whether to include it. Studies excluded from the full-text screening will be listed with the reason for exclusion, and all screening and selection processes will be reported through the PRISMA flow diagram [21].

Data Extraction

Data will be independently extracted to electronic data extraction sheets by two authors, and they will be mutually re-evaluated. Information extracted from the studies will include trial characteristics, including first author, publication year, and participant number; intervention and control/comparison group characteristics, including diagnosis, diagnostic criteria characteristics, means of providing intervention, duration of intervention, and intervention contents; and outcome characteristics (outcome measures and results). If additional confirmation of unreported data or details is required, the study authors will be contacted to request materials. The extracted data will be saved and managed in the Excel (Microsoft Corporation) sheet (Multimedia Appendix 1). Based on the data in the Excel sheet, the diagnosis and inclusion criteria of patients to whom the intervention was applied, the type of intervention, the type of outcome measurements to evaluate the effect, and the results will be summarized and presented in a table.

Risk of Bias and Quality Assessment

For the final selected randomized controlled trial studies, two authors will conduct an independent quality assessment using the Cochrane Risk of Bias tool [22]. This tool consists of five areas where bias can be applied to research results. The five areas are as follows: (1) risk of bias arising from the randomization process, (2) risk of bias due to deviations from the intended interventions, (3) risk of bias due to missing outcome data, (4) risk of bias in the measurement of the outcome, and (5) risk of bias in the selection of the reported result. Disagreements between the authors will be resolved through discussion. Even if the result of the quality assessment for the final selected study has a high risk of bias, the study will not be excluded.

Results

Systematic literature searches, data extraction, narrative synthesis, meta-analysis, and final writing of the systematic review and meta-analysis are expected to be completed by 2023.

Narrative Synthesis

We will discuss important features of the final selected study, such as publication year, number of participants, gender, age range, diagnosis and diagnostic criteria characteristics, and the type and nature of interventions provided.

Meta-analysis

We will calculate risk ratios for dichotomous outcomes and standard mean differences (SMDs) for continuous data using complex meta-analysis software such as Review Manager (RevMan) or R (R Foundation for Statistical Computing). We will also define outcomes based on all follow-ups and adopt the most well-validated psychometric measure if there are multiple measures of the same outcome. If possible, we will contact the original author to request missing data. The statistical method of handling missing data will depend on whether the data are randomly missing. We will figure out the effect size for the intervention outcome using the SMD. The effect size will be calculated by applying either a random-effects model or a fixed-effects model according to the I^2 statistic that confirms homogeneity. In addition, we will analyze whether the direction of the effect size of each study and the confidence interval between the studies overlap through a forest plot. Funnel plots will be used to estimate the presence of publication bias. If sufficient studies are available, we will conduct the following subgroup analysis: CBT-based interventions, psychoeducation-based interventions, and CBT and psychoeducation mixed interventions.

Discussion

This protocol has outlined detailed inclusion and exclusion criteria for determining eligible studies, which include a description of the target population and intervention of interest as well as comparisons, study design, and outcome measures. We also have mentioned our search strategy, data extraction, quality assessment, and synthesizing method such as meta-analysis to inform the direction of this study.

Depressive disorder and bipolar disorder have a high potential to become chronic diseases due to frequent relapses, so the importance of self-management is increasingly emphasized. Recently, due to the impact of COVID-19, interest in remote interventions without time and place restrictions has increased. Therefore, our research will systematically review and analyze the evidence for the effectiveness of online-based self-management interventions as a complementary approach for the recovery of patients with mood disorders. To comprehensively approach interventions for the self-management of patients with mood disorders, this study includes CBT and psychoeducation as intervention studies.

The strength of this systematic review is that it will take a standardized approach to the review method by adhering to systematic review guidelines such as the PRISMA 2020 statements and checklist. In addition, the inclusion of unpublished dissertations without limitation by year of publication will reduce publication bias and increase the range of our search. However, this review will have potential limitations in language bias, since it will only include studies published in English and Korean that the researchers can read and interpret.

Nevertheless, considering the increasing prevalence and severity of mood disorders, the effectiveness of online self-management interventions derived from this systematic review and meta-analysis can be used as clinically meaningful evidence in terms of mental health. Additionally, we believe that this study will provide the necessary data to form the theoretical basis for the development of online-based self-management interventions for the recovery of patients with mood disorders in the future.

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Acknowledgments

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Data Availability

Data sharing was not applicable to this paper as no data sets were generated or analyzed during this study.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Data extraction sheet.
[PNG File , 35 KB - resprot_v12i1e45528_app1.png]

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Abbreviations

CBT: cognitive behavioral therapy
MeSH: Medical Subject Headings
PICOS: Participants, Interventions, Comparisons, Outcomes, and Study Design
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols
RISS: Research Information Sharing Service
SMD: standard mean difference

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Protocol

The Effect of Vitamin D on Inflammation and Dyslipidemia in Type 2 Diabetes Mellitus: Protocol for a Systematic Review and Meta-analysis of Randomized Controlled Trials

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Abstract

Background: Type 2 diabetes mellitus is a chronic disease that contributes to an increasing global burden on the health system. It has a high chance of leading to macrovascular complications and cardiovascular disease. As an inflammatory condition, it would be essential to target inflammatory pathways when developing therapeutic drugs for type 2 diabetes mellitus.

Objective: We aimed to evaluate the effect of vitamin D on markers of inflammation and lipid profile among adult patients with diabetes.

Methods: A systematic review will seek studies published on Embase, Google Scholar, PubMed, Web of Science, and Science Direct. This planned systematic review and meta-analysis will be limited to randomized controlled trials; moreover, the search will include published studies regarding the effects of vitamin D on pro-inflammatory cytokines and lipid profiles. The review will include studies published from inception until December 30, 2022. The study identification and selection will be based on the eligibility criteria by 2 independent reviewers. Additionally, a meta-analysis will only be performed if more than 2 studies are available and explore the same outcomes, and this will be analyzed using RevMan (version 5.4.1). The quality and risk of bias will be assessed following the Cochrane risk of bias tool and Jadad checklist.

Results: The process for searching literature review has already started, and this is conducted independently by 2 reviewers using a predefined eligibility and "participants, intervention, comparator, and outcome" criteria. This systematic review and meta-analysis will not require any direct involvement of patients and the public; thus, no ethical approval was required.

Conclusions: The findings obtained from the proposed study will be presented in scientific seminars, journal clubs, and conferences and published in peer-reviewed journals.

Trial Registration: International Platform of Registered Systematic Review and Meta-analysis Protocols INPLASY202260022; https://inplasy.com/?s=INPLASY202260022

International Registered Report Identifier (IRRID): PRR1-10.2196/42193

(JMIR Res Protoc 2023;12:e42193) doi:10.2196/42193

KEYWORDS

vitamin D; dyslipidemia; inflammation; hyperglycemia; type 2 diabetes mellitus; systematic review; chronic disease; mortality

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Introduction

Type 2 diabetes (T2D) mellitus is a chronic disease associated with an increased mortality rate [1] due to impaired pathways that regulate homeostatic and inflammatory responses. According to the 2021 International Diabetes Federation report, about 537 million people are estimated to have diabetes worldwide, and this number is expected to reach 783 million in 2045 [2]. T2D is challenging; it affects individual health, while putting a financial burden on the health care system [3,4].

Despite the availability and use of glucose-lowering pharmacological drugs, such as metformin [5], there is a continuous rise in death due to secondary complications associated with T2D globally. The population with T2D reportedly dies from cardiovascular disease more frequently than healthy individuals [6]. Moreover, other patients experience severe side effects from pharmacological drugs [7]. Thus, this is the motivation for exploring different pharmacological and nutraceutical agents to find one with potent antihyperglycemic and hypolipidemic potentials.

Other studies have explored the beneficial impact of natural antioxidants on glucose control, inflammation, and lipid metabolism in metabolic conditions [8-11]. For their distinct antioxidant benefits, many dietary compounds, including vitamin D, are increasingly being taken as supplements. Vitamin D, also called calciferol [12], is a membrane antioxidant and a member of fat-soluble vitamins that alleviates inflammation by inhibiting nuclear factor kappa-beta activity [13,14]. The direct stimulation of pancreatic β cells to release insulin [15], anti-inflammatory effects [16] to reduce chronic inflammation brought on by insulin resistance, and downregulation of elevated parathyroid hormone levels [17], which inhibit insulin secretion [18], are some of the protective mechanisms of vitamin D that have been proposed. In addition to being present in dietary supplements, a small amount can be found in oily fish, red meat, egg yolk, liver, and fortified cereals [19].

A previous meta-analysis confirmed vitamin D's beneficial effects in regulating blood glucose; however, the improvement was minimal [20]. This effect might be attributed to vitamin D's unique property in alleviating oxidative stress and inflammation [21]. Although previous quantitative studies have shown that vitamin D supplementation in patients with T2D can reduce inflammation [22,23] and lipid profiles [24], the results are inconsistent, and the markers evaluated are not common. Additionally, the effect of vitamin D supplementation on diabetes-related complications is controversial since most randomized controlled trials (RCTs) conducted used small sample sizes or have used different doses of vitamin D. Consistently, quantitative evidence has not looked at these parameters simultaneously to explore the antioxidant effect of vitamin D in T2D. This led us to propose this systematic review and meta-analysis that will simultaneously investigate the antioxidant benefits of vitamin D in all these parameters in T2D. We aimed to conduct this systematic review and meta-analysis to evaluate the impacts of vitamin D supplementation in T2D and help to further clarify its beneficial impact on inflammation and lipid profile in patients with T2D. This information is essential for understanding the health benefits of this dietary antioxidant and reducing the number of T2D individuals who succumb to cardiovascular disease complications associated with T2D.

Methods

Overview

This systematic review and meta-analysis protocol is prepared in accordance with the PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist [25] and the population, intervention, comparison, and outcome (PICO) guideline [26]. The protocol for this systematic review and meta-analysis is registered with the International Platform of Registered Systematic Review and Meta-analysis Protocols (INPLASY202260022) and is reported according to the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) checklist (Multimedia Appendix 1).

Purpose of the Study

This proposed study aimed to evaluate the effect of vitamin D on markers of inflammation and lipid profile among adult patients with T2D.

The research question is "Can supplementation with vitamin D improve inflammation and ameliorate dyslipidemia in T2D?" This protocol will subscribe to PICO guidelines [26]. Participants are adult patients with T2D. The intervention will be vitamin D supplementations of any dose, and the comparators are placebo or healthy patients without treatment.

The outcomes are inflammation and dyslipidemia, and the study design includes RCTs.

Inclusion and Exclusion Criteria

The inclusion and exclusion criteria will be carried out following our PICO guidelines. The review will include RCTs that have focused on adult patients with T2D. There will be no language limitations, and all studies published from inception until December 30, 2022, will be considered. The reviews, books, letters, and animal studies experimenting with diabetes will be excluded. Furthermore, cross-sectional studies, cohort studies, case-control studies, and case reports will all be excluded.

Search Strategy and Information Sources

Reviewer 1 (RM) and reviewer 2 (KM) will independently conduct a comprehensive literature search through different databases (eg, Embase, Google Scholar, Web of Science, PubMed, and Science Direct). The following keywords (Medical Subject Headings terms), including their synonyms, will be applied in all databases: "Vitamin D," "calciferol," "Dihydroxycholecalciferol," and "type 2 diabetes mellitus." Furthermore, the evidence will be sought from RCTs published from inception until December 30, 2022, with no restriction regarding publication language. The preliminary search strategy is presented in Table 1 and Table 2.

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Table 1. Search strategy adapted to indicate preliminary search in a database (PubMed).

Item	MeSH[a] terms	Search
1	Vitamin D	vitamin D[MeSH Terms]
2	Calciferol	Calciferol[MeSH Terms]
3	1,25-Dihydroxycholecalciferol	1,25-Dihydroxycholecalciferol[MeSH Terms]
4	Type 2 diabetes mellitus	Type 2 diabetes mellitus[MeSH Terms]1
5	1,2, and 3	((Vitamin D[MeSH Terms]) OR (Calciferol[MeSH Terms])) OR (1,25-Dihydroxycholecalciferol[MeSH Terms])
6	4 and 5	(Type 2 diabetes mellitus[MeSH Terms]) AND (((vitamin D[MeSH Terms]) OR (Calciferol[MeSH Terms])) OR (1,25-Dihydroxycholecalciferol[MeSH Terms]))

[a]MeSh: Medical Subject Headings.

Table 2. Search strategy on PubMed with filter according to study designs (randomized controlled trials).

Items	MeSH[a] terms	Search
7	6	(Type 2 diabetes mellitus[MeSH Terms]) AND (((vitamin D[MeSH Terms]) OR (Calciferol[MeSH Terms])) OR (1,25-Dihydroxycholecalciferol[MeSH Terms])). Filters: Randomized Controlled Trial

[a]MeSh: Medical Subject Headings.

Study Selection

The search will be conducted independently by 2 reviewers (RM and KM) to ensure accuracy and consistency based on the eligibility criteria. Firstly, keywords, titles, and abstracts will be screened, followed by retrieval of the full study. Mendeley desktop reference manager (version 1.19.4) will be used to save studies retrieved through web-based database search or manual reference screening. All studies that meet the inclusion criteria will be subjected to a data collection process and quality assessment. For any discrepancy, the 2 reviewers will conclude by discussing and reevaluating the study in dispute. The Shiny app [27] will be used to create a PRISMA flow diagram showing study selection.

Data Items and Collection

The data will be extracted following the eligibility criteria. The 2 reviewers RM and KM will conduct data extraction independently and then compare the spreadsheet; in case of disagreement, they will discuss and review the study again. The information sought from each study for extraction will include the author and year of publication, the country where the study was conducted, sample size, participants' gender and age, form of vitamin D and its dosage, duration of treatment, lipid profiles, and pro-inflammatory markers. Data will be confirmed by contacting investigators if insufficient information has been provided in the published article.

Risk of Bias

The risk of bias will be assessed using the methods recommended in the Cochrane risk of bias assessment tool [28]; assessment includes 6 domains; selection, attention, reporting, performance, attrition, and other bias. Judgments will be used to determine whether the bias is a high-risk or low-risk bias, is unclear due to insufficient information, or is a potential bias. The Jadad guideline will be used to assess the quality of individual studies [29]. The author (RM) and supervisor (KM) will discuss and resolve any bias and come to a consensus should there be any disagreement.

Subgroup Analysis

Following initial data analysis, we will evaluate the level of heterogeneity based on I^2 [30] and Q tests. If the I^2 is moderate ($I^2 \geq 50\%$), we will explore the source of heterogeneity by performing subgroup analysis [31]. This will be based on the form of vitamin D, its dosage, BMI, study quality, the origin of the study, age, and the duration of the intervention.

Publication Bias

Publication bias among the included studies will be assessed and visualized graphically through funnel plots [32] if there are more than 10 studies included in the meta-analysis. In case of no publication bias, the funnel plot will form a symmetrical (ie, inverted) funnel. In contrast, if bias is present due to smaller studies without statistically significant effects, the funnel plot will show an asymmetrical shape.

Sensitivity Analysis

Sensitivity analyses will be performed to evaluate the robustness and stability [33] of our effect size by using one study exclusion approach at a time based on the study with a high risk of bias, small sample size, or the largest sample size.

Certainty of Evidence

We will evaluate the certainty of our evidence by using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) approach [34] using the web-based GRADEprofiler. This approach takes into consideration the risk of bias, imprecision, inconsistency, indirectness, publication bias, and effect size. The evidence will be rated as low, moderate, or high based on 2 independent reviewers' ratings. The overall findings will be presented in a summary of the findings table.

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Data Analysis

Statistical analysis will be conducted using the Review Manager (RevMan; version 5.4; Cochrane Collaboration). Each study reviewer (RM and KM) will independently extract data as mean, SD, and sample size in each group. Where mean and SD values are not reported, the estimation will be made using a web-based calculator by Hozo et al [35]. The forest plots will be used to determine the pooled estimates and classify the level of heterogeneity based on I^2 and P values [36]. The estimated pool will be reported as either mean difference or standardized mean difference and 95% CIs.

Furthermore, a chi-square test (χ^2) and I^2 will assess the heterogeneity among the included studies [37,38]. An I^2 of 0% to 50% will be considered low to minimal heterogeneity, while an I^2 above 50% will be considered moderate heterogeneity.

Consistently, sources of heterogeneity will be explored through subgroup analysis, and sensitivity analysis will be used to assess the stability of the re-analyzed pool estimates. $P<.05$ will be considered statistically significant. In case meta-analysis cannot be performed due to insufficient data or the number of studies, qualitative synthesis will be performed [39].

Ethical Considerations

There will be no involvement from patients and the public in this study. This study synthesizes data from studies that were already peer-reviewed and published. Thus, no ethical approval is required.

Results

The proposed systematic review and meta-analysis is anticipated to be complete and submitted for review by December 30, 2023. Hence, the full results will be discussed in detail following a comprehensive search and data analysis. This systematic review and meta-analysis will not require any direct involvement of patients and the public; thus, no ethical approval is required. The search for literature has already started on MEDLINE using PubMed as a search engine; this is performed independently by 2 reviewers to avoid risk of bias.

Discussion

In this proposed systematic review and meta-analysis, we will explore the impacts of vitamin D supplementation on markers of inflammation, including tumor necrosis factor-alpha, interleukin-6, and C-reactive protein in patients with T2D. Furthermore, we will evaluate the effect of vitamin D on lipid profile (triglycerides, total cholesterol, low-density lipoprotein, and high-density lipoprotein) in adult patients with T2D. Thus, the findings in this systematic review and meta-analysis will provide insights into the use of this natural antioxidant, vitamin D, as a supplementation in patients with T2D to aid in the prevention of complications associated with T2D. The proposed review will include studies published from inception to December 2022, thus gathering old and current evidence about vitamin D. Additionally, the review will be conducted independently to avoid bias in selection and extraction. One of the major anticipated limitations is methodological heterogeneity due to the use of different doses of vitamin D and duration of intervention, different age groups, and patients with other metabolic conditions in addition to T2D. However, subgroup analysis will be performed according to these confounders to find the source of heterogeneity. This will be through classification of studies based on quality (eg, good or low), doses, age, and duration of intervention. Our discussion will examine the implications of our findings, the limitation of the systematic review, and directions for further research on the use of vitamin D as a supplement in T2D for the amelioration of inflammation and dyslipidemia and prevention of secondary complications.

Acknowledgments

We thank the University of South Africa for the payment of article processing charges. The author(s) received no specific funding for this work.

Data Availability

Information and data involving literature search, data extraction, and data analysis will be made available by the corresponding author upon request following the publication of the manuscript.

Authors' Contributions

KM and RM were in charge of the study conceptualization and design as well as methodology. KM provided resources and RM prepared the original draft and wrote the manuscript. KM supervised the study. KM also helped in the writing, reviewing, and editing of the manuscript. Both authors (RM and KM) have read and approved the final version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA-P checklist. PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols.
[DOC File , 110 KB - resprot_v12i1e42193_app1.doc]

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Abbreviations

GRADE: Grading of Recommendations, Assessment, Development, and Evaluations
PICO: participants, intervention, comparator, and outcome
PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT: randomized controlled trial
T2D: type 2 diabetes

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Protocol

Completeness of Reporting in Diet- and Nutrition-Related Randomized Controlled Trials and Systematic Reviews With Meta-Analysis: Protocol for 2 Independent Meta-Research Studies

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Abstract

Background: Journal articles describing randomized controlled trials (RCTs) and systematic reviews with meta-analysis of RCTs are not optimally reported and often miss crucial details. This poor reporting makes assessing these studies' risk of bias or reproducing their results difficult. However, the reporting quality of diet- and nutrition-related RCTs and meta-analyses has not been explored.

Objective: We aimed to assess the reporting completeness and identify the main reporting limitations of diet- and nutrition-related RCTs and meta-analyses of RCTs, estimate the frequency of reproducible research practices among these RCTs, and estimate the frequency of distorted presentation or spin among these meta-analyses.

Methods: Two independent meta-research studies will be conducted using articles published in PubMed-indexed journals. The first will include a sample of diet- and nutrition-related RCTs; the second will include a sample of systematic reviews with meta-analysis of diet- and nutrition-related RCTs. A validated search strategy will be used to identify RCTs of nutritional

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interventions and an adapted strategy to identify meta-analyses in PubMed. We will search for RCTs and meta-analyses indexed in 1 calendar year and randomly select 100 RCTs (June 2021 to June 2022) and 100 meta-analyses (July 2021 to July 2022). Two reviewers will independently screen the titles and abstracts of records yielded by the searches, then read the full texts to confirm their eligibility. The general features of these published RCTs and meta-analyses will be extracted into a research electronic data capture database (REDCap; Vanderbilt University). The completeness of reporting of each RCT will be assessed using the items in the CONSORT (Consolidated Standards of Reporting Trials), its extensions, and the TIDieR (Template for Intervention Description and Replication) statements. Information about practices that promote research transparency and reproducibility, such as the publication of protocols and statistical analysis plans will be collected. There will be an assessment of the completeness of reporting of each meta-analysis using the items in the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) statement and collection of information about spin in the abstracts and full-texts. The results will be presented as descriptive statistics in diagrams or tables. These 2 meta-research studies are registered in the Open Science Framework.

Results: The literature search for the first meta-research retrieved 20,030 records and 2182 were potentially eligible. The literature search for the second meta-research retrieved 10,918 records and 850 were potentially eligible. Among them, random samples of 100 RCTs and 100 meta-analyses were selected for data extraction. Data extraction is currently in progress, and completion is expected by the beginning of 2023.

Conclusions: Our meta-research studies will summarize the main limitation on reporting completeness of nutrition- or diet-related RCTs and meta-analyses and provide comprehensive information regarding the particularities in the reporting of intervention studies in the nutrition field.

International Registered Report Identifier (IRRID): DERR1-10.2196/43537

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KEYWORDS

nutrition; diet; randomized controlled trials; CONSORT; TIDieR; PRISMA; spin; risk; bias; research; intervention; literature; limitations; PubMed

Introduction

Background

Nutrition research provides evidence to support public health policies, advances in clinical practice, and improved quality of life for patients. Reporting diet- and nutrition-related randomized controlled trials (RCTs) requires particular attention to field-specific methodological aspects, such as baseline dietary patterns, food intake assessment instruments, and statistical analysis methods [1-3]. Strategies to deal with methodological limitations and increase transparency in nutrition research include prioritizing large and long-term RCTs, pre-registering protocols and statistical analyses, clearly defining and standardizing methods for data collection and outcomes assessment, and promoting data sharing [4-7]. Guidelines on how to handle sensitive issues, such as public-private partnerships and working with industry, are available [8,9]. All of these recommendations, however, require complete and transparent reporting, which is also crucial when these nutrition- or diet-related RCTs are pooled in a systematic review or meta-analysis. Clearly specified methods for identifying, selecting, and appraising primary studies included in systematic reviews are essential to a systematic review being of high enough quality to inform clinical practice [10,11]. Systematic reviews are the cornerstones of therapeutic evaluation as they assess and grade the available body of evidence on interventions.

Inappropriate reporting of research often means an important and avoidable source of that research wasted [12], with consequences for research consumers such as scientists, clinicians, policy makers, the media, and patients [13,14]. Researchers can minimize this source of waste by adhering to reporting guidelines, which define a minimum set of information required when reporting medical research to ensure its usefulness [15]. One of the first reporting guidelines was the Consolidated Standards of Reporting Trials (CONSORT) for writing up reports of RCTs, developed in 1996 and updated in 2001 and 2010. CONSORT consists of a 25-item checklist and flow diagram to help authors report their RCTs [16]. Item 5 of CONSORT 2010 concerns an RCT's intervention. To improve reporting completeness and replicability of interventions, CONSORT item 5 was extended into a 12-item reporting guideline, "the Template for Intervention Description and Replication" (TIDieR) [17]. Other extensions are also available for specific designs (eg, crossover trials) [18], interventions (eg, nonpharmacologic treatment interventions) [19], and data (eg, harms) [20]. Similar guidance to improve reporting completeness for systematic reviews and meta-analyses—the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) Statement—was developed in 2009 and updated in 2020 [21].

Journal endorsement of these reporting guidelines is associated with better reporting [22-24]. For example, a Cochrane review including meta-research studies assessing the reporting completeness of RCTs demonstrated a standardized mean difference of 0.68 (99% CI 0.38 to 0.98) on the aggregate score of all CONSORT items in favor of CONSORT-endorsing journals over nonendorsers. Allocation concealment, scientific rationale in the introduction, sample size, and sequence generation were also more adequately described in RCTs published in CONSORT-endorsing journals [22]. A study evaluating journal instructions for authors found that 27 out of 33 high-impact nutrition and dietetic journals with an impact factor over 2.88 mentioned CONSORT [23]. In a cross-sectional

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study in the field of nursing, the median rates of adherence to the PRISMA statement were 73% (IQR 59.5%-94.6%) for reviews published in journals that endorsed PRISMA and 64.9% (IQR 17.6%-92.3%) for reviews published in journals that did not endorse PRISMA [24]. As far as we know, the correlation between reporting completeness and journal endorsement of PRISMA has not been explored in the nutrition field.

Few studies assessed reporting completeness of nutrition research. Although previous studies have found poor reporting in nutrition- and diet-related studies [25-31], most focused on the association of particular funding sources with methodological and reporting quality [25-27,30,31] or risk of bias [28,29]. We identified only 1 systematic review of RCTs assessing the quality of reporting in RCTs of dietetic interventions in primary care. The authors found that none of the 27 included RCTs reported all CONSORT items, with a median of 11.5 of the 28 items completely met, 8 partially met, and 10 not met at all. The items most often not reported were "a description of where the full protocol can be accessed (n=26, 96%), "registry number and name of trial registry" (n=23, 85%), "mechanism used to implement the random allocation sequence" (n=22, 81%), and "who generated the random allocation sequence, enrolled participants and assigned participants" (n=22, 81%) [32]. We did not find any study assessing the completeness of reporting of systematic reviews in nutrition. One scoping review evaluated 57 studies that assessed adherence to individual PRISMA items, where 79% (n=45) of them focused on therapeutic interventions and related to surgery clinical areas. It identified 11 items that are fewer than 67% of systematic reviews adhered to, including structured summary, protocol and registration, search, data items, risk of bias in individual and across studies (in both methods and results sections), additional analyses, and funding [11].

CONSORT and TIDieR do not cover all possible practices to enhance research reproducibility, such as the inclusion of data-sharing and code-sharing statements. A survey of a random sample of 149 biomedical articles published between 2015 and 2017 found that 18.3% discussed publicly available data [33]. Similarly, an automated assessment of all PubMed Central articles estimated that in 2020, overall 15% of articles had a data-sharing statement and 3% had a code-sharing statement [34].

"Spin," as defined by Boutron et al [35], is the use of specific reporting strategies, from whatever motive, to highlight that the experimental treatment is beneficial, despite a statistically nonsignificant difference for the primary outcome, or to distract the reader from statistically nonsignificant results.

Spin is frequently found in the medical literature, regardless of study design, and its presence can affect the interpretation of results. A systematic review of 35 reports which investigated spin found that more than 56% of trials included spin in their abstract (n=13) and main text (n=16) and that 26.3% of systematic reviews (n=2) included spin in their main text [36]. We did not identify any studies assessing reproducible research practices or the presence of spin in nutrition systematic reviews or meta-analyses.

Objectives

This protocol describes 2 independent meta-research studies that aim to (1) assess the reporting completeness of diet- and nutrition-related RCTs, identify their main reporting limitations, and estimate the frequency of reproducible research practices among them; and (2) assess the reporting completeness of systematic reviews with meta-analysis of diet- and nutrition-related RCTs, identify their main reporting limitations, evaluate their risk of bias, and estimate the frequency of spin among them.

Methods

Design and Research Questions

Two meta-research studies will be conducted to answer the research questions presented in Textbox 1. Both protocols are registered in the Open Science Framework (doi: 10.17605/OSF.IO/BF47G and 10.17605/OSF.IO/ZTFYX).

Textbox 1. Research questions.

Meta-research study of diet- and nutrition-related randomized controlled trials (meta-research study 1)

- What is the proportion of items adherent to CONSORT (Consolidated Standards of Reporting Trials) and TIDieR (Template for Intervention Description and Replication) in a sample of published randomized controlled trials of diet- or nutrition-related interventions?
- What is the frequency of reproducible research practices among these randomized controlled trials?

Meta-research study of systematic reviews with meta-analysis of diet- and nutrition-related randomized controlled trials (meta-research study 2)

- What is the proportion of items adherent to PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) in a sample of published systematic reviews with meta-analysis of diet- and nutrition-related randomized controlled trials?
- What is the risk of bias in these reviews?
- What is the frequency of spin in the abstract and the main text of these reviews?

Eligibility Criteria

For meta-research study 1, we will include diet- and nutrition-related RCTs published in peer-reviewed journals. We will consider self-identification as an RCT as an inclusion criterion. All diet- and nutrition-related RCTs, regardless of the population or outcomes evaluated or the framework design will be included (eg, noninferiority, superiority, or exploratory).

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There will be an exclusion of non-RCTs, pilot and feasibility trials, studies that assess pharmaceutical or herbal medicines as an intervention, and trials without isolated nutrition- or diet-related interventions (meaning that trials combining more than 1 intervention will not be eligible). RCTs that do not include any term related to the categories of intervention described in Textbox 2 in their titles or abstracts will be excluded.

For meta-research study 2, systematic reviews will be included with meta-analysis of diet- and nutrition-related RCTs published in peer-reviewed journals. All Cochrane publications will be excluded as their moderate to high methodological quality is likely to ensure a high level of reporting completeness [37].

Textbox 2. Categories of nutrition- or diet-related interventions.

- Food (whole food, food products, specially formulated foods)
- Breastfeeding
- Complete diet or dietary patterns
- Complete nutrition formulas (enteral or parenteral)
- Supplementation or supplements (single or multiple nutrients, bioactive nonnutrients, and plant components)
- Nutrition education, counseling, and coordination of care

We adapted the categories proposed by Naude et al [37] to include "shared foods of complete diet and dietary patterns" and "enteral or parenteral formulas" and remove "nutrition-related policies."

For both meta-research studies, the language of publications will not be an eligibility criterion aiming to avoid language bias. Our team has researchers proficient in English, Portuguese, and Spanish. If necessary, Google Translate or private translation services will be used to extract data from publications in other languages. The nutrition intervention categories of interest are listed in Textbox 2 [37].

Literature Research

For meta-research study 1, we will use the search strategy developed by Durão et al [38] to identify RCTs of nutritional interventions [32]. For meta-research study 2, a search strategy is constructed using nutrition- and diet-related terms [38] combined with a validated search strategy to identify systematic reviews or meta-analyses [39]. No limitation will be set for language during the literature search. PubMed search is conducted (via the National Library of Medicine) using the search strategies presented in Multimedia Appendices 1 and 2. There will be a search for RCTs (June 1, 2021, to June 1, 2022) and systematic reviews with meta-analysis (July 01, 2021, to July 01, 2022) indexed in 1 calendar year.

Study Selection and Sample Size

For both meta-research studies, we will organize the retrieved reports in EndNote (Clarivate). We will remove duplicates using EndNote's automated deduplication, then manually check for and exclude any remaining duplicates. The final library without duplicates to Rayyan will be imported [40], where 2 reviewers will independently determine the eligibility of each report in a 2-stage process. They will screen titles and abstracts and select all RCTs and systematic reviews with meta-analysis assessing any diet- or nutrition-related intervention. Liberal acceleration will be applied, in which both reviewers must exclude a record for it to be excluded, while only 1 reviewer must include a record for it to be included. The reviewers will then read the full texts to confirm study eligibility. In both screening rounds, any discrepancies will be resolved through discussion between the reviewers (FS and JL, acknowledged), with adjudication by a third reviewer (MSM). All reviewers have experience in conducting systematic reviews.

The eligible RCTs and systematic reviews with meta-analysis will be grouped according to the intervention categories described in Textbox 2, and the proportion of RCTs and systematic reviews in each category is calculated. A convenience sample of 100 RCTs will be randomly selected for inclusion in meta-research study 1 and 100 random systematic reviews with meta-analysis for meta-research study 2 that meet the above criteria, with no formal sample size calculation. We aim to maintain the proportion of each intervention category (Textbox 2) in both meta-research studies, for example, for a given intervention category that comprises, say, 50% of the total sample of potentially eligible RCTs, we will randomly select 50 of those for our sample of 100 RCTs. A web-based random number generator will be used to create the list of publications to include from an enumerated sequence of all studies in each intervention category [41].

A flowchart will be presented to demonstrate each step of the study selection process. A list of the studies excluded at the full-text screening stage will be presented with reasons for their exclusion for both meta-research studies.

Data Extraction

For meta-research study 1, a total of 2 reviewers will independently extract data from the selected RCTs to evaluate their reporting completeness, identify their main reporting limitations, and assess their use of predefined reproducible research practices. We have developed a data extraction form (Multimedia Appendix 3) that includes (1) publication data, such as PMID, first author's name, journal in which the RCT was published, and the journal's field according to Web of Science. (2) Basic description of RCT data, categorized into population, intervention, comparator, outcome, and study design (PICOS) domains, adapted from Naude et al [37]. (3) Use of practices that promote research transparency and reproducibility, such as the use of CRediT [42] to acknowledge authorship;

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availability of a full protocol publication, statistical analysis plan, and materials/data/code; open access; disclosure of funding source; and disclosure of conflicts of interest. All these practices will be categorized as "yes or no."

An additional data extraction form to evaluate adherence to items from CONSORT [16], its extensions for abstracts [43], harms [20], crossover [18], nonpharmacological [19], cluster trials [44], and TIDieR [15] statements will be developed. Each item will be evaluated as fully reported, not reported, partially reported, or not applicable. As there is an inclusion of RCTs published after the COVID-19 pandemic began, items from the CONSERVE reporting guideline will also be included. CONSERVE was developed to improve the reporting completeness of trials modified due to the COVID-19 pandemic or other extenuating circumstances [45] (Multimedia Appendix 4).

For meta-research study 2, a total of 2 reviewers will independently extract data from the selected systematic reviews with meta-analysis of nutrition- or diet-related RCTs. We have developed a data extraction form (Multimedia Appendix 5) to capture (1) Publication data, such as PMID, first author's name, journal in which the meta-analysis was published, and the journal's field according to Web of Science. (2) Meta-analysis research questions, categorized into PICOS domains, adapted from those used by Naude et al [37]. (3) The presence of spin in the abstract and the main text, classified into four main categories: (A) misleading reporting, including 10 items in the main text and 8 items in the abstract; (B) misleading interpretation, including 13 items in the main text and 10 items in the abstract; (C) inappropriate extrapolation, including 5 items in the main text and 3 items in the abstract, as proposed by Yavchitz et al [46]; and (D) methodological quality according to the ROBIS tool. Phases 2 and 3 of the tool will be followed to make an overall judgment of risk of bias (which will be rated as low, high, or unclear) [47].

An additional data extraction form to evaluate adherence to PRISMA [21], its extensions [48,49], and TIDieR [15] items was also developed (Multimedia Appendix 6).

For both studies, we will pilot-test the data extraction forms on 5 randomly selected full-texts before proceeding with full data extraction to ensure consistency in the interpretation of data items and refine the data extraction form, if necessary. All extracted information will be entered directly into the study databases using REDCap [50]. Any disagreement between the pairs of reviewers will be resolved by a third reviewer.

Data Analysis

For both meta-research studies, descriptive aspects of included publications (ie, data on bibliometrics, PICOS, research transparency practices, presence of spin, and risk of bias) will be presented both as absolute and relative frequencies, either in diagrams or tables.

For meta-research 1, calculation of an aggregate score of adherence to all CONSORT, its extensions, CONSERVE, and TIDieR items will be presented. The items of relevant reporting guidelines' checklists in 170 questions with categorical answers (Multimedia Appendix 3) were fragmented. Most questions presented 2 options as answers (yes or no), whereas some questions presented 3 or 4 options as answers (yes, no, partially, or not applicable). Answers "yes" will be scored as 1 point, while answers "no" will be scored as 0 points and answers "partially" will be scored as 0.5 points. Answers such as "not applicable" will be discounted for that particular study. Therefore, the final score can range from 0 to 170.

For meta-research 2, we will similarly calculate an aggregate score of adherence to all PRISMA, its extensions, and TIDieR items. For meta-research 2, all items of the corresponding reporting guidelines were fragmented into 114 questions with the same possible categorical answers (and respective attributable scores) described above (Multimedia Appendix 6). Thus, the final score for the meta-research of meta-analyses can range from 0 to 114.

In the final report, the results will be presented as frequencies (and respective percentages in relation to the total number of relevant studies) for individual items and proportion of the total achievable score for individual studies. No data aggregation or cutoff points are anticipated for the descriptive analyses.

The general features between RCTs and meta-analyses with above-average and below-average reporting score proportions were also compared, which are stratified by the mean or median value (depending on the distribution) using the Student *t* test or Mann-Whitney test for quantitative variables and the chi-square test for categorical variables. Logistic regression models will be constructed to explore the determinants of reporting completeness.

Any changes to the protocol will be detailed and justified in the publications describing the results of the study.

Ethical Considerations

As both meta-research studies will involve reviewing and collecting evidence from previously published papers, ethical approval is not required. Both meta-research studies will be reported according to the PRISMA adaptation for meta-epidemiological methodology research [51]. Any updates and amendments to this protocol will be described and justified in the final publications. The results will be published in peer-reviewed journals.

Results

The literature search for the first meta-research study retrieved 20,030 records and 2182 were potentially eligible. Among them, 100 nutrition- or diet-related RCTs were randomly selected for data extraction.

The literature search for the second meta-research study retrieved 10,918 records and 850 were potentially eligible. Among them, a random sample of 100 systematic reviews with meta-analysis was selected for data extraction.

Data extraction of both meta-research studies is currently in progress and the completion is expected by the beginning of 2023.

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Discussion

We presented the protocols of 2 independent meta-research studies aiming to investigate the completeness of reporting and the frequency of research transparency practices in a random sample of nutrition- or diet-related RCTs and meta-analyses published in journals indexed in PubMed.

Nutrition interventions have particular challenges that need careful consideration during all study phases and detailed communication of research questions and findings. Thus, well-written and complete reporting of RCTs and meta-analyses of RCTs are crucial to support scientific integrity, ethical standards, safety, and validation of study methods and findings [4]. Inappropriate reporting of research frequently means an important and avoidable source of research waste [12], with consequences for scientists, clinicians, policy makers, the media, and patients [13,14]. Researchers can minimize this waste by adhering to CONSORT [16], TIDieR [17], and PRISMA [21] when reporting their work. Indeed, additional practices to enhance research reproducibility such as the adoption of reproducible workflows and open science practices, including data and code-sharing, can benefit nutrition- and diet-related research [52].

The complexity of reporting intervention studies depends on the type of intervention under investigation, as well as knowledge of relevant extensions of general reporting guidelines for specific fields. Nutrition- or diet-related interventions have several particularities, and a detailed evaluation of whether RCTs and meta-analyses of nutritional interventions adhere to CONSORT [16] and PRISMA [21] statements, respectively, is essential. As per our knowledge, this will be the first meta-research study addressing the main reporting limitations of nutrition- or diet-related intervention studies.

At 1-year interval, we identified 2182 and 850 publications describing potentially eligible RCTs and systematic reviews with meta-analysis, respectively. These numbers illustrate the relevance of these types of publications in the nutrition research field, as well as the need for a detailed evaluation of their reporting completeness and transparency. The fact that our samples do not represent all publications in this field has been acknowledged as a study limitation. However, our search strategy choices are based on the premise that the eligible publications retrieved should provide enough evidence to fulfill our aims, as they reflect a recent body of scientific literature indexed in the main database for medical research. While not including Cochrane reviews is also a limitation of our research, their inclusion could bias our findings since these publications follow specific guidelines (eg, for content, structure, and format), and have overall higher methodological quality than standard peer-reviewed publications. Future research could explore the main differences between Cochrane and non-Cochrane systematic reviews of nutritional- or diet-related interventions.

These meta-researchers will inform further deliberations around the need to develop specific reporting guidelines for nutrition- and diet-related RCTs and systematic reviews with meta-analysis since this evaluation can shed light on the main reporting limitations in the area. Our meta-research studies will fill this gap. Therefore, we aim to help increase in the transparency and reproducibility of studies involving nutrition- or diet-related interventions.

Acknowledgments

We are grateful to Julia Lima, who was one of the reviewers involved in the title and abstract screening of the retrieved records for both meta-researches.

Data Availability

Data will be maintained in .csv, .txt, .ris, .docx, and .pdf format for storage for the period of the study and beyond. Extracted data will be deposited in digital open access repositories, such as UK Data Service or Oxford Research Archive.

Authors' Contributions

All authors have made substantial contributions to the development of this protocol through discussions on the topic. MMS, SK, SH, GK, GSC, JC, SL, ARAA, CJV, and FG jointly conceived the idea of this project. FS, MMS, SK, SD, CC, CL, ARAA, MP, LCI, CJV, and GK contributed to the study design and development of research questions. FS and SK constructed the search strategy for both meta-research and ran them. FS, MMS, and GC constructed the data extraction forms. FS and MMS led the writing of the manuscript. All authors provided detailed comments on earlier drafts and approved this final version.

Conflicts of Interest

FS received a postdoctoral fellowship from COPPETEC Foundation. MMS, SK, JAdeB, and GC are funded by Cancer Research UK (grant number C49297/A27294). MP is supported by an Australian Research Council Discovery Early Career Researcher Award (DE200101618). CJV has received honoraria from The Obesity Society and his University has received funds to support his research from National Cattlemen’s Beef Association, Alliance for Potato Research and Education, the Gordon and Betty Moore Foundation, and NIH.

Multimedia Appendix 1

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Full search strategy for PubMed database (meta-research study 1—nutrition- and diet-related RCTs).
[DOCX File , 15 KB - resprot_v12i1e43537_app1.docx]

Multimedia Appendix 2
Full search strategy for PubMed database (Meta-research study 2—systematic reviews with meta-analyses of nutrition- and diet-related RCTs).
[DOCX File , 14 KB - resprot_v12i1e43537_app2.docx]

Multimedia Appendix 3
Standardized form for data extraction for diet- or nutrition-related RCTs published as scientific articles in peer-reviewed journals.
[DOCX File , 16 KB - resprot_v12i1e43537_app3.docx]

Multimedia Appendix 4
Data extraction form: completeness reporting of a recent sample of nutrition- or diet-related RCTs published in peer-reviewed journals.
[DOCX File , 57 KB - resprot_v12i1e43537_app4.docx]

Multimedia Appendix 5
Standardized form for data extraction for systematic reviews with meta-analyses of diet- or nutrition-related RCTs published as scientific articles in peer-reviewed journals.
[DOCX File , 21 KB - resprot_v12i1e43537_app5.docx]

Multimedia Appendix 6
Data extraction form: completeness reporting of a recent sample of meta-analyses of nutrition or diet-related RCTs published in peer-reviewed journals.
[DOCX File , 41 KB - resprot_v12i1e43537_app6.docx]

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Abbreviations

CONSORT: Consolidated Standards of Reporting Trials
RCT: randomized controlled trial
TIDieR: Template for Intervention Description and Replication
PICOS: population, intervention, comparator, outcome, and study design
PRISMA: Preferred Reporting Items for Systematic reviews and Meta-Analysis

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Protocol

Effectiveness of the Internet of Things for Improving Working-Aged Women's Health in High-Income Countries: Protocol for a Systematic Review and Network Meta-analysis

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Abstract

Background: Women often experience many unique health issues and conditions throughout their working lives. The Internet of Things (IoT) is a system of interrelated digital devices that can enable data exchanges over a network without human-to-human or human-to-computer interaction. The usage of applications and IoT in improving women's health has recently increased worldwide. However, there has been no consensus on the effectiveness of IoT in improving women's health outcomes.

Objective: This systematic review and network meta-analysis (NMA) aims to assess and synthesize the role of apps and the IoT in improving women's health and to identify the ranking of interventions for ensuring better results for each stated outcome.

Methods: Our systematic review and NMA will be conducted in accordance with the guidelines of the Cochrane Handbook. We will comprehensively search the following electronic databases: PubMed (including MEDLINE), Cochrane Central Register of Controlled Trials, Embase, Cumulative Index to Nursing and Allied Health Literature (ie, CINAHL), PsycINFO, ClinicalTrials.gov, and the World Health Organization International Clinical Trials Registry, along with other resources to identify relevant randomized controlled trials that have assessed the effects of various apps and the IoT with regard to improving working-aged women's health in high-income countries. We will segment and analyze the results of the included studies based on age categories (women undergoing a preconception period, those undergoing gestational and postpartum periods, and menopausal and pre- and postmenopausal women) and the medical history (women who have a specific medical condition—eg, cancer or diabetes—and women who do not have them) separately. Two independent reviewers will perform the study selection, data extraction, and quality assessment. Our primary outcomes include health status, well-being, and quality of life. We will perform pairwise meta-analysis and NMA to estimate the direct, indirect, and relative effects of apps and the IoT on women's health outcomes. We will also assess the hierarchy of interventions, statistical inconsistencies, and certainties of evidence for each outcome.

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Results: We plan to conduct the search in January 2023 and are currently discussing search strategies with the literature search specialists. The final report is planned for submission to a peer-reviewed journal in September 2023.

Conclusions: To the best of our knowledge, this review will be the first to identify the ranking of IoT intervention for ensuring working-aged women's health outcomes. These findings may be of great use to researchers, policy makers, and others with an interest in the field.

Trial Registration: International Prospective Register of Systematic Reviews (PROSPERO) CRD42022384620; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=384620

International Registered Report Identifier (IRRID): PRR1-10.2196/45178

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KEYWORDS

Internet of Things; IoT; women's health; network meta-analysis; apps; meta analysis; meta analyses; review method; systematic review; high income; mHealth; mobile health; health app; application; digital health

Introduction

Since the 1990s, the global labor force participation rate has been decreasing gradually. The Asia-Pacific region has experienced an overall decline in labor participation, which is believed to be mainly responsible for the global decline [1]. However, for regions outside of Africa, it has been estimated that the labor force participation rate will decrease, and this trend is projected to continue until at least 2030 [1,2]. Although women are less likely to participate in the labor market than men [1], women's participation has increased gradually owing to increased education and employment opportunities [3].

However, certain lifestyle changes, which occurred because of women's social advancement, have affected their health. For instance, women often perceive their health to be worse than do men because of certain social and biological factors [4], and consistently report higher stress levels [5]. A delay in marriage and the increasing age of conception have been correlated with higher chances of infertility in women, and over 186 million people (both men and women) have experienced infertility worldwide [6]. As opposed to primary infertility, secondary infertility is mainly related to lifestyle-related risks. A previous review has provided evidence of an association between lifestyle behaviors and infertility, including obesity, stress, a disturbed circadian clock, smoking, alcohol, and exercise [7]. Women's social advancement is associated with changes in their daily lives. Compared to working men, the double burden of job demands and domestic responsibilities has made women vulnerable to developing noncommunicable diseases [8].

Moreover, women experience considerable hormonal changes, unique health issues, and conditions throughout their lives [9,10]. Life stages of working-aged women are generally divided into reproductive age, pregnancy and delivery, and a climacteric period [9]. They may experience many unique health issues and conditions throughout their lives (eg, from preconception periods and menopause to several gynecological conditions) [11,12]. The prevalence of obesity in women of reproductive age has been increasing worldwide. Furthermore, it is associated with the risk of reduced fertility and the development of obesity-related comorbidities [13]. During pregnancy, maternal medical conditions, including hypertension, diabetes, and obesity, increase the risk of adverse outcomes, such as preterm delivery, low birth weight, and infant death [14-16]. Furthermore, the development of maternal medical conditions is associated with a risk of developing chronic disease later in life [13,17]. For example, women who develop gestational diabetes have a higher risk of developing type 2 diabetes in the future [17]. Women in the climacteric periods are exposed to the risk of developing chronic diseases, such as obesity, metabolic syndrome, diabetes, cardiovascular disease, depression, and cancer [18]. These diseases are associated with their lifestyle habits [9,18,19]. Lifestyle factors can impact the gynecological well-being of women throughout their lives and will affect the future health of subsequent generations [20]. Thus, it is necessary to strive to prevent and improve common medical conditions in women, taking into account their lifestyles throughout the overall life stages.

While women live longer than men [21], women are more affected and bear a heavier burden of living with disability [22]. Ensuring women's health and control over their own fertility can contribute to economic development; furthermore, ensuring women's health is important for ensuring the health and economic well-being of subsequent generations [23]. In summary, continuous care throughout women's lives is necessary, which, in turn, is important for maintaining community- and national-level economic development.

In 2022, a total of 5 billion people (63% of the global population) used the internet, and this figure continues to increase annually [24]. In 2009, the concept of smart health care was introduced. Since then, attempts to use the Internet of things (IoT) and other technologies to manage information related to people's health and address health care have been expanded [25]. IoT is a system of interrelated digital devices that can enable data exchanges over a network without human-to-human or human-to-computer interactions [26,27]. The IoT is increasingly being used to ensure and improve women's health worldwide (eg, monitoring [28-30] and providing interventions [30,31]). The IoT, which can be used daily and continually without human interactions, could successfully provide the opportunities and motivation necessary for women to engage in good lifestyle behaviors. Among IoT interventions, smart health care systems are used for health prevention and improvement. Smart health care is mainly used in home care, self-care, and acute care settings, where self-care systems allow

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people to monitor their own health conditions and access that information through wearable devices and smartphones [26,32]. Working-aged women would use these devices throughout the day, including at work and at home, to manage their lifestyles on their own. Previous studies have revealed the effectiveness of IoT in encouraging lifestyle behavioral changes and improving people's health. A previous systematic review has shown that personalized mobile interventions for people (64% of which were women) improved lifestyle behaviors [33]. Some primary studies have reported that interventions that use IoT have improved women's lifestyles [34-36] and health outcomes (eg, adverse pregnancy outcomes [35] and markers indicating hemodynamic functions [36]). However, there are various types of IoT interventions, such as exercise, diet, sleep, and combinations of these. Nonetheless, there are no systematic reviews assessing the effectiveness of the IoT among working-aged women, and no true consensus about the effectiveness of the IoT in improving women's health outcomes has been established [33,37]. Systematic reviews and network meta-analyses (NMAs) can compare 3 or more interventions simultaneously on the basis of the results of existing primary studies in a single analysis and provide an overall statistic and up-to-date summary of the state of research knowledge on an intervention [38]. Therefore, a rigorous evaluation that considers all forms of the IoT is necessary for generating evidence and promoting appropriate integration and usage of technologies within existing health systems in order to improve women's health outcomes.

Methods

Study Design

This systematic review and NMA aims to assess and synthesize the role of IoT in improving women's health and to identify the ranking of interventions of apps and IoT for ensuring better results among women in high-income countries. NMA can combine any direct and indirect evidence into a single effect size [38]. Our NMAs will estimate the direct, indirect, and relative effects of IoT on women's health outcomes and identify the ranking of interventions for ensuring the best results for each stated outcome.

This protocol adheres to the guidelines of the Cochrane Handbook for Systematic Reviews of Interventions [38] and reports its review findings based on the Preferred Reporting Items for Network Meta-Analyses (PRISMA-NMA) extension statement for reporting systematic reviews incorporating NMA of health care interventions [39]. We will report the results of each population group (women who are undergoing their preconception period, women undergoing their gestational and postpartum periods, and menopausal and pre- and postmenopausal women) separately. The review protocol is registered under the "International Prospective Register for Systematic Reviews" (PROSPERO) database (CRD42022384620) [40].

Inclusion and Exclusion Criteria

This study used the PICOS framework (P: participants, I: interventions, C: comparison, O: outcomes, and S: study design) to determine the eligibility criteria for including studies in its review.

Participants

The study participants are working-aged women in high-income countries, as defined by the World Bank in 2023 [41]. To prevent heterogeneity in the objectives and settings of IoT interventions, we focused on high-income countries because the global burden of disease differs across high-income and low- and middle-income countries [42]. The Organization for Economic Co-operation and Development (ie, OECD) has defined the working-age population as those aged from 15 to 64 years [43]. We will segment and analyze studies based on women who are undergoing their preconception period, women undergoing their gestational and postpartum periods, and menopausal and pre- and postmenopausal women. This study will include women of reproductive age (15-49 years old) as women in the preconception period. It will also include middle-aged women (40-64 years) as menopausal and pre- and postmenopausal women. Although this study's inclusion criteria show some overlap between the age categories, we will segment on the basis of the purposes of IoT interventions and populations of the included studies. Regarding studies focused on mixed populations (eg, those that include men), we will include only those studies that separate the data based on gender or those that include over 80% of women participants who meet our inclusion criteria.

Intervention and Comparison

We will include studies that have investigated IoT interventions to improve women's health compared to the use of standard care, no intervention, or another intervention not using the IoT (eg, education or exercise without the IoT). The IoT in the medical field includes functions such as relaying medical information through mobile health or telemedicine, collecting data, and monitoring. Although there are various types of IoT, we will include the application areas, such as collecting and monitoring data with the sensors of smartphones and wearable devices, as the form of IoT. We will include studies that have targeted both male and female populations if the relevant IoT intervention has been designed to improve women's health. If studies have investigated combinations of IoT interventions with other modes, we will also include studies that revealed IoT intervention as the primary intervention component.

Outcomes

Primary Outcomes

The outcomes for all included populations will be health status, including the number of cases diagnosed or treated (eg, cases of obesity and mental disorder), well-being, and quality of life.

Outcomes for women in their preconception periods include live birth (defined as the delivery of a live fetus after 20 completed weeks of gestation) or ongoing pregnancy (defined as evidence of a gestational sac with fetal heart motion at 12 weeks, as confirmed through ultrasonography.

Outcomes for women in the gestational and postpartum periods include health status, including the number of cases diagnosed

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or treated, including those of high-risk pregnancy (eg, gestational hypertension, gestational diabetes, and preterm birth).

Neonatal outcomes include low birth weight (defined as a birth weight less than 2.5 kg) and perinatal mortality.

Outcomes for middle-aged women include health status, including the number of cases diagnosed or treated (eg, diabetes, metabolic syndrome, hyperlipidemia, and hypertension).

Secondary Outcomes

Outcomes for all included populations are lifestyle and behavioral changes, including maintaining a healthy weight (measured as BMI in kg/m², % weight loss, or number of people with a BMI between 18.5 and 25 kg/m² [2]), maintaining healthy sleep behavior (sleeping 7 or more hours per night on a regular basis), stopping or reducing alcohol intake (measured as alcoholic drinks per day, with 1 drink of >10 g of ethanol), increasing physical activity (in accordance with the World Health Organization's standards; measured as minutes of moderate to vigorous physical activity per week or number of people reaching the World Health Organization's recommendation of doing 150 minutes of moderate - intensity physical activity per week, preferably based on the Global Physical Activity Questionnaire or other validated scales), and quitting or ceasing smoking and other substances (measured as the number of people not smoking or the number of people not using other substances).

If the studies report outcomes across different time points, this review will select the time point at the end of the relevant intervention.

Types of Study

We will include individual randomized controlled trials (RCTs) and cluster-RCTs to investigate the effects of IoT interventions on women's health. We will exclude reviews, qualitative studies, observational studies, cross-sectional studies, case studies, commentaries, editorials, expert opinions, and letters.

Searching the Literature

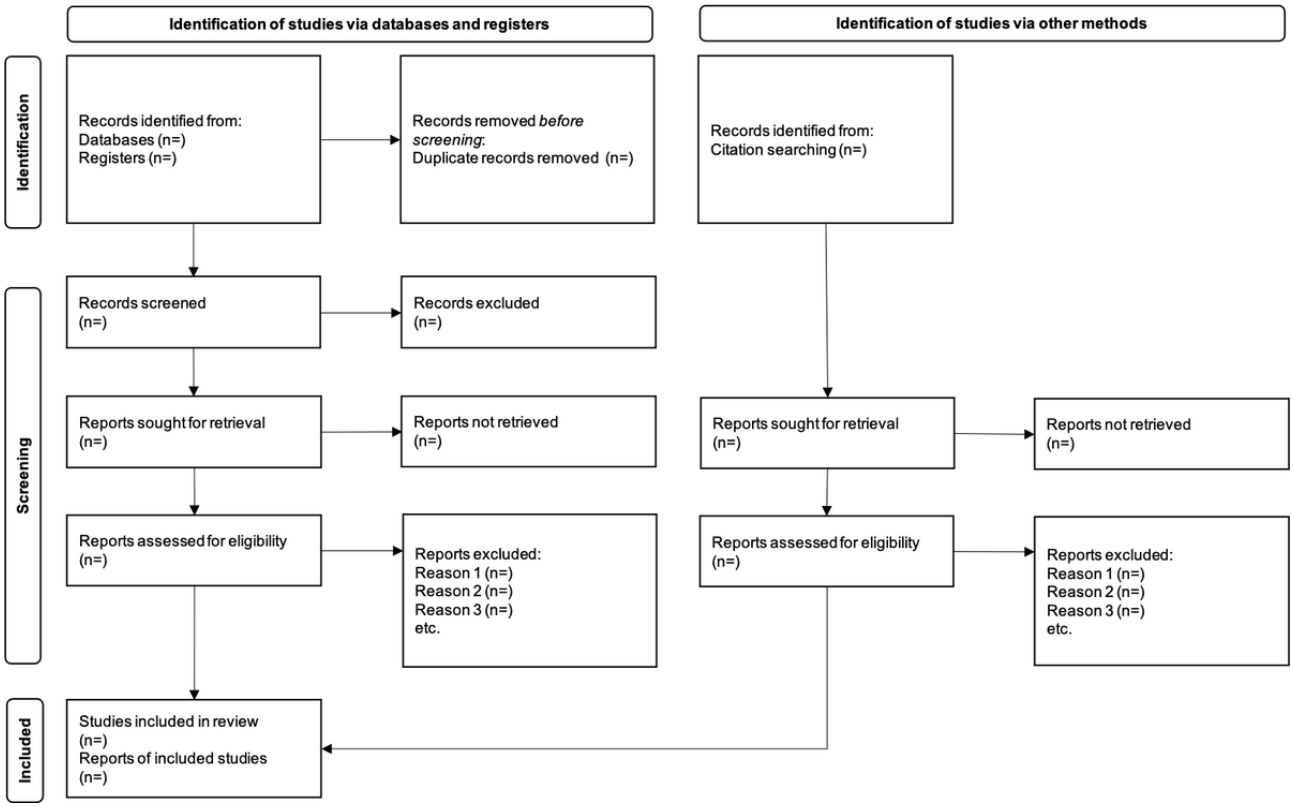
We will perform a comprehensive search to identify any relevant studies that meet our eligibility criteria by using the following electronic databases: PubMed (including MEDLINE), Cochrane Central Register of Controlled Trials, Embase, Cumulative Index to Nursing and Allied Health Literature (ie, CINAHL), and PsycINFO; there will be no restrictions on languages and publication dates. We will search ClinicalTrials.gov (clinicaltrials.gov) and the World Health Organization International Clinical Trials Registry (apps.who.int/trialsearch/) to identify additional ongoing studies. We will develop search strategies for each electronic database addressing the review question. The search strategies will use keywords and controlled vocabulary as follows: participants: *woman*, interventions: *IoT* (eg, *mobile application*, *wearable electronic device*, and *smart device*), and study design: *RCT*. We will also check the reference lists of included reports and relevant systematic reviews to identify additional potential studies. The complete review will report the detailed search strategies for all electronic databases.

Study Selection

We will screen the relevant studies in accordance with the PRISMA guidelines (the PRISMA flow diagram is shown in Figure 1) [44]. First, we will exclude any duplicate studies. Two reviewers will independently screen the titles and abstracts of all the retrieved studies. Furthermore, 2 authors will independently assess the full texts of all potentially eligible studies. The Rayyan tool will be used for screening during the study selection. Any disagreements between reviewers will be resolved through discussion. If an agreement is not reached, we will discuss the issue with a third reviewer to make the final decision. We will also manage the selected studies by using the bibliographic citation management software EndNote X9.

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Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram.



Data Extraction

Two authors will independently extract data from each of the included studies using a predesigned data extraction form using Excel (Microsoft Inc). We will extract data regarding the characteristics of included studies (eg, study setting, participants, interventions, comparisons, study design, and outcome measures, including primary and secondary outcomes). Any discrepancies will be resolved through discussion with a third author. In case of any unclear or missing information, we will contact the authors to collect the relevant data.

Risk of Bias Assessment

Two reviewers will independently assess the risk of bias for each outcome using the Cochrane Collaboration's risk of bias assessment tool 2.0 [45]. We will assess the following domains: those related to the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcomes, and selection of the reported results. The overall risk of bias will be discerned as follows: low risk of bias, some concerns, or high risk of bias [45]. Any disagreement will be resolved through discussion with a third reviewer.

Data Synthesis

We will perform the NMA on age categories (preconception periods, gestational and postpartum periods, and middle-aged women) and medical history (women who have a specific medical condition; eg, cancer or diabetes, and women who do not have them) separately. We will present the network structure of IoT interventions and the estimated direct, indirect, and relative effects for each outcome. First, we will conduct a pairwise meta-analysis using a fixed effects model to estimate the pooled effect size of all direct evidence for each combination of outcomes. In case of considerable heterogeneity, we will use a random effects (DerSimonian and Laird) model. Then, we will perform NMAs for primary and secondary outcomes to compare the individual IoT interventions. For dichotomous variables, we will use risk ratios or odds ratios and the corresponding 95% CIs. For continuous variables, we will calculate the mean difference or standardized mean difference using 95% CIs. If the measurements of intervention effects with regard to each outcome have been reported using different scales, we will use a standardized mean difference and 95% CIs. We will narratively describe the results if studies are insufficient for conducting a meta-analysis. Heterogeneity will be examined using the estimated value of τ and the chi-square test and assessed graphically using horizontal lines in the forest plots for each outcome. Furthermore, heterogeneity will be examined using I^2 statistics, with a value greater than 75% indicating considerable heterogeneity [38]. For pairwise meta-analysis with an adequate number of included studies, publication bias will be tested using funnel plots and the Egger test; for NMA, we will use a comparison-adjusted funnel plot to identify possible-small study effects [46,47]. A surface under the cumulative ranking curve (SUCRA) will be used for ranking probabilities of interventions to identify the most effective intervention. A larger SUCRA value indicates a better rank of intervention [46]. A subgroup analysis for the primary outcome will be performed for the types of IoT (single approach and combination) and types of IoT devices (wearable devices worn on the body and other devices not worn). To assess the robustness of the results, sensitivity analysis will be performed, excluding studies at a high risk of bias.

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Inconsistency Assessment

We will assess any inconsistencies between direct and indirect evidence by using local and global approaches. Regarding the evaluation of global inconsistencies, we will demonstrate the design by using a treatment interaction model and infer the presence of any inconsistency based on a chi-square test. Regarding the evaluation of local inconsistencies, we will use the side-splitting method and assess the disagreement between direct and indirect effects. We will consider a *P* value of <.05 to indicate statistical significance.

Certainty of Evidence Assessment

We will assess the certainty of the evidence for primary outcomes by using the Grades of Recommendation, Assessment, Development and Evaluation method for NMA [48]. We will assess the following factors: risk of bias, inconsistency, indirectness, imprecision, and publication bias; furthermore, we will classify the certainty of evidence as follows: high, moderate, low, or very low. We will also aim to assess the certainty of evidence for each of the direct estimates, indirect estimates, and relative estimates. If only direct or indirect evidence is available for a given comparison, we will consider their ratings as the network ratings. If both types of evidence are available, we will consider the higher ratings of the evidence as the network ratings. We will summarize the results for primary outcomes in a "summary of findings" table (Multimedia Appendix 1) [49].

Results

We aim to conduct our search in January 2023 and are currently discussing search strategies with literature search specialists. We will estimate their relative ranking for women's health outcomes by conducting the NMA. This study is expected to identify the most effective IoT modality in improving women's health outcomes. The final report is planned for submission to a peer-reviewed journal in September 2023.

Discussion

To the best of our knowledge, this will be the first comprehensive systematic review and NMA of RCTs, which aims to assess and synthesize the role of apps and the IoT in improving women's health and to identify the ranking of interventions for ensuring better results among women for each stated outcome. Recently, the number of women with issues and conditions related to their lifestyle habits has been increasing [8]. Problems with lifestyle habits are known to lead to the development of future noncommunicable diseases [7], and improving women's lifestyles will help prevent and improve their common medical conditions. As such, our systematic review's findings will have the potential to influence a large proportion of the population, including women and their subsequent generations. These findings may be of great use to health care providers, policy makers, and others who have an interest in this field. Furthermore, our results can be extensively used in improving the health of women both presently and in subsequent generations.

Acknowledgments

We would like to thank Cochrane Japan for providing their support in our search for relevant studies for our review.

Data Availability

All data generated or analyzed during this study will be included in the full review article and its supplementary information files.

Conflicts of Interest

There are no conflicts of interest to declare. This work is supported by the Japan Agency for Medical Research and Development (22rea522103h0001).

Multimedia Appendix 1
Dummy table of summary of findings.
[DOCX File , 16 KB - resprot_v12i1e45178_app1.docx]

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Abbreviations

IoT: Internet of things
NMA: network meta-analysis
PRISMA-NMA: Preferred Reporting Items for Network Meta-Analyses
PROSPERO: International Prospective Register for Systematic Reviews
RCT: randomized controlled trial
SUCRA: surface under the cumulative ranking curve

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Protocol

The Pharmacoeconomic Impact of Pharmaceutical Care in the Hospital: Protocol for an Overview of Systematic Reviews

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Abstract

Background: The clinical activities developed by pharmacists in a hospital environment can improve health outcomes and generate savings for hospitals. However, to determine whether pharmaceutical interventions are cost effective, it is essential to define a method according to which cost-effectiveness is intended to be measured. In addition, the quality of economic assessments and the amount of information present in systematic reviews in the literature make it difficult to analyze the effects of this intervention.

Objective: This paper aims to provide an overview of systematic reviews on the pharmacoeconomic impact of the performance of pharmaceutical care in hospitals.

Methods: A systematic search of the Cochrane Library databases, PubMed or MEDLINE, LILACS, Scopus, Web of Science, Google Scholar, and Open Thesis will be performed using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement. The search will involve the use of keywords determined using the Medical Subject Headings database to define the search terms and include the following terms: “pharmacoeconomics,” “pharmaceutical care,” and “hospital.” The study designs to be included will be systematic reviews of good quality. Studies will be included that address pharmacoeconomics; studies that evaluated pharmaceutical care in hospitals; and studies published in Portuguese, English, or Spanish. The primary outcome sought in the systematic reviews will be the cost ratio in monetary units and the outcomes in monetary or natural units. The secondary economic outcomes considered will be determined based on factors associated with the drugs and translated into benefit, efficacy, or utility.

Results: It is intended to start this overview in January 2023. Thus far, only previous searches have been carried out to contextualize the theme and build the protocol.

Conclusions: This overview will determine the pharmacoeconomic impact of pharmaceutical care interventions in the hospital environment. In addition, this study will point out which clinical outcomes in natural units are impacted by the performance of pharmaceutical care and the strengths and limitations of each approach. It will also identify gaps in the literature and areas for future work.

Trial Registration: PROSPERO CRD42019140665; https://tinyurl.com/bddwnz43

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KEYWORDS

pharmacoeconomics; pharmaceutical care; hospital; overview; cost-effectiveness; cost benefit; cost-utility

Introduction

Within the scope of pharmacy, clinical pharmaceutical services promoted actions that improve clinical and economic outcomes [1-3]. In clinical practice, pharmaceutical activities focused on patient care are performed in close cooperation with the health team to offer the best patient care. Clinical activities developed by these pharmacists in a hospital environment can minimize medication errors, improve the results of pharmacotherapy, and decrease treatment costs [4-6]. In this sense, research that describes and economically evaluates the provision of pharmaceutical care in hospitals has been identified in the literature since the 1970s [7].

However, to determine whether pharmaceutical interventions are cost effective, it is essential to define a method according to which the intervention is intended to be measured, taking into account the limitations of each step and the potential for generalizing the results to assist in the decision-making process [7,8]. There are 4 basic types of studies related to this issue, which are cost-minimization, cost-benefit, cost-effectiveness, and cost-utility analyses. These analyses differ fundamentally from each other in terms of how health outcomes are measured and compared [1,7].

Pharmacoeconomics has, therefore, emerged as a tool to optimize the use of financial resources for health care without prejudice about the quality of treatment, to reconcile therapeutic needs with the costing possibilities for decision-making, having a crucial role in clinical decisions, management pharmacotherapy, and drug use guidelines [2,9].

It is worth mentioning that several studies, systematic reviews, and meta-analyses have shown that pharmaceutical care generates savings for hospitals and health systems, and pharmaceutical care is one of the strategies to improve patient health outcomes [9-12]. However, there is no information synthesis of the existing information about this service, making it difficult to take the data resources used [13]. Thus, this study is aimed at providing an overview of systematic reviews on the pharmacoeconomic impact of the performance of pharmaceutical care in hospitals [14-16].

Methods

Overview

This study protocol is reported according to the reporting guidelines provided in the Statement of Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) [17]. The review protocol was registered in PROSPERO (CRD42019140665).

Information Sources and Search Strategy

A systematic search of the Cochrane database, PubMed, Medline, LILAC, Scopus, Web of Science, Google Scholar, and Open Thesis will be conducted. The search strategy will use terms from the Medical Subject Headings and Descriptores en Ciencias de la Salud databases, as follows: (pharmacoeconomics); (‘Pharmaceutical economics’) (‘pharmacy economics’); (‘Pharmacy economic’); (‘Pharmaceutical economics’); and (‘Clinical pharmacy services’), (‘clinical pharmacy service’), (‘pharmaceutical care’), (‘pharmacy service, hospital’), (hospital), (hospitals). See Textbox 1 for a detailed search strategy.

Textbox 1. Search strategy—PubMed or Medline (no time limit).

((“economics, pharmaceutical”[MeSH Terms] OR (“economics”[All Fields] AND “pharmaceutical”[All Fields]) OR “pharmaceutical economics”[All Fields] OR “pharmacoeconomics”[All Fields]) OR (“economics, pharmaceutical”[MeSH Terms] OR (“economics”[All Fields] AND “pharmaceutical”[All Fields]) OR “pharmaceutical economics”[All Fields] OR (“pharmaceutical”[All Fields] AND “economics”[All Fields])) OR (“economics, pharmaceutical”[MeSH Terms] OR (“economics”[All Fields] AND “pharmaceutical”[All Fields]) OR “pharmaceutical economics”[All Fields] OR (“pharmacy”[All Fields] AND “economics”[All Fields]) OR “pharmacy economics”[All Fields]) OR (“economics, pharmaceutical”[MeSH Terms] OR (“economics”[All Fields] AND “pharmaceutical”[All Fields]) OR “pharmaceutical economics”[All Fields] OR (“pharmacy”[All Fields] AND “economic”[All Fields]) OR “pharmacy economic”[All Fields]) OR “economics, pharmaceutical”[mesh]) AND ((“pharmacy service, hospital”[MeSH Terms] OR (“pharmacy”[All Fields] AND “service”[All Fields] AND “hospital”[All Fields]) OR “hospital pharmacy service”[All Fields] OR (“clinical”[All Fields] AND “pharmacy”[All Fields] AND “services”[All Fields]) OR “clinical pharmacy services”[All Fields]) OR (“pharmacy service, hospital”[MeSH Terms] OR (“pharmacy”[All Fields] AND “service”[All Fields] AND “hospital”[All Fields]) OR “hospital pharmacy service”[All Fields] OR (“clinical”[All Fields] AND “pharmacy”[All Fields] AND “service”[All Fields]) OR “clinical pharmacy service”[All Fields]) OR “pharmacy service, hospital”[mesh]) AND ((“hospitals”[MeSH Terms] OR “hospitals”[All Fields] OR “hospital”[All Fields]) OR “hospitals”[mesh])

Inclusion Criteria

The eligibility criteria were defined according to the PICO strategy (that is, population, intervention, comparison, and result) with the following variables: (1) pharmacoeconomic studies (cost-minimization, cost-benefit, cost-effectiveness, and cost-utility analyses), (2) studies that evaluated pharmaceutical care in hospitals, and (3) studies published in Portuguese, English, or Spanish.

Exclusion Criteria

Systematic reviews in which the interventions performed by pharmacists in the health team are not distinguishable—(1) overviews; (2) systematic reviews that analyze nonclinical activities, such as medication handling, storage, administration (including vaccines); or (3) other logistical activities—will be excluded.

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Study Design

This study will provide an overview of systematic reviews. The overview seeks to meet the need for evaluating and synthesizing the results of systematic reviews. In addition to optimizing and improving access to information and decision-making, assisting in the synthesis of information for health professionals, managers, researchers, and patients is also crucial [18]. Thus, the following publications obtained from a systematic search of more than one database of literature will be considered: publications that specify the review question, eligibility criteria, and selection of the studies involved; in which data collection was performed by two or more reviewers; in which the risk of bias in the included studies was evaluated; and in which information is synthesized using a quantitative or qualitative approach.

Population of the Included Studies

Studies that included hospitalized patients who were using at least one medication will be considered.

Scenarios of the Included Studies

Studies conducted in hospitals anywhere in the world will be considered as long as they meet the inclusion criteria.

Intervention or Comparison

Studies comparing the clinical results of patients receiving pharmaceutical care services to those of patients for whom there were no pharmacist interventions will be considered.

Outcomes of Interest

The primary result will be the ratio of cost (currency unit) to the outcome (currency unit or natural units, for example, years of life or quality-adjusted life-years). This is usually presented as an outcome. The secondary economic results will be the determinants or factors associated with medications translated into benefits (such as days of hospitalization avoided; days of work that will be lost; and materials, labor, and equipment that could be relocated), effectiveness (in terms of parameters such as years of life gained, lives saved, cholesterol reduction, mmHg of reduced blood pressure, number of cases prevented, time of symptoms, and reduction of recurrence rates), and usefulness (quality-adjusted life-years).

Screening and Selection of Studies

All articles identified in the literature search will be screened by 2 reviewers, regardless of duplicate removal using EndNote (Clarivate Plc). The titles and abstracts of the articles returned from the initial searches will be selected based on the eligibility criteria described above (“Inclusion Criteria”). The full texts will be examined in detail and selected for eligibility. The references of all articles considered will be searched manually to identify any relevant reports lost in the search strategy. Any disagreements will be resolved by discussion, if necessary. A PRISMA flowchart showing details of the included and excluded studies at each stage of the study selection process will be provided.

Data Extraction and Management

A data extraction form will be designed using Google Forms. Google Forms will allow the management of articles and allow authors to collaborate simultaneously. The review team will receive training on how to use Google Forms before the start of the study to ensure the calibration of the forms and methods of data collection. The data to be collected in this overview will be conducted via the items described in Table 1.

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Table 1. Elements for data collection.

Aspects of data collection	Description of key items to be extracted
Research site characteristics of the studies included in the review	• Review objectives • Numbers of studies and patients included • Period chosen to search for studies • Eligibility criteria • Profile of the patients included in the studies • Diagnostics or comorbidities of the patients studied
Hospital characteristics of the studies included in the review	• Size of the hospital characterized by the number of beds and employees • Geographic locations of the primary studies • Any other relevant resources presented in each review about the primary studies
The pharmacoeconomic evaluation method used	Economic: • Cost-benefit • Cost-effectiveness • Cost minimization • Cost utility Humanistic: • Quality of life • Patient preferences • Patient satisfaction
Results of clinical services	• Reduced hospital stay • Hospital readmission • Decrease in adverse drug events • Types of pharmaceutical care • Improvement or worsening of the clinical parameters evaluated

Study Characteristics

The following data will be extracted from the studies selected: name of the first author, study design, year of publication, journal, year (or period) of the study, sample size, scenario, and geographic location of the study, among others. Data relevant to the evaluation of the methodological quality of the studies will be collected.

Methodological Quality Assessment

The evaluation of the methodological quality of systematic reviews will be performed using the Revised Assessment of Multiple Systematic Reviews (R-AMSTAR) instrument. R-AMSTAR is a revised version of AMSTAR, which consists of 11 items with good content validity for measuring the methodological quality of systematic reviews. It is widely accepted and used because of its reliability and reproducibility. Before the start of the assessment, the items that make up the list will be widely discussed, and a manual will be created to guide the interpretation of the R-AMSTAR items to ensure consistency in the analysis.

For the evaluation of systematic reviews, the following items will be considered: conducting a project; the selection of studies and data extraction search in pairs; the scope of the bibliographic research; the analysis of the type of publication (for example, theses, dissertations, and book chapters); the availability of the included and excluded studies; providing the characteristics of the included studies, evaluation, and documentation of the scientific quality of the included studies; the use of the scientific quality of the studies included in the formulation of the conclusions; the suitability of the methods used to combine the findings of the studies; the assessment of the likelihood of publication bias; and the inclusion of conflicts of interest.

Summary of the Data

Data from each study will be used to create tables of evidence for a general description of the included studies. Monetary values will be presented as mean and standard deviation, and natural outcomes will be presented by descriptive methods. We will also establish a model of quality effects to examine how the quality of each study changes the average result. A comparison of the review methods will be performed in terms of the eligibility criteria (ie, criteria used to identify eligible patients, study designs, and end points of interest), details of bibliographic search (ie, dates, databases, main differences in the strategies employed, and taking into account language restrictions), end point definitions used, and rigorous review methods (as reflected by variations in R-AMSTAR assessments and other aspects of the study methodology). The statistical program SPSS version 17.0 (IBM Corp) will be used to calculate the kappa index to verify the agreement in the selection of studies included among the authors, thus decreasing the chance of missing out on a study and the possibility of bias. In addition to the above, the Risk of Bias in Systematic Reviews tool will be used, which assesses both the risk of bias and the relevance of the research question to be answered [19].

Ethics Approval and Dissemination

The review will be performed under “Master's research” approved by the Ethics Committee of the University Hospital of the Federal University of Sergipe (CAAE:

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66439017.3.0000.5546; seem: 2.300.170). The results will be submitted to indexed journals. We will present at national and international meetings.

Results

It is intended to start this protocol in January 2023. Thus far, only previous research has been carried out to contextualize the topic and build the protocol. Our objective is to understand the economic impact of pharmaceutical care performance in hospitals, especially about the ratio between cost (economic unit) and outcome (economic or natural units). We also hope to achieve the following: understand the determinants or factors associated with drugs translated into tools, effort, and utility; support health care policy decision makers to improve the optimization of the treatment of these patients so that it can be replicated in other settings of the health care system; and increase the safety and lives of the patients.

Discussion

This protocol will determine the pharmacoeconomic impact of pharmaceutical care interventions in the hospital environment. In addition, this study will point out which clinical outcomes in natural units are impacted by the performance of pharmaceutical care. Although studies have shown the positive clinical, economic, and human benefits of the interventions of pharmaceutical care for patients and institutions, the subject is not yet exhausted, and the analysis of robust scientific evidence can improve the significance of the results. This study will identify and fill the knowledge gaps in the field [20].

According to De Rijdt et al [21], the economic evaluations of clinical pharmacy services, for the most part, have a series of methodological limitations related to the absence of a control group without pharmaceutical care interventions, the limited scope of costs and results, focus being limited to direct health costs, the exclusion of the cost of employing pharmacists, the use of intermediate outcomes, the exclusion of health benefits, and the absence of incremental cost analysis.

In their assessment of pharmaceutical care, Touchette et al [20] reported that most studies were conducted in hospitals with the most common types of pharmacotherapeutic monitoring and disease management services. The authors highlight the variation in the quality of studies, with less than half being considered good or reasonable [19]. In this sense, it is necessary to better understand the effects of these pharmaceutical interventions, which makes it possible to define strategies to facilitate their implementation and integration in hospital care. Consequently, it is possible to overcome their negative effects and optimize the positive effects to use them to their full potential as a tool to support pharmaceutical care and ultimately improve the results [22].

Any changes made to this protocol during the course of the study will be reported in the final manuscript and reported in PROSPERO. The results will be made public through publication in a peer-reviewed journal. There are several limitations to our planned systematic review. We plan to identify reviews that are indexed in specific databases, which may restrict the inclusion of systematic reviews that are not in the selected databases. Furthermore, there is a limitation related to the language, since the search for manuscripts will be performed in only 3 languages (Portuguese, English, and Spanish).

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Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during this study.

Authors' Contributions

Concept and design of the study were carried out by FJRdA, FVF, CASS, IMdCB, and DdPLJ. FJRdA, MCR, CASS, and ADdOF refined the methodology and used the data extraction tools. FJRdA, FVF, MCR, CASS, and DPdLJ drafted the manuscript. IMdCB, ADdOF, and DPdLJ revised the manuscript critically for content. The final approval of the version to be published was done by FJRdA, FVF, and DPdLJ.

Conflicts of Interest

None declared.

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Abbreviations

PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols

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R-AMSTAR: Revised Assessment of Multiple Systematic Reviews

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Protocol

Fibroblast Activation Protein Overexpression in Gastrointestinal Tumors: Protocol for a Systematic Review and Meta-analysis

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Abstract

Background: A hallmark of gastrointestinal cancer, especially pancreatic cancer, is the dense stromal tumor microenvironment in which cancer-associated fibroblasts (CAFs) represent the major stromal cell type. Preclinical studies have demonstrated that depletion of fibroblast activation protein (FAP)–positive CAFs results in increased survival.

Objective: We present the protocol for a systematic review and meta-analysis that aim to assess the currently available evidence on the effect of FAP expression on survival and clinical characteristics in gastrointestinal cancers.

Methods: The literature search and data analysis will be conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 statement. The databases PubMed/MEDLINE, Web of Science Core Collection, Cochrane Library, and ClinicalTrials.gov will be searched via their respective online search engines. A meta-analysis comparing patients with and without FAP overexpression with the following outcomes will be performed: postoperative survival (overall and median survival; 1-, 2-, 3-, and 5-year survival rates), histological differentiation (grading), local tumor invasion, lymph node metastases, and distant metastases. Odds ratios will be calculated for binary data, and weighted mean differences and relative SD differences will be determined for continuous data. The 95% CI, heterogeneity measures, and statistical significance will be reported for each outcome. The chi-square and Kruskal-Wallis tests will be used to evaluate statistical significance. A *P* value of <.05 will be considered statistically significant.

Results: Database searches will commence in April 2023. The meta-analysis will be completed by December 2023.

Conclusions: In recent years, several publications on FAP overexpression in gastrointestinal tumors have been published. The only published meta-analysis on this topic dates to 2015. It included 15 studies on various solid tumors and only 8 studies focusing exclusively on gastrointestinal tumors. The expected results of the present analysis will provide new evidence on the prognostic value of FAP in gastrointestinal tumors and thereby support health care professionals and patients in their decision-making.

Trial Registration: PROSPERO CRD42022372194; https://tinyurl.com/352ae8b8

International Registered Report Identifier (IRRID): PRR1-10.2196/45176

(JMIR Res Protoc 2023;12:e45176) doi:10.2196/45176

KEYWORDS

fibroblast activation protein; cancer-associated fibroblasts; survival; fibroblast; protein; gastrointestinal; GI; gastrointestinal tumor; cancer; oncology; review method; systematic review; meta-analysis; meta-analyses; cell biology; proteomic

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Introduction

Cancers of the gastrointestinal (GI) tract include colorectal, esophageal, liver, pancreas, and stomach cancer. These 5 major types of GI cancer represented 26% of the global cancer incidence and 35% of all cancer-related deaths in 2018 [1]. A hallmark of GI cancers, especially pancreatic cancer, is the dense stromal tumor microenvironment where cancer-associated fibroblasts (CAFs) represent the major stromal cell type [2]. CAFs reprogram the immune microenvironment and promote cancer proliferation, migration, invasion, and metastasis [3,4]. To that end, depleting CAFs has been considered a promising therapeutic strategy for patients with GI cancer. However, in a preclinical pancreatic cancer mouse model, depletion of the major CAF marker α–smooth muscle actin (α-SMA)–positive cells led to invasive, undifferentiated tumors and reduced animal survival [5]. Thus, targeting CAFs may also have tumor-promoting effects due to their functional heterogeneity. Therefore, identification and specific targeting of tumor-promoting CAF subtypes and markers are emerging strategies [6]. CAFs represent highly heterogeneous subpopulations with different functions, which can be both tumor promoting and tumor restraining [7]. To identify and characterize CAF subtypes, a number of markers have been identified, such as desmin, fibroblast activation protein (FAP), fibroblast-specific protein, podoplanin, α-SMA, and vimentin [8,9].

FAP is a type II transmembrane serine protease, which shares a high-sequence identity with dipeptidyl peptidase 4 [10]. In most adult tissues, expression of FAP is low to undetectable. FAP expression becomes highly upregulated in multiple types of cancer, and it is predominantly observed in CAFs [11]. In a preclinical study, it was shown that FAP activates macrophages and promotes liver inflammation and fibrosis [12]. FAP plays a key role in promoting tumor progression and metastasis, further shaping the immunosuppressive tumor microenvironment [13]. Other preclinical studies have demonstrated that pharmacological inhibition or deletion of FAP-positive CAFs results in the attenuation of tumor growth and increased survival in pancreatic cancer models [14,15]. A recent study further consistently showed that tumor-promoting FAP-positive CAFs and tumor-restraining α-SMA–positive CAFs regulate signaling pathways differently [15].

To assess the currently available evidence on the effect of FAP expression on survival and clinical characteristics in GI cancers, we plan to conduct a systematic review and meta-analysis. With this research protocol, we further aim to achieve reproducibility and transparency of our meta-analysis on the published literature as previously demonstrated [16,17].

Methods

The literature search and data analysis will be conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 statement [18]. The study has been registered in the PROSPERO (International Prospective Register of Systematic Reviews) database (CRD42022372194) [19].

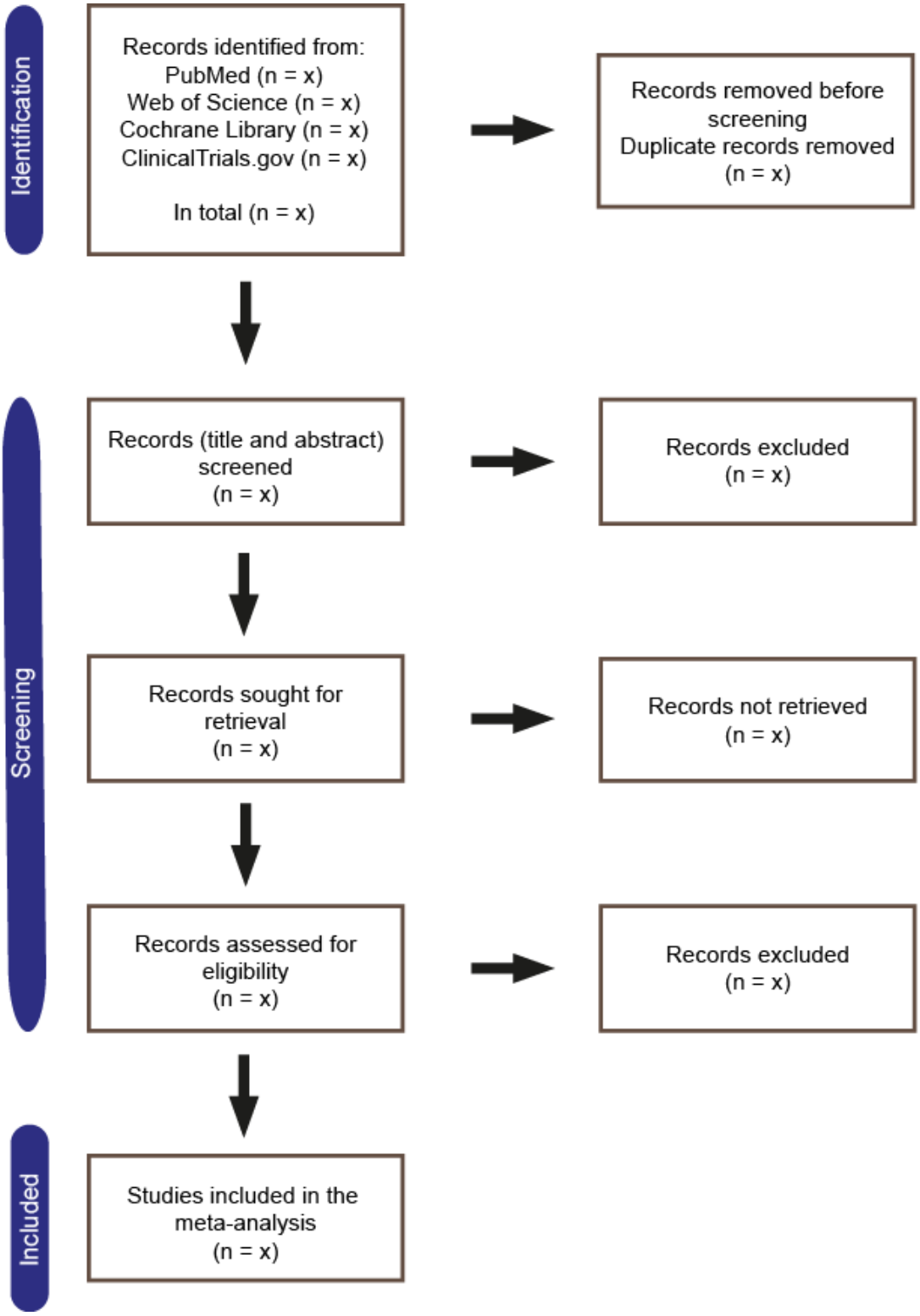
Search Strategy

The databases PubMed/MEDLINE, Web of Science Core Collection, Cochrane Library, and ClinicalTrials.gov will be searched via their respective online search engines. Citavi 6 (Swiss Academic Software GmbH) will be used as an automatic deduplication system for the studies retrieved from the various databases (Figure 1). The search will be performed on studies published between database inception and a defined search date. The search strategies used in each database are displayed in Table 1.

Titles and abstracts will be evaluated independently in a standardized manner by 2 authors to assess eligibility for inclusion or exclusion. All the potential studies identified from the search will be coded as either “retrieve” (eligible, potentially eligible, or unclear) or “do not retrieve.” For studies coded “retrieve,” 2 reviewers will independently screen the full text and recommend inclusion or exclusion. Disagreements between the reviewers will be resolved by consensus; if no agreement can be reached, a third reviewer will decide whether to include the respective study. The reference lists of the included studies will be manually searched to find additional relevant articles.

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Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart.



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Table 1. Search strategy.

Database	Search strategy
PubMed/MEDLINE	“surface expressed protease”[tw] OR “seprase”[tw] OR “FAPalpha”[tw] OR “fibroblast activation protein-alpha”[tw] OR “FAP protein”[tw] OR “fibroblast-activating protein”[tw] OR “fibroblast proliferation factor”[tw] OR “fibroblast activation protein, alpha”[tw] OR “fibroblast activation protein”[tw] OR “seprase protein”[tw] AND “neoplasms”[Mesh]
Web of Science Core Collection (all fields)	(“surface expressed protease” OR “seprase” OR “FAPalpha” OR “fibroblast activation protein-alpha” OR “FAP protein” OR “fibroblast-activating protein” OR “fibroblast proliferation factor” OR “fibroblast activation protein, alpha” OR “fibroblast activation protein” OR “seprase protein”) AND (“tumor” OR “neoplasm” OR “tumors” OR “neoplasia” OR “neoplasias” OR “cancer” OR “cancers” OR “malignant neoplasm” OR “malignancy” OR “malignancies” OR “malignant neoplasms” OR “neoplasm, malignant” OR “neoplasms, malignant”)
Cochrane Library (title, abstract, keyword)	(“surface expressed protease” OR “seprase” OR “FAPalpha” OR “fibroblast activation protein-alpha” OR “FAP protein” OR “fibroblast-activating protein” OR “fibroblast proliferation factor” OR “fibroblast activation protein, alpha” OR “fibroblast activation protein” OR “seprase protein”) AND (“tumor” OR “neoplasm” OR “tumors” OR “neoplasia” OR “neoplasias” OR “cancer” OR “cancers” OR “malignant neoplasm” OR “malignancy” OR “malignancies” OR “malignant neoplasms” OR “neoplasm, malignant” OR “neoplasms, malignant”)
ClinicalTrials.gov	*Condition or disease:* Neoplasms *Other terms:* “surface expressed protease” OR “seprase” OR “FAPalpha” OR “fibroblast activation protein-alpha” OR “FAP protein” OR “fibroblast-activating protein” OR “fibroblast proliferation factor” OR “fibroblast activation protein”

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Inclusion and Exclusion Criteria

Only articles in the English language will be considered. Studies comparing patients with and without FAP overexpression in GI tumors and reporting on at least one of the following a priori defined outcomes will be included: postoperative survival (overall and median survival; 1-, 2-, 3-, and 5-year survival rates), histological differentiation (grading), local tumor invasion (as defined in the included studies), lymph node metastases, and distant metastases. Review articles, case reports, case series with less than 5 patients, commentaries, and letters will not be included (Table 2). Details of the study selection process will be summarized in a flowchart according to the recommendations of the PRISMA 2020 statement (Figure 1).

Table 2. Inclusion and exclusion criteria.

	Inclusion criteria	Exclusion criteria
Article or study type	• Comparative observational studies • Randomized controlled trials	• Reviews • Case reports • Case series with less than 5 patients • Commentaries • Letters
Study population	• Patients with gastrointestinal tumors in which fibroblast activation protein expression was measured	• Other patients
Reported outcomes	Any of the following: • Median overall survival • 1-, 2-, 3-, or 5-year survival • Histological differentiation (grading) • Local tumor invasion • Lymph node metastases • Distant metastases	• None of the outcomes mentioned as inclusion criteria
Language	• English	• Other languages

Data Collection

Data from the included studies will be extracted separately by 2 authors and stored in a dedicated database. The following descriptive data will be documented for each selected study: first author, year of publication, inclusion period of the study, country and city where the study was conducted, sample size, and mean or median follow-up time. The distribution of the following patient characteristics will be documented: tumor type, histopathological tumor stage (using the UICC [Union for International Cancer Control] TNMG [tumor, node, metastasis, grade] classification system), presence and type of neoadjuvant therapy, presence and type of adjuvant therapy, FAP detection method, FAP antibody, FAP location, number of FAP-positive cases, and cutoff for overexpression.

The following predefined outcomes will be extracted: postoperative survival (overall and median survival, 1-, 2-, 3-, and 5-year survival rates), histological differentiation (grading), local tumor invasion (as defined in the included studies), lymph node metastases, and distant metastases. Subgroup analysis will be performed for location of FAP expression (tumor stroma or tumor cells or both) and tumor type (colon cancer, esophageal cancer, gastric cancer, hepatocellular carcinoma, cholangiocellular carcinoma, pancreatic cancer, and rectal cancer).

For each observational study, the risk of bias will be assessed using the ROBINS-I (Risk of Bias in Non-randomized Studies of Interventions) tool suggested by the Cochrane Collaboration [20]. For randomized controlled trials, the RoB 2 (Risk of Bias 2), the Cochrane risk-of-bias tool for randomized trials, will be used [21].

Statistical Analysis

A meta-analysis comparing patients with and without FAP overexpression with the following outcomes will be performed: postoperative survival (overall and median survival, 1-, 2-, 3-, and 5-year survival rates), histological differentiation (grading), local tumor invasion (as defined in the included studies), lymph node metastases, and distant metastases. Random-effects models will be used. The ReviewManager (RevMan) software (version 5.4; Cochrane Collaboration) will be used. The magnitude of the effect estimate will be visualized by forest plots. Odds ratios will be calculated for binary data, and weighted mean differences and relative SD differences will be determined for continuous data. The 95% CI, heterogeneity, and statistical significance will be reported for each outcome. The chi-square and Kruskal-Wallis tests will be used to evaluate statistical significance. A P value of <.05 will be considered statistically significant. If studies do not report mean and SD, these will be calculated using the methods described by Cochrane Collaboration guidelines [22] and Hozo et al [23].

Sensitivity analyses will be conducted according to the ascertained risk of bias as described above. For these, all studies with a high or serious risk of bias will be excluded, and the analyses of the outcomes, as described above, will be conducted.

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Results

Database searches will commence in April 2023. Extraction of data from individual studies will be performed by May 2023. Data appraisal, preparation, summarization, and analysis will start in June 2023. The meta-analysis will be completed by December 2023.

Discussion

This systematic review and meta-analysis will synthesize all available evidence on the clinical implications of FAP overexpression in GI tumors.

In recent years, several studies on this topic have been published. The last published meta-analysis on this topic dates to 2015 and included 15 studies about various solid tumors and only 8 studies focusing exclusively on GI tumors [24].

The main limitation of the present meta-analysis is that we do not expect randomized controlled trials on this topic to be available. Nevertheless, to ensure transparency and reduce the risk of bias, this review will be conducted according to the defined protocol presented here and will be reported following the recommendations stipulated in the PRISMA 2020 statement [18].

The expected results will provide new information on the prognostic value of FAP in GI tumors and thereby support health care professionals and patients in their decision-making, as well as aid in patient selection for multimodal cancer therapy.

Data Availability

The data sets generated during this study will be available from the corresponding author upon request.

Conflicts of Interest

None declared.

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Abbreviations

α-SMA: α–smooth muscle actin
CAF: cancer-associated fibroblast
FAP: fibroblast activation protein
GI: gastrointestinal
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO: International Prospective Register of Systematic Reviews
RoB 2: Risk of Bias 2
ROBIN-I: Risk of Bias in Non-randomized Studies of Interventions
TNMG: tumor, node, metastasis, grade
UICC: Union for International Cancer Control

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Protocol

The Inflammatory Biomarkers Behavior Profile of Patients Following Elective Degenerative Spine Surgery and Differences Compared to Those Coursing With a Postoperative Spinal Infection: Protocol for a Systematic Review

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Abstract

Background: The incidence of postoperative spinal infection (PSI) ranges from 0% to 10%, with devastating effects on the patient prognosis because of higher morbidity while increasing costs to the health care system. PSIs are elusive and difficult to diagnose, especially in the early postoperative state, because of confusing clinical symptoms, rise in serum biomarkers, or imaging studies. Current research on diagnosis has focused on serum biomarkers; nevertheless, most series rely on retrospective cohorts where biomarkers are studied individually and at different time points.

Objective: This paper presents the protocol for a systematic review that aims to determine the inflammatory biomarker behavior profile of patients following elective degenerative spine surgery and their differences compared to those coursing with PSIs.

Methods: The proposed systematic review will follow the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement. This protocol was registered at PROSPERO on January 19, 2022. We will include studies related to biomarkers in adult patients operated on for degenerative spinal diseases and those developing PSIs. The following information will be extracted from the papers: (1) study title; (2) study author; (3) year; (4) evidence level; (5) research type; (6) diagnosis group (elective postoperative degenerative disease or PSI); (7a) region (cervical, thoracic, lumbosacral, and coccygeal); (7b) type of infection by anatomical or radiological site; (8) surgery type (including instrumentation or not); (9) number of cases; (10) mean age or individual age; (11) individual serum biomarker values from the preoperative state up to 90 days postoperative for both groups, including (10a) interleukin-6, (10b) presepsin, (10c) erythrocyte sedimentation rate, (10d) leukocyte count, (10e) neutrophil count, (10f) C-reactive protein, (10g) serum amyloid, (10h) white cell count, (10i) albumin, (10j) prealbumin, (10k) procalcitonin, (10l) retinol-associated protein, and (10m) Dickkopf-1; (11) postoperative days at symptoms or diagnosis; (12) type of organism; (13) day of starting antibiotics; (14) duration of treatment; and (15) any biases (including comorbidities, especially those affecting immunological status). All data on biomarkers will be presented graphically over time.

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Results: No ethical approval will be required, as this review is based on published data and does not involve interaction with human participants. The search for this systematic review commenced in February 2021, and we expect to publish the findings in mid-2023.

Conclusions: This study will provide the behavior profile of biomarkers for PSI and patients following elective surgery for degenerative spinal diseases from the preoperative period up to 90 days postoperative, providing cutoff values on the day of diagnosis. This research will provide clinicians with highly trustable cutoff reference values for PSI diagnosis. Finally, we expect to provide a basis for future research on biomarkers that help diagnose more accurately and in a timely manner in the early stages of illness, ultimately impacting the patient's physical and mental health, and reducing the disease burden.

Trial Registration: PROSPERO CRD42022304645; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=304645

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KEYWORDS

biomarker behavior profile; biomarkers; C-reactive protein; degenerative spinal diseases; Dickkopf-1; erythrocyte sedimentation rate; inflammatory biomarker; inflammatory disease; neuroscience; postoperative spinal infection; procalcitonin; serum biomarkers; spinal infection; spinal surgical site infection; spine surgery; review; systematic review

Introduction

Overview

The incidence of postoperative spinal infection (PSI) ranges from 0% to 10% depending on several factors related to the patient, the surgical intervention [1], and conditions of the health care system. PSI, otherwise called surgical site infection, has devastating effects on the patient prognosis because of higher morbidity [2] and mortality while increasing costs to the health care system [3]. PSI accounts for half of the readmissions following spinal surgery [3] and increases the cost of health care from US $150,000-$200,000 [4,5] per patient. Spinal infections affect the patient's physical and mental health but also the health care system and the society by increasing the burden of economic cost and even indirect expenditures such as absence from work that will affect the patient's capability to afford its treatment, making this a negative circle of factors that will ultimately affect the patient's quality of life [6].

PSI occurs either by direct inoculation during surgery, by the incursion of skin pathogens through the skin incision [7], or because of hematogenous spread [8] where *Staphylococcus aureus* and *Escherichia coli* are the pathogens most frequently involved. Multiple studies have determined the clinical factors involved in the genesis of PSI, including diabetes, coronary artery disease, traumatic injuries, male gender, age >60 years, BMI>35, smoking, malnutrition, a score >3 in the American Society Anesthesiologist, a posterior approach, spinal fusion, prolonged surgical time, multilevel surgery, and transfusion [9-15]. Unfortunately, most patients requiring spinal surgery have these conditions, where multiple comorbidities increase the burden [16]. Therefore, preoperative evaluation and management of any preventable risk factor are of utmost importance to prevent PSI, which can lead to significant morbidity, sepsis, and even death [17].

PSIs require a high level of suspicion as they are difficult to diagnose [18], especially in the early postoperative state, because of many confounding factors. The mainstay for diagnosing de novo spine infection is a triad of clinical symptoms, serum tests (biomarkers and blood cultures), and correlative imaging [19]. All these 3 parameters are affected in PSI, as clinical symptoms (usually pain) can be attributed to postoperative pain and muscle contracture, rise in serum biomarkers can be explained by inflammatory changes or conditions associated with surgery, and early postoperative imaging studies such as simple or enhanced MRI cannot distinguish between these entities clearly as postoperative changes are not so different [18-20]. These situations lead us to rely on blood cultures [20] that often take 5 days to offer accurate results with high false negative rates, ultimately requiring reintervention with tissue sample as the last step in the diagnosis, where under challenging cases it is not infrequent to repeat the diagnostic protocol because of negative results on biopsy or failed response to medical treatment.

Current research has focused on serum biomarkers to detect spinal infection at the early stages of disease [21,22]; nevertheless, most rely on retrospective cohorts or case series and a scarcity of prospective cohorts. Adding to this problem is that serum biomarkers are studied individually and at different time points while having a heterogenous group of patients who had undergone spinal surgery because of a diversity of spine affections treated with different surgical procedures. Therefore, this protocol aims to collect all the available information currently investigated related to biomarkers and PSI and elective surgery for degenerative spinal disease in order to provide the biomarkers' behavior profile from the preoperative day up to postoperative day 90 to guide differential diagnosis based on cutoff values among these groups.

We made a simple revision on PubMed before proceeding to the protocol and systematic review to look in advance for any research of this type, finding no similar review on biomarkers in current literature.

Objective

This systematic review aims to determine the behavior profile of inflammatory biomarkers among patients following elective degenerative spine surgery and their differences compared to those coursing with PSI.

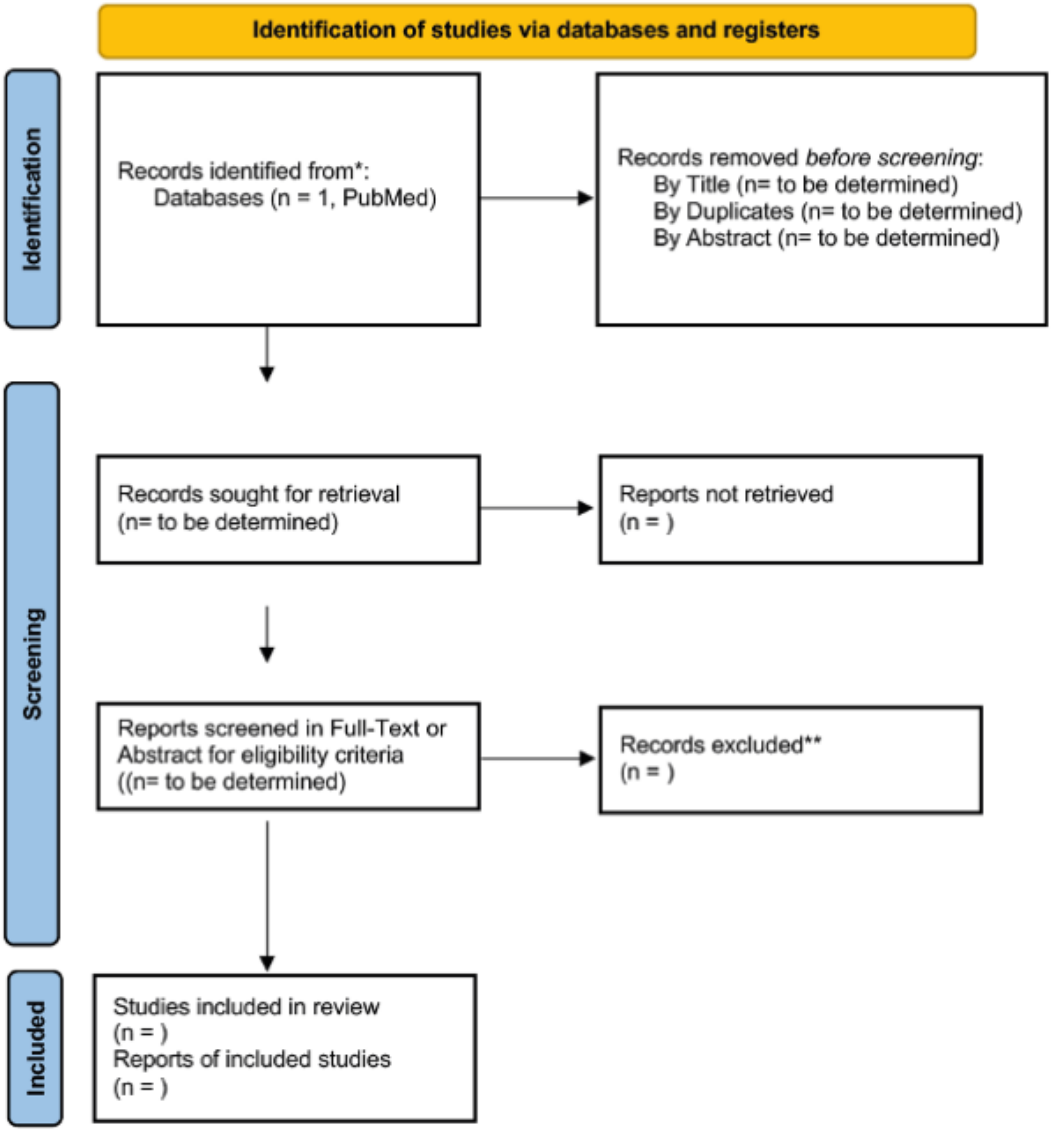
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Methods

Overview

The proposed systematic review will follow the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement [23]. This protocol was registered on PROSPERO on January 19, 2022, with registration number CRD42022304645 (February 19, 2022). Figure 1 presents the flow diagram of the methodology.

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram.



Search Strategy

The search strategy will aim to locate all published studies on biomarker evaluation among patients following elective degenerative spine surgery and their differences with those coursing with PSI. An initial search was made on the PubMed database to identify if there was any other review on the topic that would reunite all biomarkers in a single study, finding no one. We will use the PubMed, Embase, and Latindex databases to search among titles and abstracts for the specific word search criteria from 1984 to the present.

Keyword criteria included "Postoperative spinal infection" and a combination of either one of the following: "Biomarker," "Marker," "Detection," "C Reactive Protein," "CRP," "Erythrocyte Sedimentation Rate," "ESR," "Procalcitonin," "PCT," "Retinol Binding Protein," "Albumin," "Prealbumin," "Transferrin," "Neutrophil/Lymphocyte Count," "Neutrophil," "Lymphocyte," "Dickkopf1," and "DKK1." Multimedia Appendix 1 shows the full search strategy for PubMed in detail. We will include papers predominantly in English and other languages where information is readily available.

Review Question and Keywords

Our review question is as follows: What is the behavior profile of inflammatory biomarkers among patients following elective degenerative spine surgery and their differences from those coursing with a PSI?

Keyword criteria included the following: "Postoperative spinal infection" and a combination of either one of the following: "Biomarker," "Marker," "Detection," "C Reactive Protein," "CRP," "Erythrocyte Sedimentation Rate," "ESR," "Procalcitonin," "PCT," "Retinol Binding Protein," "Albumin,"

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"Prealbumin," "Transferrin," "Neutrophil/Lymphocyte Count," "Neutrophil," "Lymphocyte," "Dickopf1," and "DKK1" from January 1, 1984, to June 4, 2022. Multimedia Appendix 1 shows the full search strategy for PubMed in detail. We will include papers predominantly in English and other languages where information is readily available.

Inclusion Criteria

Participants

We will include studies with adult patients (>15 years old), studies related to biomarkers in patients operated on for degenerative spinal diseases, and those developing a PSI, and studies with raw data and means. We will exclude all studies of pediatric patients (<15 years old) and patients operated on for any other etiology such as tumors, trauma, congenital diseases, and so on, and studies where the biomarker parameters could not be obtained within the text, figures, or tables.

Concept

The concept is to gather all the information related to the inflammatory biomarker's behavior profiles among patients following elective degenerative spine surgery and their differences with those coursing from PSI in the perioperative period, the early postoperative period (in hospital) up to 90 days (most agreed time limit to consider an early spinal infection). This information will help us draw a profile curve for biomarkers and each group of patients, aiding in differential diagnosis among them.

Context

Types of Sources

The review will be limited to Evidence Level IV and above (case series, case-control studies, retrospective, prospective cohorts, randomized and nonrandomized clinical trials, and previous systematic reviews, if any). We will not include editorials, individual case reports, or experimental, nonhuman, or nonclinical studies.

Information Sources

We will only conduct this systematic review in the PubMed, Embase, and Latindex databases.

Study and Source of Evidence Selection

We will collect the full search strategy results in Excel. At this point, the first author (RRJAI) and the second author (FJP) will make the first exclusion process based on titles and duplicates. Later, they will make the second exclusion process based on abstracts. Next, all papers that will require full-text reading will be handled in Mendeley; both authors will read them independently for inclusion criteria; in case of disagreement, we will include papers after a joint decision with the third author (RMWC). Then, the former author will perform the data extraction, and the second author will verify this process; we will also solve any disagreement in a joint decision with the third author. Next, we will record the reasons for exclusion in Excel. Finally, we will report the full results of the search in the final paper and present it using the PRISMA checklist.

Data Extraction

The first author will perform data extraction manually, and the second author will verify this process. The following information will be extracted from the papers: (1) study title; (2) study author; (3) year; (4) evidence level; (5) research type; (6) diagnosis group (elective postoperative degenerative disease or PSI); (7a) region (cervical, thoracic, lumbosacral, and coccigeal); (7b) type of infection by anatomical or radiological site; (8) surgery type (including instrumentation or not); (9) number of cases; (10) mean age or individual age; (11) individual serum biomarker values from the preoperative state, postoperative day 1 up to 90 days for both groups and also at day of diagnosis (within the 90 postoperative days) for the PSI group including (10a) interleukin-6 (IL-6), (10b) presepsin (PSP), (10c) erythrocyte sedimentation rate (ESR), (10d) leukocyte count, (10e) neutrophil count, (10f) C-reactive protein (CRP), (10g) serum amyloid, (10h) white cell count (WCC), (10i) albumin (Alb), (10j) prealbumin, (10k) procalcitonin (PCT), (10l) retinol-associated protein, and (10m) Dickkopf-1 (DKK1); (11) postoperative days at symptoms or diagnosis; (12) type of organism; (13) day of starting antibiotics; (14) duration of treatment; and (15) any biases (including comorbidities, especially those affecting immunological status).

We will modify the proposed data extraction schema as needed. We will detail any modifications in the full review report. We will solve any disagreements between the reviewers through discussion with the third author.

Data Analysis and Presentation

We will present the extracted data in a tabular form and as a narrative summary as required. The table will report the following variables: (2) study author; (3) year; (4) evidence level; (5) research type; (6) diagnosis group; (7a) region (cervical, thoracic, lumbosacral, coccigeal); (7b) type of infection by anatomical or radiological site; (8) surgery type (including instrumentation or not); (9) number of cases; (10) mean age or individual age; (11) postoperative days at symptoms or diagnosis; (12) type of organism; (13) day of starting antibiotics; (14) duration of treatment; and (15) any biases (including comorbidities, especially those affecting immunological status).

We will use graphical representations for the following variables to compare the behavior profile of each biomarker concerning time from the preoperative state up to 90 days postoperative among the 2 groups (elective postoperative spine degenerative disease vs PSI): (10a) IL-6, (10b) PSP, (10c) ESR, (10d) leukocyte count, (10e) neutrophil count, (10f) CRP, (10g) serum amyloid, (10h) WCC, (10i) Alb, (10j) prealbumin, (10k) PCT, (10l) retinol-associated protein, and (10m) DKK1.

Results

No ethical approval will be required, as this review is based on published data and does not involve interaction with human participants. The search for this systematic review commenced in February 2021, and we expect to publish the findings in mid-2023. The plan for dissemination, however, is to publish the review's findings in a peer-reviewed journal and present

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findings at high-level international conferences to share knowledge to help establish more timely and accurate diagnoses to benefit patients.

Discussion

Overview

PSI is an elusive illness that can be challenging to demonstrate even in the context of advanced laboratory and imaging diagnostic studies [24,25]. Early diagnosis aids in achieving a good prognosis and contains the devastating consequences of spinal infections, reducing morbidity and health care costs [26,27]. Current research is focused on the behavior of serum biomarkers in the early postoperative period [17], where the white blood cell count, CRP, ESR, serum amyloid A, and PCT have been established as the conventional biomarkers [24]. Research for these biomarkers, as well as other new ones, relies primarily on retrospective cohorts on a single-measurement basis [11,22,28-32] with few prospective studies performed up to date [17,24,29], representing a significant limitation in the validity of results. Although several biomarkers exist in current research, they are studied individually [17] for a heterogenous group of illnesses in the spectrum of spinal infection with patients undergoing different surgical procedures [17]. As a result, cutoff values to determine abnormal inflammatory biomarker response in the postoperative period are lacking and vary widely depending on the severity of the illness [17] and the extent of the surgical procedure [33].

To have a point of comparison, we will summarize key findings in each of the biomarkers studied up to date. The acute-phase CRP is the biomarker most studied in the scientific literature related to spinal infections due to its availability and feasibility in clinical practice [34]. Its serum concentrations have served to diagnose spinal infection, monitor response to treatment, and detect relapse [34]. The difficulty in using it to detect PSI is having a trustable cutoff value for the inflammatory response expected from the surgical procedure itself [34], which depends on the extent of the procedure [33] and the severity of the illness [17]. Although no clear cutoff values can be drawn from the conclusion of the research and there exist contrasting evidence, it seems that CRP rises in the second and third postoperative day of noninfected patients, lowering its concentrations thereafter; this rise is dependent on the extent of surgery, but the behavior is similar for both of them [34]. As a result, secondary rises [32] or persistently high CRP serum concentrations beyond this period are suspicious of PSI, specifically after postoperative day 7 [35,36]. Nevertheless, these findings can derive from other noninfectious conditions in the postoperative period or have no obvious explanation [32]. Provided that CPR is most sensitive but not that specific (100% and 91.7%), other biomarkers such as PCT have demonstrated remarkable usefulness in differentiating inflammatory response as a result of surgery from that of spinal infection (100% specificity and 95.2% specificity) [37] provided that PCT does not seem to be affected because of the extent of surgery and rises in the first postoperative day remaining steadily low there forward [37]; unfortunately, it does not differentiate infection in other anatomical regions and there also exists evidence reporting no difference in PCT concentration among patients with and without postoperatory spinal infections [38], adding to the lack of a clear cutoff value to consider infection. The neutrophil-to-lymphocyte ratio is another marker that has constantly demonstrated diagnostic usefulness in the early postoperative period, with reported cutoff values ranging from 3.21 to 3.87 for differentiating postoperatory state from a spinal infection; however, this information is based on retrospective cohorts [25,38]. Finally, many other biomarkers, such as IL-6, retinol-binding protein, prealbumin, and PSP, among others, have been studied with contradictory evidence and no clear practical usefulness [1,11,22,24]. The expression of DKK1 has been recently evaluated in the context of osteomyelitis [39] and infectious processes [40-42] but as far as we know, there exist no reports of spinal infections. We include this marker in the systematic review to confirm that there exist no previous studies in this respect as to establish a starting point for a research line in this direction. We consider DKK1 a valuable marker to be investigated provided that its expression affects bone repair after damage by the Wnt/β-catenin molecular signaling pathway for osteoclast and osteoblast induction, where DKK1 functions as an inhibitory factor (that can be induced by infections), therefore impeding bone renewal [40]. By the relationship DKK1 has with infections and impeding bone repair after damage (such as a surgical insult), we consider it an important factor to be investigated in the context of postoperatory spinal infection.

Therefore, this protocol aims to direct many of these limitations found in previous research. We expect to reunite all the information gathered from previous retrospective and prospective series to provide results based on a large sample. Simultaneously, we expect to obtain the mean serum concentrations for different biomarkers over time from the preoperative period up to the postoperative day 90 by extracting data from different series with different time approaches. By using these 2 strategies, we aim to draw time-dependent behavior profiles for each of the biomarkers to have a robust reference of average values and confidence intervals in the postoperative period and abnormal cutoff values and ranges for PSI. Also, we expect to be able to draw specific cutoff values for the different surgical procedures performed; nevertheless, this objective will be ultimately dependent on finding an appropriate surgical procedure description and the sample size obtained from the included studies. We consider that our findings will help clinicians and surgeons make more evidence-based timely decisions that benefit the patients with early treatment, avoiding long-term complications and increases in health care costs with the ultimate impact on morbidity, disability, and mortality. Additionally, our study will be the first and more robust research in this respect by relating all the biomarkers that have shown utility in the diagnosis of spinal infection on a single systematic review taking into consideration the full perioperative period and the different surgical techniques employed.

Finally, there are also limitations to consider in our research. For example, several studies have an incomplete reporting of results due to data gathering bias, such as a lack of protocol for taking blood samples derived from retrospective research. Also,

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some retrospective and prospective studies that evaluate biomarkers have directness biases as they are evaluated as a secondary objective that impacts outcomes, prognosis, or are considered among different risk factors. Nevertheless, these limitations are unavoidable based on the available literature.

Conclusions

In conclusion, this study will provide the biomarkers' behavior profile for PSI and patients following elective surgery for degenerative spinal diseases from the preoperative period up to 90 days postoperative and provide cutoff values on the day of diagnosis. Our research will hopefully aid in the differential diagnosis of these groups early by summarizing all research done in this respect. It will eventually provide clinicians with a better background to establish their diagnosis based on highly trustable information based on cutoff values from this systematic review. Shortly, we also expect this review to provide a basis for more robust prospective studies and even clinical trials on biomarkers to establish a more accurate and timely diagnosis of the early stages of the disease, which will ultimately impact the patient's physical and mental health, reducing the burden of disease.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PubMed search strategy.
[XLSX File (Microsoft Excel File), 56 KB - resprot_v12i1e41555_app1.xlsx]

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Abbreviations

Alb: albumin
CRP: C-reactive protein
DKK1: Dickkopf-1
ESR: erythrocyte sedimentation rate
IL-6: interleukin-6
PCT: procalcitonin
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSI: postoperative spinal infection
PSP: presepsin
WCC: white cell count

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Protocol

Adoption of mHealth Technologies by Community Health Workers to Improve the Use of Maternal Health Services in Sub-Saharan Africa: Protocol for a Mixed Method Systematic Review

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Abstract

Background: Studies have shown that mobile health technologies (mHealth) enhance the use of maternal health services. However, there is limited evidence of the impact of mHealth use by community health workers (CHWs) on the use of maternal health services in sub-Saharan Africa.

Objective: This mixed method systematic review will explore the impact of mHealth use by CHWs on the use of the maternal health continuum of care (antenatal care, intrapartum care, and postnatal care [PNC]), as well as barriers and facilitators of mHealth use by CHWs when supporting maternal health services.

Methods: We will include studies that report the impact of mHealth by CHWs on the use of antenatal care, facility-based births, and PNC visits in sub-Saharan Africa. We will search 6 databases (MEDLINE, CINAHL, Web of Science, Embase, Scopus, and Africa Index Medicus), with additional articles identified from Google Scholar and manual screening of references of the included studies. The included studies will not be limited by language or year of publication. After study selection, 2 independent reviewers will perform title and abstract screening, followed by full-text screening to identify the final papers to be included. Data extraction and risk-of-bias assessment will be performed using Covidence software by 2 independent reviewers. We will use a Mixed Methods Appraisal Tool to perform risk-of-bias assessments on all included studies. Finally, we will perform a narrative synthesis of the outcomes, integrating information about the effect of mHealth on maternal health use and barriers and facilitators of mHealth use. This protocol follows the PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols) guidelines.

Results: In September 2022, we conducted an initial search in the eligible databases. After removing duplicates, we identified 1111 studies that were eligible for the title and abstract screening. We will finalize the full-text assessment for eligibility, data extraction, assessment of methodological quality, and narrative synthesis by June 2023.

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Conclusions: This systematic review will present new and up-to-date evidence on the use of mHealth by CHWs along the pregnancy, childbirth, and PNC continuum of care. We anticipate the results will inform program implementation and policy by highlighting the potential impacts of mHealth and presenting contextual factors that should be addressed to ensure the success of the programs.

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International Registered Report Identifier (IRRID): DERR1-10.2196/44066

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KEYWORDS

community health worker; maternal health; mobile health; sub-Saharan Africa; systematic review; review method; maternal; maternity; gynecology; mHealth; narrative synthesis; review method; antenatal; post natal; women's health; health care provider; health worker; health care worker

Introduction

Background

Sub-Saharan Africa (SSA) continues to have the highest burden of maternal morbidity and mortality in the world [1]. About two-thirds of all maternal deaths occur in this region alone [2], despite containing only 15% of the global population [3]. Low use of antenatal care (ANC), unattended home births, and low use of postnatal care (PNC) have been identified as some of the biggest contributors to high maternal morbidity and mortality [4]. Consequently, policy makers and researchers in many SSA countries are beginning to realize the need for innovative ways of increasing access to and improving the quality of care along the pregnancy, childbirth, and postpartum continuum of care [5].

In SSA, mobile health (mHealth) technologies hold the potential to enhance use and quality of care during pregnancy, childbirth, and postpartum continuum of care, and thereby contribute to the reduction of maternal morbidity and mortality [6]. Currently, there is no universal definition of mHealth [7,8]. The World Health Organization defines mHealth as the use of mobile and wireless devices to support public health and medical practices [9]. When used appropriately, mHealth can be used to enhance use and quality of care. Additionally, mHealth can improve communication between providers and patients, and serve as a tool for education and mobilization [10]. Due to these anticipated benefits, there is a push to introduce mHealth to community health workers (CHWs) [11]. This is now possible in many SSA countries due to increased mobile and wireless device coverage and reduced cost of mHealth technologies [12,13].

CHWs act as a bridge between communities and health facilities by directly providing preventive health services, health promotion, and social mobilization among other home-based services [14,15]. Their role in the provision of health services is also vital as they help to address cultural barriers to accessing health services [16]. Finally, CHWs act as voices of social change by advocating for the health and social needs of the communities they serve [17]. If implemented well, these roles help improve the use of key health services, including maternal health services. Mobile health technologies may enhance the key roles of CHWs.

Despite the potential positive impact, the use of mHealth technologies is associated with challenges, especially in low- and middle-income countries. These include technological challenges, such as concerns with data security and privacy [18], multiple platforms of mHealth, some of which are not interoperable [19], poor network [13], lack of power [20], and high initial and maintenance costs [21]. Additional social factors also affect the use of mHealth including low literacy [22], insufficient training [23], cultural unacceptability [24,25], apps designed in languages other than the language of the users [24], and lack of integration into national health systems [10].

Recent reviews of the use of mHealth among CHWs have mainly focused on pilot projects and the mHealth implementation process and uptake [21,26]. Some reviews have shown that mHealth use by CHWs is linked to increased motivation, performance, and overall retention of CHWs [19,23]. Mobile health has supported the training of CHWs [27], improved patient adherence to scheduled appointments [28], and improved data collection, analysis, and use [29]. However, little is known about the effect of mHealth use by CHWs on the use of maternal health services in SSA.

Study Objectives

Due to the relative novelty and potential challenges associated with implementation in SSA, the impact of mHealth on maternal health outcomes will depend on addressing barriers while building on facilitators to implementation. This review will explore the use of mHealth by CHWs in SSA along the pregnancy, childbirth, and postpartum continuum of care. Specifically, we will assess the evidence on the effect of mHealth on maternal health use, while exploring how programs identified barriers and facilitators that may impact the implementation of mHealth.

Review questions include the following:

1. Does the use of mHealth by CHWs increase utilization of maternal health services (ANC, facility-based births, and PNC) in SSA?
2. What are the facilitators and barriers of mHealth use by CHWs in programs designed to increase the utilization of maternal health services (ANC, facility-based births, and PNC) in SSA?

While the first review question will be answered by quantitative study designs, the second review question will be answered by

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both qualitative and quantitative study designs. Initially, we conducted a preliminary search of PROSPERO, MEDLINE, and JBI Evidence Synthesis, and no current or in-progress systematic reviews on the topic were identified.

Methods

We have used the PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols) guidelines to structure this protocol [30].

Ethics Approval

Ethical approval is not required as the data collection will not directly involve any human subjects or identifiable patient data.

Eligibility Criteria

Participants

In this review, participants include (1) pregnant women at any gestational age, (2) pregnant women during intrapartum care, and (3) women within 42 days after giving birth. We will include these women when using ANC, intrapartum care, and PNC. Women accessing these services and having coexisting conditions, for example eclampsia, will also be included.

Intervention

The use of mHealth by CHWs to improve maternal health use is the focus of the review. Mobile health devices will include portable and wireless devices such as cell phones, feature phones, tablets, portable media players, and GPS trackers, among others. We will classify the mHealth tools based on the 12 "signal functions" defined by Labrique et al [31] (Table 1).

Table 1. Common mobile health uses.

Number	Common mobile health uses
1	Client education and behavior change communication
2	Point of care diagnostics and sensors
3	Registries or vital events tracking
4	Data collection and reporting
5	Electronic health records
6	Clinical decision support
7	Provider-to-provider communication
8	Scheduling and work plan management
9	Provider capacity building
10	Human resource management
11	Supply chain management
12	Financial transactions and incentives

CHWs will be defined based on the World Health Organization definition, "health workers based in communities, who are either paid or volunteers, who are not professionals, and who have fewer than 2 years of training but at least some training" [32]. We developed the CHW search strategy based on commonly known names for CHWs in various contexts [33]. We will include CHWs who were working in mHealth programs designed to increase the use of maternal health services (as stand-alone programs or integrated with other clinical programs), and which are implemented in SSA as defined by the World Bank Group country classification [34].

Comparator

For interventional studies included in this review, the comparator will be CHW programs that are not using mHealth interventions.

Outcomes

Our outcomes will include the following:

1. Measures of the use of mHealth on the use of maternal health services along the continuum of care:
   - ANC: total number of ANC visits, women who attended ANC in the first trimester, women who attended 4 or more ANC visits, and women with 8 or more ANC visits
   - Facility-based births: women who gave birth at health facilities
   - PNC: total number of PNC visits; women who attended PNC within 2 days, 3-7 days, and 8-42 days after giving births
   - Other maternal and reproductive health outcomes or services such as abortions, caesarean sections, family planning, and neonatal and child health outcomes will be excluded.
2. Facilitators to mHealth use by the CHWs
3. Barriers to mHealth use by the CHWs

Study Designs

We will include the following study designs: (1) randomized controlled designs, (2) observational studies with competent counterfactual designs (eg, quasi-experimental studies), (3) nonexperimental quantitative studies, (4) qualitative studies, and (5) mixed methods studies. Protocols, case series or reports, abstracts and conference proceedings, commentaries, policy briefs and other policy documents, systematic reviews, and

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other summary-type articles will be excluded. Although systematic reviews and other summary-type articles will be excluded, we will check the references in these articles to identify additional papers.

Information Sources and Search Strategy

We will search the following databases for potential studies: (1) Scopus, (2) MEDLINE, (3) CINAHL, (4) Web of Science, (5) Embase, and (6) Africa Index Medicus. Additional articles will be searched using Google Scholar and hand searching in references of all included studies. Study search will not be limited to a time or language. The sample component of search terms and search strategy is presented in Table 2. The search strategy was formulated by JCFK, who is a medical information specialist at Vrije Universiteit Amsterdam, the Netherlands.

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Table 2. Sample search strategy (MEDLINE).

Title	Search strategy
Part 1: defining the study population	• exp Pregnant Women/ or exp Pregnancy/ or Midwifery/ or Nurse Midwives/ or exp Postpartum Period/ or Maternal Health Services/ or exp Maternal-Child Health Services/ or exp Perinatal Care/ or exp Prenatal Care/ or exp Parturition/ or Reproductive Health Services/ or Reproductive Health/ or exp Labor, Obstetric/ or Maternal Death/ or (pregnan* or obstetr* or midwive* or midwife* or mid-wive* or mid-wife* or antenatal or postnatal or postpartum or post-natal or post-partum or gravid* or partur* or birth* or neonatal* or neo-natal* or lactat* or puerper* or labor or labour or term-birth or prenatal* or perinatal* or child-birth* or childbirth* or newborn* or (obstetr* adj5 deliver*) or breastfe* or breast-fe* or bottle-fe* or reproductive-health* or (maternal adj5 (health* or care* or welfare* or healthcare* or service* or death* or mortal*)) or reproductive-health* or reproductive-service* or pre-natal* or prenatal* or antenatal* or safe-motherhood* or safe-mother-hood or breech*).ti,ab,kf.
Part 2: defining intervention—mHealth[a]	• exp Cell Phones/ or exp Computers, Handheld/ or exp Internet/ or exp Medical Informatics/ or exp Mobile Applications/ or exp Multimedia/ or exp Nursing informatics/ or exp Patient Portals/ or exp Public Health Informatics/ or exp Telemedicine/ or exp Telenursing/ or exp User-Computer Interface/ or (android or app or apps or cell-phone* or cellular-phone* or desktop* or desk-top* or digital-health or digital-diagnostic-device* or distance-consult* or distance-counsel* or distant-consult* or e-diagnos* or e-coach* or econsult* or e-consult* or ediagnos* or ehealth* or e-health* or 7frica7n* or facebook or face-book or feature-phone* or fixed-laptop* or game or games or gamification or gaming or global-positioning-system* or gps or health-app* or health-kiosk* or health-technolog* or interactive-voice-response* or internet* or ipad or ipads or iphone* or i-pad or i-pads or i-phone* or laptop* or lap-top* or mhapp* or mh-app* or mhealth* or m-health* or mobile-app* or mobile-health* or mobile-technolog* or mobile-device* or mobile-phone* or palm-top* or palmtop* or patient-portal* or pda or pdas or personal-digital-assistant* or personal-electronic-health-record* or personal-health-record* or phone-app* or portable-media-player* or radio-frequency-identification* or rfid* or remote-consult* or remote-counsel* or satellite-phone* or serious-gam* or smartphone* or smart-phone* or smart-phone* or sms or social-media* or tablets or tablet or tele-app* or tele-care or tele-consult* or tele-counsel* or tele-diagnos* or tele-health or tele-medic* or tele-monitor* or tele-nursing or telecare or teleconsult* or telecounsel* or telediagnos* or telehealth* or telemedic* or telemonitor* or telenursing or telephone-app* or text-messag* or wearable* or web-portal* or webportal* or whatsapp* or whats-app* or world-wide-web or worldwideweb or www or 7frica7n or twitter or 8frica8nd or x-box or xbox or smart-watch*).ti,ab,kf.
Part 3: defining the CHWs[b]	• Community Health Workers/ or (accompagnateur* or accredited-social-health-activist* or asha* or animator* or auxiliary-nurse* or allied-health* or basic-health-worker* or barefoot* or bare-foot* or birth-attendant* or bridge-to-health-team* or care-group* or case-coordinator* or child-health-worker* or community-health-worker* or chw* or close-to-community-provider* or community-agent* or community-aide* or community-based-practitioner* or community-case-management* or community-coordinator* or community-drug-distributor* or community-health-assistant* or community-health-aide* or community-health-agent* or community-health-care-provider* or community-healthcare-provider* or community-health-extension-worker* or community-health-nurse* or community-health-representative* or community-health-surveyor* or community-health-volunteer* or community-healthcare-worker* or community-health-care-worker* or community-healthcare-provider* or community-health-care-provider* or community-health-promoter* or community-health-care-provider* or community-liaison* or community-nutrition-worker* or community-practitioner* or community-resource-person* or community-surveillance-volunteer* or community-volunteer* or community-worker* or care-group* or dame-health-worker* or door-to-door* or extension-service* or extension-officer* or extension-staff* or extension-worker* or family-planning-agent* or family-advocate* or family-support-worker* or family-welfare-assistant* or family-welfare-worker* or field-based* or grassroots* or grass-roots* or hard-to-reach* or health-activist* or health-aide* or health-agent* or health-care-agent* or healthcare-agent* or health-assistant* or health-auxiliar* or health-care-worker* or healthcare-worker* or health-coach* or health-counselor* or health-development-army* or health-distributor* or health-education* or health-extension* or health-nurse* or health-officer* or health-motivator* or health-outreach* or health-out-reach* or health-promoter* or health-promotor* or health-surveillance-assistant* or health-visitor* or health-worker* or health-volunteer* or home-based-care* or home-care* or home-health* or home-service* or home-visit* or iccm* or imci* or intake-specialist* or lady-health-worker* or lay-aide* or lay-attendant* or lay-consultant* or lay-counselor* or lay-health-advisor* or lay-health-worker* or lhw* or lay-visitor* or lay-worker* or lead-mother* or link-worker* or malaria-agent* or child-health-worker* or child-health-worker* or medical-assistant* or midwife* or mid-wife* or midwive* or mid-wive* or mobile-clinic-team* or mother-coordinator* or mother-leader* or navigator* or nutrition-agent* or nutrition-counselor* or outreach-advocate* or outreach-case-manager* or outreach-educator* or outreach-worker* or out-reach-advocate* or out-reach-case-manager* or out-reach-educator* or out-reach-worker* or parent-liaison* or peer-advisor* or peer-counselor* or peer-educator* or peer-health-advisor* or peer-leader* or peer-supporter* or promotora* or rural-health-auxiliar* or support-worker* or surveillance-volunteer* or traditional-birth-attendant* or village-health-volunteer* or village-health-worker* or vhw* or village-drug-kit-manager* or village-health* or village-health-helper* or voluntary-health-worker* or voluntary-worker* or volunteer*).ti,ab,kf.

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Title	Search strategy
Part 4: defining context	• exp "Africa South of the Sahara"/ or (angol* or benin* or botswan* or burkina-faso* or 11frica11* or cabo-verd* or 11frica11n* or cape-verd* or central-african-republic* or chad* or comoros* or congo* or cote-d-ivoire* or cote-diIvoire* or 11frica11n* or equatorial-guinea* or 11frica11* or eswatini* or 11frica11n* or gabon* or gambia* or ghana or ghanes* or guinea* or ivory-coast* or kenya* or 11frica11* or 11frica11* or madagasca* or 11frica* or mali or malines* or 11frica11nd11* or mauriti* or mozambiq* or 11frica11* or niger or 11frica11* or 11frica11n* or ruand* or rwand* or sao-tome-and-principe* or sao-tome-principe* or 11frica11* or seychell* or sierra-leone* or 11frica11* or south-africa* or rio-muni or 11frica11nd11n-africa* or sub-saharan-africa* or subsahara-africa* or sub-sahara-africa* or sudan* or 11frica11nd* or swazi-land* or tanzan* or togo or togoles* or ugand* or 11frica* or zimbabw* or central-africa* or east-africa* or eastern-africa* or southern-africa* or west-africa* or western-africa* or 11frica-south-of-the-sahara).ti,ab,kf,pl,in.
Part 5: subject combinations	• 1 and 2 and 3 and 4
Parts 6 and 7: setting predefined criteria	• 5 not (exp Animals/ not exp Humans/) • 6 not case reports/

[a]mHealth: mobile health.

[b]CHW: community health worker.

Study Selection and Data Extraction

JCFK will retrieve all studies from eligible databases based on the search strategy. CK will export all articles to Covidence computer software [35]. Covidence is a web-based collaboration software that is used to screen studies, perform risk-of-bias assessment and extract data. After the removal of duplicates, CK and HRZ will independently review titles and abstracts to select potential articles that meet the inclusion criteria. Following the identification of potentially eligible studies, CK and HRZ will independently review the studies in full to identify studies that meet the inclusion criteria. Disagreements during the title and abstract review and the full-text screening will be resolved by TvdA. An audit trail regarding the included and excluded studies and studies that required discussion will be maintained. Reasons for study exclusion will include studies conducted outside SSA, mHealth use by cadres of health care workers other than CHWs, and studies reporting outcomes other than those specified in this study.

We will design and pretest a data collection tool that will be used in Covidence software (Figure 1). The data collection tool will include the following:

1. Study characteristics: author, year of publication, and study design
2. Context: country and geographical scope
3. Programmatic context: type of CHWs and description of CHW work
4. Mobile health intervention characteristics: mHealth platforms, devices used, delivery method, and intervention description
5. Summary of main findings

Figure 1. Data extraction tool. CHW: community health workers.

Date	Author	Year of publication	Country	Study design	Context	Geographical location/context	CHW description and roles	Outcome description	MHealth devices	MHealth platform	MHealth delivery methods	MHealth Signal functions	Description of mHealth Intervention	Main Findings

Assessment of Methodological Quality

All included articles will undergo an independent assessment of methodological quality using the Mixed Methods Appraisal Tool (MMAT), 2018 version, by CK and HRZ [36]. MMAT is used to systematically appraise qualitative, quantitative, and mixed methods studies. MMAT is short but comprehensive and easy to use and has been validated and used extensively in reviews [37-40]. Disagreements will be resolved by TvdA. Details of the main domains of the MMAT tool are found in Multimedia Appendix 1. All studies, regardless of the results of their methodological quality, will undergo data extraction and synthesis.

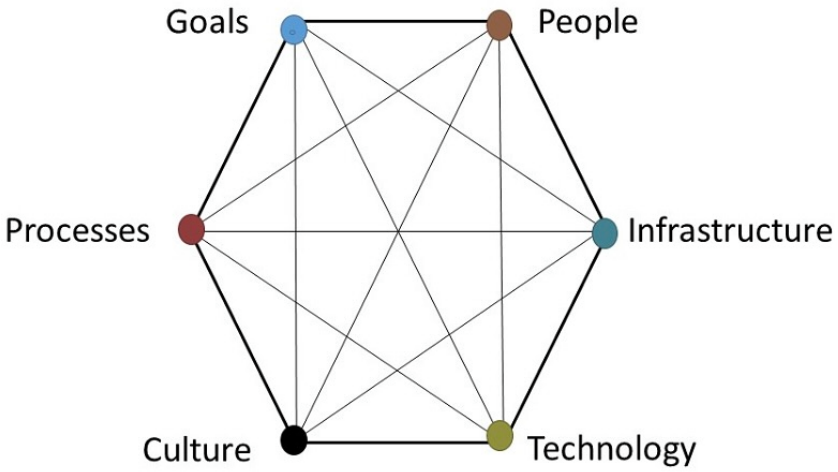
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Data Analysis and Synthesis

Since we are including a diverse range of mHealth tools, we anticipate heterogeneous findings from the included studies. As such, we will conduct a narrative synthesis of the results. We will not perform meta-analyses or subgroup analyses. We will follow 3 of the 4 steps of narrative synthesis as outlined by Popay et al [41], which are as follows:

1. A preliminary synthesis of summary findings of the included studies—we will tabulate all results and describe all variables as extracted from eligible studies. For research question 1, we will describe the direction and size of the effect of mHealth across the maternal health continuum of care: ANC, facility-based births, and PNC. For research question 2, we will qualitatively identify barriers and facilitators using a thematic analysis approach [42]. Using this approach, familiarization with the studies will occur during full-text eligibility and data extraction. This will be followed by the development of codes, which will then be organized as themes. The themes will be categorized using the socio-technical analysis framework by Davis et al [43] to group the barriers and facilitators into the following 6 main domains: people, goals, building and infrastructure, technology, culture, and processes and procedures (Figure 2) [43].
2. Exploring the relationships in the data within and between the studies, including explanations of variability in summary findings—we will describe factors that explain the differences in outcomes and barriers and facilitators to mHealth within and between the studies separately. This will be followed by the integration of the results of the two research questions. This is the process in which the two study aims will be linked to describe how mHealth might have led to the effect on maternal health outcomes.
3. A methodological quality assessment for the included studies, as described above.

Figure 2. Socio-technical analysis framework.



Results

In September 2022, we conducted an initial search in the 6 databases plus hand searching in Google Scholar. After removing duplicates, we identified 1111 studies that were eligible for the title and abstract screening. We anticipate finalizing the full-text assessment for eligibility, data extraction, assessment of methodological quality, and narrative synthesis by June 2023. Dissemination of results, including publication of the final manuscript, will follow the PRISMA reporting guidelines [44].

Discussion

This systematic review will present new and up-to-date evidence on the use of mHealth by CHWs along the pregnancy, childbirth, and PNC continuum of care. Based on the selected databases, we will present a comprehensive synthesis of the existing evidence on the effect of mHealth on the use of maternal health services. Additionally, we will explore the barriers and facilitators of mHealth use, allowing the exploration of factors that shape the implementation of mHealth.

The review is focused on SSA, a region that is currently struggling with the low use rates of maternal health services and identifying ways to improve maternal health outcomes, including a reduction in morbidity and mortality, is a priority [45]. As mHealth use continues to be promoted as one of the innovative ways to improve maternal health use in SSA, we anticipate the results of this review to be important to program implementers, policy makers, and researchers [46,47]. For implementers and policy makers, the results will inform how to use mHealth interventions based on what has been shown to work in other contexts. Additionally, the review will also highlight the present contextual factors that should be addressed to ensure the success of the programs. In the context of implementation, the review has the potential of providing valuable insights on how to modify programs that are currently being implemented to optimize outcomes, support justification for program scale-up, and support the inclusion of mHealth recommendations in policy guidelines. For researchers, we hope that the findings will open a scholarly discussion, create a reproducible process that enables future updates of the review, and based on identified gaps, inform areas of future research. This systematic review is also part of a PhD thesis by the first author.

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The review has 2 main limitations. Firstly, we will include peer-reviewed publications only. This may lead to publication bias as some of the information on mHealth may be found in gray literature or may not be published at all. Secondly, we are including maternal health continuum of care outcomes, leaving out other maternal health outcomes.

This systematic review will present the current evidence on the use of mHealth by CHWs in SSA. Therefore, we hope the review will support the use of mHealth for improved maternal health outcomes in SSA.

Acknowledgments

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Authors' Contributions

CK, THD, TvdA, and IOOA conceptualized and designed the study. CK, HRZ, THD, DP, and JCFK were responsible for validity and data collection. Writing of the original draft was done by CK. Review and approval for submission were carried out by CK, THD, AVK, JCFK, JM, DP, IOOA, and TvdA.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Details of the main domains of the Mixed Methods Appraisal Tool (MMAT) tool.
[DOCX File , 15 KB - resprot_v12i1e44066_app1.docx]

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Abbreviations

ANC: antenatal care
CHW: community health worker
mHealth: mobile health
MMAT: Mixed Methods Appraisal Tool
PNC: postnatal care
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analysis
PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols
SSA: sub-Saharan Africa

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Protocol

Fertility Preservation Techniques in Neuro-Oncology Patients: Protocol for a Systematic Review

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Abstract

Background: Advancements in cancer treatments have successfully improved central nervous system (CNS) cancer survivorship and overall quality of life. As a result, the awareness of the importance of fertility preservation techniques is increasing. Currently, a range of established techniques, such as oocyte cryopreservation and sperm cryopreservation, are available. However, oncologists may be hesitant to refer patients to a reproductive specialist.

Objective: The primary aim of the proposed systematic review is to assess the best evidence for fertility preservation techniques used in patients with CNS cancers. It also aims to evaluate outcomes related to their success and complications.

Methods: This protocol was produced in adherence with the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols). Electronic databases will be systematically searched to identify studies that meet our eligibility criteria. Studies will be included if they report at least one type of fertility preserving or sparing technique in male patients of any age and female patients aged <35 years. Animal studies, non-English studies, editorials, and guidelines will be excluded from the review. From the included studies, data will be extracted and synthesized by using a narrative approach and summarized in tables. The primary outcome will be the number of patients successfully undergoing a fertility preservation technique. The secondary outcomes will include the number of retrieved oocytes, the number of oocytes or embryos vitrified for cryopreservation, clinical pregnancy, and live birth. The quality of the included studies will be assessed by using the National Heart, Lung, and Blood Institute risk-of-bias tool for any type of study.

Results: The systematic review is expected to be completed by the end of 2023, and results will be published in a peer-reviewed journal and on PROSPERO.

Conclusions: The proposed systematic review will summarize the fertility preservation techniques available for patients with CNS cancers. Given the improvement in cancer survivorship, it is becoming increasingly important to educate patients about fertility preservation techniques. There are likely to be several limitations to this systematic review. Current literature is likely to be of low quality due to insufficient numbers, and there may be difficulty in accessing data sets. However, it is our hope that the results from the systematic review provide an evidence base to help inform the referral of patients with CNS cancers for fertility preservation treatments.

Trial Registration: PROSPERO CRD42022352810; https://tinyurl.com/69xd9add

International Registered Report Identifier (IRRID): PRR1-10.2196/44825

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KEYWORDS

fertility; reproduction; central nervous system; CNS cancer; neuro-oncology; cancer; awareness; electronic database; tool; fertility preservation; patient; treatment; reproductive; oncology; infertility; in vitro fertilization; artificial insemination; human reproduction; reproduction; gynecology; gynecologist; assisted reproductive technology; gestational surrogacy; surrogate; fertility tourism; test tube baby; intracytoplasmic sperm injection

Introduction

Central nervous system (CNS) cancers are the most prevalent cancers in 15- to 19-year-olds [1]. Infertility is one of the most common long-term issues experienced by young, female cancer survivors [2]. With advances in chemoradiotherapy and surgery meaning that survival from these cancers has considerably improved, there is an increased awareness of the impact that this has on cancer survivors' quality of life [1]. CNS cancers can impact patients' fertility in a variety of ways. Tumor infiltration, radiotherapy, and cranial surgery can all damage the hypothalamic-pituitary axis. In addition, chemoradiotherapy treatments can also be gonadotoxic, resulting in premature ovarian insufficiency and impaired fertility [3,4]. National Institute for Health and Care Excellence guidelines recognize the clinical importance of establishing fertility preservation techniques in those wishing to preserve their future reproductive potential [5].

There are several techniques available to women who are concerned about their future fertility, although many of these techniques have been considered experimental until recently. Embryo cryopreservation is the most established fertility preservation technique [6]. However, recent advances make oocyte cryopreservation an alternative option for those without a partner. Embryo or mature oocyte cryopreservation involves the hyperstimulation of the ovary to induce multiple follicles to grow [7]. Following retrieval, mature oocytes or embryos obtained via in vitro fertilization are cryopreserved and stored for use in the future [8]. For prepubertal girls, there is only one emerging technique available [9]. Ovarian tissue cryopreservation involves the transplantation of frozen-thawed ovarian tissue into the pelvic cavity after treating the CNS tumor. Although previous studies have shown successful results with this technique, there are concerns about tumor reseeding [10]. For patients undergoing radiotherapy, ovarian transposition, or oophoropexy, may be utilized as a fertility sparing method; the ovaries are surgically repositioned to be outside of the radiation field, thus minimizing their radiation damage [11]. For men, sperm cryopreservation is an established and effective technique for fertility preservation [12].

More young adults with CNS cancers see future family building as a possibility. However, oncologists may be hesitant to refer patients to a reproductive specialist, despite societal support and patient interest. This may be due to a reluctance to send mixed messages about prognoses, discomfort in discussing fertility or sexuality, and a lack of knowledge or time [12]. Our systematic review aims to summarize the available evidence concerning fertility preservation techniques used in the context of patients with CNS cancers.

Methods

Protocol and Registration

The protocol was developed in adherence with the recommendations of the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) guidelines. The systematic review will also adhere to the recommendations of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. The protocol has been prospectively registered on PROSPERO (registration number: CRD42022352810). Any changes in the protocol will be amended in PROSPERO and reported once the systematic review is complete.

Eligibility Criteria (Study Designs and Types of Studies)

Studies will be included in this systematic review if they are a systematic review, case series, case report, interventional trial (nonrandomized and randomized controlled studies), cohort study, case-control study, or cross-sectional study reporting at least one type of fertility preservation technique among neuro-oncology patients. If multiple publications report results from the same patient cohort, then each study will be included, provided that distinct outcomes are reported. If these publications report duplicate outcomes, only the study with the largest population will be included. Grey literature will not be included in the review. Animal studies, non-English studies, editorials, and guidelines will be excluded from the review.

Participants, Population, and Exposure

The review will focus on male and female patients of any age with a primary CNS tumor of any World Health Organization tumor grade. Such tumors may include medulloblastomas, ependymomas, astrocytomas, primitive neuroendocrine tumors, glioblastomas, germinomas, pineal tumors, gliomas, craniopharyngiomas, pineoblastomas, and CNS lymphomas. Participants must have received at least one type of fertility preservation or fertility sparing technique to be included. These may include medical therapy before chemotherapy, ovarian transposition, embryo cryopreservation, oocyte vitrification, ovarian tissue cryopreservation, or sperm cryopreservation. Participants who did not receive or were not referred for a fertility preservation technique will be excluded. If aggregate data prevent the identification of data meeting all the inclusion criteria, the paper will be excluded.

Outcome of Interest

The primary outcome of the systematic review will be the number of patients successfully undergoing a fertility preservation technique. The systematic review is interested in fertility-related outcomes for patients undergoing fertility preservation techniques. These may be reported quantitatively or qualitatively. Therefore, the secondary outcomes include the

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success rates of different fertility preservation techniques, including, for example, the number of retrieved oocytes, the number of oocytes or embryos vitrified for cryopreservation, the rate of sperm cryopreservation, clinical pregnancy, and live birth. The number of oocytes retrieved reflects the effectiveness of fertility preservation protocols, and the number of oocytes or embryos vitrified for cryopreservation implies the potential for oocyte fertilization and embryo transfer [13]. A clinical pregnancy will be defined as at least one intrauterine pregnancy sac with yolk sac or original cardiac pulsations on a B-ultrasound examination. A live birth will be defined as the birth of a healthy infant not requiring admission to the neonatal intensive care unit, at 28 weeks gestation or more, during the follow-up period [14].

Search Methods

We will perform a literature search of the following databases: PubMed, MEDLINE, Cochrane, Google Scholar, and Embase. A combination of Medical Subject Headings terms will be used to identify relevant articles. The search strategy will be developed in collaboration with a university librarian (Textbox 1). The search will be limited to articles published in the English language. To ensure the relevance of papers, the search strategy will be limited to papers published in the last 20 years (2002-2022). References will be hand-searched to identify other potential sources to be included. Grey literature will not be searched for the review.

Textbox 1. Provisional search terminology.

Search string

- ("Fertility preservation" OR "Ovary preservation" OR "Oocyte preservation" OR "Gonadal preservation" OR "Sperm preservation" OR "Semen preservation" OR "Fertility cryopreservation" OR "Ovary cryopreservation" OR "Embryo cryopreservation" OR "Gonadal cryopreservation" OR "Sperm cryopreservation" OR "Testicular cryopreservation" OR "Ovariopexy" OR "Ovarian transposition" OR "Fertility sparing" OR "Ovarian tissue cryopreservation" OR "cryopreservation" OR "oocyte retrieval" OR "Ovary retrieval" OR "Gonadal retrieval" OR "OTC") AND ("Brain tumour" OR "Brain cancer" OR "Brain neoplasm" OR "Cerebral neoplasm" OR "Cerebellar neoplasm" OR "Medulloblastoma" OR "Ependymoma" OR "Primitive neuroectodermal tumour" OR "Primitive neuroectodermal cancer" OR "Primitive neuroectodermal neoplasm" OR "Astrocytoma" OR "Glioblastoma" OR "Germinoma" OR "Central nervous system tumour" OR "CNS tumour" OR "Central nervous system cancer" OR "CNS cancer" OR "Central nervous system neoplasm" OR "CNS neoplasm" OR "Pineal tumour" OR "Pineal cancer" OR "Pineal neoplasm" OR "Pinealoma" OR "Glioma" OR "Craniopharyngioma" OR "Pineoblastoma" OR "CNS lymphoma")

Selection of Studies

The titles and abstracts of studies produced by the search will be collated by using reference management software, and duplicates will be removed. Two authors will jointly screen the titles and abstracts of the search results. The full texts of potentially relevant studies will then be retrieved and assessed against the predefined inclusion and exclusion criteria. When a consensus cannot be reached, a third reviewer will be consulted. When a full-text article cannot be obtained, the corresponding author of that article will be contacted. The selection process will be documented by using the PRISMA flowchart to report how studies were identified, screened, and included.

Data Extraction, Management, and Synthesis

A standardized data extraction form will be developed and piloted before use. Data will be extracted from 10% of the selected studies by 2 reviewers independently. Concordance between the two reviewers will be statistically assessed by using the Kendall τ statistic. If concordance is met, the reviewers will each extract data from 50% of the remaining papers. If concordance is not met, discrepancies will be resolved via discussion, and data will be extracted from a further 10% of the studies and reassessed.

The following parameters will be extracted from each paper: primary author, publication date, study design, country, participant demographics (number, gender, age, duration of symptoms, type of brain tumor, tumor stage, age at treatment, radiation dose to ovaries [grays], radiation dose to the hypothalamic-pituitary axis [grays], and description of study participants), inclusion and exclusion criteria, the existence of pre-existing conditions affecting fertility, the type of neuro-oncology intervention(s), the type of fertility preservation, age at fertility preservation, the method of conception, the number of attempts at pregnancy, the outcome(s) measured and the value of the outcome(s) measured, and treatments (including teratogenic treatments) received during pregnancy. Individual study data will be combined and synthesized in a table. The following outcomes and end points may be included: pregnancy outcomes, the number of oocytes retrieved, ovarian tissue cryopreservation, follicle characteristics, sperm characteristics, rates of sperm cryopreservation, the number of metaphase-2 oocytes retrieved and vitrified, and neonatal outcomes. When data are missing, the authors will be consulted for further completing data.

Given the anticipated heterogeneity in study designs and outcomes, a meta-analysis may not be feasible. A narrative synthesis of the data will be performed. Tables will be used to summarize and present participant demographics, fertility preservation techniques, and outcomes. If possible, a subgroup analysis will be performed by stratifying women into age groups (<35 years and >35 years of age) and by pre-existing conditions affecting fertility (eg, polycystic ovary syndrome).

Quality Assessment

All included studies will be assessed for quality and risk of bias by using the National Heart, Lung, and Blood Institute risk-of-bias tool for any type of study. The two reviewers will rate each domain of the included studies as having a low, high, or unclear risk of bias. These ratings will then be used to provide an overall quality score for the methodology of the article. Discrepancies between the two reviewers will be resolved through discussion with a third reviewer to achieve a consensus.

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Results

This is a protocol for a systematic review; therefore, the results cannot be presented. The results of the study will be submitted for publication in a peer-reviewed journal and presented on PROSPERO. The systematic review is expected to be completed by the end of 2023.

Discussion

Given that cancer survivorship is increasing, it is becoming increasingly important to educate oncologists about fertility preservation techniques for patients who wish to preserve their fertility. Our systematic review aims to present a comprehensive summary of fertility preservation techniques used in neuro-oncology patients. To the best of our knowledge, this will be the first systematic review to evaluate these techniques in neuro-oncology patients. Current literature on the subject is largely comprised of small case series and is likely to be of limited quality due to insufficient numbers, difficulty in accessing data sets, and combined cohorts. This may limit the conclusions drawn in the systematic review. Our hope is that the review classifies the success rates of fertility preservation techniques and any complications experienced by the patients undertaking them.

Current guidance recommends that patients should be provided with information about the effects of cancer therapies on fertility before or during cancer treatment and that patients should be recommended for fertility preserving or sparing treatments as appropriate [15]. Through our review, we hope to provide clinicians with an overview of appropriate treatments to develop the understanding of treatments available. We also hope that the review facilitates the future development of frameworks to help guide clinician and patient discussions.

There are likely to be several limitations for the systematic review. The quality of current literature is likely to be low due to insufficient case numbers, difficulty in accessing data sets, and aggregate cohorts, limiting the conclusions that may be drawn from the systematic review. There is also likely to be significant heterogeneity in the outcomes reported in the studies. Therefore, it is likely that a meta-analysis will not be able to be performed. Moreover, there are multiple mediating variables, such as treatment type, tumor stage, and radiation dose, that must be considered when assessing fertility outcomes.

Data Availability

Data are available on request.

Conflicts of Interest

None declared.

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Abbreviations

CNS: central nervous system
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols

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Protocol

Opioid Agonist Therapies and Pregnancy Outcomes for Pregnant People With Opioid Use Disorder: Protocol for a Systematic Review

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Abstract

Background: Opioid use disorder (OUD) during pregnancy presents a significant risk to maternal, fetal, and neonatal health, increasing the likelihood of adverse events, such as maternal overdose, pregnancy loss, stillbirth, preterm birth, low birth weight, and neonatal abstinence syndrome. In order to reduce the risk of these outcomes, the standard of care for OUD during pregnancy in many jurisdictions within the United States and Canada is opioid agonist therapy (OAT). OAT refers to prescription medications that alleviate or eliminate opioid withdrawal symptoms, so that opioid use can be managed more safely. Although OAT has been recognized as a safe option for pregnant people with OUD, many jurisdictions do not have treatment guidelines regarding pharmacological options, dosing recommendations, side effect management, and individual preferences. There is currently a lack of systematic evidence on the impacts of different OAT regimens on pregnancy outcomes.

Objective: We aim to evaluate the impacts of specific OAT agents on pregnancy outcomes and inform recommendations for practitioners treating pregnant people with OUD.

Methods: The MEDLINE, Embase, CINAHL, and PsycINFO databases will be searched for published quantitative studies assessing pregnancy outcomes for individuals on OAT. Given the substantially increased risk of preterm birth, low birth weight, small for gestational age, and stillbirth among pregnant people with OUD, these four end points will comprise our primary outcomes. Database searches will not be restricted by date, and conference abstracts will be restricted to the past 2 years. Titles, abstracts, and full-text articles will be independently screened by 2 reviewers. Data will be extracted independently and in duplicate, using a data extraction form to reduce the risk of reviewer bias. The risk of bias within individual studies will be assessed by using the appropriate CASP (Critical Appraisal Skills Programme) checklists. For studies that consider the same research questions, interventions, or outcomes, meta-analyses will be conducted to synthesize the pooled effect size. In the event that studies cannot be compared directly, results will be synthesized in a narrative account. Between-study heterogeneity will be measured by using the τ^2 statistic. If more than 10 studies are available for pooling, publication bias will be evaluated by using the Egger regression test.

Results: As of January 2023, a total of 3266 abstracts have been identified for screening. Data extraction is expected to commence in February 2023.

Conclusions: The topic of OAT and its effect on pregnancy is an understudied area that has the potential to improve health outcomes, clinical practice, education, and community advocacy. The results of our review will be used to inform clinical practice guidelines and improve health outcomes for pregnant people. Findings will be disseminated to diverse groups of stakeholders, including policy makers, clinicians, community partners, and individuals with lived experience of drug use.

Trial Registration: PROSPERO CRD42022332082; https://tinyurl.com/2p94pkx5

International Registered Report Identifier (IRRID): DERR1-10.2196/42417

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KEYWORDS

opioid agonist therapies; opioid use disorder; pregnancy; opioid; drug; symptoms; treatment; screening; data; risk; clinical; policy makers; community

Introduction

Opioid use disorder (OUD) during pregnancy presents a significant risk to maternal, fetal, and neonatal health, increasing the likelihood of adverse events, such as maternal overdose, pregnancy loss, stillbirth, preterm birth, low birth weight, and neonatal abstinence syndrome [1,2]. Although OUD during pregnancy is associated with considerable harms, the withdrawal symptoms associated with sudden cessation are also extremely harmful to both the person who is pregnant and the fetus [3,4].

In order to reduce the risk of these outcomes, the standard of care for OUD during pregnancy in many jurisdictions within the United States and Canada is opioid agonist therapy (OAT) [3]. OATs are prescription medications that alleviate or eliminate opioid withdrawal symptoms so that OUD can be managed more safely. Buprenorphine and methadone are both recommended as first-line treatments in many jurisdictions, with buprenorphine increasingly being recommended as the preferred therapeutic option, given its established safety profile and simple treatment regimen [3]. Other options, such as slow-release oral morphine, can also be used for individuals who do not respond to first- or second-line therapies [3]. The ongoing use of OAT throughout pregnancy is considered safe for both the person who is pregnant and the fetus [3-5].

Although OAT offers a relatively safe option for managing OUD during pregnancy, many health care providers are unfamiliar with how best to prescribe OAT throughout a pregnancy, and many jurisdictions do not have established treatment guidelines. A consistent dosage can be difficult to maintain as the body changes during pregnancy, putting the person who is pregnant at risk of experiencing withdrawal symptoms or overdose both during the pregnancy and post partum [6-8]. These limitations, in combination with the fact that OAT can produce side effects (eg, nausea, vomiting, and constipation) [9] and that some pregnant people may simply prefer to continue using opioids, can increase the complexity of treatment regimens and approaches for ensuring that pregnant people receive prenatal care that is the most appropriate for them.

Although there is considerable literature to suggest that OAT is preferable to opioid use during pregnancy, to our knowledge only 1 systematic review has been conducted that considers the impacts of OAT on pregnancy outcomes. This living systematic review, which was conducted by Minozzi and colleagues [10], offers the most up-to-date evidence from randomized controlled trials (RCTs) to support the use of OAT during pregnancy. However, the authors note that the small number of RCTs considering this topic (n=4) makes it difficult to draw firm conclusions about the relative benefits of different OAT regimens, and further research is still needed [10]. Given the limited number of studies and participants available for inclusion from RCTs, we sought to build upon the existing knowledge base by evaluating observational studies that have been conducted to evaluate impacts of various types of OAT on pregnancy outcomes. Although observational studies include greater bias and heterogeneity when compared to RCTs, the inclusion of additional studies containing larger numbers of participants can offer valuable insights into the real-world impacts of OAT on pregnancy outcomes.

Methods

Protocol and Registration

This systematic review protocol follows the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) checklist [11] and has been registered in the PROPSERO database (ID number: CRD42022332082). The full systematic review will also follow the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.

Research Question

The systematic review will seek to address the question “What impact do different forms of OAT have on pregnancy outcomes among pregnant people with opioid use disorder?”

Eligibility Criteria

The population of interest in our review will be pregnant people with OUD. The exposure will be OAT (eg, methadone, buprenorphine/naloxone [Suboxone], slow-release oral morphine, hydromorphone, and naltrexone). The primary outcomes of interest for the review will be preterm birth (ie, gestational age<37 weeks), low birth weight (ie, <2500 g), small for gestational age birth weight (ie, birth weight<10th percentile for gestational age), and stillbirth. Although many other maternal and infant health outcomes are impacted by OAT, we have opted to limit the scale of our results by restricting our analysis to these four outcomes, given the substantially increased risk of these outcomes among people with OUD [12-14] and the widespread availability and uniformity of the data that have been collected on these outcomes, which will facilitate comparisons between studies. Study eligibility criteria are presented in Table 1. Our planned start date for data extraction is February 1, 2023.

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Table 1. Study eligibility criteria.

	Inclusion criteria	Exclusion criteria
Article type	• Published studies • Randomized clinical trials • Case-control studies • Cohort studies • Cross-sectional studies • Conference abstracts published within the previous 2 years	• Unpublished or grey literature • Case studies • Case series • Editorials • Opinion pieces • Commentaries • Conference abstracts older than 2 years
Study design	• Inclusion of individuals who engage in illicit opioid use • Comparison of one form of opioid agonist therapy to another or to no intervention	• Inclusion of only individuals who engage in other forms (ie, nonopioid) of drug use • No comparator group
Language	• English	• All other languages
Date Range	• No restrictions	• None
Setting	• No restrictions	• None

Information Sources and Search Strategy

We will search MEDLINE, Embase, CINAHL, and PsycINFO to identify studies relevant to our review. Search terms are aligned with the eligibility criteria described above, including variations on "opioid agonist therapy," "pregnancy," "opioid use," and each of the pregnancy outcomes of interest. These terms were used as keywords and mapped onto Medical Subject Headings terms. Our search strategy was developed in consultation with a medical librarian at the University of British Columbia to ensure that there were no major omissions in our approach (the MEDLINE search strategy is presented in Textbox 1).

Textbox 1. Search strategy for Embase.

Searches

1. *exp Buprenorphine/ or Opiate Substitution Treatment*
2. *Methadone/*
3. *((methadone or methadose or "opioid agonist therap*'" or "opioid agonist treatment*" or "opiate agonist therap'" or "opiate agonist treatment* or "medication assisted treatment'" or "medication assisted therap*" or OAT or "medication assisted recovery" or "opioid replacement therap*" or buprenorphine or suboxone or "opiate treat*" or "opioid treat*" or "Injectable hydromorph*" or medication*) adj2 "opioid use disorder").tw,kw.*
4. Searches 1 *or* 2 *or* 3
5. *(pregnan* or prenatal or perinatal or "birth weight" or birthweight or stillbirth or miscarriage or preterm birth or pre-term birth or remature* or "gestational age").mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]*
6. Searches 4 *and* 5
7. Limit search 6 to English language
8. Limit search 7 to "humans only (removes records about animals)"
9. Limit search 8 to "remove preprint records"
10. Limit search 9 to conference abstracts
11. Limit search 10 to *yr="2019-Current"*

Study Selection and Data Extraction

From our database searches, we will remove any duplicate articles and then import all articles into Covidence (Veritas Health Innovation Ltd) [15]. Titles and abstracts will be reviewed in 1 stage, followed by a separate full-text screening of the remaining articles. During each stage, studies that do not meet the review criteria will be excluded. Each stage will be conducted by 2 investigators independently and in duplicate. Any disagreements will be resolved by consensus.

A data extraction form will be developed prior to article analysis. Data on study types, settings, sample sizes, types of OAT, primary and secondary outcomes, main study results, and recommendations will be extracted. Extraction will be conducted by 2 investigators independently and in duplicate and then reviewed collaboratively. Any additions that need to be made

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to the extraction form will be discussed between the two investigators.

Risk of Bias

Given our inclusion of observational studies, which inherently contain some risk of bias, the risk of bias within individual studies will be assessed by using the CASP (Critical Appraisal Skills Programme) cohort study checklist and CASP case-control study checklist [16]. These checklists comprise 12 and 11 questions, respectively, that seek to analyze a study's validity, results, and clinical utility; bias is assessed with regard to the exposure, outcome, study design, and analysis. Bias in each full-text study will be assessed by 2 reviewers independently using the CASP checklists. Disagreements will be resolved by consensus. Issues such as heterogeneity in outcome measures, OAT dosage, and reporting will be explored as potential issues.

Data Synthesis

A PRISMA flowchart will be developed to indicate the number of articles identified and how many were excluded (including reasons for exclusion) at each stage of evaluation. For studies that consider the same research questions, interventions, or outcomes, meta-analyses will be conducted to quantitatively synthesize the pooled effect size of OAT on each outcome (ie, preterm birth, stillbirth, low birth weight, and small for gestational age) [17]. Subgroup analyses will be conducted by outcome and type of OAT regimen. However, given the likelihood of heterogeneity between studies, a meta-analysis may not be appropriate in all cases. In the event of studies with research designs, interventions, and outcomes that cannot be compared directly, the results of the data extraction will be synthesized in a narrative account [17,18]. Between-study heterogeneity will be measured by using the τ^2 statistic, which captures the variance between studies and is better suited than other measures of heterogeneity to evaluate observational studies with large sample sizes [19]. If more than 10 studies are available for pooling, publication bias will be evaluated by using the Egger regression test [20]. If publication bias is detected, pooled estimates will be adjusted by using the trim and fill technique, which corrects for publication asymmetry [20,21].

Results

A search strategy has been finalized with a medical librarian at the University of British Columbia. The initial search has yielded 3266 abstracts for screening. Data extraction is expected to commence in February 2023, and final results should be available within 6 months of the publication of this protocol.

Discussion

Our proposed systematic review will be the first to synthesize observational data on the effect of different OAT options on pregnancy outcomes for people with OUD. The topic of OAT and its effect on pregnancy is an understudied area that has the potential to improve health outcomes, clinical practice, education, and community advocacy. The results of our review will primarily be used to inform clinical practice guidelines for OAT prescribing practices among pregnant people and subsequently improve health outcomes for both pregnant individuals and their infants. The results of our study will generate pertinent considerations for future research to continue improving the knowledge available on the effect of OAT on pregnancy.

This systematic review faces some limitations. There will be a degree of heterogeneity among the studies selected due to the variability of the research methodologies, settings, and OAT regimens and dosages being studied. We will evaluate this issue during data extraction and will adjust our analysis strategy accordingly. Further, in order to mitigate the risk of reviewer bias, we will have 2 reviewers independently screen and assess (ie, quality assessment) each study in our review. There is also a risk of missing pertinent literature on our research topic. We have consulted a medical librarian at the University of British Columbia and developed a broad search strategy to maximize the likelihood of identifying relevant articles. Lastly, publication bias is a general limitation of systematic reviews. We will attempt to mitigate this issue by including abstracts that have been published within the last 2 years, but we may miss some studies that did not reach the publication stage. We will adjust our conclusions based on evidence of publication bias as appropriate.

Our systematic review will synthesize relevant literature and integrate the vast observational data available on OAT and its impacts on adverse events during pregnancy. The findings of our study will contribute to improved clinical care and health for all pregnant people who use opioids for the duration of their pregnancies and beyond.

Acknowledgments

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We would like to acknowledge Ursula Ellis, the medical librarian at the University of British Columba, for her assistance in creating the search strategy to be used in the systematic review and Dr Lianping Ti for her guidance in developing the study and protocol.

Data Availability

Data sharing is not applicable to this article, as no data sets were generated or analyzed during the study.

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Authors' Contributions

LAW conceptualized this project, conducted the primary literature review, and authored the first draft of the manuscript. PG reviewed and revised the first draft. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

CASP: Critical Appraisal Skills Programme

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OAT: opioid agonist therapy
OUD: opioid use disorder
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols
RCT: randomized controlled trial

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Protocol

The Use of Social Media for Dissemination of Research Evidence to Health and Social Care Practitioners: Protocol for a Systematic Review

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Abstract

Background: Effective dissemination of research to health and social care practitioners enhances clinical practice and evidence-based care. Social media use has potential to facilitate dissemination to busy practitioners.

Objective: This is a protocol for a systematic review that will quantitatively synthesize evidence of the effectiveness of social media, compared with no social media, for dissemination of research evidence to health and social care practitioners. Social media platforms, formats, and sharing mechanisms used for effective dissemination of research evidence will also be identified and compared.

Methods: Electronic database searches (MEDLINE, PsycINFO, CINAHL, ERIC, LISTA, and OpenGrey) will be conducted from January 1, 2010, to January 10, 2023, for studies published in English. Randomized, nonrandomized, pre-post study designs or case studies evaluating the effect of social media on dissemination of research evidence to postregistration health and social care practitioners will be included. Studies that do not involve social media or dissemination or those that evaluate dissemination of nonresearch information (eg, multisource educational materials) to students or members of the public only, or without quantitative data on outcomes of interest, will be excluded. Screening will be carried out by 2 independent reviewers. Data extraction and quality assessment, using either the Cochrane tool for assessing risk of bias or the Newcastle-Ottawa Scale, will be completed by 2 independent reviewers. Outcomes of interest will be reported in 4 domains (reach, engagement, dissemination, and impact). Data synthesis will include quantitative comparisons using narrative text, tables, and figures. A meta-analysis of standardized pooled effects will be undertaken, and subgroup analyses will be applied, if appropriate.

Results: Searches and screening will be completed by the end of May 2023. Data extraction and analyses will be completed by the end of July 2023, after which findings will be synthesized and reported by the end of October 2023.

Conclusions: This systematic review will summarize the evidence for the effectiveness of social media for the dissemination of research evidence to health and social care practitioners. The limitations of the evidence may include multiple outcomes or methodological heterogeneity that limit meta-analyses, potential risk of bias in included studies, and potential publication bias. The limitations of the study design may include potential insensitivity of the electronic database search strategy. The findings from this review will inform the dissemination practice of health and care research.

Trial Registration: PROSPERO CRD42022378793; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=378793

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KEYWORDS

dissemination; health care; podcast; practitioners; research evidence; social care; social media; social networking; Twitter; videos

Introduction

Background

Health and social care researchers aim for their research findings to be accessible and useful for practitioners to help them deliver best, evidence-based clinical care and improve patient outcomes [1-4]. Thus, as part of continuing professional development, practitioners need to access relevant high-quality research evidence [5,6]. Research evidence is defined as information provided by a research study; information may derive from original studies (primary research), reviews (secondary research), or evidence-based guidelines [6]. Effective strategies are required to deliver relevant research evidence to practitioners [2,7,8] because dissemination of research evidence without delay is recommended to maximize its benefits [9,10].

Dissemination is defined as active approaches that use specific channels and planned strategies to get research evidence to a specific audience (who can make use of it and enact research benefits) [10]. Challenges of dissemination to practitioners include organizational barriers, limited professional opportunities, time constraints, and accessing relevant articles within the exponentially increasing volume of research evidence produced each year [8,11-13]. Social media has potential to overcome some of the barriers to dissemination [7,8].

Social media is defined as a collection of web-based platforms that allow the creation and exchange of user-generated content [14]. Open social media are accessible to anyone; closed social media groups have eligibility parameters that limit user participation [15]. The number of people who use social media globally has risen from millions to billions in the last 20 years; its advantages include not being limited in time and space [7,16]. Thus, professional use of social media by health and social care practitioners represents an opportunity for effective dissemination of research evidence [15]. Indeed, social media is increasingly used to disseminate health and social care research [8,15,17-21].

Social media use in health care has been studied and reviewed extensively [22-28]. Reviews concur about benefits and risks of social media for reputation, communication, information sharing, and public health messages. For health care professionals, social media has also been used effectively for education and day-to-day communications [25,29,30].

The existing reviews of social media for dissemination of health care research have narratively synthesized benefits and risks, described similarities, differences, and qualitative experiences, or provided commentaries on the mechanisms and potential uses of social media for dissemination [15,25,26,31]. However, they are heterogeneous in terms of study design and perspectives [15,26,31]. In 2018, a review of reviews about effective uses of social media in public health and medicine included little evidence concerning dissemination [25]. In 2020, a review highlighted 4 research dissemination case studies [26]. An unpublished preprint review, which identified 4 randomized controlled trials and 37 quantitative or descriptive studies, identified Twitter as a prominent platform for dissemination [31]. A subsequent review in 2022 highlighted the communication mechanisms and potential of social media for both 1-way knowledge mobilization (ie, dissemination) and 2-way knowledge mobilization (ie, more complex multidirectional integrated knowledge translation involving collaborative interactions between researchers and practitioners) [15]. The existing reviews are health care focused; no reviews have investigated dissemination to social care practitioners.

Although quantitative reports and comparisons of social media for dissemination of research evidence in health care are emerging [18-20,32], it is not yet clear how consistent or robust their findings are. To date, no quantitative synthesis or meta-analysis has been undertaken to investigate the effectiveness of open social media for dissemination of research evidence to health and social care practitioners.

Objective

The objective of this systematic review is to quantitatively synthesize evidence of the effectiveness of social media, compared to no social media, for dissemination of research evidence to health and social care practitioners. The social media platforms, formats, and sharing mechanisms used for effective dissemination of research evidence will also be identified and compared.

The specific research questions are as follows: (1) how effective is open social media for dissemination of research evidence for health and social care practitioners, compared to no social media input? (2) Which social media platforms, formats, and sharing mechanisms are used for dissemination of research evidence for health and social care practitioners? (3) What is the comparative effectiveness for dissemination of research evidence to health and social care practitioners between different social media platforms (eg, Facebook vs Twitter), different formats of social media posts (eg, text vs infographic vs video), and different social media–sharing mechanisms (eg, site-wide shares vs special interest groups vs live social media events vs influencer endorsements)

Methods

Design

The inception and design of this systematic review, of articles available from January 1, 2010, to January 10, 2023, incorporated patient and public involvement via consultations with a stakeholder group. This protocol follows PRISMA-P (Preferred Reporting Items for Systematic Reviews and

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Meta-Analyses) guidelines [33]. The protocol has been registered with the International Prospective Register of Systematic Reviews (PROSPERO; registration number: CRD42022378793).

Eligibility

Table 1 summarizes the population, intervention, comparisons, and outcomes of interest. The target population will be practitioners, defined as health and social care professionals, including, but not limited to, some of the largest groups of registered practitioners in the United Kingdom; that is, nurses, doctors, social workers, midwives, pharmacists, physiotherapists, occupational therapists, radiographers, and paramedics [34-38]. We will include both individual professions and collective groups of practitioners.

Table 1. Definitions of participants, intervention, comparisons, and outcomes. The numbers in square brackets denote prioritization for analyses if more than one outcome is reported in a single study, according to the most reported outcomes. Prioritization will ensure outcomes are only represented once per study in quantitative synthesis and meta-analysis.

Term	Definition
Participants	
Practitioners	• Postregistration health and social care professionals, either as groups incorporating a range of disciplines (eg, workers at hospitals and other health and social care settings, clinicians and health and social care professionals) or as individual professions (eg, the largest registries of UK practitioners include 758,303 nurses and midwives [34], 355,250 doctors [35], 91,191 social workers [36], 79,628 pharmacists and pharmacy technicians [37], 60,783 physiotherapists [38], 41,732 occupational therapists [38], 39,497 radiographers [38], and 33,219 paramedics [38], and other disciplines. Similar profiles of common health and social care professions were expected in other geographical locations).
Intervention	
Research evidence	• Human, health and social care–related research, originating from published, peer-reviewed journal articles, that could be relevant for practitioners. Information posted on social media might be a direct link to these research articles, abstracts, or repackaged information from a single peer-reviewed research article source; eg, summaries such as microblogs, blogs, press articles, conference presentations or posters, infographics, or educational videos.
Social media	• Open social media platforms, including, but not limited to, social networking and media-sharing sites and apps, that allow any user to make a one-to-many post and to interact by responding to posts. The largest of these social media sites in 2018 in terms of active users included Facebook (2.26 billion), YouTube (1.90 billion), WhatsApp (1.33 billion), Instagram (1 billion), WeChat (1 billion), Tumblr (624 million), TikTok (500 million), Reddit (355 million), Twitter (329.5 million), and Pinterest (245.5 million) [16].
Comparison	
Dissemination	• Comparison of effectiveness of dissemination to practitioners using open social media vs no social media (between and within group comparisons) and comparison between social media platforms, sharing mechanisms, and formats.
Outcomes	
Reach	• Number of practitioners who access a research evidence–related social media post. • Number of impressions [1], views [2], or accesses [3] of a research evidence–related social media post.
Engagement	• Number of positive responses (eg, likes) to a research evidence–related social media post. • Number of interactions (eg, shares [1], comments [2], or fresh social media posts triggered [3]) with a research evidence–related social media post.
Direct dissemination	• Number of times an original research article is accessed (eg, link clicks [1] or HTML views [2]). • Number of times an original research article is downloaded (eg, PDF download). • Altmetric score of an original research article.
Impact	• Number of citations [1] of an original research article or [2] impact factor of journal. • Measures of changes in thinking or practice of health and social care practitioners linked to a research evidence–related social media post targeted at health or social care practitioners.

The intervention will be open social media used for dissemination of research evidence. We define research evidence as information from peer-reviewed articles featuring empirical findings that have met the publication standards of their specialty. Evidence may take the form of an original research article, or a group of original research articles identified and synthesized systematically. In this review, only research evidence that is professionally relevant to health and social care practitioners will be considered; however, our definition includes open-access research evidence (and social media posts where practitioners are the target audience), even when other audiences, like the general public, also have access.

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We define open social media as social networking and media-sharing sites or platforms that allow any user to make a one-to-many post and to interact by responding to posts. Our definition of social media differs from broader existing definitions of social media, such as that of Kaplan and Haelein [14], who consider social media as web-based applications that allow the creation and exchange of user-generated content. Our more focused definition was used to target social media with the greatest potential for knowledge mobilization between the different communities of research and clinical settings. The current literature in knowledge mobilization has highlighted the importance of open, 2-way interaction to create linkage between communities and facilitate knowledge sharing. In this context, dissemination of research is an active, relational, multidirectional, and collaborative process that interacts with the standpoint of those who access, share, discuss, and use it [39,40]. Thus, we do not include mass media press articles, wikis, and blogs with no, or limited, facility for user interactions, purely communication-based applications or closed, fee-paying, or invite-only social media groups. However, these will be considered if they are highlighted using open social networking or media sharing sites, used as part of onward information sharing, or are groups that can be freely joined by any interested user (eg, by following a link available on open social networking and media-sharing sites).

We define social media–sharing mechanisms as the ways in which research evidence might be featured or interacted with, including, but not limited to, open sharing to the entire forum, live social media events, influencer endorsement, and accessible special interest groups that can be joined or followed. We define social media formats as including a variety of media types, including, but not limited to, text, illustrative pictures, visual abstracts, infographics, videos, and podcasts.

The study inclusion and exclusion criteria are summarized in Textbox 1. Full-text, English-language studies will be included if they make quantitative comparison between dissemination of research evidence for health and social care practitioners using social media versus a controlled “no social media” condition (between group). Studies will also be included that quantify changes from baseline conditions to follow-up after an open social media campaign for dissemination of research evidence to health and social care practitioner (within group or case series data). Studies quantitatively comparing dissemination of research evidence for health and social care practitioners between different social media platforms, sharing mechanisms, and formats will also be included. Studies comparing topics of social media posts or research evidence will be excluded.

Textbox 1. Summary of inclusion and exclusion criteria.

Inclusion criteria:

- Peer-reviewed journal articles, study types including randomized controlled trials, case-controlled comparisons nonrandomized comparisons, pre-post designs, cohort studies, and case reports.
- Articles published after 2010.
- English-language articles or translations in English available.
- Articles that quantitatively evaluate and compare open group social media in terms of reach, engagement, dissemination, and impact of research evidence for postregistration health and social care practitioners.

Exclusion criteria:

- Study types including protocols, reviews, opinion pieces, and conference abstracts.
- Articles published before 2010.
- Articles not available in English.
- Study populations not including health and social care practitioners (eg, no mention of practitioners, only focused on students, service users, patients, or the general public).
- Social media interventions used only for sharing non health and social care–related research topics or other sorts of information (eg, multisource clinical education delivery, day-to-day interpersonal communications, and organizational or administrative information), closed, private, or invite-only groups, professional identity and reputation purposes, recruitment, or posts without a social networking component (eg, a blog or press article without signposting on social media networking sites).
- Comparisons between information topics only (without other comparisons, eg, between social media and control conditions, or between social media sites, or types of media).
- Articles that do not provide sufficient quantitative data on outcomes of interest or those reporting only qualitative data.

Information Sources

Searches will be carried out from January 1, 2010, to January 10, 2023. Preliminary searches revealed that there was unlikely to be relevant literature prior to 2010; whereas after 2010, reports of social media use in research dissemination increased. Searches will be carried out in electronic bibliographic databases including MEDLINE (Ovid), PsycINFO (Ovid), CINAHL plus (EBSCO), ERIC (EBSCO), LISTA, and OpenGrey. Search engines, including PubMed, elicit, and Google Scholar, will also be used for citation searches and reference harvesting. Bibliographic hand-searching of relevant systematic reviews and included articles will also be carried out. The search strategy

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is likely to be adequate to ameliorate selection and detection biases.

Search Strategy

The search strategies were informed by previous review searches [15,31,41] (see the search terms in Table 2 and the example search strategies in Multimedia Appendix 1).

Table 2. Summary of key search terms.

Key term	Search terms
Practitioners	• [Health, healthcare, health care, medical, hospital, social care] and [practitioner, professional, provider, staff, employee] or clinician • Nurse, midwife, doctor, physician, social worker, pharmacist, physiotherapist, physical therapist, occupational therapist, radiographer, or paramedic
Intervention	• Research evidence, information, research, data, knowledge, dissemination, sharing, knowledge mobilisation, knowledge translation.
Social media	• Social media, social network, open network, media sharing, social web, or social software • Facebook, YouTube, WhatsApp, Instagram, WeChat, Tumblr, TikTok, Reddit, Twitter, Pinterest, Flickr, Googl,, microblog, podcast, webcast, Tweet, or video sharing
Outcomes	• Dissemination, reach, engagement, impact, quantitative, evaluation, comparison, access, views, impressions, likes, share, comments, posts, HTML views, altmetric, download, citation, in practice, knowledge use
Timeframe	• January 2010-January 2023
Language	• English
Subjects	• Human

Data Management

The search results will be exported to, and deduplicated in, Endnote online (Clarivate), then imported into Rayyan software (Rayyan Systems) for title, abstract, and full-text screening [42].

Selection of Studies

Two reviewers (SRL and SQM) will independently screen titles and abstracts for eligibility. Potentially eligible studies will be obtained in full text and the eligibility criteria applied. Two of 5 independent reviewers (from a team including SRL, SQM, LB, HG, and FL) will screen all full-text articles against the eligibility criteria. If no consensus can be reached between reviewers, eligibility will be settled by a third reviewer (HB). Articles will be included only if they provide sufficient quantitative data to allow extrapolation of mean (SD) outcome data per social media post for 2 comparable groups. Reasons for article exclusion will be recorded according to the PRISMA recommendations [43].

Data Extraction

The data will be extracted from included full-text articles by 2 of 5 reviewers (SRL and SQM/LB/HG/FL) independently using a data extraction form developed a priori and adapted from the previous relevant reviews [26,31] (see Multimedia Appendix 2). Consensus on extracted data accuracy will be achieved by discussion and settled by a third reviewer (HB) in the case of disagreement. Corresponding authors of eligible studies will be contacted to request additional data when required.

Outcome Data

The quantitative outcomes will be grouped into 4 domains (reach, engagement, dissemination, and impact; Table 1) [27,44]. Outcome measures will be grouped by domain because a heterogeneous range of outcomes and study designs are characteristic of the social media literature [15,25]. There is no primary outcome because dissemination of research evidence via social media is a complex multidimensional behavior that cannot be distilled into a single outcome [25,27]. Different outcomes measuring the same concept will be combined for meta-analysis wherever appropriate. Where multiple outcomes reporting the same concept are reported in a single study, hierarchical outcome prioritization will be used, preferentially selecting the most frequently reported variables (see Table 1).

The difference between group means for each comparison group will be obtained, or the mean difference from baseline to follow-up in pre-post designs. To accompany means, SD and 95% CI will be extracted. Wherever possible missing means and SDs will be calculated from other reported statistics (eg, median and IQR, as per Cochrane Handbook instructions Section 5.6 and Chapter 6) [45]. For each outcome, data will be simplified by dividing by the number of social media posts, to yield comparable quantitative data per research evidence–related social media post.

Risk of Bias and Quality Rating of Evidence

For randomized controlled trials, the Cochrane tool for assessing risk of bias (ROB-2) will be used [46]. For nonrandomized controlled trials, the Newcastle-Ottawa Scale (NOS) [47] will be used to assess risk of bias, as per 2019 Cochrane recommendations [45]. Both the ROB-2 and the NOS will be

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adapted to suit the types of studies selected in this systematic review because studies testing social media dissemination are unlikely to use typical participant grouping designs. The NOS was selected in preference to the latest Cochrane tool for assessing risk of bias in nonrandomized studies (ROBINS; consisting of ROBINS-I for intervention studies and ROBINS-E for exposure studies [48,49]). This was because the complexity of these tools will not allow adaptation to alternative study designs and 1 tool (ROBINS-E for exposure studies) is still in development.

ROB-2 consists of 34 items, divided into 6 scoring domains that differentiate between lower risk of bias and higher risk of bias [46]. The maximum rating of the NOS is 9, a score of 0-3 is considered high risk of bias, 4-6 considered a medium risk of bias, and 7-9 considered a low risk of bias (Multimedia Appendix 3) [47]. Risk of bias will be included in results tables and figures that describe each included study.

Data Synthesis

Results will be summarized narratively with text, tables, and figures. Quantitative comparisons between studies and groups will include mean, SD, and simplified group means weighted per research evidence–related social media post.

Between, and within for pre-post designs, group differences, SDs, and standardized effect sizes (eg, Cohen *d* or Hedges *g*) will be used to compare effects between included studies. Effect sizes of ≥0.8 will be defined as large, ≥0.5 as moderate, and ≥0.2 as small [50].

For outcomes that are available in a sufficient number of studies, pooled effects will be tested in meta-analyses using RevMan (version 5.3; The Cochrane Collaboration). Heterogeneity will be tested using I^2. To test pooled effects, a fixed-effects model will be used if I^2 is less than 50% or a random-effects model will be used if I^2 is greater than 50%. If a comparison has I^2>75% it will be removed from meta-analysis and synthesized narratively instead. Subgroup analyses will be used for heterogeneous study groups. Publication bias will be assessed using funnel plots.

Confidence in Cumulative Evidence

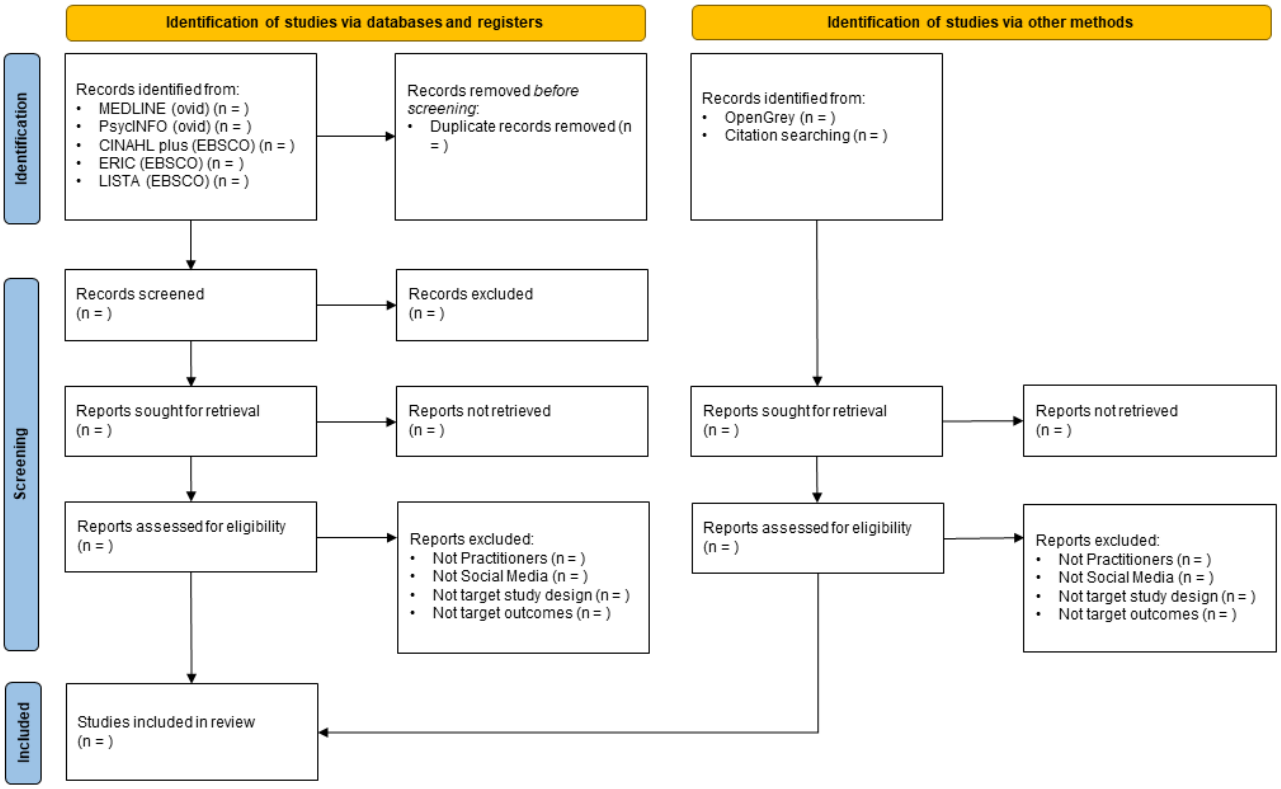
For each outcome, the uncertainty of the evidence base will be evaluated based on the grading of recommendations assessment, development, and evaluation approach [51]. This includes the following 5 domains: study limitations, imprecision, indirectness, inconsistency, and publication bias. The grading of recommendations assessment, development, and evaluation domains will be used to upgrade or downgrade evidence after initial assessment. Quality of evidence will be categorized as high, moderate, low, or very low [52,53].

Results

Searches and screening will be completed by the end of May 2023 and recorded in a PRISMA flowchart (Figure 1) [43].

Data extraction and analyses will be completed by the end of July 2023, after which findings will be synthesized.

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart.



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Discussion

Overview

We expect that this study will be completed by the end of October 2023. This review will synthesize evidence of the effectiveness of open social media for dissemination of research evidence to health and social care practitioners. We anticipate that we will find evidence that social media is effective, although there may be variation between its effect on the 4 outcome domains (reach, engagement, direct dissemination, and impact).

The previous reviews have highlighted the potential of social media for a variety of purposes in health care [15,25,26,31,54], although dissemination of research evidence currently accounts for only 1% of health research concerning social media [55]. Two existing reviews suggest that social media might be effective to improve direct dissemination and impact of research articles [31] and reach and engagement with clinical guidelines [54]; however, quantitative syntheses and meta-analyses were not performed.

Qualitative reviews have highlighted strategies that may enhance the dissemination of research evidence on social media [15,26,31,54]. These include enlisting people with expertise in social media at the planning stage, using professional social media marketing services and involving target users in content design. Use of multiple social media platforms is implicated, although Twitter is most often highlighted for professional use. Social media formats include using media that are accessible, relevant, useful, authentic, credible, and visually appealing to target users, a range of multimedia formats (including good quality images and infographics, text, videos, and podcasts, with images highlighted as being particularly important for social media reach and engagement). Social media–sharing mechanisms include involving key influencers and networks with the most connectedness in the field (such as organizational newsletters, journals, or individuals) to enhance social filtering, creating or enlisting existing web-based communities of practice, identifying and using key hashtags, posting at planned times (potentially including weekdays, weekday evenings, and weekends), posting regularly for a sustained campaign, and coordinating engagement events (such as journal clubs, question and answer sessions, or live interviews).

This systematic review will be the first to use quantitative, meta-analytical synthesis of evidence for the effectiveness of social media for research dissemination to practitioners. The limitations of the evidence may include multiple outcomes or methodological heterogeneity that limit meta-analyses, potential risk of bias in included studies, and potential publication bias. The limitations of the study design may include potential insensitivity of the electronic database search strategy to specific professional disciplines or social media platforms; however, bibliographic citation searching of included articles and relevant systematic reviews is likely to compensate for this. As social media are rapidly evolving, this systematic review will need to be repeated regularly to consider the impact of new and favored platforms and the search strategy revised to account for this.

The conclusions of this systematic review will inform the use of social media for the dissemination of research evidence to health and social care practitioners. This information will be important for researchers, research funders, and governmental bodies who have a remit to share their research evidence to inform practice and care. The findings of this review could be complemented by investigation of different practitioners' attitudes and experiences of professional social media use so that targeted dissemination strategies could be developed. Future research directions include quantitative synthesis and meta-analysis of evidence for the effectiveness of closed social media groups for the dissemination of research evidence to health and social care practitioners. The interaction between closed and open social media may enhance knowledge sharing and engagement [15].

Dissemination Plan

The findings from this systematic review will be disseminated through a peer-reviewed journal article, presentations at academic conferences and promoted using social media.

Acknowledgments

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Data Availability

The data sets generated and analyzed during this study will be available from the corresponding author on reasonable request. The full search strategy is available in Multimedia Appendix 1.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search strategy.
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Multimedia Appendix 2
Data extraction form.
[DOCX File , 14 KB - resprot_v12i1e45684_app2.docx]

Multimedia Appendix 3
Risk of Bias tools.
[DOCX File , 21 KB - resprot_v12i1e45684_app3.docx]

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Abbreviations

NOS: Newcastle-Ottawa Scale
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
ROB-2: Cochrane tool for assessing risk of bias
ROBINS: Cochrane tool for assessing risk of bias in nonrandomized studies

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Protocol

Clinical Efficacy of Deep Transcranial Magnetic Stimulation in Psychiatric and Cognitive Disorders: Protocol for a Systematic Review

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Abstract

Background: Transcranial magnetic stimulation (TMS) is a widely used noninvasive brain stimulation technique for psychiatric and cognitive disorders. In recent years, deep TMS (dTMS) has shown promise as an enhanced form of TMS able to stimulate deeper brain structures and target broader networks. Various magnetic Hesed-coil (H-coil) designs—a novel feature of dTMS—have been used to stimulate brain regions implicated in the pathophysiology of specific psychiatric and cognitive disorders, thereby producing therapeutic effects. Given the novelty of dTMS in psychiatry, little is known about the clinical efficacy of dTMS across psychiatric and cognitive disorders—that is, whether dTMS performs superiorly to sham or control.

Objective: In this paper, we outline a protocol for a systematic review investigating the clinical efficacy of dTMS. The primary objective is to conduct a systematic review of the literature on dTMS for psychiatric and cognitive disorders and, if feasible, a meta-analysis to compare the efficacy of active dTMS versus sham/control for psychiatric disorders. Dementia and related cognitive disorders will also be examined. A secondary objective will be to examine subgroup differences (by age, sex, H-coil design, and dTMS parameters [ie, pulses per session, percentage of motor threshold, etc]) to evaluate whether dTMS differentially influences clinical outcomes based on these factors.

Methods: A comprehensive search of the APA PsycINFO, Embase, MEDLINE, and PubMed databases will be conducted using keywords such as “H-coil” and “dTMS.” Two authors (AD and MD) will be responsible for screening relevant articles, assessing article eligibility (according to predetermined inclusion and exclusion criteria), and data extraction. All included articles will undergo a quality and risk of bias assessment. Data from included articles will be summarized qualitatively in a systematic review. If a sufficient number of equivalent studies are available, a meta-analysis will be performed to (1) determine the effect of active versus sham dTMS (or another control arm) across psychiatric and cognitive disorders, and (2) examine subgroup effects of clinical outcomes.

Results: The preliminary search rendered a total of 1134 articles from the APA PsycINFO, Embase, and MEDLINE databases. After full-text screening, 21 eligible articles remained. One additional article was identified from the references section of an existing systematic review. In total, 22 eligible articles were included. Data extraction and quality of assessment procedures are ongoing.

Conclusions: We will outline the evidence relating to the clinical efficacy of dTMS in various psychiatric and cognitive disorders. The results of the prospective systematic review will provide clinicians with valuable insight into the clinical (ie, participant age,

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sex, psychiatric or cognitive disorder, etc) and methodological factors (ie, H-coil design, dTMS parameters, etc) which may contribute to dTMS efficacy, and thereby may assist clinicians in their decision to prescribe dTMS for specific psychiatric and cognitive disorders.

Trial Registration: PROSPERO CRD42022360066; https://tinyurl.com/5ev6byrn

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KEYWORDS

cognitive disorders; deep rTMS; deep TMS; deep transcranial magnetic stimulation; dTMS; H-coil; prospective meta-analysis; psychiatry; systematic review protocol

Introduction

Psychiatric [1,2] and cognitive disorders [3] are leading causes of disability and burden worldwide and are associated with substantially poorer quality of life [4-7]. From 1990 to 2019, the number of disability-adjusted life-years due to psychiatric disorders has increased globally from 80.8 million to 125.3 million. [2] Of greater concern, it is estimated that 20%-60% of patients with psychiatric disorders are treatment-resistant to first-line medications [8]. In particular, treatment resistance occurs in approximately one third of patients with major depressive disorder [9,10], 30%-60% of patients with schizophrenia [11-13], and 40%-60% of patients with obsessive-compulsive disorder [14,15]. As for cognitive disorders, dementia is on the rise as a leading cause of global mortality [16]. Further, older adults with mild cognitive impairment show an increased risk of mortality [17,18]. Currently, there are no effective treatment options to delay the progression of mild cognitive impairment and dementia [19], nor are there effective interventions to manage the behavioral and psychological burdens of such conditions [20-23].

Given the prevalence of treatment resistance in response to first-line pharmacological interventions in psychiatric disorders, as well as the lack of available treatment options to effectively treat and manage cognitive disorders, new effective treatments are urgently needed. One such technique is brain stimulation.

Brain stimulation methods have shown increasing promise and widespread acceptance as nonpharmacological interventions to treat various psychiatric [24,25] and cognitive disorders [26,27]. Electroconvulsive therapy [28] and transcranial magnetic stimulation (TMS) [29,30] are the most commonly used treatments, which involve the stimulation of the brain through electrical currents and magnetic pulses, respectively. Traditional single-pulse TMS is used to explore brain functioning, whereas repetitive TMS (rTMS) is administered to induce brain activity that lasts beyond the stimulation period [31]. These noninvasive stimulation techniques offer potentially propitious therapy for neurological and psychiatric disorders [32]. Research on other therapy options, such as vagus nerve stimulation [33,34] and deep brain stimulation [35-37], have continued to accumulate, offering further insight into these treatment options for psychiatric disorders.

Another promising method—known as deep TMS (dTMS)—is a noninvasive technique allowing for stimulation of deeper cortical areas and presumably deeper neural networks [38,39]. Since the approval of dTMS in 2013 by the US Food and Drug Administration for major depressive disorder [40], this method of intervention has gained popularity for the treatment of diverse psychiatric disorders.

The aim of dTMS is to modulate brain activity by applying an electrical current over the scalp. Brief magnetic pulses cause widespread neural depolarization in deep regions of the brain, resulting in reduced focal distribution of the electric field [41]. Trains of pulses can be delivered at high-frequency stimulation (>5 Hz) to increase neuronal excitability or at low-frequency stimulation (~1 Hz) to reduce neural excitability [42]. The use of a Hesed-coil (H-coil) dTMS system is a relatively novel noninvasive method that stimulates deeper regions of the brain in comparison to traditional rTMS [43,44]. While traditional TMS figure-8 coils generally stimulate subdural cortical targets up to 0.7 cm [44], dTMS target areas are up to 4 cm beneath the surface depending on the chosen H-coil [45]. More than 20 different types of H-coils have been developed to effectively stimulate specific brain structures [46]. The H-coil configuration received clearance from the US Food and Drug Administration for the treatment of major depression (H1-coil), obsessive-compulsive disorder (H7-coil), and smoking cessation (H4-coil), and anxious depression, in 2013, 2018, 2020, and 2021, respectively. Various H-coil designs have been shown to be safe and efficacious in the treatment of various neuropsychiatric conditions [47-49].

H-coils have complex winding designs and broad dimensions to encompass a larger surface area for stimulation of the electric field [46]. The different types of H-coil designs reflect the subdural depth and volume of stimulation, as well as the region of stimulation. The H1-coil was designed to stimulate the bilateral prefrontal cortex with preference to the left dorsolateral prefrontal cortex of approximately 1.8 cm subdurally [50]. The volume of stimulation for the H1-coil configuration typically encompasses 18 cm^3 [51]. Further, the H7-coil design primarily stimulates 3 cm of subdural depth and 40.3 cm^3 of breadth in the medial prefrontal cortex and anterior cingulate cortex [51], while the H4-coil targets the bilateral insula and ventrolateral and dorsolateral prefrontal cortex with a depth of 1.5 cm and a volume of 15.2 cm^3 [45]. In comparison, the traditional figure-8 coil used in rTMS stimulates 0.7 cm below the scalp, encompassing a volume of 3 cm^3 [51]. The most commonly used dTMS protocol involves high-frequency (18-20 Hz) and high-intensity (120% of the resting motor threshold) stimulation delivered for 20 days [41].

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Given the increasing interest in the application of dTMS in psychiatry [52], it is critical that its clinical effects are systematically appraised. As dTMS is a relatively novel form of therapy for psychiatric and cognitive disorders, assessments of its clinical efficacy are limited within the empirical body of literature.

A single systematic review and meta-analysis have examined the clinical efficacy of dTMS for treatment-resistant depression [52]. The authors highlight dTMS as an effective intervention, especially when administered in conjunction with antidepressants. However, systematic reviews examining the clinical efficacy of dTMS for other psychiatric conditions remain sparse. One systematic review [53] explored the effects of rTMS in patients with posttraumatic stress disorder. However, only 1 sham-controlled dTMS study [49] was included in this review. Another systematic review [54] examined the effects of dTMS for substance use disorders; however, clinical efficacy was not appraised due to the limited number of sham-controlled trials.

To date, no systematic review has investigated the clinical efficacy of dTMS across multiple psychiatric and cognitive disorders, as determined by the examination of sham-controlled or controlled (without sham coil) trials. There is a growing need for a new systematic review to synthesize the findings of recent dTMS clinical trials in patients with various psychiatric and cognitive disorders, including Alzheimer disease [55], attention-deficit or hyperactivity disorder [56], obsessive-compulsive disorder [57], posttraumatic stress disorder [58], and substance use disorder [59]. Thus, the objective of the proposed systematic review and prospective meta-analysis is to compare the efficacy of dTMS active treatment versus sham stimulation (or another type of control treatment) across psychiatric disorders and pertinent cognitive disorders.

Specifically, the proposed systematic review that follows this paper's protocol will aim to:

1. Systematically review and summarize existing research to examine the clinical efficacy of dTMS versus sham/controls for psychiatric disorders and (if available) cognitive disorders.
2. Integrate statistical results of included clinical trials in a meta-analysis, if feasible (ie, adequate numbers of substantively equivalent studies are present), to determine the effect of dTMS active stimulation versus sham (or control arm) across psychiatric and pertinent cognitive disorders.
3. Conduct subgroup analyses (by age, gender, coil design, and dTMS parameter) to determine if dTMS differentially influences clinical outcomes within these subgroups.

Methods

Search Strategy

A systematic search of the PubMed, APA PsycINFO, Embase, and MEDLINE databases will be conducted to identify relevant articles. The Cochrane database will also be explored for pertinent articles. Two authors (AD and MD) will be responsible for independently conducting the searches. The core keywords used in the searches will include "dTMS," "deep rTMS," "deep TMS," "deep transcranial magnetic stimulation," and "H-coil." Table 1 provides a summary of the search terms that will be used for each database. Automatic filters will be applied to limit search results to clinical trials and randomized controlled trials. No date limits will be applied. Moreover, a manual search of existing meta-analyses and systematic reviews on dTMS for psychiatric and cognitive disorders will be conducted to identify other potential articles from the reference section.

Table 1. Search strategies used to identify relevant articles from databases. Searches will be limited to clinical trials and randomized controlled trials written in English. No date limits will be applied.

Databases	Search strategy	Final search terms
PubMed, Cochrane, and OVID (APA PsycINFO, Embase, and MEDLINE)	1. dTMS 2. "deep TMS" 3. "deep transcranial magnetic stimulation" 4. "deep rTMS" 5. "deepTMS" 6. "H-coil*" 7. "H coil*"	1 or 2 or 3 or 4 or 5 or 6 or 7

Study Selection: Inclusion and Exclusion Criteria

All articles will be independently screened and assessed for eligibility by 2 authors (AD and MD) according to the predetermined inclusion criteria. We will include clinical trials reporting the clinical effect of dTMS interventions for psychiatric and cognitive disorders compared to a sham-controlled or control arm. The full inclusion and exclusion criteria are presented in Textbox 1.

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Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria:

- Article type
  - Clinical trials and randomized controlled trials
  - Studies including a sham or control condition
  - Studies comparing active deep transcranial magnetic stimulation to a sham or control condition
  - Articles of any publication year
- Study participants
  - Participants with a valid diagnosis of a psychiatric or cognitive disorder according to a recognized diagnostic manual (ie, the Diagnostic and Statistical Manual of Mental Disorders, Fourth or Fifth edition [DSM-IV, DSM-5], the International Classification of Diseases, Eleventh edition [ICD-11]), or a clinician
- Language
  - Articles written in English

Exclusion criteria:

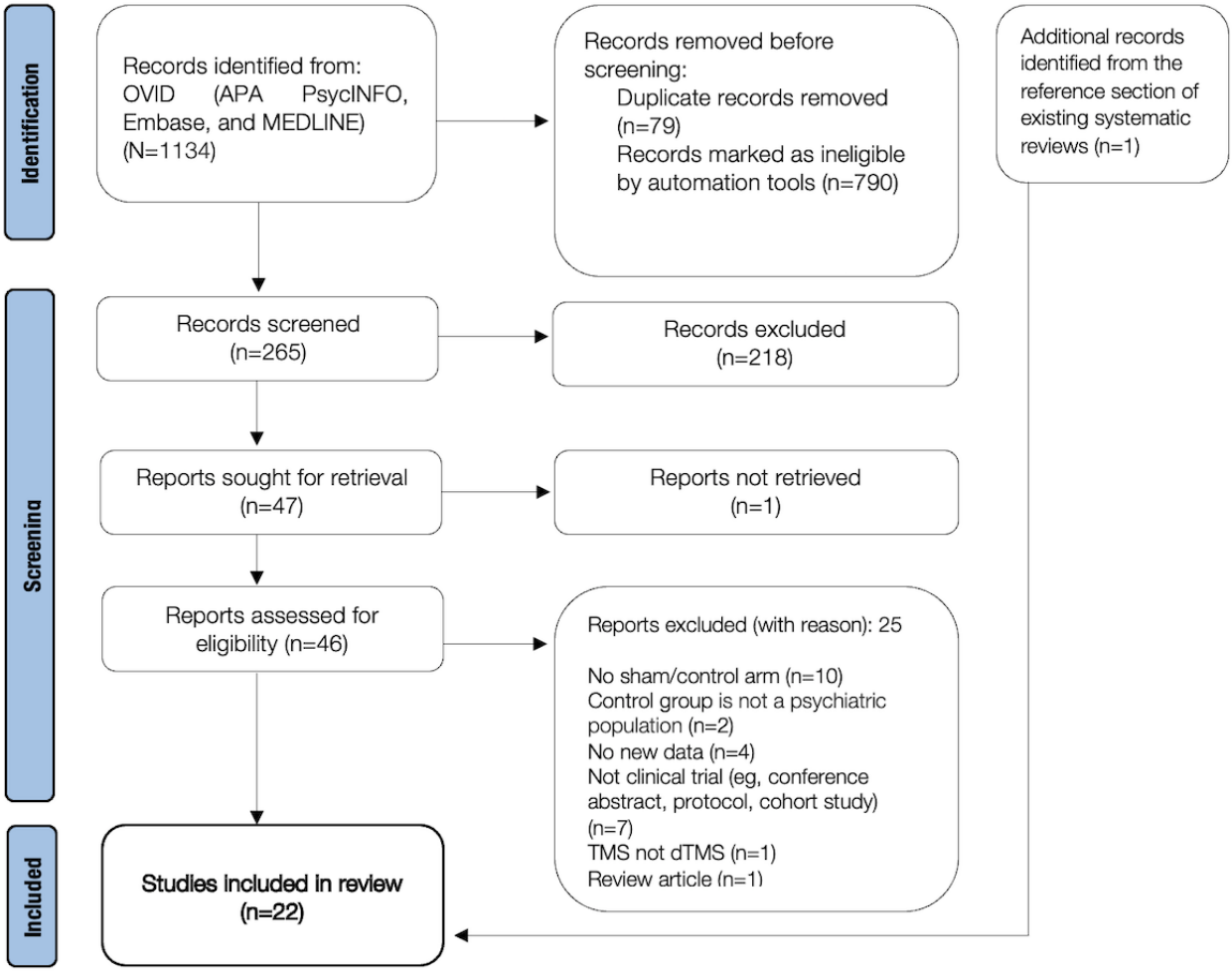
- Article type
  - Conference abstracts
  - Letters to the editor
  - Books
  - Literature reviews, systematic reviews, or meta-analyses
  - Case reports or case studies.
- Study participants
  - Participants are healthy individuals
- Language
  - Articles not written in English

Article Screening

Two authors (AD and MD) will conduct the abstract and full-text screening of relevant articles. Articles will be screened in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [60] guidelines. In line with PRISMA guidelines, authors are required to report the number of records identified, included, and excluded articles (with reasons) at each stage of the screening process. PRISMA guidelines help authors ensure that potentially eligible records are being appropriately sorted and organized throughout the early systematic review process. Articles that meet the inclusion criteria upon the initial abstract screening will then become eligible for the full-text screening. Articles that meet the inclusion criteria after the full-text screening will be included in the review. The number of articles included and excluded (and the reasons for exclusion) will be reported at each stage in the screening process and will be visually represented by a PRISMA flowchart (Figure 1). The 2 reviewers (AD and MD) will consult with each other in the case article eligibility is unclear. Article eligibility discrepancies that cannot be resolved by the 2 reviewers (AD and MD) will be resolved by a third reviewer (JM).

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Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart. The title-abstract and full-text screenings of potentially eligible reports were performed. Articles were excluded at each stage of the screening progress according to the inclusion and exclusion criteria. dTMS: deep transcranial magnetic stimulation; TMS: transcranial magnetic stimulation.



Risk of Bias and Quality Assessment

All articles will be assessed according to the grading of recommendations, assessment, development, and evaluations (GRADE) checklist [61,62] to evaluate the quality of data and risk of bias. Two reviewers (AD and MD) will rate articles as having a "high" or "low" risk of bias. Specifically, included articles will be assessed for selection bias, performance bias, detection bias, attrition bias, and reporting bias. Selection bias will be evaluated by identifying whether researchers used a random sequence generation and allocation concealment. Assessment of performance bias will involve determining if study personnel and participants were blinded. To calculate detection bias, reviewers will verify if studies implemented a blinding of outcome assessment. Attrition bias will be assessed by determining if at least 80% of enrolled participants were included in the final analyses (ie, comparing intention-to-treat participants to per-protocol analyses). We will also assess article quality by taking into consideration participant sample sizes and study design (ie, inclusion of control condition, baseline vs posttreatment assessment of psychiatric or cognitive symptoms) while determining the clinical efficacy of dTMS treatment.

Data Extraction

The following data variables will be extracted from each included article: country of publication, study type, comparison type (ie, active dTMS vs sham, or standard drug therapy, or another control type), participant sample size, participant sex, and mean age. The psychiatric or cognitive disorder diagnosis and diagnostic criteria (eg, Diagnostic and Statistical Manual of Mental Disorders, 4th edition; Diagnostic and Statistical Manual of Mental Disorders, 5th edition; International Classification of Diseases, 11th edition) of patients will be recorded. Regarding treatment procedures, this study will report treatment duration, number of treatment sessions, H-coil type, and the brain regions of interest (ie, target region of stimulation). Additionally, this study will report the dTMS parameters, including frequency (Hz), intensity, pulses per session, time per session, trains per session, and intertrain interval duration. Posttreatment comparisons between dTMS efficacy in active versus sham/control groups will be reported, including data on remission rates, response rates, or posttreatment score changes on psychiatric and cognitive rating scales. Remission criteria and response criteria will also be reported. Additionally, we will include data related to side effects and adverse events. Table 2 provides an outline of the specific variables that will be extracted from studies, with respect to sample characteristics,

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dTMS parameters, clinical efficacy outcomes, and study design. Data from included articles will be collected and stored using Excel (Microsoft Corp) or other equivalent software. Additionally, quality assessment according to the GRADE guidelines [61,62] will be conducted for each article and recorded in a table.

The proposed systematic review will evaluate the clinical efficacy of dTMS for psychiatric and cognitive disorders by comparing active versus sham dTMS treatment groups (ie, sham-controlled trials), as well as active versus control groups (ie, without a sham coil). To do this, we will compare response rates, remission rates, and the overall efficacy of the dTMS treatment in active versus sham/control conditions. Additionally, if at least 4 substantively equivalent investigations are present in a given area, we will perform a meta-analysis to ascertain aggregate clinical effects across studies in sham/control trials. Further subgroup analyses will be conducted on age, sex, H-coil type, and dTMS parameters to the extent possible. Risk of bias and article quality assessments will be used when considering evidence and analyzing data from included studies. Moreover, the study will summarize the proposed review's findings on the clinical efficacy of dTMS for psychiatric and (if available) cognitive disorders, identify evidence that may assist clinicians in their practice, and highlight future directions for research.

Table 2. Study characteristics that will be recorded from eligible articles.

Information category	Data to be extracted
Sample characteristics	• Age • Gender • Psychiatric or cognitive disorder diagnosis • Diagnostic criteria • Sample size
Deep transcranial magnetic stimulation (dTMS) parameters	• Brain region of interest (ie, location of brain stimulation) • Coil type or design (ie, H-coil variety) • dTMS stimulation frequency (Hz) • dTMS stimulation intensity (MT%) • Pulses per session • Time per session (min) • Trains per session; inter-train intervals
Results: clinical efficacy	• Test statistics for active versus sham/control group comparisons • Test statistics for subgroup comparisons (ie, age, sex, dTMS parameter, coil design, etc) • *P* values, CI values, t test values, Cohen d, Hedges g (where reported), for active vs sham/control group comparisons • Adverse events • Remission rates and remission criteria • Response rate and response criteria • Qualitative statistics for active versus sham group comparisons
Study design	• Control type (ie, sham-controlled; control activity) • Comparison type (eg, active vs sham stimulation) • Treatment duration • Randomized versus nonrandomized • Single-blind vs double-blind

Statistical Analysis

For the prospective meta-analysis, analyses will be conducted using Stata (StataCorp). Heterogeneity will be assessed using the Q test, I^2, and τ^2. A random effects model will be used, if appropriate, to account for potential between-studies variance in treatment effect.

Results

The proposed systematic review aims to evaluate the clinical efficacy of active dTMS versus sham/control in various psychiatric (and if available) cognitive disorders. Additionally, a meta-analysis will be performed (if a sufficient number of studies are available) exploring the effects of dTMS parameters, age, sex, and H-coil type on clinical outcomes.

Thus far, 22 eligible studies have been included from the following databases: APA PsycINFO, Embase, and MEDLINE (refer to Multimedia Appendix 1). A search of the APA PsycINFO, Embase, and MEDLINE databases resulted in 1134 articles. A total of 790 articles were removed by OVID automation tools which limited articles to English, human participants, and clinical trials. Additionally, 79 duplicate records were removed by automation tools. After screening the abstracts of the remaining 265 articles, 218 were excluded. The full texts of the remaining 47 articles were then screened for eligibility. One report could not be retrieved. Following the full-text screening, 25 articles were excluded for the following reasons: (1) not having a sham or control condition (n=10); (2) the control group was not a psychiatric population (n=2); (3) no new data were reported (n=4); (4) not a clinical trial (n=7); (5) intervention was with TMS, not dTMS (n=1); and (6) being a review article (n=1). One additional article was identified

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from the reference section of an existing systematic review. The PubMed search did not render any additional articles.

A search of the Cochrane database still needs to be performed to identify other potential articles. The data extraction process is ongoing. Once the data extraction is complete, we will determine if there are enough suitable articles to conduct a meta-analysis. We aim to have this project complete by the end of 2023.

Discussion

Objectives and Limitations

The preliminary screening stages of the ongoing systematic review have rendered a total of 22 eligible articles comparing the efficacy of dTMS to a sham/control condition. While dTMS treatment has been shown to effectively alleviate clinical symptoms for psychiatric and cognitive disorders, the current state of literature lacks insight into the clinical efficacy of dTMS interventions across such disorders. Data from all 22 articles identified in the preliminary search may help to bridge this gap in the literature by conducting a comprehensive systematic review, and prospective meta-analysis, to determine the efficacy of dTMS across diverse psychiatric and cognitive disorders.

The proposed review will be the first, to our knowledge, to evaluate the clinical efficacy of dTMS across psychiatric and pertinent cognitive disorders. The knowledge gathered from this systematic review holds great clinical value. First, it can inform clinicians about the potential clinical benefits of dTMS in specific psychiatric populations. Second, by further conducting subgroup analyses (whereby a meta-analysis is deemed appropriate), this study aims to identify subgroup variables that may affect clinical outcomes following dTMS treatment. This subgroup data has valuable clinical implications, as the identification of such clinical and methodological factors may influence clinicians' decisions to support dTMS over another treatment regimen. Thus, future dTMS treatments can be tailored to fulfill the patient's needs and customize treatments to optimize therapeutic effects.

The systematic review that follows this protocol may have limitations. First, sham-controlled studies exploring the clinical efficacy of dTMS are limited. Second, there may not be sufficient studies to examine the clinical efficacy of dTMS for each psychiatric and cognitive disorder. Thus, a meta-analysis may not be possible for all conditions, which may hinder assessments of subgroup variables potentially influencing dTMS efficacy.

Conclusions

In this protocol, the authors openly review the methodological procedures of a systematic review (and prospective meta-analysis) designed to effectively determine the clinical efficacy of dTMS for psychiatric and cognitive disorders. This protocol was published to ensure the originality of this research and to contribute to data availability.

Acknowledgments

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Data Availability

The data set generated and analyzed during this study will be made available by the corresponding author upon reasonable request.

Authors' Contributions

DD is credited with developing the original conception of the protocol for the systematic review. AD and MD conducted initial bibliographic searches to screen for eligible articles and prepared the original manuscript. JM contributed substantive conceptual input and edited the manuscript. All authors approved the final version of the manuscript.

Conflicts of Interest

JM is a principal in BEAM Diagnostics Inc and a consultant to Clairvoyant Therapeutics Inc. The other authors declare no potential competing interests.

Multimedia Appendix 1
Full search strategy and articles retrieved.
[DOC File , 120 KB - resprot_v12i1e45213_app1.doc]

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Abbreviations

dTMS: deep transcranial magnetic stimulation
GRADE: grading of recommendations, assessment, development, and evaluations
H-coil: Hesed-coil
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
rTMS: repetitive transcranial magnetic stimulation
TMS: transcranial magnetic stimulation

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Protocol

The Relationship Between Nonsuicidal Self-injury and Attachment: Protocol for a Systematic Review and Meta-analysis

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Abstract

Background: The prevalence of nonsuicidal self-injury (NSSI) is a major concern in public health. Two main factors (individual and environmental) cause NSSI. Studies addressing NSSI often consider it as an emotion regulation strategy. Studying NSSI within the framework of attachment theory is reasonable since the capacities to regulate emotion come into existence in the framework of attachment in the first periods of a child's growth. Primary studies addressing this topic are not frequent, and no systematic review has been conducted.

Objective: This systematic review and meta-analysis protocol aims to investigate the relationship between NSSI and attachment style and finding its relationship based on study design, study type, different types of attachments, and gender.

Methods: All studies on the relationship between NSSI and attachment will be included in this systematic review. We will include observational studies (cross-sectional, cohort, and case control) through searches in electronic databases via PubMed, CINAHL, Embase, Web of Science, ProQuest, Scopus, PsycINFO, and Google Scholar as complementary search. Qualitative studies, case studies, case series, and letters to the editor will be excluded. There will be no language limitation. Moreover, there will be no limitations regarding the study participants' age, gender, nationality, sexual orientation, and psychological problems. Funnel plots were examined if 10 or more studies are included, and the Begg and Egger statistical tests were used to assess the risk of bias. All similar data will be combined through the "metan" command by Stata statistical package (StataCorp). A fixed-effects or random-effects model, considering methodological similarities or differences, will be selected to determine a combination model.

Results: We will summarize the selection of the eligible studies using a flowchart. The results will be presented in a table of evidence. The results of the meta-analysis will be depicted using diagrams and tables.

Conclusions: It seems necessary to carry out such systematic and comprehensive meta-analysis to present a summary of the published articles in terms of the relationship between NSSI and attachment. The results from this review will be used to improve our knowledge of the role of the upbringing of children and NSSI behavior and will help design appropriate interventions to address NSSI.

Trial Registration: PROSPERO CRD42021226455; https://tinyurl.com/yc77wny8

International Registered Report Identifier (IRRID): PRR1-10.2196/40808

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KEYWORDS

nonsuicidal self-injury; NSSI; attachment; emotion regulation; systematic review; review methodology; search strategy; library science; librarian; self-injury; self-harm; self-injurious; self-destructive; self-mutilation; review protocol; meta-analysis; meta-analyses

Introduction

Background

Nonsuicidal self-injury (NSSI) is defined as a direct [1], repeated and socially unacceptable injury to a person's body tissue [2], a deliberate destruction of one's own body tissue [3], and without suicidal thoughts [4]. It includes cutting, scratching, or burning the surface of one's body, as well as hitting with objects, and inflicting direct damage to one's skin or bones by a person [5]. This is a common character in borderline personality disorder [6], and was one of the initial criteria of borderline personality disorder [7]. The criteria for NSSI were presented in Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), but it needs further empirical study to be mentioned in the next version of DSM. The criteria for NSSI include the following: the person having intentionally injured surface parts of their own body such as cutting, burning, biting, and scratching skin for at least 5 days over the past year; this act cannot have been culturally influenced [8]; the intentional injury should have been associated with negative emotions and feelings such as pervasive anxiety, stress, anger, and confusion; and this act must have been committed to achieve a specific goal [9].

It usually begins in adolescence, the age of onset has been reported to be between 14 and 16 years [10], and its rate decreases in late adolescence [11]. As a common psychiatric symptom, it puts adolescents at greater risk than other age groups [12]. The prevalence of this disorder in teenagers has been reported 16% [13]. Sex differences are also important in this disorder, which occurs more commonly in girls [14]. The prevalence of NSSI in teenage girls is reported to be 19% [15]. There are also cultural differences in the prevalence of these behaviors. The overall prevalence of NSSI (32.6%) is higher in Asian countries compared with Western countries (19.4%) [16].

According to the prevalence of this disorder in different ages and cultures, there are various predisposing factors based on the results of qualitative research. One of the etiological factors, for instance, is attachment styles [17,18]. Generally, the predisposing factors for the development of NSSI can be divided into individual and environmental factors [19]. Adolescence is a period of physical and psychological growth, and it is important because of changes related to puberty, identity, and independence. This stage is accompanied by important and sudden changes such as physical, sexual, cognitive, emotional, and moral changes, as well as changes in desires, values, and patterns. All these factors together create difficulties for teenagers, and training, support, time, and patience are required to answer their questions or have their problems solved. If teenagers cannot manage and solve their problems, they may turn to inappropriate practices such as NSSI [20].

On the other hand, attachment styles are known to be one of the environmental factors, which play an important role in the onset, formation, and maintenance of NSSI in adolescents [21]. Based on the research results, insecure attachment plays an important role in the tendency of people to NSSI [22]. Unfavorable family conditions in the early years of life have been identified as risk factors for presenting NSSI. There are correlations between NSSI and parental absence [23], poor quality of relationship with parents [24,25], and a lack of social support [26].

Attachment is a deep and enduring emotional bond that connects one person to another across time and space. Attachment is an emotional bond between child and the primary caregiver. The caregiver's response pattern can help regulate the child's emotional states so that the child can develop a secure attachment style. On the other hand, an inconsistent response pattern or less responsive caregiving can lead to an insecure attachment pattern that causes emotional dysregulation [21]. Some empirical studies have discussed the relationship between insecure attachment and NSSI. In a sample of adult psychiatric patients, they found that preoccupied attachment was associated with lifelong NSSI, but emotional pain partially moderated the relationship between a dysfunctional attachment pattern and NSSI [27].

A longitudinal study showed that the dysfunctional attachment between adolescents and their mothers is associated with a higher frequency of NSSI, which is mediated by increased rates of confused identity style [28]. The quality of attachment to parents through self-compassion, as self-reported by patients, provides us with insights into how such a disorder can emerge in adolescents. All of these results indicate that an insecure attachment pattern increases the likelihood of engaging in NSSI or can maintain it [29]. Despite the importance of these findings, studies in this field, especially among the adolescent population, are scarce [21]. Therefore, the authors will conduct a systematic review and meta-analysis to investigate the relationship between NSSI and attachment.

Objectives

The primary goal of this systematic review is to investigate the relationship between NSSI and attachment. The secondary objectives are as follows: (1) examine the relationship between NSSI and attachment according to the study type (interventional and observational studies); (2) examine the relationship between NSSI and attachment according to the study approach (cross-sectional, retrospective, and longitudinal); (3) examine the relationship between NSSI and attachment based on different types of attachment (attachment to the primary caregiver, romantic attachment, attachment to peers, etc); (4) examine the relationship between NSSI and attachment based on gender; (5) examine the relationship between NSSI and attachment based on different age groups; and (6) examine the relationship between NSSI and attachment based on studying the difference in findings (heterogeneity) in this relationship and investigating its potential reasons.

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Methods

Guidelines and Registration

This study is a systematic review that will be reported based on the recommendations of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2009 checklist. The study protocol was registered with the International Prospective Register of Systematic Reviews (CRD42021226455).

Eligibility Criteria

Study Type

We will include observational studies (cross-sectional, cohort, and case control) that have investigated the relationship between NSSI and attachment. Qualitative studies, case studies, case series, and letters to the editor will be excluded. There will be no limitation regarding the language of the citations.

Participants

Patients of all age groups (including children, adolescents, youth, and adults), nationalities, sexual orientations, and psychological disorders will be eligible to be included.

Intervention

This study will investigate the relationship between NSSI and attachment. Any study that has defined NSSI with any instrument and has assessed its relationship with at least one of the attachment types, including caregiver attachment, romantic attachment, or peer attachment (by any definition criteria or means) will be eligible. In addition, the studies that have defined NSSI according to the description provided by DSM-5 for NSSI, considering the abovementioned factors, will be eligible.

Data Sources and Search Strategy

Electronic Databases

To identify the relevant literature, Search Syntax is developed for 6 platforms to search in different databases. The search will run in MEDLINE (PubMed), SCIE, SSCI, ESCI, CPCI-S, BKCI-S (Web of Science), Scopus, Embase, PsycInfo, Coronavirus Research Database, Publicly Available Content Database (ProQuest) for thesis and dissertations, and other gray literature.

There will be no language restrictions. There will be no publication date restrictions. Google Scholar will be used as a complementary search. Multimedia Appendix 1 shows the search syntax in each database.

Other Sources

In addition to electronic databases, other sources, including conference proceedings, dissertations, and previously published review articles, will be searched. Furthermore, 2 key journals (the first 2 journals with the highest record in Scopus search output) will be searched, and citation searching of the previous review articles as well as the included citations will be performed.

Data Collection and Analysis

Selection

After completing the search in the databases, the outputs will be exported to the Mendeley reference manager (Elsevier). The titles and abstracts will be screened for possible selection. In order to increase productivity between the 2 individuals who perform the screening, a checklist was prepared. This checklist includes a table consisting of 3 to 5 inclusion and exclusion criteria, categorized as “yes,” “no,” and “not reported,” to which the screeners can respond by reading the abstract or the title of the article. The report of the 2 main variables of the study (attachment and NSSI) is necessary in these articles, and the answer to rest of the inclusion criteria can be “yes” or “not reported for inclusion.” This table is shown in Multimedia Appendix 2. Subsequently, the full texts of the preliminary studies likely to be included in this article will be reviewed. Based on the criteria defined in the protocol, 2 researchers will review the full texts. Any inconsistency between the 2 researchers will be resolved through consensus to make the final list of the included studies.

Data Extraction

The data extraction process will be accomplished independently by 2 reviewers through the reading of the full texts of the preliminary studies using a data collection form, which comprises the following: (1) study identification data (ie, first author, publication date, journal name, type of the study, study design, sampling method, and location); (2) background data (ie, age, gender, number of participants studied, specific population groups, inclusion and exclusion criteria of the studies, and education level of the participants); and (3) data related to the primary objective of the systematic review (ie, the relationship between NSSI and attachment) as well as the secondary objectives (ie, the relationship between NSSI and attachment based on study type, study approach, different types of attachment, gender, and age groups). In order to select the appropriate effect size, we will use correlation coefficient and mean difference or standardized mean difference.

We will use the sample size as well as the mean and standard deviation of the independent variable or its subsets in NSSI and non-NSSI groups in those studies that have not reported the desired effect size measures directly. In addition, in case the required data are depicted in graphs, these will be converted to numerical data using the web-based WebPlotDigitizer tool (Ankit Rohatgi). Further, when the required data are not reported in the preliminary studies, we will try to acquire the missing data via correspondence with the corresponding authors. If the required data cannot be acquired after 3 contacts via email, that particular study will be excluded. Two reviewers will be responsible for the data extraction process separately. In case of any inconsistency between the reviewers, this will be resolved by consensus.

Data Analysis

The relative data of one of the effect size measures mentioned earlier will be combined through the “metan” command by Stata, version 13.0 (StataCorp). In order to determine a combination model, a fixed-effects or random-effects

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model—considering the methodological similarities or differences—will be selected.

Quality Assessment

The quality assessment of the included studies will be performed using the Joanna Briggs Institute checklist. Two reviewers will conduct this process separately. Then, the agreement between the 2 reviewers will be assessed, and in case of inconsistency, consensus will be used.

Heterogeneity Assessment

To assess the heterogeneity between the primary studies, we will use Cochran *Q* test and the inconsistency index (I^2). In addition, heterogeneity classification will be conducted using the classification method proposed by Higgins as follows: 0% to 24.9% (mild heterogeneity), 25% to 49.9% (moderate heterogeneity), 50% to 74.9% (severe heterogeneity), and 75% to 100% (highly severe heterogeneity).

Subgroup Analysis

Subgroup analysis will be performed based on variables such as age, gender, type of the study, design of the study, quality of the study, different types of attachments, and time periods.

Publication Bias

In order to assess publication bias, funnel plots (if 10 or more primary studies are included) will be depicted and examined. In addition, the Begg and Egger statistical tests will be used to assess the publication bias. *P* values of <.1 will be considered as considerable publication bias.

Sensitivity analysis will be conducted using the one-out remove method and the "metaninf" command in Stata software. Furthermore, subgroup analysis or meta-regression will be used in order to explore the effect of methodologic quality on the meta-analysis results. In case of considerable difference between high- and low-quality studies, the conclusion will be made using high-quality studies.

Ethical Considerations

Since this systematic review is limited to the published articles, it does not require ethical approval.

Results

We will summarize the selection of the eligible studies by a flowchart. The results will be presented in a table of evidence. The results of the meta-analysis will be depicted using diagrams and tables.

Discussion

We will investigate studies regarding the relationship between NSSI and attachment without any limitations regarding the age, nationality, gender, or psychological problems of the participants. We will analyze heterogeneity sources among the primary studies. Despite increasing attention to this phenomenon in recent years, we have observed the lack of meta-analyses on the relationship between attachment—in particular, various types of attachment—and NSSI. Therefore, it seems necessary to conduct a comprehensive systematic review with meta-analysis to elucidate this relationship in detail. The findings of this review will be used to improve our knowledge of the role of the upbringing of children and NSSI behavior and will help design appropriate interventions to address NSSI. Additionally, this review will provide new evidence for psychologists and health policy makers. The advantage of this review is that we will search the gray literature and will not impose any language restriction.

Acknowledgments

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Authors' Contributions

SA and MAM conceived the study idea and design. All authors drafted the first protocol. SA and FM reviewed the protocol. All authors developed the search strategy and methods of the systematic review. LF extensively reviewed the manuscript and incorporated intellectual inputs. All authors have read and approved the final version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search syntax in each database.
[DOCX File , 17 KB - resprot_v12i1e40808_app1.docx]

Multimedia Appendix 2

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Decision of the screening process.
[DOCX File , 13 KB - resprot_v12i1e40808_app2.docx]

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Abbreviations

DSM: Diagnostic and Statistical Manual of Mental Disorders
NSSI: nonsuicidal self-injury
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

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Protocol

The Efficacy, Safety, and Efficiency of the Off-Label Use of Bevacizumab in Patients Diagnosed With Age-Related Macular Degeneration: Protocol for a Systematic Review and Meta-Analysis

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Related Article:

This is a corrected version. See correction statement: https://www.researchprotocols.org/2023/1/e50411

Abstract

Background: Age-related macular degeneration (AMD) is recognized as the leading cause of vision loss in older people. Considering the phenomenon of aging societies worldwide, the prevalence of AMD is expected to increase gradually in the future. AMD can be divided into early, intermediate, and late stages, with the early and intermediate stages being mainly asymptomatic, and the late stage being classified as geographic atrophy, neovascular AMD, or both. Current pharmacological treatments for neovascular AMD include anti–vascular endothelial growth factor agents, such as ranibizumab, pegaptanib, and aflibercept. Additionally, it has been reported that the off-label use of intravitreally administered bevacizumab is effective. It is also lower cost than other agents, which makes it an interesting pharmacological approach.

Objective: This review aims to evaluate the efficacy, safety, and efficiency of bevacizumab for the treatment of neovascular AMD.

Methods: This review will only consider randomized controlled clinical trials that compare the use of bevacizumab with another pharmacological agent or a placebo in patients aged 50 years and older who are diagnosed with vascular AMD. It will exclude studies that include participants diagnosed with polypoidal choroidal vasculopathy or retinal angiomatous proliferation. To identify and select relevant articles, we will develop a highly sensitive search strategy and apply it in MEDLINE via the PubMed platform. Upon selection of the studies and analysis of the titles, abstracts, and full texts, the results will be presented according to the Preferred Reporting Items of Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The analysis and extraction of the data will be performed by 2 independent reviewers. Risk of bias will be evaluated with the Critical Appraisal Skills Programme (CASP) checklist. Finally, the same reviewers will also perform a quality assessment of the included studies with the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) tool.

Results: The search strategy, after the application of the inclusion and exclusion criteria, identified 15 randomized clinical trials, which are currently being analyzed. This project has no funding and it has been developed by a multidisciplinary research team of pharmacologists and orthoptists. The study was initiated in May 2021 and it is expected to conclude by the end of 2023.

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Conclusions: This review will provide a synthesis of current information and underlying evidence about the off-label use of bevacizumab in neovascular AMD. It will provide a clearer vision of a possible new pharmacological approach, as well as the most suitable treatment designs, for the treatment of neovascular AMD.

Trial Registration: PROSPERO CRD42021244931; https://tinyurl.com/p6m5ycpk

International Registered Report Identifier (IRRID): DERR1-10.2196/38658

(JMIR Res Protoc 2023;12:e38658) doi:10.2196/38658

KEYWORDS

wet macular degeneration; age-related macular degeneration; AMD; neovascular age-related macular degeneration; nAMD; bevacizumab; drug therapy

Introduction

Age-related macular degeneration (AMD) is closely associated with visual impairment and is considered the leading cause of vision loss in elderly people [1-3]. Indeed, it is reported that 9% of all cases of blindness are related to the progression of this disease [4]. AMD frequency increases with age, and the disease is known to be progressive and degenerative [1,5]. It is estimated that around 200 million people are affected by AMD, and in aging societies, the prevalence of this disease may increase in the near future [3-6]. In addition to age, there are other risk factors for AMD, such as environmental factors, obesity, atherosclerosis, smoking, genetic background, and metabolic and functional factors [2,7].

AMD can be divided into early, intermediate, and late stages. The early and intermediate stages are mainly asymptomatic and represent about 90% of cases [6-8]. Late AMD is classified into 2 main types: dry (geographic atrophy) AMD and neovascular (wet or exudative) AMD. Late AMD is the main cause of AMD-associated visual impairment [2,4,5,8]. AMD diagnosis and grading are based on color fundus examinations in people aged 50 years and older [9]. There are some differences to be aware of between the 2 main types of AMD. Nonadvanced AMD is characterized by typical whitish-yellow focal drusen localized between the retinal pigment epithelium and the Bruch membrane (BrMb). On the other hand, wet AMD is known to induce new abnormal vessels in the macula, resulting in neovascular AMD (nAMD) [10].

AMD pathogenesis is not yet fully understood, but there is already evidence to elucidate the process underlying the onset and progression of this disease [8,10,11]. Both atrophic AMD and nAMD are related to the dysfunction or death of all constituents of the photoreceptor–retinal pigment epithelium–(RPE)–BrMb–choriocapillaris complex, as these constituents work in combination. The development of each type of AMD seems to be associated with the location where the initiating events occur [11]. Atrophic AMD development is characterized initially by the formation of large, confluent drusen and hyperpigmentation, which can be accompanied by RPE dysfunction, leading to risk of geographic atrophy [11,12]. On the other hand, neovascular AMD is associated with the initial loss of choroidal vasculature, which affects the photoreceptor-RPE-BrMb-choriocapillaris complex and appears to be caused by reduced blood supply due to stenosis of the large vessels. An inflammatory environment is established by the accumulation of proinflammatory cytokines, promoting the progression of AMD [11,13]. The RPE remains intact due to the stenosis in the large vessels, but becomes hypoxic and starts to release angiogenic substances, including vascular endothelial growth factor (VEGF), which stimulates the formation of new vessels in the choriocapillaris; this is known as choroidal neovascularization [11].

Because of the process underlying the development of nAMD, current pharmacological treatments are characterized by the intravitreal administration of molecules specifically targeting VEGF [4,14]. The drugs currently accepted by the regulatory authorities for the treatment of this condition include pegaptanib, ranibizumab, aflibercept, and brolucizumab [4,8]. The off-label use of bevacizumab has also been reported for the treatment of nAMD. Bevacizumab is a drug commonly used in oncology for the treatment of metastatic colorectal cancer, breast cancer, and lung cancer [2,4,14]. Indeed, some authors have reported that the intravitreal administration of bevacizumab has a positive influence in cases of nAMD; furthermore, it has a lower cost for the community in comparison with currently used drugs, such as ranibizumab [2,14,15]. Therefore, given the rise in bevacizumab use in nAMD, it would be interesting to specifically evaluate its long-term influence on the onset and progression of this disease. Thus, this project aims to undertake a systematic review and meta-analysis of the evidence concerning the off-label use profile of bevacizumab in the treatment of nAMD through the identification and critical appraisal of clinical studies. One of our specific objectives is to summarize and analyze the current evidence on the clinical outcomes regarding the efficacy, safety, and efficiency of bevacizumab treatment for nAMD. In addition, considering the lack of evidence from current reviews regarding different treatment designs and their influence on outcomes, this review will also aim to fully describe different regimens and determine if there are significant differences between them.

Methods

Research Question

The research group follows the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis–Protocols (PRISMA-P) for the elaboration of this protocol [16]. This study proposes to answer the following research question: Is bevacizumab more efficient than other pharmacological approaches while having a comparable efficacy

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and safety profile for the treatment of patients diagnosed with nAMD?

Participants

In accord with the natural history of AMD and the American Academy of Ophthalmology Preferred Practice Patterns, the study will only include participants diagnosed with nAMD aged 50 years or older [17]. Textbox 1 shows the eligibility criteria.

Textbox 1. Eligibility criteria.

Inclusion criteria

- Participants diagnosed with neovascular age-related macular degeneration and aged 50 years or older
- Treatment with bevacizumab and another pharmacological agent or placebo
- Presentation of outcomes related to the efficacy, safety, and efficiency of the treatment
- Randomized clinical trial

Exclusion criteria

- Participants diagnosed with polypoidal choroidal vasculopathy or retinal angiomatous proliferation
- Treatment switched during the study
- Studies written in a language other than English
- Studies published before 2010

Intervention and Comparison

Patients diagnosed with nAMD and treated with intravitreal bevacizumab will be compared to patients who receive other accepted treatments, such as other anti-VEGF drugs (eg, ranibizumab), or to those who receive a placebo.

Outcomes

We will analyze several outcomes to evaluate the influence of intravitreal bevacizumab in nAMD in comparison with other established treatments or placebo; these outcomes are related to the efficacy, safety, and efficiency profiles.

Study Design

This review will only consider randomized controlled trials.

Search Strategy

This review will use MEDLINE, via the PubMed platform, to develop a highly sensitive search strategy to identify and select relevant and eligible studies. Multimedia Appendix 1 presents the search strategy developed for the MEDLINE database.

Selection Process

Titles and abstracts of retrieved studies will be screened, and the full text of potentially eligible articles will be assessed by 2 independent reviewers. In case of discrepancies, a third reviewer will be included to make a final decision. Inclusion and exclusion criteria will be applied throughout this process to decide whether a study is included or excluded. Relevant data will be extracted from the included studies and inserted in a customized data extraction document by the 2 independent reviewers. The search results will be presented in the final systematic review and presented as a PRISMA flow diagram. In addition, the reasons for excluding studies will be organized and will also be presented in the final flow diagram. As previously mentioned, we will only include articles written in English and published after 2010.

Data Collection Process

The retrieved studies from the MEDLINE database will be exported and analyzed through a systematic reviews web application (Rayyan; Qatar Computing Research Institute), which will be used throughout the review for study screening and overall management. The data will be extracted by the same 2 independent reviewers and will include specific parameters concerning the population, intervention, and comparison, as well as outcomes related to the efficacy, safety, and efficiency profiles of the treatments applied. Once again, in case of conflict between the reviewers, a third reviewer will be included to make a final decision. The included studies will be descriptively analyzed and presented in a tabular format. Additionally, the studies excluded from the quantitative synthesis will be subjected to a qualitative analysis in order to gather all available important data. For methodologically and statistically homogeneous studies, we will perform meta-analyses using random effects models to quantify a pooled estimate of the effect of systemic versus ocular adverse events. Meta-analyses will be undertaken separately for each specific study design. We will also consider other subgroup analyses, for instance, of age groups (ie, 50-70 years and >70 years). We will also quantify heterogeneity of the studies using the I^2 statistic and the Kendall τ rank correlation if high values are found; to try to explain heterogeneity across studies, a meta-regression will be conducted. This technique can be performed if there is a suspected variable that may lead to differences in treatment effects across studies. For meta-analysis, we will use the R (version 4.0.5; R Foundation for Statistical Computing) packages *metafor* and *meta*.

Data Items

During the process of data collection, we will consider several parameters that we will extract and organize, including efficacy outcomes (visual acuity, presence of neovascularization, and retinal thickness), safety outcomes (presence of macular atrophy,

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endophthalmitis, leakage, and increased intraocular pressure), and efficiency outcomes (administered dose, number of administrations, frequency of administration, duration of treatment, and cost versus benefits of the treatment compared with ranibizumab or placebo).

Risk of Bias Assessment

All the selected studies will be assessed to evaluate their methodological quality and potential for risk of bias by the same 2 independent reviewers. In case of discrepancies between these 2 reviewers, an additional reviewer will be included to make a final decision. To evaluate the quality and risk of bias in experimental studies, the Critical Appraisal Skills Programme (CASP) randomized controlled trials checklist will be used. We will derive domain-specific and overall quality grading for each study as follows: low risk of bias (A), moderate risk of bias (B), and high risk of bias (C). In addition, we will evaluate the potential of publication bias with funnel plots and the Begg test and Egger test with the trim and fill approach to explore the possible influence of publication bias on the results.

Registration and Reporting

The protocol for this systematic review was submitted and registered in 2021 in PROSPERO (CRD42021244931). This protocol follows the PRISMA-P guidelines for the development of systematic reviews and meta-analysis. In case there are modifications to the protocol, they will be reported in the final paper with the rationale behind the origin of such amendments.

Results

The study has included 15 randomized controlled clinical trials after applying the inclusion and exclusion criteria, and the data of interest are being thoroughly extracted. A multidisciplinary research team of pharmacologists and orthoptists has been working on the review since May 2021, as well as on the delineation of the protocol, and it is expected that the final results will be released by the end of 2023.

Discussion

AMD is closely associated with blindness and has a significant impact on social, health, and economic factors in society. Currently, this disease has no cure and pharmacological treatment aims to slow its rate of progression. Current drug therapies that are accepted for the treatment of nAMD are costly, and bevacizumab may be a possible alternative treatment. The off-label use of bevacizumab in the treatment of nAMD was first reported in 2006, and since then an increase in its use has been demonstrated [2]. Indeed, this drug is now associated with treatment for this disease, taking into account that its efficacy is noninferior compared to ranibizumab, a well-known drug used in this context [18]. According to some of the data being evaluated at the moment, it is already possible to affirm that bevacizumab demonstrates noninferiority compared to ranibizumab and that both drugs need a similar number of administrations to have a comparable effect on outcomes related to efficacy [19,20].

Considering the latest reviews on this topic, it is possible to observe that there is already sufficient information regarding the efficacy and safety profiles of bevacizumab in comparison to other pharmacological approaches [21,22]. However, it is also essential to understand the efficiency of bevacizumab compared with other options, since current approaches are relatively costly, and continuous administration is necessary to slow the rate of progression of the nAMD. After understanding the cost-benefit profile of bevacizumab in comparison with other established treatment molecules, it will be possible to make clinical decisions more effectively, benefiting both the health system and patients.

Thus, the findings from this review will allow a clearer vision of the use of bevacizumab in the treatment of nAMD, as well as its efficacy, safety, and efficiency compared to other drugs and to placebo. Additionally, this key strengths of this study will include synthesizing the information available about the off-label use of bevacizumab in patients diagnosed with nAMD; clarifying the current evidence on the off-label use of bevacizumab in the nAMD context for its efficacy, safety, and efficiency; and developing a comprehensive and highly sensitive search strategy, which will allow the identification of current papers and their underlying evidence. Based on the currently available literature, we are in a position to objectively evaluate bevacizumab for the treatment of nAMD in comparison to other drugs accepted by the respective regulatory authorities.

Acknowledgments

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Search strategy for the MEDLINE database.
[DOCX File , 12 KB - resprot_v12i1e38658_app1.docx]

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Abbreviations

AMD: age-related macular degeneration
BrMb: Bruch membrane
CASP: Critical Appraisal Skills Programme
nAMD: neovascular age-related macular degeneration
PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analysis–Protocols
RPE: retinal pigment epithelium
VEGF: vascular endothelial growth factor

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Protocol

The Efficacy of a Diet Low in Fermentable Oligo-, Di-, Monosaccharides, and Polyols in Irritable Bowel Syndrome Compared to Its "Real-world" Effectiveness: Protocol for a Systematic Review

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Abstract

Background: Irritable bowel syndrome (IBS) is associated with various gastrointestinal and nongastrointestinal symptoms and reduced quality of life. A diet low in fermentable oligo-, di-, monosaccharides, and polyols (FODMAPs) is one therapeutic option for IBS. Although the efficacy of the low FODMAP diet has been reported in several systematic reviews, the efficacy-effectiveness gap of the low FODMAP diet has not yet been assessed.

Objective: This systematic review aims to compare the efficacy of the low FODMAP diet from efficacy randomized controlled trials (RCTs) with the effectiveness of studies conducted in "real-world" settings.

Methods: RCTs, prospective and retrospective cohort studies, and retrospective audits assessing the low FODMAP diet in adults with IBS will be searched in 4 databases: Embase, MEDLINE, CENTRAL, and CINAHL. Two independent reviewers will perform study selection, data extraction, and risk of bias assessment and assess selected quality aspects from the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) protocol. Outcomes assessed are stool frequency, stool consistency, abdominal pain, overall symptom scores, adequate symptom relief, IBS-specific quality of life, and diet adherence. Data will be summarized with forest plots without summary statistics, tables, and narrative descriptions.

Results: The search, title and abstract screening, and full-text screening were completed in March 2021, and an updated search was done in May 2022. As of May 2023, data analysis is almost finished, and manuscript writing is in progress. Submission of the manuscript is expected by July 2023.

Conclusions: The findings of this systematic review will compare the efficacy of the low FODMAP diet for IBS found in RCTs to the diet's real-world effectiveness.

Trial Registration: PROSPERO CRD42021278952; https://tinyurl.com/32jk43ev

International Registered Report Identifier (IRRID): DERR1-10.2196/41399

(JMIR Res Protoc 2023;12:e41399) doi:10.2196/41399

KEYWORDS

FODMAP diet; irritable bowel syndrome; dietetics; efficacy-effectiveness gap; meta-analysis; systematic review

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Introduction

Chronic disorders are a major contributor to the global burden of disease [1]. Many of the health problems contributing to the burden of disease involve inflammatory processes [2]. Dietary risks accounted for 255 million disability-adjusted life-years globally in 2017 [3]. Thus, nutrition and nutrition interventions play a key role in improving global health and reducing the impact of inflammatory processes [4,5].

Irritable bowel syndrome (IBS) is a chronic disease common in both Western and developing countries, affecting up to 20% of the global population [6]. It is associated with various, sometimes severe, gastrointestinal, and nongastrointestinal symptoms and often results in a reduced quality of life, reduced work performance, and increased use of health care services [7,8]. IBS belongs to the disorders of the gut-brain axis, which are characterized by abnormalities in intestinal motility, visceral sensitivity, mucosal and immune function, intestinal microbiota, and stimulus processing by the central nervous system. To this day, only symptomatic treatments are available [9].

In the past 2 decades, research has shown that a diet low in fermentable oligo-, di-, monosaccharides, and polyols (FODMAPs), or the "low FODMAP diet," reduces gastrointestinal symptoms in patients with IBS. The rate of patients with IBS reaching a clinically relevant symptom reduction may even be higher with the low FODMAP diet than with spasmolytics [10]. Several systematic reviews have summarized available data on the efficacy of the low FODMAP diet for IBS [11-20]. The majority concluded that patients with IBS benefit from following the low FODMAP diet, in comparison to either a usual diet, a high FODMAP diet, other IBS diets, or "sham" diets [11-18]. Accordingly, several IBS guidelines now list the low FODMAP diet as one possible therapeutic intervention [21-24]. Additionally, a recent expert review on the role of diet in IBS concluded that the low FODMAP diet is "currently the most evidence-based diet intervention for IBS" [25].

The low FODMAP diet includes an initial elimination phase, during which FODMAP-rich foods are excluded to individually confirm the diet's efficacy [26]. Subsequently, the individual tolerance of the FODMAPs should be tested to allow patients with IBS to follow an individually adapted FODMAP diet [27]. The therapeutic efficacy of reducing the intake of FODMAPs is explained by decreased osmotic activity due to the remaining carbohydrates retaining less water in the intestine, reduced gas production by gut microbiota, and influences on intestinal motility [28]. Evidence on the long-term efficiency of the low FODMAP diet is still limited. Recently, studies have reported on the long-term maintenance of symptom improvement after FODMAP reintroduction. After 1 year, 65% of the participants of a small follow-up study (n=18) reported adequate symptom relief [29], and in a questionnaire study, at least 50% of participants (n=211) reported improvement of abdominal pain, bloating, wind, urgency to open bowels, and also reduced health care usage [30].

Health service research distinguishes between efficacy and effectiveness studies. The former examines the fundamental efficiency of new interventions under ideal conditions, while the latter measures the efficiency of the same interventions in everyday practice [31]. Efficacy studies tend to overestimate the efficiency because of strictly defined study populations and study procedures [32]. The magnitude of this efficacy-effectiveness gap varies from no gap detected to large differences. For example, the systematic review by Ankarfeldt et al [33] concluded that there was no efficacy-effectiveness gap on blood glucose–lowering drugs—although this may have been influenced by the limited number of included studies and different biases masking such an effect. In comparison, a meta-analysis of current systemic cancer therapies found that the median overall survival was 5.2 months less in real-world data than reported in randomized controlled trials (RCTs) [34]. To date, the potential efficacy-effectiveness gap has not been investigated in the low FODMAP diet. Therefore, the systematic review described in this protocol aims to compare the efficacy of the low FODMAP diet conducted by RCTs with the effectiveness of studies conducted in "real-world" settings.

"Real-world" refers to data collected in a setting as close as possible for usual outpatient or ambulatory treatment of patients with IBS. The term was deliberately chosen because "effectiveness studies" sometimes refer to RCTs with a broader defined population and treatment protocol but not necessarily a true representation of real-world data.

Methods

Overview

The review was registered with the International Prospective Register of Systematic Reviews (PROSPERO) in November 2021 (CRD42021278952). If not mentioned otherwise, this protocol has been developed based on the Cochrane Handbook for Systematic Reviews of Interventions version 6.1 [35] and the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) reporting guidelines [36]. The guidance for the clinical evaluation of drugs for the treatment of IBS published by the United States Food and Drug Administration (FDA) [37] served as "core outcome set" but had to be adapted because of the different nature of nutrition care–related studies. Also, the FDA guideline focuses on IBS constipation and IBS diarrhea, but a range of studies investigating the low FODMAP diet included patients with IBS with all subtypes or did not report outcomes per IBS subtype.

Eligibility Criteria

The eligibility criteria are structured according to Population, Intervention, Comparison, Outcomes, and Study Design (PICOS). To address the objective of this study, the review will apply 2 PICOS. The first includes RCTs on the low FODMAP diet's efficacy. The second focuses on the low FODMAP diet's effectiveness in real-world settings (Table 1).

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Table 1. Study eligibility criteria based on the PICOS[a] criteria, with time points and settings.

PICOS part	Efficacy PICOS	Real-world data PICOS
Population		
Inclusion	• Adults (≥18 years of age). • Diagnosed with IBS[b] according to Rome II, III and IV, NICE[c], the German S3 guideline, Manning criteria, and Kruis score. • Patients likely to represent the subjects studied in efficacy studies (eg, excluding patients with additional conditions potentially influencing the efficacy of the low FODMAP[d] diet, such as gastrointestinal surgery). • Patients with clinically relevant baseline outcome scores, allowing for relevant improvements through the intervention.	• Adults (≥18 years of age). • Diagnosed with IBS according to Rome II, III and IV, NICE, the German S3 guideline, Manning criteria, and Kruis score. • Patients likely to represent the "usual" patients in the institution conducting the study.
Exclusion	• Animal studies. • Studies on FODMAP contents and reduction of FODMAP contents in foods.	• Animal studies. • Studies on FODMAP contents and reduction of FODMAP contents in foods.
Intervention		
Inclusion	• Low FODMAP diet for at least 4 weeks. • Low FODMAP diet is either carried out independently by participants or provided to them.	• Low FODMAP diet for at least 4 weeks. • Low FODMAP diet is carried out by participants independently in their daily life.
Exclusion	• Studies conducted with exclusive enteral nutrition. • Studies investigating single FODMAPs. • Studies in which the low FODMAP diet was implemented without any support from a health professional.	• Studies conducted with exclusive enteral nutrition. • Studies investigating single FODMAPs. • Studies in which the low FODMAP diet was implemented without any support from a health professional.
Control		
Inclusion	• Other dietary interventions for IBS for at least 4 weeks, such as a high FODMAP diet, traditional IBS diets, sham diets, anti-inflammatory diets, probiotics, and fiber supplements. • Control intervention is either carried out independently by participants or provided to them (eg, high FODMAP meals provided).	• No control group is necessary. • If there is a control intervention, participants need to carry it out independently at home.
Exclusion	• Studies conducted with exclusive enteral nutrition. • Studies conducted with healthy controls.	• Studies conducted with exclusive enteral nutrition.
Outcomes—critical		
Inclusion	• Stool frequency. • Stool consistency. • Abdominal pain.	• Stool frequency. • Stool consistency. • Abdominal pain.
Exclusion	• N/A[e]	• N/A
Outcomes—important		
Inclusion	• Overall symptom scores such as IBS-SSS[f] or assessment of gastrointestinal symptoms with a visual analog scale. • Number or percentage of patients with adequate symptom relief. • IBS-specific quality of life. • Adherence to the low FODMAP diet.	• Overall symptom scores such as IBS-SSS or assessment of gastrointestinal symptoms with a visual analog scale. • Number or percentage of patients with adequate symptom relief. • IBS-specific quality of life. • Adherence to the low FODMAP diet.
Exclusion	• N/A	• N/A
Time points		
Inclusion	• Baseline. • After the FODMAP elimination phase (sometimes also the end of intervention). • After the FODMAP reintroduction (if part of the study). • After the follow-up time point (if part of the study).	• Baseline. • After the FODMAP elimination phase (sometimes also the end of intervention). • After the FODMAP reintroduction (if part of the study). • After the follow-up time point (if part of the study).

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PICOS part	Efficacy PICOS	Real-world data PICOS
Exclusion	• N/A	• N/A
Study design		
Inclusion	• Randomized controlled trials with inclusion and exclusion criteria typical for efficacy studies (see above), including crossover trials.	• Randomized controlled trials with openly formulated inclusion and exclusion criteria (see above), prospective and retrospective cohort studies as well as retrospective audits.
Exclusion	• All other types of studies.	• Case reports and qualitative studies.
Context		
Inclusion	• Studies in any ambulatory or outpatient setting.	• Studies in any ambulatory or outpatient setting.
Exclusion	• N/A	• N/A

[a]PICOS: Population, Intervention, Comparison, Outcomes. and Study Design.

[b]IBS: irritable bowel syndrome.

[c]NICE: National Institute for Health and Care Excellence.

[d]FODMAP: fermentable oligo-, di-, monosaccharides, and polyols.

[e]N/A: not applicable.

[f]IBS-SSS: IBS Severity Scoring System.

The publication period is not restricted, as the first studies on the low FODMAP diet were published in 2006. Publication language is limited to English, German, French, and Italian because of practical reasons. Studies must be published as a full manuscript, or authors must provide relevant information.

The criterion of clinically relevant symptoms has been included in the efficacy PICOS based on the FDA Guidance for Industry: *Irritable Bowel Syndrome—Clinical Evaluation of Drugs for Treatment* [37]. The definition in the guidance will be applied. Alternatively, we will accept other literature-based descriptions of "clinically relevant symptoms" or when study authors have considered the baseline data as clinically relevant. Studies included in the real-world data PICOS do not need to meet this criterion, as the FDA guidance focuses on efficacy studies, and literature on instituting the low FODMAP diet in practices reports that the low FODMAP diet can be applied in mild IBS symptoms as well [26].

For the differentiation between patients in efficacy or real-world studies, we developed a rating system based on the "eligibility" domain of the Pragmatic Explanatory Continuum Indicator Summary (PRECIS-2) tool. The PRECIS-2 tool allows studies to be designed explicitly on a 5-point continuum scale (5=very pragmatic, 4=rather pragmatic, 3=equally pragmatic and explanatory, 2=rather explanatory, and 1=very explanatory) [38].

According to the literature [26], the low FODMAP diet can be applied in practice in the following situations: (1) there is a diagnosis of IBS but no "red flags" that would require further investigation; (2) mild to severe symptoms are present, and a relationship between the symptoms and the diet is assumed; and (3) there is no history of eating disorders or orthorexia.

Studies will be included in the real-world data PICOS, if they receive more than 3 points (more pragmatic), and in the efficacy PICOS, if they receive 3 points or less. This cutoff was chosen based on a pilot test of the system, in which studies scoring 3 points or less still tended to be "classic RCTs," while those scoring more than 3 points were more pragmatic studies.

Deductions of a half or full point per aspect mentioned below will be applied if subjects are excluded because: (1) they are not expected to respond equally to the intervention (based on health conditions or dietary restrictions in the exclusion criteria list); (2) there are challenges (eg, from ethics) unrelated to the intervention (based on the exclusion of specific population groups where the low FODMAP diet would be applied in usual practice); (3) they were unable to meet strict guidelines regarding medication adjustments, including prebiotics, probiotics, and supplements; (4) they are expected to be less able to attend appointments (eg, psychological problems, lower motivation); and (5) they have not strictly adhered to the intervention.

The outcomes are divided into critical and important outcomes as recommended by the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) criteria [39]; outcomes of limited importance have not been defined. The critical outcomes are based on the FDA guidance for the clinical evaluation of IBS drugs [37] but have been adapted. The important outcomes include outcomes often applied in studies on the low FODMAP diet, which are relevant from a patient's or dietitian's perspective. Studies will not be excluded based on the outcomes reported, but reporting will focus on the critical and important outcomes.

Search Strategy

The search strategy includes databases: Embase (Elsevier interface, 1947 onward), MEDLINE (PubMed interface, 1966 onward), Cochrane Central Register of Controlled Trials (Wiley interface, current issue), and CINAHL (EBSCOhost interface, 1937 onward); trial registries: ClinicalTrials.gov and WHO-Portal International Clinical Trial Registry Platform; dissertations: LILACS, Open Access Theses, and Dissertations,

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and ProQuest Dissertation & Theses Global; gray literature; and hand searched journals: *Gut*, *American Journal of Gastroenterology*, *Journal of Gastroenterology and Hepatology*, *Gastroenterology*, *Alimentary Pharmacology and Therapeutics*, *Neurogastroenterology & Motility*, *Journal of Human Nutrition and Dietetics*, *Journal of the Academy of Nutrition and Dietetics*, *European Journal of Nutrition*, *Clinical Nutrition*, *International Journal of Clinical Practice*, *Journal of Nutrition*, and *Nutrients*.

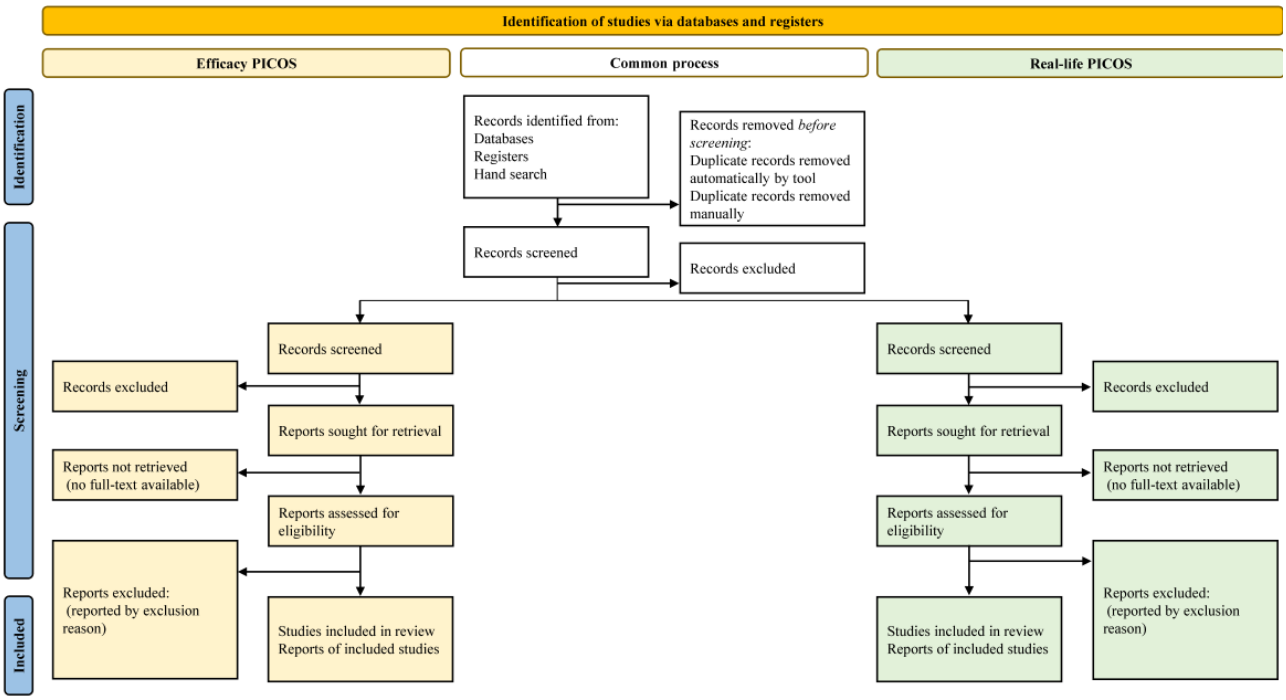
The search will be conducted once for both PICOS categories together. The search criteria will include the terms and synonyms of FODMAPs and IBS listed below and the Medical Subject Headings (MeSH) term for IBS. At the time of the search, no MeSH term existed for FODMAPs. The search criteria will be adopted to the different databases based on the following: synonyms for FODMAPs: "FODMAP" OR "FODMAPS" OR "Fermentable, poorly absorbed, short-chain carbohydrates," OR "Fermentable oligosaccharides, disaccharides, monosaccharides, polyols"; synonyms for IBS: "Irritable Bowel Syndromes" OR "Syndrome, Irritable Bowel" OR "Syndromes, Irritable Bowel" OR "Colon, Irritable" OR "Irritable Colon" OR "irritable bowel syndrome" (MeSH Terms).

Further restrictions in the search (eg, study design) will not be applied to not miss potentially eligible studies. Search results will be imported in Covidence (Veritas Health Innovation Ltd), a web-based software facilitating study selection, quality assessment, and data extraction in systematic reviews.

Study Selection

Reports found in the search process will be imported to Covidence, where duplicates detected by the system will automatically be removed. Two reviewers will do the screening independently. After each round, the 2 reviewers and the first author of this study protocol will resolve conflicts. The title and abstract screening will be done in 2 rounds. First, reports clearly not eligible for both PICOS categories will be excluded (eg narrative reviews, FODMAP content analyses, pediatric studies, and studies on other disorders than IBS). Then, the remaining reports will be separated in 2 distinct "reviews" in Covidence, and eligible studies will be determined by a second round of title and abstract screening followed by full-text screening performed for each "review" separately, based on the eligibility criteria of each PICOS (Figure 1).

Figure 1. Example overview of the search strategy, reported according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement [36]. PICOS: Population, Intervention, Comparison, Outcomes, and Study Design.



Data Extraction

Data extraction will be done in Covidence, using both predefined and added fields by the review team. Data extraction will be piloted with some studies, and educational sessions will facilitate a common understanding of data extraction. Two reviewers will independently extract the data. Conflicts will be resolved by the 2 reviewers, and the first author of this protocol will be rechecking the original information in the publications. For each study, the information found in Table 2 will be extracted. If needed, the study authors will be contacted to clarify uncertainties or be asked for additional information. Data will be transferred into RevMan (version 5.4; Cochrane Collaboration) software for data synthesis.

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Table 2. Overview of the data to be extracted.

Covidence field	Data to be extracted
Study identification	Sponsorship, country, setting, author's contact details, year of study, aim of study, type of publication, ethical approval, and publication language.
Methods	Study design, number of centers, method of randomization, blinding, and analysis (intention to treat per protocol).
Intervention	Interventions (name for each group), intervention description, definition of symptom improvement after the intervention, duration of participation, duration of the treatment period, duration follow-up, timing, providers, and implementation.
Population	Inclusion criteria, exclusion criteria, group differences, sample size calculation, and baseline characteristics (assessed for eligibility randomized, participants per group, dropouts per group, dropout reasons, age, gender, BMI, predominant bowel habit, and diagnostic criteria).
Outcomes	Outcome measures based on the critical and important outcomes for this review, time points evaluated.

Risk of Bias and Quality Assessment

Two reviewers will independently assess the studies' risk of bias. In Covidence, disagreements will be resolved by rechecking the original information in the publications and by a discussion among the reviewers. Several tools will be used due to the range of studies included [35]: the revised tool for Risk of Bias in randomized trials (RoB 2) [40], the newly available test version of RoB 2 for crossover studies [41], and the Risk Of Bias In Non-randomized Studies—of Interventions (ROBINS-I) assessment tool for nonrandomized studies [42]. The RoB 2 version for crossover studies will be applied despite being a test version because it is largely identical to the original RoB 2 but has been supplemented with an additional domain for bias due to period and carryover effects [42]. We will not fully implement the GRADE system but still use specific parts of it for additional quality assessment, such as indirectness of evidence, imprecision, large magnitude of an effect, and the effect of plausible residual confounding.

Data Analysis

Data analysis will be done in RevMan (version 5.4; Cochrane Collaboration). We will not perform a meta-analysis, as we expect heterogeneous outcome measures in the real-world data PICOS. Where available, mean values of measurements of a specific period (eg, mean or median of a screening period, mean or median of the last 2 weeks of the elimination phase) will be reported. If not available, single measurements will be included. Dichotomous data (adequate symptom relief) will be reported as risk ratios and risk differences with 95% CIs. In studies without a control group, results will be presented as a percentage of participants reaching adequate symptom relief. Continuous data will be reported as "mean difference" or as "standardized mean difference" if different measures were applied, both with 95% CIs. We will also apply this to studies without a control group, using baseline data as a comparison. Results will be presented as forest plots without the summary measure, in tables, or narratively.

Data will be analyzed per PICOS separately. If at least 5 studies per subgroup can be included, we will apply the following subgroups: (1) Efficacy PICOS: diet is provided during the intervention period, elimination phase only; diet is implemented independently, elimination phase only; diet is implemented independently, elimination, and reintroduction phase; and multicomponent interventions (not only low FODMAP diet). (2) Real-live data PICOS: diet is implemented independently, elimination phase only; diet is implemented independently, elimination and reintroduction phase; and multicomponent interventions (not only FODMAP nutrition).

These subgroups have been chosen as the effects measured may be influenced by the individual factors.

Ethical Considerations

Ethical approval is not required for this study because only data made available through publication are used for the systematic review. The results will be submitted for publication in a relevant peer-reviewed journal. Any changes from the protocol during the conduct of the systematic review will be described in the manuscript.

Results

The literature search, title and abstract screening, and full-text screening were completed in 2021. As of May 2023, we are in the progress of finalizing data analysis and writing the publication. We expect to submit the publication by July 2023. This work has been financially supported by the "Spendenstiftung Bank Vontobel" in Zurich, Switzerland.

Discussion

Principal Findings

In the systematic review, we will compare the effectiveness of the low FODMAP diet in efficacy RCTs to the effectiveness of real-world data in adult patients with IBS. This comparison will focus on the following outcomes: stool frequency, stool consistency, abdominal pain, overall symptoms, adequate symptom relief, IBS-related quality of life, and adherence to the low FODMAP diet. The findings of this systematic review will allow health professionals to compare their outcomes with the results of this systematic review and potentially initiate quality improvement projects if their results are lower than expected in comparison to the results of this systematic review.

Current Research

Research output on the effect of the low FODMAP diet is still high. Current research topics include the long-term efficiency, impact on gut microbiota, and response predictors. Data on long-term outcomes of the low FODMAP diet, however, are still scarce. Nevertheless, these data are of great importance as

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the effort of a restrictive 3-phase diet, such as the low FODMAP diet, is only worthwhile if symptom relief persists. Few recent studies confirmed maintenance of symptom improvement after FODMAP reintroduction with 1- or 2-year follow-up. Two recent studies reported a 50% or more symptom improvement among participants who followed an individualized low FODMAP diet after almost 1 year [29,30]. Symptom improvement may be related to continued partial adherence to the low FODMAP diet. In a retrospective cross-sectional study (n=90), almost 80% of the participants reported partial adherence after nearly 2 years, which was associated with less abdominal pain [43]. In acknowledgment of the limited RCTs available assessing long-term effect, this systematic review will still endeavor to assess all available evidence on such long-term outcomes.

There are known potential negative effects of the low FODMAP diet on the gut microbiota, due to the elimination of fructans and galactans, which are both important prebiotics. A recent meta-analysis on the effect of the low FODMAP diet on gut microbiota concluded that studies consistently reported a reduction of bifidobacteria during the low FODMAP elimination phase, but they found no indications for broad systematic changes in the gut microbiota [44]. Thus, more research on the long-term effects of the low FODMAP diet on the gut microbiota is needed. Promisingly, a small follow-up study (n=18) found no difference in bifidobacteria abundance between baseline and 1 year [29].

Evidence on predictors of symptom relief is essential as studies have reported roughly a 70% rate of satisfactory symptom relief after following the low FODMAP diet [45]. Therefore, a better understanding of such predictors would enable applying the low FODMAP diet only in patients with IBS with a probability of a higher success rate, while those with a lower chance of symptom relief could be given alternative therapies sooner. Baseline gut microbiota has been discussed as one predictor by Vervier et al [46], who identified 2 distinct microbiota clusters in patients with IBS. The health-like cluster had a gut microbiota profile similar to healthy household members, whereas the pathogenic-like cluster gut microbiota differed greatly from the healthy-household members. When eating a low FODMAP diet, gut microbiota of the pathogenic-like cluster shifted toward a more health-associated profile, and participants experienced strong symptom improvement (measured by a decrease of 194 points on the IBS Severity Scoring System). In the health-like cluster, the low FODMAP diet did not affect the gut microbiota, and participants experienced a clinically relevant but less pronounced symptom reduction (−114 points) [46]. Therefore, having a gut microbiota of the pathogenic-like cluster may lead to better symptom improvement and could be an important predictor for the benefit of the low FODMAP diet.

Systematic reviews and meta-analyses directly assessing the efficacy-effectiveness gap remain scarce. In contrast, systematic reviews seem to increasingly include observational data due to the faster availability of such data but often without sufficient differentiation between efficacy and effectiveness data [47]. Some of the systematic reviews and meta-analyses on the low FODMAP diet in patients with IBS included a range of study designs but did not clearly distinguish between these designs in data analysis [12,14-16,18]. This may be critical, especially if meta-analyses are performed [47]. This systematic review will prevent this by categorizing the included studies as either efficacy or real-world studies and summarizing the outcomes separately.

Limitations of this systematic review are related to the aim of comparing efficacy RCTs with real-world data. First, we will include RCTs in both PICOS categories, as RCTs may be clearly efficacy studies but also report on effectiveness, which would fit more in the “real-world” category. Our systematic review includes 2 PICOS to enable the differentiation of efficacy and effectiveness studies by using specific eligibility criteria representing these 2 types of studies. However, the differentiation between study populations representative of typical efficacy or effectiveness studies remains a challenge. Therefore, we developed and pretested a rating system based on the eligibility domain of the PRECIS-2 tool [38]. Based on the pretest, we are confident that the rating system will sufficiently distinguish between efficacy and real-world studies. Furthermore, the PRECIS-2 (by using all domains) has already been successfully used retrospectively by other researchers [48-50]. However, it should be acknowledged that the retrospective use of PRECIS-2 has not been well established. Second, to include as much real-world data as possible, we will include studies with different study designs in the real-world PICOS. We hypothesize that this will entail some challenges in data analysis and interpretation as some of the data will be from observational studies without control group.

Conclusions

This protocol describes the methods of a systematic review that will compare the effectiveness of the low FODMAP diet in efficacy RCTs to the effectiveness of real-world data in adult patients with IBS. To our knowledge, this will be the first systematic review with this focus. The results will help to fill the efficacy-effectiveness evidence gap of the impact of the low FODMAP diet in adult patients with IBS and help identify research needs related to the efficacy-effectiveness gap in this field. Furthermore, the systematic review may reveal research needs with regards to long-term efficiency of the low FODMAP diet. Lastly, the systematic review will allow us to compare outcome measurements currently used in efficacy and real-world studies and whether the quality of reports on real-world studies is sufficient to compare data to efficacy studies.

Acknowledgments

SJ mainly developed the proposal. All authors contributed to developing the protocol and read, provided feedback for, and approved the final proposal. We greatly thank Joyce Haddad for the thorough language revision. This work has been financially supported by the “Spendenstiftung Bank Vontobel” in Zurich, Switzerland.

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Conflicts of Interest

None declared.

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Abbreviations

FDA: United States Food and Drug Administration
FODMAP: fermentable oligo-, di-, monosaccharide, and polyol
GRADE: Grading of Recommendations Assessment, Development, and Evaluation
IBS: irritable bowel syndrome
MeSH: Medical Subject Headings
PICOS: Population, Intervention, Comparison, Outcomes, and Study Design
PRECIS-2: Pragmatic Explanatory Continuum Indicator Summary
PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols
PROSPERO: International Prospective Register of Systematic Reviews
RCT: randomized controlled trial

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RoB 2: Risk of Bias in randomized trials
ROBINS-I: Risk Of Bias In Non-randomized Studies—of Interventions

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Protocol

Artificial Intelligence Applications for Assessment, Monitoring, and Management of Parkinson Disease Symptoms: Protocol for a Systematic Review

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Abstract

Background: Parkinson disease (PD) is the second most prevalent neurodegenerative disease, with around 10 million people with PD worldwide. Current assessments of PD symptoms are conducted by questionnaires and clinician assessments and have many limitations, including unreliable reporting of symptoms, little autonomy for patients over their disease management, and standard clinical review intervals regardless of disease status or clinical need. To address these limitations, digital technologies including wearable sensors, smartphone apps, and artificial intelligence (AI) methods have been implemented for this population. Many reviews have explored the use of AI in the diagnosis of PD and management of specific symptoms; however, there is limited research on the application of AI to the monitoring and management of the range of PD symptoms. A comprehensive review of the application of AI methods is necessary to address the gap of high-quality reviews and highlight the developments of the use of AI within PD care.

Objective: The purpose of this protocol is to guide a systematic review to identify and summarize the current applications of AI applied to the assessment, monitoring, and management of PD symptoms.

Methods: This review protocol was structured using the PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols) and the Population, Intervention, Comparator, Outcome, and Study (PICOS) frameworks. The following 5 databases will be systematically searched: PubMed, IEEE Xplore, Institute for Scientific Information's Web of Science, Scopus, and the Cochrane Library. Title and abstract screening, full-text review, and data extraction will be conducted by 2 independent reviewers. Data will be extracted into a predetermined form, and any disagreements in screening or extraction will be discussed. Risk of bias will be assessed using the Cochrane Collaboration Risk of Bias 2 tool for randomized trials and the Mixed Methods Appraisal Tool for nonrandomized trials.

Results: As of April 2023, this systematic review has not yet been started. It is expected to begin in May 2023, with the aim to complete by September 2023.

Conclusions: The systematic review subsequently conducted as a product of this protocol will provide an overview of the AI methods being used for the assessment, monitoring, and management of PD symptoms. This will identify areas for further research in which AI methods can be applied to the assessment or management of PD symptoms and could support the future implementation of AI-based tools for the effective management of PD.

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KEYWORDS

artificial intelligence; machine learning; Parkinson disease; Parkinson; neurodegenerative; review method; systematic review

Introduction

Parkinson disease (PD) is the second most prevalent neurodegenerative disease worldwide, with around 10 million people with PD worldwide [1]. This number represents a 2.5-fold increase in prevalence over the past generation [2,3]. PD is a neurological disorder associated with motor and nonmotor features [4] affecting multiple aspects of movement, including planning, initiation, and execution [5]. Management of PD is very complex over the course of the disease due to its progressive nature [6]. Developments of digital technologies have allowed for the remote, objective monitoring of symptoms, allowing care teams to take data-driven approaches to care, producing large amounts of data [7]. Artificial intelligence (AI) methods have been applied to data sets to improve the timeliness of care for patients, assist with analysis, and reduce health care provider burden [8]. The existing research has primarily focused on the application of AI methods in the diagnosis of PD or the management of motor symptoms [9,10], despite nonmotor symptoms (NMS) causing a significant burden for people with PD, as well as reduced quality of life, and being the main contributor to the overall cost of care [11,12]. It is important to understand how the range of AI methods can be applied to all symptoms experienced by people with PD to aid with monitoring and disease management, as well as assisting the patient to understand their disease profile more clearly and facilitate better self-management [13].

PD is most commonly characterized by a resting tremor, bradykinesia, and rigidity, accompanied with changes in posture and gait. During the development of PD, motor symptoms are observed prior to cognitive and behavioral changes, such as dementia [14]**.** Despite being defined as a movement disorder, people with PD can also be affected by a wide range of symptoms spanning beyond the classic motor symptoms [4]. NMS affect all people with PD and can include constipation, urinary dysfunction, sleep disturbances, and depression [15,16]. The National Institute for Health and Care Excellence acknowledges that NMS are considered a significant burden for people with PD, and their recognition and management is an important yet unmet need of PD [17]. Evidence shows that NMS can occur at any stage of the disease, with some NMS occurring prior to the onset of motor symptoms [18]. Generally, the assessment and characterization of both motor and NMS rely on clinical assessment with follow-ups occurring every 6-12 months for stable patients, according to the National Institute for Health and Care Excellence guidelines [19]. The appropriate assessment of symptoms affecting people with PD is vital for an effective clinical management and managing symptom severity [20,21]. This assessment methodology aims to allow for both the subjective and objective assessment of the impact of PD to achieve a clear overall impact of the disease for people with PD [22]; however, this is not always achieved. These assessments lack granularity during disease or medication cycles; these assessments represent only a small portion of a patient's life and may not adequately capture the nuances of a highly variable condition [7,23]. The quality of the information collected is limited by patients' and care partners' recall about their recent symptom burden, which can be worsened by the cognitive impairments associated with PD. An international survey published in 2010 highlighted that 62% of patients with PD do not declare NMS including pain, sexual difficulty, sleep dysfunction, or bowel incontinence either due to embarrassment or not being aware that such symptoms are linked to PD [16]. As a result, some symptoms, particularly NMS, are often overlooked or undeclared by people with PD, which results in incorrect disease management, impacting upon quality of life for both the patient and their care partner, and increased care needs and costs [16].

The remote monitoring of PD symptoms has become increasingly common because it can allow patients to self-manage their condition at home [24-26]. Digital technologies allow for the at-home monitoring of patients through smart devices, sensors, and other tools. At-home monitoring allows for the continuous oversight of disease presentation in an objective manner to ensure no symptoms are forgotten, overlooked, or misinterpreted [23,27]. Several studies have proposed and evaluated the use of wearable devices and smartphones with built-in sensors for monitoring both motor and NMS for people with PD [27-30]. By enabling long-term data collection in a nonclinical setting, digital technologies can reduce the burden on clinical data collection and allow clinicians to spend contact time with patients more meaningfully. The wealth of available data and improved clinical efficiency has the potential to facilitate the diagnosis, monitoring, and management of PD. The present applications of wearable devices include assessing gait (including freezing of gait), tremor, bradykinesia, rigidity, sleep dysfunction or disturbance, blood pressure, and detecting falls [31]. Data from accelerometers and gyroscopes on various parts of the body can also allow for the estimation of the Unified Parkinson's Disease Rating Scale scores and determine bradykinesia in both scripted and unscripted conditions [32-35]. The analysis of such large amounts of data, however, can be extremely time-consuming and subject to variation in analyses [23].

The implementation of AI is being extensively used in a variety of health care and medical contexts, including biomedicine, diagnostics, living assistance, biomedical information process, and biomedical research [36-38]. In PD, AI has been explored for both diagnostic support and disease monitoring. Wearables combined with machine learning algorithms have been reported to sufficiently discriminate between healthy participants and patients with PD, with an accuracy of over 90%. The prediction of symptom severity using motor symptoms and various algorithms and sensors has also reported high accuracy results [39]. Specific data sets that have been used to support clinical decision-making in PD care include handwriting patterns [40],

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gait [41], and neuroimaging [42]. At present, the application of AI appears to be primarily focused on the motor aspects of the disease, despite some NMS data being routinely recorded via wearable or smart devices [43]. The assessments of NMS in PD carry the same limitations as any other semiobjective rating scale, including intra- and interobserver inconsistencies and bias. Further, many NMS are not as easy to track remotely in the way motor symptoms are; for example, multiple motor symptoms, including tremor, bradykinesia, and gait or freezing of gait are detectable using gyroscopes and accelerometers usually embedded within wearable devices. Due to the large amount and wide range of NMS, as well as accessibility for the assessment of the symptom, a large portion cannot be objectively identified in the same way. Multiple research studies have focused on NMS being present in early disease states and are therefore focused on use for diagnostic purposes [44-46]. The tracking of NMS using digital technologies reduces the likelihood of the patient or carer misreporting symptoms and provides a much larger data set, eradicating the issue with clinical assessments providing only a *snapshot* in time. Implementing AI methods for NMS assessment and management can contribute toward improving patient and carer quality of life by addressing NMS more appropriately [47], staging people with PD [48], providing more tailored care [49], and potentially reducing the likelihood of NMS being overlooked.

A vast number of publications and systematic reviews have assessed the application of AI into the diagnosis of PD [9,39]. Additional reviews have focused on the management of individual symptoms [50], assessment using wearables [31], individual treatment options in relation to machine learning [51], or both diagnosis and management [21,39]; however, no systematic reviews were identified that comprehensively identify the use of all AI methods specifically for disease and symptom management following diagnosis. A search of PROSPERO and PubMed for a range of keyword combinations including "artificial intelligence," "machine learning," "deep learning," and "Parkinson" identified a range of different reviews; however, none focused on AI for PD symptom and disease management.

To address this lack of comprehensive reviews, this review aims to identify the current uses of all AI applications across the assessment, management, and monitoring of symptoms of PD and identify the challenges and pitfalls of the current application of AI in PD. To achieve this aim, we will provide a comprehensive overview of the current state of the literature; assess and compare the type of AI applied; and identify the challenges and barriers and provide recommendations for the use of AI within this population.

Methods

Overview

The methodology for this review has been generated in accordance with the PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) [52], as displayed in Multimedia Appendix 1, as well as the population, intervention, comparison, outcomes, and study (PICOS) framework [53,54].

Eligibility Selection Criteria

The PICOS-type framework, as detailed in Table 1, is based on the research aim stated above.

Table 1. Population, intervention, comparison, outcomes, and study (PICOS) framework.

Population	People diagnosed with PD[a]
Intervention	AI[b] tools, including all machine learning approaches and deep learning approaches for the assessment, management, or monitoring of PD symptoms.
Comparator	No comparator is required.
Outcomes	The primary objective is to identify and summarize the AI methods for the assessment, monitoring, and management of PD symptoms. Therefore, the primary outcome will be to identify and compare the different AI methods used in the assessment, monitoring, and management of PD symptoms. Comparison between models will be made using accuracy data. The secondary outcome is to identify the current challenges, barriers, or pitfalls with the application of AI in PD.
Study types	Qualitative, quantitative, and mixed methods studies that use any form of AI in the assessment, monitoring, or management of PD symptoms will be eligible for inclusion. Reviews, protocols, and papers that describe interventions without evaluating them will be excluded.

[a]PD: Parkinson disease.

[b]AI: artificial intelligence.

Search Strategy

Five databases will be searched for appropriate publications—PubMed, IEEE Xplore, Institute for Scientific Information's Web of Science, the Cochrane Library, and Scopus. The databases were chosen as they were frequently searched in previous systematic reviews on PD and machine learning and have a wide range of coverage of digital technology and health. The following search terms were developed following an initial review of the literature and used to develop the search terms and search strategy. Search items will include Medical Subject Headings (MeSH) terms and keywords related to machine learning, PD, and symptom management. The search terms that will be used in this review are grouped into 3 themes (Table 2). The search string will be created using the following structure: "Artificial intelligence" (MeSH or keyword) AND "Parkinson's disease" (MeSH or keyword) AND "intended use" (MeSH or keyword). Multimedia Appendix 2 shows a sample search string. The reviews will be hand searched for relevant studies.

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Table 2. Search terms.

Category	MeSH[a]	Keywords (in title or abstract)
Artificial intelligence	"Artificial intelligence" and "Machine learning"	"Artificial intelligence" OR "machine learning" OR "deep learning" OR "neural network" OR "neural networks" OR "supervised machine learning" OR "unsupervised machine learning" OR "reinforcement learning"
Parkinson disease	"Parkinson's disease"	"Parkinson's disease" OR "Parkinson's" OR "Parkinson" OR "Parkinson disease"
Intended use	N/A[b]	"assessment" OR "monitoring" OR "management"

[a]MeSH: Medical Subject Headings

[b]N/A: not applicable.

Inclusion Criteria

Any study will be included that uses any AI method (ie, machine learning, deep learning, or algorithm) to detect (ie, the identification of symptoms), monitor (ie, maintain an objective oversight of symptoms), or manage (ie, use of symptoms data to reduce symptom burden, reduce prevalence of symptom, or support clinical decision-making) any symptom of PD. The AI method will not be limited and will include all machine learning, deep learning, or algorithm approaches. No restrictions will be placed on the symptom in question; however, a diagnosis of PD must be present. Studies with any type of sampled population will be eligible for inclusion, with no restrictions on age, gender, or country. Interventions with comparisons to control groups with no intervention, irrelevant interventions, or minimal interventions will all be included.

Exclusion Criteria

Due to the progressive nature of the digital health field with continuous adaptations being made, in addition to a clear increase in the number of papers published from this date, any study published before 2010 will be excluded [55]. Studies that address the use of AI in the diagnosis of PD or the management of symptoms related to PD without a diagnosis of PD (eg, Alzheimer disease, sleep disturbance, etc) will be excluded. Studies that assess symptoms in the context of diagnosis or assess related symptoms with a different neurological diagnosis will be excluded. Studies written in any other language aside from English will be excluded, as the research team do not have the capabilities to read them or the resources to have them translated. Studies that focus on Parkinsonian conditions (eg, progressive supranuclear palsy and multiple system atrophy) that are not PD will be excluded. Reviews, protocols, and papers that describe interventions without evaluating them will be excluded (Textbox 1).

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Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Year: 2010 to present
- Article type
  - Detection, monitoring, or management of one or more symptoms of Parkinson disease (PD) using any artificial intelligence (AI) method
  - Randomized controlled trials; qualitative, quantitative, cohort, and case studies
- Language: English
- Population
  - Human studies of any gender, age, or country
  - Diagnosis of PD

Exclusion criteria

- Year: any article published before 2010
- Article type:
  - Studies that assess symptoms in the context of diagnosis
  - Symptoms of PD without a diagnosis
  - Reviews, protocols, practice guidelines, commentaries, letters, editorials, conference abstracts, and posters without full texts
  - Studies that assess related symptoms with a different neurological diagnosis
  - Studies using Parkinsonian conditions that are not PD (eg, multiple system atrophy or progressive supranuclear palsy)
- Language: non-English
- Population: animal models

Screening and Article Selection

The references returned from the database searches will be exported into the citation management software EndNote 20 (Clarivate) for storage and duplicate removal. The screening will take place in the following three stages: (1) EndNote's search function will be used to screen the articles using keywords in comparison to the inclusion and exclusion criteria, and exclude any studies that are evidently ineligible; (2) the remaining references (titles and abstracts only) will be screened by 2 independent reviewers; and (3) the full texts of the studies will then be screened by 2 independent reviewers to determine the final set of papers for inclusion. Any disagreement between the reviewers will be discussed until a consensus is achieved. If a consensus cannot be achieved, a third reviewer will be consulted to determine the outcome. Details of the screening and selection process will be recorded in a PRISMA-P [52] flow diagram to ensure reproducibility of the study. Stage 1 EndNote 20 searches will be recorded and included in the final review as an appendix.

Data Extraction

The full text of each article included in the final set will be assessed by 2 independent reviewers to extract the data outlined in Table 3. As outlined above, any discrepancies between reviewers will be discussed and resolved by an additional reviewer if a consensus cannot be achieved.

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Table 3. Article information and data extraction.

Article information	Data to be extracted
General study information	• Year of publication • Country of study • Sample demographics (including age, gender, and target population) • Initial sample size • Analyzed sample size
Model characteristics	• AI[a] method • Delivery of the AI method (eg, app, web portal, etc) • Aim of intervention • Target user or audience of intervention (eg, people with PD[b], PD care partners, or HCPs[c]) • Purpose of the AI method (ie, symptom assessment, monitoring, and management) • Symptoms assessed • Data collection method or technique (eg, wearable sensor, smartphone app, etc)
Evaluation or validation	• Effectiveness, accuracy, specificity, or sensitivity of method (if reported) • Test training sets of data and their percentages • Effectiveness, efficacy, usability, acceptability, and feasibility outcome measures (if reported)

[a]AI: artificial intelligence.

[b]PD: Parkinson disease.

[c]HCP: health care provider.

Quality Appraisal and Risk of Bias Assessment

Risk of bias for all of the included studies will be independently assessed by 2 reviewers. Any discrepancies between reviewers will be discussed and resolved by a third reviewer if necessary. For randomized controlled trials, risk of bias will be assessed using the Cochrane Collaboration Risk of Bias 2 tool [56,57]. For nonrandomized studies, the Mixed Methods Appraisal Tool will be used [58] due to its appraisal of most common study types and designs.

Data Analysis and Synthesis

If there are sufficient studies, we plan to conduct a meta-analysis of outcome measures; however, there is a possibility that it may not be feasible due to the expected heterogeneity of studies. If meta-analysis is possible, the design will be guided by [59], and heterogeneity will be assessed using I^2 statistic [60]. The primary outcome for meta-analysis will be classification accuracy of symptoms and is expressed at a proportion between 0 and 1 (eg, percentage rate and area under the curve). The extracted data will be summarized using descriptive analysis to provide the outcomes measured, machine learning tools used, and symptoms assessed. The risk of bias in the studies will be considered in the synthesis.

Ethical Considerations

There are no ethical issues of concern in this secondary analysis of published data.

Results

As of April 2023, database searches have not yet begun. The full systematic review is expected to be completed and submitted for publication by September 2023.

Discussion

Principal Findings

This paper describes the protocol for a systematic review to identify the current uses of AI for people with PD in the assessment, monitoring, and management of PD symptoms. The results from this review will improve knowledge about the way PD is managed using AI methods. With increasing need for the effective management of the wide-ranging symptoms of PD and the accelerated use of computational technologies in PD care, a comprehensive analysis of the research surrounding the use of these tools for symptom assessment, monitoring, and management is necessary. This review will identify how AI is currently being used with this population, as well as its potential benefits and limitations.

There has been a recent increase in the focus of digital health and computational technologies for the diagnosis and management of PD, and several reviews have been conducted [10,31,39,61]. This review aims to be the first to summarize the evidence of the use of AI for disease and symptom management for PD. This review differs from the aforementioned reviews as it places no restriction on the symptom in question; for example, in [61], the authors focus on freezing of gait or on the diagnosis of PD only. The results from this review will therefore provide a more thorough overview of the management of PD using AI methods and the potential benefits to the patient, health care professional, and service.

Limitations

A limitation from this review that may impact the conclusions we are able to make is the inclusion of all PD symptoms and their assessment or management via AI. As there are reportedly over 40 symptoms of PD [62], some symptoms may feature more heavily within the literature than others; therefore, conclusions for certain symptoms may be easier to draw than

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others. It is anticipated that there will be a high level of heterogeneity of outcomes in addition to the inclusion of qualitative and quantitative studies, which may result in difficulty when comparing the effects. When extracting data, it may be possible to compare the effects in subgroups (eg, symptom type, gender, etc). Finally only studies written in the English language will be included in this review; therefore, relevant articles may be missed as a result.

Conclusions

From this review, we anticipate that the findings will provide insight into the current uses of AI in disease management for people with PD and may inform future research or developments for the implementation of AI-based tools for PD management from research to practice. As this review has the potential to impact upon technological advancements and clinical management, the results will be disseminated through peer-reviewed publication.

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Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during this study. Data sets generated and analyzed from the prospective full review will be available from the corresponding author upon request.

Authors' Contributions

The review topic was conceived by KB. The protocol was written by KB, with final revision by MMI, AH, EM, and CC.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist.
[DOCX File , 18 KB - resprot_v12i1e46581_app1.docx]

Multimedia Appendix 2
Sample search strings.
[DOCX File , 14 KB - resprot_v12i1e46581_app2.docx]

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Abbreviations

AI: artificial intelligence
MeSH: Medical Subject Headings
NMS: nonmotor symptoms
PD: Parkinson disease
PICOS: Population, Intervention, Comparator, Outcome, and Study
PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols

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Protocol

Accumulation of Biological and Behavioral Data of Female Sex Workers Using Respondent-Driven Sampling: Protocol for a Systematic Review

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Abstract

Background: Respondent-driven sampling (RDS) is a nonprobability sampling technique that allows the extrapolation of its outcome to the target population. This approach is typically used to overcome the difficulties in studying hidden or difficult-to-reach groups.

Objective: The purpose of this protocol is to generate a systematic review on the accumulation of biological and behavioral data of female sex workers (FSWs) through different surveys that use the RDS method from around the world in the near future. The future systematic review will discuss the initiation, actualization, and problems of RDS during the accumulation of biological and behavioral data of FSWs through surveys from around the world.

Methods: The behavior and biological data of FSWs will be extracted from peer-reviewed studies published between 2010 and 2022 and that are acquired through RDS. Using PubMed, Google Scholar, the Cochrane database, Scopus, Science Direct, and the Global Health network, all papers that are available will be obtained using the search phrases “respondent-driven” and “Female Sex Workers” OR “FSW” OR “sex workers” OR “SW.” According to STROBE-RDS (Strengthening the Reporting of Observational Studies in Epidemiology for Respondent-Driven Sampling) criteria, the data will be retrieved through a data extraction form and will be organized using World Health Organization classifications of areas. The Newcastle-Ottawa Quality Assessment Scale will be used to measure bias risk and overall study quality.

Results: The future systematic review that will be generated from this protocol will offer evidence for or against the claim that using the RDS technique to recruit participants from “hidden” or “hard-to-reach” populations is the best strategy. The results will be disseminated through a peer-reviewed publication. Data collection started on April 1, 2023, and the systematic review is expected to be published by December 15, 2023.

Conclusions: A minimum set of parameters for specific methodological, analytical, and testing procedures, including RDS methods to evaluate the overall quality of any RDS survey, will be provided by the future systematic review, in accordance with this protocol, to assist researchers, policy makers, and service providers in improving RDS methods for the surveillance of any key population.

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KEYWORDS

respondent-driven sampling; RDS; female sex worker; FSW; systematic review; review method; sex worker; sampling method; sample design

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Introduction

Background

The respondent-driven sampling (RDS) method is a nonprobability sampling method that approximates probability sample design, allowing for the extrapolation of results to the target population. This method is generally used to address the limitations of studying hidden or hard-to-reach populations [1]. The term "hard-to-reach population" emerged in the early 1990s in public health to refer to the comparatively lower socioeconomic and moderate to low literacy groups, ethnic minority groups, and those who are not successfully reached by health workers from different health campaigns. Social science workers coined the term "hidden population" to refer to the group of people with an inadequate sampling frame. This situation can occur when they belong to an unorthodox occupational group (female sex workers [FSWs]) or closed social groups (men who have sex with men) or have outlawed behaviors (people who inject drugs) or small population size, among others [1].

Initially, RDS was developed [2] as a chain-reference sampling technique by which a data-tracing path is obtained from one person to another, based on their relationship consecutively. This method combines aspects from snowball sampling, stochastic Markov chain modelling, and the theory of biased networks (homophily model) [1]. The authors also rely on the theory describing the "small world" phenomenon that each person indirectly associates with another person through approximately 6 intermediaries, no matter how large the network. If this premise is true, it would mean that even the most socially isolated individuals can be reached in the sixth wave of a reference chain, starting from any arbitrarily chosen individual [2]. Other theoretical bases for the "small world" phenomenon come from sociology—particularly from behavioral theories that study obedience or social control based on the group of belonging [2]. This theoretical background justifies the idea of incentive and peer involvement in recruitment [2].

RDS has been used in several countries to collect data from populations at high risk of HIV exposure, FSWs, men who have sex with men, people who use or inject drugs, and other such people considered "hard-to-reach" due to social stigma and the exercise of unsocial activities [1,3]. Over the decades, this widely accepted sampling technique is used, with the recommendations of organizations such as the US Centers for Disease Control and Prevention, the Joint United Nations Programme on HIV/AIDS (UNAIDS), the World Health Organization (WHO) Global Fund, and others, to generate data on the baseline, conduct trend analysis for prevalence estimation, and study risk behaviors and the impact of the program on HIV and other sexually transmitted infections through biological and behavioral assessments [3]. The sampling technique has proved feasible and successful in recruiting hidden populations of people who inject drugs in a variety of settings, resulting in the rapid acquisition of long and varied recruitment chains. It has been used in several countries to collect both behavioral and biological data from sex workers (eg, Vietnam and India) and men who have sex with men (eg, Bangladesh, Cambodia, Uganda, and the United States) [3,4]. RDS starts with a fixed number of participants called "seeds," which are carefully chosen by the surveillance team from the target population, and samples are built through the passing of a coupon from one peer to the next. A small number of coupons are generated for each participant, limiting the overcontribution of participants with a greater number of ties to other people in the same network. These coupons allow researchers to observe the procedure of recruitment by limiting participants from having to deliver individual information about their recruits [5]. Individuals who are participating and recruiting peers for the survey are provided with "incentives" to ensure ongoing participation and proper recruitment. This participation and recruitment process may result in a long recruitment chain made up of plentiful "waves" of recruits. The arrangement of the sample becomes less reliant on the purposefully selected seeds as recruitment chains get elongated [6]. Statistical modifications for variation in network sizes and recruitment efforts are used after the sample collection to generate data on estimates that are representative of the population's network [1,2,5].

FSWs are also hard to reach because they are mostly mobile and regularly change solicitation points—districts and towns within and across states or provinces [7-9]. Some FSWs are difficult to locate as they engage in part-time sex work. Higher-paid sex workers, such as those who solicit through the internet and agents, have the capacity to remain hidden [8-10]. However, previous involvement with RDS is limited and needs further evaluations to validate these methods. Furthermore, little is known about the feasibility of this sampling technique as a method of recruiting hidden populations of FSWs in settings where the organization of sex work and access to FSWs is highly controlled and where there is little or no contact between the target population and local services [7,11].

Objective

In the context of this background, the purpose of this protocol is to generate a systematic review on the accumulation of biological and behavioral data of FSWs through different surveys that use the RDS method from around the world in the near future. The future systematic review will discuss the initiation, actualization, and problems of RDS during the accumulation of biological and behavioral data of FSWs through surveys from around the world.

Methods

Overview

The protocol has been developed in accordance with the STROBE-RDS (Strengthening the Reporting of Observational Studies in Epidemiology for Respondent-Driven Sampling) guideline (Multimedia Appendix 1) [11]. This protocol has been registered in PROSPERO (CRD42022346470).

Review Items

According to the STROBE-RDS [12] guideline, the following items will be captured in the review:

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2. Year of publication along with period of study
3. Country or geographical location of study
4. Presurvey assessment (if any)
5. Number of RDS data collection sites
6. Interview methods
7. Numbers of initial and final seeds along with the maximum number of waves
8. Amount of primary and secondary incentives
9. The target sample size and sample size obtained finally
10. Design effect used in sample size calculation
11. The duration of data collection (in weeks)
12. Maximum number of coupons distributed to each recruiter
13. Whether equilibrium or convergence was assessed or not
14. Whether the data were adjusted for network size
15. Use of software for statistical analysis

Electronic Database and Search Terms

All available articles will be retrieved using PubMed, Google Scholar, the Cochrane database, Scopus, Science Direct, and the Global Health network. Search terms will include "respondent-driven" OR "RDS" and "Female Sex Workers" OR "FSW" OR "sex workers" OR "SW." The full search terms are presented in Multimedia Appendix 2.

Inclusion Criteria

The inclusion criteria are as follows:

1. Peer-reviewed literature published only in English in a physical or web-based format that reported using RDS
2. Article published from January 2010 to December 2022
3. Articles on FSWs only

FSWs are defined as those who are cisgender female and have ever exchanged sex for money or goods within the last 12 months.

Exclusion Criteria

Duplicates, irrelevant articles (eg, protocols, presentations, flyers, and those not strictly addressing RDS methodology) along with reviews, opinion pieces, editorials, commentaries, and studies that are not intended to report population-based estimates will be excluded from the initial extraction.

Selection of Eligible Studies

We will obtain the full text of articles or other documents reporting studies identified as being potentially eligible for inclusion. Two suitably qualified reviewers will screen titles and abstracts of articles identified by the search strategy independently using the data extraction form (Multimedia Appendix 3). Any study selected as being potentially eligible by either reviewer will be retained for review of the full text. If no abstract is available electronically and eligibility cannot be judged from the title alone, the full text of the article will be retrieved and screened. The abstracts of articles identified through additional searches will be reviewed in the same manner as those identified through database searches.

Strategy for Data Synthesis

The data will be extracted from full-text published articles through Epi Inf (version 6.0) [13] using a modified data extraction form (Multimedia Appendix 3) according to the STROBE-RDS guideline.

The data will be arranged into 6 subtables in a Microsoft Excel spreadsheet based on WHO classifications of regions [14], such as the African Region, Region of the Americas, South-East Asian Region, European Region, Eastern Mediterranean Region, and Western Pacific Region.

Deduplication

Mendeley bibliographic software [15] will be used for reference management. The following rules will be used to remove duplicate hits from the database:

1. Compare the title or various combinations of the author, year, secondary title, volume, issue, and pages through "deduplication";
2. Visually compare the full records of suspected duplicates; and
3. Save duplicates in a separate database.

Risk of Bias and Quality Assessment

The evaluation of articles through the title, abstract, and entire text of the manuscripts will be performed prior to the addition of it to the ultimate analysis. Assessment will be performed with the help of the Newcastle-Ottawa Quality Assessment Scale [16].

Ethical Consideration

Formal ethical approval is not required as primary data will not be collected.

Results

The future systematic review that will be generated from this protocol will offer evidence for or against the claim that using the RDS technique to recruit participants from "hidden" or "hard-to-reach" populations is the best strategy. The results will be disseminated through a peer-reviewed publication. Data collection started on April 1, 2023, and the systematic review is expected to be published by December 15, 2023.

Discussion

A systematic review will be generated from this protocol and will provide evidence in support of or against the hypothesis that the application of the RDS technique is an effective approach to recruiting participants from "hidden" or "hard-to-reach" populations. This peer-to-peer recruitment is driven by legitimate coupons, making it successful among populations that are stigmatized or who practice behaviors that are considered illegal in the existing social structure.

Similar to any systematic review protocol, this protocol and the future review will also be restricted by the comprehensiveness of the published articles and whether researcher publish their study in open access and peer-reviewed journals. Moreover, the included articles on surveys that accumulate biological data would lead to further studies.

As sex work also carries occupational risk, this approach is expected to be appropriate and the best suited for this high-risk

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population [17]. The future systematic review, as conducted according to this protocol, will help researchers, policy makers, and service providers to improve the RDS methods for the surveillance of any key population, by providing a minimum set of parameters of specific methodological, analytical, and testing procedures, including RDS methods to evaluate the overall quality of any RDS survey [18].

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Conflicts of Interest

None declared.

Multimedia Appendix 1
STROBE-RDS (Strengthening the Reporting of Observational Studies in Epidemiology for Respondent-Driven Sampling) study reporting checklist.
[DOCX File , 44 KB - resprot_v12i1e43722_app1.docx]

Multimedia Appendix 2
Search terms.
[DOCX File , 12 KB - resprot_v12i1e43722_app2.docx]

Multimedia Appendix 3
Data extraction form.
[DOCX File , 203 KB - resprot_v12i1e43722_app3.docx]

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Abbreviations

FSW: female sex worker
RDS: respondent-driven sampling
MSM: male sex with male
STROBE-RDS: Strengthening the Reporting of Observational Studies in Epidemiology for Respondent-Driven Sampling
UNAIDS: United Nations Programme on HIV/AIDS
WHO: World Health Organization

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Protocol

Comparing Decentralized Learning Methods for Health Data Models to Nondecentralized Alternatives: Protocol for a Systematic Review

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Abstract

Background: Considering the soaring health-related costs directed toward a growing, aging, and comorbid population, the health sector needs effective data-driven interventions while managing rising care costs. While health interventions using data mining have become more robust and adopted, they often demand high-quality big data. However, growing privacy concerns have hindered large-scale data sharing. In parallel, recently introduced legal instruments require complex implementations, especially when it comes to biomedical data. New privacy-preserving technologies, such as decentralized learning, make it possible to create health models without mobilizing data sets by using distributed computation principles. Several multinational partnerships, including a recent agreement between the United States and the European Union, are adopting these techniques for next-generation data science. While these approaches are promising, there is no clear and robust evidence synthesis of health care applications.

Objective: The main aim is to compare the performance among health data models (eg, automated diagnosis and mortality prediction) developed using decentralized learning approaches (eg, federated and blockchain) to those using centralized or local methods. Secondary aims are comparing the privacy compromise and resource use among model architectures.

Methods: We will conduct a systematic review using the first-ever registered research protocol for this topic following a robust search methodology, including several biomedical and computational databases. This work will compare health data models differing in development architecture, grouping them according to their clinical applications. For reporting purposes, a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 flow diagram will be presented. CHARMS (Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modelling Studies)–based forms will be used for data extraction and to assess the risk of bias, alongside PROBAST (Prediction Model Risk of Bias Assessment Tool). All effect measures in the original studies will be reported.

Results: The queries and data extractions are expected to start on February 28, 2023, and end by July 31, 2023. The research protocol was registered with PROSPERO, under the number 393126, on February 3, 2023. With this protocol, we detail how we will conduct the systematic review. With that study, we aim to summarize the progress and findings from state-of-the-art decentralized learning models in health care in comparison to their local and centralized counterparts. Results are expected to clarify the consensuses and heterogeneities reported and help guide the research and development of new robust and sustainable applications to address the health data privacy problem, with applicability in real-world settings.

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Conclusions: We expect to clearly present the status quo of these privacy-preserving technologies in health care. With this robust synthesis of the currently available scientific evidence, the review will inform health technology assessment and evidence-based decisions, from health professionals, data scientists, and policy makers alike. Importantly, it should also guide the development and application of new tools in service of patients' privacy and future research.

Trial Registration: PROSPERO 393126; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=393126

International Registered Report Identifier (IRRID): PRR1-10.2196/45823

(JMIR Res Protoc 2023;12:e45823) doi:10.2196/45823

KEYWORDS

decentralized learning; distributed learning; federated learning; centralized learning; privacy; health; health data; secondary data use; health data model; blockchain; health care; data science

Introduction

Background

The current health paradigm challenges are unprecedented in their nature and scope. Stemming from a growing [1], aging [1], and comorbid [2] global population, disability is becoming an increasingly large share of the burden of disease and of the already unsustainable health care costs [3-6]. Faced with the need to invest in more effective and preventive strategies, improved research and development are essential to address these unwavering issues [2].

To do so, robust evidence-based health knowledge is needed, as a way of enabling improved planning and provision of care. Presently, many data-driven approaches are commonplace in biomedical sciences and clinical research. These include examples from epidemiological surveillance [7] and cancer prognosis [8] to drug discovery [9,10] and mortality prediction [11].

Thus, access to data has been the foundation for better health models, both in their precision and validity to represent different medical conditions [12,13] and patients [14,15]. In parallel, alongside recent digital transitions and new tools and infrastructures, data analysis has become more powerful and faster than ever [16]. This gave rise to data science [17], resulting from the complex merger of traditional statistics disciplines combined with other subjects.

In particular, data mining techniques have elevated the computational functionality, especially for cognitive and analytic processes that are hard to develop algorithmically [18]. Thus, machine learning models, such as decision trees, linear regression, and support vector machines are now abundant in health research [19,20]. Deep neural networks brought to light even more sophisticated applications of natural language processing and computer vision, both effective and powerful [21,22].

Supported by robust software and hardware, these new model development approaches rely on the availability of large and high-quality training databases. Hence, the concept of big data emerged, referring to the need for comprehensive data sets to sustain the inferential process in both their internal and external validities. While it is often characterized by a few key dimensions (volume, variety, velocity, value, veracity, and variability), many other features (eg, venue and volatility) can be of relevance [23,24]. However, concerns regarding privacy protection—a fundamental human right [25]—are rising amid increasing numbers of misconducts and violations [26,27].

Limitations of Current Strategies

In response to both data demands and privacy challenges, 2 groups of arguments can be made in favor of transitioning traditional approaches toward a new data science paradigm.

First, to generate and use high-quality big data to support precision and generalizability assumptions, findable, accessible, interoperable, and reusable (FAIR) principles [28] ought to be adopted. In theory, following these criteria is important to develop new scientific studies and validate, or otherwise reproduce, at least part of already available works [29,30]. In practice, FAIR principles are hard to comply with, for several reasons.

Starting with "findable," few health data catalogs are available, and some are no longer being updated [31-33]. Considering access, while new instruments [34-37] have presented legislation and guiding frameworks on how data should be used and shared, their impact is controversial and their implementation is often complex, especially for medical research purposes [38-44]. Even follow-up developments, like the European Health Data Space [45], are viewed with skepticism by some member states regarding its practical feasibility and results [46,47].

Furthermore, data use is often limited by its interoperable characteristics. Technical heterogeneity due to different electronic health record systems, data standards, and data exchange protocols makes it difficult to share and integrate health data across multiple parties. Given all the challenges stated, reusability is practically impossible, outside some rare contexts [48,49].

Additionally, another set of arguments can be presented referring to the need for a systematic approach that does not rely on individuals' actions nor benefits from their limitations. First, we recognize that individuals are not capable of always acting with their own (or collective) interests in mind [50]. Specifically in their health data sharing attitudes, even though people may be aware of the value of data and potential privacy issues, their actions are often contrasting to their stated beliefs [51,52].

Then, we place the onus and burden of sustainable privacy protection on the system itself and are not reliant on the constant and best behavior of every individual agent [53]. Some

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successful global data sharing efforts [48,54,55] have already proven that after the demanding set up, it is possible to not only improve access to data but also protect privacy by design [56].

New Technological Solutions

In response to these demands, recent breakthroughs in some computational domains, including secure processing units [57,58], differential privacy [59,60], and homomorphic encryption [61,62], have offered technical alternatives for the use of data in a privacy-preserving fashion. Being one of the more interesting approaches, decentralized learning architectures [63,64] enable data scattered across different silos (eg, health care providers) to be used to develop or validate pre-existing models. By combining the information derived from data present in each silo, it is possible to create more precise and generalizable models.

In general, local models are first developed using the party's own data. Second, only the model parameters (ie, information) are shared, usually with a central coordinator, responsible for aggregating the different local instances to create a new decentralized model. Throughout this process, data remain unmoved and are not accessed or manipulated by third parties.

Accordingly, such models can be produced without mobilizing or otherwise sharing the data set itself by parceling out the inferential process, on top of distributed computation principles [65]. By cyclically repeating this process, we can improve the model performance and include newly available data, fostering the development of continuously updated real-world evidence-based knowledge.

The potential for developing health care applications and generating value is clear [66]. Sharing models developed using different data sets can make the distributed solutions more comprehensive and adequate, due to robust internal and external validations. These approaches are useful to study medical conditions [67-69], especially those with limited prevalence or few observations, and prevent inadequate care due to mis- or underrepresentation of certain groups of patients [70].

Subsequently, significant agreements, like the one achieved between the United States and the European Union [71], promise a new platform for these technologies to be implemented while respecting their differing legislative frameworks. Such consensus can have a seismic impact on the way data science is conducted.

In the meantime, there still are many ongoing challenges regarding decentralized learning [18,72]. Some relevant issues are a lack of objective and measurable standard definitions of privacy and security [73], and server-client trust and honesty assumptions to computationally intensive and energetically demanding tasks [61,74]. Other important problems are the heterogeneity in distributed data and environments as well as fairness and respect for individual and local preferences [73].

However, above all else, the most pressing undertaking remains assessing the validity, relevance, and applicability of already published and available tools to inform and justify subsequent health technological appraisals and their implementation in real-world settings.

To do so, we must address the following questions: are decentralized health data models' performance superior (or noninferior) to current (centralized and local) approaches? and what are the reported privacy gains and the main resource demands?

Aims and Objectives

The systematic review based on this protocol aims to, first, compare the performance among health data models developed or validated using decentralized learning approaches (eg, federated and blockchain) to those developed using nondecentralized methods (eg, centralized and local). These can include applications such as automated diagnosis, segmentation of lesions or features, as well as mortality prediction.

The performance metrics used for model comparison will be the following: area under the receiver operating characteristic (AUROC) curve, F_1 score, Jensen-Shannon distance, sensitivity (or recall), specificity, accuracy, precision (or positive predictive value), negative predictive value, Dice score, as well as any metrics regarding the convergence step. Comparisons will be made only among models using the same type of data (eg, tabular and images) and clinical application (eg, diagnostic and survival). Our secondary aims are to compare the privacy compromise (eg, privacy budget) and resource use (eg, computation power and wall-time) among these health data models using different architectures.

With this review study, our goal is to summarize the progress and findings from state-of-the-art decentralized learning models in health care, in comparison to their currently used counterparts. These results are expected to clarify the consensuses and heterogeneities reported and help guide the research and development of new robust and sustainable applications to address the health data privacy problem, with applicability in real-world (clinical) settings.

Methods

Eligibility Criteria

Regarding the inclusion criteria, relevant studies are original research papers (including published, unpublished, and preprints) targeting one or multiple specific human medical conditions. They should be comparing 2 types of health model learning approaches—one decentralized (eg, federated and blockchain) and other nondecentralized (eg, centralized and local). For this review, decentralized learning architectures are defined as a machine learning approach to use data available from multiple parties, without sharing them with a single entity, to extract information [18].

As there may be some confusion regarding the terms "decentralized" and "distributed," we consider the first as the most appropriate and rigorous designation of our study field, including federated and blockchain architectures. The latter is broader in scope and refers to a computational subject that includes, but also precedes, the current advances and innovations [65]. Nevertheless, studies will be included regardless of the adopted terminology if the definition or methodologies used

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are in accordance with the above definition of decentralized learning architectures. Both types of models must report at least one of the following model performance metrics: AUROC curve, F_1 score, Jensen-Shannon distance, sensitivity (or recall), specificity, accuracy, precision (or positive predictive value), negative predictive value, Dice score, as well as any metrics regarding the convergence step.

Regarding the exclusion criteria, papers published before 2012 will not be considered for this analysis, due to the following reasons. First, the earliest decentralized learning framework proposals in health care are only introduced [75,76] or applied [77] after this year. Second, seminal studies detailing and developing the current definition of these concepts were published in 2016 [78,79], with related works being as available as early 2014 [63,80,81]. Moreover, in no systematic review for health care implementations are there primary studies published before 2016 [82-86].

Each synthesis will consider studies with common types of clinical applications (intervention, diagnosis, etiology, prevention, prognosis or prediction, quality of life or meaning, and therapy), types of models, and types of data used. Whenever possible, they will be grouped by health problems.

Information Sources

Recognizing the interdisciplinarity nature of the research being made on health data models, several databases will be queried—some more specific to biomedical scientific research (ie, PubMed, SpringerLink, and Lippincott Williams & Wilkins), some more specific to computer science and informatics engineering (ie, the Association for Computing and Machinery Digital Library or Guide to Computing Literature and IEEE Xplore), while others were more general (ie, Wiley Online Library, Scopus, Web of Science, and Lens).

Moreover, 2 registries for systematic reviews (Cochrane Database of Systematic Reviews and PROSPERO) were surveyed for submissions related to these topics, in order to look for additional primary papers. Furthermore, queries were also conducted in databases, which included research papers not peer-reviewed or otherwise unpublished (eg, medRxiv and arXiv). For every listed source, searches are expected to be conducted during March 2023.

Five experts in relevant scientific fields (from data science, health informatics, and decentralized learning approaches) will be contacted to ask for suggestions of additional bibliography not included in the selection process, without the knowledge of the selected or rejected papers. Such recommendations will be considered worthy of consideration and included if eligibility criteria are met. Due to the reasons stated in the eligibility criteria, it was deemed appropriate to restrict the search to papers published in 2012 or later.

Search Strategy

Overview

Given the recency of this research domain and the expected limited number papers, it was imperative to devise a broad search strategy. This was materialized in choices such as including several databases, as well as using synonyms and wildcards in the query.

However, due to the popularity of some of the query terms—for example, distributed, model, training, and health—some procedures were adopted to filter noise. For instance, words like “distributed” and “model” should have a limited number of words in between, for the finding to be relevant. Moreover, search engines have heterogeneous features, which make it difficult to conduct the desired exploration.

Hence, a composite search strategy was adopted. The first part, optimizing for comprehensiveness, was focused on writing the query and electing relevant filters for each database used (see “Part 1—Database Query” section, Table 1, and Figure 1). Subsequently, a filtration process was applied, using regular expressions (RegEx) code, to make up for the lacking features of the databases used—such as word proximity limits, operators, and metadata fields searched (see “Part 2—Results Filtration” section).

Table 1. General query terms by group.

Group	Terms
A—Model architecture	decentrali*, distributed, federated, central*, multi-party computation, blockchain
B—Model synonym	learn*, model*, network*, AI[a], artificial intelligence, ML[b], machine learning, train*, tensor*, perceptron, algorithm*
C—Health related	health*, medic*, clinic*, patient*, physician*, doctor*
D—Performance metrics	AUROC[c], ROC[d], receiver operating characteristic curve, F_1, Jensen-Shannon, sensitivity, recall, specificity, accuracy, precision, predictive value, Dice, conversion

[a]AI: artificial intelligence.

[b]ML: machine learning.

[c]AUROC: area under the receiver operating characteristic.

[d]ROC: receiver operating characteristic.

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Figure 1. Example of search query as used on Lens database. AI: artificial intelligence; AUROC: area under the receiver operating characteristic; ML: machine learning; ROC: receiver operating characteristic.


Scholar Search Results
Hide Query Details
Edit Search
Search Patents
Scholarly Works (12,321) = (Title: (distributed) OR (Abstract: (distributed) OR (Keyword: (distributed) OR (Field of Study: (distributed) OR (Title: (federated) OR (Abstract: (federated) OR (Keyword: (federated) OR (Field of Study: (federated) OR (Title: (decentrali*) OR (Abstract: (decentrali*) OR (Keyword: (decentrali*) OR (Field of Study: (decentrali*) OR (Title: (centrali*) OR (Abstract: (centrali*) OR (Keyword: (centrali*) OR (Field of Study: (centrali*) OR (Title: (blockchain) OR (Abstract: (blockchain) OR (Keyword: (blockchain) OR (Field of Study: (blockchain) OR (Title: ("multi-party computation") OR (Abstract: ("multi-party computation") OR (Keyword: ("multi-party computation") OR Field of Study: ("multi-party computation")))

risk of bias assessment [88]. These forms will be piloted before the data collection process.

After completion, retrieved data will be compared to check for errors or inconsistencies and discuss any doubts. The researchers will decide by consensus on the last version of the database of the data collected.

Data Items

A pilot study was conducted to refine the list of relevant data variables to collect, using 100 papers of a developing query. The complete list of variables for collection (whenever available) is the following.

First, general attributes are to be collected, namely, title, author or authors, abstract, publication date, country or countries of the research institutions, type of publication, the journal or publisher, as well as the PICO (Population, Intervention, Comparison, and Outcomes) question.

Specific data points regarding health topics, the type of clinical application (eg, diagnostic and survival), and the applicable medical domain will also be registered.

Concerning the data used, information about the data set size, namely, the number of observations or cases, the number of variables, and the volume in megabytes or gigabytes will be detailed. As far as the nature of the data goes, it will be marked as either synthetic or real, and, in the latter, whether the data were collected for the study (primary source) or not (secondary source). The original data holders will be described by their number, type, and localization, as well as the storage architecture used (eg, centralized, decentralized, and local). Other data points will be the places (geographical and institutional) where data were analyzed, the ethics and legal permissions reported, as well as the data type used (eg, text and images), alongside their format (eg, tabular), and conversion processes.

The type of all models reported are, for example, deep neural network and decision trees, and their performance metrics are specifically AUROC curve, F_1 score, Jensen-Shannon distance, sensitivity or recall, specificity, accuracy, precision or positive predictive value, negative predictive value, Dice score, as well as any metrics regarding the convergence step. The training methods will also be registered, including their update routine (rounds, epochs, quorum, update frequency, update content, and protocols for data communication) and statistical methods used. The validation process used will also be described.

Regarding the architectures used, their type, data flow, and client type (cross-silo vs cross-device vs both) will be extracted, as well as the personalization or customization step and the aggregation methods used. Importantly, we will detail all the model architectures and types compared, and their hypothesis tests.

For our secondary aim, we will collect data on the privacy cost measures (privacy budget, k-anonymity, fingerprinting, entropy, or others) and resource consumption (from computer resources, hardware and software specs, and energy to time and number of rounds), as well as additional security and privacy protection measures.

Lastly, we will record the reason for using decentralized approaches, whether the data and code used are available, and the reported challenges and limitations. No assumptions will be made regarding missing or unclear information—those findings will be reported as such.

Study Risk of Bias Assessment

For each selected paper, the CHARMS [88] and PROBAST (Prediction Model Risk of Bias Assessment Tool) [89] checklists will be used to assess the risk of bias of included research works. The full results of such an appraisal will be presented on a table and considered for the discussion of the results. If deemed relevant, depending on the final list of results, other more specific tools may be used.

Effect Measures

All the effect measures in the original studies will be presented. Whenever unavailable, and if possible, the difference between the AUROC curve estimates for the models of different architectures will be calculated. When multiple rounds of model development, validation, or application exist, the difference in time and rounds to a set performance target will be calculated.

If multiple values for each model are available, the median and mean values will also be used to calculate the differences. If AUROC curve values are not available, other commonly found metrics may also be used.

Synthesis Methods

A qualitative analysis of the evidence will be conducted alongside a descriptive synthesis of the results. Each synthesis will consider the types of clinical applications, models, and data used. Whenever possible they will be grouped by health problems.

Missing data will be reported as “Missing.” Whenever a synthesis method is not applicable, it will be labeled as “Not Applicable.”

Due to the heterogeneity of the applications and model characteristics, it is not expected to be able to synthesize results in a quantitative fashion. Accordingly, neither a meta-analysis nor a sensitivity analysis will be performed.

Reporting Bias Assessment

For every eligible study, the authors will look up preresearch registers of protocols and check for differences in the published work. Additionally, they will assess whether any pertinent statistics or analyses are unreported. All corresponding authors will be contacted to assess if they have any nonreporting experience with any version of their published work or regarding other unpublished research, as suggested by Ammenwerth and de Keizer [90].

Questions may include the following: Which information systems did you evaluate in the last 3 years? Where did you publish the results? and If you did not publish them, what were the reasons for that decision? (here, some common reasons could be selected or added using free text fields).

Moreover, specific efforts will be made to identify omissions of some measured outcomes, as well as selective reporting of

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only "significant" findings from among several analyses undertaken.

Certainty Assessment

Certainty assessment procedures will be performed if appropriate instruments are available at the time of review completion.

Other Information

Efforts will be made to make available the query links (or prompts) for each database used, as well as the RegEx filtering code, the templates for data collection forms, and the data extracted from the included studies, and any other resources, which might be used for the subsequent review.

Results

The queries and data extractions are expected to start on February 28, 2023, and end by July 31, 2023. The research protocol was registered with PROSPERO, under the number 393126, on February 3, 2023.

It is expected that the systematic review will summarize the progress and findings from state-of-the-art decentralized learning models in health care, in comparison to their local and centralized counterparts. These results will help in clarifying the consensus and heterogeneities reported among different models and studies, as well as guide the research and development of new robust and sustainable applications to address the health data privacy problem, with applicability in real-world (clinical) settings.

Discussion

Principal Findings

As the systematic review is yet to be conducted, no specific results can be reported at this time. However, this will be the first systematic review on the comparison of decentralized health data models to more common local or centralized approaches that is both comprehensive and focused on objective performance metrics. Due to our exhaustive search strategy and the plurality of data sources identified, this work will present the clearest situational assessment yet of the application of these technologies in health care.

We hope that, by highlighting effective models and their developments, as well as identifying those which underperformed, we can shed light on more fruitful and interesting directions for our peers. In addition, by considering the development costs and privacy gains, as reported in the primary papers, it is expected that this review may be useful for health technology assessment and evidence-based decisions, from health professionals, data scientists, and policy makers alike.

By providing the original search queries and documentation on the methods used, we open the possibility for researchers to use this protocol and upcoming supplemental materials to not only audit and validate our work but also conduct updated versions of this review as new evidence is published.

Strengths and Limitations

While decentralized health data models are a nascent and growing field of research, all appropriate steps will be taken to ensure a comprehensive and exhaustive search of available literature. To do so, we will consider a variety of sources (both specific to bio- and computational sciences and generalist databases), as well as preprint works. Alongside these efforts, a substantive yet clear search and selection procedures have been detailed, with 3 authors selecting primary papers for inclusion in the review. Together, these will also increase the sensitivity and specificity of the search results and the studies included for analysis.

Moreover, this protocol is already registered with PROSPERO and is written in accordance with the PRISMA 2020 guidelines, which will confer more validity and accountability for the results provided. In conjunction with the review, these actions will allow for reproducible and auditable work. For instance, it may be useful, with the necessary adaptations, to repeat this study, when even more evidence is available.

Some limitations of this work include the expected heterogeneity among primary studies, complicating synthesis and comparability among models, and the rapid evolution of the field. Given the unusual population (the P in PICO) of this systematic review, the appraisal of the primary studies may be made difficult by a lack of appropriate tools to assess the risk of bias, especially in reporting, and the certainty of the findings.

Comparison With Prior Work

While there are some systematic reviews on the topic already available, they present several important shortcomings in the size and scope [82-84], the specificity of health care applications [85], and the capability and comprehensiveness of query prompts [86]. Moreover, to the best of our knowledge, none of them were accompanied by a protocol publication or registry before the corresponding review.

Therefore, a more robust and valid synthesis of the currently available scientific evidence must be conducted. We consider the proposed systematic review is capable of achieving that result.

Conclusions

Increasing pressure to develop better, more effective, and cost sensitive care, juxtaposed with the privacy-preserving principles and methodologies, has created a considerable demand for alternative health data model development, validation, and application procedures.

While decentralized approaches, such as those built with federated and blockchain architectures, promise considerable gains for extracting information out of health data, there is much uncertainty regarding how they compare to current centralized and local models, as well as their associated privacy gains and their resource consumptions.

This protocol is the first, at the time of this writing, to outline a systematic review on health data decentralized models, aiming not only to capture the rich variety and complexity of available

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research but also to generate a rigorous and comprehensive assessment of the synthesis of their results and conclusions.

It is expected that such work will have implications for this budding research field and policy making, especially for those working with health data privacy matters. This review will highlight the advances and shortcomings of these approaches to better inform the development and application of new tools in service of patients' privacy while hoping to guide future research.

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Data Availability

Documentation will be provided regarding the specific queries used, tailored to each source, including their adapted formulation and filters, to ease reproducibility. Whenever possible, a direct URL link will be included. In addition, the code used to compile and filter the results of the various extraction files will be freely available in a GitHub repository. The original lists of all papers (as extracted) as well as other reports with all those subjected to the screening process will be accessible in the same repository. Moreover, the original data collected from each of the studies included in the review will be shared in a Research Data Repository.

Conflicts of Interest

None declared.

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Abbreviations

AUROC: area under the receiver operating characteristic
CHARMS: Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modelling Studies
FAIR: findable, accessible, interoperable, and reusable
PICO: Population, Intervention, Comparison, and Outcomes
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROBAST: Prediction Model Risk of Bias Assessment Tool
RegEx: regular expression

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Protocol

The Effectiveness of Early Food Introduction in Preventing Childhood Allergic Diseases: Protocol for a Systematic Review and Meta-Analysis

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Abstract

Background: Allergic diseases affect around 40% of the pediatric population worldwide. The coexistence of asthma, allergic rhinitis, eczema, and food allergy renders allergy treatment and prevention challenging. Infant feeding strategies recommend avoiding allergenic foods to prevent allergy development and anaphylaxis. However, recent evidence suggests that early consumption of food allergens during weaning in infants aged 4-6 months could result in food tolerance, thus reducing the risk of developing allergies.

Objective: The aim of this study is to systematically review and carry out a meta-analysis of evidence on the outcome of early food introduction for preventing childhood allergic diseases.

Methods: We will conduct a systematic review of interventions through a comprehensive search of various databases including PubMed, Embase, Scopus, CENTRAL, PsycINFO, CINAHL, and Google Scholar to identify potential studies. The search will be performed for any eligible articles from the earliest published articles up to the latest available studies in 2023. We will include randomized controlled trials (RCTs), cluster RCTs, non-RCTs, and other observational studies that assess the effect of early food introduction to prevent childhood allergic diseases.

Results: Primary outcomes will include measures related to the effect of childhood allergic diseases (ie, asthma, allergic rhinitis, eczema, and food allergy). PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines will be followed for study selection. All data will be extracted using a standardized data extraction form and the quality of the studies will be assessed using the Cochrane Risk of Bias tool. A *summary of findings* table will be generated for the following outcomes: (1) total number of allergic diseases, (2) rate of sensitization, (3) total number of adverse events, (4) improvement of health-related quality of life, and (5) all-cause mortality. Descriptive and meta-analyses will be performed using a random-effects model in Review Manager (Cochrane). Heterogeneity among selected studies will be assessed using the I^2 statistic and explored through meta-regression and subgroup analyses. Data collection is expected to start in June 2023.

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Conclusions: The results acquired from this study will contribute to the existing literature and harmonize recommendations for infant feeding with regard to the prevention of childhood allergic diseases.

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KEYWORDS

protocol; systematic review; childhood allergic disease; weaning; early food introduction; food allergy; allergy; anaphylaxis; randomized controlled trial; pediatric; infant; childhood

Introduction

Background

There has been a steep increase in the reported prevalence of common childhood allergic diseases (namely asthma, allergic rhinitis, eczema, and food allergy) in the last few decades [1-3]. According to Asher and Pearce [1], the International Study of Asthma and Allergies in Childhood concluded in the early 2000s reported that the prevalence of asthma, allergic rhinitis, and eczema had risen to over 30% in most industrialized countries. In addition, asthma is prevalent among approximately 300 million people worldwide, and by 2025, a further 100 million will likely be affected [4]. It is therefore crucial to evaluate the effectiveness of early life prevention techniques in order to lower the burden of childhood allergic diseases.

Infant feeding guidelines recommend early initiation of breastfeeding, including exclusive breastfeeding for the first 6 months of life and continued breastfeeding up to and after 2 years of age. Additionally, weaning or complementary feeding—defined as the provision of nutrition in the form of liquid or solid other than breast milk or infant milk formula—is introduced to neonates by 6 months of age, depending on the achievement of developmental milestones and the availability of safe complementary foods [5,6]. Besides providing essential nutrients to the growing infants, weaning exposes the developing gut microbiome to different antigens, thus influencing immune system development [7]. Food sensitization frequently occurs early in life and is often the first sign of future allergic disease; this is because the infant's immune system has yet to develop, if at all, an allergic phenotype [8]. Food items with allergenic properties may resist digestion and enhance allergenicity. Hence, susceptible infants who did not develop tolerance will manifest an allergic phenotype. Additionally, the preservation of "beneficial" gut microbiota in the neonate prevents immunity alteration that subsequently predisposes him/her from developing an allergy [9]. As a result, many researchers propose nutritional allergy interventions during this period, such as prolonged breastfeeding, early introduction of foods, maternal avoidance diets during pregnancy and lactation, use of hypoallergenic formulas, and early allergen avoidance, albeit with varying degrees of success [8,10,11].

The landmark study, Learning Early About Peanut Allergy, was one of the first to suggest early introduction of peanuts to reduce the development of peanut allergies [12]. In 2016, the Enquiring about Tolerance study expanded to multiple allergenic food items (ie, peanuts, cooked eggs, cow's milk, sesame, whitefish, and wheat) and observed a significant reduction in the prevalence of food allergies in the studied population [13]. These studies, along with others, appear to offer an effective and robust strategy to minimize the burden of allergy in the general population [10,14].

Living with allergic disease affects the quality of life of both patients and their guardians, considering the increasing health care costs. The determinants of health-related quality of life (HRQoL) in children with allergies traverse beyond biophysiological parameters and the symptom status of the child (such as physical limitations and emotional stress) and may include family dynamics and socioeconomic status, the community in which they live (ie, restrictions on participation in activities and social interaction), and organizational and policy-related factors (eg, inadequate food labelling and public information on allergies) [15-17]. Thus, effective allergy management strategy, including allergy prevention is imperative to avert allergic episodes that can be life-threatening.

Current recommendations for infant feeding require more consensus in the area of early life nutrition, specifically for prevention of childhood allergic diseases [18]. Moreover, an increasing number of studies have been examining the effect of early food introduction on reducing allergic sensitization, thus promoting allergy tolerance in these children [19-21]. We acknowledge earlier reports; however, most reviews have focused on the development of food allergies as well as having a diverse methodological approach [22-25]. In addition, there are diverse dietary patterns that may influence the development and progression of allergic diseases and their phenotypic expression in Asian populations. Although the published studies might have promising findings, less is understood about the potential harm that might result from the population-based guidelines and public health programs [26]. Thus, the aim of this systematic review is to identify evidence regarding the effect of early food introduction in preventing childhood allergic diseases.

Objective

This study aims to systematically review and carry out a meta-analysis of the effectiveness of early food introduction in preventing childhood allergic diseases.

Methods

This systematic review and meta-analysis will be conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement [27]

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(Multimedia Appendix 1) and the Cochrane Handbook for Systematic Reviews of Interventions [28].

Study Population and Selection Criteria

Inclusion Criteria

Our inclusion criteria will be based on the PICOS framework where the population of interest ("P") is defined as comprising healthy infants who were introduced to early feeding, the intervention ("I") is early introduction of complementary food (allergenic and nonallergenic) as a method of weaning when an infant approaches 4 months of age (ie, before turning 6 months old)—complementary food introduction is defined by the provision of nutrition other than breast milk or infants' milk formula [29]. Weaning may involve liquid food, as in formula feeding, or solid food that provides essential nutrients to an infant and the developing gut microbiome while influencing immune development [30]. We will accept other interventions that were not specified in this study and were defined by individual authors if they do not involve any pharmacological agent. We will compare ("C") our study cohort with infants who have been initiated on complementary feeding (ie, weaning) in accordance with the standard infant feeding guidelines as described by the studies included in this meta-analysis. The World Health Organization and United Nations International Children's Emergency Fund recommend early initiation of breastfeeding, including exclusive breastfeeding for the first 6 months of life followed by continued breastfeeding for up to 2 years and beyond [31]. Additionally, adequate complementary foods are recommended from the beginning of 4 months to latest 6 months of age to all neonates [32]. The outcomes ("O") are categorized as (1) primary outcomes including the total number of cases presented with asthma, allergic rhinitis, eczema, and food allergy (a reproducible hypersensitivity reaction to certain food items) and (2) secondary outcomes such as allergic sensitization (ie, the presence of elevated total and specific immunoglobulin E (IgE) levels to an allergen [33]) and total number of adverse events from allergen exposure. We will also evaluate studies reporting improvement in HRQoL, measured using validated scales (eg, Pediatric Allergic Disease Quality of Life Questionnaire, Food Allergy Quality of Life Questionnaires, and Pediatric Quality of Life Inventory) as well as all-cause mortality. We will include studies ("S") that are randomized controlled trials (RCTs) or cluster-RCTs, non-RCTs, and other observational studies that evaluate the effectiveness of early food introduction for preventing childhood allergic diseases. All published reports from inception up to October 2023 will be included.

Exclusion Criteria

Excluded studies are those that enrolled infants older than 6 months, those that involved food interventions among infants with congenital abnormalities (eg, dysmorphism), those not published in English, all unpublished trials and abstracts, and those describing multicomponent management (studies including the use of drugs). We will also exclude studies where infants initiated on supplementary feeding before the age of 4 months and those in which infants were initiated on certain immune suppressors (eg, steroids). We will exclude cross-over studies due to concerns about the carryover effects. We will also exclude all observational studies, any short communication, case report, and guidelines. Table 1 summarizes the PICOS search strategies, and sources of review for this study.

Table 1. PICO[a] search strategies and sources of review.

	Sources based on the PRISMA[b] checklist
Population	Healthy infants at recruitment as outlined by study authors.
Intervention	Early food introduction or early weaning when an infant approaches 4 months of age and before turning 6 months old.
Comparison	Infants initiated on complementary feeding (weaning) in accordance with standard infant feeding guidelines as described by the author.
Outcome	Primary outcome: total number of events of allergic disease (including asthma, allergic rhinitis, eczema, and food allergy). Secondary outcomes: rate of sensitization (level of total and specific immunoglobulin E), total number of adverse events, improvement of health-related quality of life measured using validated scales, and all-cause mortality.

[a]PICOS: population, intervention, compare, outcomes, and studies.

[b]PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Search Strategy

A systematic and comprehensive literature search will be conducted in various databases including PubMed, CENTRAL, Embase, Scopus, PsycINFO, CINAHL, and Google Scholar from inception to October 2023. A search strategy will be developed for PubMed and adapted for use with other electronic databases (Multimedia Appendix 2). The search will include MeSH terms and keywords relating to the study population ("childhood" OR "children" OR "paediatric" OR "pediatrics" OR "infants"), intervention ("early food introduction" OR "weaning" OR "complementary feeding" OR "supplementary feeding"), and outcomes ("allergies" OR "allergy" OR "allergic diseases" OR "asthma" OR "allergic rhinitis" OR "eczema" OR "dermatitis" OR "food allergy" OR "sensitization").

Data Collection

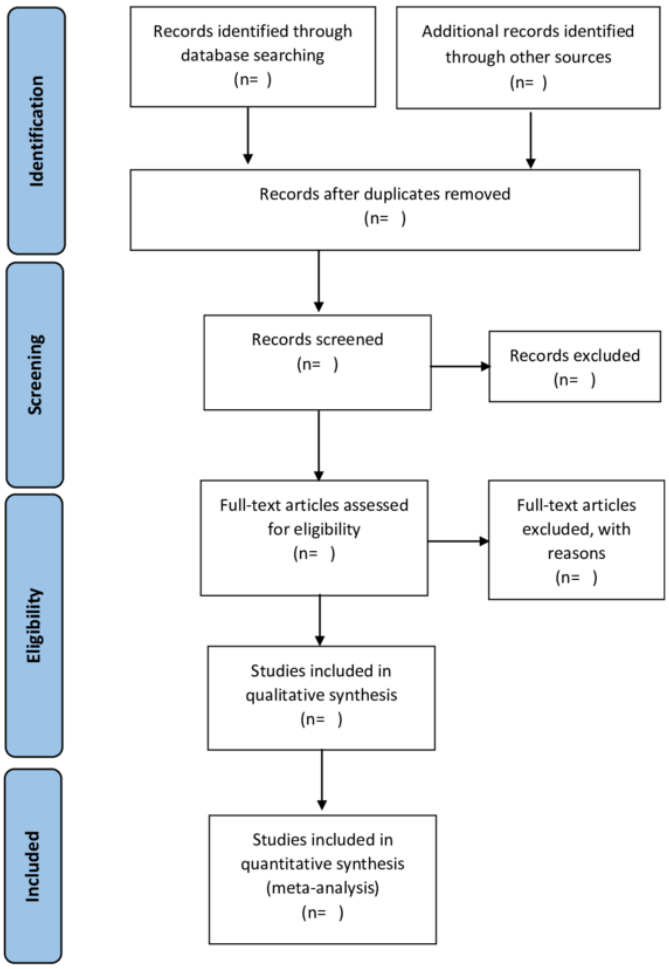
Standard Cochrane methods will be used, as described in the Cochrane Handbook for Systematic Reviews of Interventions [34]. Two authors will independently screen all the titles and abstracts to examine all the potential studies. We will code them as "retrieve" (eligible, or potentially eligible or unclear) or "do not retrieve." We will retrieve full-text reports or publications, and 2 other review authors will independently screen the full text to identify studies for inclusion and will identify and record the reasons for exclusion of the ineligible studies. We will use

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a standardized data extraction form in accordance with the Cochrane Handbook for Systematic Reviews of Intervention [28]. Data will be independently extracted in accordance with general information (author, source, date of publication, country, and language), study (type of study, study duration, sample size, and control group selection), participants (age, sex, and type of allergy), types of intervention (food avoidance upon diagnosis and food challenge), and, lastly, outcomes (allergic episodes, admissions or emergency visits, duration of illness, and quality of life measured using validated scales) [28].

We will resolve any disagreement through discussion or consult a third review author if necessary. We will identify and exclude duplicates, and if multiple or overlapped reports of the same study are found, we will group them under a single study ID, and assign the report with the most amount of relevant information as the primary publication. We will record the selection process in sufficient detail to complete a PRISMA flow diagram (Figure 1) and construct a table describing the characteristics of the excluded studies [35]. We will resolve any discrepancies through discussion and by involving a third author.

Figure 1. The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart for reporting studies.



Quality Assessment of the Included Studies

Two reviewers will independently assess the quality of the included studies. The methodological quality of selected studies will be assessed using the Cochrane Risk of Bias Tool [36] for RCTs and cluster-RCTs, which includes the following domains: allocation concealment of random sequence generation, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other bias. We will use ACROBAT-NRSi (A Cochrane Risk Of Bias Assessment Tool for Non-Randomized Studies), which evaluates the risk of bias in the results of non-RCTs studies that compare the health effects of 2 or more interventions [37]. We will use Newcastle-Ottawa scale for observational studies and evaluate the quality parameters (selection, comparability, and outcome) of the selected studies [38]. We will make judgments on each of the abovementioned criteria regarding whether the study has a high, low, or unclear risk of bias. We will summarize the risk-of-bias judgements with justification for each of the domains listed in the *Risk of bias* table. Any disagreement among the review authors will be resolved by discussion to achieve a consensus.

Summary of Findings Table

We will create a *summary of findings* table by tabulating the following outcomes: (1) total number of allergic diseases (asthma, allergic rhinitis, eczema, and food allergy), (2) rate of sensitization (level of total and specific IgE), (3) total number of adverse events, (4) improvement of HRQoL measured using validated questionnaires, and (5) all-cause mortality [39]. We will use the following 5 GRADE (Grading of Recommendations Assessment, Development and Evaluation) elements to assess

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the quality of the body of evidence as it relates to the prespecified outcomes: quality of evidence, consistency of effect, imprecision, indirectness, and publication bias. We will assess the quality of evidence for all outcomes using the GRADE methodology [40].

Data Analysis

Statistical Analysis

A meta-analysis will be conducted if there are at least 2 similar studies with broadly similar populations, interventions, and outcome measures using a random-effects model in Review Manager (Cochrane) [41]. A random-effects model will be used if studies are statistically heterogeneous; otherwise, we will use a fixed-effects model. For the random-effects model, we will conduct a sensitivity check by using the fixed-effects model to reveal differences in the results. We will include a 95% CI for all estimates. We will report skewed data as medians and IQRs. Studies will be considered as being sufficiently similar if the relevant outcome data are available in the group originally allocated or if the intervention, such as early food introduction in the allocated group, belongs to the same category—for example, the same amount of food (eg, frequency or total daily intake)—and if only frequencies are reported, we will include binary comparisons; for example, weekly versus never and daily versus never. The primary data analysis will include proportions or the frequency of childhood allergic diseases and types of food (allergenic and nonallergenic).

Assessment of Heterogeneity

The clinical heterogeneity of the results of the included studies will be assessed on the basis of the similarity of their populations, interventions, outcomes, and follow-up if we can pool sufficient studies together. We will consider populations as similar when they are in the same categories of age with outcomes measured in similar ways as stated in the eligibility criteria. We will consider interventions as similar if they fall into the same category as indicated in the abovementioned types of interventions. The outcomes will be considered as similar when they are measured at similar events as stated in the eligibility criteria. We will estimate the treatment effects of individual RCTs and examine heterogeneity among RCTs by inspecting forest plots and quantifying the impact of heterogeneity using the I^2 statistic [42].

Assessment of Reporting Biases

We will generate and examine a funnel plot to explore possible small biases in studies if we can pool more than 5 RCTs in a single meta-analysis.

Ethics and Dissemination

This systematic review is registered with the National Medical Research Register, Ministry of Health Malaysia (ID: NMRR ID-22-01049-HQ4). This protocol registered in PROSPERO (CRD42021256776). We will present the findings of this review in National and international conferences and continuous medical education initiatives, and we will disseminate our findings to policy makers and top managements (stakeholders) of Ministry of Health Malaysia.

Results

The protocol has been registered in PROSPERO and we initiated the review on June 1, 2023, and the results are expected by October 1, 2023. This systematic review and meta-analysis shall contribute an update to the existing literature on infant feeding with emphasis on the risk of childhood allergic diseases.

Discussion

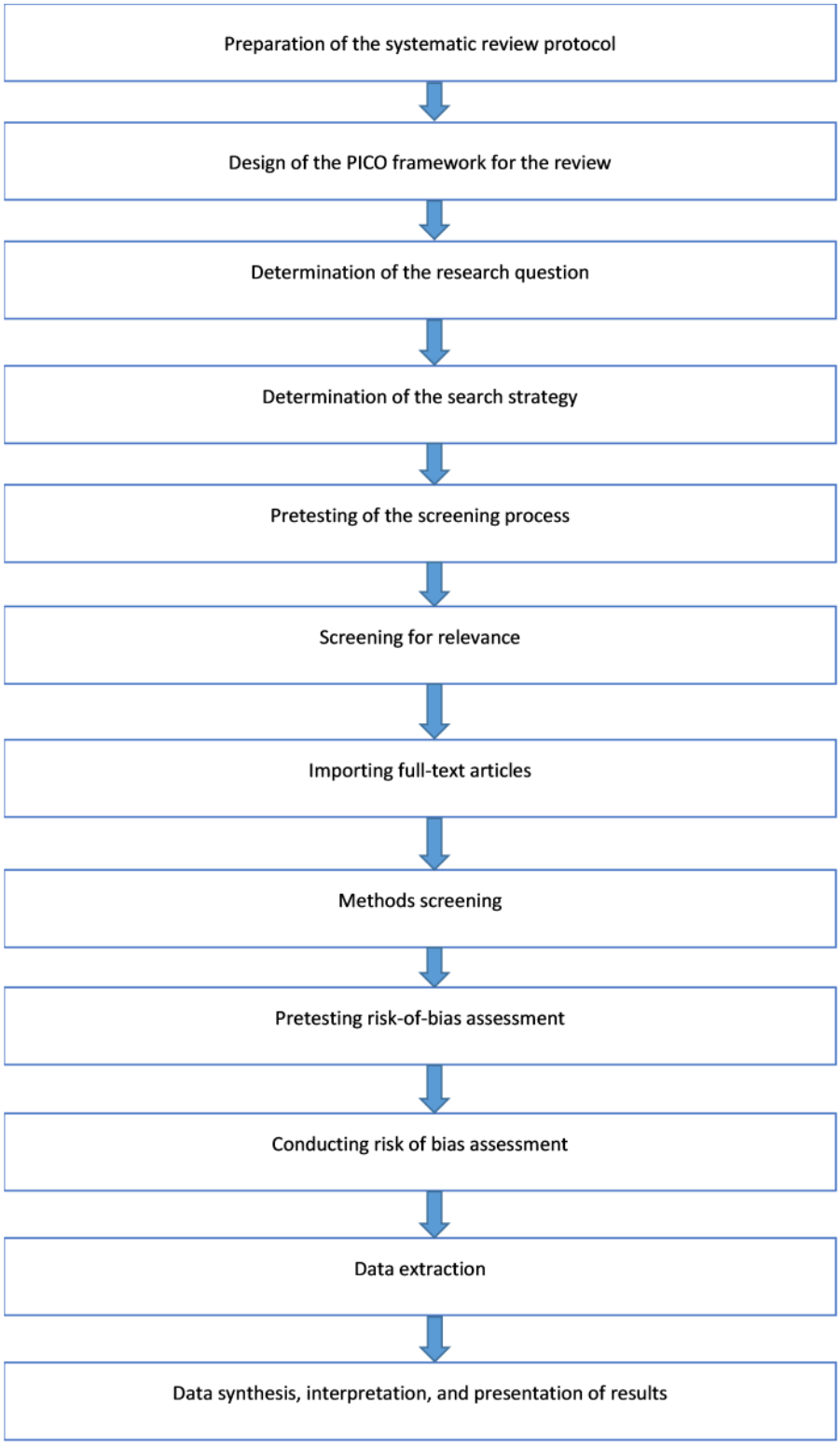
Anticipated Findings

This protocol outlines the methods for a systematic review of the literature to assess the effectiveness of early food introduction in the prevention of childhood allergic diseases. Figure 2 illustrates a flow diagram of the study process to be followed as a guide for this review in terms of literature search using keywords identified through discussion among authors, the screening of shortlisted studies following a standardized framework, and the process of full text retrieval. This will be followed by quality assessment with data extraction for evidence synthesis and finally publishing of the study results.

We take note of 2 similar systematic reviews and meta-analyses that are closely related to our study [23,43]. However, their methodology (in terms of population variability and age of weaning) and diverse outcomes are different from those based on our study objective. In our study, we aim specifically to evaluate the effectiveness of early food introduction in infants aged 4-6 months irrespective of risks, and to evaluate outcomes related to 4 common allergic diseases in children. We believe that our findings will provide a reasonable and robust update to the existing literature.

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Figure 2. Flow diagram of the study process. PICOS: population, intervention, compare, outcomes, and studies.



Reaching Conclusions

We will base our conclusions only on findings from the quantitative or narrative synthesis of the studies included in this review. The conclusions can be used as guidelines for top managers and stakeholders for evidence-informed policy on infant feeding guidelines for the prevention of childhood allergic diseases. Our implications for research will suggest priorities for future research and outline the remaining uncertainties in the area.

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Acknowledgments

We would like to thank the Director General of Health, Ministry of Health Malaysia, for his support in this study.

Data Availability

The original contributions shown in the study are contained within this systematic review and its multimedia appendices; further inquiries can be addressed to the corresponding author.

Authors' Contributions

All authors contributed to conceptualization and the development of the study plan. AFAA, C-LT, and NAM are responsible for title registration, development of the overall study methodology, and evidence rating schemes. AFAA and RMAG will conduct the literature searches, manage the references, and draft the intellectual content. NAM, SMS, and AFAA and will oversee the data extraction process and revision of the final manuscript with specific input from all other coauthors.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols) checklist.
[PDF File (Adobe PDF File), 81 KB - resprot_v12i1e46816_app1.pdf]

Multimedia Appendix 2
Search strategy developed for PubMed.
[PDF File (Adobe PDF File), 115 KB - resprot_v12i1e46816_app2.pdf]

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Abbreviations

ACROBAT-NRSi: A Cochrane Risk Of Bias Assessment Tool for Non-Randomized Studies
GRADE: Grading of Recommendations Assessment, Development and Evaluation
HRQoL: health-related quality of life
IgE: immunoglobulin E
PICOS: population, intervention, compare, outcomes, and studies
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT: randomized controlled trial

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Protocol

Physical Activity Interventions for Improving Cognitive Functions in Children With Autism Spectrum Disorder: Protocol for a Network Meta-Analysis of Randomized Controlled Trials

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Abstract

Background: Autism spectrum disorder (ASD) is a neurodevelopmental disorder that affects millions of children worldwide, with a current prevalence of approximately 1 in 54 children in the United States. Although the precise mechanisms underlying ASD remain unclear, research has shown that early intervention can have a significant impact on cognitive development and outcomes in children with ASD. Physical activity interventions have emerged as a promising intervention for children with ASD, but the efficacy of different types of interventions remains unclear.

Objective: This study protocol aims to update the knowledge on extant literature and explore the efficacy of physical activity intervention strategies on cognitive functions in children with ASD.

Methods: A systematic review and network meta-analysis (NMA) will be conducted following the PRISMA-NMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols for Network Meta-Analyses) statement. A total of 9 bibliographic databases (APA PsycInfo, CENTRAL, Dimensions, ERIC, MEDLINE Complete, PubMed, Scopus, SPORTDiscus, and Web of Science) will be systematically searched to screen eligible articles based on a series of inclusion and exclusion criteria. A study will be considered for inclusion if it is not classified as a systematic review with or without meta-analysis, was published from inception to present, includes children aged 0 to 12 years with ASD, quantitively measures cognitive outcomes, and examines treatment comprising at least 1 physical activity intervention strategy. The internal validity and quality of evidence will be evaluated using the Grading of Recommendations Assessment, Development, and Evaluation framework. Statistical analyses will be performed in the RStudio software (version 3.6; RStudio Inc) with the *BUGSnet* package and the Comprehensive Meta-Analysis software (version 3.3; Biostat Inc). The results of our NMA will be illustrated through network diagrams accompanied by geometry and league tables. Further, to rank the interventions based on their efficacy, we will use the surface under the cumulative ranking curve.

Results: Our preliminary search identified 3778 potentially relevant studies. The screening of the studies based on the inclusion and exclusion criteria is ongoing, and we anticipate that the final number of eligible studies will be in the range of 30 to 50.

Conclusions: This study will provide a comprehensive review of the literature on physical activity interventions for children with ASD and will use NMA to compare the efficacy of different types of interventions on cognitive outcomes. Our findings will have important implications for clinical practice and future research in this area and will contribute to the growing body of evidence supporting the use of physical activity interventions as a key component of early intervention for children with ASD.

Trial Registration: PROSPERO CRD42021279054; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=279054

International Registered Report Identifier (IRRID): DERR1-10.2196/40383

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KEYWORDS

children; autism spectrum disorder; physical activity; cognitive outcomes; network meta-analysis

Introduction

Background

Autism spectrum disorder (ASD) is a lifelong developmental disorder. Individuals with ASD commonly present symptoms of insufficient social interaction and communication and repeated and restricted behavior patterns that have a negative impact on daily functions. The lack of adapting, planning, and organizing skills has a negative influence on personal, physical, mental, academic, vocational, and social domains. The onset of ASD typically presents during the ages of 1 to 2 years, whereas some symptoms may be observed during the first year after birth [1]. Some categories of ASD have been specified such as Asperger syndrome, childhood disintegrative disorder, and pervasive developmental disorder [2]. The World Health Organization has indicated that children with ASD exhibit deficits in cognitive functions, characterized by social impairment, abnormalities, and repetitive stereotypic behavior [3,4]. Approximately 17% of children were diagnosed with a range of complex neurodevelopmental disabilities between the ages of 3 and 17 years; 1 in 54 children was diagnosed with ASD [5,6]. The diagnosis rate in children has continuously increased, moving from 1.1% to 2.5% in the past decades [7,8]. Although the prevalence of diagnoses is increasing, many evidence-based interventions are still in their developmental stages. Specifically, the effectiveness of physical activity interventions in children with ASD is not yet fully understood.

Childhood is a critical period for neurodevelopment, especially for the development of children's memory, attention, creativity, motor skills, and executive functions (EFs) [9]. ASD is a complex neurodevelopmental disorder, and its prognosis is impacted by environmental, genetic, and physiological factors [1]. Several neurotransmitters, including brain-derived neurotrophic factors, which contribute to brain development, demonstrate correlations with ASD and other neurodevelopmental impairments [10]. The connectivity of the frontal cortex and prefrontal cortex with other parts of the brain was found to be related to ASD behavioral symptoms [11-13]. High risk for an atypical development of the ability to recognize and attribute mental states was found in the autism population [14]. Language and joint attention for social functioning and cognitive control behaviors have been shown to be linked to changes in the early maturation of the brain [9,14-16]. An imbalanced process of integrating information such as contextual or sensory perception might be related to ASD symptoms [17].

Cognitive function is manifested as the ability to process thoughts, such as learning and solving problems [18]. Cognitive function has been categorized into EFs and non-EFs. EFs present an individual's adaptive skills and ability to conduct goal-oriented meaningful actions [19]. Non-EFs include complex attention, learning and memory, visual function, language function, and social function [1]. Solomon et al [20] indicated that EF hypothesis is an influential cognitive theory of ASD, which proposes that "deficits in planning, inhibitory control, attentional set shifting and working memory are central to the disorder." Social and communication skills are part of the characteristics of cognitive function, which individuals with ASD usually lack, and are also impacted by the age and development window [21]. In children, cognitive function develops along with the human brain [22]. An example of proneurogenic modulators is exercise, which increases the level of brain-derived neurotrophic factors, endocannabinoids, and microbiota diversity, leading to hippocampal neurogenesis and long-term changes in cognitive function [23,24]. Various interventions for children with ASD have been studied, such as music therapy, which has been shown to improve social interaction in preschool children with ASD [14]. In addition, physical activity is an effective approach to improve cardiovascular fitness and cognitive function in children and adolescents [25].

Evidence shows that physical training positively impacts the cognitive function of adults and their offspring, which is encouraging for investigations on the effect of physical activity on youth [26]. In this study, we expect to use a statistical methodology to explore the effectiveness of different types of physical activity intervention strategies (PAIS) on cognitive function in children. We believe that this study is a promising starting point to guide future health-related practices in youth. Closely related to the release of dopamine in the human body, physical activities have also been proven to provide emotional support to children, such as by lowering levels of anxiety or depression [27]. Promising evidence has been accumulated of physical activity leading to improvements in cognition, including improvements in both academic and behavioral performances in children with ASD [3,28-31]. Liang et al [32] reported that chronic exercise interventions are beneficial for overall EFs, especially for cognitive flexibility and inhibitory control in children and adolescents with ASD. Several studies have indicated a significant increase in social engagement in children with ASD after they participated in physical activities, especially in group activities [33-35]. Furthermore, physical activity proved beneficial in reducing stereotypical behaviors within the population of children with ASD [36].

In prior research, various types of PAIS were investigated individually or through narrow groups. In this study, a full range of PAIS will be examined. PAIS include aerobic exercises, mindfulness practices, school physical education programs, and Montessori methods [32,37]. Fang et al [38] concluded favorable results for the effect of exergaming interventions on cognitive functions, but synthesis results from a follow-up meta-analysis are lacking. Horseback riding was found to be beneficial for cognitive functioning, social interaction, and sensory processing improvement in children with ASD [33,35]. Some other physical activities, such as yoga and dance, were also introduced as interventions for children with ASD, which led to positive outcomes in behavioral functioning [39]. The clinical conditions

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of participants, as well as the session frequencies and lengths of the interventions, need to be researched more. Hence, there is an urgent need for researchers to explicitly examine what type of PAIS is the most beneficial for children with ASD.

Systematic reviews and pairwise meta-analyses cannot be used to compare treatment effects across interventions and indirect effects. Therefore, the network meta-analysis (NMA) is proposed as a novel analysis technique in the field of physical activity and health promotion to fill this gap and satisfy the urgent need [40]. To the best of our knowledge, this will be the first NMA applied to systematically review and analyze the efficacy of PAIS on cognitive functions in children with ASD. Therefore, our expectation is to explore PAIS based on selected direct and indirect head-to-head trials to suggest important considerations for decision-making in the field of pediatric health promotion.

Mini Review

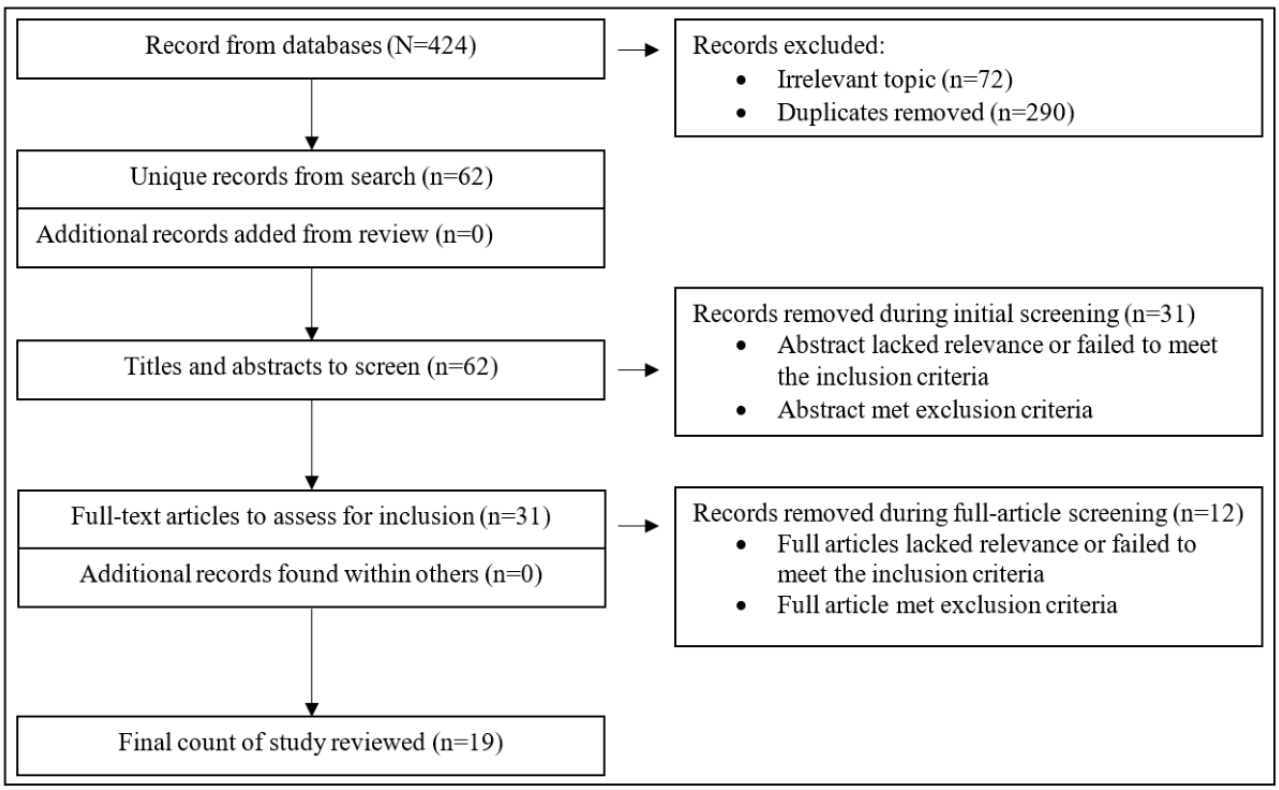
Overview

To gain a comprehensive overview of the existing literature as well as justify the necessity of conducting an NMA on PAIS for children and adolescents with ASD, we conducted a mini review based on the systematic reviews and meta-analyses in the current literature. The literature search was conducted on PubMed, APA PsycInfo, SPORTDiscus, Web of Science, CENTRAL, ERIC, SocINDEX, MEDLINE Complete, and Dimensions. The keywords used for the literature search involved 4 domains: intervention mode, cognitive performance, population, and autism. Combinations of the keywords regarding each domain were “physical activity OR PA OR exercise OR sport*” AND “cognitive function OR cognition OR executive function OR inhibitory control OR memory OR communication OR stereotyp* behavior*” AND “children OR kid* OR teenager OR students” AND “autism spectrum disorder OR ASD.” Eligible studies should meet the following criteria: (1) systematic review or meta-analysis written in English and published between 2001 and 2021, (2) inclusion of children or adolescents with ASD, (3) review of PAIS, and (4) examination of the effects of PAIS on cognitive functions.

Literature Search

Two authors (LL and AW) independently conducted the search and screening process. The initial search resulted in 424 studies. Of these 424 studies, after the removal of 362 (85.4%) duplicate and irrelevant items, 62 (14.6%) items remained for the next phase of screening. Of these 62 articles, 31 (50%) articles were excluded based on abstract examination, leaving 31 (50%) articles for full-text review. Of these 31 articles, the final step of screening removed 12 (39%) articles because of the following reasons: no cognitive outcomes were measured (n=10, 32%) and populations other than children or adolescents were included (n=2, 6%). Therefore, a total of 19 (61%) of the 31 systematic reviews with or without meta-analysis met the inclusion criteria. The process of study selection is presented in Figure 1.

Figure 1. Flowchart of searching and screening in mini review.



Characteristics of the Included Studies

The median publication year of these studies was 2019 (range 2008-2021), which implies a rapid increase in the number of published review papers on the relevant topic in recent years. The number of studies included in each review ranged from 7 to 41. A variety of types of the included review papers was identified, such as systematic review (9/19, 47%), meta-analysis

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(7/19, 37%), and systematic review with meta-analysis (3/19, 16%). In addition to individuals with ASD, the included review studies also examined individuals with cognitive impairment due to one of the following reasons: attention-deficit/hyperactivity disorder, cerebral palsy, developmental delay, developmental coordination disorder, and Down syndrome. Common symptoms observed in individuals with these disorders are difficulties in paying attention, performing tasks, and engaging in social interaction [1]. Most studies focused on children and adolescents [14,32,34,41-51], whereas Fang et al [38], Fragala-Pinkham et al [52], Healy et al [53], Lang et al [54], Ruggeri et al [55], and Sowa and Meulenbroek [56] conducted studies involving both children and adult participants. Experimental groups were compared with their counterparts, that is, active behavioral control groups, waiting list control groups, or standard care groups. The study characteristics are illustrated in Table 1.

The PAIS applied in the intervention arms typically consisted of two or three 30- to 60-minute sessions per week for 8 to 16 weeks. Overall, 3 (16%) of the 19 studies included only randomized controlled trials (RCTs) [14,47,50], and others (16/19, 84%) partially included quasi-experimental designs with controlled trials [32,41-44,48,49,51,53-56], cohort study [34], pre- and posttest and case-control studies [38,45,52], and descriptive study [46]. Moreover, 1 (5%) of the 19 studies lacked a clear definition of the age range of children and a discussion of the risk of bias (RoB) [41]. The interventions implemented in the included studies were conducted through various types of physical activities. Physical exercise– and motor skill–related interventions, such as aerobic exercise, resistance training, and aquatic activities, were mostly adopted in the clinical practice [32,34,41-56]. In addition, 2 (11%) of the 19 studies investigated effects of exergaming and technology interventions for individuals with ASD [38,43].

The included studies investigated the effects of physical activity interventions on cognitive functions, with small to moderate effect sizes on the improved global EF [32,50]. Specifically, the included reviews reported enhanced performance in terms of working memory, attention, task switching, and inhibitory control [34,50]. The evidence also indicated the beneficial effects of social functioning and communication skills, which can be attributed to the group-based activity performed during the interventions [42,44]. Learning and memory outcomes due to PAIS were not fully explored in the selected studies. The other limitation of the included systematic review and meta-analysis studies was the combination of children and adolescent groups. However, age was recognized as a significant confounder in ASD research. Although common clinical treatments, including educational, family, speech, and occupational therapies, showed favorable effects, widely supportive evidence showed that physical activity was beneficial for children's lifelong cognitive and motor development. Therefore, it is necessary to explore the effects of PAIS treatment on children's cognitive outcomes from the perspective of physical activity and health promotion. Results are encouraging because various types of evidence showed that PAIS were effective in enhancing cognitive function in children with ASD; the foundation for the future in-depth data analysis has been established.

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Table 1. Characteristics of the studies included in the mini review.

Study	Study type	Participant, n	Study population	Intervention used (intervention arm)	Outcome measures[a]	Main outcomes
Aleksandrovic et al [41], 2016	SR[b]	13	Children (aged <18 years and with ASD[c])	Aquatic activities (Armbruster or Halliwick methods or the constant time delay procedure for learning swimming skills and social and floor warm-up activities)	MS[d] (ABC-2[e], WOTA[f], HAAR[g], YMCA[h] checklist, and Aquatic Skills Assessment)	Aquatic skills were effectively improved
Bremer et al [34], 2016	SR	13	Children and youth (aged ≤16 years; at least one participant with a diagnosis of ASD or PDD[i])	Physical exercise intervention (jogging, swimming, yoga or dance, horseback riding, and martial arts)	CF[j]+SF[k] (GARS-2[l], SRS[m], sensory profile, ABC-C[n], ABC[o], VABS-2[p], frequency of child specific behaviors, BOSS[q], SSBS-2[r], and BASC-2[s])	Improvements in stereotyped behaviors, social behavior cognition, and attention
Cameron et al [42], 2020	SR	17	Children (aged 3-6 years) with autism, CP[t], Down syndrome, DCD[u], DD[v]	Fundamental motor skill group intervention by primary researcher	MS (PDMS-2[w]: GMQ[x])	Results were inconclusive to support motor-based interventions in this age group owing to variability in intervention types
Case and Yun [43], 2019	MA[y]	18	Preschool (aged 3-5 years) and school-aged children (aged 6-17 years) with ASD	FMS[z] (direct instruction activities), PA[aa] (whole body movement and coordination activities), technology (eg, video games), EAT[ab] (eg, horseback riding)-based interventions	MS (PDMS, PDMS-2, TGMD[ac], TGMD-2, TGMD-3 BOT-2[ad], M-ABC[ae], and M-ABC-2)	Overall effect size on gross motor outcomes (δ=0.99; *P*<.001), FMS (*g*=0.68; *P*<.001), PA (*g*=1.20; *P*=.003), technology (*g*=1.42; *P*=.21), and EAT (*g*=1.20; *P*=.005)
Chan et al [44], 2021	MA	12	Children and adolescents (aged <18 years and with ASD)	Individual, combined, or group-based PA (eg, Karate, horseback riding, aquatic, mind-body, football, outdoor adventure, or active recreation)	SF (GARS-2, SRS, VABS, ATEC[af], and SSIS[ag])	COM[ah] (SMC[ai]=.27, 95% CI 0.06 to 0.48) and social functioning (SMC=.39, 95% CI 0.15 to 0.63)
Fang et al [38], 2019	SR	10	Children and young adults (aged 5 to 21 years and with ASD)	Exergaming (eg, platforms and games included DDR[aj], cybercycling, FroggyBobby, Xbox Kinect, Nintendo Wii, and Makoto Arena)	CF+MS (physical outcomes [eg, BMI and jump distance] and cognitive outcomes [eg, BRIEF[ak]])	Favorable results for the effect of exergaming interventions on participants' physical and cognitive functions
Ferreira et al [45], 2019	SR and MA	8 (SR) + 8 (MA)	Children and youngsters (aged <16 years and with ASD)	Aerobic exercise, Kata techniques training, and ball exercise	CF (GARS-2, SSB[al], and stereotypic behavior observations)	PA was effective in reducing stereotypic behavior (SMD[am]=1.11; *P*=.009)
Fragala-Pinkham et al [52], 2021	SR	8	Children and young adults (aged 7 to 26 years and with ASD, Down syndrome, or UID[an])	Lower extremity cycling (eg, learning to ride a 2-wheeled bicycle, stationary cycling, and CO-OP[ao] approach)	CF+MS (eg, cycling time and distance, cycling skill checklist, KT[ap], KTFist[aq], TOLT[ar], and PPT-C[as])	Weak evidence and heterogeneous results regarding MS and CF in children and young adults with intellectual disabilities between cycling and control groups
Healy et al [53], 2018	MA	29	Youth (aged 2 to 22 years and with ASD)	Recreational activities in APE[at], PE[au], and other settings (eg, yoga, kata program, aquatic skill program, dance, mind-body exercise, and a combination of all activities)	CF+MS (psychometric tools or scales were not specifically discussed)	Overall positive moderate effect exhibited (*g*=0.62; *P*<.001); cognitive function (*g*=0.28, 95% CI −1.19 to 1.74), psychomotor function (*g*=1.21, 95% CI 0.41 to 1.66)

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Study	Study type	Participant, n	Study population	Intervention used (intervention arm)	Outcome measures[a]	Main outcomes
Howells et al [46], 2019	SR and MA	11 (SR) + 7 (MA)	Children (aged 5 to 12.9 years and with ASD)	Individual and group PA (eg, included a range of blocking, punching, sticking, and kicking techniques; climbing rope ladder or rope elevator; horse riding; group sport games)	SF+COM (VABS, SRS, BASC-T, and GARS-2)	Nonsignificant effect for communication (g=0.13, 95% CI −0.12 to 0.38) and a significant improvement in overall social functioning (g=0.45, 95% CI 0.19 to 0.72)
Huang et al [47], 2020	MA	12	Children and adolescents (aged 3 to 18 years and with ASD)	PA interventions (eg, Kata techniques, therapeutic horseback, outdoor activity, karate, aquatic sport, trampoline, table tennis, Tai Chi, and exergaming)	CF+MS+SF+COM (GARS-2, BOT-2, SRS, PPVT-4[av], SALT[aw], ATEC, ABC, MABC-2[ax], CBS[ay], and WCST[az])	Significant positive effects on social interaction (SMD=−0.58, 95% CI −0.87 to −0.29), COM (SMD=−0.29, 95% CI −0.55 to −0.04), stereotyped behavior (SMD=−0.13, 95% CI −0.46 to 0.20), and motor skills (SMD=1.02, 95% CI 0.33 to 1.71)
Lang et al [54], 2010	SR	18	Children, adolescents, and adults (aged 3 to 41 years and with ASD)	PA (eg, walking, jogging, playing catch with a ball, riding a stationary bike, swimming, and weight training)	CF+PF (psychometric tools or scales were not specifically discussed)	Exercise decreased stereotypy, aggression, off-task behavior, and elopement
Liang et al [32], 2021	SR and MA	14 (SR) + 7 (MA)	Children (aged 5 to 17 years and with ASD)	Physical activity or exercise on EFs[ba] (exergaming, jogging, table tennis, progressive muscle relaxation, martial arts, basketball, etc)	CF (BRIEF, Stroop, CTT[bb], HKLLT[bc], DSFBT[bd], FPT[be], TOLT, GNG[bf], CBTT[bg], Hearts and Flowers test, and attention sustained test)	Positive effect on global EFs (g=0.34, 95% CI 0.08 to 0.60), CF (g=0.31, 95% CI 0.05 to 0.57), IC[bh] (g=0.49, 95% CI 0.19 to 0.80]), and WM[bi] (g=0.21, 95% CI −0.09 to 0.51)
Petrus et al [48], 2008	SR	7	Children (aged 4 to 15 years and with ASD)	PA or exercise (eg, aquatic, jogging, ball playing, and aerobic exercise)	CF+MS (stereotypical behaviors and MS were observational measured in frequency, duration, or counts)	Exercise might reduce stereotypic behaviors in the short term
Ruggeri et al [55], 2020	SR	41	Children and adolescents (aged 3 to 19 years and with ASD)	Motor and physical activity (eg, soccer, exergaming, throwing, aquatic, fitness or strength, horse riding, hippotherapy, stationary biking, gymnastic, and indoor climbing programs)	MS+ML (eg, VABS-2, BOT, BOT-2, MABC-2, PDMS-2, TGMD-2, TGMD-3, m-PEDI[bj], ASC[bk], YMCA checklist, HAAR, SCS[bl], and GAS[bm])	Motor skill and learning, body structure, and function outcomes were improved with various PA interventions
Semple [49], 2019	SR	8	Youth (aged 3 to 18 years and with ASD)	Yoga, mindfulness-based interventions, Qi Gong, and meditation	CF+MS+SF+COM (psychometric tools or scales were not specifically discussed)	Improvements in prosocial behaviors, social cognition, communication, motivation, and motor control via yoga and mindfulness-based interventions
Sowa and Meulenbroek [56], 2012	MA	16	Children, adolescents, and adults (aged 4 to 41.3 years and with ASD)	Individual and group PA interventions (eg, jogging, therapeutic horseback rides, bike riding, walking, stationary cycling, aquatic exercising, and swimming)	MS+SF+COM (psychometric tools or scales were not specifically discussed)	Individual programs exhibited positive effects on motor skills (r=−0.32; P=.004) and social interactions (r=−0.62; P<.001) compared with group programs
Zhang et al [50], 2020	MA	11	Children (age: N/A[bn]) with ADHD[bo] or ASD	Chronic PA intervention (eg, rhythm, integrated PA, modified aerobic games, exergaming, and taekwondo)	CF+MS (BOT-2, WCST, TGMD-2, Stroop test, Flanker task, CBTT, etc)	Significant improvement in overall EF, IC, cognitive flexibility, and gross MS (SMD ranged from 0.85 to 1.30); no significant improvements in working memory and fine MS

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Study	Study type	Participant, n	Study population	Intervention used (intervention arm)	Outcome measures[a]	Main outcomes
Teh et al [51], 2021	MA	22	Children (N/A with ASD)	Physical exercise interventions (jogging, cycling, exergaming, ball exercise, therapeutic horse riding, martial arts)	CF (GARS-2, ATEC, ABC, BASC-2, observational measures or time intervals on targeted behaviors, etc)	Large overall ES[bp] (g=1.16) on reducing stereotyped motor behaviors across participants, treatment, and levels from a multilevel modeling MA

[a]Only autism spectrum disorder–relative interventions and outcomes are summarized because of the established inclusion criteria of this study.
[b]SR: systematic review.
[c]ASD: autism spectrum disorder.
[d]MS: motor skills.
[e]ABC-2: Assessment Battery for Children, Second Edition.
[f]WOTA: Water Orientation Test Alyn.
[g]HAAR: Humphries Assessment of Aquatic Readiness.
[h]YMCA: Young Men's Christian Association.
[i]PDD: pervasive developmental disorder.
[j]CF: cognitive flexibility.
[k]SF: social functioning.
[l]GARS-2: Gilliam Autism Rating Scale, Second Edition.
[m]SRS: Social Responsiveness Scale.
[n]ABC-C: Aberrant Behavior Checklist–Community.
[o]ABC: Aberrant Behavior Checklist.
[p]VABS-2: Vineland Adaptive Behavior Scales, Interview Edition.
[q]BOSS: Behavioral Observation of Students in Schools.
[r]SSBS-2: School Social Behavior Scales, Second Edition.
[s]BASC-2: Behavioral Assessment System for Children, Second Edition.
[t]CP: cerebral palsy.
[u]DCD: developmental coordination disorder.
[v]DD: developmental delay.
[w]PDMS-2: Peabody Developmental Motor Scales, Second Edition.
[x]GMQ: gross motor quotient.
[y]MA: meta-analysis.
[z]FMS: fundamental motor skills.
[aa]PA: physical activity.
[ab]EAT: equestrian-assisted training.
[ac]TGMD: Test of Gross Motor Development.
[ad]BOT-2: Bruininks-Oseretsky Test of Motor Proficiency, Second Edition.
[ae]M-ABC: Movement Assessment Battery for Children.
[af]ATEC: Autism Treatment Evaluation Checklist.
[ag]SSIS: Social Skills Improvement System.
[ah]COM: communication.
[ai]SMC: standardized mean change.
[aj]DDR: Dance Dance Revolution.
[ak]BRIEF1: Behavior Rating Inventory of Executive Function.
[al]SSB: Self-stimulatory Behaviors.
[am]SMD: standardized mean difference.
[an]UID: unspecified intellectual disability.
[ao]CO-OP: Cognitive Orientation to daily Occupational Performance.
[ap]KT: Knock-Tap.
[aq]KTFist: Knock-Tap-Fist.
[ar]TOLT: Tower of London Test.
[as]PPT-C: Purdue Pegboard Test–Combined.
[at]APE: adapted physical education.
[au]PE: physical education.

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[av]PPVT-4: Peabody Picture Vocabulary Test, Fourth Edition.
[aw]SALT: Systematic Analysis of Language Transcripts.
[ax]MABC-2: Movement Assessment Battery for Children - Second Edition.
[ay]CBS: Clancy Behavior Scale.
[az]WCST: Wisconsin Card Sorting Test.
[ba]EF: executive function.
[bb]CTT: Color Trails Test.
[bc]HKLLT: Hong Kong List Learning Test.
[bd]DSFBT: digit span forward and backward test.
[be]FPT: Five-Point Test.
[bf]GNG: Go-No-Go task.
[bg]CBTT: Corsi Block-Tapping Task.
[bh]IC: inhibitor control.
[bi]WM: working memory.
[bj]m-PEDI: mobility scale of the Pediatric Evaluation of Disability Inventory.
[bk]ASC: Aquatic Skills Checklist.
[bl]SCS: Swimming Classification Scale.
[bm]GAS: Goal Attainment Scaling.
[bn]Criteria of age was not mentioned in search strategy.
[bo]ADHD: attention-deficit/hyperactivity disorder.
[bp]ES: effect size.

The Present NMA Protocol

An insight into the direction of future research was provided based on the preliminary findings of the mini review. Previous outcomes suggested that varying types of PAIS were effective in improving cognitive functions and motor performance, reducing frequency of the symptoms, and enhancing social and communication skill development in children with ASD and other cognitive impairments. The quality of evidence is concerning because of the limited number of meta-analyses on RCTs [53]; we expected to simply include true experimental designs (eg, RCTs), which might ensure robust synthesis results and increase the power to detect the effects of interventions [51,57]. The age groups were heterogeneous in nature, whereas we expected to focus particularly on children and explore the efficacy of PAIS on their cognitive performances. However, the limitation of the pairwise meta-analysis procedure was that it was only appropriate for discerning outcome effects "between a selected intervention strategy and a selected comparison or control condition" [40]. Whereas pairwise meta-analyses only allowed the comparison of multiple outcomes from a single treatment, NMA would allow the comparison of the efficacies of multiple PAIS on multiple outcomes [58]. Concomitantly, there is a need to conduct an NMA to obtain a more accurate estimation of the efficacy of PAIS in the population. We aim to provide an updated review of the extant literature in the field of physical activity and health promotion using an appropriate network meta-analytic model. Therefore, the following protocol was developed based on the findings and limitations identified in the mini review.

Methods

Overview

This review protocol has been registered in PROSPERO (CRD42021279054). The NMA will comply with the PRISMA-NMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols for Network Meta-Analyses) statement [59,60]. A component-based Bayesian framework NMA will be conducted following the procedures described in the subsequent sections [61].

Search Strategy

The following 9 bibliographic databases will be searched: APA PsycInfo, CENTRAL, Dimensions, ERIC, MEDLINE Complete, PubMed, Scopus, SPORTDiscus, and Web of Science. In general, the search will be limited to RCTs in English published from inception to present. Keywords combinations and MeSH (Medical Subject Headings) terms used in the search are listed in Table 2.

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Table 2. Flowchart of search strategy.[a]

Concept	Keywords
1. Outcome: cognitive functions	• "Cognitive function*" or "cognitive outcomes" or executive function* or "neurocognitive tasks" or questionnaires or inventory or task* or restricted repertoire or autism spectrum disorder (MeSH[b] terms) or children behavior disorder (MeSH terms) or autistic disorder (MeSH terms) or stereotypic movement (MeSH terms) or motor skills disorder (MeSH terms) or cognition (MeSH terms) or communication disorder (MeSH terms) or learning disabilities (MeSH terms) or DSM-V[c] (MeSH terms)
2. Participants: children and adolescents	• Children or adolescent* or young people or school-aged or teen or young adult* or youth or kids or teenager* • Exclude (NOT): smoking or drinking or criminal* or injury or injuries or accident* or trauma or adult* or older adult* or elderly or seniors or geriatric*
3. Exposure: comparator	• Control* or "control group" or subject* or "human subjects" or human-related or waiting list
4. Exposure: exercise types	• "Physical activity" or intervention* or exercise* or fitness or "physical exercise" or sport* or psychomotor or motor activity or recreational sport* or school-based or computerized training or hybrid or games or aerobic or "martial arts" or Tai Chi or "mindfulness practice" or classroom curricula or Montessori methods or "resistance training"
5. Design	• Experimental* or clinical trial or randomized control trial* or RCT[d] or nonrandomized comparison or NRS[e] • Exclude (NOT): observational studies or cross-sectional or case control or cohort or systematic review or meta-analysis or report or protocol or qualitative or mixed method

[a]The bibliographic databases will be searched including PubMed, SPORTDiscus, APA PsycInfo, MEDLINE Complete, ERIC, Scopus, Web of Science, CENTRAL, and Dimensions. We will use "OR" to separate keywords within each concept and "AND" to separate each concept. MeSH terms will be used for PubMed search only. Google Scholar will be used for cross validation for search results from multiple bibliographic databases.

[b]MeSH: Medical Subject Headings.

[c]DSM-V: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.

[d]RCT: randomized controlled trial.

[e]NRS: nonrandomized studies.

Inclusion and Exclusion Criteria

The following subsections on population, intervention, comparator, outcomes, and study design explicate the various elements of Population, Intervention, Comparison, Outcome Measures, and Design (PICOS), which is the framework used in this study to facilitate the literature search [58].

Population

Studies including children aged between 0 and 12 years with a diagnosis of ASD (Asperger syndrome, autism, or unspecified developmental disorder) with varying severity (mild, moderate, or severe) will be accepted. The study should include at least 1 diagnostic criterion regarding the Diagnostic and Statistical Manual of Mental Disorder [1], International Statistical Classification of Diseases and Related Health Problems, or Autism Diagnostic Observation Schedule. In addition, demographic information, including age, gender, and sample size, should be reported.

Intervention

Studies intended to increase cognitive functions in participants with ASD using physical activity or exercise interventions will be included. Studies evaluating physical activity exhibited in school-based physical education, exergaming, mindfulness practice (eg, yoga, martial arts, and Tai Chi), aerobic exercise and sports, and any types of therapeutic physical activity interventions will be included.

Comparison

Studies with comparators such as active behavioral control group, waiting list control group, and standard care group will be eligible for inclusion in the network of evidence.

Outcome Measures

Studies should report mean differences in cognitive function measurements between the beginning of the intervention and follow-up test. Studies should have obtained at least 1 validated outcome measurement of cognitive functions. Study features must include the measurement tool with either objective or self-reported patterns.

Design

RCTs should have assessed the outcome measures before (baseline) and after the intervention; the study should have included >1 session of intervention.

Exclusion Criteria

The following studies were excluded: studies including participants who were aged >12 years or were unable to conduct psychomotor movements, studies not involving an RCT, studies where the intervention lasted <8 weeks, and studies not written in English.

Study Selection and Data Extraction

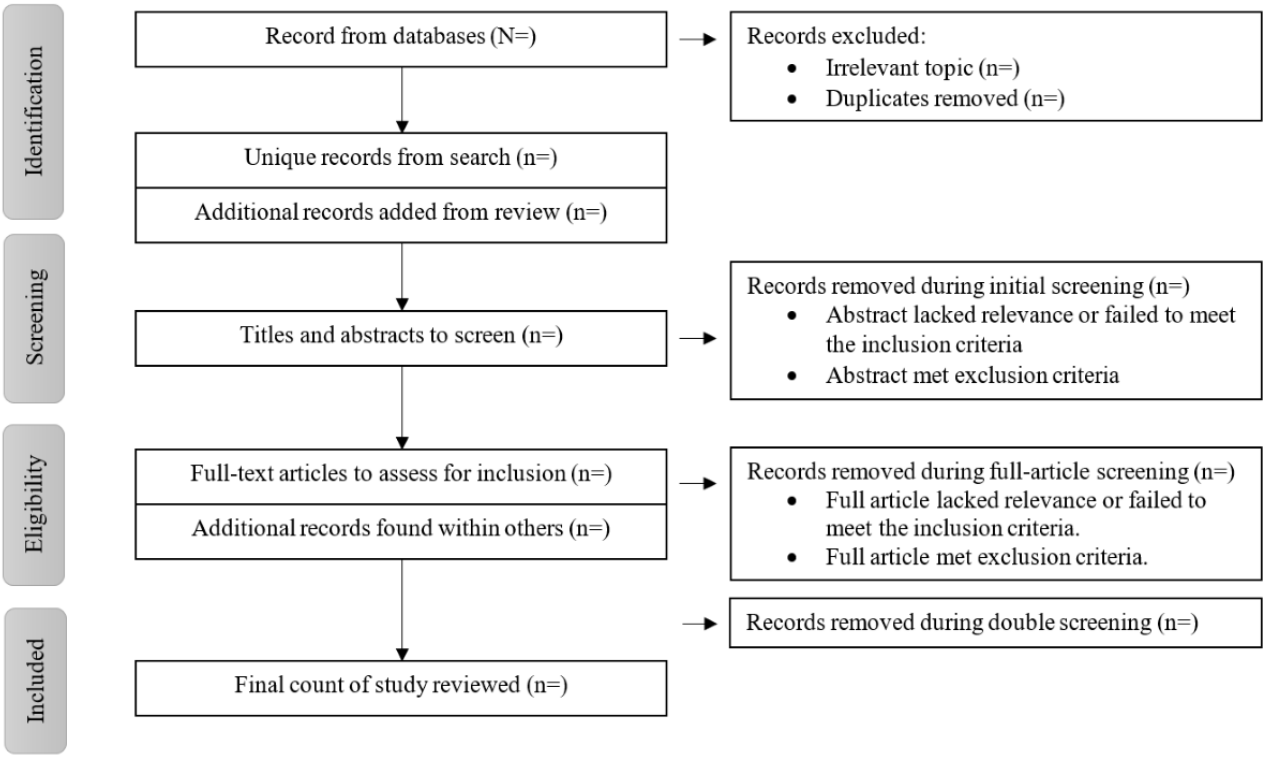
Recording and managing related literature will be accomplished using the Mendeley software (Mendeley Ltd). Two authors will independently screen the titles and abstracts of the searched

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peer-reviewed studies based on the preestablished criteria for inclusion. A third reviewer will be involved to initiate a full-text evaluation if any conflicted selections occur. The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart illustrates the search and screening processes (Figure 2).

Study characteristics, including author information, publication year, mean age in sample, diagnostic criteria for ASD, study period, intervention arms, and study design, will be summarized using Microsoft Excel (version 2010; Microsoft Corp). Specifically, we will adopt a thematic organization approach to categorize intervention arms within all relevant RCTs into six predefined categories: (1) school physical education programs, (2) exergaming, (3) aerobic exercise and sports, (4) mindfulness practice, (5) computerized and noncomputer games combination, and (6) therapeutic physical activity interventions [32,37]. The project administrator will serve as the coordinator, dealing with potential disagreements or unclearly defined PAIS categories. Internal discussions and consultation with an experienced researcher in physical activity and health promotion are considered 2 solutions for disagreements and uncertainties. The interrater agreement rate, Cohen *k*, between reviewers regarding the eligibility criteria of the study will be reported [62]. Note that grouped and ungrouped or supervised and unsupervised intervention arms will be separated as 1 effect size per treatment [51]. Quantified outcomes (mean of the intervention arms and comparators, SDs, and 95% CIs) will be extracted from the aforementioned categories, including measurement results regarding cognitive functions (eg, global EFs, working memory, thinking flexibility, inhibitory control, attention, or memory outcomes). In the NMA, we will compare the effects of the predefined intervention categories on participants' cognitive performance. Raw data (eg, sample sizes and *t*, *F*, or *P* values) will be extracted to help estimate the effect size if the means and SDs were not reported [51]. When necessary, the corresponding authors of selected studies will be contacted to obtain unpublished and missing data to allow for effect size estimates.

Figure 2. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart of searching and screening.



Assessment of RoB

The Grading of Recommendations Assessment, Development, and Evaluation will be used to assess the quality of the selected studies in the NMA and pairwise meta-analysis [63-65]. Two authors will independently assess bias due to randomization, deviations from intervention, missing data, outcome measurement, and the selection of reported results in the selected RCTs. Each item is classified as high, some concerns, or less or unclear or no information upon RoB, and the results of the grading of evidence quality will then be generated as a table (Cochrane RoB tool; version 2.0 [66]). Homogeneity will be assessed by summarizing the selected study characteristics in a general table and observing whether the treatments and participant characteristics are suitable and comparable across all studies [40,58]. Consistency should be ensured such that direct evidence and indirect evidence essentially agree with each other without any discrepancies [40]. The R package (R Foundation for Statistical Computing) developed by van Valkenhoef et al [67] will be used to evaluate the inconsistency between indirect and direct comparisons via the node-splitting method. We evaluated consistency using a node-splitting technique that compares the direct and indirect estimates for each comparison. Transitivity will be qualitatively examined to ensure that direct trials do not differ with respect to the distribution of effect modifiers in which all treatments are jointly randomizable [68].

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Statistical Analysis

The primary outcome for this study will be changes in cognitive functions. However, unlike physiological and biochemical indexes, cognitive performances were measured through preestablished validated psychometric instruments (illustrated in Table 1). Guiding through the approach applied by Désaméricq et al [69], the effect size will be calculated for each extracted result, and these effect sizes will then be combined into 3 cognitive scores, as listed in Multimedia Appendix 1. An omnibus composite unit free score of cognitive outcomes will be created by averaging all subordinate domain effect sizes within a study per intervention arm. Studies including multiple treatments or outcomes will provide the effect size of each treatment or outcome. Extracted data, such as sample size, treatment and control means and SDs for between-group designs, and preintervention and postintervention mean and SDs for within-group designs, will be converted to correlated summary results, standardized mean differences (SMDs), for NMA to explore the efficacy of PAIS on cognitive performance [70]. The effect sizes will be computed using SMD with 95% CIs between groups [32,71]. Hedges *g* in a random model will be used in consideration of potential variances across the selected studies if the number of studies is <20 [32,51,72]. Effect sizes will be classified as small, moderate, or high, respectively, with regard to the cutoff values of 0.2, 0.5, and 0.8 [32,73]. The calculations will be computed through a between-case SMD estimator, the web application *scdhlm* [74]. Heterogeneity will be evaluated through the means of Q test and I^2 values, considering statistical heterogeneity of 25% as low, 50% as medium, and 75% as high [32,75,76]. Sensitivity analyses will be conducted to determine whether any study separately influenced the overall results [77]. To minimize the impact of heterogeneous outcomes or extreme values, we will apply the threshold of *z* score 3.29 to screen out outliers in the mean effect scores [46,53,78]. The level of significance will be set at.05 in this study. The NMA will be performed in RStudio (version 3.6; RStudio Inc [79]) using the *BUGSnet* package (version 1.1.0 [80]).

Moderation Analysis

Moderation analysis will be conducted to examine the variability among potential sources owing to heterogeneous PAIS settings. Moderators such as participant age, exercise intensity, and intervention setting (eg, group vs individual) will be examined using robust variance estimation [51]. Our expectation is to provide another perspective of synthesis results to elicit the higher order outcomes from NMA. Moderation analysis will be performed in the Comprehensive Meta-Analysis software (version 3.3; Biostat Inc).

Ethical Considerations and Dissemination

The ethics approval process is exempted because this study will be based on findings of previous studies. This review protocol has been registered in PROSPERO with the aims of promoting transparency and minimizing the RoB [81]. Future results will be submitted to a peer-reviewed journal of the relevant field for consideration for publication.

Expected Findings

We expect to compare the effects of different PAIS on cognitive outcomes (overall and by domain) over a period of treatment (at least 8 weeks). We will perform an NMA; we will select all RCTs that consider PAIS as a treatment for cognitive outcomes in children with ASD. This study will bridge the gap and provide a novel perspective and robust evidence to clinicians and practitioners for future decision-making in children with ASD. Forecasted results will include study characteristics, qualitative appraisal of cognitive tasks and intervention technologies, and quality of the selected studies; visual demonstration of synthesis results such as network diagrams and associated geometry will be generated and evaluated, respectively. Expected results will be able to rank the efficacy of multiple PAIS (eg, aerobic exercise, mindlessness practices, school-based physical education programs, and exergaming) with effect size differences demonstrated between multiple treatments. In addition to network plots, results will be illustrated in tables of network characteristics, data plots, league tables and league heat plots, surface under the cumulative ranking curve plots, and rankograms. An in-depth discussion will be held. In general, results may reveal the rank efficacy of PAIS, in combination or as single treatment, on promoting cognitive functions and further social and communication skills in children with ASD. In addition, owing to the COVID-19 pandemic, social restrictions and isolation were enforced, which led to an increase in sedentary behavior and physical inactivity, which, in turn, increased the risks of cardiovascular disease and mental wellness crisis in children [82-84]. There are more concerns especially regarding children with ASD [85,86]. We will include an in-depth discussion of feasible interventions along with safety suggestions for programming during the global pandemic.

Results

Our preliminary search identified 3778 potentially relevant studies. The screening of the studies based on the inclusion and exclusion criteria is ongoing, and we anticipate that the final number of eligible studies will be in the range of 30 to 50.

Discussion

Principal Findings

With the described protocol, we aim to address the urgent need for effective PAIS to reduce the negative impact on cognitive outcomes in children with disabilities, including those with ASD. As noted in our mini review, research suggests that PAIS may have a positive impact on cognitive function in children with ASD, but there is limited information on the comparative effectiveness of different types of PAIS. Therefore, our study represents an important contribution to the field, as it is the first systematic review and NMA protocol to propose to examine the efficacy of PAIS on cognitive performance in children with ASD.

Preliminary results from the mini review suggested that several types of PAIS, including yoga, martial arts, and aerobic exercise, may have positive effects on cognitive performance in children with ASD. Specifically, we found that these interventions were

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associated with improvements in cognitive flexibility, attention, and memory. Notably, our NMA will allow us to indirectly compare the effectiveness of different types of PAIS, providing valuable insights into which interventions may be most effective for improving cognitive function in this population.

Our study represents an important contribution to the literature on the efficacy of PAIS in improving cognitive performance in children with ASD. Although we have taken steps to minimize bias and ensure the quality of the study, as listed in Multimedia Appendix 2, there are some limitations that should be considered when interpreting our results. First, our study is limited by the quality and heterogeneity of the included studies. Although we have conducted a comprehensive search of multiple databases and used rigorous inclusion criteria, some relevant studies may have been missed. Second, as with any systematic review and NMA protocol, our study is limited by the quality and consistency of the data extracted from the included studies. We took steps to mitigate these issues by using a rigorous assessment of the RoB and data extraction processes. In addition, the statistical and moderation analyses we have planned will allow us to explore the sources of heterogeneity and potential moderators of treatment effects. Finally, we have adhered to ethical guidelines and plan to disseminate our findings to relevant stakeholders to facilitate the translation of research into practice.

Conclusions

Despite these limitations, we believe that our study provides valuable insights into the efficacy of PAIS for improving cognitive performance in children with ASD. Our findings suggest that clinicians and policy makers should consider incorporating PAIS into interventions aimed at improving cognitive function in this population. Furthermore, our study highlights the need for additional research in this area, including larger, well-controlled studies to further examine the comparative effectiveness of different types of PAIS. Overall, we hope that our study will contribute to the development of evidence-based interventions that can help improve outcomes for children with ASD.

Data Availability

This is not applicable at present, as this is a protocol paper. However, future and final data sets will be available from the corresponding author upon reasonable request.

Authors' Contributions

LL conceptualized this study. LL and AW contributed to the study conception and design and drafting the protocol. MEM and QF revised the draft critically for important intellectual content and gave final approval of the version for publication. MEM monitored the project administration. All authors contributed to the manuscript and approved the submitted version.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Cognitive measures in effect calculation.
[DOCX File , 19 KB - resprot_v12i1e40383_app1.docx]

Multimedia Appendix 2
PRISMA-NMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols for Network Meta-Analyses) checklist.
[DOCX File , 24 KB - resprot_v12i1e40383_app2.docx]

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Abbreviations

ASD: autism spectrum disorder
EF: executive function
MeSH: Medical Subject Headings
NMA: network meta-analysis
PAIS: physical activity intervention strategies
PICOS: Population, Intervention, Comparison, Outcome Measures, and Design
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-NMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols for Network Meta-Analyses
RCT: randomized controlled trial
RoB: risk of bias
SMD: standardized mean difference

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Protocol

Parent Versus Individual Cognitive Behavioral Therapy for Youth Anxiety: Protocol for an Overview of Systematic Reviews Over Time

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Abstract

Background: Cognitive behavioral therapy (CBT) has shown to be highly effective for treating youth anxiety; yet, there is ongoing debate as to whether involving parents improves outcomes. For example, parents who attend may learn CBT skills to help their child in an ongoing way; yet, they could also distract their child from treatment depending on how they interact. As evidence has accumulated, reviews and meta-analyses have attempted to examine the most effective treatment format. These reviews often have high impact in the field; however, they use varied methodologies and draw on different primary studies. Different formats of CBT for youth anxiety have been developed in relation to parental involvement, including youth-only CBT (Y-CBT; where the youth alone attends treatment), youth and parent or family CBT (F-CBT; where youths and their parents attend together), and, most recently, parent-only CBT (P-CBT; where the parent alone attends).

Objective: This protocol describes an overview of systematic reviews comparing the relative efficacy of different formats of CBT for youth anxiety (Y-CBT, F-CBT, and P-CBT) over the study period. The protocol will also examine the moderating effects of variables on the efficacy of different formats; for example, youths' age and long-term outcomes.

Methods: We will analyze the results of systematic reviews that compare different levels and types of parental involvement in CBT for youth anxiety over the study period. A systematic review of medical and psychological databases (PsycINFO, PubMed, SCOPUS, Web of Science, Cochrane Library, and Embase) will identify reviews comparing the efficacy of different formats of parent involvement in CBT for youth anxiety. Data extraction will include (1) author names (and year of publication), (2) review design, (3) age range, (4) analysis type, (5) conclusions, and (6) moderators. This overview will present the relative efficacy of formats chronologically in a table and then describe the main results longitudinally in a narrative summary. A Measurement Tool to Assess Systematic Reviews, 2nd Edition (AMSTAR 2), quality rating will be given to each review, and the amount of primary study overlap across reviews will be quantified.

Results: The last search was conducted on July 1, 2022. The reviews were published between 2005 and 2022. We found a total of 3529 articles, of which we identified 25 for the final analysis.

Conclusions: This overview will compare and report the relative efficacy of Y-CBT, P-CBT, and F-CBT for youth anxiety over the study period, describe the heterogeneity across reviews and primary studies, and consider the moderating effect of relevant variables. It will describe the limitations of an overview, including the potential for nuance in the data to be lost, and provide conclusions and recommendations for conducting systematic reviews regarding parental involvement for CBT for youth anxiety.

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KEYWORDS

anxiety; cognitive behavioral therapy; systematic review; youth; overview; review

Introduction

Background

Cognitive behavioral therapy (CBT) represents a revolution for treating anxiety in adults and children. The efficacy of CBT for youth anxiety has been established in systematic reviews [1-3] and overviews [4,5]. During CBT, the therapist transfers skills to young clients so they can better manage their anxiety symptoms. As researchers have attempted to improve CBT protocols, they have examined whether it is advantageous to also involve parents in treatment. This approach seems logical, as parents and families are sometimes implicated in the maintenance of a child's anxiety [6,7]. During CBT, parents can be coached in skills to manage their child's anxiety and these skills can vicariously help the parent manage their own anxiety [3,8]. Yet, researchers have questioned the necessity of parental involvement in every intervention [2,7]. For example, a parent's presence could increase the youth's reliance on them and reduce their autonomy [9]. Barmish and Kendall [3] influentially stated, "we must resist the intuitive appeal to conclude that the inclusion of parents as active participants in CBT is preferable to child-focused CBT until the data provide the needed support for such a claim." Whether parents enhance CBT for youth anxiety is one of the most frequently examined and contested topics in clinical psychology over the last 20 years.

Much of the debate regarding the merits of parental involvement in CBT has taken place in systematic reviews that have high impact in the field. These reviews provide a high-level analysis as they aggregate data from several primary studies. Yet, while these reviews are influential, they typically use different methodologies and only represent the accumulated evidence at a given time point. For example, the inclusion and exclusion criteria, types of studies available, and type of analysis conducted influences a systematic review's outcomes and conclusions. Overviews (systematic reviews of systematic reviews) can potentially provide greater coverage over time and a higher level of analysis than an individual systematic review [10,11]. Understanding how different reviews summate and report on available evidence regarding treatment formats over time provides context as to how the field has developed. Furthermore, while early studies on this topic examined youth-only CBT (Y-CBT; where the youth alone attends treatment) versus youth and parent or family CBT (F-CBT; where the youth and parent attend treatment together), newer formats have examined parent-only CBT (P-CBT; where the parent alone attends treatment; [1,12]) so that parents can learn skills on how to manage their children's anxiety. P-CBT can be advantageous when there is limited engagement with the youth or practical reasons prevent direct treatment. Moderating variables could also influence the efficacy of different treatment formats. For example, greater parental involvement may be influential for younger children [7], for longer-term outcomes [13], or when the parent is experiencing their own psychopathology [14].

This paper describes a novel protocol for an overview investigating the effects of parental involvement in CBT for youth anxiety over the study period. As results examine consistency and trends across individual reviews over time, we have permitted overlap (allowing primary studies in multiple reviews). As the reviews use varied methodologies and there is overlap, we displayed results as a narrative summary describing results for systematic reviews over time, rather than aggregating data (as in a meta-analysis). To our knowledge, this is the first overview to examine the effects of parental involvement in CBT for youth anxiety.

Objectives

Primary Research Question

Our primary objective is to explore the relative efficacy of CBT for youths with anxiety by comparing Y-CBT, P-CBT, and F-CBT over the study period. The dependent variable is any quantitative indication of the youth's anxiety (eg, recovery rates, youth- or parent-reported anxiety, treatment efficacy based on the level of evidence, etc).

Secondary Research Question

If the data permit, we will examine the moderating effect of variables including the youths' age, parents' psychopathology, and the long-term effects of Y-CBT, F-CBT, and P-CBT on youth anxiety. If any other theoretically interesting moderators are identified in the course of the literature review process, they may be included as well. This analysis will consider the effects of moderators on the relative efficacy of formats, and the results will be described in a narrative and interpreted in the discussion.

Methods

Protocol Registration

The protocol of this review is registered with the Open Science Framework [15].

Search Strategy

The search will be undertaken by clinical psychologists who treat anxious youths (SB and M Richardson). The final set of articles will be developed in conjunction with a university librarian (M Riba). The search strategy involves searching databases for articles that have 4 general categories: "Cognitive Behavior Therapy" AND "Youths" AND "Anxiety" AND "Review." Of the articles identified in this broad search, the screeners (M Richardson and SB) will hand-search articles related to "Parent/Family" treatments. We will also attempt to identify any additional eligible articles in a hand search. See Multimedia Appendix 1 for search queries in each database.

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Databases

The search will be conducted in the following electronic databases: PsycINFO, Web of Science, PubMed, Cochrane Library, SCOPUS, and Embase.

Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines have been followed in this systematic review. Data will be presented in a PRISMA flowchart.

Inclusion and Exclusion Criteria

The inclusion and exclusion criteria for articles are summarized in Textbox 1.

Textbox 1. Inclusion and exclusion criteria for articles.

Inclusion criteria:

- The article must state that it is a systematic review and involves a systematic search of medical or psychological databases (or both).
- The review must state that the treatment used is primarily cognitive behavioral therapy (CBT).
- The review must exclusively focus on the treatment of anxiety.
- The review should focus on treatment for a variety of anxiety disorders (mixed anxiety; >1 diagnoses) to reduce the potential differential effects of treatment on a particular anxiety disorder.
- The review must report a quantitative measure (eg, effect size, percent remission, etc) related to youth anxiety.
- Parental involvement in CBT can take any form (eg, cotherapist, psychoeducation, etc), as long as it is the focus of treatment.
- The review must discuss the relative efficacy of different formats for CBT; for example, it must make a direct comparison (eg, randomized controlled trials) or an indirect comparison (eg, comparison with to a control group) among the different formats of CBT for youth anxiety (youth-only CBT, youth and parent or family CBT, or parent-only CBT).
- The treatment must be intended for youths, so participants in reviews must be ≤21 years old.
- The treatment should be primarily face-to-face psychotherapy (ie, it should not be web-based or e-therapy).
- The included reviews must be in English-language peer-reviewed journals published from 2000 onward.

Exclusion criteria:

- Primary studies that are not systematic reviews.
- Reviews that focus on CBT and another concurrent treatment for the youth's anxiety (eg, CBT and psychiatric medication). However, if a review includes primary studies where some participants are receiving a concurrent treatment, it will be included.
- Reviews should not focus on comorbidity between anxiety and another disorder as the target of treatment (eg, anxiety and autism or epilepsy); however, if a review involves primary studies where participants have comorbid conditions, it will be included.
- A review with only a narrative description of results and no analysis.
- In line with the most recent Diagnostic and Statistical Manual, 5th Edition [16], reviews that focus on obsessive compulsive disorder and posttraumatic stress disorder are excluded; however, if studies within the selected reviews include youths with these diagnoses among anxiety disorders, they will be included.

Population, Intervention, Comparison, and Outcomes

The PICO is described as (1) population, comprising youths with anxiety; (2) intervention, involving P-CBT, Y-CBT, or F-CBT; (3) comparison, including other CBT formats different from the intervention (eg, P-CBT, Y-CBT, or F-CBT); and (4) outcome being the analysis of anxiety levels.

Screening Stages

Two clinical psychologists (SB and M Richardson) will be involved in screening all articles with the following steps: (1) duplicates will be removed in EndNote (Clarivate), (2) articles will be transferred to Covidence for data screening and extraction, (3) articles will initially be screened based on the title and abstract by the 2 independent coders who are clinical psychologists, (4) the full text of the remaining articles will be screened by the 2 independent clinical psychologists to identify the final articles to be included, and (5) any discrepancies in screening decisions will be resolved through discussion between the 2 clinical psychologists.

Data Extraction

The extracted data will include (1) author names (year of publication), (2) overall study design, (3) age range, (4) primary analysis type between different CBT formats (eg, controlled effect size where efficacy for a format is compared to another condition), and (5) conclusions regarding superiority among CBT formats. We may also code for other moderators such as youths' age, parents' psychopathology, long-term outcomes, and other variables identified through the literature review should there be adequate data.

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Management of Extracted Data and Synthesis

The coders (SB and KI) will extract the abovementioned variables for all included studies. To provide the most comprehensive overview, we shall describe the main results from systematic reviews with a variety of outcome measures over time. In this overview, we are interested in the relative performance of different formats of CBT for youth anxiety over the study period. Data extracted from this overview will initially be chronologically tabulated. The results will then be summarized in a narrative, based on the analysis type and outcome of each review (the results will not be presented as an overall meta-analysis, and results of individual reviews will be described over time). The analysis will include comparison among treatment formats. A primary analysis will examine the relative efficacy of P-CBT, Y-CBT, and F-CBT over time. A secondary analysis will be exploratory considering the effects of moderating variables, such as the youths' age, parents' psychopathology, and long-term outcomes, if the data permit. A general discussion will follow at the end of the review.

Management of Overlap

In this overview, for the main analysis, we are interested in the relative performance of different CBT formats for youth anxiety over the study period. As individual systematic reviews were studied over time, overlap in primary studies across reviews is considered acceptable (ie, the same studies are included in multiple reviews published at different times). We are interested in how the accumulated data in each systematic review are reported over time.

In order to report the extent of overlap, we will include a citation matrix that visually displays the citation overlap across reviews [11,17,18]. We will also report the corrected covered area, which is a quantitative measure of primary study overlap across reviews [11,17,18]. We will also include some information or statistics about the degree of overlap across reviews (eg, the number of overlapping studies present in each review) [11].

Quality Assessment

Each systematic review will be graded using the Measurement Tool to Assess Systematic Reviews, 2nd Edition (AMSTAR 2) [19]. It has 16 items and 7 critical domains: protocol registration, adequate literature search, justification of excluding studies, risk of bias of individual studies, appropriateness of meta-analysis, consideration of risk of bias when interpreting results, and assessment of publication bias. We will report the proportion of studies that meet each critical domain. For the purposes of this study, the AMSTAR 2 rating was calculated as high (none or 1 noncritical weakness), moderate (more than 1 noncritical weakness), or low (1 or more critical weaknesses). Uncertainty in quality ratings will be resolved through discussion between the 2 clinical psychologists (SB and M Richardson).

Results

The last search was conducted on July 1, 2022. We identified 3529 articles across the search, which yielded 2189 unique articles. We found 25 systematic reviews that meet our criteria and compare CBT formats.

Discussion

Expected Findings

Youth anxiety is common and disruptive; however, CBT is a highly effective treatment for these conditions. Yet, there is ongoing debate regarding the most effective way to deliver CBT [3]. Parental involvement for youth anxiety has often been the norm; however, evidence for this approach has been mixed [2,8]. There are several systematic reviews examining parental involvement; yet, the majority of these are inconclusive [3]. This paper presents a novel protocol to answer this question by examining the results and conclusions of systematic reviews over time, rather than examining primary studies that are subject to heterogeneity. This overview examines trends and consistency in the efficacy of CBT formats as reported by reviews over time. This provides a high-level view of the topic by drawing on several systematic reviews over time. This overview will also consider potentially important moderators including youth's age, long-term outcomes, and parents' psychopathology.

Strengths and Limitations

The strengths of this overview are that it will be conducted as a complex search across several medical and psychological databases. We will also take stringent measures of quality using AMSTAR 2, involve experienced child anxiety clinicians for coding, and analyze study overlap across reviews. The inclusion criteria also allow for a broad search across reviews with varying methodologies in order to maximize the search. A potential limitation of this overview approach is that nuance in the data may be lost due to our focus exclusively on systematic reviews rather than primary studies; for example, recent primary studies may not be included in this analysis as they are not included in systematic reviews. Furthermore, this study only considers efficacy, such that other important variables including cost, acceptability, and impact on functioning are not analyzed. Finally, while trends and directions in effects described in this overview are informative, they do not imply statistical significance.

Conclusions

The results of this overview will inform clinicians about the most effective way to conduct anxiety interventions with youths. To date, clinical decisions regarding parental involvement are often based on mixed evidence and clinical intuition. This study will provide insight regarding how to tailor CBT for youths with anxiety by varying parental involvement depending on factors including the child's age. This overview will also provide recommendations for conducting and reporting systematic reviews regarding parental involvement for CBT for youth anxiety. The overview methodology over time may help to examine other clinical questions, where there is high heterogeneity across primary studies. The results of this novel overview will be widely disseminated and they are expected to influence clinical practice.

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Data Availability

All relevant data will be made available once the overview is complete.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search queries for systematic reviews.
[DOCX File , 23 KB - resprot_v12i1e48077_app1.docx]

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Abbreviations

AMSTAR 2: Measurement Tool to Assess Systematic Reviews, 2nd Edition
CBT: cognitive behavioral therapy
F-CBT: youth and parent or family cognitive behavioral therapy
P-CBT: parent-only cognitive behavioral therapy
PICO: population, intervention, comparison, and outcomes
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
Y-CBT: youth-only cognitive behavioral therapy

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Protocol

Implementation of Home-Based Telerehabilitation of Patients With Stroke in the United States: Protocol for a Realist Review

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Abstract

Background: Stroke is a common cause of mortality and morbidity. Insufficient and untimely rehabilitation has been associated with inadequate recovery. Telerehabilitation provides an opportunity for timely and accessible services for individuals with stroke, especially in remote areas. Telerehabilitation is defined as a health care team's use of a communication mode (eg, videoconferencing) to remotely provide rehabilitation services. Telerehabilitation is as effective as facility-based rehabilitation; however, it is infrequently used due to implementation barriers.

Objective: The aim of the study is to explore the interaction between the implementation strategies, context, and outcomes of telerehabilitation of patients with stroke.

Methods: This review will follow four steps: (1) defining the review scope, (2) literature search and quality appraisal, (3) data extraction and evidence synthesis, and (4) narrative development. PubMed via MEDLINE, the PEDro database, and CINAHL will be queried till June 2023 and supplemented with citation tracking and a gray literature search. The relevance and rigor of papers will be appraised using the TAPUPAS (Transparency, Accuracy, Purposivity, Utility, Propriety, Accessibility, and Specificity) and Weight of Evidence frameworks. The reviewers will extract and synthesize data iteratively and develop explanatory links between contexts, mechanisms, and outcomes. The results will be reported according to the Realist Synthesis publication standards set by Wong and colleagues in 2013.

Results: The literature search and screening will be completed in July 2023. Data extraction and analysis will be completed in August 2023, and findings will be synthesized and reported in October 2023.

Conclusions: This will be the first realist synthesis, uncovering the causal mechanisms to explain how, why, and to what extent implementation strategies impact telerehabilitation adoption and implementation.

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KEYWORDS

telerehabilitation; telemedicine; stroke; implementation; realist review

Introduction

Telerehabilitation of Patients With Stroke

Stroke is a common cause of mortality and morbidity in the United States, affecting nearly 800,000 persons yearly [1]. Even though early rehabilitation of patients with stroke is pivotal for adequate recovery [2], rehabilitation is frequently delayed and underused [3]. Insufficient and untimely rehabilitation has been partly attributed to distance and transport challenges to rehabilitation facilities, especially for rural dwellers, inducing geographic disparity [4]. Nevertheless, both urban and rural residents experience various limitations to accessing facility-based rehabilitation: increasing rehabilitation costs, medical staff shortages, inadequate transportation systems and, after March 2020, pandemic-related contact restrictions [5,6]. In addition, more restriction to care is inflicted by the attitudinal, architectural, economic, and sensory barriers representing the omnipresent societal discrimination against people with disability [7].

Telerehabilitation is at least as effective as facility-based rehabilitation [8-10] and is typically less costly [11]. For that, home-based telerehabilitation is a promising solution that provides an opportunity for timely, effective, and accessible services to a large base of patients [12], especially in low-resource rural areas [13].

Multiple forms of technology provide a medium for telerehabilitation: telephone, messaging, email, videoconferencing, web-based platforms, robots, and virtual reality [14]. Currently, telerehabilitation via phone and videoconferencing is considered a basic technology [15,16]. Advanced technology includes virtual reality as it creates a physical experience with multiple sensory inputs: tactile, visual, auditory, and olfactory [12,17,18]. Robotics use in telerehabilitation is another advanced and evolving technology with great potential to enhance motor functions and measure patient progress [19].

Telerehabilitation Implementation and the Interplay Between Context and Mechanisms

Most studies addressing telerehabilitation are feasibility and efficacy studies, leaving a gap in understanding the effective implementation of telerehabilitation [13,20]. Implementation science is “the scientific study of methods to promote the systematic uptake of research findings and other evidence-based practices into routine practice, hence aiming to improve the quality and effectiveness of health services” [21]. Many barriers hinder implementation: lack of knowledge and misbeliefs about the effectiveness of the intervention, inadequate planning for implementation, insufficient engagement of different stakeholders, and lack of resources, among others [22]. To overcome those barriers, implementation science pivots to designing and studying implementation strategies [23]. Implementation strategies are “methods or techniques to enhance a clinical program or practice’s adoption, implementation, and sustainability” [24]. Training, audit and feedback, coaching, and piloting are examples of implementation strategies.

While using the same strategies to enable implementation across various contexts is appealing, it brings limited success [25]. This is attributed to the multicomponent nature of implementation strategies and the complexity of the process of implementation that represents the interactions between the implementation strategy, the context of the setting in which implementation occurs, and the change process required for implementation [26,27].

Understanding the mechanisms of implementation strategies is vital to determine how and which strategies work and in what context for telerehabilitation [24,28,29]. Mechanisms are dynamic processes that drive and generate outcomes, often involving the understanding and reasoning of actors involved in implementation [30]. Establishing a telerehabilitation Community of Practice is an implementation strategy that might enhance telerehabilitation adoption; however, it does not directly result in adoption [31]. Through an underlying mechanism (eg, cognitive participation of the Community of Practice members), stakeholders may decide to adopt the change. Mechanisms are not observable by themselves, but observable data suggest their existence [31]. For example, increased adoption could be measured, but cognitive participation might be inferred to but not directly observed.

Context, Mechanisms, and Outcomes (CMO) configurations are at the heart of realist synthesis. CMO configurations are hypothetical until they are tested and found explanatory to the relationship between the strategies and the outcomes of interest [32]. CMO configurations explain what worked, how it worked, and what the involved mechanisms are [33]. Ultimately, researchers can respond to “will it work in a different context?” [33]. Realist researchers understand that implementation strategies work selectively, and outcomes vary in different settings [34,35]. Thus, recognizing implementation strategies patterns, as well as outcomes patterns, provide insight into the success or failure continuum [34].

This realist review aims to develop generalizable theories by examining each study to uncover the mechanism through which an implementation strategy works and the effects of various contexts on making it work [35]. The reviewers will untangle the complexity of implementation strategies through a frequent enhancement of the theoretical explanations of the empirical findings [36,37]. The output of this realist synthesis is a refinement of how the strategy “works, for whom, in what circumstances, in what respects and why?” [38].

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The purpose of this realist review is to synthesize a theoretical explanation of the adoption and implementation of telerehabilitation of patients with stroke. For practitioners, this review will offer empirically rooted strategies for facilitating the implementation of telerehabilitation.

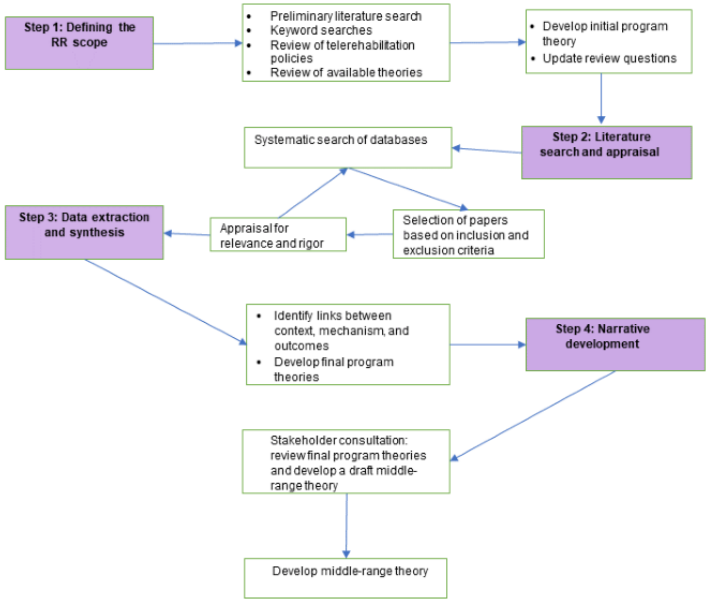
Methods

Study Design

This study will follow the guidelines proposed by Rycroft-Malone et al [39] and Pawson [34]. To explain how the implementation of telerehabilitation of patients with stroke operates, we will develop a middle-range theory (MRT), subject to refinement and validation as it can be used in the future implementation of telerehabilitation.

The review steps are (1) clarifying the scope and initial program theory (IPT) development, (2) searching for evidence appraising primary studies, (3) extracting data and synthesizing evidence, and (4) narrative development of conclusions. Figure 1 summarizes the main steps involved in this realist review.

Figure 1. Flowchart of the RR steps. RR: realist review.



Step 1: Defining the Scope of the Review

The review team will formulate a descriptive and explanatory theoretical framework from the reviewed evidence. The focus of this review is on the implementation strategies of telerehabilitation. Implementation strategies are based on an initial practical understanding of the most effective way to deliver and implement an intervention, focusing on better implementation outcomes and addressing context-specific barriers to implementation.

Constructing a presynthesis conceptual framework marks the initial step in conducting a realist review [38]. This initial framework is referred to as IPT [40], which will provide an initial theoretical understanding of the implementation of telerehabilitation, necessary to explore implementation mechanisms. We will develop the IPT using concepts from multiple theoretical frameworks that researchers use for studying telemedicine adoption and implementation [41], namely: the Technology Acceptance Model, the Diffusion of Innovation Theory, the Theory of Interpersonal Behavior, the Perceived Usefulness, the Perceived Ease of Use, the Unified Theory of Acceptance and Use of Technology, and the Theory of Reasoned Action [42]. In addition, the review team will contribute their implementation science, telerehabilitation, and quality improvement knowledge and experience to refine the IPT [41]. The IPT will be refined and expanded as evidence arises throughout the iterative synthesis process [43]. The continuous iteration of the theory is essential to follow logic trails discovered in the literature to develop the understanding of telerehabilitation and its implementation.

Step 2: Literature Search and Quality Appraisal

The literature search is iterative and directed to answer the questions that arise as the review progress [34,44]. To gain familiarity with the size and type of the available literature, one reviewer (MMH) will use *PubVenn* [45], which provides a graphical display of the extent of the literature, and *PubReMiner* [46], which analyzes the literature indexed in the PubMed MEDLINE database for frequent terms, journals, and authors.

The review team will use the 4 theoretical domains of the Realist Synthesis of Implementation Strategies (RES-IS) model to guide literature search and data extraction [39]. RES-IS is developed to research implementation strategies using the realist synthesis approach. It represents implementation strategies in 4 theoretical domains: properties of change agents, system change, technologies, and education interventions [39]. The change agent refers to the individuals' attributes and the strategies they use to implement telerehabilitation successfully. Many terms are synonyms for change agents like facilitators, opinion leaders, knowledge brokers, champions, and experts. Systems changes refer to the organizational characteristics that facilitate the implementation and sustainment of telerehabilitation. Other

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terms related to systems change include social networks, culture, leadership, learning organizations, teamwork, and collaboration. Properties of technologies refer to the telerehabilitation technology itself and other technologies involved in facilitating its implementation. Education and training include academic detailing, reflection, action learning, and adult learning [39].

The context of implementation is at the center of the RES-IS model for its ubiquitous influence on the use and effect of strategies. In addition, an implementation strategy can target different levels: audits can induce changes in policies at the organizational level or alter local practices at the unit or individual level [47]. The term dose refers to the needed frequency and intensity of an implementation strategy (eg, training) to activate mechanisms that bring about outcomes [24,39].

The review team will use PubMed via MEDLINE, the PEDro database, a physical therapy evidence database, and CINAHL to conduct the topical search. A health information specialist (MB) leads the literature search. After reviewing the outcome of this topical search, we will rerun the search strategy, applying a search filter to limit the results to systematic reviews, logic models, and opinion pieces rich in concept-based discussions [48].

After identifying index papers, the review team will use the CLUSTER approach to search for Citations, Lead Authors, Unpublished Material, Scholar Searches, Theories, Early Examples, and Related Projects [48]. The CLUSTER search will be iterative and repeated to enhance the finding of relevant theories. The reviewers will also explore telerehabilitation-specialized journals (eg, *International Journal of Telerehabilitation*, *Smart Homecare Technology and Health*, and *Annual Review of Cybertherapy and Telemedicine*). As part of the CLUSTER approach, the reviewers will use the identified index documents to conduct a citation search of the index documents on Google Scholar using *Publish or Perish* software (Anne-Wil Harzing). To reach more resources, the reviewers will consult the American Telemedicine Association, the American Physical Therapy Association, and The American Occupational Therapy Association.

Documenting the literature search—The literature search is iterative and sometimes opportunistic [48]. The reviewers will use the EndNote software (Clarivate) [49] to manage the literature search process. To keep track of the literature search output, a new folder on EndNote will be added. Each literature search (a folder on EndNote) will document the sampling strategy, type of studies included, approaches, range of years, limits, inclusions and exclusions, terms used, and electronic sources [48,50].

The review team will use Rayyan (Oatar Computing Research Institute), a review management platform [51], to facilitate papers' review and data extraction. To exclude irrelevant papers, 2 reviewers (MMH and AT) will screen the titles and abstracts. Based on the inclusion and exclusion criteria (Textbox 1), 3 reviewers (MMH, AT, and ST) will independently review the included full papers. The reviewers will meet regularly to discuss their decision on papers' inclusion. Disagreement will be resolved by examining the paper's language, focus, and inclusion criteria with another reviewer (MRR). Copies of papers or book chapters will be attached to the citation on Rayyan. Once saturation of the themes is achieved, the analysis of the included literature will conclude. Based on this analysis, the team may identify new inclusion criteria.

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Textbox 1. Review inclusion and exclusion criteria.

Inclusion criteria

- I—Intervention
  - Home-based physical telerehabilitation of patients with stroke.
- S—Implementation strategy
  - Implementation strategies for telerehabilitation of patients with stroke.
- C—Context
  - Health care providers, for example, physicians, nurses, physiotherapists, and allied health professionals, are involved in home-based stroke telerehabilitation.
  - Patients with stroke and their caregivers (eg, family members, professional caregivers, volunteers, and so on).
  - Policy makers, decision makers, managers, leaders, and facilitators are involved in telerehabilitation.
  - Any setting (eg, inpatient, outpatient, and home) involved in the implementation and delivery of telerehabilitation for patients with stroke.
  - Studies based in the United States.
- M—Mechanisms
  - Fundamental processes are involved in or responsible for action or reaction triggered by the implementation strategy.
- O—Outcomes
  - Implementation outcomes guided by RE-AIM framework: Reach, Effectiveness of Implementation, Adoption, Implementation (fidelity and cost), and Maintenance. In addition, we will review Proctor's implementation outcome framework: acceptability, appropriateness, feasibility, efficiency, speed, timeliness, and representativeness or equity related to reaching and adoption.

Study design

- All study designs will be included.
- Include empirical and nonempirical sources (eg, books, guidelines, policies, editorials, opinion papers, dissertations, among others).
- Other materials such as podcasts and recorded lectures as supplementary materials to published scientific evidence will be sought for insights.

Exclusion criteria

- Non-English papers.
- Studies that are done outside the United States.
- Studies that show low rigor.
- Papers address telerehabilitation in patients with conditions other than stroke (eg, postoperative rehabilitation) or other than in patients' homes (eg, in the community).
- Papers with mere focus on cognitive and psychiatric rehabilitation of patients with stroke.
- Papers focused on the efficacy or effectiveness of telerehabilitation with no implementation-related details or insights.

The quality appraisal of the included papers will pass through 2 stages: the first stage will focus on relevance of the included papers to the objective of the review and the second one will evaluate their rigor. The review team developed criteria of relevance for this study (Textbox 2). The criteria for the relevance are to guide the team to include studies that can inform the MRT development [34].

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Textbox 2. Criteria of study relevance to inform theory development.

High relevance

- Describe contextual factors of implementation of telerehabilitation for patients with stroke.
- Describe stakeholders' perspectives on the implementation of telerehabilitation.
- Describe implementation strategies of telerehabilitation for patients with stroke.
- Describe implementation outcomes of telerehabilitation for patients with stroke.
- Describe theories of implementation of telerehabilitation for patients with stroke

Moderate relevance

- Same as high relevance criteria but includes telerehabilitation for mixed patient populations that include other conditions in addition to stroke.

Low to no relevance

- Comparative studies of the effectiveness of telerehabilitation for patients with stroke that do not include implementation-related info.
- Describe the process of engineering the design of telerehabilitation technology for patients with stroke.
- Studies of prototypes and proofs-of-concept.

Assessment of rigor will be conducted through a combination of 2 different frameworks: TAPUPAS (Transparency, Accuracy, Purposivity, Utility, Propriety, Accessibility, and Specificity) framework, devised by Pawson et al [52], and Weight of Evidence (WoE) framework, devised by Gough [53,54].

TAPUPAS stands for Transparency, Accuracy, Purposivity, Utility, Propriety, Accessibility, and Specificity [52]. *Transparency* addresses whether the process of knowledge generation is open to external review and scrutiny [52]. Transparency extends beyond reporting research methods to how the researchers develop the research question, aims, and objectives [55]. *Accuracy* examines whether the researchers made accurate claims based on the results of their study [52,55,56]. *Purposivity* assesses the fit of the used methods for the purpose of the study [55]. Purposivity ensures the process of inquiry is methodologically sound and contextually appropriate. *Utility* considers the needs of the stakeholders and the fit of the study to satisfy those needs [56]. *Propriety* focuses on the ethical aspects of conducting the research [55]. *Accessibility* necessitates the dissemination and implementation of the research findings [55]. Both academic and nonacademic routes are appropriate for dissemination depending on who the end users are [55]. *Specificity* evaluates the methodological quality of the study and its conformance with the available standards [56].

WoE framework allows the opportunity to provide a grade for each of its 3 focus areas to be added up to an average grade for each paper [53]. WoE focus area A addresses the trustworthiness and coherence of the study, focus area B addresses appropriateness of the methods to the research question, focus area C assesses the relevance of evidence to the research question, and focus area D is the total grade based on the focus areas A, B, and C [53].

The focus area A of the WoE comprises 4 factors of the TAPUPAS framework: transparency, accuracy, accessibility, and specificity. The focus area B comprises purposivity. The focus area C comprises utility and propriety. Each focus area will be assigned a grade range from 1 (low quality), 2 (medium quality), or 3 (high quality) based on the TAPUPAS criteria within each of the WoE focus areas. For example, if a study is considered transparent and accurate, but it is not accessible or specific, it will receive a grade of 1.5 for WoE A [54]. The same logic will follow in the other focus areas. The score of WoE D will then reflect an overall average score, adding the scores of WoE A + B + C and dividing the total score by 3. Papers with WoE D score of 2 or more will be included. However, some papers with lower score, which provides important insight into the theory development will be included. In this case, the evidence generated out of inclusion of lower-quality studies will be marked as low-quality evidence.

Step 3: Data Extraction and Evidence Synthesis

Overview

As this is an explanatory review that uses original papers to answer the study questions, a realist approach will be used for data extraction and synthesis. Data extraction will be conducted based on Multimedia Appendix 1 [1,2,5-42,57-59] forms. Essential text from the primary studies will be included to answer the review question [60]. All parts of the included papers will be examined to identify pertinent information. The reviewers (MMH and AT) will extract and code text from each of the papers. Then the coded texts will be synthesized together to search for a relationship between the intervention, implementation strategy, context, mechanisms, and outcomes (ISCMO) [61]. The identified intervention, ISCMO will consider different strategies and telerehabilitation modes. Discussions of the review team will guide the evidence synthesis, and each ISCMO configuration will be examined against the available empirical evidence [61].

Coding

A coding manual developed by May et al [62] will be used to guide the coding process. This manual is based on Normalization Process Theory (NPT), linking its 12 primary constructs to the CMO configurations [62]. NPT is a sociological theory that was developed to support studying and evaluating the implementation of complex health care interventions [62-64].

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In addition, the constructs of the NPT have been mapped to the CMO configuration [62], rendering it a perfect fit for this realist review. Four NPT constructs conceptualize the context: strategic intentions, adaptive execution, negotiating capability, and reframing organizational logics. Another 4 constructs inform the mechanism of implementation: coherence building, cognitive participation, collective action, and reflexive monitoring. Lastly, outcomes include intervention mobilization, normative restructuring, relational restructuring, and sustainment. May et al [62] provided descriptions and examples of the NPT constructs as part of the coding manual (Multimedia Appendix 2).

Three reviewers (MMH, AT, and ST) will independently code the primary studies using NVivo (version 12; QSR International), a computer-assisted qualitative data analysis platform [65]. NVivo supports code-based inquiry, searching, and theorizing combined with the ability to annotate and edit documents [66]. Given the complex and iterative nature of conducting a literature search and synthesis in realist review, it is essential to prioritize and maintain transparency in methods to ensure the credibility and rigor of the review process [57], an endeavor NVivo will support [65]. In addition to detailing analytical microprocesses that lead to theory generation, another key feature of NVivo is its ability to integrate different data sets [65]. NVivo will be used early in the synthesis process. Each concept of the initial theory will be given a node in NVivo, and each node will be a hub for related materials used in the analysis. Each node will be linked to a memo to describe the review team discussions and thoughts behind concepts. For subconcepts, we will create child nodes. Concepts that are not supported by empirical evidence will be kept within the NVivo file as "unsubstantiated." Once new evidence arises to support unsubstantiated concepts, we will bring those concepts back to the framework.

Coding will support the data extraction by assigning a salient and summative attribute to the extracted texts [58]. Data extraction and coding will link the primary studies, the research question, and the study findings [58]. Reviewers will meet regularly to discuss and consolidate the results.

Data will be combined and synthesized based on the following steps:

1. Three reviewers (MMH, AT, and ST) will organize extracted data into evidence tables; for example, to address the impact of systems characteristics on the implementation of telerehabilitation, the reviewers will form a table that includes the extracted data and source papers.
2. Three reviewers (MMH, AT, and ST) will independently identify themes from each paper. Themes are patterns across the included studies that are important to explain the implementation of telerehabilitation. Codes will then be refined based on discussions among the review team [59]. The same reviewers will meet regularly to discuss and challenge the themes.
3. Four reviewers (MMH, ST, AT, and MRR) will discuss and resolve differences, combine themes, and develop chains of inference (connections across papers linking the identified themes) through an iterative process [39]. The chains of inference will function as a basis for the ISCMO configurations,
4. Three reviewers (MMH, AT, and ST) will identify papers that contain the themes used to identify chains of inference.
5. Four reviewers (MMH, ST, AT, and MRR) will make connections among chains of inference, which will be an iterative process.
6. Four reviewers (MMH, ST, AT, and MRR) will use the chains of inference to generate ISCMO configurations confirmed by connecting back to the themes that emerged from the literature. The outcome of this step will be a comprehensive picture of implementation strategies, mechanisms, contexts, and outcomes chains [39,59]. The produced hypothesis will be used to create new program theories or refine them [39,59]. Then, we will provide a narrative based on the available evidence to support such a hypothesis.

Multimedia Appendix 3 contains outlines of the tables that will be used in each step.

Step 4: Narrative Development

A narrative synthesis will summarize the nature of the implementation strategy, context, mechanism, and outcome configurations, and the supportive evidence from the primary studies. One reviewer (MMH) will take the lead in coordinating the presentation of the narrative synthesis using text, summary tables, and a logic model. After developing the theoretical framework, one reviewer (MMH) will write the review for publication. The origins of the inferences, the hypothesis, the developed MRT, and the source of the primary evidence on which they are based will be documented and defended. The reasoning process used to create the chains of inference, the hypotheses, and the final MRT will be documented and reported to enhance transparency [59].

Ethics and Dissemination

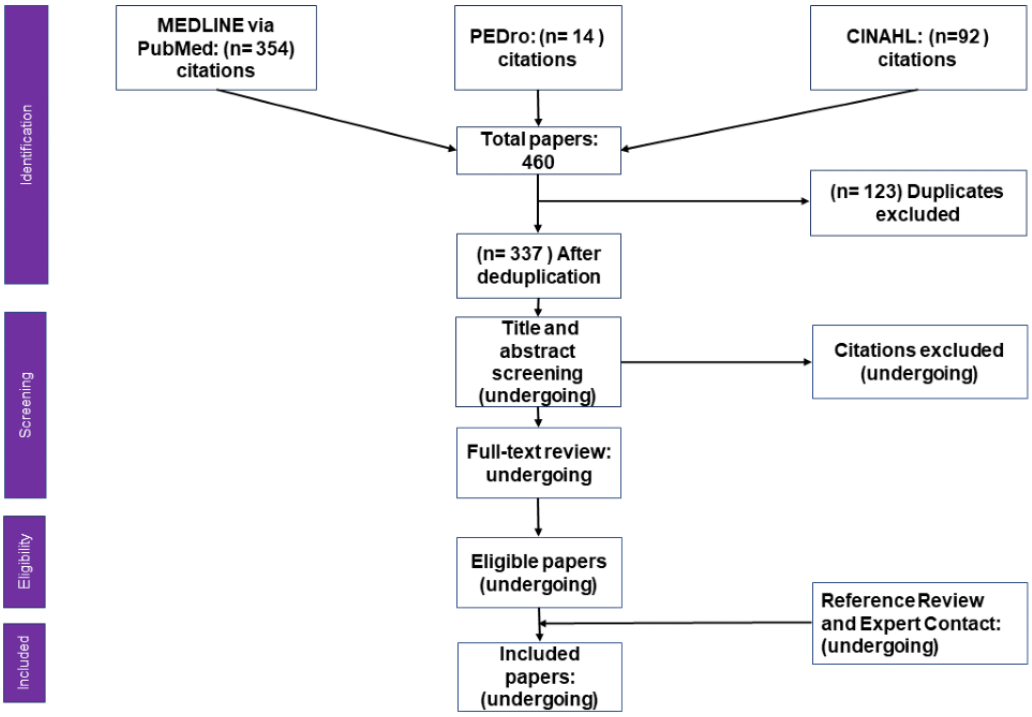
Ethics approval is not required for this study as it is secondary research, synthesizing evidence from primary studies. The review team will disseminate the findings through peer-reviewed publications and conference presentations.

Results

Literature search and screening will be completed by the end of July 2023 and will be recorded in a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart (Figure 2) [67]. A detailed search strategy is in Multimedia Appendix 4. Data collection will be based on the RES-IS model through forms that focus on the 4 domains (ie, properties of change agents, system change, technologies, and education interventions), their specific characteristics, and the impact of their interactions with the setting. Multimedia Appendix 1 gives more details on the planned data collection. The results of the review will be reported, following the RAMESES (Realist and Meta-Narrative Evidence Syntheses) standards (Multimedia Appendix 5) [36].

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Figure 2. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart.



Discussion

Telerehabilitation has the potential to bridge the access and timeliness gap of rehabilitation of patients with stroke. Yet, research on telerehabilitation implementation is still in its infancy. This review will enhance this field by developing a conceptual understanding of the interactions between different contexts and mechanisms of implementation. That will guide both implementation efforts at the practice level and future research at the academic level.

To our knowledge, this is the first realist review of the implementation of telerehabilitation for patients with stroke. A key strength of this review is that it will vet the causal mechanisms to explain how, why, and to what extent implementation strategies impact telerehabilitation implementation, a research gap not adequately explored. A further strength of the review is that it will examine the complex contexts in which various causal mechanisms are and are not activated. In addition, this review will inform future reviews by sharing our experience on using the recent NPT's coding manual [62].

Nonetheless, this review has some limitations. First, the evidence will be dependent on the availability and quality of relevant useful published data. This means that this review's findings and conclusions are limited to what have been published and it may restrict the ability to completely understand and describe the active causal mechanisms. To address this risk, the review team will use a comprehensive and iterative literature search that is expert-guided and source-diverse.

The potential impact of this review extends beyond academia and health care providers; policy makers stand to benefit from the insights gained as well. Delving into the causal mechanisms underpinning effective telerehabilitation implementation will yield essential information for designing experimental research studies that investigate how various strategies impact adoption, implementation, and sustainability. Armed with a deeper comprehension of these inner workings, decision makers can navigate adaptation efforts required for localizing policies pertaining to telerehabilitation implementation. This could lead to improved access and delivery of telerehabilitation services, ultimately resulting in better health outcomes for patients served by policy makers' initiatives.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Data extraction.
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Multimedia Appendix 2
Coding manual.

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[DOCX File , 16 KB - resprot_v12i1e47009_app2.docx]

Multimedia Appendix 3
Evidence synthesis steps.
[DOCX File , 14 KB - resprot_v12i1e47009_app3.docx]

Multimedia Appendix 4
Search strategies.
[DOCX File , 14 KB - resprot_v12i1e47009_app4.docx]

Multimedia Appendix 5
Reporting guidelines.
[DOCX File , 16 KB - resprot_v12i1e47009_app5.docx]

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Abbreviations

CLUSTER: Citations, Lead Authors, Unpublished Material, Scholar Searches, Theories, Early Examples, and Related Project

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CMO: Context, Mechanisms, and Outcomes
IPT: initial program theory
ISCMO: implementation strategy, context, mechanisms, and outcome
MRT: middle-range theory
NPT: Normalization Process Theory
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RAMESES: Realist and Meta-Narrative Evidence Syntheses
RES-IS: Realist Synthesis of Implementation Strategies
TAPUPAS: Transparency, Accuracy, Purposivity, Utility, Propriety, Accessibility, and Specificity
WoE: Weight of Evidence

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Protocol

Reasons for Ethnic Disparities in the Prehospital Care Pathway Following an Out-of-Hospital Cardiac Event: Protocol of a Systematic Review

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Abstract

Background: Substantial inequities in cardiovascular disease occur between and within countries, driving much of the current burden of global health inequities. Despite well-established treatment protocols and clinical interventions, the extent to which the prehospital care pathway for people who have experienced an out-of-hospital cardiac event (OHCE) varies by ethnicity and race is inconsistently documented. Timely access to care in this context is important for good outcomes. Therefore, identifying any barriers and enablers that influence timely prehospital care can inform equity-focused interventions.

Objective: This systematic review aims to answer the question: Among adults who experience an OHCE, to what extent and why might the care pathways in the community and outcomes differ for minoritized ethnic populations compared to nonminoritized populations? In addition, we will investigate the barriers and enablers that could influence variations in the access to care for minoritized ethnic populations.

Methods: This review will use Kaupapa Māori theory to underpin the process and analysis, thus prioritizing Indigenous knowledge and experiences. A comprehensive search of the CINAHL, Embase, MEDLINE (OVID), PubMed, Scopus, Google Scholar, and Cochrane Library databases will be done using Medical Subject Headings terms themed to the 3 domains of context, health condition, and setting. All identified articles will be managed using an Endnote library. To be included in the research, papers must be published in English; have adult study populations; have an acute, nontraumatic cardiac condition as the primary health condition of interest; and be in the prehospital setting. Studies must also include comparisons by ethnicity or race to be eligible. Those studies considered suitable for inclusion will be critically appraised by multiple authors using the Mixed Methods Appraisal Tool and CONSIDER (Consolidated Criteria for Strengthening the Reporting of Health Research Involving Indigenous Peoples) framework. Risk of bias will be assessed using the Graphic Appraisal Tool for Epidemiology. Disagreements on inclusion or exclusion will be settled by a discussion with all reviewers. Data extraction will be done independently by 2 authors and collated in a Microsoft Excel spreadsheet. The outcomes of interest will include (1) symptom recognition, (2) patient decision-making, (3) health care professional decision-making, (4) the provision of cardiopulmonary resuscitation, (5) access to automated external defibrillator, and (6) witnessed status. Data will be extracted and categorized under key domains. A narrative review of these

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domains will be conducted using Indigenous data sovereignty approaches as a guide. Findings will be reported according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 guidelines.

Results: Our research is in progress. We anticipate the systematic review will be completed and submitted for publication in October 2023.

Conclusions: The review findings will inform researchers and health care professionals on the experience of minoritized populations when accessing the OHCE care pathway.

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KEYWORDS

health equity; ethnicity; Indigenous peoples; out-of-hospital cardiac arrest; emergency responders; health care; patient care; cardiovascular; cardiology

Introduction

Cardiovascular diseases (CVDs) are the leading cause of mortality and morbidity globally [1,2]. However, the burden of disease is distributed inequitably between and within countries [3], contributing to the double burden of disease in low- and middle-income countries [4] and widening ethnic inequities in high-income countries [5-7]. Reducing the burden of CVDs will require a multipronged approach: reducing the exposure to the risk factors for disease as well as optimizing equitable access to existing treatment options [8,9].

Despite advances made in the treatment and prevention of CVDs, ethnic inequities remain. The widespread health inequities experienced by Indigenous populations and other ethnic groups in colonial nations [10,11] are driven by the differential exposure to the social determinants of health [12], racism [13-16], and the ongoing impacts of colonization [17,18]. As such, achieving health equity becomes an ethical imperative, underpinned by a fundamental right to health [19,20] and the understanding that some groups have experienced barriers to realizing these rights.

Addressing inequities in health requires a broad understanding of both the etiology and treatment of disease and the complex interplay between the social determinants of health. Further, the dominant attention on health behaviors and biological responses must be replaced by greater emphasis and critical appraisal of the root causes of inequitable health outcomes, particularly the effects of institutional racism and societal institutions [16] have on health outcomes. Lifting the research gaze further upstream provides the necessary information to inform interventions that will reduce ethnic health inequities. One area within the CVD care pathway that requires further exploration is access to prehospital care following an out-of-hospital cardiac event (OHCE).

The timeliness of care is crucial for positive outcomes. Every 30-minute delay to reperfusion (the restoration of blood flow to a damaged heart) following an ST-elevation myocardial infarction is associated with a 7.5% increased risk of death, and every 10-minute delay is associated with an additional 3.31 per 100 deaths [21]. The timeliness of care is even more important following a cardiac arrest, with the likelihood of survival increasing significantly if bystander cardiopulmonary resuscitation (CPR), defibrillation, or both is performed before emergency medical staff (EMS) arrive [22]. Within this field of research, differential access to care by ethnicity is well-documented [23], particularly following a cardiac arrest. However, no systematic review or attempt to map the care pathway has been undertaken for all nontraumatic, acute OHCEs.

This review will be undertaken as part of the Manawataki Fatu Fatu for Achieving Cardiovascular Care for Equity Studies (ACCESS) program [24], which has a specific focus on achieving equity for Māori and Pacific Islander peoples in Aotearoa, New Zealand. The initial scoping for this review identified that CVD inequities exist between ethnic groups in Aotearoa, New Zealand, with significantly higher CVD hospitalization and mortality rates among Māori (the Indigenous people of New Zealand) and Pacific Islander peoples compared with New Zealand European populations [25-27]. Poorer access to care for Māori and Pacific Islander peoples is likely to be an important contributor to these established inequities [28-30]. There is very little research about the experience of the care pathway for Māori and Pacific Islander peoples following an OHCE. What is known is that despite the higher burden of disease, Māori and Pacific Islander peoples experience delays to treatment [31] and barriers to CPR and defibrillation in the community [28,32]. Importantly, there appears to be limited (1) published literature in New Zealand and (2) opportunities to learn from the experiences of similar communities (ethnic minority groups) internationally. Therefore, a wider review, beyond New Zealand, was preferred.

The objective of this review is to identify the barriers and enablers to care for minoritized populations following an OHCE. The review also seeks to describe the OHCE care pathway that different ethnic groups experience, from the onset of symptoms until the receipt of care from a registered health professional. Within the review, prioritization will be given to research that illustrates the experience of the care pathway for Indigenous communities.

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Methods

Overview

A pragmatic approach to this systematic review [33] will be undertaken. The overall research question seeks to simplify a complex interaction of diverse populations, systems, and variables that operate in the prehospital cardiac care space. Within this context, the review seeks to determine the service and system-level variables that affect a patients' journey along the care pathway. For the purposes of this review, the working definition of OHCE will be broad and includes (but is not limited to) cardiac arrest, myocardial infarction, arrhythmia, and chest pain.

Objectives

This systematic review aims to answer the question:

> *Among adults who experience an OHCE, to what extent and why might the care pathways in the community differ for minoritized populations compared with nonminoritized populations?*

The systematic review also aims to:

- Identify the barriers and enablers that could influence variations in the access to care for minoritized ethnic populations
- Describe what the care pathway in the community looks like for minoritized ethnic populations after an acute cardiac event compared to nonminoritized populations

Search Strategy

The search strategy, developed in consultation with a specialist librarian, will use a number of medical literature databases and search engines to identify literature for review. The sources include:

- CINAHL
- Embase
- MEDLINE (OVID)
- PubMed
- Scopus
- Google Scholar
- Cochrane Library

Different combinations of Medical Subject Headings (MeSH) terms and keywords related to ethnicity and race, equity, and CVD will be used. During the initial scoping for this review, a very limited number of articles related to the out-of-hospital care pathway in New Zealand were identified. The research question and therefore the search terms for the population of interest were broadened to include other minoritized ethnic communities globally. Although the scope of the review was expanded, the review will be underpinned by Kaupapa Māori research, which seeks to validate Māori experiences in the context of a colonized society [34]. Therefore, the MeSH terms for Māori and Pacific Islander peoples were added as specific search terms in recognition of this. The MeSH terms for Indigenous peoples have been included to capture research specific to other Indigenous or First Nations populations.

As relevant articles are identified, the reference lists will be checked for additional studies and reviews. The search will include articles relating to original research that are published in English with no exclusions due to research design or country setting. The date of publication will be limited to between January 1, 2000, and January 1, 2023. Textbox 1 outlines the search terms that will be used.

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Textbox 1. Search terms.

Setting

- Prehospital
- First responder
- Ambulance
- Out of hospital
- Emergency medical
- Transportation of patients
- Emergency medical service
- Rescue
- Paramedic
- Emergency medical technician
- Community

Health condition

- Cardiac
- Coronary
- Cardiovascular
- Heart attack
- Arrest
- Myocardial infarction
- ST-elevation myocardial infarction (STEMI)
- Non-STEMI (NSTEMI)
- Chest pain
- Arrhythmia
- Ischemia
- Angina
- Acute coronary syndrome

Context

- Ethnicity
- Race
- Culture
- Indigenous peoples
- Disparity
- Inequity
- Inequality
- Equity
- Māori peoples
- Pacific Islander peoples

Inclusion and Exclusion Criteria

Textbox 2 outlines the inclusion and exclusion criteria that will be used.

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Textbox 2. Inclusion and exclusion criteria.

Inclusion criteria

- Outcomes are relevant to the research question
- Publication language: English
- Study population aged >18 years
- Cardiac event is nontraumatic
- Human subjects
- Based in prehospital settings
- All study types

Exclusion criteria

- Conference proceedings
- No English translation available
- No full text available
- Study population aged <18 years
- Cardiac event is a result of trauma

Types of Studies and Settings

All peer-reviewed, original research studies will be considered for inclusion. The "community" setting will include all settings in the prehospital phase, up to arrival at a hospital or emergency medical center. There will be no restriction by country.

Population

The population is broadly defined as all adults, aged 18 years and older, from minoritized ethnic communities who experience an acute, nontraumatic cardiac event outside of a hospital. The term "minoritized" is purposely chosen to reflect communities whose "collective cultural, economic, political, and social power has been eroded" [35]. The reference group is nonminoritized ethnic populations.

All types of acute cardiac events with a nontraumatic etiology will be considered, including but not limited to cardiac arrest, chest pain, arrhythmia, and myocardial infarction.

Outcomes

Any type of outcome measures will be included where ethnic and racial specific comparisons within a country are conducted. Analyses may include stratified analyses, the investigation of interactions or effect modification, and comparisons using qualitative data. Outcome measures from multicountry studies will be included if the ethnic groups analyzed are comparable. The primary outcomes will include the analysis of any factors that affect the pathways of care (time, journey, and the process taken to care) and barriers and enablers to prehospital care. This will include outcomes related to comorbidities, health education, symptom recognition, patient and EMS decision-making, care-seeking processes, access to CPR and automated external defibrillator, or informal care received before EMS contact. The secondary outcomes will be any gender analysis by ethnicity and race.

Critical Appraisal

The first author will undertake the literature search. Identified studies will be collated and managed in an EndNote library created for this review once the studies have been imported to the library. Duplicate entries will be removed before stage 1 of the critical appraisal process. During the initial review process, 2 authors will screen the title and abstract of each article to ensure that papers meet the inclusion criteria.

At stage 2 of the critical appraisal, the full text will be obtained for all articles, and every study will be evaluated by at least 2 authors using the Mixed Methods Appraisal Tool (MMAT) [36]. The MMAT provides a standardized table of quality assessment criteria that can be used for qualitative and quantitative research designs. All studies with Indigenous populations will also be reviewed using the CONSIDER (Consolidated Criteria for Strengthening the Reporting of Health Research Involving Indigenous Peoples) statement [37]. The CONSIDER statement provides a checklist that serves to strengthen Indigenous health outcomes by improving research practice and reporting. Study authors will be contacted to clarify results, resolve any uncertainties, and obtain additional information if needed. Risk of bias will be undertaken using the Graphic Appraisal Tool for Epidemiological studies. Assessment will be done at both study and outcome levels. Articles for inclusion will be identified by all review authors. The included reference lists for included articles will be scanned to identify further articles that may be eligible for inclusion. Articles identified at this stage will also be appraised using the MMAT and CONSIDER statement where appropriate. During the critical appraisal, any disagreement about the inclusion or exclusion of a paper will be resolved by discussion with all review authors.

Data Extraction

Data for extraction will include general study information, study characteristics, participant characteristics, and study results

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measured on outcomes identified in this protocol. Appraisals and data extraction will be independently extracted by the authors and recorded in a form. A standardized data extraction form will be used, which will be piloted and refined to ensure that there is consistency between the multiple reviewers. Once finalized, the completed form will populate a Microsoft Excel spreadsheet that will be used for data analysis.

Each eligible study will have data extracted under 4 domains (Textbox 3).

Textbox 3. Extracted domains.

General study information

- Author
- Article title
- Year
- Country

Study characteristics

- Aims and objectives
- Study design and type
- Inclusion and exclusion criteria
- Recruitment procedures

Participant characteristics

- Sample size
- Ethnicity and race
- Number of male and female participants

Study results (outcomes)

- Primary outcomes
  - Variables in the care pathway from symptom onset to arrival at a hospital, including but not limited to:
    1. Time, journey, access to cardiopulmonary resuscitation or automated external defibrillator, witnessed by bystander or emergency medical staff (EMS), and informal care before EMS contact
    2. Health outcomes (comorbidities and survival)
    3. Barriers and enablers (health education; decision-making by EMS, patient, or witness; symptom recognition; and care-seeking processes)
- Secondary outcomes
  - Any gender analysis by ethnicity and race

Synthesis of Included Studies

The synthesis of the data will be underpinned by an Indigenous data sovereignty approach that requires researchers to critique how data about Indigenous peoples are collected, used, and analyzed [38,39]. A convergent integrated approach to the data synthesis [40] will be undertaken, whereby quantitative findings will be "qualitized" before conversion to narratives.

It is unlikely that this review will obtain sufficient data that are similar enough to conduct a meta-analysis. It is therefore expected that the authors will conduct a narrative synthesis of the data.

Reporting

The review findings will be reported according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [41]. The PRISMA 2020 flow diagram will be used to guide the recording of the number of articles identified, screened, included, and excluded.

Patient and Public Involvement

This is a protocol for a systematic review; therefore, no patients or public will be involved. However, the proposal and approach were informed by discussion with service providers in the prehospital sector in New Zealand. Patient consent for publication is not required.

Ethical Considerations

Ethics approval is not required for this systematic review as it is reviewing already anonymized, published data.

Results

Our research is in progress. We anticipate the systematic review will be completed and submitted for publication in October

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2023. The findings of this review will be disseminated via a publication in a peer-reviewed journal as well as conference presentations and stakeholder meetings.

Discussion

Expected Findings

This paper presents a methodological description of a systematic review process that seeks to inform equity-based intervention and practice. CVD is the leading cause of mortality and morbidity globally. The rates of CVD-related morbidity and mortality have increased, particularly in low- to middle-income countries, [42]. Although population aging contributes to increasing CVD rates globally, barriers to accessing care widens the gap between countries [43] and within countries. For Indigenous and other minoritized ethnic peoples experiencing inequities, identifying the barriers to accessing care is vital for creating culturally grounded interventions that reduce the health inequities they experience [44,45]. This review will contribute to the existing body of knowledge by identifying the factors that improve access to care for different ethnic groups following an OHCE. By integrating an Indigenous quality appraisal tool and research methodology, the review will provide evidence with a uniquely positioned equity lens. It is intended that this will provide insight into areas where interventions can be targeted to increase access to care for ethnic groups in New Zealand and globally. The resulting systematic review will present an unbiased and detailed summary of the current evidence available about the experiences of minoritized populations accessing care following an OHCE compared with nonminoritized populations. The results of this review will inform researchers and emergency service providers on variables related to equity-centered service provision and intervention in the community setting.

Strengths and Limitations

The strengths of the resulting systematic review include the following:

- This systematic review of factors that facilitate access to care will be based upon a detailed search strategy that includes all study types from any country.
- The review will use a robust reporting tool and a validated quality appraisal checklist for critical appraisal of the literature.
- A social justice and equity lens will be applied to the selection and analysis of identified research.

The limitations of the resulting systematic review include the following:

- By restricting to the English language, this research is limited in its ability to identify articles relevant to other Indigenous people that are published in another language.
- By excluding gray literature, we will not capture the prehospital care reporting mechanisms that are often published as technical reports, for example.
- There is also the risk of publication bias where studies with nonsignificant findings may not be published and therefore will not be captured in our review.

Conclusion

This systematic review protocol illustrates the transparency of the research and provides a process for conducting a similar review.

Acknowledgments

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Data Availability

The data sets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' Contributions

RN developed the protocol and wrote the manuscript. MH, CG, BD, and SA critically reviewed and edited the manuscript. All authors contributed to the final review.

Conflicts of Interest

None declared.

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Abbreviations

ACCESS: Achieving Cardiovascular Care for Equity Studies

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CONSIDER: Consolidated Criteria for Strengthening the Reporting of Health Research Involving Indigenous Peoples
CPR: cardiopulmonary resuscitation
CVD: cardiovascular disease
EMS: emergency medical staff
MeSH: Medical Subject Headings
MMAT: Mixed Methods Appraisal Tool
OHCE: out-of-hospital cardiac event
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

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Protocol

Mediators and Moderators in the Co-Occurring Anxiety and Alcohol Use Relationship: Protocol for a Systematic Review and Meta-Analysis

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Abstract

Background: Anxiety and alcohol use commonly co-occur. Previous research has demonstrated the bidirectional and mutually reinforcing nature of this relationship, with an increasing body of research investigating the mediating and moderating mechanisms driving this association. Within the existing mediation and moderation research, however, there have been contrasting findings and, at times, null results among some population groups.

Objective: This protocol outlines a systematic review and meta-analysis aiming to synthesize and clarify mediators and moderators in the anxiety-alcohol and alcohol-anxiety relationships.

Methods: Systematic searches will be conducted in the electronic databases Medline, PsycINFO, Embase, Cochrane Central Register of Controlled Trials, Scopus, and Web of Science to identify studies that investigated mediators and moderators of the relationship between anxiety and alcohol use, including clinical and subclinical levels. Studies that look at the relationship between anxiety and alcohol use outcomes, as well as alcohol use and anxiety outcomes, will be included in order to capture an in-depth understanding of the mechanisms driving the association in either direction. No limits will be placed on study year or study language. Included study designs will be observational studies, including cohort, cross-sectional, and longitudinal studies, and secondary analyses of randomized controlled trials reporting quantitative results. Selected studies will also have their reference lists hand-searched for other relevant papers. Study quality will be assessed with the Joanna Briggs Institute Checklists for Analytical Cross-Sectional Studies and Cohort Studies. Mediators and moderators will be narratively synthesized in line with the biopsychosocial framework, where results will be grouped into biological, psychological, and social or environmental factors. If the data are sufficiently homogeneous, a meta-analysis will be conducted with mediation and moderation analyses synthesized separately. The Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) framework will also be used to assess the strength of cumulative evidence.

Results: Electronic database searches were conducted in September 2022. After duplicates were removed, a total of 7330 titles and abstracts were screened. Full-text reviewing is currently under way, with the results expected to be available by the end of 2023.

Conclusions: Given the significant individual and societal impacts of co-occurring anxiety and alcohol use, this review will help clarify mechanisms linking these two concerns. Identified mechanisms, where possible, can then be targeted in prevention, early intervention, and treatment approaches to improve the outcomes for individuals experiencing co-occurring anxiety and alcohol use.

Trial Registration: PROSPERO CRD42023358402; https://tinyurl.com/2m2e3enp

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KEYWORDS

alcohol use; alcohol; anxiety; comorbidity; drinking; electronic databases; mediator; meta-analysis; moderator; prevention; systematic review

Introduction

Globally, anxiety disorders are the most common psychiatric disorders, with an estimated 301 million individuals experiencing one or more anxiety disorders in their lifetime [1]. Alcohol use is also highly prevalent, with an estimated 32.5% of people aged 15 years or older globally being current drinkers [2]. Among drinkers, high rates of risky drinking and alcohol use disorders are seen. A large nationally representative survey of 36,309 adults in the United States found 12.9% of individuals drink at high-risk levels, defined as 4+ standard drinks for women and 5+ standard drinks for men, at least weekly [3]. Additionally, among those who drink, 17.5% experienced an alcohol use disorder in the past year [3]. Comorbidity between mental health and substance use concerns is common, most notably between anxiety and alcohol use. Indeed, among individuals with an anxiety disorder, it is estimated that 20%-40% will also experience an alcohol use disorder in their lifetime [4]. When anxiety and alcohol use co-occur, symptom severity can be worse, and treatment adherence and outcomes are typically poorer compared to individuals with an anxiety or alcohol disorder alone [5,6].

Several theories have been proposed to explain the comorbid, bidirectional relationship between anxiety and alcohol use. Arguably, the most common is the self-medication model [7,8] which suggests individuals drink alcohol to alleviate symptoms of anxiety or general negative affect, in turn leading to a reliance on alcohol over time and the development of a subsequent alcohol use disorder. The use of alcohol for self-medication also aligns with other theories, including the tension-reduction theory [9] and the stress response dampening model [10]. Conversely, there is the opposite causal explanation that alcohol misuse and alcohol use disorders promote anxiety disorders, known as the substance-induced anxiety model or kindling or stress hypothesis [6,11,12]. Following prolonged periods of heavy alcohol consumption, withdrawal or cessation can lead to adaptations in the brain and wider nervous system, which can induce or worsen anxiety [6,11]. In addition to evidence of causal, bidirectional pathways between anxiety and alcohol, there is also support for a mutual-maintenance model also referred to as the "vicious cycle of comorbidity" [13]. This model demonstrates how the biopsychosocial outcomes of one disorder (eg, anxiety) will often serve to maintain or exacerbate the other disorder (eg, alcohol use disorder). An example of such a relationship can be seen when an individual with social anxiety who is self-medicating with alcohol develops a reliance on alcohol and over time experiences alcohol-related consequences like decreased productivity, interpersonal issues, and anxiety-induced withdrawal. These consequences exacerbate the initial anxiety and result in further drinking, thus maintaining the problematic feed-forward cycle [6,13]. Together, these theoretical frameworks suggest a complex bidirectional relationship between anxiety and alcohol use, with longitudinal and prospective studies confirming that experiencing an anxiety disorder or an alcohol use disorder can increase the risk of developing the other [14,15].

Previous critical and systematic reviews have established a strong body of evidence for a relationship between anxiety and alcohol use [12,16]. These reviews have typically focused on the temporal sequencing of the anxiety-alcohol relationship [16,17]; comorbidity between a specific anxiety disorder, for example, social anxiety disorder, and alcohol use [5,18-21]; the treatment of comorbid anxiety and alcohol use disorders [22-25]; or all of the above [12,26]. Yet, despite substantial existing research, the specific mechanisms driving anxiety and alcohol comorbidity are still poorly understood. The proposed systematic review will be the first to synthesize and clarify the specific mediators and moderators driving the relationship between anxiety and alcohol use.

Given the bidirectional nature of comorbid anxiety and alcohol use, the planned review will investigate the relationship in both directions. Figures 1 and 2 are path diagrams visually demonstrating the relationships that will be examined. Figure 1 illustrates anxiety as the exposure/predictor variable (X) and alcohol use as the outcome variable (Y), while Figure 2 illustrates the relationship in the opposite direction, where alcohol use is the exposure/predictor (X) and anxiety is the outcome (Y). As illustrated in Figures 1 and 2, a mediator or moderator is a third variable that affects the relationship between the exposure and outcome of interest [27]. Investigating mediators is warranted to better understand causal mechanisms that account for a relationship between X and Y [28]. In short, by identifying mediators, the proposed review will highlight factors explaining *how* or *why* the association between anxiety and alcohol, or alcohol and anxiety, occurs. If modifiable, these mediators can then be targeted in prevention, early intervention, and treatment approaches. To get a complete understanding of the anxiety and alcohol relationship, investigating the role of moderating variables is also necessary. The synthesis of moderators will highlight factors that affect the direction or strength of the relationship between X and Y [27]. As such, moderators can help understand *when* the relationship between anxiety and alcohol or alcohol and anxiety will occur. Given the breadth of possible mediating and moderating mechanisms studies can investigate, the review may identify mechanisms that can act as both a mediator and a moderator in the anxiety-alcohol relationship. An example of such a factor is positive alcohol use expectancies, with previous research identifying it as both a mediator and moderator in the relationships of interest [29-31].

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Figure 1. Diagram demonstrating the possible mediator (Me) and moderator (Mo) pathways between the exposure variable anxiety (X) and outcome variable alcohol (Y).

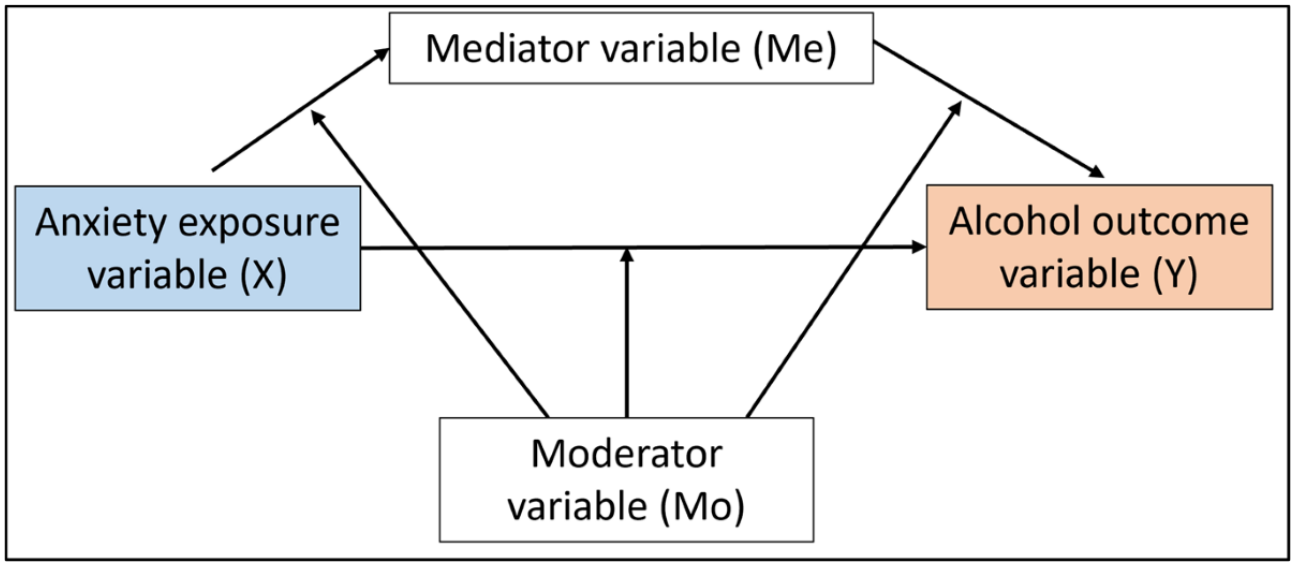
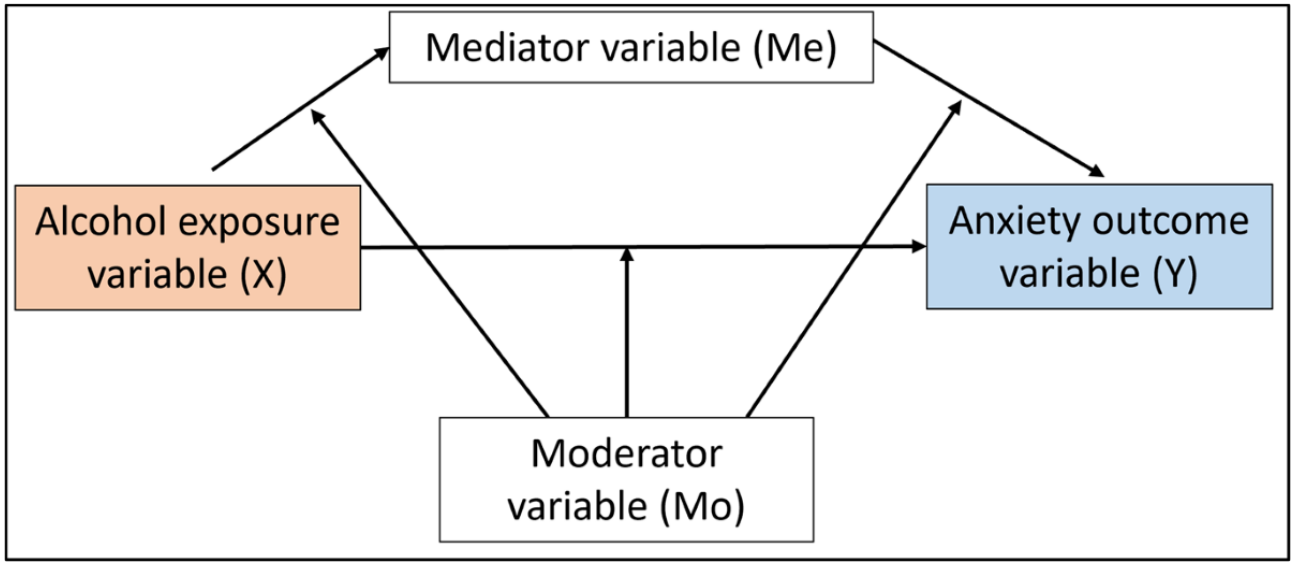


Figure 2. Diagram demonstrating the possible mediator (Me) and moderator (Mo) pathways between the exposure variable alcohol (X) and outcome variable anxiety (Y).



To our knowledge, this will be the first study to systematically identify and synthesize research on mediators and moderators of the comorbid anxiety and alcohol relationship. The outcomes of the review will specifically answer the following questions:

- What mediates the relationship between anxiety and alcohol use?
- What moderates the relationship between anxiety and alcohol use?

Methods

Guidelines and Registration

This protocol was written in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guidelines [32]. The systematic review has been registered in PROSPERO, the International Prospective Register of Systematic Reviews (CRD42023358402).

Eligibility Criteria

Guided by the population, exposure, outcome (PEO) framework for conducting systematic reviews of association (etiology) [33], the below criteria will be used to determine eligible studies and structure the search strategy.

Population

All human populations are of interest for the proposed systematic review, and as such, no limits will be placed on the study population or participant type. Animal studies will be excluded.

Exposure and Outcome

Given the bidirectional nature of anxiety and alcohol comorbidity, the proposed systematic review will include studies investigating these concerns in either direction. Therefore, studies where anxiety is the exposure and alcohol use is the outcome, as well as studies where alcohol use is the exposure and anxiety is the outcome, will be included.

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A broad classification will be used to define the anxiety exposure and outcome in this review. Anxiety will be conceptualized in line with the Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition (DSM-5), where anxiety disorders are differentiated from obsessive compulsive and related disorders, and trauma and related-stressor disorders [34]. Per the DSM-5, anxiety disorders include generalized anxiety, social anxiety (social phobia), separation anxiety, selective mutism, specific phobia, agoraphobia, and panic disorder. Both studies that assess disorder-level measures or subclinical symptom measures will be included in the review. In addition to these definitions of anxiety, studies reporting broad symptoms of anxiety or anxious traits, such as anxiety sensitivity (eg, Anxiety Sensitivity Index-3), will also be included.

Like anxiety, a broad classification will be used to define the alcohol use exposure or outcome. This review is interested in the full spectrum of alcohol use and related difficulties and will include, but is not limited to, studies reporting frequency or quantity of alcohol consumption; hazardous, binge, or risky drinking; and alcohol use disorders.

Only studies where both the exposure and outcome are measured in the same individual will be included in this review. Studies looking at mediators or moderators between parents and offspring will be excluded.

Study Characteristics

Observational studies including cohort, cross-sectional, and longitudinal studies, and secondary analyses of randomized controlled trials reporting quantitative results will be included. Studies only evaluating intervention or treatment outcomes, including mediators or moderators of an intervention, will be excluded. Additionally, studies only reporting prevalence data will be excluded. Studies must be published in a peer-reviewed journal, with reviews, meta-analyses, and information in books, reports, letters, or conference abstracts being excluded from this systematic review. No limits will be placed on publication year or study language.

Information Sources and Search Strategy

Searches will be conducted in the electronic databases Medline (Ovid), PsycINFO (Ovid), Embase (Ovid), Cochrane Central Register of Controlled Trials (Ovid), Scopus, and Web of Science. Search strategies will be tailored to each database and use a combination of keywords and subject headings or medical subject headings (MeSH) where appropriate. A total of 3 overarching themes of anxiety, alcohol, and mediator or moderator will be used to structure the search, with search terms combined using the Boolean operators “AND” and “OR.” No year or language limits will be imposed on any of the searches. The reference lists of eligible studies will also be hand-searched to find additional studies not picked up in the electronic database searches. Full search strategies for each database are presented in Multimedia Appendix 1.

Study Selection and Extraction

All identified studies will be imported into the web-based systematic review software Covidence [35], where duplicates will automatically be removed. All titles and abstracts will be screened by a primary reviewer, with a random sample of 50% screened independently by a second reviewer. The full text of potentially eligible studies, identified through screening, will then be reviewed and assessed against the eligibility criteria by both reviewers. Disagreement between reviewers at both stages will be resolved through consultation, and if required, a third reviewer. Cohen κ will be calculated at the screening and full-text stage to determine the interrater agreement between reviewers, with a κ statistic of 0.8 considered a strong level of agreement [36]. The results of the screening and study selection process will be summarized with a PRISMA flow diagram in the final systematic review.

Data will be independently extracted by a primary reviewer using a data extraction spreadsheet in Excel (Microsoft Corp). A second reviewer will check and confirm all extracted data, with any disagreements reconciled through discussion. The following information will be extracted, and, if needed, the corresponding authors of included studies will be contacted for missing information:

- Publication details, including study authors and publication year
- Study characteristics, including study design, location, and sample size
- Sample population characteristics; for example, age, sex, ethnicity, socioeconomic status, and education
- Characteristics of anxiety exposure or outcome; for example, type of anxiety or anxiety disorder (if applicable), measure to assess anxiety, and age of onset
- Characteristics of alcohol use exposure or outcome; for example, frequency or quantity of use, age of initiation, hazardous or binge drinking, and alcohol use disorder
- Relevant information on the mediators and moderators examined, including the statistical analysis approach used; for example, mediator or moderator classification, assessment of mediator or moderator, single or multiple mediators or moderators assessed, whether confounders were controlled for, and overall strength of effect

Risk of Bias

Studies deemed eligible for inclusion in the systematic review will have their quality and risk of bias assessed independently by 2 reviewers. Disagreements between reviewers will be resolved through discussion and consultation with a third reviewer if required. Appraisal will be done using the Joanna Briggs Institute Critical Appraisal Tools [37]. Both the Checklist for Analytical Cross-Sectional Studies and the Checklist for Cohort Studies will be used to accommodate the different research designs of the included studies. These checklists evaluate the study sample, measurement of exposure and outcome variables, confounding, appropriateness of statistical analysis, and follow-up reporting (cohort checklist only) across 11 questions in the cohort studies checklist and 8 questions in the cross-sectional studies checklist.

Data Synthesis

Overview

A narrative synthesis of individual mediators and moderators from the included studies will be performed, with results

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grouped in line with the biopsychosocial model [38]. This model encompasses biological factors like sex and age, psychological factors including cognitive and behavioral facets, and social factors, which encompass an individual's broader environment and the society in which they live. Furthermore, it is likely the relationships between anxiety and alcohol use will change between different groups; therefore, subgroup synthesis is planned for age subgroups (as defined by the World Health Organization), anxiety subgroups (as defined by the DSM-5), alcohol use sub groups broken down by severity (eg, mild, moderate, severe alcohol use disorder), and lastly, population types (eg, college students, veterans, specific cultural groups, etc). The inclusion of these subgroups will be reliant on data within the included studies, and if other key groupings emerge, further sub-group analyses may be conducted. Other information extracted, including publication details, study characteristics, sample population characteristics, and exposure and outcome characteristics, will also be narratively synthesized.

Given the broad inclusion criteria, it is anticipated that there will be high heterogeneity across studies. However, if the available data within the included studies is sufficiently homogenous, a meta-analysis will be conducted, with mediation and moderation analyses synthesized separately. Studies with comparable exposure and outcome measures and comparable mediator and moderator variables will be included in the meta-analysis. The indirect effects of mediation models will be synthesized using the methods defined in Cheung [39]. The synthesis of moderating variables will be dependent on the statistical analysis within individual studies but will include pooled estimates of coefficients.

Confidence in Cumulative Evidence

The cumulative strength of evidence from included studies will be assessed using the GRADE framework [40]. This framework enables a conclusion to be drawn on whether there is high, moderate, low, or very low confidence in the findings.

Results

This systematic review is currently underway. In September 2022, initial database searches identified 7330 unique studies for title and abstract screening. It is anticipated that the review, including data extraction and synthesis, will be completed by December 2023. Upon completion, results will be reported in line with PRISMA and disseminated in a peer-reviewed journal. Before submission, searches will be rerun to capture any additional articles that have been published since the initial database searches.

Discussion

This paper summarizes the protocol for a systematic review and prospective meta-analysis on mediators and moderators in the co-occurring anxiety and alcohol relationship. The review will incorporate studies from a wide spectrum of anxiety and alcohol classifications, including from anxiety symptoms to anxiety disorders and from alcohol use to alcohol use disorders. The biopsychosocial model will be used to synthesize identified factors to determine the distinct roles of biological, psychological, and social mechanisms.

Existing studies often examine a single mediator or moderator, despite evidence of multiple mechanisms contributing to the alcohol and anxiety relationship [12]. In light of this, this review will be the first to consolidate the literature to date on mediators and moderators driving this common comorbidity. Identified mediators and moderators can then be used as targets to develop and refine prevention, early intervention, and treatment approaches for comorbid anxiety and alcohol use concerns. In some cases, the identified mediating and moderating factors may not be modifiable in interventions; nonetheless, synthesizing this evidence will help advance the theoretical basis underlying this common comorbidity. As this review will focus on both the pathway from anxiety to alcohol use and the pathway from alcohol use to anxiety, findings may suggest different prevention and intervention approaches are needed depending on the temporal sequencing of the two disorders. One limitation, however, of the planned review is the inclusion of cohort and cross-sectional studies, which will limit the ability to draw causal conclusions for all results. The inclusion of these study designs is warranted nonetheless, as preliminary searches indicated most mediation and moderation studies for anxiety and alcohol were not longitudinal.

The findings of this review will offer critical insights into the conceptualization of comorbid anxiety and alcohol use, providing a foundation for researchers, clinicians, and policy makers to enhance outcomes in addressing this complex clinical manifestation. These results have the potential to drive advancements in understanding, prevention, and treatment strategies, thereby positively impacting individuals experiencing anxiety and alcohol use concerns.

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Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during this study.

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Authors' Contributions

All authors (TG, KP, NCN, and LAS) conceived the initial idea for the systematic review. TG drafted the manuscript, and KP, NCN, and LAS provided critical insights. All authors contributed to the revision of the manuscript and approved the final version.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Electronic database searches.
[DOCX File , 24 KB - resprot_v12i1e48875_app1.docx]

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Abbreviations

DSM-5: Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition
GRADE: Grading of Recommendations, Assessment, Development, and Evaluations
MeSH: medical subject headings
PEO: population, exposure, outcome
PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols

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Protocol

Wearable Devices and Nurses' Health: Protocol for an Integrative Review

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Abstract

Background: Nurses comprise over half of the global health care workforce, and the nursing care they provide is critical for the global population's health. High patient volumes and increased medical complexity have increased the workload and stress of nurses. As a result, the health of nurses is often negatively impacted. Wearables are used within the health care setting to assess patient outcomes; however, efforts to synthesize the use of wearable devices focusing on nurses' health are limited.

Objective: The primary objective of our integrative review is to synthesize available data concerning the utility of wearable devices for evaluating or improving (or both) the health of nurses.

Methods: We are conducting an integrative review synthesizing data specific to wearable devices and nurses' health. The research question for this review aims to answer how wearable devices are used to evaluate health outcomes among nurses. We searched the following electronic databases from inception until July 2022: PubMed, Embase, CINAHL, Web of Science, IEEE Explore, and AS&T. Titles and abstracts were imported into Covidence software, where citations were screened and duplicates removed. Title and abstract screening has been completed; however, full-text screening has not been started. Further screening is being conducted independently and in duplicate by 2 teams of 2 reviewers each. These reviewers will extract data independently.

Results: Search strategies have been developed, and data were extracted from 6 databases. After the removal of duplicates, we collected 8603 studies for title and abstract screening. Two independent reviewers conducted the title and abstract review, and after resolving conflicts, 277 full-text articles are available for review to determine whether they meet the inclusion criteria.

Conclusions: This integrative review will provide synthesized data to inform nurses and other stakeholders about the extent of wearable device–related work done with nurses and provide direction for future research.

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KEYWORDS

nurse; wearable; wearable device; mHealth; mobile health; health technology adoption and use; health outcome; adoption; usage; health technology; digital health; integrative review; literature review

Introduction

Globally, nurses constitute the largest body of regulated health care professionals and account for the greatest proportion of direct patient care hours [1-3]. Patient volumes and medical complexity have increased due to organizational factors (eg, understaffing) and population aging, increasing the workload and stress of nurses—these are 2 factors known to negatively

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influence their overall health, quality of life, and job satisfaction [4-6]. In addition, the physical and psychosocial demands of nursing have resulted in many nurses leaving direct patient care or the profession, increasing the burden of care on an already strained profession [7-9]. The negative consequences on nursing staff are reported to have a spillover effect on patient outcomes, and high-stress environments are known to negatively influence the quality of care by nurses [4,10].

The use of wearable devices is growing among the general public [11]. Wearable devices are small electronic devices that are noninvasive and are attached to a piece of clothing that a person is wearing, worn as a device anchored directly to the body, or attached directly to the skin, and have embedded sensors with wireless mobility (eg, Fitbit tracker and Apple Watch) [12-14]. There is growing interest in the use of wearables in the health care setting to provide data for monitoring and to improve the delivery of care for patients in both outpatient and inpatient settings [15-18].

Another potential application of wearable devices in the health care setting is with the staff providing patient care, including the nursing staff. Some nursing staff are already using wearable devices for personal or work-related reasons, such as physical activity monitoring [19], highlighting the feasibility of collecting wearable data and assessing its utility in informing decision-making about nurses' health. However, efforts to synthesize wearable devices that focus on nurses' health are limited, with previous reviews focused heavily on sleep health [20,21] or those not specific to nursing [22]. Given the increasing popularity of wearables, coupled with the health challenges that nurses are currently facing, conducting a rigorous review of how wearables are being used to assess the health of nurses would provide evidence-based knowledge to inform how to move forward with the use of wearables to address the health of nurses.

Therefore, the primary objective of our integrative review is to synthesize available data concerning the utility of wearable devices for evaluating or improving (or both) the health of nurses. Specifically, we seek to evaluate the frequency of their use and the associations between wearable devices and health outcomes (physical or psychosocial) among nurses. We hypothesize that the current body of literature is suitable for synthesis, though outcomes and devices are heterogeneous.

Methods

Overview

We aim to conduct an integrative review synthesizing all data specific to wearable devices and the health of nurses. We used the PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols) checklist to guide the reporting of this protocol [23]. For the final manuscript, we will use the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines to guide the reporting of the review [24].

Research Question

The research question for this review aims to determine how wearable devices are used to evaluate health outcomes among nurses. A PICO (population, intervention, control, and outcomes) format was used to guide this study [25], with the population being nurses, the intervention being wearable devices, the control being usual care, and the outcomes being health outcomes (including physical and psychosocial).

Data Sources and Search Strategy

We searched the following electronic databases from inception until July 2022: PubMed, Embase, CINAHL, Web of Science, IEEE Explore, and AS&T. We consulted an academic-affiliated librarian for the literature search. In addition, we will conduct citation tracking for all eligible studies to highlight articles potentially missed by our search strategy. Textbox 1 displays the specific search and MeSH terms used to identify articles during the search with 2 of the databases. Outcome terms were not included in the search strategy to ensure the search was as inclusive as possible, given the exploratory nature of this review.

Textbox 1. Search Strategy for PubMed and CINAHL.

PubMed:

(wearable* OR “wearable technology” OR “wearable technologies” OR “wearable device” OR “wearable devices” OR “Wearable Electronic Devices”[MeSH] OR “wearable electronic device” OR “wearable electronic devices” OR “Fitness Trackers”[MeSH] OR fitbit* OR smartwatch* OR “apple watch” OR garmin OR actigraph* OR “Actigraphy”[MeSH] OR (“eye-based” AND wearable) OR PolarH10 OR “wearable sensor” OR “wearable sensors” OR (posture AND monitor*) OR (wearable AND monitor*) OR “Wearable Electronic Devices”[MeSH] OR “activity tracker” OR “activity trackers” OR “fitness tracker” OR “fitness trackers” OR “google glass” OR “Smart Glasses”[MeSH] OR “smart glasses” OR smartglass* OR (stress AND wearable*) OR (“blood pressure” AND wearable) OR (sweat AND wearable*) OR (stress AND monitor*) OR (“blood pressure” AND monitor*) OR (sweat AND monitor*) OR (“blood pressure” AND sensor*) OR (sweat AND sensor) OR (stress AND sensor)) AND (Nurse* OR “Nurses”[MeSH])

CINAHL:

(wearable* OR “wearable technolog*” OR “wearable device*” OR fitbit* OR “apple watch” OR garmin OR actigraph* OR smartwatch* OR (“eye-based” AND wearable) OR PolarH10 OR “wearable sensor” OR “wearable sensor*” OR (posture AND monitor*) OR “wearable electronic device*” OR (wearable AND monitor*) OR activity tracker*” OR “fitness tracker*” OR “google glass” OR “smart glass*” OR smartglass* OR (MH “Fitness Trackers”) OR (MH “Wearable Sensors”) OR (MH “Actigraphy”) OR (stress AND wearable*) OR (“blood pressure” AND wearable*) OR (sweat AND wearable*) OR (“blood pressure” AND monitor*) OR (sweat AND monitor*) OR (stress AND monitor) OR (“blood pressure” AND sensor*) OR (sweat AND sensor*) OR (stress AND sensor*)) AND (nurse* OR (MH “Nurses”))

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Study Selection and Screening

To be included in this review, studies must meet the following four inclusion criteria: (1) nurses must be in the population studied (>80% of the sample), (2) a wearable device must be included (which the nurses have attached to their clothing, worn as a device anchored directly to their body, or attached directly to their skin, and that has embedded sensors with wireless mobility), (3) there must be a health outcome studied, including physical and psychosocial outcomes, and (4) the study has an observational or interventional design (prospective and retrospective). Studies are excluded if they meet 1 or more of the following exclusion criteria: (1) they do not report on health outcomes, (2) they are specific to nursing students, (3) they use wearable devices with patients, (4) they are not published in English, (5) they are protocols, (6) they are reviews, or (7) they are located only in the gray literature.

Titles and abstracts were imported into Covidence software, where citations will be screened and duplicates removed. Title, abstract, and full-text screening will be conducted independently and in duplicate by 4 reviewers. Cohen κ statistics will be reported to evaluate the interreviewer agreement at different stages. Inclusion and exclusion criteria guide the full-text screening. Cases of disagreement between reviewers regarding study inclusion will be resolved through discussion.

Data Extraction and Analysis

Four reviewers will extract data independently and in duplicate. We will collect citation information, study design and location, recruitment data, sample information, wearable device data, outcome data, and biometric cross-reporting data using an author-developed data extraction form (Table 1). Given the nonsystematic nature of this review, statistical pooling of inferential estimates will not be conducted. We will report measures of frequency and central tendency to describe sample and study characteristics.

Table 1. Data extraction form.

Citation information	Study design and location	Recruitment data	Sample information	Wearable device data	Outcome data	Biometric cross-reporting
First author (year), title	Type of study design, single versus multisite, and type of site	Inclusion and exclusion criteria, time frame, location of data collection	Total sample size, gender and age data, and country	Type and use of wearable device and measures used in reporting	Primary and secondary health outcomes, assessment time points, and key findings	Reporting of biometric wearable sensor data with nurse activities

Results

Search strategies were developed, and data were extracted from 6 databases in July 2022. After the removal of duplicates, we collected 8603 studies for title and abstract screening. Three independent reviewers conducted the title and abstract review, and after resolving conflicts, there were 277 full-text articles to review. The initial title and abstract review had an overall agreement value of 95.7%, resulting in a moderate Cohen κ of 0.43 for interrater reliability [26]. After the full-text articles are reviewed independently for study eligibility by 4 reviewers, data will be extracted. Additional data may be located after we check the eligible article references. All extracted data will be reported using narrative and tabular formats. We will organize the reported data in accordance with 4 key factors: the type of wearable devices, the wearable measures reported, the health outcomes reported, and the methodology used. Considering the size and depth of this review, we will not report on the feasibility or acceptance of wearable devices in nursing. Results are expected to be available in the fall of 2023.

Discussion

This integrative review aims to carefully examine studies available in the global literature that have used wearable devices to improve health among nurses. The goal is to evaluate and inform on the measurement of health outcomes obtained via wearable devices among nurses. These studies will include the results of both descriptive and correlational and interventional studies that tested a wearable device to assess the effect on the nurses' health. Given the importance of physical and psychological health for nurses, we are examining both facets of health. Synthesized results from this review will inform multiple stakeholders, including the nursing workforce, health system administrators, wearable device developers, health insurance companies, policy makers, and mobile health researchers.

As wearable devices continue to evolve rapidly and improve, becoming easier to use while providing richer data sources, it is pertinent that nursing and those supporting their health consider its use and value [27,28]. Using wearable devices for assessing, informing, and providing the information needed to develop healthier behaviors should positively impact the nurses' health and well-being. This should consequently positively affect health care systems that employ nurses, especially in light of nursing labor shortages. Further, the downstream impact of healthy nurses can improve the care and outcomes of the patients they care for in inpatient, outpatient, and community settings.

This work can inform existing movements focused on improving nurses' health; for example, *Healthy Nurse, Healthy Nation*, a program designed by the American Nurses Association Enterprise [29]. The overarching goal of this program, which has existed in the United States since 2017, is to improve nurses' health in the nation. The 6 domains they focus on are activity, rest, nutrition, quality of life, mental health, and safety. Longitudinal data have been collected on hospital workers, including nurses, where several of these domains have been studied, including collecting data on physical and mental health markers, demonstrating how data can be collected over time in

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nurses [30]. In addition, several domains, including physical activity and rest, have been studied with nurse shift workers using commercially available sensors, where they found poorer health outcomes in night shift nurses [31]. For the safety domain, wearable devices are already known to assess these areas with other populations (eg, military and construction workers) [32,33].

Using biometric screening and tracking of occupational activities performed by the nurse provides an opportunity to assess which activities may contribute to poor physical outcomes for the nurse [34]. In addition, predictive analytics can provide context for mitigating those occupational activities that put nurses at risk for adverse health consequences [27]. However, obtaining data from biometric monitoring devices is a field that continues to evolve, and methodological specificities of tools used to obtain biometric data must be carefully reported [35].

Nurses comprise over half of the global health care workforce, and the nursing care they provide is critical for the global population's health [3]. Understanding existing work that has been done to date with the use of wearable devices and focused on nurses' health has the potential to inform how to improve the health of the nursing workforce. This integrative review will provide synthesized data to inform nurses and other stakeholders about the extent of wearable work done with nurses and provide direction for future research.

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Data Availability

The research team will make available all synthesized data within the text of the manuscript or supplemental files. The data used will already be published and available.

Conflicts of Interest

None declared.

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Abbreviations

PICO: population, intervention, control, and outcomes
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols

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Protocol

Barriers and Enablers to Implementing Teledentistry From the Perspective of Dental Health Care Professionals: Protocol for a Systematic Quantitative, Qualitative, and Mixed Studies Review

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Abstract

Background: There is growing literature on the potential of digital technologies for improving access to, ensuring continuity and quality of health care, and to strengthen health systems. Some studies have reported the cost-effectiveness of teledentistry, its reliability for remote dental screening, diagnosis, consultation, and treatment planning. Nonetheless, current evidence suggests that teledentistry implementation faces many challenges and is not yet adopted by dental health care providers (DHCPs). Developing strategies to improve teledentistry adoption requires an understanding of the factors that promote or hinder its successful implementation.

Objective: This systematic review aims to identify and synthetize barriers and enablers to implementing teledentistry as perceived by DHCPs in their clinical practices, using the Theoretical Domains Framework (TDF) and the Capacity, Opportunity, and Motivation Behavior (COM-B) model.

Methods: This protocol follows the PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Protocols) checklist. Literature will be searched in the following databases: PubMed, Cochrane Library, Web of Science, CINAHL, Embase, and PsycINFO. We will perform additional searches on Google, Google Scholar, and ProQuest Dissertations & Theses Global, screen the references of the included studies to capture additional relevant studies, and contact the authors of studies if we need more details. We will consider studies using qualitative, quantitative, and mixed methods. There will be no restrictions on the publication date and dental setting. We will include studies published in French, English, and Portuguese. Two independent reviewers will select the study, extract data, and assess methodological quality using the Mixed Methods Appraisal Tool's checklist. Data analysis will include a descriptive and a thematic content analysis. We will synthetize and categorize the barriers and enablers using the TDF and COM-B model and present a narrative synthesis of our results using tables, figures, and quotes.

Results: By March 2023, the literature search has retrieved 7355 publications. We will identify the range of barriers and enablers to implementing teledentistry through DHCPs' perspectives. Considering the critical need for theory-based implementation interventions to improve the use of evidence-informed practices, we will synthesize the factors influencing the adoption of teledentistry based on the TDF domains and the 3 essential conditions predicting behavior change in accordance with the COM-B model. As needed, we will include additional determinants if not included in the TDF. We will conduct some subgroups analyses if studies are sufficient. We expect to complete the review by July 2024.

Conclusions: This review will provide some insights on the determinants of teledentistry implementation as perceived by DHCPs in dental settings. These findings will cater to patients, families, DHCPs, researchers, academic and professional

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decision-makers, and policy makers. The results of the systematic review could be used to develop theory-led interventions in improving teledentistry implementation.

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KEYWORDS

teledentistry; oral health; barrier; enabler; dental health care providers; information and communication technology; protocol; dental; dentist; telehealth; telemedicine; theoretical domain framework; remote care; virtual care; perception; facilitator; systematic review; review method; librarian; PRISMA

Introduction

Oral diseases significantly affect overall health, well-being, and quality of life and cause an increased economic burden at the patient and society levels. The Global Burden of Disease study in 2019 estimated that oral diseases affect close to 3.5 billion people across the world [1]. Despite interventions developed to improve oral health, numerous oral health inequalities persist over time and space with the greatest burden among marginalized people [1,2], resulting in poor oral health status. Considering the social and economic burdens related to oral health diseases and conditions, and their interconnection with some prevalent noncommunicable diseases [3], there is an international movement toward the imperative need to place oral health care within universal health coverage (UHC) and to improve essential oral health care [4], and to identify optimal strategies to improve oral health and oral health-related quality of life. Consequently, digital health tools are a promising means to address peoples' health needs related to expanding UHC [5], in improving access to, continuity of, and quality of care and to strengthen health systems [6,7].

A growing body of evidence reports the potential of teledentistry, at the intersection of dentistry and telecommunications, as highly pertinent to the future of dentistry [8]. Teledentistry aims to use technologies and related services to deliver oral health care. It has proven to be effective and reliable for remote dental screening, diagnosis, consultation, and treatment planning [9,10]. Several reviews have reported the effectiveness and validity of teledentistry for prevention and health promotion and its accuracy for the diagnosis of oral diseases with results that are comparable to those of face-to-face interventions [10-13]. Dental health care providers (DHCPs), patients, and caregivers also have favorable attitudes and good satisfaction regarding digital interventions in dentistry [8]. Teledentistry has the potential to improve patients' experiences [14,15], population health [16-18], DHCPs' experiences [8,19] and to reduce oral care costs [20-22].

While valuable insights to the implementation of teledentistry can be obtained from decision-makers, patients, and caregivers, it is greatly recognized that DHCPs are among the key actors for the successful digital transformation [6,22,23]. As health professionals, DHCPs' clinical acceptance are among the most important influences on the successful uptake, spread, and sustainability of teledentistry [23]. Consequently, DHCPs' behaviors are an important proximal determinant of the quality of care provided to patients [24]. In their position as sources of information and opinion leaders who shape the clinical encounter, they could ensure teledentistry implementation and sustainability [25]. Their perspective is important to increase the expansion of teledentistry implementation and to deliver the right information to the right people at the right time. A better understanding of barriers and enablers that influence DHCPs' behavior is a prerequisite to the successful implementation of teledentistry, as its adoption can help improve the patients' outcomes and experiences.

Despite the promises of teledentistry, some empirical and theoretical studies have shown that teledentistry implementation remains a challenge [23,24,26,27]. Previous studies have reported that teledentistry has not yet been widely adopted by DHCPs [28-30]. The variation in the use of web-based oral health care cannot be explained by clinical factors or technical aspects alone. Structural, organizational, and DHCP- and patient-related factors including the absence of legal regulation of teledentistry, poor internet connection, lack of reimbursement, lack of training, and lack of familiarity with teledentistry [31,32] have been identified as barriers to implementing teledentistry. To maximize teledentistry implementation, it is crucial to understand DHCPs' perspectives and to support them to modify their clinical behavior toward this modality of the delivery of oral health care. Understanding the barriers and enablers to the implementation of teledentistry is imperative to inform the design and the development of successful theory-led interventions, as well as the appropriate educational resources for the future implementation of teledentistry in dental practices.

Currently, there is no strong evidence available to inform decision-making, nor is there a tailored theoretically informed intervention designed to enhance its successful implementation. Systematic reviews offer a way to synthesize the broad range of barriers and enablers reported in the literature and to provide a broader, in-depth understanding of the factors influencing teledentistry implementation. Furthermore, many studies have reported the relevance of a theoretical framework to categorize the factors that influence health care professionals' behaviors, inform the selection of behavior change techniques (BCTs) [24,33], and develop theory-driven and tailored strategies to support the effective implementation of any innovation [34-36]. To our knowledge, there has been no review of available evidence regarding DHCPs' perspectives about the determinants of teledentistry implementation, nor has there been a previous systematic review using a theoretical framework to describe factors that may influence its implementation. This systematic

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review, therefore, aims to identify and synthesize barriers and enablers reported by DHCPs to implementing teledentistry in their clinical practices, using the theoretical domain framework and the Capacity, Opportunity, and Motivation Behavior (COM-B) model to determine factors predicting behavior change. This review protocol will address the question: "what are the barriers and enablers to teledentistry implementation that are reported by DHCPs in dental settings?"

Findings from this review will be valuable to inform the designing, planning, and implementation of teledentistry in any dental setting.

Methods

Study Design

The protocol for this review is registered on PROSPERO (CRD42021293376). This protocol has been written in accordance with the PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Protocols) checklist [37]. The systematic review will be reported in accordance with the PRISMA checklist [38].

Eligibility Criteria

We will follow the PICOS (participants, interventions, comparators, outcomes, and settings) framework [39].

Participants

We will include studies about the adoption of teledentistry by DHCPs. The DHCPs are dental professionals directly involved in clinical acts with patients. This review will include any dental professionals involved in oral health care. These DHCPs include general and specialist dentists, dental hygienists, dental therapists, dental nurses, dental students, dental hygiene students, and dental therapy students. All specialties in dentistry will be considered (eg, orthodontics, oral medicine, oral pathology, prosthodontics, periodontics, endodontics, pedodontics, and oral and maxillofacial surgery). If other participants such as patients, other health professionals, or managers are involved in a study with these DHCPs, the study will be included.

Intervention

We will include only those studies that use teledentistry for the delivery of oral health care. Teledentistry interventions could be compared to usual or standard dental care or face-to-face dental visits (in-person) or no comparator. DHCPs can use several devices including cell phones, tablets, telephones, computers, personal digital assistants, text messaging, and apps [40-44] to interact with colleagues, other health professionals, or patients. We will include any studies on teledentistry delivered through different modalities such as synchronous (in real time; ie, direct interaction between a person [patient, caregiver, or health professional] and a DHCP) and asynchronous (store and forward; ie, transmission of health information to DHCPs to evaluate a patient's condition or render a service outside of a real-time or live interaction) modalities. These interventions can be delivered through videoconference (eg, Zoom), telephone, websites, or any applications such as WhatsApp or other web-based mechanisms.

Types of Studies to Be Included

We will include all studies with an original data collection. If there are several publications on the same project presenting similar data, we will include only the most recent publication, and if results are complementary and relevant, we will include all of them. We will include quantitative, qualitative, and mixed methods studies.

Outcomes

We will include studies with different synonyms related to teledentistry implementation such as adoption, usage, uptake, readiness, and intent to its use. We will include studies reporting factors that could influence teledentistry implementation as reported by DHCPs; for instance, knowledge, intention, behavior, self-efficacy, satisfaction, skills, social influences, environmental context, and resources. We will include studies where data are collected using a variety of techniques, including individual interviews, focus groups, or questionnaires. We will include studies using validated or nonvalidated measurement tools to collect data. In this review, we will consider an enabler as any circumstance, factor, or variable that positively influences teledentistry implementation. A barrier will refer to any circumstance, factor, or variable preventing teledentistry implementation.

Settings

We will consider all dental settings such as dental offices, community-based care, hospitals, schools, long-term care facilities, nursing homes, home dental care, university, and private or public dental settings. We will consider any geographical setting (eg, rural or urban regions) and any country (low-, middle-, or high-income).

Exclusion Criteria

We will exclude any study using teledentistry only for education, training, and research. Studies may include other participants such as patients and other health care professionals, but DHCPs must be part of the studied population in the methodology, with the possibility to extract information from DHCPs. We will exclude studies that do not have a clear distinction between DHCPs and other participants' findings. We will exclude any study focusing on health care providers other than DHCPs. We will exclude any studies focusing on the features of a platform for teledentistry, or the validity of teledentistry. Studies that are limited to describing the feasibility, usability, or technical evaluation of certain systems, interfaces or platforms will also be excluded. We will exclude editorials, letters, abstracts, reviews, commentary reports, legal issues, protocols, and press releases.

Information Sources and Search Strategy

A health science information specialist will assist us in developing the literature search strategy in PubMed and will translate it after validation and revision in other electronic databases. A second health science information specialist will review the initial search strategy with the Peer Review of Electronic Search Strategies Tool [45]. The main concepts considered in the search strategy are "teledentistry," "telemedicine oral health," or "remote dental care," "remote

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oral care," "virtual dental care," or "virtual oral care" and "dental health care providers," "health personnel," or "dentistry." The electronic search will be carried out to identify all relevant studies from the following databases: PubMed, Cochrane Library, Web of Science, CINAHL, Embase, and PsycINFO. We will perform additional searches in Google, Google Scholar, and ProQuest Dissertations & Theses Global. We will screen the references of included studies to capture additional relevant studies.

There will be no restriction on the date of publication of the studies. We will include studies published in French, English, and Portuguese. A draft search strategy for MEDLINE has been developed with the support of a health science information specialist and is available in Multimedia Appendix 1.

Selection Process and Data Collection Process

Data Management

We will import the list of generated references into EndNote X9 (Clarivate Analytics) software. We will identify and remove all duplicates. Retained studies will be uploaded in Covidence [46] for data screening and selection.

Selection Process

Two independent reviewers will select the retrieved studies. They will perform a calibration exercise with 10% of the total number of identified studies to ensure a mutual understanding of the eligibility criteria and to identify areas where further clarification is needed. Following the conclusive pilot test, the 2 reviewers will independently select studies at 2 levels: the first level of selection will be based on the titles and abstracts only (providing codes of "Yes," "No," or "Maybe"), and the second level will concern the full texts. All studies coded as "Yes" or "Maybe" will be further reviewed in full text by both reviewers. We will report the reasons for the exclusion of any retrieved or selected study.

Discrepancies will be resolved though discussion and consensus or with the consultation of a third reviewer. The selection stage will be considered an iterative process, allowing the eligibility criteria to be refined by the research team. We will contact authors for articles that cannot be obtained through institutional holdings.

Data Extraction

Two reviewers will extract the data independently using an Excel (Microsoft Corp) data extraction sheet. A calibration exercise will be independently performed by both reviewers on 5% of the included studies. The data extraction sheet will be modified and revised as necessary during the process of extracting data. Consistent with the abovementioned steps, data charting will be considered an iterative process as the review develops. Any disagreements that arise between the reviewers will be resolved through discussion and consensus, or with the consultation of a third reviewer. The draft extraction form is provided in Multimedia Appendix 2. The following data will be extracted:

- Characteristics of the included studies (eg, title, main author, year of publication, country of publication, language of publication, aims, funding, type of publication, study design, dental care settings, use of a theoretical framework, name of the theoretical framework, methods of data collection, limitations, and conclusions)
- Participant characteristics (eg, profile, sample size, sex, gender, age, general dentist or specialist, type of specialty, type of practice, and region of practice)
- Characteristics of teledentistry (eg, synchronous or asynchronous)
- Study outcomes (eg, knowledge, practices, beliefs, self-efficacy, time, compliance, behavior, teledentistry adoption and use, training, reimbursement, and equipment).

We will contact the authors if we need additional information on the study.

Risk of Bias and Quality Assessment

Two independent reviewers will assess the methodological quality of the included studies using the core quality criteria in the Mixed Methods Appraisal Tool (MMAT) [47]. The MMAT is a reliable tool, and its use has been widely reported in the literature to facilitate the critical appraisal of mixed studies reviews [48-51]. It was first reported in 2009 as a single tool to evaluate the methodological quality of 5 categories of study designs: qualitative studies, randomized controlled trials, nonrandomized studies, quantitative descriptive studies, and mixed methods studies [50]. Further attempts to refine and improve the MMAT led to the development of its current version in 2018, based on the findings from a literature review on critical appraisal tools, pilot and interrater reliability testing, interviews with MMAT users, and the Delphi approach [52]. There are 5 questions each for quantitative and qualitative study designs and 15 for mixed method studies. The answer categories include "yes," "no," or "can't tell" [47]. As required by Hong et al [47], we will present in detail the ratings of each criterion to better inform the quality of the included studies. We will present the overall quality score of the included studies using a descriptor such as an asterisk (*) or the percentage of quality criteria met [49]. For instance, 1 (*) refers to 20% of the quality criteria met, while 5 (*) refers to 100% of the quality criteria met. For mixed methods studies, we will provide 3 scores including one for qualitative, one for quantitative, and one for mixed methods components. The overall quality of the mixed methods study cannot exceed that of its weakest component [49].

We will consider for the included studies the following cutoff: studies with 1 and 2 (*) will be considered as being of low quality, 3 stars as medium quality, and 4 and 5 stars as high quality. Any discrepancy will be resolved through discussion and consensus or with the consultation of a third reviewer.

Data Synthesis

A narrative synthesis will be conducted. We will analyze the data extracted using descriptive statistics (eg, frequencies and percentages). For instance, we will report the types of study designs, type of teledentistry interventions, countries where studies were conducted, and the study characteristics. We will synthesize and map the factors influencing teledentistry implementation in accordance with the theoretical domains of Theoretical Domains Framework (TDF) [53] and the context

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of information reported by the authors in order to allocate the factor to the appropriate theoretical domain. The likelihood is relatively low to miss a potential determinant of teledentistry implementation considering the wide range of factors considered within the TDF. We will report any new construct that is not considered in the TDF.

The robust theoretical model of TDF is more appropriate for this review because of its comprehensiveness. It is a promising and useful way of mapping the broad range of factors that influence a range of behaviors. It has been used in the literature to synthesize and classify the different determinants of a behavior and to target the relevant interventions [54,55]. In its original version, the TDF was composed of 12 theoretical domains (eg, knowledge, skills, social or professional role and identity, beliefs about capabilities, beliefs about consequences, motivation, goals, memory attention and decision processes, environmental context and resources, social influences, emotion, and action planning) that were derived from 33 behavior change theories using a process of expert consensus. The domains are considered as potential determinants of behavior and clearly indicated as barriers and enablers or factors positively or negatively influencing the behavior being studied. Some years later, the TDF has been refined and included in its revised version 14 theoretical domains and 84 theoretical constructs that can influence behavioral change [54]. These 14 individual and environmental theoretical domains include knowledge; social or professional role and identity; beliefs about capabilities; beliefs about consequences; skills; goals; optimism; reinforcement; intention; memory, attention, and decision processes; environmental context and resources; social influences; emotion; and behavioral regulation [54] (Multimedia Appendix 3).

Authors of previous reviews on teledentistry implementation have identified several potential factors influencing its implementation such as awareness, attitudes, knowledge, skills, training, lack of reimbursement, lack of infrastructure, self-confidence, organizational difficulty, quality of information, fear, lack of evidence, lack of guidelines, and data security issues [16,30,31,56]. These constructs can fit under the TDF domains of knowledge, skills, beliefs of capacities, beliefs about consequences, reinforcement, goals, emotion, identity and social roles or responsibilities, environmental context, and resources. In a systematic review of reviews on the barriers and facilitators to clinical behavior change by primary care practitioners, the authors have reported that 3 TDF domains were most commonly reported across many reviews, regardless of the type of behavior change and context: knowledge, environmental context and resources, and social influences [57].

Based on this information and our experience in dentistry, the preliminary step of selection of the TDF domains' constructs could include without exhaustivity: procedural knowledge, knowledge, skills, skills assessment, competence, professional identity or role, self-efficacy, beliefs, attitudes, incentives or reimbursement, resources, infrastructures, social norms, fear, stress, and breaking habits.

The domains of the TDF are further mapped in 3 major essential conditions predicting behavior change, which are components of the COM-B model [33]. The COM-B component "Capability" can be psychological or physical and includes knowledge and skills. The component "Opportunity" can be social or physical and could include social influences and environmental context or resources. Finally, the component "Motivation" can be a reflective process, or automatic process and could include intention and emotions. This approach guides the understanding of behavior in all contexts. The COM-B model is a part of the "behavior system," which helps to design interventions [33] through BCTs [58]. According to the analysis of the nature of behavior and the relevant mechanisms to elicit change, the Behavior Change Wheel is a reliable framework that aims to link the determinants of the target behavior to the design and selection of interventions and policies (Multimedia Appendix 4). Considering the critical need for theory-based implementation interventions to improve the use of evidence-informed practices, we will organize the barriers and enablers by these essential conditions, which could be behavioral change components with high potential to improve teledentistry implementation. If possible, we will perform subgroup analysis based on the number of eligible studies with the following variables: age, gender, type of dental professionals (eg, dentists versus dental hygienists), category of dentists (eg, generalist and specialists), type of setting (eg, private or public), and time period (before and after 2020 with the COVID-19 pandemic), and their methodological quality. Results will be reported in tabular form, graphics, and quotes to reflect the extent of included literature.

At the end of the review, we will have an in-depth understanding of barriers and enablers from DHCPs' perspectives as well as the comprehensiveness of TDF domains, constructs, and predicting factors.

Results

As of March 2023, we have updated the search strategy. The search strategy identified 7355 studies. This systematic review will aim to identify and synthetize the barriers and enablers to teledentistry implementation from DHCPs' perspectives. We will present the sociodemographic information or moderators reported by the authors of these studies, which could influence behavior change. Furthermore, possible research gaps may be identified to guide future studies. Our results will be reported in accordance with the PRISMA-P checklist [38]. We expect to complete the review and publish the results within a year of publication of this protocol—around July 2024.

Discussion

Anticipated Findings

This review will identify and synthesize the enablers and barriers influencing teledentistry implementation from DHCPs' perspectives. These factors can represent micro to macro levels of analysis, which will affect implementation success and predict implementation efforts. The TDF, one of the robust and common theoretical frameworks used in implementation science, will allow us to comprehensively classify the range of barriers and enablers related to teledentistry implementation, which could assist later in the development of tailored implementation

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interventions [35]. The TDF has also been used as a coding framework for the analysis of barriers in systematic reviews [34,59,60]. However, to our knowledge, its use is limited in dentistry and was not used to synthetize the factors influencing teledentistry implementation as reported by DHCPs. The knowledge of determinants from the TDF and COM-B model will inform the selection of targeted BCTs, which, in turn, can be used to design behavior change interventions to improve the implementation of teledentistry. We will present the strengths and limitations of this review. As such, implications of the review findings for future research, practice, and policy will be discussed and presented.

Conclusions

This systematic review protocol presents the methodological steps aiming to identify and synthetize the barriers and enablers to implementing teledentistry from DHCPs' perspectives using strong theoretical frameworks. The results of this review can be relevant for different knowledge users including patients, DHCPs, researchers, managers, academics, policy makers, and professional decision-makers in regulatory bodies to design behavioral change interventions to improve the success of teledentistry implementation in dental settings.

Acknowledgments

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Data Availability

The data sets generated and analyzed during this study will be available upon request to the corresponding author after publication of the review.

Amendments

We will publish any changes to this protocol as amendments on our PROSPERO protocol web page. We will declare any changes and the date of the amendments, including the rationale for them.

Authors' Contributions

PKT conceptualized the study, developed the draft, and wrote the manuscript. PKT, CI, AD, DZ, FB, and FC contributed substantially to writing and editing the manuscript. All authors read and approved the final study protocol.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search strategy.
[DOCX File , 125 KB - resprot_v12i1e44218_app1.docx]

Multimedia Appendix 2
Data extraction sheet.
[DOCX File , 18 KB - resprot_v12i1e44218_app2.docx]

Multimedia Appendix 3
Definition of theoretical domains.
[DOCX File , 16 KB - resprot_v12i1e44218_app3.docx]

Multimedia Appendix 4
Match between TDF and COM-B.
[DOCX File , 248 KB - resprot_v12i1e44218_app4.docx]

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Abbreviations

BCT: Behavior Change Technique
COM-B: Capacity, Opportunity, and Motivation Behavior
DHCP: Dental health care providers
MMAT: Mixed Methods Appraisal Tool
PICOS: Participants, Interventions, Comparators, Outcomes, and Settings
PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Protocols
TDF: Theoretical Domains Framework
UHC: Universal Health Coverage

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Protocol

Cognitive Interventions in Individuals With Chronic Respiratory Diseases: Protocol for a Systematic Review

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Abstract

Background: Chronic respiratory diseases (CRDs) may cause reduced oxygen availability to organs and body tissues, leading to an increased risk for ischemic damage, which can result in brain tissue injury. This damage can lead to a myriad of neurological symptoms contributing to cognitive decline. Cognitive interventions may attenuate cognitive deficits in people with CRDs; however, the effects have not yet been systematically summarized in the literature.

Objective: The purpose of this systematic review is to assess the effects of cognitive interventions (including cognitive behavioral therapy and transcranial brain stimulation) on cognitive function (primary outcome), HRQL, self-management, symptoms, physical activity, physical function, ability to complete activities of daily living (ADLs), hospital admissions, functional capacity, functional performance, psychological and social outcomes, exacerbations, healthcare utilization, and survival in individuals with CRDs.

Methods: This review will be conducted in accordance with the Cochrane handbook for systematic reviews of interventions and reported following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. Searches will be performed in MEDLINE, Embase, Emcare, PsycINFO, Scopus, and CINAHL. Articles will be included if they focus on the effects of cognitive interventions on adults with CRDs, are published in peer-reviewed journals, and are written in English, French, or Portuguese. Risk of bias will be evaluated with the Cochrane Risk of Bias 2 tool for randomized controlled trials, and the Risk of Bias in Non-randomized Studies of Interventions tool for nonrandomized studies. Meta-analyses will be performed if at least 2 studies provided sufficient data for a specific outcome. The GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) assessment will be used to evaluate the overall quality of the evidence.

Results: This systematic review was initiated in November 2022 and registered with PROSPERO in February 2023, prior to title and abstract screening. Full-text screening of articles will be completed in June 2023. Data extraction and drafting of the manuscript will occur from July 2023 to August 2023, with expected publication in February 2024.

Conclusions: This systematic review will summarize the effects of cognitive interventions on cognitive function in people with CRDs. It will guide health care professionals in selecting evidence-based strategies to enhance cognitive well-being and overall health outcomes for individuals with CRDs. Additionally, it will identify research gaps and highlight areas for future exploration, supporting researchers in advancing knowledge in this field.

Trial Registration: PROSPERO CRD42023396234; https://tinyurl.com/mwjrfbxv

International Registered Report Identifier (IRRID): PRR1-10.2196/48235

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(JMIR Res Protoc 2023;12:e48235) doi:10.2196/48235

KEYWORDS

chronic pulmonary disease; cognitive therapy; memory training; brain exercise; cognitive function; pulmonary; lung; COPD; review methodology; systematic review; cognitive; cognition; memory; CRD; respiratory

Introduction

Chronic respiratory diseases (CRDs) are the leading causes of morbidity and mortality, contributing to three million deaths per year worldwide and US $170.8 billion in health care–related costs in 2016 [1]. Clinical presentation of CRDs includes both pulmonary and extrapulmonary symptoms, including dyspnea, cough, musculoskeletal impairments, and cognitive decline, ultimately limiting individuals' abilities to engage in activities of daily living (ADLs) [2].

Cognitive decline is reported in 60% of people with CRDs and has been related to a state of reduced oxygen availability in tissues, resulting in an increased demand for oxygen to maintain homeostasis [3,4]. As CRDs progress, physiological changes such as airway obstruction, inflammation, fibrosis, septal thickening, interstitial edema, intra-alveolar exudate, and destruction of alveolar capillaries can reduce airflow and pulmonary gas diffusion. Such changes lead to impaired exchange of oxygen and carbon dioxide, resulting in hypoxemia, hypoxia, and hypercapnia [5,6]. If maintained, hypoxemia can affect the synthesis of neurotransmitters essential for brain function, such as acetylcholine [4], and cause ischemic brain damage [5,6].

Consistent cerebral hypoxia can present as a multitude of neurological symptoms associated with cognitive decline, including deficits related to memory, information processing, language, attention, visuospatial abilities, judgment, and executive functioning [3,7-9]. As a result, an individual's ability to manage their disease, such as medication tracking and symptom monitoring, may be impeded by this cognitive decline [9,10]. Thus, maintaining and improving cognitive status is crucial to help promote disease self-management and independence in individuals with CRD.

Cognitive interventions encompass a range of targeted approaches designed to maintain or improve specific cognitive functions, such as attention, memory, and reasoning [11,12]. These interventions may involve structured training programs, therapeutic techniques, and innovative methods like transcranial brain stimulation (TBS). They are aimed at improving impaired cognitive function, preventing cognitive decline, or preserving the individual's functional level, drawing from diverse theoretical constructs [13]. Previous studies on non-CRD populations have reported improvements in general cognitive functioning, processing speed, and cognitive abilities related to everyday task performance following cognitive interventions [14]. In addition, these interventions have been reported to slow the progression of cognitive decline, particularly in populations with cognitive impairment [15]. However, the literature on the effects of cognitive interventions for people with CRDs is inconclusive, as it is heterogeneous in terms of sample characteristics, interventions, and outcome measures. Several studies, including randomized controlled trials (RCTs) investigating cognitive interventions in patients with chronic obstructive pulmonary disease, have produced inconsistent and variable findings [16-18]. Although there are possible benefits of cognitive interventions in those with CRDs, such as improvements in cognitive function, self-management, health-related quality of life (HRQL), and performance in trained tasks [16,17], overall, no significant improvement has been found related to cognitive performance, healthy lifestyle behaviors, susceptibility to cognitive stress and cognitive performance [16-18]. Consequently, a review is needed to systematically review and summarize the evidence, and establish its quality to help inform clinical practice as it pertains to the use of cognitive interventions in those with CRDs.

This systematic review primarily aims to assess the effects of cognitive interventions (ie, attention, memory, and reasoning on cognitive function) in people with CRDs. The secondary objectives are to summarize the content and structure of cognitive interventions used within this population and their effects on HRQL, self-management, symptoms, physical activity, physical function, ability to complete ADLs, hospital admissions, functional capacity, functional performance, psychological and social outcomes, exacerbations, healthcare utilization, and survival.

Methods

Overview

This systematic review will be conducted according to the Cochrane Handbook for Systematic Reviews of Interventions [19] and reported following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [20]. The protocol was registered in PROSPERO (CRD42023396234).

Search Strategy

The following electronic databases will be searched in June 2023: MEDLINE (1946-Present), Emcare, Embase, CINAHL, PsycINFO, and Scopus. The search strategy was created in consultation with a health sciences librarian at McMaster University and will involve database-specific MeSH terms in combination with keywords (keywords will be consistent across databases). The reference list of the selected studies will be manually searched to identify further relevant articles. The search strategy was validated in MEDLINE, Emcare, and Embase databases by testing whether it could identify 3 relevant articles to be included, previously sought through Google Scholar [16-18].

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Eligibility Criteria

Study Design

Studies will be included if they are RCTs, non-RCTs, pre-post study designs, cohort studies, and case-control studies (all published in peer-reviewed journals). Studies will be excluded if they have been published in conference proceedings, magazines, news articles, dissertations, theses, abstracts, and editorials. Systematic, scoping, literature, and narrative reviews will be excluded but their references will be screened for potential articles. Articles that are not written in English, French, or Portuguese will also be excluded.

Population

Studies will be included if they included participants 18 years of age or older (adult participants) with a diagnosis of a CRD (ie, asthma, bronchiectasis, chronic obstructive pulmonary disease, cystic fibrosis, interstitial lung disease, chronic respiratory tract diseases, post–COVID-19 syndrome, tuberculosis, or lung cancer). Studies will be excluded if they include participants whose primary diagnosis is a cognitive disease or participants presenting with complications such as dementia, Alzheimer, psychological disorders (ie, bipolar disorder), stroke, or trauma, resulting in cognitive impairment.

Intervention

Studies will be included if reporting on the effects of cognitive interventions. Cognitive interventions that help improve or maintain cognitive processes or address the impact of cognitive impairment on overall function will be included. These interventions may involve formally structured training in domains such as information processing speed, attention, memory, or problem-solving. The focus should be on improving the reasoning or cognitive process itself rather than developing a specific skill [21]. As per our definitions, cognitive training and cognitive interventions that include cognitive behavioral therapy (CBT) or TBS focused on improving cognition will be included [22-24]. Cognitive training can be defined as nonpharmacological interventions that involve structured and guided training that aims to maintain or improve certain aspects of cognitive function, including attention, memory, and learning [21]. CBT is defined as an intervention that involves increasing participants' knowledge and understanding of the problem (ie, cognitive function, including attention, memory, and learning); identifying and restructuring dysfunctional thinking and maladaptive beliefs; and developing emotional and behavioral compensatory strategies for the core deficits [22]. It is a diverse group of treatments that include cognitive therapy, CBT, acceptance and commitment therapy, dialectical behavior therapy, schema-focused therapy, rational-emotive behavior therapy, mindfulness-based cognitive therapy, metacognitive therapy, cognitive behavioral analysis system of psychotherapy, and cognitive processing therapy [23]. Transcranial brain stimulation is a non-invasive brain stimulation technique that passes an electrical current through the cortex of the brain to alter brain function [24]. It may include transcranial direct current stimulation, alternating current stimulation, and random noise stimulation [24].

Studies that primarily focus on improving and changing behavioral, emotional, or physical outcomes, single-trial training, and interventions implemented in direct combination with another distinct experimental intervention will be excluded [21].

Having a comparator or control group is not a requirement for inclusion in this review. Accepted types of control groups will be no intervention, usual care, sham intervention, another type of intervention, or multidimensional care (cognitive intervention plus another intervention). Control groups involving another type of cognitive intervention will not be accepted, as this will only determine the effectiveness of one intervention versus the other and not whether cognitive interventions are effective compared to no intervention or another type of intervention.

Outcomes

The primary outcome of this study is cognitive function, which encompasses the mental processes involved in acquiring knowledge, manipulating information, and reasoning [25]. This includes the domains of perception, memory, learning, attention, decision-making, and language abilities [25]. Secondary outcomes include HRQL, self-management, symptoms, physical activity, physical function, ability to complete ADL, hospital admissions, functional capacity, functional performance, psychological and social outcomes, exacerbations, health care usage, and survival.

If sufficient data are available from 2 or more studies, subgroup analyses will be performed for the type of CRD and the structure (ie, duration, frequency, and setting) or components of the cognitive intervention. Such analysis will help determine whether patients with different CRDs respond differently to cognitive interventions, or whether there is a difference in outcomes depending on the cognitive intervention structure or components.

Data Management

EndNote reference manager (Clarivate) will be used to filter duplicate studies. Studies will subsequently be imported into Covidence (Veritas Health Innovation), which will be used for further removal of duplicates, screening, and selecting studies. Excel (Microsoft Corp) will be used for data extraction and management.

Selection Process

Abstracts and full-text screening will be pilot-tested by all reviewers with 12 articles to calibrate the selection process and ensure interrater reliability. An 80% or higher agreement will be sought before proceeding with screening [26]. Six reviewers will independently screen titles and abstracts, with each study requiring consensus between 2 reviewers before a final decision to include or exclude the study for the full-text screening is made [26]. Two authors will independently perform the full-text screening process. At any stage of the screening process, if articles do not meet the inclusion criteria or meet any of the exclusion criteria, they will be excluded and reasons for exclusion will be recorded [26]. Disagreements will be resolved through consensus, and if no consensus is reached, a third reviewer will be consulted.

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Data Extraction

Two authors will independently extract the data to a predefined data extraction table, including title, authors, year and country of publication, study design, study setting, sample size per group, population (age, gender, chronic respiratory disease, disease severity, and comorbidities) per group, intervention (type, frequency, components, and duration) per group, outcome measures used, the timing of data collection, follow-up times if applicable, adverse events, and results of the interventions or comparator groups (including the mean, SD, and sample size).

Any disagreements on the extracted data will be resolved by discussion, and a third reviewer will be consulted if no consensus is reached. In the case there are missing data, study authors will be contacted by email to request these data. A follow-up request will be sent after 2 weeks, and if there continues to be no response after 2 more weeks, there will be no further attempts to retrieve the data. If the data are reported only in figures and the authors did not provide the requested data, whenever possible WebPlotDigitizer will be used [27].

Risk of Bias Assessment

Risk of bias assessment will be performed independently by 2 authors at a study level using the Cochrane Risk of Bias 2 tool for RCTs (randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result) or the Risk of Bias in Non-randomized Studies of Interventions tool for non-RCTs (bias due to confounding, bias of selection of participants into the study, bias in classification of interventions, bias due to deviations from intended interventions, bias due to missing data, bias in measurement of outcomes, and bias in selection of the reported result) [28,29]. Disagreements will be solved through discussion, and if no consensus is reached, a third reviewer will be consulted.

Data Analysis and Synthesis

Tables will be used to describe the various types of studies, patient populations, characteristics of cognitive interventions and comparators, and outcomes. Meta-analysis will be performed using the Review Manager (version 5; Cochrane) software. If at least 2 studies reported the same outcome, that outcome will be included in the meta-analysis. Results will be reported as mean difference if the studies used the same outcome measures or standardized mean difference if studies assessed the same outcome using different measures. Depending on the level of heterogeneity between applicable studies, a fixed effects or a random effects model will be used for meta-analysis (ie, a high level of heterogeneity between applicable studies would warrant the use of a random effects model). If a meta-analysis cannot be performed, data will be synthesized narratively, explaining the main findings as they relate to the impact of cognitive interventions for people with CRDs.

Quality of Evidence

For the quality of evidence assessment, the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) system will be used to upgrade or downgrade the evidence [30]. The GRADE assessment will be performed independently by 2 authors and disagreements will be solved through consensus or consulting a third reviewer if a consensus cannot be reached. The domains to be looked at are as follows: risk of bias, imprecision, inconsistency, indirectness, and publication bias. Based on these domains, the quality of evidence will be determined to be high, moderate, low, or very low. The outcome of the GRADE assessment will be presented in a summary of the findings table.

Results

The project was initiated in November 2022. After formalizing the study methods and prior to title and abstract screening, the protocol was registered with PROSPERO in February 2023. Abstract screening is planned to be completed in June 2023 and full-text screening will be completed in July 2023. Data analysis and drafting of the manuscript will occur from July 2023 to August 2023, with expected publication in February 2024.

Discussion

Principal Findings

The beneficial effects of cognitive interventions for healthy individuals and those with various cognitive impairments have been discussed in several studies [14-17]. However, its effects on people with CRDs have never been systematically documented [4,16-18]. To our knowledge, this is the first systematic review focusing on the effects of cognitive intervention in individuals with CRDs. The nature of this systematic review is a strength, as it provides an objective perspective on this topic while minimizing bias, by following established procedures and reporting guidelines. Other strengths include its robust search strategy as demonstrated by searching 6 databases, reporting on the percentage of agreement among reviewers and including a variety of health domains in the secondary outcomes.

One of the predicted limitations of this study is that it will collect data from various study types, not limited to RCTs. This may affect the quality of the literature included in the paper. However, due to the novelty of this rehabilitation topic, there may be a limited number of primary articles (RCTs) available. Despite this limitation, it is still essential to synthesize the current literature on the effects of cognitive interventions for people with CRDs to inform evidence-based clinical decisions and plan future research. Another limitation of the study is the inclusion of articles written only in English, Portuguese, and French. This may exclude relevant data published in other languages. To capture a broader range of articles, future research on this topic should include studies written in other languages. Finally, to ensure a focused and manageable analysis, we have made the decision to include only the most commonly reported forms of cognitive interventions in the literature. This selective approach allows us to streamline our review process and maintain clarity in our findings. Although this decision may exclude certain less frequently reported interventions, it enables us to provide a comprehensive evaluation of the widely recognized and established cognitive intervention techniques.

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Conclusions

The systematic review's findings will assist in displaying the effectiveness of cognitive interventions as a potential treatment approach in reducing cognitive deficits in those with CRDs. This innovative field of clinical research is relevant to all health care disciplines as it impacts decisions related to screening and interventions and informs clinical practice for all health care professionals.

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Data Availability

All data generated or analyzed during this study will be included in the published manuscript as a supplementary information file.

Conflicts of Interest

None declared.

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Abbreviations

ADL: activity of daily living
CBT: cognitive behavioral therapy
CRD: chronic respiratory disease
GRADE: Grading of Recommendations, Assessment, Development, and Evaluation
HRQL: health-related quality of life
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT: randomized controlled trial
TBS: transcranial brain stimulation

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Protocol

Developing a Core Outcome Set for Assessing Clinical Safety Outcomes of Prostate Cancer in Clinical Trials of Traditional Chinese Medicine: Protocol for a Mixed Methods Study

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Abstract

Background: Among the common malignant tumors in men worldwide, the incidence of prostate cancer ranks second to lung cancer. This disease will bring an economic burden to patients and their families and can reduce the quality of life of patients. Researchers have conducted numerous clinical trials on the efficacy and safety of different interventions in the treatment of prostate cancer with traditional Chinese medicine (TCM) combined with standard treatment regimens. However, the currently published clinical trials exhibit inconsistent and irregular reporting of outcome measures.

Objective: The objective of this paper is to emphasize the need for a core outcome set (COS) to facilitate future prostate cancer research, aiming to improve the quality of trials and generate high-quality evidence.

Methods: This mixed methods project has three phases, as follows: (1) a scoping review of the literature to identify outcomes that have been reported in clinical trials and systematic reviews of interventions involving TCM for the treatment of prostate cancer as well as a qualitative component using interviews to obtain the views of patients with prostate cancer, their families, and their caregivers who have a history of TCM treatment; (2) a Delphi survey among stakeholders to prioritize the core outcomes—Participants will include traditional Chinese and Western medicine clinicians in prostate cancer–related directions, nurses, and methodology experts who will participate in 2 rounds of the Delphi method expert consultation to score each outcome in the list of outcome indicators; and (3) a face-to-face consensus meeting to discuss and agree on the final COS for the application of TCM in the treatment of prostate cancer.

Results: The protocol has been registered in PROSPERO (CRD42022356184) before the start of the review process, and we will initiate the review on August 1, 2023; results should be expected by September 1, 2023. The Delphi survey among stakeholders is expected to start in October 2023.

Conclusions: The development of a core outcome set for assessing clinical safety outcomes of prostate cancer in clinical trials of TCM will provide a significant first step to assist Chinese doctors, researchers, and policy makers.

Trial Registration: PROSPERO CRD42022356184; https://tinyurl.com/ysakz74r

International Registered Report Identifier (IRRID): PRR1-10.2196/46794

(JMIR Res Protoc 2023;12:e46794) doi:10.2196/46794

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KEYWORDS

core outcome set; safety outcomes; prostate cancer; traditional Chinese medicine; clinical trial; study protocol; quality of life; efficacy; clinical safety outcome; men

Introduction

Among the common malignant tumors in men worldwide, prostate cancer ranks second to lung cancer in terms of incidence, accounting for 14.1% of the total number of malignant tumors; the mortality rate for prostate cancer is 6.8%, ranking fifth in male cancer mortality, and making it the most common type of cancer in 112 countries globally [1]. According to the new cancer data in China in 2019, the incidence of prostate cancer ranks sixth among men, its mortality rate ranks ninth, and the incidence is on the rise in the country [2]. Some scholars predict that by 2030, prostate cancer will surpass gastric cancer to become the third most common cancer in men [3]. Patients with prostate cancer do not have obvious clinical symptoms in the early stages, 50%-80% of patients are diagnosed at an advanced stage [4], and approximately 80% of patients diagnosed with advanced prostate cancer may develop bone metastasis [5]. Currently, follow-up observation, surgical treatment, endocrine therapy, chemotherapy, external radiation therapy, and seed implantation internal radiation therapy can be used for prostate cancer treatment. Among these options, endocrine therapy—represented by Androgen Deprivation Therapy (ADT)—has become an internationally recognized standard treatment for advanced prostate cancer. The advantage of ADT is that it can significantly delay the progression of the tumor, but the treatment period is not long, usually lasting only 1-2 years. If the treatment time exceeds 2 years, the body will easily develop resistance to ADT, and almost all of patients will progress to castration-resistant prostate cancer in later stages or metastatic castration-resistant prostate cancer [6]. Once the disease progresses to castration-resistant prostate cancer, radiotherapy, chemotherapy, targeted therapy, and other methods are difficult to effectively slow down the progress of the disease; ADT usually produces many adverse reactions [7], reducing the quality of life of patients during treatment [8]. Therefore, modern medicine still has many deficiencies in the diagnosis and treatment of prostate cancer, and there is still a lack of effective treatment methods.

In recent years, with the in-depth understanding of traditional Chinese medicine (TCM) regarding the etiology, pathogenesis, and treatment of prostate cancer, clinical research on TCM for the treatment of prostate cancer at various stages has gradually increased [9,10]. Numerous clinical trials and systematic reviews have been conducted on TCM or integrative medicine for prostate cancer to improve the efficacy and safety outcomes [11-14]. However, due to the lack of guidance on a core outcome set (COS), there is obvious heterogeneity in the selection of outcome measures among different studies. Meanwhile, TCM treatment includes a variety of interventions, such as Chinese medicine decoction, Chinese medicine capsule, Chinese medicine injection, and topical Chinese medicine patch therapy [15,16]. Hence, the complexity and diversity of clinical trials of TCM for prostate cancer makes it even more important to evaluate the efficacy of different interventions. How to select high-quality outcome indicators based on clinical trials is an urgent problem to be solved. A point that cannot be ignored is that the inconsistent and nonstandard reporting of outcome indicators and the status of adverse events is often underestimated or ignored, which may lead to a waste of medical resources, a reduction in clinical treatment efficacy, and an impact on the foundation of clinical trials and evidence-based clinical decision-making.

Therefore, to facilitate future research on TCM treatment of prostate cancer, we need to develop a COS. COS, as an agreed-upon set of standard outcomes for a specific disease or condition, can reduce the risk of reporting bias by prompting researchers to focus their reporting on a more specific set of outcomes that stakeholders agree are best suited to their field [17-19]. There is also the potential to reduce economic waste; improve the utility of randomized controlled trials; facilitate comparison of treatments across different sources of evidence; and aid in the development of systematic reviews, meta-analyses, and evidence-based clinical guidelines through standardized reporting of results in specific areas [20].

Methods

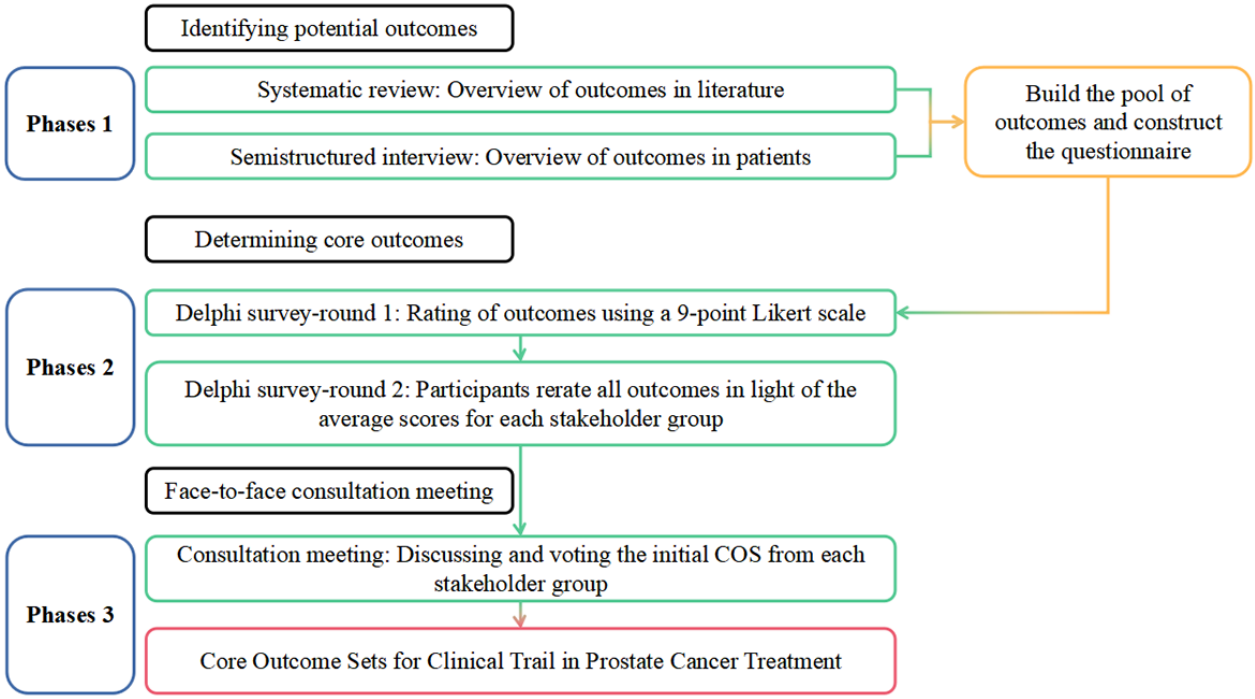
Methods Overview

This COS initiative was registered in January 2022 with the Core Outcome Measures in Effectiveness trial (COMET) initiative. We followed the Core Outcome Set-STAndards for Development [17], the Core Outcome Set-STAndards for Reporting [18], and the Core Outcome Set-STAndardised Protocol items [21] (Multimedia Appendix 1) for developing and reporting this COS. This section describes the 4 phases of the COS development using an international, web-based Delphi study, following the guidelines for a COS development [19]. Figure 1 presents an overview of the 3 phases.

Meanwhile, we will set up a research working group who will be responsible for the planning, guidance, and supervision of the research process of this project. The research group will comprise 5 experts, including 2 TCM or integrated TCM specialists in oncology, a Western medicine specialist in oncology, a nurse, and a methodologist. The Steering Committee will review and confirm the research protocol, identify a list of preliminary results, make decisions in case of confusion, and attend consensus meetings to facilitate the development of the core indicator set.

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Figure 1. Overview of the core outcome set (COS) development process.



Ethics Approval

This study has been granted ethics approval by the First Teaching Hospital of Tianjin University of Traditional Chinese Medicine Research Ethics Committee (TYLL2022[K]-21).

Phase 1: Identifying Potential Outcomes

We will identify potential outcomes used in studies evaluating the TCM clinical efficiency and safety in the treatment of prostate cancer by performing a systematic review. A semistructured interview will also be organized to identify outcomes that patients perceive as relevant and important (phase 1).

Identification of Outcomes Through a Scoping Review

A scoping review will be performed following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) checklist. This study protocol was registered in the PROSPERO database (CRD42022356184) before the start of the review process.

We will search 8 databases (PubMed, Embase, Cochrane, Clinical Trials, China National Knowledge Infrastructure, Wanfang Data knowledge service platform, and Chinese Scientific Journal Database), including search terms that encompass TCM and related preparations, prostate cancer, and controlled trials.

The English search strategy is presented in Multimedia Appendix 1. Studies will be included if they meet the following criteria: (1) clinical research (the type of research is not limited); (2) the research participants are patients with prostate cancer; (3) there are clear inclusion and exclusion criteria; (4) the intervention measures are Chinese medicine and Chinese medicine combined with Western medicine treatment, and the control measures are Chinese medicine and Western medicine treatment, a placebo, or blank control; (5) randomized controlled trials that have at least 30 patients in each group, and observational studies with at least 50 patients; (6) for published research, the language is limited to Chinese and English.

Data extraction included the name of the first author, number of participants, outcome measures (including primary and secondary outcomes), the definition of outcome measures, outcome measurement tools, and timing. In addition, the quality of outcome reporting and methodological quality will be assessed. After the data extraction is completed, it is necessary to standardize and merge the outcome index domain or the outcome index. Two researchers will jointly standardize and merge the outcome index domain or the outcome index and reach an agreement through negotiation.

Subsequently, 2 reviewers will independently extract relevant data from the included studies using a standardized data extraction sheet. Information will be extracted regarding the study design, study population, intervention characteristics, reported outcomes, and measurement tools. Disagreement will be resolved through discussion with a third reviewer. Results will include all unique outcomes and a frequency table of the most reported outcomes, sorted per outcome domain [22]. This list of unique outcomes will be presented to the expert panel (phase 2).

Identification of Outcomes Through Semistructured Interviews

It is necessary to consult patients on prostate cancer. Semistructured interviews will be conducted to ensure that certain topics are discussed, while giving the patient the flexibility to delve into details when needed. During patient interviews, information will be collected about health status, previous treatments and expectations, and inconveniences experienced during treatment. Patients aged ≥18 years who were diagnosed with prostate cancer in pathology and regularly

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received TCM or integrated Chinese and Western medicine treatment over 3 months and their family members or caregivers will be invited to participate in the semistructured interviews. Informed consent is required to recruit participants to this study. Patients will be assured at the start of the interview that they can choose to opt out at any time during the interview if they feel unable or uncomfortable to complete the interviews. The specific inclusion and exclusion criteria are presented in Textbox 1.

Textbox 1. The inclusion and exclusion criteria for the semistructured interview.

Inclusion criteria

- Patients with prostate cancer (pathological diagnosis according to the national guidelines for diagnosis and treatment of prostate cancer 2022 in China [23])
- Patients ≥18 years of age
- Traditional Chinese medicine (TCM) treatment or integrated TCM and Western medicine treatment ≥3 months
- Patients who signed the informed consent forms

Exclusion criteria

- Patients with a severe mental disease, cancer, and other life-threatening diseases
- Primary malignancies other than prostate cancer
- Participants judged by the investigator to be inappropriate for participation
- The patient refuses to participate in the study

Recruitment of Interviewees

Patient interviews will be conducted in China to ensure that the representative views of patients are included. We plan to interview potential patients in inpatient wards and outpatient clinics of the First Affiliated Hospital of Tianjin University of Traditional Chinese Medicine. There is no strict standard for the sample size of semistructured interviews. To achieve data saturation [24], based on the previous research experience, more than 30 patients will be recruited to ensure obtaining comprehensive results [25,26]. We believe that this sample size will be sufficient to achieve saturation in the semistructured interviews. However, if new viewpoints emerge during the interview, the sample size of the interview will increase. Patients participating in the interviews can complete questionnaires with the help of researchers. To improve the representativeness of the sample in the sample selection process, we will select patients with different ages, disease stages, disease severity, education, occupation, and family income.

Data Collection and Analysis

The questions in the semistructured interviews are as follows:

1. What are the most physiological and psychological effects of prostate cancer on you?
2. What kind of treatment (eg, radical prostatectomy, radiation therapy, and androgen deprivation therapy) have you received after the prostate cancer diagnosis?
3. What therapeutic effect do you want to achieve?
4. What kind of inconvenience does the current Chinese medicine treatment bring to you?
5. Which outcomes are important to you? Which one is the most important?

The patient interviews were audio recorded. After each interview, the recording was transcribed into text and read word by word to form a thematic framework and extract relevant outcome indicators [27]. The outcome indicators were standardized by 2 investigators and compared with the original outcome indicator list formed by the systematic review. If an outcome indicator was judged to be new, it was included in the Delphi survey.

Pooling and Grouping of Study Outcomes

After completing the original list of outcome indicators, according to the recommendations of the "COMET Handbook" [20], the standardized and merged outcome indicators were classified to form a list of outcome indicators of clinical safety outcomes of prostate cancer in clinical trials of TCM. Specific steps for this procedure are as follows:

1. Translating English into Chinese according to the terms formulated by the National Science and Technology Terminology Committee; if there are no relevant terms, 2 researchers will determine the appropriate translation.

2. Extracting the combined results as separate results.

3. Combining overlapping results into one result according to the definition of the result (eg, death, death from any cause, mortality, and total mortality)

4. Discarding results without definition or measurement tools.

5. Classifying the outcomes into different outcome areas according to the classifications developed by the COMET initiative (two researchers will cross-validate the results).

Any inconsistencies will be discussed further by the 2 researchers until a consensus is reached. Next, the results will be formatted as questions and submitted to the Delphi survey [28].

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Phase 2: the Delphi Survey

Stakeholders' Involvement

We will invite health industry stakeholders, such as prostate cancer clinicians, senior nurses, and researchers, and evidence-based medicine methodologists, to participate in 2 rounds of the Delphi survey [29]. The inclusion criteria for the participants in the Delphi survey are shown in Textbox 2. There are no exclusion criteria.

Textbox 2. The inclusion criteria for health professionals in the Delphi survey.

Inclusion criteria

- Health professionals with a bachelor's degree or above.
- Health professionals who have at least a senior title or above.
- Clinicians and nurses should have work experience in tertiary hospitals.
- There will be no restriction on the professionals' geographical area.
- The researchers (ie, first author, corresponding author, or other authors) should have published at least one clinical study related to traditional Chinese medicine.

Sampling

There is no consensus on the optimal sample size for the Delphi study, and based on the content of published literature, sample sizes for health professionals typically range from 30 to 120 participants [22,25,26]. In this study, following the research purpose of the project, we adhered to the principles of authority, representativeness, and regionality. We invited about 50 TCM or integrated TCM clinicians, nurses, and methodological experts specializing in prostate cancer–related areas to participate in 2 rounds of the Delphi survey.

Round 1 of the Delphi Survey

The first round of the Delphi survey will include all candidate results and ratings in different outcome areas. The questionnaire will be on a 9-point scale [20], where "1-3" indicates that the result is not important in the COS, "4-6" indicates that the result is important but not critical in the COS, and "7-9" indicates that the result is critical in the COS. At the end of the questionnaire, there will be an open-ended question: "What results do you think are important but not included in the questionnaire?"

Data analysis for the first round of the Delphi survey will include calculating the frequency of response options for each outcome. If no more than 10% of the participants who completed the questionnaire scored an outcome measure of 7-9, that result will be excluded from the second round of the Delphi survey. If participant-recommended results were not included in the first Delphi survey, 2 researchers will determine whether they are new or overlapping with existing outcomes. The new results will be included in the second round of the Delphi survey. Questionnaires for the Delphi law experts were distributed via email or WeChat (a Chinese web-based social software) and returned within 2 weeks.

Data Analysis for Round 1 of the Delphi Survey

We will use Microsoft Excel and SPSS 21.0 software (IBM Corp) and include descriptive analysis of the expert's basic information, including the expert's title, professional field, education, and years of experience, to understand the authority of expert consultation. We will analyze the responses from the first round, calculating the response rate and frequency of response options for each outcome. Moreover, we will analyze the distribution of scores for each stakeholder group. All results will be carried over to round 2 of the Delphi survey.

Round 2 of the Delphi Survey

The second round of the Delphi survey will be sent to participants who completed the first round. In the questionnaire, participants will receive scores from the first round of the Delphi survey and their stakeholder score distribution. They will be asked to rescore the results within 3 weeks. We will send an email or message to the participants, reminding them to complete the Delphi survey by the end of week 2. If the response rate is <80%, we will extend the opening hours of the Delphi survey or invite other eligible individuals to participate in the survey.

Data Analysis for Round 2 of the Delphi Survey

Data analysis for round 2 of the Delphi survey will include response rates; frequency of responses for each outcome option; distribution of scores for each stakeholder group; the outcomes that achieve "consensus in," "consensus out," and "no consensus"; and attrition bias. As shown in Table 1, each outcome will be defined into 3 categories [29]. SPSS 21.0 (IBM Corp) will be used to calculate the positive coefficient, degree of authority, and coordination coefficient of participants to demonstrate the validity of the 2 rounds of the Delphi expert consultation.

Attrition bias resulting from missing data will be determined by calculating the average score for each outcome among participants who completed or did not complete the 2 Delphi survey rounds. The missing data will not be considered if there is no attrition bias. The missing data will be considered as "unclear" if there is an attrition bias or if participants did not score all safety outcomes [30,31].

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Table 1. Definition of consensus.

Classification consensus	Criteria	Interpretation
Consensus in	• ≥70% of the participants rated the outcome 7-9 • <15% of the participants rated the outcome 1-3 • The average patient rating is ≥7, regardless of other scores	Outcome is important
Consensus out	• ≥70% of the participants rated the outcome 1-3 • <15% of the participants rated the outcome 7-9	Outcome is not important
Consensus to be further discussed	• All other results	Potentially important outcome

Phase 3: Consensus Meeting

Stakeholder Selection

We will invite experts who have completed the 2 rounds of the Delphi survey to conduct a face-to-face consensus meeting to discuss and vote on the final core set of outcomes; this core set of outcomes consists of the outcomes that were initially included and excluded from the 2 rounds of the Delphi survey. At this stage, we will invite members from systematic review groups, clinical guideline developers, health care workers, and journal editors; we will also invite patients and caregivers to participate in the meeting. The inclusion criteria for health professionals are shown in Textbox 3. There are no exclusion criteria.

Textbox 3. The inclusion criteria for health professionals in the meeting.

Inclusion criteria

- Health professionals with a bachelor's degree or above.
- Health professionals who have a senior title or above.
- Clinicians and nurses should have work experience in tertiary hospitals.
- Researchers who have conducted systematic reviews of prostate cancer in the past 10 years.
- Journal editors should have at least 3 years of work experience.
- Policy makers should have at least 5 years of work experience.
- There will be no restriction on the professionals' geographical area.

Sampling

Based on the published literature, there is no clear calculation method for the number of participants in consensus meetings [20]. However, to gather input from different stakeholders and improve consensus, we need to invite 20 professionals and 2-3 patients to participate.

Consensus Meeting Process

Participants who have participated in the 2 rounds of the Delphi survey will be requested to attend a web-based questionnaire meeting. In the consensus meeting, we will report the results of round 2 of the Delphi survey for health professionals and the results of the survey for patients. The outcomes labeled as "consensus out" by all stakeholders will be excluded. The outcomes labeled "consensus in" by all stakeholders will be sent to the Steering Committee and participants on the day preceding the consensus meeting.

In the consensus meeting, if participants disagree with an outcome that has achieved "consensus in" by all stakeholders to be included in the COS, they will further discuss it. Outcomes that do not reach a consensus will be individually addressed. Then, all participants in the consensus meeting will be anonymously asked to vote on these outcomes as "controversial" or "no consensus" outcomes. Any outcomes that receive votes from ≥ 70% of the participants will be included in the final COS.

Results

The protocol has been registered in PROSPERO; we will initiate the review on August 1, 2023, and results should be expected by September 1, 2023. At the time of the revised submission, the systematic reviews have been completed. The Delphi survey among stakeholders is expected to start in October 2023. We will publish our results through TCM-related associations and the COMET platform to promote recognition and application of the core indicator set in a wider range.

The finished COS will follow the recommendation of recent studies on dissemination strategies [30-32]. Each participant of the COS will be asked to implement the COS in their future clinical trials about the application of TCM in prostate cancer treatment and recommend this COS to their colleagues and other potential researchers. We will communicate our results via peer-reviewed publications, conference presentations, professional societies, and our institution's social media platforms. We will post our final COS information on the COMET website.

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Discussion

Constructing a core indicator set for the treatment of prostate cancer with TCM can improve the clarity of clinical research outcomes, thereby reducing the risk of publication bias and facilitating horizontal comparisons between different research results.

Prostate cancer is one of the most common malignant tumors affecting male individuals worldwide, posing a threat to patients' health and quality of life [1,33]. However, currently published clinical trials focusing on TCM treatment for prostate cancer have encountered problems related to inconsistent and nonstandard reporting of outcome indicators [11-13].

Of note, there are certain limitations to this study. For instance, due to literature search strategies or language restrictions, it is possible that not all relevant clinical trials have been included in our analysis. Additionally, although we strive to fully adopt the views of multiple stakeholder groups, some biases may still be present.

This protocol design establishes a comprehensive review of both international and Chinese literature by conducting semistructured interviews, Delphi surveys, and a consensus meeting to fully adopt the views of multiple stakeholder groups, which can ensure the feasibility and promotion of the COS in future clinical studies. The development of a COS ensures the consistency of reporting clinical study outcomes for prostate cancer in the future, assisting in reducing reporting bias. This allows for easier comparison and integration of results from different clinical trials in the future, improving the value of these clinical studies and minimizing the waste of research resources.

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Data Availability

The data sets generated and analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

XL and HT designed this project and wrote the manuscript; YZ and RM arranged the figures and tables. CW and YJ contributed to reviewing and editing the paper. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search terms used in the literature review.
[DOCX File , 24 KB - resprot_v12i1e46794_app1.docx]

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Abbreviations

ADT: androgen deprivation therapy
COMET: Core Outcome Measures in Effectiveness Trials
COS: core outcome set
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analysis
TCM: traditional Chinese medicine

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Protocol

e-Cigarette Use and the Cessation of Tobacco Cigarette Smoking: Protocol for an Umbrella Review

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Abstract

Background: Electronic nicotine delivery systems (ENDS), commonly called e-cigarettes, have been examined in clinical studies for their effects on tobacco smoking cessation. In the past 2 years, a dozen or more systematic reviews on ENDS and cigarette smoking cessation have been published that present differing conclusions and recommendations on the use of ENDS.

Objective: Our umbrella review aims to synthesize the findings from current systematic reviews to investigate the quit rates and the percentage of participants abstinent from cigarette smoking using ENDS. Additionally, we will examine the quit rates with ENDS in comparison to other established cessation treatments.

Methods: The search will retrieve systematic reviews that include both clinical trials and experimental studies on the use of ENDS for smoking cessation. We will also include nonrandomized cohort studies that track ENDS use and the subsequent abstinence from smoking. Databases searches will be conducted in Embase, Scopus, PubMed, and 7 additional registries. Secondary searches will include reference checking, citation chasing, and consultations with topic experts. Two reviewers will perform a title and abstract exclusion followed by a full-paper inclusion process. Data extraction will be conducted by 1 reviewer and completely checked by a second reviewer. Each systematic review will be assessed by 2 reviewers for methodological quality using AMSTAR2 (A Measurement Tool to Assess Systematic Reviews, version 2) and for reporting bias using categories from the Centre for Evidence-Based Medicine's Catalogue of Bias. Unreported discrepancies between the protocol and the published review will be identified.

Results: The umbrella review started on March 1, 2023. At the time of publication, the study selection was being conducted and the pilot testing of the data extraction and bias assessment forms were in progress. The review is expected to be completed by December 31, 2023, followed by the submission of the review for journal publication. A second-order meta-analysis will calculate the range and average of quit rates for ENDS. A vote counting of the direction of effect, based on quit rates, will be used to present the relative effectiveness of ENDS for smoking cessation compared to other cessation treatments (including no treatment). A citation matrix will list primary studies with their bias ratings from all the systematic reviews. The effect of overlapping studies between the systematic reviews will be calculated using the corrected coverage area analysis. A sensitivity analysis will examine the impact of the intensity of cessation treatment on quit rates. Depending on the availability of data, subgroup analyses will be conducted based on participants' gender, age, prior quit attempts, and nicotine dependence. The strength or weakness of the evidence synthesis will be assessed using a stratification of evidence technique. Reporting bias will be presented with a tabulation of bias indicators. Publication bias will be assessed.

Conclusions: The use of ENDS for smoking cessation is a highly controversial subject. Through an exhaustive synthesis of the available data, we will present the quit rates of cigarette smoking cessation obtained with ENDS and how they compare to quit rates obtained from other established cessation treatments. The critical quality and bias assessment of the systematic reviews will indicate the most reliable sources to inform treatment considerations and policy development.

Trial Registration: PROSPERO CRD42023406165; https://tinyurl.com/4ekzpbrj

International Registered Report Identifier (IRRID): PRR1-10.2196/47711

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(JMIR Res Protoc 2023;12:e47711) doi:10.2196/47711

KEYWORDS

e-cigarettes; electronic nicotine delivery systems; ENDS; umbrella review; cessation; systematic reviews; A Measurement Tool to Assess Systematic Reviews, version 2; AMSTAR2; review methodology; systematic; cigarette; smoking; smoker; quit; meta-analysis; meta-analyses

Introduction

e-Cigarettes, termed electronic nicotine delivery systems (ENDS), were invented in 2003 to be a cigarette cessation device [1]. The substantially reduced toxicant profile of ENDS compared to cigarettes [2,3] has motivated researchers to investigate its potential for supporting cigarette smoking cessation. As the number of clinical studies piled up, the first systematic review on ENDS for smoking cessation was published in 2014 by the Cochrane Group [4], and 21 systematic reviews were published by 2017 [5]. Even after excluding studies with a cessation outcome of less than 6 months' duration, the number of primary studies included in 2 current systematic reviews was 61 and 64, respectively [6,7]. Our preliminary search in PubMed for systematic reviews published since 2021 retrieved 20 potential publications.

Another systematic review is unlikely to make a significant contribution until more experimental studies are published. Our purpose for conducting an umbrella review is to provide the widest overview of the clinical evidence on the use of ENDS and their impact on cigarette smoking abstinence for an audience of researchers and clinicians highly polarized over the use of ENDS [8-10]. An umbrella review systematically searches and retrieves systematic reviews, critically appraises them, and synthesizes their results [11].

We have 4 research questions: 2 focus on cigarette smoking abstinence outcomes, and the other 2 focus on the quality of the evidence. These questions are as follows:

1. Are ENDS more, less, or equally effective in quit rates (ie, the percentage of participants who abstained from smoking), compared to other cigarette smoking cessation treatments?

2. What is the range of quit rates with ENDS in absolute numbers?

3. How weak or strong is the evidence base on the effectiveness of ENDS for smoking cessation?

4. Is reporting bias present in systematic reviews of ENDS for smoking cessation?

Methods

Structure of Review

Our protocol has been designed with reference to the Methods for Overviews of Reviews (MOoR) framework [11,12]. It has 20 steps with 54 substeps. Our protocol is reported based on the checklist provided in the recently published Preferred Reporting Items for Overviews of Reviews (PRIOR) statement by Gates et al [13]. It consists of 27 main items, 46 in total, and is specifically designed for health care interventions.

The population, intervention, comparator, and outcome (PICO) criteria below define the scope of our umbrella review for evidence on cigarette smoking cessation or abstinence with the use of ENDS. These criteria are as follows:

- Population: adults who formerly smoked and currently use ENDS or clinical trial participants who smoked cigarettes at baseline before using ENDS.
- Intervention: personal use of ENDS or ENDS use in a clinical trial.
- Comparator: cigarette smoking cessation treatments, including no treatment.
- Outcome: (1) quit rates, that is, the percentage of participants who abstained from smoking or quit smoking and (2) the quit rate with ENDS compared to other cessation treatments.

Search and Selection Processes

Database search sources will include Embase (Ovid), Scopus (Elsevier), PubMed, Cochrane Database of Systematic Reviews, PROSPERO, and Epistemonikos. For grey literature, database search sources will include MedNar, National Technical Information Service, WorldWideScience, and Open Grey.

The search parameters include keywords related to the intervention (eg, "cessation" OR "quit" OR "abstinence"), ENDS (eg, "e-cigarettes" OR "electronic nicotine" OR "electronic cigarettes" OR "vaping" OR "vape"), and the study design (eg, "systematic review"). The search fields include title, abstract, and keywords. A filter for systematic reviews will be applied, whenever available. One researcher will review the applicable keywords, fields, and filters specific to the database. Syntaxes will vary by database. The search syntaxes for each database will be recorded with a screenshot, counted, and dated; the retrieved records will be downloaded into an EndNote library. The library will be deduplicated, and the count will be recorded. The publication date starts from 2021 for 2 reasons. First, current systematic reviews are most likely to include the most recently published primary studies. Second, a preliminary scoping search was conducted to explore the possibility of an umbrella review study, and it retrieved 20 potentially eligible systematic reviews published from 2021, which is a substantial number for inclusion in an umbrella review.

Two researchers will independently screen the records by title and abstract (or summary). They will include the systematic reviews that cover the PICO components. Discrepancies will be resolved through discussion and referred to the project leader for a final disposition, if necessary. The interrater agreement and the count of excluded studies will be reported.

The next stage of the selection process is a full-paper review. Two reviewers will independently examine each study for

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inclusion and exclusion based on the criteria presented in Table 1.

Industry-funded studies, if any, will be discussed separately from the analyses.

Two researchers will independently evaluate the reviews for inclusion. Discrepancies will be resolved by discussion, and if unresolved, will be referred to the project leader for a final disposition and recorded for interrater reliability. All systematic reviews excluded during the full-paper examination will be listed, along with the reason for exclusion, in an appendix.

In a second round of searching, the systematic reviews selected for inclusion will be citation chased (snowball search) in Google Scholar by 2 researchers who independently examine the title and abstract of the papers. The selected papers will be downloaded and organized as a separate group within the library. Discrepancies between the 2 retrievals will be resolved through discussion or referred to the project leader for a final disposition, and the interrater agreement will be reported. Systematic reviews retrieved from this search will be selected using the criteria for full-paper review. The completed full-paper search will be reviewed by 2 topic experts, who will provide recommendations for any additional publications.

Table 1. Inclusion and exclusion criteria.

Criteria	Inclusion	Exclusion
Article type	Systematic review	All other study designs
Language	English, French, Italian, and other languages that may be translated	Reviews without an English abstract or summary
Publisher	Academic journals, government reports, and medical organizations	Predatory journals (not indexed in PubMed or Directory of Open Access Journals)
Primary study designs	Clinical trials, experimental studies, observational cohort studies, and randomized or nonrandomized studies	Cross-sectional studies, surveys, case studies, and qualitative studies
Population	Adults who use ENDS[a], who smoke, or who have stopped smoking cigarettes	Youth or participants who did not smoke before using ENDS
Data	Quit rates with ENDS and comparison of quit rates with ENDS and with other treatments	Reduction of cigarette use and dual use of ENDS and cigarettes
Duration of cessation	Explicitly defined	Duration not specified
Bias assessment of primary studies	Individual primary studies assessed using any method	No bias assessment of individual primary studies
Analysis or synthesis method	Meta-analysis and tabulation of quit rates across primary studies	Solely narrative or descriptive

[a]ENDS: electronic nicotine delivery systems.

Data Collection

The data extraction and quality assessments of a systematic review and its supplementary materials will be conducted simultaneously.

Data extraction will be performed using a prespecified data extraction form covering bibliographic information; funders; locality and setting; databases searched and dates; inclusion and exclusion criteria; outcome definition; primary studies with their bias assessments; data analyses (including sensitivity analyses); meta-analyses; any subgroup analyses; and the conclusion, quoted directly from the study. The specific items for data extraction will be identified by the research team. The form will be pilot-tested by the research team on 3 reviews and revised as needed. Data collection will be conducted by 1 researcher, and a second reviewer will cross-check the data extractions.

In cases where data items are missing, we will contact the author. Reviews lacking multiple data items may be excluded at this stage of the umbrella review. Any studies excluded for missing data items will be reported.

Quality Assessment

After completing the data extraction, the 2 reviewers will independently complete the AMSTAR2 (A Measurement Tool to Assess Systematic Reviews, version 2) checklist [14] to assess the overall confidence in the results of the review as high, moderate, low, or critically low. The research team will decide in advance which of the 16 domains will be designated as noncritical weaknesses or critical weaknesses. The rating assigned to these domains will be used as a proxy for assessing the risk of bias, with higher ratings indicating a lower risk of bias. Discrepancies in scoring will be discussed and referred to the project leader for disposition, if necessary. The interrater reliability will also be reported.

After completing the data extraction and the AMSTAR2 checklist, 2 reviewers will independently assess each review for reporting bias. Reporting bias will be identified by the following indicators: spin bias of nonsignificant findings, omitted findings, one-sided reference bias, framing by over- or underemphasis of outcomes, overreliance on *P* values, and data discrepancies [15]. The reporting of the review will be compared to its protocol or trial registration, and any deviations will be noted. Any indicators of reporting bias will be verified by the project leader.

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Before conducting the syntheses, we will conduct a sensitivity analysis to examine the overlap of primary studies across the systematic reviews. Analyzing overlaps is critical because they can result in certain studies being overweighted in the analysis. Currently, there is no one standard method in an umbrella review to correct or weight the meta-analysis for the overlap of primary studies across reviews [16]. Based on its long-term use and validation, we have selected the corrected covered area (CCA) [17]. The formula is CCA=(N-r)/(rc-r) where N is the total number of publications, r is the number of index studies, and c is the number of reviews. To calculate the CCA, a citation matrix of primary studies will be tabulated, and it will be included in our published review. The CCA score is classified as slight (0%-5%), moderate (6%-10%), high (11%-15%), and very high (>15%). The CCA analysis will be conducted with the 5-step process developed by Hennessy and Johnson [18].

The CCA score will inform the selection of systematic reviews for the meta-analyses using the decision tool developed by Pollock et al [19]. We will include the highest rated review by AMSTAR2 score where the reviews have a higher level of overlap. If a 90% overlap in primary studies is found among 3 or more reviews, they will be included together in a subgroup analysis.

Before conducting the syntheses, the primary study data items will be tracked across the reviews to identify any data discrepancies. Data discrepancies will be corrected by examining the primary study. This process constitutes data cleaning.

Results

Overview

The umbrella review started on March 1, 2023. At the time of publication, the study selection was being conducted and the pilot testing of the data extraction and bias assessment forms were in progress. The review is expected to be completed by December 31, 2023, followed by the submission of the review for journal publication.

The search and selection results will be reported with the PRIOR diagram.

A table of review characteristics will display pertinent information, data, and the AMSTAR2 ratings. Comprehensive review tables and the AMSTAR2 scoring will be presented in supplementary materials.

A citation matrix will present all the primary studies included in the systematic reviews and will list the bias rating given to the primary study by each review.

Analyses of heterogeneity across systematic reviews will be conducted on inclusion and exclusion criteria and the comparator used (eg, other cigarette smoking cessation treatments or no quit intention).

A check for publication bias based on quit rates will be conducted if there are 10 or more reviews with meta-analysis data available. A funnel plot will be graphed and analyzed.

Depending on the availability of data in the systematic reviews, we will conduct sensitivity analyses on 3 effect modifications related to smoking cessation: nicotine dependency, prior quit attempts, and treatment intensity (eg, counseling vs no support). A total of 3 data points will be required to conduct the analysis. If an effect modification is reported in fewer than 3 reviews, the findings will be presented in a narrative summary.

Planned Syntheses—Quit Rates and Comparative Quit Rates of Cessation Treatments

For the first research question, which pertains to the relative effectiveness of ENDS compared to other methods (including no method), we will conduct a vote counting of direction of effect for each individual cessation treatment.

For the second research question, which pertains to the quit rate for ENDS, we will conduct a second order meta-analysis by combining the odds ratios for quit rates obtained from various systematic reviews. The data from the meta-analyses in the reviews will be converted to odds ratios by using the conversion formulas listed by Fusar-Poli and Radua [20] in cases where they were not computed as such.

Each of the syntheses conducted for the 2 cessation questions will be tested with 3 sensitivity analyses: length of cessation (any vs >6 months vs longer durations), the AMSTAR2 rating (high rating vs all others), and the inclusion or exclusion of industry-funded primary studies in the systematic review.

For each of the cessation analyses, a subgroup analysis by gender and age will be conducted, where feasible.

Planned Syntheses—Quality of Evidence

For the third research question, which focuses on the strengths or weaknesses of the evidence, we will evaluate the strength of the evidence base by conducting a stratification of evidence with the criteria published by Fusar-Poli and Radua [20]. This method rates a meta-analysis as convincing, highly suggestive, suggestive, weak, or nonsignificant, as stratified by the number of cases, the P values, the I^2 values, and biases. The method will require a slight adaptation to suit the requirements of an umbrella review.

For question 4, which is related to reporting bias, we will tabulate the number of incidences identified for each reporting bias indicator (as described above), grouped by review and for each bias indicator.

Additional Items

To assess the overall confidence in the findings of the umbrella review, a scoring system will be used based on the number of study designs included and their AMSTAR2 rating, with a modification of the GRADE (grading of recommendations, assessment, development, and evaluations) system.

The “Discussion” section will include a summary of the main findings, any contradictory findings between the systematic reviews, limitations of the systematic reviews, limitations of the umbrella review, recommendations for future research, and the relevance of the findings to clinicians and policy makers.

All deviations from this protocol will be documented and justified in the published study.

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Discussion

Regarding the projected quit rates for smoking cessation, we expect them to be low, which unfortunately is the case for all cigarette smoking cessation treatments.

Our umbrella review will be subject to limitations. First, we will have a small research team of 4 members. Fortunately, the team has expertise in systematic and umbrella reviews with decades of research experience on ENDS. Regarding staffing constraints, we are well aware from prior experience that the identification of reporting bias is time intensive, but in our estimation, it is absolutely essential for credibility in our highly contested field.

Our dissemination plans are also subject to funding limitations. As a minimum, we will publish our umbrella review in an open-access journal and produce a white paper in plain language with infographics and post it on our research unit's website. We will also submit it for conference presentations after publication if team members are available. Low-cost avenues of knowledge translation will be considered as time permits.

The methods and processes specified in this protocol are all aimed at achieving one goal: to identify data on the effectiveness of ENDS for cigarette smoking cessation. Our purpose is to provide clinicians, policy makers, and individuals who smoke with the published evidence, enabling them to make evidence-informed decisions. With 15 or more systematic reviews published in just the past 2 years on ENDS for cigarette smoking cessation, the literature is ripe for an umbrella review.

Acknowledgments

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The contents, selection, and presentation of facts, as well as any opinions expressed in this systematic review are the sole responsibility of the authors and under no circumstances shall be regarded as reflecting the positions of the Foundation for a Smoke-Free World, Inc.

Data Availability

All data will be available in the systematic reviews. For Open Science, the completed data extraction forms, the AMSTAR2 checklists, and bias reports will be uploaded to Zenodo.

Authors' Contributions

RO and RP were in charge of the study conceptualization, writing the original draft, as well as reviewing and editing the final draft. RP was responsible for funding acquisition.

Conflicts of Interest

RO is supported by a contract with ECLAT Srl. ECLAT Srl has received funding from the Foundation for a Smoke-Free World. RP has received grants from U-BIOPRED and AIR-PROM, Integral Rheumatology & Immunology Specialists Network (IRIS), Foundation for a Smoke-Free World, Pfizer, GlaxoSmithKline, CV Therapeutics, NeuroSearch A/S, Sandoz, Merck Sharp & Dohme, Boehringer Ingelheim, Novartis, Arbi Group Srl, Duska Therapeutics, Forest Laboratories, and Ministero dell'Universita' e della Ricerca (MUR) Bando PNRR 3277/2021 (CUP E63C22000900006) and 341/2022 (CUP E63C22002080006), funded by NextGenerationEU, the European Union (EU) economic recovery package. He is the founder of the Center for Tobacco Prevention and Treatment (CPCT) at the University of Catania and of the Center of Excellence for the Acceleration of Harm Reduction at the same university. He receives consultancy fees from Pfizer, Boehringer Ingelheim, Duska Therapeutics, Forest Laboratories, CV Therapeutics, and Sermo Inc. He is being paid textbook royalties from Elsevier. He is also involved in a patent application for ECLAT Srl. He is a pro bono scientific advisor for Lega Italiana Anti Fumo (LIAF) and the International Network of Nicotine Consumers Organizations (INNCO). He is Chair of the European Technical Committee for Standardization on "requirements and test methods for emissions of electronic cigarettes" (CEN/TC 437/WG4).

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Abbreviations

AMSTAR2: A Measurement Tool to Assess Systematic Reviews, version 2
CCA: corrected coverage area
ENDS: electronic nicotine delivery systems
GRADE: grading of recommendations, assessment, development, and evaluations
MOoR: Methods for Overviews of Reviews
PICO: population, intervention, comparator, outcome
PRIOR: Preferred Reporting Items for Overviews of Reviews

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Protocol

Game Elements in the Design of Simulations in Military Trauma Management Training: Protocol for a Systematic Review

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Abstract

Background: Military trauma teams are commonly operating in civilian hospitals during peacetime; in a war situation they must adjust their practices to the austere conditions. Simulations can replicate austere conditions to allow training in a safe environment that tolerates errors. Gamification, understood as the use of game elements to motivate and engage learners in nongame contexts, is gaining interest in medical education and military training. Applying game elements in the design of military trauma management simulations has the potential to provide learners with active learning opportunities and prepare them for providing medical services under austere conditions. Although gamification is known for its engaging and motivational benefits, there are controversies about its pedagogical value. The controversies can be attributed to the fact that various gamification strategies may consist of a different combination of game elements, leading to different outcomes.

Objective: This systematic review aims to understand how game elements are used in the design of simulations in military trauma management training and their reported outcomes.

Methods: We have designed a search strategy for the purpose of the review. Two researchers will independently assess the identified studies based on the defined inclusion and exclusion criteria. The selection process will be represented using a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram. The search will be repeated and updated as necessary prior to publication of the review. Two reviewers will independently extract and manage the data for each of the articles using a structured data extraction form. Any disagreement that arises between reviewers will be resolved through discussion, and a third review author will be consulted when needed. We are going to conduct a thematic synthesis of the extracted game element descriptions. The results are going to be presented in a diagrammatic or tabular form, alongside a narrative summary. The quality of the studies will be assessed.

Results: We implemented and tested the developed search strategy in May 2023. We retrieved 1168 study abstracts, which were reduced to 630 abstracts after deduplication. We have piloted the screening on 20% (126/630) of the identified abstracts in groups of 2 reviewers.

Conclusions: Although gamification has the potential to motivate learners in various ways, there is a lack of understanding about specific game elements and how they can inform instructional design in different contexts. Our findings will increase the understanding of how game elements are used in the design of simulations in military trauma management training and, thus, contribute to more effective development of future simulations.

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KEYWORDS

gamification; game elements; military medicine; trauma; medical education; military training; systematic review; game; gaming; simulation

Introduction

Background

Trauma injury is one of the leading causes of death in Western countries and is a significant threat to public health [1]. Hemorrhage is the leading cause of preventable death in both military and civilian trauma [2]. In many nations, including Sweden, trauma team members work in both civilian and military settings, with military trauma teams commonly operating in civilian hospitals during peacetime [3]. Usually, the multidisciplinary trauma team consists of a variety of specialized health care professionals who collaborate with first responders and medics. Trauma patient outcomes are highly impacted by the performance of trauma teams, requiring a combination of technical and nontechnical skills. In a war situation, the trauma teams must adjust their practices to the austere conditions outside the fully equipped civilian hospital, operate with reduced numbers of team members, and deal with significantly higher numbers of patients than they might be accustomed to.

Prehospital trauma care differs significantly between a civilian and a deployed setting [4]. In the latter, resources in terms of personnel and equipment are limited, and there is a risk that multiple injured casualties can overburden the capacity of the resources. In the deployed setting the environment may hinder the provision of trauma management, due to challenging weather conditions and darkness. The environment may be hostile with the risk of gunfire hindering immediate patient care [5,6]. Additional tactical considerations may limit the possibilities for providing equipment and resources, as well as evacuating the patients requiring further care.

According to a recently published study [6], research and education may overlook the conditions of a truly austere environment. Health care professionals should be adequately trained to use a wide range of skills in environments with constrained resources in contemporary conflicts. Training does not stop at medical personnel but extends to the soldiers who are often the first responders. All combatants should be familiar with tourniquets and basic life support techniques. However, the learning opportunities to practice such skills are limited, due to the lack of exposure to trauma patients in austere conditions. In most cases, military medical personnel receive training in civilian settings for the tasks they will face in conflict. Simulation training has the potential to support the training and amend this imbalance [3].

Simulation can replicate austere conditions and allow the training in a safe environment that tolerates errors [7]. Simulation may refer to various technologies, from virtual reality equipment to mannequins and field exercises. Some simulation types can be resource-intensive regarding cost, facilities, faculty time, and the alignment of curricular and learners' schedules while others can provide more flexibility and scalability [8]. Different simulation technologies can be used to train different competencies in trauma [9]. A previous study [10] identified examples of emerging technologies used for trauma training that have the potential to support the education and training toward challenges that civilian trauma teams face when moving to an austere environment. Examples included virtual reality, virtual reality combined with haptics and manikins or requiring special equipment, virtual patients, and gamification.

Gamification is gaining interest in medical education [11] and military training [8,12]. Gamification is a strategy in simulation design understood as "the use of game mechanics as a further dimension... in an endeavor to nudge participants to perform certain actions, by adopting a playful attitude" [13]. For instance, the learner might be required to solve a problem under time pressure, compete or collaborate with other users, and earn points or badges [14].

Incorporating game elements in health professions education can increase motivation and improve learning outcomes, specifically when employing game elements that promote learning behaviors and attitudes [15]. Applying game elements in the design of military trauma management simulation has the potential to provide learners with active learning opportunities to prepare for providing medical services under austere conditions [12].

Previous work analyzing game elements in health care education, as well as in education in general, has led to frameworks that can support the design and evaluation of gamification design in learning environments [14,16]. Although gamification is known for its engaging and motivational benefits, there are controversies about its pedagogical value [13,15]. The controversies can be attributed to the fact that various gamification strategies may consist of a different combination of game elements, leading to different outcomes [17]. Although gamification has the potential to motivate learners in various ways there is a lack of understanding about specific game elements and how they can inform the instructional design in different contexts [17].

Aim

This systematic review aims to understand how game elements are used in the design of simulations in military trauma management training and their reported outcomes. Our research questions are:

1. What game elements are used in the design of educational simulations in the context of military trauma management?
2. How are the identified game elements used?
3. What is the purpose of using game elements in the designing of educational simulations in military trauma management?
4. What outcomes are reported related to the game elements?

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Methods

Inclusion and Exclusion Criteria

We will include both qualitative and quantitative empirical and design studies that address different types of simulation interventions, identified in our previous study [10], which incorporate game elements. Game elements will be identified using published gamification frameworks [14,16]. We will include game elements that support the education and training of military trauma management. The simulation interventions of the studies included should have an educational purpose in the context of military trauma management. Studies in which participants are passively observing rather than actively interacting with the intervention will be excluded. Studies that are using interventions primarily for patient education, rehabilitation, telementoring, treatment, surgical assistance, or planning are not within the scope of this review. We will exclude studies where the training only focuses on individual body parts. We will exclude studies that gamification is only used for assessment unless the assessment has an educational purpose and is not intended to assess the outcome of the study. Table 1 outlines our inclusion and exclusion criteria.

Table 1. Inclusion and exclusion criteria.

Criteria	Include	Exclude
Context and participants	All participants that are receiving training in the context of military trauma management. Participants are military medicine service providers (physicians, nurses, health care–qualified soldiers) at all stages of education. Included are also military personnel without health care qualifications who are trained to perform lifesaving procedures under combat conditions. Included are also health care personnel receiving military medicine education which requires immediate response and collaboration under austere conditions.	• Studies involving only civilian health care professionals without a clear link to military—for example, residents in an emergency medicine program participating in a gamified trauma simulation.
Education and training	All forms of learning opportunities both implemented in formal curricula and one-time educational events with the intention to gain knowledge, skills or improve attitudes.	• Scenarios where the gamified simulation is used merely as a form of outcome measurement and the educational impact of the assessment itself is not considered. • Simulations containing game elements with planned therapeutic health effect—for example, in treatment of posttraumatic stress disorder; those that aim to be used for diagnostic purposes or as motivational elements to improve compliance with treatment regimen. Excluded are also studies that are using interventions primarily for patient education, rehabilitation, telementoring, treatment, surgical assistance, or planning.
Trauma	Scenarios in which people were physically injured and require stabilizing, time-critical decisions with incomplete information, performance of concurrent medical aid tasks, multidisciplinary management, and collaboration. Both simple (one body system) and complex injuries (more than one body system) are included.	• We exclude psychological trauma without physical injuries that required immediate attention. • We also exclude studies that focus only on individual injured body parts without considering the context of the injury.
Simulation	Empirical or design studies including a simulation modality such as virtual and mixed reality, virtual worlds, digital and non-digital games, interactive scenarios such as virtual patients, mannequins, part task trainers, artificial wounds and cut suits, standardized patients, and deliberately designed realistic field exercises employing role-playing.	• Studies where participants are passive observers without interacting in the simulation.
Game element	At least one game element is included in the simulation as defined by Maheu-Cadotte et al [14]. We will also include studies with game elements going beyond the classification framework by Maheu-Cadotte et al [14] provided the activity or feature is explicitly and detailed enough described as designed to introduce game elements into the simulation. The included simulations must have an interactive plot as a game element.	• Simulations, where the plot is in the form of a case vignette without interactive unfolding during the intervention, are going to be excluded.

Search Methods for Identification of Studies

We will explore the databases or search engines Medline (Ovid), PubMed, IEEE Xplore, ERIC, Web of Science, and ACM Digital Library CINAHL with the help of librarians at Karolinska Institutet. We will include all articles regardless of publication language.

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Searching Other Sources

For all included studies, we will search reference lists and conduct author and citation searches. We will search the lists of references of other systematic reviews that are identified while running our electronic searches.

Selection of Studies

We will import all references identified to the Rayyan open-source web system. Two researchers will independently assess the identified studies based on the inclusion and exclusion criteria. Any disagreements will be resolved through discussion between the 2 reviewers. If no agreement can be reached, a third author will be consulted. The selection process will be represented using a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram, including the actual number and the inclusion and exclusion criteria of each stage of screening [18]. The search will be repeated and updated as necessary prior to publication of the review.

Data Extraction and Management

Two reviewers will independently extract and manage the data for each of the articles using a structured data extraction form. The data extraction process will be piloted among the researchers. Any disagreement that arises between reviewers will be resolved through discussion and if needed mediation of a third review author. If any articles are in a language the authors are not familiar with, the text in a non-English language will be first automatically translated by an artificial intelligence–powered translation tool (DeepL; DeepL SE), and if needed, a researcher native to the language will be consulted. We deem this strategy to be sufficient as we aim to analyze the manifest presentation of game elements and are not investigating the latent, culture-based, meaning of game elements. The data extraction form will be based on our previous systematic review [19] and will include extraction categories such as research aim, learning objectives, setting, subject, group of learners, instruments used for assessment if any, outcome of the intervention, and will be extended by fields such as type of simulation, game elements, type of trauma, and austere factors. To answer the second and third research questions, qualitative data (ie, text passages describing the game element design and purpose and images like screenshots showing game elements) will be extracted for thematic synthesis. To provide answers to the first and fourth research questions, we will extract data based on prespecified categories, inspired by the identified gamification frameworks and former systematic reviews [14,16,19]; the data extraction form corresponding to these topics is enclosed in the Multimedia Appendix 1.

Data Analysis, Synthesis, and Reporting

A qualitative data analysis combined with a thematic data synthesis will be conducted. In particular, the extracted data will be synthesized following the processes outlined by Thomas and Harden [20]. First, the data are going to be coded in a reductant way to encapsulate the meaning of the extracted text. Codes will be developed from the text and extend and modify prespecified codes adopted from the identified gamification frameworks [14,16]. Next, descriptive themes are going to be established to unify codes that have been identified in more than one study. In the third and last stage, analytical themes will be generated; this step will aim to interpret the identified descriptive themes in a way that can support answering of the research questions. The data synthesis will be performed by the first author (NS) and will be discussed and reviewed by all authors. The results are going to be presented in a diagrammatic or tabular form, alongside a narrative summary.

Quality Appraisal

The quality of studies will be assessed with the use of the Medical Education Research Study Quality Instrument (MERSQI) [21] and the grid suggested by Côté and Turgeon [22].

Results

We implemented and tested the developed search strategy in May 2023. We retrieved 1168 study abstracts, which were reduced to 630 abstracts after deduplication. We have piloted the screening on 20% (n=126) of identified abstracts in groups of 2 reviewers. Our search strategy may be found in Multimedia Appendix 2.

Discussion

Anticipated Findings

Gamification has the potential to motivate learners in various ways, and it is showing promising results in improving forward combat casualty care performance in a simulated tactical environment [23,24]. The effectiveness of games as instructional tools has been debated over the years as there is a lack of understanding about specific game elements and how they can influence the reported outcomes. A recent systematic literature review about the application of virtual reality and haptic interfaces for civilian and military open trauma surgery training reports mixed and poor-quality evidence about their realization in education [25]; we envision that an enhanced understanding of game elements in educational simulations would inform the design of educational technologies and simulations.

Our starting point to interpret and configure the game elements is based on existing frameworks to understand gamification as a concept [14,16]. Several definitions exist for gamification, with the most widespread definition to be from Deterding et al [26] as the use of game elements in nongame contexts. In this protocol, we use a relatively new definition proposed by Pfeiffer et al [13] that emphasizes the principle of nudging [27] the participants with playful elements to engage in simulation, and therefore it can be understood as a tool for triggering positive behaviors towards learning.

We acknowledge that our backgrounds may influence the data analysis and synthesis. NS and AAK have a background in health informatics and research interests in educational technologies, specifically virtual patients; CS is a military surgeon and researcher in surgical education; and KK has a background in interaction design, technology-enhanced learning, and medical education.

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Limitations

A potential limitation of the upcoming systematic review might be that evidence published in gray literature is not going to be retrieved; we might therefore overlook evidence about gamification applications that have not been reported in peer-reviewed journals. Additionally, we may not retrieve papers that did not include keywords that we have a priori associated with game elements. To control this challenge, we have collaborated with a team of professional librarians to design a complex search strategy and will hand-search references in included studies.

Conclusions

To our knowledge, this is going to be the first systematic review to explore game elements in the design of educational simulations in the context of military trauma management. Our findings will increase the understanding of how game elements are used in the design of simulations in military trauma management training and by that hopefully contribute to more effective development of future simulations.

Acknowledgments

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This study is financially supported by the Swedish Armed Forces.

Data Availability

The data sets generated or analyzed during this study are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Data extraction sheet and initial coding frame for game elements and outcomes in the included studies.
[DOCX File , 20 KB - resprot_v12i1e45969_app1.docx]

Multimedia Appendix 2
Search strategy and number of results retrieved.
[DOCX File , 44 KB - resprot_v12i1e45969_app2.docx]

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Abbreviations

MERSQI: Medical Education Research Study Quality Instrument
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

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Protocol

Implementation of Machine Learning Applications in Health Care Organizations: Protocol for a Systematic Review of Empirical Studies

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Abstract

Background: An increasing interest in machine learning (ML) has been observed among scholars and health care professionals. However, while ML-based applications have been shown to be effective and have the potential to change the delivery of patient care, their implementation in health care organizations is complex. There are several challenges that currently hamper the uptake of ML in daily practice, and there is currently limited knowledge on how these challenges have been addressed in empirical studies on implemented ML-based applications.

Objective: The aim of this systematic literature review is twofold: (1) to map the ML-based applications implemented in health care organizations, with a focus on investigating the organizational dimensions that are relevant in the implementation process; and (2) to analyze the processes and strategies adopted to foster a successful uptake of ML.

Methods: We developed this protocol following the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) guidelines. The search was conducted on 3 databases (PubMed, Scopus, and Web of Science), considering a 10-year time frame (2013-2023). The search strategy was built around 4 blocks of keywords (artificial intelligence, implementation, health care, and study type). Based on the detailed inclusion criteria defined, only empirical studies documenting the implementation of ML-based applications used by health care professionals in clinical settings will be considered. The study protocol was registered in PROSPERO (International Prospective Register of Systematic Reviews).

Results: The review is ongoing and is expected to be completed by September 2023. Data analysis is currently underway, and the first results are expected to be submitted for publication in November 2023. The study was funded by the European Union within the Multilayered Urban Sustainability Action (MUSA) project.

Conclusions: ML-based applications involving clinical decision support and automation of clinical tasks present unique traits that add several layers of complexity compared with earlier health technologies. Our review aims at contributing to the existing literature by investigating the implementation of ML from an organizational perspective and by systematizing a conspicuous amount of information on factors influencing implementation.

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KEYWORDS

artificial intelligence; barriers; facilitators; health care organization; implementation; machine learning

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Introduction

Rationale

After a period of so-called artificial intelligence (AI) winter, AI has re-emerged into the scientific and public consciousness by virtue of new technological breakthroughs and marketed solutions [1]. Recent machine learning (ML) applications have expanded the frontiers of AI. In this scenario, finding an operational definition of AI and ML is challenging. While the term AI has been embraced for regulatory purposes [2], various technical domains view it as a descriptor for the latest advancements in computer science. Consequently, as AI becomes more pervasive and integrated into mainstream applications, experts gradually disassociate it from its original designation [3]. ML instead refers to the subset of AI encompassing all the non–knowledge-based techniques that automatically learn from data without being explicitly programmed [4,5]. Recent advances in ML promise remarkable improvements in medical diagnosis and prognosis [6,7], generating tremendous enthusiasm surrounding these innovations. The use of ML in clinical environments has hitherto experienced diverse adoption patterns, with the field of radiology raising considerable attention due to the notable capability of ML (in particular, deep learning [DL]) models to extract valuable information from medical images [7]. Other clinical areas are also a fertile environment for ML-based applications, as their outcome prediction capabilities are expected to help health care systems improve the quality of care and use resources more accurately and efficiently [8].

Regulatory science has tried to keep up with these advances by adopting a permissionless innovation approach with low barriers for the entry of new algorithms [9]. Despite the European Union and the United States regulating AI with distinctiveness [10], regulatory approaches to ML are still under definition, ultimately impacting on the access strategies of developers [11] and contributing to delaying the deployment of ML in clinical practice and in specific settings.

Previous literature has well documented the implementation of expert systems and knowledge- or logic-based applications [12], all included in the definition of AI proposed by the High-Level Expert Group on Artificial Intelligence appointed by the European Commission [13]. Instead, ML-based applications assumed a prominent role only recently, thanks to greater data availability and computing capabilities [14]. Nevertheless, due to the incremental complexity of ML-based applications [12], their incorporation into health care processes is fraught with different challenges that need to be organically steered by various stakeholders [15]. ML-based applications that encompass the characteristics of autonomy, inscrutability, and learning [16] hence need further investigation from the implementation science community.

Recent scholarly contributions have shown that a theoretical understanding of the dimensions and dynamics associated with the implementation of AI in health care organizations is still in its infancy [14]. Empirical knowledge about the implementation of AI comes mostly from systems with a low level of autonomy and learning (ie, knowledge-based applications) and looks at either clinical effectiveness, technical efficiency, or regulatory and legal issues of such technologies, overlooking the organizational aspects [17]. For this reason, our work focuses exclusively on non–knowledge-based ML, namely tools that use some form of either supervised or unsupervised learning, and not on traditional knowledge-based AI algorithms.

Research on ML implementation has been predominantly conceptual in nature, with the identification of distinguishing issues in the development and dissemination in clinical practice, such as the opacity or black-box effect, and concerns surrounding equity, data privacy, and security [7,18]. Conversely, the consequences that such characteristics have on the implementation of ML in health care organizations have been poorly investigated empirically. A recent scoping review by Chomutare and colleagues [19] adopted a mixed deductive-inductive approach to extract barriers and facilitators to the implementation of ML and map them onto the Consolidated Framework for Implementation Research (CFIR) [20], identifying generalizability, interoperability, and data quality as the main barriers and engagement in the implementation process as the main facilitator [19]. However, additional inquiry is needed to gauge whether the current body of empirical studies of ML adequately acknowledges distinguishing implementation challenges such as trust and explainability and to analyze which implementation strategies have been adopted to address them.

Objectives

Given the potential disruptiveness of recent developments of ML in health care and the lack of knowledge about how to overcome the organizational challenges associated with their implementation, our research objectives are to identify and explore cases of real-life implementation of ML within health care organizations as documented in the literature and to synthesize the processes adopted to foster a successful implementation of ML. We plan to conduct a systematic literature review with the following goals in mind:

1. To examine the stages and characteristics of implementation processes described in empirical studies on ML under the lens of implementation science, namely the scientific study of methods to promote the uptake of evidence-based innovations into routine practice [21]. Specifically, the CFIR will be adopted as a practical theory-based guide for assessing the implementation outcome and complemented with implementation considerations associated with the distinctive features of ML.
2. To analyze the observed or suggested determinants of successful uptake of ML, thereby identifying the implementation processes and strategies currently adopted by health care organizations.

Methods

Study Design

This systematic review protocol follows the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) statement [22,23] and was registered within the PROSPERO (International Prospective Register of

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Systematic Reviews) on March 3, 2023 (registration number 403873).

Eligibility Criteria

This review will be focused on studies that investigate aspects related to the implementation of ML-based applications in health care organizations. For the purposes of this review, by implementation, we define the "active and planned effort to mainstream innovation within an organization" [24], while the term "health care organization" refers to entities that deliver health services, including hospitals (general, community, teaching, or research hospitals), outpatient centers, and primary care and public health facilities. Studies will be selected based on the eligibility criteria described below and summarized in Textbox 1.

Textbox 1. Eligibility criteria.

Inclusion criteria

- Study design: empirical studies based on implementation research designs (experimental or quasi-experimental, observational, hybrid, and simulation study designs)
- Intervention: implementation of machine learning (ML)–based applications including considerations on the inner setting and/or implementation process domains
- Stakeholder groups: ML-based applications used at least by health care professionals
- Settings: hospitals, outpatients, and other community care settings

Exclusion criteria

- Study design: effectiveness research study designs, literature reviews, commentaries, editorials, opinion articles, study protocols, studies collecting perceptions on implementation, and unrelated to specific ML-based applications
- Intervention: implementation of knowledge-based applications
- Stakeholder groups: ML-based applications targeting patients and other nonclinical stakeholders (eg, caregivers, policy makers, and regulators) only

Study Design and Publication Type

We will select peer-reviewed empirical studies documenting the implementation of ML-based applications, thereby including experimental or quasi-experimental, observational, hybrid, and simulation study designs [25]. In the context of implementation research, experimental studies typically aim to evaluate the impact of specific strategies to improve implementation, whereas observational designs examine the implementation in service delivery using approaches that are quantitative, qualitative (eg, semistructured interviews with involved end users), or mixed methodologies. We will also consider hybrid designs, which blend the components aimed at testing clinical effectiveness with those that analyze the implementation process by investigating potential barriers and facilitators to the implementation and assessing outcomes such as adoption, reach, acceptability, and fidelity [26]. We will exclude comparative effectiveness study designs (such as randomized controlled trials that only aim at generating clinical evidence and do not imply organization-wide implementation), as well as nonempirical designs, including editorials, commentaries, opinion articles, and other published reviews of the literature. Works based on surveys and interviews with subject matter experts will be excluded if they broadly investigate issues concerning the adoption of ML-based applications and do not report on the implementation process of specific technologies in a given organizational setting.

Intervention

Studies will be considered eligible if they analyze the implementation of tools based on ML in health care organizations and discuss the associated processes, context, barriers, or facilitators. As part of ML, we will include both DL techniques, unanimously considered as a subset of ML [5], and natural language processing models when based on ML. The latter, by their very nature, do not necessarily involve learning techniques. However, DL techniques have been widely used to overcome the limitations of symbolic approaches applied to natural language processing, and most of its recent development is unanimously attributed to DL approaches [27-29].

Based on the constructs of the updated CFIR [20], only articles including considerations on either the inner setting in which the innovation has been adopted or the activities and strategies being used to implement the innovation will be included. Studies only focusing on the clinical implications of the implementation or based on logic- and knowledge-based applications (expert systems) will be excluded.

Stakeholder Groups

We will include studies focused on ML-based applications available for use by health care professionals. Applications used by patients, caregivers, health care administrators, and policy makers will only be included if they are also used by clinicians and other health care professional groups.

Setting

We will include studies with a spotlight on the implementation of ML-based applications in clinical practice, biomedical research, and public and global health, as per the classification provided by the European Parliament [30]. All possible organizational settings related to these practices will be considered, including inpatient units, emergency departments, outpatient settings, and primary care. ML-based applications used in administrative settings will be excluded.

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Time Frame

Considering the rapid evolution and changes in ML-based applications, we will only consider studies published in the past 10 years (since 2013).

Information Sources

Literature searches were conducted in MEDLINE (PubMed), Scopus, and Web of Science and replicated in top-tier management journals (ie, Academy of Management Journal, Organization Science, MIS Quarterly, Journal of Management Studies, Organization Studies, and Academy of Management Annals). In addition, the reference list of all included studies and of the reviews identified will be scanned to ensure that any relevant work is captured. Gray literature was not considered.

Search Strategy

The search strategy was developed, including a combination of keywords around four main concepts: (1) AI, (2) implementation, (3) health care, and (4) study type.

The list of search concepts and associated terms used is provided in Textbox 2.

The exact search stream was developed by the research team following an iterative process. The general term "artificial intelligence" has been used to encompass studies that address the terms AI and ML as synonymous. The search strategy was initially finalized for PubMed and then adapted to the syntax and subject headings of the other databases. The initial search was performed in April 2023.

Textbox 2. Concepts to be used to define the search string.

Main search concepts, to be combined using "AND"

- Artificial intelligence
- Implementation
- Healthcare
- Study type

Search concepts synonyms, to be combined using "OR"

- Artificial Intelligence, Machine Learning, Deep Learning, Natural Language Processing
- Implementation, Adoption, Diffusion, Uptake
- Healthcare, Health*, Therap*, Patient*, Clinic*, Care, Professional, Medic*, Doctor, Hospital, Life Science, Pharma
- Empirical, quantitative, trial, qualitative, interview*, case stud*, case report, field stud*, field research, mixed-method*, mixed method*, focus group*, observational stud*, hybrid design, hybrid stud*, trial

Study Records

Data Management

The records retrieved from the literature search were uploaded and merged into RefWorks, a reference management tool that simplifies the process of research and collaboration among the review team. Duplicates were removed, and the identified list of records was extracted into an Excel (Microsoft Corp) spreadsheet for title and abstract screening.

Selection Process

A total of 2 researchers (VA and LMP) screened the first 100 retrieved articles based on titles and abstracts. Interrater agreement was measured using kappa statistics [31]. Once aligned on the eligibility criteria, the remaining papers were screened independently by the review team (VA and LMP) based on titles and abstracts. Disagreement over final inclusions was solved with a third researcher (FP). Studies deemed eligible for full-text reading will be assessed in depth (VA, LMP, and FP). Disagreements will be solved by dialogue with 2 other researchers (GC and AC). The entire research team will read all the studies eventually included in the analysis.

Data Collection Process

The data collection process will be performed by 3 reviewers (VA, LMP, and FP). Data will be extracted using an ad hoc Excel (Microsoft Corp) spreadsheet, preliminarily developed by the research team. To ensure consistency across reviewers, the extraction sheet will be tested by each reviewer and possibly recalibrated before starting the data collection process. Disagreements will be resolved by discussion, and 1 of 2 arbitrators (GC and AC) will adjudicate unresolved disagreements. Information on the implementation process of ML-based applications will be collected, as specified in the following section.

Data Items

Data items to be extracted from the selected studies will include the following fields, based on preexisting, established classifications or schemes, where possible:

1. Demographic information: study identifiers, authors, journal outlet, publication year, and keywords.
2. Methodology: study design.
3. Setting: country, organizational setting (eg, hospital inpatient, emergency department, and primary care), organizational nature (eg, public and private), and unit of implementation of the ML-based application.
4. Implementation stages: stages of the implementation process described in the study, adapted based on Aarons et al [32].
5. Intervention: name and description of the ML-based application, level of integration with other technologies, main practice (ie, clinical practice, biomedical research,

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public and global health, and health care administration) [30], steps of the clinical workflow impacted by the ML-based application [33], ML capabilities (eg, recognizing sounds vs images vs texts) [34], type of learning system (ie, supervised vs unsupervised vs semisupervised learning) [35,36], level of autonomy that the ML-based application foresees (from data presentation only to full autonomation following the classification by Bitterman and colleagues [37]), underlying data fed in the ML-based application (ie, quantity, quality, and data inputs), and previous evaluation of effectiveness [14].

6. Individuals: actors involved in the development and implementation of the ML-based application.
7. Inner setting: factors related to the organizational context in which the innovation is implemented, including both persistent general characteristics of the organization and properties specific to the delivery of the innovation. These include implementation capacity and readiness, as well as ML-specific domains such as the consideration of ethical concerns [38] and computational resources (ie, any references to the availability of substantial computing power, either proprietary or through cloud-based analytics, and organizational policies or strategies that have favored data storage and processing) [39].
8. Outer setting: considerations on the setting in which the inner setting exists, such as legislative, regulatory, accreditation, and reporting authorities and aspects [40], partnerships and connections with external entities, and external pressure from either social movements, peer organizations already adopting the technology, or benchmarking metrics [20].
9. Implementation process, including activities and strategies used to implement, assimilate, and routinize the innovation, encourage participation, and collectively discuss the success of the process.
10. Barriers and facilitators explicitly cited in the study.
11. Outcomes: observed, measurable outcome domains and metrics associated with the implementation process.

Data Synthesis

A narrative analysis will be adopted to synthesize the findings from the included studies, as the characteristics of the implementation processes will be tabulated and summarized through descriptive statistics according to the implementation-science domains selected for data collection. Given the objectives of this systematic review, the wide variety in the study designs and outcome domains considered, and the prospected predominance of qualitative studies, no quantitative synthesis of the results will be performed.

Results

The systematic review is ongoing. As of June 1, 2023, we have finalized the identification of records and the title and abstract screening of the 3520 records that met our search criteria. A full-text review is currently underway and will be completed by September 2023. After data synthesis, we plan to disseminate the study results by submitting the corresponding manuscript to a peer-reviewed journal in November 2023.

Discussion

ML-based applications have proliferated exponentially in recent years and demonstrated to have high potential both to streamline the clinical workflows and to improve patient outcomes. Yet, available studies have focused mainly on the technical components of ML-based applications and on their clinical efficacy, while the organizational preconditions or determinants needed to facilitate or sustain their implementation have been overlooked, emphasizing the need to identify effective strategies and foster the use of theories, models, and frameworks to facilitate implementation [41].

Therefore, our research will systematically review and synthesize the evidence of empirical studies reporting on implemented ML-based applications that are used in the real world. To comprehensively investigate implementation factors at the organizational level, ML-based applications that impact the activities of health care professionals at large will be considered.

In this context, the domains of the updated CFIR will be used as a practical tool to guide the data extraction and interpretation of the organizational factors that drive implementation, adopting the theoretical lens of implementation science. As such, we expect that our review will contribute to the field of implementation science research, a field that seeks to systematically close the gap between what we know and what we do (ie, the know-do gap) [21], adding insightful knowledge to the implementation science literature on ML.

The strengths of our prospective literature review are that it will follow a standardized methodological approach by adhering to systematic review guidelines (ie, PRISMA statements and checklist for systematic reviews) [42] and that it will aim at systematizing a conspicuous amount of information on factors influencing implementation. On the contrary, potential limitations lie both in language barriers, as only articles published in English will be scrutinized, and on the exclusion of the gray literature.

This work is part of larger research whose overarching aim is to develop a conceptual framework for the implementation of ML in health care organizations in an effort to support the adoption and deployment of health care innovations. In perspective, the theoretical basis of this work will therefore pave the way for the later conceptualization of an implementation framework that will stem from the available implementation science frameworks, but will be tailored to also account for the distinctive features of ML. This process will be additionally informed by the engagement of expert stakeholders employed in health care organizations, who will provide qualitative inputs based on their real-life experience with ML to fine-tune and finalize the framework. All in all, starting with the current review, the aim of our research is twofold: building a practical tool for health care practitioners while transitioning toward the use of ML-based applications within their organization, while also contributing theoretically to management and innovation theories.

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Acknowledgments

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Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed for this research protocol. All data extracted from the literature and generated during the prospective systematic review will be included in the published article or made available upon request.

Authors' Contributions

GC and AC conceived the initial concept for the review. VA, FP, and LMP generated the first draft of the manuscript. VA and LMP carried out the search strategy and initial screening of the records. All authors contributed to developing the data extraction form and revised and approved the final version of this manuscript.

Conflicts of Interest

None declared.

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Abbreviations

AI: artificial intelligence
CFIR: Consolidated Framework for Implementation Research
DL: deep learning
ML: machine learning
MUSA: Multilayered Urban Sustainability Action
PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols
PROSPERO: International Prospective Register of Systematic Reviews

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Protocol

Policies and Management Interventions to Enhance Health and Care Workforce Capacity for Addressing the COVID-19 Pandemic: Protocol for a Living Systematic Review

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Abstract

Background: Countries and health systems have had to make challenging resource allocation and capacity-building decisions to promote proper patient care and ensure health and care workers' safety and well-being, so that they can effectively address the present COVID-19 pandemic as well as upcoming public health problems and natural catastrophes. As innovations are already in place and updated evidence is published daily, more information is required to inform the development and implementation of policies and interventions to improve health and care workforce capacity to address the COVID-19 pandemic response.

Objective: The objective of this protocol review is to identify countries' range of experiences with policies and management interventions that can improve health and care workers' capacity to address the COVID-19 pandemic response and synthesize evidence on the effectiveness of the interventions.

Methods: We will conduct a living systematic review of quantitative, qualitative, and mixed methods studies and gray literature (technical and political documents) published in English, French, Hindi, Portuguese, Italian, and Spanish between January 1, 2000, and March 1, 2022. The databases to be searched are MEDLINE (PubMed), Embase, SCOPUS, and Latin American and Caribbean Health Sciences Literature. In addition, the World Health Organization's COVID-19 Research Database and the websites of international organizations (International Labour Organization, Economic Co-operation and Development, and The Health System Response Monitor) will be searched for unpublished studies and gray literature. Data will be extracted from the selected documents using an electronic form adapted from the Joanna Briggs Institute quantitative and qualitative tools for data extraction. A convergent integrated approach to synthesis and integration will be used. The risk of bias will be assessed with Joanna Briggs Institute critical appraisal tools, and the certainty of the evidence in the presented outcomes will be assessed with the Grading of Recommendations, Assessment, Development and Evaluation.

Results: The database and gray literature search retrieved 3378 documents. Data are being analyzed by 2 independent reviewers. The study is expected to be published by the end of 2023 in a peer-reviewed journal.

Conclusions: This review will allow us to identify and describe the policies and strategies implemented by countries and their effectiveness, as well as identify gaps in the evidence.

Trial Registration: PROSPERO CRD42022327041; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=327041

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KEYWORDS

COVID-19; health and care workforce policy; health and care workforce capacity; management interventions; SARS-CoV-2; pandemic

Introduction

Health systems worldwide have been challenged by the COVID-19 pandemic, which affected about 670 million people as of May 2023 [1]. The need for the health and care workforce (HCWF) to be adaptable and flexible in the face of constant change was emphasized, as almost all countries affected by the pandemic faced a surge in reported cases and disruptions of essential health services [2].

The pandemic resulted in a high incidence of SARS-CoV-2 infections and deaths among health and care workers (HCWs); increased workload (accentuated by absenteeism and quarantine); and exposure to work-related health hazards and their consequences, including fatigue, psychosocial stress, despair, violence, and a shortage of personal protective equipment, among others [3,4]. Moreover, it highlighted preexisting weaknesses in health and care systems and services, such as a shortage of HCWs, as well as other sorts of imbalances that are long-standing challenges observed in almost every country [5].

A recent study concerning HCWs' perceptions of government responses, support, and the impact of their measures on public and private health sectors identified dissatisfaction in most cases [6]. Particularly, they were discontent with the lack of health system organization; unequal distribution of support across health facilities; and the perception of government policies as disorganized, confused, and even contradictory [6]. Countries and health systems had to make challenging resource allocation and capacity-building decisions to promote proper patient care, ensure staff safety and well-being, and innovate to address the pandemic as well as upcoming public health problems and natural catastrophes. The widespread and far-reaching repercussions of this pandemic and other recent crises signal an urgent appeal to leaders and health and care systems around the world to be better prepared. Specifically, there should be clear and comprehensive disaster response management strategies [7] and a strong public health system, with HCWs who are fit for the purpose, well supported, better protected, and provided with decent working conditions.

The World Health Organization (WHO) has made an effort to synthesize high-quality, timely evidence and contribute guidance to inform the decision-making process. Their aim is to "assist health managers and policy-makers at national, subnational, and facility levels in designing, managing and preserving the workforce necessary to manage the COVID-19 pandemic and maintain essential health services" [8]. With the development of the epidemic, innovations are already in place and updated evidence is published frequently; however, more information is required to inform the development and implementation of policies and interventions.

Hence, we intend to conduct a living systematic review (LSR) to identify the range of experiences across countries with various policies and management interventions that can improve HCWs' capacity to address the COVID-19 pandemic response, gather and synthesize evidence on the effectiveness of the interventions, and identify gaps and maintain the currency of the evidence.

Methods

Study Design

An LSR is a systematic review that is regularly updated, adding pertinent new information as it becomes available and serving as a crucial connection between health research findings and evidence-based health care decision-making [9].

With the current LSR (registered at PROSPERO; CRD42022327041 [10]), we intend to address the following review question: What strategies and policies have been adopted by countries to improve HWCs' capacity to address the COVID-19 pandemic and how effective have they been?

An LSR is particularly appropriate to address this review question given that the issue under analysis is a priority for decision-making, the level of uncertainty in the existing evidence is high, and emerging evidence might impact the conclusions of a traditional systematic review. Most methodological guidelines still do not address the specificities of LSRs. Therefore, the proposed LSR will be conducted by adopting and adapting the Joanna Briggs Institute (JBI) methodology for mixed methods systematic reviews [10].

Eligibility Criteria

The eligibility criteria for this LSR are as follows:

- Types of study: This review will include quantitative, qualitative, and mixed methods studies and gray literature (technical and political documents). Quantitative studies will include observational (eg, case-control, cohort, and cross-sectional), experimental, and quasi-experimental studies. Advocacy materials, opinion letters, news releases, editorials, and opinion documents will be excluded from the review but can be used to discuss the findings.
- Interventions: This review will consider countries' range of policies and management interventions implemented to improve HCWF capacity to address the COVID-19 pandemic response, including the following domains: supporting and protecting health workers; strengthening and optimizing health workforce teams; and increasing capacity, strategic health worker deployment, and

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system-level human resources for health interventions as proposed by the WHO interim guide [8].

- Participants: The review will consider studies that address policies or management interventions implemented by countries regarding HCWs, hereby understood as all health-related occupations in the health and social sectors of employment, those working in health facilities offering all levels of care, and various employment settings.
- Context: This review will consider studies that investigate the range of interventions in different countries, whether implemented at supranational, national, or state levels.

Search Strategy

The search strategy will aim to identify both published and unpublished studies. Search terms (preferably Medical Subject Headings [MeSH]) will be used to search the databases. To search relevant documents in databases that do not index using MeSH terms, we will use other thesaurus databases (eg, Descritores em Ciências da Saúde and Emtree) and the entry terms for each relevant keyword combined using the Boolean commands AND, OR, and * to capture various terms of the same word or expression (Multimedia Appendix 1).

The search of all data sources will be conducted by 1 researcher. After this process is complete, a second researcher will select a random sample of the databases to be used in a quality check. The reference list of all studies selected for critical appraisal will be screened for additional studies. Researchers from ongoing studies might be contacted to request preliminary or unpublished data to complete the publicly available data.

Studies published in English, French, Hindi, Portuguese, Italian, and Spanish will be included. The initial literature review will include studies published from January 1, 2020, to March 1, 2022. Since this systematic review is an LSR, monthly updates will be run for electronic databases. Studies identified will be incorporated in the review or noted in the "What's new" section and included in the updates. Gray literature and international organizations or databases on workforce will be updated every 3 months.

The databases to be searched are MEDLINE (PubMed), Embase, SCOPUS, and Latin American and Caribbean Health Sciences Literature. Sources of unpublished studies and gray literature to be searched are the WHO's COVID-19 Research Database [11] and the websites of international organizations: International Labour Organization [12], Economic Co-operation and Development [13], and The Health System Response Monitor [14].

Study Selection

We will use EndNote Web (Clarivate) to collect, organize, and manage references retrieved from the searches of the different databases.

Data on eligibility will be collected through Rayyan (Rayyan Systems Inc.) [15]. Inclusion and exclusion criteria will be first applied to the abstracts of the retrieved documents. In case no abstract is available, the criteria will be applied either to the executive summary or the introduction of the documents. Titles and abstracts of the initial searches will be screened, and if eligibility criteria are met, the documents will be selected for full-text analysis. An initial pilot test will be performed in this phase ("Title+Abstract phase") by reviewers until a sufficient level of agreement is reached. After that, the remaining publications will be divided between the reviewers. In this second phase, the eligibility criteria will again be applied to the full text independently by 2 researchers. If the text meets the criteria, we will then extract relevant data from the document to answer the research question. The reviewers are expected to collaborate whenever questions or doubts arise, and a third reviewer will be consulted in case of disagreement. κ statistics, sensibility, and sensitivity will be computed to assess interreviewer agreement and the quality of this process [16]. The inclusion of studies will be described according PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) recommendations, including the number of documents retrieved; identified as duplicates; screened for abstract; excluded and the reason for exclusion; and included during full-text analysis and the number of documents for data extraction [17].

Risk of Bias and Quality Assessment

If the inclusion criteria are met, the documents will be selected for full-text analysis. In this phase, the eligibility criteria (as well as the exclusion criteria) will be again applied, and if they are met, we will then use the JBI critical appraisal tools (CATs) to assess the risk of bias in the included studies [18]. Quantitative and qualitative studies selected for retrieval will be assessed by 2 independent reviewers for methodological validity prior to inclusion in the review using the standardized critical appraisal instrument from JBI SUMARI; these instruments are designed to be study specific and facilitate cross-study comparisons. We have selected the following appraisal tools: randomized controlled trials, cohort studies, case-control studies, economic evaluations, qualitative studies, as well as text and opinion.

According to the assessment, we will then categorize the study into low, medium, and high quality, as follows:

1. Each item in the CAT has 4 options of answer (yes, no, unclear, or not applicable), to which we will assign the following points: yes=2 points, no=0 points, unclear=1 point, and not applicable=missing value and will not be considered for scoring.
2. We will compute a score per study by adding the points of each item.
3. For each CAT, the maximum score will be computed by multiplying the total number of items by the maximum score in each item (as detailed in Table 1.
4. Low quality is set at ≤quartile 2 of the maximum score, medium quality is set between quartile 2 + 1 and quartile 3, and high quality is set as ≥quartile 3 + 1. In case an integer value was not obtained, the next integer value was set as a cut-off.

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Table 1. Critical appraisal tool (CAT) scores (adapted from Fronteira et al [19]).

CAT	Items	Maximum score	Quality and score range		
			Low	Medium	High
Checklist for Analytical Cross-Sectional Studies	8	16	≤8	9-12	≥13
Checklist for Case Control Studies	10	20	≤10	11-15	≥16
Checklist for Cohort Studies	11	22	≤11	12-17	≥18
Checklist for Prevalence Studies	9	18	≤9	10-14	≥15
Checklist for Qualitative Research	10	20	≤10	11-15	≥16
Checklist for Quasi-Experimental Studies	9	18	≤10	10-14	≥15
Checklist for Randomized Controlled Trials	13	26	≤13	14-20	≥21

The level of bias will be considered in the synthesis of the results on the evidence found. The CATs will be applied by 2 reviewers. The critical appraisal results will be reported in a narrative form and in a table. All studies, regardless of the results of their methodological quality, will undergo data extraction and synthesis (when possible).

The quality of the evidence supporting study findings regarding the outcomes of the policies and management interventions implemented by countries will be analyzed using the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach developed by the GRADEpro Working Group [20].

Data Extraction and Synthesis

Data will be extracted from the selected documents, including bibliographic information (author, year, location, and setting), study design type, interventions type, country, level or location, sector and actors involved, participant profession, sample size, delivery model, outcomes, and implementation context according to the data extraction instrument (Multimedia Appendix 2). The reviewers will use electronic forms adapted from the quantitative and qualitative tools for data extraction from the JBI Manual of Evidence Syntheses [21].

Study data will be collected and managed using REDCAP (Research Electronic Data Capture; Vanderbilt University) tools hosted at Universidade Estadual do Rio de Janeiro, Instituto de Medicina Social; the REDCAP form was specifically developed for the study design (quantitative or qualitative) [22,23]. The quantitative data will then be converted into "qualitized data." This will involve transformation into textual descriptions or narrative interpretation of the quantitative results in a way that answers the review questions.

The primary outcomes to be considered are HCWF availability, distribution, performance, efficiency, productivity, retention, protection, working conditions, and satisfaction. Additional outcomes cover absenteeism, deaths, infection, cases of violence and harassment, turnover, intention to leave, workplace hazards, financial protection, service delivery disruptions or disrupted access to essential health services (continuity of treatment of chronic diseases), and coverage. Furthermore, additional outcomes not mentioned here can be added during the LSR.

This review will follow a convergent integrated approach according to the JBI methodology for mixed methods systematic review using JBI SUMARI that "refers to a process of combining extracted data from quantitative studies (including data from the quantitative component of mixed methods studies) and qualitative studies (including data from the qualitative component of mixed methods studies) and involves data transformation" [24]. It is recommended that quantitative data be "qualitized," as codifying quantitative data is less error-prone than attributing numerical values to qualitative data [10] by assembling the qualitized data with the qualitative data. Assembled data are categorized and pooled together based on similarity in meaning to produce a set of integrated findings in the form of a line of action statements. This transformation leads to the creation of qualitative categories, which can be compared with other qualitative observations to identify patterns or discrepancies, thus extracting additional information from the quantitative data and validating its interpretation.

We will be grouping the findings in each specific policy and intervention domain per type of intervention and outcome. For each outcome, we will summarize the study type and method in selected studies, intervention context, population, outcomes, and risk-of-bias assessment results. We will discuss the body of evidence for each policy and intervention domain, the type of intervention and outcome, and the overall quality of the evidence by using the risk assessment results and GRADE recommendation system.

The type of quantitative synthesis of data will be determined by evidence for a prespecified comparison, the completeness of the reported outcome, differences in the effect measures, bias in the evidence, clinical and methodological diversity, and statistical heterogeneity.

Results

The database and gray literature search retrieved 3378 documents. Data are being analyzed by 2 independent reviewers. The results are expected to be published in a peer-reviewed journal by the end of 2023.

Discussion

Expected Findings

The COVID-19 pandemic has revealed significant vulnerabilities and challenges within global health and care systems, particularly in terms of HCWF capacity and resilience. Policies

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and management interventions implemented to improve the HCWF's capacity to address the COVID-19 pandemic response have been discussed in different studies [25-30]. For example, one study suggested methods to measure and improve the resilience and preparedness of countries to face the pandemic through timely and responsive strategies for crisis management to mitigate negative impacts on public health, economies, and societies [30]. It has also been identified that failures in the management of the pandemic with regard to ensuring workers' well-being can result in exacerbated inequality and highlight the importance of politics in countries, where political authority also shapes decision-making processes [29]. In addition, sound leadership and ownership lead to the successful execution of initiatives and overall preparedness. The adaptability of health services plays a crucial role in achieving positive outcomes [31]. However, only a few studies have mentioned the outcomes of the interventions and addressed it in a systematic manner [27].

To the best of our knowledge, this is the first LSR that represents a comprehensive examination of policies and management interventions across 4 levels—individual, management, organizational, and system—in the context of pandemics. The study design; the incorporation of scientific, technical, and political documents; and the use of a framework are strengths of this review, as they offer a broad perspective on the identities of the interventions implemented (encompassing information that, by its nature, does not make it into scientific documents). This presents an objective view of the topic while minimizing biases by following established procedures and reporting guidelines. Other strengths include the robust search strategy, which includes published and unpublished literature in 6 languages across 5 databases and the websites of international organization. In addition, we will report the percentage of agreement between reviewers.

On the contrary, the limitations of this systematic review may include publication bias, as studies with favorable outcomes are more likely to be published, resulting in an overrepresentation of effective interventions. In the context of a pandemic, policies and strategies to enhance the HCWF are also rapidly evolving. In addition, the impact of the pandemic may evolve over time, making it difficult to assess the long-term effects and sustainability of the proposed policies and strategies.

Conclusions

This review can shed light on measures to improve the HCWF; the results can guide policy makers in developing evidence-informed policies and strategies that optimize the HCW response to future pandemics. Findings can inform future policy decisions and resource allocation. In addition, by conducting an LSR that incorporates the latest evidence, health care systems can respond more swiftly to the changing demands of HCWs. Furthermore, identifying gaps in knowledge can contribute to the development of a research agenda to inform the development of policies and strategies related to the HCWF.

Acknowledgments

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Data Availability

The database of the living systematic review is available upon request from the authors.

Authors' Contributions

APCdO designed the study, oversaw all stages of its implementation, was the chief writer of the PROSPERO protocol registration, and contributed to the writing of this manuscript. MDP and PF were major contributors to the design of the project. PF wrote the first draft of this manuscript, and MLG conducted the final checklist verification. RC was the librarian advisor for this project. All authors contributed to the methodological discussions. All authors read and approved the final manuscript. The authors alone are responsible for the content of this protocol.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search strategy.
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Multimedia Appendix 2
Data extraction instrument.
[DOCX File , 14 KB - resprot_v12i1e50306_app2.docx]

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Abbreviations

CAT: critical appraisal tool
HCW: health and care worker
HCWF: health and care workforce
HSRM: The Health System Response Monitor
JBI: Joanna Briggs Institute
LSR: Living Systematic Review
MeSH: Medical Subject Headings
WHO: World Health Organization

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Protocol

The Impact of Heat Waves on Health Care Services in Low- or Middle-Income Countries: Protocol for a Systematic Review

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Abstract

Background: Heat waves significantly impact ecosystems and human health, especially that of vulnerable populations, and are associated with increased morbidity and mortality. Besides being directly related to climate-sensitive health outcomes, heat waves have indirectly increased the burden on our health care systems. Although the existing literature examines the impact of heat waves and morbidity, past research has mostly been conducted in high-income countries (HICs), and studies on the impact of heat waves on morbidity in low- or middle-income countries (LMICs) are still scarce.

Objective: This paper presents the protocol for a systematic review that aims to provide evidence of the impact of heat waves on health care services in LMICs.

Methods: We will identify peer-reviewed studies from 3 online databases, including the Web of Science, PubMed, and SCOPUS, published from January 2002 to April 2023, using the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines. Quality assessment will be conducted using the Navigation Guide checklist. Key search terms include *heatwaves*, *extreme heat*, *hospitalization*, *outpatient visit*, *burden*, *health services*, and *morbidity*.

Results: This systematic review will provide insight into the impact of heat waves on health care services in LMICs, especially on emergency department visits, ambulance call-outs, hospital admissions, outpatient department visits, in-hospital mortality, and health care operational costs.

Conclusions: The results of this review are anticipated to help policymakers and key stakeholders obtain a better understanding of the impact of heat waves on health care services and prioritize investments to mitigate the effects of heat waves in LMICs. This entails creating a comprehensive heat wave plan and ensuring that adequate infrastructure, capacity, and human resources are allocated in the health care sector. These measures will undoubtedly contribute to the development of resilience in health care systems and hence protect the health and well-being of individuals and communities.

Trial Registration: PROSPERO CRD42022365471; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=365471

International Registered Report Identifier (IRRID): DERR1-10.2196/44702

(JMIR Res Protoc 2023;12:e44702) doi:10.2196/44702

KEYWORDS

heat wave; burden; health care service; morbidity; low- or middle-income countries; LMICs; mortality

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Introduction

The world is facing significant climate change with a variety of impacts, especially from rising temperatures and more frequent heat wave episodes. Globally, the annual average temperature has been rising since the beginning of the 20th century, and it is now higher than the 1901 to 2000 average [1]. Global warming as a result of the continuous increase in greenhouse gas production has contributed to heat waves with increasing frequency, severity, and duration [2]. Moreover, the effects of heat waves are aggravated by rapid urbanization, population growth, and the urban heat island effect [3]; more than half of the world's population lived in urban settings in 2017 [4]. The Intergovernmental Panel on Climate Change (IPCC) has projected that global warming of 1.5 °C could be reached in the 2030s if countries do not adhere to the Paris Agreement and do not create a mitigation action plan [5,6]. Major heat wave events have caused widespread casualties and strain on health care systems worldwide. The impacts were observed during the 2003 European heat wave, with the deaths of an estimated 72,000 people, and the 2010 Russian heat wave, with 56,000 deaths [7]. The number of deaths is projected to increase in the future, with 250,000 additional deaths per year between 2030 and 2050 [8]. An extended time-series study demonstrated increased risks of mortality of 5.1%, 2.9%, and 5.5% for every degree rise in temperature above the identified threshold for London, Budapest, and Milan, respectively [9].

Heat waves are generally defined as prolonged periods of exceptionally high or extreme temperatures and are characterized by the magnitude, duration, severity, and extent of the event [10,11]. Up to now, there has been no agreed definition of a heat wave, as the best definition would largely depend on the specific climatic zone of a geographical area, time trends, and individual acclimatization [12]. The unavailability of a unified global index further complicates research that seeks to compare results [12] and discuss patterns, trends, and impacts [13] for the development of health warning systems. The World Meteorological Organization and the Centre for Research on the Epidemiology of Disasters define heat waves as 2 or more consecutive days of temperatures exceeding the local region's given temperature or a percentile threshold [14-16]. A heat wave index (HI) can be defined using temperatures alone or in combination with other meteorological factors, such as humidity and wind speed, for a specified duration, ranging from 1 to several consecutive days [10,13]. Some researchers prefer to use daily mean temperature [17], while others have used daily maximum and apparent temperature [18] to understand the exposure relationship. For instance, Kent et al [12] and Zhang et al [19] found a relative mean temperature HI was the most predictive of adverse heat-related health effects compared to other HIs. According to Wu et al [20], the diversity in heat wave definitions could lead to uncertainty of approximately 22% in predictions of mortality risk.

An increase of 1 °C in temperature above a city-specific threshold is a serious public health concern due to increased mortality and hospital admissions [21-23]. Health effects following heat waves are usually acute, ranging from immediate effects to effects that persist until 7 days later [24,25]. Heat waves have been linked directly to multiple medical conditions, such as heat-related illnesses [26], accelerated complications and deaths from cardiorespiratory and renal diseases, endocrine disorders, food and waterborne diseases, vector-borne diseases [27], accidents [28], increased preterm births [12], and many more. Furthermore, morbidity and mortality in urban areas are higher due to the urban heat island effect [29,30]. On the other hand, improvements in living conditions, urban green space, and awareness of heat waves [31] have been shown to reduce the adverse health effects.

Heat waves will create a surge in demand for health care services and subsequently increase the burden on these services at all levels, including primary care, elective admissions, and intensive care. This includes increased ambulance call-outs, slower response time [32], increased emergency and outpatient department visits [33], increased hospitalization [34], shortages of medicine, and ultimately increased health care expenditures, both direct and indirect [35]. Even though a few previous studies found that emergency hospital admissions were lower compared to mortalities during heat waves [36,37], the number of excess emergency department visits can still be high and thus impose an extra burden on health care services. For instance, during heat wave events in California in 2006, an excess of 16,166 emergency department visits was documented [38]. Health care systems will be under pressure with high bed occupancy rates and constrained resources, which may ultimately affect the care plans of patients [39] and lead to greater economic costs [40].

The effects of heat waves are more pronounced in vulnerable groups. Numerous systematic reviews have examined the effects of heat waves on older people [31]; children [41,42]; men and women [43]; pregnant women [44]; people with chronic conditions, such as mental illness [45,46], cardiovascular disease [47-50], and kidney disease [51]; people experiencing homelessness; people with low socioeconomic status and poor access to green areas [52]; and people in certain occupational sectors, such as agriculture, forestry or fishing, construction, and manufacturing [53]. Reviews that examined the impact of heat waves on health services in low- or middle-income countries (LMICs) are still scare [52,54], with the majority concentrating on high-income countries (HICs) [34] or a combination of LMICs and HICs [55,56]. Moreover, LMICs have limited access to health care systems, lack of adequate infrastructure, and a lower allocation of gross domestic product (GDP) to health care [52]; they also have more vulnerable populations due to low adaptive capacity to heat waves [57-59], lower socioeconomic status, and lack of cooling facilities such as air-conditioning in homes [60,61].

Thus, it is necessary to understand the specific, isolated impact of heat waves on health care services in LMICs in order to ensure adequate preparedness, health promotion, and risk management and allow preventive measures to be carried out effectively to protect vulnerable people from the harmful effects of extreme weather, as highlighted by the World Health Organization and the US National Climate Assessment Program 2014 [62]. Moreover, previous research in China has demonstrated that public health divisions and clinical divisions were unprepared to act confidently in facing challenges related to climate change due to lack of logistical support, capacity

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building, and funding [27,63]. The enhancement of health care services ultimately aims to reduce morbidity and mortality arising from heat wave exposure.

This systematic review aims to evaluate the impact of heat waves on health care services in LMICs. Moreover, this study aims to identify critical research gaps in the existing literature for future research and to aid in the dissemination of important research findings to policymakers and relevant stakeholders for strategic policy planning and implementation.

Methods

Protocol Registration

This study has been registered with the international Prospective Register of Systematic Reviews (PROSPERO; CRD42022365471). This paper presents a protocol for a systematic review of literature reporting on the impact of heat waves on health care services, particularly in LMICs.

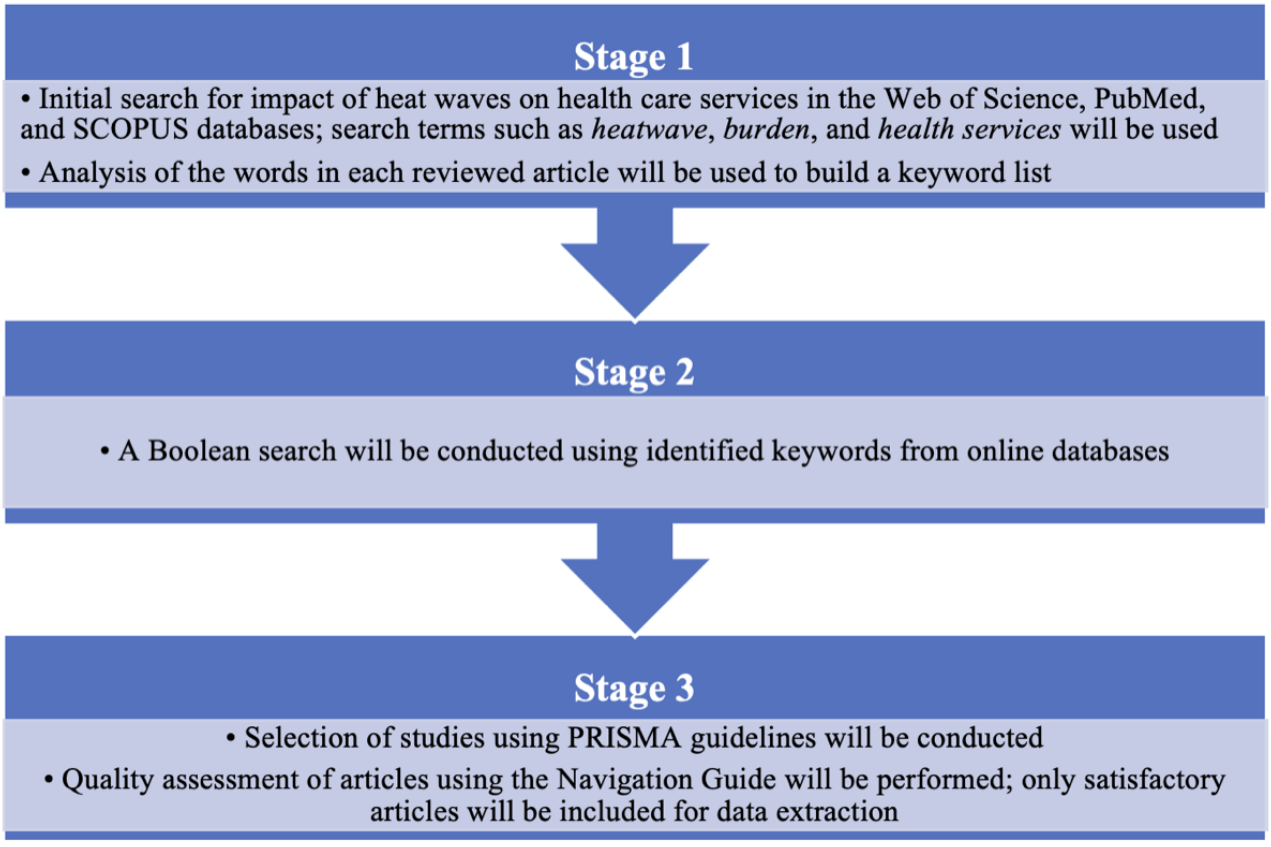
Identifying the Research Question

The main research question is "How do heat waves place a burden on health care systems, particularly in LMICs?" The specific questions are (1) "What are the impacts of heat waves on health care systems—emergency department visits, hospital admissions, outpatient department visits, ambulance call-outs, in-hospital mortality, and health care operational costs?" and (2) "What are the risk factors involved?"

Search Strategy

A comprehensive literature search of electronic databases for peer-reviewed literature published between January 2002 and April 2023 will be conducted on the Web of Science, PubMed, and SCOPUS using a common search strategy. The process of the review started in March 2023 and is currently still in the screening phase. This process involves a 3-stage protocol, as depicted in Figure 1, using the Boolean operators "AND" and "OR." A search strategy combining MeSH terms and keywords that will be used in the 3 online databases is described in Multimedia Appendix 1. As a preliminary search, these keywords will be used on each database using the following search terms: ("heat wave" OR "extreme heat" OR "heat wave") AND ("hospitalization" OR "hospital admission") OR ("morbidity" OR "heat-related illness") OR "ambulance" OR "outpatient visit" OR "emergency department" OR "health services."

Figure 1. Schematic flow chart of the systematic review process. PRISMA: Preferred Reporting Items for Systematic reviews and Meta-Analyses.



Selection of Eligible Studies

To increase the feasibility of this review, studies that have been published during the past 20 years will be included. Subsequently, eligibility criteria will be developed using the PECO (population, exposure, comparison, and outcomes) analytical framework, as detailed in Textbox 1.

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Textbox 1. Inclusion and exclusion criteria, developed using the PECO (population, exposure, comparison, and outcomes) analytical framework.

Inclusion criteria

- Population: The general population of low- or middle-income countries (LMICs) that are affected by heat waves and seek treatment in health care services, regardless of their age, gender, location, or ethnicity. The International Monetary Fund definition of LMICs will be used [64,65]; the list of included countries is provided in Multimedia Appendix 1.
- Exposure: All studies related to heat waves will be included, regardless of their definition of a heat wave.
- Comparison: The same population at a time they are not exposed to a heat wave event or a comparable population that are not exposed to a heat wave event.
- Outcomes: Health care services, including ambulance-call-outs, emergency department visits, outpatient department visits, hospitalization, and in-hospital mortality.

Exclusion criteria

- Population: Morbidity and mortality outside of health care services (ie, hospitals, outpatient clinics, and ambulance dispatches); populations in high-income countries
- Exposure: No definition of heat wave provided; studies on ambient temperature that do not examine heat waves; studies on cold temperatures

All observational studies on heat waves will be included. Intervention studies (eg, randomized controlled trials, single-arm studies), case reports, guidelines, book chapters, commentaries, reviews (eg, systematic reviews, scoping reviews), editorials, protocols, short communications, guidelines, surveillance studies, qualitative research, and non-English publications will be excluded. The full text of selected studies is required to be retrievable for further review. The epidemiological measures must be reported as relative risks, odds ratios, or incidence rate ratios with the 95% CI.

Study Selection Process

Before starting the screening process, a standardized questionnaire for study selection will be developed based on the predetermined eligibility criteria followed by a training session at each level of screening to ensure high interrater reliability (>75% agreement).

Eligible articles will be exported into EndNote X9 (Clarivate) for data management, which will include identifying and removing duplicates, by one reviewer. Subsequently, the data will be exported into Covidence (Level 10) for screening and data extraction. All attempts will be made to obtain the full text of selected articles, including web searching, engaging with the University Teknologi Mara librarian, or, if necessary, contacting the author.

After removing all duplicate articles, 2 reviewers will examine the eligibility of the articles in a 2-stage process. During the first screening, the list of titles and abstracts in the search results will be evaluated for relevancy. In the second screening, potentially relevant full-text papers will be reviewed according to the eligibility criteria. Articles that do not fulfill the criteria will be excluded from the study. Three reviewers will independently execute both stages of study selection, and cross-validation will be conducted for any potential disagreements. Cross-validation will be used to analyze inconsistencies in the list of included and excluded studies. In the event of a disagreement, a fourth reviewer will be assigned before considering the involvement of a fifth verifier. All disagreements will be resolved through discussion, and agreement will be assessed using the κ statistic, with a value of more than 0.8 considered good agreement.

The selection process will be conducted following the PRISMA-P (Preferred Reporting Items for Systematic reviews and Meta-Analyses protocol) checklist [66]. We expect that this systematic review will be completed in December 2023.

Data Items and Data Abstraction Process

Three independent reviewers will perform data abstraction to ensure high interrater reliability and minimize error. Prior to this process, a standardized data collection form will be pilot-tested by 3 independent reviewers. Any discrepancies identified will be resolved by a fourth and fifth reviewer.

Data items will include all relevant information on (1) study characteristics (author, publication year, study design, study location, study years); (2) exposure definition; (3) population characteristics (study population geographical area, vulnerability factors such as age, gender, medical conditions), (4) measures of exposure and outcome, (5) confounders, and (6) effect estimates and outcome characteristics (ambulance call-outs, emergency department visits, outpatient department visits, and in-hospital admissions).

Charting the Data

A data charting form will be used to capture all relevant information for each included study in the review. This process will be conducted by 2 independent reviewers. A thematic analysis approach will be used to identify the key concepts from the full-text articles and code them into non–mutually exclusive themes. All relevant articles will be coded manually in the spreadsheets and presented in the evidence table. The third reviewer will verify the charted data.

Critical Appraisal

Overview

The included papers will be assessed in accordance with the Navigation Guide, which provides criteria for evaluating the quality of systematic reviews of environmental health observational studies in order to minimize the risk of bias (RoB) and maximize transparency [67]. The assessment will be

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conducted in three stages: (1) individual study RoB assessments, (2) assessment of the overall quality of the evidence across all included papers, and (3) rating of the overall strength of the evidence across studies. This process will be independently conducted by 2 reviewers and followed by discussion to reach agreement on ratings. Whenever there is disagreement, a third reviewer will be called in for further discussion on the appraisal.

RoB Assessment

The quality of the individual studies will be assessed using the Office of Health Assessment and Translation (OHAT) RoB assessment tool to examine internal validity and whether the study's design and execution jeopardized the validity of the association between exposure and outcome [68]. This tool was adapted from several guidelines, such as those of the Agency of Health Care Research and Quality [69], the Navigation Guide [70] and the Cochrane Handbook [71]. Since OHAT does not specifically consider time-series environmental health study design, 2 subject-matter experts will modify some of its domains according to our research questions. The RoB domains that will be used are selection, confounding, exposure assessment, outcome assessment, selective reporting, conflict of interest, and other possible bias. The overall rating will be categorized as "definitely low," "probably low," "probably high," or "definitely high."

Assessment of Overall Quality of Evidence Across All Included Papers

Based on the Navigation Guide, the certainty of evidence will be assessed using the Grading of Recommendation Assessment, Development and Evaluation (GRADE) system for each exposure outcome. The body of evidence will be initially graded as moderate based on priority criteria in human observational evidence [67] and then downgraded according to 5 domains (individual study limitations, inconsistency of results, indirectness of evidence, imprecision, and publication bias) and upgraded based on 3 domains (dose-response gradient, large magnitude of effect, and confounding). The final assessment will be as "high," "moderate," "low," or "very low" [72].

Rating of Overall Strength of Evidence Across Studies

The Navigation Guide further outlines four considerations when rating the overall strength of evidence across studies [67], which include (1) the quality of the body of evidence, (2) the direction of effect estimates, (3) confidence in the effect estimates, and (4) any other attributes that might affect certainty. The rating will be either "sufficient," "limited," "inadequate," or "evidence of lack of effect." The final rating will indicate the level of certainty of effect [70].

Ethical Approval

Formal ethical approval is not required as this study does not use primary data.

Results

We anticipate publishing the systematic review by May 2024. To enhance the transparency and clarity of the results and provide a comprehensive overview of the results obtained from each database during preliminary screening, we present our current results in Table 1, which includes a few examples.

Table 1. Characteristics of the studies during preliminary screening.

Title	Year	Journal name	Database	First screening	Second screening	Reason for exclusion
"Cause-specific risk of hospital admission related to extreme heat in older adults" [73]	2014	*JAMA*	SCOPUS	Included	Excluded	Conducted in high-income country
"Increased risk of emergency hospital admissions for children with renal diseases during heatwaves in Brisbane, Australia" [74]	2014	*World Journal of Pediatrics*	SCOPUS	Excluded	N/A[a]	Conducted in high-income country
"The effects of heatwaves on human morbidity in primary care settings: a case-crossover study" [75]	2022	*Scholarly Community Encyclopedia*	Web of Science	Excluded	N/A	Short communication
"The burden of extreme heat and heatwave on emergency ambulance dispatches: A time-series study in Huainan, China" [76]	2016	*Science of the Total Environment*	PubMed	Included	Included	N/A
"Burden of non-accidental mortality attributable to ambient temperatures: a time series study in a high plateau area of southwest China" [77]	2019	*BMJ Open*	PubMed	Included	Excluded	Mortality outside health care services

[a]N/A: not applicable.

Descriptive Analysis

A narrative report will be produced to summarize the extracted data related to the research questions in the final review. The results will be presented in the final evidence tables; Figures 2, 3, and 4 represent samples of these tables, which include the following information: (1) the study characteristics, including author, publication year, study design, study location, the years the study covers, and the definition of a heat wave; (2) population characteristics and vulnerability (ie, risk factors), including age, gender, race, location (urban vs rural); (3) type

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of disease according to body system, such as cardiovascular disease, respiratory disease, and renal disease, which will be presented in the effect estimates sections of the tables in Figures 3 and 4; and (4) the burden on health care services, including ambulance call-outs, emergency department visits, outpatient department visits, hospital admissions, in-hospital mortality, and health care operational costs.

Figure 2. Sample table for characteristics of articles selected for the study.

Author (ref)	Location (country)	Study design and period	Target population	Heatwave definition and matrices	Statistical analysis	Adjustment for confounding factors	Health care service outcome

Figure 3. Sample table for impact on hospital admissions.

Reference (location)	Heat wave definition and matrices	Effect estimates	Vulnerable groups	Summary

Figure 4. Sample table for impact of heat waves on other health care services.

Impacts and reference (location)	Heat wave definition and matrices	Effect estimates	Vulnerable groups	Summary
Emergency ambulance call-outs				
Emergency department visits				
Outpatient department visits				
In-hospital mortality				
Health care expenditures				

Statistical Analysis

This study will not conduct a meta-analysis of the results due to the heterogeneity of outcome measures. Hence, only descriptive thematic analysis will be performed. Nevertheless, the RoB assessment will be performed using SPSS (version 27; IBM Corp) for categorical outcomes, which will be presented as frequencies and percentages.

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Discussion

Principal Findings

It is anticipated that the strain on health care systems will increase significantly if heat wave events rise in frequency, length, and severity. This review's findings are expected to demonstrate that heat waves significantly increase ambulance call-outs, emergency department visits, hospitalization, outpatient department visits, and in-hospital mortality, as well as health care operational costs. Previously, Campbell et al [78] found that ambulance call-outs increased by 34% during extreme heat waves, 10% during severe heat waves, and 4% during low-intensity heat waves. Davis and Novicoff [79] found significantly increased risk for emergency department visits and hospitalization for White and Black people, as well as men and women aged 20 to 49 years, with a variety of presentations, including diabetes, pregnancy complications, poisoning, and traffic crashes, [80] in addition to common presentations such as renal disorder [81,82], cardiovascular disease, respiratory disease [83,84], mental disease [85], and heat-related illness [86].

To our knowledge, this study will be the first to review the impacts of heat waves on health care systems in LMICs and thus fill a knowledge gap. Since the impact of heat waves is more pronounced in LMICs due to their inadequate infrastructure, low access to health care [52], and dense populations of vulnerable people [87], it will be beneficial if LMICs can identify temperature thresholds and vulnerable groups in their region so that targeted interventions can be implemented effectively. Moreover, morbidity indicators such as ambulance call-outs, hospital admissions, and emergency department visits should be used during heat wave impact assessments and the development of early warning systems. Wang et al [88] recommended examining ambulance dispatch data to develop a real-time surveillance heat health warning system that would allow early detection of residents' health demands and health status in a region. Toloo et al [89] demonstrated that the implementation of an early warning system can be cost-effective and reduce mortality and ambulance call-outs. Indeed, many HICs have developed and implemented heat health action plans [90,91]. However, Ahmedabad, India, has become the first South Asian city to develop and implement an early warning system and heat preparedness plan based on collected evidence, such as an analysis of local temperature and mortality data and surveys of the population vulnerable to heat. Nevertheless, evaluation and continuous improvement are still ongoing [92].

The findings of this review also could assist public health and health care systems in allocating resources effectively, such as by allocating more GDP to health care, improving existing infrastructure [26], increasing human resources, and promoting health. Apart from this, health care workers must be provided with adequate training and updates on the latest information or guidelines related to heat waves [16]. Enhanced diagnostic accuracy and speed, followed by immediate treatment, is vital for hospitals and other community medical institutions in order to reduce morbidity and mortality [26]. Lastly, understanding the impact of heat waves on health care services underscores the need for climate change mitigation and adaptation, such as increasing the resilience of health care systems and being responsive to the effects of heat waves [93,94].

Among the limitations that we expect in this review are the inability to access full texts and some of the articles not being in English. This could limit the overall findings of the review. Secondly, during our search, we found numerous articles that examined the impact of ambient temperature on health care services but few that examined the impact of heat waves. In fact, some of the articles did not provide a definition of a heat wave. This might be due to underrepresentation of some LMICs [95], which will further limit the findings of the review. However, we believe that this finding could encourage these countries to participate and conduct more research on this topic, as well as highlight to HICs that funding to these countries is necessary for them to conduct more research.

Conclusion

Undeniably, heat waves pose a significant health risk to individuals and the community. Therefore, understanding the burden on health care services due to exposure to heat waves is of paramount importance as heat waves are becoming more frequent and increasing in intensity. This proposed systematic review is expected to provide a better understanding of the impact of heat waves on health care systems in LMICs; this will be critical for optimal planning, preventive activities, policymaking, and climate action. By prioritizing this understanding and disseminating this information to policymakers and relevant stakeholders, we can better protect individuals' and communities' health and well-being, as well as construct a more resilient health care system in the face of climate change.

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Authors' Contributions

All authors contributed to conceptualization, formal analysis, investigation, methodology, validation, visualization, and review and editing of the manuscript. HS, MIS, RI, and WRWM contributed to resources. HS, MIS, and MRI contributed to data curation and software. HS and MIS contributed to project administration and funding acquisition. MIS and MRI supervised the project. HS wrote the original draft.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search strategy, list of low- and middle-income countries, and risk of bias assessment.
[DOCX File , 52 KB - resprot_v12i1e44702_app1.docx]

Multimedia Appendix 2
PRISMA-P (Preferred Reporting Items for Systematic reviews and Meta-Analyses protocol) checklist.
[DOCX File , 41 KB - resprot_v12i1e44702_app2.docx]

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Abbreviations

GDP: gross domestic product
GRADE: Grading of Recommendation Assessment, Development and Evaluation
HI: heat wave index
HIC: high-income country
IPCC: Intergovernmental Panel on Climate Change
LMIC: low- or middle-income country
OHAT: Office of Health Assessment and Translation
PECO: population, exposure, comparison, and outcomes
PRISMA-P: Preferred Reporting Items for Systematic reviews and Meta-Analyses–Protocols
PROSPERO: Prospective Register of Systematic Reviews
RoB: risk of bias

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Protocol

Pediatric Tui Na for Feeding Intolerance in Premature Infants: Protocol for a Systematic Review and Meta-Analysis

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Abstract

Background: Feeding intolerance (FI), frequently resulting from gastrointestinal immaturity, is prevalent among premature infants. Current practices are gradually prioritizing nonpharmacological treatments, such as massage or "Tui na," considering the potential side effects of prolonged medication use. Pediatric Tui na, a specialized massage therapy based on traditional Chinese medicine, has been widely studied for treating FI in premature infants. However, to our knowledge, no systematic review specifically focusing on the effectiveness and safety of traditional Chinese medicine–based pediatric Tui na for FI in premature infants has been published yet.

Objective: This study aims to develop a protocol for a systematic review and meta-analysis for evaluating the safety and efficacy of pediatric Tui na for premature infants with FI.

Methods: We will perform a comprehensive search in the following databases: Springer, Cochrane Library, Embase, MEDLINE, Clarivate Analytics, Physiotherapy Evidence Database (PEDro), CINAHL, PubMed, Scopus, World Health Organization (WHO) International Clinical Trials Registry Platform, and Chinese biomedical databases (Wanfang database, the China National Knowledge Infrastructure, Chinese Scientific Journals Database, and Chinese Biomedical Literature Databases), limited to studies published in Chinese and English languages between January 2000 and January 2023. The search strategy will use MeSH (Medical Subject Headings) terms and database-specific keywords. A total of 2 independent reviewers will initially screen the studies based on titles and abstracts, followed by a full-text evaluation of the eligible studies. Studies will include any nonrandomized controlled trials, nonrandomized clinical studies, randomized controlled trials, and quasi-experimental studies wherein the treatment group involves premature infants with FI given pediatric Tui na. Primary outcomes will be necrotizing enterocolitis, gastric residual volume, emesis, and stool blood. Secondary outcomes will be abdominal distension weight gain, time to achieve full enteral feeding, any adverse effects associated with pediatric Tui na, and length of hospital stay. The Cochrane Collaboration Risk of Bias Tool will be used to assess the risk of bias and methodological quality. Funnel plots will be used for evaluating publication bias. Meta-analysis will be conducted using the Review Manager software (version 5.4; Cochrane Collaboration). Subgroup analyses will be considered according to treatment received, country or setting, sex, and birth weight of premature infants (if heterogeneity is high, $I^2 \geq 50\%$).

Results: This is a systematic review and meta-analysis protocol, so the results are not yet available. The protocol has been registered with PROSPERO (CRD42023390021). We are currently in the study selection phase. Results are expected to be completed by the end of 2023.

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Conclusions: Following this protocol, a comprehensive and rigorous literature synthesis will be developed to assess the impact of pediatric Tui na treatment on premature infants with FI, enabling the determination of its efficacy and safety.

Trial Registration: PROSPERO CRD42023390021; https://tinyurl.com/bdf4kn23

International Registered Report Identifier (IRRID): PRR1-10.2196/46375

(JMIR Res Protoc 2023;12:e46375) doi:10.2196/46375

KEYWORDS

feeding intolerance; pediatric tui na; premature infants; protocol; systematic review

Introduction

Feeding intolerance (FI) is usually a consequence of gastrointestinal immaturity and commonly occurs in premature infants [1]. It typically presents as increased gastric residual volume (GRV), abdominal distention, vomiting, stool blood, and emesis [2], affecting 33.8%-53.45% of premature infants in China [3]. Furthermore, there is an association between high GRV and increased morbidity of necrotizing enterocolitis (NEC) [4,5]. These gastrointestinal immaturity–associated intestinal system problems can affect the nutritional intake and gut morbidity of premature infants, leading to several complications such as prolonged hospitalization and weight loss, and even increased mortality [6,7], thus placing a heavy burden on health care services.

There is no ideal or effective treatment available for FI as its pathobiology remains to be fully understood and identified [8-10]. Previous guidelines and studies have primarily focused on pharmacotherapies for managing FI [11]. However, long-term use of medications such as erythromycin, probiotics, metoclopramide, and cisapride has been reported to be associated with many adverse effects (AEs), including neurological disorders and cardiovascular dysfunction [12-16], leading to a greater expenditure of time and money and posing a significant burden on patients [10]. Consequently, current guidelines and practices increasingly focus on nonpharmacological treatments such as massage or Tui na [4,17]. Pediatric Tui na, based on the principles of the meridian theory [18] of traditional Chinese medicine (TCM) [19], is widely used as a complementary and alternative medicine in East Asia [20-23]. It treats a range of pediatric diseases by applying various manipulations on the body surface, including pressing, kneading, circling, nipping, and pushing [24,25]. Studies have indicated that Tui na and other similar touch therapies can regulate hormones such as cortisol and dopamine and accelerate blood and lymphatic circulation, thereby improving the function of the gastrointestinal system [3,21,22,26-29]. Many studies [24,25,29-32], especially those conducted in China, have explored pediatric Tui na as a treatment for FI in premature infants. However, the results of these studies are inconsistent. For instance, several investigations [24,25,30] have indicated that pediatric Tui na provides significant benefits to premature infants with FI, including improved weight gain; reduced time to achieve full enteral feeding; reduction in GRV, emesis, and abdominal distention; and a notable reduction in the average length of hospital stay. However, Liu and Zhang [31] did not find any significant difference between the control group and the pediatric Tui na group in terms of weight gain or the time required to return to birth weight (P>.05). Additionally, a meta-analysis [33] suggested that massage benefits premature infants with FI. However, this analysis was limited to studies published in Persian and English. Furthermore, it primarily evaluated the effects of massage on GRV and did not specifically address the efficacy and safety of pediatric Tui na regarding intestinal function and other FI-associated factors in premature infants. Therefore, despite the research mentioned above, to our knowledge, no studies have specifically addressed the safety and efficacy of pediatric Tui na in premature infants with FI, highlighting a gap in understanding its role as a nonpharmacological treatment for these infants. Moreover, no published systematic review, meta-analysis, or review protocol focusing on TCM-based pediatric Tui na for premature infants with FI is yet available.

Considering the high heterogeneity of previous studies and their varying outcomes, as well as the absence of any comprehensive evidence on this subject, it is crucial to assess the effectiveness and safety of pediatric Tui na for premature infants with FI. We intend to conduct a systematic review and meta-analysis to enhance the current evidence base on the effectiveness of pediatric Tui na for FI in premature infants. To ensure the most comprehensive data collection, minimize publication bias, and summarize the currently available evidence, we will conduct electronic searches for studies published both in English and Chinese.

Methods

Overview

The protocol for this review has been registered with the National Institute for Health Research (PROSPERO 2023 CRD42023390021) [34]. This protocol will be reported and conducted according to the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Extension for Protocols) 2015 guidelines [35] and the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) guidelines [36].

Study Selection Criteria

The eligibility criteria of studies will be presented in the PICOS (Patient, Intervention, Comparison, Outcome, and Study) design framework [37,38].

Types of Studies

The following types of studies will be included: (1) any nonrandomized clinical studies, nonrandomized controlled trials,

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randomized controlled trials, and quasi-experimental studies, wherein the treatment group involved premature infants with FI who received pediatric Tui na; (2) interventional studies, retrospective or prospective observational studies, or case series; and (3) studies that reported and included data associated with specific primary (NEC, GRV, emesis, abdominal distension, and stool) and secondary outcomes (weight gain, time to achieve full enteral feeding, length of hospital stay, and any AEs associated with pediatric Tui na). Single-case reports will not be included.

Participants

On the basis of any definition of FI, we included studies in which premature infants received pediatric Tui na to prevent or treat FI. We will identify prematurely born infants as per the definition of the World Health Organization (WHO); this includes infants born within 259 days from the first date of the mother's last menstrual period or before 37 full weeks of gestation [39].

Intervention

We will include all trials evaluating pediatric Tui na intervention for FI.

Comparison

We will include studies with different control interventions, such as placebo and other currently used interventions (eg, physiotherapy, acupuncture, gentle touch, and medication), and those without any control group.

Outcomes

Emesis, NEC, GRV, and stool blood will be included as primary outcomes. Any AEs associated with pediatric Tui na, abdominal distension, time to achieve full enteral feeding, length of hospital stay, and weight gain will be included as secondary outcomes.

Search Strategy

A comprehensive search will be performed in the following databases: Springer, Cochrane Library, Embase, MEDLINE, Clarivate Analytics, Physiotherapy Evidence Database (PEDro), CINAHL, PubMed, Scopus, WHO International Clinical Trials Registry Platform, and Chinese biomedical databases (Wanfang database, the China National Knowledge Infrastructure, Chinese Scientific Journals Database, and Chinese Biomedical Literature Databases), limited to studies published in Chinese and English languages between January 2000 and January 2023. The database searches will include only studies published in peer-reviewed journals and reporting results within their full text. Experts will be consulted for including additional studies. With inputs from the principal investigator of the study, an experienced librarian at Nanjing University of Chinese Medicine will design and carry out a comprehensive literature search. For searching publications on the safety and effect of pediatric Tui na on premature infants with FI, we will use controlled vocabulary and keywords. Table 1 shows the search strategy for the PubMed database.

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Table 1. Search strategy for the PubMed database.

Number	Search terms
1	Feeding intolerance [MeSH[a]]
2	(Feeding intolerance OR feeding difficulties OR gastrointestinal motility OR gastroesophageal reflux OR gastric residuals, abdominal distension, OR emesis): ti, ab[b]
3	1 OR 2
4	Tui na therapy [MeSH]
5	(Tui na OR pediatric Tui na OR massage OR tactile-kinesthetic stimulation OR massaging OR massotherapy OR manipulation OR chiropractic therapy OR abdominal Tui na therapy OR spinal manipulation OR Tui na using a single thumb): ti, ab
6	4 OR 5
7	Randomised: ti, ab
8	Randomized: ti, ab
9	Randomly: ti, ab
10	Clinical trials [MeSH]
11	Trial: ti, ab
12	Randomized controlled trial [MeSH]: ti, ab
13	Randomized controlled trial [MeSH]: ti, ab
14	Controlled trial [MeSH]: ti, ab
15	7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14
16	Premature infants
17	15 AND 16
18	3 AND 6 AND 17

[a]MeSH: Medical Subject Headings.

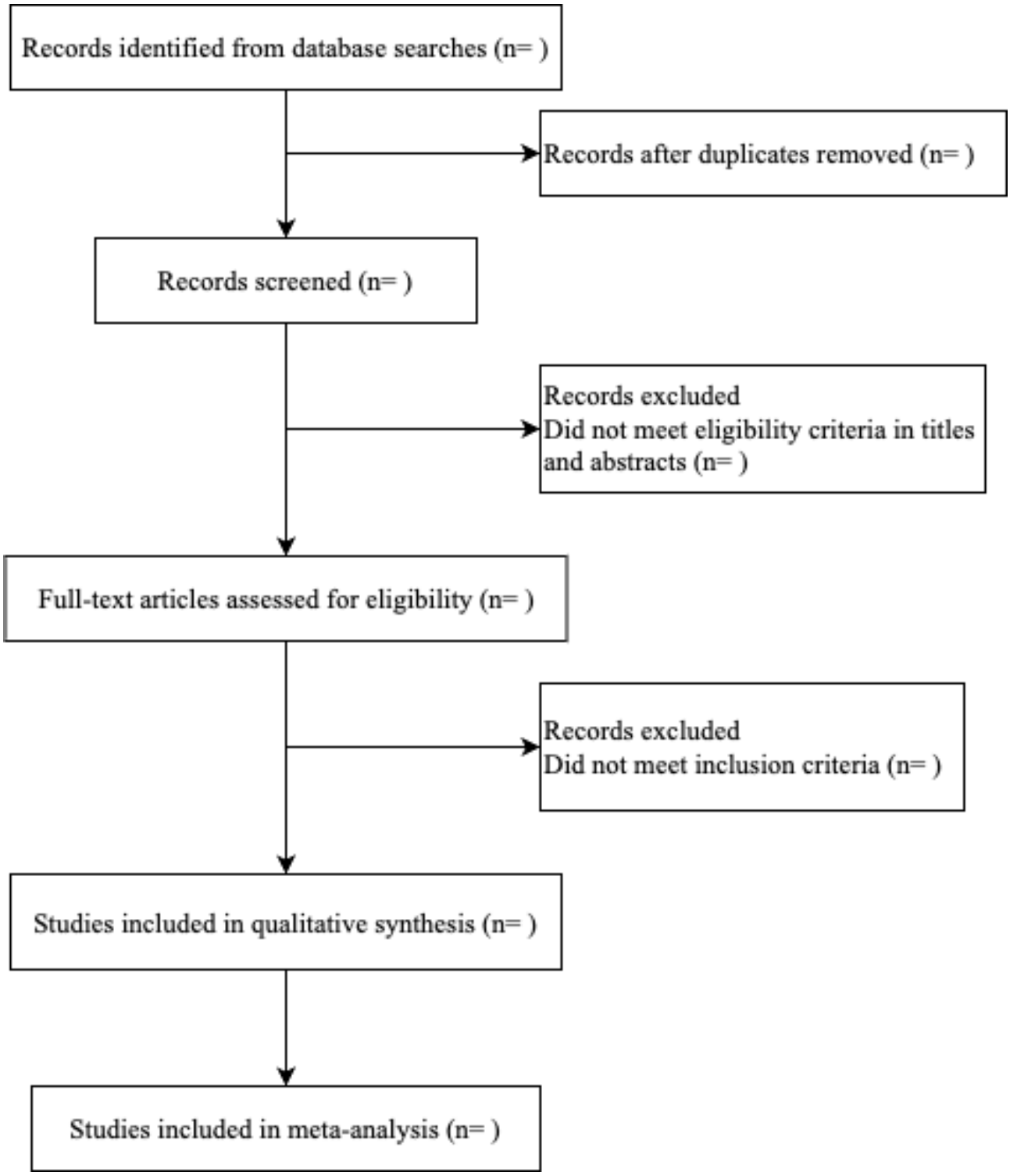
[b]ti, ab: terms in either title or abstract fields.

Study Selection

The retrieved literature will be imported into Endnote X9 (Clarivate Analytics); duplicate literature will be removed. A total of 2 authors will independently screen the titles and abstracts. Studies not meeting the inclusion criteria will be excluded. To seek full-text copies of studies or clarification of methods or results, study authors will be contacted through email if required. The latest or most comprehensive literature information will be extracted if multiple articles report the findings of the same study. Figure 1 shows the flow diagram for study selection.

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Figure 1. Flow diagram for study selection.



Methodological Quality and Risk of Bias Appraisal

A total of 2 researchers will evaluate the quality of the literature using the quality evaluation method of the Cochrane Collaboration System evaluator manual on the following 6 aspects [40]: concealment of the allocation scheme, generation of a random allocation scheme, complete data results, selective reporting results, blinding method, and other risks of bias.

Data Extraction

A total of 2 independent reviewers will extract information using a predesigned form after identifying the studies to be included. The form will include data on the following aspects:

1. Identification information (first author, publication year, study design, country, and setting)
2. General information (study type, country, sample size, number of centers, and study design)
3. Participants (weight, sex, and age of premature infants)

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4. Interventions (pediatric Tui na, type of pediatric Tui na, pediatric Tui na technique, pediatric Tui na position selection, and frequency and duration of sessions)
5. Comparator (if available, treatment details, including dosage, name, course, and frequency)
6. Outcomes (safety, efficacy data, and time points for each measurement)

If any information is missing or there is a need to seek further clarification, we will attempt to contact the corresponding authors.

Assessment of Reporting Bias

We will use funnel plots to detect publication bias in the overall estimate and Egger and Begg tests to examine the funnel plot asymmetry. Symmetry and asymmetry in the funnel plot indicate low and high risks of reporting bias, respectively.

Data Synthesis

Meta-analyses or descriptive analyses will be performed as per the measurement results, heterogeneity levels, and intervention measures. Conversely, we will report quantitative research results descriptively. Continuous variables will be analyzed according to mean differences and 95% CIs. Dichotomous variables will be assessed using risk ratios. Standardized mean differences and 95% CIs will be calculated if the outcome measure scales differ. Heterogeneity assessments will be performed within each pairwise comparison by the Cochran *Q* test and the I^2 statistic. Negative I^2 values will be treated as 0%, indicating no heterogeneity. I^2<50% indicates low heterogeneity, while I^2≥50% indicates high heterogeneity [41]. For sensitivity analysis, the results will be compared with those of other meta-analysis models, which would exclude trials with a high risk of bias and include fixed-effects models. We will perform a meta-analysis using a random-effects model if at least two included trials are found to be sufficiently homogeneous for the aspects of the comparator, outcome measurement, and study design. For performing the meta-analysis, the Cochrane Collaboration's software Review Manager (version 5.4) will be used. Subgroup analyses will be considered according to the treatment received, country or setting, sex, and birth weight of premature infants (if heterogeneity is high, I^2≥50%).

Dissemination

This meta-analysis and systematic review will be submitted to a peer-reviewed journal. The findings are expected to shed some light on the efficacy and safety of pediatric Tui na for premature infants with FI.

Results

This is a systematic review and meta-analysis protocol, so the results are not yet available. This protocol has been registered with PROSPERO (CRD42023390021) on February 8, 2023 [34]. We are currently in the study selection phase. Results are expected to be completed by the end of 2023.

Discussion

This study aims to conduct a systematic review and meta-analysis of relevant research articles to comprehensively summarize the current evidence regarding the efficacy of pediatric Tui na for premature infants with FI. Pediatric Tui na, originated in China over 2300 years ago, was first recorded in *Wushierbingfang* (*Prescriptions for Fifty-two Diseases*) [42]. It is a commonly used, convenient, noninvasive, and cost-effective intervention therapy suitable for children [43]. Xie et al [44] reported that working on specific acupoints of the skin surface in pediatric Tui na can improve the gastrointestinal function of children. Xiao et al [24] and Chen [29] have reported that pediatric Tui na can accelerate gastrointestinal tract maturity, promote intestinal evacuation, and increase gastrointestinal motility in premature infants, thus alleviating FI. Although many clinical trials [24,25,30-32] have evaluated pediatric Tui na for treating FI in children, its efficacy and clinical evidence have not yet been established. The current clinical guidelines in China recommend massage therapy for treating FI in premature infants [17]. Despite being a TCM-based approach, pediatric Tui na is currently not included in the guidelines for treating FI in premature infants. This omission has prevented it from being widely and successfully adapted as a potential treatment for FI in premature infants. This study will be the first to evaluate the effect and safety of TCM-based pediatric Tui na for FI in premature infants by objectively synthesizing the currently available publications.

Some limitations should be considered in this systematic review. First, it will consider only studies published in Chinese and English, which could introduce potential language bias, resource constraints, difficulty locating non-English studies, and the possibility of bias in data extraction and analysis. Second, the specific focus of our research question might restrict the number of eligible studies for inclusion in the proposed review. Nonetheless, our objective is to extract valuable insights from the available evidence to offer preliminary guidance for current FI practices and future research. To stay updated with new evidence, we plan to conduct updates to the systematic review and meta-analysis every 3 years.

This protocol intends to aggregate current research, provide greater insights into the efficacy and safety of pediatric Tui na for FI, and offer a comprehensive assessment of the evidence for pediatric Tui na treatment of FI in premature infants for health care providers worldwide. Additionally, it will lay the groundwork for future research in pediatric Tui na and serve as a reference for the potential inclusion of pediatric Tui na in the treatment guidelines for premature infants with FI.

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Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during this study.

Authors' Contributions

ZB and MW wrote the original draft of the manuscript. YT and XL curated the data. ZB and XL analyzed the data. YT reviewed and edited the manuscript. MW contributed to project administration and supervision.

Conflicts of Interest

None declared.

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Abbreviations

AE: adverse effect
FI: feeding intolerance
GRV: gastric residual volume
NEC: necrotizing enterocolitis
PEDro: Physiotherapy Evidence Database
PICOS: Patient, Intervention, Comparison, Outcome, and Study
PRISMA: Preferred Reporting Items for Systematic Review and Meta-Analysis
PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Extension for Protocols
TCM: traditional Chinese medicine
WHO: World Health Organization

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Protocol

Guidelines and Standard Frameworks for AI in Medicine: Protocol for a Systematic Literature Review

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Abstract

Background: Applications of artificial intelligence (AI) are pervasive in modern biomedical science. In fact, research results suggesting algorithms and AI models for different target diseases and conditions are continuously increasing. While this situation undoubtedly improves the outcome of AI models, health care providers are increasingly unsure which AI model to use due to multiple alternatives for a specific target and the "black box" nature of AI. Moreover, the fact that studies rarely use guidelines in developing and reporting AI models poses additional challenges in trusting and adapting models for practical implementation.

Objective: This review protocol describes the planned steps and methods for a review of the synthesized evidence regarding the quality of available guidelines and frameworks to facilitate AI applications in medicine.

Methods: We will commence a systematic literature search using medical subject headings terms for medicine, guidelines, and machine learning (ML). All available guidelines, standard frameworks, best practices, checklists, and recommendations will be included, irrespective of the study design. The search will be conducted on web-based repositories such as PubMed, Web of Science, and the EQUATOR (Enhancing the Quality and Transparency of Health Research) network. After removing duplicate results, a preliminary scan for titles will be done by 2 reviewers. After the first scan, the reviewers will rescan the selected literature for abstract review, and any incongruities about whether to include the article for full-text review or not will be resolved by the third and fourth reviewer based on the predefined criteria. A Google Scholar (Google LLC) search will also be performed to identify gray literature. The quality of identified guidelines will be evaluated using the Appraisal of Guidelines, Research, and Evaluation (AGREE II) tool. A descriptive summary and narrative synthesis will be carried out, and the details of critical appraisal and subgroup synthesis findings will be presented.

Results: The results will be reported using the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) reporting guidelines. Data analysis is currently underway, and we anticipate finalizing the review by November 2023.

Conclusions: Guidelines and recommended frameworks for developing, reporting, and implementing AI studies have been developed by different experts to facilitate the reliable assessment of validity and consistent interpretation of ML models for medical applications. We postulate that a guideline supports the assessment of an ML model only if the quality and reliability of the guideline are high. Assessing the quality and aspects of available guidelines, recommendations, checklists, and frameworks—as will be done in the proposed review—will provide comprehensive insights into current gaps and help to formulate future research directions.

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KEYWORDS

artificial intelligence; biomedical; guidelines; machine learning; medicine

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Introduction

Rationale

Artificial intelligence (AI) has become a hot topic in biomedical and clinical routines in the past decade [1,2]. In fact, an increasing number of scientific publications suggest algorithms and AI models for target diseases and conditions [3]. The application of AI in health care ranges from medical image analysis to text mining, targeting prognosis, diagnosis, event and outcome prediction, and treatment [1]. The number of scientific contributions in peer-reviewed journals focusing on AI applications in medicine is also highly increasing [4,5].

The comparison of algorithm performance for a target condition has become a common way of presenting and evaluating machine learning (ML) models. The diversity of ML models leads to competition and fast progress. However, the current situation leaves health care providers unsure about which ML model to use given multiple alternative models for a specific target [6] and the "black box" nature of ML [7]. Moreover, the fact that studies do not use guidelines consistently in developing and reporting AI models poses another challenge in trusting and adapting models for practical implementation [8-10].

In fact, guidelines and recommended frameworks for developing and reporting AI studies have been published by different experts and work groups to facilitate reliable assessment of model validity and consistent interpretation [11-14]. In addition, the authors have proposed recommendations for the evaluation of AI studies [15-18]. This review protocol describes the planned steps and methods of a future review that aims to synthesize evidence regarding the quality of available guidelines and frameworks developed to facilitate AI applications in medicine and summarize their content.

Objective

The systematic review will address the following scientific questions:

- What are the available guidelines and frameworks with regard to predictive AI model development and reporting in medicine?
- What are the main aspects (target or purpose) of the available guidelines and frameworks?
- What is the quality of the available guidelines with respect to the Appraisal of Guidelines, Research and Evaluation (AGREE II) domains?
- What are the reported implementation challenges in the available guidelines?

Methods

Eligibility Criteria

All guidelines, standard frameworks, best practices, checklists, and recommendations will be included, irrespective of the study design. Studies will be limited to English and to the time period between database inception and June 2023 (the time of data collection).

Search Strategy and Information Sources

This protocol adheres to the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) 2015 [19]. A systematic literature search will be commenced using Medical Subject Headings (MeSH) terms and keywords for medicine, guidelines, and ML (Table S1 in Multimedia Appendix 1). The initial search will be conducted on 3 web-based repositories: PubMed, Web of Science, and EQUATOR (Enhancing the Quality and Transparency of Health Research). The EQUATOR network is a global initiative working toward improving the value of research by promoting robust reporting guidelines [20]. A Google Scholar search will also be performed to identify gray literature. References in selected literature will be scanned, and relevant papers will be included after discussion among the reviewers.

After the comprehensive search, all bibliographic information will be uploaded to a web-based systematic review tool (Rayyan) and afterward processed with CADIMA [21] for further screening and preliminary analysis.

Study Selection

After removing duplicate results, a preliminary scan for titles will be done by 2 reviewers. After the initial scan, the reviewers will rescan the selected literature for abstract review, and any incongruities about whether to include the article for full-text review will be resolved by the third reviewer based on the predefined criteria.

Data Extraction, Collection, and Management

Once the selection process has been finalized, relevant information from the selected literature will be extracted by the 2 reviewers independently using a predefined information extraction sheet. At this stage, discrepancies will be resolved by the third and fourth reviewers.

The information extraction sheet will be designed to collect relevant information such as study characteristics (authors, year of publication, study type, aspect, specific disease or condition focused, and standard followed) from selected literature for further synthesis. "Study type" in this context refers to whether the study is a guideline, a framework, a suggestion, a checklist, a best practice, or a recommendation. The term "aspect" entails the purpose for which the guideline or the framework is primarily designed. Guidelines or frameworks could be designed for different purposes. For instance, if a guideline is developed to elaborate on or declare how ML studies should report their findings, the aspect or purpose will be a "reporting aspect." If, however, the guideline emphasizes the ethical dimension of ML in medicine, the aspect will be referred to as "ethical aspect." A study can have multiple aspects (sometimes a guideline or a framework could be about both the development and reporting procedures and sometimes only the reporting or the development procedure), and it will also be extracted under the "aspect" category. The column "specific disease or condition focused" refers to whether the guideline or framework is subject to or validated for a specific disease or condition. Sometimes, researchers suggest customized and focused guidelines for a specific condition. Based on the predefined data extraction Excel (Microsoft Corp) sheet, 2 reviewers will extract the data

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independently, and any sort of discrepancy will be discussed with the 3rd and 4th reviewers after every 10 extractions. The data extraction template is presented in Table 1.

Table 1. Data extraction template.

Sections	Description
Section 1: study characteristics	
First author's name	For example, John Smith
Year of publication	For example, YYYY
Title	The title of the study
Journal	The name of the journal. For example, scientific reports
Country of first author	For example, United States of America
Section 2: research questions	
Type of outcome	Provide a description about the study whether it is a guideline, standard framework, recommendation, checklist, best practice, or expert opinion.
Aspect	Provide the primary purpose for which the guideline or the framework is designed. For example, reporting, development, ethics, and governance.
Standard followed	Provide a description of the standard followed during the development of the proposed guideline or framework. For example, the EQUATOR[a] network.
Guidelines and frameworks with regard to predictive artificial intelligence model development and reporting in medicine	Provide a description of the content and domain of the guideline or framework.
The quality of the available guidelines	Provide a quantified quality assessment of the identified guidelines based on AGREE II[b] assessment.
Reported gaps in the available guidelines	Describe the reported gaps and implementation challenges.
Specific target domain	Provide information if the guideline or framework is designed for a specific disease domain.

[a]EQUATOR: Enhancing the Quality and Transparency of Health Research.
[b]AGREE II: Appraisal of Guidelines, Research, and Evaluation.

Quality and Risk of Bias Assessment

The quality of identified guidelines will be evaluated using the AGREE II tool [22]. AGREE II assesses the quality of guidelines in terms of the methodological rigorousness and transparency of the guideline development process [22]. It consists of 23 key items organized within 6 domains (scope and purpose, stakeholder involvement, rigor of development, clarity of presentation, applicability, and editorial independence) and 2 global rating items for overall assessment. As recommended by the AGREE II user manual, 4 appraisers will individually appraise the selected guidelines and frameworks, and the percentage of quality will be calculated based on the ratings of each quality domain [22]. Other frameworks and best practices proposed by researchers will be systematically summarized.

Analysis

A descriptive summary and narrative synthesis will be carried out, and the details of critical appraisal and subgroup synthesis findings will be presented. This systematic review will present the list of available guidelines, frameworks, suggestions, checklists, best practices, or recommendations for developing and reporting AI studies in medicine and assess the quality of the guidelines and discuss the aspects.

Results

We anticipate finishing the systematic literature review by November 2023. The expected result from this review will explore and highlight the quality of the available guidelines and point out the existing gaps. Furthermore, the synthesis from the checklists and recommendations will provide a comprehensive set of standardized tools.

Discussion

Guidelines are important sets of instructions that facilitate transparent and reproducible scientific processes [23]. The potential benefits of guidelines are, however, only as good as the quality of the guidelines themselves. This protocol describes the setup of a systematic review to identify available guidelines, frameworks, best practices, and recommendations for developing and reporting AI studies in medicine. The review will assess the quality of guidelines, summarize the gap in guidelines, and identify critical considerations in the application of AI in medicine. As the search is limited to English due to resource limitations, there might be language bias, indicating that some important studies conducted in different languages might be missed. Thus, conclusions should be drawn carefully.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Keywords.
[DOCX File , 13 KB - resprot_v12i1e47105_app1.docx]

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Abbreviations

AGREE II: Appraisal of Guidelines, Research and Evaluation
AI: artificial intelligence
EQUATOR: Enhancing the QUAlity and Transparency Of health Research
MeSH: medical subject headings
ML: machine learning
PRISMA: Preferred Reporting Items for Systematic Review and Meta-Analyses
PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols

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Protocol

Digital Self-Monitoring Tools for the Management of Gestational Weight Gain: Protocol for a Systematic Review

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Abstract

Background: Gestational weight gain (GWG) exceeding the recommendations of the Institute of Medicine (in the United States) is associated with numerous adverse maternal and infant health outcomes. While many behavioral interventions targeting nutrition and physical activity have been developed to promote GWG within the Institute of Medicine guidelines, engagement and results are variable. Technology-mediated interventions can potentially increase the feasibility, acceptability, and reach of interventions, particularly for pregnant women, for whom integration of interventions into daily life may be critical to retention and adherence. Previous reviews highlight GWG self-monitoring as a common intervention component, and emerging work has begun to integrate digital self-monitoring into technology-mediated interventions. With rapid advances in technology-mediated interventions, a focused synthesis of literature examining the role of digital self-monitoring tools in managing GWG is warranted to guide clinical practice and inform future studies.

Objective: The proposed review aims to synthesize the emerging research base evaluating digital GWG self-monitoring interventions, primarily focusing on whether the intervention is effective in managing GWG. Depending on the characteristics of the included research, secondary focus areas will comprise intervention recruitment and retention, feasibility, acceptability, and differences between stand-alone and multicomponent interventions.

Methods: This protocol was developed following the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) guidelines for systematic review protocols. The proposed review would use a planned and systematic approach to identify, evaluate, and synthesize relevant and recent empirical quantitative studies (reported in English) examining the use of digital weight self-monitoring tools in the context of technology-mediated interventions to manage GWG in pregnant US adults, with at least 2 instances of data collection. Literature eligible for inclusion will have a publication date between January 2010 and July 2020. The Effective Public Health Practice Project Quality Assessment Tool for Quantitative Studies will be used to assess the methodological quality of included studies across various domains, and results will be synthesized and summarized per the synthesis without meta-analysis guidelines.

Results: The initial queries of 1150 records have been executed and papers have been screened for inclusion. Data extractions are expected to be finished by December 2023. Results are expected in 2024. The systematic review that will be generated from this protocol will offer evidence for the use of digital self-monitoring tools in the management of GWG.

Conclusions: The planned, focused synthesis of relevant literature has the potential to inform the use of digital weight self-monitoring tools in the context of future technology-mediated interventions to manage GWG. In addition, the planned review has the potential to contribute as part of a broader movement in research toward empirically supporting the inclusion of specific components within more extensive, multicomponent interventions to balance parsimony and effectiveness.

Trial Registration: PROSPERO CRD42020204820; https://tinyurl.com/ybzt6bvr

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KEYWORDS

protocol; systematic review; gestational weight gain; self-monitoring; digital health; review methods; review methodology; pregnant; pregnancy; gestational; weight; maternal; mobile phone

Introduction

Background

Gestational weight gain (GWG) is currently assessed by comparison to recommendations provided by the Institute of Medicine (IOM) [1]. These guidelines are based on prepregnancy BMI, such that GWG falling below the recommended range is considered "inadequate," and GWG above the recommended range is considered "excessive." Excessive gestational weight gain has demonstrable associations with adverse maternal and infant health outcomes, such as pregnancy complications (eg, hypertension and preeclampsia) [2-4], postpartum weight retention with implications for long-term maternal obesity [5], large-for-gestational-age [2,3,6], macrosomia [6], cesarean delivery [2,3,6], elevated child BMI [5,7,8], among others.

Recent systematic reviews have primarily supported health behavior change (eg, diet or physical activity) to reduce the prevalence of excessive GWG [9-13]. However, these multiple review papers have described concerns about the generalizability of findings due to the inclusion of studies characterized by small sample sizes, low participant recruitment and retention, lack of diversity, or a lack of information about these areas [10,11,14-17]. Moreover, the prevalence of excessive gestational weight gain remains high, with nearly half (48%) of pregnant women in the United States reporting weight gain above the recommended ranges across categorizations of prepregnancy BMI [18-20]. A recent meta-analysis of GWG-focused interventions during pregnancy [21] reflected a notably nonrepresentative sample (over 80% White women). Homogenous samples such as these call for researchers to assess how specific interventions have addressed acceptability, feasibility, and effectiveness for certain subpopulations. Notable efforts to recruit and test different lifestyle intervention strategies to modify GWG in diverse populations have been successful through a consortium model [22].

As new technologies emerge, technology-mediated interventions have been proposed as a potential solution for expanding the reach and scope of behavioral and interpersonal (eg, provider-directed) interventions [12,23-25]. Internet websites, text messaging, and smartphone apps have been identified as accessible resources for a diverse population of racial or ethnic and socioeconomic groups [24,26], and other potential methods may include activity and lifestyle tracking technologies such as wearable devices or scales with Bluetooth or other wireless capabilities. For example, a technology-based intervention that incorporated skills training, prompts, personalized feedback, counseling, and peer support via text messaging, health coaching phone calls, and Facebook group involvement was noted to be a significant improvement over usual care concerning managing weight during pregnancy for urban mothers with low-income [27,28]. Such findings underscore the importance of health education and awareness around GWG outcomes for low-income women [29] and the need for complex intervention development that is adequately informed by and responsive to the risks and needs of the target population [30].

Recent reviews have specifically examined the impact of technology-supported lifestyle interventions on GWG and postpartum weight retention [31-34]. Lau et al [31] determined e-based lifestyle interventions to be acceptable among pregnant populations, calling for future work to optimize intervention components. Mertens et al [32] focused mainly on randomized controlled trials (RCTs) using telecoaching or feedback (eg, via SMS or app) that was responsive to participants' self-monitoring, with some evidence of optimization for GWG. In their review of exclusively digital health interventions (for managing GWG, improving diet, or increasing physical activity), Rhodes et al [33] highlighted that while self-monitoring components were not universally included among the effective interventions, 7 out of 11 interventions did use some self-monitoring component, revealing a potential avenue for a more nuanced understanding of the impact of specific mobile health (mHealth) approaches in managing GWG. The results indicate that in the context of marked heterogeneity in outcomes studied, digital interventions did not demonstrate evidence of effectiveness for managing GWG, highlighting that different types (ie, subareas) of digital approaches may show differing levels of effectiveness [33]. Furthermore, findings of a meta-analysis determined e-Health technology exposure was associated with a nonsignificant effect on weight management during pregnancy but in postpartum, there was a statistically significant weight reduction [34].

Technological or digital interventions may provide feasible solutions for adapting to unique life circumstances and needs [35]. However, a more focused assessment of the degree to which specific technological approaches are feasible, acceptable, and effective are essential prerequisites [36]. Despite the generally broad availability and accessibility of mobile phone technology among women in the United States [37], there are significant considerations for addressing participation barriers associated with technology, such as rural versus nonrural users, inconsistent data plans, and device sharing [38,39]. Consequently, specific characteristics and components of interventions (eg, social media versus smartphone apps or responsive wearable devices) may dictate accessibility and constrain the reach of digital approaches [40,41].

Given the high overall rate of mobile phone ownership and use and qualitative data suggesting that pregnant women desire personalized mobile tools for healthy lifestyle behaviors in pregnancy [42], mHealth interventions represent a unique

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subclass of interventions distinct from other technology-based interventions [43]. Consistent with this sentiment, the World Health Organization, in their guideline on digital interventions to strengthen health systems, specifically addressed "targeted client communication for behavior change" as a context-aware recommendation for the use and development of mHealth technologies (eg, text messaging, interactive content such as apps, games, and social media, wireless devices) [44]. Pregnancy-related smartphone apps are the largest category of medically related apps, and smartphone apps with interactive capability are the most popular and well-liked [45]. While many smartphone apps advertise themselves as focused on GWG self-monitoring, a recent review highlighted that only a small percentage provided all of the key features of GWG monitoring (ie, tracking tools and guidelines or recommendations) [46].

A systematic review examining weight self-monitoring in nonpregnant populations seeking weight loss or management noted that the use of weight self-monitoring differs considerably between studies concerning aspects such as frequency, tools used, instructions provided, and role of weight self-monitoring (ie, as the only intervention versus as one part of a multicomponent intervention) [47]. Overall, across studies, participants perceived weight monitoring positively and feasibly. However, Zheng et al [47] highlighted the variability and inaccuracies that may present with self-report assessments of weighing behavior and weight and joined a broader call for more objective assessment methods. Moreover, the use of "smart" (ie, cellular-connected) scales tied to personalized feedback has been associated with weight loss, adherence to weight self-monitoring, and decreases in caloric consumption in comparison to a waitlist control group [48]. Thus, digital health approaches to weight self-monitoring have the potential to address the need for objectivity and improve adherence while maintaining the feasibility associated with self-monitoring.

Notably, the goals of pregnant individuals engaged in a GWG management program may differ considerably to those seeking weight loss or management outside of pregnancy. This highlights the need to closely examine and understand the impact of weight self-monitoring in this unique population. While a systematic review has been conducted to investigate the effect of routine weighing during pregnancy as a standalone intervention to manage GWG, this review (which included only 2 published RCTs) included both self-weighing and clinician weighing, was unable to identify any studies using digital health approaches to weight self-monitoring, and ultimately failed to support the effectiveness of weight monitoring for GWG management [49]. In a subsequent comment, the authors acknowledged that while the systematic review results were inconclusive, research in this area continues to accumulate [50,51]. In sum, though digital approaches provide a method to maintain benefits previously observed across pregnant and nonpregnant populations (about weight monitoring) while also increasing feasibility and adherence, uncertain quality of consumer-facing options (ie, publicly available smartphone apps) and a rapidly evolving research base highlight the need to evaluate the potential role of digital self-monitoring tools for the management of GWG.

Thus, the proposed review aims to summarize and synthesize the emerging research base evaluating digital GWG self-monitoring interventions for managing GWG during pregnancy. The primary outcome focus of this systematic review is GWG because prior RCT methods targeting nutrition or physical activity have yielded promising but modest effects on the reduction of GWG by about 20% [11]. There is a need to identify more effective and sustainable approaches to intervention delivery.

Objectives

Overview

The proposed review would aim to answer the following research questions relating to interventions, including a digital GWG self-monitoring component with a primary or secondary focus on the management of adult GWG.

Primary Focus

- How effective are interventions, including digital self-monitoring tools, in the management of GWG?

Secondary Foci

- Are interventions including digital GWG self-monitoring components associated with increased retention of participants in comparison to usual care or other care in control groups?
- Are interventions including digital GWG self-monitoring components associated with indicators of feasibility and acceptability among participants?
- Are there differences in the effects of standalone digital GWG self-monitoring interventions compared to multicomponent interventions, including digital GWG self-monitoring components?
- How diverse are the samples used to study GWG self-monitoring with digital components?

Methods

Study Designs

This protocol followed the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) guidelines for developing systematic review protocols (the PRISMA-P checklist is provided herewith). Studies will be selected according to the following criteria. The proposed review would include RCTs, feasibility trials, acceptability trials, pilot studies, nonrandomized trials, and controlled before-and-after studies. The proposed review will consist of studies examining adult pregnant individuals (18 years or older, as adolescent growth and development may further complicate the measurement of GWG and associated recommendations). It will include studies that examine individuals with chronic conditions, diseases, or disorders, as long as the primary or secondary outcome relates to GWG. Studies will be selected for inclusion in the proposed review only if at least 2 time points of data are available (ie, no studies that report only on cross-sectional data would be included). Additionally, though no restrictions will be placed on the length of follow-up for outcomes, follow-up data will be reported if available.

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Interventions

Of interest in the proposed review would be mHealth interventions for the management of GWG, which include a digital weight self-monitoring component (eg, mobile app weight tracker). For the proposed review, interventions will be considered "mHealth" if the primary components of the intervention is delivered via a wireless device (eg, tablet, iPad, wearable device, and wireless scale) or mobile telephone (eg, cell phone, smartphone, and mobile website), and would be considered to have a weight self-monitoring component if they require the user to enter their weight, whether these data are collected automatically or input manually by the user. However, interventions that do not require any interactional component (ie, do not use the advanced functionality in mobile or wireless devices, eg, appointment reminders and static informational websites accessed via mobile devices) would not be considered mHealth interventions. Given the proposed review's focus on a descriptive (rather than reductive) summary of the extant literature on the use of digital self-monitoring technologies in interventions for the management of GWG, studies with any comparison group are eligible for inclusion, as are studies with no comparison group.

Evaluation Outcomes

In the proposed review, included studies would have an outcome relating to GWG as the primary study outcome (ie, interventions that attempt to prevent excessive GWG or promote adequate GWG within IOM guidelines). For the proposed review, GWG would be considered to be reflected by the total weight gain from pre- or early pregnancy to the time of delivery, the rate of weight gain per week from pre- or early pregnancy to the time of delivery, or the IOM categorization of the adequacy of pregnancy weight gain. Secondary study outcomes (if provided) would include physical activity or exercise behaviors (measured indirectly via self-reported or directly via activity tracker data reflecting frequency, intensity, or duration), diet or eating behaviors or diet quality (measured via self-reported dietary intake records or food frequency questionnaires, reflected as nutrient or energy intakes or as evaluation of dietary quality in comparison to established guidelines, eg, Healthy Eating Index-2015), sleep behaviors (measured indirectly via self-reported or directly via activity tracker data reflecting duration or quality), or psychosocial well-being or mood (measured via self-report surveys).

Exclusion Criteria

The proposed review will be restricted to studies conducted within the United States, given how guidelines for GWG vary considerably between countries [52]. We will include papers reported in English only, though a list of possibly relevant titles in other languages will be provided as a supplemental resource. Inclusion and exclusion criteria are summarized in Textbox 1.

Textbox 1. Inclusion or exclusion criteria.

Included criteria

- **Paper type:** Randomized controlled trials, feasibility trials, acceptability trials, pilot studies, nonrandomized trials, and controlled before-and-after studies
- **Sample:** Adult pregnant individuals 18 years or older, with or without chronic health conditions
- **Outcomes:** Primary or secondary outcomes relate to gestational weight gain
- Additional psychosocial or behavioral outcomes, including physical activity or exercise, diet or eating, sleep, or well-being or mood
- **Study timespan:** Longitudinal or prepost designs, with or without postpartum follow-up period
- **Intervention:** mHealth interventions focused on managing gestational weight gain; primary components of the intervention are delivered over the wireless device or mobile telephone; participants are required to monitor weight (either automatically or via manual entry)
- **Comparison:** Studies with and without intervention comparison groups (eg, waitlist control group, treatment-as-usual, no comparison group)
- **Study location:** Conducted in the United States
- **Language:** English

Excluded criteria

- **Paper type:** Qualitative studies, studies that do not contain an intervention component
- **Sample:** Adolescent pregnant individuals, nonpregnant individuals
- **Outcomes:** No outcomes relating to gestational weight gain or gestational weight gain was not measured
- **Additional outcomes:** Not applicable, if other outcomes are collected, they will not be reported (eg, blood pressure and blood glucose)
- **Study timespan:** Cross-sectional studies
- **Intervention:** No digital weight self-monitoring component; no interactional component; static informational websites
- **Comparison:** Not applicable
- **Study location:** Conducted outside of the United States
- **Language:** Languages other than English (list of possibly relevant titles published in other languages will be included as a supplemental resource)

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Search Strategy

Electronic databases will be searched for literature published between January 2010 and July 2020 (to encompass the past decade given the rapid and ongoing development of digital health technology): PubMed or MEDLINE, Web of Science, Google Scholar, CINAHL, Academic Search Complete, PsycINFO, Embase. Both keywords and MeSH (Medical Subject Headings) terms relating to GWG, eHealth, mHealth, and variations of these terms. Boolean logic (ie, use of AND Mesh OR) will be implemented where appropriate.

Reference lists of studies initially selected for the review and lists of studies citing the studies originally chosen for the review will be assessed to identify additional studies that may meet eligibility criteria. Additionally, studies included in extant systematic reviews relevant to the proposed review will be evaluated against the proposed eligibility criteria. Finally, authors of registered protocols (for which published works summarizing results cannot be located) will be contacted to solicit any unpublished or unfinished work that may be incorporated into the narrative synthesis.

A university librarian with content coverage in public health provided preliminary consultation in developing the search strategy to ensure it captured all relevant terms. An example of the PubMed database search strategy is provided in Multimedia Appendix 1. It will be amended for other search engines to use database-specific or -compliant subject headings and keywords (ie, controlled vocabularies).

Data Management

Excel (Microsoft Corp) will be used to review literature search result lists. These results from all searched databases will be combined, and duplicate entries will be removed. The process will be described using a PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) flow diagram. A checklist based on the inclusion and exclusion criteria will be created to facilitate the initial title screening of papers. Further, 1 reviewer will independently screen titles. In total, 2 reviewers will screen the abstracts associated with the resultant list of relevant titles to identify studies for which the entire text will be reviewed. The Kappa statistic will be used to assess the inter-reviewer agreement on this list before pulling the selected studies' full text. Finally, studies for which full text is reviewed will be independently assessed for inclusion by 2 reviewers, with any discrepancies brought to a third reviewer for additional feedback to reach a consensus on the final list of included studies.

Quality Assessment

The Effective Public Health Practice Project Quality Assessment Tool for Quantitative Studies will be used to assess the methodological quality (indicated as “strong,” “moderate,” or “weak”) of selected studies in each of the following areas: study design, analysis, withdrawals and dropouts, data collection practices, selection bias, invention integrity, blinding as part of a controlled trial, and confounders. Both reviewers will conduct quality assessments, and any discrepancies will be brought to a third reviewer for additional feedback to reach a consensus on quality evaluation. Additionally, these ratings will be presented in a tabular format to aid in contextualizing the narrative summary. Ratings over 2 SDs below the mean quality assessment rating will be excluded from any synthesis of outcome data.

Data Extraction and Synthesis

Descriptive details of interventions, including details of this study (setting and length), participant characteristics, the overall role of digital self-monitoring technology in the intervention, features of technology used in the intervention, description of any other intervention components, and outcomes will be extracted for narrative synthesis. Further, 2 reviewers will independently extract relevant information. Disagreements on the categorizations for selected studies will be discussed, and a third reviewer will be consulted as necessary until a consensus is reached. See Multimedia Appendices 2 and 3 for the data extraction tool and variables of interest.

A summary of findings and evaluation of the strength of the body of evidence will be provided in accordance with the synthesis without meta-analysis guidelines [53] in narrative and tabular format based on the outcomes reported in the studies reviewed, along with an indication of the quality of the studies as indicated by the Effective Public Health Practice Project Quality Assessment Tool. For continuous outcomes (eg, total GWG, rate of GWG per week), means and SDs would be used for comparison purposes. For categorical outcomes (eg, adequacy of GWG according to IOM guidelines), relative risk or odds ratios would be used for comparison purposes. If at least 2 studies are available examining intervention impact on pregnant women categorized as “overweight” or “obese” based on currently used BMI categorizations, a separate narrative synthesis section would evaluate intervention use and outcomes in this subpopulation.

Results

The research protocol was registered with PROSPERO (CRD42020204820), on September 29, 2020. The initial queries resulting in 1150 total records have been screened. Data extractions are expected to be finished by December 2023. The systematic review generated from this protocol will offer evidence for using digital self-monitoring tools in the management of GWG. The research to practice translation may have implications for OB or GYN care by summarizing the feasibility and acceptability of digital self-monitoring tools for GWG. The results will be disseminated through a peer-reviewed publication, expected in 2024.

Discussion

Principal Results

While advancements in intervention science have primarily supported the use of behavior change techniques (eg, physical activity and diet changes) for the management of GWG from the perspective of efficacy, much uncertainty remains regarding their broader feasibility and acceptability, as well as their impact on related health outcomes (eg, pregnancy and birth complications), constraining evidence for more general effectiveness. However, the continuing and rapid development

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of new intervention approaches, particularly in the area of weight self-monitoring mHealth technology (given its accumulated support in nonpregnant populations), necessitate an updated and focused systematic review to more specifically address the potential of digital weight self-monitoring technology to address current gaps in feasibility, acceptability, and broad reach of interventions for managing GWG. If the proposed review finds that digital weight self-monitoring components are associated with desirable GWG outcomes or with improvements or maintenance of health behaviors (secondary outcomes), this would suggest that digital weight self-monitoring is an essential and necessary component of technology-mediated interventions focused on GWG.

Comparison With Prior Work

While previous reviews have examined effectiveness in the broadly defined use of e- and mHealth technologies to intervene concerning a variety of pregnancy health outcomes, limited consideration of such aspects as acceptability, feasibility (eg, retention), participant perceptions, and unique features specific to digital self-monitoring interventions uniquely positions the proposed review as both an extension of prior work and a much-needed reorientation toward a more practical understanding of the utility of digital self-monitoring tools for GWG management.

Limitations

The proposed review would include non-RCT studies, which may reduce the number of included studies with a comparison group and limit the conclusions that can be drawn regarding the impact of digital GWG self-monitoring interventions. Further, much of the research conducted to date (as suggested by previous reviews) has occurred with mostly White pregnant individuals. Consequently, any systematic reviews focusing on this body of literature will likely have limited applicability for Black, indigenous, or other racial or ethnic minority groups [54]. Given the notion of the "digital divide," it is possible that larger socioeconomic systems may dictate access to specific technologies.

Similarly, digital weight self-monitoring tools are primarily designed from a personal behavior change perspective. Thus, research captured in the context of the proposed review may not reflect how sociocultural systems (eg, familial or cultural context, interpersonal relational dynamics) may shape individuals' perceptions of and engagement with the apps. Finally, the authors acknowledge that their socioeconomic positions, racial or ethnic identities, and life histories may constrain the degree to which they can recognize, acknowledge, and consider the unique contexts and barriers experienced by socioeconomically, racially, ethnically, and culturally diverse pregnant women who do and do not engage with pregnancy weight management interventions.

Conclusions

The proposed review could help identify the degree to which digital GWG self-monitoring (as reflected by published empirical studies) can impact the prevalence of healthy GWG and the degree to which participants find the interventions feasible and acceptable. Furthermore, identifying effective strategies within interventions can inform future intervention research and, in the long term, individualized selection of efficacious interventions (and their constituent components) in clinical practice settings.

Acknowledgments

JM and AAD wrote this protocol, and JM conducted initial searches.

Data Availability

Data sharing does not apply to the above-described protocol, as no data sets were generated or analyzed in the production of the protocol. The proposed data set described in the protocol would consist of information gathered primarily from published research. Any additional data generated during the proposed systematic review (eg, quality ratings for specific papers) will be described as appropriate within the paper describing the review results. Any data not related will be available from the corresponding author upon reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PubMed search strategy.
[DOCX File , 13 KB - resprot_v12i1e50145_app1.docx]

Multimedia Appendix 2
Data extraction tool—study details.
[DOCX File , 14 KB - resprot_v12i1e50145_app2.docx]

Multimedia Appendix 3
Data extraction tool—study outcomes.

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[DOCX File , 16 KB - resprot_v12i1e50145_app3.docx]

Multimedia Appendix 4
PRISMA-P Checklist.
[DOCX File , 17 KB - resprot_v12i1e50145_app4.docx]

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Abbreviations

GWG: gestational weight gain
IOM: Institute of Medicine
MeSH: Medical Subject Headings
mHealth: mobile health
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols
RCT: randomized controlled trial

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Protocol

Reasons for Crown Failures in Primary Teeth: Protocol for a Systematic Review and Meta-Analysis

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Abstract

Background: There is a tendency nowadays to restore large defects in primary dentition with pediatric crowns instead of conventional restorations. Thus, understanding the factors contributing to the survival or failure of dental crowns in pediatric dentistry is essential for optimizing treatment outcomes.

Objective: The primary objective of this protocol is to outline the methodological approach for analyzing data from observational studies and randomized controlled trials to investigate reasons for the failure of dental crowns in primary teeth and to compute their survival and failure rates.

Methods: A comprehensive literature review will be performed in electronic databases, including PubMed (MEDLINE), Cochrane, Embase, and Web of Science. As per predefined inclusion criteria, we will include observational studies (prospective clinical studies) and randomized clinical trials that have an English abstract and involve children aged 1-10 years undergoing crown restorations. Two independent reviewers will independently screen all retrieved records and full-text articles and extract data. The study's methodological quality will be appraised using suitable tools. Assessments of publication bias will be performed using funnel plots. The findings will be described qualitatively for the systematic review. If possible, a meta-analysis will be performed to estimate failure rates by dividing the number of failures by the total exposure time. A Poisson regression model, assuming constant event rates, will be used to compute 3-year and 5-year survival proportions. The Pearson goodness-of-fit statistics will be used to assess the heterogeneity of the model. A P value <.05 will be considered significant. All analyses will be performed using R Statistical software (version 4.1.2; R Core Team).

Results: This systematic review and synthesis aim to assess the survival and failure rates of dental crowns in pediatric dentistry. By following this rigorous methodology, we seek to provide valuable insights into the factors contributing to the success or failure of these restorations. The results of our full review will have implications for pediatric dentists, researchers, and policy makers, helping to improve dental care for children.

Conclusions: This systematic review protocol helps in establishing a thorough approach for reviewing failures in pediatric crowns. By following this methodology, standardization and transparency of the process as well as accountability for the stated methods and outcomes will be ensured. The findings of this review and analysis will provide useful data on the survival of crowns to pediatric dentists and researchers.

Trial Registration: PROSPERO CRD42023442266; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=442266

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International Registered Report Identifier (IRRID): PRR1-10.2196/51505

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KEYWORDS

crowns; primary teeth; biological complications; technical complications; survival rates; pediatric; dental; dentistry; teeth; dentists; survival; quality assessment

Introduction

Apart from maintaining space for permanent teeth, primary teeth serve important functions in mastication and speech development [1-3]. Structural damage to primary teeth caused by caries, bruxism, and other parafunctions, such as jaw clenching and tooth grinding, are relatively common presentations in pediatric dentistry. In 2010, it was shown that untreated caries in deciduous teeth affected 9% of the global population or 621 million people worldwide [4]. Furthermore, the prevalence of bruxism could be in the range of 3.5% to 40.6% among children and adolescents [5]. This high prevalence of caries and structural damages caused by caries and other parafunctions warrant restorative interventions that are safe and effective in the long term [4,5].

Pediatric dental crowns are commonly used as a restorative measure to preserve the tooth's functionality and prevent premature loss. Several materials, such as stainless steel, zirconia, composite resins, and polycarbonate materials, have shown satisfactory properties for fabricating dental crowns [6-8]. Despite advancements in dental materials and techniques, crown failures do occur, leading to potential complications and the need for further interventions [9].

Although secondary caries seem to be a common reason for the failure of these crowns, several other biological and technical factors also contribute to the failure of crowns [9]. Several studies have investigated the outcomes and success rates of dental crowns in pediatric dentistry, but there remains a lack of comprehensive synthesis and analysis regarding the specific reasons for crown failure. Therefore, conducting a systematic review and meta-analysis to pool and analyze available evidence on the reasons for crown failure in pediatric patients will provide valuable insights into this important clinical concern.

The objective of the systematic review and meta-analysis proposed in this protocol is to comprehensively analyze the reasons for the failure of crowns in primary teeth. By synthesizing existing evidence, we aim to identify the common causes of failure, assess their prevalence, and explore potential risk factors associated with crowns in primary teeth.

Methods

Protocol Registration and Reporting Information

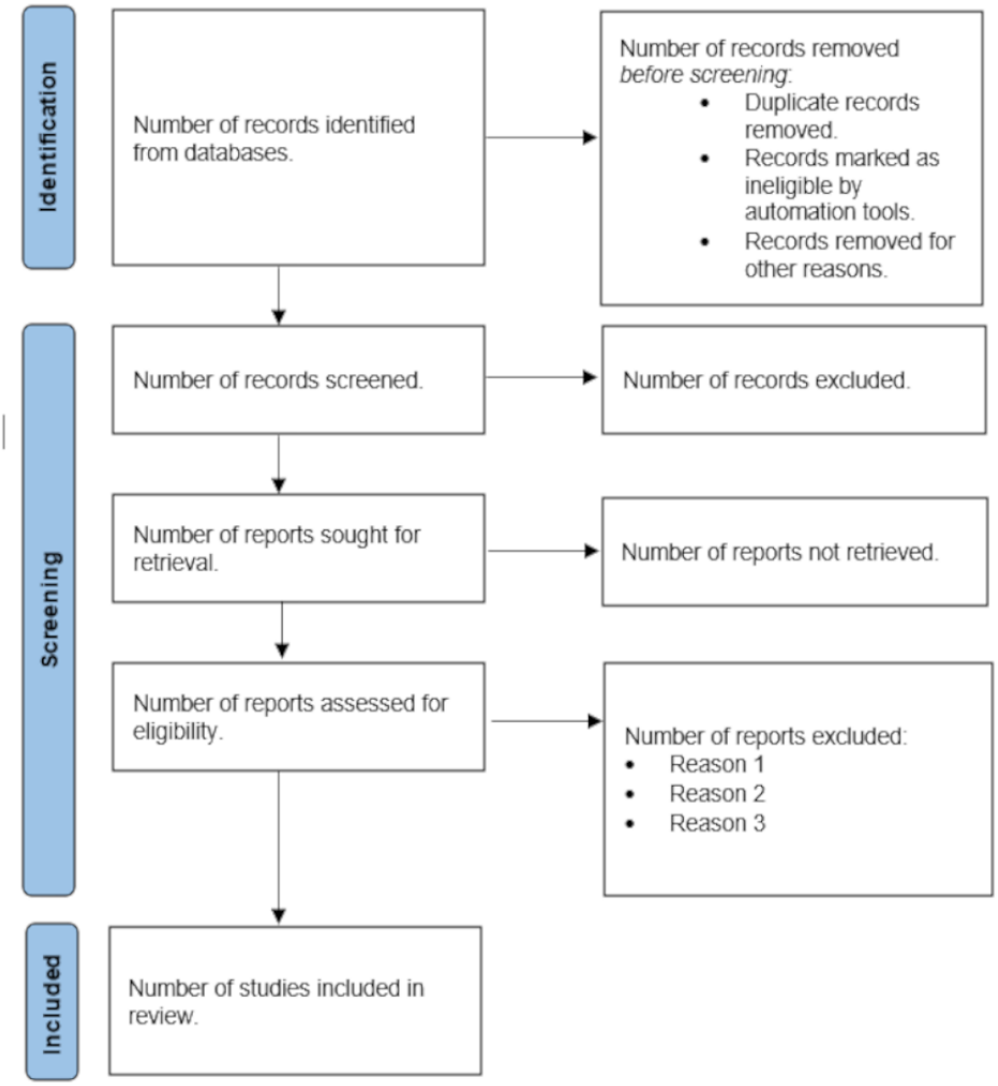
This protocol is registered in the PROSPERO database (CRD42023442266) and has been written according to the MOOSE (Meta-Analysis Of Observational Studies in Epidemiology) and the PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols) guidelines [10,11].

Data Sources, Search Terms, and Search Strategy

Under the supervision of the principal investigator, we will conduct a systematic search of electronic databases, including Cochrane, Embase, PubMed (MEDLINE), and Web of Science to identify relevant articles published up to the date of our search. The search strategy will be developed using appropriate keywords and Medical Subject Headings terms related to “child,” “children,” “toddler,” “crowns,” “pediatric dentistry,” and “treatment failures.” Additionally, we will manually search the reference lists of selected articles and relevant systematic reviews to identify any additional studies. The searches will not be limited by historical time constraints. The search strategy will be considered adequate to reduce the risk of selection and detection bias. The search results will be exported to Zotero, where duplicates will be excluded. Included studies will be manually searched to select other relevant studies. A PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram (Figure 1) will be reported to describe the study selection process.

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Figure 1. Conceptual PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) diagram for identification of studies via databases and registers.



Inclusion and Exclusion Criteria

We will include clinical studies, randomized controlled trials (RCTs), and prospective longitudinal studies (nonrandomized clinical studies and cohort studies) that meet the following criteria: (1) evaluate crown restorations in pediatric patients aged 1-10 years, (2) report reasons for crown failure or complications, and (3) have abstracts available in English. Qualitative interviews, quasi-experimental studies, single-case studies, and series of single-case studies will be excluded. Furthermore, studies without sufficient data on the survival of crowns or duplicate publications will be excluded. Secondary caries, endodontic complications, and periodontal pathology will be considered biological complications in this analysis. The technical complications to be considered in this analysis will include fractures of the crown (not the tooth itself), loss of retention, debonding, and occlusal wear. Data based on conference abstracts and dissertations will not be included.

Data Extraction and Analysis

Two independent reviewers will screen the articles for eligibility; they will extract data and assess the quality and risk of bias of the included studies. Any discrepancies will be resolved through discussion or consultation with a third reviewer. The extracted data will include study characteristics, sample size, patient demographics, types of materials, reasons for failure, and reported complications. A narrative synthesis will be performed to summarize the findings, and if feasible, a meta-analysis will be conducted to calculate pooled estimates of the prevalence of restoration failures in pediatric dentistry.

Assessment of Methodological Quality

The risk of bias in the included RCTs will be systematically assessed using the RoB 2 (Risk of Bias 2) tool developed by the Cochrane Collaboration [12]. Using this tool, 2 independent reviewers will evaluate the various domains of bias in RCTs, including randomization, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias. Each included RCT will be assessed for risk of bias in accordance with the domains specified by the RoB 2 tool, and an overall risk of bias judgment (low, some concerns, or high) will be assigned to each trial [12]. Furthermore, a checklist proposed by Moga et al [13] will be adapted for assessing the risk of bias in prospective clinical studies. Only studies with a moderate or low risk of bias will be included in the current

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analysis. Although this tool was originally developed for case series, a modification of this tool has been adapted previously for assessing the risk of bias in studies that have a missing comparator [14]. Using this tool, seven domains will be assessed for risk of bias (Table 1) and an overall risk of bias judgment (high risk of bias, serious risk of bias, low risk of bias, or no information) will be assigned to each study [13,14].

Table 1. Risk of bias domains to be assessed for prospective clinical studies. Assessments will be reported as high risk of bias, serious risk of bias, low risk of bias, or no information [13,14].

Domains	Assessment item
Domain 1	Study design
Domain 2	Study population
Domain 3	Interventions
Domain 4	Outcome measures
Domain 5	Statistical analysis
Domain 6	Results and conclusion
Domain 7	Competing interests

Assessment of Publication Bias

To enhance the transparency and accuracy of the findings, assessments of publication bias (less likelihood of publishing studies that failed to show statistical significance) using funnel plots will be undertaken in the evaluation of the survival and failure rates of dental crowns in pediatric dentistry. If present, publication bias will be reflected as an asymmetry in the funnel plot [15,16].

Meta-Analytic Approach

For the purposes of quantitative analysis, survival will be defined as a number of crowns that were in situ, regardless of complications (technical and biological), which include secondary caries, marginal integrity, marginal discoloration, and loss of anatomical form along with surface roughness, endodontic complications, loss of retention, and fractures. Failure rates resulting from biological and technical failures will be calculated by dividing the number of failures by the total exposure time. Exposure time for each included study will be calculated by taking the sum of exposure time for all fixed dental prostheses. A Poisson regression model will be used to analyze the calculated rates. Survival proportions for 3 years and 5 years will be estimated with an assumption of constant event rates. The Pearson goodness-of-fit statistics will be used to assess the heterogeneity of the model. A P value <.05 will be considered significant. All analyses will be performed using R Statistical software (version 4.1.2; R Core Team).

Results

Overview

The search and screening for the systematic literature review are anticipated to be finished in October 2023. Data extraction, quality appraisal, and subsequent data synthesis began in October 2023. The review is expected to be completed by November 2023, and attempts to publish the study results will be made in December 2023.

Protocol Amendments

If this protocol is substantially amended after an initiation that may impact the conduct of the study (including eligibility criteria, study objectives, study design, study procedures, and analysis), then an amendment will be agreed upon by all collaborators prior to the implementation and will be documented in a later report.

Discussion

Key Findings

This planned systematic review and meta-analysis will systematically identify the common causes of failure, assess their prevalence, and explore potential technical and biological factors associated with crown failures in pediatric patients. Furthermore, a meta-analysis will be attempted, if feasible; a Poisson regression model, assuming constant event rates, will be used to compute 3-year and 5-year survival proportions. The findings of the systematic review and meta-analysis will assess the quality of available studies and provide important insights for methodological aspects of future research. Thus, the findings of this review and its quantitative assessments could inform researchers and clinicians.

Comparison to Previous Research

Chisini et al [9] reported a systematic review on survival and reasons for failure of primary teeth restorations [9]. This systematic review included data from 31 studies conducted between 1996 and 2016 [9]. However, this review looked at all restorative materials used in pediatric dentistry and was not restricted to crowns on primary teeth. Apart from this study, a systematic analysis of the technical and biological factors affecting the survival of crowns for primary teeth has been scanty. Our review will analyze pediatric crowns only and, therefore, will add valuable insights for understanding the technical and biological factors contributing to the success or failure of crowns for primary teeth.

Limitations

Although it has been suggested that researchers must include unpublished literature in meta-analyses and systematic reviews,

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the inclusion of data from unpublished studies can itself introduce bias [17]. Thus, data from unpublished studies and non–peer-reviewed literature (eg, reports) will be excluded. However, assessments of publication bias will be performed using funnel plots [15,16]. Despite this potential limitation, the findings of the proposed systematic review and meta-analysis will contribute to the existing body of knowledge by identifying common causes of failure, highlighting potential risk factors, and guiding future research and clinical practice to improve the success rate of crowns in children with structural damage of the primary teeth.

Conclusions

This systematic review and meta-analysis protocol is designed to provide a comprehensive assessment of the common causes of crown failures in primary teeth, explore associated technical and biological factors, and estimate survival proportions over 3-year and 5-year periods. Although building upon the existing body of knowledge, the proposed study distinguishes itself by focusing on the unique challenges and intricacies of crown failures in primary teeth. By systematically identifying factors influencing crown outcomes, our findings will inform dentists in clinical practice about possible causes of pediatric crown failures, helping to minimize these potential failures. This study will also guide future research efforts to improve material properties to increase the clinical longevity of these pediatric crowns.

Data Availability

All data generated or analyzed during the systematic review and meta-analysis proposed herein will be made available as supplementary files as part of any forthcoming publications.

Conflicts of Interest

None declared.

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Abbreviations

MOOSE: Meta-Analysis Of Observational Studies in Epidemiology
PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT: randomized controlled trial
RoB 2: risk of bias 2

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Protocol

Effectiveness of Interventions to Improve Digital Health Literacy in Forced Migrant Populations: Protocol for a Mixed Methods Systematic Review

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Abstract

Background: Digital health literacy is considered a health determinant that can influence improved health and well-being, health equity, and the reduction of social health inequalities. Therefore, it serves as an asset for individuals to promote their health. However, low digital health literacy is a major problem among forced migrant populations. They do not always have the capacity and skills to access digital health resources and use them appropriately. To our knowledge, no studies are currently available to examine effective interventions for improving digital health literacy among forced migrant populations.

Objective: This paper presents the protocol for a systematic review that aims to assess the effectiveness of digital health literacy interventions among forced migrant populations. With this review, our objectives are as follows: (1) identify interventions designed to improve digital health literacy among forced migrant populations, including interventions aimed at creating enabling conditions or environments that cater to the needs and expectations of forced migrants limited by low levels of digital health literacy, with the goal of facilitating their access to and use of eHealth resources; (2) define the categories and describe the characteristics of these interventions, which are designed to enhance the abilities of forced migrants or adapt digital health services to meet the needs and expectations of forced migrant populations.

Methods: A mixed methods systematic review will be conducted according to the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) checklist. The research will be conducted in an iterative process among the different authors. With the help of a medical information specialist, a specific search strategy will be formulated for the 6 most relevant databases (ie, MEDLINE, Embase, CINAHL, Web of Science, Academic Search Premier, PsycINFO, and the Google Scholar search engine). A literature search covering studies published between 2000 and 2022 has already been conducted. Two reviewers then proceeded, individually and independently, to conduct a double selection of titles, abstracts, and then full texts. Data extraction will be conducted by a reviewer and validated by a senior researcher. We will use the narrative synthesis method (ie, structured narrative summaries of key themes) to present a comprehensive picture of effective digital health literacy interventions among forced migrant populations and the success factors of these interventions.

Results: The search strategy and literature search were completed in December 2022. A total of 1232 articles were identified. The first selection was completed in July 2023. The second selection is still in progress. The publication of the systematic review is scheduled for December 2023.

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Conclusions: This mixed methods systematic review will provide comprehensive knowledge on effective interventions for digital literacy among forced migrant populations. The evidence generated will further inform stakeholders and aid decision makers in promoting equitable access to and use of digital health resources for forced migrant populations and the general population in host countries.

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KEYWORDS

intervention; digital health literacy; forced migrant populations; health literacy; digital literacy; migrant; migrants; immigrant; immigrants; knowledge synthesis; review methods; review methodology; systematic; eHealth literacy

Introduction

Overview

Forced migration is a growing global phenomenon. It is defined by the International Organization for Migration [1] as "a non-voluntary, coerced and suffered migratory movement, caused by various factors, but involving the use of force, coercion." According to Keely and Kraly [2], the reasons for forced migration include wars and armed conflicts, persecution and violence, human rights violations, climate change, natural disasters, and famine. In 2021, there were approximately 1 billion migrants worldwide, accounting for 1 in 7 people in the world [3,4]. Of this population, 82.4 million are forced migrants [3]. An estimated 48 million are internally displaced, 26.4 million are refugees, and 4.1 million are asylum seekers [3]. On host lands or countries, migrants often live with minimal public services and face many complex problems [5]. Due to a lack of regular migration status, stigmatization, xenophobia, racism, discrimination, language and cultural barriers, as well as low income levels, forced migrants have limited access to social and health services and health promotion interventions [6-8]. All these difficulties negatively affect their physical and mental health and well-being and make them more vulnerable [6,9].

The use of information and communication technologies (ICTs) for health, called digital health or eHealth [10,11], could be a promising avenue to address the challenges faced by these forced migrant populations, including internally displaced persons, refugees, asylum seekers, and economic, political, or climate migrants [2,12-17]. Indeed, digital health technologies could play an important role in preventing and promoting the health and well-being of forced migrant populations [18,19]. Chae et al [20] and Wang and Yu [21] explain that forced migrant populations use digital technologies as tools or sources of health information to circumvent barriers in host countries. For example, the internet is regularly used as a cost-effective or free alternative route to search for web-based health information [20]. The study by Chae et al [20] found that about 3%-6% of surveyed women of Korean descent living in the United States used the internet as their primary source for health information. Accessing health information via the internet can also overcome language barriers by using either the language of the country of origin or the language of the host country [21].

Smartphones and digital platforms are digital solutions that could help forced migrant populations understand and connect with complex health systems in host countries [12,17,22]. These digital tools allow these populations, who are unfamiliar with the organization of health systems in host countries, to find doctors, clinics, and hospitals [17]. They also facilitate access to health services, including appointment scheduling and geolocation, especially those in close proximity to their living environment [17]. For example, digital platforms like the Ssyla Digital Therapy Platform, an initiative based in the United Kingdom, connect refugees and migrants to a global network of mental health therapists [12].

In the face of various stressors and challenges experienced by migrants in host countries, digital technologies are resources contributing to improving their well-being. Digital forced migrant resilience was repeatedly linked to social ties [17,23]. Social networks are digital spaces for forced migrant populations to strengthen and create cultural ties (or shared identities) and gather emotional and social support [23]. Connecting with members of their community who are already settled in the host country strengthens feelings of security and trust, belonging to a community, social inclusion, a sense of value, recognition of social status, and nondiscrimination [23]. In addition, contact via mobile phone and social media with family and relatives back home is an important social support for forced migrants, allowing them to overcome physical barriers as well as feelings of social isolation and manage stress [17,24].

Although ICTs have many opportunities and benefits, there are barriers that could prevent forced migrant populations from accessing and using digital health technologies. The first level of difficulties faced by forced migrants is accessing digital media and equipment (eg, internet, computers, tablets, and phones, as well as necessary infrastructure). For example, asylum seekers in Australia were unable to access the internet due to the unaffordable cost or unavailability [25]. Afghan migrants in Iran could not access mobile devices and networks due to infrastructure and legal restrictions [26].

The second category of barriers faced by forced migrants is related to their ability to use available digital health resources. Forced migrants with adverse personal characteristics (eg, advanced age, cognitive impairment, lack of experience, and lack of digital skills) face more barriers to using the internet and apps [27]. For example, older migrants whose health is deteriorating face more barriers to internet use than their healthier counterparts. According to Kouvonen et al [27], the most frequently mentioned challenges were that these digital

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tools were too complicated or difficult to learn and they presented security challenges.

Finally, the third category of barriers faced by forced migrants is related to their ability to search, find, understand, evaluate, and use health information via the internet. Indeed, language barriers, the complexity of the organization of health systems in host countries, and certain medical terminologies limit access to web-based services for forced migrant populations [28-31]. Moreover, faced with the flood of information on social media, forced migrants do not always have the skills to assess and differentiate between reliable and unreliable health information [32]. This category of barriers is also observed in the general population of the host land or country [33].

Thus, low digital health literacy is an important issue among forced migrant populations [29,34]. Norman and Skinner [35] define digital health literacy as "the ability to search, find, understand and evaluate health information from numerical, electronic sources and use the information to make decisions about one's health." In the face of constant digital evolution and the increasing complexity of society and health care systems, forced migrants require additional skills, such as the ability to recognize information needs, trust web-based health information, and interact with the digital health system to improve their health and well-being [36]. To do so, several authors [37-39] indicate that there is a need to conceptualize digital health literacy by considering dimensions such as context (eg, the ability to recognize the existence of an information need and trust web-based health information) and the interactions between migrants and the digital health system. Low levels of digital health literacy could lead to poor health and well-being outcomes [40]. In addition, they may exacerbate disparities (or digital inequalities) in accessing and using digital health services (or digital exclusion), and above all, they may contribute to health inequalities between communities [33]. Low levels of digital health literacy are not conducive to health equity.

To address these major challenges, many initiatives aimed at promoting better health behaviors among forced migrant populations have been developed by different actors [13,37,40]. A comprehensive understanding of these interventions to support digital health literacy among forced migrant populations and their effectiveness is essential to enable policy makers to develop programs and interventions tailored to their needs. However, to our knowledge, there is limited literature on interventions favorable to the digital health literacy of forced migrant populations, which underscores the interest in a research protocol for a mixed methods systematic review.

Objectives

The overall aim of the systematic review is to assess the effectiveness of interventions aimed at improving digital health literacy among forced migrant populations. To achieve this general objective, 2 specific objectives are pursued, as follows:

- Identify interventions designed to improve digital health literacy among forced migrant populations, including interventions aimed at creating enabling conditions or environments that cater to the needs and expectations of forced migrant populations limited by low levels of digital health literacy, with the goal of facilitating their access to and use of eHealth resources.
- Define the categories and describe the characteristics of these interventions, which are aimed at improving the abilities of forced migrants or adapting digital health services to meet the needs and expectations of forced migrant populations limited by low levels of digital health literacy.

Methods

Reporting Standards

This systematic review protocol uses the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocol) checklist [41]. The systematic review will be conducted by a research team in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist for systematic reviews [42].

Eligibility Criteria

Eligibility criteria will be based on the PICOS (population, intervention, comparison, outcomes, and study design) model [43] and are described in Table 1. To be selected for review, studies should target forced migrant populations, including internally displaced persons; refugees; asylum seekers; as well as political, economic, and climate migrants. In addition, all studies on interventions related to the theme will be included (ie, if they focus on interventions aimed at digital health literacy among vulnerable migrant populations). As for the types of studies, there will be no restrictions. All quantitative empirical studies, qualitative or mixed methods studies, and studies with or without a control group will be included without distinction. We will consider only studies published in English or French. This systematic review will cover the period from 2000 to 2022. Frank [44] introduced the concept of "digital health" in the early 2000s. We will exclude editorials, commentaries, conference abstracts, protocols, and test recordings.

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Table 1. Eligibility criteria based on the PICOS (population, intervention, comparison, outcomes, and study design) model [1,2,45].

PICOS model categories	Description

Population (P)	• The population consists of forced migrant populations, including internally displaced persons, refugees, asylum seekers, as well as political, economic, and climate migrants. It should be noted that forced migrant populations research is challenged by the diversity of terminology and definitions used [2]. For the purposes of this systematic review, we will rely on definitions from the International Organization for Migration [1] glossary, as follows:
	  ◦ Internally displaced persons are "persons forced to flee or leave their homes or places of habitual residence within their own country, including as a result of or to prevent the effects of conflict, violence, human rights violations or natural or man-made disasters" (free translation) [1].
	  ◦ Refugees (convention 1951) means to refer to any "person who, owing to a well-founded fear of being persecuted for reasons of race, religion, nationality, membership of a particular social group or political opinion, is outside the country of his nationality and who is unable or, owing to such fear, does not want to claim the protection of this country" (free translation) [1].
	  ◦ Asylum seeker refers to a "person seeking international protection. In countries with individualized examination procedures, the asylum seeker is a person whose asylum application has not yet been the subject of a final decision by the potential host country. Not every asylum seeker is necessarily recognized as a refugee at the end of the process, but every refugee has initially been an asylum seeker" (free translation) [1].
	  ◦ Migrants include all persons who leave their place of habitual residence to settle, temporarily or permanently, either in another region within the same country or in another country, thus crossing an international border, and for various reasons [1]. When people move in search of a better life or work, we speak of economic migration. In addition, when they migrate to escape persecution due to their political opinions, it is referred to as political migration [1].
	  ◦ Climate migration means to refer to any "movement of a person or group of persons who, essentially for reasons related to a sudden or gradual change in the environment as a result of climate change, are forced to leave their place of habitual residence, or leave it on their own initiative, temporarily or permanently, to go elsewhere in the territory of a state or across an international border" (free translation) [1].
	• All studies on interventions related to promoting digital health literacy among forced migrant populations will be included.

Intervention (I)	• All studies on interventions related to promoting digital health literacy among forced migrant populations will be included. • All types of interventions will be considered and classified according to the "Behaviour Change Wheel" model [45]. Indeed, this model makes it possible to systematically characterize interventions aimed at modifying or changing behavior at the individual, organizational, and societal levels.
Comparative (C)	There will be 2 types of comparisons: • A specific intervention to promote digital health literacy in forced migrant populations, compared to no specific intervention or usual services. • A specific intervention to promote digital health literacy in forced migrant populations, compared to any other intervention, to promote digital health literacy in these populations.

Outcomes (O)	The following elements will be examined:
	• Categories: the following categories will be reviewed:
	  ◦ Level of intervention: individual, group, or mixed
	  ◦ Mode of design: theory, evidence, or none
	  ◦ Targeted behavior: opportunities, motivations, attitudes, and abilities or skills
	• Characteristics of interventions: interventions will be classified according to the following 9 functions of an intervention (ie, types of interventions) based on the model proposed by Michie et al [45]: education, persuasion, incentive, coercion, training, restriction, environmental restructuring, modeling, and empowerment.
	• Results and success factors of interventions: outcomes related to behavior change, self-care behaviors, and resolution of health problems through interventions will be examined along with their success factors. We will also explore outcomes related to access to basic health information and improved quality of life through digital health technologies.

Study design (S)	• As for the types of studies, there will be no restrictions. All quantitative empirical studies, qualitative studies, or mixed methods studies, and studies with or without a control group will be included without distinction.

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Review Question

The review question for this systematic review is the following: what are some effective interventions to improve digital health literacy among forced migrant populations, including internally displaced persons, refugees, asylum seekers, as well as economic, political, and climate migrants?

Search Strategy

The search strategy will be developed by a research team in collaboration with a librarian from Laval University (FB), who specializes in medical information and is experienced in systematic reviews. The research will be carried out in an iterative process between the different authors. First, the systematic literature search will be conducted in the following relevant bibliographic databases: MEDLINE (OVID), Embase, CINAHL, Web of Science, Academic Search Premier, and PsycINFO. We will also search the Google Scholar search engine. The search terms used will be based on a combination of 2 key concepts, which are "Digital Health Literacy" and "forced Migrant Populations." Research terms for each of these concepts will be developed from the literature and thesauri. Specific details of the strategies will be presented in the form of tables. Then, the search results will be imported to the web-based collaboration tool Covidence (Veritas Health Innovation) [46], a review management software, where duplicates will be removed using the automation function. Missing duplicates will be removed manually.

Study Selection and Extraction

The selection of studies will be done in Covidence [46]. Individual reviewers from the research team will perform a double selection of titles and abstracts, then the full text of relevant studies. After study selection, data will be extracted by a reviewer and validated by a senior team member, using an extraction grid designed and pilot-evaluated by the research team. Conflicts or discrepancies will be resolved through discussion and consensus within the research team.

Bias or Quality Assessment

Quality assessment is used to describe the selected articles and to interpret the data in the synthesis [47]. In this review, the quality of studies will be assessed using the Mixed Methods Appraisal Tool (MMAT). This tool will make it possible to simultaneously evaluate the different types of studies selected, whether qualitative, quantitative, or mixed [47].

Data Synthesis and Analysis

To synthesize the data, we will use narrative synthesis as a method, regardless of the type of study (eg, quantitative, qualitative, or mixed). We will provide a descriptive synthesis of the results of the included studies. A narrative summary of the main results will be produced. Outcomes related to behavior change, self-care behaviors, and health problem–solving (as a result of using the interventions) and the success factors of these interventions will be presented. Additionally, we will present the results related to access to basic health information and improved quality of life through digital health technologies.

Ethical Considerations

Ethics approval is not required for this systematic review, as it does not require primary data collection. The protocol will be registered with the International Prospective Registry of Systematic Reviews [48]. The results of this systematic review will be disseminated through publication in an academic journal and scientific conferences.

Results

The search strategy was completed in December 2022. The literature search identified 1232 studies. The first stage of study selection was completed in July 2023. A total of 82 studies were retained for the second selection, which is still in progress. Publication of the paper is scheduled for December 2023.

Discussion

The Main Contributions of This Systematic Review

Although literature reviews on health literacy interventions among migrants exist, they have not explicitly included studies on digital health literacy interventions among forced migrants. Fernández-Gutiérrez et al [49] published a systematic review in 2018 that focused solely on health literacy interventions among migrants and included only 9 studies and targeted health care professionals, including nurses. In 2022, a systematic review published by Fox and colleagues [50] on the same topic reviewed the existing literature documenting randomized controlled trials, including 23 articles. To our knowledge, there is no mixed methods literature review on the subject. Our review is the first attempt to examine interventions to improve digital health literacy among forced migrant populations and their effectiveness and challenges.

Potential Impact and Future Directions

Digital health literacy or eHealth literacy refers to the basic skills required for individuals to take advantage of digital technologies for the benefit of their own health [51]. The importance of these skills is well established for populations with low digital health literacy, such as forced migrants [52]. These skills enable forced migrant populations to promote their own health and well-being. Because of their vulnerability, it is essential to support the development of the skills needed to search, find, understand, and especially, critically evaluate health information among forced migrant populations. Thus, these populations represent important targets for the development of interventions conducive to their digital health literacy as well as the evaluation of the effectiveness of these interventions. This research aims to provide a synthesis of knowledge and generate evidence that will guide effective interventions promoting digital health literacy and the use of eHealth among forced migrant populations.

Determining the level of digital health literacy in forced migrant populations and associated factors contributes to the development of effective and innovative interventions that meet the needs of these populations [28]. Based on the socioecological model [53], 4 factors are identified: individual, interpersonal, community, and societal. The literature shows that there is

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considerable variability in the methodology of digital health literacy assessments in forced migrant populations [28]. Chesser et al [28] indicate that some of these measurement tools used for evaluation have inherent limitations. The wide variability in intervention designs to support digital health literacy in forced migrant populations could be explained by the variety of measurement tools and the plurality of associated factors. They also explain why some interventions are more effective than others. There is, therefore, a need to comprehensively understand and highlight effective interventions that support digital health literacy among forced migrant populations and the factors that these interventions have addressed. Mixed methods will be used in this systematic review to provide a broader and more comprehensive picture of the existing literature on effective interventions for improving digital health literacy in forced migrant populations.

Conclusions

The results of this systematic review will provide a comprehensive picture of effective interventions that promote digital health literacy among forced migrant populations. They will share knowledge and evidence on digital health and the use of eHealth among the forced migrant populations with different stakeholders. This evidence and knowledge, in turn, will aid decision makers in promoting equitable access to and use of digital health resources among forced migrants and the general population in host countries.

Acknowledgments

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Data Availability

Data relating to the search strategy for this review are available in Multimedia Appendix 1. All data generated or analyzed during this study (including the PRISMA [Preferred Reporting Items for Systematic Reviews and Meta-Analyses] flow chart) will be included as multimedia appendices. Databases created during the data extraction process will be available upon reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search strategies for each database.
[DOCX File , 27 KB - resprot_v12i1e50798_app1.docx]

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Abbreviations

ICT: information and communication technology
MMAT: Mixed Methods Appraisal Tool
PICOS: population, intervention, comparison, outcomes, study design
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocol

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Protocol

Comparing Oral Versus Intravenous Antibiotics Administration for Cellulitis Infection: Protocol for a Systematic Review and Meta-Analysis

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Abstract

Background: Cellulitis is defined as an infection of the skin that is usually characterized by localized but poorly demarcated areas of erythema, swelling, and pain. Erysipelas is a subtype of cellulitis that is characterized by a more superficial infection, often involving the face. Because gram-positive bacteria are the most common infective agent, beta-lactam antibiotics such as cephalosporins are commonly used. However, guidelines and physician preference vary widely as different antibiotic options and routes of administration exist, in addition to the fact that most cases are treated empirically without microbiological lab guidance. This lack of standardization in evidence, guidelines, and physician practice prompted this systematic review and meta-analysis of both randomized trial data and cohort studies to aggregate the currently available evidence for the optimal routes of antibiotic administration in cellulitis treatment.

Objective: The primary objective of our review is to compare the efficacy of oral versus intravenous antibiotic administration for cellulitis infections, thereby providing clinicians with evidence-based guidelines for treatment.

Methods: We will search MEDLINE, Embase, and CENTRAL through Ovid as well as Web of Science and CINAHL for all available literature comparing different routes of antibiotic administration in the treatment of cellulitis and erysipelas. We will perform title and abstract as well as full-text screening in duplicate according to the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) guidelines and then extract the relevant data using a prepiloted data sheet. The primary outcome for our review is the duration of infection resolution, and secondary outcomes such as incidence of sepsis, mortality, hospital admission, and Clostridium difficile infection. We will assess the risk of bias in our included studies using the RoB 2.0 (revised tool for Risk of Bias in randomized trials) and ROBINS-I (Risk of bias in non-randomized studies for interventions) tools, with a final quality assessment using the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) framework and a sensitivity analysis to examine heterogeneity.

Results: We will publish the final results of our systematic review in a peer-reviewed academic journal. This project received no funding or financial assistance. Data analysis is currently underway, and the results are expected to be submitted for publication in late November 2023.

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Conclusions: To our knowledge, this will be the most up-to-date review of the best available evidence comparing different routes of antibiotic administration for cellulitis. Because of the vast selection of antibiotic options available and the empirical nature of the treatment, we anticipate heterogeneity within our data but nonetheless hope to provide aggregated evidence on the efficacy of intravenous versus oral administration of antibiotics in cellulitis treatment. We hope the results from this study will better inform physician practices in the future for cellulitis infections.

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KEYWORDS

antibiotics; cellulitis; infection; intravenous; oral

Introduction

Cellulitis is defined as a bacterial infection of the skin, usually involving the epidermal and dermal layers, with occasional involvement of the subcutaneous fat and lymphatic tissues. It is commonly characterized as poorly demarcated but localized swelling and pain, most often in the lower limbs [1]. Erysipelas is a subtype of cellulitis where the infection is more superficial in the epidermal layer and is often referred to by its clinical name when it affects the face or legs. The presentation of cellulitis also varies in severity and in bacterial species. Most patients only have mild systemic symptoms such as fevers, with only around 10% of hospitalized patients experiencing severe complications such as sepsis and necrotizing fasciitis [1,2]. However, around 18% of initial antibiotic treatment still fails. The most common causative agents include beta-hemolytic streptococci, such as group A and group G, as well as *Staphylococcus aureus*. The presence of methicillin-sensitive versus methicillin-resistant species of *S aureus* is also crucial in directing antibiotic treatment [2]. However, because of the nonsterile site of cellulitis infection with the presence of numerous commensal bacteria, empiric treatments are usually started without specimen collection. Microbiological studies are often only conducted in a research setting, to a limited effect, as the presence of commensal colonies can often confound the culture results. In rare cases, through opportunistic infections, fungal species can be implicated as well [3].

Based on the prominent bacterial species possibly found in common cellulitis infections such as beta-hemolytic streptococci and staphylococci, gram-positive antibiotics covering these organisms have been the empiric drug of choice [3,4]. However, a wide range and different classes of antibiotics are available to fill this demand, and there have been no cohesive guidelines for standardization. Beta-lactam inhibitors such as penicillin or different generations of cephalosporins such as cefazolin, cephalexin, or ceftriaxone have been commonly used. Other classes of antibiotics such as macrolides, doxycycline, and clindamycin have all been used and reported in the literature [3]. Additionally, antibiotics used for the broader coverage of methicillin-resistant *S aureus*–related cellulitis also vary, from vancomycin to trimethoprim-sulfamethoxazole or clindamycin. These antibiotics all differ in their efficacy and side effect profiles, such as *Clostridium difficile* risks. This lack of standardization and reliance on physician preference points to the need for evidence-based reviews for the optimal treatment of cellulitis [3-5]. These antibiotic options also differ in their routes of administration, with some available in both oral and intravenous (IV) routes, while other antibiotics can only be administered through one of the options. Because of its potential involvement in deeper layers of skin, topical antibiotic administration is unlikely to show efficacy against the infection. Despite some evidence showing that oral therapies are at least as effective as IV administration, some guidelines still recommend the IV routes for high-risk patients, such as those with obesity or venous stasis [3,6].

It is for these reasons mentioned above that we have decided to perform this systematic review. The primary objective of our review is to compare the efficacy of oral versus IV antibiotic administration for cellulitis infections, thereby providing clinicians with evidence-based guidelines for treatment.

Methods

Overview

This systematic review and meta-analysis will be conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) guidelines [7]. This protocol is also registered with PROSPERO (International Prospective Register of Systematic Reviews; registration ID CRD42023413590). Any major changes to this protocol will be reported within the final review itself.

Search Methods

We will conduct a systematic search of MEDLINE, Embase, and CENTRAL through Ovid, as well as CINAHL and Web of Science, from inception to February 2023. We will also use medical subject headings terms, when possible, for broad inclusion of studies. Examples include “erysipelas.tw,kf.” and “(antimicrob* or antibiotic*).tw,kf.” A detailed sample search strategy for MEDLINE through Ovid is outlined in Multimedia Appendix 1. We will not have any language restrictions on the data in our search. The bibliography of previous literature and systematic reviews will also be hand-searched for relevant or potentially missed articles.

Eligibility Criteria

Types of Studies

We will include parallel group randomized controlled trials (RCTs) as well as both prospective and retrospective cohort studies. Studies with skin and soft tissue infection as its main focus and cellulitis as one of its subgroups will also be included in the review. Case control, case series, and case reports will

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be excluded. Studies focusing on other skin conditions such as necrotizing fasciitis with noncellulitis sources will also be excluded. The detailed inclusion and exclusion criteria are organized into a table format in Table S1 in Multimedia Appendix 2.

Types of Participants

Our review will focus on all adult patients (aged 18 years or older) who were diagnosed with cellulitis or erysipelas in any health care setting. Cellulitis diagnostic criteria are based on individual studies.

Type of Intervention

We will include all studies comparing oral versus IV administration of antibiotics for the treatment of cellulitis. The antibiotic agent does not have to be the same across the different treatment groups within the study, nor does it have to be from the same class. For example, if a study compares IV cephalosporin versus an oral macrolide, it will be included in our analyses. Studies comparing antibiotics against placebos or other types of alternative treatments will be excluded. We are only focusing on antibiotics; hence, other rarer causes of cellulitis such as fungal infections will be excluded.

Outcomes

The primary outcome of our review will focus on the duration of infection resolution, which may vary across studies and may need to be adjusted based on our included articles' definition of infection resolution. Our second outcomes include incidence of severe systemic infection or mortality, patients' quality of life (QOL) as measured by QOL scores based on each included study, incidence of adverse events such as nausea and vomiting, length of hospitalization for inpatients or number of hospitalizations for cellulitis in studies measuring outpatients, and incidence of *C difficile* infection.

Study Screening

A total of 2 independent authors will perform title and abstract screening individually and in duplicate using Covidence, a web-based systematic review tool [8]. If both reviewers are in agreement, a study will move on to full-text screening. Any conflicts between reviewers will be resolved through discussion involving a third author. Full-text screening will also be conducted in the same manner. If a full text cannot be found on publicly available domains, attempts will be made to reach out to the authors for a potential copy of the article with relevant data.

Data Collection

All data will be collected using a priori developed data collection sheet within Excel (Microsoft Corp), with 2 reviewers working independently and in duplicate, resolving conflicts through discussion and third-party arbitration. The prepiloted forms will be tested using 10 of the first included studies. For any full texts that are not available in the public domain or databases and for any missing data, we will attempt to contact the authors for further clarification and assistance.

Risk of Bias Assessment

The risk of bias (RoB) assessments of each analyzed study will be performed by 2 independent reviewers in duplicate. The RoB of RCTs will be assessed through RoB 2.0, a revised tool to assess RoB in randomized trials [9]. The reviewers will assess bias across the 5 outlined domains: bias arising from the randomization process, from deviation from intended interventions, from missing outcome data, from the measurement of outcomes, and from the selection of reported results. The overall RoB will be compiled using the calculation algorithm provided within the tool.

For cohort studies, the ROBINS-I tool will be used, which is a tool for assessing RoB in nonrandomized trials for interventions [10]. The 7 domains included in the assessment include bias from confounding, from selecting patients into the study, from classification of intervention, from deviations from intended intervention, from missing data, from the measurement of outcomes, and from the selection of reported outcomes. The overall risk will also be calculated using the algorithms provided within the tool itself.

Data Items

Our prepiloted data extraction form will include the following data items:

- Bibliometric data: authors, year of registration, trial registration number, and digital object identifier.
- Methodology: number of participating centers, location of the study, method for blinding, randomization methods, treatment setting (inpatient vs outpatient), and follow-up duration.
- Baseline data: total sample size, mean age, sex with number of female patients included, comorbidities, choice of antibiotic, route of administration, frequency and duration of administration, daily and cumulative dosage, and species of organisms identified if performed.
- Outcome data: duration to infection resolution, duration to symptom improvement, incidence of severe infection, mortality, QOL scale and respective score, length of hospitalization, incidence of adverse events, and incidence of *C difficile* infection.

Statistical Analysis

We will first provide a comprehensive qualitative synthesis of all of the included studies, summarizing their characteristics and findings in organized text and table format in accordance with the PRISMA reporting guidelines.

If there are sufficient similar studies that will be meaningful for an aggregate analysis, we will perform meta-analyses for a weighted effect of the interventions across different studies. We will conduct our quantitative analysis using the computer program Review Manager (RevMan, version 5.4; Cochrane) [11]. We will use a random-effects model, and in cases where the heterogeneity cannot be explained, we will perform a sensitivity analysis using a random-effects model as well. For continuous outcomes such as duration of infection resolution and length of hospitalization, a mean difference with a 95% CI will be used. For dichotomous outcomes such as mortality or

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incidence of severe infection, a Mantel-Haenszel odds ratio with 95% CIs will be used. If the events are rare, a Peto odds ratio will be used instead. If there are not enough meaningful data for meta-analysis for any particular outcome, we will qualitatively describe the results across studies.

The heterogeneity of the included studies will be assessed using a combination of visual inspection of the forest plots along with the I^2 statistic according to the Cochrane Handbook. We will consider an I^2>50% to be seriously heterogeneous and an I^2>75% to be very seriously heterogeneous.

In the case of missing data, we will attempt to contact the authors of the original study. Missing SDs will be inputted using methods outlined in the Cochrane Handbook for Systematic Review of Interventions using correlation coefficients.

Regarding the overall assessment of the quality of evidence included in the review, 2 independent reviewers will perform the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) analysis [12]. Any discrepancies will also be resolved through discussion.

Ethical Considerations

Ethics approval is not applicable to this study as this is a review study and no original data pertaining to humans or animals will be collected. No individual patient data are collected and all research data collected from original studies will remain anonymized.

Results

We will share the results of this study through peer-reviewed academic publications and conference presentations. We will continue to perform updating the searches in all databases every 2 months for any new data to be included in the systematic review. This project received no funding or financial assistance. Data analysis is currently underway, and the results are expected to be submitted for publication in late November 2023.

Discussion

This protocol outlines the planned systematic review and meta-analysis to compare the efficacy of oral and IV antibiotic administration in the treatment of cellulitis. Because of the vast selection of options available to physicians and the lack of quality evidence or rigorous reviews, there has been significant variation between guidelines and physician preferences. Some antibiotics may be available for both IV and oral administration, while others may only be suitable for one of the routes. Therefore, we also hope to aggregate the evidence from the literature first and then elucidate the indications for the usage of either route of administration, potentially also comparing their usage for similar infection profiles to assess their efficacy.

Our review will have several strengths and weaknesses. In terms of strengths, we will not be placing any language or time restrictions in our search strategy to ensure broad inclusion of all currently available evidence. We will also include both prospective and retrospective cohort studies in addition to RCTs to increase our pooled sample size. As a weakness, the quality of our meta-analysis may be limited by our inclusion of cohort studies, which is inherently weaker on the hierarchy of evidence with a potentially higher RoB. However, to mitigate this, we will analyze RCTs and cohort studies in separate pools, as well as using tools such as RoB 2.0 and ROBINS-I to rigorously assess the quality of the included studies based on the Cochrane Handbook. We will also conduct a subgroup analysis with only high-quality evidence and compare those with the pooled results. Additionally, because of the variations that exist within guidelines and physician practices, we also expect potentially significant heterogeneity between our included studies. We will assess this heterogeneity quantitatively and report on it in our final review. An additional limitation of our review is that, despite placing no language restrictions, the databases searched are primarily Western, English-based databases, meaning additional non-English data may be missed. We are only focusing on adults aged 18 years or older; hence, the value of this study for patients aged 18 years or younger may be limited.

There have been several attempts at assessing the different routes of antibiotic administration for the treatment of cellulitis. Brindle et al [3] conducted a systematic review on cellulitis treatments with the route of administration as a subfocus, finding that there are only a few low-quality randomized trials comparing the different routes, showing no difference between IV and oral treatments. Cross et al [6], with their primary focus on the duration of therapy, arrived at a similar conclusion. This study hopes to build upon these previous findings, as we have the routes of administration as our primary comparison [6]. We will also include observational studies and place no language barriers in our inclusion criteria, with the hope that it could provide additional valuable data upon Brindle et al's [3] and Cross et al's [6] conclusions on oral and IV treatments being equivalent. We hope the results of this study will inform the future prescribing practice of physicians treating cellulitis, especially in deciding oral versus IV treatments. This would not only benefit the patients but also help control the widening spread of antibiotic resistance in the community.

Acknowledgments

The authors received no funding or financial assistance for the drafting of this paper. All data from the included studies will remain anonymized, and the privacy of the individual subjects will be respected.

Data Availability

Data sharing is not applicable to this article, as no data sets were generated or analyzed during this study.

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Authors' Contributions

RY, JJ, YW, and WH were responsible for the inception of the project, including this protocol for the planned systematic review, and made significant contributions to the writing and revision of the manuscript. YJ, EQ, and CY made significant contributions to the drafting of the protocol as well as its revision before submission. CJ, MW, KX, XZ, and YJ made contributions to drafting the final manuscript, substantially reviewed it, and assisted in its final revision.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Detailed sample search strategy of MEDLINE through OVID.
[DOCX File , 12 KB - resprot_v12i1e48342_app1.docx]

Multimedia Appendix 2
Inclusion and exclusion criteria.
[DOCX File , 17 KB - resprot_v12i1e48342_app2.docx]

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Abbreviations

GRADE: Grading of Recommendations, Assessment, Development, and Evaluation
IV: intravenous
PRISMA: Preferred Reporting Items for Systematic Review and Meta-Analyses
PROSPERO: International Prospective Register of Systematic Reviews
QOL: quality of life
RCT: randomized controlled trial

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RoB: risk of bias
RoB 2.0: revised tool for risk of bias in randomized trials
ROBINS-I: risk of bias in nonrandomized studies for interventions

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Protocol

The Effects of Antenatal Interventions on Gestational Weight Gain in Low- and Middle-Income Countries: Protocol for a Systematic Review

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Abstract

Background: Gestational weight gain (GWG) is a crucial determinant of maternal and child outcomes yet remains an underused target for antenatal interventions in low- and middle-income countries (LMICs).

Objective: This systematic review aims to identify and summarize educational, behavioral, nutritional, and medical interventions on GWG from randomized controlled trials conducted in LMICs.

Methods: Randomized controlled trials that documented the effects of antenatal interventions on GWG in LMICs will be included. The interventions of interest will be educational, behavioral, nutritional, or medical. A systematic literature search will be conducted using PubMed, Embase, Web of Science, CINAHL (Cumulative Index to Nursing and Allied Health Literature), and the Cochrane Library from the inception of each database through October 2022 (with an updated search in January 2024). A total of 2 team members will independently perform the screening of studies and data extraction. A narrative synthesis of all the included studies will be provided. The risk of bias will be assessed using the Cochrane Risk of Bias tool. The certainty of the evidence for each homogeneous group of interventions will be assessed using the GRADE (Grading of Recommendation, Assessment, Development, and Evaluation) approach. A narrative synthesis of the included studies will be conducted to summarize mean differences (with 95% CIs) for continuous outcomes and risk ratios, rate ratios, hazard ratios, or odds ratios (with 95% CIs) for dichotomous or categorical outcomes. Available information on the costs of interventions will also be summarized to facilitate the adoption and scale-up of effective GWG interventions.

Results: The development of the research questions, search strategy, and search protocol was started on September 20, 2022. The database searches and the importation of the identified records into Covidence were performed on October 7, 2022. As of September 2023, the title and abstract screening was ongoing. The target completion time of this systematic review is April 2024.

Conclusions: Without effective interventions to manage GWG, the potential to improve maternal and child health through optimal GWG remains unrealized in LMICs. This systematic review will inform the design and implementation of antenatal interventions to prevent inadequate and excessive GWG in resource-limited settings.

Trial Registration: PROSPERO (International Prospective Register of Systematic Reviews) CRD42022366354; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=366354

International Registered Report Identifier (IRRID): PRR1-10.2196/48234

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KEYWORDS

low- and middle-income countries; pregnant women; gestational weight gain; maternal nutrition; interventions; randomized controlled trials; systematic review; protocols; RCT; maternal; pregnant; pregnancy; review methodology; nutrition; gestational; weight; prenatal; LMIC; low income; middle income

Introduction

Gestational weight gain (GWG) refers to the gain in body weight during pregnancy. GWG can be measured as total weight gain over the course of pregnancy or the rate of weight gain over a specific period (eg, in a week or in a month). The National Academy of Medicine, formerly the Institute of Medicine (IOM), recommends that women with underweight, normal weight, overweight, and obesity before pregnancy gain, respectively, 12.5 to 18 kg (0.44 to 0.58 kg/week in the second and third trimesters), 11.5 to 16 kg (0.35 to 0.50 kg/week), 7 to 11.5 kg (0.23 to 0.33 kg/week), and 5 to 9 kg (0.17 to 0.27 kg/week) [1]. Weight gain below or above these thresholds is considered inadequate or excessive GWG.

GWG is an important determinant of short- and long-term maternal and child health. On the one hand, pregnant women who gain inadequate gestational weight have elevated risks of small-for-gestational-age births [2], preterm birth [2], low birthweight [3], and infant mortality [4]. On the other hand, pregnant women with excessive GWG experience higher risks of macrosomia [2], large-for-gestational-age births [2], maternal morbidity [5], postpartum weight retention [6], and an increased risk of overweight and obesity among their children [7]. In addition to the critical impacts of GWG on pregnancy outcomes, maternal weight can also be monitored and feasibly modified during pregnancy. Therefore, GWG is a critical indicator for monitoring the overall health of the pregnancy and an important target for antenatal care [1].

Exceptionally high levels of inadequate GWG have been documented in low- and middle-income countries (LMICs). We previously reported that the mean levels of GWG were well below the IOM recommendation in almost all low- and middle-income world regions [8]. The regional level of GWG is particularly low in sub-Saharan Africa and South Asia, both of which meet only around 60% of the IOM recommendation [8]. In the meantime, an emerging burden of excessive GWG has become of concern in LMICs, as several countries in sub-Saharan Africa have over 15% of pregnant women gaining excessive GWG [9]. This concerning trend of excessive GWG may be a consequence of and further compounded by the nutrition transition to Westernized diets, sedentary lifestyles, and the rising prevalence of overweight and obesity [10-12].

Previous interventions on GWG were conducted primarily in high-income countries, often focusing on preventing excessive GWG through lifestyle interventions on dietary intake and physical activity [13-17]. In low- and middle-income settings, the effects of various interventions on inadequate GWG are unclear, and interventions to prevent excessive GWG are scarce. As a result, GWG remains severely underused in antenatal monitoring and intervention in LMICs. An evidence synthesis of interventions for GWG management will fill this critical gap and guide the design and implementation of culturally appropriate and context-relevant interventions on GWG in resource-limited settings.

This systematic review aims to identify and summarize educational, behavioral, nutritional, and medical interventions on GWG from randomized controlled trials (RCTs) in LMICs. This review will provide critical information to inform the design of antenatal interventions or intervention packages aimed at helping pregnant women prevent inadequate and excessive GWG.

Methods

Research Question

What are the effects of antenatal interventions (eg, educational, behavioral, nutritional, and medical) on GWG in LMICs?

Eligibility Criteria

Inclusion Criteria

The inclusion criteria were as follows:

1. RCTs, which could be individually randomized, cluster randomized, or have a mixture of individual and cluster randomization.
2. Participants were pregnant at enrollment or enrolled before pregnancy and followed up in pregnancy.
3. Studies conducted in a low-income, lower-middle-income, or upper-middle-income economy defined by the World Bank country classification for the 2023 fiscal year.
4. Interventions provided to women during pregnancy. The intervention could be educational, behavioral, nutritional, or medical. This scope of the interventions is based on the conceptual framework provided by the IOM guidelines regarding the determinants of GWG [1]. Examples of potential interventions include counseling about healthy eating, physical activity, or overall lifestyle; nutrition education on dietary intake; counseling on gestational weight management; anti-infectious regimen; single or multiple micronutrient supplementation; and macronutrient and food supplementation.
5. GWG was included as one of the study outcomes. GWG could be quantified by any metrics, including (but not limited to) total GWG in absolute amount, GWG z-score or adequacy ratio based on references or recommendations, and weekly or monthly rate of GWG. We will include GWG outcomes calculated based on body weights objectively measured by study teams.
6. The intervention could be provided alone or in combination with a cointervention that was similar across study arms.
7. At least 1 arm in the study did not receive the intervention of interest.

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8. No restrictions will be placed on the year or sample size of the study.

Exclusion Criteria

The exclusion criteria of the studies included:

1. Studies that did not report GWG as 1 of the study outcomes.
2. Studies that used body weight measures based on self-reports or medical record abstraction due to the concern of measurement error.
3. Studies conducted exclusively among women with pre-existing health conditions, such as anemia, human immunodeficiency virus infection, or diabetes. However, studies restricted to women with underweight and women with overweight or obesity will still be included.
4. Observational studies (eg, cohort, case-control, and cross-sectional studies).
5. Interventional studies that did not use individual or cluster randomization.
6. Editorials, commentaries, opinions, or review papers (these will, however, be used to identify relevant original studies).
7. Studies reported in languages other than English.

Information Source

We will conduct the literature search using PubMed, Embase, Web of Science, CINAHL (Cumulative Index to Nursing and Allied Health Literature), and the Cochrane Library from the inception of each database through October 2022. Our search covers the 3 databases (ie, MEDLINE, Embase, and the Cochrane Library) recommended by the Cochrane Handbook for Systematic Reviews of Interventions [18]. We will also review the references of the previous systematic reviews of a similar topic to locate additional studies.

Search Strategy

We developed the PubMed search strategy first and then translated the search strategy into the syntax appropriate for the other databases. The search strategies for different databases are provided in Multimedia Appendices 1-5. We examined the sensitivity of the search strategies by confirming that several sentinel papers were identified. The initial search occurred on October 7, 2022, and an updated search will be conducted in January 2024.

Data Management

We will use EndNote (version 20; Clarivate Analytics) to store the records retrieved from the databases. We will then import the records into Covidence (Veritas Health Innovation), an internet-based program that facilitates the streamlined management of systematic reviews. Duplicate records will be detected and removed first by EndNote and then by Covidence.

Selection of Studies

A total of 2 team members will independently screen the titles and abstracts of the identified studies based on the eligibility criteria, and 2 team members will then independently review the full texts of the remaining studies to confirm final eligibility. Disagreements between reviewers will be resolved by discussion or by a third reviewer, when necessary, at both the stage of title and abstract screening and the full-text screening. The interrater agreement will be quantified by calculating the raw percentage of agreement and the Cohen κ coefficient. Specific reasons for study exclusions will be documented and summarized using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram [19].

Data Extraction

We will conduct data extraction using the extraction function in Covidence. A total of 2 reviewers will independently extract the data of the retained studies using a data extraction form that will be pilot-tested on 5 randomly selected studies. Disagreements in the extracted information between reviewers will be resolved by discussion or by a third reviewer. We will extract the following information: study reference, setting and country of the study population, calendar year of intervention, randomization approach, sample size (number of clusters for each group, and number of participants in each group), sample characteristics (eg, age and socioeconomic status), timing and duration of intervention, description of the intervention, control, primary and secondary study outcomes, approach to defining and measuring GWG, main findings (with point estimates and measures of variance), and cost of the intervention (if available). If a publication is missing or unclear on any important study detail, we will contact the corresponding authors of the studies to obtain the information. Multiple reports of a single study will be collated as additional results may be provided in different reports. The data extraction tables are provided in Multimedia Appendices 6 and 7.

Risk of Bias Assessment

A total of 2 reviewers will independently assess the risk of bias, and any disagreement will be resolved by discussion and by a third reviewer when necessary. We will use version 2 of the Cochrane risk-of-bias tool (RoB 2) [20], which considers the following 5 domains: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in the measurement of the outcome, and bias in the selection of the reported results. For cluster-randomized trials, we will additionally consider bias from the timing of identification and recruitment of individual participants in relation to the timing of randomization [21]. Each domain will be judged as “low risk of bias,” “high risk of bias,” or “some concerns.” We will consider a study to be of low risk of bias if all domains are judged to have a low risk. We will consider a study to be of high risk of bias if at least 1 domain is judged to have a high risk or ≥3 domains are judged to have some concerns. We will consider a study to have some concerns if 1 or 2 domains are judged to have some concerns, but none of the domains is judged to have a high risk [20]. We will summarize the risk of bias assessment in tabular form and present the judgment for each domain with a justification [20].

Data Synthesis

A narrative synthesis of all included studies will be presented in the data extraction tables shown in Multimedia Appendices 6 and 7. Effect estimates for continuous outcomes will be expressed as mean differences (with 95% CIs) comparing the intervention group with the control group. Effect estimates for dichotomous and categorical outcomes will be expressed as risk

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ratios, rate ratios, hazard ratios, or odds ratios (with 95% CIs), comparing the intervention group with the control group. In addition to the narrative synthesis, we will conduct meta-analyses if a consistently defined intervention-outcome effect was reported in at least 3 studies.

Assessment of Certainty of Evidence

The overall certainty of the evidence for each reasonably homogeneous group of interventions will be assessed using the Grading of Recommendation, Assessment, Development, and Evaluation (GRADE) approach, which considers the risk of bias, publication bias, imprecision, inconsistency, and indirectness [22-27]. The strength of the overall evidence will be judged as high, moderate, low, or very low [22].

Registration and Reporting

This protocol was registered with PROSPERO (International Prospective Register of Systematic Reviews). The registration ID is CRD42022366354. In the event of protocol amendments, the date of each amendment will be accompanied by a description of the change and its rationale on PROSPERO. We prepared this protocol following the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) [28]. We will report the systematic review following the Cochrane Handbook for Systematic Reviews of Interventions [18] and the PRISMA guidelines [19].

Results

We started the development of the research questions, search strategy, and search protocol on September 20, 2022. On October 7, 2022, we performed the searches of all databases based on the search strategies and imported the identified records into Covidence. As of September 2023, the title and abstract screening was ongoing. We identified 33,664 nonduplicate records from all databases. As of September 25, 2023, a total of 8958 (26.6%) records had received 2 votes, and 8351 (24.8%) records had received 1 vote. The target completion time of this systematic review with the complete paper is April 2024.

Discussion

GWG has critical implications for the short- and long-term health of the mother and the child. Adequate GWG supports the growth and development of the fetus, while both inadequate and excessive GWG lead to adverse outcomes. LMICs have exceptionally high levels of inadequate GWG [8] and an emerging burden of excessive GWG [9]. Previous interventional studies on GWG were predominantly in high-income countries, with a focus on the prevention of excessive weight gain through dietary and physical activity interventions. Due to differences in stature, body composition, dietary practice, food environment, access to obstetric services, and other contextual factors, the effective and appropriate interventions on GWG differ between high-income countries and LMICs. There is, however, a limited understanding of the effective GWG interventions in low- and middle-income contexts. This systematic review will fill this knowledge gap and provide an updated evidence base to guide future interventions on GWG in resource-limited settings.

Food insecurity, inadequate dietary intake, and maternal undernutrition are the main nutritional contributors to inadequate GWG [1]. It is critical to ensure appropriate energy, macronutrient, and micronutrient intake to meet maternal and fetal needs during pregnancy [29]. Several nutritional interventions have been proposed or evaluated to accommodate the increased maternal nutritional needs during pregnancy [30]. Besides nutritional interventions, previous studies in sub-Saharan Africa also suggest alarmingly poor knowledge and practice of gestational weight management among pregnant women [31-33] and antenatal health care providers [34] in LMICs. Therefore, educational and behavioral interventions also hold promise for achieving optimal GWG for pregnant women in resource-limited settings.

In a recent systematic review and meta-analysis, Teede et al [17] evaluated the effects of antenatal lifestyle interventions pertaining to dietary intake and physical activity on GWG based on randomized trials in high-income countries and LMICs from 1990 to 2020. It was reported that, compared to routine antenatal care, overall lifestyle intervention (–1.15 kg; 95% CI –1.40 to –0.91 kg), lifestyle interventions on diet (–2.63 kg; 95% CI –3.87 to –1.40 kg), lifestyle interventions on physical activity (–1.04 kg; 95% CI –1.33 to –0.74 kg), and lifestyle interventions on dietary intake with physical activity (–1.35 kg; 95% CI –1.95 to –0.75 kg), were all associated with lower total GWG [17]. The review focused on lifestyle and behavioral interventions, and few included trials were from LMICs. Our systematic review will complement this work by covering all types of antenatal interventions with an explicit focus on low- and middle-income settings.

This systematic review will have several important strengths. First, we will cover the full spectrum of potential educational, behavioral, nutritional, and medical interventions that have shown promise in previous RCTs. Therefore, this review will contribute useful information to the design of antenatal intervention packages that seek to combine multiple forms of evidence-based interventions. Second, we will consider all metrics of GWG, including total GWG as an absolute value, GWG adequacy ratio based on references and recommendations, and weekly or monthly rate of GWG. As a result, this work will be informative for a nuanced understanding of the potential mechanisms of how different interventions affect the accrual of gestational weight. Finally, we plan to extract available information on the costs of the interventions that will facilitate the adoption and scale-up of effective GWG interventions. Potential limitations of this systematic review include the restriction to studies published in English and the expected heterogeneity of interventions and GWG metrics to be identified from the literature, which may make meta-analyses infeasible.

Without effective interventions to prevent both forms of inappropriate (inadequate and excessive) GWG, the potential to improve maternal and child health through optimal GWG remains unrealized in LMICs. This systematic review will provide a comprehensive and updated body of evidence that will contribute to the design, implementation, and scale-up of practical, effective, and cost-effective antenatal interventions or integrated intervention packages that help pregnant women in LMICs achieve optimal GWG.

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Acknowledgments

DW conceptualized the research question and developed the search strategy, the risk of bias assessment strategy, and the data extraction form. CHN contributed to the finalization of the search strategy. WWF contributed to the revision of the selection criteria. DW drafted the paper. All authors read, provided feedback, and approved the final paper.

CHN's contributions to this work are enabled by a graduate research assistantship from George Mason University. The institution has no role in the development of this protocol or the decision to submit it for publication.

Data Availability

All data generated and analyzed during this study will be included in the published paper or its supplementary files.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PubMed search strategy for interventions on gestational weight gain in low- and middle-income countries.
[DOCX File , 21 KB - resprot_v12i1e48234_app1.docx]

Multimedia Appendix 2
Embase search strategy for interventions on gestational weight gain in low- and middle-income countries.
[DOCX File , 21 KB - resprot_v12i1e48234_app2.docx]

Multimedia Appendix 3
Web of Science search strategy for interventions on gestational weight gain in low- and middle-income countries.
[DOCX File , 18 KB - resprot_v12i1e48234_app3.docx]

Multimedia Appendix 4
CINAHL (Cumulative Index to Nursing and Allied Health Literature) search strategy for interventions on gestational weight gain in low- and middle-income countries.
[DOCX File , 21 KB - resprot_v12i1e48234_app4.docx]

Multimedia Appendix 5
Cochrane Library search strategy for interventions on gestational weight gain in low- and middle-income countries.
[DOCX File , 25 KB - resprot_v12i1e48234_app5.docx]

Multimedia Appendix 6
Extraction of basic study characteristics for the systematic review of antenatal interventions on gestational weight gain in low- and middle-income countries.
[DOCX File , 16 KB - resprot_v12i1e48234_app6.docx]

Multimedia Appendix 7
Extraction of interventions, outcomes, and key findings for the systematic review of antenatal interventions on gestational weight gain in low- and middle-income countries.
[DOCX File , 16 KB - resprot_v12i1e48234_app7.docx]

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Abbreviations

CINAHL: Cumulative Index to Nursing and Allied Health Literature
GRADE: Grading of Recommendation, Assessment, Development, and Evaluation
GWG: gestational weight gain
IOM: Institute of Medicine
LMIC: low- and middle-income country
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols
PROSPERO: International Prospective Register of Systematic Reviews
RCT: randomized controlled trial
RoB: risk-of-bias

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Protocol

The Pharmacological Effect of Hemin in Inflammatory-Related Diseases: Protocol for a Systematic Review

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Abstract

Background: Hemin is a commonly used drug in the treatment of acute attacks of porphyria, due to its capability of restoring normal levels of hemoproteins and respiratory pigments. In addition, this drug has demonstrated the capacity to induce the heme oxygenase (HO) enzyme. At the moment, there are 3 known HO isoenzymes in mammals: HO-1, HO-2, and HO-3. The first of these shows cytoprotective, antioxidant, and anti-inflammatory effects. Currently, medicines used in inflammatory disorders have increased toxicity, especially over longer time frames, which highlights the need to investigate new, safer options. Indeed, the current nonclinical evidence demonstrates the potential that hemin has a significant anti-inflammatory effect in several animal models of inflammation-related diseases, such as experimental colitis, without significant side effects. However, the underlying mechanism(s) are still not fully understood. In addition, past nonclinical studies have applied different therapeutic regimens, making it relatively difficult to understand which is optimal. According to the literature, there is a lack of review articles discussing this topic, highlighting the need for a summary and analysis of the available preclinical evidence to elucidate the abovementioned issues. Therefore, a qualitative synthesis of the current evidence is essential for the research and medical communities.

Objective: This systematic review aims to summarize and analyze currently available nonclinical data to ascertain the potential anti-inflammatory effect of hemin in animal models.

Methods: Throughout the development of this protocol, we followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) protocol. The comprehensive search strategy will be carried out in MEDLINE (PubMed), Web of Science, and Scopus without any filters associated with publication date. Only in vivo, nonclinical studies that evaluated the potential anti-inflammatory effect of hemin will be included. The evaluated outcomes will be the observed clinical signs, inflammatory and other biochemical markers, and macroscopic and microscopic evaluations. To analyze the potential risk of bias, we will use the risk of bias tool developed by the Systematic Review Centre for Laboratory Animal Experimentation (SYRCLE).

Results: Currently, it is not possible to disclose any results since the project is still in initial steps. More specifically, we are currently engaged in the identification of eligible articles through the application of the inclusion and exclusion criteria. The work was initiated in April 2023, and it is expected to be finished at the end of 2023.

Conclusions: Concerning the major gap in the literature regarding the underlying mechanism(s) and treatment-related properties, this systematic review will be essential to clearly summarize and critically analyze the nonclinical data available, promoting a clearer vision of the potential anti-inflammatory effect of hemin.

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KEYWORDS

hemin; inflammation; animal models; nonclinical studies; in vivo

Introduction

Hemin, or ferriprotoporphyrin IX chloride, is an iron-containing metalloporphyrin that has been commonly used in clinical practice for several decades in the treatment of acute attacks of hepatic porphyria [1,2]. The development of porphyria is closely related to deficiency in the heme biosynthesis pathway, resulting in a lack of heme, which is necessary to produce several hemoproteins. In addition, heme precursors, which are directly and indirectly toxic to the human body, can also accumulate [3,4]. Treatment with hemin shows the capability of reducing heme deficiency by suppressing delta-aminolaevulinic acid synthase activity. Furthermore, this treatment also promotes the reduction of porphyrins and toxic precursors of heme [4,5]. Once hemin restores the normal levels of hemoproteins and respiratory pigments, the biological disturbances observed in patients with porphyria are attenuated [4,5].

However, the administration of hemin can also induce the expression of the heme oxygenase (HO) enzyme, which is known as a rate-limiting enzyme for heme catabolism and is responsible for the production of biliverdin, free iron, and carbon monoxide [2,6,7]. Currently, there are 3 identified HO isoenzymes in mammals: HO-1, HO-2, and HO-3 [2,6]. HO-1 is expressed as a response to tissue damage and demonstrates cytoprotective action capable of inhibiting the inflammatory response and oxidative stress [8]. On the other hand, the HO-2 and HO-3 isoenzymes are expressed constitutively in tissues involved in heme catabolism, which regulates the normal functioning of cells [7,9]. Considering the nonclinical evidence currently available, it has been suggested that HO-1 concentration and HO-1 mRNA are significantly elevated in cases of inflammation, such as in active ulcerative colitis [2,6,10]. In fact, through histological studies, it has been observed that HO-1 expression occurs mainly in macrophages; however, it can also be found in epithelial cells when there is an inflammatory response [11,12]. The capability of hemin to induce the expression of HO-1 makes it an interesting drug to evaluate for use in inflammatory-related diseases to ascertain its anti-inflammatory effect.

Considering the high toxicity of commonly used drugs for inflammation-related diseases, especially over the longer term, it is essential to investigate safer approaches that have comparable efficacy [13]. Several nonclinical studies have demonstrated that hemin is a significant anti-inflammatory without relevant side effects, highlighting it as a new potential pharmacological approach for the future. Considering the vast number of therapeutic regimens adopted in nonclinical studies, different animal models of disease, and different evaluated outcomes, it is essential to perform a review to clearly analyze and criticize the current evidence. Thus, this project will aim to develop a systematic review of the potential anti-inflammatory effect of hemin by summarizing and analyzing the nonclinical data currently available.

Methods

Overview

This protocol follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline [14]. During the development of the systematic review, 2 authors from the research group will be responsible for all steps concerning the selection of studies, including the title and abstract screening and assessment of study eligibility, as well as the data extraction process. In case of discrepancies during these steps, a third reviewer will be included to make a final decision. The project is currently ongoing, having been initiated in April 2023 with an anticipated completion date at the end of 2023.

Eligibility Criteria

Studies will be included for further analysis if they meet the follow PICOD (population, intervention, comparator, outcomes, study design) eligibility criteria:

- Population: Studies that use rodent models of inflammatory-related diseases. There will be no limitations in terms of species, strain, age, sex, or body weight since the purpose of this study is to analyze and synthesize all nonclinical data available.
- Intervention: Studies that administer hemin at any dosage, frequency, or treatment duration and with any route of administration in animal models of inflammatory-related diseases will be included, while studies that combine hemin treatment with another active drug or drugs will be excluded to clearly evaluate hemin's anti-inflammatory effect, excluding potential bias related to the use of other medicine.
- Comparator: Studies will be included if they have a nonexposed control group that is treated with any other pharmacological molecule, or even a placebo or usual care.
- Outcomes: All biochemical markers related to inflammation, with and without hemin treatment, will be analyzed. Studies with no relevant reported outcomes or that evaluate hemin administration for diseases as part of a summary of product characteristics will not be included.
- Study design: Only analytic, experimental, in vivo, nonclinical studies will be included.

Furthermore, studies written in languages other than English will not be included.

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Information Sources and Search Strategy

The biomedical electronic databases used for the highly sensitive search strategy will be MEDLINE (PubMed), Web of Science, and Scopus. The search will not be limited in terms of publication date. A comprehensive search strategy will be developed using descriptors related to 3 key terms: *hemin*, *inflammation*, and *nonclinical study*, as well as their synonyms, combined with the Boolean operators "AND" and "OR" to identify and select the eligible studies. The search strategies adopted for each biomedical electronic database are available in Multimedia Appendix 1.

Study Selection

Upon the application of the comprehensive search strategy in each database, the retrieved articles will be exported from the MEDLINE (PubMed), Web of Science, and Scopus databases to a systematic reviews web application (Rayyan QCRI; Rayyan). The first step will be to detect and exclude duplicates, and afterward the titles and abstracts will be analyzed by 2 independent reviewers in order to select relevant and potentially eligible studies according to the inclusion and exclusion criteria. After this process is completed, the same 2 independent reviewers will assess the full text of each study, deciding whether the article is eligible or not considering the inclusion and exclusion criteria. In case of discrepancies and lack of consensus between the 2 reviewers in these steps, a third reviewer will be included to make a final decision. The process of selection will be summarized using a PRISMA flowchart.

Data Collection Process

Upon selection of eligible studies, the 2 independent reviewers will extract them to a standardized data extraction document in Excel (Microsoft) that will be developed to extract the data of interest, including article identification (authors' names and year of publication), animal-related parameters, disease-related parameters, hemin treatment conditions, and outcomes of interest. Once again, in case of discrepancies between the reviewers, a third reviewer will be included to make the final decision. The data of interest will be extracted from the text, graphs, and tables from each included article.

Data Items

Population

We will only consider studies based on animal models, and the data of interest to be extracted will be related to species, strain, sex, age, and body weight.

Intervention

We will only consider studies that administer hemin to the subjects. The parameters of interest will be dosage, frequency of administration, route of administration, and duration of treatment.

Comparator

We will not consider any comparator-related parameters.

Outcomes

The data concerning the outcomes will be related to observed clinical signs (dichotomous measures), inflammatory and biochemical markers (continuous quantitative measures), macroscopic evaluation (dichotomous measures), and microscopic evaluation (dichotomous measures).

Study Design

Throughout the analysis of the in vivo nonclinical studies, the data of interest to be extracted will be related to identification of inflammatory-related diseases, their severity, and their chronicity.

Risk of Bias Assessment

The potential risk of bias will be identified and analyzed using the risk of bias tool of the Systematic Review Centre for Laboratory Animal Experimentation (SYRCLE) [15]. For each study, each component of the SYRCLE tool and the global study rating will be graded as low, moderate, or high. The final grade will be also decided considering an average of all individual components. The reporting quality and the risk of bias assessments will be independently performed by 2 different reviewers, after the data collection process is completed. Any disagreements will be discussed and arbitrated by a third reviewer.

Registration and Reporting

This systematic review protocol has been registered in an international prospective register of systematic reviews (PROSPERO CRD42023406160). Throughout the development of this systematic review, any potential modification of the protocol will be reported.

Results

Currently, the project has included 50 of the 1110 retrieved articles for qualitative synthesis based on the established inclusion and exclusion criteria. The data of interest are being carefully extracted by the 2 independent reviewers. The work is being performed by a pharmacologist team without any external funding and was initiated in April 2023. It is expected to be finished at the beginning of 2024.

Discussion

Current systematic reviews make it is possible only to determine that there is substantial variability in protocols for treatment with hemin, such as the dose, frequency of administration, and duration. However, even with different therapeutic regimens, this drug has shown a significant anti-inflammatory effect, mainly related to its capability to induce HO-1 without any relevant side effects.

It is clear that the majority of pharmacological approaches used in chronic inflammatory-related diseases aim to induce and maintain a remission phase in patients [13]. However, these approaches normally have several side effects, especially considering the long time frame of the treatment regimens, which can significantly decrease the overall quality of life of patients [13]. Thus, it is essential to investigate safer pharmacological tools, either by developing new drugs or by repurposing already accepted and extensively studied ones. Hemin is one of the latter, and it represents an interesting

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pharmacological approach to treatment of inflammatory-related diseases, considering its efficacy and safety over the short or long term. Indeed, several nonclinical studies have already demonstrated that hemin has a significant anti-inflammatory effect in different contexts, such as in inflammatory bowel disease [2,6,16,17], kidney dysfunction [18-20], sepsis [21-23], arthritis [24,25], pancreatitis [26-28], cardiac infarction [29], and airway inflammation [30-32].

We emphasize a major limitation regarding the methodology of this project, which is the absence of clinical evidence. Indeed, it would be interesting to analyze clinical data regarding the potential anti-inflammatory effect of hemin; however, the number of studies is relatively small and there have been no clinical trials on this topic. Therefore, we only considered nonclinical in vivo studies, since this approach allowed for the most controlled environment possible.

In conclusion, the main findings from this project may have a pivotal role in the research and medical communities, since we will summarize and discuss, for the first time, preclinical evidence regarding the potential anti-inflammatory effect of hemin. Indeed, considering the need to investigate safer pharmacological approaches for inflammatory diseases, this review should highlight an interesting new tool for future consideration, revealing its efficacy and safety as demonstrated in animal models.

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Data Availability

All data generated or analyzed during this study are included in this published article and its supplementary information files.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search strategies for each biomedical electronic database.
[PDF File (Adobe PDF File), 111 KB - resprot_v12i1e48368_app1.pdf]

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Abbreviations

HO: heme-oxygenase
PICOD: population, intervention, comparator, outcomes,
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses.
SYRCLE: Systematic Review Centre for Laboratory Animal Experimentation

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Protocol

Resistance Training in Patients After Metabolic and Bariatric Surgery: Protocol for a Systematic Review

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Abstract

Background: Resistance training has been consistently shown to have multiple health benefits, especially for patients who have undergone bariatric surgery. Patients who have undergone bariatric surgery are recommended to participate in resistance exercise; however, protocols and guidelines for resistance training remain poorly implemented.

Objective: This is a protocol for a systematic review and possibly a meta-analysis that will synthesize evidence of the effects of resistance exercise on changes in body composition, muscular strength, overall weight loss or maintenance of weight loss, and quality of life in patients after metabolic and bariatric surgery (MBS). The findings of this study may provide practice recommendations for resistance training among patients who have undergone MBS.

Methods: We registered this systematic review on PROSPERO (CRD42023464928) on September 18, 2023. A systematic search of electronic databases (Embase, PubMed, Scopus, Web of Science, and CINAHL) was conducted on studies published from January 1, 1991, to May 15, 2023, to identify English-language human studies on adult patients who have undergone MBS that include a resistance training intervention and describe outcome measurements of body composition or strength. Screening will be performed using PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines, and relevant data elements will be extracted.

Results: Searches and screenings commenced in May 2023. Data extraction and analyses will be completed by the end of December 2023, after which findings will be synthesized and reported by the end of March 2024.

Conclusions: This systematic review will summarize the evidence regarding resistance training in patients after MBS. The findings from this systematic review and possible meta-analysis may provide practice recommendations for resistance training protocols in this patient population and identify characteristics of protocols with the best adherence and outcomes. With these results, we anticipate that we will gain a deeper understanding of the role of resistance training after MBS.

Trial Registration: PROSPERO CRD42023464928; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=464928

International Registered Report Identifier (IRRID): PRR1-10.2196/49513

(JMIR Res Protoc 2023;12:e49513) doi:10.2196/49513

KEYWORDS

bariatric surgery; bariatric; body composition; exercise; meta-analyses; meta-analysis; muscle; muscular; physical activity; physiotherapy; post-metabolic; resistance training; resistance; review methodology; review methods; systematic; weight lifting; weight

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Introduction

Obesity negatively affects nearly every organ system. Since the National Institutes of Health published a statement on gastrointestinal surgery for severe obesity in 1991, metabolic and bariatric surgery (MBS) has been extensively studied over the last 30 years. Surgical procedures as well as perioperative protocols continue to evolve. The benefits and favorable outcomes of MBS have been consistently proven to be durable for up to 20 years after surgery. These outcomes include greater than 60% excess body weight loss (%EBWL); superiority over diet, exercise, and other lifestyle interventions in attaining significant and durable weight loss; improvement in obesity-related comorbid conditions such as glycemic control in type 2 diabetes mellitus [1], obesity-associated cancers [2], and nonalcoholic steatohepatitis [3]; and improvement in quality of life and overall mortality [2,4]. The evidence has been so robust that the American Society for Metabolic and Bariatric Surgery and the International Federation for the Surgery of Obesity and Metabolic Disorders have convened to produce a joint statement on the current available scientific information on MBS in 2022, which has expanded the indications for MBS to include individuals with a BMI ≥35 kg/m^2, regardless of the presence, absence, or severity of comorbidities; individuals with metabolic disease and a BMI of 30-34.9 kg/m^2; individuals in the Asian population with a BMI ≥27.5 kg/m^2; and appropriately selected children and adolescents [4].

To augment the health benefits of MBS, patients who have undergone bariatric surgery are recommended to participate in regular physical activity [5], although the recommended guidelines remain somewhat nonspecific. The American College of Sports Medicine recommends the same amount of physical activity for both individuals with obesity and patients who have undergone bariatric surgery [6]. Patients who have undergone MBS may require different recommendations than those who have not undergone surgery, as patients after MBS consume what is considered a very low-calorie diet and experience large and rapid weight loss. The rapid weight loss is not only fat mass, but it has been shown to also be fat-free mass, including muscle mass, which is associated with a decrease in muscle strength [7,8].

Resistance training is defined as a form of physical activity that is designed to improve muscular fitness by exercising a muscle or a muscle group against any external resistance [6]. This can include modalities such as machines, free weights, bands, and body weight movements. Resistance training should be implemented to mitigate sarcopenia or skeletal muscle loss, which has in turn been shown to improve strength in patients who have undergone MBS [9-11]. Resistance exercise has been proven to have many benefits. It may assist in the prevention and management of type 2 diabetes by decreasing visceral fat and improving insulin sensitivity [12,13]. It improves physical performance, movement control, walking speed, functional independence, cognitive capabilities, and self-esteem [13,14]. It has also been shown to improve balance and reduce the risk of falls in older adults, which may be a major cause of morbidity and death [15]. Therefore, muscle mass and strength are arguably the most crucial elements of body composition, given their contribution to independence and longevity.

Studies have shown that maintenance of (and in some cases gains in) muscle strength occurred in the context of massive lean body mass loss in patients who have undergone MBS [5,9,10]. The implementation of effective resistance training programs specifically designed for patients who have undergone MBS could help this patient population with favorable body recomposition by increasing fat loss while retaining and even building lean mass, bone mass, and muscular strength. Efforts toward creating specific recommendations for resistance training protocols in patients after MBS have been made based on a systematic review by Morales-Marroquin et al [16]. However, this review was small and based on 9 randomized controlled trials. The effects of resistance exercise in patients after MBS have not yet been assessed through meta-analysis.

With the new 2022 statement on the expansion of patients who should be considered for MBS in mind, the population of patients who have undergone MBS will likely continue to increase, necessitating clearer recommendations and practice guidelines for resistance training in this population.

This study aims to be the largest and most comprehensive systematic review of resistance training protocols and their effects on patients who have undergone MBS with regard to body composition, muscular strength, and relevant health outcomes. More importantly, it also aims to review which protocols have superior adherence and compliance after the implementation of resistance training. Lastly, we hope to offer practice recommendations for resistance training protocols that can be applied in this patient population with the ultimate goal of long-term healthy weight loss and weight maintenance.

Methods

Ethical Considerations

As this study does not have the direct involvement of human participants, an institutional ethical review will not be warranted. However, to adhere to a strict methodology, the protocol of this systematic review and meta-analysis has been registered on PROSPERO (CRD42023464928) [17]. PROSPERO is an international database of prospectively registered systematic reviews, which provides a unique permanent registration number to the protocol that prevents duplication, thereby reducing reporting bias.

Review Question

Our review question is as follows: “What are the effects of resistance training on patients after MBS? Additionally, which resistance training intervention demonstrated the most improvement regarding body composition and relevant health outcomes, and which intervention had the best adherence?”

Inclusion and Exclusion Criteria

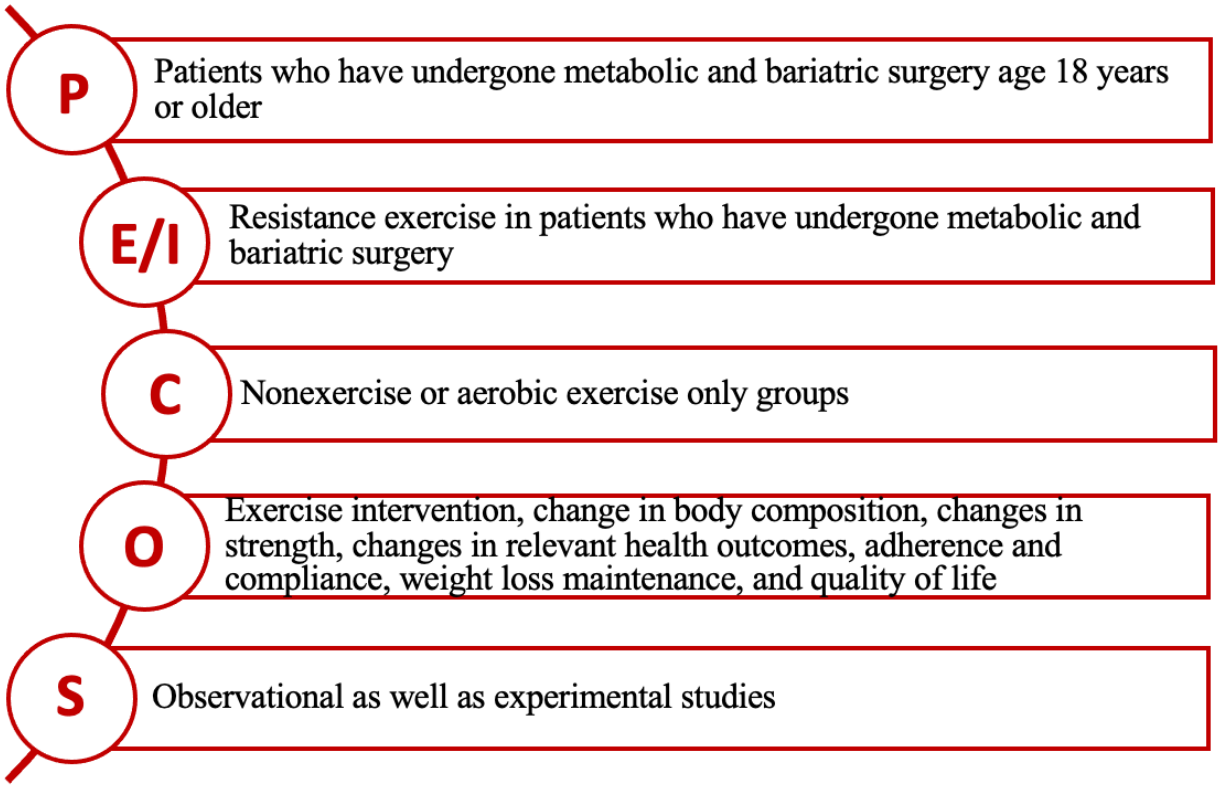
The PECOS (Population, Experiment, Comparator, Outcome, Study Design) framework was used to formulate eligibility criteria for this systematic review and meta-analysis [18]. Case series, case-control studies, retrospective and prospective cohorts, and randomized and nonrandomized clinical trials will

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be eligible for inclusion. Studies published in other languages, case studies, editorials, posters, abstract-only studies, conference proceedings, animal studies, and reviews will be excluded. Studies that do not include resistance training as a component of the exercise intervention or those without quantitative data on outcomes of interest will also be excluded. We will use the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist.

Study eligibility criteria in the form of PECOS criteria are as follows (Figure 1): we will include studies with adult patients aged 18 years or older; individuals who have undergone MBS, including the following procedures—Roux-en-Y gastric bypass, sleeve gastrectomy, biliopancreatic diversion with duodenal switch, single anastomosis duodenal-ileal bypass with sleeve gastrectomy, gastric band, or revisional bariatric surgery; and those who have undergone a resistance exercise intervention; studies that include outcome measurements of body composition or strength; and articles that were published in English and were performed on humans. We will exclude studies that were not performed on adult human participants, are not in English, included patients who have not undergone MBS, did not include body composition or strength components as outcome measures, and had no resistance exercise component in the intervention.

Figure 1. PECOS (Population, Experiment, Comparator, Outcome, Study Design) framework of the study.



Informational Sources and Search Strategy

A systematic search of bibliographical electronic databases was conducted on studies published from January 1, 1991, to May 15, 2023, to identify English-language human studies. A comprehensive search and article retrieval strategy was planned by the study's investigators, guided by a library subject matter expert, to find potentially relevant articles in the following databases: Embase, PubMed, Scopus, Web of Science, and CINAHL. In accordance with the search development and optimization method proposed by Bramer et al [19], the search strategy was developed in Embase and then translated into the syntax of each of the other databases. The search strategy was optimized for each database using a thesaurus, free-text search terms, as well as Medical Subject Headings terms. Informed by the PECOS framework (Figure 1), search strings for each database were developed iteratively and revised as new search terms were discovered. The search strategy will be peer-reviewed by a second research librarian using the Peer Review of Electronic Search Strategies (PRESS) 2015 Evidence-Based Checklist [20].

Multimedia Appendix 1 includes the full search strategy in detail. Keyword criteria included combinations of the following words and phrases: bariatric surgery, gastric bypass, sleeve gastrectomy, gastric band, biliopancreatic diversion with duodenal switch, resistance training, and weight lifting. We will include studies on humans and in English from all geographical locations.

Screening

All records or articles will be imported into an intelligent, systematic review tool called Rayyan (Rayyan Systems Inc) for screening. After the deduplication, all records will be assessed by 2 independent reviewers to check for inclusion and exclusion criteria (Figure 1). Titles, abstracts, and full texts of articles will be screened in a systematic and sequential manner. All reasons for exclusion will be documented at each step of screening. A

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PRISMA flow diagram will be used for describing the study selection process [21].

Data Extraction and Main Data Elements

A total of 2 reviewers will independently extract the relevant data elements from the eligible full texts of the articles and record these variables in a standardized code book. A double extraction method will be used to ensure accuracy and completeness. After data extraction, disparities will be resolved by consensus and discussion with the third reviewer, or a "tiebreaker." Attempts to contact the corresponding authors of the included articles will be made if more information about the individual study's data is needed. The following data elements will be extracted: (1) study title; (2) study author; (3) year; (4) evidence level; (5) quality score; (6) study design; (7) sample size; (8) sex (menopausal status, if in female individuals); (9) age; (10) geographic location (country); (11) operation (Roux-en-Y gastric bypass, sleeve gastrectomy, gastric band, revision bariatric surgery, biliopancreatic diversion with duodenal switch, or single anastomosis duodenal-ileal bypass with sleeve); (12) exercise intervention (type of exercise training [resistance, resistance + aerobic, aerobic only, or none]), postoperative initiation of intervention, frequency (days per week and minutes per session), intensity (sets and repetitions), and the duration of program (weeks or months); (13) exercise setting (supervised, nonsupervised, individual, group, and combined); (14) diet (protein intake); (15) key findings; (16) changes in body composition (%EBWL, total body weight loss [%TBWL], fat mass, fat-free mass, muscle mass, strength, and bone density); (16) how changes in body composition were measured; (17) how strength was measured; (18) changes in relevant health outcomes (heart disease, diabetes mellitus, obstructive sleep apnea, and osteoarthritis or degenerative joint disease); (19) measure of nonexercise physical activity; (20) adherence or compliance; (21) weight loss maintenance; (22) quality of life; (23) self-esteem; (24) habitual physical activity; and (25) length of follow-up.

The primary outcomes of interest in this study are changes in body composition (%EBWL, %TBWL, fat mass, fat-free mass, muscle mass, strength, and bone density). The secondary outcomes of interest include (1) relevant health outcomes (heart disease, diabetes mellitus, obstructive sleep apnea, and osteoarthritis or degenerative joint disease), (2) adherence and compliance, and (3) quality of life and self-esteem.

Quality or Risk of Bias Assessment

For the quality assessments of the included studies, the National Heart, Lung, and Blood Institute quality assessment tool will be used. A total of 2 reviewers will assess the quality of the full texts and will perform scoring independently. The kappa statistics will be calculated to measure the interrater agreement. The National Heart, Lung, and Blood Institute tool has 14 items in the checklist (Figure 2) to evaluate all essential components of original research studies. Quality will be rated as poor (0-4 out of 14 questions), fair (5-10 out of 14 questions), or good (11-14 out of 14 questions) as guided by the tool.

Figure 2. National Heart, Lung, and Blood Institute health quality assessment tool for observational, cohort, and cross-sectional studies.

NIH National Heart, Lung, and Blood Institute

Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies

Criteria	Yes	No	Other (CD, NR, NA)*
1. Was the research question or objective in this paper clearly stated?			
2. Was the study population clearly specified and defined?			
3. Was the participation rate of eligible persons at least 50%?			
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?			
5. Was a sample size justification, power description, or variance and effect estimates provided?			
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?			
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?			
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?			
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?			
10. Was the exposure(s) assessed more than once over time?			
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?			
12. Were the outcome assessors blinded to the exposure status of participants?			
13. Was loss to follow-up after baseline 20% or less?			
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?			

Quality Rating (Good, Fair, or Poor) (see guidance)
Rater #1 initials:
Rater #2 initials:
Additional Comments (If POOR, please state why):

*CD, cannot determine; NA, not applicable; NR, not reported

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Statistical Plan

The first results of all the finally included studies will be described succinctly in the form of a summary table. The pooled estimates with a 95% CI will be generated using the Comprehensive Meta-Analysis software (version 3.0; Biostat). A random-effects model will be used to calculate pooled estimates, as this is a more robust estimate regardless of heterogeneity [22]. Cochran Q and I^2 statistics will be used as indicators of heterogeneity. If enough studies are available in subgroups, then further analyses based on moderator variables, such as sociodemographic variables, country, and type of intervention, will also be conducted. Sensitivity analysis will be conducted to identify studies that may severely affect the pooled prevalence. A funnel plot and Egger linear regression test will be used to assess publication bias [23]. The significant level will be set as 2-sided and $P<.05$. Forest plots will be used to present the data.

Data Analysis and Presentation

We will present the extracted data in tabular form and as a systematic summary as required. A data extraction form will be developed before article analysis. The table will report the extracted variables as listed above in the *Data Extraction and Main Data Elements* section. If the findings are poolable, quantitative analysis will be conducted.

Our meta-analysis plan is as follows: the number of studies with positive, null, or negative findings will be presented. Effects of resistance exercise on changes in body weight, fat mass, lean body mass, muscle strength, quality of life, changes in health outcomes, and adherence will be examined using random effects models. The Comprehensive Meta-Analysis software will be used to analyze the data. The mean (SD) of the absolute change in the intervention and control groups will be reported. Pooled-effect estimates (effect size) will be expressed as the weighted mean difference (MD) between exercise and control groups for the outcomes listed above and as the weighted standardized MD for changes in the outcomes. $P<.05$ will be considered statistically significant. Heterogeneity will be assessed using I^2, with values interpreted as low at 25%, moderate at 50%, and high at 75%. The τ^2 and test of homogeneity will also be reported. Prediction intervals (PIs) will be calculated using the formula 95% PI = MD ± 2 τ^2. To identify sources of heterogeneity, sensitivity analyses with the one-study-removed procedure will be performed. Publication bias will be assessed with a visual inspection of the funnel plot and Egger regression test.

The reason a meta-analysis is a possibility and not definite is because we do not yet know if the group of studies will be sufficiently homogenous in terms of subjects involved, type of intervention (eg, resistance training), outcome, and the type of effect measure reported in each study to provide a meaningful summary. In other words, if studies are too heterogeneous to be comparable, the true effects in meta-analytical evidence may be obscured. It is possible to produce a narrative synthesis (systematic review) of the entire pool of studies and perform quantitative analysis (meta-analysis) only on the randomized controlled trials.

Results

The search for this systematic review commenced in May 2023. Data extraction and analyses will be completed by the end of December 2023, after which findings will be synthesized and reported by the end of March 2024. The plan for dissemination, however, is to publish the review's findings in a peer-reviewed journal and present findings at high-level conferences to share knowledge to help establish specific resistance exercise protocols in patients after MBS. A timeline is provided in Table 1.

Table 1. Timeline table for review.

Tasks	May 2023	Jun 2023	July 2023	Aug 2023	Sept 2023	Oct 2023	Nov 2023	Dec 2023	Jan 2024	Feb 2024	Mar 2024
Initial design and searches	✓										
Screening of duplicates and titles		✓									
Screening of abstracts			✓								
Screening of full-text articles				✓	✓						
Search references of included studies					✓						
Data extraction					✓	✓	✓				
Synthesis and risk of bias assessment								✓	✓	✓	
Abstract and manuscript drafting										✓	✓
Submission to conferences and peer-reviewed journals											✓

Discussion

Overview

Our proposed systematic review will be a comprehensive review that synthesizes the effects of resistance training on the health outcomes of patients after MBS. We anticipate that this study will demonstrate the benefits of resistance training on weight loss, weight maintenance, increased strength, increased bone density, maintenance of lean muscle mass, and improvement in comorbid conditions. In addition, we anticipate there will be

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an improvement in mental health, self-esteem, and quality of life.

The results of our review will be used to design resistance training protocols that may be prescribed to patients after MBS for optimal weight management and strength gains, as this population is at high risk of fat-free mass loss due to their very low-calorie diets and rapid weight loss. This will subsequently improve longevity in this patient population, as age-related sarcopenia, fragility, and increased risk of falls and fractures have high mortality rates [13]. Lastly, the results of this study will generate pertinent considerations for future research to continue improving the knowledge available on the benefits and application of resistance training in patients after MBS. If results from the review are suitable for pooling, this will be the largest review with quantitative analysis specific to resistance training protocols in patients after MBS.

Ultimately, the optimal protocol for resistance training is the one the patient will adhere to. Even with a clearly superior protocol, if the adherence rate is low, it will be of minimal benefit to the patient. According to a review by Bellicha et al [24], most patients do not reach the recommended levels of physical activity after bariatric surgery. A recent systematic review by Bond et al [25] demonstrated that participants who were assigned to the exercise interventions achieved only modest weight loss after 12 months, although none of the exercise interventions aligned with the 250-300 weekly minutes of moderate-intensity physical activity recommended by the American College of Sports Medicine and the 2018 physical activity guidelines for the management of obesity and prevention of weight recurrence. This study also showed that adherence rates were only reported in 2 studies [25]. The ideal protocol will look different for all patients; however, this study may provide further insight on which protocols have the highest adherence rates and what the characteristics of those protocols are. We will distinguish if there are differences in supervised versus nonsupervised sessions as well as individual versus group settings. Studies have shown that a critical component of sustained weight loss includes a sense of "reinvention" and an identity shift to a new lifestyle after successful weight loss [26,27]. Whatever the superior protocol is, it must be sustainable and habit-forming for patients who have undergone MBS.

Limitations

This systematic review will have limitations. There will be a degree of heterogeneity among the studies selected due to the variability of the research methodologies, settings, exercise interventions, diets, and outcome measurements. There is an inherent risk of reviewer bias, which will be mitigated by the use of tools for assessing risk of bias. We will attempt to minimize the bias in this review by following strategies: (1) we will perform a sensitivity analysis to examine if overall findings are sensitive to the exclusion of a study with low quality or a risk of bias; (2) we will ensure transparency on the methods; (3) at every stage of the systematic review, we will solicit inputs from subject matter experts; and (4) we will perform a risk of bias assessment in each study using the standardized tools. There is also a risk of missing pertinent literature on our research topic. A medical librarian at the first author's home institution was consulted and assisted in developing a broad search strategy to maximize the likelihood of identifying relevant articles. Additionally, many aspects related to resistance training are fully subjective, and many outcomes are not reflected in a continuous mathematical figure. There is a chance that any recommendations made after this study may not be statistically significant, but the goal is to perform as comprehensive a review on multiple study methodologies as possible and to report on multiple outcomes of interest that may potentially guide protocols in the future.

Dissemination Plan

The findings from this systematic review will be disseminated through a peer-reviewed journal article and presentations at academic conferences.

Conclusion

This study will provide a comprehensive review of the effects of resistance training in patients who have undergone MBS and will include data on outcomes regarding changes in body composition, strength, relevant health outcomes, adherence, and quality of life. This research will hopefully lead to the development of optimal resistance training practice recommendations for this patient population. This study may also shed light on a resistance training protocol that is best for adherence and long-term weight loss maintenance. With these results, we hope to provide a deeper understanding of the role of resistance training after MBS.

Acknowledgments

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Data Availability

The data sets generated during and/or analyzed during this study are available from the corresponding author on reasonable request.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Detailed search strategy.
[DOCX File , 16 KB - resprot_v12i1e49513_app1.docx]

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Abbreviations

%EBWL: excess body weight loss
%TBWL: total body weight loss
MBS: metabolic and bariatric surgery
MD: mean difference
PECOS: Population, Experiment, Comparator, Outcome, Study Design
PI: prediction interval
PRESS: Peer Review of Electronic Search Strategies
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

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Protocol

Efficacy of mHealth Interventions for Improving Maternal and Neonatal Outcomes Among Pregnant Women With Hypertensive Disorders: Protocol for a Systematic Review

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Abstract

Background: Hypertension is one of the most prevalent medical conditions that arise during pregnancy, resulting in maternal and neonatal complications. Mobile health (mHealth) has emerged as an innovative intervention for delivering maternal and child health care services. The evidence on the effectiveness of mHealth interventions in improving the health outcomes of pregnant women with hypertensive disorders is lacking. Therefore, there is a need for evidence synthesis using systematic review methods to address this evidence gap.

Objective: This review aims to determine the efficacy of mHealth interventions in improving maternal and neonatal outcomes among pregnant women with hypertensive disorders. The review will answer the following research questions: (1) What are the types of mHealth interventions used in pregnant women with hypertensive disorders? (2) Are the various mHealth interventions effective in improving maternal and neonatal health outcomes, health behaviors, and their knowledge of the disease? and (3) Are mHealth interventions effective in supporting health care providers to make health care decisions for pregnant women with hypertensive disorders?

Methods: This review will include randomized controlled trials, nonrandomized controlled trials, and cohort studies focusing on mHealth interventions for pregnant women with hypertensive disorders. Studies reporting health care providers use of mHealth interventions in caring for pregnant women with hypertensive disorders will be included. The search strategy will be tailored to each database using database-specific search terms. The search will be conducted in PubMed-MEDLINE, ProQuest, CINAHL, Scopus, Web of Science, and CENTRAL. Other literature sources, such as trial registries and bibliographies of relevant studies, will be additionally searched. Studies published in English from January 2000 to January 2023 will be included. A total of 2 review authors will independently perform the data extraction and the quality appraisal. For quality appraisal of randomized controlled trials, the Cochrane Risk of Bias 2 tool will be used. The Risk of Bias in Nonrandomized Studies of Interventions (ROBINS-1) tool will be used for nonrandomized controlled trials, and the Critical Appraisal Skills Programme checklist for

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cohort studies will be used. Any disagreements between the 2 reviewers will be resolved through discussion and a third reviewer if required. A meta-analysis will be performed based on the availability of the data.

Results: As per the protocol, the study methodology was followed, and 2 independent reviewers conducted the search in 6 databases and clinical registries. Currently, the review is in the full-text screening stage. The review will publish the results in the first quarter of 2024.

Conclusions: The evidence synthesized from this systematic review will help guide future research, support health care decisions, and inform policy makers on the effectiveness of mHealth interventions in improving the maternal and neonatal outcomes of pregnant women with hypertensive disorders.

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KEYWORDS

digital health; gestational hypertension; hypertension; hypertensive; knowledge synthesis; maternal health outcomes; maternal; mHealth; mobile health application; mobile health; neonatal health outcomes; neonatal; neonates; preeclampsia; pregnancy; pregnant; review methodology; review methods; SMS; systematic; telemedicine; text messaging; sustainable development goal

Introduction

Background

Hypertensive disorders of pregnancy (HDP) complicate 5% to 10% of pregnancies, leading to maternal, fetal, and neonatal morbidity and mortality [1]. According to American College of Obstetricians and Gynecologists guidelines, hypertension in pregnancy is classified as chronic or preexisting hypertension, gestational hypertension, preeclampsia or eclampsia, chronic or preexisting hypertension with superimposed preeclampsia-eclampsia, mild hypertension, and severe hypertension [2]. Globally, the incidence of hypertensive disorders during pregnancy had a 10.92% increment from 16.30 million (95% uncertainty interval [UI] 13.56-19.42 million) to 18.08 million (95% UI 15.26-21.11 million) in the last decade from 1990 to 2019. Regionally, the highest incidence of HDP in 2019 was detected in South Asia (3.84 million, 95% UI 3.16-4.62 million), followed by western sub-Saharan Africa (3.71 million, 95% UI 2.64-3.63 million) and eastern sub-Saharan Africa (3.12 million, 95% UI 2.64-3.63 million), respectively. Conversely, Australasia (30,110, 95% UI 23,080-38,670), Oceania (37,060, 95% UI 29,640-46,290), and Central Europe (78,060, 95% UI 64,040-94,230) had the lowest incidence estimates. There were approximately 27,830 deaths due to hypertensive disorders during pregnancy in 2019. Countries with low sociodemographic and human development indexes have an increasing burden [3]. According to the World Health Organization (WHO), maternal mortality remains “unacceptably high” worldwide every day, with some 830 women dying from a preventable cause of pregnancy or childbirth-related complications [4]. Most of these deaths (94%) that occurred in low-resource settings could have been prevented. High blood pressure during pregnancy is a major complication that accounts for nearly 75% of maternal deaths [5]. Therefore, tackling hypertension during pregnancy is an important global public health concern to date.

Some of the significant risk factors for HDP include a higher BMI, anemic conditions, and poor education. Maternal age, primiparity, multiple pregnancies, HDP in a previous pregnancy, gestational diabetes mellitus, preexisting hypertension, preexisting type 2 diabetes mellitus, preexisting urinary tract infection, a family history of hypertension, type 2 diabetes mellitus, and preeclampsia are possible nonmodifiable risk factors [6]. HDP was also associated with poor maternal, perinatal, and neonatal outcomes, especially in pregnant women with preeclampsia and eclampsia [7]. A higher burden of stillbirth was found in multiparous women with HDP [8]. A systematic review and meta-analysis reported that pregnant women with chronic hypertension showed high pooled incidences of superimposed preeclampsia (25.9%), cesarean section (41.4%), preterm delivery (28.1%), low birth weight (16.9%), neonatal unit admission (20.5%), and perinatal death (4%) [9]. Therefore, the identification and management of HDP should take priority in pregnant women to avoid preventable deaths and morbidities among mothers and their babies.

There is a moderate quality of evidence that recommends antihypertensive therapy for the management of HDP [10]. Single interventions are not likely to significantly reduce pregnancy-related mortality and morbidity. Instead, improving the overall quality of antenatal care across the health care system is required [11].

An innovative health intervention increasingly being used and tested in maternal and child health is mobile health (mHealth). mHealth refers to “the use of wireless and mobile information and communication technologies to support health and health care” [12]. Globally, mobile phone use is continuously expanding [13]. The International Telecommunication Union reported that about 4.9 billion people were using the internet in 2021. This has increased by 17% since 2019 [14]. The portability, instantaneous access, and direct communication capabilities of mobile technology enable prompt dissemination of health information, which improves medical and public health practices cost-effectively [15]. These qualities characterize mHealth, which enables better health care access and facilitates improved delivery of health care services. In the face of this technological reality, mHealth plays an innovative role in the delivery of health care. However, though the global use of mHealth is increasing, the effect it has on the improvement of outcomes is still unknown [16]. Although current evidence suggests that telemonitoring provides benefits for managing

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patients at high risk for HDP, more research is needed to prove its safety and effectiveness [17].

Aim

This review aims to collate relevant data and provide evidence related to the effectiveness of mHealth interventions in improving maternal and neonatal outcomes among pregnant women with hypertensive disorders. This review will also identify the evidence gap in mHealth for antenatal care, which will guide further research, support health care professionals in their practice decisions, and inform policy makers as well as other stakeholders to implement changes in the health care system.

Methods

Overview

The systematic review protocol was designed based on the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) 2015 checklist [18]. The review has been registered in PROSPERO (CRD42022321686). The review will be conducted in accordance with the *Cochrane Handbook for Systematic Review of Interventions* [19].

Study Eligibility Criteria

The inclusion and exclusion criteria for the review are given in Textbox 1.

Textbox 1. The inclusion and exclusion criteria.

Inclusion criteria

- Randomized controlled trials, nonrandomized controlled trials, and cohort studies
- Studies with the population of pregnant women with hypertensive disorders (chronic hypertension; gestational hypertension; preeclampsia-eclampsia; chronic hypertension with superimposed preeclampsia; and the "hemolysis, elevated liver enzymes, low platelet count" syndrome) and health care providers using mobile health (mHealth) in providing care for pregnant women with hypertensive disorders
- mHealth interventions that use mobile technology, such as mobile phones, personal digital assistants, and other wireless devices such as wearables and tracking sensors, to support the health of pregnant women with hypertensive disorders and health worker decisions
- Studies with a control group receiving standard care, no intervention, other forms of digital interventions, antenatal counseling, dietary plans, yoga, and any form of breathing exercises
- Maternal mortality, maternal morbidities, perinatal death, and neonatal morbidities; knowledge of the disease and its management; and health behaviors such as early identification of warning signs
- English language
- Conducted between January 2000 and January 2023
- All settings across the globe

Exclusion criteria

- Noninterventional observational studies
- Other high-risk pregnancies, such as gestational diabetes; pregnant women with autoimmune diseases, fibroids, and thyroid disorders; and postnatal women with hypertensive disorders
- Nonmobile digital devices such as desktop computers, which are used for health management information systems and electronic health records
- Studies without comparison groups
- Outcomes other than health outcomes, such as the usability or feasibility of mHealth interventions
- Languages other than English

Search Methods for Identification of Studies

A search will be conducted in the following databases: PubMed-MEDLINE, ProQuest, CINAHL, Scopus, Web of Science, and CENTRAL by 2 independent reviewers (TP and AD). Medical Subject Headings (MeSH) terms, subject headings, and keywords will be searched electronically in all fields. Search strings will be developed using database-specific filters and tailored to each database using the search given in Multimedia Appendix 1.

Searching Other Sources

Additionally, ClinicalTrials.gov, the Clinical Trial Registry of India, and the WHO International Clinical Trials Registry platform will be searched for unpublished and ongoing trial reports. The reference list of retrieved articles will also be searched.

Data Management

Selection of Studies

The first stage of the screening process will involve 2 authors who will independently screen the titles and abstracts of the included studies (TP and AD). They will independently scrutinize the studies for inclusion and exclusion criteria with a prespecified form. For studies with insufficient data in the abstract, the full text will be retrieved and assessed for eligibility. If there is any disagreement between the 2 authors, they will discuss it, and if needed, the third author (ML) will be asked for an opinion. If any inexplicit data are found or any

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data are missing, then the authors of the corresponding study will be contacted.

Data Extraction

Data will be extracted independently by 2 authors (TP and AD) using a standard data extraction form developed by the review authors (BN and JS). The variables recorded will be the authors' name, publication year, study period, journal of publication, the country where the study was performed, participant age, sample size, variables adjusted for in the analysis, and findings. The data extracted from each included study will be based on the following: type of mHealth interventions used, outcomes assessed, funding source, type of publication, source of the study if not published, and other study details necessary for risk of bias assessment. Disagreements will be resolved by discussion with the third author (JN).

Quality Appraisal

A total of 2 review authors (TP and AD) will independently assess the risk of bias in studies. The authors will independently assess randomization sequence generation, treatment allocation concealment, blinding, completeness of outcome data, selective outcome reporting, and other sources of bias for randomized controlled trials using the Cochrane Risk of Bias 2 tool [19]. The Risk of Bias in Nonrandomized Studies of Interventions (ROBINS-1) tool will be used to appraise the quality of nonrandomized controlled trials [20]. The Critical Appraisal Skills Programme checklist for cohort studies will be used [21]. We will resolve disagreements, if any, by discussing them with the third author to reach a consensus.

Data Synthesis and Analysis

Statistical analysis will be performed by SN and RN, referencing the *Cochrane Handbook for the Systematic Review of Intervention*. If there are adequate data, a meta-analysis will be performed using a random-effects model. Categorical data will be summarized using the odds ratio, relative risk, or hazard ratio. Continuous data will be summarized using the standardized mean difference. A forest plot will be generated. Sensitivity analysis will be performed if applicable.

Assessment of Heterogeneity and Bias Reporting

A funnel plot and Egger test will be performed to assess publication bias. When data from included studies can be pooled, statistical heterogeneity will be assessed by visual inspection of forest plots using the chi-square test and the I^2 statistic.

Subgroup Analyses

Trial characteristics (participants, design, interventions, outcomes, and risk of bias) will be examined, and based on them, subgroup analysis will be performed.

However, if we are not able to perform a meta-analysis due to insufficient studies or heterogeneity, the findings will be reported descriptively.

Ethical Considerations

The systematic review will be done using previously available data and will not include any personal information about individual participants. As a result, permission from a research ethics committee is not required.

Results

As per the protocol, the study was conducted following the methodology according to the *Cochrane Handbook for Systematic Review of Interventions*. A total of 2 independent reviewers conducted the search in the following 6 databases: PubMed-MEDLINE, ProQuest, CINAHL, Scopus, Web of Science, and CENTRAL. Additional sources, such as clinical trial registries (ClinicalTrials.gov, the Clinical Trial Registry of India, and the WHO International Clinical Trials Registry), were searched using the search strategy developed by the team. Currently, the review is in the full-text screening stage, and data collection is ongoing. The findings of the review will be published in the first quarter of 2024.

Discussion

Overview

This review is designed to evaluate the effectiveness of mHealth interventions on maternal and neonatal health outcomes among pregnant mothers with hypertensive disorders.

mHealth interventions are implemented and researched extensively. Evidence from systematic reviews shows that mHealth interventions are effective in increasing the use of antenatal and postnatal care, including attendance at antenatal and postnatal care check-ups, facility-based deliveries, and skilled attendance at birth and vaccination rates [22]. Conversely, another systematic review and meta-analysis concluded that most studies conducted in low- and middle-income countries are of poor methodological quality, and few have evaluated impacts on patient outcomes [23]. Therefore, there is a need for a rigorous systematic review that addresses health end points as primary or secondary outcomes and includes recent studies and rigorous study designs that are considered the gold standard components to determine an intervention's effect, that is, a randomized controlled trial. Apart from health outcomes, evidence also indicates that health workers can be empowered to accept and use mHealth in circumstances where it is appropriate for their requirements, workload, training, and abilities [24]. In turn, mHealth may provide health care professionals with skills and confidence when technology is viewed as beneficial and simple to use in settings that encourage acknowledgment from clients, peers, or superiors.

The review will enable the critical appraisal and synthesis of evidence on the use of mHealth interventions among pregnant women with hypertensive disorders. As there is a rapid increase in technological development and the relative newness of mobile apps as a tool for health care providers in the management of hypertensive disorders during pregnancy, more primary research has been published [25]. Therefore, the evidence pointing toward the use of these services must be put together, which will help in formulating local policies that can be generalized and promulgated for use in all health care settings and communities. Additionally, the extent to which clear conclusions can be drawn

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about the usefulness of mHealth interventions in terms of health outcomes may be limited. However, this review will provide clarity on the existing evidence and its implications for health care providers.

Limitations

The possible limitations might be the inclusion of nonrandomized controlled trials and cohort studies that may not provide a strong evidence base. However, we planned to include those in this review as we do not intend to miss any available evidence. The strength of the evidence depends on the quality of the involved studies. The publication bias of the included studies might affect the results, but they will be reported. Meta-analysis and meta-regression may not be possible due to different methodological approaches in varying studies; however, subgroup analysis will be done.

Conclusion

The review results will highlight the available evidence on mHealth apps and their effectiveness in terms of maternal and neonatal health. The review results provide directions for further practice and further research in this area. It will inform policy makers and those in the hospital and community settings to implement mHealth interventions at the local level as well as scale up to a wider population.

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Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed in this study protocol.

Authors' Contributions

JAN, MSL, BSN, RN, and SN participated in conceptualization and designing of the study protocol. AD and TP wrote the manuscript. All authors reviewed and approved the final version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search strategy (PICOS).
[PNG File , 111 KB - resprot_v12i1e51792_app1.png]

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Abbreviations

HDP: hypertensive disorders of pregnancy
MeSH: Medical Subject Headings
mHealth: mobile health
PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols
ROBINS-1: Risk of Bias in Nonrandomized Studies of Interventions
UI: uncertainty interval
WHO: World Health Organization

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Protocol

Treatments for Trauma-Induced Coagulopathy: Protocol for a Systematic Review and Meta-Analysis

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Abstract

Background: Trauma-induced coagulopathy (TIC) is a common and potentially life-threatening coagulopathy as a result of traumatic injury, characterized by abnormal blood clotting and bleeding. Although several treatments have been proposed for TIC, their effectiveness and safety remain unclear. Further, numerous systematic reviews and meta-analyses on trauma have been conducted; however, to our knowledge, there is no systematic review and meta-analysis that specifically focuses on TIC management. Therefore, a comprehensive synthesis of the available evidence on interventions for TIC is needed.

Objective: This systematic review and meta-analysis aim to evaluate the effectiveness and safety of interventions for the management of TIC.

Methods: We will conduct a systematic review and meta-analysis of randomized and nonrandomized controlled trials as well as observational studies regarding severe trauma in patients with TIC. The interventions will include administration of coagulation factor concentrates, tranexamic acid, and blood component products. The control group will be managed with an ordinal transfusion or administered placebo. The primary outcome will be in-hospital mortality. We will search the electronic databases of MEDLINE (PubMed), Web of Science, and the Cochrane Central Register of Controlled Trials. Two reviewers will independently screen the titles and abstracts, retrieve the full text of the selected articles, and extract essential data. We will apply uniform criteria for evaluating the risk of bias associated with individual randomized controlled trials and nonrandomized trials based on the Cochrane risk-of-bias tool. Risk ratio values will be expressed as point estimates with 95% CIs. Continuous variables will be expressed as the mean difference along with their 95% CIs and *P* values. We will assess the strength of evidence using the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach. This review will be the first systematic review and meta-analysis providing information on the effectiveness and safety of interventions for the management of TIC, including the administration of coagulation factor concentrates, tranexamic acid, and blood component products. Ethics approval and patient consent were not required for this study protocol, as we conducted a systematic review and meta-analysis of publicly available data, without any direct involvement of human participants.

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Results: We will summarize the selection of the eligible studies using a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart. The results will be presented in a table summarizing the evidence. The results of the meta-analysis will be depicted using figures and forest plots.

Conclusions: This systematic review will provide updated information on the efficacy and safety of using coagulation factor concentrates, tranexamic acid, and blood component products for patients with TIC. To our knowledge, there is no systematic review and meta-analysis that specifically focuses on treatments for TIC.

Trial Registration: UMIN registry UMIN000050170; https://tinyurl.com/yr8pcrj6

International Registered Report Identifier (IRRID): DERR1-10.2196/49582

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KEYWORDS

trauma-induced coagulopathy; coagulation factor; transfusion; blood; clot; clotting; coagulation; coagulopathy; systematic; review methods; review methodology; meta-analysis; meta-analyses; bleeding; trauma; hemorrhage; traumatic; injury

Introduction

Trauma remains a major cause of death globally [1]. Death during the early phase of trauma is primarily attributable to uncontrolled bleeding, which is exacerbated by trauma-induced coagulopathy (TIC) [2-4]. Pathophysiology and clinical aspects of TIC comprise blood loss, consumption of coagulation factors, dilution, and fibrinolytic activation [2-5]. TIC correlates with an increased demand for massive transfusion as well as higher mortality. Thus, effective treatment of TIC is crucial for decreasing deaths following trauma [3-5]. Although the conceptual definition of TIC was proposed by the International Society on Thrombosis and Haemostasis, the clinical definition of TIC has not reached a consensus [3].

Randomized controlled trials (RCTs) have investigated the effectiveness of transfusion, administration of coagulation factor concentrates, and tranexamic acid for hemostasis following severe trauma [5-12]. Several systematic reviews and meta-analyses have also been conducted based on these studies [13-15]. However, the inclusion criteria for these reviews were mostly for trauma with severe bleeding or traumatic brain injury with severe consciousness disturbance, and they were not focused on patients with TIC. We speculate that the effectiveness of interventions for coagulation abnormalities is greatest in patients with TIC.

In addition, the administration of tranexamic acid for severe trauma has been investigated by large RCTs, and it is now globally used for early-stage trauma management with a proven lifesaving benefit [6,8,16]. Furthermore, a meta-analysis has indicated the beneficial effect of tranexamic acid on trauma [15]. Tranexamic acid is a potent antifibrinolytic agent, and its clinical effectiveness demonstrated in previous RCTs is presumably based on this antifibrinolytic effect. Therefore, tranexamic acid administration is likely to be more effective for severe trauma with TIC. However, the inclusion criteria of these RCTs and the meta-analysis were not focused on patients with TIC [6,8,15].

To our knowledge, there is no systematic review and meta-analysis specifically focusing on treatments for TIC. From late 2010 to 2020, RCTs investigating the efficacy of coagulation factor concentrates for TIC were published [5,11,12,17]. Due to the small number of RCTs and the biased setting of open-label interventions in these RCTs, observational studies continue to provide novel and helpful insights [18-20]. Therefore, a comprehensive synthesis of the available evidence on interventions for the management of TIC is needed. This is the first systematic review and meta-analysis aimed at evaluating the effectiveness and safety of interventions for TIC, including the administration of coagulation factor concentrates, tranexamic acid, and blood component products.

Methods

Protocol Registration

The study protocol was registered in the University Hospital Medical Information Network (UMIN000057146). This systematic review and meta-analysis will be reported according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols) guidelines.[21]

Database Search

To retrieve relevant articles, we will perform a literature search of the following electronic bibliographic databases: MEDLINE (PubMed), Web of Science, and the Cochrane Central Register of Controlled Trials. We will examine the references cited in relevant articles to ascertain whether additional studies can be found. The details of the search strategy are available in Multimedia Appendices 1-3.

Study Types

We will include controlled trials (including RCTs and other controlled trials) and observational studies published until December 17, 2022. Studies will be excluded if they do not clearly report the population, treatment, or outcomes of interest. Animal studies will also be excluded. Grey literature, such as conference proceedings and abstracts, will be included. If 2 or more studies are published using the same or overlapping cohorts, the one with the most recent or larger cohort will be included. Only articles published in English will be included.

Study Population

We will include patients with severe trauma and TIC admitted to the hospital. However, there are no international diagnostic criteria for TIC. Therefore, we will include patients with some abnormalities in coagulation or fibrinolysis upon admission to

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the hospital as patients with TIC and collect the definition of abnormality in coagulation or fibrinolysis in each study.

Intervention and Control

Intervention types will include the supplementation of coagulation factor concentrations, such as prothrombin complex concentrate (PCC), fibrinogen concentrate, tranexamic acid, and blood component products during the acute phase of trauma. The control group will be managed with an ordinal transfusion or administered placebo. We will not restrict our review to the product type and amount or the timing of the administration of coagulation factors.

Outcomes

The primary outcomes will be all-cause mortality and the quantity of transfusion. The secondary outcomes will be thrombotic events (ie, deep venous thromboses, pulmonary embolism, myocardial infarctions, and strokes), length of intensive care unit stay, and hospital stay.

Study Selection

Citations will be stored, and duplicates will be removed using EndNote Software (Thomson Reuters). Rayyan software will also be used for the systematic review process [22]. The titles and abstracts of studies retrieved using the search strategy will be screened independently by 2 reviewers (YI and YT) to identify studies that potentially meet the inclusion criteria. The full texts of these potentially eligible studies will be retrieved and assessed independently by 2 reviewers (YI and YT). Any disagreement about the eligibility of studies will be resolved through consultation with a third reviewer (MH).

Data Extraction

Using a standardized prepiloted form, data from the included studies will be extracted to assess the quality of the studies and methods of data synthesis. The extracted information will include data on the following variables: study setting, study population, baseline characteristics of the participants, details of the interventions and control conditions, study methodologies, outcomes, and assessments of the risks of bias. Two independent reviewers (YI and YT) will independently extract the data, and discrepancies will be resolved through discussion with a third author (MH). Missing data will be obtained through requests from the authors.

Assessment of Risk of Bias in Individual Studies

Two independent reviewers (YI and YT) will assess risk of bias in individual studies as well as the methodological quality of the articles, and disagreements will be resolved by discussion with a third reviewer (MH). We will apply uniform criteria for evaluating the risk of bias associated with individual RCTs based on the tool for assessing risk of bias in randomized trials [23]. Each study will be assessed for (1) random sequence generation, (2) allocation concealment, (3) blinding of participants and personnel, (4) blinding of related outcome assessment, (5) incomplete outcome data, (6) selective reporting, and (7) other bias. We will also use the "Risk Of Bias In Non-randomised Studies – of Interventions" tool for individual nonrandomized studies [24].

Data Summary

We will perform a meta-analysis when data are available in 1 or more trials according to the Cochrane Handbook for Systematic Reviews of Interventions. For binary variables, values for the risk ratio or odds ratio will be expressed as a point estimate with 95% CIs. Continuous variables, such as the length of intensive care unit stay, will be expressed as their mean difference with 95% CIs and *P* values. If quantitative synthesis is not appropriate for a particular outcome, we will provide a qualitative summary.

Data Synthesis

We will provide estimates of the findings from the included studies according to a random effects model. A random effects model incorporates statistical heterogeneity and provides a more conservative estimate of the pooled effect size compared to a fixed effects model. We will not perform any multiple imputations for missing data, data synthesis, or analysis of randomized trials. All statistical analyses, including risk of bias within studies or across studies, will be performed using Review Manager (RevMan; version 5.4; Cochrane Collaboration 2019) [25]. The level of statistical significance will be set at $P<.05$.

Assessment of Heterogeneity

Statistical heterogeneity will be assessed using the Mantel-Haenszel χ^2 test and I^2 ($I^2>50\%$=significant heterogeneity) [26]. The presence of clinical heterogeneity will be considered in the decision to conduct a quantitative synthesis of data or perform sensitivity analyses.

Sensitivity Analysis

We will examine the robustness of this meta-analysis by conducting a sensitivity analysis according to the different components of the Cochrane risk of bias tool. We will also perform sensitivity analyses by excluding studies in which the overall risk of bias is high or unclear.

Subgroup Analysis

Subgroup analyses will be performed according to the type of coagulation factors, type of trauma (traumatic brain injury will be separately investigated), timing of administration, or type of coagulopathy by each clinical criterion.

Assessment of Reporting Bias

To assess publication bias, we will create funnel plots for mortality.

Rating the Strength of Evidence Using the GRADE Approach

Two authors (YI and YT) will assess the strength of evidence independently using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach [27]. The quality of evidence will be assessed for each outcome and categorized as high, moderate, low, or very low according to the GRADE approach.

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Patient and Public Involvement and Study Dissemination

Patients and the public were not involved in the design of this protocol. Our findings will be presented at relevant scientific conferences and disseminated through publication in peer-reviewed journals.

Ethical Considerations

Approval from an ethics committee was not required because in this study, we conducted a systematic review and meta-analysis of publicly available data, without any direct involvement of human participants.

Results

We will summarize the selection of eligible studies using a PRISMA flowchart. The results will be presented in a table summarizing the evidence. The results of the meta-analysis will be depicted using figures and forest plots.

Discussion

The use of a coagulation factor concentrate enables a rapid and strong supply of coagulation factors and is recommended in patients with severe trauma in recent international guidelines [28]. Recently, RCTs on the use of fibrinogen concentrates in patients experiencing trauma have increased [5,10-12,29,30]. As per a meta-analysis conducted in 2020 [14], fibrinogen concentrates do not decrease the mortality rate. However, the inclusion criteria in this study did not focus on patients with TIC [14]. A meta-analysis of PCC administration focused on patients with Prothrombin Time-International Normalized Ratio >1.5 was reported in 2021 [13]. In this study, PCC was shown to reduce the mortality rate compared with fresh frozen plasma alone. Although platelets play a fundamental role in hemostasis and have a close counteraction with coagulation factors [2], the effectiveness of early supplementation of platelets for trauma is poorly investigated [31]. Tranexamic acid is now proven to be beneficial for life-threatening conditions [6,8,16] and is recommended by European guidelines [32] with high-quality trials. However, the studies mentioned above were not focused on patients with TIC. TIC is present in up to 25%-35% of patients experiencing trauma upon admission to the emergency department and is associated with a poor prognosis [4,33-35]. Therefore, we speculate that the intervention's effectiveness in addressing coagulation and fibrinolysis abnormalities is greatest in patients with TIC, and a systematic review and meta-analysis focused on the management of patients with TIC is needed.

This study will be the first endeavour to undertake a systematic review and meta-analysis on the effectiveness of early interventions for the management of TIC, involving the provision of coagulation factors and the administration of tranexamic acid. Patients with TIC, who represent a substantial subpopulation with severe and high mortality rates, require special attention [2]. Determining the effectiveness of treatments for this cohort of patients would yield significant advantages. In addition, further studies on interventions that influence the coagulation-fibrinolytic system, such as the use of coagulation factor concentrates and tranexamic acid, may offer more precise insights into their effectiveness in patients with TIC, as opposed to those without TIC. Additionally, this study may facilitate further research focused on assessing the diagnostic measures of TIC and thresholds of abnormal lab data for defining TIC by collating existing studies. As such, our findings will contribute to the current knowledge on the treatment of TIC.

Acknowledgments

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We would like to thank Editage for English language editing.

Authors' Contributions

MH, Y Sakamoto, SK, YE, Y Seki, and KO were guarantors and contributed to the conception of the study. The manuscript protocol was drafted by YI and revised by MH. The search strategy was developed by all authors and will be performed by YI and MH. YI and YT will independently extract data from the included studies, assess risk of bias, and complete the data synthesis. MH will arbitrate in cases of disagreement and ensure the absence of errors. All authors have approved the publication of this protocol. YI was responsible for the funding acquisition.
The Scientific and Standardization Committee on Disseminated Intravascular Coagulation (DIC) of the Japanese Society on Thrombosis and Hemostasis sponsored and funded this study.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Cochrane Central Register search strategy.
[DOCX File , 16 KB - resprot_v12i1e49582_app1.docx]

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Multimedia Appendix 2
MEDLINE (via PubMed) search strategy.
[DOCX File , 16 KB - resprot_v12i1e49582_app2.docx]

Multimedia Appendix 3
Web of Science search strategy.
[DOCX File , 16 KB - resprot_v12i1e49582_app3.docx]

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Abbreviations

GRADE: Grading of Recommendations Assessment, Development and Evaluation
PCC: prothrombin complex concentrate
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols
RCT: randomized controlled trial
TIC: trauma-induced coagulopathy

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Protocol

Economic Burden of Mosquito-Borne Diseases in Low- and Middle-Income Countries: Protocol for a Systematic Review

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Abstract

Background: Globally, among all the vector-borne diseases, mosquito-borne diseases are responsible for a substantial number of cases and deaths and amount to an economic cost of US $12 billion per year. However, there is a dearth of systematic research conducted on the economic burden of mosquito-borne diseases. To address the lack of comprehensive information on this topic, a systematic review will be conducted to synthesize evidence for informing targeted policies and strategies addressing this growing burden and for better financial protection of households.

Objective: The systematic review aims to review the economic burden of mosquito-borne diseases in low- and middle-income countries (LMICs). The review estimates the total cost, which is the compilation of both the direct costs and indirect costs. Additionally, it reports cost estimates per disease, country, and patient. The review outcome will also discuss the impact of the economic burden in terms of out-of-pocket expenditure, catastrophic health expenditure, impoverishment, and gross domestic product impact due to mosquito-borne diseases in LMICs.

Methods: Systematic searches will be conducted in PubMed (MEDLINE), Ovid Embase, Scopus, the cumulative index of nursing and allied health literacy, and Cochrane CENTRAL. Additionally, websites of the World Bank, World Health Organization, and Asian Development Bank as well as grey literature (eg, Malaria No More and the Ministry of Health websites) will be searched to gather comprehensive information on the topic and identify studies published in the English language. The titles and abstracts will be independently screened by 2 reviewers, followed by a full-text review against the inclusion criteria. Disagreements will be resolved through discussion with a third author. The methodological reporting quality of the studies will be evaluated using the Larg and Moss checklist, Cochrane risk-of-bias tool for randomized trials, and the Consensus on Health Economic Criteria. Data will be extracted using a standardized data extraction form.

Results: The protocol was registered in PROSPERO (CRD42023427111) prior to the initiation of the search strategy. The review is currently ongoing and will synthesize information from the identified studies through a process involving structured screening, data extraction, and critical appraisal in the form of tables and a narrative summary of studies reporting the economic burden incurred due to mosquito-borne diseases in LMICs.

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Conclusions: This review seeks to report the economic burden of mosquito-borne diseases. It will act as evidence for policymakers to prioritize their decisions regarding containing the prevalence of mosquito-borne diseases and the means to lowering the incidence of diseases spread by mosquitoes.

Trial Registration: PROSPERO CRD42023427111; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=427111

International Registered Report Identifier (IRRID): PRR1-10.2196/50985

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KEYWORDS

cost of illness; economic burden; out-of-pocket expenditure; OOPE; mosquito-borne diseases; vector-borne diseases

Introduction

Background

Vector-borne diseases are diseases transmitted to humans by vectors (eg, aquatic snails, mosquitos, fleas, blackflies, ticks, lice, sandflies, triatome bugs, and tsetse flies) infected either with viruses, parasites, or bacteria. These account for greater than 17% of all infectious diseases and play a huge role in the economic and disease burden. Among these vectors, mosquito-borne diseases are responsible for almost 700 million cases and more than a million deaths each year. The most important mosquito vectors are *Aedes*, *Anopheles*, and *Culex*, which are responsible for the diseases chikungunya, lymphatic filariasis, dengue, Rift Valley fever, Zika, malaria, yellow fever, West Nile fever, and Japanese encephalitis [1,2].

Every year, more than 1 million people die after contracting a mosquito-borne disease. The US Centers for Disease Control and Prevention reported that more than 1 million people die because of malaria in a year. The pace of infection dissemination has substantially increased during the past few years [3]. It has been estimated that 3.4 billion people are in danger of contracting malaria, which is spreading in 97 countries [4]. The frequency of dengue has increased 30-fold over the past 50 years, and the disease has begun to move from urban to rural areas [5]. As stated by the World Health Organization, there are 50 to 100 million cases of dengue, an arboviral disease, per year [6]. *Aedes albopictus* and *Aedes aegypti* are the primary vectors of dengue [7]. Yellow fever has a high fatality rate, and many patients need supportive care to manage the fever, respiratory failure, and dehydration [8]. Around 10,000 people every year die from Japanese encephalitis, predominantly in Asia [9].

The estimated total economic burden of lymphatic filariasis was US $5.8 billion annually [10]. For the period 2011-2020, the total productivity loss was US $10.5 billion, and for 2021-2030, the anticipated loss is US $13.8 billion [11]. Dengue fever was reported to have a US $8.9 billion yearly global cost in 2013 [12]. The estimated socioeconomic impacts of Rift Valley fever ranged from US $5 million to US $470 million [13]. It has been estimated that the Zika virus costs the global economy a total of US $8.9 billion [14]. In 2016, the total cost of malaria worldwide, including both government and out-of-pocket expenditure (OOPE), was US $4.3 billion [15]. Mosquito-borne diseases contribute to acute and long-term complications, thus affecting the gross domestic product (GDP) of a country.

Nations suffer the loss of billions of dollars annually by investing in treatments for mosquito-borne diseases. For example, households lose an estimated 25% of their income to OOPE for treating malaria, treatment-related travel, and other diagnosis-related expenses, which amount to an average cost of US $3 per case [16]. Most low- and middle-income countries (LMICs) have many cities with high-density populations in urban areas that are associated with poor hygiene and poor water quality, which are characteristics that lead to increased mosquito breeding and the rapid spread of mosquito-borne diseases. Most LMICs have limited universal health coverage (UHC) due to low public health investments, resulting in a substantial proportion of the population being exposed to OOPE, with some of these populations experiencing catastrophic health expenditure and impoverishment.

A preliminary systematic search of the PROSPERO (International Prospective Register of Systematic Reviews), PubMed (MEDLINE), Cochrane Database of Systematic Reviews, Joanna Briggs Institute (JBI) Evidence Synthesis, and Epistemonikos databases identified no published or ongoing systematic reviews on the topic. Systematic reviews on the economic burden of individual diseases (eg, dengue and malaria) have been conducted previously [15,17-19]. However, these reviews have either focused on a specific country or a specific disease and did not consider other mosquito-borne diseases. To fill this information gap, a systematic review of the literature on the economic burden on households and countries due to mosquito-borne diseases in LMICs will be performed. The primary objective is to synthesize available evidence on costs (direct medical, direct nonmedical, and indirect), resources used, and health care expenditure due to mosquito-borne diseases in LMICs. Financial protection is at the core of UHC, as outlined in Sustainable Development Goal 3.8.2 related to indicators of financial hardship, such as catastrophic health expenditure and poverty impact [20]. The review will help to evaluate currently available evidence on OOPE, catastrophic health expenditure, impoverishment, and GDP impact due to mosquito-borne diseases in LMICs. Hence, our review findings will be crucial toward framing targeted policies focusing on increased prevention and health protection strategies to address the growing burden of mosquito-borne diseases in LMICs.

Operational Definitions

The following are operational definitions pertinent to the systematic review:

- Chikungunya: “Chikungunya fever is an acute febrile illness caused by an arthropod-borne alphavirus, Chikungunya

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virus (CHIKV). The virus is primarily transmitted to humans via the bite of an infected *Aedes* species mosquito" [21].
- Dengue: "Dengue (break-bone fever) is a viral infection that spreads from mosquitoes to people. It is more common in tropical and subtropical climates" [6].
- Lymphatic filariasis: "Lymphatic filariasis, often known as elephantiasis, is a human infection that is caused by the transmission of parasites called filarias through mosquitoes, including those of the genus *Culex*, which is widespread in urban and semi-urban areas" [22].
- Rift Valley fever: "Rift Valley fever is a neglected, mosquito-borne and direct contact viral zoonosis associated with significant morbidity, mortality and an expanding geographical scope" [23].
- Yellow Fever: "Yellow fever (YF) is a viral acute hemorrhagic illness caused by infected mosquitoes of the flavivirus family" [24].
- Zika: "Zika is spread mostly by the bite of an infected *Aedes* species mosquito (*Ae. aegypti* and *Ae. albopictus*). These mosquitoes bite during the day and night" [25].
- Malaria: "Malaria is a parasitic infection transmitted by the *Anopheles* mosquito that leads to acute life-threatening disease and poses a significant global health threat" [26].
- Japanese encephalitis: "Japanese encephalitis (JE) is a vector-borne disease caused by the Japanese encephalitis virus (JEV), which is a single-stranded ribonucleic acid (RNA) virus belonging to the genus *Flavivirus* (Flaviviridae family) and is closely related to the West Nile encephalitis virus" [27].
- West Nile fever: "West Nile fever is an acute febrile illness associated with malaise, rash, headache, myalgia, and lymphadenopathy. Infection involves a bird-mosquito-human cycle" [28].
- Economic burden: "Economic burden captures the economic impact of a disease or illness of interest on both the health sector and non-health sectors at both microeconomic and macroeconomic levels. Economic burden is defined by cost-of-illness studies that estimate direct and indirect costs due to disease" [29].
- Direct costs: "Direct costs are defined as costs related to the use of resources due to either the disease or its treatment. Direct costs include costs to the health care system (direct medical costs) and costs to social services and to patients themselves or to their relatives (direct non-medical costs)" [30].
- Indirect costs: "Indirect costs or loss of production are defined as costs that occur to society related to loss of production, due either to the disease or its treatment" [30].
- Catastrophic health expenditure: "Population with household expenditures on health greater than 10% of total household expenditure or income" [31].
- Financial hardship: "Households incur 'hardship financing' when they are exposed to a less stable or worsened financial state brought about by additional costs/losses due to borrowing or selling assets" [32]. "Out-of-pocket (OOP) health care payments financed through borrowings or sale of household assets are referred to as distressed health care financing" [33].
- Impoverishment: "Impoverishment occurs when a 'non-poor' household becomes 'poor' after paying for health services" [34].

Review Question

The systematic review seeks to determine the economic burden associated with mosquito-borne diseases in LMICs by answering the following questions: (1) What are the direct and indirect costs associated in treating mosquito-borne diseases in LMICs? (2) What is the impact of the economic burden in terms of OOPE, catastrophic health expenditure, impoverishment, and GDP due to mosquito-borne diseases in LMICs? (3) What is the per patient cost involved in the treatment of mosquito-borne disease? The review will also aim to present evidence across specific mosquito-borne diseases and across all specific LMICs.

Methods

Reporting

The PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols) was used to develop the protocol and will follow the JBI protocols for economic evaluations [35,36]. The final systematic review will be undertaken using the JBI methodology for economic evaluations and reported as per PRISMA 2020 guidelines [37,38].

Inclusion Criteria

Participants

This review will consider studies that include patients of all age groups who are affected with mosquito-borne diseases and residing in LMICs.

Conditions

This review will focus on studies that report the costs of the population affected with chikungunya, lymphatic filariasis, dengue, Rift Valley fever, Zika, malaria, yellow fever, West Nile fever, and Japanese encephalitis.

Contexts

This review will include studies conducted in any setting and in any geographical location in LMICs as per the World Bank criteria (Multimedia Appendix 1). For the current 2024 fiscal year, low-income economies are defined as those with a gross national income per capita of US $1135 or less in 2022, and lower middle-income economies are those with a gross national income per capita between US $1136 and US $4465, as calculated using the World Bank Atlas method. Annexure provides the list of LMICs included in the review [39].

Study Designs

This systematic review will consider study designs published in English that involve full or partial economic evaluation, which may include cost analysis, cost comparison, cost of illness or economic burden, cost effectiveness, cost utility, cost benefit, and cost minimization studies. All studies that focus on the economic burden of vector-borne diseases spread by mosquitos in LMICs will be included as per the World Health Organization's definition.

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Exclusion Criteria

The following studies were excluded from review: (1) studies with costs pertaining to the comorbidities associated with mosquito-borne illnesses; (2) studies that only report utilities, quality of life, and patient-related outcomes without costs; (3) editorials, methodological articles or commentaries, and reviews (however, the bibliographies of systematic reviews will be used to identify relevant studies to be included); (4) studies conducted in high-income countries; and (5) studies published in a language other than English.

Outcomes

The outcomes of this review will consist of metrics relating to cost components that contribute to the economic burden of mosquito-borne diseases.

Measures of Costs

Cost outcomes will be expressed as total costs per patient, per country, and per disease as per the data available in the included studies. Costs will be categorized as direct or indirect as per the availability of the data.

Measures of Resource Use

The costs associated with clinical outcomes (recovery, morbidity, and mortality) will be measured in terms of the total number of units of resources used. Resources used will be measured in 3 categories. Direct medical resources include consultations, number and length of outpatient visits, hospitalization days, provider services, devices, drugs, supplies, procedures (laboratory and clinical), and investigations. Direct nonmedical resources include the number or duration of services (housekeeping and administration), transportation, accommodation, food, clothing, overhead costs, waiting time, and property losses. Indirect resources include the number of days or hours of work lost due to the disease and productivity loss by patients and their caregivers due to morbidity, disability, or premature death.

Measures of Health Care Expenditure

Health care expenditure includes costs reported in terms of OOPE and the percentage of the population exposed to catastrophic health expenditure, financial hardship, impoverishment, and GDP impact.

Search Strategy

The first step is to develop a search strategy that will include combinations of medical subject heading (MeSH) terms and free texts. Search terms will be developed for the domains, mosquito-borne diseases (conditions), costs (outcomes), and LMICs (contexts). The search terms for mosquito-borne diseases will include the following MeSH terms: “chikungunya,” “lymphatic filariasis,” “dengue,” “Rift Valley fever,” “Zika,” “malaria,” “yellow fever,” “West Nile fever,” and “Japanese encephalitis.” The MeSH terms for the costs will include “economics,” “cost,” and “cost analysis.” The MeSH term for the LMICs will be “developing countries.” The search filters for costs and LMICs were adapted from Canada’s Drug and Health Technology Agency search filters database [40] and the School of Health and Related Research LMIC filter [41], respectively.

These search terms will be combined using the “OR” and “AND” Boolean operators. “OR” will be used to combine search terms within a particular domain, and “AND” will be used to combine different domains. In the next step, the search strategy used in PubMed (MEDLINE) will be peer reviewed following the Peer Review of Electronic Search Strategies 2015 guideline statement [42]. After the search strategy is peer-reviewed, corrections will be made for any suggestions or errors. Once the search strategy is updated, the same will be replicated in all other databases included. No specific date range will be applied (Multimedia Appendix 2).

The search strategy will include databases such as PubMed (MEDLINE), Ovid Embase, Scopus, the cumulative index of nursing and allied health literacy, and Cochrane CENTRAL. Additionally, the websites of the World Bank, World Health Organization, and Asian Development Bank will also be searched. Grey literature will also be identified through a manual search of relevant organizations working in the field, such as Malaria No More, and Ministry of Health websites.

Study Selection

All references retrieved through searches will be imported into Zotero and duplicates will be removed. Following a pilot test to check for interrater reliability, titles and abstracts will be screened by 2 independent reviewers for assessment against the inclusion criteria for the review. Potentially relevant studies will be retrieved in full, and their citation details will be imported into Covidence software [43]. The full text of selected citations will be assessed in detail as per the inclusion criteria by 2 independent reviewers (VL and NC). Reasons for the exclusion of full-text studies that do not meet the inclusion criteria will be recorded and reported in the systematic review. Any disagreements that arise between the reviewers at each stage of the study selection process will be resolved through discussion or adjudication by a third reviewer (SK).

The results of the search and study selection and inclusion process will be reported in full in the final systematic review and presented in a PRISMA flow diagram [38].

Assessment of Methodological Quality

The methodological quality of the included studies will be individually evaluated by 2 authors (VL and NC) and then reviewed independently by 2 other authors (SK and AR). When necessary, the authors of the included papers will be contacted for clarification on any missing information or additional data. The tools used will include an adapted checklist by Larg and Moss [44] for cost of illness studies, the Cochrane risk-of-bias tool (RoB 2) [45] for randomized controlled trials, and the Consensus on Health Economic Criteria [46] for economic evaluation studies. Data extraction and synthesis will be applied to all studies, regardless of their methodological quality.

Data Extraction

Data extraction will be performed in Excel (Microsoft Corp) using a standardized form (Multimedia Appendix 3). The form will be pilot tested by 3 independent authors (VL, NC, and SK)

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and reviewed by 2 additional authors (AR and DJ). It will then be used to collate relevant information from the included studies and will be tested by all authors. Data extraction will be performed by 3 independent authors (VL, NC, and SK), and any disagreements will be resolved through discussion with a senior reviewer (AR or GT). Where required, authors will be contacted for any missing or additional information.

Data Synthesis

The studies selected for review will be presented in tables and a narrative summary. The summary will evaluate and compare the methods and primary outcomes across the studies and will be organized according to the country where the study was published, timing, intervention type, economic evaluation type, and the methodology used. The studies will be categorized according to the kind of economic assessment conducted, sources of data, effect size of the intervention, resources usage, costs, epidemiological data, and effectiveness estimates. Further, to facilitate comparison of the studies, they will be summarized in a table. The table will facilitate the collection of information on the year of analysis, currency, type of intervention, and costs reported by the authors of the studies. A table named "characteristics of the included studies" will be created to present the methodological features of the studies included in the review.

For comparison across studies, all costs will be converted into a single currency (USD) and reference year (2022) using the cost calculator provided by the Campbell and Cochrane Economics Methods Group and the Evidence for Policy and Practice Information Centre [47].

Results

The protocol has been registered in PROSPERO. The systematic review is self-funded and was started on May 20, 2023. A systematic search was conducted without any restriction on time period by adapting search filters for economic evaluations from Canada's Drug and Health Technology Agency search filters database and the School of Health and Related Research LMIC filter in May 2023. The title and abstract screening of 13,444 studies was conducted, and 267 studies met the criteria for full text review. Data extraction is currently underway. After data synthesis, we intend to disseminate the results through the submission of a manuscript to a peer-reviewed journal by November 2023. The systematic review conducted as per this protocol will present the results evaluating and comparing the methods and primary outcomes across the included studies and will be presented in the form of tables and a summary.

Discussion

Overview

Mosquito-borne diseases pose a significant economic burden in LMICs. Irrespective of age, race, and income level, anyone can become affected by these diseases. The systematic review will comprehensively synthesize all the existing literature on the economic burden of mosquito-borne diseases and will provide an estimate of their total economic burden. The gap in the existing literature [15,17-19]—that studies have concentrated only on either a specific disease or a specific country—will be addressed in this review. The review's findings will compile the direct and indirect costs associated with treating mosquito-borne diseases. Also, it will offer estimates on the total economic burden caused by mosquito-borne diseases in specific LMICs. Furthermore, the review will determine the disease contributions in the accumulation of economic burden specific to LMICs, as well as per patient cost estimates involved in the treatment of mosquito-borne diseases.

Due to the low number of populations with health care coverage, OOPE has increased considerably in LMICs. This has significantly increased the economic burden on individuals living in LMICs. The outcome of the review will help governments and international bodies to prioritize decisions about how to contain the prevalence of mosquito-borne diseases and inform actions to lower the incidence of diseases spread by mosquitoes.

The most significant limitation of this systematic review will be the necessity that each study included in the review be a full-text, primary study, as conference abstracts will be excluded. Another limitation will be that only studies in English will be included. However, we do not foresee any issues due to these limitations since conference abstracts provide limited information with regard to the methods of economic burden estimation and do not provide sufficient information for conducting a proper critical appraisal using standard tools. Also, the review will not include studies regarding the prevention of mosquito-borne diseases. Studies published in regional language databases, for example Spanish and Chinese language databases, will be excluded; however, this will not have a large impact on the number of studies that will be excluded due to this criterion.

Conclusion

The purpose of this review is to explore the extent of the literature available on mosquito-borne diseases in LMICs. As reported in the literature, given that the burden of mosquito-borne diseases in LMICs is high, a comprehensive review will help to explore the economic burden associated with these diseases in this context. The review outcome will reveal the economic burden caused by mosquito-borne diseases in specific countries and LMICs on the whole. Further, based on the available studies, the review will also identify specific diseases that are increasing the economic burden of individual LMICs. The review will help to evaluate the currently available evidence on OOPE, catastrophic health expenditure, impoverishment, and GDP impact due to mosquito-borne diseases in LMICs. Hence, our review findings will help frame targeted policies focusing on decisions for containing the prevalence of mosquito-borne diseases and inform a means to lower the incidence of diseases spread by mosquitoes. The review will also guide future researchers in designing country-specific studies by choosing an appropriate mosquito-borne disease that increases the economic burden. Also, based on the findings of our full economic evaluation study, future researchers can engage in treatment-based cost-effectiveness studies based on country-specific treatment protocols.

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Acknowledgments

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Data Availability

Our review is ongoing; therefore, we do not currently have a data set to share. As our study period ends in November 2023, we can share the data with the readers on request thereafter.

Conflicts of Interest

None declared.

Multimedia Appendix 1
World Bank list of low- and middle-income countries.
[DOCX File , 17 KB - resprot_v12i1e50985_app1.docx]

Multimedia Appendix 2
Search strategy.
[DOCX File , 21 KB - resprot_v12i1e50985_app2.docx]

Multimedia Appendix 3
Data extraction form.
[DOCX File , 16 KB - resprot_v12i1e50985_app3.docx]

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Abbreviations

CCEMG: Campbell and Cochrane Economics Methods Group
CHIKV: chikungunya virus
GDP: gross domestic product
JBI: Joanna Briggs Institute
LMIC: low- and middle-income countries
MeSH: medical subject headings
OOPE: out-of-pocket expenditure
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO: International Prospective Register of Systematic Reviews
UHC: universal health coverage

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Protocol

The Effects of Reinforcement Techniques in Sleeve Gastrectomy and Roux-en-Y Gastric Bypass: Protocol for a Web-Based Survey, Systematic Review, and Meta-Analysis

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Abstract

Background: The effects of reinforcement are still controversial in bariatric surgery, and variations may exist in using this technique.

Objective: This protocol describes a study that aims to survey the views of bariatric surgeons on reinforcement techniques and evaluate the effects of applying reinforcement techniques in sleeve gastrectomy (SG) and Roux-en-Y gastric bypass (RYGB).

Methods: This study is composed of 2 parts. Part 1 will investigate the differences of using reinforcement techniques among surgeons worldwide who perform SG or RYGB through a survey. The survey will be conducted by email and social media. Part 2 will evaluate the safety and effectiveness of using omentopexy or staple line reinforcement in SG and RYGB by systematic review and meta-analysis. In this part, literature searches will be performed in English databases, including CENTRAL, EMBASE CINAHL, Web of Science, and PubMed, and Chinese databases, including Wanfang, China National Knowledge Infrastructure, Database of Chinese Technical Periodicals, and Chinese Biological Medicine, from their establishment to November 2023. Randomized controlled trials and case-control studies will be included. The primary outcomes are rates of postoperative bleeding and gastric leakage. The secondary outcomes include anastomotic stenosis, surgical site infection, reoperation, estimated intraoperative blood loss, operative time (minutes), length of hospital stay (days), overall complications, and 30-day mortality. The meta-analysis will be conducted using RevMan 5.4 under the random-effects model, as well as through extensive subgroup and sensitivity analyses. *P* values <0.05 will be considered statistically significant. This study was registered with PROSPERO (Prospective Register of Systematic Reviews) in accordance with the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols).

Results: The results of this study will be published in a peer-reviewed journal. The web-based survey and initial title or abstract review of papers identified by the search strategy will be completed in November 2023. The second round of title or abstract review and downloading of the papers for full-text inclusion will be completed in January 2024. We aim to complete data extraction and meta-analysis by February 2024 and expect to publish the findings by the end of March 2024.

Conclusions: This study aims to investigate the impact of reinforcement techniques on reducing the incidence of postoperative complications in SG and RYGB procedures and provide assistance for standardizing the procedures of SG and RYGB operations for bariatric surgeons.

Trial Registration: PROSPERO CRD42022376438; https://tinyurl.com/2d53uf8n

International Registered Report Identifier (IRRID): PRR1-10.2196/50677

(JMIR Res Protoc 2023;12:e50677) doi:10.2196/50677

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KEYWORDS

protocol; reinforcement technique; sleeve gastrectomy; Roux-en-Y gastric bypass; systematic review; meta-analysis; bariatric surgery; survey; effectiveness; surgical site; blood loss; blood; gastric bypass; gastrectomy

Introduction

The prevalence of obesity is steadily rising globally, resulting in a decline in the quality of life of those affected and an increase in mortality rates [1-3]. Various methods are available for managing obesity, including behavioral therapy, pharmacological therapy, and bariatric surgery. Metabolic bariatric surgery has long-lasting weight loss effects, and its positive impact on the treatment of obesity-related comorbidities (eg, hypertension, type 2 diabetes, and obstructive sleep apnea) has also been observed [4,5].

Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG) are the most frequently performed bariatric surgeries [6,7], which typically involve the use of reinforcement techniques to reduce potential postoperative complications, such as gastroesophageal reflux, gastric leakage, and food intolerance. There are variations of reinforcement techniques used by different surgeons and in different countries [8-11], which can be categorized by material (eg, seamguard, peri-strips, fibrin sealant, absorbable polymer membrane, medtronic), suture methods (eg, oversew, burying, and whole layer continuing), the degree of reinforcement (partial or full), and types (staple line reinforcement or omentopexy). These variations may be related to differences in the effectiveness of reinforcement techniques in SG and RYGB, which make it a challenge to decide if a reinforcement technique is needed and which one is most appropriate for the patient (Table 1). For example, in terms of SG operations, 4 systematic reviews [12-15] reported that staple line reinforcement did not have any clear benefit concerning gastric leakage rate, overall morbidity, and mortality rate, while 3 other systematic reviews [16-18] found that staple line reinforcement overperformed in reducing the rate of gastric leakage and bleeding compared to no reinforcement. With regard to RYGB, a meta-analysis of 3 randomized controlled trials found a reduction in the rate of leakage in participants with staple line reinforcement [19], whereas another systematic review demonstrated that the rate of gastric leakage was no different with or without staple line reinforcement [20].

Apart from staple line reinforcement, omentopexy is another type of reinforcement technique, which uses sutures to fix the rest of the stomach to the free edge of the greater omentum [21]. The effect of SG with omentopexy on the rate of postsurgery complications was investigated in 3 systematic reviews [22-24], which reported inconsistent results. Of the 3 reviews, 2 [22,24] suggested that SG with omentopexy outperforms SG without omentopexy in reducing gastrointestinal adverse reactions (eg, nausea, reflux, and vomiting), while in terms of reducing gastric leakage, they showed the opposite effects. Opposing results were also observed in 2 reviews [23,24] in terms of the length of hospital stay.

According to Table 1, we found that previous systematic reviews of reinforcement techniques either focused on a single type of operation (SG or RYGB) or a single type of reinforcement technique (staple line reinforcement or omentopexy), and the design of the included studies was also relatively simple. Thus, an up-to-date and comprehensive meta-analysis and systematic review is needed to fill the gaps and confirm the effect of reinforcement techniques in SG and RYGB. Therefore, a web-based survey to ascertain the variations in the utilization of reinforcement techniques among surgeons worldwide who perform SG or RYGB will be performed in this study, which aims to elucidate the necessity and rationale for conducting the ensuing meta-analysis and systematic review. The goal of these analyses is to investigate the impact of reinforcement techniques on reducing the incidence of postoperative complications in SG and RYGB procedures.

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Table 1. Summary of previous systematic reviews on reinforcement techniques in sleeve gastrectomy (SG) and Roux-en-Y gastric bypass (RYGB).

Study	Type of surgeries	Type of reinforcement techniques	Design of included studies	Meta-analysis	Subgroup analyses	Sensitivity analyses	Quality assessment	Other analyses	Number of studies included
Giannopoulos et al, 2010 [12]	SG, BPD-DS[a], RYGB, VBG[b]	SLR[c]	RCTs[d], non-RCTs	Yes	No	No	No	PB[e]	17
Sajid et al, 2011 [19]	RYGB	SLR	RCTs	Yes	No	No	No	N/A[f]	3
Choi et al, 2012 [20]	SG	SLR	RCTs, Cs[g]	No	No	No	No	N/A	8
Aurora et al, 2012 [13]	SG	SLR	RCTs, Cs	No	No	No	No	No	29
Parikh et al, 2013 [15]	SG	SLR	Retrospective	Yes	No	No	No	LRA[h]	112
Knapps et al, 2013 [14]	SG	SLR	Retrospective, Prospective, RCTs	Yes	Yes	No	No	No	30
Gagner and Buchwald, 2014 [16]	SG	SLR	Retrospective, Prospective, RCTs, No report	No	No	No	No	No	88
Wu et al, 2019 [17]	SG	SLR	RCTs	Yes	Yes	Yes	Yes	PB	11
Zarzycki et al, 2021 [22]	SG	Omentopexy	RCTs, CCSs[i], Cs	Yes	No	No	Yes	N/A	4
Aiolf et al, 2022 [18]	SG	SLR	RCTs	Yes	No	No	Yes	NMA[j]	17
Chen et al, 2022 [23]	SG	Omentopexy	RCTs	Yes	No	No	No	N/A	5
Wu et al, 2023 [24]	SG	Omentopexy	RCTs	Yes	Yes	Yes	Yes	PB	13
Our protocol	RYGB, SG	SLR, Omentopexy	RCTs, CCSs	Yes	Yes	Yes	Yes	PB, WSBS[k]	50[l]

[a]BPD-DS: biliopancreatic diversion with duodenal switch.

[b]VGB: vertical banded gastroplasty.

[c]SLR: staple line reinforcement.

[d]RTC: randomized controlled trial.

[e]PB: publication bias.

[f]N/A: not applicable.

[g]Cs: cohort study.

[h]LRA: linear regression analysis.

[i]CCS: case-control study.

[j]NMA: network meta-analysis.

[k]WSBS: web-based survey for bariatric surgeons.

[l]Estimated number of eligible studies according to the searching test.

Methods

This study consists of 2 parts. Part 1 aims to survey global bariatric surgeons via the web and part 2 aims to perform a systematic review and meta-analysis. The specific procedures are illustrated in Figure 1.

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Figure 1. Conceptual framework. HLOS: hospital length of stay; OT: operative time; RYGB: Roux-En-Y gastric bypass; SG: sleeve gastrectomy; SSI: surgical site infection.

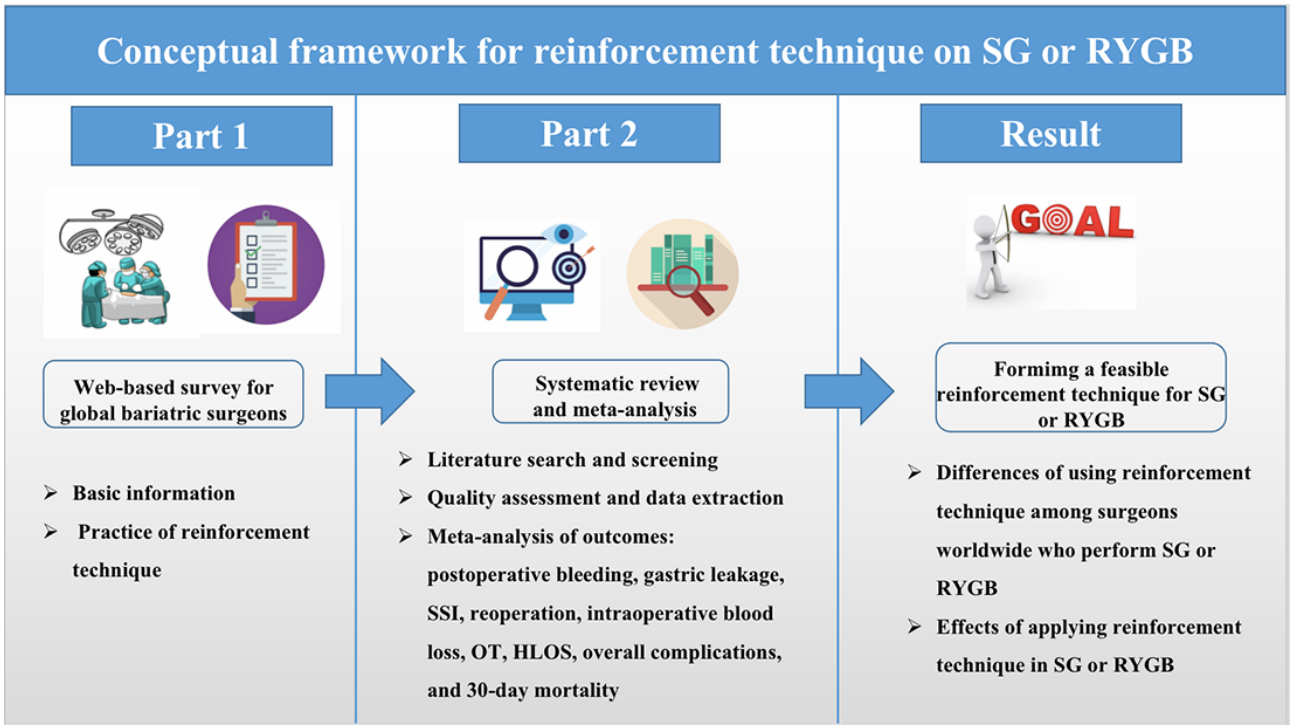
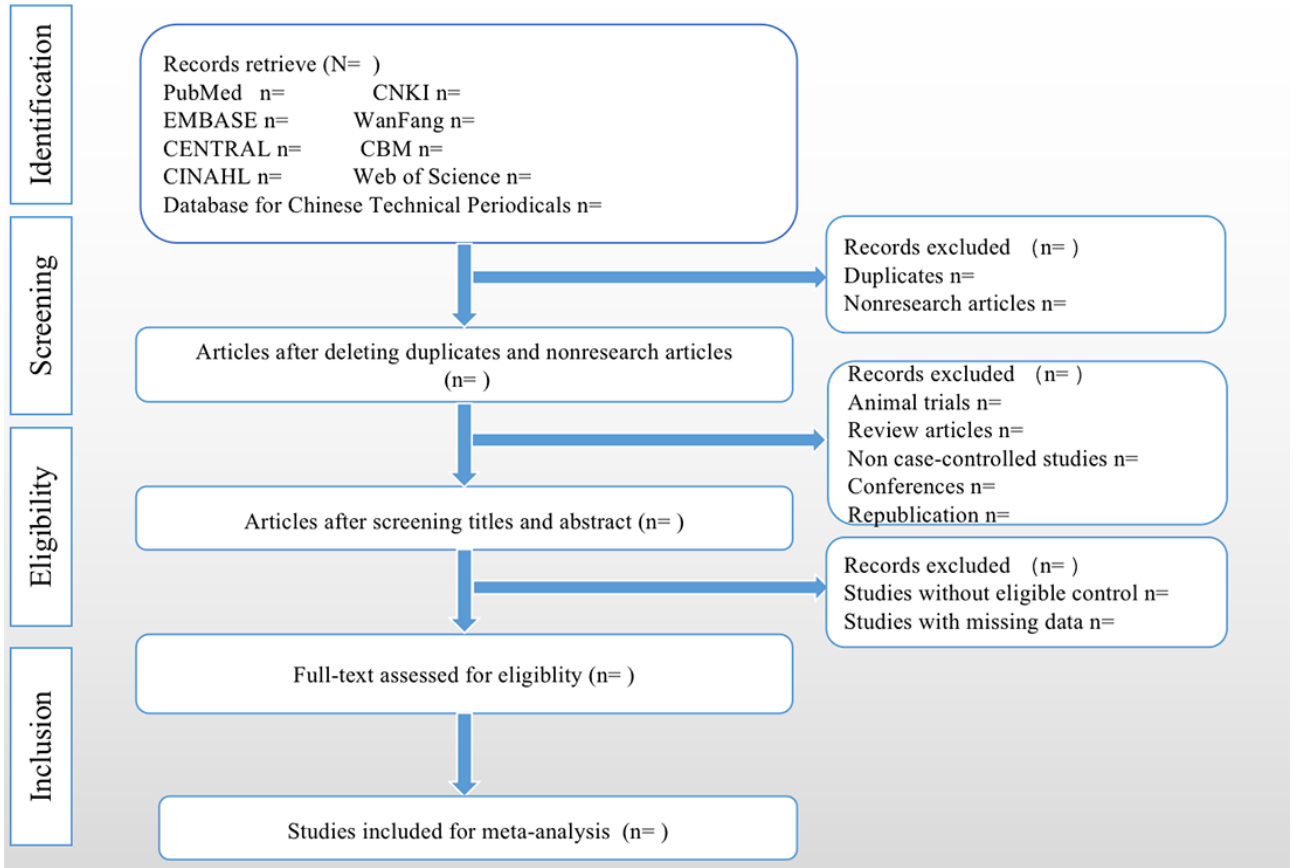


Figure 2. PRISMA flow chart of study.



Part 1: Web-Based Survey for Global Bariatric Surgeons

A global survey will be conducted using Questionnaire Star to collect basic information and differences in the use of reinforcement techniques among bariatric surgeons from October 30, 2023, to November 30, 2023. The survey includes 6 questions inquiring about basic information, including age, sex, work experience in bariatric surgery, time required for per SG or RYGB surgery (minutes), country, and institution.

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Additionally, 11 questions pertain to information on reinforcement, including whether to perform SG with staple line reinforcement, the degree of staple line reinforcement in SG, forms of staple line reinforcement in SG, whether to perform SG with omentopexy and their reasons, the degree of omentopexy in SG, whether to perform RYGB with staple line reinforcement and their reasons, the degree of staple line reinforcement in RYGB, and forms of staple line reinforcement in RYGB. The survey will be sent to surgeons through social media (eg, WeChat, Meta) and email. The email addresses of possible surgeons who have published articles in either one of the official journals of The International Federation for the Surgery of Obesity and Metabolic Disorders and the American Society for Metabolic and Bariatric Surgery, namely *Obesity Surgery* and *Surgery for Obesity and Related Diseases*, in the 3-year period from 2020 to 2022 will be captured and used. Only responses from surgeons who perform SG or RYGB will be eligible in later analysis. The survey is shown in Multimedia Appendix 1.

Part 2: Systematic Review and Meta-Analysis

This systematic review and meta-analysis has been registered on PROSPERO (Prospective Register of Systematic Reviews) with the registration number CRD42022376438. The protocol is reported in accordance with the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) 2015 [25], which includes the search strategy, eligible criteria, study selection, data extraction and quality assessment, statistical analysis, subgroup analyses, sensitivity analyses, and publication bias.

Eligibility Criteria

Eligible studies have to meet all of the following inclusion criteria:

1. Population: studies in which all patients underwent SG or RYGB.
2. Intervention: studies in which the intervention was SG or RYGB with omentopexy or staple line reinforcement.
3. Comparison: studies in which the comparison was SG or RYGB without omentopexy or staple line reinforcement.
4. Outcomes: studies that reported at least one of postoperative bleeding and gastric leakage assessment as primary outcomes and secondary outcomes including surgical site infection, reoperation, estimated intraoperative blood loss (milliliters), operative time (minutes), length of hospital stay (days), overall complications, and 30-day mortality. Overall complications are defined as the incidence of peritonitis, abdominal abscess, puncture hernia, intraperitoneal hernia, intestinal adhesion, and gastroesophageal reflux.
5. Study design: randomized controlled trials (RCTs) and case-control studies (CCSs).

Studies will be excluded if they are animal trials or noncontrol studies or do not report sample size and outcome.

Search Strategy

Searching work will be conducted by 2 researchers (YX and JW) in November 2023. English databases, including CENTRAL, EMBASE CINAHL, Web of Science, and PubMed, and Chinese databases, including Wanfang, China National Knowledge Infrastructure, Database of Chinese Technical Periodicals, and Chinese Biological Medicine, will be searched. The elements like titles, abstracts, and keywords in a combination of medical subject headings (MeSH) terms and free text terms will be searched to ensure an accurate and comprehensive study. The following MeSH and free text terms will be used: gastric bypass, sleeve gastrectomy, omentopexy, and reinforcement. There is no restriction on language and publication date. The detailed search strategy for PubMed is shown in Table 2.

Table 2. Search strategy for PubMed.

Search	Query
1	(((gastric bypass[Title/Abstract]) OR (sleeve gastrectomy[Title/Abstract])) OR (SG[Title/Abstract] OR (RYGB[Title/Abstract])
2	(((omentum*[MeSH Terms])) OR (omentopexy[Title/Abstract])) OR (reinforce*[Title/Abstract])
3	(((gastric bypass[Title/Abstract]) OR (sleeve gastrectomy[Title/Abstract])) OR(SG[Title/Abstract] OR (RYGB[Title/Abstract]) AND (((omentum*[MeSH Terms])) OR (omentopexy[Title/Abstract])) OR (reinforce*[Title/Abstract])

Study Selection and Data Extraction

The literature management software Endnote X9 will be used to retrieve studies and exclude duplicates. The studies' contents and abstracts will be independently reviewed by 2 authors (YX and JW) according to the precise search strategies after they initially screened the studies that satisfy the inclusion criteria. Data extraction from the included studies, including authors, country, sample size, gender, race, time frame, other comorbidities, type of bariatric operations, reinforcement technique, and reported outcomes, will be collected and managed in Excel (Microsoft Corp; see Multimedia Appendix 2 for a sample table). The full text will then be read by 2 authors (YX and JW) to further determine suitability for inclusion. Any disputes will be settled through discussions or consultation with a third author (HZ).

Quality Assessment

Quality assessment will be performed based on the study design of the included studies. For RCTs, the Cochrane Risk of Bias tool [26] will be used, which focuses on 6 domains, including randomization, allocation concealment, application of blinding, integrity of the outcome data, selective reporting, and other biases. For CCSs, the quality of the included studies will be assessed by the Newcastle-Ottawa Scale (NOS) [27], which includes the appropriateness of the case and control, representativeness of the case, selection of the control, comparability of the case and control in the design, and

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statistical analysis of exposure factors. The top score of the NOS is 9, and the higher the score, the higher the quality. Quality assessment will be done by 2 researchers (YX and JW). Any disagreements will be resolved through discussion or consultation with a third researcher (HZ).

Statistical Analysis

This study will use RevMan 5.4 software (Cochrane) for meta-analysis with the random effects model. We will use odds ratios as the effect measure for dichotomous variables (eg, postoperative bleeding, gastric leakage assessment, and reoperation), and mean differences for continuous variables (eg, estimated intraoperative blood loss, operative time, and length of hospital stay). All effective measures will be accompanied by their corresponding 95% CI. Heterogeneity will be evaluated using the Q test method, which calculates χ^2 and I^2 values. $P<0.05$ will be considered statistically significant.

Subgroup Analyses

The following predefined subgroups will be analyzed: study design of the included studies (RCTs or CCSs), age (≤65 years or >65 years) [28], gender (woman or man), type of bariatric surgery (SG or RYGB), materials of staple line reinforcement (eg, seamguard, fibrin sealant, absorbable polymer membrane), suture methods (eg, oversew, burying, whole layer continuing), the degree of reinforcement (partial or full), and the type of reinforcement (staple line reinforcement or omentopexy).

Sensitivity Analyses

Sensitivity analysis will be performed to assess the robustness of the findings using the leave one out approach [17], and studies involved in this meta-analysis will be removed in turn. Sensitivity analyses on the quality and sample size of the included studies will be conducted as well, and the meta-analyses will be repeated after excluding studies whose sample sizes are <5 or those with 3 domains rated as high risk for RCTs or with a NOS score <5 for CCSs.

Publication Bias

Publication bias in this study will be assessed using a funnel plot. A Begg test [29] and Egger test [30] will be performed using the Stata 15 software (StataCorp) to evaluate the statistical significance of the publication bias.

Ethical Considerations

The web-based survey has obtained ethics approval (2023-S-25). As for systematic reviews and meta-analyses, ethics approval is not required because the data used are derived from published papers. Informed consent was not applicable.

Results

The results of this study will be published in a peer-reviewed journal. The web-based survey and initial title or abstract review identified by the search strategy will be completed in November 2023. The second round of title or abstract review and downloading of the papers for full-text inclusion will be completed in January 2024. We aim to complete the data extraction and meta-analysis by February 2024 and expect to publish the findings by the end of March 2024.

Discussion

Principal Findings and Implications

Obesity is a disease caused by excessive accumulation of body fat due to the imbalance between energy intake and consumption [31], which is defined as a body mass index above 30 kg/m^2 [32]. According to the World Health Organization, more than 1.9 billion people worldwide were overweight in 2016, and more than 650 million had obesity [33]. Bariatric surgery associated with a reduction of obesity-related comorbidities has been gradually recognized globally [34,35]. However, the application of reinforcement techniques in SG or RYGB bariatric surgery remains a challenge for surgeons. In this study, we aim to investigate the opinions of bariatric surgeons on reinforcement techniques using web-based surveys and to evaluate the effectiveness of reinforcement techniques in reducing postoperative complication rates by meta-analyses and systematic review. To our knowledge, few studies have investigated the impact of different reinforcement techniques (staple line reinforcement or omentopexy) on 2 types of bariatric surgery (SG or RYGB) and included 2 study designs (RCT or CCS); these represent the strengths of our study. We will also perform subgroup analysis according to study design, age, race, type of bariatric surgery, materials of staple line reinforcement, suture methods, the degree of reinforcement, and types of reinforcement techniques. Our research will fill previous gaps and help standardize SG and RYGB procedures for bariatric surgeons and other researchers.

Limitations

Our study has several limitations. First, given the broad inclusion criteria, there may be high heterogeneity among the included studies. We will minimize the potential heterogeneity by performing subgroup and sensitivity analyses. Second, due to language limitations, we will only search English and Chinese databases. We will search for references included in studies to reduce the issue of incomplete inclusion of literature due to language limitations. Third, we are aware that the email addresses obtained from the studies may include authors who are not bariatric surgeons. Therefore, we have indicated on the questionnaire that participants must be bariatric surgeons for subsequent questions to be answered.

Conclusions

The web-based survey is designed to reveal variations in reinforcement techniques used by bariatric surgeons in SG and RYGB procedures, while the meta-analyses and systematic review are expected to shed light on the effectiveness of these techniques in reducing the incidence of postoperative complications.

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Acknowledgments

This project was funded by the Chengdu High-level Key Clinical Specialty Construction Project and Chengdu Medical Research Project (grant 2022188) and the Project of Chengdu Municipal Health Commission (grant 2022188).

Data Availability

The data sets generated and analyzed throughout the study will be provided as supplementary files in a peer-reviewed journal. Additionally, detailed descriptions and comprehensive analyses of the data will be included to enhance the understanding of the research findings for the bariatric discipline.

Authors' Contributions

HZ and YL conceptualized the study. YX performed the formal analysis. YX and JW carried out the investigation. HZ designed the methodology. YL supervised the study. HZ and YX performed the validation. HZ performed the visualization. YX wrote the original draft. YX, JW, HZ, and YL reviewed and edited the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Supplementary file.
[DOCX File , 16 KB - resprot_v12i1e50677_app1.docx]

Multimedia Appendix 2
Sample table.
[DOCX File , 15 KB - resprot_v12i1e50677_app2.docx]

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Abbreviations

CCS: case-control study
NOS: Newcastle-Ottawa Scale
PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols
PROSPERO: Prospective Register of Systematic Reviews
RTC: randomized controlled trial
RYGB: Roux-en-Y gastric bypass
SG: sleeve gastrectomy

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Protocol

Economic Evaluations and Equity in the Use of Artificial Intelligence in Imaging Exams for Medical Diagnosis in People With Skin, Neurological, and Pulmonary Diseases: Protocol for a Systematic Review

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Abstract

Background: Traditional health care systems face long-standing challenges, including patient diversity, geographical disparities, and financial constraints. The emergence of artificial intelligence (AI) in health care offers solutions to these challenges. AI, a multidisciplinary field, enhances clinical decision-making. However, imbalanced AI models may enhance health disparities.

Objective: This systematic review aims to investigate the economic performance and equity impact of AI in diagnostic imaging for skin, neurological, and pulmonary diseases. The research question is “To what extent does the use of AI in imaging exams for diagnosing skin, neurological, and pulmonary diseases result in improved economic outcomes, and does it promote equity in health care systems?”

Methods: The study is a systematic review of economic and equity evaluations following PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and CHEERS (Consolidated Health Economic Evaluation Reporting Standards) guidelines. Eligibility criteria include articles reporting on economic evaluations or equity considerations related to AI-based diagnostic imaging for specified diseases. Data will be collected from PubMed, Embase, Scopus, Web of Science, and reference lists. Data quality and transferability will be assessed according to CHEC (Consensus on Health Economic Criteria), EPHPP (Effective Public Health Practice Project), and Welte checklists.

Results: This systematic review began in March 2023. The literature search identified 9,526 publications and, after full-text screening, 9 publications were included in the study. We plan to submit a manuscript to a peer-reviewed journal once it is finalized, with an expected completion date in January 2024.

Conclusions: AI in diagnostic imaging offers potential benefits but also raises concerns about equity and economic impact. Bias in algorithms and disparities in access may hinder equitable outcomes. Evaluating the economic viability of AI applications is essential for resource allocation and affordability. Policy makers and health care stakeholders can benefit from this review’s

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insights to make informed decisions. Limitations, including study variability and publication bias, will be considered in the analysis. This systematic review will provide valuable insights into the economic and equity implications of AI in diagnostic imaging. It aims to inform evidence-based decision-making and contribute to more efficient and equitable health care systems.

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KEYWORDS

artificial intelligence; economic evaluation; equity; medical diagnosis; health care system; technology; systematic review; cost-effectiveness; imaging exam; intervention

Introduction

Traditional health care systems encounter a multitude of challenges that have persisted for decades. These challenges include patient diversity, the vast geographical areas they are often required to cover, and the ever-present financial constraints that limit their capacity to deliver optimal care [1]. However, in recent years, the advent of artificial intelligence (AI) has introduced a transformative dimension to health care, showing immense potential in mitigating these challenges [2,3].

AI, a multidisciplinary field, integrates computer science and engineering to generate intelligent machines skilled in emulating human cognition and problem-solving [4]. Its subfield, machine learning, refines algorithms through the extensive analysis of data sets, thus enabling decision-making and predictions across various contexts [5,6]. An advanced offshoot, deep learning, has found particular prominence in medical imaging, bolstering the system's capacity for human-like reasoning [7]. Within health care, AI technologies serve critical roles in enhancing the accuracy and efficiency of disease detection, segmentation, and classification in medical imaging [8]. These advancements contribute to improved clinical decision-making, cost reduction, and error mitigation [9].

Nevertheless, there are pressing concerns that must be urgently addressed to maximize the clinical use of AI in health care. Methodological limitations, such as the lack of transparent algorithms and insufficient validation studies, risk hindering the wider adoption and efficacy of AI systems in clinical settings [10,11]. Moreover, the issue of data set bias warrants immediate attention; many of the data sets currently used for training and validating AI models are inherently skewed toward specific ethnic or demographic groups [12]. This imbalance may result in algorithms that are less effective or even misleading when applied to populations not adequately represented in the training data, thereby perpetuating existing inequalities in health care outcomes [13]. Such weaknesses not only constrain the clinical impact but could also exacerbate existing health disparities by delivering suboptimal or biased care [14].

Health equity refers to the principle that everyone should have equal access to health care and the opportunity to attain the best possible health, regardless of personal characteristics such as race, ethnicity, gender, socioeconomic class, or other factors that can contribute to health disparities [15]. Moreover, it is crucial to acknowledge that even when data related to equity or social determinants of health are incorporated, they can inadvertently introduce biases into algorithms if not adequately integrated and interpreted [16]. Recently, AI has gained significant attention due to its equity implications, underscoring the imperative to promote population well-being while taking into account differences in gender, race, and socioeconomic status, as evidenced by multiple sources [17-19].

Brazil, a large upper-middle–income country, has the world's largest free public health care system, which is relied upon by the majority of its population. However, several socioeconomic barriers hinder access to diagnoses in impoverished and remote areas. Digital health initiatives, including AI-powered clinical decision support systems, have proven effective in reducing health disparities and facilitating access to services [20]. To tackle these challenges, the Brazilian Ministry of Health's Support Program for the Institutional Development of the Unified Health System (in Portuguese, "Programa de Apoio ao Desenvolvimento Institucional do Sistema Único de Saúde", known as PROADI-SUS) supports a collaborative project named "Banco de Imagens" (Bank of Images) to create a nationwide cloud-based repository of medical images, as well as to develop and validate AI algorithms to assist in disease diagnosis. Currently, clinical validation is underway for performance assessment of diagnostic decision-support algorithms, specifically engineered to address conditions of Brazilian public health importance. These algorithms target dermatological lesions such as melanoma, radiological markers indicative of pulmonary tuberculosis, and volumetric alterations in cerebral computed tomography scans for the evaluation of conditions, including microcephaly, brain atrophy, and hydrocephaly. To ensure the effectiveness and accessibility of these AI algorithms, the clinical validation process also aims to measure the economic and equity impact of implementing these technologies in real-world.

Hence, this protocol outlines a systematic literature review that aims to investigate the economic performance or viability of using AI in diagnostic imaging exams, particularly for skin, neurological, and pulmonary diseases. The review will also assess the possible equity outcomes of this intervention in health care systems. The research question guiding this review is "To what extent does the use of AI in imaging exams for diagnosing skin, neurological, and pulmonary diseases result in improved economic outcomes, and does it promote equity in health care systems?" A preliminary search for existing systematic reviews on this topic has been conducted in databases such as PubMed and PROSPERO, and no identical review to the proposed study was found.

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Methods

Overview

The study is designed as a systematic review of economic evaluations, which will be reported in accordance with the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) checklist [21]. To ensure good reporting practices for economic evaluations, the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) tool [22] will be used along with the CHEERS (Consolidated Health Economic Evaluation Reporting Standards) checklist [23]. Additionally, we will adhere to guidelines provided by Preferred Reporting Items for Systematic Reviews and Meta-Analyses with a Focus on Health Equity (PRISMA-E) for conducting equity-focused systematic reviews [24]. The research question was structured following the population, intervention, comparison, and outcomes structure, as shown in Table 1.

Table 1. Population, intervention, comparison, and outcomes (PICO) structure for the systematic review of global economic evaluations and equity studies in the use of artificial intelligence (AI) in medical diagnosis of people with skin, neurological, and pulmonary diseases.

Acronym	Description	Criteria
P	Population	Patients screened for pulmonary, neurological, and cutaneous diseases, considering the entire world population, regardless of the income and development of that country
I	Intervention	Use of AI for diagnostic decision support in any type of imaging exam
C	Comparison	Conventional or human-based diagnostic methods
O	Outcomes	Full economic evaluations, such as cost-effectiveness, cost-usefulness, cost-benefit, or cost-minimization. We will assess changes in patient outcomes related to health care access and demographic factors like age, gender, race, and income, with a focus on equity.

Eligibility Criteria

Publications on economic evaluations or equity in diagnostic imaging use AI-based tools will be included. The thematic focus will align with the specialization areas of the Bank of Images project, particularly emphasizing conditions of critical importance to public health. These include (1) dermatology, specifically melanoma and skin carcinomas; (2) neurology, targeting disorders with notable radiological findings; and (3) pulmonology, concentrating on conditions such as tuberculosis, lung consolidation, pleural effusion, atelectasis, pneumothorax, mediastinal widening, lung edema, lung opacity, lung lesion, lung cancer, other pleural diseases, and lung nodules. Detailed inclusion and exclusion criteria, encompassing language and publication year, are provided in Textbox 1.

Textbox 1. Inclusion and exclusion criteria for the systematic review of global economic evaluations and equity studies in the use of artificial intelligence in medical diagnosis of people with skin, neurological, and pulmonary diseases.

Inclusion criteria

- Article type: Original articles reporting economic evaluation or equity. Cost-effectiveness, cost-usefulness, or cost-benefit or cost-minimization analysis will be considered as economic evaluation studies. Regarding equity, the authors will analyze reported improvements or declines in patient outcomes based on access to health care and demographic indicators such as age, gender, race, and income level.
- Study object: Use of artificial intelligence–based tools in diagnostic imaging exams in dermatological, pulmonary, and neurological fields.
- Language: There will be no restrictions based on language.
- Year of publication: There will be no restrictions based on year of publication.

Exclusion criteria

- Article type: Partial economic evaluations, such as cost analysis, cost-description studies, and cost-outcome descriptions. Regarding equity, we will exclude studies that stratify the study sample into a homogeneous population, not representative of the general population.
- Study object: We will exclude studies that focus on other medical fields, such as heart diseases, breast cancer, and diabetes. Also, validation studies of artificial intelligence will be excluded.

Information Sources

We will conduct a search in the PubMed, Embase, Scopus, and Web of Science databases and perform supplementary searches to locate references cited in the retrieved articles.

Search Strategy

We will define a customized search strategy for each database, using terms related to AI, relevant diseases or health conditions as aforementioned, economic evaluations, and equity. Separate searches will be conducted for each field of medicine, as well as a general search without a specific field. The final search terms are provided in Tables S1-S4 in Multimedia Appendix 1.

Data Management

We will use an Excel (Microsoft) spreadsheet to manage and organize records and data throughout the review process.

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Selection Process

The Rayyan platform (Qatar Computing Research Institute) will be used for article selection, with duplicates excluded by the platform and documented accordingly.

The selection process will consist of 2 phases. In the first phase, 2 researchers will independently evaluate and select articles. Researchers GOS and RML will evaluate titles and abstracts related to the neurological and pulmonary fields, while researchers GOS and BCRSF will assess titles and abstracts related to the dermatological field. Researchers GOS and RdMC will review titles and abstracts from the additional search that encompasses various fields of medicine.

In the second phase, the selected articles from the first phase will undergo full-text review. Researchers GOS and RML will evaluate full texts related to neurological and pulmonary fields, while researchers GOS and BCRSF will evaluate full texts related to the dermatological field. Researchers GOS and RdMC will review full texts resulting from the general search. Any disagreements will be resolved by a third researcher (RdMC for searches in neurological, pulmonary, and dermatological fields, and RML for the general search).

After the search strategy is completed, the authors will compile the final list of publications using EndNote software (version X9.3.3; Clarivate).

Data Collection Process

After completing the article selection process, 2 researchers (GOS and RdMC) will collect the variables of interest for the systematic review from each publication with available data. A pilot form will be used to collect data from a subset of studies, following which data will be collected independently. The extracted data by each researcher will be compared and merged into a single Excel spreadsheet.

Data Items, Outcomes, and Prioritization

List 1 registers the variables that will be collected from each study: ID, publication title, year of publication, publisher, authors, URL, type of study, language, time horizon, place of study, study population, study perspective, corresponding author's contact, brief summary, objectives, methodology, sample size, statistical significance, applied AI, outcome measures, such as incremental cost-effectiveness ratio (ICER), cost-benefit, QALY (quality adjusted life years), applied model, sensitivity analysis, demographic characteristics of participants, health indicators of subpopulations, access to health services, measures of equity such as odds ratio and relative risk, direction of effect (favorable or not), first analysis of methodological quality, conflict of interest, funding, transferability of results, observations.

Risk of Bias in Individual Studies and Transferability

The quality of the methodology evaluation will be assessed using the CHEC (Consensus on Health Economic Criteria) checklist [25], which includes a question on distributional effects to evaluate the equity aspects of economic evaluation studies. For selected studies that are not economic evaluations but were chosen for their equity results, the EPHPP (Effective Public Health Practice Project) quality assessment tool for quantitative studies [26] will be used to assess the risk of bias. The Welte checklist [27] will be used to evaluate the transferability.

For the CHEC checklist, points will be awarded for each of the met criteria, totaling a total of 20 items for evaluation. The point will not be awarded if the criterion is not fully met. A percentage value will be calculated based on the number of points awarded divided by the total points on the checklist multiplied by 100.

Regarding the EPHPP tool, each section will be assigned a rating of 1 (strong), 2 (moderate), or 3 (weak). At the end, a global score will be calculated according to the ratings evaluated for each section where, 1 when there is no section as weak, 2 when there is at least 1 weak section, and 3 when there are at least 2 or more weak sections.

For the Welte checklist, points will be awarded according to the following criteria: perspective (2 points), discount rate (2 points), addressing medical costs (2 points), absolute and relative prices in health care (1 point), clinical practice variability (1 point), incidence and prevalence (1 point), mix of cases (1 point), life expectancy (1 point), productivity and lost work time (1 point), making a total of 12 points. Studies that obtained a result greater than or equal to 10 points will be considered transferable.

Data Synthesis

We will create summary tables that include descriptive data from the studies, such as sample size, methods, cost-effectiveness rates, and other results. Information related to the country and health care system, year of publication, as well as the quality of methods and potential conflicts of interest, will be used to categorize results. Relevant findings from the studies will be summarized in the text. The main outcomes that we will focus on are (1) ICER, a cost-effectiveness measure that compares 2 health interventions; (2) cost-benefit results, an economic evaluation that compares the costs and benefits of a technology expressed in monetary units; and (3) equity results for studies that report them.

The methodologies used in the studies will be analyzed, and their robustness will be discussed. To facilitate comparisons between studies, all reported currencies will be converted to US dollars and adjusted for inflation using the US Consumer Price Index (CPI).

Meta-Bias

We will consider the potential for meta-bias resulting from the selective reporting of studies and outcomes, where negative results are often omitted from publication. To mitigate this issue, we will conduct funnel plot analyses to identify possible asymmetries, particularly in the context of cost-effectiveness outcomes. This is crucial as non–cost-effective results may be underreported in the literature.

Results

This systematic review began in March 2023 and has been registered with PROSPERO under registration number CRD42023407755. The literature search identified 9,526 publications and, after full-text screening, 9 publications were included in the study. Data summarization is currently

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underway. We plan to submit a manuscript to a peer-reviewed journal once it is finalized, with an expected completion date in January 2024.

Discussion

Principal Findings

The systematic review presented in this protocol aims to address the use of AI in imaging exams for the diagnosis of skin, neurological, and pulmonary diseases. Considering the challenges faced by traditional health care systems, such as patient heterogeneity, geographic disparities, and financial constraints, the integration of AI technology offers a promising avenue to enhance health care delivery [1-3]. This systematic review seeks to synthesize existing evidence to cost-evaluate AI-driven diagnostic interventions and their potential impact on promoting equitable health care.

The inclusion of AI algorithms in health care has shown promise in various domains, particularly in medical imaging analysis. AI can assist in the detection, segmentation, and classification of medical images, potentially improving clinical decision-making and reducing diagnostic errors [8,9]. Moreover, AI has the potential to streamline health care processes, minimize costs, and facilitate earlier disease identification, which is of utmost importance in the context of skin, neurological, and pulmonary diseases [9].

Equity concerns in the implementation of AI-based tools for diagnostic imaging exams have gained significant attention in recent years. While these technological advancements hold immense promise for enhancing health care outcomes, they also carry the risk of exacerbating existing disparities in access to high-quality care. A major concern revolves around the potential for bias in AI algorithms, which could disproportionately affect marginalized and underrepresented patient groups. If AI systems are not adequately trained on diverse data sets, they may exhibit biases related to race, gender, or socioeconomic status, leading to inaccurate diagnoses or recommendations for specific demographic segments. Furthermore, the significant costs of adopting AI technologies could create disparities in access, favoring well-funded health care institutions over underresourced ones. Additionally, the digital divide, wherein not all communities are afforded equal access to essential technology and infrastructure, can further compound inequities in AI-supported diagnostic imaging. Addressing these challenges in an effective manner is crucial for the equitable distribution of AI's benefits in health care, ensuring that they reach all patient demographics irrespective of their socioeconomic or cultural backgrounds [1-3].

The measurement of the economic impact of AI-based tools in diagnostic imaging holds profound significance for several reasons. First, a comprehensive understanding of this impact enables health care systems to allocate their resources more judiciously, ensuring that investments yield tangible benefits and lead to cost savings. Also, AI has the potential to optimize the use of resources and, in turn, reduce the overall expenses associated with health care delivery. Moreover, assessing the economic viability of AI tools plays a pivotal role in determining their affordability and accessibility. By discerning their cost-effectiveness, it becomes feasible to identify potential obstacles to access and devise strategies that guarantee the availability of state-of-the-art health care to all individuals, regardless of their income or geographic location. Finally, identifying AI applications with the most promising economic potential can guide investment decisions, foster innovation, and expedite the development of tools that have a positive impact on patient care.

As with any systematic review, certain limitations are anticipated. One potential limitation is the availability and quality of the included studies. Variability in study designs, data sources, and methodological approaches may present challenges in synthesizing findings and drawing conclusive results. Regarding the topic of AI, as it is a recent object of study and because terms are delimited into 3 medical areas (dermatological, neurological, and pulmonary), there may be a shortage of available primary studies. This can limit the ability to perform robust statistical analyses or draw definitive conclusions. Publication bias is also recognized, in which researchers tend to publish only positive results. Furthermore, some technologies developed in specific contexts (eg, high-income or White-majority countries) may not be applicable in other realities or countries.

Conclusions

The findings of this systematic review will hold significant implications for policy makers, health care practitioners, and researchers. By comprehensively evaluating the economic performance and equity outcomes of AI use in diagnostic imaging for skin, neurological, and pulmonary diseases, we aim to provide valuable insights into the integration of AI into clinical practice. These insights can inform evidence-based decision-making, potentially leading to more efficient and equitable health care systems.

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Data Availability

All data generated or analyzed during this study are included in this published article and its supplementary information files.

Authors' Contributions

GOS is the primary author of the systematic review, with assistance in research and protocol writing. RdMC is the secondary author and researcher of the systematic review, who provided support in research and protocol writing. RML and BCRSF are also secondary authors and researchers of the systematic review. ETR provided technical support throughout the protocol and systematic review processes. JPQdP supervised the project and critically reviewed the systematic review protocol. LRC is the main author of the systematic review protocol, responsible for project administration and supervising the systematic review.

Conflicts of Interest

The authors are participants in the Brazilian Ministry of Health through the Support Program for Institutional Development of the Unified Health System (PROADI-SUS) Banco de Imagens project, a collaboration between the Brazilian Ministry of Health and Hospital Israelita Albert Einstein, aimed at enhancing public health in Brazil.

Multimedia Appendix 1
Search strategy.
[DOCX File , 37 KB - resprot_v12i1e48544_app1.docx]

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Abbreviations

AI: artificial intelligence
CHEC: Consensus on Health Economic Criteria
CHEERS: Consolidated Health Economic Evaluation Reporting Standards
CPI: Consumer Price Index
EPHPP: Effective Public Health Practice Project
ICER: incremental cost-effectiveness ratio
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-E: Preferred Reporting Items for Systematic Reviews and Meta-Analyses with a Focus on Health Equity
PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols
QALY: quality adjusted life years

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Protocol

Co-designing a Sexual Health App With Immigrant Adolescents: Protocol for a Qualitative Community-Based Participatory Action Research Study

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Abstract

Background: Canada is one of the world's most ethnically diverse countries, with over 7 million individuals out of a population of 38 million being born in a foreign country. Immigrant adolescents (aged 10 to 19 years) make up a substantial proportion of newcomers to Canada. Religious and cultural practices can influence adolescents' sexual attitudes and behaviors, as well as the uptake of sexual and reproductive health (SRH) services among this population. Adolescence is a time to establish lifelong healthy behaviors. Research indicates an alarming gap in adolescents' SRH knowledge, yet there is limited research on the SRH needs of immigrant adolescents in Canada.

Objective: The purpose of this study is to actively engage with immigrant adolescents to develop, implement, and evaluate a mobile health (mHealth) intervention (ie, mobile app). The interactive mobile app will aim to deliver accurate and evidence-based SRH information to adolescents.

Methods: We will use community-based participatory action research to guide our study. This research project will be conducted in 4 stages based on user-centered co-design principles. In Stage 1 (Empathize), we will recruit and convene 3 adolescent advisory groups in Edmonton, Toronto, and Vancouver. Members will be engaged as coresearchers and receive training in qualitative and quantitative methodologies, sexual health, and the social determinants of health. In Stage 2 (Define and Ideate), we will explore SRH information and service needs through focus group discussions with immigrant adolescents. In Stage 3 (Prototype), we will collaborate with mobile developers to build and iteratively design the app with support from the adolescent advisory groups. Finally, in Stage 4 (Test), we will return to focus group settings to share the app prototype, gather feedback on usability, and refine and release the app.

Results: Recruitment and data collection will be completed by February 2023, and mobile app development will begin in March 2023. The mHealth app will be our core output and is expected to be released in the spring of 2024.

Conclusions: Our study will advance the limited knowledge base on SRH and the information needs of immigrant adolescents in Canada as well as the science underpinning participatory action research methods with immigrant adolescents. This study will address gaps by exploring SRH priorities, health information needs, and innovative strategies to improve the SRH of immigrant adolescents. Engaging adolescents throughout the study will increase their involvement in SRH care decision-making, expand efficiencies in SRH care utilization, and ultimately improve adolescents' SRH outcomes. The app we develop will be transferable to all adolescent groups, is scalable in international contexts, and simultaneously leverages significant economies of scale.

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KEYWORDS

adolescent health; health promotion; immigrants; information needs; mHealth; sexual and reproductive health; access to care

Introduction

Background

Canada is one of the world's most ethnically diverse countries, with over 7 million individuals born in a foreign country [1]. Globally, Canada has one of the highest percentages of immigrants, who comprise 21.9% of the total population [2]. Of all these newcomers, approximately 34% are under the age of 25, with over 60% of immigrant youth coming from Asia, the Middle East, and Africa [1]. Given these statistics, understanding health care service information needs and utilization by immigrant adolescents is vital for health care planning, policy, and delivery. Adolescence is a critical period in the transition from childhood into adulthood, during which young individuals aged 10 to 19 years undergo substantial physical, psychological, social, and emotional changes [3]. Adolescents are a vulnerable population because of their age-related psychosocial and biological changes and the challenges associated with navigating these changes [4]. As part of this development, it is common for adolescents to explore their sexual identities and feelings through sexual experimentation [5]. Depending on their knowledge about sexuality and social support, some may experience unintended consequences, such as unplanned pregnancy and sexually transmitted infections (STIs). Neglect of adolescents' sexual and reproductive health (SRH) needs can affect their physical and mental health, future employment, economic well-being, and ability to reach their full potential [6-8]. A small but growing body of literature suggests that immigrant youth lack SRH knowledge, use fewer sexual health services, and receive fewer sex education resources than nonimmigrant youth [9-11]. This difference appears to be heavily influenced by religious and cultural practices [12]. Immigrant families from Southeast Asia and the Middle East have diverse cultural and religious views on dating, relationships, adolescent sexuality, gender roles and identity, and sexual orientation [13]. Studies have shown that many immigrant adolescents find it challenging to balance family expectations, cultural standards, and religious demands; dissonance can cause internal and external conflict [13-15]. In addition, many adolescents experience intergenerational conflict, a competition between their own values and those of elders of the community [16].

Despite the large number of immigrant adolescents in Canada, there is limited research on the SRH of this population. COVID-19 pandemic–driven changes in how services are provided, such as limiting in-person care and deferring new and walk-in patients, have created barriers for adolescents to access confidential SRH information and services. Individuals may want to avoid obtaining in-person care during this time to reduce the risk of viral transmission. Hence, it is imperative to promote and adopt innovative approaches such as digital health (mobile apps, information through SMS text messaging) to deliver culturally appropriate SRH and sexuality education to immigrant adolescents in Canada. Beyond pandemic concerns, there is evidence to suggest that mobile apps have the potential to promote adolescent health [17]. This study will address these gaps by exploring the SRH priorities and health information needs of immigrant adolescents and will develop an interactive sexual health promotion mobile app for immigrant adolescents in Canada.

SRH Needs of Adolescents

The transition from adolescence to adulthood is complex, as new responsibilities materialize and confidence and independence emerge [18,19]. Yet, teens often have inadequate knowledge about the consequences of unprotected sex and are novices when it comes to implementing safe sex practices. These consequences include unwanted pregnancy, complications of unsafe abortion, and STIs [11]. In addition, due to fear, stigma, and confidentiality issues, many do not reveal their SRH problems and underutilize the health care services they need [9]. SRH is an important aspect of adolescent health and well-being, and it interconnects with various physical and mental health issues [20-22].

Globally, the SRH needs of adolescents have been largely unmet and pose a significant threat to the health and well-being of adolescents [9,23-25]. They are biologically more vulnerable to infections, more susceptible to peer pressure, developmentally more disposed to risk-taking, and lack the skills and confidence to negotiate safer sexual practices. STI rates among Canadian adolescents are on the rise [24-28]. Studies on adolescent SRH have found that the unintended teenage pregnancy rate is rising again in Canada [29]. The Canadian Community Health Survey reported that almost 15.5% of Canadian youth are at high risk of unintended pregnancy due to the nonuse of contraceptives [30,31]. The consequences of teenage pregnancy include anemia, hypertension, renal disease, eclampsia, and depressive disorders [29]. Research has found that adolescent mothers experience more mental health problems and higher rates of postpartum depression than women aged 25 and older [32]. Moreover, children of teenagers are more likely to have low birth weights and experience associated health problems [29]. Studies highlight an alarming gap in the sexual health knowledge of adolescents in Canada despite their completion of sexual education requirements in school [27,33-36]. Studies also found that sexually active Canadian teenagers commonly engage in risky sexual behaviors, including unprotected sex, multiple sexual partners, and intercourse before 15 years of age [35,37,38]. Moreover, many Canadian youths do not consider themselves at risk for HIV/AIDS, and their overall knowledge base about the disease has declined over the last 2 decades [9,39,40].

Mobile Phone–Based App to Increase Awareness and Uptake of SRH Services

Mobile app platforms have the potential to advance SRH. Nearly 100% of youth in Canada aged 15 to 24 years use the internet

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daily or own a smartphone [41]. The use of mobile technology for health promotion offers privacy [42-47], access to personalized information [42,44,46,48], and convenience [42,47,49], making it a valuable way to provide accurate information about sexual health to adolescents [43-48]. Furthermore, young people are responsive to and excited about using new technologies for SRH promotion [42,45,50,51]. Innovative ways to deliver sexual health information are more important than ever before due to the impact of the COVID-19 pandemic on access to SRH services globally [52]. The absence of adolescent SRH services from "essential" health services during COVID-19 amplifies the potential role of technology to meet the SRH needs of vulnerable groups like adolescents. Amid the pandemic, technology has largely provided the means to support the recalibration of health systems, service provision, and information delivery [53]. Just as digital behavior changes, campaigns on hand washing, social distancing, and wearing masks have supported the pandemic response, we can digitally connect with young people to support their access to SRH information and services during times of social isolation and crisis. Although there are many mobile apps addressing SRH worldwide, we could not locate any research on co-designing a mobile app to improve immigrant adolescent SRH in Canada. Research has demonstrated that access to socially inclusive and culturally relevant SRH information significantly improves SRH knowledge and communication skills with partners and parents, improves contraceptive knowledge and use, and reduces risk-taking sexual behaviors by young people [15,27,54]. Therefore, the aim of this study is to engage immigrant adolescents in developing, implementing, and evaluating a mobile health (mHealth) app that will deliver evidence-based SRH information to this population.

Methods

Theoretical Framework

Intersectionality places an explicit focus on differences among people and seeks to illuminate various interacting social factors that affect human lives, including social locations, health status, and quality of life [55]. Intersectionality asserts that people are often disadvantaged by multiple interlocking sources of oppression (ie, their race, class, gender identity, sexual orientation, religion, and other identity markers) [56]. The intersection of race, gender, age, and socioeconomic status may pose barriers to young immigrant populations seeking SRH education and services. This framework will help us understand these differences, considering gender, race, class, sexual orientation, and migration histories, as they impact immigrant adolescents seeking SRH services.

Study Design

A community-based participatory action research (CBPAR) framework will guide our study [57-61]. CBPAR is a context-specific process driven by participants that requires innovative methodological approaches [62,63]. The principal outcome of this adolescent-partnered project is to develop an mHealth intervention that responds to SRH needs. Incorporating the end users' voices into the design and development of these interventions is crucial, as it has been noted that few mobile interventions are truly effective and scalable [64-66]. A user-centered co-design approach will increase the likelihood that adolescents will use the app and that it will be scalable and transferable to other contexts. Our goal for this engagement approach is to create an environment that supports the metacriterion of respect, trust, legitimacy, fairness, competence, and accountability in the development of knowledge [66]. This project will have 4 stages based on user-centered co-design principles [67].

Key Stages of the Research Project

Stage 1: Empathize

For a user-centered design, it is important that we engage the people for whom we are planning to design the product. Therefore, we will first develop and convene adolescent advisory groups (AAGs) in Edmonton, Toronto, and Vancouver. These cities have the highest percentages of immigrant populations from all geographic locations [2,68]. Having a multisite project will help ensure that the app will reach and be disseminated to immigrant adolescents across Canada. The AAGs will participate actively throughout the project (ie, in data collection, data analysis, mobile app development, gathering feedback on app usability, and knowledge mobilization). AAGs will be informed through our national environmental scan of youth advisory groups [69]. To recruit adolescents for the AAGs, we will hire 3 research assistants (RAs) (one at each site) who are skilled in research methods and have substantial youth facilitation expertise and experience working with diverse communities. Peer RAs will also collaborate with RAs to facilitate the recruitment of participants for AAGs. AAG members will be recruited from immigrant communities, public agencies, community and recreation centers, and immigrant service agencies. Participants aged 12 to 19 years from diverse ethnic backgrounds will be invited to participate in the AAG. Based on the developmental stage of young people, particularly in terms of physiological, psychological, and social development processes, we anticipate that it might be hard for younger adolescents to share common "cultural" beliefs and values. In addition, older teens may not allow young adolescents to share their thoughts and may dismiss younger teens. To provide equal opportunity for all to participate, we will create 2 separate groups. Adolescents aged 12 to 15 years will be placed in 1 group, and adolescents aged 16 to 19 years will be in a separate group. We anticipate that a reasonable target size of between 8 and 12 adolescents will create meaningful engagement [65,69] and that we will meet for 2 hours via Zoom or Google Meet every 2 months for approximately 18 to 24 months. To foster meaningful engagement, AAG members will receive training in qualitative and quantitative methodologies, sexual health, and the social determinants of health (see Multimedia Appendix 1).

Stage 2: Define and Ideate

Overview

To explore the experiences, information needs, and challenges of immigrant adolescents related to SRH and how to address these challenges, we will conduct qualitative individual interviews or focus groups (FGs) following the CBPAR

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methodology [59,60]. SRH is a sensitive topic, and adolescents sometimes feel uncomfortable discussing their SRH needs in front of others. Participants comfortable with FGs will be invited to FGs. If participants are not comfortable, they will be invited for individual interviews.

Participants

We will recruit immigrant adolescents aged 12 to 19 years who were born in a country other than Canada and who immigrated in the last 10 years or are part of a second-generation cohort. We will focus on this age group because we aim to understand the factors in early and late adolescence that predispose young people to subsequent sexual health risks. In addition, adolescents aged 12 to 19 years are generally mature enough to participate in individual interviews or FGs [70-72].

We will use a multifaceted, community-based strategy to recruit immigrant adolescents from diverse ethnic groups. Public, community, and immigrant service agencies will support participant recruitment. In addition, social marketing campaigns (eg, Instagram advertising as well as posting of study ads by youth and health-oriented organizations) and snowball sampling will be used to recruit participants. Peer RAs and graduate RAs hired as part of this project will also assist with recruitment. We will also include non-English speaking participants. Our peer RAs are bilingual, and we will hire multilingual graduate RAs for this project who speak Canada's most common languages other than English to provide safe interpretation services for participants who do not speak English fluently.

We will conduct between 20 and 25 individual interviews or 3 to 4 FGs in each city. The participants for FGs will be divided into 2 groups (12 to 15 years and 16 to 19 years) to ensure that our data also capture the SRH needs of younger teens. The individual interviews or FGs will occur in person or over Zoom. The final sample size will be based on data saturation [73]. Individual interviews and FGs will be consistent in their delivery. Discussion topics will focus on issues related to SRH, sexual orientation, gender identity, sexual health history, dating and relationship experiences, source of information about SRH, cultural relevance and trustworthiness of those sources, challenges to receiving SRH information and services, and familiarity with SRH mobile apps and websites. We will conduct separate FGs for male and female participants and a mixed-gender FG based on participants' comfort and availability. Transcripts will be digitally recorded and transcribed verbatim by a professional.

Data Analysis

In accordance with CBPAR, we will use the DEPICT (dynamic reading, engaged codebook development, participatory coding, inclusive reviewing and summarizing of categories, collaborative analyzing, and translating) model for participatory analysis (Multimedia Appendix 2) [74]. Data analysis will occur in four stages: (1) conversations will be digitally recorded and transcribed verbatim by a professional transcriptionist; (2) 2 graduate RAs, peer RAs, and 2 members of the research team will read transcripts in detail several times; (3) the nominated principal applicant and the principal applicant will lead the team in conducting open coding of all transcripts and then group codes into preliminary themes using thematic analysis [75]. The themes will be presented to the larger investigator team and AAGs for feedback and additional comments, which will then be incorporated into the analysis; and (4) themes across cases will be grouped into an organizational framework. To achieve reliability and validity and to ensure rigor, we will employ verification strategies that will identify when to continue, stop, or modify the research process. Verification strategies will include (1) methodological coherence, ensuring congruence between the research questions; (2) appropriate sampling to ensure efficient and effective saturation of categories with optimal quality; (3) collecting and analyzing data concurrently; (4) developing a coding system that will be discussed and verified with research team members and AAG members; (5) keeping a detailed audit trail and field notes [76]; and (6) member checks. Then, we will share the transcripts, results, analyses, and reports with participants so they can review and provide feedback on the results and analyses. NVivo software (version 12; QSR International) will be used to manage the data analysis process.

Stage 3: Prototype

Informed by the Stage 2 findings and with integrated, continuous input from the AAGs, we will develop a prototype of a mobile app to house SRH content. The content of the app will stem from two primary sources: (1) evidence-based resources such as the Society of Obstetricians and Gynecologists of Canada, the Public Health Agency of Canada, and the World Health Organization; and (2) themes and experiences generated from individual interviews and FGs in Stage 2. The app will include age-specific information separately so that adolescents of different age groups can easily navigate the information related to them. In addition, information related to accessing SRH services will also be provided to connect adolescents to SRH services in their community.

The AAGs and peer RAs will work with the app developer to iteratively revise and build the app to address questions of clarity, potential sources of bias or marginalizing design elements, ease of use, relevance, and other factors determined by the AAGs. The app will use an internal analytics system to run analysis on user demographics, feedback, and content views to gather information on how the app is being used. The app content will be approved by team members who have expertise in SRH to ensure evidence accuracy and appropriate evidence interpretation. We will initially develop the interventions in English only to consolidate the findings and best practice functionality. Once the app has demonstrated usability and effectiveness in English, we plan to apply for new funding to translate the app content into languages used by immigrant communities.

Stage 4: Usability Testing of Mobile App Prototype

At the end of the project, we will run several FGs to evaluate the usability, acceptability, and effectiveness of the app; seek further input for refining it; evaluate the effectiveness of the project; and seek direction for future research. For usability testing of the app, we will conduct (1) 6 FGs with 5 to 10 immigrant adolescent participants (n=30-60) in Edmonton, Toronto, and Vancouver (2 FGs in each city) and (2) 3 FGs

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with 5 to 8 service providers, policy makers, and members of the communities' informal support channels (n=15-20).

At the start of each FG, participants will be asked to download the app and use it on their own. Then, the researcher will begin the FG. Semistructured FGs will focus on questions about the app informed by a systematic search of over 180 usability evaluations [77]: participants' views, their preferences regarding receipt of health information, useful attributes, unhelpful elements, perceptions of the utility to improve adolescent's SRH, and recommended revisions and additions. Each aspect of the app (eg, narrative, visual appeal, audio appeal, health information, engagement, and interactivity) will be explored in the FGs. Interviews will be audio recorded, transcribed verbatim, and thematically analyzed [75]. We will integrate these findings into the app. The final version will then be disseminated using established social media platforms, such as TikTok, Twitter, and Instagram. The AAG members and peer RAs will participate in dissemination activities. The app will be available for free download on the Apple App Store and Google Play. In the future, we will conduct pragmatic trials to evaluate the app's effectiveness in improving SRH outcomes for adolescents.

App Sustainability

This study will develop a holistic, prescriptive model that can be used to ensure the sustainability and scalability of mHealth apps in the public health care sector in Canada and other countries. Our long-term community partners in all 3 cities will support the sustainability of the app. These organizations will host the app, as they need an evidence-based tool to help immigrant adolescents increase their awareness and uptake of SRH services to improve SRH outcomes.

Ethics Approval

This study received ethics approval from the University of Alberta Ethics Board (Pro0013664).

Results

Recruitment and data collection will be completed by February 2023, and we will begin co-designing the mobile app in March 2023. We expect to share a prototype of the app, gather feedback on its usability, and then refine and release the app in the spring of 2024. We will engage immigrant adolescents and service providers as partners in the development of the mobile app to ensure that immigrant adolescents are aware of this tool and will use the app, helping contribute to positive SRH outcomes. This study will also evaluate the usability of the mobile app. In the future, we will conduct pragmatic trials to evaluate the effectiveness of the app in improving the SRH outcomes of adolescents.

Discussion

Expected Findings

This study aims to develop a mobile SRH app designed by and targeted to immigrant adolescents in Canada. Our exciting and novel adolescent-engaged methods and mobile app have the potential to rapidly address the unmet SRH needs of immigrant adolescents and to improve the SRH of immigrant adolescents across Canada. This app is important because it allows immigrant adolescents to independently access resources related to SRH and mitigates the impact of familial bias on teens' ability to seek out such information. Further, young people are very comfortable utilizing mobile apps. This engaging modality will make it easier for immigrant adolescents to learn about safe SRH practices and may support them in having the knowledge and motivation to access services. The expected outputs of this study include:

- We will be able to identify the SRH needs of an underresearched population (ie, immigrant adolescents) in Canada.
- Voices of the full spectrum of gender diversity (including transgender and gender nonconforming adolescents), cultural knowledge, and agency will inform the mobile app.
- An innovative, adolescent-centered knowledge translation tool (ie, the mobile app) will be developed to help improve the SRH of immigrant adolescents in Canada.

The potential impact of this mobile app development includes increasing SRH knowledge and awareness, access to SRH services, and the use of contraception while decreasing unintended pregnancies and the need for abortion among adolescents. Our overall program of research is to build upon the active engagement of immigrant youth to develop, evaluate, and implement innovative and evidence-based digital knowledge translation tools and to build the resilience that immigrant youth need to successfully integrate into Canadian society. This research epitomizes creativity and innovation by merging the arts, sciences, and the engagement of youth in research.

Conclusion

Targeting adolescents and using engaging modalities has a strong potential to effectively increase their involvement in SRH care decision-making, expand efficiencies in SRH care utilization, and ultimately improve adolescents' SRH outcomes. We will disseminate the mobile app, along with other findings of our study, via community symposiums; public training sessions in Edmonton, Toronto, and Vancouver; and a website hosted by the University of Alberta Faculty of Nursing. Our findings will also be presented at academic conferences and published in open-access, peer-reviewed journals, advancing the body of knowledge on immigrant adolescents' SRH needs.

Acknowledgments

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Data Availability

The data generated during this study are not publicly available yet because data collection is ongoing, and results have not yet been analyzed. However, data collection materials are available from the corresponding author upon reasonable request.

Authors' Contributions

SM designed the study protocol and wrote the initial manuscript draft. All authors made substantial contributions to revising the initial manuscript and read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Adolescent advisory group training activities.
[DOCX File , 15 KB - resprot_v12i1e45389_app1.docx]

Multimedia Appendix 2
DEPICT steps, roles, and guiding questions.
[DOCX File , 14 KB - resprot_v12i1e45389_app2.docx]

Multimedia Appendix 3
Canadian Institutes of Health Research / Instituts de recherche en santé du Canada (CIHR/IRSC) - Operating Grant: Early Career Investigator Grants in Maternal, Reproductive, Child & Youth Health/Subv. de fonct.: Subventions de chercheurs en début de carrière en santé maternelle, en santé reproductive, et en santé des enfants/adolescents - Committee/Comité: Operating Grant: New Investigator Grants in Maternal, Reproductive, Child & Youth Health/Sub. de nouveaux chercheurs en santé maternelle, santé reproductive, et enfants/adolescents (Canada).
[PDF File (Adobe PDF File), 116 KB - resprot_v12i1e45389_app3.pdf]

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Abbreviations

AAG: adolescent advisory group
CBPAR: community-based participatory action research
DEPICT: dynamic reading, engaged codebook development, participatory coding, inclusive reviewing and summarizing of categories, collaborative analyzing, translating
FG: focus group
mHealth: mobile health
RA: research assistant
SRH: sexual and reproductive health
STI: sexually transmitted infection

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Protocol

Strengthening Digital Transformation and Innovation in the Health Care System: Protocol for the Design and Implementation of a Multidisciplinary National Health Innovation Research School

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Abstract

Background: Digital health technologies have the potential to transform health care services to be more cost-effective, coordinated, and accessible on equal terms for entire populations. In the future, people will be assisted by such technologies to monitor their health status, take preventive measures, and have more control of their health situation. An increase in digital supplementation or substitution of physical care visits can potentially add value to patients and care providers by increasing accessibility, safety, and quality of care. However, health care organizations struggle with the challenges of developing and implementing digital health technologies and services in practice. As a response to this, we have developed a national multidisciplinary research school to increase competence and capacity for research on the development, implementation, and dissemination of digital health technology solutions. The overall aim of the research school is to increase national competence and capacity for the development, implementation, and dissemination of digital health technology to increase the preparedness to support and facilitate the ongoing digital transformation in the health care system.

Objective: The purpose of this paper is to outline the protocol for the development and implementation of a national multidisciplinary doctoral education program of health innovation supporting digital transformation in the health care system.

Methods: A national multidisciplinary research school for health innovation was planned in collaboration between 7 Swedish universities and their partners from industry and the public sector. The research school will run over 6 years, of which 5 years are dedicated for the doctoral education program and 1 year for the project start-up and closing. In this paper, we outline the methodological approach of the research school; the combining of knowledge and expertise of the universities that are important to run the research school; the jointly formulated research-oriented and societally relevant research focus, goals, and objectives for the research school; the established and developed relationships with partners from industry and the public sector for joint research training projects; the forms of collaboration in the research school; and the format of the doctoral education process.

Results: The research school was funded in December 2021 and started in March 2022. The research school starts with an initiation period from March 2022 to December 2022 where the infrastructure and the action plans to run the school are set up. The PhD projects start in January 2023, and these projects will be completed in 5 years. Additional activities within the research program are doctoral courses, networking activities, and dissemination of results.

Conclusions: The network of several partners from industry, public sector, and academia enables the research school to pose research questions that can contribute to solving relevant societal problems related to the development, evaluation, implementation, and dissemination of methods and processes assisted by digital technologies. Ultimately, this will promote innovation to improve health outcomes, quality of care, and prioritizations of resources.

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KEYWORDS

digital health technology; doctoral education; health; health care; health innovation; implementation; improvement; innovation; research school

Introduction

Background

Health care systems around the globe are facing major challenges and need to adapt to changes in demographics and patient needs, transitions from hospital care to home care, limitations in recourses, and requirements for reducing costs while maintaining and improving the quality of care [1,2]. One of the most important resolutions to support and facilitate this ongoing transformation of the health care system is through digitalization [3,4]. Advances in digital health technologies could both reduce costs and revolutionize health care. However, the uptake of health and welfare technology is often slow and with variable results [5]. Thus, the success of digitalization places great demands on the health care system and requires specific competences and close collaboration with industry and universities.

The Sustainable Development Goals for health and well-being lay out ambitious targets for disease reduction and health equity for 2030 [6]. Health systems are highly labor intensive, and health care providers and professionals play a key role in transforming the health care system to achieve these goals. However, an effective health care delivery system also depends on the coproduction with patients [7,8]. In Sweden, the health care reform *God och nära vård* (Good and close care) emphasizes the role of the patients as an active agent in their own care and the health care systems need to revise the focus of care processes, from organizational perspectives to the care pathways of patients [9]. Swedish health care has historically invested in emergency hospitals and specialist care rather than primary care and home care. This has resulted in a health care system that, in international comparison, is of high quality in terms of medical results, but has poor results in continuity, patient participation, and accessibility [9-11]. Thus, a transition of focus of care from organization to patient-provider relationship perspectives, from being reactive to proactive, from being fragmented to coherent, and from seeing patients as passive recipients to becoming active actors is desirable [9]. To be able to respond to these new demands and expectations, educational, research, and innovation initiatives need to address the ongoing digital transformation of health care, to ensure health care professionals can make use of such opportunities [12,13].

The definition and meaning of digitalization are broad and can, in the health care context, be understood as the use of a variety of converging digital tools and systems, such as wireless sensors, information systems, social networking, and mobile connectivity in health-related products and services, that is, a technology-based intervention that aims at maintaining or promoting health, well-being, quality of life, or increasing efficiency in the service delivery system of welfare, social, and health care services, while improving working conditions of the staff [14]. Digital health technologies will, in the future, increasingly enable people to better monitor their health status, take preventive measures, and take more control of their health situation. Such supplementation or substitution to physical care visits can potentially create value to patients and care providers by increasing accessibility, safety, and quality of care [15]. However, many health care systems struggle with the aspiration to stimulate the development and implementation of digital health technologies and services, as part of an undertaking to improve and evaluate health system performance [16,17]. A major challenge when it comes to the use of digital innovations for the transformation of health care is the dissemination and implementation in practice and to make sure it results in actual improvement and value for patients and the health care system [18,19]. The prolonged time for translating research into practice needs attention and improvements to be based on increased influence from patients, clients, and practitioners [20]. There is scarce evidence about how digital health technologies are implemented in health care practice and how they improve health care and health outcomes in patients [18,21]. Given this context, there is a need for additional educational offerings and research about the benefits of the process of digitalization of health services and how they outweigh efforts made and investments in costs [22]. This points to a need to advance theory and empirical evidence on coproduction requirements of digital technologies in the health care sector and opportunities to bring together insights from research on technological development and existing knowledge about innovation, implementation, and improvement science.

As a response to this challenge, we have developed and recently established a national multidisciplinary research school for health innovation in collaboration between 7 Swedish universities and their partners from the industrial and public sectors. The ambition of the research school is to strengthen the national capacity for health care improvement through digital health innovation and to significantly increase competence in the industrial and public sectors. Through enhanced collaboration across academic, industrial, and public sector partners, the overall purpose of this research school is to increase national competence and capacity for the development, implementation, and dissemination of digital health technology to increase the preparedness to support and facilitate the ongoing digital transformation in the health care system.

The intention of the research school is for all partners to benefit from each of the specializations, positions, and expertise, to create a multidisciplinary learning environment with added value for the doctoral students, the involved researchers, and partners. Through this environment, the participating partners

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will develop expert competence in areas directly relevant for their business and increased capacity for research and development in the long term. Additionally, access to and broadening of already existing networks and international collaborations will increase.

Aim

The purpose of this paper is to outline the protocol for the development and implementation of a national multidisciplinary doctoral education program of health innovation supporting digital transformation in the health care system.

Methods

Research School Approach

The research school will use a coproduction approach [23] as a theoretical and methodological starting point. Coproduction is proposed as a means to deal with different forms of uncertainty and the complex nature of problems, both in the present and in the future. The approach is value driven and built on principles of shared power and reciprocal exchange between diverse stakeholders. Coproduction processes can harness the synergistic effect of collaborations and offer insights into experience, inspiration, values, goals, and shared vision among stakeholders. This project further involves creating permanent structures for coproduction through building a network for communication of results and impacts, strengthening translation of the knowledge generated in the research school into practice.

A collaboration network of universities, companies, and public sector organizations in Sweden was established during 2019-2021 (prephase) to create a closer connection between research, higher education, health services, and industry through the formation of a research school. The process started and formed the basis for a 2-year coproduction prephase that resulted in a structure and guidelines for running the research school. During the 2-year coproduction prephase, the 7 universities met biweekly, with workshops and meetings being held with companies, regions, and municipalities in several stages to explore what values were of importance for them. This prephase also aimed to narrow down which collaborators were potential participants in the research school. Letters of intent were written with those who were interested in joining the research school, and at a later stage final agreements were written.

The research school runs over 6 years (between 2022 and 2027), of which 5 years are dedicated for the doctoral education program and 1 year for the project start-up and closing. In the following section, we outline the approach and structure of the research school. First, we present the combining of knowledge and expertise of the universities that are important to run the research school. Second, we describe the jointly formulated, research-oriented, and societally relevant research focus, goals, and objectives for the research school. Third, we describe the established and developed relationships with partners from industry and the public sector for joint research training projects. Finally, we present the forms of collaboration in the research school and the format of the doctoral education process.

Combining of Knowledge and Expertise From the Universities to Run the Research School

The 7 universities committed to the research school formation all have research specializations related to the area of digitalization in health care, in different academic disciplines. The 7 universities together have 16 doctoral education programs in different subject areas related to the intention of the research school (Table 1); 9 of these doctoral programs are connected to the theme “Supporting real-world implementation,” 4 are connected to the theme “Developing valuable digital technologies,” and 3 are connected to the theme “Coordinating and optimizing the innovation process.” Some of the universities have doctoral education programs in more than 1 subject area. Accordingly, the universities contribute to the research school with doctoral education programs in different subject areas which, based on both similarities and differences, create unique perspectives to the 3 overall themes in the research school. This will make the scope of the research school broad and allow for cutting-edge research on different multidisciplinary aspects of health innovation. An important value is that the universities contribute to lectures, seminars, and supervision held by leading national researchers. Thus, the 7 universities collaborating on this effort are, in terms of areas of strength, both supporting and complementing each other.

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Table 1. Contributions and scientific position of the participating universities.

Participating university/institute	Subject areas	Theme contributions[a]	Research specializations	Research initiatives and centers	Innovations centers[b]
Blekinge Institute of Technology	Applied health technology	Technologies	Gerontechnology	SNAC[c]	Health Technology Research Lab
Halmstad University	Information technology, innovation science, health, and lifestyle	Technologies, implementation, and innovation	Health innovation and information-driven care	RFI[d], CAISR Health[e], and IDC[f]	Leap for life
Jönköping University	Health and care science, welfare and social science, disability research	Implementation	Quality improvement, innovation, and leadership in health and welfare	Jönköping Academy for Improvement in Health and Welfare	—[g]
Mid Sweden university	Health science, quality management	Implementation	Rehabilitation science and quality technology and management	—	—
Mälardalen University	Health and welfare, embedded systems, innovation, and product realization	Implementation and innovation	Medical and health technology for diagnosis and prevention	Embedded sensor systems for health plus	—
University of Skövde	Health science, information technology	Technologies and implementation	Health in the digital society	INFINIT[h] and DHEAR[i]	—
University West	Work-integrated and workplace learning, production technology	Implementation and innovation	Work-integrated learning	LINA[j] and LOV[k]	Health Academy West

[a]Technologies (Developing valuable digital health technologies), implementation (Supporting real-world implementation), innovation (Coordinating and optimizing the innovation process).

[b]The 7 universities have a history of research and education in complementary areas relating to health innovation. A distinguishing feature of this research and education is a high degree of collaboration and coproduction with industries and public sectors and strategic ambitions that combine goal setting for achieving both scientific excellence and value creation in society. Each university has specific research areas and specializations that position them nationally and internationally, and that contribute in different ways with relevant and specialized input to the 3 research themes of the research school (Table 2). The intention of the research school is to benefit from each of the specializations, positions, and expertise, and thereby create a multidisciplinary learning environment with added value for the doctoral students, the involved researchers, and partners.

[c]SNAC: Swedish National Study on Ageing and Care.

[d]RFI: research for innovation.

[e]CAISR Health: Center for Applied Intelligent Systems Research Health.

[f]IDC: information-driven care.

[g]Data not available.

[h]INFINIT: Research directed towards the generation, quality assurance, analysis and visualization of data using information technology systems and models.

[i]DHEAR: Digital Health Research.

[j]LINA: learning in and for the new working life.

[k]LOV: learning and caring for sustainable health.

Table 2. Themes of health innovation for successful transformation of the health care system.

Theme	Focus
Developing valuable digital technologies	Focus on the coproduction of digital technologies that address the needs of stakeholders and users, and can be adopted easily in practice
Supporting real world implementation	Focus on the coproduction of theoretical and applied knowledge on challenges and opportunities of implementing digital technologies in health and welfare
Optimizing adoption and diffusion of health innovations	Focus on the coproduction of improvement processes in health and welfare transformation

Research Focus, Goals, and Objectives for the Research School

In designing the research school, a multidisciplinary approach is taken to integrate theoretical, empirical, and experiential knowledge from the 16 doctoral education programs at the 7 participating universities relating to the entire health innovation pathway. By combining the 16 doctoral education programs the aim is to integrate research of different content, from different perspectives, supported by unique specializations and methodological competencies. Based on several discussions and multidisciplinary workshops between the universities, 3

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overarching and interdependent themes of digital innovation for successful transformation of the health care system are defined (Table 2) for the research school: (1) Developing valuable digital health technologies, (2) Supporting real-world implementation, and (3) Coordinating and optimizing the innovation process (Table 2).

The studies within the themes will focus on 6 identified overarching research questions to which the doctoral projects relate and contribute with new knowledge:

- How health innovations can be developed, implemented, and evaluated to provide various actors with knowledge and support to achieve high-quality services and improved health outcomes for user groups? (Themes 1 and 2)
- How user and stakeholder needs and involvement can be applied to overcome barriers in the coproduction of health innovations—in the spectrum from problem elicitation to implementation? (Themes 1 and 2)
- How knowledge and understanding from private and public stakeholders can improve the capacity for quality improvement and innovation in health and welfare? (Themes 2 and 3)
- How can the multidimensional effects and values of innovations in health and welfare be evaluated on individual and system levels? (Themes 2 and 3)
- How health innovations can be integrated into business models and long-term strategies within private and public sectors? (Themes 1 and 3)
- How private and public partners can collaborate to implement digital technologies for sustainable adoption and diffusion within health and welfare? (Themes 1-3)

The most important goal of the research school is the opportunity for participating partners to create expert competence in areas directly relevant for their business. The more long-term goal for the partners is to increase competence and capacity for research on the development, implementation, and dissemination of digital health technology solutions.

Established Relationships With Partners From Industry and the Public Sector for Joint Research Training Projects

In the research school formation, it was decided that all doctoral students should be employed by the partner industry or public sector organization, and that at least one senior mentor should be tied to the project. The partners could then choose whether to have additional members active in the research school network.

An essential part of the uniqueness of the research school is related to both industry and public sector being part of the constellation. It is otherwise difficult for the public and private sectors to get access to each other's needs and demands, which is crucial for both parts to be successful in the digital transformation of health care. By having these different types of organizations represented in the research school network, activities can focus on raising important questions related to the challenges of working within this sector.

Every company will contribute with their specific expertise in their area, which brings a variety of perspectives to the 3 overall themes in the research school and increases the relevance and impact of the research. Some companies are well established within the health care sector, whereas others see this as an opportunity to gain insights into a new market area. The public partners (regions and municipalities) participating in the research school contribute with contextual competence and understanding of the needs, problems, and challenges they face in their operations. In total, the research school comprises partners from 10 companies and 10 public sector organizations, besides the 7 universities.

Further, the research school establishes a network to create personal relationships between the companies' strategic functions (eg, research and development, managerial levels) and customer representatives (eg, managers of strategic and care departments in the public sector), which are functions that do not often meet in business relation procedures. The research school thereby creates opportunities for participants to discuss common challenges from a strategic or managerial point of view. Integrating these activities within the research school will facilitate learning opportunities for the doctoral students, who are likely to become valuable resources in the companies' and public organizations' future strategic work. The partners are responsible for aligning the research questions with challenges relevant to the industry, regions, and municipalities. Their commitments are both to their research project and to that of the research school and they will take part in annual network meetings, providing study visits and contributing to the management of the research school.

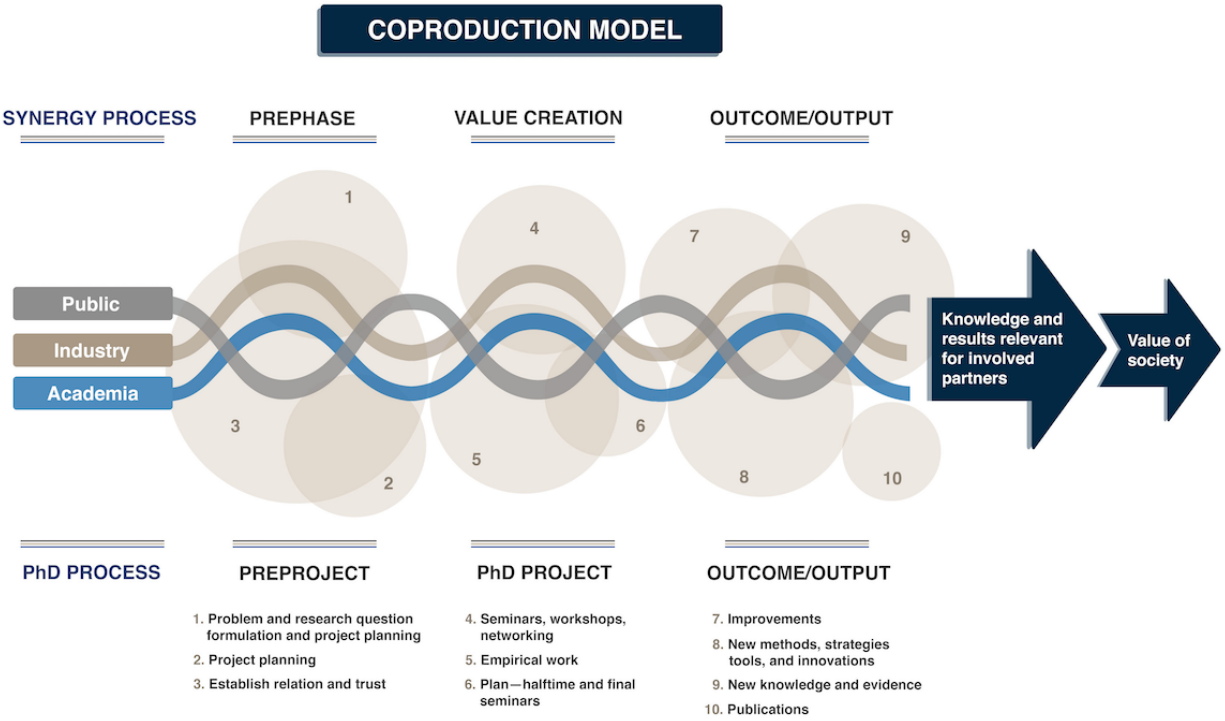
Forms of Collaboration Within the Research School

Overview

The research school will follow an established process of working in coproduction (Figure 1), which means that researchers and partners come together to share and create knowledge that can be used to face the current digital challenges in health care, while increasing capacity to problem solving in the future. The coproduction approach intends to support learning across partners with the purpose to create new practices for research collaboration that better address real-world problems and mirror the complexities we are facing regarding digitalization in health care.

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Figure 1. Coproduction model in the research school.



The model presented in Figure 1 is inspired by Sannö's model [24] and illustrates how value can be developed throughout the research school process, from the preproject initiatives taken to connect interested parties to a research school, through finding the common themes, needs, and contexts that such a research school wishes to address, and then to actual implementation of the project. The model describes our 2 main processes, both the individual PhD process and the synergy process between partners, within the research school.

Initially, different partners come together to jointly discuss the real-world problem, discuss the key assumptions, prerequisites, purposes and rules of the collaboration, and build trust. In relation to the PhD process, the doctoral students and their supervisors and mentors jointly formulate the problem and research questions as well as design the project. Following this, the value-creation chain for the research school starts, where all partners are engaged in mutual learnings in seminars, workshops, and networking activities. Thus, new knowledge and results for all involved partners are discussed and transferred between partners and integrated to reach new and more comprehensive knowledge in relation to the problem. The doctoral students work on their dissertation project, conduct joint courses within the research school, and participate in seminars and other research activities, in addition to the requirements of their respective doctoral education program. Finally, the comprehensive and solution-oriented knowledge, results, and publications generated in the research school are evaluated in terms of their relevance and impact in relation to the problem being addressed and converted into improvements, new methods, solutions, strategies, and innovations of relevance for included partners.

One of the main tasks of the research school is to arrange joint activities for all partners in the research school, to provide a learning environment focusing on relevant topics related to the scope, the research themes, and the overall research questions of the research school (Table 3).

The aim of the activities is to enrich the progress and training for the doctoral students, as well as strengthening collaboration and coproduction between participating organizations. The legitimacy and relevance of the activities are ensured by creating learning meetings and a learning organization where all participants are actors in the process. Common research questions and results are expected to arise as an outcome of all the different types of activities performed in the research school. The doctoral students' contribution to a common area of knowledge, in this case related to the 3 themes of the research school, will highlight the expertise that is developed through the research school. By emphasizing the multidisciplinary perspectives that are combined and encouraging contribution to an increased understanding of other perspectives, the knowledge that is created between the different projects goes beyond the scope of the individual project. This is where interesting aspects arise, such as potential synergies and contradictions. To enable impact of this approach, it is of importance to involve both supervisors and mentors, as well as other organization representatives, to take an active part in the research school activities.

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Table 3. Types of joint activities for all partners in the research school.

Activity	Format	Content	Purpose
Seminars and networking activities	Two-day network activities every 6 months for all participants of the research school (ie, doctoral students, supervisors and mentors, academic stakeholders, company and public organization representatives) ambulating between the participating universities.	Activities will range from lectures to sharing progress reports, seminars, workshops, and study visits. Activities will be designed to meet the partner's needs and focus on the 3 research themes of the research school.	To give stakeholder groups a chance to meet in various constellations, to identify, develop, and share both specific and generic commonalities and knowledge development.
Doctoral students' network	Several meetings per year with physical meetings specifically targeted to the doctoral students concurring with international conferences, the joint network days, and the doctoral courses. Digital meetings will be held in between to facilitate continuity in interaction.	Activities will circle around doctoral education domain–specific topics and the 3 themes of the research school and will form a tight constellation among the doctoral students.	To enrich the doctoral students at both a professional and a private level, aiming for connections for future collaborations.
Supervisors and mentor activities	Several meetings per year concurring with the joint network days.	Activities will be in a workshop format and include supervisors and mentors from both university and partners.	To delve into the role as supervisor and mentor, coproduction experiences, scientific course development, and questions on dissemination and impact.

International Collaborations

For the research school to be successful it needs to be grounded in international state-of-the-art science and based on cooperative research involving international collaborations. The universities and many of its researchers have established international partners and ongoing research based on existing international networks. The same applies to most of the business and public partners. It is one of the goals of the research school to deliver added value to participating organizations by accessing new, and broadening already existing, networks and striving to further enable and broaden international collaborations. Another goal will be to strive for an understanding of what kind of mechanisms the partners need to be aware of when approaching new markets or diffusing research results and health innovations internationally. The research school will work in several ways to address the internationalization goals. To navigate and receive the best knowledge exchange and outcomes from international collaborations, doctoral students, their supervisors, and the partners need an intercultural and multidisciplinary competency, which will therefore be included as part of the research school's network activities. The joint network's meetings and specific seminar sessions will address the topic, and relevant guest speakers will be invited. Another approach will be to encourage and support international mobility, such as study visits to international universities, research institutes, or companies suitable to the contexts of the student's projects. The students will also be encouraged to participate in international conferences or longer stays at international research institutes, companies, or universities. If possible, a larger group of participants from the research school should aim to jointly attend, thus make a significant impact on the content of a relevant international conference.

Organization and Management

As the research school is a collaboration between numerous partners from industry, academia, and public organizations, appropriate project organization and management are crucial to achieve targeted outcomes and set goals for the doctoral students as well as research and educational environments of the participating universities and industry and public partners (Table 4). The management structure aims to strengthen the dialog and transparency between groups and boards when devising, implementing, and assessing strategies and goals in the research school.

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Table 4. The format, role, and purpose of different groups in the research school.

Group	Format	Role	Purpose
Steering group	Twice per year	Oversees that the research school's goals and outputs are achieved and suggests actions if required	To provide strategic development advice for the management group and provide support, guidance, and oversight of the progress and direction of the research school
Management group	Every week in the initial phase (first year) and thereafter every second week	Manages all organizational and scientific processes	To coordinate all partners and ensure that the goals of the research school can be achieved at high quality and have an impact
Operational group	Every second week	Executes all activities, such as reports, budget follow-up, routine setup, and communication	To ensure quality control processes and goal fulfillment
Supporting staff	Continuous	Runs local budget administration, local communication, local doctoral student administration, and coordination of tasks related to partner organizations	To assist in execution and securing alignment with the local routines, regulations, and organization of the universities
Scientific advisory board	Once per year. Includes 5-7 senior researchers	Provides advice and support to the management team in scientific issues related to needs, relevance, development, content, focus, and aggregated results and synergies	To represent the themes of the doctoral program
Stakeholder advisory board	Once per year. Includes 5-7 stakeholders	Provides support and guidance by contributing with expertise and experience-based knowledge and skills relevant to the projects	To identify and support opportunities for synergies, dissemination, and implementations

Format of the Doctoral Education Process

Credits for the Doctoral Program

A PhD degree in Sweden requires 4 years of full-time studies and a total of 240 higher education credits. At least half of these credits should be connected to the thesis. The doctoral students within the research school must acquire their PhD degree within 5 years of studies, of which 80% are spent on their studies and the remaining 20% on ordinary organization-specific work tasks.

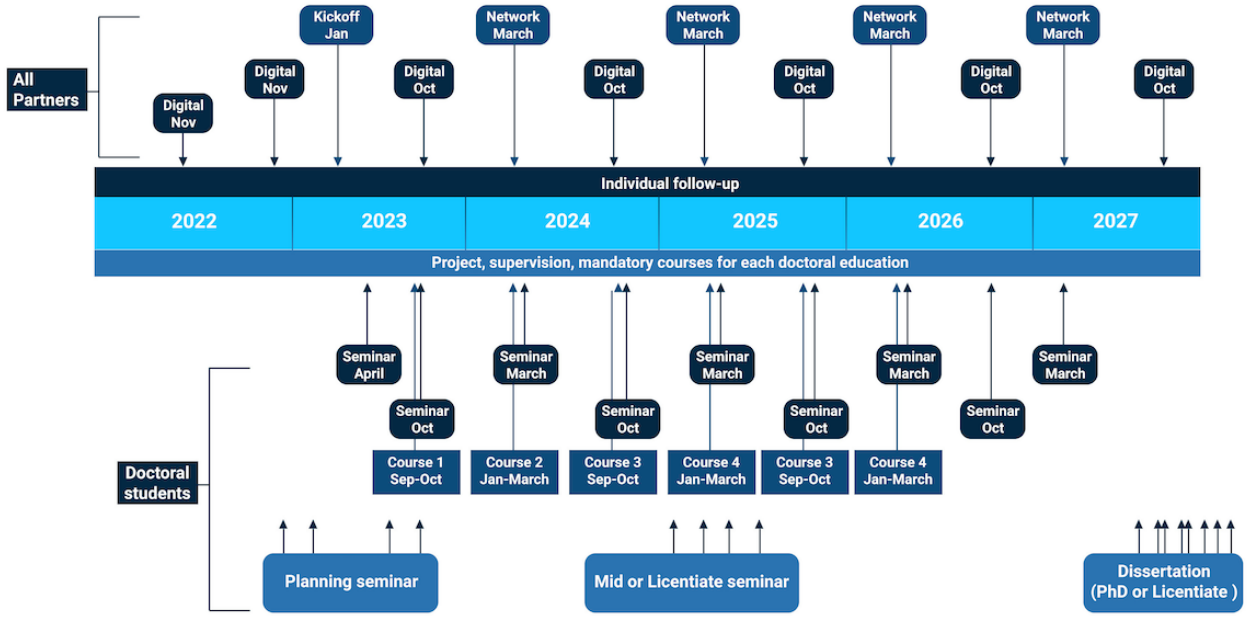
The students within the research school will follow the rules and regulations applied to the respective doctoral education, as specified in the general syllabi. Students participating in the research school, however, can specialize and receive significant added value through the research school activities and the large collaborative network that they are a part of (Figure 2). The research school organizes regular network activities for students, supervisors, and industry and public organization partners, in the form of networking days, consisting of lecturers, seminars, workshops, and study visits. The activities focus to a large extent on creating a collaborative environment between these stakeholders, and facilitate discussions supporting the common goals, challenges, commonalities, and state-of-the-art related to digitalization in the health and health care sectors. This approach should lead to a close contact network between the doctoral students, the cluster of supervisors, partner representatives, and the project organization, which can form support structures related to the doctoral education programs and foundations for further collaboration in other forms. It is, however, important that students participating in the research school are not added an extra amount of workload compared with the fellow doctoral students at their doctoral education programs. Therefore, the supervisory role within the research school is important so that research school activities can be acknowledged as results within the doctoral education, and that compulsory elements in the doctoral education are not duplicated in the research school.

In the doctoral education process, there are several checkpoints (Figure 2). These will be followed up by the research school management group, although formally administered by the university doctoral education. After being admitted to 1 of the doctoral education programs, an individual study plan will be drawn up within the first 3 months and will thereafter be updated once a year. This is the formal document explaining the progress of the student throughout the doctoral education program, and its role and use are highly regulated in the Swedish Higher Education Act (Högskoleförordningen 1993:100). The student's research proposal plan is also finalized within the first 3 months and revised continuously as the project progresses.

The doctoral students present their project progress on at least three occasions within their doctoral education program (ie, a research proposal seminar, a midterm seminar, and a dissertation seminar), and in at least two other occasions during network activities in the research school (at doctoral and joint network activities; Figure 2). The presentations during network activities have specific focus on the impact of results in the own (or other) organizations or society.

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Figure 2. Format of the doctoral education process.



Recruitment and Admission of Students

The research school has 2 admissions. The research school allows for a total of 10 industrial doctoral students and 10 doctoral students from regions and municipalities that are publicly funded in the first admission. A potential second admission will add another 10 industrial doctoral students, and again matched by an equal number of students from public sector organizations.

To be admitted to the research school, the doctoral student will be assessed and able to qualify in accordance with the general syllabi at the doctoral education program at the university where the student is to be enrolled. Further, the student will have their employment at the participating company or public sector organization. The doctoral students can be someone already employed at the company but can also be a new recruitment for the specific project. In cases of new recruitments, the recruitment process will be led by the company or public sector organization, with support from the local research school manager and potential supervisors of the admitting university.

The doctoral student will be enrolled in the doctoral education program with the most suitable subject area related to the project. The admitting university is responsible for the administration related to the enrollment of each doctoral student and for making suitable supervisors available for the project.

Supervision of Doctoral Students

Each doctoral student has a main supervisor, 1 or 2 assistant supervisors from the universities, and a mentor from the organization where they are employed. If applicable, an assistant supervisor can be affiliated to 1 of the other participating universities to build relations between universities, ensure valuable knowledge transfer, and enrich the project. All supervisors are expected to participate in the research school activities. Mentor candidates from the participating organizations (both business and public) who have a PhD degree and are interested in becoming supervisors will be offered the chance to enroll and participate in the respective university's supervisory education courses. This education is part of the quality assurance of graduate education and a requirement for being eligible as an academic supervisor.

The team of academic supervisors plays a continuous quality control role in the doctoral student's educational process, including the study design, empirical and analytical work, research article production, thesis development, and participation in doctoral education courses and research school activities. The supervisory team and the doctoral student agree on the individual study plan, set up milestones, and supervision arrangements including regular and formal progress meetings. The supervision arrangements are formally and regularly followed up within the organization for each doctoral education at each university. It is also reviewed yearly by the project coordinator of the research school, through the individual study plan for the doctoral students and through dialogs with the doctoral students and supervisors.

It is of importance that supervisor roles in the research school are diversely represented with regard to gender and ethnicity. A broad representation will add value to the doctoral students' perspectives and to the discussion during network activities. It will be the role of the management group to lift these aspects in relation to supervisor appointments.

Doctoral Courses

All doctoral educations require a specific amount of compulsory and elective courses, although the number of credits varies between different doctoral educations. The elective courses are chosen to optimize the students' competence in relation to project needs and interests and should provide a knowledge depth in the field. Students participating in the research school will be offered several small courses (2.5 ETCS credits each) for their elective credits, which are specifically tailored to the research school agenda (Textbox 1).

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Textbox 1. Selective courses for elective credits.

Related to content/research focus:

- Health innovations, application, and value (2.5 credits)
- Coproduction in research and practice (2.5 credits)
- Needs-driven implementation, innovation, and quality improvement (2.5 credits)

Related to skills and abilities:

- Communication of research and value (2.5 credits)
- Academic writing (2.5 credits)
- Ethics in coproduction of health innovations (2.5 credits)

The first course (ie, Health innovations, applications, and value) brings up aspects of innovation with specific relevance to the health and health care context. All courses offered in the research school are developed in collaboration between different universities and disciplines and involve listening to collaborating partners to gather needs. Because of the limited space for further elective courses within the doctoral education programs, further needs for developing shared multidisciplinary knowledge among doctoral students will be accomplished through other research school activities.

Ethical Considerations

All data and personal data, for both the research school and the separate doctoral projects, will be handled in accordance with the European General Data Protection Regulation (EU) 2016/679. Ethical approval will be obtained from the Ethical Board in Sweden for each doctoral project where this is applicable.

Some ethical considerations could be important to reflect on. For example, ethical challenges can arise in coproduction projects when different perspectives, ambitions, and priorities from stakeholders meet. In the research school, each doctoral project involves 1 doctoral student from either company/region or municipality, 2 supervisors from 1 or 2 universities with expertise in different areas, and 1 supervisor or mentor from either company/region or municipality. The coproduction approach highlights the importance of respecting the perspectives and values of all stakeholders involved in a project [23]. However, while acknowledging that a researcher's main goal may be to get the results published in scientific journals, it is also necessary to understand that this is not always the goal for other partners. Thus, in each project it is essential to discuss how these issues should be handled to address transparency and common understanding in relation to goals, expectations, and ambitions.

Results

The research school was funded in December 2021 (Knowledge foundation dnr: 20210047). The research program started in March 2022 and is progressing according to the time plan presented in Figure 3. Briefly, the research school was started between March 2022 and December 2022. During this period, we had set up its infrastructure and the action plans to run the school. Thereafter, the PhD projects will be executed, and these projects will be completed in 5 years. The first group of students have been admitted during autumn 2022 and spring 2023 (in total 15 students). The first results from the PhD projects are expected in 2024 and the first dissertation is expected to be produced in 2026. Additional activities within the research program will include doctoral activities (eg, courses, seminars), networking activities, and dissemination of results.

To achieve the overall goal, expected outcomes are stated, which contribute to desired impact for the participants involved. To allow for an overview of desired impact and expected outcomes for the different stakeholders in the project, these are presented from the perspective of doctoral students, university and industry, region, and municipalities (Figures 4-6). In the figures outputs, measurable results are also stated.

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Figure 3. Timeline of the research school.

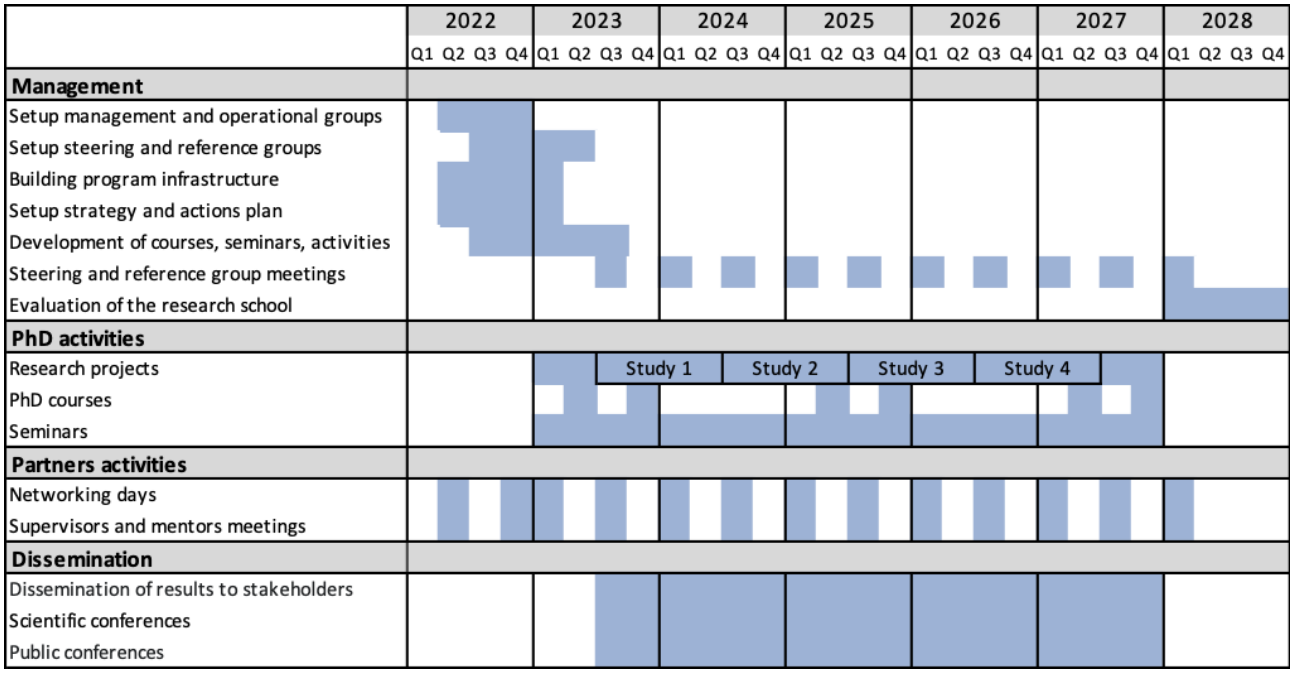
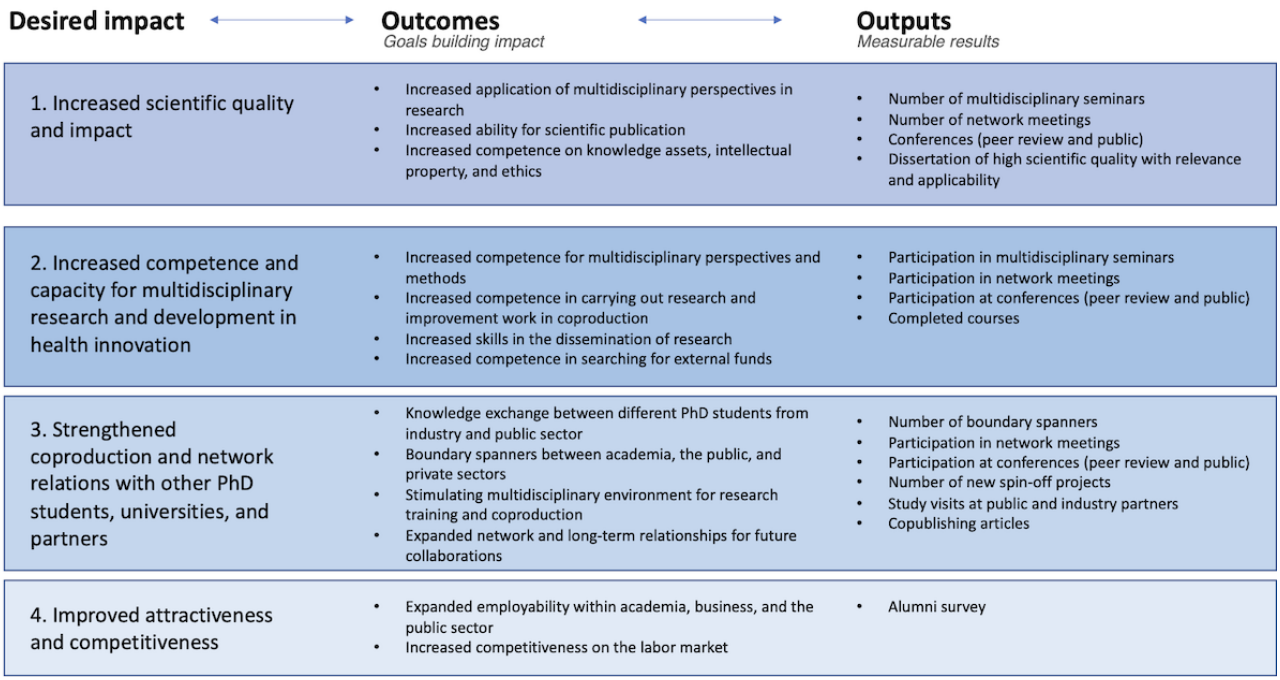


Figure 4. Program logic—PhD students' perspectives.



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Figure 5. Program logic—universities' perspectives.

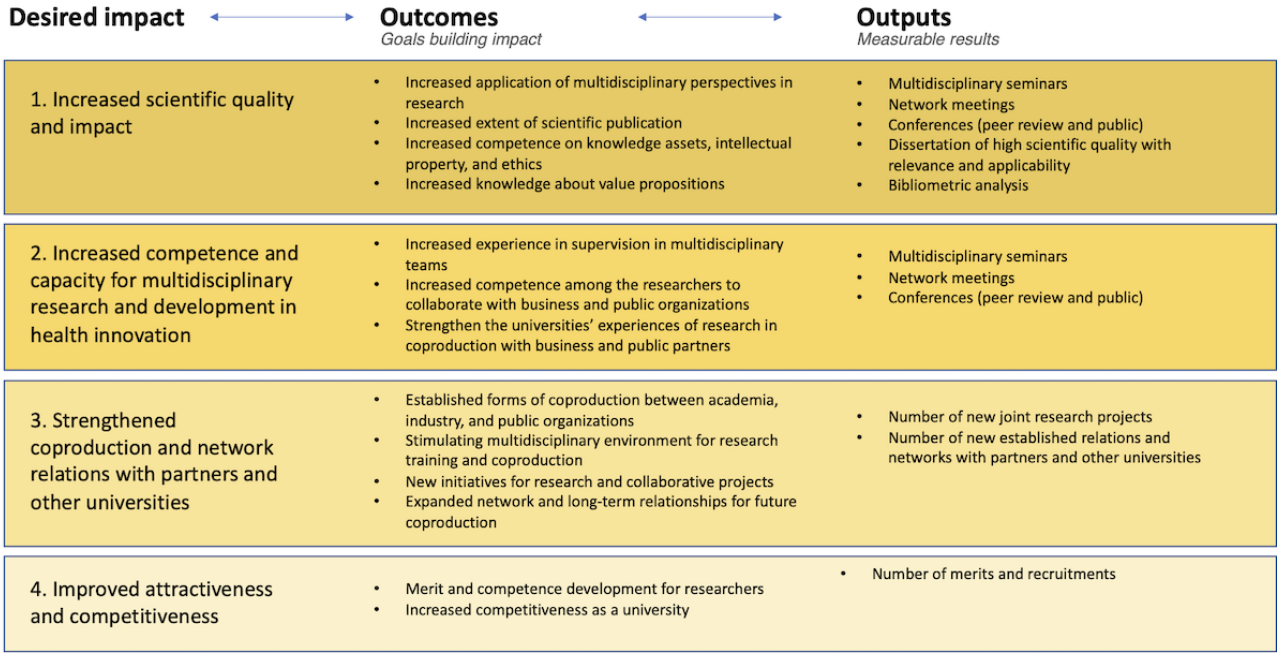
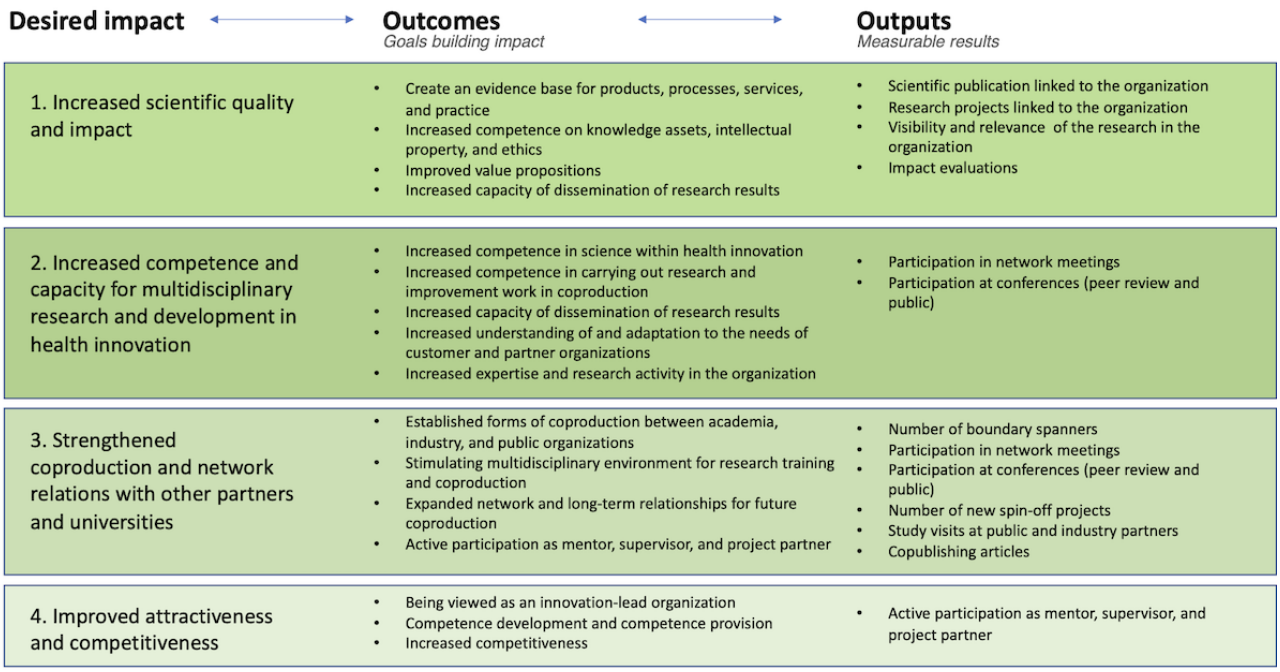


Figure 6. Program logic—company/region/municipalities' perspectives.



Discussion

Expected Findings

The research school is a collaborative network of higher education institutions and stakeholders from the public and private sector across Sweden. The universities all have a strategic focus on different aspects of health innovation, which together forms a unique constellation of complementary competencies around this topic. By tradition, the health sciences field has extensive experience of collaborating with public sector partners, whereas the engineering and computer sciences field often has more experience in working with industrial partners. By bringing these 2 groups together, the research school is expected to provide a multifaceted added value to the participating partners [25], involving the following:

- Close collaboration with industry or public sector organizations through supervision, project implementation, and research school activities.
- Forming a network with other universities with similar or complementary positioning in the field.
- Facilitation of discussions and plausible collaboration between scholars from different subject areas within the universities (different academic environments).
- Strengthening multidisciplinary research related to health innovation, thus increasing the positioning of the

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universities, as well as the national academic capacity, in this field.
- Ensuring research of high relevance to industry and public sectors.
- Development of doctoral education programs by integrating industrial doctoral students as well as public sector students.

The benefits of achieving these aspects through an industrial research school are several, and at different systemic levels. For example, the involved academic staff at each university will collaborate closely with the doctoral students and their mentors, which will bring interorganizational and intersectoral understandings and competencies. By developing a better understanding of the health care sector, the shared experiences and perspectives will broaden the horizon and understanding for different research approaches, as well as contextual perspectives [26]. These competencies will be further brought into the research environments and doctoral education programs at each of the universities through the doctoral students, supervisors, and local project coordinators, who act as carriers of this knowledge.

By meeting supervisors from the different participating universities, the research school will facilitate development of supervisory skills, in terms of both insights from adjacent knowledge areas and pedagogic exchange [27]. These aspects of the supervisory role are important to focus on research school activities, to ensure goal fulfillment and relevance related to the supervisors. By being part of a national initiative, rather than a local research school, this effect will have a greater diffusion and impact beyond the academic, business, and public organizations involved in the research school. Further, all involved participants will improve their understanding of the benefits of the synergistic effects resulting from the interaction between academia, industry, and public sector in collaborative development and innovation, as well as the challenges of working interorganizational, which will be problematized within the research school. Another important aspect of the universities' participation in this research school is related to the capability of keeping up with state-of-the-art within this field. The rapid development of technology and the need for digital technology implementation in the public sector make this industry move very fast [16,28,29]. There is a risk that universities will not be able to keep up with the pace, unless being involved in such development projects. By identifying projects that are of high relevance for industry, research, and public sector, we can ensure that competence and collaborations are being established to continuously keep partners in the forefront of the development. The long-term collaborations formed through the research school also form a great platform for other possible collaborative activities. There are many diverse forms of partnerships between the industrial sector and academia, and the interaction taking place within the research school will open up for new forms of collaborations (eg, student projects in educational programs at the university, a broad pallet of different types of professional research projects, educations for lifelong learning, larger consortiums that strengthen the international positioning within the field, and long-term strategic partnerships).

Despite increased recognition of coproduction in research, there are still demands on research to show its values in practice [23,30]. There is a diversity of coproduction models [31], and how different stakeholders conceptualize, understand, and use research in practice. Most coproduction models that are described and investigated in the scientific literature focus on the collaboration between researchers and users such as health care professionals, citizens, patients, and service users [31], not involving stakeholders from industry. There is evidence that coproduction can lead to benefits and practice change, but there is still a knowledge gap on the success and impact of coproduction between stakeholders from universities, companies, and public actors. Thus, the learnings from this research school are of importance and can tell us something about how coproduction can lead to benefits, value, usability, uptake, and practice change.

Conclusions

The research school will contribute to a strong development of competence for industry; solve research questions relevant for academia, public sector, and industry; and build stronger ties between the participating organizations promoting value creation, increased competitiveness, and the potential for future collaboration within and outside of the research school partner network. The forms of collaboration between the health care sector, industry, and academia fostered through the research school is vital to build increased competence and to promote knowledge generation and innovation. This requires multidisciplinary constellations that combine the technological development with research and innovation related to stakeholder values and implementation. Succeeding in bringing these perspectives together is a necessity if this advantage in competence is to be applied within the life science sector.

Acknowledgments

We are grateful to the people, from the universities, companies, regions, and municipalities, who participated in the discussions about the application for the research school in health innovation. There were several meetings and workshops discussing research schools' topics, design, and implementation involving the following staff members of the participating universities in addition to the authors of this protocol: Anderberg Peter (Professor in Applied Health Technology, Blekinge University), Lena-Karin Erlandsson (Professor in Occupational Therapy, Halmstad University), Fristedt Sofi (Associate Professor in Applied Gerontology, Jönköping University), Gellerstedt Martin (Professor in Public Health, Skövde University), Landstad Bodil (Professor in Health Science, Mid University), Lindén Maria (Professor in Health Technology, Mälardalen University), Lindgren Eva-Carin (Professor in Sport Science, Halmstad University), Mårtensson Anna-Maria (Coordinator, Halmstad University), Ramstrand Nerrolyn, (Professor, Orthopaedic Technology, Jönköping University), Roxberg Åsa (Professor in Nursing, University West), Svensson Ann (Professor in Informatics, University West), and Åhlfeldt Rose-Mharie (Assistant Professor in Informatics, Skövde University).

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review report from granting agency.
[PDF File (Adobe PDF File), 89 KB - resprot_v12i1e46595_app1.pdf]

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Abbreviations

CAISR Health: Center for Applied Intelligent Systems Research Health
DHEAR: Digital Health Research
IDC: information-driven care
INFINIT: Research directed towards the generation, quality assurance, analysis and visualization of data using information technology systems and models
LINA: learning in and for the new working life
LOV: learning and caring for sustainable health
RFI: research for innovation
SNAC: Swedish National Study on Ageing and Care

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Protocol

The Design, Development, and Usability Testing of an eHealth Program for Youths With Osteogenesis Imperfecta: Protocol for a 2-Phase User-Centered Mixed Methods Study

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Abstract

Background: Innovative approaches are needed to address the self-management needs of youths with osteogenesis imperfecta (OI) transitioning into adult-oriented health care systems. Using a sequentially phased research approach, the goal is to design, develop, and test the usability of an innovative eHealth program called "Teens Taking Charge: Managing OI Online," hereafter named "Teens OI." This program seeks to optimize self-management, facilitate a successful transition to adult care, and address a critical gap in the quality of care for youths with OI.

Objective: The study objectives are to (1) design and develop an English and French version of the Teens OI and (2) test the usability of the Teens OI in terms of efficiency, effectiveness, and satisfaction from the perspectives of youths with OI and their parents.

Methods: A user-centered design is presently in progress to design and develop Teens OI. A "Website Design and Development Council" (ie, Council) has been convened, with 20 youths and parent dyads recruited and global experts surveyed at an international meeting. With unanimous support from the Council, usability testing of the Teens OI will ensue in 4 iterative cycles with 32 youth-parent dyads. All sociodemographic and usability metrics will be descriptively analyzed. All recorded interview and focus group data are analyzed using content analysis techniques involving an iterative process of data reduction, data display, conclusion drawing, and verification.

Results: As of December 2022, an 8-person, interdisciplinary Teens OI council, comprising 4 health care professionals, 3 youths and young adults with OI, and 1 parent, has been convened to oversee the design and development of Teens OI. Two cycles of interviews have been conducted with 10 youths with OI with or without their parents (n=6) from December 2021 to September 2022. Data analysis has been in progress since April 2022. Aim 2 is ethically approved and will commence following the completion of content development, expected by late July 2023. Preliminary analysis indicates that the following topics need to be prioritized for the youths: mental health, pain, accessibility, medical care, education, community, and parental care.

Conclusions: The proposed study will design and develop a self-management and transitional care program for youths with OI in partnership with patients, caregivers, and health care professionals. This study leverages youths' openness to adopt eHealth technologies to meet their needs and has the potential to actively engage them to autonomously manage their lifelong conditions, and facilitate a successful transition to adult health care. Finally, the proposed study will also address a critical gap in the quality of care and the growing concern that the OI population transitioning from pediatric to adult care is at risk of various adverse events associated with the transition.

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International Registered Report Identifier (IRRID): DERR1-10.2196/47524

(JMIR Res Protoc 2023;12:e47524) doi:10.2196/47524

KEYWORDS

eHealth program; osteogenesis imperfecta; self-management; youth; transition of care

Introduction

Background

There is a critical demand for effective self-management and transitional care programs to optimize the quality of care and quality of life of youths and young adults with rare diseases worldwide. Transition is "the purposeful, planned movement of adolescents and young adults with chronic physical and medical conditions from child-centered to adult-oriented health care systems" [1]. Barriers impede a successful transition [2], leading to adverse events for the transitioning youths [3-8]. eHealth offers an innovative approach to address the self-management needs of transitioning youths [9,10]. Self-management is "the interaction of health behaviors and related processes that patients and families engage in to care for a chronic condition" [11]. In a burgeoning field, self-management interventions, delivered over the internet, can improve selected outcomes in certain childhood illnesses [9]. One promising program is Teens Taking Charge. Our team aims to develop this program for youths with osteogenesis imperfecta (OI). Our preliminary work showcases the critical need and motivation of youths with OI, their parents, and clinicians to engage in such a program [12-18] while addressing the global gap in OI self-management and transitional care programs [12,14,16-19]. Priority topics include a description of OI [16]; self-management of symptoms such as pain [20-22] and constipation [23]; coping with isolation, feeling different, and fear of fractures [24]; need for social support [24,25]; preparing for the transfer and navigation of the adult health care system [16-18]; managing costs [26]; and understanding the clinical manifestations of OI in adulthood [27].

"Teens Taking Charge" is a promising self-management and transitional care program available for youths with OI. Stinson et al [28] designed and developed "Teens Taking Charge," which is currently available for youths with juvenile idiopathic arthritis (JIA), cancer, hemophilia, or organ transplants. These multilayer programs contain self-guided, interactive, multicomponent modules that consist of disease-specific education, self-management strategies, and social support. To help encourage healthy behavior among youths, 2 modules specifically target parents. Recent findings from the 10-site, randomized controlled trial in the United States, using an "active" control group (n=144), supported a modest benefit for pain and quality of life for the Teens JIA group (n=145) [29]. The program is now publicly available and being adapted for use in Ireland [30]. Pilot randomized control trial studies suggest design feasibility, program benefits, and significant improvements in disease-specific knowledge (P=.004), self-efficacy (P=.007), and transition preparedness (P=.046) than the control group (n=13) [31-33]. The pilot testing of "Teens Cancer" is presently in progress.

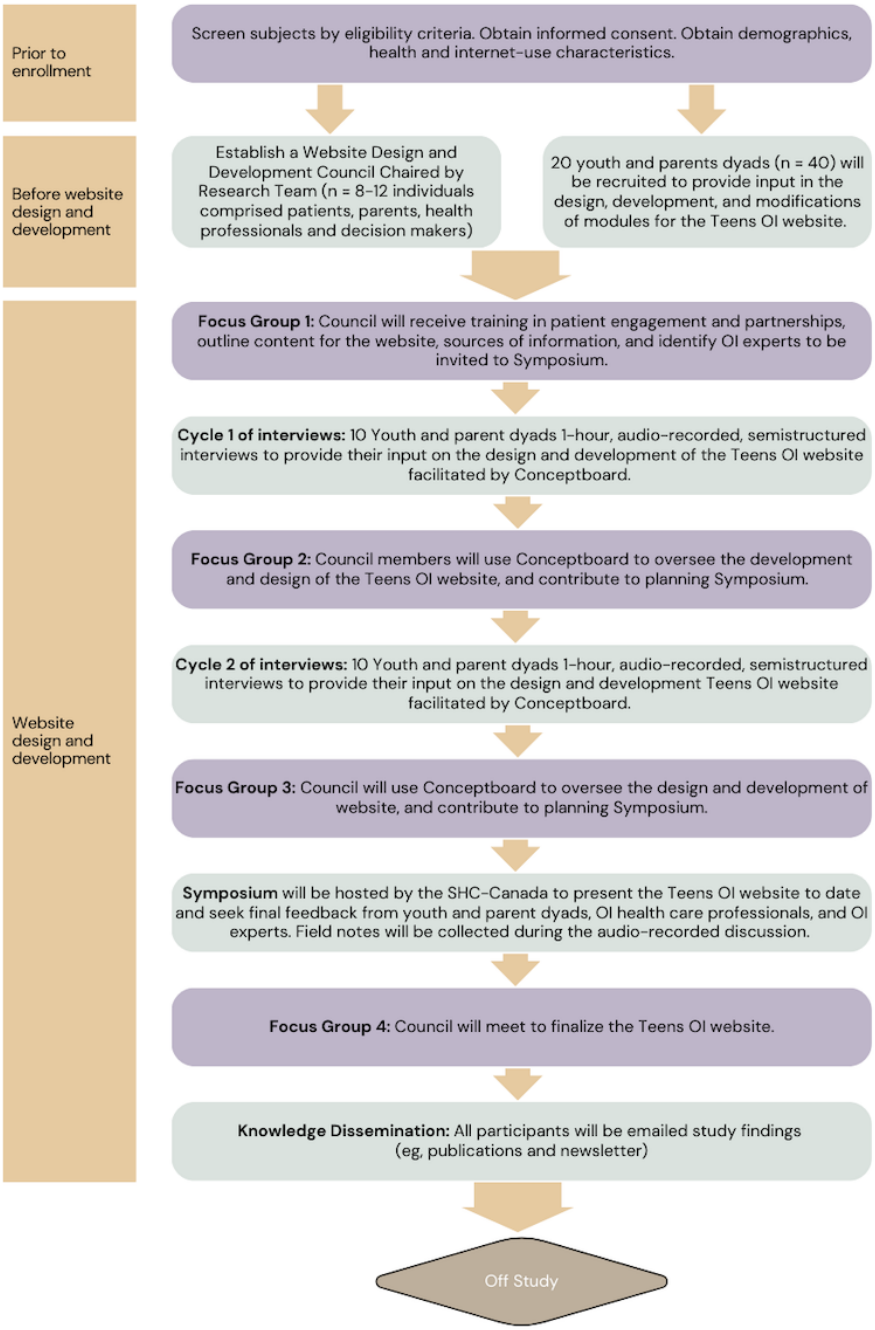
To our knowledge, there are currently no eHealth interventions designed for youths with OI and their parents, resulting in unmet needs. The typical clinical appearance of youths with OI, a rare genetic disorder (1:10,000), is bone fragility [34]. In North America, the largest cohort of pediatric patients with OI (n=400) is followed at Shriners Hospitals for Children-Canada (SHC-Canada; ie, the study site of this protocol). The health care team is internationally acclaimed for establishing the worldwide standard of care, pioneering the treatment, and testing its effectiveness. Despite these accolades, ongoing multistakeholder service evaluations conducted at the study site have identified a critical need to develop a self-management and transitional care program delivered over the internet [12,14,16-18].

Study Goals and Aims

With multistakeholder input from patients, families, clinicians, and the greater OI community, our research team seeks to design, develop, and test the usability of Teens Taking Charge: Managing OI Online (Teens OI). This study protocol incorporates the preliminary work led by the research team. The approach is modeled after similar and successful approaches conducted with youths with JIA [29,30,32,35], hemophilia [31,36,37], cancer [38,39], and solid transplant [33,40,41]. A sequential phased approach of (1) needs assessments [14,16] (completed), knowledge syntheses [17,18,24,25,27,42,43] (completed), and preliminary symptom assessments [22,23] (completed); (2) program design, development, and usability testing [28,31,41] (this protocol), and (3) feasibility testing and outcome evaluation [32] (future research) has been adopted. The program design, development, and usability testing have 2 study aims. Aim 1 consists of designing and developing an English and French version of the Teens OI program (Figure 1). Aim 2 entails testing the usability of Teens OI in terms of (1) efficiency, (2) effectiveness, and (3) satisfaction, including perceived ease of use (ie, error prevention, other outcomes, information needs, and memorability), and perceived usefulness (ie, learnability, competency, performance speed, flexibility, and customizability) from the perspective of youths with OI and their parents (Figure 2).

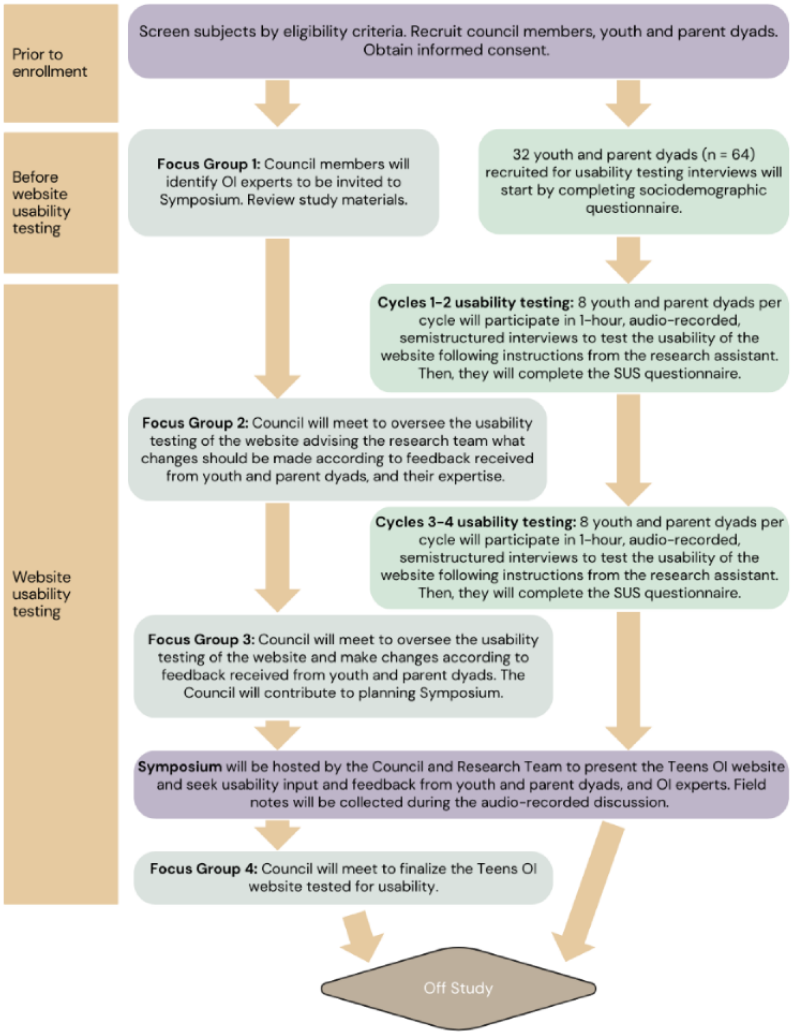
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Figure 1. Study schema: Teens OI Phase I. OI: osteogenesis imperfecta.



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Figure 2. Study schema: Teens OI Phase II. OI: osteogenesis imperfecta; SUS: System Usability Scale.



Preliminary Work for Aims 1 and 2

The preliminary work conducted for aim 1 consisted of needs assessments, knowledge syntheses, and the hiring of a former patient to inform the development of Teens OI. A usage-focused evaluation of the OI transitional care program at the study site revealed the need for a web-based self-management program [14]. Efforts to advance this mandate by the study site included the hiring of Chougui, a former patient and young adult with OI who is now a doctoral student in psychology, as a research team member since 2015. Chougui has contributed to drafting the preliminary content of Teens OI and creating varying transition-related tools [17,18,20,25-27,42]. The drafts have been informed by our completed study on self-management [16] and varying knowledge syntheses [17,18,24,25,27,42,43] and preliminary symptom assessments [22,23].

The preliminary work conducted for aim 2 has consisted of 4 qualitative usability studies conducted with 56 English-speaking and 26 French-speaking youths with JIA (n=19) [28], cancer (n=24) [38], hemophilia (n=18) [31], or transplant (n=21) [41], and one of their respective parents, to determine the usability of the user interface and content areas and refine the prototype accordingly using 2-4 iterative cycles. Youths and parents provided similar as well as differing suggestions on how to improve the website's user interface and usability. Participants reported suggestions for minor prototype changes across all 4 programs. They also responded positively to the website's content, use, appearance, and theme; indicated that the program was easy to navigate and understand; and perceived the program as helpful and acceptable. Many participants responded that the interactive features made them feel supported and "not alone" in their illness and that they felt enriched by their experience. No major differences between English- and French-speaking participants were found. Usability themes that arose from the 4 studies were: (1) aesthetics, (2) content and features, (3) functionality, (4) understandability, (5) comprehensiveness, (6) quality and credibility, (7) sociability, (8) intent for future use, (9) user satisfaction, and (10) overall impression [44]. Members of the research team have extensive training and experience designing, developing, and testing innovative eHealth technologies [28,31,38,41,45].

Methods

Aim 1

Study Design, Setting, and Context

A user-centered design is presently being conducted at SHC-Canada, a bilingual (French and English),

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university-affiliated orthopedic hospital, inviting input on a global scale. Adoption of a user-centric design and a "user experience of websites" conceptual framework [46,47] will guide the collaborative and participatory design and development of Teens OI, addressing prior limitations including developing eHealth interventions without explicit theoretical frameworks, using single measures with limited end user input, and neglecting environmental factors [48]. By partnering with the end users (ie, youths with all OI Types and their parents) from study onset [49], we will lay the foundations for an effective eHealth program and ensure the content and format of the program are relevant, acceptable, and culturally sensitive [16,35,39,40,50]. Aligned with Shriners' Mission and FOCUSED philosophy of care [51,52], we are seeking to close the transitional care gap encountered by youths with OI and their families, improve the quality of health care services, and help youths and their families better manage OI. Our analysis of all education material for patients with OI at SHC-Canada revealed the dearth of resources available, targeting solely the parents of patients with OI [53]. Hence, our team has partnered with the end users from the study onset with the goal of introducing a series of eHealth programs to complement our existing health care services and enhance the global reach of Shriners [12,54].

Participants

A "Website Design and Development Council" (ie, Council) has been convened. Membership comprises patients, parents, health professionals, and decision makers (n=8-12) from the study site and the greater OI community. Maximum variation sampling techniques were used to recruit 20 youth-parent dyads from SHC-Canada over 5-10 cycles. The inclusion criteria consisted of (1) youths between 12 and 21 years of age; (2) youths receiving OI care at the study site; and (3) both youths and parents able to speak and read English or French. The exclusion criteria excluded youths if they had major cognitive impairments or comorbid medical or psychiatric illnesses that may impact their ability to understand and use the program. The power of the maximum variation sampling technique used lies in selecting information-rich cases for in-depth study, which maximizes variation and diversity. The variability affords a more comprehensive understanding of the many diverse experiences that will enhance the design and development of Teens OI and the transferability of the proposed eHealth platform. While a sample size of 20 youths and parent dyads was proposed, the sample size was tentative and may change based on achieving data saturation and the desire for a diverse sample (eg, cultural, linguistic, OI type, and severity of disability) [55,56]. About 150 eligible patients with OI were followed at the study site. Our experiences suggest there is substantial interest in study participation, with over >90% of participation rated as experienced at the study site [22]. Our youths and their parents remain concerned about their impending transition and welcome the proposed support [12,14,16].

Recruitment

A multipronged approach was used to announce the study and commence recruitment (Multimedia Appendix 1). To protect the families' privacy, the health care team assisted by identifying, screening, and approaching the families to determine if they were interested in hearing more about the study. If the patients express interest in hearing more about the study, their names and contact information are provided to the clinical research coordinator, who approaches the patients, provides a verbal and written explanation of the study, and, if agreeable, obtains written informed consent for study participation and audio-taping. Parents consent for their child to participate, and they consent for themselves to participate. Youths aged 12-13 years, provide assent and youths aged 14-21 years provide consent (Multimedia Appendix 2). Each study participant receives a copy of the consent. The health care professionals consider patients' health status and interest in participating in the study during regularly scheduled clinic appointments and in-patient visits. The recruitment method will be supplemented, if needed, by sending a study postal information letter, signed by their medical doctor and principal investigator, inviting them to participate at home.

Procedures

The Council will oversee the design and development of Teens OI using Garrett's Theory of User Experience [47]. Garrett proposed the following 5 different planes of a website that affect the user experience: surface, skeleton, structure, scope, and strategy, which have been used for understanding and improving youths' exposure to internet-delivered interventions [46,47]. The Council will receive training in patient engagement and partnerships, which includes topics of cultural competency [57], mutual respect, and inclusivity [58]. Conceptboard, a centralized hub for content and ideas for visual projects, will be used to facilitate the web-based, real-time, collaborative design and development of Teens OI with the global OI community and eliminate social distancing barriers due to COVID-19 [44]. Varying data will be collected in English and French by conducting youths' and their parents' interviews and focus groups; hosting 2 symposiums at SHC-Canada; presenting ongoing work; soliciting input from OI experts; and surveying the OI community using Qualtrics. Presently, we foresee 12 interactive, multicomponent modules adapted from Teens JIA [28] being designed for our diverse English- and French-speaking populations. Although draft modules have been created, we will inquire about topics and create, modify, or eliminate draft modules as needed. Other features such as multimedia (eg, video and audio) and other interactive, technological features (eg, discussion boards, animations, quizzes, stories of hope, and video clips) will be designed and developed with input from the end users.

Instrumentation, Interview, Focus Group, and Symposia Guides

Guided by Garrett's 5 planes contributing to users' experiences of websites [47], interview guides (Multimedia Appendix 3) outlining the procedures, questions, and probes have been created to guide discussions of website development and design, user experiences, and tools to solve related problems (1-2 cycles per plane). While each plane will be addressed individually, the discussion will naturally combine all planes. Field notes and feedback from the first cycle of interviews and focus groups will inform the discussion for subsequent cycles of data

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collection. With 117 user experience instruments available, the Council will decide on the quantitative metrics of the design and development of Teens OI [59]. One sociodemographic survey will be used to collect demographic, health, and internet-use characteristics [12,16].

Data Management, Analysis, and Interpretation

All survey data are being descriptively analyzed using SAS (version 9.4; SAS Institute Cary). Observations, field notes, and transcribed data will be imported into NVivo (version 12; QSR International Pty Ltd) for data management and analysis. The qualitative data are analyzed using content analysis techniques involving an iterative process of data reduction, data display, conclusion drawing, and verification [60]. All data will be analyzed and triangulated in each of the 5 planes, fostering the process of "building from the bottom to the top" and "moving from abstract to concrete," allowing for refinement of Teens OI between each cycle within each of the 5 planes [47]. Individual and aggregate comparisons and contrasts of subgroups (eg, parent or youth [22,61,62]; English or French; OI Types and disability severity) are lending insight into how to synergize results and establish consensus with participants and the Council to maximize the inclusivity of Teens OI. An audit trail, composed primarily of methodological and analytical documentation, will be kept to permit the transferability of this innovative process [63]. Unanimous support from the Council to proceed to Aim 2 will be sought.

Aim 2

Study Design, Setting, and Context

A user-centered, mixed methods, concurrent design will be used to test usability. Usability testing is critical to ensure content relevancy; determine if the eHealth program is easy to use and efficient to complete; and confirm the end user product acceptability [28,31,38,41,45]. Using varying data sources, the usability testing will ensure the end users are able to access, understand, and use the Teens OI content and that the Teens OI can be delivered in an efficient, effective, and satisfying manner. The study setting and context will be the same as in aim 1.

Participants

Maximum variation sampling techniques will be used to recruit up to 32 youth-parent dyads from SHC-Canada. The inclusion and exclusion criteria will be the same as described in aim 1. Usability testing produces informative results with small sample sizes [64], with 80% of usability problems detected with 4 or 5 participants and 95% of problems identified with 9 participants [65,66]. Previous usability studies of Teens Taking Charge included sample sizes of 18 [31], 19 [28], 21 [41], and 37 [38]. Iterative rounds of testing with 8 youths per round will be conducted until 95% of usability issues have been determined.

Recruitment

The process for recruitment will be the same as that in aim 1.

Procedures

The usability testing will occur in 4 iterative cycles to assess the user performance and level of satisfaction of Teens OI and determine the need for refinement after each cycle. Consenting participants (8 in each of the 4 cycles) will complete a sociodemographic questionnaire, followed by a one-on-one observation recorded with Morae 3.3 (TechSmith Corp) usability software, and a semistructured interview with the research assistant (RA). Participants will access the website via a laptop computer for use at the point of care. Morae, activated at the beginning of instruction, will be used for the automatic recording of user performance and level of satisfaction. Once the automatic recordings have begun, the RA will direct the participants to the main navigation menu and prompt them to select one of the modules of interest to them. The RA will use a standardized script to instruct participants to select one or more key features or functions within the selected module. Participants will be encouraged to "think aloud" and comment on any difficulties, as they explore various features and functions within each module and complete various usability tasks (eg, select a module from the main navigation menu, click on a video, and complete an exercise). Scripted instructions will continue until the participant has viewed all of the modules or shows disinterest in exploring further. After each cycle iteration, changes to the website will be made accordingly, and usability testing will continue until no further significant issues have been identified. Participants will be instructed that they can stop participating in the study at any time. They will also have opportunities to debrief, ask questions, offer feedback, and receive assistance as needed. During the testing, the RA will also record their observations and take field notes. It is anticipated that the interviews will take 45-60 minutes, with length varying depending on the participants' schedules and interests.

Measures and Standardized Scripts

Guided by the Health IT Usability Evaluation Model (Health-ITUEM) [67,68], standardized scripts outlining the procedures, questions, and probes will be adapted from previous Teens Taking Charge research and used [28,31,38,41]. Usability surveys will also be used [69,70]. The sociodemographic survey in aim 1 will be used [12,16].

Data Management and Analysis

All sociodemographic data will be imported into SAS 9.4 for descriptive statistical analysis. Recorded Morae data will be downloaded, coded, and analyzed using descriptive statistics. Observations, field notes, and transcribed data will be imported into NVivo 12 for data management and analysis. The qualitative data will be analyzed using content analysis techniques involving an iterative process of data reduction, data display, conclusion drawing, and verification [60]. All data will be analyzed in 2-4 cycles to allow for prototype refinement between each cycle. Teens OI will also be compared to other OI websites using relevant evaluation indexes from the Alexa website ranking system [71] and Google Analytics [72]. An audit trail, composed primarily of methodological and analytical documentation, will be kept to permit the transferability of this innovative process [63]. As a benchmark of success, the team will strive to resolve 95% of problems, and have mean System Usability Scale and Health Information Technology Usability Evaluation Scale scores of 70% corroborated with positive findings.

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Ethics Approval

This minimal-risk study has received feasibility, scientific, and administrative approvals from the Department of Research Programs at SHC International Headquarters and ethical approval from the institutional research ethics board (phase 1: A04-B31-21B, and phase 2: A10-B97-22B). Most participants for study inclusion (n=150) have been followed at the study site for several years, with follow-up visits at least biannually. The burden is relatively small, with no additional visits required for participation. While study participation is not associated with a greater risk than expected or encountered in daily life, distress from discussing self-management needs or preparing for transitioning into the adult health care system may occur. If periods of increased distress arise for the participants, data collection sessions will be postponed and resumed at a later time. Similarly, at any time during or after the study, the participants are free to decline to answer any question that makes them uncomfortable, to stop the interview, or to withdraw from the study. Instructions on how to withdraw are also provided to the participants and their parents during the informed consent discussion. If our team is experiencing any problems during the course of study, we will revisit as a team to strategize, offer solutions, or allocate resources as deemed necessary. Presently, the alternative to participating in the study is to not participate and to seek information and support for self-management and transition from published materials available for free or for purchase (eg, books), attend caregiver programs that exist in the community, or seek help from physicians, mental health practitioners, or other allied health care providers that exist in the community. If a potential participant screens out or does not want to participate but requests information about resources, we will refer the individual to the OI clinical team with their permission.

Knowledge Dissemination

The research team is actively presenting the research in progress at varying meetings to share and solicit input from the global OI community. Preliminary findings have been presented at 2 international meetings [73,74] and awarded a New Investigator Award. Feedback received is being shared and discussed with the Advisory Council, which may influence the research process, including data analysis, interpretation, and discussion of findings, or the content creation process of Teens OI. The findings will be subsequently published in peer-reviewed journals and mobilized via the global community network through social media, newsletters, and community, and academic events.

Results

Aim 1 received ethical approval on June 28, 2021. As of December 2021, an 8-person, interdisciplinary Teens OI council, comprised of 4 health care professionals (nurse practitioner, care coordinator, nurse, and social worker), 3 youths and young adults with OI, and 1 parent, has been convened to oversee the design and development of Teens OI. Two cycles of interviews have been conducted with 10 youths with OI with or without their parents (n=6) from December 2021 to September 2022. There have been no withdrawals. Attrition rates, including dropouts and those lost to follow-up, may range from 10% to 15% (which is similar to Teens JIA [32] and considered low compared to other internet-based studies in adolescents (0-28, mean 14.3) and adults, in which higher dropout rates were found [9,32]). Data analysis has been in progress since April 2022. Aim 2 is ethically approved and will commence following the completion of content development, expected by late July 2023. Preliminary analysis indicates that the following topics need to be prioritized for the youths: mental health, pain, accessibility, medical care, education, community, and parental care.

Discussion

Principal Findings

The survival of youths with chronic health conditions into adulthood has created a critical demand for effective self-management and transitional care programs to optimize the quality of care and quality of life of children with rare diseases worldwide. SHC-Canada, internationally acclaimed for establishing the worldwide standard of care for children with OI, is of no exception. Ongoing, multistakeholder evaluation of transitional care services at SHC-Canada has identified the need for a web-based self-management program to better prepare patients with OI and their families for transition into the adult health care system. Preliminary work consisting of needs assessments, knowledge syntheses, and symptom assessments has ensued to inform the creation of such an evidence-based program with priority topics identified. A long-standing partnership with Stinson, who has led similar studies (registered on clinicaltrials.gov) with youths with arthritis (ID NCT01572896), cancer (ID NCT02299219), hemophilia (ID NCT01477437), and organ transplants, has subsequently catalyzed our efforts to offer Teens OI. Collectively, our interdisciplinary research team is uniquely positioned to address the transitional care gap in the OI community. Our team has led studies of self-management and transitional care in OI [14,16-18] and begun developing eHealth innovations (ie, OI Good to Go Passport [17] and Sisom OI [47]). However, the need for this Teens OI is global. After presenting our in-progress work at 2 international OI meetings [73,74], there is a global request to merge our efforts, knowledge, and expertise. To further catalyze efforts and mobilize the community to enhance the paucity of resources available for this rare disease patient population, we encourage interested individuals, patient organizations, and institutions from the public, private, and industry sectors to express their interest and reach out to the team. A significant amount of content needs to be created amidst the dearth of evidence available in OI, especially tailored to the youth audience. We welcome the sharing of resources, especially any gray source material (eg, pamphlets, policies, tools, pictures, graphics, videos, or teaching materials), to determine how to ideally integrate into Teens OI and to recognize the contributions of others. Moreover, translators will be needed to render Teens OI accessible to communities unable to comprehend English or French and to collaborate on tailoring Teens OI to the respective languages, cultures, and contexts.

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Troubleshooting

Due to COVID-19 restrictions imposed at the study site related to large crowd gatherings, our research team opted to solidify global input on our in-progress findings at 2 international OI meetings to date [73,74]. This warranted an ethical amendment allowing us to survey the global OI community with questions generated from our in-progress design analysis [73]. Once large-scale, in-person meetings are reconvened, the research team will host a symposium related to self-management and transitional care at the study site to further inform the content creation process. Software restrictions in the study have precluded the use of Conceptboard. Hence, this innovative feature permitting real-time, collaborative design and development of Teens OI with the global OI community was not used. Rather, design features are transferred to PowerPoint slides shared via Microsoft Teams in individual or focus groups for feedback.

Strengths and Limitations

A rigorous and innovative approach is being used to design, develop, and test the usability of Teens OI. This self-management and transitional care program will be designed, developed, and tested in partnership with youths with OI, their parents, and the greater OI community. This user-centric approach will advance the neglected OI field of research, align with the mission and philosophy of care (FOCUSED) of the study site, and capitalize on youths as early adopters of eHealth technologies to meet their needs. Findings will generate the provision of the Teens OI eHealth prototype, which will be ready for feasibility testing and outcome evaluation. The development of Teens OI will address a critical gap in the quality of care and our growing concerns that the OI population transitioning from our study site and other pediatric hospitals is at risk of various adverse events in terms of morbidity, mortality, social, educational, and vocational outcomes. Moreover, this research program will address a serious lack of health care resources designed with patients to improve the quality of care and life. Finally, actively engaging our patients in the provision of their care is their fundamental right, and it is our duty as health care professionals to offer these quality services. Presently, the findings generated from this study will be primarily derived from English- and French-speaking youths, parents, and clinicians. Efforts are in place to seek evidence (eg, documents, videos, and input) from the global community to guide the design and development of content. While the participants are from varying ethno-cultural backgrounds, they are primarily from Canada and treated at a study site internationally renowned for the treatment of OI. The transferability of the Teens OI prototype will need to be assessed and tailored to other contexts accordingly.

Acknowledgments

We would like to thank all participants, Shriners, and the greater OI community for their ongoing support. This project was awarded a SHC Development Grant (Multimedia Appendix 4). AT is the recipient of a Junior 1 Research Scholar Award (2019-2023) from the Fonds de recherche du Québec - Santé (FRQS).

Data Availability

Congruent with the study site policies, any unique research resources developed through SHC-sponsored research will be available to individuals upon request from any research team member. These resources may include consent forms, instruments, interview guides, databases, coding frameworks, methods, the Teens OI prototype, and dissemination material. These resources will be available for research purposes to qualified individuals within the scientific and OI communities through academic and nonacademic publications and consultations.

Authors' Contributions

AT and JS conceived and wrote the initial protocol. KT, FR, RH, KC, SA, TP, MB, ND-O, and L-NV reviewed, edited, commented on, and finalized the awarded protocol and study materials and will be contributing to the content development of Teens OI. SA and LMNP are research staff coordinating, collecting, and analyzing data. LMNP is coordinating the design and development of Teens OI. RPDS is a postdoctoral fellow collects and analyzes data as part of her training. AT wrote the manuscript. All authors reviewed, edited, commented on, and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Recruitment Flyers.
[PDF File (Adobe PDF File), 671 KB - resprot_v12i1e47524_app1.pdf]

Multimedia Appendix 2
Assent and Consent Forms.
[PDF File (Adobe PDF File), 2996 KB - resprot_v12i1e47524_app2.pdf]

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Multimedia Appendix 3
Interview Guides.
[PDF File (Adobe PDF File), 1020 KB - resprot_v12i1e47524_app3.pdf]

Multimedia Appendix 4
Peer review report by Shriners Hospitals for Children.
[PDF File (Adobe PDF File), 392 KB - resprot_v12i1e47524_app4.pdf]

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Abbreviations

JIA: juvenile idiopathic arthritis
OI: osteogenesis imperfecta
RA: research assistant
SHC-Canada: Shriners Hospitals for Children-Canada
Teens OI: Teens Taking Charge: Managing OI Online

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Protocol

A Web-Based Dyadic Intervention to Manage Psychoneurological Symptoms for Patients With Colorectal Cancer and Their Caregivers: Protocol for a Mixed Methods Study

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Abstract

Background: Patients with colorectal cancer (CRC) receiving chemotherapy often experience psychoneurological symptoms (PNS; ie, fatigue, depression, anxiety, sleep disturbance, pain, and cognitive dysfunction) that negatively impact both patients' and their caregivers' health outcomes. Limited information is available on PNS management for CRC patient and caregiver dyads.

Objective: The purposes of this study are to (1) develop a web-based dyadic intervention for patients with CRC receiving chemotherapy and their caregivers (CRCweb) and (2) evaluate the feasibility, acceptability, and preliminary effects of CRCweb among patient-caregiver dyads in a cancer clinic.

Methods: A mixed methods approach will be used. Semistructured interviews among 8 dyads will be conducted to develop CRCweb. A single-group pre- and posttest clinical trial will be used to examine the feasibility, acceptability, and preliminary effects of the intervention (CRCweb) among 20 dyads. Study assessments will be conducted before (T1) and after intervention (T2). Content analysis will be performed for semistructured interviews. Descriptive statistics will be calculated separately for patients and caregivers, and pre-post paired *t* tests will be used to evaluate treatment effects.

Results: This study was funded in November 2022. As of April 2023, we have obtained institutional review board approval and completed clinical trial registration and are currently recruiting patient-caregiver dyads in a cancer clinic. The study is expected to be completed in October 2024.

Conclusions: Developing a web-based dyadic intervention holds great promise to reduce the PNS burden in patients with CRC receiving chemotherapy and their caregivers. The findings from this study will advance intervention development and implementation of symptom management and palliative care for patients with cancer and their caregivers.

Trial Registration: ClinicalTrials.gov NCT05663203; https://clinicaltrials.gov/ct2/show/NCT05663203

International Registered Report Identifier (IRRID): PRR1-10.2196/48499

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KEYWORDS

chemotherapy; colorectal cancer; intervention; symptoms; web-based program

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Introduction

Colorectal cancer (CRC) is the third most common cancer and the second leading cause of cancer-related deaths in the United States [1]. Patients with CRC receiving chemotherapy often experience severe and distressing psychoneurological symptoms (PNS) that include fatigue, depression, anxiety, sleep disturbance, pain, and cognitive dysfunction [2-5]. When these multiple co-occurring symptoms are undertreated, they negatively affect functional status, survival rates, and quality of life (QOL) of patients and decrease health outcomes (eg, QOL and mood) of their family caregivers (hereafter "caregivers," defined as family members or significant others identified by the patients as their primary source of emotional and physical support) [6-8]. Current interventional studies in context of CRC are mainly focused on CRC screening and treatment regimens [9,10]. Limited information is available on symptom management for patients with CRC and their caregivers, which underscores the critical need to develop an innovative and effective intervention to manage PNS for patient and caregiver dyads.

Evidence has shown that PNS may share similar mechanisms, such as increases in proinflammatory responses or neurotransmitter alterations, which partially explains why they cluster together [11,12]. Our prior work shows that depression and fatigue are core symptoms within PNS networks and that PNS are highly interconnected with each other over time, suggesting that symptom management for these clustered symptoms may decrease multisymptom burden at the same time [13]. Moreover, addressing multiple symptoms simultaneously is cost-effective as shown in prior research [14,15]. Although interventions have been developed for managing single symptoms (eg, pain and fatigue) [16,17], little is known about multiple PNS management.

Among current interventional programs, psychosocial strategies that decrease stress and improve psychosocial adaptation for individuals have demonstrated the potential of alleviating PNS as a cluster [18-22]. One evidence-based psychosocial intervention, the FOCUS program (ie, Family involvement, Optimistic attitude, Coping effectiveness, Uncertainty reduction, Symptom management), has shown to improve multiple co-occurring symptoms including PNS for patients with heterogeneous cancer diagnoses (eg, breast cancer and advanced CRC) and their caregivers [23-25]. However, FOCUS has several notable limitations, including an in-person delivery format that is costly and time-consuming. It is also not specific to PNS management and does not target patients with CRC receiving chemotherapy.

In addition, patients with CRC are facing unequal access to palliative care and disparities in treatment [26]. Prior studies reported that patients with CRC on Medicare and living in rural areas were more likely to experience severe symptom burden and treatment disruptions compared with those on private insurance and living in urban areas [27,28]. A technology-based approach (eg, web program) using computers and mobile devices allows high flexibility and accessibility for disproportionately affected patients with CRC and caregivers, especially during and after COVID-19, and minimizes the cost of the intervention in hectic and costly cancer clinics [29,30]. Therefore, developing a web-based dyadic intervention holds great promise to reduce PNS burden for both patients and their caregivers as well as to advance intervention development and implementation in cancer palliative care and health equity.

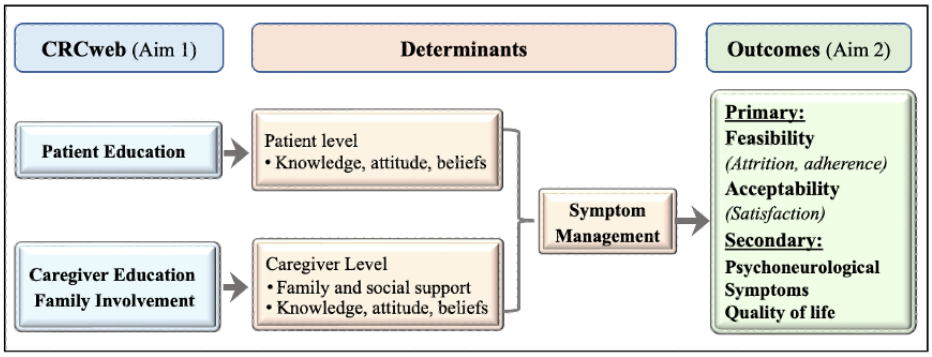
To our knowledge, there is no current web-based dyadic intervention for PNS management among patients with CRC and their caregivers. Therefore, the aims of this study are to (1) develop a web-based dyadic intervention to manage PNS for patients with CRC receiving chemotherapy and their caregivers (CRCweb) and (2) evaluate the feasibility, acceptability, and preliminary effects of CRCweb among patient-caregiver dyads in a cancer clinic.

Methods

Conceptual Model

Leveraging the FOCUS program [23-25] and health education theory [31], we developed a web-based dyadic intervention model (Figure 1). The FOCUS program provides the rationale for psychosocial education (eg, coping strategies) [32] and family involvement and support by including family members in the care process and educating families to cope with multiple demands [33]. Health education theory provides the basis for enhancing the patient-caregiver communication process and working in team science [31]. We hypothesize that the CRCweb intervention will enhance PNS management by reducing symptom burden and increasing QOL through improving psychosocial education and family involvement and support for patients with CRC receiving chemotherapy and their caregivers.

Figure 1. The web-based dyadic intervention model (CRCweb).



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Design

The proposed study will be conducted in 2 phases—CRCweb development in phase 1 and a pilot clinical trial in phase 2. A mixed methods approach will be used. In phase 1, we will determine tailored content through qualitative interviews with patient-caregiver dyads, develop a web-based program prototype, and test program usability and refine the program to yield a final version of CRCweb. In phase 2, we will conduct a single-arm, pre- and posttest clinical trial to evaluate the feasibility, acceptability, and preliminary effects of the intervention on PNS and QOL among patient-caregiver dyads in a cancer clinic.

Participants and Settings

In phase 1, we will recruit 8 patient-caregiver dyads; in phase 2, we will recruit 20 dyads. The inclusion criteria for patients will be age ≥18 years, diagnosed with CRC (any cancer stage), life expectancy >12 months, receiving active chemotherapy, self-reported at least 2 PNS (based on the symptom measures' cutoff scores described in Table 1), identified primary caregiver, access to the internet, and fluent in English. Patients who have a Karnofsky Performance Scale score of <50 will be excluded. The inclusion criteria for caregivers will be age ≥18 years, primary caregiver, self-reported at least 2 PNS (based on the symptom measures' cutoff scores described in Table 1), access to the internet, and fluent in English. Caregivers who have severe diseases such as cancer and heart disease will be excluded. Patients will be recruited at the Gastrointestinal Oncology Clinics of Emory Winship Cancer Institute.

Table 1. Measurements.

Outcome and variable	Time point[a]	Description
Primary outcomes		
Feasibility		
Attrition	T2	• Attrition is measured by the number of patients and caregivers who drop out before completing the intervention. We will consider the intervention to have low attrition if >80% dyads remain enrolled.
Adherence	T2	• Adherence is measured by the number of modules completed for dyads. It is determined by high adherence if dyads complete >80% of the modules.
Acceptability		
Satisfaction	T2	• Participant satisfaction with CRCweb is assessed by the 8-item Client Satisfaction Questionnaire (Cronbach α=.93; 8-item; 4-point Likert) among patients and caregivers at the end of the intervention.
Secondary outcomes[b]		
Intervention effect		
Psychoneurological symptoms	T1, T2	• Fatigue: 20-item Multidimensional Fatigue Inventory. A cutoff score of ≥43.5 indicates moderate-to-severe fatigue. • Depression: 8-item Patient Health Questionnaire. A cutoff score of ≥10 indicates clinically significant depression. • Anxiety: Spielberger State Anxiety Inventories. A cutoff score of >32.2 indicates high levels of state anxiety. • Sleep disturbance: Pittsburgh Sleep Quality Index (PSQI). PSQI score of ≥5 indicates a significant level of sleep disturbance. • Cognitive dysfunction: Attentional Function Index (AFI). AFI score of <5 indicates a significant level of cognitive dysfunction. • Pain: Brief Pain Inventory. A cutoff score of ≥4 indicates moderate to severe pain.
Quality of life	T1, T2	• The Short Form-12 consists of 12 questions about physical and mental health as well as overall health status. It is scored into 2 components: physical component score (PCS) and mental component score (MCS). Higher PCS and MCS scores indicate a better quality of life.

[a]T1: before intervention, at baseline; T2: after intervention.

[b]The details for the measures can be found in Multimedia Appendix 1.

Ethics Approval

The study was approved by the institutional review board at Emory University (STUDY00004750) and registered at the ClinicalTrials.gov (NCT05663203). Participants will be recruited from May 2023 to August 2024 at the Emory Winship Cancer Institute. The research staff will screen eligible patients in the electronic health record system (Epic); they will then reach out to health care providers at the clinic who will confirm eligibility and suitability and give permission for the research staff to reach

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out to the patient-caregiver dyads to assess their interests. If the research staff find that both patients and caregivers are interested, they will explain the study to dyads and obtain dyads' written informed consent in person at the clinic.

Phase 1—CRCweb Development

Semistructured Interviews

We will conduct semistructured interviews with patient-caregiver dyads using an interview guide developed from the existing literature that includes open-ended questions and probes. Dyads (n=8) will be asked about their needs for the intervention, perspectives, and suggestions for a web-based intervention to manage their symptoms, what they like and do not like about the proposed CRCweb intervention components (ie, family involvement, symptom management, and coping effectiveness) and delivery mode (eg, doses and intervals), and what modifications they would recommend being made. The interview will last 30 to 45 minutes and be conducted by the principal investigator (PI) in a private conference room at the clinic or in a Zoom meeting based on the dyad's preference. All interviews will be audio recorded and transcribed, and field notes will be taken to capture nonverbal expressions.

Development of a CRCweb Prototype

We will develop the CRCweb prototype and deploy it to Amazon Web Services (AWS) at Emory. AWS at Emory is a certified cloud service provided by AWS. A technology expert (WC) who has developed several rigorous web programs such as TCOLA (a technology-based CRC support program for Asian American women) will provide technical support. Two full-stack web designers will develop the CRCweb prototype (in 4-6 months). We will also collaborate with Health Information Technology Core at Emory University School of Nursing for the web program development. The research team will review the CRCweb prototype to provide feedback and make modifications.

Usability Testing

After the CRCweb prototype is developed, we will ask 4 patient-caregiver dyads to use the CRCweb prototype and provide feedback about the usability of the program [34]. Semistructured interviews (30-45 minutes) will probe for participants' experiences with using CRCweb (eg, design, navigation, structure, and language). Interviews will be recorded and transcribed; field notes will capture dyads' interactions with the program and document problems with using the websites. Five clinicians or researchers in oncology area will serve as content experts and provide feedback on the program. Feedback will guide the refinement of the CRCweb program, yielding a final version that will be used in the clinical trial.

Phase 2—Pilot Clinical Trial

We will conduct a single-arm, nonrandomized, and nonblinded pre- and posttest clinical trial among patients with CRC receiving chemotherapy and their caregivers (n=20 dyads). Primary outcomes (feasibility and acceptability) will be assessed at the completion of intervention among patients and caregivers. Secondary outcomes (PNS and QOL) will be assessed at baseline (T1, before intervention) and 8 weeks (T2, after intervention) for patients and caregivers. We will collect quantitative assessment data on internet-accessible devices via REDCap self-administered surveys. We will avoid collecting symptom data at the acute symptoms stage (within 1 week after chemotherapy administration) to reduce measurement bias. Additionally, semistructured formative evaluation interviews will be conducted after the intervention among these participants regarding their experiences and suggestions on the intervention to inform the future refinement.

Intervention

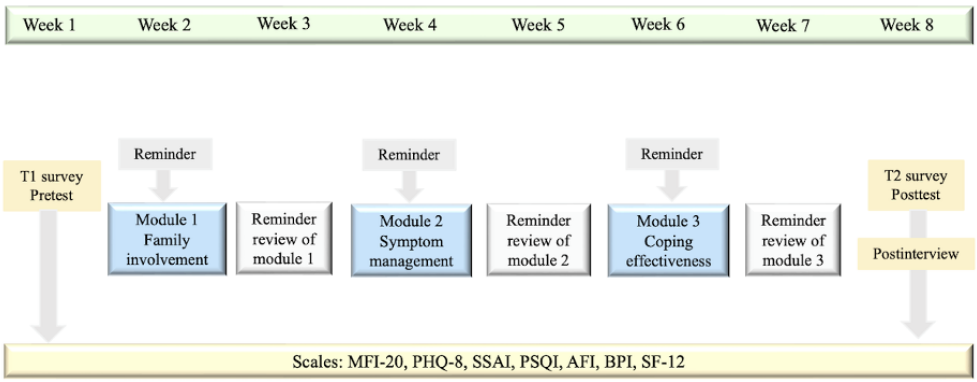
CRCweb is designed to create opportunities for patients and caregivers to obtain information and interact with each other. Patient-caregiver dyads (n=20) will participate together in an 8-week CRCweb intervention using assigned accounts and passwords to access to CRCweb with the help of the research staff. An introductory video (5 minutes) on the CRCweb page will teach patients and caregivers how to use CRCweb and navigate the websites. Dyads can use the program at any time and any place during the 8 weeks. They are encouraged to log on the program using their own devices and complete modules together, sitting side by side if possible. Three modules (ie, family involvement, symptom management, and coping strategies) are selected because they are more relevant to symptom management. Each module will be presented 2 weeks apart to enable dyads to absorb the information sequentially and practice the module's principles before moving to the next module. The content of modules is shown in Table 2. Each module has 4 sections: video-enhanced lectures (10-20 minutes) and audio-enhanced texts, resources and web links, assignments, and evaluations. The video-enhanced lectures and audio-enhanced texts contain the same contents, allowing users to acquire the material according to their own learning styles. Modules include relevant resources and web links (eg, organizations, guidelines, and support services) for those who want additional information and resources. The modules for patients and caregivers are the same except tailored resources and web links. Assignments encourage dyads to practice learning skills and activities, discuss the symptoms and their effects on their daily lives, and brainstorm strategies to minimize the negative effects. After each module, a self-evaluation survey (score range 0-10) assesses the dyad's learning. If they receive a score 0 to 5, a reminder message appears suggesting they take more time in the next week to review the module; if the score is 6 to 8, they can use the same amount of time next week to review the module; and if the score is 9 to 10, they are ready to move to the next module. We will track website activity data (eg, number of logins and time spent on the site) to assess if patients and caregivers engage in the learning modules. Additionally, we will send them weekly emails or SMS text messages to remind them to complete modules and surveys. The intervention flow is shown in Figure 2.

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Table 2. Module content.

Module and goal	Content
Family involvement	
Promoting open communication	•Discuss benefits of open communication versus concealment •Emphasize the importance of communication •Encourage open discussion of concerns •Use "I" statements to express feelings, use humor •Encourage sharing perspectives on any issues, concerns, or feelings •Address issues or concerns and reassure feelings
Encouraging mutual support and teamwork	•Discuss that cancer can affect both patient and family, making mutual support essential •Recognize the contributions of both members of the dyads and encourage the expression of appreciation
Identifying family strengths	•Help patients and family members identify individual and family strengths •Keep up positive outlook and face challenges together
Introducing family to information and resources	•Identify resources for the family to manage the recurrent illness •Give names and contact numbers of support groups for patients with colorectal cancer and their family
Symptom management	
Assessing symptoms	•Assess symptoms experienced by patients and their caregivers •Talk about the most severe, frequent, or distressed symptoms •Discuss effects of treatment on family relationships and the importance of caregiver's health
Teaching self-care strategies	•Review patients' and their caregivers' symptom management and learn symptom management strategies •Provide information, guidelines, resources, and support services
Establishing realistic and short-term goals	•Set up easy goals to achieve for symptom management •Document and monitor symptoms, write symptom diary
Coping effectiveness	
Dealing with overwhelming stress	•Encourage day-to-day efforts to cope •Allow opportunities to discuss death and dying issues or concerns
Encouraging healthy coping and lifestyle behaviors	•Discuss benefits of active versus passive coping strategies •Educate about the importance of healthy lifestyle behaviors for patients and family members: eating and exercise, sleep and rest patterns, use of chemical substances, and support networks
Helping caregivers manage the demands of illness	•Encourage caregivers to accept offers of help from others •Help caregivers identify activities to restore their mental and physical energy (eg, hobbies and recreational activities)

Figure 2. Flow of the intervention and assessments. AFI: Attentional Function Index; BPI: Brief Pain Inventory; MFI-20: 20-item Multidimensional Fatigue Inventory; PHQ-8: 8-item Patient Health Questionnaire; PSQI: Pittsburgh Sleep Quality Index; SF-12: Short Form-12; SSAI: Spielberger State Anxiety Inventories.



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Intervention Fidelity

The PI will check CRCweb login information every Friday and send the reminder nudge messages with a checklist to patient-caregiver dyads who have not completed the modules and surveys. Given competing demands on patients and caregivers, we allow them to use CRCweb in their available time and limit the time of learning modules (less than 1 hour per week).

Measurement

A demographic questionnaire will be used to collect information such as age, gender, race or ethnicity, marital status, education, employment status, exercise, income, insurance, and dyadic relationships. Medical records will be reviewed for patients' disease and treatment information, such as cancer sites, cancer stage (TNM, tumor-nodes-metastasis), treatment types, chemotherapy regimens and cycles, surgery, and radiotherapy. The measures that include primary outcomes (ie, attrition, adherence, and satisfaction) and secondary outcomes (ie, PNS and QOL) are shown in Table 1. As indicated, all the instruments are valid and reliable.

Data Analysis

In phase 1, content analysis will be used to analyze the qualitative data [35,36]. Coding will be conducted by 2 researchers (including the PI) with backgrounds in cancer and qualitative methodology. The NVivo software (QSR International Pty Ltd) will be used to support data analysis, which is completed in four steps:

1. Data preparation [37]: 2 researchers read the transcripts together to get a sense of the whole picture; they identify key topics and storylines and categorize informational content (eg, patients' perspectives).
2. Writing memos: using the transcripts and filed notes, 2 researchers write analytic memos and a brief case description of each participant.
3. Coding [38]: 2 cycles of coding will be used. The PI uses a priori codes from the literature and clinical practice to create a codebook. The first cycle includes codes developed a priori coding, descriptively, and in vivo [38]. The second researcher reviews the coding scheme and provides feedback; the PI revises the codebook by adding or combing codes. Once the first cycle of coding is completed, 2 researchers review the findings and develop larger categories of data using pattern coding and theoretical coding [38]. The second cycle will be used to organize and group codes that are similar or shared common characteristics.
4. Categorizing and connecting: 2 researchers construct tables and matrices to organize, condense, and display the codes and data samples into categories; all researchers help search for patterns, trends, and paradoxes across all participants and then summarize the descriptions and develop the themes [39].

In phase 2, quantitative data will be analyzed using SPSS Statistics (version 27.0; IBM Corp). Descriptive analyses will be conducted to determine the frequencies, percentages, means, and SDs of major variables. Feasibility of study attrition and adherence will be assessed by calculating attrition rates, identifying reasons for refusal, and assessing completeness of the data. Accessibility of participant satisfaction will be evaluated by calculating descriptive statistics to summarize responses to the poststudy evaluation items. Pre-post paired *t* tests (and nonparametric equivalents as needed) will be used to evaluate the changes between secondary outcomes (PNS, using the same calculating methods as described in our previous publication [13]) from pre- to postintervention stages for patients and caregivers. We will use dyadic analyses because of the increasing evidence that patients' and their family caregivers' responses to illness are interrelated [14]. Time and level (ie, patient vs caregiver) will be treated as within-subject variables to control for the interdependent nature of the data. The main effect by time will be examined to determine the overall effect of intervention on PNS for patient-caregiver dyads as a unit (average scores across dyads) [40]. We will also analyze time-by-level interactions to determine if there will be a differential effect of the intervention on patients' and caregivers' outcomes [14]. As needed (for an adjusted analysis), potential covariates (eg, age, insurance, and income) will be included in the planned models as appropriate. Additionally, qualitative data from postintervention interview will use the same analysis as in phase 1. Convergent parallel analysis will be used to compare and merge the quantitative and qualitative data when they have been completed [41]. We will discuss areas of convergence or divergence between the quantitative and qualitative results to refine the intervention.

Results

Given that it is a study protocol, we do not yet have any results to report from the study. This study was funded in November 2022. As of April 2023, we have obtained institutional review board approval and completed clinical trial registration, and we are currently recruiting patient-caregiver dyads at a cancer clinic. The study is expected to be completed in October 2024. Expected results will be published in spring 2025.

Discussion

To our knowledge, this study is the first to develop and evaluate a web-based dyadic intervention to manage PNS for patients with CRC during chemotherapy and their caregivers. The findings from this study will advance intervention development and inform implementation in cancer symptom management and palliative care.

There are several strengths that may enhance its impact. First, we develop and test an intervention to manage multiple co-occurring symptoms or symptom cluster (ie, a PNS cluster) for patients with CRC and their caregivers. Existing interventions have focused on managing single symptoms such as pain and fatigue, but interventions for a PNS cluster are still in early infancy [42]. Our program is designed to help improve PNS management for patients with CRC and their caregivers by providing dyads with information and support through educational sessions (eg, family support, symptom management, and coping) that are tailored to fit the needs of dyads.

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Second, we will develop and evaluate a web-based intervention (CRCweb) that is accessible to patients and caregivers who may experience disparities in symptom management and palliative care. More than 76% of underserved populations have a smartphone or computer device that could provide access to web-based interventions [43]. Symptom management interventions have typically been delivered in person (eg, FOCUS), resulting in many barriers to participation (eg, long distance, limited provider availability, and high costs) [14]. In-person interventions can be problematic for patients and caregivers who tend to have many competing commitments and for providers who have limited time in clinic [44]. Web-based interventions have produced improvements in symptom management for patients with cancer and caregivers in several clinical trials [40,45-47], and the use of technologies and telemedicine has significantly increased during and after the COVID-19 pandemic [48]. A web-based dyadic intervention program may enhance feasibility and acceptability relative to in-person interventions by avoiding interruptions to treatments and reducing financial burden for patients and their families [49].

Third, we will evaluate the feasibility, accessibility, and preliminary effects of the intervention (CRCweb) to improve both patient and caregiver outcomes (eg, adherence, symptoms, and QOL). It is essential to focus on both patient and caregiver outcomes because caregivers experience increasing symptoms and distress while caring for patients [50]. To date, limited research has focused on symptom management and palliative care of both patients with CRC and caregivers. The proposed study will address the urgent need to develop a dyadic intervention to improve health outcomes for patient with CRC receiving chemotherapy and their caregivers and accelerate the development of palliative and psychosocial cancer care.

The study also has several potential pitfalls that should be considered. First, the study might have potential selection bias because the inclusion criteria are speaking English and the access to the internet using smartphones or computers. We estimated 10% to 20% of patients who may be interested in the study without mobile devices or internet access. We will provide them with smartphones and data plans. In addition, we will develop the web program in different languages in the future. Second, there might be attrition rate among participants due to treatment burden (eg, chemotherapy) or other issues. We developed several strategies for participant retention. (1) We planned a recruitment strategy that follows recommended guidelines [51] for recruiting and retaining seriously ill patients and underserved populations in longitudinal research and focuses on enrolling interested, completely informed participants. (2) We will train research staff to establish rapport from the time of initial contact and demonstrate rapport and flexibility throughout all study activities. (3) We will send reminder emails or SMS text messages to participants to complete intervention modules and surveys every week. (4) We will minimize participant burden through web-based data collection, limiting the number of measurements, and allowing flexibility in learning modules. (5) Participant concerns will be responded to immediately, within reason. (6) To promote retention between data collections, we will send “thank you” notes, birthday cards, and holiday greetings. (7) We will reimburse each dyad member for participating in the study (eg, US $25 per person for interview, US $50 per person for clinical trial using a prorated incentive plan that reimbursements are disbursed at weeks 1, 5, and 8).

The brevity of the intervention and delivery via web-based format enhance dissemination possibilities. Results from this proposed study may lead to advances in translation into clinical practice. For future research, we may develop a web-based multilevel interventions that include more levels (eg, clinician team, clinic, local, state, and nation level), conduct larger and multicenter interventions (eg, cluster randomized clinical trials), and implement the web-based intervention program in multiple clinical sites nationally and internationally (eg, effectiveness-implementation hybrid design). In addition, we will incorporate potential biomarkers along with interventions to further understand the effects of the interventions. The ultimate goals will be to develop the web-based dyadic intervention (CRCweb) program and disseminate and translate it into clinical settings. The website will become publicly available to equip patients and caregivers with tools to better manage their multiple co-occurring symptoms and improve QOL.

In conclusion, developing a web-based dyadic intervention holds great promise to reduce PNS burden and improve QOL for patients with CRC receiving chemotherapy and their caregivers. The findings from this study will advance intervention development and implementation in cancer symptom management and palliative and psychosocial care as well as accelerate the transformation of technology-based programs into clinical practice.

Acknowledgments

The study was supported by the Oncology Nursing Foundation Research Grant (2022 RE03). The authors also appreciate the support from Emory University School of Nursing and Winship Cancer Institute.

Data Availability

Data sharing is not applicable to this protocol paper as no data were generated or analyzed. The data set generated and analyzed in the interview and clinical trial will be shared with other users only under a data sharing agreement that provides a commitment to the following: (1) use of these data for research purposes only and not for the purposes of identifying individual participants, (2) the securing of the data and any copies (soft or hard) generated from these data using secure filing and appropriate secure computer technology, and (3) destroying or returning the data after analyses are completed. The PI (YL) will coordinate requests

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for data and maintain documentation for requests and distributions. Emory University has an established Institutional Data Use Agreement that can easily be adapted and deployed.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Measures.
[DOCX File , 38 KB - resprot_v12i1e48499_app1.docx]

Multimedia Appendix 2
Peer review report by Oncology Nursing Foundation Research Grants (USA).
[PDF File (Adobe PDF File), 314 KB - resprot_v12i1e48499_app2.pdf]

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Abbreviations

AWS: Amazon Web Services
CRC: colorectal cancer
FOCUS: Family involvement, Optimistic attitude, Coping effectiveness, Uncertainty reduction, Symptom management
PI: principal investigator
PNS: psychoneurological symptoms
QOL: quality of life

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Protocol

Increasing Physical Activity in Persons With Spinal Cord Injury With an eHealth-Based Adaptive Exercise Intervention: Protocol for a Sequential Multiple Assignment Randomized Trial

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Abstract

Background: Participating in an adequate amount of physical activity to acquire health benefits is challenging for people with spinal cord injury (SCI) due to personal and logistic barriers. Barriers in the built and social environments may include lack of transportation, lack of accessible facilities or programs, and lack of training among fitness personnel. Low self-efficacy, lack of self-regulation skills, and improper outcome expectations are examples of personal barriers. Current approaches to investigating physical activity programs in people with SCI have been limited to traditional “one-size-fits-all” design, which has yielded low adherence rates, high dropout rates, and participants not maintaining physical activity levels at follow-up.

Objective: The primary aim of this study is to test the feasibility of a tele-exercise program that applies an adaptive intervention design for 30 adults with SCI, targeting increases in adherence to the exercise program and physical activity participation.

Methods: The Sequential Multiple Assignment Randomized Trial for Home-based Exercise and Lifestyle Tele-Health (SMART-HEALTH) is a 12-week, home-based, movement-to-music (M2M) program. The goal of a SMART-designed study is to develop an adaptive intervention that modifies support provisions based on response levels. In SMART-HEALTH, 2 groups of participants will undergo 3-week and 6-week asynchronous M2M interventions in the first phase. Participants who did not achieve the desired adherence rate (≥95% of video watch minutes) will be rerandomized into M2M Live (switch) or individualized behavioral coaching (augmented with the asynchronous M2M program). The study will primarily assess rates of recruitment or enrollment, adherence and retention, timing to identify nonresponders, and scientific outcomes (eg, physical activity and exercise self-efficacy). The study will qualitatively evaluate the acceptability of the study using semistructured interviews among participants who complete the 12-week intervention.

Results: Recruitment procedures started in June 2022. All data are expected to be collected by September 2023. Full trial results are expected to be published by March 2024. Secondary analyses of data will be subsequently published. Results will include exercise adherence rates; changes in self-reported physical activity levels and blood pressure; and changes in secondary conditions including pain, sleep, and fatigue. Thematic analysis of semistructured interviews will include results on participant enjoyment and acceptability of SMART-HEALTH and inform modifications for future delivery of the program.

Conclusions: This study will strengthen our understanding of the potential benefits of the tele-exercise intervention for people with SCI and build upon adaptive intervention design and its delivery strategies that aim to increase adoption and sustainable

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exercise behavior. This pilot trial will inform future SMART-designed studies and provide new and innovative strategies for investigating intervention effects on physical activity behavior in the SCI population.

Trial Registration: ClinicalTrials.gov NCT04726891; https://classic.clinicaltrials.gov/ct2/show/NCT04726891

International Registered Report Identifier (IRRID): DERR1-10.2196/47665

(JMIR Res Protoc 2023;12:e47665) doi:10.2196/47665

KEYWORDS

exercise; physical activity; spinal cord injury; adaptive intervention

Introduction

Approximately 302,000 individuals in the United States are living with spinal cord injury (SCI) [1]. Substantial evidence supports the benefits of exercise training for improving health and functional outcomes and managing the risk of chronic disease and secondary conditions related to the SCI (eg, cardiometabolic disease, obesity, and depression) [2-8]. Despite the benefits, people with SCI engage in considerably lower levels of exercise and physical activity participation compared with the general population of adults and individuals living with other health conditions [4,9,10]. This may have resulted from a multilevel of barriers that people with SCI experience with exercise and physical activity participation in the community (eg, a lack of accessible facilities or options, knowledgeable instructors, transportation, or social support) [9].

Furthermore, people with SCI, who initiated engaging in an exercise behavior, often have varying rates of success in standardized exercise interventions, which have been designed using a traditional "one-size-fits-all" approach (ie, exercise group vs control) [11,12]. Previous studies have often demonstrated low levels of adherence to exercise programs, high dropouts, and a large portion of the sample not continuing exercise behavior throughout the follow-up [13-15]. In addition, home-based exercise programs are a desirable approach for overcoming barriers and facilitating full participation that could be of great assistance to people with SCI. Tele-exercise programs are potentially more cost-efficient and convenient (ie, do not require transportation or large travel times) than programs offered in the community, making it easier to reach larger groups of people with SCI [16]. Collectively, these findings suggest that the design of future home-based exercise training studies should be more targeted and tailored interventions for people with SCI.

Adaptive interventions provide a flexible treatment regimen based on the participant's evolving status and specific needs, previously used in healthy behavior promotion research (eg, smoking cessation and weight loss) [17-20]. Sequential Multiple Assignment Randomized Trial (SMART) is an experimental design that enables investigators to answer whether, when, and how to alter treatment intensity and type to build an evidence-based adaptive intervention [21]. The use of the SMART design has the potential to optimize the design and delivery strategies of an exercise promotion intervention for maximizing adherence to the program in people with SCI; yet we are unaware of exercise interventions applied and tested this design for people with SCI.

We further note the importance of embedding behavioral approaches to increase physical activity in people with SCI. Based on prior research [22], the study design and delivery are grounded in social cognitive theory (SCT) [23,24], which has been used successfully to improve many health behaviors, such as diet and exercise adherence, in individuals with SCI. The main concept of SCT is the interplay between personal, environmental, and behavioral factors [25]. Outcome expectations [26-29], self-efficacy [28,30-32], social support [26,28,30,31], and self-regulation [26,31,33] are key constructs of SCT that have been associated with changes in various health behaviors in past studies, including several studies involving a broader group of people with mobility disability [27,30,33,34].

We propose a pilot, 2-phase SMART examining the feasibility of a 12-week tele-exercise intervention for improving adherence to the program and physical activity behavior in 30 adults with SCI, named the Sequential Multiple Assignment Randomized Trial for Home-based Exercise And Lifestyle Tele-Health (SMART-HEALTH). The applied exercise intervention is a novel movement-to-music (M2M) video program that incorporates enjoyable movement routines accompanied by music to improve cardiovascular capacity, muscular strength and endurance, balance, and range of motion. Evidence supports the efficacy of M2M in enhancing functional mobility (the timed up and go and 6-minute walk test) among adults with multiple sclerosis [35]. Also, 1 ongoing tele-exercise trial is testing the effectiveness of the M2M video program that includes >400 adults with physical disabilities (NCT03024320) [36]. The modified and scaled-up M2M program was delivered at a state-of-the-art exercise facility for people with disabilities (Lakeshore Foundation). This program integrates the principles of SCT through weekly newsletters that contained educational information aligned with the key constructs of SCT (self-efficacy, outcome expectation, knowledge, self-regulatory strategies, facilitators, or barriers) for promoting and maintaining behavior change.

The primary aim of this study is to assess the feasibility of the 12-week tele-exercise intervention with the SMART design application. The assessment of the feasibility focuses on recruitment or enrollment, adherence, and retention rates, resources and management issues, timing to identify nonresponders, and adverse events (AEs). The secondary aim is to qualitatively assess the acceptability of the SMART-HEALTH intervention. Acceptability will be assessed qualitatively via thematic analysis of semistructured exit interviews conducted at 3 months from baseline, with participants who complete the pilot study. The tertiary aim is to estimate average intervention effects and variability on the

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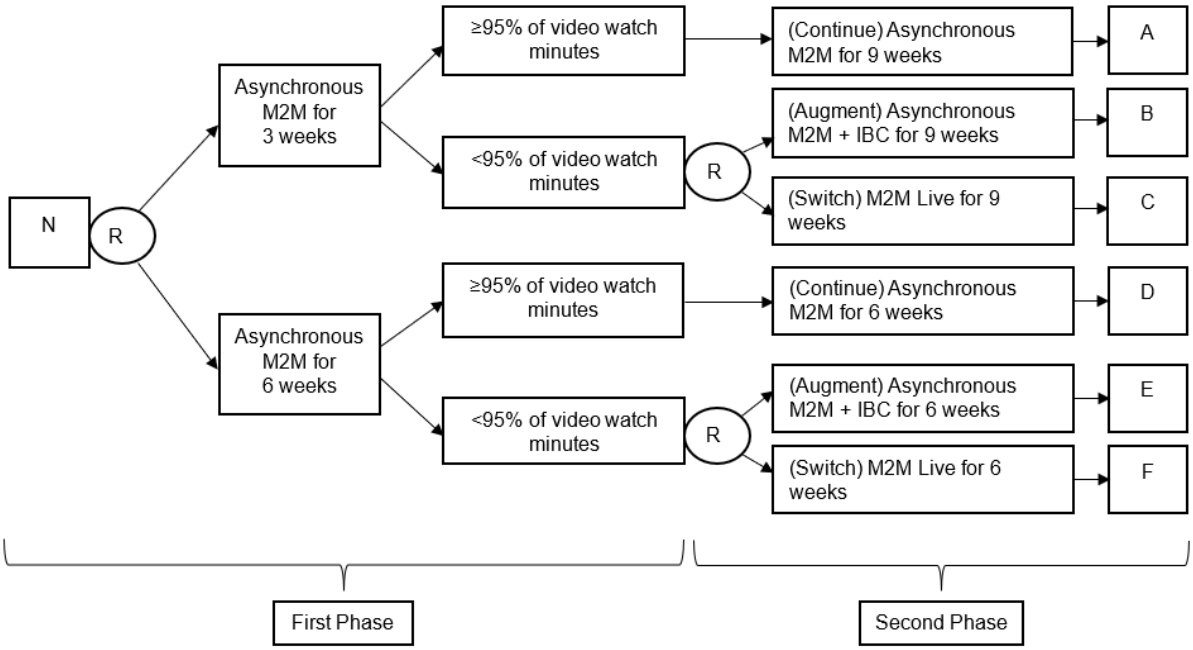
scientific outcomes (eg, video watch minutes, self-reported vs objectively measured physical activity) to determine effect sizes and potential for a larger trial. The information yielded by such a feasibility study will be critical for designing larger-scale projects that can establish the actual efficacy and effectiveness of the future SMART-HEALTH study.

Methods

Study Design

This pilot study applied a 2-phase SMART design. Thirty adults with SCI will be randomized with equal probability into 1 of 2 asynchronous, M2M exercise programs (using prerecorded videos) at the first phase of the intervention. The exercise minutes of the pre-recorded videos are set to progressively increase from 30 to 150 minutes per week throughout the 12 weeks. The response assessment will be administered at weeks 3 (group 1) and 6 (group 2) based on the predetermined adherence criteria to the intervention (average of 95% video watch minutes, ranging from 29 minutes to 143 minutes). Participants who meet or exceed the criteria will be considered as responders and continue the asynchronous program for the entire intervention period, whereas those who did not meet the criteria (nonresponders) will be rerandomized with equal probability into either synchronous, instructor-led M2M exercise program (ie, switch to M2M Live group) or behavioral coaching with asynchronous M2M exercise program (ie, augment with individual behavioral coaching; IBC). The study flow diagram includes the details of the interventions offered in each arm (Figure 1).

Figure 1. Sequential Multiple Assignment Randomized Trial for Home-based Exercise and Lifestyle Tele-Health (SMART-HEALTH) study design for people with spinal cord injury. IBC: individualized behavioral coaching; M2M: movement-to-music intervention; N: sample; R: randomize.



Ethics Approval

Ethics approval was obtained from the institutional review board (IRB) of the University of Alabama at Birmingham on March 10, 2021 (IRB-300006746), and registered at ClinicalTrials.gov (NCT04726891). Informed consent will be obtained from all participants prior to the research activities. For privacy and confidentiality protection, all data will be collected and stored on a secure, web-based database application, referred to as Research Electronic Data Capture (REDCap; Vanderbilt University). Participants will receive up to US $160 of monetary incentives using direct deposit in a reloadable debit card (ie, ClinCard). This includes US $25 for baseline assessments, US $60 for weekly post workout surveys (US $5 for each survey×12 surveys), US $50 for post intervention assessments, and US $25 for an exit interview at the end of the 12-week intervention.

Eligibility Criteria

The inclusion criteria are (1) age 18 years and older; (2) diagnosis of a traumatic SCI that occurred more than 12 months before enrollment; (3) ability to use the arms to exercise (ie, complete [C5 and below] or incomplete paraplegia and tetraplegia); (4) willingness and ability to participate in a 3-month home-based exercise program and study procedures (eg, having internet access, not having visual impairment that prevents watching exercise videos on a computer screen, having complete assessments available, ability to wear an accelerometer, and willingness to undergo multiple randomizations); (5) being physically inactive (defined as ≥150 minutes of moderate-to-vigorous intensity activities in a typical week) [37], and (6) having 1 or more affirmatives on the Physical Activity Readiness Questionnaire for Everyone (PAR-Q) [38] or physician approval for undertaking exercise training for those with 2 or more affirmatives on the PAR-Q. More than 1 affirmative on the PAR-Q indicates that the participant is at more than minimal risk for exercise-related complications, and therefore, physician approval will be required prior to enrolling such participants in this study. Exclusion criteria are (1) history (<6 months) of cardiovascular or pulmonary disease; (2) any unstable medical condition that is likely to compromise safety, like active pressure ulcer,

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pregnancy, or renal failure; and (3) any cognitive dysfunction or language barriers that would prevent participants from following English instructions.

Recruitment and Enrollment

We reviewed our database and identified 1016 persons who fit our inclusion criteria (disability status and expressed interest to participate in future research). Additionally, we identified 347 people with spinal cord dysfunction through an external database. We sent out invitation emails to all potential participants across the United States.

We advertised the study information through social media channels and the Lakeshore Foundation. The Lakeshore Foundation has the ability to distribute an electronic newsletter for people with SCI and other disabilities, social media channels, community events, and through the National Center on Health, Physical Activity and Disability (a center funded by the US Centers for Disease Control and Prevention).

Interested individuals can contact the study staff via phone, email, or online application linked with REDCap. A digital form of informed consent is given to eligible participants to review the study details, signed, and submitted. A project coordinator, who is responsible for participant communications and process management, follow-ups with the prospective participant via phone call, verbally reviews the consent form, answers any study-related questions and concerns, and guides the following study procedures.

Randomization Allocations and Other Trial Considerations

Participants are potentially randomized up to twice throughout the 12-week intervention period. A study statistician generated 3 randomization sequences a priori using a computer-generated random schedule (SAS version 9.4; SAS Institute) with a 1:1 allocation ratio and a permuted block approach. The sequences were stored into a randomization module in the REDCap and external program, which allows project staff to unfold the randomization schedule when needed (after completing baseline assessment and after a 3-week or 6-week check-in call). One sequence was used to perform the first randomization of 30 participants into one of the asynchronous M2M exercise groups (group 1 vs group 2), whereas other 2 sequences were used to perform the second randomization of participants who need a transition from asynchronous M2M exercise to M2M Live or IBC based on the adherence rate to the intervention. Response assessment (ie, adherence rate to the program) will be administered at week 3 and week 6, respectively, for the intervention groups 1 and 2. Participants identified as responders who watched the video more than 95% (accounting for 5% error rate) will continue with the first treatment regime. Participants will be considered nonresponders if they adhere to the exercise program less than 95% using video watch minutes. This is based on observation with a few weight loss studies that suggested sessions 3 and 7 as potential time points for intervening with participants to assess needs and difficulties and make necessary changes to maximize the treatment response [39-42].

The outcome assessor will be blinded to group allocation (single-blinded trial design). Due to the nature of the intervention, it is not plausible to blind participants and study staff who enroll participants and monitor the intervention delivery. However, study investigators and staff who are involved in data analyses and reporting will be blinded to group assignments throughout the study period.

Access to the REDCap database will be given to the study personnel only, including the biostatistician and data entry or management personnel. Data that are analyzed will be exported in a deidentified format. The identities of participants will not be revealed in the presentation or publication of any result from this project.

Home-Based Intervention

Overview

The interventions will be delivered through Canvas, which is a secured, commercialized learning management system. First, all participants will receive weekly notifications when a new module is available on Canvas, including exercise videos and educational studies. The weekly notifications can be delivered through the Canvas system and email. Third, participants will be able to leave comments and questions on exercise videos, educational studies, and post workout comment section. Fourth, to ensure any questions or technical issues can be addressed in a timely manner, participants will be able to reach the study team via multiple communication channels, including a study phone number, email, or messaging via the Canvas system.

Prerecorded, Asynchronous M2M Videos

Both groups of participants receive the same exercise prescriptions at the first phase of the intervention. The M2M program provides a sequence of exercise routine, which is accompanied by music to improve range of motion, muscular strength and endurance, cardiovascular capacity, and balance or proprioception. The weekly exercise video is set to progressively increase the exercise minutes to enable the participants to reach and exceed the recently published SCI exercise guideline [38]. Both groups of participants will begin with 30 minutes of exercise (twice weekly or 15 minutes per session) and increase the minutes incrementally until they reach the SCI guideline of 90 minutes at week 6 (3 times weekly or 30 minutes per session) and 150 minutes at week 9 (3 times weekly or 50 minutes per session). The detailed exercise prescription is presented in Table 1.

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Table 1. Description of exercise components and prescriptions in minutes per week.

Exercise Component	Week 1, minutes	Week 2, minutes	Week 3, minutes	Week 4, minutes	Week 5, minutes	Week 6, minutes	Week 7, minutes	Week 8, minutes	Week 9, minutes	Week 10, minutes	Week 11, minutes	Week 12, minutes
ROM I[a]	5	5	5	5	5	N/A[b]	N/A	N/A	N/A	N/A	N/A	N/A
ROM II	N/A	N/A	N/A	5	5	5	5	5	5	5	5	5
Muscular Strength I	5	5	5	5	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Muscular Strength II	N/A	N/A	N/A	N/A	5	5	5	5	N/A	N/A	N/A	N/A
Muscular Strength III	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	5	5	5	5
Aerobic I	N/A	N/A	N/A	5	5	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Aerobic II	N/A	N/A	N/A	N/A	N/A	10	10	10	10	10	10	10
Aerobic III	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	10	10	10	10
Aerobic IV	N/A	N/A	N/A	N/A	N/A	N/A	N/A	10	10	10	10	10
FSB I[c,d]	5	5	5	5	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
FSB II[c,d]	N/A	N/A	N/A	N/A	5	5	5	5	N/A	N/A	N/A	N/A
FSB III[c,d]	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	5	5	5	5
Cooldown	N/A	5	5	5	5	5	5	5	5	5	5	5
Total exercise per session	15	20	20	30	30	30	30	40	50	50	50	50
Total exercise per week	30	40	40	60	60	90	90	120	150	150	150	150

[a]ROM: range of motion.

[b]N/A: not available.

[c]FSB: functional strength and balance.

[d]Participants will be instructed to repeat the prerecorded videos 2 times per week for the first 5 weeks (week 1-5) and then increase the repetition to 3 times per week for the second 7 weeks (weeks 6-12).

At week 3 and week 6, adherence to the exercise program will be administered using Canvas video analytics. Participants who did not adhere to more than 95% of prescribed video watch minutes will be considered as nonresponders. These individuals will be communicated with by research staff at a prescheduled check-in date and guided to the changes of the program at the second phase intervention period:

IBC Group

Participants who are allocated into the IBC group will receive the remaining asynchronous M2M exercise prescriptions and augmented with weekly behavioral coaching. The first session was 50 minutes, and the remaining sessions were approximately 15 minutes. The coaching is designed to improve self-regulatory skills based on prior research and help them stick to the exercise prescription. An example of tailoring the exercise prescribed involves setting a goal of completing the exercise routine 1 time for the upcoming week instead of 3 times. The coach will be trained in motivational interviewing to help the participants modify their exercise habits. Telehealth coaching alone has been shown to increase self-reported physical activity in adults with SCI.

Synchronous, Instructor-Led M2M Program

Participants who are allocated into M2M Live will switch to one-on-one, synchronous tele-exercise training with an M2M instructor. M2M Live provides accountability and immediate, tailored feedback along with custom movements and music. Videoconference-delivered exercise has been shown as feasible among adults with SCI. During the first session of M2M Live, the participant will meet 1 time per week with the M2M instructor and perform an exercise session. The session will be video recorded, so participants can go back and complete the remaining sessions of the week.

Educational Newsletter

All participants will receive an educational newsletter per week, discussing health behavior change strategies such as goal-setting, planning, and coping with barriers. The purpose is to educate participants on self-regulation strategies and health-promoting behaviors.

Remote Study Procedures

All study procedures, including screening, consent, data collection, and intervention, are conducted remotely at home. Survey data are collected through REDCap. Participants who complete baseline assessments will receive all equipment via

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mail and will be randomly allocated to 1 of the 2 M2M interventions. After randomization, each participant will receive an invitation email with a link to the Canvas platform, instructed to create a password, and schedule a check-in date at week 3 or 6 based on the group assignment. Participants will be instructed to perform the exercise program at least 3 times per week. Data collection equipment includes: (1) Chromebook (Lenovo Chromebook or Acer Chromebook 15); (2) Fitbit (Inspire 2, Fitbit); (3) Digital peak flow meter (Peak Flow Meter SMPF-1 and SONMOL); (4) blood pressure monitor (Omron 3 Series Upper Arm, Omron); (5) Two 454-gram wrist weights (Neoprene, thumb hole weights, Biicoon).

Outcomes

Aim 1: Feasibility Metrics

All feasibility outcomes will be collected throughout the 12-week study period. This study will gather metrics of feasibility, including recruitment or enrollment (eg, frequency of contact with potential participants and recruitment sources, with questions such as, Where did you hear about our study? and the percentage of individuals who follow through the enrollment procedure); adherence and retention rates (eg, video watch minutes, attendance of M2M Live or IBC coaching sessions); resources and management issues (eg, preparation and completion time in minutes for functional outcome assessment; time in minutes for survey assessment); timing to identify nonresponders; and AE. The study team will monitor AEs throughout the study period and report them followed by the Behavior Change Consortium of the National Institutes of Health. The four types of AEs are (1) falls, (2) cardiovascular-related episodes, (3) musculoskeletal-related events, and (4) health care use. The severity and causality of each AE will be assessed and will be reported to IRB and relevant regulatory parties when necessary.

Aim 2: Acceptability

Acceptability will be assessed qualitatively via thematic analysis of semistructured exit interviews conducted at 3 months from baseline with participants who complete the pilot study.

Aim 3: Scientific Outcomes

Table 2 shows the physical and psychosocial outcomes, the schedule of data collection, and instruments used.

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Table 2. Measures, instruments, and time points.

Variables and instruments	Time point
Exercise adherence	
Tracking exercise video watch minutes (percentage)	12-week intervention period
Physical activity	
Leisure Time Physical Activity Questionnaire for People with Spinal Cord Injury	Pre or post
Postworkout survey	12-week intervention period
Lung function	
Spirometry	Pre or post
Pain intensity	
NIH[a] PROMIS[b] Pain Intensity Adult Short Form 3a	Pre or post
Pain interference	
NIH PROMIS Pain Interference Adult Short Form 8a	Pre or post
Sleep quality	
NIH PROMIS Sleep Disturbance Adult Short Form 8a	Pre or post
Fatigue	
NIH PROMIS Fatigue Adult Short Form 7a	Pre or post
Health-related quality of life	
NIH PROMIS 10 Global Health Items	Pre or post
NIH PROMIS Ability to Participate in Social Roles and Activities Short Form 8a	Pre or post
Exercise enjoyment	
Physical Activity Enjoyment Scale	Post
Social cognitive theory constructs	
Exercise Self-Efficacy Scale	Pre or post
Multidimensional Outcomes Expectations for Exercise Scale	Pre or post
Exercise Goal-setting and Planning Scale	Pre or post
Barriers in Physical Activity Questionnaire–Mobility Impairment	Pre or post
Social Provisions Scale	Pre or post
Demographics and health history	
Questionnaire	Pre
Blood pressure	
Blood pressure monitor	Pre or post
App quality and usability	
Systems Usability Scale	Post

[a]NIH: National Institutes of Health.

[b]Patient-Reported Outcomes Measurement Information Systems.

Adherence to the Exercise Program

Video statistics (as a percentage) will be recorded through a secured, commercialized learning management system.

Physical Activity

Physical activity will be administered using both objective and self-reported measures. Objective physical activity will be measured using Fitbit throughout the 12-week intervention period, while self-reported physical activity will be measured using the weekly Leisure Time Physical Activity Questionnaire for People With SCI.

Postworkout Survey

Weekly survey will be administered within the learning management system to capture the perceived intensity of exercise and any verbatim comments to the program.

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Physiological Function

All functional teleassessment will be conducted via videoconferencing calls (teleassessments). Data collection toolkits (eg, blood pressure monitors and spirometry) will be mailed to the participants' location upon the completion of randomization. The data collection will take approximately half an hour and led by an exercise physiology specialist.

Psychosocial Health

Psychosocial health outcomes will include pain, sleep, fatigue, perceived exercise enjoyment, quality of life, and SCT constructs. These outcomes will be collected via REDCap. All self-report data will be collected directly through electronic questionnaire packets delivered via REDCap at baseline and post intervention assessments. All question items of the questionnaire packets are made as required to answer to prevent any missing data. Each questionnaire packet is also set to be delivered to participants' email 3 times, within a span of 3 days if it is not completed. Research staff will be notified via REDCap when the third packet was sent out to participants. A follow-up phone call will be made to ensure participants receive the packet and remind them to complete it within the next 3 days. Packets that are incomplete within the 3 days after the phone call will be closed and recorded as incomplete, missing data.

Analysis

Overview

All data will be exported and analyzed using SPSS (version 22.0; IBM). Data will be initially examined for variations, outliers, errors, and patterns of missing values. Missing data will be inputted using multiple imputation techniques where necessary based on the assumption that the missingness mechanism is at random. All statistical analyses will be conducted in an intent-to-treat manner at the individual level.

Aim 1

The primary outcomes of this pilot study will include enrollment rate, retention rate, and completion rate of surveys and physiological measures. Process, resource, and management feasibility will initially be examined via percentage, frequency analysis, and descriptive statistics.

Aim 2

A qualitative study of participants' experiences, perceptions, and suggestions regarding the SMART-HEALTH program will be completed at week 12. This study will refine the study components and implementation processes for a future trial. In brief, participants who complete the SMART-HEALTH program will take part in single, one-on-one semistructured interviews with questions focusing on what worked and did not work. Interviews will be audio-recorded, transcribed, and analyzed using thematic analysis using a qualitative descriptive design [43].

Aim 3

The study will estimate recruitment and retention rates, as well as estimate outcomes and variability of efficacy outcomes for a larger clinical trial (aim 3), which will measure rates of physical activity, psychosocial variables (eg, depression), and physiological variables (eg, lung function). Additional fidelity measures will include adherence to exercise intervention (minutes of sessions viewed), number of coaching sessions completed, and intervention safety (number of AEs).

Power

We will aim to enroll at least 40 people with SCI, considering 25% of the attrition rate based on the preliminary data obtained in the exercise intervention study with the M2M program [44]. The sample size of 30 participants aligns with the statistical recommendations for pilot trials to determine precise estimates, and the expectation that at least 5 participants will move each rerandomization group aligns with the statistical recommendations for the pilot SMART trial to determine precise estimates [45,46].

Results

This study was approved by the university IRB on March 10, 2021, and initiated on May 1, 2021. Recruitment started on June 22, 2022, and the first participant was enrolled on June 15, 2022. The trial is expected to be completed in September 2023.

Discussion

Principal Findings

This paper has presented the background and design for a SMART-HEALTH study investigating the feasibility of a home-based M2M exercise program, using an adaptive design for adults with SCI. Exercise is a critical health-enhancing behavior; yet, substantial evidence supports various challenges of engaging in the recommended physical activity levels for many people with SCI. Tele-exercise programs may be suitable to overcome logistic barriers to exercise participation (eg, lack of transportation, travel time, and accessible facilities) and potentially more cost-efficient and convenient than programs offered in the community [16]. In addition, the application of the adaptive design to exercise intervention allows investigators to provide more tailored and targeted program delivery for people with SCI based on their needs while maintaining systematic approaches and scientific rigor. The ultimate goal of the SMART-HEALTH study is to find effective strategies to help guide and shape the exercise behavior of people with SCI toward higher levels of adoption and sustainable exercise participation. The SMART-HEALTH study will test multiple sets of adaptive intervention designs and their delivery strategies to optimize future intervention.

Strength and Limitations

The trial uses an innovative study design to address adherence to exercise interventions among people with SCI. It addresses a growing need among physicians treating patients with mobility disabilities to have easily accessible eHealth home-based exercise videos that can be tailored to the functional level of their patients. This is a pilot trial to assess the feasibility of using a SMART design and is not powered for effectiveness.

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Conclusions

The trial serves to inform the development of adaptive interventions, including whether, how, or when to alter treatment intensity, type, or delivery. In addition, this can determine the actual efficacy of home-based exercise based on the SCI-specific physical activity programs for improving adherence to the program and physical activity.

Acknowledgments

This study was supported by the Craig H. Neilsen Foundation (645335). The contents of this study do not necessarily represent the policy of these groups or the endorsement of the US federal government.

Data Availability

The data generated as part of this study will be made available through a data repository. Deidentified data sets will be shared upon reasonable request.

Authors' Contributions

JW contributed to the conception and design of the study protocol, exercise intervention, drafted and manuscript writing, and supervision of the entire process of the study. JR, HJY, and BL contributed to the conception and design of the study protocol, exercise programs, and editing of the manuscript. DP contributed to this study as the study physician and reviewed and signed the medical clearance for participating in an exercise program. TM supervised the statistical aspects of the trial and contributed to editing the manuscript. YK and JG contributed to the recruitment strategy; design, delivery, and evaluation of the trial; and drafting of the manuscript. All the authors approved and critically revised the manuscript.

Conflicts of Interest

TM served as a consultant to Novo Nordisk through a consulting arrangement to serve on Obesity Management in Primary Care Advisory Board. He is serving as a consultant providing design and consulting support to Heart Rhythm Clinical Research Solutions. TM also served as a consultant to New Balance Foundation Obesity Prevention Center. All other authors declare that they have no conflicts of interest.

Multimedia Appendix 1
Peer-review report by the Neilsen Foundation (USA).
[PDF File (Adobe PDF File), 372 KB - resprot_v12i1e47665_app1.pdf]

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Abbreviations

AE: adverse event
IBC: individual behavioral coaching
IRB: institutional review board
M2M: movement-to-music
PAR-Q: Physical Activity Readiness Questionnaire for Everyone
REDCap: Research Electronic Data Capture
SCI: spinal cord injury
SCT: social cognitive theory
SMART: Sequential Multiple Assignment Randomized Trial
SMART-HEALTH: Sequential Multiple Assignment Randomized Trial for Home-based Exercise and Lifestyle Tele-Health

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Protocol

Examining the Use of Text Messages Among Multidisciplinary Care Teams to Reduce Avoidable Hospitalization of Nursing Home Residents with Dementia: Protocol for a Secondary Analysis

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Abstract

Background: Reducing avoidable nursing home (NH)–to-hospital transfers of residents with Alzheimer disease or a related dementia (ADRD) has become a national priority due to the physical and emotional toll it places on residents and the high costs to Medicare and Medicaid. Technologies supporting the use of clinical text messages (TMs) could improve communication among health care team members and have considerable impact on reducing avoidable NH-to-hospital transfers. Although text messaging is a widely accepted mechanism of communication, clinical models of care using TMs are sparsely reported in the literature, especially in NHs. Protocols for assessing technologies that integrate TMs into care delivery models would be beneficial for end users of these systems. Without evidence to support clinical models of care using TMs, users are left to design their own methods and protocols for their use, which can create wide variability and potentially increase disparities in resident outcomes.

Objective: Our aim is to describe the protocol of a study designed to understand how members of the multidisciplinary team communicate using TMs and how salient and timely communication can be used to avert poor outcomes for NH residents with ADRD, including hospitalization.

Methods: This project is a secondary analysis of data collected from a Centers for Medicare & Medicaid Services (CMS)–funded demonstration project designed to reduce avoidable hospitalizations for long-stay NH residents. We will use two data sources: (1) TMs exchanged among the multidisciplinary team across the 7-year CMS study period (August 2013-September 2020) and (2) an adapted acute care transfer tool completed by advanced practice registered nurses to document retrospective details about NH-to-hospital transfers. The study is guided by an age-friendly model of care called the 4Ms (What Matters, Medications, Mentation, and Mobility) framework. We will use natural language processing, statistical methods, and social network analysis to generate a new ontology and to compare communication patterns found in TMs occurring around the time NH-to-hospital transfer decisions were made about residents with and without ADRD.

Results: After accounting for inclusion and exclusion criteria, we will analyze over 30,000 TMs pertaining to over 3600 NH-to-hospital transfers. Development of the 4M ontology is in progress, and the 3-year project is expected to run until mid-2025.

Conclusions: To our knowledge, this project will be the first to explore the content of TMs exchanged among a multidisciplinary team of care providers as they make decisions about NH-to-hospital resident transfers. Understanding how the presence of evidence-based elements of high-quality care relate to avoidable hospitalizations among NH residents with ADRD will generate knowledge regarding the future scalability of behavioral interventions. Without this knowledge, NHs will continue to rely on ineffective and outdated communication methods that fail to account for evidence-based elements of age-friendly care.

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KEYWORDS

age-friendly health systems; Alzheimer disease; communication; dementia; nursing homes; older adults

Introduction

Overview

There are over 15,000 nursing homes (NHs) in the United States, where care is delivered to over 1.3 million residents [1]. Approximately 48% of NH residents have a diagnosis of Alzheimer disease or a related dementia (ADRD) [2]. NH residents with ADRD are at high risk for hospital transfer due to high incidence of comorbidities, polypharmacy, and progressive loss of language, resulting in difficulty communicating preferences [3-5]. Reducing avoidable NH-to-hospital transfers of residents with ADRD has become a national priority due to the physical and emotional toll it places on residents and the high costs to Medicare and Medicaid [6-8]. NH-to-hospital transfers result in expenditures of more than US $2.6 billion annually [9] and in as many as 60% of cases, they are avoidable, meaning the resident could have been safely managed in the NH [10,11]. Early illness recognition and treatment could prevent the need for hospital transfer altogether, ultimately reducing morbidity in residents with ADRD while controlling costs [7,9].

Avoidable NH-to-hospital transfers refer to transfers that follow acute flare-ups of clinical conditions that could have been avoided if appropriate preventative care had been provided in the NH [10]. Recent studies have identified clinical factors such as falls, fever, urinary symptoms, and incontinence that contribute to avoidable transfers [11]. Dementia was the only high-risk clinical condition associated with avoidable NH-to-hospital transfers [11]. Other factors contributing to the decision to transfer, for those deemed avoidable, included a condition that could have been safely managed in the NH, better communication, early detection of new signs or symptoms, and earlier discussion of resident or family preferences [11]. Others have reported communication problems as barriers to timely care for NH residents [12,13]. Specifically, barriers include failure of the communication medium, evening or weekend illness onset with concomitant difficulty contacting an on-call physician, clinical decision-makers who interact through intermediaries, and communication of inappropriate or inaccurate information [13]. Improving communication among health care team members could have a considerable impact on reducing avoidable NH-to-hospital transfers.

NH-to-hospital transfer decision-making is complex and relies on the timely transmission of information among the multidisciplinary team. Unfortunately, many NHs rely on antiquated methods of communication (eg, phone and fax) rather than leveraging modern, convenient, and low-cost options, like exchanging text messages (TMs), which could improve health information sharing, especially in resource-limited settings [12,14-16]. In a pilot analysis using 6 months of TMs exchanged among a multidisciplinary team, the most common messages sent (3244/8946) and received (2319/8946) were about patient updates (updates on symptoms, vital signs, and lab and test results) [17]. However, greater understanding is needed regarding how communication differs between residents with and without ADRD and how TMs can be used among the NH multidisciplinary team to decrease avoidable transfers.

We propose to examine the content of TMs using a framework from Age-Friendly Health Systems that includes 4 evidence-based elements of high-quality care called the 4Ms (What Matters, Medication, Mentation, and Mobility) [18]. Age-Friendly Health Systems is an initiative builds upon a number of fundamental characteristics common to existing geriatric care models, including reliable use of evidence-based care, staff who are specifically trained and proficient in the care of older adults, high-performing care teams focused on measurable outcomes, a systematic approach for coordinating care with other organizations, and engaging patients and their families in a clear process for eliciting goals and priorities and using those goals to individualize care [19]. The 4M framework addresses the core issues that should drive all decision-making in the care of older adults and is a way of systematically rethinking care in ways that improve patient health and satisfaction. A critical need exists to examine how convenient, low-cost communication options like TMs can reduce avoidable NH-to-hospital transfers of residents with ADRD.

Aims and Research Questions

The objective of this study is to understand how members of the multidisciplinary team communicate and how TMs can be used to avert poor outcomes for NH residents with ADRD, including hospitalization. Our scientific premise is that if multidisciplinary communications are timely and centered around the evidence-based elements of high-quality care for older adults (4Ms), more appropriate decisions will be made, in this case regarding hospital transfer. Thus, the project will consist of complementary steps aimed at (1) identifying documentation of the 4Ms in health information shared by the multidisciplinary team through electronic TMs 2 weeks before NH-to-hospital transfer of residents with ADRD, (2) exploring the association between the 4Ms found in TMs and avoidable NH-to-hospital transfers, and (3) comparing communication patterns of multidisciplinary teams making transfer decisions about residents with and without ADRD.

Methods

Overview

Using a retrospective design, we will identify documentation of the 4Ms in health information shared by multidisciplinary teams through electronic TMs and compare communication patterns that occur when making transfer decisions about residents with and without ADRD. This project will use data collected from a Centers for Medicare & Medicaid (CMS)–funded demonstration project designed to reduce avoidable hospitalizations for long-stay NH residents [20,21]. The goals of the project for long-stay NH residents were to

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reduce the frequency of avoidable hospital admissions and readmissions, improve resident health outcomes, improve the process of transitioning between inpatient hospitals and NHs, and reduce overall health care spending. The project included a multifaceted intervention implemented within 16 NHs in the midwestern United States. The intervention included an advanced practice registered nurse (APRN) embedded full-time within each NH, use of the Interventions to Reduce Acute Care Transfers (INTERACT) tool [22], and an expert support team comprising nurses, social workers, technology experts, and medical directors. Further, the project included enhanced electronic communication using health information exchange, specifically the use of a collaborative text messaging system.

Ethics Approval

All procedures were approved by the University of Missouri Institutional Review Board (2092039).

Data Sources

We will use two data sources for this project: (1) TMs and related attributes (eg, sender, recipient, date, and timestamp) and (2) a survey completed by APRNs about NH resident transfers. The TMs were exchanged through a Health Insurance Portability and Accountability Act (HIPAA)–compliant communication and clinical collaboration tool primarily designed to be used among providers, pharmacies, and prescribers. The messaging platform includes the capability to communicate with outside vendors, patients, and anyone seeking to communicate protected health information in a secure environment that meets the requirements of the National Institute of Standards and Technology as well as the Health Information Technology for Economic and Clinical Health Act [23]. Users can access the messaging platform using a browser or mobile device (app). The platform includes workflow features specifically designed for the long-term care and postacute setting, such as read receipts, average response time tracking, adding and removing users from a message, and multiuser accounts with shared names for easy identification. The data set includes sender, recipient, date, and time stamp for each message. Crosswalks have been developed linking individual users to their roles (eg, bedside nurse, unit manager, director of nursing, APRN, and medical doctor [MD]).

The second data source is a Qualtrics survey completed by APRNs that included the INTERACT tool every time a resident transfer occurred during the study period (August 2013-September 2020). Broad categories of the survey included resident characteristics, risk factors for hospitalization, acute change in condition, nonclinical factors contributing to the transfer, and actions taken to evaluate and manage the change in condition before transfer. Individual items within each of the broad categories described common clinical and nonclinical factors that helped clinical staff understand the reasons for the transfer and process improvement considerations to avoid future transfers. APRNs completed the tool for each transfer using a combination of chart review and nurse interviews. These procedures included (1) monthly review of all INTERACT surveys by a team composed of the APRN, project coordinator, and APRN supervisor; (2) identification of resident and NH factors contributing to the transfer; and (3) agreement by the team on the question “Was the transfer potentially preventable (avoidable)?” using the “five whys” quality improvement technique [24]. This technique is an iterative interrogative approach to exploring cause and effect and was used by the team to assure root causes of transfers were considered when establishing agreement on which transfers were deemed avoidable versus unavoidable.

Sample

We will extract TMs and merge them with resident transfer data for NHs that participated in the CMS demonstration project. Between August 2013 and September 2020, there were 2551 resident transfers, of which 528 had a diagnosis of ADRD. We will extract TMs for 2 weeks before the resident transfer date. This time period was selected because there is evidence that technology can facilitate earlier detection of declining conditions (1-2 weeks earlier) when used to assess older adults [25].

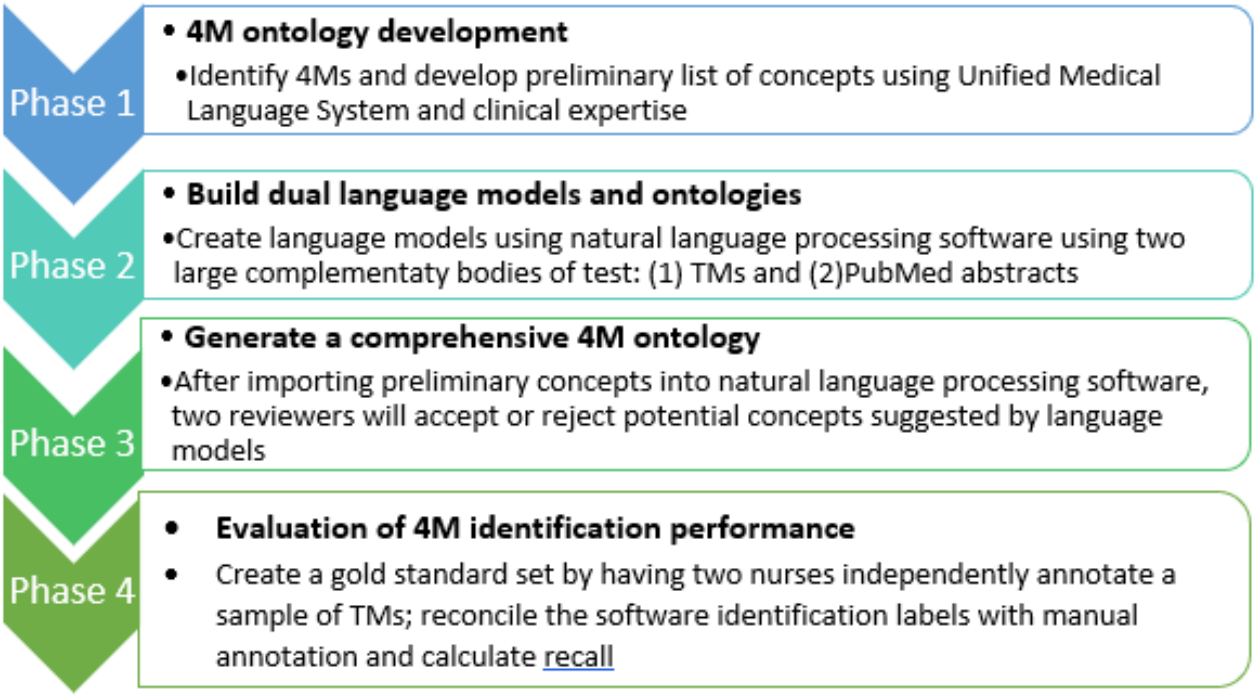
4M Ontology Development (Aim 1)

Overview

We will use a 4-phased approach (see Figure 1) using standardized vocabularies, clinical expertise, and natural language processing (NLP) to generate a 4M ontology and quantify the 4M content in TMs sent or received 2 weeks before NH resident transfer to the hospital. To enable the extraction of 4M knowledge from TMs, we first need a taxonomy (a set of terms) that formalizes the hierarchical relationships among concepts and specifies the terms to be used to refer to each. From the taxonomy, we can begin to develop an ontology that identifies and distinguishes concepts and their relationships. In information science, ontology is a data model that represents a set of concepts within a domain and the relationships between those concepts [26]. Ontology formalizes the relationships among concepts, which allows computers and humans to interpret the semantic relationships among concepts and infer implicit knowledge [27].

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Figure 1. Four phases to generate the 4M ontology. 4M: what matters, medication, mentation, and mobility; TM: text message.



Phase 1: 4M Taxonomy Development

While many clinical (eg, Systematized Nomenclature of Medicine Clinical Terms [SNOMED]) and nursing (eg, International Classification for Nursing Practice [ICNP]) standardized languages exist, they might not adequately describe the TMs. The first step in creating our 4M ontology is to use Metamap, the NLP tool provided by the Unified Medical Language System, to extract concepts from our TMs that have relevant semantic types such as “mental process” (menp), “sign or symptom” (sosy), or “clinical drug” (clnd) [28]. The Unified Medical Language System is a compendium of many health terminologies, including SNOMED, INCP, North American Nursing Diagnosis Association, and others, that only extracts concepts with relevant semantic types [29]. Extracted concepts will be reviewed by nurse-clinician scientists with extensive research expertise in NH care and arranged in a taxonomy. The resulting taxonomy will be enriched by the same experts with concepts that might not appear in our TMs. The nurse-clinician scientists will review these lists and make recommendations for changes (eg, addition and removal of concepts and addition and removal of synonyms). The NLP pipeline will be implemented in the Python Natural Language Toolkit and will use the newly developed taxonomy. The NLP pipeline is the set of ordered stages from a labeled data set to create a classifier that can be applied to new samples (ie, supervised machine learning classification). The above procedure will be performed several times, followed by a taxonomy refinement, until at least 90% of the 4M information (ie, 90% recall) is extracted from the entire sample.

Phase 2: Building Dual Language Models

We will use two large bodies of text to generate two possibly complementary language models with the NLP software: (1) TMs and (2) PubMed abstracts. These 2 sources were selected because they will allow us to extract a complementary and diverse range of concepts. TMs include clinical jargon and abbreviations, whereas PubMed abstracts have more standardized concepts used in the scientific literature. For the TM source, we will obtain all TMs pertaining to residents with ADRD who had a hospital transfer across the entire CMS demonstration project period (August 2013-September 2020). For the PubMed source, we will extract all available PubMed abstracts containing relevant Medical Subject Headings (MeSH) descriptors. Text from each source will be converted into a single text (.txt) file and uploaded into Metamap. We will use Metamap to perform text preprocessing, convert frequently co-occurring words into triadic expressions (eg, “nurse communicates to physician”), and build language models as described in phase 1.

Phase 3: Generating a Preliminary 4M Ontology

We will harmonize the TMs and PubMed versions of the 4M ontology. Two nurse-clinician scientists will independently review and accept or reject suggested concepts for each of the 4Ms. The 2 reviewers will compare lists of words and expressions and discuss discrepancies. If the 2 reviewers cannot come to an agreement on whether a word or expression should be included as a 4M concept synonym, an adjudicator will make the final decision. The output from this step will be a preliminary ontology for each of the 4Ms.

Phase 4: Evaluation of NLP 4M Identification Performance Using a Gold Standard Set

We will collect a random sample of TMs, using stratified sampling, from 10% of the resident transfers during the study period. Two nurse-clinician scientists will manually review each TM for the presence or absence of each of the 4Ms.

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Relative observed agreement (percent agreement between 2 raters) and interrater reliability (Cohen) will be calculated for each of the 4Ms. The 2 nurses plus a third nurse adjudicator will discuss nonagreement until consensus is achieved. Next, we will use our Natural Language Toolkit NLP software to identify 4Ms in the same gold standard TM set. We will then compare the NLP identification labels to the manual annotation and calculate recall (the NLP software's ability to identify all notes with a positive occurrence of a particular symptom), precision (proportion of notes with a particular symptom endorsed by NLP), and *F*-measure (a measure of test accuracy that considers both precision and recall). *F*-measures range from 0 (no precision and recall) to 1 (perfect precision and recall). Last, we will review all instances of disagreement between the NLP software identification labels and gold standard annotations. After we validate our 4M extraction pipeline, we will label each TM in our data set with a 4-dimensional vector that would represent the amount of each of the 4Ms that it contains (ie, matter, medication, mentation, mobility). For example, the TM "Resident was depressed after falling and breaking hip" will be labeled as (0,0,1,1). The 4M content will be further used in the analysis for aim 2.

Exploring the Association Between the 4Ms Found in TMs and Avoidable NH-to-Hospital Transfers (Aim 2)

Using our rich data set, we will compare the representation of the 4Ms in TMs about avoidable and unavoidable transfers while controlling for resident characteristics. We will build a generalized linear model of the Poisson process to compare the representation of the 4Ms in TMs about transfers that were avoidable and unavoidable while controlling for resident characteristics including sex, race or ethnicity, severity of ADRD, and advanced directive status. Our hypothesis is that TMs about avoidable transfers will have more evidence (higher frequency of terms) of the 4Ms compared to TMs about unavoidable transfers.

Comparing Communication Patterns of Multidisciplinary Teams Making Transfer Decisions About Residents With and Without ADRD (Aim 3)

Using the same 2 data sources, we will use social network analysis (SNA) to discern communication and organizational patterns found in TMs occurring in the 2 weeks before NH-to-hospital transfers of residents with and without ADRD. This analysis will allow us to visualize networks and calculate social network measures including density, clustering coefficient, hierarchy, and centralization. Our hypothesis is that TM communication about residents with ADRD will have more decision-making interactions (network density), higher rates of information exchange (clustering coefficient), and more individuals communicating with each other (centralization) compared to TM communication about residents without ADRD. Our premise for this hypothesis is that the gradual loss of language that occurs with ADRD will impact the individual's ability to communicate with the care team in the earliest stages, regardless of dementia severity [5]. This progressive decline sometimes leaves the person living with ADRD unable to make autonomous decisions. Understanding communication patterns both visually and quantitatively when the multidisciplinary team is making decisions about residents with and without ADRD could help inform decision-making.

Results

Data Extraction and Preparation

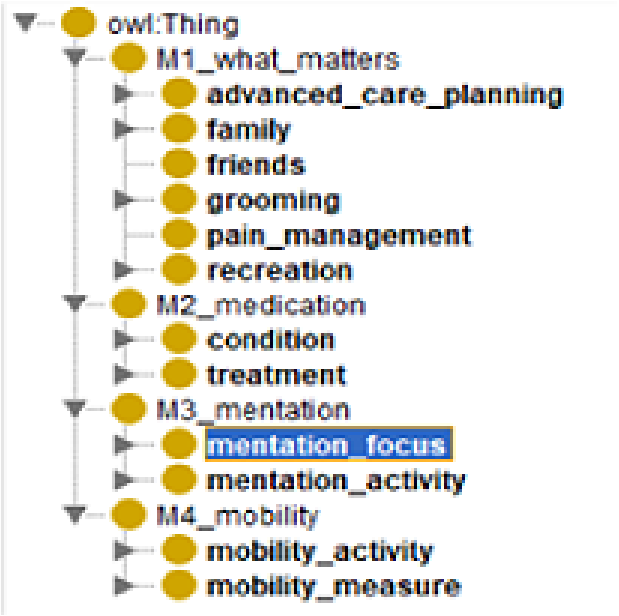
The initial extraction of TMs resulted in over 77,000 messages that were exchanged by NHs that participated in the CMS demonstration project. We used a stepwise approach to preprocess the TMs. First, we removed TMs where no resident was discussed. For example, there were TMs of a personal nature (eg, "how are you" and "what's for lunch today"). After removing messages where no resident was discussed, we identified messages about NH residents who had a NH-to-hospital transfer during the study period. NH staff were able to use TMs to communicate about all residents at their facility; therefore, we needed to remove any resident who did not have a hospital transfer during the study period. We excluded over 43,000 messages that were about NH residents that were not in our resident transfer data set, resulting in 30,067 TMs available for analysis. Our next step is to begin identifying the roles of individuals (eg, MD, APRN, bedside nurse, and unit manager) exchanging TMs in preparation for SNA.

Building the 4M Ontology

The methodology for building the 4M ontology uses 2 strategies. One strategy is expert-based and top-down, in which the clinical expert outlines the most important concepts for each of the 4Ms. For example, using the concept "what matters," some concepts we have identified are advanced care planning, family, friends, grooming, pain management, and recreation (see Figure 2). The second strategy is data-driven and bottom-up and consists of extracting meaningful terms from the TMs and inserting them at the right location in the top-level ontology framework created by the expert. The data-driven strategy ensures that we can identify the 4M content of each TM. Expected results to be published in fall 2025.

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Figure 2. Top level of the 4M ontology. 4M: what matters, medication, mentation, and mobility.



Discussion

Study Implications

To our knowledge, this project will be the first to explore the content of TMs exchanged among a multidisciplinary team of NH care providers as they make decisions about NH-to-hospital resident transfers. Our goal is to apply existing methodologies (SNA and NLP) in a new way, that is, to analyze TMs in NH settings. SNA uses visualization techniques to illustrate patterns of relationships formed among clinical partners, which provides novel quantitative measures of relationship strength and hierarchical structures. NLP is crucial for advancing health care research because it is needed to transform relevant information locked in text into structured data, a prerequisite to quantitative analysis of large amounts of text. The results of the proposed study have the potential to shift both research and clinical paradigms.

This study will produce knowledge of the mechanisms and principles necessary for the successful development and implementation of behavioral interventions using TMs to enhance multidisciplinary team communication in NHs. Knowledge of these principles will make it easier to predict who might respond well to a future intervention and who might not, so that the intervention might be better personalized and given only to those who are likely to benefit from it [30]. Findings from this study, specifically the 4M structured language ontology, could also inform TM interface design, creating the opportunity for standardized, seamless portability of information centered around what matters to older adults. The idea is to address, as much as possible, issues of real-world fidelity and the ability to implement before the intervention is studied at later stages to maximize the chances of success. This approach aligns with the National Institute for Aging Stage Model for Behavioral Intervention Development, with the proposed project falling between stages 0 and 1A [30]. Demonstrating how the 4Ms are represented in TMs must be done before intervention development (stage 0). Understanding how the presence of the 4Ms in TMs relates to avoidable hospitalizations among NH residents with ADRD will inform the evidence base regarding future scalability (stage 1A). Without this knowledge, NHs will continue to rely on ineffective and outdated communication methods that fail to account for evidence-based elements of age-friendly care.

Limitations

This study will generate knowledge that will have far-reaching implications for NH residents with ADRD. Nonetheless, there are potential limitations to generalizability to consider. Our data set is limited to NHs that participated in the CMS demonstration project. The NHs that participated in the project each had an APRN working as an essential staff member in the facility. Not all NHs have an APRN presence in the facility, so generalizability beyond NHs with this support in place could be limited. To address this limitation, we will consider the wide variability of the use of TMs among APRNs. For example, in our pilot analysis using 6 months of TM data, we found the total number of TM sent by APRNs ranged from 0 to 607 [17]. In the CMS demonstration project, data were captured only for residents who had a NH-to-hospital transfer, so comparing residents who transferred to those who were not transferred is not possible from this data set. To address this limitation, we will compare transfers according to whether they were considered avoidable or unavoidable.

In some cases, NH-to-hospital transfer is appropriate and necessary. Our focus on reducing avoidable NH-to-hospital transfers accounts for this limitation. Although our data set includes novel components, including TMs sent and received between a multidisciplinary care team, resident characteristics, and transfer data, it does not include direct communication with family members of NH residents. To address this limitation, we will account for indirect family communication. For example, family preferences were frequently mentioned in TMs shared among the care team and can be conceptualized with “what matters.” Finally, while the focus of the proposed study is

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improving communication using TMs, we recognize other factors such as staffing, workload, and skill mix of the NH staff could impact the outcome, that is, avoidable NH-to-hospital transfers. To address this limitation, we will use SNA, which accounts for skill mix by identifying roles (eg, MD, registered nurse, licensed practical nurse, and certified nursing assistant), interactions between social positions and groups, and relationships among groups.

Conclusions

Identifying evidence-based elements of communication in TMs exchanged among NH health care team members can potentially decrease avoidable hospitalizations and ultimately morbidity and mortality in NH residents with ADRD. The development of a structured language ontology using an evidence-based framework (4M) to improve communication among NH team members is a direct and effective implementation strategy designed to address issues of real-world fidelity before the development of interventions to promote timely and seamless portability of information across the complete spectrum of care, optimizing the health of individuals and populations.

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Data Availability

The data sets generated or analyzed during this study will be available from the corresponding author upon reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review report by the Interdisciplinary Clinical Care in Specialty Care Settings Study Section of the University of Missouri-Columbia.
[PDF File (Adobe PDF File), 152 KB - resprot_v12i1e50231_app1.pdf]

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Abbreviations

4Ms: What Matters, Medication, Mentation, and Mobility
ADRD: Alzheimer disease or a related dementia
APRN: advanced practice registered nurse
CMS: Centers for Medicare & Medicaid
HIPAA: Health Insurance Portability and Accountability Act
ICNP: International Classification for Nursing Practice

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INTERACT: Interventions to Reduce Acute Care Transfers
MD: medical doctor
MeSH: Medical Subject Headings
NH: nursing home
NLP: natural language processing
SNA: social network analysis
SNOMED: Systematized Nomenclature of Medicine Clinical Terms
TM: text message

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Protocol

Assessment of Knowledge and Attitudes Over Time in Postacute COVID-19 Environments: Protocol for an Epidemiological Study

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Abstract

Background: Globally, COVID-19 is in transition from the acute pandemic phase into a postacute phase, and special attention should be paid at this time to COVID-19 control strategies. Understanding public knowledge and attitudes plays a pivotal role in controlling COVID-19's spread and provides information about the public's adherence to preventive and control measures.

Objective: This study protocol describes the planning and management of a survey to investigate the persistent or changing trends in knowledge and attitudes regarding COVID-19, vaccination, and nonpharmaceutical preventive measures among COVID-19 cases' household contacts aged 18 years and older, after the acute phase of the pandemic in Catalonia and Navarre in Spain. The secondary objectives include investigating the rate of secondary transmission in households, taking into account the demographic characteristics, clinical manifestations, and preventive measures toward COVID-19.

Methods: A telephone questionnaire was designed to assess the changing trends in knowledge, preventive measures, and attitudes toward COVID-19 in 3 rounds (after identification as a household contact, 3 months later, and 6 months later). The questionnaire was developed following an extensive literature review and through discussions with a panel of experts who designed and assessed the validity of the questionnaire in terms of relevance, consistency, completeness, and clarity. The questionnaire consists of the following 7 sections: social and demographic characteristics (ie, gender, age, educational level, and workplace), comorbidities and risk factors (according to the recommendations from the COVID-19 vaccination strategy), epidemiological data (ie, exposure time, relationship with index cases, and frequency of use of nonpharmaceutical preventive measures), COVID-19 vaccination status (ie, the number and date of doses received), knowledge and attitudes toward COVID-19 (assessed using a 5-point Likert scale—totally agree, agree, neither agree nor disagree, disagree, and totally disagree), and sources of information (including traditional mass media, social media, and official sources).

Results: A pilot study was performed in May 2022 to evaluate the questionnaire with 22 household contacts. Preliminary findings indicated that the questionnaire was feasible and acceptable in the general population. The average response time was 15 minutes, with greater variations in responses by older participants. After the pilot study, recruitment of participants began and is expected to be completed at the end of the year 2023, after which the final results will be available in 2024.

Conclusions: Despite the low transmission levels of SARS-CoV-2 and the relaxation of containment measures, the implementation of the survey during the postacute phase will provide valuable insight to assist public health decision-making and control the

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transmission of SARS-CoV-2 and other respiratory viruses, thereby attenuating the negative effects of COVID-19 at individual and population level.

International Registered Report Identifier (IRRID): DERR1-10.2196/52114

(JMIR Res Protoc 2023;12:e52114) doi:10.2196/52114

KEYWORDS

COVID-19; knowledge; attitudes; household contact; vaccination; preventive measures; survey

Introduction

Overview

The COVID-19 pandemic has demonstrated that infectious diseases are a continuous challenge for public health. Prevention and control measures to diminish the burden of SARS-CoV-2 infection in the population have changed over time, from exclusively implementing nonpharmaceutical interventions to extensive vaccination programs [1-3].

According to the last report of the European Centre for Disease Prevention and Control (ECDC) [4], many European countries are currently de-escalating their response measures due to the transitional process of the acute pandemic phase into the postacute phase. However, the ECDC encourages governments and national authorities to monitor pandemic trends and key indicators, focused on preventing and managing not only SARS-CoV-2 variants but also the long-term health consequences due to COVID-19 [4]. Although many studies on knowledge and attitudes related to COVID-19 have been published [5,6], there are still several knowledge and behavioral gaps, which can serve as a guide to address future emergencies relating to SARS-CoV-2 variants and other pandemics, considering that knowledge, attitude, and behavior can change over time [6].

It is generally recognized that populations' levels of knowledge and attitudes regarding COVID-19 and its preventive measures are important factors for controlling transmission during the pandemic [4]. In the acute phase of the COVID-19 pandemic, some studies evaluating knowledge and attitudes have been conducted worldwide, both in the general population and in specific groups [7-10]. However, many gaps in the knowledge and practices concerning COVID-19 need to be filled. For example, in a multinational sample, including 22 countries, authors showed that almost one-third of participants did not know that infected individuals can be asymptomatic, increasing their risk of exposure to COVID-19 [5]. In addition, a higher correlation was found between attitudes and practices compared to knowledge and practices, indicating that knowledge itself is not enough and that effective interventions to improve practices should aim to encourage both adequate knowledge and positive attitudes [5]. Other studies demonstrate that the probability of transmission is higher for people who meet the criteria of close contacts, due to their exposure to COVID-19 cases with laboratory-confirmed infection. Close contacts include household contacts, among whom exposure is usually more intense and repeated; therefore, the risk of transmission may be high, even in the absence of other factors that enhance transmission [11,12].

At this time, the population has access to accurate real-time information on the evolution of the pandemic and the recommendations to follow, which could be reliably disseminated by health authorities and official institutions through various secure communication channels [1-3]. Nevertheless, the population is also exposed to other media sources that spread unreliable and contradictory information about the evolution of the pandemic, causing confusion regarding the measures to be followed. In addition, it must be noted that the absence of knowledge and inappropriate beliefs about the importance and best methods of prevention may increase the risk of infection [13]. In this context, data about gaps in knowledge and behavioral information is crucial to the prevention and management of future resurgences of SARS-CoV-2 variants.

Objectives

The main objective of this study is to investigate the persistent or changing trends in knowledge and attitudes about COVID-19, vaccination, and nonpharmaceutical preventive measures in household contacts of COVID-19 cases after the acute phase of the pandemic in Spain.

The secondary objectives of the study are as follows:

- To compare the characteristics of index cases and primary cases of COVID-19
- To investigate the rate of secondary transmission, taking into account factors such as age, sex, clinical manifestations, and preventive measures related to the first case in the household
- To determine the rate of secondary transmission in households with primary cases of COVID-19 caused by new variants of SARS-CoV-2 and the existence of vaccination failures

Methods

Study Design

This study is a prospective epidemiological study using a telephone survey addressed to household contacts of confirmed COVID-19 cases in 2 regions of Spain: Navarre and Catalonia. The telephone survey is being conducted in 3 rounds: the first round is directly after the identification of an eligible contact; the second round will be 3 months later, and the third round will be 6 months after the initial contact. These interviews are currently in progress, with most participants having completed the second interview as of the date of this paper's submission.

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Ethical Considerations

The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Ethics Committee of the University of Barcelona (protocol code IRB00003099) on March 2, 2023. Oral consent is requested from participants by the Institutional Ethics Committee of the University of Barcelona, and an informative document about the study is sent by email to whoever requests it.

Participants

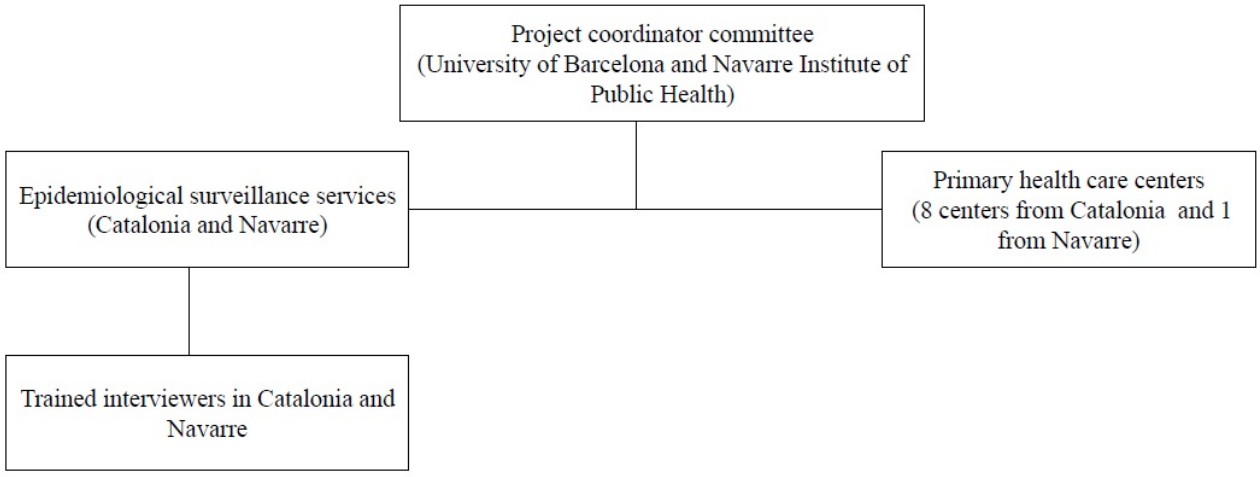
The recruitment of household contacts is currently being conducted in 9 primary health care centers (1 from Navarre and 8 from Catalonia) associated with COVID-19 cases. The inclusion criteria are as follows: patients who are positive for COVID-19 (cases) and household contacts aged ≥18 years at the time of selection, who agree to participate in the study and provide oral consent. Those aged <18 years and those with the presence of severe and uncorrectable cognitive, visual, or hearing impairments that hinder the participants' ability to complete interviews are excluded from the study.

Organization and Coordination Activities

The study was managed by Centro de Investigación Biomédica en Red de Epidemiología y Salud Pública through the University of Barcelona and the Institute of Public Health of Navarre, in coordination with the epidemiological surveillance services of both regions. The main function of the project coordination committee is to supervise and monitor the adequate application of the methodology and working plan to achieve the project objectives. The selection of COVID-19 cases is being carried out by primary health care professionals who also report the COVID-19 cases to the epidemiological surveillance services. COVID-19 cases are being selected if they have had at least 1 eligible household contact who could be identified. All household contacts of COVID-19 cases reported to the epidemiological surveillance services in both regions are selected to participate in this study. All participants are informed of the objectives of the study and invited to participate. Individuals included in the study have provided prior oral consent to be contacted and are informed that all information will be treated anonymously in the subsequent statistical analyses.

Qualified interviewers are conducting the surveys by telephone in both regions (Figure 1). Complete information on the coordination of activities is accessible to all researchers involved in the study through a manual of procedures developed by the coordinating committee.

Figure 1. The organizational structure of the project team.



During the initial stages of screening, household contacts of COVID-19 cases will be identified through the epidemiological surveillance services or primary health care centers from Catalonia and Navarre. Trained study personnel will perform a formal screening evaluation to confirm eligibility for the study, which will take place after the patient has provided oral informed consent.

Data Collection

Literature Review and Design of the Questionnaire

The first step of the questionnaire design, an exhaustive literature review, was carried out by the coordination committee [14]. After this literature review, the questionnaire was structured, taking into account the recommendations against COVID-19 provided by the World Health Organization, ECDC, and the Spanish Ministry of Health [1-3,15]. The research team, composed of professionals with experience in epidemiological and public health research, held a series of preliminary meetings to develop all sections of the survey, including the selection of questions and the number of items included. Discussion of the survey focused on the relevance, consistency, completeness, and clarity between linked questions, the length of the survey, and the overlap of questions between sections of the survey. All the sections of the questionnaire, especially the items related to knowledge and attitudes, were adapted from instruments used in other publications related to the study topic, specifically the questionnaires used by Xu et al [16] and Geldsetzer [17]. The questions were adapted to the specific circumstances of the Spanish population, ensuring conceptual and semantic equivalence. Following an iterative process that resulted in several major revisions of the first draft.

The survey was developed in Spanish, and it consisted of 7 sections: social and demographic information, comorbidities and risk factors, epidemiological information, COVID-19

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vaccination status, knowledge concerning COVID-19 and its preventive measures, attitudes toward COVID-19 and its preventive measures, and participants' sources of information about COVID-19.

The questionnaire also includes demographic information, variables related to comorbidities, and COVID-19 vaccination status, which could be validated through electronic health record linkage with the regional vaccination registers and databases of epidemiological surveillance.

Questionnaire Structure

Social and Demographic Characteristics

Demographic variables include participants' gender; age; educational level (according to the International Standard Classification of Education by the United Nations Educational, Scientific and Cultural Organization); workplace (remote work, on-site work, or both); and the severity of the index case, including whether or not their treatment involved hospitalization.

Comorbidities and Risk Factors

Information about the prior presence of major chronic conditions is being collected according to the recommendations from the COVID-19 vaccination strategy, including chronic obstructive pulmonary disease, coronary heart disease, stroke, diabetes mellitus, immunodeficiency (eg, HIV/AIDS and immunosuppression), chronic kidney disease, chronic liver disease, neurological and psychiatric disease, and cancer [18]. Information about risk factors, including tobacco use (smoker, former smoker, or nonsmoker), obesity (BMI>30, BMI>40), and hypertension, is also obtained from the household contacts. These data are collected in dichotomous variables according to the presence or absence of each one of them.

Epidemiological Information

The epidemiological section registers data related to whether the participants have had close contact with the index case (first positive case in the household); the exposure time; the relationship with the index case (ie, partner, father, or mother); whether they have shared a vehicle or bedroom with the index case; and whether the contact has symptoms, and if so, which ones. Other data collected include the frequency of use of nonpharmaceutical preventive measures at home (eg, ventilation, use of mask, distance, and frequency of hand washing); the results of, and the type of COVID-19 test (eg, polymerase chain reaction test or rapid antigen test) they may have had after the positive test results of the index case; and any previous COVID-19 infection, including details about severity, possible hospitalization, and any other relevant details.

COVID-19 Vaccination Status

This section provides data concerning COVID-19 vaccination history, including the date of administration and brand of each dose. The data provided by the participants in this section can be validated by the vaccination records. To evaluate vaccination hesitancy, if the participant has not received any vaccine, they are asked for possible reasons for their lack of willingness to receive it.

Knowledge Concerning COVID-19 Disease and Its Preventive Measures

In this section, the patients' knowledge of COVID-19 is evaluated, considering that adequate knowledge about COVID-19 infection, severity, and preventive measures are important factors associated with the decision of vaccine uptake, and therefore, the spread of infection [19]. This section consists of 6 questions, and participants are asked about COVID-19 modes of transmission and preventive measures during a situation of COVID-19 circulation (Table 1). The knowledge about COVID-19 disease and preventive actions, such as vaccination and nonpharmaceutical measures, are assessed using a 5-point Likert scale (totally agree, agree, neither agree nor disagree, disagree, and totally disagree) [10].

Table 1. Items concerning knowledge of COVID-19 disease and its preventive measures.

	Totally disagree	Disagree	Neither agree nor disagree	Agree	Totally agree
All people who become ill with COVID-19 develop severe cases.	__[a]	—	—	—	—
Asymptomatic persons diagnosed with COVID-19 can transmit the infection.	—	—	—		—
Persons diagnosed with COVID-19 can transmit infection despite vaccination.	—	—	—	—	—
The COVID-19 virus is spread by respiratory droplets from infected individuals when coughing, sneezing, talking, laughing, and singing.	—	—	—	—	—
Handwashing is important to reduce the risk of contracting COVID-19.	—	—	—	—	—
To prevent transmission of COVID-19, measures such as wearing face masks and avoiding crowds in enclosed spaces should be maintained.	—	—	—	—	—

[a]To be filled.

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Attitudes Toward COVID-19 Disease and Its Preventive Measures

This section consists of 6 questions, evaluating attitudes toward COVID-19 vaccination; stigma against symptomatic individuals; and the effects of COVID-19 on daily life, considering the current situation (Table 2). For this section, participants are being asked to state their level of agreement with specific attitudes and preventive actions related to COVID-19 again, expressed on a 5-point Likert scale [7].

Table 2. Items related to attitudes toward COVID-19 disease and its preventive measures.

	Totally disagree	Disagree	Neither agree nor disagree	Agree	Totally agree
I consider myself susceptible to developing a severe disease if I become ill with COVID-19.	__[a]	—	—	—	—
I consider that my inner circle has complied with the preventive measures to avoid becoming ill with COVID-19.	—	—	—	—	—
I consider that my inner circle has complied with the vaccination recommendations given by the health authorities.	—	—	—	—	—
I consider that it is better to develop immunity by getting sick with COVID-19 than by getting vaccinated.	—	—	—	—	—
It is convenient for the general population to wear a facemask correctly (covering the nose and mouth) to prevent COVID-19 in crowded, closed environments.	—	—	—	—	—
I consider that COVID-19 had a negative influence on my daily life.	—	—	—	—	—

[a]To be filled.

COVID-19 Information Sources

Additionally, the survey includes a section regarding the most common source of information on COVID-19 disease and the preventive measures consulted by the participants. The survey contains a list of possible information sources as the primary source used by the participant and has the following options: nonofficial sources, such as traditional mass media (eg, television and written or web-based press); social media (eg, Instagram, Facebook, and Twitter); and official sources, such as medical professionals and government or other official sources (eg, World Health Organization, ECDC, or Spanish Ministry of Health).

Results

Pilot Test

The content validity of the questionnaire was evaluated in a pilot study performed in Navarre, consisting of a sample of 22 household contacts during the period between April and June 2022. In the pilot test, participants were presented with a set of items and questions by a trained staff interviewer. The interviews were performed by telephone, and all observations were collected during this phase. No changes to the initial questionnaire's items related to the knowledge and attitudes toward COVID-19 disease, its preventive measures, or information sources were needed. The pilot test confirmed that the questionnaire had established content and was well understood and concise.

The final questionnaire consisted of 23 questions distributed in 7 sections (described in the previous section). The average response time was 15 minutes, with older participants exhibiting a more noticeable variation in their responses.

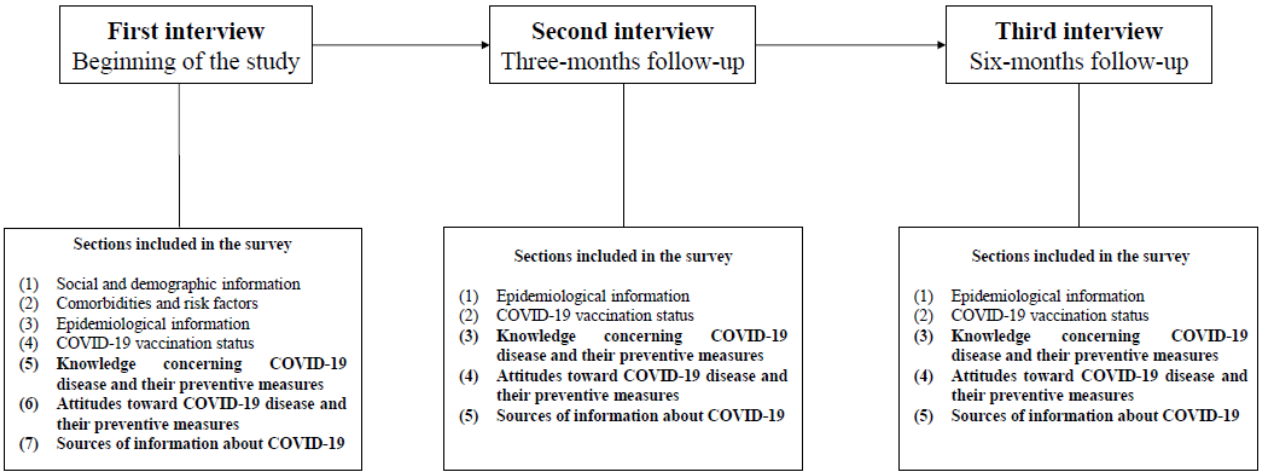
Evaluation of the Trends in Knowledge and Attitudes Over Time

To evaluate the persistence or changing trends in knowledge and attitudes about COVID-19, vaccination, and nonpharmaceutical preventive measures, the telephone survey of household contacts is being conducted in 3 rounds, at different epidemiological moments. The first round is done just after their identification as a household contact, and the second and third rounds are done 3 and 6 months later, respectively.

In the first round, all the information from the questionnaire is collected, thus obtaining reference information at the time of contact with the index case. In the 3-month and 6-month follow-up rounds, we will inquire whether they have had any change in their COVID-19 vaccination status or whether they have become infected by the SARS-CoV-2 since the last call; we will also inquire about various items related to knowledge and attitudes about COVID-19 and its preventive measures as well as the information sources upon which they rely (Figure 2). The background information is not collected again, as it is not subject to change over time. After the pilot study, participant recruitment began and is expected to be completed by the end of 2023. The final results will be available in 2024.

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Figure 2. Study design and follow-up timetable of the study.



Discussion

Principal Findings

This study will provide valuable insights into the knowledge and attitudes of household contacts of confirmed COVID-19 cases, after the acute phase of the pandemic, toward the disease and its preventive measures, including vaccination and nonpharmaceutical preventive measures, and will allow for evaluating the trends in these data over time.

At this moment, this study is still in the recruitment process. It must be mentioned that this study is being carried out within the framework of the postacute phase of COVID-19, where infections continued to decrease. Therefore, including a preliminary analysis of this questionnaire, considering the recruited population at this moment, could provide biased results. However, despite the abundance of information available about infection and preventive measures for COVID-19, studies have shown that there are still some gaps related to the use and maintenance of preventive measures during this transitional phase of the pandemic, especially in households, where the probability of SARS-CoV-2 transmission is higher [11,12]. Preventive measures, such as vaccination and nonpharmaceutical measures, are of special relevance for controlling this infection. More than 50% of transmission chains are generated in households, and the use of nonpharmaceutical preventive measures before the occurrence of cases is probably limited [20].

Some studies reported that nonpharmaceutical public health measures, such as physical distancing and wearing masks, had a strong impact on person-to-person COVID-19 transmission at the individual level [21,22]. Funke et al [22] evaluated the containment of nonpharmaceutical measures during the first 3 pandemic waves in countries from North and South America, Europe, and Asia-Pacific. Results showed a dual cause-effect channel where nonpharmaceutical interventions had a direct impact on several health outcomes and an indirect effect on voluntary changes in social distancing. Some authors have identified that accurate knowledge is essential in managing epidemic situations caused by infectious agents and that nonadherence to nonpharmaceutical preventive measures is likely to be the consequence of a knowledge gap [23-25].

Detecting the weak points in the population's attitudes and knowledge regarding the studied preventive measures, as well as monitoring the persistent or changing nature of adherence to them over time, is important for planning strategies to improve prevention and health promotion. It also serves as a benchmark for future epidemics of respiratory viruses that affect the population every winter. This issue is particularly relevant in the current scenario in which vaccines do not totally reduce the risk of transmission [26].

The current situation of the COVID-19 pandemic, following the acute phase during the emergence of the Omicron wave, indicates a notable decrease in the number of new cases, which many might interpret as a sign of the end of the pandemic. Corresponding with this, we have seen a change in the surveillance and control strategy against COVID-19 implemented by the Spanish government and health authorities. This shift is accompanied by reductions in the compulsory and recommended use of nonpharmaceutical interventions, such as the compulsory use of face masks [27]. This will naturally result in the lower use of these measures in the population and possibly a shift in their beliefs regarding these measures and COVID-19 itself.

A key factor is to understand how containment measure strategies impact pandemic stages to minimize the risk of further waves of SARS-CoV-2. Cascini et al [28] compared the impact of COVID-19 containment measures in 5 European countries on the epidemic curves. Authors indicated 3 main factors that affected COVID-19 transmission. First, the time when preventive measures were adopted—as long as these measures were implemented early, they showed better results; second, the duration of containment measures; and finally, the number of COVID-19 cases before relaxing containment measures. It is important to emphasize that the effectiveness of preventive measures depends on their adherence.

The attitude of acceptance of the recommended measures is essential to control the transmission of SARS-CoV-2 and reduce its incidence, especially in situations in which these measures

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are extended over time with different intensities, and as a consequence, the population is liable to reduce their compliance [29,30]. Knowledge and attitudes are important cognitive keys in public health regarding prevention and health promotion. Other factors that influence noncompliance may include a range of beliefs about the causes of the disease, knowledge of the identification of symptoms, available methods of treatment, consequences, and possible long-term complications [25]. Some studies related to knowledge and attitude regarding COVID-19 have been conducted, but most of them were performed on the general population [31-34], in which the risk of transmission is lower than in a closed environment, such as a household. Evidence from these studies on knowledge and attitudes during epidemics allows us to recognize and identify key attitudes and practices to prevent the spread of the disease. Consequently, several policies and political interventions have been established and reinforced to optimize the management of the COVID-19 pandemic by health authorities.

We believe that it is important to monitor such changes over time and assess any knowledge gaps to understand both the current situation and how such knowledge and beliefs evolve over time. The low current incidence of COVID-19 cases reflects a complex matrix of influences rather than being a reliable sign of the end of the pandemic. A combination of high vaccination coverage, an increase in immunity in the population generated by natural infections, and the cumulative effects of compulsory and recommended preventative measures [35-37], along with other factors, create the situation we currently experience. In the case that a new outbreak may occur, information about the ongoing beliefs, preventative practices, and knowledge gaps in the population will be invaluable in designing new strategies to combat the disease.

A strength of this study is that the coordination committee is composed of professionals with expertise in communicable diseases and vaccination research. They have been involved in the surveillance and monitoring of the infection in Catalonia and Navarre since the beginning of the COVID-19 pandemic, which facilitates the implementation of the study in both regions and allows adequate management of fieldwork, with a unified work protocol. Another strength of the study is that it is being carried out in 2 regions of Spain (Catalonia and Navarre) that present different situations of SARS-CoV-2 household transmission, increasing the representation of the Spanish population. Additionally, conducting a longitudinal study assessing changing beliefs and knowledge in the community during the postacute phase of the pandemic provides, in our view, an essential dimension to understanding the social landscape in which the measures are being applied. The combination of these 3 factors makes the results of this study uniquely valuable in disease prevention.

This study has some limitations. First, it is being carried out at a time when the epidemiological situation presents a low incidence of COVID-19 cases, which could alter the sample size of the contacts to follow. Therefore, we have planned to contact every single reported case during the study period and carry out an exhaustive census of household contacts to maximize participation. Second, it is a survey-based study, and the information will be self-reported, so information biases could possibly be introduced in the outcome variables and information about vaccination status. However, demographic characteristics, comorbidities, and COVID-19 vaccination status can be verified with electronic health records and vaccination registers. Third, the relaxation of the containment measures might have an impact on the attitudes toward COVID-19 over time, but our study could provide relevant information on attitudes toward preventive measures during this postacute phase of the pandemic [4].

Conclusions

The development of a questionnaire to assess knowledge and attitudes about COVID-19, vaccination, and nonpharmaceutical preventive measures over time after the acute phase of the pandemic will provide valuable insights regarding the control of infection in the population, in a low transmission scenario. This questionnaire will provide information about knowledge and attitudes over time and will be important for public health decision-making during the relaxation of containment measures in the event of an increase in COVID-19 cases or a new health emergency due to respiratory viruses.

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Data Availability

Study data will be available upon reasonable request from the corresponding author. The data will not be published on a public platform for ethical reasons. Data will be anonymized if an access request is received.

Authors' Contributions

IMB, MGC, PG, AD, and DT participated in the conceptualization and methodology of the protocol. IMB, VBV, and DT drafted the manuscript, and all authors revised and approved the final version.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review report from the Centro de Investigación Biomédica en Red Epidemiología y Salud Pública (CIBERESP) (Madrid, Spain).
[PDF File (Adobe PDF File), 1712 KB - resprot_v12i1e52114_app1.pdf]

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Abbreviations

ECDC: European Centre for Disease Prevention and Control

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Protocol

Spatio-Temporal Analysis of Leptospirosis Hotspot Areas and Its Association With Hydroclimatic Factors in Selangor, Malaysia: Protocol for an Ecological Cross-sectional Study

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Abstract

Background: Leptospirosis is considered a neglected zoonotic disease in temperate regions but an endemic disease in countries with tropical climates such as South America, Southern Asia, and Southeast Asia. There has been an increase in leptospirosis incidence in Malaysia from 1.45 to 25.94 cases per 100,000 population between 2005 and 2014. With increasing incidence in Selangor, Malaysia, and frequent climate change dynamics, a study on the disease hotspot areas and their association with the hydroclimatic factors would further enhance disease surveillance and public health interventions.

Objective: This study aims to examine the association between the spatio-temporal distribution of leptospirosis hotspot areas from 2011 to 2019 with the hydroclimatic factors in Selangor using the geographical information system and remote sensing techniques to develop a leptospirosis hotspot predictive model.

Methods: This will be an ecological cross-sectional study with geographical information system and remote sensing mapping and analysis concerning leptospirosis using secondary data. Leptospirosis cases in Selangor from January 2011 to December 2019 shall be obtained from the Selangor State Health Department. Laboratory-confirmed cases with data on the possible source of infection would be identified and georeferenced according to their longitude and latitudes. Topographic data consisting of subdistrict boundaries and the distribution of rivers in Selangor will be obtained from the Department of Survey and Mapping. The ArcGIS Pro software will be used to evaluate the clustering of the cases and mapped using the Getis-Ord Gi* tool. The satellite images for rainfall and land surface temperature will be acquired from the Giovanni National Aeronautics and Space Administration EarthData website and processed to obtain the average monthly values in millimeters and degrees Celsius. Meanwhile, the average monthly river hydrometric levels will be obtained from the Department of Drainage and Irrigation. Data are then inputted as thematic layers and in the ArcGIS software for further analysis. The artificial neural network analysis in artificial intelligence Phyton software will then be used to obtain the leptospirosis hotspot predictive model.

Results: This research was funded as of November 2022. Data collection, processing, and analysis commenced in December 2022, and the results of the study are expected to be published by the end of 2024. The leptospirosis distribution and clusters may be significantly associated with the hydroclimatic factors of rainfall, land surface temperature, and the river hydrometric level.

Conclusions: This study will explore the associations of leptospirosis hotspot areas with the hydroclimatic factors in Selangor and subsequently the development of a leptospirosis predictive model. The constructed predictive model could potentially be used to design and enhance public health initiatives for disease prevention.

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KEYWORDS

leptospirosis; hotspot areas; hydroclimatic factors; Selangor; geographical information system; GIS; predictive model

Introduction

Background

Leptospirosis is a neglected zoonotic disease caused by the bacteria agent from the genus *Leptospira* [1,2]. The disease primarily affects vulnerable populations in the urban slums, especially in developing countries, rural farmers, and those involved with water recreational activities [3,4]. Outbreaks are also reported during heavy rainfall and flood seasons and in areas with higher humidity and temperature climates [5].

Although animals are the primary reservoir of *Leptospira*, a human could acquire the infection through the percutaneous contact of contaminated water or soil with the urine of infected animals [1,6]. The clinical presentation could range from afebrile flu-like symptoms to severe manifestations such as pneumonia, acute kidney injury, pulmonary hemorrhages, and even death. Although most infection causes are mild symptoms and can resolve without requiring treatment or be settled with antibiotics, the spread of infection is best controlled by applying preventive measures to minimize potential outbreaks and mortality [6]. Furthermore, better surveillance and disease control could be achieved by integrating hydroclimatic factors of the disease with spatio-temporal hotspot area analysis [7].

Based on morbidity and mortality from hospital-based surveillance studies, the global burden of leptospirosis was estimated to be 1.03 million cases, with 58,900 deaths per year [3,8]. From these data, the disease burden in terms of disability-adjusted life years was 2.90 million per annum, translating to 2.80 million years of life lost and 103,200 years lived with a disability [3]. The Leptospirosis Epidemiology Reference Group of the World Health Organization was established in 2009 to estimate the global burden of leptospirosis. According to the Leptospirosis Epidemiology Reference Group report in 2011 summarizing studies on leptospirosis complications and case fatality in a systematic review, there were 36% (range 0%-88%) of patients reported having an acute renal injury, while 17% reported acquiring acute lung injury (range 0%-62%). Among them, 12% and 25% had died from disease complications, respectively [8]. Pulmonary hemorrhage syndrome is another severe manifestation of leptospirosis that could be life threatening [8].

Leptospirosis is endemic in humid and tropical regions in South Asia, Southeast Asia, and Southern America. Developed countries in temperate zones, such as in the United States and Europe, report fewer cases due to unfavorable environmental conditions for the bacteria's animal reservoirs, thus considering the disease neglected [9]. However, outbreaks in the aforementioned regions have been reported as having been linked to travel-related reasons to endemic countries or to water activities [1,6].

The disease occurs more in suitable environments with poor sanitation and hygiene conditions, favoring the survival and proliferation of the rodent population, the leading animal reservoir in the South East Asia (SEA) region. [9]. The SEA countries are in the tropical belt, which experiences warm to hot climates with high rainfalls during wet seasons. This phenomenon promotes soil moisture, favoring *Leptospira* growth, subsequent contact, and transmission to humans [10]. An epidemiological study on the agent for human leptospirosis prevalent in the SEA countries identified the main *Leptospira* species pathogenic to humans; *L. interrogans* and *L. borgpeterseni* [11].

A meta-analysis studying the risk factors for leptospirosis following flooding discovered that the presence of rodents squirming near human settlements following the catastrophe and adult males having abrasion wounds or walking barefoot were significantly associated with the infection [12]. For instance, a massive flood following heavy rainfall hit Kerala, India, which took around 500 lives, and approximately 70 were reportedly killed by leptospirosis or dengue fever [13]. Indonesia, a country in the SEA region in the tropical rain belt, has seen 122 deaths from 920 leptospirosis cases reported in 2019 [14,15]. The country often experiences floods that commonly act as a catalyst for stagnant water, and poor sewer and sanitation systems are risk factors for leptospirosis infection [15].

Malaysia has the climate of a dynamically alternating, moderately hot and humid environment throughout the year, with bouts of heavy rains that could cause floods in prone regions. These characteristics are known to influence regional leptospirosis occurrence in Argentina, where the monthly precipitation, monthly river hydrometric level, and Oceanic Nino Index were the hydroclimatic indicators of the disease [16]. On the other hand, a study in Africa demonstrated that rainfall influences the population of rodents, which act as vectors for leptospirosis [17].

Leptospirosis is endemic in Malaysia, affecting mainly 5 states from 2005 to 2014, namely Kelantan, Selangor, Sarawak, Sabah, and Perak. The incidence in these states was constantly increasing and caused a peak of cases in 2014 [18]. Significant leptospirosis outbreaks have occurred on several occasions, such as during an Eco-Challenge in Sabah in 2000 and following a major flood event that mainly hit the northeastern states of Malaysia in 2014 [19,20]. Out of the 304 athletes who participated in the adventure sport in Borneo, 80 had met the clinical case definition of leptospirosis, with 26 of them testing positive for leptospirosis immunoglobulin M by enzyme-linked immunosorbent assay [19]. Meanwhile, Kelantan, one of the states hit by a major flood in 2014, saw more than 1000 leptospirosis cases identified during and after the flood incident [20].

Selangor is one of the states facing a high incidence of leptospirosis. The state recorded the highest cases in 2013, with the highest incidence rate of 24.68 per 100,000 population [21]. Even though there has been a steady rise in reported leptospirosis cases, the actual incidence might be underestimated as the clinical symptoms resemble other endemic acute febrile

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illnesses such as dengue fever and malaria [22]. The impacts of climate change with increased flood intensities and frequent weather fluctuations increase vector population and enhance pathogenic *Leptospira* growth [23].

The geographic information system is a tool to analyze disease patterns through techniques such as spatial and temporal analysis [24,25]. A spatio-temporal study combines geographic data as well as trends of disease patterns over a specified period, subsequently generating a predictive model for disease management [25,26]. Walter Langbein, a Scientific Hydrologist, defines hydroclimatology as the "study of the influence of climate upon the waters of the land" [27]. The study of hydroclimatic factors concerned with leptospirosis infection would include factors of temperature, precipitation events, watercourses such as rivers and streams, and floods [16,28].

Objectives

This research aims to explore the spatio-temporal distribution of leptospirosis hotspot areas and their association with the hydroclimatic factors to develop a predictive hotspot area using geographic information system and remote sensing methods. Therefore, this study conducted in Selangor would be able to (1) describe the characteristics of leptospirosis cases in Selangor from 2011 to 2019; (2) map the spatio-temporal distribution of the leptospirosis cases; (3) develop leptospirosis hotspot maps; (4) explore the hydroclimatic characteristics (monthly rainfall, monthly river hydrometric level, and monthly land surface temperature) for Selangor; (5) examine the association between hydroclimatic factors and leptospirosis hotspot areas; and (6) develop a leptospirosis hotspot predictive model based on the hydroclimatic factors.

This potentially life-threatening condition will be challenging to address if potential outbreaks are not predicted with hotspot areas not being outlined. Furthermore, this research may act as a pilot study in the country for the spatio-temporal analysis of leptospirosis with its association with hydroclimatic factors. The predictive model produced in this study can be replicated for future applications and studies.

Methods

Regional Setting

Study Location

The state of Selangor is located in the central part of the west coast of Peninsular Malaysia, bordered to the North, East, and South by Perak, Pahang, and Negeri Sembilan. Selangor lies to the west of the Titiwangsa range between the latitudes of 2°39'18.0" and 3°50'54.4" north to the equator and longitudes of 101°44'49.0" and 100°52'07.7" east. The state covers an area of approximately 8100 km^2. There are 55 subdistricts, also known as mukim, in 9 districts within Selangor (ie, Sabak Bernam, Hulu Selangor, Kuala Selangor, Gombak, Klang, Petaling, Hulu Langat, Kuala Langat, and Sepang). Generally, the irrigation in Selangor comes from 4 main river basins, namely Sungai Selangor and Sungai Bernam to the north, and Sungai Langat and Sungai Klang to the south. Historically, these major rivers were seen as the major drivers of early community settlements around these areas.

Study Design

This will be a retrospective, hydroclimatic study concerning leptospirosis, whereby secondary data of leptospirosis cases and hydroclimatic factors (rainfall, land surface temperature [LST], and river hydrometric data) will be obtained over a period of 10 years, from January 2011 to December 2019.

Study Population

The study population of this study will be leptospirosis cases in the Selangor state from January 2011 to December 2019.

Sampling Method

The sample population includes all mukim polygons in Selangor. The sampling frame will be the lists of mukim areas in Selangor, with each polygon representing a sampling unit. The sampling size of the study will be 54 mukim polygons in Selangor using a universal sampling method of notified leptospirosis cases.

Data Collection

Data on leptospirosis cases from 2011 to 2019 will be obtained from the Zoonosis Unit, Selangor State Health Department. A period of 9 years was taken to compare the results from other similar studies in Argentina and Malaysia [16,29]. The data obtained will be analyzed for the sociodemographic information of the cases and locations of possible sources of infection with their longitude and latitude coordinates. Permission for data collection from relevant agencies has been obtained from the Medical Research and Ethics Committee, the Ministry of Health, and the Ethics Committee for Research Involving Human Subjects before the commencement of the study.

The topographical data for the Selangor state will be obtained from the Department of Survey and Mapping (JUPEM). The data will be in the shapefile format. Satellite images from the Integrated Multi-satellite Retrievals for Global Precipitation Management will be used to derive rainfall data for the Selangor state from January 1, 2011, to December 31, 2019. Images will be obtained from the Giovanni NASA EarthData website [30]. The LST is measured using the MOD11A2 satellite through the onboard Moderate Resolution Imaging Spectroradiometer sensor. It captures 1 km/pixel images at an emissivity of 8 days. Data will be downloaded in a Network Common Data Form format [30]. Meanwhile, the river hydrometric level of rivers in Selangor will be obtained from the Department of Drainage and Irrigation (DID) over a period from January 1, 2011, to December 31, 2019.

Operational Definition of Variables

Dependent Variable

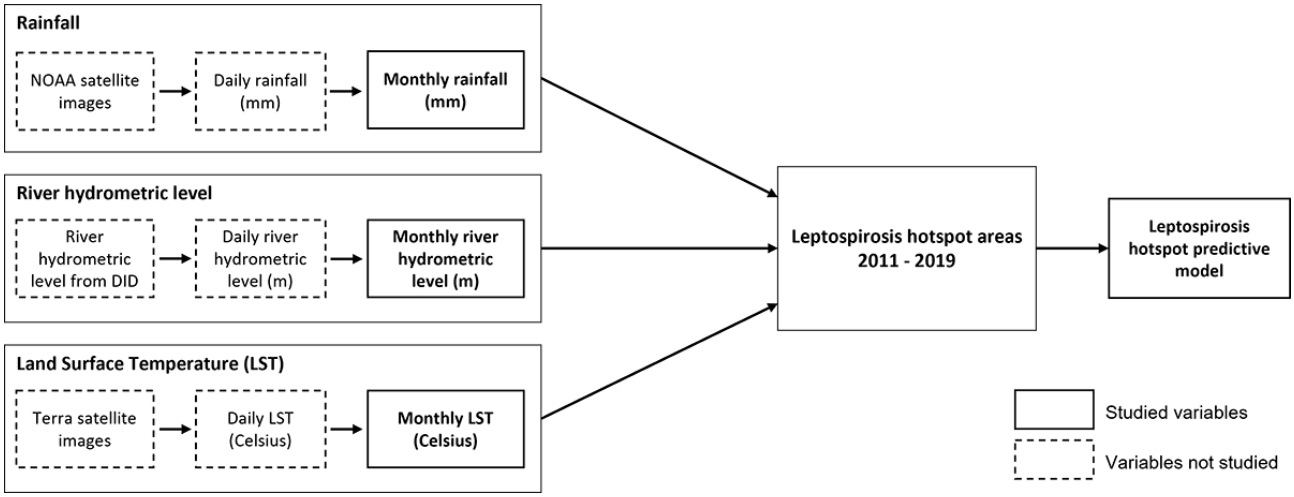
Leptospirosis hotspot area is defined as zones that are hydroclimatically hotspots for leptospirosis transmission in Selangor. The zones will be divided into buffer zones according to color coding based on susceptibility, which are as follows: (1) green zone, not susceptible; (2) yellow zone, less susceptible; (3) orange zone, susceptible; and (4) red zone, highly susceptible.

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Independent Variables

The independent variables for the study are as follows: (1) the rainfall images in millimeters captured by the satellite will be analyzed to obtain the average monthly rainfall; (2) the LST is the earth's surface temperature captured by the satellite in degrees Celsius; and (3) the river hydrometric level is the water level threshold classified for risk of flooding according to the DID, into normal, alert, warning and danger. The alert level is when the level increases significantly above average. In the warning stage, the level increases to near flooding, and preparation for evacuation is commenced. When the level reaches the danger level, a significant flooding event would likely occur, and the evacuation of people is initiated. Figure 1 shows the conceptual framework of this study. The framework outlines the geospatial processes of satellite photography images and river hydrometric level and their association with leptospirosis hotspot areas in Selangor from 2011 to 2019.

Figure 1. Conceptual framework. DID: Department of Drainage and Irrigation; LST: land surface temperature; NOAA: National Oceanic and Atmospheric Administration.



Data Processing

Processing Leptospirosis Data

The data cases will be cleaned and mapped according to the spatio-temporal variability to identify areas and periods with the highest incidence. The longitudes and latitudes of the possible source of infection of cases will be determined and reconfirmed with JUPEM. Subsequently, the coordinate table in Excel (Microsoft Corporation) will be added in the CSV format and imported to the ArcGIS Pro software (Esri) to determine the spatial distribution of leptospirosis cases. After analysis with the independent variables, leptospirosis hotspot areas will be generated and clipped with mukim polygon areas in Selangor.

Processing Topographical Data

The shapefile obtained from JUPEM will be projected in ArcGIS Pro software and extracted to thematic layers. The river hydrometric level data will be averaged into monthly data, tabled in Excel, and then saved in the CSV file format. Zonal statistics will be used for the analysis of each polygon.

Processing Satellite Data

Images obtained will be processed to obtain average monthly data for rainfall and LST for each mukim using the clipping tool in the ArcGIS Pro software to extract temperature and rainfall data for each polygon.

Data Analysis

The descriptive statistics of leptospirosis cases for each month from 2011 to 2019 will be analyzed using SPSS, version 27.0 (IBM Corp). The data will be presented using the frequency, percentage table, and appropriate bar charts or graphs for the variables studied.

The spatio-temporal analysis of patterns and distribution of leptospirosis hotspot areas in Selangor will be analyzed using the Moran I and Getis-Ord Gi* spatial statistical tools in ArcGIS Pro. Meanwhile, the relationship between leptospirosis hotspot areas and the hydroclimatic hotspot areas will be analyzed using Pearson correlation. Next, a generalized linear mixed model will be used to examine the correlation between the studied variables. The best-fitted model will be determined through the multivariate analysis by equations that give the lowest value of the Akaike information criterion result.

A predictive model for leptospirosis hotspot areas will be developed using the Phyton intelligent software to run the artificial neuron network analysis. The Phyton software will be able to examine the best-fit model for the association between leptospirosis hotspot areas with its hydroclimatic indicators.

Ethical Consideration

The study protocol obtained ethical approval with expedited review by the Medical Research and Ethics Committee, Ministry of Health Malaysia, on August 25, 2022 (NMRR ID-22-01548-C0Z). Data collection began in October 2022 and is expected to complete in March 2023.

Results

The results of this study are expected to be published by the end of 2024. The leptospirosis distribution and clusters are expected to be significantly associated with rainfall, land surface temperature, and the river hydrometric level. Both models,

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constructed through the use of statistical analysis and Python intelligent software, possess the potential to offer a comprehensive and multidimensional assessment of leptospirosis distribution and clustering. This integrated approach may enhance the comprehension of disease dynamics and facilitate the development of more effective strategies for prevention and control.

Discussion

Principal Findings

Globally, leptospirosis occurs in humid and tropical regions favoring the dwelling of mammals, including rodents, the main reservoirs of *Leptospira* causing the disease [6]. The threat of leptospirosis as an emerging neglected zoonotic disease is due to world climate changes and globalization. Flooding, rising temperatures, and the concurrent increase in rodent density greatly influence its distribution [5]. Domestic animals may harbor the organisms, but rodents are the main reservoirs of leptospires that incidentally transmit infections to humans through contact with contaminated water soiled with the reservoirs' urine [31].

Most infections with the pathogenic *Leptospira* cause subclinical manifestations or remain asymptomatic [1]. Symptomatic patients can have clinical manifestations, from mild fever, chills, headache, and muscle tenderness to severe forms characterized by dysfunction of multiple organs, including the liver, lungs, kidneys, and brain [1,32]. Commonly noticed manifestations are muscle pain involving the lower back and calves as well as conjunctival suffusion [32]. Severe forms of the disease are found in 10% of affected individuals who develop life-threatening pulmonary hemorrhages, Weil syndrome, and acute kidney injury [1].

The influence of climate change, such as the variations in rainfall, land temperature, and frequent floods, increases leptospirosis cases [5]. Studies in South America and East Asia ascertained the association of these factors to the disease, where heavy rainfall and flood events during the El Nino phenomenon and rainfall events that cause an increase in soil moisture impact regional leptospirosis [16,33]. A local study using weather data and artificial neuron network modeling to link leptospirosis occurrence in Seremban discovered their significant correlation with temperature and rainfall at a lag between 12 and 20 weeks [29].

Targeting hotspot areas for disease control is one of the widely used strategies. A hotspot can be described as an area that shows evidence of increased disease incidence, a higher risk of transmission, or a greater chance of disease emergence [34]. Many environmental factors influence leptospirosis incidence. They include factors involving occupation, natural disasters, and recreational or avocational exposure [9]. This study will focus on the major hydroclimatic factors for leptospirosis, including rainfall, river hydrometric level, and land surface temperature, due to global climate change dynamics and concurrent increase in disease incidence [16,18,28].

Strengths

This research will act as a pilot study for the whole country for a spatio-temporal analysis of leptospirosis with its association with the hydroclimatic factors. The predictive model developed could be used to replicate and improve similar studies in the future by investigating other hydroclimatic factors, such as water storage in the ground and in vegetation.

Limitations

The limitation of the study is that it only evaluates 3 main hydroclimatic factors in Malaysia that might only be applicable to regions or countries with the same climate. There may be additional hydrological factors that contribute to leptospirosis hotspot areas. Furthermore, this study did not analyze other significant environmental or nonenvironmental factors that might contribute to leptospirosis hotspot areas.

Conclusion

In conclusion, this study may illuminate whether leptospirosis infections occur in clusters and the role of hydroclimatic factors in contributing to the emergence of leptospirosis hotspot areas in Selangor. Moreover, public health managers can use the findings from the hotspot map and statistical models, along with the Python intelligent software analysis, to identify areas of high disease prevalence and implement targeted interventions to prevent and control the spread of leptospirosis more effectively.

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Data Availability

Data availability can be accessed on the NASA EarthData website for satellite images and the DID for hydrological data on river hydrometric levels. Data were also made available from respective agencies with requests and approval letters.

Conflicts of Interest

None declared.

Multimedia Appendix 1

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Peer-review reports from the Jawatankuasa Penilaian Permohonan Geran Putra Berfokus Jabatan Kesihatan Komuniti (GP-F/JKK) (Malaysia).
[PDF File (Adobe PDF File), 385 KB - resprot_v12i1e43712_app1.pdf]

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Abbreviations

DID: Department of Drainage and Irrigation
JUPEM: Department of Survey and Mapping
LST: land surface temperature
SEA: South East Asia

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Protocol

The Indigenous Australian Human Papillomavirus (HPV) Cohort Study 2, Continuation for 5 to 10 Years: Protocol for a Longitudinal Study

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Abstract

Background: Human papillomavirus (HPV) infection, a common sexually transmitted disease, is associated with cancers of the cervix, vulva, vagina, penis, anus, and head and neck. Oropharyngeal squamous cell carcinoma (OPSCC; throat cancer) is a type of cancer involving the head and neck area that is rapidly increasing across the globe. There are higher rates of OPSCC among Indigenous populations relative to non–Indigenous Australian populations, although the HPV-attributable fraction remains unknown. For the first time at a global level, we plan to extend an Indigenous Australian adult cohort to monitor, screen, and ultimately prevent HPV-associated OPSCC and to undertake extensive cost-effectiveness modelling around HPV vaccination.

Objective: This study aims to (1) extend follow-up to a minimum of 7 years post recruitment to describe the prevalence, incidence, clearance, and persistence of oral HPV infection; and (2) conduct clinical examinations of the head and neck, oral cavity, and oropharynx and collect saliva samples for early-stage OPSCC testing.

Methods: We will continue to implement a longitudinal design for the next study phase, where we will ascertain the prevalence, incidence, clearance, and persistence of oral HPV infection at 48, 60, and 72 months; undertake clinical examinations/saliva assessments to detect early-stage OPSCC; and refer for treatment. The primary outcome measures are changes in oral HPV infection status, biomarker measures of early HPV-related cancer, and clinical evidence of early-stage OPSCC.

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Results: Participant 48-month follow-up will commence in January 2023. The first results are expected to be submitted for publication 1 year after 48-month follow-up begins.

Conclusions: Our findings have potential to change the way in which OPSCC among Australian Indigenous adults is managed, with desired impacts including cost-savings on expensive cancer treatments; improved nutritional, social, and emotional outcomes; and improved quality of life for both Indigenous adults and the Indigenous community more broadly. Continuing a large, representative Indigenous adult cohort to track oral HPV infection and monitor early OPSCC is essential to yield critical information to include in the management armamentarium of health and well-being recommendations for Australia's First Nations.

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KEYWORDS

Aboriginal South Australian; human papillomavirus; oral HPV infection; oral pharyngeal squamous cell carcinoma; OPSCC

Introduction

Human Papillomaviruses

Human papillomaviruses (HPVs) are a heterogeneous group of circular, double-stranded DNA viruses that grow in stratified epithelium (skin and mucosa). Prior to the implementation of vaccination, HPV was the most common sexually transmitted infection in Australia, with an estimated 4 out of 5 Australians having an HPV infection at some point in their lives [1]. HPV is a precursor to a range of cancers, including cervical cancer, other anogenital cancers, and oropharyngeal cancer. It is usually transmitted within 2-5 years of sexual activity debut [2]. The prevalence of HPV infection at a population level in Australia is unknown as there is no national level or representative survey data, and almost all surveys have focused on females only. There is reasonable HPV DNA data on prevaccination cervical HPV infection in females in both general and Indigenous populations. For example, prior to HPV vaccination, a survey of females aged 15-40 years attending routine Papanicolaou screening at 16 Indigenous health services, 8 family-planning services, and 10 community clinics sites across Australia estimated the age-standardized prevalence of any high-risk (oncogenic) HPV type as 31.3% and 30% among 655 Indigenous and 1494 non–Indigenous females, respectively [3]. The prevalence of HPV 16/18 in this group was 12.2% among Indigenous and 12.8% among non–Indigenous females, respectively.

HPV and Oropharyngeal Squamous Cell Carcinoma

Oropharyngeal cancers include cancer of the middle part of the throat: the tonsils, soft palate, and the base of the tongue [4]. HPV-associated oropharyngeal squamous cell carcinoma (OPSCC) has one of the most rapidly increasing incidences in high-income countries [5], with survival rates of HPV-attributable OPSCC being much higher than non–HPV-attributable OPSCC [6]. The increased incidence, which is particularly notable among males and younger cohorts, may be attributable to increased carriage of high-risk HPV types (especially HPV 16 or 18) via increased oral exposure to infected anogenital sites with changing sexual behaviors, as opposed to the more traditional risk factors such as smoking and alcohol [7,8]. Although estimates vary by setting, the proportion of OPSCC attributable to HPV (mainly HPV 16) has been cited in high-income countries as between 65% and 83% [9-11]. OPSCC has now surpassed cervical cancer as the most common HPV-driven cancer [12,13].

Burden of OPSCC in Australia

In 2008, age-standardized rates of lip, oral cavity, and oropharyngeal cancer in Australia were 11.0 per 100,000 for males and 4.1 per 100,000 for females [14]. Overall rates of overall lip, oral cavity, and oropharyngeal cancer declined between 1982 and 2008, but when considered in isolation, OPSCC rates increased during this time (1.2% per annum for males and 0.8% per annum for females), possibly due to an increased incidence of oral HPV infection [14]. Hocking and colleagues [15] similarly found a significant increase in OPSCC in Australia between 1982 and 2005, with an annual percentage increase of 1.4% for males and 1.0% for females. Hong and colleagues [16] reported that the proportion of OPSCCs that were positive for HPV DNA and p16 increased in males from 19% in 1987-1990 to 47% in 2001-2005 and 60% in 2005-2006. In 2 Brisbane-based studies, the HPV prevalence in patients with OPSCC diagnosed from 2004-10 was 49% and increased to 72% in patients diagnosed from 2013-15 [17,18].

There is little documented evidence of the incidence of OPSCC among Australian Indigenous persons. Indigenous persons living in Queensland were more likely than the total Queensland population to be diagnosed with head and neck cancers between 1997 and 2012, specifically in the base of the tongue/tonsil/oropharynx; the standardized incidence ratio was 2.16 (n=81) [18]. The incidence of oral cavity and oropharyngeal cancer among Aboriginal South Australians between 1977 and 2001 was 29.7 annual cases per 100,000 compared with 8.5 per 100,000 in the non-Aboriginal population [19]. It was the fourth most common cancer type in Aboriginal women, after lung cancer, gynecology-related cancer, and breast cancer. Between 1991 and 2005 in the Northern Territory, oral cavity and oropharyngeal cancer incidence for Indigenous Australians was 2.5 times that of the general Australian population, with the mortality rate being 4.8 times higher in Indigenous men and 4.0 times higher in Indigenous women [20]. In 2015, the rate ratio of disability-adjusted life years due to oral cavity and oropharyngeal cancer among Indigenous Australians was 3.8 times that reported for the total Australian population [21].

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Early Detection of OPSCC

HPV 16-E6 antibodies are detectable in peripheral blood before diagnosis in the majority of HPV 16–driven OPSCCs. Using data from 743 incident OPSCC cases and 5814 controls from 9 population groups across Australia, North America, and Europe, Kreimer and colleagues [13] reported that HPV 16-E6 seropositivity increased with lead time: 0%, 13.5%, 23.7%, and 38.9% with lead times of >30 years (n=24 cases), 20-30 years (n=148), 10-20 years (n=228), and <10 years (n=301), respectively (*P*<.001). Of the 47 HPV 16-E6 seropositive cases with serially collected samples, 17 cases seroconverted during follow-up, ranging from 6 to 28 years before diagnosis. For the remaining 30 cases, robust seropositivity was observed up to 25 years before diagnosis. The authors concluded that the immune response to HPV 16–driven tumorigenesis is detectable several decades before OPSCC diagnosis.

Accuracy of Saliva Samples for the Detection of Early-Stage OPSCC

Saliva covers the oropharyngeal mucosa and can be collected noninvasively, making it an ideal bodily fluid for early biomarker detection of HPV-induced OPSCC. Recent studies have examined HPV mitochondrial RNA (mRNA) in oral (oropharyngeal swab or saliva) samples from patients with head and/or neck squamous cell carcinoma. The high rates for HPV E6 oncoproteins and E6/E7 mRNA suggest that most patients were experiencing transcriptionally active HPV-related OPSCC [22,23]. The clinically validated Hologic Aptima assay gives a result for the presence of HPV E6/E7 mRNA for 14 HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68). There is also an option to examine whether the specific HPV type is HPV 16 or HPV 18/45. As with the findings from Kreimer and colleagues [13], the persistence of HPV 16 is a precursor for OPSCC.

The Indigenous Australian HPV Cohort Study

The first phase of this prospective longitudinal cohort study was developed in partnership with Aboriginal communities in South Australia and funded by the National Health and Medical Research Council in 2016. The study is governed by an Aboriginal Reference Group, with data collected by trained Aboriginal research officers [24]. To be eligible at baseline, participants needed to identify as being Aboriginal and/or Torres Strait Islander, aged 18+ years, and residing in South Australia. Participants were recruited from February 2018 to January 2019 across 8 South Australia sites, primarily through Aboriginal Community Controlled Health Organisations (ACCHOs) whose chief executive officers are key stakeholders. The 1011 participants recruited at baseline represented 5% (1011/20,220) of Aboriginal South Australian adults eligible during the recruitment period, 8.2% (633/7720) of those eligible in nonmetropolitan locations, and 3% (376/12,533) of those in metropolitan locations. Participants were followed-up at 12 months (March 2019 to March 2020), with data from 749 (74.1%) out of 1011 participants obtained (suspended early due to COVID-19 restrictions). Follow-up at 24 months ceased in December 2021, with data from 815 participants obtained. Across baseline and 12- and 24-month follow-ups, saliva samples to test for oral HPV infection were collected in commercially available kits, and the DNA was tested for HPV detection.

Study Aims

In continued partnership with Aboriginal South Australian stakeholders and study participants, the aims of the second phase of the Indigenous Australian HPV cohort study are as follows:

Aim 1: To extend follow-up to a minimum of 7 years post recruitment to describe the prevalence, incidence, clearance, and persistence of oral HPV infection, including high-risk types, across 48-, 60-, and 72-month follow-ups and to correlate with lifestyle and sociodemographic characteristics

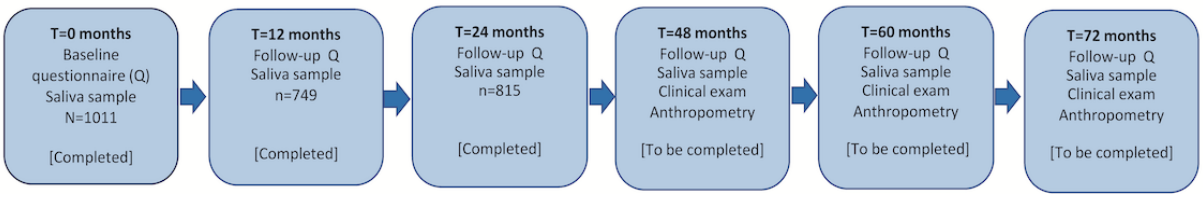
Aim 2: To conduct a thorough clinical examination of the head and neck, oral cavity, and oropharynx and to collect anthropometrics and saliva samples for OPSCC testing

Methods

Study Design

We will continue to implement a longitudinal design for the next study phase. A study schema is included in Figure 1.

Figure 1. Timing of data and sample collection. T: time point.



Inclusion Criteria and Retention

All participants initially recruited will be eligible for the 48-, 60-, and 72-month follow-ups. Retention strategies will involve those successfully used thus far: (1) continuing to employ Aboriginal staff who have built up personal relationships with participants and who are committed to following up participants despite challenges in doing so; (2) ensuring participants are contacted regularly to ensure the accuracy of contact details; (3) ascertaining contact details of 3 new key personnel who may know the whereabouts of participants should the study team be unable to contact them; (4) sending birthday and Christmas cards to participants; and (5) facilitating one-on-one relationships between study staff and participants, with study staff ideally seeing each of their participants for each research phase. We perceive no difficulties in continuing with the high retention of participants given our past success.

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Ethical Approval

Ethics approval has been received by the Aboriginal Health Council of South Australia's Human Research Ethics Committee (04-22-1001) and the University of Adelaide's Human Research Ethics Committee. Prior to being recruited, all participants will be required to sign an informed consent form, which includes consent for the authors to publish the findings in the peer-reviewed scientific literature.

Data Collection

After completing informed consent with the assistance of the Aboriginal research staff, participants will be again asked to provide saliva samples using a commercially available kit from which microbial DNA and mRNA for genotyping will be extracted. This will involve the participant (1) not eating or drinking for 30 minutes prior to collection; (2) removing the funnel lid on the container; (3) spitting until 2 mL of saliva reaches the fill line on the container (this will take 2 minutes); (4) closing the lid and unscrewing the lid from the funnel; and (5) placing the small cap on the tube and shaking the tube for 5 seconds. The saliva samples will be sent to Victorian Cytology Services Ltd for analysis.

A thorough clinical examination of the external head and neck, intraoral cavity, and oropharynx will be undertaken by trained and calibrated dental professionals. Soft and hard tissue characteristics, caries experience, periodontal disease, and gingivitis will be assessed through standardized oral epidemiological examinations used in national oral health surveys. Weight will be measured in duplicate to the nearest 0.1 kg using Seca model 803 scales and averaged. Height will be measured in duplicate to the nearest 1 mm using a Seca model 213 portable stadiometer, using a standard anthropometric procedure. Any pathology detected via the clinical examination or saliva results will be immediately fed back to participants, with referrals to specialist or local primary care services promptly arranged.

Data collection will be at participants' homes, ACCHOs, or wherever participants feel the most comfortable.

Data Analysis

In brief, the analysis plan for each aim is as follows:

Aim 1: Oral HPV Infection Prevalence, Incidence, Clearance, and Persistence at 48, 60, and 72 Months

Saliva samples will be stabilized at the point of collection using PreservCyt media. Samples will be run on the real-time polymerase chain reaction–based Seegene HPV 28 assay using the Starlet extraction platform and the BioRad CFX96 amplification/detection instrument. The Seegene HPV 28 assay is the benchmark for HPV surveillance [25] due to its high level of automation, which reduces variation in the sensitivity/specificity between specimens processed at different time points. The Seegene HPV 28 assay gives individual HPV type outputs from 28 HPV types (19 high-risk HPV types: 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 69, 73, and 82; and 9 low-risk HPV types: 6, 11, 40, 42, 43, 44, 54, 61, and 70), including the 14 HPV types defined by the International Agency for Research on Cancer (IARC) as oncogenic, the additional 2 nononcogenic types covered by HPV vaccination (HPV 6 and HPV 11), and β-globin (for DNA integrity check). HPV 13 and HPV 32 are not included in the Seegene HPV assay but the DNA extraction from this assay is able to be run on a separate polymerase chain reaction based on the protocol by Bolis and colleagues [26]. The prevalence, incidence, clearance, and persistence of oral HPV types across all time points from recruitment at an individual level and collectively will be calculated using simple descriptive analysis.

Aim 2: Oral Clinical Examinations/Saliva Samples for OPSCC Testing

The prevalence, extent, and severity of dental diseases, including early clinical signs of OPSCC, will be calculated using standard World Health Organization (WHO) oral health benchmarks [27]. The recently completed 2017-18 National Survey of Adult Oral Health data set [28] will enable comparison with both general and Indigenous population-level estimates. General analysis will comprise chi-square and Student *t* test (2-tailed) within the study sample and nonoverlapping 95% CIs when comparing population estimates. Antibodies against HPV 16-E6 will be measured using saliva samples (Aptima HPV assay) [22]. Assay results will be interpreted based on the signal-to-cutoff ratio, with values ≥ 0.5 considered positive.

Results

Of the 1011 participants recruited, 910 (90%) provided β-globin positive saliva samples (β-globin is a DNA integrity check). Of these 910, 35.1% (n=319) were positive for any HPV infection [29]. This was 15 times the prevalence reported in a study of young non–Indigenouss Australians [30] and 5 times the prevalence reported in a systematic review involving the United States, Brazil, Mexico, and Finland [31]. Antonsson and colleagues [32] described a longitudinal study (0, 6, 12, and 24 months) of 704 people from Brisbane (18-70 years old). They reported an oral HPV infection prevalence of 10.7% (high-risk HPV prevalence of 6.4%) at baseline in 636 people who were β-globin positive. In our study, the most prevalent HPV types at baseline were those associated with Heck disease (multifocal epithelial hyperplasia; 207/910, 23% of the HPV types found)—a relatively benign and rare condition caused by oral HPV 13 or 32 infection that is more prevalent among Indigenous populations [33-35]. Clinically, Heck disease presents as soft, distinct, mostly multiple, and smooth papules or nodules having the same color as the surrounding mucosal epithelium (a "cobblestone" appearance), predominantly affecting the lower and upper labial mucosa and tongue. The condition usually regresses naturally but can be treated by surgical excision or cryotherapy when lesions are aesthetically unpleasing [36]. The next most prevalent HPV types were those associated with OPSCC (HPV 16 or 18; 30/910, 3.3% of the types found) [29,32].

In our Indigenous Australian HPV Cohort study, of the 749 participants retained at 12-month follow-up, 645 (86.1%) provided β-globin positive saliva samples. Of these, 43% (277/645) were positive for any HPV infection. The most prevalent HPV types at 12-months were again those associated with Heck disease (213/645, 33% of the HPV types found),

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followed by HPV types associated with OPSCC (HPV 16 or 18; 16/645, 2.5%). A total of 588 participants had samples at baseline and 12-month follow-up that were β-globin positive. The prevalence of any oral HPV infection increased from 34% (200/588) to 44% (259/588). This increase was largely due to increases in HPV types 13 or 32 (Heck disease): from 20% (118/588) at baseline to 34% (200/588) at 12 months. The prevalence of HPV 16 or 18 decreased from 3.9% (23/588) at baseline to 2.7% (16/588) at 12 months. The prevalence of high-risk HPV types according to the IARC definition [37] decreased from 8.5% (50/588) at baseline to 7.1% (42/588) at 12 months [38]. A total of 473 participants had samples at baseline and 12- and 24-month follow-up that were β-globin positive. The prevalence of any oral HPV infection was 24.7% (117/473), the prevalence of HPV type 13 or 32 was 15.6% (74/473), and the prevalence of HPV type 16 or 18 was 1.7% (8/473).

Participant follow-up for this study will commence in January 2023. We anticipate the first results to be submitted for publication 1 year following initial recruitment.

Discussion

Expected Findings

Our findings have potential to change the way in which OPSCC among Australian Indigenous adults is managed, with desired impacts including cost-savings on expensive cancer treatments; improved nutritional, social, and emotional outcomes; and improved quality of life for both Indigenous adults and the Indigenous community more broadly.

Approaches to Aboriginal Community Engagement

The strong Aboriginal partnership, engagement, and buy-in of the first study phase were reported against the Consolidated Criteria for Strengthening Reporting of Health Research involving Indigenous Peoples (CONSIDER) statement [39,40]. The success of our community engagement processes was summarized as (1) engaging with ACCHOs as equal partners very early in the research process; (2) having an Aboriginal Reference Group; (3) having ACCHOs actively promote the study; (4) having a flexible agenda that is responsive to broader environment demands; and (5) including Aboriginal capacity building. Specific lessons learned include the need for active and wide Aboriginal community consultation that is initiated early in the research process, strong and sustained Aboriginal capacity building, and an active Aboriginal Reference Group—all of which we will continue to incorporate in the proposed second phase. There are additional benefits in having Aboriginal staff as representatives in each of the field sites. These representatives have been able to build their reputation in a new area of Aboriginal health, with oral HPV infection not being noticeably recognized previously. Australian Indigenous communities now have a contact, with study continuation facilitating improved HPV knowledge for both the ACCHO workforce and broader community. The next phase of this study will continue to implement and strengthen these community engagement strategies.

Why Is Continuation of This Cohort Important?

By December 2021, study participants had been followed for a median of 3.5 (range 3.0-3.9) years from baseline, allowing the analysis of short-term outcomes including oral HPV infection prevalence, quality of life, health state valuations of OPSCC, and incidence/clearance in the 12-24 months after baseline. There is not, however, sufficient follow-up to assess whether oral HPV infections, especially persistent high-risk HPV infections, lead to early-stage OPSCC and what the attributable risk from HPV will be. Continuing the largest Indigenous HPV cohort in the world to track oral HPV infection and to monitor the early stages of OPSCC is essential to yield critical information to include in the management armamentarium of health and well-being recommendations for Australia's First Nations. It is especially relevant in light of the imminent rollout of self-sampling HPV testing initiatives in Australia.

Strengths and Limitations

There are 2 main strengths of the Indigenous Australian HPV Cohort study. The first of these has been the engagement of South Australia's Aboriginal communities. This has contributed to the excellent recruitment and follow-up rate (approximately 749/1011, 74% to 815/1011, 80.6%), which needs to be taken into context. For example, this study has been undertaken over vast distances (travelling 700 km west, 400 km east, and 800 km north of the city of Adelaide), involving highly disadvantaged participants who have, in the past, not always enjoyed positive research interactions. The fact that over 1000 participants were recruited in less than 12 months demonstrates the widespread community support. The second strength is the multidisciplinary skill set of the team that is Aboriginal led. The main limitation is the lack of clinical examinations, anthropometrics, and samples to detect HPV 16-E6 antibodies that would yield important biomarker estimates, with funding not provided for this in the first 3 waves of the study.

In conclusion, by continuing the follow-up of the Indigenous Australian HPV Cohort, we will generate novel information regarding oral HPV exposure and OPSCC, including a range of cost-effectiveness modelling to ascertain cost-savings of extending HPV vaccination initiatives beyond what is currently available. This information has potential to vastly increase the relatively unknown causes of such dramatic HPV-related OPSCC incidence rates. Over the past 7 years, we have established excellent community buy-in with Aboriginal groups across South Australia. Everything is in place to continue the follow-up of this essential cohort, with findings likely to be game-changing in terms of influencing Indigenous HPV vaccination policy, oral HPV infections, OPSCC, health policy, and clinical guidelines throughout Australia and, indeed, the world.

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Data Availability

The data sets generated and/or analyzed during the current study are not publicly available due to privacy issues of the participants. Data are available from the corresponding author on reasonable request.

Authors' Contributions

All authors are named investigators on the project; they all contributed to the intellectual input of the study design and in writing this protocol.

Conflicts of Interest

KC is co—principal investigator (PI) of an investigator-initiated trial of cervical screening, “Compass”, run by the Australian Centre for Prevention of Cervical Cancer (ACPCC), which is a government-funded not-for-profit charity. Compass receives infrastructure support from the Australian government and the ACPCC has received equipment and a funding contribution from Roche Molecular Diagnostics, USA.
KC is also co-PI on a major implementation program Elimination of Cervical Cancer in the Western Pacific which has received support from the Minderoo Foundation and the Frazer Family Foundation and equipment donations from Cepheid Inc.

Multimedia Appendix 1
Peer-review reports from the National Health and Medical Research Council - 2021 Clinical Trials and Cohort Studies - Australian Government (Canberra, Australia).
[PDF File (Adobe PDF File), 90 KB - resprot_v12i1e44593_app1.pdf]

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Abbreviations

ACCHO: Aboriginal Community Controlled Health Organisation
CONSIDER: Consolidated Criteria for Strengthening Reporting of Health Research involving Indigenous Peoples
HPV: human papillomavirus
IARC: International Agency for Research on Cancer
mRNA: mitochondrial RNA
OPSCC: oropharyngeal squamous cell carcinoma
WHO: World Health Organization

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Protocol

Investigating Metabolic and Molecular Ecological Evolution of Opportunistic Pulmonary Fungal Coinfections: Protocol for a Laboratory-Based Cross-Sectional Study

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Abstract

Background: Fungal-bacterial cocolonization and coinfections pose an emerging challenge among patients suspected of having pulmonary tuberculosis (PTB); however, the underlying pathogenic mechanisms and microbiome interactions are poorly understood. Understanding how environmental microbes, such as fungi and bacteria, coevolve and develop traits to evade host immune responses and resist treatment is critical to controlling opportunistic pulmonary fungal coinfections. In this project, we propose to study the coexistence of fungal and bacterial microbial communities during chronic pulmonary diseases, with a keen interest in underpinning fungal etiological evolution and the predominating interactions that may exist between fungi and bacteria.

Objective: This is a protocol for a study aimed at investigating the metabolic and molecular ecological evolution of opportunistic pulmonary fungal coinfections through determining and characterizing the burden, etiological profiles, microbial communities, and interactions established between fungi and bacteria as implicated among patients with presumptive PTB.

Methods: This will be a laboratory-based cross-sectional study, with a sample size of 406 participants. From each participant, 2 sputa samples (one on-spot and one early morning) will be collected. These samples will then be analyzed for both fungal and bacterial etiology using conventional metabolic and molecular (intergenic transcribed spacer and 16S ribosomal DNA–based polymerase chain reaction) approaches. We will also attempt to design a genome-scale metabolic model for pulmonary microbial communities to analyze the composition of the entire microbiome (ie, fungi and bacteria) and investigate host-microbial interactions

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under different patient conditions. This analysis will be based on the interplays of genes (identified by metagenomics) and inferred from amplicon data and metabolites (identified by metabolomics) by analyzing the full data set and using specific computational tools. We will also collect baseline data, including demographic and clinical history, using a patient-reported questionnaire. Altogether, this approach will contribute to a diagnostic-based observational study. The primary outcome will be the overall fungal and bacterial diagnostic profile of the study participants. Other diagnostic factors associated with the etiological profile, such as incidence and prevalence, will also be analyzed using univariate and multivariate schemes. Odds ratios with 95% CIs will be presented with a statistical significance set at $P<.05$.

Results: The study has been approved by the Mbarara University Research Ethic Committee (MUREC1/7-07/09/20) and the Uganda National Council of Science and Technology (HS1233ES). Following careful scrutiny, the protocol was designed to enable patient enrollment, which began in March 2022 at Mbarara University Teaching Hospital. Data collection is ongoing and is expected to be completed by August 2023, and manuscripts will be submitted for publication thereafter.

Conclusions: Through this protocol, we will explore the metabolic and molecular ecological evolution of opportunistic pulmonary fungal coinfections among patients with presumptive PTB. Establishing key fungal-bacterial cross-kingdom synergistic relationships is crucial for instituting fungal bacterial coinfecting etiology.

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KEYWORDS

pulmonary mycoses; fungal-bacterial coinfection; metabolic; evolutionary; opportunistic infections; cross-kingdom interaction; tuberculosis

Introduction

Overview

Fungi are ecologically regarded as environmental saprophytes that feed on decaying organic matter. However, over the past 30 years, fungi have transitioned into key etiological agents for difficult-to-manage infections, killing at least 1 million people each year. Yet they remain among the most neglected diseases worldwide [1,2]. The most serious invasive fungal infections often occur in the immunocompromised patients, such as those with HIV, cancer, and organ transplant, all of which have increased dramatically in the last 20 years [2]. Clinical manifestations of fungal infections have ranged from superficial to disseminated diseases with rates of invasive opportunistic fungal infections having upsurged during recent decades. Opportunistic pulmonary fungal coinfections are also emerging due to recent changing trends in predisposing factors and etiology. In Africa, pulmonary fungal coinfections are reported in about 15%-35% of cases, mainly within the cohort of individuals coinfected with HIV and tuberculosis (TB) [3,4]. This is posing enormous challenges to health care professionals, especially in resource-limited settings, where the diagnosis is not precise.

The chronic pulmonary disease has been linked with fungal etiology in the past but is often ignored. However, there is an emerging and interesting twist to fungal etiology, where cross-kingdom interactions appear to impact fungal virulence but are not fully explored. For instance, there are reports that bacteria can influence eukaryotic biology through various roles, such as parasites, commensals, or beneficial symbionts, in addition to acting as sources of new genetic sequences through subtle mechanisms like horizontal gene transfer [4-7]. In this context, the coexistence of fungi with other microbes, such as bacteria, in the same infection niche may unveil highly coordinated metabolic or molecular interaction profiles. This has been shown in chronic wound infections, where fungal-bacterial coexistence disrupts the highly controlled sequence of wound healing [3,8]. In fact, chronic wound microbiome and mycobiome studies reveal that fungal coinfections contribute to impaired wound healing [8]. A study by Mucunguzi and colleagues [9] reported a 22.2% prevalence of pulmonary fungal infections among people living with HIV in Southwestern Uganda. Therefore, it is possible that fungi also affect the outcome of chronic pulmonary diseases but are missed due to the lack of specific clinical or diagnostic signatures, leading to high rates of morbidity and mortality [3,10,11].

In the immunocompromised cohort, pulmonary infections can be exacerbated by a range of pulmonary opportunistic fungal coinfections. Unfortunately, infected individuals often present with symptoms similar to those of the most prevalent diseases, such as pulmonary tuberculosis (PTB) or bacterial pneumonia [3]. This propagates their rapid spread and augments poor prognosis. Hitherto, fungi co-isolated with bacteria have been considered irrelevant and often regarded as environmental contaminants [12]. This is further worsened by limited exposure of clinicians and laboratory fraternity to fungal infection biology. Nevertheless, patients could benefit from the definitive diagnosis of these infections and an exploration of the underlying mechanisms that drive saprophytic fungi to cause diseases in this patient population.

The changing trend of fungal etiology calls for the employment of advanced technology in profiling etiological agents. The synergistic ability of fungi to interact with other microbes, such as bacteria, in health and disease proves complex and can unveil new etiological agents and highlight novel virulence traits and antimicrobial targets. In this project, we propose to study the coexistence of fungal and bacterial microbial communities

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during chronic pulmonary disease, with a keen interest in underpinning fungal etiological evolution and the predominating interaction relationships that may exist between fungi and bacteria. There is already evidence that such interactions may culminate into properties distinct from those of their individual consortia [4,7,13-17]. Three hypotheses define this study, specifically that the following: (1) the burden of opportunistic pulmonary fungal coinfections is higher than what culture-dependent data suggest; (2) culture-independent data complement culture-dependent data in supporting therapeutic decisions; and (3) fungal-bacterial coexistence influences fungal and bacterial virulence. Thus, through these questions, we hope to reveal elusive interplays between the 2 microbial communities during disease development to explain differences in patient outcomes.

Significance of the Study

Through this study, we can improve diagnosis and enhance clinical relevance as well as our epidemiological understanding of cross-kingdom etiological interactions. Pilot explorations of polymicrobial interactions, including bacterial-fungal interactions, can mediate a shift in substrate consumption, enzyme production, sexuality, thermostolerance, antimicrobial resistance, metabolism, and virulence [4,7,17-26]. For instance, some Mucorales fungi harbor bacterial endosymbionts that significantly modulate their metabolic profiles and virulence attributes in plants [16,17,27,28]; a similar interaction strategy is suggested in animal hosts [29,30].

During blight light disease of rice seedlings, a saprophytic fungus, *Rhizopus microsporus*, benefits from a toxicogenic alliance formed between this fungus and its endosymbiont bacteria, *Burkholderia rhizoxinica* or *Burkholderia endofungorum*; this alliance enables them to produce a potent anti–beta-tubulin toxin rhizoxin, which is a hepatotoxic cyclopeptide [17,27,31]. In addition, a range of phytotoxins with the potential to mediate virulence, which is thought to be produced by fungi, is a consequence of such interaction [16].

Although the impact of such relationships on clinical outcomes remains unclear, we recently demonstrated that another bacterial endosymbiont, *Ralstonia pickettii*, enabled *Rhizopus microsporus* to modulate innate immune responses in an animal model via a novel secreted factor [29,30]. Removing the endosymbiont using antibiotics rendered *Rhizopus microsporus* completely avirulent. These bioactive compounds are, therefore, important for fungal virulence as well as having potentially exploitable activities as demonstrated by the long history of fungal natural products in medicine, agriculture, and research [32].

Study Aims

This study aims to determine and characterize the burden, etiological profiles, microbial communities, and interaction relationships established between fungi and bacteria implicated in pulmonary fungal coinfections.

Methods

Study Design

This study will be a laboratory-based observational cross-sectional study.

Study Setting and Population

The study is being conducted at Mbarara Regional Referral and Teaching Hospital (MRRH) in Southwestern Uganda among patients suspected of having PTB.

Selection Criteria

The target population under study consists of patients suspected of TB at MRRH. Participants will be included if they are 18 years and older, provide consent, and have at least one of the following qualities: presenting with PTB-like symptoms, having no prior history of TB, testing positive or negative on smear test and GeneXpert test, exhibiting lipoarabinomannan antigen positivity along with persistent respiratory symptoms, and being on anti-TB treatment and severely ill yet able to produce sputum. Conversely, HIV-positive or HIV-negative patients who have TB-like symptoms but are on anti-TB treatment with a favorable prognosis will also be included. Patients who are on anti-TB treatment and severely ill but unable to produce sputum, critically ill patients, and pregnant women will be excluded from the study. Patients who are critically ill are excluded because their condition may cause delays in sample collection and obtaining consent, which would impact the recruitment process. Additionally, pregnant women suspected of TB are excluded since they are managed differently according to TB guidelines.

Statistical Analysis Plans and Power Calculations (Sample Size)

Based on the preliminary study, the prevalence of fungal coinfections among patients suspected of TB has been previously determined to be 40% using Kish-Leslie formula ($n=Z^2$ P (1-P)/ d^2) for determining the sample size in a cross-sectional study. In this formula, n is the sample size, Z (1.96) is the statistic for the level of confidence, P (0.4) is the estimated prevalence, and d (0.05) is the margin of error for the confidence interval. Using the Open Epi calculator, considering a population of 195,013 for Greater Mbarara, the sample size was determined to be 369 patients. Since we anticipate a 10% dropout rate, we will recruit 406 patients. From these patients, only 2 sputum samples will be collected—an on-spot sample on the day of recruitment and an early morning sample the following day, making a total of 812 samples to be collected. Obtained data will be analyzed using appropriate software, such as GraphPad (GraphPad Software Inc), Stata (StataCorp), or Epi Info (Centers of Disease Control and Prevention), among many others.

Recruitment Strategy and Retention

Patients will be recruited by convenient sampling as they report for medical services at the HIV/TB clinic of MRRH. The recruitment of the participants will follow the existing diagnosis and point-of-care procedures at both study sites. The clinic receives an average of 10 new cases per day. Considering both

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our inclusion and exclusion criteria, we hope to recruit an average of 4 patients per day, resulting in an average total of 88 patients per month. This recruitment plan is achievable based on the rate of patients' inflow at the clinic. Additionally, sputum sample collection is not an invasive method that would scare away patients, so we do not anticipate any major challenges with patient retention. However, we will factor in a possible 10% dropout rate among patients, and thus, the final sample size will be increased by 37 more patients, resulting in a total of 406 patients, as previously mentioned.

Recruitment Site Selection

We have selected Uganda for this study because the country ranks high among the severely affected nations with HIV and TB pandemics. This is particularly true in western Uganda, where Mbarara (the proposed study site) is located. This subpopulation is also ranked among those most at risk of opportunistic fungal coinfections, yet it has been grossly ignored. Opportunistic pulmonary fungal coinfections are not uncommon among the immunosuppressed cohort, such as patients with HIV. We have selected patients suspected of having TB because most of the opportunistic pulmonary fungal infections present like TB, and therefore, are often missed during routine diagnosis. We have selected Mbarara Hospital as the study site because it is a regional referral hospital for the western region of Mbarara and a treatment center for patients with HIV or TB. Thus, we will have easy access to our study cases due to the high incidence of HIV or TB in this community. However, several population-based studies have been conducted in the past, focusing on HIV and TB, but are not associated with fungal coinfections [33,34]. Additionally, Mbarara University of Science and Technology has the infrastructure to handle most of the study demands. For instance, the Department of Microbiology in the Faculty of Medicine hosts a microbiology laboratory with medical mycology and TB units that have the capacity to respectively perform routine fungal or TB-based sputum analytical protocols, such as TB and GeneXpert testing, potassium hydroxide, and lactophenol cotton blue staining, as well as fungal and bacterial cultures. Additionally, the department has the capacity to do molecular-based procedures, including DNA isolation, polymerase chain reaction (PCR) amplification, and sequencing. The Department of Microbiology has also established collaborations with both national and international institutions, such as the Infectious Diseases Institute of Makerere University, Gulu University, Soroti University, and Muni University in Uganda; Massachusetts General Hospital and University of Minnesota in the United States; University of Birmingham, Sheffield University, and University of Exeter in the United Kingdom; and University of Aberdeen in Scotland.

Approach and Methodology

Aim 1: Determining the Burden and Etiological Profiles of Fungal Coinfections Among Patients Suspected of TB

Patients' sputum samples will be collected and cultured on both fungal and bacterial media for either organism's isolation. The isolates will be identified and profiled accordingly using conventional phenotypic and genomic-based assays. Total DNA will be extracted from the same sputum samples using a bead-beating phenol-chloroform approach. PCR primers targeting region 2 intergenic transcribed spacer (ITS2) will be used to amplify the fungal DNA present in the sputum samples; the amplified DNA will then be sequenced by Illumina MiSeq technology. This approach has been demonstrated to sensitively identify and determine the relative abundance of all fungi present in similar respiratory samples [35]. In this study, we will use this approach to identify the most abundant fungi present and detect any potential coinfections, which maybe challenging to identify using traditional culture methods. Fungal data will be analyzed using Mothur and the R statistical package Phyloseq (R Core Team) and will be speciated with reference to the UNITE2 database. Fungal quantitative PCR will be applied to determine the total burden of fungi present in each sample. Shotgun metagenomics will also be applied to a subset of samples. This metagenomics approach will reveal genomic detail of the fungi present, which will potentially include antimicrobial resistance genes and virulence genes and provide further typing information that reveals common clones or transmission among patients. Using long-read technology, the Oxford Nano pore GridION has the advantage of being a rapid sequencing technology that has shown promise as a rapid point-of-care test for the identification of microorganisms in clinical samples. As such, the use of this technology in this study may also reduce the time until diagnosis for fungal infections.

Aim 2: Establishing and Characterizing Microbial Communities Associated With Patients Suspected of Having TB

16S ribosomal RNA (rRNA) gene sequencing will be used to target the bacterial communities present in the same samples, using the same DNA extract, to identify bacterial coinfections. The results obtained will be used to describe the bacterial communities present in the sputum samples and then will be integrated with ITS2 fungal data [13,36-38]. To determine the association with the host phenotypes, the clinical metadata, including but not limited to age, gender, BMI, race or tribe, behaviors, and immune status, will be used to determine the association between fungal and bacterial communities with host phenotypes. For correlations between taxa, a combination of 16S rRNA gene and ITS2 sequencing data from the same samples will be used. Co-abundance patterns of bacteria and fungi will reveal potential interactions between and within fungal-bacterial communities, which can be further explored using DNA-independent methods in Aim 3. Both fungal-fungal, bacterial-bacterial and fungal-bacterial relationships will be interrogated using appropriate software packages, such as SparCC [38,39].

Aim 3: Characterizing Potential Interaction Relationships Established Between Fungal and Bacterial Communities

We will use a metabolomics approach in which sputum samples will be homogenized with methanol for metabolite extraction and derivatization. The extract and derivatives will then be analyzed for chemical composition using quantitative gas chromatography-mass spectrometry technique based on

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metabolite profiling [40]. Gas chromatography-mass spectrometry–based metabolite raw data will be processed using the XCMS toolbox; this processing will involve peak detection, alignment, and multivariate statistical analysis using the XCMS outputs.

We will also attempt to design a genome-scale metabolic model for pulmonary microbial communities to infer the entire microbiome (bacteria and fungi) and host-microbial interactions under different patient conditions. This will be based on the interplays of genes (identified by metagenomics and inferred from amplicon data) and metabolites (identified by metabolomics) by analyzing the full data set and using specific computational tools, including but not limited to Meta-genomic Operationalized Assembly and Annotation Tool 2 for functional categorization and Human Microbiome Project Unified Metabolic Analysis Network 2 for profiling abundance of microbes and activity of their metabolic pathways. A genome-scale model will be developed to explore complex relationships between microbial components, such as genes, using assembly of gut organisms through reconstruction and analysis, a reconstruction-based tool used for microbial-host metabolism, and interactions' analysis [41,42]. In this manner, a genome-scale metabolic model will help us to postulate and test the underlined hypotheses that could link the burden, genotype, and phenotype of pulmonary microbial communities. Through these analyses, we also hope to infer ecological relationships, including but not limited to mutualism, commensalism, competition, antagonism, and symbiosis.

Expected Deliverables

The following will be expected deliverables to be achieved during the project:

- Total fungal burden in 406 patients and its changes over time (using quantitative PCR)
- Fungal microbiome analysis: relative abundance of sputum fungi and their identity (using ITS2 sequencing)
- Bacterial microbiome analysis: relative abundance of sputum bacteria and their identity (using 16S rRNA gene sequencing)
- Whole community metagenomics: detailed genomic identification and characterization of abundant members of the sputum microbiome, including gene-level detail
- Metabolomics profiling of sputum: analysis of host and microbial metabolites in longitudinal sputum samples
- Integration of culture-dependent and culture-independent data with clinical information to understand disease processes in the patient cohort
- A genome-scale metabolic model of the disease
- Identification of fungal and bacteria in the disease to support subsequent epidemiological, treatment, and basic research investigations
- Training and knowledge transfer in cutting-edge microbiome techniques

Study Safety

Study participants will be patients with infectious diseases and will be subjected to minimal risks during sample collection. However, the study will involve the collection, handling, and processing of contagious infectious human biological materials, such as sputum. Additionally, some of the proposed laboratory procedures will involve the use of hazardous reagents, which raise health and safety issues for both study staff and the general environment. However, to mitigate the anticipated risks, we will perform risk assessment procedures to identify the associated risks. Following risk assessment, we will develop standard operating procedures and comply with Control of Substances Hazardous to Health Regulations. These procedures will highlight health and safety measures conforming to the relevant local, national, or international guidelines. To this end, necessary precautions will be taken to ensure that these legislations are followed by both participants and staff involved in the metabolic and molecular ecological evolution of opportunistic pulmonary fungal coinfections (MeMoF) project.

Study Registration

After a careful audit of the protocol and design, the study was registered in the International Standard Randomized Controlled Trial Number registry (ISRCTN33572982).

Ethics Approval

The study has been approved by the Uganda National Council of Science and Technology (HS1233ES) and Mbarara University Research Ethics Committee (MUREC1/7-07/09/20) and will be conducted according to Uganda National and European Union legislation.

Informed Consent

Target patients will be fully informed of the purpose and procedures of this study, their obligations, potential benefits, and risks. To this effect, an informed consent form was prepared and approved by the institutional review board of Mbarara university for use; the form will be signed voluntarily by each of the study participants prior to enrolment.

Results

Study design, ethical review, approval, and research registration have all been completed. Patient enrollment commenced in March 2022. Most of the enrolled patients have completed their 2 visits. Patient enrollment was completed in June 2023, and the study results will be submitted for publication in late 2023.

We will share the study findings with the department of Microbiology, Faculty of Medicine, Mbarara University of Science and Technology; Ministry of Health Uganda; and other partner nongovernment organizations working with TB and related coinfections. We will discuss the scope, impact, and limitations of pulmonary fungal coinfections and bacterial fungal synergism based on our study findings. We hope to achieve technical and policy-level interventions, conduct capacity building, and increase public awareness of microbial ecological evolution. Finally, we will write abstracts and manuscripts for international conferences to an international audience and for peer-reviewed journals, respectively.

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Discussion

Expected Findings

We anticipate that the findings of our study will enhance understanding and awareness of invasive pulmonary fungal coinfections among patients suspected of having TB. We hope that the diagnosis of invasive pulmonary fungal infections will improve, thereby advancing patient prognosis. In this study, we highlight an important aspect of cross-kingdom synergism during infection. In particular, we will highlight that fungal-bacterial coinfection is common among the susceptible cohorts of patients, particularly patients suspected of having TB. Our study aims to establish and characterize a network of microbial communities associated with chronic pulmonary diseases, in addition to TB. In doing so, we also hope to characterize potential interaction relationships established between fungal and bacterial coinfected communities.

Previous Findings

PTB is the most common opportunistic pulmonary disease, especially among the cohort infected with HIV/AIDS [3,33]. However, the prevalence of TB has been masked by other possible and somewhat endemic infections that can be as common [43-45]. Accordingly, invasive pulmonary fungal coinfections have been highlighted. Several studies show that endemic pulmonary mycoses are not uncommon; however, clinically, many of them manifest with similar signs to TB [45]. This seems to have promoted the misdiagnosis of many pulmonary fungal infections. In other instances of fungal infections, such as aspergillosis, the treatment of PTB is further complicated with residual activation. Thus, in many parts of the world, pulmonary fungal infections continue to be missed or misdiagnosed.

The spectrum of fungal etiology has evolved over the years, expanding from the commonly isolated Candida species to encompass clinically rare but commonly environmental opportunists, such as *Cladosporium* spp, *Acremonium* spp, *Alternaria* spp, *Aspergillus* spp, and *Fusarium* spp, among others. This evolutionary event seems to be directly proportional to a recent dramatic increase in predisposing conditions, such as solid organ transplantation, prolonged chemotherapy, and hematological malignancies, which have more than doubled over the last 20 years.

Although the etiology of chronic pulmonary infections is often attributed to *Mycobacterium tuberculosis*, several data reveal that numerous unappreciated fungal opportunists and other non-TB bacterial pathogens can also coinfect or serve as the primary cause of the chronic pulmonary disease [43,45]. Our preliminary hospital data show that up to 92% of patients suspected of having PTB develop pulmonary fungal colonization. Previously, Njovu et al [35] determined a 70.7% prevalence for pulmonary fungal coexistence among patients suspected of having TB. However, the causal profile of disease by most of these cocolonizers has not been explored yet. The challenge is that current diagnostic approaches are not designed to routinely assess polymicrobial infections, and therefore, may fail to detect the presence of fungal-bacterial coinfections.

In this protocol, we hypothesized that cocolonization of a host by multiple microbial communities is influenced by the environmental frequency and antimicrobial resistance profiles of both commensal bacterial and fungal opportunists; furthermore, understanding the nature, diversity, and environmental origin of these communities will provide important insight into their pathological potential. Sadly, not much attention has been given to the possibility of cross-kingdom etiology linking TB and pulmonary mycoses. Polymicrobial infection of the pulmonary system is not uncommon. Importantly, how the different etiological entities influence each other is mostly unknown. However, stemming from the wider environment, we know that bacteria and fungi interact on several levels and can have various effects within each consortium [4,7,17-26]. Yet the impact of these effects is barely known.

Taken together, our data so far suggest that fungal-bacterial coexistence may influence their virulence attributes and antimicrobial resistance patterns, with relevance to patient outcomes. Therefore, in this project, we will investigate how these cross-kingdom synergistic interactions in the wider environment shape the evolutionary trajectories of fungi and bacteria, priming them for antimicrobial resistance and virulence in mammals. Importantly, the diversity of pulmonary infective fungi and bacteria and their complex population structures pose challenges to the analysis and interpretation of conventional data.

Strengths and Limitations

The main strength of our study is that it is the first research project to integrate fungal-bacterial interactions at the interface of metabolic and molecular ecological evolution of fungal-bacterial etiology that is conducted using direct patient samples. Thus, the methodological setup has been designed to enhance awareness of fungal etiology and fungal-bacterial interactions among patients suspected of having TB. Through this study, we hope to improve the diagnosis and management of pulmonary coinfections. The downside of the study is purely technical; we anticipate a limitation in our methodological approach to study key co-interaction effects of the etiological agents at the metabolic level. This limitation might be associated with our lack of capacity to perform metabolomics experiments.

Conclusions

We present the protocol of a laboratory-based cross-sectional study involving patients with TB-like symptoms. Through this study, we will explore the metabolic and molecular ecological evolution of invasive opportunistic pulmonary fungal coinfections. This will be achieved by determining the fungal burden, characterizing the associated microbial communities and exploring the potential interaction relationships established between fungal and bacterial etiologies. Through this study, we aim to create diagnostic profile schemes that can be used to infer patient prognostic outcomes in at-risk individuals. Establishing key fungal-bacterial cross-kingdom synergistic relationships is crucial for instituting fungal-bacterial coinfecting etiology.

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Data Availability

All the data sets generated during this study will be available from the corresponding author as governed by the data-sharing act of Mbarara University of Science and Technology. All generated data sets will be deposited in publically available repositories or published as study manuscripts.

Authors' Contributions

HI, ERB, MJC, RM, and JKM developed the study concept. HI, ERB, EN, MJC, and LA developed the study design. HI, ERB, IKN, BM, KK, JKM, JSI, PPN, JSK, FB, RK, AB, and BM provided input into the biological sample collection. HI drafted the paper, and all authors read and commented on the paper and agreed on the final version.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review reports from the European & Developing Countries Clinical Trials Partnership (Netherlands).
[PDF File (Adobe PDF File), 99 KB - resprot_v12i1e48014_app1.pdf]

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Abbreviations

ITS2: intergenic transcribed spacer 2
MeMoF: metabolic and molecular ecological evolution of opportunistic pulmonary fungal coinfections
MRRH: Mbarara Regional Referral and Teaching Hospital
PCR: polymerase chain reaction
PTB: pulmonary tuberculosis
rRNA: ribosomal RNA
TB: tuberculosis

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Protocol

Improving Children's Mental Health Literacy Through the Cocreation of an Intervention and Scale Validation: Protocol for the CHILD-Mental Health Literacy Research Study

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Abstract

Background: Children's mental health is a public health priority, with 1 in 5 European children younger than 12 years having a behavioral, developmental, or psychological disorder. Mental health literacy (MHL) is a modifiable determinant of mental health, promoting psychological well-being and reducing mental health problems. Despite its significance, no interventions or scales currently exist for increasing and measuring MHL in this population.

Objective: This study has dual objectives: (1) cocreating and evaluating an intervention on children's MHL, and (2) developing and validating a scale that measures children's MHL.

Methods: Our study focuses on children aged 9-11 years attending primary school classes in various settings, including urban and rural areas, and priority education zones within a French department. Using a participatory research approach, we will conduct workshops involving children, parents, teachers, and 1 artist to cocreate an intervention comprising multiple tools (eg, a pedagogical kit and videos). This intervention will undergo initial evaluation in 4 classes through observations, interviews, and satisfaction

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questionnaires to assess its viability. Concurrently, the artist will collaborate with children to create the initial version of the CHILD-MHL scale, which will then be administered to 300 children. Psychometric analyses will validate the scale. Subsequently, we will conduct a cluster randomized controlled trial involving a minimum of 20 classes, using the CHILD-MHL scale scores as the primary end point to evaluate the intervention's efficacy. Additional interviews will complement this mixed methods evaluation. Both the intervention and the scale are grounded in the Child-Focused MHL model.

Results: The first tool of the intervention is the pedagogical kit Le Jardin du Dedans, supported by the public organization Psycom Santé Mentale Info and endorsed by UNICEF (United Nations Children's Fund) France. The second tool is a handbook by the Pan American Health Organization and the World Health Organization, which is addressed to teachers to sensitize them to children's mental health problems. The third is a 5-page supplementary leaflet produced by the nongovernmental organization The Ink Link, which teaches children the notion of MHL. Finally, we produced 56 items of the MHL Scale and listed existing education policies for children's mental health.

Conclusions: After its robust evaluation, the intervention could be extended to several schools in France. The scale will be the first in the world to measure children's MHL. It will be used not only to evaluate interventions but also to provide data for decision makers to include MHL in all educational policies. Both the intervention and the scale could be translated into other languages.

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KEYWORDS

child; mental health; literacy; intervention; scale

Introduction

Children's Mental Health

Children's mental health is a public health priority [1]. Promoting their mental health means strengthening their capacity to learn and build meaningful relationships. Good mental health during childhood strongly contributes to positive outcomes in adulthood [2]. It is during this period of life that we learn to reinforce protective factors, as well as internal and external resources. A good home environment, convenient conditions at school, a healthy lifestyle, child protection policies, and adequate mental health services promote children's mental health [3]. Without mental health, there can be no physical health [4]. Nevertheless, children's mental health has been largely ignored, including by public policies [5].

Only recently, in the aftermath of the COVID-19 pandemic, children's mental health has been put under the spotlight. Repeated lockdowns, movement restrictions, and school closures have had an undeniable negative impact on children's mental health status. Statistics report that levels of anxiety and depression in preadolescents increased by 57.4% and 39.3%, respectively [6]. However, the pandemic has been the tip of the iceberg when it comes to poor mental health outcomes in children who represent an undoubtedly vulnerable population.

Previous studies report alarming statistics: in Europe, 1 child out of 5 is affected by a mental health problem before the age of 12 years [7]. While the prevalence of mental disorders is unstable across national and international studies, all statistics confirm that children are especially suffering from, in order of frequency, anxiety, attention-deficit/hyperactivity disorder, depression, learning disability, and autism [8]. Their onset can be detected between ages 3 and 11 years [9]. These problems have irreversible consequences on adulthood if they are not treated early, even leading to premature death [10]. In fact, 50% of adult mental illnesses have their origins in childhood [11].

Paradoxically, previous studies report that mental health problems in children are often underdiagnosed and untreated. Their signs and symptoms can be difficult to detect, thus delaying appropriate access to care.

When talking about children's mental health, it is important not to reduce it to problems or illness, but to help children adopt and maintain healthy lifestyles and provide supportive living conditions and environments. Accordingly, to increase children's psychological well-being, mental health promotion strategies have been encouraged worldwide [12,13]. The objective was to improve resilience and develop psychosocial skills so that children could learn to overcome adversity and enhance positive mental health through the encouragement and increase of protective factors and healthy behaviors.

The Population Under Study

Among different childhood stages, mid-late childhood or preadolescence (9-11 years old) deserves attention as it is a vulnerable transition period during which children have many developmental tasks to accomplish and difficulty in achieving them [14]. The age between 9 and 11 years corresponds to the last 2 years of primary school across the world according to the UNICEF (United Nations Children's Fund) definition [15]. Children at this age are cognitively, emotionally, behaviorally, and socially developing: they build their self-esteem, their mood changes, and they acquire skills in communicating personal experiences and feelings [16]. They have a level of cognitive maturity that enables mental health representations and stigma to develop [17], and they are particularly prone to receive accurate mental health information [18]. At this age, children are a perfect target population for early interventions to modify the trajectory of many mental health issues, prevent progression to more chronic conditions, and promote resilience. Learning proactive coping skills can guide them in the transition into adolescence and middle school, laying the foundation for lifelong positive mental health. Although the incidence of mental illness is high in this age span [19], only a few programs on

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mental health have been implemented in primary schools [20]. Nonetheless, on an international level, several reports from the World Health Organization (WHO), the Centers for Disease Control and Prevention, and the National Institutes of Health, among others, have advocated for the development and implementation of multisectoral, evidence-informed, and human rights–based interventions for the promotion of mental health and prevention of mental health problems worldwide [21].

Mental Health Literacy: Definition, Scales, and Interventions

Overview

In the field of mental health promotion and prevention, mental health literacy (MHL) is a growing multidisciplinary (psychology, communication sciences, education sciences) theory [22]. It was first conceptualized by Jorm [23] as "knowledge relating to the recognition of a mental health disorder, help-seeking, accessing mental health information, causes and risk factors, professional help and treatments available, self-help strategies, and general attitudes about mental illness." Kutcher et al [24] have later added to this definition the notion of promoting well-being and developing coping skills. According to MHL, knowledge, information, and understanding are the simplest, quickest, and best ways to overcome mental health problems and enhance positive mental health. Mental health literate people can detect personal and others' signs of psychological disorders, thus prompting timely help-seeking and access to care. MHL contributes to destigmatizing mental health problems and sensitizing them without any preconceived opinions. Thus, the higher the MHL level, the lower the prevalence of mental health problems [25]. In this sense, MHL is considered a modifiable determinant of mental health [23] because its improvement can contribute to the individual's empowerment and intervene in mental health behavior change [26].

MHL is defined as "multiconstruct" and "evolving," meaning that it continuously adjusts depending on the population under study and the context [22]. In this line, in 2020, an Australian team developed an MHL conceptual framework adapted to children below 12 years of age: the Child-Focused MHL model [27]. According to this model, children's MHL includes 6 dimensions: (1) understanding of mental health and recognition of its fluctuations; (2) help-seeking actions; (3) supports available; (4) influences on mental health; (5) coping and resilience; and (6) stigma.

According to this model, children with good MHL can identify early the signs of distress [28], avoiding late recognition of a mental health problem. MHL encourages help-seeking or the ability to help others promptly. Children can identify the roles of teachers, school nurses and psychologists, pediatricians, and psychiatrists in helping them in case of need. On the one hand, the child learns about risk factors such as difficulties at school, with friends, with the family, or with bullying [29]. On the other, they recognize protective factors such as individual, family, and social resources (optimism and parental support) [30]. Children learn to remain calm, to face their difficulties, and to sympathize with others. Finally, MHL also reduces stigma: mental health problems are common and a child does not have to be ashamed or shame another child.

In its report "The State of the World's Children 2021 – On My Mind" [31], UNICEF invites all of us to raise MHL to challenge stigma, break the silence about mental health, and ensure the voices of children in distress are heard. According to the Organization for Economic Co-operation and Development (OECD), "good prevention and promotion policies should ensure MHL across populations" [32]. There is thus an urgent need to promote MHL in children before the age of 12 years.

MHL Scales

Validated scales are essential for providing precise and reliable data concerning the evaluation of interventions. They have 3 objectives: (1) providing baseline information to monitor health behaviors; (2) providing information for planning and developing an intervention; and (3) raising awareness and improving the agenda for health promotion [33].

Only a few scales are measuring MHL. The very first MHL instrument comprised brief vignettes about people with depression, schizophrenia, attention-deficit/hyperactivity disorder, and anxiety disorder [34]. Individuals were asked to identify the disorder and answer questions about symptoms and treatment. Other measurement tools were quizzes with true/false answers [35]. The Mental Health Literacy Scale (MHLS) [36] is currently the most known tool to measure MHL in the general adult population and includes several close-ended questions and Likert scales.

Concerning young people, there exist only a few scales for adolescents/high school students [37], ranging from telephone interviews [38] to open-ended responses or vignettes [39]. They mostly cover only 1 of the 6 dimensions of MHL [40,41]. There is also no scale for children younger than 12 years, apart from a scale on stigmatization [42] and another scale addressed only to children having a parent with mental illness [43]. Thus, a scale covering all 6 MHL dimensions addressed to primary school children (ages 9-11 years) does not exist so far. Only an attempt has been made by Bale et al [27], but the work has not been finished.

MHL Interventions for Young People

To date, most MHL programs have targeted adolescents (12-18 years old), while little attention has been paid to improving MHL among primary school children younger than 12 years. A systematic review synthesized data from 27 articles on MHL interventions in teenagers and young adults [44]. Formats were classroom lectures or presentations, video-watching group discussions, posters, role-playing, drama, internet searching, serious games [45], educational lectures [46], art courses [47], mental health first aid training [48], etc. Concerning the evaluation of their effectiveness, the quality of the evidence was low due to the lack of validated measures and the absence of a robust study design and methodologies (eg, randomized controlled trial [RCT] or mixed methods). Furthermore, there was no collection of data on their acceptability and children's satisfaction. Identified interventions were only 1 of the dimensions of MHL among either knowledge acquisition or stigmatizing attitudes toward mental illness or help-seeking

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behaviors. Another systematic review [49] collected information on 20 middle school–based MHL interventions including storytelling and discussions/lectures in class. Once again, evidence of their effectiveness was moderate. Globally, there does not exist any school-based MHL intervention addressed to children aged 9-11 years whose effectiveness has been demonstrated under rigorous scientific conditions.

Building an Effective Intervention

Several studies [50-52] have shown that school-based interventions have positive effects on children's well-being. These interventions are inclusive because they are addressed to all pupils without distinction (socioeconomic background or presence of a mental health problem) considering that the large majority of children spend a large amount of their time at school [45,49]. Thus, interventions conducted in this setting can palliate the social gradient enabling children to appraise the concept of mental health and seek help without disparities through an educational approach [53]. In general, the whole-school approach [54] has proved to be effective, as reported by the WHO [55,56]: teachers, school psychologists and nurses, school principals, parents, and children themselves are all involved in promoting organizational MHL [57]. The role of teachers is pivotal. They are the key actors in any school-based intervention. Their implication is essential to the implementation of these interventions.

The effectiveness of interventions is enhanced also by cocreation following the principles of participatory research. The WHO states that collaboration must be initiated from the beginning of the development of interventions as this can contribute to a wider acceptability from the target population and feasibility of the intervention under real-world conditions [58]. To ensure that the intervention is appropriate for the target audience, end users are included in the intervention design and development process. Any other actor in the life of the child is also called upon: for example, teachers, parents, or school psychologists [59].

Theory-based interventions target change in modifiable mechanisms to maximize their effect [60]. Theory-driven approaches can increase our understanding of how a health-related action contributes to an outcome and provide guidelines for producing a successful intervention [61]. The Child-Focused MHL model by Bale et al [27] will be used as the theoretical construct of this project. It explains how knowledge and information build the representations and behaviors of children as far as mental health is concerned. It refers to the mechanisms of actions and beliefs of children for their well-being and those of their entourage. MHL is based on both individual and population-based determinants (eg, socioeconomic status, place of residence, history of a mental health problem) within a specific context explaining the accomplishment of an MHL intervention.

Finally, using several tools (images, videos, or audio) and teaching techniques (transmissive, interactive, experimental, or playful) helps reinforce the transmission of a message, following a communication mix approach [62].

Objectives, Hypotheses, and Scope

The principal objective of the CHILD-MHL project is 2-fold. It aims to (1) implement an intervention and evaluate its effectiveness concerning children's MHL and (2) develop and validate a scale measuring children's MHL.

The CHILD-MHL intervention and the CHILD-MHL scale are the core outputs of the project. They are built in parallel, and they are strongly associated with one another. The effectiveness of the intervention cannot be tested without a scale whose responsiveness can be proved only by an intervention.

The specific objectives are to (1) enhance the effectiveness of the CHILD-MHL intervention using different features—cocreation and design thinking, whole-school approach, theory-based approach, and multitools; (2) outline the CHILD-MHL scale—defining and testing items, administering the scales to a large sample of children, and conducting psychometric analyses for the final validation; and (3) evaluate the effectiveness of the CHILD-MHL intervention using different techniques and methods—performing a viability evaluation, performing a cluster RCT (cRCT), and using mixed methods.

The first hypothesis is that a cocreated, whole-school, theory-based, and multitool intervention makes the intervention itself effective. The second hypothesis is that, to be robust, a scale should be developed through different steps, from an inventory of items (the largest number as possible), their test among the target audience, and the administration in a large sample. The third hypothesis is that strong evidence of the effectiveness of an intervention is provided by the combination of several types of study and the collection of as much data as possible (quantitative and qualitative).

Methods

Setting and Participants

This study will be conducted in the department of 1 of the French academies. These are state services that relay, at the local level, the decisions taken by the central administration, the Ministry of National Education and Youth. Each academy is placed under the authority of a rector, appointed by the President of the Republic. For this study, the academy will be selected voluntarily. Each department includes public and private primary schools, in urban, peri-urban, and rural areas. Within each area exist priority education zones (REP) and high-priority education zones (REP+). These schools are considered in need of reinforced pedagogical policies and activities as they face more socioeconomic challenges.

Academies will give access to schools voluntarily (approval by school principals), but we will monitor the inclusion of schools from different geographical and socioeconomic areas and private versus public. We also aim to include localized units for inclusive education. The quota sampling method will be used to ensure the representability of all aforementioned types of schools. All children from recruited classes will participate in the study without any exclusion criteria. Only children whose legal guardians have not given their consent will be excluded. We are targeting children aged 9-11 years.

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Creation: Developing the Intervention and Setting Up the Scale

Cocreation of the Intervention

The intervention will be cocreated by different stakeholders: (1) the consortium of the project covering different disciplines (developmental psychology, clinical psychology, educational sciences, child psychiatry, health communication, statistics, public health, and human and social sciences); children; parents; teachers; and 1 designer/artist. Previous reviews on the mechanisms facilitating the effectiveness of school-based interventions will be considered for the development of the intervention [63].

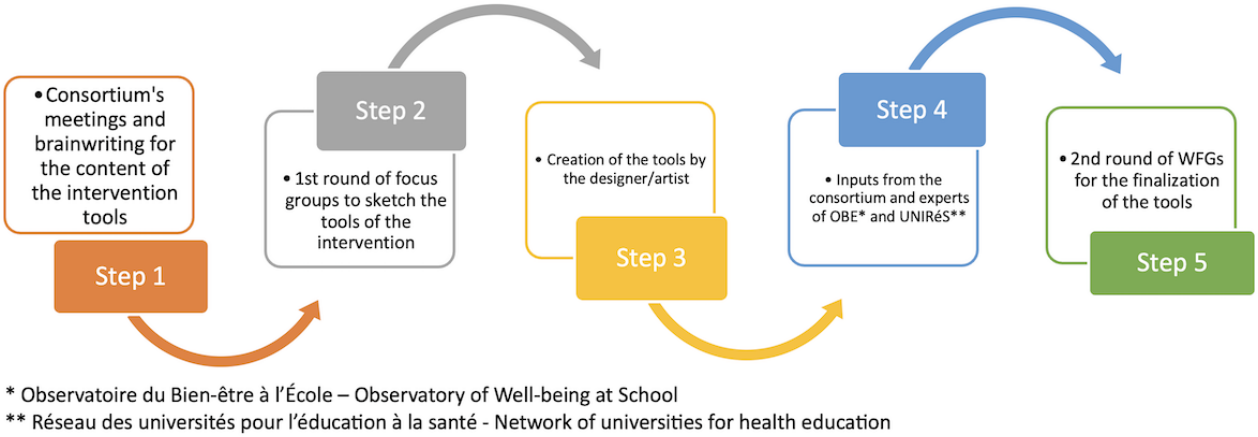
Ahead of the cocreation phase, a survey will be conducted to assess the relevance of an MHL intervention for teachers. An online form will be sent out to teachers from the selected academy. Teachers will then be asked to state whether this intervention is a priority for them and if they can include it in their work plan, among other questions. Some questions will also explore the characteristics that an MHL intervention should have to be easily implemented with positive outcomes.

The cocreation process will be developed in 5 steps as shown in Figure 1 and Textbox 1.

All working focus groups will last no more than 2 hours to help children focus and pay attention to the tasks.

The entire cocreation process uses the design thinking methodology, involving multiple iterations with all stakeholders until the final production of the tools.

Figure 1. The 5 steps of the co-creation of the CHILD-MHL intervention. MHL: mental health literacy; WFG: working focus group.



Textbox 1. Steps involved in the cocreation process.

Step 1

The consortium will define the contents of the intervention following the Child-Focused Mental Health Literacy model and covering its 6 dimensions. The consortium will meet online every 2 weeks for 2 months. Using the brainwriting technique (brainstorming through writing and commenting on a shared document), the consortium will produce a report with the key concepts to be transmitted to the target audience.

Step 2

During the initial 3 months, a first round of working focus groups (WFGs) will be conducted in 4 classes (priority education zones [REP] or high-priority education zones [REP+], NO-REP, urban, and rural) with a purposive sample of 2 children, 2 parents, 2 teachers, the principal investigator, and 1 designer/artist for each WFG. We plan to have a first round of 4 WFGs, with each corresponding to an end user of the intervention: children, teachers, parents, and school environment (represented by teachers or a school principal). The objective of this step is to transform the contents produced by the consortium into tools adapted to the target audiences. Participants for the WFGs will be recruited voluntarily, and they will draft the first version of the tools, sketching prototypes.

Step 3

The designer/artist that participated in the WFGs will collaborate with a colleague to produce mock-ups of the intervention tools based on fieldwork.

Step 4

The mock-ups of the tools will be shared with the consortium and other health promotion/education experts and researchers for their feedback.

Step 5

After integrating the inputs from the consortium, the tools will be finalized in the second round of the WFGs (3 months), which will take place over 3 months as outlined in step 2.

Preparation of the CHILD-MHL Scale

A total of 95 items have already been identified by the founders of the Child-Focused MHL model [27] through a rigorous Delphi study with more than 30 experts. The principal investigator and the research assistant will add items from other MHL scales for adolescents and adults [37,42,64] (inventory

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of MHL scales) to have a comprehensive list of items necessary to use a reflective model in the definition of the MHL construct. All items will be translated into French and categorized according to the 6 dimensions of the Child-Focused MHL model. We expect a maximum of 150 items.

The consortium will convene online, exchange emails, and use shared documents to streamline the number of items to 60 (ie, 10 per dimension), which corresponds to the first draft of the scale. This number is planned with the objective of limiting the final scale to a maximum of 24-30 items for ease of administration, especially for children who may encounter difficulties due to factors such as limited attention span or the complexity of the tasks. Literature suggests that a preliminary scale must contain 2-3 times the number of items of the final scale and that there must be at least three or four items per dimension [65].

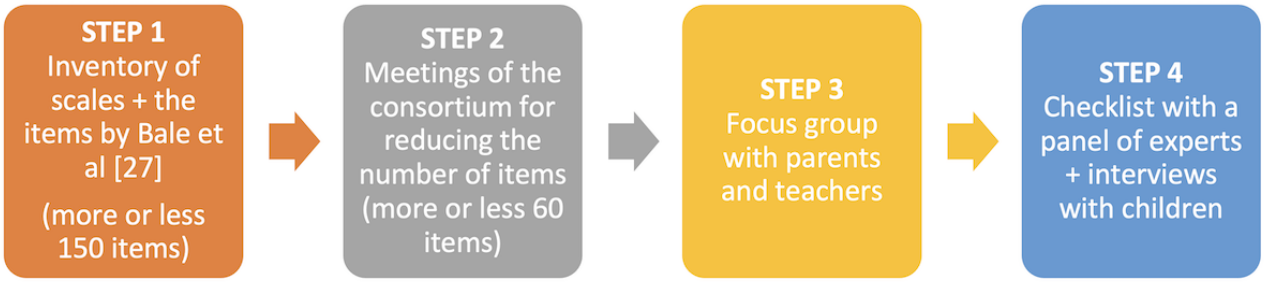
The items will be discussed with a group of 5 parents and 5 teachers to adapt them to children (language and contents). A group of 5 children, who will be recruited from a recreation center (*centre de loisirs*) in a randomly selected area, will then codraw with 1 designer/artist, as a craft activity, the items to obtain a more understandable digital visual scale during a 2-hour workshop. Finally, this scale will be administered to 25 or 30 children from a class randomly selected by a French academy. Each child will be interviewed to assess whether the items are understandable and clear.

In parallel, the same scale will be sent to around 30 experts (eg, psychologists, teachers, health promotion professionals, researchers, and statisticians) who will have to rate each item and complete a checklist measuring the practicality, acceptability, clarity, and appropriateness of the scale.

Qualitative data from children and quantitative data from the checklist will be discussed by the consortium to adapt the items and finalize the scale items. This phase corresponds to the content validity of a scale. This refers to "the degree to which the content of a measurement instrument is an adequate reflection of the construct to be measured" [66], which, in this case, refers to the Child-Focused MHL model.

Figure 2 illustrates the 4 steps for defining the items of the scale.

Figure 2. The steps of the content validity of the CHILD-MHL scale. MHL: mental health literacy.



Refinement: Viability Evaluation of the Intervention and Scale Validation

The Viability Evaluation of the Intervention

Conducting a viability evaluation refers to collecting stakeholders' views and experiences regarding whether the intervention is acceptable, practical, affordable, suitable, integrable, helpful, and sustainable in real-life conditions. For this purpose, a pilot test will be conducted in 4 randomly selected classes, representing various settings (1 REP, 1 rural, 1 urban, and 1 private), within the participating department, involving about 130 children. This number is defined by convenience in an attempt to consider social and territorial disparities.

The principal investigator and the research assistant will monitor how the intervention is carried out and identify the barriers and levers for its implementation. About 15 people among teachers, school psychologists, nurses, school directors, parents, and pupils (purposive sample) will be interviewed for feedback. In particular, the directors of the school will be interviewed to comment on the intervention, its advantages and disadvantages, and whether they think that it can be routinely conducted in their schools. Satisfaction questionnaires will be administered to all participants in the viability study. Data from observations, semistructured interviews, and questionnaires will be analyzed through the mixed methods design.

The intervention (contents, form, and language elements) will also be adapted considering the socioeconomic inequalities. For instance, some tools could be canceled or repeated. Teachers from REP areas will receive extra incentives (salary or learning credits) subject to authorization by the academy.

The viability evaluation conditions will mirror the real implementation of the intervention in the cRCT, with the objective of identifying and addressing potential difficulties and inaccuracies on a tool-by-tool basis.

At this stage, we will define and test the process of recruitment: how to inform schools and teachers (eg, through the academy with flyers, mailing, and videos) and how to obtain the consent of parents (eg, an explanation of the intervention through a detailed booklet, access to all tools for checking their contents). Parents will be informed through school mobile apps, contact book (carnet de liaison), and school meetings. All information will help assess the intervention's replicability. The viability evaluation will study whether and how teachers can conduct the program autonomously.

This pilot phase is also useful for the implementation of the cRCT because we will record all difficulties encountered while

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conducting the intervention (eg, access to schools and teachers' availability).

Analysis of Current Policies for Promoting Mental Health in Schools

To verify whether the effectiveness of the intervention is driven by a favorable political environment, we will identify and analyze policies and road maps promoting school-based mental health programs at the micro (department) and macro (France) levels. This mapping will involve approximately 5 semistructured interviews with rectors from various regions and departments, and ideally, some members of the Ministry of National Education and Youth's cabinet. All collected materials will be synthesized in a narrative review and used to write a policy brief aimed at explaining the need for including MHL interventions in schools in addition to existing mental health–related programs. If the CHILD-MHL intervention effectively increases children's MHL, we will investigate if this success is emphasized by the local political environment. This might reinforce the need for decision makers to include MHL in all educational policies.

Validation of the CHILD-MHL Scale

We will use a specific procedure called COSMIN (Consensus-Based Standards for the Selection of Health Measurement Instruments) [67] for scale validation. The questionnaire including the scale and other variables of interest will be initially administered to children from 10 classes from different schools (ie, around 250 children). Half of these classes are those of the viability evaluation. The sample size of 250 respondents is acceptable, considering feasibility and following the rule of thumb of 10 respondents per item [68]. Besides, feasibility must be considered for data collection. Data will be recorded on a tablet for each child consecutively, with supervision provided by the principal investigator and the research assistant. The research assistant will be the only person in possession of a document containing the child's name and the corresponding code, allowing for matching the questionnaire administrations. The data from the initial administration will be analyzed to assess the scale's dimensionality and whether the 60 items adequately cover the 6 dimensions of the Child-Focused MHL model. Exploratory and confirmatory factor analyses will be performed. At this stage, it will be possible for the consortium to add or remove items to cover the 6 dimensions.

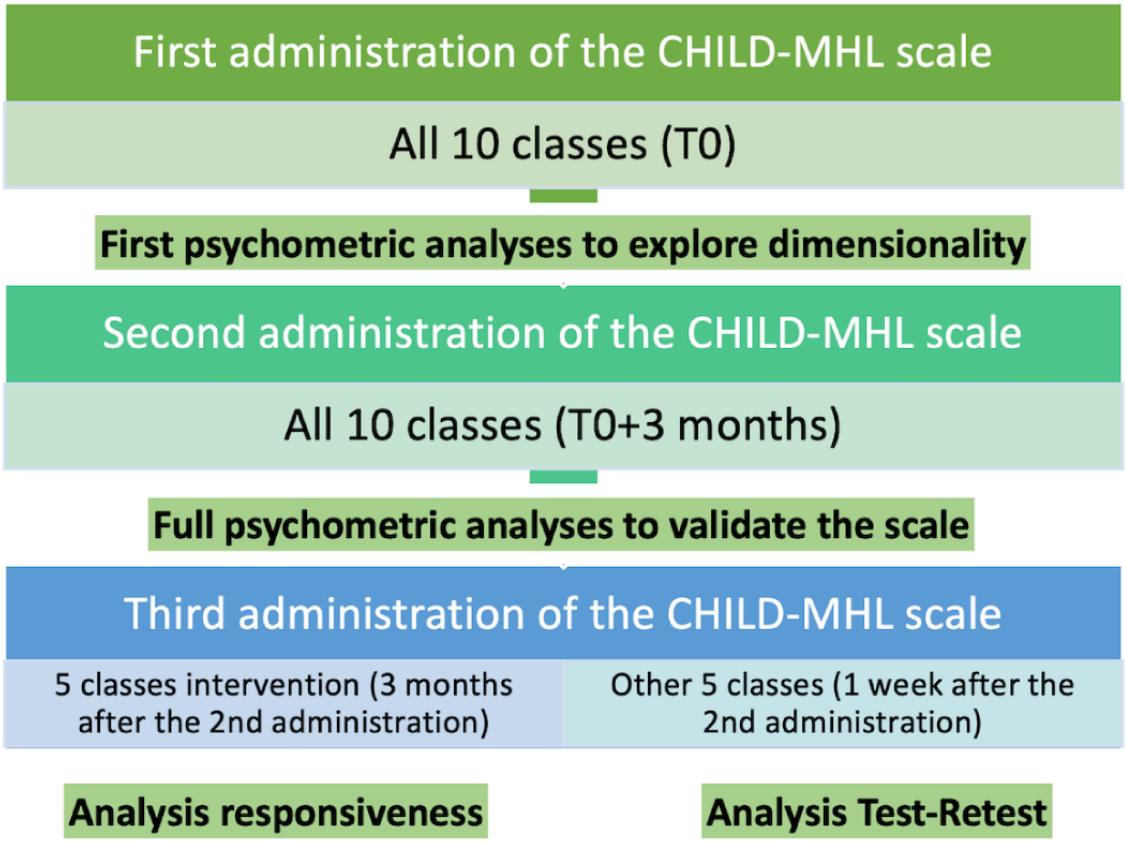
After 3 months, the questionnaire with the scale, which might have been modified, will be readministered for the second time to all 250 children from the 10 classes during the week preceding the start of the viability evaluation intervention. This second data collection is essential if the scale has been modified and is highly recommended to refine the scale dimensions. Using this large data set, analyses will be performed to reduce the number of items by employing the Classical Test Theory and the Item Response Theory [69]. Exploratory and confirmatory factor analyses will be performed again to assess the dimensionality and structural validity of the scale. For the convergent and discriminant validity of the scale, the questionnaire will include other variables, including, sex, age, or emotional status measured by the KIDSCREEN-10 [70]. We will check for variations in the scores of scale dimensions among different groups.

Children from the 5 classes of the viability evaluation intervention will complete the questionnaire for the third time after a 3-month interval (ie, the maximum time of the intervention). Data collected from these classes will be used to assess the sensitivity to change or responsiveness of the scale. If the score changes after the intervention, it indicates that the scale can measure the effect of the intervention on children's MHL. In this case, the items are expected to be "actionable," meaning that interventions can influence them and lead to changes in the results.

Finally, children not receiving the intervention will answer the questionnaire for the third time after a month. Data will be used to assess the test-retest reliability, determining whether answers remain consistent between administrations and if the items are stable over time. Figure 3 illustrates the phases of the data collection and data analyses for scale validation.

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Figure 3. The flow of data collection and analysis for the CHILD-MHL scale. MHL: mental health literacy.



Assessment: cRCT and Semistructured Interviews

Implementing the cRCT

We will conduct the cRCT in a minimum of 16 new classes, representing all typologies under the study, from different schools: 4 REP, 4 rural, 4 urban, and 4 private ones (quota sampling). Feasibility will be a major criterion for participant inclusion. Therefore, a minimum of 400 children will be involved in this small-scale cRCT, which is a substantial sample size, as the literature suggests a minimum of 300 participants is sufficient for a cRCT in children [71]. Furthermore, a limited number of participants will allow us to explore in depth the mechanisms influencing the effectiveness of the intervention by analyzing results for each class.

Classes will be randomly assigned to either the intervention group or the control group (on a waiting list without engaging in any activities). Randomization will involve creating matched pairs based on class types, such as pairing 1 urban school class with the intervention and 1 urban school class without the intervention. The CHILD-MHL scale will be administered 1 week before and 2 weeks after the intervention in all classes. We will collect covariates related to children and their environment, including sex, age, school characteristics (geographical and socioeconomic area, population density), parental background (at least one parent not being French, divorced/separated parents), family size (number of siblings), and self-perceived health and emotional status measured by the KIDSCREEN-10 [70]. If possible, with parental consent, teachers will be asked to report whether there is at least one child with a diagnosed mental health problem in the class and provide information on the parents' socioeconomic situation. Macro-level data will be also included in the analyses (eg, precariousness indexes). The data from the second administration may offer insights into the intervention's potential impact on children's well-being and help-seeking actions. Furthermore, participants who received the intervention will respond to closed-ended questions regarding their intention to help someone with a problem, seek help, and their ability to apply strategies for feeling better and recognizing signs of personal distress. The statistical analysis plan will encompass mixed linear models, multilevel models, descriptive statistics, and random effects, with an intention-to-treat primary analysis.

Conducting Semistructured Interviews and Analyzing Data Through Mixed Methods

This phase marks the conclusion of the project, during which we will gather and collate all data to demonstrate the effectiveness of the intervention in improving children's MHL. We will conduct semistructured interviews with a deliberate selection of 30 pupils and 10 parents from various schools participating in the cRCT. All teachers of involved classes will be also interviewed. These stakeholders will comment on the effects of the intervention on children's attitude toward mental health: self-perceived benefits of the intervention, what children have learned, and how they will reuse their new knowledge and competencies (from help-seeking to detection of a mental health problem). Interview texts will be coded and treated per theme.

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Quantitative and qualitative data, collected separately, will be combined and analyzed using a convergent design [72]. When combining the data, we will also consider contextual factors, location, the study population, and other relevant elements that might influence the results. The mixed methods analysis will provide a comprehensive understanding of the intervention.

Ethics and Regulatory Affairs

Given that children constitute a vulnerable population with limited autonomy, we will implement stringent measures to safeguard their well-being. The CHILD-MHL scale itself should not raise any privacy concerns as it does not collect private or sensitive information. However, variables such as emotional status or self-perceived mental health may introduce potential delays in the procedures. Their inclusion in the questionnaire will be thoroughly justified, but if collecting these data proves challenging, we will rely exclusively on macro-level data (eg, school geographical area, class size) for analysis.

Quantitative data will be collected through a secure tablet-based self-administration software, while qualitative data will be gathered via recorded interviews and subsequently transcribed. We will conduct a Privacy Impact Assessment (PIA) and risk analysis. Additionally, a data management plan will be established to outline data handling procedures throughout and after the project, covering collection, storage, analysis, preservation, and sharing. All collected data will be anonymized.

Ethics Approval

Ethical approval for the study is going to be obtained from the People Protection Committee (Comité de Protection des Personnes), which is the French Ethical Review Authority. We will strictly adhere to the requirements of the Helsinki Declaration for research involving humans. As a systematic examination of ethical considerations is also needed in the survey study, additional ethical approval will be sought from external researchers. We will make sure that project staff are trained and supervised on ethical issues, with specific attention paid to collecting data from children. In case participants (children, parents, or teachers) have questions, the contact information of the responsible researchers will be provided. In the information letter, study participants will be informed about confidentiality and their right to withdraw from the study at any time. The letter will be adapted for young people. All data will be collected and stored in compliance with the requirements of the Ethical Review Authority and the GDPR (General Regulations for the Protection of Personal Data), as well as the French National Commission on Informatics and Liberty (Commission nationale de l'informatique et des libertés).

Results

After obtaining the ethical approval, data collection and analyses will be conducted from March 2024. The first paper is expected to be submitted at the beginning of 2025. Finally, the results from all parts of the study will be synthesized in 2026.

We started working on the project in 2022 to predefine some contents and tools. The first tool of the intervention is the pedagogical kit Le Jardin du Dedans, supported by the public organization Psycom Santé Mentale Info and endorsed by UNICEF France. The kit is composed of 12 storyboards introducing MHL to children through an animated story. Each storyboard corresponds to a drawing with specific text. Two manuals are given to educators (eg, teachers, parents) to animate the story and discuss its content with children through tips and key messages. The animation includes 3 sessions conducted in 2 weeks covering the 12 storyboards. Le Jardin du Dedans is based on a metaphor stating that mental health is like an inner garden that we need to take care of across all seasons, from joyful summer to dark winter.

The second tool is a handbook that is addressed to teachers to sensitize them to children's mental health problems. In 35 pages, teachers are taught the meaning of mental health, the importance of well-being in school, child development and related influences, and main emotional and behavioral disorders (from anxiety disorder to autism spectrum disorder). After reading it, teachers are expected to feel empowered and more confident in dealing with children with mental health problems. The handbook is produced by the Pan American Health Organization and the WHO.

In a 5-page leaflet produced by the nongovernmental organization The Ink Link, children become acquainted with the notion of MHL by discovering its 6 dimensions. Each dimension is illustrated by some examples (eg, the description of mental health professionals and risk and protective factors).

We have also compiled the initial list of items (n=56) for the scale. These 56 items were listed by 2 public health researchers, and revised by 11 experts in the field of child health, including child psychiatrists and developmental psychologists. These items will then undergo further review by a panel of at least 30 experts, including psychologists, educators, and public health researchers. Following this selection process, 1 artist will collaborate with children to illustrate the items. Subsequently, the scale will be administered to several hundred children to collect data for psychometric analyses.

Finally, we compiled a report listing the existing education policies for children's mental health in France.

Discussion

Anticipated Findings

We have started cocreating the intervention to increase children's MHL. The current partial intervention is composed of 3 tools: a pedagogical kit, a handbook, and a leaflet. In the cocreation process, experts provided the contents of each tool, and artists shaped/transformed them into visually appealing illustrations. These tools were tested with small groups of children and teachers to gather feedback; particularly, the pedagogical kit was animated in several classrooms, the handbook was proofread by teachers, and the leaflet underwent refinement in a classroom setting. The involvement of renewed institutions, namely, UNICEF France, the Pan American Health Organization/WHO, and the nongovernmental organization The Ink Link, ensures a solid foundation for this global intervention [73].

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The inclusion of children, teachers, and parents from the outset of the cocreation process proved challenging due to their availability and time constraints, which often conflicted with project funders' requirements and local service expectations, such as school complexes. These challenges align with findings in the literature [74,75], with logistics and timeline management being the most commonly cited difficulties. However, our study is among the few to employ cocreation with children on a sensitive topic such as mental health, allowing them to play an active role in designing and producing a health-related intervention [76]. Moving forward, our goal is to involve all stakeholders in the cocreation process from the project's inception.

Few multitool interventions, especially those involving the target audience and the child's environment, including teachers and parents currently exist [55,77]. Accordingly, we have adhered to a whole-school approach to enhance the tool's effectiveness. Additionally, it is worth noting that the theory of MHL remains unaddressed in existing interventions.

Usually, only 1 type of support is used (eg, videos or courses). The novelty and uniqueness of our intervention lie in the integration of several tools, potentially enhancing its acceptability and effectiveness [78].

Once all the tools are produced, they will be pieced together and evaluated. Data from viability assessment, cRCT, and interviews will be combined through a mixed methods approach to produce the most accurate evidence [79]. Initial testing of the first tools has shown promising results, particularly with positive feedback from children regarding the pedagogical kit. Furthermore, we have initiated contact with schools to collect data, and the project is gaining recognition within the French academies.

Simultaneously, we have begun developing the scale. Following a rigorous approach, we plan to create an initial version of the scale that aligns with the dimensions of the Child-Focused MHL model. According to the guidelines for scale development [80], the first essential step involves defining a substantial number of items that capture the concept being measured. To ensure content validity (ie, the adequacy with which a measure assesses the domain of interest [81]), we have engaged one of the founders of the Child-Focused MHL model in the item inventory process.

In the end, conducting an inventory of policies in the French academies related to educational programs for children's mental health is crucial to gauge the acceptability of our intervention. We will assess whether the intervention is more effective in schools with existing mental health programs and a general sensitivity to this topic [82]. Thus, we have initiated a viability evaluation to provide initial evidence on the factors, such as policies, influencing the adoption of the intervention in real-life conditions.

Limitations

The project is complex, with dual objectives requiring extra effort. Significant human resources are required, particularly for the intervention, which involves recruiting a large number of children. These challenges must be carefully addressed during project planning. However, ambitious studies become feasible with the support of multiple funders (3 are involved in this project, contributing a total of over US $300) and collaboration among researchers from diverse disciplines.

Concerning the cocreation process, the number of participants is small, which might hinder generalizability. However, we hypothesize that the characteristics of the stakeholders involved in our study are representative of children, teachers, and parents in the selected department in France. Therefore, adapting the approach for use in other departments and translating it for other countries will be necessary.

In terms of evaluation, the design we will implement is arduous. While producing robust results, it will be difficult to put into practice. It will require strong logistic capacities and numerous staff members for the cRCT. The multiple semistructured interviews will be time-consuming. Similarly, the statistical analysis of both the evaluation and the scale will require the expertise of 1 or more statisticians for several months.

Conclusions

Currently, only a few interventions are designed to enhance children's MHL. Therefore, this project will offer unique insights and practical applications in the field. While the intervention has the potential to reach children in French-speaking countries, its effectiveness must first be demonstrated through rigorous experimental and real-world testing. The project's findings will inform decisions regarding the extent of implementation efforts. Additionally, this project will pioneer the creation of the world's first children's MHLS. Once validated in French, it will be translated into other languages, with English and Spanish taking priority, enabling the measurement of children's MHL at an international level.

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Data Availability

The pedagogical kit Le Jardin du Dedans by Psycom Santé Mentale Info, with the support of UNICEF France, is freely available online [83]. The handbook by the Pan American Health Organization and the World Health Organization is also freely available

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online [84]. The scale items and the list of policies are available upon request. The other tools of the intervention are under construction and will be freely available in the months to come.

Authors' Contributions

FF-O wrote the protocol and the first version of the manuscript, as well as defined the methodologies. CL, CG, AM, R Shankland, R Salamon, EP, LG, and MO wrote the protocol and edited the manuscript. CG and EG edited the manuscript. JLG-C wrote the protocol, performed the methodologies listed, and edited the manuscript. IM conceptualized the project, performed the methodologies listed, reviewed and edited the manuscript, and supervised the work.

Conflicts of Interest

None declared.

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Abbreviations

COSMIN: Consensus-Based Standards for the Selection of Health Measurement Instruments
cRCT: cluster randomized controlled trial
GDPR: General Regulations for the Protection of Personal Data

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MHL: mental health literacy
MHLS: Mental Health Literacy Scale
OECD: Organization for Economic Co-operation and Development
PIA: privacy impact assessment
RCT: randomized controlled trial
REP: priority education zones
REP+: high-priority education zones
UNICEF: United Nations Children's Fund
WFG: working focus group
WHO: World Health Organization

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Protocol

Determining the Impact of Opioid Policy on Substance Use and Mental Health–Related Harms: Protocol for a Data Linkage Study

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Abstract

Background: Increasing harms related to prescription opioids over the past decade have led to the introduction of a range of key national and state policy initiatives across Australia. These include introducing a mandatory real-time prescription drug–monitoring program in the state of Victoria from April 2020 and a series of changes to subsidies for opioids on the Pharmaceutical Benefit Scheme from June 2020. Together, these changes aim to influence opioid supply and reduce harms related to prescription opioids, yet few studies have specifically explored how these policies have influenced opioid prescribing and related harms in Australia.

Objective: The aim of this study is to examine the impact of a range of opioid-related policies on hospital admissions and emergency department (ED) presentations in Victoria, Australia. In particular, the study aims to understand the effect of various opioid policies and opioid-prescribing changes on (1) the number and rates of ED presentations and hospital admissions attributed to substance use (ie, opioid and nonopioid related) or mental ill-health (eg, suicide, self-harm, anxiety, and depression), (2) the association between differing opioid dose trajectories and the likelihood of ED presentations and hospital admissions related to substance use and mental ill-health, and (3) whether changes in an individual's opioid prescribing change the risk related to ED presentations and hospital admissions related to substance use and mental ill-health.

Methods: We will conduct a population-level linked data study. General practice health records obtained from the Population Level Analysis and Reporting platform are linked with person-level data from 3 large hospital networks in Victoria, Australia. Interrupted time series analysis will be used to examine the impact of opioid policies on a range of harms, including the rates of presentations related to substance use (opioid and nonopioid) and mental ill-health among the primary care cohort. Group-based trajectory modeling and a case-crossover design will be used to further explore the impact of changes in opioid dosage and other covariates on opioid and nonopioid poisonings and mental ill-health–related presentations at the patient level.

Results: Given that this paper serves as a protocol, there are currently no results available. The deidentified primary health data were sourced from electronic medical records of approximately 4,717,000 patients from 542 consenting general practices over a 6-year period (2017-2022). The submission of results for publication is planned for early 2024.

Conclusions: This study will add to the limited evidence base to help understand the impact of opioid policies in Australia, including whether intended or unintended outcomes are occurring as a result.

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KEYWORDS

data linkage; drug policy; general practice; opioid; primary care

Introduction

Over the past decade, Australia has witnessed an almost 2-fold increase in opioid-related deaths [1], which led to the introduction of a range of national and state policy changes [2-4]. On April 1, 2020, a mandatory real-time prescription drug–monitoring program (PDMP) was introduced in the state of Victoria [5], which was followed by other Australian jurisdictions also implementing voluntary and mandatory PDMPs [6]. In June 2020, a series of changes to subsidies for opioids on the pharmaceutical benefits scheme were also implemented, including reduced pack sizes, limits on long-term use of opioids for chronic pain, and more restricted indications for opioids [7]. Together, these changes aim to influence opioid supply and reduce harms related to prescription opioids, yet few studies have specifically explored the outcomes of these policy changes in Australia.

In the United States, supply-side policies, including the implementation of PDMPs, were identified as a key precipitating factor for the current opioid crisis, including driving harms related to illicit drug use [8]. In Australia, most opioids are prescribed in primary care settings, and most opioid mortality is still attributed to prescription opioid use [9-11]. Yet, we have little understanding of how similar supply-side interventions are influencing opioid prescribing in primary care and whether changes in prescribing lead to their intended outcome of reducing harms. This is particularly important to study among subgroups of people who are prescribed opioids, such as patients receiving high doses or high-risk medication combinations, who are often the intended target of these policy changes.

Opioid deprescribing has been identified as a key clinical strategy for reducing opioid-related adverse effects and improving quality of life [12-14]. However, policies that have aimed to reduce opioid prescribing have had mixed outcomes elsewhere, including a range of unintended adverse consequences [15,16]. For example, in the United States, hydrocodone rescheduling led to an increase in total opioid prescribing [17], while PDMP implementation led to an increase in heroin-related mortality [15]. Other adverse unintended consequences that have been reported in patients prescribed opioids following opioid restrictions include increases in withdrawal symptoms (eg, uncontrolled pain and psychological distress), uncontrolled pain, psychological distress, illicit opioid use, and suicide attempts [18-20].

Emergency department (ED) presentations and hospital admissions are considered crucial indicators when evaluating outcomes of policies targeting opioid prescribing due to their ability to capture acute incidents (eg, overdose poisonings or opioid-related injuries or accidents), assess the severity of complications, and provide valuable population-level insights [21,22]. Hospitalizations and ED presentations were common outcomes examined in US studies of PDMP implementation [23-25]. Yet, to date, few studies outside the United States have examined similar outcomes following the introduction of opioid-related policies. Given the adverse outcomes reported following the introduction of opioid-prescribing interventions elsewhere, this study seeks to examine the impact of introducing a range of opioid-related policies on hospital admissions and ED presentations in Victoria, Australia. In particular, the study aims to understand the effect of various opioid policy and opioid-prescribing changes on the following:

- The number and rates of ED presentations and hospital admissions attributed to substance use (ie, opioid and nonopioid related) or mental ill-health (eg, suicide, self-harm, anxiety, and depression).
- The association between differing opioid dose trajectories and the likelihood of ED presentations and hospital admissions related to substance use and mental ill-health.
- Whether changes in an individual's opioid prescribing change the risk related to ED presentations and hospital admissions related to substance use and mental ill-health, after considering other confounding factors, using a case-control design.

Methods

Study Design and Setting

This is a retrospective data linkage study using data from Victoria, Australia. Patient-level data from primary health networks (PHNs), extracted from the Population Level Analysis and Reporting (POLAR) platform provided by Outcome Health, and admission and ED data sets from 3 metropolitan hospital networks will be linked. These data were chosen because they provide patient-level demographic, diagnosis, medication, and hospital attendance information, and they can be accessed in a timely manner to address the research questions.

The state of Victoria is the second-most populous state in Australia, with 26% of the nation's population residing there. The current POLAR database covers approximately 30% of general practices across southeastern Victoria [26]. A total of 3 hospital networks in Victoria (Monash Health, Eastern Health, and Peninsula Health) that align with the Eastern and Southeast PHN catchments were chosen to examine opioid harms due to the high number of POLAR-participating practices in these 3 health regions. These hospital networks are located in the greater Melbourne metropolitan area and have catchments of nearly 2.6 million people, covering 40% of Victoria's population, with their EDs managing around 500,000 presentations per year. The areas represented by these data are geographically, demographically, and socioeconomically diverse [27].

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Population

The study population will include people 18 years or older who had at least 1 attendance at general practice sites participating in POLAR data provision during the study period (2017-2022).

Medications of Interest

We will include all opioids prescribed for pain (ie, codeine, dextropropoxyphene, fentanyl, hydromorphone, morphine, oxycodone, pethidine, tapentadol, tramadol, buprenorphine [transdermal products only], and methadone [tablet formulations only]). Formulations that are only used as cough suppressants (eg, dihydrocodeine) or for opioid replacement therapy (eg, high-dose sublingual buprenorphine-naloxone and methadone liquid) will be excluded (Table S1 in Multimedia Appendix 1). The use of nonopioid medicines (eg, gabapentinoids and benzodiazepines) will be considered as covariates.

Outcomes of Interest

The main outcomes of interest are ED presentations and hospital admissions attributed to substance use (both opioid and nonopioid) or mental ill-health (eg, suicide, self-harm, anxiety, and depression). We focus on these outcomes as opioid- and nonopioid-related substance use, mental health crises, and suicide have all been demonstrated to be key outcomes related to changes in opioid prescribing [18-20].

Primary and secondary diagnoses related to ED presentations and hospital attendance are coded according to the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification (ICD-10-AM). Opioid-related presentations will be identified where the primary or additional diagnoses include (1) F11.0-F11.9 (opioid-related disorders) and (2) T40.0-T40.4, T40.6 (poisoning by, adverse effects of, and underdosing of narcotics and psychodysleptics).

Non–opioid-related substance use will include substances such as alcohol, heroin, and cannabis. The ICD-10-AM codes F10, F12-F19 will be used to identify cases of unintentional poisoning. Cases of suicide attempts and self-harm that satisfy the following criteria will be included: (1) a principal diagnosis in the ICD-10-AM range S00-T75, T79 (injury, poisoning, and certain other consequences of external causes); (2) the first reported external cause code in the record in the ICD-10-AM range X60-X84, Y87.0 (external causes of morbidity); and (3) suicide-related behaviors (R45.81 [suicidal ideation]). A full list of ICD-10-AM diagnosis codes used to define mental ill-health–related hospital separations by the Australian Institute of Health and Welfare is provided in Table S2 in Multimedia Appendix 1.

Data Source, Data Variables, and Data Linkage

Population-Level Analysis and Reporting Data

Primary health data are collected from constituent general practice clinics in 3 participating Victorian PHN regions (Eastern Melbourne PHN, Gippsland PHN, and Southeastern Melbourne PHN) by the POLAR system. POLAR is a cloud-based clinical intelligence platform that extracts, processes, and organizes deidentified information from clinical information systems within participating practices. The subset of the deidentified primary health data was sourced from electronic medical records of approximately 4,717,000 patients from 542 consenting general practices over a 6-year period (2017-2022). A total of 4 sub–data sets from POLAR will be used for this study:

- Patient data set: It contains data relating to patients' demographic details such as age, gender, postcode, concession, and marital status.
- Prescription data set: It contains data on medications prescribed by the general practitioner (GP), including the date each prescription was written, generic ingredient name and brand prescribed, medication dose, strength and frequency, and Anatomical Therapeutic Chemical Classification.
- Diagnosis data set: It contains data on patients' diagnoses as extracted from the clinical information system, including diagnosis recorded dates and documented diagnoses that have been coded and validated by Outcome Health using SNOMED CT (Systematized Nomenclature of Medicine Clinical Terms).
- Activity data set: Details of patient activity at the primary care practices are coded in POLAR, including the type of consultation provided (eg, face-to-face, telehealth, and telephone) and the date the activity occurred.

Hospital Data

Monash Health, Eastern Health, and Peninsula Health will provide data on (1) hospital admissions and (2) ED presentations. Hospital admission data contain hospital admission records of admitted patients between 2017 and 2022, including dates of admission, separation date and mode (the process by which an episode of care for an admitted patient ceases), and diagnostic and procedure ICD-10-AM codes. ED data are provided separately with a single record for each presentation episode, including dates of presentation and departure, referral source, arrival mode, visit type, triage, and diagnosis.

Data Linkage

POLAR and hospital data will be linked at the patient level. A privacy-preserving method using a set of 3 statistical linkage keys (SHA-256 HASH keys) using personal identifying information contained in each of the data sets is used for data linkage. These linkage keys enable the identification of the same patients at different practices (removing patient duplication) without the need to export personal identifying data. The keys are developed through "ORCA," specialist linkage software developed and used by Outcome Health that can generate the same linkage keys in each of the hospital systems and the POLAR database.

The linkage keys are generated within the practice and hospital data environments based on available identifiable data fragments (eg, name, gender, date of birth, and Medicare number), and the ORCA tool ensures that identifiable information does not leave the clinical practice environment. Each linkage key is hashed and irreversible; that is, it cannot be used by the researcher to reidentify individuals or their data.

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This linkage process follows a method described in detail elsewhere [28]. When the linkage is complete, the linkage keys allow the matching of records across both the hospital and POLAR data. The use of multiple keys and probabilistic matching maximizes linkage accuracy.

Deidentified data with linkage keys will be released by each of the organizations into Monash University's Secure eResearch Platform, a secure environment that provides a high-powered computing environment that ensures secure storage of linked data with remote access and a clear audit trail of access.

Covariates

Analyses will adjust for key covariates associated with opioid-related outcomes such as age, sex, physical and mental health comorbidity, and substance use (including alcohol and nicotine use; Textbox 1) [29-34].

Textbox 1. Covariates from the Population Level Analysis and Reporting database.

- **Sociodemographic**

Age, sex, Socioeconomic Indexes for Areas status for residence, and concessional status

- **Prescription medicine use**

All prescription medicine use and analysis of medication classes of interest including benzodiazepines, gabapentinoids, antidepressants, and antipsychotics

- **Physical health comorbidity**

Documented diagnoses

- **Mental health**

Treatment for mental disorders with medicines, mental health care plans, and documented diagnoses

- **Pain**

Relevant documented diagnoses

Mental Health

Individuals will be classified as having a mental health condition if there is evidence of a recorded diagnosis based on the lists of SNOMED (Systematized Nomenclature of Medicine) codes (Table S3 in Multimedia Appendix 1), a prescription for medication used in the treatment of mental health issues, or enrollment in mental health care plans. This integrated approach overcomes a common limitation where some individuals may receive treatment with medication for a mental health condition or a formal diagnosis but not both [35,36]. Mental health conditions will be further categorized into major groups, including anxiety, depressive disorder, psychotic disorder, and suicidal and distressed behaviors.

Pain

We will use established lists of SNOMED codes and relevant keywords from previous research (Table S4 in Multimedia Appendix 1) to identify patients diagnosed with pain conditions that are likely to be treated with opioid analgesics [37,38]. However, conditions that are not primarily treated with opioids despite having potentially painful symptoms (eg, epilepsy and seizures) will not be included in our analysis.

Comorbidity

A modified Cambridge Multimorbidity Score (CMS) will be used to categorize comorbidities using SNOMED codes in the POLAR data [39]. There have been a number of approaches to measuring comorbidity, with the modified CMS recently validated for use in primary care, offering an advantage over the Cambridge Comorbidity Index, which, while widely used, was developed, and valued for use in secondary hospital settings.

Other Prescribed Medicine Use

Other medications of interest that may be prescribed for pain management, including nonsteroidal anti-inflammatory drugs, benzodiazepines, gabapentinoids, and tricyclic antidepressants, will also be extracted.

Data Preparation and Quality Assessment

Before the analysis, data will be prepared, and a quality assessment undertaken. Preparation involves (1) archiving a copy of primary data on the secure environment in original format and creating a copy for use in further analysis; (2) converting data from the received format (often .csv or .xls format) to formats used in statistical packages such as STATA (StataCorp), R (R Foundation for Statistical Computing), and SPSS (IBM Corp); (3) checking naming conventions for indicators and fields to ensure that these are consistent with data dictionaries; and (4) developing a study data dictionary and creating metadata.

Data validity and quality assurance will be conducted on the linked database. This will involve examining the missingness of individual data fields, inconsistency between data sets, inaccurate and unreasonable data values (eg, prescription quantity >200), identification and removal of duplicate records, and merging multiple episodes that occur within a single presentation (eg, where a patient may move between wards within a hospital).

Data Exploration and Description

Data exploration and visualization will be undertaken to enable the research team to examine the properties of the data sets, such as dispersion or distribution of values, correlation between

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variables, and time trends. Descriptive statistics (counts, means, medians, etc) will be calculated based on demographic data, diagnosed conditions, and medication use. Preliminary methods for defining key variables will be developed. Next, we will check the internal consistency of the linked data. This will help quantify the success of data linkage across POLAR, hospital, and ED data. We will define and examine the consistency of a range of indicators, such as patients' age and gender.

Analysis Plan

Aim 1

The first aim was to examine the effect of opioid policies on the number and rates of ED presentations and hospital admissions attributed to substance use (ie, opioid and nonopioid related) and mental ill-health (eg, suicide, self-harm, anxiety, and depression).

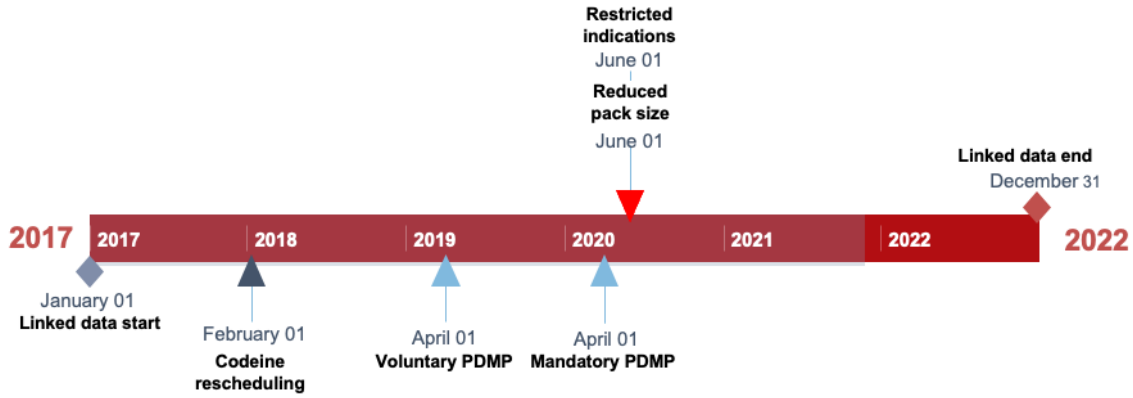
Hypotheses

The 3 hypotheses were:

- Hypothesis 1: Reduced prescription opioid harm will follow each policy change.
- Hypothesis 2: Unintended outcomes in the form of non–opioid-related presentations and mental ill-health–related presentations will occur following policy changes restricting opioid access.
- Hypothesis 3: There will be disparities in policy impacts in different populations, with greater reductions in those prescribed opioids and no impact on harm among subpopulations who are not targets of the policy changes (eg, those with cancer pain).

The key policies of interest in this study will be national and state policies that aim to restrict opioid supply (Figure 1).

Figure 1. Key exposure of interest. Australian national and state policies relating to opioids. PDMP: prescription drug–monitoring program.



State-Level Policy

Victoria's PDMP "SafeScript" was implemented in April 2019, before use became mandatory for all community prescribers and pharmacists on April 1, 2020. It indicates potential risk to prescribers and dispensers at the time of medication supply by issuing amber and red-flag alerts, for example, with higher opioid doses (above 50 mg oral morphine equivalent) and high-risk drug combinations such as fentanyl and benzodiazepines [6].

National-Level Policy

On February 1, 2018, all codeine preparations became available only on prescription after lower-dose (up to 15 mg) codeine products were removed from "pharmacist only" (Schedule 3) sale. On June 1, 2020, changes were made to the listings of many opioids and multiple formulations listed on the Pharmaceutical Benefits Scheme (PBS) General Schedule. Changes included new listings for smaller pack sizes, increased restrictions on indications, and additional requirements for a second opinion to continue long-term opioid prescribing.

We will use an interrupted time series study design to understand the effects of these policy interventions. This method is widely used in public health research studies, particularly where randomization is neither feasible nor ethical [40]. Interrupted time series goes beyond a simple prepost design by considering the comparison of slopes generated across multiple time points and taking into account the underlying secular trends and random fluctuations. It allows researchers to examine the changes in the outcome variable and determine whether they are attributed to the intervention or other factors.

The primary outcomes of interest for this analysis are changes in ED and hospital admissions related to substance use (opioid and nonopioid) and mental ill-health. A total of 2 types of denominators will be used to estimate monthly rates: total patients' exposure to opioid prescription in the POLAR primary cohort before and after the policy changes and total patients who had GP consultations in the whole POLAR primary care cohort in the same month.

To evaluate the impact of codeine rescheduling on the same outcomes, the observation period will be 12 months before and 12 months after the policy change, with data points defined by calendar month. The same observation period will be applied to evaluate the impact of the mandated implementation of PDMP, and reduced pack size policies using data from 24 months before and after the intervention change. As these 2 policies were implemented within a 2-month period, we will consider a policy intervention window between April 1, 2020, and June 1, 2020, with outcome data during the intervention implementation period excluded.

Outcomes will be measured by comparing level changes and trends over time during the study period using segmented regression modeling. This method involves partitioning outcome

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data into time intervals consistent with the times at which intervention interruptions occur and fitting a separate regression line segment to each time interval. Sensitivity analyses using different lags will be conducted to account for autocorrelation and determine the robustness of the primary results. If statistically significant, harmonic terms will be added to the models to account for seasonality. Additional segmented regression models will be used to examine the outcome among certain subpopulations such as patients with cancer diagnoses, those prescribed opioids, and those not prescribed opioids.

Aim 2

The second aim was to examine the association between differing opioid dose trajectories and the likelihood of ED presentations and hospital admissions related to substance use (opioid and nonopioid related) and mental ill-health (eg, suicide, self-harm, anxiety, and depression).

Hypothesis

Compared with patients with gradual dose discontinuation or a stable opioid dose, those with a rapid dose reduction or a gradual dose increase will have a higher risk for substance use and mental ill-health–related presentations.

This analysis will compare the trajectories of prescription opioid doses and the risk of ED presentations due to opioid-related and other adverse events. This analysis will be limited to patients receiving long-term opioid therapy, defined as those who were prescribed opioids regularly and continuously for 90 days or more [41,42]. Patients with a cancer diagnosis record in the POLAR data will be excluded from this analysis. The exposure of interest in this study is a distinct trajectory of opioid prescriptions among long-term opioid users. We will identify these trajectories by calculating the average daily oral morphine equivalent during the 6 months after the first eligible opioid prescription, when the persistence was identified (ie, 90 days of persistent opioid use and an additional 90 days). The index date is the first day following this 180-day period of long-term opioid therapy. Then, we will identify distinct opioid prescription patterns based on doses over time using group-based trajectory models. This model is a statistical method used to identify subgroups of individuals with similar patterns. The primary outcome is defined as the time to the first ED presentation, captured in the hospital data in the 6 months following the 6-month opioid prescription trajectory measurement period. The Cox proportional hazards models will be used to compare time-to-event, adjusting for covariates. These covariates included demographics (eg, age, gender, and socioeconomic status), characteristics of opioids prescribed, chronic pain diagnoses recorded (eg, musculoskeletal, neuropathic, migraine, and headache), polypharmacy (defined as having 5 or more different medications daily [43]), comorbidities (as measured by the modified CMS [39]), and ED presentations during the trajectory measurement period.

Aim 3

The third aim was to determine whether an individual's opioid-prescribing changes lead to ED presentations related to substance use (opioid and nonopioid related) and mental ill-health (eg, suicide, self-harm, anxiety, and depression), after considering other key covariates using a case-crossover design.

Hypothesis

Opioid dose tapering or abrupt discontinuation during the case period will be associated with an increased risk of opioid- and nonopioid-related harms and mental ill-health–related presentations.

This analysis will evaluate whether changes in opioid prescribing increase the risk of related outcomes through the application of a case-crossover design. The case-crossover design is an epidemiological design used for studying potential causes of sudden events and has previously been used for investigating the association between substance use and suicidal behavior [44]. It uses each case as its own control, thereby eliminating the time-invariant characteristics among individuals (eg, age, sex, and chronic substance use). In this study, adverse outcomes will be ED presentations across the 3 hospital data sets. The index date will be defined as the date of arrival. Each enrolled case for the case-crossover analysis will be restricted to patients who received opioids at least once during the hazard or control periods. The hazard period will be 60 days before the index date, and a single hazard period will be matched with 5 sets of 60-day control periods before and after without an ED attendance.

Comorbid mental health conditions will be the main confounding factors and will be assessed during the 12 months before the index date. Individuals will be identified as having a mental health condition using the aforementioned definition. It is common for individuals who die by suicide or attempt suicide to also have additional comorbidities related to mental health disorders. Therefore, referring to previous patient diagnoses, CMS will also be determined for the 12 months before the index date. Concurrent use of benzodiazepines and antidepressants, tricyclic antidepressants, and pregabalin will also be included as a confounding factor. Discordant pairs of these confounders between the hazard and control periods will be adjusted in the outcome models.

Odds ratios and 95% CIs will be determined by conditional logistic regression. We will evaluate the risk of substance use–related attendance for opioid dosage tapering and abrupt discontinuation, adjusting for confounding factors, and perform sensitivity analyses by varying the time window of the exposure period from 60 to 30 days to evaluate the robustness of the results. Additional sensitivity analyses will be performed by varying the number of controls from 5 sets of control periods (main analyses) to 2 or 3 sets of control periods to confirm whether the exposure trend affects the estimated odds ratio.

Management of Missing Data

To ensure comprehensive and accurate demographic information, a cross-check will be conducted to address missing data in both hospital records and the POLAR data set. When key demographic information is absent in hospital data, the gaps will be filled by leveraging the variable field from the POLAR data. Similarly, in instances where the POLAR data lack essential demographic details, an imputation process will be used based on the available hospital data. In cases where a

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discrepancy in demographic information is identified between the hospital data and the POLAR data set, priority is given to the values recorded in the hospital records. The demographic details present in the hospital data are considered more reliable and representative of the specific patient population being studied. In addition, where key prescription-related information in the POLAR data is missing (eg, quantity prescribed or dose), these will be imputed based on standard pack sizes and the most common formulations used. Missing data for all variables will be checked and quantified. Multiple imputation methods will be considered where there are more than 5% missing data within variables.

Ethics Approval

The process of collection, transfer, and storage of general practice data on the POLAR platform was granted ethics approval in August 2017 (NREEC RACGP Protocol ID: 17-008). Consent for the use of deidentified patient data for research extracted and processed on the POLAR platform occurs as follows: practices that contribute data to the POLAR system enter into an agreement with their local PHN. The agreement articulates the responsibility of practices to inform their patients that data are being collected and of their potential use for research. As an additional layer of assurance, practices contributing data to the POLAR platform adhere to the RACGP Accreditation Standards, which stipulate requirements for responsible management of health data. Patients are informed at the point of collection and are presented with the opportunity to opt out. POLAR data are deidentified at the point of collection, according to Outcome Health's Data Deidentification Decision-Making Guide, developed with guidance from the Office of the Australian Information Commissioner. Hospital data are proposed to be used without the consent of individuals. A multisite ethics application was approved by Monash Health as the lead Human Research Ethics Committee (ID 76744), with site-specific applications approved by Monash Health (RES-22-0000-026A), Peninsula Health (SSA/76744/PH-2022), and Eastern Health (S22-032-76744). A waiver of consent was granted by the respective Human Research Ethics Committees for linkages between the POLAR data and hospital data. Privacy-preserving encrypted linkage software was used to link the data, and deidentified content data were submitted into a secure e-research environment by each of the data custodians for analysis by the research team. Ethics approval has been obtained from the Monash University Human Research Ethics Committee (ID 76744), Monash Health (RES-22-0000-026A), Peninsula Health (SSA/76744/PH-2022), and Eastern Health (S22-032-76744).

Results

Data linkage commenced in January 2023 and was completed in August 2023. Data analysis has not yet commenced. Submission of results for publication is planned for early 2024.

Discussion

Overview

Policies restricting access to medications such as opioids are commonly implemented, with limited evidence of their effect on reducing opioid-related or other harms. This study will add to the limited evidence base to help understand the impact of these policies in Australia, including whether intended or unintended outcomes are occurring as a result. By closely monitoring and analyzing ED presentations and hospital admissions as markers, policy makers can assess the impact of interventions, identify areas for improvement, and drive evidence-based policy changes that effectively address the complex challenges associated with opioid use and promote healthier communities.

Strengths

This study will link primary care and hospital data to investigate opioid exposure and adverse outcomes. POLAR data contain rich patient-level data, including diagnoses and comorbidities, that are often missing from existing administrative data such as Medicare Benefits Schedule and PBS data in Australia. The linked data set will also capture both publicly subsidized and nonsubsidized prescriptions, making it distinct from the more commonly used PBS (government subsidy) database. Moreover, the linkage key is consistent throughout POLAR participating practices, which will allow for a more comprehensive capture of covariates, particularly coprescribing and hospital readmission.

Limitations

There are several limitations to note. First, the use of prescribing data does not enable confirmation that prescribed medicines were dispensed or taken by the patient. Second, as both primary care and hospital data are drawn from 3 specific geographical areas, there is potential for selection bias. This concern is lessened by the inclusion of 3 PHNs whose average opioid-prescribing patterns are consistent with national opioid-prescribing patterns [45]. Further, there is established geographic and sociodemographic diversity across these health areas that limits concerns about generalizability [46]. Third, patients who visited non-POLAR GP practices and were admitted to hospitals other than the selected ones are not captured in this study; however, it is noted that the 3 large hospital networks serve the majority of the population in each of the catchment areas. Fourth, a list of ICD-10 codes will be used to identify study outcomes. However, there are limits to the completeness of the coding. For instance, suicide in EDs is commonly recorded using a single diagnostic code [47], and opioid-poisoning presentations can be coded under the more generic code T50: "Poisoning by diuretics and other and unspecified drugs, medicaments and biological substances" [48]. Therefore, our opioid-related poisoning and suicide and self-harm estimates are likely to be an underestimate of the true prevalence. In addition, deaths that occur before reaching the hospital and harm that occur outside the hospital setting (eg, ambulance attendances) would not be captured unless the patient was later transferred to a hospital.

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Data Availability

Data sharing is not applicable to this protocol paper as no data sets were generated or analyzed during its writing. Those wishing to access the data should approach Outcome Health (the data custodians of Population Level Analysis and Reporting platform), Monash Health, Eastern Health, and Peninsula Health. Access fees for data and analyses may apply.

Authors' Contributions

SN conceptualized and received funding for the study with chief and associate investigators (NEA, RB, JSB, CP, and SL). TX, LP, and SN constructed the data linkage and key covariates for the study. The original draft was produced by TX, LP, and SN. All authors were involved in manuscript revision and jointly took responsibility for all aspects of the work.

Conflicts of Interest

LP, NEA, RB, CP and TX have no conflicts. JSB has received grant funding or consulting funds from the National Health and Medical Research Council, Medical Research Future Fund, Victorian Government Department of Health and Human Services, Dementia Australia Research Foundation, Yulgilbar Foundation, Aged Care Quality and Safety Commission, Dementia Centre for Research Collaboration, Pharmaceutical Society of Australia, Society of Hospital Pharmacists of Australia, GlaxoSmithKline Supported Studies Programme, Amgen, and several aged care provider organisations unrelated to this work. All funds were paid to his employing institution. SN has received untied educational grants to study pharmaceutical opioid-related harm from Seqirus and is a named investigator on an implementation trial of buprenorphine depot funded by Indivior (no funding received by SN personally or through her institution). DL is supported by a NHMRC Leadership Fellowship (1196892) and has received untied educational grants from Camurus and Seqirus Pty Ltd, unrelated to this work.

Multimedia Appendix 1
Supplemental materials.
[DOCX File , 120 KB - resprot_v12i1e51825_app1.docx]

Multimedia Appendix 2
National Health and Medical Research Council (NHMRC, Australia) application assessment summary.
[PDF File (Adobe PDF File), 134 KB - resprot_v12i1e51825_app2.pdf]

Multimedia Appendix 3
Grant outcome and scoring from the National Health and Medical Research Council (NHMRC, Australia).
[PDF File (Adobe PDF File), 159 KB - resprot_v12i1e51825_app3.pdf]

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Abbreviations

CMS: Cambridge Multimorbidity Score
ED: emergency department
GP: general practitioner
ICD-10-AM: International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification
PBS: Pharmaceutical Benefit Scheme
PDMP: prescription drug–monitoring program
PHN: primary health network
POLAR: Population Level Analysis and Reporting
SNOMED: Systematized Nomenclature of Medicine Clinical Terms
SNOMED CT: Systematized Nomenclature of Medicine Clinical Terms

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Protocol

Oral Health, Social and Emotional Well-Being, and Economic Costs: Protocol for the Second Australian National Child Oral Health Survey

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Abstract

Background: Given the significant investment of governments and families into the provision of child dental care services in Australia, continued population oral health surveillance through national oral health surveys is imperative.

Objective: The aims of this study are to conduct a second National Child Oral Health Survey (NCOHS-2) to (1) describe the prevalence, extent, and impact of oral diseases in contemporary Australian children; (2) evaluate changes in the prevalence and extent of oral diseases in the Australian child population and socioeconomic subgroups since the first National Child Oral Health Study (NCOHS-1) in 2012-2013; and (3) use economic modeling to evaluate the burden of child oral disease from the NCOHS-1 and NCOHS-2 and to estimate the cost-effectiveness of targeted programs for high-risk child groups.

Methods: The NCOHS-2 will closely mimic the NCOHS-1 in being a cross-sectional survey of a representative sample of Australian children aged 5-14 years. The survey will comprise oral epidemiological examinations and questionnaires to elucidate associations between dental disease in a range of outcomes, including social and emotional well-being. The information will be analyzed within the context of dental service organization and delivery at national and jurisdictional levels. Information from the NCOHS-1 and NCOHS-2 will be used to simulate oral disease and its economic burden using both health system and household costs of childhood oral health disease.

Results: Participant recruitment for the NCOHS-2 will commence in February 2024. The first results are expected to be submitted for publication 6 months after NCOHS-2 data collection has been completed. Thematic workshops with key partners and stakeholders will also occur at this time.

Conclusions: Regular surveillance of child oral health at an Australian level facilitates timely policy and planning of each state and territory's dental public health sector. This is imperative to enable the most equitable distribution of scarce public monies, especially for socially disadvantaged children who bear the greatest dental disease burden. The last NCOHS was conducted in 2012-2014, meaning that these data need to be updated to better inform effective dental health policy and planning. The NCOHS-2 will enable more up-to-date estimates of dental disease prevalence and severity among Australian children, with cost-effective analysis being useful to determine the economic burden of poor child dental health on social and emotional well-being and other health indicators.

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KEYWORDS

Australian children; cost-effective analysis; dental caries; social and emotional well-being

Introduction

Overview

Dental caries is the most common childhood condition in Australia, resulting in costly treatment (up to Aus $ 1 billion [US$ 651,190,049] dollars annually), poor school performance, inadequate nutrition, problems with sleeping, and adverse mental health (social and emotional well-being) [1]. In addition to treatment costs, there are productivity losses due to caregiver absenteeism from work [2]. The burden of child oral diseases is overrepresented among socially vulnerable groups. For example, in the first National Child Oral Health Study (NCOHS-1) from 2012-2014, a total of 23% of children aged 5-10 years had dental caries in the primary dentition compared to 36% of Indigenous children, and 41% of non-Indigenous children aged 6-14 years had dental caries in the permanent dentition compared to 61% of Indigenous children [3]. From 2016-2017, approximately 70,200 hospitalizations for dental conditions could have been prevented; these hospitalizations were highest among socially vulnerable children [4].

As described in Australia's National Oral Health Plan 2015-2024 [5], there is a lack of routinely collected population-based dental data in Australia. This affects the capacity to effectively evaluate the impact of local and national policies, programs, and service models, which, in turn, makes it difficult to translate research and evaluation findings into policy and improved models of care. The NCOHS-1 has been influential in the development of public policy in Australia. It has provided valuable information on the oral health outcomes of children from different socioeconomic backgrounds and identified a number of underlying causes of oral health inequities, thus providing a sound evidence base for selecting interventions to reduce these inequalities.

Impact of Child Dental Disease on Social and Emotional Well-Being and Economic Productivity

Evidence shows that chronic illness is a major contributor to school absenteeism in childhood, thus impacting child school performance and social or emotional well-being [6]. Guarnizo-Herreno and Wehby [7] assessed associations between poor dental health and school performance or psychosocial well-being in a nationally representative sample of over 40,000 children in the United States. They reported that children with dental caries were more likely to have problems at school (odds ratio [OR] 1.52, 95% CI 1.37-1.72), more likely to miss school (OR 1.42, 95% CI 1.23-1.64), and less likely to do all required homework (OR 0.76, 95% CI 0.68-0.85). Dental problems among schoolchildren were associated with shyness, unhappiness, feelings of worthlessness, and a reduced ability to make friends. This may have far-reaching consequences in adulthood, affecting both economic productivity and meaningful engagement in civic activities. To the best of our knowledge, there has been no analysis of the association between poor dental health and Australian children's social and emotional well-being; this is an important strategic priority with the Australian Government launching the world's first National Children's Mental Health and Wellbeing Strategy in October 2021 [8]. Poor oral health in childhood also has an immediate impact on caregiver workplace productivity, with some dental procedures for children requiring care under a hospital-based general anesthetic. These services are only available in major metropolitan locations and typically have long waitlists [9]. This means caregivers need to take substantial leave from employment, with out-of-pocket costs including transport, accommodation, and childcare arrangements [10].

Provision of Dental Care for Australian Children

The provision of dental services for children varies by jurisdiction in Australia, although the federally operated (through Medicare) Child Dental Benefits Schedule (CDBS) is available for families already receiving other benefits, such as the Family Tax Benefit [11]. This scheme provides each eligible child up to Aus $1052 (US $ 668.96) over 2 calendar years for covering checkups, routine cleaning, simple restorations, extractions, and root canals. It does not cover orthodontic treatment, hospital-based dental care, or cosmetic dental procedures. Children who are eligible for the CDBS can receive treatment in any public dental clinic, with the claim being bulk billed with no out-of-pocket costs. Waitlists in public dental services, up to 2 years in some jurisdictions, are common. Some, but not all, private dentists also accept CDBS payments. Children not eligible for the CDBS need to pay for dental care out-of-pocket, or through dental insurance, in the private sector. In 2019, the Australian Government paid CDBS benefits of US $324,483,573 for 5,450,996 dental services across Australia, averaging US $59.53 in benefits per service. The average benefits paid per service ranged from US $40 for a diagnostic service to US $138 for a restorative service [12]. Data from the 2014-2015 National Health Survey indicated that around 1 in 5 children aged 2-14 years had never visited a dental professional [13]. Estimates from the 2013 National Dental Telephone Interview Survey showed that around 1 in 5 children aged 5-14 years had last visited a school dental service and around 2 in 3 had last visited a private dental practice. The proportion of children aged 5-14 years who had last visited a school dental service more than halved over the 1994-2013 period, from 54% to 21% [14].

Dental-Related Child Hospitalizations

Reducing rates of hospital-based child dental service provision is a key performance indicator of the 2015-2024 National Oral Health Plan [5]. The rate of preventable hospitalizations for dental conditions is influenced by the adequacy of preventive and primary dental care services, the prevalence of severe dental disease in the community, and the availability and accessibility of appropriate community and hospital-based dental services [5]. From 2017-2018, the rate of preventable hospitalizations due to dental conditions was highest among those aged 5-9 years (9.5 per 1000 population). Some children receive dental care under general anesthesia, usually due to the severity of the disease or other medical, physical, or behavioral complications.

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Dental care under general anesthesia is resource intensive and not without risk.

Calculating the Economic Impact of Child Dental Disease

In Australia, it has been estimated that over 10,000 days of work and 2.5 million school hours are lost each year because of dental-related illnesses [15]. Identifying the economic burden of child dental disease is useful to understand the maximum number of resources that could be saved or gained if that disease were partially or fully eradicated. While there has been some attempt to quantify the indirect costs to government and society of child dental disease on the health system, there is a lack of consistent quantitative analysis and information. Robust data and economic analysis are urgently required to quantify these costs and the indirect financial pressures that child dental disease places on government and society. While treatment is a direct and costly consequence of child oral disease, reductions in morbidity may also imply other economic benefits. For example, indirect costs include productivity losses due to absenteeism from school and work, yet relatively little evidence exists in this regard.

Child Oral Health Surveys in Australia

The 2012-2014 NCOHS-1 was a cross-sectional study of the child population aged 5-14 years in Australia [3]. A total of 24,664 children from 841 participating schools were involved. Children were selected using a complex, multistage, and stratified sampling design, with a sophisticated weighting procedure implemented to adjust for variations in probabilities of selection and response rates. Information was collected through a parental questionnaire and a detailed dental examination by trained dental professionals. The findings suggested substantial social patterning of oral health status, dental service use, and dental and general health behaviors among Australian children. It was clear that addressing factors at the child, family, school, and community levels was necessary for reducing social inequalities in child oral health.

The proposed research will build upon the already established population-based epidemiological platform of the NCOHS-1, with the conduct of a second National Child Oral Health Survey (NCOHS-2), enabling a follow-up snapshot of a large and representative national child cohort. The specific study aims to (1) describe the prevalence and extent of oral diseases and their associations with social and emotional well-being and other outcomes in contemporary Australian children, (2) evaluate changes in the prevalence and extent of oral diseases in the Australian child population and socioeconomic subgroups since the NCOHS-1, and (3) use economic modeling to evaluate the burden of child oral disease from the NCOHS-1 and NCOHS-2 and to estimate the efficacy and cost-effectiveness of targeted programs for high-risk child groups.

Methods

The NCOHS-2 will be the second representative child oral health survey conducted in Australia in partnership with the dental public health sector of each of Australia's states and territories and the Federal Department of Health.

Study Design

The study design will closely mimic the NCOHS-1 in being a cross-sectional survey of a representative sample of Australian children aged 5-14 years. The survey will comprise oral epidemiological examinations and questionnaires to elucidate the impacts of dental disease on social and emotional well-being and other outcomes. The information will be analyzed within the context of dental service organization and delivery at national and jurisdictional levels. A key goal is to evaluate changes in the prevalence and extent of oral diseases in the Australian child population and socioeconomic subgroups since the NCOHS-1, using age-period-cohort analysis (NCOHS-1 and NCOHS-2, with both cohorts aged 5-14 years).

Sampling and Recruitment

As with the NCOHS-1, in the NCOHS-2, a multistage, stratified, and clustered random sampling design will be implemented to ensure sufficient geographic representation from both urban and rural settings in all states and territories while optimizing the efficiency of fieldwork for dental examiners. The sampling frame will include public and private schools in all states and territories. As with the NCOHS-1, NCOHS-2 participants will be selected in each state or territory using a 2-stage stratified clustered sampling design with a combined allocation of children per state proportional to population size.

Data Collection

Oral Epidemiological Examination

All selected children will be invited to undergo a standardized oral epidemiological examination at school-based units organized by state- or territory-appointed dental professionals. Small teams of examiners and data recorders (3-10 examining teams per state or territory) will be trained in the clinical assessment of key oral epidemiological outcomes. All NCOHS-2 examiners will be calibrated and tested in the field against a gold standard examiner to estimate interexaminer reliability and to ensure rigor and consistency of measurement. To facilitate comparisons across time, the oral outcome measures in the NCOHS-2 will be the same as those assessed in the NCOHS-1 using accepted indices and benchmark measures for large oral epidemiological surveys. The outcomes will include the number of teeth, experience of dental caries, dental fluorosis, molar incisor hypomineralization, dental plaque, and dental trauma.

Self-Report Questionnaire

The caregiver-reported questionnaire in the NCOHS-2 will comprise items on sociodemographics, self-rated oral health, self-rated general health, items used for cost-effective analysis (Dental Caries Utility Index) [16], oral health-related quality of life (Child Perceptions Questionnaire 11-14) [17] and Caries Impacts and Experiences Questionnaire for Children quality of life [18]), dental service use, dental behaviors, psychosocial factors, and social and emotional well-being. Social and emotional well-being will be assessed using the Stirling Children's Wellbeing Scale, a 15-item instrument developed by the Stirling Educational Psychology Service to measure emotional and psychological well-being among children aged 8-15 years [19]. The Stirling Children's Wellbeing Scale has

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been validated and displayed good psychometric properties across multiple countries, including Scotland [19], Japan [20], and Bangladesh [21], among others [22].

Sample Size

The minimum required sample size was determined using standard methods to address the specific aims of the NCOHS-2 [23]. The main outcomes evaluated were the "decayed, missing, and filled teeth" (DMFT) index, the "decayed, missing, and filled surfaces" index, the percentage of children with untreated decay, and the percentage of children with overall caries experience. These outcomes were evaluated for primary dentition, among the age groups of 5-6, 7-8, and 9-10 years, and permanent dentition, among the age groups of 6-8, 9-11, and 12-14 years. The sample size was calculated to detect a 40% difference in the mean of the outcome or a 40% difference in the prevalence of the outcome with a power of 80% and a significance level of 5%. Sample size requirements were calculated for a simple random sample and then adjusted by the design effect to account for the NCOHS-2–stratified, 2-stage sampling design [24]. The design effect values were estimated based on existing NCOHS 2012-2014 data, which included information on children's oral health status (for all abovementioned outcomes) [3] and were used as a proxy in the calculation formula to estimate sample sizes for the NCOHS-2 [25]. The estimated sample size analysis was conducted with R software [26] and the R packages *survey* [27] and *pwr* [28]. The minimally required overall sample size of the NCOHS-2 was based on the outcome that required the largest sample—the percentage of children with untreated decay in the permanent dentition (n=16,678)—meaning that the NCOHS-2 would be adequately powered to detect all other outcomes. Because the percentage of children with untreated decay in the permanent dentition was not evaluated for children aged 5 years, an additional sample size (n=885)—estimated based on the sample required to evaluate the percentage of children with untreated decay in the primary dentition at age 5 years—was added to constitute the NCOHS-2 minimally required overall sample size (n=17,563). The sample allocation per state was conducted using combined allocation, consisting of an unweighted sum of equal allocation and proportional allocation [29]. The state and territory sample sizes were then further upwardly increased to meet jurisdiction objectives (N=18,700; Northern Territory, n=1400; Australian Capital Territory, n=1400; Tasmania, n=1400; South Australia, n=1850; Western Australia, n=2150; Queensland, n=3000; Victoria, n=3500; Norfolk Island, n=4000).

Economic Modeling

Information from the NCOHS-1 and NCOHS-2 will be used to simulate oral disease and its economic burden using both health system and household costs of childhood oral health disease. The cost of illness approach will be used to estimate the economic burden of dental disease. Direct and indirect costs will be estimated using available and collected information. Direct health system costs will include dental, pharmaceutical, emergency department, hospitalization, specialist appointments, diagnostic testing or pathology, and other health care services related to the provision of dental treatment. Indirect patient costs (out-of-pocket) will include Medicare Benefits Schedule and Pharmaceutical Benefits Scheme item copayments and other out-of-pocket costs, income loss for parents and children after attaining adulthood, and travel costs. Indirect societal financial costs will include other direct health system costs, patient financial costs, business financial costs, and government costs.

Statistical Analysis

We will specifically test for each aim.

- Aim 1: to evaluate the prevalence and extent of oral diseases and their association with social and emotional well-being and other outcomes in contemporary Australian children
- Aim 2: to evaluate changes in Australian child dental disease

The design of 2 cross-sectional, nationally representative surveys will enable comparisons between 2 time points from the NCOHS-1 and NCOHS-2 to be conducted. The main outcomes will be the prevalence and extent of decayed, missing, and filled teeth in the primary and permanent dentition (percentage of DMFT>0 and mean DMFT). Analysis will be performed progressively from descriptive to explanatory multivariable analysis, multilevel regression models, and causal inference models, accounting for systematic differences between the 2 periods, including family and area socioeconomic status, model of dental service provision, exposure to fluoride, dental behaviors, and diet. SAS (SAS Institute) or SUDAAN (RTI International), STATA (StataCorp), and R software will be used to generate sample estimates and standard errors and adjust for the complex sampling design of each survey.

- Aim 3: to evaluate the child oral disease burden from the NCOHS-1 and NCOHS-2 and estimate the efficacy and cost-effectiveness of targeted programs for high-risk child groups

Economic modeling using the R and TreeAge software (TreeAge Software, LLC) will be used to assess variations in cost-effectiveness according to accessibility and cost of child dental care. Different cutoffs and thresholds will be used to determine the most cost-effective models for targeted child oral health programs, preventive dental services, and insurance plans for optimal economic productivity. The analysis will involve the estimating costs incurred by the child population and population subgroups. Other costs will be estimated from a societal perspective, including productivity effects (based on expected time off work associated with child dental conditions and treatment) and dental service costs incurred by insurance companies and taxpayers. In collaboration with the Australian Institute of Health and Welfare's Australian Burden of Disease Unit, NCOHS-1 and NCOHS-2 estimates will be used to project the burden of child oral diseases in the 2020 decade and beyond. Markov models will use both health system and societal perspectives according to the cost being considered. The economic analysis will use cost-effectiveness (natural units as outcome measures) and cost utility analysis (quality-adjusted life years as outcome measures) depending on the outcome measure. Deterministic and probabilistic sensitivity analyses will be performed for all model base-case analyses.

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Ethical Considerations

Ethics approval has been obtained from the University of Adelaide Human Research Ethics Committee (37659 H-2023). Before being recruited, all participants will be required to sign an informed consent form, which includes consent for the authors to publish the findings in peer-reviewed scientific literature. Data will be de-identified and there will be no compensation provided. All authors are named investigators on the project; they all contributed to the intellectual input of the study design and in writing this protocol.

Results

Participant recruitment for the NCOHS-2 will commence in February 2024. The first results are expected to be submitted for publication 6 months after NCOHS-2 data collection has been completed. Thematic workshops with key partners and stakeholders will also occur at this time.

Discussion

Overview

Regular surveillance of child oral health at an Australian level facilitates timely policy and planning in each state's and territory's dental public health sector. This is imperative to enable the most equitable distribution of scarce public monies, especially for socially disadvantaged children who bear the greatest dental disease burden. The last NCOHS was conducted in 2012-2014, with these data being effectively outdated in terms of contemporary and effective dental health policy and planning [30]. The NCOHS-2 will enable more up-to-date estimates of dental disease prevalence and severity among Australian children, with cost-effective analysis being useful to determine the economic burden over a lifetime of poor child dental health on social and emotional well-being and other health indicators.

As described in the National Oral Health Plan 2015-2024, there is a lack of comprehensive, routinely collected population-based dental data in Australia. This affects the capacity to effectively evaluate the impact of local and national policies, programs, and service models, which, in turn, makes it difficult to translate research and evaluation findings into policy and improved models of care. Both the National Oral Health Plan 2015-2024 and the previous National Oral Health Plan 2004-2013 call for regular national data collections of oral health to ensure quality planning, monitoring, and evaluation at both population and service levels. The previous NCOHS has been influential in the development of public policy in Australia. It has provided valuable information on the oral health outcomes of children from different socioeconomic backgrounds and allowed the diagnosis of a number of underlying causes of inequalities in oral health, thus providing a sound evidence base for selecting interventions to reduce these inequalities. It is expected that the results derived from this project will be important in informing public policy at both the state and national level over the next decade.

Optimal prevention and treatment of child dental disease, which in turn will improve child social and emotional well-being and economic productivity in the long term, requires appropriate health care systems, organizational governance, infrastructure, and resources that are evidence-based.

Outcomes and Significance

The National Children's Mental Health and Wellbeing Strategy, launched by the Australian Government in 2021, identifies the importance of improving Australian child health and well-being [8]. Evidence shows that dental problems among schoolchildren are associated with shyness, unhappiness, feelings of worthlessness, and a reduced ability to make friends. Linking the impact of poor dental health on Australian child school and social and emotional well-being using a large, nationally representative data set will lead to crucial insights regarding this prevalent and preventable childhood condition. Using cutting-edge cost-effectiveness modeling will be a significant contribution to dental service policy and planning to estimate the projected burden of child oral disease from 2012 and beyond, the impact on economic productivity over the life course, and the efficacy and cost-effectiveness of targeted programs for high-risk child groups. With strong partnerships with key state and territory and Commonwealth stakeholders, the findings of the NCOHS-2 will enable complex questions to be answered that will guide policy on improving child oral health that is relevant for all Australian children.

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Data Availability

The data sets generated during this study are not publicly available due to privacy issues of the participants but are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

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Multimedia Appendix 1
Peer-review report by the Australian Government National Health and Medical Research Council.
[PDF File (Adobe PDF File), 200 KB - resprot_v12i1e52233_app1.pdf]

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Abbreviations

CDBS: Child Dental Benefits Schedule
DMFT: decayed, missing, and filled teeth
NCOHS-1: first National Child Oral Health Study
NCOHS-2: second National Child Oral Health Survey
OR: odds ratio

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Protocol

Spontaneous Scaling of a Primary Care Innovation in Real-Life Conditions: Protocol for a Case Study

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Abstract

Background: Scaling effective primary care innovations to benefit more people is of interest to decision makers. However, we know little about how promising innovations are being scaled "spontaneously," that is, without deliberate guidance.

Objective: We aim to observe, document, and analyze how, in real-life conditions, 1 primary care innovation spontaneously scales up across Quebec, Canada.

Methods: We will conduct a participative study using a descriptive single-case study. It will be guided by the McLean and Gargani principles for scaling and reported according to the COREQ (Consolidated Criteria for Reporting Qualitative Research) guidelines. Informed by an integrated knowledge translation approach, our steering committee will include patient users throughout the project. Inspired by the Quebec College of Family Physician's "Dragons' Den" primary care program, we will identify a promising primary care innovation that is being or will be scaled spontaneously. We will interview the innovation team about their scaling experiences every month for 1 year. We will conduct interviews and focus groups with decision makers, health care providers, and end users in the innovation team and the target site about their experience of both scaling and receiving the scaled innovation and document meetings as nonparticipant observers. Interview transcripts and documentary data will be analyzed to (1) compare the spontaneous scaling plan and implementation with the McLean and Gargani principles for scaling and (2) determine how it was consistent with or diverged from the 4 McLean and Gargani guiding principles: justification, optimal scale, coordination, and dynamic evaluation.

Results: This study was funded in March 2020 by the Canadian Institutes of Health Research. Recruitment began in November 2023 and data collection began in December 2023. Results are expected to be published in the first quarter of 2024.

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Conclusions: Our study will advance the science of scaling by providing practical evidence–based material about scaling health and social care innovations in real-world settings using the 4 guiding principles of McLean and Gargani.

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KEYWORDS

scaling; spread; primary care; spontaneous; knowledge translation; implementation science; scaling science

Introduction

The subject of scaling has long been present in various knowledge areas such as renewable energy sources [1], sustainability [2], and education [3]. Scaling is now rapidly gaining the attention of decision makers in health and social care, particularly in high-income countries [4]. In the literature and practice record, there are numerous means proposed for scaling innovations [5]. Many of these propose modifiers, such as scaling up or out and vertical or horizontal scaling, are used in an attempt to describe the different ways in which innovations are scaled or spread. ExpandNet, a World Health Organization–affiliated group, has produced several widely used practical guides on the topic and defines scaling up as an action that aims to increase the impacts of successfully tested innovations to benefit more people [6]. Thus, it is no surprise that alongside this World Health Organization practice–oriented initiative, scaling science is emerging as a distinct complement to applied or implementation science [7-9]. The term "scaling science" has a double meaning: the first referring to approaches to bringing innovations to optimal scale for the public good and the second referring to the critical and systematic (ie, scientific) study of these approaches to scaling [7,8].

Unfortunately, Canada is a country notorious for promising pilot projects that do not get scaled [10]. Explanations for this include the fact that Canada is comprised of multiple distinct health and social care systems [11]. In addition, the most effective scaling seems to occur in low- and middle-income countries, which may reduce the opportunities for decision makers from high-income countries to improve their knowledge and competencies in scaling [5]. Another potential explanation lies in the complexity of scaling health and social innovations [12,13] and the methodological traditions that prioritize testing with randomized controlled trials before scaling up [14,15]. This contributes to lengthening the scaling process, while decision makers are often focused on short-term impact. Finally, there is increasing pressure on high-income countries to reduce waste and implement effective innovations already scaled in low- and middle-income countries [16]. Now that high-income countries face a rapidly changing society with increasing resource constraints, effective scaling of beneficial innovations has become a high priority [17].

Most scaling occurs in the absence of scaling guidelines [5]. While there are attempts to establish rigorous and standardized guidelines, there is also a pressing need for studies that look at how scaling currently occurs on the ground when a promising or effective health care innovation is naturally or "spontaneously" expanded to reach a broader population. We adopted ExpandNet's definition of spontaneous scaling as "diffusion of the innovation without deliberate guidance" [18]. The likelihood of spontaneous scaling is highest when the innovation effectively meets a clearly recognized need in a population or when a significant and urgent harmful event brings attention to the need to scale, for example, the COVID-19 pandemic [18]. Although the effectiveness of the innovation to be scaled should be demonstrated by its positive impacts on the public good, that is, it improves the well-being of individuals and populations through an increase in the quality of care [5,8], many experts and decision makers recognize that this is not always possible when facing a public health emergency [15,19]. Observation and analysis of spontaneous scaling are necessary to capture this process of adjusting plans and practice in real-life situations and will inform the knowledge base of scaling. Therefore, we aimed to observe, document, and analyze the spontaneous scaling (ie, that reflects the needs of a population but does not follow guidelines) of a promising primary care innovation within a specific health care context, compare it with the guiding principles of scaling described by McLean and Gargani [7-9], and make recommendations.

Methods

Overview of Study Design and Context

This study is a descriptive case study [20-22] adhering to the Rosenberg and Yate [23] recommendations for case study designs, which aim to comprehensively explore a particular case, including exploration of the phenomenon of interest and its contextual factors. Specifically, we define the case as the spontaneous process of scaling a promising primary care innovation within a specific health care context. The health care context is 2 large regional primary care organizations (an Integrated Health and Social Services Center [*Centre Intégré de Santé et de Services Sociaux*; CISSS] and an Integrated University Health and Social Services Center [*Centre Intégré Universitaire de Santé et de Services Sociaux*; CIUSSS]) within the Quebec health and social care services system. These 2 organizations are the administrative entities responsible for the delivery of health and social care services within their designated regions and for coordinating and integrating various facilities, such as hospitals, long-term care centers, rehabilitation centers, and community health centers.

Case Study Approach

To gain insights into the real-life spontaneous scaling process of a promising innovation, we will delve into a specific case and draw broader conclusions about the phenomenon at conclusions. This research will also take an interpretative epistemological approach [24] to understand the context of the case from different perspectives. By using these approaches,

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we will shed light on the various factors and challenges associated with the scaling of spontaneous primary care innovations in real-world settings. We will report our findings using the COREQ (Consolidated Criteria for Reporting Qualitative Research) checklist [25].

Scaling Framework

The documentation and analysis of the scaling process for this case study will be guided by a framework inspired by guiding principles proposed by McLean and Gargani [7-9]. This framework is based on a retrospective review of over 200 research and innovation projects funded by Canada's International Development Research Centre. The choice to use the McLean and Gargani principles was influenced by three factors: (1) they allow for adaptability and flexibility throughout all phases of the scaling process, which is coherent with a spontaneous approach and with the real-life context of this study (ie, unexpected changes can be accommodated and plans adapted); (2) the guidelines apply an equity lens and emphasize the importance of ethics in assessing scaling impacts; and (3) the principles support our aim of focusing on the impacts of scaling on the public good, a focus that promotes placing the main emphasis on the end users in all scaling initiatives.

The 4 guiding principles for scaling impact described by McLean and Gargani [8,9] are justification, optimal scale, coordination, and dynamic evaluation. "Justification" addresses both ethical and technical issues. Before asking how to scale, one must ask why or whether to scale and about its technical feasibility. For example, does this web-based course for social workers have the necessary infrastructure to reach more professionals (technical justification)? What kind of impact on the public good will the course provide (ethical justification)? "Optimal scale" challenges the logic of "the more the merrier" and involves making informed decisions about choosing a scale that creates an optimal mix of magnitude, variety, sustainability, and equity [7]. This requires careful consideration of the potential benefits and risks and requires judgment in balancing desirable and undesirable impacts. For instance, if the course is scaled up to 1000 social workers but is only available temporarily, and only to those working in private settings, scale-up meets the magnitude goals but not the sustainability or equity goals. "Coordination" addresses relational issues; demands flexible articulation among the complex systems; and connects the diverse actors in the scaling process, such as the initiators, the enablers, the competitors, and the people affected by scaling. For example, coordination among those involved in identifying the need for the social workers' course, those who developed the course, those who adapted and scaled it to further contexts, those who are evaluating it, those who are receiving the scaled-up version, and those who are receiving services from the newly trained social workers. For example, coordination in the case of the social workers' course would involve coordination among those who identified the need for the course, the course developers, those responsible for adapting and scaling it to diverse contexts, the evaluators assessing its effectiveness, and recipients of the scaled version. Coordination involves complexity, and this involves flexibility that requires an iterative process [8]. "Dynamic evaluation" addresses assessments in all phases of scaling: before, during, and after. Dynamic evaluation is not a linear before-after comparative assessment, but a constant application of evaluative thinking to check and adapt when necessary since scaling is a process that can change depending on the context of the site and innovation.

Coproduction Approach and Project Governance

Following the integrated knowledge translation approach [26,27], this study embraces the active engagement of knowledge users as equal partners working alongside researchers in all research steps. Through coproduction [28,29], we aim to generate knowledge that is valuable and meaningful to all stakeholders involved in the research process.

To ensure effective project governance, the research team will establish a steering committee consisting of key stakeholders who will provide expert advice, recommendations, and feedback on questions as they arise. This committee will oversee and coordinate each stage of the study and focus on topics that directly impact the project. The committee members will include the project leader; study coordinator; coinvestigators (1 or 2); knowledge users (1 or 2); and end users, who may include citizen or patient partners (1 or 2). This diversity of stakeholders ensures inclusive representation throughout the project's duration.

Participants

Criteria for Choice of Innovation, Innovation Team, and Target Site

We will choose an innovation from a previous edition of the *Innovation Symposium*, a program organized by the Quebec College of Family Physicians inspired by the TV program "The Dragon's Den" [30]. This event allows innovators, most of whom are from a clinical context and not from a research background, to pitch their promising innovations to clinical leaders and influential stakeholders (the Dragons) in Canada's primary care ecosystem. If the Dragons consider the innovation promising, they will contribute toward accelerating its growth and scaling it. Based on our research team's firsthand experience as attendees at previous symposiums (2017, 2019, and 2022), we will identify a spontaneous primary care innovation with considerable potential for scaling.

We will determine if the team is willing to participate in the project and, through a three-part questionnaire, whether (1) the innovation, (2) the innovation team, and (3) the context in which the innovation is embedded meet the following inclusion criteria based on our previous work [31-33] (Figure 1).

1. Inclusion criteria for the innovation: there is a spontaneous demand for scaling, the innovation aims to meet a demand for relevant primary care and services in the province of Quebec, the innovation has an epidemiological justification, the innovation is part of a health organization in Quebec, and the innovation has already been piloted and shown to be effective.
2. Inclusion criteria for the innovation team: it has a committee or governance for the development and scaling of the innovation, it is part of a health organization in Quebec, it accepts that the research team participate as an observer in its strategic meetings, it agrees to nominate a person to be

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the coordinator responsible for the monthly and weekly follow-up with the members of the research team, the innovation team coordinator accepts the responsibility for connecting the research team with managers and health professionals in the target scaling setting, and the innovation team will be available during the research period (1 year) for monthly update meetings to respond to weekly ad hoc email requests from the research team on the innovation and the scaling process.

3. Inclusion criteria for the target site: a specific geographical place is targeted to receive the innovation or there are professionals already using the innovation in the place where it is exposed who are not members of the innovation team, the plan for receiving the scaled innovation is embedded in a health organization in Quebec, an organizational structure is available for receiving the scaled innovation, and partners in the target site are in place to support the scaling plan.
4. Inclusion criteria for individual participants: participants must be at least 18 years old; able to provide informed consent; able to actively participate, read, understand, and communicate in English or French; involved; in contact with or affected by the scaling initiative; and a decision maker in a health and social care organization, a health care provider, or a scaling expert working in the province of Quebec.

Figure 1. Process flow for choosing a promising innovation. CQMF: Quebec College of Family Physicians.



Support for Scaling

The steering committee will establish a support network for the innovation team. Supporting organizations will be instructed to offer support and advice for scaling without providing a ready-made scaling plan. We will conduct semistructured interviews and focus groups, with the following four categories of interviewees: (1) decision makers from health and social care organizations (n=1-4), (2) health care providers (n=3-8), (3) members of the innovation team responsible for scaling (n=2), and (4) end users (n=2-4).

Recruitment

The innovation team will be asked to appoint a coordinator who will act as the primary point of contact between the research team and the innovation team. This individual will serve as a facilitator and work closely with decision makers, health care providers, end users, and the research team to ensure effective communication and collaboration. Additionally, the coordinator will be responsible for identifying potential participants and providing their names to the research team for consideration for semistructured interviews and focus groups. Once potential participants have been identified, the research team will send them an email inviting them to participate in the study. The email will outline the main objectives of the research and extend an invitation to participate.

Qualitative Data Collection

Innovation Team

We plan to ask the team about (1) the components of the innovation (including technical requirements and costs) and its impacts on patients and health care professionals, (2) their opinions on how and why it should be scaled, (3) their scaling plan and strategies, and (4) their experiences of creating and implementing the scaling plan. We will also document any challenges encountered and how they were addressed in practice. We will follow developments with weekly emails and monthly follow-up meetings for 1 year.

Target Site

We intend to seek input from a range of decision makers (n=1-4), health care professionals (n=3-8), and end users (n=2-4) at the target site, as identified by the innovation team, regarding their firsthand experience with implementing the scaled innovation. We will conduct 1-hour semistructured interviews and focus groups (n=6-8). Participants in both interviews and focus groups will be asked about the innovation and their experience of scaling the health innovation, their view on the successful adaptation or not of the innovation, suggestions for improvement, potential factors influencing its implementation in their context, and possible complementary actions to be put into practice. One-hour individual structured interviews will be conducted face-to-face or on digital platforms (Teams [Microsoft Corp] or Zoom [Zoom Technologies Inc]) and adapted to accommodate the availability of participants. We will hold focus groups with the health care providers lasting 2 hours (maximum) outside office hours to reduce the impact on the services offered. Interviews will be conducted in English or French. One of the research team members with expertise in scaling and training in health care research innovation will conduct the interviews and focus groups. The interviews and focus groups will be recorded and transcribed, while an assistant moderator will be responsible for taking meeting notes during the interviews and focus group sessions. We will also participate as nonparticipant observers in some key meetings of the innovation team or training sessions given by the innovation team. During the

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observation periods, the research team will take observation notes about the meeting and the scaling process.

Interview Guide

The interview guide will be based on the 4 McLean and Gargani guiding principles of scaling and will be adapted to the different roles of the interested parties (1 interview guide for decision makers, health professionals, and the innovation team and another one for end users).

We plan to carry out supplementary descriptive quantitative data collection that includes self-administered questionnaires to collect sociodemographic information from each participant (eg, age, sex, gender, civil status, and employment status) involved in the semistructured interviews in addition to a descriptive data collection of organizational characteristics of the target scaling site. The second source of quantitative data will be the various documents describing the scaling process (eg, archival records, reports on the innovation development, minutes of meetings, email exchanges, data from the monitoring of scaling, training manuals and materials, and postintervention feedback) to complement and support our qualitative analysis [34]. We will proceed to content analysis and direct analysis based on the 4 McLean and Gargani guiding principles, providing a comprehensive account of the execution of the scaling plan for detailed analysis.

Data Analysis

Theoretical Model

Using a framework approach [35], we will develop an a priori template of codes based on the McLean and Gargani guiding principles. We will use the data collected, both qualitative (interview transcripts and documentation) and quantitative (questionnaires and documentation), to (1) compare the innovation team's scaling plan with how scaling was implemented in practice at the target site and (2) determine the concordances or discordances between the 4 principles and participants' observations regarding their experience of developing the innovation, planning scaling, implementing scaling, and receiving the scaled innovation at the target site.

We will conduct a directed analysis by reading the full transcripts of the focus groups and the semistructured interviews as well as the third-party observations to obtain a sense of the overall data and compare coders' findings to reach agreement about the key themes identified based on the McLean and Gargani guiding principles. Using intracode methods, the research team will compare findings to reach a consensus on the key themes. Participants will be sent summaries of the results of the interviews and focus groups that they participated in and asked to verify their accuracy. A descriptive analysis of organizational (sites, decision makers, and health care providers) and sociodemographic (decision makers and health care providers) characteristics will also be conducted.

Validation

To ensure the internal validity of the analysis, the principal investigators will perform triangulation of data, cross-referencing data from multiple sources. To ensure external validity, a detailed description of the context in which scaling takes place will be provided, that is, the target clinic and its professional health care provider team. To further ensure the accuracy and credibility of the final report, it will be circulated among the collaborators and the committee to validate its content.

Knowledge Mobilization

Our knowledge mobilization plan is to involve knowledge users (eg, investigators, health care providers, and decision makers) and end users (eg, patient partners) in the steering committee. They will meet every 3 months via teleconference to discuss research progress and provide guidance on research directions. Our team already has extensive experience in the involvement of end users in the design, development, and implementation of health care solutions. Our approach considers the opinions of all end users as equally important. We will send out a newsletter every 4 months for all stakeholders.

We will produce and deliver an adapted and improved scaling plan, based on our results as seen through the lens of the McLean and Gargani guiding principles, to the innovation team. An executive report will be made available free of charge on the research team's website. We will prepare summaries of our research results tailored to specific knowledge user groups such as clinicians' organizations (family physicians, nurses, psychologists, and social workers) and researchers (peer-review publications).

Finally, we will disseminate study results in the form of (1) recommendations for preparing and monitoring scaling in primary care with an ethical lens, (2) presentations at scientific and professional conferences, (3) publications in peer-reviewed journals, and (4) through relevant networks such as the Research on Patient-Oriented Scaling-up network, the Strategy for Patient-Oriented Research (SPOR) Evidence Alliance, the Quebec College of Family Physicians and Réseau-1 Québec.

Ethical Considerations

Ethical approval was obtained from the CIUSSS de la Capitale-Nationale ethics board (MP-13-2023-2770). All stages of this research project will be carried out in accordance with Canadian procedures for informed consent (Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans) [36].

Results

This study was funded in March 2020 by the Canadian Institutes of Health Research. The steering committee has been formed and is giving expert advice and recommendations. The innovation has been identified, and the innovation team has agreed to contribute to this study by informing potential participants for interviews. Participants recruitment started in November 2023, and data collection began in December 2023. The interview guide has been developed through collaboration with 1 of the authors of the McLean and Gargani guiding principles, and a second interview guide has been adapted for conducting interviews with end users. Results are expected to be published in the first quarter of 2024.

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Discussion

This study aims to use a single descriptive case study to observe, document, and analyze how, in real-life conditions, a promising health care innovation is being or will be spontaneously scaled in a health and social care organization across the province of Quebec. During the process of scaling, many external factors that may not be accounted for in most guidelines, such as the type of innovation being scaled, may influence the outcome. By taking a holistic approach that considers multiple interested parties (eg, patient or citizen partners, decision makers, professionals, researchers, and community members), we will gain a broad perspective on the spontaneous scaling process, enabling us to better understand real-life situations and the challenges that arise during scaling. One of the expected results is a better understanding of the role of flexibility and adaptability in scaling. Few studies have documented the actual process of spontaneous scaling and its practical implications.

By using the McLean and Gargani guiding principles, we also expect our results will give us insight into the ethical aspects of scaling that are overshadowed by the technical aspects and often given insufficient attention, despite their importance. The choice to use this framework was influenced by a need to better define and distinguish ethical considerations in scaling guidelines [5]. While "justification" may seem to be the most critical ethical principle of scaling among the 4, the other 3 also integrate ethical considerations. For instance, "coordination" is sometimes described by McLean and Gargani [9] as *inclusive coordination* because it involves engaging with stakeholders who are usually excluded in impact studies (eg, patients) to ensure the success of the innovation. By using these principles, we can single out the equity-related processes of an innovation and explore its ethical aspects in greater detail.

This study will provide valuable insights into the strategies, challenges, and outcomes of scaling innovations in real-life practical settings. It will provide evidence-based material to support scaling projects to integrate ethical considerations and to incorporate the flexibility to accommodate real-life demands.

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Data Availability

The data sets generated and analyzed during this study are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review report by the Canadian Institutes of Health Research (CIHR).
[PDF File (Adobe PDF File), 112 KB - resprot_v12i1e54855_app1.pdf]

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Abbreviations

CIUSSS: Centre Intégré Universitaire de Santé et de Services Sociaux (Integrated University Health and Social Services Center)
CISSS: Centre Intégré de Santé et de Services Sociaux (Integrated Health and Social Services Center)
COREQ: Consolidated Criteria for Reporting Qualitative Research
SPOR: Strategy for Patient-Oriented Research

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Protocol

Development of an Artificial Intelligence–Guided Citizen-Centric Predictive Model for the Uptake of Maternal Health Services Among Pregnant Women Living in Urban Slum Settings in India: Protocol for a Cross-sectional Study With a Mixed Methods Design

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Abstract

Background: Pregnant women are considered a “high-risk” group with limited access to health facilities in urban slums in India. Barriers to using health services appropriately may lead to maternal and child mortality, morbidity, low birth weight, and children with stunted growth. With the increase in the use of artificial intelligence (AI) and machine learning in the health sector, we plan to develop a predictive model that can enable substantial uptake of maternal health services and improvements in adverse pregnancy health care outcomes from early diagnostics to treatment in urban slum settings.

Objective: The objective of our study is to develop and evaluate the AI-guided citizen-centric platform that will support the uptake of maternal health services among pregnant women seeking antenatal care living in urban slum settings.

Methods: We will conduct a cross-sectional study using a mixed methods approach to enroll 225 pregnant women aged 18-44 years, living in the urban slums of Delhi for more than 6 months, seeking antenatal care, and who have smartphones. Quantitative and qualitative data will be collected using an Open Data Kit Android-based tool. Variables gathered will include sociodemographics, clinical history, pregnancy history, dietary history, COVID-19 history, health care facility data, socioeconomic status, and pregnancy outcomes. All data gathered will be aggregated into a common database. We will use AI to predict the early at-risk pregnancy outcomes (in terms of the type of delivery method, term, and related complications) depending on the needs of the beneficiaries translating into effective service-delivery improvements in enhancing the use of maternal health services among pregnant women seeking antenatal care. The proposed research will help policy makers to prioritize resource planning, resource allocation, and the development of programs and policies to enhance maternal health outcomes. The academic research study has received ethical approval from the University Research Ethics Committee of Dehradun Institute of Technology (DIT) University, Dehradun, India.

Results: The study was approved by the University Research Ethics Committee of DIT University, Dehradun, on July 4, 2021. Enrollment of the eligible participants will begin by April 2022 followed by the development of the predictive model by October 2022 till January 2023. The proposed AI-guided citizen-centric tool will be designed, developed, implemented, and evaluated using principles of human-centered design that will help to predict early at-risk pregnancy outcomes.

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Conclusions: The proposed internet-enabled AI-guided prediction model will help identify the potential risk associated with pregnancies and enhance the uptake of maternal health services among those seeking antenatal care for safer deliveries. We will explore the scalability of the proposed platform up to different geographic locations for adoption for similar and other health conditions.

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KEYWORDS

citizen centric; maternal health; informatics; predictive model; artificial intelligence; development; evaluation; machine learning

Introduction

Background

The World Health Organization has defined maternal mortality as the annual number of female deaths from any cause related to or aggravated by the pregnancy or its management (excluding accidental or incidental causes) during pregnancy and childbirth or within 42 days of termination of pregnancy, irrespective of the duration and site of the pregnancy, which is estimated to be 295,000 globally each year [1]. Of the total maternal deaths, 94% occur mostly in low-resource settings, which could have been prevented in most cases. In India, there has been a significant decline in maternal deaths in 2015 by 68.7% (n=130 in 2016) against a global maternal mortality rate of 216 (2015) compared with 556 (1990) women dying during childbirth per hundred thousand live births as per the UN Maternal Mortality Estimation Interagency Group report. It has been targeted to reduce below 70 by 2030 under the Sustainable Development Goal [2,3].

There have been various factors contributing to maternal mortality found between the onset of obstetric complications and its outcome. If prompt, adequate treatment is provided, the outcome will usually be satisfactory; therefore, the outcome is most adversely affected by delayed treatment. A review of delayed decisions to seek care and delay in accessing adequate care can provide the actual picture to address the satisfactory utilization of maternal health care services in the context of low- and middle-income countries (LMICs) [4].

There are various national maternal health programs initiated by the Government of India under National Health Mission. Some of them are as follows: (1) Janani Shishu Suraksha Yojana, which is a new approach to health care that emphasizes entitlements and elimination of out-of-pocket expenses for both pregnant women (free delivery including cesarean section in public health facilities) and sick infants [5]; (2) Janani Suraksha Yojna, which provides safe motherhood intervention for reducing maternal and neonatal mortality by promoting institutional deliveries among poor pregnant women by providing conditional cash assistance to below poverty line/schedule caste/schedule tribe women for giving birth in a public health care institution or accredited private hospitals [6]. The Anganwadi center is one of the types of rural childcare service providers in India under the scheme of Integrated Child Development Services, which is one of the flagship programs of the Government of India launched in 1975. It is unique and one of the world's largest programs for early childhood care and development. With a history of high maternal and infant mortality and morbidity in LMICs like India, the scheme provides preschool nonformal education, on one hand, and breaks the vicious cycle of malnutrition, morbidity, reduced learning capacity, and mortality, on the other, to the beneficiaries including children in the age group of 0-6 years, pregnant women, and lactating mothers [7].

The application of citizen-centric design in this study will primarily keep pregnant women as the beneficiary by understanding user characteristics, needs, and preferences that are critical for developing a human-centered artificial intelligence (AI)–guided predictive model. Analysis of demographic parameters such as gestational age, medical history, immunization, education, and socioeconomic status as well as prior exposure knowledge, practice, and attitude toward the use of antenatal care (ANC) services plays a key role in ensuring optimal use of maternal health services in slums [8].

In urban slums, pregnant women are a "high-risk" group with limited access to health facilities. Barriers to utilization of health services are well documented in a few studies where the urban poor cannot be treated as homogeneous entities because of strong evidence on important sociodemographic variations within the urban poor population with their use of services and the barriers faced in service usage [2,9,10]. On the assessment of social-economic barriers, women reported the poor attitude of health workers. Other barriers reported were men's stigma-related refusal to accompany their spouses for HIV screening and some bylaws that restrict women who had pregnancy outside marriage to seek an authorization letter from local traditional leaders for ANC services at the health facility [11].

Rationale of the Study

Most of the urban slums comprise immigrant families bearing their area-specific social customs, rituals, and taboos. Depending on these factors, the slums may differ from one another in their health indicators, which acts as a barrier to timely and appropriate utilization of maternal health care services under the national programs [12,13].

The identified barriers in the utilization of maternal health care services at a local level may differ significantly between slums that need to be recognized, identified, and addressed in the district-level planning for health [14]. Poor families are unable to seek maternal services because of various cultural and demographic factors. The public health care delivery system plays a vital role in the national programs that have been

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reported to be inefficient; even the minimum facilities are not often made available to the target groups [13,15].

Research shows that AI, automation, and data science can support overburdened health systems and health workers when responsibly deployed. AI-enabled platforms can be used to communicate timely information to the public, support self-care, and communicate initial recommended preventive options and even psychosocial care [16-20]. Hence, we plan to develop an AI-guided citizen-centric predictive model that will help to identify the gaps in using maternal services during ANC and enhance the uptake in utilizing maternal health services during the antenatal period and related pregnancy outcomes.

Research Hypothesis

The research hypotheses are as follows:

- Is there an association between sociodemographic factors, health behaviors, health care access, clinical factors, and use of maternal health care services such as ANC services?
- Is the design and development of an internet-enabled AI-guided predictive model using a human-centered approach a good fit for enhancing the uptake of maternal health services among pregnant women living in urban slum settings?
- Can the proposed AI-guided predictive model be useful to enhance maternal health services to improve pregnancy-related health outcomes?

Aims and Objectives

Aims

The study has three aims:

1. Identify the factors that affect the uptake of maternal health services such as ANC among pregnant women living in urban slum settings of South Delhi
2. Use community data to design and develop a comprehensive AI-guided citizen-centric tool for improved utilization of maternal health services among pregnant women
3. Evaluate the usefulness and effectiveness of the proposed AI-guided citizen-centric tool to enhance the uptake of maternal health services for ANC services

Objective

The objective of our study is to develop and evaluate the AI-guided citizen-centric platform that will support the uptake of maternal health services among pregnant women seeking ANC and living in urban slum settings.

Methods

Study Design

A cross-sectional mixed methods study will be conducted to gather both qualitative and quantitative data on an android-based electronic platform.

Study Site

The study will be conducted in the urban slums of South Delhi, and participants will be enrolled from the Anganwadi centers. The Anganwadi workers will assist in mobilizing the eligible participants seeking ANC services to participate in the study.

Inclusion and Exclusion Criteria

The inclusion criteria are as follows:

- Eligible married pregnant women aged between 18 and 44 years regardless of pregnancy order
- Pregnant women residing in urban slum settings for the last 6 months
- Participants who gave written/e-informed consent
- Participants having a smartphone

Participants who are not willing to participate are not included in the study.

Study Population

Eligible pregnant women seeking ANC and aged between 18 and 44 years will be enrolled in the study.

Sample Size

A convenience sampling approach will be employed in selected urban slums across 4 geographic zones of South Delhi where only 10% of the households in each slum site will be selected from each zone. Very few studies reported ANC utilization in urban slums in Delhi. Using a reference of this indicator for urban Delhi considering an expected proportion of 30% of participants completing at least 3 ANC visits, with 95% confidence levels, 6% of absolute precision, and a nonresponse rate of 10%, the estimated sample size of the study will be 225.

Study Tools

Data collection will be done at the Anganwadi centers using prevalidated instruments adapted from the National Family Household Survey (NFHS). The data will be collected using the electronic data collection tool (Multimedia Appendix 1) focusing on certain predictors that will help in predicting the pregnancy outcomes by measuring the risk associated with the type of delivery method, the term (preterm/full term), and related complications during the delivery. The proposed predictors (Textbox 1) will help in analyzing and comparing the pregnancy outcomes using machine learning from the primary data set.

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Textbox 1. Pregnancy predictors to be evaluated in model development: definition.

Age

- Age of the women at the time of data collection during pregnancy

Duration of pregnancy

- The current duration of pregnancy from the last menstrual period until the date of data collection

Education

- The literacy level of the participant to understand the importance of antenatal care

Birth order

- The order a child is born in their family

Abortion history

- History of medical termination of pregnancy

History of diabetes

- A family history that can make women with a family history of diabetes more at risk for developing the disease

Hypertension

- Family history of high blood pressure inducing the pregnancy

Thyroid

- Family history of hypo- or hyperthyroidism inducing the pregnancy

Number of visits

- Frequency of seeking antenatal care services through Anganwadi centers

Immunization

- Immunization against tetanus toxoid during pregnancy

Supplements

- Iron folic acid supplements are prescribed during pregnancy

Ultrasonography

- Ultrasonography for fetus growth, development, and monitoring of pregnancy

Related complications

- Pregnancy-related complications during the prepartum, antepartum, and postpartum period

COVID-19 history and its related complications

- History of COVID-19 during pregnancy and its related complications

Immunization

- Vaccinations against COVID-19 infection

Height

- Height of women during pregnancy at the time of data collection

Weight

- Weight of women during pregnancy at the time of data collection about the duration of pregnancy

Blood pressure

- Monitoring blood pressure of women during pregnancy

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Pregnancy BMI

- Body mass divided by the square of the body height

Knowledge of national maternal and child health programs and benefits

- Knowledge about various maternal and child health schemes under the Government of India

Antenatal care accessibility

- Women seeking antenatal care from health care providers and distance from their residence

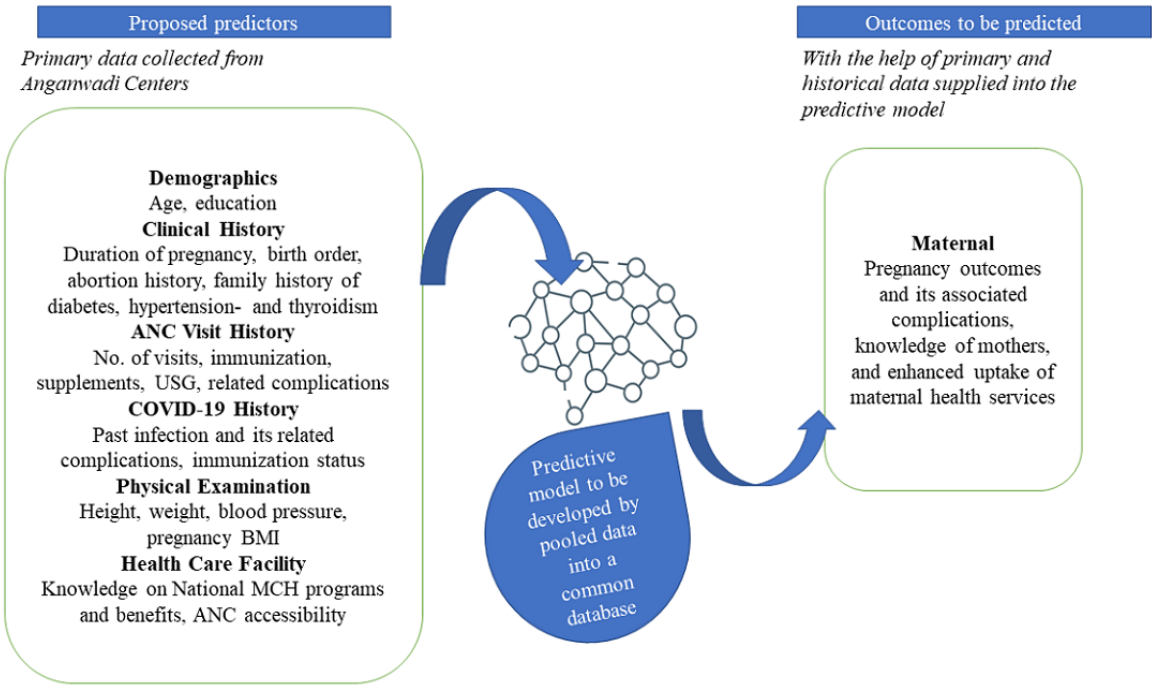
Predictive Model Design

We will develop a machine learning predictive model for early at-risk pregnancy outcomes using citizen-centric design to enhance the uptake of maternal health services among the beneficiaries seeking ANC. This includes some common parameters based on which the model will be developed (Figure 1).

The data pool will be structured following well-established common data models (CDM), which will facilitate harmonizing the data set providing access to relevant data concurrently for ease of consistent and accurate analysis. The CDM, identified at this stage, will include the Observational Medical Outcomes Partnership (OMOP) for clinical data extracted from sources and the customized Community-Based Demographic model for data extracted from communities (Figure 2). The OMOP CDM will allow the organization to standardize medical terms used across the data set for analysis. This platform will focus on algorithm development using evidence-based guidelines [21], existing gaps, and available literature [22,23] to create "IF," "AND," and "OR" logics to create a guide for logical thinking and future research, and will help to understand how these data will be processed at the backend, which would help policy makers and other public health researchers in decision-making.

The participants will be followed every 3 months from the date of enrollment until their pregnancy outcomes through telephonic calls. The data collected from the first 100 participants will help to develop the AI-guided tool, and the same will be evaluated for its potential competitiveness in the next 125 participants' data (Figure 3).

Figure 1. Predictors for comparison in a predictive model of pregnancy outcomes. ANC: antenatal care; MCH: maternal and child health; USG: ultrasonography.



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Figure 2. Conceptual framework of data flow to develop the decision support system. AI: artificial intelligence; CBD: community-based demographic model; CDM: common data model; DSS: decision support system; ML: machine learning.

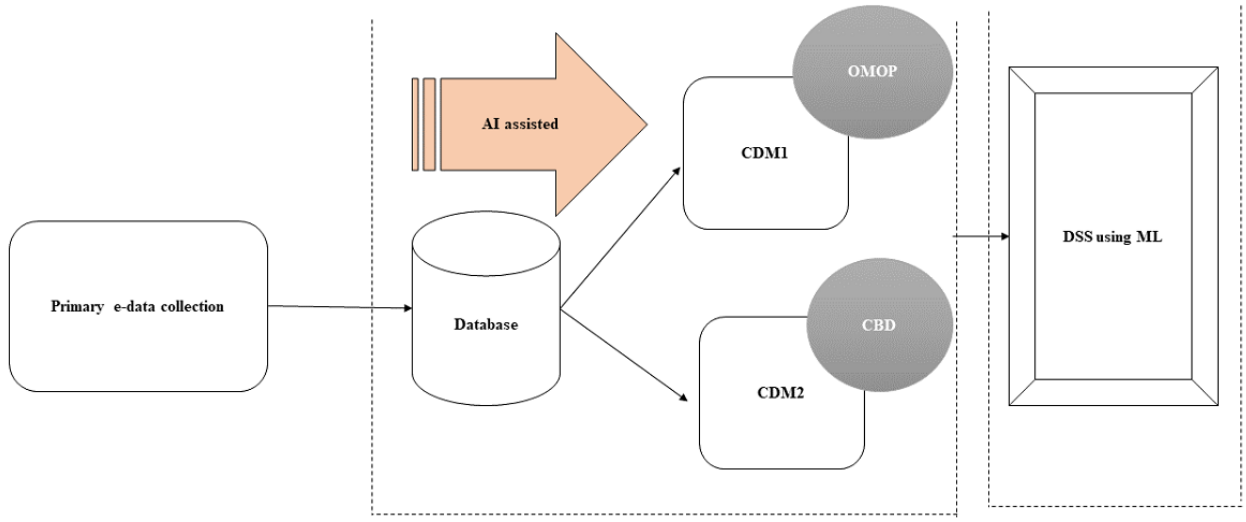
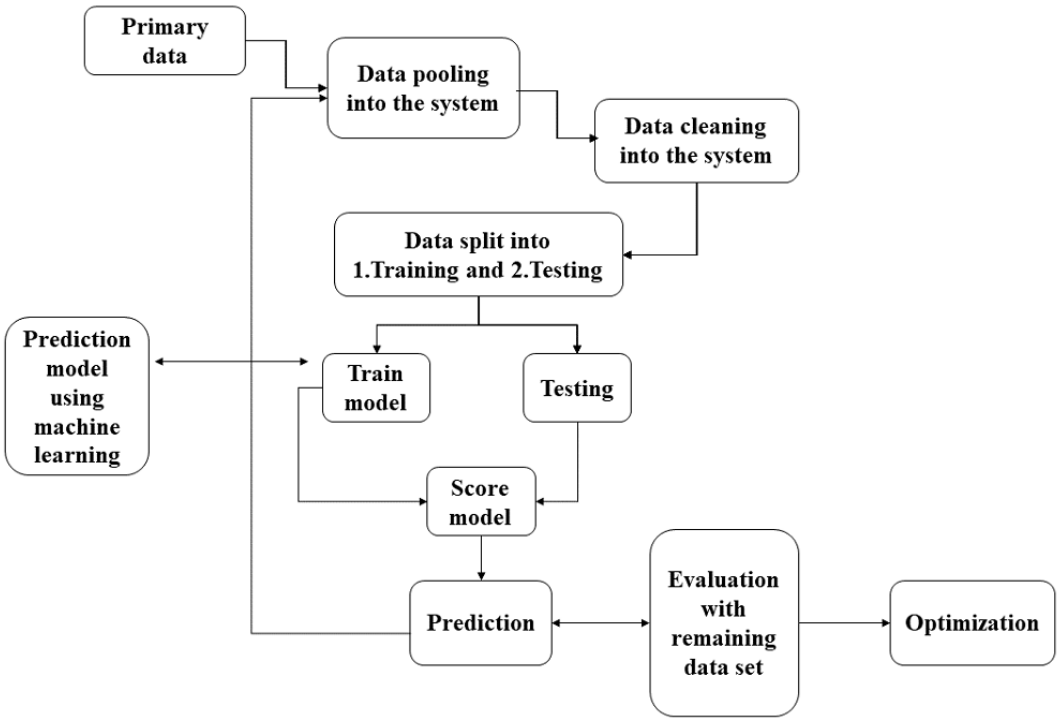


Figure 3. Analytic framework for prediction model of pregnancy outcomes.



Data Management and Availability

The data will be collected in bilingual languages (English and Hindi) electronically. Source data verification and quality control will be managed by the team of researchers. The anonymized data set for the entire study will be stored in Amazon Web Server (cloud server) and will be used in the model.

Statistical Analysis

Data will be analyzed using a multivariate regression model that may account for the clustered nature of the pooled data. Uptake in the utilization of maternal health services especially during the antenatal period and pregnancy outcomes (dependent variables: number of ANC visits, tetanus toxoid injections, iron folic acid tablets) will be tested against all independent variables: maternal morbidity, pregnancy outcome, complications of previous pregnancy, literacy, and availability of health care facility using the SPSS statistical tool. Predictive analysis will be compared for accurate future outcomes through the supplied data sets using machine learning to further optimize the model.

Expected Outcome Measures

The anticipated outcome from this study will be more focused on the epidemiology of maternal health in terms of a better quality of life through the uptake and proper utilization of maternal health services in terms of ANC service utilization efficiently through behavior change communication, advocacy, and health monitoring defining the aspects other than the clinical side in urban slums. Different parameters based on which the efficacy of this proposed platform will be assessed are as follows:

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1. Monitoring the trend of the utilization of maternal health services by pregnant women seeking ANC through local service providers (Anganwadi centers) in urban slums
2. Risk identification during the antenatal period
3. Mapping of health care facilities (Anganwadi centers)
4. Evaluating the competencies of the proposed platform in predicting early at-risk pregnancy outcomes.

Quality Assurance

Three levels of data security will be implemented, namely participant level, data transmission level, and server level, ensuring no harm to study participants (neither physical nor mental) while collecting primary data. For secondary data access from individuals or institutions, prior permissions from respective data owners unless the aforesaid data are in the public domain are obtained (if applicable).

Ethics Approval

The academic research study has received ethical approval from the University Research Ethics Committee (UREC) of the Dehradun Institute of Technology (DIT) University, Dehradun, India, bearing the approval letter number Protocol DITU/UREC/2021/07/4 dated July 4, 2021. The results will be disseminated at various presentations, seminars, and conferences; as a part of a PhD thesis in Population Health Informatics at DIT University, Dehradun; and in a manuscript that will be submitted to peer-reviewed journals only. The evaluation of the proposed outcome areas will be completed by January 2023.

Results

The study was approved by the University Research Ethics Committee of DIT University, Dehradun, on July 4, 2021. Enrollment of the eligible participants will begin by April 2022 followed by the development of the predictive model by October 2022 until January 2023. The proposed AI-guided citizen-centric tool will be designed, developed, implemented, and evaluated using principles of human-centered design that will help to predict early at-risk pregnancy outcomes. The results of the study will identify the factors that affect the proper use of maternal health services during the antenatal period. The study results will also intend to make an important contribution by evaluating the usefulness and effectiveness of the proposed predictive model, further evaluating the model for accuracy.

Discussion

Principal Findings

In India, slums have been identified in 2613 towns including 20 census towns (19 from the National Capital Territory of Delhi and 1 from Uttar Pradesh) irrespective of their population size in the Census 2011 report, wherein the slum population was enumerated as 22.4% of the total slum population in cities/towns and 17.4% of the total urban population of all the states and union territories [24-27]. The significant community representation from the urban slum population and experience of maintaining population cohorts in the selected study sites are being leveraged to fill knowledge gaps related to the actual burden of maternal morbidity and mortality.

Operational challenges unique to the COVID-19 pandemic, in the form of barriers due to administrative lockdown, restrictions in field mobility in containment zones, and outbreaks at the study site, are anticipated in the study. Hesitance on the part of potential participants toward commonplace data collection at Anganwadi centers and a guarded attitude toward disclosing any health issues due to COVID-19–associated stigma are expected in some communities. We expect that functional linkages with the local health system will be established at each Anganwadi from where the potential participants can be enrolled and benefit from this research study. The study tools adopted from the NFHS will assist in collecting reliable data that are a part of the Indian census enumeration program. The NFHS is a large-scale, multiround survey conducted every 10th year in a representative sample of households throughout India to provide state and national information on fertility, infant and child mortality, the adoption rate of family planning, maternal and child health, reproductive health, nutrition, anemia, and utilization and quality of health and family planning services [28]. Thus, the data collected electronically will thereby help in transforming the raw data into meaningful interpretations and representations for other researchers.

The recruitment sites represent the residents living in the periurban area, generally defined as slum dwellers/*Jhuggi Basti*.

This study will establish the clinical need for a robust prediction model for adverse event–related pregnancy outcomes during the antenatal period to support therapeutic decision-making and continuum of care. Engagement with stakeholders in the model design stage will improve the clinical acceptability of the model and will also support future implementation efforts in the field through the references to a systematic review.

There are a few limitations of this study, such as difficulty in enrollment due to the COVID-19 pandemic, the potential loss to follow-up given the current increase in COVID-19 cases and its complications, participants of the first trimester to be followed until the third trimester down the line to strengthen the system, and results cannot be generalized as the study is limited to one geographic setting with a small sample size.

In this study, no possible risk is anticipated as of now other than the exposure of participants to an infected individual who could be a point of transmission for COVID-19 (considering mega vaccination drives in India) and the emergence of a new variant (Omicron) in the community.

The design of the study will enable us to understand the dynamics of the community, household, and individual due to the inclusion of basic demographic parameters and the socioeconomic status of the family, which will help to analyze the root cause of the underuse of maternal health services and leading complications related to pregnancy outcomes. Subsequent follow-up with the participants will help to evaluate and optimize the model.

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Conclusions

The proposed internet-enabled AI-guided predictive model will help to identify the potential risk associated with pregnancies and enhance the uptake of maternal health services among those seeking ANC for safer deliveries. This study will help to get an insight into various sociodemographic factors other than clinical aspects for underutilization of maternal health services in the community, which will motivate pregnant women to use the government-facilitated national maternal health care program more efficiently, thereby reducing maternal mortality and morbidity during pregnancy. We will explore the scalability of the proposed platform to different geographic locations for use with similar and other health conditions.

Data Availability

For data security, we will implement and maintain appropriate technical and organizational measures following applicable data protection laws to ensure a level of security appropriate to the risks. Information will be collected in an electronic format and will be stored in a secure database. The data will be accessible only to authorized research staff during the study. All the records will be identified with a code and the results/findings may be presented at meetings or in publications; the participant's identity will not be revealed at any point in time. All possible measures will be taken before the data are made publicly accessible by removing all information that could identify any participant.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Case Record Form.
[PDF File (Adobe PDF File), 598 KB - resprot_v12i1e35452_app1.pdf]

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Abbreviations

AI: artificial intelligence
ANC: antenatal care
CDM: common data models
DIT: Dehradun Institute of Technology
LMIC: low and middle-income country
NFHS: National Family Household Survey
OMOP: Observational Medical Outcomes Partnership
UREC: University Research Ethics Committee

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Protocol

The Integration of Live Video Tools to Help Bystanders During an Emergency Call: Protocol for a Mixed Methods Simulation Study

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Abstract

Background: Early action by bystanders is particularly important for the survival of individuals in need of emergency care, especially those experiencing a cardiac arrest or an airway obstruction. However, only a few bystanders are willing to perform cardiopulmonary resuscitation. The use of a live video during emergency calls appears to have a positive effect on the number of cardiopulmonary resuscitations performed by bystanders.

Objective: The objective of this study is to propose and evaluate the relevance of a living lab methodology involving video calls in simulated life-threatening emergency situations.

Methods: The first study aimed at analyzing the process of dealing with out-of-hospital cardiac arrest at a dispatch center and identifying the needs of the dispatchers. The second study is a pretest of a living lab. The third study focuses on a living lab in which 16 situations of cardiac arrest and airway obstruction are simulated. The simulation includes both a live video and transmission of a video demonstration of emergency procedures. The measures focus on 3 areas: the impact of video tools, development of collaboration within the community, and evaluation of the method.

Results: The results of the first study show that dispatchers have an interest in visualizing the scene with live video and in broadcasting a live demonstration video when possible. The initial results also show that collaboration within the community is enhanced by the shared simulation and debriefing experiences, clarifying regulation procedures, and improving communication. Finally, an iterative development based on the lessons learned, expectations, and constraints of each previous study promotes the existence of a living lab that aims to determine the place of live video tools in the sequence of care performed by dispatchers.

Conclusions: Living labs offer the opportunity to grasp previously undetected insights and refine the use of the applications while potentially developing a sense of community among the stakeholders.

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KEYWORDS

emergency care; dispatcher; engaging citizens; living lab; apps; mobile phone

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Introduction

Background

The care provided in life-threatening emergencies is constantly evolving, partly because of the technological advances that are leading to changes in health care and further improvements in the way dispatchers respond to and handle emergency calls. Current health recommendations emphasize that all available resources, both human and technological, should be used to achieve better outcomes in terms of patient care [1]. For instance, in France, a new law has been in place since July 2020 establishing the status of citizen rescuers, whereby citizens can and should attempt to rescue an individual in a critical situation and will not be held responsible for any consequences related to this attempt. This legislation has the broad goal of improving survival after an out-of-hospital cardiac arrest (OHCA). In addition, since 2015, European and International recommendations for the treatment of OHCAs have included the use of digital applications dedicated to train citizens to promote rapid response to individuals experiencing an OHCA [2-4]. This concern stems from the fact that individuals experiencing an OHCA have a very low probability of survival (around 10%) despite the numerous measures taken, such as training citizens in first aid, prevention, and massive deployment of automatic electric defibrillators [5-7]. Furthermore, OHCA is not the only emergency situation where rapid intervention, by a bystander, for example, can be crucial. In the case of a sudden airway obstruction (choking), particularly prevalent among children and older adults, who are a high-risk population [8,9], it is the speed of the action that is pivotal. In choking situations, it is recommended that back blows (Mofenson maneuver), abdominal thrusts (Heimlich maneuver), or chest thrusts be performed. These have been shown to be effective in relieving foreign body airway obstruction (FBAO) [10]. In both situations, the direct intervention of a bystander results in better survival rates. As for OHCA, 13.6% of the patients discharged alive were the ones who received bystander cardiopulmonary resuscitation (CPR), compared with 7.3% of the patients who did not receive early CPR [11]. When defibrillation is performed by a bystander using an automated electrical defibrillator, the rate of increase in survival is similar to that seen among patients who received bystander CPR: 47% of patients survived to hospital discharge, compared with 28% of the patients initially defibrillated by a first responder who arrived later [12]. As for sudden airway obstructions, direct witness action resulted in a 68% survival rate, compared with 44.7% survival rate among the patients who received intervention at a later stage [13]. However, bystanders rarely intervene when they witness an emergency. With respect to cardiac arrest, the rate varies from 1% to 18% for defibrillation and from 10% to 40% for CPR [14,15]. Similarly, although bystanders performing the Heimlich maneuver have been shown to be essential in improving the outcome of individuals who are unconscious or unresponsive because of choking, only 25% of these individuals receive this assistance [16].

Components Affecting the Willingness of Bystanders to Act

Several elements can affect a bystander's willingness to intervene. A study showed that in terms of performing CPR, the fear of hurting the patient is the first barrier (reported by 63.1% of the respondents for older adults and 50.9% for children), followed by a perceived lack of appropriate skills (13.4% for older adults and 23.4% for children) and fear of parental blame (5.2%) in cases involving child CPR [17]. Numerous other studies have indeed shown that bystanders were afraid of causing injury to individuals in need of emergency care [18-20]. Therefore, to reduce these barriers, it is necessary to better inform citizens about the consequences of individuals not receiving adequate assistance in emergency situations and to train the population more widely in first aid. In addition, health professionals have limited trust in bystanders, specifically those who are in initial contact with dispatchers. For example, several studies have shown that dispatchers perceive bystanders as a nuisance because of their inexperience, limited training in first aid, and insufficient knowledge [21-24]. This mistrust is compounded by the fact that interactions between both populations are very rare, which can lead to tension and misunderstanding during their communication [22,25]. Moreover, neither of them is accustomed to collaboration [26], and during a call involving an emergency-related interaction, there is no time to build the necessary trust for effective collaboration [27]. To improve the relationship between the dispatcher and the bystander who can perform first aid procedures, two pathways can be considered: (1) establish a common frame of reference between bystanders and health professionals that allows for more efficient collaboration based on already established trust and (2) providing new tools (eg, live video) to overcome the lack of knowledge and training in bystanders and allow them to overcome their fear of performing emergency procedures while providing a sense of confidence to the dispatcher.

Use of Live Video to Enhance Communication Between the Bystander and the Dispatcher

The use of live videos is an emerging trend in handling emergency calls. Live videos can be used to assess the condition of the patient or the context and thus provide feedback to the dispatcher, allowing them to have better visibility of the situation. Indeed, there seems to be a discrepancy between the reality of the situation in the field and what the dispatcher perceives when receiving only audio information [28,29]. Live video feedback has also proven to be an asset in guiding CPR [30]. In England and Denmark, video feedback is currently used at certain dispatch centers using the app GoodSAM [30,31]. The dispatcher also has the option of sending a live video demonstration of the rescue actions that can be performed by the bystander. Studies have shown that viewing a live video demonstration of CPR increases the rate of bystander CPR [31] and improves the quality of chest compressions (rate, frequency, depth of compressions; reduction in interruptions; and the accuracy of one's hand placement) [32-36]. Therefore, it is needless to prove the beneficial effect of bystander CPR on medical care. However, this study aims to understand the subjective effect of using such applications in a high-fidelity

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simulation context [37,38]. The high-fidelity context refers to the inclusion of all the real actors in the survival chain.

The Living Lab as a Space to Create a Shared Referential

The living lab is a method developed in the 1990s at the Massachusetts Institute of Technology, which aims to provide a meeting place for all the stakeholders involved in a situation to test a technological innovation [37,39]. This method allows a test in a situation close to reality and makes it possible to identify and confront the real constraints even before reaching a more advanced development process. It also provides opportunities for different populations, varying in their level of familiarity, to interact and collaborate. Living laboratories are sometimes used in the medical industry and show positive effects on the development of trust between participants owing to a better understanding of the reality of others [38]. Moreover, living laboratories offer the opportunity to use a diverse set of complementary methodologies. For life-threatening emergencies, simulation seems to be the most appropriate setting. It is important to point out that to preserve the safety of individuals in need of emergency care and the potentially traumatic effects on the participants, it is not possible to conduct this experimentation in a real context [40]. The use of simulations with scenarios in a semireal context seems adequate and can genuinely benefit the participants in moments of emergency or crisis [40,41]. Experiencing the simulations together contributes to the creation of a discourse and a common frame of reference allowing for a more efficient cooperation later [40,42]. We also hypothesize that learning first aid in this type of setting will allow for a longer retention of skills than learning through more typical training, in which case the learning tends to dissipate after6 months [43]. Simulation helps induce strong emotions, and such induction and feeling of strong emotions are a prerequisite for experiential learning [44] and are demonstrated to be an effective method to retain the acquired knowledge.

Research Aim

The objective is to propose and evaluate the relevance of a living lab methodology in simulated life-threatening emergency call situations where live video tools are introduced into the call sequence with the aim of developing skills, trust, and collaboration among all emergency chain stakeholders (bystanders, first responders, dispatchers, and paramedics).

Methods

Research Questions and Settings

The 2 objects of this study are apps that allow video feedback (Urgentime) and video demonstration of rescue actions (SARA) during vital emergencies for cardiac arrest and FBAO. The emphasis lies on 1 main research question (QR; QR1) and 2 secondary QRs (QR2 and QR3):

- QR1 focuses on the practitioner: does the inclusion of videos have an influence on the early treatment of a patient by a bystander in the context of an emergency call?
- QR2 focuses on the community: does the shared workshop have an influence on the building of a common frame of reference among stakeholders?
- QR3 focuses on the method: does the living lab methodology adapt to the needs and constraints of the stakeholders during the process?

The emergency medical communication center (EMCC) of the Geneva region (emergency number 144) in Switzerland is part of the University Hospitals of Geneva (HUG). In 2021, this center responded to 115,000 emergency calls from the entire region of Geneva (500,000 inhabitants and 120,000 cross-border commuters). Paramedics (50% of the team) or certified nurses (the other 50%) take calls, assess situations and patients, dispatch ambulances and other rescue teams, and assist callers in performing rescue procedures. Geneva's emergency medical system is a 2-tier (or 3-tier) system, with the paramedic ambulance as the first tier and an emergency physician as the second tier. The third level consists of a senior specialist physician. In addition to these professional teams, the center can dispatch volunteer first responders for OHCAs or choking situations. A "Save a Life" first responder community was created in 2019, which currently consists of 1500 people, who are notified by an alarm app (Momentum [DOS Group]). Sending instant notification to these first responders is extremely simple (with the push of a button) in the computerized aid dispatch system used by the dispatchers. These first responders usually arrive between 2 and 4 minutes before a paramedic ambulance.

Materials

Overview

The videos used during the experimentation come from SARA, an app developed by The Paris Fire Brigade in 2017. It consists of a smartphone or web application and a back office for the dispatch center. Dispatchers can transmit 1 of the 8 videos demonstrating life-saving techniques CPR and Heimlich maneuver, etc to the bystander. The first aid applications allow acting on the situation only when the volunteer arrives at the site, whereas SARA videos launch an initial relay of information with the calling witness. As the living lab is a living project that evolves based on the needs of the end users (in this case, citizens and dispatchers), choosing a flexible and diversified application was important and appealing to us.

InstantView is a web application that allows the dispatcher to see the patient and the environment through the caller's smartphone camera. The dispatcher sends a URL via SMS text message, and when the caller selects this link, the smartphone camera is activated. If the bystander has called the EMCC with the same phone as the one the link was sent to, there is no interruption in the audio communication. The video stream is simply added via data exchange (Wi-Fi, 4G, or 5G). Once the connection is established, the InstantView platform can also allow for documents or demonstration videos to be broadcasted on the smartphone that is connected directly to the EMCC's dispatcher. In light of this innovative context, this is a mixed methods study, which is divided into 3 parts, the first being a comprehension study, followed by 2 experiments (a pretest and living lab). The sequence of the steps is outlined in Figure 1.

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Figure 1. Gantt chart. T: task; WP: work package.

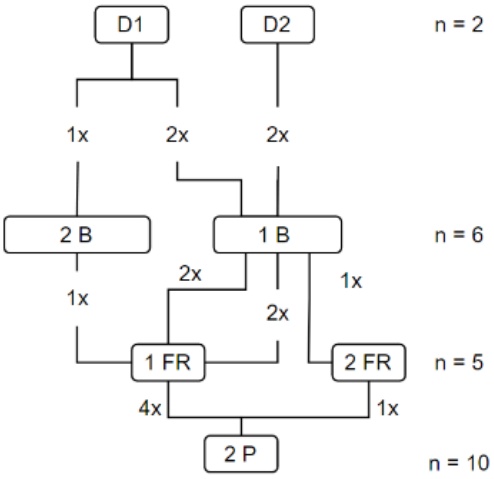
Months	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
WP 1 References framework																								
T1.1 Review state of the art	T1.1																							
T1.2 Bibliographic monitoring							T1.2																	
WP 2 Field studies																								
T 2.1 Study 1																								
T 2.1.1. Data collection							T2.1.1																	
T 2.1.2 Data analysis								T2.1.2																
T 2.2 Study 2																								
T 2.2.1 Methodological design									T2.2.1															
T 2.2.2 Data collection										T2.2.2														
T 2.2.3 Data analysis											T2.2.3													
T 2.3 Study 3																								
T 2.3.1 Methodological design													T2.3.1											
T.2.3.2 Data collection														T2.3.2										
T.2.3.3 Data analysis															T2.3.3									
T2.4 Evaluation																					T 2.4			
WP3 Valorisation																								
T3.1 Research valorisation									T 3.1															
T3.2. Public valorisation																		T 3.2						

Population

In the first study, there were 5 participants: 2 (40%) dispatchers, 1 (20%) dispatch coordinator, 1 (20%) assistant dispatcher, and 1 (20%) physician. Our objective was to obtain an overall view of the stakeholders at the center. We solicited the individuals currently working in the dispatch center and interviewed them on a volunteer basis. For the second study, we recruited 23 participants: 6 (26%) citizens, 2 (9%) dispatchers, 5 (22%) first responders, and 10 (43%) paramedics, distributed as shown in Figure 2.

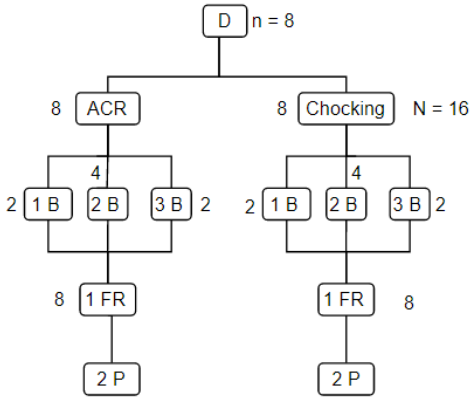
The citizens were solicited via the Geneva Association of Partner Patients, which is a network of former hospital patients who have registered as volunteers to participate in studies conducted at the HUG. There were no exclusion criteria in this study. The regulators were the volunteer regulators working on that day. As this study was planned within the context of the National Heart Day, jointly organized by the HUG, the ambulance service, and the Save a Life Association, we previously solicited first responders and ambulance attendants to participate in the simulations if they were interested. Concerning the third study, the distribution of participants was planned as shown in Figure 3. We were able to reach 34 citizens via the ads in social networks of the Geneva hospitals. Citizens who wanted to participate in a simulation were invited to register via the web. Those who received first aid training in the past 5 years and those were a health care professional were excluded from the study. We set a minimum threshold of 30 participants in congruence with studies on qualitative methods demonstrating saturation (the absence of contribution of new elements) beyond this number [45,46]. Of the 22 participants we recruited on a voluntary basis, 8 (36%) were dispatchers (each dispatcher carried out 2 simulations), 8 (36%) were first responders, and 6 (27%) were ambulance attendants.

Figure 2. Participant distribution in study 2 (n=23). B: citizens; D: dispatchers; FR: first responders; P: paramedics.



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Figure 3. Participant distribution in study 3. ACR: cardiac arrest; B: citizens; D: dispatchers; FR: first responders; P: paramedics.



Methodological Approaches and Data Collection

For the exploratory study, we constructed a semistructured interview guide that allowed us to collect the following information:

1. Description of the current procedure of a cardiac arrest call (eg, "Can you describe how a call is taken?")
2. Perceived benefits of and barriers to using an app to send emergency actions (eg, "In what situation do you think it would be beneficial to use SARA?")
3. Dispatcher needs (eg, "Would there be any other apps that you perceive as useful? Why?")

We conducted 5 interviews (with a mean duration of 24.14, SD 6.05 minutes).

During the pretest, 1 scenario was tested: "You find a 60-year-old unconscious man in Chaumettes Park. You call 144 and follow the instructions the dispatcher gives you." The dispatcher assesses the patient via audio communication. The patient turns out to be in cardiac arrest and the dispatcher sends the relevant demonstration video via SARA. The dispatcher then asks the participants to perform CPR on the mannequin until the paramedics arrive (8 minutes in the Geneva region). Save-a-Life first responders join the participant around the 6-minute mark.

The living lab tests 2 scenarios:

1. "You find a 60-year-old unconscious man. You call 144 and follow the instructions the dispatcher gives you." A live video feed allows for the assessment of the patient (Urgentime). Once the dispatcher diagnoses the patient as having a cardiac arrest, he sends the SARA recorded video demonstration of CPR. Participants start to perform CPR on the mannequin until the arrival of the ambulance (8 minutes in the Geneva region). Save-a-Life first responders join the participant around the 6-minute mark. Overall, 8 situations are performed with 1 participant and 8 with 2 participants.
2. "You encounter a panicked person with an infant who appears to be choking. You call 144 and follow the instructions the dispatcher gives you." A live video feed allows for the assessment of the patient (Urgentime). The dispatcher determines that the infant is experiencing sudden airway obstruction. The dispatcher sends the recorded video demonstration of the Mofenson maneuver. The participants are invited to perform the maneuver until the child cries (responsive mannequin) or until the situation deteriorates into cardiac arrest (2 out of 8 situations). Overall, 8 situations are performed with 1 participant and 8 with 2 participants.

All simulations were filmed and recorded in an audio format.

Collective elicitation interviews were conducted after each simulation with the respective participants (for approximately 24 minutes). Elicitation interviews [47] are an interview technique aiming for the interviewee to focus on their experiences and feelings during a particular event. The interviewer aims on deepening the lived experience and sensations while avoiding questions that lead to a rationalization of discourse [47,48]. This technique can be used with a single person or a group [43].

We built an interview guide that allowed us to collect the following details:

1. Feelings related to the use of the applications: benefits, constraints, and perceived helping elements (eg, the citizen was asked, "When you received the SARA video, how did you feel?")
2. Subjective contributions of the method: perceived contributions in terms of learning, understanding of the course of an action, and feeling of community (eg, the dispatcher was asked, "Did the simulation make you aware of elements that you had not perceived until then?")

Throughout the construction process of the living lab, an artist follows the preparatory meetings between researchers and stakeholders and collects information on how the living lab evolves based on the results of the preliminary experiment. They contribute to the added value by proposing to photograph a particularly crucial scenes coconstructed with the participants during the living lab.

Data Analysis

First, we transcribed all the audio recordings (interviews and debriefings), which allowed us to obtain a corpus for our studies 1, 2, and 3. In the filmed sequences (studies 2 and 3), we also recorded the times from the moment the dispatcher picked up the phone, including the recognition of the cardiac arrest, implementation of the emergency procedures, transmission of

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the video, and reception of the video. We then compared our data with those from the literature. We also noted the number of times the applications were not successful. We then categorized the different simulations into action sequences (discovery of the individual in need of emergency care, call for help, 144 call, evaluation of the individual's condition, implementation of gestures, arrival of the first responder, implementation of the defibrillator, and arrival of the paramedics) to compare the situations among them in terms of actions carried out (observations) and feelings (debriefings). Second, we performed a thematic analysis using ATLAS.ti (version 8.1; ATLAS.ti Scientific Software Development GmbH) on our corpus. Thematic analysis is a method that "consists of systematically identifying, grouping and, subsidiarily, examining the discourse of the themes addressed in a corpus" [49] by categorizing the verbatim accounts according to the themes of the QRs. Thus, for study 1, we had 3 main themes (OHCA procedure, interest in and obstacles to using SARA, and the need for regulators), which we were able to divide into subthemes (eg, for the OHCA procedure: an evaluation procedure, a procedure for implementing the gestures, and difficulties mentioned). Likewise, for study 2, we had 3 themes: the impact of SARA on care (with the subthemes difficulties, obstacles, and benefits mentioned), the benefits for the community (with the subthemes learning, awareness, and confidence), and the subjective evaluation of the method (with subthemes obstacles mentioned, bias, and elements to be modified). Finally, for study 3 as well, we had 3 themes: impacts of the applications (with subthemes SARA, InstantView, feelings related to use, and evoked benefits), evoked benefits of the method (confrontation with reality, training, feeling of federation, and discovery of the chain of survival), and subjective evaluation of the method (with the same subthemes as those of the study 2 counterpart). This categorization into subthemes allowed us to link the sequences of actions and the related feelings to understand which elements allowed for a positive feeling and which ones were more of an obstacle. Finally, for studies 2 and 3, we used the times we recorded to evaluate the reliability of the applications and their temporal impact. For quantitative analysis, we used Microsoft Excel (version 2016; Microsoft Corp).

Ethical Considerations

We provided a document to all the participants explaining that we were collecting data (photographic, audio, and video) as part of the research and that these data would be used only to analyze the process and as support for scientific presentations. At the beginning of the session, all the participants were asked to read and then sign the consent forms or indicate their opposition before the experiment. The analysis and presentation of the data and their results are anonymized (participants are identified using a coding system). The compensation offered was 1 hour of free training in first aid and emergency procedures by certified professionals. Each participant signed a General Data Protection Regulation consent form, providing permission for audio and video recording and the use of the recordings for research purposes.

Results

In this section, we present the results of the first 2 phases and elaborate on the results expected from the living lab.

Understanding Study

According to the physician who participated in our study, approximately 2 cardiac arrests occur each day in Geneva, 33% of which are in public areas (streets, public transport, etc). With cardiac arrest being first priority, the dispatcher has 90 seconds to send resources from the moment the telephone call starts. An automated cardiac arrest procedure appears when the dispatcher completes gathering the information related to the patient's condition, which is done according to a specific process. Currently, dispatchers can assess the patient via a video feed (Urgentime) or an audio phone call. First, they must obtain the patient's location and then assess their state of consciousness and breathing. If the patient is unconscious and if there is a breathing anomaly (or not), the dispatcher sends an ambulance as first priority, then sends a first responder via the Save-a-Life button, and helps the bystander perform CPR.

It appeared throughout the interviews that asking the bystander to perform CPR is a difficult task for the dispatchers. They described witnesses who were not always willing to come close to the patient during the assessment phase, "even to put their hand on the stomach [to check for breathing]." They specified that the bystander often does not perform CPR because they do not want to take responsibility for the action, and they are frightened.

When asked about the use of SARA videos, the dispatchers expressed that they would need the videos to be integrated directly into the computer-aided dispatch system to avoid going to a separate computer for the video. They also raised concerns about the target population of the application; individuals having a cardiac arrest and older adults are more likely to be at home. Nevertheless, they believed that the CPR video offered a benefit and could be an asset in motivating some hesitant witnesses. Dispatchers also expressed a need to be able to receive video feedback to "keep the connection with the caller." They could gain more insight into the bystander's actions: "you can see the CPR being performed and guide it further" and identify potential mistakes in the execution of CPR. "We think people understand and at the end of the day, what is done in reality may not look so good."

Preliminary Study

The dispatchers recognized the cardiac arrests in 1 minute and 9 seconds, 1 minute and 32 seconds, 1 minute and 21 seconds, 2 minute and 51 seconds, and 1 minute and 56 seconds after picking up the call. The video was described as "useful," "a good input," and "stimulating" by 83% (5/6) of the participants. Overall, they identified 2 advantages of using a video during CPR: a better posture and more accurate performance of CPR. The participants also valued having a sound that signaled each compression to perform. Thus, it was easier for them to follow the right chest compression rhythm compared with if they were alone. It aided the participants to synchronize with the video and follow the "right rhythm."

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Early feedback shows that the video had a reassuring effect on the participants emotionally affected by the situation: “emotionally it is quite strong, we imagine the person lying down.” As the dispatchers hinted during the exploratory study, the video does help initiate a massage in cases of hesitation by the witness. It also seems to reassure the bystander regarding the gestures they perform: “I was glad that I could have a link, to be able to see it, it made me feel secure.” Finally, the video provides comfort through words of support: “I felt more like I was getting good support, even encouragement to keep doing well.” The dispatchers also found that sending the video was reassuring: “the fact that they are watching, they are going to correct themselves and for us it is reassuring.” They also sensed more “serene” and “reassured” witnesses on the phone. However, in the subsequent interview with the dispatchers, they actually described being “falsely reassured” because they were ultimately unsure whether CPR was being performed or not, and the fact that they were sending the video prevented them from providing voice guidance over the phone. The simulations also allowed all the stakeholders within the survival chain to interact and collaborate. In contrast to what appears in the literature, professionals (first responders, paramedics, and dispatchers) did not consider the witness to be an obstacle but rather an additional resource to accomplish an essential act. A first respondent told us, “I have other skills; I will let the bystander do the massage.” The bystander can also maintain the link established with the emergency services “By the time the ambulance arrives, you start to get tired and being able to have someone who has a contact with the professionals, even psychologically, helps.” The bystander is, therefore, an additional resource that enables a more optimal distribution of the tasks carried out (a relay for compressions, placing the defibrillator patches, etc). However, both the first responder and the dispatcher must have confidence in the bystander to delegate. The first respondent obtains this trust based on whether the witness appears to be active, calm, and focused. As for the dispatchers, confidence is based on the witness’s ability to understand and respond. The simulation also led some participants to gain a better understanding of the regulation process. This could help prevent frustration in the future. For example, 5% (2/10) of the participants did not understand why they should not act immediately. The joint debriefing gave the dispatchers the opportunity to explain this process.

One of the first obstacles to consider are technical difficulties, as they increase the response time. When fully functional, as in simulation 1, the app enabled cardiac massage to begin within 3 minutes and 15 seconds. However, dispatchers stated that they were unsure whether they saved any time compared with audio guidance. In addition, as the application is still at the prototype stage, its stability is uncertain, and the transmission of video is not always optimal in terms of time or quality. We also chose to give all the participants the same “standardized” cell phone to avoid any differences in participants’ personal phones. However, this led to 2 problems: the difficulty in handling a new phone in an emergency and a very low output sound. Dealing with a phone that was not their own was described as an additional challenge, and even stressful, as the participants were not always able to identify where the speaker was located and where to go to get the SMS text message to open the video or web application on the phone loaned for the test. In a real emergency situation, it can be more complex to perform these simple gestures on one’s own phone; we can assume that the fact that they were given a new phone accentuated these confusing effects. Sound-related problems further negatively affected the handling of the patient. The participants also reported experiencing trouble hearing the instructions given by the dispatcher. As a result, the dispatcher sometimes had to repeat the instructions several times, and in some cases, the participants were unable to understand the action to be performed (especially in the evaluation phase). These elements led to a deterioration of the relationship between the dispatcher and the participant, as they prevented a proper establishment of communication. This can result in a feeling of isolation on both sides.

Results Expected From the Living Lab

The expected results for the practitioner are oriented toward a better handling of the patient by the bystander, both in terms of time and performance of the emergency procedures. For this purpose, a comparison will be made between OHCA and FBAO control situations (audio tapes of real situations) and simulations to understand whether the video saves time during the assessment of the patient’s condition (Urgentime) and the execution of first aid actions (SARA). A comparison of 1-witness situations with 2-witness situations will also be carried out to determine the most appropriate context for using videos. Therefore, we expect the situation to be easier to manage when there are 2 witnesses (one holding the phone and the other performing first aid). In addition, we will evaluate whether the use of live video and demonstration video can reassure the witness and possibly convince them if they are hesitant to perform emergency actions. Finally, we will evaluate whether the use of 2 functionalities (live video and demonstration video) leads to cognitive overload for the dispatcher.

As in the preliminary study, we expect that the shared experiences (simulations, debriefing, and artistic staging) would allow both populations to exchange and learn to collaborate. We expect effects in terms of knowledge transfer, mainly a better understanding of emergency procedures among the participants, and that enhancing communication (with videos) lead to better and faster trust building among the stakeholders. Analyzing the debriefings and the construction of the restaging process provide insights into the key elements for the participants as well as clues for future living lab–focused activities.

As in the previous study, the stakeholders will review and analyze the challenges encountered to facilitate the replication of the living lab tool kit in other emergency dispatch centers. In addition, they will assess the direct benefits (expected) and the secondary benefits (reported by the participants, but not anticipated).

Discussion

Overview

We collected results in 3 areas: practitioner, community development and method insights. The first area provided us

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subjective elements for understanding the effects of the inclusion of a video on the early treatment of a patient by a bystander. We were interested in understanding the effects on the experience of the different stakeholders, in particular, on the dispatchers. The second area focused on gathering evidence on whether the simulation developed a sense of community and collaboration among the participants. Finally, the third highlighted the contributions of the living lab methodology in terms of learning and confrontation with reality.

Principal Findings

Regarding the use of applications, the main results involve the identification of the dispatcher's feelings when using an application to help with emergency procedures. Indeed, they expressed that they felt substituted by the application because it took precedence over them, allowing them to neither follow the patient's treatment nor realize that there was a need to restart the guidance on the cardiac massage when there was a technical failure. From a community perspective, we found that all the stakeholders were willing to work together and that there was no reluctance on the part of dispatchers, paramedics, or first responders to work together. Citizens are seen as members of the chain of survival. Regarding the methodological aspect, we found that the approach is flexible and allows for the adaptation of scenarios according to new inputs from the previous steps. Consequently, we were able to integrate the needs of the regulators (feedback) and address the identified constraints. At this stage, the main results concern the fact that the simulation allows us to apprehend difficulties beyond those addressed; it allows us to identify the constraints of internal procedures or the effect of having 3 different tools simultaneously. This advantage is a result of the inclusion of all the stakeholders to ensure that the simulation resembles the reality as closely as possible. It could not have been detected in simulations with a single citizen and a dummy.

Comparison With Prior Work

The dispatchers expressed a strong interest in using a video feedback app to gain visibility of the situation and of CPR guidance, which is consistent with the literature reviewed [28,29]. Since the time this study was carried out, the central office has implemented the Urgentime app, which allows this video feedback. InstantView achieved results similar to those described for the GoodSAM app in the literature [30,31]. The app reaches a reliability of 80%, and allows the dispatcher to recover the view and facilitates the evaluation and guidance. In this setting, we coupled SARA (video demonstration) and InstantView (visual feedback), which has never been done before to our knowledge. The dispatchers showed an interest in testing an application that would allow them to send demonstrations of emergency procedures, as they admitted finding it difficult to convince a bystander to perform CPR just by guiding them via audio calls. Indeed, in the preliminary study, one reluctant bystander performed CPR because he felt "reassured" by the video. Research indicates that a demonstration video can improve CPR quality in terms of the rhythm, number, and depth of the compressions; reduction of interruptions; and accuracy of one's hand placement [32-36]. The depth and number of compressions could not be assessed in the preliminary study. However, when the participants followed the video, a more adequate and sustained rhythm was observed (owing to the rhythmic sound they heard), and their posture was more adequate (by mimicking the expert they saw). To conclude this section, we would like to highlight that a high level of investment is made by the EMCC in the deployment of all possible technological (Save a Life, SARA, and Urgentime) and human resources to improve the handling of cardiac arrests in line with recent European and international recommendations [2-4]. Researchers point out 3 main reasons behind the limited reliance on bystanders in emergency situations: citizens' fear of taking any action [18-20], professionals' mistrust toward them [21-24], and the absence of any prior collaboration [22,25]. Although the dispatchers confirmed this fear of action on the part of citizens during the exploratory study, the results of the preliminary study did not show this element. Some participants expressed that they were intimidated by the situation but felt reassured by the dispatcher's assistance. The dispatchers and first responders never reported any reluctance to rely on a bystander, in contrast to the literature. Furthermore, health professionals have developed skills to quickly assess whether the witness present can be a trustworthy relay. For first responders, it is a matter of seeing an active, calm, and focused person on the task. For the dispatcher, this consists of evaluating how the individual understands and responds to their questions while assessing the patient's condition. Within this short period to recognize cardiac arrest and start CPR, which, in Geneva, is limited to 90 seconds, the dispatcher already knows whether they are communicating with a reliable bystander. Throughout the preparation of the living labs, it became apparent that adapting to the needs of the different stakeholders was crucial to come as close to reality as possible and to try to secure a better commitment from the participants [40,41]. Initially, the end users selected for living labs were only dispatchers and citizens. However, during the exploratory study, we became aware that the Geneva EMCC was working closely with the first responder application Save a Life. Consequently, first responders were integrated into the simulations to remain as close as possible to a real-life cardiac arrest in the Geneva region, where first responders would be alerted. This highlights how the living lab is built upon a preexisting territory and is constantly evolving according to the feedback provided by, difficulties encountered by, and needs and expectations of the stakeholders. Regarding experiential learning [44], we found that the simulations provoked strong emotions in the participants, which is a prerequisite for this learning to occur. We also found that the debriefings were a space to exchange new knowledge with the bystanders, potentially facilitating future collaboration [40,42]. To evaluate the retention rate of knowledge, we will conduct a debriefing with the participants in 6 months.

Strengths

The main strength of these studies is the adoption of a perspective that allows the comprehension of emotions and subjective evaluation of the impact of the applications and of the methods used among the various stakeholders. This perspective makes it possible to document aspects that were not previously addressed. In particular, it allowed us to discover

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that the use of applications provoked uncertainty in the dispatcher, an aspect that had not been detected in the simulations in the other studies mentioned in the literature. The integration of all the actors of the survival chain can potentially have a concrete effect on the real care provided in Geneva, as it enables the community to gain a better understanding of each other and to collaborate more efficiently. The aims of our studies are to not only evaluate an application in technical terms but also use the experiments as a pathway to work on the development of collaboration.

Limitations

The main limitation of this study is that the pretest was conducted in the context of National Heart Day, so the citizen volunteers were all sensitive to the issue, and none of them refused to perform cardiac massage. Moreover, the fact that it was only the dispatchers who wanted to participate biased the results because we could not know the possible resistance to using this application. Finally, to achieve broader community development, ongoing sessions of a regular living lab is required with various communities; however, this process is costly in terms of time and investment from all the stakeholders, making it difficult to implemented to be on a large scale.

Data Availability

The data sets generated during or analyzed during this study are not publicly available because of the right to privacy but are available from the corresponding author upon reasonable request.

Conflicts of Interest

None declared.

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Abbreviations

CPR: cardiopulmonary resuscitation
EMCC: Emergency Medical Communication Center
FBAO: foreign body airway obstruction
HUG: University Hospitals of Geneva
OHCA: out-of-hospital cardiac arrest
QR: research question

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Proposal

“An Ounce of Prevention is Worth a Pound of Cure”: Proposal for a Social Prescribing Strategy for Obesity Prevention and Improvement in Health and Well-being

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Abstract

Background: Social and behavioral determinants of health are increasingly recognized as central to effective person-centered intervention in clinical practice, disease management, and public health. Accordingly, social prescribing (SP) has received increased attention in recent times. The rampant global prevalence of obesity indicates that the customary, reductionistic, and disease-oriented biomedical approach to health service delivery is inadequate/ineffective at arresting the spread and mitigating the damaging consequences of the condition. There is an urgent need to shift the focus from reactive downstream disease-based treatments to more proactive, upstream, preventive action. In essence, this requires more effort to affect the paradigm shift from the traditional “biomedical approach of care” to a “biopsychosocial model” required to arrest the increasing prevalence of obesity. To this end, an SP approach, anchored in systems thinking, could be an effective means of moderating prevalence and consequences of obesity at a community level.

Objective: The proposed SP intervention has the following three key objectives: (1) build a sustainable program for Circular Head based on SP, peer education, and health screening to minimize the incidence of obesity and related lifestyle diseases; (2) increase service and workforce connectivity and collaboration and initiate the introduction of new services and activities for obesity prevention and community health promotion; and (3) enhance health and well-being and minimize preventable adverse health outcomes of obesity and related lifestyle diseases through enhancement of food literacy and better nutrition, enhancement of physical literacy and habitual personal activity levels, and improvement of mental health, community connectedness, and reduction of social isolation.

Methods: This paper describes a prospective SP strategy aimed at obesity prevention in Circular Head, a local government area in Northwest (NW) Tasmania. SP is a prominent strategy used in the Critical Age Periods Impacting the Trajectory of Obesogenic Lifestyles Project, which is an initiative based in NW Tasmania focused on assessing obesity prevention capacity. A social prescription model that facilitates the linkage of primary health screening with essential health care, education, and community resources through a dedicated “navigator” will be implemented. Four interlinked work packages will be implemented as part of the initial plan with each either building on existing resources or developing new initiatives.

Results: A multimethod approach to triangulate insights from quantitative and qualitative research that enables the assessment of impact on individuals, community groups, and the health care system will be implemented within the initial pilot phase of the project.

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Conclusions: Literature is replete with rhetoric advocating complex system approaches to curtail obesity. However, real-life examples of whole-of-systems interventions operationalized in ways that generate relevant evidence or effective policies are rare. The diverse approach for primary prevention of obesity-related lifestyle diseases and strategies for improvement of health and well-being described in this instance will contribute toward closing this evidence gap.

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KEYWORDS

capacity building; community development; determinants of health; health care delivery; health care management; obese; obesity; patient education; peer education; prevention; screening; service delivery; social prescribing; social prescription; weight

Introduction

Despite the absence of a widely accepted definition, social prescribing (SP) generally refers to the enablement of health care professionals to refer a patient or client to a social prescriber (eg, link worker, community connector, community navigator, health coach, health trainer, and so on). The social prescriber is responsible for the co-design of interventions to improve the individual's health and well-being [1]. Once seldom acknowledged, or at best, paid "lip service," social and behavioral determinants of health are now becoming increasingly more recognized as centrally critical to the provision of effective person-centered intervention in clinical practice and disease management [2]. Accordingly, a spate of SP-based interventions have been reported in recent times, including those from the United Kingdom and Americas [3], Scandinavia [4], and Australia [5,6]. Despite a paucity of definitive evidence regarding SP, benefits cited include improvements in health behaviors, mental health, and reductions in the use of tertiary care facilities for lifestyle diseases [1,7-10].

Obesity, one of the more prominent contemporary lifestyle-related diseases, has reached pandemic proportions globally and shows no signs of abating [11,12]. Consistent with global trends, the prevalence of obesity in Australia has increased in the past few decades, with 63.4% of adults and 27.6% of children with overweight and obesity in 2014-2015 [13]. If left unchecked, adult obesity and rates of severe obesity in Australia are predicted to reach 35% and 13%, respectively, by 2025 [14]. A further complication is that people living in geographically remote parts of Australia have a disproportionately higher prevalence of obesity. For instance, adults from regional (1.53 times higher) and rural areas (1.32 times higher) were more likely to have obesity than their counterparts from major city or urban areas [15]. Obesity also disproportionately affects low socioeconomic communities with a greater disease burden [16]. Tasmania, as a regional state with low socioeconomic status, has some of the highest rates of adult and childhood obesity and requires urgent intervention.

The rampant global prevalence of obesity is also an indication that the prevailing, disease-oriented biomedical approach to health service delivery is inadequate/ineffective at arresting the spread and mitigating the damaging consequences of the condition [17]. There is an urgent need to shift the focus from reactive disease-based treatments to incorporate some consideration of how individuals and communities are influenced by a growing global, regional, and local interdependence and an increasingly complex array of interlinking factors. Accordingly, more proactive, upstream, preventive efforts, and action to improve health and reduce obesogenic factors are required to arrest the increasing prevalence of obesity [18]. In essence, this requires a paradigm shift from the traditional "biomedical approach of care," wherein the cause of illness is primarily thought to reside in the body, to a "biopsychosocial model," which provides a basis for understanding the broader determinants of disease to arrive at treatment and service response plans [19].

Recent evidence from whole-of-community approaches anchored in systems science principles holds some promise in denting the harmful impact of obesity [20-22]. Dynamic systems theory posits that biological, social, and contextual factors interact in dynamic ways to influence health and participation across the lifespan [18]. Bronfenbrenner person-centered ecological framework allows the varied interactive interpersonal dynamics that influence development (and therefore health and obesity) to be examined [23]. At the center of the system, the individual brings their own unique characteristics, such as their age, genetics, life experiences, temperament, and coping strategies, and other familial, social, economic, and political layers of influence that sit around them [23]. Fundamentally, effective whole-of-system approaches are not limited by predefined agendas; instead, they are reliant on localized community input for context-specific, holistic, preventive work that acknowledges the synergistic interaction of a myriad of biological, social, economic, and environmental factors [24]. This approach has a commonality with effective SP interventions [25]. Following this logic, a community-driven SP approach could be just as effective in obesity prevention as any other initiative anchored in systems thinking. Herein, we discuss an SP protocol aimed at obesity prevention in Circular Head, a local government area (LGA) in Northwest (NW) Tasmania.

Methods

Ethical Considerations

Ethics approval was obtained for all procedures from the Human Research Ethics Committee (Tasmania) Network (H001864) and will be implemented in accordance with relevant guidelines and regulations stipulated in the Declaration of Helsinki. Both written and verbal consent (where practicable) will be obtained from all participants. This work was funded by a National Health and Medical Research Council (NHMRC) grant as part of the Critical Age Periods Impacting the Trajectory of Obesogenic

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Lifestyles (CAPITOL) Project. The study funder had no role in study design, collection, analysis, or interpretation of the data, in writing the report, or in the decision to submit the article for publication. The contents of this article are the responsibility of the authors and do not reflect the views of the NHMRC.

Setting: CAPITOL Project NW Tasmania

The CAPITOL Project is a community-based "systems thinking" initiative based in the NW with an intentional focus on assessing obesity prevention capacity (OPC), engaging the community in developing OPC, and evaluating OPC development efforts. The central tenet of this work acknowledges the sustained multidisciplinary collaborations required to manage lifestyle risk factors, including nutrition, physical inactivity, smoking, and mental health, which can either be a cause or a consequence of excess adiposity. While NW Tasmania represents an expansive land mass, for reasons of practicality, the CAPITOL project operations are limited to 3 sentinel sites (Burnie, Circular Head, and Devonport). Sentinel sites are communities from which in-depth data can be collected, which has a high degree of transferability [26].

The current health profile of NW Tasmania, combined with its predominantly rural, geographically dispersed and socioeconomically disadvantaged population, is a hotbed for the proliferation of lifestyle-related disease. By virtue, the region also has a high demand/need for health promotion [27,28]. Nonetheless, the existing preventive health system in the region is underdeveloped and underresourced, which compounds existing health issues and stymies the progress of well-intentioned preventive efforts [29]. In addition to the lack of resourcing, the predominant narrative in the region has traditionally been a deficit-based view of health. To help circumvent these challenges, the holistic systems design of the CAPITOL Project is focused on asset-based community development alongside a primary prevention focus (ie, keeping healthy people healthy) with heightened attention on critical life stages (ie, mothers, infants, children, adolescents, and so on).

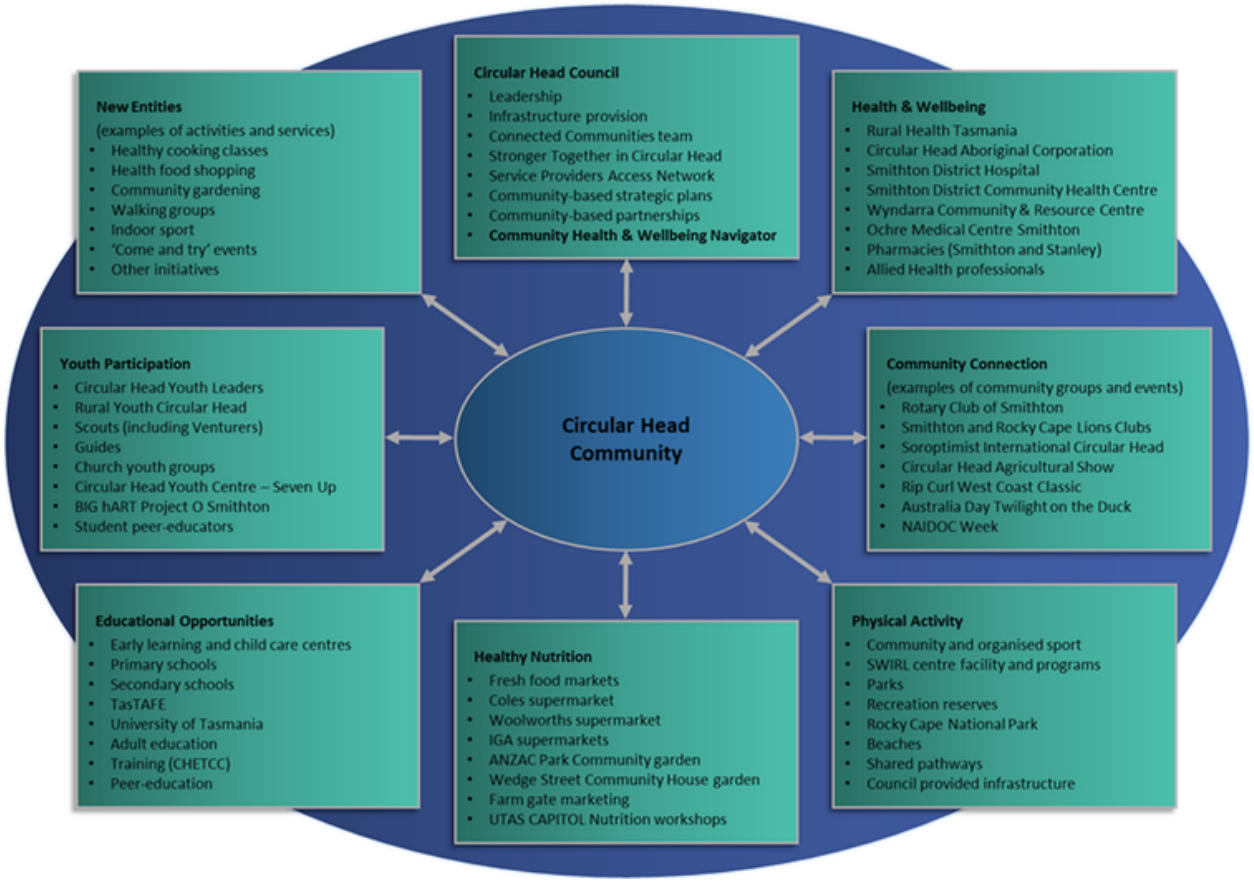
Context: Circular Head

Consistent with other socioeconomically disadvantaged and remote areas, the Circular Head community displays an elevated prevalence of "risk factors" that contribute to adverse health and well-being outcomes. For instance, over 95% and 54% of the population does not meet the vegetable and fruit intake guidelines, respectively [30]. Further, one-fourth of the adult population do not take part in sufficient levels of moderate and vigorous physical activity (PA). Unfortunately, many of these risks are associated with the social determinants of health, including educational attainment, employment status, and housing conditions [31,32]. Low levels of health literacy, particularly in relation to food and PA, help to exacerbate the suboptimal health profile of the LGA (CAPITOL, unpublished data).

Poor access to health professionals, including in allied health, medicine, nursing, and midwifery, is also endemic in the area [33]. Recent situational analyses revealed significant shortages of general practitioners, specialists, dietitians, exercise physiologists, and physiotherapists in Circular Head. Many health professionals are itinerant with the community, frequently enduring long wait periods for health care, extensive travel to access health care, and poor availability and access to preventative health care options (CAPITOL, unpublished data). Despite the availability of a range of community and health services (Figure 1), there is also a perceived lack of preventive services and health promotion interventions in the region. While explanations for the shortcomings cited are manifold, primary reasons include poorer community engagement, a declining volunteer base, and adverse climatic conditions (CAPITOL, unpublished data).

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Figure 1. Assets and strengths of Circular Head.



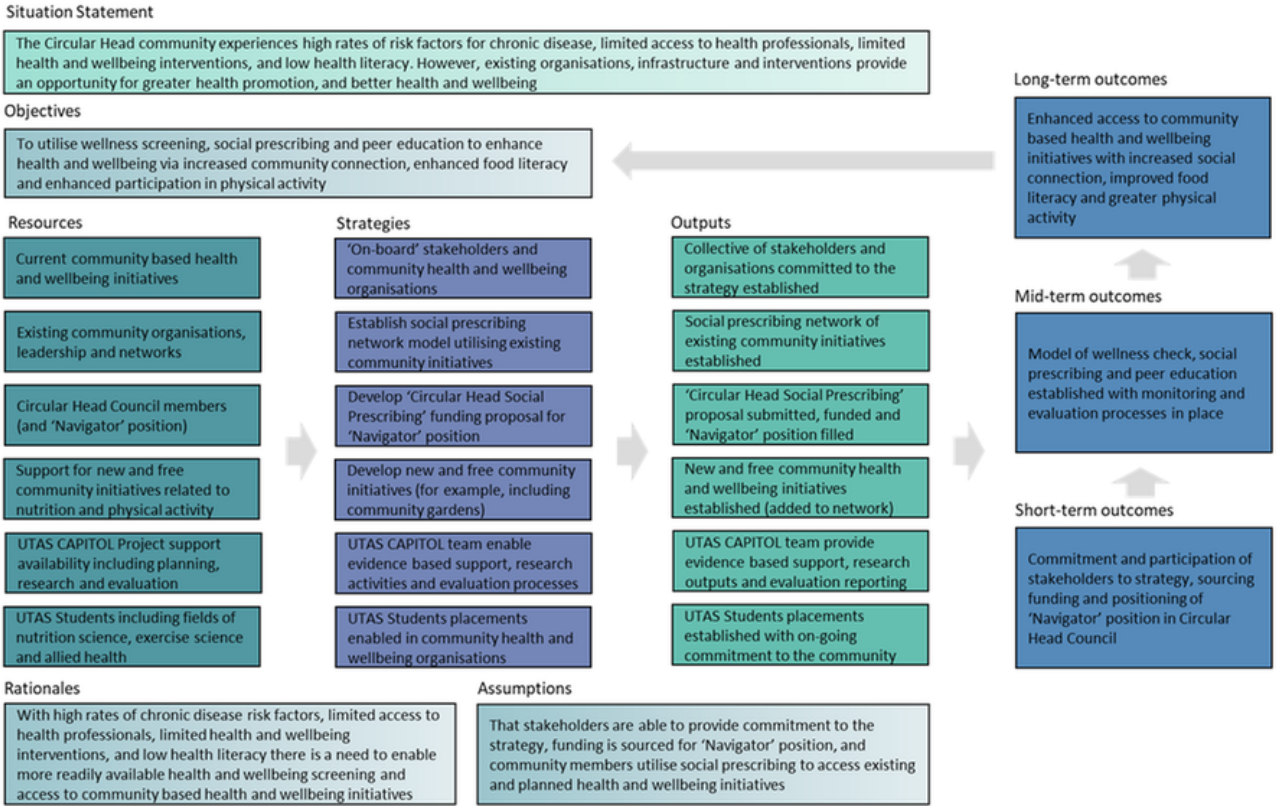
Objectives

Despite the challenges, the Circular Head region has many significant assets that, if utilized optimally, may enable and help sustain community-driven change (Figure 1). To maximize success, there is an urgent need to link existing strategies, networks, committees, infrastructure, community-based interventions, organizations, and partnerships (Figure 2). The harnessing of existing capacity requires buy-in and leadership from local government and service organizations in the community.

The proposed SP intervention has the following three key objectives: (1) to build a sustainable program for Circular Head based on SP, peer education, and health screening to minimize the incidence of obesity and related lifestyle diseases; (2) to increase service and workforce connectivity and collaboration and initiate the introduction of new services and activities for obesity prevention and community health promotion; and (3) to enhance health and well-being and minimize preventable adverse health outcomes of obesity and related lifestyle diseases in the Circular Head LGA through enhancement of food literacy and enabling better nutrition, enhancement of physical literacy and increasing habitual personal activity levels, and improvement of mental health through increased community connectedness and reduction of social isolation.

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Figure 2. Circular Head social prescription logic model.



Strategy Mix

Theoretical Background

Historically, overcoming obesity has proven to be extremely challenging given the multifarious etiology of the condition, including individual and societal influences [34]. Prevention of contemporary lifestyle diseases, including obesity, requires multilevel, strategic, cross-sectoral, and systems-thinking solutions implemented in a practice environment supported by realist and capacity building approaches [35-41]. As such, all health promotion and the SP that derives from this research will be guided by realist principles, situated, and informed by evidence, and local context. The identification of context-mechanism-outcome configurations applicable to a variety of scenarios will be utilized to gather intel and explore causal mechanisms of the current lifestyle-related disease predicament in Circular Head.

Project Governance

The University of Tasmania (UTAS) will be the facilitating partner and legal entity responsible for this place-based project. The Circular Head Council will act as the intermediary organization along with key stakeholders to ensure place-based representation and insights. All procedures are informed by the specifications of the Human Research Ethics Committee (Tasmania) Network and will conform to the guidelines of the NHMRC's National Statement on Ethical Conduct in Human Research 2007 (updated 2018). To this end, both written and informed consent will be obtained from the participants where practicable. A project steering group (ie, Circular Head Health and Well-being Coalition) will be formed with the imprimatur of key place-based partners and composed of members from the wider stakeholder group. Key stakeholders will be identified in a process of individual stakeholder consultation and stakeholder identification (through purposive sampling using publicly accessible contact information and professional networks) in line with the methodology of the formative stage of the CAPITOL Project. Specifically, key stakeholders will be individuals living in the sentinel site with attributes including high levels of interest, influence, expertise, or community connection as evidenced by occupational position/role, social standing in the community, or as nominated by other stakeholders consulted in previous community consultations. Each step of the governance process will be structured to ensure that the voice of key stakeholders informs or guides the research and the interpretation of findings across each work package. The Circular Head Council will be responsible for oversight of the co-design, development, and implementation of the project, with accountability for outcomes and impacts intended to be shared by all parties involved.

Project Implementation

Overview

Overall, a social prescription model that facilitates the linkage of primary health screening with essential health care resources through a dedicated navigator will be implemented. Four (interlinked) main work packages will be implemented as part of the initial plan with each focus either building on existing resources or developing new initiatives (Figure 3). The opportunity to partake in this SP initiative will be open to all residents of the Circular Head LGA with recruitment exclusively based on convenience and snowballing. While the realist approach and the fluidity of study confines (as is typical for most SP interventions) renders precise a priori sample size

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calculations nonviable, where practicable, we intend to recruit as many participants as needed to achieve meaningful outcomes. For instance, the upper limit of the sample size for focus groups will be based on the attainment of "theoretical saturation."

Figure 3. Social prescription model.



Health and Well-being "Checkup"

The primary aim of health and well-being "checkup" screening is to assist in the accurate identification and assessment of causative risk factors for poor health outcomes. This would involve regular community-level lifestyle screening at local events, workplaces, and sporting groups by qualified as well as trainee (eg, nutrition science, exercise science, nursing, and medical students) health care professionals. It is anticipated that these additional checkups will complement the extant visitations to health care professionals (eg, general practitioners, specialists, and allied health professionals), although they are not intended to replace any existing service. Overall, the checkups will initiate the SP referral process that will primarily be managed by a dedicated navigator.

Health and Well-being "Navigation"

Linking assessment and referral to community resources will be realized via a navigator or "link worker." As evidenced in literature to date, SP protocols in the past have utilized a wide array of (mostly) health workers for the navigation role [6]. Responsibilities of the link worker can be manifold and may include coproducing health goals and action plans, enabling of resident-health service and activity interaction, and providing feedback at multiple stakeholder levels. Existing evidence indicates that such roles have been particularly efficacious in disadvantaged communities where more intensive support is inherently required due to accentuated complexity of health challenges [42]. In this study, the navigator would be employed by the Circular Head LGA and act as the conduit between residents, health care services, and preventive activities.

Community "Education"

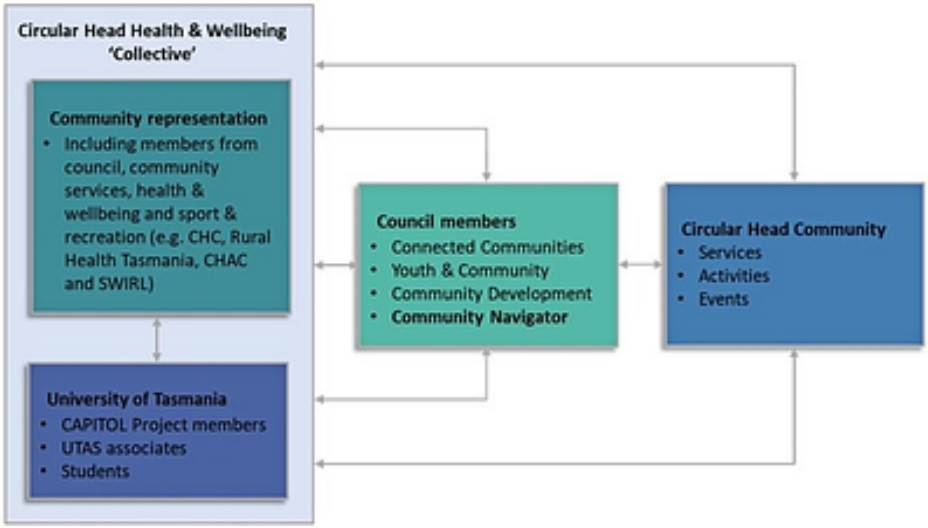
Peer education is the process of learning and sharing information with peers in the community and is a key strategic component to amplify health and well-being messaging. In this proposed work model, community educators are tasked with providing community outreach and incentivizing people to seek appropriate health information outside of traditional educational confines. Upskilling community volunteers and leaders would provide a source of community-based support and education for other components of the strategy. Specifically, a smorgasbord of group-based education sessions cofacilitated by project staff, generation of culturally and contextually appropriate education material, and the provision of appropriate technologies to provide information on nutrition and PA will be of central focus within this package. Working examples will be drawn from existing programs such as the Family Food Patch program which uses peer education to help improve health and well-being of Tasmanian children and families through promotion of healthy eating and PA.

New Health and Well-being Activities

This strategy entails the development of new nutrition, PA, and social connection activities to complement existing services and initiatives. A key component of this work model will include the establishment of the Circular Head Health and Well-being Coalition (Figure 4), which will provide guidance and direction for all co-designed health promotion activities within the SP framework. The basis of the coalition is entrenched in the legacy partnerships between the CAPITOL Project and the Circular Head Council and will be emboldened by further collaboration with community and service organizations, including Rural Health Tasmania, Circular Head Aboriginal Corporation, and the Smithton Well-being Indoor Recreation and Leisure center. While it is premature to confirm precise details about the potential activities in this SP initiative, extant literature highlights examples of multifarious "prescribing schemes" including arts, books, education, and exercise [43].

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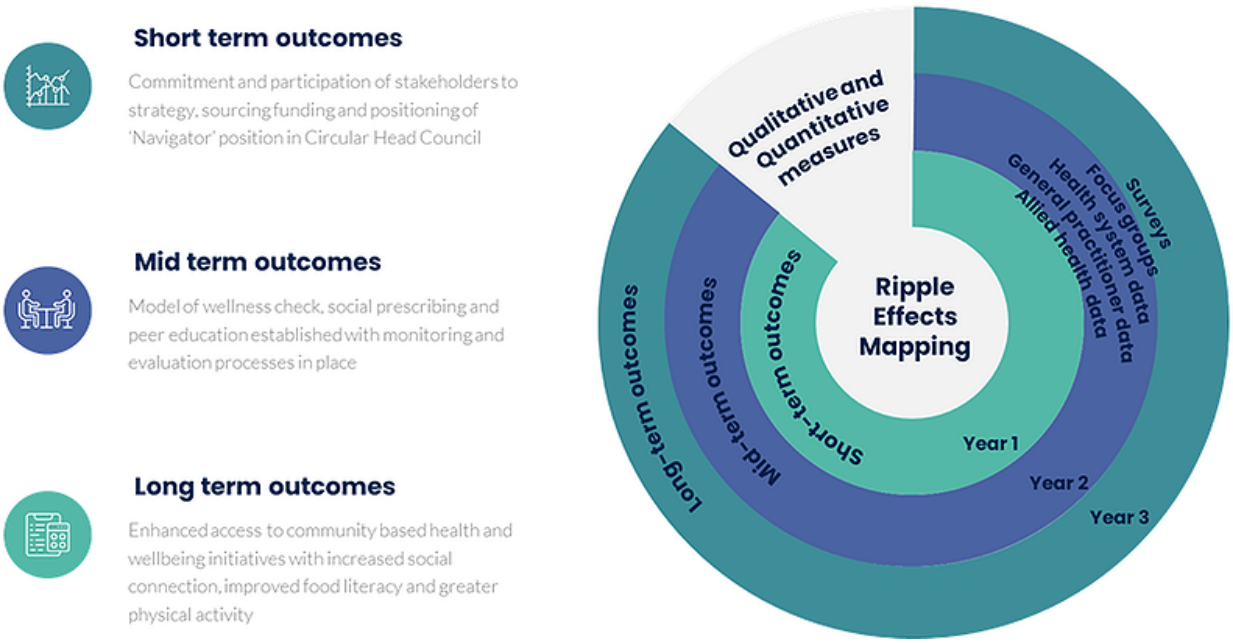
Figure 4. Organizational structure of the Health and Well-being Coalition.



Results

It is imperative that SP models undergo rigorous evaluation using systems science approaches and mixed methods research to ensure understanding of what worked, why it worked, and in what contexts. A multimethod approach to triangulate insights from quantitative and qualitative research that enables the assessment of impact on individuals, community groups, and the health care system will be implemented within the initial 3-year pilot phase of the project. For instance, a range of health and well-being and health care usage outcomes will be measured (Figure 5) to evaluate the efficacy of the SP program. Evaluation will include a review of implementation efforts, project impacts, plans for sustainability, and feedback from participants, educators, administrators, and stakeholders.

Figure 5. Summary of outcome and evaluation strategies. Notwithstanding the complexities of simultaneous measurement of numerous interlinked components of the systemwide SP initiative, a robust set of evaluative frameworks will be applied to all levels (development, formative and summative) and activities.



Given traditional evaluation tools are often ill-suited for co-design work in community settings, we intend to use a ripple effects mapping approach, a participatory technique to engage stakeholders in visually mapping project efforts and results to collect impact data [44]. Specifically, focus group techniques to work with participants to process and reflect on their lived experiences and collectively and visually map project efforts and results. We envisage that the use of mapping will trigger verbal responses, increase the frequency and depth of responses, and aid participants in recalling, organizing, and reflecting on experiences. It is intended that a series of modified nominal group technique (mNGT) consensus method group processes will be executed annually to evaluate progress. The core steps (silent generation, round robin, clarification, and voting [ranking and rating]) [45] of the mNGT approach will facilitate collaborative decision-making and, importantly, enhance equitable participation of stakeholders. Where possible, the progress of key components will also be compared against the

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5 pillars (a common agenda, shared measurement systems, mutually reinforcing activities, continuous communication, and backbone support organizations) of the "collective impact" framework [46].

Exact details of the outcome measures will be decided in consultation with the community, as their suitability will be based on nature of referrals, prescribed activities, participant needs, and resourcing. Nevertheless, in line with the popular approaches in contemporary SP initiatives, it is envisaged that a mix of subjective well-being, quality of life, behavior change, physiological changes, frequency of health service access, medication usage, and development of social networks will be measured either quantitatively or qualitatively [43,47]. In addition, where practicable, the social return on investment will also be measured using contextually appropriate inputs [48,49].

Discussion

This proposal describes a diverse approach for primary prevention of obesity-related lifestyle diseases and strategy for improvement of future health and well-being in a remote and socioeconomically disadvantaged population. The SP approach anchored in systems thinking described above could be an effective means of moderating prevalence and consequences of obesity at a community level. Key focal points of this intervention include peer education, health screening, service accessibility, workforce connectivity, food literacy, better nutrition, physical literacy, habitual PA, mental health, social isolation, and community connectedness. The Circular Head Health and Well-being Coalition will be established to address health and well-being inequities affecting people in the region. This collective will be responsible for providing direction for the implementation of the whole-of-community Circular Head Health and Well-being Strategy, broadly based on principles of SP.

As per the global accord in contemporary times, Australia also has a health care system that has a treatment-oriented and reactive bias. For instance, the extant 31 Primary Health Networks of Australia that prioritize mental health, First Nation people's health, population health, health workforce, digital health, aged care, and alcohol/drugs are fundamentally designed for "commissioning of health services" for consumers with diagnosed conditions. Further, Australia is one of the lowest spenders on preventive health (~2 billion per annum; ~1.5% of the total health budget; ~US $89 per person every year) among the Organisation for Economic Co-operation and Development nations such as Canada, the United States, and New Zealand. This is despite public health research consistently indicating that most preventive health interventions are cost-effective (mainly through cost reductions in treating complex conditions), improve quality of life and longevity, and minimize the burden on the health care system as a whole [50]. Therefore, considering the urgency of obesity prevention and health intervention in Circular Head, the SP approach we describe is both timely and necessary.

The effectiveness of an SP initiative may also rely on the collective buy-in from the wider stakeholder group, including, most importantly, the community members. As such, consistent and frequent education regarding the nature and benefits of the program from inception to conclusion will be vital. Further, expansive networking and development of governance structures that entail strong leadership from all stakeholder groups is also of utmost importance. The whole-of-systems approach proposed in this research with SP as the central tenet is expected to address all of the above and improve community cohesion, social engagement, reciprocity in peer support, and community confidence in accessing pertinent resources for improving health and well-being outcomes. Community ownership of public health initiatives has shown significant promise in other settings [51-54], with a satisfactory compromise between community lived experience and contemporary scientific evidence being the key driver of success.

Translation of lifestyle disease–related research findings into sustainable practice is a public health priority. However, existing research indicates that this transition is largely ineffective due to limitations such as insufficient scaling-up for systemwide integration and lack of emphasis on the nonlinear and complex overlapping of various (development, implementation, sustainment, etc) program stages [55-57]. Much of the existing evidence base being underpinned by linear models of cause and effect is also exacerbating this issue. The whole-of-systems approach of the CAPITOL Project, along with 3 years of preliminary work [58-60] and early and frequent engagement of stakeholders in all aspects of project planning, is expected to elicit maximal translatory potential of the current SP initiative. Further, community-wide, representative consultation and equity in decision-making and agenda setting is also considered best practice in this line of intervention [53].

This proposed SP approach can have several limitations. Despite the potential benefits, a robust and generalizable protocol for satisfactory data collection and evaluation of any SP protocol will be challenging. For instance, given the inherent heterogeneity of designs in SP initiatives [61], it is not feasible to gain a wider consensus on the most appropriate outcome measures [62]. Further, nonlinearity of SP initiatives and the inevitability of multiple, fleeting, and intersecting components can also exacerbate this complexity [63]. Consequently, we posit that a realist approach, which acknowledges a set of context-specific outcomes (both biomedical and social determinants) of importance, will yield the most effective SP system in any given setting. As the outcomes will be reliant on local contextual factors, the generalizability of the findings will also be limited and might not be particularly applicable outside of the area under study. Further, any number of commonly reported practical challenges to generating evidence around SP, such as forging collaborative relationships while maintaining researcher independence, lack of a control group for outcome comparison, accuracy of health and social care service usage data, sustained resourcing, and consent and privacy matters, can also be relevant in this instance [64].

The need for complex processes and outcomes that drive change within a whole system and the necessity of doing away with linear approaches to mitigating complex public health issues has been echoed consistently in recent times [65]. Nevertheless, the practicalities of real-life implementation of whole-of systems approaches are ill-defined. This proposal describes a practicable

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set of approaches for stakeholder engagement and community participation in uplifting health and well-being standards in a locality with poor socioeconomic and health outcomes.

The Tasmanian Charter of Health Rights and Responsibilities states the following:

> *When viewed as a partnership, the relationship between the health service consumer and the health service provider is more likely to benefit the health outcomes of the service consumer. While the health service provider has a responsibility to meet certain rights of the health service consumer, the consumer in turn, should also assume some responsibility for their own health care.*

The proposed SP initiative will provide a viable opportunity to the residents in Circular Head to have a real-life, at scale attempt to co-design a sustainable solution to their health and well-being challenges while inculcating democratic partnerships between all project members as collaborators through every stage of the project. Further, the proposed program will help to increase access to peer and other support workers able to assist community members to navigate the system and receive adequate, timely, and situational support—a need frequently highlighted in the region [66].

Acknowledgments

The authors would like to thank members of the Circular Head community for their ongoing engagement in this work.

Data Availability

The data sets generated during or analyzed during the current study will be available from the corresponding author on reasonable request.

Authors' Contributions

SJ and APH contributed in conceptualization/design of the study, formulating research questions, writing, and editing drafts. RS, KAEP, KDKA, RH, SM, TPH, LD, and NMB carried out conceptualization or design of the study, review, and editing of the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

CAPITOL: Critical Age Periods Impacting the Trajectory of Obesogenic Lifestyles
LGA: local government area
mNGT: modified nominal group technique
NHMRC: National Health and Medical Research Council
NW: Northwest
PA: physical activity
OPC: obesity prevention capacity
SP: social prescribing

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Protocol

A Computational Platform to Support the Detection, Follow-up, and Epidemiological Surveillance of Mental Health and Substance Use Disorders: Protocol for a Development and Evaluation Study

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Abstract

Background: According to the World Health Organization, approximately 15% of the global population is affected by mental health or substance use disorders. These conditions contribute significantly to the global disease burden, which has worsened because of the direct and indirect effects of COVID-19. In Mexico, a quarter of the population between the ages of 18 and 65 years who reside in urban areas present a mental health condition. The presence of a mental or substance abuse disorder is behind a significant percentage of suicidal behaviors in Mexico, where only 1 in 5 of those who have these disorders receive any treatment.

Objective: This study aims to develop, deploy, and evaluate a computational platform to support the early detection and intervention of mental and substance use disorders in secondary and high schools as well as primary care units. The platform also aims to facilitate monitoring, treatment, and epidemiological surveillance ultimately helping specialized health units at the secondary level of care.

Methods: The development and evaluation of the proposed computational platform will run during 3 stages. In stage 1, the identification of the functional and user requirements and the implementation of the modules to support the screening, follow-up, treatment, and epidemiological surveillance will be performed. In stage 2, the initial deployment of the screening module will be carried out in a set of secondary and high schools, as well as the deployment of the modules to support the follow-up, treatment, and epidemiological surveillance processes in primary and secondary care health units. In parallel, during stage 2, patient applications to support early interventions and continuous monitoring will also be developed. Finally, during stage 3, the deployment of the complete platform will be performed jointly with a quantitative and qualitative evaluation.

Results: The screening process has started, and 6 schools have been currently enrolled. As of February 2023, a total of 1501 students have undergone screening, and the referral of those students presenting a risk in mental health or substance use to primary care units has also started. The development, deployment, and evaluation of all the modules of the proposed platform are expected to be completed by late 2024.

Conclusions: The expected results of this study are to impact a better integration between the different levels of health care, from early detection to follow-up and epidemiological surveillance of mental and substance use disorders contributing to reducing the gap in the attention to these problems in the community.

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KEYWORDS

computational platform; mental health; substance use; epidemiological surveillance; digital screening; substance use disorder; suicidal behavior; level of health care; mHealth; substance abuse; addiction; mental health and addiction; addict; IVDU; intravenous drug; opioid

Introduction

Background

According to the World Health Organization (WHO), health is not merely the absence of a disease, but it is a state of complete physical, mental, and social well-being [1]. Nevertheless, it is estimated that the number of individuals who have a mental disorder worldwide is approximately 792 million, representing 10.7% of the world population. This percentage is increased to 15% when individuals presenting conditions associated with substance abuse are considered [2]. The consequences of mental and substance use disorders are highly negative; in 2010, these disorders constituted 10.4% of the global burden of disease and were the leading cause of years lived with disability among all disease groups [3]. Moreover, these problems have been exacerbated because of the direct and indirect effects of COVID-19 as already evidenced in recent studies [4-8]. Mental and substance use disorders also produce high mortality rates. For example, major depression (the most prevalent mental disorder in the world population) is the main cause of the 800,000 suicides committed every year [9]. Other studies estimate 585,000 deaths only in 2017 associated with the addiction of different substances such as hepatitis C, liver cancer, or cirrhosis [10].

Mental health and substance use problems are also present in Mexico. According to the results obtained from the WHO World Mental Health Survey Initiative, one-fourth of Mexican respondents aged 18 to 65 years and residents in urban areas present with a mental health condition [11]. The most frequent mental disorder was anxiety, followed by other affective disorders such as depression and substance abuse. These results vary according to the sex of the individuals; men reported a more significant number of substance abuse disorders (particularly alcohol) than women. In contrast, women reported more frequent anxiety and affective disorders than men [12]. Similar to the worldwide statistics, in Mexico, the presence of a mental or substance abuse disorder is strongly associated with suicidal behaviors; about half of people with suicidal ideation (48.8%) and two-thirds (65.2%) of those who have tried it at least once have these types of disorders [13]. These percentages highlight the importance of detecting and treating these types of disorders, especially considering a growing trend in the suicide rate from 3.5 suicides per 100,000 inhabitants in the year 2000 to 5.2 in 2017, reaching a rate of 9.3 among the young population (20-24 years old), which represent the second cause of death in this population group [14].

Despite these statistics, mental health care and addiction prevention have been pending issues for public health for years in many countries, and unfortunately, Mexico is not the exception. Although 1 in 4 Mexicans have had a mental disorder at some point in their life, only 1 in 5 of those who have it receive any treatment [15]. Recent studies have revealed that the treatment gaps for severe mental disorders, severe to moderate mental disorders, and substance use disorders in Mexico and other countries across the Americas are 77.4%, 78.7%, and 83.7%, respectively. This gap in treatment is even greater in children and adolescents, reaching up to 86% in Mexico [16]. Some of the main causes of the lack of care for people with mental and substance use disorders in Mexico are the low percentage of resources invested; not enough psychiatric hospitalization units in general hospitals as well as specific services for children and adolescents; the lack of evaluation and treatment protocols for this type of disorder in primary care; and the low rate of psychiatrists, doctors, and psychologists per 100,000 inhabitants [15].

The Pan American Health Organization has proposed different strategies to reduce the gap in attention to mental health problems and addictions in the region. Some of these strategies include the development of national plans, policies, and laws on mental health; the promotion of mental health and the prevention of psychosocial disorders with an emphasis on children and adolescents; decentralization of outpatient mental health services; the need to develop and expand mental health care in primary care; and the need to strengthen the development of national mental health information systems [17]. For the specific case of Mexico, the gradual increase in health spending for mental health and the restructuring of its distribution mode has also been identified as vitally important. Additional recommended actions are strengthening mental health teaching in medical careers, maintaining continuous training for primary care personnel, and increasing society's participation in establishing solid links with the health sector [15].

Implementing these strategies must have an interinstitutional and multidisciplinary approach allowing for maximum efficiency and does not entirely leave the responsibility to the health sector. In this sense, information and communication technologies are a fundamental tool that would improve the current care model from the phases of detection, early intervention, and continuous monitoring of patients in the community to the creation of information systems for epidemiological surveillance. These computational tools would help in the decision-making and evaluation of the public policies implemented. These digital-based tools would also facilitate a smooth integration between the different levels of health care, offering timely and comprehensive care for people detected with mental health and substance use problems.

One of the main benefits of digital tools for the prevention and treatment of mental and substance use disorders is the increment of access to health care services due to the wide availability of, for example, web-based and mobile apps. Through these apps, adolescents and young adults can be more easily reached and intervened because they are familiar with new technologies or

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are more technologically literate and mainly involved in using these digital solutions [18]. Examples of these digital solutions and their reported effectiveness can be found in different reviews for both mental health and substance use disorders (see, eg, [19-22]). Moreover, digital platforms also facilitate the screening of substance use disorders and subsequent referral of patients to specialized services [23], expanding and enhancing their treatment [24], or performing analysis for epidemiological studies and supporting clinical decision-making [25].

Objective

This protocol describes the implementation and evaluation of a computational platform to support the early detection and intervention of mental and substance use disorders at the scholar community level and in primary care units and facilitate monitoring, treatment, and epidemiological surveillance at the second level of care. Three specific objectives lead to the development of the computational platform:

1. Facilitate the early detection of symptoms and risk factors associated with mental and substance abuse disorders through a web-based module for the screening of symptoms and risk factors related to mental and substance abuse disorders in the scholar community.
2. Support the follow-up process and the surveillance of detected cases through the module to collect, process, and visualize the information of individuals screened and under treatment. Integrating the collected information from the screening, the first contact in primary care, and the treatment and follow-up provided at the secondary care level will optimize the whole care process of individuals with mental health and substance use disorders.
3. Support early interventions and the continuous monitoring of patients under treatment. These applications aim to prevent and minimize the appearance of risk behaviors or promote and motivate the change of these behaviors to maintain an adequate state of health.

Consortium

The development and evaluation of this computational platform is a collaborative effort between 4 institutions located in the state of Nayarit, Mexico. The Centre for Scientific Research and Higher Education at Ensenada is a public research center and is the project's coordinating institution. Moreover, it contributes to the technical development of the computational platform integrating artificial intelligence and human-computer interaction techniques in the different modules of the platform. The Health Services of Nayarit is the local government institution responsible for the health services in Nayarit. The clinical specialists of this institution contribute to defining the screening, intervention, and follow-up processes supported by the computational platform. The specialists of this institution are also involved in the deployment and evaluation of the platform involving the patients at different stages of the detection and follow-up processes. The Public Education Department of Nayarit is the institution that coordinates with the educative institutions in Nayarit. The participants from this institution contribute to facilitating access to the selected secondary and high schools for the early detection process. They will also contribute to evaluating the platform's impact on the scholar community. The Autonomous University of Nayarit is the fourth participant institution. The researchers of this institution contribute to the definition of the functional and user's requirements, participate in the detection and follow-up process of students from high schools, and evaluate the platform.

Methods

Modules of the Computational Platform

The achievement of the specific objectives guides the identification of the different functionalities that the computational platform provides to all the users involved: clinicians, teachers, and individuals at risk or detected with mental health and substance use disorders. Three main modules make up the proposed computational platform:

1. The module to support the screening of symptoms and risk factors. This module implements a set of standardized and validated instruments to detect individuals at risk. The screening module can be accessed from the scholar community (secondary and high schools) and primary care units. Based on the screening results and when necessary, this module provides personalized suggestions to refer detected individuals to the different services offered by the health sector. Moreover, the personnel responsible for the prevention and early detection processes (clinical specialists and school staff) will be informed about those individuals at risk to continue with the follow-up process.
2. The module to facilitate the referral, intervention, treatment, and epidemiological surveillance of the detected cases of mental health and substance use disorders. The specialists will use this module at the primary and secondary care to aid in the management and monitoring of individuals under treatment in both care levels. All the collected information from the detected cases is processed to generate graphical and statistical reports at the aggregated level for epidemiological surveillance purposes.
3. The module to support early intervention and continuous monitoring. This component includes the integration of web-based or mobile apps used by patients or individuals at risk. Our research group has experience in developing these types of apps with advanced interaction and artificial intelligence techniques such as embodied conversational agents and serious games (eg, [26,27]). Together with clinical specialists of our research consortium, we are assessing the development of the most appropriate strategy according to the characteristics and conditions of the target population.

The visual representation of the components and deployment of the computational platform to be developed is shown in Figure 1. Each of the computational platform modules is accessible by different users according to the phases of detection, intervention, monitoring, and epidemiological surveillance. The screening module can be accessed from any device, and the implemented questionnaires can be answered directly by the individuals to assess with the guidance of a specialist. This process makes it easier to reach a greater number of people and can be applied anywhere: schools, primary care units, or emergency areas of hospitals. Depending on the

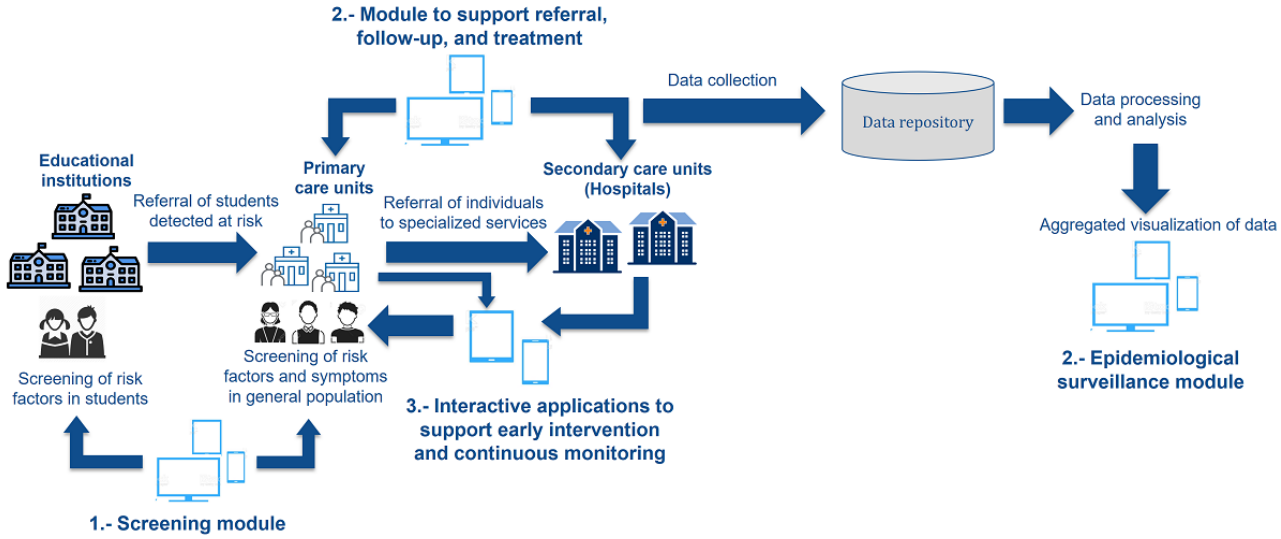
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obtained results, individuals' referral to primary or secondary health care services is also supported by the platform.

The collected information during the screening process is sent to the primary care units facilitating an early identification of those individuals detected at risk who would require a complementary medical assessment. All these detected individuals are asked to attend the primary care unit. When the person arrives at the primary care unit, the computer platform will facilitate recording the data and the complementary assessment and, if required, referring to the second level of care to receive specialized treatment. The information collected during this process is stored in a central information repository available to all the specialists involved in the care process. Additionally, the analysis and processing of the collected information in an aggregated and anonymized fashion is performed for epidemiological surveillance purposes.

Finally, as part of the computational platform, web- or mobile-based apps are considered to support early intervention or complement psychotherapeutic treatment through continuous monitoring. Examples of these apps are serious games to help in the prevention of alcohol and drug consumption, or an interactive app for the monitoring of, for example, emotional states, behavioral activities, or frequent thoughts would help to assess the evolution of the patient's condition. The information collected from these apps is integrated into the patient's electronic file stored in the data repository for subsequent consultation by the specialist. This information has proven helpful for specialists as it makes it easier to get relevant details about a patient's condition during interconsultation periods.

Figure 1. Functional architecture of the computational platform.



User-Centered Design

One of the main issues when developing computer-based systems within the health sector is the failure to adopt these solutions as part of the activities within clinical practice. Scientific evidence in the area agrees that technological factors do not cause this problem, but it is caused by the systematic lack of consideration of human and sociotechnical factors from the target users, especially during the design and implementation stages of these solutions [28]. The lack of adequate involvement of end users leads to a poor understanding of the functional requirements, suboptimal usability of these systems, and an exacerbated resistance to the change and adoption of these systems. To minimize these risks and maximize the acceptability (and consequently the effective adoption) of the proposed computational platform, we follow a user-centered design methodology, which is widely used in developing software and technological solutions. The most relevant characteristics of this methodology are as follows [29]:

1. Emphasize the identification of the needs and requirements of end users that the technological product must cover.
2. Identify and understand the context in which the technological product will be implemented.
3. Design the technological solution based on these real needs of the users and the identified context and not on preconceived ideas of the developers or established and rigid guidelines.

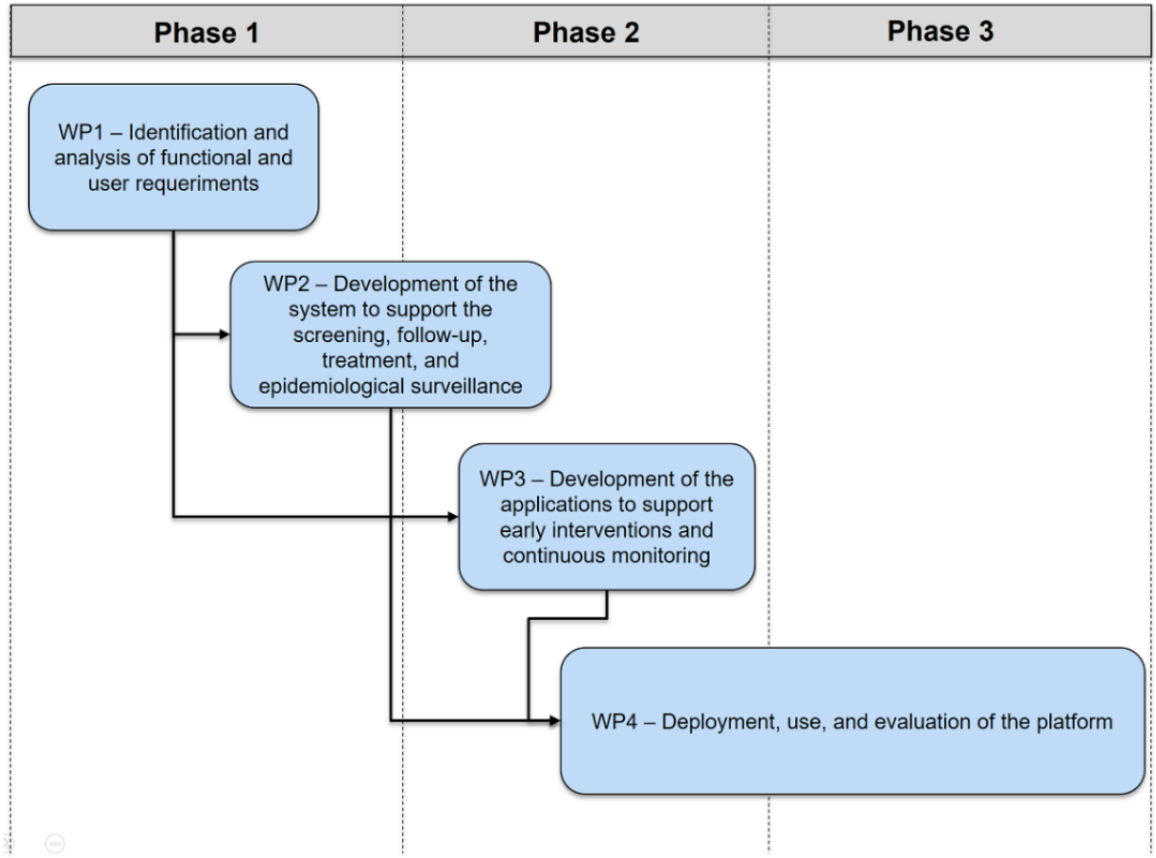
Thanks to the participation of the different institutions in the consortium, the adoption of the user-centered design methodology will be facilitated by involving all the direct and indirect users of the platform: clinical specialists at the different levels of care, personnel from the educational institutions, and people at risk or under treatment of mental health and substance use disorders. All these users collaborate from the beginning of the project and throughout its final deployment and evaluation.

Workplan

The designed workplan for the development of the computational platform considers the 4 work packages (WPs), as illustrated in Figure 2, distributed into 3 annual stages: WP1 identification of the functional and user requirements; WP2 development of the system to support the screening, follow-up, treatment, and epidemiological surveillance; WP3 development of the apps to support early interventions and continuous monitoring of patients; and WP4 deployment and evaluation of the platform.

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Figure 2. Overview of the work packages defined for the development of the computational platform. WP: work package.



The activities defined in WP1 are focused on identifying functional requirements for every module of the computational platform. Examples of these requirements include the selection of all the standardized and validated—in the Mexican population—instruments used in the screening process. Depending on the characteristics of the individuals (eg, the age) to screen, the system will show the adequate set of instruments (eg, the Problem-Oriented Screening Instrument for Teenagers [POSIT] [30]) that the specialist selects to detect the type of mental health or substance use problem. This WP1 also define the data to collect from each screened person, the recommendations provided according to the screening results, and the process to facilitate the follow-up and treatment of the individuals detected at risk in the subsequent attention at primary and secondary health units.

Other activities in this WP1 include the identification of the user and functional requirements for the development of the apps to support early interventions and continuous monitoring. Different focus groups with the target users will be considered to identify the specific objectives of these apps. Examples of these apps are to support (universal or particular) prevention of substance use through a gamified app for teenagers or an app for the remote and continuous monitoring of individuals with a mental health disorder (eg, depression and anxiety) based on cognitive behavioral therapy contents. Moreover, in this WP1, the selection of the scholar community forming the study sample for the screening process is performed. The schools' selection follows a set of agreed criteria (eg, geographical location, the quantity of student population, number of cases previously detected, or students' sociodemographic characteristics). Sensibilization sessions will be carried out with the personnel of the selected schools to inform them about the characteristics and objectives of the project.

WP2 and WP3 contain all the activities for the design and development of the different modules of the computational platform. The design, development, and testing process are iterative and follow the user-centered design methodology. Based on the information identified in WP1, each module is designed for the collection and processing of the data at different stages of the health care process: screening, intervention, treatment, monitoring, and epidemiological surveillance. Focus groups with different types of users have been considered since the first iterative design process. The result of these 2 WPs is the integration of the different modules forming the computational platform ready for its deployment and use in the selected educative institutions and health units.

The last WP4 includes all the activities required for the deployment, use, and evaluation of the computational platform. The deployment is planned to be gradual along the project's final year in the selected schools and health units. Training sessions will be carried out with the personnel of all the institutions where the platform is deployed. All technical issues that could emerge during the platform use are collected for the functional improvement of each module. Moreover, the collected information from the use of the platform will be processed for usability, acceptability, and impact evaluation in the health care process. Activities for the diffusion and dissemination of the project and the obtained results are also included in this WP4.

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Recruitment

The study participants from whom information will be collected in the computational platform are of two types:

1. Participants in the scholar community (secondary and high schools) will be screened using a set of validated and standardized questionnaires to detect symptoms and risk factors associated with mental or substance abuse disorders.
2. People attending a health unit because of the presence of a mental or substance abuse problem. These participants can be 12 years and older and of both sexes. Personal data and relevant information related to the follow-up process will be recorded, for example, reference data between the different levels of health units, personal data, and notes of diagnostic evolution that will form their electronic clinical file.

For the screening process in the scholar community, the participants are the students (males and females aged 12-18 years) of the selected schools for the study sample. In coordination with the school personnel in each school, the health professionals select the specific groups for the screening. Explicit informed consent is asked from each student and their parents or legal guardians. Then, the screening instrument (the POSIT questionnaire) is applied to all the students who provide their explicit authorization. The teacher or the health specialist provides the instructions to respond to the questionnaire and is available to answer any questions during the process. The screening session is expected to last around 45 minutes for each group.

For the people who attend primary care units to receive medical attention, the doctor who receives them will inform them that the screening is part of the diagnostic assessment process. If the patient is a minor, an explicit authorization to carry out the screening process must be provided by the minor and by the accompanying adult. The duration of the session will be the time of the medical visit that the specialist decides.

In both groups, depending on the obtained results provided by the computational platform, health personnel identify those individuals who require a follow-up intervention delivered by a specialist and are referred to the corresponding health care unit.

The recruitment of participants who will use the apps to support early intervention and continuous monitoring will be carried out by the specialist responsible for their treatment. In the case of minors, explicit authorization from their parents or guardians will be asked before the provision of the application. In all the cases, the following exclusion criteria are considered:

1. A diagnosis of schizophrenia, psychosis, or borderline personality disorder
2. Not having a digital device to execute the app
3. Any disability that makes the individual unable to use a digital app
4. Requirement to be under personal surveillance due to current symptoms associated with a mental health or substance use disorder.

Data Collection

The collected data from all the participants include personal and sociodemographic data such as age and sex. For participants of secondary and high schools, the answers to each of the POSIT's questions and the final score are also collected. For the individuals recruited in primary care units, the results obtained from different instruments to assess their condition (eg, the Alcohol, Smoking, and Substance Involvement Screening Test questionnaire [31], a suicide risk measure [32], or the Hamilton Anxiety Rating Scale [33]) are also collected. The epidemiological surveillance module uses the final scores and the corresponding interpretation of these instruments to visualize the type of risks or disorders detected in schools and health care units. Moreover, all the information produced during the follow-up process is also collected to support the specialists with the whole treatment of the individuals who require the services of a secondary level of care. The data generated during the use of the web- or mobile-based apps by the participants are also collected, and the information is used for a continuous patient evolution monitoring. These data include, for example, the current mood, frequent—rational or irrational—thoughts, or the planning and development of specific activities.

Storage and Security of the Information

The data collected at schools and health units will be sent via the internet, using a secure data transfer protocol (https) to a central information repository. All data will be textual, and no multimedia files such as photographs and audio or video recordings are included. The data repository is located in the central offices of the Health Services of Nayarit, with the appropriate access and security protocols and the necessary data backup processes. The collected data are accessed through a username and encrypted password through the developed computer platform. The access depends on the user's role; the personnel who analyze the screening results have access to consult the data that allow the person screened to be located and recommend the appropriate follow-up. The specialists responsible for clinical treatment have access to all the information collected in the electronic health record created for each patient. Finally, the users of the epidemiological surveillance module have access to the aggregated and anonymized data to know the incidence and prevalence of the different mental and substance use disorders registered in the computer platform.

Evaluation

According to the WHO, the evaluation of a digital health intervention involves the measures taken and analysis performed to assess two main issues: (1) the interaction of users or a health system with the digital health intervention strategy or (2) the changes attributable to the digital health intervention [34]. The assessment of the interaction between the platform and the target users will be performed through a mixed methods approach [35] with an explanatory design study using validated and standardized questionnaires to get information about the usability, acceptability, and perceived usefulness from the users of the different modules of the platform: health specialists, teachers and personnel of the educational institutions, and individuals at risk or patients. Existent validated instruments

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will be applied to a representative set of users after the deployment and use of each module. Qualitative information will be gathered throughout focus groups with a Logical Framework Approach.

For all web-based modules, the System Usability Scale and the Technology Acceptance Module will be provided to the users to rate the platform modules' usability, acceptance, and ease of use. The System Usability Scale consists of a 10-item questionnaire with 5 response options for respondents: from *strongly agree* to *strongly disagree*. This instrument allows evaluating a wide variety of products and services, including web-based health apps [36,37]. The Technology Acceptance Module measures the constructs of perceived usefulness, ease of use, and user acceptance of the technological product in the participant's workflow by explaining the user's "behavioral intention" with the system. This instrument is based on the theory of reasoned action [38], a psychological approach that seeks to explain behavior, and has also been widely applied in eHealth systems [39]. If any of the platform modules is deployed through a mobile device (eg, the apps for early intervention and continuous monitoring of patients in the community), a complementary instrument such as the Mobile App Rating Scale will be used to evaluate these modules. The Mobile App Rating Scale is a simple, objective, and reliable tool for classifying and assessing the quality of mobile health apps [40].

The changes in the health care process attributable to the platform will be assessed through a quantitative study by comparing the population coverage achieved with the computational platform in relation to current and historical data. Moreover, a Logical Framework Approach will be adopted to identify individual, social, and contextual factors affecting the mental and substance use health care process at primary and secondary levels. This approach has previously used to identify relevant factors and characteristics in different health care processes such as emergency care [41], hospital-based health care services [42], or rural health missions [43]. The Logical Framework Approach will be implemented through focus group sessions involving specialists and asking to identify the main problems (barriers) and solutions (facilitators) each participant faces during the different stages of the health care process. These sessions will be carried out before the platform's implementation and then after its deployment and use by the different specialists and patients or individuals at risk. The collected information from these sessions will allow the identification of specific problems that could be minimized or removed due to the different functionalities of the platform. The detected changes will help to assess the impact of the digital intervention along the process: from the early detection in the scholar community to the follow-up and treatment of individuals with mental health and substance use disorders in primary and secondary health units.

The evaluation results will be disseminated among the community and public health policy makers, emphasizing the platform advantages of adopting it as part of a public health program. Moreover, these results will lead to the identification of lessons learned during the deployment and use of the platform providing valuable recommendations to maximize the benefits for the attention of mental health and substance use disorders in other regional and national health systems.

Ethics Approval

The study has obtained research ethics approval from the institutional review board of the Health Services of Nayarit (CEBN/04/2020). Participation will be voluntary, and informed written consent or digital consent will be obtained from participants and from parents of those participants younger than 18 years. The participants will be informed about the confidentiality of their answers to the applied questionnaires. All identifiable information will not be accessible, except for the clinicians who will provide formal care services to the participants. Participants' data will not be identifiable in any publication or report. No monetary compensation will be offered to the participants.

Results

The project has been running since July 2021 and is intended to complete in June 2024. An initial version of the modules to support the screening and follow-up treatment processes has been developed, and the initial deployment and testing of these modules in a school sample of 10 secondary schools and 10 high schools located in the city of Tepic has started during the second semester of 2022. Currently, 6 schools have used the screening module implementing the POSIT questionnaire, and as of February 2023, a total of 1501 students have undergone screening. The referral of those students presenting a risk in mental health or substance use to primary care units has also started. The second stage includes the development of the interactive apps to support early intervention and continuous monitoring and the epidemiological surveillance module. The use and evaluation of the complete platform are the main activities for the final year of the project, and the obtained results will be disseminated between the research community, health specialists, and the general public.

Discussion

Principal Findings

This protocol describes the development and evaluation of a computational platform to support the detection, intervention, treatment, and epidemiological surveillance of mental health and substance use disorders in the community and primary and secondary health units. Three main modules form the computational platform: (1) a module to support the screening of symptoms and risk factors; (2) a module to facilitate the referral, intervention, treatment, and epidemiological surveillance of the detected cases; and (3) interactive apps to support and complement the provision of early intervention and continuous monitoring. Some modules of the platform are currently under development, and their complete deployment and evaluation are expected at the end of 2024.

It is expected that the proposed platform will contribute to a better integration of the involved institutions, professionals, and processes in the attention to mental health and substance use disorders. The early detection of risks in the scholar community will contribute to a timely referral to formal health services,

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minimizing the future chronicity of these disorders and the subsequent associated problems, including suicides. The functionalities of the computational platform to support the follow-up and monitoring of patients under formal treatment, as well as the generation of epidemiological information on the incidence and prevalence of these disorders, will help to perform qualitative and quantitative analyses to target better public policies and strategies implemented as responses to this problem, as well as their evaluation.

Limitations

This study has some limitations that require consideration. First, the recruitment of participants aged 13 to 17 years is restricted to those attending secondary and high schools. In Mexico, there are a significant number of individuals within this age range who are not in school and are at high risk of substance use. Second, the platform will only be used by clinicians belonging to the public health services of Nayarit. However, there are various public health systems in Mexico, even within the same city or region, and individuals identified with risk factors or symptoms will be referred to the corresponding institution where they receive their health services. Therefore, individuals referred to health units outside of the public health services of Nayarit will not be followed up or treated with the platform. It is expected that positive results, such as a better integration between the different levels of care, from early detection to follow-up and epidemiological surveillance, will encourage the adoption of the platform by other public health systems.

Conclusions

Digital-based solutions designed to support health care processes have the potential to increase the accessibility of the general population to health services, mainly due to the wide availability of, for example, web-based and mobile apps. This is particularly important for mental health and substance use disorders, where treatment gaps reach percentages above 75% in Mexico. The development, deployment, and evaluation of the computational platform proposed in this study have the potential to contribute to the reduction of this treatment gap by improving the integration and exchange of information between the different specialists and health care units involved in the different processes of attention: from the early detection of these health problems in the community to the analysis and visualization of the identified cases with epidemiological surveillance objectives.

Acknowledgments

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Data Availability

Data are not publicly available but can be obtained via contacting the corresponding author.

Conflicts of Interest

None declared.

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Abbreviations

POSIT: Problem-Oriented Screening Instrument for Teenagers
WHO: World Health Organization
WP: work package

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Proposal

V-CarE—A Conceptual Design Model for Providing COVID-19 Pandemic Awareness: Proposal for a Virtual Reality Design Approach to Facilitate People With Persistent Postural-Perceptual Dizziness

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Abstract

Background: Virtual reality (VR) technology has been solidifying its ground since its existence, where engagement and a sense of presence are key. The contemporary field of development has captured the attention of researchers due to its flexibility and compatibility attributes. During the COVID-19 pandemic, several research outputs have shown promising prospects of continuing research in the field of VR design and development—in health sciences including learning and training.

Objective: In this paper, we aim to propose a conceptual development model named V-CarE (Virtual Care Experience) that can facilitate the understanding of pandemics when it comes to a crisis, taking precautionary measures where needed, and getting used to certain actions for preventing pandemic spread through habituation. Moreover, this conceptual model is useful to expand the development strategy to incorporate different types of users and technological aid as per need and requirement.

Methods: For a detailed understanding of the proposed model, we have developed a novel design strategy to bring awareness to the user about the current COVID-19 pandemic. VR research in health sciences has shown that with appropriate management and development, VR technology can efficiently support people with health issues and special needs, which motivated our attempts to explore the possibility of employing our proposed model to treat Persistent Postural-Perceptual Dizziness (PPPD)—a persistent nonvertiginous dizziness that could last for 3 months or more. The purpose of including patients with PPPD is to get them engaged in the learning experience and to make them comfortable with VR. We believe this confidence and habituation would help them get engaged with VR for treatment (dizziness alleviation) while practicing the preventive measures during the pandemic in an interactive environment without actually facing any pandemic directly. Subsequently, for advanced development using the V-CarE model, we have briefly discussed that even contemporary technology like internet of things (IoT) for handling devices, can be incorporated without disrupting the complete 3D-immersive experience.

Results: In our discussion, we have shown that the proposed model represents a significant step toward the accessibility of VR technology by creating a pathway toward awareness of pandemics and, also, an effective care strategy for PPPD people. Moreover, by introducing advanced technology, we will only further enhance the development for wider accessibility of VR technology while keeping the core purpose of the development intact.

Conclusions: V-CarE–based developed VR projects are designed with all the core elements of health sciences, technology, and training making it accessible and engaging for the users and improving their lifestyle by safely experiencing the unknown. We suggest that with further design-based research, the proposed V-CarE model has the potential to be a valuable tool connecting different fields to wider communities.

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KEYWORDS

COVID-19; immersion; pandemic; Persistent Postural–Perceptual Dizziness; PPPD; virtual reality

Introduction

Recently, virtual reality (VR) technology has received growing attention in diverse areas and a plethora of research. VR creates an immersive 3D visual experience and sensory environment trying to mimic the real world using simple wearable devices. Interestingly, VR technology has been widely used as a cost-effective tool in advanced fields of education, health, engineering, and medicine. Immersion, presence, and interactivity are key factors in VR [1-5]. We believe that these factors mark the prominent capability of VR, which has drawn great attention in the field of education, learning, and health sciences [6-11]. VR has significantly improved the education and skills of health professionals [10,12], but further research is still required to study the effectiveness of more immersive and interactive forms of VR in different settings. In this study, we have proposed a VR-based model that incorporates education and health science elements to examine and evaluate the effectiveness of a 3D immersive experience in learning and training.

The proposed VR conceptual framework, V-CarE (Virtual Care Experience) model, can be applied by VR developers to create a 3D simulation incorporating educational and health elements (Figure 1). The desired 3D environment would give the users an immersive experience to practice how to react in a serious situation, which would eventually benefit their health through their actions. The proposed model is flexible and can be generalized for different purposes, including engagement and habituation. This would cater for a wider acceptance of the technology, which will contribute to public health and serve the community. It is worth noting that the internet of things (IoT) would be incorporated within our proposed model for providing a 3D and fully immersive simulation. The users would experience real situations developed objectively with required surroundings and settings for different training cases and purposes. IoT is a system that connects different objects or things in one network that has been widely used in numerous applications in a wide range of domains like health care, agriculture, and smart homes [13-15].

Furthermore, the V-CarE model aims to enhance awareness of pandemics during unforeseen circumstances, implement necessary preventive measures, and encourage habitual actions for disease prevention. The COVID-19 respiratory illness outbreak started in China in 2019 [16]. It spread all over the world, resulting in a global pandemic in less than a year [17]. In an attempt to control its spread, preventive measures, and social distancing were suggested based on the situation and conditions of the outbreak [18].

With the rise of the prevalence of COVID-19, VR played an important role in fighting the pandemic by providing a virtual and safe environment for leveraging remote interactions and connecting people. It can be used to change individual behavior while maintaining social distancing through immersive learning and training through 3D simulation. A web-based survey was introduced to study the importance of using VR to help people improve their mental health and physical well-being during the lockdown [19]. Many VR-based apps have been recently introduced in the context of the COVID-19 pandemic to help in cognitive and physical rehabilitation therapies, web-based education, training, and treatments [20-23]. However, there is no strategy for implementing and practicing preventive measures such as social distancing to accommodate performing normal work procedures in the industry, education, health care, and other fields. The proposed V-CarE model is developed to educate people about COVID-19 through VR immersive environment experience, focusing on implementing preventive measures, and social distancing strategies for controlling the disease spread.

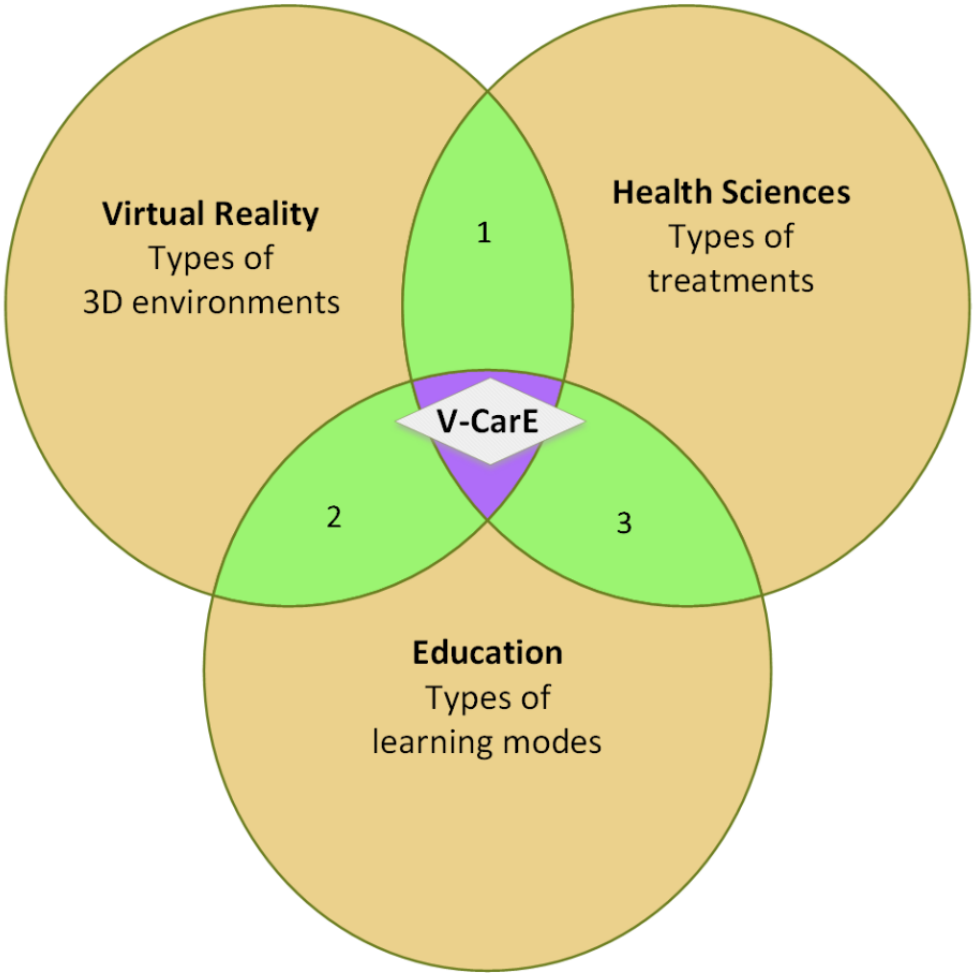
To test and validate the extendible capabilities of V-CarE, we have applied our proposed model to people with Persistent Postural–Perceptual Dizziness (PPPD). V-CarE model has been designed with strategies for preventive measures to avoid triggering the symptoms. PPPD has been identified as a vestibular disorder that causes persistent dizziness and unsteadiness for 3 months or more [24]. Other than this study, very limited research has been done on using VR simulation as a cost-efficient tool for understanding and managing patients with PPPD through exposure therapy [25-28]. It is very challenging for patients with PPPD to follow the preventive measures that are crucial nowadays to control the current COVID-19 pandemic. Recently, there has been some significant work conducted on the application of VR and its capabilities to handle situations during the COVID-19 pandemic. Telemedicine services, mental health support, remote work collaborations, and similar engaging activities have been potential areas of research in VR development. Engagement and interactive rehabilitation experiences have been the main focus of the research as COVID-19 largely impacted daily life activities and approaches toward looking at day-to-day activities for the future [29-32]. Despite progress, there has been no discussion on how VR development strategies are made to keep the elements of entertainment, engagement, and interactivity intact for the wider audiences. In this study, we have highlighted the need for a proper visual map and introduced a conceptual model that can involve experts in their fields to connect strongly and develop an effective 3D simulation addressing the needs of the users. Moreover, we have also suggested that V-CarE, being a promising development model, can also facilitate people with PPPD who are already going through the complexity of living that comes with the symptoms [33].

Therefore, this study aims to employ the proposed V-CarE conceptual model for VR developers to provide people with awareness of the pandemic and its preventive measures through 3D immersion. Also, we have highlighted that the similar 3D simulation developed here can facilitate people with PPPD. The

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product can further be enhanced with little to no major change, whereas contemporary technology (eg, IoT) can be incorporated into the V-CarE–based design for a wider accessibility. Finally, we have concluded that the V-CarE approach positively impacts daily life at a time when the pandemic crisis and personal dizziness struggles are the major health issues.

Figure 1. V-CarE (Virtual Care Experience) conceptual model.



Methods

The Proposed V-CarE Model

The term V-CarE is inspired by the term "We Care," which stands for Virtual Care Experience, which refers to the concept that VR technology positively impacts people's lives. People would learn and train themselves to remain safe and keep themselves healthy using this technology. V-CarE is designed to be a general and flexible learning and training model that provides an immersive 3D experience for the users to have a healthy lifestyle through improved habits and daily activities. It can also help in understanding and building awareness of different pandemics, as well as practicing its required preventative measures through habituation. In addition, V-CarE represents a conceptual framework that facilitates further refining the investigation process of understanding primary symptoms among patients (users) for researchers and clinicians. In addition, it can assist researchers to handle cross-disciplinary work more objectively.

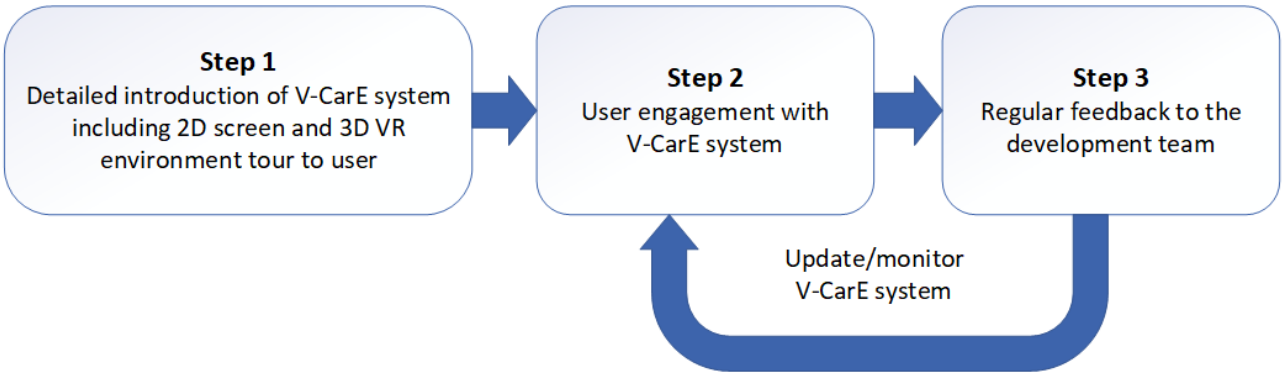
As the V-CarE concept resides at the core of 3 different major fields, including VR (3D environment), education, and health sciences, it is important to go through each field and reach the core (V-CarE) design as shown in Figure 1. In this way, the design can be easily customized as per the needs of the development. Table 1 describes how the 3 generic areas are set together and blended into 1 core that would have the essence of all the major fields. Based on the required type of VR environment, the order of considering mapping of sets would vary in each row of Table 1, but it would remain in the same column sequences (from left to right). To develop the right product at the end, the V-CarE team are expected to have experts in the 3 fields (education, VR, and health sciences), so that all common elements of the 3 major fields are addressed accurately. Once the V-CarE–based product is ready, to continue keeping the positive impact of the product based on the V-CarE concept, we have proposed a standard protocol as depicted in Figure 2 to make users feel comfortable with the VR experience.

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Table 1. Descriptive table for the proposed V-CarE conceptual model in Figure 1.

V-CarE–the 3 sets and common elements		
Types	Venn diagram number–types	V-CarE model components
Virtual reality (VR)–3D environments (commercial entertainment, educational, medical, manufacturing, therapy, mixed reality, etc)	1. Virtual reality and health sciences: medical VR, VR therapy.	VR-based experience model to improve user and patient's symptoms, learning, and awareness affecting virtual rehabilitation therapy.
Education–modes (learning and training; conventional classrooms, web-based environment, virtual environment, blended environment, etc)	2. Virtual reality and education: educational virtual environment	VR-based experience model to improve user and patient's symptoms, learning, and awareness affecting virtual rehabilitation therapy.
Health sciences–treatments (medicine therapy, cognitive behavioral therapy, vestibular rehabilitation therapy, etc)	3. Health sciences and education: patient education in general (learning about therapies and their effectiveness)	VR-based experience model to improve user and patient's symptoms, learning, and awareness affecting virtual rehabilitation therapy.

Figure 2. V-CarE (Virtual Care Experience) standard engagement protocol. VR: virtual reality.



V-CarE Model's Design and Development Framework

As mentioned earlier, V-CarE is a conceptual model that can be used with flexibility for different situations as long as it is linked with training, learning, and maintaining good health (Table 1). The V-CarE team would involve individuals from areas of health sciences, VR, and education.

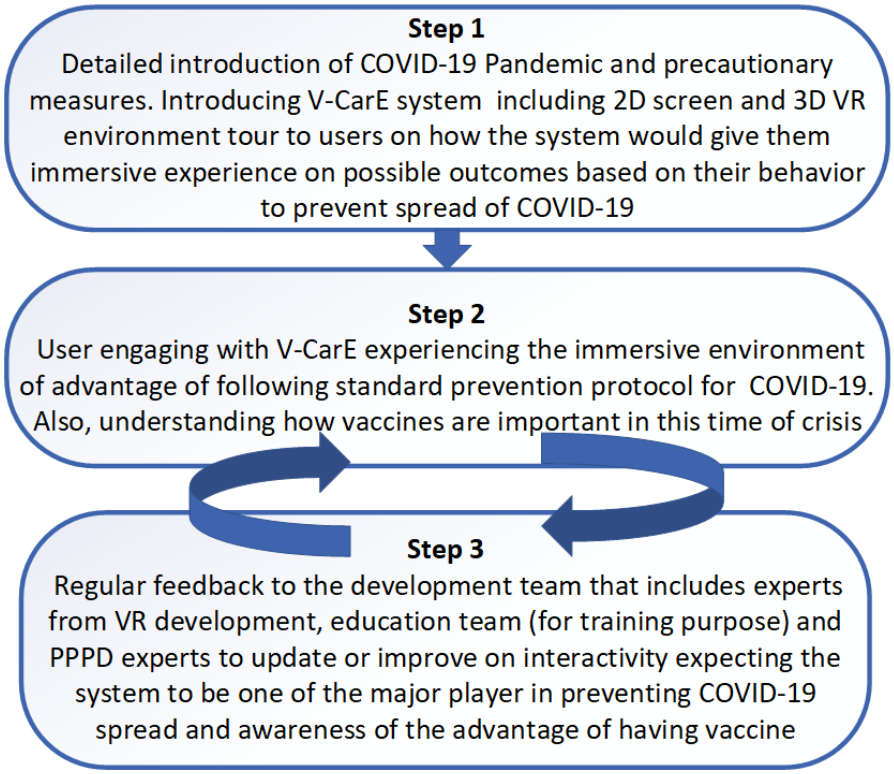
The Protocol of Introducing V-CarE to Users

A standard protocol has been laid out to introduce the V-CarE system, aiming to make users comfortable with the VR experience based on the V-CarE concept. The user would go through the proposed standard process when using V-CarE as described in Figure 2. They would be introduced to the system thoroughly, including the VR experience at first. Then, the product will be used by the users at home at their convenience. With every growing demand and experience requirement, the system would continuously improve through feedback where necessary to give the user an ultimate experience of a VR environment.

In this case, we will use the proposed general process of using the V-CarE system for COVID-19 pandemic awareness. Figure 3 shows the updated protocol that was designed toward introducing an immersive experience dedicated to providing an understanding and awareness of the current pandemic, as well as facilitating a pathway for the user to get used to the required preventive measures and the vaccination process.

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Figure 3. The protocol for using V-CarE (Virtual Care Experience) system for COVID-19 pandemic awareness. PPPD: Persistent Postural-Perceptual Dizziness; VR: virtual reality.



Design Strategy—Educating to Combat (COVID-19) Pandemic

In this study, looking at the seriousness of the COVID-19 pandemic, we have proposed a virtual learning environment design using the V-CarE model that would help people to understand the pandemic, educate themselves, and take necessary measures consistently in a hassle-free manner. The 3 design steps for implementing the VR immersive strategy and experience are as follows:

1. From the 3 broad sets (highlighted in yellow color in Figure 1)—the V-CarE design requires understanding the elements to choose for subsets to develop a relevant VR environment. For our purpose, our final set should have these 3 components: a VR environment for an interactive experience, education about COVID-19, and exposure therapy to impact the users' lives positively.
2. From the 3 blended sets (highlighted in green color in Figure 1)—the V-CarE design requires a VR environment with an educational aspect in it. Education about what measures can reduce the chances of getting infected with COVID-19, its symptoms, information on SARS-CoV-2, and the 3D immersive experience of the measures to keep oneself safe.
3. From the core V-CarE set (highlighted in gray)—The V-CarE design requires a VR environment where users can experience the results of preventive measures at home during the lockdown through a 3D simulation. The virtual simulated environment is designed to be an indoor environment; however, it can be developed to be outdoors when required. In the 3D-immersion experience, users can safely interact with the VR environment and perceive a deep awareness of the COVID-19 virus.

Development Strategy—3D-Simulated Experience

In this section, we provide an example of developing strategies through a simulated environment for users to practice key preventive measures and social distancing procedures. The virtual simulation will have the following different scenes in a house:

1. Scene in the bathroom where a user must wash hands thoroughly for 20 seconds (timer is active). If any part of the hand is left unattended, a red spot will be added to the simulation environment. This spot would grow if the user does not attempt to wash hands again for 20 seconds.
2. Scene in the house where there is a grocery item that is located on the table. The red spots on the item would be an indication of the possible risk of COVID-19. A wipe, and a water tap in the kitchen would be available. The user would be required to clean the item with a suitable option.
3. Someone knocks at the door and the user would be asked to take action; (1) open the door, and (2) ask the person to keep a 2-meter distance (social distancing) from the door before interacting.
4. Social distancing scene where green circles depict moving users if they are moving or standing at 2-meter distances or more. If the distance becomes smaller, the circle's color will turn red accompanied by a warning alarm.
5. To keep the immersion engaging, these proposed scenarios would undergo a slight change with each experience, which can be decided by the developers. Also, these scenarios can be easily adapted or redesigned to address different procedures and precautions (matching the rules of the

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lockdown's level). Consequently, more scenes can be added to address more of the suggested and updated preventive measures for indoors and outdoors, aiming for a complete training and therapy system. Moreover, a scene can be added for understanding and getting familiar with the special polymerase chain reaction (PCR) test used to diagnose COVID-19 and for the vaccination process. With VR immersion, telepresence, and real-time interactions, people would get more engaged and motivated to use VR technology to increase their awareness about COVID-19 and practice preventive measures instead of just reading and hearing about the disease through media. User-centered tutorials and demonstrations would be used to assist the users in using the system independently and would provide further support to the users [34].

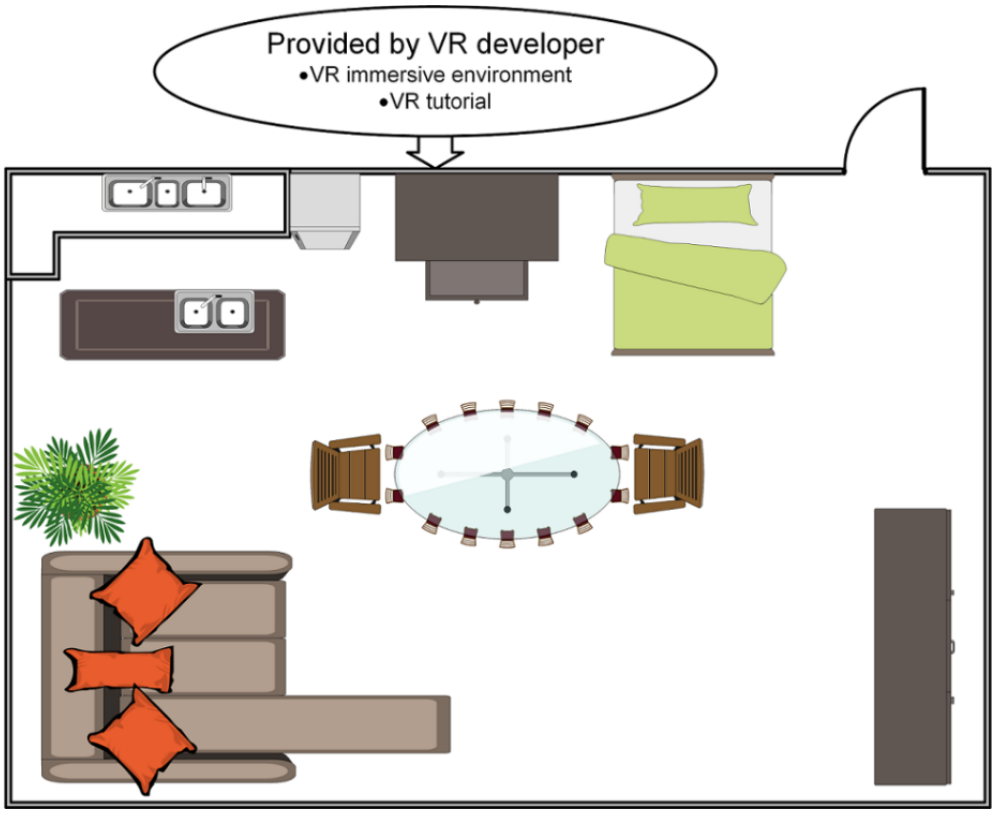
Sample Simulation Process Using V-CarE–Visual Aid

For a visual understanding of V-CarE, we have provided an example of a studio room (in 2D for simplification purposes): the VR version can be customized as needed. Users would go into a 3D simulation of the room. In a conventional VR development environment, understanding interactions with objects in the room will be decided by the VR developers, whereas in the V-Care framework, these interactions will be guided by expert judgement through guided tutorials. It is expected that the interactions in the room can either be a part of a VR-based game or solely a VR experience (Figure 4).

If the environment is developed using the V-CarE framework, the elements in the VR experience would have attributes infused by experts from different disciplines and the purpose would be narrowed down to specific yet common goals. In this study, the focus would be to understand the actions required to avoid COVID-19. As mentioned before, experts from the 3 disciplines would be involved in the V-CarE–based product development. The user would (1) interact with the environment (VR developer would be involved), (2) receive continuous input feedback (educators and trainers would be involved) to be informed of the necessary steps to avoid COVID-19, and (3) get prompts of health information on the actions they took in the immersion (Figure 5).

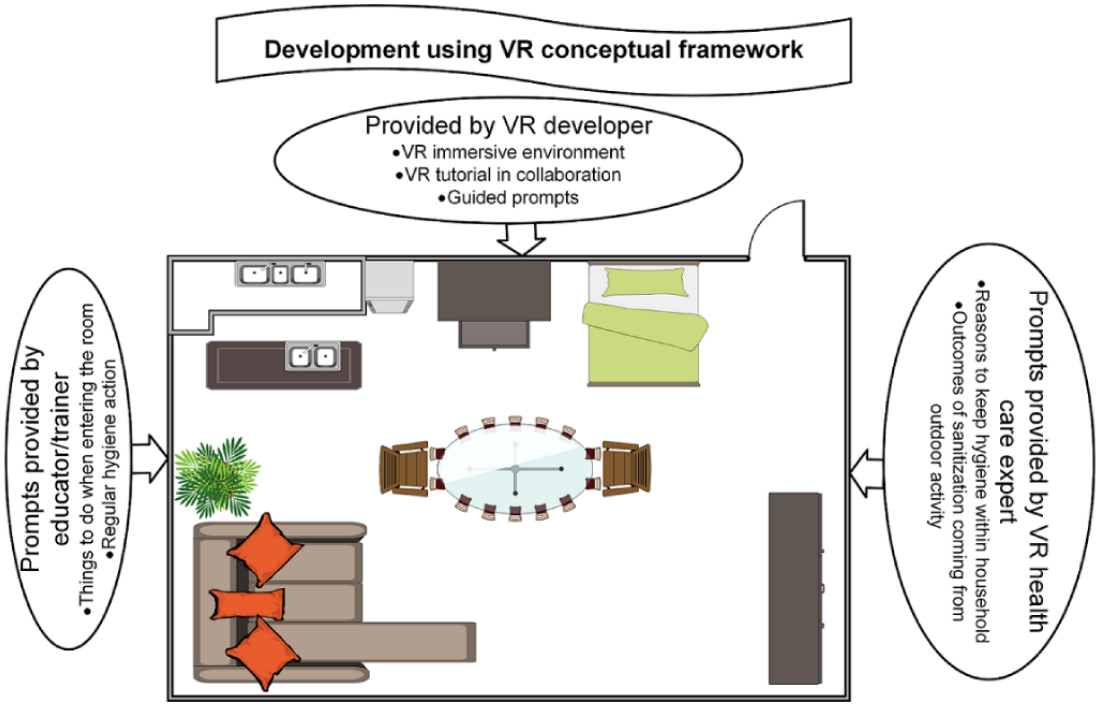
As the virtual environment is flexible to the users' needs, the idea of a descriptive VR environment is left to the developers. Figure 5 illustrates VR environments that can be created from different perspectives. At the same time as design layout II in Figure 5 shows, a simple environment like a studio room can be used as an insightful interactive space to tackle the spread of COVID-19 through community contribution and awareness of the pandemic. Some of the recent research work showed that the developers have started investigating strategies around creating casual VR simulations for certain groups of audiences [35-38]. In this study, we have proposed a conceptual framework to engage experts from other disciplines to keep the scope of VR simulation balanced to the needs of the users. This scope can easily be expanded to the direction of selected disciplines without compromising on the quality of the developed VR product.

Figure 4. Design layout I–studio room. VR: virtual reality.



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Figure 5. Design layout II–studio room from V-CarE perspective. VR: virtual reality.



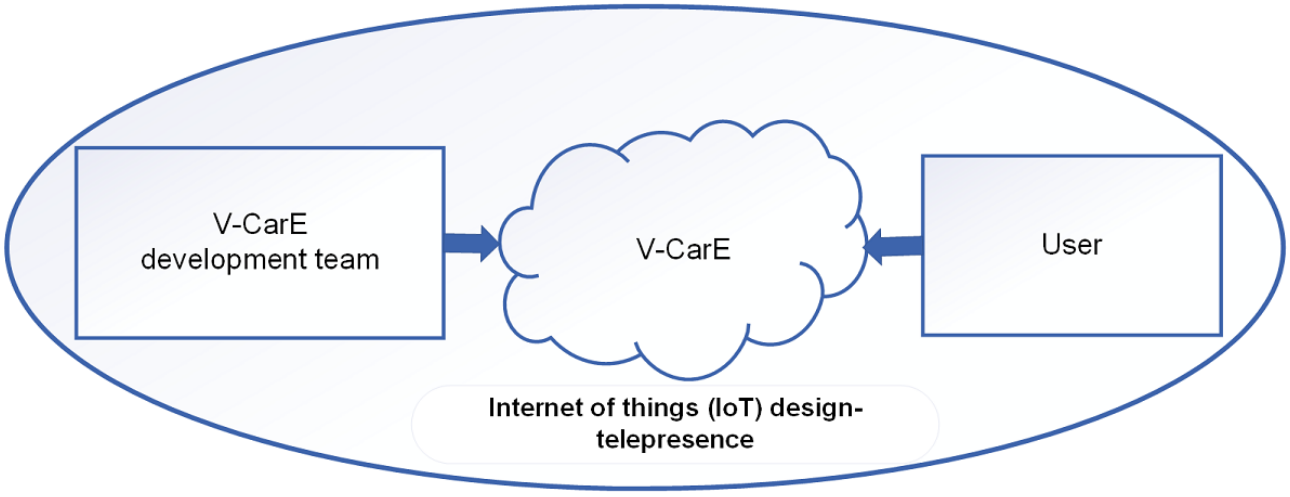
Incorporating Internet of Things into V-CarE Design Strategies

The development of our proposed V-CarE model will require the involvement of people from 3 different fields of expertise including education, VR, and health. It is important to see how V-CarE can collect the users' feedback and reaction to connect them to the right resources. The IoT has been around for some time and the promising attribute is the integration and communication of several technologies [13], and it fits well with the proposed conceptual V-CarE model.

In the integration of VR and IoT, Empathic VR is an appropriate example that can support the advantages of V-CarE for its flexibility in adopting IoT. Empathic VR uses a VR head-mounted display with a mobile remote–controlled robot. This enables 2 people at distant locations to connect and move freely within a real world and virtual workspace while creating a strong sense of telepresence of actually being in the same location [39]. In the proposed V-CarE model, an IoT-based system can be designed to suit the users' needs by involving the relevant health experts to facilitate a deeper understanding of the user experience and to support users in line with health care practices.

Figure 6 depicts our proposed framework that engages both the developers and users using the V-CarE model, aiming for an efficient and dedicated IoT-based VR immersive engagement. As for COVID-19, it is evident that social distancing and isolation are necessary to alleviate the spread of the virus, and IoT-based design would be ideal to connect everyone involved in helping the society become COVID-19-free. Interestingly, modern IOT and internet of medical things technologies have been studied to assist in managing the current pandemic [35]. Therefore, our proposed model will be empowered by incorporating these promising technologies, aiming to achieve an efficient system with a variety of applications including managing the COVID-19 pandemic.

Figure 6. V-CarE (Virtual Care Experience)–proposed framework for IoT compatibility with the V-CarE model.



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Extending V-CarE for Patients With PPPD

With V-CarE, users can immerse and experience reality through 3D simulation and learn according to their engagement preferences. The Venn diagram–based model (Figure 1) can adapt to changes and various considerations as long as the core V-CarE has all the common elements from the 3 big sets (VR, education, and health sciences). Also, we would like to stress that the V-CarE model can help people with different disorders, symptoms, and phobias. In this case, we would like to see how people with PPPD can benefit from the current setup. PPPPD is an inconsistent chronic vestibular nonvertiginous form of dizziness and unsteadiness that persists for 3 months or more [24]. It exacerbates by upright position, passive and active motion of oneself, and exposure to static and dynamic complex environments which are overwhelming to visual perception. Having entered the list of the International Classification of Disorders-11 in 2015, there are very limited research studies on the treatments and effects of PPPD and the impact on the affected people [36]. Recently, VR technology has been exploited for vestibular rehabilitation through balance and habituation exercises [37]. There are very limited studies, including this work, on using VR to understand PPPD through exposure therapy [25-28]. None of the studies discussed the encouragement and trust factors of VR technology.

Considering the triggers of PPPD and its symptoms, using VR would be a promising starting point for patients with PPPD to get used to the environments and to understand and practice immersion [28,40]. They would be able to see and feel the environment of a house where their daily activities would be similar to what they are expected to do, especially during the COVID-19 pandemic. The proposed V-CarE model with the designed strategy for COVID-19 will provide the required immersion and sense of achievement for PPPD users to practice following all preventive measures. This will make them engaged while experiencing the outcome of their actions in the real world. Not only would they have a virtual experience of learning, but they might also get comfortable with virtual headsets through habituation. This will lead to their acceptance of VR technology and, later, using it by choice for their treatment (self-therapy) under the supervision or advice of PPPD experts.

Moreover, if the simulation is similar to their home environment (that does not trigger dizziness symptoms), people with PPPD would interact comfortably, reducing fear responses. Furthermore, for the sake of knowing COVID-19 and doing their part to control the spread, they would take initiative in practicing COVID-19 preventive measures through 3D immersion. The proposed protocol introduced in Figure 3 will help in creating awareness for patients with PPPD and assisting them to overcome the symptoms. The PPPD experts would be involved in the development process of the system and introduce it efficiently to patients with PPPD. In addition, incorporating IoT into the proposed model would offer a more relaxed environment with familiar surroundings, aiming to improve habituation and adaptation. Additionally, the proposed model would help people with PPPD to understand the PCR test, as well as the vaccination process, which would assist in controlling the COVID-19 spread.

The proposed model presents a simple and feasible VR-based solution that can be applied to help patients with PPPD (besides regular users) understand the COVID-19 pandemic and practice the needed precautions and preventive measures.

Electronic Equipment for V-CarE Design and Development

VR has come a long way to get the attention of potential users and create a competitive market, with various companies putting in effort to keep their products as one of the leading equipment in the market [41,42]. HTC Vive and Oculus are keeping their gadgets accessible for consumers and developers with several models and compatible software design kit. The latest graphics cards combined with powerful machines have been the major contributors to the VR success, considering the framerates, and close to real-world development of simulation. Augmented reality has even gone one step further to cater for the necessary engagement and interactive factor which VR is providing to the users [43]. V-CarE can be applied to any design methodology using the hardware in line with the users' and participants' needs.

Ethical Considerations

The paper proposes a theoretical design conceptual model without involving any human subjects. The design element focuses on the possible development of VR interventions that can sustain positive behavior and mitigate the negative effects of the pandemic and PPPD symptoms on daily life activities.

Usability Testing

To materialize the conceptual framework, we suggest rigorous usability and user testing to make the product reliable and effective for end users. Experts in the areas of VR, health sciences, and education, can collaborate in cross-disciplinary domains to harvest quality outcomes using VR technology [10,12,27,44]. The proposed V-CarE framework suggests that for the development phase, the relevant stakeholders would be involved in testing the system's usability. The process should engage experts in their fields and select users from a group of people who would be directly impacted. It is important to involve the people at the right time for the right role in the development of the VR environment [34,45]. Tools like System Usability Scale and me CUE have been extensively used by researchers and practitioners to measure usability and user experience [46,47]. Furthermore, the agile project management approach and scrum methodology [40] would be appropriate methods to move to the development phase of the V-CarE model, considering its nature of involving researchers from different fields.

Sample Size

Although the study primarily focuses on users' COVID-19 *a*wareness, we have also emphasized that the design has the potential to cater to a broader audience, including individuals with PPPD. Preliminary research and investigation have been performed as proof of concept for using VR technology to help patients with PPPD in their journey of exposure therapy and improving symptoms. For example, in recent studies, a VR prototype has been proposed, paving the way toward an efficient VR-based intervention tool for improving exposure therapy

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through immersion strategy [27]. In addition, a smart VR-based e-diary is proposed for improving PPPD therapy and facilitating habituation [28]. For appropriate sample size calculation, priori analyses were performed to estimate a suitable sample size for a reasonable power level. The G*Power (version 3.1; Universität Düsseldorf) statistical program was used for sample size calculation and power analysis [49,50]. It was calculated that 54 participants can designate 95% power of the study based on a medium effect size Cohen d=0.5, with significance level α=.05 (*2*-tailed *t* test). Therefore, we suggest including a total of 54 participants *and* patients (assuming some dropout), aiming to achieve 95% statistical power of the study. The sample of participants can include both genders (male *and* female). For gathering information and collecting feedback for the experiment, an efficient questionnaire *or* survey is required based on the standards for developing questionnaires for educational research and using the handbook of questionnaire development as a guide [50].

Results

We have proposed a model that provides a significant step toward enhancing the accessibility of VR technology. The methods section highlights that VR development using V-CarE can strengthen public awareness regarding pandemics. Also, VR development can provide effective care to individuals with PPPD without making major VR exposure training improvements. In addition, we have determined that incorporating cutting-edge technology, for example, IoT, into the model will facilitate the expansion of VR accessibility while preserving the primary purpose of the development.

Discussion

Principal Findings

The V-CarE conceptual model is a major leap forward in the strategic use of VR technology for health care; and educational purposes–at a user level. By developing a fully immersive, semi-immersive, or nonimmersive 3D simulation, researchers from the fields of education, health, and creative technology can work together to improve health care outcomes and address the challenges posed by the COVID-19 pandemic. The model provides a pathway to develop a virtual experience that helps people understand COVID-19 and the recommended preventive actions. In addition, the model has the potential to be applied in a wide range of settings, from medical clinics and hospitals to educational institutions and home-based settings. The flexibility of the model makes it accessible to a wide range of people, regardless of their location or background. By using VR technology, people with PPPD can receive effective treatment without feeling any reluctance. This is due to the proper guidance provided by the model, which enables habituation therapy to be used to treat PPPD dizziness symptoms effectively by reducing fear and anxiety as well as promoting better health outcomes. The integration of IoT is also suggested as a way to promote contemporary technology into the developed system in order to enhance the capability of the VR experience by adding a feature.

Limitations

Further investigation is needed to determine the applications of the V-CarE model in various settings, from medical clinics and hospitals to educational institutions and home-based environments. To ensure the feasibility of the study and the usability testing, a power analysis and sample size calculation can be performed using G*Power.

Conclusions

In conclusion, the purpose of the V-CarE model is to provide a tool that effectively uses VR technology for interdisciplinary collaboration between health care, creative technology (in this case, VR), and education. It lays the foundation for exploring and understanding the effects of VR technology on human behavior and cognition, with its ability to address the challenges posed by the COVID-19 pandemic. Moreover, it provides effective treatment solutions for PPPD for improvements in health care outcomes, and people's lives. As the V-CarE model has the potential to make a positive impact in day-to-day activities of the users, it is, therefore, suggested to continue to conduct further research and support interdisciplinary collaboration to help bring these innovative solutions to our lives.

Conflicts of Interest

None declared.

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Abbreviations

IoT: internet of things
PCR: polymerase chain reaction
PPPD: Persistent Postural-Perceptual Dizziness
V-CarE: Virtual Care Experience
VR: virtual reality

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Protocol

Testing the Impact of Phone Texting Reminders for Children's Immunization Appointments in Rural Cameroon: Protocol for a Nonrandomized Controlled Trial

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Abstract

Background: Globally, over 20 million children are unvaccinated and over 25 million missed their follow-up doses during the COVID-19 pandemic; thus, they face vaccine-preventable diseases and unnecessary deaths. This is especially the case for those with HIV or living in vulnerable settings. Using cell phones to send reminders to parents has been shown to improve vaccination rates.

Objective: We aim to determine whether implementation of an automated SMS reminder will improve child vaccination rates in a turbulent, semiurban/semirural setting in a low-income country.

Methods: This will be a nonrandomized controlled trial that will be conducted at Azire Integrated Health Centre, Bamenda, Cameroon.

Results: A total of 200 parents per study group (aged over 18 years) who are registered at the clinic at least one month prior to the study will be recruited. The intervention group will receive 2 reminders: 1 week and 2 days prior to the scheduled vaccination. For those who miss their appointments, a reminder will be sent 1 week after their missed appointment. The control group will receive the regular care provided at the clinic. Baseline information, clinical visit data, and vaccination records will be collected for both groups. Descriptive statistics will be used to summarize baseline characteristics between and within clusters and groups. The Fisher exact test will be used to compare parent-child units who return for follow-up visits (as a percentage) and children vaccinated as scheduled (as a percentage) between the study groups. Finally, we will compare how many members of both study groups return for 1 follow-up visit using Kaplan-Meier survival analysis.

Conclusions: Due to limited effective child vaccination interventions in unstable settings, this study will be of high importance for suggesting a holistic approach to improve child vaccination and public health.

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KEYWORDS

immunization; children; Cameroon; digital health; global health; nonrandomized controlled trial; child vaccination

Introduction

Child immunization is a key component of the World Health Organization (WHO) and United Nations Children's Fund (UNICEF) child survival intervention package [1]. Immunizing children is an essential strategy in primary health care services and a crucial public health objective. Yet internationally, there are up to 19.4 million children who are still unvaccinated and face unnecessary deaths [2], including an especially high number of children living either in resource-limited settings or living with HIV. Therefore, children are considered a high-risk group for acquiring vaccine preventable diseases (VPDs) Also, the WHO and UNICEF warn of an increased number of missed follow-up doses for children due to the COVID-19 pandemic since 2020; over 25 million children have missed their follow-up doses. Such a decrease in child vaccination is considered a serious threat to the health of children, especially children living with HIV, in comparison to their immunocompetent similar-aged peers [3].

The vaccination system in Cameroon, including the administration of follow-up doses, has been weakened, and herd immunity has been compromised. In September 2022, the government of Cameroon announced a strategy to promote immunization among zero-dose children [4]. In 2021, UNICEF reported that different regions of Cameroon face the challenge of low vaccination coverage for several reasons, including armed conflict, insecurity, and underfunding of national vaccination programs [1]. Using cell phones to send reminders to parents about vaccination appointments has been shown to support adherence [5,6].

In 2019, we tested a smartphone app called Children Immunization App (CIMA) at a refugee camp in northern Jordan [6]. CIMA was developed to record the vaccination history of children according to the Jordanian national vaccination guidelines, provide health education information, and generate automated reminders for parents. The app was specially designed to target people with low literacy, with consideration of usability and technical concerns in a marginalized context [2]. CIMA was tailored to meet the needs of the target population. The messages and visuals were all customized to fit the local context [2].

In 2021, in collaboration with the University of Yaoundé and the United Nations Office on Drugs and Crime (UNODC) [7], we modified the CIMA functions. The penetration of smartphones is low in Cameroon; therefore, installing CIMA for parents would create a large selection bias. However, non-smartphone cell phones have an estimated penetration of over 95% [8]. Therefore, we have modified the app so information is saved locally in the clinic and reminders and health education messages are sent in the form of SMS texts to the registered cell phone numbers of the parents. We used English and French messages in order to fit the needs of the Cameroonian context. The main aim of this study is to implement an automated SMS system at Azire Integrated Health Centre, Bamenda. The objective is as follows: analyze the effect of the cell phone reminder intervention on the percentage of parent-child units returning for follow-up visits and the percentage of children receiving immunization as scheduled.

Methods

Study Setting

The study will be conducted at Azire Integrated Health Centre, Bamenda. Bamenda is located in the northwestern part of Cameroon (known for the volcanic Bamenda Highlands). Bamenda is considered a cosmopolitan town, with an area of 5250 km^2; it includes 7 subdivisional councils and over 800,000 inhabitants. Since 2016, a sociopolitical crisis has been ongoing in Bamenda and it has become a turbulent zone. Today, it is estimated that over 95% of households in Bamenda own at least one cell phone.

The national vaccination schedule for children takes place during the first 11 months after birth at 5 clinic visits. The first contact is at birth and includes (1) the bacillus Calmette-Guérin (BCG) vaccine again tuberculosis and (2) the oral polio vaccine (OPV). The second contact is at 6 weeks and includes vaccination against diphtheria, tetanus, pertussis, hepatitis B, *Haemophilus influenzae* type b (DTP-HepB-Hib), OPV, pneumococcal infections (pneumococcal vaccine [PCV] 13 and rotavirus vaccine 1). The third contact is at 10 weeks and includes DTP-HepB-Hib, OPV, PCV 13, and rotavirus vaccine. The fourth contact is at 14 weeks and includes DTP-HepB-Hib, OPV, inactivated poliovirus vaccine, PCV 13, and rotavirus vaccine. The fifth contact is at 9 months and includes vaccination against measles, rubella, and yellow fever. Additionally, vitamin A is given during months 6 to 11 (Table 1) [9]. This study aims to assess the impact of an automated reminder at the second contact appointment.

The team members have different areas of expertise: epidemiology and the usefulness of digital tool reminders for clinic appointments for vaccination [3-5], the usefulness of telemedicine [6], adherence to taking antiretroviral treatment on time using cell phone reminders [7], and insulin supply pickup using SMS versus phone call reminders [8]; all members are experts in the study context of Bamenda and Cameroon.

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Table 1. Vaccination schedule for children during the ages of 0 to 11 months in Cameroon.

Contact (age), vaccine	Preventable disease	Route of administration
First contact (birth)		
Bacillus Calmette-Guérin vaccine	Tuberculosis	Intradermal
OPV[a] 0	Poliomyelitis	Oral
Second contact (6 weeks)		
DTP-HepB-Hib[b] 1	Diphtheria, tetanus, pertussis, infection due to *Haemophilus influenzae* type b, hepatitis B	Intramuscular
OPV 1	Poliomyelitis	Intramuscular
PCV[c] 13 1	Pneumococcal infections	Oral
Rotavirus 1	Rotavirus diarrhea	Intramuscular
Third contact (10 weeks)		
DTP-HepB-Hib 2	Diphtheria, tetanus, pertussis, infection due to *Haemophilus influenzae* type b, hepatitis B	Intramuscular
OPV 2	Poliomyelitis	Intramuscular
PCV 13 2 ; rotavirus 2	Pneumococcal infections; rotavirus diarrhea	Intramuscular; oral
Fourth contact (14 weeks)		
DTP-HepB-Hib 3	Diphtheria, tetanus, pertussis, infection due to *Haemophilus influenzae* type b, hepatitis B	Intramuscular
OPV 3; IPV	Poliomyelitis	Oral; intramuscular
PCV 13 3	Pneumococcal infections	Intramuscular
Fifth contact (9 months)		
Measles, rubella	Measles, rubella	Subcutaneous
Yellow fever	Yellow fever	Subcutaneous

[a]OPV: oral polio vaccine.

[b]DTP-HepB-Hib 1: diphtheria, tetanus, pertussis, hepatitis B, Haemophilus influenzae type b.

[c]PCV: pneumococcal vaccine.

Sample Size

The current proportion of children returning back on time to complete their immunization in the clinic is estimated to be around 75%. We therefore aim to improve participation in the intervention clinic. With a study power of 80%, α=.05, and β=.2, we need to recruit a total of 400 participants (at a 1:1 ratio, ie, n=200 participants per study arm). We will include patients lost to follow-up in an intent-to-treat analysis strategy.

Inclusion and Exclusion Criteria

All registered parent-child units who fulfill the following inclusion criteria will be invited to participate in the study: (1) registration at the clinic within the past month at the time of the study; (2) subsequent immunization scheduled for newborns; (3) parents aged more than 18 years; (4) at least one parent owns a cell phone, and (5) residency in the northwestern province. Potential participants will be excluded if the baby is coming for its second or later immunization visit or if the parents are not residents of the northwestern province.

Intervention and Control Groups

The recruitment will be done through two steps. In step 1, the intervention group will be recruited. Then, in step 2, when the sample size is achieved, recruitment of the control group will be conducted until we reach the required sample size.

Intervention Group

Study participants in the intervention group will receive the CIMA automated reminders on their cellphones. Messages will be sent to them to remind them of their appointments. Also, the CIMA system will provide educational information to the parents based on the parenting skills materials from the UNODC [7,10].

After obtaining informed consent, we will give each baby a study ID number that starts with the letter *I* (for “intervention”) and a continuous ID number that starts with the number 1001. Then, we will write the study ID number on a sticker that will be placed on the vaccination card of the newborn, so we can identify the baby in later visits as being enrolled in the CIMA intervention study group. For example, the first baby that will be enrolled in the intervention group will be given the ID number I-1001 and the last baby will have the ID number I-1201.

After the newborn receives the first vaccine, the vaccination nurse provides the parent an appointment date for the second contact vaccine. Then, we will record the appointment date in

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the CIMA database and schedule an automated reminder for the parents that will be sent at two time points: (1) 1 week before the appointment and (2) 2 days prior to the second contact appointment date. For example, if the second contact appointment date is scheduled for a Thursday, the automated SMS reminder will be sent out on the Thursday of the previous week and on the Tuesday of the same week. The content of the message will be as follows: "Dear parent, this is a kind reminder for the vaccination appointment of your child, scheduled on Thursday [date] at the Azire Integrated Health Centre." This message has a total of 150 characters and can thus fit in 1 SMS; SMS messages have a maximum number of characters of 160. When the parents come to the second contact appointment, we will be able to identify enrolled newborns by the sticker that was placed on the vaccination card. We will record the date of arrival at the second contact appointment in the CIMA database. Each week, we will auto-generate a list of newborns that have missed their second contact appointment, and we will send a reminder to the parents about missing the appointment. The content of the message will be as follows: "Dear parent, your child has missed the vaccine appointment this week. You are requested to come as soon as possible to the Azire Integrated Health Centre"; this message includes a total of 153 characters and can fit into 1 SMS.

Each week, the parent will receive one SMS that has an educational message on parenting skills. We will use the UNODC parenting skills toolkit [9], which was tested in the past with CIMA in Jordan [10]. The last SMS educational message will be sent out on week 4 of the study (Table 2).

Table 2. Overview of the action plan for the intervention and control groups.

	Study week							
	0[a]	1	2	3	4	5	6[b]	7
Intervention group								
Explain the study, ask for consent, administer the questionnaire (Multimedia Appendix 1)	✓							
Register the cell phone number of the parent in the CIMA[c] database	✓							
SMS education message		✓	✓	✓	✓			
SMS reminder for the appointment						✓		
Automatically scheduled reminder 1 week prior the appointment							✓	
Mark in the CIMA registry if the newborn came back on time							✓	
SMS reminder for parents that have missed the appointment								✓
Control group								
Explain the study, ask for consent, administer the questionnaire (Multimedia Appendix 1)	✓							
Register the expected date for the second contact (for comparison with the intervention group)	✓							
Mark the date when the newborn came back to the clinic							✓	

[a]First contact.

[b]Second contact.

[c]CIMA: Children Immunization App.

Control Group

Participants in the control group will continue to receive regular routine messages from the health facility. After obtaining consent, we will use the same procedure to give ID numbers to the babies in the control group, except that the letter *C* (for "control") will be used instead of *I*. The control group will receive usual care at the clinic. For example, the vaccination nurse will review the schedule of vaccine appointments at the end of the month, then call parents that have missed their baby's appointment to remind them about the second contact vaccine appointment and to invite them to come back to the clinic. No educational messages and no SMS reminders will be sent out to the participants enrolled in the control group.

Measures

The key measures for this study are the percentage improvement in parent-child units who return for follow-up visits and the percentage improvement in children who receive immunization as scheduled. We will send reminders to the parents of children that do not come back to their appointments within 1 week after the scheduled appointment.

Data Collection

At the time of study enrollment, we will approach parents of newborns coming for their first immunization dose. In the intervention and control arms, we will collect baseline information using a questionnaire (Multimedia Appendix 1). As we plan to monitor adherence to vaccination appointments from birth to the age of 6 months, we will use the clinic ID

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number to monitor visits using the clinic health care records for both study groups.

Both clinical visits and vaccination attendance will be collected from the health facility registration records. Informed consent will be obtained at the baseline visit from clients after an explanation of the study purpose and the data analysis. No personal identifiers will be collected (ie, names or personal addresses), but we will collect the phone numbers of one of the parents, as this will be used to send the SMS messages. All data will be stored in a secured location. No financial compensation will be offered to the parents, and they will have the choice to ask to stop being enrolled in the study.

Data Collection Tool

Data will be collected from the clinic registration books for the upcoming second contact appointment visit. The baseline questionnaire (Multimedia Appendix 1) will be used to collect basic demographic and household information, including the type of household (rented house, rented apartment, informal settlement, other, or no answer), date of birth of the father and mother, level of education of the father and mother (don't know how to read and write; know how to read and write; primary or elementary school; secondary school; postschool technical level; university level; don't know or don't remember, or refused to answer), the availability of a private toilet inside the household (yes or no); professional status of the father and mother (full-time job, part-time or hourly job, self-employed, do not work, returned, or refused to answer), total number of children living at home, who is the decision-maker for vaccination (both parents, mother, father, or other); total number of children younger than 5 years at home; and amount of money spent by the household in the month prior the date of the interview.

Data Analysis

The data analysis will be conducted in 3 steps. First, we will summarize the characteristics of the babies and their parents using a general descriptive statistical analysis and compare these characteristics between the intervention and control groups. We will use the Fisher exact test to detect any statistically significant differences in the key measures between the intervention and control groups (P values <.05 will be considered statistically significant). Second, we will calculate the attrition rate of the babies and compare the attrition rate in each of the intervention and control groups. Third, we will compare how often both study groups return for 1 follow-up visit using a Kaplan-Meier survival analysis. We will determine the proportion of babies that did come back on time at the end of each week to help the clinic to visually identify the proportion of latecomers and which geographical areas they live in. We will use R (R Core Team) for the statistical analysis. For the descriptive analysis, we will use the *dplyr* library package in R; for the Fisher exact test, we will use the *stats* library package; for the Kaplan-Meier survival analysis, we will use the *survival* library package.

Ethical Considerations

Ethical approval was received from the Cameroon Ministry of Public Health, Northwest Regional Delegation of Health (324/ATT/NWR/RDPH/BRIGAD).

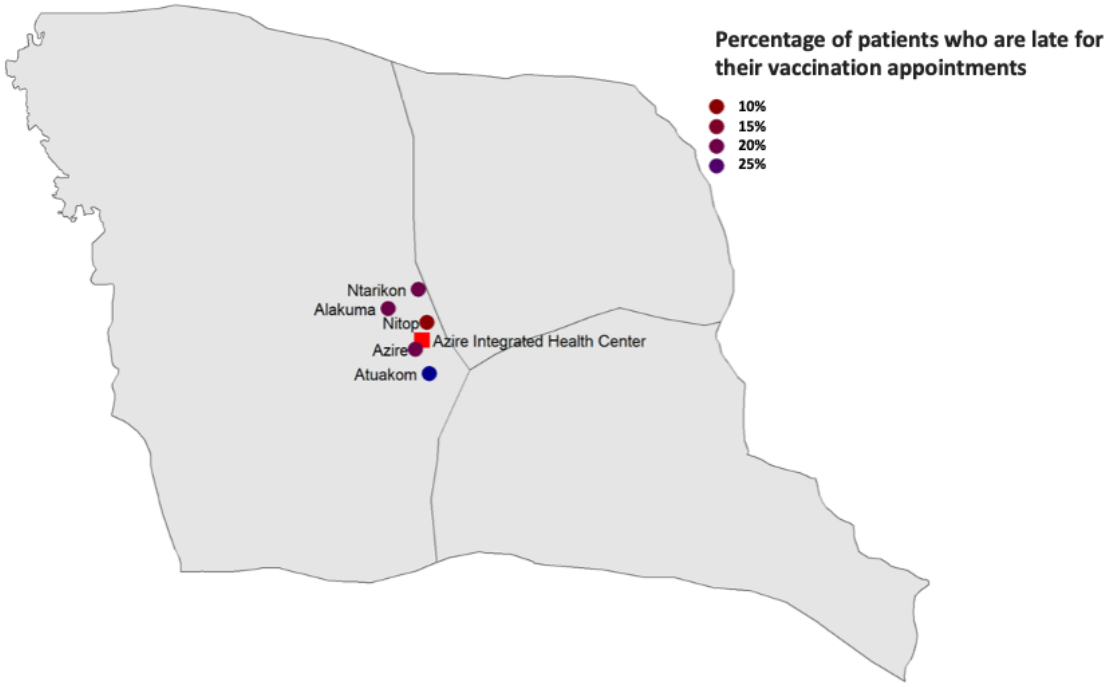
Results

Study enrollment was planned for the beginning of 2023. Usually, the clinic schedules child vaccination 2 days per week (Tuesdays and Thursdays). Approximately 20 of 50 babies are newborns and receive their first-contact vaccine (Table 1). This means that we estimate that we will need to approach 40 of 100 parents per week to explain the study and ask for consent. We estimate we will recruit a total of 200 babies in each study group during a total period of 5 weeks (pending the response rate per week of the parents). Therefore, the total duration of recruitment might be between 10 and 12 weeks.

We expect to complete the study by July 2023 and complete the data analysis and submission of the final report by 2024. We include a dummy example of how the data will be visualized for the vaccination clinic site (Figure 1). The general characteristics of the babies in both study groups are presented in a table, including the characteristics of the babies that did not come back to the clinic. The Kaplan-Meier survival analysis will be shown as a figure.

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Figure 1. Fictional figure projecting how the data for patients in Bamenda who are late for their vaccination appointments will be visualized.



Discussion

Anticipated Findings

Child immunization is a crucial public health objective and an essential strategy in primary health care services. However, globally, there are still millions of children who are unvaccinated and at risk for VPDs. Prior to the COVID-19 pandemic, the effectiveness of automated reminders for children attending vaccination appointments was tested either by the team members of this project in the context of a refugee camp in Jordan [6,7] and the general community in Canada [3] or by other authors in Ethiopia [11], Nigeria [12], and other contexts [13,14].

The COVID-19 pandemic has also led to an increase in the number of missed follow-up doses for children. In Cameroon, the vaccination system has been weakened, and herd immunity is compromised. Also, UNICEF has warned about the impact of spreading false information (known as misinformation) about national vaccination programs in Cameroon [15]. The spreading of misinformation is considered one of the major threats to public health interventions, especially during and after COVID-19.

In this paper, we described version 1.0 of a study protocol for a nonrandomized controlled trial of child vaccination reminders in a turbulent, semiurban/semirural setting in a low-income country. The main goal of the study is to implement an automated SMS reminder system at the Bamenda primary health care center. The objectives of the study are to analyze the effect of the cellphone reminder intervention on the percentage of parent-child units returning for follow-up visits and the percentage of children receiving immunization as scheduled. Instability in northwestern Cameroon makes it important to improve childhood vaccination, and to the best of our knowledge, this is the first study to support a national vaccination program by (1) using an automated system to send reminders in the form of SMS messages and (2) send health educational messages about vaccines, as well as about parenting skills. Ames et al [16] found that childhood vaccination communications have focused on national campaigns against polio, instead of routine vaccination programs. Therefore, we think this study might have the secondary impact of promoting routine vaccination among parents.

We have previously tested this concept among refugees at the Zaatari camp in Jordan, a vulnerable group [5]. We used the same questionnaire in Jordan but provided CIMA in the form of an Android smartphone app because the majority of households in the camp owned at least one Android smartphone. The market share of smartphones in sub-Saharan Africa is growing, but they have not yet reached the majority of the population; therefore, we are using an SMS reminder system. The authors have experience in the field setting up such systems in vulnerable contexts, such as in the Central African Republic [17].

The adoption of digital health solutions is becoming important and a crucial means of enhancing the health care system in general. The testing of digital health for the improvement of childhood vaccination programs in resource-limited settings will be a great help in improving equity of access to vaccination [18]. So far, digitization has not been done in a systematic fashion, and this study in Cameroon will contribute to the learning process on how to implement and use such digital health solutions in resource-limited settings.

The outcome of this study will be of high importance for finding a holistic approach to the improvement of childhood vaccination schedules in unstable contexts such as northwest Cameroon. Parents experience stress, especially during times of uncertainty. Therefore, this study will support new studies on assessing perceptions among parents of parenting-skills health education messages sent in the form of regular SMS messages. These

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messages were developed by the UNODC and have been tested in different contexts around the world, including in our study of CIMA in the Zaatari camp in Jordan [5]. In our planned study in Cameroon, we will send the messages via SMS, which will be done for the first time. Finally, the results of this testing may lead to the development of a holistic approach and eventually a tool to digitally register, enhance, and monitor the vaccination schedule of children in settings such as Cameroon.

We should note that the outcome of this study will open new opportunities to explore the usefulness of automated SMS reminder systems in resource-limited settings. Childhood vaccination programs have been weakened during the COVID-19 pandemic, and we hope that our intervention will empower both parents and the vaccination clinic staff to improve vaccination coverage [19]. Finally, by improving vaccination coverage, we will be able to reduce the risk of VPD-related outbreaks in resource-limited settings.

Limitations

We foresee the following points as potential limitations of our planned study: (1) The language context of the study is predominantly English, so the study may not be generalizable to the rest of Cameroon, where French is spoken. (2) We plan to test the effect of the SMS reminders for 1 vaccination appointment only, so further studies will be needed to ensure effectiveness over longer periods of time (for example, to ensure that parents will not have SMS fatigue). (3) The scalability of the SMS reminders needs to be evaluated from a cost-effectiveness perspective to ensure that we can provide an estimated cost for policymakers if the Ministry of Health of Cameroon scales the project (however, we performed a cost-effectiveness analysis for the CIMA-Jordan project and found that the cost was low in the context of a low-income country [20]). (4) Bamenda is considered a turbulent location due to the current crisis; this might affect the study if the situation becomes more turbulent. Such situations, labeled "armed conflicts," are known strongly impact childhood vaccination [21], as they may lead to either forced migration of the parents out of Bamenda or short-term closure of the Azire Integrated Health Centre.

Conclusion

There is limited evidence on effective interventions to improve childhood vaccinations in turbulent settings [14]. It is crucial to ensure parents receive reminders and correct information about all vaccines. Therefore, this project will have an impact on the health of the children and on the public health system. Also, we expect that this study will support the work of sharing correct information with parents. After the end of this study, we foresee planning to expand the implementation of CIMA to other primary health care centers in Cameroon in order to reach a larger population of children, including an evaluation of the effectiveness of the SMS reminder intervention on vaccination coverage and adherence to follow-up visits. Additionally, we will explore the potential for integrating CIMA with other health care systems, such as electronic medical records, to improve data collection and analysis.

Acknowledgments

The authors alone are responsible for the views expressed in this article and they do not necessarily represent the views, decisions, or policies of the institutions with which they are affiliated.

Data Availability

The data sets generated during and/or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

YEN, UN, GIM, and ZEK conceptualized the study; YEN, UN, GIM, and ZEK designed the methodology; all authors contributed to writing, including original draft preparation, review, and editing; UN, GIM, and ZEK supervised the study. All authors have read and approved the published version of the paper.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Questionnaire for baseline information for the Children Immunization App (CIMA).
[DOCX File , 20 KB - resprot_v12i1e47018_app1.docx]

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Abbreviations

BCG: bacillus Calmette-Guérin
CIMA: Children Immunization App
DTP-HepB-Hib: diphtheria, tetanus, pertussis, hepatitis B, Haemophilus influenzae type b
OPV: oral polio vaccine
PCV: pneumococcal vaccine
UNICEF: United Nations Children's Fund
UNODC: United Nations Office on Drugs and Crime
VPD: vaccine-preventable disease
WHO: World Health Organization

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Protocol

Technology Acceptance of a Social Robot (LOVOT) Among Single Older Adults in Hong Kong and Singapore: Protocol for a Multimethod Study

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Abstract

Background: Given the rapidly aging nature of our global population, policy makers around the world are now emphatically promoting active aging. To address the psychosocial needs of older persons and support active aging, researchers are exploring the use of assistive technologies, specifically social robots as companions. However, there is limited evidence on the efficacy of social robots in promoting active aging for older people in the Hong Kong and Singapore contexts.

Objective: This study presents the protocol of a study that investigates the acceptance and quality of interaction between a Japanese social robot, LOVOT, and single older adults in Hong Kong and Singapore.

Methods: We used a baseline assessment to measure the primary outcome, participants' acceptance of technology, and a sense of loneliness, namely, the participants' differences in responses to LOVOT before and following their interaction with the social robot in this multimethod study design. The baseline assessment consisted of the Qualtrics survey, which measures senior technology acceptance, loneliness, older people's quality of life, subjective happiness, cultural values, willingness to pay, and demographic characteristics, along with the LOVOT's sociability and system usability. In the study, participants interacted with LOVOT in 3 sessions before being surveyed to measure the older people's acceptance and attitudes toward LOVOT. A pre–social robot intervention also occurred in the first session. The study was conducted in both Hong Kong and Singapore. A total of 15 single older adults (ie, individuals who live alone) from Hong Kong and another 15 from Singapore were recruited. Participants were 60-75 years of age, lived by themselves, and had no known cognitive or mental issues.

Results: The study began recruiting in March 2022, and recruitment was completed at the end of October 2022. Data collection and data set construction were completed at the end of January 2023. Analysis of the data is currently being conducted, and we plan to publish the results by mid-2023.

Conclusions: At an individual level, the study will clarify if LOVOT influences single older adults' psychosocial well-being by reducing their loneliness. At a community level, the study's findings will illustrate whether LOVOT can provide increased social connectedness while decreasing individual loneliness. Last, this study's conclusions can inform policy makers to provide social robots to older people to improve their quality of life. Findings can also inform gerontechnology developers on which aspects and cultural considerations to take into account for future inventions.

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KEYWORDS

gerontechnology; older people; senior technology acceptance; single people; social robot

Introduction

Background and Theory

The field of gerontechnology explores the development and use of technology that caters to the needs of the aging population [1]. In light of the COVID-19 pandemic and in recognition of research that has shown that feelings of social isolation and loneliness can result in serious health risks for older people, gerontechnology researchers and inventors are increasingly seeking solutions for the "loneliness epidemic" through assistive technologies [2]. Indeed, recent research has found that certain robots can support the independent living of older people primarily by improving their "mobility, self-care, and interpersonal interaction" [3,4].

In the realm of interpersonal interactions, a proposed solution to the issue of loneliness among older people is the use of socially assistive robots (SARs) in older people's care settings [5,6]. SARs engage in social interactions with older people by acting as companions or service robots [3]. There is a paucity of studies available on the use of SARs for improving the quality of life of older people in Hong Kong and Singapore. Existing Technology Acceptance Models [7,8] were applied to the general population without a specific focus on older adults. Chen and Chan [9] proposed the Senior Technology Acceptance Model (STAM) to explain the mechanisms of gerontechnology acceptance in older adults.

LOVOT, a Japanese social robot created by Groove-X Japan in 2019, was developed with the aim of acting as a pet-like companion for families. It is equipped with artificial intelligence as well as advanced sensor features. As such, LOVOT evolves over time based on its interactions with its user through its machine learning technology (eg, deep learning), which allows it to develop a unique personality as well as enact intelligent real-time movements [10]. Moreover, LOVOT also has special features, including its internal temperature regulation, which grants it the average body temperature of humans, and its customizability through a phone application. In addition, LOVOT enacts verbal and physical responses to human interactions, such as using animated eye expressions and flapping its wings to greet someone. With its ease of use, its artificial intelligence technology, and its pet-like features, LOVOT is an ideal companion for older people as shown in Figure 1.

Figure 1. Social robot: LOVOT.



Objectives

This study outlines the protocol of a pioneer study on the acceptance of LOVOT by single older adults in Hong Kong and Singapore. The protocol involved a baseline assessment and 3 interaction sessions with a LOVOT. The study used a mixed methods design to measure these primary outcome measures: senior technology acceptance [11], loneliness [12], older

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people's quality of life [8,13] subjective happiness [14], cultural values [15], willingness to pay, demographic characteristics, and the LOVOT's perceived sociability [16] and system usability [17]. These quantitative measures, along with observational data from interaction sessions and pre- and postinteraction interviews, will be holistically analyzed to investigate the factors affecting the acceptance of LOVOT among the participants. Fundamentally, this protocol aimed to answer 2 questions: (1) What factors affect single older adults' acceptance and nonacceptance of social robots? and (2) What is the experience like interacting with social robots?

Methods

Ethical Approval

We obtained ethical approval from the Human Research Ethics Committee at The University of Hong Kong (#EA220116). Informed consent was obtained from all participants included in the study. This study was conducted between June and December 2022.

Recruitment

The criteria for participants were as follows: (1) 60-75 years of age; (2) live alone; (3) speak English, Mandarin Chinese, or Cantonese; (4) have no known cognitive impairments; and (5) participate in the study voluntarily. In Hong Kong, participants were recruited through networks of researchers. In Singapore, participants were recruited through collaboration with a local older adult activities center. Before recruitment, participants were briefed on the purpose and requirements of the study, and informed consent was obtained. Fulfillment of participant criteria was checked upon recruitment and confirmed by researchers during the additional screening before the baseline assessment. A total of 15 participants were recruited from Hong Kong and 15 from Singapore, comprising a total of 30 participants.

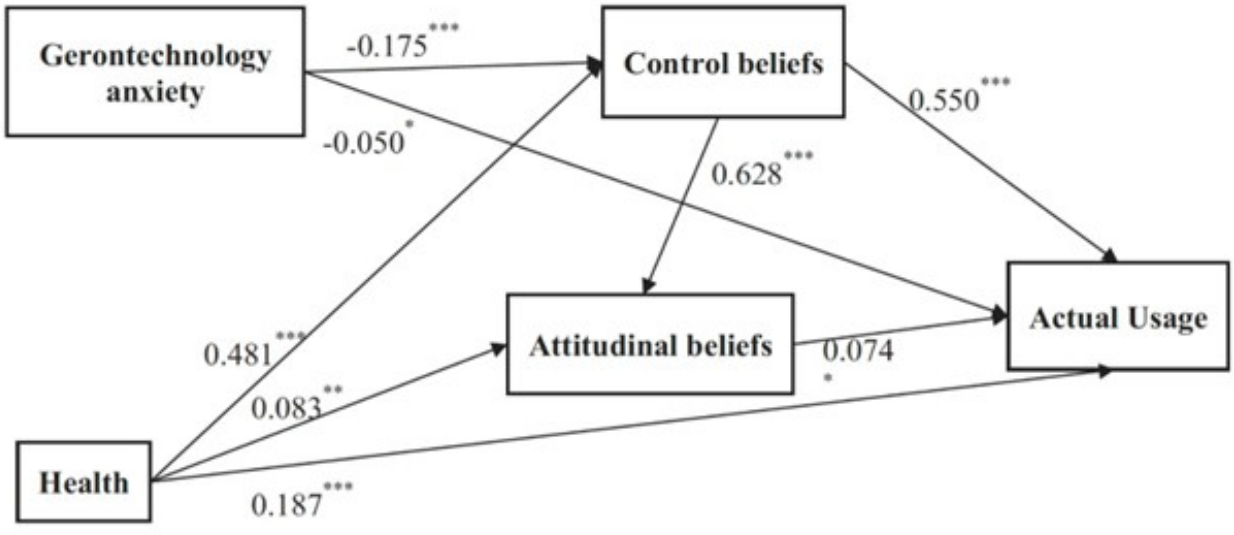
Measurements

Senior Technology Acceptance

The Technology Acceptance Model, first developed by Davis et al [7,18], uses the main attitudinal factors of perceived usefulness (PU) and perceived ease of use (PEOU) to predict acceptance and rejection of information technology. PU is defined as "the degree to which a person believes that using a particular system would enhance his or her job performance," and PEOU is defined as "the degree to which a person believes that using a particular system would be free of effort" [7]. Though the model proves to have a strong empirical basis based on self-reports of technology usage, this requires a model that incorporates attitudinal factors that may be affected by aging [7].

Chen and Chan [9] proposed the STAM to better account for the "physical, psychological, and social characteristics" that influence technological acceptance by older people. Along with PU and PEOU, Chen and Chan [9] took into consideration "age-related health and ability factors such as self-reported health conditions, functional abilities, cognitive abilities, and attitude to aging and life satisfaction" to predict the acceptance of technology by older people. Figure 2 illustrates the STAM Model.

Figure 2. Senior Technology Acceptance Model (STAM) [11]. Significant at *P<.05; **P<.01; ***P<.001 (two-tailed).



To measure senior technology acceptance, improve accessibility so that respondents of diverse educational levels can easily answer STAM questionnaires, and improve response rates, Chen and Lou [11] developed a shorter 14-item scale by more effectively following a "sequential 4-step item-reduction strategy.". The scale measured the influence of attitudinal beliefs, control beliefs, gerontechnology anxiety, and health on technology acceptance and explained up to "81.5% variance in usage," which was even higher than the original model [11]. This modified questionnaire was fully adapted for this study by specifying "technology" as LOVOT, the social robot, to investigate the acceptance of LOVOT as a companion for single older adults. The 14-item scale included responses rated on a 10-point Likert scale, with scores ranging from 0 (strongly disagree, very poor, very uneasy, and very unsatisfied) to 10 (strongly agree, very good, very easy, and very satisfied) [11].

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The finalized, adapted version of the STAM questionnaire has 5 items to measure behavioral intention added, following previous literature [7,8].

Sociability of Robots

Another factor influencing the acceptance of technology, specifically of assistive social robots in older people's care contexts, is the sociability of robots. Sociability refers to the robot's ability to perform social or interactive behaviors [19]. While older adults may be hesitant to use technology due to "stigmatization, nonadaptability, or social influences," the sociability of robots, particularly their extraverted behaviors, could positively affect their use and acceptance [19]. Due to the "low explanatory power" of theories like Venkatesh and Davis's [8] Unified Theory of Acceptance and Use of Technology, Heerink et al [19] suggested a model to illustrate the effect of robot sociability on acceptance by older users. The model consisted of 40 statements, and its strength lies in its suitability for repeated testing, to measure the change of variables such as attitude and trust [19]. The 11 most relevant questions were chosen and adapted for the study; responses were rated on 5-point Likert scales, with 1 being totally disagree and 5 being totally agree [16].

Loneliness

Feelings of loneliness among older people and its consequences on their physical and mental health is a globally recognized public health issue [2]. To measure whether feelings of loneliness were impacted by interactions with LOVOT, the University of California, Los Angeles loneliness scale, a "20-item scale designed to measure one's subjective feelings of loneliness as well as feelings of social isolation," was used [20]. Responses were rated on a 4-point Likert scale, with 1 being never and 4 being always [12,21]. This scale was proven to have high internal consistency and test-retest reliability as well [12,21].

Older People's Quality of Life

Along with loneliness, the influence of the companionship of LOVOT on older people's quality of life was also measured in this study. Models measuring the quality of life among older people in particular should take into account the socially relevant factors that come with aging [13]. Bowling et al's [13] research found that "the foundations of Quality of Life emphasized by (older) people were psychological well-being and positive outlook, having health and functioning, social relationships, leisure activities, neighborhood resources, adequate financial circumstances, and independence." Bowling et al's [13] 13-item scale that measures older people's quality of life is centered around these aforementioned factors; hence, it was used for this study. The scale has responses rated from 1 (strongly disagree) to 5 (strongly agree).

Subjective Happiness

To examine the difference in self-perceived happiness of participants before and after their interaction with LOVOT, a happiness questionnaire with a subjectivist approach was used. The subjectivist approach emphasized the role of individual subjective experiences and their influence on self-perceived well-being. This scale, developed by Lyubomirsky and Lepper [14], involved 4 brief items: the first 2 items involved completion of a sentence by choosing a number on a 7-point scale, and the latter 2 had participants choose how closely they identified with a statement, again on a 7-point scale. These measures involved reverse coding to ensure respondent consistency. According to an examination of studies using this measure of subjective happiness, the measure maintained internal consistency even across 14 samples of various ages, occupations, and cultures [14], emphasizing the scale's cross-cultural applicability.

Perceived System Usability

To measure the older adults' perceived usability of LOVOT, Brooke's [17] "Quick and Dirty Usability Scale" was used. This scale measured 3 key factors: effectiveness, "the ability of users to complete tasks using the system and the quality of the output of those tasks"; efficiency, "the level of resource consumed in performing tasks"; and satisfaction, "users' subjective reactions to using the system" [17]. The scale consisted of 10 items, with responses rated on a 5-point Likert scale, from 1 (strongly disagree) to 5 (strongly agree) [17].

Perceived Willingness to Pay

For a better understanding of the amount of money that participants would be willing (and not willing) to spend on LOVOT, 4 open-ended questions were asked. Participants were not informed of the retail price of the LOVOT and were asked to provide subjective answers, not what they assumed could be the price.

Demographic Information

Participants' demographic information, including gender, age, housing, educational level, family status, self-perceived financial status, and pet ownership, was obtained through self-reporting measures.

Protocol

Overview

Data were collected over a 4- to 6-week period with 30 participants. Previous experiments measuring senior technology acceptance of social robots had similar sample sizes, such as Heerink et al's [22] study on "The Influence of a Robot's Social Abilities on Acceptance by Elderly Users," which had a total of 36 older patients. This study, however, had a larger sample size compared to other longitudinal studies on social robot acceptance by older people, which mostly recruited 6-10 participants [8,23,24].

The study design consisted of a baseline assessment and three 15-minute interaction sessions. Each interaction took place within the first 2 weeks of the previous interaction and was recorded for later qualitative analyses. The 15-minute interaction time was chosen based on previous studies on robot acceptance by older users. For example, Heerink et al's [22] study had a total of 10 minutes of robot-human interactions, while Marti et al's [25] study included 20-minute group interaction sessions, twice a week, over a month-long period [8,22].

As depicted in Table 1, for this study, a baseline assessment (T0) was first conducted through a survey administered through

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Qualtrics. To ensure optimal comprehension, the researchers read out and manually completed the survey on behalf of the participants. The baseline survey adapted globally renowned questionnaires to measure STAM, perceived sociability of the robot, loneliness, older people's quality of life, general quality of life, subjective happiness, the robot's system usability, participants' willingness to pay, cultural values, along with general demographic information.

Table 1. Survey and interview outcomes breakdown.

	T0: baseline assessment	T1: first interaction (15 minutes)	T2: second interaction (15 minutes)	T3: third interaction (15 minutes)
Survey outcomes measured	• STAM[a] • Sociability of robot • Loneliness • Older people's quality of life and general quality of life • Subjective happiness • System usability • Willingness to pay • Demographics • Cultural Values	• STAM • Sociability of robot • Loneliness • Older people's quality of life and general quality of life • Subjective happiness • System usability • Willingness to pay	• Loneliness • Older people's quality of life and general quality of life • Subjective happiness	• STAM • Sociability of robot • Loneliness • Older people's quality of life and general quality of life • Subjective happiness • System usability • Willingness to pay
Interviews	N/A[b]	Pre- and Postinterview	N/A	Postinterview

[a]STAM: Senior Technology Acceptance Model.

[b]N/A: not applicable.

Before the first interaction (T1) with the LOVOT, participants were interviewed about their attitudes toward technology. To prepare them for LOVOT appearance, participants were briefed on the background of LOVOT and how it was invented to be a pet-like social robot in Japan. They were shown a 5-minute video covering the basic instruction of interacting with LOVOT, which includes calling LOVOT's name, hugging and feeling LOVOT's warm body, tickling LOVOT's nose, rubbing LOVOT's arms, looking at LOVOT's eyes, and taking a selfie with LOVOT. They were asked to choose an outfit from a selection for the LOVOT. After that, they shall freely interact with the LOVOT for 15 minutes while the researcher left the room. During the first interaction, the LOVOT was set on "immobile" mode and placed on a table in front of the participant; participants were asked to think of a name for the LOVOT as well as a story about them and LOVOT during this time. Following the interaction, participants completed the same Qualtrics survey without the demographics and cultural inclination sections. Participants were then asked to share their choice of the name and story behind LOVOT, along with their thoughts about their interaction.

The second interaction (T2) took place within 2 weeks of the second interaction. The LOVOT was placed on the floor for this interaction and permitted to move around. After the interaction, participants completed 3 sections of the Qualtrics questionnaire, measuring their loneliness, older people's quality of life, general quality of life, and subjective happiness. The third interaction (T3) began with the 15-minute interaction session with the LOVOT; similar to the second session, in the third session, the LOVOT was permitted to move around the room freely. However, this time, the participants were given the option to play music to the LOVOT for them to dance to and were told that if they sang or hummed to LOVOT, it would hum back. After this third and final interaction, the participants completed the same Qualtrics survey administered after the first interaction. They were then interviewed again about their experience interacting with the LOVOT.

Additional Interaction Period

Participants were asked if they would like to take the LOVOT home for further interaction and were asked to provide reasons for their responses. For those who did not consider taking the LOVOT home, the intervention was considered complete. Those who did consider taking the LOVOT home were offered a 7-day interaction period with the LOVOT. When they returned LOVOT, a follow-up individual interview was conducted to explore the participants' feedback and experience during the 7-day interaction period.

Results

Interview Outcomes

Before the first interaction with LOVOT (T1), participants were asked about their use and acceptance of technology. Specifically, participants were asked about their most commonly used device, its system usability, the features they find easy to use, and who they would turn to if they required advice or help, among other items. Participants were then asked similar questions about a technological device they struggled with using or did not want to learn to use and what caused them difficulties in using it. These questions aimed to measure the degree of the participants' general acceptance and anxiety toward using technology.

Following the first interaction with LOVOT (T1) and the last interaction with LOVOT (T3), participants were asked about their feelings and experiences with playing with LOVOT, how it compared with pets, and their acceptance of it. Questions were phrased in a neutral manner to ensure no response biases. These questions provided a deeper understanding of the participants' acceptance of LOVOT. All interviews were recorded and transcribed verbatim for further analysis.

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Each 15-minute interaction with the LOVOT was recorded and analyzed by the researchers. Researchers analyzed and categorized observations based on these 3 categories: exclusively verbal actions, physical actions, and combination actions (including simultaneous verbal and physical actions). These observations were analyzed for common trends and phrases. The interactions were recorded for further postinterview analysis by the researchers.

Timeline

The study began recruiting in March 2022, and recruitment was completed at the end of October 2022. A total of 30 participants successfully completed the longitudinal study. Data collection and data set construction were completed at the end of January 2023. Analysis of the data is currently being conducted, and we plan to publish the results by mid-2023. The interventional protocol is available in English and Traditional Chinese and will be available upon request from the corresponding author.

Discussion

Overview

This study aimed to measure the efficacy of LOVOT, a Japanese social robot, among single older adults in Hong Kong and Singapore. Namely, the study investigated the acceptance and quality of interaction between LOVOT and participants. With a sample size comparatively larger than other longitudinal studies on social robot acceptance among older people, this study protocol allowed for robust and multimodal data collection. The protocol used a combination of highly cited and globally recognized scales to ensure high construct validity. The data from our multitude of survey outcomes measures qualitative data from observation analysis, and the findings from our interviews will offer a unique, complex perspective on the acceptance of social robots. Though the baseline assessment that is used in this protocol was on the longer side, it captured the great diversity of elements that influence the attitudes of older people. By assessing self-perceived health, happiness, and financial situations, to name a few, researchers can gain a better understanding of how various factors intersect to impact social robot acceptance.

At an individual level, the study will clarify if LOVOT influences single older adults' psychosocial well-being by reducing their loneliness. At a community level, the study's findings will illustrate whether LOVOT can provide increased social connectedness while decreasing individual loneliness. Last, this study's conclusions can inform policy makers to provide social robots to older people to improve their quality of life. Findings can also inform gerontechnology developers on which aspects and cultural considerations to take into account for future inventions.

Limitations

The study has some limitations. For one, the primary participants are mainly older women; thus, the implications of the study may not be generalized to older men. Another limitation is the potential bias and effect resulting from confounding factors. However, we have provided preintervention training to all assessors to minimize bias during the intervention. Last, the interaction time is limited to 15 minutes per session due to time constraints and restrictions due to the COVID-19 pandemic. Nevertheless, the literature review has been conducted to verify that 15-minute interactions are sufficient for exploratory longitudinal studies.

Acknowledgments

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Data Availability

The data sets generated and analyzed during this study are available from the corresponding author upon reasonable request.

Conflicts of Interest

None declared.

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Abbreviations

PEOU: perceived ease of use
PU: perceived usefulness
SAR: socially assistive robot
STAM: Senior Technology Acceptance Model

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Protocol

Improving Medication Safety in Cancer Services for Ethnic Minority Consumers: Protocol for a Pilot Feasibility and Acceptability Study of a Co-Designed Consumer Engagement Intervention

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Abstract

Background: People from ethnic minorities are often exposed to unsafe care contributing to poorer health care outcomes. Medication safety is a high-risk area requiring intervention to improve care outcomes. Using an adapted, experience-based co-design process with cancer service staff and patients from ethnic minorities, a medication communication tool was created: Making it Meaningful (MiM).

Objective: We aim to test whether the MiM tool is feasible and acceptable for use with ethnic minority consumers in cancer services in Australia.

Methods: A single site, controlled before and after this pilot study, will be used. Patients from Mandarin- and Russian-speaking backgrounds are eligible for inclusion. In total, 40 patients from these cultural backgrounds will be recruited and stratified by language to the intervention and control groups, with 20 participants in the intervention and 20 in the control group. Further, 4 health practitioners will be recruited and trained to use the MiM. Clinicians providing care for patients in the intervention will use the MiM during their usual appointment while providing medication communication using standard care processes for the control group. Telephone surveys will be conducted with participants at 3 time points, T1 before the intervention, T2 1 week post intervention, and T3 1 month post intervention, to assess knowledge and self-efficacy in medication management, perceived usability, and acceptability of the MiM. Qualitative interviews with clinicians who have used the MiM will be conducted 1 month postintervention to explore their perceptions of MiM feasibility and acceptability.

Results: Ethical approval for this research has been provided by the South Eastern Sydney Area Health Human Research Ethics Committee (HRECXXX). Bilingual field-workers, 1 Mandarin-speaking and 1 Russian-speaking, are contacting eligible patients to enroll. It is anticipated that recruitment will be completed by October 2023, with data collection completed by December 2023.

Conclusions: Using experience-based co-design, we identified communication about medication, particularly between appointments, as a key issue impacting the safety of care for patients from ethnic minorities accessing cancer services. Increasing consumer engagement in medication management was identified as a strategy to reduce medication safety problems in cancer care; the MiM strategy was developed to address this issue. It is anticipated that by using the MiM, patient knowledge about prescribed medications and confidence in medication management will increase. Evidence from the pilot study will be used to

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inform a full-scale trial of the MiM tool with a range of ethnic minority communities accessing cancer services. A full-scale trial will seek to determine whether the MiM intervention is effective in knowledge and confidence about medication management, but also whether this improves patient outcomes in cancer care.

Trial Registration: Australian New Zealand Clinical Trials ACTRN12622001260718p; https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=384658&isReview=true

International Registered Report Identifier (IRRID): DERR1-10.2196/49902

(JMIR Res Protoc 2023;12:e49902) doi:10.2196/49902

KEYWORDS

co-design; ethnic minority; health care equity; patient engagement; patient participation; patient safety; medication safety; medication therapy; medication therapy management; patient transfer; consumer; engagement; intervention; ethnic minority

Introduction

Background

People from ethnic minority backgrounds can experience more unsafe care in health services than the general population. Specifically, current evidence indicates that people from ethnic minority backgrounds experience a higher rate of medication errors, infections, and face systemic barriers to communication with health care providers [1,2]. A range of factors are identified as contributing to experiences of unsafe care. These include; language proficiency, individual or organizational health literacy, socioeconomic factors, and ineffective communication and collaboration between health professionals, patients, and their families [1].

Medication management has been identified as a particular challenge to patients and the family and friends who support them. In this protocol, the family, caregivers, or friends who provide this support will be referred to as carers. More effective engagement between patients and health care providers has been identified as an important strategy to address this issue in several studies [3-5]. For example, medication errors can be reduced by increasing patients' knowledge about the purpose and use of their medications via supply of tools such as handheld medication lists [6]. Evidence of unsafe care among ethnic minority communities suggests that periods of transition in care (eg, hospital discharge and discharge from emergency department) pose particular risks to patient safety that may be addressed by improved patient engagement [7]. Hospital discharge is a period of high-risk for communication errors relating to medication [3,4]. Although there are strategies currently available to manage patients' participation in this transition, which are collectively described as patient engagement strategies, the potential for cultural and language diversity to moderate the effectiveness of these strategies is an important issue requiring further research [8,9].

Involving patients and carers in health care decision-making and care planning has been shown to improve health care safety in the general population [10-12]. Common approaches include encouraging patients and family members to raise questions or concerns with health professionals, to engage in learning about how to manage their own health, and to use preformatted tools or resources to plan care or guide decision-making processes [11]. Current patient engagement strategies rely heavily on effective individual communication skills and health literacy among patients and families. A recent review of strategies used to involve patients and families at point-of-care highlighted that none of the 26 identified strategies were explicitly developed for, or evaluated with, people from ethnic minority backgrounds [8]. In further work to explore the appropriateness of patient engagement strategies for people from ethnic minority backgrounds in an Australian health system context, we established that some existing strategies may be suitable but that adaptations were needed [13]. We therefore sought to develop an adapted patient engagement intervention using co-design with flexibility to meet the needs of a diverse patient population attending cancer services in New South Wales, Australia [14].

The Making it Meaningful Intervention

Making it Meaningful (MiM) is a co-designed medication management tool that aims to increase patients' and family members' understanding of medication management to enable them to contact health care staff between appointments, and following hospital discharge in order to raise concerns about their medications. The MiM is an adaptation of an existing medication management tool used in New South Wales cancer services. The adapted form provides translated information about medication side effects, in plain language and using images in order to meet the needs of populations with low English language proficiency. During the co-design process to develop MiM, the participating service identified that people from Russian- and Mandarin-speaking populations have low English language proficiency patients and commonly attend the participating service. These 2 language groups are therefore targeted in this pilot study. Full details of the co-design and development process have been reported elsewhere [14]. The MiM is attached as Multimedia Appendix 1.

Methods

Aim

To determine whether MiM is feasible and acceptable for use with ethnic minority consumers in cancer services in Australia, this study will seek to address the following objectives: (1) to investigate how patients and staff engage with MiM; (2) to assess the feasibility and acceptability of MiM; (3) to investigate the suitability of trial recruitment, retention, and data collection materials and processes; (4) to explore barriers and enablers of implementing the MiM; (5) to gather evidence of the nature and frequency of medication management issues that lead to

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emergency department visits and readmissions to inform the sample size required for a full-scale trial; and (6) to determine whether a full-scale effectiveness trial is warranted.

Design

This is a pilot, single-site, feasibility randomized controlled trial designed in concordance with SPIRIT guidelines (Multimedia Appendix 2).

Setting

The setting is a metropolitan cancer service in New South Wales, Australia, providing surgery, oncology, radiotherapy, and palliative care in inpatient and outpatient settings.

Sample

In total, 40 patients will be recruited to participate in this feasibility and acceptability study, 20 will take part in the control group using the current standard medication management tool and 20 in the intervention group using the MiM medication management tool.

Eligibility Criteria

Inclusion Criteria

Inpatients and outpatients aged 18 years or older, who are receiving treatment or care at a participating cancer service, and identify their primary language as Russian or Mandarin will be eligible to take part.

Exclusion Criteria

Patients who are under 18 years old, who are not currently accessing a participating cancer service for their care, or do not identify Russian or Mandarin as a primary language are not eligible to participate.

Recruitment

Potential participants who fulfill eligibility criteria will be provided written and verbal information about the study by their treating clinician or care coordinator in Russian or Mandarin, as appropriate. Potential participants will be asked by health service staff to indicate whether they wish for the research team to phone them to discuss the study, with no obligation to take part. A member of the research team will contact those who wish to learn more about the study via phone with support from an interpreter or multilingual worker if required. Consent will be audio-recorded with the participant's permission and a translated consent form will be provided. This approach will make sure that accurate information is provided in an accessible form (ie, spoken in their first language and translated hard copy). Consent will further be confirmed verbally by the researcher prior to the commencement of telephone surveys.

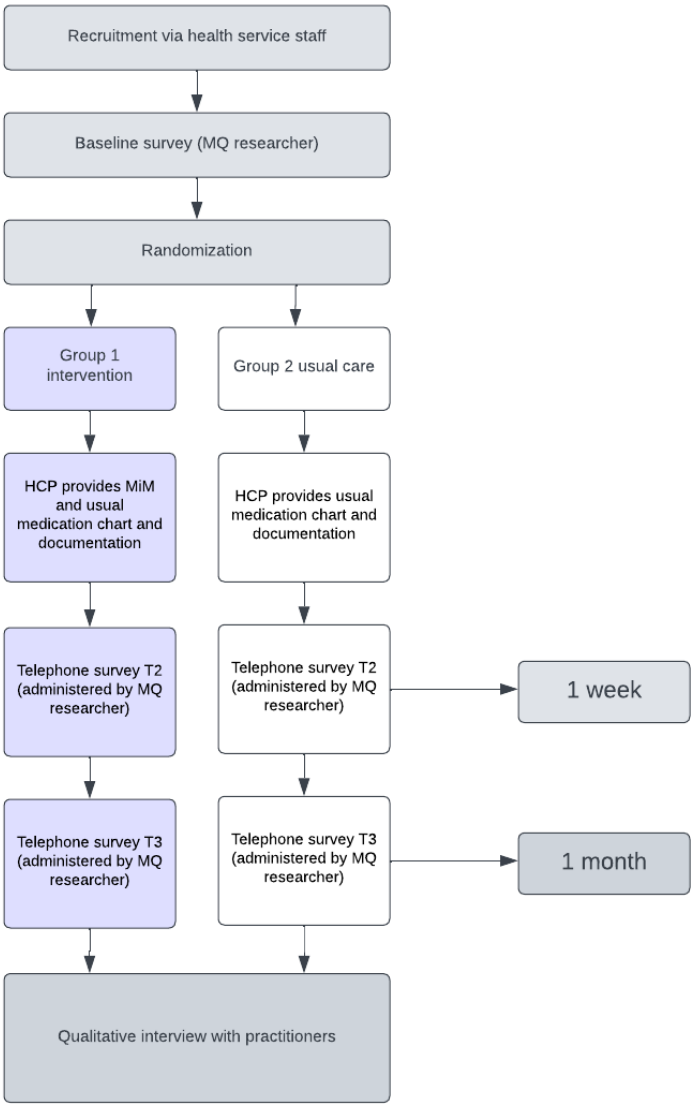
Randomization

Participants will be randomized to group 1 (intervention) or group 2 (comparison) during the recruitment process using a web-based randomization tool. Allocation will be stratified by language group.

Figure 1 provides a flow diagram describing the data collection process.

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Figure 1. Flow diagram of data collection. HCP: health care practitioner; MiM: Making it Meaningful; MQ: Macquarie University; T2: time point 2, 1 week post intervention; T3: time point 3, 1 month post intervention.



Procedure

Intervention Group

Participants allocated to the intervention group will attend their usual consultation or appointment. The health practitioner (treating oncologist) will use MiM to facilitate communication at the appointment and provide a paper-translated copy of the MiM in Mandarin or Russian language as appropriate for the patient to take away from the appointment. Participants will take part in verbal phone surveys conducted by bilingual field-workers at 3 time points; before discharge or outpatient appointment, a week after discharge or outpatient appointment, and a month after discharge or outpatient appointment (Figure 1). These time points have been selected to provide opportunity for patients to use the MiM tool during and after they leave the appointment setting.

Control Group

Participants allocated to the control group will receive usual care from their health care practitioner, which includes communication about medications using the existing medication management tool available in the participating service. Participants will also complete a verbal phone survey at 3 time points (Figure 1).

Ethics Approval

This protocol has been reviewed by the South Eastern Sydney Local Health District Human Research Ethics Committee and received approval for data collection. Appropriate ethics approvals have been obtained (HREC approval 2022/ETH01865). All participants will be required to provide consent prior to participation.

Informed consent will be gained from all participants prior to survey commencement, this will be confirmed verbally by bilingual workers in the participant's preferred language at the time of the survey. For participating staff, written consent will be obtained prior to interview commencement.

All data will be stored on a secure, password-protected cloud-based system only accessible to the research team. All findings will be deidentified prior to sharing or reporting results beyond the research team.

Patient participants will receive an Aus $20 (is equal to US $12.81 [exchange rate accurate on 22 August 2023]) voucher

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to acknowledge their participation. This will be sent via post at the completion of each survey.

Outcome Measures

Patients

An 11-item survey tool with closed and free-text items will be administered verbally over the phone (Multimedia Appendix 1). The survey comprises six components to capture (1) demographic information, (2) patient knowledge of medications and their side effects (n=4), (3) patient knowledge of how to contact the health service regarding medication concerns (n=3), (4) patient self-efficacy to contact the service about medication concerns (n=2), (5) patient engagement in medication management (n=3), and (6) patient perceptions of the safety of their care (n=2). Further, 2 systematic reviews of current measures of patient engagement demonstrated a lack of suitable existing scales for capturing consumer engagement in relation to discrete medication management activities relevant to the current project [15,16]. Drawing upon the key domains of patient engagement articulated in these reviews, we developed a set of 11 items to capture patient engagement in medication.

In total, 6 free-text items will be used in the final survey only to capture process information about the trial, including the feasibility of using MiM. This is to investigate the suitability of trial recruitment, retention, and data collection materials and processes (objective 3) and to explore barriers and enablers of implementing the MiM (objective 4). Researchers will seek to prevent pressure on patients to provide socially desirable responses by reminding the participants that researchers are independent of the health care team and this information is not being shared with their health care service or staff. The telephone survey will be administered by the research team supported by multilingual field-workers, at 3 time points (Figure 1). The researcher will record responses on Qualtrics (Qualtrics).

Researchers will contact participants via telephone and will attempt 2 follow-up calls. If participants are not available after 2 failed attempts to contact the patient the participating oncologist will be notified so that the patient contact details and willingness to participate can be confirmed. Phone surveys will be audio-recorded to facilitate the analysis of qualitative data.

Practitioners

Semistructured interviews with participating oncologists (health practitioners) will be conducted by a member of the research team at project completion, or when the practitioner finishes involvement with the project. Researchers will use a semistructured interview schedule to explore the feasibility of using the MiM in cancer services from a clinician perspective. This is to investigate the suitability of trial recruitment, retention, and data collection materials and processes (objective 3) and to explore barriers and enablers of implementing the MiM (objective 4).

Analytic Strategy

To address objectives 1-4, free-text data from the final patient survey and from the health practitioner interviews will be subject to thematic analysis. Further, 2 researchers will independently code data using Braun and Clarke's 6-step approach to generate themes regarding patient and clinician experience using MiM, its feasibility and acceptability and factors influencing MiM implementation [17]. The clinician and patient data sets will be coded and analyzed separately, and then synthesized. Two researchers will (1) independently familiarize themselves with the data, (2) independently generate codes and then meet to confirm codes, (3) collaboratively construct themes, (4) review and revise potential themes in consultation with the research team, (5) define and name themes, and (6) finalize findings to address relevant objectives.

To inform objective 5, data about the nature and frequency of medication management issues will be obtained from survey data and recorded in an Excel spreadsheet. To address objective 6, data assessing the impact of MiM on knowledge about medication and self-efficacy for medication management will be compared between the control and intervention groups. Specifically, we will compare changes in self-efficacy for medication management, patient engagement, and patient perceived safety before and after the intervention, and between the intervention and control groups.

Results

Appropriate ethical approval has been gained from the Human Research Ethics Committee and relevant governance body at the participating cancer service. Study enrollment has commenced with Mandarin-speaking participants; an oncologist and a bilingual field-worker. Survey collection will commence for users of Mandarin MiM participants who have been enrolled. Once data collection processes have been embedded with Mandarin-speaking patients, recruitment of participants from Russian-speaking backgrounds will commence.

Discussion

Principal Findings

This study seeks to determine whether MiM is feasible and acceptable for use with ethnic minority consumers in cancer services in Australia. The proposed study will test an adapted intervention that has been co-designed with people from ethnic minority backgrounds and health care staff to improve safety in the management of medication. By providing feasibility and process evaluation data about the MiM, trial materials and methods, this study will provide preliminary data about the implementation and impact of MiM on knowledge, behavior, and self-efficacy for people from Mandarin- and Russian-speaking backgrounds. We will gain insight into the use of the MiM tool but also of the research processes and outcome measures. Patient and practitioner views on the suitability and effectiveness of the MiM and commentary around useful features and suggested changes will provide the evidence base required to determine whether a full-scale effectiveness trial is warranted, and whether MiM, the study materials, or processes require adaptation to progress to a full trial. Current evidence highlights that many trials exclude or inhibit the participation of people from ethnic minority backgrounds, especially where there is low English language proficiency [18-20]. Determining through this research whether translated materials and support from multilingual field-workers is

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sufficient to support participation and data collection is critical to inform a full trial.

Limitations

A key challenge for co-designed interventions is the difficulty often faced in seeking to implement interventions into practice [21]. By gathering evidence of the barriers and enablers to implementation of the MiM from patient and practitioner data collection, we seek to produce knowledge that supports services to facilitate the implementation process. While this study is limited to 2 language groups and in cancer services, there may be opportunities to explore the relevance and value of MiM for addressing medication safety in further population groups and health settings.

Conclusions

This research is being conducted with a view to expanding the study to test whether the intervention is effective in improving patient outcomes in cancer care.

Acknowledgments

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Data Availability

Data and materials will be made available in publication of the pilot findings. The data sets generated or analyzed during this study will be available from the corresponding author on reasonable request.

Authors' Contributions

The MiM tool was developed at a co-design workshop, and MC, LR, AC, BN, and RH were engaged in this process and in the development of this protocol. RH and BN developed the measures in consultation with CW and EM who provided input in the development of the measures and protocol.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Making it Meaningful tool draft.
[PDF File (Adobe PDF File), 156 KB - resprot_v12i1e49902_app1.pdf]

Multimedia Appendix 2
Spirit checklist.
[PDF File (Adobe PDF File), 150 KB - resprot_v12i1e49902_app2.pdf]

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Abbreviations

MiM: Making it Meaningful

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Protocol

e–Mental Health Program to Prevent Psychological Distress Among French-Speaking International Students in a Linguistic-Cultural Minority Context (Ottawa, Alberta, and Quebec): Protocol for the Implementation and Evaluation of Psy-Web

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Abstract

Background: Based on experiences with the COVID-19 pandemic, postsecondary institutions were most affected by the restrictions. Students, especially international students, have borne the brunt associated with in-person learning restrictions imposed by public health recommendations. Canada is among the top 3 countries hosting international students (ISs), including Francophone students in provinces such as Quebec and other anglophone regions. Academic restrictions were accompanied by other measures such as quarantine, self-isolation, social distancing, and travel ban, to cite some. This has had a wide-ranging impact on these ISs. The resulting psychological distress and burden may have a much greater impact on Francophone ISs in anglophone settings, many of whom had ordinarily limited access to active offers of care in French in addition to cultural barriers and low literacy of the health care system. In order to take advantage of the effectiveness of eHealth as a pertinent and promising avenue, our project intends to build a web-based application that is cost-effective, user-friendly, anonymous, and capable to prompt interactive interventions as a first-line resource for psychological distress. In fact, internet applications have been increasingly used for the management of psychological distresses, and internet-based cognitive behavioral therapy is one of the preferred methods to prevent or control them.

Objective: The aims of this study are to (1) design, implement, and maintain Psy-Web for the psychological support of ISs and (2) analyze the results of the implementation of the Psy-Web platform, the additional resources solicited, and the results obtained.

Methods: This interventional project will use a sequential mixed design in the exploratory phase (phase 1) including the construction of the Psy-Web platform. A quantitative prospective component (phase 2) will include the intervention content of the Psy-Web platform. In total, 105 ISs participants (study group) and 52 ISs (control group), based on a ratio of 1:2, will be considered. The control group participants include those who did not use the web platform.

Results: The project is at the data collection stage (phase 1). Psy-Web will be built in accordance with the DMAIC (Define, Measure, Analyze, Improve and Control) model with the perspective of boosting its robustness. As a first-line resource to prevent

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psychological distress and ultimately improve their academic performance, Psy-Web is an innovative opportunity for high education managers. The project involves a multisectoral and a multidisciplinary partnership.

Conclusions: The project will develop a promising web-based solution to prevent psychological distress. Ultimately, Psy-Web will be operable in multiple languages including French.

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KEYWORDS

international students; psychological distress; Covid-19 pandemic; web-based; internet-based; peer support; distress; loneliness; isolation; isolated; psychological; student; students; immigrant; immigrants; foreign; social interaction; French; design; develop; development

Introduction

Overview

The COVID-19 pandemic has affected the operations of Francophone postsecondary institutions, the latter being at the forefront of the vitality and resilience of the French community in a linguistic minority context. As a constitutionally bilingual country, the education system should normally follow that requirement. Francophone students, in English Canada, may study in their first language at postsecondary institutions and vice versa. Indeed, Francophone postsecondary institutions outside Quebec promote the French language and culture in Canada, thanks to the Canadian Charter of Rights and Freedoms [1]. This subsequently contributes to the upward trend in international student (IS) enrolment in Canadian universities over the last decade (from 5.2% in 2009-2010 to 13.2% in 2017-2018 [2]), placing Canada among the preferred host destinations. Today, member countries of the Organisation for Economic Co-operation and Development (OECD) including the United States, the United Kingdom, and Canada remain the top host of ISs [3].

Even so, these students experience many vulnerabilities related to their status as ISs, especially given the minority context in which they live. This situation has been amplified with the sudden onset of the COVID-19 pandemic, as the latter represents the worst human health threat of modern times [4,5]. In response to this global health emergency [6,7], Canada along with the rest of the world instituted public health measures, which included widespread confinement [8]. This was accompanied by other measures such as quarantine, self-isolation, social distancing, travel ban, to name a few. These measures have had a wide-ranging impact on these ISs. Added to the health burden brought about by COVID-19 were instances of racism and xenophobia [9,10].

Brook et al's [11] review of COVID-19 notes a negative impact of midlife, self-isolation, and social distancing on psychological well-being. This impact may be more significant for ISs who are already subject to "triple-acculturative stress," as this entails the new culture dominating the study environment, the new university, and new university supervisors [12], and adjustment challenges that combine psychosomatic symptoms [13,14] and poor academic performance [15,16]. In Canada, the burden of psychological distress may be much greater for Francophone ISs in minority settings (Francophones living in English-speaking areas). Although services in French or English are constitutionalized, the literature reports limited access to active offers of care in French. Even so, Francophone patients may experience delays in treatment, limited understanding of prescriptions, or receive misdiagnoses, because of linguistic and cultural barriers. It is also well noted that students from underrepresented backgrounds had significantly higher odds of experiencing financial hardships [17]. Despite this systemic disadvantage, ISs make little use of the support resources available to them both on campus and in the public system [18]. Smith and Khawaja [19] who analyzed acculturative stress in their review of the scientific literature on ISs, found several determinants and harmful consequences of acculturative stress. The reasons fall under cultural conflicts, communication challenges, and low literacy of the care system.

In light of the effectiveness of e–mental health platforms [20-22], prompt and interactive interventions via the internet are becoming relevant tools and first-line recourses for mitigating the psychological distress of quarantined Francophone ISs, in a linguistic-cultural minority context.

For more than a decade, the internet has been increasingly used for the management of mental health issues [21], while internet-based cognitive behavioral therapy has been favored [20,22]. This alternative is cost-effective, timely, user-friendly, anonymous, and efficient for both the prevention [23-26] and the cure [27] of mental health problems. A recent systematic review with meta-analysis reported the equivalent effects of face-to-face and web-based therapy (Hedges g=0.05; 95% CI 0.09-0.20) [28]. Other studies using the same methods assessed the effectiveness of CBT in anxiety therapy [22,29-31], social phobia and fear [30,32], depression [22,29,30], stress [29-31], eating disorders, or sleep disorders [31].

Considering the current status of COVID-19 and the vulnerability of ISs, this research project aims to design and implement Psy-Web, a first-line intervention platform to improve access to psychological support resources. The scope of the project is 4-fold.

Growing Number of ISs in Canada

Estimated in 2011 at 11% of the university student population [33], ISs have grown dramatically (987.7%) between 2004 and 2019 [33,34] placing Canada in third place worldwide. For example, Université Laval has nearly 7000 ISs enrolled annually, representing 14% of the total student population. The

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University of Saint-Boniface, the only Francophone university in Manitoba, has 18.1%; some programs are almost entirely made up of ISs.

Double Minority Situation

Being abroad and Francophone in Manitoba, Alberta, or Ontario, students are in a double minority context, which limits their use of services. In fact, access to active offer of care for Francophones in a linguistic minority context is limited [35,36]. This limitation is even more problematic for Francophone ISs in terms of access to health services, putting them in a double minority situation.

Low Usage of Support Resources by ISs

Smith and Khawaja's [37] shows that ISs make little use of support resources. Reasons for this include cultural conflicts in seeking help [19,38-41], communication challenges [18], confidentiality, low literacy in the care system [42], or to avoid further stigmatization than that which they would already experience by being an IS [43]. Those who seek help usually do so for situations that are deemed urgent [39,40].

Social Capital

The physical closure of educational institutions due to COVID-19, the suddenness of the containment measures, and the lack of a predicted exit horizon disrupts the lives of the ISs and would exacerbate the negative emotions felt [44,45]. Quarantine measures lead to financial insecurity resulting from the inability to work and receive financial support from parents, who are also confined elsewhere. Also, because of their status, they are ineligible for Canadian financial support measures (eg, Canada Emergency Benefit). This precariousness could lead to promiscuity due to the inability of some to pay their rent. For instance, to our knowledge, there are no studies that indicate an avenue for psychological interventions related to the effects of the COVID-19 quarantine on Francophone ISs in a linguistic minority context. Given the scope of the issue and the evidence in the literature, this project provides an avenue for improving the psychological well-being of Francophone ISs in Manitoba in a dual linguistic-cultural minority context.

This project will implement a free interactive web-based tool "Psy-Web," to be developed through an agile and iterative process with ISs, and educational psychologists. Three outcomes are expected: (1) prevalence of psychological disorders, (2) intervention effects and perceived quality, and (3) acceptability and usability of Psy-Web.

The specific objectives are to (1) identify evidence-based interventions adapted to ISs experiencing stress, depression, and anxiety disorders; (2) design, implement, and maintain Psy-Web for the psychological support of ISs and; (3) analyze the results of the implementation of Psy-Web, the additional resources solicited, and the results obtained.

Methods

Overview

The design, implementation, and evaluation of the project are based on three strengths: (1) a multidisciplinary team that specializes in psychology, nursing, informatics, education, and immigration; (2) a partnership with postsecondary institutions and organizations in the Francophone IS community; and (3) the hosting and adaptive maintenance of Psy-Web and operational support.

Design

This interventional project will use an exploratory sequential mixed methods approach (phase 1). Phase 2 will be run as a quantitative prospective component divided into subphases. In subphase 1, the Psy-Web platform will be built using the DMAIC (Define, Measure, Analyze, Improve and Control) model [46]. This includes pretesting the entire system (website and application) for validation. Concomitantly in subphase 2, besides data gathering, we will conduct (1) an information campaign of the project through posters in university residence halls; individual texts and emails, student union emails, and home page of partner universities' websites; (2) a pretest of Psy-Web; and (3) prospective data compilation, biweekly evaluations, and individualized follow-ups as needed. The qualitative component will occur in the fall semester of 2023.

Participants and Variables

Due to the interventional nature of the study, we aim for a 90% power sample to detect the true proportion of psychological distress with a 95% CI, (conservative) prevalence (π) of 50%, precision (δ) of 0.05, and confidence level (β) of 1.96:  participants. A 10% gross-up will be considered in order to substitute participants with major missing data (n=105). A control group will include 52 ISs (ratio of 1:2) who did not use the web platform or already returned to their families. We will exclude those ISs who hold a permanent resident status prior to the crisis. The reason being that permanent residents were entitled to the financial support offered to postsecondary students, and to recent postsecondary and high school graduates who were unable to find work due to the COVID-19 pandemic; the Canada Emergency Student Benefit (CESB) [47] being a prime example.

Besides the conception of the Psy-Web platform, we are ultimately targeting, through data collection, the type of psychological distress (eg, anxiety and depression) experienced as the dependent variable of interest. Independent variables will include age, gender, postsecondary program, level of education, region of origin, languages spoken, history of psychological disorders, and the coping system used. Social capital variables include institutional support programs (eg, university) and type of solidarity deployed. Immigration history and 2019 income will be the control variables.

Psy-Web Design and Content

From needs analysis to usability assurance, the design process will incorporate consultation with 15 ISs from the University of Ottawa and Université Laval. There will be 2 stages in the design process.

First, a heuristic test known as the "Monkman heuristics" [48] and the use of the health literacy checklist [49] on the internet by 4 experts including 2 coinvestigators (MPG and IB) at each stage of the DMAIC to theoretically calibrate the website. The

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DMAIC cycle will optimize the efficiency, usability, and functionality of the process. The following indicators will be measured: optimization of results, aesthetics, usability, functional reliability, and sustainability [50].

Second, testing of the website with the abovementioned students. Simple classification algorithms that suggest content to the selection of symptoms listed will be preferred. At the first visit, the participant will fill in demographics, physical, mental, and social functioning, activities of daily living, and instrumental activities of daily living. Using the algorithms, selected signs and symptoms will lead to a psychoeducational activity.

Data Collection

To ensure the representativeness of participants, maximum variation purposive sampling [51] will be used to inform the design stage (phase 1). This will consist in surveying a sample of 15 ISs from the University of Ottawa and the Université Laval. The qualitative component will be done through individual interviews (by Zoom, Zoom Video Communications) [52]. Phase 2 consists in the intervention component of the built Psy-Web platform. In total, 105 IS participants (study group) and 52 ISs (control group), based on a ratio of 1:2, will be considered. The control group participants include those who did not use the web platform. During that (testing) phase, daily, at 11 AM, the usage data of Psy-Web (ie, visits, content viewed, and ratings) and the patterns of occurrence (ie, reason and time) will be collected and discussed twice a week by the research team.

Analysis Plan

Three phases are defined. Phase 1: analysis of automatically compiled data to assess the impact of identified issues. A biweekly assessment will be conducted by the researchers to inform interventions with the ISs. Concurrently, a historical analysis will compare pre-, peri-, and postpandemic prevalence. The quantitative analysis will include an ANOVA (or *t* test, as appropriate). Due to the categorical nature of the dependent variable, logistic regression will be preferred. A sensitivity analysis will be performed by the Generalized Estimating Equation (GEE) to test the correlated nature of the data to the region of origin [53]. A total of 94.7% of ISs are from 3 regions of Africa (West, Central, and North) with possible cultural differences. The SPSS Statistics (version 27; IBM Corp) software will be used with $P<.05$ considered significant. Phase 2 will analyze the verbatims of individual interviews using NVivo 13 (2020, R1) software. IB, JR, and MPG will thematically analyze the content according to Graneheim and Lundman [54] to capture the experience of the participants [55] and the emerging themes identified by consensus [56]. Phase 3 will conduct a sequential triangulation [57]. The acceptability and usability of Psy-Web will be assessed by the technology assessment model and system usability scale [58]. The NASSS (nonadoption, discontinuation, scaling up, diffusion and sustainability) framework of Greenhalgh et al [59] will be developed to analyze the different outcomes of the project.

Ethics Approval

The ethics certificate has been obtained from the Research Ethics Board of Laval University (CERUL 1820). The enrollment of ISs to pilot test the Psy-Web platform has started. The recruitment is done through project website and through mouth-to-ear. An advertisement has also been posted on the faculty billboard. Recruitment enrollments are totally anonymous. No compensation is offered because we want the entire process to be anonymous, as we are dealing with a very sensitive issue. Because the questionnaires are built on Lime survey, the consent and information forms are embedded. The participant is given the choice to tick "YES," hence consenting before moving on to completing the questionnaires. This approach of data collection and data analysis plan were discussed in June 2023 between the research team, expert ISs, and the Psy-Web platform developer for the purpose of adjustment. In early winter of 2023, we plan to disseminate the results generated nationally and internationally and to submit a manuscript to a peer-reviewed journal.

Results

This project is at the data collection stage (phase 1). However, the website is built [60] and the core application conception is undergoing. The executive team has met in May 2023 for a follow-up. It was noticed that the initial data repository embedded on the captured Psy-Web data on a format that were difficult to retrieve. Therefore, the Université de Laval Information and Technology office suggested to bridge data repository using Institutional Lime survey package. Study recruitment started in April 2023, and data collection is expected to be concluded in January 2024. No results are available yet as it pertains to manuscript preparation.

Discussion

This ongoing project intended ultimately to co-design and implement a first-line web-based toll, Psy-Web for the psychological support of ISs. This interactive web-based intervention project is tailored to millennials mainly and is highly relevant to addressing the psychological distress for which ISs are at high risk. The project anticipates several early benefits: (1) Using the DMAIC model, the project will coconstruct with ISs the Psy-Web application for which robustness will be data-driven. The study will capture the extent of the impact of COVID-19 quarantine among ISs at Université Laval, University of Alberta, and the University of Ottawa. Also, the platform itself offers a free, immediate, and interactive opportunity alternative (group discussion and with a psychologist) to support students. The daily collection of data and their biweekly multidisciplinary analysis constitute a continuous transfer of knowledge to inform practices and policies of dedicated universities services for ISs through Psy-Web. (2) The relevance of the project derives from the year-to-year growth of the Francophone IS population in Canada and contributes to the improvement of their quality of life and study conditions. (3) Finally, Psy-Web is a first-line resource designed to monitor and prevent psychological distress, and to ultimately improve their academic performance.

In terms of sustainability, this project will serve as a pilot for the expansion to other Francophone ISs in a Canadian minority context and beyond. The results will inform the formulation of

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policies related to IS issues and subsequently promote the continued attractiveness of Francophone ISs in linguistic minority settings.

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Data Availability

Data generated and analyzed during this study, which would be necessary to interpret, replicate, and build on the results reported in the study, will be made available to the public upon request from the Secrétariat du Québec aux relations canadiennes, the funding institution. However, this must be requested from the corresponding author as they must be stored on a secure server at Laval Université.

Authors' Contributions

IB and JR conceived the initial idea for the study. IB, DS, ENT, MPG, AA, and JR were involved in securing the grant and in writing and reviewing this protocol. All authors read and approved the final version of the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

CESB: Canada Emergency Student Benefit
DMAIC: Define, Measure, Analyze, Improve and Control
GEE: Generalized Estimating Equation
IS: international student
NASSS: nonadoption, discontinuation, scaling up, diffusion and sustainability
OECD: Organisation for Economic Co-operation and Development

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Protocol

Web-Based Presence for Social Connectedness in Long-Term Care: Protocol for a Qualitative Multimethods Study

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Abstract

Background: The COVID-19 pandemic and resultant restrictions on social gatherings significantly impacted many peoples' sense of social connectedness, defined as an individual's subjective sense of having close relationships with others. Older adults living in long-term care homes (LTCHs) experienced extreme restrictions on social gatherings, which negatively impacted their physical and mental health as well as the health and well-being of their family caregivers. Their experiences highlighted the need to reconceptualize social connectedness. In particular, the pandemic highlighted the need to explore novel ways to attain fulfilling relationships with others in the absence of physical gatherings such as through the use of a hybridized system of web-based and in-person presence.

Objective: Given the potential benefits and challenges of web-based presence technology within LTCHs, the proposed research objectives are to (1) explore experiences regarding the use of web-based presence technology (WPT) in support of social connectedness between older adults in LTCHs and their family members, and (2) identify the contextual factors that must be addressed for successful WPT implementation within LTCHs.

Methods: This study will take place in south western Ontario, Canada, and be guided by a qualitative multimethod research design conducted in three stages: (1) qualitive description with in-depth qualitative interviews guided by the Technology Acceptance Model (TAM) and analyzed using content analysis; (2) qualitative description and document analysis methodologies, informed by content and thematic analysis methods; and (3) explicit between-methods triangulation of study findings from stages 1 and 2, interpretation of findings and development of a guiding framework for technology implementation within LTCHs. Using a purposeful, maximum variation sampling approach, stage 1 will involve recruiting approximately 45 participants comprising a range of older adults, family members (30 participants) and staff (15 participants) within several LTCH settings. In stage 2, theoretical sampling will be used to recruit key LTCH stakeholders (directors, administrators, and IT support). In stage 3, the findings from stages 1 and 2 will be triangulated and interpreted to develop a working framework for WPT usage within LTCHs.

Results: Data collection will begin in fall 2023. The findings emerging from this study will provide insights and understanding about how the factors, barriers, and facilitators to embedding and spreading WPT in LTCHs may benefit or negatively impact older adults in LTCHs, family caregivers, and staff and administrators of LTCHs.

Conclusions: The results of this research study will provide a greater understanding of potential approaches that could be used to successfully integrate WPTs in LTCHs. Additionally, benefits as well as challenges for older adults in LTCHs, family caregivers, and staff and administrators of LTCHs will be identified. These findings will help increase knowledge and understanding of how WPT may be used to support social connectedness between older adults in LTCHs and their family members.

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KEYWORDS

social connectedness; web-based presence technology; long-term care homes; older adults; research protocol; mobile devices; social interaction; social interactions; connectedness; lonely; loneliness; older adult; gerontology; ageing; geriatric; geriatrics; elder; elderly; nursing home; assisted living; web-based presence; conceptual; isolation; mobile phone

Introduction

The Impact of Restrictions on Social Connectedness

The COVID-19 pandemic and resultant restrictions placed upon Canadians and residents of many other countries (ie, stay-at-home orders and social distancing mandates) significantly impacted elements of many people's social connections over the last 2 years [1,2]. *Social connectedness*, defined as an individual's subjective sense of having close relationships with others [3,4] is necessary for health and well-being [5]. During multiple phases of the pandemic, social connectedness was severely compromised for many people both directly and indirectly by restrictions placed on face-to-face engagements [6]. In Canada, older adults in congregate or institutional living environments, such as long-term care homes (LTCHs), were greatly affected during these times [7]. Older adults in LTCHs experienced some of the highest rates of COVID-19 mortality and morbidity of any population group [8,9]. Along with the systematic failure of some LTCH facilities [10], almost all LTCHs were mandated to implement extreme restrictions on visitors and staff, as an emergency infection control [11]. These drastic measures increased isolation and decreased the emotional well-being of older adults in LTCHs [6,12,13].

Progression of Social Isolation Impact on Older Adults

Before the COVID-19 pandemic, older adults in LTCHs were at risk of experiencing social isolation due to a variety of factors such as challenges with building new relationships, decreased autonomy, and geographical constraints on maintaining face-to-face or in-person connections with friends and family [14]. In older adults, social isolation is associated with negative health impacts such as reduced motor function, depression, cognitive decline, and mortality [15-19]. Similarly, loneliness is also implicated in health declines [20]. As people age, their likelihood of experiencing social isolation and loneliness increases [21,22]. In the United States, upwards of 40% of people older than 60 years reported feeling lonely [23]. In Canada, older adults also report elevated rates of loneliness and social isolation [24]. Moving to LTCHs can increase older adults' likelihood of being lonely or socially isolated with reported rates of loneliness in older adults living in LTCHs varying from 22% to 75% [20,25,26].

With the start of the pandemic, social connectedness among older adults within LTCHs was severely compromised both directly and indirectly by restrictions placed upon visitors and other infection control measures [27]. This physical isolation of older adults in their rooms thereby compounded any preexisting impacts of isolation [6]. Detrimental impacts on older adults' mental health associated with quarantine measures include emotional disturbance, insomnia, and low mood [28,29]. While these visitor restrictions were implemented in good faith as an effort to mitigate the spread of COVID-19, many older adults during the height of the pandemic died alone, with little to no connection with their family members or friends [30].

In the initial stages of the COVID-19 pandemic, research findings suggested that older adults may be less vulnerable to detrimental mental health effects of the disease and associated health measures, than their younger peers [30,31]. However, with time, additional studies indicated that the impacts of COVID-related restrictions and the resultant social isolation will have long-lasting repercussions on older adults' health and well-being [27]. Furthermore, the protracted restrictions associated with the ongoing nature of the pandemic continue to negatively impact the physical and mental health of older adults and their family caregivers [9,12,30]. In Canada, during the first wave of the COVID-19 pandemic, when families were prohibited from in-person visits, there were 7260 deaths of older adults across LTCHs and retirement homes, representing 79% of all COVID-19 deaths [7]. Consequently, during the height of the pandemic, many older adults died isolated and alone [30-33]. Since that time, the policy changed first resulting in modified visitor restrictions that allow family members to be together in palliative circumstances and then removing visitor restrictions altogether [34]. However, challenges relating to the social isolation of older adults within LTCHs remain.

As COVID-19 led to widespread limitations on in-person gatherings and for a time halted in-person visits to LTCHs, attention turned to technology as a means to communicate and facilitate social connectivity between family members and older adults [35]. As we move forward from the pandemic it is critical to develop robust systems now, to mitigate the harmful unintended side effects (eg, decreased social connectedness and well-being) of infection control policies.

Web-Based Presence Technology

Web-based presence is the use of networked digital telecommunications technology to create the impression that a user is present in another environment [36]. Digital apps (eg, Zoom [Zoom Video Communications] and FaceTime [Apple Inc]) provide web-based face-to-face connection and may support social connectedness by providing meaningful social engagement in addition to being a point of access to community environments for older adults [37]. For LTCHs, web-based presence technology (WPT) has the potential to support social connectedness as a supplement to in-person engagement or a stand-in during outbreak situations such as the current COVID-19 pandemic. Acknowledgement of this potential has been highlighted by the COVID-19 pandemic, which has been a catalyst for myriad and lasting social changes, including the vastly accelerated use of WPT for communication in people's personal and professional lives. However, the general uptake

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of WPT across LTCHs has lagged behind other sectors [38] for reasons including age-related bias about older adults' physical and cognitive ability to use technology, costs of equipment, and a lack of education and support of staff, family, and older adults to use technology devices such as tablets or other mobile devices [39].

Early efforts to explore the application of technology within LTCH settings focused on aspects such as resident safety. However more recently, the role of technology to support social connectedness is also being investigated [40]. Emerging findings suggest that challenges of implementing WPT in LTCHs include limitations in staff shortages, training for staff on the use of WPT, dated LTCH building infrastructure, funding to support additional staffing and technology equipment, and processes supporting consistent use of WPT [41]. Addressing these challenges entails more than just the provision of additional funding. Instead, it asks for an enhanced systemic and context-specific understanding of technology implementation [42]. This understanding has to be cocreated with all relevant LTCH stakeholders (eg, residents, family members, staff, and administration) to effectively address user needs as well as financial, operational, and administrative constraints.

WPT can provide family members of older adults in LTCHs with the opportunity to visually observe the well-being of the older adult in real time. Visual confirmation of these older adults' well-being can contribute to family members' trust and confidence in the care being provided by LTCH staff [43]. Admittedly, WPT is not a panacea for fostering social connectedness among older adults in LTCHs [44]. However, it may be profoundly important to supplement in-person activities with *hybridized web-based and in-person approaches* for social connectedness in the context of distancing measures or other constraints on in-person engagement.

Objectives

Given the potential benefits of WPT within LTCHs and the need to understand associated shortcomings, the proposed research goal is to explore experiences regarding the use of WPT in support of social connectedness between older adults in LTCHs and their family members, and to identify the contextual factors that must be addressed for successful WPT implementation in LTCHs. This study has 3 aims. First, to explore how older adults in LTCHs, their family members, and LTCH staff members experience, benefit from, and envision the role of WPT to support social connectedness in LTCHs. Second, to interview key stakeholders such as managers and directors of LTCHs, and to examine LTCH policy, funding, management, and operations in order to identify institutional challenges and facilitators impacting the uptake and spread of WPT within LTCHs. Third, to triangulate the findings from stages 1 and 2 to develop a framework that can inform the formal implementation of WPT in support of social connectedness within LTCH**.**

Methods

Study Team

The faculty team recognizes that there is an implicit bias against some groups' progression to academia's higher ranks. Our faculty team is deeply committed to equity and diversity in recruiting, hiring, and training students. This research team will comprise emergent and seasoned scholars and researchers and a research assistant who is a graduate student at the university where the principal investigator is employed.

Approach

Overview

This study will use a qualitative multimethod research design conducted in 3 stages. The multimethod design will be informed by the Technology Acceptance Model (TAM) and entail the use of qualitative description using content analysis (stage 1) and thematic and document analysis methodologies (stage 2). The overarching objective will be to triangulate the findings from stages 1 and 2 to create a working framework to inform the implementation of WPT in LTCHs. Stage 1 is focused on data collection through in-depth interviews with stakeholders (older adults living in LTCHs, their family members and LTCH staff) to inform an initial understanding of the perceived usefulness, ease of use, challenges, attitude toward, and human resource availability to support social connectedness using WPT. Stage 2 will involve the examination of relevant documents (eg, information technology and operational policy documents, budgetary documents and training manuals) and in-depth interviews with key LTCH administrators such as directors and managers as well as salient staff (eg, information technology) that will describe the LTCH environment, its functioning, and regulations to develop an understanding of the institutional factors that have a bearing on potential web-based presence implementation. In stage 3, the data from stages 1 and 2 will be used to triangulate the findings and interpret them to develop a working framework for WPT implementation within LTCHs.

Stage 1: Interviews and Framework Development

Design

The first stage of this study will use qualitative description to explore how older adults in LTCHs, their family members, and LTCH staff experience and understand the use of WPT in support of the social connectedness of older adults in LTCHs [45]. The outcome of this exploratory enquiry will be combined with the outcome of stage 2.

Ethical Considerations

As the initial step of stage 1, ethics approval for the proposed study will be sought from the applicable research ethics boards (Western University Health Science Research Ethics Board). Once ethics approval has been obtained, data collection will be initiated. The research team anticipates beginning the participant recruitment phase in late autumn 2023.

The principal investigator will manage all data generated with this research to ensure effective data use and security. Standardized data file naming, storage (including metadata) and

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backup procedures will support data sharing and protect the data against catastrophic loss. Data will be stored on a password-protected university server to protect against unauthorized access, in keeping with research ethics board requirements (ID#2023-121993-78969).

Participants

To conduct the interviews in stage 1, we will use purposeful and maximum variation sampling to recruit a range of older adults, family members (30 participants) and staff (15 participants) within several LTCH settings with a total recruitment goal of approximately 45 participants [46]. A review of the literature on sample size across 55 qualitative descriptive studies found that about half of studies (24 studies) had a sample size ranging from 8 to 20 participants and approximately 15% (8 studies) of included studies had a sample size of up to 50 participants [46]. Therefore, a total sample size of 45 for stage 1 is deemed to be congruent with other research conducted using a qualitative descriptive method. Data collection and analysis will take place simultaneously and will continue until the data provides a rich description of the participants' experience in using or supporting the use of WPT for the purposes of social connection. It is expected that data collection will conclude once data saturation has been obtained across the range of participants [47]. Participants will be recruited from 3 LTCHs (anonymized). Given the goal of gaining a holistic understanding of the role of WPT implementation in LTCHs, we hope to recruit a broad range of participants (older adults, family members and staff including, registered practical nurses, registered nurses, personal support workers, and recreation therapists).

Inclusion criteria for this stage will be English speaking and the ability to participate in a one-on-one interview using Zoom technology. Potential older adult participants with mild cognitive decline living in LTCHs or receiving outpatient care will be assessed for suitability to participate in this study by LTCH staff first before any study information will be shared with them. Exclusion criteria applied will be the inability to converse in English and advanced cognitive decline.

Screening Process

The screening process will be conducted by partnering organizational staff. As part of LTCH guidelines a regular Montreal Cognitive Assessment screening [48] is used to assess residents' cognitive dimensions such as language, memory, visual and spatial thinking, reasoning, and orientation status. Upon receiving study information, partnering staff will identify potentially suitable participants and share this study's information with them on behalf of the researchers.

Setting

Individual in-depth interviews with older adults, their family members, and LTCH staff will take place in-person, via phone, or Zoom call depending on participant preferences and applicable COVID-19 restrictions at an agreed-upon date and time.

After the screening and deeming an older adult eligible to participate in this study, a research assistant will connect with a recreational therapy department staff or a caregiver in order to assist older adult participants with setting a study interview appointment, securing a quiet room, accessing an electronic device at their LTCHs, and helping them join a Zoom meeting to participate in an interview at an agreed upon date and time.

Data Collection

We will conduct semistructured in-depth interviews with a range of older adults, family members, and staff in several LTCHs. The purpose of conducting these interviews will be to explore participants' perceptions of how WPT has been used and can be used, and to identify potential barriers to supporting social connectedness between older adults and family members within LTCH settings using WPT. Interview questions will be informed by extended the TAMs as widely applied to questions of health technology implementation [49-51]. The TAM and its extensions are based on 2 belief constructs: perceived technology usefulness and perceived ease of technology use [50,51]. Building on these constructs, a range of interview questions tailored for type of participant (staff, older adult living in LTCHs, and family member) will be posed to participants (eg, can you describe your experience with using technology such as smartphones or tablets for speaking with your family). For a full list of interview questions please see Multimedia Appendix 1. In addition to in-depth interviews, observational field notes will be kept throughout this study thereby enhancing the data set [52].

Data Analysis

Data will be analyzed using directed content analysis, a qualitative analytic technique characterized by a structured stepwise process of coding the data and organizing it into categories or themes [53]. The goal of the analysis will be to provide the initial data for a framework to guide web-based presence implementation in LTCHs. As such, the key constructs of the TAM, perceived usefulness and ease of use of technology, will serve as initial codes to guide analysis. Data that do not lie within one of the key codes will be labeled with a new code and organized into new categories or organized depending on their suitability as subcategories under the initial codes [53]. Throughout the entire sampling and data collection process, data analysis will be conducted in a concurrent and iterative process. Interviews with participants (in-person, via phone or Zoom depending on participant preferences and applicable COVID-19 restrictions) will be audio recorded, transcribed verbatim prior to analysis. Study rigor will be ensured through member checking, verifying data by contacting a subset of participants a second time to verify their intended meaning [54]. In addition, those engaged in the research process will practice reflexivity, acknowledging biases they may introduce to the research, and other strategies such as ethical conduct and ensuring the trustworthiness (eg, confirmability of data through triangulation between interviews and field notes) of this study data will be used [55].

Stage 2: Interviews With Key Stakeholders and Document Analysis

Design

To further develop insights related to the challenges and facilitators impacting the spread of WPT within LTCHs, stage 2 will consist of 2 elements: interviews with stakeholders using a qualitative descriptive approach, and document analysis. The

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in-depth interviews will be analyzed using conventional content analysis, an analytic technique that will facilitate increased understanding in the absence of guiding theory [53]. Document analysis, a systematic process of evaluating documents, is often used in conjunction with other qualitative methods in order to facilitate triangulation. Including a wide variety of documents (eg, policy documents, correspondence, and institutional reports), document analysis will be used as a means to enhance this study's findings with its potential to provide greater insight, information, and understanding [56].

Participants and Setting

Approximately 10-15 stakeholder participants will be recruited using convenience sampling. Given the focused nature of the interviews in stage 2, it is expected that fewer participants will be required to reach data saturation (approximately 5 to 8 per participating LTCHs). Participants will be invited to participate through targeted outreach via the (anonymous) Long-term Care Associations and through current relationships with LTCHs and professional nursing organizations. Key stakeholders will involve a range of functions or positions including directors of care, chief executive officers, director of community connections, and director of information technology innovation. Interviews with key stakeholders will take place in person, via phone or Zoom call depending on participant preferences and applicable COVID-19 restrictions at an agreed-upon date and time.

Data Collection

A qualitative description will be the methodological approach used to conduct in-depth interviews with key stakeholders (eg, IT personnel and LTCH management) [45,53]. Purposeful sampling techniques such as theoretical sampling are commonly used to recruit individuals or focus groups and data is often analyzed using content analysis when using a qualitative description approach [46]. Prior research in health technology implementation has stressed the importance of the role that system factors play in successful technological implementation in clinical settings [57]. Insights gained during stage 1 (eg, identification of barriers to the use of WPT) will inform the development of an interview guide targeted at increasing understanding of how potential modifications in structural and institutional factors could facilitate the spread of WPT in LTCHs.

Contributing documents to the document analysis component of this stage of this study will include annual LTCH budget reports, annual reports, strategic plans, LTCH funding policy documents, and regulatory documents as well as relevant communication documents (anonymous). These documents can potentially add information that can inform understanding of WPT use in LTCHs such as resource and budgetary allocation for technology and support personnel.

Data Analysis

In-depth interviews with participants will be audio recorded, transcribed verbatim, and analyzed using conventional qualitative content analysis with codes emerging through an iterative process of data collection and analysis [53]. Identified key documents will be analyzed using *conventional content analysis.* This will be an iterative process of reading the interviews, identifying initial coding categories based on the results from the interviews with key stakeholders and then organizing the codes into categories [53].

Analysis of documents will entail an iterative process which includes scanning documents, preliminary reading in detail, and finally organizing the data using strategies such as coding and categorizing the data. Concomitant to the analysis will be ensuring that the documents are credible, accurate, and able to inform the research questions [56].

Stage 3: Explicit Between-Methods Triangulation and Conceptual Framework Development (Methods)

In the concluding stage, there will be *explicit between-methods triangulation* of the findings of the respective methodological approaches (qualitative description using directed content analysis and conventional content analysis and document analysis) used in stages 1 and 2 to develop a final conceptual framework [58,59]. Findings from the various methodological approaches used in stages 1 and 2 will be systematically gathered and sorted to allow discerning patterns of overlapping and complementing evidence to establish the emerging final conceptual framework [60].

Results

The result of this iterative analytic process will inform theoretical understanding of how older adults in LTCHs, their family members and staff experience and envision the application of WPT to support social connectedness. After stage 1, a total of 45 participants will have completed in-depth interviews and their data will have been used to generate theory related to how WPT can be used within LTCHs to support social connectivity. The findings emerging from stage 1 will be used to directly inform stage 2's data collection as well as the overall development of a conceptual framework (stage 3).

Findings emerging from key stakeholders' interviews as well as document analysis will be used to inform *explicit between-methods triangulation* in stage 3 by expanding on findings through the inclusion of data obtained through other methods [61]. Expected contributions from the document will include a greater understanding of factors such as fiscal constraints, an organizational structure including staffing complement, and controlling regulatory and policy frameworks required for the successful implementation and spread of WPT for social connectedness within LTCHs.

The findings emerging from this study will provide deeper insights and understanding about the factors, barriers, and facilitators to embedding and spreading WPT in LTCHs and benefit older adults in LTCHs, family caregivers, and staff and administrators of LTCHs. Going forward, the conceptual framework will have utility to inform approaches to embedding web-based presence as a mainstreamed communication tool to support social connectedness among older adults in LTCHs and their family members.

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Discussion

Principal Findings

A growing body of literature demonstrates the benefits of various communications technologies such as social networking apps on older adults' well-being, independence, and sense of connectedness with friends and family [62]. Knowing that social connectedness is a key contributor to the well-being of older adults in LTCHs [2], it will be important to optimize communications web-based technology in an efficient and timely way to avoid compounding further unintended detrimental effects to limit transmission of COVID-19, or any other future pandemics or epidemics.

As society continues to experience evolving disruptions to the ability to engage with one another, there is a need to reconceptualize social connectedness and to identify novel ways to attain fulfilling relationships with others particularly in the context of LTCHs. In the context of LTCHs, this could be represented by a hybridized system of web-based and in-person presence. However, more evidence is required to determine whether older adults in LTCHs and their family members benefit from WPT (eg, smartphones and tablets) as an approach to support their social connectedness. Further, there is a need to better understand how WPT can be implemented in LTCHs.

While WPT may have the potential to support meaningful social connectedness among many older adults in LTCHs and their family members, to date numerous uncertainties remain regarding leveraging WPT for social connectedness. These uncertainties include (1) the effectiveness of using WPT for social connectedness by older adults with cognitive impairments, (2) best practices related to the use of WPT by older adults with cognitive impairment, and (3) the role of extra supports for older adults with cognitive impairment when using WPT [44]. Additionally, it will be important to identify how an older adults' physical condition could impact their ability to use WPT. For example, arthritis, vision impairments or neurodegenerative conditions such as Parkinson disease could necessitate the need for adaptive technology or additional assistance [63,64].

Limitations

The proposed multistage approach and methodological triangulation will require the engagement of multiple stakeholders. Potential limitations may include challenges associated with conducting interviews with older adults living in LTCHs who may have cognitive or physical conditions that could limit their participation in in-depth interviews. Additional support from family members, LTCH staff or researcher staff may be required to facilitate interviews with older adults. Researchers will use flexible approaches to interviewing including in-person and zoom interviews, accommodating interview times and an honorarium to recognize their time and contribution. Researchers will also use strategies that can support older adults' participation such as providing documentation in larger font size and providing a list of questions ahead of time.

The data obtained through qualitative description will consist of subjective perceptions and recollections of using technology for social connectedness and therefore may be biased toward a particular type of experience. Direct user observations, attained using an ethnographic approach, might be able to produce data that have a lower likelihood of being biased toward memorable experiences. However, actualizing this approach within LTCHs would be very challenging to practically implement.

Conclusions

The conceptual framework arising from this research on the role of WPT to support social connectedness between older adults in LTCHs and their family members will have a key role in informing LTCHs how to embed web-based presence as a mainstream communication tool to redefine and support social connectedness among older adults in LTCHs and their family members.

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Data Availability

Attached is the interview guide to be used in stage 1 of this study. See Multimedia Appendix 1.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Interview guide.
[DOCX File , 25 KB - resprot_v12i1e50137_app1.docx]

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Abbreviations

LTCH: Long-term care home
TAM: Technology Acceptance Model
WPT: web-based presence technology

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Protocol

Experiences and Priorities in Youth and Family Mental Health: Protocol for an Arts-Based Priority-Setting Focus Group Study

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Abstract

Background: During the COVID-19 pandemic, eHealth services enabled providers to reach families despite widespread social distancing restrictions. However, their rapid adoption often occurred without community partners' involvement and without an understanding of how they prioritize aspects of their mental health and associated service provision, both of which promote family and community-centered health care delivery. Establishing priorities in health care is essential for developing meaningful and reliable health services. As such, there is an urgent need to understand how eHealth service users, especially families who may have historically faced oppression and systemic barriers to service access, can best benefit from them. Arts-based approaches can elicit an understanding of priorities by providing an engaging and expressive means of moving beyond readily expressible discursive language and stimulating meaningful dialogue reflective of participants' lived experiences.

Objective: The purpose of this research is to determine the priorities and preferences of youth; parents or caregivers; newcomers and immigrants; and Indigenous community members regarding the use of eHealth in supporting their mental health using an innovative arts-based priority-setting method.

Methods: This study uses a mixed-methods approach combining qualitative, quantitative, and arts-based research. It follows a survey used to identify key knowledge partners who are interested in improving eHealth services for mental health support in Manitoba, Canada. Knowledge partners interested in group-based priority setting will be contacted to participate. We will facilitate approximately two focus groups across each subgroup of youth, parents or caregivers, newcomers or immigrants, and Indigenous community members using an integrative, quantitatively anchored arts-based method termed the "Circle of Importance" to understand participants' mental health priorities and how eHealth or technology may support their mental well-being. The Circle of Importance involves placing small objects, whose meaning is determined by participants, on a visual board with concentric circles that correspond to a 5-point Likert scale of importance. Following each focus group, we will evaluate participants' and focus group facilitators' experiences of the Circle of Importance using a survey and follow-up structured in-person interviews to garner how we can improve the arts-based approach used in the focus groups.

Results: The PRIME (Partnering for Research Innovation in Mental Health through eHealth Excellence) theme received institutional ethics approval on August 23, 2023. Data collection is projected for August 2023, with follow-up focus groups occurring in early 2024 as required. Data analysis will occur immediately following data collection.

Conclusions: Findings will directly inform a multiyear applied research agenda for PRIME aimed at improving mental health services through engaging key knowledge partners. The results may inform how arts-based methods in a priority setting can reflect aspects of experience beyond the capacities of qualitative or quantitative methods alone, and whether this approach aligns well with a positive experience of research participation.

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KEYWORDS

arts-based methods; priority setting; mental health; eHealth; arts-based; art-based; preference; preferences; perspective; perspectives; opinion; opinions; youth; adolescent; adolescents; immigrant; immigrants; native; natives; aboriginal; aboriginals; Indigenous; digital health; telehealth; telemedicine

Introduction

Background

As the world recovers from the COVID-19 pandemic, health service providers have increasingly turned toward digital technologies to support family mental health. Extensive research documents the disruption that COVID-19 exerted on the lives of families. These disruptions are characterized by challenges across health service access, provider availability, workplace, and home life stress, along with infractions upon coping ability [1-4]. In response to these obstacles, digital technologies, including app-based mental health supports, telehealth, and remote therapy delivery options, helped support in-person service delivery. These digital technologies, henceforth referred to as eHealth, include the provision of mental health support services through digital technology, such as conducting therapy remotely through videoconferencing platforms such as Zoom (Zoom Technologies Inc), Microsoft Teams (Microsoft Corp), or apps.

Although eHealth proved valuable during the COVID-19 pandemic by reducing the strain on health service delivery, its rapid usage made it difficult to adequately develop best practices—and for service providers to have evidence-based guidance—in their absence [5]. The urgency of health system response meant that, in many cases, families and other community knowledge partners were not engaged in determining priorities for and tailoring approaches to maximize the benefits of eHealth services. As the world recovers from the COVID-19 pandemic and in-person services resume, there remains a paucity of literature considering how eHealth services can and should be a part of mental health services for families moving forward. These are essential questions for communities that experience systemic barriers to access related to racial and ethnic oppression, geography-based proximity to care, and mobility challenges due to health status or transportation access. These marginalized communities include Indigenous and newcomer groups in Canada, as well as bedridden or homebound individuals, who benefit from the extension of particular eHealth services such as telehealth [6-9]. This paper presents a protocol for using an arts-based qualitative approach to understanding the family mental health and eHealth priorities and experiences for youth, parents, and caregivers, with particular consideration of the experiences of Indigenous and newcomer communities in the Canadian context.

Use of eHealth for Mental Health Support

eHealth is a well-accepted component of many mental health services, but during the COVID-19 pandemic, eHealth services were often used as mitigation for an absence of in-person delivery options [10]. eHealth delivery was necessary for reaching individuals in light of quarantine, social distancing, and safety protocols [11-14]. The time-sensitive nature of response mandated by service providers meant that many eHealth services were generated, and many more transformed, to meet public demand [6,8,15,16].

Reviews conducted prior to the emergence of COVID-19 highlight the promise of eHealth in preventing and treating mental health challenges and promoting mental health [15]. For instance, MacKinnon et al [17] found better self-reported mental health and improved anxiety and depressive symptoms for parents of young children, and reduced parenting stress for parents using eHealth interventions. eHealth also shows encouraging results for reducing mental health challenges at the population level, which could help address the adverse effects of the pandemic [15]. The feasibility and acceptability of eHealth are often positively assessed by end users; for example, individuals living with serious mental illness have reported eHealth interventions as feasible and accessible [18]. Additional reviews highlight the promise of eHealth interventions for improving health service delivery; however, further research is needed to identify ways to increase intervention efficacy [16,19,20].

Research conducted during the pandemic was a rapid response to lockdown protocols in the face of increasing need and often without sufficient time to build relationships and ethically engage in best practices with other professionals and knowledge partners. Thus, reviews conducted specifically on the impact of interventions used during the pandemic demonstrate that the lack of legislation, guidelines, and engagement with communities results in a lack of quality of care in some eHealth programs [21-23]. The proliferation of eHealth has outpaced the evidence base, which has functioned as a barrier to policy developments [24] and uptake within particular user groups (eg, older adults) [25], with the strength and quality of evidence being a key characteristic impacting eHealth implementation across contexts [26]. This study context provides a unique and timely opportunity to learn how communities and families want to engage with eHealth moving forward and to identify their priorities for future research and clinical services.

While eHealth services demonstrate promising results for service provision, including reducing commute and wait times, reducing the spread of infections, and improving access to health services [10], understanding how specific groups may benefit from and use eHealth supports is integral to maximizing the benefits for such services. Indeed, eHealth services failed to reach their full potential before the COVID-19 pandemic but have strong potential to enhance health service accessibility [10]. To improve eHealth services, there is a need to understand the experiences of mental health from the individuals and groups who should benefit from them. This understanding is paramount to developing eHealth programs, interventions, and services that align with user priorities.

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Priority Setting and the Benefits of Arts-Based Methods

Priority setting identifies various knowledge user priorities around a topic and, from these, seeks consensus [27]. It is often used to identify and understand health care users' experiences to inform the health service of health user needs and thus is particularly useful within the context of codevelopment [27]. Priority setting can improve research credibility and practicality for real-life problems and help in developing systematic, user-centered, and applied research programs and associated projects [27]. Within the context of eHealth for mental health services, priority setting can help align eHealth supports with family experiences and needs and inform their improvement and integration within other in-person services, which are sensitive to the users' local context.

Popular priority-setting methods, such as the James Lind Alliance and the Delphi technique, begin with identifying gaps in the literature, meeting with multiple knowledge users, and voting in multiple rounds before reaching a consensus [27,28]. Consensus is obtained through scoring, ranking, voting, and ordering of items, often achieved through surveys or workshops [27]. Some authors incorporate participatory and playful methods when ranking by using colored sticky notes, cards, and stickers [29,30]. While many of these methods promote empirical ways of knowing, there are opportunities to explore other forms of knowledge that go beyond discursive communication.

Knowledge exists in various forms and can be expressed in a multitude of ways, including more experiential and embodied forms. For instance, children and youth often express themselves using the creative arts, which are regarded as developmentally appropriate in this context [31]. Arts-based methods probe into other forms of knowing—embedded, tacit, emotional, and subconscious—enabling new ways of engaging with experience, new representations, and expressions to emerge, and therefore, new insights to be constructed through and within the relational research space [32]. Despite this knowledge, most priority-setting approaches rely upon discursive knowledge (ie, asking participants to state their priorities and to complete a questionnaire on priorities). On the contrary, arts-based methods provide an opportunity to explore experiences differently and more profoundly and bring to the center what may be missed by traditional research methods. Combining arts-based methods with other narrative methods, such as focus groups, can provide a more holistic understanding of priorities than would otherwise be impossible. Further combining arts-based methods within mixed-methods frameworks can advance complementarity, extend understandings, and provide real-time integration of diverse knowledge forms [33,34]. While arts-based research is proliferating across the health and social sciences, its use in priority settings is nascent. Here, we will engage youth, parents or caregivers, newcomers, and Indigenous community members in arts-based priority setting of their mental health and technology priorities to generate deeper understandings.

Research Context

The research theme PRIME (Partnering for Innovation in Mental Health through the eHealth Excellence) is the fourth research theme at CHRIM (Children's Hospital Research Institute of Manitoba). CHRIM is the Canadian Prairie province's first children's research facility with the overarching goal of holistically improving the health of children and youth through equitable and innovative research, policies, and interventions [35]. PRIME was developed to address the growing need for mental health services for children, youth, and families that were inflated due to the COVID-19 pandemic [35]. PRIME is developing eHealth models to address youth and children's mental health needs in Manitoba through equitable partnerships with local communities [35]. The foundational research proposed here directly addresses extant gaps to identify youth mental eHealth needs in Manitoba with broader methodological relevance, and uses and advances the methods for assessing mental health and technology priorities across a variety of knowledge user groups.

Methods

Overview

This is a convergent mixed design inclusive of arts-based priority-setting activities and focus groups across the 4 subgroups of youth, parents or caregivers, Indigenous communities, and newcomer and immigrant families [36]. It follows a survey used to identify interested parties and knowledge users in ongoing research engagement in eHealth for mental health in Manitoba, Canada. Arts-based data collection involving the innovative priority-setting approach titled the Circle of Importance will be used to concurrently gather narrative, quantitative, and visual data and will be used as a visual elicitation tool to catalyze focus group interviews. Graphic recording, wherein an illustrator is present during each focus group to visually capture emerging thematic content, will be used as a member checking and dissemination device. This study will be conducted in a large urban capital of a central Canadian province (population 749,607) [37]. We will iteratively collect data at the centrally located CHRIM and analyze the data over a 4-month period across Manitoba.

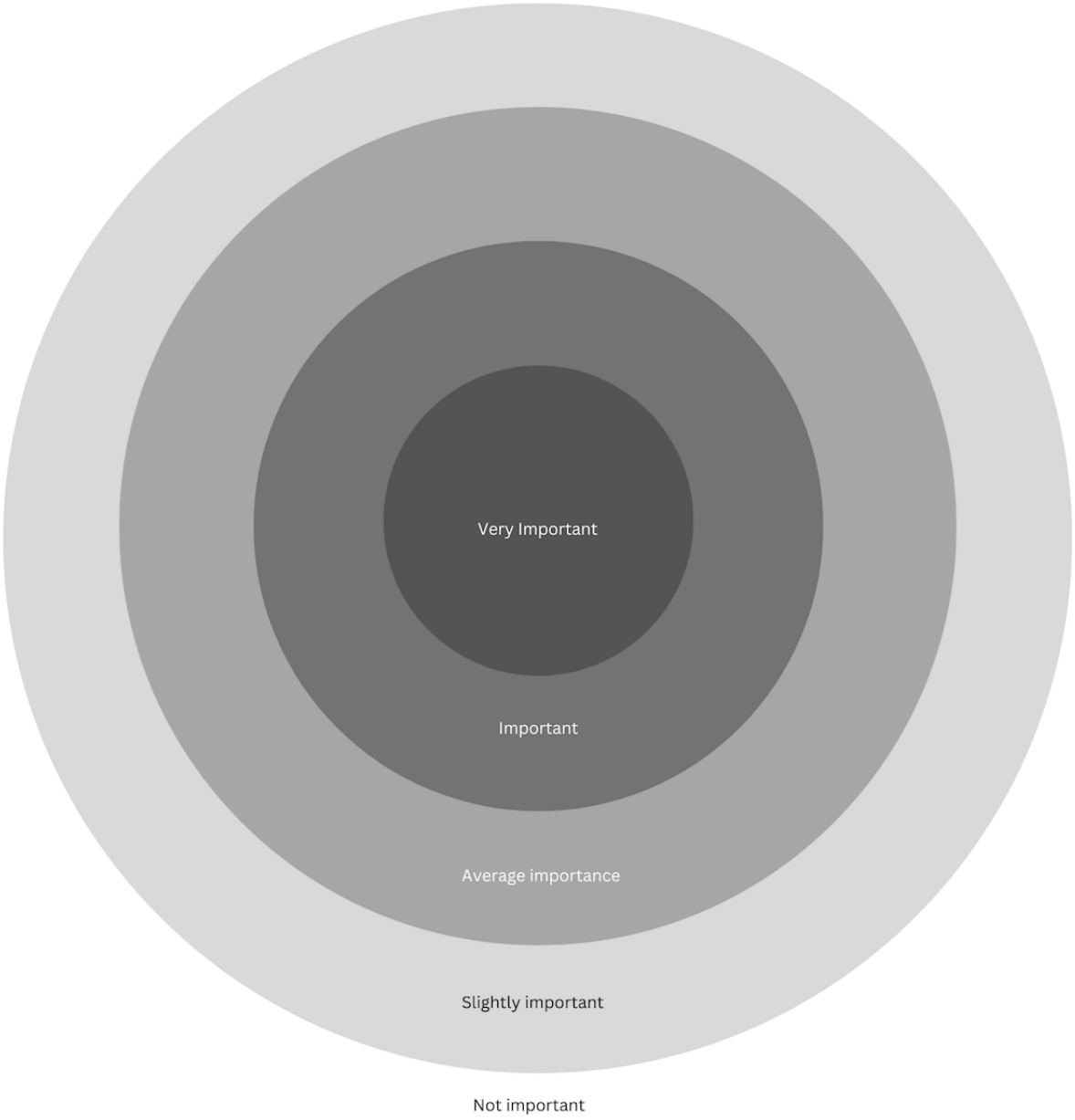
Theoretical Framing

Arts-Based Priority Setting Using the Circle of Importance

we have developed an innovative arts-based approach to priority setting entitled the Circle of Importance (see Figure 1), integrating aspects of existing priority setting, mixed methods design considerations, arts-based methodologies and theories, and professional experience across arts-based, mixed methods, and qualitative research traditions, building on the first author's (MA) extensive work in this area [33,36,38-40]. The Circle of Importance draws from a number of methodological traditions and methods applications, including the Center Stage approach. Center Stage involves positioning found objects on a blank board, wherein the center represents the core elements impacting a person's experience [41]. The participant places other objects of importance in the peripheral areas on the board, with more peripheral placement indicating less significance [42]. As such, center staging encourages participants to reflect and organize their experiences into themes that can be visualized [41].

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Figure 1. The Circle of Importance, incorporating concentric circles with the embedded Likert scale of importance.



However, given our specific interest in priority setting and our orientation toward integrating multiple data sources to increase holistic understanding, we adapted the Center Stage process to strengthen the mixed-methods integration potential and mitigate analytic challenges likely to be faced in using the method [39]. Specifically, we extend the blank boards of Overs et al [41] to incorporate 5 concentric circles, which embed a visual 5-point Likert scale on the board for object placement. Participants have the option to select objects provided by the investigative team or objects they have brought themselves and assign meaning to these objects prior to placing them on the board. Each icon or object position is anchored to a quantitative indicator (1-5) aligned with their respective qualitative descriptions (very important to not important) and serves as a visual elicitation stimulus for narrative data attained through the focus group. This approach enables real-time qualitative and quantitative data integration—an area of increasing focus in the mixed methods research context wherein methodological integration and participatory integration methods are garnering interest [34,43]. Here, participants can more readily externalize change in their responses between interview questions.

Participants and Recruitment

As foundational work to the current proposal, a survey was distributed across Manitoba to identify partners and parties interested in, experiencing, or supporting family mental health. For this study, participants will be purposively recruited from the phase 1 survey. Participants must be aged 16 or older; have experience, interests, or provide support for youth mental health; and identify with 1 of the 4 subgroups (youth, parents or caregivers, newcomer and immigrant families, and Indigenous community groups). These criteria apply to Indigenous and non-Indigenous people with lived experience of mental health and experience as a caregiver or parent of someone experiencing

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mental health needs. All individuals must reside in Manitoba and be fluent in English. Recruitment will consider age, gender, location, and demographic identity. Five to eight participants will be selected for each subgroup. Youth in this study refers to individuals aged 16-20 years—a definition adopted from the United Nations [44] with modifications made to the upper age category of our sample, recognizing the changing nature of stressors and life stages beyond 20 years of age (eg, increased independence, including place of residence; higher likelihood of employment and postsecondary schooling). The research team will conduct 2 focus group sessions for each subgroup. All participants will receive a CAD $30 per hour (US $22.38) reimbursement through a gift card as a token of appreciation for their participation.

Data Collection

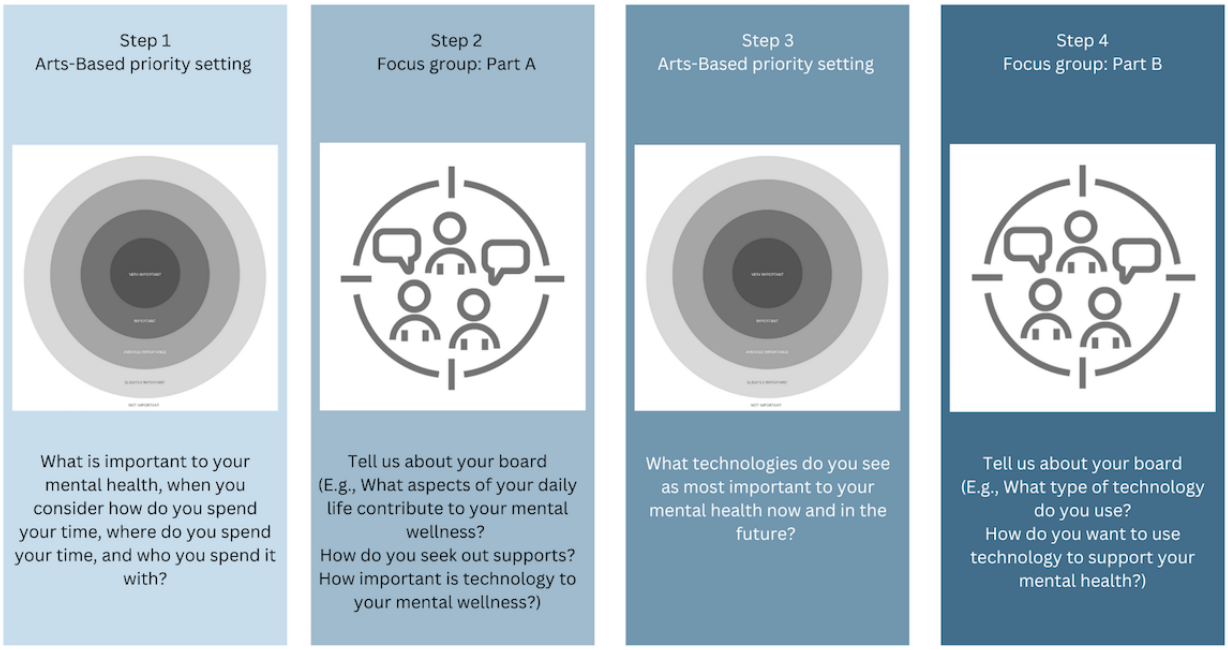
Focus groups spark discussions among participants and allow them to share similar and dissimilar views [45]. Aside from group restrictions (ie, youth, caregivers, Indigenous community members, and newcomers and immigrants), groups will be heterogeneous in composition to allow diverse perspectives on the topic [45]. Heterogeneity will include age, ethnicity, geographic location, sex, and gender, where appropriate. Furthermore, youth will be subdivided into focus groups reflecting more discrete age ranges (eg, group 1: 15-17 years; group 2: 18-20 years). The lead author has extensive experience in qualitative and arts-based methodologies and will play a key role in conducting the focus groups through facilitation and staff training. A graduate trainee of Indigenous ancestry and with significant qualitative experience will lead the facilitation of the Indigenous community subgroups with instruction and assistance from the lead author. Furthermore, 2-3 facilitators will be present at each focus group to ensure smooth operations and take observational notes of group interactions. Focus groups will be facilitated at CHRIM. A professional graphic recording company will graphically record each focus group to allow for a visually integrative output per subgroup to aid dissemination and member checking.

Focus Group Approach

Overview

Focus groups will involve 4 steps, including 2 cycles of the Circle of Importance method followed by semistructured focus group interviews (see Figure 2). Each respective focus group will commence with an icebreaker activity selected based on the specific group. A brief evaluation of participant and facilitator experiences of the Circle of Importance activity will directly follow the completion of each focus group (Multimedia Appendix 1).

Figure 2. Study sequence.



Step 1: Arts-Based Priority Setting Using the Circle of Importance

The first stage includes identifying what is essential to each person's mental health using the Circle of Importance (Figure 2). Participants will be instructed to select up to 10 objects that they feel represent an aspect of their life and mental health and directed to position the objects on the Circle of Importance board to reflect what is most important to them. No distinct meaning will be assigned to each object by the facilitators. Instead, participants will be advised to decide what each object represents. Approximately 15 minutes will be provided for each respective Circle of Importance board placement. Facilitators will photograph each board and label the photo with the participant identification number to allow integration with narrative responses throughout the analysis.

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Step 2: Focus Group Interview—Part A

Following the selection of the items, a facilitator trained in qualitative methods will guide a discussion on the participants' boards. Two additional facilitators will be present to assist with note-taking of participant nonverbal communication and group interactions and assist with the Circle of Importance method as necessary. The focus group interview will progress from general to specific, beginning with an invitation for participants to describe their board. Participants will also be asked what aspects of their daily life contribute to mental wellness, what contributes to when things are going well, how they seek out support, the importance of technology to their mental wellness, how they use technology, and the importance of technology to receiving mental health services. A simple definition of technology will be provided to participants during the focus group introductions and icebreaker activity.

Step 3: Arts-Based Priority Setting Using the Circle of Importance

Subsequent to a break, step 3 will resume with participants reimagining their board in response to the question: What technology do you see as most important to your mental health in the future? Participants will have the option to exchange their icons before partaking in the Circle of Importance method if they so desire. As with step 1, participants will have 15 minutes to complete the Circle of Importance method. At completion, facilitators will photograph each board and label it with the participant ID.

Step 4: Focus Group Interview—Part B

After the prioritization method in stage 3, participants will again be invited to discuss their board. The facilitator will first invite participants to describe their board generally, before asking more specific questions about the use and desired use of technology in the context of mental health. Questions will center upon how participants use and want to use technology to support mental health, the types of technologies used, and the technologies regarded as most important to participants' mental health, now and in the future. Participants will then be asked about the negative impacts of technology use on their own or their family's mental health, the importance of privacy and confidentiality in the context of technology, preferences around the separation of digital spaces, and perspectives on tracking mental health in app-based technologies. The information gathered during these focus groups will be used to inform the development of a new research theme at the Children's Hospital Research Institute and associated family and community-centered research and care activities.

Evaluation of the Circle of Importance

Arts-based approaches to understanding health priorities are an emerging area [46]; as such, feedback from the participants and facilitators on this methodology is crucial for informing its ongoing development. Following the completion of the focus groups, we will evaluate participants' experiences—including benefits and challenges—of engaging with the Circle of Importance for priority setting. The experiences of facilitators will also be evaluated. We have previously used comparable methods to evaluate methodological innovations, which proved both feasible and useful to methods refinement (eg, Archibald et al [47]). Findings will be used to further refine the Circle of Importance, with sensitivity to the various contexts of its use.

The evaluation will involve descriptive statistics and brief structured follow-up interviews and last approximately 10 minutes per participant. First, participants and facilitators will be provided with a brief questionnaire containing 7 items, structured as a 5-point Likert scale. Questions will center around the feasibility, acceptability, and use of the Circle of Importance for priority setting, as well as challenges and opportunities to improve the method. Following the survey, participants will take part in brief structured interviews containing approximately 6 questions with facilitators to provide an opportunity for additional feedback and to explain the survey responses in a convergent design [45]. Evaluation interviews will occur immediately after the focus group interviews and in the same location.

Data Analysis

An integrated mixed-methods analytic approach is used in this study. MAXQDA (VERBI GmbH) will be used for data management and to support. Analysis will proceed at the individual and focus group levels. At the individual level, each participant's artboard, narrative responses, and quantitative Likert response will be analyzed holistically as a case (ie, photos of the participant's artboard will be analyzed individually as a case and in reference to the focus group context; participants' Likert scale responses will be recorded in reference to the image on their Circle of Importance, their discussions during the focus group, and in the larger contexts of the focus groups). Inductive thematic analysis will be used. Analysts trained in qualitative and mixed methods will view the photographs of the artboards in tandem while reading the interview transcriptions repeatedly to gain a sense of the whole. Codes will be constructed and applied in accordance with the research questions and assigned descriptions. Case outlines will be provided for each participant and compared within and across subgroups to generate inductive explanatory insights.

With the focus groups, data will be analyzed and organized by subgroups (ie, youth, parents or caregivers, and Indigenous communities). Likert scale responses will be pooled and analyzed descriptively once the objects have been clustered categorically. Thematic labels will be assigned to the objects and reported by prevalence across and within subgroups. Transcripts will be inductively coded; previous transcripts will be reviewed once again when new codes have been identified to ensure comprehensive coding. A variety of strategies, such as joint displays wherein data of various forms are presented in dialogue within a table, will be used to facilitate integration and aid dissemination [48].

The evaluation of the Circle of Importance method will involve data cleaning of the transcribed audio files, and uploading of the transcriptions and survey responses into the mixed-methods software for analysis. Statistical analysis software (SPSS; IBM Corp) will be used to descriptively analyze quantitative data; these will be linked with corresponding narrative explanations of responses and presented using the integrative method of joint displays.

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Ethics Approval

Ethical approval was received from the University of Manitoba Research Ethics Board (HE2023-0139). To protect confidentiality during the focus groups, participants will be asked to keep all information discussed private. Participant quotations will be carefully reviewed to ensure anonymity and to ensure that identifying information is removed.

Results

Data collection will commence in August 2023. The findings from the study will be used to develop and inform numerous initiatives, including the development of a context-sensitive research theme within the Children's Hospital Research Institute, a series of publications regarding subgroup level analysis of priorities inclusive of the multiple data sources, and a methodological paper describing the use and evaluation of the Circle of Importance method. Results will be reported at each subgroup level and published approximately in August 2024.

Discussion

Priority Setting for eHealth in Mental Health

eHealth has the potential to increase access to health services and improve mental health services for various communities [15]. Every individual experiences mental health differently; therefore, people may have similar or varying values and priorities regarding enhancing their well-being. Similarly, how individuals experience and cope with mental health symptoms varies depending on several factors such as gender, ethnicity, culture, age, access to services, and the intersections of these elements. For example, newcomer and immigrant groups in Canada often face acculturation stressors that affect their mental well-being, and report distress from reporting distress from learning a new language and integrating into a different culture [49]. They experience systemic hurdles to mental health service access, such as language barriers, fear of stigma or discrimination from service providers, and difficulty finding information about accessing needed services [50,51]. Notably, there are different ways of experiencing, defining, and treating mental health and well-being across cultures. For example, spirituality can be a significant cultural factor in one's experience, with some individuals viewing mental well-being as an inner peace, while others view mental illness as an evil to be expelled [51,52]. Even when born in Canada, children of newcomers and immigrants may experience unique mental health challenges. Studies indicate that they may struggle with a sense of belongingness both in relation to their family's country of origin and the country they currently reside in [53]. Thus, it is possible that mental health experiences and priorities differ among various groups (eg, parent or caregiver, youth, newcomer, and Indigenous communities). For many Indigenous nations in Canada, well-being is defined holistically, encompassing balance between physical, mental, emotional, and spiritual components of the self. Connections to land, traditional languages, and cultural practices are additionally noted as central to wellness among Indigenous people [54-58]. Wellness also extends beyond the individual, being dependent upon the whole family and community's well-being through relational considerations [59,60]. The concept of mental illness is a western construct that does not often resonate with traditional ways of knowing, being, and doing nor does it account for systemic and social determinants that influence well-being [61,62]. Therefore, encouraging participants to self-identify priorities and needs aligned with personal and cultural values is critical in promoting safe and respectful practice in research.

Arts-based approaches are well-suited to reflect these unique experiences and priorities for mental health and eHealth that other approaches may fail to identify. Though an emerging methodology, arts-based priority setting has the potential to improve user-centered priority-setting research. Literature highlights popular prioritization methods such as the James Lind Alliance, the Delphi process, and the Nominal Group Technique for involving end users and other knowledge users [63,64]; however, these techniques demonstrate higher ontological and epistemological rigidity than creatively situated approaches. Arts-based methods, for instance, stimulate critical knowledge about human experience from the unconscious mind while provoking transformation [46]. Because of their ability to encourage authentic participation and elicit new and deeper responses to experiential questions, arts-based approaches to priority setting offer unique potential in discovering meaningful experiences and mental health and eHealth priorities across diverse subgroups [32]. There is often a lack of clarity in evaluating arts-based methods in research and priority-setting contexts [46]. This study addresses this challenge using a 5-point Likert scale with the Circle of Importance, quantifying priorities while remaining flexible enough to qualitatively convey participant priorities and experiences. Furthermore, using surveys and semistructured interviews in this study permits the evaluation of the effectiveness of arts-based methods for priority setting while enabling future tailoring of the approach to various subgroups commonly engaged in priority setting.

Limitations

The Circle of Importance method is a novel innovation, and while we will evaluate its use and acceptability, the activity may not go as planned and may not produce the anticipated results. However, related research suggests that participants will respond well to this form of visual elicitation and arts-based methodology [41,65]. Additionally, there may be some limitations in recruitment. Despite our best efforts, we may not be able to recruit equal numbers across the 4 subgroups.

Future Directions

While data collection has not yet commenced, we recommend that researchers consider the use of arts-based approaches in trying to capture complex and varying experiences among individuals. It is also important to try and be aware of the different factors (eg, ethnicity, age, and the intersection of multiple identities) that can contribute to individuals' experiences of their mental health and well-being. Thus, collecting data from various groups with differing identities can provide a richer and fuller picture of their experiences.

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Data Availability

The data sets generated and analyzed during this study are not publicly available due to the identifying nature of the data. Data cannot be made public in order to protect participant confidentiality and privacy. However, deidentified data sets are available from the corresponding author upon reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Circle of Importance and participant evaluation questions.
[PDF File (Adobe PDF File), 152 KB - resprot_v12i1e50208_app1.pdf]

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Abbreviations

CHRIM: Children’s Hospital Research Institute of Manitoba
PRIME: Partnering for Innovation in Mental Health through the eHealth Excellence

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Protocol

Designing Implementation Strategies for a Digital Suicide Safety Planning Intervention in a Psychiatric Emergency Department: Protocol for a Multimethod Research Project

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Abstract

Background: Suicide prevention is currently a national health priority in Canada. Emergency departments (EDs) are critical settings for suicide prevention, and in our local psychiatric ED at the Centre for Addiction and Mental Health, we plan to embed an app-based tool called the Hope app to support suicide safety planning intervention. The app is free and available on app stores, and usability tests have been completed. As a next step to embed this new tool into the routine clinical workflow, research is needed to assess determinants of and design strategies for implementation with the end goal of routinization.

Objective: The purpose of this 2-phased research is to implement the app in the routine clinical workflow in our local psychiatric ED. The specific objectives are as follows: (1) understanding ED clinicians' perceptions and experience of implementing the app in routine practice and identifying barriers to and facilitators of implementation (phase 1) and (2) using findings and outputs from phase 1 and collaborating with service users, families, and ED clinicians to co-design implementation strategies for the app (phase 2).

Methods: We will use an integrated knowledge translation approach throughout this project. In phase 1, we will conduct interviews with ED clinicians to identify implementation determinants using a behavior change framework. In phase 2, a co-design team comprising clinicians, ED service users, and families will design implementation strategies that align with the determinants identified in phase 1.

Results: This protocol presents detailed information about the entire structure of the 2-phased research project. Ethics approval for conducting the qualitative descriptive study (phase 1) has been obtained, and the recruitment and data collection processes will be completed no later than December 2023. Ethics approval for phase 2 is underway.

Conclusions: Involving multiple knowledge user groups early in the research and decision-making process is crucial for successful implementation. Although co-designing is commonly practiced during innovation development, there is often a misconception that the responsibility for implementing what has been designed falls on others. This research aims to fill this methodological gap in the health informatics literature. By the end of this project, we will have developed theory-informed implementation strategies to support Centre for Addiction and Mental Health ED clinicians in adopting the Hope app to complete safety planning intervention. These strategies, guided by a behavior change framework, will target clinicians' behavior change and seamlessly integrate the app into the routine clinical workflow. In addition, this research project will provide recommendations

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on how to involve multiple knowledge user groups and offer insights into how the methodology used can be adapted to other areas within the health informatics literature.

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KEYWORDS

implementation science; suicide prevention; eHealth; mental health; health informatics; integrated knowledge translation; co-design; research protocol; mobile phone

Introduction

Background

Suicide is currently the second leading cause of death among youth in Canada [1]. Emergency departments (EDs) are critical settings for suicide prevention for many reasons [2]. First, individuals, both adult and pediatric patients, requiring mental health services visit EDs more frequently than those who do not [3-5]. Second, EDs frequently provide care to individuals who attempt suicide and are often the first point of contact for individuals who experience suicidal crises [2,6,7]. Third, when looking at service use patterns for people who died by suicide, many of them were already in contact with health services, including EDs [8-10]. For example, a Canadian study published in 2014 examined 8851 suicide deaths in Quebec and found that one-third of these individuals had visited an ED within the month before death [9]. Finally, some individuals living with suicide-related thoughts and behaviors seek help in the ED as a last resort [11,12]. Although this indicates a promising fact that individuals are continuing to seek help, suicide risk may not always be obvious, recognized, or addressed [13-18]. As such, there is a critical need for research to bridge the evidence-to-practice gap in suicide prevention practices within ED settings, and EDs present a critical window of opportunity for identifying and providing care to patients at risk of suicide.

Currently, safety planning intervention (SPI) [19] is one of the best available practices for suicide prevention [20,21]. There is an evidence base (ie, systematic reviews) to support the effectiveness of SPI in reducing suicidal behaviors [20,21]. For example, SPI has been shown to decrease suicidal behaviors by up to 45% [22]. SPI is a collaborative process between clinicians and patients for developing a plan regarding coping strategies, emergency contacts, and restriction of lethal means [19]. SPI is traditionally delivered pen-on-paper, which limits portability. Patients report trouble locating or losing the paper safety plan [23,24], which can be a dire challenge during crises as SPI cannot generate its intended benefit given that it is not available *at hand*. Studies have shown that mobile phones as an intervention modality are acceptable, feasible, and useful for mental health patients [25-27], including those managing suicide-related thoughts and behaviors [28,29]. Moreover, the use of apps and various forms of information and communications technologies (ICTs) has the potential to enhance suicide prevention efforts through the elimination of geographical limitations while also increasing the accessibility and availability of evidence-based interventions [30].

At the Centre for Addiction and Mental Health (CAMH) in Canada, a research team collaborated with clinicians and patient partners and developed an app-based tool for SPI called the Hope app by CAMH [31]. In 2019, at the Innovation Expo held at CAMH, the Hope app was introduced as an innovative solution [32,33]. The idea for the app was presented by an individual with lived experience who had cared for a family member who had attempted suicide [32,33]. The Hope app has several strengths, with its primary advantage being its accessibility “at hand” for individuals living with suicide-related thoughts and behaviors. The idea of having a suicide prevention tool readily available was the main reason behind its recognition at the Innovation Expo [32,33]. In addition, the app provides other valuable resources, including the ability to email the safety plan. It is well documented in the literature that friends and families play a significant role in helping individuals who are seeking assistance when dealing with suicidal thoughts and behaviors [34-39]. As suicide-related symptoms worsen and suicidal thoughts and behaviors become more frequent, friends, families, or other trusted individuals can offer emotional support and encourage professional help if necessary [34-39]. The Hope app’s feature of sending a safety plan is a valuable tool for patients to inform their close social network.

The Hope app is free on app stores and is compatible with Android and Apple phones. A usability test of the app was completed at the CAMH, and a total of 54 REDCap (Research Electronic Data Capture; Vanderbilt University) surveys were administered [40]. Among the respondents, 57% found wellness activity content in the app, such as grounding techniques, to be the most frequently used, and 67% reported that the app increased their knowledge of safety planning [40]. Second, a total of 10 usability participants were recruited, and the research team administered the System Usability Scale, a validated 10-item questionnaire [41]. This yielded an overall usability score of 88.2 out of 100, with higher scores indicating better usability [40]. To better understand users’ perspectives, 18 interviews were conducted [40]. It was found that the app was helpful in prompting self-reflection, which made the safety planning process easy [40]. For instance, the paper-based safety plan used at the CAMH requires patients to provide their own answers for coping strategies, whereas in the app, users are presented with potential strategies and can choose relevant ones or add text if the provided options do not align with their needs. In addition, interview participants reported that the app is a useful tool to accompany mental health appointments [40]. Finally, user feedback was obtained from a public avenue at the Apple App Store “Ratings and Reviews” section [42]. As a next step, theory-informed research is needed to develop

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implementation strategies to ensure the successful delivery of the Hope app to patients who are at risk of suicide.

Implementation in health services research is about promoting the systematic uptake of evidence-based practices into routine care [43-45]. The systematic uptake of evidence-based practices is dependent on the behaviors of individuals who are involved in health services, including clinicians [46,47]. Although changing behavior is challenging, it is most effectively achieved when behavior change strategies are informed by evidence-based principles and theories of behavior change [48-50]. New innovations or ICTs such as the Hope app do not implement themselves. Implementation requires "organizational effort directed toward diffusing [ICTs] within a user community," with the end goal of routinization [51]. Implementation efforts may include training, making changes in the clinical settings and workflow, providing technical support, or clarifying professional responsibility related to an innovation, all of which are determinants of behavior change influencing one's knowledge, motivation, and opportunity [52]. The organizational decision to adopt the Hope app was based on existing evidence of SPI effectiveness and the organization's priority goal for suicide prevention. As mentioned previously, there are existing systematic reviews supporting the effectiveness of SPI in reducing suicide behaviors [20,21]. Although ICT-based interventions for suicide prevention are still in their early stages, they show promise. For instance, a meta-analysis of these interventions demonstrated a small but significant efficacy in reducing suicide ideation [53]. However, one could argue that, owing to the limited clinical integration of apps [54], the current literature lacks evidence to support the effectiveness of SPI *when* it is delivered via an app (ie, changing the mode of delivery) [55]. This question of concern falls beyond the scope of our study and is an area for future investigation. Nonetheless, the findings from our study can inform the feasibility of conducting a larger experimental design to assess the effectiveness of the Hope app and facilitate its initial integration into routine clinical practice.

EDs are a critical setting for suicide prevention [56], which makes them a priority setting for the implementation of the Hope app. Implementation occurs after organizations make decisions to adopt a new innovation [51], and the end goal of implementation—routinization—involves changing clinicians' behavior [49]. Given the organizational-level decision at the CAMH to adopt the Hope app, this proposed research will concentrate on the subsequent stages of implementation; these stages include adaptation, acceptance, and routinization [51], primarily focusing on changing clinicians' behavior. Adaptation is about developing and revising departmental procedures, such as making changes to the workflow or training staff for new ICTs [51]. Acceptance is about promoting staff's commitments to using new ICTs, and finally, routinization means integrating new ICTs into a normal workflow [51].

Problem and Rationale for This Study

To date, research on mental health apps lacks rigorous implementation and a theoretical basis [54]. In addition, a recent call was made for research to consider the complex contexts in which apps are being implemented to tailor implementation efforts [57]. Without a careful investigation of the context, implementation strategies have often been mismatched with existing barriers in a given context [58,59]. As a prior work for this study, Shin et al [52] conducted a scoping review of ICTs (eg, apps) for suicide prevention that have been implemented in clinical settings and identified that barriers and facilitators collectively influence clinicians' capability, opportunity, and motivation to implement innovations. Therefore, implementation strategies must be tailored and multifaceted to simultaneously target these determinants of behavior change to maximize implementation [60]. However, most of the reported implementation strategies focus on improving knowledge and building skills (ie, capability) without addressing clinicians' motivation and opportunity [52]. The fact that implementation strategies are often developed nonsystematically and do not match contextual implementation determinants is a consistently reported gap in the literature [61].

Another concern with implementing a new innovation of this type is that not everyone owns or has access to a smartphone and unlimited internet or data or has digital literacy skills [62]. Inequities in accessing and using ICTs, as well as the associated outcomes of using ICTs, constitute a phenomenon called the digital divide [63]. There are three levels to the digital divide: (1) access to ICTs and necessary connections, (2) literacy to use these ICTs, and (3) capacity to convert the use of ICTs into outcomes [64]. The digital divide is rooted in social factors such as education, income, age, and place of residence [63,65,66]. To prevent digital divide amplification and avoid unintended harm, implementation strategies must be developed with digital equity considerations in mind [67]. This research is not sufficient to address the structural factors that perpetuate the digital divide but will consider its second and third levels. For example, we will adopt a set of recommendations made by Shaw et al [67] to promote digital health equity in the context of implementing ICTs in health care, such as supporting patients with low digital literacy, collaborating with service users, and providing alternatives (eg, traditional paper format of SPI and emailing electronic copies of safety plans). In addition, the interview guide and co-design session goals in this study include prompts related to digital equity.

Research Objectives

To implement the Hope app with digital equity considerations, this proposed research aims to leverage the integrated knowledge translation (IKT) approaches as well as implementation science frameworks to develop tailored implementation strategies in a psychiatric ED at the CAMH. This project has two main objectives with two corresponding phases, as follows:

1. Understand clinicians' perceptions and experiences of implementing the Hope app in routine practice in the psychiatric ED and identify barriers to and facilitators of implementation (phase 1)
2. Use the findings and outputs from phase 1 and engage with knowledge users to co-design implementation strategies for the Hope app (phase 2).

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Methods

Theoretical Frameworks

There is evidence strongly suggesting that theory-informed strategies are more likely to be effective in changing behavior [48-50]. A combined use of theories, models, and frameworks is appropriate to meet the needs of researchers [68]. In this study, several frameworks will be used to address the research objectives.

One way to solve complex problems is to work with knowledge users [69] who will be delivering or receiving the Hope app. Knowledge users are people who will be using research findings to inform their decision on practice, policies, and programs, as well as people who will be affected by research findings and making informed decisions based on them [70]. As such, knowledge users include but are not limited to health care professionals, service users, and health care managers [70]. Collaborative research approaches such as IKT are perceived to be the best ways to produce relevant research outputs to address health care issues and generate a greater impact on practice [71,72]. Although co-designing is common for innovation development, people often think that implementing what has been designed is the responsibility of others [73]. This is not true; researchers can co-design changes in the workflow to support implementation [74].

IKT approaches will be used throughout this proposed research. Specifically, a medical head of the CAMH ED and a CAMH nursing chief clinical informatics officer are coauthors of this paper and members of the steering committee who will oversee the current project throughout phases 1 and 2, ensuring that the research objectives and outputs are relevant to the implementation setting. Securing leadership support for this project is an important facilitator for maintaining commitment to coproduction, as indicated in the IKT literature [71,75]. Patient partners (ie, ED service users) are also a critical knowledge user group, but they will not be part of the steering committee. However, we consulted the CAMH Lived Experience Advisory Group in February 2023. Feedback was received and has been incorporated into this protocol. Such feedback includes co-design team formulation, consensus-achieving activities, and strategies to mitigate dropout. In addition, patient partners and families or caregivers will be closely involved as co-designers in phase 2.

The Knowledge-to-Action (KTA) cycle [76] is a process model that outlines the steps and activities required to integrate a new innovation into practice [48]. We are using KTA to guide the overall research. Specifically, the research objectives have been guided by the KTA action phases leading to effective implementation. Not all stages of KTA will be addressed in this research, and this flexibility of KTA application is one strength that can fit researchers' needs. The objectives of this research will address the following 3 steps of KTA: adapt the identified knowledge or research to the local context; assess barriers to using the knowledge; and select, tailor, and implement interventions to promote the use of knowledge. A previous study addressed steps 1 and 2 of KTA, in which we used a scoping review methodology to explore the breadth of existing evidence on ICT-based interventions for suicide prevention and collated identified implementation characteristics [52]. This step was necessary to make sense of all the relevant knowledge and identify gaps that require new research. Phase 1 in this project will then address steps 3 and 4 using a qualitative design to investigate barriers and facilitators specific to our implementation setting. Phase 2 will then address step 5 selecting and tailoring implementation strategies using a co-design approach to address barriers and leverage the identified facilitators.

KTA outlines steps to translate knowledge into practice, but it does not inform how we can achieve these steps. Therefore, we will use the Behavior Change Wheel (BCW) [77] and the Theoretical Domains Framework (TDF) [78] to further guide this research. The BCW and TDF are comprehensive and evidence-based behavior change frameworks. The BCW was developed from a synthesis of 19 behavior change frameworks. The BCW comprises multiple components, and at its core, it presents the Capability, Opportunity, and Motivation–Behavior (COM-B) model, which is an implementation theory that explains the relationships between internal and external influences of behavior change [46,77]. The TDF is often used as a supplement as it provides a granular breakdown of the COM-B [79]. The BCW can assist with barrier and facilitator assessment and inform the design of implementation strategies [46,77]. The BCW also offers step-by-step guidance on making theory-informed choices of strategies that link to the determinants of behavior change based on the barrier and facilitator analysis [46,77].

There are several related tools that augment the use of the BCW. The Affordability, Practicability, Effectiveness, Acceptability, Safety, and Equity (APEASE) selection criteria are a tool to support decision-making [46,77]. As the BCW provides a wide range of options, it may not be feasible to leverage all possible intervention options. This is when the APEASE criteria can be used to rank options and carefully select the top choices based on the knowledge users' assessment of options considering all domains of APEASE. Next, the behavior change technique (BCT) Taxonomy version 1 provides a granular level of the 9 intervention types [80]. BCTs are the smallest unit and the "active ingredients" of an intervention that generate behavior change [80]. The development of the taxonomy was an international consensus project, and it provides a common language between researchers and allows for clear communication and replication of interventions [80]. Finally, the Theory and Technique Tool provides information on linkages between mechanisms of action (ie, how behavior can be changed) and specific BCTs [81]. It is based on the synthesis of evidence for the links, expert consensus, and triangulation of these 2 sources of findings [82]. This tool provides links between 74 BCTs and 24 mechanisms of action (ie, COM-B) to change behavior [81].

Lynch et al [83] suggest using the BCW and TDF when researchers investigate individual experiences as a preparation for implementation. This is because clinicians' behavior is a determinant of implementing new ICTs, and therefore, it is vital to conduct a thorough behavioral analysis, such as barriers to and facilitators of performing the desired activity. In this study,

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our desired behavior change for the clinical team is to deliver the SPI using the Hope app on patients' own devices. The BCW and TDF have been used in a wide range of disciplines such as health promotion [84-87] and health informatics [88-90] to characterize barriers to and facilitators of implementation. For example, in the field of health informatics, the BCW and TDF have been used to inform implementation strategies to facilitate the completion of electronic discharge summaries [90].

Study Setting

This study will take place in the CAMH Gerald Sheff and Shanitha Kachan ED located in an urban academic tertiary care center in Ontario that provides care to approximately 1200 adult patients each month [91]. The CAMH ED is Ontario's only stand-alone psychiatric ED that provides emergency assessment and treatment exclusively focused on adults (aged ≥16 y) with mental health and substance use issues. Approximately 150 staff members (both full time and part time) are employed in this ED. On a daily basis, the ED is staffed by a total of 16 to 20 nurses, program assistants, psychiatrists, residents, and social workers.

Intervention: Hope App

The Hope app by CAMH is a free smartphone app that provides suicide prevention information, resources, and tools to support individuals who are experiencing suicide-related thoughts and behaviors. This app is evidence-based, meaning that it adheres to the best practices available for safety planning [20,21], and was developed in collaboration between service users and clinicians. The collaborative approach to developing the Hope app is a strength, and it has been well documented in the literature that research outputs (eg, interventions) generated through partnerships are more useful and relevant to end users [92]. A core component of the Hope app is a "Safety Plan" (ie, SPI) that includes five items for completion: (1) warning signs, (2) reasons for living, (3) coping strategies, (4) support network, and (5) environmental safety. Multimedia Appendix 1 provides screenshots of the app and its content.

In addition to the SPI, the app includes a direct 9-1-1 line, mental health resources (eg, link to community resources), and wellness activities (eg, journaling and relaxed breathing). This app does not track the user's location and cannot store or access personal data such as names, addresses, and phone numbers. Only when users want to can they share their safety plan with their clinicians or social network via email. The Hope app allows users to send an email copy of the safety plan using the default email app, and users can edit the subject or body of the email before sending it.

Phase 1

In phase 1, we will conduct a qualitative descriptive study [93] to understand clinicians' experiences and perspectives of implementing the Hope app in routine practice in the psychiatric ED and identify barriers to and facilitators of implementation (objective 1).

Sampling and Recruitment

We will use purposeful sampling strategies to recruit a heterogeneous sample to obtain broad insights and information-rich data [94]. All CAMH ED clinicians (ie, physicians, nurses, social workers, and program assistants), including trainees such as residents, will be invited for an interview regardless of their age, gender, and years of experience. The composition of the sample will be purposeful to maintain sufficient representation from each clinician group (ie, at least 2 members/discipline). Nurses make up the majority clinician group in the CAMH ED, so the sample may have a large proportion of nurses. Since the launch of the Hope app without systematic effort for integration, some staff members have been voluntarily using the app, whereas others continue to use the paper-based safety plan or a mixture of both. All clinicians will be invited whether they use the app or not. Both perspectives (ie, users and nonusers) will be valuable to gain insights into adopting the Hope app in routine practice. A specific number of participants will not be predetermined, but instead, data collection and analysis will occur concurrently such that recruitment will stop after data saturation (ie, information redundancy) [95]. Qualitative descriptive studies tend to have an average sample size ranging from 20 to 35 [96]. However, based on a systematic review of empirical tests assessing the number of interviews needed for data saturation, 9 to 17 interviews are sufficient for achieving data saturation [97]. As such, it is possible to reach saturation with <20 interviews. In short, phase 1 aims to recruit a minimum of 20 interview participants, but it could potentially be <20 if data saturation is achieved. Snowball sampling may be used as a secondary method if faced with recruitment challenges using posters and emails.

Data Collection

A semistructured 1:1 interview guide was informed by the COM-B and TDF (Multimedia Appendix 2). The guidelines provided by Atkins et al [79] and Michie et al [77] on applying the COM-B and TDF in research processes and example interview questions to assess each domain of the COM-B and TDF were reviewed. In addition, published examples by other researchers on how to phrase questions to assess all the domains in the COM-B or TDF were reviewed [98-100]. Through this review, adaptations were made to our interview guide to better fit our research context. In addition, a few prompts were added related to digital equity concerns. For example, clinicians will be asked whether they have encountered any challenges while using the app with individuals who have low digital literacy and faced difficulties in providing technical support to these individuals and their thoughts on the potential drawbacks of using either the paper or app format of SPI. In particular, the provision of technical support to patients in the ED aligns with the recommendation by Shaw et al [67] to integrate supportive intermediaries. However, this needs to be explored in the CAMH ED for its feasibility and for redefining professional responsibilities as the role of providing technical support may or may not be perceived as a clinical responsibility of the ED team. Open-ended questions in the interview guide are mapped according to the COM-B and TDF domains, and they are designed to identify what clinicians need, what they are capable of, and what their motivation is for using the Hope app in their normal clinical workflow. In addition, the sustainability potential of the Hope app within the CAMH ED and scalability beyond

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the CAMH ED will be explored. The interview guide will be pilot-tested with the internal research team to minimize any ambiguity in wordings. All interviews will be 45 to 60 minutes in length, via web-based video call, telephone, or in person, at a suitable time for the clinicians. Recognizing that accessing interviews with clinicians is challenging, we will need to be flexible with the interview format, setting, and timing and strive for conversation-like interviews, which are less formal in structure. For instance, interviews may be initiated on-site at the CAMH ED, and the remainder of the questions may be completed off-site. Questions that can be asked on-site (eg, questions 2, 3, 9, and 17 in Multimedia Appendix 2) will aim to highlight "in the moment experience" [101] in the ED context as it relates to SPI with the Hope app. All interviews will be audio recorded and transcribed verbatim and have identifying information removed to maintain privacy. We will also collect participant characteristics (eg, age, sex, gender, discipline, and years in practice) at the end of each interview via a web survey using REDCap [102]. Demographic and interview data will not be linked.

Data Analysis

Participant demographic characteristics will be tabulated (ie, descriptive statistics) and narratively described. Interview transcripts will be analyzed using directed content analysis [103] for barriers and facilitators using the COM-B and TDF as a codebook along with operational definitions for all domains. First, 2 reviewers will read the transcripts to categorize relevant statements into the COM-B domains and subcategories of the 14 TDF domains. These categorized segments, known as coding stripes, will be compared between the 2 reviewers for consistency. Once all transcripts are initially coded into COM-B and TDF domains, we will generate specific belief statements in relation to the 14 TDF domains. The belief statements, or initial themes, are a group of similar responses that suggest a potential influence on the target behavior [79]. These belief statements will then be further refined into themes and aligned with the COM-B domains. The final themes organized into COM-B domains will represent the barriers and facilitators perceived to influence clinicians' behavior when delivering the SPI using the app downloaded on the patients' own devices in the ED.

As advised by Atkins et al [79], it is important to emphasize that, although the TDF domains are intentionally designed as broad groupings of potential factors influencing behavior, the primary goal is to examine these domains in greater depth. Some statements from the transcripts may overlap across multiple domains, illustrating the intricate nature of human behavior [79]. The main domains of behavioral influences have been identified a priori, but there may be new behavioral factors unique to the CAMH ED and the Hope app. Therefore, new codes and categories may emerge during the categorization step [103]. At least 2 researchers will first trial the codebook with 1 or 2 transcripts to ensure consistency in the coding strategy. We then will independently code all transcripts. The research team will meet regularly to resolve any interpretation discrepancies through discussion or with a third person. During these regular meetings, we will also look for repetition in participants' responses to determine whether data saturation has been reached. We will use the NVivo software (Lumivero) [104] for data management and analysis. A summary of the findings will be presented via web meetings or email communications to participants for member checking [105] to determine whether they feel that the identified themes are accurate. Outputs from phase 1 will include a list of implementation barriers and facilitators mapped to the COM-B.

Strengths and Limitations

Barriers and facilitators do not linearly affect clinicians' behavior and subsequent implementation. The clinical context as well as human behavior are complex; it is not individual factors that facilitate the implementation of a new innovation but the dynamic interaction between them [106,107]. Nonetheless, the COM-B accounts for interactions between both internal (ie, capability and motivation) and external (ie, opportunity) factors that influence behavior change. Data analysis using the COM-B and TDF as guiding theoretical frameworks will help explain the relationship between factors that influence clinicians' behavior leading to delivering the Hope-app. Therefore, the application of the COM-B and TDF will not downgrade the complexity of human behavior but, rather, will help us organize the data in a way that makes them accessible to work with and facilitates the understanding of complexity.

Phase 1 is limited to clinicians' perspectives, but other ongoing studies at CAMH focusing on patients' perspectives on SPI can be leveraged. Furthermore, we will involve patients (ie, ED service users) in the subsequent phase 2 to co-design implementation strategies with clinicians to integrate the Hope app in the CAMH ED. Patients' insights will be sought during phase 2, and there will be opportunities to identify convergence with and divergence from clinicians' perspectives.

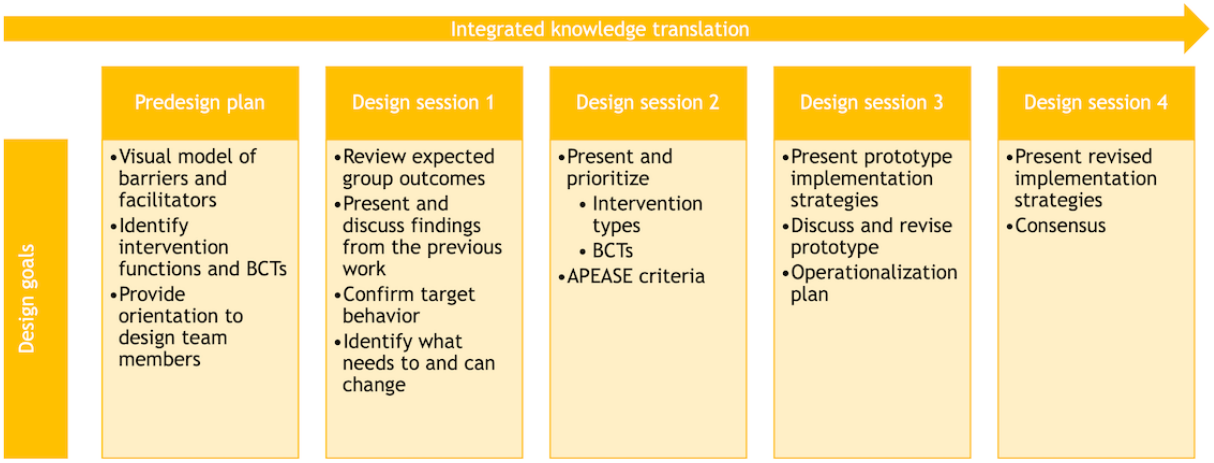
Phase 2

Overview

In phase 2, we will use a co-design approach to develop implementation strategies based on the outputs from phase 1. Specifically, we will select BCTs (ie, active ingredients of implementation strategies) that can mitigate barriers and enhance facilitators. The development of implementation strategies is envisioned in at least 4 co-design sessions, with specific design goals guided by semistructured, open-ended questions, and the findings from each session will feed into the next. All 4 co-design sessions will follow the steps (Figure 1) based on the BCW guide for intervention design and recommendations for co-design [108,109].

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Figure 1. Proposed co-design process informed by the Behavior Change Wheel. APEASE: Affordability, Practicability, Effectiveness, Acceptability, Safety, and Equity; BCT: behavior change technique.



Sampling and Recruitment

A co-design team will consist of ED service users (ie, patients), families, and ED clinicians. The representation of clinicians on a team will include at least one nurse and one psychiatrist currently working in the CAMH ED. The composition of the co-design team will be purposely chosen to maintain sufficient representation from each knowledge user group and ensure adequate peer support for patients and families in each co-design session. At least 6 members (ie, 2 service users, 2 family members, and 2 clinicians) but no more than 10 will form a co-design team. The team will ideally stay the same throughout phase 2, facilitating rapport building. However, time and availability of participants may lead to challenges in recruitment and retention, so snowball sampling may be used as a secondary method.

Design Procedures

Overview

All co-design sessions will last approximately 1.5 to 2 hours, either on the web or in person depending on participants' preferences and convenience. To minimize attrition, we will provide a tailored orientation to prepare all participants before each design session for effective collaboration. During this preparation, we will ensure that participants' level of knowledge of the Hope app and the purpose of phase 2 are the same, ensuring that everyone is on the same page. Participants will not enter each design session blindly; instead, they will have a clear idea and expectations for each design session. This strategy was informed by the CAMH Lived Experience Advisory Group meeting in February 2023. Email progress updates will be used to communicate with participants (ie, members of the co-design team) between sessions. We will also inform participants about how we have incorporated their feedback into the implementation strategies. All participants will have access to web-based or telephone support between meetings to address any questions or concerns. The following sections detail the goals of each co-design session.

Predesign Plan

When designing an implementation strategy, it is important to consider the full range of available intervention options [77]. The BCW links the COM-B to the full range of 9 "intervention functions" (ie, strategy types) that can change behavior [77]. Using the BCW, we will identify a full range of strategies that match to the determinants of behavior change based on phase 1 outputs. In addition, we will prepare a list of BCTs that match to the selected strategies.

Co-Design Session 1

There will be an opportunity to get to know the team members. Then, the findings from phase 1 (ie, the list of barriers and facilitators mapped to the COM-B) will be presented with visual aids. As a team, we will confirm the target behavior and then identify which barriers are modifiable and which facilitators can be leveraged. Activities will be used to generate insights into what change is needed to integrate the Hope app into the normal workflow. Ideas will be sought regarding *when* (ie, timing within discharge), *who* (eg, psychiatrists, nurses, or both), and *how* clinicians should deliver the Hope app.

Co-Design Session 2

A summary of the findings from session 1 will be shared with the design team before the meeting. During the design session, prematched strategies and possible content or contents of the implementation strategies (eg, BCTs) will be presented. We will come up with lay language alternatives to BCTs to enable better understanding. The design team's views on the relevance and importance of BCTs will then be asked. Activities using both voting and discussion will focus on prioritizing the content and modes of delivery. The design team will then be asked to identify and discuss potential challenges regarding feasibility associated with the selected content or contents and mode or modes. The discussion will be guided by the BCW APEASE criteria, with a strong emphasis on the *equity* domain of APEASE.

Co-Design Session 3

The prototype of the implementation strategies will be developed based on the findings from session 2. This will be presented

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before the meeting and during the co-design session for review following the reporting criteria by Proctor et al [110] for describing implementation strategies. We will also provide a visual representation of how strategies intend to work, linking anticipated behavioral outcomes with mechanisms of action (ie, underlying theoretical assumptions and BCTs that will target the barriers). We will then discuss the operationalization of the strategies and their usability.

Co-Design Session 4

During the last session, we will present the revised implementation strategies along with the operation plan. We will present a visual storyboard, from triage to discharge, and illustrate how a patient is expected to receive the SPI via the Hope app. Specifically, we will highlight how, when, and by whom the Hope app will be delivered. The design team will have the opportunity to provide additional feedback.

Data Collection

All design sessions will be audio recorded, transcribed verbatim, and deidentified. There is great flexibility in the ways in which people approach co-design [111]. We will use a range of activities (eg, think-aloud and voting) to engage participants and provide them with interactive ways to develop and share ideas. We will have a mock-up trial with the internal research team and receive feedback from the ED medical head before finalizing the activities. Other data may include participants' sticky notes of ideas or web-based comments. A cofacilitator will take notes and capture details of the design process (eg, decisional conflicts and group dynamics). In addition, at the end of each design session, we will collect data to evaluate and monitor the experience and engagement of participants. The evaluation questions will consist of Likert scales adapted from the Public and Patient Engagement Evaluation Tool [112]. The questions will ask participants to rate their experience and self-perceived engagement.

Data Analysis

The analysis of transcripts and notes will be pragmatic, focusing on the specific design goals outlined in Figure 1. At least 2 researchers will use NVivo [104] to independently analyze transcripts using directed content analysis [103] to categorize design considerations using the BCW as a codebook. Design session notes made by a cofacilitator will supplement data analysis to provide contextual information. We will meet regularly to resolve any coding discrepancies through discussion. In addition, we plan to do a recap of the previous design session at the start of each design session for member-checking purposes [105]. We will review the evaluation data between each design session to monitor and assess whether any changes are required to improve engagement. We will report engagement evaluation data using descriptive statistics. Outputs from phase 2 include discrete implementation strategies that not only match the determinants of implementation from phase 1 but are also reflective of inputs from several knowledge user groups.

Anticipated Challenges and Mitigation Strategies

There may be concerns about placing service users, family members, and clinicians in the same group as service users may feel uncomfortable speaking up. However, previous research has shown that forming a heterogeneous co-design team with patients and clinicians can be done well [113-116]. Furthermore, the CAMH Lived Experience Advisory Group supported this as an effective approach for reaching a consensus. The principal investigator of this work (HDS) also has previous co-design experience as a clinician participant in a mixed group with youth and parents [113]. To provide a trusting and safe space for all participants to share their ideas and speak respectfully to each other, the project lead (HDS) and cofacilitator will put great effort into practicing transparent dialogue and power sharing, developing a common language and avoiding medical jargon, and fostering mutual respect and making it clear to knowledge user groups that their different expertise is equally valued [117]. The Lived Experience Advisory Group also highlighted the importance of providing orientation to the co-design team members, ensuring that everyone is on the same page and has a clear understanding of the research agenda. Research team members of phase 2 will also practice humility and self-reflexivity, which are facilitators for conducting collaborative research [118]. Finally, we will be collecting progress outcomes on engagement to identify whether modifications are needed for subsequent co-design sessions.

Trustworthiness

There are four criteria for ensuring the trustworthiness of qualitative studies (phase 1-2): (1) credibility, (2) confirmability, (3) dependability, and (4) transferability. Credibility will be achieved by representing research findings drawn from the participants' original data and accurate interpretations of the participants' original views [119]. We will select and show representative quotations from the interviews when reporting the findings. Member checking will further ensure credibility. Confirmability is about ensuring that findings are the result of the experiences and ideas of the participants rather than the characteristics and preferences of the investigator [119]. Therefore, data analysis will involve ≥2 researchers. To demonstrate dependability, all processes and rationales within the study will be recorded and reported in detail [120]. Such documentation will include operational detail regarding sampling, data collection, process logs, memos, and reflexive notes. We will strive for detailed reporting using the COREQ (Consolidated Criteria for Reporting Qualitative Research) checklist [121] for phase 1 and the GRIPP (Guidance for Reporting Involvement of Patients and the Public) reporting checklist [122] for the co-design phase 2. Any deviations from the protocol because of the iterative nature of qualitative studies will be transparently described in the full report. Transferability may be limited as this study takes place in 1 clinical setting (ie, the CAMH ED) given its unique characteristics as a stand-alone psychiatric ED. However, one approach to enhance transferability is to provide detailed contextual information about the study and the setting, so called "sending context" to readers [120]. It is suggested to provide a clear description of culture and context, selection and characteristics of participants, data collection, and process of analysis [119]. Therefore, readers of the study report can make judicious transfers and inferences and apply the study findings to other settings.

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Ethical Considerations

Ethics approval for phase 1 was obtained from the Research Ethics Board of the CAMH (REB 2023/078). Recruitment and data collection in phase 1 have started. All participants are provided with both written and oral information about the study, which includes details on the voluntary nature of participation and their ability to ask questions or withdraw from the study at any time without having to provide reasons. After reviewing the study procedures, all participants provide informed consent through an electronic platform (ie, REDCap) where they provide their signature before participating in audio recording. The study data will be deidentified before publication. Clinicians participating in phase 1 will receive a CAD $50 (US $36.44) e–gift card of their choice as compensation for their time and knowledge. At the end of the phase 1 interviews, clinicians are invited to express their interest in participating in phase 2. Ethics approval for phase 2 is underway at the time of writing and will be obtained from the Research Ethics Board of the CAMH.

Results

The protocol presents the entire structure of the research project involving 2 sequential studies, with the first phase feeding into the next. Ethics approval from the CAMH for phase 1 has been obtained, and we expect to complete recruitment and data collection for phase 1 no later than December 2023. We anticipate that each phase will last a maximum of 1 year.

Discussion

Expected Findings

In the end, we will have developed theory-informed implementation strategies to support CAMH ED clinicians' uptake and subsequent delivery of the Hope app to patients. These developed strategies will facilitate the implementation of the Hope app by addressing barriers and leveraging facilitators in the local context, thereby maximizing SPI delivery. The co-design approach is expected to ensure that strategies are targeted to meet the needs of knowledge users (ie, both patients and clinicians) and are feasible, acceptable, and appropriate for the CAMH ED. In addition, the strategies driven by the BCW will change clinicians' behavior and be compatible with their routine clinical workflow.

The patients' behavior after ED discharge is beyond the scope of our study and also beyond the control of the ED clinical team. However, we recognize that it is another significant contributor to the effective use of the SPI. Changes in clinicians' behavior in the ED can trigger a chain of behavior changes among patients and families. If patients and their families receive the safety plan through the Hope app in the ED, along with instructions on how to use it, as a result of successful behavior change within the ED team, this could hypothetically lead to changes in the behavior of patients and their families. After being discharged from the ED, patients may incorporate the app into their self-care routine, engage with its features, and review their safety plan and participate in self-reflection. However, if patients do not use their safety plan on their phones after ED discharge, it will not generate its intended benefits, and they may return to the ED in the event of another crisis (eg, a suicide attempt). Nevertheless, changes in patients' and families' behavior are beyond the scope of our study and also outside the control of the ED team. This falls into another important area for future exploration related to user engagement in health informatics.

Strengths and Limitations

The systematic and replicable reporting of the behavioral mechanisms of action behind the implementation strategies is a strength of this study. Furthermore, the proposed co-design process is highly collaborative. The design team members will work together in equal and active partnership. In addition, this research project can provide recommendations on how to involve multiple knowledge user groups and offer insights into how the collaborative approaches can be used and adapted to other areas within the health informatics literature. However, this study does not intend to generate generalizable implementation strategies for an app. Instead, the findings can be adapted to different contexts, and we will take the necessary steps to ensure the transferability of this work outlined in the Trustworthiness section. We would also like to acknowledge the limitations of this study concerning digital equity. Digital equity encompasses more than the acquisition of digital literacy skills and ensuring affordability. This study does not address structural factors contributing to the digital divide, such as socioeconomic status and place of residence. Moreover, it cannot resolve the access divide, which reinforces our decision to keep the paper-based SPI in the ED as an option. Although we recognize that digital equity surpasses digital literacy, it is also important to acknowledge that equity must extend beyond ensuring affordability; even with access to technologies, the reported outcomes of using health technologies have been inconsistent [64]. In our study, we prioritize digital literacy and the engagement of various knowledge user groups in the design process, aiming to alleviate potential challenges associated with the app's use among individuals with limited digital skills. Finally, co-design team members will be self-selected, often motivated individuals, and their views may not be representative of diverse ED service users and clinicians at the CAMH.

Conclusions

This proposed work will contribute to the current literature by addressing several identified gaps. First, this work will contribute to the identified knowledge gap regarding the contextual implementation characteristics of ICTs for suicide prevention in clinical settings. Using the BCW, this work will also tease apart the nuanced influences of behavior change leading to ICT implementation. Second, this theory-informed and collaborative work will fill the methodological gap regarding nonrigorous implementation research for mental health apps.

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Acknowledgments

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Data Availability

All data generated and analyzed in this study will not be publicly available in accordance with the Centre for Addiction and Mental Health ethical review guidelines as all data are securely stored on an internal server. However, they can be obtained from the corresponding author upon reasonable request.

Authors' Contributions

HDS, JZ, JT, and GS conceptualized the study. HDS designed the protocol, including data collection, analysis, and interpretation planning. HDS wrote the first draft of the manuscript and worked on revisions. GS supervised all phases of the work. All the authors (HDS, JZ, JT, and GS) critically reviewed and provided feedback on the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Hope app content.
[DOCX File , 402 KB - resprot_v12i1e50643_app1.docx]

Multimedia Appendix 2
Semistructured interview guide for phase 1.
[DOCX File , 16 KB - resprot_v12i1e50643_app2.docx]

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Abbreviations

APEASE: Affordability, Practicability, Effectiveness, Acceptability, Safety, and Equity
BCT: behavior change technique
BCW: Behavior Change Wheel
CAMH: Centre for Addiction and Mental Health
COM-B: Capability, Opportunity, and Motivation–Behavior

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COREQ: Consolidated Criteria for Reporting Qualitative Research
ED: emergency department
GRIPP: Guidance for Reporting Involvement of Patients and the Public
ICT: information and communications technology
IKT: integrated knowledge translation
KTA: Knowledge-to-Action
REDCap: Research Electronic Data Capture
SPI: safety planning intervention
TDF: Theoretical Domains Framework

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Protocol

Identifying Game-Based Digital Biomarkers of Cognitive Risk for Adolescent Substance Misuse: Protocol for a Proof-of-Concept Study

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Abstract

Background: Adolescents at risk for substance misuse are rarely identified early due to existing barriers to screening that include the lack of time and privacy in clinic settings. Games can be used for screening and thus mitigate these barriers. Performance in a game is influenced by cognitive processes such as working memory and inhibitory control. Deficits in these cognitive processes can increase the risk of substance use. Further, substance misuse affects these cognitive processes and may influence game performance, captured by in-game metrics such as reaction time or time for task completion. Digital biomarkers are measures generated from digital tools that explain underlying health processes and can be used to predict, identify, and monitor health outcomes. As such, in-game performance metrics may represent digital biomarkers of cognitive processes that can offer an objective method for assessing underlying risk for substance misuse.

Objective: This is a protocol for a proof-of-concept study to investigate the utility of in-game performance metrics as digital biomarkers of cognitive processes implicated in the development of substance misuse.

Methods: This study has 2 aims. In aim 1, using previously collected data from 166 adolescents aged 11-14 years, we extracted in-game performance metrics from a video game and are using machine learning methods to determine whether these metrics predict substance misuse. The extraction of in-game performance metrics was guided by literature review of in-game performance metrics and gameplay guidebooks provided by the game developers. In aim 2, using data from a new sample of 30 adolescents playing the same video game, we will test if metrics identified in aim 1 correlate with cognitive processes. Our hypothesis is that in-game performance metrics that are predictive of substance misuse in aim 1 will correlate with poor cognitive function in our second sample.

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Results: This study was funded by National Institute on Drug Abuse through the Center for Technology and Behavioral Health Pilot Core in May 2022. To date, we have extracted 285 in-game performance metrics. We obtained institutional review board approval on October 11, 2022. Data collection for aim 2 is ongoing and projected to end in February 2024. Currently, we have enrolled 12 participants. Data analysis for aim 2 will begin once data collection is completed. The results from both aims will be reported in a subsequent publication, expected to be published in late 2024.

Conclusions: Screening adolescents for substance use is not consistently done due to barriers that include the lack of time. Using games that provide an objective measure to identify adolescents at risk for substance misuse can increase screening rates, early identification, and intervention. The results will inform the utility of in-game performance metrics as digital biomarkers for identifying adolescents at high risk for substance misuse.

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KEYWORDS

game-based digital biomarkers; cognition; adolescent substance misuse; cognitive risk factors; game-based measurement of cognitive function; biomarker; adolescent; screening; game; barrier; digital; substance; use; misuse

Introduction

Background

Despite existing evidence-based interventions, many adolescents continue to misuse substances [1]. In 2021 alone, over 1 in 5 adolescents aged 12-17 years misused substances (illicit drugs and alcohol or tobacco products) [2] and 2 million adolescents had a substance use disorder [2]. Adolescent substance misuse, defined as "the unhealthy use of alcohol or drugs to relieve stress, alter reality or bring about pleasure" [3], increases the risk of developing a substance use disorder. Adolescents with substance use disorders are more likely to engage in criminal activity, contract sexually transmitted infections, develop comorbid mental disorders, and die early [4]. In addition, between 2019 and 2020, there was a 44% increase in drug-involved deaths among adolescents aged 10-19 years [5]. The negative consequences arising from substance misuse underscore the need to identify at-risk adolescents early to deliver timely prevention and treatment interventions.

Less than 10% of adolescents in need of substance use treatment receive it [6] in the setting of poor screening uptake and referral for treatment [7]. Many adolescents with substance misuse are not identified early, and barriers in screening adolescents for substance misuse contribute to this. The American Academy of Pediatrics and the Substance Abuse and Mental Health Services Administration recommend universal screening to identify at-risk adolescents. Yet, fewer than half of primary care providers [8] and fewer than a fifth of School-Based Health Center providers [9] screen adolescents for substance misuse [8,9]. Identifying at-risk adolescents early and delivering effective prevention interventions can prevent substance misuse-associated morbidity and mortality [10,11]. Barriers to screening adolescents for substance misuse include the lack of time, concern that adolescents will not be forthcoming about misuse, discomfort with conducting screening, and difficulty with providing a confidential space to conduct screening [8,12-15]. Innovative solutions that address or mitigate these barriers and lead to early identification of at-risk adolescents are urgently needed.

Digital tools hold great potential to mitigate identified barriers in screening for substance misuse given the ubiquity of mobile devices. These digital tools can be accessed anywhere and include mobile phones, wearables such as smart watches or Fitbits, mobile or web-based apps, and game software. Serious games—"games designed for a primary purpose other than play" [16]—are frequently used by over 95% of adolescents [17]. Serious games are increasingly being used for delivering health interventions among adolescents [18,19] and, more recently, are also being used for assessment of mental health outcomes [20,21]. During gameplay, in-game metrics reflective of performance in the game are being collected by the game software [18,22]. These metrics may reflect digital biomarkers of health outcomes [22].

Digital biomarkers are "consumer-generated physiological and behavioral measures collected through connected digital tools that explain, influence or predict health-related outcomes" [22,23]. Although most studies investigating the utility of digital biomarkers for health screening and monitoring have focused more on data collected from mobile phones [24,25] and wearables [26,27], games offer another source of data that could potentially measure digital biomarkers [22]. In-game performance metrics [18], such as the amount of time to complete a game task, accuracy of choices in a game task, or style of gameplay (ie, choosing a game task without attention to outlined rules), may reflect cognitive processes such as working memory, processing speed, and inhibitory control [22]. These cognitive processes (working memory and inhibitory control) affect in-game performance and can therefore be measured using in-game performance metrics [28,29]. Deficits in working memory [30,31] and inhibitory control [32] are also associated with substance misuse among adolescents [33] and may explain by up to 33% of the variance in future risk of substance misuse [33]. As such, in-game performance metrics may reflect digital biomarkers of cognitive function, which may be used in predicting adolescents at risk for substance misuse. Digital biomarkers have been used to predict health risk among adults [34,35] and adolescents [25,27]. Prior studies have also investigated the utility of digital biomarkers for a range of psychiatric disorders [24,26,34,36,37]. In these studies, the digital biomarkers captured were primarily from phone or

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wearable sensors and included measures such as movement, location, sleep, heart rate, and social interaction through call or text logs [24-27,34,37]. Although games are increasingly being used for measuring health outcomes such as cognitive function [38], their utility as digital biomarkers is yet to be widely investigated. In addition, all of the studies that have investigated the utility of game-based digital biomarkers have focused on adults [21,39,40]. A study by Dechant et al [39] demonstrated that participants with social anxiety exhibited in-game behavior that was different compared to participants without social anxiety. Specifically, participants with social anxiety were more likely to have their avatar stand at a larger distance to nonplayer characters in the game. In another study by Gielis et al [40], they investigated the utility of in-game performance metrics to identify adults with mild cognitive impairment (MCI). Adults identified as having MCI took more time to think about a move and made more errors in the game compared to adults without MCI.

To the best of our knowledge, we are not aware of any studies that have investigated the utility of game-based digital biomarkers for adolescent substance misuse. Given the easy access to games and the high level of motivation and engagement with games among adolescents [17,41,42], game-based digital biomarkers hold promise for risk identification among adolescents. The use of games as a screening tool could also mitigate barriers in screening since these games can be deployed without supervision and can be completed in private. In addition, prior studies have indicated that adolescents are more forthcoming when completing digital screeners compared to provider interviews and prefer this form of screening [43]. Finally, future apps of game-based screening and monitoring tools could integrate with the electronic health record to make results readily accessible to providers.

Study Objectives

This paper describes the protocol for a proof-of-concept study to develop and test a predictive model for identifying adolescents at risk for substance misuse using in-game performance metrics. The primary objective of this study is to identify game-based digital biomarkers of cognitive risk factors implicated in the development of substance misuse among adolescents using available in-game performance metrics from an existing serious video game intervention, *PlayForward: Elm City Stories*, developed by the play2PREVENT Laboratory in partnership with Schell Games (hereafter referred to as *PlayForward*) [19].

Methods

Overall Study Design

The purpose of this pilot study is to identify game-based digital biomarkers of cognitive risk factors implicated in adolescent substance misuse by developing and testing a machine learning predictive model. This study is led by a team with expertise in machine learning, game design, cognitive function, adolescent substance misuse, and the conduct of pilot trials. This study's team demonstrates a team science approach to solving public health problems with investigators from Yale University, Carnegie Mellon University, and International Business Machines Corporation.

Aim 1

Objective

The objective of aim 1 is to identify game-based digital biomarkers of adolescent substance misuse.

Overall Study Design of Aim 1

Using data collected in a previous study [19], we will determine specific in-game performance metrics—digital biomarkers—that more strongly associate with a high risk for substance misuse. Adolescents will be grouped in 2 groups—high and low risk for substance misuse—based on their baseline responses to questions about substance misuse behaviors (eg, "in the past 30 days, have you used cannabis?" and "How sure are you that you can refuse if a friend offers you alcohol and you do not want it?"). We will have 2 prediction tasks (substance misuse and self-efficacy to refuse drugs). For each task, we will identify an effective prediction model by testing 6 machine learning classification models (eg, logistic regression, random forest, decision trees, support vector machine, gradient boosted decision tree, and neural networks). We will assess the feasibility of using a logistic regression model to compute a digital biomarker score for each adolescent that ranges from 0 to 1, where an adolescent with a higher score has a higher substance misuse risk.

Data Source

PlayForward is an evidence-based video game intervention developed in the play2PREVENT laboratory for HIV prevention and reduction of high-risk behaviors such as substance misuse [18,19,44,45]. *PlayForward* includes 12 Challenge Stacks or levels (the narrative and story-based components of the game) and 5 minigames (People Sense, Refusal Power, Me Power, Priority Sense, and Know Sense). Each of the minigames has 10 levels. The minigames are designed to help the adolescent develop and practice adaptive skills—such as learning to say no to an invitation to use drugs—that can be translated into real life. Players earn stars and points during gameplay, which allow them to advance in the game. *PlayForward* was tested in a randomized controlled trial of 333 adolescents, aged 11-14 years, where 166 adolescents were assigned to play the *PlayForward* video game [19]. At baseline, self-report data on substance misuse and self-efficacy to refuse drugs were collected. During gameplay, data related to their performance in the game (Table 1) were collected by the game software and later stored as log files. The game developers (Schell Games) developed reference files for decoding information stored in the log files.

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Table 1. Potential in-game biomarkers.

Minigame or subsection of minigame	Potential in-game biomarkers	Hypothesized neurocognitive domains (DSM-5[a])
People sense		
Deciding friends: checking out each person's information	• Time spent checking peer's characteristics • Correctly sorting peers into the right social or friendship circles • Time spent completing social or friendship circles	• Working memory, attention, inhibitory control, and processing speed • Working memory and decision-making • Working memory and processing speed
Accepting or rejecting invites	• Correctly accepting or declining invitations based on risk and social circles • Proportion of accepted unsafe invitations	• Working memory, decision-making, and judgement • Decision-making, and judgement
Refusal power		
Think	• Correctly identifying the type of peer pressure	• Decision-making and inhibitory control
Prepare	• Correctly choosing reasons to say no	• Decision-making and inhibitory control
Refuse	• Time spent completing the sentence portion of minigame	• Working memory and processing speed
Priority sense	• Number of times priority dropped to zero	• Working memory
Know sense	• Total credibility score at the end of the minigame	• Working memory, decision-making, and processing speed

[a]DSM-5: Diagnostic and Statistical Manual, 5th Edition.

Data Extraction and Analysis

Three authors (KA, MGJ, and IGdlV) played the *PlayForward* game and reviewed the literature and gameplay guides for *PlayForward* to identify in-game performance metrics that likely used cognitive function and could therefore be potential in-game digital biomarkers of cognitive function (Table 1). We have identified 285 in-game performance metrics (eg, the number of times the player lost the minigame; Multimedia Appendix 1). One of the authors (SK) extracted all identified in-game performance metrics from log files into a CSV file and uploaded this into R statistical software (R Foundation for Statistical Computing) [46]. In-game performance metrics that are found to predict substance misuse risk following analysis will be identified as digital biomarkers for adolescent substance misuse risk.

In total, 2 outcomes (described in the assessments section below)—substance misuse and self-efficacy—to refuse drugs will be used in 2 prediction models. Based on adolescent baseline response to questions on substance misuse and self-efficacy to refuse drugs in a previous study [19], a substance misuse score and self-efficacy to refuse drugs score have been derived. For each score, adolescent participants are categorized into 2 groups (high risk and low risk) based on the score distribution. A preliminary examination of the log files of the 166 participants who played the *PlayForward* game resulted in dropping 6 log files due to file errors. As such, analysis of aim 1 will occur with a final sample of 160 participants.

Outcome Measures

Substance Misuse

In total, 20 questions on cigarette, alcohol, and drug use behaviors from the Youth Risk Behavior survey [47] were administered to 11- to 14-year-old adolescents in the *PlayForward* randomized controlled trial at baseline [19].

Questions included whether participants had ever tried using cigarette, alcohol, or other drugs (marijuana, cocaine; inhalants; over-the-counter drugs; and nonprescribed prescription drugs such as opioids, methamphetamines, and injection drugs); substance use in the previous 30 days; and age at first use (for cigarette and alcohol).

In total, 15 questions on ever use and past 30-day use (for substances other than alcohol or cigarette) had options of yes, no, and decline to answer. In total, 2 questions on age at first use (for cigarette and alcohol) had 9 options: "I have never smoked a whole cigarette/I have never had a drink of alcohol other than a few sips"; 8, 9, 10, 11, 12, 13, and 14 years or older; and decline to answer. Further, 1 question on past 30-day use of cigarettes had 8 options: I did not smoke cigarettes during the past 30 days, less than 1 cigarette/day, 1 cigarette per day, 2-5 cigarettes/day, 6-10 cigarettes/day, 11-20 cigarettes/day, more than 20 cigarettes/day, and decline to answer. Furthermore, 1 question on past 30-day use of alcohol had 8 options: 0 days, 1 day, 2 days, 3-5 days, 6-9 days, 10-19 days, 20 or more days, and decline to answer.

In addition, if participants answered "no" to a particular question about having ever used cigarette or alcohol or drugs, they skipped subsequent questions about past 30-day use and age at

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first use (for cigarettes and alcohol). A participant could skip up to 9 questions.

Coding

For this age group, we considered any type of substance misuse to be high risk. As such, if any adolescent answered "yes" to any of the above questions, we coded them as high risk. Based on this criterion, 107 (66.9%) of 160 adolescents were low risk because they answered "no" to all the substance misuse questions.

Self-Efficacy to Refuse Drugs

In total, 10 questions from the Drug Use Resistance Self-Efficacy [48] scale were used to calculate a score. The Drug Use Resistance Self-Efficacy scale asks questions relating to confidence in one's ability to refuse drugs in a variety of situations. The options to each question include "not sure at all," "not very sure," "pretty sure," and "definitely sure." Each option was recoded as follows: "definitely sure"=0, "pretty sure"=1, "not very sure"=2, and "not sure at all"=3. As such, scores could range from 0 to 30, and higher scores meant lower self-efficacy to refuse drugs. In this sample of 160 adolescents, scores ranged from 0 to 27 with a mean of 2.38 (SD 4.40). Adolescents were grouped into 2 groups (high risk and low risk) based on the score distribution. Adolescents with a total score of 0 were considered low risk (n=82, 51.2%), whereas adolescents with a total score greater than 0 were considered high risk (n=78, 48.8%).

Analyses

Machine learning models [49] will be used to predict each outcome. We will use k-fold cross-validation [50] to evaluate the performance of 6 machine learning classification models (logistic regression, random forest, decision trees, support vector machine, gradient boosted decision trees, and neural networks) to predict each of the outcomes. These 6 models are representative of a range of popular classification models that have been previously used in substance use research [51]. These models vary in their underlying mathematical approaches and often offer reasonable to good performance across a variety of data sets. For example, while regression models are easy to implement, the underlying assumption is that predictors are independent [51]. Decision trees on the other hand do not require elaborate preprocessing but perform relatively worse than other models [51]. Support vector machine performs well using unstructured data but requires extensive tuning [51]. The primary evaluation metric used will be the area under the receiver operating characteristic (AUROC) curve [50]. For each outcome, the model with the AUROC value closest to 1 is the one that has the best ability to discriminate between risk classes, across all classification threshold levels ranging from 0 to 1 [50]. Ideally, an AUROC value of greater than 0.7 can be achieved by the best model. We will also report the sensitivity and specificity for a range of classification thresholds. In the event that AUROC values are similar across candidate models, it may be useful to identify the best model as the model that offers the most appropriate trade-off between sensitivity and specificity, even if the AUROC value of that model may not be the highest [50,52]. Existing screening tools for substance use have sensitivity ranging from 0.71 to 0.94 and specificity ranging from 0.87 to 0.97 [53,54]. As such, to identify an adolescent at risk for substance misuse, we want to achieve comparable sensitivity and specificity above 0.7. Given the risk of negative outcomes such as an overdose that can occur with adolescent substance misuse, a model that produces a higher sensitivity compared to its specificity would be consistent with existing recommendations for substance use screening tools [53]. For the best model identified for each outcome, we use Shapley additive explanations [55,56] to explain the relative importance of the features used to predict the outcome class (ie, high risk vs low risk). We will define features (ie, predictor variables used to inform the classification) from in-game performance metrics. When selecting features to be used for classification, the variance threshold method will be used to remove features with 0 (or low) variance because they are unlikely to be useful for discriminating between classes [49]. We will reduce multicollinearity between features by selectively removing a subset of highly correlated features before performing classification [49]. In addition, we will assess in-game metrics for multicollinearity and drop in-game performance metrics with a variable inflation factor larger than 10 [57].

Aim 2

Objective

The objective of aim 2 is to determine the association between identified digital biomarkers and cognitive function.

Overall Study Design of Aim 2

We will test the hypothesis that digital biomarker scores will negatively correlate with cognitive function scores. To test this hypothesis, we will conduct a pilot study using a new sample of 30 high school adolescents aged 14-15 years. After screening, consent, and baseline assessments, adolescents will play the *PlayForward* game. To validate the model developed in aim 1, the digital biomarkers identified in aim 1 will be extracted following completion of gameplay, and a digital biomarker score will be derived. We will then test the association between the computed digital biomarker score and cognitive function.

Participants and Source

Adolescents from 1 to 3 Connecticut high schools will be recruited. To be eligible for this study, participants must (1) attend a high school in Connecticut, (2) be aged between 14 and 15 years, (3) be willing to sit for 60 minutes per session to play the game, and (4) be able to provide assent and parental or guardian consent. Following screening, eligible adolescents who provide parental consent and assent will complete baseline assessments. Adolescents who complete baseline will be grouped into high-risk and low-risk groups based on their response to assessment of substance misuse, depression, and anxiety. High risk will be determined using their report at baseline of monthly use of any substance (alcohol, tobacco, marijuana, prescription drugs, inhalants, illegal drugs, and synthetic drugs), a score of >2 on the Patient Health Questionnaire-2 [58], and a score of >2 on the Generalized Anxiety Disorder 2-item scale [59]; low risk will be determined by no substance use in the past year, <2 on the Patient Health Questionnaire-2, and <2 on the Generalized Anxiety Disorder 2-item scale. We chose a higher age range (14-15 y) for aim 2

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(in contrast to the age range of 11-14 y in aim 1) to ensure that we can recruit a high-risk sample (adolescents with substance misuse).

Recruitment and Informed Consent

This study will take place in high schools where the laboratory has established partnerships and has conducted trials in the past. Adolescents in participating high schools will be informed about this study. Adolescents who express interest will be provided a flyer with a QR code to complete a contact form if interested in participating in the study. Parents of interested adolescents who complete the contact form will be contacted to obtain parental permission. Following parental permission, adolescents will be screened for eligibility for participation in this study through a Qualtrics (Qualtrics) survey. Eligible adolescents will be asked to provide assent prior to enrollment into this study.

Data Collection and Storage

We will use Qualtrics, a web-based data collection software to obtain parental permission and adolescent assent, screen adolescents for study eligibility, obtain demographic information, and generate a study ID. Study IDs will be automatically generated after the adolescent has screened as eligible. PsyToolkit [60,61], an open source, web-based psychological instrument will be used to administer baseline assessments and conduct the tasks of cognitive function. PsyToolkit has been used in studies measuring working memory and response inhibition in adolescents [62,63] and has been shown to produce comparable results to tasks conducted in a laboratory [64]. Baseline assessment and task performance scores will be retrieved from the PsyToolkit website.

Gameplay data collection will be stored on iPads (Apple Inc) during gameplay. Following study completion, data for each participant will be retrieved from Qualtrics and PsyToolkit into a CSV file and merged by participant ID. Data from iPads will also be retrieved as log files. All retrieved data will be stored on secured data storage locations on the Yale server. Data collection will occur between April 2023 and February 2024.

Assessments and Cognitive Tasks

Table 2 [48,58,65-70] lists measures to be used for screening and administered at baseline. All listed measures have been validated among adolescents.

Table 3 [71-74] lists cognitive tasks to be completed by adolescents at baseline. All listed cognitive tasks have been validated among adolescents.

Table 2. List of screening and baseline assessments for aim 2.

Construct	Name of questionnaire and reference	Number of items	Screening	Baseline
Demographics	Age, sex, and school name	—[a]	✓	—
Depression	Patient Health Questionnaire-2, Richardson et al [58]	2	✓	—
Anxiety	Generalized Anxiety Disorder-7, Bentley et al [65]	2	✓	—
Substance misuse	Screening to Brief Intervention scale, Levy et al [66]	7	—	✓
Substance use risk	Car, Relax, Alone, Forget, Friends, Trouble (CRAFFT) scale, Knight et al [70]	6	✓	—
Emotion regulation	Difficulties in Emotion Regulation Scale–Short Form, Kaufman et al [67]	18	—	✓
Cognitive function	Teenage Executive Function Inventory Scale, Thorell et al [68]	20	—	✓
Impulsivity	Urgency, Premeditation (lack of), Perseverance (lack of), Sensation Seeking, Positive Urgency, Impulsive Behavior scale, Pechorro et al [69]	20	—	✓
Self-efficacy to refuse drugs	Drug Use Resistance Self-Efficacy scale, Carpenter and Howard [48]	24	—	✓

[a]Not applicable.

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Table 3. Baseline cognitive tasks.

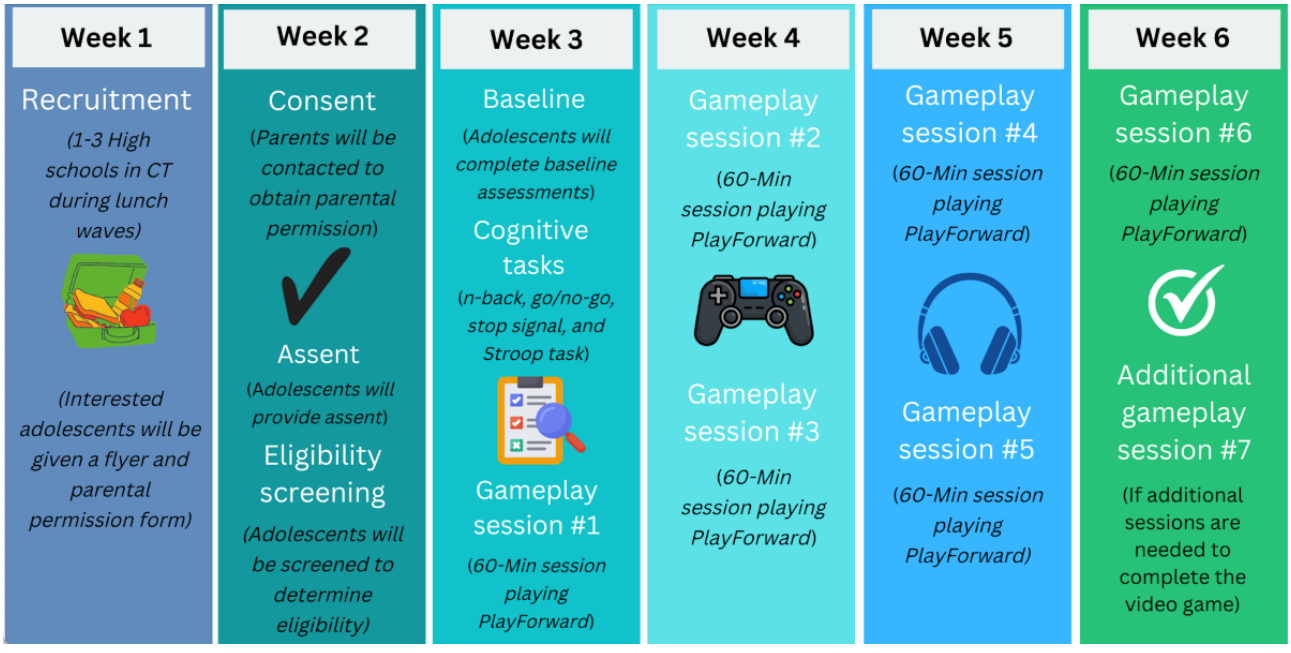
Construct or cognitive task and reference	Description	Metrics recorded
Working memory		
n-back task, Pelegrina et al [71]	The 2-back task will be used. In the 2-back task, a series of letters will be shown to participants in a sequential order. Participants are to click a prespecified key on their device if the letter shown matches the letter shown 2 turns back.	• Percentage of correct matches • Percentage of missed matches • Percentage of false alarms • Mean response time
Inhibitory control		
Go or no-go task, Bezdjian et al [72]	In the go or no-go task, participants are asked to click the spacebar when they see the "go" sign but do nothing when they see the "no-go" sign.	• Response speed • Number of errors • Mean response time
Stop-signal task, Kulendran et al [73]	In the stop signal task, 2 arrows, 1 pointing to the right and the other pointing to the left, will be shown in random order. In the first round, without the stop signal, the participant will click a prespecified key when the left pointing arrow is shown and a different prespecified key when the right pointing arrow is shown. In the second round which includes the stop signal, participants are to stop from clicking the arrows when the red signal appears.	• Mean response time • Error rate
Selective attention, processing speed, and cognitive flexibility		
Stroop task, Stroop [74]	In the Stroop task, names of different colors (blue, green, yellow, and red) will be printed in either of the 4 colors. Participants are to use prespecified keyboard keys to identity the color in which the word is printed in and not the meaning of the word. If the word "yellow" is printed in green, the correct response would be to click on the key that corresponds to green.	• Mean response time for congruent and incongruent stimuli

Study Setting and Study Flow

Figure 1 outlines study procedures. After obtaining verbal parental permission and adolescent assent, participants will be provided with their study ID to log-in to PsyToolkit to complete baseline procedures, which include 7 validated questionnaires and 4 performance-based cognitive tasks as described above.

Following the completion of baseline assessments or tasks, all enrolled participants will be provided a National Institutes of Mental Health–approved information sheet about the teen brain with resources on finding help. In addition, all participating schools have a school-based health center where students can seek help. Enrolled participants will use iPads to complete the entire *PlayForward* game over 6 to 7 sessions lasting 60 minutes each (the average number of 60-min sessions needed to complete the *PlayForward* game is 6). Gameplay sessions will occur 1 to 2 times/wk. The order in which the 4 cognitive tasks will be presented to participants will be random and generated by PsyToolkit. Adolescents will be compensated US $50 following the completion of baseline and US $70 after the completion of this study.

Figure 1. Aim 2 procedures. CT: Connecticut.



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Statistical Analyses

Primary Outcomes

Working memory: the percentage of correct matches, percentage of missed matches, and percentage of false alarms from the 2-back task will be used to compute a working memory score.

Inhibitory control: the response speed and number of errors from the go or no-go task and average response time from the stop-signal task will be used to compute an inhibitory control score.

Secondary Outcomes

Selective attention and processing speed: the average response time from the Stroop task will be used to compute the selective attention score.

Predictors

In-game performance metrics extracted in aim 1 will also be extracted in aim 2. We will test if specific in-game performance metrics are predictive of cognitive function (working memory and inhibitory control) measured by performance-based tasks in a sample of adolescents (n=30).

Planned Analyses

The model trained in aim 1 will be applied to the data collected in aim 2, and digital biomarker scores will be computed such that higher scores equate to higher risk for substance misuse. We will carry out a test of correlation (r) to determine the correlation between the digital biomarker score and (1) working memory score, (2) inhibitory control score, and (3) selective attention score.

Power

With an expected moderate correlation of 0.5 between in-game performance score and validated measures of cognitive function [28], a total of 29 participants will provide 80% power at the .05 2-sided significance level. A larger sample size will yield conventional levels of statistical significance for lower correlation coefficients (n=30 for r=0.5 and n=47 for r=0.4). For this pilot project, we anticipate a correlation of 0.5 based on prior validation studies comparing game-based cognitive assessment to standardized assessment [75-77].

Ethical Considerations

The Yale institutional review board approved this study and its procedures on October 11, 2022 (IRB #2000033084). This study is covered by a Certificate of Confidentiality from the National Institutes of Health. Given the sensitive nature of this study, a Health Insurance Portability and Accountability Act waiver and waiver of written parental consent was obtained.

Results

This study was funded by the National Institute on Drug Abuse through the Center for Technology and Behavioral Health at Dartmouth Pilot Core in May 2022. For aim 1, we completed cleaning of in-game log files in preparation for data extraction. In total, 166 log files were initially available for data extraction. Following data cleaning, 6 files were excluded for reasons such as the data storage files were corrupted, the data structure of log files was different from the rest of the files, and it was impossible to determine the reason for this difference. As such, a final sample of 160 is being used for analysis. The number of extracted in-game performance metrics is 285 (Multimedia Appendix 1). The R software [46] was used in extracting metrics from game log files, and codes are being stored on GitHub. Analyses are currently underway. For aim 2, data collection is ongoing and is projected to end in February 2024. Currently, we have enrolled 12 participants. Data analysis for aim 2 will begin once data collection is completed. The results from both aims will be reported in a subsequent publication, which we expect to publish in the winter of 2024.

Discussion

Adolescent substance misuse is a predominant public health problem. However, most adolescents at risk for substance misuse are not identified early [78]. Early identification of high-risk adolescents can inform the delivery of targeted interventions that prevent the development of negative outcomes. However, identifying adolescents at risk for substance misuse is not routinely done due to a myriad of factors. Although mobile phones and wearable devices have been used to identify and measure digital biomarkers for health outcomes [24-27], the use of games is less widely studied. The use of game-based assessment for mental health purposes has been on the rise and may be used to capture potential biomarkers of health outcomes that can be used for screening and monitoring [22]. The use of games for risk identification offers a promising solution as these can be deployed without the need for provider supervision, can offer privacy to the adolescent completing the game-based screener, and has benefits over self-report data as it would provide a more objective assessment of risk.

In this proof-of-concept study, we will test the utility of in-game performance metrics—digital biomarkers—to identify adolescents at risk for substance misuse. We will also test the hypothesis that adolescents with poor cognitive function will perform worse in the game and be at higher risk for substance misuse. We will be assessing aspects of cognitive function that are implicated in the development of substance misuse and impacted by substance misuse. We build on prior studies that have successfully used game metrics to measure cognitive function [38,40] and extend prior knowledge in the field by applying it to substance misuse. Games offer an engaging way to assess a wide range of factors among adolescents, most of whom play games [17]. This study has several strengths. To the best of our knowledge, we will be the first to test the utility of in-game performance metrics to be used as digital biomarkers of substance misuse. We will also be the first to investigate game-based digital biomarkers in an adolescent population.

This study has several limitations. We are using a game that was not initially designed to measure cognitive function. As such, the game metrics may be poor representations of working memory and inhibitory control. However, other studies have demonstrated that performance metrics collected in a game could be useful in predicting cognitive functions [38,40]. We are using a game that is designed to change behavior related to substance use risk. As such, this game may not be ideal as an

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assessment tool since the tools' predictive ability may wane with repeated use in the setting of positive behavior change. However, other studies have documented that even games designed primarily for assessment can change cognitive processes in ways that can threaten the validity of the game-based tool [79,80]. We chose to use this game-based intervention due to the availability of existing data for this proof-of-concept study, which, if successful, will provide preliminary data for future development of a game-based assessment tool for substance misuse risk. Another limitation is that the initial sample on which the prediction model will be trained has a low prevalence of substance misuse. This imbalance may limit the performance of the prediction models to predict substance misuse. To address this, we will use data augmentation methods such as Synthetic Minority Oversampling Technique [81]. In addition, our eligibility criteria for aim 2 will allow us to recruit a sample of adolescents with higher risk for substance use than in aim 1, which may enhance the performance of the model.

Despite limitations, this study represents a novel and likely highly impactful examination of the use of digital games as not only interventions but also potentially as screening and data collection tools. If found to be successful in predicting substance use, it will inform the future design of game-based assessment tools for substance misuse risk. With their broad level of reach and high engagement, games could seamlessly provide data on adolescent substance misuse risk and help to close the gap in screening and early intervention, leading to improved health outcomes in adolescents.

Acknowledgments

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Data Availability

The data set containing the relevant in-game metrics extracted are included in this published paper in Multimedia Appendix 1 (n=285).

Authors' Contributions

KA contributed to study conceptualization and design, identification of relevant in-game performance metrics, analyses, writing, review, and editing. CHC contributed to study conceptualization, analyses, and paper review and editing. JM contributed to paper writing and drew Figure 1. YTC contributed to study conceptualization and reviewed and edited the paper draft. ZCL contributed to study conceptualization. SK contributed to data extraction, analyses, and paper preparation. MGJ contributed to study conceptualization and identification of relevant in-game performance metrics. IGdlV contributed to study conceptualization and identification of relevant in-game performance metrics. FAU contributed to paper preparation. RAM contributed to data preparation and paper preparation. LEF contributed to study conceptualization and paper editing and review. All authors reviewed and approved the final paper.

Conflicts of Interest

LEF is the Founder and on the Board of Directors of a Yale company, Playbl, that distributes game products. CHC is an employee and shareholder of IBM. The other authors have no conflicts of interest to disclose.

Multimedia Appendix 1
Extracted in-game performance metrics.
[XLSX File (Microsoft Excel File), 32 KB - resprot_v12i1e46990_app1.xlsx]

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Abbreviations

AUROC: area under the receiver operating characteristic
MCI: mild cognitive impairment

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Protocol

Evaluating a Public Health Information Service According to Users' Socioeconomic Position and Health Status: Protocol for a Cross-Sectional Study

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Abstract

Background: The increasing use of information technology in the field of health is supposed to promote users' empowerment but can also reinforce social inequalities. Some health authorities in various countries have developed mechanisms to offer accurate and relevant information to health care system users, often through health websites. However, the evaluation of these sociotechnical tools is inadequate, particularly with respect to differences and inequalities in use by social groups.

Objective: Our study aims to evaluate the access, understanding, appraisal, and use of the French website *Santé.fr* by users according to their socioeconomic position and perceived health status.

Methods: This cross-sectional study involves the entire French population to which *Santé.fr* is offered. Data will be collected through mixed methods, including a web-based questionnaire for quantitative data and interviews and focus groups for qualitative data. Collected data will cover users' access, understanding, appraisal, and use of *Santé.fr*, as well as sociodemographic and socioeconomic characteristics, health status, and digital health literacy. A validation of the dimensions of access, understanding, appraisal, and use of *Santé.fr* will be conducted, followed by principal component analysis and ascendant hierarchical classification based on the 2 main components of principal component analysis to characterize homogeneous users' profiles. Regression models will be used to investigate the relationships between each dimension and socioeconomic position and health status variables. NVivo 11 software (Lumivero) will be used to categorize interviewees' comments into preidentified themes or themes emerging from the discourse and compare them with the comments of various types of interviewees to understand the factors influencing people's access, understanding, appraisal, and use of *Santé.fr*.

Results: Recruitment is scheduled to begin in January 2024 and will conclude when the required number of participants is reached. Data collection is expected to be finalized approximately 7 months after recruitment, with the final data analysis programmed to be completed around December 2024.

Conclusions: This study would be the first in France and in Europe to evaluate a public health information service, in this case the *Santé.fr* website (the official website of the French Ministry of Health), according to users' socioeconomic position and health status. The study could discover issues related to inequalities in access to, and the use of, digital technologies for obtaining health information on the internet. Given that access to health information on the internet is crucial for health decision-making and empowerment, inequalities in access may have subsequent consequences on health inequalities among social categories. Therefore, it is important to ensure that all social categories have access to *Santé.fr*.

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KEYWORDS

internet; health information seeking; literacy; social health inequalities; evaluation; digital health; public health; socioeconomic position; health status; user; empowerment; social inequality; mobile phone

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Introduction

Digital Technologies and Health

The health sector is characterized by an exponential use of digital health technology that serves both for care and for coordination among professionals and facilities and for health care system users (eg, health information, appointments scheduling, and communication with caregivers). Digital health technologies are intended to enhance the autonomy of users, including patients and individuals who use these technologies to support the health of their relatives. This implies that users, whether for themselves or for their loved ones, should have access to health information that enables them to better manage health-related concerns.

Although digital health is promising in terms of technology, its increasing use can lead to unintended negative consequences [1-3]. Indeed, digital health technology can mitigate some geographic location–related barriers, but access to, and the use of, these technologies can be influenced by various factors, including socioeconomic position. Geographic location and socioeconomic position remain important factors influencing the use of digital health technologies.

Individuals' socioeconomic characteristics and their overall health status can affect how different social groups adopt digital health technologies [4]. Consequently, the growing digital divide may worsen existing social health inequalities. The COVID-19 pandemic has accelerated and amplified the digital divide [5]. The lockdown showed that many people were at a loss when faced with the necessity of carrying out web-based procedures. This health, social, and economic crisis has amplified the risks of digital exclusion. Existing digital tools, such as telemedicine and health websites, have been useful in enabling remote medical consultations or keeping up to date with the spread of the virus. By contrast, countless websites are designed according to technical criteria, rather than on the basis of the experience of users in all their diversity [5]. Therefore, it is important to carefully examine the unexpected, undesirable, and negative consequences of digital health to understand its real impact on people and ensure that public health policies address these issues [1-3].

Social Gradient in Access to Digital Health

Studies highlight a social gradient in the access, use, and appraisal of digital health technologies in other countries [6,7], but data are lacking in France, where individuals belonging to the working classes have less access to computers and are less likely to search for health information on the internet [8].

More recently, using data from the *Baromètre Santé* study conducted between 2010 and 2017, French researchers showed that the profile of health information seekers versus nonseekers has remained consistent over time [9]. Seekers were more likely to be younger, more educated female individuals, with higher household incomes and holding executive positions. In 2017, as in 2014, general health websites remained the top source of information (38.6%), followed by social media and commercial websites, whereas institutional websites ranked as the third source (8.1%) [9]. These authors recommended that health authorities should improve citizens' digital health literacy and provide reliable and accessible sources of web-based health information.

In response to this issue, some health authorities in different countries have progressively developed mechanisms to provide relevant, accurate, and useful information to health care system users, often through health information websites [10,11]. However, the use of these new sociotechnical tools has been poorly assessed, particularly in terms of differences and inequalities in use among social groups.

Evaluation of Health Information Websites

The literature includes several studies that have evaluated the quality of health information websites. Some studies have primarily focused on specific information related to particular diseases [12-23] or prevention measures [24-28], whereas other studies have analyzed general health information websites [29-35].

Studies evaluating the quality of health information websites often use automated tools and manual evaluations by professionals. These assessments focus on various criteria, such as readability, the ease of use, reliability, and the quality of information. Tools such as Flesch-Kincaid [14,18,21,22,30,36-41], Flesch Reading Ease [12,18,21,28,30,36-38,41], Simple Measure of Gobbledygook [14,18,21,22,24,30,40], Gunning Fog Index [14,21,22], Coleman-Liau Index [14,21,22], and Automated Readability Index [14,21] measure reading comfort. The Health on the Net Foundation Code of Conduct assesses reliability [17,30,36,42], and the DISCERN tool evaluates health information quality [19,20,28,38,42,43]. The Lida instrument assesses design and content [12,19,37,40], whereas the Clear Communication Index, a tool developed by the Centers for Disease Control and Preventions, evaluates written health materials [32,44]. Some studies also include user perspectives to evaluate website usability and information quality [45,46].

Access to clear and understandable health information is important for informed decision-making, but many health websites are difficult to navigate and read, especially for those with low literacy levels [12,32,37,47]. This can lead to health inequalities [39] and delay the adoption of appropriate health behaviors. Although government websites are usually easier to read [14], improvements are still necessary. Website design and content can also present barriers to use [48]. Few studies focus on the evaluation of a single website, and evaluations often overlook users' sociodemographic characteristics, health status, and health literacy levels. Therefore, it is important to conduct evaluations that take into account these factors to identify any population groups facing barriers to accessing and understanding health information on these websites.

To make health information websites accessible and user-friendly, it is important to involve users in the evaluation process [32]. Understanding users' needs and preferences can ensure that the information provided is clear, relevant, and actionable [39]. It is crucial to assess issues related to the accessibility of health information to ensure that all individuals can take advantage of the wealth of health information available

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on the internet, given the growing focus on patient empowerment in health [48].

Santé.fr, the Website of the French Public Health Information Service

In France, the *Santé.fr* website is a public service website that provides general health information selected for its quality and usefulness. This website is under the Ministry of Health's responsibility, and its mission is to provide free information on health care as well as medical and social services to the public. The information is adapted and accessible to people with disabilities and aims to encourage citizen participation in health choices, improve patient management, and simplify the adoption of preventive behaviors.

> *Santé.fr serves as a reference health website and offers access to resource directories, prevention and health education information services, and more. It is accessible anytime and anywhere, making it a reliable and convenient source of health information.*

As *Santé.fr* is an information and support tool for users, it is crucial to track and evaluate its use and identify any disparities among different population groups. Therefore, it is important to explore the experiences and evaluations of *Santé.fr* users to determine to what extent the information provided meets their needs and expectations. The objective is to ensure that *Santé.fr* proves to be a genuine advantage for users and does not exacerbate the existing social inequalities by promoting the use of a tool that is inaccessible or unsuitable for a portion of the population because disparities in the access, understanding, appraisal, and use of digital health technology can worsen social health inequalities, depending on individuals' social position.

Objectives of the Study

The main objective of this study was to evaluate the access, understanding, appraisal, and use of *Santé.fr* by users according to their socioeconomic position and health status. Our specific objectives were to (1) determine users' profiles in terms of the access behavior, understanding, appraisal, and use of *Santé.fr* based on their socioeconomic position and health status; (2) examine the association between users' socioeconomic position and health status and their access, understanding, appraisal, and use of *Santé.fr*; and (3) determine the reasons why users of *Santé.fr* use this service.

Methods

Research Design

The *Évaluation du service public d'information en santé* (the *Santé.fr* website) *selon le statut socio-économique de ses utilisateurs* (evaluation of the public health information service [the *Santé.fr* website] according to the socioeconomic status of users) study is a cross-sectional observational study of the French population using *Santé.fr*. It will use mixed methods, that is, it will combine quantitative and qualitative research methods [49]. The study period will last 1 year so that there will be enough time to collect the necessary quantitative and qualitative data.

Study Population

The study target population is the entire population to which *Santé.fr* is offered, that is, the general French population. The source population is made up of all health care system users, whether or not they use *Santé.fr*; the respondents to this study; and the study sample. All inhabitants of metropolitan France and the *Départements et régions d'outre-mer et collectivités d'outre-mer* (overseas departments and regions and overseas communities) will be concerned by this study. The quantitative and qualitative study inclusion criterion is as follows: any adult (aged ≥18 y) living in metropolitan France or *Départements et régions d'outre-mer et collectivités d'outre-mer*.

Recruitment

The quantitative study will include both users and nonusers of *Santé.fr* who visit the website and voluntarily complete the questionnaire. Before participation, all participants will receive comprehensive and adequate information through an information note. *Santé.fr* users are individuals who have previously consulted *Santé.fr* or are visiting it for the first time when completing the questionnaire. Nonusers of *Santé.fr* are individuals who, although aware of this public health information service, have never accessed it before coming across the questionnaire or were not previously familiar with it.

The questionnaire will be self-administered by *Santé.fr* users, using a computer-assisted web interviewing method (ie, completed on the web). An article on *Santé.fr* will be developed to present the research team and the study to participants and to share the external link to the questionnaire. A poster will be designed to encourage users to participate in the study. The article and the questionnaire will be displayed on *Santé.fr* at several navigation levels (eg, thumbnail on the home page, contextual message block, end of an article, and thematic folder) to increase access to the questionnaire. Users connecting to *Santé.fr* will be able to click directly on the poster and reach either the article or the questionnaire. Users will decide whether to participate in the study. A communication plan will be elaborated by the research team to disseminate the study as much as possible.

The qualitative study will include individuals, who may or may not be users of *Santé.fr*, with a variety of profiles, including different sexes, age groups, geographic origins, and socioeconomic positions. Specifically, socioeconomic position will be assessed based on criteria such as education level, occupational category, and income level.

Participants will be recruited through the following channels:

- Relatives or persons in the professional and personal environment of the research team will be requested to identify interested individuals.
- Snowball method: the research team members will ask some of their contacts to identify people they know from different geographic locations and ask them to agree to be contacted by the research team.
- Associations such as Emmaüs Connect, Point Information Mediation Multi Services, and La Mednum will be contacted to identify individuals with digital difficulties. Emmaüs Connect helps individuals experiencing social and

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digital insecurity to access essential web-based tools. La Mednum helps to develop mediation and digital inclusion programs all over France, as does Point Information Mediation Multi Services.
- Assistance will be requested from the France Assos Santé network, an interassociative organization that represents health system patients and users and defends their interests, to identify patients or users of the health care system.
- Additional resources may be used.

For the quantitative study, a sample size calculation was performed. As we had no information on the proportion of *Santé.fr* users, we calculated the number of participants necessary according to the estimation formula in the case of an expected prevalence of 50% with a risk of error α of 5% and a precision of 5%. A sample of 385 people was deemed necessary. For the qualitative study, we estimate conducting 30 interviews, taking into account feasibility and the need for a wide range of respondent profiles.

Data Collection

Quantitative Study

Overview

A questionnaire was developed according to the literature to collect the necessary quantitative and qualitative data to address the objectives. The 5-section questionnaire, described in detail in the following subsections, is available in Multimedia Appendix 1. A feasibility test of the questionnaire will be conducted to ensure that the questions are clear, simple, and understandable.

Section 1: Access or Use

This section includes questions to determine whether users or nonusers have the necessary equipment (computer, tablet, smartphone, and internet connection) to access the internet and the general skills needed to use the internet effectively on these devices. The questions also explore their interest in using the internet to find health information and seek to understand how often they use *Santé.fr* for health information. To develop these questions, we used questions from the French *Baromètre Santé* periodic surveys and the Website Quality Evaluation Tool [50]. The *Baromètre Santé* surveys have been conducted since 1992 to better understand French people's knowledge, behavior, beliefs, and practices concerning health [51].

Section 2: Understanding

This section consists of questions related to users' ability to find and understand health information on *Santé.fr* and their ability to evaluate, in general, health information presented on the internet. These indicators will help determine whether *Santé.fr* is accessible and user friendly. Some items from the eHealth Literacy Scale (eHEALS), discussed in the *eHealth Literacy* subsection, were used [52]. We also used questions from the *Baromètre Santé* periodic surveys [51], the DISCERN tool [53], a systematic literature review by Sun et al [54] on relevant criteria and indicators for evaluating the quality of health information on the internet, and a critical analysis of evaluation criteria for health websites [55].

Section 3: Application

This section concerns the appraisal and adoption of *Santé.fr* by users, either for themselves or for relatives. These questions assess whether this website helps users to make informed decisions about their own health. The questions on the intention of users to reuse *Santé.fr* and to recommend it to relatives will allow us to evaluate their satisfaction and to assess their degree of confidence in the provided information. To develop these questions, we were inspired by the technology acceptance model [56] as well as items from the eHealth Impact Questionnaire [57] and items used in the study by Kang and An [33], which evaluated health-related sites for older adults and assessed whether the sites take into account factors that affect older adults' intention to use them for health information seeking.

Section 4: Sociodemographic and Economic Characteristics

This section collects the respondents' sociodemographic and economic characteristics. The questions cover their indirect geographic origin or native area (and that of their parents), their job status (employed or not) and socioprofessional category or social position, their economic and financial situation (income, origin of income, social benefits, and self-declared financial situation), and their geographic place of residence (postal code and the name of the town of residence). These variables will make it possible to estimate the respondents' socioeconomic situation. These questions were inspired by data on socioeconomic situations collected from the French Constances study [58].

Section 5: Health Status

This section includes questions to evaluate the respondents' perceived health status, addressing the general, physical, and psychological dimensions of health as well as the presence of an illness or chronic health problem. To develop these questions, we were inspired by the questions from the *Enfants et familles sans logement* (Children and families experiencing homelessness) survey [59] and the periodic *Baromètre Santé* surveys [51].

eHealth Literacy

To calculate a digital health literacy score for each respondent and to be able to compare the total scores between *Santé.fr* users and nonusers, the eHEALS items are used [52]: in their original form for nonusers of *Santé.fr* and adapted for users of *Santé.fr* to match the digital tool being evaluated. The corresponding items are presented in Multimedia Appendix 2 and are distributed in the questionnaire's different sections.

Qualitative Study

To explore users' and nonusers' perceptions regarding their access, understanding, appraisal, and use of *Santé.fr*, as well as their general use of the internet for searching and using health information, semistructured individual interviews will be conducted. The interview guide will be developed based on the questionnaire used in the quantitative study. Regarding the interview's organization, an initial telephone contact with the participant will allow us to briefly explain the study to them, obtain their consent to participate in the interview, and set up an appointment for the interview. The participant's main characteristics will also be collected during this first contact by

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the interviewer to ensure a wide-range sample. If a participant agrees to participate in the study and has never consulted *Santé.fr*, the interviewer will ask them to navigate through the website before the interview and browse the health topics of interest. On the day of the interview, if the participant has been able to access *Santé.fr*, the interviewer will ask them to describe their overall experience and ask the interview guide questions. If a participant has not been able to access the website, the interviewer will ask them to explain why, which will be considered a result per se.

These interviews will take place via videoconference, telephone, or face-to-face, depending on the participants' preference, at a time and date of their choice.

Focus groups will also be conducted by the research team. The objective is to enable the participants to provide their reactions to the *Santé.fr* website. Participants will have to navigate the website and share their experience: what they think of *Santé.fr* in general, the difficulties or problems faced, the elements to be improved according to them, their ability to carry out a search and obtain answers to their questions, whether the navigation is easy, and so on. Participants may or may not already know each other and have varied sociodemographic profiles.

Statistical Analysis

Quantitative Analysis

Descriptive Analyses

The sociodemographic and socioeconomic characteristics, health status, and digital health literacy score measured by the eHEALS will be described. The variables related to the access, understanding, appraisal, and use of *Santé.fr* will also be presented. Qualitative variables will be analyzed using frequencies and proportions, whereas the digital health literacy scores will be described using mean and SD as well as median and IQR.

A validation of the dimensions of access, understanding, appraisal, and use of *Santé.fr* will be conducted to ensure their reliability and validity. This validation process will involve assessing the internal consistency of items as well as evaluating convergent and discriminant validity. To assess internal consistency, the Cronbach α coefficient will be calculated. In addition, correlation analysis will be conducted to examine the relationships among variables and to evaluate convergent and discriminant validity.

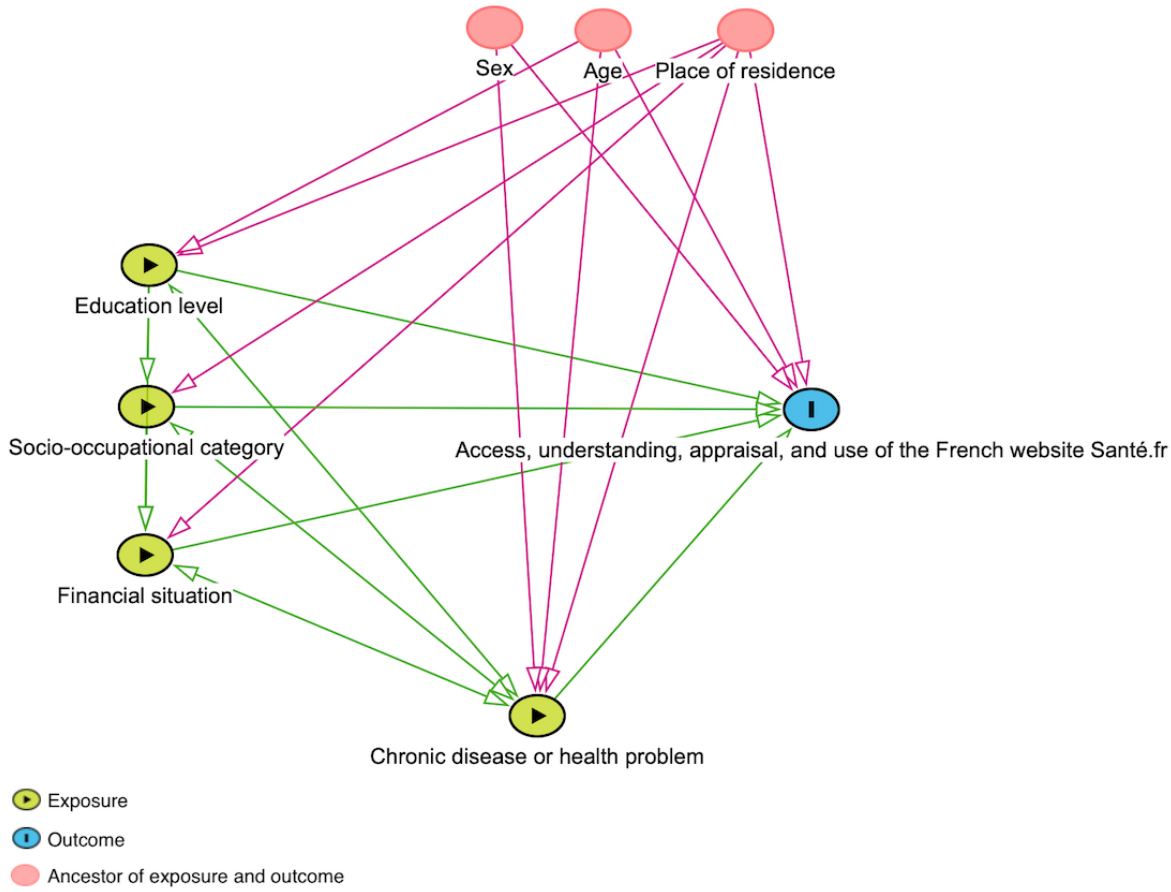
Principal component analysis will be performed for each dimension, using the variables specific to that dimension as active variables. Subsequently, ascendant hierarchical classification will be conducted based on the 2 components of principal component analysis to characterize homogeneous users' profiles based on their access, understanding, appraisal, and use of *Santé.fr*. The sociodemographic, socioeconomic, and health status variables will be used as illustrative variables to characterize users' profiles.

Analytical Analyses

On the basis of the results of the dimension validation in the descriptive part of the statistical analyses, different approaches will be used for the analytical analyses. If the dimension (ie, access, understanding, appraisal, and use of *Santé.fr*) is validated, a quantitative score will be used as a continuous variable. However, if the dimension is not validated, a specific questionnaire variable related to that dimension will be used instead. Depending on the nature of the outcome variable, different regression models will be developed. If the outcome variable is continuous, a linear regression model will be conducted. If the outcome variable is binary, a logistic regression model will be performed. In the case of a variable with >2 categories, a multinomial logistic regression model will be applied. Regardless of the model used, the explanatory variables will include education level, socio-occupational category, and financial situation. Confounding variables such as sex, age, and place of residence will also be included in the analyses to account for potential biases. This approach follows an etiological explanatory perspective, for which a directed acyclic graph will be used (Figure 1).

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Figure 1. Directed acyclic graph applied to the relationships between socioeconomic position and health status and the access, understanding, appraisal, and use of Santé.fr.



All quantitative analyses will be conducted using RStudio (version 2023.03.1+446; Posit Software, PBC).

Qualitative Analysis

The first step of the qualitative analysis will consist of transcribing all interviews and focus groups. The analysis grid will be constructed from the interview guide and the focus groups and completed inductively based on new items that may appear during the transcripts analysis. Using NVivo 11 software (Lumivero), the interviewees' comments will be classified within each preidentified theme or themes emerging from the discourse and compared among types of interviewees to understand the reasons why people access, understand, evaluate, and use (or do not) *Santé.fr*. A profile analysis of people with similar responses will be conducted to see whether any profile types emerge.

Mixed Analysis

Quantitative and qualitative data will be collected simultaneously using the convergent parallel design approach. The analyses will then be combined to meet the overall objectives of the study.

Ethical Considerations

The data collection and processing implemented in this research conforms to the *Commission nationale de l'informatique et des libertés* (National Commission of Informatics and Liberties) reference methodology MR-004 (research not involving human persons, studies, or evaluations in the health field).

An information note at the beginning of the questionnaire informs participants about the study, its objectives, its progress, the processing of personal data, and their rights. By completing the questionnaire, the participants implicitly agree to share their data for scientific purposes. For the interviews, the participants will give their oral consent.

Personal data will be processed to analyze the results of the research in relation to its objectives. The data collected will be recorded in a digital file that complies with several data security and confidentiality conditions. The data will be deidentified (ie, anonymized) using the following techniques: we have ensured that the nature of the response modalities is broad enough to prevent the recognition of the person who completed the questionnaire (such as age group and income group); we do not collect nominative data; and we assign a numerical identifier specific to the study to pinpoint the respondent that is known only to the research team.

No compensation will be offered to users for participating in the study.

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Results

Recruitment is scheduled to begin in January 2024 and will conclude when the required number of participants is reached. Data collection is expected to be finalized approximately 7 months after recruitment, with the final data analysis programmed to be completed around December 2024.

Discussion

Difficulties and Limitations of the Study

The first difficulty concerning the quantitative part of the study could be linked to the recruitment of participants, given that participation in the study will be on a voluntary basis. Despite our efforts to aim at a wide dissemination at several navigation levels on *Santé.fr* (eg, thumbnail on the home page, contextual message block, end of an article, and thematic folder) to multiply access to the questionnaire, the response rate could prove to be too low to allow statistical analyses to be conducted. For the time being, owing to the different waves of the COVID-19 pandemic, the current pop-in dedicated to screening and vaccination against COVID-19 and appearing on any page after a few minutes of navigation could not be removed and replaced by a message presenting the study. It would therefore be advisable to provide maximum visibility for the study on *Santé.fr*; for example, a pop-in would make it possible to make the study visible to each user and thus increase the chances of response. Moreover, as Santé.fr users prefer to access the website on their mobile phones, if the study does not appear on the home page on mobile phones, the number of respondents could be insufficient can be used.

By contrast, people who feel uncomfortable using the internet could also have difficulties accessing the questionnaire. A lack of motivation or time to complete the questionnaire as well as a low interest in digital health topics and research could decrease the response rate to the study. Compensation for participating in the study could give users a reason to complete the questionnaire.

For the qualitative study too, the lack of sufficiently diverse respondents could be a challenge. In addition, the risk of social desirability bias in the interviewees' responses to the interviewer could be an issue.

Strength of the Study

This study would be the first of its kind in France and, more widely, in Europe to focus on the evaluation of a digital health information website according to users' socioeconomic position.

The study that we intend to set up is thus essential because it will make it possible to fill a gap in the existing literature. More precisely, it will allow us to discover the issues related to inequalities in access to, and the use of, digital technologies to obtain health information. This study will give an insight into the digital divide that accounts for the poor access to these digital health information services for people who do not have access to the necessary material conditions such as digital devices and an internet connection. This study will discover the social inequalities that affect the access, understanding, appraisal, and use of health information found on the internet, particularly among people with lower levels of education, income, and digital health literacy.

As access to health information on the internet is crucial for health decision-making and for people's empowerment, if inequalities in access are discovered by this study, then they may also be related to inequalities in the health status of social groups. It would therefore be important to ensure that all social groups have equal access to *Santé.fr*, a quality digital health information service offering reliable health information.

With regard to our research subject, using mixed methods is a relevant choice because it will allow us to combine quantitative methods (questionnaire) and qualitative methods (interviews and focus groups). The quantitative methods will make it possible to obtain an overview of access to *Santé.fr* and to measure specific indicators (access, understanding, appraisal, and use) that constitute the digital health literacy determinants. The combination of these 2 methods will give a complete and more accurate view of this evaluation through quantitative results and user experiences that may be influenced by users' socioeconomic position. Reasons for the use or lack of use can be obtained through the qualitative component of the study.

Directions for Future Research

This study could serve as a feasibility study for collecting data on the French population's habits regarding the use of the internet to access health information, which could be incorporated into general national health surveys for regular monitoring purposes as well as *Santé.fr* follow-up surveys.

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Authors' Contributions

ME, with IM's contribution and under the direction of VR, designed the protocol and the study design. ME, IM and VR elaborated the main conceptual ideas. ME, VR and IM developed the questionnaire and the interview guides. SD provided critical expertise on the statistical analysis plan. ME, VR and IM wrote the manuscript. All authors contributed to finalizing the manuscript and read and approved the final version. VR and IM supervised all the steps involved in elaborating the protocol and the manuscript. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Study questionnaire.
[DOCX File , 40 KB - resprot_v12i1e51123_app1.docx]

Multimedia Appendix 2
Original eHealth Literacy Scale and items adapted to this study.
[DOCX File , 23 KB - resprot_v12i1e51123_app2.docx]

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Abbreviations

eHEALS: eHealth Literacy Scale

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Original Paper

Evaluating the Added Value of Digital Contact Tracing Support Tools for Citizens: Framework Development

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Abstract

Background: The COVID-19 pandemic revealed that with high infection rates, health services conducting contact tracing (CT) could become overburdened, leading to limited or incomplete CT. Digital CT support (DCTS) tools are designed to mimic traditional CT, by transferring a part of or all the tasks of CT into the hands of citizens. Besides saving time for health services, these tools may help to increase the number of contacts retrieved during the contact identification process, quantity and quality of contact details, and speed of the contact notification process. The added value of DCTS tools for CT is currently unknown.

Objective: To help determine whether DCTS tools could improve the effectiveness of CT, this study aims to develop a framework for the comprehensive assessment of these tools.

Methods: A framework containing evaluation topics, research questions, accompanying study designs, and methods was developed based on consultations with CT experts from municipal public health services and national public health authorities, complemented with scientific literature.

Results: These efforts resulted in a framework aiming to assist with the assessment of the following aspects of CT: speed; comprehensiveness; effectiveness with regard to contact notification; positive case detection; potential workload reduction of public health professionals; demographics related to adoption and reach; and user experiences of public health professionals, index cases, and contacts.

Conclusions: This framework provides guidance for researchers and policy makers in designing their own evaluation studies, the findings of which can help determine how and the extent to which DCTS tools should be implemented as a CT strategy for future infectious disease outbreaks.

(JMIR Res Protoc 2023;12:e44728) doi:10.2196/44728

KEYWORDS

contact tracing; digital tools; citizen involvement; COVID-19; infectious disease outbreak; framework; mobile phone

Introduction

Background

One of the most essential strategies to help mitigate the spread of infectious diseases is contact tracing (CT) [1], which was the driving strategy leading to the global eradication of smallpox and is still used to control the transmission of infectious diseases, such as the regularly resurging Ebola [2]. Studies conducted during the COVID-19 pandemic have also shown CT to be effective in preventing a substantial number of new infections [3,4]. CT traditionally consists of 3 phases: identification (first

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phase) and notification (second phase) of the contacts of individuals with COVID-19 and monitoring the health (third phase) of individuals with COVID-19 and their contacts. These tasks are generally conducted by public health services (PHSs) that are responsible for CT in many countries.

In 2020, the new SARS-CoV-2 coronavirus led to an unexpected global disruption at various levels, owing to the substantial morbidity and mortality it caused and the ease at which it spread. Although the Netherlands and many other Western countries were previously designated as being within the most prepared tier for handling epidemics and pandemics [5], the COVID-19 pandemic exposed weaknesses in the ability to contain the spread of the virus even within this tier. As has been reported in many countries worldwide, the high infection rates have caused CT for COVID-19 to be labor-intensive and time-consuming, and health services have been overwhelmed [6,7]. The potential of digital tools to rapidly access and transmit information to large numbers of individuals is being explored and used as ways to help contain the spread of the coronavirus and reduce the burden on overwhelmed health services [8,9].

Proximity-Based Apps

Given the increased use of smartphones, many mobile apps have already been developed for detecting those who have been in close proximity to and possibly exposed to a person with an infection [9]. The first such well-known app for COVID-19 was developed in Singapore (TraceTogether) [10]. This app and many other apps that were subsequently developed, including the Dutch CoronaMelder [11,12], use Bluetooth, Wi-Fi, or GPS to detect individuals who have been in close proximity to those who have contracted COVID-19 within a critical time frame of infectiousness [13,14]. Positive effects of proximity-based apps in containing the virus have mainly been shown by modeling studies, and a few real-life studies have found some promising preliminary results when comparing Bluetooth-based and other proximity-based apps with traditional CT [15-17]. Using such apps may identify at least twice as many infected cases as traditional CT does and could potentially help to avert hundreds of thousands of positive cases owing to the feature of being able to notify individuals who are presymptomatic [18]. However, proximity-based apps require a high adoption rate by the general population (irrespective of whether they are infected with SARS-CoV-2) to be effective. Besides privacy concerns [19-21] and interoperability issues between countries [22,23], however, there are practical implications and expectations from citizens to be effective, such as needing to carry a smartphone wherever one goes, continually keeping Bluetooth on, and correctly following the instructions and abiding by the measures upon receiving a notification of having been in contact with a positive case. As the data from these proximity-based apps are generally not shared with health services conducting CT, these apps do not directly alleviate the burden of traditional CT experienced by public health professionals (PHPs). PHPs will still not have insight into the contacts that have been identified and who need to be informed and will therefore still need to conduct CT as usual when they have contact with positive cases (henceforth, referred to as index cases).

Digital CT Support Tools

To complement traditional CT and proximity-based apps in helping to contain the virus, there are other types of tools that have been developed and are continuing to be developed. These tools are referred to as digital CT support (DCTS) tools and enable citizens to assume at least some of the tasks required for traditional CT. As has been reported with proximity-based apps, people may also have some privacy concerns, regarding the privacy of their own and their contacts' personal data in the tool and what happens when these data are transmitted to the PHP conducting CT. When compared with traditional CT and proximity-based apps, DCTS tools offer unique advantages. They can alleviate the work of PHPs, by potentially shortening the time needed in traditional CT to collect contact details from them over the phone and to notify their contacts. Other possible benefits are more time for index cases to be able to recall more contacts they may have exposed and higher chance of recording more accurate contact details, compared with when sharing this information during a phone call with the PHP. Depending on the national CT measures being implemented, index cases may also notify and convey the correct instructions to their contacts more rapidly than if this responsibility is left to PHPs. A functionality in the tool that enables the index case to indicate to the PHP which contacts have already been notified would save PHPs time in having to reach the contacts themselves. DCTS tools that enable index cases and contacts to assess and monitor their own symptoms are already well known; in some cases, they can send these data to PHPs for further support, thereby contributing to the monitoring phase (third phase) of CT [24-26]. Much less attention has been given to DCTS tools that mimic the first 2 phases of CT: identification and notification of contacts.

During the COVID-19 pandemic DCTS tools were developed that had proximity-based and contact diary features where index cases themselves could actively collect their contacts and their contacts' personal details [27]. Once this information had been gathered by the index case, they could choose to share it with a PHP. An app developed in the Netherlands (GGD Contact app), for example, had an interactive functionality enabling index cases to directly receive data from and share data with the municipal PHSs that are tasked with CT [28]. Data collected by the index case (eg, the test date and information about contacts) could be transmitted directly into the case management system used by the PHPs conducting CT, theoretically saving data entry time for the PHP. Another functionality in this app enabled the index case to retrieve contact details, such as telephone numbers, directly from the standard contact list already stored on their mobile phone.

When using such a DCTS tool during the first phase of CT, the index case recalls the contacts whom they may have exposed to the virus and enters information into the tool (eg, website or app) about the type of contact (eg, whether the contact is a partner or household member); nature of the meeting with the contact (eg, whether they were closer than 1.5 meters for >15 min); and finally, their contact details, such as telephone numbers and email addresses. The index case can then share this information with the PHPs conducting CT. During the second phase of CT, the index case or the PHP informs the

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contacts about their possible risk of infection and provides them with instructions about the steps to take to mitigate the further spread of infection (eg, to quarantine). Instructions may be provided in these DCTS tools customized to the type of contacts identified by the index case; these instructions can subsequently be shared by the index case with the relevant contacts. The index case can also use this DCTS tool to indicate which contacts they have notified and have provided with instructions. This information can also be shared with the PHP.

Besides the traditional CT approach (approach A in Figure 1), we distinguish 3 main approaches representing differing levels of citizen involvement that could potentially be taken with respect to DCTS tools for this process (approaches B to D in Figure 1). In traditional CT (approach A), the PHP plays the greatest role and the index case plays the smallest role. Going from approach B to approach C and finally approach D, the efforts of the index case in the CT process increase.

In approach B, using DCTS tools (PHP-initiated CT), the PHP calls the index case to start the CT process. Together, they complete a questionnaire to gather relevant demographic and medical details about the index case. The index case is then asked if they are willing to enter their relevant contact details into the DCTS tool, such as a designated website or app. The PHP and index case arrange a new appointment shortly afterward to review the contacts that have been provided by the index case, to determine whether additional information is needed and to agree on who will inform the contacts and provide them with instructions about further steps to take.

In approach C, using DCTS tools (index case–initiated CT) may be more efficient for CT (eg, alleviating the burden experienced by PHPs and increasing the speed of CT), as the index case is made aware of the DCTS tool before the call with the PHP during which the CT process is initiated. The designated medium to communicate test results to citizens (such as a website or email) can direct index cases to enter their contact details into the DCTS tool. This information is then ready to be discussed and shared digitally before the call with the PHP. This approach could lead to increased accuracy in contact details (such as telephone numbers), as these will not be conveyed verbally during the phone call. During the call, the provided information can be checked; additional details can be shared, if necessary; and further steps can be discussed.

In approach D, using DCTS tools (index case–conducted CT), the entire CT process is transferred into the hands of citizens or at least to a selection of citizens with low risk. In this situation, there is no contact at all between the PHP and the index case. The index case independently uses the DCTS tool to help recall and notify relevant contacts about their possible exposure risk and provides contacts with appropriate instructions already programmed in the tool. This could potentially free up time for PHPs to focus on index cases with greater health risks or with limited access to DCTS tools. This approach may be beneficial if the virus variant is very infectious (leading to high numbers of index cases) but relatively less severe with regard to its effects on morbidity and mortality.

Additional features of DCTS tools could facilitate the recording of events that the index case had attended or venues they had visited during the period that they were infectious, where they may have exposed groups of people. This recording of events could occur by various means, each varying in terms of privacy and ease of use, including digital tracking of attendees, scanning of a QR code by attendees, or self-reporting by index cases. Information regarding the event, such as its name, location, and address; phone numbers; time it occurred; and how many people were possibly exposed could be recorded. These details could be transmitted to the PHP conducting CT or directly to a representative of the event, so that they could alert the other attendees about their exposure risk.

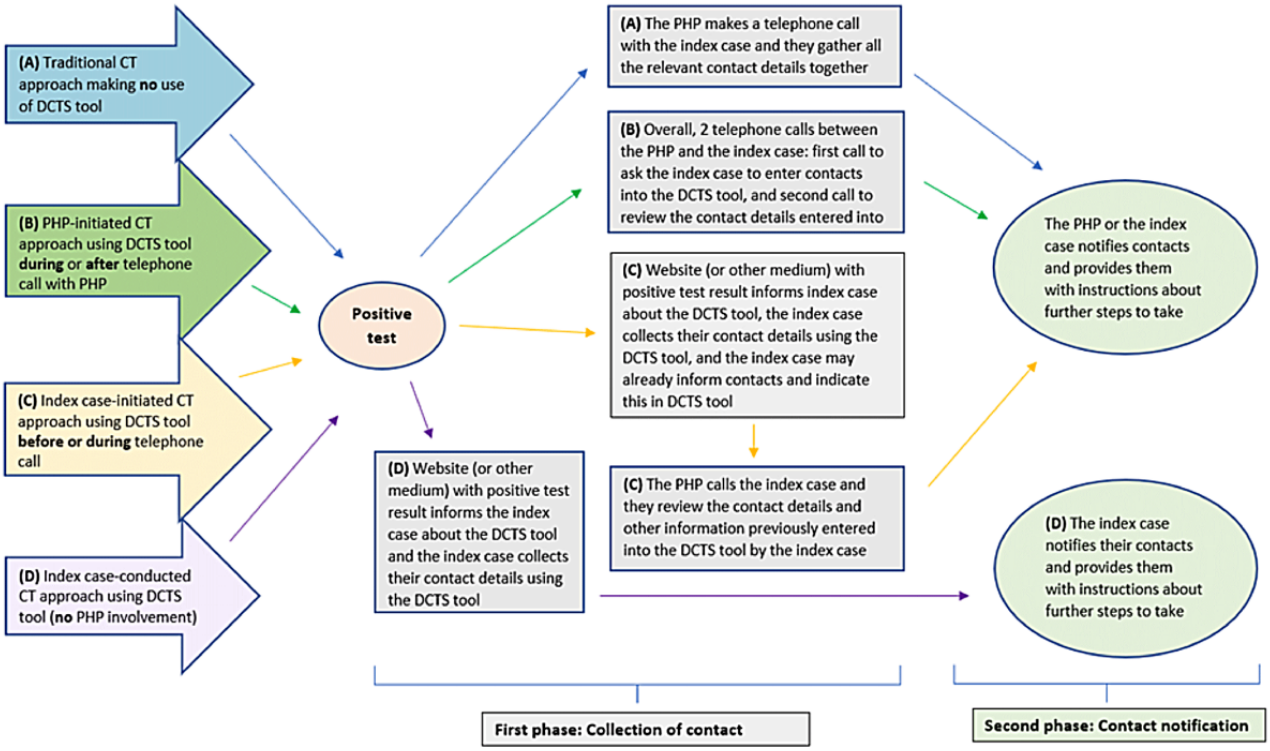
Irrespective of the extent of PHP involvement, enabling the index cases to notify their contacts and provide them with instructions themselves may lead to an earlier awareness and more rapid action by contacts, compared with traditional CT, and ultimately mitigate the further spread of the virus. This type of technology requires more effort by citizens; however, its success will depend heavily on the ability and willingness of citizens to actively contribute in this manner, by mimicking the traditional CT process in a digital way.

It is currently unknown whether DCTS tools that encourage citizens to support the CT process (approaches B to D) could contribute to a more effective and efficient CT process; reduce the workload of PHPs; and ultimately, help to mitigate the spread of infectious diseases, such as COVID-19. It is therefore important that evaluations are performed to determine empirically the added value for public health with respect to the current COVID-19 pandemic and potential future infectious disease outbreaks.

Frameworks about how to evaluate proximity-based apps and the effectiveness of CT in general have been published already [29-31], but none, to the best of our knowledge, have been published about how to assess the effectiveness of DCTS tools. This paper presents a framework for how DCTS tools can be assessed when compared with traditional CT, with regard to various important factors that are necessary to curb the transmission of infectious diseases, such as increasing the speed and comprehensiveness of the CT process and relieving the burden on PHPs. This framework may be useful for researchers and policy makers to help determine the extent to which DCTS tools would have a positive impact on CT during future infectious disease outbreaks and to make evidence-based decisions regarding the implementation of these tools (eg, in conjunction with traditional CT and proximity-based apps).

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Figure 1. Flowchart showing 4 contact tracing (CT) approaches—(A) the traditional CT approach, (B) public health professional (PHP)-initiated CT approach making use of a digital CT support (DCTS)-tool, (C) index case-initiated CT approach making use of a DCTS tool, and (D) index case-conducted CT approach making use of a DCTS tool.



Methods

Overview

The evaluation framework was developed by researchers from the National Institute for Public Health and the Environment (*Rijksinstituut voor Volksgezondheid en Milieu*; RIVM) in the Netherlands, in collaboration with municipal PHSs conducting CT. The idea for a framework for DCTS tools was partly based on an evaluation model that was developed for measuring the effectiveness of the Dutch proximity-based app [32]. A team of scientific experts from various disciplines including infectious disease control, epidemiology, health behavior, data privacy, and technical innovations was established to provide advice to the research team conducting the study. Evaluation topics and accompanying research questions were formulated to assess the potential effects of using the Dutch DCTS tool. These topics and their rationale were based on the experiences of PHPs and the CT indicators already developed by infectious disease experts at RIVM [33]. A previous concept of the framework was presented several times to various expert groups, including the Ministry of Health, Welfare, and Sport and medical nurses and physicians specialized in infectious diseases, who were working in the municipal PHSs. They provided feedback and suggestions leading to adjustments in the framework. The framework was further refined and developed into this research paper by reviewing the relevant international and national scientific literature on CT.

In this paper, the evaluation topics and research questions have been embedded within an outcome evaluation and a process evaluation, which are considered to be beneficial for evaluating the effectiveness, efficiency, validity, and usability of an intervention [34]. The research questions formulated under the *Outcome Evaluation* section are designed to measure the effects of the DCTS tools on CT, including the number of contacts identified and informed, speed at which this process occurred, accuracy and comprehensiveness of the information provided, number of positive cases detected among contacts, and actual time spent by PHPs on CT when these tools are used. The research questions formulated in the *Process Evaluation* section are designed to examine whether the DCTS tool was used as intended by index cases and PHPs and to expose any unintentional factors influencing its effectiveness. The process evaluation consists of examining the adoption rate of the tool; demographics of the users of the tool and those of their contacts; and user experiences of index cases, their contacts, and PHPs.

First, we discuss some legal, ethical, and technical issues to be considered before the evaluation study can be conducted. Next, we present the finally established framework containing the evaluation topics, research questions, and rationale behind each of them. In addition, we suggest and describe the potential study designs, methods, and measures that may be used to explore and answer the research questions (Multimedia Appendix 1). Finally, we discuss the implications of the framework for various types of future infectious diseases.

Legal, Ethical, and Technical Feasibility

Overview

Before starting an evaluation process, it is important to explore the legal, ethical, and technical possibilities when it comes to collecting citizen data, transferring the data to a research data management system, and analyzing and storing the data. The use of technology in general is increasing rapidly, and increasing

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amounts of personal data are being shared globally to help organizations improve their services, reach more clients, and generate more income. This flow of data also comes with the risk of misuse and theft of personal information. Even during emergency situations leading to substantial morbidity and mortality, it is broadly considered important that any type of CT and the collection and storage of personal information is conducted in an ethically responsible and secure manner and that individuals' data are protected [35]. Various countries and regions have legal frameworks in place for the handling of personal data, including the Personal Information and Electronic Documents Act in Canada, Health Insurance Portability and Accountability Act in the United States, and General Data Protection Regulation (GDPR) in Europe [36].

Legal Feasibility

If a digital intervention such as the DCTS tool is implemented, there should be transparency to the public about how their data will be used and if and how the data will be transmitted to a centralized CT system, protected from hacking, and stored safely [37]. There are established laws when it comes to citizens sharing their personal data. When index cases in the Netherlands download the DCTS tool, for example, they are required to indicate that they have read the terms and conditions, which include the use of their personal data. These state that the use of personal data is necessary in the interests of public health and that these data are handled in accordance with GDPR [38]. They also state that the data sent and received by the users are encrypted and conveyed via a secure server. Users are informed that they can send and receive data for up to 48 hours after the DCTS tool is activated. They are notified that their data will be deleted after 2 weeks from the web portal (that is linked to the centralized database). They are also informed that they are not obligated to provide personal information but that doing so will serve the process of CT.

Ethical Feasibility

In a similar manner to providing data for CT, there must be transparency and clear communication to individuals regarding which personal data will be used by researchers in the evaluation study, how their data will be transferred to a research database, how secure the database will be from hacking and misuse, how long the personal data will be stored before deletion, what data will be anonymized, and how the data will be used for evaluation purposes. There must be good collaboration with the health services collecting these data from index cases to ensure that all parties understand the purpose and relevance of conducting the evaluation study. Judicial advice must be sought regarding the ethics of obtaining limited personal data that are collected by health services for purposes other than CT, such as research, as stated in article 6 (4) of GDPR and how these data can best be anonymized. Morley et al [39], for example, have considered these aspects when it comes to implementing proximity-based apps, by developing guidelines consisting of 16 questions to be answered, to help ensure their ethical justification.

Technical Feasibility

In conducting evaluation studies, researchers will be dependent on the stability and consistency of the data that are obtained from the digital tool. However, technology is constantly changing; the tool they plan to evaluate may have changes to its algorithms, features removed or added, or updates made, or its implementation may even be discontinued [40]. It is therefore important that potential barriers are anticipated and that there are contingency plans in place during the writing of their research protocols. As the data collected for CT will pertain to potentially millions of people, it will be of practical importance to consider, before starting the evaluation, how this vast amount of data can best be transmitted, stored, organized, and analyzed for research purposes and who should be able to access the data. The advice of cybersecurity experts will be essential to ensure that the data provided by index cases are safe and protected. Ideally, the principles of the Privacy by Design approach should be adhered to, where privacy is assured by default within the design of IT and data storage systems, throughout each phase from data collection, transmission, storage, and elimination [41].

Ethical Considerations

The development of this study framework did not involve human participants. This study is part of the larger project Strategic Program of the RIVM (SPR IZB2.0 S/070008), which was conducted in accordance with the Declaration of Helsinki—Ethical Principles for Medical Research involving Human Subjects. Ethical clearance was obtained from the Medical Ethics Review Committee of the University Medical Centre Utrecht. The Committee confirmed that the Medical Research Involving Human Subjects Act (WMO) does not apply to this project (reference 21/062).

Results

Framework and Rationale Behind Evaluation Topics

In this section, we have first presented the evaluation framework in Table 1. It contains an overview of the evaluation topics and research questions, divided into an outcome evaluation and a process evaluation. The rationale behind each of these evaluation topics and research questions has been discussed. Tables S1 and S2 in Multimedia Appendix 1 contain potential study designs, methods, and other considerations that may be helpful for examining the research questions.

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Table 1. Outcome and process evaluation framework for comparing the use of digital contact tracing support (DCTS) tools (approaches B to D) with traditional contact tracing (CT; approach A)[a].

Evaluation topics	Research questions
Outcome evaluation	
Speed	What are the effects of DCTS tools (approaches B to D) when compared with traditional CT (approach A) regarding the length of time between the positive test result and having notified all relevant contacts about the further steps to take?
Comprehensiveness	What are the effects of DCTS tools (approaches B to D) when compared with traditional CT (approach A) regarding the number of contacts and the completeness of contact information provided by the index case?
Contact notification	What are the effects of DCTS tools (approaches B to D) when compared with traditional CT (approach A) regarding the proportion of contacts notified and provided with instructions?
Positive case detection	What are the effects of DCTS tools (approaches B to D) when compared with traditional CT (approach A) regarding the number (and proportion) of positive cases detected among identified contacts?
PHP[b] workload	What are the effects of DCTS tools (approaches B to D) compared with traditional CT (approach A) when it comes to time, effort, and human resources?
Process evaluation	
Diverse demographic adoption and reach	How do demographic groups differ with regard to those who adopt DCTS tools (approaches B to D) and those who experience traditional CT (approach A) among (i) index cases and (ii) contacts who are reached by PHPs and by means of these tools?
Experiences of index cases	What are the experiences and views of index cases regarding DCTS tools (approaches B to D) when it comes to aspects such as their usability, effectiveness, and information security? Why do some index cases choose not to use these tools?
Experiences of contacts	What are the contacts' views toward and experiences with receiving instructions from the index case? What CT approaches (A to D) do contacts prefer? To what extent do contacts adhere to the instructions?
Experiences of PHPs	What are the experiences and views of PHPs conducting CT with DCTS tools (approaches B to D) with respect to aspects such as their usability? What are PHPs' views about leaving the CT process completely in the hands of index cases?

[a]For each question, the various approaches to using this technology can be compared (Figure 1).

[b]PHP: public health professional.

Outcome Evaluation: Evaluation Topics and Rationale Behind the Research Questions

Speed: Effectiveness of DCTS Tools in Terms of the Duration of the CT Process

Some infectious agents, such as the virus leading to COVID-19, can spread extremely quickly from one person to another, which makes it important that those at risk are identified as quickly as possible, preferably before symptoms occur, to prevent them from inadvertently spreading the virus to others. A systematic review and meta-analysis revealed that the average incubation periods for COVID-19 caused by the Alpha, Beta, Delta, and Omicron variants were 5, 4.50, 4.41, and 3.42 days, respectively [42]. Considering that one can be infectious from 2 days before symptoms appear, identifying the contacts of a person who has tested positive must be done as quickly as possible. A DCTS tool may enable the rapid retrieval of existing contact details stored in the standard contact list on a mobile phone or the index case can enter the contact details manually into a DCTS tool. As index cases can inform their contacts themselves and send them customized guidelines using the DCTS tool according to the type of contact, the contacts may be informed either before or shortly after the call with the PHP with the correct information. It is plausible that DCTS tools may, therefore, help to save time and lead to contacts testing themselves for COVID-19 immediately, seeking medical help, going into quarantine, or being aware of exposure to and possibly having acquired the virus. In contrast, index cases may be unable, hesitant, or unwilling to notify their contacts themselves, which would lead to contacts not being aware of their exposure on time and possibly spreading the virus to others. It is therefore important that the time between receiving the positive test result and having notified all relevant contacts is evaluated. The average duration of the CT process can be compared among those using the various DCTS tool approaches (approaches B to D) and those experiencing traditional CT (approach A).

Comprehensiveness: Effectiveness of DCTS Tools in Terms of the Number of Contacts Identified and the Completeness of the Information Provided

For CT to be effective, it is important that no exposed contacts or at least as few as possible are left unidentified or with missing contact details. The potential number of contacts identified will likely depend on the memories of index cases, their willingness to share contact details, availability of these contact details, and ease with which these details can be shared [43]. The average numbers of contacts shared by index cases will also possibly be influenced by public precautionary measures implemented at the time of the study, such as working from home or avoiding too many visitors. PHPs may be trained to ask index cases the right questions while conducting traditional CT to elicit as many contacts as possible. However, it is also plausible that the use

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of DCTS tools may buy more time for index cases to calmly jog their memories and remember everyone they have recently encountered. This may lead to them remembering more contacts than they would have with traditional CT and to retrieving more accurate contact details, such as telephone numbers and email addresses. It would be beneficial, therefore, to compare the number of contacts (with complete and accurate information) between those using DCTS tools (approaches B to D) and those undergoing the traditional CT process (approach A).

Contact Notification: Effectiveness of DCTS Tools in Terms of the Proportion of Contacts Notified and Provided With Instructions

Solely collecting a list of contacts and sufficient contact details will not ensure effective CT. Contacts also need to be notified and provided with instructions about what steps to take. Although there are contacts that will appreciate being notified about their possible exposure, index cases may have concerns about causing discomfort for them, by notifying them about the steps they need to take [44]. Having to quarantine can be associated with negative feelings, such as anxiety, loss of freedom, loneliness, anger, and boredom and can have a financial impact [45,46]; thus, conveying instructions to contacts who may not have been infected will not be an easy task. Index cases may also feel hesitance in notifying contacts themselves, owing to possible stigma and feelings of shame. In contrast, index cases may prefer notifying their contacts themselves, owing to hesitance in sharing personal contact details with the PHP. The more contacts that are notified and informed with instructions, the more likely the virus can be controlled. It is important, therefore, to evaluate DCTS tools (approaches B to D) by examining the number of contacts that are notified and provided with instructions, compared with traditional CT (approach A).

Positive Case Detection: Effectiveness of DCTS Tools in Terms of Detecting Positive Cases Among Contacts

The main aim of CT is to identify infected cases before they have the chance to transmit the virus to others. Measuring the ability of a CT strategy to identify the number of contacts who have contracted the virus is therefore important to determine how effective it is [47]. For the same reasons described previously, an increased number of contacts may or may not be notified earlier with the help of DCTS tools, compared with traditional CT. It is plausible that if more contacts are notified earlier, they will also take a self-test or be tested by the PHS immediately, and greater number of positive cases will be identified sooner. If the DCTS tool has such a functionality, it may enable the identification of contacts who become new index cases by matching identical identification numbers. It would be beneficial to examine whether DCTS tools (approaches B to D) have any value compared with traditional CT (approach A) with respect to the average number and proportion of identified contacts per index who have tested positive for the infectious agent, such as SARS-CoV-2.

PHP Workload: Effectiveness of DCTS Tools When It Comes to Time Spent by PHPs, Effort, and human resources

CT during the COVID-19 pandemic has required huge amounts of resources (in terms of staff, time, and required efforts) to keep up with cases and to conduct CT thoroughly [6]. The consequences can be that those conducting CT are overburdened and have less time to conduct CT comprehensively and for other health care tasks. In many countries, individuals from other professional fields, medical students, and volunteers have been trained to work as contact tracers to keep up with the number of infected cases [7]. It is unknown what the effects would be on the PHP workload if the index case, using a DCTS tool, takes over part of the process by identifying their own contacts, collecting contact details, and then informing the contacts themselves. Although there could be some work for PHPs, if they need to check whether contacts have indeed been notified and provided with the correct instructions, for example, in theory, the index case conducting most CT themselves could save time for PHPs and possibly lead to a more comprehensive and effective CT process. This could also reduce the need for more human resources and having to hire individuals from other fields with limited experience in CT and leave those who can conduct CT skillfully to handle the groups that have higher risk and are more vulnerable.

Process Evaluation: Evaluation Topics and Rationale Behind the Research Questions

Diverse Demographic Adoption and Reach: Differences Between Demographic Groups of Index Cases and Contacts Across the Various CT Approaches

Ideally, DCTS tools will appeal to and be of use to all relevant segments of the population in terms of, for example, age, ethnicity, education, income, and health status. The use of digital technology, however, tends to be associated with and is easier to use for younger, more highly educated, wealthier, and healthier people [12,48,49]. There are some sociodemographic disparities when it comes to contracting the SARS-CoV-2 infection, degree of experiencing severe respiratory disease after contracting the virus, and mortality owing to the virus, all to the disadvantage of older people, ethnic minority groups, and those with lower incomes [50-52]. Although the Netherlands, for example, is a wealthy country with relatively little income inequality compared with many other countries, a study using national statistics data covering the early months of the pandemic (March 2020 to June 2020) found that those with the lowest incomes were twice as likely to die from COVID-19 as those with the highest incomes [53]. It will be beneficial to take all these sociodemographic factors into account when assessing the effectiveness of DCTS tools. It is also plausible that such a tool facilitating more citizen autonomy in CT could enable index cases to be a bridge to those in sociodemographic groups that are normally hard to reach when it comes to health care. In instances where traditional CT is being conducted alongside the use of DCTS tools, it is also possible that mainly low-risk index cases will conduct CT themselves with the DCTS tool, leaving more time for PHPs to focus on traditional CT with higher-risk groups. Regardless of the effects of the DCTS tool,

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it is advisable to examine whether DCTS tools can contribute to diminishing the health disparities caused by the infectious disease.

Experiences of Index Cases: Experiences and Views of Index Cases Regarding DCTS Tools When It Comes to Aspects Including Usability, Effectiveness, and Information Security

The success of CT by means of such DCTS tools will depend on the ability and willingness of index cases and PHPs to actively participate in and support the CT process. Supporting and motivating individuals to be involved will be key to making CT with DCTS tools effective. It will be of interest to examine the views of index cases toward becoming more involved in the CT process as a citizen and what they think about using DCTS tools to facilitate this process.

Traditionally, two main types of citizen involvement have been distinguished: (1) patient participation, in which a person contributes to their own health care, and (2) public participation, where a person contributes to the health care of others in the public domain [54]. The type of participation required for DCTS tools appears to have some elements of both types. Using this technology requires that index cases not only assist in their own care and those close to them but also contribute to protecting public health by actively helping to contain the infectious disease. Some benefits associated with citizen participation in health care are increased empowerment, improved patient experience, lower health costs, and decreased burden on and improved health care services. One review reported that although many people felt a collective responsibility to participate in CT for infectious diseases, including COVID-19, there was also some mistrust and concerns about their privacy [55]. This review concluded that individuals appeared to be motivated by contributing to public health in general but especially if there was some personal benefit to it.

Besides gaining further insight into individuals' general feelings toward citizen involvement in CT, it will be important to examine the experiences and views toward using DCTS tools for this purpose. Such technology should ideally be considered user-friendly, useful, and sufficiently trustworthy for index cases to be willing to enter personal data and details pertaining to their contacts.

There are likely to be similar factors expressed by users of proximity apps that could also influence the adoption of DCTS tools, such as privacy and trust issues, perceived personal and social benefits, and perceived ease of use [56], but there may also be other experiences to explore that are unique to users of DCTS tools. To gain further understanding of these experiences, it is important to hear from both the users of the tools themselves and from those who are unable or have chosen not to use them.

Experiences of Contacts: Experiences and Views of Contacts Regarding the Various CT Approaches When It Comes to Receiving and Following Instructions

Involving citizens more in the CT process depends not only on the ability and willingness of index cases but also on the ability and willingness of contacts to be notified and to follow the instructions. Contacts may have questions about or disagree with the instructions or feel they cannot follow them and may need additional support from PHPs [57]. Contacts may also prefer being notified verbally instead of digitally or may not appreciate being notified by an index case instead of a PHP. A previous Dutch study conducted among PHPs before the COVID-19 pandemic showed that although PHPs recognized the potential of a digital system in which index cases could play a large role in identifying and informing their contacts, there was some concern that contacts may not be provided with the correct instructions, that the contacts would not take these instructions seriously if they did not come directly from a PHP, or that contacts may be left with unanswered questions and worries that could best be discussed with a PHP [58]. It is essential to examine whether the manner in which contacts receive instructions affects their feelings toward and acceptance of these instructions and their ability to follow them.

Experiences of PHPs: Experiences and Views of PHPs Regarding DCTS Tools, Including Their Usability and Transferring the CT Process Into the Hands of Citizens

As PHPs conducting CT have traditionally played the largest role in this process, their opinions about transferring all or a part of the CT process into the hands of citizens will be invaluable. They can be asked about their views regarding the willingness and ability of index cases to identify all relevant contacts and provide them with the correct information. According to a joint World Health Organization and European Centre for Disease Prevention and Control meeting report, countries anticipate that the CT of the future may require an approach that is more focused on groups that are vulnerable and at high risk [59]. PHPs may need to play an important role in determining which index cases can assume the CT role themselves with DCTS tools and which index cases would benefit more from traditional CT. Gaining some insight into how they will make these decisions, how they may encourage index cases to use the DCTS tool, and their views in general about involving citizens more in CT will be beneficial. It will also be important to examine their views regarding the usability (including user-friendliness) of DCTS tools; they can be asked about the features needed in DCTS tools to maximize their adoption by index cases. To provide context for and help to explain their views, it will be helpful to collect personal PHP characteristics. Their age and how long they have been conducting CT, for example, may influence their views in general about using new technology.

Study Designs

To conduct the evaluation of DCTS tools, it is important to consider appropriate study designs and methods by which these study questions could be answered as optimally as possibly, despite the backdrop of a pandemic. The varying types of research questions will require a mix of study designs that need to be combined to answer all those questions. Some questions will require the quantitative examination of data collected from CT case management systems. These data may be obtained from centralized case management systems used by PHPs for CT or they may come from more decentralized databases collecting data from DCTS tools at a more local level, bypassing

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PHS. Other research questions will require the quantitative and qualitative assessments of information provided by users of DCTS tools themselves (index cases and PHPs) and their contacts, by means of surveys or interviews. In Tables S1 (outcome evaluation) and S2 (process evaluation) in Multimedia Appendix 1, study designs, methods, study measures, and relevant points of consideration are proposed, to answer each of the research questions outlined in the framework.

Discussion

Summary

The aim of this study was to develop and present a framework containing a set of research questions and accompanying study designs that may be valuable for a complete assessment of the identification and notification of contacts in CT using DCTS tools. Our framework is divided into an outcome and a process evaluation that assess the effects of DCTS tools, when compared with traditional CT. For the outcome evaluation, relevant topics to examine are the speed and comprehensiveness of the CT process, proportion of contacts who are notified and provided with instructions, proportion of contacts who test positive, and PHP workload (in terms of time, effort, and human resources). For the process evaluation, it is important to examine the demographics of those using the tools when compared with those who experience traditional CT and hear about the personal experiences of index cases, contacts, and PHPs when it comes to using these tools.

DCTS tools combine the advantages of digital technology with the ability and willingness of citizens to play a role in protecting their own health and that of others by assuming all or a part of the CT process themselves. The main added value of DCTS tools for CT of COVID-19 was that citizens could alleviate the work of PHPs when there were high numbers of cases. These types of tools could be of benefit to curb other future infectious disease outbreaks with high infection rates. For smaller-scale infectious disease outbreaks, particularly those with short incubation periods or those that are very infectious (requiring rapid CT), those leading to large numbers of contacts (requiring time, memory, and accuracy by the index case to collect contact details), and those associated with stigma (requiring more discrete or anonymous CT), DCTS tools could also potentially be of value [44]. Infectious diseases such as mpox (monkeypox) and sexually transmitted infections may have some stigma attached to them, forming a potential barrier to sharing contacts' details with a PHP or notifying contacts [60-62]. DCTS tools can assist with partner identification and notification [63]. If index cases are uncomfortable with notifying contacts themselves or prefer to stay anonymous, contact details can be collected using the tool and shared with the PHP. The PHP can then reach out to the contacts and notify them, while enabling the index cases to remain anonymous. If index cases are concerned about sharing their contacts' details with the PHP, contact notification could bypass the PHP, and the tool could facilitate the notification of and provision of instructions to contacts by the index cases themselves. If index cases prefer to stay anonymous, they could inform their contacts anonymously using an additional feature in the tool.

DCTS tools could theoretically be customized to any infectious disease for which CT is conducted, for example, by containing disease-specific information to help cases identify potential contacts who are at risk of exposure and through notification messages to advise contacts about further steps to take. DCTS tools may have added value when it comes to CT and curbing a wide range of future infectious disease outbreaks, and this framework can be used to measure the extent to which they are effective.

Conclusions

This framework was developed to help researchers and policy makers design studies for their own evaluation of DCTS tools. The findings of these evaluation studies can provide guidance in determining how and the extent to which DCTS tools should be implemented as part of the CT strategy used for future infectious disease outbreaks.

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Authors' Contributions

RB, NH, YBH, RC, HMG, and MLS played substantial roles in the design of the study and in the writing of the manuscript. RB drafted the manuscript and incorporated all further feedback. All authors approved the final version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Proposed study designs, methods and measures, as well as additional considerations for the outcome and process evaluations.

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Abbreviations

CT: contact tracing
DCTS: digital contact tracing support
GDPR: General Data Protection Regulation
PHP: public health professional
PHS: public health service
RIVM: Rijksinstituut voor Volksgezondheid en Milieu (National Institute for Public Health and the Environment)

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Protocol

Investigating the Impact of Automation on the Health Care Workforce Through Autonomous Telemedicine in the Cataract Pathway: Protocol for a Multicenter Study

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Abstract

Background: While digital health innovations are increasingly being adopted by health care organizations, implementation is often carried out without considering the impacts on frontline staff who will be using the technology and who will be affected by its introduction. The enthusiasm surrounding the use of artificial intelligence (AI)–enabled digital solutions in health care is tempered by uncertainty around how it will change the working lives and practices of health care professionals. Digital enablement can be viewed as facilitating enhanced effectiveness and efficiency by improving services and automating cognitive labor, yet the implementation of such AI technology comes with challenges related to changes in work practices brought by automation. This research explores staff experiences before and after care pathway automation with an autonomous clinical conversational assistant, Dora (Ufonia Ltd), that is able to automate routine clinical conversations.

Objective: The primary objective is to examine the impact of AI-enabled automation on clinicians, allied health professionals, and administrators who provide or facilitate health care to patients in high-volume, low-complexity care pathways. In the process of transforming care pathways through automation of routine tasks, staff will increasingly "work at the top of their license." The impact of this fundamental change on the professional identity, well-being, and work practices of the individual is poorly understood at present.

Methods: We will adopt a multiple case study approach, combining qualitative and quantitative data collection methods, over 2 distinct phases, namely phase A (preimplementation) and phase B (postimplementation).

Results: The analysis is expected to reveal the interrelationship between Dora and those affected by its introduction. This will reveal how tasks and responsibilities have changed or shifted, current tensions and contradictions, ways of working, and challenges, benefits, and opportunities as perceived by those on the frontlines of the health care system. The findings will enable a better understanding of the resistance or susceptibility of different stakeholders within the health care workforce and encourage managerial awareness of differing needs, demands, and uncertainties.

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Conclusions: The implementation of AI in the health care sector, as well as the body of research on this topic, remain in their infancy. The project's key contribution will be to understand the impact of AI-enabled automation on the health care workforce and their work practices.

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KEYWORDS

artificial intelligence; autonomous telemedicine; clinician burnout; clinician wellbeing; conversational agent; digital health; health communication; health information technology; health services; healthcare; medical informatics; socio-technical system approach; systems approach; technology acceptability

Introduction

Background and Rationale

There has recently been a rise in the use of artificial intelligence (AI) and automated technologies within health care that come with the promise of increasing efficiency and improving clinical workloads [1]. These AI technologies are already being shown to perform tasks previously entirely within the scope of human clinicians, from reading scans to replacing entire clinical consultations [2-4]. Despite the potential for AI to result in organizationally valuable outcomes, research shows that this is not always the case [5]. Many organizations invest effort, resources, and time into emerging technologies yet do not experience desired results, ultimately deeming these initiatives unsuccessful. It is evident that for AI implementation to be successful, the interrelationship between individuals, technologies, and the system should be observed holistically. It is important to take this holistic view into account because, as with the industrial revolution or more recent waves of digitization, workers who experience their role directly impacted by automation or digitization can either be empowered to "work at the top of their license" or feel even further disempowered and left behind.

Investigating the impact of such technologies on individuals is paramount in the current context of the global health care workforce crisis. Clinicians' well-being is at risk, with studies to date showing that several factors can contribute to poor acceptance and adoption, leading to a negative impact on workloads and thus well-being. There are many definitions of well-being, and in this study, we define the term, in the context of the workplace (based on the Stanford Professional Fulfillment model) [6], as "the degree of intrinsic positive reward we derive from our work, including happiness, meaningfulness, contribution, self-worth, satisfaction, and feeling in control when dealing with difficult problems at work."

This has great implications given the burnout epidemic and is becoming increasingly important to address after the recent COVID-19 pandemic, which took an unprecedented toll on an already pressurized system [7-9]. Burnout has been described as a "work-related syndrome" commonly characterized by high levels of emotional exhaustion, depersonalization, and dissatisfaction with one's career and is associated with high turnover rates [10]. In this study, burnout is seen as an element within the broader concept of well-being when the negative impact on one's well-being is at its extreme. The World Health Organization (WHO) projects a global needs-based shortage of health care workers at over 14.5 million in 2030 [11]. This workforce shortage has been deemed the "biggest, most pressing threat to the viability of services for people who need them" within the National Health Service (NHS) [12]. A bidirectional link between burnout and medical errors resulting in clinician distress has been observed, while conversely, better physician well-being was associated with improved patient satisfaction, improved treatment, and lower rates of hospital-acquired infections [13]. Thus, it is essential to find ways to improve well-being, for the benefit of the individual clinician, for patient care and safety, and to reduce provider costs [6].

Electronic health records (EHRs) are one example of an innovative tool that promised to empower clinicians; however, they have ended up being the focus of multiple studies of technologies' negative impact on physician well-being [14,15]. The increased use of EHRs in health care organizations coincided with the need for prompt clinical data entry, and the lengthy and onerous clinical documentation process has been widely reported to have added to clinician frustration and, in many cases, been perceived to have added to administrative workload and time spent documenting rather than providing patient care [16,17]. Other dramatic changes in the ways clinicians work have been brought about with telemedicine [18], with studies also exploring the challenges of implementing AI, focusing on managers' or users' perspectives [19-21].

To date, research around burnout has mainly focused on doctors and nurses, with limited emphasis on other health care staff [22-24] and a holistic understanding of AI-enabled automation adoption. Some studies have shown several work system factors having a significant impact on predicting clinician burnout, including excessive workload, lack of job control through poor perceived autonomy and flexibility [11], misaligned values and expectations, lack of intrinsic motivation, and high administrative burden [9]. Other work system factors include workflow interruptions, poor technology usability that adds to the considerable workload and hinders workflow processes, moral distress, and time pressure. Recent research shows that health care staff perceive AI-driven tools to have the potential to help prevent burnout [25], and therefore, understanding the clinical environment and the impact of automation is crucial to improving the quality of care and patient safety.

The rising tide of AI-enabled digital health solutions places a growing emphasis on understanding the systemic impacts of implementing such technologies in health care and the

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subsequent impact on individuals. This study seeks to explore how staff members are impacted before and after the implementation of an autonomous clinical conversation agent in a routine elective care pathway.

Intervention Used

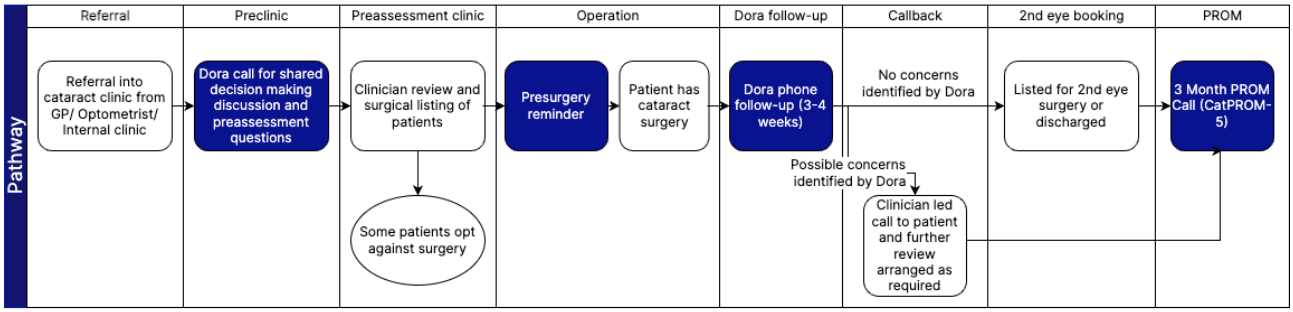
This study will examine the impact on staff of the implementation of a UK Conformity Assessed-marked autonomous, voice-based, natural-language clinical assistant, "Dora" (Ufonia Ltd). Dora is simple and easy to use [3], as patients answer a telephone call they receive with no need for an internet connection, a smartphone, or a web interface. The technology can have a consultation with patients over the telephone, and thus the entire clinical conversation is tasked to Dora, which replaces the human conversation. For example, the key elements of a postoperative conversation in the cataract pathway with Dora are as follows:

- Greetings and introduction
- Confirmation of the identity of the patient
- Validated cataract follow-up questions
- Opportunity for the patient to ask Dora questions
- Decision regarding next steps of care
- Questions about acceptability (Net Promoter Score)
- Closure of the call

The technology has already demonstrated acceptability with patients in the cataract follow-up pathway, where it can reduce the number of patients needing a clinician-led consultation by up to 60% [3].

Clinicians do not use any new interface. The department simply lists patients for a Dora call. Once Dora has conducted the clinical conversation, the results are fed back to the clinical team, who receive outcomes through a static report that summarizes the key domains assessed and the resulting outcome. This report is usually in the form of either a structured PDF file or a CSV file, depending on the required workflow. The Dora call can be implemented at multiple time points along the cataract pathway, as demonstrated in Figure 1. Apart from the patient pathway demonstrated in the figure below, this study will aim to shed light on the extent to which tasks and work practices are transferred or redesigned as a result of the introduction of Dora.

Figure 1. Example of an end-to-end Dora patient pathway for cataract surgery. PROM: patient-reported outcome measures.



NHS South East (NHS-SE) has commissioned the regional use of Dora in the cataract pathway. Cataract surgery is the most common operation in the NHS, with over 450,000 procedures per year. Dora can have multiple conversations with patients, from preoperative assessment to postoperative review to assessing patient-reported outcome measures. The technology promises to automate these often stereotyped clinical interactions, potentially reducing the burden on clinicians multifold by replacing the conversation as well as automating the subsequent clinical documentation. In a pathway with Dora, rather than a clinician needing to consult every patient, only those with clinical concerns identified by Dora need a clinician review. This increases staff capacity while removing the stressors associated with repetitive routine conversations and administrative tasks such as documentation, targeting a major cause of clinician distress [26,27].

Theoretical Framework

It is acknowledged that perception is a significant indicator of organizational readiness. Technology adoption theories, such as the Technology Adoption Model and diffusion of innovation theory, consider perception as a predictor of acceptance and use. These theories identified that previous experience, knowledge, and user skill sets influenced technology adoption in health care. For example, health care professionals willingly accepted the technology into their practice if it was aligned with professional values, was easy to use, trusted, and improved job performance [28,29].

While these perspectives could yield valuable insights, the sociotechnical system (STS) approach adds another dimension by acknowledging the interdependencies existing between organizations, individuals, and technology. This study adopts the STS perspective as a theoretical framework to analyze the impact of AI-enabled automation on the health care workforce and their work practices. The STS approach considers an organization as a work system with 2 interconnected subsystems: the technical dimension and the social dimension. The interactions between these 2 systems together produce the outputs of a work system, creating economic outcomes such as

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efficiency, productivity effectiveness, and cost reduction, in addition to humanistic outcomes such as well-being and engagement [30]. It is argued that performance is maximized only when the interdependence of these subsystems is explicitly recognized [31]. Sociotechnological studies on health care and technology implementation found that stakeholders hold different perspectives depending on their goals and expectations. For example, the organization's goal of addressing workload productivity or maximizing financial performance may be different from a health care professional's focus on improving patient outcomes and clinical decision-making. When introducing new technology into the health care industry, the challenge is determining the best method for comprehending the perceptions of all stakeholders. While the technical dimension of digital technologies and AI is currently dominating research studies, the impact on engagement, acceptance, and well-being of the individual is less well understood [25,30].

Methods

Study Design

To investigate the complex interactions between structures, people, organizations, technology, and contextually specific issues, a mixed methods research orientation will be adopted. This involves collecting, analyzing, and combining qualitative and quantitative data to obtain "complete analysis" [32,33] in understanding the relationship between technology and people and subsequent impact that cannot be fully understood by using a single methodology (ie, either qualitative or quantitative) [34,35]. Novel findings facilitate further investigation and expand the depth and scope of the data obtained. Furthermore, a mixed methods approach is suitable to answer both explanatory and confirmatory research questions.

The study will last for 12 months and consist of qualitative and quantitative data collection methods over 2 distinct phases, namely phase A (preimplementation) and phase B (postimplementation). Longitudinal data collection will assist in forming a richer understanding of the context, drawing further insights into how the change (ie, the intervention) impacts the workforce over time. The unit of analysis is the activity itself (the impact of AI-enabled automation on multiple stakeholders within the health care workforce), and within this focus of interest, tensions and contradictions will be identified and given particular priority and importance.

Participant Recruitment

We will perform a multiple case study analysis as it favors the collection of rich data in multiple contexts, and the methodology allows for cross-case comparisons to clarify if the findings can be applied to several cases or are idiosyncratic to a single case. This will take place at multiple NHS hospital trusts. These sites represent a varied geographical location, baseline operational processes, management structure, demographics, and volume of patients. According to Benbasat et al [36], leveraging the case study approach is valuable for "problems... in which research and theory are at their early, formative stages and sticky, practice-based problems where the experiences of the actors are important and the context of action is critical." Furthermore, multiple case study analysis enables the establishment of patterns or links between constructs within and across cases, together with their underlying logical explanations.

Participants will include doctors, nurses, allied health professionals, and administrators in the department where Dora is being implemented. Invitations to participate will be sent out through email and informed consent will be gained from participants before data collection. We intend to adopt a purposeful sampling technique, complemented by the snowballing technique, to identify knowledgeable informants. Participants will be chosen based on their role and knowledge of the study topic, as well as their involvement in the Dora pathway.

The final number of interviews will be determined while analyzing the data. For example, when no new codes and themes are emerging from the data and the analysis does not yield new themes but confirms current ones, it would suggest that a theoretical saturation point is obtained [37] and no new data are required.

Data Collection

Multiple sources of evidence will be used, including semistructured interviews, focus groups, questionnaires, document analyses, and site visits, conducted by 2 researchers (SK and FZ). Using several forms of evidence enables the research team to understand the complexity of the context, obtain a rich data set, and facilitate triangulation, which improves the accuracy of the gathered data and enhances the credibility of the findings and conclusions [38]. Table 1 provides a summary of the methodology across the phases of intervention implementation.

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Table 1. Summary table of methodology across phases of implementation.

Study and Dora implementation phases	Methodology	Description of workstream
Phase A: preimplementation		
	Structured survey	Distribute a survey to members of staff across multiple NHS[a] sites to collect quantitative data before Dora implementation. Questions will focus on perceived acceptability, benefits, usability, and challenges associated with Dora.
	Interviews and focus groups	Conduct focus groups and semistructured interviews to understand the preconceptions that staff hold about automation using Dora and its potential impact on their work practices and well-being. Field notes will be taken during the interviews and consolidated after.
Phase B: postimplementation		
	Structured survey	Distribute the same survey as in phase A to enable comparisons between the initial data gathered before Dora implementation and after, highlighting any changes on an individual level.
	Interviews and focus groups	Conduct similar focus groups and interviews as in phase A to explore emergent themes in more depth and understand the postimplementation impact of Dora.

[a]NHS: National Health Service.

The questionnaire is designed to collect descriptive data about user acceptability, awareness, and well-being to aid in the interpretation of the findings (Table 2 provides an overview of the survey components). Before distributing the survey, it will first be piloted and validated by experts in the fields of health and information systems to ensure that it accurately measures health care professionals' perceptions of the Dora intervention. The questionnaires will be complemented with focus groups and semistructured interviews (lasting between 30 and 60 minutes) to offset the lack of flexibility and depth of the survey and are developed to elicit critical process information that could add value to the survey data collected.

Table 2. Overview of questionnaire components and description.

Questionnaire component	Description
Demographics	Information about the hospital, job role, experience, work hours, age, gender, and ethnicity.
Dora involvement a understanding	Assesses the participant's role in the Dora pathway and their self-rated knowledge of the system.
Stanford Professional Fulfillment and Burnout Index	Measures intrinsic positive reward derived from work and symptoms of work exhaustion and disengagement.
Impact of Dora on burnout	Evaluates the perceived impact of Dora on burnout symptoms.
Perceived acceptability	Gauges the acceptability of the Dora system, including user satisfaction and the system's perceived value.
AI-related questions	Explores perceived benefits, performance anxiety, communication barriers, benefits, privacy concerns, liability, and risks.

Qualitative research methods involve the study of participants in their natural settings in order to interpret phenomena and the meanings individuals attribute to them. The fundamental goal is to understand participants from their own perspective [39]. To ensure trustworthiness, the study will be reported in accordance with the Consolidated Criteria for Reporting Qualitative Research (COREQ) 32-item checklist [40].

Preimplementation

A survey, based on the theoretical framework of acceptability and a validated well-being instrument (ie, Stanford Model of Professional Fulfillment), will be distributed to members of staff (both directly and indirectly affected by the intervention) across multiple NHS sites to collect quantitative data on well-being and perceptions before the implementation of Dora. The aim of the survey is to gain an understanding of how AI-enabled automation, introduced by the intervention in this study, is perceived by the health care workforce. Questions will be based on perceived acceptability, benefits, and challenges associated with the implementation of Dora. This phase will also involve a focus group and semistructured interviews (conducted face-to-face or remotely, depending on convenience) to gain an understanding of the preconceptions held regarding automation using Dora, the impact of automation on themes such as autonomy, as well as the impact this may have on staff's well-being. We will explore the system "as-is" to understand current ways of working, tensions and contradictions, and potential opportunities for Dora, to enable comparisons and further investigation. This will allow us to obtain baseline data to facilitate comparisons further into the study.

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Focus groups enable participants to discuss this topic in greater depth and interact with, as well as react to, other participants [41], which can reveal shared opinions, reactions, and ideas on these phenomena. Field notes will be taken during the focus group and consolidated after.

The protocol used for the focus groups and interviews will be prepared based on the underlying constructs of the theoretical framework and literature review. These will provide a list of "intellectual bins" that structure the data collection and analysis [42]. Questions will largely be open-ended, giving participants the freedom to convey their personal views and experiences with respect to the socially complex context of AI implementation and automation in health care. The interviews will be conducted in a reflexive and responsive manner to enable the research team to follow up on insights and adjust the content of the interview accordingly. All interviews will be transcribed, annotated, and proofread. Furthermore, venting will be used, whereby interpretations and responses will be discussed with medical and academic professionals.

To enhance the robustness of the case studies, we will triangulate our findings by means of several evaluators (eg, researchers), multiple respondents, and different sources (ie, interviews, internal documentation).

Postimplementation

This phase involves the distribution of the same survey that was used in phase A as well as conducting a focus group and semistructured interviews with the same individuals contacted in phase A to explore emergent themes in more depth. This will enable comparisons between the initial data gathered before the implementation of Dora and the postimplementation, highlighting the changes that have occurred, if any, on an individual level.

Data Analysis

The interview and focus group data will be thematically analyzed by the research team, which includes 2 researchers who are experienced in analyzing qualitative data. The first phase will involve the researchers familiarizing themselves with the data by reading and rereading the transcripts and field notes (also known as the "data immersion phase"). The raw data will be transferred to a qualitative analysis software (NVivo; QSR International) where it can be coded (ie, systematized and labeled). In this research, NVivo will facilitate the management and organization of data and the merging of codes, where appropriate, as part of the analysis.

A third researcher will further analyze a subset of the data to identify concepts that may have been missed, offer an alternative perspective, and detect possible bias in data analysis. We intend to adopt an insider and outsider approach to our coding and analysis to ensure rigor and help reduce bias. Coding will be regarded as complete when consensus is achieved on each construct, aiming to achieve a high intercode reliability score between the coauthors and the outsider researcher.

Guided by the research questions and theoretical lens, a set of initial codes will be applied to the data, forming the first-order codes. There is a possibility of creating additional codes, derived from open coding [43], to gain an in-depth understanding of the impact automation has on staff and their work practices, as framed by the participants (ie, in an inductive manner). This process will be followed by performing axial coding, where codes are categorized and organized into interpretive concepts. Finally, we will perform selective coding by aggregating the second-order codes into overarching theoretical constructs. The process will involve us cross-checking our analysis and looking for contradictions instead of seeking coherent and conformity interpretations [44].

During the data collection and analysis period, the research team will meet frequently to discuss the codes, review emerging themes, and develop and question each other's ideas and underlying assumptions. The debriefings will enable us to develop a contextually specific shared understanding as well as determine a consolidated list of codes.

The quantitative data will be analyzed using quantitative analysis techniques to describe, explore, and examine the trends and relationships within the data. The results will be presented using charts and graphs to facilitate understanding.

Data Handling

Before the interviews, participants will be contacted in writing to explain the study, and they will be asked to confirm their willingness to take part, which will be taken as consent to participate. There is no need for deception of any form in the research, and an information sheet outlining the research aim, purpose, and objectives, the right to withdraw, confidentiality assurances, and researchers' contact details will be sent to all participants by email. With respect to the questionnaires, details about the study and a consent statement will be included at the start of the survey.

Data obtained from interviews will be anonymized and coded. Participants will be advised that any information given will be treated with strict confidence. All participants will be assured that their identity and names will not be included in later write-ups, work, or documents submitted or published.

Participants will be advised that they may stop being part of the study at any time without giving a reason, but information already collected by the research team will be kept.

Results

The evaluation received funding from the MPS Foundation in December 2022, and the study will last 12 months. The expected results aim to reveal the interrelationship between the autonomous clinical conversational assistant and those affected by its introduction in the pathway, seeking to understand task redesign, changes in responsibilities, impacts on well-being, tensions, benefits, and opportunities.

The implementation of AI-enabled automation relies on the trustworthiness of the system, and any sense of insecurity may be stressful to the individual, impacting their own well-being and subsequently affecting system success. Employees' attitudes and perceptions are argued to impact technology acceptance and attitudes toward change, which in turn affect the success of the intervention. Therefore, to achieve organizationally

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desired results from the adoption of AI-enabled automation technology, managers and leaders need to understand the opportunities and threats associated with its implementation and the impact this has on their workforce and their work practices.

The results from the thematic analysis of the qualitative data will be presented as the main themes that have been realized in the pre- and postimplementation phases. The data from the questionnaires will be presented in graphical format for each domain that has been assessed (Table 2 presents the questionnaire components).

Discussion

Given the rising wave of AI-enabled digital health technologies, it has become paramount that the systemic impact of implementing such initiatives on individuals and the system overall be understood. AI advancements have created new possibilities for addressing a range of health care–related problems, with the promise of a positive impact on the working lives of frontline clinicians and other health care professionals. While most of the existing research on the impact of health information technology on well-being is concerned with clinicians' EHR use, our current understanding of how AI impacts different members of staff and their roles and responsibilities remains opaque [25].

The primary aim of this study is to examine the real-world impact of AI-enabled automation on clinicians and health care professionals who provide health care to patients in high-volume, low-complexity perioperative care pathways. The results aim to shed light on concerns stakeholders have regarding automation and the use of telemedicine solutions, perceived benefits, and how the intervention impacts their work practices, if at all. The study will also highlight critical sociotechnical factors impacting adoption and whether there are any differences across different members of the health care workforce, which may allude to how managers can successfully integrate such technology into their organization and address the impact of such challenges. The study aims to bring original and novel contributions to the current body of knowledge as well as yield critical practical implications.

A few limitations have been identified. First, the study will be conducted within the specific research setting of the United Kingdom; therefore, some findings and interrelationships between them may be mainly applicable to contexts that are similar to the United Kingdom. Another limitation, and possibly an interesting direction of future research, is that although we aim to explore perceptions and experiences before and after implementation, there is opportunity to explore if there are any further changes over time and how these affect usage and deployment as the system becomes further embedded into the context.

Acknowledgments

This work was supported by The MPS Foundation Grant Programme. The MPS Foundation was established to undertake research, analysis, education and training to enable health care professionals to provide better care for their patients and improve their own well-being. To achieve it supports and funds research across the world that will make a difference and can be applied in the workplace.

Data Availability

Data sharing is not applicable to this paper, as no data sets were analyzed for the creation of this study protocol.

Conflicts of Interest

SK, AH, EL, and NDP are employees of Ufonia Ltd. LAC is funded by the National Institute of Health (NIBIB R01 EB017205).

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Abbreviations

AI: artificial intelligence
COREQ: Consolidated Criteria for Reporting Qualitative Research
EHR: electronic health record
NHS: National Health Service
NHS-SE: National Health Service–South East
STS: sociotechnical system
WHO: World Health Organization

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Protocol

A Christian Faith-Based Facebook Intervention for Smoking Cessation in Rural Communities (FAITH-CORE): Protocol for a Community Participatory Development Study

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Abstract

Background: Tobacco smoking remains the leading cause of preventable morbidity and mortality in the United States, with significant rural-urban disparities. Adults who live in rural areas of the United States have among the highest tobacco smoking rates in the nation and experience a higher prevalence of smoking-related deaths and deaths due to chronic diseases for which smoking is a causal risk factor. Barriers to accessing tobacco use cessation treatments are a major contributing factor to these disparities. Adults living in rural areas experience difficulty accessing tobacco cessation services due to geographical challenges, lack of insurance coverage, and lack of health care providers who treat tobacco use disorders. The use of digital technology could be a practical answer to these barriers.

Objective: This report describes a protocol for a study whose main objectives are to develop and beta test an innovative intervention that uses a private, moderated Facebook group platform to deliver peer support and faith-based cessation messaging to enhance the reach and uptake of existing evidence-based smoking cessation treatment (EBCT) resources (eg, state quitline coaching programs) for rural adults who smoke.

Methods: We will use the Integrated Theory of Health Behavior Change, surface or deep structure frameworks to guide intervention development, and the community-based participatory research (CBPR) approach to identify and engage with community stakeholders. The initial content library of moderator postings (videos and text or image postings) will be developed

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using existing EBCT material from the Centers for Disease Control and Prevention Tips from Former Smokers Campaign. The content library will feature topics related to quitting smoking, such as coping with cravings and withdrawal and using EBCTs with faith-based message integration (eg, Bible quotes). A community advisory board and a community engagement studio will provide feedback to refine the content library. We will also conduct a beta test of the intervention with 15 rural adults who smoke to assess the recruitment feasibility and preliminary intervention uptake such as engagement, ease of use, usefulness, and satisfaction to further refine the intervention based on participant feedback.

Results: The result of this study will create an intervention prototype that will be used for a future randomized controlled trial.

Conclusions: Our CBPR project will create a prototype of a Facebook-delivered faith-based messaging and peer support intervention that may assist rural adults who smoke to use EBCT. This study is crucial in establishing a self-sufficient smoking cessation program for the rural community. The project is unique in using a moderated social media platform providing peer support and culturally relevant faith-based content to encourage adult people who smoke to seek treatment and quit smoking.

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KEYWORDS

community; participatory; community-based participatory research; faith; smoking cessation; Facebook; social media; mobile phone

Introduction

Background and Significance

Tobacco smoking remains the leading cause of preventable morbidity and mortality in the United States, contributing to approximately 480,000 premature deaths annually [1]. This comes at a high economic cost to our society. Data from a recent national report showed that smoking-related illnesses cost the United States over US $600 billion in 2018 [2]. Evidence-based smoking cessation treatments (EBCTs) are greatly underused by people who smoke. For example, the use of state quitline coaching programs and pharmacotherapy enhances smoking quit attempts and cessation [3], but many people who smoke are unaware of or do not use state quitlines [4-6]. Schauer et al [7] analyzed data from the 2009 to 2010 National Adult Tobacco Survey and found that quitline awareness was 53.9% among people who smoke. Further, among individuals who attempted to quit smoking in the past year and had knowledge of the quitline's existence, their use rate was only 7.8%. Therefore, efforts to improve access, information, and acceptance of EBCTs are required.

Significant rural-urban disparities exist in the United States concerning tobacco smoking, smoking-related health outcomes, and smoking cessation treatment access. Adults who live in rural areas of the United States have among the highest tobacco smoking rates in the nation and experience a higher prevalence of smoking-related deaths and deaths due to chronic diseases for which smoking is a causal risk factor [8]. Trends from the last several years show that rural areas experience higher rates of smoking-related chronic diseases than their urban counterparts [9,10]. Compared to urban residents, people living in rural areas are generally older, have lower adherence to preventative screening [10-12], and face significant treatment barriers related to social determinants of health, which puts them at a higher risk of developing chronic diseases [13,14]. A lack of health care specialists in rural areas further exacerbates these barriers to seeking care [15,16]. For example, a recent study by the Centers for Disease Control and Prevention (CDC) found that people living in rural areas had lower rates of cancer diagnoses but experienced higher death rates for all cancer types when compared to people living in nonmetropolitan and metropolitan areas, highlighting rural patients' challenges in accessing necessary health care [17]. Rural communities face tobacco-related disparities that expose them to difficulty seeking access to smoking cessation treatment support, ultimately leading to a higher prevalence of chronic diseases. For example, rural communities have a higher rate of cigarette smoking than urban areas, a trend observed for both women (rural vs urban: 25% vs 13%) and men (rural vs urban: 29% vs 19%), but tobacco control policies and cessation efforts tend to favor urban areas more than rural areas [8]. Due to difficulties such as geography, infrastructure, and corporate barriers, those living in rural areas have difficulty accessing tobacco cessation services [8].

One approach for improving access and overcoming barriers to engagement in underserved populations is through the use of digital technology and social media platforms. There has been a growing recognition that leveraging digital technology could encourage the positive behavior change necessary to quit smoking and manage chronic conditions like cancer and heart disease. By doing so, barriers that impede access to EBCT can be lessened [18]. For example, the use of social media, such as Facebook, could be used to deliver smoking cessation behavioral interventions such as motivational interviewing (MI) and peer support and encourage the use of EBCT interventions. Facebook is the most used social media platform in the United States and has a broad reach. It promotes engagement and connection among peers that can be used in smoking cessation efforts at a relatively low cost. In addition, Facebook is a helpful tool for supporting smoking cessation through online communication and sharing of experiences among users. The experience allows users and study staff to share intervention-related pictures, videos, and images to encourage discussion. This represents a distinct advantage over face-to-face approaches or web-based services [19,20]. In recent years, many studies have used social media, including Facebook, for smoking cessation interventions. However, the use of Facebook to deliver EBCT with a

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faith-based component developed by the community-based participatory research (CBPR) approach is lacking.

Another approach to improve access and uptake of evidence-based interventions is by culturally adapting them to fit the specific needs and contexts of individuals who underuse them. Studies have shown that the implementation of EBCT with community co-design and engagement enhances its receptivity and uptake [21]. One such effective approach is CBPR, a model that equitably involves community members, organizations, and academic researchers in all aspects of the research process. As a result, all partners can contribute their expertise with shared ownership and responsibility; knowledge gained is enhanced, and action is integrated to improve community members' health and well-being [22]. Evidence also shows that culturally relevant messaging delivered through CBPR approaches increases [23,24] study recruitment, EBCT resources acceptance, and cessation rates [25-27]. This approach is particularly important for hard-to-reach marginalized rural populations, by empowering them to be agents of maintained change in their communities. Therefore, our study will use the CBPR strategy to center rural end users to co-design the intervention to promote its maintainability and lasting impact in the rural community.

Numerous research studies have evaluated the effect of spirituality and religious beliefs on positive health behaviors. For example, these beliefs may help to reduce stress through engagement with coping skills and lifestyle factors such as improved diet, attendance to preventive care, exercise, and reduction in alcohol drinking, and so forth, which ultimately improves cardiovascular health and general well-being [28-31]. In addition, many studies have shown a negative correlation between faith-based involvement and cigarette smoking [32-37]. Research suggests that individuals participating in faith-based activities are less likely to smoke or begin smoking in the future [37,38]. Whooley et al [37] found that nonsmoking individuals who attended religious services less than once a month were at twice the risk of starting smoking compared to those who attended services regularly over 3 years. In addition, a study conducted by Kim et al [39] among Korean men found that church attendance may assist individuals in quitting smoking due to social prohibitions from other members of the congregation. The mechanism behind this phenomenon is theorized that religious attendance offers spiritual support, an essential source of resiliency, and reduces stress [31] that would otherwise perpetuate cigarette smoking [40]. In addition, faith-based congregants may provide peer support in the smoking cessation journey [31,41]. Since religious participation offers an avenue for smoking cessation and the faith-based CBPR approach has not been thoroughly evaluated among the rural population for smoking cessation, our study attempts to fill this research gap.

Participants' access to clinical trials in rural areas can be a challenge due to transportation barriers in traveling to clinical trial centers and the difficulties associated with spending several hours away from daily wages to participate in research studies. Therefore, participation rates in rural substance use treatment clinical trials are low. Decentralization of clinical trials using digital tools, as we propose in this study, could mitigate this problem.

Study Aims and Objectives

In this report, we describe a study protocol focused on developing and beta testing an innovative faith-based Facebook intervention for rural smokers. The overall objective of this study is to develop a private, moderated, faith-based Facebook group intervention platform using peer and pastoral support for rural people who smoke to enhance the use and reach of existing EBCT resources.

Our study-specific aims are (1) to describe the process we will use to develop a faith-based Facebook group intervention for smoking cessation that promotes access to and use of EBCT using the CBPR approach and (2) to assess the preliminary feasibility and uptake of the intervention with a 1-month beta test.

Methods

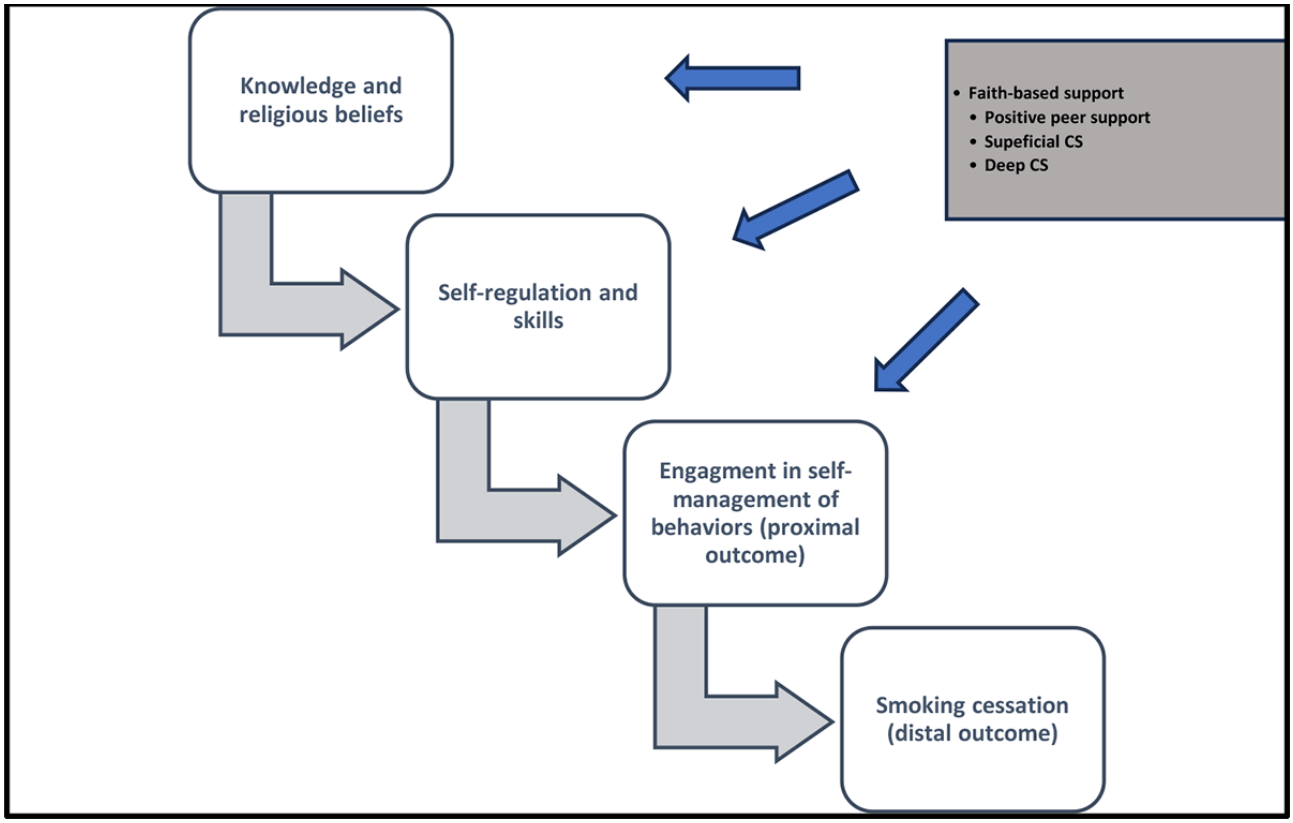
Theoretical Framework

We will use the Integrated Theory of Health Behavior Change (ITHBC) [42] and surface or deep structure [43] frameworks as guidance for intervention development (Figure 1). According to the ITHBC framework, an individual is more likely to engage in a behavior change when they understand the disease-related risk factors they are indulging in and if treatment recommendations (including minimizing risk factors) align with their personal beliefs. Therefore, the content of our intervention will be evidence-based (EBCT in this case) and will be prepared to increase the participants' knowledge about chronic diseases and their risk factors, such as smoking, to enhance their self-efficacy, outcome expectations, and goal congruence.

Self-regulation, a second key factor in making a behavior change, may be enhanced through increased knowledge and reflection on one's beliefs. Self-regulation involves setting goals, monitoring, reflecting, decision-making, planning, execution, self-evaluation, and managing emotions during change. We will design intervention content to facilitate self-regulation through Facebook posts aimed at increasing knowledge about smoking cessation content (eg, thoughts, intentions, and actions) in congruence with faith-based beliefs.

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Figure 1. Theoretical framework. CS: cultural sensitivity.



The third construct, social facilitation, involves social support that encourages behavior change. Participants will receive supervised social support through Facebook engagement with peers on the same journey of smoking cessation. Before the desired outcome (distal outcomes) of smoking cessation, the individual will engage in several self-management behaviors (proximal outcomes), such as calling the state quitline and engaging in Facebook conversations and posts that take them to their final or distal outcome of smoking cessation. For this study, we plan to develop an intervention that will target proximal outcomes (distal outcomes not the scope of this study) of self-management behaviors, measured by actions such as calling a quitline and engaging in Facebook conversations and posts. As noted earlier, since proximal outcomes are influenced by an individual's knowledge, beliefs, and self-regulation skills, we will use evidence-based material and faith-based messages to facilitate proximal outcomes.

To ensure our messages are culturally aligned and faith-based, we will use the surface and deep structure framework [44,45]. Surface structure considers observable social and behavioral characteristics of participants, such as race, gender, and family structure, while deep structure takes into account cultural beliefs and values. Finally, we will use a planning framework based on the CDC recommendations for developing social media and other digital health communication tools [46] to guide the critical content components of Facebook messages, consistent with behavioral therapy.

Study Design

The study will use the CBPR approach and will be conducted at Mayo Clinic Health System, Eau Claire, Wisconsin. Before the start of the study, several small-group in-person and online meetings were held in the community with faith-based leaders of local churches to gauge their interest in forming a partnership and brainstorming the study idea. The local faith-based leaders agreed to collaborate and participate in the review of the study design and intervention materials and provide general input on faith-based topics. The pastors were informed that they will be part of the "core research team" and will approve documents including manuscripts, flyers, and other materials before publication and community dissemination. Our other partners for this study included the Mayo Clinic Center for Clinical and Translational Science (CCaTS), community engagement and rural health programs, and the Center for Health Equity and Community Engagement Research (CHCR) that will facilitate the formation of a community advisory board (CAB) and engage the services of the community engagement (CE) studio to get community feedback on the development of the intervention.

Recruitment

Community Advisory Board

The CAB will consist of 10-12 individuals from the community. We will ensure that the board comprises diverse individuals from different sexes, races, and age groups with fair representation. Print and e-flyers highlighting roles and responsibilities will be used to facilitate recruitment. The flyers will be posted on the Mayo Clinic display board and emailed or mailed to the community partner organizations, including church partners. CAB members will receive an honorarium of US $150 per meeting.

CE Studio

CHCR staff will assist in recruiting CE studio members, consisting of community members who represent end users of

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the intervention. Advertisement flyers will be used to facilitate the recruitment. The CE studio will consist of 6-8 rural community experts who will join a 1-time 90-minute online meeting to give feedback on the content of smoking cessation material for the faith-based Facebook intervention. Eligibility criteria for participation are as follows: (1) aged >18 years, (2) lives in the rural area of Wisconsin or Minnesota, (3) smoked at least 1 cigarette per day over the past 7-day period, and (4) Christian faith. Community experts will receive a US $50 visa card for their time.

Beta Test

A Facebook group size of 10 was the minimum number for optimal engagement in previous studies [47,48]. Thus, we will beta test the Facebook group with an estimated purposeful sample of 15 individuals who currently smoke and attempt to ensure that the sample comprises diverse individuals from different sexes, races, and age groups with fair representation. A 1-page information sheet or flyer codeveloped with the core research team and CAB will be posted on the Mayo Clinic display board and emailed or mailed to the community partner organizations, including local church partners. Study staff will administer an initial set of screening questions over the phone to screen for eligibility.

The eligibility criteria for participation are (1) aged >18 years; (2) smoked at least 1 cigarette per day over the past 7-day period; (3) have access to the internet on a mobile phone, computer, or tablet; (4) willing to create a Facebook account and willing to participate in the Facebook intervention for 1 month; and (5) either self-identify as a person of Christian faith or recognize that study posts will include Christian faith-based content, including Bible verses. Ineligible individuals (positive for smoking but unwilling to engage with Facebook intervention) will receive EBCT referral information via postal mail (printed materials) or email. The material will include information on their state tobacco quitline. Participants will also receive information on the National Cancer Institute's free population-level smokefree.gov website resources. The website, tailored to all readiness levels to quit smoking, includes a quitting guide, texting program, smartphone apps, online live chat, URL, and a toll-free number (1-800-QUIT-NOW) for state quitlines [26].

Procedures

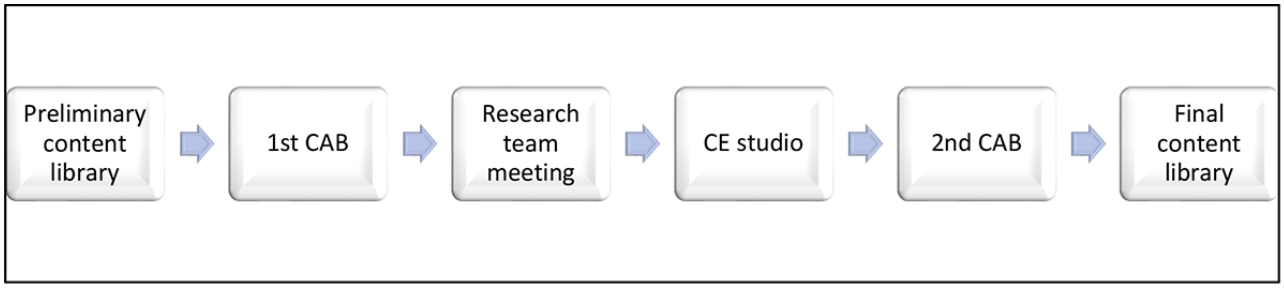
Phase 1: Intervention Development

Our research team is comprised of rural health, substance use, and health disparities researchers, pastors from local churches, and rural patient advocates from the Mayo Clinic enterprise. We will compile the initial items for the content library by drawing on empirical research, existing literature, and our research team's combined clinical research and pastoral experience. We will use existing EBCT videos and other content postings from the CDC Tips from Former Smokers Campaign that promote the use of EBCTs to various disparate groups, including rural people who smoke. The preliminary content library will feature various topics related to quitting smoking, such as dealing with stress, nicotine withdrawal, cravings, personal health, and culturally relevant activities that can help smokers quit associated with relevant faith-based messages or bible quotes, for example, how prayer, faith, connection to others, grace, temptation, patience, forgiveness, and so forth, can support with the use of evidence-based smoking cessation intervention. The content topic will also discuss motivations for quitting, like the importance of family and preventing relapse, and encouraging EBCT, such as using state quitlines and pharmacotherapy. Each topic will have corresponding Facebook posts in text and embedded videos and images. Further, for each topic of content, a sample of the supplementary text is provided for Facebook group moderators (who will oversee the posting and engage participants in conversation) and a probe for generating further discussion or ways to respond to users' questions. Facebook group moderators will select posts based on ongoing group conversations and respond to individual posts and queries while posting for the entire group.

Phase 2: Community Members' Feedback

The preliminary content library will be evaluated for content validity through the guidance and advice obtained from CAB members and a CE studio [49,50]. The community feedback process consists of 3 critical steps. First, we will conduct a CAB meeting to gather feedback and input on the preliminary content library. The core research team will use this feedback to revise the content library further. Second, the CE studio will be used to obtain additional feedback on the revised content library. Finally, we will conduct the second and final CAB meeting, where we will thoroughly discuss the feedback provided by the CE studio and how we implemented feedback from the first CAB meeting. Their consolidated feedback will be incorporated with input from the core research team, and the content library will be considered final (Figure 2).

Figure 2. Community engagement plan for the development of the content library. CAB: community engagement board; CE: community engagement.



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Community Advisory Boards

Each CAB member will receive the meeting agenda, an electronic version of the preliminary content library, and the Zoom (Zoom Video Communications) meeting link in preparation for the online meeting. The online CAB meeting will last for approximately 90 minutes and will be recorded. During the meeting, the study's principal investigator, PS, will summarize the study and facilitate introductions among the attendees. In addition, PS will present each topic within the preliminary content library and facilitate the discussion. During the discussion, each topic will be displayed, and members will provide feedback on the selected images or video, the bible quotes and their alignment with the associated Facebook post, and overall post understandability and relevance to the topics. Study staff (BT and CK) will take detailed meeting notes. The CAB members will also have an opportunity to provide open-ended feedback.

CE Studio

The CE studio will be a 90-minute online meeting facilitated by the CHCR staff. A CHCR staff will begin the meeting with introductions, and then PS will provide a 10 to 15-minute presentation of the study, and a CHCR staff will facilitate the discussion. Similar to the CAB, each topic will be displayed during the discussion, and community experts will provide feedback on the selected images or video, the bible quotes and their alignment with the associated Facebook post, and overall post understandability and relevance to the topics. A CHCR staff will take detailed notes and provide a summary at the end of the CE studio.

Phase 3: Prototype Development and Moderator Training

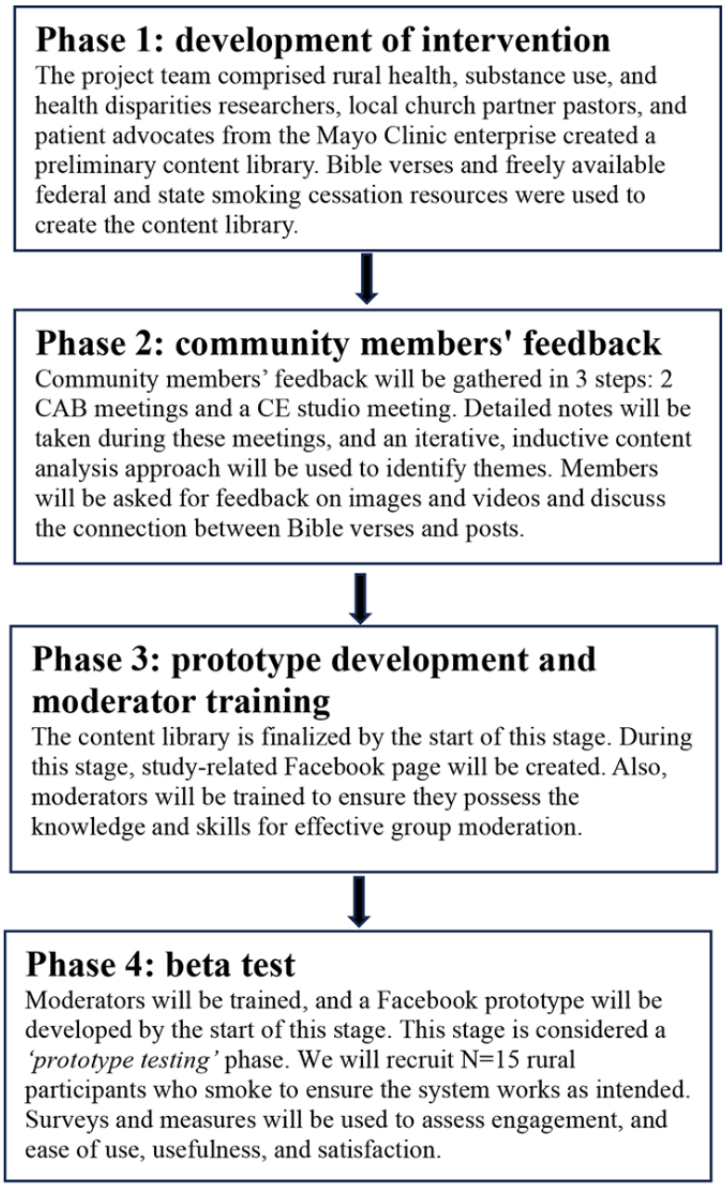
The Mayo Clinic Social Media Department will assist in creating a study-related Facebook page. The group will be private, hidden, and moderated to facilitate confidentiality. By this stage, the content library will be finalized, and additional postings, including Bible verses and images, will be added on an as-needed basis based on insights and feedback from CBPR processes. The moderators' interactions with group members are critical for sparking conversation among the group members. As a result, we will choose moderators who have knowledge of the Christian faith and are familiar with Bible verses. Given that our research team includes pastors from local churches, they will be consulted on an ongoing basis by the moderators if any guidance is required. The moderators will receive comprehensive training to ensure they possess the knowledge and skills for effective group moderation. The training will cover the principles of moderation, including the best ways to engage participants, promote appropriate conversations, and redirect engagement [51,52]. They will also be trained to handle challenging situations that may arise in a web-based group. Additionally, the moderators will participate in didactic training to learn basic communication principles, such as active listening, MI, and cognitive behavioral therapy. The ultimate goal is group participant interaction and partaking. Therefore, moderators will be encouraged to help generate daily interaction among members and not just post the content daily. Moderators will post 1 selection from the intervention content library every 1-2 days. In order to stimulate engagement from participants, the moderators will reply to the posts with 1-2 prompt questions (included in the content library) directed at specific individuals and using MI techniques. They will check the group several times daily to engage with participants and address inappropriate content or misinformation.

Phase 4: Beta Test

After completing baseline assessments, eligible participants will be emailed an invite link to the intervention Facebook group. Participants will be given instructions on how to register on Facebook. Those who already have a Facebook account can either create a new user profile or use the existing one to join the group. The research staff will ensure that the participants enroll in the group within 24 hours of receiving the link. If participants experience technical difficulties, the staff will assist them. The smokefree.gov resources will also be mailed to the participants. This phase will expose participants to 30 days of moderator postings and obtain feedback to ensure the system works as intended. In addition, we will conduct a preliminary assessment of feasibility and intervention uptake (engagement) to facilitate any needed refinements prior to future randomized controlled trial (RCT) (Figure 3).

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Figure 3. Overview of the process to develop faith-based Facebook intervention prototype and beta test to help rural people quit smoking. CAB: community advisory board; CE: community engagement.



Measures

Overview

For aim 2, the beta testing phase, we will use an internet-based survey to measure the following. The participants in this study will receive a survey via email through REDCap (Vanderbilt University). The survey will be open for 7 days, and participants will receive 2 reminders to complete it. The email address on file is required for this process.

Baseline Smoking Characteristics

We will assess the average number of cigarettes per day, the age when the person started smoking, pack-years of smoking, the number of days the person smoked in the past 30 days [53], readiness to quit using the contemplation ladder [54], the average number of quit attempts in the past 30 days, and other commercial tobacco and nicotine product use.

Baseline Sociodemographic Characteristics

Sociodemographic measures selected from the PhenX Toolkit assessed age, sex, gender, ethnicity, race, education, employment status, and marital status [55].

Study Recruitment and Retention

Recruitment feasibility measures include the number of potential participants screened, the number of eligible participants, and the number of enrolled participants from the eligibility pool. Additionally, study retention will be evaluated by determining the proportion of participants who complete postintervention assessments.

Treatment Satisfaction

The satisfaction with the Facebook intervention will be measured in three domains: (1) perceived ease of use, (2) usefulness, and (3) satisfaction by using the Usefulness, Satisfaction, and Ease of Use (USE) questionnaire. The scale contains 13 items and participants will rate these items on a

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5-point Likert scale, ranging from 1 (strongly disagree) to 5 (strongly agree). We will examine the Facebook intervention engagement patterns using Facebook metrics and qualitatively explore common topics that emerged in participant postings [56]. Additionally, we will include open-ended questions to gather more detailed feedback from users.

Intervention Uptake or Engagement

In order to measure the adoption of our intervention, we will use Facebook's objective engagement metrics such as views, reactions (such as likes and loves), comments, posts, and poll votes (where participants can make multiple selections). By calculating the total number of times participants engaged with the intervention, we can accurately assess its uptake.

Statistical Analysis

Aim 1 will have 2 CAB meetings and 1 CE studio session. Members will be asked to provide helpful feedback on the content's flow, understandability, and relevance. Detailed notes will be taken during these meetings, and an iterative, inductive content analysis approach will be used to identify themes. A total of 2 investigators will work together to code the responses, and a third investigator will resolve any disagreements until a consensus is reached. Aim 2 will summarize sample characteristics, social media usability measures, and most and least preferred concepts using descriptive statistics, including means, percentages, and frequencies. Open-ended responses will be summarized, and themes will be generated using content analysis as described in aim 1.

Missing Values

Because assigning missing data as smoking is not necessarily a conservative approach [57], we will also explore multiple imputation methods [58,59] to classify lost to follow-up as cigarette smokers or nonsmokers and conduct sensitivity analyses as appropriate.

Ethical Consideration

The study was deemed exempt by the Mayo Clinic Institutional Review Board (23-000837). The CAB members will receive a US $150 honorarium. CE studio community experts will receive US $50. The participants will receive US $25 for completing the baseline assessment and US $25 for the postintervention assessment. For the beta test phase, study data will be deidentified.

Results

The results of this project will lead to the development of a faith-based smoking cessation content library. In addition, we are planning a pilot 2-arm parallel group, RCT, which will include evaluation of control (mailed materials and smokefree.gov information) versus Facebook intervention (information mailed to the control group plus Facebook intervention developed during this study) among diverse populations.

Discussion

Principal Findings

Our study focuses on collaborating with community stakeholders to co-design a faith-based, peer-supported Facebook-delivered intervention prototype to address smoking cessation among rural people who smoke. This study is essential to a self-maintaining smoking cessation program for the rural population. We believe that Facebook group moderation is an important component of this program to increase participant engagement and provide behavioral support and access to cessation treatment resources and service linkages when required. In addition, the supervised Facebook group may lead to better peer support among participants who can learn from each other's experiences and share their smoking cessation journey.

No such Facebook group exists that uses faith-based support as a component and encouragement to use EBCTs such as quitlines and cessation pharmacotherapy. During the preliminary meetings, our community stakeholders have shown interest in being trained as moderators and ensuring the continuity of the proposed Facebook group so that the intervention is self-maintained within the community once the study is over.

Limitations

Our sample is restricted to the Midwest population and stakeholders, which may limit the generalizability to other rural populations. However, this phase is focused on prototype development, and future pilot study steps will pave the way toward larger, more generalizable evaluations of digitally enhanced interventions. Our study will recruit individuals with access to the internet and smart devices to access Facebook, which may lead to selection bias. For future studies, investigators may consider providing a loaner digital device to participants with no digital access to eliminate this selection bias.

Conclusions

Our study will provide preliminary steps, including possible challenges before the RCT for a faith-based, Facebook-delivered EBCT intervention for rural populations that smoke. Our study has a broader interest in faith-based stakeholders and potentially be self-maintainable within the community. This approach can potentially support rural communities by granting them access to community-based health care that is maintainable. Our study design has the capability to provide a tailored online intervention with fidelity. Furthermore, our study uses existing federal and state EBCTs, using available resources to aid in smoking cessation.

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Conflicts of Interest

None declared.

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Abbreviations

CAB: community advisory board
CBPR: community-based participatory research
CCaTS: Center for Clinical and Translational Science
CDC: Centers for Disease Control and Prevention
CE: community engagement
CHCR: Center for Health Equity and Community Engagement Research
EBCT: evidence-based smoking cessation treatment
ITHBC: Integrated Theory of Health Behavior Change
MI: motivational interviewing
RCT: randomized controlled trial
USE: Usefulness, Satisfaction, and Ease of Use

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Protocol

NephroCAGE—German-Canadian Consortium on AI for Improved Kidney Transplantation Outcome: Protocol for an Algorithm Development and Validation Study

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Abstract

Background: Recent advances in hardware and software enabled the use of artificial intelligence (AI) algorithms for analysis of complex data in a wide range of daily-life use cases. We aim to explore the benefits of applying AI to a specific use case in transplant nephrology: risk prediction for severe posttransplant events. For the first time, we combine multinational real-world transplant data, which require specific legal and technical protection measures.

Objective: The German-Canadian NephroCAGE consortium aims to develop and evaluate specific processes, software tools, and methods to (1) combine transplant data of more than 8000 cases over the past decades from leading transplant centers in Germany and Canada, (2) implement specific measures to protect sensitive transplant data, and (3) use multinational data as a foundation for developing high-quality prognostic AI models.

Methods: To protect sensitive transplant data addressing the first and second objectives, we aim to implement a decentralized NephroCAGE federated learning infrastructure upon a private blockchain. Our NephroCAGE federated learning infrastructure enables a switch of paradigms: instead of pooling sensitive data into a central database for analysis, it enables the transfer of clinical prediction models (CPMs) to clinical sites for local data analyses. Thus, sensitive transplant data reside protected in their original sites while the comparable small algorithms are exchanged instead. For our third objective, we will compare the performance of selected AI algorithms, for example, random forest and extreme gradient boosting, as foundation for CPMs to predict severe

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short- and long-term posttransplant risks, for example, graft failure or mortality. The CPMs will be trained on donor and recipient data from retrospective cohorts of kidney transplant patients.

Results: We have received initial funding for NephroCAGE in February 2021. All clinical partners have applied for and received ethics approval as of 2022. The process of exploration of clinical transplant database for variable extraction has started at all the centers in 2022. In total, 8120 patient records have been retrieved as of August 2023. The development and validation of CPMs is ongoing as of 2023.

Conclusions: For the first time, we will (1) combine kidney transplant data from nephrology centers in Germany and Canada, (2) implement federated learning as a foundation to use such real-world transplant data as a basis for the training of CPMs in a privacy-preserving way, and (3) develop a learning software system to investigate population specifics, for example, to understand population heterogeneity, treatment specificities, and individual impact on selected posttransplant outcomes.

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KEYWORDS

posttransplant risks; kidney transplantation; federated learning infrastructure; clinical prediction model; donor-recipient matching; multinational transplant data set

Introduction

End-stage kidney disease is growing globally affecting already up to 800 million (10%) people worldwide. Dialysis or kidney transplantation are current options for renal replacement therapy. There are 100,000 dialysis patients in Germany, and 50,000 in Canada [1,2]. In total, 1992 kidney transplantations in Germany and 1673 kidney transplantations in Canada were performed in 2021 [3,4]. Kidney transplantation is the preferred way of renal replacement therapy because it improves the quality of life for patients, extends life expectancy, and saves resources of the health care system [5-7]. However, there is a shortage in donor organs. As a result, in total 6593 patients in Germany and 3060 in Canada were on a waiting list for a suitable donor kidney in 2021 [4,8]. Despite the advances in medicine and improvement of short-term graft survival rates within the first year, long-term graft survival remains stagnant. It shows an attrition rate of approximately 5% annually after the second year resulting in reinitiation of dialysis or transplantation in approximately 50% of patients after 10 years [2,9]. After transplantation, regular follow-up visits especially in the first year are required to detect and prevent fatal outcomes, for example, infections, kidney rejections, or cancer due to over- or underimmunosuppression. Today, nephrologists lack adequate diagnostic measures for assessing and stratifying the individual patient's risk for posttransplant outcomes, for example, graft failure or rejection [10]. Early detection of patients at high risk would open an additional prevention path: clinicians would have the opportunity to initiate countermeasures earlier and prevent fatal outcomes.

The NephroCAGE consortium was initiated as a strategic lighthouse project supported by the national governments of Germany and Canada to combine medical and technical expertise to build a real-world demonstrator and evaluate the added value of artificial intelligence (AI) in a very specific medical use case from nephrology. It brings together worldwide excellence from transplant centers, academia, and industry from Germany and Canada to join forces as depicted in Figure 1. In total, 4 major clinical kidney transplant centers from both nations have contributed transplants to form the first-of-its-kind international NephroCAGE data set; it forms a longitudinal database of patient-level data from more than 8000 transplant cases over the past 2 decades. The NephroCAGE data set builds the foundation for detailed retrospective data analysis using AI learning techniques and the development of clinical prediction models (CPMs) for prospective identification of posttransplant outcomes of kidney transplant patients. With the help of the CPM predictions, clinicians are expected to improve the quality of care for future patients with kidney disease in Canada, Germany and worldwide by identifying individual patient risks even earlier than possible today.

Immunological differences play a key role in the development of organ rejection reactions, which might lead to graft failure or even graft loss [11,12]. It has been proven that transplant patients sharing compatible serologic human leukocyte antigen (HLA) types with the organ donor have better outcomes compared to patients with incompatible HLA types [13]. Today, only a subset of HLA genes is considered for matching of immunological factors from donors and recipients. The HLA genes located on chromosome six are responsible for encoding of proteins that fold complex structures, so-called epitopes. Today, it is known that checking for HLA compatibility requires in addition to pure genetic information also the assessment of the protein's 3D structure, which might trigger immunological response. However, current organ allocation algorithms in productive use include only very limited aspects of HLA compatibility, for example, number of mismatches per HLA, to reduce the immunological risk for graft rejection and donor-specific HLA antibodies [14,15]. Recently, new matching methods have been developed to optimize assessment of organ compatibility between donors and recipients incorporating more functional aspects, for example, on biological level and additional molecular specifics [16-18]. Selected methods showed improved precision in predicting immunological risk, some of them being also relevant for organ allocation [11,17,19,20].

The NephroCAGE consortium aims to show advantages of using molecular compatibility for matching of organ donors and recipients. Therefore, we aim to incorporate the latest research results on B cell and T cell epitope matching as a specific feature of our CPMs. Furthermore, we will investigate

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the applicability of tree-based machine learning (ML) algorithms such as random forest (RF) and Extreme Gradient Boosting as a foundation for the development of CPMs trained on real-world transplant data in nephrology.

Therefore, access to high-quality real-world data is crucial to train and validate high-quality AI models for clinical use. At the same time, clinical data are considered as highly sensitive data, which typically cannot be exposed for training of AI models. The NephroCAGE consortium as the first of its kind has access to multicenter transplant data from 2 nations for the development of AI-based CPMs. One of our hypotheses is that AI-based CPMs combining both clinical and immunological data will lead to improved detection of patients at high risk for graft loss and rejection. Conversely, we will focus on data from patient follow-ups and immunological data, for example, presence of donor-specific antibodies (DSA) for HLA.

Over the past decades, hospitals and transplant centers have developed individual clinical information systems for management of their transplant patient data. As a result, data are scattered across multiple silos using various data formats, which makes multisite research a complex data management task. Thus, the use of standardized data formats, common data dictionaries, shared terminologies and ontologies, and open application programming interfaces (APIs) are required to facilitate the deployment and integration of innovative AI-based solutions into existing clinical IT systems.

Combining data from multiple clinical data sources for development of CPMs traditionally involves complex data preprocessing steps, for example, data harmonization, data transformation, enable semantic interoperability, legal agreements, and data privacy measures [21]. The use of a federated learning infrastructure (FLI) turns around the paradigm of centralized data storage: it enables transfers of algorithms to the data to perform local data processing, thereby keeping data at its original protected location [22,23]. In a decentralized FLI, network nodes located at collaborating transplant centers communicate on a peer-to-peer basis, that is, all network communication is performed between individual network partners without the need for any central instance. This raises the questions about how access control to the nodes is enforced, how CPMs are trained, and how to exchange CPMs between sites. Recently, distributed ledger technology (DLT) emerged to guarantee immutable transactions between untrusted parties. These transactions are kept in a consistent state through automated, algorithm-based consensus-building mechanisms, which eliminates the need for third-party trust enforcement [24]. The aggregation of models in FLIs, that is, the combination of individual CPM versions from different partners, is well-established for parameter-based AI approaches such as neural networks. However, only limited research investigates the aggregation of tree-based or kernel-based AI approaches, such as RFs or support vector machines, which are relevant for the given nephrology use case.

Figure 1. For the first time, the NephroCAGE consortium brings experts from nephrology, academia, and industry on both sides of the Atlantic Ocean together to investigate privacy-preserving ways to enable combination of real-world transplant data from Germany and Canada for design of clinical prediction models to predict the patient-specific probability for severe posttransplant risks.



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Methods

NephroCAGE Consortium

The founding partners of the German-Canadian NephroCAGE consortium are depicted in Figure 1 and their functions in the consortium are outlined in the following:

- Transplant centers: Charité – Universitätsmedizin Berlin, McGill University Health Centre and Centre Hospitalier de l'Université de Montréal both located in Montréal, Quebec, Canada, and Vancouver General Hospital of the University of British Columbia are internationally known hospitals, each of them with kidney transplant centers covering large patient populations. For example, Charité performs about 200 transplants per year and covers major parts of North-Eastern Germany. Our hospital partners provide access to real-world clinical data, which is key for training and evaluation of CPMs. Furthermore, they provide access to clinical subject-matter experts, drive the clinical focus and lead the development of a clinical demonstrator to evaluate our findings.
- Academia: All university hospital partners are universities affiliated. Furthermore, the Karlsruhe Institute of Technology and the Hasso Plattner Institute for Digital Engineering contribute international expertise in software engineering, AI technology, and digital health. Academic partners contribute through applying the latest AI research findings for building CPMs and to design and implement the NephroCAGE FLI enabling a privacy-preserving way of combining transplant data.
- Industry: PIRCHE AG is an internationally operating company headquartered in Berlin, Germany, having expertise in donor-recipient HLA molecular compatibility assessment. Thus, PIRCHE will work on integration of molecular donor-recipient matching incorporating HLA data from HLA laboratories.

Ethical Considerations

All methods were carried out in accordance with relevant guidelines and regulations in the participating countries Germany and Canada. The project was approved by the following ethics committees: (1) Charité – Universitätsmedizin Berlin (EA4/104/21) and (2) Research Ethics Board of the McGill University Health Centre and Centre Hospitalier de l'Université de Montréal research center (MP-37-2022-8003). Available data are retrospective data obtained from patients, who gave their informed consent prior to their transplantation for the use of their data for retrospective analyses. All data will be handled in accordance with the corresponding data protection regulations, that is, the European General Data Protection Regulation and the Personal Information Protection and Electronic Documents Act, respectively. Data access was given to clinicians after deidentification only. Prior to the use of data for CPM training, data were in addition pseudonymized to minimize any eventual reidentification risk. There were neither specific compensations nor benefits provided to patients by the NephroCAGE consortium for the use of their data. We use retrospective data, which were gathered during routine care.

NephroCAGE Data Set

Table 1 provides an overview of the NephroCAGE data set, which consists of more than 8000 transplant patient cases across the past 2 decades with an average age of 51.7 years. Approximately two-thirds of the transplanted patients in our data set are male and one-third are female patients, which aligns with the sex distribution known from related studies [25]. Table 2 provides a summary of available categories of transplant data in our NephroCAGE data set.

Data of transplant patients resides in individual hospital information systems (HIS), for example, laboratory information management system, digital pathology system, or patient management system. For example, patient data are collected during dialysis, at transplantation, and for each of the individual follow-up visits after successful transplantation. Before we can use such data for training of CPMs, each clinical site needs to extract relevant data from their internal source systems and transform them into the common NephroCAGE data schema [26]. Some of the clinical transplant centers have already performed extraction of data from internal sources and its harmonization to a common data schema, for example, due to the presence of a local clinical data warehouse. As a result, local efforts for extraction and harmonization of data are reduced at these sites. Extraction and harmonization of data should be automated to establish a reproducible process to allow the continuous integration of new transplant data into the NephroCAGE data set. Thus, the NephroCAGE data set can also be used for answering future research questions in the clinical domain nephrology.

In the NephroCAGE consortium, we have conducted the following steps to make transplant data available for development of CPMs. All clinical sites defined a study protocol and applied for approval by their individual institutional review boards. It involved the detailed description of required data attributes and what kind of algorithm and models will be implemented on the data, for example, the following details were provided: the goal of the project, research hypotheses, patient cohort description, list of variables, incorporated data protection regulations, exclusion criteria, and methods in particular details about the incorporated AI methods and epitope matching algorithms.

Each clinical transplant center has to identify and extract relevant transplant data from their local HIS. Figure 2 depicts the involved process steps per category of data from top to bottom. After data extraction and format harmonization, the quality of retrieved data needs to be assessed by subject-matter experts. For example, selected cases need to be checked for inconsistencies in reported data. We will only address inconsistencies that occurred as part of the data extraction process. If data are confirmed to be inconsistent in the primary system, we have to exclude the patient case from further processing until these inconsistencies are addressed by the clinical transplant centers. Furthermore, outliers will also be removed from further processing.

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Table 1. Overview of the NephroCAGE data set: time period, covered years, number of patients, sex ratio, and age distribution. For MUHC[a] and CHUM[b] only patients consented Kidney Disease Biorepository–from Birth to Adulthood with first-time kidney transplant were included.

Items	NephroCAGE data set	Charité	UBC[c]	MUHC	CHUM
Period	1998-2020	1998-2020	2008-2018	2012-2019	2011-2019
Duration (years)	23	23	11	8	9
Patients	8067	4742	2510	415	400
, n (%)	5081 (63%):2986 (37%)	2940 (62%):1802 (38%)	1606 (64%):904 (36%)	279 (67%):136 (33%)	256 (64%):144 (36%)
Age (years), mean (SD)	51.7 (14.3)	51.3 (14.0)	51.9 (15.3)	55.6 (12.4)	52.0 (12.8)

[a]MUHC: McGill University Health Centre.

[b]CHUM: Centre Hospitalier de l'Université de Montréal.

[c]UBC: University of British Columbia.

Table 2. Categories of transplant data available within the NephroCAGE consortium.

Data category	Description	Selected examples
Recipient data	Measurements of patient data for transplant procedure	Weight, age, sex, HLA[a] data, transplantation date, type of dialysis, time on dialysis, number of transplantations, delayed graft function, cold ischemia time, death date, DSA[b], and MFI[c] of DSA
Donor data	Measurements of donor data for transplant procedure	Weight, age, sex, and HLA data
Laboratory data	Laboratory values, for example, blood and urine	Creatinine, proteinuria (ratio and dip stick), albumin, and CRP[d]
Pathology reports	Medical pathology report	Rejection diagnosis, Banff lesion scores, and Banff diagnostic categories
Clinical notes	Information collected during clinical examination	Diagnoses, symptoms, medical history, physical examination, and written medications
Medications	Information relevant to immunosuppressants	Encoded medication using ATC[e] codes
Hospitalization data	Details about hospitalizations and clinical assessments	Admission and discharge date, blood pressure, urine volume, pulse rate, and temperature
Follow-up data	Details acquired during regular follow-ups	Weight, blood pressure, urine volume, pulse rate, temperature, and DSA

[a]HLA: human leukocyte antigen.

[b]DSA: donor-Specific antibodies.

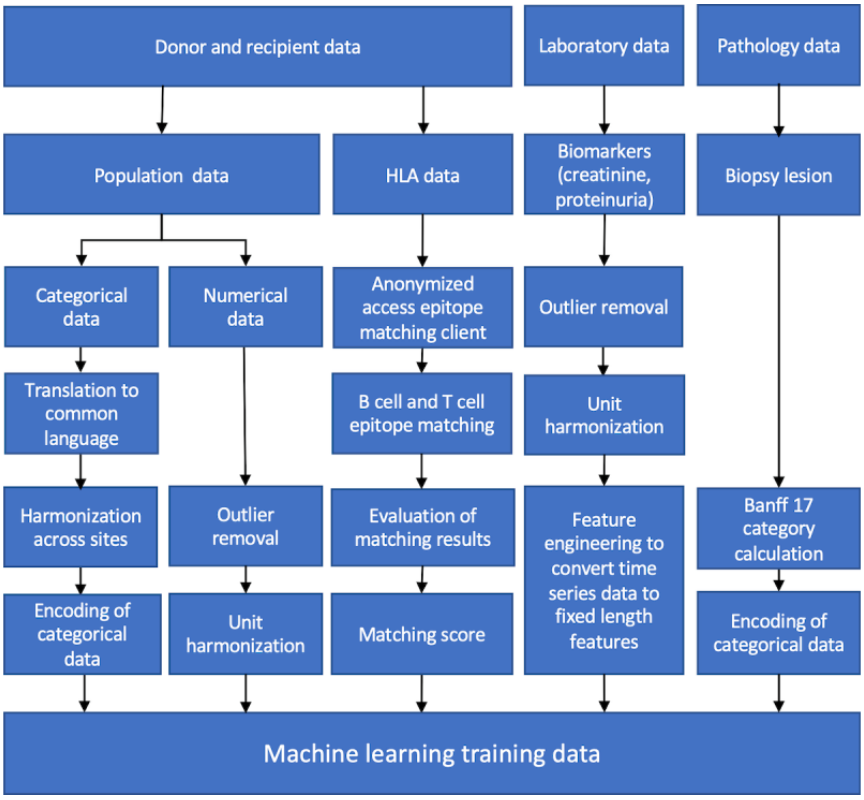
[c]MFI: mean fluorescence intensity.

[d]CRP: C-reactive protein.

[e]ATC: anatomical therapeutic chemical classification.

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Figure 2. Selected process steps involved in extraction and harmonization of data from NephroCAGE transplant centers to form the NephroCAGE data set. HLA: human leukocyte antigen.

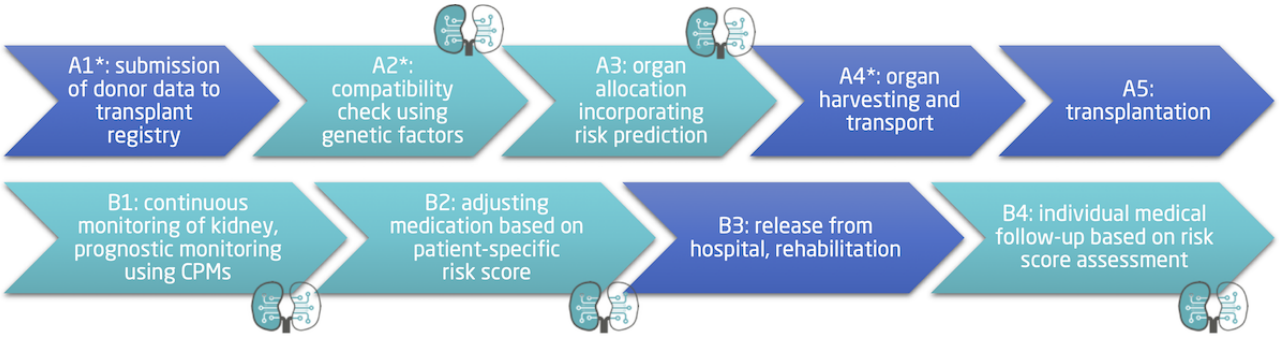


Improving the Kidney Transplantation Process

Figure 3 outlines selected clinical steps in the traditional kidney transplantation process: pre- and posttransplant. If a new organ becomes available via organ donation, its specifics are added to a transplant registry (A1), compatibility checks are conducted (A2), for example, blood group, HLA compatibility, and an allocation decision is taken incorporating donor and recipient specifics (A3). While the organ is retrieved from the donor and transported to the transplant center of the recipient (A4), the recipient is prepared for transplantation (A5). After surgery, the function of the donor organ is closely monitored incorporating common laboratory values (B1) and required medication is set up (B2). After a period of recovery, the patient's release from the hospital is possible, and rehabilitation can start (B3). Regular follow-up appointments for monitoring of kidney function are required to identify eventual risks for the patient and the graft as early as possible (B4).

We will incorporate B cell and T cell epitope matching for donors and recipients as well as our CPMs to provide new insight for clinicians to decide on a donor kidney allocation in steps A2 and A3. If the decision is made for transplantation, the data from surgery and the recipient's lab data from the hospital stay will be used as input for the CPMs design in steps B1 and B2. Thus, our CPMs can help to provide patient-specific risk scores to clinicians, for example, to adjust immunosuppressant medication accordingly, and improves continuous posttransplant patient monitoring in step B4.

Figure 3. Top: selected clinical process steps taken pretransplant. NephroCAGE aims to enhance the current compatibility assessment between donor and recipient by incorporating genetic testing providing the foundation for advanced organ allocation to minimize the risk of incompatibility of human leukocyte antigen between donor and recipient before organ allocation. Bottom: posttransplant, the function of the graft will be monitored continuously. Comparing data with historical references using the NephroCAGE CPMs enables the definition of a patient-specific risk score to develop clinical end points of interest. As a result, medication and follow-up appointments can be adapted to allow fine-grained monitoring by clinicians. CPM: clinical prediction model.



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Molecular-Genetic Matching

Recently, several algorithms to predict molecular HLA compatibility have been proposed. These algorithms model different immunological pathways of allorecognition. Eplet matching translates HLAs into a set of conformational epitopes, toward which the recipient may form HLA antibodies based on the absence of a corresponding self-epitope [16,17,27,28]. Activation of B cells via conformational epitopes is known to require substantial T cell activation. The model provided by PIRCHE predicts linear T cell epitopes, that may be targeted by the hypervariable T cell receptors. Thus, a combination of specific methods has been shown to further improve histocompatibility prediction [29]. Following this strategy, NephroCAGE aims to combine molecular antibody and T cell epitope matching in a CPM. We aim to implement the molecular matching algorithm as a cloud-based software as a service (SaaS) due to high requirements for storage and computing hardware. The use of a SaaS solution allows flexible control of service quality and user experience. However, submitting genetic data to the SaaS provider may cause conflicts with privacy regulation dependent on local legislation.

Within the NephroCAGE consortium, we aim to develop an open-source command line client for anonymization of HLA data of recipients and donors. For computing the molecular matching scores for donor-recipient pairs, common strategies reducing the resolution of shared information, for example, binning or shuffling, are not applicable given the requirement to obtain exact in silico test results. Therefore, the accurate donor-recipient pair HLA typing will be supplemented by obfuscated HLA data sets. This process considers HLA domain-specific information about haplotype and allele frequencies complicating the identification of individuals in the transmitted data set for the service provider and potential intruders. The molecular matching scores will be correlated to transplant outcome compared to results shown in the literature. Considering these findings as a baseline, we will validate modifications to the prediction pipeline, including a peptide cleavage prediction model.

Using ML for CPMs

Various related work showed that AI approaches based on medical input data can result in accurate and robust statistical models to predict patient outcomes [30-34]. For example, supervised tree-based ML algorithms, for example, RF and Extreme Gradient Boosting, have shown promising results for classification tasks for posttransplant risks, for example, for graft failure, patient survival, or graft loss within a certain time period [35-40]. However, most of the existing approaches were research-driven and had only limited access to real-world medical data for their work, for example, using the Scientific Registry of Transplant Recipients data set [41]. Loupy et al [42] developed a risk score for kidney transplant recipients in context of a multicenter study making use of multivariable Cox regression analysis to predict graft loss in patients. Among others, they incorporated the following features: estimated glomerular filtration rate, proteinuria, histology, and HLA antibody [42]. Furthermore, recently advanced approaches based on neural networks making use of large proteomic databases occurred for assessment of immunogenicity and probability to generate antibodies [27,43,44].

From a clinical perspective, NephroCAGE aims to prevent the occurrence of adverse posttransplant end points, for example, loss of function, graft failure, and patient death. Nowadays, regular monitoring is applied to help identifying individual risk factors as early as possible. The use of digital patient records in hospitals for more than a decade provides the data foundation for our work because they form a longitudinal database of historic patient cases, medical decisions, therapies, and disease progression. Today, historical case data are only rarely used for current patient care. Our research hypothesis is that the analysis of historical cases can help to derive prognostic predictions for the individual patient risk to reach severe clinical end points. Based on the analysis of patient-specific parameters, a current patient case will be assigned to a group of similar, historic patient cases.

We will use the existing real-world data from historic patient cases from our clinical partners as a foundation for the definition of specific CPMs per clinical end point of interest [45,46]. Together with our clinical experts, we have defined specific CPMs to predict selected short- and long-term posttransplant events, for example, transplant failure and organ rejection. For example, a CPM trained for prediction of graft failure will cover whether this event will happen (yes or no) within 1 year (short-term) or 5 years (long-term). Such a CPM will predict a floating-point probability $p \in [0,1]$, which will be mapped to positive and negative outcome classes. We will minimize the complexity of CPMs by incorporating the principle of data economy, that is, we will only use a minimal set of clinical parameters required to achieve a stable prediction quality. Therefore, we will make us of automatic and manual feature selection approaches to identify most descriptive features for the specific end point from the provided input data set [48-50]. Among others, our CPMs will make use of the following input parameters: recipient and donor data, laboratory values, biopsy results, medication, hospitalization records of the recipient, and HLA compatibility score. Recipient data include sex, weight, height, age at transplantation, end-stage kidney disease, HLA compatibility data, age at graft failure, cause of graft failure, age at death, and many others. Different kinds of follow-up data, for example, weight, and blood pressure, as well as laboratory values, for example, serum creatinine and daily protein-urea. In the case of kidney rejection or failure, a biopsy is performed and analyzed by a pathologist. For interpretation of renal allograft biopsies, Banff classifications are also available in the NephroCAGE data set.

Once a CPM has been trained at a clinical site, it will be shared with other clinical partners in Canada and Germany for validation and continuous training. CPM release versions will be packaged and deployed for execution to individual clinical sites using Docker containers. Thus, comparable small CPMs are exchanged whilst sensitive transplant data do not leave their protected clinical sites.

The current clinical transplantation process outlined in Figure 3 depicts multiple steps where prognostic predictions provided by NephroCAGE CPMs can support clinicians. In the following,

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we distinguish between pre- and posttransplant use of NephroCAGE CPMs: (1) pretransplant: the use of CPMs prior to transplantation can support more advanced genetic matching of donor and recipients and provide helpful insights for organ allocation; and (2) posttransplant: after transplantation CPMs can also incorporate patient-specific details on the graft function, for example, by including the latest prognosis, which provides a more specific view on the graft. We will focus on binary classifiers predicting short-term (1 year) and long-term (up to 8 years) outcomes post transplantation.

Patient-Specific Risk Score

The use of patient-specific risk scores is well known in medicine, for example, Glasgow Coma Scale, acute physiology and chronic health evaluation, and sepsis-related organ failure assessment for intensive care patients [51-53]. Risk scores are often used to stratify patients at risk or to predict selected aspects for patient care. They are often designed to use multiple values, for example, latest observational and laboratory values, and combine them toward a single numeric value for a selected clinical outcome. When a patient has a follow-up appointment or encounters any complication, latest data can be incorporated to update the patient-specific risk score.

We aim to define a patient-specific risk score for selected posttransplant events to provide additional insights for nephrologists during posttransplant care. The risk score is a low-dimensional metric representing the overall risk of developing posttransplant complications and will contribute to steps B1, B2, and B4 of the clinical process outlined in Figure 3. It will be calculated by combining the outcome of multiple CPMs and additional patient-specific parameters into a single clinical parameter. Thus, it can support clinicians in continuously monitoring selected kidney function parameters or initiating adequate action as early as possible. Based on the risk score, we will be able to classify patients into low-, medium-, and high-risk patients comparable to a traffic-light schema. Patients classified as high-risk patients will require increased systematic monitoring to prevent complications as early as possible, whereas patients classified as low-risk patients are not expected to develop severe events in the near future. This helps to use the available clinical workforce more efficiently, especially in times of a shortage of skilled labor.

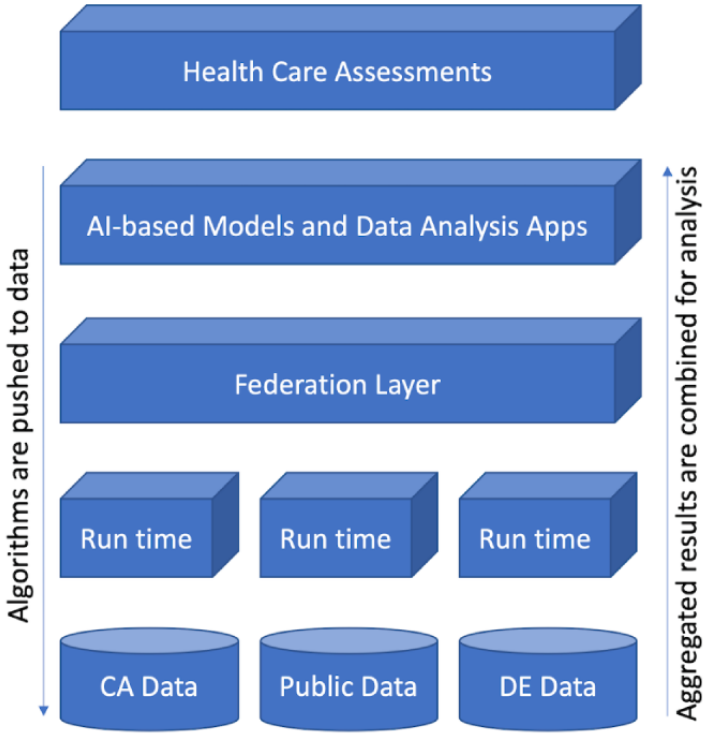
NephroCAGE FLI

Figure 4 depicts the building blocks of the NephroCAGE FLI, that is, from bottom to top: local transplant data accessed by local FLI runtimes, a federation layer for exchange of CPMs and data, as well as AI-based model making use of the NephroCAGE FLI to support clinicians in gaining medical insights. Each NephroCAGE clinical partner will join the NephroCAGE FLI by installing and configuring a local NephroCAGE FLI runtime environment on a dedicated host. After transplant data have been extracted from local clinical systems and harmonized, the host running the local FLI runtime environment is granted access to the data. Afterwards, the training of CPMs can be performed on the local data set. Once a stable CPM version becomes available, it will be released for sharing between partners using the NephroCAGE FLI. As a result, pretrained CPMs can be exchanged via the NephroCAGE FLI to facilitate model training even across country borders.

We will use DLT such as an Ethereum blockchain network to have decentralized storage for communicating model updates and code between clinical transplant centers without the need for a dedicated central authority [54]. For support of model training, we will implement an institutional incremental learning approach, where members retrain models one after another and compare different collaborative learning mechanisms with each other [23]. The aggregation of model values is well-established for parameter-based approaches like neural networks. However, only limited research investigates the aggregation of tree-based or kernel-based approaches like RFs or support vector machines, which are relevant for the NephroCAGE use cases.

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Figure 4. Building blocks of the NephroCAGE FLI. From bottom to top: individual clinical transplant centers from Germany and Canada contribute with more than 2 decades of transplant data enriched by publicly available data, for example, population and research data. Data are only accessible through local runtimes of the NephroCAGE FLI per clinical site, enabling training and sharing of model results whilst keeping data protected. All local FLI runtimes are interconnected through a federation layer, for example, providing access to a data repository for sharing model code and a DLT persistence to store transaction data. The federation layer provides harmonized data access by exposing an API, for example, for training and deployment of AI models and site-spanning data analysis. The results of the CPMs can be assessed by subject-matter experts, for example, to derive patient-specific risk scores for severe posttransplant risks. AI: artificial intelligence; API: app programming interface; CA: Canadian; CPM: clinical prediction model; DE: German; DLT: distributed ledger technology; FLI: federated learning infrastructure.



Deployment and Integration Into Clinical Information Systems

An expert-facing web app will be developed by the consortium as clinical demonstrator. It will be designed using a representation state transfer (REST) API, which allows integration into existing clinical information systems, for example, T-Base at Charité [55]. The NephroCAGE clinical demonstrator will be used by clinicians to gain insights into patient-specific risk scores including additional information for prospective treatment. Therefore, selected data about individual patients will be exchanged with the CPM to calculate the individual probability for posttransplant risks. As a result, we will provide our CPMs in a local deployable way, that is, the CPMs will be executed by the clinical partners, to preserve privacy of any kind of patient data. Furthermore, the clinical demonstrator will serve as an evaluation platform to identify features that can be intervened in to improve outcome.

To facilitate the integration into existing clinical IT infrastructures, we will follow widely adopted internet protocols (HTTP and HTTPs) and well-known software development paradigms for the development of our CPMs and the clinical demonstrator. Therefore, we will develop the NephroCAGE CPMs as modular software components in Python providing an open API to expose their provided functionality for integration into existing software systems. Thanks to the API of the CPMS, the incorporated programming language and software stack remains transparent for the use of the client app. Through the API a stable software interface describing the required in- or output parameters is available, which will facilitate the integration into our clinical demonstrator and other existing clinical software systems. The REST software paradigm guides the development of web app upon established internet protocols [56]. Hence, RESTful APIs could be designed independent of the existing system with which they will be integrated, making them highly decoupled and modular. We will make use of REST API in our CPM design because it will build on well-established communication protocols for exchange of messages and therefore facilitates the integration into existing clinical IT systems. The execution environment for CPMs requires a diverse set of software dependency to function. Virtualization tools, such as Docker (Docker), can support the packaging of CPM software code, automatically install required software dependencies, and improve software deployment reducing maintenance efforts and hospital IT staff [57]. Thus, our CPMs will be packaged using a Docker container, which reduces deployment and maintenance efforts per clinical site.

Results

We have received initial funding for NephroCAGE in February 2021. Data owners from all clinical transplant centers have successfully received ethics approval for participating in the project in 2022. The process of exploration of clinical transplant database for variable extraction and harmonization has started at all centers in 2022. Therefore, we have developed software

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tools to facilitate the extraction, cleansing, and harmonization of relevant transplant data.

For the harmonization of data, we have defined the NephroCAGE data dictionary (DD) together with all clinical partners. The DD covers all attributes per data element, for example, data type, valid data ranges, and harmonized measurement unit. We have 2 types of attributes in the NephroCAGE DD: numerical and categorical. For numerical attributes, we have defined harmonized measurement units, for example, creatinine in µmol/L, age in years, and weight in kg. For categorical data, we have defined all valid categories per attribute, for example, $sex_{recipient} \in \{♀, ♂\}$. Some attributes correspond to numerical or categorial attributes depending on the way it was measured. For example, proteinuria can be stored as numerical attribute with the unit mg/day if it was acquired through a 24-hour urine collection or as categorical attribute using the set {+,++,+++} (+=low, ++=medium, +++=high) if it was acquired using a dipstick quick test.

As of August 2023, a total of 8120 patient records have been retrieved by all clinical partners for use in the NephroCAGE data set as depicted in Table 1. We will calculate the molecular epitope matching score for donors and recipients and extend our data set by it to gain insights in formation of donor-specific antibody formation and impact on the clinical outcome. Subsequently, we will use the NephroCAGE data set to train and validate CPMs for selected posttransplant clinical end points. Locally pretrained CPMs will be retrained and validated by clinical sites through the use of the NephroCAGE FLI. We will focus on ensemble methods to aggregate models trained on individual clinical sites. Setting up the NephroCAGE FLI runtime at each clinical site requires compliance with data compliance regulations of pertaining individual clinical sites and geographies. Our NephroCAGE FLI will facilitate the development of CPMs, enable continuous training at each site without the need for pooling sensitive transplant data in a central database or data warehouse.

Discussion

Findings on Using Sensitive Health Data for Development of CPMs

Transplant data used to form the NephroCAGE data set—as any patient data—are very sensitive and requires dedicated protection measures. However, the accessibility of such data is crucial to enable training of CPMs with high prognostic value. Running a multinational project requiring access to data from different geographic jurisdictions is complex, for example, due to compliance with individual data protection regulations and variety of data formats and semantic meaning. The NephroCAGE consortium develops the privacy-preserving NephroCAGE FLI to comply with the regulations of Canada and Germany. Furthermore, the NephroCAGE data set is unique in its size, details, and longitudinal completeness. As a result, we believe that the NephroCAGE data set can also serve future research as a profound foundation. For example, we plan to use the NephroCAGE data set to analyze the impact of demographics and health care systems on the posttransplant outcomes in Germany and Canada.

The complexity of transplant data stems from its multiple attributes originating from different sources. It contains longitudinal data about clinical events typically occurring years or decades after transplantation and comorbidities related to the underlying disease, for example, creatinine from laboratories and hospitalization data from HISs. Data extraction and harmonization across partners is one of the most challenging parts of our project, because each center has its individual IT infrastructure to store transplant data. Due to our federated setup, we do not make use of a central data warehouse. Therefore, harmonizing transplant data before developing CPMs is more crucial than in a traditional data warehouse setup. Thus, we will perform specific data preprocessing activities, for example, harmonizing categorical variables with the same name and units and checking numerical variables for outliers.

We will work together with nephrologists and clinical experts to identify clinical end points of interest as basis for CPM development. We will start to investigate the applicability of tree-based models and artificial neural networks as ML methods based on our literature review, because tree-based methods perform better on imbalanced tabular data than neural networks. Furthermore, tree-based methods show better explainability by providing explicit feature importance. Finally, an imbalance of data in kidney transplantation might lead to over-fitting for the majority classes. Consequently, we will apply resampling methods to reduce this effect [58-60].

Genomic data for the HLA compatibility algorithm are among the most sensitive transplant data. Therefore, we aim to implement an anonymization client so that the HLA is not susceptible to various privacy threats. Today, only 5 genetic loci from HLA-A, -B, and -DR are used by Eurotransplant's graft allocation algorithm despite a total of 11 clinically relevant HLA loci being associated with immunologic risk [15]. Molecular matching, such as PIRCHE, has been shown to provide additional value to serologic HLA matching in assessing risk of developing donor-specific HLA antibodies, thus having the potential to improve long-term transplant outcomes. Furthermore, donor-specific antibodies are a major factor for rejection that deteriorate organ function and result in graft loss. Although we will use the NephroCAGE FLI to share CPMs between partners, still concerns remain about the privacy of patient data in the case of backtracking the ML model coefficient into individual patient outcomes. Therefore, we will incorporate only deidentified data as basis for CPM training, that is, anonymization of sensitive attributes such as follow-up visit dates, surgery date, and birth date.

Furthermore, the prediction results of CPMs alone are not sufficient to fully explore the reasons. Therefore, we will add additional information to the results, which will enable clinicians to perform informed decision-making, for example, most important features used by the model or details about the specific subtree the individual is assigned to. Thus, clinicians will be enabled to assess the provided prediction and also provide feedback about their final decision, which might be different from the prediction. Thus, we trust that clinicians can incorporate additional insights provided by CPMs into their decision-making process, but still remain the final and human decision maker responsible for clinical treatment decision.

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Limitations

We use observational retrospective data over different time periods and different centers. For example, the majority of transplant data contributed to the NephroCAGE data set is provided by 1 center as outlined in Table 1. Furthermore, transplant data from individual centers was collected across different time periods, thus they might differ due to advances in medical practice. This limits data integration from all centers, including preprocessing and modeling of the data in a similar fashion. Different times and eras of transplantation may infer time bias in the model. Different center practices and demographics may be challenging to interpret and might influence the prediction of CPMs. Therefore, CPMs will show the differential importance of features on the desired clinical outcome. However, clinically actionable features must be determined as certain features cannot be changed, for example, the donor's age. For some clinically relevant factors, interventions must be found, and randomized controlled trials must be established to find appropriate therapy. By diminishing worse outcomes, training and improvement of the CPM may change over time, resulting in inferior model performance, thus deteriorating identifying patients at risk. All the hospitals represent independent cohort in our federated learning setup and hence a particular attention needs to be given in the order of learning to be done on these data set [61].

Conclusions

We have introduced the overall goals of our German-Canadian NephroCAGE consortium, addressing multiple challenges in implementing latest federated learning methods to enable privacy-preserving training of CPMs using real-world transplant data from transplant centers in Germany and Canada. We have highlighted the need to perform data harmonization and develop automated data extraction pipelines per transplant center to ensure reproducibility and scalability of the developed CPMs. Our NephroCAGE FLI will be used for privacy-preserved training and exchange of CPMs, which incorporate data from various hospitals. By including molecular epitope matching into our CPM, we aim to gain insights on donor and recipient HLA-matching beyond the current standard of care. The goal of our CPMs is to support clinicians by identifying severe posttransplant risks as early as possible for individual transplant patients. We aim to develop a clinical demonstrator, which will be used for evaluation of CPMs in a clinical setting. The CPM needs to be verified in randomized clinical studies and evaluated to assess factors that can be used for treatment and modification to improve outcomes. This will especially be achieved if more transplant centers join the consortium and share their transplant data via the NephroCAGE FLI.

Acknowledgments

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Data Availability

The NephroCAGE data set is not publicly available. However, detailed information on the data dictionary is available from the authors on reasonable request and will be released to the project website [62].

Conflicts of Interest

TK is CEO and founder of PIRCHE AG and owns stock in the company.

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Abbreviations

AI: artificial intelligence
API: application programming interface
CPM: clinical prediction model
DD: data dictionary
DLT: distributed ledger technology
FLI: federated learning infrastructure
HIS: hospital information system
HLA: human leukocyte antigen
ML: machine learning
REST: representation state transfer
RF: random forest
SaaS: software as a service

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Protocol

Multisite Agricultural Veterans Affairs Farming and Recovery Mental Health Services (VA FARMS) Pilot Program: Protocol for a Responsive Mixed Methods Evaluation Study

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Abstract

Background: Veterans Affairs Farming and Recovery Mental Health Services (VA FARMS) is an innovative pilot program to provide supportive resources for veterans with interests in agricultural vocations. Implemented at 10 pilot sites, VA FARMS will provide mental health services and resources for veterans while supporting training in gardening and agriculture. As each pilot site project has unique goals, outreach strategies, and implementation efforts based on the local environment and veteran population, evaluating the pilot program provides a unique challenge for evaluators. This paper describes the protocol to evaluate VA FARMS, which was specifically designed to enable site variation by providing both site-specific and cross-site understanding of site implementation processes and outcomes.

Objective: The objectives of this paper are to (1) describe the protocol used for evaluating VA FARMS, as an innovative Department of Veterans Affairs (VA) agriculturally based, mental health, and employment pilot program serving veterans at 10 pilot sites across the Veterans Health Administration enterprise; and (2) provide guidance to other evaluators assessing innovative programs.

Methods: This evaluation uses the context, inputs, process, product (CIPP) model, which evaluates a program's content and implementation to identify strengths and areas for improvement. Data collection will use a concurrent mixed methods approach. Quantitative data collection will involve quarterly program surveys, as well as three individual veteran participant surveys administered upon the veteran's entrance and exit of the pilot program and 3 months postexit. Quantitative data will include baseline descriptive statistics and follow-up statistics on veteran health care utilization, health care status, and agriculture employment status. Qualitative data collection will include participant observation at each pilot site, and interviews with participants, staff, and community stakeholders. Qualitative data will provide insights about pilot program implementation processes, veterans' experiences, and short-term participation outcomes.

Results: Evaluation efforts began in December 2018 and are ongoing. Between October 2018 and September 2020, 494 veterans had enrolled in VA FARMS and 1326 veterans were reached through program activities such as demonstrations, informational presentations, and town-hall discussions. A total of 1623 community members and 655 VA employees were similarly reached by VA FARMS programming during that time. Data were collected between October 2018 and September 2020 in the form of 336 veteran surveys, 30 veteran interviews, 27 staff interviews, and 11 community partner interviews. Data analysis is expected to be completed by October 2022.

Conclusions: This evaluation protocol will provide guidance to other evaluators assessing innovative programs. In its application to the VA FARMS pilot, the evaluation aims to add to existing literature on nature-based therapies and the rehabilitation outcomes

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of agricultural training programs for veterans. Results will provide programmatic insights on the implementation of pilot programs, along with needed improvements and modifications for the future expansion of VA FARMS and other veteran-focused agricultural programs.

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KEYWORDS

veteran; evaluation; farming; farm; agriculture; nature; agricultural; mental health; mental health services; support; vocation; gardening; training; nature-based therapy; pilot program; posttraumatic stress disorder; PTSD; rehabilitation; reintegration

Introduction

Background

In a health care organization as large and complex as the Veterans Health Administration (VHA), successful innovations are a strategic priority [1]. Health care service innovation and continuous quality improvement help meet the diverse needs of the over 9 million veterans who receive care from VHA's 1293 health care facilities. The VHA's primary goal is to deliver greater care and treatment choices "by improving experiences and outcomes" for veterans [2]. Rigorous evaluation ensures innovations are both fiscally responsible and support the public's interest. Evaluative analysis is the foundation for data-driven decisions about the ultimate value of a practice [3]. Evaluating innovation is challenging because processes are new, and typical evaluation approaches are summative and emphasize averages, metrics, and short-term program outcomes [4]. This paper describes the protocol for evaluating an innovative VA agriculturally based mental health and employment pilot program, which serves veterans at 10 pilot project sites across the VHA enterprise.

Pilot Program

VHA's Office of Rural Health (ORH) was established by US Congress in 2006 with a mission to improve health outcomes and increase access to care for the 2.7 million rural veterans enrolled in VHA care [4]. Given ORH's mission, Senate Report (SR) 115-130 directed US $2,000,000 of funding to ORH to implement the Veterans Affairs Farming and Recovery Mental Health Services (VA FARMS) pilot program. In the spring of 2018, ORH partnered with VHA's Office of Care Management and Social Work, Office of Mental Health and Suicide Prevention's Therapeutic and Supported Employment section, Nutrition and Food Services, and Office of Community Engagement to develop a request for applications (RFA) that met the requirements outlined in SR 115-130. The RFA was open to VHA facilities and encouraged each applicant to partner with an existing community organization engaged in agricultural training. Guidelines for implementation were purposely broad so that each pilot site could tailor projects to meet the unique needs of their local population and the structure of their site. The RFA received 23 applications. Representatives from each partner office reviewed all applications with a standard set of criteria that examined feasibility, probability for success, and compliance with the congressional mandate. Ten applicants were chosen to participate in the pilot program (see Figure 1) [5]. Each VA FARMS pilot site project is unique in its design, goals and desired outcomes, duration, target veteran population, and programming. In general, pilot projects offer educational programming using a variety of modalities. These include virtual and in-person education, and some combination of classroom and hands-on project–based learning. Some pilot site projects include internships or other forms of direct job placement.

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Figure 1. Map of funded pilot sites.



The goal of the VA FARMS pilot program is to provide supportive resources to veterans who desire agricultural-based treatment activities, specifically targeted to veterans diagnosed with posttraumatic stress disorder (PTSD) to complement evidence-based standard care approaches. Due to high rates of PTSD and suicide among veterans of all service eras [6], the VHA has prioritized the implementation of programs that connect veterans to critical mental health services and resources. The VHA also recognizes that there are many other social determinants of veteran health, such as economic stability and education. For this reason, programs that address multiple social determinants of health are of great value [7-9].

Nature-Based Innovation for Veterans With PTSD and Mental Health Needs

The VA FARMS pilot program combines the benefits of nature-based therapies (NBTs) for veterans experiencing PTSD and other mental health issues with opportunities for vocational rehabilitation and training. This is in line with the Department of Veteran Affairs (VA)'s prioritization of the diagnosis and treatment of PTSD in veterans and their efforts to improve access to VA benefits to treat PTSD symptoms [10-12]. VA FARMS uses agritherapy, "an approach that incorporates mental health care and services with agricultural vocational training to support veterans' behavioral and mental health needs" [13]. This is a novel approach that can positively influence community reintegration for veterans, especially those who face physical and psychological health issues, substance abuse, and unemployment [14].

Facilitation of community reintegration (CR) is part of the mission of the VA [2]. Veteran community reintegration refers to a military service member's transition from active duty to participation in life outside of the military [15]. Key components of CR are (1) employment or other productive activities, (2) independent living, and (3) social relationships [15]. A substantial proportion of veterans report difficulties with CR following discharge from military service [16]. These difficulties are associated with poor social and family relationships, unemployment, financial strain, homelessness, and poor physical and mental health [17].

VHA's commitment to veteran-centered care has improved veteran access to complementary and integrative health approaches [18]. One such example is NBT, which is an umbrella term for therapeutic approaches that incorporate nature as a key element of the therapeutic process [19]. These approaches can include outdoor programs, therapeutic landscapes, healing gardens, adventure-based counseling, and outdoor-based therapeutic recreation, as representative examples [11,20-23]. There are increasing numbers and types of outdoor programs that specifically offer different therapeutic opportunities for veterans to be immersed in natural environments [21]. Some veterans with PTSD symptoms seek to complement standard psychotherapy and medication treatments with NBTs [20,21,24-27]. For example, community gardens and other green spaces are recognized as safe, therapeutic community spaces [28,29]; they support reintegration by encouraging veterans to interact and socialize with other veterans and civilian community members while engaging in a personally and physically satisfying activity [11,30].

NBTs are not new treatment options for veterans. Historically, they were used to treat "shell shock," war-related stress, traumatic stress, and PTSD among veterans returning from

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combat [14,31,32]. Although these NBTs are not considered standard care, there is some evidence that they are beneficial for the treatment of PTSD; however, much of this literature lacks measurement tools, precise descriptions of the therapeutic approach used, and clear distinctions between outdoor activities and NBT [23].

Evaluation of the VA FARMS Pilot Program

Evaluating the VA FARMS pilot program will be challenging, in part because of its novelty. The rollout will be purposefully broad, allowing each pilot site's goals, outreach, and implementation to differ based on the local environment and the unique needs of their veteran population. While mandated to provide training in agricultural vocations and access to behavioral health care services by licensed providers, each VA FARMS pilot site project is unique in its design and tailored to provide agricultural opportunities that meet local veteran needs. The evaluation protocol described herein will evaluate VA FARMS as a mechanism that supports tailored approaches to agricultural vocational training. The protocol allows for a site-specific and cross-site understanding of pilot project design and implementation processes. Programmatic data will provide a broad understanding of administrative logistics, promising practices, and modifications that may be needed to improve VA FARMS models. The protocol includes an assessment of the feasibility of measuring individual participant outcomes over time. By describing the protocol, this paper aims to provide guidance to other evaluators who are assessing innovative programs.

Study Objectives

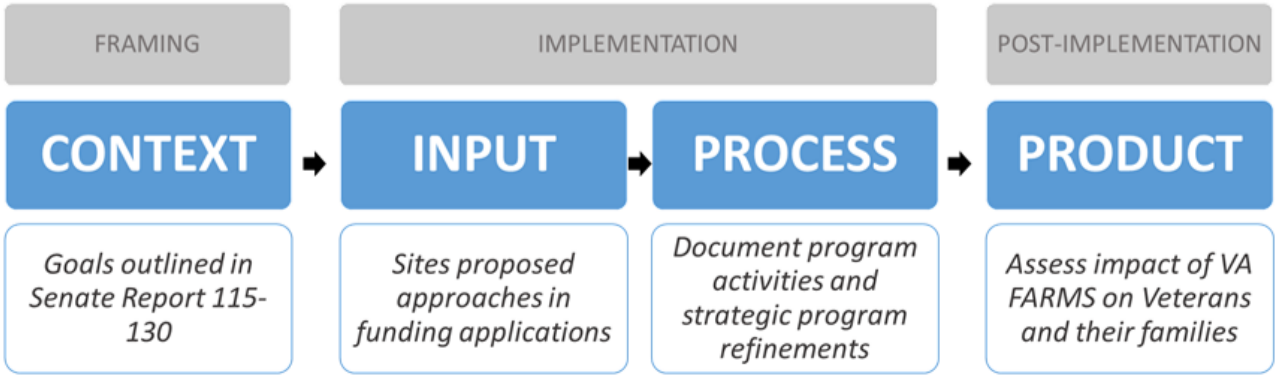
The specific objectives of this evaluation are to: (1) identify barriers and strategies to implement sustainable ORH-funded agritherapy pilot site projects; (2) identify best practices that can be used to inform future VA agritherapy programing; (3) describe barriers, benefits, and personal experiences of veterans who participated in VA FARMS programming; and (4) assess pilot program implementation processes, barriers, facilitators, strategies, and outcomes for providing mental health care referrals and developing pathways toward employment in the agricultural sector.

Conceptual Framework

The context, inputs, process, product (CIPP) model [33] is well-suited to guide the evaluation of VA FARMS because it has been successfully used to evaluate training and educational programs [34] and innovations in dynamic real-world settings [35,36]. According to Stufflebeam and Shinkfield [35], the most important purpose of evaluation is not to "prove" but to "improve." The CIPP model systematically evaluates a program's content and implementation to identify strengths and areas for improvement. It enhances program effectiveness and supports program planning efforts [34]. Thus, this model is applicable to both formative and summative evaluations as it emphasizes "learning by doing" and promotes continuous program improvement [36].

The VA FARMS's goals (*context*) were outlined in the congressional legislation. The pilot sites proposed unique approaches (*input*) in their funding applications to ORH. For example, they outlined budget and staffing needs, partnerships, and implementation strategies. The evaluation will record each pilot site program model and the degree to which this approach helped them achieve their goals; however, the primary focus will be to assess pilot program *processes* and *products* to suggest optimal models and promising practices. The process evaluation will document pilot program activities and strategic refinements. The product evaluation will assess the impact of participating in VA FARMS on veterans. Figure 2 schematically describes application of the CIPP framework in the VA FARMS evaluation.

Figure 2. Scheme of application of the context, inputs, process, product (CIPP) framework to evaluation of the Veterans Affairs Farming and Recovery Mental Health Services (VA FARMS) pilot program.



Methods

Data Collection Procedures, Participants, and Recruitment

This 3-year evaluation will use a concurrent mixed methods approach to collect process and product data [37]. VA FARMS processes will be evaluated by collecting data about pilot program activities, implementation barriers, and modifications. These data will be collected through (1) quarterly surveys of project directors; (2) planned monthly *project status* conference calls between staff at individual pilot sites, ORH program management, and the evaluation team; (3) participant observation of activities at planned yearly site visits; and (4) *program implementation interviews* with VA FARMS pilot site staff and community stakeholders.

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Products of VA FARMS will be evaluated by assessing the individual impact of participating in the pilot site projects. These data will be collected through (1) Individual *veteran participant surveys* administered by each pilot site at baseline (within 2 weeks of initial VA FARMS programming exposure), at exit (when a VA FARMS veteran participant ends their training activities), and at 3 months after the exit survey; and (2) *veteran voice interviews* with veteran participants who completed an *individual veteran participant survey* at baseline and/or exit. Interviews will be collected via telephone in years 2 and 3 of the pilot. The activities of data collection and the associated timeline are summarized in Table 1.

Table 1. Evaluation activities, methods, and timeline.

Method	Timeline	Participants	Procedure	Analysis	CIPP[a] outcome
Project status conference calls	Years 1, 2, and 3	Program coordinators at all pilot sites	Collected monthly in a 1-hour meeting via teleconferencing technology	Content analysis of meeting minutes	Process evaluation
Individual veteran participant survey: baseline, exit, 3 months postexit	Years 1, 2, and 3	Veteran participants at all pilot sites	Collected on a rolling basis, distributed by pilot sites in paper-based or online format	Descriptive statistics: RMANOVA[b], paired *t*-tests/ Wilcoxon signed-rank tests	Product evaluation
Quarterly program surveys	Years 1, 2, and 3	Program coordinators at all pilot sites	Collected every 3 months; administered online	Descriptive statistics	Process evaluation
Participant observation	Years 1, 2, and 3	Participants, staff, and stakeholders	Conducted yearly at annual site visits in person	Content analysis of field notes	Process evaluation
Implementation interviews	Years 1, 2, and 3	Year 1: Pilot site staff and community stakeholders; year 2: pilot site staff; year 3: pilot site staff and community stakeholders	Collected yearly in a 1-hour semistructured interview	Noticing, collecting, and thinking (NCT) analysis	Process evaluation
Veteran voice interviews	Years 1, 2, and 3	Veteran participants at all pilot sites	Conducted yearly in 30-minute semistructured interviews in person and via telephone	NCT analysis	Product evaluation

[a]CIPP: context, inputs, process, product.

[b]RMANOVA: repeated-measures analysis of variance.

Data Collection Procedures

Individual Veteran Surveys

Individual veteran participant surveys (see Multimedia Appendix 1) will be offered in two formats: paper-based and web-based. Completed paper-based hard copies will either be submitted to the evaluation team via United States Postal Service or scanned and sent via encrypted email. Surveys submitted via the online platform Qualtrics [38] will be accessible only to evaluation staff and stored on a secure drive. Each individual veteran participant survey includes a 16-item demographic questionnaire and the following validated measures: (1) Military to Civilian Questionnaire (M2CQ) [39], a validated measure of veteran community reintegration; (2) PTSD Checklist–Military Version (PCL-M) [40], a validated PTSD self-report questionnaire that assesses 20 Diagnostic and Statistical Manual of Mental Disorders (DSM)-5 symptoms of PTSD; (3) Patient-Reported Outcomes Measurement Information System (PROMIS) Global Health (10) SF: Quality of Life [41], a validated self-report measure that assesses overall physical health, mental health, social health, pain, fatigue, and overall perceived quality of life; and (4) Work and Meaning Inventory (WAMI) [42], a validated self-report measure that assesses the personal meaning people draw from the work they perform, as well as how work broadens life purpose and contributes to the greater good.

Individual veteran participant surveys that are administered at exit and 3 months postexit will also include a 20-item satisfaction survey.

Quarterly Program Surveys

Throughout the pilot period, quarterly program data will be reported to ORH electronically. Awardee sites will report the number of veteran participants recruited, attrition, completion, number of referrals for mental health services, number of participants who gained employment in agriculture, type and amount of service use/referrals made, and number and type of outreach events (see Multimedia Appendix 2). The evaluation team will rely on site-reported numbers of referrals as we are not able to access participant medical records.

Participant Observation and Field Notes

Evaluators will attend annual site visits lasting approximately 2.5 days. Site visits will include participant observation of classes, demonstrations, and field activities. This method will allow evaluators to participate in VA FARMS activities and observe the day-to-day operations from both a programmatic and veteran participant perspective. A field notes template (see

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Multimedia Appendix 3) will capture evaluator impressions during site visits, and a debrief worksheet (see Multimedia Appendix 3) will allow evaluators to write a formal postvisit report.

Interviews With VA FARMS Staff, Community Stakeholders, and Participants

Interview guides will be developed iteratively based on pilot program goals and site-specific context, as well as evaluation survey results and conversations with VA FARMS program staff and ORH partners during monthly project status update calls. All interview guides will be based on 30-minute semistructured interviews. In Year 1, *implementation interviews* (See Multimedia Appendix 4) will be conducted in person during annual site visits with VA FARMS pilot program staff and community stakeholders. Interviews with pilot site staff will focus on start-up and implementation processes, including facilitators and barriers. Interviews with community stakeholders will document how community partnerships impacted program goals and veteran service provision. Also in year 1, evaluators will conduct in-person *veteran voice interviews* during annual site visits. Interviews will focus on veterans' experiences and short-term participation outcomes (eg, service access, goal attainment, satisfaction).

In year 2, *implementation interviews* with VA FARMS pilot site staff will focus on VA FARMS program modifications and lessons learned that were driven by implementation needs and barriers. *Veteran voice interviews* (see Multimedia Appendix 5) will be conducted via telephone to capture the lived experiences, meaning, and intermediate outcomes (eg, new knowledge, increased skills, service access, goal attainment, satisfaction) of veterans who participated in a VA FARMS pilot program in year 1.

In year 3, final *implementation interviews* will be conducted with VA FARMS staff, administrative leadership at facilities hosting pilot sites, and community stakeholders to holistically describe barriers and facilitators to program implementation, changes to VA FARMS programming, outcomes of community partnerships, and long-term sustainability prospects. *Veteran voice interviews* will be conducted via telephone to capture the lived experiences, meaning, and long-term outcomes of participating in VA FARMS (eg, changes in attitudes or values, modified behavior, perceived improved condition).

Participant Recruitment

Evaluation participants will be recruited from each of the 10 local VA FARMS pilot project sites. Pilot project site directors will be required to provide quarterly pilot program data as a condition of funding. All other evaluation activities will be voluntary. A convenience sample of pilot project staff, partners, and veteran participants of VA FARMS pilot projects will be invited to take part in *implementation interviews*. Participants will be recruited based on exit survey data where veterans will indicate a willingness to participate in an interview discussing their experiences in the VA FARMS pilot program at each site. In years 2 and 3, *veteran voice interview* participants will be recruited based on exit survey data where veterans will indicate a willingness to participate in an interview discussing their experiences in the VA FARMS pilot program at each site.

Data Analysis

Quantitative Data Analysis

Descriptive statistics will be provided for all quantitative measures, which will include frequencies and percentages for categorical variables, as well as means, medians, standard deviations, and ranges for continuous variables. For variables measured over multiple time points, statistics will be provided both cumulatively and per time point (ie, quarterly or annually). Where appropriate, paired *t*-tests (ie, comparing change at two time points), Wilcoxon signed-rank tests (ie, nonparametric test to compare change at two time points when data are not normally distributed), or repeated-measures analysis of variance (RMANOVA) will be used to compare changes in continuous outcomes over multiple measurement time points.

To understand implementation processes (ie, pilot program activities and strategic refinements), quarterly pilot program surveys will be analyzed using descriptive statistics, and information will be presented both per quarter and cumulatively. In addition, data about veteran enrollments, outreach activities, and community partnerships will be collected to describe the number of participants who receive VA and non-VA health care and resource referrals, and the number of participants who became employed in agriculture.

To understand implementation products (ie, the impact of VA FARMS on veterans and their families), baseline descriptive statistics will be provided for veteran demographics, previous experience with gardening or agriculture, health care utilization, and PTSD and associated factors. Demographics will include gender, age, race/ethnicity, education, baseline employment and student status, military service branch, military service era, and service-connected disability rating. Previous experience with gardening or agriculture will be quantified in months. Health care utilization will include frequency of primary care visits, specialist visits, other provider visits, and hospital stays. Factors associated with PTSD will include reintegration, global physical health, and global mental health (encompassing pain, fatigue, depression, and overall quality of life).

In addition to baseline descriptive statistics, follow-up statistics on participant outcomes will be obtained from self-reports and validated measures (M2CQ, PROMIS, PCL-M). Veterans will report on health care utilization, PTSD, and PTSD-related symptoms. It is important to note that the selected measures are not diagnostic but allow veterans to self-report the presence of the 20 DSM-5 symptoms of PTSD. Descriptive statistics will be provided for scores at pilot program exit and at 3 months postexit. Additionally, RMANOVA, paired *t*-tests, or Wilcoxon signed-rank tests—depending on the data distribution and satisfaction of analysis assumptions such as normality and sphericity—will be performed to compare baseline to exit scores and to compare exit scores to 3 months postexit scores. Participants will also be asked about their agriculture employment status.

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Qualitative Data Analysis

Monthly Project Status Updates and Field Notes

Note-taking templates will be created to structure notes from project status update calls and observations from site visits. Project status call templates will include sections to record information about reported implementation activities, successes, and challenges. Field note templates (see Multimedia Appendix 3) will include sections to record information about observed program activities, reflections, emerging questions and analyses, and future actions.

Data will be analyzed using a matrix analysis process [43]. Notes will be summarized and added to individual rows of a Microsoft Excel spreadsheet. Evaluators will read each summary and identify important concepts. These concepts will be summarized with a single word or short phrase called a "code." Each Microsoft Excel column header will be labeled with a qualitative code. Summaries will be coded by typing a "1" in the cells that join rows (summaries) and columns (qualitative codes) to indicate that a piece of text is meaningfully connected to a specific concept. Evaluators will compare coding structures, discuss discrepancies, and reach consensus about the essential meaning of the data.

Interviews With VA FARMS Staff, Stakeholders, and Participants

Semistructured interviews with VA FARMS staff, community stakeholders, and veteran participants will be conducted primarily over the phone, except during site visits where interviews will be conducted in person. In both cases, two experienced qualitative evaluation team members will conduct the interviews in tandem, one as the primary facilitator and the other as the notetaker and timekeeper. Detailed notes and an overall summary of the interview will be completed using the interview summary template. This template will be used as a first-level analysis document that will be integrated into the principal analysis effort using ATLAS.ti v8.0 [44].

Data collection and analysis will occur concurrently allowing for insights from data analysis to iteratively guide subsequent data collection (eg, modification of interview questions). The detailed note summaries will be uploaded into ATLAS.ti v8.0. Interview data will be analyzed using the noticing, collecting, and thinking (NCT) analysis model [45]. As defined, the NCT consists of three basic components: noticing, collecting, and thinking about interesting things in the data. The NCT model will use coding structures, writing memos, process mapping, and diagramming to describe, categorize, and connect the data. This process will help to determine common themes, patterns, and inconsistencies related to the participants' experiences, perceptions, and opinions. The qualitative team will systematically develop a code book (ie, operationalize codes and thematic categories) by meeting routinely to review ongoing coding results, resolve coding issues that arise, and discuss the development of thematic coding categories. Hyperlinks may be used to compare sections of text that occur in different interviews. Advanced search techniques including Boolean, code co-occurrence, and cross-tabulation searches will be used to sort and compare important pieces of text by VA FARMS staff, community stakeholders, and veteran participants.

Ethical Considerations

This evaluation has been determined by the local VA Research and Development Service at the James A Haley Veterans' Hospital to be a quality improvement project and will thus not be subject to the Institutional Review Board review for research [46]. Given this assessment, no written informed consent will be required. However, all participants, including veterans, VA FARMS staff, administrative leadership, and community stakeholders, will be verbally assured of confidentiality and will complete required VA verbal and written consent for use of photographs and audio recordings (VA Form 10-3203).

Privacy and Security

Interviews will be audio-recorded with the permission of each participant, including veterans, VA FARMS staff, administrative leadership, and community stakeholders. All data will be kept in a secured folder behind the VHA firewall. The folder will only be accessible to members of the evaluation team. After interviews have been summarized, audio recordings will be deleted.

Ensuring Inclusion and Accessibility

Interview guides and recruitment invitations will be drafted at a sixth-grade reading level using "plain language" principles for clear communication [47]. These materials will also be drafted in Spanish for participants at the Puerto Rico pilot site. Veterans with hearing impairment will be interviewed via email using tailored methods [48,49].

Expert Advisory Board

An advisory board of subject matter experts (SMEs) will assist the evaluation team in quarterly meetings as well as on an as-needed basis. Advisory board participants will include SMEs in farm safety, PTSD, veteran farming programs, and disability and farming issues. They will assist with instrument development, face validity, pilot testing, and technical and agricultural issues that may arise during the evaluation, along with data collection and interpretation questions. Additionally, they will be available for general technical and programmatic issues that may arise for awardee sites. They will not see any data, and any information provided will be in aggregate or deidentified form.

Results

In July 2018, a total of 10 sites were awarded with funding to implement their proposed pilot projects [5] and were subsequently enrolled in evaluation efforts starting in December 2018. Data analysis will be ongoing to fulfill quarterly and annual reporting. Overall findings are expected to be submitted for publication by October 2022. As of the end of September 2020, some data had been collected and analyzed (Tables 2 and 3).

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Table 2. Implementation outcomes in 2019 and 2020.

Evaluation period	Number of veterans enrolled[a]	Number of veterans reached[b]	Number of communities reached[c]	Number of VA[d] employees reached[e]
October 2018 to September 2019	229	1326	1623	655
October 2019 to September 2020	265	2341	1696	1816
Total	494	3667	3319	2435

[a]Total number of unique individual veterans enrolled in the VA FARMS pilot program in a fiscal year. These are veterans who had never been enrolled in the VA FARMS pilot program previously.

[b]Total number of veterans reached by the VA FARMS pilot program in a fiscal year. This number includes veterans who are not enrolled in VA FARMS but participated in pilot program activities such as demonstrations, informational presentations, and town-hall discussions.

[c]Total number of community members reached by the VA FARMS pilot program in a fiscal year. This includes face-to-face contact with people who are not enrolled in VA FARMS through demonstrations, informational presentations, town-hall discussions, etc.

[d]VA: Department of Veteran Affairs.

[e]Total number of VA employees reached by the VA FARMS pilot program in a fiscal year. This includes face-to-face contact with VA employees through demonstrations, presentations, grand rounds, etc.

Table 3. Data collection activities and outcomes October 2019 to September 2021.

Data collection activities	October 2018 to September 2019, n	October 2019 to September 2020, n	Total, N
Project status updates	114	32	146
Baseline surveys	191	59	250
Exit surveys	36	34	70
3-month follow-up surveys	7	11	18
Quarterly program surveys	36	36	72
Site visits	8	0	8
Pilot site staff interviews	17	10	27
Pilot site community partner interviews	11	0	11
Veteran voice interviews	15	15	30

Discussion

Projected Significance

Agricultural programs have been found to provide physical and behavioral health benefits to veterans who are struggling to transition from military to civilian life. European studies on the impact of horticulture and agriculture on the health and well-being of veterans and service members have found positive benefits for veteran participants with PTSD, including feeling relaxed, secure, and safe; having a sense of purpose; a decrease in PTSD symptoms; and learning new skills [50-52]. In the United States, findings on the benefits associated with farming and horticulture on veterans and service members are sparse, and primarily come from studies and evaluations of regional programs and populations that are veteran-focused. For example, an evaluation of a veteran-oriented community agricultural initiative in western Washington found that participation in the program contributed to improved mental, physical, and emotional health; increased vocational skills, community connectedness, interpersonal communication, a sense of satisfaction, and a sense of belonging; and helped decrease stigma surrounding veteran status [53-56]. A recent pilot horticultural therapy intervention showed significant improvements in reported stress, depressed mood, pain, and loneliness, and a decline in suicidal ideation in high-risk veterans [57]. Overall, findings from the United States are similar to those found in European studies, including promotion of the formation of trusted interpersonal relationships and community connectedness [30,31,56]; improved vocational skills [30,31,55,58]; improvement in pain, self-efficacy, and quality of life [58]; and better nutritional quality of diet [59].

Despite a long history of farming as therapy for veterans [11,14,52,60] and positive coverage in the news media [13,61], there is limited scientific evidence supporting the specific use of agritherapy for mental health and vocational rehabilitation in this population. For this reason, rigorous evaluation of the VA FARMS pilot program processes and products will be critical for understanding the benefits, barriers, and outcomes of implementing innovative programs within the VA system of care. This mixed methods evaluation protocol is designed to inform on diverse VA FARMS pilot projects with site-specific contexts for a rich understanding of program context and local definitions of successful reintegration for veterans. This will be critical given the many contextual factors known to influence CR in veterans [62-65]. Both the funding mechanism and evaluation design will allow for multiple models of VA FARMS to be implemented and is uniquely situated, as the VA is deeply aware of the multifaceted, heterogeneous needs of veterans

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[63,66,67]. Ideally, this will allow for multiple promising practices and programs to emerge, which can act as models for other VAs to choose from and tailor as they implement for their veteran communities. For example, pilot programs such as VA FARMS that follow an ecological approach provide opportunities for veterans to practice CR, increase self-efficacy, increase social support, coordinate with trusted community members or organizations, and meet in nonstigmatizing community locations have been found to facilitate veteran CR and program participation [62,68]. Many of the VA FARMS pilot site projects will include some or all of these elements and will be assessed through this multisite evaluation.

Notably, there are no validated quantitative measures that capture CR or rehabilitation outcomes of agricultural training programs in the civilian or veteran population [23]. The need for research focusing on CR outcome measures in rehabilitation-related studies and the study of CR outcomes was proposed by a VA Rehabilitation Research and Development Work Group on Community Reintegration [15,69]. This evaluation will also help to address identified gaps in the NBT literature, notably a lack of measurement tools and poor descriptions of the therapeutic approach used [23]. In this evaluation, PTSD and associated factors such as reintegration, global physical health, and global mental health (encompassing pain, fatigue, depression, and overall quality of life) will be measured at baseline, exit, and 3 months postexit using validated scales. These data, along with self-report of health care utilization (frequency of primary care visits, specialist visits, other provider visits, hospital stays) and agriculture employment status, will provide a basis for comparing participant outcomes from the individual pilot site projects and VA FARMS as a whole. In addition, individual pilot site project activities, including therapeutic approaches, will be clearly described and categorized through quarterly reporting as well as observation during site visits.

Conclusions

This 3-year evaluation will employ a concurrent mixed methods approach and a CIPP model to collect process and product data. The evaluation will allow for a site-specific and cross-project understanding of project designs and implementation processes, as well as an assessment of the feasibility of measuring individual participant outcomes over time. Results of this evaluation will contribute rigorous evaluation findings of veteran agritherapy programs to the literature, an area that is notably sparse. Additionally, this evaluation will address the lack of measurement tools and poor descriptions of the therapeutic approach used in the NBT literature [23]. Programmatic insights will include a broad understanding of administration impacts, needed improvements, and modifications for expansion of VA FARMS models. Additionally, since this evaluation protocol will be designed to provide a rich understanding of contexts and local pilot site definitions of successful veteran reintegration, promising practices that emerge will be able to be applied to not only the implementation of VA FARMS models but also may be extended to other veteran-focused agricultural programs with consideration of CR and PTSD.

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Data Availability

The data sets generated during and/or analyzed during the current study are not publicly available due to veteran confidentiality but are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Participant surveys.
[PDF File (Adobe PDF File), 501 KB - resprot_v12i1e40496_app1.pdf]

Multimedia Appendix 2
Quarterly program surveys.
[PDF File (Adobe PDF File), 218 KB - resprot_v12i1e40496_app2.pdf]

Multimedia Appendix 3
Field notes template.

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[PDF File (Adobe PDF File), 43 KB - resprot_v12i1e40496_app3.pdf]

Multimedia Appendix 4
Implementation interview guides.
[PDF File (Adobe PDF File), 92 KB - resprot_v12i1e40496_app4.pdf]

Multimedia Appendix 5
Veteran voice interview guides.
[PDF File (Adobe PDF File), 76 KB - resprot_v12i1e40496_app5.pdf]

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Abbreviations

CIPP: context, inputs, process, product model
CR: community reintegration
DSM: Diagnostic and Statistical Manual of Mental Disorders
M2CQ: Military to Civilian Questionnaire
NBT: nature-based therapy
NCT: noticing, collecting, and thinking
ORH: Office of Rural Health
PCL-M: PTSD Checklist–Military Version
PROMIS: Patient-Reported Outcomes Measurement Information System
PTSD: posttraumatic stress disorder
RFA: request for applications
RMANOVA: repeated-measures analysis of variance
SME: subject matter expert
SR: Senate Report
VA: Veterans Affairs
VA FARMS: Veterans Affairs Farming and Recovery Mental Health Services
VHA: Veterans Health Administration
WAMI: Work and Meaning Inventory

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Proposal

Students' Perception of Formative Assessment as an Instructional Tool in Competency-Based Medical Education: Proposal for a Proof-of-Concept Study

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Abstract

Background: In competency-based medical education (CBME), "Assessment for learning" or "Formative Assessment" (FA) plays a key role in augmenting student learning. FAs help students to measure their progress over time, enabling them to proactively improve their performance in summative assessments. FAs also encourage students to learn in a way where they address their knowledge gaps and gaps in their conceptualization of the subject matter. The effectiveness of an FA, as a learning and development instrument, relies on the degree of student involvement in the corresponding educational intervention's design and implementation. The extent of students' engagement in FA can be evaluated by appraising their perception regarding the educational intervention itself.

Objective: This proof-of-concept study aims to develop a systemic understanding of a Formative Assessment as an Instructional Tool (FAIS) implemented in a biochemistry course in the Basic Medical Sciences component of an undergraduate entry, CBME.

Methods: The educational intervention in question is an FAIS, which is implemented in a biochemistry course in the first semester of a 6-year bachelor of medicine, bachelor of surgery program. When developing the FAIS, each area of knowledge, skills, and attitudes were considered. Assessment formats are developed per Miller's learning pyramid. This multiphase study is meant to rely on a convergent mixed methods design, where qualitative and quantitative data are independently collected and analyzed. Thereafter, the outputs of analyses are systematically merged using joint display analysis process. Qualitative data are collected through a focus group session that captures the students' perception toward the FAIS. Data collection, integral to this focus group session, is exploratory. The inductive qualitative data analysis follows Braun and Clarke's 6-step framework. The quantitative component of this study revolves around investigating the effect of the FAIS on the course's summative assessment. The summative assessment performance of the 71 students, enrolled in the FAIS cohort, will be compared to that of the students in the non-FAIS cohort. The total duration of the proposed multiphase research study is 6 months.

Results: This proposed multiphase study is expected to showcase, from a systemic perspective, the effectiveness of the respective educational intervention. It will shed light on the participating students' attitudes in relation to the usefulness of FA in achieving competency goals and in fostering self-directed learning. The proposed study could also uncover the hypothesized association between the FA intervention and enhanced performance in summative assessments.

Conclusions: Our findings will generate evidence regarding the application of FAs, which can be leveraged by other medical educators in contexts similar to those under investigation.

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KEYWORDS

medical education; formative assessment; summative assessment; student; education; competency-based; proof-of-concept; perception; biochemistry; curriculum; teacher; educator; medical school; skill assessment; knowledge assessment; knowledge evaluation

Introduction

Background

A pivotal challenge in implementing competency-based medical education (CBME) is the consequential assessment of competence. The transfer to CBME has raised awareness of the confines and limitations of existing assessment methods [1]. It has also highlighted the need to develop approaches to assess the competencies expected of today's physicians in an era portrayed by increasing interdependence and collaboration among health care professionals, the recognition that patients' safety is everyone's responsibility, and an expectation of pellucidity and accountability.

In designing an assessment program, the intention is to articulate its purpose. Assessment has been shown to influence students' excellence and allocation of their efforts. While experts might differ with regard to when and how the effects of assessment are exerted, the existence of such a relationship is irrefutable [2]. The influence of assessments on students' learning, often referred to as the "educational impact" of the assessment, "testing effect," "consequential validity," "test-enhanced learning," "backwash," "washback," and "testing phenomenon," is an imperative element of the effectiveness of an assessment system [3]. Two fundamental and essentially different rationales are "assessment of learning" and "assessment for learning." "Assessment of learning" or "Summative Assessment" evaluates a student's learning progress and archetypally provides concrete grades or other objective measures [4]. The intended purpose of summative assessments is to measure the students' achievement to make decisions about promotion or progression, direct what and how students learn, and motivate students to learn [5].

"Assessment for learning" or "Formative Assessment" (FA) is used to bolster the learning process. It focuses on providing the student with feedback on their performance to improve their skills [6], knowledge, and learning behavior. FAs focus on specific content, topics, and skills, and can be conducted as frequently as needed.

FAs also serve the purpose of measuring students' progress over time, which can assist the students to incessantly improve and support students in focusing their learning efforts on gaps in knowledge and their conceptualization of the subject matter. The key objectives of FAs are to inform the students of required knowledge for the future, identify student's lag in performance, assist with timely performance improvement, and provide feedback to teachers about how best to assist and facilitate student learning. Miller [7] identified 4 levels of learning, conceptualized as a pyramid as shown in Figure 1. Beginning at the base, the learner "knows," which forms the base of the pyramid and the groundwork for developing clinical competence, and then proceeds through "knows how," where the learner uses knowledge in the gain, analysis, and elucidation of data and the development of a learning blueprint, to proceed through "shows how," where the learner is required to demonstrate the integration of knowledge and skills in clinical performance, to progress to the apex level "does," which focuses on methods and strategies to assess the performance of the user in routine clinical performance.

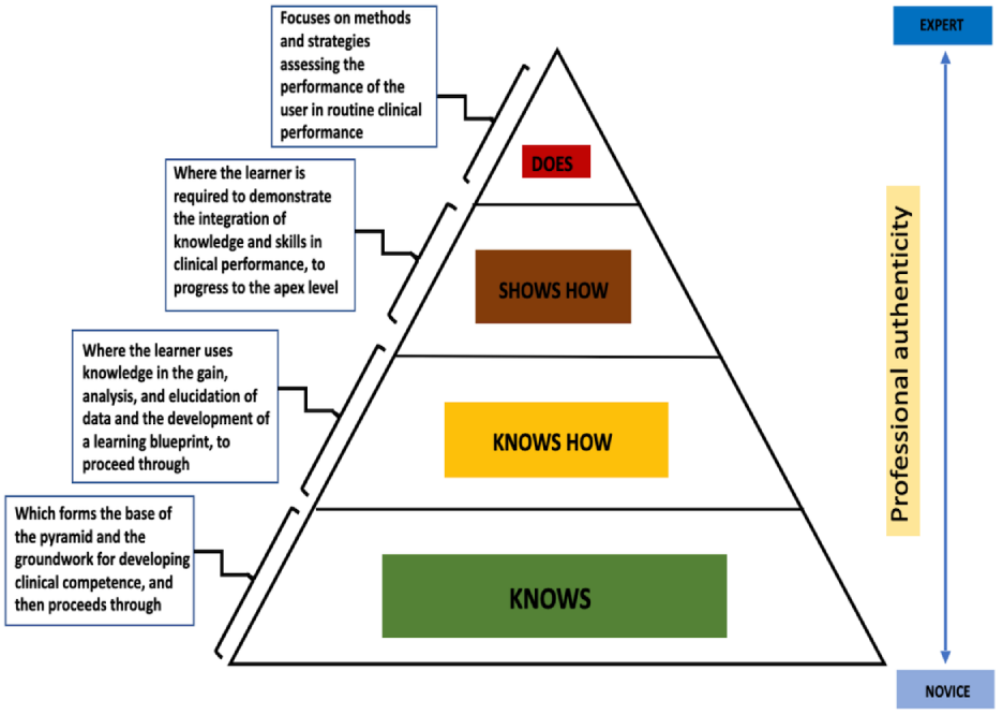
The assessment strategies tied to each level inform and contribute to learning as well as assessment, provided that formative feedback is given. At the "does" level, assessment becomes part of the authentic context in which one works and learns; learning provides deeper meaning for the trainee and builds a substrate for the cognitive processes of clinical decision-making [8].

Key to the effectiveness of an FA as a learning and development instrument is the degree of student involvement in the design and implementation of the FA used to train them. The extent of students' engagement in FA can be effectively evaluated by appraising the students' perception regarding the educational intervention itself.

Five specific features are essential to secure a sufficient level of student involvement: (1) congruence (ie, the tasks of an FA must reflect the instructional content), (2) authenticity (ie, the tasks of an FA should be related to students' backgrounds and study contexts), (3) consultation (ie, students should have a say in how their answers are evaluated and based on which criteria), (4) transparency (ie, no "mystery items"; the wording of the items must clearly address the targeted content), and (5) accommodation (ie, all students should have the same chance to complete the items of a FA).

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Figure 1. Miller's pyramid of learning [7].



Objective of the Proposed Study

The overall objective of the multiphase proof-of-concept study proposed in this protocol is to develop a systemic understanding of the effectiveness of a Formative Assessment as an Instructional Tool (FAIS) implemented in a biochemistry course in the Basic Medical Sciences component of an undergraduate entry, competency-based medical curriculum at the Mohammed Bin Rashid University (MBRU) of Medicine and Health Sciences, Dubai, the United Arab Emirates.

Methods

Study Context

The CBME at MBRU comprises 3 phases. Each phase of the curriculum includes integrated courses and builds on the preceding one, such that the curriculum is "spiral." The students purposefully repeat subjects, where with each successive encounter, concepts build upon those acquired in the previous round. The medical school, in which the proposed multiphase study will be conducted, caters to a student population from more than 19 different countries and from 20 different high school curricula. Approximately 75% of the students are female [9].

Research Team

CBME requires medical educators to reimagine almost every aspect of undergraduate medical training, including curriculum delivery and assessments. Therefore, the proposed multiphase study is meant to be conducted through a reliable student-faculty partnership, which is expected to facilitate the entailed processes. This includes involving students as coinvestigators, where they are considered partners in the entailed decision-making processes, through their active engagement in collaborative meetings. The 3 student researchers who are involved in the proposed multiphase study include MG, IF, and AA, who are drawn from across the spectrum of the respective medical curriculum. Further, as the proposed study forms a part of a process whereby MBRU engages in continuing self-evaluation to measure achievements and outcomes as they relate to the institution's preset goals (ie, effectiveness of MBRU as an institution in disseminating medical and health sciences education), a member of the strategy and institutional excellence (SIE) team (ie, the entity handling the MBRU Quality Assurance and Institutional Effectiveness portfolio), FO, is part of the team as a co–principal investigator. She is a senior specialist in the SIE unit with expertise in research design and quantitative and qualitative data analyses. Her research interest is focused on means of nurturing health professionals to equip them with competences complementary to basic and clinical medical sciences and how this affects the health professionals' clinical performance and, in turn, outcomes of care. The global aspect of this study is overseen by YB. His research expertise in medical education is primarily focused on epistemology, ethnography, delineation of strategies for integration, and contextualization of basic sciences in the medical curriculum to inform clinical practice, change-management models, and Pierre Bourdieu's multifaceted concept of habitus with the aim to understand and transform how groups with diverse clinical proficiency work together to improve patient outcomes. The involvement of a multidisciplinary student-partnered team is, therefore, meant to raise the reliability of the proposed research project and its findings.

The Educational Intervention Under Investigation

The FAIS was implemented in a biochemistry course in the first semester of a 6-year bachelor of medicine, bachelor of surgery program. The reason the FAIS was implemented in this course is because one of the key aims of this course is to develop explicit associations among basic research, medical

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understanding, and the patients' perspectives. When developing the FAIS, each area of knowledge, skills, and attitudes was considered. Assessment formats were developed in alignment with the Miller's learning pyramid (Figure 1) [7]. The "student knows" and "student knows how" were assessed with multiple-choice questions and long cases. "Student shows" was assessed with laboratory examinations and objective structured practical examinations. "Student does" assessed the students' competences of analysis of biochemical data. The assessments used to assess "student knows," "student knows how," and "student shows" were standardized assessments. "Student does" level assessments were unstandardized.

Research Design

The multiphase study, proposed in this protocol, is meant to rely on a convergent mixed methods design [10], where the qualitative and quantitative data are independently collected and analyzed. Following that, the output of analysis is systematically merged using joint display analysis process [11,12]. Integration of the output of analyses, as such, is expected to raise the reliability of the study findings, enabling the generation of a holistic understanding of the subject matter. The study comprises 4 phases: data collection, data analyses, information integration, and knowledge generation (Table 1).

Table 1. Outline of the design of the proposed proof-of-concept study.

Phase 1: data collection	Phase 2: data analyses	Phase 3: information integration	Phase 4: knowledge generation
Qualitative: focus group session	Braun and Clarke's [13] 6-step framework	Joint display analysis to generate meta-inferences	Interpretation of study findings
Quantitative: students' performance in the summative assessment	ANOVA with a *P* value of ≤.05	Joint display analysis to generate meta-inferences	Interpretation of study findings

Ethical Considerations

Since the proposed study entails "no more than minimal risk" on human participants, and all the data are already collected as part of institutional research functions and handled by the SIE team at MBRU (which adhere, by virtue of design, to the ethical principles of autonomy, justice, and beneficence), an exempt review will suffice. Progressing with the analyses, reflected upon in this protocol (namely qualitative and quantitative analyses and joint display analysis), is contingent upon the exempt review clearance of the institutional review board of MBRU.

Evaluation of Students' Perceptions

The qualitative component of the study, as illustrated in Table 1, revolves around carrying out a focus group session [14-16] composed of 7-10 randomly selected students from the cohort of 71 students who were exposed to the FAIS. One of the study investigators, who is experienced in socio-behavioral research and was not involved in planning or implementing the FAIS, facilitated the focus group session based on a preset focus group protocol designed for this study (Multimedia Appendix 1). Prior to conducting this focus group session, the protocol underwent face and content validation. The students' participation in this focus group session was completely voluntary, and each participant was required to provide verbal consent prior to the commencement of the session. The data collection, integral to this component of the study, was exploratory, where the participants were invited to externalize their thoughts in relation to their individualized experiences with the FAIS.

Student investigators attended the focus group session in order to ensure flow of the entailed discussions and to take notes and arrange for the recording of the session. The inductive qualitative data analysis will follow Braun and Clarke's [13] 6-step framework recently endorsed in health professionals' education research [17].

Evaluation of the Impact of the FAIS on Students' Performance in Summative Assessments

The quantitative component of the study, as illustrated in Table 1, revolves around the investigation of the effect of the FAIS on the students' performance in the summative assessment. As such, the performance in the summative assessment of the 71 students enrolled in the cohort that was exposed to the FAIS will be compared to that of the students enrolled in a cohort that was not exposed to the FAIS. ANOVA will be performed with the scores of the summative assessments of all students enrolled in both cohorts. A *P* value of ≤.05 will be considered the level of significance.

Joint Display Analysis

The output of analyses of the qualitative and quantitative components of this study (ie, first level of inferences), as illustrated in Table 1, will be integrated using the iterative joint display analysis process [11,12], which enables the development of a macrolevel understanding of the subject matter.

Study Plan

The total duration of the proposed study is 6 months. The key milestones and time line are shown in Table 2.

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Table 2. Plan of the proposed multiphase study.

Milestones	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6
Planning for the formative assessment intervention	✓[a]					
Developing and validating the focus group protocol	✓					
Implementing the formative assessment intervention		✓	✓	✓		
Recruiting study Participants				✓		
Conducting the focus group session					✓	
Analyzing data (qualitative and quantitative, and joint display analysis process)					✓	
Reporting on generated information					✓	
Preparing for knowledge sharing						✓

[a]✓: indicates completion of the task at the set deadline.

Results

The mixed methods study proposed in this protocol is expected to generate a systemic understanding of the effectiveness of the respective FAIS educational intervention. This involves exploring the students' perceptions regarding the FAIS, along with investigating the intervention's effectiveness in enhancing the participating students' performance in the corresponding summative assessment. It will shed light on the participating students' attitudes in relation to the use of FA in achieving competency goals and in fostering self-directed learning. It could also uncover the hypothesized association between the FA intervention and enhanced performance in summative assessments.

Discussion

Anticipated Findings

A systemic understanding of the effectiveness of the FAIS in enhancing academic performance and enabling self-directed learning will be developed through the proof-of-concept study proposed in this protocol. The multistage inductive qualitative analysis is expected to generate a conceptual framework that describes the educational intervention from the viewpoint of the learners. The respective framework is expected to highlight the students' reactions and the perceived effects of the FAIS (short- and long-term) and opportunities for improvement. The quantitative component is meant to investigate the association between the FAIS and academic performance (in the summative assessment). The joint display analysis will reveal the lessons learned from the firsthand implementation of the FAIS in the context of the study, and the factors (ie, enablers) that need to be taken into account to maximize the value of such an educational intervention to all involved parties.

Within the context of the study, our findings will shed light on opportunities to maximize the value of the educational intervention, especially in relation to engaging and empowering the students and fostering self-directed learning. The perception of the students of the experience will be factored into the design of upcoming rounds of the FAIS, which is expected to raise the reliability of such interventions [18]. Additionally, if the outcomes are favorable, the long-term goal is to implement the designed and improved FA intervention across all courses in the program under investigation, for which we will strategize a change management approach using Mento's change management model [19].

Self-directed learning has gained widespread recognition [20]. Medical educators have been experimenting with differing techniques to foster self-directed learning and in turn lifelong learning habits [18,21,22]. The study proposed in this protocol is likely to prove that the FAIS is effective in enhancing academic performance through fostering self-directed learning [23,24]. It is expected to enable learners to develop self-regulatory strategies by promoting cognition (ie, learning) and meta-cognition (ie, learning to learn) [25]. Hence, critical and higher-order thinking, along with integration of disciplinary knowledge, are likely to be improved [26]. This will enhance the students' preparedness for summative assessment. It will be interesting to explore the students' perceptions of the learning experience, since it is believed that active student engagement and learner agency can only be ensured when the learners (actually) perceive the benefits of the educational intervention. The proposed study is meant to suggest evidence-driven ways to make the true value of the educational intervention prominent to the learners.

Limitations

The proposed study is characterized by certain limitations. The mixed methods research design, systematically integrating qualitative with quantitative data, enables the generation of thorough insights into the subject matter [27]. Yet, given that the FAIS is implemented in a single biochemistry course in the Basic Medical Sciences component of an undergraduate entry, competency-based medical curriculum at MBRU, the generalizability of the findings is limited. The context of the study is described in detail to enable the transferability of the findings to contexts similar to those under investigation. Also, the study design, especially how the quantitative component is structured, enables investigations of potential associations. Yet, it does not allow for the uncovering of causalities. It would be worthwhile for future studies to take longitudinal approaches that actually reveal the intricacies of the relationship of FAs and academic performance and other desired skills (eg,

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self-directed learning and academic resilience) [12], which may turn out to play a moderating (or even mediating) role.

Conclusions

The findings of the proposed study constitute evidence in relation to the application of FAs, which can be leveraged by other medical educators in contexts similar to those under investigation.

Acknowledgments

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Data Availability

All data analyzed during this study are included in this published article (and its supplementary information files).

Conflicts of Interest

None declared.

Multimedia Appendix 1
Online Focus Group Protocol.
[PDF File (Adobe PDF File), 63 KB - resprot_v12i1e41626_app1.pdf]

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Abbreviations

CBME: competency-based medical education
FA: formative assessment
FAIS: Formative Assessment as an Instructional Tool
MBRU: Mohammed Bin Rashid University
SIE: strategy and institutional excellence

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Protocol

Sociocultural and Behavioral Features of Anticipated COVID-19 Vaccine Acceptance in Papua New Guinea: Protocol for a Mixed Methods Study

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Abstract

Background: COVID-19 was characterized by the World Health Organization (WHO) as a pandemic in 2020. Papua New Guinea (PNG) has remained on high alert ever since, and its National Control Centre continues to coordinate national preparedness and response measures, guided by its Emergency Preparedness and Response Plan for COVID-19. As part of the WHO and the Global Alliance for Vaccines and Immunization's COVID-19 Vaccines Global Access (COVAX) program, PNG received several shipments of COVID-19 vaccine doses. A nationwide vaccine rollout for COVID-19 was initiated in PNG in May 2021. Despite the availability of vaccines and the capacity of health systems to vaccinate frontline workers and community members, including high-risk groups, there are still critical issues related to vaccine safety, confidence, and acceptance to ensure the effectiveness of the COVID-19 vaccination campaign. Evidence from studies on COVID-19 vaccine acceptance and demand in low- and middle-income countries (LMICs) suggests that sociocultural characteristics of the community and the behaviors of different vaccine stakeholders, including vaccine recipients, vaccine providers, and policymakers, determine the effectiveness of vaccination interventions or strategies.

Objective: This study will examine sociocultural determinants of anticipated acceptance of the COVID-19 vaccine in urban and rural areas of different regions in PNG and health care providers' views on vaccine acceptance.

Methods: The study design uses a mixed methods approach in PNG's coastal and highlands regions. The first research activity will use a qualitative methodology with an epistemological foundation based on constructivism. This design elicits and listens to community members' accounts of ways culture is a rich resource that provides meaning to the COVID-19 pandemic; the design also measures adherence to *niupela pasin* ("new normal" in Tok Pidgin) and vaccination acceptance. The second activity will be a cross-sectional survey to assess the distribution of features of vaccine acceptance, priorities, and practices. The third activity will be in-depth interviews of health care providers actively involved in either COVID-19 clinical management or public health–related pandemic control activities.

Results: The project proposal has been reviewed and approved by the Medical Research Advisory Committee of Papua New Guinea. Qualitative data collection started in December 2022, and the survey will begin in May 2023. The findings will be disseminated to the participating communities later this year, followed by publication.

Conclusions: The proposed research on community views and experiences concerning sociocultural and behavioral features of acceptance of the vaccine will provide a better understanding of communication and education needs for vaccine action for COVID-19 control in PNG and other LMICs. The research also considers the influence of health care providers' and policy makers' roles in the awareness and use of the COVID-19 vaccine.

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KEYWORDS

COVID-19 vaccine; vaccine acceptance; vaccine demand; community views on vaccine; vaccine stakeholders; health care workers; Papua New Guinea; emergency preparedness; public health intervention; COVID-19; health promotion; community health; Melanesian culture; vaccine uptake; vaccine awareness; vaccine priorities

Introduction

Background

COVID-19 affected almost every country in the Pacific region, including Papua New Guinea (PNG). As of August 2022, a total of 45,133 confirmed COVID-19 cases were reported in PNG, resulting in 668 deaths [1]. However, these numbers may be an underestimate caused by nonoperational information systems in rural areas. Globally, as a pandemic preventive strategy, countries have been using nonpharmaceutical interventions (NPIs), such as enforced use of face masks, hand sanitization, physical distancing, travel restrictions, avoidance of large gatherings, school closures, and partial or complete lockdowns. [2]. The health department in PNG has introduced the *niupela pasin* ("new normal" in Tok Pidgin) policy, referring to the changes in behavior and habits that individuals and communities need to adopt to prevent the spread of the virus [3]. Despite these NPIs and policies, there have been increased new cases and deaths each day throughout the world.

COVID-19 Vaccines

Vaccines are the most reliable and effective public health intervention to prevent many infectious diseases [4,5]. Other interventions, like developing practical diagnostic tools and therapeutic drugs, also help clinical management and reduce mortality and morbidity. Therefore, developing and producing safe and effective vaccines remains one of the essential tools for ending the COVID-19 pandemic, along with NPIs [6]. In collaboration with global research institutions, the World Health Organization (WHO) and other global agencies accelerated the development process of COVID-19 vaccines while maintaining the highest standards of safety [7]. The WHO emergency use listing approved several vaccines developed on different platforms. The COVID-19 Vaccines Global Access (COVAX) program is a groundbreaking collaboration between the WHO, the United Nations Children's Fund (UNICEF), the Global Alliance for Vaccines and Immunization (GAVI), and the Coalition for Epidemic Preparedness Innovations (CEPI) to accelerate the development and production of vaccines and equitable access to them for every nation in the world [8]. So far, the COVAX program has provided 71 million vaccine doses to 125 participating countries [9]. Many countries have initiated vaccine rollouts at a national level since 2021. However, with equitable access to and availability of COVID-19 vaccines, the issue of vaccine acceptance and uptake among different high-risk groups, including frontline health workers and the general population, remains critical.

Research on COVID-19 Vaccine Acceptance

Although vaccines are generally well-received, the fast-tracking of COVID-19 vaccine development procedures and the use of new platforms, such as RNA-based vaccines, has created some doubts about vaccine safety and reduced confidence. Vaccine confidence can be defined as the trust and willingness of individuals and communities to accept and use vaccines, and it is important to measure vaccine confidence to identify and address community concerns about vaccination [10]. In general, vaccine hesitancy undermines vaccine acceptance and demand. The WHO's Strategic Advisory Group of Experts (SAGE) on immunization defined vaccine hesitancy as a delay in acceptance or refusal of vaccination despite the availability of vaccination services [11,12]. It is crucial to assess the determinants of vaccine acceptance among vaccine recipients to deal with vaccine hesitancy.

Almost all countries in the world prioritized frontline workers for COVID-19 vaccination. However, research suggests that health care workers' anticipated COVID-19 vaccine acceptance rates vary from low to high [13-15]. A global survey based on 13,426 participants from 19 countries showed that global acceptance of COVID-19 vaccines ranges between 54.8% in Russia to 88.6% in China [16]. In a narrative review of 15 studies, frequently given reasons for refusing the COVID-19 vaccine were related to the fast-tracked vaccine development and vaccine safety and effectiveness [17]. Nevertheless, the WHO has stated that vaccine safety was not compromised by fast-tracking development [7]. With careful evidence-based communication strategies, it is possible to convey the safety of COVID-19 vaccines to the general population.

Public Health Priority of COVID-19 Vaccines in PNG

PNG is the largest country in the Pacific region. The health system of PNG has been struggling for decades to provide universal access to quality services [18]. Nevertheless, PNG has remained on high alert ever since COVID-19 was characterized by the WHO as a pandemic in 2020, and its National Control Centre (NCC) continues to coordinate national preparedness and response measures guided by its Emergency Preparedness and Response Plan for COVID-19 [19]. As in many low- and middle-countries (LMICs), even PNG, vaccination is the only way of protecting frontline workers and community members during the COVID-19 pandemic. As part of the COVAX program, 588,000 COVID vaccine doses were allocated for PNG. The National Department of Health initiated a nationwide vaccine rollout for COVID-19 on May 4, 2021 [20]. So far, more than 348,938 doses have been administered in 22 provinces of PNG [1].

Rationale for This Research

Despite the availability of vaccines and the capacity of health systems to vaccinate frontline health care workers and community members, issues related to vaccine safety, confidence, and acceptance remain critical for the effectiveness of the COVID-19 vaccination campaign. Evidence from studies on differing vaccine acceptance in LMICs suggests that

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sociocultural factors in the community and the behaviors of different vaccine stakeholders, including vaccine recipients, vaccine providers, and policy makers, determine the effectiveness of vaccination interventions or strategies. So far, no literature exists on determinants of COVID-19 vaccine acceptance in the PNG context.

Understanding the local context is critical for an effective vaccination program at the community level. The proposed research on community views and experiences concerning sociocultural and behavioral features of anticipated vaccine acceptance will enable a better understanding of communication and education needs for vaccine action for COVID-19 control in PNG and other LMICs. Our pilot study, which explored views on COVID-19 vaccines among students (n=90) with different cultural backgrounds at the Faculty of Medicine and Health Sciences of Divine Word University, indicated 50% tentative acceptance and highlighted the role of the media in determining vaccine acceptance.

Objectives

This study will examine sociocultural determinants of anticipated acceptance of the COVID-19 vaccine in urban and rural areas of different regions in PNG. The following are the specific study objectives: (1) understand community members' accounts of experiences, meaning, and behavior concerning the COVID-19 pandemic, as well as their awareness of and adherence to *niupela pasin* and their perceptions of vaccines based on Melanesian culture, and (2) assess the role of health care providers in determining COVID-19 vaccine acceptance in the coastal and highlands regions, considering their awareness, acceptance and personal use, and vaccine recommendation practices.

Methods

Study Design

The research project will use a mixed methods design. The first research component will use a qualitative methodology with an epistemological foundation that is based on constructivism and embraces meaningful reality as it is socially constructed [21]. This design elicits and listens to community members' accounts of ways culture is a rich source of meaning in the COVID-19 pandemic, their adherence to *niupela pasin*, and their vaccination acceptance. In the context of health, adherence to the new normal is an indicator of the behavior of communities toward their health and is important for understanding these communities. This design will proceed with individual, in-depth, semistructured interviews with community members, community opinion leaders, and church leaders.

The second component, a cross-sectional survey, will use data collected from ethnographic key informant interviews to develop an instrument with open-ended and closed questions. The survey design adapts the WHO immunization and vaccine-related implementation research advisory committee's vaccine stakeholder framework to assess the awareness, priorities, and practices of community members. This design includes an integrated quantitative and qualitative methods approach, and the data collected will indicate the distribution of key features of vaccine acceptance and demand [22].

The third component, semistructured interviews with health care providers actively involved in either COVID-19 clinical management or public health–related pandemic control activities, will determine vaccine acceptance factors. This component will focus on assessing health care providers' views on personal vaccine acceptance and their role in facilitating community vaccination.

Study Sites

This study will proceed in urban and rural areas in the coastal and highlands regions of PNG. Most of the PNG population lives in rural areas (85%), and the economy is primarily agricultural. We selected the Momase region as the coastal region in our study. The Momase region is composed of 4 constitutional provinces with a population over 1.8 million (2011 census). Madang is one of the provinces in this region; it has a population of 493,906 (2011 census). The study will be conducted in urban and rural villages in Madang district.

The Highlands region is the most densely populated region of PNG, with 23% of the total PNG population (2011 census). This region is composed of 7 provinces. The Eastern Highlands province is in the central highland's cordillera and has a population of 579,825 (2011 census). Goroka is the capital of this province. The study will be conducted in Goroka and in rural villages of the Lufa district. These study sites are culturally and linguistically diverse. Tok Pidgin is the lingua franca.

Study Groups and Sampling

Community Members

The criteria for including community members in interviews and the cultural epidemiological survey are being aged between 18 to 65 years and being cognitively able and willing to participate. The study will be conducted in either English or Tok Pidgin and participants should be able to communicate in either of these languages.

In-depth Interviews

A purposive sampling strategy will be used for recruiting participants for in-depth interviews. The sample will be distributed equally among male and female participants (ie, a 50% gender distribution). Community members are key stakeholders in adhering to *niupela pasin* and providing meaning to vaccine acceptance and demand. Starting with exploring and understanding their views is therefore critical.

A collaborating team of research assistants at each study site will initially meet local communities in urban and rural sites to establish rapport. Community opinion leaders and leaders of formal and informal community groups will be contacted, and we will explain the purpose and anticipated value of the study. Further, we will request their participation and assistance to facilitate community participation. Engaging these urban and rural opinion leaders and enlisting their cooperation will facilitate the planning and implementation of in-depth interviews. We will interview church leaders from the selected study sites.

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The team of research assistants will go from house to house in parts of the selected study area to identify potential participants and achieve the desired sample compositions of urban and rural and male and female participants. The team will explain the purpose of the visit, solicit potential participants' willingness to participate in the study, and, if they agree, obtain their informed consent (one-to-one) in confidence and with due attention to privacy. A total of 48 in-depth interviews will be conducted (12 community opinion leaders, 24 community members, and 12 church leaders). All interviews will be audio-recorded. The duration of each interview will be approximately 30 to 45 minutes.

Vaccine Acceptance Survey

A random sampling strategy will be used to select the participants for this survey. We plan to use either the voters' list or household listings to randomize the sample at an individual level or use village maps to randomize households to select the eligible participants. This will be achieved in collaboration with the provincial health authority (PHA). However, randomization depends on the availability of these resources. Otherwise, a convenience sample will be selected from the urban and rural areas of the selected study sites, stratified by gender (with a 50% distribution) and age group (18-40 years and 41-65 years). Trained research assistants working in 2 teams will conduct the survey, one interviewing and the other responsible for maintaining the data records. Approximately 360 interviews will be conducted (180 in each of the two regions. We calculated the sample size at a 5% margin of error with a 95% confidence level and a 50% response distribution.

Health Care Providers

Health care providers involved in either COVID-19 clinical management or public health–related pandemic control activities in the selected study sites will be interviewed. We will identify key informant health care providers during earlier stages of the study based on respondent-provided information that identifies health care professionals engaged in relevant activities.

This sample will be selected purposively, and a question guide will guide the in-depth interview. The rationale for using in-depth interviews is to allow health care professionals to share their experiences and views privately without having another person in the room. A total of 16 interviews will be conducted with clinicians, health extension officers, nurses, midwives, and community health workers in health facilities (government and church-based), including provincial hospitals and health centers of urban and rural study areas.

Data Management and Analysis Plan

The study instruments were pilot-tested during training workshops for validity and feasibility. The interview guides for community members and health care workers were developed after consulting experts in the field and the literature. They were pilot-tested with potential participants for rigor and credibility. For the quantitative survey, we adapted an instrument developed by one of the authors for a vaccine acceptance study in India. After completing the qualitative component, we will further develop this questionnaire to ensure feasibility in the study context. This instrument will be tested for content and face validity. All the interview guides and initial questionnaires were developed in English and translated into Tok Pidgin. All instruments were then back translated to English for accuracy.

Data Collection

In-depth interviews will be audio-recorded, and notes will be taken by the field investigators and research assistants. Qualitative data from in-depth interviews will be transcribed verbatim, translated into English, and imported into MAXQDA (version 2020; VERBI Software) for analysis.

The data collection and management of cultural epidemiology will be done using the Open Data Kit (ODK) tool (GetODK). Data will be collected digitally on an Android tablet using the ODK Collect application. Later, the data will be uploaded to a cloud server. From there, the data set will be downloaded as an Excel (Microsoft Corp) spreadsheet.

Data Security

All interviews will be recorded for documentation. The information recorded is confidential. Data sheets, audio records, and transcripts will have unique identifier codes. They will not bear the participant's name. Soft copies (ie, audio records and transcripts) will be stored electronically on password-protected external hard disks or drives. Hard copies (ie, data sheets) will be stored under lock and key at the faculty office. Informed consent forms will bear participants' names and signatures. Therefore, they will be kept under lock and key separately from data sheets, audio records, and transcripts. They will be accessible through only the principal investigator or coinvestigators, with lists linking unique identifier codes to names. Data sheets, audio records, transcripts, and informed consent forms will be destroyed (by incineration or digital erasure) 3 years after study completion.

Analysis Plan

The primary goal of the study is to clarify descriptive, comparative, and analytic accounts of explanatory models of COVID-19 and how they explain awareness, acceptance, and use of vaccines. Comparative analysis will focus on questions of gender and rural-urban features of the COVID-19 pandemic and determinants of anticipated acceptance or refusal of COVID-19 vaccines.

Qualitative Analysis

The in-depth interviews of community members will provide their views on the risk of contracting the virus, behavior to prevent the virus, experience and meaning of COVID-19, and their perception of COVID-19 vaccination. The interviews with health care workers will provide their views about COVID-19 vaccine priorities and practices and their recommendations for promoting the rollout of vaccination. All these in-depth interviews will be transcribed verbatim, verified against the audio tapes, and translated into English. The English transcripts will then be imported into MAXQDA software for managing the data. Thematic analysis will be used as an inductive and deductive process. Analysis involves familiarization with the data, generation of codes, and discovery of initial themes. Themes will be refined through an interactive process, and a

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coding framework will be developed that reflects the core themes [23]. A team of research assistants with author ES will develop codes using an inductive approach, allowing themes to emerge from the data. A coding framework will be used to categorize codes and identify meaningful and potential themes. We will perform peer debriefing regularly to discuss the emerging themes and interpretations, ensuring the rigor of the analysis.

Quantitative Analysis

The epidemiological survey will be conducted on tablets with ODK software. All interviews will be uploaded electronically to Google Spreadsheets (Google Inc). The final data set will be downloaded as Excel spreadsheets. STATA/SE (version 16.1; Stata Corp) will be used for statistical analyses. A descriptive analysis will be conducted to summarize the important results. The sociocultural and demographic characteristics of the participants will be summarized. Illness-related questions, such as perceived causes, distress patterns, and help-seeking behaviors, will be presented and compared between different gender and age groups across study areas. The explanatory variables in this study will be social and cultural features of illness experience, meaning and behavior, and questions of awareness and use of the COVID-19 vaccines for prevention. Inferential analysis using regression models will assess the determinants of COVID-19 vaccine acceptance. Narratives of statistically significant factors will be reviewed to better understand their importance.

Ethical Approval

The study has been approved by the Medical Research Advisory Committee of PNG (MRAC#22.19), the Medical Research Committee of Madang PHA (MAPHAREC 06.22), and the Research and Ethics Committee of Eastern Highlands Province PHA. All participants will provide written informed consent in either English or Tok Pidgin before participating in the study. In the case of illiterate participants, verbal informed consent will be obtained in the presence of a family member or relative. The purpose, procedure, and potential risks of the study will be explained to the participants, and they will be informed that they can withdraw from the study at any time without consequences.

Results

The project proposal has been reviewed and approved by the Medical Research Advisory Committee of PNG. The permissions required from the provincial health authority to conduct data collection in the selected provinces have been obtained. The research team has recruited participants for in-depth interviews, including key informants in the communities and health facilities. The qualitative data collection started in December 2022, and the preliminary analysis of these data is underway. The insights from the in-depth interviews will be used to further refine the survey instrument by adapting it to the local context. We plan to pretest the survey instrument for validity and proceed with the survey in May 2023. The findings from the interviews and the survey will be disseminated to the participating communities and key stakeholders in a professional dissemination meeting, followed by publication.

Discussion

Expected Outcomes

This study's experiences and findings will contribute to the effective planning and implementation of the COVID-19 vaccine program in PNG. Furthermore, our findings and approach to health social science vaccine research will have implications and potential applications elsewhere for strategic planning of effective action for other vaccines. The following are anticipated specific contributions of the study: (1) identify priorities and approaches for community action based on Melanesian culture to contribute to health system preparedness for control of pandemics; (2) understand the awareness and acceptance of vaccines for COVID-19, indicating the potential value of COVID-19 vaccines in PNG; (3) clarify current views of clinicians and other health professionals concerning their enthusiasm or reluctance to promote vaccine action to control COVID-19; (4) develop and clarify the value of an approach to studying vaccine acceptance in local settings so that planning may consider the relevance of cultural features of health and illness on anticipated and actual vaccine acceptance; (5) clarify features and determinants of COVID-19 vaccine acceptance that can guide policy to ensure that efficacious vaccines are also effective in the context of actual public health action (findings should guide strategic planning to address knowledge gaps and misunderstandings about the benefits and risks of COVID-19 vaccines); and (6) contribute to the National Research Agenda of PNG to strengthen the operation and delivery of the health system and services.

Potential Impact on Participants

It is possible that participating in the study may influence participants' views on COVID-19 vaccines. For example, exposure to information about the COVID-19 vaccine or discussions about vaccine hesitancy during data collection may lead participants to change their attitudes or beliefs about the vaccine. To mitigate any unintended consequences and ensure the ethical conduct of the study, we will maintain (1) informed consent, (2) accuracy of information, (3) voluntary participation, and (4) confidentiality. First, all participants will be provided with detailed information about the study and its purpose and will be asked to provide informed consent before participating. This will ensure that participants fully understand the nature of the study and the potential impact it may have on their views. Second, all participants will be provided with accurate and unbiased information about the COVID-19 vaccine, both before and after participating in the study. This will help to ensure that participants have access to the information they need to make informed decisions about the vaccine. Third, participation in the study will be completely voluntary, and participants will be free to withdraw from the study at any time without penalty. This will help to minimize any potential for coercion or undue influence on participants. Fourth, all data collected during the study will be kept confidential and participants' identities will be protected. This will help to ensure that participants feel comfortable sharing their views and that their privacy is respected.

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By taking these steps, we hope to minimize any unintended consequences of the study design on participants' views on COVID-19 vaccine acceptance and ensure that the study is conducted ethically and with the informed consent of participants.

Limitations

The proposed study design does not include any provinces from the Southern or Islands regions of PNG. We recognize that the generalizability of our study findings will be limited to the Highlands and Coastal regions. However, the Southern and Islands regions can also be categorized as coastal areas. In addition, this study might be subject to social desirability bias. In general, participants will provide responses that they believe are socially acceptable, rather than responding truthfully. To address this potential bias, open-ended questions and follow-up probes will be used to encourage participants to provide detailed and honest responses. However, some participants may still be hesitant to disclose certain information. In addition, the study will be limited by the potential impact of stigma on recruitment and participation. Participants might be hesitant to participate or disclose certain information due to concerns about stigma or judgment. Efforts will be made to address these concerns, including providing a safe and confidential environment for participation, but the impact of stigma on the findings will be considered when interpreting the results.

Acknowledgments

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Data Availability

The data sets generated and/or analyzed during this study will be available in subsequent papers.

Authors' Contributions

JGG and ES are responsible for the study design. JGG and CM will be responsible for the quantitative data collection and analysis. ES will be responsible for qualitative data collection and analysis. All authors contributed equally to the writing and critical review of the protocol for important intellectual content. The final manuscript was read and approved by all authors.

Conflicts of Interest

None declared.

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Abbreviations

CEPI: Coalition for Epidemic Preparedness Innovations
COVAX: COVID-19 Global Vaccine Access
GAVI: Global Alliance for Vaccine and Immunization
LMICs: low- and middle-income countries
NCC: National Control Centre
NPI: nonpharmaceutical interventions
ODK: Open Data Kit
PHA: provincial health authority
PNG: Papua New Guinea
SAGE: Strategic Advisory Group of Experts
UNICEF: United Nations Children's Fund
WHO: World Health Organization

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Protocol

Prevalence of Antibiotic-Resistant Pathogenic Bacteria and Level of Antibiotic Residues in Hospital Effluents in Selangor, Malaysia: Protocol for a Cross-sectional Study

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Abstract

Background: Antimicrobial resistance (AMR) has emerged as a major global public health challenge due to the overuse and misuse of antibiotics for humans and animals. Hospitals are among the major users of antibiotics, thereby having a large contribution to AMR.

Objective: The aim of this study is to determine the prevalence of antibiotic-resistant pathogenic bacteria and the level of antibiotic residues in the hospital effluents in Selangor, Malaysia.

Methods: A cross-sectional study will be performed in the state of Selangor, Malaysia. Tertiary hospitals will be identified based on the inclusion and exclusion criteria. The methods are divided into three phases: sample collection, microbiological analysis, and chemical analysis. Microbiological analyses will include the isolation of bacteria from hospital effluents by culturing on selective media. Antibiotic sensitivity testing will be performed on the isolated bacteria against ceftriaxone, ciprofloxacin, meropenem, vancomycin, colistin, and piperacillin/tazobactam. The identification of bacteria will be confirmed using 16S RNA polymerase chain reaction (PCR) and multiplex PCR will be performed to detect resistance genes (*ermB*, *mecA*, bla_{NDM-L}, bla_{CTX-M}, bla_{OXA-48}, bla_{SHV}, *VanA*, *VanB*, *VanC1*, *mcr-1*, *mcr-2*, *mcr-3*, *Intl1*, *Intl2*, and *qnrA*). Finally, the level of antibiotic residues will be measured using ultrahigh-performance liquid chromatography.

Results: The expected outcomes will be the prevalence of antibiotic-resistant *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* (ESKAPE) bacterial species from the hospital effluents, the occurrence of antibiotic resistance genes (ARGs) from the isolated ESKAPE bacteria, and the level of antibiotic residues that may be detected from the effluent. Sampling has been conducted in three hospitals. Data analysis from one hospital showed that as of July 2022, 80% (8/10) of *E. faecium* isolates were resistant to vancomycin and 10% (1/10) were resistant to ciprofloxacin. Further analysis will be conducted to determine if the isolates harbor any ARGs and effluent samples

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are being analyzed to detect antibiotic residues. Sampling activities will be resumed after being suspended due to the COVID-19 pandemic and are scheduled to end by December 2022.

Conclusions: This study will provide the first baseline information to elucidate the current status of AMR of highly pathogenic bacteria present in hospital effluents in Malaysia.

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KEYWORDS

ESKAPE; antimicrobial resistance; hospital effluent; antibiotics; health care; antibiotic resistance; antimicrobial; hospital setting; antibiotic residues; wastewater

Introduction

Background

Antibiotics have been the most crucial medications for the treatment of infections since the 1940s. However, some bacteria have developed resistance to practically all of the widely accessible antibiotics, which makes them capable of causing serious illness, resulting in a significant public health issue. Due to the selective pressure caused by the overuse of antibiotics, antibiotic-resistant bacteria (ARB) have developed and spread among human and animal populations worldwide [1].

The overuse and abuse of antibiotics have contributed to the global epidemic of antimicrobial resistance (AMR). Environmental contamination with antibiotic residues and resistant microorganisms and genes due to human activity has been demonstrated in pharmaceutical plants and may be a leading driver of the spread of ARB. Insufficient wastewater management by bulk drug manufacturing facilities has led to unprecedented levels of contamination of water resources with antimicrobial pharmaceuticals, which seems to be associated with the selection and dissemination of carbapenemase-producing pathogens [2]. In India, the concentration of the most abundant drug, ciprofloxacin (up to 31,000 µg/L), was reported to exceed the toxicity level by over 1000-fold [3].

Several hospital-acquired outbreaks caused by gram-negative bacteria such as *Acinetobacter baumannii* and *Pseudomonas aeruginosa* have been associated with contaminated water distribution systems [4-6]. The presence of *Escherichia coli* has been used as an indicator of fecal contamination in drinking water. Multidrug-resistant *E. coli* have been isolated from food sources [7] and urinary samples [8], as well as from hospital and municipal effluents [9]. However, the relationship between environmentally driven and clinically acquired resistant bacteria remains unclear; therefore, it is important to determine whether this effect is either strictly environmental or clinical.

The hospital setting has been the focus of AMR as one of the primary sources owing to the high usage of a wide range of antibiotics and the spread of antibiotic resistance genes (ARGs) that may be transferred by the ARB released into the environment from hospital effluents [10]. Some antibiotic-resistant pathogens such as methicillin-resistant *Staphylococcus aureus* (MRSA), carbapenem-resistant Enterobacteriaceae (CRE), and vancomycin-resistant enterococci (VRE) may pose significant risks to human health [11-13]. Ignorance that these possible effluent sources such as hospitals, including ARB or ARGs from clinical sources, can be dispersed and even thrive in the environment is likely to accelerate the development of multiple antibiotic–resistant bacteria.

Although antibiotics remain effective at treating many bacterial infections, some strains are extremely difficult to treat, and therapeutic options are becoming increasingly scarce. The term “ESKAPE” encompasses six such pathogens with growing multidrug resistance and virulence: *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *A. baumannii*, *P. aeruginosa*, and *Enterobacter* species [14]. ESKAPE pathogens are responsible for most nosocomial infections and are capable of resisting the biocidal action of antimicrobial agents. This phenomenon is caused by bacterial evolution; thus, AMR has increasingly become a problem with rapid rates of development and spread, and we are lacking new drugs to challenge these new superbugs.

The World Health Organization (WHO) has called for coordinated actions to minimize the emergence and spread of AMR by providing technical assistance for countries to develop national health action plans and urging more research and development on AMR [15]. In Malaysia, the collaborative effort between the Ministry of Health and the Ministry of Agriculture and Agro-based Industry resulted in the Malaysian Action Plan on Antimicrobial Resistance (MyAP-AMR) 2017-2021. The MyAP-AMR details plans to minimize AMR in both health care practices and agricultural sectors, including increasing awareness of antimicrobials, appropriate usage of antibiotics in clinical settings, and pollution influenced by the direct use of antibiotics in poultry farms [16].

The Bacteriology Unit, Infectious Diseases Research Centre in the Institute for Medical Research has performed profiling of antibiotic resistance from a poultry farm and clinical samples in Malaysia. Some published studies also reported the presence of pharmaceutical residues from surface water in Malaysia. Al-Odaini et al [17] documented the presence of human pharmaceutical products—including antidiabetic, antihypertensive, and hypolipidemic agents; β2-adrenergic receptor agonists; antihistamines; analgesics; and sex hormones—in river water and sewage effluents, although no antibiotics were measured. Praveena et al [18] reported the presence of pharmaceutical residues, including antibiotics, in three rivers in Selangor, Malaysia. The researchers detected ciprofloxacin in all samples, which was the most common pollutant in the rivers. Recently, Bong et al [19] found that

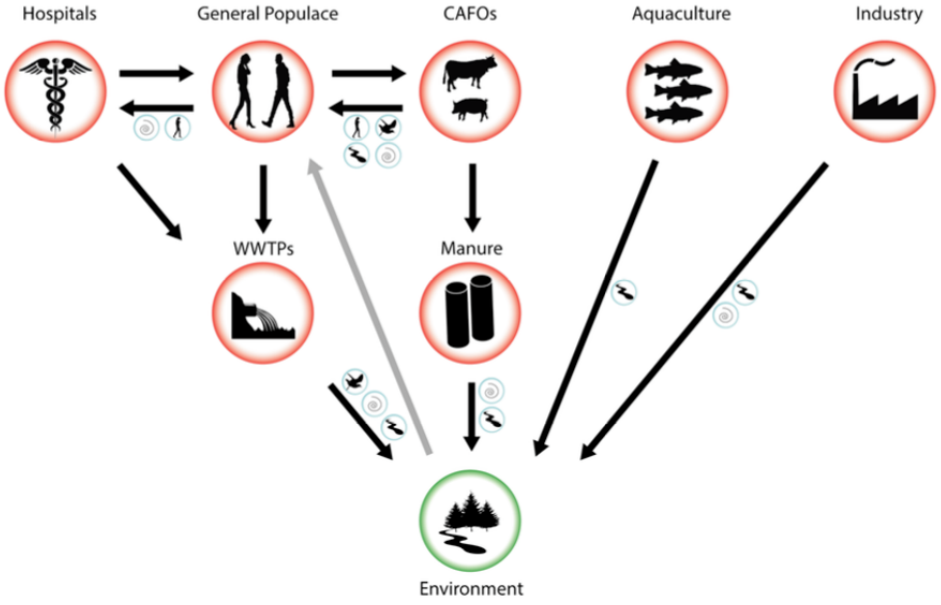
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multiple antibiotic-resistant phenotypes of *E. coli*, harboring the *tet* and *sul* resistance genes, were more prevalent in wastewater effluents than in the river waters. A concerted effort has been carried out to address the issue of AMR in clinical settings and the misuse of antibiotics in the current practice of poultry farming and pharmaceutical manufacturing industries. However, Malaysia lacks research on environmental aspects that may contribute to AMR, particularly the possibility of ARB and ARGs that may be released from hospitals into the environment through various modes. Moreover, no study has investigated whether antibiotic residues present in the hospital effluent contribute to the AMR problem in Malaysia. Since hospitals are the major users of antibiotics, it is important to determine the status of the effluent water from our hospitals that is released into the environment. However, to date, there has been no monitoring of the antibiotic residues under wastewater management in Malaysia. Therefore, this proposed study represents a first step to fill this gap to better address the AMR issues in Malaysia.

Dissemination of Antibiotic Resistance

Antibiotics can enter the environment through several different routes. Antibiotics and their metabolites are released from hospitals with urine and feces from patients as hospital wastewater effluent [20]. Similarly, antibiotics are released into the wastewater treatment system from people taking antibiotics in their homes [21]. Antibiotics are also used therapeutically or as growth promoters in livestock and poultry in Malaysia. Antibiotics and their metabolites will spread through animal excrement and end up in fields and groundwater, or in the case of antibiotic use in fish farms directly into the aquatic environment [22] (Figure 1). Regardless of the routes for antibiotics disseminating in the environment, it is also likely that resistant bacteria follow the same routes of dispersal [23]. This results in an environment where antibiotics, ARGs, resistant bacteria, and the environmental bacterial flora are mixed. However, the environment is likely becoming a resistance hotspot where ARGs can proliferate and undergo a process of evolution to result in the development of new resistant strains. Pathogens can acquire an ARG from the environmental gene pool by either conjugation, transformation, or transduction. The most important genetic elements capable of being transferred by conjugation are plasmids and integrative conjugative elements, which may carry ARGs and potential virulence genes.

Figure 1. Schematic flow of antibiotic-resistant bacteria (ARB) and antibiotic resistance genes (ARGs) from hotspots of evolution and transmission (red circles) to the environment (green circle). Blue circles indicate possible vectors that may aid transmission between specific environments, including air, surface waters, humans, and other animal vectors. Black arrows indicate known flows of ARB and ARGs. The grey arrow indicates a possible transmission route from a contaminated environment back to the general populace. CAFO: concentrated animal feeding operation; WWTP: wastewater treatment plant (reproduced from Kraemer et al [22], which is published under Creative Commons Attribution 4.0 International License [24]).



Scale of the Problem

A total of 88 pathogen-drug combinations were used to quantify the worldwide burden of drug-resistant diseases in 2019. This resulted in an estimated 495 million fatalities, of which 127 million deaths were directly attributed to drug resistance [25]. By 2050, it is estimated that approximately 10 million lives will be at risk annually as a consequence of the rise in drug-resistant infections [26].

Furthermore, antibiotic resistance is a substantial economic burden worldwide. In 2006, approximately 50,000 Americans died due to two common hospital-acquired infections (HAIs), namely pneumonia and sepsis, costing approximately US $8 billion [27]. In Europe, the levels of antibiotic resistance are varied. The common causes of infections are used as indicators to focus on AMR in *S. aureus*, specifically against methicillin (ie, MRSA) as a common cause of severe infections in health facilities and the community. MRSA is among the resistant pathogens that are widely recognized to pose an urgent or serious threat to human health. CRE such as *K. pneumoniae and E. coli* are also recognized as major causes of HAIs, including pneumonia. The WHO has listed MRSA as a high-priority (priority 2) pathogen for research and development

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of new antibiotics, while CRE have been listed as critically important (priority 1) [28].

In Asia, India has been documented as one of the largest burdens of drug-resistant pathogens worldwide, including the highest burden of multidrug-resistant tuberculosis, along with alarmingly high resistance rates among gram-negative and gram-positive bacteria even to newer antimicrobials such as carbapenems and faropenem since its introduction in 2010 [29]. Regional studies in India reported high AMR among pathogens such as *Salmonella typhi*, *Shigella*, *Pseudomonas*, and *Acinetobacter* [30].

In Thailand, approximately 88,000 infections were attributed to AMR, resulting in at least 3.24 million additional days in the hospital and 38,000 deaths [31]. The Global Antimicrobial Resistance Surveillance System (GLASS) launched by the WHO was implemented in Siriraj Hospital in Bangkok, reporting that in-hospital mortality was significantly higher in patients with antibiotic-resistant bacteremia than in patients with antibiotic nonresistant bacteremia (40.5% vs 28.5%, $P<.001$) [32]. The same study concluded that patients with antibiotic-resistant bacteremia utilized more resources than those with antibiotic nonresistant bacteremia [32].

MRSA emerged in Singapore in the 1970s [33], rapidly becoming endemic in local health care facilities, with 35.3% of all *S. aureus* isolates reported to be methicillin-resistant in 2006 [34]. In another study, the prevalence of MRSA was found to be significantly higher in intermediate (29.9%) and long-term (20.4%) care facilities than in acute-care hospitals (11.8%) [35], and the organism has also been sporadically reported in the community as well as in local retail food and animals [36-38].

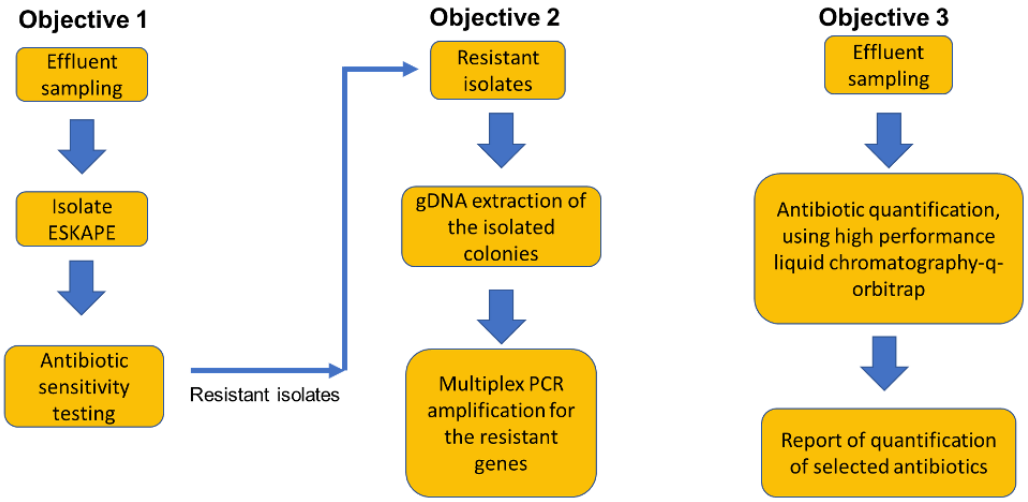
Nonetheless, there are limited studies examining the role of hospital effluents in contributing to the development of drug-resistant pathogens in the environment. Hospitals are the major users of antibiotics and may become one of the major contributors to AMR in the environment. Furthermore, the levels of antibiotic resistance in hospital effluents may be different from those of other water environments such as homes or agriculture. Therefore, the general aim of this study is to determine the prevalence of antibiotic-resistant pathogenic bacteria and the level of antibiotic residues in hospital effluents in Selangor, Malaysia. This study will also be determining the prevalence of ARB (specifically ESKAPE) present in the effluents of hospitals with an individual sewage treatment system, the occurrence of ARGs among ESKAPE bacteria, and the residual concentrations of antibiotics based on their usage at the selected hospitals. The findings from this study will provide important scientific evidence relevant to stakeholders that can help to reduce or interrupt the spread of AMR from clinical settings into the environment.

Methods

Study Design

A cross-sectional study will be performed at preidentified hospitals with three specific objectives as depicted in the workflow diagram in Figure 2. Objective 1 is to obtain resistant isolates of ESKAPE bacteria from the hospital effluent and to perform antibiotic susceptibility testing (AST). Objective 2 is to extract the genomic DNA of the resistant isolates from objective 1 to identify the isolates and the ARGs present in the isolates. Objective 3 is to quantify the level of targeted antibiotic residues from the hospital effluent samples. The targeted antibiotics that will be quantified are ceftriaxone, ciprofloxacin, meropenem, vancomycin, colistin, piperacillin, and tazobactam, which are the most highly used antibiotics in the hospital setting. The outcome of activities in objective 1 and 2 will provide estimates of the prevalence of the ARB in the hospital effluent, while the outcome of objective 3 will determine the level of antibiotic residues in the hospital effluent to address the overall aim of this study.

Figure 2. Summary of the workflow for this study. ESKAPE: Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, Enterobacteriaceae; gDNA: genomic DNA; PCR: polymerase chain reaction.



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Selection of Study Area

We will identify all the tertiary hospitals in Selangor, one of the states in Malaysia, prior to effluent sample collection, based on the following inclusion and exclusion criteria.

Hospitals with individual sewage treatment plants will be included. An individual sewage treatment plant is a system whereby the sewage from the hospital is the only source that enters the sewage treatment plant, as depicted in Figure 3. Hospitals with nonindividual sewage treatment plants will be excluded. A nonindividual sewage treatment plant is defined as a communal sewage treatment plant whereby the sewage entering the sewage treatment plant is coming from various sources such as housing, farming, and manufacturing industries, as illustrated in Figure 4.

Figure 3. The sampling point for the effluent sample to be collected is at the final effluent for the disposal outlet, as depicted in the diagram. This is the outlet after the treatment before entering the river system that is going to be treated by the Indah Water Treatment Plant to be used as a clean water source for the public.

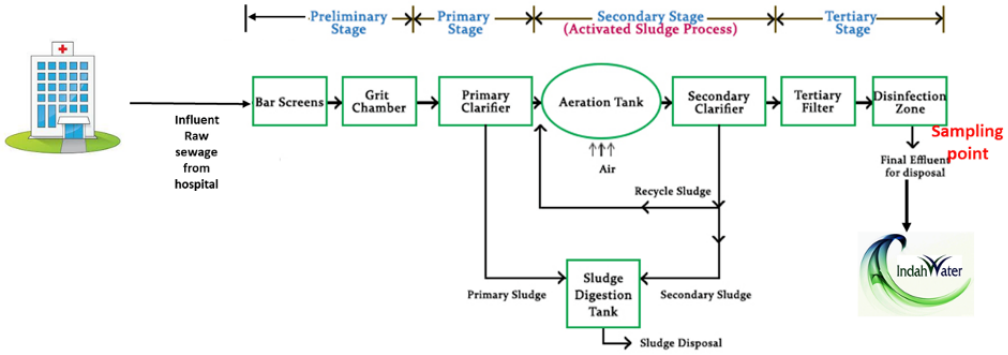
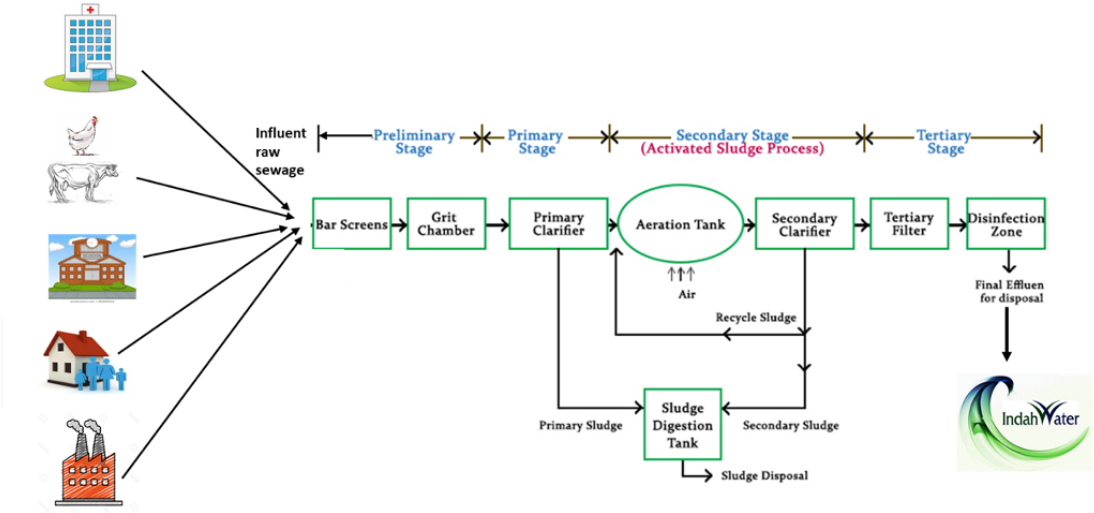


Figure 4. The waste from multiple human activities such as farming, domestic, school, factory, and hospital activities is concentrated into same sewage treatment plant before release to the river to be treated by Indah Water Treatment Plant as a clean water source for the public.



Sample Size Calculation

Calculation of sample size is based on the prevalence using the following formula [39]: $N=Z^2p(1-p)/d^2$, where N is the sample size, Z is the statistic for a level of confidence, and p is the expected prevalence or proportion (considering a total proportion of 100%, if 20% then p=0.2), and d is precision. For this study in proportion of 100%, if 5%, d=0.05. Considering a conventional 95% CI as the level of confidence, the Z value is 1.96. The sample size was determined from prevalence estimates of previous studies of ESKAPE isolates from the hospital or wastewater treatment plant with the 95% CIs, as shown in Table 1. This calculation served as the guidance for the number of plates to be used to isolate the targeted ESKAPE bacteria.

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Table 1. Prevalence of antibiotic-resistant bacteria from related studies.

Study and bacterial species	Prevalence, %	Sample size (number of plates to isolate ESKAPE[a] bacteria)
Haller et al [40]		
Pseudomonas spp.	28.2	312
Klebsiella spp.	28.2	312
Enterobacter spp.	18.3	230
Citrobacter spp.	11.3	155
Hrenovic et al [41]: *Acinetobacter baumannii*	57.0	377
Thompson et al [42]: methicillin-resistant *Staphylococcus aureus*	81.0	237
Varela et al [43]		
Enterococcus spp. on vancomycin	0.7	11
Enterococcus spp. on ciprofloxacin	3.4	54
Karimi et al [44]		
Enterococcus faecium	6.03	88
Enterococcus faecalis	0.63	10

[a]ESKAPE: *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter.*

Sample Collection and Preparation

In total, two bottles of effluent water will be collected. Samples for objective 1 and objective 2 will be collected in a 1-L sterile screw-capped Schott Duran (Germany) amber bottle. In addition, samples for antibiotics quantification (objective 3) will be collected in a 1-L high-density polyethylene (Kris Plastic Industries, Malaysia) sample bottle. All samples will be kept in an ice-packed cooler box maintained at 4°C and transported back to the Environmental Microbiology Laboratory, Institute for Medical Research, for immediate processing. The samples will be collected at the final effluent disposal point of the sewage treatment system before reaching the Indah Water Treatment Plant Malaysia (Figure 3).

Microbiological Analysis

Isolation of ESKAPE ARB

Ten-fold serial dilutions for each water sample will be prepared in 50-mL sterile saline solution and 10 mL of the sample will be filtered through sterile 0.45-µm pore size cellulose acetate filters (Sartorious Singapore Pte Ltd) in triplicate (Figure 5). The filter will be then placed onto the selective media to isolate ESKAPE pathogens. The selective media to be used in this process of isolation are listed in Table 2. Identification of the ESKAPE bacteria will be carried out using the 16S RNA polymerase chain reaction (PCR) technique with a universal primer pair (forward, CCT ACG GGA GGC AGC AG; reverse, ATT ACC GCG GCT GCT GG) under the following condition: polymerase activation at 94°C for 2 minutes, denaturation at 94°C for 5 seconds, annealing at 60°C for 10 seconds, extension at 72°C for 20 seconds, and holding at 4°C.

The positive colonies will be subjected to AST using the disk diffusion method (Kirby Bauer) referring to the Clinical Laboratory Standards Institute (CLSI) guidelines. The antibiotics that will be used for AST are ceftriaxone (30 µg), ciprofloxacin (5 µg), meropenem (10 µg), vancomycin (30 µg), colistin (10 µg), and piperacillin/tazobactam (110 µg). For the bacteria that are not available in CLSI guidelines, measurement will refer to European Committee of Antimicrobial Susceptibility Testing (EUCAST) guidelines. The minimal inhibitory concentration of colistin will be determined using a liquid broth dilution test as recommended by EUCAST with cation-adjusted Mueller-Hinton broth (NutriSelect Plus, Germany), because the disk diffusion method is not reliable for this antibiotic since its large molecular size results in poor diffusion into the agar medium, leading to inaccurate results with a high error rate and poor reproducibility [45].

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Figure 5. The number of plates to be used to isolate ESKAPE (Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acitenobacter baumannii, Pseudomonas aeruginosa, and Enterobacter) pathogens from the hospital effluent based on the calculated sample size. See Table 2 for the selective media used for each species.

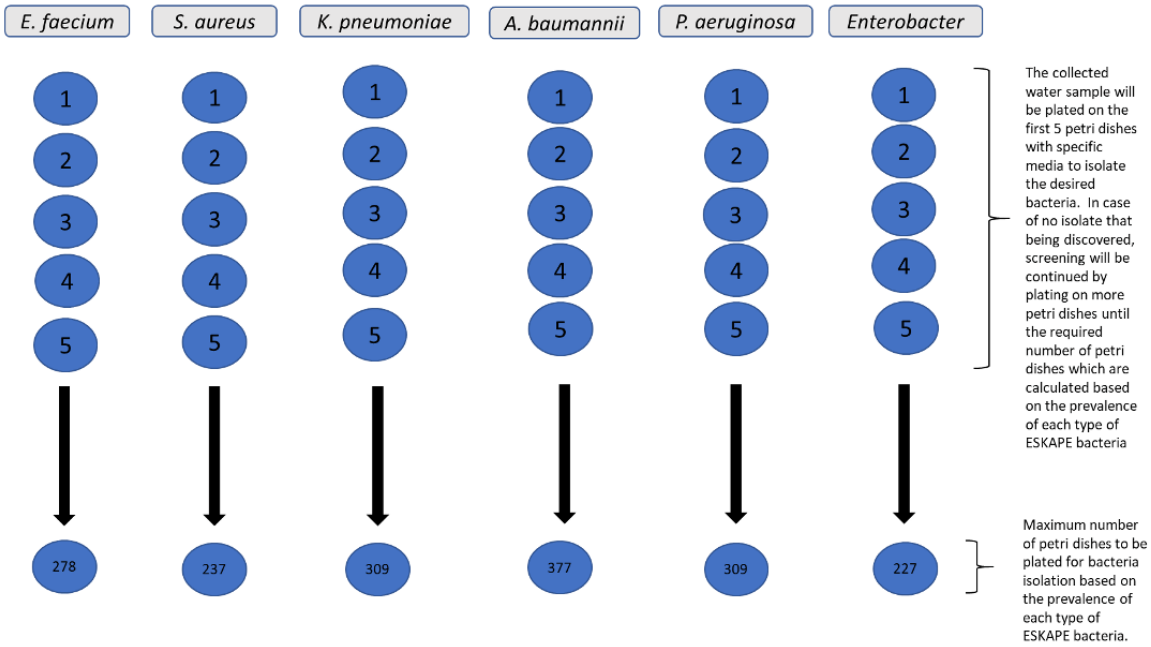


Table 2. Selective media and the incubation condition to isolate pathogens from the effluent samples.

Selective organism	Medium	Incubation condition
Enterococcus faecium	Chromogenic *E. faecium* Agar (Himedia, India)	37°C, aerobic, 24-48 hours
Staphylococcus aureus	Mannitol Salt Agar (BD, Germany)	37°C, aerobic, 24-48 hours
Klebsiella pneumoniae	Eosin Methylene Blue Agar Modified (HHT) (BD-BBL, USA)	37°C, aerobic, 24-48 hours
Acinetobacter baumannii	Chromagar Acinetobacter (CHROMagar, Paris France)	37 °C, aerobic, 24-48 hours
Pseudomonas aeruginosa	Cetrimide Agar (Neogen USA)	37°C, aerobic, 24-48 hours
Enterobacter	MacConkey II Agar (BD-BBL, USA)	37°C, aerobic, 24 hours

Detection of ARGs Among ESKAPE Isolates

Each colony found to be resistant to any of the tested antibiotics will be cultured and inoculated in tryptone soy broth medium (CM0129, Oxoid). The culture will be incubated at 37°C for 18-24 hours. The genomic DNA will be extracted using the PureGene Bacteria Kit (Qiagen, Germany) following the manufacturer's instructions. The concentration of the extracted DNA will be measured using a Multiskan SkyHigh microplate spectrophotometer (Thermo Scientific) before multiplex PCR amplification. Primers were selected to amplify the targeted ARGs based on published findings [46-56] (see Multimedia Appendix 1). The extracted DNA will be amplified using multiplex PCR following the single-template PCR method. The PCR conditions will be optimized according to published methods. The size of the amplified products will be confirmed by 3% agarose gel (NextGene) electrophoresis at 90 V for 90 minutes. The PCR products will be sent to an outsourcing service for Sanger sequencing. The sequencing results will be analyzed using the Basic Local Alignment Search Tool nucleotide (BLASTn) tool in the National Center for Biotechnology Information database to identify the correct amplified relevant genes.

Chemical Analysis

Quantification of the Concentrations of Selected Antibiotics

An ultrahigh-performance liquid chromatography (UHPLC) system will be used to quantify the levels of antibiotics from all samples following the method reported by Kim et al [57]. Samples will be collected and treated by preconcentration using a nitrogen evaporator. The samples will then be cleaned by an automated solid-phase extraction system. The analysis will be performed using Q-exactive liquid chromatography-mass spectrometry. External standards of antibiotics will include ceftriaxone, ciprofloxacin, meropenem, vancomycin, colistin, piperacillin, and tazobactam. The internal standards will be ciprofloxacin-d8 (molecular weight: 339.38) and piperacillin-d5 (molecular weight: 522.59). The analytical column will be Waters Xbridge C18 Column (50 mm × 2.1 mm, 2.5 µm inner diameter) run at 35°C. Two types of solvents will be used: 0.1% formic acid (solvent A) in water and 100% acetonitrile (solvent B). The solvent gradients with a flow rate of 0.2 mL/min for this experiment are shown in Table 3.

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Table 3. Solvent gradients with a flow rate of 0.2 mL/min.

Time (minutes)	Solvent A (0.1% formic acid), %	Solvent B (100% acetonitrile), %
0.0	98	2
4.9	35	65
13.5	2	98
21.0	2	98
21.5	98	2
26.0	98	2

Data Analysis

The prevalence of ARB will be calculated using the following formula:

> Prevalence (%)=(number of resistant isolates/number of resistant isolates + number of susceptible isolates) × 100

To detect ARGs carried by ESKAPE bacteria, nucleotide results from the sequencing will be checked using Chromas, a DNA sequencing software to view and edit the chromatograms (traces) from automated Sanger sequencers. The edited chromatograms from the sequencing results will be sent to the BLASTn database to confirm the amplified genes.

The concentration of the antibiotic residues quantified using UHPLC will be compared to the antibiotic usage in the hospitals.

Ethics Considerations

No primary data will be collected and thus no ethical approval is required. The study protocol was approved by the Medical Research and Ethical Committee, Ministry of Health Malaysia. This study is also registered under the National Medical Research Registry (NMRR-19-3637-51680) Malaysia.

Results

The primary outcome measure for this study is the prevalence of resistant ESKAPE bacteria isolated from antibiotic-selective media. The bacteria will be identified by 16S RNA PCR to determine species. The secondary outcome of this study is the occurrence of ARGs that may be discovered from the resistant ESKAPE bacteria isolates as the likely cause of the resistance toward the antibiotics (Table 2). The multiplex PCR method will be applied to screen the ARGs present. As of July 2022, effluent sampling has been conducted in three hospitals and analysis of samples is ongoing to determine the level of antibiotic residues. ESKAPE bacteria were isolated and AST is ongoing to determine the resistant isolates. Some preliminary findings for *E. faecium* from Hospital A showed that 80% (8/10) were resistant to vancomycin and 20% (2/10) were susceptible, whereas only 10% (1/10) were resistant, 60% (6/10) had intermediate resistance, and 30% (3/10) were susceptible to ciprofloxacin. Moreover, 100% (10/10) of *E. faecium* isolates from Hospital B were resistant toward vancomycin but susceptible toward ciprofloxacin. Resistant isolates will be processed for further screening of ARGs using PCR. Effluent sampling activities were suspended for a few months due to the COVID-19 pandemic, which caused a delay in the downstream analysis. The findings of the study will be disseminated through peer-reviewed journals and scientific conferences.

Discussion

VRE represent an issue of both medical and public health importance, as these bacteria are commonly associated with multidrug-resistant infections and persistent colonization in patients [58]. From our early findings, the prevalence of vancomycin-resistant *E. faecium* from two hospitals was more than 80%, which was higher than the prevalence of 11% reported in a study performed in the Czech Republic on isolates collected from Military Hospital Olomouc and University Hospital Olomouc [59].

The outcomes of this study will fill the gap of important information for clinical practitioners to determine whether the hospitals in Malaysia are main contributors to the AMR problem in the country. This study will provide baseline information on the prevalence of antibiotic resistance from hospital effluents in Malaysia to assist in hospital wastewater management and improve antibiotic stewardship in Malaysia.

This study will have an impact on the improvement of hospital sewage treatment because the data will provide information to the Engineering Service Division of the Ministry of Health that reflects the efficiency of the current sewage treatment in Ministry of Health hospitals. This should facilitate the hospital's sewage manager in the Engineering Service Division in effective service improvement.

Moreover, the findings from this study will help in the optimization of antimicrobial stewardship programs by recommending strategies for infectious disease physicians and pharmacists in their prospective audit and feedback of antimicrobial prescriptions to clinicians, formulary restriction, education, and guidelines. Antimicrobial stewardship programs are aiming to optimize antimicrobial selection, dosing, route, and duration of therapy to maximize a clinical cure or prevention of infection, while limiting unintended consequences such as the emergence of resistance, adverse drug events, and extra costs.

Ultimately, this study will contribute to the improvement in public health. The improvement in the hospital sewage system will eventually lead to controlling antibiotics pollution in the environment by reducing the spread of clinically driven ARB and ARGs into the environment. This will in turn reduce the unnecessary demand for stronger antibiotics or even failure to treat many types of resistant infections.

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Acknowledgments

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Data Availability

The authors confirm that the data supporting the findings of this study are available within the article and supplementary materials.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Published primers representing the occurrence of bacterial DNA and antibiotic resistance genes.
[DOCX File , 19 KB - resprot_v12i1e39022_app1.docx]

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Abbreviations

AMR: antimicrobial resistance
ARB: antimicrobial-resistant bacteria
ARG: antibacterial resistance gene
AST: antibiotic susceptibility testing
BLASTn: Basic Local Alignment Search Tool nucleotide
CLSI: Clinical Laboratory Standards Institute
CRE: carbapenem-resistant Enterobacteriaceae
ESKAPE: Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae Acinetobacter baumannii, Pseudomonas aeruginosa, Enterobacteriaceae
EUCAST: European Committee of Antimicrobial Susceptibility Testing
GLASS: Global Antimicrobial Resistance Surveillance System
HAI: hospital-acquired infection
MRSA: methicillin-resistant Staphylococcus aureus
MyAP-AMR: Malaysian Action Plan on Antimicrobial Resistance
PCR: polymerase chain reaction
UHPLC: ultrahigh-performance liquid chromatography
VRE: vancomycin-resistant enterococci
WHO: World Health Organization

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Protocol

Intervention in Mothers and Newborns to Reduce Maternal and Perinatal Mortality in 3 Provinces in South Africa Using a Quality Improvement Approach: Protocol for a Mixed Method Type 2 Hybrid Evaluation

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Abstract

Background: The COVID-19 pandemic undermined gains in reducing maternal and perinatal mortality in South Africa. The Mphatlalatsane Initiative is a health system intervention to reduce mortality and morbidity in women and newborns to desired levels.

Objective: Our evaluation aims to determine the effect of various exposures, including the COVID-19 pandemic, and a system-level, complex, patient-centered quality improvement (QI) intervention (the Mphatlalatsane Initiative) on maternal and neonatal health services at 21 selected South African facilities. The objectives are to determine whether Mphatlalatsane reduces the institutional maternal mortality ratio, neonatal mortality rate, and stillbirth rate (objective 1) and improves patients' experiences (objective 2) and quality of care (objective 3). Objective 4 assesses the contextual and implementation process factors, including the COVID-19 pandemic, that shape Mphatlalatsane uptake and variation.

Methods: This study is an implementation science type 2 hybrid effectiveness, controlled before-and-after design with quantitative and qualitative components. The Mphatlalatsane intervention commenced at the end of 2019. For objective 1, intervention and control facility-level data from the District Health Information System are compared for changes in institutional maternal and neonatal mortality and stillbirth rates and associations with QI, the COVID-19 pandemic, and both. This first analysis includes data from 18 facilities, regardless of their allocation to intervention or comparison, to obtain a general idea of the effect of the COVID-19 pandemic. For objectives 2 to 3, data collectors abstract data from maternal and neonatal records, interview participants, and conduct neonatal facility assessments. For objective 4, interviews, program documentation, surveys, and observations are used to assess how contextual factors at the macro-, meso-, and microlevels explain variation in intervention uptake and outcome. The intervention dose is measured at the microlevel only in the intervention facilities. The study assesses the Mphatlalatsane Initiative from 2020 to 2022.

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Results: From preliminary analysis, across the 3 provinces, maternal and neonatal deaths increased during the COVID-19 pandemic, whereas stillbirths remained unchanged. Maternal satisfaction with quality of care was >90%. The COVID-19 pandemic severely disrupted the QI teams functioning. However, the QI teams regained their pre–COVID-19 momentum by adapting the QI model, with advisers providing mentoring and support. Variation in adoption at the mesolevel was related to stable and motivated leadership (particularly at the facility level), poor integration into routine processes, and buy-in from senior district managers who were affected by competing priorities. Varying referral and specialist outreach systems, staff availability and development, and service delivery infrastructure are plausible factors in variable outcomes.

Conclusions: Few evaluations rigorously evaluated the effect of health system interventions on improving health services and outcomes. Results will inform the scaling up of successful intervention components and strategies to mitigate the effects of the COVID-19 pandemic or similar emerging epidemics on maternal and neonatal mortality.

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KEYWORDS

health systems; quality improvement; antenatal; postnatal; maternal; child; HIV; mixed methods evaluation

Introduction

Background

The emergence of COVID-19 caused by SARS-CoV-2 in 2020 had a detrimental effect on maternal and infant health gains. Pregnant and breastfeeding women are at a high risk for COVID-19–related morbidity and mortality [1,2]. Given the high number of pre–COVID-19 medically complicated pregnancies in low- and middle-income countries, the pandemic substantially increased the risks to pregnant and breastfeeding women and their infants [3] and undermined gains made in reducing maternal and perinatal mortality [4].

South Africa invested in improving sexual, reproductive, maternal, and neonatal health (SRMNH) services but did not reach the Millennium Development Goals targets for maternal and child health by the end of 2015. Aligned with the United Nations Sustainable Development Goals (SDG) of reducing maternal mortality to <70 per 100,000 live births and neonatal mortality to 12 deaths per 1000 live births [5], South Africa aims to reduce the institutional maternal mortality ratio (iMMR), neonatal mortality, and stillbirths by 50% by 2030 [6]. In 2019, the iMMR of 120 per 100,000 live births was well above the SDG target [6]. Moreover, although the institutional neonatal mortality rate (12 per 1000 live births in 2021) meets the SDG, almost 50% of neonatal deaths are avoidable (2021) [6]. This is despite the substantial reduction in iMMR since 2011, attributable to South Africa's antiretroviral treatment program, which increased access to lifelong maternal antiretroviral treatment at higher CD4 cell counts [7].

National policies and strategies for SRMNH have been in place but lack a cohesive quality improvement (QI) strategy. These challenges have been exacerbated by the COVID-19 pandemic, which has complicated access to health care and delivery of maternal and perinatal interventions [4]. Furthermore, despite the strengths of South Africa's existing maternal, perinatal, and child mortality audits, the availability of real-time data to address frontline challenges is undermined by outdated software and fragmented systems with inherent data quality issues and data gaps. These data gaps became more apparent as the pandemic necessitated rapid access to real-time maternal and perinatal data on COVID-19.

Optimal health care provides quality services that are effective and safe while also being timely, equitable, integrated, and efficient [8], with a focus on people-centered care as an essential component [9]. Quality of care is defined as the extent to which health services can increase the probability of desired health outcomes [10].

QI interventions in low- and middle-income countries have improved access to care, skilled delivery, and viral load monitoring. In a South African stepped-wedge randomized controlled trial, a continuous QI intervention resulted in a notable rise in viral load monitoring (relative risk [RR] 1.38, 95% CI 1.21-1.57; *P*<.001) [11]. However, there was no improvement in repeat HIV testing (RR 1.00, 95% CI 0.88-1.13; *P*=.96). In Ethiopia, there was a favorable effect on health workers' adherence to safe childbirth practices immediately after birth (β=8.22, 95% CI 5.15-11.29) [12]. In Ghana, a QI intervention to reduce waiting time for emergency obstetric care and hand hygiene in the neonatal intensive care unit (ICU) improved hand hygiene compliance by 93%. Moreover, the percentage of mothers needing emergency cesarean surgery with unacceptable waiting times decreased by 4 times, and 93% of the sickest mothers were correctly identified [13].

Conversely, in 2 randomized controlled trials conducted at the primary care level in Nigeria and Malawi, continuous QI was ineffective [14,15]. The researchers rigorously measured continuous QI in terms of impact on neonatal and perinatal mortality rates in the Malawi study [14] and 6-month postpartum retention in the Nigerian study [15]. However, these end points do not reflect the QI activities that occurred in the primary care centers. The variability of these end points is likely related to elements outside the remit of the QI, such as emergency care availability, road infrastructure, and mothers' educational attainment.

In 2017, the Mphatlalatsane Initiative was launched to provide a national unified response to improve the quality and equity of SRMNH care at the cusp of the National Health Insurance reform, using the Institute for Health Improvement QI methodology [16]. The final output is anticipated to be a proven

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and replicable model of catalytic health systems and clinical interventions to reduce unintended pregnancies and maternal and newborn deaths. These can be tested for sustainability and scaled up to emulate achievements across the rest of the country.

In this study, we report the protocol for the evaluation of the Mphatlalatsane Initiative. The initial aim of the protocol was to determine if a complex area–based QI initiative would reduce iMMR, neonatal mortality, and stillbirth rate by 50% in 5 years. Given the emergence of COVID-19 in March 2020 in South Africa with concomitant increased public health measures and national level-5 lockdown [17], the Mphatlalatsane Initiative was adapted to provide the much-needed support for maternal and perinatal care during the pandemic. The evaluation protocol was reframed to account for these adaptations and to determine the effect of the Mphatlalatsane Initiative on maternal and perinatal health care and outcomes, implementation processes, and health care system functioning during the pandemic from 2019 to 2022.

Study Aims and Objectives

The evaluation primarily aims to measure the effectiveness of the Mphatlalatsane Initiative on iMMR, neonatal mortality rate, and stillbirth rate (objective 1). We also assess whether patients' experiences of care (objective 2) and quality of maternal (objective 3a) and neonatal care (objective 3b) were affected by the pandemic. Objective 4a explores the macrolevel (regional and national) and mesolevel (subdistrict and district) factors, and objective 4b explores the microlevel (facility) process and contextual factors, including the COVID-19 pandemic, to explain variations in QI uptake and program outcomes and implications for scale-up. Partner interviews (objective 4a) commenced in early 2020, and data collection for objective 4b began in May 2021.

Outcome Measures

The primary end points are (1) iMMR, (2) neonatal mortality rate, and (3) stillbirth rate. The secondary end points include patient experiences of health care quality and facility processes during the antenatal and postpartum periods (objective 2) and the quality of maternal (objective 3a) and neonatal care (objective 3b). The study also explores *macro-*, *meso-*, *and microlevel contexts* and implementation processes for improved quality and outcomes of maternal and neonatal health (MNH). Additional details on the secondary outcomes are provided in Multimedia Appendix 1.

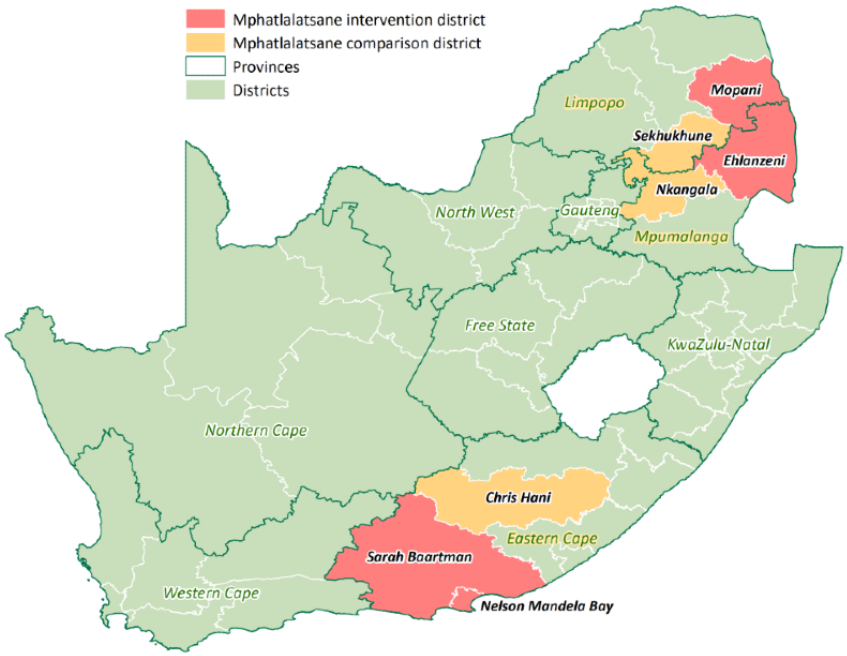
Methods

Study Setting

The evaluation is underway in 4 intervention and 3 nonoverlapping comparison districts across 3 provinces: the Eastern Cape, Limpopo, and Mpumalanga. All catchment areas are in 1 district, except for the Eastern Cape intervention catchment area, which spans across 2 districts.

The catchment area is subdivided into a wedge with 2 arms within each wedge. Each wedge has a district hospital at the apex. The hospital is linked to a regional hospital, 2 community health care centers, and 2 primary health care clinics in each arm. The intervention study districts in the Eastern Cape, Limpopo, and Mpumalanga are highlighted in red in Figure 1. The comparison facilities and the intervention facilities are in different districts to avoid contamination, and the former will not have the same apex district hospital as the intervention site. The comparison districts (Figure 1 in yellow) are not evaluated for objective 4.

Figure 1. Mphatlalatsane intervention and comparison districts in the Eastern Cape, Limpopo, and Mpumalanga Provinces in South Africa. Produced by the Health GIS Centre of the South African Medical Research Council. Copyright ESRI 2016; ArcGIS Desktop: Release 10.4. Redlands, CA: Environmental Systems Research Institute.



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Study Design

We are conducting a mixed methods implementation science type 2 hybrid effectiveness design to study the intervention effect (objectives 1-3) and implementation (objective 4) during the COVID-19 pandemic. Given that the intervention facilities were preselected, the quantitative component will be implemented as a quasi-experimental controlled before-and-after study (nonrandomized assignment of the intervention and comparison groups) to measure the effect of a QI intervention implemented during the COVID-19 pandemic on maternal and neonatal outcomes. Data on the iMMR, neonatal mortality rate, and stillbirth rate will be analyzed from 2019 to 2021, including the time before and during the COVID-19 pandemic in South Africa (objective 1). Study data on maternal experiences of care (objective 2) and maternal and neonatal quality of care (objectives 3a and 3b) were collected between 2021 and 2022. Objective 4 data collection commenced in early 2020 and ended in August 2022.

Eligibility Criteria and Recruitment of Facilities

Overview

The intervention facilities were purposively identified by the National Department of Health (NDOH) as sites with MNH service performance and capacity below the national average in South Africa. In addition, the selected intervention sites reflect the clinical and referral pathways and represent both urban and rural settings. For objectives 2 and 3, the comparison districts were purposively selected to match the intervention districts in as many respects as possible, including iMMR, stillbirth rate, neonatal mortality rate, sociodemographic characteristics, service organization, and setting (rural, urban, and periurban), and to provide the NDOH standard of care. In total, 3 facilities (2 district hospitals and 1 regional hospital) in the comparison district were selected and matched to the intervention district based on the total number of births. Data collection for objectives 2 and 3 is conducted in 18 hospitals (15 district- and 3 regional-level hospitals). Objective 4b is being conducted in 15 hospitals, purposively selected from the 21 intervention facilities.

Participant Inclusion Criteria for Maternal Interview Shortly After Delivery (Objective 2) and Data Abstraction From Maternity Records (Objective 3)

To assess patient experiences of care and determine the quality of maternal care, participants who are aged ≥18 years, has a pregnancy diagnosis, who accessed care within the participating health facilities during their pregnancy, or who are within 1 week post partum are eligible. Research assistants will screen for eligibility using specified inclusion criteria. All women meeting any of the following criteria will be eligible: (1) pregnant women at ≥36 weeks gestation without any complications, (2) pregnant women at ≥36 weeks gestation with HIV before pregnancy and on antiretroviral therapy and diagnosed with HIV at first antenatal visit, (3) positive repeat antenatal HIV test following the first negative antenatal HIV test, (4) pregnant women at ≥36 weeks' gestation with eclampsia, (5) pregnant women at ≥36 weeks' gestation with primary postpartum hemorrhage, (6) postpartum women at ≤7 days with a premature baby, (7) postpartum women at ≤7 days with a healthy term baby, and (8) postpartum women at ≤7 days with a baby in the ICU. The medical records of eligible cases will be retrieved for a thorough review at hospital discharge or on transfer to another hospital.

Data collectors will conduct daily visits to maternity wards to recruit maternal participants and determine the antenatal quality of care during the pandemic era. During the daily visit, the admission and maternity registers are screened for participants who meet the study inclusion criteria. Stable women with recent deliveries are approached by an interviewer for recruitment before leaving the facility and are interviewed in a private space to ensure confidentiality or via telephones if on-site interviews are not possible. Women are excluded from participation if they are aged <18 years, delivered at home or on the way to the facility, are acutely ill in the ICU or with life-threatening conditions, or are emotionally distressed. Women whose infants are admitted to the ICU or who experienced a stillbirth or neonatal death will be approached for interview, and if they agree, they will be interviewed at a time that suits the mother.

Participant Inclusion Criteria (Objective 4)

At the macrolevel (provincial and national) and mesolevel (subdistrict and district; objective 4a), the study team will purposively recruit subdistrict, district, and area managers and those specifically responsible for managing maternal and neonatal care services across subdistricts, districts, provinces, and areas. At the microlevel (facility; objective 4b), we include all QI advisers, that is, persons who provide QI expertise and support to participating facilities' health workers who are organized in QI teams as well as the operational managers of the sampled facilities.

Procedures

Conceptual Framework

Our initial hypothesis was that the QI methodology will enhance the quality of MNH care by creating an enabling environment for leadership and governance to flourish, ensuring that clinical processes are delivered safely and reliably. A key component of the QI approach is ensuring respectful care and support for patients. We further hypothesize that optimizing the environment and processes will improve the health care system, leading to improved health outcomes and patient experience of care. Our underlying causal assumptions are that QI will empower macro- and mesolevel management and microlevel health workers to drive and implement change.

Implicit assumptions are staff participation in QI training, a facility QI team that continues QI activities throughout study implementation, and a leader within that team with continuity of participation are integral to its success. At the start of the intervention, the Mphatlalatsane Initiative implemented the Institute for Healthcare Improvement model for improvement as a framework to guide its implementation strategy [10]. The strategy involves the identification of a specific goal for improvement and a plan to measure progress and then commences with change ideas that may lead to improvement over a short duration. As the change ideas are refined and successfully applied, the interventions are broadened to increase

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the magnitude of the changes. The Institute for Healthcare Improvement stresses initiating improvement on a small scale and leveraging the obtained knowledge to plan for wider implementation and eventual scale-up. Additional assumptions included that other competing programs or priorities implemented by the NDOH would not be conducted in the intervention catchment areas. However, the COVID-19 pandemic disrupted QI team functioning. The consortium partners prioritized the immediate needs of facilities, which broadened the initial intervention scope (described below under *Intervention Dose* section) of the Mphatlalatsane Initiative.

A framework of mesolevel (district and subdistrict) enabling environments was developed a priori, which included factors of distributed leadership and buy-in, area-based mechanisms of service delivery coordination and review, referral and outreach systems, and the allocation of resources in response to identified needs at the facility level.

Intervention Package

The Mphatlalatsane Initiative initially aimed to improve the quality of maternal and neonatal care in the participating facilities through QI activities. A QI adviser has been appointed in each catchment area to manage and support these teams. We anticipate that these teams will become nodes of "learning practices," with team members pooling their efforts and skills toward solving targeted service problems [18]. We view the respective microlevel health systems, in which the QI teams function, as social systems, with the agency of staff and the relationships, existing and to-be-established, within these systems [19], as key to understanding the teams' performance. The evaluation and intervention teams are independent to minimize bias. The intervention design of in-person support shifted based on facility responses during the COVID-19 pandemic. Initial attempts to use digital platforms to support QI teams were unsuccessful, and QI advisers subsequently supported QI teams through telephonic messages and calls. Other design changes included providing emotional support and guidance and improving the efficiency of supply chain management for infection control and personal protective equipment. Once the acute demands were met, the Mphatlalatsane intervention was revised to mitigate the interruptions in access to routine MNH services.

QI activities comprise the repeated and rapid implementation of Plan-Do-Study-Act (PDSA) cycles [20,21]. The *Plan* refers to problem identification and development of solutions; the *Do* refers to implementation of the solutions; the *Study* refers to the evaluation of effects of the solutions and then *Acting* on the outcome of the evaluation by adopting, adapting, or rejecting the solutions [20,21]. QI teams have been established in each participating facility to engage maternal and neonatal staff in relevant PDSA activities [21,22].

Comparator

Health care providers in the control district facilities continue to provide the NDOH standard of care to antenatal and postnatal attendees as per the policy and guidelines. The usual training for staff involves weekly 1-hour in-service training on current evidence-based guidelines. The usual training does not include a coaching or mentoring component and is not a data-driven process for evaluating the implementation of evidence-based guidelines.

Data Sources

Objective 1

Mortality data from 2017 to 2022 were extracted from the District Health Information System (DHIS; Table 1).

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Table 1. Mphatlalatsane data sources.

Objective	Data source	Variable or theme	Level of analysis
1	• DHIS[a]	• Mortality data (maternal, neonatal, and stillbirths) extracted quarterly from 2019 to 2022	District and facility
2	• Participant interview shortly after delivery in regional or district hospitals	• The effect of the QI[b] intervention over time on patients' experience of the quality of antenatal and postnatal health care services from 2021 to 2022	Individual
3a	• Maternal records from regional or district hospitals	• Facility audit of maternal records will be conducted to measure adherence to clinical protocols on normal pregnancy, HIV, eclampsia, and postpartum hemorrhage from 2021 to 2022	Individual
3b	• Structured observation checklists will be interviewer administered in selected facilities based on the Newborn QI Toolkit norms and standards for newborn care, which were developed to collect data in each facility [23]	• Availability of equipment and supplies • Availability of guidelines or policies • Distribution and availability of drugs • Data quality and use • Staffing • Infrastructure	Facility
4a	• Semistructured interviews and FGDs[c] with the QI advisers, operational managers, and management staff	• Stakeholder analysis: coordination processes, nature and quality of social networks, decision-making processes, formal and informal communication, and collaboration between key actors. We will set up monthly individually open-ended debriefing meetings with the QI advisers, and they will reflect on their work and engagement with the QI teams. We will also review program documentation, including the documentation that the QI teams will generate during the PDSA[d] cycles. We will also conduct other program meetings at the macro- and mesolevels.	National, provincial, district and subdistrict
4b	• Interviews and FDGs with QI teams • QI team surveys • QI adviser debriefings • Program documentation	• QI advisers, teams, and facility managers: setting up, management structures, systems of communication, translation of their PDSA cycles into everyday practices, climate for QI activities, relational dynamics in the teams, ownership of change, resource use, experiences, and perceptions of implementation changes over time, perceived benefits, and challenges of the QI work in their facilities. • QI team outcomes: packaging learning practices for scale-up and identify the "leverage points" for change.	Facility

[a]DHIS: District Health Information System.

[b]QI: quality improvement.

[c]FGD: focus group discussion.

[d]PDSA: Plan-Do-Study-Act.

Objective 2

In-person or telephonic interviews were conducted with pregnant women shortly after delivery to measure participants' subjective experiences of care. The survey used a 5-point Likert scale based on a prior study of maternal patient satisfaction with services in Tanzania [24]. Data collectors administered paper-based surveys at the midline, which were then captured using REDCap (Research Electronic Data Capture; Vanderbilt University) software.

Objective 3a

Data collectors took photographs or abstracted data from maternal records, which were then entered into the REDCap database. Facility audit of maternal records were conducted by an experienced nurse to measure adherence to the guidelines and implementation of care. Data were collected at a single time point within 1 week of delivery.

Objective 3b

Interview-administered structured observation checklists were completed in all selected facilities based on the Newborn QI Toolkit [23] norms and standards for newborn care.

Data were also collected using a series of checklists to determine the quality of record keeping for the newborns. Staff members in the neonatal unit were requested to provide the clinical records of a sample of newborns with the following conditions: (1) low birth weight, (2) infection, and (3) asphyxia. A review of these records was conducted to determine the quality of record keeping. Data collection for objective 3 was at the end line (approximately June 2022 to August 2022).

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Objective 4a

Semistructured interviews and focus group discussions (FGDs) were conducted with the QI advisers, QI teams, operational managers, and management staff at the subdistrict, district, and provincial levels.

Objective 4b

The data collection comprised (1) interviews and FGDs with the QI team leaders and members, (2) digital surveys to leaders and teams to assess their performance, (3) regular debriefings with the advisers, and (4) a review of program documentation. The debriefings and documentation reviews commenced in February 2020, and the interviews, FGDs, and surveys began in May 2021. As of November 2022, we conducted 32 interviews with leaders and 51 interviews or FGDs with team members.

Sample Size

Objective 1

Using the number of deliveries and maternal and perinatal deaths in 9 regional and district facilities in the chosen intervention catchment areas (the Eastern Cape, Limpopo, and Mpumalanga) between 2018 and April 2019, rates were found to be 115.4 maternal deaths per 100,000 live births, 14.4 neonatal deaths per 1000 live births, and 22.5 stillbirth births per 1000 facility births. For this study, an intraclass correlation estimator from a random intercept logistic regression model was used. Using the average facility size (based on deliveries in the intervention catchment areas during the baseline period), the variance inflation factor was estimated at 1.0, 1.4, and 1.3 for the maternal mortality ratio, neonatal mortality rate, and stillbirth rate, respectively. To test the hypothesis that there was no improvement against a 50% increase in the baseline, with 80% power at a 5% two-sided significance level, the number of live births would be 40,524 and 4512 for testing maternal and neonatal mortality rates and 2666 for stillbirth rates. We will observe at least 41,000 deliveries pooled across the 3 catchment areas over a 3-year period to have minimum power for all outcome comparisons. The same would accrue in the control facilities.

Objective 2 and 3a

Literature on patient satisfaction in South Africa is scarce; in other studies, patient satisfaction varies from <50% to as high as 75% [25]. The impact of the intervention on patient satisfaction may likely be less compared with that before the COVID-19 era because of disruptions in service delivery. For the 18 facilities in the intervention arm and 18 facilities in the control arm, at a power of 80%, and an expected increase in patient satisfaction from 50% to 60%, given an intraclass correlation coefficient of 0.06, the number of pregnant women required is 102, with a total sample size of 1529 per arm in the pre- and postintervention periods.

Objective 3b

The study team will evaluate 18 facilities (3 in each of the intervention and control catchment areas).

Objective 4

Sampling at the meso- and macrolevels will be linked to the microlevel sampling. The subdistricts and districts where facilities have been selected and their respective area levels will be included in the evaluation at the macro- and mesolevels. At minimum, 2 subdistricts, 2 districts, and 3 areas (total 7 “units” of assessment) will be selected, although additional units could be added if primary health care clinics, community health care centers, and district hospitals are not all from the same subdistrict. We anticipate approximately 90 and 120 interviews or FGDs, respectively, for the macro-, meso-, and microlevel interviews or FGDs over the 18 months of data collection. At the microlevel, we sampled QI teams across the 3 catchment areas, as follows:

Objective 4b facilities (Table 2) were sampled based on readiness assessment scores from the NDOH (this was done before the start of the intervention to assess the state of maternal and neonatal care in the intervention facilities) and input from the QI advisers and represent the range of facility types; MNH care packages; and urban, semiurban, and rural areas.

Table 2. Type of objective 4b facilities sampled in Eastern Cape, Limpopo, and Mpumalanga from 2020 to 2022 (N=15).

	Eastern Cape (n=4), n (%)	Limpopo (n=5), n (%)	Mpumalanga (n=6), n (%)
Regional hospital (n=3)	1 (7)	1 (7)	1 (7)
District hospital (n=4)	1 (7)	1 (7)	2 (13)
Community health care center (n=5)	1 (7)	2 (13)	2 (13)
Primary health care clinic (n=3)	1 (7)	1 (7)	1 (7)

Intervention Dose

The intervention dose, defined as the “quality and quantity of an intervention and participation” [26], may be necessary to determine the barriers or enablers of the Mphatlalatsane Initiative. However, measuring the intervention dose is complex and requires substantial data collection to quantify the various intervention dose dimensions. Moreover, there are currently no accepted methods for measuring this dose. McHugh et al [26] outlines 8 dimensions of intervention dose that may affect whether or not a QI initiative succeeds. In the Mphatlalatsane Initiative, the measurement of the intervention dose is further complicated by the COVID-19 pandemic. The implementation of the Mphatlalatsane Initiative was ongoing for approximately 6 months when the first case of COVID-19 was diagnosed in South Africa in March 2020 [27]. Following the national state of the disaster and level-5 lockdown, the Mphatlalatsane Initiative was redefined to provide support to the intervention

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sites. This support took the form of a web-based platform, telephonic meetings, and in-person QI adviser support when lockdown restrictions eased. However, the use of the web-based platform to provide support was unsuccessful owing to issues with internet connectivity, the lack of equipment, and user competence. As such, the Mphatlalatsane Initiative implementation may have varied at the micro-, meso-, and macrolevels. To determine the Mphatlalatsane intervention dose at the microlevel, a scoring system is in development based on prior work [26]. The first 2 domains, exposure and intensity, relate to the QI adviser. *Exposure* is the number of interactions between the adviser and the QI team; *intensity* is the nature of the interaction between QI advisers and QI teams, for instance, face-to-face support to the team in reviewing their change ideas and offering technical advice during the support visit (high intensity) or a mobile call from the adviser to find out when the team will send their QI documentation (low intensity). The remaining 4 domains relate to the adopted change idea. Quantity is the number of adopted (ie, change ideas with quantifiable evidence that it improves care) change ideas; *reach* is the number of facility workers involved; *duration* is the implementation period in months; *scope* is the 5 Mphatlalatsane outcomes that have been targeted for the change ideas in terms of leadership, clinical care, health systems, patients' experience of care, and patients' health. For the period from September 2019 to December 31, 2021, retrospective data are collected by QI advisers for 4 domains: quantity, reach, duration, and scope (Multimedia Appendix 2). For the period from January 1 to December 31, 2022, all domains will be extracted from the adviser's routine reports (Multimedia Appendix 2). The scoring of each domain and assessment of the intervention dose are evolving and will be finalized once the data have been collected. It is envisaged that 2 members of the evaluation team will independently score each domain, and disagreements will be resolved by a third member.

Statistical Analysis

Objective 1

The institution maternal and perinatal mortality indicators will be calculated using DHIS data. Trend in iMMR, neonatal mortality rate, and stillbirth rates (with SE bars) during the pre- and postintervention periods will be disaggregated by intervention arms. RR and 95% CI will be calculated along with data on confounding variables, such as antenatal care coverage before 20 weeks, delivery at health facility access by tar road, deliveries of female participants aged <19 years, and deliveries of female participants aged ≥19 years (derived from total deliveries and deliveries of female participants aged <19 years). The trends in mortality and stillbirths will be compared before the COVID-19 pandemic (January 2019-March 2020) and during the COVID-19 pandemic (April 2020-March 2021) and in the context of the COVID-19 waves. The baseline period (2017-2018) will also be provided. Observed numbers and rates will be determined monthly and quarterly across all 9 provinces in the country and overall. To compare the Mphatlalatsane Initiative intervention and control arm trends in mortality, an interrupted time series regression model using Poisson regression model with Newey-West SEs to account for autocorrelation and possible heteroskedasticity will be used.

Objective 2

This study will use quantitative descriptive analyses and exploratory factor analysis to examine associations between sociodemographic characteristics, childbirth characteristics, and maternal participants' experience of health care quality and the health care facility during the antenatal to postpartum period.

Objective 3a and 3b

Quantitative data analysis will be conducted on demographic data as well as specific management elements offered to participants with hypertension in pregnancy and primary postpartum hemorrhage based on predetermined criteria [28]. Patients with normal pregnancies will be scored against the NDOH clinic checklist for booking and follow-up of patients without HIV [29]. A study nurse will allocate the score based on antenatal and intrapartum data abstracted from maternity records. The scoring system will be as follows: for any variable that is fully met, 1 unit will be awarded; if partially met, half of a unit will be awarded; whereas if absent, 0 will be awarded. If a patient is managed for more than one of the specific complications, each entity will be assessed separately. The criteria scores for each patient will be individualized. The level of care for each complication will then be assessed as follows:

$$\textit{Care score/Criteria score} \times 100 \quad \textbf{(1)}$$

and is similar to a prior study evaluating QI in neonatal services in KwaZulu-Natal, South Africa [30].

Objective 4

Assuming that attitudes will be complex, grounded theory will be used during this research to keep an open view. Instead of beginning with hypotheses about attitudes, a theory will be developed during the data collection. The interviews and FGDs will be analyzed with qualitative data analysis by using coding, concepts, and categories to develop a theory. The interviews and FDGs will be recorded and transcribed using Microsoft Word (Microsoft Corp). First, a South African Medical Research Council (SAMRC) and a University of Western Cape (UWC) staff member will read through all texts, look for patterns, and assign codes for these patterns. These codes will be assigned to all texts using a qualitative data analysis software program, Atlast.ti (version 8; ATLAS.ti Scientific Software Development GmbH). The SAMRC and UWC staff will then jointly describe these codes and develop categories from combinations of codes and triangulation of concurrent quantitative and qualitative data and then develop hypotheses based on relationships between these concepts, which will form the theoretical framework. The survey data will be imported into Excel, and descriptive analysis techniques will be used to analyze the data.

All quantitative data will be entered into an electronic format and stored in a web-based interface. The quantitative questionnaires will be analyzed using Stata (version 16; StataCorp) [31].

Ethics Approval

Overview

This study has been approved by the SAMRC Human Research Ethics Committee (EC019-11/2019). The proposal for objective

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4 was approved by the UWC Biomedical Research Ethics Committee (BM19/10/16). All participants sign written informed consent or provide verbal consent when the participant is illiterate, with an independent witness present to confirm that the relevant information was understood by the participant.

Objectives 1 to 3

We inform all patients and staff about the evaluation and elicit written informed consent before all interviews, photographs, and data abstraction from the maternity registers and maternity records. Data are deidentified before photographs are taken, and the interview takes approximately 30 minutes with participant confidentiality maintained. Survey administration entails minimal risks to patients and health staff. The results are anonymous and kept confidential. Although participants may decline the interview, we obtained permission from the NDOH to access and analyze data from the DHIS from the relevant catchment areas of the Eastern Cape, Limpopo, and Mpumalanga. We also have approval from the National and Provincial Department of Health to access routine records and photograph maternity case records.

Objective 4

Recruitment of Participants: Interviews, FGDs, and Observations

Written informed consents are obtained from all the individuals who participate in the interviews, FGDs, and observations. A detailed explanation of the purpose and nature of the study is provided to all the participants verbally and in writing with the information sheet in English. For the digital survey, participants receive the same study information as for the other data collection components and provide a digital signature to prove their consent.

Voluntary participation and the right to withdraw from the study at any point is emphasized during this explanation. Participants can consider their participation and ask questions before signing the informed consent form. Data collection occurs at a time and place that is convenient for the participants to ensure that health care delivery is not disrupted. Although anonymity cannot be guaranteed in FGDs, participants are requested to treat the information discussed as confidential. Participants who complete the surveys using personal devices are reimbursed with a data voucher. The NDOH requested that the interview and FGD participants not be reimbursed, given that they participate in working hours.

Accessing Facility Service Data Used by the QI Teams

Permission to access these data has been obtained from the NDOH and the respective Provincial Departments of Health.

Results

Institutional Live Births, Maternal Deaths, Neonatal Deaths, and Stillbirths

Data from the DHIS in the Eastern Cape, Limpopo, and Mpumalanga revealed 1,093,372 live births during the pre–COVID-19 period from March 2019 to March 2020 versus 1,037,528 during the COVID-19 pandemic (April 2020-March 2021). There were 1024 maternal deaths reported from March 2019 to March 2020 versus 1315 maternal deaths during the COVID-19 pandemic. There was a small decline in neonatal deaths from 13,095 during the pre–COVID-19 period to 13,026 deaths during the COVID-19 pandemic. The number of stillbirths also decreased from 22,030 during the pre–COVID-19 period to 20,891 during the COVID-19 pandemic.

Maternal Satisfaction With Care

From October 27, 2021, to July 8, 2022, there were 3934 completed maternal interviews across 18 hospitals. In the maternal interviews, participants were largely satisfied with their antepartum care (3556/3841, 92.58%). Approximately 5.88% (226/3841) of the participants self-reported complicated deliveries.

Microlevel Contexts and Implementation Processes

In the preliminary analysis, although the COVID-19 pandemic severely disrupted the functioning of the QI teams, the pre–COVID-19 momentum was regained, with advisers providing mentoring and support and teams adapting the QI model.

Mesolevel (Subdistrict and District) Enabling Environments

Variation in adoption was related to stable and motivated leadership (particularly at the facility level) and buy-in from senior district managers (affected by competing priorities and a lack of integration into routine processes). Referral and specialist outreach systems, staff availability and development, and service delivery infrastructure also varied, which are plausible factors in variable outcomes.

Discussion

Overview

In our preliminary results, the routine mortality data on maternal and neonatal deaths and stillbirths reflected a mixed picture regarding maternal and perinatal care in South Africa before and during the COVID-19 pandemic. Across the intervention and control facilities, the participants were satisfied with the antepartum and intrapartum care received.

The increase in institutional maternal and neonatal deaths from the Eastern Cape, Limpopo, and Mpumalanga is consistent with prior evidence from Pattinson et al [4] and Pillay et al [32], who note that increased maternal and neonatal mortality was a direct effect of COVID-19–related deaths in pregnant women and an indirect effect of poor access to health services during the pandemic. This study reports on 3 provinces where the Mphatlalatsane Initiative was implemented versus the national reports from Pattinson et al [4] and Pillay et al [32]. Stillbirth rate appeared to remain relatively unchanged during the COVID-19 pandemic in these provinces. The major data limitation is the reliance on a single data source, the DHIS. Further analyses will stratify the catchment areas according to intervention and control facilities. The preliminary objective 4b data point to important contextual and implementation process differences across districts; for instance, a travel embargo in 1 district restricted the district management support

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visits to the intervention facilities, which have been reported by other districts to be an important motivation for QI teams. We are also observing differences between facilities in the same district, for example, some leaders are more motivated to implement the intervention than others. Unpacking the contextual and implementation processes that are shaping the QI intervention may facilitate the understanding of the Mphatlalatsane Initiative outcomes.

Globally, health systems have faced unprecedented strain and uncertainty during the COVID-19 pandemic [33]. Policy makers and health care providers made rapid shifts in all aspects of the health system to mitigate the COVID-19 risk [33] and accommodated the growing COVID-19–related morbidity and mortality. These changes included performing remote patient consultations [34]; repurposing wards and hospitals for COVID-19 [34]; and developing innovations, including vaccines [35], to counter the COVID-19 risk.

Several authors have suggested ways in which QI might be applied during the pandemic; for instance, rapid learning collaboratives, which are the most successful interventions when changes are occurring concurrently [36]. QI could enhance the health system, provide a methodology for systematic change, and improve learning [37,38].

When a swift response to changing circumstances is required, rapid learning cycles, such as through the PDSA structure, can enable teams to adapt quickly with minimal risk and interruption to clinical work. Having a mechanism to try, and refine, ideas and ensuring that they are plausible before implementing them can support teams in responding to challenges that have no known solution, as described by Fitzsimons [36].

This evaluation protocol aims to determine the effect of the Mphatlalatsane Initiative on maternal and perinatal health during the COVID-19 pandemic. A key strength of this evaluation is that the study is embedded within the public health system and implemented within routine structures, processes, and data and importantly within available human resources. Moreover, the QI initiative ran for approximately 6 months before the pandemic arose in March 2020 in South Africa. Thus, it is possible to evaluate how various exposures, including the COVID-19 pandemic and the Mphatlalatsane Initiative, affected maternal and perinatal care in the intervention districts. In particular, the evaluation will consider the COVID-19 burden of disease in intervention and control districts and the heterogeneity in maternal and perinatal care during and between COVID-19 waves. As the Mphatlalatsane intervention broadened from the QI methodology to supporting MNH health services during the COVID-19 pandemic [16], we cannot discount the effect of the pandemic when evaluating the causality between the Mphatlalatsane intervention and MNH outcomes. Moreover, the process evaluation will capture the nuanced changes that were occurring as the Mphatlalatsane Initiative was evolving and the iterative way the intervention was delivered with changes responsive to health system requirements (adaptive *function*).

Limitations

This study has some limitations. As mortality data are extracted from the DHIS, which contains summary-level data on maternal and neonatal deaths and stillbirths, we cannot account for missing or incomplete data. A further limitation is that the QI intervention dose was not equally applied across facilities in the chosen districts, as the pandemic interrupted QI training and support structures that were necessary to implement the intervention. Although the evaluation team will strive to measure the intervention dose in a structured manner, the complex manner in which the intervention adapted to the requirements of the health system, particularly during the COVID-19 pandemic, may mean that only a few dimensions of the intervention dose may be captured in the analysis [26]. Moreover, the QI advisers collected intervention dose data both retrospectively and prospectively, which limits interpretation. There were also several Mphatlalatsane staff changes during the implementation period, which further limited the collection of the intervention dose data. Furthermore, data on policy and change at the macro- and mesolevels may not be able to draw narrow causal relationships between the Mphatlalatsane Initiative and outcomes at the facility (micro) level. However, qualitative data from the macro-, meso-, and microlevels may provide a more nuanced picture of the complexity of the Mphatlalatsane Initiative.

The results of the Mphatlalatsane evaluation will inform whether the Mphatlalatsane Initiative in the context of the COVID-19 pandemic is effective at improving maternal and neonatal mortality and stillbirth rate in a resource-limited setting. The results will inform strategies to mitigate the effects of the COVID-19 pandemic or similar emerging epidemics on maternal and neonatal mortality.

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Data Availability

The data sets generated and analyzed during this study are not publicly available because some data are owned by the South African National Department of Health but are available from the corresponding author on reasonable request.

Authors' Contributions

The evaluation team comprise of AG (South African Medical Research Council [SAMRC]) as the principal investigator, with TC (SAMRC) and HS (University of Western Cape [UWC]-SAMRC) as coprincipal investigators and YS (SAMRC), SM (UWC), WO (SAMRC), SM (SAMRC), and NA as coinvestigators. The protocol was jointly written by AG, TC, HS, WO, YS, and SM. AG and TC assumed responsibility for the overall evaluation and conduct of the study objectives 1 to 3 along with YS. HS and SM are responsible for conducting objective 4a. WO assumed responsibility for conducting objective 4b. AG, TC, HS, WO, YS, and SM conceived the study design. TC wrote the first draft of the manuscript. SM and NA performed the statistical analyses. All authors commented on the manuscript and contributed to all subsequent manuscript drafts.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Mphatlalatsane secondary outcomes.
[DOCX File , 15 KB - resprot_v12i1e42041_app1.docx]

Multimedia Appendix 2
Mphatlalatsane quality improvement scorecard.
[DOCX File , 31 KB - resprot_v12i1e42041_app2.docx]

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Abbreviations

DHIS: District Health Information System
FGD: focus group discussion
ICU: intensive care unit
iMMR: institutional maternal mortality ratio
MNH: maternal and neonatal health
NDOH: National Department of Health
PDSA: Plan-Do-Study-Act
QI: quality improvement
REDCap: Research Electronic Data Capture
RR: relative risk
SAMRC: South African Medical Research Council
SDG: Sustainable Development Goals
SRMNH: sexual, reproductive, maternal, and neonatal health
UWC: University of Western Cape

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Protocol

Predictors and Consequences of Homelessness: Protocol for a Cohort Study Design Using Linked Routine Data

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Abstract

Background: Homelessness is a global burden, estimated to impact more than 100 million people worldwide. Individuals and families experiencing homelessness are more likely to have poorer physical and mental health than the general population. Administrative data is being increasingly used in homelessness research.

Objective: The objective of this study is to combine administrative health care data and social housing data to better understand the consequences and predictors associated with being homeless.

Methods: We will be linking health and social care administrative databases from Northern Ireland, United Kingdom. We will conduct descriptive analyses to examine trends in homelessness and investigate risk factors for key outcomes.

Results: The results of our analyses will be shared with stakeholders, reported at conferences and in academic journals, and summarized in policy briefing notes for policymakers.

Conclusions: This study will aim to identify predictors and consequences of homelessness in Northern Ireland using linked housing, health, and social care data. The findings of this study will examine trends and outcomes in this vulnerable population using routinely collected health and social care administrative data.

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KEYWORDS

administrative data; data linkage; health care use; homelessness; housing; mortality

Introduction

Overview

Worldwide, it is estimated that more than 100 million people are homeless [1]. Determining an accurate picture of the scale and impact of homelessness is challenging given the diverse definitions of homelessness that are used within and between countries [2-5]. The United Nations Office of the High Commissioner for Human Rights proposed that "experiencing homelessness means not having stable, safe, and adequate housing, nor the means and ability of obtaining it" [6]. The European Typology of Homelessness and Housing Exclusion framework explicitly categorized the different elements of housing insecurity and defined homelessness as "living in a place of habitation (during the reference period) that is below a minimum adequacy standard; and lacking access to adequate housing" [7].

The state of experiencing homelessness results from a complex range of connected factors, including social and economic contexts and policies [8]; cyclical housing markets, during which renters experience rent inflation during the upswing and risk eviction during a downturn; and the availability and quality of housing [9]. Within a society, there are factors that predict which individuals are at greatest risk of becoming homeless. Experiences of physical abuse, foster care experiences, incarceration, suicide attempts, and psychiatric problems, especially drug use problems, have been reported to be associated with an increased risk of becoming homeless in a

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systematic review and meta-analysis [10]. Taken together, the allocation of housing can be conceived as a complex queueing process that is stochastic on both the demand side (individuals in need of housing) and the supply side (when housing becomes available [11]).

The state of being homeless is important because people who experience it can be at increased risk of adverse outcomes compared to their peers who do not, especially those experiencing long-term and repeated homelessness [12,13]. Individuals who experience homelessness may have complex health care needs [14-18]. Homeless individuals are at greater risk of death, hospital admission related to substance use, and poor mental and physical health [14-16,19,20].

In the specific context of Northern Ireland, homelessness is a growing health and social issue [20-23], exacerbated by Northern Ireland's history of conflict [24] and the current cost of living crisis [25]. A recent study found that 18 people were observed to be sleeping rough in Northern Ireland's most recent survey in autumn 2020 [26], which was fewer than in previous years, likely due to service changes during the COVID-19 pandemic. The incidence of statutory homelessness in Northern Ireland cannot be easily compared to the rest of the United Kingdom because of the use of different definitions [7,27,28], but the Department for Communities reported 4306 households presenting as homeless between January and March 2021, of which 2717 were accepted as homeless (or threatened with homelessness), in priority need, and unintentionally homeless. The most common reason for homelessness (27%) was "accommodation not reasonable," and for three-quarters of these, the underlying reason was physical health, disability, or mental health [29]. Homelessness among young adults is a growing public health concern in Northern Ireland [30]. Current figures estimate that around 3824 young adults, male and female, aged between 18 and 25 years presented as homeless to the Northern Ireland Housing Executive (NIHE) between 2018 and 2019 [31]. Over the past decade in Northern Ireland, there has been interest in using children's social care data [21,31-33] to better understand the factors associated with young people becoming homeless. Social services may have a duty to accommodate children where they are without parents or if the parents cannot obtain long-term accommodation through a homeless application, for example, due to problems with their immigration status. There is limited information about how frequently children who experienced homelessness had repeated contact with child and family social services over time, through rereferrals, reregistration on the child protection register, and readmission to care rates, and how this is associated with deprivation and other child, family, and case characteristics.

People who experience homelessness are among the most deprived in society, may be underrepresented in government statistics, and are largely omitted from household surveys [23,24,34], making it difficult for researchers and policy makers to identify and address the needs of this vulnerable population group [23]. Administrative linkage data, once linked and appropriately analyzed, can be a useful source of insight to help policymakers with the consequences of homelessness and the policy interventions that might reduce harm and support health and well-being [35-37]. Information about the relationship between homelessness and health is limited in Northern Ireland [21-23,29,38]. Anonymized, linked health and social care (HSC) administrative data sets have considerable potential for measuring outcomes for individuals who are homeless. Linkage of data sets is powerful for conducting large-scale, longitudinal epidemiological research. Studies have also used emergency department (ED) administrative data to track trends and health inequalities and examined outcomes associated with being homelessness [39-41].

Linking homelessness records in Northern Ireland to HSC data sets and analyzing the data with epidemiological and reproducible modern data science methods will create knowledge with practical application in Northern Ireland, which will also be of interest to an international audience [32]. A careful study design is required to measure the effects of homelessness because of potential confounding between risk factors for and consequences of homelessness [42]. We aim to measure the scale of the issue of homelessness and its trends by place and over time, to understand what factors affect the risk of homelessness, and to understand the consequences of homelessness. This protocol describes our analysis plan to achieve this.

Research Aims and Objectives

The aim of this work is to provide information for policy makers, practitioners, and the public about the causes and consequences of homelessness in Northern Ireland using linked health care and administrative data.

To achieve this, we seek to do the following:

1. Measure the incidence, prevalence, and duration of homelessness over time and place, overall, and in subgroup analysis by the reason for homelessness.
2. Describe the characteristics of people who have been homeless, overall and in subgroup analysis by the reason for homelessness, compared to the Northern Ireland population.
3. Investigate the risk factors for becoming homeless, based on personal characteristics, the time period, geographical factors, health-related factors, and social factors (eg, being a looked-after child).
4. Investigate the association between homelessness and health and social outcomes, including physical and mental health, and the use of HSC services.

Methods

Study Design

The primary study design is a retrospective cohort study with nested matched cohort analysis. Homelessness will be defined as individuals registered as homeless with NIHE. Controls will be selected through propensity score matching [43] to the cases based on age, sex, geographical region, year and month of homelessness application, and a propensity score quantile from a multivariable logistic regression model. If assumptions are met, we will conduct a self-controlled case series study [44] as a sensitivity analysis.

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Study Population

We will access and analyze national data from Northern Ireland (approximately 1.9 million people). Individuals in Northern Ireland HSC (equivalent to the National Health Services of the rest of the United Kingdom) have a health and care number (H&C number), which is a unique identifier that is used across HSC in Northern Ireland. We will include individuals who were alive, had an H&C number, and had been registered with a general practitioner in Northern Ireland since 2010.

Data Sources

The study will use administrative data obtained from several database sources, including the National Health Authority Information System (NHAIS), Electronic Prescribing Database (EPD), NIHE homelessness applications, patient administration system (PAS), ED information systems, Northern Ireland Maternity Information System (NIMATS), the Social Services Care Administrative and Records Environment (SOSCARE), and Pillar 1 and Pillar 2 COVID-19 data sets. The NHAIS contains information on all patients registered with a primary care physician. Northern Ireland has a universal, tax-financed, free at the point of service health care system with almost 100% population registration. It includes a unique address identifier (unique property reference number; UPRN). A list of temporary accommodations for people experiencing homelessness was compiled from stakeholder organizations and will be used to assign a binary indicator of whether an individual was registered as resident in such accommodation and the date registered to that address. NHAIS receives regular updates on the date and cause of death from the general register's office. International Classification of Diseases, Tenth Revision (ICD-10) codes on death records derive from diagnoses recorded by the certifying the doctor on the death certificate. The PAS data set will be used to collate data relating to admitted patient care delivered by HSC hospitals in Northern Ireland, generated by the PASs within each hospital. These data are held centrally by the HSC Regional Data Warehouse. The SOSCARE data set will be used to collate data regarding information on children registered with social care services, including family support services, children in need services, and the child protection register. The PAS will be used to collate data on general hospital admissions and COVID-19 hospital admissions. The NIMATS data set will contain maternity care data on women and their children. The EPD data set contains detailed information on prescriptions issued in Northern Ireland. The Pillar 1 data sets are extracted from the laboratory information systems in Northern Ireland hospitals on a daily basis into a central repository in the HSC Regional Data Warehouse. It contains details of COVID-19 antigen tests carried out in each of the hospital laboratories, including those processed on behalf of primary care, social care, and community settings. Pillar 2 data processed by NHS Digital and extracted for Northern Ireland residents are sent to the Northern Ireland HSC Regional Data Warehouse. The NIHE data set will contain social housing data for information reasons for applying to be considered homeless, type of accommodation, and previous accommodation and assessment outcome. Table 1 lists the data sets for linkage and potential predictors of homelessness that will be analyzed.

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Table 1. Data items or variables and data sources.

Data item	Data set
Patient characteristics and confounders	
Age	NHAIS[a]
Gender	NHAIS
Socioeconomic status	NHAIS
Underlying medical condition	EPD[b]
History of health care use (eg, general practitioner consultations and hospital admissions)	Admissions and discharge data set
Outcomes	
Maternity outcomes	NIMATS[c]
Hospital admission	Admissions and discharge data set
Emergency department	HBS[d]
Prescribed medications	EPD
Type of settlement (eg, private home, care home, or social housing)	NHAIS
Homeless applicant status	NIHE[e]
Homeless presenting reason	NIHE
History with social services	SOSCARE[f]
Cause of death	NHAIS
COVID-19–related death	NHAIS
Laboratory confirmed SARS-CoV-2 infection	Pillar 1 and Pillar 2
Secondary SARS-CoV-2 infection due to household transmission	Pillar 1 and Pillar 2

[a]NHAIS: National Health Authority Information System.

[b]EPD: Electronic Prescribing Database.

[c]NIMATS: Northern Ireland Maternity Information System.

[d]HBS: Honest Broker Service.

[e]NIHE: Northern Ireland Housing Executive.

[f]SOSCARE: Social Services Care Administrative and Records Environment.

Deidentification and Linkage

Linkage will be conducted by the Honest Broker Service (HBS). The personal data transfer to the Business Services Organisation (BSO) will be managed by separating the direct identifiers (name, date of birth, and address) from the rest of the data set at its source in NIHE and sending the 2 parts of the data sets to different teams in BSO for processing. A trusted third-party linkage team will only see the identifiers but never the individual attribute data. The researchers only see the attribute data but not the identifiers. A simple placeholder ID will be used to allow the information to be joined to other data sets without the use of the personal identifiers. The data processing steps are (1) NIHE will transfer a table of direct identifiers only to a "trusted third party" (the Family Practitioner Service; FPS) within the BSO, which is managerially separate and on separate computer networks from the HBS in the BSO. The FPS will aim to match the identifiers in the NIHE and NHAIS data sets (and thus to H&C numbers) using deterministic and fuzzy matching. (2) NIHE will send the main data set without identifiers (but with the placeholder ID) to the HBS. (3) The HBS will prepare all of the other data sets required for the project, assign a pseudonymous study ID to them, and upload the pseudonymized data to the secure research platform. (4) HBS will share with FPS a table (linkage key) that links all H&C numbers in Northern Ireland to the study ID. (5) FPS will join the NIHE identifier list with the matched H&C numbers to the junction table to assign a study ID. (6) Both HBS and FPS will destroy the pseudonymization key. (7) FPS will send a table of the study ID for each individual in the NIHE data set to HBS. (8) HBS will join the study ID from the NIHE to the homelessness data set using the placeholder identifier (eg, row number). The NIHE data set will then have a fully anonymized study ID that can be linked to all the other data sets in the project. HBS will upload the anonymized NIHE data to the secure research platform. The links between the tables will then rely on deterministic linkage. We will use the UPRN, time points, NIMATS, SOSCARE, and information about household size from the NIHE database to create groups of individuals who are associated together as households.

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Study Outcomes

For this study, 2 analytic epidemiological studies will be conducted: (1) study 1 will analyze the risk factors for homelessness, while (2) study 2 will examine homelessness as a risk factor for health and health care-related outcomes.

Primary and Secondary Outcomes

In study 1, the primary outcome of interest will be statutory homelessness. For the purpose of propensity score matching, becoming homeless (ie, meeting the NIHE threshold for homeless in the housing data) in the quarterly time period will be dichotomized into a binary variable (true or false). We will explore whether residence in temporary accommodation should be combined in a composite indicator after exploratory data analysis. For the Cox regression analysis (described below), the time from the study start date to the first episode of homelessness in the NIHE data set will be used as the primary outcome. Secondary analyses will be conducted by the established reasons for homelessness.

In study 2, the primary outcome of interest will be death. Secondary outcomes will examine ED attendances, emergency hospital admissions, emergency hospital admissions with COVID-19, and COVID-19 vaccination. All will be measured as time from homelessness onset (of the person who experienced homelessness or their matched pair) to the event.

Statistical Methods

We will commence analysis by conducting descriptive analyses to visually inspect trends in homelessness, trends over time in demand, supply, waiting list size, and waiting times for social housing, and risk factors (hospitalizations and deaths), including by age group, sex, geographical location, and index base year. We will undertake univariable and multivariable logistic regression for the first episode of homelessness. This will be conducted in R using *glm(family = "binominal")*. We will use *glm.predict()* to produce propensity scores for matching. We will use the propensity score to match individuals who have experienced homelessness with controls who have not experienced homelessness. We will match 1:1 on propensity score, age, sex, geographic area, and pregnancy status. Matching will be conducted over quarterly time periods to assign controls who shared characteristics at the time of homelessness. This will be implemented in a loop or apply function in R. Matched variables will not be used as independent variables. We will also undertake 2 alternative analyses to support the primary analysis. First, we will use a Cox proportional hazards model to investigate the hazard ratio of homelessness on the outcomes (censoring at death). Second, if the assumptions can be met, we will conduct a self-controlled case series analysis, which will give an alternative approach to managing confounding, fitting a spline for age.

For study 2, a Cox proportional hazards model will be used, comparing the propensity-matched groups over time to the primary and secondary outcomes producing hazard ratios and 95% CIs.

All tests will be 2-tailed, and a $P<.05$ will be considered statistically significant. All analyses will be carried out using R-Studio. Statistical analysis code will be shared on GitHub alongside publications.

Data Storage and Management

The HBS will carry out the data linkage and offer a secure environment for researchers to access and analyze the pseudonymized individual-level data. The NIHE housing data set will be provided to the BSO family practitioner unit without the H&C number identifier. This unit will undertake deterministic and fuzzy matching according to their normal protocols to assign a H&C number. We will describe in our report the fraction of records that could not be assigned a H&C number. The H&C number will be used to link individuals' data, though it will be replaced with an anonymous study ID in the analysis data set. All data will be securely stored on the HBS systems, and access will be revoked at the end of the project. HBS will archive and later destroy data according to its disposal schedule.

Dissemination and Data Sharing

To enhance reporting transparency, this study will be reported in accordance with the guidelines for the Reporting of Studies Conducted Using Observational Routinely Collected Data (RECORD), which is an extension of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement. The results from this work will be published as a full-length, peer-reviewed manuscript and presented at participant events and to a representative subgroup of key stakeholders from the homeless sector in Northern Ireland.

Dissemination Plan

Our findings will be presented at national and international conferences and submitted for peer-reviewed publication to inform policy, practice, and research about the causes and consequences of homelessness.

Ethical Considerations

Ethical approval was granted by Queen's University governance and HBS. This study was approved by the National Research Ethics Service (Integrated Research Application System project ID 299887, Research Ethics Committees reference 22/SC/0065). The study was also approved by the HBS governance board (project 073). Data access agreements between the NIHE and the HSC BSO were established to manage the transfer and privacy-preserving deidentification and linkage of data. The research team will not have access to human participant information that can directly identify participants (eg, name, identifier, date of birth, or small geographic-level data). Informed consent was not required for this project. The research team will follow the statistical disclosure policy of the HBS, guided by the statistical disclosure control handbook. All outputs will be checked by the HBS team before being released. The analysis of individual-level data takes place within a safe setting at HBS from which data cannot be removed. Any potentially disclosive findings (eg, cross-tabs with small cell counts that may allow participant identification) will not be permitted to leave the safe setting.

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Results

This project is the results of a partnership grant between the Administrative Data Research Northern Ireland (ADR NI), HBS, and NIHE. The transdisciplinary, multi-institutional team brings wide-ranging technical and stakeholder management experience, as well as many years of health prevention and evidence-based public health policy knowledge. The results from this project will aim to identify predictors and consequences of homelessness in Northern Ireland for the first time using linked homelessness, social services, and health administrative data. The results of our analyses will be shared with stakeholders, reported at conferences and in academic journals, and summarized in policy briefing notes for policymakers. As of September 2023, initial data analysis is expected to commence on this project and continue until March 2026.

Discussion

Overview

Our planned study will analyze HSC administrative data to investigate the characteristics, exposures, and outcomes of people who experience homelessness. Research from the United Kingdom [45], Ireland [46], Scotland [47], and Canada [35] has elicited useful policy insights for those contexts at the time points at which they were conducted. Our work will add to the understanding of the relationship between homelessness and health, which is an important contemporary social justice concern [48].

The complex nature of homelessness and its interactions with health require a tailored study design to provide evidence about the direction of causality in associations. For example, ill health could conceivably lead to or result from experiencing homelessness. Our study design introduces a time component that will allow us to understand the order of events and an approach to controlling confounding that will allow us to separate the contribution to homelessness of many interrelated socioeconomic factors. People who reside in temporary accommodations may face challenges around crowding. The impacts of the pandemic on the incidence and prevalence of homelessness remain uncertain at the time of writing [49,50]. However, there is emerging global evidence of higher COVID-19 infection and death rates among individuals who experience homelessness [51-53].

Strengths of this study include the use of a large, whole-population cohort, which should have a relatively low risk of bias. We also have access to a range of routine, whole-population data sources. However, there are limitations to this study. First, our definition of homelessness is restricted to individuals registered as being homeless with the NIHE. This will not detect individuals who were homeless but did not seek housing from NIHE. We will explore the use of residence in temporary accommodations, but at this point in planning, we do not have evidence about the usefulness of this indicator, given that it would require individuals to update their health care registration address. Second, our study will be limited to the Northern Ireland health care context, and results may not be applicable to other settings. There is a risk of bias if individuals experiencing homelessness have a greater risk of health care records not containing their unique identifier.

Conclusion

The findings of this study will be useful for researchers and policymakers seeking to study trends and outcomes associated with being homeless within a Northern Ireland context and will also be applicable to other contexts. Our study will provide evidence that can inform policymakers and highlight the potential societal benefits from the safe use of deidentified administrative data.

Acknowledgments

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Data Availability

The data sets generated during and/or analyzed during this study are not publicly available, due to being controlled by the HSC Regional Business Services Organisation (RBSO/BSO). Data is available from the Honest Broker Service within RBSO/BSO upon request.

Authors' Contributions

EM and DB wrote the manuscript and provided the data for Table 1. All authors reviewed the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

ADR NI: Administrative Data Research Northern Ireland
BSO: Business Service Organisation
ED: emergency department
EPD: Electronic Prescribing Database
FPS: Family Practitioner Service
H&C number: health care number
HBS: Honest Broker Service
HSC: health and social care
ICD-10: International Classification of Diseases, Tenth Revision
NHAIS: National Health Authority Information System
NIHE: Northern Ireland Housing Executive
NIMATS: Northern Ireland Maternity Information System
PAS: patient administration system
RECORD: Reporting of Studies Conducted Using Observational Routinely Collected Data
STROBE: Strengthening the Reporting of Observational Studies in Epidemiology
SOSCARE: Social Services Care Administrative and Records Environment
UPRN: Unique Property Reference Number

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Protocol

Peer Support Self-Management Intervention for Individuals With Type 2 Diabetes in Rural Primary Care Settings: Protocol for a Mixed Methods Study

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Abstract

Background: The increasing prevalence of diabetes is placing important demands on the Chinese health care system. Providing self-management programs to the fast-growing number of people with diabetes presents an urgent need in rural primary care settings in China. Peer support has demonstrated effectiveness in improving self-management for individuals with diabetes in urban communities in China. A priority then becomes developing and evaluating a peer support program in primary care settings in rural communities of China and determining whether it is feasible and acceptable.

Objective: The aims of this study are (1) to evaluate the feasibility and acceptability of a peer support approach to type 2 diabetes self-management in rural primary care settings; (2) to identify enabler and facilitator factors likely to influence the peer support implementation; (3) to provide primary data and evidence for developing a version of the program suitable for a randomized controlled trial in rural primary care settings.

Methods: Three townships will be sampled from 3 different counties of Anhui province as the study setting. Participants will be recruited based on these counties' local primary care health record system. The peer supporters will be recruited from among the participants. The peer support program will be led by peer supporters who have completed 12 hours of training. It will be guided by primary care providers. The program will include biweekly meetings over 3 months with varied peer support contacts between meetings to encourage the implementation of diabetes self-management. Mixed methods will be used for evaluation. Qualitative methods will be used to collect information from health care system professionals, individuals with diabetes, and peer supporters. Quantitative methods will be used to collect baseline data and data at the end of the 3-month intervention regarding psychosocial factors and self-management practices.

Results: The results will include (1) quantitative baseline data that will characterize type 2 diabetes self-management practices of individuals with diabetes; (2) qualitative data that will identify enablers of and barriers to self-management practices for individuals with type 2 diabetes in rural communities; (3) both qualitative and quantitative evaluation data, after the 3-month intervention, to demonstrate the feasibility and acceptability of the peer support approach for individuals with type 2 diabetes.

Conclusions: Our findings will inform the design of a tailored intervention program to improve self-management among individuals with type 2 diabetes in rural primary care settings. If we find that the peer support approach is feasible and acceptable, we will develop a larger randomized controlled trial to evaluate effectiveness in multiple rural settings in the province.

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KEYWORDS

type 2 diabetes; peer support; self-management; rural primary care setting; mixed study; rural; primary care; diabetes; diabetic

Introduction

Background

Challenges of the Diabetes Situation in China

Diabetes is a growing public health challenge. Diabetes mellitus (DM) imposes a huge economic burden on national health care systems worldwide, including in China. The prevalence of diabetes among adults in China has reached 11.6%, comprising about 114 million people and making China the country with the largest number of individuals with diabetes in the world [1]. The prevalence of diabetes in rural areas increased from 8.2% in 2008 to 10.3% in 2010. Although the prevalence is still lower than in urban areas, the growth rate is higher than in urban areas [2]. Furthermore, two-thirds of Chinese adults with diabetes have complications, and only 20.3% exhibit satisfactory glycemic control [3]. To improve noncommunicable disease prevention and control in diseases including diabetes, the National Basic Public Health Service Program (NBPHSP) was launched as part of China's health care reform initiated in 2009. Subsidized by national and local government budgets, the NBPHSP is mainly implemented by community and township health service centers and health stations in urban areas and village clinics in rural areas [4]. Health management of patients with hypertension and diabetes is an integral and pivotal part of the NBPHSP. However, gaps still exist between guidance on modifiable risk factors and field implementation in primary health care settings. Patients with type 2 diabetes blood glucose and related risk behavior interventions have not been sufficiently studied in primary care settings [5]. Chronic illnesses are largely self-managed, with most of the care becoming the responsibility of patients and their families or others involved in the daily management of their illnesses.

Diabetes Self-Management

Early users of the term *self-management* included Thomas Creer et al [6] in a 1976 book on the rehabilitation of chronically ill children. Creer and colleagues said that "the term of self-management indicated that the patient was an active participant in treatment." Since that time, the term has been widely used, mainly in referring to chronic disease patient education programs. Self-management has been defined as referring to "whether one is engaging in a health promoting activity such as exercise or is living with a chronic disease such as asthma, he or she is responsible for day-to-day management." [7] Prominent approaches emphasize 3 sets of tasks: medical or behavior management, role management, and emotional management [8]. Additionally, 5 core self-management skills are commonly emphasized: problem-solving, decision-making, resource use, forming a patient–health care provider partnership, and taking action [9].

DM is a progressive and chronic condition lasting the remainder of the patient's life. It is widely recognized that self-management is the cornerstone of DM care and has the potential to prevent relevant complications and improve quality of life [10]. Accordingly, the success of the treatment for DM depends on the ability of the individual to successfully sustain effective self-management behaviors that include taking prescribed medications, following diet and exercise regimens, self-monitoring blood glucose, and emotionally coping with the rigors of living with diabetes [8]. The goals of diabetes self-management are to optimize metabolic control, prevent acute and chronic complications, and optimize quality of life while keeping costs acceptable. The management of type 2 DM (T2DM) has traditionally been provided by health care professionals who focus on medication and lifestyle changes that can improve glycemic control.

A meta-analysis of self-management programs in diabetes by Norris and colleagues [11] found that diabetes self-management education provided by health care professionals is effective for improving clinical outcomes and quality of life, at least in the short term, but that these benefits sharply decline only a few months after the intervention ends. Therefore, while essential, education is generally not sufficient for most patients to maintain these behaviors over a lifetime of diabetes. To avoid such declines in benefits, evidence indicates that interventions should include elements of social support from families, engagement of multidisciplinary health care professionals, and support from others with diabetes. It is useful for the person with T2DM to recruit allies in supporting self-management who understand the condition, other people with diabetes who can share experiences and tips, or professionals who encourage a collaborative relationship in which they offer advice and the individual chooses how best to use it based on their knowledge of their own body and condition [12].

Studies show that without sustained support, many adults will not succeed in managing their condition well, leading to worse health outcomes including expensive hospitalizations and avoidable complications [13]. Among all these approaches to ongoing follow-up, peer support for diabetes self-management has been considered a promising strategy to achieve sound long-term outcomes for diabetes patients.

Peer Support for Diabetes Self-Management

Peer support has been formally defined as "the provision of emotional, appraisal, and informational assistance by a created social network member who possesses experiential knowledge of a specific behavioral stressor and similar characteristics as the target population, to address a health-related issue of a potentially or actually stressed focal person" [13]. Peer support may reduce feelings of isolation and loneliness, provide information about access to health services or the benefits of behaviors that positively improve health and well-being, and encourage more positive health practices [14]. Peer support programs have been widely recognized as promising for facilitating self-management behaviors among individuals with T2DM. Evidence demonstrates that the self-management practices of patients with diabetes are influenced by their knowledge, attitude, self-efficacy, and the presence of a supportive interpersonal, community, and policy environment

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[15]. The peer support approach emphasizes bringing a group of people with the same condition together to share their self-management challenges and address them as a group rather than using a professional leader who may focus purely on education. Peer group sharing and learning increase knowledge, enhance self-efficacy, and change attitudes for self-management practice [16,17].

Diabetes Management in Primary Care Settings in China

Since the 1990s, China has initiated diabetes self-management education programs that have included nurse-based information delivery or clinic counseling targeting inpatients. Literature has shown those programs can improve patients' knowledge and adherence to medication after intensive short-term interventions [18]. However, the beneficial results could not be sustained in the long term because patients lacked self-efficacy, motivation, and ongoing follow-up support [19,20]. Health policy in China has led to diabetes care and management being delivered mainly in local primary care settings. However, it is difficult to provide personalized health management in rural primary-care settings due to the challenges of professional shortages and limited capacity relative to urban settings [21,22]. Moreover, rural populations often live in worse socioeconomic conditions and have lower health literacy. In rural settings, knowledge, adherence to management practices, and blood sugar control are far from meeting national goals [23,24]. Studies have shown, however, that friends, peers, family members, and community lay health workers may all be important supporters of self-management among individuals with diabetes, especially in areas with restricted health resources [25-27]. Additionally, peer support relies on nonhierarchical, reciprocal relationships, which provide a flexible supplement to formal health system services for people with diabetes. In addition, peer support fosters understanding and trust of health care staff among groups who otherwise may be alienated from or have poor access to health care [28,29]. Peer support implemented through primary care is gaining increased interest in urban China [25,30], while few programs exist in rural areas.

Given the needs in rural areas, and the benefits peer support approaches have achieved in urban settings, this project will explore and assess the feasibility and acceptability of peer support approaches in rural areas. We propose to develop community-based peer support for individuals with type 2 diabetes in rural areas in China. In particular, the study is designed to integrate a peer-support approach into local primary care settings. This study outcome will provide valuable information about the effectiveness, acceptability, and feasibility of a program to improve diabetes self-management in rural, resource-limited communities.

Study Purposes

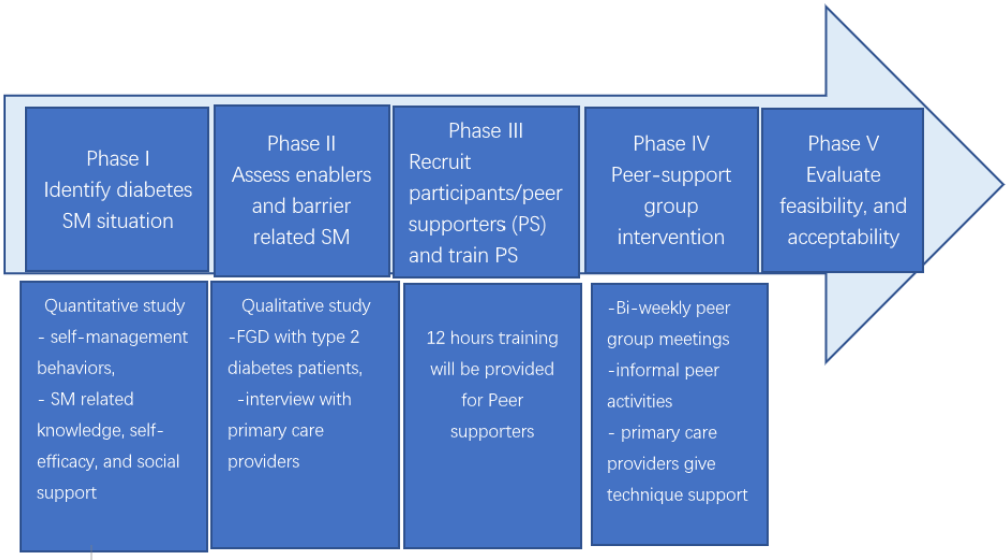
Peer support is a culturally adapted, complex intervention; evaluating such an intervention presents challenges to researchers. This study will pursue the following objectives: (1) to evaluate the feasibility and acceptability of a peer support approach to type 2 diabetes self-management in rural primary care settings; (2) to identify enabler and facilitator factors likely to influence the peer support implementation; (3) to provide primary data and evidence for developing a version of the program suitable for a randomized controlled trial in a rural primary care setting.

Methods

Overview

This project will include formative evaluation to develop and then implement and evaluate a peer support approach to improve diabetes self-management in rural primary care. Figure 1 shows each phase in the study.

Figure 1. Study phases in detail.



Study Setting

This study will be conducted in rural communities in Anhui province. Anhui province is located in eastern China and has about 61 million people. It is divided into 3 geographic areas based on the Huai River and Changjiang River. The 3 areas are north of the Huai River, between the Huai River and Changjiang River, and south of the Changjiang River. These 3 different

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areas have different customs, cultures, and dietary habits. Stratified sampling will identify 1 county in each of the northern, southern, and middle regions. One township will be randomly recruited in each county. Within each township, the village that has the largest number of adults with T2DM will be selected based on the electronic management system of the local primary care system. This will result in 3 villages representing 3 areas in Anhui province with high numbers of adults with T2DM.

Participant Recruiting

Study participants will be identified through the Community Chronic Disease Management System (CCDMS), which was established as a national primary care package program in communities in both urban and rural areas. Primary care providers (family doctors and public health physicians) in local primary care settings (township hospitals or village clinics) will contact eligible patients to explain the purpose of the study and details of the program. Since this is an exploratory study with a new intervention approach that has never been tested before in rural Anhui Province, no formal calculation of the sample size will be performed. All patients who are registered in the CCDMS in the sampled study setting (villages) and meet the inclusion criteria will be included if they are willing to participate. An estimated 15 to 20 patients will be recruited in each county, yielding a total sample of 45 to 60 participants. Based on the recommendations of Hertzog [31], a sample of 10 to 40 people is sufficient for a pilot study using a single group to estimate the sample size for a future trial.

Inclusion Criteria

The inclusion criteria are (1) having T2DM and being registered in the electronic CCDMS in the primary care settings (township hospitals and village clinics), (2) declaring voluntary participation in the study program with the signed informed consent form, and (3) having lived in the study village community at least 6 months.

Exclusion Criteria

The exclusion criteria include (1) major psychiatric conditions, (2) serious diabetes complications (eg, blindness) that would impede participation in the program, (3) other serious health conditions (eg, terminal cancer), and (4) current enrollment in other research programs.

Data Collection

Both qualitative and quantitative data will be collected in phases I and II, program development, and phase V, program evaluation. In each phase, there will be 2 stages: first, qualitative data will be collected and analyzed; second, quantitative data will be collected. Here, we describe the general methods of qualitative and quantitative data collection and analysis. The content of these assessments is described in detail in subsequent descriptions of the individual phases.

Qualitative Data Collection

Researchers will conduct 3 focus group discussions and interviews, with 1 focus group being devoted to each of the following roles: primary care professionals, recruited participants, and peer supporters. Each focus group (6-8 participants) will be led by 2 research team members with a third team member taking notes to be checked for accuracy against audiotapes of the group meetings. Content analyses will identify the common concepts across sites and across roles (patients, professionals, peer leaders). Similar methods will be used to evaluate implementation at the end of the study, also including interviews with patients, peer supporters, and primary care providers.

Quantitative Data Collection

The questionnaire will be developed by the research team. The questionnaire survey will be administered as face-to-face interviews for self-reported data by trained investigators.

Quantitative Data Analyses

Social demographic data and health status of the study subjects will be presented as frequencies (percentages) for categorical variables and means (SDs) for continuous variables. Comparison of patients' characteristics between the 3 settings will be checked by means of 2-tailed t tests, χ^2 tests, or nonparametric equivalents. In phase V, the evaluation will include an analysis of differences at 3 months compared to baseline in self-management practice, knowledge, self-efficacy, and perception of social support.

Ethics Approval and Informed Consent to Participate

The study was approved by the Biomedical Ethics Committee of Anhui Medical University (83220455) on October 13, 2022.

All participants are asked to provide informed consent by responding to the program survey. Participants are informed that consent includes their data being linked to primary care basic program electronic health records and agreeing to surveys and extraction of health record data at the end of the intervention during the evaluation in phase V without additional consent.

Each participant who attends the program will sign a consent form at the start of the intervention. Participants will be informed about the purpose of the study, about the course of the intervention, that it will be conducted in accordance with the study protocol, and that they are free to withdraw from the study at any time. All study data will be deidentified prior to analysis and presented only in anonymized forms.

Implementation Development

Phase I: Understanding the Current Situation of Diabetes Self-Management

Understanding the current situation regarding self-management practice and identifying factors that influence patients' self-management practice is crucial to developing the intervention program. A study questionnaire will be developed to collect patients' demographic data, current health status, and diabetes self-management practices. Psychosocial data will be collected by using validated measurement instruments (Table 1). Self-efficacy will be measured by the Chinese Diabetes Self-Efficacy Scale (C-DSES) [32]. Social support will be measured by the Medical Outcome Study Social Support Survey (MOS-SSS) [33], and self-management practices will be measured by the Summary of Diabetes Self-Care Activities (SDSCA) [34].

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Table 1. Measurement domains and survey tools used at each data collection time point.

Variables	Quantitative measurement instruments	Baseline	3 months
Demographic and health status	Sex, age, ethnicity, education, marital status, occupation (ie, source of livelihood), co-habitants (ie, family members), length of diagnosis with diabetes, complications, and comorbidities	✓	
Psychosocial factors	CDSES[a], MOS-SSS[b]	✓	✓
Self-management practices	SDSCA[c]	✓	✓

[a]Chinese Diabetes Self-Efficacy Scale.

[b]Medical Outcome Study Social Support Survey.

[c]Summary of Diabetes Self-Care Activities.

Phase II: Identify Enablers and Barriers

Health programs and interventions most likely to be successful and achieve desired outcomes are based on a clear understanding of targeted health behaviors, the factors that influence them, and the environmental context in which they occur [13]. It is critical to thoroughly understand the local primary and chronic disease care delivered by family doctors or township public health professionals in rural communities and the factors that might influence the program implementation process. Meanwhile, it is also important to understand the current social network and support for the self-management of individuals with diabetes in the rural context. It is also necessary to know the characteristics of peer group meetings or activities (eg, frequency, duration, place, content, peer leader tasks) that individuals with diabetes, professionals, and peer leaders would find helpful and feasible. The research team will develop interview and focus group discussion guidelines to gather qualitative data regarding these issues. As described above, focus groups will include individuals with diabetes, professionals, and peer supporters. The results will guide development of real-world peer support intervention activities, contents, and delivery methods.

Phase III: Peer Supporter Recruitment and Peer Supporter Training

Peer supporters will be recruited by recommendations from both participating patients and village clinic doctors.

Inclusion Criteria

The inclusion criteria are as follows: (1) having been diagnosed with type 2 diabetes for ≥1 year; (2) commitment to attending a 12-hour training session at the beginning of the program; (3) commitment to organizing activities with other patients at least 2 times every month; (4) a basic education level, including reading and writing skills; (5) having supportive, nonjudgmental communication skills; (6) willingness to lead group meetings and activities; and (7) willingness to cooperate with primary care providers, including willingness to follow guidelines for when to let primary care providers know about problems participants may be having.

Peer Supporter Training

Recruited peer supporters will receive 12 hours of training. Training content will include the following: (1) an introduction to the peer support intervention program in terms of purpose, contents, group activities, and peer leader roles; (2) basic knowledge and skills in diabetes self-management practices; (3) basic health communication skills; (4) the key functions of peer support promoted by Peers for Progress [28], including assisting and encouraging daily diabetes management, providing social and emotional support, linking with community resources and primary care, and providing ongoing support; and (5) guidelines and rehearsal of when and how to seek support from primary care providers regarding participant concerns or problems that are outside their competence.

A peer supporter handbook that includes training materials will be developed for use with training participants.

Because the implementation of peer support needs to be supported within its organizational setting, primary care providers will also receive training related to program implementation, their role in encouraging participation in peer support, and how they can support the peer supporters.

Phase IV: Peer Supporter–Led Group Meetings and Activities

Participants will be divided into groups with 6 to 10 people and assigned to peer leaders for 3 months based on how close they live to the peer leaders. Groups will be encouraged to take part in biweekly (ie, every second week) group activities with peer supporters. Peer group members will also be encouraged to organize weekly casual activities such as phone calls, WeChat voice messages, physical exercise groups, and group member family visits.

The biweekly meeting content will be based on findings from phase II and adapted and developed together with primary care providers and peer supporters. The peer group sessions will aim to achieve the following key self-management practice objectives: increasing physical activity; promoting healthy eating habits; ceasing tobacco use; reducing alcohol consumption; adhering to medication; engaging in regular clinical care and diabetes management services provided in primary care settings, such as health education classes, blood sugar and blood pressure monitoring, and physical examinations; and coping with negative emotions.

Peer supporters will also be encouraged to contact participants in their groups between the formal group sessions in order to reinforce the program objectives, update on and discuss the content of missed sessions, and encourage goal attainment and attendance at the next peer group session. These contacts may be informal through meetings within their neighborhoods.

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Phase V: Evaluation of Feasibility and Acceptability

The aim of this last phase is to evaluate the feasibility and acceptability of the peer support approach in rural primary care settings. Quantitative outcome variables will be measured at baseline and after 3 months to evaluate program feasibility. Qualitative assessments will evaluate the feasibility and acceptability of peer support implementation.

Quantitative Evaluation

Key evaluations will be the assessment of differences between baseline and after 3 months (after completion of the peer leader program) in terms of self-management practice, knowledge, self-efficacy, and perception of social support. Additionally, changes will be compared between villages through 2-tailed *t* tests or nonparametric equivalents.

Qualitative Evaluation

After 3 months, a descriptive parallel qualitative analysis will be carried out to evaluate the acceptability and feasibility of the program. Semistructured questionnaires and interview guides will be used to collect perceptions of the program from participants, peer supporters, and primary care providers. Questions will include barriers and benefits, individuals' experiences in the peer-led activities, and suggestions for future program revision and implementation. These will follow the methods for qualitative data collection from peer leaders, professionals, and participants and data analysis described above.

Focus group discussions of participants will be conducted to collect their perceptions, attitudes, experiences, and suggestions for improvement of the peer support program. The focus group discussion and interviews will be audio-recorded and transcribed.

The semistructured interviews with peer supporters will include their experience of the delivery of group interventions, as well as their experience of the process of receiving training and leading group activities. Peer supporters will be encouraged to discuss their feelings and sense of efficacy, the training experience, their motivations, and any positive or negative impacts on their own diabetes management.

Results

This study was funded in December 2021. Due to COVID-19 restrictions, the project implementation plan for activities in 2022 had to be delayed almost half a year. As of July 2022, we had developed and validated the survey questionnaires and completed interview guidelines. As of January 2023, focus group discussions with both primary care providers and individuals with diabetes had been completed.

Discussion

Anticipated Findings

The findings of this study will identify whether a peer support approach is an acceptable and feasible intervention in the rural primary care setting. It will provide evidence on whether the peer support program can enhance uptake, engagement, and maintenance of behaviors to reduce the risk of progression to diabetes. Findings from the study will provide invaluable information on required staff effort and key facilitators and barriers to implementing and sustaining this type of peer supporter–led group program. In addition, it will explore how the peer support self-management approach may be integrated into the NBPHSP in rural areas [4].

Generally, residents who live in the same village are familiar with each other and help each other. Group activities, such as playing mah-jongg and square dancing, are traditional in Chinese culture. This may enhance participation in the groups based on shared experiences and learning from each other. It may also contribute to participants' knowledge and self-efficacy for self-management through group sharing and activities [35].

There is an accumulating body of studies exploring feasible and acceptable diabetes self-management programs around the world, including those that use peer support. To our knowledge, however, no previous research has examined the feasibility, acceptability, and benefits of peer support for diabetes management in primary care settings in rural China. Thus, the results of this study will provide evidence and insights for developing a peer-led support program for diabetes self-management in this important setting.

We anticipate that the peer support approach for diabetes self-management will be adopted and accepted in rural China, and that participants in a peer supporter–led intervention will show improvement in psychosocial outcomes, adherence to health recommendations in the primary care setting, and better self-management practices. In addition, we hypothesize that the recruitment and training of volunteers with T2DM as peer supporters for participants with the same conditions will be integrated into current chronic disease management practices in primary care in rural areas. We expect that this qualitative research will reveal an in-depth perspective on the impact of this approach, both at the level of the patient as an individual and at the primary care setting level. Successful implementation of this study will provide evidence of the key functions of peer support. Moreover, the results of this study will influence future policies on diabetes management, as well as other chronic diseases in China.

Potential Limitations and Bias

This study has some limitations. First, outcome measures are primarily self-reported. Second, the study might be subject to selection bias since only voluntary and motivated patients will be included in our study. Third, the study design does not include a control group. The comparison of outcomes before and after the intervention may be biased by social desirability, as well as by other influences.

Impact and Future Directions

If the peer support approach is feasible and acceptable, we plan to develop the program further and test its effectiveness in a well-powered randomized controlled trial also focusing on the rural setting.

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Data Availability

The data sets generated during and/or analyzed during this study will be made available from the corresponding author upon reasonable request.

Authors' Contributions

The principal investigator, XZ, conceived the proposal, obtained funding, contributed to the study design and manuscript writing, and approved the final draft. ML and XM participated in the literature review for proposal development and will be involved in data collection and analysis. SL participated in the study design and prepared the first manuscript draft. EBF provided advice for program design and implementation and assisted with manuscript revision. All authors reviewed this manuscript and approved the final version. All authors will participate in the implementation of the program.

Conflicts of Interest

None declared.

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Abbreviations

C-DSES: Chinese Diabetes Self-Efficacy Scale
CCDMS: Community Chronic Disease Management System
DM: diabetes mellitus
MOS-SSS: Medical Outcome Study Social Support Survey
NBPHSP: National Basic Public Health Service Program
SDSCA: Summary of Diabetes Self-Care Activities
T2DM: type 2 diabetes mellitus

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Protocol

Nudging Health Care Providers' Adoption of Clinical Decision Support: Protocol for the User-Centered Development of a Behavioral Economics–Inspired Electronic Health Record Tool

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Abstract

Background: The improvements in care resulting from clinical decision support (CDS) have been significantly limited by consistently low health care provider adoption. Health care provider attitudes toward CDS, specifically psychological and behavioral barriers, are not typically addressed during any stage of CDS development, although they represent an important barrier to adoption. Emerging evidence has shown the surprising power of using insights from the field of behavioral economics to address psychological and behavioral barriers. *Nudges* are formal applications of behavioral economics, defined as positive reinforcement and indirect suggestions that have a nonforced effect on decision-making.

Objective: Our goal is to employ a user-centered design process to develop a CDS tool—the pulmonary embolism (PE) risk calculator—for PE risk stratification in the emergency department that incorporates a behavior theory–informed nudge to address identified behavioral barriers to use.

Methods: All study activities took place at a large academic health system in the New York City metropolitan area. Our study used a user-centered and behavior theory–based approach to achieve the following two aims: (1) use mixed methods to identify health care provider barriers to the use of an active CDS tool for PE risk stratification and (2) develop a new CDS tool—the PE risk calculator—that addresses behavioral barriers to health care providers' adoption of CDS by incorporating nudges into the user interface. These aims were guided by the revised Observational Research Behavioral Information Technology model. A total of 50 clinicians who used the original version of the tool were surveyed with a quantitative instrument that we developed based on a behavior theory framework—the Capability-Opportunity-Motivation-Behavior framework. A semistructured interview guide was developed based on the survey responses. Inductive methods were used to analyze interview session notes and audio recordings from 12 interviews. Revised versions of the tool were developed that incorporated nudges.

Results: Functional prototypes were developed by using Axure PRO (Axure Software Solutions) software and usability tested with end users in an iterative agile process (n=10). The tool was redesigned to address 4 identified major barriers to tool use; we included 2 nudges and a default. The 6-month pilot trial for the tool was launched on October 1, 2021.

Conclusions: Clinicians highlighted several important psychological and behavioral barriers to CDS use. Addressing these barriers, along with conducting traditional usability testing, facilitated the development of a tool with greater potential to transform clinical care. The tool will be tested in a prospective pilot trial.

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KEYWORDS

health informatics; clinical decision support; electronic health record; implementation science; behavioral economics; user-centered design; pulmonary embolism

Introduction

Background

US citizens receive only half of the recommended medical care [1], and one-third of the care received is unnecessary [2]. The disparity between usual and evidence-based clinical practice is the reason behind one-third of hospital deaths [3] and results in an estimated loss of US $380 billion each year [4]. Computerized clinical decision support (CDS) attempts to close this gap by bringing meaningful and relevant evidence to health care providers at the point of decision-making. Health care providers, policy makers, experts, and consumers have identified CDS tools as key tools for revolutionizing health care [5-7]. However, the moderate improvements in care resulting from CDS [8-14] have been significantly limited by consistently low health care provider adoption [15,16]. There is a critical need to identify strategies for increasing health care providers' adoption of CDS.

Health care provider attitudes toward CDS, specifically psychological and behavioral barriers, are not typically addressed during any stage of CDS development, although they represent an important barrier to adoption [17]. Psychological and behavioral barriers to use must be addressed along with traditional barriers to usability to improve adoption and, as a result, improve clinical impact. Our study's objective is to employ a user-centered design process to develop a CDS tool—the pulmonary embolism (PE) risk calculator (PERK)—for PE risk stratification in the emergency department that incorporates a behavior theory–informed nudge to address identified behavioral barriers to use.

PE Risk Stratification

The use of PE risk stratification tools in the emergency department setting can reduce unnecessary computed tomography (CT) scans [18,19]. The 2-tiered *Wells score for PE* clinical prediction rule classifies patients as those with a low or high probability of PE based on key elements of their histories and physical exams. This rule recommends the use of a laboratory value—the dimerized plasmin fragment D (D-dimer) assay—to rule out PE in low-risk patients. This eliminates the need for imaging in patients with a low probability of PE and a negative D-dimer assay result. The use of clinical prediction rules to assess pretest probability before performing a CT scan reduces testing by 25%, without any missed PEs [18,19]. This reduction in CT scan use is important, as each test carries a 14% risk of contrast-induced nephropathy [20] and a lifetime malignancy risk that can be as high as 2.76% [21]. Additionally, incidental findings requiring diagnostic follow-up are found in 24% of tests, increasing both the costs and the harms from repeat imaging [22].

Nudges and Behavioral Economics

The field of behavioral economics studies the effects of psychological, social, cognitive, and emotional factors on the economic decisions of individuals. This field is contributing to a growing body of research demonstrating the usefulness of addressing subtle attitudes, beliefs, and habits that result in individuals behaving irrationally [23,24]. In behavioral economics, nudges are used to influence behavior. *Nudges* are defined as positive reinforcement and indirect suggestions that have a nonforced effect on decision-making [25]. For example, the default options for organ donation consent result in striking differences in enrollment [26]. An example in health care is comparing health care providers to peers, which has been effective at reducing antibiotic prescribing for upper respiratory infections [27].

Nudges have been successful in influencing health care provider decision-making. There is a growing body of evidence demonstrating that health care provider decisions are also subject to variability resulting from psychological and emotional factors [28-30]. A recent meta-analysis found that direct education approaches did not result in sustained reductions in inappropriate antibiotic prescriptions [31]. However, a large randomized controlled trial found that a social comparison nudge decreased the rate of health care provider antibiotic prescribing for upper respiratory infections from 19.9% to 3.7% [27]. These results were durable at 3 months [32]. Integrating behavioral economics strategies into electronic health records (EHRs) by using CDS tools is a novel approach to improving guideline adherence that also seeks to minimize negative impacts on clinical workflows and cognitive loads.

The Observational Research Behavioral Information Technology Model for Behavioral Intervention Development

Our developmental work was guided by the revised Observational Research Behavioral Information Technology (ORBIT) model, which provides a tested framework for behavioral intervention development [33]. The model includes several phases with well-defined outcomes and milestones, culminating in the testing of the intervention in a large-scale effectiveness trial. The model features several bidirectional arrows, encouraging iterative development and refinement. The use of this model to support the development of behavioral interventions is key to ensuring that scientific developments contribute to the development of effective interventions. The work described herein details the development of our intervention (ie, Phase 1 Design).

Methods

Our study used a user-centered and behavior theory–based approach to achieve the following two aims: (1) use mixed methods to identify health care provider barriers to the use of an active CDS tool for PE risk stratification and (2) develop a new CDS tool—the PERK—that addresses behavioral barriers to health care providers' adoption of CDS by incorporating nudges into the user interface. These aims were guided by the revised ORBIT model.

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Ethics Approval

All study activities took place at a large academic health system in the New York City metropolitan area and were approved by the Northwell Health Institutional Review Board (IRB# 18-0714).

Aim 1: Identification of Barriers to CDS Tool Adoption (Discovery)

Original CDS Tool for PE Risk Stratification

We previously developed a CDS tool for PE risk stratification in the emergency department, based on the Wells criteria for PE, that was found to be effective when used, with a 37% reduction in unnecessary CT scan use among adopters [34]. However, it was only used by 15% of health care providers. Low health care provider adoption significantly limited the impact of the tool on overall health care provider behavior. The original tool was active at 2 large academic emergency departments at the time of the development of the new tool, that is, emergency departments at the same institution where our study took place.

Additional details about the design, implementation, and evaluation of the original tool are available in a previous publication [34]. Briefly, emergency clinicians entering any electronic order for the diagnosis of PE (D-dimer testing, ventilation/perfusion scan, or CT scan) are routed to the tool if they answer "yes" to a dialog box asking "Are you considering PE?" The tool functions as an expanded order set that allows clinicians to formally calculate the pretest probability of PE, using the 3-tiered Wells criteria for PE. For low-risk patients, the tool only allows clinicians to order D-dimer laboratory testing, and for patients with an intermediate or high risk of PE, it allows for the ordering of D-dimer testing, ventilation/perfusion scans, or CT scans. At any time however, the tool can be dismissed by clinicians. The tool was developed by using adaptive principles of web and health information technology design, which are detailed in several previous publications [35-38].

Quantitative Assessment of Barriers to CDS Adoption

To determine the reasons for the low rate of health care provider adoption (15%), we surveyed 50 users (emergency department residents and attending physicians) of the original tool with a quantitative instrument that we developed based on the Capability-Opportunity-Motivation-Behavior (COM-B) behavior theory framework. The COM-B framework specifies that changing behavior requires changing capabilities, opportunities, and/or motivations (Figure 1) [39]. It divides *capability*, *opportunity*, and *motivation* into specific subcategories to allow for a detailed assessment of barriers in each category. These are further broken down into theoretical domain functions. The COM-B framework is intended to be comprehensive, parsimonious, and applicable to all behaviors, and it was developed based on existing theories of behavior at a US consensus meeting of behavioral theorists [39]. Our survey assessed the prevalence of 12 behavioral barriers. These 12 behavioral barriers were selected from the theoretical domain functions based on their relevancy to CDS use. Users identified 4 barriers as primary barriers to adoption; they were reported by greater than 70% (35/50) of participants. Almost all (91%, 45/50) of the users who reported low social opportunity also reported not having the intention to use the tool (Table 1).

Figure 1. The Capability-Opportunity-Motivation-Behavior model.

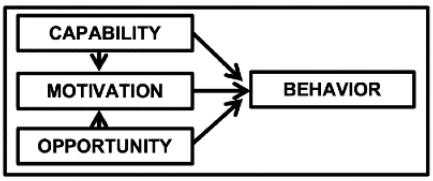


Table 1. Major barriers to clinical decision support tool use identified by the survey (N=50).

Example quotes	Capability-Opportunity-Motivation-Behavior domain	Respondents reporting the same barrier, n (%)
"my colleagues don't use the tool"	Low social opportunity (cultural norms)	35 (70)
"good doctors don't need the tool"	Low reflective motivation (professional identity)	39 (78)
"when I see the tool pop up I feel annoyed"	Low automatic motivation (emotion)	43 (86)
"the EMR has too many alerts to address"	Low psychological capability (attention)	45 (91)

Qualitative Assessment of Barriers to CDS Adoption

Based on the survey results and the COM-B framework, we developed a semistructured interview guide to further our understanding of behavioral barriers to tool use. Thematic saturation was reached after the 12th interview, with no new insights obtained by the 12th participant's interview. Inductive methods were used to analyze session notes and audio recordings, using the COM-B framework as a guiding theory. Interviews were conducted with 12 health care providers, (emergency department residents, attending physicians, and physician assistants). The interviews were 30 to 60 minutes long and were conducted by study personnel. Complete study methods and results are available in a previous publication [40].

The following six major barriers were identified: (1) *Bayesian reasoning*, (2) *fear of missing PEs*, (3) *time pressure/cognitive load*, (4) *gestalt includes the Wells criteria for PE*, (5) *missed risk factors*, and (6) *social pressure* (Table 2). Clinicians highlighted the belief that the tool was not useful to them because all elements of the Wells criteria for PE were

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incorporated into their gestalt. The *fear of missing PEs* was another major theme. Clinicians felt worried about department quality improvement reviews or legal action. *Time pressure/cognitive load* was also highlighted as a major barrier to tool use. Although clinicians denied that cognitive loads kept them from using the tool, many clinicians spontaneously mentioned that they preferred the PE rule-out criteria due to their simplicity. The PE rule-out criteria are validated for use to rule out PE in low-risk patients if 8 criteria are not met [41].

Table 2. Major barriers to clinical decision support tool use refined by the semistructured interviews (n=12; adapted from *Barriers to the Use of Clinical Decision Support for the Evaluation of Pulmonary Embolism: Qualitative Interview Study* by Richardson et al [40]).

Theme	Quotes
Bayesian reasoning	"I don't think [pretest probability] matters for the CT scan.... I've been told if you order a CT, you'll either see it or you won't."
Fear of missing pulmonary embolisms	"…the environment with [quality improvement oversight] and the medical-legal situation, I might argue the threshold to test here is 0%."
Time pressure/cognitive load	"the biggest takeaway that you could take from interviewing ER providers is time, like that's the thing that matters most to us. Time and like ease of use."
Gestalt includes the Wells criteria for pulmonary embolism	"I never use [the clinical decision support tool], I have done the scoring in my head."
Missed risk factors	"my clinical gestalt has red flags for things that are not on Wells'....it doesn't have some of the younger woman risk factors like OCPs and smoking history"
Social pressure	"it does happen once in a while that I'll think this person, the patient, can get away with a D-dimer alone but the [physician assistant] or the learner wants to do a CT Scan, and I'm not averse to letting that go"

Additional themes included *Bayesian reasoning*, *missed risk factors*, and *social pressure*. The *Bayesian reasoning* theme reflected some clinicians not recalling that the posttest probability of PE would be impacted by the pretest probability of PE, which is predicted by the CDS tool, regardless of the results of the CT scan. The *missed risk factors* theme reflected clinicians' mistrust of the CDS tool, as the Wells criteria for PE do not explicitly include a few known risk factors for PE. The *social pressure* theme reflected many clinicians reporting that other members of the care team, including patients and their primary care physicians, could influence their decision to not use or not follow the recommendations of the tool.

Clinical Workflow Analysis

To discover clinical workflow barriers to CDS tool use that might not be provided by users during interview sessions, we shadowed 3 emergency department attending physicians for 1 to 2 hours each. The workflow analysis was adapted from the Agency for Healthcare Research and Quality recommendations on workflow assessments [42]. Direct observation sessions highlighted the significance of the barrier *time pressure/cognitive load* in the analysis of interview themes. All health care providers shadowed demonstrated high patient loads, task complexity, and task fragmentation. Health care providers juggled multiple complex patients simultaneously with constant interruptions. The clinical workflow steps were consistent with the reports that were detailed during the interviews for our study and the formative work for the development of the original tool. Health care providers typically reviewed the emergency department triage notes for patients' initial vitals and chief complaints. Afterward, they saw patients in their room to perform a history and physical examination. Finally, they placed orders in the EHR.

Aim 2: Develop a New CDS Tool—the PERK (Design—Phases 1A and 1B)

Development of Potential Nudges

Based on the survey results, semistructured interviews, and clinical workflow analysis, wireframes of 6 potential nudges were developed. Each potential nudge wireframe was designed to target an identified barrier to tool use and was informed by a COM-B category and subcategory (theoretical domain; Table 3). Wireframes are nonfunctional depictions of the user interface. Wireframes were reviewed and revised during a design thinking workshop and then developed into functional tool prototypes.

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Table 3. Major barriers to clinical decision support use, Capability-Opportunity-Motivation-Behavior (COM-B) categories, theoretical domains, and potential nudges.

Barriers	COM-B categories	Theoretical domain	Potential nudge
Bayesian reasoning	Capabilities, psychological	Knowledge	Quiz addressing the false-positive rate of computed tomography scans for low-risk patients
Fear of missing pulmonary embolisms	Motivation, reflective	Beliefs about consequences	Text communicating the health system's support of tool use
Time pressure/cognitive load	Capabilities, psychological	Memory, attention, and decision processes	Estimated time to completion (12 seconds)
Gestalt includes the Wells criteria for pulmonary embolism	Motivation, reflective	Personal identity	Peer comparison (user compared to tool adopter)
Missed risk factors	Capabilities, psychological	Knowledge	List of conditions for showing when it is appropriate and inappropriate to use the tool
Social pressure	Opportunity, social	Social influences	Peer comparison (user compared to department mean)

Design Thinking Workshop

The results of the survey and semistructured interviews, the refined identified barriers to tool use, and the results of the workflow analysis were presented to several experts in health informatics, usability testing, behavioral science, and health services research and emergency department clinicians during a formal design thinking workshop. The session was guided by a user-centered design facilitation protocol that was used to lead the group through a presentation about behavioral economics concepts, CDS, and the emergency department clinical workflow before an idea generation exercise. Barriers were presented first, and participants were asked to create their own potential nudges for increasing health care provider adoption. Attendees worked in groups and submitted answers by using Post-it notes. Groups presented their ideas in a sharing and discussion session. Later wireframes of potential nudges were presented to the group for feedback. Insights from this workshop were used to further revise the potential nudges and build the tool prototypes.

Results

This section focuses on the initial testing of the decision support tool and how feedback from each phase of testing further influenced the content and design of the tool. The 6-month pilot trial for the tool was launched on October 1, 2021.

Usability Testing

CDS tool prototypes were built, using the prototype development software Axure RP 8 PRO (Axure Software Solutions). Think-aloud usability testing was conducted by using these prototypes with 6 health care providers (emergency department residents, attending physicians, and physician assistants). Prototypes are functional representations of the final user interface that mimic the full user experience. During think-aloud usability testing sessions, participants verbalized their thought processes while interacting with the tool prototype [43]. They were asked to complete the specific steps necessary for using the tool. They were given written clinical scenarios involving low-, intermediate-, or high-probability PE cases.

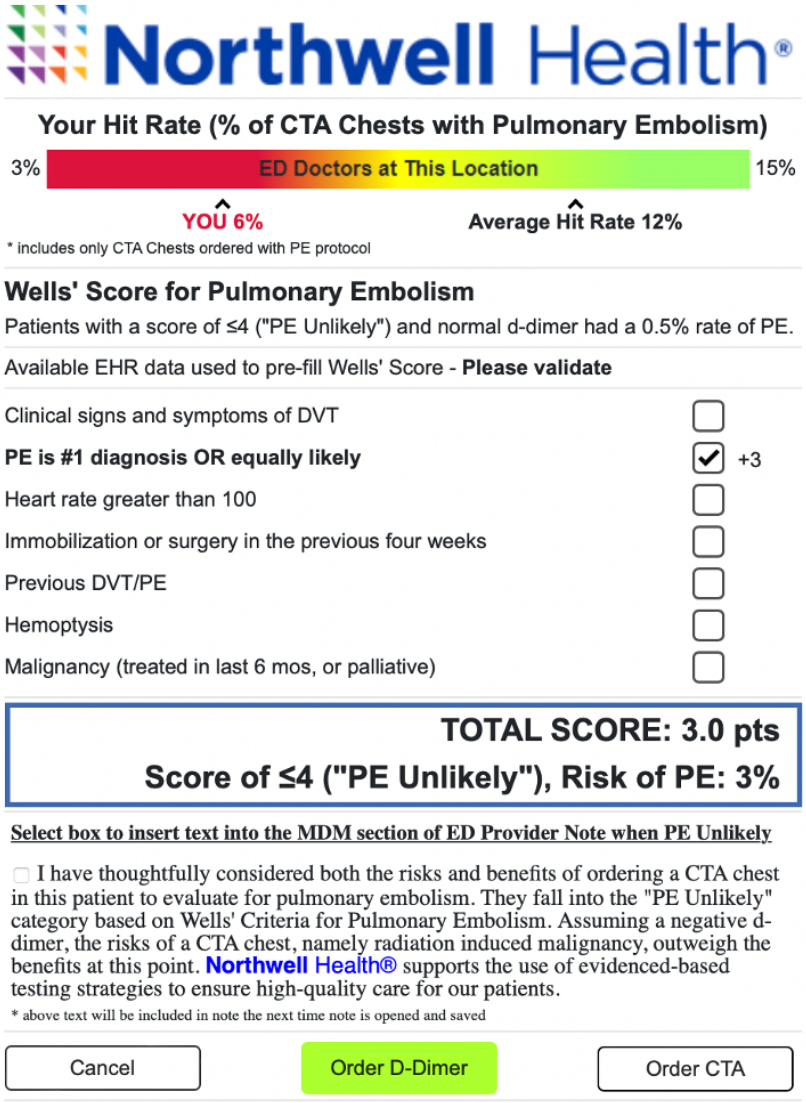
Following the usability testing sessions, the potential nudges were revised based on participant feedback. The layout, text, colors, and placement of each element of the CDS tool were all iteratively revised to facilitate ease of use and perceived usefulness. Several nudges were eliminated, and 2 were selected to be included in the final design. The nudge directed at the *Bayesian reasoning* barrier was eliminated based on feedback that health care providers would not take the time to respond to even a 1-question quiz during a patient care session. The nudge directed at the *fear of missing PEs* barrier was revised so that the language was clearer, more directed, and insertable into health care providers' notes. The nudge directed at the *time pressure/cognitive load* barrier was eliminated based on feedback that no estimated length of time for tool completion could be short enough to be perceived positively.

The nudge directed at the *gestalt includes the Wells criteria for PE* barrier was eliminated based on feedback from the health care providers that they did not see the relevance of comparing themselves to physicians outside of their department who might care for different patient populations. The nudge directed at *social pressure* was revised several times to address health care provider questions about how the data were calculated and to facilitate fast understanding. The final user interface was built to address the *fear of missing PEs*, *gestalt includes the Wells criteria for PE*, *time pressure/cognitive load*, and *social pressure* barriers. To address major concerns about *time pressure/cognitive load*, we developed an automated method for calculating the Wells criteria for PE, as well as a tool activation and suppression algorithm to reduce alert fatigue. A default was added to the user interface; recommended orders are highlighted in green, and 1 click is needed to proceed to ordering. Orders that are not recommended turn yellow if they are clicked once and are ordered if they are clicked a second time.

After iterative revision, the final PERK tool user interface was developed, as shown in Figure 2.

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Figure 2. The pulmonary embolism risk calculator tool user interface.



Automatic Calculation of the Wells Criteria for PE

To address the major barrier *time pressure/cognitive load*, we designed an automated process by using data elements from the EHR and health information exchange to fill in information for each Wells criterion. A detailed description of the methodology for and results of the validation study are presented elsewhere [44]. Briefly, we used a combinatorial keyword search method to query free-text chief complaint and chief complaint quote fields for the criteria “clinical signs and symptoms of DVT” and “hemoptysis.” We used diagnoses listed in past medical histories for the “history of PE/DVT,” “malignancy,” and “immobilization or surgery in the previous 4 weeks” criteria. The presence of brief operative notes, including those regarding general anesthesia, was also used to identify patients who underwent recent surgery for the “immobilization or surgery in the previous 4 weeks” criterion. Vital signs taken during an encounter were used for the “heart rate greater than 100” criterion. All patients were given 3 points for the subjective criterion “an alternative diagnosis is less likely than PE” if a CT scan was ordered for the patients to evaluate for PE.

To validate the automated process, automatically calculated Wells scores were compared to those derived from a 2-clinician chart review. Patients classified as “PE likely” by the automated process (126/202, 62.4%) had a PE prevalence of 15.9% (20/126), whereas those classified as “PE unlikely” (76/202, 37.6%) had a PE prevalence of 7.9% (6/76). With respect to the classification of the patients as “PE likely,” the automated process achieved an accuracy of 92.1% when compared with the chart review. This methodology was used to automatically calculate patients’ Wells criteria for PE when the tool was triggered, as well as to prefill information for each criterion when the CDS was displayed to health care providers.

Tool Triggering and Suppression Algorithm

An algorithm was created to dictate the rules for triggering and suppressing the CDS tool. Our goals were to integrate the tool into the current clinical workflow for patients with suspected PE and to suppress the tool in cases where it was not likely to be helpful. The final rules for triggering and suppression were as follows. First, an assessment is triggered based on the placement of a “CTA Chest PE Protocol w/ IV Contrast” (CT scan) order. This assessment considers the automatically

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calculated Wells criteria for PE and any orders that were placed for a D-dimer laboratory test during the patient encounter. Second, the tool is suppressed for patients with a Wells score >4 and/or if any order has been placed for a D-dimer laboratory test during the patient encounter. The tool is not suppressed for patients with a Wells score of 4 for whom a D-dimer test was not ordered.

Patients with a Wells score of >4 and/or a positive D-dimer test result are classified as "PE Likely" and should undergo a CT scan without interruption. Health care providers placing an order for a CT scan for patients with a Wells score 4 for whom a D-dimer test was not ordered are interrupted by the tool, as shown in Figure 1. The decision was made to suppress the tool for patients for whom a D-dimer test was not ordered, as opposed to suppressing the tool only for patients for whom the laboratory test was ordered and showed abnormal results, as the tool primarily attempts to prompt health care providers intending to order a CT scan for low-risk patients to instead place an order for a D-dimer test. If this has already been done and the health care provider has decided to not wait for the results or to place a CT scan for a low-risk patient with a normal D-dimer test result, then suggesting that they order a D-dimer test would not be likely to effectively influence their decision-making. Our goal was to minimize alert fatigue by increasing the efficiency of the tool.

Discussion

We describe the development of a CDS tool for PE risk stratification in the emergency department setting that incorporates behavior theory–informed nudges to address barriers to health care provider use. Behavioral barriers are not typically addressed during any stage of CDS development, although they represent an important barrier to adoption. We employed user-centered design principles and were guided by the ORBIT model, which advocates for an iterative development approach. Our developmental work included a mixed methods assessment of barriers to tool use and the frequent usability testing of functional prototypes. The COM-B behavioral framework guided the assessment of barriers to tool use. The final user interface included 2 nudges, in addition to a default, and addressed 4 of the 6 identified major barriers to tool use.

Our use of one of the tools of behavioral economics—nudges—is an innovative way to address common psychological, behavioral, and environmental barriers to CDS use. The development of the user interface of the PERK served as a key step and demonstrated that nudges can be incorporated into CDS. The next step is to establish the effectiveness of nudges in clinical practice. Such an evaluation is currently underway, with results expected in the coming months. If, as expected, we find that the adoption of the tool increases, we will conduct studies to evaluate which nudge works best, whom the nudges work best for, and when the nudges work best. These subsequent studies will be conducted by using the multiphase optimization strategy and will allow for the identification of the most effective intervention strategies [45]. This will pave the way for more tailored CDS tools.

There are several strengths and limitations to our approach. The strengths include the fact that the tool was designed for the emergency department clinical setting. The emergency department is one of the more difficult clinical settings to design CDS tools for, due to the high-pace, urgent, and fragmented nature of clinical care. The limitations include the single-center nature of our work. We included several types of emergency department health care providers from 2 hospitals in the same large academic medical center. Therefore, our results may not apply to other hospital systems.

Incorporating principles from behavioral economics into the development of CDS tools has shown increasing promise as a strategy for improving tool effectiveness while minimizing health care provider time and cognitive load burdens. Others have used principles of behavioral economics to influence health care provider behavior through asynchronous peer comparison emails, posters, and the grouping of treatment options [27,29,32,46]. Our work serves as a proof of principle for using this novel approach for CDS development.

Acknowledgments

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Data Availability

The data that support the findings of our study are not publicly available due to restrictions, as making them publicly available could compromise the privacy of the research participants. The data restrictions are being imposed by Northwell Health.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review report.
[PDF File (Adobe PDF File), 161 KB - resprot_v12i1e42653_app1.pdf]

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Abbreviations

CDS: clinical decision support
COM-B: Capability-Opportunity-Motivation-Behavior
CT: computed tomography
D-dimer: dimerized plasmin fragment D
EHR: electronic health record
ORBIT: Observational Research Behavioral Information Technology
PE: pulmonary embolism
PERK: pulmonary embolism risk calculator

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Protocol

The Influence of Social Media Interactions and Behaviors on Depressive Symptoms Among Sexual and Gender Minority Young Adults in the United States: Protocol for a Mixed Methods Longitudinal Study

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Abstract

Background: Sexual and gender minority (SGM; ie, lesbian, gay, bisexual, transgender, and otherwise queer) young adults experience disparities in depression and other internalizing psychopathology. Although social media use is widespread and SGM people have more social media accounts and are more socially active on them than non-SGM individuals, few studies have examined the impact of social media on depression in this group.

Objective: The PRIDE iM study will be the first longitudinal, mixed methods research conducted to determine the impact of social media interactions and behaviors as pathways to depressive symptoms among SGM young adults living in the United States.

Methods: PRIDE iM uses a *bookends variation* of the longitudinal sequential mixed methods design. Participants will be recruited nationally from social media. First, between July 2019 and February 2020, we conducted a qualitative phase (T1) comprising web-based individual interviews (N=58) to inform the building and content of the quantitative survey. Second, from February 2022 to September 2022, we will conduct a series of web-based surveys (N=1000 at baseline) with 4 data points (T2-T5), each one collected every 6 to 8 weeks. Third, from October 2022 to December 2022, we will conduct a second qualitative phase (T6) of web-based interviews using outcome trajectories found in the longitudinal survey analyses to purposively sample survey participants and conduct web-based interviews to contextualize and explain survey findings. Qualitative data from T1 and T6 will be analyzed using a reflexive thematic analysis approach. As we sought to capture change over time in the association between the main predictors (ie, social media interactions and behaviors) and depressive symptoms, we propose analyzing T2 to T5 data using latent growth models with a structural equation modeling framework. Data integration at the method, interpretation, and reporting levels will be achieved through building and connecting and the use of a staged approach and joint displays, respectively. At all stages, we will assess the fit of data integration as recommended by the principles of best practice for mixed methods research in psychology.

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Results: Data collection will be completed by December 2022. Qualitative data analyses will be completed by March 2023, and quantitative analyses of the primary outcome of interest will be completed by June 2023.

Conclusions: PRIDE iM will confirm, reject, or uncover the presence of potential relationships between social media interactions and behaviors and depressive symptoms among SGM people. This study represents fundamental groundwork to develop social media–based interventions that target modifiable interactions and behaviors that are most likely to influence mental health outcomes, thus seizing the opportunity to merge the popularity of this medium among SGM people with evidence-based approaches.

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KEYWORDS

mixed methods; longitudinal; depression; sexual and gender minorities; social media

Introduction

Background

Sexual and gender minority (SGM; ie, lesbian, gay, bisexual, transgender, and otherwise queer [LGBTQ+]) young adults experience well-documented disparities in both internalizing [1,2] and externalizing psychopathology [3] compared with their cisgender heterosexual peers. These mental health disparities persist into adulthood and are present even among SGM people who identify as such late in their adolescence or young adulthood [4]. Minority stress theory [5] poses that, given the dominant culture, norms, and social structure, SGM people are likely subjects of an incongruence between information provided by society on how the world works and the minority person's experience of the world, determining stress processes that may worsen depression. Minority stress is the prevalent framework used to explain disparities seen in depression among SGM people; expansions of it have been developed for specific conditions such as substance use [6], cardiovascular disease [7], suicidal thoughts and behavior [1] and certain SGM groups such as adolescents [8,9] and transgender persons [10-13].

Social media encompasses a variety of websites and mobile apps (eg, TikTok, Snapchat, and WhatsApp) that enable users to create and share content and participate in web-based social networking [14]. Over 90% of adults in the United States have at least one social media account, which they use for an average of 2 to 4 hours daily, with YouTube, Facebook, and Instagram among the most popular platforms, and people aged 18 to 30 years being the group with the most sustained use growth among adults [15]. In addition, the affordances of social media (eg, asynchronicity, absence of physical cues, permanence of interactions, quantifiability via likes, and upvotes) have deeply changed the way in which people socialize, connect with others, build relationships, and seek and receive support and information [16,17].

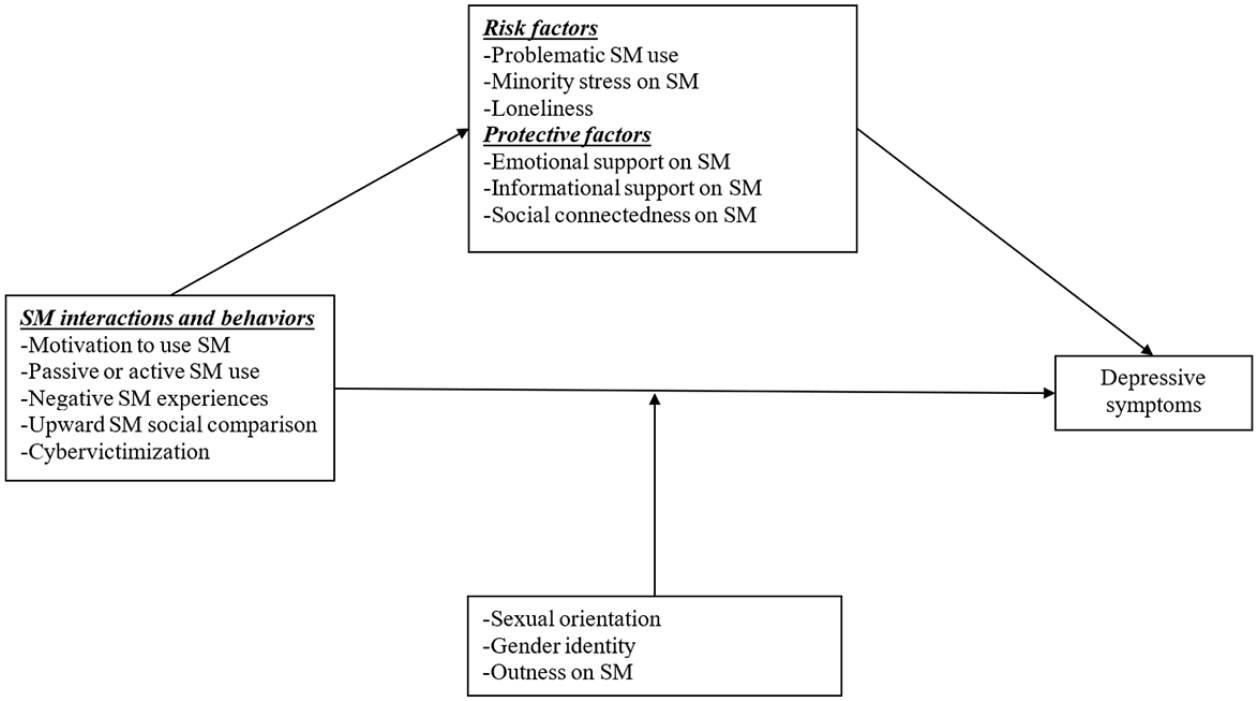
On average, SGM people are more socially active on social media and more likely to have multiple social media accounts than non-SGM individuals [18-20]. Moreover, SGM persons seek and engage with more web-based support chats than their non-SGM peers [21]; seek web-based support resources to help them navigate challenging settings where both racial and sexual minority stigma might be salient [22,23]; and use social media to connect with others like them, increase their sense of belonging, and increase emotional well-being [24]. Despite these positive experiences, negative social media interactions also give way to social comparison, stigmatization, cybervictimization, and other forms of discrimination, which in turn might influence depressive symptoms [25,26] and other psychopathology [27,28].

Current Research Gaps

Although there is qualitative evidence available from SGM people indicating the salience of social media interactions to them [23,26], few studies have been conducted to determine the impact of social media interactions on mental health outcomes among SGM individuals, mostly among college students [29]. Moreover, the available studies follow the recent literature trend of focusing on determining the effect of the amount of time spent on social media (eg, time elapsed while using social media, number of checks per unit of time, and number of platforms used) on mental health. In the general population, the former approach showed mixed findings of positive [30,31], bidirectional [32], or no association [33] between quantity of social media use and mental health outcomes over time. These conflicting findings are indicators that we need a new approach that focuses on studying the factors that matter to SGM social media users, including the types of interactions and behaviors on social media platforms and their impacts on mental health. This is relevant as it is during these experiences on social media that SGM persons might encounter some of the minority stressors or protective factors [5,8]. On the basis of minority stress and our preliminary work [25], we propose a mediation model (Figure 1) in which the relationship between specific social media interactions and behaviors and depressive symptoms is mediated by both protective and risk factors (eg, emotional support experienced on social media). An additional issue that arises is that quantitative results alone are inadequate to describe and fully explain SGM young adults' social media behaviors and interactions or their effect on their mental health. Therefore, a mixed methods approach has the potential to unveil stressors and protective factors uniquely shaped by the affordances of social media, which may influence mental health outcomes in ways that could be different from similar offline interactions and behaviors.

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Figure 1. Model depicting risk and protective factors in the pathways of characteristics of social media interactions and behaviors and depressive symptoms among sexual and gender minority young adults. SM: social media.



Study Objectives

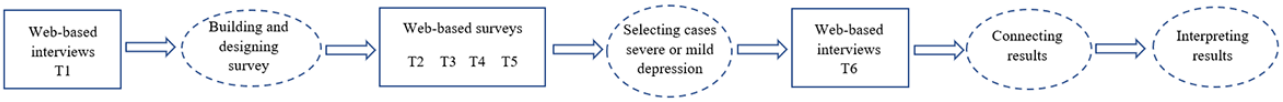
The PRIDE iM study will be the first longitudinal, mixed methods research conducted to determine the impact of several forms of social media interaction and behavior on the pathways of depression and other mental health outcomes among SGM young adults living in the United States (Multimedia Appendix 1). To address critical methodological factors needed to ensure a high-quality longitudinal study with SGM people, the main characteristics of PRIDE iM include (1) recruitment via social media to reach members of an often-marginalized group who are users of the technology under study, (2) recruitment of young adults aged 18 to 30 years as this age group recently experienced the most sustained growth in social media users, (3) presurvey qualitative assessments to identify relevant SGM-specific social media interactions and behaviors and add them to the survey, (4) repeated measures of potentially critical risk and protective interactions and behaviors on and off social media, (5) postsurvey qualitative assessments with survey participants to contextualize the trajectory of depressive symptoms, and (6) a mixing analysis phase to identify similarities and differences across groups. Upon completion, the PRIDE iM study will provide critical data in terms of intervention targets, such as reducing the occurrence or impact of risk factors (eg, upward social comparison) or boosting protective factors (eg, social connectedness) for depression and other negative mental health outcomes among SGM people—a high-need, underserved, and hardly reached population.

Methods

Study Design

Given the longitudinal nature of our study, we leveraged a multistage mixed methods framework in which we combined both exploratory and explanatory approaches [34]. PRIDE iM uses a *bookends variation* of the longitudinal sequential mixed methods design [35], which is a combination of prospective and retrospective studies. In this design, we gather qualitative data in the form of individual interviews at both the beginning (T1) and the end (T6) of the study and collect quantitative data in the form of 4 longitudinal web-based surveys (T2, T3, T4, and T5) at nonconcurring times with the collection of qualitative data. Figure 2 provides an overview of the study design, including timing of data points for both quantitative and qualitative data strains as well as for analyses, data mixing, and interpretation of results. Throughout this paper, we use T1 to T6 to designate each point of data collection.

Figure 2. PRIDE iM study design. T: time.



The design that we chose was appropriate for 3 reasons. First, we used a qualitative phase (T1) comprising web-based individual interviews to inform the building and content of the quantitative survey. Although the existing literature provided a list of potentially relevant risk and protective forms of social media interactions and behaviors for depression among the general population [36,37], we focused on social media experiences involving minority stress that are unique to SGM persons and that might help explain depressive symptoms among this group. We decided to conduct individual interviews, and

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this was appropriate to balance a need for an in-depth understanding of the impact of social media experiences on mental health with the need to protect individuals' privacy and sensitive information. Second, we used a longitudinal web-based survey study with 4 data points (T2-T5), each one collected every 6 to 8 weeks. We sought to capture change in the association between the main predictors (ie, social media interactions and behaviors) and outcome variables (ie, depressive symptoms) over time. Using these 4 data points, our analyses will be able to identify trajectories of depressive symptoms over time. Third, given the limitation of quantitative data to fully explain the change in social phenomena over time, we will conduct a second qualitative phase of web-based interviews (T6). We will use the outcome trajectories identified in the T2 to T5 quantitative analyses and form groups based on these trajectories for conducting web-based interviews with SGM persons who participated in the survey in each of these groups. We will use the interviews to contextualize trajectories found in survey analyses and then conduct a comparative analysis of qualitative findings by groups identified in the survey (eg, respondents with severe vs mild depressive symptoms) to describe similarities and differences between said groups.

Ethics Approval

All recruitment and data collection procedures were approved by the University of Pittsburgh Institutional Review Board (study 19050007; approval June 20, 2019). We sought and obtained informed consent from potential participants before completing any of the research activities (web-based interviews or web-based surveys) of the study. Given that PRIDE iM study participants can be located anywhere in the United States and as the study posed minimal risk for participants, we obtained a waiver for documenting consent. We included all the standard components in the web-based informed consent forms, including study goals and description and estimated time required to complete the activity. Participants receive web-based gift cards in compensation for their time taking part in each of the research activities. We collected no identifiable information other than participant email addresses, phone numbers, and IP addresses (which were collected automatically by the web-based survey platform). This was necessary to schedule participation in the web-based interviews and to send gift cards to the participants after completing a research activity. Given the inclusion of sensitive topics and questions in both the interview and survey, we inform participants that they can choose to stop taking part at any time if they feel uncomfortable. In the web-based surveys, if the participant answers affirmatively to any of the suicide-related questions, a pop-up screen appears where we provide the contact information of nationally available resources for both SGM people and persons with suicidal ideation. These same resources appear listed at the end of the survey, and we provide the name and contact information of the principal investigator for more personalized resources.

Recruitment and Data Collection Procedures

Sample Selection

We used a purposive sampling approach throughout the 3 phases of the PRIDE iM study. This was appropriate as purposeful sampling permits identifying and selecting study participants who experience firsthand the phenomenon under study, making this approach ideal for mixed methods research studies [38]. To recruit participants, we used targeted advertisements on social media, which have been previously used with success for the recruitment of SGM people to both cross-sectional and cohort studies [39,40]. This was appropriate for multiple reasons. As noted previously, SGM people are heavy social media users, and social media recruitment facilitates the enrollment of a diverse sample of SGM individuals, including those who have not disclosed their sexual orientation or gender identity, those who live in rural areas, and those who do not participate in community-based organizations that serve SGM persons [41]. Throughout the 3 phases of the study, individuals were eligible if they were aged 18 to 30 years; resided in the United States (as determined by zip codes); identified as LGBTQ+; and had at least one social media account and used it on at least a weekly basis.

First Series of Web-Based Interviews (T1)

Recruitment

The recruitment approach described previously was appropriate for the purpose of these interviews, which was to inform constructs and items for survey development through learning from the lived experience of SGM young adults who use social media and whether and how this use affected their mental health and well-being. In this way, the qualitative data strain served the purpose of integration through *building*, in which the results of one data collection and analysis activity inform the data collection of the other research activity [34]. Recruitment took place between July 2019 and February 2020. To create our advertisements, we used the advertisement creation feature on Meta Ads Manager (Meta Platforms, Inc; which allows for cross-posting to Facebook and Instagram) and set advertisements to be shown solely to people living in the United States. At the time, the Facebook advertisement manager allowed for targeting specific audiences based on location, age, interests (including "Interest tags" specific to the LGBTQ+ community and LGBTQ+ topics), and activity. After seeing the advertisements, interested individuals clicked on "Learn more" and were redirected to a study website that provided more information about the study goals, expected involvement, information about compensation, and an anonymous link to an eligibility questionnaire housed on the Qualtrics survey platform (Qualtrics International, Inc). Eligible individuals were invited to provide their preferred method of contact (ie, phone number or email address) so that a research assistant could contact them to schedule a time and date for the interview.

A total of 72 hours before the web-based interview, potential participants were sent an email with a link to the web-based informed consent form for their preliminary review. We encouraged potential participants to read the informed consent form and reply to the email with any clarification questions they might have. The day before the interview, we sent a final email with the link to the web-based conference platform where the interview would take place. At the date and time agreed upon for the interview, potential participants clicked on the link provided; this link took them to the formal informed consent

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form, and after providing consent, participants were admitted to the web-based conference room.

Data Collection

The web-based interviews were 60 minutes long. We used a Health Insurance Portability and Accountability Act–compliant platform [42]. To protect the individuals' privacy, only audio was recorded during each interview. The interviews explored motivations for using social media and perspectives on both positive and negative social media interactions as well as the perceived impact on mental health and well-being. After completing the interview, participants received US $50 gift cards in compensation for their time. The recordings were transcribed verbatim using a professional web-based service.

Web-Based Longitudinal Survey (T2-T5)

Recruitment and Initial Screening

Recruitment for the baseline assessment (T2) took place from February 2022 to March 2022 via targeted advertisements through Meta Ads Manager. However, as of January 2022, Meta updated its new audience targeting policy to protect the privacy of vulnerable populations [43]. The new policy eliminated the option of specifically targeting interests related to LGBTQ+ identities as well as religious or political interests. We chose an alternative option that consisted of creating a "custom audience" within the Meta Ads Manager tracking system to target future advertisements to a "lookalike audience." After publishing a set of advertisements, a custom audience is created using the first 1000 to 5000 users that click or tap on the ads. This custom audience is then used so that ads can be seen by people who previously interacted with content on Instagram and Facebook [44]. A "lookalike audience" comprises users who are similar to the custom audience that first interacted with the advertisement published on Instagram and Facebook [45]. Once this custom audience is created, future iterations of the advertisements are shown to new people who share similar characteristics (ie, "lookalike") with the custom audience.

In total, 7 copyright-free images that would appeal to a broad base of SGM persons were purchased from iStock by Getty Images for web-based advertisements. Images depicted same-sex or queer-gendered couples, a group of smiling young adults of various backgrounds and hairstyles, and a rainbow-colored heart light-emitting diode light without any humans. Figure 3 shows an example of one of the advertisements published on social media. After clicking on the advertisement, persons were directed to an institutional study website where they could find more detailed information that was beyond the character limit allowed on social media advertisements, including the goals of the study, eligibility criteria, expected commitment (ie, completing four 30-minute surveys over 7-8 months), and participant compensation. Those who remained interested were able to click on a link to an eligibility screening questionnaire housed on the Qualtrics survey platform. If eligible, potential participants were invited to provide informed consent so that they could gain immediate access to the full web-based baseline questionnaire.

After completing the baseline survey, participants were asked to provide their email address for payment, their phone number, and their preference for a contact methodology (eg, email, phone call, or SMS text message). Email addresses were used to send web-based gift cards to all participants who completed at least half of the baseline questionnaire as well as reminders for follow-up surveys.

Figure 3. Example of one of the PRIDE iM social media recruitment advertisements. LGBTQ+: lesbian, gay, bisexual, transgender, and queer.



Participant Retention Strategies for Follow-up Surveys (T3-T5)

Given both the web-based nature and the longitudinal design of this study phase, reducing participant attrition was a major concern. A recent meta-analysis found that using a mix of retention strategies delivered via the internet improved participant retention rates in longitudinal cohort studies [46]. First, we sought to reduce barriers to participation by prioritizing survey measures hypothesized to have an association with the primary outcome of interest (ie, depression) according to the existing literature and our conceptual model (Figure 1) and

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allowing for extended data collection windows (up to 1 week) for each wave. Second, to build a community around the study and our research program, we created a study brand (PRIDE iM study) and a logo, website, and social media presence on 3 social media platforms (Twitter, Instagram, and Facebook). Social media accounts and websites were created 6 to 12 months before the formal study started and were used to update our followers about ongoing research conducted by our team and others on the topic of use of communication technologies and LGBTQ+ mental health. Third, we used a variety of reminders and follow-up strategies, including bimonthly e-newsletters (sent using Mailchimp [Rocket Science Group], a web-based platform and email service that allows for managing mailing lists) in between periods of data collection, email reminders sent 72 hours before the next follow-up survey, SMS text message reminders (only in cases of participants who authorized being sent SMS text messages), and incentives of increasing value over time (gift cards of US $10 for T2, US $15 for T3, US $20 for T4, and US $25 for T5). Finally, toward the end of each data collection period, we sent targeted emails or SMS text message reminders (according to each person's preference) to participants whose responses we still had not received.

Eligibility Determination for Follow-up Surveys (T3-T5)

Preventing and detecting fraud in web-based survey studies with participants recruited from social media is an ongoing challenge among researchers [47]. Fraudulent surveys include duplicate responses from the same participant using different email addresses, providing response patterns, or reaccessing the survey with false responses after being deemed ineligible in the first attempt. To minimize these risks, we implemented a series of combined red flags based on previous literature [39,40,48,49] and our own team's experience. Once data collection for the baseline (T2) survey was completed, we downloaded all the data from Qualtrics. A team of research assistants not involved in data analysis or interpretation created variables representing aspects related to survey participation that could be useful to identify fraudulent responses, such as geographic location (including approximate latitude and longitude), IP address, start and end date and time, survey completion and time duration for completion, attention-control questions [50], phone number, and email address. We used 3 criteria to determine fraudulent responses (Textbox 1).

Textbox 1. Criteria to determine fraudulent survey responses.

1. Location outside the United States according to *one* of the following:
   - Location data from Mailchimp (Rocket Science Group)
   - Latitude and longitude data from Qualtrics (Qualtrics International, Inc)
2. More than 1 response per IP address:
   - If only 2 responses, keep both if they did not meet criterion 1
   - If >2 responses, keep the first 2 if none of the responses met the previous criterion 1; if any of the responses meet criterion 1, remove all of them
   - Responses that started or ended <3 minutes apart (in these cases, only the first response was retained as part of the data)
3. More than 1 response per either email address or phone number (in these cases, only the first response was retained as part of the data)

Responses that met any of the criteria listed in Textbox 1 were removed from the baseline data; those participants did not receive compensation and were no longer contacted for the follow-up surveys. In addition, some baseline participants completed the survey but provided low-quality data, either because their completion time was <6 minutes or because they completed less than two-thirds of the survey. In these cases, participants were compensated for the baseline survey but were no longer contacted for follow-up surveys, and their responses were removed from the data.

Data Collection for Follow-up Surveys (T3-T5)

Eligible participants were sent email invitations and reminders for T3 to T5 surveys starting in early April 2022 (1 week after we completed baseline data collection). Follow-up surveys were hosted on Qualtrics, and responses were collected for 30 days during May 2022 (T3), July 2022 (T4), and September 2022 (T5). On the first day of each month, we sent an email to each participant with a unique link to the survey. To protect individuals' right to timely information about the study, we sought reconsent from all participants before allowing access to every follow-up survey. To maintain rapport and participants' interest in the study, we sent 1 e-newsletter during the month in between data collection (mid-April, mid-June, and mid-August) and 1 reminder 3 days before sending the survey links. Finally, we sent target emails or SMS text message reminders (depending on their preference for receiving direct communication) to the participants who had not yet completed the follow-up survey 1 week before the end of each data collection period.

Survey Measures

The baseline (T2) and follow-up (T3-T5) surveys incorporated different sections in which we administered the measures outlined in Textbox 2 based on our conceptual model (Figure 1).

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Textbox 2. Measures administered during the baseline (T2) and follow-up (T3-T5) surveys.

Primary outcome of the study

- We seek to determine changes in depressive symptoms, which have been consistently described in the literature as disproportionately more prevalent among sexual and gender minority (SGM) individuals. *Depressive symptoms were assessed* using the 9-item Patient Health Questionnaire [51]. In addition, we assessed other mental health problems that have been consistently found to be more prevalent among SGM people, including *generalized anxiety disorder symptoms*, measured using the Generalized Anxiety Disorder-7 [52]; *sleep disturbance symptoms*, measured using the 4-item Patient-Reported Outcomes Measurement Information System (PROMIS) [53]; *suicide ideation in the past month*, measured using a subscale of the Columbia Suicide Severity Rating Scale [54]; *eating disorder symptoms*, measured using the Sick, Control, One, Fat, Food screening questionnaire [55,56]; *cigarette smoking*, measured using 2 modified items from the Behavioral Risk Factor Surveillance System questionnaire [57]; *alcohol use in past month*, measured using a modified version of a 1-item screener by Smith et al [58]; and *marijuana use in the past month*, measured using an item modified from the Youth Risk Behavior Survey [59].

Primary predictor

- Given that the focal interest of this study is determining the influence of social media behaviors and interactions on mental health symptoms, our main predictors comprise a variety of individual characteristics, behaviors, and interactions that users may have while using social media, including *passive and active social media use* [60], *motivations for using social media* [29], *negative social media experiences* (measured using a 4-item scale [25]), *upward social comparison on social media* (measured using a 2-item scale [61]), *cybervictimization on social media* (measured using an 8-item scale [62]), and *time elapsed during and frequency of social media usage* (measured using items previously developed by our team [63-65]).

Demographic variables

- We used the following items to determine study eligibility: *current location* (in or outside the United States); *age in years*(<18, 18-24, 24-29, and >30); *current sexual orientation*, measured using the item "Which of the following best describes your current sexual orientation?" (lesbian; gay; bisexual; pansexual; asexual; queer; same gender–loving; straight or heterosexual; and other, with a text box to type in) as recommended by the Sexual Minority Assessment Research Team group [57,66]; *sex assigned at birth*, measured using the question "What gender were you assigned at birth, on your original birth certificate?" (male or female); and *current gender identity*, measured using the item "Which best describes your current gender identity?" (woman, man, transgender woman, transgender man, and nonbinary or genderqueer) [57,67]. Both the current gender identity and current sexual orientation questions were also part of the attention-control questions and were asked twice (first in the eligibility screener and then in the demographics section). Other sexual identity questions included *sexual behavior*, measured using the item "In the last 5 years, who did you have sex with? By sex we mean any activity you personally define as sexual activity. Please mark all that apply" (*women, nontransgender*; *men, nontransgender*; *transgender women*; *transgender men*; *nonbinary/genderqueer*; and I have not had sex with anyone in the last 5 years) [57,66]; *sexual attraction*, measured using the question "Please indicate how sexually attracted you are to the following types of people" (*women, nontransgender*; *men, nontransgender*; *transgender women*; *transgender men*; and *nonbinary/genderqueer*) [68]; and *gender nonconformity*, measured using a 2-item scale that asked "A person's appearance, style, or dress may affect the way people think of them. On average, how do you think people would describe your appearance, style, or dress?" and "A person's mannerisms (such as the way they walk or talk) may affect the way people think of them. On average, how do you think people would describe your mannerisms?" Both items had responses on a 7-point Likert-type scale from "very feminine" to "very masculine" [69]. Other demographic variables included *current relationship status* (member of an unmarried couple, in a polyamorous relationship with more than 1 person, legally married or recognized civil union, and not currently in a relationship or a special commitment to someone) [57]; *current living situation*, which allowed for multiple choices (by myself; with a parent or guardian, significant other, spouse, child or children, friends, or roommate or acquaintance; or other, with a text box to type); *month and year of birth* (our team decided not to collect day of birth to preserve the privacy of study participants, crucial given the longitudinal nature of the study and the repeated contact with participants via email or SMS text messages); *race/ethnicity*, which allowed for multiple answers (American Indian or Alaskan Native; Asian or Asian American; Black or African American; Hispanic or Latina, Latino, or Latinx; Native Hawaiian or other Pacific Islander; White; or other, with a text box to type); *educational attainment* (never attended school or only attended kindergarten, grades 1 to 8, grades 9 to 11, grade 12 or general educational development, 1 to 3 years of college, college graduate, and graduate school [some or completed]); *household income* (US <$15,000, US $15,000 to <$25,000, US $25,000 to <$50,000, US $50,000 to <$75,000, US $75,000 to <$100,000, and US ≥$100,000); *current employment situation* (employed for wages; self-employed; out of work for ≥1 year; out of work for <1 year; homemaker; student; unable to work; and other, with a text box to type); *current zip code*; and *current state of residence*. Finally, the T5 survey included 1 item asking participants whether they would be willing to be recontacted within the subsequent three months for additional research opportunities *(yes or no)*.

Covariates

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Covariates (protective and risk factors) were selected as they related to constructs included in minority stress [5], and whenever possible, we included modified items or measures to explore the same factors on social media. These included *outness in offline life*, measured using the question "In your everyday life (NOT on social media), are you out as an LGBTQ+ person to all, most, some, or to none of you're a) family, b) straight friends c) co-workers" and the options "all, most, some, none, do not know" [57,70]; *outness on social media*, measured using a modified item that asked "On the social media site/app you use the most to keep in touch with the people you care about, are you out as an LGBTQ+ person to all, most, some, or to none of your..." with the same categories of people and options as in the previous question; *emotional and informational support offline*, measured using the PROMIS 8-item scale for these constructs [71]; *emotional and informational support on social media*, measured using a modified version of the PROMIS 8-item scale [72]; *social connectedness offline*, measured using a 20-item scale [73]; *social connectedness on social media*, measured using a 20-item scale [74]; *adverse childhood experiences*, measured using the Adverse Childhood Experiences 10-item questionnaire [75]; *loneliness*, measured using the 3-item University of California, Los Angeles Loneliness Scale [76]; *social isolation*, measured using a PROMIS 4-item scale [77]; *problematic social media use*, measured using a 6-item scale [78]; and *minority stress experiences offline and on social media*, measured using 24 items modified from the Sexual Minority Adolescent Stress Inventory (SMASI) [8]. Although the original instrument includes 11 subscales to cover a wide array of discriminatory experiences, we selected items to cover experiences that would most likely match those of young adults both offline and on social media. These included the following SMASI subscales (and their respective items): negative expectancies (3 items), negative disclosure experiences (5 items), homonegative communications (5 items), intersectionality experiences (3 items), and social marginalization (8 items).

Additional measures

- Although not the principal focus of our study, later waves of data collection included additional scales to explore emerging topics in the literature related to objective measures of social media use and use of geospatial dating apps. These included instructions for participants to take screenshots of their screen time app, average use time, most used apps, number of check-ins, use of mobile dating apps in the past year and past 2 weeks, number of check-ins on these apps, time elapsed during use, motivation for using dating apps, success in using dating apps, belongingness scale, perceived thriving, and reasons for stopping the use of mobile dating apps.

Second Series of Web-Based Interviews (T6)

The primary goal of the second qualitative phase in the PRIDE iM study is to help describe, compare, and explain the quantitative results from the longitudinal survey conducted in T2 to T5. We will group survey participants according to their outcome trajectories (eg, severe or mild depressive symptoms). Next, we will use a purposive sampling approach [38] among outcome trajectory groups identified in T2 to T5 for interviewing select "case" participants and contextualizing trajectories found in survey analyses. For example, if we identify 2 trajectory groups—"severe" and "mild" depressive symptoms—we will recruit 20 participants from each group (n=40). This approach is appropriate when the study goals include explaining significant results, positive performing cases, outliers, or confusing results [79].

The "cases" will be identified once we complete the statistical analysis of the longitudinal relationship between social media experience and behaviors and depressive symptoms. Within 30 days of completing the T5 survey, a research assistant with access to the contact information of survey participants will link the participant ID number with the respective contact information. This team member will contact "case" survey participants via email or SMS text message and invite them to participate in a web-based interview with the purpose of reviewing and contextualizing their survey results to shed light on what (if anything) other than their experiences and behaviors on social media might have influenced the results. Interested individuals will be offered to schedule a date and time for the web-based interview. Preinterview reminder activities on the day of the interview, data collection procedures and software, and postinterview transcribing will mimic those already described for T1. We plan to start recruitment for T6 in November 2022.

Data Analysis Plan

Qualitative Analyses

Transcriptions will be entered into NVivo (version 12; QSR International) [80] for analysis. For both T1 and T6, we will analyze the data using reflexive thematic analysis with an experiential and realist framework [81-83]. This approach will allow us to describe and connect themes driven by the data collected from SGM participants, highlighting the specific meanings and perspectives from their lived experiences. Coding will be conducted using a hybrid inductive and deductive approach, which is appropriate given that our coding framework will partly derive from research on social media use and mental health among some groups of SGM young adults [25]. However, the paucity of research related to the impact of specific social media interactions and behaviors on depression among SGM persons requires describing concepts that are not clearly articulated in the empirical evidence available [84]. We will train independent coders and triangulate among the members of the study team to enhance trustworthiness [84].

Quantitative Analyses

We propose analyzing T2 to T5 data using latent growth models (LGMs) with a structural equation modeling (SEM) framework. LGMs in SEM are appropriate for our data as our assessments will measure the same construct at each data point, will have the same metric across time, and are tested at the same time intervals [85]. Crucial to our study, SEM allows for the use of latent variables or constructs in the models (eg, attitudes toward and beliefs about social media) as well as modeling mediating and moderating effects [86]. We will conduct descriptive analyses, including means, SDs, and bivariable associations between all variables included in the study. We will build SEM models at baseline and cross-sectionally and then, with each wave of longitudinal data, test whether baseline predictor characteristics are associated with depressive symptoms over the study period, as well as between- and within-person effects

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[87]. We will examine model fit, including fit statistics such as standardized root mean square residual and comparative fit index, according to standard guidelines [88,89]. We will use Stata software (StataCorp) [90] for conducting these analyses and follow best-practice guidelines for reporting latent trajectory studies [91].

To estimate the sample size, guidelines for estimating power to detect mediated effects using the product of coefficients test suggest that, for power >0.8 with an α level of .05, a sample size of 100 is needed to detect medium effects, and a sample size of 500 is needed to detect small effects [92]. Thus, we proposed starting at T2 with 1000 participants and, with an overall attrition rate of 50% throughout T3, T4, and T5, we will have 500 participants who completed T2 to T5, which gives us power to detect small, mediated effects. For the longitudinal mediation using LGM, a sample size of approximately 200 is needed for power >0.8 to detect a medium effect size with 5 measurement occasions. As statistical power increases as the number of measurement occasions increases and we will have 4 measurement occasions, we expect adequate power for longitudinal mediation models [92,93]. Although an attrition of 50% is expected, previous studies on risk or protective factors and health outcomes have shown that this phenomenon did not significantly affect estimates of associations between variables or demographic differences between groups [94-96].

Integrative Analyses

Our mixed methods study integrates quantitative and qualitative strains of data at the design, method, and interpretation and reporting levels [34,97]. We addressed the integration at the design level in the previous sections. In this section, we will describe other levels of mixed methods data integration and analyses that we will conduct in PRIDE iM. We will achieve method integration through *building* and *connecting* [97].

First, qualitative data from T1 helped us *build* the T2 to T5 quantitative surveys in that we were able to identify important constructs and potential items that were included in the questionnaires. Next, we will *connect* the quantitative data collected during T2 to T5 with the qualitative data that will be collected in T6 through purposive sampling. To do this, we will use outcome trajectories (eg, depressive symptoms) found in structural equation models and form groups based on these trajectories for inviting potential participants to the web-based interviews in T6, with the goal of describing similarities and differences across groups and explaining these differences [79].

Finally, we will integrate our quantitative and qualitative data at the interpretation and reporting level using narrative manuscripts with a *staged approach* comprising separate manuscripts to report the results of each phase of the study. This is often the case with mixed methods studies such as PRIDE iM that have a multistage approach [34]. We will use *joint displays* to bring the data together and present new insights beyond those gained from the separate quantitative and qualitative results. At all stages, we will assess the fit of data integration as recommended by the principles of best practice for mixed methods research in psychology [98,99].

Results

Data collection will be completed by December 2022. Qualitative data analyses will be completed by March 2023, and quantitative analyses of the primary outcome of interest will be completed by June 2023.

Discussion

Principal Considerations

To our knowledge, PRIDE iM is the first national mixed methods study with a longitudinal quantitative phase (T2-T5) conducted in the United States to determine the relationship between a variety of social media interactions and behaviors and depression and other mental health problems that overburden SGM young adults. Moreover, our study is the first to adapt the minority stress model to explain the path by which social media interactions and behaviors may affect depressive symptoms among SGM young adults. Since the time when minority stress theory was initially developed [5], social media has disrupted most societal processes, from the way young adults make friends to the way they keep themselves informed and become involved with their communities, and this seems to be even more true for minoritized groups. The proposed study is appropriate, timely, and innovative in several aspects, from the social media–based recruitment (which allows for the participation of SGM persons who may not interface with offline recruitment venues and, thus, may be less likely to participate in research) to the study and survey design. Our study will dramatically expand on previous research [26] that focused on identifying that social media and other communication technologies influence resilience and coping among SGM youth. PRIDE iM results will provide important information about the impact of social media on mental health for researchers that seek to better understand health inequities among persons who are minoritized because of their sexual orientation, gender identity, and race or ethnicity and reduce those inequities via interventions.

Limitations

This study has limitations to consider. First, our recruitment through social media (ie, Instagram and Facebook) might represent a barrier to participation for SGM young adults who do not use these specific platforms. However, this is unlikely given that a large majority of young adults who use social media have an Instagram or Facebook account [15]. Second, our surveys assessed social media interactions and behaviors via self-report, which subjects these reports to recall bias related to experiences on social media. To reduce this, surveys were collected every 6 to 8 weeks, and all measures asked participants only about their social media experiences “over the last 30 days.” Nevertheless, future studies would benefit from more objective methods for collecting social media data related to individuals’ interactions and behaviors. Third, we used survey assessments that are quite comprehensive, which might discourage some participants from responding to all survey items or cause them to do so hastily. To remedy this, we implemented several forms of participant engagement (eg, progressively increasing incentives, building a community

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around the study, and survey reminders) and data quality checks (eg, survey completion time, attention-control questions, and survey completion progress).

Conclusions

PRIDE iM builds upon minority stress theory, a foundational model used to understand mental health disparities among minoritized groups, and will contribute to our current understanding of how sociocultural factors influence SGM individuals' depression outcomes in a new media environment such as social media. Our study will confirm, reject, or uncover the presence of potential relationships between social media interactions and behaviors and depressive symptoms as well as temporality and direction. We will disseminate our findings via relevant academic journals and infographics on the PRIDE iM social media presence on Instagram, Twitter, and Facebook. This study will provide fundamental groundwork to develop social media–based interventions that target modifiable interactions and behaviors that are most likely to influence mental health outcomes, thus seizing the opportunity to merge the popularity of this medium among SGM people with an evidence-based approach.

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Data Availability

The data sets generated and analyzed during this study are not publicly available yet because of (1) the ongoing nature of the study and (2) preliminary and main outcome analyses being conducted at the time of publication of this protocol, but specific data sets might be available from the corresponding author upon reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
External peer review from the National Institute on Minority Health and Health Disparities Special Emphasis Panel NIH Pathway to Independence Award (grant R00 - MD012813).
[DOCX File , 60 KB - resprot_v12i1e43627_app1.docx]

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Abbreviations

LGBTQ+: lesbian, gay, bisexual, transgender, and queer
LGM: latent growth model
SEM: structural equation modeling
SGM: sexual and gender minority

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Protocol

Clinical Validation of an Artificial Intelligence–Based Tool for Automatic Estimation of Left Ventricular Ejection Fraction and Strain in Echocardiography: Protocol for a Two-Phase Prospective Cohort Study

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Abstract

Background: Echocardiography (ECHO) is a type of ultrasonographic procedure for examining the cardiac function and morphology, with functional parameters of the left ventricle (LV), such as the ejection fraction (EF) and global longitudinal strain (GLS), being important indicators. Estimation of LV-EF and LV-GLS is performed either manually or semiautomatically by cardiologists and requires a nonnegligible amount of time, while estimation accuracy depends on scan quality and the clinician's experience in ECHO, leading to considerable measurement variability.

Objective: The aim of this study is to externally validate the clinical performance of a trained artificial intelligence (AI)–based tool that automatically estimates LV-EF and LV-GLS from transthoracic ECHO scans and to produce preliminary evidence regarding its utility.

Methods: This is a prospective cohort study conducted in 2 phases. ECHO scans will be collected from 120 participants referred for ECHO examination based on routine clinical practice in the Hippokration General Hospital, Thessaloniki, Greece. During the first phase, 60 scans will be processed by 15 cardiologists of different experience levels and the AI-based tool to determine whether the latter is noninferior in LV-EF and LV-GLS estimation accuracy (primary outcomes) compared to cardiologists. Secondary outcomes include the time required for estimation and Bland-Altman plots and intraclass correlation coefficients to assess measurement reliability for both the AI and cardiologists. In the second phase, the rest of the scans will be examined by the same cardiologists with and without the AI-based tool to primarily evaluate whether the combination of the cardiologist and the tool is superior in terms of correctness of LV function diagnosis (normal or abnormal) to the cardiologist's routine examination practice, accounting for the cardiologist's level of ECHO experience. Secondary outcomes include time to diagnosis and the system usability scale score. Reference LV-EF and LV-GLS measurements and LV function diagnoses will be provided by a panel of 3 expert cardiologists.

Results: Recruitment started in September 2022, and data collection is ongoing. The results of the first phase are expected to be available by summer 2023, while the study will conclude in May 2024, with the end of the second phase.

Conclusions: This study will provide external evidence regarding the clinical performance and utility of the AI-based tool based on prospectively collected ECHO scans in the routine clinical setting, thus reflecting real-world clinical scenarios. The study protocol may be useful to investigators conducting similar research.

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KEYWORDS

artificial intelligence; clinical validation; computer-aided diagnosis; echocardiography; ejection fraction; global longitudinal strain; left ventricle; prospective cohort design; ultrasound

Introduction

Background

Echocardiography (ECHO) is a type of ultrasonographic scan used for examining the cardiac function and morphology [1]. Due to the practicality of image acquisition, relatively low cost, and little-to-no-risks for the patient, ECHO remains the most widely used cardiac imaging examination [2]. Of pivotal importance for patient evaluation is the assessment of the left ventricular (LV) systolic function [3], with recommended evaluation parameters being the ejection fraction (EF) and global longitudinal strain (GLS) [4]. EF is the percentage of blood ejected from the ventricle in each contraction, measured as the ratio of stroke volume (difference between end-diastolic and end-systolic volume) over the end-diastolic volume. GLS describes the myocardial deformation across the ventricular longitudinal axis, measured as the relative length change of the ventricular myocardium between end-diastole and end-systole.

Estimation of LV-EF and LV-GLS from ECHO scans is performed by cardiologists either manually or semiautomatically using a dedicated software [5]. One or more cardiac cycles and apical views of the LV can be used in the estimation of both parameters. Different apical views (typically 4-chamber, 2-chamber, and apical long axis views) are obtained by different placements of the ultrasound probe relative to the heart apex [1]. The estimation process is usually laborious and time-consuming, especially when considering medical emergencies, while accuracy depends on the cardiologist's experience in ECHO and the quality of scans [6], leading to considerable measurement variability [4,7]. Improving measurement precision and reliability is necessary, as it has been shown that EF and GLS values and their impairments are closely connected to patients' prognosis and course [8,9].

Deep learning [10], the most recent advancement in artificial intelligence (AI), has revolutionized computer vision over the past decade. Deep neural networks can be trained on annotated images without the need for feature engineering and perform fully automated image analysis. Inevitably, deep learning–based systems have been used in medical imaging, with a recent surge in applications for cardiovascular imaging [11]. Such advanced AI and associated software could support cardiologists of various levels of expertise in LV function assessment with the automatic and more accurate estimation of LV-EF and LV-GLS, and at the same time reduce the time of ECHO examination and the variability of measurements. In conjunction with point-of-care ultrasonography, such AI-based assistance may significantly improve relevant case management in demanding health care settings, such as emergency departments.

Objectives

This study aims at evaluating the clinical performance and producing preliminary evidence regarding the utility of a trained AI-based tool that automatically estimates LV-EF and LV-GLS from transthoracic ECHO scans. Two study phases are planned. The specific primary and secondary objectives of each study phase are listed in Textbox 1.

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Textbox 1. Primary and secondary objectives of the 2 phases of the study.

Phase 1

- Primary objective
  - Determine if the automatic estimation of left ventricular ejection fraction and left ventricular global longitudinal strain from echocardiography scans by the artificial intelligence–based tool is noninferior in terms of accuracy to semimanual estimations by cardiologists of different experience levels.
- Secondary objective
  - Evaluate the time required for left ventricular ejection fraction and left ventricular global longitudinal strain measurement from echocardiography scans by the artificial intelligence–based tool and by semimanual estimations of cardiologists of different experience levels.

Phase 2

- Primary objective
  - Determine if the combination of the cardiologist and the artificial intelligence–based tool is superior to the routine examination practice of the cardiologist in terms of correct diagnosis of left ventricular function (normal or abnormal) based on examination of echocardiography scans, accounting for the cardiologist's level of experience.
- Secondary objective
  - Evaluate the time required for diagnosis with and without the assistance of the artificial intelligence–based tool.
  - Evaluate the usability of the artificial intelligence–based tool based on cardiologists' feedback after use.

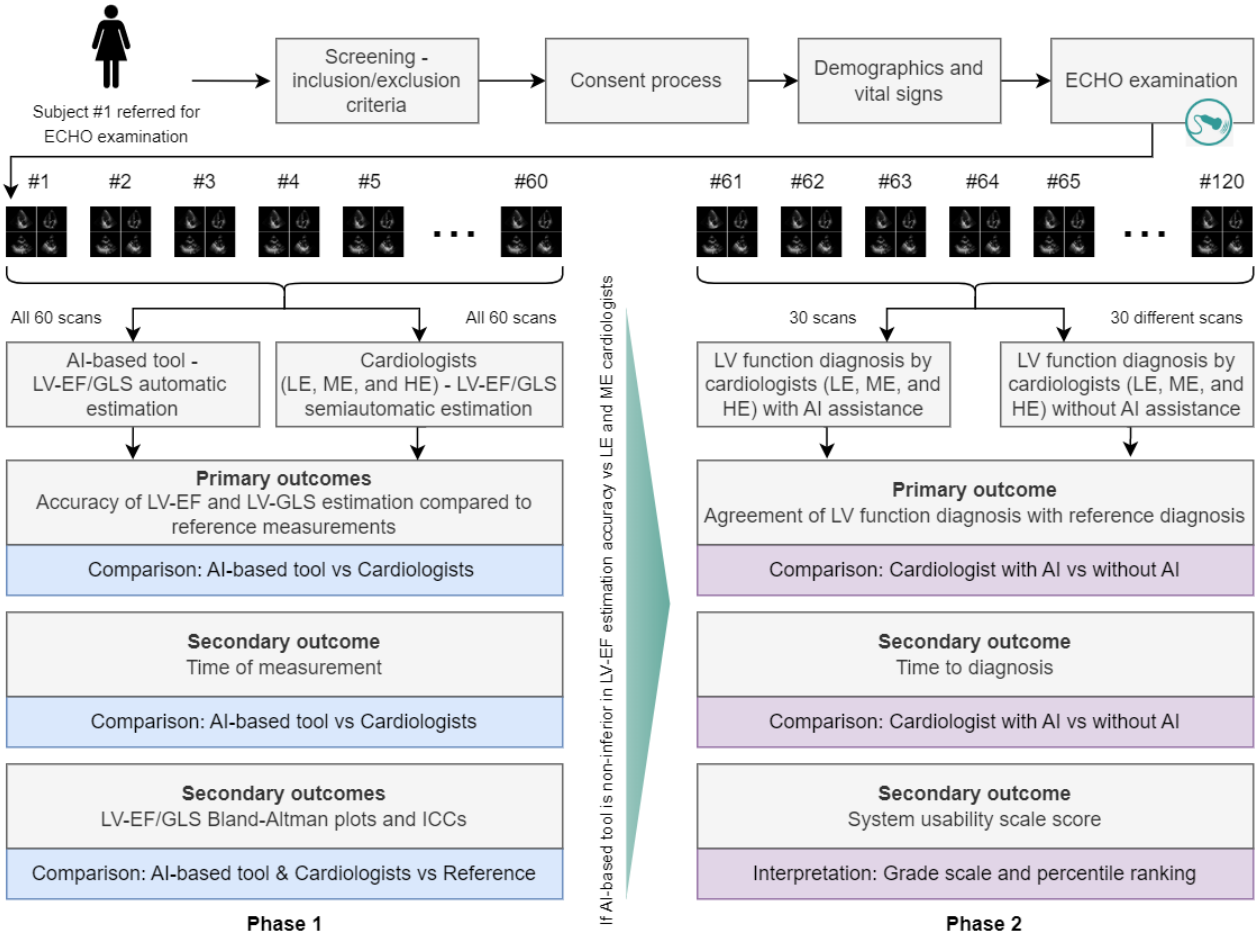
Methods

Study Design

This is a prospective cohort study conducted in 2 phases, involving multireader, multicase diagnostic measurement, and diagnostic performance evaluation. Data (ECHO scans) collection is common between the 2 phases. The specific objectives of each study phase were detailed in Textbox 1. In both phases, reference measurements and reference diagnoses will be provided by a panel of 3 highly experienced cardiologists, via a collective intelligence process. We will proceed with the second phase if and when the AI-based tool is proven to be noninferior in terms of (at least) LV-EF estimation compared to (at least) low- and medium-experienced cardiologists in the first phase. Figure 1 provides an overview of the study.

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Figure 1. Study overview. After enrollment in the study, an ECHO scan will be acquired from each participant. In total, 120 scans are planned to be collected, with 60 scans used in the first phase of the study evaluating the performance of the AI-based tool in LV-EF and LV-GLS estimation compared to the semimanual estimation by cardiologists of different experience levels and the rest in the second phase evaluating the utility of the AI-based tool in LV function diagnosis by cardiologists of different experience levels. AI: artificial intelligence; ECHO: echocardiography; EF: ejection fraction; GLS: global longitudinal strain; HE: high experience; ICC: intraclass correlation coefficient; LE: low experience; LV: left ventricle; ME: medium experience.



Clinical Site

The study will be conducted in the Third Cardiology Department of the Aristotle University of Thessaloniki (AUTH) in the Hippokration General Hospital, Thessaloniki, Greece. The hospital is equipped with a dedicated laboratory for ECHO acquisition (ECHO laboratory).

Participants

ECHO scans will be acquired from 120 participants (data collection participants) referred for transthoracic echocardiography as part of routine clinical practice in Hippokration Hospital. In total, 15 cardiologists will be involved in the study (serving as comparators in phase 1), divided into three groups according to the relevant level of experience: (1) the low experience (LE) group will include residents of cardiology with ECHO experience of fewer than 5 years, (2) the medium experience (ME) group will include cardiologists with ECHO experience of more than 5 and less than 10 years, and (3) the highly experienced (HE) group will include cardiologists with more than 10 years of experience or certification in echocardiography from the European Association of Cardiovascular Imaging (EACVI) or the National Cardiac Society.

A panel of 3 expert cardiologists (reference panel) with more than 10 years of experience and certification in echocardiography from the EACVI or the national cardiac society, not participating in the HE group, will provide the reference measurements and diagnoses.

Recruitment

Data collection participants will be recruited in the Third Cardiology Department of the Hippokration General Hospital. In particular, participants referred for transthoracic ECHO as part of routine clinical practice, including all possible diagnoses except those constituting exclusion criteria, will be invited to participate in data collection. Cardiologists serving at the Third Cardiology Department of the Hippokration General Hospital will be invited to participate in the examination of acquired echocardiograms.

Inclusion and Exclusion Criteria for ECHO Acquisition

Participants eligible for data collection must meet the following criteria: (1) female or male, (2) older than 18 years, and (3) participants must be in sinus rhythm during the examination.

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Participants will be excluded from data collection and processing based on the following criteria: (1) presence of atrial fibrillation, (2) presence of sinus or other tachycardia (heart rate>100 bpm), (3) presence of pacing rhythm, (4) complex congenital heart disease, (5) myocardial hypertrophy, (6) need for a contrast agent to improve echocardiographic resolution, (7) bad imaging quality with 2 or more myocardial segments not viewed in each apical view, and (8) incapability of providing full consent.

Duration

The study is expected to last for approximately 2 years. The study is estimated to complete the enrollment of participants for data collection and of cardiologists within 6 months from initiation. However, enrollment in both cases will remain open until the study goal is met. Each cardiologist is expected to complete the tasks of both study phases in a maximum of 18 months. The second phase will only begin if and when the tool is proven to be noninferior in (at least) LV-EF measurement accuracy compared to (at least) the LE and ME groups of cardiologists in the first phase.

Data Collection

Enrollment of Data Collection Participants and ECHO Scan Acquisition

Participants referred to the Third Cardiology Department of the Hippokration General Hospital for cardiovascular examination including ECHO (see “Recruitment” section) and deemed eligible for data collection will be invited to participate in the study. Enrollment in the study and ECHO scan acquisition will be performed on the same day. Participants will first review the study information sheet and undergo informed consent. Once consented, participants will be assigned a coded identification number. Afterward, basic demographics, anthropometrics, and vital signs (age, gender, height, weight, and blood pressure), as well as relevant medical history (known cardiovascular conditions), will be recorded. ECHO acquisition will follow the standard clinical practice. All ECHO scans will be performed at the Hippokration Hospital ECHO laboratory, by 1 experienced cardiologist with EACVI certification in ECHO. Scans will be acquired using the GE Vivid S5 ultrasound system (GE Healthcare) or the Clarius PA HD ultrasound scanner (Clarius Mobile Health Corp). Three views (a 2-chamber, a 3-chamber, and a 4-chamber apical view) will be acquired per scanning procedure, with 3 cardiac cycles per view. Views will be reviewed for diagnostic quality, and if a view does not meet the criteria set, the acquisition will be repeated.

Enrollment of Cardiologists

Cardiologists serving at the Hippokration Hospital will be invited to participate in the study. Cardiologists will first review the study information sheet and undergo informed consent. Once consented, they will be assigned a coded identification number. Demographics (age and gender) and experience, including career stage and experience in ECHO, will be recorded. Each cardiologist will be assigned to 1 of the 3 experience groups (LE, ME, and HE) according to the self-reported experience in ECHO.

Reference Measurements and Diagnoses

Acquired scans will be independently examined by the highly experienced cardiologists of the reference panel, who will estimate LV-EF and LV-GLS and provide a binary diagnosis of LV function (normal or abnormal) for each case. Examination of scans by the reference panel will take place on a single, dedicated computer (also referred to as a workstation) in the ECHO laboratory of the Hippokration Hospital. Cardiologists will examine scans in batches on different days, depending on their availability.

LV-EF and LV-GLS will be estimated using the same methods and standards applied in routine clinical practice. A commercially available speckle-tracking software (EchoPAC version 202.0, GE Healthcare) will be used. LV-EF will be estimated using the biplane Simpson method [4] from 2 and 4-chamber apical views after cardiologist-adjusted tracing of the LV cavity. For LV-GLS, the 2-dimensional speckle-tracking method [7] will be used. For each captured view, the cardiac cycle with the best image quality will be first selected out of the 3 captured cycles. If the image quality is similar among all 3 cycles, the intermediate one will be selected. To reduce bias due to user interaction, the beginning and end of the cardiac cycle will be the time points that will be automatically defined by the software, usually based on automatic QRS detection on the echocardiogram. In the second step, the endocardial border will be traced, and a region of interest will be constructed. Manual adjustments will be made after visual inspection of the segmental tracking results throughout the cardiac cycle, to obtain the best possible tracing of all myocardial segments. The peak systolic strain value per view, as automatically provided by the software, will be noted. Finally, LV-GLS will be calculated as the average peak strain of the 3 apical views.

Regarding LV-EF and LV-GLS, the reference measurement for each scan will be the average of measurements estimated by the 3 cardiologists, provided that there is a <20% discrepancy between the measurements. Regarding LV function, the reference diagnosis will be the majority diagnosis among the 3 equally weighted diagnoses, that is, at least 2 out of the 3 cardiologists of the reference panel arrived at this diagnosis. For cases where there is a discrepancy of ≥20% between at least 2 of the 3 LV-EF and LV-GLS measurements provided by the reference panel, the 3 cardiologists will examine them and estimate the reference measurements together.

Phase 1: Processing of ECHO Scans for LV-EF and LV-GLS Measurement

Out of the 120 ECHO scans to be acquired, the first 60 scans will be used for assessing the noninferiority of the AI-based tool in measuring LV-EF and LV-GLS.

Processing of scans by the AI-based tool will take place on the dedicated computer of the ECHO laboratory. For each scan, the AI-based tool will output an LV-EF and an LV-GLS measurement, along with the time required for producing both measurements. All 3 values will be recorded.

Comparator cardiologists of the 3 experience groups will independently examine each scan and estimate the LV-EF and LV-GLS. LV-EF and LV-GLS will be estimated using the same

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software and semimanual methods as in the case of the reference panel. For each scan, the LV-EF and LV-GLS values will be recorded along with the time required for estimation. The time required for estimation is defined as the time (in minutes) that elapsed from the moment a scan is loaded by the software until both measurements are estimated.

Cardiologists will examine scans in batches on different days, during working hours, and depending on their availability. A schedule with time slots will be communicated to them based on which they will be able to indicate their availability for the examination of each batch. Examination of scans will take place at the dedicated workstation of the ECHO Lab. At the end of phase 1, all 60 scans are expected to be processed by each cardiologist.

Phase 2: Examination of Scans for LV Function Diagnosis

In phase 2, the second batch of 60 scans will be used for assessing the superiority of the combination of the cardiologist and the AI-based tool in terms of LV function diagnosis from ECHO scans. Cardiologists of the 3 experience groups will independently examine batches of ECHO scans with and without the AI-based tool, and for each case, they will be asked to provide a binary diagnosis of LV function (normal or abnormal) based on visual inspection of the echocardiogram and measurements of LV-EF and LV-GLS. The decision will be recorded along with the time required to arrive at the diagnosis. For scans examined with AI assistance, cardiologists will use the AI-based tool that will allow them to view scans and automatically produce LV-EF and LV-GLS measurements. For scans examined without AI assistance, cardiologists will use the same software for viewing and estimating LV-EF and LV-GLS as in phase 1. For each cardiologist, ECHO scans reviewed with AI assistance will be different from those reviewed without AI assistance.

Before examining phase 2 cases, each cardiologist will be presented with materials describing how to use the AI-based tool and they will be given the opportunity to practice using the tool with 2 sample cases (independent of the study cases).

Examination of scans will take place on the same workstation of the ECHO laboratory as in phase 1, via scheduled time slots. At the end of phase 2, each cardiologist is expected to review and provide a diagnosis for 30 scans with AI assistance and 30 without AI assistance. Cardiologists that will examine at least 10 scans with AI assistance will be asked to complete the Greek version of the system usability scale (SUS).

Outcomes

Phase 1

Primary Outcomes

The primary outcomes of phase 1 are the accuracy of LV-EF and LV-GLS measurements with respect to the reference measurements defined as the absolute error of estimated average LV-EF and the absolute error of estimated average LV-GLS over 3 apical views (2-chamber, 3-chamber, and 4-chamber), respectively.

Secondary Outcomes

The following secondary outcomes will be produced in phase 1: (1) a Bland-Altman plot of LV-EF measurements produced by the AI-based tool with respect to reference measurements; (2) Bland-Altman plots of LV-EF measurements produced by LE, ME, and HE cardiologists with respect to reference measurements; (3) a Bland-Altman plot of LV-GLS measurements produced by the AI-based tool with respect to reference measurements; (4) Bland-Altman plots of LV-GLS measurements produced by LE, ME, and HE cardiologists with respect to reference measurements; (5) intraclass correlation coefficient (ICC) of LV-EF measurements produced by the AI-based tool with reference measurements; (6) ICCs of LV-EF measurements produced by LE, ME, and HE cardiologists with reference measurements; (7) ICC of LV-GLS measurements produced by the AI-based tool with reference measurements; (8) ICCs of LV-GLS measurements produced by LE, ME, and HE cardiologists with reference measurements; (9) time required by the AI-based tool for producing LV-EF and LV-GLS measurements from an ECHO scan; and (10) time required by LE, ME, and HE cardiologists for producing LV-EF and LV-GLS measurements from an ECHO scan.

Phase 2

Primary Outcomes

The primary outcome of phase 2 is the agreement rate of the LV function diagnosis of LE, ME, and HE cardiologists with the reference diagnosis.

Secondary Outcomes

The secondary outcomes of phase 2 are the time required by LE, ME, and HE cardiologists for examining an ECHO scan and arriving at the diagnosis of LV function and the SUS score.

Statistical Analysis Plan

Sample Size

The sample size of this study was determined based on realistic recruitment goals and comparability to the sample sizes of similar landmark studies [12,13]. In total, the study will recruit 120 individuals and each one will undergo a single ECHO examination. Half the scans will be used for phase 1 and the rest for phase 2. In total, 15 cardiologists, approximately 5 per experience group (LE, ME, and HE), will be recruited and participate in both study phases.

Statistical Analyses

In phase 1, errors of LV-EF and LV-GLS measurements produced by the AI-based tool will be compared to errors in the same measurements estimated semimanually by cardiologists, accounting for their experience level. We will use noninferiority tests for these comparisons. We will also compare the time required by the AI-based tool and by the comparator cardiologists to produce the measurements, using a superiority test. Bland-Altman analysis will also be performed to evaluate the agreement between the AI-based measurements, measurements by cardiologists of the 3 experience groups, and reference measurements and to detect bias and outliers. Moreover, ICC to assess interobserver variability regarding

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both LV-EF and LV-GLS measurements will be used. In phase 2, agreement rates of cardiologists' diagnosis with the reference diagnosis with and those without the help of the AI-based tool will be compared. The same applies to the time to diagnosis. We will use superiority tests for these comparisons. Regarding usability, the SUS score will be interpreted according to a grade scale [14] and percentile ranking [15].

Ethical Considerations

Approval

The study has been approved by the research ethics committee of AUTH, Thessaloniki, Greece (protocol 102808/2022). Any modifications to the protocol, which may impact the conduct of the study or may affect participant safety, will require a formal amendment to the protocol and subsequent review and approval by the research ethics committee of AUTH before the changes are implemented to the study.

Consent

Prospective participants will be provided with a participant information sheet and a consent form. They will be given sufficient time to read the material and ask any questions. Participants will be informed of the study aim, requirements for participation, risks and benefits, their rights, the usage and storage of personal data, and the contact for any issues related to the study. They will be explicitly informed that study participation is voluntary and that choosing against participation will not affect the care received for treatment, in the case of data collection participants, and their residency or work, in the case of cardiologists. Written and informed consent will be obtained from all participants before any study-related procedures.

Data Confidentiality and Management

All data collected will be handled in compliance with the General Data Protection Regulation (GDPR) of the European Union. The collection of personal participant information is limited to the amount necessary to achieve the aims of the research. Participants will be assigned a coded identification number that will be used for reference in all records to protect participant confidentiality through pseudonymization. All records, electronic or hard copy, will be securely stored in password-protected computers or locked cabinets, respectively, while those containing direct identifiers, such as signed consent forms, will be stored separately from other records, with limited access.

Only pseudonymized data will be used for data analysis. Investigators who are authorized by the principal investigator will be given access to the acquired, pseudonymized data sets. In case of data transfer over a computer network, this will take place via the secure shell (SSH) file transfer protocol (SFTP). Study participants will be able to request access, correction, limited processing, or deletion of the data they contributed to the study, in compliance with the respective mandates of the GDPR. Participants will also have the right to data portability.

Withdrawal

All participants, including data collection participants and cardiologists, are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice. Participants can also request for the data they contributed to be deleted. Reasonable attempts will be made by the investigator to provide a reason for participant withdrawals.

Safety

Data will be collected from participants referred for echocardiography based on routine clinical practice. Thus, there are no additional safety concerns arising from their participation in the study. Standard clinical procedures will be followed for acquiring ECHO scans. Any distress or other adverse effects that may occur during ECHO will be handled according to standard clinical practice. Measurements and diagnoses produced during both phases of the study will only be used for evaluating the performance and utility of the AI-based tool, and they will not affect the formal diagnosis, treatment, or care that the participant will receive, which will be based on standard clinical practice.

Results

Enrollment began in September 2022. Participant recruitment and ECHO scan collection are ongoing. The results of the first phase are expected by summer 2023. The study is expected to conclude in May 2024, with the completion of the second phase.

Discussion

Principal Anticipated Findings

This is a 2-phase, prospective cohort study aiming at externally validating the clinical performance of and producing preliminary utility evidence regarding an AI-based tool that automatically estimates LV-EF and LV-GLS from transthoracic ECHO scans. ECHO scans will be collected from 120 participants referred for ECHO examination in the Hippokration General Hospital, Thessaloniki, Greece. The first phase will evaluate the accuracy of the AI-based tool, its reliability, and measurement time compared to semimanual estimations of cardiologists of different experience levels. We expect to find that the AI-based tool is noninferior in terms of LV-EF and LV-GLS estimation accuracy compared to at least LE and ME cardiologists, yields more consistent measurements, and is superior in terms of time required for LV-EF and LV-GLS estimation compared to cardiologists of all experience levels.

Provided that the AI-based tool proves noninferior in terms of at least LV-EF estimation accuracy compared to at least LE and ME cardiologists, the second phase will determine whether the tool can assist cardiologists of different experience levels in classifying LV function as normal or abnormal correctly and in less time. We expect to find that the combination of the cardiologist and the AI-based tool is superior in terms of agreement with the reference LV function diagnosis (normal or abnormal) and time to diagnosis compared to the cardiologist's routine examination practice, at least in the cases of LE and ME cardiologists. The second phase will also yield usability evidence regarding the tool.

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Comparison to Prior Work

To our knowledge, at the time of approval, this was the first prospective cohort study aiming to evaluate the clinical performance and utility of an AI-based tool for automatic estimation of both LV-EF and LV-GLS from ECHO scans. Prior studies focused on evaluating the performance of AI-based tools for either EF or GLS automatic estimation. In the study of Salte et al [13], the performance of an AI-based system for automatic LV-GLS estimation was assessed by comparing AI-based GLS measurements to reference, semiautomatic GLS measurements by a single experienced observer in 200 ECHO scans. Pearson correlation coefficient, the mean absolute difference, and Bland-Altman analysis metrics were used to compare the 2 types of measurements, with LV function (measured using LV-EF) and the quality of scans considered as covariates. The study also investigated intraobserver variability by comparing initial GLS measurements with measurements performed after 4 weeks by the same observer in 25 ECHO scans, as well as interobserver variability by comparing the GLS measurements of the experienced observer to measurements by a second experienced observer performed on the same 25 scans. In a recent work [16], a retrospective study was carried out to compare LV-EF measurements of an AI-based tool to physician-measured LV-EFs with cardiac magnetic resonance imaging–derived EFs as the reference. ECHO scans from 242 patients were used, while physician-measured LV-EFs were obtained from formal clinical reports. Pearson correlation coefficient and Bland-Altman analysis metrics were used for comparisons, with the use or not of ultrasound-enhancing agent during ECHO acquisition considered as a covariate.

Strengths and Limitations

This study has several strengths. First, it will generate external evidence regarding the clinical performance of a trained AI-based tool for automatic estimation of LV-EF and LV-GLS based on prospective data collected in the routine clinical setting, thus reflecting real-world clinical scenarios. Second, it will provide preliminary evidence of the utility of such a tool in the diagnosis of LV function. Last, it will take into account the experience of the cardiologist in ECHO as a covariate both in EF and GLS measurement, as well as the diagnosis of LV function. A key limitation of this study is that the sample size was not determined through exhaustive power analysis but based on a realistic recruitment rate and sample sizes of previous studies with similar objectives and outcomes.

Dissemination Plan

After the completion of the study, we plan to publish the findings in peer-reviewed, open-access biomedical journals with a multidisciplinary readership spanning medicine, data science, and engineering. We will also report on the findings in deliverables and on the website of the associated project, at medical and biomedical engineering conferences, as well as in events with relevant stakeholders. The publication or presentation of any study findings will be done with respect to participants' privacy. Publications or presentations will not include any identifying participant information.

Future Directions

Depending on the findings of the study, future work may include the design and conduct of a randomized control trial to comprehensively evaluate the clinical utility of the AI-based tool, that is, its potential to lead to improved patient outcomes when used in a specific clinical setting.

Conclusions

Through the present study, we anticipate generating evidence on the clinical performance and utility of an AI-based tool for the automatic estimation of LV-EF and LV-GLS from echocardiograms. Such a tool has the potential to advance the process of ECHO examination through accurate, consistent, and fast estimation of key LV functional parameters that may lead to improved patient outcomes, especially in demanding care settings such as emergency rooms. Validation of clinical performance and preliminary proof of utility are the first steps in the assessment process of the tool toward its regulatory approval and use in clinical practice. The detailed description of the protocol presented here may be useful for clinicians and researchers planning similar studies.

Acknowledgments

This work is part of the HosmartAI—"Hospital Smart development based on AI" project that is funded by the European Union's Horizon 2020 Research and Innovation Programme (grant agreement ID 101016834).

Data Availability

The data sets generated and analyzed during the current study are not publicly available due to GDPR compliance and in order to safeguard participants' privacy but will be available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review report by European Union Horizon 2020 - Research and Innovation Framework Programme.
[PDF File (Adobe PDF File), 237 KB - resprot_v12i1e44650_app1.pdf]

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Abbreviations

AI: artificial intelligence
AUTH: Aristotle University of Thessaloniki
EACVI: European Association of Cardiovascular Imaging
ECHO: echocardiography
EF: ejection fraction
GDPR: General Data Protection Regulation
GLS: global longitudinal strain
HE: high experience
ICC: intraclass correlation coefficient
LE: low experience
LV: left ventricle or left ventricular

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ME: medium experience
SFTP: secure shell file transfer protocol
SSH: secure shell
SUS: system usability scale

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Protocol

Real-time Assessment of the Bidirectional Relationship Between Affective States and Glucose: Protocol for a 14-Day Observational Study

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Abstract

Background: Glucose variability increases cardiometabolic disease risk. While many factors can influence glucose levels, postprandial glucose response is the primary driver of glucose variability. Furthermore, affect may directly and indirectly impact glucose variability through its effect on eating behavior. Continuous glucose monitors (CGMs) facilitate the real-time evaluation of blood glucose, and ecological momentary assessment (EMA) can be used to assess affect in real time. Together, data collected from these sources provide the opportunity to further understand the role of affect in glucose levels.

Objective: This paper presents the protocol for a study that aims to (1) evaluate the feasibility and acceptability of using CGMs along with EMA in nondiabetic populations and (2) examine the bidirectional relationship between affect and glucose in nondiabetic adults with overweight or obesity using a CGM and EMA.

Methods: Eligibility criteria for the study include participants (1) aged 18 to 65 years old, (2) with a BMI of ≥25 kg/m^2, (3) who are able to read and write in English, and (4) who own a smartphone. Individuals will be excluded if they (1) have type 1 or 2 diabetes or have any other condition that requires glucose monitoring, (2) are pregnant, (3) use any medications that have the potential to alter blood glucose levels or interfere with the glucose sensing process, or (4) have a diagnosed gastrointestinal condition or eating disorder. In a 14-day observational study, participants will wear a FreeStyle Libre Pro CGM sensor (Abbott) and will receive mobile phone–based EMA prompts 6 times per day (randomly within six 2-hour windows between 8 AM and 8 PM) to assess positive and negative affect. Participants will also wear a Fitbit Inspire 2 (Fitbit) to continuously monitor physical activity and sleep, which will be included as covariates in the analysis. Multilevel linear regression models will be used to evaluate the acute relationship between glucose level and affect.

Results: Recruitment started in October 2022 and is expected to be completed in March 2023. We will aim to recruit 100 participants. As of December 12, 2022, a total of 39 participants have been enrolled.

Conclusions: The results of this study will further elucidate the role of affect in glucose variability. By identifying affective states that may lead to glucose excursions, our findings could inform just-in-time behavioral interventions by indicating opportunities for intervention delivery.

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KEYWORDS

affect; glucose; eating behavior; glucose variability; glucose excursion; ecological momentary assessment; continuous glucose monitoring; continuous glucose monitor

Introduction

Effective intervention strategies are required to reduce the immense burden of cardiometabolic disease. Standard behavioral interventions to reduce cardiometabolic disease risk are typically based on population averages [1,2]; however, variability in response to dietary interventions suggests the need for personalized approaches [3]. Precision approaches aim to tailor interventions to an individual's unique characteristics and contexts [4,5]. For example, just-in-time adaptive interventions aim to facilitate behavior change by delivering an intervention at times and in contexts when individuals are more receptive to behavior change [6]. Identifying opportunities for change requires an understanding of the time-varying factors that influence behaviors.

The potential to measure time-varying factors has increased with the availability of wearable sensors. The use of continuous glucose monitors (CGMs) has resulted in the identification of glucose variability, that is, intraday fluctuations in blood glucose, as a risk factor for the development of cardiometabolic disease [7]. Greater glucose variability predicts increases in glycated hemoglobin (HbA_{1c}) in both diabetic and nondiabetic populations [8,9]. Among persons with type 2 diabetes who maintain good glycemic control ($HbA_{1c} \leq 7.0\%$), greater glucose variability was an independent risk factor for coronary artery disease during a 10-year follow-up period [10]. Though evidence in nondiabetic populations is sparse, mechanistically, it has been proposed that glucose variability increases cardiovascular disease risk through increased oxidative stress and inflammation [11], an effect that has been observed among individuals with normal insulin function [12].

While several factors influence glucose levels (eg, stress, physical activity, etc), glucose variability is primarily driven by increases in postprandial glucose [13]. Controlled laboratory studies have demonstrated that several dietary factors impact postprandial glucose, such as meal composition [14,15], meal timing [16], and meal frequency [17]. In real-world settings, eating behavior, and thus glucose variability, is influenced by several individual-level factors. One example of an individual factor that influences eating behavior is affect [18-21]. The relationship between eating behavior and affect appears to be bidirectional as fatigue, stress, and negative mood are associated with increased cravings and food consumption [19-22], while variations in glucose in response to eating may relate to affective and physical feeling states [23-26]. However, research in this area has primarily relied on dietary assessment recall methodologies, which may be prone to bias and recall error [27]. Pairing data from CGMs with data on affect using ecological momentary assessment (EMA), which involves repeated sampling of affect in real time and in an individual's natural environment, improves the validity of responses [28] and dramatically decreases the time between measurement of mood and glucose.

Combining CGM and EMA data to investigate the relationship between affective states and glucose variability presents an opportunity to support the development of precision interventions to prevent chronic disease by identifying situations that are likely to lead to large glucose increases (ie, an opportunity for change). A recent review [29] of mood and glucose variability in type 1 and 2 diabetes identified only 1 study that used CGMs and EMA to evaluate mood and glucose [25] and called for more research evaluating the relationships between mood or affect and glucose variability. To date, only a small (n=15) pilot study has combined EMA responses with CGM data to evaluate its association with affective and physical feeling states in nondiabetic samples [18]. Thus, the aims of this study are to (1) evaluate the feasibility of conducting a study using CGMs and EMA and (2) examine the bidirectional relationship between affect and glucose in adults using CGM and EMA data.

Methods

This is a 14-day observational study. Enrolled participants (N=100) will wear a CGM and receive EMA prompts to assess affect 6 times per day over the 14-day period (detailed below).

Ethics Approval

The study protocol was approved by the Texas A&M University Institutional Review Board (IRB2021-1412F).

Participants

Participants will be recruited through online social media advertisements, flyers in community settings, and emails to community members who have indicated previous interest in research participation. Interested individuals will complete a brief web-based screening questionnaire to determine study eligibility. Inclusion and exclusion criteria for the study are outlined in Textbox 1.

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Textbox 1. Inclusion and exclusion criteria for study participation.

Inclusion criteria:

- Aged 18 to 65 years old
- Have a BMI of ≥25 kg/m^2
- Able to read and write in English
- Own a smartphone

Exclusion criteria:

- Diagnosed with type 1 or type 2 diabetes or any other condition that requires glucose monitoring
- Pregnant women
- Use of any medications that have the potential to alter blood glucose levels or interfere with the glucose sensing process (eg, corticosteroids, metformin, ascorbic acid, aspirin, acetaminophen, etc)
- Diagnosed with a gastrointestinal condition
- Diagnosed with an eating disorder

Baseline Visit

Upon confirmation of eligibility, participants will attend a baseline visit. Prior to completing any study-related activities, participants will sign an institutional review board–approved consent form. Participants will complete questionnaires to collect demographic data (age, sex, gender, race, ethnicity, and zip code), and study staff will measure participants' height and weight. Height will be measured with a Seca 213 stadiometer (Seca GmbH). Two measurements will be taken and recorded in centimeters. If a discrepancy of greater than 0.5 cm is noted, additional measurements will be taken until 2 consecutive measurements within 0.5 cm occur. An average of those 2 measures will be recorded for height. Similarly, weight will be measured using a Seca Clara 803 scale, recorded in kilograms, and taken until 2 consecutive measures within 0.5 kg occurs.

Glucose Monitoring

Participants will wear a FreeStyle Libre Pro CGM sensor (Abbott) on the upper arm of the participant's choosing for 14 days. The FreeStyle Libre Pro collects blinded interstitial glucose levels at 15-minute increments.

Affect

During the 14-day data collection period, participants will receive EMA prompts delivered to their smartphone via the Ethica mobile app (Ethica Data). Prompts will be delivered 6 times per day. One prompt will be delivered at a random time within each 2-hour window between 8 AM and 8 PM (8 AM-10 AM, 10 AM-12 PM, 12 PM-2 PM, 2 PM-4 PM, 4 PM-6 PM, and 6 PM-8 PM). Each prompt will consist of 10 Likert-scale items that will assess both positive and negative affect, with responses ranging from 1 (not at all) to 4 (extremely): "How (happy, cheerful, relaxed, stressed, anxious, angry, sad, energetic, tired, lonely) do you feel?" The survey will also include 2 "yes" or "no" questions: "Are you (bored, hungry) right now?"

The order of the 10 items will be randomized at each time point. Assessment questions have been validated for their use in daily or momentary assessment [30-32].

Covariates

Physical Activity and Sleep

Each participant will be provided a Fitbit Inspire 2 (Fitbit) to track physical activity and sleep over the 14-day data collection period. In the primary analyses, these variables will be included as covariates, but collection of this data will also facilitate secondary analyses of the complex interaction effects of physical activity, sleep, and affect on glucose level. Data from the Fitbit devices will be processed using Fitabase (Small Steps LLC).

Survey

A baseline survey will collect participants' demographic information and the following covariates:

- Depression symptoms; Patient Health Questionnaire-9 (PHQ-9): the 9-item PHQ-9 is designed to measure depressive symptoms [33].
- Anxiety symptoms; Generalized Anxiety Disorder-7 (GAD-7): the 7-item GAD-7 is a brief scale to identify probable cases of generalized anxiety disorder and to assess symptom severity [34].
- UCLA (University of California, Los Angeles) Loneliness Scale: this is a 20-item scale designed to measure one's subjective feelings of loneliness as well as feelings of social isolation with established validity and reliability [35].
- Self-Compassion Scale–Short Form (SCS-SF): the 12-item SCS-SF is a short version of the original Self-Compassion Scale [36].
- Coping Strategy Indicators (CSI): the 33-item CSI is a self-report measure of situational coping encompassing the strategies of avoidance, problem-solving, and seeking social support [37].
- Salzburg Stress Eating Scale (SSES): the 10-item SSES questionnaire measures eating in response to stress [38].
- Weight Efficacy Lifestyle Questionnaire–Short Form (WEL-SF): the 8-item WEL-SF measures patients' confidence in their ability to control eating behavior in challenging situations and was developed as a brief measure for use in research and clinical practice [39].

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- Food Cravings Questionnaire-Trait-reduced (FCQ-T-r): the 15-item FCQ-T-r questionnaire measures the frequency and intensity of food craving experiences [40].
- Experience in Close Relationship Scale (ECR-S): the 12-item ECR-S questionnaire concerns romantic relationships [41].

Follow-up Visit

Upon completion of the 14-day study, each participant will be asked to complete a follow-up visit. Poststudy weight will be measured at the visit (to potentially control for weight change in statistical analysis), and participants will complete a questionnaire to assess their experience during the study. The questionnaire will include both Likert-scale and open-ended questions aimed at identifying any barriers to device compliance. Participants will return the Fitbit and CGM sensor at this follow-up visit.

Analysis

We will determine compliance to CGM and Fitbit wear (% of wear time) and response rates to EMA prompts (% of prompts responded to). Predetermined compliance values (CGM and Fitbit wear ≥80%) and EMA response rates (75%) will be used to assess the feasibility of the study procedures.

Multilevel linear regression models, which adjust the standard errors for the clustering of EMA and glucose data within individuals and partition the variance of between- and within-person effects, will be used to evaluate the acute relationship between glucose level and affect. The following two outcome variables will be evaluated: (1) average glucose level in the time period between 2 EMA prompts and (2) occurrence of a glucose excursion (defined as a glucose level greater than 1 SD above the mean 24-hour glucose level). Predictor variables will be 2 separate composite scores for positive affect (average of "happy," "cheerful," "relaxed," and "energetic") and negative affect (average of "stressed," "anxious," "angry," "sad," and "tired"). Secondary analyses will be used to predict the interaction effects of physical activity, sleep, and affect on glucose level. Similar models will evaluate positive and negative affect as the outcome variable and average glucose level in the hour prior as the predictor. Covariates in the model will include age, sex, BMI, time of day, day of week, physical activity since the previous EMA prompt, and previous night's sleep. Additional baseline measures will be evaluated as potential covariates and included in the final model if found to significantly improve model fit. Instances of missing EMA or CGM data will be excluded from the analysis.

Results

Recruitment started in October 2022. As of December 12, 2022, a total of 39 participants have been enrolled. We expect to enroll 100 participants by a target completion date of March 2023.

Discussion

This project will generate data to elucidate the relationship between affective states and glucose variability, with an aim of ultimately informing intervention development to reduce glucose variability. We hypothesize that a bidirectional relationship exists by which greater negative affect will predict greater glucose variability, while greater glucose variability will predict greater negative affect.

Technological innovations hold promise for improving approaches to understand the relationship between affective states and glucose variability in real-world settings. CGMs allow for real-time collection of data related to postprandial response, while EMA allows for real-time collection of mood states. Pairing these approaches will facilitate a more valid evaluation of the relationships between affective states and eating behavior, as well as provide opportunities for real-time precision nutrition interventions that consider individuals' physiological and cognitive states. Precision intervention approaches, such as just-in-time interventions, aim to intervene during moments of opportunity [6]. Compliance data, along with the postparticipation questionnaire, will inform changes to study procedures to address the barriers experienced by participants. Evaluation of the relationship between glucose level and affect will aim to identify situations in which glucose excursions occur (opportunity) and can inform interventions to be delivered during those opportunities (ie, meditation or physical activity to improve affect and dietary suggestions that minimize glucose excursions).

Acknowledgments

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Data Availability

The data sets generated during this study will be available from the corresponding author upon reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review report by Texas A&M Nutrition & Obesity Research Center (tNORC) Pilot and Feasibility Projects (USA).
[PDF File (Adobe PDF File), 159 KB - resprot_v12i1e45104_app1.pdf]

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Abbreviations

CGM: continuous glucose monitor
CSI: Coping Strategy Indicators
ECR-S: Experience in Close Relationship Scale
EMA: ecological momentary assessment
FCQ-T-r: Food Cravings Questionnaire-Trait-reduced
GAD-7: Generalized Anxiety Disorder-7
HbA_{1c}: glycated hemoglobin
PHQ-9: Patient Health Questionnaire-9
SCS-SF: Self-Compassion Scale–Short Form

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SSES: Salzburg Stress Eating Scale
UCLA: University of California, Los Angeles
WEL-SF: Weight Efficacy Lifestyle Questionnaire–Short Form

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Protocol

The Detection of Acute Risk of Self-injury Project: Protocol for an Ecological Momentary Assessment Study Among Individuals Seeking Treatment

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Abstract

Background: Nonsuicidal self-injury (NSSI) is a major mental health concern. Despite increased research efforts on establishing the prevalence and correlates of the presence and severity of NSSI, we still lack basic knowledge of the course, predictors, and relationship of NSSI with other self-damaging behaviors in daily life. Such information will be helpful for better informing mental health professionals and allocating treatment resources. The DAILY (Detection of Acute rIsk of seLf-injurY) project will address these gaps among individuals seeking treatment.

Objective: This protocol paper presents the DAILY project's aims, design, and materials used. The primary objectives are to advance understanding of (1) the short-term course and contexts of elevated risk for NSSI thoughts, urges, and behavior; (2) the transition from NSSI thoughts and urges to NSSI behavior; and (3) the association of NSSI with disordered eating, substance use, and suicidal thoughts and behaviors. A secondary aim is to evaluate the perspectives of individuals seeking treatment and mental health professionals regarding the feasibility, scope, and utility of digital self-monitoring and interventions that target NSSI in daily life.

Methods: The DAILY project is funded by the Research Foundation Flanders (Belgium). Data collection involves 3 phases: a baseline assessment (phase 1), 28 days of ecological momentary assessment (EMA) followed by a clinical session and feedback survey (phase 2), and 2 follow-up surveys and an optional interview (phase 3). The EMA protocol consists of regular EMA surveys (6 times per day), additional burst EMA surveys spaced at a higher frequency when experiencing intense NSSI urges (3 surveys within 30 minutes), and event registrations of NSSI behavior. The primary outcomes are NSSI thoughts, NSSI urges, self-efficacy to resist NSSI, and NSSI behavior, with disordered eating (restrictive eating, binge eating, and purging), substance use (binge drinking and smoking cannabis), and suicidal thoughts and behaviors surveyed as secondary outcomes. The assessed predictors include emotions, cognitions, contextual information, and social appraisals.

Results: We will recruit approximately 120 individuals seeking treatment aged 15 to 39 years from mental health services across the Flanders region of Belgium. Recruitment began in June 2021 and data collection is anticipated to conclude in August 2023.

Conclusions: The findings of the DAILY project will provide a detailed characterization of the short-term course and patterns of risk for NSSI and advance understanding of how, why, and when NSSI and other self-damaging behaviors unfold among individuals seeking treatment. This will inform clinical practice and provide the scientific building blocks for novel intervention approaches outside of the therapy room that support people who self-injure in real time.

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KEYWORDS

nonsuicidal self-injury; suicidal thoughts and behaviors; real-time; experience sampling; ecological momentary assessment; digital interventions; mobile phone

Introduction

Background

Nonsuicidal self-injury (NSSI), the direct and deliberate damage of one's body tissue without suicidal intent (eg, cutting and hitting oneself), is a major mental health concern worldwide. Epidemiological surveys indicate that 1 in 5 individuals engage in NSSI before the age of 25 years [1-3], with 12-month rates in the 8% to 19% range [1,2] and many individuals reporting persistent NSSI for several years [4]. These rates are considerably higher among individuals seeking treatment [5-7], with more than half of adolescent inpatients and 1 in 10 emerging adult and adult outpatients reporting monthly NSSI [8,9]. Furthermore, the presence of NSSI predicts rehospitalization [10], is highly stigmatized [11], and is uniquely associated with an increased risk for psychiatric disorders [2,9,12-15] and suicidal thoughts and behaviors (STB). For instance, research shows that people who engage in NSSI are more likely to make a suicide attempt independent of mental disorders [16,17], with those engaging in repetitive persistent NSSI being most likely to attempt suicide and experience adverse psychosocial outcomes [18]. As such, there is an urgent need to better understand, predict, and prevent self-injury among people who frequently engage in these behaviors.

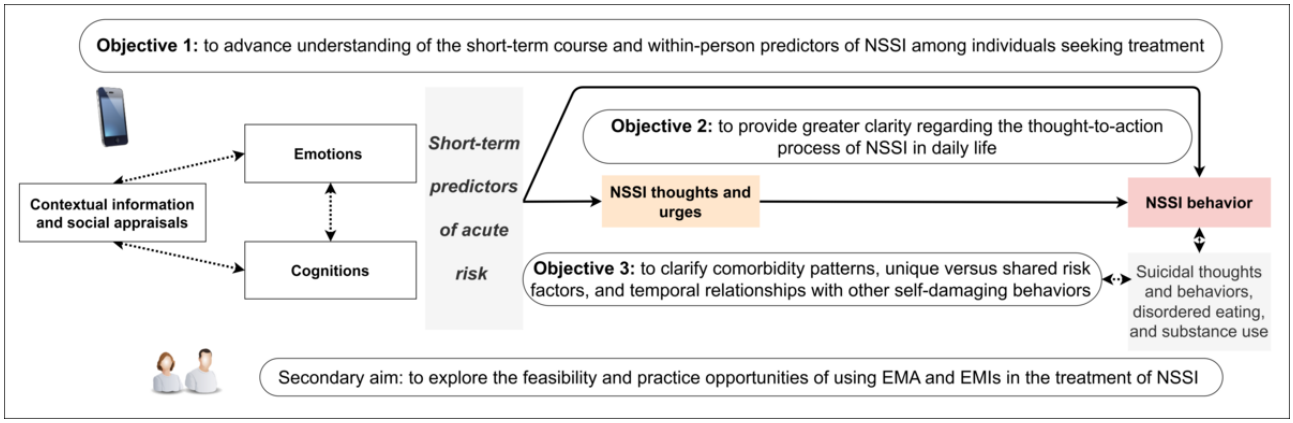
Unfortunately, we still lack basic knowledge of the descriptive nature of NSSI and how, why, and when self-injury unfolds in everyday life [19], a prerequisite for risk screening and intervention to prevent NSSI and clinically associated outcomes (eg, suicide attempts). This lack of progress is largely because most empirical studies have focused on establishing the prevalence and correlates of the presence and severity of NSSI using cross-sectional designs. Although longitudinal studies have been conducted, they typically used observation windows from months to years [19-21], providing a long-distance view of who is at greater risk of engaging in NSSI compared with others. However, such a nomothetic approach does not clarify *when* someone is at risk in the short term and in what daily life contexts they are more at risk and will thus not help clinicians to decide whether an individual is likely to self-injure within the next days and weeks. Making these decisions requires an idiographic approach and knowledge of the course, contexts of risk, and the relationship of NSSI with other self-damaging behaviors in daily life. Such information would be helpful for better informing mental health professionals and allocating treatment resources.

Similar to other frequently co-occurring self-damaging behaviors (eg, attempting suicide, binge eating, purging, and binge drinking) [2,13,22], NSSI cannot be ethically induced in the laboratory but occurs in people's everyday lives. Although studying NSSI as it unfolds in real time has historically been challenging, recent technological advancements have made it possible to do exactly this, which has the potential to substantially improve our understanding and inform prevention efforts [19,23]. Ecological momentary assessment (EMA; also called experience sampling, ambulatory assessment, or real-time monitoring) involves prompting individuals multiple times per day via their mobile phone to provide in-the-moment information on social appraisals, emotions, cognitions, and behavioral patterns as they are lived in the flow of daily life [24-26]. Prior research suggests that NSSI thoughts can change substantially across hours [27], essentially necessitating EMA to (1) capture these real-time changes and (2) enable the identification of factors that predict these changes in daily life.

Advancing insight into the course and contexts of elevated risk for NSSI thoughts (ie, *thinking about deliberately hurting oneself*), NSSI urges (ie, *a difficult-to-control desire to self-injure*), self-efficacy to resist NSSI (ie, *confidence in one's ability not to engage in self-injury*), and NSSI behavior (ie, *engagement in self-injury*) would uniquely inform researchers and clinicians about how self-injury unfolds and is experienced by those at highest risk. This *in-the-moment* information can transform our ability to prevent and manage NSSI among individuals seeking treatment by providing the scientific building blocks for novel digital interventions that support people who self-injure in real time [19,28,29]. The DAILY (Detection of Acute rIsk of seLf-injurY) project aims to address these gaps using a 28-day EMA protocol among individuals seeking treatment. This protocol paper presents the project's aims, design, and materials used. Figure 1 provides a graphical presentation of the primary objectives of the DAILY project.

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Figure 1. Graphical overview of the study objectives. EMA: ecological momentary assessment; EMI: ecological momentary intervention; NSSI: nonsuicidal self-injury.



Objectives

The first primary objective is to clarify the short-term course and within-person predictors of NSSI. Initial work among community samples suggests that NSSI thoughts are usually short-lived and moderate in intensity [30-32], with a higher risk of more intense and persistent NSSI thoughts toward the evening [32] and an average of 1.6 (SD 1.1) NSSI behaviors per week [30]. Surprisingly, however, the short-term clinical course of NSSI remains to be comprehensively investigated among individuals seeking treatment. The intensive nature of the longitudinal data we collect will allow for a detailed picture of the thought and behavioral patterns and help us to address several critical unanswered questions about the course of NSSI among individuals seeking treatment: how much do NSSI thoughts, NSSI urges, self-efficacy to resist NSSI, and NSSI behavior (1) vary between people seeking treatment, (2) vary within people seeking treatment, (3) vary throughout the day and the week, and (4) covary and predict each other prospectively in daily life?

Guided by contemporaneous models of NSSI [33-35] and emerging work [36-38], we will evaluate contextual information, social appraisals, emotions, and cognitions as within-person risk and protective factors for cognitive and behavioral NSSI outcomes. We hypothesize that the risk of NSSI behavior will be higher when people are alone [30], after situations characterized by negative social appraisals and perceived conflict [39,40], and after increased negative and decreased positive affect [41]. Given that specific emotions may incrementally predict higher risk (eg, feeling stressed) [30,42] or protect more strongly against NSSI (eg, feeling relaxed) [27], the findings will also be analyzed using specific emotions as units of analysis. On the basis of the benefits and barriers model of NSSI [34,43], which argues for a unique role of self-critical thoughts in explaining NSSI behavior, we will evaluate the association between momentary fluctuations in self-critical thinking and NSSI urges and NSSI behavior. Building upon the emotional cascade model [35,44], which posits that reinforcing cyclic cascades between rumination and negative affect form a dynamic process in which self-injury is suggested to break this cycle by distracting from rumination, the utility of momentary ruminative thinking and the interplay with negative emotions in predicting NSSI behavior will be investigated. However, because the relevance of these theoretically inspired within-person risk factors for NSSI might differ between individuals [45,46], we will also determine variability in individual risk associations.

A second primary objective is to advance understanding of the transition from NSSI thoughts and urges to NSSI behavior. Although existing theoretical models of NSSI do not distinguish between NSSI thoughts or urges and NSSI behavior, contemporary “ideation-to-action” theories of suicide explicitly make this distinction [47] and suggest that the factors that lead to suicidal thoughts or urges are not necessarily the same factors that lead to behavior (ie, suicide attempts). Emerging evidence indicates that incorporating ideation-to-action thinking might be equally relevant for NSSI. For instance, preliminary work suggests that previously identified risk factors for NSSI behavior (eg, emotional factors) might uniquely predict NSSI thoughts but not the occurrence of NSSI behavior [27]. Inspired by the cognitive-emotional model of NSSI [33], we anticipate that momentary self-efficacy to resist NSSI will be a potent protective factor against NSSI behavior. People retrospectively report that the transition between NSSI thoughts or urges and NSSI behavior is typically <30 minutes [30,31], meaning that there might be a brief window of opportunity to intervene during these moments of acute risk for NSSI behavior. Therefore, in an attempt to inform and facilitate such intervention efforts, we will make a thought-to-action distinction and clarify the specificity of risk and protective factors to identify factors that increase or decrease the likelihood of transitioning from NSSI thoughts or urges to NSSI behavior in real time among individuals seeking treatment.

A third primary objective is to provide novel data on the co-occurrence of NSSI with other self-damaging behaviors in daily life that may represent different forms of behavior that serve the same function (ie, disordered eating, substance use, and STB) [13,30,48-51]. For example, previous daily diary studies found that 42% to 53% of the adolescents and emerging adults who engage in NSSI reported at least 1 episode of disordered eating and suicidal ideation [40,52], with suicidal thoughts being present on most days when adolescents engaged in NSSI [53]. Similarly, Nock et al [30] observed that NSSI thoughts co-occurred 13% to 18% of the time with thoughts of substance use and disordered eating. Therefore, disordered eating (ie, restrictive eating, binge eating, and purging),

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substance use (ie, binge drinking and smoking cannabis), and STB will be assessed as secondary outcomes. From a transdiagnostic approach, this will help to clarify comorbidity patterns, unique versus shared risk factors, and temporal relationships with other self-damaging behaviors in daily life [13,19,54]. In addition, it will allow us to address whether the dynamic characteristics of NSSI thoughts or urges (ie, an individual's within-person average and variability) and frequency of NSSI behavior—as observed in the EMA—predict changes in NSSI trajectories and the presence of comorbid self-damaging behaviors among individuals seeking treatment [55]. For instance, it may be that persistently high NSSI urges and frequent NSSI behavior increase the risk of STB [53]. Alternatively, there could also be a behavior shift such that a reduced frequency of NSSI leads some individuals to take up another behavior that serves a similar function.

Finally, a secondary aim is to evaluate the perspectives of individuals seeking treatment and mental health professionals regarding the feasibility, scope, and utility of digital self-monitoring and novel interventions. There is a growing awareness that the clinical implementation of EMA and ecological momentary interventions (EMIs), which use EMA to deliver support in real-time, provides new opportunities to make individuals more actively involved in their treatment and to better match treatments to their needs [19,24,56,57]. For instance, EMA could facilitate self-insight about relevant processes [19,58,59], whereas EMIs would allow for providing support outside of the therapy room in daily life. Initial findings indicate the acceptability and potential of EMIs for NSSI and suicide prevention [29,60,61], but, despite the clear clinical potential, this remains a largely underexplored area. Importantly, however, the development of EMIs will advance more rapidly and be more easily clinically implemented when a user-centered design is employed. Such a design actively involves and acknowledges end users from the initial stage of development to understand the goals, challenges, and motivations for future EMIs that seek to facilitate young people's recovery from self-injury and other self-damaging behaviors [62].

Methods

Target Population and Recruitment

To investigate the objectives of the DAILY project, the target population is adolescents (aged 15-18 years), emerging adults (aged 19-29 years), and adults (aged 30-39 years) seeking treatment and their mental health professionals. They are recruited from mental health services across the Flanders region of Belgium, including 9 inpatient services, 8 outpatient services, and 4 services with a hybrid care model. Of these services, 11 focus on emotion dysregulation and mood disorders, 5 focus on social-emotional difficulties in transitioning from adolescence to emerging adulthood, 3 focus on eating disorders, and 2 are private practices. Potential eligible participants are informed about the study via mental health professionals, study flyers, and information moments at these mental health services. The inclusion criteria for patients are as follows: (1) being aged between 15 and 39 years, (2) having sufficient Dutch-language proficiency, (3) past-month NSSI thoughts/behaviors, and (4) receiving inpatient or outpatient treatment. Individuals with cognitive deficits that preclude comprehension of materials are excluded from participation. Although adult participants (aged ≥18 years) could opt to continue participation when they decided to stop treatment, a treating mental health professional had to be involved for minors (<18 years) during the entire monitoring period, meaning that participation automatically ended when they interrupted their treatment before the end of the 28-day EMA protocol. The inclusion criterion for mental health professionals is being a licensed psychiatrist, clinical psychologist, or mental health nurse.

Ethics Approval

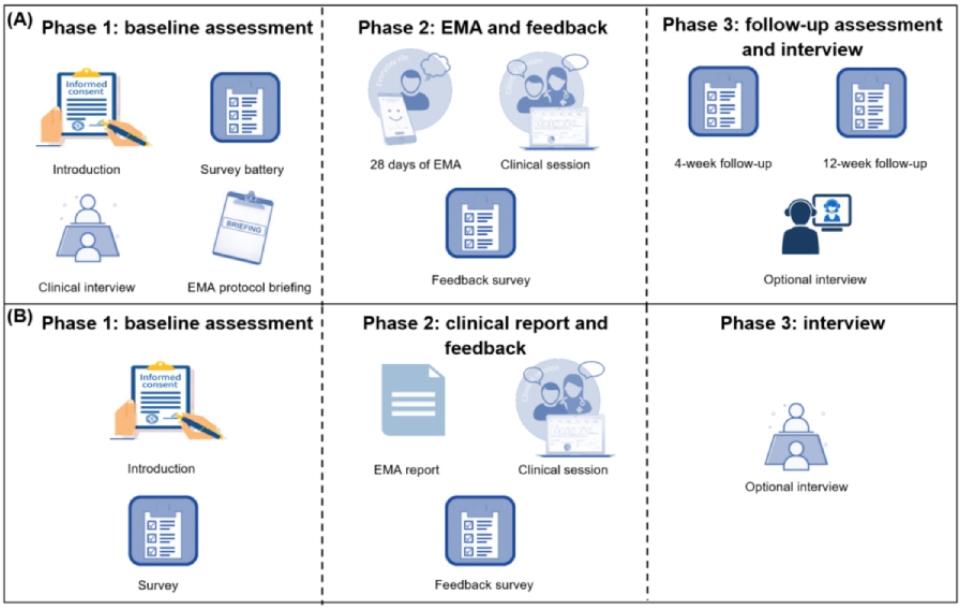
All phases of the DAILY project were approved by the Ethics Committee Research UZ/KU Leuven on February 10, 2021 (s64989 and B3222020000343), and all procedures align with the 1964 Helsinki declaration and its later amendments.

Procedure and Protocol

The DAILY project consists of 3 phases, including a baseline assessment (phase 1), 28 days of EMA followed by a clinical session and feedback survey (phase 2), and 2 follow-up surveys and an optional interview (phase 3). Figure 2 provides a graphical overview of the project.

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Figure 2. Graphical overview of the study procedures for (A) individuals seeking treatment and (B) mental health professionals. EMA: ecological momentary assessment.



Phase 1: In-Person Baseline Assessment of Individuals Seeking Treatment

In the first phase, a psychologist meets with the patient (hereinafter referred to as the participant) to give them detailed information, conduct the baseline assessment, and provide training on completing the EMA protocol. The informed consent process informs participants about the study demands and goals, the safety protocol, reimbursement scheme, the researchers' responsibility concerning risk monitoring, and the implications of this responsibility (ie, when the duty of care overrides the confidentiality principle). All participants provide written informed consent or assent. In addition, parents or legal caregivers provide written informed consent for minors aged 15 to 17 years. The baseline assessment consists of a survey battery and a clinical interview. Table 1 presents the constructs covered in the survey battery assessed via REDCap (Research Electronic Data Capture; Vanderbilt University) [63]. The clinical interview assesses the participants' history of NSSI and STB using the well-validated Self-Injurious Thoughts and Behaviors Interview [64,65]. In addition, the Structured Clinical Interview for DSM-5 [66], is used to assess common comorbid mental disorders, including major depressive disorder, alcohol use disorder, substance use disorder, panic disorder, generalized anxiety disorder, posttraumatic stress disorder, and eating disorders [2,15,22]. Interrater reliability will be examined within a subset of 20% of the diagnostic interviews (approximately 24 participants) by calculating the percentage of agreement and Cohen κ coefficients for overall diagnosis [67]. During the clinical interview, participants are asked about personal strategies that they consider helpful to resist engaging in NSSI and other self-damaging behaviors (see *Phase 2: Safety Measures and Risk Monitoring* section).

Phase 1 concludes with an orientation and training on completing the EMA protocol via m-Path, a user-friendly and secure smartphone app and platform created by researchers at KU Leuven that is General Data Protection Regulation (GDPR)–compliant for real-time and real-world data collection [68]. We assign all participants a study alias to ensure that no identifying information is shared with the software platform. All communication between participants' smartphones and the server is end-to-end encrypted and securely uploaded after each interaction [68]. Participants without a smartphone are loaned a device with a prepaid data plan for data collection. Study staff help participants to download the app on their phone (Android or IOS) or the loaned device (Android), discuss the EMA protocol's content and procedures, answer participants' questions, and initiate a practice EMA survey for the participant. Phase 1 takes approximately 3 to 4 hours to complete.

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Table 1. Overview of the variables assessed in the baseline survey battery and clinical interview.

Baseline assessment	Measure	Source	Items, n; response scale
Survey battery			
Sociodemographic information	Age, gender, education, profession, and sexual orientation	Items from Kiekens et al [2] and self-developed	6; mixed
Trait negative and positive affect	Positive and Negative Affect Schedule	Original [69] and Dutch translation [70]	20; 5-point Likert scale
Trait rumination	Ruminative Response Scale	Original [71] and Dutch translation [72]	22; 4-point Likert scale
Trait perseverative thinking	Perseverative Thinking Questionnaire	Original [73] and Dutch translation [74]	15; 5-point Likert scale
Trait self-criticism and self-reassurance	Forms of Self-Criticizing or Attacking and Self-Reassuring Scale	Original [75] and Dutch translation [76]	22; 5-point Likert scale
Trait emotion dysregulation	Difficulties in Emotion Regulation Scale-Short Form	Original [77] and Dutch translation [78]	18; 5-point Likert scale
Trait negative and positive urgency	UPPS-P[a] Impulsive Behavior Scale	Original [79] and Dutch translation [80]	26; 4-point Likert scale
Identity	Identity scale from the Erikson Psychosocial Stage Inventory	Original [81] and Dutch translation [82]	12; 5-point Likert scale
Depression, anxiety, and stress[b]	Depression, anxiety, and stress scales (past week)	Original [83] and Dutch translation [84]	21; 4-point Likert scale
NSSI[c] expectancies	Nonsuicidal Self-Injury Expectancy Questionnaire	Original [85] and Dutch translation: FBT[d]	25; 5-point Likert scale
Self-efficacy to resist NSSI in the next weeks and across contexts	Adapted Self-Efficacy to Avoid Suicide Action Scale; Self-Efficacy to Resist Nonsuicidal Self-Injury Scale	Original [86] and Dutch translation [27]; Original [87], and Dutch translation: FBT	6; 10-point scale; 24; 4-point Likert scale
Disordered eating behaviors and attitudes[b]	Eating Disorder Examination Questionnaire (version 6.0)	Original [88] and Dutch translation [89]	30; mixed
Positive body image	Body Appreciation Scale-2	Original [90] and Dutch translation [91]	10; 5-point Likert scale
Expectancies about eating	Subscales of the Eating Expectancy Inventory	Original [92] and Dutch translation [93]	28; 7-point Likert scale
Eating and body image self-efficacy	Eating Disorder Recovery Self-Efficacy Questionnaire	Original [94] and Dutch translation: FBT	23; 7-point Likert scale
Borderline personality disorder	McLean Screening Instrument for Borderline Personality Disorder	Original [95] and Dutch translation [96]	10; dichotomous scale
Damaging and impulsive behaviors[b]	Self-developed assessment of 13 behaviors	N/A[e]	13-26; mixed
Self-efficacy to resist drinking	Drinking Refusal Self-Efficacy Questionnaire-Revised	Original [97] and Dutch translation [98]	19; 6-point Likert scale
General self-efficacy	General Self-Efficacy Scale	Original [99] and Dutch translation [100]	10; 4-point Likert scale
Perceived social support	Multidimensional Scale of Perceived Social Support	Original [101] and Dutch translation [102]	16; 5-point Likert scale
Rejection	Perceived Rejection Scale of Adult Toolbox Social Relationship Scales	Original [103] and Dutch translation: FBT	8; 5-point Likert scale
Affinity with technology	Adapted Affinity for Technology Scale	Original [104] and Dutch translation: FBT	10; 7-point Likert scale
Clinical interview			
NSSI thoughts, NSSI behaviors, DSM-5[f] NSSI disorder, suicide ideation, suicide plan, suicide attempt, age of onset, frequency, recency, functions of NSSI, experience of pain during NSSI, and impact of NSSI[b]	Adapted Self-Injurious Thoughts and Behaviors Interview	Original [64] and Dutch translation [22]	29-41; mixed

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Baseline assessment	Measure	Source	Items, n; response scale
Self-efficacy to resist suicide[b]	Self-Efficacy to Avoid Suicide Action Scale	Original [86] and Dutch translation [27]	6; 10-point scale
Major depressive disorder, alcohol use disorder, substance use disorder, panic disorder, generalized anxiety disorder, posttraumatic stress disorder, and eating disorders	Structured Clinical Interview for DSM-5	Original [66] and Dutch translation [105]	18-310; mixed

[a]UPPS-P: urgency, premeditation, perseverance, sensation seeking, and positive urgency.

[b]Reassessed in the web-based follow-up surveys 4 and 12 weeks after the 28-day real-time monitoring period.

[c]NSSI: nonsuicidal self-injury.

[d]FBT: forward-backward translation.

[e]N/A: not applicable.

[f]DSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.

Phase 1: Web-Based Baseline Assessment of Mental Health Professionals

Each mental health professional also provides informed consent the first time and completes a brief survey assessing sociodemographic (age and gender) and professional information (profession, level of education, and years of experience). In addition, they can provide the research team with 1 to 3 additional EMA questions when considered relevant for a specific individual.

Phase 2: EMA Sampling Design and Content

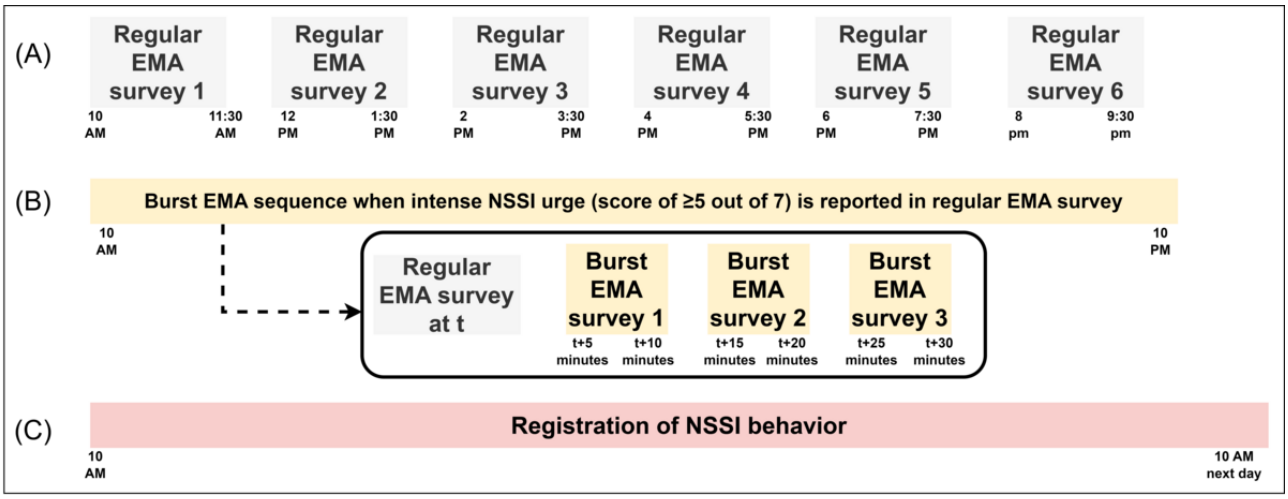
The second phase starts on the morning after the baseline assessment. It involves a 28-day EMA protocol that consists of (1) six semirandom regular EMA surveys administered on average every 2 hours during waking hours between 10 AM and 9:30 PM, (2) three burst EMA surveys spaced at a higher frequency of 5 to 10 minutes apart in the 30 minutes after intense NSSI urges are reported in the regular EMA surveys (score of ≥5 on a 7-point item), and (3) event registrations via a push button to record the timing of NSSI behavior. Figure 3 shows the sampling schedule of the DAILY project, which includes a minimum of 168 regular EMA surveys and a theoretical maximum of 672 EMA surveys (when a burst sequence is triggered during each regular survey). To ensure that we capture people in their ongoing activities and to avoid retrospective reporting, participants must register responses to the regular EMA within 15 minutes of receipt and to the burst EMA surveys within 5 minutes of receipt. In case of nonresponse to the regular EMA surveys, 1 reminder is sent after 10 minutes. After the first day and each week subsequently, a team member telephoned the participants to check whether everything is going well, provide feedback about study compliance, and respond to concerns or difficulties concerning the app and the self-monitoring.

Table 2 presents the EMA constructs and items in the DAILY project, including emotions and cognitions (block A); contextual information and social appraisals (block B); NSSI thoughts, NSSI urges, self-efficacy to resist NSSI, and NSSI behavior (block C); and the screening of other self-damaging behaviors and experienced momentary burden (block D, part 1). EMA items were as much as possible selected or modified from prior EMA studies and conventional survey questionnaires [27,86,90,106-108]. Questions are branched so that participants only have to complete relevant EMA items (eg, social appraisals are context specific). The order in which emotions and cognitions are presented is randomized within individuals across the EMA surveys (because these items are not conditional on each other). Specific emotions for negative and positive affect are selected because they represent all 4 quadrants of the affective circumplex defined by valence and arousal dimensions [109]. All continuous EMA items are assessed on 7-point rating scales ranging from not at all or absent to very much or very strong (Table 2). Although NSSI behavior is assessed retrospectively during each EMA survey (ie, “Since the last beep, have you deliberately hurt yourself without wanting to die?”), participants are instructed to register the timing of NSSI behavior through an event marker. This occurred on a wearable wireless device (Chill Band +; IMEC International) for the first 12 participants. However, owing to practical and technical issues with these devices, the remaining participants used an event registration push button in the m-Path app [68].

During each regular EMA survey, we also screened whether participants experienced thoughts, had an urge, or engaged in 6 other self-damaging behaviors, including restrictive eating, purging, binge eating, STB, binge drinking, and smoking cannabis (block D, part 1). If they answer ≥1 of these self-damaging behaviors affirmatively, additional items assess thoughts, urges, behavior engagement, and self-efficacy to resist the endorsed behavior(s) (block D, part 2, Table 3). Finally, participants rate the extent to which they consider an EMA survey burdensome. The regular EMA surveys include 28 to 31 items (excluding optional individual-specific questions), with 4 additional items for each of the other self-damaging behaviors endorsed on the screening item (Table 3). The burst EMA surveys include 21 to 22 items, assessing only emotions and cognitions (block A) and NSSI outcomes (block C).

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Figure 3. Graphical overview of the ecological momentary assessment (EMA) sampling schedule. (A) Six semirandom regular EMA surveys taken on average every 2 hours during waking hours between 10 AM and 9:30 PM. (B) Three burst EMA surveys spaced at a higher frequency of 5 to 10 minutes apart in the 30 minutes after intense nonsuicidal self-injury (NSSI) urges in the regular EMA surveys. (C) Event registrations via a push button to register the timing of NSSI behavio.



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Table 2. Ecological momentary assessment (EMA) constructs and items.

EMA constructs[a]	Items	Response category
Block A: emotions and cognitions (17 items)		
Momentary negative affect	• [Right now]: "I feel anxious," "I feel stressed," "I feel irritated," "I feel sad," and "I feel insecure"	• 7-point scale (ranging from not at all to very much)
Momentary positive affect	• [Right now]: "I feel cheerful" and "I feel relaxed"	• 7-point scale (ranging from not at all to very much)
Momentary emptiness	• [Right now]: "I feel empty"	• 7-point scale (ranging from not at all to very much)
Momentary loneliness	• [Right now]: "I feel lonely"	• 7-point scale (ranging from not at all to very much)
Momentary emotion dysregulation	• [Right now]: "My emotions are overwhelming me"	• 7-point scale (ranging from not at all to very much)
Momentary rumination	• [Right now]: "I am repeatedly thinking about the same problem"	• 7-point scale (ranging from not at all to very much)
Momentary self-criticism	• [Right now]: "I am disappointed in myself"	• 7-point scale (ranging from not at all to very much)
Momentary other-criticism	• [Right now]: "I am disappointed in others"	• 7-point scale (ranging from not at all to very much)
Momentary body image	• [Right now]: "I am satisfied with the way I look" and "I feel at ease in my body"	• 7-point scale (ranging from not at all to very much)
Momentary identity	• [Right now]: "I doubt who I am" and "I know what I stand for"	• 7-point scale (ranging from not at all to very much)
Block B: contextual information and social appraisals (5-7 items)		
Momentary situational context	• "Where are you?"	• (a) At home; (b) at a friend's or family's place; (c) school or work; (d) car, train, bus; (e) other indoors; (f) other outdoors
Momentary activity	• "What were you doing just before the beep?" • (If g) "Please describe briefly what you are doing"	• (a) Nothing, (b) work or studying, (c) household chores, (d) conversation, (e) leisure active (eg, sports), (f) leisure passive (eg, watching television), (g) something else
Momentary appraisal of activity	• "I enjoy this activity"	• 7-point scale (ranging from not at all to very much)
Momentary social context	• "Are you alone or with others?" • (If b) "Who are you with physically?" • (If c) "Who are you with online?"	• (a) Alone, (b) others physically, (c) others on the web • (a) Partner, (b) family, (c) friends, (d) colleagues, (e) acquaintances, (f) other patients, (g) unfamiliar people
Momentary appraisal of social context	• (If a): "I like being alone" • (If b): "I enjoy the company of these people" • (If c): "I feel connected to those I am online in contact with"	• 7-point scale (ranging from not at all to very much) • 7-point scale (ranging from not at all to very much) • 7-point scale (ranging from not at all to very much)
Block C: NSSI[b] (4-5 items)		
Retrospective thoughts	• "Since the last beep, have you considered deliberately hurting yourself without wanting to die?"	• 7-point scale (ranging from not at all to very much)
Momentary urge	• "Right now, how strong is the urge present to hurt yourself without wanting to die?"	• 7-point scale (ranging from absent to very strong)
Retrospective behavior	• "Since the last beep, have you deliberately hurt yourself without wanting to die (for example, cut, scratched, or hit yourself)?"	• (a) No, (b) yes

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EMA constructs[a]	Items	Response category
Retrospective behavior (method)	• (If b): "How have you self-injured?"	• (a) Cutting or carving, (b) scratching, (c) hitting, (d) burning, (e) biting, (f) head banging, (g) wound interfering, (h) other method (describe briefly)
Momentary self-efficacy to resist	• "Right now, how confident are you that you can resist engaging in NSSI?"	• 7-point scale (ranging from not at all to very)
Block D (part 1): screen other self-damaging thoughts or behaviors and interference (2 items)		
Screen comorbid thoughts or behaviors	• "Indicate all other behaviors you thought about or engaged in since the last beep, or for which you have an urge right now"	• (a) Restrictive eating, (b) binge eating, (c) vomiting deliberately, (d) killing myself, (e) binge drinking, (f) using cannabis, (g) none of these
Interference	• "This beep disturbed me."	• 7-point scale (ranging from not at all to very much)

[a]Blocks A to D are assessed in the regular EMA surveys. Blocks A and C are only assessed in the burst EMA surveys.

[b]NSSI: nonsuicidal self-injury.

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Table 3. Ecological momentary assessment of other self-damaging behaviors[a].

Block D (part 2): Other self-damaging behaviors and items	Response category
Restrictive eating (4 items)	
Retrospective thoughts	
Since the last beep, have you thought about eating less to control your weight?	7-point scale (ranging from not at all to very much)
Momentary urge	
Right now, how strong is the urge to eat less to control your weight?	7-point scale (ranging from absent to very strong)
Retrospective behavior	
Since the last beep, have you eaten less to control your weight?	(a) No, (b) yes
Momentary self-efficacy to resist	
Right now, how confident are you that you can resist eating less to control your weight?	7-point scale (ranging from not at all to very)
Binge eating (4 items)	
Retrospective thoughts	
Since the last beep, have you thought about eating an unusually large amount of food?	7-point scale (ranging from not at all to very much)
Momentary urge	
Right now, how strong is the urge to eat an unusually large amount of food?	7-point scale (ranging from absent to very strong)
Retrospective behavior	
Since the last beep, have you experienced a binge-eating episode?	(a) No, (b) yes
Momentary self-efficacy to resist	
Right now, how confident are you that you can resist eating an unusually large amount of food?	7-point scale (ranging from not at all to very)
Purging (4 items)	
Retrospective thoughts	
Since the last beep, have you thought about vomiting deliberately?	7-point scale (ranging from not at all to very much)
Momentary urge	
Right now, how strong is the urge to vomit deliberately?	7-point scale (ranging from absent to very strong)
Retrospective behavior	
Since the last beep, have you vomited deliberately?	(a) No, (b) yes
Momentary self-efficacy to resist	
Right now, how confident are you that you can resist vomiting deliberately?	7-point scale (ranging from not at all to very)
Suicidality (4 items)	
Retrospective thoughts	
Since the last beep, have you thought about killing yourself?	7-point scale (ranging from not at all to very much)
Momentary urge	
Right now, how strong is the urge to kill yourself?	7-point scale (ranging from absent to very strong)
Retrospective behavior	
Since the last beep, have you made a suicide attempt?	(a) No, (b) yes
Momentary self-efficacy to resist	
Right now, how confident are you that you can resist attempting suicide?	7-point scale (ranging from not at all to very)
Binge drinking (4 items)	
Retrospective thoughts	
Since the last beep, have you thought about consuming an unusually large amount of alcohol?	7-point scale (ranging from not at all to very much)
Momentary urge	

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Block D (part 2): Other self-damaging behaviors and items	Response category
Right now, how strong is the urge to consume an unusually large amount of alcohol?	7-point scale (ranging from absent to very strong)
Retrospective behavior	
Since the last beep, have you consumed an unusually large amount of alcohol?	(a) No, (b) yes
Momentary self-efficacy to resist	
Right now, how confident are you that you can resist consuming an unusually large amount of alcohol?	7-point scale (ranging from not at all to very)
Cannabis use (4 items)	
Retrospective thoughts	
Since the last beep, have you thought about smoking cannabis?	7-point scale (ranging from not at all to very much)
Momentary urge	
Right now, how strong is the urge to smoke cannabis?	7-point scale (ranging from absent to very strong)
Retrospective behavior	
Since the last beep, have you smoked cannabis?	(a) No, (b) yes
Momentary self-efficacy to resist	
Right now, how confident are you that you can resist smoking cannabis?	7-point scale (ranging from not at all to very)

[a]These other self-damaging behaviors are only assessed when screened positively in block D (part 1; Table 2) in the regular ecological momentary assessment surveys.

Phase 2: Safety Measures and Risk Monitoring

Participants are provided a 1-page information sheet with the contact information of the research team (study-specific telephone number and email address) as well as suicide and crisis hotlines during the baseline enrollment (phase 1). Although research suggests no reactivity or iatrogenic effects of repeated questioning about self-injurious thoughts and behaviors [110-112], there should be a proper safety protocol that not only matches participants' needs [113] but also does not inadvertently defeat the study's observational purpose [19,114]. Therefore, several measures are in place to support and safeguard participants' safety during the EMA period. First, an automatic pop-up screen with resources is shown at the end of a regular EMA survey whenever a participant indicates an intense urge for NSSI or any other self-damaging behavior (response 6 or 7 on a 7-point scale). This pop-up item contains either standard resources that signpost participants to relevant support organizations, family and friends, and their mental health professional or the personal resources provided by the participant during phase 1 (randomized within individuals across surveys with an equal probability of 0.5).

Second, a safety protocol is activated whenever a participant reports having attempted suicide or is at imminent risk for attempting suicide, operationalized as having an intense urge to attempt suicide (response 6 or 7 on a 7-point scale) combined with momentary low self-efficacy to resist this suicidal urge (responses 1-3 on a 7-point scale). A second automatic pop-up screen is triggered whenever this response pattern occurs, encouraging participants to provide more in-the-moment information within an open text field. After submitting this item (even when left blank), this response pattern issues an alert to the research team (ie, flagged email to the study account that is consistently monitored during recruitment hours). This information is then shared via telephone with clinical staff members on duty at the care facility for inpatients, after which they take appropriate action. The participating mental health professional also receives an email with this information. When the safety alert concerns an outpatient, a licensed clinical psychologist from the research team conducts the risk assessment by telephone. For minors, the parents or legal guardians are also contacted by telephone when a minor participant cannot be reached or when the clinical psychologist of the research team considers this necessary after a risk assessment.

Phase 2: Feedback Report, Clinical Session, and Feedback Surveys

After the EMA period, a feedback report is shared with the mental health professional to be discussed during a regular therapy session. The report contains person-specific data on (1) general psychological functioning (ie, emotions and cognitions) and contextual information (eg, distribution of time alone vs with others face-to-face or on the web and activities in daily life); (2) the course of NSSI thoughts, NSSI urges, self-efficacy to resist NSSI, and NSSI behavior; and (3) the occurrence and intensity of other self-damaging thoughts and behaviors during the 28-day monitoring period. The section on general functioning includes pie charts displaying the proportion of time that someone spends across different contexts and box plots showing the median and variability of emotional and cognitive states. The section on NSSI provides information on the distribution and single-day average of NSSI thoughts, urges, and self-efficacy to resist NSSI (box plot and time series graphs). For example, high-risk days are operationalized as days on which the single-day average urge of NSSI is high (ie, mean response between 5-7 on a 7-point scale), coupled with low single-day average self-efficacy to resist NSSI (ie, mean response between 1-3 on a 7-point scale). In addition, the frequency of NSSI behaviors and types of methods are

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described, and NSSI urges are visualized across different situational, activity, and social contexts (bar charts). We also provide information about the occurrence of other self-damaging behaviors during the 28-day monitoring period. If the enrolled mental health professional cannot discuss the EMA feedback report (eg, because of treatment dropout or organizational issues), the patient can decide to have this session with another mental health professional or a clinical psychologist from the research team.

After the clinical session, an email is sent containing a link to a survey that assesses patients' and mental health professionals' experience of EMA and their perspectives on the EMA feedback report (Table 4). In case of nonresponse, 2 weekly reminders are sent. At this initial stage, we explore intrapersonal (ie, self-reflection and insight, self-efficacy, and subjective experiences) and interpersonal changes (ie, working alliance and helpful aspects during the clinical session) associated with the experience of EMA and the use of the EMA feedback report in treatment. The feedback survey also includes open questions assessing attitudes about self-monitoring, the content of the items, the feasibility of EMA, and the potential of EMIs for NSSI and other self-damaging behaviors (Table 4).

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Table 4. Overview of constructs assessed in the feedback survey.

Survey battery	Measure and example item	Source	Items, n; response scale
Self-insight and reflection in general[a]	Adapted Self-Reflection and Insight Scale: "The self-monitoring made me more aware of my feelings and thoughts"	Original [116] and Dutch translation: FBT[b]	8; 6-point Likert scale
Self-efficacy in general	Adapted Self-Efficacy Scale: "By what I learned about myself through the self-monitoring, I feel that I am better able to solve difficult problems if I try hard enough"	Original [99] and Dutch translation [100]	10; 4-point Likert scale
Self-insight and reflection with respect to NSSI[c] and other self-damaging behaviors[a]	Adapted Self-Reflection and Insight Scale: (1) experience of EMA[d]: "The self-monitoring made me more aware of my triggers for self-injury" and (2) use of EMA in therapy: "Discussing the monitoring results together with my clinician made me more aware of my triggers for self-injury"	Original [116] and Dutch translation: FBT	10; 6-point Likert scale
Self-efficacy resisting NSSI and other self-damaging behaviors	Adapted Self-Efficacy Scale: (1) experience of EMA: "By what I learned about myself through the self-monitoring, I now know better what to do when I am experiencing an urge to self-injure" and (2) use of EMA in therapy: "By discussing the monitoring results together with my clinician, I now know better what to do when I am experiencing an urge to self-injure"	Original [99] and Dutch translation [100]	10; 4-point Likert scale
Effect of discussing EMA results in therapy on the working alliance[a]	Adapted Working Alliance Inventory (short version): (1) task: "Discussing the results together helped us to understand which changes I need to make," (2) bond: "I feel my clinician understands me better because of the monitoring results," and (3) goal: "Discussing the results together makes me feel we are both working toward the same goals in therapy"	Original [117] and Dutch translation: FBT	12; 6-point Likert scale
Helpful aspects during clinical session[a]	Questions assessing any helpful or hindering aspects of the session and experience of clinician and therapeutic session as engaging and supportive, open and authentic, empathic, explorative, confrontational, and making positive progress: "I believe that my problems can be addressed through therapy"	Original [118] and Dutch translation [119]	40; mixed
Subjective experiences of EMA	Questions assessing (1) negative experience: "The self-monitoring questions caused me stress," (2) positive experience: "I enjoyed the self-monitoring," (3) learning experience: "I would describe the self-monitoring as a learning experience," and (4) facilitates self-regulation: "The self-monitoring questions helped me to structure my thoughts"	Self-developed	12; 5-point Likert scale
Expectations of feedback and compensation	Questions assessing the overall and relative importance of receiving study findings, personal feedback, and financial compensation	Items from Kiekens et al [19] and self-developed	11; mixed
Qualitative feedback	Questions assessing attitudes about self-monitoring, content of the items, length of questionnaires, experience and feasibility of self-monitoring, utility and potential effect on the therapy process, and utility and scope of future interventions	Self-developed	10; open questions

[a]Clinician version also included these questions.

[b]FBT: forward-backward translation.

[c]NSSI: nonsuicidal self-injury.

[d]EMA: ecological momentary assessment.

Phase 3: Follow-up Surveys After 1 and 3 Months and (Optional) Interviews About Experiences and Attitudes Toward EMA and EMIs

Phase 3 includes 2 brief web-based follow-up surveys after 4 and 12 weeks and an optional interview. The surveys assess past-week psychological distress and the presence of NSSI and other self-damaging behaviors since completing the self-monitoring (first survey) or between the follow-up surveys (second survey; see questionnaires indicated with subscript in Table 1). In case of nonresponse, 2 weekly reminders are sent. The qualitative interviews assess more in depth the experiences of using EMA and the utility, content, and design of future EMIs for NSSI among a voluntary subsample of individuals seeking treatment (online after the feedback session) and mental health professionals (on site after they have participated with at least

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2 patients in the study). The interview guides can be consulted on the project's Open Science Framework (OSF) page [115].

Participant Incentives and Engagement

Participants are recognized as valued contributors to the research and receive financial incentives, information about the overall findings, and feedback on their data. Patients are financially compensated via a structured financial scheme when (1) the feedback survey (if the EMA report was discussed) and (2) at least 1 of the follow-up surveys are completed: €35 (approximately US $38) if compliance with the monitoring protocol is >33% (or >55 EMA surveys), €70 (approximately US $76) if compliance is >65% or (>109 EMA surveys), and €100 (approximately US $109) if compliance is >83% (or >139 EMA surveys). Otherwise, patients receive €20 (approximately US $22) in financial compensation. In addition, personalized feedback reports are provided so that relevant information can be fed back into the therapy room. Patients can also opt in to receive updates on the general findings of the project. Finally, mental health professionals receive €10 (approximately US $11) as compensation for completing the feedback survey after the clinical session in which they discuss the EMA feedback report. We do not provide a financial incentive for participation in the interviews (phase 3).

Research Training and Well-being

All research activities are performed by clinically trained research staff. Risk monitoring of people who frequently self-injure requires good-quality training in working with individuals who engage in NSSI and are at increased risk for suicide [19]. Therefore, research staff who interact with participants and are part of the risk-monitoring team are licensed clinical psychologists who have received additional training that covered how to support participants during an acute suicidal crisis. In addition, although there is a psychologist *on call* outside of office hours, responsibility is always shared with the first and second authors (GK: PhD level and good clinical practice certified and LC: PhD level and cognitive behavioral therapist), who are available for supervision by telephone during recruitment hours. Finally, there are regular debriefings to ensure the well-being of all team members throughout the study's data collection period.

Statistical Analyses

Overview

The psychometric properties of baseline measures (eg, Cronbach α), EMA multi-item scales (eg, multilevel reliability [120]), and interrater reliability of diagnostic interviews (a subset of 20% of the sample, approximately 24 participants) will be reported. To accommodate the hierarchical structure of the EMA data (eg, observations nested within individuals), our 3 primary aims will be analyzed by using a combination of statistical techniques. First, descriptive statistics (eg, means, modes, SDs, intraclass coefficients, and correlations) will be used to describe the sample in terms of baseline characteristics; compliance rates; presence; comorbidity patterns; and moment-to-moment variability of NSSI outcomes across minutes, hours, days, and weeks. Second, we will use dynamic structural equation modeling (DSEM), which integrates three modeling approaches [121,122]: (1) time series analysis, which allows for modeling the lagged relation between repeated measures in a single participant; (2) multilevel modeling, which takes the higher-order data structure into account and models these relationships for multiple participants while capturing variability within and between persons over time; and (3) structural equation modeling, which takes measurement error into account and allows for multiple outcome variables, latent variables, and mediation effects [123].

Using DSEM will clarify the extent to which momentary factors at time point t_{-1} (eg, negative affect) predict NSSI thoughts, NSSI urges, self-efficacy to resist NSSI, and NSSI behavior (or other self-damaging behaviors) at time point *t*, above and beyond the lagged version of the outcome variable (ie, the autoregressive parameter) and confounding variables at time point t_{-1} (eg, NSSI urges in the prediction of NSSI behavior). We will attempt to include random intercepts (predictors and outcomes) and random slopes (predictors) for momentary variables, with an unrestricted correlation structure if models converge (the maximum number of iterations is 50,000 by default). The time interval (Tinterval) statement will account for unequally spaced intervals owing to missing data and random sampling within blocks, with missing data handled using a Kalman filter approach [122]. Given that all participants have a recent history of NSSI but do not necessarily engage in other self-damaging behaviors, models that investigate within-person associations with disordered eating, substance use, and STB will be based on a subsample of participants that show variation in these secondary outcomes.

Third, we will use group iterative multiple model estimation (R package *gimme* [124]) to assess between-person variability in risk associations. Group iterative multiple model estimation estimates a unified structural equation model that includes lagged and contemporaneous relations in a network model [124,125] and accurately recovers group-, subgroup-, and individual-level associations in time series data. Fourth, fully idiographic modeling will be applied based on each participant's time series data to identify the most relevant factors for each individual without overfitting models [126,127]. Elastic net regularization will be used as a statistical classification approach, which produces sparse models through coefficient penalization with k-fold cross-validation (R package *glmnet* [128]). Fifth, survival analysis will be used to investigate the factors that predict the transition from intense NSSI urges to behavior [129]. Importantly, however, as the analysis of intensive longitudinal data is a burgeoning field, newly available methods will also be considered (eg, continuous-time and Markov switching models [130-133]).

Finally, the secondary objective will be analyzed using a mixed methods approach. We will use thematic analysis to evaluate open-ended questions and interview data regarding end users' experiences and perspectives [134]. Quantitative questionnaire data will be analyzed using descriptive statistics and regression analyses to explore associations with demographic and clinical characteristics.

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Expected Sample Size

We intend to recruit 120 individuals seeking treatment. Analyses that include 100 to 120 participants will yield sufficient statistical power (≥0.80) to detect within-person effects as small as 0.07 to 0.09 in multilevel autoregressive models. These power calculations were conducted using Monte Carlo simulations with the following conservative estimates [135]: a 1:0.67 ratio of random intercept to within-person residual deviation, a 1:0.25 ratio of random intercept to random slope SD, first-order and slope-intercept correlations of 0.5, and compliance of 60% to the regular EMA surveys. Recent studies have used pooled machine learning models with fewer observations and participants [127]. In addition, it has been shown recently that as few as 60 assessments from 25 individuals allow robust estimation of general, shared, and person-specific temporal associations in intensive longitudinal data [136].

Open Science Statement

All materials of the DAILY project can be consulted on the project's OSF page [115]. We will make the analysis plan, materials, and code of results in scientific publications available on the OSF page [137]. In addition, preprints will be uploaded on the PsyArXiv platform to ensure that findings are available to the wider research community. We do not have institutional review board approval to make the master data set publicly available, but we will make deidentified data available upon request for reproducibility purposes.

Results

The study is funded by a postdoctoral fellowship from the Research Foundation Flanders (Belgium) awarded to the first author (June 2020: 12ZZM21N; Multimedia Appendix 1). The recruitment of participants began in June 2021 and data collection is anticipated to conclude in August 2023.

Discussion

Principal Findings

The DAILY project is expected to advance scientific knowledge of (1) the short-term course and within-person risk and protective factors of NSSI thoughts, NSSI urges, self-efficacy to resist NSSI, and NSSI behavior among individuals seeking treatment; (2) the transition from NSSI thoughts and urges to NSSI behavior; and (3) the comorbidity patterns, unique versus shared risk factors, and temporal relationships of NSSI with other self-damaging behaviors. Such information will inform clinical practice about how, why, and when self-injury and other self-damaging behaviors unfold in the everyday lives of individuals seeking treatment. Building upon these findings, we will explore the experiences and perspectives of end users (ie, people with lived experience and their mental health professionals) about the feasibility, scope, and utility of EMA and EMIs as digital clinical tools in treatment. This will provide the scientific building blocks for novel intervention approaches outside of the therapy room to support individuals who self-injure in real time. For instance, a sophisticated EMI that shows promise for dynamic behaviors such as NSSI and STB is just-in-time adaptive interventions [29,138,139]. This highly innovative intervention design adapts the provision of support in terms of type, intensity, and timing to an individual's changing status and context to facilitate real-time interventions when and where they are needed most in everyday life and in ways that are appropriate and evidence based [140].

Limitations

Although EMA is a powerful methodology that can now more readily be used to provide previously unavailable information about the course, within-person predictors, comorbidity patterns, and clinical outcomes of NSSI in daily life [19], it is crucial to consider the implications and limitations of the protocol used and the design when interpreting the project's findings. First, although measures are in place to ensure that recruitment is inclusive and geographically representative, with recruitment sites spread across the entire Flanders region of Belgium, it should be acknowledged that we use convenience sampling, with the targeted sample comprising individuals currently receiving mental health treatment. This implies that the findings should not be generalized to nonclinical populations because the short-term course of NSSI will likely differ in severity for community samples. Relatedly, adolescents can only participate from the age of 15 years, meaning that the findings are not generalizable to early adolescents (aged 10-14 years) and should be studied in this population. Second, the intensive sampling scheme matches the project's research objectives but involves a higher burden than traditional longitudinal studies (typically 1-5 surveys months to years apart) and most EMA studies (typically lasting 1 week) [26]. Although scholars have observed increased burden with longer questionnaires but not with increased sampling frequency among community samples [141], it should be investigated to what extent the current EMA sampling scheme and duration were considered feasible by all individuals seeking treatment. Third, we implemented safety measures for NSSI and other self-damaging behaviors (including the monitoring of suicide risk) based on prespecified cutoffs of momentary urges and low self-efficacy to resist a behavior. Future research would benefit from evaluating risk thresholds and the utility of different safety measures (eg, personal vs standard message and human-led vs automatic action) at varying risk levels for self-damaging behaviors.

Fourth, we operationalize NSSI and other self-damaging behaviors comprehensively (ie, thoughts, urges, and behavior) and assess a broad range of theoretically relevant factors (emotions, cognitions, contextual information, and social appraisals); however, as a consequence, most constructs rely on single EMA items that were selected from prior EMA studies or modified from conventional survey questionnaires to keep the workload for participants under control [141]. However, against the backdrop of a lack of psychometrically validated items for assessing psychological constructs with EMA [142] and a need to develop standardized measures [143], we will calculate the multilevel reliability of composite constructs (eg, negative affect) and made all EMA items (for the original Dutch items see the OSF page) publicly available [107]. Fifth, we provided additional (shorter) EMA surveys when participants report intense NSSI urges and contact participants and clinical staff when there is an increased suicide risk, which might result in underreporting of NSSI urges and STB. Sixth, because all

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participants receive mental health treatment, there might be structural changes in the descriptive patterns of self-damaging thoughts and behaviors across the monitoring period. We will evaluate this, and if the assumption of stationarity is violated, we will include days since study enrollment as a covariate for the outcome under investigation. Finally, we may miss moments leading up to self-damaging behaviors in the late evening and overnight as no EMA surveys are scheduled after 10 PM. Although we can assess to what extent this is the case for NSSI behavior (as people could register self-injury via the push button in the m-Path app), future research might benefit from sampling schemes adapted to people's sleep and wake-up times.

Conclusions

Notwithstanding the limitations, the findings of the DAILY project will provide a detailed characterization of the course and patterns of risk for NSSI during treatment by considering NSSI thoughts, NSSI urges, self-efficacy to resist NSSI, and NSSI behavior in the daily lives of individuals seeking treatment. This will help to increase our understanding of how NSSI unfolds across minutes, hours, days, and weeks. Filling these critical knowledge gaps using EMA will lay the foundation for, and guide, the development of novel interventions that support people when and where it matters most in daily life [29,138]. This scientific endeavor may facilitate young people's recovery from self-injury and ultimately could help us prevent loss of life.

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Data Availability

Data sharing is not applicable to this paper as no data sets were analyzed.

Conflicts of Interest

MKN receives publication royalties from Macmillan, Pearson, and UpToDate. He has been a paid consultant in the past 3 years for Microsoft Corp, the Veterans Health Administration, and COMPASS Pathways, as well as for legal cases regarding a death by suicide. He has stock options in Cerebral Inc. He is an unpaid scientific advisor for Empatica, Koko, and TalkLife.

Multimedia Appendix 1
Peer review reports from Fonds voor Wetenschappelijk Onderzoek – Vlaanderen (FWO)/ Research Foundation Flanders (Belgium).
[PDF File (Adobe PDF File), 880 KB - resprot_v12i1e46244_app1.pdf]

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Abbreviations

DAILY: Detection of Acute rIsk of seLf-injurY
DSEM: dynamic structural equation modeling
DSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
EMA: ecological momentary assessment
EMI: ecological momentary intervention
GDPR: General Data Protection Regulation
NSSI: nonsuicidal self-injury
OSF: Open Science Framework
REDCap: Research Electronic Data Capture
STB: suicidal thoughts and behaviors

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Protocol

Real-Time Real-World Digital Monitoring of Adolescent Suicide Risk During the Six Months Following Emergency Department Discharge: Protocol for an Intensive Longitudinal Study

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Abstract

Background: Suicide is the second leading cause of death in adolescents, and self-harm is one of the strongest predictors of death by suicide. The rates of adolescents presenting to emergency departments (EDs) for suicidal thoughts and behaviors (STBs) have increased. Still, existing follow-up after ED discharge is inadequate, leaving a high-risk period for reattempts and suicide. There is a need for innovative evaluation of imminent suicide risk factors in these patients, focusing on continuous real-time evaluations with low assessment burden and minimal reliance on patient disclosure of suicidal intent.

Objective: This study examines prospective longitudinal associations between observed real-time mobile passive sensing, including communication and activity patterns, and clinical and self-reported assessments of STB over 6 months.

Methods: This study will include 90 adolescents recruited on their first outpatient clinic visit following their discharge from the ED due to a recent STB. Participants will complete brief weekly assessments and be monitored continuously for their mobile app usage, including mobility, activity, and communication patterns, over 6 months using the iFeel research app. Participants will complete 4 in-person visits for clinical assessment at baseline and at the 1-, 3-, and 6-month follow-ups. The digital data will be processed, involving feature extraction, scaling, selection, and dimensionality reduction. Passive monitoring data will be analyzed using both classical machine learning models and deep learning models to identify proximal associations between real-time observed communication, activity patterns, and STB. The data will be split into a training and validation data set, and predictions will be matched against the clinical evaluations and self-reported STB events (ie, labels). To use both labeled and unlabeled digital data (ie, passively collected), we will use semisupervised methods in conjunction with a novel method that is based on anomaly detection notions.

Results: Participant recruitment and follow-up started in February 2021 and are expected to be completed by 2024. We expect to find prospective proximal associations between mobile sensor communication, activity data, and STB outcomes. We will test predictive models for suicidal behaviors among high-risk adolescents.

Conclusions: Developing digital markers of STB in a real-world sample of high-risk adolescents presenting to ED can inform different interventions and provide an objective means to assess the risk of suicidal behaviors. The results of this study will be the first step toward large-scale validation that may lead to suicide risk measures that aid psychiatric follow-up, decision-making, and targeted treatments. This novel assessment could facilitate timely identification and intervention to save young people's lives.

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KEYWORDS

suicide; suicide ideation; suicide prevention; adolescents; real-time assessment; digital phenotyping; risk assessment; mobile phone

Introduction

Background

Suicide is the second-leading cause of death globally among adolescents. Adolescence is a critically vulnerable developmental period for suicidal thoughts and behaviors (STBs). Youth emergency department (ED) visits for STB increased in many countries, particularly during the COVID-19 pandemic [1,2]. These incidents extend into long-term risk, as a history of suicide behaviors among youth is associated with an increased risk of repeat attempts and subsequent death [3]. The weeks and months following ED admission are at the highest risk for reattempts and suicide [4]. Suicidal crises in adolescents are often brief and episodic, with considerable potential for recurrence [5]. Adolescents are susceptible to interpersonal belonging, rejection, and conflict that may predispose them to imminent STB [6]. They have limited ability to regulate emotions and use cognitive control to inhibit problem behaviors, including suicidal acts when facing acute stress [5]. Therefore, the rapid-fluctuating acute suicidal states in adolescents warrant an improved proximal prediction of imminent STB.

Identifying proximal predictors for STB is critical to a better understanding of when individuals are most at risk [7]. It is distinguished from the unsuccessful scientific and clinical attempts to predict who is at risk [8] at the population level. In other words, the critical problem is to predict whether an individual with well-known preexisting risk factors is at imminent suicide risk (ie, within the next hours, days, or weeks) [9]. Two presuicidal mental state-specific diagnoses have been recently proposed in this context. Acute affective disturbance and suicide crisis syndrome are 2 conditions suggested to lead to imminent suicidal thoughts or behaviors [10,11]. Acute suicidal affective disturbance [12] is characterized by a sudden increase in suicidal intent and marked social alienation. Suicide crisis syndrome [13] is characterized by an intense sense of being trapped or unable to see any other way out. This condition is accompanied by experiencing affective disturbance, loss of cognitive control, and difficulty functioning in their social lives. The transdiagnostic approach suggested by these 2 diagnoses not only enables a more accurate and objective assessment of imminent suicide risk but could also facilitate research in developing digital markers of suicide risk.

Intensive longitudinal methods (ie, repeatedly assessing individuals over time) provide the unique opportunity to study proximal predictors of STB within individuals. Recent studies have begun using real-time mobile and wearable devices to predict STB, and the feasibility and acceptability of intensive monitoring in adolescents have been established [14,15]. Existing efforts are mainly focused on using intensive self-report assessments such as ecological momentary and daily diaries. These studies provided valuable information about the temporal dynamics of suicidal ideation [16,17] and significant proximal predictors, such as sleep problems and interpersonal stress [18-20]. However, the substantial reliance on self-reports requires insight and compliance, and the associated assessment burden limits study durations and applicability to real-world settings. Passive sensing of mobile data has been proposed as a promising direction for future research [14,21]. It allows naturalistic and continuous data collection with minimal burden, including social, communication, activity, and sleep patterns [22], in which change may indicate imminent STB. Recognizing objective web-based and offline social behavior patterns preceding STB may be particularly beneficial for adolescents. Pioneering studies have demonstrated that passive mobile sensing by actigraphy [23-26] may predict STB. An existing study demonstrated the usefulness of predicting symptoms in patients with major depressive disorder through passive data collection (electrodermal activity, sleep patterns, motion, communication, location changes, and phone usage patterns) from built-in sensors in phones and a wearable device [23-26]. Another study demonstrated the feasibility of predicting patients' moods using machine learning algorithms with privacy-preserving techniques through multimodal data collection (text, audio, and sensor data) from patients' mobile devices [23-26]. However, to our knowledge, there are no studies investigating proximal predictors of youth STB via real-time mobile passive sensing, including communication and activity patterns, and clinical and self-reported assessments over 6 months.

Unlike previous research that considered individual risk factors, a machine learning approach to passive mobile sensing can examine multiple risk factors and their combinations to build superior prediction models. This approach may identify complex real-life patterns and relationships and improve the near-term identification of risk and timely interventions [27,28]. However, the performance of passive sensing and machine learning over traditional methods for suicide risk classification and the interpretability of their findings demand further research [29-31]. Additional work in naturalistic settings is needed to unlock the potential of active and passive sensing and machine learning prediction models for suicide prevention. In addition, further research is required to develop prediction models optimized for implementation in clinical settings [28-30,32,33]. A longer follow-up period is needed to examine proximal predictors of suicidal behaviors (ie, recurrent attempts, ED admissions, and hospitalization) that may be clinically informative for suicide risk management in clinical settings. Furthermore, previous studies typically involved substantial payments for study participation, intensive compliance strategies, and safety procedures that may not be generalizable to real-world settings. This study addresses these challenges and will use intensive digital monitoring of self-reported and behavioral data in a real-time and real-world outpatient clinical setting.

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Study Aims and Objectives

Overview

This study will address the knowledge gap in real-time proximal predictors of youth STB. It will be the first to use active and passive digital monitoring in a longitudinal prospective study among high-risk adolescents in a real-world clinical setting. The current research, therefore, attempts to provide a proof of concept for digital markers of imminent STB to classify adolescents with high-risk STB versus those with lower risk, enabling a more accurate and objective assessment of imminent suicide risk. The project's objectives integrate multiple digitally derived data sources, including behavioral, interpersonal, and frequent subjective self-reports, using comprehensive and nonintrusive techniques. This project has 2 main aims.

Aim 1

The first aim is to demonstrate the clinical utility of digital weekly self-reports in the identification of adolescents at risk for STB in a real-world high-risk clinical setting.

- Hypothesis 1: There will be satisfactory compliance (>60%) for weekly digital assessments of STB and main risk factors, and it will be accepted among adolescents, parents, and mental health professionals for routine clinical suicide risk management and care.
- Hypothesis 2: The weekly digital assessments of STB and main risk factors will demonstrate concurrent and prospective associations with clinical assessments of STB at the 1-, 3-, and 6-month follow-up, measured by the Columbia Suicide Severity Scale (C-SSRS) [34], and ED admissions.

Aim 2

The second aim is to develop an integrated prediction model using passive mobile sensing data for STB prediction.

- Hypothesis 3: The passively derived mobile usage data will accurately classify adolescents with high-risk STB versus those with lower risk over 6 months of follow-up as determined by clinical evaluations.
- Hypothesis 4: The passively derived mobile usage data will predict same- and next-week adolescents' self-reported STB.
- Hypothesis 5: Integrating passive sensing and active self-reports will predict high-risk STB more accurately than each data source alone.

Overall, this project aims to use state-of-the-art digital technologies to identify proximal predictors of youth STB. These methods may provide the invaluable capacity to develop real-time prediction models, crucial steps toward clinical applications, and life-saving interventions.

Methods

Study Design

The study target sample includes 90 high-risk adolescents aged 11-18 years presenting to the ED with recent STB and recruited at the Depression and Self-Harm Clinic at Schneider Children's Medical Center of Israel. All eligible patients identified in the ED will be referred to the Depression and Self-Harm Clinic. Participants will complete brief weekly assessments and be monitored continuously for their mobile app usage, including mobility, activity, and communication patterns, over 6 months using the iFeel (inManage Ltd) research app. Participants will complete 4 in-person visits for clinical assessment at baseline and at the 1-, 3-, and 6-month follow-ups.

Procedures

Consecutive admissions to the clinic will be recruited for the study. Clinical staff will notify the research staff of potential eligible recruitment. Senior research staff will explain the study in detail according to local ethical requirements, followed by signed parental consent and the child's signed assent (if over 16 years). Study participation, or lack thereof, will not affect the standard psychosocial and pharmacological services provided to participants. The response rate and time between ED admission and clinic admission will be recorded and examined in this study.

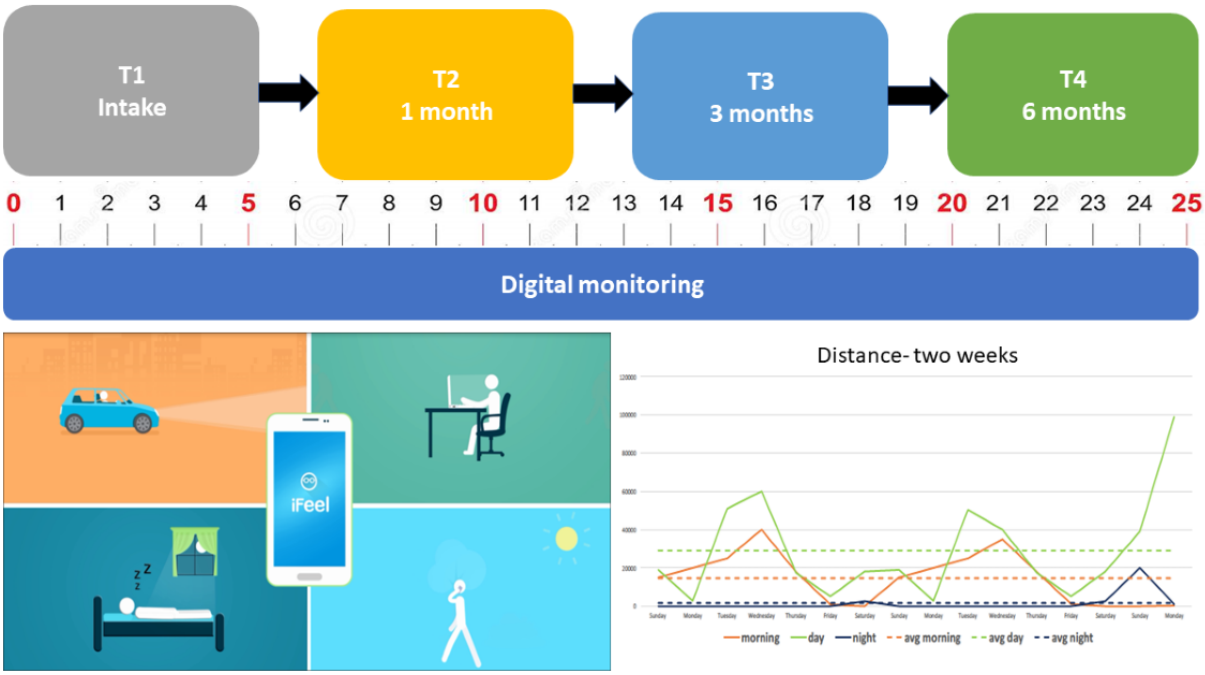
The inclusion criteria includes (1) adolescents between the ages of 11 and 18 years presenting with recent (past month) suicidal ideation or suicidal behavior (3 months), as defined by the C-SSRS [34] (preparatory acts, aborted, interrupted, and actual suicide attempts, or nonsuicidal self-injury), and (2) Android phone users (required for the iFeel app).

The exclusion criteria includes participants with acute medical conditions, mental retardation, cognitive impairment, or linguistic limitations preclude understanding the research questions.

Participants will complete a comprehensive assessment battery (T1) and download the iFeel app using a random app-generated code. Once downloaded, the app will gather relevant information from the mobile phone for the next 6 months and prompt participants to respond to weekly brief questionnaires, including STB measurements and main risk factors. Research assistants will train the participants on the weekly survey protocol and questions, emphasize the importance of adherence, provide examples, and instruct them on how to use the subjective rating scales. Research assistants will contact participants during the follow-up period in cases of missing active or passive data collection and assist with technical or adherence issues. Participants will be invited for extended follow-up evaluations at 1 (T2), 3 (T3), and 6 months following the initial assessment (T4; see Figure 1). These will include in-person or remote video clinical assessments and self-report assessment scales administered via secured web-based surveys.

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Figure 1. Illustration of study assessments. Initial and 1-, 3-, and 6-month extended assessments; 25 weekly digital self-report assessments over 6 months; and continuous passive mobile data usage monitoring (including mobility, activity, communication, and sleep patterns).



Real-Time Mobile Data Collection via the iFeel App

iFeel is an innovative digital health research platform that enables passive and active digital monitoring and provides continuous objective measurements for any given disorder. iFeel will harness mobile phone data to find associations between digital markers and STB ratings obtained via weekly self-reports and clinical assessments during study visits. The data will be collected using the iFeel mobile phone app. The information to be measured via mobile phones using the app will consist of the following:

- Communication patterns: number of phone calls (without phone numbers), duration of incoming and outgoing phone calls, communication app usage duration
- Activity patterns: accelerometer data and total distance accumulated
- Device usage: number of devices and screen opens and locks, time of screen active, Wi-Fi connections, Bluetooth connections, data usage (bits), battery usage, log of app usage, luminosity, device positioning (horizontal or vertical), and screen touch parameters (strength and frequency of touch)

All the collected information has no identifiable information and no intention to change the patient's treatment in this study.

Weekly Data Collection for STB

A brief self-report questionnaire will be generated by the iFeel app using push notifications once a week. Three items were selected to assess the main risk factors for STB based on the presuicidal mental state–specific diagnoses (ie, acute suicidal affective disorder and suicide crisis syndrome). These include general mood ("In general, how was your mood this week?"), entrapment ("Did you feel like there was no way out?"), and social isolation ("Did you feel isolated?"), rated on a visual analog scale between 1 and 5. The STB items are adapted from the C-SSRS [34] and include assessing suicidal ideation intensity (rated on a visual analog scale between 1 and 5), intent, plan, behavior, attempt, and nonsuicidal self-injury. If a participant indicates yes to a suicidal plan, current intent, or behavior, a safety protocol will be initiated whereby crisis and community services are made available to the adolescent, and contact is made with a parent (see the Ethics Approval and Adverse Events and Safety Procedures section).

In-Person Visits Measures (T1-T4)

The in-person visits measures include the following:

1. The Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID) [35] will be administered at the initial assessment.
2. C-SSRS (Child Version) [34]: Evidence-based and commonly used suicidality scale.
3. Youth Suicide Crisis Inventory (Y-SCI) [36]; patient, parent, and clinician reports. The Y-SCI includes items derived, abridged, and adapted for adolescents from the original scale [37].
4. Strengths and Difficulties Questionnaire (SDQ) [38]: A 25-item questionnaire for assessing the psychological adjustment of children and youth, including 5 subscales—emotional symptoms, conduct problems, hyperactivity or inattention, peer-relationship problems, and prosocial behaviors.
5. Mood and Feelings Questionnaire (MFQ) [39]: A 13-item scale assessing depressive symptoms.
6. Social Adjustment Scale-Self-report (SAS-SR) [40]: A measure of social functioning in the family, school, and peer group domains.

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7. Affective Reactivity Index (ARI) [41]: A 7-item parent- and self-reported concise dimensional measure of irritability.
8. Athens Insomnia Scale (AIS) [42]: An 8-item scale rated on a 0-3 scale for insomnia symptoms.
9. Sociodemographic and clinical information: Data will be collected on demographics, household composition, place of birth, parental employment, and religiosity. Information on medications, psychotherapy, ED visits, psychiatric hospitalizations due to STB, and other causes will be recorded.
10. Satisfaction survey: A 5-question (Likert-scale and open-ended) patient- and parent-satisfaction survey questionnaire about their experience and concerns about the monitoring app and procedures. A compatible, adapted version of the patient satisfaction survey will be used to capture clinicians' experiences with ease of use and perceived utility.

Data Analysis

Missing Data

While we will attempt to minimize missingness, missing data is typical and expected. Missing data will be examined for their possible clinical meaning by attrition and compliance analyses (eg, comparing completers to noncompleters and clinical correlations with missingness rate). We will investigate the pattern of missingness and use recommended methods [43] that consider the temporal nature of the data while constructing embedded, dense representations for sparse input data. We will adjust for the influence of the missingness rate on the prediction models.

Aim 1

We will conduct a descriptive analysis of the sample and compliance rate (mean, SD, frequency, and within-person correlations for the primary study variables). Given the expected low base rate of different suicidal behaviors, we will group the responses of the adapted C-SSRS into high-risk STB presence (Yes or No) based on their frequencies. We will assess the prediction of STB using logistic regression analyses and machine learning models (eg, random forest) for high-risk STB and nonhigh-risk STB group classification as the outcome. We will conduct multilevel modeling with a random intercept and random slope model (linear or logistic models). Predictors will be person-centered to compute within-person weekly fluctuations compared to an individual's mean. Level 2 predictors will include the corresponding individual mean level. Sociodemographic effects and treatment intervention type and duration will be examined for their effect on the results and adjusted for. The predictive accuracy of STB by weekly surveys will be estimated by a receiver-operating characteristic curve, the generalized area under the curve, precision, recall, and F_1 score [44]. We aim to identify the optimal prediction model by comparing different prediction models. The results of the satisfaction questionnaires will be analyzed using descriptive statistics and qualitative processing of open-ended text answers.

Aim 2

The analyses will include feature extraction, scaling, selection, embedding, and dimensionality reduction [22]. Our modeling approach uses unsupervised methods to learn useful representations using, for example, variational autoencoders [45] and underlying structures (eg, classical clustering methods). Multimodality will be handled using classical ensemble methods and the more advanced attention mechanism [46]. Similarly, sparsity will be handled using classical imputation methods and embedding (learned representation) processes [43]. Next, we will train and validate predictive models to infer higher-level activities (eg, conversation, activity and social media use) from raw sensor data. The labels will be used to train and validate the predictive models. A major challenge stems from the fact that the number of available labels is relatively small, while there is much more unlabeled (digital) data captured (continuously and passively) from the mobile phone. To use both labeled and unlabeled data, we will use semisupervised methods in conjunction with a novel method that is based on anomaly detection notions. The data will be split into training and test (holdout) data sets. Digital markers and predictive models are trained and cross-validated with k-fold cross-validation using the training set. Next, we use the test set (hold out data) to perform statistical validation and get an unbiased evaluation of the final model. The data split is stratified and performed at the patient level into 75% train and 25% test. Prediction models with STB as the outcome will adjust for potential confounders such as missingness rate, between-subject variability, diurnal and seasonal effects, and interventions. We will use classification modeling approaches (eg, random forest) appropriate for the sparsity of the data and relatively small sample size [28,47]. The performance of the machine learning methods using different data sources will be tested and compared using the generalized area under the curve, precision, recall, and F_1 score [44].

Power Statement

For multilevel models, we considered an unconditional 2-level model of the within-person longitudinal data with repeated weekly assessments (Level 1) collected across subjects (Level 2). Assuming a 75% completion rate with a power of 80%, repeated measures=25 (ie, weekly entries over 6 months), and ICC=0.5 (based on prior longitudinal studies), we need a sample of 90 adolescents. For machine learning models, the sample size represents the data held out for validation. Based on our previous studies in this population [48], over 6 months of follow-up, we expect at least 15% of the patients will have one or more self-harm incidents and 10% will have repeated ED admissions and hospitalizations. For chi-square goodness of fit, a medium effect size (d=0.5), and a power of 80%, 55 incidents are needed for validation, which will be approximately 10 unique patients. A Mann-Whitney-Wilcoxon test with similar power, effect size, and alpha provides similar results.

Ethics Approval

Study procedures were approved by the Rabin Medical Center Institutional Review Board (ID #0433-20). Specific ethical considerations that were included in the study protocol are detailed below.

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Data Management and Confidentiality

The study assessment battery, including demographic information and self-reported outcome measures, will be completed through a secured web-based survey. The iFeel app ensures user privacy and anonymity with proper security data server protection software (eg, no data could be paired to a specific user). Privacy and information security comply with the European Union's privacy requirements. The data will not include any other identifying information. The research coordinator will record the key to identifying details on a secured log, which will be kept separately and password protected.

Adverse Events and Safety Procedures

Study assessments are performed by clinical research staff trained in suicide risk assessment using the study scales. Senior clinical staff and principal investigators will be available to the research staff by cell phone. Patients and parents will be informed that confidentiality will be kept unless there is a serious and imminent safety concern. In such an event, the disclosure will be made to a licensed clinician on the study team, the principal investigators, and the child's therapist. The surveys will only be sent during regular business hours (8 AM-4 PM) to ensure the research team has the capacity to respond to weekly surveys that positively endorse STB. If a participant rates STB above the predefined clinical cut point, a follow-up question will be triggered to confirm their valid response. If they confirm active intent to self-harm, a text box will be prompted, providing information on emergent clinical services. Immediately following these endorsements, the principal investigators and study staff will receive an email regarding the participants' responses. The principal investigators or licensed clinicians will thoroughly assess the participant during the same business day and respond according to the clinical practice guidelines of the medical center. In the case of adverse events (suicide attempt or other health-risk behaviors such as substance use intoxication, as well as hospitalization for suicide risk), a full report will be submitted to the institutional review board, principal investigators, and directors of the depression clinic. Our approach is consistent with expert consensus statements on ethical and safety practices for conducting digital monitoring studies with individuals at risk for suicide [49].

Results

We expect to find longitudinal, concurrent, and prospective associations between the digital markers and self-reported and clinical assessments of STB outcomes. Successful outcomes of the proposed study will: (1) develop the ability to predict imminent STB using mobile data in a real-time, real-world setting, (2) provide an innovative and robust methodology for future studies and clinical trials to examine mental states with minimal burden and self-report bias, and (3) provide a powerful tool to identify youth at risk for suicide. The technology for this project was developed and made available for participant recruitment. Participant recruitment and follow-up started in February 2021 and are expected to be completed by 2024. The digital monitoring and clinical follow-up assessments will continue until the last participant has finished enrollment in the study. The interim data analysis began after 6 months of recruitment, and the final data analysis will be done after recruitment and follow-up assessments are completed.

Discussion

This study aims to fill the knowledge gap in real-time predictors of STB using active and passive digital monitoring in a clinical setting. The study has 2 main objectives: (1) to demonstrate the clinical utility of weekly digital self-reports in identifying adolescents at risk for STB and (2) to develop an integrated prediction model using passive mobile sensing data for STB prediction. Based on the study hypotheses, the main anticipated findings of this study would be the significant associations between digital assessments and clinical assessments of STB, accurate classification of adolescents with high-risk STB using passive mobile usage data, and improved prediction of high-risk STB by integrating active self-reports and passive mobile sensing.

This study will contribute to the scientific and clinical efforts to understand, detect, and prevent STB in youth. While most previous studies used intensive self-reports, previous studies have also demonstrated the usefulness of predicting symptoms in patients with major depressive disorder and mood prediction in patients using machine learning algorithms with multimodal data collection from mobile devices [23-26,50]. However, this is one of the first studies to investigate proximal predictors of youth STB using real-time mobile passive sensing, including communication and activity patterns, and clinical and self-reported assessments over 6 months. Furthermore, this study will add to the limited body of literature providing results in a naturalistic setting, which is crucial to developing optimized prediction models for practical implementation in clinical settings [29].

This study has several limitations that are important to consider. As is common in intensive longitudinal studies, there are challenges in participant recruitment and retention, expected missing data due to equipment failures and nonadherence to study protocol, concerns about the power and limitations of weekly digital self-report assessments instead of daily assessments, disruptions in passive sensing information through mobile phones, psychometric validity concerns with digital self-reports, and concerns about overfitting and generalizability. To address these limitations, the study has developed a protocol for participant recruitment and retention, implemented reminder protocols and positive reinforcements, has backup systems for data, followed recommended practices for self-report reliability and validity, and will perform robust testing methodologies for working with small data sets and outcome points. The study will also adjust for mental health interventions received and document each contact.

While more intensive daily reports could better capture STB fluctuations and associations, we believe weekly assessments will be novel, feasible, and most generalizable for clinical settings. Moreover, the substantial reliance on daily self-reports requires greater compliance, which could burden patients, and weekly digital assessments of STB rather than daily could lead to greater satisfactory compliance, which can be translated to

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clinical practice. The goal of the study is to provide proof of concept for using digital technology through mobile phones to identify the risk of youth suicidal behaviors more effectively. The results of this study will be the first step toward large-scale validation that may ultimately result in practical prediction models and immediate interventions to prevent suicide.

The results of this study can have a significant impact on developing future technology-based projects for suicide prevention. To ensure that the findings reach a wider audience, we plan to disseminate the study results through multiple channels, including manuscripts, social media, webinars, and conferences. The aim is to reach a broad audience of health care professionals, researchers, and policy makers. By disseminating the study's results through multiple channels, we hope to maximize its impact and ensure that it reaches a broad audience, including clinicians, researchers, policy makers, and advocacy groups. Future investigations have the potential to expand upon the findings of this study and contribute to the development of more advanced prediction models for STB in adolescents. Due to the relatively rare occurrence of suicidal behaviors, it may be beneficial to conduct a large-scale study or engage in collaborative research efforts focused on digital monitoring and prediction of STB. In addition, by combining physiological measurements obtained through wearable devices, valuable information on activity and arousal can be incorporated, validating the smartphone-based digital markers and addressing certain limitations. Therefore, the combination of these approaches in future studies offers advantages. Moreover, future advancements may involve the inclusion of additional data sources such as acoustic features and natural language processing, which were not considered in this particular study. By expanding the scope of data collection, a more comprehensive understanding of STB prediction can be achieved. Finally, to accomplish the goal of prevention, future studies should also concentrate on developing and evaluating adaptive interventions that take into account individual circumstances indicated by digital monitoring. These interventions should be informed by data obtained through both active and passive monitoring, allowing for effective responses to digital prompts and the provision of timely support.

Defining proximal risk factors in youth may significantly improve the clinical evaluation of imminent suicide risk. Relying more on passive sensing than self-reported data to identify the risk for suicidal behavior will make interventions more scalable and effective. With minimal assessment burden and reliance on patient disclosure of suicidal intent, digital markers can inform different interventions and provide an objective means to measure psychosocial or pharmacological treatment efficacy. Integrating multiple self-reported and passive data sources into a validated prediction model can improve the identification of adolescents at risk for STB. The ability to predict STB using mobile data in real-time, real-world settings has tremendous potential for suicide risk identification and prevention. It can enable personalized and just-in-time interventions triggered based on passive mobile usage and self-reported data, preventing adolescent injury and mortality.

Acknowledgments

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Data Availability

The data sets that will be generated or analyzed during the study can be obtained from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

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Abbreviations

ED: emergency department
STB: suicidal thoughts and behavior

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Protocol

Reduction of Sleep Medications via a Combined Digital Insomnia and Pharmacist-Led Deprescribing Intervention: Protocol for a Feasibility Trial

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Abstract

Background: Chronic insomnia is one of the most common health problems among veterans and negatively impacts their health, function, and quality of life. Although cognitive behavioral therapy for insomnia (CBT-I) is the first-line recommended treatment, sedative-hypnotic medications remain the most common. Sedative-hypnotics, however, have mixed effectiveness, are frequently prescribed longer than recommended, and are associated with numerous risks and adverse effects that negatively impact veteran function. Meeting the treatment needs of veterans impacted by insomnia requires delivering gold standard behavioral care, like CBT-I, and the reduction of sedative-hypnotics through innovative methods.

Objective: The objective of this feasibility clinical trial is to test a digital CBT-I approach combined with deprescribing to improve the success of sedative-hypnotic reduction among veterans. The intervention combines Noctem Health Clinician Operated Assistive Sleep Technology (COAST), an effective and efficient, scalable, and adaptable digital platform to deliver CBT-I, with clinical pharmacy practitioner (CPP)–led deprescribing of sedative-hypnotic medications.

Methods: In this nonrandomized single-group clinical trial, 50 veterans will be recruited and enrolled to receive CBT-I delivered via Noctem COAST and CPP-led deprescribing for up to 12 weeks. Assessments will occur at baseline, posttreatment, and 3-month follow-up. The aims are to (1) assess the feasibility of recruiting veterans with chronic sedative-hypnotic use to participate in the combined intervention, (2) evaluate veterans' acceptability and usability of the COAST platform, and (3) measure changes in veterans' sleep, sedative-hypnotic use, and function at baseline, posttreatment, and 3-month follow-up.

Results: The institutional review board approved the study in October 2021 and the trial was initiated in May 2022. Recruitment and data collection began in September 2022 and is anticipated to be completed in April 2024. Aim 1 will be measured by tracking the response to a mail-centric recruitment approach using electronic medical records to identify potentially eligible veterans based on sedative-hypnotic use. Aim 2 will be measured using the Post-Study System Usability Questionnaire, assessing overall usability as well as system usefulness, information quality, and interface quality. Aim 3 will use the Insomnia Severity Index and sleep diaries to measure change in insomnia outcomes, the Patient-Reported Outcome Measurement Information System Profile to

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measure change in physical function, anxiety, depression, fatigue, sleep disturbance, participation in social roles, pain, cognitive function, and self-reported sedative-hypnotic use to measure change in dose and frequency of use.

Conclusions: Findings will inform the utility of a combined digital CBT-I and CPP-led deprescribing intervention and the development of an adequately powered clinical trial to test the effectiveness in a diverse sample of veterans. Further, findings will help inform potential new approaches to deliver care and improve access to care for veterans with insomnia, many of whom use sedative-hypnotics that may be ineffective and increase the risk for negative outcomes.

Trial Registration: ClinicalTrials.gov NCT05027438; https://classic.clinicaltrials.gov/ct2/show/NCT05027438

International Registered Report Identifier (IRRID): DERR1-10.2196/47636

(JMIR Res Protoc 2023;12:e47636) doi:10.2196/47636

KEYWORDS

insomnia; sedatives and hypnotics; mHealth; deprescribing; cognitive behavioral therapy; clinical pharmacist; veterans

Introduction

Background

Chronic insomnia is one of the most common health problems among veterans and has a significant negative impact on health, function, and quality of life [1-3]. Insomnia impacts over 50% of veterans [2,4] and contributes to functional impairment, fatigue, reduced alertness, and impaired memory, attention, concentration, and work performance [5-8]. Insomnia also negatively affects comorbid health problems and increases the risk of depression, anxiety, substance use, chronic pain, cardiometabolic disorders, and suicidal behaviors [9-11]. In the general population, COVID-19 pandemic continues to cause significant stress and worry about health and has been associated with increased rates of insomnia as high as 38% and concurrent increases in prescriptions for sedative-hypnotic medications (eg, non–benzodiazepine receptor agonists, such as zolpidem, eszopiclone, zaleplon], temazepam, trazodone) [12-14].

Nonpharmacological treatments of insomnia are the first-line recommended treatment for insomnia. However, sedative-hypnotics (eg, non–benzodiazepine receptor agonists known as z-drugs, such as temazepam and trazodone) are the most common treatment for insomnia, ranging from 5% to 14% in large cohort studies, and even higher rates in survey studies (upward of 25%) [15,16]. Sedative-hypnotic use is associated with increased risks, functional impairment, and negative quality of life and health outcomes [14-16]. Daytime fatigue, impaired cognitive and psychomotor functioning, falls and fractures [17], as well as rare, yet serious, events such as sleep-driving, are linked with the use of sedative-hypnotics [18]. Although considered effective for short-term treatment of insomnia, meaning a few weeks to months, these medications are often taken well beyond 1 year [19,20] despite epidemiological research indicating sleep medications taken for at least one year may be related to elevated incidence of cancer and an increased risk of death (controlling for prior cancer diagnosis) [19]. Use of sedative-hypnotics, especially benzodiazepines, can result in tolerance, dependence, or abuse [20]. Furthermore, these medications only treat insomnia symptoms rather than underlying causal factors, and discontinuation often results in rebound insomnia [20]. Importantly, many patients prefer to avoid sedative-hypnotics if an alternative treatment is available [21]. In sum, sedative-hypnotics are the most common treatment for insomnia by a wide margin, [16,22] but are not the recommended first-line treatment for chronic insomnia [3,23,24].

The state of the science specifies that behavioral interventions, like cognitive behavioral therapy for insomnia (CBT-I), are the first line treatment for chronic insomnia [3,23,24]. Studies within and outside the Veterans Health Administration (VHA) demonstrate that CBT-I significantly improves insomnia symptoms, nighttime sleep quality, and daytime function [25-27]. CBT-I is a multicomponent evidence-based psychotherapy that includes stimulus control [28], sleep restriction [29], cognitive therapy [30], sleep hygiene [31], and relaxation [32]. CBT-I is typically 5-8 sessions (face-to-face; in-person or telehealth) delivered by psychologists or other mental health providers [33]. Randomized controlled trials and meta-analyses have established CBT-I as effective for adults with primary insomnia [34] and those with comorbid insomnia [35], including psychiatric disorders (eg, depression and anxiety [35-37]) and medical disorders (eg, chronic pain [38]). A Veterans Affairs (VA) study with nearly 700 veterans found that 60% who completed CBT-I achieved a treatment response (ie, reduction ≥8 points per the Insomnia Severity Index; ISI). These veterans had a mean ISI change of 20.7 to 10.9, a large effect size (pre- to posttreatment Cohen *d*=2.3) [26]. In terms of long-term treatment gains, a recent review found 50% of patients responded to CBT-I and maintained treatment effects for 4-10 years [39]. CBT-I is also more effective than sedative-hypnotics at reducing sleep onset latency and is equally effective at improving wake after sleep onset and sleep quality [40]. It is important to note that combining CBT-I and sedative-hypnotics may not improve outcomes beyond CBT-I alone [41].

Considering the recommendation of behavioral interventions like CBT-I compared to the high use of sedative-hypnotics and risks involved, it is vital to consider methods to decrease sedative-hypnotic use and increase engagement in CBT-I. Deprescribing is the reduction or withdrawal of a medication managed by a health care professional that aims to reduce harm and improve outcomes [42,43]. Deprescribing interventions to reduce sedative-hypnotic use range from patient-centered approaches (eg, written instructions, relaxation strategies, therapy) to provider education and training [44,45]. A typical intervention will involve gradual dose reduction (GDR), or tapering, and is sometimes accompanied by psychological

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treatment, like CBT-I [45]. GDR and tapering approaches, including the use of telehealth [46,47], often involve dose reductions of 25%-50% every 1-3 weeks until cessation is achieved [44]. Cessation, however, has varying rates of success (27%-80%). Adding psychological treatments (eg, CBT-I) helps to reduce rebound insomnia and improve cessation rates compared to routine care (odds ratios [OR] 3.38-5.96). However, the results of combining medication tapering and psychological interventions have been mixed [47-49]. Two key challenges to deprescribing sedative-hypnotics are rebound insomnia symptoms and the lack of personalized care (eg, educational brochures) [49]. Many individuals report being unaware of the risks associated with sedative-hypnotics, thus education and multidisciplinary collaboration are critical, especially as these factors are associated with enhanced deprescribing outcomes [50]. Considering these barriers and prior research on CBT-I and sedative-hypnotic tapering [46], a personalized approach that can effectively combine CBT-I and deprescribing has the promise to improve insomnia and sedative-hypnotic outcomes among veterans.

Access to both deprescribing and behavioral interventions would provide maximum impact for veterans; however, access to both interventions remains a barrier. Sedative-hypnotic use is highly prevalent, with many chronic users [16,19,49,51]. While medication prescribers and clinical pharmacists can provide patient education and lead tapering efforts, they do not have training in behavioral insomnia interventions. Despite strong evidence of improved sleep quality and daytime function and with minimal adverse effects and long-term treatment gains [3], CBT-I continues to have limited availability. Even with significant training dissemination efforts by the VA (>1100 trained since 2011), there is still a shortage of trained CBT-I clinicians, especially outside of urban VA medical centers. Additional barriers involve the location of CBT-I delivery, often in mental health clinics, which remains stigmatized for many veterans. Of note, many trained CBT-I clinicians are generalist therapists and insomnia care represents only a small portion of their caseload. CBT-I, like all evidence-based psychotherapies, requires regularly scheduled visits (in-person or telehealth), usually weekly or biweekly, which are not always possible for veterans who work, have caretaking responsibilities, or have transportation challenges.

Digital sleep therapeutics offer personalized, efficient, effective, and scalable treatment for insomnia treatment. Digital CBT-I mobile apps are available, including several developed by the VA, that have similar sleep outcomes as in-person CBT-I [52]. However, these mobile apps are self-management programs—patients do not engage with clinicians via the app—that focus only on improving insomnia symptoms. There are no remote or digital interventions that combine personalized sedative-hypnotic tapering with CBT-I. The Clinician Operated Assistive Sleep Technology (COAST) platform (Noctem Health) offers capabilities for supervised clinical care that allows clinicians to prospectively monitor patients' symptoms, progress, and adherence to clinician-driven treatment recommendations and to deliver personalized interventions remotely. Thus, COAST can fill the gap for veterans who can benefit from a combined approach of deprescribing and CBT-I with direct and just-in-time supervision, albeit remote, of their care management team.

The COAST platform, unlike other digital insomnia mobile apps, is a decision support tool for clinicians that offers personalized and responsive evidence-based recommendations for each individual patient [53,54]. Data from the initial validation trial and recent quality improvement data from military treatment facilities show that CBT-I delivered via COAST significantly decreases insomnia symptoms per sleep diaries and self-report measures (eg, ISI) to a greater extent than a recent in-person CBT-I trial with active duty military [55]. COAST has been iteratively refined through testing with military personnel, veterans, health care providers, and clinical partners in the Department of Defense Military Health System and academic medical settings [54]. While COAST's focus is on behavioral sleep assessments and interventions, the platform is flexible and can integrate additional interventions, such as clinical pharmacy practitioner (CPP)–led sedative-hypnotic deprescribing, unlike existing insomnia mobile apps. The COAST platform consists of a provider dashboard and a patient-facing mobile app. It offers a safe, no-contact, or remote, intervention. Assisted by the platform's technology, providers monitor patient-reported behaviors, while a Health Insurance Portability and Accountability Act (HIPAA)–secure messenger allows just-in-time communication between patients and their treatment team. The integrated secure communication feature is uniquely valuable during the deprescribing process as it promotes rapid feedback for potential adverse effects of GDR or tapering. COAST's algorithms facilitate the detection of disordered sleep patterns based on patient input, resulting in timely clinical decision-making and personalized sleep interventions based on the core components of CBT-I. COAST's efficiency helps to significantly reduce clinician time involved in treatment to as low as 10 minutes total per patient versus 30-60 minutes per session for in-person and telehealth modalities (typically 5-8 sessions). COAST also promotes participant engagement [56] and reduces burdensome aspects of face-to-face CBT-I by bringing tools and clinical expertise directly to the patient through their mobile device.

Specific Aims

Chronic insomnia is one of the most common health problems among veterans and negatively impacts their health, function, and quality of life. Although CBT-I is the first-line recommended treatment, sedative-hypnotic medications remain the most common despite mixed effectiveness and associated risks and adverse effects. To address this gap and reduce sedative-hypnotic use, we are conducting a nonrandomized, single-group pilot clinical trial with 3 aims:

1. To assess the feasibility of recruiting veterans with chronic sedative-hypnotic use to participate in a 12-week combined deprescribing and CBT-I intervention, delivered through the COAST platform
2. To assess veteran acceptability and usability of the COAST platform
3. To assess change in veteran sleep, sedative-hypnotic use, and function pre- to postintervention

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The results will inform the design of a larger clinical trial to test the effectiveness of a combined deprescribing and CBT-I intervention delivered via COAST versus usual deprescribing care.

Methods

Ethics Approval

This study has been approved by the Institutional Review Board (IRB) of the VA Pittsburgh Health Care System (VAPHS) (1638783). It is registered at clinicaltrials.gov (NCT05027438) with methods reported following Standard Protocol Items: Recommendations for Intervention Trials (SPIRIT) guidelines [57]. All protocol changes and amendments have been reviewed and approved by the VAPHS IRB. Protocol deviations are documented in a deviation log and submitted to the IRB as part of the annual renewal. Any reportable events (eg, serious adverse events) are reported according to the VAPHS IRB and Office of Research and Development guidelines. An audit, independent of the principal investigator, study team, or sponsor, is conducted by the VAPHS Research Compliance Officer at least once every 3 years, or upon study closure if no audit has been completed yet.

All participants undergo the informed consent process prior to enrollment. The informed consent process is administered via video telehealth with the study coordinator. Informed consent documents and HIPAA forms are reviewed during the video consent process and then sent to veterans for completion using DocuSign; veterans are not considered enrolled until signed documents are returned to the study coordinator. veterans also have the option to opt-in for their study data to be included in a research repository, which will allow their deidentified data to be used in other research with appropriate approval of the VAPHS IRB; this is optional and does not impact their ability to participate in the clinical trial. Participants are compensated up to US $175 if they complete all study procedures including the baseline assessment (US $50), posttreatment assessment (US $50), 3-month follow-up assessment (US $50), and the brief interview (US $25).

All participant data are kept private and confidential. Data collection will occur through the COAST platform and stored on Noctem's Amazon Web Services GovCloud secure cloud-based server behind a firewall with a security policy that includes a dedicated server, regular backup of data, use of a monitored network with active security measures, and well-defined role-based access control. No protected health information (PHI) is stored on the COAST platform. After secure data transfer from Noctem to VA, security protocols in place include study data stored on secure dedicated study drives behind the VA firewall and only study team personnel with access to the data. Participants are assigned a unique identification number to ensure their study-related data are deidentified. While some PHI is collected as part of the informed consent process (ie, email address for DocuSign), no PHI will be included in the data analysis and dissemination of findings.

Participants and Eligibility

Participants will include 50 veterans recruited from VAPHS and affiliated community based outpatient clinics. See Textbox 1 for inclusion and exclusion criteria.

The medications and doses selected for inclusion were based on clinical practice guidelines and medications indicated for the treatment of insomnia (on or off label) [58]. Medications used to treat insomnia but also used to treat other disorders, such as benzodiazepines (eg, clonazepam) and sedating antidepressants (eg, amitriptyline) were not included. In addition, as this is a feasibility pilot trial, the medications were limited to the most commonly prescribed sleep medications [59].

The primary recruitment method will occur via mail. The study team will mail letters to potentially eligible veterans (see Textbox 1) identified from VA medical records. A prescreen list of potentially eligible veterans will be generated by the study's data analyst through the VA's corporate data warehouse. Participants with preliminary eligibility will be stratified by age (<65 or ≥65 years), sex (male or female), and race (White or non-White, including American Indian or Alaska Native, Asian, Black or African American, and Native Hawaiian or other Pacific Islander) with an equal number of letters mailed for each group, until a group's sample is depleted (see Table 1) and recruitment goals are met (n=50 enrolled). If feasible, depending on COVID-19 restrictions, secondary recruitment methods will be in-person (eg, flyers, clinician-assisted) at VAPHS clinics (eg, primary care, behavioral health, and sleep medicine).

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Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- VA Pittsburgh Health Care System (VAPHS) veterans aged ≥18 years
- Medical record documentation and self-reports of active sedative-hypnotic use ≥3 days/week for ≥3 months, including zolpidem ≤10 mg immediate release, ≤12.5 sustained release; zaleplon ≤20 mg; eszopiclone ≤3 mg; trazodone ≤400 mg; temazepam ≤30 mg; and hydroxyzine ≤100 mg; veterans on higher doses may be eligible on a case-by-case basis
- A desire to reduce or stop using sedative-hypnotics
- Access to a mobile device

Exclusion criteria

- A self-report of a medical or psychiatric disorder that would significantly impair participation (eg, cancer, uncontrolled pain, severe depression)
- A self-report of a medical or psychiatric disorder that can be exacerbated by changes in sleep (ie, seizure disorder, psychotic disorders, bipolar I disorder)
- A self-report of an active substance use disorder
- High risk of suicide per the Columbia-Suicide Severity Rating Scale (C-SSRS)
- Currently engaged in an evidence-based, time-limited psychotherapy (eg, prolonged exposure, cognitive processing therapy, cognitive behavioral therapy for depression, and cognitive behavioral therapy for insomnia)

Table 1. Estimated initial recruitment sample (N=1435).

	White (n=1287), n		Non-White[a] (n=148), n	
	Age <65 years	Age ≥65 years	Age <65 years	Age ≥65 years
Female (n=142)	92	23	26	1
Male (n=1293)	405	767	63	58

[a]Non-White included American Indian or Alaska Native, Asian, Black or African American, and Native Hawaiian or other Pacific Islander.

Interventions

Overview

This is a single-group, nonrandomized clinical trial lasting up to 12 weeks with assessments at baseline (T0), posttreatment (T1), and 3-month follow-up (T2). The intervention will combine CPP-led sedative-hypnotic deprescribing with CBT-I, delivered through the COAST platform and managed by a psychologist trained in CBT-I [53].

COAST Delivered CBT-I

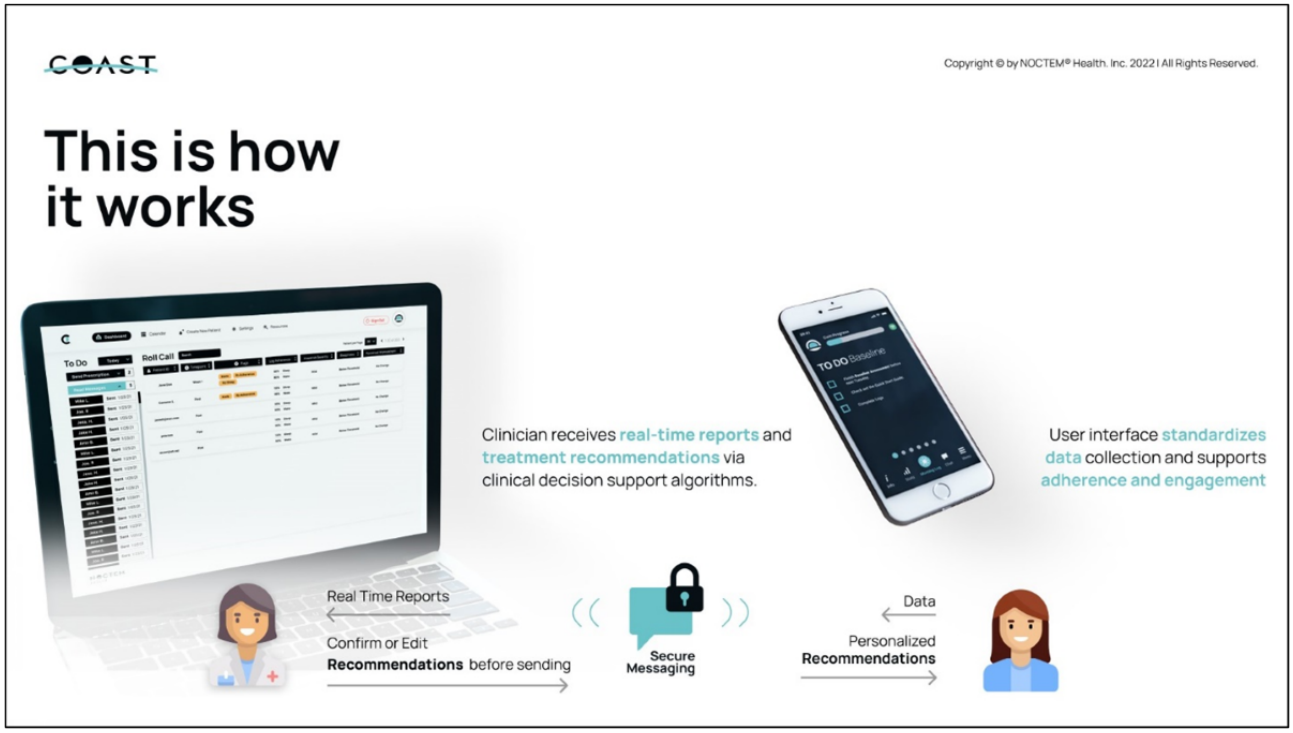
The COAST algorithms, based on participant data (eg, sleep diary, self-report measures), will generate treatment recommendations after approximately 1 week of participant data entry [54]. COAST's treatment recommendations align directly with the core components of CBT-I—stimulus control, sleep restriction, cognitive therapy, and relaxation—with additional strategies targeting nightmares and daytime fatigue as needed. Weekly assessments and daily sleep diaries drive recommendations offered to the clinician. Because COAST is clinical decision support software, the study clinician (ie, a psychologist trained in CBT-I) must review and approve or change algorithm-generated recommendations before they are sent to the participant via the patient-facing mobile app (see Figure 1). This tailored approach allows for modification of COAST's recommendations based on clinician expertise and knowledge of the participant (eg, a recent stressor that indicates slowing or pausing treatment). To further enhance the treatment process, the clinician is available by secure message (ie, in-platform texting) during business hours to provide rapid support or schedule an appointment as needed (eg, phone, VA Video Connect). The messaging feature also allows for the study team to rapidly notify the participant if daily diaries are incomplete or assessments are missed. As needed, the study team will contact participants by phone or video telehealth for treatment adherence issues. These features offer personalization for each participant, consistent with a case-conceptualization approach based on the veteran's sleep needs. CBT-I via COAST is typically delivered over 4-6 weeks but has been adapted for this study to last up to 12 weeks as deprescribing can vary and ongoing COAST recommendations may further support deprescribing efforts.

The COAST recommendations are based on CBT-I and the rationale that modifying behaviors impacts the homeostatic and circadian drives. Modifying sleep and daytime behaviors helps regulate wakefulness, which can increase the homeostatic sleep drive and restructures and optimizes sleep and wake times to reinforce the circadian drive. Stimulus control limits the bed for sleep, sexual activity, and sickness, which strengthens the positive association between bed and sleep. Staying in bed while awake and engaging in nonsleep activities perpetuates the cycle of wakefulness, frustration, and arousal. When unable to sleep, it is recommended patients get out of bed and go to another room until sleepiness returns. Sleep restriction, or sleep efficiency training, matches the patients' sleep opportunity, or prescribed time in bed, to their average total sleep time. This

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allows the homeostatic and circadian drives to become better aligned. A consistent wake time is (1) the most important cue for setting the biological clock, (2) regulates exposure to morning light, and (3) helps increase the homeostatic sleep drive for subsequent nights. Going to bed only when sleepy, but not before a prescribed bedtime, increases the sleep drive and the likelihood of falling asleep quickly. Intrusive thoughts and worry can result in wakefulness and can contribute to cognitive and physiological arousal. Reduction of intrusive thoughts and worry helps to reduce nighttime stress through the identification and challenging of dysfunctional beliefs. Targeted strategies can help to reduce intrusive thoughts at night and the wake or frustration cycle during awakenings. Relaxation exercises help reduce physical and cognitive arousal that can perpetuate wakefulness. Breathing exercises, guided imagery, and progressive muscle relaxation help to reduce arousal and increase readiness to sleep.

Figure 1. COAST features. COAST: Clinician Operated Assistive Sleep Technology.



CPP-Led Deprescribing

Approximately 1 week after CBT-I is initiated in COAST, participants will meet with a CPP to begin deprescribing. For the deprescribing intervention, the study CPPs will develop a personalized taper for each participant based on their medication, dosage, and factors such as anxiety about the taper, duration of use, comorbid disorders, and insomnia severity. The deprescribing plan will be communicated to each participant either through COAST's secure messaging or verbally (eg, phone, VA Video Connect). The study CPP will, as needed for the personalized taper, place appropriate orders for different doses or new medications in the VA's medical record system, the Computerized Patient Record System, concurrent with the scope of practice or for the participant's VAPHS prescribing provider to review or approve of a controlled substance. As needed, the taper can be extended to 12 weeks, and if necessary, participants can be referred to their VAPHS prescribing provider for further deprescribing assistance after the intervention and posttreatment assessment are complete (T1). At any point during the intervention, the taper can be paused if the participant is struggling to adjust or experiences withdrawal symptoms. All withdrawal symptoms will be self-reported through the COAST platform using the secure messaging or the daily sleep diary and will be responded to within 1 business day by a study team member. Outside of business hours (Monday-Friday, 8 AM-4:30 PM), if necessary, participants can contact emergency services.

Outcomes Measures

Demographics and VA Medical Record

On downloading the COAST app, participants will complete a demographic questionnaire recording their biological sex, gender identity, age, time served in military, and combat status. Psychiatric disorders and psychotropic medications will be collected from participants' VA medical records, as will their service connection—disabilities and disorders caused by military service (0%-100% [60]).

ISI Scores

The ISI will serve as the primary sleep outcome. The ISI is a brief measure of nighttime sleep disruption (eg, severity of sleep onset) and daytime impact (eg, interference with function) [61]. The ISI has 7 items scored 0-4, with higher scores indicating greater severity or impairment. The total score (0-28) is categorized as follows: no insomnia (0-7), subthreshold insomnia (8-14), moderate insomnia (15-21), and severe insomnia (22-28). A reduction pre- to posttreatment ≥8 points indicates a treatment response and a posttreatment score ≤7 indicates remission. The ISI demonstrates good psychometric properties, with validity endorsed by its correlation with sleep

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diaries [62]. The ISI will be assessed at T0, T1, and T2 as well as biweekly during the intervention.

Self-Report of Sedative-Hypnotic Medication

Sedative-hypnotics will be measured by participant self-report, as part of a daily entry in COAST: "I took the following sleep medications: Zolpidem (Ambien), Eszopiclone (Lunesta), Zaleplon (Sonata), Trazodone (Desyrel), Temazepam (Restoril), or None." As medications will be reduced over the course of treatment, veterans will enter the dose of medication as free text. The daily COAST entry will also involve assessments for adverse effects and withdrawal symptoms (ie, the Clinical Institute Withdrawal Assessment–Benzodiazepines; CIWA-B [63]). Outcomes will include posttreatment (T1) and 3-month follow-up (T2) medication dosage relative to starting dosage at baseline (T0), and binary outcomes of a ≥50% reduction (yes or no) and total cessation (yes or no). Furthermore, medication information from participants' VA health records will be used to help validate their self-report of sedative-hypnotic use throughout the study.

Sleep Diary

Additional sleep outcomes will be measured with a daily sleep diary [64]. Sleep diaries provide information about participants' sleep behaviors, such as bedtime, rise time, total time in bed, total sleep time, sleep onset latency, number of nighttime awakenings, duration of wake after sleep onset, and sleep efficiency. The sleep diary exhibits good psychometric properties and significant correlations with objective data [65]. Sleep diaries will be completed daily from baseline (T0) through posttreatment (T1) and for 7-days at 3-month follow-up (T2). Daily sleep diary data are used by COAST's algorithms to generate personalized recommendations for each participant.

Patient-Reported Outcome Measurement Information System Adult Profile

Secondary clinical and functional measures will come from the Patient-Reported Outcome Measurement Information System Adult Profile (PROMIS) 29+2. This includes measures of physical function, social roles, anxiety, depression, fatigue, sleep disturbance, pain interference, pain intensity, and cognitive function. Each construct is scored individually (4 items scored 1-5 with a total score range of 4-20) except cognitive function (2 items scored 1-5 with a total score range of 2-10), with higher scores indicating more of the construct being measured. All constructs have high internal validity, with a ranging α=.86-.96. Raw scores are translated to a T-score with a mean of 50 and SD of 10. When all constructs are scored together, a preference score is calculated, representing health - related quality of life ranging from 0 (as bad as dead) to 1 (perfect or ideal health) [66].

Post-Study System Usability Questionnaire and Qualitative Interviews

COAST usability and acceptability will be measured with the Post-Study System Usability Questionnaire (PSSUQ) [67], which measures perceived satisfaction with systems such as websites or mobile apps. The PSSUQ has 16 items, scored 1-7 (1=strongly agree, 7=strongly disagree). The overall usability score is the average (total score divided by number of questions answered). The 3 subscales are usefulness (items 1-6), information quality (items 7-12), and interface quality (items 13-16). Lower scores (<3) indicate higher satisfaction and above-average usability. The measure has a high validity score (α=.94). The PSSUQ will be assessed at 2 time points. First, after the initial sleep or wake schedule recommendation is delivered (T0+1 week), as this will give participants a chance to learn the COAST platform and second, at posttreatment (T1), to measure change over time. To further assess usability or acceptability, 15 veterans will be interviewed (via phone or Microsoft Teams; Microsoft Corp) to gain additional context on their COAST user experience and potential changes or new features that could improve COAST. Veterans will be interviewed based on their PSSUQ scores to get a range of perspectives, if available, per score distribution (eg, 5 low, 5 medium, 5 high; see Table 2 for timeline of assessments).

Table 2. Timeline of assessments.

Measures	T0[a]	TX[b]	T1[c]	T2[d]
Demographics	✓			
Sleep diary[e]	✓	✓	✓	✓
Sleep medication[f]	✓	✓	✓	✓
Insomnia Severity Index[g]	✓	✓	✓	✓
Patient-Reported Outcome Measurement Information System Profile 29+2	✓		✓	✓
Post Study System Usability Questionnaire[h]	✓		✓	

[a]T0: baseline.

[b]TX: treatment.

[c]T1: posttreatment.

[d]T2: 3-month follow-up.

[e]T0/T1/T2 baseline: twice daily (morning or evening) for 1 week; during treatment: twice daily for up to 12 weeks.

[f]Integrated into daily sleep diary.

[g]Every 2 weeks during treatment.

[h]At baseline and week 1 assessment during treatment.

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Data Collection, Management, and Quality Control

Primary data collection will be through the COAST participant-facing mobile app with additional data collected via the posttreatment qualitative interviews (phone) and VA medical records. All participants will be assigned a unique study identifier that is not related to any personal identifier such as social security or medical record number. During all phases of the study, participants will be encouraged to enter data in a timely fashion with reminders via the messaging feature on COAST as well as phone calls, as needed. Data submitted via COAST are not stored on participants' personal devices but directly stored on Noctem Health's NoSQL database, which is located on an Amazon Web Services GovCloud US-East region server. The database and servers adhere to US Government and Department of Defense security standards and use identity and access management (IAM) controls for its infrastructure services, which are limited to appropriate personnel and are continuously reviewed. Data quality control is enhanced by required responses to questions and limited data response ranges to enhance validity. Prior to secure data transfers from Noctem Health to VAPHS, all PHI will be removed from the data set and data will be reviewed for completion, redundancies, and quality. After data transfer, the study's VA data analysts will review deidentified data to ensure no PHI is included before data are available to the study team for review and analysis. Noctem and VA co-own all the data. The VAPHS study team will have access to the final data set used for analyses. Noctem will retain a copy of the deidentified data set. A limited data set will be created and shared pursuant to a data use agreement appropriately limiting the use of the data set and prohibiting the recipient from identifying or reidentifying (or taking steps to identify or reidentify) any individual whose data are included in the data set.

Analytic Plan

Power Analysis

Given the estimates from prior work on sedative-hypnotic deprescribing and digital insomnia interventions [46,68,69], we can expect an effect size (Cohen *d*) range for pre-post ISI between 1.09 and 2.26 with an average effect size of 1.73 (small, 0.3, medium, 0.5, large, 0.8) [70]. Given 50 enrolled participants and accounting for a 25% dropout (ie, 37 with pre-post data), we will still have 95% power to detect an effect size of 0.65.

Aim 1

To determine the feasibility of recruiting veterans to participate in this combined deprescribing and CBT-I intervention, a CONSORT (Consolidated Standards of Reporting Trials) diagram will be used to track the recruitment, enrollment of eligible participants, and their progression through treatment. During recruitment, the number of participants who contact the coordinator, undergo the study screen, and provide consent will be recorded relative to number of letters sent. To track treatment participation, the number of participants who download and activate the COAST app, complete baseline assessments, engage in treatment beyond the initial recommendation, and complete the intervention will be noted. Chi-square analyses will be used to determine group differences (age, sex, and race) in recruitment response and participation rates.

Aim 2

Usability and acceptability of COAST will be evaluated by the PSSUQ. Usability or acceptability will be measured early in treatment (T0+1 week) and at posttreatment (T1), as well as change over time (T1–T0+1 week). Change will be assessed using an intention-to-treat (ITT) approach and fitting mixed effects linear models that test change in usability or acceptability (change in PSSUQ scores over the course of treatment) and include a main effect of time (T0+1 week to T1) and random effects for the veteran.

Audio-recorded qualitative interviews will help to gain more nuanced information on COAST usability or acceptability. The interviews will be interpreted using rapid qualitative inquiry [71,72] to ensure that results are delivered in a timely manner to be meaningful to the study. Interviews will be summarized by the study's qualitative analyst into a template of categories that reflect topics of interest. The summaries will be coded by 2 analysts to develop the basis of content and thematic analyses.

Aim 3

Veteran clinical and functional outcomes will be evaluated using an ITT approach. We will fit mixed effects linear models that measure change over the course of treatment for our outcome measures (ISI, sleep diary, PROMIS) that includes a main effect of time (T0-T1, T0-T2, and T1-T2) and include random effects for the veteran (multiple measurements during treatment). Sedative-hypnotic change will be determined by an ITT approach and fitting a mixed methods logistic model that tests for medication dose reduction (≥50%, yes or no) and medication cessation (yes or no) over the course of treatment that includes a main effect of time (T0-T1, T0-T2, and T1-T2) and random effects for the veteran. Additional analyses will compare completers versus noncompleters and responders versus nonresponders.

Results

This study was approved by the VAPHS IRB in October 2021 with study initiation in May 2022. Recruitment and data collection began in September 2022 and is ongoing. As of June 1, 2023, there were 25 participants enrolled. The study is expected to be completed by summer 2024. Trial results will be posted on clinicaltrials.gov and disseminated through peer-reviewed journals. The study findings will be communicated to the study sponsor, but the sponsor will not be involved in the dissemination of findings.

Discussion

Sedative-hypnotic use, as a treatment for chronic insomnia, is highly prevalent among veterans and is associated with considerable health and safety risks. Importantly, use of sedative-hypnotics does not align with best practices for treating insomnia or veteran preferences per the VA/Department of Defense Clinical Practice Guidelines [3]. This pilot study offers deprescribing of sleep medications managed by experts (ie,

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CPPs) while offering personalized, first-line insomnia treatment with CBT-I integrated and managed by a digital sleep platform. The COAST platform is unique, as it enables the efficient and effective delivery of CBT-I with the capability of integrating CPP-led deprescribing to combine these commonly siloed treatments. Patient-centered and personalized care is important to increase the likelihood of successful reduction or cessation of sedative-hypnotics. The combined and personalized care, from the CPP and psychologist, may result in better veteran outcomes compared to separate interventions, that is sedative-hypnotic deprescribing and CBT-I alone. Offering veterans a digital format of care reduces concerns regarding stigma and addresses barriers such as a lack of transportation and allows for the maintenance of social distancing. Notably, in the wake of COVID-19, older veterans (mean age 63.14 years) have demonstrated an increased preference for digital treatment over in-person treatment [73].

Focus on treating insomnia and reducing sedative-hypnotic use is of high value for veterans and their providers. Treatment response and remission of insomnia improve sleep quality, daytime function, and quality of life. Furthermore, treating insomnia reduces symptom severity in comorbid psychiatric disorders (ie, depression, anxiety, and posttraumatic stress disorder), reduces the risk of developing psychiatric disorders (ie, depression and suicidal behaviors), and reduces the risk associated with sedative-hypnotic use.

The long-term objective of this study is to inform the development of an adequately powered clinical trial to test the effectiveness of the combined deprescribing/CBT-I intervention in a diverse sample of veterans. Future clinical trials may also include a comparison of the combined intervention against treatment as usual or the combination of deprescribing and other digital insomnia platforms, such as the VA's Insomnia Coach. Beyond large-scale clinical trials, additional information is needed regarding cost and cost-effectiveness of using third-party software to support deprescribing and CBT-I delivery, like COAST, within the VA. In addition, implementation and dissemination are vital for success at scale in an integrated health care system like the VA and in the general community. If deemed cost-effective and if scaled appropriately, digital platforms like COAST can help reduce chronic sedative-hypnotic use, improve sleep quality, enhance functional outcomes for patients, and improve the access, efficiency, and effectiveness of delivering evidence-based care for veterans with insomnia.

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Data Availability

Consistent with the VA Office of Research and Development Data Management and Access Plan, a limited and deidentified data set generated or analyzed during this study will be available from the corresponding author. Any available data set will be pursuant to a data use agreement appropriately limiting the use of the data and prohibiting the recipient from identifying or reidentifying any individual whose data are included in the data set.

Authors' Contributions

ADB conceptualized the study and was responsible for funding acquisition, leading the investigation, developing methods, obtaining resources, supervising staff, and writing the original draft. CEH was responsible for project administration and writing the original draft. AG contributed to project administration, obtaining resources and software, and writing and editing revisions. Other coauthors contributed to investigation, writing, editing, and revising.

Conflicts of Interest

CTT receives royalties from SAGE Publishing for activities unrelated to the submitted work. AG owns equity and is employed by Noctem Health, Inc.

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Abbreviations

CBT-I: cognitive behavioral therapy for insomnia
CIWA-B: Clinical Institute Withdrawal Assessment–Benzodiazepines
COAST: clinician operated assistive sleep technology
CONSORT: Consolidated Standards of Reporting Trials
CPP: clinical pharmacy practitioner
GDR: gradual dose reduction
HIPAA: Health Insurance Portability and Accountability Act
IAM: identity and access management
IRB: institutional review board
ISI: Insomnia Severity Index
ITT: intention-to-treat
PHI: protected health information
PROMIS 29+2: Patient-Reported Outcome Measurement Information System Profile
PSSUQ: Post-Study System Usability Questionnaire
VA: Veterans Affairs
VAPHS: VA Pittsburgh Health Care System
VHA: Veterans Health Administration

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Protocol

Transfer Validity of Pediatric Supracondylar Humeral Fracture Pin Placement Practice on In-Theater Performance by Orthopedic Trainees Using an Augmented Reality Simulator: Protocol for a Pilot Interventional Cohort Study With a Retrospective Comparator Cohort

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Abstract

Background: Supracondylar humeral fractures (SCHF) are a common cause of orthopedic morbidity in pediatric populations across the world. The treatment of this fracture is likely one of the first procedures involving x-ray–guided wire insertion that trainee orthopedic surgeons will encounter in their career. Traditional surgical training methods of “see one, do one, teach one” are reliant on the presence of real-world cases and must be conducted within an operative environment. We have developed an augmented reality simulator that allows trainees to practice this procedure in a radiation-free environment at no extra risk to patients.

Objective: This study aims to examine whether training on a simulator in addition to traditional surgical training improves the in-theater performance of trainees.

Methods: This multicenter, interventional cohort study will involve orthopedic trainees from New Zealand in their first year of advanced training between 2019 and 2023. Advanced trainees with no simulator exposure who were in their first year in 2019-2021 will form the comparator cohort, while those in the years 2022-2023 will receive additional regular simulator training as the intervention cohort. The comparator cohort’s performance in pediatric SCHF surgery will be retrospectively audited using routinely collected operative outcomes and parameters over a 6-month period. Data on the performance of the intervention cohorts will be collected in the same way over a comparable period. The data collected for both groups will be used to determine whether additional training with an augmented reality training shows improved real-world surgical outcomes compared to traditional surgical training.

Results: As of February 2022, a total of 8 retrospective comparator trainees have been recruited by email. The study is financially supported through an external grant from the Wishbone Orthopaedic Research Foundation of New Zealand (September 2021) and an internal research grant from the University of Otago (July 2021).

Conclusions: This protocol has been approved by the University of Otago Health Ethics committee (reference HD21/087), and the study is due for completion in 2024. This protocol may assist other researchers conducting similar studies in the field.

Trial Registration: Australian New Zealand Clinical Trials Registry ACTRN12623000816651; https://tinyurl.com/mtdkecwb

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KEYWORDS

pediatric orthopedics; augmented reality simulator; supracondylar humeral fractures; closed reduction and percutaneous pinning; transfer validity; fracture; surgeons; education; practice; trainees; pediatric; orthopedic; training; surgical procedure

Introduction

Background

Supracondylar humeral fractures (SCHF) of the elbow are one of the most common orthopedic causes of morbidity in children. SCHF represent 3.3% to 16.6% of all childhood fractures, 32.6% of upper extremity fractures, and 57.5% of elbow fractures across localities [1-4]. The Gartland classification system is used for characterizing the extension type of SCHF and is dependent on the degree of humeral fragment displacement [5]. The gold standard for the management of operative cases is closed reduction and percutaneous pinning (CRPP), unless severe neurovascular compromise or an open fracture is present [6-8]. CRPP is seen as a more effective and safer method for treating displaced SCHF than nonoperative and open reduction methods [9-12].

Current Training

The status quo of apprenticeship-style orthopedic training does not enable standardized hands-on skill practice outside of the operating room. The “see one, do one, teach one” methodology is becoming increasingly insufficient as trainees face a decrease in work hours for necessary well-being needs. This decrease in work hours means there are fewer opportunities for trainees to participate in and therefore learn from real cases. Limiting training to the operating room also incurs both financial and opportunity costs to the health care system as trainees require more time to complete procedures than consultants [13,14]. In addition to costs and reduced availability of the current method of training, there is also the question of whether apprenticeship-style teaching is really the most effective form of teaching available. Numerous studies on learning and teaching for adults have shown that independent, deliberate, and repeated practice is most effective for skill acquisition [15-18]. By nature, apprenticeship-style training allows for the repetition of individual case types but not a deliberate practice of certain aspects of the skills, such as only percutaneous pinning in CRPP.

An Alternative Training Method

Improvements in computer technology have afforded the development of a new method of surgical training—augmented reality (AR) simulation. Using AR technology, skill acquisition can take place before entering the operating room. CRPP requires a high level of hand-eye coordination, visuospatial reasoning to interpret the X-ray image, and haptic interpretation to be able to feel the wire entering or leaving the bone. One such example was developed by our research team. The “BoneDoc AR” simulator (University of Otago) that we have produced uses an iPad app to provide real-time simulated X-ray images, while trainees are drilling through a physical model of the elbow. This physical model is made of silicone soft tissue and 3D-printed plastic bones. In addition, the simulator can provide objective measures of proficiency, such as exact pin placement, which are not possible without the use of computed tomography scans. These objective measures may be of value in providing feedback on skills acquisition during surgical training.

Study Overview

Appropriate validation of the BoneDoc AR simulator is necessary to determine its usefulness in surgical training. Transfer validity, the ultimate test of a surgical simulator, is the transfer of skills acquired on a simulator into the real-world operating theater. Validity tests are necessary to ensure the efficacy of a simulator in a training environment [19]. There are few surgical AR simulators, which have shown positive transfer validity, and none on AR simulators of SCHF treatment [20]. There is a clear paucity in the literature of this field, and there is a need for further research. This pilot study aims to examine the transfer validity of orthopedic trainee practice on the BoneDoc AR simulator.

We hypothesize that training with the simulator will improve in-theater performance as defined by a reduction of theater time, number of fluoroscopy images taken, postsurgical complication rates, and an increase in pinning accuracy. In all metrics, intervention trainees will be compared with retrospective-matched comparator trainees.

Methods

Study Setting

This multicenter, interventional cohort study will involve first-year orthopedic trainees stationed in New Zealand hospitals between 2019 and 2023.

Trainee performance will be collected across hospitals located in Invercargill, Rotorua, Timaru, Palmerston North, Whanganui, Taranaki, Tauranga, Christchurch, Waikato, and Auckland for 2022. The locations of first-year trainees in 2023 are yet to be determined. Retrospective comparator performances will be collected through training logbooks and electronic patient records.

Eligibility Criteria

The inclusion criterion was being a full-time registered first-year orthopedic trainee in New Zealand between 2019 and 2023.

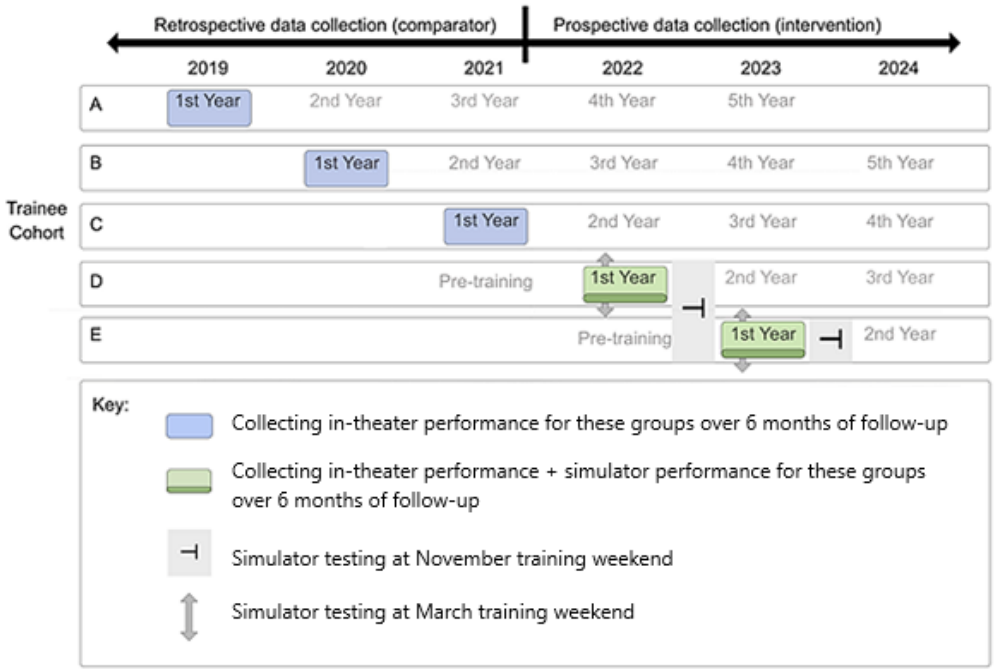
Study Design

The intervention cohort is composed of trainees using the BoneDoc AR simulator at least once per month over a follow-up

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period of 6 months (May to November) in the years 2022-2023 (Figure 1).

Figure 1. Schematic representation of the intervention and comparator data collection timeline.



Recruitment

Intervention group trainees will be approached at training weekends to inform them about the study, to assess eligibility, and to receive consent. Comparator group trainees will be identified from the New Zealand Orthopaedic Association trainee registry and approached via email for this process. Enrollment for comparator group trainees will begin in February 2022, and enrollment for intervention group trainees will occur in the March training weekends of 2022 and 2023.

We aim to include data for 14 trainees in 2022; however, the number of trainees in 2023 is not yet known. The comparator cohort data will be retrospectively audited from trainees who undertook traditional training without exposure to the simulator during their 6 months of follow-up in the years 2019, 2020, and 2021 (n=41). We expect a total sample size of approximately 65 trainees, given an average of 12 new trainees per annum. The comparator group is matched based on their length of registered training at the start of follow-up, that is, first-year trainees with 2 months of registered training.

The in-theater performances of the comparator and intervention groups will be compared using cumulative sum charts for each of the primary outcomes to determine any differences in trends of skill acquisition according to the method of training. The simulator performance of the intervention group will be used to establish a learning curve and compared with in-theater learning curves.

Retrospectively matched trainees have been chosen instead of prospective randomized ones for the comparison group in order to maximize sample size and to avoid contamination. New Zealand only introduces 10-15 trainees per year into the orthopedic training program, and thus a prospective randomized trial will greatly limit the statistical power. There is also the chance of cross-group contamination as there is no way of ensuring comparator trainees located in the same area as intervention trainees will not use the simulator.

Interventions and Comparators

Intervention

The simulator will be first administered at the March training weekends for each year. We will use these training weekends to test participants at baseline on the simulator and collect demographic data via survey. The simulator will be set up as one of the 15-minute assessment stations in the training weekend. Simulator sets will be distributed to individual trainees following the training weekend. Upon delivery of the simulator sets, the principal investigator will also provide aid to the trainee in identifying an appropriate environment for the simulator and address any setup issues.

It is then expected that trainees will undertake, at minimum, monthly 15-minute practices on the simulator for the next 6 months of training. These practice data are sent to a cloud server after each use. Note that the simulator training will be in addition to any routine training they will receive at their respective hospitals. Over this time, primary end points for each in-theater case will be taken over the course of follow-up through District Health Board (DHB) records, including patient picture archiving and communication system (PACS) records and trainees' logbooks.

We will request intervention trainees to write out relevant patient data and end point results as the cases present to maximize accuracy. Trainees will be reminded monthly by email to provide case data and practice on the simulator. Their simulator performance will be assessed again in a controlled environment during the November training weekend. At this point, secondary end points will also be collected via survey.

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Comparators

The comparator cohort's follow-up will begin in February of each year. This is due to the change to the training schedule instated at the end of 2020 whereby trainees began their rotations in February instead of the prior December.

Primary outcomes will be collected retrospectively via trainee logbooks and patient PACS records for retrospective data. Secondary outcomes will not be collected for comparators.

Data Collection

Outcomes

Primary End Points—Collected for Each In-Theater Case Over Follow-up

- Theater time and radiation time in seconds (radiation time may not be available from retrospectively assessed notes but will be attained where possible)—collected from procedure reports from electronic patient records
- Number of fluoroscopy shots—collected from patient PACS records
- Pin accuracy—accuracy is defined based on procedural recommendation literature—analyzed from patient PACS records
- Complication/nonideal union incidence—stratified for types of complications (nerve injury, vascular injury, loss of reduction, compartment syndrome, and infection)—collected from reviews of medical records and letters of referral from electronic patient notes

These primary end points have been determined as measurements of trainee performance, which are relatively easily retrieved from patient records and trainee logbooks.

The number of fluoroscopy shots and radiation time can be used to approximate the amount of radiation patients and staff are exposed to. In particular, for patients, theater time and radiation exposure have been shown to correlate to a higher chance of complications and thus should be avoided [21]. Studies have shown a decrease in both measurements for SCHF treatments with increased trainee proficiency [22,23]. Pin accuracy affects the stability of union, and there are well-established guidelines for ideal position of pins.

Ultimately, postoperative complications and nonideal union are the most crucial outcomes the trainees should aim to avoid. We do not expect to see high rates of these for either group, but overall rates will be monitored for comparison.

Secondary End Points—Experience With the Simulator and Surgery—Collected at the End of Follow-up Training Weekend for Intervention Trainees

- Total number of times using the simulator over follow-up—collected from the BoneDoc AR app
- Frequency of using the simulator—collected from the BoneDoc AR app
- Perceived familiarity with SCHF by the end of the follow-up—determined from a 5-point Likert scale administered with a brief electronic survey:
  - Unfamiliar
  - Somewhat unfamiliar
  - Neither familiar nor unfamiliar
  - Somewhat familiar
  - Familiar
- Total number of SCHF treatments undertaken over follow-up—calculated using the entries from trainee logbook
- Number of mistakes while using the simulator—defined by the number of times the trainee reconsiders pin, collected from the BoneDoc AR app
- Pinning accuracy on simulator—final pin and range of mistakes as calculated by the simulator—collected from the BoneDoc AR app

Patient Data

Data such as the National Health Index (NHI) number and surgical details will be collected from trainee logbooks. The following data will be collected from the corresponding DHB records: NHI number; time and date of presentation to the emergency department; age; sex; ethnicity; side of fracture; Gartland classification of fractures—type I, type II, type III, and type IV; the presence of consultant or any other assistants in surgery.

Statistical Analysis

Operative outcomes using data taken before or without ongoing exposure to the simulator will be compared to outcomes using data from trainees who have used the simulator after 1 year. Comparisons will be performed using Student *t* tests or Wilcoxon Rank Sum tests (depending on the distribution of the data) for theater time and chi-square or Fischer exact tests (depending on the count of the outcome) for the number of complications, number of accurate pin placements, and number of mistakes.

Primary end points will be plotted on separate cumulative sum curves to show trends in performance over the course of follow-up by individuals and aggregated according to pre- and post–1-year simulator training. Control limits will be determined based on values identified in the literature and consultation with senior orthopedic consultants [22-24].

Accuracy of pin placements in subsets of images measured twice must be based on anterior-posterior, lateral, and oblique radiographs. Measurements taken will need to be compared for intra- and interobserver reliability using Bland-Altman plots and intraclass correlation scores.

The results from the familiarity questionnaire will be summarized as responses per category.

Univariable ordinary least squares regression analyses will be used to examine the association of theater time, number of complications (including nonideal unions), and number of x-ray shoots with independent variables. Logistic regression will be used to examine the association of accurate pin placement (yes or no) with independent variables. Independent variables will be the number of times the simulator is used, the number of SCHF procedures performed prior to intervention, Gartland classification, scores on tests of spatial awareness, and the number of SCHF procedures performed during the intervention. Independent variables that are significantly associated with a

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primary end point ($P<.05$) will be included as covariates in multivariable analyses. Appropriate model diagnostics, and where required, data transformations will be used.

Software

All analyses will be performed using the statistical analysis software R (R Foundation) [25].

Data Management

Adverse events are unexpected with the use of the simulator, as trainees have operative experience and there is a low infection risk. Nevertheless, an independent data monitoring committee (DMC) has been setup consisting of 2 clinicians and will be reported to by a study researcher. Any adverse events will be reported immediately to the committee by trainees directly, and the committee may request an interim analysis of the data collected up to that point. The committee can request that the study be paused or discontinued based on the data they receive. The DMC will meet every 6 months to discuss this project.

Study researchers will ensure that the participants' anonymity is maintained. The participants will be identified only by a participant's ID number. Individual patients will not be contacted by a researcher. Identifiable patient and participant data will be anonymized and stored on secure University of Otago servers, and will only be accessible by the researchers directly involved with this data collection. Analysis will be performed only on anonymized data sets with an anonymous identifier instead of NHI numbers. The study will comply with the Data Protection Act, which requires all data to be anonymized as soon as it is practical to do so. Data will be stored for 10 years after the conclusion of the study and subsequently destroyed.

Ethical Considerations

The principal investigator will ensure this that study is conducted in full conformity with the current revision of the Declaration of Helsinki (last amended in October 2000, with additional footnotes added in 2002 and 2004). The principal investigator will ensure that this study is conducted in full conformity with relevant regulations and with the ICH Guidelines for Good Clinical Practice (CPMP/ICH/135/95) July 1996. Our study was approved by the University of Otago Health Ethics committee (reference HD21/087).

Any important protocol modifications will be communicated in a timely manner to trial participants already enrolled and the DMC in a timely manner.

The results of this study will be disseminated through peer-reviewed publications and conference proceedings. Trial participants will be provided with the option to receive notification of any disseminated results upon enrollment.

Results

As of February 2022, a total of 8 retrospective comparators have been recruited by email.

Discussion

Strengths and Limitations

This study is not a randomized trial and uses historical comparators, which may limit our ability to generalize the results due to confounding factors. We aim to mitigate the effects of potential confounding factors by matching comparators based on training experience. Potential confounding variables will be collected at baseline for both groups and explored for associations with our outcome measures. In monitoring the learning curves of both groups over time, a difference-in-difference analysis will be performed to explore simulator effects. The quality of patient data and logbook entries by historical trainees will determine the quality of our comparator data; however, we are confident that the primary outcomes we have chosen are sufficiently routinely collected for surgical cases.

This is the first surgical simulator validation study conducted across all New Zealand centers with early-stage trainees and will be invaluable for establishing a pathway for future New Zealand studies. In collaborating with the training organization at the early stages of testing, and continuous collaboration over the course of the project, the formal integration of this simulator into training can be streamlined. Collaborations for this study also exist with orthopedic surgeons in the United States. Successful multicenter testing in New Zealand is likely to lead to further testing in the United States, thereby improving the external validity of this simulator and possible integration into international training programs.

Conclusions

The results of this pilot study will show the feasibility and efficacy of simulator use within New Zealand's public health system. The long-term benefits to society will be both for the education of registrars and the health outcomes of patients. In particular, for trainees in localities with lower populations, this simulator can address the disparity in case volumes for those that would otherwise have been deprivileged by their location. Moreover, this simulator has been developed with minimizing costs and increasing accessibility as key objectives; it is cheaper than many currently available models and has low requirements for the environment. We envisage its frequent use as a valuable tool within hospital systems.

Acknowledgments

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Data Availability

The deidentified data will be attached as a multimedia appendix to the final published manuscript once the study is completed.

Authors' Contributions

PB and JG conceptualized the study, JG, KC, and PB designed the study methodology. NH and HC provided clinical guidance for the study methodology. JG and PB acquired the funding for this study. JG drafted the manuscript. KC, PB, NH, and KC critically reviewed the manuscript. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

PB has ownership of the intellectual property rights of the BoneDoc AR simulator app. All other authors declare that they have no conflicts of interest.

Multimedia Appendix 1
Peer-review reports (1) from the University of Otago - Dunedin School of Medicine Research Student Support Committee (New Zealand).
[PDF File (Adobe PDF File), 229 KB - resprot_v12i1e38282_app1.pdf]

Multimedia Appendix 2
Peer-review reports (2) from the University of Otago - Dunedin School of Medicine Research Student Support Committee (New Zealand).
[PDF File (Adobe PDF File), 209 KB - resprot_v12i1e38282_app2.pdf]

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Abbreviations

AR: augmented reality
CRPP: closed reduction and percutaneous pinning
DHB: District Health Board
DMC: data monitoring committee
NHI: National Health Index
PACS: picture archiving and communication system
SCHF: supracondylar humeral fractures

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Protocol

Effectiveness of an Emergency Department–Based Machine Learning Clinical Decision Support Tool to Prevent Outpatient Falls Among Older Adults: Protocol for a Quasi-Experimental Study

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Abstract

Background: Emergency department (ED) providers are important collaborators in preventing falls for older adults because they are often the first health care providers to see a patient after a fall and because at-home falls are often preceded by previous ED visits. Previous work has shown that ED referrals to falls interventions can reduce the risk of an at-home fall by 38%. Screening patients at risk for a fall can be time-consuming and difficult to implement in the ED setting. Machine learning (ML) and clinical decision support (CDS) offer the potential of automating the screening process. However, it remains unclear whether automation of screening and referrals can reduce the risk of future falls among older patients.

Objective: The goal of this paper is to describe a research protocol for evaluating the effectiveness of an automated screening and referral intervention. These findings will inform ongoing discussions about the use of ML and artificial intelligence to augment medical decision-making.

Methods: To assess the effectiveness of our program for patients receiving the falls risk intervention, our primary analysis will be to obtain referral completion rates at 3 different EDs. We will use a quasi-experimental design known as a sharp regression discontinuity with regard to intent-to-treat, since the intervention is administered to patients whose risk score falls above a threshold. A conditional logistic regression model will be built to describe 6-month fall risk at each site as a function of the intervention, patient demographics, and risk score. The odds ratio of a return visit for a fall and the 95% CI will be estimated by comparing those identified as high risk by the ML-based CDS (ML-CDS) and those who were not but had a similar risk profile.

Results: The ML-CDS tool under study has been implemented at 2 of the 3 EDs in our study. As of April 2023, a total of 1326 patient encounters have been flagged for providers, and 339 unique patients have been referred to the mobility and falls clinic. To date, 15% (45/339) of patients have scheduled an appointment with the clinic.

Conclusions: This study seeks to quantify the impact of an ML-CDS intervention on patient behavior and outcomes. Our end-to-end data set allows for a more meaningful analysis of patient outcomes than other studies focused on interim outcomes, and our multisite implementation plan will demonstrate applicability to a broad population and the possibility to adapt the intervention to other EDs and achieve similar results. Our statistical methodology, regression discontinuity design, allows for

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causal inference from observational data and a staggered implementation strategy allows for the identification of secular trends that could affect causal associations and allow mitigation as necessary.

Trial Registration: ClinicalTrials.gov NCT05810064; https://www.clinicaltrials.gov/study/NCT05810064

International Registered Report Identifier (IRRID): DERR1-10.2196/48128

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KEYWORDS

falls; emergency medicine; machine learning; clinical decision support; automated screening; geriatrics

Introduction

Falls are highly prevalent among older adults in the United States [1,2] and are a common reason for emergency department (ED) visits [2-4]. They often precipitate a decline in the patient's overall health and ability to perform activities of daily living, such as dressing, bathing, and toileting [3,5]. ED providers are important collaborators in preventing at-home falls because they are often the first providers to see a patient after a fall (secondary prevention) [1] and because outpatient falls are often preceded by previous ED visits (primary prevention) [6]. This phenomenon is especially true for patients being discharged from the ED [3].

Patients presenting to the ED are at higher risk of falls than the general population and are more likely to face barriers that limit their access to screening and interventions available in other health care settings [7-12]. While previous work has shown that ED referrals to falls prevention interventions can reduce the risk of an at-home fall by 38% [13], ED-based interventions to identify and refer high-risk older adults for falls prevention services have not been widely implemented [14]. Major barriers to fall risk screening in the ED include the additional time and resources necessary to perform in-person screening, but the integration of machine learning (ML) and clinical decision support (CDS) offers the possibility of automating the screening process, thereby making it feasible to incorporate in routine ED practice at scale without adding to provider cognitive burden [15-19]. However, it remains unclear whether the automation of such screening and referral systems can reduce the risk of future falls among older patients. The goal of this paper to is describe a research protocol for a study evaluating the effectiveness of an automated screening and referral intervention, both in terms of leading to evaluations at the Mobility and Falls Clinic and preventing future falls.

More generally, this study will provide data on the effectiveness of a model of an automated intervention to identify and refer patients during an ED visit. This model of care is extensible to many other conditions and situations in which ED patients would benefit from screening and primary or secondary prevention services.

Methods

Setting and Patient Population

This study takes place at 3 EDs, described in Table 1, within a health system in the Midwestern United States. All 3 EDs share an instance of the electronic health record (EHR) developed by Epic, though system configuration (eg, nursing flow sheets and order sets) is not identical at the 3 sites.

Table 1. Intervention settings.

ED[a] site	Type	Intervention implementation date	Approximate annual volume of patients, n	Staffing
ED 1	Academic, level 1 trauma center	February 22, 2022	60,000 (25% geriatric)	Attending group 1, advanced practice providers, residents
ED 2	Community	September 27, 2022	22,000 (28% geriatric)	Attending group 1, advanced practice providers
ED 3	Community	Planned September 2023	65,000 (20% geriatric)	Attending group 2, advanced practice providers

[a]ED: emergency department.

The patient population for our study is individuals aged 65 years or older who present to participating EDs between February 22, 2022, and spring 2026, were discharged, and who had (at the time of ED visit) a primary care provider practicing within the health system in which this study is based. Because the ML-based CDS (ML-CDS) will be implemented in a rolling fashion at different EDs within the system, the start date for data will vary at different study sites. Dates were chosen to have at least two years' worth of index ED data for each site and an additional 6 months of follow-up ED visits to identify subsequent falls.

Intervention

These patients will be evaluated by our ML algorithm, and patients at high risk for an at-home fall within the next 6 months were flagged by our CDS when a provider documented a disposition of discharge from the ED [20,21]. The intervention, as well as training and validation of the algorithm, are limited to this in-system patient population for 2 reasons: first, these patients have a more complete patient history in the EHR for

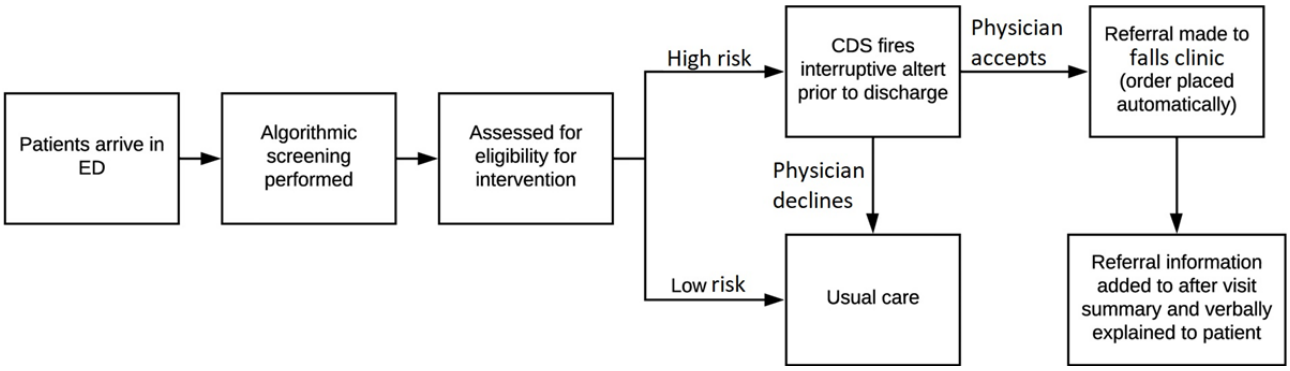
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the algorithm to draw on, and second, this restriction mitigates the possibility that access to care or insurance coverage network would be a barrier to patients being seen in the falls clinic.

The study intervention applies automation to harness existing data resources and information systems both to estimate risk at the patient level and to facilitate referral among high-risk patients. This risk estimate drives a CDS tool that presents a referral recommendation to the physician within the ED workflow. This selective application of automation is aligned with human factors principles [21-24] and allows busy clinicians to improve patient care without interruption to existing workflows.

To support efforts by ED providers to prevent falls among older adults, our team has developed an ML-based CDS algorithm to identify the risk of a return to the ED for a fall for discharged patients [20]. This algorithm was subsequently incorporated into the EHR (Epic Systems). When providers are preparing to discharge a patient, this CDS alerts the ED provider if the ML algorithm identified the patient as at high risk of an at-home fall in the next 6 months and recommends referral to an outpatient mobility and falls clinic [21]. This process is illustrated in Figure 1 [21]. The ML algorithm will be retrained with the same feature set for each site prior to implementation. Implementation at each site will be done in compliance with institutional practice for CDS changes, following human factors engineering principles [23,24], and using best practices for ML-based CDS implementations [25].

Figure 1. Operationalization of automated falls risk screening and referral process in the ED (adapted from Jacobsohn et al, reused with permission from Elsevier [21]). CDS: clinical decision support; ED: emergency department.



At the outpatient clinic, patients receive an evidence-based, multidisciplinary intervention to help them reduce their risk of a fall [13]. Together, the algorithm and associated CDS tool form a novel automated screening and referral intervention that was designed and implemented using a human factors engineering framework to ensure both usability and an emphasis on patient safety [21-23].

Outcomes

Our primary outcome is the rate of completed referrals to the Mobility and Falls Clinic among patients identified as high-risk. We define a completed referral as a patient completing an initial visit with a falls prevention specialist at the mobility and falls clinic.

Our secondary outcome is return visits to any ED for a fall within 6 months of the index ED visit, the outcome our ML algorithm was trained to predict. This outcome is meant to reflect the overall effectiveness of the intervention in preventing falls among patients identified as high-risk.

Additional process outcomes will be investigated to deconstruct steps from the identification of high-risk patients to completed referrals. These include whether a patient was referred to the outpatient mobility and falls clinic after being identified as high risk, whether referred patients were reached by schedulers, and whether referred patients scheduled an initial appointment, regardless of whether they attended.

Data Collection

Variables

Variables for analysis were selected conceptually based on the Andersen behavioral model of health services use, a well-established model that provides a context for characterizing the many factors which lead to health care use [26-29]. Within this model, both contextual and individual factors influence patients' initial ED visits and downstream health care use and outcomes. This model has been used to frame numerous prior studies involving ED use and falls among older adults [30,31], as well as the initial design and validation study of this intervention. During previous work, we have built a rich data set of covariates with over 700 potential EHR data features at ED 1 and will add data from ED 2 and ED 3 using the same data definitions [20]. These include patient factors, such as age, sex, race, ethnicity, and previous health system use; enabling factors, such as financial and physical availability of care; and ED encounter level factors, such as treatment team composition, ED length of stay, reason for visit, emergency severity index, diagnostic tests, and pharmaceutical and therapeutic interventions.

Data Retrieval Process

Data will be collected from the EHR in 4 steps. First, we will retrieve data about the patient, their index ED visit, and falls risk information—ML algorithm risk score, walking aids, history of falls, and acute care usage—from the EHR. Second, these data and information about referral orders and subsequent scheduled visits with the mobility and falls clinic will be

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uploaded to a Health Insurance Portability and Accountability Act (HIPAA)-compliant database built in a Research Electronic Data Capture (REDCap; Vanderbilt University) database [32]. This REDCap database is needed so documentation about the reason a patient did not ultimately schedule or attend the clinic visit can be abstracted. Specific reasons for not completing the referral are not always documented discretely, so they will be abstracted from free-text scheduler notes by 2 trained reviewers. Specifically, the reviewers will look for reasons the patient was documented to be ineligible. Reasons include whether the patient is in other physical therapy, in hospice, or in memory care; is too advanced to benefit, immobile, or wheelchair-bound; and whether the patient or caregiver declined or was unreachable. Third, after verifying outcome variables and the reason for not scheduling a visit, the data on the clinic visit will be joined with the curated data described above into a limited data set for analysis. Finally, falls outcome data will be merged with Medicare claims data to determine if the patient was treated for a fall at an outside ED.

Statistical Analyses

Primary Outcome: Completed Referrals

The primary association of interest is whether an ED-based referral from an ML-based CDS can successfully cause patients to complete a specialist appointment. To assess the effectiveness of our program for patients receiving the falls risk intervention, our primary analysis will be to obtain point estimates and the 95% Wald CI of referral completion rate by site. We will perform a similar analysis to identify rates for prespecified process metrics, including referral orders placed among flagged patients and clinic appointments scheduled among at-risk patients. Further, we will perform a secondary analysis to identify subgroups at risk for lower odds of referral completion using a logistic regression model for each site to predict referral completion as a function of demography (sex, age, race, ethnicity, and education) and fall risk score. A model built for each site will account for site-level variability. Estimated coefficients and their 95% CIs will indicate risk factors for poor referral completion. This will help inform future implementation by, for example, identifying risk score thresholds for obtaining target rates of completed referrals for a given patient population.

Secondary Outcome: Return Visits to ED for a Fall

Although the intervention is not randomized, our study has a quasi-experimental design known as a sharp regression discontinuity with regards to intent-to-treat, since the intervention is administered to patients whose risk score falls above some threshold. This design allows for causal inference, provided that differences in outcomes for patients with similar risk scores can be attributed to the intervention (formally, expected potential outcomes are continuous in risk score). This occurs when patients are not manipulating their assignment to the intervention. Assuming this holds, we will primarily analyze only those patients whose risk scores fall within a band around the risk score threshold. Additionally, patients will be stratified by ED arrival date to account for changes to this threshold to be aligned with a sharp research continuity design. A conditional logistic regression model will be built to describe 6-month fall risk at each site as a function of the intervention, patient demographics, and risk score. The odds ratio of a return visit for fall and the 95% CI will be estimated by comparing those identified as high risk by the ML-CDS algorithm and those who were not but had a similar risk profile. Sensitivity analyses will be performed to examine the influence of bandwidth choice and key assumptions (ie, continuity of potential outcomes and linearity in risk score) on estimates. A secondary analysis will be to investigate the effect of covariates on completed referrals and falls using a stratified Cox proportional hazards model for time-to-fall events (right-censored by follow-up time).

Statistical Power

With the plan to flag 5 patients per week at each referral site, we plan to refer 520 patients per site, generating 1560 total patients referred. A sample size of 520 would lead to 95% Wald CI for referral completion rate by site that is 8.6% in width or smaller. This width provides sufficient precision for our study, considering that (1) a completion rate as small as 10% would be clinically meaningful and (2) we expect to observe a referral completion rate of 50% or higher—in which case, there would be nearly 100% power to reject a referral completion rate of 10% at a significance level of .05 when n=520.

For reference, very few patients were referred from the ED to the mobility and falls clinic prior to our intervention, and the clinic estimates that 80% of their patients referred from other providers visit the clinic. Power can be estimated for detecting a significant intervention effect on fall risk, provided additional covariates are ignored. In this case, a score test for this effect is equivalent to a Cochran-Mantel-Haenszel test of independence in a stratified sample. Such a test has 89.7% power to detect a difference in fall risk of 10% in a stratified sample size of 12 groups (in twelve 8-week periods over 2 years) assuming (1) a significance level of .05, (2) 40 patients receive the intervention and 40 patients do not who have similar risk scores, and (3) an average fall risk of 25%. For reference, our preliminary work predicted a number to treat of about 10 (ie, a fall risk difference of 10%) when setting the risk score threshold so that 5 persons per week receive the intervention (or 40 persons per 8 weeks) and an average fall risk of about 25% for individuals with a fall risk score above or near the fall risk score threshold. We plan on exploratory analysis of pooled data to evaluate the effect of specific covariates on rates of referral; in these cases, power will be lower based on the incidence of specific covariates in the data.

Data Protection

The major potential risk to subjects is that of loss of confidentiality. We have policies and procedures in place to protect the confidentiality and security of patient data, and our data protection measures (for protected health information) are consistent with HIPAA privacy and security rules. Only persons directly involved in the project will have access to patient data. Access to computer-stored information will be strictly controlled with data stored on servers physically sequestered and protected behind both physical and digital access controls. All servers are behind our organization's HIPAA firewall. All project personnel have successfully completed institutionally required human subjects training (required every 3 years) and HIPAA privacy and security training (required every year).

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Dissemination

Our multidisciplinary team spans emergency medicine, engineering, health services research, and biostatistics, facilitating dissemination to a diverse and multidisciplinary audience. We will leverage institutional resources across the health system and university and capitalize on the breadth of professional networks offered by our interdisciplinary team to ensure broad dissemination. Dissemination of findings and of the final intervention will be accomplished through 2 channels. Academic dissemination will occur through publication in relevant peer-reviewed journals and presentations at national conferences focused on aging research, informatics, human factors, and emergency medicine. We will also share findings at end-user and EHR-focused conferences to reach potential adopters who might not be reached by more formal outlets.

Ethics Approval

This research plan was reviewed and approved by the University of Wisconsin Health Sciences Institutional Review Board (2021-0776). This observational quasi-experiment is registered with clinicaltrials.gov (NCT05810064).

Results

As of April 30, 2023, the CDS tool has been implemented at 2 of the 3 sites. Providers at ED 1 have written 303 referral orders for 260 unique patients, or 5 referrals per week on average, which is our goal. ED 2, the community ED, has not been live with the ML-CDS as long, and providers have written 91 referral orders for 86 different patients, or just over 3 referrals per week. Both EDs refer roughly 30% of patient encounters the algorithm identifies: 303 referrals for 1007 patients flagged at ED 1 and 91 referrals for 319 patients flagged at ED 2. The patient populations between these 2 EDs have substantial overlap, and 6 patients have received referrals from both EDs. After conversations with the mobility and falls clinic, we do not see repeat referrals as a problem unless the patient has already completed 1 of the referrals, so our ML-CDS tool was updated to exclude patients with a completed or scheduled appointment at the mobility and falls clinic. Notably, the patient uptake of the final intervention is about 15% of patients referred—45 patients of 339 unique patients; 1 patient was seen at and referred by both ED 1 and 2—which is less than the 80% that the clinic estimates for other referral sources. While not surprising that uptake would be lower from ED provider referrals than from primary care provider referrals, this conversion rate is lower than we anticipated, and we have taken steps to improve messaging, patient follow-up, and providers' ability to talk to patients about the program, and we have taken other steps that have shown some improvement appointment conversion in recent months. Additionally, waning concerns about COVID-19 have seemed to increase patients' willingness to consider completing the referral.

Discussion

Hypothesis and Expected Findings

We expect that this research will show the beneficial impact of automated screenings on both patients receiving recommended care (completed referrals) and preventing adverse outcomes (falls). Even for patients who are not referred, we anticipate providers having conversations with patients who are flagged as high risk for a fall, which could still lead to increased compliance with ongoing treatment or seeking falls prevention treatment outside our partner clinic (eg, physical therapy available at an assisted living facility). These findings will inform ongoing discussions about the use of ML and artificial intelligence to augment medical decision-making.

Significance of Principal Findings

Previous work with ML-CDS tools has focused on their implementation in a specific context [33] or on the predictive performance [34] of the underlying algorithm. Our unique data set will include information about patient's health history (eg, health care use) prior to the ED index visit, referral completion, and subsequent ED return visits for falls (either in the system or from Medicare claims), providing a more complete picture of a given patient's trajectory than most studies. We will use this unique data set to track not just ML-CDS performance in the context of its implementation, but in the context of larger patient health outcomes, which, to our knowledge, has not been done for this kind of long-term, preventative ML-CDS system. Similarly, the multisite implementation plan will demonstrate applicability to a broad population and the possibility to adapt the intervention to other EDs and achieve similar results.

Our statistical methodology (a regression discontinuity design) allows for an intent-to-treat causal inference about the impact flagging high-risk patients can have on patients' future falls. Conversations with patients about the referral, even if a referral is not written, could have impacts on patients' risk awareness and compliance with physical therapy, so ML-CDS flagging is the correct epidemiologic exposure to assess with respect to the outcomes of completed mobility and falls visits or return ED visits for falls. A staggered implementation strategy allows for the identification of secular trends that could affect causal association and mitigation as necessary.

Limitations

To achieve the desired number of clinic referrals per week, the falls risk threshold for the CDS identification will be changed over time. Because regression discontinuity designs typically assume a static threshold for analysis, we will need to approach the regression discontinuity analysis carefully and with sufficient sensitivity analyses to ensure that these threshold changes do not compromise the findings. Simulation studies will be conducted to ensure the assumptions of regression discontinuity analysis are met.

Clinically, our assumptions about the effectiveness of the mobility and falls clinic intervention are based on PROFET (Prevention of Falls in the Elderly Trial) [13], which specifically evaluated patients referred from the ED. The intervention is based on evidence from a randomized clinical trial, but the magnitude of the effect may be different in our patient population—for example, due to endogenous factors like demographic composition of the community or exogenous factors related to changes in care patterns during the COVID-19 pandemic. In addition to methodological concerns, there are

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some pragmatic limitations. First, the intervention was implemented during the COVID-19 pandemic. During the study period and community, there were—and could continue to be—multiple waves of elevated SARS-CoV-2 infections and case counts that may dissuade some patients from scheduling an appointment at the mobility and falls clinic. Similarly, in order to maximize patient impact and to study the human factors inputs to this system, efforts were made to increase referral rates and referral completion with providers and patients. While these efforts will likely increase the statistical power over time, it is also likely that there will be secular effects in the imperfect compliance with referral rates and referral completion rates that are present in the data as a result of these efforts.

Acknowledgments

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Authors' Contributions

DJH wrote and edited the manuscript and designed and built the data extraction and retrieval process. ALC performed substantial editing and review of the manuscript, is a coinvestigator on the Agency for Health Care Research and Quality R18 grant, and provided biostatistical expertise for the analysis plan presented in the manuscript, research plan, and R18 grant. APM and HJB reviewed and edited the manuscript, gave substantial feedback on data management processes, and helped manage the team. BWP is the principal investigator on this project and provided substantial manuscript editing and review and clinical expertise for the intervention design and implementation. MNS, DW, MAS, and FL provided manuscript review and substantial contributions to the study conception and design.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Summary Statement and Peer Review from Healthcare Information Technology Research (HITR) - Agency for Healthcare Research and Quality (USA).
[PDF File (Adobe PDF File), 128 KB - resprot_v12i1e48128_app1.pdf]

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Abbreviations

CDS: clinical decision support
ED: emergency department
EHR: electronic health record
HIPAA: Health Insurance Portability and Accountability Act
ML: machine learning
ML-CDS: machine learning–based clinical decision support
PROFET: Prevention of Falls in the Elderly Trial

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Protocol

A Live Video Dyadic Resiliency Intervention to Prevent Chronic Emotional Distress Early After Dementia Diagnoses: Protocol for a Dyadic Mixed Methods Study

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Abstract

Background: By 2030, approximately 75 million adults will be living with Alzheimer disease and related dementias (ADRDs). ADRDs produce cognitive, emotional, and behavioral changes for persons living with dementia that undermine independence and produce considerable stressors for persons living with dementia and their spousal care-partners—together called a “dyad.” Clinically elevated emotional distress (ie, depression and anxiety symptoms) is common for both dyad members after ADRD diagnosis, which can become chronic and negatively impact relationship functioning, health, quality of life, and collaborative management of progressive symptoms.

Objective: This study is part of a larger study that aims to develop, adapt, and establish the feasibility of Resilient Together for Alzheimer Disease and Related Dementias (RT-ADRD), a novel dyadic skills-based intervention aimed at preventing chronic emotional distress. This study aims to gather comprehensive information to develop the first iteration of RT-ADRD and inform a subsequent open pilot. Here, we describe the proposed study design and procedures.

Methods: All procedures will be conducted virtually (via phone and Zoom) to minimize participant burden and gather information regarding feasibility and best practices surrounding virtual procedures for older adults. We will recruit dyads (up to n=20) from Mount Sinai Hospital (MSH) clinics within 1 month of ADRD diagnosis. Dyads will be self-referred or referred by their treating neurologists and complete screening to assess emotional distress and capacity to consent to participate in the study. Consenting dyads will then participate in a 60-minute qualitative interview using an interview guide designed to assess common challenges,

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unmet needs, and support preferences and to gather feedback on the proposed RT-ADRD intervention content and design. Each dyad member will then have the opportunity to participate in an optional individual interview to gather additional feedback. Finally, each dyad member will complete a brief quantitative survey remotely (by phone, tablet, or computer) via a secure platform to assess feasibility of assessment and gather preliminary data to explore associations between proposed mechanisms of change and secondary outcomes. We will conduct preliminary explorations of feasibility markers, including recruitment, screening, live video interviews, quantitative data collection, and mixed methods analyses.

Results: This study has been approved by the MSH Institutional Review Board. We anticipate that the study will be completed by late 2023.

Conclusions: We will use results from this study to develop the first live video telehealth dyadic resiliency intervention focused on the prevention of chronic emotional distress in couples shortly after ADRD diagnoses. Our study will allow us to gather comprehensive information from dyads on important factors to address in an early prevention-focused intervention and to explore feasibility of study procedures to inform future open pilot and pilot feasibility randomized control trial investigations of RT-ADRD.

International Registered Report Identifier (IRRID): PRR1-10.2196/45532

(JMIR Res Protoc 2023;12:e45532) doi:10.2196/45532

KEYWORDS

dyad; dementia; emotional distress; intervention; diagnosis; telehealth

Introduction

Background

Alzheimer disease and related dementias (ADRDs) are already experienced by 55 million individuals worldwide, and this number is projected to increase to roughly 75 million by 2030 [1]. ADRDs produce early symptoms (eg, increased forgetfulness, communication challenges, loss of recognition of places, time, and routines) that progress over time and undermine the independence, health, well-being, and relationships of persons living with ADRDs and their family care-partners [2-4]. Over 11 million family members are primarily responsible for supporting persons living with dementia for activities of daily living, and many are romantic or spousal care-partners [1,5,6]. Spousal care-partners are often considered “the second patient” [1] due to their shared experience of the life disruptions and stress experienced as a result of ADRDs and their instrumental role in assisting in medical care, daily activities, and transitions in functional independence [7-9]. Among care-partners, spouses and romantic partners are recognized as an important group to target for early support given their role in at-home caregiving activities, experience of relational disruptions, and greater likelihood of experiencing mental and physical health consequences of caregiving [6].

From symptom onset to receiving a formal or suspected diagnosis, both persons living with dementia and their spousal care-partners experience substantial changes in roles, plans, and expectations [8,10,11]. While some adjust well to these disruptions, many individuals (23%-52%) and spousal care-partners (35%-50%) experience “clinically elevated emotional distress” (ie, depression and anxiety) in the weeks and months leading up to and after diagnosis [12-17]. Dyads’ distress amplifies amid the progressive symptoms and lack of sufficient treatments for ADRDs and the impact on their daily life and relationships [18-20]. Dyads’ distress is also interdependent (ie, mutually experienced and bidirectional) and interferes with their ability to effectively communicate and problem-solve challenges [12,18,21,22]. Without adequate support or treatment, emotional distress is likely to become chronic and negatively impact dyads’ relationship functioning, mental and physical health, and quality of life [12,22,23]. At present, individuals living with ADRDs and their care-partners have little support available after diagnosis to manage stressors, cope with distress, communicate effectively, and collaboratively plan for the future [22,24]. There are no established treatments to date that substantively alter the course of ADRDs and no available psychosocial interventions to promote positive dyadic adjustment to challenges experienced early after diagnosis [11,25].

Both individuals living with ADRDs and their spousal care-partners describe having insufficient support and a lack of resources to assist them in managing early symptoms, expressing personal needs, and learning to address shared challenges together [26,27]. Dyads each express an interest in participating in psychosocial interventions together in order to learn skills to cope with the diagnosis and symptoms and prepare for future challenges [27-31]. Dyadic interventions exist for early-late stage ADRDs that demonstrate promise in reducing dyads’ emotional distress and neuropsychiatric symptoms in the person living with ADRD [32]. However, no available interventions target the period early postdiagnosis, thereby missing the window of opportunity to meaningfully include persons with ADRDs in collaborative treatment and planning before symptoms progress [11,33,34].

Dyadic interventions delivered early after ADRD diagnoses may be an optimal avenue for promoting adjustment to the challenges experienced by persons living with dementia and their spousal care-partners while they are still able to engage collaboratively in treatment and care planning. Such approaches are capable of simultaneously providing both partners with individual and interpersonal skills training to (1) effectively cope with adversity, thereby reducing emotional distress, and (2) preserve the quality of life by maintaining identity and normalcy, preserving social connections, and communicating to better navigate shared challenges and long-term care plans

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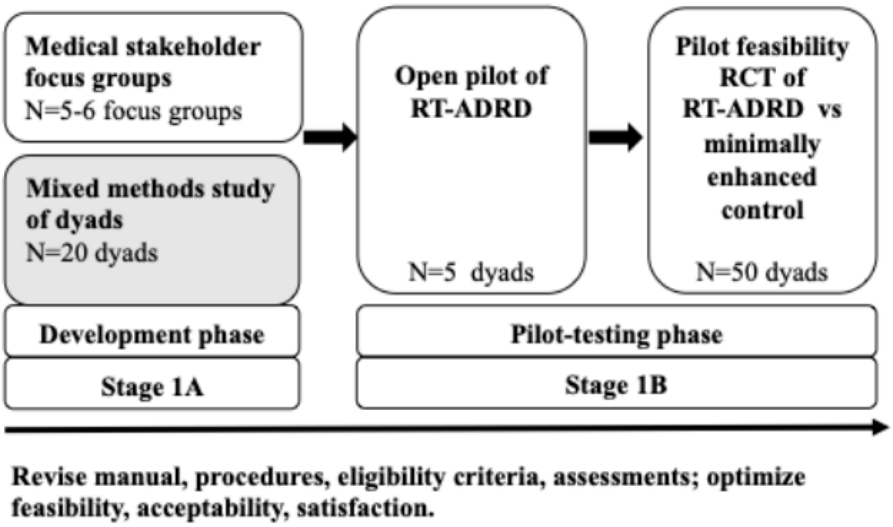
[35]. Dyadic interventions are more effective and economical than those focused on patients or care-partners alone [36] and are feasible and demonstrate some positive effects on the dyadic relationship in the context of early-stage ADRD [26]. Recent advances in telehealth approaches also allow these interventions to be delivered via live video telehealth (eg, Zoom), which can increase access and equity in care and allow for the personalization of skills-based interventions. Dyads coping with ADRD report similar preferences for telehealth and in-person visits, with fewer barriers using telehealth technology [37-39].

This Study

Early dyadic interventions have the potential to promote positive adjustment to ADRD by improving dyads' individual and interpersonal resiliency (ie, the ability to adjust effectively to significant adversity) [40] and provide skills and support to actively contribute to care-planning, preserve their autonomy, and express needs and preferences [41,42]. Many dyadic interventions include resiliency skills linked to positive adjustment after stress and trauma, including (1) mindfulness—staying present and deferring judgment in the face of adversity [43], (2) coping—building and applying cognitive, behavioral and emotional strategies to navigate challenges [44], (3) dyadic coping—open dialogue about stressors, preferences, and needs; approaching challenges as a unit [45,46], (4) social support—engaging social resources to meet needs [47], and (5) general self-efficacy (GSE)—perceived resourcefulness to adapt to adversity [48].

Members of our team developed Recovering Together, a brief dyadic resiliency intervention that prevents chronic emotional distress in patients and informal care-partners shortly after intensive care unit admission for acute neurological conditions (eg, traumatic brain injury, stroke) [49,50]. This study is part of a larger 5-year study that aims to use the prior research, methodology, program content, and procedures of the Recovering Together program as a basis for developing the novel Resilient Together for Alzheimer Disease and Related Dementias (RT-ADRD). RT-ADRD will be developed sequentially using the National Institutes of Health stage model and prior research to guide intervention development [9,51]. The purpose of this paper is to describe the protocol for a mixed methods study involving patient and spousal dyads early after ADRD diagnosis that will inform the development of the first version of RT-ADRD (Figure 1). Through this study, we hope to gather comprehensive information on dyads' challenges, needs, and intervention preferences to develop a program that is feasible, acceptable, and capable of meaningfully improving target outcomes for persons living with dementia and their spousal care-partners early after ADRD diagnoses.

Figure 1. Proposed iterative development of RT-ADRD. RCT: randomized controlled trial; RT-ADRD: resilient together for Alzheimer disease and related dementias.



Methods

Ethics Approval

This study was approved by the Mount Sinai Hospital (MSH) Independent Review Board (22-01623).

Study Design

We are currently conducting a mixed methods investigation involving persons living with ADRD and their romantic or spousal care-partners (target N=up to 20 dyads; recruitment scheduled to begin April 2023). This study is designed to (1) gather impressions of dyads' challenges and needs early after ADRD diagnosis, and (2) obtain feedback on proposed RT-ADRD program procedures (eg, screening, recruitment, consent, intervention delivery, survey assessment) and intervention content. Quantitative assessment measures will be used to explore the feasibility of assessment procedures and gather data to explore preliminary associations among hypothesized intervention mechanisms and target outcomes (see Figure 2 and Table 1).

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Figure 2. Study conceptual model.



Table 1. Study measures.

Construct	Measure or description and type
Covariates	
Demographics	• Medical chart review and participant self-report: gender, age, race, ethnicity, marital status, education level, employment (status, occupation, and income), mental health history
Clinical characteristics	• Medical chart review and participant self-report: type of ADRD[a] diagnosis, age at diagnosis, date of diagnosis, symptoms
Primary outcomes	
Emotional distress	• Hospital Anxiety and Depression Scale (14 items) (depression and anxiety subscales)–emotional distress • Geriatric Depression Scale–Short Form (15 items)–depression • Perceived Stress Scale (4 items)–stress
Quality of life	• World Health Organization Quality of Life–Short Form (26 items)–quality of life
Relationship satisfaction	• Couple Satisfaction Index (16 items)–relationship satisfaction and communication
Primary intervention targets	
Mindfulness	• Cognitive and Affective Mindfulness Scale–Revised (12 items)–mindfulness skills
Individual coping	• Brief Coping Orientation to Problems Experienced (28 items)–adaptive and maladaptive coping strategies
Dyadic coping and communication	• Dyadic Coping Inventory–common dyadic coping subscale (5 items) and negative dyadic coping (4 items) subscale–dyadic stress management • Dyadic Relationship Scale (10 items for patients, 11 items for caregivers)–relationship strain
Social support	• Social Support Questionnaire-Short Form–Revised (12 items)–social support availability and satisfaction
Self-efficacy	• General Self-Efficacy Scale (10 items)–self-efficacy
Caregiver readiness	• Preparedness for Caregiving Scale (8 items; caregiver only)–preparedness for caregiving

[a]ADRD: Alzheimer disease and related dementias.

Inclusion and Exclusion Criteria

We will recruit dyads with English fluency and literacy who are willing to participate and comply with the requirements of the study (including surveys and an interview). Eligible persons living with ADRD will be individuals aged 65 years or older who have a chart-documented ADRD diagnosis within the past month, ADRD symptom onset after the age of 65 years, and cognitive assessment scores and symptoms consistent with early-stage dementia (as determined by provider impressions and test scores such as the Clinical Dementia Rating Scale [52] scores of 0.5 or 1.0 or Montreal Cognitive Assessment [53] scores between 18-21). To be included in the study, they will also be required to (1) demonstrate cognitive awareness of their problems (as determined by the treating providers), and (2) capacity to understand the study and research protocol (confirmed during study screening using scores >12 on the University of California Brief Assessment of Capacity to Consent [UBACC] 10-item scale [54], described in detail

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below). In addition, at least 50% of dyads will exhibit clinically elevated emotional distress (as determined by self-report measures listed below) in order to compare dyads' responses by level of distress and inform future selection criteria. Exclusion criteria for persons living with dementia are (1) a diagnosis of frontotemporal dementia-behavioral variant or other ADRD variant that would interfere with the ability to meaningfully participate, (2) inability to provide informed consent due to cognitive or behavioral impairments, and (3) being deemed inappropriate to participate by the referring providers. Additional exclusion criteria for dyads are comorbid terminal illness diagnosis in either partner. Both dyad members must be eligible and provide informed consent in order for either member of the dyad to participate.

Recruitment and Screening

Dyads will be recruited via the MSH dementia care clinical infrastructure, including the departments of neurology, psychiatry, and geriatrics. The recruitment team will present the aims to medical staff in department clinics, explain the purpose and potential benefits of participation, and discuss ways to best facilitate referrals. As part of routine procedures, treating providers conduct assessments of each patient's understanding (knowledge of facts) and appreciation (recognition of factors that apply to that person) of the presence and severity of cognitive impairment. Results of these assessments are included in patient's medical records, and can be used as a metric for facilitating appropriate referrals. Treating providers will confirm diagnoses of ADRDs and clear patients for participation in the study before facilitating referrals. Potential participants will first hear about the study from their treating providers, who will introduce the study around the time of diagnostic disclosure and provide interested dyads with a study flyer. Providers will also obtain permission for the dyad to be contacted by the research team for recruitment purposes.

With dyads' permission, providers will refer potentially eligible patients by sharing relevant dyad information with the study team, including (1) patient and spouse names and contact information, (2) medical record numbers, (3) diagnosis, and (4) date of diagnosis. Dyads can also contact the study team directly via a screening survey accessed through the study flyer on the Research Electronic Data Capture (REDCap) program. The research team will contact dyads via email to complete screening procedures using the REDCap survey and a screening call (Zoom video or telephone). The screening call will be used to provide dyads with more information about the study, answer questions, and assess eligibility. A member of the research team will speak with persons living with ADRD and spousal care-partners individually while administering initial screening measures to ensure privacy. Once determined eligible on these initial measures, dyads will have the option to complete the remaining screening and consent procedures individually or together according to preference. If either dyad member is deemed unable to meaningfully participate in the study based on screening procedures (eg, assessment of capacity to consent, described below) but is eligible based on the remaining criteria, the study staff will provide the dyad with a resource sheet containing local and national resources for ADRDs. If eligible, a member of the research team will document informed consent for dyads using an e-consent feature on REDCap.

Assessment of Capacity to Consent

Individuals' ability to understand the study and research protocol will be determined by a standardized teach-back method. Research staff will receive extensive training and supervision to administer the assessment, which will consist of the 10-item UBACC scale [54]. Scores >12 indicate ability to consent. After reviewing the consent form, individuals will be asked to repeat aspects of the consent back to the research staff. We will ask 4 questions about the expectations and risks of the study for participants, which have predetermined acceptable answers. Individuals who respond with 100% accuracy will be eligible to consent to the study, whereas individuals who do not achieve 100% accuracy will be prompted to reread the consent form and will be reasked the questions. If the individual does not achieve 100% accuracy a second time, they will not be eligible for the study.

Qualitative Data Collection

After both dyad members consent to participate in the study, a member of the research team will schedule a 60-minute joint interview with a PhD-level clinical psychologist with expertise in conducting dyadic interviews. In advance of the interview, we will send dyads an interview guide with potential discussion topics and tips for using the secure live video software. A member of the research team will also be available to provide technology support and orientation to Zoom before and during the scheduled interview session. During the 60-minute interview, the clinical psychologist will follow a semistructured interview guide (see Multimedia Appendix 1). Another member of the study team will attend the interview to complete a rapid data analysis template developed by the research team. The rapid data analysis template will be used to inform formal coding and will capture observations within key interview domains, poignant participant quotes, researcher reflexivity, and important notes and observations (see Multimedia Appendix 2). During the interview, the clinical psychologist will work to generate information from dyad members on their convergent and divergent perspectives regarding their early experiences after ADRD diagnoses and unmet support needs and to gather feedback surrounding the proposed intervention content and procedures. Following the completion of the joint interview, dyad members will have the opportunity to participate in optional 15-minute individual interviews to share anything that they would prefer to discuss with the research team without their partner present.

Quantitative Data Collection

Overview

Following the completion of the qualitative interviews, we will send each dyad member a quantitative survey to complete individually via the web-based REDCap platform which will take approximately 30-50 minutes to complete. Dyad members will have the option to complete the survey independently or over Zoom with assistance from a member of the research team. If completing the survey over Zoom, the research team member will use the "Share Screen" feature to gather responses to survey

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items and progress through the questionnaires. Questionnaires were selected to gather additional information surrounding the hypothesized intervention targets (ie, mechanisms of change), and outcomes, as well as selection criteria for individuals to target in the context of an early dyadic intervention. We selected questionnaires for the survey that each have strong psychometric properties and were feasible and acceptable in prior dyadic studies. Survey responses will be stored on the REDCap platform and accessed via password-protected laboratory computers. Paper data files (with coded subject identification) will be stored in a locked filing cabinet accessible only to the research team.

Demographics

We selected demographic variables to assess factors that may impact dyad experiences and adjustment to ADRD diagnoses. We will collect information on participants' gender, age, race, ethnicity, marital status, education level (number of years in school), employment (status, occupation, and income), and mental health history.

Clinical Characteristics

We selected clinical characteristics to assess dyads' experiences in the context of their ADRD symptoms and medical care. For the person living with dementia, we will collect information on their ADRD diagnosis and symptoms via electronic medical records, including clinical characteristics, type of diagnosis, age at diagnosis, and date of diagnosis.

Proposed Outcomes

We selected proposed outcomes based on prior research documenting the prevalence and correlates of emotional distress and low quality of life among dyads experiencing dementia and recent calls for interventions to promote positive adjustment early after diagnosis. We will use the 14-item Hospital Anxiety and Depression Scale (HADS) [55] total score to assess emotional distress. Scores range from 0-42 with higher scores indicating more emotional distress. We will also examine the 7-item depression and anxiety subscales of the HADS (HADS-D and HADS-A, respectively). Scores range from 0 to 21, with higher scores indicating more depression or anxiety. We will also use the 15-item Geriatric Depression Scale (GDS)–Short Form [56] to assess the past week depression symptoms. Scores range from 0-15, with higher scores indicating more depression. We will assess perceived stress over the past month using the perceived stress scale (PSS-4) [57]. Scores range from 0-16, with higher scores indicating greater perceived stress. To assess perceived quality of life, we will use the 26-item brief World Health Organization Quality of Life (WHOQOL-BRIEF) assessment [58]. The WHOQOL-BRIEF assesses quality of life across 4 subscales (physical health, psychological, social relationships, and environment). The first 2 items provide a global assessment of the quality of life, and subscale scores are calculated by summing items and transforming scores to a 0-100 point interval, with higher scores indicating greater perceived quality of life. To assess dyadic relationship satisfaction, we will use the 16-item Couple Satisfaction Index (CSI) [59]. Total scores range from 0-81, with higher scores indicating greater relationship satisfaction.

Treatment Targets

We selected treatment targets assessing individual and dyadic coping and relationship functioning based on our hypothesized mechanisms underlying changes in proposed outcomes (ie, emotional distress, quality of life). We will use the 12-item Cognitive and Affective Mindfulness Scale, Revised (CAMS-R) [60] to assess mindfulness. Total scores range from 12-48 with higher scores indicating greater engagement in mindfulness practices. We will use the 28-item Brief Coping Orientation to Problems Experienced (Brief COPE) [61] to measure ways of individually coping with stressful events. The Brief COPE includes 3 subscales that assess coping styles: (1) problem-focused (8 items), (2) emotional-focused (12 items), and (3) avoidant coping (8 items). Scores for each subscale are calculated with the sum of item scores divided by the number of subscale items, which higher scores indicating a greater degree of using the subscale coping style. To assess perceptions of dyadic coping, we will use the items from the Dyadic Coping Inventory [62,63] subscales: common dyadic coping and negative dyadic coping. The common dyadic coping subscale includes 5 items that assess dyads' ability to cope with problems together and search for solutions. Scores range from 5-25, with higher scores indicating greater perceptions of the dyad's use of common coping. We will also use the 4 items of the negative dyadic coping subscale of the Dyadic Coping Inventory to assess negative coping interactions. Scores range from 4-20, with higher scores indicating greater perceptions of the dyad's use of negative dyadic coping. In addition, we will assess dyadic relationship strain in the context of caregiving using the dyadic strain subscale of the Dyadic Relationship Scale (DRS) [64], which has a 10-item patient version and an 11-item caregiver version. Subscale scores range from 1-10 and 1-11 for DRS-Patient and DRS-Caregiver, respectively, with higher scores indicating greater relationship strain. We will use the 12-item brief Social Support Questionnaire (SSQR) [65] to assess social support availability and satisfaction. The SSQR consists of 2 subscales: support network availability (SSQR-N) and overall satisfaction (SSQR-S). Each item assesses support availability and satisfaction in separate parts; participants will be asked to (1) indicate how many people they can count on for various types of support, and (2) indicate how satisfied they are with the support. The SSQR-N subscale composite is calculated by adding the total number of people for all items and dividing it by the total number of items for an average support number. For the SSQR-S subscale total scores are calculated by adding subscale items and range from 6-36, with higher scores indicating greater social support satisfaction. We will assess perceived self-efficacy with the 10-item GSE [66] scale. Total scores range from 10-40, with higher scores indicating greater perceived self-efficacy. Finally, for spousal care-partners we will use the 8-item Preparedness for Caregiving scale to evaluate readiness for caregiving in relation to their spouse. Total scores range from 0-32 with higher scores indicating greater preparedness for caregiving.

Qualitative Analyses

Audio data from dyadic and individual interviews will be transcribed verbatim using a transcription service and then deidentified. We will upload and analyze deidentified transcripts

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using the Dedoose qualitative analysis software [67]. Our approach to data analysis will involve a hybrid deductive-inductive approach that will allow us to explore our key research aims surrounding experiences and treatment preferences of spousal dyads early after ADRD diagnosis. Specifically, our approach will be deductive, in the sense that our interview guide, rapid data analysis template, and codebook domains will be influenced by (1) prior research on early psychosocial challenges following ADRD diagnosis, (2) prior studies focused on dyadic intervention development and adaptation, and (3) theories of dyadic adjustment to chronic and progressive illness. For example, our interview guide will include questions surrounding dyads' perceptions of available psychosocial supports, which we will explore further using a-priori defined rapid data analysis template and codebook domains. The remainder of our approach will be primarily inductive in nature, in the sense that our research team will document observations during rapid data analysis in a generative manner based on dyads' discussion. We will refine our initial codebook using these observations and assess when thematic saturation is reached for key aims. Formal qualitative data analysis will then be guided by the framework method. Members of the research team involved in qualitative analysis will begin with line-by-line review of 1-2 dyadic interview transcripts and open code poignant observations, which we will organize into the a-priori deductive domains and revise our initial codebook through team discussion. Next, 2 members of the research team will code 25% (approximately 5/20) of the interview transcripts (n=5) in the Dedoose software package [67] during the initial codebook. Coders will resolve discrepancies through discussions in weekly meetings with the larger research team. We will ensure high agreement between coders before they code transcripts individually. We will then refine coded data into themes and subthemes within each domain through team discussion.

Quantitative Analyses

We will use descriptive statistics to characterize the number and proportion of individuals approached, screened for eligibility, screened eligible, consented, and retained through interviews and surveys. For proposed outcome measures and treatment targets, we will calculate means and standard deviations of scores for each dyad member, and average scores of each dyad member to assess average responses across dyads. We will examine preliminary associations between treatment primary targets and emotional distress and quality of life outcomes using bivariate correlations. In addition, we will conduct a preliminary assessment of dyadic interdependence (similarity in patterns of responses) by calculating bivariate correlations of dyad members' scores on survey composites.

Comparison and Combined Interpretation of Qualitative and Quantitative Findings

We will use a convergent parallel mixed methods approach to evaluate and interpret qualitative and quantitative findings simultaneously [68,69]. This design involves concurrent, separate collection and analysis of qualitative and quantitative data followed by a detailed examination of convergence or divergence between qualitative and quantitative findings. Specifically, we will examine whether qualitative themes surrounding couples' perception of psychosocial stressors correspond with perceptions on relevant quantitative measures (described as triangulation of findings; eg, with survey constructs such as emotional distress, quality of life, individual and dyadic coping). We will also examine whether correlations between quantitative measures are explained by qualitative descriptions of underlying processes. If observed, divergent findings will be further explored by examination of dyads' demographic and clinical characteristics as well as through the integration of knowledge from prior research, consistent with guidelines for mixed methods research [70].

Results

This study is funded by the National Institute on Aging grant 1K23AG075188 to SMB, who recently moved to MSH. This study was approved by the institutional review board of MSH. Recruitment started in April 2023. Data collection is anticipated to be completed by September 2023, and data analysis is anticipated to be completed by November 2023.

Discussion

Receiving a diagnosis of ADRDs can have a devastating impact on individuals and their care-partners given the lack of available ameliorative interventions or cures and insufficient support early postdiagnosis [18,34]. Prior research suggests that (1) dyads of individuals and their care-partners are interested in participating in early psychosocial interventions together, and (2) that it is feasible to adapt existing dyadic interventions to effectively and efficiently address early challenges to dyads following an ADRD diagnosis [26,32,51]. Comprehensive feedback from dyads can facilitate the development of such programs, and be used to promote alignment between patient, caregiver, and health care system perspectives on ways of optimizing ADRD clinical care.

This paper describes a mixed methods study design that is part of the development phase of a larger study that aims to develop a novel postdiagnosis dyadic resiliency intervention for couples facing ADRDs. We describe the study aims and details of the procedures for recruitment, screening, data collection, and data analysis. This description is valuable for future studies focused on the adaptation and tailoring of dyadic interventions for ADRDs as well as other chronic and progressive conditions. Results of this trial will critically support the development of the first version of the proposed RT-ADRD intervention content and procedures. In addition, findings can be used in conjunction with our prior study of ADRD medical stakeholders to elucidate ways of integrating the RT-ADRD intervention and other supports within existing clinical infrastructures, and to navigate barriers and facilitators to dyads' recruitment and participation in the RT-ADRD intervention. Our approach is consistent with National Institutes of Health stage model recommendations [9] to leverage findings to guide the development and refinement of program content and procedures prior to further testing.

This mixed methods study aims to gather comprehensive information from persons living with dementia and their spousal

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care-partners surrounding their experiences, unmet support needs, and feedback on proposed intervention content and procedures for a postdiagnosis dyadic intervention. The overarching goal is to inform the design, procedures, and content of the novel RT-ADRD program prior to subsequent pilot testing, clinical trials, and implementation efforts. Findings from this study also have the potential to increase available information surrounding dyads' experiences following ADRD diagnosis and perceptions of helpful supports, which has implications for ADRD clinical care and can extend to other chronic and progressive neurological conditions.

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Data Availability

Data collection and analysis instruments are available in Multimedia Appendices 1 and 2. The data sets generated or analyzed during this study are available from the corresponding author upon reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Rapid data analysis template.
[DOCX File , 23 KB - resprot_v12i1e45532_app1.docx]

Multimedia Appendix 2
Interview guide.
[DOCX File , 66 KB - resprot_v12i1e45532_app2.docx]

Multimedia Appendix 3
Peer-review report by the Career Development for Clinicians/Health Professionals Study Section, National Institute on Aging (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 140 KB - resprot_v12i1e45532_app3.pdf]

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Abbreviations

ADRD: Alzheimer disease and related dementias
Brief COPE: Brief Coping Orientation to Problems Experienced
CAMS-R: Cognitive and Affective Mindfulness Scale, Revised
CSI: Couple Satisfaction Index
DRS: Dyadic Relationship Scale
EMR: electronic medical record
GDS: Geriatric Depression Scale
GSE: general self-efficacy
HADS: Hospital Anxiety and Depression Scale
MSH: Mount Sinai Hospital
PSS-4: Perceived Stress Scale
REDCap: Research Electronic Data Capture
RT-ADRD: Resilient Together for Alzheimer Disease and Related Dementias
SSQR: Social Support Questionnaire
UBACC: University of California Brief Assessment of Capacity to Consent
WHOQOL: World Health Organization Quality of Life

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Protocol

Feasibility of Implementation of a Mobile Digital Personal Health Record to Coordinate Care for Children and Youth With Special Health Care Needs in Primary Care: Protocol for a Mixed Methods Study

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Abstract

Background: Electronic health record (EHR)–integrated digital personal health records (PHRs) via Fast Healthcare Interoperability Resources (FHIR) are promising digital health tools to support care coordination (CC) for children and youth with special health care needs but remain widely unadopted; as their adoption grows, mixed methods and implementation research could guide real-world implementation and evaluation.

Objective: This study (1) evaluates the feasibility of an FHIR-enabled digital PHR app for CC for children and youth with special health care needs, (2) characterizes determinants of implementation, and (3) explores associations between adoption and patient- or family-reported outcomes.

Methods: This nonrandomized, single-arm, prospective feasibility trial will test an FHIR-enabled digital PHR app's use among families of children and youth with special health care needs in primary care settings. Key app features are FHIR-enabled access to structured data from the child's medical record, families' abilities to longitudinally track patient- or family-centered care goals, and sharing progress toward care goals with the child's primary care provider via a clinician dashboard. We shall enroll 40 parents or caregivers of children and youth with special health care needs to use the app for 6 months. Inclusion criteria for children and youth with special health care needs are age 0-16 years; primary care at a participating site; complex needs benefiting from CC; high hospitalization risk in the next 6 months; English speaking; having requisite technology at home (internet access, Apple iOS mobile device); and an active web-based EHR patient portal account to which a parent or caregiver has full proxy access. Digital prescriptions will be used to disseminate study recruitment materials directly to eligible participants via their existing EHR patient portal accounts. We will apply an intervention mixed methods design to link quantitative and qualitative (semistructured interviews and family engagement panels with parents of children and youth with special health care needs) data and characterize implementation determinants. Two CC frameworks (Pediatric Care Coordination Framework; Patient-Centered Medical Home)

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and 2 evaluation frameworks (Consolidated Framework for Implementation Research; Technology Acceptance Model) provide theoretical foundations for this study.

Results: Participant recruitment began in fall 2022, before which we identified >300 potentially eligible patients in EHR data. A family engagement panel in fall 2021 generated formative feedback from family partners. Integrated analysis of pretrial quantitative and qualitative data informed family-centered enhancements to study procedures.

Conclusions: Our findings will inform how to integrate an FHIR-enabled digital PHR app for children and youth with special health care needs into clinical care. Mixed methods and implementation research will help strengthen implementation in diverse clinical settings. The study is positioned to advance knowledge of how to use digital health innovations for improving care and outcomes for children and youth with special health care needs and their families.

Trial Registration: ClinicalTrials.gov NCT05513235; https://clinicaltrials.gov/study/NCT05513235

International Registered Report Identifier (IRRID): DERR1-10.2196/46847

(JMIR Res Protoc 2023;12:e46847) doi:10.2196/46847

KEYWORDS

digital health; personal health record; children with special health care needs; care coordination; mixed methods; mobile phone

Introduction

Background

Care coordination (CC) is an essential intervention for children and youth with special health care needs that involves clinicians and patients or families collaborating to coordinate numerous health and related services across multiple service sectors within the "complex care ecosystem" of each child and youth with special health care needs [1]. Children and youth with special health care needs are children and youth aged 0-21 years that "have or are at increased risk for chronic physical, developmental, behavioral, or emotional conditions and who also require health and related services of a type or amount beyond that required by children generally" [2]. Among children and youth with special health care needs, family-centered CC is associated with better outcomes (eg, fewer emergency visits and missed school days) [1,3-6]; however, many children and youth with special health care needs receive inadequate CC [7,8] and 86% of children and youth with special health care needs lack a well-functioning system of services [2]. These critical CC gaps contribute to higher health care usage and parental stress and isolation [9] as parents and caregivers (referred to as families) of children and youth with special health care needs are forced to primarily manage their child's CC needs in the absence of a well-functioning system of care [10].

To fill CC gaps, some families of children and youth with special health care needs have developed strategies to organize details of their child's lifelong health records (eg, longitudinal care plans, manual notebooks, or binders) [11,12]; however, better solutions are needed because these approaches have limitations. For example, manually curated records by families are labor-intensive, not synchronized with electronic health records (EHRs), and largely invisible to clinicians, thereby limiting their impact and obscuring family insights into their child's health progress at home. Digital health innovations offer promising solutions for children and youth with special health care needs and families to manage CC needs at home. In particular, digital personal health records (PHR) [13] enabled by Fast Healthcare Interoperability Resources (FHIR) for secure data access and sharing between mobile apps and EHRs [14,15] could assist families of children and youth with special health care needs to directly manage health information and facilitate family-centered CC [16]. FHIR-enabled digital PHRs accomplish this by synchronizing EHR and family-reported information with a personal mobile device, sharing family-reported insights longitudinally with providers (eg, care goals), and facilitating family and provider communication.

Despite their potential as digital health innovations and the clinical need for solutions for children and youth with special health care needs, FHIR-enabled digital PHRs have not yet been broadly adopted due to logistical and research challenges. Key logistical challenges include technical barriers, funding and infrastructure support, and lack of end user engagement in co-design [17]. In the research domain, as adoption of digital health innovations (eg, telehealth, mobile apps, and remote monitoring) accelerates, early phase pragmatic clinical research is needed [18] to elucidate implementation outcomes (eg, feasibility and acceptability) [19] and identify implementation barriers and facilitators that can inform future larger scale implementation efforts [20]. Methodologically, mixed methods research (MMR) is well-suited for pragmatic studies [21] but under-used in digital health research. MMR could be particularly valuable for digital health research because integration of multiple data sources can augment understanding of implementation more than quantitative or qualitative data alone [22,23]. As such, MMR provides an approach to achieve nuanced understanding of how, why, and for whom a digital health innovation might work best in real-world settings.

Objectives

The objectives of this study are to (1) evaluate the feasibility of a digital PHR mobile app with FHIR-enabled EHR integration to coordinate care for children and youth with special health care needs, (2) identify and describe barriers and facilitators (determinants) of mobile app implementation, and (3) explore associations between mobile app adoption and patient or family-reported outcomes.

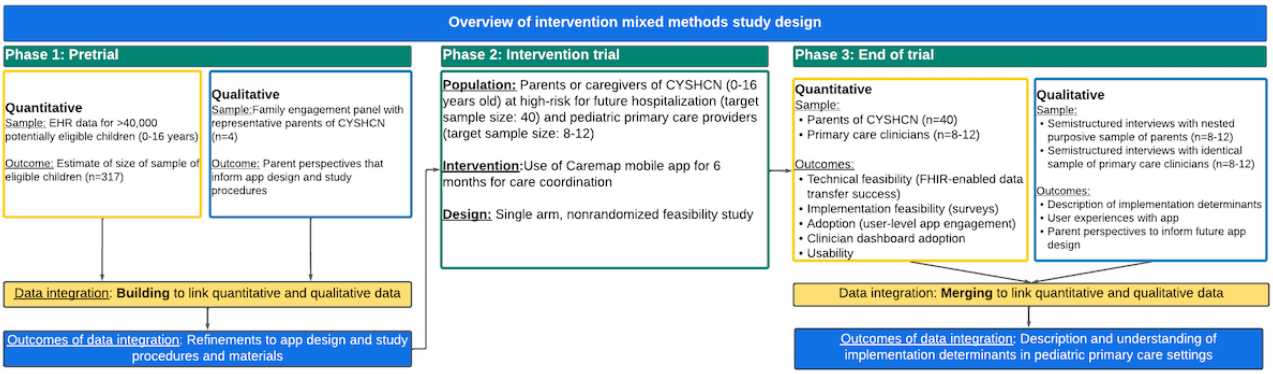
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Methods

Study Design

This study protocol describes a nonrandomized, single arm, prospective feasibility trial of a FHIR-enabled digital PHR mobile app used as a CC tool by families of children and youth with special health care needs in primary care settings for a 6-month period. We will apply an intervention MMR study design [24] within the clinical trial to link quantitative and qualitative data collection and analysis at multiple points in order to characterize implementation determinants (Figure 1).

Figure 1. Overview of mixed methods study design and data integration method. CYSHCN: children and youth with special health care needs; EHR: electronic health record; FHIR: Fast Healthcare Interoperability Resources.



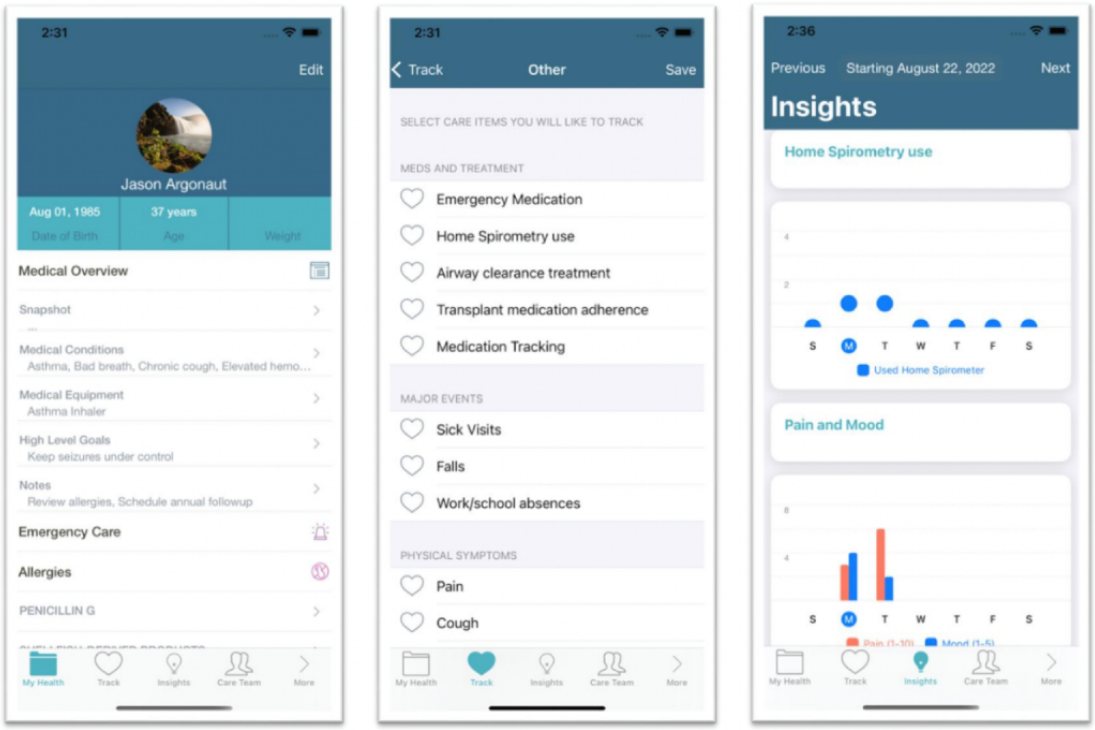
Intervention Description and Preliminary Proof-of-Concept Testing

The intervention under evaluation in this study is a FHIR-enabled digital PHR mobile app (Caremap). The app is a digital health innovation designed to facilitate family-centered CC for children and youth with special health care needs through several key features. One key CC feature of the app is FHIR-enabled access to structured data elements from the child's EHR chart (eg, medication list, allergies, and problem list), thereby allowing families to view health information as seen by their child's primary care provider (PCP) in the EHR (Figure 2, left). A second key app feature is that families can track self-selected patient or family-centered care goals (eg, fewer missed school days due to illness and adherence to routine medications; Figure 2, middle) and graphically display progress over time (Figure 2, right) that is visible within the EHR to their child's PCP via a clinician dashboard.

Core app features were developed to maintain the locus of control for the child's health information with their families; development of the clinician dashboard involved input from practicing clinicians. After initial app development was completed, parents of children and youth with special health care needs with established pediatric specialty care within our health system and a sample of parents of children and youth with special health care needs with care external to our health system tested an early app prototype [25]. These early experiences of family users provided proof-of-concept for the app's core features and laid the groundwork for this study protocol's evaluation of the app in real-world settings.

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Figure 2. Caremap mobile app screenshots.



Study Setting and Population

This study will be conducted at a large health system in the southern United States that includes a tertiary care children's hospital and multiple primary care pediatric practices using an enterprise-wide EHR system (Epic). The study will recruit adult parents or guardians of children and youth with special health care needs aged 0-16 years old with primary care established within a network of pediatric primary care sites that are academically affiliated with our institution.

PCPs will be recruited as study participants in order to include clinician perspectives on the feasibility of a dashboard as a companion to the mobile app. The clinician dashboard is accessible from within the EHR and includes a summary of information recorded by families on their personal device and synchronized with the EHR, thereby providing PCPs with view-only access to family-reported longitudinal health insights at the point-of-care during clinical visits.

Eligibility Criteria

Eligibility criteria for study participation will include (1) patient age of 0-16 years, (2) primary care attribution to a participating site, (3) PCP clinical determination that the child has complex needs that can benefit from additional CC support, (4) child is at high-risk for hospitalization in the next 6 months defined using a novel EHR-based machine learning clinical predictive model [26], (5) English-speaking, (6) family has requisite technology at home (internet access and Apple iOS mobile device), and (7) an active web-based EHR (Epic) patient portal account to which parent or caregiver has full proxy access. An active web-based EHR portal account with parental proxy access is required at our institution for FHIR-enabled data access and sharing between the app, the child's EHR chart, and the clinician dashboard within the EHR.

Recruitment Procedures

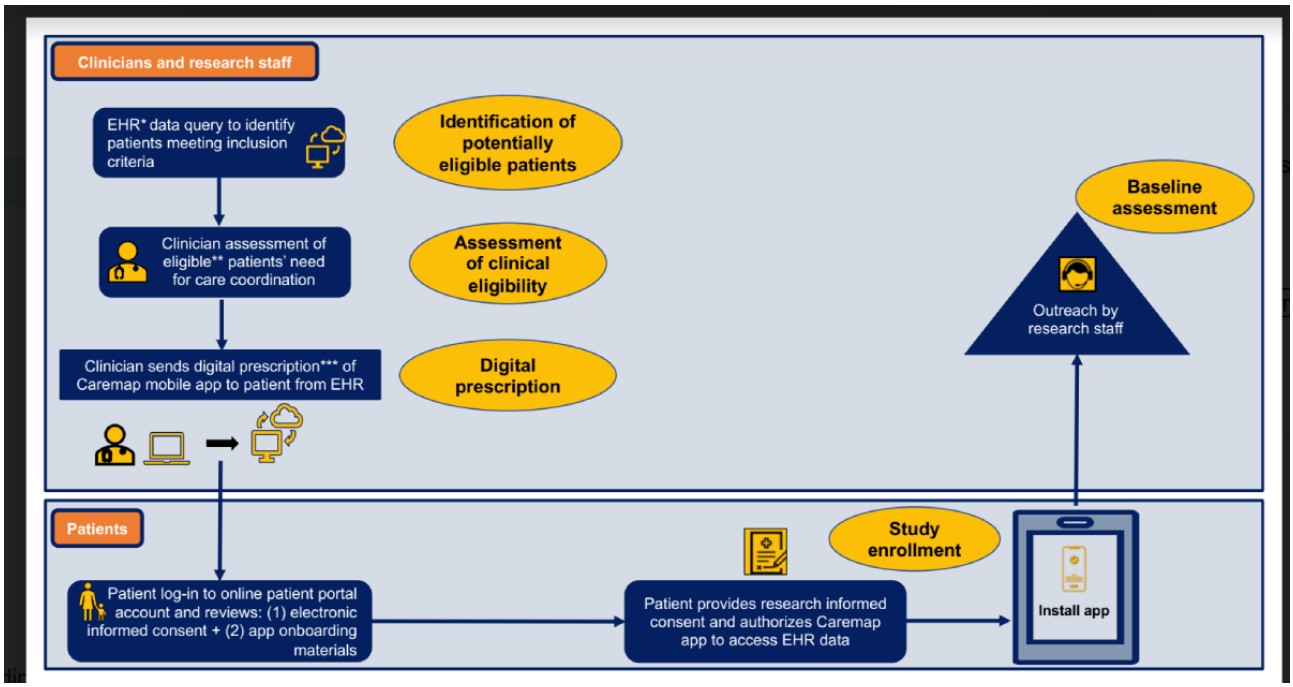
A 3-step process (Figure 3) will be used to recruit and enroll the planned sample of 40 study participants. The first step—identification of potentially eligible patients—will be an EHR data query to identify patients meeting inclusion criteria identifiable within health system data (ie, 0-16 years old, primary care attribution to a participating site, active web-based portal account with full proxy access, English-speaking, and high-risk for future hospitalization).

The second step in recruitment—assessment of clinical eligibility—will be an assessment by each potentially eligible child's PCP to determine whether the child has complex needs that can benefit from additional CC support. If the PCP determines that more CC support would be beneficial, the study will be introduced to parents of children and youth with special health care needs during an upcoming PCP office visit or via a mailed recruitment letter.

The third, final step of recruitment will be direct delivery of detailed study materials (eg, recruitment letter, study flyer, links for downloading the app, and tutorial videos and instructional guide for how to use the app) as a digital prescription (Figure 3). The digital prescription will be transmitted to parents of eligible participants via the patient's web-based portal account. Transmission of digital prescription study materials will be facilitated by a digital health platform (Xealth) for prescribing and monitoring digital health tools within EHR workflows. After parents of children and youth with special health care needs review all materials, they will be able to consent or decline study participation from within the app (Apple Research Kit); those who consent will be contacted by research staff for baseline study assessment.

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Figure 3. Study recruitment procedures. *EHR: electronic health records. **Eligible: established at pilot site + complex needs + active EHR online patient portal account (Epic MyChart©). ***Digital prescription: study materials and app onboarding materials sent via online patient portal to patient device.



Theoretical Frameworks

Guiding this study are 2 categories of extant theoretical frameworks focused on CC and evaluation (Table 1). The 2 CC frameworks central to this research are the Patient-Centered Medical Home (PCMH) and the Pediatric Care Coordination Framework [5,6]. The standard for longitudinal care of children and youth with special health care needs is the PCMH [27]; and CC is a core pillar of PCMH. The Pediatric Care Coordination Framework specifies functions and competencies for systems of care to meet patient or family needs across the ecosystem of essential services for children and youth with special health care needs (eg, medical, social, community, and schools).

To complement these 2 CC frameworks, in this study we are also applying 2 theoretical frameworks focused on evaluation: the Technology Acceptance Model (TAM) and the Consolidated Framework for Implementation Research (CFIR). The TAM is a theoretical model widely applied in digital health research to explain adoption and use of new technologies by end users [28]; the TAM proposes that technology use is mediated by users' perceptions of usefulness and ease of use, leading to acceptance and actual use [29,30]. CFIR is an implementation framework [31,32] developed to comprehensively evaluate implementation barriers and facilitators (referred to as "determinants") within and across multiple domains (process, individuals, intervention, inner setting, and outer setting) [33]. CFIR has been applied in combination with other frameworks [34] and across all phases of implementation research [35]. The combination of TAM and CFIR has been proposed to be complementary [36] and together are well-positioned to guide implementation of digital health innovations.

Despite potential for integration of CFIR with the TAM within digital health research [37], we are unaware of previously published examples. Our approach was to map core components of the Technology Acceptance Model (version 3; TAM-3) [38] and CFIR frameworks with one another to facilitate application of both in an integrated, parsimonious manner (Figure 4). An example of how these 2 theoretical frameworks can be integrated is that multiple CFIR-defined implementation determinants can be mapped to key TAM domains—for example, the CFIR-defined construct of compatibility aligns with perception of external control, which is a TAM-3-defined determinant of perceived ease of use [39]. The recently published CFIR Outcomes Addendum [40] provides additional theoretical foundations to inform this study's conceptual framework. As defined by the CFIR Outcomes Addendum, the mobile app in this study is an example of an innovation and this study's planned primary outcomes are "innovation outcomes." These CFIR-defined innovation outcomes map to TAM-3–defined constructs (eg, behavioral intention to use, perceived usefulness, and perceived ease of use) that function as determinants of actual use of the innovation. Measurement of these innovation outcomes are then interrelated to CFIR implementation determinants and implementation outcomes (Figure 4).

Selection of primary and secondary study outcome measures was guided by operationalizing the TAM-3 and CFIR theoretical frameworks as a study-specific logic model of hypothesized associations between mobile app use and process, proximal, and distal outcomes (Figure 5). Our study logic model was informed by a combination of published studies from the pediatric complex care and CC literature, our prior research, and clinical experience caring for children and youth with special health care needs.

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Table 1. Overview of guiding theoretical frameworks.

Framework	Category	Purpose
Patient-Centered Medical Home	Care coordination	Gold-standard ambulatory care model with 5 core functions: accessible, comprehensive, patient or family-centered, coordinated, and high-quality or safe care
Pediatric Care Coordination Framework	Care coordination	American Academy of Pediatrics' framework outlining purpose, scope, and features of care coordination
Technology Acceptance Model	Evaluation	Approach to understand reasons for acceptance and use of new technologies
Consolidated Framework for Implementation Research	Evaluation	Framework for assessing determinants (barriers and facilitators) of effective implementation of interventions

Figure 4. Applied conceptual framework: integration of CFIR, TAM-3, and CFIR Outcomes Addendum frameworks. CFIR: Consolidated Framework for Implementation Research. TAM-3: Technology Acceptance Model (version 3). CFIR Outcomes Addendum: adapted from from: Damschroder, et al [32] (CFIR), Venkatesh, et al [38] (TAM-3), and Damschroder, et al [40].

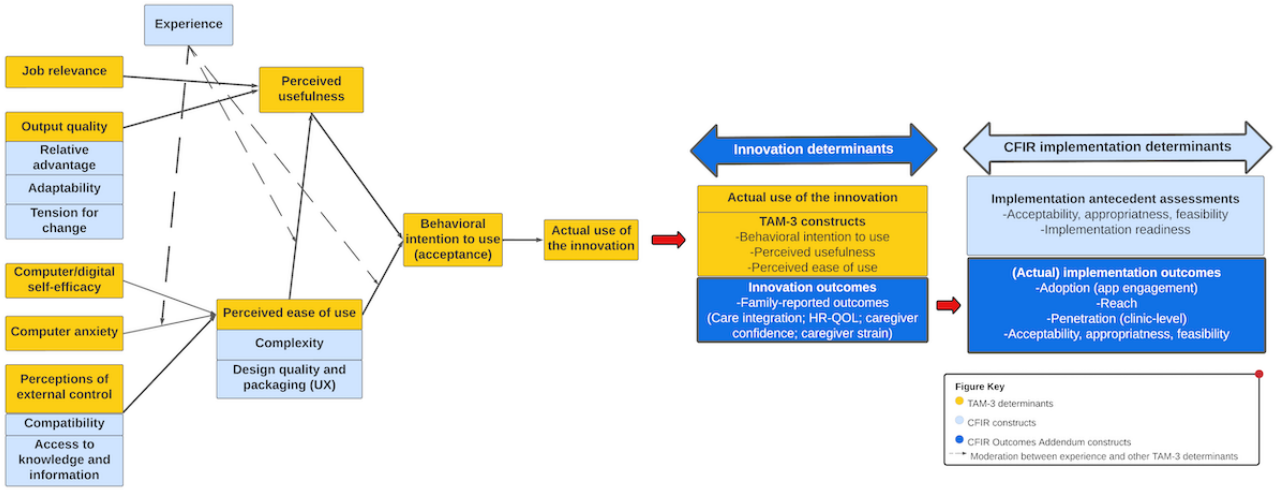
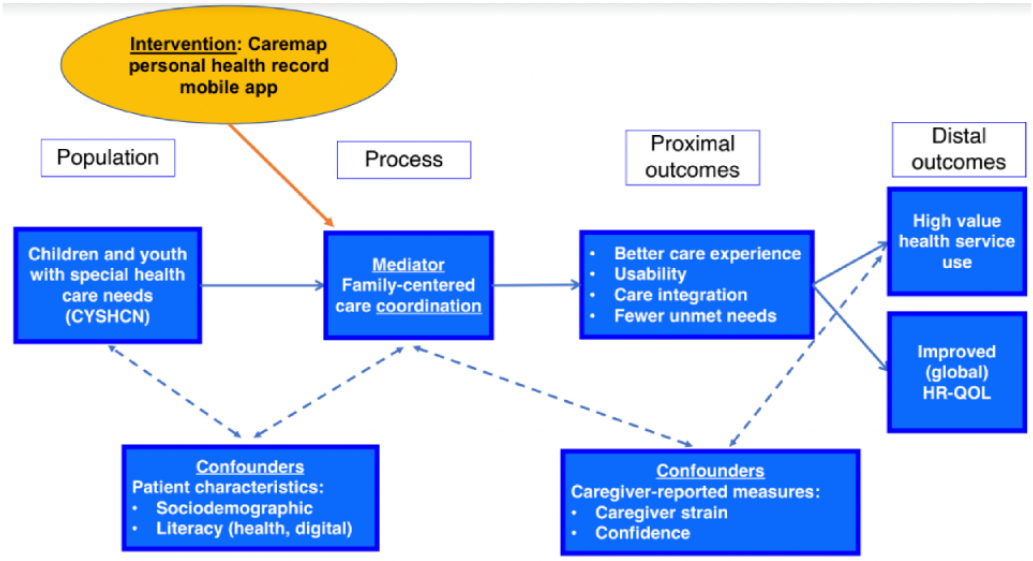


Figure 5. Study logic model. CYSHCN: children and youth with special health care needs; HR-QOL: health-related quality of life.



Quantitative Measurement and Outcomes

A summary of quantitative measures is shown in Table 2. Feasibility is the primary outcome and will be measured as technical and implementation feasibility. Secondary outcome measures will be adoption (app log-ins by families and EHR dashboard use by clinicians) and parent-reported outcomes (eg, care integration and health-related quality of life) measured by parent-reported surveys.

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Table 2. Summary of quantitative measures.

Measure name	Definition or approach	Frequency	Source
Primary outcomes			
Technical feasibility	Measurement of key technical processes: (1) success rate of FHIR[a]-enabled data transfer from EHR[b] to app and (2) success rate of FHIR-enabled transfer of parent-reported health insights from app to clinician dashboard	Weekly	Mobile app and EHR
Implementation feasibility	Parent and clinician report of mobile app feasibility based on 4-item Feasibility of Intervention Measure	End of study (6 months)	Parent and provider surveys
Secondary outcomes			
Adoption	Measurement of: (1) app engagement (number of log-ins), (2) clinician engagement (view of EHR clinician dashboard), and (3) number of times mobile app digitally prescribed to families by clinicians	Weekly (parents), monthly (clinician)	Mobile app and EHR
Care integration	Parent report of degree of care integration using 19-item Pediatric Integrated Care Survey	Baseline, 6 months	Parent survey
HR-QOL[c]	Parent report of HR-QOL for child using 9-item PROMIS[d] global HR-QOL survey (parent-proxy)	Baseline, 3 months, 6 months	Parent survey
App usability	Parent and clinician report of app usability based on 10-item System Usability Scale	Baseline, 6 months	Parent and clinician survey
Caregiver strain	Parent report of degree of strain experienced by providing care for their child's health conditions using the 7-item Caregiver Strain Questionnaire-Short Form 7	Baseline, 3 months, 6 months	Parent survey
Parent confidence	Parent report of level of confidence in avoiding hospitalization using single item	Baseline, 3 months, 6 months	Parent survey
Net promoter score	Parent report of likelihood of recommending the (Caremap) app to others using single item	End of study (6 months)	Parent survey
Global health status	Parent-reported global assessment of child's general health status	Weekly	Parent survey
Implementation outcomes	Parent and clinician report of mobile app acceptability and appropriateness based on 4-item Acceptability of Intervention Measure and 4-item Intervention Appropriateness Measure	End of study (6 months)	Parent and provider surveys

[a]FHIR: Fast Healthcare Interoperability Resources.

[b]EHR: electronic health record.

[c]HR-QOL: health-related quality of life.

[d]PROMIS: Patient Reported Outcomes Measurement Information System.

Qualitative Measurement and Outcomes

Qualitative measures, data collection, and analytical procedures are summarized in Table 3. The primary objective for qualitative data collection will be to identify and describe key implementation determinants (study aim 2). One source of qualitative data will be semistructured interviews with a nested purposive sample of 8-12 parents of children and youth with special health care needs and 8-12 PCPs participating in the study; we expect that this interview sample size will be sufficient to reach information saturation and information power [41,42]. The approach for participant interviews will be qualitative description [43]; interviews will be recorded and analyzed using rapid and value-adding qualitative analysis [44,45].

A second source of qualitative data will be family engagement panels (FEP) with a group of parents of children and youth with special health care needs purposively sampled to reflect a diversity of lived experiences. FEPs are modeled after Community Engagement Panels, a consultative model that engages patients, families, and other community stakeholders for project-specific input [46]. Rooted in principles of community-engaged research, these panels emphasize the importance of bidirectional communication, colearning, flattening of the hierarchy between researchers or project leaders and community stakeholders, and identifying mutual benefits of the project [47]. An initial FEP was conducted in fall 2021 prior to trial launch to gather formative feedback. A second FEP after completion of data analysis will be conducted to return findings to community partners and gather recommendations for future directions with an emphasis on enhancing inclusion and access with future app iterations.

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Table 3. Summary of qualitative measures.

Qualitative data type	Approach	Timing	Analyses
Semistructured interviews (parents)	In-depth interviews with nested convenience sample of parents of children and youth with special health care needs (n=8-12) participating in the study; interview guide mapped to TAM[a] and CFIR[b] framework constructs	End of study	Rapid qualitative
Semistructured interviews (clinicians)	In-depth interviews with identical samples of primary care pediatricians (n=8-12) caring for study participants; interview guide mapped to TAM and CFIR framework constructs	End of study	Rapid qualitative
Family engagement panels	Small group discussions with purposive sample of 4-6 parents of children and youth with special health care needs to gather stakeholder input on study design or procedures and future direction	Baseline (prestudy), end of study	Qualitative description

[a]TAM: Technology Acceptance Model.

[b]CFIR: Consolidated Framework for Implementation Research.

Integration of Quantitative and Qualitative Data

To address the study aim of identification and description of implementation determinants, we will use the MMR data integration method of embedding to link quantitative and qualitative data collection and analysis at multiple points within the intervention MMR study design [24] Consistent with an embedded data integration method, we will also apply other data linking strategies [24]. For example, we will use building to link pretrial FEP qualitative data with quantitative counts of eligible patients identified in EHR data to inform study recruitment procedures; and we will use merging to link collection and analysis of quantitative and qualitative data (feasibility data, surveys, and interviews) after the trial period. An overview of the intervention mixed method study design and embedded data integration methods is shown in Figure 1.

Ethics Approval

The study protocol has been reviewed and approved by our institutional review board Duke Health (Pro00109514). Informed consent for eligible parents or caregivers will occur on their personal device. Eligible participants will review and sign the written electronic informed consent form prior to beginning the study. Participant confidentiality will be protected by collecting only information needed to assess study outcomes, and study data used for final summative quantitative analyses will be deidentified. All qualitative interviews will be conducted by a trained interviewer from the study team on the telephone, via video call (Zoom), or in-person. Interviews will be video-recorded or audio-recorded and transcribed; if an interviewee wishes to not be recorded, detailed notes will be taken instead. Parent or caregiver participants will receive US $50 compensation for completion of surveys (US $25 at baseline, US $25 at 6 months); participants who complete an interview will receive an additional US $50 compensation.

Results

Participant recruitment began in October 2022. We expect that data analyses will be completed by early 2024. We anticipate that quantitative and qualitative findings will address primary and secondary outcomes outlined in Table 2.

Analyses of pretrial quantitative and qualitative data gathered to-date have informed study procedures and design. A pretrial FEP was conducted in fall 2021 with 4 parents of children and youth with special health care needs. Formative qualitative feedback gathered during this first FEP informed changes to app design and user-facing materials, monetary incentives for study participation, and recruitment procedures. An initial EHR data analysis was conducted in January 2022 to estimate the size of the eligible population for the study. From a population of >40,000 children with primary care attributed to the 3 participating PCP sites, our preliminary analysis identified 317 patients who met all inclusion criteria based on available EHR data; it is expected that this sample will be of sufficient size to enroll the goal of 40 study participants to use the mobile app.

We have used these preliminary quantitative and qualitative findings to refine study recruitment procedures. Specifically, based on feedback from parents of children and youth with special health care needs during the first FEP, recruitment procedures were revised to introduce the study to eligible patients directly during a PCP office visit instead of via automated web-based patient portal electronic messaging. Additionally, detailed patient-facing videos and written tutorials were developed in response to family requests for user-friendly onboarding materials. Quantitative estimate of the potentially eligible patient population led to procedural revisions so that PCPs will be familiar with study aims (to facilitate introduction of the study during office visits) and study materials can be delivered via digital prescription in order to better align with real-world clinical workflows.

Discussion

Anticipated Principal Findings

Findings from this study will characterize the feasibility and implementation barriers and facilitators (determinants) for a digital PHR mobile app used by parents of children and youth with special health care needs for CC in primary care settings. Novel study procedures that can contribute to the digital health literature include the protocol's use of digital prescriptions for participant recruitment. Additionally, application of MMR and implementation research methods offers a novel methodological approach that could address recent calls for innovative and pragmatic evaluation of digital health solutions [48].

This study protocol describes a pragmatic approach for integrating theory into digital health study design by combining

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the established CFIR and TAM-3 frameworks [28,32,33,38], thereby facilitating application of implementation science methods within early phase clinical studies. It is recognized within the implementation research field that earlier phase research—for example, pilot and feasibility studies [20]—presents opportunities to establish foundations for future intervention dissemination and to test promising implementation strategies within the context of implementation determinants. Additionally, available implementation science models, theories, and frameworks [31] provide a strong theoretical basis for digital health intervention studies to integrate implementation science and digital health research frameworks.

Similar to implementation science, methodological approaches from the MMR field that systematically integrate quantitative and qualitative data [21,22] can generate insights needed to understand how best to implement, evaluate, and improve digital health innovations. In our preliminary work to-date, use of the MMR analytical technique of building to integrate pretrial quantitative and qualitative data informed improvements in study procedures that would have been challenging to identify without mixed methods data integration. We anticipate that continued collection of both forms of data with embedded data linking at multiple points in the trial will deepen understanding of the feasibility and implementation of the digital health mobile app. These methodological approaches are well-positioned for exploration and adoption by other digital health researchers.

In addition to integrating MMR and implementation science methods into digital health research, there are opportunities to streamline study procedures. For this protocol in particular, the use of digital prescriptions will be used to facilitate dissemination of study materials directly to eligible participants via existing web-based patient portal accounts. This approach may help improve study workflow efficiency and mitigate infectious risk in the face of the ongoing COVID-19 pandemic by reducing study personnel's reliance on in-person recruitment. Digital prescriptions are also positioned for future studies where they could facilitate scaled recruitment via automated delivery of study materials to large numbers of eligible patients identified by EHR data. Although a digital prescription-based approach is promising for study recruitment, caution should be exercised. More efforts are needed to close the digital divide [49], mitigate inequitable access to web-based patient portals [50], and provide tailored support for historically marginalized populations (eg, instructions for web-based portal access and use in multiple languages; interpreter access for patients with limited English proficiency).

This study has several limitations that should be acknowledged, including the study's single center design and limited size and scope. Smaller scope is necessary at this early stage to focus on feasibility and to gather in-depth feedback from participants that can inform subsequent app improvements. Additionally, our inclusion criteria that study participants have existing internet access, a digital device, and an active web-based patient portal account may introduce barriers to research participation. Factors that could mitigate these barriers include national-level data that demonstrated that 81% of US adults own a smartphone [51] and data from our previously conducted digital health trial when parents were successfully recruited using similar technology requirements [52]. Finally, this study's lack of randomization and effectiveness evaluation will limit the strength of conclusions. Although evaluation of effectiveness of the mobile app on health outcomes is beyond the scope of this study, we will systematically explore family and clinician-reported data by including validated measures of health-related quality of life and perceptions of care integration [53,54].

Digital health tools have the potential to improve care and outcomes for children and youth with special health care needs; however, the evidence base is early in development. The methodological rigor of early phase digital health studies could be enhanced by incorporating novel study procedures and methods from research fields outside of traditional pediatric clinical trials. By doing so, strengthened conclusions from early phase digital health studies will be positioned to serve as foundations for future multisite prospective trials that measure effectiveness for health and implementation outcomes. Ultimately, these future directions can serve to accelerate the pace of investigation so that clinicians and families of children and youth with special health care needs will have the evidence base needed to determine the impact of new digital health tools on patient and family-centered outcomes.

Conclusions

This study will evaluate the feasibility of integrating a FHIR-enabled digital PHR mobile app as a CC tool for children and youth with special health care needs into clinical care. Application of MMR and implementation science methods is anticipated to facilitate understanding of implementation determinants in primary care settings. The findings of this study are positioned to inform future pragmatic trials that can further advance knowledge of how to use digital health innovations for improving care and outcomes for children and youth with special health care needs.

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Data Availability

The data sets generated during or analyzed during this study are available from the corresponding author on reasonable request.

Conflicts of Interest

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Multimedia Appendix 1
Peer-review reports.
[PDF File (Adobe PDF File), 141 KB - resprot_v12i1e46847_app1.pdf]

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Abbreviations

CC: care coordination
CFIR: Consolidated Framework for Implementation Research
EHR: electronic health record
FEP: family engagement panel
FHIR: Fast Healthcare Interoperability Resources
MMR: mixed methods research

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PCMH: Patient-Centered Medical Home
PCP: primary care provider
PHR: personal health record
TAM: Technology Acceptance Model
TAM-3: Technology Acceptance Model (version 3)

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Protocol

Daily Functioning of Veterans With Type 2 Diabetes: Protocol for an Ambulatory Assessment Study

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Abstract

Background: Diabetes impacts nearly 25% of veterans. Many veterans do not engage in recommended physical activity and other diabetes self-management behaviors. Type 2 diabetes is generally asymptomatic; as such, the long-term consequences of inadequate self-management and benefits of consistent self-management are not salient in the short term. Furthermore, self-management behaviors typically take place outside of medical visits; however, self-management–related factors are only assessed during medical visits, likely missing large amounts of variability. Thus, ambulatory assessment methods such as ecological momentary assessment (EMA), accelerometry, and continuous glucose monitoring are needed to understand the dynamics of daily self-management and identify potential intervention targets.

Objective: The overarching goal of this study is to understand daily, time-varying factors (comorbid affective symptoms and social context) that influence physical activity, diabetes self-management, glycemic management, daily functioning, and quality of life in participants' natural environments.

Methods: We are recruiting veterans with type 2 diabetes (target N=100). Participants are required to complete a battery of baseline assessments related to mental health, psychosocial factors, and self-management behaviors. Participants then receive 5 momentary EMA surveys and 1 daily EMA survey per day, in which veterans report comorbid affective symptoms (mood, stress, and pain), social support, social interactions, physical activity, and other self-management behaviors. Momentary surveys are delivered randomly during daily preprogrammed intervals over a 14-day sampling period. Accelerometry and continuous glucose monitoring are also used to assess physical activity and blood glucose, respectively. The first 6 participants also completed interviews assessing their experience in the study and barriers to participation. These test participants informed modifications to the protocol for the remaining participants.

Results: The project received funding in April of 2023. Enrollment began in March of 2023 and is planned to be completed in April 2025. Among the 6 test participants, the overall EMA response rate was 87% (range 74%-95%). The response rate for the EMA survey including daily items (67%, range 21%-93%) was lower than the earlier shorter EMA surveys (89%, range 81%-96%). The mean rate of valid accelerometer wear of at least 20 hours per day was 93% (SD 11%), and continuous glucose monitoring data were available for 91% (SD 17%) of days on average. Participants reported few barriers to completing EMA surveys but noted the random timing of questions made it difficult to plan around, and the end-of-day survey was long. Two participants reported survey items reminded or motivated them to engage in diabetes self-management behaviors.

Conclusions: Assessment tools developed from this study can inform clinical decision-making by considering barriers to self-management that occur in daily life. Clinical applications include tailored, adaptive technology–supported interventions to improve self-management that provide the right type and amount of support at the right time by adapting to an individual's changing internal and contextual state.

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KEYWORDS

type 2 diabetes mellitus; ecological momentary assessment; ambulatory assessment; intensive longitudinal assessment; physical activity; self-management behavior; functioning; social support

Introduction

Background

Almost 1 in 4 veterans have type 2 diabetes (T2D), which is over double the prevalence of the general population [1]. Engaging in regular diabetes self-management behaviors, including physical activity, medication taking, following dietary recommendations, and monitoring blood glucose, greatly improves diabetes outcomes [2], but many veterans with T2D do not consistently engage in these behaviors [3]. A more nuanced understanding of veteran-specific barriers to daily engagement in self-management behaviors is needed to develop personalized and impactful interventions to improve self-management.

This study is informed by temporal self-regulation theory, a framework for explaining individuals' health behaviors, which accounts for temporal dynamics, context (eg, social contact, mood, and pain), and individual factors (eg, beliefs and executive functioning) on health behaviors [4]. Specifically, one of the temporal self-regulation theories posits that engagement in health behaviors is more contingent on immediate outcomes (eg, convenience and discomfort) and less contingent on long-term outcomes (eg, improved health status) and that social, internal, and environmental contexts can influence these temporal contingencies. For individuals with T2D, the long-term consequences of suboptimal self-management may not be immediately salient, as suboptimally managed T2D is often asymptomatic but can lead to several long-term complications [5]. However, other daily experiences, including comorbid affective symptoms and social contextual factors, may have a stronger proximal impact on diabetes self-management behaviors. Comorbid conditions with affective symptoms such as depression, anxiety, stress, and pain are common among veterans with T2D [6-8] and may influence their engagement in self-management behavior. Additionally, veterans' social context, especially social support, plays a crucial role in daily diabetes self-management [9]. Research suggests that high social support is associated with engagement in diabetes self-management behaviors, which contribute to improved glucose levels, mood, and quality of life [10], while low social support is linked to depression symptoms and functional disability [11], all of which may impede engagement in diabetes self-management behaviors.

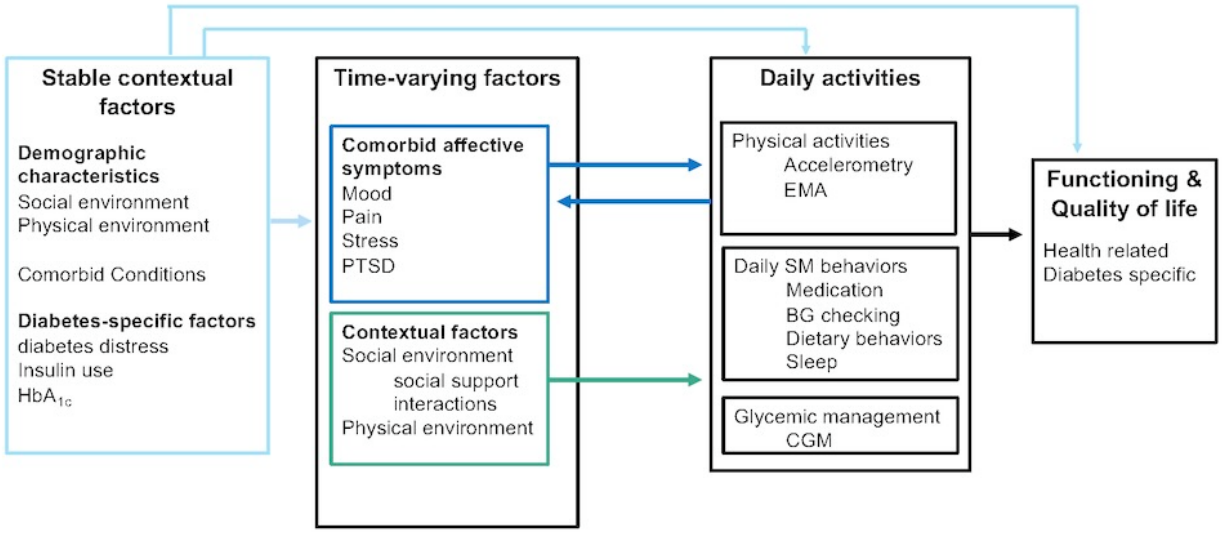
Prior research on such influences on diabetes self-management behaviors has mostly relied on cross-sectional studies, which examine static between-person relationships. Few studies have explored within-person variability over time, specifically the moment-to-moment associations between comorbid affective symptoms, psychological states, social support, and daily engagement in diabetes self-management. Intensive longitudinal studies are needed to capture and model fluctuations over short periods of time, context-specific fluctuations, person-specific patterns in behavior [12], interactions between processes at different time scales [13], and both concurrent and lagged temporal dynamics. This study uses ecological momentary assessment (EMA), a real-world ambulatory assessment method that allows for the assessment of mood, behavior, and contextual factors in participants' own physical and social environments combined with accelerometry and continuous glucose monitoring to continuously assess physical activity behavior and blood glucose levels, respectively. These intensive longitudinal methods can provide valuable insights into these dynamics and help tailor interventions to the specific needs of veterans.

Aims

The overarching goal of this study is to understand daily, time-varying factors (comorbid affective symptoms and social context) that are particularly relevant to veterans and that influence physical activity, diabetes self-management, daily functioning, and quality of life (Figure 1). The specific aims of the study are to (1) use EMA to examine how daily and within-day fluctuations in comorbid affective symptoms influence engagement in physical activity, other diabetes self-management behaviors, and glycemic management; (2) examine social support as it relates to physical activity, diabetes self-management, and glycemic management; (3) capitalize on the advantages of intensive longitudinal data by exploring relationships among other within-person time-varying factors, social contextual factors, between-person demographic and T2D-specific characteristics, and T2D self-management behaviors that may impact daily functioning and quality of life; and (4) leverage intensive longitudinal data to explore temporal relationships among study variables using network analysis. We hypothesize that (1a) greater comorbid affective symptoms will be associated with less concurrent and future engagement in physical activity, diabetes self-management behaviors, and glycemic management; (1b) time-varying within-person factors will predict physical activity, diabetes self-management behavior, and glycemic management even after accounting for stable between-person factors; and (2) daily social support and social interactions will each independently attenuate the association between daily comorbid affective symptoms and subsequent physical activity, diabetes self-management behaviors, and glycemic management. Aims 3 and 4 are exploratory.

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Figure 1. Conceptual model. CGM: continuous glucose monitor; EMA: ecological momentary assessment; HbA_{1c}: glycated hemoglobin; PTSD: posttraumatic stress disorder; BG: background.



Methods

Overview of Study Design

Participants use a smartphone app to report comorbid affective symptoms (mood, stress, and pain), social support, social interactions, physical activity, and other self-management behaviors, multiple times per day randomly, during preprogrammed intervals in their natural environment over 14 days. Participants also wear accelerometers and continuous glucose monitors (CGMs) to passively assess physical activity and glycemic management, respectively. The first 6 participants were interviewed about their experience in the study and barriers to responding to EMA items and wearing study devices as well as their understanding of the EMA items. Interview responses in combination with the data collected were used to refine study procedures for the remainder of the participants.

Target Population and Eligibility

Participants are included if they are users of the VA health care system, diagnosed with T2D, older than 18 years, ambulatory with or without a cane, able to stand without a cane, able to read and understand English, and able to provide informed consent. Participants are excluded if they do not meet the aforementioned criteria or if they are diagnosed with serious or unstable psychiatric illness (ie, unmanaged psychosis, manic episode, or substance use within the past 6 months), psychosocial instability (eg, homelessness) that could compromise study participation, serious or unstable medical illness (eg, dialysis and terminal illness), active suicidal ideation or history of suicide attempt within the past 3 years, concurrent and ongoing engagement in treatment specifically targeting diabetes management, self-reported illness or conditions that would impair the cooperation with the study team or the ability to complete the study, use of a walker, wheelchair, or other assistive devices that will interfere with accelerometry or a score of < 22 on the Montreal Cognitive Assessment (MoCA) or <18 on the MoCA blind [14].

Recruitment

Participants are recruited using flyers and advertisements posted in the local VA hospital common areas and in clinic spaces likely to serve individuals meeting the eligibility criteria. Additionally, targeted recruitment letters are sent to potentially eligible veterans inviting them to participate in the study, and participants are recruited from lists of veterans who participated in other research studies and expressed interest in being contacted for future studies.

Ethical Considerations

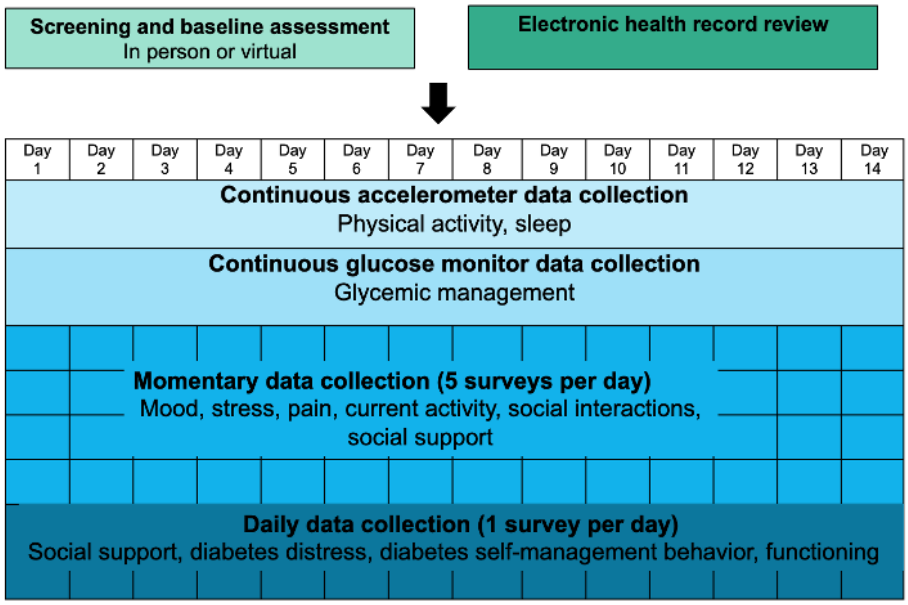
All participants provide informed consent, and the protocol was approved by the VA San Diego Health Care System institutional review board and R&D Committee (protocol 1227858). Data are deidentified, and key linking participant identifying information to data is kept on a secure server that is only accessible by the research team. Participants receive up to US $200 compensation for participation in the study based on EMA survey response rates and accelerometer wear rates. Specifically, participants receive US $15 for completing the baseline assessment, US $15 for returning devices at follow-up, US $2 for each end-of-day survey, and US $1 for each in-the-moment survey. Participants also receive an additional US $15 for completing 75% (52/70) of EMA questions, an additional US $20 for completing 100% (70/70) of EMA questions, an additional US $15 for wearing their accelerometer for at least 20 hours a day for 75% (10/14) of days, and an additional US $22 for wearing their accelerometer at least 20 hours a day for 100% (14/14) of days. Finally, participants receive a copy of their blood glucose data report collected from the CGMs worn during the study.

Procedures

An overview of data collection procedures is shown in Figure 2.

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Figure 2. Overview of data collection procedures.



Prescreening

Initial screening for interest and eligibility takes place in person or via telephone by the study coordinator. Participants are given an overview of the study and, after providing verbal consent, are screened with a questionnaire covering the inclusion and exclusion criteria. The study coordinator also reviews the veteran's electronic health record for eligibility criteria. Veterans who are not excluded based on the initial screen and who express interest in participating in the study are invited for continued evaluation of eligibility and the baseline assessment either in person or via a video call.

Baseline Assessment Visit

Participants provide written informed consent and Health Insurance Portability and Accountability Act (HIPAA) authorization, followed by the Mini International Neuropsychiatric Interview [15] and the battery of baseline assessments. Participants download the *RealLifeExp* app (LifeData, LLC) to their phones or are provided with EMA devices with the app already downloaded. Participants are trained in the EMA procedures, including how to operate the application, the meaning of all questions and response choices, the timing of the prompts, and procedures for responding to prompts. Each participant is provided with written information on responding to EMA surveys and contact information for crisis lines and all study staff. We also provide participants with an Actigraph wGT3X-BT (Actigraph, LLC) accelerometer and instructions for use. Participants are asked to wear the accelerometer for 14 consecutive days during the EMA period. Participants are also provided 2 CGMs (G6pro, Dexcom) that each last for 10 days, the first of which is placed by the research coordinator on the participant's right abdomen. Participants are instructed to place the second CGM on their left abdomen on day 9 of the study and remove the first CGM on day 10. CGM data are blinded to participants. Participants already using a CGM will also be asked to wear the study CGMs. Following the baseline assessment visit, participants practiced with the EMA device and accelerometer at home independently for 24 hours. The study team will be available to help the participants in problem-solving any barriers to participation identified during the 24-hour training period.

Ambulatory Assessment Procedures

After the 24-hour training period, participants complete 14 days of EMA data collection in which they respond to a set of questions on comorbid affective symptoms, social context, and daily activities 5 times throughout the day, including 1 longer end-of-day survey that also contains questions pertaining to social support and daily T2D self-management behaviors. Prompts are delivered randomly within 2-3–hour time windows. Participants choose between 3 response window options: early (prompts delivered approximately between 7 AM and 7 PM), standard (prompts delivered approximately between 8 AM and 8 PM), and late (prompts delivered approximately between 10 AM and 10 PM). Research staff contact participants after 24 hours, 7 days, 9 days (day of CGM switch), and on day 14 to check in about any issues. Additionally, research staff continually monitor participants' response rates to EMA survey questions and accelerometry wear time using remote dashboards.

Follow-up Visit

Participants return their accelerometer and CGM sensors to the research team after the 14-day data collection period and complete forms for compensation. The first 6 participants completed brief interviews about their experiences in the study, experiences with the EMA platform, completing EMA items, and wearing the accelerometer and CGM.

Measures

Baseline Assessment

Participants complete standardized measures of stable contextual factors including social support, diabetes-specific factors, mental health symptoms, self-management behaviors, functioning, and quality of life. Participants also complete a 24-hour diet recall interview and physical functioning assessment. The full baseline assessment battery is shown in Multimedia Appendix 1 [14-36].

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Ecological Momentary Assessment

EMA items are shown in Multimedia Appendix 2 [34,37-45]. Items were adapted from existing standardized measures or prior EMA studies when possible. Items were refined based on performance in terms of within-person versus between-person variability and interviews conducted in our pilot study and the initial 6 participants of this study.

Actigraphy

Actigraph wGT3X-BT accelerometers assess time spent in light, moderate, and vigorous activities as well as total physical activity counts between each within-day assessment interval and averaged across each day [46]. Total activity counts will be computed for the 60 minutes before and after each prompt, and total activity counts will be computed for each day. Accelerometers will also assess sleep including total sleep time, sleep efficiency, and sleep latency. Accelerometer recordings are time stamped to be combined with EMA data at each prompt. A minimum of 20 valid hours a day will be considered as a valid day for both activity and sleep. A minimum of 10 hours a day will be considered a valid day for activity only.

Continuous Glucose Monitoring

Blinded Dexcom G6pro CGMs are used to assess the measures of glycemic management including glycemic management indicator, glycemic variability, percent time in range, percent time in low, percent time in very low, percent time in high, and percent time in very high blood glucose ranges.

Analytic Plan

Protocol Refinement

Data from the initial 6 participants along with their interview responses were used to inform modifications to the protocol. Interview responses were summarized in a table and reviewed with the study team. Response rates for EMA surveys and the number of valid accelerometer and CGM wear days were computed. Intraclass correlations (ICCs) were computed for all EMA items to examine the proportion of the total variance in each EMA survey item attributable to between-person differences versus within-person (ie, day to day) variability.

Data Cleaning and Preliminary Analyses

EMA data will be included for all participants completing at least 30% (21/70) of programmed EMA assessments. Additionally, the pattern of missing data will be examined to determine whether missing values are random or systematic omissions. The proportion of participants who complete >80% (56/70) of assessments (including momentary and daily assessments) and the overall dropout rate will be computed. We will examine data completeness using a paired *t* test to evaluate whether participants completed fewer EMA surveys during the second half of the study than during the first half.

We will examine descriptive statistics for all study variables as well as inspect scatterplots subject by subject. Continuous outcome variables will be screened for normality. We will examine bivariate relationships between a set of potential covariates (eg, gender, age, race, comorbid conditions, and diabetes-specific factors) and the primary outcomes. These significant covariates will be included simultaneously in multilevel models (MLMs).

Primary Analyses

Overview

For aims 1-3, we will estimate MLMs [47]. Models will be estimated with up to 3 levels (prompt, day, and person) with the full-information maximum likelihood method, the between-within method for the denominator degrees of freedom option, and the unstructured variance-covariance matrix for the random effects and residuals. For aim 4, we will use network analysis.

Aim 1: Use EMA to Examine How Daily and Within-Day Fluctuations in Comorbid Affective Symptoms Influence Engagement in Physical Activity, Other Diabetes Self-Management Behaviors, and Glycemic Management

To examine the concurrent association between within-day comorbid affective symptoms and engagement in physical activities, we will use MLM to test whether comorbid affective symptoms (depressed mood, stress, and pain) are associated with concurrent (ie, from the same prompt) engagement in physical activity. Physical activity will be assessed using both EMA-reported engagement in physical activity at each prompt (EMA survey) and accelerometer-assessed minutes spent performing physical activity at each prompt interval (total activity counts). The within-person (level 1, prompt-level) version of each comorbid affective symptom predictor variable (ie, depressed mood, stress, and pain) will be entered into each model to partition the variance allowing for the interpretation of within-person results. The within-person terms will be centered on the person-mean, or the participant's mean value of each comorbid symptom predictor across all prompts for that day, and represent the deviation in each prompt's comorbid affective symptoms as compared to that individual's mean value. Within-person comorbid affective symptoms averaged across each day will be included in level 2 (day level). To examine the direction of the association between daily comorbid affective symptoms and daily engagement in future physical activities (EMA survey and accelerometry), we will test multilevel autoregressive cross-lagged path models. These cross-lagged models will examine whether EMA measurements of each comorbid symptom will predict time spent in physical activities the following day while controlling for the effects of time spent in physical activities the previous day, and also whether time spent in physical activities predicted subsequent comorbid affective symptoms after controlling for previous symptoms. In both concurrent and cross-lagged models, we will include covariates in level 3 (person level) to control for between-person differences in these characteristics. We will use an analogous approach for other diabetes self-management behaviors (medication taking, blood glucose monitoring, and diet behavior) and glycemic management (time in range and glycemic variability).

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Aim 2: Examine Social Support as it Relates to Physical Activity, Diabetes Self-Management, and Glycemic Management

Similar to aim 1, we will examine whether social interactions (ie, alone or with someone else; level 1), companionship or emotional social support (level 2) and instrumental or informational social support (level 2) obtained from EMA surveys are each associated with time spent in concurrent and future physical activity (EMA survey and accelerometry) using MLM. We will include covariates in level 3 (person-level) to control for between-person differences.

Aim 3: Capitalize on the Advantages of Intensive Longitudinal Data by Exploring Relationships Among Other Within-Person Time-Varying Factors, Social Contextual Factors, Between-Person Demographic and T2D-Specific Characteristics, and T2D Self-Management Behaviors That May Impact Daily Functioning and Quality of Life

We will examine the relationship between the between-person demographics and diabetes-specific characteristics that may impact daily activities and quality of life using the statistical approaches described above. We will examine the relationship between time-varying comorbid affective symptoms (depressed mood, stress, and pain) and social context (social support and social interactions) with other diabetes self-management behaviors including exercise, diet behaviors, blood glucose monitoring, and medication taking from EMA questions modified using the same statistical approaches described above. We will also examine whether social contextual factors moderate the relationships between comorbid affective symptoms and each outcome variable (physical activity, diabetes self-management behaviors, and glycemic management).

Aim 4: Leverage Intensive Longitudinal Data to Explore Temporal Relationships Among Study Variables Using Network Analysis

Network analysis will be conducted to visualize, understand, and compare the associations and covariances among time-varying study variables (eg, comorbid affective symptoms and social contextual factors), physical activity, other diabetes self-management behaviors, and glycemic management. We will estimate within-person networks and between-person networks based on variables in our conceptual model [48]. We will estimate and graph network models in which associations between variables included in the network are drawn if they correlate after controlling for all other variables in the network. Networks will be computed based on partial correlation methods [48]. We will create between-person networks by averaging values from each participant for each physical activity variable, each self-management behavior, and each time-varying factor across the 14 (daily) or 70 (momentary) time points. We will create within-person networks by subtracting the mean of each participant's score across all time points, such that we estimate a network of interrelationships, centered on each person's average value during the study. This will allow us to test whether deviations from the mean level for a given variable are associated with variations from the mean of other variables. We will also explore whether network patterns differ based on between-person characteristics (eg, sex and insulin use) that could influence the associations between factors in the network.

Sample Size

To estimate the sample size needed to detect statistically significant effects for the outcomes outlined in aim 1, we used a power program *EMAtools*, a software specifically designed for EMA data, prior research, and estimates of response rates from our pilot data. There is little prior research with similar populations in terms of examining within-person variability of diabetes self-management behaviors and glycemic management. In terms of physical activity, prior research suggests that we should expect medium effect sizes for aim 1 and small-to-medium effect sizes for aim 2 [37,49]. ICCs for physical activity in similar populations range from 0.12 to 0.34 [49,50]. Specifying 14 days of data collection, and 5 momentary prompts per day, showed that with 100 participants, we are adequately powered to detect the expected effect sizes for aim 1 and small-to-medium effect size for any given outcome (ie, aims 2-3) at 80%. Additionally, we are powered to detect small-to-medium effect sizes with response rates as low as 75%. Network analysis (aim 4) is a relatively new field and research on power requirements is ongoing, but prior studies have found that as few as 30 participants are needed for adequate power to detect variability in network structures [51]. Taken together, the target sample size for this study is 100, with a maximum of 7000 EMA survey responses. Conservatively estimating a 75% response rate, this target would produce 5250 completed EMA surveys that can be combined with corresponding accelerometry and CGM data points. Data from this study can be used in a Monte Carlo simulation to more precisely determine the most appropriate sample size for future studies.

Results

The study was funded by the Department of Veterans Affairs Rehabilitation Research and Development Service for 5 years. Enrollment began in September of 2022 to collect a sample of 6 test participants which informed subsequent modifications to the protocol. Enrollment restarted in March of 2023 and is planned to be completed in April 2025. Results are planned to be analyzed and published in March 2026.

Among the 6 test participants, the overall EMA response rate was 87% (range 74%-95%). The response rate for the EMA survey including daily items (67%, range 21%-93%) was lower than the earlier shorter EMA surveys (89%, range 81%-96%). The mean rate of valid accelerometer wear of at least 20 hours per day was 93% (SD 11%; range 71%-100%), and CGM data were available for 91% (SD 17%) of days on average (range 57-100). Participants generally reported few barriers to completing EMA surveys but noted that the random timing of questions made it difficult to plan around, and the end-of-day survey was long. Two participants reported accelerometers were uncomfortable at times and 1 participant's second CGM did not collect data. Two participants reported that survey items reminded or motivated them to engage in diabetes self-management behaviors.

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Discussion

Summary

There are very few EMA studies examining physical activity and other self-management behaviors in T2D, and there are no studies that we are aware of that examine daily objective physical activity, EMA-assessed self-management behaviors, and CGM-assessed glycemic management among veterans with T2D. Furthermore, the combination of accelerometry and EMA provides both objective and subjective assessments of overall physical activity levels while also distinguishing among activity types.

Methodological Challenges and Decisions

Modifications to the design of this protocol were made based on a prior pilot study and our test participants [52,53]. Based on response rates lower than 80% and participant feedback from our test participants, we reduced the number of questions delivered at each EMA to 1 per construct. Given our interests in within-person variability, we examined ICC values, representing the amount of within-person versus between-person variability of each item, to inform decisions about which items to drop. Items with lower ICC values, representing greater within-person variability, were favored. Participants in our target population vary in terms of occupational and retirement status and thus participants varied in terms of what times during the day were most ideal for having EMA prompts delivered. To balance variability among participants and capture participants' typical waking hours and response rates, we decided to offer 3 time window options. Participants also requested to know the exact time EMA prompts would be delivered; however, we decided to keep prompt delivery within random time windows to best capture participants' experiences across the day.

Social desirability and measurement reactivity pose challenges to assessing daily diabetes self-management behaviors. We initially adapted the Summary of Diabetes Self-Care Activities Assessment scale [16] for daily use but found little variability in responses from participants, and found that most participants endorsed engaging in all self-management behaviors. With our initial test participants, we tried including a response option "this survey reminded me to complete *X* behavior" to gauge reactivity bias; however, no participant selected this option. Additionally, participants reported in interviews that they found the assessment helpful to their diabetes management. We added a component to our instructions emphasizing that we are not intending to change their behaviors in this study. We also modified dichotomous rating scales to be continuous (0-100) to capture variability in behaviors and added new dietary items that included representative food groups without labeling the nutritional value of the food to reduce social desirability biases. We also adapted much of our protocol for remote delivery; however, to date, many participants choose to complete baseline assessment in person.

Significance

Diabetes is a significant and drastically growing problem among veterans [54] and is related to disability, poor quality of life, and substantial health care costs. Most diabetes self-management activities take place outside of medical visits; however, factors related to self-management are only assessed at the time of medical visits, likely missing large amounts of variability. This study targets this problem by examining time-varying influences of daily diabetes self-management behaviors and daily life functioning, in real-time, in veterans' own environments.

Results will identify barriers and facilitators of diabetes self-management that when intervened may unleash a cascade of improvement through their interrelationships with other factors. For example, if comorbid affective symptoms are important predictors of physical activity or other self-management behaviors, interventions for T2D management that include additional evidence-based strategies for targeting comorbid symptoms, such as pain management, may need to be evaluated. Adaptive just-in-time interventions can be developed to deliver personalized patient-centered feedback in real time. For example, an intervention could deliver a behavioral activation strategy when a veteran reports high levels of depression. Interventions can be designed to include appropriate timing of prevention strategies or the use of supportive services to help break self-sustaining cycles of poor functioning. Furthermore, assessment tools developed from this study could inform clinical decision-making and treatment planning that considers barriers to self-management that occur outside of medical visits.

Acknowledgments

JSW was supported by a Career Development Award (1IK2RX003634) from the United States Department of Veterans Affairs Rehabilitation Research and Development Service. JLM was supported by the VA Office of Academic Affiliates advanced fellowship in women's health.

Data Availability

The data sets generated and analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

JSW and NA contributed to the conceptualization and design of the study and the acquisition of funding. JSW drafted and edited the manuscript. JD contributed to the acquisition of data and reviewed the manuscript draft. JLM and NA reviewed and edited the manuscript draft.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Summary of baseline assessment measures.
[PDF File (Adobe PDF File), 127 KB - resprot_v12i1e53874_app1.pdf]

Multimedia Appendix 2
Summary of ecological momentary assessment items.
[PDF File (Adobe PDF File), 122 KB - resprot_v12i1e53874_app2.pdf]

Multimedia Appendix 3
Peer-review report from the Career Development Program- Panel II, Rehabiliation Research and Development Parent, IRG Office of Research and Development (RRD9).
[PDF File (Adobe PDF File), 141 KB - resprot_v12i1e53874_app3.pdf]

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Abbreviations

CGM: continuous glucose monitor
EMA: ecological momentary assessment
HIPAA: Health Insurance Portability and Accountability Act
ICC: intraclass correlation
MLM: multilevel model
MoCA: Montreal Cognitive Assessment
T2D: type 2 diabetes

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Protocol

AI Conversational Agent to Improve Varenicline Adherence: Protocol for a Mixed Methods Feasibility Study

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Abstract

Background: Varenicline is a pharmacological intervention for tobacco dependence that is safe and effective in facilitating smoking cessation. Enhanced adherence to varenicline augments the probability of prolonged smoking abstinence. However, research has shown that one-third of people who use varenicline are nonadherent by the second week. There is evidence showing that behavioral support helps with medication adherence. We have designed an artificial intelligence (AI) conversational agent or health bot, called "ChatV," based on evidence of what works as well as what varenicline is, that can provide these supports. ChatV is an evidence-based, patient- and health care provider–informed health bot to improve adherence to varenicline. ChatV has been programmed to provide medication reminders, answer questions about varenicline and smoking cessation, and track medication intake and the number of cigarettes.

Objective: This study aims to explore the feasibility of the ChatV health bot, to examine if it is used as intended, and to determine the appropriateness of proceeding with a randomized controlled trial.

Methods: We will conduct a mixed methods feasibility study where we will pilot-test ChatV with 40 participants. Participants will be provided with a standard 12-week varenicline regimen and access to ChatV. Passive data collection will include adoption measures (how often participants use the chatbot, what features they used, when did they use it, etc). In addition, participants will complete questionnaires (at 1, 4, 8, and 12 weeks) assessing self-reported smoking status and varenicline adherence, as well as questions regarding the acceptability, appropriateness, and usability of the chatbot, and participate in an interview assessing acceptability, appropriateness, fidelity, and adoption. We will use "stop, amend, and go" progression criteria for pilot studies to decide if a randomized controlled trial is a reasonable next step and what modifications are required. A health equity lens will be adopted during participant recruitment and data analysis to understand and address the differences in uptake and use of this digital health solution among diverse sociodemographic groups. The taxonomy of implementation outcomes will be used to assess feasibility, that is, acceptability, appropriateness, fidelity, adoption, and usability. In addition, medication adherence and smoking cessation will be measured to assess the preliminary treatment effect. Interview data will be analyzed using the framework analysis method.

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Results: Participant enrollment for the study will begin in January 2024.

Conclusions: By using predetermined progression criteria, the results of this preliminary study will inform the determination of whether to advance toward a larger randomized controlled trial to test the effectiveness of the health bot. Additionally, this study will explore the acceptability, appropriateness, fidelity, adoption, and usability of the health bot. These insights will be instrumental in refining the intervention and the health bot.

Trial Registration: ClinicalTrials.gov NCT05997901; https://classic.clinicaltrials.gov/ct2/show/NCT05997901

International Registered Report Identifier (IRRID): PRR1-10.2196/53556

(JMIR Res Protoc 2023;12:e53556) doi:10.2196/53556

KEYWORDS

evaluation; health bot; medication adherence; smoking cessation; varenicline; artificial intelligence; AI

Introduction

Medication adherence presents a significant and pressing challenge worldwide across health care systems [1]. This problem spans across various medical conditions, from chronic illnesses such as hypertension, diabetes, and cardiovascular disease to acute infections [2]. Nonadherence to medication regimens can lead to a cascade of problems, including decreased treatment effectiveness, a higher risk of disease progression or complications, medication resistance, increased health care costs, and a reduced overall quality of life for patients [3]. It also places an additional burden on health care providers, who must constantly navigate the complexities of patient adherence to optimize treatment outcomes. Addressing medication adherence is not only a matter of improving individual health but also a vital step toward more efficient health care systems and improving population health.

One notable area where medication adherence could have a significant effect on public health is with smoking cessation medications. Tobacco smoking is not only extremely addictive [4], but it also damages almost every organ in the body [5] and is a leading cause of health inequalities [6]. Despite decades of efforts to reduce the smoking prevalence in Canada [7], over 4 million (15%) Canadians smoked in 2020 [8]. Tobacco use remains the leading cause of preventable death in Canada [9], and following smoking cessation, the risk of developing tobacco-related diseases gradually decreases over time [10].

Varenicline, a partial agonist of the α-4 β-2 nicotinic receptor, is one of the most effective smoking cessation medications associated with a doubling of long-term quitting with 12 weeks of continuous treatment [11]; however, adherence is a major barrier to achieving and maintaining abstinence [12-14]. Among those who take varenicline for smoking cessation, over one-third stop taking the medication by the second week of treatment, and these patients are significantly less likely to quit smoking [15-18]. In addition, several studies that have examined the correlation between sociodemographics and adherence to varenicline have found male sex [15,19], older age [15,19-21], White race [21,22], and higher education to be associated with better adherence [21]. Conversely, 1 study found that greater age was associated with poorer adherence [21].

One of the most effective strategies to improve adherence to medication is tailoring behavioral interventions [23]. Research has also shown that the use of technological solutions is crucial to providing personalized, cost-effective, and evidence-based interventions [24]. One such digital health solution is a web-based program integrating artificial intelligence (AI) conversational agents, or "health bots," that can be helpful in improving adherence to medication [25]. Health bots have greater functionality compared with applications providing simple text message reminders since they can track medication intake, provide information about side effects, and answer medication-related questions [26,27].

The "ChatV" health bot is an example of such a digital health solution that we developed to improve adherence to the smoking cessation medication varenicline [28]. We used a theory-based, patient-centered approach through the Discover Design Build and Test framework [29] to design the health bot; we conducted a rapid review to explore the barriers and facilitators to varenicline adherence and interviewed 20 patients and 19 health care providers to understand similar barriers and facilitators as well as features to be included in a health bot that may improve varenicline adherence. The data from these sources were analyzed using the capability, opportunity, motivation-behavior change (COM-B) [30] model of behavior change and its associated framework (theoretical domain framework) [31] and taxonomy (behavior change techniques taxonomy) [32] to identify the features to be included in the health bot. We used the Wizard of Oz methodology [33] to build a library of responses that were programmed in the health bot to answer users' questions. We are currently beta testing the minimal viable product that has the following features: (1) scheduling and receiving reminders for varenicline dosing; (2) setting a smoking quit date; (3) answering questions related to varenicline (eg, guidance for missed doses) and smoking cessation (eg, strategies to reduce cravings); (4) providing information and strategies to manage side effects [12,15,18]; (5) tracking medication use and smoking; and (6) encouraging participants to increase their motivation to maintain medication intake and continue their quit attempts. Throughout the development of the health bot, a health equity lens was adopted to address any disparities in varenicline use and health bot features between different demographic characteristics.

In this protocol, we detail our plans to examine the uptake, usability, acceptability, and appropriateness of ChatV (ie, feasibility) [34] and to determine whether progression to a fully powered randomized controlled trial (RCT) is warranted.

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Methods

Design

We will conduct a nonrandomized, single-arm feasibility study.

Participant Recruitment

We will recruit 40 participants. In order to ensure diversity with respect to age, gender, race, and socioeconomic status, we will purposefully recruit participants through a variety of methods, including the research boards of Centre for Addiction and Mental Health (CAMH), where recruitment flyers are posted for patients to explore research opportunities; health care providers at CAMH programs (eg, Smoking Treatment for Ontario Patients [STOP] program, Aboriginal services, and Rainbow services) and partnering organizations (Rainbow Health Ontario); the STOP program's list of people who are seeking treatment for smoking and who have consented to be contacted for future research studies; and social media and community boards. Research staff members will conduct a prescreening for those who are interested, and if eligible, participants will be enrolled in the study.

Inclusion Criteria

The inclusion criteria include individuals who are seeking treatment for their tobacco use who smoke 10 or more cigarettes a day, are willing to set a quit date in the next 30 days, are willing to take varenicline for 12 weeks, are aged 18 years, speak and read English, have a smartphone with a data plan, report being committed to answering questions during follow-up, and live in Ontario.

Exclusion Criteria

The exclusion criteria include having contraindications to varenicline use, being pregnant, planning to become pregnant, breastfeeding, or participating in the co-design phase.

Ethical Considerations

The CAMH Research Ethics Board (REB #050/2022) has provided approval to conduct the study, and all participants will provide written informed consent before participation. It has been registered at ClinicalTrials.gov (NCT05997901). Any amendments to the protocol are noted, and substantial changes will be reported to the ethics committee. All interested participants will receive an information sheet and a consent form describing the study and providing sufficient information for the participant to make a decision regarding study participation. A research staff member will arrange a personal meeting with the prospective participants and inform them again about all study procedures, benefits, risks, and their rights regarding study participation. Afterward, the consent form is signed by both the participant and the research staff before the participant undertakes any study procedure. The informed consent process is documented in Research Electronic Data Capture (REDCap; Vanderbilt University).

All study-related documents and data will be held in strict confidence and stored on CAMH servers that will follow CAMH policies and procedures to ensure participant privacy and confidentiality. Any data collected as part of the participants' completion of the electronic consent form will be securely stored in REDCap, a CAMH-approved data collection tool.

In addition to free medication (for 12 weeks), participants will receive an honorarium in the form of a CAD $30 (US $22) gift card after completion of the 4-week follow-up survey and a CAD $40 (US $30) gift card after completion of the 12-week interview.

Procedures

The research team will inform potential participants about the study and evaluate if they meet the inclusion criteria. If they qualify, participants will receive a consent form and arrange a phone-based discussion to obtain consent. After obtaining consent, participants (n=40) will complete an internet-based questionnaire covering sociodemographic characteristics, nicotine dependence [35], and an adapted scale to measure varenicline adherence self-efficacy [36-38]. After completing the questionnaire, participants will have an internet-based or in-person visit with a health care provider for eligibility confirmation and to obtain a prescription for varenicline for the first 4 weeks (1 tablet [0.5 mg] daily for the first 3 days, 1 tablet [0.5 mg] twice daily for the next 4 days, and 1 tablet [1 mg] twice daily for 3 weeks). In addition, research staff will show participants how to use the health bot on their phones. Medication will be provided in person or, in the case of internet-based contacts, mailed to the participants. A follow-up visit will be scheduled at 2 weeks, where health care providers will assess the participant's tolerance of varenicline and provide a prescription for the remaining 8 weeks (1 tablet [1 mg] twice daily or a different dose depending on the tolerance of each participant). Any unanticipated problems (ie, adverse events that are unexpected in terms of severity, nature, or frequency; are related or possibly related to participation in the research; and suggest that the research places other research participants at greater risk of harm) will be documented and reported to the research ethics board, and adverse drug reactions will be reported to the market authorization holder (Apotex) as applicable.

Participants will be required to complete surveys at 1, 4, 8, and 12 weeks. When participants join the study, they will be able to opt to respond to these questions using either the health bot or an internet-based platform. Those who do not complete the internet-based or health bot follow-up within the designated time frame will receive a phone call from our research staff. Additionally, after 12 weeks of joining the study, participants will be invited to participate in a 1-hour semistructured phone interview.

Measures

Overview

The taxonomy of implementation outcomes of Proctor et al [39] guides our selection of implementation outcomes (Table 1).

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Table 1. Summary of measures.

Measures	Survey timeline					Interview	Analytics
	Baseline	Week 1	Week 4	Week 8	Week 12	Week 12	Weeks 1-12
Demographics	✓						
Adoption						✓	✓
Acceptability		✓[a]	✓[a]	✓[a]	✓[a]	✓	
Appropriateness		✓[b]	✓[b]	✓[b]	✓[b]	✓	
Fidelity						✓	
Usability		✓[c]	✓[c]	✓[c]	✓[c]	✓	
Medication Adherence		✓[d]	✓[d]	✓[d]	✓[d]	✓	
Smoking Status		✓	✓	✓	✓	✓	

[a]Acceptability of Intervention Measure.

[b]Intervention Appropriateness Measure.

[c]System Usability Scale.

[d]Timeline Followback.

Acceptability

Acceptability is the extent to which an innovation is agreeable, palatable, or satisfactory to a stakeholder [39]. In order to measure acceptability, we will use the Acceptability of Intervention Measure (AIM) in the follow-up surveys as well as in the semistructured phone interviews.

Appropriateness

Appropriateness is the perceived fit or compatibility of an innovation with a practice setting or context [39]. In this study, appropriateness will be assessed on an individual basis, including factors such as alignment with users' attitudes, needs, and background, as measured in the 12-week survey with the Intervention Appropriateness Measure (IAM), a validated 4-item intervention appropriateness scale [40], and explored in depth in the semistructured interviews.

Fidelity

Fidelity is the extent to which an intervention is used as intended [39]. For this study, in the semistructured interviews, we will investigate the functions of the health bot that participants used; the purposes for which they used it (such as answering questions or seeking support); the frequency of usage; and the quality, specifically whether the health bot provided accurate information.

Adoption

Adoption is the intention, decision, or initiation of use for an evidence-based practice, characterizing it at the level of the provider or organization [39]. Since the concept of adoption is closely related to the actual use of systems, researchers investigating behavioral intervention technologies, such as the health bot, have extended this level of analysis to include consumer behavior [41]. In this study, we will measure the adoption of the health bot by analyzing analytics data throughout the 12 weeks that the participant is scheduled to take varenicline. These data will allow us to evaluate the timing (day and time) of user interactions with the health bot, the specific features used, and the duration of engagement. Thus, we will have objective data on the actual adoption of the health bot by each participant. Additionally, during the semistructured interviews, we will probe for participants' subjective perceptions of their use of the health bot.

Usability

Usability will be assessed using the System Usability Scale (SUS) [42]. The SUS is a 10-item measure assessing usability and user satisfaction with technology.

The AIM, IAM, and SUS all have items that are rated on a 5-point Likert scale (1=completely or strongly disagree to 5=completely or strongly agree).

Medication Adherence and Smoking Status

Participants will be asked about their smoking status [43] and adherence to varenicline using the Timeline Followback (TLFB) [44] in the surveys collected at 1, 4, 8, and 12 weeks. Participants will report the number of pills taken since the previous assessment. Participants who log their varenicline use in the health bot will be able to refer to these data when filling out the TLFB. We chose the TLFB method for assessing adherence because the 12-week TLFB measure demonstrates a moderate correlation with saliva varenicline levels and is widely regarded as the most practical measure of varenicline adherence [16]. In order to assess the feasibility and accuracy of measuring adherence using TLFB, participants will also be asked to send pictures of their varenicline blister packs at 1, 4, 8, and 12 weeks. This additional measure will also help explore which method to assess adherence should be used for any future research studies (eg, RCT). Smoking abstinence will be defined by a negative response to the dichotomous 7-day point prevalence question, "Have you had a cigarette, even a puff, in the last 7 days?"

Analysis of Survey Data

We will calculate descriptive statistics, including means, medians, ranges, and SDs, for the demographic data as well as

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for the AIM, IAM, and analytics data captured by the health bot internal logs. All scores will be analyzed using the appropriate guidelines provided by Weiner et al [40] (acceptability and appropriateness) and Brooke [42] (usability). Consistent with previous studies, adherence will be defined as taking ≥80% of the prescribed varenicline [45-48]. We will not treat adherence as a continuous variable because it is likely to be strongly bimodal and is not necessarily linearly associated with the cessation outcome. We will calculate the percentage of participants who were adherent at week 12 and who reported not having smoked in the last 7 days. These results will serve as progression criteria to determine whether a full-scale RCT is warranted. Although the sample size will be insufficient for meaningful regression analysis, especially given the potentially nonlinear effects of age, we will also test for differences across age and gender groups using 2-tailed *t* tests and chi-square tests. The power for these comparisons will be low; therefore, this analysis will be an exploratory evaluation of large adherence or outcome differences that may be important to future study design, and interpretation will focus on observed differences and CIs.

Analysis of Semistructured Interviews

We will use framework analysis [49] to analyze the data. Specifically, we will use the implementation outcomes of Proctor et al [39] with an intersectional lens as the a priori framework. Framework analysis is a method used to draw descriptive and explanatory conclusions from qualitative data and includes the following six steps: (1) verbatim transcription of interviews, (2) familiarization of interviews, (3) coding and labeling the data, (4) developing a framework by grouping and categorizing codes, (5) indexing transcripts using the developed framework, and (6) reducing and charting data into a matrix. Interview findings will help us contextualize the findings from the surveys and the information collected from the use of the health bot. For example, we will understand why the health bot was or was not used (adoption); if it was used as intended (fidelity), what about the health bot the participants found agreeable and what they did not (acceptability); what features, if any, aligned with participants' attitudes, needs, and background (appropriate); and how other features would need to change in order to align with their needs. In addition, we will be able to understand how social identity (eg, age and gender) and power structures (eg, ageism and sexism) played a role in these results. This will provide us with important information to improve the health bot through an equity lens.

Triangulation of Findings

Once the survey data and interviews are analyzed, we will triangulate the results by listing all the findings on the same page to identify instances where findings from each method align (convergence), provide additional insights on the same topic (complementarity), or seem to conflict with one another (discrepancy or dissonance) [50,51]. Triangulating the data will allow us to contextualize the quantitative findings and explore "intermethod discrepancy" that might lead to a better understanding of how the health bot works and the modifications needed.

Exploring the Feasibility of the Approaches on Recruitment, Retention, and Data Collection

This study, using "stop, amend, and go" progression criteria for pilot studies [51], will help determine if proceeding with an RCT is a logical next step and whether additional adjustments are necessary. We will only conduct a full-scale RCT if none of the criteria outlined in Table 2 meet the "stop" criterion (unless we see that there are contextual issues that can be modified to overcome the identified problems). If 1 or more of the concepts in Table 2 meet the "amend" criterion, the trial will proceed to an RCT only if the issues can be addressed. If all concepts in Table 2 satisfy the "go" criterion, we will proceed with planning an RCT.

Table 2. Criteria to decide if a randomized controlled trial is warranted.

Criteria	Stop	Amend	Go
Patient recruitment	If <30 patients are recruited within 12 months	If 30-40 patients are recruited within 12 months	If 40 patients are recruited within 12 months
Patient retention	If <25% of patients answer the 12-week survey	If 25.1%-79.9% of patients answer the 12-week survey	If ≥80% of patients answer the 12-week survey
Missing data, medication adherence, or smoking status	If >60% of adherence data and smoking status are missing	If 21%-59% of adherence and smoking status data are missing	If ≤20% of adherence and smoking status data are missing
Acceptability and appropriateness	If mean score for the AIM[a] or IAM[b] is ≤8	If mean score for the AIM or IAM is 9-12	If mean score for the AIM or IAM is ≥13
Usability	If mean SUS[c] score is ≤40	If mean SUS score is 41-67	If mean SUS score is ≥68
Adoption	If mean use is ≤ 20 times	If mean use is 21-79 times	If mean use is ≥80 times

[a]AIM: Acceptability of Intervention Measure.

[b]IAM: Intervention Appropriateness Measure.

[c]SUS: System Usability Scale.

Results

Participant enrollment for the study will begin in January 2024.

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Discussion

Despite the proven effectiveness of varenicline in aiding smoking cessation [52], a significant number of individuals attempting to quit continue to smoke because they struggle with adhering to their varenicline regimen [12-14]. While there are proven strategies to help people adhere to their medications, they have been hard to implement. Digital technology for medication adherence has started to emerge [53,54]; whether these tools can be feasibly implemented and adopted, especially within diverse and disadvantaged populations, remains largely unknown.

In this protocol, we outline the methodology to assess the uptake, usability, acceptability, and appropriateness of ChatV and assist in determining whether it is appropriate to advance to an RCT to gauge the effectiveness of the intervention. This study will address many limitations of previous mobile health trials [55,56], including using an intervention that clearly outlines the behavior-change theory used and the intervention content. In addition, this study provides well-outlined a priori criteria for progressing to an RCT. This will enhance its replicability. Furthermore, this study will provide insights into potential mechanisms underlying the intervention's impact, shed light on the effectiveness, or ineffectiveness, of its various components, and offer possible explanations.

In summary, the results of this feasibility study will provide much-needed data and insight into the potential implementation of ChatV to augment adherence to smoking cessation medications. In addition, this project has the potential to increase our understanding of how digital tools can improve adherence to other medications in a cost-effective manner.

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Data Availability

The data sets generated during this study will be available from the corresponding author upon reasonable request.

Authors' Contributions

NM conceived the study with the support of JR, PS, SV, LZ, and MR. NM (lead), KM, ME, SH, RTAK, and PS have shaped the intervention (health bot). NM (lead), KM, and ME were involved in gaining ethical approval. NM and KM wrote the first draft of the manuscript. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

Conflicts of Interest

The authors declare that they have no conflicting interests with respect to this manuscript; however, some authors have general disclosures to report. NM reports receipt of funding from the Canadian Institutes of Health Research, the Canadian Cancer Society, and the discovery fund of the Centre for Addiction and Mental Health (CAMH). PS reports receipt of funding from the Canadian Institutes of Health Research, the Canadian Cancer Society, Pfizer Inc, Pfizer Canada, and the Ontario Lung Association. PS also reports that, through an open-tender process, Johnson & Johnson, Novartis, and Pfizer Inc are vendors of record for having provided smoking cessation pharmacotherapy for research studies at free or discounted rates. PS holds the Vice-Chair, Research, and Giblon Professor in Family Medicine Research, a university-named professorship at the University of Toronto. OCM reports receiving grant and salary support from the Centre for Addiction and Mental Health and the Department of Family and Community Medicine at the University of Toronto through the New Investigator Award.

Multimedia Appendix 1
Peer-review report by the Canadian Institutes of Health Research.
[PDF File (Adobe PDF File), 78 KB - resprot_v12i1e53556_app1.pdf]

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Abbreviations

AI: artificial intelligence
AIM: Acceptability of Intervention Measure
CAMH: Centre for Addiction and Mental Health
COM-B: capability, opportunity, motivation-behavior change
IAM: Intervention Appropriateness Measure
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
STOP: Smoking Treatment for Ontario Patients
SUS: System Usability Scale
TLFB: Timeline Followback

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Protocol

Improving Health for Older Adults With Pain Through Engagement: Protocol for Tailoring and Open Pilot Testing of a Mind-Body Activity Program Delivered Within Shared Medical Visits in an Underserved Community Clinic

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Abstract

Background: Chronic musculoskeletal pain is prevalent and disabling among older adults in underserved communities. Psychosocial pain management is more effective than pharmacological treatment in older adults. However, underserved community clinics often lack psychosocial treatments, in part because of a lack of trained providers. Shared medical appointments, in which patients undergo brief medical evaluation, monitoring, counseling, and group support, are an efficacious and cost-effective method for chronic disease management in underserved clinics, reducing the need for specialized providers. However, shared medical visits are often ineffective for chronic pain, possibly owing to lack of inclusion of skills most relevant for older adults (eg, pacing to increase engagement in daily activities).

Objective: We have described the protocol for the development and initial pilot effectiveness testing of the *GetActive+* mind-body activity intervention for older adults with chronic pain. *GetActive+* was adapted from GetActive, an evidence-based intervention that improved pain outcomes among mostly affluent White adults. We aim to establish the initial feasibility, acceptability, fidelity, and effectiveness of *GetActive+* when delivered as part of shared medical appointments in a community clinic.

Methods: We conducted qualitative focus groups and individual interviews with providers (n=25) and English-speaking older adults (aged ≥55 y; n=18) with chronic pain to understand the pain experience in this population, perceptions about intervention content, and barriers to and facilitators of intervention participation and implementation in this setting. Qualitative interviews with Spanish-speaking older adults are in progress and will inform a future open pilot of the intervention in Spanish. We are currently conducting an open pilot study with exit interviews in English (n=30 individuals in total). Primary outcomes are feasibility (≥75% of patients who are approached agree to participate), acceptability (≥75% of patients who enrolled complete 8 out of 10 sessions; qualitative), and fidelity (≥75% of session components are delivered as intended). Secondary outcomes include physical function—self-reported, performance based (6-minute walk test), and objective (step count)—and emotional function (depression and anxiety). Other assessments include putative mechanisms (eg, mindfulness and pain catastrophizing).

Results: We began enrolling participants for the qualitative phase in November 2022 and the open pilot phase in May 2023. We completed the qualitative phase with providers and English-speaking patients, and the results are being analyzed using a hybrid, inductive-deductive approach. We conducted rapid analysis of these data to develop *GetActive+* before the open pilot in

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English, including increasing readability and clarity of language, reducing the number of skills taught to increase time for individual check-ins and group participation, and increasing experiential exercises for skill uptake.

Conclusions: We provide a blueprint for the refinement of a mind-body activity intervention for older adults with chronic pain in underserved community clinics and for incorporation within shared medical visits. It will inform a future, fully powered, effectiveness-implementation trial of *GetActive+* to help address the chronic pain epidemic among older adults.

Trial Registration: ClinicalTrials.gov NCT05782231; https://clinicaltrials.gov/study/NCT05782231

International Registered Report Identifier (IRRID): DERR1-10.2196/52117

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KEYWORDS

chronic pain; mind-body; underserved; musculoskeletal pain; pain; older adults; pain management; feasibility; intervention

Introduction

Background

Chronic musculoskeletal pain (pain that persists for >3 mo [1]) is highly prevalent among older adults and is associated with substantial clinical, economic, and societal burden [2-4]. Chronic pain tends to be more complex in older adults, with approximately 60% to 70% describing pain in multiple sites alongside multiple comorbidities [5]. Among older adults, chronic pain leads to significant decline in physical and emotional function, with substantial disability from reduced mobility, avoidance of activity, falls, depression, anxiety, sleep impairment, and social isolation [2,3,6,7] regardless of the location and severity of pain [8,9]. Sedentariness, lack of engagement in activities of daily living, and impairments in balance and gait [10] are common in older adults with chronic pain and further increase the risk for morbidity and mortality [2].

For older adults, pain medications, including opioid analgesics, have limited efficacy [11,12], increase the risk for adverse events such as falls [13], and can lead to confusion and cognitive decline [14]. Nonpharmacological treatments for chronic pain such as cognitive behavioral therapy or mindfulness-based interventions are safe for older adults and can improve pain outcomes including physical and emotional function [15,16]. However, access to timely treatment is scarce [17], and treatments often fail to target physical function components that are critical in older adults, including walking and activities of daily living [18].

Importantly, treatment access is not evenly distributed. Older adults from communities of high socioeconomic status have substantially greater likelihood of receiving psychosocial pain management, whereas individuals from underserved communities often lack psychosocial treatment options, despite being at the highest risk for negative pain outcomes [19,20]. Disparities in chronic pain management are multidimensional, including divisions in patient and health care provider communication, variability in decision-making, and gaps in access to effective treatment [19,21]. Furthermore, older adults from underserved communities receive most of their care from primary care practitioners. However, many primary care practitioners do not have the time or training to provide psychosocial pain management and tend to primarily focus on pharmacological treatment. Access to nonpharmacological therapies is limited for many older adults from disadvantaged populations because therapies are not affordable, not recommended by providers, or not available in their community [22-25].

There is a need to implement psychosocial pain management interventions within primary care that are accessible to underserved older adults with chronic pain. Shared medical visits may be a viable model to overcome the many barriers to implementation in these communities [26,27]. Shared medical visits seek to improve patient health through a blend of medical care, education, and peer support [28]. They include group conversations, individual check-ins, and peer interactions as key elements [29]. Shared medical visits are often used to provide greater access to complementary and integrative health approaches to pain management, including mindfulness-based interventions [30]. Patients report that shared medical visits allow them to learn from peers' experiences and create a sense of connection [31,32], with many preferring them to individual primary care appointments [33]. There is evidence to suggest that pain management can be delivered successfully in shared medical visits [34,35], including with economically and ethnically diverse populations [36-38]. Patients qualitatively support shared medical visits and demonstrate increases in quantitative measures of quality of life [33,35,39]. However, pain outcomes, including pain interference and pain catastrophizing, are often not adequately targeted by existing shared medical visit interventions [34,39]. Existing interventions are often broad in their scope, including using mindfulness, guided imagery, health behaviors (eg, exercise and nutrition education), yoga, chiropractic education, and acupuncture [33,35,37,39], without enough attention to skill uptake and integration into daily life. Although experiential exercises are sometimes incorporated, less time is allocated for repetition and troubleshooting skills use to acquire mastery. Furthermore, many of these programs were developed for young populations; there is an absence of skills focused directly on activities of daily living, which is particularly important to older adults [40].

Objective

To address the need for accessible, psychosocial, group pain management for older adults, we are iteratively adapting our evidence-based chronic pain intervention, the GetActive program [41], for implementation in an underserved community clinic using shared medical visits performed in English and Spanish. GetActive uses cognitive behavioral therapy (eg,

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identifying and challenging negative thoughts) and mind-body skills (eg, deep breathing and mindfulness) to promote engagement in physical activity [42]. Our team has previously reported on the development and testing of GetActive including (1) strong feasibility, acceptability, and credibility [43,44]; (2) moderate to large significant improvements in self-reported physical function, performance-based physical function (6-minute walk test; 6MWT), pain, and emotional function (depression and anxiety) [43,45]; and (3) improvements through the mechanistic intervention targets (pain catastrophizing, fear of pain, pain resiliency, mindfulness, coping, and self-compassion) [44,46-48]. However, the original >*GetActive* program was developed in a predominantly White and affluent sample and did not use the shared medical visit format.

Our new intervention, *GetActive+*, will be delivered within the shared medical visit format. Each group session will include both pain management skills and a medical check-in with a nurse practitioner, to monitor fall risk and ability to engage in the physical activities that form the cornerstone of the program. Our approach to developing *GetActive+* is informed by the socioecological model [49], Aarons' stage model [50], and Proctor's framework for implementation [51]. Development will be iterative and will entail (1) using qualitative methods (focus groups and individual interviews) to assess provider and patient perceptions about the program and treatment needs and (2) conducting an open pilot with qualitative exit interviews to examine feasibility, acceptability, fidelity, and preliminary effectiveness in improving physical and emotional function and putative mechanisms. We will use qualitative information from the exit interviews to triangulate acceptability and obtain patient feedback about the treatment components and study procedures. We hypothesize that *GetActive+* will be feasible (≥75% agree to participate), be acceptable (≥75% of those enrolled complete 8 out of 10 sessions), be delivered with fidelity (≥75% sessions are delivered as intended), and show evidence for effectiveness in improving quantitative outcomes. We will use the information gained from the open pilot to refine the intervention and finalize the manual, assessments, and study protocol to support the successful completion of a future, hybrid, type-1, effectiveness-implementation trial. As a large portion of older adults in community clinics speak Spanish, we are also developing a Spanish version of *GetActive+*. Our ultimate goal is to create a program that can be delivered by providers of any specialty in a group format, to enhance the feasibility of dissemination to any community clinic. Given that different clinics have different resources, provider availability, and patient payment systems, this flexibility will maximize patient access while minimizing copayments.

In this paper, we have described the protocol and status of the qualitative phase and open pilot of *GetActive+*. We have discussed the challenges and flexibility required to refine and adapt a manualized chronic pain treatment for this setting. Ultimately, we aim to provide a framework for increasing access to evidence-based psychosocial pain management for older adults with chronic pain in underserved communities.

Methods

Phase 1: Qualitative Interviews

Study Design

We elicited feedback from stakeholders (providers and patients) through qualitative focus groups and individual interviews, with the goal of identifying and addressing barriers to and facilitators of implementation. Interviews were delivered in person at the clinic or via secure, live videoconferencing. Staff participants included primary care physicians, nurses, physical therapists, medical interpreters, and administrative staff. Ongoing interviews with Spanish-speaking patients are conducted by trained native speakers.

Setting and Participants

This study was conducted at the Massachusetts General Hospital (MGH)–Revere HealthCare Center (RHC), a community health care clinic that serves an economically and ethnically diverse population, approximately half of whom identify as immigrants, Asian, Black, Latino, or multiracial.

The inclusion criterion for providers for the qualitative interviews was as follows: any staff member of RHC. The inclusion criteria for patients for the qualitative interviews were as follows: (1) a patient at RHC; (2) aged ≥55 years; (3) self-reported chronic musculoskeletal pain (ie, pain duration >3 mo); (4) pain score ≥4 on the Numerical Rating Scale [52]; (5) no self-reported cognitive challenges that would interfere with participation (eg, cognitive impairment or dementia); (6) no self-reported, currently active, untreated psychotic or substance use disorder; (7) self-reported ability to walk for at least 6 minutes, including with assistive devices; and (8) English or Spanish fluency. Exclusion criteria were as follows: (1) current serious medical illness that is expected to worsen in the next 6 months (eg, advanced cancer) and (2) currently active and untreated serious mental health condition (eg, bipolar disorder, schizophrenia, or substance use disorder) that could interfere with focus group participation. Focus groups were conducted separately with patients and providers.

Recruitment, Screening, and Enrollment

The RHC medical director or study champions—primary care physicians in the clinic who assisted in recruitment—identified potential participants for the qualitative phase with RHC staff. All RHC staff were notified that their participation in the focus groups or interviews was voluntary, that results would not be reported to leadership, and that they will be able to withdraw at any time. Participants reviewed the institutional review board–approved study fact sheet independently using REDCap (Research Electronic Data Capture; Vanderbilt University) tools hosted at MGH; a HIPAA (Health Insurance Portability and Accountability Act)-approved electronic data capture system) [53]. Those who indicated their verbal agreement to participate were enrolled.

Potential participants for the focus groups and interviews with RHC patients were recruited via referrals from study champions and other RHC medical providers. Study champions encouraged referrals from fellow staff. Patient participants were also

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recruited through flyers posted in the clinic and an advertisement on the MGH web research recruitment platform. Following eligibility screening by a research assistant, participants reviewed a study fact sheet and provided verbal consent to participate. Participants were notified that their participation in the focus groups or interviews was voluntary and that they will be able to withdraw at any time. Patients who were ineligible or uninterested were given a chronic pain resource sheet.

Qualitative Interviews

We used a similar semistructured, qualitative interview guide for both provider and patient interviews. Qualitative interview guides centered on three major domains: (1) needs and characteristics of older adults with chronic pain at RHC, including how environmental, sociocultural, behavioral, and medical factors influence and are influenced by pain and perceptions about pain treatments; (2) program preferences, including feedback about the general program content, structure, format, and skills (including audio examples of program skills); and (3) potential barriers to and facilitators of program participation and implementation, including questions related to transportation and homework completion. Interviews were conducted by trained facilitators, primarily, clinical psychologists and a trained research assistant. A trained bilingual research assistant conducted the Spanish focus groups and interviews.

Multiple reminder calls were conducted, and emails were sent before the focus groups. Nevertheless, on multiple occasions, attendance was not sufficient to conduct the group. Potential participants expressed that they had other competing responsibilities (eg, caregiving roles and medical appointments) that interfered with focus group participation. Therefore, we adopted a more flexible procedure, allowing for the completion of individual interviews via Zoom (Zoom Video Communications) or phone to ensure that we could get the information needed to inform program refinement while working with the needs of the clinic population.

Data Coding and Analysis

We conducted rapid data analysis (RDA) following each interview to determine real-time data saturation and develop *GetActive+* and the study protocol before conducting more extensive qualitative analyses [54]. RDA is a valid and reliable qualitative data analysis method that is recommended in studies where there is a need for real-time data to inform intervention adaptation and implementation [54-56]. RDA bypasses the process of transcription and in-depth coding; instead, data are organized immediately following qualitative interviews based on a template created from the interview script [57]. In this study, RDA was conducted within 24 hours of the interview, typically immediately after its completion. Our RDA template was organized into the following domains: (1) living with chronic pain: challenges, needs, and treatment (eg, description of the clinic population); (2) program implementation and preferences (eg, feedback about the core program skills); and (3) barriers to and facilitators of program implementation (eg, barriers to and facilitators of patient participation and homework completion). On the basis of the RDA literature, the completed template was reviewed by another member of the study team and entered into a matrix of responses [55,58], which informed the manual and procedure adaptations before the open pilot. The matrix was organized in a hybrid, inductive-deductive manner based on a combination of the domains from the RDA template and the information that emerged from qualitative interviews that was most useful in guiding the program adaptations. Each row consisted of one of the following domains: clinic population, usual pain care at the clinic, initial reactions to the program, format and delivery modality, core skills, program barriers and facilitators, and focus group recommendations. Each column represented a single group or individual interview.

Formal, planned, qualitative analyses are ongoing and will be used to provide an in-depth synthesis of the qualitative data, including comparisons between provider and patient feedback. These analyses involve the transcription of audio recordings and data analysis using the program, Dedoose [59]. We generated a qualitative codebook using a hybrid, deductive-inductive approach [60], wherein codes are created based on a priori categorizations using theoretical frameworks (eg, the socioecological model) and then revised based on novel content identified from the data. We allowed for new codes to be created directly from the data analysis process. Overall, 2 trained research assistants coded the first 20% of the transcripts under the guidance of a psychologist to resolve discrepancies between coders until sufficient concordance was achieved, following which the codebook was solidified, and the remaining transcripts were coded by a single coder.

Intervention Refinement

We used RDA to inform intervention refinement. We made the following modifications: (1) added psychoeducation about the nature of chronic pain to increase the understanding of core program principles and improve treatment buy-in; (2) simplified the program language and presentation to ensure that the manual was concise and at a sixth-grade reading level; and (3) consolidated the skills and ensured more time for experiential learning, check-ins, and group discussions to facilitate both skill mastery and social connection. In addition, because of high rates of stress, trauma, and grief in this clinic population, we focused the program skills on the impact of these factors on the pain experience and discussed how program skills can target both pain and these psychosocial factors. For example, the importance of using mindfulness to facilitate awareness about the impacts of stressors on pain was noted throughout the refined intervention. Finally, consistent with the goals of our subsequent effectiveness trial, the program emphasizes flexibility within fidelity, whereby we aim to deliver the active ingredients of the program while allowing flexibility with regard to the delivery format (eg, in-person or virtual), skill delivery contextualization, and support for the interventionist to adapt and differentiate support based on need [61]. Additional modifications and cultural tailoring of the intervention are expected as we develop the Spanish version of *GetActive+*.

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Phase 2: Open Pilot of *GetActive+* With Exit Interviews

Study Design

GetActive+ is a 10-week group program designed to be led by any provider available in a community clinic. The open pilot English version of *GetActive+* is delivered by a mental health professional and a nurse practitioner in groups of 3 to 10 members. The nurse practitioner conducts 5-minute, individual, medical check-ins before or after the group session to assess current pain levels and discuss medical concerns that could interfere with activity engagement (eg, acute injuries and fall risk). The medical check-ins are optional. The nurse practitioner can refer to additional medical care, including contacting primary care providers, as needed.

The open pilot study is registered on ClinicalTrials.gov (trial registration: NCT05782231).

Setting and Participants

Inclusion criteria for the open pilot are identical to those for the qualitative phase, with the following exceptions: patients must be cleared for participation by medical staff and cognitive functioning is assessed using the Short Portable Mental Health Questionnaire [62] with a requirement of <4 errors to participate. An additional exclusion criterion was added that excluded those unable or unwilling to wear an ActiGraph, a device required for baseline and postintervention assessment of objective physical function.

Initial recruitment, screening, and enrollment procedures are identical to those of phase 1. Once a patient referral is received, a research assistant conducts a phone screening call with the patient. The research assistant provides a detailed introduction of the program, explaining the aim, format, modality, and participant requirements. All patient information, contacts, screening outcomes, and participant status are recorded in a secured, study-specific tracking log. If a patient is eligible and interested in participating, the research assistant collects their availability and preferred method of contact. If a patient is deemed ineligible, they are emailed a chronic pain resource sheet with information about pain management. Eligible participants are scheduled for an in-person clinic visit, where they provide written informed consent and complete the baseline assessments. Baseline sessions are scheduled based on the availability of the group leader, participants, and room to work within the clinic's existing programming. The research assistant conducts a scheduling call to all participants, encouraging each individual to record the date and time of the baseline session in their phone, in their calendar, or on their refrigerator. Owing to our issues with focus group attendance, as documented previously, we instituted a system of reminder calls to ensure attendance. Participants receive one call in the week before the baseline session and another on the day of the baseline session. Once the program begins, participants receive 1 reminder call in the morning of the session. They additionally receive calls if there are missing assessments or if follow-up information is needed regarding a concern that arose in the group (eg, safety considerations after a fall). We use a flexible approach in adapting to the needs of the group members, including providing GrandPad tablets for older adults with low income, giving them secure access to the study website (including skill recordings), assessments, and Zoom (for those who attend virtually).

Intervention

GetActive+ session contents are described in Table 1. The program begins with pain education, including information about how pain originates in the brain rather than because of tissue damage, that any stressors that dysregulate the nervous system can increase pain, and that chronic pain often involves a false alarm that fires in the absence of actual ongoing harm to the muscles and tissues. This information is presented to reinforce that participation in activities of daily living including light activity (eg, walking) is safe, regardless of the presence of pain. Participants are informed that the purpose of the program is to increase the time they spend in being active, such as engaging in walking, active hobbies, or chores. They are asked to reflect about their typical day and to contemplate what their day would look like if the program was successful and how they would like to increase their activity in ways that are meaningful to them. *GetActive+* then focuses on a series of skills in 4 categories, with primary focus on activity engagement skills including participating in active chores and hobbies that are meaningful and quota-based pacing to safely break the connection between pain and activity. Quota-based pacing is the cornerstone of the intervention and consists of setting weekly, realistic activity goals to increase participants' engagement in active hobbies, chores, and walking over time (eg, increasing activity by 5-10 min/d each week). The purpose of quota-based pacing is to build a sustainable habit that can be continued after the program ends. Emphasis is placed on the individuality of the participant's experience such that they are encouraged to choose activities that are meaningful to them. Similarly, they are provided with a range of complementary skills throughout the program to assist them in increasing activity and reducing pain interference; they are encouraged to choose those that are most applicable to their individual goals and experience. These skills are mind-body skills (eg, deep breathing, body scan, mindful walking, self-compassion, social support, and acceptance) to change one's relationship with pain (eg, reduce reactivity, fear, and ruminative self-talk through relaxation response and mindfulness exercises) and to facilitate activity engagement, pain behavior awareness skills to understand the "downward spiral" (eg, how lack of activity perpetuates chronic pain and emotional and physical disfunction), and cognitive skills to learn to identify and challenge negative automatic thoughts. All participants receive a treatment manual with descriptions of the skills and worksheets to record their individual cognitions, emotions, and behaviors surrounding pain and their weekly pacing plans to increase activity engagement.

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Table 1. *GetActive+* intervention content in each session.

Session	Topic	Skills
1	Chronic pain education	Identifying the true vs false pain alarms and understanding the downward spiral of pain disability
2	Catching unhelpful thoughts and increasing activity	Identifying negative automatic thoughts that lead to pain interference and introducing quota-based pacing
3	Becoming aware	Mindfulness and body scan
4	Staying engaged with life	Mindful walking and engagement in meaningful activities
5	Working with unhelpful thoughts	Education about cognitive distortions and challenging negative automatic thoughts
6	Taking a pause to check in	Review of all skills, progress in activity engagement, and motivation to continue
7	Caring for yourself when you are in pain	Mindfulness of pain and self-compassion
8	Feeling connected with others	Discussion about the impact of pain on social connection and how to increase connection, including through walking with others
9	Promoting acceptance	Acceptance, including finger trap demonstration
10	Staying on track and maintaining your progress	Review of skills and plan for continuing engagement in activity following treatment

The beginning of each session consists of an overview and check-in regarding activity goals and skill use. Depth rather than breadth is emphasized in the check-in, in that clinicians are instructed to troubleshoot a particular skill, activity goal, or barrier to increasing activity, rather than reviewing the week in its entirety. Clinicians form a case conceptualization to individualize the intervention and target participant-specific barriers to activity engagement. For example, a participant with increased anxiety might be encouraged to use mindfulness skills to notice how fears about pain are preventing them from engaging in activity, whereas a participant who tends toward stoically increasing activity regardless of consequences would be encouraged to use mindfulness skills to notice when they are entering a boom-and-bust cycle. Participants are encouraged to try all the skills and are informed that skills are often most helpful with practice; however, it is also noted that the program represents a toolkit of skills and that, ultimately, they can choose those they feel are most applicable to them. We anticipate that the *GetActive+* Spanish version will retain the core components of the program, with additional tailoring based on information from qualitative interviews and focus groups.

Clinicians note the feedback about the intervention components following each session, including whether skills are understood, require additional clarification, and are perceived as useful. This information will be used to further refine *GetActive+* at the end of the open pilot phase.

Treatment Fidelity

Consistent with our ultimate goal of creating a skills-based activity program that can be flexible and delivered by any provider, we are using interdisciplinary clinician teams. English-speaking groups are currently led by a Doctor of Philosophy–level clinical psychologist in conjunction with a nurse practitioner. The psychologist has experience with both chronic pain management and skill training intervention groups. The nurse practitioner is experienced in geriatrics, including pain management and medical considerations of older adult populations. In the open pilot, we used a sequential approach to training in which the nurse practitioner completed training on the program, consisting of a description of the development and initial testing of GetActive, theoretical rationale and core principles of the program, core skills, and role plays. She observed 1 group led by the clinical psychologist, codelivered the second group, and is currently leading the delivery of the third group, which will be recorded and rated for competency. She will be rated on (1) *GetActive+* general intervention principles and theoretical background; (2) *GetActive+* skill delivery; and (3) nonspecific competencies such as establishing rapport with participants, problem solving, and time management. The lead clinician, in conjunction with the study team, created a clinician version of the manual, informed by the experience of conducting the intervention in the open pilot. The clinician manual consists of guidance about timing, suggested language, and advice about how to maximize the key targets of the intervention. We opted to have the open pilot sessions cofacilitated by a mental health professional (psychologist and social worker) and nurse practitioner together as a way to allow the nurse practitioner to contribute to the clinician manual with real-time feedback. This manual will allow for wide dissemination, so that any provider, regardless of background, will be able to deliver the intervention.

Intervention Fidelity

We use session content adherence checklists to ensure that all components of the intervention are delivered in compliance with the study protocol. Clinicians complete an adherence checklist and a session note summarizing the session content and any issues that arise regarding individual concerns and progress and any information that is important for case conceptualization. Sessions are recorded, and 20% (6/30) will be reviewed for fidelity. Feedback is provided during weekly supervision, led by one of the study's principal investigators (A-MV). Participants who miss a session are offered one-on-one makeup sessions. Home practice is logged manually by

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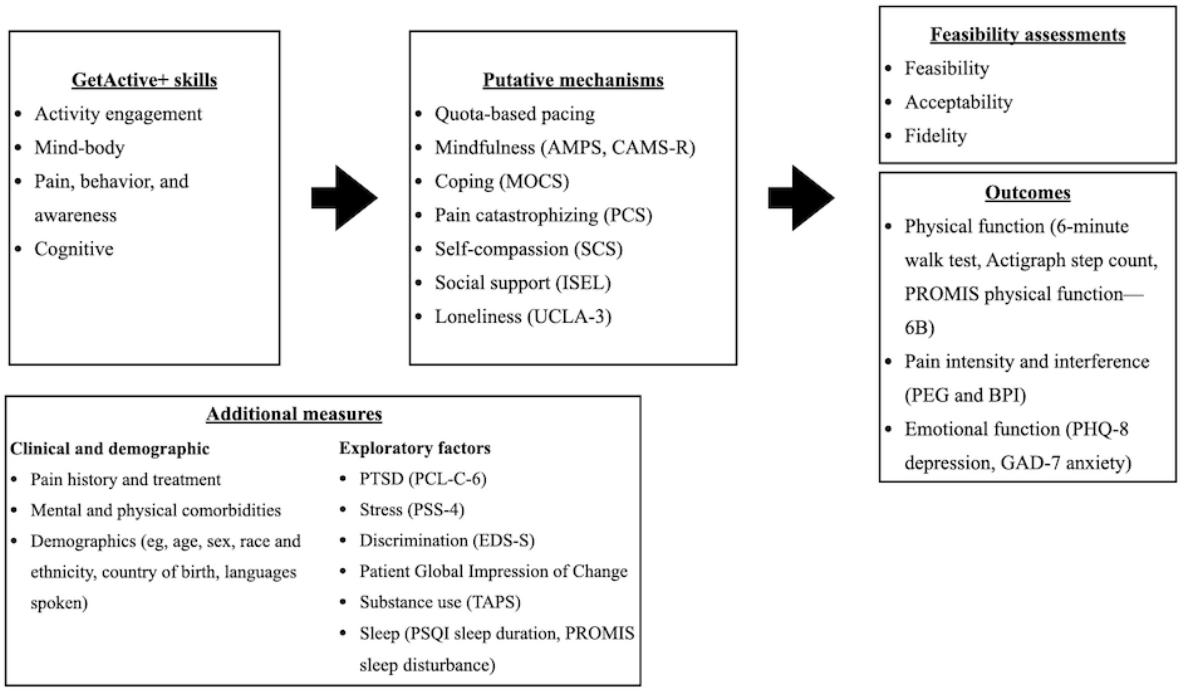
participants, tracked through the completion of web-based surveys sent either through email or SMS text message, and discussed in each session by the clinicians. Issues with compliance are discussed in supervision. Procedures follow the National Institutes of Health (NIH) Science of Behavior Change recommendations [63] and have been used by the multiple principal investigators and in previous clinical trials.

Assessments

Overview

Study assessments are depicted in Figure 1. Self-report measures and behavioral assessments of physical function (6MWT and ActiGraph-measured step count) are administered at baseline (1 week before session 1) and after the intervention (1 wk following session 10). Measures are collected either electronically (using the secure, HIPAA-approved REDCap platform on a study device) or using pen and paper, depending on device availability and participant preference. Measures are administered before and after the intervention, with the exception of the demographic questions (baseline only) and Patient Global Impression of Change (after the intervention only).

Figure 1. Diagram of *GetActive+* skills and assessments. AMPS: Applied Mindfulness Process Scale; BPI: Brief Pain Inventory; CAMS-R: Cognitive and Affective Mindfulness Scale–Revised; EDS-S: Everyday Discrimination Scale–Short; GAD-7: 7-item Generalized Anxiety Disorder Scale; ISEL: Interpersonal Support Evaluation List; MOCS: Measure of Current Status; PCL-C-6: 6-item Post-Traumatic Checklist–Civilian Version; PCS: Pain Catastrophizing Scale; PEG: Pain, Enjoyment of Life, and General Activity scale; PHQ-8: 8-item Patient Health Questionnaire; PROMIS: Patient-Reported Outcomes Measurement Information System; PSQI: Pittsburgh Sleep Quality Index; PSS-4: 4-item Perceived Stress Scale; PTSD: posttraumatic stress disorder; SCS: Self-Compassion Scale; TAPS: Tobacco, Alcohol, Prescription Medications, and Other Substance; UCLA-3: University of California Los Angeles–3 Loneliness Scale.



Primary Outcomes

Primary outcomes for the open pilot feasibility trial are described in Table 2 and include a priori benchmarks for feasibility, acceptability, and fidelity, informed by Aarons' stage model [50] and Proctor's framework for implementation [51].

Table 2. Feasibility benchmarks.

Implementation outcome	Definition	Recommended implementation step in the model by Aaron et al [50]	Benchmark
Feasibility	Suitability and practicality	Early (steps 1-3)	≥75% of those who are approached agree to participate in intervention; qualitative feedback
Acceptability	Satisfaction with or tolerability of the proposed approach	Early (steps 1-3)	≥75% of those who are enrolled complete at least 8 out of 10 sessions; qualitative feedback
Fidelity	Delivery of *GetActive+* as intended	Early to middle (steps 2-3)	≥75% of the session components are delivered by clinicians as intended; 20% of the sessions are rated

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Secondary Outcomes

We will include the following: (1) performance-based, objective, and self-reported physical function; (2) pain intensity and interference; (3) depression symptoms; and (4) anxiety symptoms.

Performance-based physical function is measured using 6MWT [64,65]. 6MWT is designed to measure the total distance covered by an individual in 6 minutes, with greater distances covered indicating better physical function. Objective physical function is assessed using ActiGraph GT3X-BTLE [66], which measures average step count over the course of a 5-day to 7-day period. Self-reported physical function is assessed using the Patient-Reported Outcomes Measurement Information System Physical Functioning Short Form 6b [67], a measure of the ability to engage in physical activities, including active household tasks. Scores range from 8 to 40, with higher scores indicating greater physical function. Self-reported physical function will be the primary outcome in the subsequent fully powered trial.

We assess pain intensity and interference using the Brief Pain Inventory–Short Form [68]. The pain severity subscale measures pain at its worst, least, average, and current state. The pain interference subscale assesses interference of pain in general activity, mood, walking ability, work, relationships, sleep, and enjoyment of life. Scores for both subscales range from 0 to 10, with higher scores indicating more severe pain severity or interference. Depressive symptoms are assessed using the 8-item Patient Health Questionnaire [69]. Scores for the 8-item Patient Health Questionnaire range from 0 to 24, with higher scores indicating more severe depressive symptoms. The 7-item Generalized Anxiety Disorder scale [70] is used to assess symptoms of generalized anxiety, with scores ranging from 0 to 21 and higher scores indicating greater anxiety.

Other Assessments

Other assessments include the following: (1) putative mechanisms, (2) exploratory measures including NIH Helping to End Addiction Long-Term Initiative Core Data Elements measures, and (3) other auxiliary measures. These measures are included in the open pilot to test for feasibility of these assessments before the effectiveness-implementation trial.

Putative Mechanisms

Quota-based pacing is measured using a 4-item scale consisting of a subsection of items from the Activity Pacing Questionnaire [71]. Scores range from 5 to 20, with higher scores indicating increased pacing. The 13-item Pain Catastrophizing Scale [72] is used to assess pain rumination, magnification of the intensity of pain, and helplessness regarding the ability to cope with pain. Scores range from 0 to 52, with higher scores indicating increased pain catastrophizing. The Applied Mindfulness Process Scale [73] is used to assess the use of mindfulness in response to challenges of daily living. It consists of 15 items, and total scores range from 0 to 60, with higher scores indicating greater use of mindfulness. Similarly, participants' broad conceptualization of mindfulness is assessed using the 12-item Cognitive and Affective Mindfulness Scale–Revised [74]. Its scores range from 12 to 48, with higher scores representing increased levels of mindfulness. We assess self-reported social support using the Interpersonal Support Evaluation List [75]. This measure consists of 12 items, and scores range from 12 to 48, with higher scores indicating strong social support. In contrast, the University of California Los Angeles–3 Loneliness Scale [76] is used to assess social isolation and perceived lack of social support. Total scores on this scale range from 3 to 9, with higher scores indicating greater social isolation. The participants' ability to practice healthy coping skills is assessed using the Measure of Current Status [77]. Total scores on the Measure of Current Status range from 0 to 52, with higher scores reflecting stronger ability to recognize and cope with stress. The Self-Compassion Scale–Short Form [78] is used to assess a participant's level of self-compassion. Scores are calculated by averaging the responses to the 12-item measure and range from 1 to 5. Higher scores are associated with higher levels of self-compassion. Finally, fear of physical activity is assessed by the Tampa Scale for Kinesiophobia–11. Scores range from 11 to 44, with higher scores reflecting more severe kinesiophobia [79].

This study is funded by the NIH Helping to End Addiction Long-Term Initiative, which requires core data elements to ensure that data can be compiled and analyzed across studies. In accordance with the data collection standards, pain interference is measured using the Pain, Enjoyment of Life, and General Activity scale [80], which assesses pain intensity and related interference in the enjoyment of life and activities of daily living. Scores range from 0 to 10, with higher scores indicating more severe pain and related interference. The Patient Global Impression of Change [81] is used to assess changes in pain in response to treatment. Scores range from 0 to 6, with higher scores indicating worse outcomes. The Tobacco, Alcohol, Prescription Medications, and Other Substance [82] screening questionnaire is used to assess substance use. Each substance is scored individually on a single-item scale of use ranging from 0 to 4, with lower scores indicating more frequent use. Sleep duration per night is measured using a single item from the Pittsburgh Sleep Quality Index [83]. Sleep quality is assessed using the Patient-Reported Outcomes Measurement Information System–Sleep Disturbance scale. Scores range from 6 to 30, with greater scores indicating more sleep disturbance.

Other Auxiliary Measures

We included measures to assess the elevated rates of trauma, stress, and discrimination in this population. We are using the 6-item Post-Traumatic Checklist–Civilian Version [84] to assess current symptoms of posttraumatic stress disorder. Scores range from 6 to 30, with higher scores indicating high posttraumatic stress disorder symptoms. The 4-item Perceived Stress Scale [85] is used to measure participants' self-perception about stress levels. Total scores for this scale range from 0 to 16, with higher scores representative of more severe stress. To assess another significant stressor for many in this patient population, experiences of discrimination are measured using the Everyday Discrimination Scale–Short [86]. Total scores for this scale range from 0 to 25, with higher scores indicating greater frequency of discriminatory experiences.

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Clinical and Demographic Variables

We assess general, pain-related information using the author-constructed Pain, Medication, and Medical History questionnaire, which measures self-reported (1) type of pain, (2) pain location and intensity, (3) pain treatments, (4) pain medications, (5) cannabis use for pain, (6) medical comorbidities, and (7) mental health conditions and medication. We additionally obtain the following demographic variables: age and birth date, gender, biological sex, race, ethnicity, education level, employment status, marital status, household income, disability status, language fluency, people in the household, Rural-Urban Commuting Area code (ie, zip code), country of birth, country lived in before the age of 12 years, years lived in the United States, parents' countries of origin, ethnic identity, and languages spoken at home. There is no summary score; each item is scored individually.

Finally, exit interviews assess participants' perceptions about the treatment and study procedures. Topics include what was the most and least helpful about the intervention, any topics that were not addressed that could be included, perceptions about each of the mind-body skills, comfort with participating in a skills-based treatment as opposed to a support group, and barriers to and facilitators of engagement with the material. Perceptions about the providers, assessments, homework, and group format will also be evaluated. RDA is used to analyze the exit interview data to inform the remaining open pilot groups and the subsequent trial.

For our Spanish open pilot, we used validated Spanish versions of the abovementioned questionnaires when they were available. A native speaker translated the remaining study measures.

Data Analysis

Feasibility-related open pilot study measures will be assessed using a priori determined benchmarks for feasibility, acceptability, and fidelity based on our previous studies and recommendations in the field (Table 2) [87,88]. Given the concerns regarding the use of open pilot studies to calculate effect sizes [89,90], sample size estimates and proposed analyses were determined with the primary goal of establishing feasibility, as opposed to powering for specific effects for the quantitative outcomes. Preliminary effectiveness of the secondary outcomes will be examined using simple 2-tailed *t* tests. Evidence of effectiveness will be determined if the minimal clinically important difference for the specific quantitative outcome is included within the 95% CI for the change score.

Ethical Considerations

The MGH institutional review board approved all the study procedures and determined that phase 1 of the study was exempt from written informed consent (institutional review board number for phase 1: 2022P001691). All phase 2 procedures were approved by the institutional review board before data collection (institutional review board number for phase 2: 2023P000362).

Results

We began enrolling participants for the qualitative phase in November 2022 and the open pilot phase in May 2023. We conducted 25 provider interviews and 3 focus groups and 8 interviews with 18 English-speaking patients. The average age of the providers was 48.56 (SD 11.66) years. Most providers were women (21/25, 84%), non-Latino (22/25, 88%), and White (15/25, 60%). On average, they had 18.84 (SD 11.15) years of experience in working with patients, and approximately half (11/25, 44%) reported that they received mental health training as part of their degree. For demographic information about the patient qualitative and open pilot samples, refer to Table 3. RDA was completed before the initiation of the open pilot to inform the manual and program adaptations. The open pilot phase is ongoing. Older adults who participated in the qualitative phase were also invited to participate in the open pilot, with 44% (8/18) enrolling in the open pilot. We completed 2 English-speaking focus groups (group 1: 8/20, 40% and group 2: 6/20, 30%), and one is ongoing (6/20, 30%). In the first group, 100% (8/8) of the participants attended all the sessions, with only 1 dropout across the 2 groups so far. We have also conducted 3 individual interviews with Spanish-speaking older adults and will continue to obtain qualitative assessments with Spanish-speaking participants. We plan to conduct 2 open pilot groups in Spanish.

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Table 3. Demographics for the patient qualitative assessments and open pilot.

Characteristics	English-speaking participants (qualitative; n=18)	Spanish-speaking participants (qualitative; n=3)	Open pilot participants (n=20)
Age (years), mean (SD)	65.72 (7.46)	59.67 (4.51)	70.20 (9.44)
Sex (female), n (%)	12 (67)	2 (67)	16 (80)
Gender (women), n (%)	12 (67)	2 (67)	16 (80)
Ethnicity, n (%)			
Hispanic or Latino	1 (6)	3 (100)	3 (15)
Non-Hispanic or Latino	16 (89)	0 (0)	15 (75)
Unknown or not reported	1 (6)	0 (0)	2 (10)
Race[a], n (%)			
American Indian or Alaska Native	0 (0)	0 (0)	0 (0)
Asian	0 (0)	0 (0)	0 (0)
Black or African American	3 (17)	0 (0)	3 (15)
Native Hawaiian or Pacific Islander	0 (0)	0 (0)	1 (5)
White	15 (83)	1 (33)	13 (65)
Unknown, not reported, or prefer not to answer	0 (0)	2 (67)	3 (15)
Education, n (%)			
Less than high school	0 (0)	0 (0)	0 (0)
Some secondary school or high school	2 (11)	1 (33)	2 (10)
Completed high school or secondary school	8 (44)	0 (0)	8 (40)
Completed associate or technical degree	1 (6)	0 (0)	2 (10)
Completed college or baccalaureate degree	7 (39)	1 (33)	5 (25)
Doctoral or postgraduate education	0 (0)	0 (0)	3 (15)
Prefer not to answer	0 (0)	1 (33)	0 (0)
Employment status, n (%)			
Full-time employment	3 (17)	1 (33)	3 (15)
Not employed	2 (11)	2 (67)	17 (85)
Part-time employment	13 (72)	0 (0)	0 (0)
Household income (US $), n (%)			
<10,000	0 (0)	0 (0)	1 (5)
10,000-24,999	6 (33)	1 (33)	7 (35)
25,000-34,999	1 (6)	0 (0)	4 (20)
35,000-49,999	3 (17)	0 (0)	2 (10)
50,000-74,999	1 (6)	1 (33)	1 (5)
75,000-99,999	0 (0)	0 (0)	2 (10)
100,000-149,999	0 (0)	0 (0)	0 (0)
150,000-199,999	1 (6)	0 (0)	0 (0)
≥200,000	0 (0)	0 (0)	0 (0)
Prefer not to answer	6 (33)	1 (33)	3 (15)
Language or languages spoken[a], n (%)			
English	18 (100)	0 (0)	20 (100)
Spanish	0 (0)	3 (100)	1 (5)
Arabic	1 (6)	0 (0)	0 (0)

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Characteristics	English-speaking participants (qualitative; n=18)	Spanish-speaking participants (qualitative; n=3)	Open pilot participants (n=20)
Other	3 (17)	0 (0)	1 (5)
Country of birth, n (%)			
United States	15 (83)	0 (0)	15 (75)
Other (ie, Egypt, Russia, Costa Rica, Honduras, Guatemala, Puerto Rico, Malta, or Sudan)	3 (17)	3 (100)	5 (25)
Mother's country of origin, n (%)			
United States	13 (72)	0 (0)	13 (65)
Other (ie, Egypt, Russia, Costa Rica, Guatemala, Puerto Rico, Honduras, Malta, Sudan, Ireland, Italy, or Canada)	5 (28)	3 (100)	7 (35)
Father's country of origin, n (%)			
United States	13 (72)	0 (0)	11 (55)
Other (ie, Jordan, Belarus, Costa Rica, Guatemala, Puerto Rico, Honduras, Malta, Sudan, Italy, Philippines, Oman, or Ireland)	5 (28)	3 (100)	9 (45)

[a]Participants may select multiple options; therefore, total percentages might exceed 100%.

Discussion

Principal Findings

This paper describes the study protocol for the adaptation and pilot effectiveness testing of a mind-body activity intervention, *GetActive+*, delivered as part of shared medical visits to older adults with chronic pain in an underserved community clinic. Older adults with chronic pain in community settings often lack access to evidence-based psychosocial treatment options. Given that their pain experience may be affected by socioeconomic factors that may influence the generalizability of interventions, we used a sequential approach to refine *GetActive+* for this setting. First, we conducted focus groups and qualitative interviews with patients and providers to evaluate patient experiences with pain and socioeconomic impacts on the pain experience; we also solicited feedback about the intervention components and logistical barriers to and facilitators of success. Next, we are conducting an open pilot with exit interviews to assess the intervention's feasibility and acceptability and evaluate the signals of improvement in key outcomes, including physical function. We are conducting ongoing English-speaking groups. We are also simultaneously conducting focus groups and qualitative interviews with Spanish-speaking older adults to inform the open pilot in Spanish, which will be conducted by a Spanish-speaking provider.

Chronic pain interventions need to be adaptable to be easily disseminated to the millions of older adults with chronic pain, most of whom receive their treatment in community settings as opposed to academic medical centers where treatment trials are typically conducted. Shared medical visits represent an important avenue for increasing the access to evidence-based pain management interventions [38,91]; however, existing interventions have shown limited effects on key pain outcomes, including pain interference [34,39], possibly owing to overemphasis on broad education rather than skill training [35,37]. *GetActive+* is unique in its emphasis on activity engagement and the use of mind-body skills to facilitate increases in activity. Furthermore, our program emphasizes the development of skill mastery and group cohesion by reserving one-third to half of each session for checking in and troubleshooting skill use.

This protocol demonstrates the importance of flexibility in adapting an intervention to a community setting. We used an observational approach to training that allowed a nurse practitioner to work side by side with a psychologist to learn to deliver the intervention. In turn, the nurse practitioner contributed to the development of the clinician manual and training protocol. We will use a similar approach to train a social worker for the open pilot focus groups in Spanish. We reduced the number of skills in the intervention to increase the opportunity for group discussion and interpersonal connection. We increased the psychoeducation about the impact of stressors on pain, including incorporation of discussions about how stress, trauma, and grief influence the experience of pain throughout the treatment. We changed the language in the manual to be less wordy and increased the number of experiential exercises.

Results of this trial will inform a subsequent hybrid, implementation-effectiveness trial (N=200) to evaluate the effects of *GetActive+* on physical function (self-report, performance based, and step count), depression, and anxiety. In preparation for the trial, we will continue to refine the intervention based on both the quantitative and qualitative findings from the open pilot and feedback from the clinicians delivering the intervention. In the long term, if *GetActive+* proves to be successfully implemented and effective in this community clinic, we will aim to disseminate it broadly. The goal is to have an intervention that can be taught by any health professional, including those who have the most regular access to and strongest relationships with patients in these settings, such as medical interpreters or community health workers. Provider resources are limited, and consequently, there needs to be flexibility in who can administer psychosocial treatment. Thus, we aim to have an intervention for which any health practitioner can be trained to successfully deliver the group. To

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facilitate wide dissemination, our final training protocol and clinician manual for *GetActive+* will include specific guidelines and strategies oriented to address the training needs based on the type of provider, previous training, and expertise. If successful, this program will offer the potential for wide dissemination of mind-body skills with a focus on increasing physical activity, a key predictor of physical, cognitive, and emotional functioning in older adults.

Limitations

Although we are currently only conducting focus groups or interviews and open pilot groups in English and Spanish, we aim to include groups for Cambodian-speaking and Arabic-speaking patients in the future. We hope to improve on this limitation in the subsequent trial. Furthermore, this clinic, although ethnically diverse, lacks a substantial proportion of African American patients; thus, they are underrepresented in our groups compared with the general US population.

Conclusions

We have iteratively adapted and are currently testing the *GetActive+* mind-body activity intervention for older adult patients with chronic pain in a community clinic setting using shared medical visits. By the end of this trial, we will have a finalized intervention and study procedures that will enable us to test implementation and effectiveness in this setting. This trial has the potential to address the chronic pain epidemic by informing the adaptation of psychosocial pain management programs for wide dissemination in community clinics broadly. Such studies are essential for reducing health disparities and ensuring that historically underserved older adults with chronic pain have access to evidence-based pain management programs.

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Data Availability

Once the trial is complete, data will be made available upon request.

Conflicts of Interest

None declared.

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Abbreviations

6MWT: 6-minute walk test
HIPAA: Health Insurance Portability and Accountability Act
MGH: Massachusetts General Hospital
NIH: National Institutes of Health
RDA: rapid data analysis
REDCap: Research Electronic Data Capture
RHC: Revere HealthCare Center

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Protocol

Bio-Experiential Technology to Support Persons With Dementia and Care Partners at Home (TEND): Protocol for an Intervention Development Study

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Abstract

Background: Alzheimer disease and related dementias are debilitating and incurable diseases. Persons with dementia and their informal caregivers (ie, dyads) experience high rates of emotional distress and negative health outcomes. Several barriers prevent dyads from engaging in psychosocial care including cost, transportation, and a lack of treatments that target later stages of dementia and target the dyad together. Technologically informed treatment and serious gaming have been shown to be feasible and effective among persons living with dementia and their care partners. To increase access, there is a need for technologically informed psychosocial interventions which target the dyad, together in the home.

Objective: This study aims to develop the toolkit for experiential well-being in dementia, a dyadic, "bio-experiential" intervention for persons with dementia and their caregivers. Per our conceptual model, the toolkit for experiential well-being in dementia platform aims to target sustained attention, positive emotions, and active engagement among dyads. In this paper, we outline the protocol and conceptual model for intervention development and partnership with design and development experts.

Methods: We followed the National Institutes of Health (NIH) stage model (stage 1A) and supplemented the model with principles of user-centered design. The first step includes understanding user needs, goals, and strengths. We met this step by engaging in methodology and definition synthesis and conducting focus groups with dementia care providers (N=10) and persons with dementia and caregivers (N=11). Step 2 includes developing and refining the prototype. We will meet this step by engaging dyads in up to 20 iterations of platform β testing workshops. Step 3 includes observing user interactions with the prototype. We will meet this step by releasing the platform for feasibility testing.

Results: Key takeaways from the focus groups include balancing individualization and the dyadic relationship and avoiding confusing stimuli. As of September 2023, we have completed focus groups with providers, persons with dementia, and their caregivers. Additionally, we have conducted 4 iterations of β testing workshops with dyads. Feedback from focus groups informed the β testing workshops; data have not yet been formally analyzed and will be reported in future publications.

Conclusions: Technological interventions, particularly "bio-experiential" technology, can be used in dementia care to support emotional health among persons with a diagnosis and caregivers. Here, we outline a collaborative intervention development process of bio-experiential technology through a research, design, and development partnership. Next, we are planning to test the platform's feasibility as well as its impact on clinical outcomes and mechanisms of action.

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KEYWORDS

dementia; dyadic; bio-experiential; serious gaming; psychosocial

Introduction

Overview

Approximately 6.7 million Americans have a diagnosis of Alzheimer disease or related dementias (dementia) and rates are continuing to rise with the increasing aging population [1]. Even with the advent of disease-modifying agents [2], dementia remains a debilitating and incurable disease that impacts cognitive, emotional, social, and behavioral functioning [3,4]. In particular, psychological health concerns, such as stress, anxiety, depression, and social isolation, are common across the illness process and impact outcomes among both persons with the diagnosis and their care network.

More than 11 million Americans are the informal caregivers for a person with dementia [5]. Informal caregivers (ie, someone who provides care for a person with dementia not paid through an agency, often a family member or friend) serve a critical role in providing care for persons living with dementia. Caregivers take on a multifaceted role, including providing direct care assistance (ie, activities of daily living), instrumental activities of daily living (eg, finances and shopping), and emotional support. A large body of literature demonstrates that dementia caregivers report high levels of stress, and often, report a greater impact on mental and physical health than informal caregivers of nondementia illnesses and chronic diseases [6,7]. Depression occurs in at least a third of all dementia caregivers [8]. Increased caregiver stress relates to poor caregiver mental and physical health [9,10] and mortality among their care recipients [11].

Psychosocial factors are interdependent between persons with dementia and their caregivers, such that distress from 1 member of the dyad impacts the other. Evidence suggests that psychologically based dyadic interventions may reduce caregiver burden [12-14] and improve quality of life among persons living with dementia [13]. Dyadic interventions that target the person with dementia, the caregiver, and their interpersonal relationship can have synergistic effects on individual interventions and maximally benefit both members of the dyad [15,16].

Several barriers exist to engaging caregivers and persons with dementia in psychosocial interventions. First, many psychosocial interventions require a trained provider and protected time, often around 60-90 minutes a week for 8-12 weeks. Care is costly, and not always covered by insurance, and dyads often face the price of lost wages and transportation [10]. Furthermore, psychosocial care is overly focused on the early stages of dementia, when the focus is often on education and planning [17]. Additionally, there are few interventions that target the dyad together and even fewer in the late stages [18,19].

Technology can help bypass the barriers as interventions can be delivered at home at the convenience of the dyad and without a trained clinician. A growing body of literature supports the use of technology to provide feasible and effective psychosocial interventions among older adults, specifically those living with dementia and their care partners [20]. Technological interventions are available in several modalities for this population, including mobile apps to improve independent living and cognition among persons with dementia [21] or web-based life-review therapy to decrease depression and increase well-being [22].

A complementary area of research suggests that serious gaming, games intended for purposes other than entertainment (ie, learning) [23,24], may be enjoyable and improve mental health outcomes among older adults with dementia [25,26]. Though the field of serious gaming research is dominated by younger adults, evidence suggests that older adults enjoy serious gaming and are motivated by factors including social wellness and mutual participation to engage in serious gaming [27]. Serious gaming engages users in multiple activities and experiences. Similarly, an emerging field that combines elements of serious gaming with multisensory stimulation [28] (ie, “bio-experiential” design) represents an unexplored opportunity to support persons with dementia (including those with advanced symptoms) and their care partners with important benefits for their well-being. Such interventions can provide accessible opportunities for both persons with dementia and their caregivers to reduce stress and depression and improve well-being [29-31].

Objectives

In this paper, we aim to describe the protocol for the iterative development of the toolkit for experiential well-being in dementia (TEND), a dyadic technology-based intervention for persons with dementia and their caregivers. We partnered with Studio Elsewhere, a design and technology studio to develop the intervention. TEND combines serious gaming with bio-experiential design to provide dyads with the opportunity to engage in choice-based experiences together with the goal of regulating emotions, supporting interpersonal relationships, and increasing well-being. Furthermore, here we describe a model for the codevelopment of interventions through the partnership of design and development experts and interdisciplinary scientists from an idea to a full product.

Methods

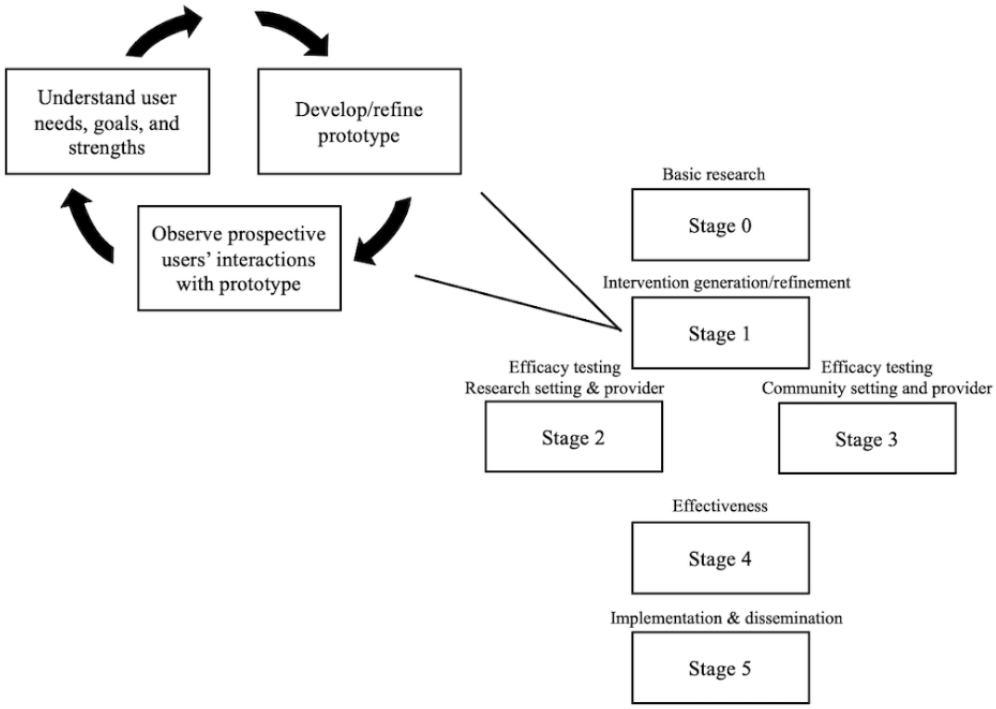
Overview

Our process follows stage 1A of the National Institutes of Health (NIH) stage model for Behavioral Intervention Development [32,33], which includes the generation of our new intervention TEND. NIH stage 1 involves stakeholder feedback, development of the intervention prototype including the conceptual model, testing through an open pilot with an exit interview, followed by refinement of the intervention and conceptual model. Consistent with guidelines for the development of

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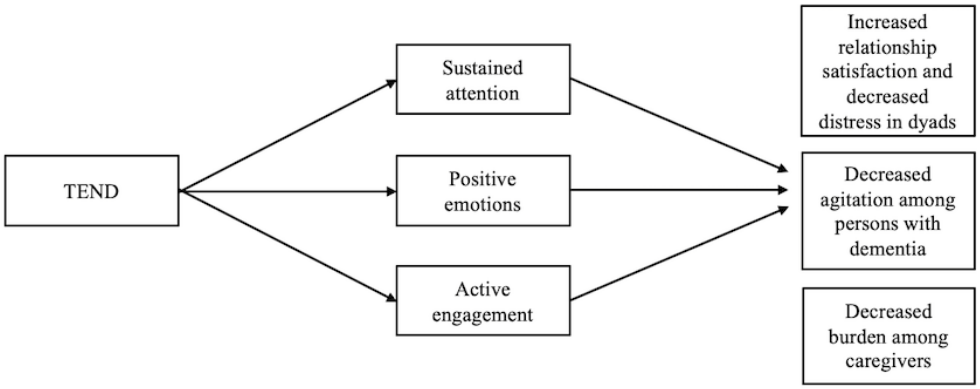
technology-enhanced interventions, we supplement the NIH model with principles of user-centered design as outlined in the process model for user-centered design [34], see Figure 1. This model was appropriate for this study as it allows for intervention development that is highly iterative and places user feedback at the forefront of design choice, which are necessities for promoting the usability of new technology among persons living with dementia [35]. Though steps may be repeated, our process consists of three key steps (and phases): (1) understanding user needs, goals, and strengths, (2) developing and refining the prototype, and (3) observing user interactions with the prototype [36]. These steps align with stage IA of the NIH stage model and position us to progress to feasibility testing (NIH stage IB), after gaining user feedback in this study.

Figure 1. National Institutes of Health stage model 1A: user-centered design.



Our initial conceptual model for TEND (Figure 2) is rooted in the theories of flow [37], positive resonance theory [38], and behavioral or unmet needs theory of dementia [39,40]. As the dyad participates together, we expect TEND to engage putative mechanisms of sustained attention, positive emotions, and active engagement, leading to improvement in outcomes of relationship satisfaction, and distress in dyads, agitation among persons living with dementia, and caregiver burden among caregivers [41].

Figure 2. TEND conceptual model. TEND: toolkit for experiential well-being in dementia.



Ethical Considerations

The Mass General Brigham Institutional Review Board approved all study procedures (2022P001401). Participants reviewed the approved fact sheet and provided verbal consent to all study procedures. In the consent process, participants were informed that all data would be deidentified and that their responses and decision to participate or not participate would not affect the care they received at Mass General Brigham. Providers received US $30 and persons with dementia and their caregivers received US $50 in gift cards respectively for their participation.

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Phase 1: Understand User Needs, Goals, and Strengths

Overview

The initial phase represented the discovery process, aimed at establishing the initial parameters and definition of the product. In this phase, we engaged in the following activities: (1) methodology and definition synthesis and (2) key stakeholder focus groups.

Methodology and Definition Synthesis

We facilitated communication within our interdisciplinary team by first establishing a common language and definitions. The team members specialize in various disciplines, including clinical psychology, geriatric and palliative medicine, and design technology. As we bridged research expertise with technological and creative design expertise, it was imperative to establish standardized terms. To address possible inconsistencies in terminology, we established a consistently evolving web-based team "dictionary" of agreed-upon definitions. The research, design, and development teams conduct in-person meetings to facilitate definition agreement. Due to the travel burden, weekly web-based meetings are conducted via Zoom (Zoom Video Communications) with the team members, each providing perspectives essential to product development. Team members participate in these weekly meetings to develop a platform by integrating perspectives from engineering, design, research, and clinical medicine together.

Key Stakeholder Focus Groups

Design

Focus groups were conducted to identify the emotional needs and technology preferences of key stakeholders, including clinicians, persons with dementia, and caregivers. The feedback from persons living with dementia, caregivers, and interdisciplinary dementia care providers was used to guide design choices.

Recruitment

We recruited 10 dementia care clinicians from dementia clinics associated with the Departments of Neurology, Psychiatry, and Internal Medicine. We recruited 11 caregivers and persons with dementia from various sources, including the dementia care collaborative program, and through direct contact with Alzheimer disease and other related dementia caregivers within an academic health system. We received institutional review board approval on August 8, 2022. Recruitment flyers were disseminated to referral sources digitally. Interested potential participants were instructed to contact the assigned research assistant. The research assistant confirmed the interest and availability of the potential participants. Inclusion criteria included the age of 18 years or older and self-identified as a dementia care provider, a caregiver for a person living with dementia, or a person living with dementia. After reading the informed consent, the research assistant assessed the persons with dementia's ability to provide verbal consent through the University of California, San Diego brief assessment of capacity to consent questionnaire [42]. If the person with dementia scored a 1 or 0 on University of California, San Diego brief assessment of capacity to consent questionnaire, suggesting they did not comprehend the purpose of the group interview nor what they would be doing, the research assistant asked them to provide assent and asked their caregiver to provide their verbal consent. Providers and caregivers provided verbal consent to participate.

Procedures

Focus groups were conducted over Zoom for approximately 60 minutes. We conducted 5 focus groups separated into groups of dementia care providers, caregivers, and dyads. Users viewed the proposed components of the platform and early content to provide feedback and identify potential uses and gaps. We selected questions for stakeholders based on themes that required high priority early on in the design process. Themes included safety considerations, barriers to use, and utility across subtypes and stages of dementia. As part of the discovery phase, focus groups allowed for generative feedback to steer the direction of the platform toward the confirmed needs and preferences of the users.

Analysis

We identified rapid data analysis (RDA) as our analysis plan to facilitate rapid intervention development while maintaining scientific rigor [43-45]. We conducted rapid qualitative analysis because our goal was not to elicit new perspectives or an in-depth understanding of dyadic relationships in dementia but to understand key intervention elements, safety issues, and facilitators and barriers to implementation of the technologically mediated biopsychosocial intervention being developed.

Phase 2: Developing and Refining the Prototype

Overview

Throughout phase II the prototype is refined through a user feedback process to increase program fidelity and user-centeredness [34,36]. Similar to the key stakeholder interviews, we are engaging in a feedback loop to effectively disseminate information from users to the research, design, and development teams. While phase I focused on understanding user needs, goals, and strengths, phase II is characterized by developing and refining the prototype.

β *Workshops*

Design

We are implementing up to 20 iterations of platform β testing workshops, a period in which a product (the platform) is released to users to test in a real-world environment to determine any issues prior to initial release [46]. The team presents platform developments to users for iterative collaborative input and feedback on feasibility, satisfaction, and usability.

Recruitment

We are recruiting dyads for platform β testing. Similar to focus group recruitment, dyads are recruited from sources including the dementia care collaborative program, and through direct contact with Alzheimer disease and other related dementia caregivers within the internal health system. Inclusion criteria are similar to that of phase I (see above) and include only persons living with dementia and their caregivers. Dyads are invited to participate in multiple workshops, if interested.

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Procedures

β testing workshops are conducted through Zoom for approximately 90 minutes and are facilitated by research staff and the design and development team. Conditions are intended to replicate a typical user scenario in which persons living with dementia and caregivers use the web-based platform together. Users are presented with a developed platform and toolkit to navigate. Research, design, and development staff are able to directly observe the usability of the platform. Furthermore, design and development staff inquire about platform use and acceptability to amend features and guide the next iteration of β testing.

Data Collection

Research staff elicit qualitative data from participants through exit interview questions gathering feedback on the platform. Additionally, staff interview participants with a series of quantitative questionnaires, including an adapted feasibility scale [47] and an adapted system usability scale [48]. Research staff records the interview to engage in behavioral observation using the Video Coding–Incorporating Observed Emotion scale [49,50] to gauge emotion, verbal engagement, visual engagement, collective engagement, and agitation among persons with dementia.

Data Analysis

We will conduct RDA. The analysis plan is similar to that of phase I (see above). We will review the recorded interviews to examine changes in emotion, engagement, and agitation among persons with dementia and the correlating platform features.

Results

As of August 2023, we have completed phase I. Focus group qualitative data has not yet been formally analyzed outside of RDA and will be reported in future publications. Key takeaways from the focus groups included prioritizing individualization, avoiding potentially confusing stimuli, and focusing on the dyadic relationship. Findings from the focus groups informed the β testing workshops. As of September 2023, we have completed 4 iterations of platform β testing workshops.

Discussion

Principal Findings

Guided by the process model for user-centered design [34] and the NIH stage model [32], above, we have delineated the initial process of user-centered design for a partnership between design and development experts and interdisciplinary scientists. We have engaged in codevelopment through methodology and definition synthesis, focus groups, and β workshops (currently ongoing). Combining serious gaming with bio-experiential design to develop the initial TEND platform, we aim to regulate emotions, support interpersonal relationships, and increase well-being. As bio-experiential technology emerges as a promising field within health care, we have the opportunity to mitigate traditional barriers to effective and equitable dementia care.

Within the development of this bio-experiential design, we outline an effective strategy for academic and design and development team partnership. Multidisciplinary team partnerships are especially beneficial in developing technologies for dementia, as scientific findings and procedures may support adaptations and user experiences [51]. For example, by partnering with researchers, developers are able to address cognitive and functional deficits through adaptations to technology including customization, errorless learning [52], and simple narratives [53]. We adapted to the challenges of codevelopment between distinct teams by establishing a common language and definitions and weekly meetings. The web-based, immersive platform and toolkit developed by Studio Elsewhere is guided by a concept generation and feedback loop incorporating key stakeholders throughout phases I and II.

Through aims 1 and 2 of our partnership, we expect to develop the experimental platform and refine and test the platform. We anticipate these efforts will result in a free interactive, immersive bio-experiential web platform and accompanying toolkit, after subsequent testing for efficacy in a large group of dyads. We anticipate that the resulting technologies will be easily implemented in the home to engage persons with dementia and caregivers in meaningful and relationship-enhancing activities. Consistent with existing literature on technology adaptations for older adults and persons living with disabilities, this study demonstrates various user design considerations, including cognitive, communication, sensory, and physical deficits common with dementia and advancing age [54,55]. In particular, our team is tasked with designing technology that is engaging for both persons with dementia and caregivers, who likely present with varying cognitive abilities and technological literacy. Further, the technology must be appealing and usable across dyads. Our approach outlined here will result in a bio-experiential technology that will be ready for more rigorous testing in the next phase of the work. Following these phases, we aim to conclude with the final stages of user-centered design, observing prospective users' interactions with the prototype [34]. In future studies, we will optimize the platform through engaging in pilot testing and efficacy testing with the goal of wide implementation.

As the field of technological interventions and serious gaming expands and the need for cost-effective and dyadic interventions increases, there is an urgency for technology-enhanced dyadic and psychosocial intervention in dementia informed by behavioral science. Not only do persons with dementia and caregivers find psychological benefit from technological interventions, but they are often highly enjoyable. Here, we outline a highly collaborative intervention development model to address traditional barriers and promote psychosocial wellness among this population through a bio-experiential intervention.

Limitations

We anticipate several limitations with this research. Participants must have access to technology equipped with audio and video capture devices to participate in focus groups and workshops, which may exclude low socioeconomic status participants. Additionally, while we engage in β testing workshops over Zoom to replicate real-life environments, the presence of

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research personnel and design and development team members may unintentionally influence participant reporting on feasibility and usability scales. Furthermore, in research with persons with advanced dementia, the reliability of data is a concern for participants and proxies.

Conclusions

In this protocol, we outline the development of bio-experiential technology for persons with dementia and their caregivers, as well as the partnership between design and development experts and interdisciplinary scientists. This program of research has the potential to address clinical challenges (eg, depression and agitation) among persons with moderate-severe dementia, a population with few evidence-based treatments, and improve outcomes among dyads. Further, the ability to deliver a technology-based intervention in the home has implications for increasing access and translatability. The novelty of a cognitively mismatched dyadic intervention developed based on user-centered design principles will provide a methodological and conceptual framework for future investigators in this field.

Acknowledgments

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Data Availability

The data sets generated and analyzed during this study are available from the corresponding author on reasonable request once the trial is complete.

Conflicts of Interest

MP is the founder and CEO of Studio Elsewhere and receives financial compensation for her role. EA is the user research and community design lead at Studio Elsewhere and receives financial compensation for his role. All other authors declare no conflicts of interest.

Multimedia Appendix 1
Peer-reviewer report from Robert Wood Johnson Foundation.
[PDF File (Adobe PDF File), 137 KB - resprot_v12i1e52799_app1.pdf]

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Abbreviations

NIH: National Institute of Health
RDA: rapid data analysis
TEND: toolkit for experiential well-being in dementia

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Protocol

Personalization of Mobile Apps for Health Behavior Change: Protocol for a Cross-sectional Study

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Abstract

Background: Mobile health apps have the potential to motivate people to adopt healthier behavior, but many fail to maintain this behavior over time. However, it has been suggested that long-term adherence can be improved by personalizing the proposed interventions. Based on the literature, we created a conceptual framework for selecting appropriate functionalities according to the user's profile.

Objective: This cross-sectional study aims to investigate if the relationships linking functionalities and profiles proposed in our conceptual framework are confirmed by user preferences.

Methods: A web-based questionnaire comprising several sections was developed to determine the mobile app functionalities most likely to promote healthier behavior. First, participants completed questionnaires to define the user profile (Big Five Inventory-10, Hexad Scale, and perception of the social norm using dimensions of the Theory of Planned Behavior). Second, participants were asked to select the 5 functionalities they considered to be the most relevant to motivate healthier behavior and to evaluate them on a score ranging from 0 to 100. We will perform logistic regressions with the selected functionalities as dependent variables and with the 3 profile scales as predictors to allow us to understand the effect of the participants' scores on each of the 3 profile scales on the 5 selected functionalities. In addition, we will perform logistic ordinal regressions with the motivation score of the functionalities chosen as dependent variables and with scores of the 3 profile scales as predictors to determine whether the scores on the different profile scales predict the functionality score.

Results: Data collection was conducted between July and December 2021. Analysis of responses began in January 2022, with the publication of results expected by the end of 2022.

Conclusions: This study will allow us to validate our conceptual model by defining the preferred functionalities according to user profiles.

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KEYWORDS

mobile health; mHealth; personalization; mobile app; behavior change theory; gamification; functionalities

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Introduction

Background

Healthy lifestyle behaviors have increased the life expectancy of those who adopt them and help individuals to live not only longer but better [1]. More specifically, adopting a healthy diet, maintaining a healthy weight, quitting smoking, drinking alcohol in moderation, and regular exercise are 5 behaviors associated with lower mortality. An increasing number of health apps aiming to help people adopt better health behaviors are reaching the market annually, with over 35,000 health apps available in 2018 [2]. Smartphone apps offer new opportunities to adopt health-related behaviors by providing immediate access to information about one's health, reminders to take medication, or help track one's progress [3].

Several scales exist to measure the quality of these health-related mobile apps, such as the Mobile App Rating Scale [4] and the App Behavior Change Scale [5]. A common feature of these scales is to consider a mobile app's personalization as a quality factor. Indeed, personalization is an important aspect to consider when creating an app that enables behavior change. For example, it has been shown that messages tailored to the user tend to be read more, recalled more, attract more attention, be better remembered, be a topic of discussion with others, and be perceived as personally relevant compared to untailored messages [6].

Development of a Mobile App Model for Behavior Change

Based on a previous literature review, we identified the personality traits more likely to adopt certain app functionalities [7]. These findings led to the development of a model indicating the type of features preferred according to a user profile. When designing a mobile app aiming at behavior change for health, designers can refer to our model as a guideline to know what functionalities they should privilege for their apps, given the profile of the intended users. For example, if a person is extroverted according to the Big Five, it will be relevant to privilege functionalities allowing comparison and cooperation between users [8].

Our model contains 17 functionalities presented in detail in Multimedia Appendix 1. For the user profile, we relied on the most common classification dimensions found in the literature, as follows: personality profiles [8-16], game preference [11,17,18], and perception of social norm [19] (Table 1). Gender and age are also important, and a recent review showed a difference in the type of functionality preferred according to gender, although no study in the review included individuals older than 31 years [17].

One of the most popular scales to measure personality is the Big Five, which defines the user's personality according to the following 5 dimensions: openness, agreeableness, conscientiousness, neuroticism, and extraversion. Game preference was measured with the Hexad Scale model [18], which defines the user's gamer profile according to the following 6 dimensions: disruptor, achievers, free spirit, player, socializer, and philanthropist. For example, participants with the profile "player" are motivated by extrinsic rewards and will do anything to earn a reward within a system. This type of profile is interesting to consider for apps that use gamification, which is also a concept widely used nowadays to incite behavior change. We can define gamification as "the use of game design elements in non-game contexts" [21]. Indeed, gamification positively affects motivation, engagement, and enjoyment [22]. Finally, the perception of social norm is the "individual's perception that other individuals important to the respondent believe that the respondent should perform the behavior of interest" [23]. This perception can help or hinder the performance of the behavior, depending on how the user's entourage perceives it. Therefore, it is important to consider this factor, and, depending on this perception, different functionalities can be included.

Table 1. Profiles considered in our conceptual framework.

Profiles	Scale
Personality	Big Five
Game's preferences	Hexad Scale [18]
Perception of social norms	Theory of Planned Behavior [20] Action

Objectives

This study aims to validate our conceptual framework by investigating if the proposed relationships between the functionalities and profiles are reflected in the preferences of our target population in an experimental setting.

Methods

Ethics Approval

The University Ethics Commission has approved this study for ethical research at the University of Geneva (CUREG_2021-04-38).

Study Design

We performed a cross-sectional study to address our aims. Participants responded to a web-based questionnaire to define their profile. Then, they were presented with a series of prototyped functionalities to be ranked according to their preferences to analyze if they corresponded to those defined in our conceptual framework. We chose to contextualize the functionalities of adopting healthy diet and fitness apps as these issues allow to target a generic public. Indeed, the desire to stay fit is a behavior that most adults want to adopt. To ensure data are completely anonymous, participants' IP addresses were not collected. We tested the questionnaire for usability and technical issues with 5 participants. This web-based survey is in

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accordance with the Checklist for Reporting Results of Internet E-Surveys [24].

Outcomes

The primary outcome is the preferred functionalities given the user profile.

Secondary outcomes are the feature preferences related to past or current use of mobile health (mHealth) apps, and the preference of functionalities according to the participant's state of motivation to change behavior.

Study Population and Sample Size

The target population for this study included all individuals older than 18 years who understood French. We chose to conduct the questionnaire in French as this population was not necessarily fluent in English and comprised mainly native French speakers. An English language questionnaire would have introduced an element of bias as it might not have been correctly understood. Recruitment was conducted by posting messages on social networks (Facebook and Twitter) targeted at students at the University of Geneva, a young student population. The message indicated that we were seeking to recruit participants for a web-based study lasting 12 minutes as part of a research study conducted by the University of Geneva, with a focus on identifying user preferences based on their profile for a mobile app aimed at helping people get in shape. We also stated that the collected data remain completely anonymous.

For the calculation of the sample size, based on the hypothesis that altruistic people according to the Big Five prefer social networks [11,17], we used the multiple regression power calculation on R (R foundation for Statistical Computing), with the following measures: u=3; f^2=0.07; P=.05; power=0.9; and variance=202.403. To estimate variance, we relied on a previous study [25] investigating the preference of users classified according to the Big Five on posters. More specifically, we looked at the variance of altruistic participants (n=46) according to the Big Five on the average ratings of a poster representing a social network promoting blood donation (score from 0 to 100). Thus, we obtained a sample size of 206.

Procedure

Participants were asked to complete the web-based questionnaire developed using Qualtrics software (Qualtrics; Multimedia Appendix 2). First, they completed the consent form describing the purpose of the study and the procedure and informing them of their right to withdraw from the study. They were asked to confirm that they have read and understood the consent form and agree to have their responses used in our research and scientific publications. They can then access the rest of the questionnaire if they accepted these clauses. If not, they were informed that without their consent, we cannot collect their data and must terminate the survey. Next, participants were asked to answer demographic questions. In the case of a participant younger than 18 years, we explain that only those aged >18 years can participate and therefore we cannot continue with the questionnaire. Eligible participants continued to answer the questionnaire online where they had to (1) respond to scales to measure their profile, and then (2) look at the 17 features, select 5, and indicate on a score from 0 to 100 how much these features would motivate them to get back in shape.

Measures and Measurement

Demographic Questions

Participants were asked to indicate their gender, age, occupation, and level of education.

Questions About Their Use of mHealth Apps

Participants were asked if they use mobile apps aiming at behavior change (such as to help them eat healthier or exercise) to find out if they were already familiar with mHealth apps and whether they already like certain functionalities. If so, we asked them to select which functionalities they used most often and which they never used. These questions allowed us to observe whether participants already familiar with mHealth prefer certain features, as well as whether they prefer the same features among the 17 proposed.

Profile Assessment

Big Five

To assess participants' personalities, we relied on the Big Five Inventory-10 scale in French, translated and validated by Courtois [26]. With Cronbach alpha coefficients ranging from .37 to .83, the internal scale reliability of the Big Five Inventory-10 is low. This is because Cronbach alpha is not designed to evaluate scales with a low number of items [26]. This scale is composed of 10 items, 2 items per Big Five dimension. Participants are asked to indicate on a 5-point Likert scale whether they strongly approve or strongly disapprove of statements about themselves. For example, “I see myself as someone who is reserved” or “I see myself as someone who is easily anxious”. The score for each dimension is calculated by adding the scores for the two statements concerning the dimension after reversing the items.

This scale was chosen because it has a factorial structure identical to that of the full version of the Big Five Inventory scale in French [26]. Therefore, it has the advantage of effectively measuring personality with a small number of items. As our protocol contains several scales, we preferred to choose the shortest valid versions to avoid participant fatigue with an excessively long questionnaire.

Gamer Profile

To identify participants' gamer profiles, we chose the Hexad Scale, created and validated by Tondello [18]. The internal scale reliability is good with Cronbach alpha coefficient for each dimension ranging from .70 to .89 [18]. This scale consists of 24 items, 4 per dimension. Users must rate how well each article describes them on a 7-point Likert scale. For example, there are items such as “I like competitions, where a prize can be won” or “Interacting with others is important to me.” Items are presented in a randomized manner, and the score is calculated by adding the scores for each dimension.

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Perception of Social Norm

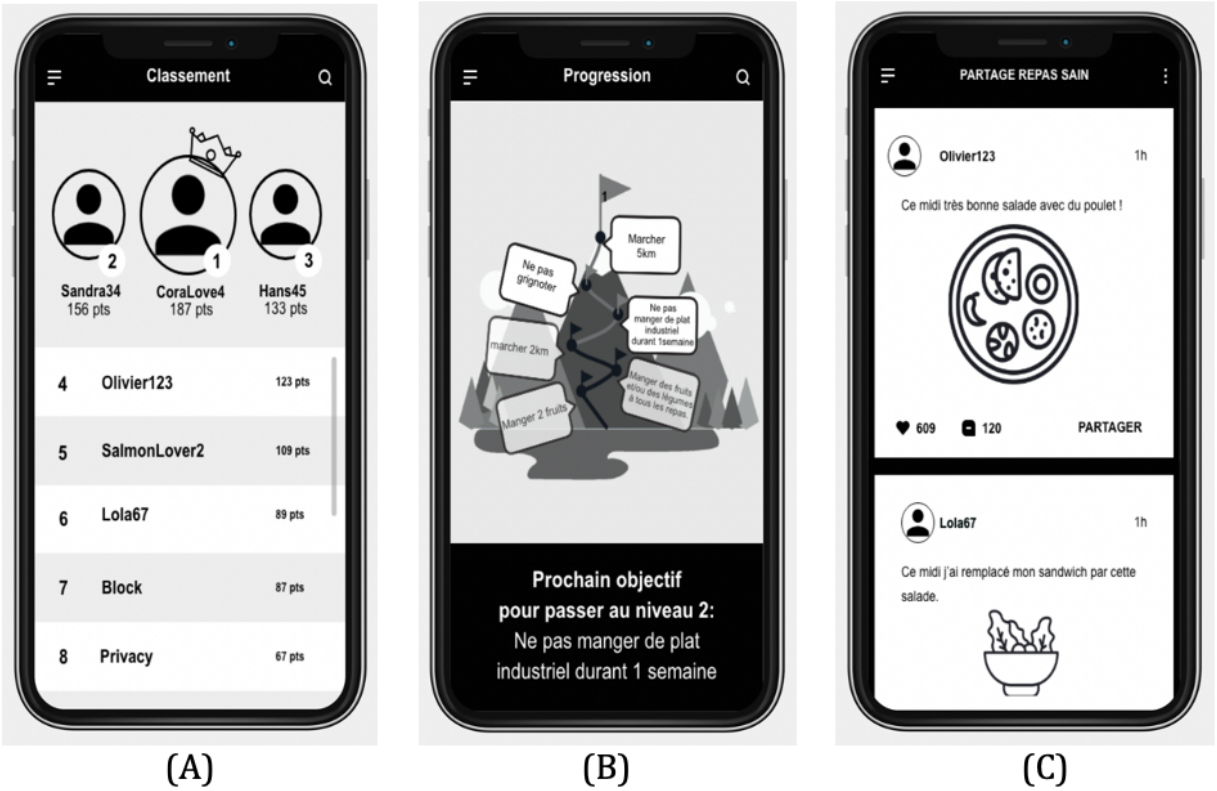
For the perception of social norm, we chose two items concerning this dimension of the Theory of Planned Behavior questionnaire of Ajzen [20]. We adapted the items to the context of our mobile app, which is to eat healthier and do more physical activity. Thus, the two items are as follows: "Most people who are important to me approve of the fact that I eat healthier and do more physical activity" and "Most people like me eat healthily and do physical activity." Participants were asked to respond to these statements on a 7-point scale ranging from "agree" to "disagree." The calculation was done by adding up the scores, with a high score indicating a heightened social norm perception.

Choice of Functionalities

Presentation of the Functionalities

From the literature, we identified 17 functionalities commonly proposed in behavior change apps. We then created a prototype for each of these functionalities. All functionalities and their definition are presented in Multimedia Appendix 1. We chose a visual design as neutral as possible for the prototypes (ie, in black and white with no images, only icons). This aims to minimize the bias due to design preference (ie, Figure 1). The 17 prototype screenshots were presented randomly to the participants to avoid a primacy or recency effect. During the study, participants discovered every functionality, one by one, by its representation in an image and accompanied by a short description. Then, they chose the 5 functionalities they considered to be the most motivating to stay fit.

Figure 1. Example of screenshots of the prototype app, including the (A) functionality competition, (B) functionality level and progression, and (C) functionality social network.



Explanation of Choice

For each functionality selected, participants were asked to indicate how much that functionality would motivate them to adopt healthier behavior on a scale of 0 to 100. Then, they were asked why they chose these functionalities. Excluded functionalities will default to a score of 0.

Analysis

Overview

We will exclude incomplete questionnaires and analyze only questionnaires that have been completed entirely.

Demographic characteristics of all participants will be presented using descriptive statistics (mean, standard deviations, or frequencies and range) in a table. A table will also provide responses about their use of mobile apps for health.

Quantitative Data

Primary Outcome

We will perform logistic regression with the functionalities as dependent variables and with scores of the 3 profile scales as predictors. This analysis will allow us to understand the effect of the participants' scores on each of the 3 scales (Big Five Inventory-10 scale in French, Hexad Scale, and perception of the social norm) on the 5 selected functionalities. By performing

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a logistic regression for each feature, it will be possible to determine whether the scores on the different scales predict the selection of the functionality.

In addition, we will perform a logistic ordinal regression with the motivation score of the functionalities chosen as dependent variables and with scores of the 3 profile scales as predictors. By performing this regression for each functionality motivation score, it will be possible to determine whether the scores on the different scales predict the functionality score.

Secondary Outcome

To test whether there is a difference in functionality selection by age or gender, we will run logistic regressions with the choice of the functionality as the dependent variable and age or gender as the independent variables. In addition, we will perform an ordinal regression with the motivation score of the functionalities as the dependent variable and age or gender as the independent variable. There will be one regression per feature.

To test whether participants indicated that they preferred functionalities that are the same as the ones already used in their current mHealth app, we will run simple regressions with the feature they already use as the independent variable and whether this feature was chosen as the dependent variable. There will be one regression per feature.

We will use the Bonferroni correction for all our regressions to avoid a type 1 error.

Qualitative Data

Qualitative analysis of the free text for the question regarding the explanation of the participants' choice was performed, and common themes extracted. Response categories will be defined when reading the responses.

Results

Recruitment and testing were conducted during July 2021. The deadline for the completion of the web-based questionnaire by participants was end of December 2021. We began analyzing the responses in January 2022, and the publication of results is expected at the end of 2022.

Discussion

Principal Findings

This study will define the preferences of functionalities of users with a specific profile (eg, what kind of functionalities are preferred by a user according to their personality). This protocol is important as its sample will enable to validate a model built on several previous studies and reviews. In turn, this will allow developers to build mobile apps that will be more efficient as adapted to each user. Thus, with this research, we will be able to better refine our conceptual framework, which will allow the mobile app designer to select features tailored to their users according to their profile and thus increase their involvement in the mHealth app.

The main interest of this research is that it gathers all the user profiles identified in the literature and all the functionalities generally implemented in mHealth. Indeed, we find studies allowing us to link personality and gamification elements [8,9,14], personality, gamer profile, and gamification elements [11], personality and sensitivity to persuasion strategies [10,27], or personality and need for cognition [28]. Moreover, these studies are not necessarily specific to the field of mobile apps for behavior change. Some studies are more focused on preferences related to video games [9,14,29] and others on the type of messages and feedback [19,30]. Therefore, our research allows to combine what has been done previously in different studies and to corroborate their findings for mHealth apps regarding user preferences according to their specific profile.

Limitations

Our study has some limitations. We designed it to be as neutral as possible to limit preferences linked to the design of one of the prototyped functionalities. However, it is still possible that participants may prefer a certain functionality because they found it more visually attractive. Our results are also possibly not generalizable to the whole population. Indeed, since recruitment was conducted at the university and on social networks, it is expected that most participants were students aged 18-25 years. Finally, as the questionnaire was in French language and only individuals living in the canton of Geneva and the surrounding area were included, it can only be generalized to this population (ie, French-speaking people of Switzerland and France).

Conclusion

It is important to help people adopt better health behaviors. Mobile apps are an interesting channel to support this effort because they integrate functionalities such as goal setting or self-monitoring that have been proven to foster behavior change. However, app efficiency can be improved by responding to user preferences according to their specific profiles. Our study will provide an additional evidence base to propose an accurate personalization conceptual framework for the development of future mHealth apps.

Acknowledgments

We thank all participants for their valuable contribution.

Data Availability

The data sets generated during this study are available from the corresponding author upon reasonable request.

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Authors' Contributions

LG conceived the study with the involvement and advice of FE and GF. MP is involved in the statistical analysis. All authors participated in the writing and reading of the manuscript and approved the final version.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Presentation of the functionalities selected for our conceptual framework with their definitions and description of the screenshot.
[PDF File (Adobe PDF File), 637 KB - resprot_v12i1e38603_app1.pdf]

Multimedia Appendix 2
Print version of the web-based questionnaire.
[PDF File (Adobe PDF File), 1482 KB - resprot_v12i1e38603_app2.pdf]

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Abbreviations

mHealth: mobile health

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Protocol

Virtual Reality Therapy for People With Epilepsy and Related Anxiety: Protocol for a 3-Phase Pilot Clinical Trial

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Abstract

Background: Anxiety is one of the most common psychiatric comorbidities in people with epilepsy and often involves fears specifically related to the condition, such as anxiety related to the fear of having another seizure. These epilepsy- or seizure-related fears have been reported as being more disabling than the seizures themselves and significantly impact quality of life. Although research has suggested that exposure therapy (ET) is helpful in decreasing anxiety in people with epilepsy, no research to our knowledge has been conducted on ET in people with epilepsy using virtual reality (VR). The use of novel technologies such as an immersive VR head-mounted display for ET in this population offers several benefits. Indeed, using VR can increase accessibility for people with epilepsy with transportation barriers (eg, those who live outside urban centers or who have a suspended driver's license owing to their condition), among other advantages. In the present research protocol, we describe the design of an innovative VR-ET program administered in the home that focuses on decreasing anxiety in people with epilepsy, specifically anxiety related to their epilepsy or seizures.

Objective: Our primary objective is to examine the feasibility of the study protocol and proposed treatment as well as identify suggestions for improvement when designing subsequent larger clinical trials. Our secondary objective is to evaluate whether VR-ET is effective in decreasing anxiety in a pilot study. We hypothesize that levels of anxiety in people with epilepsy will decrease from using VR-ET.

Methods: This mixed methods study comprises 3 phases. Phase 1 involves engaging with those with lived experience through a web-based questionnaire to validate assumptions about anxiety in people with epilepsy. Phase 2 involves filming videos using a 360° camera for the VR-ET intervention (likely consisting of 3 sets of scenes, each with 3 intensity levels) based on the epilepsy- and seizure-related fears most commonly reported in the phase 1 questionnaire. Finally, phase 3 involves evaluating the at-home VR-ET intervention and study methods using a series of validated scales, as well as semistructured interviews.

Results: This pilot study was funded in November 2021. Data collection for phase 1 was completed as of August 7, 2022, and had a final sample of 18 participants.

Conclusions: Our findings will add to the limited body of knowledge on anxiety in people with epilepsy and the use of VR in this population. We anticipate that the insights gained from this study will lay the foundation for a novel and accessible VR intervention for this underrecognized and undertreated comorbidity in people with epilepsy.

Trial Registration: ClinicalTrials.gov NCT05296057; https://clinicaltrials.gov/ct2/show/NCT05296057

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International Registered Report Identifier (IRRID): DERR1-10.2196/41523

(JMIR Res Protoc 2023;12:e41523) doi:10.2196/41523

KEYWORDS

epilepsy; anxiety; virtual reality; exposure therapy; eHealth; digital health; virtual reality exposure therapy; cognitive behavioral therapy; CBT; nonpharmacological intervention; biomedical technology

Introduction

Background

Anxiety is the most common psychiatric comorbidity in people with epilepsy, with approximately 28% of the population suffering from at least one anxiety disorder, although different studies have reported varying prevalence [1]. In addition to decreasing quality of life and self-efficacy, anxiety may limit independence in people with epilepsy, who are already facing restrictions or limitations owing to other consequences of their neurological condition, such as suspension of their driver's licenses [2]. People with epilepsy with comorbid anxiety also report more negative side effects from their antiseizure medications as well as poorer memory compared with those that do not have anxiety [2]. Moreover, anxiety may have a negative impact on seizure management; for example, individuals with idiopathic generalized epilepsy in particular have reported that sleep deprivation and stress are seizure triggers [3]. Yet, anxiety in people with epilepsy has received little research attention and is commonly not recognized nor treated [1,2].

Hingray et al [1] proposed 4 main types of anxiety disorders that are associated with epilepsy in adults: epileptic social phobia, seizure phobia, epileptic panic disorder, and anticipatory anxiety of epileptic seizures. The anxiety faced in people with epilepsy tends to stem from the uncertainty that is associated with the nature of the disorder. Moreover, people with epilepsy may fear places where they have previously experienced a seizure, as well as situations that could be physically dangerous should they have a seizure [1]. This anxiety can result in avoidance of situations that are crucial for independent daily living (such as taking public transit or a shower) [1]. In some cases, this anxiety may lead to obsessive behaviors and agoraphobia [1].

The underlying theoretical model of clinical anxiety implicates a series of cognitive and behavioral processes such as dysfunctional beliefs, classical conditioning, and operant conditioning [4]. In general, people with anxiety are characterized by two types of dysfunctional cognitions: (1) exaggerated estimates of the likelihood of negative consequences related to the feared condition and (2) exaggerated estimates of the severity of harm [5]. Over time, the fear becomes reinforced and may lead to conditioned behaviors in response to such stimuli [5]. To manage these manifestations of anxiety, individuals frequently adopt safety behaviors that reduce their feelings of fear in the short-term, such as avoiding the situation that leads to their anxiety [5]. Because of the short-term relief that they feel from these safety behaviors, individuals with anxiety often continue displaying these behaviors, which ultimately works to maintain or increase the anxiety associated with their feared situations [5]. These safety behaviors may impede everyday functioning and lead to a decreased quality of life as well as fewer opportunities for positive experiences, further impacting mood regulation [5-7]. For example, a safety behavior may include only leaving the house with trusted individuals [1,8]. However, it should be noted that in some cases, these behaviors may be warranted if they are required for seizure safety as indicated by a neurologist (ie, not considered safety behaviors fueled by anxiety) [1].

Exposure therapy (ET) is an evidence-based technique [9,10] that is helpful in facilitating the management of dysfunctional anxiety associated with a specific or generalized stimulus and associated safety behaviors [5]. Graded ET involves repeatedly exposing people to realistic situations that trigger their anxiety, often in a hierarchical manner [5]. ET targets feared stimuli that can be clustered in different categories. The categories may include situations that involve animals or specific human populations (such as spiders, people with HIV, and clowns), objects or specific spaces (eg, toilets, knives, and certain numbers), specific situations (such as driving, darkness, and feeling uncertain), thoughts and beliefs (eg, unwanted sexual thoughts, memories of traumatic events, and premonitions of untimely accidents), or interoceptive and physiological stimuli (eg, racing heart, feeling out of breath, and a skin blemish) [5].

Ultimately, ET aims to help individuals understand that they are capable of being in the situations that provoke their anxiety without needing to implement their safety-seeking behaviors that perpetuate avoidance behaviors [5]. By training individuals to overcome the thought patterns that cause their debilitating anxiety, ET may also help to interrupt the cycle of anxiety by disconfirming the individual's misperceptions of their threats [5].

Virtual reality (VR) is a computer-simulated environment that allows users to feel as though they are in a different physical place, and it has been used as a tool to deliver ET for a variety of anxiety disorders. For example, VR-ET has previously been used to treat posttraumatic stress disorder, social anxiety disorder, and panic disorder [11]. VR has also been increasingly used as a nonpharmacological therapy for a variety of conditions, such as for people with dementia [12], including veterans with dementia [13]. Recent feasibility studies have also suggested that VR may be used to decrease anxiety in patients in the intensive care unit [14]. However, people with epilepsy have commonly been excluded from VR studies owing to the concern that using it may trigger seizures in people with photosensitive epilepsy. Although limited research is available on the use of VR in people with epilepsy, hesitations regarding the use of VR in this population have not been substantiated, and clinicians and researchers are increasingly considering VR for use in this population [15-17].

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Some studies have highlighted that VR can complement imaginal and in vivo exposures [18,19], which are often otherwise difficult to implement. For instance, limitations of imaginal exposures include that individuals may try to avoid thinking about the scene that makes them anxious or they may struggle to imagine the scene accurately [5]. As VR elicits realistic sensory-motor experiences, using VR to deliver ET may be more successful than imaginal exposures for individuals who have difficulty mentally conjuring up distressing scenes or for individuals who try to avoid thinking about them [20,21]. A further limitation of in vivo exposure is treatment adherence; users commonly drop out before completing the recommended number of sessions. As VR-ET does not place individuals in the actual physical environment, participants have the opportunity to learn how to cope with the feared situation in a less threatening environment [22]. Thus, VR-ET has the potential to increase individuals' willingness to do in vivo exposures and decrease avoidance in the real physical environment because their preparedness makes the natural stimuli appear less overwhelming [23].

Research has suggested that including ET as a part of treatment for anxiety may also be helpful for people with epilepsy [24,25]. To our knowledge, no research has been conducted to date on ET in people with epilepsy using VR. In this population specifically, using an immersive VR head-mounted display (HMD) for ET has several advantages over traditional therapies. For example, research not specific to epilepsy has illustrated that VR-ET is especially useful when it is impractical to do exposures in person, such as during the COVID-19 pandemic [26]. Even outside of the pandemic, using VR to deliver this customizable therapy limits the need for travel, thereby removing a barrier for people with epilepsy because driver's licenses are typically suspended for 6 months to 1 year after a confirmed seizure. Moreover, using VR for ET offers the potential for significant time and cost savings compared with traditional ETs, in addition to increasing equitable access to mental health resources for those outside of urban centers [27].

Study Overview and Objectives

We are designing and evaluating a VR-ET program specifically for people with epilepsy and anxiety in a pilot clinical trial (Trial Registration: ClinicalTrials.gov NCT05296057) that will be divided into 3 phases. Phase 1 will involve engaging with those with lived experiences through a web-based questionnaire. The aim of phase 1 will be to validate assumptions about anxiety specifically related to epilepsy or seizures. Videos of scenes that are most commonly reported as generating anxiety in people with epilepsy will then be filmed using a 360° camera in phase 2. In phase 3, these VR exposure scenarios will be piloted by people with epilepsy in a clinical trial.

Table 1 represents a visual overview of the study methodology. This table was designed using the template provided by the Standard Protocol Items: Recommendations for Interventional Trials. It outlines the assessments at various time points: T0 (baseline), T1.1 (first day of the VR-ET intervention), T1.12 (the twelfth and last day of the VR-ET intervention, depending on each participants' progress that may be extended to T1.13 or T1.14), and T2 phases (1 week after the last exposure session).

The primary objective of this pilot clinical trial is to examine the feasibility of the study protocol, determine effect sizes, and identify suggestions for improvement when designing a subsequent larger clinical trial. The secondary objective is to evaluate whether VR-ET reduces epilepsy-related anxiety in people with epilepsy.

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Table 1. Overview of phases 1 to 3, including enrolment, virtual reality exposure therapy (VR-ET) intervention design and delivery, data collection, and outcome measures.

	Phase 1	Phase 2	Phase 3		
			T0[a]	T1.1[b]-T1.12[c]	T2[d]
Phase 1 informed consent	✓				
Phase 3 informed consent			✓		
Eligibility screen			✓		
Design and film VR[e] scenes		✓			
VR-ET intervention				✓	
Assessments					
Interview			✓		✓
Phase 1 questionnaire	✓				
Background questionnaire			✓		
VR Induced Symptoms and Effects			✓		
Diagnostic protocol proposed by Hingray et al [1]			✓		
Epilepsy Anxiety Survey Instrument			✓		✓
Perceived Stress Scale			✓		✓
Subjective Units of Distress Scale				✓	
Fast Motion Sickness Scale				✓	
Igroup Presence Questionnaire					✓
System Usability Scale					✓

[a]T0: baseline.

[b]T1.1: first day of the VR-ET intervention.

[c]T1.12: The twelfth and last scheduled day of the VR-ET intervention. Depending on each participants' progress, the intervention may be extended to T1.13 or T1.14.

[d]T2: 1 week after the final exposure session.

[e]VR: virtual reality.

Methods

Ethics Approval

The study was approved by ClinicalTrials.gov (ID: NCT05296057) on March 25, 2022, and was fully approved by the York University Human Participants Review Committee on May 31, 2022 (certificate number: 2022-105). Amendments to Phases 2 and 3 were approved by the York University Human Participants Review Committee on September 15, 2022.

Data Collection and Storage

Any digital data, such as responses to web-based questionnaires, will be uploaded and saved to a secure server. Any hard copy documents will be stored in a locked cabinet. Both digital data and hard copy documents will be retained for 10 years after the end of the study and then securely destroyed.

Phase 1

Phase 1 Overview

Very little research currently exists on the specific epilepsy-related fears that people with epilepsy experience. As such, the first phase of this study will aim to validate assumptions about the most common epilepsy-related fears in this population so that the videos recorded in phase 2 are reflective of fears that are relevant for exposure in phase 3. To gather these data, phase 1 consists of a web-based survey delivered over the Qualtrics platform to 2 groups of participants: (1) people with epilepsy and (2) people that are affected by epilepsy but do not have epilepsy themselves (eg, through a family member, as a personal caregiver, as a health professional, or if they work with people who have epilepsy).

Phase 1 Recruitment

The investigators are using a diverse recruitment strategy. First, we are leveraging our connection with relevant community associations, namely Epilepsy Toronto. Epilepsy Toronto is an association that works to support people with epilepsy and their loved ones. Epilepsy Toronto has agreed to send an advertisement on their email listserv as well as post the study advertisement on their social media accounts. Second, a snowballing strategy will be used wherein participants will be prompted at the end of the questionnaire to share the link with others in their network. Phase 1 had a target sample size of 15 participants, including individuals with epilepsy and individuals affected by epilepsy.

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Phase 1 Eligibility

Individuals aged 18 years and older who have epilepsy or are affected by epilepsy (such as through a family member that has epilepsy) may participate in this study. Phase 1 does not have any exclusion criteria.

Phase 1 Consent

The phase 1 informed consent form appears as the first page of the Qualtrics questionnaire and requires a digital signature. The Qualtrics questionnaire is configured such that participants cannot progress to the questionnaire without first providing explicit consent.

Phase 1 Protocol

Both groups of participants are asked to list up to 5 scenes (ie, locations, situations, or environments) that generate epilepsy-related anxiety in people with epilepsy, based on their personal experience. Participants are then asked to describe the scene that causes the greatest amount of anxiety in more detail. If the participant chooses, they may describe other scenes that they listed in more detail as well.

The questions included in the phase 1 questionnaire were selected and phrased so that they guide the filming of the 360° videos in phase 2 to resemble the anxiety provoking scenes as realistically as possible (Textbox 1). Analysis of phase 1 responses may identify ways in which the phrasing of questions may be improved in a later study to increase the realism of the exposures and thus the efficacy of the intervention.

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Textbox 1. Overview of the questions asked in the phase 1 questionnaire (version completed by individuals with epilepsy). Individuals affected by people with epilepsy completed a version with alternate wording appropriate to their perspective.

1. Demographics:
   - A. Year of birth
   - B. Sex at birth
   - C. Describe the type of epilepsy or seizures you have and the symptoms that you experience during a seizure. *The intention of asking this question is to determine if the symptoms that the person with epilepsy experiences during a seizure (such as losing consciousness, muscle control, etc) influences their anxiety.*
2. Scenes:
   - A. List up to 5 scenes (such as situations, locations, or environments) where you feel anxiety related to your epilepsy or seizures. Next to the open-ended spaces to list each scene, participants are asked to rank their avoidance behavior from the following options:
     - Avoid completely
     - Often avoid
     - Sometimes avoid
     - Do not avoid (but still feel anxious)
   - B. To ensure that the 360° videos, which will be recorded in phase 2, are realistic and resemble the scenes from the person with epilepsy's point of view as closely as possible, participants are asked to provide detail about the scene that causes the greatest amount of anxiety, as if they were designing a scene for a movie from their perspective. Participants are prompted to do so by asking:
     - What do you see, hear, and feel?
     - What are you and others doing in this scene?
     - What in particular about this scene makes you anxious?
     - What changes to this scene would (1) increase and (2) decrease your anxiety? *Since ET often involves exposing people to their fears in a hierarchical manner, the VR-ET program will involve exposing participants to levels of the scenes reported in phase 1. Although subject to change based on phase 1 results, exposures will have 3 levels. This question about how changes to the scene may increase or decrease anxiety will help determine the different films that should be recorded to represent the fear.*
   - C. Participants are given the option of describing additional scenes.
   - D. Closed-ended questions: Participants are provided with a series of scenes developed based on the researchers' knowledge of epilepsy or seizure-related anxiety, as well as evidence from the literature [1,25] and asked to rate how likely these scenes would generate epilepsy- or seizure-related anxiety. The rating options are as follows: strongly agree, somewhat agree, somewhat disagree, strongly disagree, and prefer not to say. The specific scenes are listed below. Ratings on these scenes will also help to inform phase 2 recordings.
     - On a subway platform
     - On a subway train
     - On a bus
     - On stairs or elevated platforms
     - In a washroom or other place with hard surfaces
     - At a shopping center
     - Completely alone
     - With a few people that I know (but not well)
     - With a few people that I have a close relationship with
     - At a large social gathering or party where I only know a few people
     - At a large social gathering or party where I know some or all people
     - Surrounded by complete strangers in a public setting
     - Going for a walk outside
     - Exercising with gym equipment
   - E. Is there anything else you'd like to share about your epilepsy- or seizure-related anxiety?

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Phase 1 Data Analysis

Sections 2A-2C and 2E of the phase 1 questionnaire (Textbox 1) will be coded by 2 researchers and then analyzed using the constant comparison method. The purpose of this analysis will be to determine which scenes were most commonly reported in the open-ended questions and the attributes that the virtual environment will reflect when they are recorded in phase 2. Section 2D of the phase 1 questionnaire (Textbox 1) will be analyzed using descriptive statistics, including calculating the frequencies of each discrete variable.

Phase 2

Phase 2 Protocol

Phase 2 will involve the development of the minimal viable product VR intervention. Although the design of the exposure hierarchies may be subject to change based on results from phase 1, we aim to record 3 sets of scenes in phase 2. Each set will have 3 scenes of different intensity levels that are designed to generate increasing amounts of anxiety (Figure 1). The scenes will be recorded using a 360° camera. Using 360° video is a cost-effective way to design photorealistic virtual environments with potential to create an increased sense of presence during exposure sessions when compared with computer-generated graphics [28,29]. An example of a scene that was recorded with a 360° camera can be seen [30] (click and drag on the video to scroll in 360°).

Participants will then be exposed to the 3 scenes of the set that most closely resemble their own epilepsy-related fears in phase 3 using the VR HMD. In summary, it is expected that phase 2 will involve filming nine 360° videos (3 sets × 3 scenes each). When filming these videos, we will ensure to the best of our abilities that any possible sensory triggers for people with epilepsy, such as common visual or auditory triggers, will not be included in the videos.

Phase 2 will not involve any data analysis.

Figure 1. Examples of virtual reality (VR) scenes that may be shown during the VR exposure therapy. Top: Toronto subway station with a few people; equirectangular frame from a 360° VR film. Bottom: A subway that has arrived at a Toronto station with no people around; 360° VR snapshot.





Phase 2 Recruitment

Phase 2 does not include any participants and only involves members of the research team. Specifically, the research team will record the 360° videos, and those who sign release forms will be actors in the videos.

The researchers will ensure that while recording the videos, any bystanders who happen to be present at the scene are at least 2 m away from the lens of the VR 360° camera. At a distance of 2 m, the resolution of a 360° video is typically too low for faces to be identifiable, and so the privacy of bystanders will be maintained. Only members of the research team involved in the recordings who have signed release forms will be within 2 m of the 360° camera, as appropriate for the scene. Researchers who will be interacting with participants face to face in phase 3 (over a video call or in person) will not be included as actors in the videos.

Phase 3

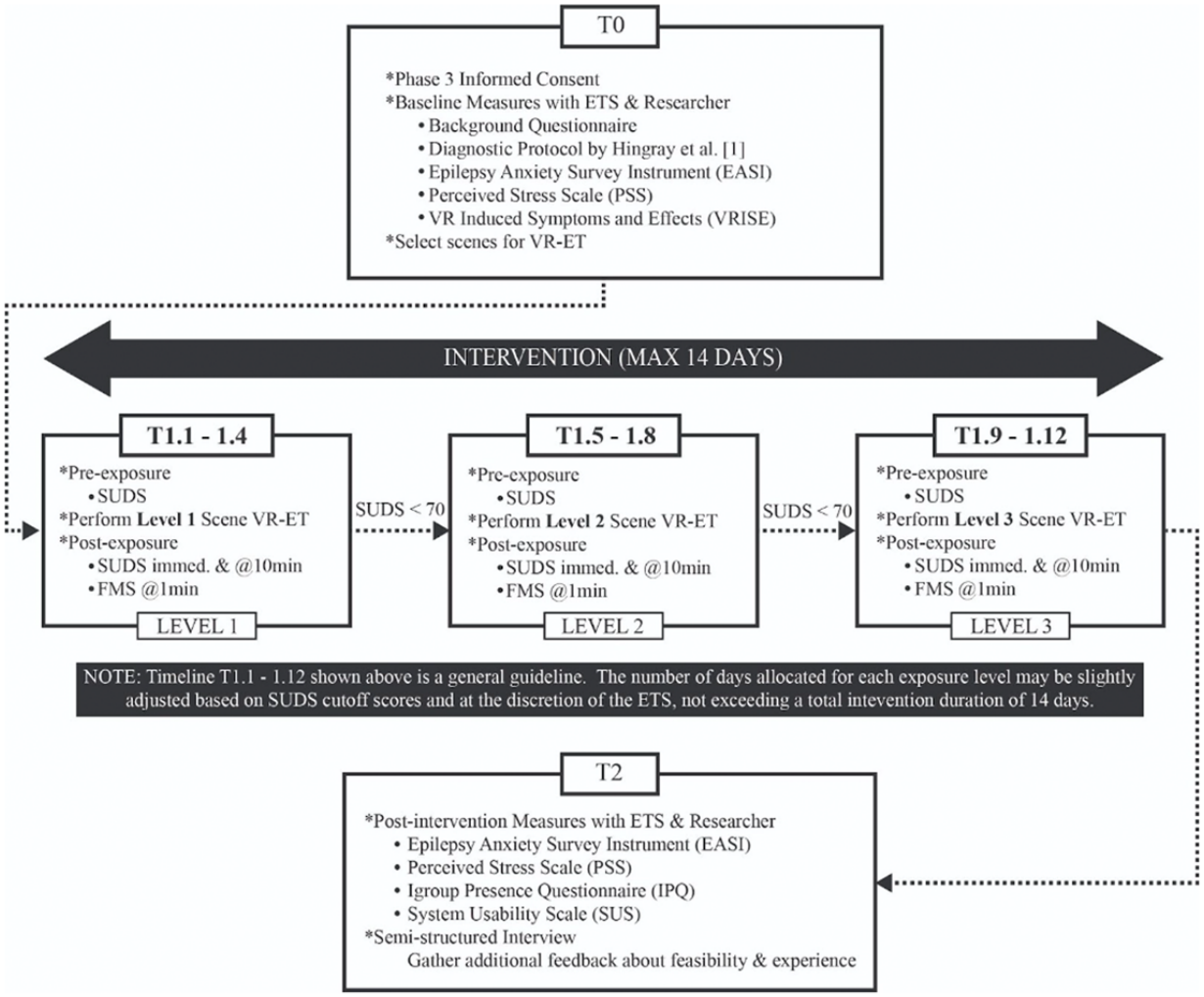
Phase 3 Overview

Participants in phase 3 will undergo the VR-ET intervention program, which will take place over approximately 2 weeks (Figure 2). Before beginning the program, participants will have an interview with an ET specialist (ETS) where they will discuss which set of scenes recorded in phase 2 fits best with their greatest anxieties. Participants will also respond to several questionnaires and assessments. Each participant will begin with the lowest exposure level (in other words, the scene that generates the least amount of anxiety) and gradually work their way up to the highest exposure level (which is the scene that generates the greatest amount of anxiety). Ideally, each exposure

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level will be performed every day for approximately 4 days, after which the participant will move onto the next level. Each day that they complete an exposure, participants will provide a score on the Subjective Units of Distress Scale (SUDS) at 3 specific time points. To help determine the efficacy of VR-ET, participants will have a second interview and repeat certain assessments 7 days after completing the ET program. It is hypothesized that VR-ET will help participants to habituate to their fears and ultimately lead to decreased anxiety.

Figure 2. Overview of the schedule for phase 3. ETS: exposure therapy specialist; FMS: Fast Motion Sickness Scale; SUDS: Subjective Units of Distress Scale; VR-ET: virtual reality exposure therapy.



Phase 3 Recruitment

Phase 3 will use the same recruitment methods as phase 1, including advertising through Epilepsy Toronto and using a snowball sampling strategy. In addition, phase 1 participants will be given the opportunity at the end of the questionnaire to enter their email address if they wish to receive more information about participating in phase 3.

Our target sample size for phase 3 is 5 people with epilepsy (people that do not have epilepsy themselves will not be included in phase 3). A sample size of n=5 was determined to be appropriate as this pilot study is evaluating feasibility of VR-ET for this population without aiming to determine clinical efficacy. In addition, sample size calculations are not necessary for feasibility studies according to the Consolidated Standards of Reporting Trials guidelines [31].

Phase 3 Consent and Eligibility

Overview

Participants will answer an eligibility screening after providing digital explicit consent through the phase 3 informed consent form (delivered over the Qualtrics platform). The eligibility screening will be completed over a telephone or video call with a member of the research team to help create rapport.

Even if the participant does not meet any of the exclusion criteria, they may be excluded from the study at any point. For example, if the research team is concerned that the treatment may have more negative consequences than positive for any reason, the principal investigator will consult with the ETS or make an executive decision to withdraw the participant from the study. However, information collected up until withdrawal may be (anonymously and in aggregate) included in the study

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analysis and findings. Participants are made aware of this in the phase 3 informed consent form.

Phase 3 Inclusions

Individuals with diagnosed epilepsy aged 18-65 years with self-reported mild or moderate epilepsy-related anxiety may participate in this study.

Phase 3 Exclusions

ET works by increasing anxiety in the short-term for the purpose of decreasing anxiety in the long-term. Because it is expected that participants' anxiety will rise during the ET sessions, anyone who was told by a neurologist or personally believes that stress has provoked their seizures in the past will be excluded from phase 3. Anyone with a self-reported diagnosis of panic disorder or self-reported severe epilepsy-related anxiety will also be excluded from this pilot study. However, should VR-ET for people with epilepsy become a standard treatment, people whose seizures are triggered by stress should decide with their medical team if the benefits of this treatment outweigh the risks. Therefore, people with epilepsy should consider whether a long-term decrease in stress from VR-ET (and a consequent decrease in seizures triggered by stress) may be worth the short-term increase in stress and the accompanying risk of seizures.

Those who have been told by a neurologist that they have photosensitivity or that they have had photoparoxysmal responses during an electroencephalogram will also be excluded from phase 3 [15]. Excluding people with photosensitivity from the study is not expected to significantly impact the sample size because only approximately 3% to 5% of people with epilepsy have photosensitive seizures [32]. However, even individuals who were never told by a neurologist that they have had photosensitive seizures but believe that photosensitivity may contribute to their seizures will also be excluded from phase 3 [15]. Similarly, individuals who previously experienced seizures after being in a VR environment will also be excluded from this study.

As depression and anxiety are common in people with epilepsy [2], many people that are interested in participating in the study may be taking psychotropic medications, such as antidepressants. Because antidepressants may take up to 12 weeks to show their full effects, it would be unclear whether improvements in anxiety from baseline are due to a response to medication or VR-ET [33]. Similarly, drugs such as benzodiazepines, which are used to treat seizures, may act to suppress the anxiety felt by people with epilepsy during VR-ET [34]. Therefore, to better evaluate the impact of VR-ET alone, people who began taking antidepressants, benzodiazepines, or medical marijuana within 12 weeks of phase 3 will be excluded.

Although individuals will not be excluded from the study if they have been taking benzodiazepines for longer than 12 weeks before starting phase 3, they will be asked to avoid taking them before the exposure session (only if possible and if it does not interrupt their antiseizure medication schedule). This is because benzodiazepines have immediate effects and may therefore artificially lower participants' SUDS scores [35]. A complicating factor in this regard is that some people with epilepsy are prescribed drugs such as benzodiazepines as a rescue medication and may therefore use them to stop or prevent seizures [34,36]. In clinical practice, it is possible that the patient may take a benzodiazepine before, during, or after performing an exposure solely out of fear that they will have a seizure (and not necessarily because they are actually about to have a seizure). In this case, the patient would be actively avoiding the anxiety that is associated with the exposure. By using avoidance, the exposure's usefulness is nullified because the patient is shielded from feelings of fear. They also momentarily lose the opportunity to learn that they are capable of handling these feelings of anxiety.

Other phase 3 exclusion criteria include individuals who have tonic-clonic seizures more than once a month, individuals who have functional seizures, individuals who cannot speak or understand English, individuals with open wounds on their face, and individuals with cervical conditions or injuries that would make it unsafe for them to use an HMD.

We will not be excluding individuals with memory deficits, as memory issues are common in people with epilepsy [37]. It is not a concern that memory difficulties will prevent participants from using the VR device properly as they will always be on a video call with a member of the research team who can guide the participant in using the VR headset as necessary.

Phase 3 Protocol

Baseline (T0)

Baseline Interview

Before beginning the VR-ET intervention, participants will have a one-on-one interview with an ETS over a telephone or video call. In this interview, the ETS will explain the 3 sets of scenes that were recorded in phase 2. Then, through discussion, the ETS and participant will determine which exposure set fits best with their individual epilepsy-related fears.

After choosing the appropriate exposure set, the ETS and participant will discuss the most appropriate order in which the 3 scenes associated with the set should be delivered during the intervention. As ET is typically delivered in a hierarchical manner, participants will be exposed to the scenes in the order of least anxiety provoking to most anxiety provoking. The order of exposure scene delivery will be individualized for each participant based on their unique experiences and fears. For example, the exposure set that fits best with 2 participants (hereinafter referred to as participants A and B) may be a shopping mall with its associated social aspects. In this case, the 3 levels may be scenes of a shopping mall with crowds of different sizes (eg, scenes with 2, 10, and 30 people). Participant A may have a fear of not being around many people in a public setting, such as a shopping mall, because it could mean that less help would be available in case they were to get a seizure. Therefore, participant A would first be exposed to the mall scene with 30 people, then 10 people, and then finally 2 people. In contrast, participant B may have a fear of being around many people in a public setting because they worry that having a seizure is embarrassing and would prefer to be surrounded by fewer people if they were to have a seizure [1]. Thus, the ETS would decide with participant B that they should first be exposed

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to the mall scene with 2 people, then 10 people, and finally 30 people. In summary, opportunities for tailoring the therapy will be built into the intervention through the (1) selection of scenario (location or theme), (2) selection of scenes (based on specific fears within a location such as the number of people in the scene), and (3) ordering of the scenes.

The aim of ET is to expose individuals to their fears until they habituate to the anxiety and learn to predict the outcome of their feared event as less anxiety provoking than they anticipated. Therefore, it is expected that participants may experience anxiety in anticipation of the exposure, during the exposure, and for a short period after completing the exposure. Although ET typically involves letting anxiety subside without instituting coping mechanisms, special considerations must be taken when working with the epilepsy population. Specifically, stress is a commonly self-reported seizure trigger for some people with epilepsy [38]. Although people with epilepsy for whom stress is a known or suspected seizure trigger will be excluded from phase 3, there is still a risk that stress may provoke a seizure in participants. To help prevent this, a number of protocols will be set in place (Textbox 2).

Textbox 2. Protocols put in place in case participants become too anxious before, during, or soon after the exposure sessions.

Coping mechanisms

- Before the baseline interview, participants will be sent a document that provides anxiety coping mechanisms, namely a mindfulness strategy, a self-compassion strategy, and a meditative technique. Participants will be encouraged to practice these coping mechanisms before the interview as they will then review them with the exposure therapy specialist.
- Before each exposure, the researcher will remind participants that, if they feel too overwhelmed during the exposure, they should remove the virtual reality head-mounted display even if they have not completed the full exposure and use the coping mechanisms that they prepared with the exposure therapy specialist. (If the participant stops the exposure early and uses a coping mechanism, the researcher will make a note of this. Postsession Subjective Units of Distress Scale (SUDS) scores will be recorded regardless.)
- If the participant scores >70 on any of the SUDS tests after completing the exposure, whether they ended the exposure early or not, they will be instructed by the research member on the video call to use the coping mechanisms. (The remaining SUDS scores will still be recorded.)

Additional strategies

- If the participant's anticipatory anxiety SUDS score (ie, the SUDS score that the participant records before performing the exposure) is >70 on the first day of beginning a new exposure level (eg, level 2), participants will still be encouraged to attempt the new level if their 10-minute postexposure SUDS score the previous day for the lower level (level 1) was <70.
- Even though we are excluding individuals who experience panic attacks, there is a risk that participants may panic before, during, or after the exposure. Therefore, members of the research team will be trained by a clinical neuropsychologist on how to identify when someone is having a panic attack and reach out to an on-call health professional.

Assessments

At baseline, the participant will also complete several assessments (Table 1 and Textbox 3), specifically the background questionnaire (Textbox 4); proposed diagnostic protocol for epilepsy-specific anxiety disorders [1]; Epilepsy Anxiety Survey Instrument (EASI); Perceived Stress Scale (PSS); and Virtual Reality Induced Symptoms and Effects (VRISE) assessment.

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Textbox 3. Assessments at T0.

Background questionnaire

- This questionnaire was created by the authors of this paper to be conducted at the baseline interview (Textbox 4). Its main purpose is to collect phase 3 participants' demographic information and information about their history with anxiety and epilepsy.

Epilepsy Anxiety Survey Instrument (EASI) [39]

- The EASI is validated for assessing epilepsy-related anxiety features and severity. Note that by using the EASI, we are simultaneously using the brief Epilepsy Anxiety Survey Instrument (brEASI) [39]. The brEASI is a validated screening tool for anxiety disorders in people with epilepsy and is made up of 8 items that are already asked in the EASI. The brEASI is based on the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders [40].

Perceived Stress Scale

- The Perceived Stress Scale assesses how an individual perceives their own levels of stress.

Proposed diagnostic protocol for epilepsy-specific anxiety disorders [1]

- Hingray et al [1] suggested a diagnostic enquiry for 4 proposed anxiety disorders specific to epilepsy: anticipatory seizure anxiety, seizure phobia, epileptic social phobia, and epileptic panic disorder. They also suggested an assessment for symptom severity of each of these disorders and an evaluation of avoidance behaviors.
    - Note: On the basis of responses to the assessment by Hingray et al [1], individuals who appear to have epileptic panic disorder according to a clinical neuropsychologist will be excluded from the study.

Virtual Reality Induced Symptoms and Effects (VRISE) assessment [41]

- The VRISE assessment is one of the 4 domains included in the Virtual Reality Neuroscience Questionnaire and evaluates the intensity of motion sickness. The 3 other domains included in the Virtual Reality Neuroscience Questionnaire (user experience, game mechanics, and in-game assistance) are not relevant to our study. A lower score on the VRISE assessment suggests greater motion sickness.
    - Note: Participants who score less than 25 on the VRISE assessment after virtual reality training during T0 will be withdrawn from the study.

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Textbox 4. Overview of the questions to be asked in the Background Questionnaire (T0).

1. Demographics
   - A. Contact information of the participant and their emergency contact
   - B. Year of birth
   - C. Sex assigned at birth and gender
   - D. Address that the participant will be doing the video calls from
2. Technology use
   - A. Previous experience with virtual reality (if any)
   - B. Comfort level on a scale of 1-10 with computers, smart phones, video call technology (specifically Zoom), virtual reality headsets
   - C. Low vision
   - D. Recent eye surgery
3. Epilepsy
   - A. Type(s) of seizures
   - B. Date of epilepsy diagnosis
   - C. Sensory triggers
   - D. Epilepsy safety protocol that should be set in place in case the participant were to have a seizure during the video call
4. Anxiety
   - A. Presence of anxiety as a side effect from any antiseizure medications currently taken
   - B. Anxiety disorder diagnoses. Participants will be asked to list any anxiety disorders that they were diagnosed with and the dates of diagnoses
   - C. History of experiencing preictal or postictal anxiety
   - D. Previous or current cognitive behavioral therapy (CBT). *If yes*:
     - i. Date the CBT program began
     - ii. Date the CBT program was completed (or the expected completion date)
     - iii. The helpfulness of the CBT program
     - iv. If the CBT program is focused on anxiety. *If yes*, if it involved targeting epilepsy-related anxiety
     - v. If the CBT included exposure therapy
   - E. If the participant has previously undergone or if they are currently undergoing any exposure therapy. *If yes*, they will be asked similar questions as 4D (i-iv)
5. Medical marijuana and medication use: (As this question and others in the study may be sensitive and yet important for evaluating the impact of the intervention, all outcome measures will be prefaced with an explanation of the importance of answering honestly and to the best of participants' abilities, as well as a reminder that participation is voluntary and that questions may be skipped without repercussion.)
   - Current antiseizure medication(s)
   - Current medical marijuana use
   - Current antidepressants or medications to treat anxiety

Equipment Setup

The only in-person aspect of T0 will be when a member of the research team visits the participant's residence to set up the VR equipment (Oculus Quest 2) and teaches them how to use and store the device. In teaching participants how to use the VR HMD, participants will practice using the device set to a neutral scene that is not expected to provoke anxiety in people with epilepsy according to phase 1 or existing literature. After using the VR HMD, participants will complete the VRISE questionnaire (Textbox 3) to record their baseline motion sickness tendencies. Note that anyone who scores below 25 on VRISE after using VR with a neutral scene will not be allowed to continue with the study.

At this time, the researcher will review the overall layout of the experiment and arrange a schedule with the participant for the exposure sessions, which will take place daily over one-on-one video calls. Ideally, the video calls (and therefore, exposure sessions) will take place at approximately the same time each day. Indeed, exposures should be performed at similar times

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each day to limit inconsistent and extraneous reasons for increased baseline anxiety levels.

Exposure Session Protocol (T1)

Overview

The VR-ET intervention will consist of an exposure session every day for up to 14 days over a one-on-one video call with a researcher. During each exposure session, the participant will be seated in a chair at their home. Exposures will be performed for approximately 5 minutes, which is lower than the recommended 10-minute threshold for mitigating motion sickness [42]. Each day that the participant performs an exposure, they will complete assessments: SUDS 3 times; the Fast Motion Sickness Scale; and, although not a formal assessment, participants will be asked about the frequency in which they used coping mechanisms during the exposure session and in the 10-minute period afterward (Textbox 5).

Textbox 5. Assessments at T1.

Subjective Units of Distress Scale (SUDS)

- The purpose of collecting SUDS scores will be to quantitatively assess:
  1. How participants' anxiety in anticipation of performing the exposure compares to their anxiety immediately after completing the exposure
  2. If their anxiety decreases over time after completing an exposure session (ie, immediately after the exposure vs 10 minutes after the exposure)
  3. If their overall anxiety progressively decreases over the course of each exposure level
- Each day that they perform an exposure, the participant will record a SUDS score at 3 time points:
  A. Before putting on the head-mounted display and beginning the exposure. This measures the anxiety that the participant feels in anticipation of performing the exposure.
  B. Immediately after completing the exposure
  C. 10 minutes after completing the exposure

Fast Motion Sickness Scale [43]

- The purpose of collecting Fast Motion Sickness Scale scores will be to quantitatively measure motion sickness, specifically the general discomfort and nausea components, that participants may have experienced during the virtual reality exposure session. Participants will complete this assessment shortly after completing the first postexposure SUDS.

Frequency of coping mechanism use

- After completing the first postexposure SUDS test, participants will be asked how often, if at all, they used the coping mechanisms provided during the exposure (Textbox 2). After completing the second postexposure SUDS test, participants will be asked again about how often, if at all, they used the coping mechanisms since performing the exposure. The purpose of collecting this information is to understand whether differences in the use of coping mechanisms is related to the efficacy of the virtual reality exposure therapy intervention.

The purpose of having a researcher on a video call with the participant during exposure sessions is 3-fold. First, it provides a safety plan in case participants were to have a seizure during the exposure. This was put in place not because it is expected that participants might be triggered by the VR-ET but rather because people with epilepsy are prone to seizures, and therefore, it is important to have a seizure protocol in place. In the background questionnaire, the participant will provide details such as their emergency contact's information, if they would like the researcher to call their emergency contact or an ambulance if they have a seizure (some people with epilepsy prefer an ambulance not to be called), and if they would prefer for the researcher to keep their video on for safety or to turn it off for privacy. Second, if the participant experiences panic, the researcher will contact an on-call health professional. Third, through discussion with a clinical neuropsychologist, being in someone's presence (even virtually) while performing an exposure acts as a behavioral commitment from the individual who is receiving the treatment. Therefore, the participant will be less likely to display avoidance behaviors in relation to performing the exposure.

Exposure Session Timeline

Each participant will begin with the exposure scene that generates the least amount of anxiety and gradually work their way up to the scene that provokes the most anxiety. Each exposure scene will be performed daily for approximately 4 days, after which the participant will move onto the next level. However, if SUDS scores are >70 and at the discretion of the ETS, the current scene may be repeated until the participant is ready to progress. If a participant's SUDS score is too high to begin the first level, they will be exposed to a different set and its associated scenes, even if it does not fit with their own anxiety as closely.

As such, the overall schedule may vary for each participant based on their individual progress. The participant is expected to complete the intervention in 12 days but will be allowed up to 14 days if additional days are required to complete a scene. If a participant has a seizure at any point during the 12 to 14 days that they are receiving the intervention, the VR-ET will be discontinued as a precautionary measure. However, data provided up until that point may still be used in analyses and they will participate in T2.

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Postintervention (T2)

One week after completing the VR-ET intervention, the participant will answer several assessments (Table 1 and Textbox 6), specifically EASI; PSS; Igroup Presence Questionnaire (IPQ) [44]; and the System Usability Scale (SUS) [45]. The proposed diagnostic protocol for epilepsy-specific anxiety disorders [1] will not be repeated at T2 and will instead inform some of the open-ended questions that will be asked in the semistructured exit interview that will take place over telephone or video conferencing (Textbox 6). The interview will be conducted either by an ETS or a member of the research team and will aim to gather additional feedback about the participants' experience. For example, participants will be asked to provide feedback on their experiences with the various devices, the subjective impact of the therapy, and what may be improved about the program and ET scenarios. Similar to T0, the only in-person aspect of T2 will take place when a member of the research team goes to the participant's residence to collect the VR equipment.

Textbox 6. Outcome measures at T2.

Repeat: Epilepsy Anxiety Survey Instrument and Perceived Stress Scale

Igroup Presence Questionnaire [44]

- The Igroup Presence Questionnaire assesses the subjective experience of being in a virtual environment when one is physically situated in another

System Usability Scale [45]

- The System Usability Scale assesses usability of the hardware and software

Semistructured Exit Interview

- To collect feedback (preferences and suggestions for improvement) on the:
  - Virtual reality system usability and training
  - Virtual reality exposure scenes
    - (ie, how realistically the videos simulated real-world scenarios that provoke anxiety for the participant)
  - Intervention impact on anxiety
  - Treatment delivery and format
  - General experience

Phase 3 Data Analysis

As both quantitative and qualitative data will be collected in phase 3, a mixed methods approach will be used. Quantitative statistical analyses will be performed using the MiniTAB statistical package [46] and SPSS software (version 27.0; IBM Corp) [47]. To investigate the normal data distributions of the dependent variables, ranges of skewness and kurtosis will be determined. The Kolmogorov-Smirnov and the Shapiro-Wilk tests will also be performed to evaluate statistical significance (mean, 95% CI) and normality of the distributions. In addition, Cronbach α will be performed for each self-report questionnaire's subscales. To explore sociodemographic features, frequencies, means, and standard deviations will be calculated.

To explore the effects of VR-ET, data collected at T0 and T2 will be compared. Clinically significant effects of the intervention will be investigated using the Jacobson-Truax method, based on the measures' clinical cut-offs (Table 2). Moreover, SUDS scores (before the exposure, immediately after the exposure, and 10 minutes after the exposure) collected every day of T1 will be compared with each other. Participants' SUDS scores that are recorded immediately after the exposure may be lower than their anticipatory anxiety levels, and if so, this may encourage the participant to do the next exposure. We will also consider our study to be successful if participants' SUDS scores remain high in the first postexposure SUDS test but decrease at the 10-minute postexposure SUDS test. However, the study may still be deemed successful with unchanging SUDS scores if participants have reduced anxiety and engage in fewer safety-seeking behaviors after completing VR-ET, as based on T2 findings.

Using thematic analysis, qualitative responses to assessments and interviews will be assessed by the research team and then reported as frequencies using the procedure outlined by Braun and Clarke [48]. The constant comparison method will be used to analyze the responses to the open-ended questions asked at T0 and T2 [49].

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Table 2. Clinically significant scoring for the phase 3 assessments.

	Items	Range	Scores	Citation
Assessments				
Epilepsy Anxiety Survey Instrument	18	0-54	Higher scores suggest more severe anxiety	Scott et al [39]
Brief Epilepsy Anxiety Survey Instrument	8	0-24	≥7 suggests a likely anxiety disorder	Scott et al [39]
Perceived Stress Scale	14	0-56	Higher scores indicate greater perceived stress levels	Cohen et al [50]

Results

This study was funded by a joint Junior Faculty Funds and Minor Research Grant from the York University Faculty of Health in November 2021. Recruitment for phase 1 was completed as of August 7, 2022, and had a final sample of 18 participants. Results for phase 1 will be published once data collection and analysis have been completed; data collected as of August 7, 2022, may be requested by contacting the corresponding author.

We are leveraging discussions with experts in the field to design the first VR-ET program specific to people with epilepsy which have led to some minor amendments (Textbox 7) to our original protocol.

Textbox 7. Summary of study amendments to improve the study's methodology.

A. Phase 1 questionnaire
   i. *Updated* the wording and layout so that it would be faster, simpler, and more intuitive for participants to fill out.
   ii. *Added* relevant questions, such as the specific prompts for each scene.

B. Phase 1 informed consent form
   i. *Updated* the wording to remove any language that may have overstated the risks of filling out the questionnaire.
   ii. *Adapted* it to be deliverable over a web-based platform.

C. Phase 2 recordings
   i. *Updated* the guidelines so that common sensory triggers for seizures will be avoided. This was added after discussion with an epileptologist about the use of virtual reality in people with epilepsy.

D. Phase 3 assessments
   i. *Added*: Epilepsy Anxiety Survey Instrument, Igroup Presence Questionnaire; System Usability Scale.
   ii. *Removed*: Beck Anxiety Inventory; Generalized Anxiety Disorder-7 scale.

E. Honorarium
   i. *Added* for phases 1 and 3.

Discussion

Principal Findings

Although the primary anxiety treatments for people with epilepsy are cognitive behavioral therapy and pharmacological treatments, minimal research has investigated anxiety treatments specifically for this population [51,52]. Moreover, few studies have investigated the use of ET for treating anxiety in people with epilepsy [24,25]. No studies to our knowledge have delivered ET to people with epilepsy using VR, despite VR-ET's efficacy in other populations and the benefits that it could offer to people with epilepsy [11].

The main amendments made to the protocol included changes to the phase 3 anxiety assessments, after consultation with a clinical neuropsychologist who specializes in treating people with epilepsy. Indeed, when assessing anxiety in people with epilepsy, it is important to use validated assessments that do not inquire about physical manifestations of anxiety that may be confused with consequences of the neurological disorder. For example, the Beck Anxiety Inventory has been shown to be potentially less accurate in measuring anxiety in people with epilepsy because it contains items that reflect antiseizure medication side effects and symptoms of epilepsy, as opposed to symptoms of anxiety [39]. The Generalized Anxiety Disorder-7 scale was removed because it focuses on generalized anxiety disorder rather than anxiety in general or epilepsy-specific fears. Instead, the EASI was added.

The IPQ and SUS were also added to assess the feasibility of the intervention as well as provide validated feedback on participants' experiences with the technology in preparation for the subsequent larger clinical trials. For example, the IPQ will help assess participants' sense of presence in the virtual scene, which is important in VR-ET so that it resembles the real-life scenes that participants fear as closely as possible [18]. The IPQ will also be useful for determining if phase 2 was successful in

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realistically capturing the scenes. The interview at T2 will expand on responses to the IPQ as participants will be asked to provide verbal feedback on how future studies could improve the realism of the VR-ET scenarios, as well as the sense of presence that they generate. Furthermore, the SUS will provide useful information for optimizing procedures for training participants on how to use the VR equipment. The SUS may also help to identify if there were greater difficulties for people with cognitive deficits and inform how we could design a system that is accessible for all potential individuals with epilepsy. To assess motion sickness tendencies and symptoms after the VR-ET sessions, the VRISE and Fast Motion Sickness Scale were also included.

Limitations

Pilot studies play a key role in the development or refinement of new interventions, assessments, and other study procedures, with the primary role of a pilot study being to examine the feasibility of a research endeavor [53]. Although the nature of a pilot study allows for a small sample size, we acknowledge that this is a limitation of both phases 1 and 3 and that, as a result, caution should be applied to the generalization of the findings. The sample sizes were determined based on resource constraints (funding and time) and are appropriate for a feasibility study that does not aim to assess clinical efficacy. To help account for the small sample size of phase 1, the baseline interview of phase 3 will act as an extension of phase 1 where we will gain more insight into the specific epilepsy- and seizure-related fears that people with epilepsy experience.

Another limitation to the generalizability of our findings is that phase 3 does not include a control group. Participants will be recruited to a known, albeit experimental, study and assessments will be conducted in an unblinded fashion. The choice to run an open-label pilot with no control group was intentional. Our primary goal is to report on the feasibility of recruitment, intervention design and implementation, as well as participant retention. Given the novelty of this initiative and our resources (funding and time), the research team agreed that this was the most appropriate way to systematically gather and incorporate user feedback before evaluating VR-ET on a larger scale. Future studies with larger sample sizes, a control group, and randomization will be necessary to evaluate clinical efficacy.

We acknowledge that it may not be feasible in clinical practice for therapists to have daily communication with their clients or patients. However, we are designing the intervention this way purposefully for the pilot study to maximize safety in case of a seizure or concerning psychological distress, such as a panic attack. In addition, as discussed with a clinical neuropsychologist, it will maximize the chances of therapeutic success if participants are in communication with someone, such as a therapist or researcher, while doing the exposures to help them form a behavioral commitment. Because this is a pilot study, it aligns more with the purpose of the research to maximize the chances of therapeutic success rather than to assess the feasibility of the proposed intervention within a professional setting. However, the ability to implement self-guided sessions in a controlled and safe virtual environment is an advantage of VR therapy. Therefore, future studies should investigate participants' adherence to VR-ET and its efficacy when they perform the exposures daily without a researcher or therapist present.

Another limitation is that while we ask participants to avoid taking a benzodiazepine before performing the exposure and after their exposure until their anxiety settles, we cannot enforce this request because benzodiazepines may be used to treat seizures [34]. As previously discussed, taking a benzodiazepine can limit the effectiveness of the ET. It may be worthwhile to conduct future clinical trials in a safe and well-monitored environment, such as a hospital epilepsy monitoring unit, where participants are restricted from taking a benzodiazepine as much as possible. In this scenario, the participants would be in a safe environment in case they were to have a seizure and potential confounding effects would be reduced.

In conclusion, we are proposing a novel VR-ET as a treatment specific to people with epilepsy and their unique fears relating to their condition. VR is an especially promising tool for ET broadly as it allows for tailored exposure and control over the visual and auditory stimuli. When considering people with epilepsy, VR-ET offers additional advantages for this population. For example, given that the therapy can be administered in the comfort of one's home, it increases accessibility for individuals with restricted independence and ability to travel. Overall, this study will contribute significantly to the fields of VR, ET, anxiety, and epilepsy and lay the groundwork for a more equitable therapy program for this population.

Acknowledgments

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Data Availability

Data sharing is not applicable to this study as no data sets were generated or analyzed. The data collection tools (eg, surveys) created for this study are available from the corresponding author on reasonable request.

Authors' Contributions

LA and HGG contributed to the conception of the study. All authors (HGG, LA, SL-F, DT, SP, and LRH) contributed to the design of the protocol. HGG wrote the first draft of the manuscript, and all authors edited and revised the final manuscript. The

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Conflicts of Interest

None declared.

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Abbreviations

EASI: Epilepsy Anxiety Survey Instrument
ET: exposure therapy
ETS: exposure therapy specialist
HMD: head-mounted display
IPQ: Igroup Presence Questionnaire
PSS: Perceived Stress Scale
SUDS: Subjective Units of Distress Scale
SUS: System Usability Scale
VR: virtual reality
VRISE: Virtual Reality Induced Symptoms and Effects

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Protocol

The Outcomes of Surgical and Nonsurgical Treatment in Patients With Spinal Metastases of Lung Cancer: Protocol for a Prospective Cohort Study

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Abstract

Background: Spinal metastases of lung cancer (SMLC) usually have a high degree of malignancy and require multimodality treatment. Patients with SMLC who experience clinical symptoms (eg, local pain, emerging or potential spinal instability, and progressive neurological dysfunction) require surgical treatment. However, there are discrepancies in the comparison of outcomes between surgical treatment and nonsurgical treatment.

Objective: This paper presents the protocol for a study that aims to compare the clinical outcomes of surgical treatment and nonsurgical treatment for SMLC, explore the prognostic factors of SMLC, and establish a survival prediction model based on these prognostic factors.

Methods: This is a prospective cohort study, with an anticipated sample size of 240 patients (120 patients in the surgical group and 120 patients in the nonsurgical group). We will collect baseline data, including demographic, clinical, and radiological information, as well as data from patient-reported questionnaires. Patients will be followed up at 3, 6, 12, and 24 months after treatment, and survival status will be assessed every 3 months. The primary outcome is the overall survival period. Prognostic factors associated with overall survival will be analyzed by univariate and multivariate Cox proportional hazards regression. Odds ratios with 95% CIs will be presented. Statistical significance is set at $P<.05$.

Results: This study has been approved by our institute's Medical Science Research Ethics Committee (IRB00006761-M2021085) after a careful audit of the design and content. Patient enrollment began in June 2022 at our hospital. Data collection is expected to be completed by early 2026, and the study results will be published by mid-2027.

Conclusions: In this study, we propose to set up a prospective cohort of patients with SMLC to investigate the outcomes between surgical treatment and nonsurgical treatment. We will explore the role of surgical treatment in SMLC and provide guidance to peer surgeons.

Trial Registration: Chinese Clinical Trial Registry, ChiCTR2100048151; http://www.chictr.org.cn/showproj.aspx?proj=129450

International Registered Report Identifier (IRRID): DERR1-10.2196/38273

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KEYWORDS

spinal metastasis of lung cancer; spinal metastases of lung cancer; lung cancer; surgery; overall survival; prediction model; protocol

Introduction

Background

The effective integration of therapeutic modalities into the treatment of metastatic lung cancer on the spine is a source of debate. Lung cancer is a moderate to high malignancy, and metastasis to the spine usually represents the end stage of the disease [1,2]. According to the scoring systems for spinal metastasis by Tomita et al [3] and Tokuhashi et al [4], patients with spinal metastases of lung cancer (SMLC) are expected to live less than 1 year. Thus, more conservative treatments have been given in the past. In recent years, advances in radiation therapy and systemic antitumor drugs, such as stereotactic body radiotherapy (SBRT), target therapies, and immunological therapies have demonstrated encouraging therapeutic outcomes and have largely expanded the survival time of patients with SMLC [5-11]. At the same time, surgical treatment has been widely accepted for some SMLC cases [12]. A comprehensive treatment, composed of antitumor drugs, radiotherapy, and surgery, has been the current state-of-the-art therapeutic modality for SMLC.

Generally, patients with SMLC experiencing the following symptoms are referred for surgery: severe and refractory local pain, emerging or potential spinal instability, and progressive neurological dysfunction [8,13-17]. After the surgery, adjuvant therapies, including radiotherapy and systemic drugs, are undertaken. Most researchers have stated that adjuvant radiotherapy should be completed around 6 weeks after the operation to spare time for physical recovery and avoid problems related to wound healing [18]; yet, this is difficult to do in a real-world setting [19]. Additionally, previous studies have described discrepancies in the efficacy of surgical treatment for patients with SMLC [20]. According to these works, the median survival time after surgery was reported to range from 2 to 14 months [21]. Because of limitations that included a retrospective study design, no control group, etc, the conclusions of related studies lack high-quality evidence.

Objective

In our study, a prospective, specific disease cohort of SMLC will be used to compare the effectiveness of surgical treatment and nonsurgical treatment. This study will provide useful information to explore the role of surgical treatment in comprehensive SMLC treatment and develop suitable treatment guidelines.

The primary aim of this study is to investigate and compare treatment outcomes in patients with SMLC. In addition, we also plan to analyze various prognostic factors of SMLC, such as treatment modalities, tumor subtypes, pre- and postoperative neurological function, and more.

Methods

Study Design

This study is a prospective cohort study. We will compare the treatment outcomes of surgical and nonsurgical methods for SMLC in a real-world clinical scenario. The study will enroll 240 patients (120 patients in the surgical group and 120 patients in the nonsurgical group) from June 1, 2022, to June 30, 2027. The patients will be visited postoperatively at 3, 6, 12, and 24 months. The study is due to be completed on June 30, 2029.

Sample Size and Study Timeline

In this study, we plan to compare the overall survival (OS) time between the two groups and explore its prognostic factors. The sample size calculation was based on the survival time and estimation of influencing factors. According to an unpublished retrospective study performed at our center and previous literature [20,21], the average OS time was 11 (SD 4) months in the surgical group and 9 (SD 3) months in the nonsurgical group. Assuming an overall Type 1 error (α) of .05 and Type II error (β) of .1, we need 66 patients in each group. Additionally, there are 12 predictive factors we plan to analyze in the prediction model. According to the sample size estimation method for multivariable regression models, 100 cases in each group are needed (the ratio of surgical to nonsurgical group is 1:1). Considering a final follow-up rate of 80%, a minimum of 120 patients will be required for each group. There were approximately 25 patients undergoing surgery per year at our center; therefore, we plan to enroll the patients over the next 5 years. Since more patients are treated nonsurgically than surgically, all nonsurgical patients treated during the first 5 years will be enrolled.

The study duration is estimated to be 7 years to ensure that all recruited patients are followed up for 2 years. Each visit's timeline and tasks are presented in Multimedia Appendix 1.

Patient Enrollment and Group Allocation

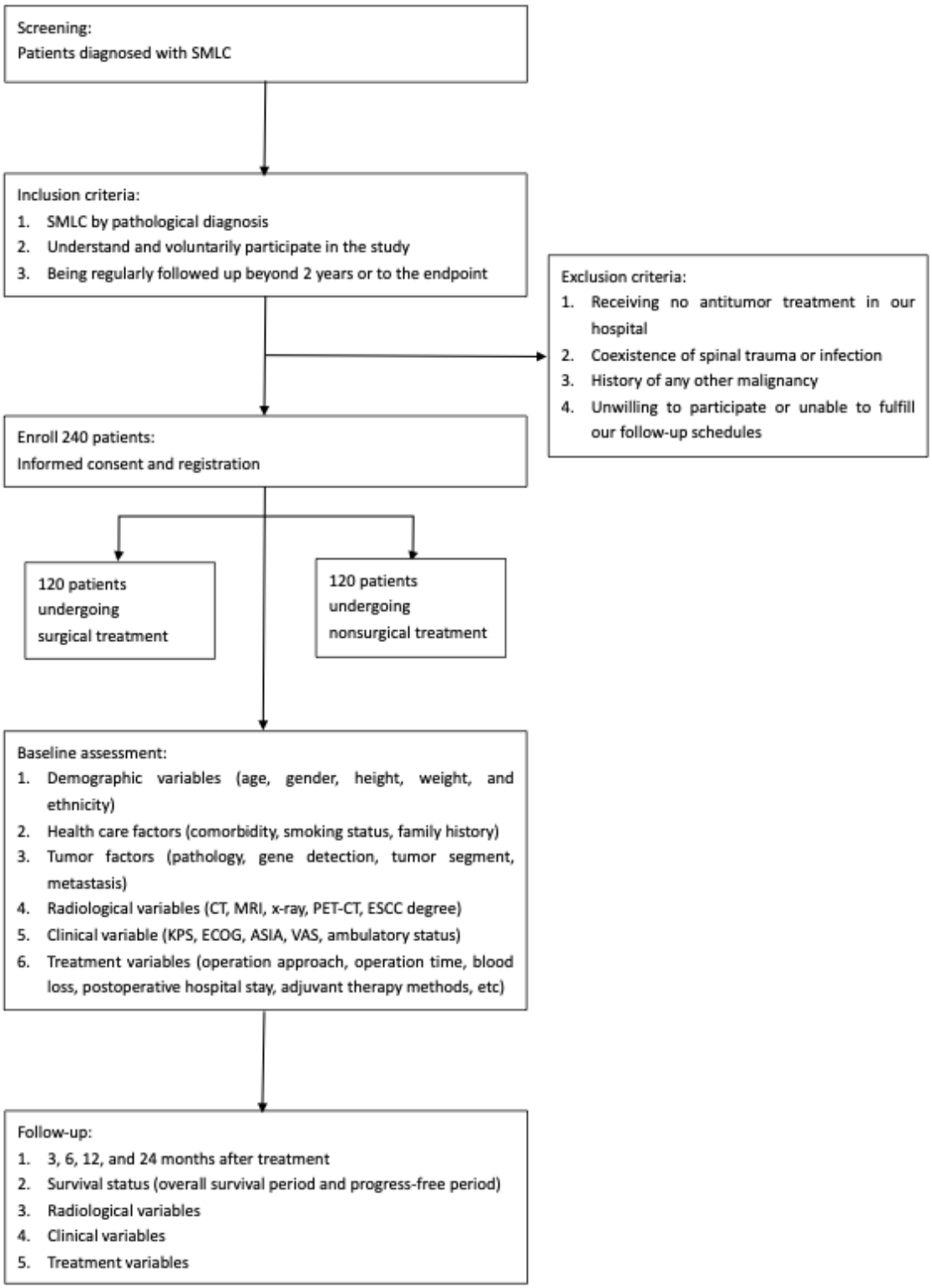
All patients with SMLC being treated at our center are potential candidates, and those who meet the inclusion and exclusion criteria will be eligible for enrollment in our study. Patients who receive surgical treatment along with postoperative systemic comprehensive treatment will be enrolled in the surgical group. Patients who receive only conservative treatment (eg, radiotherapy, chemotherapy, targeted molecular therapy, immunological therapy, etc) without surgical treatment will be enrolled in the nonsurgical group. All study procedures, as well as the participants' rights, responsibilities, benefits, and risks, will be communicated, and participants will sign an informed consent form. Figure 1 displays the study flowchart.

In order to participate, patients will need to meet certain eligibility criteria. The inclusion criteria are (1) a pathological diagnosis of SMLC, (2) understanding and voluntarily participating in the study, and (3) being regularly followed up beyond 2 years or to the endpoint. Exclusion criteria include:

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(1) not receiving antitumor treatment at our hospital, (2) coexistence of spinal trauma or infection, (3) history of other malignancies, and (4) unwillingness to participate or inability to adhere to our follow-up schedule.

Figure 1. Study flowchart. ASIA: American Spinal Injury Association; CT: computed tomography; ECOG: Eastern Cooperative Oncology Group; ESCC: esophageal squamous cell carcinoma; KPS: Karnofsky Performance Scale; MRI: magnetic resonance imaging; PET-CT: positron emission tomography–computerized tomography; SMLC: spinal metastases of lung cancer; VAS: visual analogue scale.



Treatment

A surgical decision is made following the advice of our institutional multidisciplinary treatment team for spinal metastasis. There are 3 indications for surgery at our center: severe yet drug-resistant local pain, progressive neurological dysfunction, and emerging or latent spinal instability. Otherwise, patients are referred for nonsurgical treatment.

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In the surgical group, patients are given surgical treatment, neurological rehabilitation, and adjuvant therapies (ie, SBRT and antitumor drugs). In this setting, we have established a synchronized workflow for surgery-based multimodality therapy instead of the conventional step-by-step schedule. A synchronized workflow means that neurological rehabilitation is incorporated and commenced right before the surgery and that SBRT and antitumor drugs are started early and simultaneously during the process of rehabilitation.

In the nonsurgical treatment group, patients are treated with adjuvant therapies exclusively, including radiotherapy, chemotherapy, targeted therapy, immunological therapy, etc. Considering the existence of various adjuvant modalities, this study will only enroll patients who receive both locoregional radiotherapy and antitumor drugs.

Outcomes

Primary Outcome

The primary outcome metric of the study is the OS period. OS is defined as the time after the start of any antitumor therapy for SMLC to death of any cause.

Secondary Outcomes

Secondary outcomes include the following:

1. The progress-free survival period, defined as the time after the start of antitumor therapies until disease progression.
2. Recovery of SMLC-related symptoms, defined as the relief of locoregional pain, which is measured by visual analogue scale (VAS) values, and the recovery of neurological status, which is assessed using the American Spinal Injury Association (ASIA) score. Immediate improvement in VAS and ASIA scores is assessed before discharge.
3. Recovery of self-care performance, assessed using the Karnofsky Performance Scale (KPS) score and the Eastern Cooperative Oncology Group (ECOG) performance score.
4. Quality of daily life, assessed by the Short Form 36 Health Survey Questionnaire.

Other outcomes for evaluation include complications in antitumor treatment. Surgical complications are rated according to the system proposed by Clavien et al [22], whereas toxicity of radiotherapy and antitumor drugs is graded using the National Cancer Institute's Common Toxicity Criteria for Adverse Events (version 5.0). The endpoint of the study is the death of the recruited patient. The primary outcome is assessed by the endpoint of the study, whereas secondary and other outcome metrics are assessed at each visit.

Exposure Measures

The exposure measures of interest include demographic variables, clinical data, and treatment-related factors. Demographic variables include age, gender, height, weight, and ethnicity. Clinical data are composed of health care factors (comorbidity, smoking status, family history of tumors); tumor factors (pathology, gene detection, tumor segments, and metastatic status); radiological variables (computerized tomography, magnetic resonance imaging, x-ray, positron emission tomography–computerized tomography, and degree of epidural spinal cord compression); and clinical variables, which include onset time, general status (KPS, ECOG score), neurological function (ASIA score), pain (VAS value), and ambulatory status. Treatment-related factors include operation approach, operation time, blood loss, postoperative hospital stay, adjuvant therapies, etc.

Data Management and Supervision

We will assign a specific investigation team to assess outcomes and process the data, and train the team in this regard. In addition, we will formulate some basic rules for the process of patient follow-up; outcomes assessment; and data entry, coding, and storage, namely double assessment, dual entry, and checks by independent investigators. Outcome assessors will be blinded to the patients' intervention allocation. Our institute's scientific research supervising team, which excludes all investigators in this study, will monitor the study process, data safety and authenticity, and occurrence of adverse events.

Statistical Analysis

Statistical analysis will be performed using SPSS for Windows (version 20; IBM Corp). The Lilliefors test will be used to examine whether the data are normally distributed. Data will be presented as percentages, mean (SD), or median (range) accordingly. The 1-tailed unpaired Student *t* test and Pearson χ^2 test (or the Fisher exact test) will be used to make comparisons between different groups. The OS and progress-free survival curves will be plotted using the Kaplan-Meier method, and a comparison of the two groups will be performed via the log-rank test. The influencing factors will be analyzed by univariate and multivariate Cox proportional hazards regression. Statistical significance is set at $P<.05$. The survival prediction model will be established by multivariate Cox regression models and the Kaplan-Meier survival curves. The predictive ability of the final model will be evaluated using the Harrell concordance index (C-index) and calibration curves.

Ethics Approval

This study, which will be conducted according to the Declaration of Helsinki, has been approved by the Medical Science Research Ethics Committee of the Peking University Third Hospital (IRB00006761-M2021085) after a careful audit of the design and content.

Informed Consent and Funding

We will fully inform the patients of the purpose and procedures of this study, as well as their obligations and potential costs and risks. An informed consent form has been drafted and will be signed voluntarily by each participant.

This study is a self-organized project and receives no financial support or funding from any commercial entity. Therefore, conduct of the study, data processing, and interpretation of the results will not be influenced by any commercial entity.

Results

Study design, ethical review, and research registration have been completed. Enrollment commenced in June 2022, and enrolled patients are being visited regularly. Patient enrollment

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is expected to be completed by June 2027, and the study results will be submitted for publication in early 2029.

Discussion

Expected Findings

We anticipate that the findings of our cohort study will support the use of a surgical treatment strategy for patients with SMLC. Although we understand that a combination of different antitumor therapies, namely comprehensive treatment, is recommended for patients with SMLC, there is no consensus or established guideline on how to practice it. Our study aims to explore surgery-based comprehensive treatment for patients with SMLC. Through this study, we aim to validate our proposed synchronized schedule for a multimodality therapy and eventually hope to establish a survival prediction model.

Previous Studies

Fundamentally, the primary goals of surgery are to restore spinal stability, relieve pain, and decompress tumor mass squeezing of the spinal cord, if any. Yao et al [20] reviewed studies on spinal metastasis and found that surgery could significantly improve neurological function and quality of life, even for patients with advanced lung cancer. However, we have not yet gained firm evidence on the impact of surgery on patients' survival, though many papers have reported favorable postoperation outcomes. Truong et al [17] recruited patients with SMLC undergoing surgery and found that 14 (16%) out of 87 patients survived beyond 12 months. Chen et al [23] reported the median survival of their cohort to be 12 months; patients undergoing excisional surgery had a longer survival time than those with palliative surgery. Contrarily, in a systematic review by Armstrong et al [21], the authors reported unfavorable outcomes for surgical intervention, of which a shorter median OS was found in the surgical group compared to the nonsurgical group (7.5 months vs 8.5 months). This result was echoed in Amelot et al's [24] study. These authors concluded that survival of SMLC depends merely on genotype and neurological and personal status, and scarcely on surgical resection. In the past decade, the combination of separation surgery and high-dose hypofractionated SBRT has emerged as an effective option for spinal metastasis, including SMLC [18]. The core principle of this procedure is to circumferentially remove the tumor mass encasing the spinal cord and create a safe zone between the cord and the tumor (≥3mm) for the subsequent delivery of radiation treatment [9,25,26].

As our understanding of the molecular biology of lung cancer increases, many mutated targets are being identified, including the epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase, ROS1, BRAF V600E mutation, etc [6,7,27,28]. Targeted drugs can act directly on these specific mutations and diminish tumor cells. Dohzono et al [29] compared the median OS of patients with SMLC receiving or not receiving EGFR tyrosine kinase inhibitors and found the former group enjoyed a longer OS period (21.4 months vs 6.1 months). In recent years, the application of some immunotherapeutic drugs has proven to be effective [7]. The concept of immunotherapy is to introduce specific blockers to inhibit some immunological signaling paths that are related to the development and metastasis of tumors. Currently, anti-PD-1 and anti-PD-L1 antibodies have been recognized as the choice of care for some advanced lung cancers after the failure of first-line cytotoxic therapy [30]. Borghaei et al [28] found that the median OS period of PD-L1(+) patients who received specific targeted blockers was longer than that of PD-L1(–) patients (17.7 months vs 10.5 months). Furthermore, systematic use of bone-targeted agents (eg, bisphosphonates and denosumab) has significantly reduced devastating spinal-related events, such as paralysis and loss of self-care ability [31].

Strengths and Limitations

The main strength of our study is that it is the first research project to examine the feasibility and outcomes of synchronized adjuvant therapies after surgical intervention for SMLC in a prospective cohort and using a more scientific methodology. This methodological merit will strongly empower the justification for using positive yet invasive treatment modalities instead of conventional palliative care in patients with SMLC. Second, for the purpose of rapid recovery, we are starting rehabilitative intervention at an early stage after surgery. In addition, we recognize the importance of starting adjuvant therapies early after surgery, and this practice will be implemented and examined in our clinical trial.

There are some potential biases in this study that might compromise the reliability and accuracy of the results, but we have designed some solutions to reduce bias. First, though it is difficult to blind the intervention providers and patients, outcome assessors and data processors will be blinded. Second, during the follow-ups, we will encourage face-to-face interviews, but online interviews will also be accepted, considering the possible emergence of scenarios like a COVID-19 surge, in order to reduce the rate of dropout.

Conclusions

We present the protocol for a prospective cohort study of patients with SMLC. Through this study, we will explore the outcomes of surgery-based comprehensive treatment. In addition, we will also investigate prognostic factors of SMLC and provide references for peer surgeons.

Acknowledgments

This study was funded by the National Natural Science Foundation of China (82172395).

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Data Availability

The data sets generated during and/or analyzed during this study will be available from the corresponding author upon reasonable request.

Authors' Contributions

PH and SZ contributed equally and share the first authorship. FW provided the original concept of the study. PH, SZ, and FW designed the study. PH, SZ, XL, and HC were involved in data collection, follow-up with patients, and statistical analysis. PH and SZ drafted the manuscript. FW and HC critically revised the manuscript for important intellectual content and approved the final version of the manuscript. All authors have read and approved the final manuscript. FW and HC are the study guarantors.

Conflicts of Interest

None declared.

Multimedia Appendix 1
The visit timeline and list of tasks.
[DOCX File , 18 KB - resprot_v12i1e38273_app1.docx]

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Abbreviations

ASIA: American Spinal Injury Association
C-index: concordance index
ECOG: Eastern Cooperative Oncology Group
EGFR: epidermal growth factor receptor
KPS: Karnofsky Performance Scale

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OS: overall survival
SBRT: stereotactic body radiotherapy
SMLC: spinal metastases of lung cancer
VAS: visual analogue scale

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Protocol

Voice-Based Screening for SARS-CoV-2 Exposure in Cardiovascular Clinics (VOICE-COVID-19-II): Protocol for a Randomized Controlled Trial

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Related Article:

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Abstract

Background: The COVID-19 pandemic has disrupted the health care system, limiting health care resources such as the availability of health care professionals, patient monitoring, contact tracing, and continuous surveillance. As a result of this significant burden, digital tools have become an important asset in increasing the efficiency of patient care delivery. Digital tools can help support health care institutions by tracking transmission of the virus, aiding in the screening process, and providing telemedicine support. However, digital health tools face challenges associated with barriers to accessibility, efficiency, and privacy-related ethical issues.

Objective: This paper describes the study design of an open-label, noninterventional, crossover, randomized controlled trial aimed at assessing whether interactive voice response systems can screen for SARS-CoV-2 in patients as accurately as standard screening done by people. The study aims to assess the concordance and interrater reliability of symptom screening done by Amazon Alexa compared to manual screening done by research coordinators. The perceived level of comfort of patients when interacting with voice response systems and their personal experience will also be evaluated.

Methods: A total of 52 patients visiting the heart failure clinic at the Royal Victoria Hospital of the McGill University Health Center, in Montreal, Quebec, will be recruited. Patients will be randomly assigned to first be screened for symptoms of SARS-CoV-2 either digitally, by Amazon Alexa, or manually, by the research coordinator. Participants will subsequently be crossed over and screened either digitally or manually. The clinical setup includes an Amazon Echo Show, a tablet, and an uninterrupted power supply mounted on a mobile cart. The primary end point will be the interrater reliability on the accuracy of randomized screening data performed by Amazon Alexa versus research coordinators. The secondary end point will be the perceived level of comfort and app engagement of patients as assessed using 5-point Likert scales and binary mode responses.

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Results: Data collection started in May 2021 and is expected to be completed in fall 2022. Data analysis is expected to be completed in early 2023.

Conclusions: The use of voice-based assistants could improve the provision of health services and reduce the burden on health care personnel. Demonstrating a high interrater reliability between Amazon Alexa and health care coordinators may serve future digital tools to streamline the screening and delivery of care in the context of other conditions and clinical settings. The COVID-19 pandemic occurs during the first digital era using digital tools such as Amazon Alexa for disease screening, and it represents an opportunity to implement such technology in health care institutions in the long term.

Trial Registration: ClinicalTrials.gov NCT04508972; https://clinicaltrials.gov/ct2/show/NCT04508972

International Registered Report Identifier (IRRID): DERR1-10.2196/41209

(JMIR Res Protoc 2023;12:e41209) doi:10.2196/41209

KEYWORDS

voice-based technologies; Amazon; Alexa; SARS-CoV-2; COVID-19; digital screening

Introduction

The COVID-19 pandemic has led to over 551,000,000 cases and 6,300,000 deaths across the world [1]. This high rate of mortality can be partly attributed to an aging population and the fact that comorbidities such as cardiovascular disease significantly increase the risk of death. As a consequence of COVID-19's infectiousness and high rate of mortality, the pandemic has exerted a significant pressure on health care resources such as the availability of health care professionals and their services [2]. As a result of this pressure, telemedicine and artificial intelligence (AI) technologies have proliferated to increase the efficiency of health care and address the unmet needs of a strained health care system [3]. Indeed, the rapid adoption of digital technology in health care delivery has increased as a result of the ongoing global digitalization [4]. For example, programs such as chatbots have gained popularity in promoting COVID-19 vaccination, and telemedicine-based health care delivery has become a patient-accepted and sustained addition to ambulatory care [5-7].

AI is a technology that enable machines to comprehend, act, and learn by simulating human-like intelligence. Machines and computer applications using AI can distinguish, classify, and retrieve information via algorithmic training [8]. These technologies are beneficial as they can be used in health care systems for intelligent screening, thus limiting contact between health care workers and patients. Additionally, intelligent screening systems such as interactive voice response systems have the potential to help control the spread of COVID-19 by streamlining patient monitoring, contact tracing, and continuous surveillance. However, a potential limitation of telemedicine and AI technologies is the potential for inaccurate data capture due to the absence of face-to-face communication. Telemedicine and AI technologies that use interactive voice response systems, such as Amazon Alexa, have been shown to be able to facilitate patient screening within a hospital environment [9]. In fact, previous research has demonstrated good agreement and high interrater reliability (IRR) between Amazon Alexa and health care providers [10]. However, such research has been primarily observational, resulting in a high potential for risk of bias from the priming effect, which can occur when an exposure to certain screening strategy influences responses to a subsequent one. In addition, it is unclear how such technologies perform when interacting with patients who are older and have multiple comorbidities such as those with heart failure (HF) [11]. Additional knowledge gaps include questions related to ethical and privacy concerns of patients exposed to digital tools [12].

To address this knowledge gap, we aim to conduct a two arm, crossover, randomized controlled trial to evaluate the accuracy of data capture by Amazon Alexa versus health care providers in the context of COVID-19 screening. In addition, patient-centric decision-making and concerns surrounding the use of such interactive voice response systems will be evaluated via Likert scales in a postscreening survey.

Methods

Overview

The study presents no more than minimal risk of harm to participants and involves no procedures for which written consent is required. All collected data will be anonymous, and all participants will be deidentified and given an identification number. No compensation will be offered to the participants.

Study Design and Setting

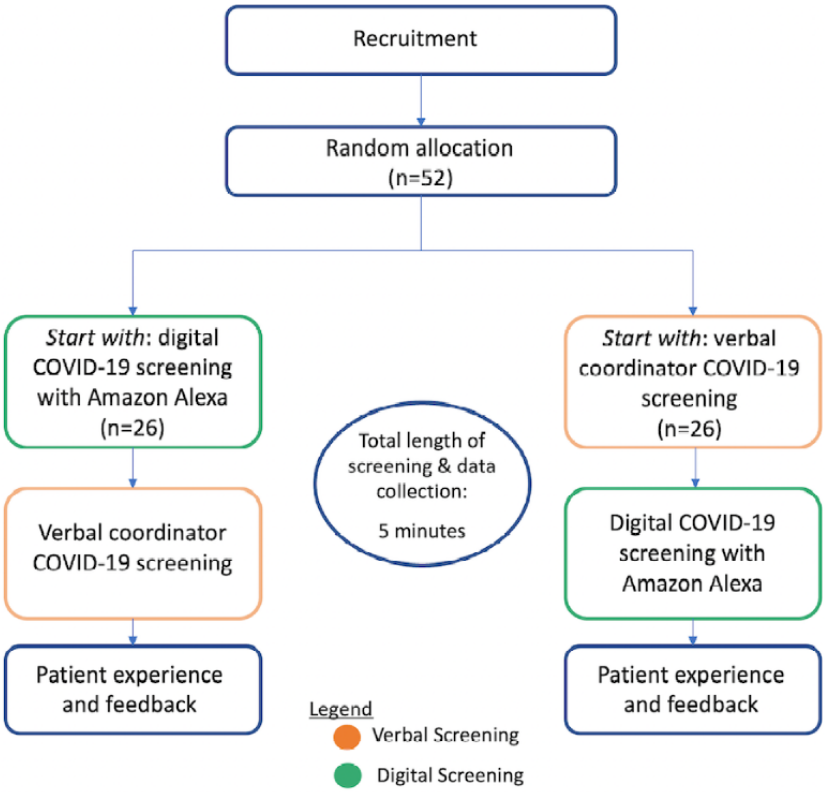
The VOICE-COVID-19-II study is designed as an open-label, noninterventional, crossover, randomized controlled trial comparing the accuracy of data capture by Amazon Alexa versus health care providers in the context of SARS-CoV-2 screening. Patients visiting an HF clinic at the Royal Victoria Hospital (RVH) of the McGill University Health Center (MUHC), in Montreal, Quebec, will be eligible for inclusion. In total, 52 participants will be recruited at the RVH HF clinic. Patients will be randomized to first be screened for symptoms of SARS-CoV-2 by either Amazon Alexa or the research coordinator; participants will then subsequently cross over and be screened by either Amazon Alexa or the research coordinator. Each patient's responses to both the Amazon Alexa– and research coordinator–administered survey will be compared.

The order of screening will be determined randomly by 1:1 block randomization. A flowchart of the study is shown in Figure 1. The Amazon device will not record any personal health information nor health data. After the completion of the SARS-CoV-2 screening, a survey will be presented by the coordinator to patients to assess their perceived user preference

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and Alexa software application engagement. The postscreening survey will evaluate the sense of privacy and data safety concerns regarding the use of digital screening, as well as the interest of patients in receiving voice response systems at home, experience with voice response systems, and interest for digital health care aid based on cohort demographics.

Figure 1. Consolidated Standards of Reporting Trials (CONSORT) diagram of the study.



Eligibility Criteria

Patients and employees aged older than 18 years at the RVH HF clinic will be eligible for inclusion. Individuals of all sexes, races, and ethnicities will be eligible to participate in the study. Exclusion criteria include inability to speak English or French and inability to interact with the device as defined by severe speaking impediments, hearing loss, and neurological problems.

Ethics Approval

This study was approved by and received a waiver of documentation of consent from the institutional Research Ethics Board (REB; approval 2020-6583) at the MUHC. Any modification to the protocol will be reported to the REB (Multimedia Appendix 1).

Device Used

The screening device that will be used is the Amazon Echo Show 8. With Amazon Web Services, an Alexa Skill will be developed using the Amazon Alexa Developer Kit. An Alexa Skill is an interactive voice interface that allows users to interact with a device, hands-free. Skills are based on vocal interaction models that help Alexa determine a user's request. The voice algorithm is first based on automatic speech recognition (ASR), followed by natural language understanding (NLU). ASR is speech recognition software that converts spoken words in text. ASR helps detect audio waveform patterns, matching each waveform with sounds from a given language (English or French for this trial). However, because vocal intonations and inflections vary widely, NLU is used for the rearrangement of spoken data into a computer-readable format. NLU processes the request by decrypting the ASR-converted message. NLU interprets the input, extracts the data, and restructures it so that machines may understand and analyze it. Together, this allows for human-computer interaction, allowing devices to understand commands without the syntax of computer languages.

In this study, the Amazon Echo 8 will be used to screen patients for SARS-CoV-2 through a series of questions. The Alexa Skill built for this study is a predetermined sequence of screening questions triggered by a vocal request. Requests include answering a question by "yes" or "no," stating numbers (subject's age and ID number), etc. To activate the SARS-CoV-2 screening process, a prespecified activating utterance is programmed: "Alexa, Clinic Visit." Each response to a question act as a trigger for the next question. The questions are based on Health Canada recommendations and clinical consultations and will be regularly updated with new guidelines and approved vaccines. The skill will be available in both French and English. Therefore, patients will be able to choose their language of preference and interact with the device in the most effective way. The screening questions used for this study are available in Table 1. No personal health data will be recorded by the Amazon Echo 8.

Alexa will be used to collect and transfer data to secure servers owned by the principal investigator. The virtual servers are located in Canada and are protected behind a secure firewall. These servers undergo daily backups of the data in case of

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corruption. No personal health care information will be stored on these servers. Furthermore, a log will be kept of the IP addresses logging on the server.

Table 1. COVID-19 screening questions.

Screening questionnaire (English)	Response type
1. Welcome to check-in assist, *bienvenue dans* check-in assist. To continue in English, say English. *Pour continuer en français, dites français.*	Binary mode (English/French)
2. We can help you see if you have symptoms of the COVID-19 virus. What is your participant number?	Numbers
3. Do you work in the hospital?	Binary mode (Yes/No)
4. What is the reason for your visit? You can say appointment, visitor, delivery, pick-up or other.	Predetermined options
5. Have you traveled outside of Canada in the last 14 days?	Binary mode (Yes/No)
6. Have you been in close contact with a confirmed case of COVID-19 without protective equipment?	Binary mode (Yes/No)
7. Do you currently have any of the following symptoms: fever, runny nose, sore throat, or diarrhea?	Binary mode (Yes/No)

Recruitment

Participant recruitment will be conducted in teams of 2 bilingual coordinators. A relative degree of quietude will be exercised to avoid issues of device communication during the digital screening portion of this study. Consequently, recruitment will be done in physicians' offices when patients with HF are either waiting for their appointment or have completed their clinic visit. Patients will undergo the screening process in a designated office to ensure privacy.

During recruitment, the number of patients who accepted or refused to participate will also be recorded. At the beginning of every HF clinic, medical staff and physicians will be alerted of the presence of research coordinators on site. The team will obtain consent from the physicians on duty to collaborate with the patients in their offices. The Amazon Echo will then be plugged into the fully charged uninterrupted power supply (UPS) and connected to the Wi-Fi. Both the tablet and the Echo device will be configured, and the activation code will be spoken to verify if the Alexa Skill is still responding and functional.

Participants meeting the eligibility criteria will undergo SARS-CoV-2 screening by both Amazon Alexa and a research coordinator in random order. No personal health information or health data will be collected through the Alexa device. Verbal informed consent forms are approved by the REB. If the participant is eligible and informed consent has been obtained, past medical history data will be collected to analyze the study's demographics. Participants will be informed that enrollment in the study is on a voluntary basis and that withdrawal from the study is possible at any stage. Withdrawal of consent will not affect subsequent medical treatment of patients nor their relationship with the treating physician.

To be able to move efficiently across the clinic, the clinical setup consisting of a tablet, the Amazon Echo, and a UPS on a mobile cart. A tablet will be used for Research Electronic Data Capture (REDCap) access, where randomization, coordinator screening, and patient feedback will be recorded. REDCap is a secure web application for building and managing online surveys and databases. Additionally, a UPS will be used to keep the Amazon Echo continuously powered. This will be done to avoid the reconfiguration period that occurs each time after the Amazon Echo device is powered off. The UPS used in this study will be a Schneider Electric 600 Volt-Amp.

Participants will remain 6 feet (1.83 m) away from the Amazon Echo. The 3 devices (Echo, tablet, and UPS) will be cleaned with bleach-based wipes in between every participant. The duration of the screening process is estimated to be 5 minutes.

Data Collection

Patient recruitment and data collection will be conducted at the site of recruitment. Data related to the trial will be anonymized and recorded in a coded, password-protected digital file behind the coordinating center's institution firewall. Only the principal investigator will have access to the code. All the information collected will remain confidential to the extent required and provided by law. The collected data will be kept for 25 years after the end of the study before being destroyed. There will be no data monitoring committee in this study as no therapeutic intervention is involved. Open access to the manuscript will not be provided.

Randomization and Blinding

The order of screening is randomized as this study is a crossover trial with a higher potential for risk of bias from the priming effect. Participants will be randomly assigned to either start with the digital SARS-CoV-2 screening or with the coordinator screening. Randomization will be done in a 1:1 ratio using a randomization procedure generated by REDCap. Both participants and coordinators involved will not be blinded to the allocation process.

Outcome Measures

The primary outcome of the study will be the concordance of screening for symptoms of SARS-CoV-2 carried out by the Amazon Alexa device compared with the manual screening carried out by a trained research coordinator. The secondary outcome will be a 5-point Likert scale and binary mode responses evaluating patients' perceived comfort interacting with Alexa. The above outcomes will be measured as part of the postscreening survey carried out by the research coordinator at the end of the SARS-CoV-2 symptom-screening process and inputted into a secure web application form. The ease of the Amazon Alexa screening process, privacy and data safety concerns, interest in digital health care at home, and willingness

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to be vaccinated will be asked with a standard 5-point Likert scale. The relationship between the participant's vaccine status and the answers regarding the participant's comfort with digital health use, as well as the relationship between interest in voice response systems use at home and cohort demographics (eg, gender, age, and relevant medical history) will be determined by a linear regression model. Finally, any technical issues will be noted manually, on the REDCap platform, as well as any comments, remarks, and questions made by the research participants. These notes will be taken into consideration in the evaluation of the efficiency and accessibility of the digital Amazon screening. However, it is important to note that given that the survey questions are clear and objective, there is little risk of bias that in-person observations will affect the internal validity of the study's results.

Statistical Analysis

The coprimary end points for this study relate to the IRR on the accuracy of the randomized screening data from Amazon Alexa compared to coordinator data as the comparator. IRR will be evaluated using simple and weighted Cohen κ statistics (where possible) and percentage concordance between responses obtained from Amazon Alexa and research coordinators. The calculated κ scores will be compared between the 2 study arms for each screening question. In addition, linear mixed-effects model will be used to investigate differences in the 2 study arms, adjusting for the fixed effect of the screening order and the random effect of correlated observations in the demographic data. Furthermore, postscreening survey questions will be examined and presented on a Likert scale. This study will aim to recruit at least 52 participants, with minimally 26 participants in each study arm. The estimation of the sample size is based on the *kappaSize* package in R (version 4.1.2; R Foundation for Statistical Computing), with a 1-tailed test null κ score of 0.6 assuming a proportion of positive ratings of 0.9 and a preliminary κ score of 0.9 [13,14]. The sample size will also be adjusted with the power analysis of one-way ANOVA and the chi-square test to obtain a power of 0.8, accounting for a large effect size of above 0.4 and a significance level of .05. The demographic data will be presented in the baseline characteristics table, with categorical variables as counts (percentages) and continuous variables as medians and interquartile ranges.

Intervention and Comparator

Participants allocated to the intervention group will initially undergo screening by the Amazon Alexa device for symptoms of SARS-CoV-2 (screening questions in Table 1). All questions, excluding the first question to determine the preferred language, allow for the collection of responses that serve as epidemiological or clinical risk factors that predict the risk of having an infection with SARS-CoV-2. These participants will then undergo the same screening process, but by a trained research coordinator. Meanwhile, patients allocated initially to the comparator group will first undergo screening by a trained research coordinator, followed by digital screening by the Amazon Alexa device.

At the end of this process, all participants will undergo a postscreening survey (Table 2) conducted by a trained research coordinator. The goal of this postscreening survey is to evaluate user preference, concerns about privacy and data storage, and the Alexa software application engagement. The survey will ask 11 questions about their screening experience and their perception of voice-based technology. Questions 1, 2, and 6 allow specific evaluation for participants comfort with utilizing technology. More specifically, answers to these questions could serve as markers for the device's perceived functionality and reliability as well as possibility for remote screening. Questions 3, 4, and 5 allow the collection of responses to assess the patient's perception relative to data security. Questions 7 and 8 measure the participant's subjective perception of the device's effectiveness. Questions 9, 10, and 11 assess the overall ease of use of the device.

Other variables will be collected in the postscreening phase of the study such as SARS-CoV-2 vaccine status, assigned sex at birth, and duration of digital screening. These variables will be utilized for stratification-based statistical analysis on the answers obtained in the postscreening survey.

Prespecified subgroups of interest include those by language (French and English), sex, and age.

Table 2. Postscreening survey questionnaire.

Postscreening survey questions	Response type
1. Did you feel comfortable speaking into the Amazon Alexa device?	5-point Likert scale
2. Have you used this type of device before or do you own this type of device?	Binary mode
3. Would you feel comfortable being screened for symptoms using the Amazon Alexa device?	Binary mode
4. Do you have any concerns about privacy or data safety?	5-point Likert scale
5. Do you feel your data would be kept secure by such a device?	5-point Likert scale
6. Can you see yourself using such a device at home to assist with any healthcare needs?	5-point Likert scale
7. Did you feel the check-in asked the screening questions appropriately?	5-point Likert scale
8. Did you feel the check-in minimized your chance of contracting COVID-19?	5-point Likert scale
9. Was the language easy to understand?	5-point Likert scale
10. Was the check-in easy to use?	5-point Likert scale
11. How would you rate this check-in overall?	5-point Likert scale

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Results

Funding for the VOICE-COVID-19-II trial was obtained in May 2021. The recruitment of participants for the VOICE-COVID-19-II trial started in May 2021, with simultaneous acquisition of data by the Amazon Echo Show 8 device, and is expected to be completed in fall 2022. Data analysis is expected to be completed in early 2023. Subsequently, trial results and analysis are expected to be published by mid-2023.

Discussion

Expected Findings

The study aims to test the concordance of screening for symptoms of SARS-CoV-2 done by Amazon Alexa compared to manual screening done by research coordinators. It also aims to evaluate the perceived comfort of patients when interacting with Alexa. Voice-based technology has the potential to improve clinical treatment for patients affected by SARS-CoV-2 by optimizing rapid and accurate data acquisition and can be extended to allow for screening of other conditions. Before implementing this interactive voice response system, the IRR of the program screening for the virus and overall patient experience, compared to the standard person-to-person screening, must be evaluated.

With standard methods of screening for symptoms and exposures, there is an increased burden on health care professionals that remains strenuous in the context of the pandemic. The use of commercially available digital tools to aid in screening for SARS-CoV-2 symptoms may be instrumental in reducing the burden on health care personnel, as well as minimizing opportunistic spread of disease via person-to-person contact [15].

A number of approaches using available digital health technologies to screen for SARS-CoV-2 symptoms are being explored, including automated text messaging and smartphone apps [16,17]. However, interactive voice response systems remain relatively unexplored. A previous study has evaluated the quality of health information dissemination on cancer screening provided by voice assistants, such as Siri, Alexa, and Cortana, but did not evaluate these devices' ability to screen for cancer [18]. One study evaluated the quality of speech intelligibility of Amazon Alexa and Google Home by providing individuals with intellectual disabilities with smart speaker devices [19]. Another recent study screened patients with major depressive disorder with the Patient Health Questionnaire 9 via randomizing screening with Amazon Alexa compared to manual screening [20]. However, manual screening was done through paper format, and the time between digital and manual screening was 1 month. The potential ease of use of voice-based commands, which, when optimized, would better simulate standard person-to-person interactions compared to requiring digital input, could prove to be optimal in situations where the use of electronic recording of data may be difficult, such as with older participants. Furthermore, the use of Amazon Alexa, a voice response system available at home and other nonclinical environments, could provide additional advantages in terms of remote data collection. A reliable method of rapid acquisition of medical data easily accessible to patients could significantly facilitate future trials and personalizing health care delivery. Similar to other remote digital technology, such as Google Home or Apple's Siri, voice response systems have potential for great scalability for larger participant numbers, given its commercial nature, cloud-based data collection, and easy access.

However, the increasing popularity of remote screening tools during the SARS-CoV-2 pandemic revealed a need for objective measures of the reliability of the data acquired by these tools. In particular, the previous phase of this study did not directly address the risk of bias in the virtual screening question answers when presented with the comparator set of in-person questions beforehand. The strengths of this study are founded upon its design to isolate a verified measure of the accuracy of the screening method and the use of commercial interactive voice response systems. This study aims to examine the reliability of the data acquired by the device while accounting for the priming bias inherent in previous similar studies, where participants would be affected by choices presented by the in-person set of screening questions used as the comparator. In addition, the Amazon Alexa program used in the skill set is based on a widely accessible commercial device designed for home use, which would provide a reasonable simulation of the technology that would be used for widespread public screening.

Limitations

The study does have some limitations. Although the sample size may be adequate in detecting IRR between the virtual screening program and the standard in-person screening questionnaire, it is too small to detect the effectiveness of the questionnaire in triaging patients exposed to COVID-19. While the use a more extensive COVID-19 questionnaire may have increased the amount of data available for analysis, a shorter questionnaire developed with clinical experts was used to enhance patient recruitment. Given that the focus of this study was the accuracy of information obtained remotely compared to an in-person standard and not specifically to screen for SARS-CoV-2, insight into its capability as a screening measure was limited. However, regarding the diagnostic and screening accuracy of voice-based digital screening for COVID-19, a larger-scale study utilizing gold standard diagnostic assays (ie, reverse transcription polymerase chain reaction) would be required. Should a survey evaluating the accuracy of the questionnaire itself be proven to be effective, interactive voice response systems, such as Amazon Alexa, could provide users with a notification for their risk of a positive diagnosis and whether testing is encouraged given a posttest likelihood of illness.

In terms of the questionnaire, it is possible that some questions regarding personal contact with COVID-19 will have some interperson variability secondary to question interpretation. However, given the objective nature of the COVID-19 questionnaire as well as individuals' lived experiences with the pandemic, the overall potential for risk of bias is low. Furthermore, although the study and questionnaire used are limited to recording answers in a 5-point Likert scale and a binary response of yes or no, speech AI is becoming increasingly

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sophisticated, with improved speech recognition and more flexible conversations in newly developing propriety speech AI. This could prove to be a unique strength of voice-based screening in future health care delivery, with a possibility of more personalized interactions with patients, nuanced screening questions, and more efficient information dissemination to patients in the form of an interactive question-and-answer program. As remote data collection develops over time, there will be new potential avenues of medical AI research for personalized health care delivery with intelligent voice-based assistants.

Conclusion

In conclusion, the second phase of the VOICE-COVID-19-II randomized controlled trial aims to evaluate the accuracy of data capture by interactive voice response systems, such as Amazon Alexa, compared to health care providers as the baseline. If the study proves to be effective, it could open additional avenues of research and would provide a novel viewpoint on implementing digital health in the context of the pandemic, allowing for screening in both hospitals and at home.

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Data Availability

In accordance with the approval granted for this study by the McGill Research Ethics Board, the data files will be stored securely and protected by Canadian virtual servers and a secure firewall. Patient level data will not be available. Request for the coding used in the Alexa Skill can be made available upon reasonable request to the corresponding author.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist.
[DOCX File , 22 KB - resprot_v12i1e41209_app1.docx]

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Abbreviations

AI: artificial intelligence
ASR: automatic speech recognition
HF: heart failure
IRR: interrater reliability
MUHC: McGill University Health Center
NLU: natural language understanding
REDCap: Research Electronic Data Capture
REB: Research Ethics Board
RVH: Royal Victoria Hospital
UPS: uninterrupted power supply

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Protocol

A Logical Framework (MYGERYFS) for Hospital Foodservice to Prevent Malnutrition Among Geriatric Patients in Hospitals, Malaysia: Protocol for a Feasibility Study

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Abstract

Background: Geriatric malnutrition in hospitals is common and can be affected by many things, including poor satisfaction toward hospital foodservice. Hospital foodservice plays an important role in a patient's recovery process by providing adequate nutrients. On top of that, patients' foodservice satisfaction can easily be afflicted by the quality of food served and the overall foodservice experience. Furthermore, malnutrition can occur from poor foodservice quality, especially among geriatric patients.

Objective: This study aims to assess the effectiveness of the Malaysian Geriatric Patients' Hospital Foodservice Protocol (MYGERYFS).

Methods: The protocol comprises 3 phases. Phase One is a cross-sectional study that took place at public hospitals with geriatric wards in the Klang Valley. Univariate data from Phase One were analyzed descriptively. Pearson correlation and chi-square were conducted to find factors associated with foodservice satisfaction. Phase Two involves the collaboration of health care professionals in the geriatric field. In Phase Three, a feasibility study will be conducted to determine the feasibility of the MYGERYFS protocol in a hospital among 60 geriatric patients. These patients will be randomized into control and intervention groups, respectively. Intervention care will be done to ensure the safety of the protocol.

Results: Data collection for Phase One of the study has been completed. A total of 233 geriatric respondents with the mean age of 71.39 (SD 7.99) years were gathered. Approximately 51.5% (n=120) of the respondents were female, while 48.5% (n=113) were male, with a mean BMI of 24.84 (SD 6.05) kg/m2. Their mean energy and protein intakes were 1006.20 kcal (SD 462.03 kcal) and 42.60 (SD 22.20) grams, respectively. Based on the Mini Nutritional Assessment, older patients who scored 12-14 (normal) were 27.9% (n=65), those who scored 8-11 (at risk) were 54.9% (n=128), and those who scored 0-7, which is the lowest (malnutrition), were 17.2% (n=40) of the study population. Hence, most patients were at risk of malnutrition. Although a majority of the patients claimed to have good foodservice satisfaction 26.2% (n=61), they also experienced at least 3 barriers during mealtimes. It was found that dietary intake and mealtime barriers were significantly associated with the respondent's foodservice satisfaction. Data for Phase Two and Phase Three are yet to be collected and analyzed.

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Conclusions: This study protocol could potentially benefit the hospital foodservice system and aid in improving geriatric nutritional status.

Trial Registration: ClinicalTrials.gov NCT04858165; https://clinicaltrials.gov/ct2/show/NCT04858165

International Registered Report Identifier (IRRID): RR1-10.2196/42496

(JMIR Res Protoc 2023;12:e42496) doi:10.2196/42496

KEYWORDS

hospital foodservice satisfaction; hospital meals satisfaction; elderly; nutrition; malnutrition in elderly; malnutrition; geriatric; patient; prevention; nutrient; feasibility

Introduction

"Older people" is defined as individuals aged 65 years or older who are deemed suitable to receive the national pension plan [1]. According to Orimo et al [1], the range of older persons can be divided into two categories. They are (1) "early elderly" (individuals aged 65-74 years) and (2) "late elderly" (individuals aged ≥75 years). In Malaysia, "elderly" is recognized as those aged 60 years and older, due to its policy and program development purposes [2]. The increasing trend of the aging population has shifted the world's demographic patterns [3]. As a developing country, Malaysia is not spared from this phenomenon [4]. The recent National Health Morbidity Survey (2018) estimated that the country's older population is at 2.3 million (6.3% of the total population) and is predicted to double within 23 years [2]. The aging process often relates to health complications [2]. Apart from the presence of comorbidities, malnutrition in older people is also common [5].

The reasons for having compromised nutritional status among older individuals are changes in physical, cognitive, psychological, and social factors (eg, living alone), as well as having limited income [6]. Other risk factors include the presence of comorbidities [7,8], poor dental status [9], and inadequate dietary intake [7,10,11]; moreover, those living in health care institutions often complain of having poor foodservice experience [12,13]. Older people with malnutrition often find themselves in a state of dependency, having prolonged hospital stays, an increase in infection rate that eventually diminishes their quality of life, and an increase in health care costs and mortality [6,7,14].

There are countless studies investigating malnutrition among hospitalized older individuals, and the prevalence is indisputable. The global prevalence of malnutrition in hospitalized older patients ranges from 12% to 75% [7]. Consistent with the worldwide trend, Malaysia also shows a prevalence of malnutrition that ranges from 21% to 55% among hospitalized geriatric patients, which appears to be a matter of concern [15].

Despite the interventions carried out thus far, the prevalence of malnutrition among geriatric patients is still appalling [16]. Most older people view themselves as healthy, in spite of their sociodemographic status (educational level, income status, and daily living activities) [17]. Despite their healthy self-image, older individuals are still vulnerable to malnutrition due to their frail condition [6]. In addition, of 52% of malnourished older patients, 18% were found to be nutritionally compromised even before admission [18]. Surprisingly, these older adults even believe that having inadequate nutritional intake is normal without realizing the consequences that malnutrition carries [6].

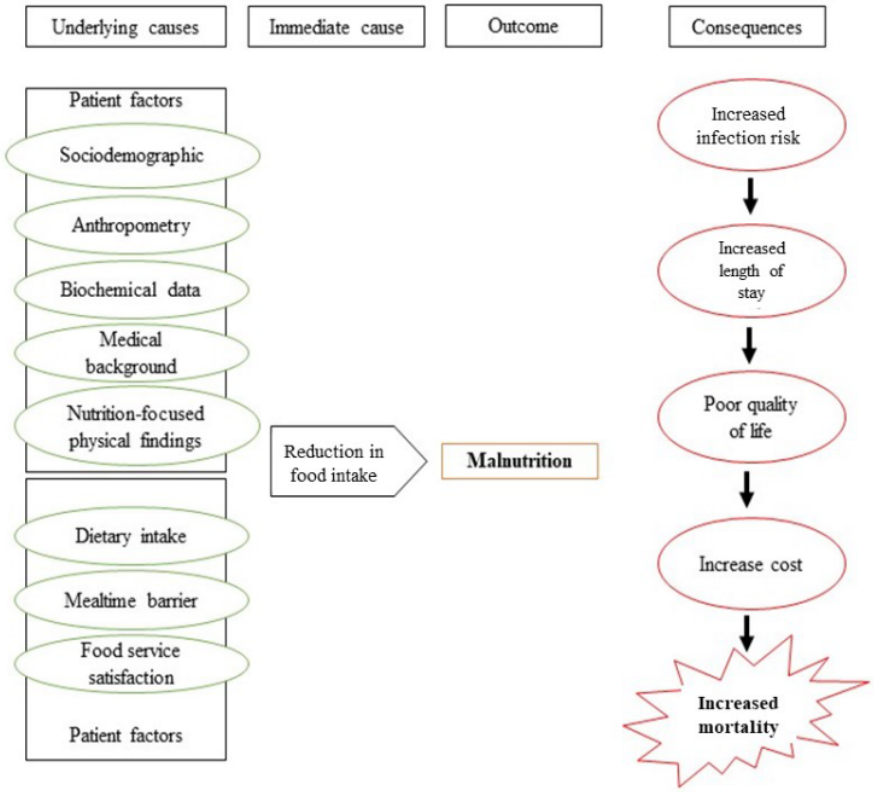
Hospital meal is considered as one of the important components of care. Hospital meals are served not only to facilitate well-being and recovery but also to contribute to the patients' satisfactions on their overall treatment experiences [19]. Looking at the hospital foodservice system, oftentimes the patients' nutritional status is impacted by it. For example, hospital-acquired malnutrition is believed to be caused by the poor quality and appearance of the food and its environment [20]. The same study reported that food quality is found to be the best predictor of patients' overall satisfaction, followed by service quality given by staff. A study in Australia has proven this by introducing a room service model to hospitalized patients. The results showed good upturns in the patients' nutritional intake and satisfaction as well as reduced plate waste and patient meal costs after the method was implemented [21].

Another study reported that patients found it tiring to order and eat their food at specific times [22]. On the contrary, these patients were also sensitive to delays and poor service. Further, the study documented that patients appreciated the presence of nonmedical foodservice staff, but at the same time felt pressured by them. According to a study conducted in a military hospital in Turkey, the patients' satisfaction levels on the hospital's foodservice system showed inconsistency. The results showed that 51.3% evaluated the foodservice quality to be adequate, while 32.4% deemed it was of inadequate quality. Accordingly, the remaining 16.3% stated that they were uncertain [23]. The different spectrum of thoughts by the patients only makes it hard to fathom, thus affecting the ways of intervention in many hospitals' foodservice systems. Therefore, the redesigning of hospital foodservice models may be needed not only to drive toward the improvement of patient satisfaction and cost but also to influence clinical outcomes associated with nutritional intake.

Figure 1 shows the conceptual framework of the causes of malnutrition and its possible consequences. This study aims to develop, implement, and evaluate the effectiveness of a Malaysian Geriatric Patients' Hospital Foodservice Protocol (MYGERYFS) in order to improve both the nutritional status of hospitalized geriatric patients and the quality of the foodservice.

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Figure 1. Conceptual framework of the causes of malnutrition and its consequences.



Methods

Study Design

The MYGERYFS project is a 2 year and 6 months intervention program, conducted among malnourished older individuals with pre- and postintervention to assess the effectiveness of the protocol. The trial comprises the nutritional status of hospitalized geriatric patients aged 60 years and above in 5 public hospitals in the Klang Valley, which are as follows: (1) Hospital Selayang, (2) Hospital Sungai Buloh, (3) Hospital Kuala Lumpur, (4) Hospital Tengku Ampuan Rahimah, and (5) Hospital Pengajar Universiti Putra Malaysia.

The study comprises the following phases: (1) Phase One—a preliminary study that identified the prevalence and factors associated with hospitalized geriatric malnutrition; (2) Phase Two—protocol development with health care professionals; and (3) Phase Three—testing the feasibility of the protocol. The trial has been registered at ClinicalTrials.gov (NCT04858165) on March 30, 2021.

Phase One

The first phase of the MYGERYFS is a cross-sectional study conducted to assess the recent nutritional status of older hospitalized patients and the factors associated. Phase One has been completed and analyzed in August 2022. Using the proportion formula by Cochran (1963) [19], a total of 233 geriatric patients were gathered as samples for this study.

In this phase, the patients or their respective caregivers were interviewed by the researchers. A series of questionnaires that hold information on the patients' sociodemographic and medical background, anthropometry measurements, dietary intake, mealtime barriers, foodservice satisfaction levels, and nutritional statuses were put together. The collected data were assessed and labeled as preliminary data.

Phase Two

Phase Two of the MYGERYFS protocol studies the current feeding practices and opinions of health care professionals. A group of geriatric health experts, specifically geriatricians, nurses, and dietitians, will be invited to review and discuss the preliminary data. Subsequently, the existing clinical procedures will be audited and improved in line with the recent research. The protocol will be finalized in a consensus meeting.

Phase Three

The newly developed protocol will be tested in a single institution. Altogether, 60 geriatric patients will be recruited. These patients will be divided into 2 groups (control and intervention groups). The control group patients will be given usual hospital care, and the intervention group patients will be cared for according to the developed protocol for approximately 3 consecutive days. Dietary recall of 3 days was thought to be better than 24-hour recall or 7-day recall [24]. This is because a single 24-hour recall could lead to overestimation of intake, while a dietary recall of more than 3 days often leads to lower intake as respondents feel burdened to report their intake further, thus omitting their food items altogether [24]. Details on their dietary adequacy and clinical outcomes will be documented. The feasibility and safety of the protocol will be evaluated. The findings will provide fundamental data to develop a foodservice protocol for Malaysian geriatric patients.

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Participants

Ethics Approval

This study was approved by the National Medical Research Register for Phase One (NMRR-20-308-52632) and was reapplied for Phase Three. In Phase One, a written consent form will be sought from all respondents before the study. Permission from each of the hospitals' clinical research centers was obtained before data collection.

Screening of Nutritional Status

Five public hospitals in the Klang Valley were listed and approached for Phase One of the study. These hospitals were purposely selected due to the availability of their geriatric wards. The selected patients will be screened using the Mini Nutritional Assessment Short Form (MNA-SF). The MNA-SF evaluates 5 components of common geriatric problems, which are food intake, weight status, mobility status, presence of psychological problems, and neurological stress level. These components will be scored based on the patients' conditions and are categorized into the following: (1) normal nutritional status (12-14 points), (2) at risk of malnutrition (8-11 points), and (3) malnourished (0-7 points) [25].

Eligibility and Recruitment

Both Phase One and Phase Three of this study shared similar inclusion and exclusion criteria, as mentioned in Textbox 1.

Textbox 1. The summary of the inclusion and exclusion criteria for Phase One and Phase Three of the Malaysian Geriatric Patients' Hospital Foodservice Protocol (MYGERYFS).

Inclusion criteria

- Patients aged 60 years and older
- Able to understand and speak Malay or English or both
- Patients who are on an oral diet or Oral Nutrition Support or both
- Patients who are admitted for more than 48 hours

Exclusion criteria

- Patients with mild dementia or adjustment disorders that are common in geriatric patients
- Critically ill patients
- Patients who are on full enteral or parenteral feeding

Sample Size Calculation

The sample size for Phase One of the study will be calculated using the proportion formula by Cochran (1963) [19]. A total of 233 geriatric patients will be gathered as samples for this study.

Meanwhile, Phase Two will only require the cooperation of health care professionals; thus, no sample size calculation will be calculated.

In Phase Three of the study, 60 geriatric patients will be recruited and divided equally into control and intervention groups. Therefore, a sample of 30 respondents per arm will be required. As suggested by Cohen [25], a sample size of 30 in each arm is needed to detect the differences between groups, which should lead to about a minimum of 80% power in a study.

Randomization and Allocation

Patients in Phase Three of the study will be randomized into control and intervention groups, respectively. To do so, patients will be allocated with the help of a computer-generated random number sequence.

Intervention

Preceding the development of the MYGERYFS protocol, a feasibility study will be conducted during Phase Three. The study will be carried out in a single institution with a total of 60 geriatric patients. These patients will be screened for their eligibility and separated into control and intervention groups, respectively. Those in the control group will receive the usual hospital care, while the other group will experience hospital care according to the developed protocol. Both groups will be observed for their dietary intake for approximately 2 days from the day of the intervention. All of this information will be compared within the 2 groups.

Outcome Measures

Primary Outcome

Nutritional Status

The nutritional statuses of geriatric patients were assessed using the MNA-SF. The MNA-SF evaluates 5 components of common geriatric problems, which are food intake, weight status, mobility status, presence of psychological problems, and neurological stress level. These components were scored based on the patients' conditions and categorized into the following: (1) normal nutritional status (12-14 points), (2) at risk of malnutrition (8-11 points), and (3) malnourished (0-7 points) [25].

Foodservice Satisfaction

The patients' levels of foodservice satisfaction were documented by the validated Acute Care Hospital Foodservice Patient Satisfaction questionnaire by Capra [26] in 2005 via an interviewing method. The questionnaire weighs 4 main foodservice aspects, which are food quality, meal service quality, staff or service issues, and physical environment. The higher the mean score is, the better the results will be [26].

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Dietary Intake

The amount of food consumed by the respondents in 2 days was recorded and analyzed using Nutritionist Pro (version 2.4.1, First Data Bank) [27]. From these data, the patients' energy and protein adequacy was compared against their requirements.

Secondary Outcomes

Anthropometric Measurements

The anthropometric measures considered for this study are as follows:

- Body weight was measured using an electronic scale (digital weighing scale; OMRON HBF-357) according to the standard techniques [28].
- Estimation of weight is done for patients who were unable to stand without assistance using knee height measurement and mid-upper arm circumference. Weight was measured using equations developed by Ross Laboratories [29].
- Height was measured using a stadiometer (SECA height rod) according to the standard techniques [30].
- Estimation of height is done for patients with distinctive conditions (eg, kyphosis, scoliosis) using knee height measurement. Height was calculated using equations developed for older Malaysian people [31].
- BMI was calculated using the following equation: weight in kilograms divided by height in meters squared—weight (kg)/height^2(m^2) [30].

Mealtime Barriers

The patients' mealtime barriers were determined and scored using the Mealtime Audit Tool questionnaire. This questionnaire prioritizes the types of potential barriers during mealtime. Each question is marked with a "Yes" or "No" answer. Scoring for this questionnaire is based on the total "No" responses. This value represents the number of barriers faced by the patients. The higher the "No" responses were, the more barriers were experienced [32].

Statistical Analysis

Data were entered and analyzed using SPSS 25.0 (IBM Corp). In Phase One of the study, descriptive statistics of the continuous data were presented using mean and standard deviation. Meanwhile, categorical data were presented as frequencies and percentages. To analyze the associations of malnutrition, Pearson coefficient correlation and chi-squared test were used. Statistical significance was set at P<.05.

In Phase Two, no analysis will be conducted as it only requires the discussion of health care professionals.

In Phase Three, the descriptive statistics will be presented using mean and standard deviation for continuous data. On the other hand, categorical data will be presented as frequencies and percentages. To compare the control and intervention groups, an independent 2-tailed t test will be used. Statistical significance is set at P<.05.

Results

Phase One of the protocol has already started. A total of 233 older respondents participated in this study. The mean age was 71.39 (SD 7.99) years, where most 51.5% (n=120) of the respondents were female and the rest 48.5% (n=113) were male.

The mean BMI of the older respondents was 24.84 (SD 6.05) kg/m^2. Based on the results showed, most (n=110, 47.2%) participants were classified as underweight, 37.8% (n=88) were normal, and 17.2% (n=40) were either overweight or obese.

The mean energy and protein intakes were 1026.82 kcal (SD 457.66 kcal) and 43.54 (SD 22.66) grams, respectively. The majority of the respondents 70.8% (n=165) had inadequate energy intake (<25-30 kcal/kg). The same trend was shown for their protein intake. Approximately 77.7% (n=181) of them consumed protein below 1.2 g/kg. It was also found that 84.5% (n=197) did not receive oral nutrition support in ward.

The percentage of older patients in hospitals in the Klang Valley who responded to the MNA-SF questionnaire—which was divided into 3 scores of "Normal" (12-14), "At Risk" (8-11), and "Malnutrition" (0-7)—was 27.9% (n=65) normal, 54.9% (n=128) at risk, and 17% (n=40) malnutrition, which is the lowest. Thus, most patients were at risk of malnutrition.

The mean Mealtime Audit Tool score was 3.27 (SD 1.89), showing that the respondents experienced at least 3 barriers during mealtimes. The most common barriers that these patients came across were as follows: (1) respondents were not paid any visits by health care staff midmeal to see if they need anything, (2) respondents were not asked or given other food if they refused to eat their meal, and (3) respondents were not offered to go to the washroom before mealtime. Most of the respondents 74.7% (n=119) experienced good foodservice satisfaction while the other 25.4% (n=59) did not.

Pearson correlation test was done to find the associations between BMI, dietary intake, mealtime barriers, and nutritional status with foodservice satisfaction. According to Table 1, there was no association found between BMI and foodservice satisfaction among hospitalized geriatric patients (r=–0.056, P=.39). As for the dietary intake, both energy (r=0.337, P<.001) and protein (r=0.255, P<.001) were significantly associated with foodservice satisfaction. A statistically significant result was also shown between mealtime barriers and foodservice satisfaction (r=–0.225, P<.01).

A chi-square test was also conducted between nutritional status with foodservice satisfaction. No significant association was found between malnutrition with foodservice satisfaction (χ^2_8=12.778, P=.12).

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Table 1. Pearson correlation between BMI, dietary intake, and mealtime barriers with foodservice satisfaction.

Variables	Foodservice satisfaction statistics	
	r	*P* value
BMI	–0.056	.39
Average energy intake	0.337	<.001[a]
Average protein intake	0.255	<.001[a]
Mealtime barriers	–0.225	.07[a]

[a]Correlation is significant at *P*<.001.

Discussion

Principal Findings

Based on the results, it can be seen that the patients' dietary intake was associated with their foodservice satisfaction. Improvement on protein and energy intake to some extent had improved patients' satisfaction within a short period of hospital stay [26].

Next, having mealtime barriers can also affect the overall foodservice satisfaction. This results negatively in the overall experience of services, including foodservice, even though the differences were not statistically significant [33].

This study has its limitations. Phase One of the study was conducted cross-sectionally, which constrained us from finding its causality. Moreover, the feasibility study that will be done may also have its negative impact. This is because feasibility studies often do not identify new concepts as they are based on assumptions. Thus, clear findings must be analyzed during Phase One, and clear decisions need to be made in Phase Two in order to prove them to be realistic.

For all we know, endless research on geriatric malnutrition has been conducted, and the results remain significantly high. To understand the issue, various factors will be studied and addressed with geriatric malnutrition. Thus, the development of the MYGERYFS is considered an unprecedented approach toward delivering a better health care quality for geriatric patients in hospitals, with an ultimate aim to improve the nutritional status of geriatric patients as well as to reduce further deterioration of nutrient intake among this population.

Besides, with the existence of this protocol, there will be a chance to further enhance public hospitals' foodservice system. The provision of a variety of nutritious meals for these patients is believed to be useful with the protocol as an aide. Each meal served to the patient will be tailored to their specific health conditions.

Another strength of this protocol is the encouragement of providing mealtime assistance to those in need. This modified service may enhance the patients' overall foodservice satisfaction. A collaboration between the health care and the foodservice system to improve the well-being of geriatric patients is imaginable.

Conclusions

In sum, the MYGERYFS protocol is designed to suit the needs of geriatric patients in hospitals. With the help of other health care professionals, we assure that this protocol will be able to minimize geriatric malnutrition and enhance the patients' overall foodservice satisfaction. Should this protocol show positive effects, the strategies included may be of help to other Malaysian older populations as well.

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Authors' Contributions

NO, SIS, SHN, RJ, SR, ZI, BNMY, HSM, HS, and NSM conceived the study design. NO secured the necessary funding and led the overall project. SIS and SHN are the postgraduate students involved in the overall project and were responsible for the writing of the manuscript. ZI, SR, and RJ acted as cosupervisors of the postgraduate students and contributed to critical input. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

MNA-SF: Mini Nutritional Assessment Short Form
MYGERYFS: Malaysian Geriatric Patients' Hospital Protocol

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Protocol

A Communication Partner Training Program Delivered via Telehealth for People Living With Parkinson's (Better Conversations With Parkinson's): Protocol for a Feasibility Study

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Abstract

Background: Parkinson's can impact people's speech, cognition, pragmatics, and language, significantly affecting their conversations with others. The speech and language therapy approach called communication partner training (CPT) is effective for a range of communication difficulties. However, speech and language therapy interventions for people with Parkinson's predominantly focus on impairments, with little provision of CPT for this population. Better Conversations is a CPT approach that involves working with a dyad (the person with the communication difficulty and a conversation partner [CP]) to build conversation skills. It is effective at reducing barriers to conversation, and for some, it significantly increases targeted facilitatory strategies. Some approaches to CPT have been adapted to be delivered via telehealth. This can maximize ecological validity and convenience. Furthermore, telehealth is widely accepted as a delivery method for other interventions for Parkinson's. This study presents the protocol for a pilot feasibility study of a Better Conversations CPT delivered via telehealth to people living with Parkinson's and their CPs, called Better Conversations with Parkinson's (BCP).

Objective: The primary aim is to evaluate the feasibility of the BCP program delivered via telehealth with a treatment group from a collaborating National Health Service (NHS) site to establish for a main trial whether BCP can be delivered as intended in an NHS setting. The aim is to establish: (1) the acceptability of the program for people living with Parkinson's, family members, and speech and language therapists (SLTs); (2) the feasibility of delivering the BCP program; (3) the recruitment and retention rates; (4) a sample size calculation; and (5) the most appropriate primary outcome measure.

Methods: Ethical approval for this study was obtained from London-Central Research Ethics Committee (reference: 22/LO/0332). This case-series feasibility pilot study will recruit 10-12 dyads to ensure 10 complete data sets. Participants will be recruited by a collaborating NHS site located in England. Participants will be involved for 16 weeks (weeks 1-2 preintervention measures, weeks 3-8 intervention, weeks 10-12 postintervention measures, week 16 follow-up interview). Quantitative and qualitative methods will be used to analyze the study data. Speech, communication, and quality of life assessment data will be analyzed statistically to determine a suitably sensitive outcome measure. Descriptive statistics will be used to report on recruitment, attendance, and attrition. Finally, acceptability and feasibility will be evaluated using participant feedback, interviews, and the reflective diary and feedback of the SLT administering the therapy (by the research assistant who is the first author). This data will be analyzed using descriptive statistics and reflexive thematic analysis.

Results: This study was approved for funding from Parkinson's UK. Study recruitment commenced in July 2022. The results of the data analysis are expected to be available by September 2024.

Conclusions: Insights from this study will provide valuable information about the acceptability and feasibility of a remotely delivered Better Conversations CPT approach for people living with Parkinson's and their CPs. An outcome of this study will

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be a manualized BCP program coproduced by people living with Parkinson's, their families, and a group of expert SLTs. The study results will guide the next stages of intervention development.

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KEYWORDS

Parkinson's; conversation; speech and language therapy; communication partner training; speech therapy; language therapy; communication difficulty; conversation skills

Introduction

The Impact of Parkinson's on Speech and Communication

Parkinson's is one of the fastest-growing neurological conditions in the world [1], with a recorded UK prevalence of around 22:10,000 women and 32:10,000 men [2]. Parkinson's is associated with a loss of nerve cells in the substantia nigra, resulting in reduced dopamine. Changes to articulation, prosody, respiration, and voice are well attested. Disruption to communication can also occur because of changes in cognition, language, and pragmatics. Self-perception ratings suggest that around 90% of those living with Parkinson's experience some speech-language changes [3,4], with speech among the top 4 concerns for 38% [3].

Current Speech and Language Therapy Provision

Speech and language therapy interventions for people living with Parkinson's have an established focus on intelligibility and volume and principally address speech impairment [5]. Intervention therefore typically focuses on approaches such as Lee Silverman Voice Treatment [6], which involves teaching people with Parkinson's to recalibrate their volume through intensive speech exercises and can result in substantial improvements to vocal loudness and intelligibility [7]. A total of 85% of people with Parkinson's who have had speech and language therapy feel that it has had a positive effect on communication and swallowing [4]. Those for whom speech and language therapy is not helpful cite reasons such as difficulty maintaining gains in day-to-day conversations; difficulty continuing exercises at home; and that therapy does not tackle all the aspects of communication relevant to them. Yorkston et al [8] similarly report difficulties maintaining therapeutic gains, and that therapy does not always address communication problems of concern, such as conversation and cognition. Suggestions for improvements to speech and language therapy include increased focus on the cognitive demands of speaking and psychosocial aspects of communication [9]. These perspectives are also reflected in the views of speech and language therapists (SLTs), who report feeling less able to address maintenance of therapeutic gains outside of therapy sessions [5] and describe lacking the necessary tools to target interaction or conversation in assessment and intervention with this client group [10].

Communication Partner Training

Communication partner training (CPT) is an umbrella term for a therapy approach that involves working with a person with a communication difficulty and their conversation partner (CP; eg, a health professional, a family member, or a friend they regularly converse with) to improve everyday conversations. CPT is effective for a range of communication difficulties, such as aphasia [11], traumatic brain injury [12], and dementia [13]. Evidence suggests that CPT is effective at improving the knowledge, communication skills, and attitudes of communication partners [11,14-16]. Furthermore, CPT can enhance functional communication, accessibility, and participation for people with communication difficulties [11,16,17]. Common components of CPT programs across communication difficulties include the provision of information; building knowledge (eg, about strategies to enhance communication and negative behaviors to avoid), developing behavioral skills (the practical actions of participants in learning and practicing skills), and skill-building techniques [18].

CPT for People Living With Parkinson's

Despite similarities across CPT programs, individual strategies vary for different etiologies of communication difficulty [18]. Thilakaratne et al [19] carried out a scoping review aiming to describe the assessment methods and interventions used to treat conversations between people with Parkinson's and their partners and to identify gaps in the literature. The authors found only 1 intervention study for people with Parkinson's, which treated conversations by implementing CPT. This multiple case study [20] with 3 dyads suggests that CPT adapted for people living with Parkinson's was well received and that the therapy may work well, although its effectiveness remains to be proven. Thilaraktne et al's [19] scoping review highlights a need for further research implementing CPT for people living with Parkinson's and incorporating a participation-based approach to intervention that involves all communication partners.

The Better Conversations Approach to CPT

Better Conversations is an approach to CPT that aims to help people with communication difficulties have more enjoyable and successful interactions in their everyday lives [21]. Rather than working with solely the person with communication difficulties or their communication partner, it involves both parties, referred to as a dyad, in building conversation skills. The SLT supports a dyad to video-record themselves in natural conversations and uses clips from the videos to help them identify what is working well in conversation (facilitators) and what gets in the way (barriers). The dyad sets individualized personal goals and is supported in practicing chosen strategies in order to build their skills in conversation. Behavior change techniques are targeted at both members of the dyad. The most established Better Conversations program is Better

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Conversations with Aphasia [22], which significantly reduces barriers to conversation at the group level and, for some individuals, significantly increases targeted facilitatory strategies [23]. Previous successful adaptations of Better Conversations include the coproduced Better Conversations with Primary Progressive Aphasia [13]. This has been deemed acceptable and feasible to deliver, and initial pilot data demonstrates promise as a means to improve self-identified communication behaviors between members of the dyad [24].

Telehealth

Telehealth or telemedicine, the "delivery of health care services where distance is a critical factor" [25], can improve access to quality, cost-effective health services. Despite barriers, in particular for those with cognitive and visual impairments [26], telehealth offers advantages, such as removing issues related to cost, travel, and inconvenience for the service user; increasing access to health care; and being able to observe people in their own environment [27,28]. Better Conversations, and CPT in general, has been adapted to a telehealth form of delivery. Beeke et al [29] introduced the term "teleCPT" to mean CPT delivered via videoconferencing technology. In this case study of a person living with primary progressive aphasia and his partner, the authors demonstrate that Better Conversations delivered via videoconferencing is effective, acceptable, and feasible to deliver. Furthermore, teleCPT can maximize the ecological validity and convenience of therapy [29]. Theodoros et al [30] suggest that telerehabilitation has particular potential to improve services for people with Parkinson's: it allows ready access to treatment, it supports the development of self-management skills, and people with Parkinson's express overall satisfaction with and support for telerehabilitation. There is, however, an absence of evidence exploring interaction-focused therapies or CPT delivered via telehealth (teleCPT) to people living with Parkinson's.

Summary

There is demand from people living with Parkinson's for speech and language therapy interventions that address broader aspects of communication beyond speech, involve family members, and consider psychosocial factors. However, there is limited evidence for CPT among people living with Parkinson's. CPT has been effective at improving communication participation for people living with other communication difficulties, and initial research suggests it is acceptable and may be beneficial for people living with Parkinson's [31]. This study presents the protocol for a pilot feasibility study of a Better Conversations CPT for people living with Parkinson's and their CPs, called Better Conversations with Parkinson's (BCP). Telehealth has been chosen as the primary method of delivery for this program due to the high levels of reported acceptability among this client group and its ability to increase access to therapy and support people within their everyday environment.

This feasibility study has been designed in line with Medical Research Council Guidance on developing complex interventions [32]. BCP has been under development through adaptation of existing Better Conversations interventions, identification of key mechanisms of behavioral change, and progressive refinement of the design through coproduction work. The program has been coproduced with people living with Parkinson's, family members, and expert SLTs. A steering group (of people living with Parkinson's, family members, and expert SLTs) was established to provide advice and feedback on all aspects of study management. This study addresses the feasibility phase of development by considering the evaluation design (recruitment, outcomes, and analysis) and the intervention (optimal content and delivery, acceptability).

Aim

The primary aim of this study is to evaluate the feasibility of the BCP program delivered via telehealth with a treatment group from a collaborating National Health Service (NHS) site to establish for a main trial whether BCP can be delivered as intended in an NHS setting.

Specifically, the aims are to establish (1) the acceptability of the program for people living with Parkinson's, family members, and SLTs; (2) the feasibility of delivering the BCP program; (3) the recruitment and retention rates; (4) a sample size calculation; and (5) the most appropriate primary outcome measure.

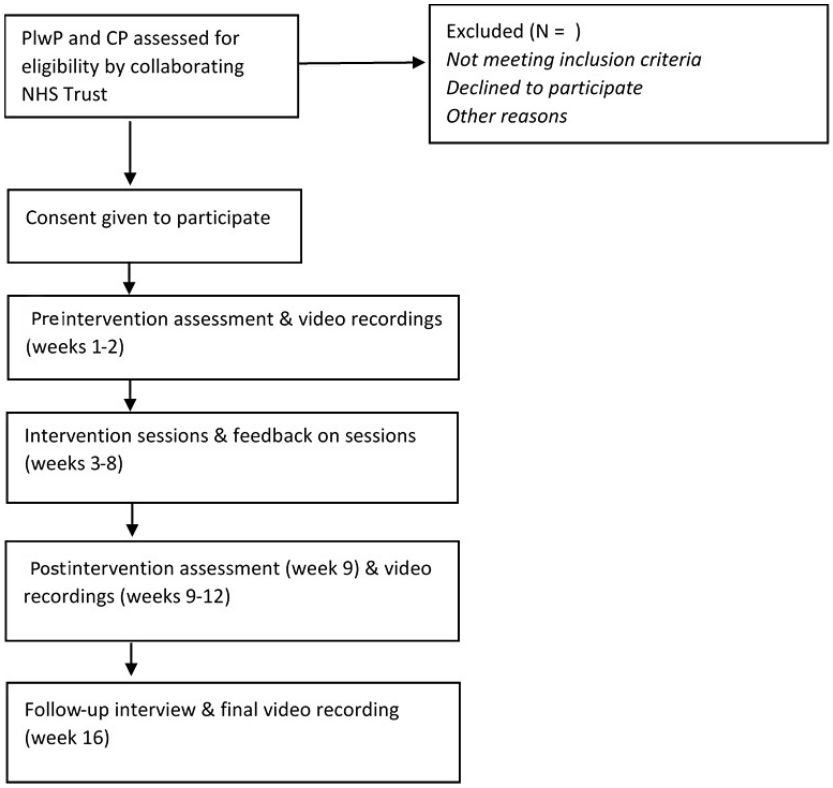
Methods

Design

This is a case-series feasibility pilot study of the BCP therapy program. Participants will be involved for 16 weeks: preintervention measures (weeks 1-2), intervention (weeks 3-8), postintervention measures (weeks 9-12), and a follow-up interview 4 weeks later (week 16). Figure 1 shows participant flow through the study.

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Figure 1. Participant flow through the study. CP: conversation partner; PlwP: persons living with Parkinson's.



Setting

Participants will be recruited by SLTs at a collaborating NHS site located in England. Consent, preintervention measures, and delivery of the BCP intervention will be carried out by a research assistant (a specialist SLT by background; the first author) employed by the study sponsor. The collection of outcome measures and delivery of therapy will be done remotely (ie, via a computer, tablet, or smartphone). Participants will be offered a tablet device to take part in the therapy if required, although an existing internet connection will be required.

Population

The study includes adults (>18 years) with a diagnosis of Parkinson's and related communication difficulties and a chosen CP. Local collaborators (SLTs) at participating NHS sites will use medical notes and a case history to judge potential participants against the inclusion and exclusion criteria (Textbox 1).

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Textbox 1. Participant inclusion and exclusion criteria.

Inclusion criteria

1. Being 18 years or older
2. Having a diagnosis of Parkinson's
3. Experiencing intelligibility or communication problems relating to Parkinson's
4. Having some ability to communicate and understand communication in order to participate in the Better Conversations with Parkinson's (BCP) program
5. Being able to see and hear well enough to participate in the program
6. Being functionally able to engage in the program (ie, able to maintain some concentration and remain in a 60-90 minute session; minimal challenging behavior so as to be unlikely to cause disruption)
7. Having English as their language of daily use
8. Having a conversation partner (CP) who is able to and consents to participating in the project
9. Being able and ready to actively participate in conversation therapy at the current time

Exclusion criteria

1. Having a history of brain lesions or major head trauma
2. Having a major physical illness or disability that could impact participation
3. Present with a major psychiatric diagnosis
4. Present with prominent behavioral disturbances
5. Present with prominent episodic memory, visual memory, or visuo-perceptual impairments
6. Currently participating in active speech and language therapist (SLT) intervention that may conflict with BCP
7. Participating in or having recently participated in research which may conflict with BCP
8. Having no access to a Wi-Fi connection in order to be able to access BCP remotely

Identification and Recruitment

SLTs at a collaborating NHS Trust will be asked to identify potential participants using the inclusion and exclusion criteria (Textbox 1) and invite them to participate via a flyer. People who meet the inclusion criteria will not be under any obligation to take part in this study, and this will be made clear from the outset. Those who express interest will be given the participant information sheet (PIS) and sent an electronic link. Potential participants can use the link to indicate their consent to being contacted by the research team and to securely share their contact details. Potential participants will be contacted for consent to participate in the study at least 48 hours after receiving the PIS and sharing contact details.

Local collaborators will complete a log to record the number of people with a diagnosis of Parkinson's who do not meet the inclusion criteria and the number of people who are eligible but decline to participate, with their reasons why if provided. Participants will be reviewed by the local collaborator SLT after finishing the study. At this point, participants will resume routine speech and language therapy with the collaborating NHS Trust.

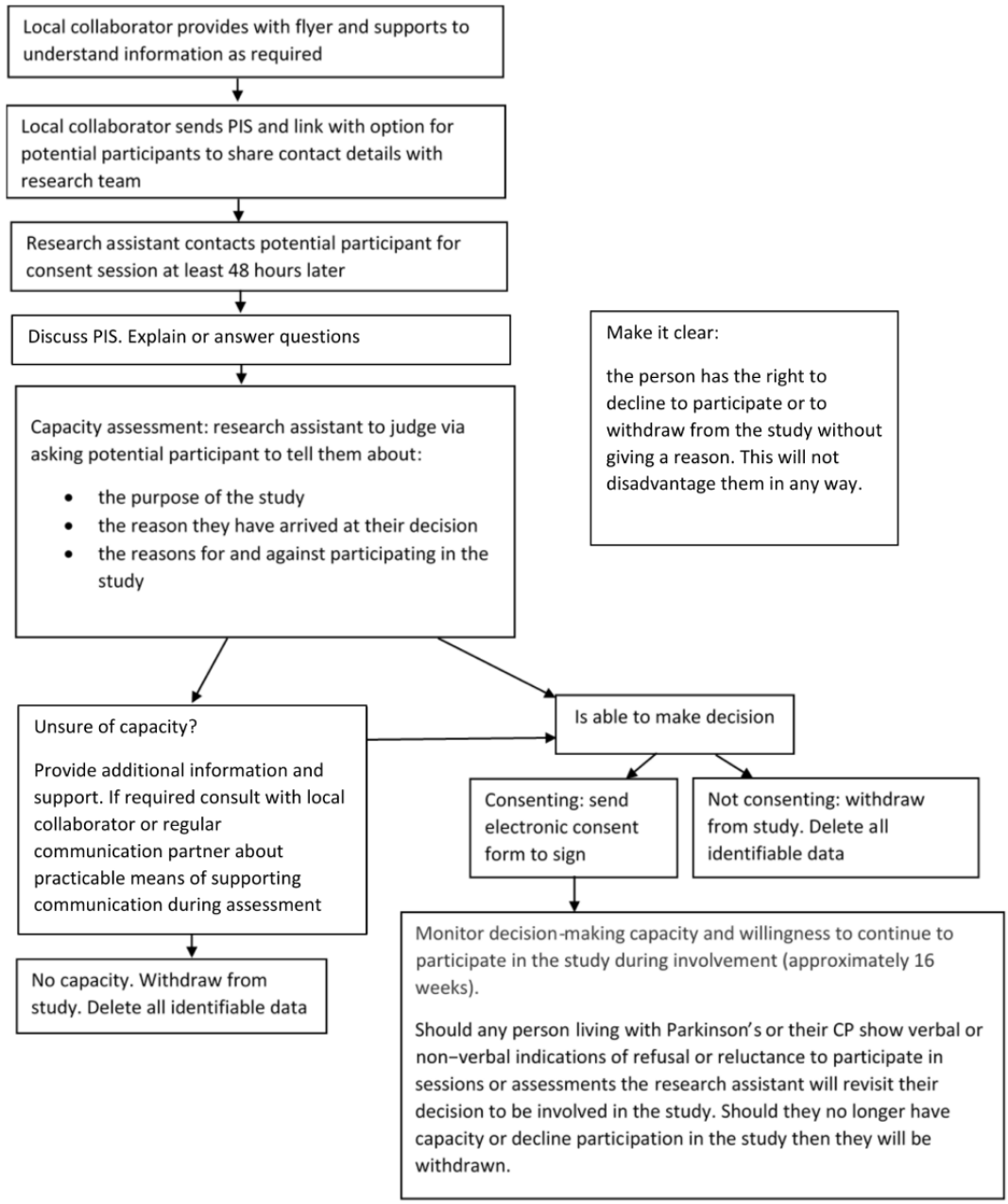
Ethics Approval

Ethical approval was granted by the London-Central Research Ethics Committee (reference 22/LO/0332). Figure 2 depicts the process of consent. Participants in the study are expected to be in the mild to moderate stages of Parkinson's and therefore likely to be competent to give informed consent to participate, provided that sufficient time is allowed for them to reach a decision. Those who are unable to give informed consent will not be able to take part in the study (see Figure 2). Informed consent will be obtained by the research assistant following the current guidance from the Mental Capacity Act [33], Royal College of Speech and Language Therapists guidelines [34], and Good Clinical Practice Standards [35]. The research assistant is a specialist SLT with considerable experience supporting people with communication impairments and issues related to obtaining consent. Potential participants will be given specialist support to understand the information sheets by the research assistant as required.

Participants will not be financially compensated for taking part in this study. All participant data will be deidentified where possible. Identifiable information will remain confidential and will be stored securely in line with the Data Protection Act 2018. See below for further information about data management.

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Figure 2. Process of consent. CP: conversation partner; PIS: participant information sheet.



Sample Size Justification

The recruitment of participants will be dealt with pragmatically, within the scope of a small feasibility pilot study. Based on related research and discussions with clinicians at the collaborating NHS Trust, who estimate an active caseload of people living with Parkinson's of approximately 90 cases (inclusive of swallowing and communication difficulties), it is judged that it will be possible to identify and recruit 10-12 couples over a 6-month period. This allows for a slight overrecruitment to ensure 10 complete data sets.

Outcome Measures

Participants will complete preintervention speech, intelligibility, functional communication, and quality of life measures (Multimedia Appendix 1) with the research assistant in weeks 1-2 of the study. Questionnaires will be delivered via a mutually accessible platform (eg, Microsoft Teams or Zoom) or through an electronic questionnaire depending on participant choice, as recommended by the research steering group. Participants will be interviewed to establish a profile of their typical interactions [36], the types of problems with interaction they experience, how often these occur, and in what situations they arise. This will include the perspectives of the person living with Parkinson's and their CP. They will also complete a case history, a rating scale of Parkinson's symptoms, and a cognition and speech assessment to allow a description of relevant individual participant characteristics. This preintervention assessment protocol mirrors routine speech and language therapy practice. Furthermore, it provides the opportunity for the research assistant to build rapport with participants before delivering the intervention.

After intervention, measures (Multimedia Appendix 1) will be repeated (weeks 9-12). These assessments will contribute to the identification of a primary outcome measure for a future trial,

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if this is warranted. Final follow-up interviews and the Better Conversations Self Rating Scale will take place 8 weeks after treatment to understand long-term acceptance and the impact of the intervention. This will include the perspectives of both the person living with Parkinson's and their CP. Repeated measures and the follow-up interview will be conducted by junior researchers (student SLTs) with training and support from the chief investigator and research assistant.

Each dyad will be supported to video-record themselves in natural conversation for 15 minutes, 3 times before and 3 times after intervention. They will be recorded via a laptop or tablet by a member of the research team using a mutually accessible platform (eg, Zoom or Microsoft Teams). The team member will set up the remote meeting, start the recording, and then turn off their camera and microphone to leave the dyad to talk unobserved. If the dyad requires it, a list of conversation topics will be provided to support this process. This form of remote data collection replicates methods used in previous teleCPT and Better Conversations research [29] and is designed to facilitate ease of data collection and security of data transfer. The timescales of sample video recordings are shown in Table 1.

Table 1. Schedule of conversation sample recordings.

	Consent session	Preintervention assessment	BCP[a] intervention (6 weeks)	Postintervention assessment	Final data collection	Follow-up interviews or rating scales
Week (expected timescale)	0	1-2	3 -8	9	10-12	16
Conversation sample recording	N/A[b]	1, 2, and 3	N/A	4	5 and 6	7

[a]BCP: Better Conversations with Parkinson's.

[b]N/A: not applicable.

Intervention

The BCP program is described in Multimedia Appendix 2, using the Template for Intervention Description and Replication (TIDieR) checklist. BCP is based on the principles of a Better Conversations approach to CPT [21] and is the first of its kind to meet the specific needs of people living with Parkinson's. It has been coproduced by people living with Parkinson's and SLTs who are experts in this area. Participants' preintervention video-recorded conversation samples will be used to provide short clips for video feedback during intervention sessions. Each member of the dyad will identify personal goals depending on their conversation challenges, but each session's objectives, activities, and types of feedback are manualized. The approach is underpinned by the COM-B model of behavior change [37] and is designed to target behavior change techniques from the Behavior Change Techniques Taxonomy [38], in particular those reliably identified as active ingredients in Better Conversations with Aphasia [39]. The BCP intervention will be administered by the research assistant.

Evaluation of Acceptability

The acceptability of the intervention and study procedures will be evaluated qualitatively. Online anonymous questionnaires submitted after each therapy session will obtain the participants' views and experiences of session delivery, objectives, and activities. Semistructured interviews will be conducted by junior researchers 8 weeks postintervention to explore acceptability, including participant attitude toward and experience of the intervention; the impact of the intervention on activity, participation, and well-being; what participants perceive to be the barriers and enablers to implementing strategies from the intervention; what participants valued about the intervention; and what changes participants might suggest to the intervention. Additionally, the research assistant administering the intervention will complete a reflective diary and feedback questionnaires on the experience of delivering therapy, whether sessions met expectations, adaptations required to sessions, and the perceived helpfulness of therapy for the dyad. This data will be analyzed by junior researchers to enhance objectivity.

Evaluation of Feasibility

Feasibility will be evaluated by collecting data on the following: recruitment and retention rates; time required to recruit to target; attrition rates; feasibility of pre- and postintervention assessment and data collection methods, including completion rates; adverse events.

Data Management

The study is compliant with the Data Protection Act 2018. All personal information (contact details, date of diagnosis, medical and social history) will remain confidential. Each participant will be given a unique research number, which will be used on all paperwork, in the names of video files and electronic records (eg, assessment data), and in analysis documents and subsequent publications. All data will be stored securely on Data Safe Haven, in accordance with the Data Protection Act 2018 and the sponsor's data protection policy.

Video recording of conversation samples between dyads is required as an outcome measure and for video feedback during the intervention. Participants will consent to being video recorded for these purposes. Faces are required to be visible for detailed analysis of the video recordings, as natural human communication is the focus of the intervention being piloted. Only the research team will have access to the full video-recorded data set. Participants will be given the choice to opt in or out of the additional use of short extracts of video recordings for presentations about the research to professional audiences, teaching purposes, and as part of an online therapy resource. It is made clear in the PIS that there are risks of being recognized, and participants will be given a choice as to whether videos are masked (voice and image altered to reduce

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recognizability) if used for these purposes. They can opt out of videos being used in this way at any point during the study.

No data management committee will be established as it is felt that this short, small-scale pilot carries minimal risks. If any information is disclosed by the participant that leads the chief investigator to believe that a participant is at risk of harm or harming others, then confidentiality will be broken to ensure the safety of the person or people involved.

Data Analysis

Quantitative and qualitative methods will be used to analyze the study data. Descriptive statistics will be used to report on recruitment, attendance, and attrition. Recruitment and retention rates will be used to support sample size calculations to inform a future full trial and plan the required number of sites to meet this target. To inform a sample size calculation, the mean pre- and postintervention scores, a mean change score, 95% CIs, and SDs will be calculated for each outcome measure. The mean change scores and standard deviations will be entered into the G*Power software, and an effect size will be calculated; this will then inform a 2-tailed sample size calculation for each measure.

Recordings of adverse events and participant feedback will be used to inform future recruitment procedures. The analysis of acceptability data will be based on participant feedback forms, interviews, and adherence data. This data will be analyzed using descriptive statistics and reflexive thematic analysis [40].

Speech, communication, and quality of life assessment data will be entered into a database and analyzed using SPSS (IBM Corp). This information will be used to determine a suitably sensitive outcome measure for a next-stage clinical trial, should this be warranted. Conversation outcomes will be captured using a procedure developed for Better Conversations with Aphasia to identify changes in the use of targeted strategies following intervention [23]. This will involve analysis of frequency counts of barrier and facilitator behaviors linked to people's personal goals for intervention in 5-minute video samples selected from the midpoint of each of 6 pre- and postintervention conversation samples. We hypothesize that dyad management of problems with intelligibility (repair) may be a key site of conversation change. Intelligibility problems typically involve both speakers in a dyad over a series of conversational turns [41]. Given this, a secondary evaluation of conversation data will be conducted using Conversation Analysis [42].

Criteria for Success

The study will be considered appropriate for a next-stage clinical trial evaluating the intervention if (1) the intervention is acceptable to people with Parkinson's and their CP, (2) the intervention is feasible to deliver for the SLT, (3) a suitable sensitive outcome measure is identified, and (4) an appropriate sample size is estimated.

Assessment and Management of Risk

This is a low-risk study. There is a possibility that participants will not experience improvements in their communication, well-being, or quality of life as a result of the intervention. However, there is no evidence to indicate that participants will experience harmful side effects, and the intervention has been coproduced with people living with Parkinson's and expert SLTs to maximize acceptability and relevance. There is evidence to suggest that this kind of intervention is effective at improving communication for adults with other communication difficulties and their partners.

Most assessments and procedures, such as videoing, are routinely used in speech and language therapy clinical practice. It is possible that distress may arise from discussions of communication difficulties and from measures or therapy tasks highlighting existing problems in conversation. The research assistant carrying out the intervention is a highly trained SLT with the ability to manage sensitive situations. The risk of distress is expected to be balanced by the opportunity to discuss communication strengths and strategies, as well as the enjoyment in targeted conversation time with a nominated partner. The process of being recorded on video and watching yourself on video can be confronting. The coproduction group (including people living with Parkinson's, their family members, and specialist SLTs) advised on how to introduce video to participants, so that as far as possible, participants are familiarized with the process and understand why video is vital to changing conversation behavior in a Better Conversations approach.

All study procedures are outlined in the PIS, which has been designed with support from people living with Parkinson's and their partners. Participants will be reminded that they can withdraw from the study at any time. Any adverse events will be recorded in the participant's medical record, and the study sponsor will be informed.

Results

This study was approved for funding from Parkinson's UK in December 2020 following peer review of the proposal by an independent committee (Multimedia Appendix 3). This study was approved for funding from Parkinson's UK in December 2020. Study recruitment commenced in July 2022. The results of the data analysis are expected to be available by September 2024.

Discussion

To the authors' knowledge, this is the first study to investigate a remotely delivered CPT approach for people living with Parkinson's. This study outlines the protocol for the study with the aim of evaluating the acceptability of the BCP program for people living with Parkinson's, family members, and SLTs, and the feasibility of delivering the BCP program in collaboration with an NHS site. The study aims to identify a sample size calculation, recruitment and retention rates, and the most appropriate primary outcome measure to guide the future development of the BCP intervention.

This study involves the adaptation of the Better Conversations approach to CPT for a new client group. There is evidence that a Better Conversations approach reduces barriers to conversation and can increase the use of facilitatory strategies [23]. This study also builds on previous research by Forsgren et al [20]

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by further investigating a CPT approach for people living with Parkinson's and, in addition, trialing teleCPT, therefore using a form of delivery that has been found to be highly acceptable for this client group [30]. Despite psychosocial and language issues being flagged as an important reason for referral for people living with Parkinson's, the evidence base and SLT clinical practice are predominantly focused on swallowing, voice, and articulation [5]. This program has the potential to address psychosocial factors and communication difficulties beyond speech and, therefore, fill a gap in research and current clinical practice.

CPT has been shown among other client groups to enhance communication and participation [11] and result in changes to CPs' knowledge, skills, and attitudes [14,15]. This study will provide valuable information about the sensitivity of measures in these areas for capturing CPT outcomes for people living with Parkinson's and CPs. Additionally, this research will provide valuable information about the acceptability and feasibility of the Better Conversations approach for people living with Parkinson's and their CPs. An outcome of this study will be a manualized BCP program coproduced by people living with Parkinson's, their families, and a group of expert SLTs and adapted following the feedback of this study's participants.

The outcomes of this study will be used to guide future phases in the development of the BCP intervention, as per Medical Research Council guidance for developing and evaluating complex interventions [32]. For example, given that this study investigates BCP delivered via telehealth, a future phase of research may compare face-to-face and telehealth delivery. A longer-term aim is to create a freely accessible intervention resource for the benefit of people living with Parkinson's and SLTs working with them.

Limitations

As a small-scale feasibility study with 10-12 dyads from 1 NHS site, the study is limited in scope. The study will therefore not seek to evaluate effectiveness or to generalize results beyond the participants. As a case-series study, which aims to describe the characteristics and outcomes at an individual level of a group of participants with Parkinson's, this study does not include a control group. The results of the study will guide future phases of research into the BCP intervention, which if appropriate may involve a randomized controlled trial design.

A possible risk is a lack of diversity due to recruiting from 1 geographic area and an SLT caseload. Ascertainment bias is also possible: outcomes may be affected by factors (eg, socioeconomic status and cultural and linguistic barriers) that might be limiting access to the local speech and language therapy service. Despite the provision of a device to access the research, exclusion is possible as a result of digital poverty due to the requirement to have an internet connection to take part. Due to resource limitations, the research assistant will carry out the initial assessment and intervention. There is a risk that participants will not feel able to be completely open with feedback following each therapy session as the SLT delivering therapy is a member of the research team. The postintervention assessment and follow-up interviews will be completed by trained junior researchers to ensure that they are unaware of premeasure values and to provide an opportunity for participants to provide feedback they might not want to disclose to the SLT research assistant.

Personalization is a key element of this therapy approach. The coproduction group, which involves people with Parkinson's and SLTs, has created a core set of activities and session plans to be used across all participants but has confirmed that personalization is essential. It is recognized that tailoring the intervention to different dyads and their goals may result in variation in the types of strategies identified and practiced; however, the session objectives, activities, and feedback tasks will be the same for all.

Dissemination

The authors aim to disseminate the results of this study in peer-reviewed scientific journals and via presentations at academic and clinical conferences. Results will also be disseminated via user group publications and will be publicized via the BCP Twitter account and Better Conversations web pages. Opportunities to disseminate outcomes of the study to people living with Parkinson's, SLTs, and researchers will be created through university and NHS Trust links and supported by the study steering group.

Conclusions

This study will provide valuable information about the acceptability and feasibility of BCP—a CPT approach for people living with Parkinson's and their CPs—delivered via telehealth. Outcomes of this study will include a manualized BCP program coproduced by people living with Parkinson's, their families, and expert SLTs, which will be refined based on feedback from study participants. The study results will guide the next phases of intervention development, with the long-term aim of creating a freely accessible intervention resource for SLTs to use with people living with Parkinson's and their regular CPs.

Acknowledgments

The authors acknowledge and thank all the steering group and coproduction group members who consulted on the development of the protocol, coproduced the participant information sheets and consent forms, and coproduced the Better Conversation with Parkinson's intervention program. We would also like to thank the local collaborators and participants at the National Health Service Trust for participating in the study. This study has been funded by Parkinson's UK (grant reference: H-2001) and is sponsored by the University College London Joint Research Office.

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Data Availability

The data sets generated and analyzed during this study are available from the corresponding author on reasonable request, subject to consent.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Outcome measures and method of collection.
[DOCX File , 27 KB - resprot_v12i1e41416_app1.docx]

Multimedia Appendix 2
Template for Intervention Description and Replication (TIDieR) Checklist.
[DOCX File , 32 KB - resprot_v12i1e41416_app2.docx]

Multimedia Appendix 3
Peer-review reports on grant proposal.
[PDF File (Adobe PDF File), 82 KB - resprot_v12i1e41416_app3.pdf]

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Abbreviations

BCP: Better Conversations with Parkinson's
CP: conversation partner
CPT: communication partner training
NHS: National Health Service
PIS: participant information sheet
SLT: speech and language therapist

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Protocol

Improving Communication in Intensive Care Unit to Ward Transitions: Protocol for Multisite National Implementation of the ICU-PAUSE Handoff Tool

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Abstract

Background: The intensive care unit (ICU)–ward transfer poses a particularly high-risk period for patients. The period after transfer has been associated with adverse events and additional work for care teams related to miscommunication or omission of information. Standardized handoff processes have been found to reduce communication errors and adverse patient events in other clinical environments but are understudied at the ICU-ward interface. We previously developed an electronic ICU-ward transfer tool, ICU-PAUSE, which embeds the key elements and diagnostic reasoning to facilitate a safe transfer of care at ICU discharge.

Objective: The aim of this study is to evaluate the implementation process of the ICU-PAUSE handoff tool across 10 academic medical centers, including the rate of adoption and acceptability, as perceived by clinical care teams.

Methods: ICU-PAUSE will be implemented in the medical ICU across 10 academic hospitals, with each site customizing the tool to their institution's needs. Our mixed methods study will include a combination of a chart review, quantitative surveys, and qualitative interviews. After a 90-day implementation period, we will conduct a retrospective chart review to evaluate the rate of uptake of ICU-PAUSE. We will also conduct postimplementation surveys of providers to assess perceptions of the tool and its impact on the frequency of communication errors and adverse events during ICU-ward transfers. Lastly, we will conduct semistructured interviews of faculty stakeholders with subsequent thematic analysis with the goal of identifying benefits and barriers in implementing and using ICU-PAUSE.

Results: ICU-PAUSE was piloted in the medical ICU at Barnes-Jewish Hospital, the teaching hospital of Washington University School of Medicine in St. Louis, in 2019. As of July 2022, implementation of ICU-PAUSE is ongoing at 6 of 10 participating sites. Our results will be published in 2023.

Conclusions: Our process of ICU-PAUSE implementation embeds each step of template design, uptake, and customization in the needs of users and key stakeholders. Here, we introduce our approach to evaluate its acceptability, usability, and impact on communication errors according to the tenets of sociotechnical theory. We anticipate that ICU-PAUSE will offer an effective handoff tool for the ICU-ward transition that can be generalized to other institutions.

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KEYWORDS

intensive care; medical error; communication; handoff; transfer; qualitative; sociotechnical theory; implementation science; medical education; communication tool; workflow; ICU; ward transition; ward transfer

Introduction

Background

The transition of a hospitalized patient from the intensive care unit (ICU) to the inpatient ward is a particularly high-risk period for the patient recovering from critical illness due to their medical complexity and often residual diagnostic uncertainty. Although transfer from the ICU is indicative of clinical improvement, this process encompasses changes in clinical environments, medical personnel, and reduced monitoring capacity. These complex patient transfers are vulnerable to provider miscommunication, which increases the risk of preventable medical errors and ICU readmissions [1-3]. The transition between medical teams is also distressing for patients and their families, particularly when there is poor communication with and among medical providers [1,4]. Although standardized practices and structured handoff tools reduce these errors and associated negative outcomes [5], these approaches are surprisingly understudied during this high-risk ICU-ward transition [6,7], which remains vulnerable to nonstandard and suboptimal practices [8].

A recent study of several teaching hospitals demonstrated high rates of communication errors—both those of commission and omission—and associated harms, including unplanned ICU readmissions, care delays, medication errors, missed results, and patient and family distress [9]. Residents compensated for suboptimal ICU-ward handoffs by recovering omitted information through the chart review, history-taking, duplicating previously completed tasks, or calling the ICU to clarify information; these inefficiencies and documentation burdens compete for trainee time that could otherwise be spent on patient care and education [2]. Prior studies demonstrate notable gaps in information that is reported by ICU providers and what is understood by ward providers, emphasizing the need for standardized written communication that accompanies the patient during the entire transfer process and mitigates the loss of essential clinical information [10].

These issues indicate the clear need for an evidence-based, standardized ICU-ward transfer tool. Given the variation in ICU systems across medical centers, successful implementation and sustainability of an ICU-ward handoff tool requires user-engaged design with potential institution-specific adaptations. Accordingly, we used human-centered design methods across multiple internal medicine residency programs to create and iteratively prototype a structured ICU-to-ward transfer tool embedded within the electronic health record (EHR) [11]. This template, ICU-PAUSE, comprises the following elements: brief ICU course and reason for admission (I), code status and goals of care (C), uncertainty of working diagnosis and diagnostic pause (U), pending tests (P), active consultants (A), deprescribing unnecessary medications and reviewing pertinent high-risk medications (U), summary of problems and uncompleted tasks (S), and exam at the time of transfer (E) [12].

The ICU-PAUSE handoff tool was piloted in the medical ICU at Barnes-Jewish Hospital (BJH) in 2019 and 2020, and will be implemented across 10 academic hospitals, with each site permitted to customize the tool to institution-specific needs. This mixed methods study will evaluate the feasibility and perceived impact of the novel EHR-embedded ICU-ward transfer tool, ICU-PAUSE, on communication failures and medical errors during the transfer of patients from the ICU to the inpatient ward.

Study Aims and Objectives

This mixed methods study will evaluate the feasibility, acceptability, and perceived impact of a novel EHR-embedded transfer tool, ICU-PAUSE, on communication failures and medical errors during the ICU-ward transfer process. Our specific aims are as follows.

Aim 1

Evaluate the feasibility, acceptability, and adoption of implementing ICU-PAUSE into the ICU-ward physician transfer workflow in a diverse group of hospitals.

Informed by the Consolidated Framework for Implementation Research (CFIR) model and Sittig and Singh's [13] sociotechnical theory [14], we will conduct quantitative surveys and semistructured interviews of faculty champions and resident trainee stakeholders from multiple institutions that have implemented ICU-PAUSE. Our thematic analysis will be based on dimensions of the sociotechnical model, which offers a framework to evaluate interdependent factors within complex ICU-ward workflows [13]. We aim to elicit perceptions of feasibility, informatics resource needs and constraints, barriers and facilitators to implementation, and cultural changes in safety surrounding ICU-ward handoffs. We will also perform a chart review of ICU-ward transfer notes to assess the frequency of ICU-PAUSE utilization as a measure of adoption.

Aim 2

Examine the perceived impact of ICU-PAUSE on communication failures and associated medical errors during ICU-ward transfers among internal medicine residents, ICU physicians, and ward physicians.

We will conduct quantitative surveys of postgraduate year 2 (PGY-2) and PGY-3 internal medicine residents, ICU attending physicians, and ward attending physicians (n=175) to assess the frequency of self-reported miscommunication events, medical errors, and adverse outcomes during ICU-ward handoffs after the implementation of ICU-PAUSE. We will compare these findings with previously collected preimplementation surveys [9].

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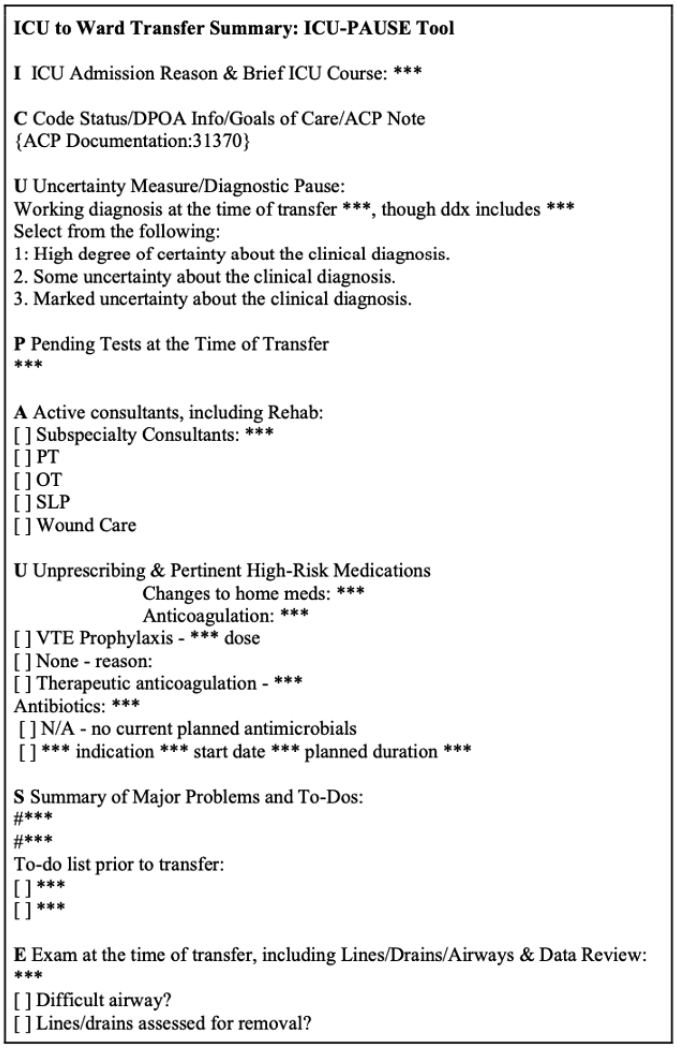
This study will provide new evidence on potential best practices for implementation of a novel handoff tool in ICU discharge. ICU-PAUSE can potentially decrease communication failures in the ICU handoff process and be disseminated for adaptation to institution-specific needs, providing a valuable evidence-based transfer tool for ICU systems at other academic medical centers.

Methods

Context

Poor handoff communication between ICU and ward teams may result in unfavorable outcomes: studies have shown that standardization of communication during the handoff process reduces preventable medical errors [5]. We aimed to address the challenges that emerge during the ICU-ward transition period as a result of poor communication between ICU and ward providers by creating a standardized written handoff tool. The ICU-PAUSE handoff tool was developed between July 2019 and July 2020 and contains the key information to facilitate a safe transfer of care as identified through focus groups of residents (Figure 1) [12]. ICU-PAUSE will be integrated into the EHR and implemented into medical ICUs at the following sites between March and August 2022: Cedars-Sinai Medical Center, Kaiser Permanente Oakland Medical Center, Ohio State University, Penn State Health Milton S. Hershey Medical Center, Rutgers University, University of Chicago (UC), University of Iowa Hospitals and Clinics, University of Kentucky, and University of California-San Francisco (UCSF). Each site has a faculty champion, defined as an intensivist who has intimate knowledge of the ICU workflow and who will participate in an education session of the ICU-PAUSE tool to facilitate its implementation at their respective academic institutions. The ICU-PAUSE tool has been in use at our pilot site, BJH (the teaching hospital of Washington University School of Medicine in St. Louis [WUSM]) since late 2019 and is now the standard transfer summary documentation at this hospital.

Figure 1. ICU-PAUSE Electronic Tool. ***: Free text placeholder; ACP: Advanced Care Planning; DPOA: Designated Power of Attorney; ICU: Intensive Care Unit; N/A: not applicable; OT: Occupational Therapy; PT: Physical Therapy; SLP: Speech and Language Pathology; VTE: Venous Thromboembolism Prophylaxis. Reproduced from Santhosh et al [12], which is published under Creative Commons Attribution Non-Commercial No Derivatives License 4.0 [15]).



ICU to Ward Transfer Summary: ICU-PAUSE Tool

I ICU Admission Reason & Brief ICU Course: ***

C Code Status/DPOA Info/Goals of Care/ACP Note
{ACP Documentation:31370}

U Uncertainty Measure/Diagnostic Pause:
Working diagnosis at the time of transfer ***, though ddx includes ***
Select from the following:
1: High degree of certainty about the clinical diagnosis.
2. Some uncertainty about the clinical diagnosis.
3. Marked uncertainty about the clinical diagnosis.

P Pending Tests at the Time of Transfer
***

A Active consultants, including Rehab:
[ ] Subspecialty Consultants: ***
[ ] PT
[ ] OT
[ ] SLP
[ ] Wound Care

U Unprescribing & Pertinent High-Risk Medications
Changes to home meds: ***
Anticoagulation: ***
[ ] VTE Prophylaxis - *** dose
[ ] None - reason:
[ ] Therapeutic anticoagulation - ***
Antibiotics: ***
[ ] N/A - no current planned antimicrobials
[ ] *** indication *** start date *** planned duration ***

S Summary of Major Problems and To-Dos:
#***
#***
To-do list prior to transfer:
[ ] ***
[ ] ***

E Exam at the time of transfer, including Lines/Drains/Airways & Data Review:
***
[ ] Difficult airway?
[ ] Lines/drains assessed for removal?

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Study Design

This convergent mixed methods implementation study will use (1) quantitative surveys, (2) a retrospective chart review, and (3) qualitative semistructured interviews to explore the feasibility and perceptions of ICU-PAUSE after implementation at multiple sites [16]. Participants will include internal medicine residents, ICU attending physicians, and ward attending physicians in medical ICUs and inpatient wards across 10 academic medical centers. ICU residents and attendings who make the decision for patient transfer will compose their transfer note using the ICU-PAUSE tool, which will be received by residents and ward physicians on the inpatient wards team. Participants of the quantitative surveys will be recruited by email invitation to a web-based survey platform. Participants of the qualitative interviews will be contacted directly by the research team. For the quantitative arm of this study, we will survey residents, ICU physicians, and ward physicians at least 3 months after successful implementation of the ICU-PAUSE tool at their respective sites. A preimplementation survey of resident trainees was already conducted at UC, UCSF, and WUSM during the 2015-2018 academic years to evaluate the frequency of communication gaps and medical errors related to ICU-ward transfers [9]. We will re-administer this survey across all sites in the postimplementation period to compare survey responses from before and after the implementation of ICU-PAUSE. We will conduct a retrospective chart review of all ICU transfer notes within a 60-day period to evaluate the rate of tool uptake. For the qualitative component of this study, we will conduct pre- and postimplementation interviews of faculty champions who will facilitate implementation at their sites, as well as postimplementation interviews of residents and ICU physicians who have used the tool. The qualitative component of this study will complement our quantitative data by capturing stakeholder experiences surrounding the implementation process that may not be captured within the survey responses. This convergent mixed method approach will allow us to quantify the feasibility and acceptability of the ICU-PAUSE tool while also qualitatively assessing user experiences with the tool using the established implementation frameworks of CFIR and sociotechnical theory [13,14,17].

Conceptual Framework

This study is informed by sociotechnical theory, which offers a paradigm for studying health information technology innovations [13]. The CFIR also provides the basis of our quantitative analysis to evaluate the implementation of ICU-PAUSE [14]. We will use these theoretical frameworks to evaluate ICU-PAUSE at both the user-technical interface and along constructs known to impact the success of implementation [18].

Participants' Inclusion and Exclusion Criteria

Aim 1 participants will include 1 faculty champion and 1 stakeholder (PGY-2 or PGY-3 internal medicine resident trainee or ICU attending physician) from each participating institution. Faculty champions have been identified a priori by word of mouth and will serve as key informants for identifying additional stakeholders for participation. Each faculty champion is an intensivist with an intimate understanding of the ICU-ward transfer workflow and will facilitate ICU-PAUSE implementation at their respective sites. The faculty champions from UC and UCSF, which we will refer to as lead sites, originally conceived of the ICU-PAUSE tool and will therefore be excluded from participation in any surveys or interviews. WUSM's faculty champion at our pilot site was not directly involved in ICU-PAUSE development and will thus provide "early adopter" perspectives in this aim [19]. The remaining participating institutions will implement ICU-PAUSE between March and July 2022 and will be referred to as validation sites.

Aim 2 participants include all PGY-2 and PGY-3 internal medicine residents, ICU attending physicians, and ward attending physicians at all participating sites. PGY-1 residents will be excluded from the study because they infrequently hold primary responsibility for ICU-ward transfer communication at our institutions [9]. Key informants at each site will recruit survey participants, with no specific exclusion criteria.

Intervention

There are 2 components to the intervention: an educational component and the ICU-PAUSE tool. In the educational component, the UCSF faculty champion conducts a 1-hour educational session on ICU-PAUSE implementation with the faculty champion from each participating site. The structured sessions entail discussing the rationale for the tool, describing how ICU-to-ward transitions are high-risk times for patients, walking through the template in detail, giving examples of template use, and answering questions. Once the educational component is completed, the ICU-PAUSE tool is made available as an EHR "dot-phrase" template that will be recreated at each site by the faculty champion (Figure 1). Local champions further the dissemination at the local site through a combination of educational sessions and flyers/handouts provided by the central ICU-PAUSE team. Adaptations will be noted and codified using the Framework for Reporting Adaptations and Modifications-Expanded (FRAME) method of tracking adaptations in our postimplementation interviews [20].

Outcomes

The primary outcome in aim 1 will be the proportion of ICU-ward transfers for which a transfer note is written using the ICU-PAUSE template. Secondary outcomes will be perceptions of acceptability, appropriateness, and feasibility of ICU-PAUSE (as measured by the Acceptability of Intervention Measure [AIM], Intervention Appropriateness Measure [IAM], and Feasibility of Intervention Measure [FIM]) [21], perceived resource needs or constraints, and barriers or facilitators to implementation.

In aim 2, the primary outcome will be self-reported communication failures, the frequency of which will be compared with baseline preimplementation surveys. Secondary outcomes will include the perceived frequency of medical errors and self-reported time spent on tasks related to ICU-ward transfers.

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Data Collection

We conducted preimplementation semistructured interviews (n=7) and surveys (n=7) with the faculty champion from each validation site in October and November 2021.

In aim 1, we will re-administer the preimplementation survey to collect postimplementation responses from the same cohort of faculty champions. Survey questions are based on AIM, IAM, and FIM outcome measures to assess the acceptability, appropriateness, and feasibility of the ICU-PAUSE implementation along a 5-point Likert scale (Table 1) [21]. Surveys will be collected using Qualtrics web-based software.

Concurrently, we will conduct a retrospective chart review of patients (n=300) who were transferred from the ICU to inpatient wards between August and October 2022 across all sites. Outcome variables on patient demographics, provider demographics, and note template type will be extracted from ICU-ward transfer notes (Table 2). The adapted ICU-PAUSE template indicates use of the ICU-PAUSE tool with user modifications (Figure 1), whereas the non–ICU-PAUSE template refers to an ICU transfer note that uses any other pre-existing note template. Free text refers to a transfer note written without the use of any template. Each faculty champion will conduct a chart review at their respective institutions. Two co-investigators will independently review and compare a subset of 10 charts to ensure consistency in data collection.

Finally, we will repeat 45-minute semistructured interviews with each faculty champion, along with one additional internal medicine resident or ICU attending physician, for a total of 2 interviewees from each institution (n=14). The postimplementation interviews with the faculty champion will be used for comparison against the preimplementation interviews conducted with the same individual. Interviews with residents and ICU physicians who were not involved in the implementation process will provide an unbiased perspective on barriers or facilitators of ICU-PAUSE implementation. All interviews will be conducted via videoconference by the faculty champion at UCSF [22]. The interview guide was previously developed based on sociotechnical theory and will explore the following key constructs (Table 3): perceptions of usefulness, resource needs and constraints, barriers and facilitators to implementation, culture of safety, and adaptations [13,23]. Interviews will capture any adaptations to the ICU-PAUSE tool based on the FRAME method, such as the timing, participants, and nature of each modification [20]. All interviews will be audiorecorded with participant consent and transcribed verbatim.

In aim 2, we will conduct a postimplementation survey across all 10 sites to assess the frequency of communication failures, handoff errors (eg, rehabilitation needs and intravenous access), and time spent on tasks related to ICU-ward transfers (Table 4). The survey is identical in content to a preimplementation survey of internal medicine residents conducted at BJH, UC, and UCSF in our prior study, which characterized types of miscommunication errors in ICU-ward handoffs [9]. The survey will be administered to house officers, ICU physicians, and receiving ward physicians (n=175). The sample size is based on our work with the preimplementation cohort, and we will aim for at least 30% respondents at each site for the postimplementation surveys [9].

All faculty champions have connections with the internal medicine residencies and will similarly facilitate survey recruitment of residents and attendings at their respective sites. From August to October 2022, we will collaborate with chief residents to recruit PGY-2 and PGY-3 residents who are currently rotating on ICU. As residents rotate through ICU at different months of the academic year, we will email residents to complete the anonymous Qualtrics survey at the conclusion of their ICU rotation. Two follow-up emails will be sent 1 week later and 2 weeks later to maximize the response rate. The faculty champion will also email all ICU and ward attending physicians to complete the Qualtrics survey.

Table 1. Survey measures of faculty champions and stakeholders.

Survey components[a]	Examples of survey items
Acceptability of ICU[b]-PAUSE intervention	• The ICU-PAUSE implementation strategy meets my approval • The ICU-PAUSE implementation strategy is appealing to me
Appropriateness of ICU-PAUSE intervention	• The ICU-PAUSE implementation strategy seems applicable • The ICU-PAUSE implementation strategy seems suitable
Feasibility of ICU-PAUSE intervention	• The ICU-PAUSE implementation strategy seems implementable • The ICU-PAUSE implementation strategy seems possible

[a]Each survey component is graded along the Likert scale (on a scale of 1 to 5): strongly disagree (1), disagree (2), neither agree nor disagree (3), agree (4), strongly agree (5).

[b]ICU: intensive care unit.

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Table 2. Chart review data extraction from ICU[a]-ward transfer notes.

Outcome variables	Items
Patient demographics	• Age • Sex/gender identity • Race
Provider demographics	• Resident • Fellow • ICU attending physician
Transfer note template	• ICU-PAUSE template • Adapted ICU-PAUSE template • Non–ICU-PAUSE template • Free text

[a]ICU: intensive care unit.

Table 3. Postimplementation semistructured interview measures.

Key concepts	Examples of interview questions
Background and current activities	• What are the current efforts related to how handoffs occur when patients are being transferred from the ICU[a] to the ward?
Perceptions of usefulness	• How is the ICU-PAUSE framework helpful to you in improving the transition of care from the ICU to the ward?
Resource needs and constraints	• What resources, personnel, informatics resources, etc. were necessary for you to implement the ICU-PAUSE framework and make this process actionable?
Barriers and facilitators	• What were challenges for you to implement and meaningfully use the ICU-PAUSE framework? • What might be the methods for measuring success?
Culture	• How did the ICU-PAUSE framework change ideas of safety surrounding transition of care from the ICU to the ward?
Adaptations	• Were there adaptations or modifications to the ICU-PAUSE framework at your institution? • When did the modification occur? • Were adaptations planned? • Who participated in the decision to modify?

[a]ICU: intensive care unit.

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Table 4. Survey measures of internal medicine residents, ICU[a] physicians, and ward physicians [9].

Survey measures	Survey items
Provider demographics	• Role (PGY-2[b] resident, PGY-3 resident, ICU fellow, ICU attending physician, or ward attending physician) • Age • Gender identity • Geographic region (Northeast, Midwest, South, West)
Frequency of omission or miscommunication of information in ICU-ward transfer note[c]	• Rehabilitation (physical therapy/occupational therapy) needs • Intravenous access and other indwelling hardware • Risk assessment for ICU readmission • Pending results • Nutrition (per oral status, diet orders) • Intravenous fluids • Antibiotics • Pain medications • Insulin needs • Venous thromboembolism prophylaxis and anticoagulation • Vital signs • Oxygen needs • Mental status • Delirium concerns • Goals of care • Health care decision-maker information
Frequency of adverse outcomes as a result of ICU-ward handoff[c]	• Missed results • Medication errors • ICU readmission • Rapid response activation • Delayed discharge • Patient lost in hospital • Upset family • Patient death
Time spent performing tasks related to ICU-ward handoff[d]	• Writing transfer note • Conducting handoff • Chart review and order placement after handoff • Repeating previously completed patient tasks • Recovering information that should have been delivered at handoff • Receiving handoff on an ICU patient who does not ultimately transfer

[a]ICU: intensive care unit.

[b]PGY: postgraduate year.

[c]Likert scale: Never (1), Rarely (<5 times/year) (2), Sometimes (~2 times/month) (3), Often (at least once weekly) (4), Always (nearly every handoff) (5).

[d]Likert scale: <15 minutes (1), 15-30 minutes (2), 30-60 minutes (3), 60-90 minutes (4), >90 minutes (5).

Sample Size Considerations

As per best practices in human-centered design and qualitative inquiry, we have designed this study to include a sufficient number of stakeholders to capture essential design information and attain thematic saturation [24]. At the end of each interview, we will ask stakeholders if they have other stakeholder interviewees to suggest in a snowball-sampling style methodology to ensure that we have had the opportunity to hear new ideas from multiple participants.

Analysis

For quantitative data, we will use descriptive statistics including frequencies, proportions, and measures of central tendency to compare pre- and postimplementation uptake, acceptability, and feasibility of ICU-PAUSE (Tables 1 and 2). We will also compare pre- and postimplementation surveys of self-reported communication failures, handoff errors, and time spent on ICU-ward transfers (Table 3) [9]. Pre- and postimplementation survey data will be compared using paired *t* tests. We will also evaluate for nonresponse bias by comparing the demographic data and survey responses of early respondents and late respondents, under the assumption that late respondents are similar to nonrespondents [25]. Early respondents are defined as participants who complete the survey within the first 2 weeks, whereas late respondents are those who complete the survey after a third reminder email is sent at 2 weeks [26]. Data analysis will be performed with Stata 17; *P* values less than .05 will be considered statistically significant.

We will analyze deidentified interview transcripts according to a deductive approach and perform thematic analysis independently on transcripts of preimplementation interviews and postimplementation interviews [27]. A coding framework rooted in the 8 dimensions of sociotechnical theory has been

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developed along the following codes: hardware and software, clinical content, human-computer interface, people, workflow and communication, internal organizational features, and external rules and regulations [13]. Along with the codes derived deductively from sociotechnical theory, we will include any codes that emerge inductively from the data in our final codebook. Two independent investigators will code the transcripts using Dedoose software (Dedoose). We will compare and resolve any coding discrepancies through an iterative process to achieve final consensus. Coded excerpts of the transcripts will be compiled to identify salient themes related to before and after ICU-PAUSE implementation.

Researcher Reflexivity

The primary investigator of this study is a stakeholder in the development of ICU-PAUSE and will be conducting the faculty champion interviews. Two medical student co-investigators will observe the interviews for any bias, and we will regularly meet to discuss how personal or professional biases may impact the interviews and qualitative analysis during our deductive process.

Ethical Considerations

We have received exemption by the institutional review board (IRB) to conduct the survey and interview arms of this study. We will apply for new IRB approval before conducting the chart review. Qualitative and quantitative data will be deidentified to ensure confidentiality. Informed consent for interview participation will be obtained verbally, whereas informed consent for survey participation will be embedded into the Qualtrics survey. Given that the outcome of ICU-PAUSE implementation impacts patient care and safety, we will cease implementation if responses reveal compromised patient safety.

Results

We have already established proof of concept with the execution of ICU-PAUSE at our pilot site, BJH, in late 2019. As of July 2022, implementation of ICU-PAUSE is ongoing at all lead sites and validation sites. We intend to complete the study in mid-2023 and publish our results in the second half of 2023. We expect to identify the factors that facilitate and impede implementation of ICU-PAUSE, as well as a reduction in the frequency of communication failures related to ICU-ward transfers.

Discussion

Currently available handoff tools [5] are informed by external resources and conceptual models [28] and lack the necessary elements to facilitate a safe transfer of information at the ICU-ward interface. These elements were identified and incorporated into our user-engaged creation of ICU-PAUSE, a novel clinical template specific to the ICU-ward transition [12]. Here, we aim to evaluate its acceptability, usability, and impact on communication errors using CFIR and sociotechnical theory [13,14]. Our work is innovative by centering the iterative process of template design [12], uptake, and customization in the hands of users who will implement ICU-PAUSE according to their institution's needs. We anticipate that ICU-PAUSE will offer an acceptable and effective handoff tool that will reduce the frequency of communication failures during the ICU-ward transition.

We hypothesize that ICU-PAUSE will be used in at least 70% of ICU-ward transfer notes [5]. We expect to gain insight into the feasibility of ICU-PAUSE implementation, barriers or facilitators to uptake, any impact on the culture of safety surrounding ICU discharge, and adaptations made to the ICU-PAUSE tool. Our qualitative data will be interpreted according to sociotechnical theory, which provides a multidimensional framework to evaluate the process of ICU-PAUSE implementation within a complex health care system [13]. This interpretation will allow us to identify adaptations and potential problems in all domains, which is pivotal to the success of the intervention. We recognize that user interaction, the EHR interface, institutional workflows, and regulatory policies are all dynamic and interdependent. House officers represent the direct beneficiaries of ICU-PAUSE, whereas faculty stakeholders possess insight into internal institutional procedures and necessary adaptations to facilitate implementation. By interviewing both groups, we aim to capture a continuum of information that ranges from individual user experiences to overarching external regulations that influence the implementation process. ICU-PAUSE also seeks to address the need for brevity, clarity, and deliberate acknowledgment of diagnostic uncertainty in the ICU transfer summary [12]. With respect to our postimplementation surveys of house officers, ICU physicians, and ward physicians, we anticipate that ICU-PAUSE will reduce the frequency of communication errors, adverse outcomes, and time spent verifying information compared with preimplementation measures [9]. Thus, we hypothesize that the use of a structured communication ICU-PAUSE tool at transitions of care from the ICU to the ward will lead to a reduction in communication-related adverse events (frequency of omission or miscommunication of information in ICU-ward transfer notes) and no change or improvements in major adverse events (eg, delayed discharge, patient death, and ICU readmission).

The strengths of our work include the implementation of ICU-PAUSE at geographically diverse hospital systems, which will increase generalizability. The ability of each study site to customize ICU-PAUSE may also lead to higher uptake by providing a tool that meets the unique needs of each institution. We will include multiple perspectives by including house officers, ICU attending physicians, and faculty stakeholders. Our pre- and postimplementation data sets will allow us to compare inefficiencies and communication failures in the transfer process and determine whether they were remedied by ICU-PAUSE.

A notable limitation is the inconsistency of our postimplementation survey cohort of internal medicine trainees and attendings, which will not be identical to the preimplementation cohort from our prior study [9]. However, this is a known limitation of medical education research with resident trainees, and we will control for unpaired groups in our statistical analysis. We presume that residency training programs have remained consistent over the past several years during which the initial survey data were collected. There may also be

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selection bias by interviewing faculty champions who may hold personal or professional interests in the success of ICU-PAUSE. We also acknowledge that this study excludes the perspectives of other stakeholders including other specialty practitioners, nursing staff, and patients. We hope to build upon this work with further studies that will include patient and nursing input to gather further stakeholder input in this internal process. Lastly, this study will be conducted at medical lCUs at academic medical centers that may preclude generalizability to specialty ICUs. We considered using patient satisfaction data as a secondary outcome; however, as most patient satisfaction data surveys are collected after discharge, it is extremely challenging to distinguish patient satisfaction data related to the ICU stay or ICU transfer process alone rather than the entire hospitalization.

We intend to disseminate the future results of our multicenter study in a peer-reviewed journal to enable other health professionals to customize ICU-PAUSE to their own institutions and ICU systems. We also recognize the potential for systematic bias with any health technology intervention, and our future research will examine for any patterns of demographic or diagnostic bias in the use of ICU-PAUSE.

Acknowledgments

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Data Availability

Transcriptions of deidentified postimplementation interviews will not be available publicly as they could easily be identified and deanonymize a specific site.

Authors' Contributions

EMF and EKM conceived the design of this study with support from LS. EMF, PGL, and LS substantively developed the paper, and all authors contributed to the revision and approval of the final manuscript.

Conflicts of Interest

LS is the primary investigator of this study and employed by the University of California-San Francisco (UCSF). EH is also an employee of UCSF. PGL is a co-author and faculty stakeholder for the Washington University in St. Louis. JCR is also a co-author and faculty stakeholder who is employed by the University of Chicago.

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Abbreviations

AIM: Acceptability of Intervention Measure
BJH: Barnes-Jewish Hospital
CFIR: Consolidated Framework for Implementation Research
EHR: electronic health record
FIM: Feasibility of Intervention Measure
FRAME: Framework for Reporting Adaptations and Modifications-Expanded
IAM: Intervention Appropriateness Measure
ICU: intensive care unit
IRB: institutional review board
PGY: postgraduate year
UC: University of Chicago

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UCSF: University of California-San Francisco
WUSM: Washington University School of Medicine in St. Louis

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Protocol

A Smartphone Intervention to Promote a Sustainable Healthy Diet: Protocol for a Pilot Study

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Abstract

Background: Changing current dietary patterns into sustainable healthy diets (ie, healthy diets with low environmental impact and socioeconomic fairness) is urgent. So far, few eating behavior change interventions have addressed all the dimensions of sustainable healthy diets at once and used cutting-edge methods from the field of digital health behavior change.

Objective: The primary objectives of this pilot study were to assess the feasibility and effectiveness of an individual behavior change intervention toward the adoption of a more environmentally sustainable healthy diet as a whole and changes in specific relevant food groups, food waste, and obtaining food from fair sources. The secondary objectives included the identification of mechanisms of action that potentially mediate the effect of the intervention on behaviors, identification of potential spillover effects and covariations among different food outcomes, and identification of the role of socioeconomic status in behavior changes.

Methods: We will run a series of ABA n-of-1 trials over a year, with the first A phase corresponding to a 2-week baseline evaluation, the B phase to a 22-week intervention, and the second A phase to a 24-week postintervention follow-up. We plan to enroll 21 participants from low, middle, and high socioeconomic statuses, with 7 from each socioeconomic group. The intervention will involve sending text messages and providing brief individualized web-based feedback sessions based on regular app-based assessments of eating behavior. The text messages will contain brief educational messages on human health and the environmental and socioeconomic effects of dietary choices; motivational messages to encourage the adoption of sustainable healthy diets by participants, providing tips to achieve their own behavioral goals; or links to recipes. Both quantitative and qualitative data will be collected. Quantitative data (eg, on eating behaviors and motivation) will be collected through self-reported questionnaires on several weekly bursts spread through the study. Qualitative data will be collected through 3 individual semistructured interviews before the intervention period, at the end of the intervention period, and at the end of the study. Analyses will be performed at both the individual and group levels depending on the outcome and objective.

Results: The first participants were recruited in October 2022. The final results are expected by October 2023.

Conclusions: The results of this pilot study will be useful for designing future larger interventions on individual behavior change for sustainable healthy diets.

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KEYWORDS

eating behavior change protocol; sustainable diet; dietary sustainability; eating behavior change; n-of-1; nutritional education; eHealth; mobile health; mHealth; mobile phone

Introduction

Background

Sustainable healthy diets have been defined as healthy dietary patterns with low environmental impact and being economically fair and affordable and culturally acceptable, which contribute to nutrition security and a healthy life for the present and future generations [1]. Such diets are characterized by being nutritionally balanced patterns, mainly (if not totally) based on unprocessed or minimally processed plant-based foods obtained from fair sources and with minimal food waste [2]. Over the past decades, the way food has been produced and consumed is far from being healthy or sustainable: unhealthy diets are the leading cause of morbidity and mortality worldwide [3]; healthy diets are not affordable and accessible to a large proportion of the world's population [4]; the current food system is among the main drivers of environmental pollution and natural resource use [5]; and from the socioeconomic and ethical perspectives, there are countless cases of forced labor conditions and unfair salaries across the food system [6]. Altogether, changing the current food system toward a sustainable and healthy one is timely. This mission requires large transformative changes in each food system phase, from production to consumption, and all stakeholders, from producers to consumers, should be involved in such a transformation [7].

To encourage the adoption of sustainable healthy diets, structural changes (ie, political actions or nudges) have to be combined with strategies explicitly tailored to individual behavior change [8,9]. To date, most individual eating behavior change interventions implemented have mainly focused on improving health and, to a lesser extent, on the dimensions of sustainable eating behaviors (ie, their environmental impacts and, with even less consideration in the literature, their social consequences [10]). Evaluating all these dimensions at once within interventions is crucial because they are not necessarily aligned. For instance, fish is a healthy food but could be obtained from overexploited fish stocks, exacerbating environmental damage [11]; even if captured from sustainable sources and using environmentally responsible techniques, labor conditions for fishery workers may not be fair, compromising their well-being [6].

Prior Work

Recently, some interventions have been designed with the aim of promoting individual eating behavior change considering different dietary sustainability dimensions. For instance, O'Sullivan et al [12] have designed an intervention to encourage the adherence to a healthy diet with low environmental impact, but they have left aside other relevant behaviors to achieve a sustainable diet, such as food waste, and the socioeconomic consequences of dietary behaviors. An intervention implemented by Monroe et al [13] among US students has targeted food waste reduction and considered the social dimension of individual eating behaviors, such as promotion of the acquisition of local foods from farmers' market. However, this intervention has not tackled the overall dietary pattern of the participants, focusing only on red meat consumption as the main outcome. Besides considering red meat reduction is key to transitioning to sustainable healthy diets, this approach lacks an assessment of the substitution effect and possibility of other changes in untargeted food groups (ie, spillovers), which could offset the overall effect of the intervention [14]. For example, if pork meat is replaced by hard cheese (one of the food products with the highest environmental impact), the dietary environmental impact would increase [15]. Therefore, eating behavior change interventions aimed at promoting sustainable healthy diets as a whole, that is, as a complex interplay of behaviors, are needed [16].

Beyond interventional studies, reviews have documented potential mechanisms of action that motivate or impede behavior change for a healthy and sustainable diet. A diversity of personal and interpersonal factors have been highlighted, such as sociodemographic determinants (ie, gender, age, socioeconomic level, and political orientation), food-related factors (ie, healthiness, taste, and affordability), generic motivational factors (ie, self-efficacy and habit), and specific motives for sustainability (ie, environmental impact, ecoanxiety, and social justice) [17-21]. By contrast, specific barriers have been identified, such as perceiving sustainable healthy food as less tasty [19]. These previous findings are useful for designing interventions (as levers to manipulate and be considered during a study) and for understanding the mechanisms of action that potentially mediate the effect of an intervention on behavior change.

At the methodological level, specific limitations of previous eating and proenvironmental behavior change interventions have also been repeatedly mentioned in the literature. They include the use of long, paper-based food frequency questionnaires that do not allow for frequent and dynamic assessment of the behavior change process [22], short or nonexisting follow-up periods that preclude the appreciation of long-term changes and potential forms of behavioral maintenance over time, and study designs inappropriate for testing causal relationships [23]. To build upon previous research, this pilot trial has been designed to promote individual behavior change for a sustainable healthy diet over a year with measurement bursts of daily eating behaviors digitally implemented through smartphones to better understand and monitor the behavior change process through the study [24].

The primary objectives of this study are as follows:

1.1 To evaluate the effectiveness of a pilot digital behavior change intervention promoting a more environmentally sustainable healthy diet (1.1.a) and relevant specific food outcomes related to dietary sustainability (1.1.b)

By sustainable healthy diet, we refer to a healthy dietary pattern with low environmental impact (objective 1.1.a), that is,

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incentivizing the consumption of fruits; vegetables; legumes; nuts; whole grains instead of their refined versions; unsaturated and nonrefined vegetable oils as main dietary fats; and water as the main beverage instead of others, such as sodas or alcoholic drinks, while promoting a reduction in the consumption of meat (especially red and processed meats), dairy products (especially cheese), sugar-added products, products high in salt, and ultraprocessed foods [25], with minimal food waste and the purchase of food from fair and ethical sources.

Specific food groups or relevant food-related outcomes that will be investigated closely (objective 1.1.b) include: the consumption of red and processed meat, fruits and vegetables, ultraprocessed foods, and dairy products, and food waste.

1.2 To examine the feasibility and acceptability of the intervention and collect relevant information for iteratively improving future interventions

The secondary objectives are as follows:

2.1. The identification of mechanisms of action, notably motivational ones, potentially mediating the effect of the intervention on behaviors

2.2. The identification of potential spillover effects and covariations among different food groups (eg, meat, fruits and vegetables, and ultraprocessed food) and dietary outcomes (ie, diet composition and food waste) occurring over the study

2.3. The identification of potential interaction effects between socioeconomic status and intervention effects on behaviors

Methods

Participants

Potential participants will be approached on the web via email and social media with the support of our institutional communication and outreach activities team (ie, Barcelona Institute for Global Health, ISGlobal). They will be invited to visit a website with a brief description of the study, which will contain a link to a Google form (Google LLC) with questions related to our inclusion and exclusion criteria (provided subsequently) that is to be completed by those interested in participating. Those meeting the inclusion criteria will be classified in 3 groups according to their subjective socioeconomic level. The reason behind this stratification is that socioeconomic level is a major determinant of food choices and individual dietary carbon footprints [26,27]. In addition, deprived populations might benefit less from interventions delivered via digital or mobile means; therefore, it is necessary to include social inequality indicators such as socioeconomic status in the evaluation of interventions to assess their potential differential impact [28,29]. We chose a subjective measure of socioeconomic level and status because it has been shown that socioeconomic status has an impact on how individuals perceive resources beyond their factual resources [30]. This indicator is also strongly associated with physical functioning and health outcomes, beyond objective measurements of socioeconomical level [31]. The MacArthur Scale of Subjective Social Status will be used [32]. This scale ranges from 1 (“perception of low social status”) to 10 (“perception of high social status”). In our study, participants scoring themselves from 1 to 3, 4 to 7, and 8 to 10 will form groups of low, moderate, and high socioeconomic statuses, respectively. Within each group, the first 7 participants meeting the inclusion criteria will be invited to participate in the study after stratification by gender, with the aim of having a balanced number of individuals identifying themselves as women and men in each group. In total, we aim to include 21 participants. The questionnaire used for checking the inclusion and exclusion criteria is provided in Multimedia Appendix 1.

Individuals will be enrolled in the study if they meet the following characteristics: adults aged from 18 to 65 years; residing in Barcelona; speaking and reading Spanish fluently; having a mobile phone supporting the installation of a smartphone app; reporting no history of eating disorders (eg, anorexia nervosa, bulimia nervosa, and binge eating) or any food intolerance or allergy (eg, celiac disease, and nut allergy) or other chronic illnesses that might directly impact eating behaviors (eg, diabetes, cardiovascular disease, cancer, and obesity); following an omnivorous diet; and scoring ≥5 out of 10 points on the dietary questionnaire included in the Google form (refer to Multimedia Appendix 2 for the scoring criteria). The exclusion criteria are being pregnant or planning to be pregnant in the next year, being in a postnatal situation for <3 months, breastfeeding, being professional athletes, following specific diets (eg, vegan, vegetarian, high protein, slimming, gluten free, and low in sugars), reporting any illnesses that might directly impact eating behaviors, and not taking their own decisions about food choices (eg, someone else, such as husband or wife or partner or mother or father, selects what they eat for most of their meals).

Participants will receive financial incentives for their participation. Over the course of the study, there will be 15 evaluation weeks, during which some questions should be answered daily and others once a week (refer to *Measurement* section). For each evaluation week, they will receive €10 (US $10.7) if they complete at least 6 out of the 7 daily questionnaires plus the weekly assessment. Thus, in total, each participant can receive €150 (US $160.4) for full participation in the study. At the end of the study, they will receive their money through bank transfer.

Study Design

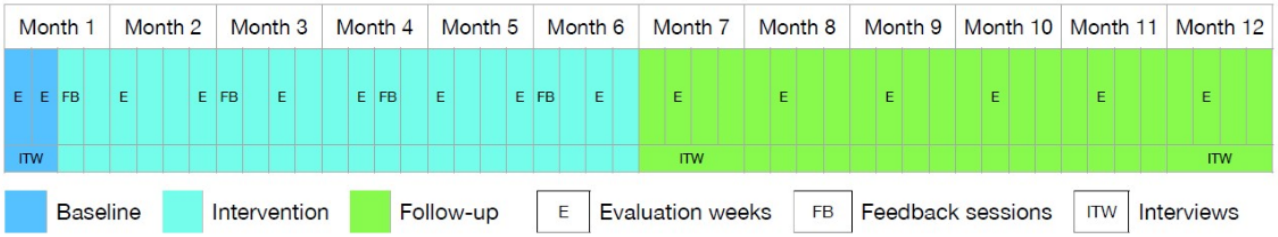
We will run a series of 1-year long ABA hybrid n-of-1 trials, with the first A phase corresponding to a 2-week baseline evaluation, the B phase to a 22-week intervention, and the second A phase to a 6-month postintervention follow-up (refer to Figure 1 for an illustration). We labeled the trials as “hybrid” because, in contrast with pure n-of-trials, we will conduct both individual and group-level analyses depending on the hypothesis tested and for maximizing statistical power, as has been done in similar pilot studies previously, for example, the study by Korinek et al [33]. Therefore, we did not rely on the available checklists for n-of-1 trials, such as the SCRIBE (Single-Case Reporting Guideline In Behavioral Interventions) guideline [34]. In addition to the n-of-1 trials, semistructured interviews will be conducted with the participants to collect contextual information that may aid in understanding the mechanisms by

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which any individual changes in the participants' outcomes may have occurred, complement the quantitative findings on the intervention's feasibility, and assess the intervention's delivery and acceptability.

We labeled this study as a pilot study because our intention is to generate pilot data to plan further iterations of this intervention in the future and build upon this previous experience. Hence, this study aims to produce generalizable knowledge and cannot be labeled as a full trial; however, benefiting from the within-participant measures, testing the effectiveness of the intervention on some specific outcomes and for some specific objectives will be possible.

Figure 1. Study timeline.



Intervention

The intervention will involve sending text messages and providing brief, individualized, web-based feedback sessions based on the eating behavior assessments completed during the study. The text messages will be distributed on 2 nonconsecutive days per week, that is, Tuesdays and Fridays, through the General Data Protection Regulation–compliant app *m-Path* [35] (the same app will be used for implementing the evaluations; refer to the next section, *Measurements*). An in-person meeting with each of the participants will be set on their first day in the study to help them install the app on their mobile phones and provide training if needed. The text messages will contain brief educational messages about human health and the environmental and socioeconomic effects of dietary choices; motivational messages to encourage the adoption of sustainable healthy diets by participants, providing tips to achieve their own objectives; or links to recipes, providing ideas on tasty sustainable healthy meals. These text messages were developed based on a previous attempt to identify relevant behavior change techniques for changing eating behaviors [14] and the compendium of self-enactable techniques to change and self-manage motivation and behavior v1.0 [36].

The understandability and relevance of each message were pretested. Six individuals from our institution matching our inclusion criteria and not implicated in the development of this study were involved in testing and refining the messages. Initially, the messages were tested for comprehension and relevance. Participants rated how understandable each text message was on a scale of 1 to 10. They also had the possibility of commenting on these as well as suggesting improvements for each text message. After this, and based on end users' suggestions, the text messages were reworded, refined, or even removed. Multimedia Appendix 3 shows the content of the final text messages and how they match specific behavior change techniques.

In addition to the text messages, individualized feedback will be provided via short web-based individual meetings (approximately 15 minutes) at the end of the baseline phase or beginning of the intervention phase and then every 6 weeks during the intervention, after 2 measurement weeks (Figure 1). During the web-based sessions, a member of the research team with extensive knowledge of sustainable healthy diets will review the assessments of the previous weeks with the participants; provide tailored advice to improve their diet with regard to its healthiness and sustainability; and answer any questions, doubts, or additional questions that they may have. No feedback session will be provided during the follow-up period.

Measurements

Both quantitative and qualitative data will be collected (Table 1).

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Table 1. Summary table for the study's objectives and their assessment.

Objective and assessment	Measurement
1.1.a Changes in the environmental sustainability and healthiness of the diet	
Quantitative	• Eating behaviors questionnaire

Qualitative	• Baseline interview:
	  • Dietary habits
	  • Healthy and sustainable diet
	• Postintervention interview:
	  • Perceived effectiveness of the intervention

1.1.b Changes in individual food groups and food waste	
Quantitative	• Eating behaviors questionnaire

Qualitative	• Baseline interview:
	  • Dietary habits
	  • Healthy and sustainable diet
	• Postintervention interview:
	  • Perceived effectiveness of the intervention

1.2. Feasibility and implementation of the intervention	
Quantitative	• Relevance of the interventional text messages

Qualitative	• Interview at baseline:
	  • Motivations and expectations from the study
	• Interview after the intervention:
	  • Acceptability of the intervention
	  • Feasibility of the intervention
	  • Elements to improve
	• Interview at the end of the study:
	  • Acceptability of the intervention

2.1. Identifying potential mechanisms of action mediating the effect of the intervention on eating behaviors	
Quantitative	• Mechanism of action questionnaire

Qualitative	• Interview at baseline:
	  • Motivations and expectations from the study
	• Interview after the intervention:
	  • Perceived effectiveness of the intervention
	  • Feasibility of the intervention
	  • Elements to improve

2.2. Identifying potential covariations and spillover effects among food groups and food composition and waste	
Quantitative	• Eating behaviors questionnaire
2.3. Potential interaction of socioeconomic status with the intervention effectiveness	
Quantitative	• Eating behaviors questionnaire

Quantitative Measurements

Questionnaires

Several self-reported questionnaires will be used to collect quantitative data. With the exception of the questionnaire collecting data about baseline characteristics, the questionnaires will be implemented through the study app (*m-Path*). These questionnaires will pop up as notifications in the app.

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Baseline Characteristics

A baseline questionnaire will be used to collect descriptive data about the sociodemographic (ie, gender, age, education, household income, political orientation and postal code, number of people they live with, and if they usually cook for others), anthropometric (ie, height and weight), and health-related (ie, self-perceived physical and mental health, supplement intake, and smoking) characteristics of the participants, together with data about their general motivation for protecting the natural environment (Multimedia Appendix 4). It will be completed once at the inclusion through a Google form.

Eating Behaviors

As shown in Figure 1, eating behaviors will be assessed daily for 15 weeks through a brief questionnaire: participants will have to report their food intake at the end of each day during the 2 weeks of the baseline period; then, every 3 weeks during the intervention period; and afterward, once per month during the follow-up period, representing a total of 105 potential measurement days per participant spread over a year (15 evaluation weeks × 7 measurement days).

A 12-item questionnaire will assess the consumption of specific food groups relevant to environmentally sustainable healthy diets as well as food waste (Table 2) [25]. The present food frequency questionnaire was designed considering the need to minimize the total number of items and make it suitable for daily assessment while adding items about relevant food groups to assess food environmental sustainability and healthiness. For each food group, the number of servings consumed during the day will be asked. Specific foods gathered in the assessed food groups will be detailed, and their serving sizes will be provided with examples that the participants can easily interpret. For instance, a serving of vegetable is reported as a medium size dish of mixed salad, cooked vegetables, or vegetable purée—1 big tomato, 2 carrots, and 1 glass of gazpacho (Figure 2). The size of a serving was established based on the Spanish Society of Community Nutrition recommendations and other Spanish documents [37,38]. The exception will be whole grains and virgin olive oil, which will be assessed in terms of their proportion among all the grains and added fats consumed during the day, respectively. The reason for assessing them as a proportion is because of the priority of healthy fat and carbohydrate intake rather than the total amount of fat and carbohydrate consumed, as the recommended amount of total added fats and carbohydrates depends on the specific energy needs of each person.

Beyond food consumption, daily food waste will be measured with a “yes/no” binary question [39]. As, to our knowledge, there are no previous validated questionnaires to objectively assess the social aspect, changes in this specific sustainability dimension will not be quantitatively assessed but will be explored via the qualitative interviews. An extra open-question item will be added at the end of the 12-item questionnaire to give participants the opportunity to provide any comment or clarification if necessary. To ensure that they understand how their food consumption should be reported, participants will be explained at the initial meeting about the quantification of each food group and provided with an explanatory document showing how to respond to the questionnaire (Multimedia Appendix 5). Eventually, this will also be discussed in feedback sessions.

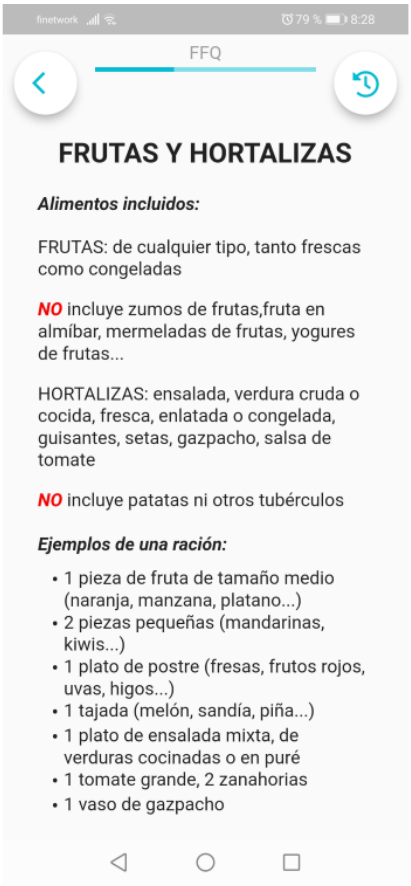
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Table 2. Items for evaluating food consumption and food waste.

Name and item	Answer options
How many servings of the following food groups have you consumed today?	
Red or processed meat	(1) 0 servings, (2) 0.5 servings, (3) 1 serving, (4) 1.5 servings, (5) 2 servings, (6) 2.5 servings, (7) 3 servings, (8) 3.5 servings, (9) 4 servings, (10) 4.5 servings, (11) 5 servings, and (12) more than 5 servings
White meat, fish or eggs	(1) 0 servings, (2) 0.5 servings, (3) 1 serving, (4) 1.5 servings, (5) 2 servings, (6) 2.5 servings, (7) 3 servings, (8) 3.5 servings, (9) 4 servings, (10) 4.5 servings, (11) 5 servings, and (12) more than 5 servings
Dairy products	(1) 0 servings, (2) 0.5 servings, (3) 1 serving, (4) 1.5 servings, (5) 2 servings, (6) 2.5 servings, (7) 3 servings, (8) 3.5 servings, (9) 4 servings, (10) 4.5 servings, (11) 5 servings, and (12) more than 5 servings
Legumes	(1) 0 servings, (2) 0.5 servings, (3) 1 serving, (4) 1.5 servings, (5) 2 servings, (6) 2.5 servings, (7) 3 servings, (8) 3.5 servings, (9) 4 servings, (10) 4.5 servings, (11) 5 servings, and (12) more than 5 servings
Fruits or vegetables	(1) 0 servings, (2) 0.5 servings, (3) 1 serving, (4) 1.5 servings, (5) 2 servings, (6) 2.5 servings, (7) 3 servings, (8) 3.5 servings, (9) 4 servings, (10) 4.5 servings, (11) 5 servings, and (12) more than 5 servings
Nuts or seeds	(1) 0 servings, (2) 0.5 servings, (3) 1 serving, (4) 1.5 servings, (5) 2 servings, (6) 2.5 servings, (7) 3 servings, (8) 3.5 servings, (9) 4 servings, (10) 4.5 servings, (11) 5 servings, and (12) more than 5 servings
Sugary, salty and ultraprocessed foods	(1) 0 servings, (2) 0.5 servings, (3) 1 serving, (4) 1.5 servings, (5) 2 servings, (6) 2.5 servings, (7) 3 servings, (8) 3.5 servings, (9) 4 servings, (10) 4.5 servings, (11) 5 servings, and (12) more than 5 servings
Alcoholic drinks	(1) 0 servings, (2) 0.5 servings, (3) 1 serving, (4) 1.5 servings, (5) 2 servings, (6) 2.5 servings, (7) 3 servings, (8) 3.5 servings, (9) 4 servings, (10) 4.5 servings, (11) 5 servings, and (12) more than 5 servings
Sodas, juices, energy drinks, etc	(1) 0 servings, (2) 0.5 servings, (3) 1 serving, (4) 1.5 servings, (5) 2 servings, (6) 2.5 servings, (7) 3 servings, (8) 3.5 servings, (9) 4 servings, (10) 4.5 servings, (11) 5 servings, and (12) more than 5 servings
What proportion of the cereals you have eaten today are whole grains?	
Whole grains	Scale 0-100: 0=no whole grains at all and 100=all cereals I ate were whole grains
What proportion of the oils and fats you have added to your food today is virgin or extra virgin olive oil?	
Virgin or extra virgin olive oil?	Scale 0-100: 0=no virgin olive oil at all and 100=all the added fat I consumed were virgin/extra virgin olive oil
Have you wasted food today? It includes foods that you discard for different reasons: expired foods, that have gone bad, leftovers both at home and in restaurants...	
Food waste	1=yes and 2=no
Do you want to comment or clarify any point? If you want to report any food that you have consumed that is not collected in the questionnaire, please, indicate the amount consumed as well.	
Comment or clarification	Open question

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Figure 2. Screenshot of the item aimed at fruit and vegetables consumption.



Eating Behavior Scoring Procedure

In terms of the scoring procedure, we designed an index for assessing dietary healthiness and environmental sustainability for every assessment week based on 10 out of the 12 items provided in Table 1. The item related to white meat, eggs, and fish is not considered in the score to avoid overrating protein groups. However, it will be used in the individual food analysis to assess whether, in the case of a reduction in the consumption of red and processed meat and not a simultaneous increase in legume consumption, red and processed meat is replaced by animal-based proteins (objective 2.2). The second item not included in the present index is the one assessing food waste. This last item will be used as a specific outcome in itself and is not included in our main score.

Therefore, the environmentally sustainable healthy diet score is computed from 10 items, each of which is treated continuously from 0 to 1 point; for example, the scoring of red and processed meat consumption is as follows: 0 points for the consumption of >2 servings of red and processed meat and 0.25, 0.5, 0.75, and 1 points for the consumption of 1.5, 1, 0.5, and 0 servings per week, respectively. Food consumption will be assessed as the average daily food consumed during the entire assessment week. The scoring criteria and rationales are listed in Table 3. The total score of the environmentally sustainable healthy diet index will be the sum of the points for each item. Thus, the environmentally sustainable healthy diet index will range from 0 to 10 points, with 0 points being the lowest score in terms of environmentally sustainable healthy diet and 10 points being the highest (best) score (Table 3). Our overall scoring criteria are based on the recommendations of reference entities in the field of nutrition, mainly the EAT-Lancet Commission, Food and Agriculture Organization, and World Health Organization [25,40,41].

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Table 3. Environmentally sustainable healthy diet index: scoring criteria.

Item	What does it assess?	Scoring criteria[a]	Rationale
Red and processed meat	Average daily red and processed meat consumption	• 1 point: 0 serv/w[b] (or <0.15 serv/d[c]) • 0 point: >2 serv/w (or >0.29 serv/d)	Ideally, no red or processed meat should be consumed in a sustainable healthy diet; however, up to 2 servings of red meat per week is acceptable [25].
Dairy products	Average daily dairy product consumption	• 1 point: ≤1 serv/d • 0 point: >2 serv/d	In a sustainable healthy diet, the optimal intake of dairy products should be at the lower end of the range 0 to 500 mL (milk equivalents) [25].
Legumes and soy	Average daily legume and soy product consumption	• 1 point: ≥1 serv/d • 0 point: 0 serv/d	Plant-based proteins should be the main protein source in someone's diet, for their own health and for that of the planet. At least 1 serving of legumes per day should be consumed in a sustainable healthy diet [25].
Fruits and vegetables	Average daily fruit and vegetable consumption	• 1 point: ≥5 serv/d • 0 points: <1 serv/d	At least 5 servings of fruits and vegetable (in total) should be consumed per day [25]. Less than 1 serving per day will be scored as 0 points owing to their crucial daily consumption for a healthy diet.
Nuts (including peanuts)	Average daily nut consumption	• 1 point: 1-2 serv/d • 0 point: 0 serv/d and ≥4 serv/d	Daily consumption of nuts is recommended owing to their health benefits. Indeed, they have been suggested even as a replacement for red meat. However, the quantity should be moderate, as some nut-tree crops are water, fertilizer, and pesticide intensive [15,25].
Sugary, salty, and ultraprocessed foods	Average daily sugary, salty, and ultraprocessed food consumption	• 1 point: 0 serv/w • 0 point: >2 serv/w (or >0.29 serv/d)	These foods should be consumed as less as possible; ideally, they should be avoided or at least consumed no more than once a week [40].
Whole grains	Proportion of servings of whole grains in relation to the total servings of all grains	• 1 point: 100% whole grains • 0 point: 0% whole grains	Whole grains should be prioritized over their refined versions [25].
Oils and fats	Proportion of servings of virgin or extra virgin olive oil in relation to the total added fat intake	• 1 point: 100% virgin or extra virgin olive oil • 0 point: 0% virgin or extra virgin olive oil	Unsaturated and nonrefined oils, mainly virgin olive oil (extra or not) in our context, should be prioritized over other dietary fats [25].
Alcoholic drinks	Average daily alcoholic drink consumption	• 1 point: 0 serv/w • 0 point: >2 serv/w (or >0.29 serv/d)	Ideally, no alcohol should be consumed. According to the World Health Organization, the impact of alcohol consumption on chronic and acute health outcomes is largely determined by the total volume of alcohol consumed [41].
Other beverages: sodas, juices, energy drinks, etc	Average daily consumption of other unhealthy drinks	• 1 point: 0 serv/w • 0 point: >2 serv/w (or >0.29 serv/d)	These foods should be consumed as less as possible; ideally, they should be avoided or at least consumed no more than once a week [40].

[a]Scores will range proportionally from 0 to 1 points. For instance, 0 points will be assigned for the consumption of >2 servings of red and processed meat per week and 1 point for 0 servings per week; 0.25, 0.5, and 0.75 points will be assigned for the consumption of 1.5, 1, and 0.5 servings per week, respectively.

[b]serv/w=servings per week.

[c]serv/d=servings per day.

Mechanisms of Action

Seven items capturing key psychological or motivational mechanisms of action that could potentially play a role in the adherence to sustainable healthy diets will be measured once during each assessment week (refer to objective 2.1 in the *Introduction* and *Statistics* sections). All items are presented in Table 4. Motives for purchasing or eating foods related to dietary sustainability and healthiness (ie, health, environment, affordability, and ethical) will be captured with 4 items adapted from eating motivation validated scales [42,43]. Another item, selected from a validated 12-item questionnaire, will be used to evaluate ecoanxiety, a construct that has been previously described as a relevant mediator of proenvironmental behavior changes [44]. Habit strength of purchasing and eating food while thinking about sustainability will be measured using an item

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adapted from the Self-Report Habit Index and Self-Report Behavioral Automaticity Index [45,46], and finally, self-efficacy toward following a sustainable healthy diet will be assessed using another item [47]. The comprehension of these questions was tested by following the same methodology as the one stated earlier for text message content.

Table 4. Items for food-related motives, ecoanxiety, habits, and self-efficacy.

Category and name	Item	Answer options
Motives		
Health	In the last 7 days, how important was the healthiness of your food when choosing what to eat?	VAS[a] 0-10: 0=not important at all and 10=very important
Environmental impact	In the last 7 days, how important was the environmental impact of your food (ie, carbon footprint, water footprint, etc) when choosing what to eat?	VAS 0-10: 0=not important at all and 10=very important
Fair and ethical sources	In the last 7 days, how important was the working conditions of the producers or sellers of your food when choosing what to eat or where to buy?	VAS 0-10: 0=not important at all and 10=very important
Price	In the last 7 days, how important was the price of your food when choosing what to eat?	VAS 0-10: 0=not important at all and 10=very important
Ecoanxiety		
Ecoanxiety	Over the last week, how often have you felt nervous, anxious or on edge, when thinking about climate change?	VAS 0-10: 0=never and 10=almost everyday
Habit strength		
Habit strength	Selecting healthy foods with low environmental impact and from fair sources is something that I do automatically, without thinking about it	VAS 0-10: 0=totally in disagreement and 10=totally in agreement
Self-efficacy		
Self-efficacy	To what extent do you feel capable of following a sustainable healthy diet?	VAS 0-10: 0=not at all confident and 10=totally confident

[a]VAS: visual analog scale.

Relevance of the Interventional Text Messages

Finally, when sending motivational and educational messages as part of the intervention, we will ask the participants to indicate whether the message is "useful, informative or motivating" or "not useful, not informative or not motivating" in a visual analog scale. This will help us refine our messages for future studies and also control for engagement with the messages, given that an absence of answers will indicate that the participants did not read the message.

Qualitative Measurements

We will conduct 3 semistructured qualitative interviews to gain a deeper understanding of the intervention's effect as well as to assess the feasibility, delivery, and acceptability of the intervention beyond the collected quantitative information. We anticipate that the qualitative data will allow us to complement the quantitative data in a way that adequately captures the contextual, social, and cultural factors that determine the intervention's efficacy and perceived influence.

The first interview will be performed at baseline (during the first 2 weeks; refer to Figure 1) to investigate the eating behaviors of the participants (ie, habitual diet; favorite foods; sources of food; frequency of eating out; and the cultural, social, and personal backgrounds that may determine their behaviors), explore aspects related to sustainable healthy diets (ie, conceptualization of a sustainable healthy diet, participants' views on what should change in their daily lives to achieve such a diet, previous attempts to improve their diet, and measures implemented in those attempts), and explore participants' expectations of the intervention and their motivation for participating in the study. The second interview will be held at the end of the intervention (month 7) to examine participants' perceptions of the effectiveness of the intervention (ie, changes in their eating habits and behaviors and other changes beyond diet, such as variations in their well-being and weight) as well as potential mediators that may have influenced outcomes that were not observable in the quantitative part; determine whether the intervention has been feasible (ie, any difficulties with the app, problems completing the questionnaires, understandability of the text messages, etc); identify potential improvements to the intervention's delivery; and examine participants' views on its acceptability, which includes engagement with both the evaluations and intervention's features and any other relevant practical aspects of the study that the participants would like to discuss. The third interview will be conducted at the end of the follow-up period (month 12) and will be less structured than the previous ones, depending on the outcomes for each participant. The objective of the third interview will be to evaluate the persistence of the acquired eating behaviors, focusing on the personal, social, and contextual facilitators and barriers that may influence the persistence of the outcomes over time, as well as the role of the intervention in this persistence. The interview guides are included in Multimedia Appendix 6.

The objectives and procedures of the interviews will be explained at the beginning of the study in the face-to-face meeting for installing the app, in which each participant will

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confirm their willingness to participate. The researcher who will conduct the interviews will contact them to schedule an interview at each of the 3 time periods. The same researcher will be in charge of all the interviews. The interviews will be conducted on the web using the preferred platform of the participants (Google Meet [Google LLC], Zoom [Zoom Video Communications Inc], Signal [Signal Messenger LLC], WhatsApp [Meta Platforms Inc], etc), will last between 45 minutes and 1 hour, and will be audio recorded. During the interviews, prompts and probes will be used to collect rich and comprehensive data. All interviews will be digitally recorded, anonymized, and transcribed verbatim. Audio files and transcripts will be imported into the NVivo software (QSR International), which will be used for the data analysis.

Data Analyses

Sample Size and Power Analyses for the Quantitative Side of the Project

The sample size for this pilot study is constrained by financial and human resources. We plan to recruit a total of 21 participants, with 7 participants in each subjective socioeconomic group (refer to the *Participants* section). However, in terms of statistical power, we will benefit from the intensive longitudinal nature of the study, that is, 15 evaluation weeks and up to 105 daily observations per participant. For objective 1.1.a, for which a weekly environmentally sustainable healthy diet index will be used, up to 315 observations will be available in total (21 participants × 15 evaluation weeks) and 105 observations per socioeconomic group (7 participants × 15 evaluation weeks). For objective 1.1.b, for which the daily raw data will be used, up to 2205 observations will be available in total (21 participants × 105 daily assessments), 735 observations in the 3 socioeconomic groups (7 participants × 105 daily assessments), and 105 observations at the individual level (as a general rule of thumb, a minimum of 70 observations are required for conducting individual-level analyses [48]). Given the pilot nature of this trial, we conducted power simulation analyses only for objective 1.1.a (ie, change in the weekly level of food healthiness and environmental sustainability). Considering group-level analyses and the analytical strategy detailed in the next section and assuming an increase of 2 units in the environmentally sustainable healthy diet score per phase, simulated power analysis indicated an adequate power value of 96%. The simulation was performed by generating the response variable as follows:

- Fixed effects: the intercept was set at 6, and the fixed coefficient for the phase was set as −2 for the initial phase and +2 for the final phase based on our average expected change in the main outcome.
- Random effects: it was assumed that each participant would have both a random slope and a random intercept and that both followed normal distributions, with SDs of 2 for the intercept and 0.5 for the slope. The correlation between them was set as 0.2. The random effect for each participant was created by drawing random numbers from a multivariate normal distribution whose covariance matrix was specified using these parameters (R mvrnorm from the package *MASS*).

Then, a linear mixed regression was performed on the data (R lme from the package *nlme*) using phase as a fixed effect and specifying a random slope and intercept for each participant across time. This process was repeated 1000 times, and the significance level for the fixed effect was 0.05.

Quantitative Data Analysis

Analyses for this project will be conducted with the statistical software R (R Foundation for Statistical Computing) [49]. The code and data generated for this study will be made open access when available.

Objective 1.1.a: Changes in the Environmental Sustainability and Healthiness of Diet

To test the main effect of the intervention on the environmental sustainability and healthiness of diet at the group level, linear mixed regression will be performed and expressed as measurement occasions (here, going from 1, first evaluation week, to 15, last evaluation week), using an ordered 3-categories phase variable as a fixed effect, which takes the values of baseline, intervention, and follow-up. Polynomial functions will also be fitted to the time variable to determine whether the index demonstrates any nonlinear patterns across time. If nonlinear patterns are detected, then other patterns (eg, quadratic, cubic, and piecewise) will be examined and selected based on visual inspections and goodness-of-fit indicators. Moderation analysis will be performed by exploring the role of the subjective socioeconomic level (ie, 3 socioeconomic groups entered as fixed effect) with regard to changes in diet. Fixed baseline characteristics will be included as control variables (ie, age, gender, education, income, and political orientation). Individual trajectories will be plotted, and heterogeneity in participants' responses to the intervention will be discussed based on visual analyses using relevant guidelines for n-of-1 trials [50] (individual weekly changes in the whole diet will not be statistically modeled because only 15 observations will be available per participant).

Objective 1.1.b: Changes in Individual Food Groups and Food Waste

An analytical strategy similar to that used for objective 1.1.a will be followed for testing the effect of the intervention on specific food groups, including red and processed meat, fruits and vegetables, ultraprocessed foods, and dairy products, and food waste. A linear mixed model similar to that performed for the first objective will be performed, but time will be expressed as measurement days instead of weeks, thus ranging from 1 to 105. In addition to the group and subgroup analyses performed for objective 1.1.a and maximizing the higher number of observations per participant within those outcomes, individual-level models will also be used to quantify the effect of the intervention on each participant separately from the others by following an idiographic approach.

Objective 1.2: Feasibility of the Intervention

This objective will mainly be investigated through the qualitative data analyses reported in the next section. Simple quantitative analyses will be conducted to examine the relevance of our motivational and educational messages (ie, scores provided to the text messages at the individual and collective levels). We

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also report the percentage of missing values for each measurement burst.

Objective 2.1: Identifying Potential Mechanisms of Action Mediating the Effect of the Intervention on Eating Behaviors

Longitudinal mediation analyses will be conducted to understand the processes through which the intervention will potentially affect the environmental sustainability of eating behaviors. These analyses will be conducted independently for the 7 potential mediators presented in the section *Mechanisms of Action* (ie, motives for health, environmental, social, and affordability; ecoanxiety; habits; and self-efficacy) and by following recent guidelines based on longitudinal multilevel structural equation models [51]. These analyses will be performed for the total sample and per socioeconomic subgroup with the environmentally sustainable healthy diet index as the first dependent variable and, in secondary analyses, with the weekly level of the relevant food outcomes mentioned in objective 1.1.b (ie, red and processed meat, fruits and vegetables, ultraprocessed food, dairy products, and food waste). These food groups and food waste will be analyzed here at the weekly level to match the temporal resolution of the mechanisms of action that are also assessed weekly (and not daily).

Objective 2.2: Identifying Potential Covariations and Spillover Effects Among Food Groups and Between Food Composition and Food Waste

Covariations and spillover effects will be examined using network visualizations of the partial correlation matrix by following published guidelines and previous applications in the health behavior domain [52,53]. The within-participant network will be computed by subtracting the mean of each participant's behavior across the 15 assessment weeks from their scores at each time, thus estimating a network of interrelationships centered on each person's "average" behavioral pattern over 12 months. This method allowed us to test whether variations from the mean level for one behavior are associated with variations from the mean for other behaviors and, hence, covariation or spillovers. These networks will be estimated for the total group and the 3 socioeconomic subgroups using the 12 items presented in Table 2. Data from the 3 phases will be combined together to maximize the statistical power.

Objective 2.3: Potential Interaction of Socioeconomic Status With the Intervention Effectiveness

As mentioned in the previous sections, the role of socioeconomic status will be explored in objectives 1.1.a, 1.1.b, 2.1, and 2.2 by conducting group-specific analyses for the low, moderate, and high socioeconomic groups (refer to the above-mentioned sections for further details).

Qualitative Data Analysis

The qualitative data will be analyzed using framework analysis, a thematic-oriented approach to qualitative data analysis that is gaining popularity in the health sciences and is well suited for analyzing data from semistructured interviews [54,55]. The output of this method is a matrix containing the participants in the rows, analytical codes in the columns, and a data summary in the cells. Using this matrix, researchers can compare the participants' views within each participant and across participants, thereby identifying patterns across the data set (ie, code-based analysis) while preserving the context of the participants' views (ie, analysis by case). In addition, because of the structured nature of the method, framework analysis is helpful in studies that involve multidisciplinary research teams with a majority of members having quantitative expertise, such as this study. In this study, framework analysis will be implemented according to the following 6 steps outlined by Gale et al [55]: familiarizing with the interview transcripts, coding the transcripts, developing a working analytical framework by grouping the codes, applying the analytical framework to the transcripts, charting data into the framework matrix, and interpreting the data. Two researchers will independently code and apply the analytical framework. Disagreements between the researchers will be discussed until a consensus is established, if required, with the assistance of a third researcher.

Integration of the Quantitative and Qualitative Data

After completing all the analyses, a back-and-forth process will be used to integrate the quantitative and semistructured interview findings [56]. Joint displays will be used to facilitate this process, an increasingly used visual tool designed for facilitating integration in mixed methods studies [57]. Specifically, using joint displays, both quantitative and qualitative findings for objectives 1.1.a, 1.1.b, 1.2, and 2.1 will be juxtaposed, and the extent to which the qualitative results confirm, reject, complement, or expand on the quantitative results will be assessed. By integrating the quantitative and qualitative findings, a more comprehensive and fine-grained understanding of the effectiveness, feasibility, and implementation of the intervention will be gained.

Ethics Approval

This study was approved by the Drug Research Ethical Committee (CEIm) of Parc de Salut MAR on October 19, 2022 (2022/10304/I), and will be conducted in accordance with the Helsinki Declaration. The participants will be required to provide written informed consent to participate in the study during the baseline visit before any study procedure.

Results

This study was approved by the Ethics Committee on 19 October, 2022. It started in October 2022. The initial results are expected to be published in May 2023. The final results are expected by October 2023.

Discussion

Principal Findings

With regard to objective 1.1.a, we expect environmentally sustainable healthy diet to positively change over time (increasing score for the environmentally sustainable healthy diet index) with small to medium effect sizes, as observed in most previous behavior change interventions [14]. With regard to objective 1.1.b, which focuses on food groups and food waste and reflects the changes in the index, we expect the consumption of meat, dairy products, and ultraprocessed food to decrease

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over time and the consumption of unprocessed or minimally processed plant-based foods to increase. However, the rate of change might differ from one food group to another; for example, an increase in fruit and vegetable consumption might occur earlier in the intervention than a decrease in meat consumption, which might indicate that this second behavior is more difficult to change. At the individual level, we also expect the shape of those changes to be heterogeneous across participants, with linear improvements, 1-step changes, and inverse U–shape, for example. Objective 1.2 (feasibility of the study) is not hypothesis driven.

With regard to objective 2.1, we expect substantial mediation effects of motivations, ecoanxiety, habit, and self-efficacy on eating behaviors, with positive changes in eating behaviors being partially explained by positive changes in these variables. More specific hypotheses can also be formulated; for example, we expect motivation for protecting the environment to mediate changes in the food groups with the highest environmental impact (eg, meat) more than those in the food groups mainly relevant for health (eg, ultraprocessed food).

We do not have clear and specific hypotheses regarding the covariations among food groups and among dietary outcomes (objective 2.2) and hypotheses regarding the moderating role of participants' socioeconomic level (objective 2.3), given that only a few studies have examined these dimensions before; overall, the participants from the lowest socioeconomic group may present a less healthy and environmentally sustainable diet than the participants belonging to the higher socioeconomic groups [27,58].

Limitations

Our primary outcome is a weekly score of environmentally sustainable healthy diet created based on daily food measures to avoid recall bias. This specific questionnaire and scoring procedure have not yet received proper validation. However, this does not constitute a limitation to us. The questionnaire gathered common food groups and framed them as in other digital food frequency questionnaires validated for the Spanish population [59]. It provides information about specific foods gathered in each group with the serving size. The reason for using this customized tool instead of any previously validated is that this study is among the first to monitor changes in environmentally sustainable healthy diet as a whole and through dynamic daily assessments (instead of lower resolution measures, eg, monthly assessment), thus justifying the use of a new and shorter measurement tool. Similarly, the lack of validation of our scoring procedure is not a major limitation given that (1) this study is a pilot study and the data gathered will also be used to refine our scoring procedure later in time and that (2) the score is developed in a straightforward manner based on the EAT-Lancet Commission, and Food and Agriculture Organization, and World Health Organization recommendations [25,40,41]. Our team is conducting parallel validation studies of this questionnaire and scoring procedure, and we also expect to use the data from this pilot intervention to examine the sensitivity of the tool to detect behavior changes (with the ultimate aim of refining this questionnaire and scoring procedure for future interventions).

Comparison With Prior Work

We prefer performing n-of-1 trials rather than adopting other traditional designs, such as parallel randomized control trials, because the former present some advantages, including (1) the possibility of developing efficient studies (in terms of time and human and financial resources) with few participants involved but providing forms of causal inference to quantify the intervention's effectiveness for each participant (ie, within-individual randomization and time effect [60]); (2) the possibility of optimizing and refining the intervention over the course of the study based on the empirical data collected from the participants' feedback [61]; and (3) the possibility of exploring heterogeneity between participants given that statistical inference can be produced at the individual level, which makes the tailoring of current and subsequent personalized interventions easier [62].

In recent years, some studies have been designed or implemented with the aim of promoting sustainable healthy eating behaviors [12,13]. However, to the best of our knowledge, this is the first study to address the overall dietary pattern, food waste, and socioeconomic dimensions of food in an intervention. In addition, the brief and continuous assessment implemented through the app will provide, for the first time in the domain of sustainable healthy diet, a high-resolution view of behavior changes useful for improving our understanding of the overall process compared with studies using traditional low-resolution measurement paradigms (eg, baseline and 3- and 6-month follow-ups). If we are able to manage potential technological issues that could happen with the app, the use of technology to monitor participants remotely should also help make this intervention minimally burdensome for the participants, as they do not need to attend in-person meetings.

Conclusions

This study will address the urgent topic of adopting overall sustainable healthy diets, thus filling a gap in the literature and providing pilot data for scaling up the intervention in a full randomized controlled trial. It will provide insights into the effectiveness of the pilot intervention in changing eating behaviors toward a sustainable healthy diet, considering the whole dietary pattern and, hence, spillovers among food groups and among dietary outcomes; it will help to determine the moderation and interaction effects of several individual characteristics, such as socioeconomic level and gender; and it will address its own feasibility to determine the barriers to and enhancers of the intervention, which will help us refine and optimize the intervention for future studies.

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Acknowledgments

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Data Availability

The data sets generated during or analyzed during this study will be available at Open Science Framework [63].

Conflicts of Interest

None declared.

Multimedia Appendix 1
Google form used for checking the inclusion and exclusion criteria (English and Spanish versions).
[PDF File (Adobe PDF File), 635 KB - resprot_v12i1e41443_app1.pdf]

Multimedia Appendix 2
Scoring criteria for the dietary questionnaire included in the Google form to select participants.
[PDF File (Adobe PDF File), 106 KB - resprot_v12i1e41443_app2.pdf]

Multimedia Appendix 3
Text messages (English and Spanish versions) to be sent to the participants during the intervention phase along with the behavior change techniques they match.
[PDF File (Adobe PDF File), 235 KB - resprot_v12i1e41443_app3.pdf]

Multimedia Appendix 4
Baseline questionnaire (English and Spanish versions).
[PDF File (Adobe PDF File), 133 KB - resprot_v12i1e41443_app4.pdf]

Multimedia Appendix 5
Supportive material showing specific food items gathered in the assessed food groups and examples of 1 and 0.5 servings (English and Spanish versions).
[PDF File (Adobe PDF File), 157 KB - resprot_v12i1e41443_app5.pdf]

Multimedia Appendix 6
Interview guide (English and Spanish versions).
[PDF File (Adobe PDF File), 159 KB - resprot_v12i1e41443_app6.pdf]

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Abbreviations

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Protocol

Improving Mental Health Literacy and Reducing Psychological Problems Among Teachers in Zambia: Protocol for Implementation and Evaluation of a Wellness4Teachers Email Messaging Program

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Abstract

Background: Primary, basic, secondary, and high school teachers are constantly faced with increased work stressors that can result in psychological health challenges such as burnout, anxiety, and depression, and in some cases, physical health problems. It is presently unknown what the mental health literacy levels are or the prevalence and correlates of psychological issues among teachers in Zambia. It is also unknown if an email mental messaging program (Wellness4Teachers) would effectively reduce burnout and associated psychological problems and improve mental health literacy among teachers.

Objective: The primary objectives of this study are to determine if daily supportive email messages plus weekly mental health literacy information delivered via email can help improve mental health literacy and reduce the prevalence of moderate to high stress symptoms, burnout, moderate to high anxiety symptoms, moderate to high depression symptoms, and low resilience among school teachers in Zambia. The secondary objectives of this study are to evaluate the baseline prevalence and correlates of moderate to high stress, burnout, moderate to high anxiety, moderate to high depression, and low resilience among school teachers in Zambia.

Methods: This is a quantitative longitudinal and cross-sessional study. Data will be collected at the baseline (the onset of the program), 6 weeks, 3 months, 6 months (the program midpoint), and 12 months (the end point) using web-based surveys. Individual teachers will subscribe by accepting an invitation to do so from the Lusaka Apex Medical University organizational account on the ResilienceNHope web-based application. Data will be analyzed using SPSS version 25 with descriptive and inferential statistics. Outcome measures will be evaluated using standardized rating scales.

Results: The Wellness4Teachers email program is expected to improve the participating teachers' mental health literacy and well-being. It is anticipated that the prevalence of stress, burnout, anxiety, depression, and low resilience among teachers in Zambia will be similar to those reported in other jurisdictions. In addition, it is expected that demographic, socioeconomic, and organizational factors, class size, and grade teaching will be associated with burnout and other psychological disorders among teachers, as indicated in the literature. Results are expected 2 years after the program's launch.

Conclusions: The Wellness4Teachers email program will provide essential insight into the prevalence and correlates of psychological problems among teachers in Zambia and the program's impact on subscribers' mental health literacy and well-being.

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The outcome of this study will help inform policy and decision-making regarding psychological interventions for teachers in Zambia.

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KEYWORDS

burnout; stress; Zambia; Africa; teacher; educator; school; anxiety; wellness; depression; e-mental health; intervention; health literacy; mental health; depressive; psychological issue; psychological problem; text message; messaging; decision-making

Introduction

Background

Teaching is a high-demanding profession, and teachers experience a high prevalence of stress, burnout, anxiety, and depression. In a study, 25.3% of teachers reported mild to moderate stress [1], and high burnout was reported by 33.3% of teachers, followed by 27.6% at risk for moderate burnout [2]. In addition, 38% of teachers reported clinically significant anxiety [3], while depressive symptoms were also found in 35.3% of the teachers in a study [4]. Burnout, also known as professional exhaustion syndrome, is characterized by extreme and prolonged or recurrent stress at work [5-7]. The prevalence of burnout ranged from 25.12% to 74%, stress ranged from 8.3% to 87.1%, anxiety ranged from 38% to 41.2%, and depression ranged from 4% to 77% when only clinically meaningful (moderate to severe) psychological conditions were considered among teachers [8]. When homeostasis is disturbed, stress is produced. According to the stress framework system, there are 3 kinds of stress: sustress (inadequate stress), eustress (good stress), and distress (bad stress) [9]. Eustress may have health benefits, but both sustress and distress may lead to the impairment of normal physiological functions and could result in pathological conditions [9]. Burnout among professionals such as teachers is a stress-related problem and a risk factor for depression and other cardiovascular diseases [10,11]. According to Gluschkoff, school-related stress may lead to depressive symptoms among teachers [12,13], and often, teachers feeling more stressed are also burned out [14]. Various studies have also reported that the type of school, income satisfaction, depression, and perceived stress were all significantly associated with burnout [15,16]. Stress and emotional demands linked with teaching can lead to emotional exhaustion and lower job satisfaction [17]. Symptoms of stress and burnout among teachers directly or indirectly affect their teaching and students' performance [17,18].

Literature has reported several predictors of teacher stress, burnout, anxiety, and depression, including age, job satisfaction, subject taught, and work-related factors [8,16,19-23]. Teachers constantly face increased challenges such as workload, role conflict, and role ambiguity, which cause work stressors and result in mental and physical health challenges [24]. Role conflict and role ambiguity also predict teachers' burnout [25]. Teachers' stress levels increase when their demand exceeds their capability [26-28], leading to burnout and anxiety [29,30]. Several studies have reported a significant overlap between stress, burnout, anxiety, and depression [31-36]. A survey by Besse et al [37] reported that teachers with moderate depressive disorder had higher levels of perceived stress, anxiety, low job satisfaction, and a relatively lower quality of life. Depression among teachers can also significantly affect their health, productivity, and functionality and it typically has persistent effects in both their personal and professional lives [37,38]. Teachers with low job satisfaction are also more susceptible to experiencing burnout, high anxiety levels, and depression [2,39].

Teachers in African countries similarly experience stress, burnout, depression, and anxiety. A cross-sectional study in Egypt by Desouky and Allam [20] reported a high prevalence of occupational stress (100%), anxiety (67.5%), and depression (23.2%) among teachers. This study also indicated that workload had a positive relationship with stress and that occupational stress scores were significantly higher among teachers with an increased workload [20]. A study in Ghana also reported that a poor workplace environment was associated with increased anxiety and depressive symptoms [40]. In Lusaka, Zambia, a teacher survey said that 81% of the participants rated stress levels as often, and 59% of the respondents acknowledged experiencing health-related problems due to stress [18]. Several studies also indicate that sources of stress among teachers include low salaries or income, work-related issues, a heavy workload, poor school climate, and large class sizes [1,18,24]. Another study in Zambia also reported that teachers moderately experienced stress that manifests emotionally in terms of feelings of fatigue, cardiovascular manifestations, and gastronomic manifestations [41]. These work-related psychological problems teachers encounter need to be addressed at institutional and professional levels. One approach to address the above-noted psychological issues is directly providing teachers with mental health support through educational programs that improve their mental health literacy. Teachers need to obtain and sustain positive mental health themselves. They have the skills to decrease the stigma associated with mental health problems and to promote and encourage students to seek timely and appropriate help when necessary [42]. Moreover, teachers play an essential role as partners in identifying, preventing, and intervening in mental health problems among children and youths [43,44]. Hence, improving teachers' mental health literacy will benefit teachers and students.

Health literacy has recently transformed into a broader concept fundamental for improving an individual's health outcome, reducing health inequities in populations, and enhancing the operation and development of health systems and policies [42,45,46]. Mental health literacy, in particular, plays a significant role in improving access to mental health care and reducing stigma related to mental problems [47]. Studies have

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shown that individuals with strong health literacy skills have better health and well-being than those with weak skills [45]. A survey by Kutcher [48] in sub-Saharan Africa noted that there are high stigma levels, poor mental health literacy, and less capacity at the community level to address this health care need. In another study, Kutcher [46] suggested that mental health literacy interventions should be appropriate and delivered within educational settings using modern electronic delivery platforms and strategies that enhance literacy competencies.

In Zambia, the number of frontline mental health workers, psychologists, and occupational therapists is limited and has been declining over time [49]. This has created mental health literacy and psychological treatment gaps that impact teachers and the public. Innovative, human resource-independent and cost-effective ways of delivering mental health literacy and psychological interventions to teachers in Zambia and other low-resource countries, particularly in sub-Saharan Africa, are urgently needed. The use of digital technology–based services such as SMS text and email messaging is an innovative and practical way to deliver mental health intervention and programs to improve access to mental health education and psychological help [50]. Cognitive behavioral therapy–inspired daily supportive messages delivered via SMS text messaging and web-based applications were effectively used to support population-level mental health in Canada during the COVID-19 pandemic and helped to reduce stress, anxiety, and depression [51,52]. Email messaging is another accessible and unique way to deliver low-cost cognitive behavioral therapy–based psychological interventions to the general public with mental health problems [50,53]. Participants' responses on the satisfaction survey associated with the use of supportive SMS text messages in Canada endorsed their desire to receive the same intervention in the form of email [54].

There are about 7 billion mobile phone users globally, and developing countries account for 80% of newly purchased mobile phone devices. Therefore, mobile phone access and ownership are on the rise worldwide, and the advancement in mobile technology has helped shape digital communication [55]. Currently, most mobile phones allow for data plans and internet Wi-Fi connectivity, which makes it possible for individuals to access their emails on their cell phones. Thus, email technology may be easily accessible to teachers with mobile phones who can readily read emails on these devices. Furthermore, teachers who do not have mobile phones can still access emails through personal, institutional, or public computers, making this intervention widely available to all teachers. A study by Shalaby et al [54] also reported that 60% of respondents agreed to receive email messages as part of their health care, an indication of the high level of acceptability of using email as an eHealth tool.

According to Mayeya [49], the mental health services situation in Zambia could be considered critical, requiring immediate attention. To the best of our knowledge, no previous studies have been conducted to assess teachers' mental health literacy levels in Zambia. For this study, 2 cities along the rail line (Livingstone and Lusaka) and 2 cities away from the rail line (Kasama and Solwezi) would be chosen. This would ensure comprehensive and acceptable findings for all teachers' mental wellness in Zambia. A supportive email messaging program for teachers in Zambia seems timely. It can reduce the gaps in psychological interventions available to teachers and improve their mental health literacy.

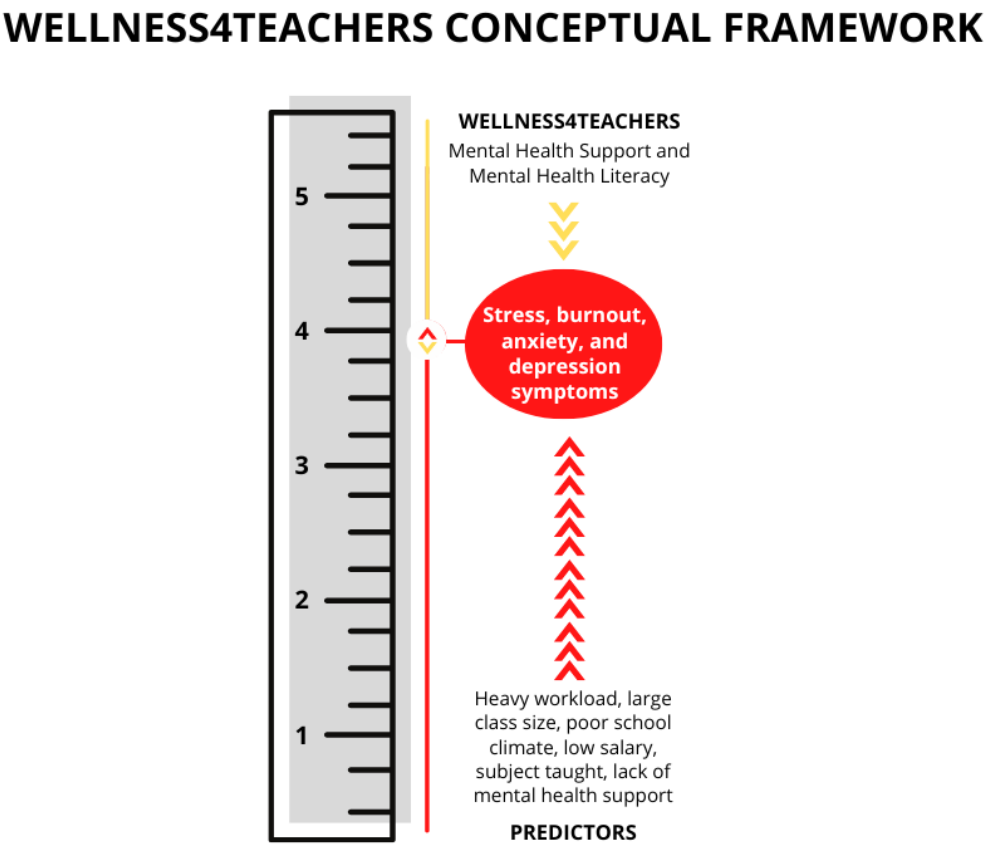
Study Objectives, Aims, and Purpose

The primary objective of this study is to determine how daily supportive email messages plus weekly mental health literacy information delivered via email would help improve mental health literacy and reduce the prevalence of moderate to high stress symptoms, burnout, moderate to high anxiety symptoms, moderate to high depression symptoms, and low resilience among schoolteachers in Zambia. The secondary objectives of this study are to map and determine the baseline prevalence and correlates of moderate to high stress, burnout, moderate to high anxiety, moderate to high depression, and low resilience among schoolteachers in Zambia. The specific objectives are as follows: (1) to determine the baseline prevalence and correlates of moderate to high stress, burnout, moderate to high anxiety, moderate to high depression, and low resilience among school teachers in Zambia. (2) To implement daily supportive email messages and weekly mental health literacy information delivered via email to improve mental health literacy. (3) To determine the effectiveness of implementing the Wellness4Teachers email messaging and mental health literacy program to reduce the prevalence of moderate to high stress symptoms, burnout, moderate to high anxiety symptoms, moderate to high depression symptoms, and low resilience among school teachers in Zambia.

Wellness4Teachers email messaging and mental health literacy program is anticipated to reduce the prevalence and severity of stress, burnout, anxiety, depression, and low resilience symptoms among Zambian teachers by at least 20%. Figure 1 is a conceptual framework illustrating the association between the various sociodemographic, personal, and work-related or organizational factors and stress, burnout, anxiety, and depression in teachers. The framework was based on empirical evidence, which showed a greater than 20% reduction in depression symptoms in 2 randomized controlled trials [56,57] and a greater than 20% reduction in anxiety symptom scores from baseline to 6 weeks and 3 months in subscribers of Text4Hope [51,52]. An increased number of predictors such as socioeconomic and demographic factors, workload, and poor organizational structure may correlate with the prevalence and severity of burnout and other psychological and mental health conditions experienced by teachers [3,16,19-23,49,58].

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Figure 1. Conceptual framework.



Wellness4Teachers Email Messaging Program

The Wellness4Teachers email messaging program is one of the many suites of ResilienceNHope messaging programs, powered by the ResilienceNHope web-based application [53,59] and facilitated by the Global Psychological eHealth Foundation [60]. Wellness4Teachers email program is a daily supportive email messaging program designed to address stress, burnout, anxiety, and depression. The messages have been crafted by mental health therapists, psychiatrists, and psychologists based on the principles of cognitive behavioral therapy and have also been reviewed by the lead author, an education specialist. Teachers can personally subscribe to the Wellness4Teachers email program through the Lusaka Apex Medical University institutional account through collaboration between the Lusaka Apex Medical University and the local teachers' unions. Teachers will receive daily supportive messages designed to address stress, burnout, anxiety, and depression and weekly links to mental health literacy information for 1 year. The email messages will be noninteractive (one-way), and subscribers will be informed of the noninteractive nature of the email messaging program during the initial welcoming and introductory message. Different messages will be received daily by subscribers from a bank of messages. The mental health crisis services number in Livingstone, Lusaka, Kasama, and Solwezi will be included in the introductory message to subscribers, which they can call if they are in crisis. Examples of messages to be delivered to subscribers of the Wellness4Teachers email messaging program include:

- Even though thoughts are often seen as accurate, they are just guesses, not facts. Burnout and stress can make you experience negative emotions, making your thoughts overly negative. Take a moment to notice how you feel. Try to replace negative thoughts with positive thoughts and actions.
- Effective goals are "SMART": Specific, Measurable, Achievable, Realistic, and Timely. Think of one thing you want to accomplish. Break it down into smaller steps. Only focus on one small step, not the big overwhelming goal. General goals (eg, Getting fit) are not motivating. Making goals more specific (eg, Walk twice this week) are more achievable.
- We each have different signature strengths. It's not about competing with others but learning our unique strengths. Strengths come in many varieties: humor, curiosity, persistence, kindness, love, forgiveness, cooperativeness, and optimism. Share your strength with others. Help a struggling colleague.

Examples of the weekly mental health literacy information sent to subscribers can be found on the Global Psychological eHealth Foundation and the Mental Health Literacy for Educators websites [60,61].

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ResilienceNHope messaging programs are evidence-based e-mental health programs designed to address mental health literacy and close the psychological treatment gap for individuals and communities globally [59]. The efficacy of the ResilienceNHope suite of programs has been evaluated and established through several randomized controlled clinical trials and evaluations of population-level programs. In a randomized controlled trial in Fort McMurray, Alberta, Canada, involving 73 patients diagnosed with major depressive disorder, the change in the mean difference in the Beck Depression Inventory scores between the intervention group (those who received twice-daily supportive SMS text messages for 3 months) and the control group (those who received a single thank-you message) was significant with an effect size (Cohen *d*) of 0.67 [62]. A similar trial was conducted in Ireland with similar results [63,64]. In addition, there were statistically significant reductions in the prevalence and mean scores on standardized measures for stress, anxiety, and depression at 6 weeks and 3 months for subscribers to the Text4Hope program [51,52].

Methods

Study Design

This will be an interventional study, specifically a quasi-experimental design, which will employ a quantitative longitudinal and cross-sectional survey methodology with data collected from subscribers of Wellness4Teachers email messaging service users.

Data Collection

Quantitative data will be collected using web-based questionnaires through the ResilienceNHope secure platform for managing web-based surveys and databases [57]. The web-based questionnaires will be designed to collect demographic and work-related variables and assess mental health literacy and clinical variables, including stress, burnout, anxiety, depression, and resilience [59]. The web-based surveys will be distributed to subscribers on enrollment at 6 weeks, 3 months, 6 months, and 12 months. The follow-up surveys will also include questions assessing subscriber experience and satisfaction with the Wellness4Teachers email messaging program.

Participants' Recruitment and Subscription

Subscription to the Wellness4Teachers email messaging program will be initiated by individual teachers accepting an invitation to subscribe from the Lusaka Apex Medical University's organizational account on the ResilienceNHope web-based application. The local principal investigator (CC) will work with the Zambian Ministry of Education, the Lusaka Teachers Association, district school boards, and heads of elementary and high schools to invite teachers to join the Wellness4Teachers email messaging program. Participants will be eligible for inclusion if they are school teachers and residents of Livingstone, Lusaka, Kasama, or Solwezi. Subscribers can unsubscribe from the program at any time by clicking the unsubscribe link associated with the messages. Based on the 10% dropout rate recorded for the Text4Hope program [51,52], the anticipated dropout rate for the email messaging program will be less than 15% [54].

Study Setting

The study will occur in Zambia. Zambia is an eastern, sub-Saharan African country with an estimated 2021 population of 18,920,657 and nearly half of the population under the age of 15 years, with almost equal proportions of males and females (49.5% and 50.5%, respectively) [65]. Zambia covers about 290,587 square miles (743,390 km^2), and the population's median age is only 16.8 years [65,66]. The country is prone to natural and man-made disasters such as floods, droughts, mine accidents, and deforestation [49]. War and other political uncertainty in surrounding states result in a refugee influx. The study will focus on 4 main cities in Zambia: Livingstone, Lusaka, Kasama, and Solwezi. Livingstone is a capital city in the southern part of the country, with a land area of 85,283 km^2 and a population of 1,799,885 in 2014. There were about 1241 basic schools in 2012 and 45 high schools in 2004. In 2014, there were 6158 teachers in school grades 1-9, and 1027 in high school [67].

Lusaka is the capital of Zambia and one of the 20 cities in Zambia, with a total land area of 375 km^2 with an approximate population of 3,042,000 in 2022, a 4.68% increase from 2021 [68]. There were 111 secondary schools and 758 primary schools in Lusaka in 2017 [66], and about 10,822 primary school teachers and 3383 secondary school teachers in Lusaka in 2016 [66]. There are several rural cities in Zambia, including Kasama (Northern Province) and Solwezi (North Western Province). Kasama had a land area of 77,650 km^2 and a population of 1,264,212 in 2014. There were 1208 basic schools and 26 high schools in 2004. In 2004, there were 5169 teachers in all schools, grades 1-9, and 656 teachers in high schools, grades 10-12 [67]. Solwezi has a land area of 125,826,656 km^2, and a total population of 811,706 was recorded in 2014. Basic schools in 2012 were 747 and 23 high schools in 2004. Teachers in all schools in grades 1-9 were 2837 in 2004, while teachers in high schools in grades 10-12 were 509 the same year [67].

Outcomes and Measures

Validated screening scales for self-reported symptoms will be used to assess clinical outcomes. These include the Mental Health Literacy Scale [69], the Generalized Anxiety Disorder 7-item (GAD-7) Scale (a GAD-7 score of ≥10 indicates moderate to high anxiety) [70], the Perceived Stress Scale (PSS-10) (a PSS-10 score of ≥10 indicates likely moderate to high stress) [71], the Brief Resilience Scale (BRS; BRS mean scores ranging from 1.00 to 2.99 indicate low resilience, scores from 3.00 to 4.30 suggest normal resilience, and mean scores from 4.31 to 5.00 suggest high resilience) [72,73], and the Patient Health Questionnaire-9 (PHQ-9; a score of ≥10 indicates moderate to high depression) [74]. Burnout will be assessed using the Maslach Burnout Inventory (MBI), specifically the MBI-Educators Survey, for use with educators [75,76]. An exploratory outcome will be to evaluate the acceptance of the Wellness4Teachers program by teachers in Zambia, which can be measured by the proportion of the target population (teachers in Livingstone, Lusaka, Kasama, and Solwezi) who subscribe

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to the program. Primary outcomes for this study will be changes in mental health literacy and the prevalence of moderate to high stress, burnout, moderate to high anxiety, moderate to high depression, and low resilience from baseline to 6 weeks, 3 months, 6 months, and 12 months among the subscribers of the Wellness4Teachers Zambia program. Secondary outcomes include the mean score on the Mental Health Literacy Scale and the prevalence of moderate to high stress, burnout, moderate to high anxiety, moderate to high depression, and low resilience at baseline in subscribers of the Wellness4Teachers email messaging program. Other secondary outcome measures will include changes in mean scores on the PSS-10, MBI, GAD-7, PHQ-9, and BRS. In addition, sociodemographic factors, work-related factors, and mental health literacy correlate with moderate to high stress, burnout, moderate to high anxiety, moderate to high depression, and low resilience at baseline among subscribers of the Wellness4Teachers program.

Sample Size Estimation

With the total teacher population in Lusaka, Livingstone, Kasama, and Solwezi of about 30,561 [66], using a web-based script [77], it is projected that the sample size needed for our prevalence estimates with 95% confidence and a 3% margin of error for moderate to high stress, burnout, moderate to high anxiety, moderate to high depression, and low resilience among teachers in Livingstone, Lusaka, Kasama, and Solwezi will be 993. Based on the maximum survey completion rate attained for the Text4Hope and Text4Mood programs in Alberta of 20% [50,78,79], to achieve an estimated 993 completed surveys at baseline, it is planned to enroll at least 4965 teachers in the Wellness4Teachers email supportive and mental health literacy messaging program within 12 months.

Statistical Analysis

SPSS (version 25; IBM Corp) [80] will be used to analyze the quantitative data from the surveys. Surveys with more than 50% missing responses will not be included in the data analysis. There will be no missing data imputation, and the analysis of the included survey responses and results will be based on completed survey data. Descriptive statistics for demographic, mental health literacy, clinical, and burnout-related variables will be provided. A 2-tailed $P \leq .05$ will be used to determine statistical significance for all analyses, and descriptive characteristics will be presented as percentages and numbers. A chi-square test and logistic regression analysis will be used to separately identify demographic, clinical, and work-related correlates of anxiety, depression, stress, low resilience, and burnout for elementary and high school teachers. Significant and borderline significant variables from the chi-square analysis would be used to develop multivariable binary logistic regression models to predict the adjusted odds of outcomes for the exposure of interest and each potential correlate. The impact of the email supportive messaging program in reducing moderate to high anxiety, moderate to high depression, moderate to high stress, burnout, and improving resilience among subscribers will be evaluated by comparing the mean changes in these parameters from baseline to 6 weeks, 3 months to 6 months, and 12 months using the paired *t* test. To assess the effects of the intervention against a control group, we will choose a defined period of 3 months during the study period (for instance, the beginning of January 2023 to the end of March 2023) and compare the prevalence and mean scores on standardized scales for stress, anxiety, burnout, and depression at 6 weeks for subscribers who have received the daily supportive SMS text messages for 6 weeks (the intervention group) to the baseline prevalence and mean scores on the same scales for new subscribers during the period (the control group).

Data Quality Assurance

At each stage of data collection, we will implement checks to ensure that we collect high-quality data, enabling us to generate accurate insights. A 3-member data quality committee will be established, which will be responsible for checking quantitative data that is uploaded to the server. All data will be checked for consistency and accuracy. Any errors and inconsistencies will be immediately communicated to the data collection team for corrective action.

Ethics Approval and Informed Consent

The study has received ethics approval from the University of Alberta Ethics Review Board (Pro00117558), Dalhousie University Ethics Review Board 2022-6231, and Lusaka Apex Medical University, Zambia, Ethics Review Board IRB 00001131.00407-22. Participants' consent to participate will be implied when they complete and submit the web-based survey responses. Participants will be informed that participation is voluntary, they can opt out anytime they desire, and the information they share is confidential. Teachers will not receive reimbursement or incentives for participating in the Wellness4Teachers email messaging program.

Hypothesis

Based on the greater than 20% reduction in depression symptom scores in the intervention group compared to the control group in 2 randomized controlled trials in Ireland and Canada [56,57], and the greater than 20% reduction in anxiety symptom scores from baseline to 6 weeks and 3 months in subscribers of Text4Hope [51,52], we hypothesize that the Wellness4Teachers email messaging program will reduce the prevalence and severity of stress, burnout, anxiety, depression, and low resilience symptoms among Zambian teachers by at least 20%. We also hypothesize that the Wellness4Teachers email program will improve mental health literacy scores in the teachers subscribing to the program by at least 20%. In addition, we hypothesize that the prevalence of moderate to high stress, moderate to high anxiety, moderate to high depression, burnout, and low resilience would be comparable to the prevalence of these conditions reported in other jurisdictions [81,82]. Finally, we hypothesize that demographic factors, socioeconomic factors, organizational factors, and class size will be associated with burnout and other psychological disorders in teachers [16,19-23,49,58].

Results

The Wellness4Teachers email messaging program is anticipated to be launched in January 2023. Enrollment will continue for 12 months, and data collection will continue for another 12 months. Results of the study will be disseminated to stakeholders

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in the education sector in Zambia, East African countries, and globally through workshops, conference presentations, and peer-reviewed publications.

Discussion

Principal Findings

Chronic stress can affect teachers, leading to burnout, anxiety, and depression. It can also indirectly affect students' academic achievement since teachers' performance is impacted by stress. In addition, this can also have a profound effect on teachers' general lifestyle, physical health, psychological safety, and well-being, leading to reduced professional fulfillment and a low level of resilience. Teachers require innovative, convenient, easily accessible, and cost-effective programs to improve their mental health literacy and support their mental health due to their busy schedules. This protocol outlines the use of supportive email messages and mental health literacy e-health tools for implementing a psychological intervention for teachers who may be experiencing stress, burnout, depression, and anxiety and improving their overall resilience. Teachers with low mental health literacy, prior mental health conditions, and those exposed to previous traumas or adverse childhood experiences are likely to benefit substantially from this program.

Results from this study will provide key information about mental health literacy levels and prevalence rates of stress, burnout, depression, anxiety, and low resilience and their correlates among teachers in Zambia (Livingstone, Lusaka, Kasama, and Solwezi). Findings will also provide valuable knowledge on eHealth approaches in the education sector. Evidence of the effectiveness of daily supportive email messaging programs to address stress, burnout, anxiety, depression, and low resilience among teachers will be ascertained. Evidence from this study will be both essential and crucial for shaping school policy and decision-making regarding psychological interventions for teachers in low- and middle-income countries. It is anticipated that the outcomes of this study will provide an impetus for integrating supportive email and mental health literacy messaging interventions into many organizations' occupational health programs.

Limitations

Like most studies, this one has some limitations. First, the supportive email messages will be delivered for 12 months, and the outcome measures will be evaluated at 6 weeks, 3 months, 6 months, and 12 months. It is not certain what the effects of the intervention would be if it were extended. It is also unclear if the benefits of the intervention would diminish with the cessation of daily email messages. Second, although standardized, the self-reported scales used to assess mental health variables, such as moderate to high anxiety, are not diagnostic. Third, it is possible that participants' demographics in the study may not reflect the demographics of the teacher population in Zambia; hence, the study findings may not be generalizable to all teachers in Zambia. In addition, web-based surveys with survey links delivered through SMS text messages usually achieve a response rate of less than 20% [54,78,79,83-86], so it is possible that we may not achieve our desired sample size with an email messaging program. Despite these limitations, this study is the first to assess the prevalence and correlates of stress, burnout, anxiety, and depression among teachers in Zambia using an email messaging program. To our knowledge, this study is also the first worldwide to assess if daily supportive email messages and mental health literacy information delivered by email would effectively reduce the prevalence and severity of psychological symptoms and improve mental health literacy among teachers.

Conclusions

This study will provide vital information about mental health literacy and the prevalence and correlates of psychological problems among teachers in Zambia. The study will also provide evidence of the effectiveness of the email messaging program, Wellness4Teachers, in reducing psychological symptoms and improving mental health literacy among teachers. The knowledge from this study will significantly impact the promotion of mental health literacy and the management of stress, burnout, anxiety, depression, and low resilience among teachers. The study outcome will help inform policy decision-making for health care resource allocation in support of the educational sector in Zambia.

Acknowledgments

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Data Availability

The data sets that will be generated and analyzed during this study will be available from the corresponding author upon reasonable request.

Conflicts of Interest

BA, VIOA, and EE are board members of the Global Psychological eHealth Foundation, a not-for-profit organization. BA is the President and Chief Executive Officer of the Global Psychological eHealth Foundation. VIOA is the founder and Principal Investigator of the ResilienceNHope messaging programs. VIOA, BA, and EE have no financial conflicts of interest with this paper.

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Abbreviations

BRS: Brief Resilience Scale
GAD-7: Generalized Anxiety Disorder 7-item
MBI: Maslach Burnout Inventory
PHQ-9: Patient Health Questionnaire-9
PSS: Perceived Stress Scale

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Protocol

Investigating the Secondary Use of Clinical Research Data: Protocol for a Mixed Methods Study

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Abstract

Background: The increasing emphasis to share patient data from clinical research has resulted in substantial investments in data repositories and infrastructure. However, it is unclear how shared data are used and whether anticipated benefits are being realized.

Objective: The purpose of our study is to examine the current utilization of shared clinical research data sets and assess the effects on both scientific research and public health outcomes. Additionally, the study seeks to identify the factors that hinder or facilitate the ethical and efficient use of existing data based on the perspectives of data users.

Methods: The study will utilize a mixed methods design, incorporating a cross-sectional survey and in-depth interviews. The survey will involve at least 400 clinical researchers, while the in-depth interviews will include 20 to 40 participants who have utilized data from repositories or institutional data access committees. The survey will target a global sample, while the in-depth interviews will focus on individuals who have used data collected from low- and middle-income countries. Quantitative data will be summarized by using descriptive statistics, while multivariable analyses will be used to assess the relationships between variables. Qualitative data will be analyzed through thematic analysis, and the findings will be reported in accordance with the COREQ (Consolidated Criteria for Reporting Qualitative Research) guidelines. The study received ethical approval from the Oxford Tropical Research Ethics Committee in 2020 (reference number: 568-20).

Results: The results of the analysis, including both quantitative data and qualitative data, will be available in 2023.

Conclusions: The outcomes of our study will offer crucial understanding into the current status of data reuse in clinical research, serving as a basis for guiding future endeavors to enhance the utilization of shared data for the betterment of public health outcomes and for scientific progress.

Trial Registration: Thai Clinical Trials Registry TCTR20210301006; https://tinyurl.com/2p9atzhr

International Registered Report Identifier (IRRID): DERR1-10.2196/44875

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KEYWORDS

data reuse; data sharing; secondary data use; clinical trials data; artificial intelligence; machine learning; individual patient data; clinical research; barriers; online survey; mixed methods; low- and middle-income country

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Introduction

The Value of Clinical Research Data

Although clinical research data are generated to answer specific questions, the data can be used for purposes other than those of the original planned analyses to increase medical understanding and improve the general health of the population [1,2].

Many recent advances in medicine are credited to the reuse of existing research data. During the outbreaks of H1N1; MERS (Middle East Respiratory Syndrome); Ebola; Zika; and, more recently, COVID-19, decision-making authorities such as the World Health Organization depended on the analysis of historical epidemiological and clinical data to understand disease progression patterns and associated risk factors. This knowledge was the basis of recommendations for nonpharmaceutical interventions to control the spread of the diseases [3-6]. Guidelines for treatment therapies and preventive medicines depend on findings from clinical trials. The design and interpretation of these clinical trials rely heavily on data from previous studies in, for instance, the calculation of sample sizes, definition of outcomes, selection of interventions and control treatments, and establishment of follow-up duration [7-10]. Existing clinical research data have also been used to answer completely new research questions for teaching purposes and to reproduce results of published research [11].

As the volume of research data continues to rise, there is greater potential for faster and innovative discoveries in diagnostics and the treatment and prevention of diseases through traditional analyses and machine learning technologies [12].

Recognizing the value of data reuse, funders, journals, and research bodies are establishing policies and making substantial resource investments in infrastructure to facilitate data sharing [13,14]. In 2003, the National Institutes of Health introduced the first funder-driven data sharing policy. By 2016, key health research funders required individual participant-level data that support findings of clinical trials to be made accessible at the time of the publication of study results [15-17]. Journals and publishers followed suit, with the majority of them mandating the inclusion of data availability statements in articles for publication [18]. These statements describe how and when data can be accessed and on which repository data are stored. Numerous repositories have been established by funders, pharmaceutical companies, academic research institutions, governments, and discipline-specific consortia [19]. In 2016, at the G20 Hangzhou Summit, the FAIR (Findable, Accessible, Interoperable, and Reusable) principles were endorsed. The FAIR principles aim to optimize the reuse of data sets by ensuring that data are findable; are accessible; are presented in a standardized, interoperable format; and exist on terms that allow reuse [20,21]. Groups such as the Clinical Data Interchange Standards Consortium have defined standard ways of describing data and metadata [22]. By standardizing data and metadata, researchers and algorithms can correctly interpret data without the need for intermediary translation or curation. Analytical tools, such as TwoRavens [23], now allow users to run statistical models and view summary statistics on data held in repositories. The implementation of this ecosystem requires staff with specialized skills; research institutions are investing in hiring and training data managers, programmers, and data scientists to develop interfaces and curate data and metadata.

It is expected that these investments in infrastructure will increase the usage of existing data and, consequently, generate a rich reference for evidence-based decision-making.

Rationale

Despite the efforts to facilitate data sharing, it is still unclear if and how shared data sets are used and whether the anticipated benefits are being realized. Previous studies described data usage trends based on data sets held in repositories and those from studies that are registered in clinical trial registries [24]. Negative results and studies terminated prematurely are often not published in repositories, yet data from these studies may hold useful insights for planning future research [25]. A substantial proportion of studies conducted in low- and middle-income countries (LMICs), especially noninterventional studies, are not registered [26]. Data sets generated in LMICs are particularly valuable, given the high disease burden in LMICs and the low volume of research being conducted in these areas [27-30]. To our knowledge, no recently published work has examined current barriers to and opportunities for maximizing data utility in LMICs.

Objectives

Against this background, our study aims to bridge the evidence gap by (1) characterizing how clinical research data sets are reused; (2) describing what impact, if any, data reuse has had on scientific research and general public health; and (3) defining barriers to and opportunities for promoting the ethical, efficient, and equitable reuse of data based on the perspectives of secondary data users.

As previous studies primarily focused on participants from high-income countries, we will target individuals working with data collected from LMICs for the interviews and aim to include respondents from both high-income countries and LMICs in the survey.

Methods

Overview

We will conduct a mixed methods study comprising an anonymous web-based survey and semistructured in-depth interviews. The survey will provide data from a large population, while the interviews will generate data on the detailed and contextualized perspectives of individual data users. We aim to include a wide spectrum of participants to reflect the diversity in research areas, career levels, and geographical locations.

Recruitment

Cross-sectional Survey

We will include at least 400 participants, of whom half will be individuals with a history of data reuse (data users), and the other half will be participants with no history of data reuse (nonusers). For the data user group, we will investigate what kinds of data sets were used, how the data were accessed, the purposes for requesting the data, and outcomes of the secondary

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analyses. We will additionally probe for information on challenges faced in accessing and using the data. For the nonuser group, we will determine reasons for not using shared data sets and identify perceptions on data reuse.

The inclusion criteria are as follows: (1) individuals aged ≥18 years, (2) researchers and professionals working in clinical research or with clinical research data, and (3) those who provide written consent to participate in the study. Individuals with no access to a computer, a mobile device, or the internet will be excluded, as data collection will be mainly conducted via the internet.

Potential participants will be requested to provide consent by ticking a checkbox to confirm that they agree to participate in the study. Respondents who do not provide consent will not be able to access the survey.

Data users will be directed to a page for data users, while nonusers will be directed to a page for nonusers. It will take 3 to 7 minutes to complete the survey for data users and 1 to 2 minutes to complete the survey for nonusers.

The survey will be designed based on existing literature. A panel of experts will be involved in the survey design, including social scientists and ethicists (for informing how questions are framed), a statistician (for the sampling strategy and the development of measurement scales and scoring schemes), a data manager (for survey development and data extractions), and a group of researchers and data users (for piloting). We will use the cognitive debriefing method to pilot the survey among respondents who are similar to the target population. The pilot testing group will be selected purposively for practical reasons and will include individuals from diverse research areas, career levels, and geographical locations. During the pilot, we will check the comprehension of each question; the ability to recall answers; and whether questions are appropriate, are clear, and have sufficient response options. Feedback from the pilot phase will be incorporated in the final survey before deployment for data collection. To achieve demographic diversity, the survey will be translated into other languages, such as Spanish, French, and Portuguese. We will translate the survey by following the TRAPD (Translation, Review, Adjudication, Pretesting, and Documentation) model [31]. Professional translators will perform the initial translations before a review by bilingual individuals. To guarantee that the translated survey accurately represents the intended meaning, it will be pretested with native speakers who are comparable to the target audience.

The survey instrument focuses on the following four main areas: respondents' demographics, the nature of data use, challenges with data use, and interventions to enhance data use (Multimedia Appendices 1-5). Conditional logic will be applied to display nested questions that are dependent on the respondents' previous answers. For example, respondents who have published results that are based on secondary analyses will be asked to indicate the number of publications generated from those analyses. Similarly, questions on the history of data use will not be displayed for nonusers.

To reach the target population, the survey will be advertised on forums for researchers and secondary data users, such as the Global Health Network and the COVID-19 Clinical Research Coalition; in conferences; and through the collaborating institutions' social media platforms. Participants will also be encouraged to share the survey with their colleagues. The survey will be conducted globally. The data will be reviewed after the number of recruited participants reaches one-third (132/400, 33%) of the target sample size to monitor the distribution of respondents by geographical location, research area, and occupation. The results of the review will be used to strategize the advertisement and distribution of the survey to target specific groups.

Interviews

Semistructured in-depth interviews will be conducted with 20 to 40 data users or until a state of data saturation is reached. Data saturation occurs when further interviews no longer produce new insights or themes [32]. Considering limitations on travel and on holding meetings resulting from the COVID-19 pandemic, we will primarily use web-based or remote methods for data collection. In-person interviews may be conducted when it is safe to do so, in compliance with local regulations.

The inclusion criteria are as follows: (1) individuals aged ≥18 years, (2) researchers or professionals using clinical research data shared by other researchers for secondary purposes, and (3) those who provide consent to participate in the study.

Potential participants will be identified through a web-based search for publications that are based on secondary analyses, focusing on researchers and professionals who have used data from LMICs. The corresponding authors will be contacted by email and invited to participate in interviews. To reach data users who have not yet generated publications, we will invite individuals who have requested data sets from institutional data repositories. Individuals who are interested in participating in the study will be sent the participant information sheet and consent form by email. The information sheet will describe the nature of the study, what the interviews will entail, and details on how data will be stored and processed during and after the study. It will be clearly stated that the participants are free to withdraw from the study at any time, for any reason, and with no obligation to give the reason for withdrawal. The participants will be allowed as much time as they wish to consider the information, and they will be given the opportunity to raise questions with the investigator or other independent parties to decide whether they will participate in the study. Interviews will then be scheduled at mutually convenient times. Audio-recorded consent will be obtained prior to asking the interview questions. The interviewer will document that verbal consent was obtained on a consent form. The investigator will keep a copy of the signed form in the study file and send a copy to the participants by email. For interviews that are held in person, the participants will sign the consent form prior to start of the interview. The interviews are estimated to last 40 to 60 minutes. Multimedia Appendix 6 shows the interview guide.

It is likely that participants of the in-depth interviews may be included in the survey. However, as the survey is anonymous, it will not be possible to identify individuals who participate in both the survey and the interviews.

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Data Management

Quantitative data will be collected on the Jisc Online Surveys platform, which is managed through the University of Oxford [33]. Data will be exported from Jisc in CSV format for analysis and long-term preservation. The survey database will be retained for 6 months after the completion of data collection, after which all data will be exported from the survey platform and stored indefinitely in access-controlled servers at Mahidol Oxford Tropical Medicine Research Unit (MORU)—a collaboration between the University of Oxford and Mahidol University that carries out clinical and public health research [34]. Deidentified data may be uploaded on data repositories or shared with other researchers, in line with the data sharing policies of MORU and collaborating institutions, as applicable.

Qualitative data will include detailed summary notes and audio recordings of the interviews. Web-based interviews will be conducted in English via Microsoft Teams (Microsoft Corporation)—a secure access-restricted platform. Transcripts of the interviews will be generated by using the Microsoft Teams transcription feature. The draft transcripts will be manually checked for accuracy line by line. Using the Health Insurance Portability and Accountability Act safe harbor method, direct and indirect identifiers, such as references to names of individuals or institutions, will be removed from the transcripts [35]. The deidentified transcripts will be uploaded to the latest version of NVivo (QSR International) software for storage and organization. Audio recordings and email correspondence will be stored separately from deidentified transcripts to preserve the confidentiality and privacy of participants. After the completion of analyses and the reporting of study results, audio recordings and original transcripts will be deleted. Deidentified transcripts, summary notes, and coded data will be stored indefinitely in access-controlled servers at MORU.

Statistical Analysis

Sampling

Participants will be enrolled through nonprobability sampling, as no suitable sample frame exists for the population being studied. A minimum of 200 participants is adequate for estimating any prevalence of a response, assuming a 50% prevalence rate, with 95% confidence and a precision of around 7%. Considering a minimum of 200 data users and 200 nonusers, the minimum total sample size for the web-based survey is 400 participants. A sample size higher than 400 participants will increase the precision of the prevalence estimates.

The sample size for the qualitative study will depend on when data saturation is reached. We estimate that a purposive sample of between 20 and 40 participants will be adequate, following the rule of thumb for the estimation of sample sizes for in-depth interviews in mixed methods studies [36].

Analysis

Quantitative survey data will be analyzed by using Stata 15.0 (or later; StataCorp LLC) software. Frequency counts and percentages will be used to summarize categorical data. Associations between categorical variables will be assessed by using Pearson chi-square tests or Fisher exact tests, as appropriate. Data will be presented in tables, graphical displays, and summary statistics. Further analyses for determining the significance of relationships between variables will be performed when necessary. Tests of significance will be performed at the 5% significance level (α=.05) for quantitative data.

Qualitative data will be synthesized by using thematic analysis [37], and the findings will be reported in accordance with the COREQ (Consolidated Criteria for Reporting Qualitative Research) guidelines. Open coding will be performed by breaking data into discrete parts and assigning them codes. Through axial coding, related codes will be combined to form subthemes. Related subthemes will then be collated to form themes, and the relationships between themes will be presented using thematic maps. The themes will be described in detail within the study report, including verbatim quotes from participants as illustrations.

To ensure the validity and trustworthiness of the study results, data will be coded by 2 independent individuals. For codes that are contradictory, divergences will be outlined and discussed in the report.

Ethical Considerations

Ethical approval was obtained in December 2020, prior to initiating the study, from the University of Oxford's Tropical Research Ethics Committee (reference number: 568-20), which will provide overall oversight of the study. Institutional review board approvals may be obtained for collaborating institutions, as applicable.

Our study will pose minimal risk and harm to participants. Although there are no immediate benefits for study participants, participation in the study will afford them an opportunity to contribute to the generation of new knowledge that will potentially increase the reuse of data for public good.

The main ethical risks relate to privacy and confidentiality, particularly in the in-depth interviews. Care will be taken to maintain privacy during interviews and interactions with participants. Data containing person-identifying information will be stored securely and confidentially. Study documents and data will be accessible to study staff and authorized personnel only. The web-based survey is completely anonymous. Names, email addresses, IP addresses, or other person-identifying details will not be collected in the survey.

The study will comply with the European Union General Data Protection Regulation, as described in the participant information sheets for the survey (Multimedia Appendices 1-5) and the interviews (Multimedia Appendix 7). Personal data will be stored until the final analyses are completed, while anonymized data will be stored indefinitely.

Data Sharing

With participants' consent, anonymized data will be uploaded on data repositories and shared with other researchers, in line with the collaborating institutions' data sharing policies. We will share the information we collect in ways that do not reveal individual participants' identities.

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Informed Consent

Participation in the study is voluntary. All participants must provide informed consent before involvement in the survey or in the interviews. Survey participants will only be able to access survey questions after providing consent. For in-depth interviews, verbal consent will be obtained at the start of the interview.

Dissemination

The results of our study will be primarily shared through the publication of results in peer-reviewed journals and through scientific presentations in webinars and seminars.

Results

The results of the analysis, including both quantitative data and qualitative data, will be available in 2023.

Discussion

Overview

Data sharing is widely regarded as a positive development for scientific and technological advancement. By making research data available beyond the primary research team, the data can be scrutinized, reused, and built upon, leading to greater insights, innovation, and collaboration. Research indicates that data sharing is becoming increasingly mandated, with funding agencies, academic institutions, and journals requiring researchers to make their data available. This is due to the belief that data sharing can lead to more reproducible and trustworthy results and an increase in the visibility of researchers in the scientific community. Despite these mandates, it is important to note that the uptake of data sharing practices among researchers is still relatively low. Although data sharing can bring significant benefits to scientific advancement and collaboration, it also requires significant investments in terms of time, resources, and technology. It remains unclear whether the benefits of data sharing are actually worth the costs. Furthermore, data sharing can also amplify challenges, such as the need for proper data curation and privacy protection. To date, there is sparse literature on the barriers and drivers of clinical research data reuse based on the perspectives of secondary data users [38-43]. Although some secondary data users cite the lack of access to quality and relevant data as a challenge, ironically, other researchers suggest that the clinical research data sets that exist in the public domain are grossly underutilized [1,44].

Expected Findings

Through our exploratory study, we aim to gain insights into how shared data sets are used, analyze the impact of secondary usage, and document barriers and facilitators of secondary data use based on the perspectives of data users.

Limitations

The survey participants will be selected by using nonrandom sampling, which means that the results may not accurately reflect the characteristics of the whole population and may be affected by bias in the selection process. Additionally, it is possible that the survey may only reach those who regularly use the web-based platforms where the survey is promoted, potentially resulting in an incomplete representation of the target population. Although it is acknowledged that the survey results may not be generalizable to a larger population, the data from our exploratory study will provide ideas and hypotheses that could guide future research. Additionally, the in-depth interviews are expected to provide valuable and contextualized information.

The study is limited to the description of the current state of data reuse, and it will not explore causal relationships. However, the findings from our study can be used as a foundation to design future studies that establish cause-and-effect relationships in secondary data use and explore perspectives of nonusers.

Conclusions

In conclusion, the findings from our work could offer insights into informing strategies for increasing the utilization of existing clinical research data sets in a manner that benefits researchers and populations, particularly in LMICs.

Acknowledgments

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Data Availability

The data sets generated and analyzed during the study will be available from the Mahidol Oxford Research Tropical Medicine Research Unit Data Access Committee on reasonable request [45].

Conflicts of Interest

None declared.

Multimedia Appendix 1
Survey instrument in English.
[PDF File (Adobe PDF File), 253 KB - resprot_v12i1e44875_app1.pdf]

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Multimedia Appendix 2
Survey instrument in Spanish.
[PDF File (Adobe PDF File), 184 KB - resprot_v12i1e44875_app2.pdf]

Multimedia Appendix 3
Survey instrument in French.
[PDF File (Adobe PDF File), 184 KB - resprot_v12i1e44875_app3.pdf]

Multimedia Appendix 4
Survey instrument in Portuguese.
[PDF File (Adobe PDF File), 181 KB - resprot_v12i1e44875_app4.pdf]

Multimedia Appendix 5
Survey instrument in Vietnamese.
[PDF File (Adobe PDF File), 2034 KB - resprot_v12i1e44875_app5.pdf]

Multimedia Appendix 6
Interview guide.
[DOCX File , 37 KB - resprot_v12i1e44875_app6.docx]

Multimedia Appendix 7
Participant information sheet: In-depth interviews.
[DOCX File , 38 KB - resprot_v12i1e44875_app7.docx]

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Abbreviations

COREQ: Consolidated Criteria for Reporting Qualitative Research
FAIR: Findable, Accessible, Interoperable, and Reusable
LMIC: low- and middle-income country
MERS: Middle East Respiratory Syndrome
MORU: Mahidol Oxford Tropical Medicine Research Unit
TRAPD: Translation, Review, Adjudication, Pretesting, and Documentation

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Protocol

Statewide Assessment of North Carolina Nurse Practitioners' Knowledge of and Attitudes Toward Suicide Awareness and Prevention: Protocol for a Statewide Mixed Methods Study

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Abstract

Background: Suicide is a major public health problem, which affects people of all ages and ethnicities. Despite being preventable, the rates of suicide have steadily climbed (more than a third) over the past 2 decades.

Objective: Nurse practitioners (NPs) must be responsible for recognizing suicide risk and providing appropriate treatment referrals in addition to having an important role in suicide prevention. The reasons why NPs may not pursue suicide prevention training are their lack of suicide awareness and prevention, limited experiences with suicidal patients, and the stigma associated with mental illness. Before we begin to address the gaps within suicide awareness and prevention skills, we need to first examine NPs' knowledge of and attitudes (stigma) toward suicide prevention.

Methods: This study will comprise a mixed methods approach. First, quantitative data will be collected using the *Suicide Knowledge and Skills Questionnaireand the Suicide Stigma Scale (Brief version)* questionnaire. An email will be sent to the NPs explaining the purpose of the study. If they consent, they will click on a link to access the surveys on a secure site. In our previous research with this sample, email reminders to nonresponders after 2 and 4 weeks were sent. The quantitative component will be used to inform the qualitative interviews of this study. *The Suicide Knowledge and Skills Questionnaire* is a 13-item questionnaire comprising 2 subscales: suicide knowledge and suicide skills. All questions are rated on a 5-point Likert scale (1=completely disagree to 5=completely agree). The survey has been shown to differentiate between those with suicide training and those without and has a Cronbach α score of .84. *The Suicide Stigma Scale* (*Brief version*) is a 16-item survey that assesses stigma regarding suicide. The items are measured on a 5-point Likert scale (1: strongly disagree to 5: strongly agree) and have a Cronbach α of .98.

Results: This study was funded by the Faculty Research Grants program through the Office of the Vice Chancellor for Research and Economic Development at the University of North Carolina at Charlotte. Institutional review board approval was obtained in April 2022. Recruitment occurred between summer and winter 2022. Interview conduction began in December 2022 and will conclude in March 2023. Data will be analyzed during spring and summer 2023.

Conclusions: The study results will add to the literature on NPs' knowledge of and attitudes (stigma) toward suicide prevention. It represents a first step in addressing gaps within suicide awareness and prevention skills, among NPs in their respective practice settings.

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KEYWORDS

mixed methods; suicide awareness; suicide prevention; nurse practitioner; knowledge and skills; stigma; suicide; awareness; nurse; public health; treatment; prevention; metal health; mental illness; United States; skills

Introduction

Background

Suicide is a major public health problem, which affects people of all ages and ethnicities [1-6]. It is a multifactorial phenomenon often influenced by events that destabilize some of the pillars of daily life, such as family bonds, job satisfaction, economic stability, recreational life, and well-being [7]. Suicide is a global public health concern costing the lives of over 800,000 people per year [8]. It is among the 3 leading causes of death in those aged 15-44 years and the second leading cause of death among children and young people aged 15-29 years [8]. Among the strongest risk factors for suicide are a history of suicide attempts, mental illness, and self-harm [8,9]. Despite being preventable, the rates of suicide have steadily climbed (more than a third) over the past 2 decades [1-6]. Between 2007 and 2017, past-year suicidal ideation among college students nearly doubled (from 5.8% to 10.8%). Based on the Household Pulse Survey by the Centers for Disease Control and Prevention conducted from February 17 to March 1, 2021, 42.2% of participants aged 18-29 years reported indicators of depression in the past week [10]. The number of people who think about or attempt suicide is even higher [1-6]. The impact of COVID-19 with social distancing and isolation has exacerbated the risk of "deaths by despair" (suicide and substance use) during the pandemic [11,12]. Studies show that the pandemic has further widened the mental health treatment gap, and outpatient mental health services have been particularly disrupted [13]. Since the COVID-19 pandemic, vulnerable people (eg, those with a history of preexisting psychiatric disorders, low-resilience people, individuals who reside in high COVID-19 areas, those who have a family member to die of COVID-19, and health care providers) have experienced more suicide ideations post pandemic than before the pandemic [14-16]. Among those who are vulnerable and at risk of suicide because of COVID-19 are also those who are more fragile to the COVID-19-related economic crisis, analogous to the 2008 economic crisis [17]. In addition, evidence suggest that various factors including stress-related disorders of depression, posttraumatic stress disorder, and sleep disorders are associated with suicidal ideation, suicide attempts, and death by suicide [18]. Several factors have been found to contribute to suicidal ideation and behavior, including the presence of economic stressors, increased consumption of addictive substances (drugs and alcohol), domestic violence, intense exposure to anecdotes of pessimism and helplessness, and persistent feelings of entrapment, isolation, and loneliness. These factors can interact and have a synergistic effect, thus creating a vicious circle [19,20].

Moreover, many recovering patients with COVID-19 or those in the postacute phase experience psychosocial difficulties and such as loss of employment and financial distress. They also experience physical symptoms for an extended period [18]. Studies have highlighted the role of physical illness, especially among the oldest patients. Physical illness exerted a stronger motivational effect for suicide in old-old (≥75 years) attempters compared to their young-old (65-74 years) and middle-aged (50-64 years) counterparts. One-third of those who are >70 years of age, who had attempted suicide, attributed their act to somatic distress. Among those who had died by suicide, a greater incidence of physical illness was reported in the old-old compared to the young-old and middle-aged adults [19,20]. Most people who died by suicide had contact with the health care system in the year before their death [19,20]. It is documented that among people who died by suicide and who attempted to commit suicide, 83% of them had visited a primary care clinician, like a medical doctor (MD), nurse practitioner (NP), or physician assistant (PA) in the prior year, whereas 50% had visited a primary care clinician rather than a psychiatrist within 30 days of their death [21]. Moreover, older individuals who attend the emergency department (ED) with a physical illness are vulnerable individuals. The ED visit often represents a "sentinel event" that may signal a medical or psychosocial fracture in their established equilibrium. In addition, the ED represents a clinical setting where the elderly with both physical illness and greater suicidality risk frequently converge [19,20]. These missed opportunities are considered significant since risk and prevention factors are being overlooked. NPs serve a vital role in today's health care system as primary care clinicians. In this role, NPs should be able to identify those at risk for suicide and intervene with prevention tactics and safety measures [22]. NPs of all specialties including family, pediatric, adult gerontology acute care, obstetrics/women's health, and psychiatry should possess effective suicide assessment skills; however, suicide prevention training in schools of nursing is inadequate and limited to a few lectures [22]. Smith et al [23] have identified that knowledge about suicidal behavior and its assessment and treatment among clinicians has lagged in research in the health care. They have identified that gaps between research and practice could be indicative to the lack of appropriate training [23]. These gaps within suicide prevention knowledge are reflective of the need to increase suicide knowledge and awareness among primary care clinicians like NPs [24]. Health care clinician training is a top research priority identified by the National Action Alliance for Suicide Prevention [24].

In North Carolina, suicide is the third leading cause of death for children and young adults aged 10-34 years, the fourth cause of death in adults aged 35 to 54 years, ninth leading cause of death for those aged 55-64 years, and 17th leading cause of death for those aged 65 years and older [25]. On average, 1 person dies by suicide every 6 hours in the state [25]. The 2012 North Carolina Suicide Prevention Plan *encourages* but does not *mandate* suicide prevention training for health care professionals [26]. NPs must be responsible for recognizing

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suicide risk and providing appropriate treatment referrals, in addition to having an important role in suicide prevention [22]. One study suggests that NPs use more varied approaches in assessing, treating, and referring their geriatric patients with mental health problems [27]. This study also identified that NPs were more likely than their MD counterparts to express a lack of training and referral resources as barriers to treating symptoms such as depression among older adults [27]. The reasons why NPs may not pursue suicide prevention training is their lack of suicide awareness and prevention, limited experiences with suicidal patients, and stigma associated with mental illness [19,20,22]. Diamond et al [27] identified that even when funding is available to provide free training, behavioral change is gradual. Before we can begin to address gaps within suicide awareness and prevention skills, we need to first examine NPs' knowledge of and attitudes (stigma) toward suicide prevention.

Aims

Our long-term research goal is to increase suicide knowledge and awareness among NPs in the state of North Carolina. The purpose of this study is to use the Theory of Nursing Care of Patients at Risk of Suicide [28] as a guiding framework to identify NPs' suicide awareness, attitudes (confidence, stigma, facilitators, and barriers), knowledge, and prevention skills. Knowledge from this study is essential to inform the development of policy and a targeted intervention to increase NPs' knowledge of and improve their attitudes toward suicide awareness and prevention.

The aims of this study are to (1) explore NPs' knowledge of and attitudes toward suicide awareness and prevention; (2) examine the differences in NPs' suicide awareness and prevention skills based on practice specialty; (3) identify enablers and barriers to NPs' awareness and confidence of suicide prevention skills.

Theoretical and Conceptual Framework

Billings [29] identified that nurses should be prepared to recognize suicide risk factors and risk predictors so that they can make sensible and sound nursing decisions. Midence et al [30] used a questionnaire to investigate a sample of nurses' (n=27) views on the effects on them of patient suicides, and 45% (n=12) of the respondents said that suicide could be prevented if all patients were assessed for suicide risk. For this study, the Theory of Nursing Care of Patients at Risk for Suicide and the Theory of Planned Behavior were used in developing the study aims, design, measure selection, and qualitative inquiry and analysis. Specifically, the Theory of Nursing Care of Patients at Risk of Suicide was used as a guiding framework to identify NPs' suicide awareness, attitudes (confidence, stigma, facilitators, and barriers), knowledge, and prevention skills [28]. Based on a grounded theory approach, the Theory of Nursing Care of Patients at Risk of Suicide guides the nurses as they initiate and maintain therapeutic relationships with patients who are at risk for suicide [28]. The core category of this theory is the provision of safe and compassionate care via the therapeutic relationship. Additional categories linked to this core category include the following: providing holistic assessments, providing protection, providing basic care, and promoting healing through advanced care [28]. This theory has been identified as one that can advance the quality of care provided by nurses with their potential to instill hope in patients that have lost their ability to cope with life's events [28]. Moreover, the theory of planned behavior posits that human behavior is guided by three considerations leading to the formation of intention and then behavior: (1) beliefs about likely outcomes and evaluations of behaviors (*behavioral beliefs*), (2) beliefs about normative expectations of others and motivation to comply (*normative beliefs*), and (3) beliefs about the presence and power of factors that may facilitate or impede the performance of the behavior (*control beliefs*) [23,31]. Increasing awareness of suicide-related facts, risk factors, and prevention approaches may increase knowledge and, in turn, confidence in skills related to suicide prevention via influencing behavioral, normative, and control beliefs. Thus, increases in knowledge and confidence in skills may make it more likely that an individual will engage in suicide prevention behaviors such as suicide risk assessments and referrals [23].

Methods

Study Design

An observational mixed methods approach will be used for this study. Because the data collection questionnaires include forced choices and the prevention needs of NPs based on specialty practice have not been explored, the mixed method design is appropriate to address the objectives of the study. Descriptive statistics will be used to compute means and SDs for numerical variables and frequencies for categorical variables. Demographic and background information regarding age, gender, professional role, education, and previous suicide prevention training will be collected [32].

Qualitative Data

A cross-sectional survey design including a series of interviews for a small selection of nurses who have completed the survey will be used. Qualitative interviews will be audio recorded and fully transcribed removing any identifiable data to preserve participant anonymity [8]. Qualitative content analysis will be conducted on the open-ended questions [33]. We will use interpretative phenomenological analysis (IPA). IPA makes sense of the participant's experiences by seeking to understand the cognitive, affective, linguistic, and physical being while maintaining the researcher as an integral part of the sense-making process [34-38]. This methodology is best used in studies where the objective is to explore the meaning behind the experiences of participants. IPA is an especially fitting research approach when the researcher intends on asking complex, broad, and open-ended questions [34-38], as is the case in this research proposal. In keeping with the open-ended nature of qualitative research, this method allows the researcher to explore the research question in a flexible nonprescriptive manner, thus facilitating a more thorough exploration [34-38].

Quantitative Data

First, quantitative data will be collected using the *Suicide Knowledge and Skills Questionnaire* [39] *and the Suicide Stigma Scale (Brief version)* [40] questionnaire. An email will be sent

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to the NPs explaining the purpose of the study. If they consent, they will click on a link to access the surveys on a secure site. In our previous research with this sample, email reminders to nonresponders after 2 and 4 weeks were sent [41]. The quantitative component will be used to inform the qualitative interviews of this study.

Quantitative Component-Measures

The Suicide Knowledge and Skills Questionnaire [39] is a 13-item questionnaire comprising 2 subscales: suicide knowledge and suicide skills. The items in this survey were based on the 100-item Suicide Opinions Questionnaire (SOQ) [23,39]. The SOQ consists of 8 subscales derived using expert consensus and empirical tests for internal consistency. The Suicide Knowledge and Skills Questionnaire has 9 items that parallel the items on the SOQ, and it will assess participants' knowledge about suicidal behavior and comfort dealing with suicidal clients [39]. The Suicide Knowledge subscale included 9 items that will reflect either truth or falsehood about suicide. Moreover, the Suicide Skills subscale has 4 items that assess the respondents' comfort dealing with suicidal clients in terms of their confidence in their training, skills, and supervision received [23,39]. All questions are rated on a 5-point Likert scale (1 completely disagree, 2 disagree, 3 don't know, 4 agree, and 5 completely agree). An example item is as follows: "I am comfortable asking direct and open questions about suicide," "I have received the training I need to engage and assist those with suicidal desire and/or intent [23,39]." The questionnaire takes 10 minutes to complete. The survey has been shown to differentiate between those with suicide training and those without and has a Cronbach α score of .84 [23,39]. *The Suicide Stigma Scale (Brief version)* [40] is a 16-item survey that assesses stigma regarding suicide. The items are measured on a 5-point Likert scale (1, strongly disagree to 5, strongly agree), has a Cronbach α of .98 and takes 10 minutes to complete [40].

Demographic Survey

Participants will report demographic data such as age, gender, specialty, education level, years of NP experience, previous suicide prevention training, and experience with suicidal patients.

Recruitment and Participants

Sampling Strategy and Power Analysis

The researchers will use the North Carolina Board of Nursing database for NPs registered to practice in the state. Inclusion criteria are as follows: (1) a licensed NP in the state of North Carolina and (2) able to give consent. Exclusion criteria include not being able to provide consent and not being a NP in the state of North Carolina. Our study is powered to detect the primary outcome of suicide knowledge subscale differences among nursing specialties and controlling for other demographic characteristics. Smith et al [23] used an analysis of covariance model (ANCOVA) design and reported between-group differences of approximately 0.2 and an interrespondent SD of 1.53, which leads to an implied effect size of f=0.13. However, since their study involves comparisons among other health professionals as well, we account for effect size uncertainty by using a mid-point between this informative choice and an uninformative small effect size of f=0.10, leading to f=0.115 [23]. We assume an attrition level in line with a recent study in which we used the same recruitment strategy and population [41]. We anticipate sufficient respondents from (or grouping respondents into) 5 core specialties (family, pediatric, adult gerontology acute care, obstetrics/women's health, and psychiatry). With an 80% power and a 5% alpha, the required sample size before attrition to detect group differences of f=0.115 among 5 specialties, with a conservative upper bound of 0.25 for the multiple correlation from demographic confounders, is 5,535 [42]. This is smaller than the population accessible by the researchers via email (N=10,916). In our previous study, we were able to obtain over 2000 responses without incentives; in this study, we will give US $10 gift cards (first 150 participants) [41].

Study Setting

First, quantitative data will be collected using survey data via a questionnaire. An email will be sent to the NPs, and upon consent, they will have to access the surveys on a secure site. The quantitative component will utilize semistructured interviews via Zoom (Zoom Video Communications, Inc). An interview guide will be developed guided by the Theory of Nursing Care of Patients at Risk of Suicide [28] and quantitative data responses (Multimedia Appendix 1). Consistent with qualitative interviewing methods, we will begin the interview with an introductory statement: "Tell me about your previous experiences with suicide." The process will continue addressing questions focused on suicide knowledge (providing protection and basic care and promoting healing) and awareness (confidence, facilitators and barriers, and experiences). Participants will receive a US $50 gift card for completing the interview process.

Data Collection, Management, and Analysis

Demographic data will be analyzed using descriptive statistics. Differences in questionnaire responses across specialists while controlling for other demographic characteristics will be analyzed with ANCOVA. These data will be analyzed using Statistics for Macintosh (version 28, IBM Corp).

Our qualitative data sampling strategy will use NPs who complete the quantitative surveys. NPs will be able to indicate if they are interested in participating in a virtual interview lasting about 50 minutes to identify facilitators and barriers to suicide knowledge and awareness. A representative sample of NPs based age, gender, ethnicity, specialty practice, and location (rural vs urban) using an address to identity (N=15 or until saturation) will be interviewed for part two of the study.

The semistructured interviews will be recorded and transcribed verbatim. The data will be managed using NVivo software (QSR International) for content analysis and analyzed for points of convergence and divergence.

Confidentiality

Participants will be informed that safeguards have been put in place to protect confidentiality and anonymity. All study-related information and spreadsheets will be stored in a locked office and file cabinet. All participant information will be coded by

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identification number to maintain confidentiality. We will protect confidentiality by removing all identifiers. Only members of the research team will have access to the data, and only aggregate data will be presented for publication.

Ethics Approval

Approval from the University of North Carolina at Charlotte institutional review board (IRB-22-0925) was required since the protocol is categorized as a research study [43]. The study's protocol, surveys, and informed consent forms were reviewed to ensure respect, fairness, and safety in human subjects research [44]. The protocol was followed in accordance with the standards for human subjects research. The study participants will be given the opportunity to opt out and will be informed of their right to privacy. Each member of the research team has completed the required training on proper methods of conducting research in compliance with federal and state requirements [44].

Instruments

The instruments and the reliability and validity values to be used in our pilot study are shown in Table 1.

Table 1. Instruments and reliability values of this study.

Study outcome	Instrument	Reliability values
Demographic survey: participants will report demographic data such as age, gender, specialty, education level, years of nurse practitioner experience, previous suicide prevention training, and experience with suicidal patients.	Demographic survey	N/A[a]
Nurse practitioner knowledge and skills-Suicide	Suicide Knowledge and Skills Questionnaire [39]	Cronbach α score of .84
Nurse practitioner stigma-suicide	Suicide Stigma Scale (Brief version) [40]	Cronbach α score of .98

[a]N/A: not available.

Timeframe

The project can be completed within 12 months. We anticipate no problems in recruiting subjects for the proposed study. The timeline for this study is shown in Table 2.

Table 2. Research tasks timeline.

Research tasks	Jan-Apr 2022	May-Dec 2022	Dec-Feb 2023	Feb-May 2023
Obtain institutional review board approval, send surveys, and email reminders	✓	—[a]	—	—
Recruit for qualitative interviews and analyze quantitative data	—	✓	—	—
Conduct interviews and analyze data	—	—	✓	—
Interpret and compare data and disseminate findings	—	—	—	✓
Apply for funding	—	—	—	✓

[a]Not applicable.

Strengths and Limitations

In this pilot feasibility study, we will have a sample of convenience, which may result in response bias. We are recruiting participants who are NPs in the state of North Carolina. Hence, the findings may be different from those who are MDs or PAs. For future research, we may consider the inclusion of additional clinicians like MDs or PAs. The strengths include the capacity to reach all registered NPs in the state of North Carolina.

Results

Overview

The institutional review board's approval was obtained in April 2022. Recruitment occurred between summer and winter 2022. Data analysis is to be completed by the second quarter of 2023. Our study is expected to conclude in the second quarter of 2023. We will submit a manuscript for publication consideration by the third quarter of 2023.

Anticipated Findings

We hypothesize that NPs will endorse self-efficacy working with suicidal clients, familiarity using evidence-based assessment procedures, and identifying best practices for suicide prevention [45].

Discussion

Principal Findings

In this study, we describe a protocol for examining NPs' knowledge of and attitudes (stigma) toward suicide prevention. This represents a first step in addressing gaps within suicide awareness and prevention skills, among NPs in their respective practice settings or sites. Telepsychiatry interventions and digital tools (eg, mobile apps, internet chatbots, and videoconferencing)

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have proliferated rapidly in response to the COVID-19 emergency [10]. It is important for NPs to be aware of the various resources to help them with their assessment of patients. One of the most effective ways to combat serious public health problems, like suicide, is to increase knowledge about risk factors, assessment procedures, and treatment options [23]. Gold-standard evidence-based training approaches aim to improve both knowledge and skills about suicide and how to intervene and include some form of didactic training (in-person or web-based) with a demonstration or modeling of suicide prevention skills, opportunities to practice these skills, and expert coaching and feedback on practicing these skills [21]. Many also target attitudes for increasing willingness and motivation to engage in suicide prevention activities given that stigma, anxiety, and unhelpful myths about suicide are common among the general population and professionals [21]. Lastly, we hope this protocol paper will provide a roadmap and resources for other researchers who would like to implement a similar approach in their studies [45]. It has been suggested that when screening programs and training programs have been implemented in different medical care settings patients at risk for suicide who would otherwise have gone unnoticed have been identified [21].

Future Directions

We have developed a strategic dissemination plan. The research process and our findings will be shared with university colleagues and clinical providers, in a peer-reviewed journal, and at a research conference.

Conclusions

This study will close the gap in identifying NPs' knowledge of and attitudes toward suicide awareness and prevention. In addition, the results with help to examine differences in NPs' suicide awareness and prevention skills based on practice specialty. Finally, we expect our results to identify enablers and barriers to NPs' awareness and confidence in suicide prevention skills. The study's findings will add to the current literature on NPs' knowledge of and attitudes (stigma) toward suicide prevention. Our study results may inform practice, policy, further research, and training. The results may shape how members of the health care system respond to people who are at risk of suicide and their families [36]. It represents a first step in addressing gaps within suicide awareness and prevention skills, among NPs in their respective practice settings.

Acknowledgments

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Data Availability

The data sets generated during or analyzed during this study are not publicly available but are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Interview guide.
[DOCX File , 22 KB - resprot_v12i1e39675_app1.docx]

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Abbreviations

ANCOVA: analysis of covariance model
ED: emergency department
IPA: interpretative phenomenological analysis
MD: medical doctor
NP: nurse practitioner
PA: physician assistant
SOQ: Suicide Opinions Questionnaire

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Protocol

Diagnostic Ability of a Smartphone App for Dry Eye Disease: Protocol for a Multicenter, Open-Label, Prospective, and Cross-sectional Study

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Abstract

Background: Dry eye disease (DED) is one of the most common ocular surface diseases. Numerous patients with DED remain undiagnosed and inadequately treated, experiencing various subjective symptoms and a decrease in quality of life and work productivity. A mobile health smartphone app, namely, the DEA01, has been developed as a noninvasive, noncontact, and remote screening device, in the context of an ongoing paradigm shift in the health care system, to facilitate a diagnosis of DED.

Objective: This study aimed to evaluate the capabilities of the DEA01 smartphone app to facilitate a DED diagnosis.

Methods: In this multicenter, open-label, prospective, and cross-sectional study, the *test method* will involve using the DEA01 smartphone app to collect and evaluate DED symptoms, based on the Japanese version of the Ocular Surface Disease Index (J-OSDI), and to measure the maximum blink interval (MBI). The *standard method* will then involve a paper-based J-OSDI evaluation of subjective symptoms of DED and tear film breakup time (TFBUT) measurement in an in-person encounter. We will allocate 220 patients to DED and non-DED groups, based on the *standard method*. The primary outcome will be the sensitivity and specificity of the DED diagnosis according to the *test method*. Secondary outcomes will be the validity and reliability of the

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test method. The concordance rate, positive and negative predictive values, and the likelihood ratio between the *test* and *standard methods* will be assessed. The area under the curve of the *test method* will be evaluated using a receiver operating characteristic curve. The internal consistency of the app-based J-OSDI and the correlation between the app-based J-OSDI and paper-based J-OSDI will be assessed. A DED diagnosis cutoff value for the app-based MBI will be determined using a receiver operating characteristic curve. The app-based MBI will be assessed to determine a correlation between a slit lamp–based MBI and TFBUT. Adverse events and DEA01 failure data will be collected. Operability and usability will be assessed using a 5-point Likert scale questionnaire.

Results: Patient enrollment will start in February 2023 and end in July 2023. The findings will be analyzed in August 2023, and the results will be reported from March 2024 onward.

Conclusions: This study may have implications in identifying a noninvasive, noncontact route to facilitate a diagnosis of DED. The DEA01 may enable a comprehensive diagnostic evaluation within a telemedicine setting and facilitate early intervention for undiagnosed patients with DED confronting health care access barriers.

Trial Registration: Japan Registry of Clinical Trials jRCTs032220524; https://jrct.niph.go.jp/latest-detail/jRCTs032220524

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KEYWORDS

digital health; digital therapeutics; dry eye disease; Japanese version of the Ocular Surface Disease Index; maximum blink interval; mobile health; smartphone; smartphone app; tear film breakup time; telemedicine

Introduction

Dry eye disease (DED) is one of the most frequently encountered ocular surface diseases, with a prevalence ranging from 5% to 50% [1,2], which is projected to increase, likely due to the worldwide trend toward an aging population and lifestyle changes associated with a digitalized society [1-4]. DED-related symptoms are detrimental to quality of life (QoL) and work productivity, leading to society-wide economic loss [5,6]. Subjective DED-related symptoms are highly variable and include ocular dryness, eye discomfort, eye strain, decreased visual acuity, and photophobia [7-11]. Additionally, DED is highly heterogeneous, with patients presenting with seemingly unpredictable combinations of the abovementioned symptoms. Therefore, patients with DED are prone to having their nonspecific presentations overlooked, and many are left undiagnosed without appropriate management [3,9,12-14]. There is no definitive cure for DED, and current standards of care comprise ex post facto symptom management, highlighting the importance of early diagnosis and intervention to prevent disease progression and longstanding damage [15-19].

Concerning DED diagnosis, Tear Film & Ocular Surface Society and Asian Dry Eye Society criteria recommend evaluating a patient's subjective symptoms and tear film breakup time (TFBUT) [20,21]. However, TFBUT measurement is inherently invasive owing to the need for sodium fluorescein application, and measurements under light microscopy are required [20-23]. The ongoing COVID-19 pandemic has also increased the demand for a noninvasive alternative that could be used in remote settings [24,25]. One major obstacle to DED diagnosis in the context of telemedicine is the inability to evaluate the ocular surface and the use of slit-lamp microscopy in TFBUT, and clinicians may be solely reliant on subjective symptoms for diagnosis. Therefore, identification of a novel proxy for existing invasive examinations is needed for a reliable, noninvasive DED diagnosis.

Recent studies have suggested the maximum blink interval (MBI) measurement as a noninvasive alternative to TFBUT, with the MBI defined as the maximum length of time a patient is able to keep their eyes open between 2 blinks [26]. A positive correlation has been reported between the MBI and TFBUT, likely owing to the MBI's capability to reflect ocular surface integrity [26-30]. The simplicity and noninvasive nature of MBI measurements underscores its candidacy as an alternative to TFBUT for screening purposes. Our earlier studies have indicated that the concomitant use of the MBI and the Ocular Surface Disease Index (OSDI) questionnaire can determine DED with similar accuracy to standard diagnostic methods using TFBUT and the OSDI [31,32].

Mobile health (mHealth) is defined by the World Health Organization as "medical and public health practice supported by mobile devices, such as mobile phones, patient monitoring devices, personal digital assistants (PDAs), and other wireless devices" [33]. The capability of mHealth to digitally perform therapeutic activities has raised the interest of clinicians and providers due to its potential use in disease prevention, diagnosis, and treatment through commonplace smart devices [32,34-39]. Previous studies concerning the validity and reliability of smartphone-based administration of MBI examinations and OSDI questionnaires yielded a satisfactory result [3,32,40]. Reported findings suggest that noninvasive and nonintrusive DED screening during activities of daily living may be possible, enabling an earlier DED diagnosis and interventions in remote settings [40,41]. More importantly, this possibility may have implications in accurately identifying undiagnosed patients with DED, allowing for timely intervention, preventing a further decrease in QoL, and reducing societal economic loss.

In this clinical study, we intend to use an in-house smartphone app, namely, the DEA01, which has been designed as an investigational device to facilitate a DED diagnosis. This study

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will aim to evaluate the capabilities of the DEA01 in facilitating a diagnosis of DED.

Methods

The DEA01 Smartphone App

The DEA01 smartphone app for DED diagnostic assistance was developed by InnoJin, Inc. It will be available on Apple's App Store and the Google Play Store. As of December 2022, it has not yet been approved as software for a medical device in Japan. The DEA01 collects dry eye symptoms using the OSDI and MBI to facilitate a DED diagnosis [32]. Blinking is measured using the smartphone camera and the *CIFaceFeature* function in the iOS interface for facial detection. DEA01 version 1.0 will be installed on an iPhone 13 Pro (Apple Inc). The app will be modified should minor issues arise during the study. Screenshots of the current version of the DEA01 (December 2022) are shown Figure 1.

Figure 1. Screenshots of DEA01: screenshots of the (A) welcome screen, (B) Ocular Surface Disease Index (OSDI) questionnaire, (C) measurement of the maximum blink interval, and (D) examination result screen for dry eye diagnostic assistance.



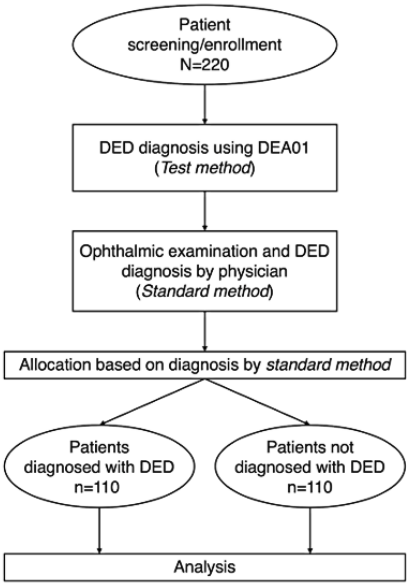
Objective

This study's primary objective is to evaluate DED diagnostic accuracy using the DEA01 smartphone app compared with standard DED diagnostic methods.

Study Design

In this multicenter, open-label, prospective, and cross-sectional study, patients will be evaluated for DED using the DEA01 (*test method*). A physician will then provide a DED diagnosis based on 2016 Asia Dry Eye Society criteria [20] (*standard method*). To ensure that the *test method* will not affect a patient's treatment plan, the physician will make a diagnosis using only *standard method* results without reviewing *test method* results. A minimum number of 220 patients will be enrolled, with patients allocated into a DED group or a non-DED group based on the diagnosis obtained using the *standard method*. The study design is shown in Figure 2.

Figure 2. Study flowchart. DED: dry eye disease.



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Ethics Approval

This study has been approved by the Juntendo University Certified Review Board, Tokyo, Japan (approved protocol V.1.1.1, dated December 19, 2022; approval number: J22-003). Patients will have the option to voluntarily provide written informed consent to participate in the study. Written consent will be obtained from a patient's parent or legal guardian for patients aged <20 years. All involved parties will make every effort to protect study patients' personal information and privacy. Patient-related data will be anonymized, and research-related data and the smartphones used in this study will be stored in locked lockers at each collaborating institution, with access strictly controlled by the research staff. All patients will receive a 1000-yen (US $7.77) voucher.

Study Setting

This study will be conducted between February 1, 2023, and November 30, 2023. Patients will be recruited from the Departments of Ophthalmology at 3 medical institutions, namely, Juntendo University Hospital, Tokyo, Japan [42]; Toho University Omori Medical Center, Tokyo, Japan; and Tokyo Dental College Ichikawa General Hospital, Chiba, Japan.

Patient Selection

Outpatients who visit the Ophthalmology Departments of the cooperating hospitals will be recruited for the study. Enrolled patients will include those with DED and other concomitant ocular diseases. Inclusion and exclusion criteria are shown in Textbox 1.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

1. Patients with dry eye disease (DED) or suspected DED
2. Patients aged ≥16 years at the time of providing informed consent
3. Patients able to use smartphones
4. Patients/guardians who, after receiving a full explanation concerning participation in the study and with a full understanding of the study, voluntarily provide written consent to participate

Exclusion criteria

1. Patients with eyelid closure disorder, ptosis, psychiatric disorders, and Parkinson disease
2. Patients who wear contact lenses
3. Patients who are unable to comply with the study protocol for physical or mental reasons
4. Patients whom the principal investigator deems unsuitable to participate in this study

Patient Withdrawal

Patients will be withdrawn from the study if, due to the occurrence of other diseases, it is deemed difficult to continue the research; if patients or their parents/guardians request to terminate their participation in the research; if the research study is discontinued; or if the principal investigator and subinvestigators determine that it is appropriate to discontinue the research.

Study Procedures

After enrollment in the study, patients will be evaluated for DED by clinical research coordinators using the DEA01. A physician will diagnose DED using the *standard method* without checking *test method* results. Details regarding the *test method* and *standard method* are shown in Textbox 2.

Textbox 2. Test and standard method.

Test method

- Dry eye disease (DED) diagnosis based on the app-based Japanese version of the Ocular Surface Disease Index (J-OSDI) and maximum blink interval (MBI), using the DEA01
- Patients will respond to the app-based J-OSDI questionnaire and be measured using the app-based MBI on the DEA01. The J-OSDI questionnaire is used to evaluate the subjective symptoms of DED on a 100-point scale [43,44]. The MBI will be defined as the length of time that a patient can keep their eyes open before blinking [26]. The app-based MBI will be measured using the smartphone's camera on the DEA01 and a visually confirmed MBI will be measured using a stopwatch.

Standard method

- DED diagnosis using a paper-based J-OSDI and tear film breakup time (TFBUT)
- Patients will respond to the paper-based J-OSDI questionnaire and be measured using TFBUT [20]. The diagnosis of DED using the *standard method* will be based on 2016 Asian Dry Eye Society criteria, with positive subjective symptoms (J-OSDI total score ≥13) and decreased TFBUT (≤5.0 s) being used to diagnose DED [20]. Based on the diagnosis using the *standard method*, patients will be allocated to DED and non-DED groups.

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Data Collection and Outcome Assessments

The data collection items are shown in Textbox 3. The assessments will be done according to a predetermined sequence. First, the assessment of subjective symptoms of DED using the app-based J-OSDI and MBI on the DEA01 will be conducted as the *test method* by trained clinical research coordinators. The physician will not be informed of the *test method* results. The physician will then perform clinical examinations for DED, using the *standard method* and ophthalmic examinations. Clinical examinations for DED will include an evaluation of subjective symptoms of DED using the paper-based J-OSDI questionnaire, slit lamp–based MBI, TFBUT, corneal fluorescein staining (CFS), and tear secretion volume using Schirmer test I. The ophthalmic examinations will include measurement of visual acuity, intraocular pressure, and slit-lamp microscopic photography. All examinations will be performed within one day.

Textbox 3. Data collection.

Patients' characteristics

- Age, sex, medical history, and medication

Test method

- Subjective symptoms of dry eye disease (DED) evaluated using the app-based the Japanese version of the Ocular Surface Disease Index (J-OSDI) on the DEA01
- Visually confirmed maximum blink interval (MBI)
- App-based MBI

Standard method

- Subjective symptoms of DED evaluated using the paper-based J-OSDI
- Tear film breakup time

Other DED examinations

- Corneal fluorescein staining
- Slit lamp–based MBI
- Tear secretion volume using Schirmer test I

Ophthalmic examinations

- Visual acuity
- Intraocular pressure
- Slit-lamp microscopy

Other outcomes

- DEA01 failure
- DEA01 operability and usability
- Adverse events

The Japanese Version of the OSDI

The Japanese version of the OSDI (J-OSDI) is a questionnaire comprising 12 questions to evaluate subjective symptoms of DED and has been validated in Japan as an OSDI-equivalent questionnaire for DED diagnosis [43-45]. Patients will answer each question on a scale ranging from 0 to 4, with 0 indicating "none of the time" and 4 indicating "all of the time." For questions 6 through 12, if a question is not applicable to a patient, they can select "not applicable." The J-OSDI results are reported on a 100-point scale to determine the severity of DED symptoms. The J-OSDI total score is calculated according to the following formula [43,44]:



(1)

TFBUT

TFBUT will be measured using sodium fluorescein to assess tear film stability [20]. To minimize the effect of a test strip on tear volume and TFBUT, a small amount of dye will be administered using wet fluorescein strips. After the dye is instilled, the patients will be instructed to blink 3 times to ensure that the dye is uniformly incorporated into the tear film. The time interval between the last blink and the appearance of the first dark spot on the cornea will be measured, and the average value from 3 measurements will be used as the test outcome. A cutoff TFBUT value of ≤5.0 seconds will be used to diagnose DED [20].

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MBI

The MBI is defined as the length of time that a patient is able to keep their eyes open before blinking during each trial [26]. In the *test method*, the app-based MBI will be measured using the smartphone's camera on the DEA01, and visually confirmed MBI will be measured using a stopwatch by a trained clinical research coordinator. In the *standard method*, the MBI will be measured by a physician using a slit-lamp microscope. In both methods, the MBI will be measured twice for each patient and the average value will be adopted as the result. An MBI exceeding 30 seconds will be recorded as 30 seconds. The MBI cutoff value will be calculated using receiver operating characteristic (ROC) curve analysis [31].

CFS

CFS will be assessed under a slit-lamp microscope with blue light and a yellow band–pass filer according to the van Bijsterveld grading system, in which the ocular surface will be divided into 3 zones: the nasal bulbar conjunctiva, temporal bulbar conjunctiva, and cornea [46]. Each zone will be evaluated on a scale from 0 to 3, with 0 indicating no staining and 3 indicating confluent staining. The maximum potential score is 9.

Schirmer Test I for Tear Secretion Volume

Schirmer test I will be performed without topical anesthesia after all other examinations. A Schirmer test strip will be placed on the outer one-third of the temporal lower conjunctival fornix for 5 minutes. The length of the moisture stain on the filter paper (in mm) will be recorded [47].

Environmental Conditions

The temperature of the examination room will be set at 26 °C in summer and at 24 °C in winter, with a constant relative humidity of 50%, following *Guidelines for Design and Operation of Hospital HVAC Systems*, established by the Healthcare Engineering Association of Japan [48].

Primary Outcome

The primary outcome will be the sensitivity and specificity of the *test method* for DED diagnosis, compared with the *standard method*. Sensitivity and specificity will be calculated based on the diagnostic results of the 2 methods. In the *test method*, an app-based J-OSDI total score ≥13 measured using the DEA01 and an MBI score greater than the cutoff value based on the secondary outcome (5) will be considered DED positive. In the *standard method*, a paper-based J-OSDI total score ≥13 and TFBUT ≤5.0 seconds will be considered DED positive.

Secondary Outcomes

Secondary outcomes are as follows:

1. An overall concordance rate between the *test method* and *standard method*
2. A positive/negative predictive value between the *test method* and *standard method*
3. A positive/negative likelihood ratio between the *test method* and *standard method*
4. An area under the ROC curve of the *test method* for DED diagnosis using the *standard method*
5. An MBI cutoff value of the *test method* for DED diagnosis using the *standard method*
6. An area under the ROC curve of the *test method* for TFBUT ≤5.0 seconds
7. An MBI cutoff value of the *test method* for TFBUT ≤5.0 seconds
8. Internal consistency of the app-based J-OSDI
9. Correlation, agreement, and comparison between the app-based J-OSDI and paper- based J-OSDI
10. Correlation, agreement, and comparison between the app-based MBI and slit lamp– based MBI
11. Correlation and comparison between TFBUT and the app-based MBI
12. Correlation and comparison between TFBUT and slit lamp–based MBI
13. DEA01 operability and usability
14. DEA01 failure
15. Adverse events

Secondary outcomes 1 to 4 were set to evaluate the DED diagnosis accuracy of the *test method* compared with that of the *standard method*. Secondary outcome 5 was included to determine the cutoff value for the app-based MBI using ROC analysis for DED diagnosis. Secondary outcomes 6 and 7 were included to determine if MBI measurements could be used as a substitute for TFBUT measurements. Secondary outcomes 8 and 9 were set to evaluate the reliability and validity of the app-based J-OSDI. Secondary outcomes 10 to 12 were set to evaluate the validity of app-based and slit lamp–based MBIs. In secondary outcome 13, patients will answer the following questions: "I think it's easy to operate this smartphone app," "I can use this smartphone app by myself," "I want to be tested using this smartphone app rather than being tested at a medical institution," and "I will continue to use this smartphone app" [49,50]. Patients will answer these questions on a 5-point Likert scale (1, strongly disagree; 2, disagree; 3, neutral; 4, agree; and 5, strongly agree) [51]. Secondary outcomes 14 and 15 were set to evaluate the safety and stability of the DEA01. DEA01 failure is defined as something not working as expected. Adverse events comprise unexpected signs, symptoms, or diseases encountered during the clinical trial, regardless of whether they are related to treatment. If serious adverse events or failure occur, these will be referred to the Juntendo Hospital Certified Review Board, and appropriate treatments will be provided as needed.

Sample Size and Statistical Analyses

In total, the enrollment of a minimum number of 220 study patients will be required. The CI for the sensitivity and specificity of the *test method* is set at ±10%. It is possible to calculate a sample size and a CI (a margin of error) using the following formula [52]:



(2)

Therefore, the minimum sample size will be 100 patients in each group. To meet the minimum required number of patients in each group, the target total number of patients will be set at

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110 for each group, assuming a 10% exclusion rate due to missing data.

For the primary end points, the sensitivity and specificity of DED diagnosis using the DEA01 will be calculated using ROC curve analysis with the cutoff value for the app-based MBI in the *test method*. This cutoff value will be calculated using ROC curve analysis [31]. The ROC curve will show sensitivity (positive rate) on the vertical axis and 1-specificity (false positive rate) on the horizontal axis, and the plots will be connected using straight lines. The point at which the sensitivity and specificity for DED diagnosis using the app-based MBI will be maximized and will be set as the cutoff value for MBI [31].

The secondary outcomes of the overall concordance rate, positive/negative predictive value, and positive/negative likelihood ratio will be calculated by comparing the DED diagnosis results from the *test method* with the results from *standard method* in a mixed matrix. The diagnostic performance of DEA01 will be evaluated through calculating the area under the ROC curve plotted from the sensitivity and specificity of the *test method*. The substitutability of MBI measurement for TFBUT measurement in DED diagnosis will be assessed using ROC curve analysis and through calculating the area under the ROC curve, using the cutoff value of the app-based MBI for TFBUT ≤5 seconds. The internal consistency of the app-based J-OSDI will be evaluated using factor analysis and Cronbach α coefficient, with $\alpha>0.70$ considered an acceptable range [53]. Correlation and consistency will be evaluated using Pearson or Spearman correlation coefficients, an intraclass correlation coefficient, and Bland-Altman analysis. In each patient group, study patients' backgrounds will be analyzed using a 2-tailed unpaired *t* test for continuous variables and a chi-square test for categorical variables. If a continuous variable does not clearly follow a normal distribution, it will be appropriately transformed to a logarithm and aggregated with the mean and SD or the median and IQR will be used as descriptive statistics. The operability and usability of the DEA01 will be evaluated in each group using the average score of the 5-point Likert scale responses to the operability and usability questions and the number of patients who answered better or worse than neutral using 2-tailed unpaired *t* and chi-square tests. For safety assessment, the frequency and rate of adverse events will be calculated for each group, and between-group comparisons will be performed using Fisher exact probability or chi-square tests.

A 2-sided level of significance will be set at 5%, and the confidence coefficient will be set at 95%, unless otherwise specified. Missing value completion will not be performed.

Data Management

Data management will be conducted at an off-campus data center designated by the Juntendo University Certified Review Board in accordance with a preprepared data management plan. Data will be collected and linked at several points in time. Following database locking, locked data will be transferred to the person responsible for statistical analysis.

Results

This study will start on February 1, 2023, at 3 medical institutions in Japan. Patient enrollment is expected to begin on February 1, 2023, and will end on July 31, 2023. Data will be analyzed in August 2023, and the results will be reported from December 2023 onward.

Discussion

A recent report suggested that a significant portion of patients with DED might currently be left undiagnosed and experiencing a preventable decrease in QoL [13]. For those who are appropriately diagnosed, barriers to receiving care remain, including limitations related to employment, education, and the ongoing COVID-19 pandemic. Hence, there is a need for a nonintrusive, telehealth-based alternative to current in-person evaluations. In this study, the capabilities of a smartphone app-based diagnostic assistive device will be investigated in a multicenter, open-label, prospective, and cross-sectional study. The results are intended to demonstrate the reliability and validity of the DEA01 as a noninvasive tool to facilitate a diagnosis of DED, through determining the appropriate MBI cutoff value. Confirmation of the value of the DEA01 is likely to facilitate early intervention and greater outreach to undiagnosed populations with DED.

The health care paradigm is rapidly shifting to promote remote and online care given societal changes implemented during the ongoing COVID-19 pandemic [32]. Notably, for glaucoma- and diabetes-related retinopathy management, a new approach has been sought to monitor disease progression at home through the use of portable devices and to offer visits for ocular anomalies of concern [54]. This study aims to establish a new means to facilitate DED diagnosis in a nonintrusive, noninvasive manner using the DEA01 smartphone app, which can yield an objective metric for clinicians to evaluate remotely. This may lead to a global shift toward endorsing telehealth and thus, increasing accessibility and helping to remove barriers to health care. The potential to promote early diagnosis and intervention can dramatically affect disease prognosis on a global scale. Additionally, such apps are well aligned with the current paradigm shift away from standard facility-oriented care and toward a daily life–oriented longitudinal, human-centered health care approach [40,55,56].

The DEA01 is used to help assess subjective symptoms and collect objective findings through OSDI administration and MBI measurements, respectively. The reliability and validity of the MBI and OSDI in a remote setting to facilitate DED diagnosis have been previously shown through a previous DEA01 app designed for DED research, namely, DryEyeRhythm [31,32]. Additionally, discrepancies between results obtained from the standard paper-based OSDI and app-based OSDI have been previously shown to be acceptable [32]. Our prior study utilized the MBI cutoff derived from a slit-lamp microscopy–based MBI study [26]. This study aims to establish an MBI cutoff for smartphone app-based diagnosis assistance for DED. The establishment of an optimal MBI cutoff value

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will enable more robust and reliable app-based remote DED diagnosis assistance through the use of the DEA01.

In this study, the diagnostic performance utilizing the app-based MBI as a proxy for the standard TFBUT will be evaluated using the DEA01. TFBUT reflects tear film stability and homeostasis, acting as a critical component of DED diagnosis. However, it requires specialized tools and materials, including fluorescein dye and slit-lamp microscopy. Moreover, the invasive nature of the examination disrupts the in vivo status of the tear film and the ocular surface [20-23]. Some studies have shown that fluorescein dye results are not consistently reproducible and that the dye may negatively affect the stability of the tear film [57-59]. The MBI has been shown to have a positive correlation with TFBUT [26], suggesting that the MBI can be used as a noninvasive, nonintrusive metric to substitute for TFBUT. An online screening test, based on a patient's self-measurement of the time from stopping blinking to feeling discomfort, has shown the utility of screening for DED detection [26,60]. However, the DEA01 may be more objective as it automatically measures the MBI using the sensors of a smartphone camera and allows for the evaluation of DED symptoms using the J-OSDI questionnaire. This study seeks to assess the viability of replacing TFBUT with app-based MBI measurements, which may enable remote, noninvasive, and nonintrusive diagnosis assistance concerning DED.

This study may have some limitations. First, this study may be affected by selection bias, as study patients are limited to those who have been evaluated in a highly specialized university hospital and those who are able to use the smartphone app [32]. Second, the study will be performed in a specific order. Patients will be required to first use the app, after which there will be a clinical evaluation for DED. This study sequence may be a confounder and might affect the results; therefore, assessing the effects of the examination order in a randomized study may be necessary [61]. Lastly, the DEA01 is designed to be an ancillary tool for initial DED diagnosis assistance, and specialized tests such as corneal staining and Schirmer test may be required to further assess disease severity and progression.

In conclusion, this study will evaluate the capability of the DEA01 in assisting a DED diagnosis. The study findings may potentially help to establish a noncontact, noninvasive, and remote consultation method for app-based DED diagnostic assistance using the mHealth DEA01 smartphone app. It is hoped that the DEA01 will provide effective diagnostic evaluation for DED in telemedicine and allow for early intervention in patients who have not been diagnosed with DED due to limited access to medical care.

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Conflicts of Interest

TI, Y Okumura, and AM-I were the owners of InnoJin, Inc, for developing the DEA01. KN is an employee of InnoJin, Inc. TI and Y Okumura have a patent pending for a simple detection method for dry eye disease (Japanese patent application 2020–162122). TI reported receiving grants from Johnson & Johnson Vision Care; SEED Co, Ltd; Santen Pharmaceutical Co, Ltd; Hogy Medical Co, Ltd; Novartis Pharma KK; Ribomic Co, Ltd; Kowa Company, Ltd; and Lion Corporation, outside the submitted work, as well as personal fees from Santen Pharmaceutical Co, Ltd; and InnoJin Inc Y Okumura and AM-I reported receiving personal fees from InnoJin Inc. The remaining authors declare no conflict of interest.

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Abbreviations

CFS: corneal fluorescein staining
DED: dry eye disease
J-OSDI: Japanese version of the Ocular Surface Disease Index
MBI: maximum blink interval
mHealth: mobile health
OSDI: Ocular Surface Disease Index
ROC: receiver operating characteristic
TFBUT: tear film breakup time
QoL: quality of life

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Protocol

Development of a ParticipACTION App–Based Intervention for Improving Postsecondary Students' 24-Hour Movement Guideline Behaviors: Protocol for the Application of Intervention Mapping

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Abstract

Background: The Canadian 24-Hour Movement Guidelines for adults provide specific recommendations for levels of physical activity, sedentary behavior, and sleep (ie, the movement behaviors) required for optimal health. Performance of the movement behaviors is associated with improved mental well-being. However, most postsecondary students do not meet the movement behavior recommendations within the Canadian 24-Hour Movement Guidelines and experience increased stress and declining well-being, suggesting the need for an intervention targeting students' movement behaviors.

Objective: We aimed to develop and implement a theory-informed intervention intended to improve the movement behaviors and mental well-being of first-year postsecondary students.

Methods: The Intervention Mapping protocol was applied in the development and implementation of the intervention. Intervention Mapping entailed performing a needs assessment, determining the intervention outcomes, selecting theory- and evidence-based change methods and applications, preparing and producing intervention plans and materials, developing the implementation plan, and finally developing an evaluation plan. The Theoretical Domains Framework and the Behavior Change Wheel were also used in conjunction with the Intervention Mapping protocol to ensure a solid theoretical basis for the intervention. This protocol led to the development and implementation of a 6-week, theory-informed ParticipACTION app–based intervention aimed at helping first-year postsecondary students improve their movement behaviors and mental well-being. The developed app content provided students with information on each of the movement behaviors and behavioral strategies (ie, goal setting, action planning, monitoring,

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and coping planning). The use of Intervention Mapping allowed for the continuous involvement of various multidisciplinary partners and end users, ensuring that the intervention design and implementation was appropriate for the target audience. The feasibility, acceptability, and potential impact of the intervention will be examined in a subsequent proof-of-concept study at 2 Canadian university campuses.

Results: Participant recruitment occurred during September 2021, and the intervention was conducted from October to December 2021. The deadline for completion of the postintervention questionnaire by participants was mid-December 2021. The analysis of data examining the feasibility, acceptability, and potential impact of the intervention began in January 2022, with the publication of the proof-of-concept evaluation expected in 2023.

Conclusions: Intervention Mapping with the Theoretical Domains Framework and Behavior Change Wheel was a useful approach to combine evidence and theoretical concepts to guide the design and implementation of a ParticipACTION app–based intervention targeting postsecondary students' movement behaviors and mental well-being. This process may serve as an example for other researchers developing multiple behavior change app–based interventions. Should the forthcoming evaluation demonstrate the intervention's acceptability, feasibility, and potential impact, the intervention may provide a scalable method of improving postsecondary students' movement behaviors and mental well-being.

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KEYWORDS

24-Hour Movement Guidelines; multiple behavior change; mobile health; mHealth; postsecondary students; physical activity; sedentary behavior; sleep; app; mobile phone

Introduction

The Canadian 24-Hour Movement Guidelines (24HMG) for adults aged 18 to 64 years and adults aged 65 years or older [1] provide specific recommendations for ideal levels of physical activity, sedentary behavior, and sleep required for optimal health. Despite the established physical and mental health benefits of increasing physical activity, decreasing sedentary behavior, and ensuring sufficient sleep [1], population-level engagement in these behaviors is suboptimal [2]. Indeed, although a guideline can signal the recommended action, it alone does not guarantee use [3]. As a result, purposefully chosen and implemented evidence-informed efforts to increase the uptake and use (ie, implementation) [4] of the 24HMG among target populations are required.

To address this gap and using an integrated knowledge translation approach [5,6] and the Knowledge-to-Action Framework [6] as an organizing model, the developers of the 24HMG established a knowledge translation team [7] comprising partners (eg, representatives from the Canadian Health Promoting Campuses Network, Canadian Sleep Society, Canadian Medical Association, and Canadian Public Health Association) and researchers who together designed, implemented, and evaluated a strategy to promote adoption of the 24HMG.

The knowledge translation team identified postsecondary students (ie, students entering or attending college or university, also known as *tertiary education institutions* internationally) as the target audience for guideline implementation (see the study by Tomasone et al [7]). Despite the evidence supporting the link between movement behaviors and impacts on their mental health and well-being [8,9] and academic performance [10], most postsecondary students engage in suboptimal levels of the movement behaviors [9]. Moreover, the COVID-19 pandemic exacerbated students' suboptimal movement levels with stay-at-home orders and widespread remote learning [11-14]. Short-term negative consequences of this change included increased stress and declining mental health and well-being (eg, higher rates of severe anxiety) [15,16]. The long-term impact on students' physical and mental health remains unknown. Thus, an intervention targeting the movement behaviors and mental well-being of postsecondary students was timely and necessary.

Interventions developed using theory may be more effective than those based on little or no use of theory [17]. To inform intervention design and implementation, we applied Intervention Mapping—a rigorous and systematic protocol for developing theory- and evidence-based behavior change interventions [18,19]. Although Intervention Mapping offers an iterative protocol for developing and tailoring an implementation intervention, it was necessary to use other frameworks in conjunction with Intervention Mapping to fully inform design and implementation. The Theoretical Domains Framework (TDF) and Behavior Change Wheel (BCW) were used to help inform the Intervention Mapping protocol. The TDF is a theoretical framework that provides a way to view the cognitive, affective, social, and environmental influences on behavior [20] and maps onto the capability, opportunity, motivation, behavior (COM-B) model within the BCW. At its core, the BCW has the model of behavior known as COM-B, referring to "capability," "opportunity," "motivation," and "behavior," which recognizes that behavior is part of an interacting system involving all these components [21,22]. The BCW identifies different intervention options that can be applied to change each of the components and policies that can be adopted to deliver those intervention options [21,22]. Finally, the BCW involves identifying content and implementation options (ie, identifying behavior change techniques [BCTs] and modes of delivery) [21,22]. Given the complexity of applying these 2 frameworks in conjunction with the Intervention Mapping protocol, this paper provides a systematic description of the process used to design and implement an intervention aimed at improving the movement

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behaviors and well-being of first-year postsecondary students (ie, students who have just graduated high school or took a single gap year before entering an undergraduate program and turning 18 years or older).

Methods

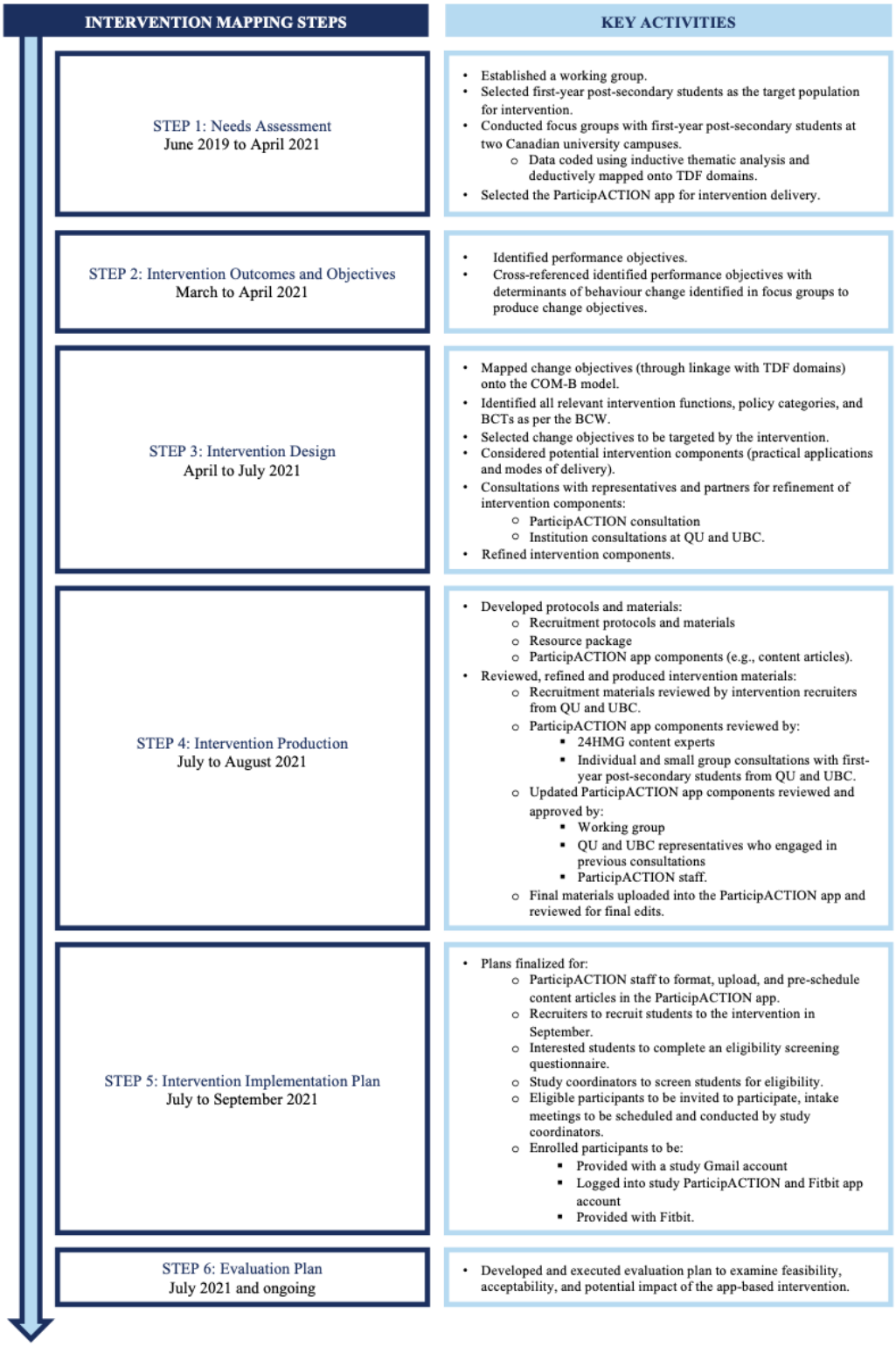
Overview

The Intervention Mapping protocol specifies 6 steps for the development of theory and evidence-based interventions [18,19]. Step 1 (the needs assessment) involves establishing a planning or working group, defining the context of the intervention in terms of the health problem and population (ie, intervention target group), establishing the determinants of behavior change (ie, the barriers and facilitators), and finally describing the intervention setting. In step 2, the intervention outcomes are determined, which include performance objectives (ie, behavioral changes necessary to achieve intervention outcomes) and change objectives (ie, specific behaviors that will lead to changes in the behavioral determinants, which are needed to achieve performance objectives). Step 3 involves choosing theory- and evidence-based change methods, selecting or designing practical applications to deliver change methods, and finally refinement of the selected intervention components. Step 4 focuses on intervention production by preparing intervention plans and drafting protocols and materials followed by the pretesting, refinement, and production of intervention materials. In step 5, the development of an intervention implementation plan occurs and includes identifying intervention program users (ie, adopters and implementers). Step 6 comprises specifying an evaluation design and developing the indicators and measures of assessment.

We implemented the first 5 steps in the development and implementation of the intervention. Step 6 (evaluation plan) will be published in detail in a forthcoming proof-of-concept evaluation paper; however, a brief synopsis of the evaluation plan is described in subsequent sections. Figure 1 outlines the 6 Intervention Mapping steps, the period over which each step was performed, and the key activities within each step.

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Figure 1. Timeline displaying the 6 Intervention Mapping steps and key activities within each step. 24HMG: 24-Hour Movement Guidelines; BCW: Behavior Change Wheel; COM-B: capability, opportunity, motivation, and behavior; QU: Queen's University; TDF: Theoretical Domains Framework; UBC: University of British Columbia.



Step 1: Needs Assessment (June 2019-April 2021)

Establish a Working Group

We formed a multidisciplinary team of partners and researchers to create a new working group (see Multimedia Appendix 1 for the working group constituency and roles). Several working group members were members of the original 24HMG Knowledge Translation Advisory Committee [7], and additional members were added to ensure comprehensive expertise for intervention development, implementation, and evaluation. The working group collectively possessed expertise in the 24HMG behaviors, tailored intervention development and delivery, postsecondary student health and well-being, and knowledge translation and behavior change research and evaluation.

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Working group members were engaged at various steps of the Intervention Mapping approach.

Description of Health Problem and Intervention Target Group

Three factors contributed to defining the health problem and intervention target group: (1) established, suboptimal performance of the movement behaviors (ie, not meeting 24HMG recommendations); (2) suitability of the intervention target group for receiving a targeted intervention; and (3) adoption of a health-promoting charter directing action at postsecondary institutions.

Postsecondary students are at risk of negative physical and mental health impacts associated with suboptimal performance of the movement behaviors. In the first deployment of the Canadian Campus Wellbeing Survey in early 2020, Weatherson et al [9] reported that only 9.9% of postsecondary students achieved 4 components of the 24HMG (moderate to vigorous physical activity, total sitting time, recreational screen time, and sleep). Large decreases in physical activity levels, sleep quantity, and sleep quality as well as increases in students' sedentary behavior are observed as students (adults aged 18-19 years) adjust to the transition from high school to postsecondary education [23-28]. This life transition, compounded with the negative impact of the COVID-19 pandemic on students' movement behaviors [11-14], may further negatively impact students' short- and long-term physical and mental health.

Fortunately, postsecondary students are malleable learners and an intervention that provides an opportunity for students to learn and develop healthy movement behaviors, especially in their first year, can facilitate the development of habits that they can continue to use in their adult years ahead [29]. In addition, physical activity and sleep have been found to be positively associated with postsecondary students' positive affect and mental health [30,31], suggesting further benefit of postsecondary students receiving this intervention.

Several Canadian postsecondary institutions have adopted the Okanagan Charter for Health Promoting Universities and Colleges [32]. The Okanagan Charter calls on institutions to embed health in all aspects of campus culture and to lead health promotion action and collaboration. The working group anticipated that campuses that have adopted the charter would be supportive in helping to develop, implement, and evaluate an intervention aimed at improving students' movement behaviors and mental well-being. Two Canadian campuses—Queen's University (QU) and the University of British Columbia (UBC)—were selected as sites for implementation of a fall 2021 intervention, as both institutions have adopted the charter and had 24HMG knowledge translation team member representation on these campuses (ie, team members GF and MD are located at UBC, while JRT, AELC, and SMF are located at QU).

Determinants of Behavior Change

Given the novelty of the 24HMG in Canada, there was a paucity of published data on the determinants (ie, barriers and facilitators) of postsecondary student-integrated movement behaviors; thus, we collected our own. Focus groups were conducted with 74 first-year undergraduate postsecondary students at QU and UBC [33]. Focus group data were coded using inductive thematic analysis before codes were deductively mapped onto TDF domains [34,35]. The TDF was used to more thoroughly understand the individual-level factors that may act as barriers or facilitators to behavior change; within Intervention Mapping, the TDF domains represent the determinants of behavior change. In total, 13 of the 14 TDF domains were identified as influencing students' movement behaviors, with the unidentified TDF domain being *optimism*. For each code within every TDF domain, a belief statement was generated to provide details about the perceived role of the domain in influencing the behavior [36], helping to exemplify the barriers and facilitators experienced by students when attempting to engage in the movement behaviors [33]. Multimedia Appendix 2 [21,22,33] provides a full list of barrier and facilitator belief statements and change objectives.

Beliefs within the *Knowledge* and *Behavioural Regulation* domains were cited as facilitators and those within the *Social/Professional Role* and *Identity* domains were cited as barriers to engaging in guideline-level movement behavior. Beliefs within 10 domains (*Skills; Beliefs about Capabilities; Beliefs about Consequences; Reinforcement; Intentions; Goals; Memory, Attention and Decision Processes; Environmental Context and Resources; Social Influences;* and *Emotions*) were cited as both facilitators and barriers to students performing the movement behaviors. Interestingly, many of the determinants operate at an individual level (eg, within the students' control, such as developing and maintaining a schedule), whereas other determinants operate beyond the students' immediate control (eg, the university's provision of standing desks and desk cycles for student use). See Multimedia Appendix 2 for more details.

Intervention Setting

Intervention development occurred during the COVID-19 pandemic; consequently, there was uncertainty about the timing of a return to campus. To minimize in-person intervention components, using an app was appealing as an intervention delivery mechanism. An app is a useful vehicle for intervention delivery for this population, as students tend to report high use of health-related apps [37,38]. Although an app-based intervention is restricted to only being able to target individual-level determinants of behavior change, given the unpredictability of the COVID-19 pandemic, opting for an app-based delivery was a pragmatic decision. Not only are app-based interventions a viable means of intervention in the target population, but previous empirical evidence has also demonstrated that apps can be effective in changing health-related cognitions and behavior [39-41].

ParticipACTION, a physical activity nonprofit organization and one of the main partners of the 24HMG, already possessed an evidence-informed app that was leveraged by the working group to help support and expedite the implementation of the intervention within a short timeframe. The ParticipACTION app was developed using the BCW framework [21,22] as its theoretical basis [42].

The free ParticipACTION app serves as both a self-monitoring device (tracking users' steps, "move minutes" and "active

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minutes" by linking the app with a fitness tracker [eg, Fitbit or Apple Watch] or having users manually add their activity) as well as a content hub (where evidence-informed articles are provided to help educate users on the 24HMG, goal setting, barrier identification and action planning)—these components work together to provide a tailored experience for users. App users are also eligible to win rewards (eg, weekly draw for a CAD $10 [US $7.4] Amazon gift card funded by ParticipACTION and its funders: the Public Health Agency of Canada and Sports Canada) by earning daily badges (ie, extrinsic motivation), where each badge releases entries in the next draw for rewards automatically. The app user earns additional badges by tracking their activity and hitting their active minute goals, engaging in challenges, reading articles, and watching videos within the app. ParticipACTION also offers "ParticipACTION+," a premium for-a-fee version that includes all standard app features as well as additional features such as in-app team challenges and leaderboards (eg, to compare step counts against other organization or team members), member engagement reporting, and customizable content and notification delivery. Fees for ParticipACTION+ are paid for by the intervention delivery team and not by app users. As the ParticipACTION app was theoretically informed and would allow for us to address many of the identified determinants of behavior change without in-person contact, it was deemed an appropriate vehicle for intervention delivery.

Step 2: Intervention Outcomes and Objectives (March 2021-April 2021)

The primary intervention outcome was to improve first-year undergraduate postsecondary students' movement behaviors, whereas the secondary outcome was to improve students' mental well-being. The performance objectives for students' movement behaviors are listed in Multimedia Appendix 2 and were drawn from each of the main 24HMG recommendations (ie, physical activity, sedentary behavior, sleep, and integration of the behaviors). Performance objectives were cross-referenced with the belief statements (ie, determinants) generated in step 1 (section *Determinants of Behaviour Change*) to produce the change objectives in Multimedia Appendix 2. The change objectives state what needed to change about a specific behavioral determinant (eg, intentions) for students to achieve a specific performance objective. In some instances, multiple belief statements were collapsed together as they represented a common change objective. Multimedia Appendix 2 includes all the performance objectives and corresponding potential change objectives identified from the focus group data.

In line with the secondary outcome of improving students' mental well-being, a final performance objective was identified: "student has positive feeling and functional aspects of mental well-being (eg, feeling optimistic, having energy to spare)." Given that following the 24HMG is associated with a lower risk of anxiety and depression and improved quality of life [1], the working group interpreted the change objectives for this final performance objective as students' performance of the movement behaviors themselves.

Step 3: Intervention Design (April 2021-July 2021)

Theoretical Methods

To move forward with intervention design and selecting change methods for step 3, we examined the theoretical links between the generated belief statements (see the section Step 1: Needs Assessment [June 2019 to April 2021]) organized by TDF domain and the antecedents of behavior, which can be selectively targeted in an intervention. Through their linkage with the TDF domains, change objectives were mapped onto the COM-B model, and accordingly, all relevant intervention functions and policy categories were identified following the process described in the BCW guide [22] (Multimedia Appendix 2). The next step was to identify intervention content in terms of which BCTs best serve the intervention functions. BCTs are considered the "active ingredients" of an intervention designed to change behavior and are the proposed mechanism of change to be used alone or in combination with other BCTs [43]. To assist in selecting candidate BCTs for the intervention, we used the Theory and Techniques Tool [44] to specify the links between TDF domains and BCTs [44-46].

Members of the working group reviewed Multimedia Appendix 2 (ie, the complete list of formulated change objectives mapped onto the TDF and BCW) and considered which change objectives could and should be addressed within the app-based intervention. The discussion included reflecting on the identified TDF domains, COM-B sources of behavior, intervention functions, policy categories, and BCTs. Selected change objectives are set in bold in Multimedia Appendix 2. Working group members believed that all 6 sources of behavior change (psychological and physical capabilities, social and physical opportunities, and automatic and reflective motivation) and 13 of the 14 TDF domains should be targeted within the intervention.

Notably, all selected change objectives focus on individual-level changes, with organizational- and community-level changes lying outside the scope of an app-based intervention. However, Multimedia Appendix 2 outlines all the identified change objectives, where some change objectives address organizational-level changes. One example is "encouraging residences to enforce quiet hours and promote an atmosphere that encourage healthy sleep habits."

Intervention Components: Practical Applications and Mode of Delivery

Overview

Multimedia Appendix 3 presents the intervention components described in this section as well as a description of the evidence and rationale that guided the formation of each component. In total, 7 out of the 9 possible BCW intervention functions were selected: education, persuasion, incentivization, training, enablement, modeling, and environmental restructuring. To support implementation of the intervention functions, 2 BCW policy categories were selected: communication and marketing and environment and social planning.

The working group considered the potential intervention components (ie, practical applications and modes of delivery)

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to facilitate the identified change methods. The BCW intervention functions and policy categories guided the selection of the intervention components. In addition, the BCW presents the affordability, practicality, effectiveness, acceptability, safety, and equity criteria, which should be applied when engaging in the process of developing, selecting, and implementing interventions [22]; the working group reflected on these criteria during the component selection process. Five intervention components, described in subsequent sections, were considered to facilitate change objectives: ParticipACTION app content articles, notifications, badges, and competition as well as a resource package outside of the ParticipACTION app.

ParticipACTION App: Content Articles

A series of content articles specific to the 24HMG would be created, tailored for first-year postsecondary students, and uploaded into the ParticipACTION app. These articles would take student participants on a "content journey," providing information about each of the individual movement behaviors and how the movement behaviors are connected, while also addressing related barriers and facilitators identified in the needs assessment. For example, content would include information about the benefits of performing the movement behaviors pertinent to postsecondary students. Articles would also persuade and enable participants to perform the movement behaviors by focusing on select BCTs (eg, action planning). Articles would provide suggestions on how to restructure physical and social environments to encourage performance of the movement behaviors (eg, improvising a standing desk and how to be active with roommates). Students would be able to visit articles multiple times if desired, and through ParticipACTION+, articles could appear on students' app home page. Although students would have the flexibility to explore the ParticipACTION app, they would be presented with the developed content articles sequentially over the intervention period.

ParticipACTION App: Notifications

The use of the ParticipACTION+ service would enable the development and delivery of both push notifications and movement behavior reminder notifications. Push notifications would inform participants of the release of new content article in the app and would link to the new article. Movement behavior reminder notifications would encourage participants to engage in a specific movement behavior. These reminder notifications would serve as a prompt for the behavior, which was identified as an important BCT.

ParticipACTION App: Content Article Engagement Badges

The development of a weekly content article engagement badge was proposed because ParticipACTION app users can already earn badges for the number of articles read and their physical activity (eg, number of steps). Participants would earn a badge for engaging with the intervention content articles each week. The allocation of badges to participants would provide general encouragement to participants, reinforcing their behavior of engaging with the content articles.

ParticipACTION App: Competition

Competition was identified within the needs assessment as a facilitator for movement behavior engagement and would offer students a form of social comparison. The working group proposed 2 types of competition: within-campus and between-campus competitions. For within-campus competition, participants attending the same institution would be placed on teams that would compete to see which team has the highest step count or the most move minutes using the ParticipACTION+ challenge app feature. Participants would be able to view scores on a leaderboard to determine how other teams were performing. A reward would be offered where participants on the winning team would each win a material reward (eg, e-gift card) at the end of the intervention. Between-campus competition would involve participants at each institution competing to see which institution can collectively accumulate more move minutes by the end of the intervention. A weekly notification would be used to inform participants of their institution's progress. Similar to the within-campus competition, participants at the winning institution would each receive a material reward (eg, e-gift card) at the end of the intervention.

Resource Package

Formative work identified that participants needed access to resources on their campus or within the city to assist with meeting the behaviors, including free and low-cost options. Rather than providing tailored resources for each institution (ie, QU and UBC) and its respective city (ie, Kingston, Ontario, and Vancouver, British Columbia) within the app content, the working group proposed developing a tailored resource package that would be shared with participants via participant email. This decision allowed for the developed app content to be applicable to both campuses rather than requiring 2 sets of app content tailored to each institution's campus and city, supporting future scalability of the intervention.

Nonintervention Components

The working group acknowledged that by giving students access to the ParticipACTION app, they would have access to the additional ParticipACTION app components (eg, "Take 10" prompts, exercise videos, and rewards). Students would not be instructed to explicitly use these additional components as part of the intervention, but they might be of benefit to those students who engaged with these additional ParticipACTION app components. In addition, the working group decided a commercial wearable device (ie, the Fitbit Inspire 2) would be provided to participants as a device-assessed measure of their movement behaviors. Fitbit was chosen instead of researcher-grade devices (eg, accelerometer) for several reasons. First, the physical activity data from Fitbit would be synced into the ParticipACTION app. Accordingly, all participants would have equal access to the full app functionality (ie, monitoring steps and active minutes directly within the ParticipACTION app). Second, because our interest was in all movement behaviors reported over a 24-hour period, we determined that using a device-assessed measure of movement behaviors would decrease participant burden and increase the accuracy of movement behaviors compared with self-report

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measures [47,48]. Finally, wrist-worn consumer-grade wearable devices increase consumer appeal and wear compliance compared with waist-worn research-grade accelerometers [47,49]; thus, we hoped that this would translate into increased compliance among our target population.

It is conceivable that Fitbit alone could have provided participants self-monitoring and feedback. However, though Fitbits (and other consumer wearables) have been linked with multiple theoretically relevant strategies associated with increased adherence and maintenance of movement behaviors such as physical activity [50], when wearable technology alone has been given to participants, without any intervention component, minimal changes in physical activity behavior are observed [51]. Consequently, Fitbit itself would not be considered an intervention component.

Considering all the above components, the working group proposed an intervention length of 6 weeks during the second half of postsecondary students' 12-week fall 2021 term, allowing sufficient time for intervention recruitment and intake while ensuring the completion of the intervention before end-of-term examinations. The working group proposed that limiting content articles to 2 succinct articles per week for the 6-week intervention for a total of 12 articles would prevent overwhelming students and may help to potentially circumvent intervention attrition. On the basis of the formative work conducted, the format of the proposed content journey would be such that the first article each week would be "informational" in nature, providing necessary knowledge with tips and benefits pertinent to participants, and the second article for each would focus on a particular behavior change strategy, describing how to perform the behavior change strategy in the context of one specific movement behavior.

Refining Intervention Components

Consultations with the broader ParticipACTION team and partners at both institutions were held to obtain further insight on the affordability, practicality, effectiveness, acceptability, safety, and equity of the proposed intervention. Engaging these additional partners allowed for the selection and further refinement of the proposed intervention components.

ParticipACTION Review

Although ParticipACTION representatives sit on the working group (Multimedia Appendix 1), broader feedback was sought from additional ParticipACTION representatives on the feasibility of the proposed intervention components. A written draft of the components was reviewed by ParticipACTION staff with knowledge in the following areas: behavior and insights, knowledge translation, marketing and communications, product marketing, strategy and insights, and health promotion. ParticipACTION staff supported the inclusion of all the proposed components with the exclusion of the content article engagement badges. Reasoning for exclusion of this component was owing to feasibility related to the creation of this app badge within the intervention development timeframe and budget. Accordingly, the working group agreed to exclude this intervention component.

Institution Representative Consultations

Consultations were held with representatives (ie, campus staff and students) from each institution using Zoom (Zoom Video Communications). The consultation at QU was held with 9 representatives from Student Wellness Services, Residence Life, Q Success (ie, a first-year peer mentorship program), the International Centre (ie, cross-cultural advisory), and first-year postsecondary students attending QU. The UBC consultation was held with 14 members of the campus Physical Activity Committee, which included individuals from Athletics and Recreation, the Office of Wellbeing Strategy, the University Neighbourhoods Association, the Student Wellness Centre, Kinesiology Undergraduate Society, and the Graduate Student Society.

Before the consultations, representatives were provided with a description of the intervention and potential evaluation components, including participant eligibility and recruitment, intervention components (eg, proposed content for the articles), and proposed evaluation components. During group-based, 60-minute consultations via Zoom, facilitated by SMF and JRT, representatives were presented with the findings of the formative research conducted as part of the needs assessment. Group discussion focused on obtaining representatives' insight on the "content journey" articles (eg, order of movement behavior content, behavior change strategies, and frequency of content) and inclusion of the competition feature of the app. Representatives were then asked to provide feedback on the proposed participant eligibility (ie, inclusion and exclusion criteria) to suggest potential avenues and strategies for intervention recruitment and to comment on proposed evaluation components. Representatives' suggestions from both consultations were summarized and brought forward to the working group for discussion.

Representatives agreed with the proposed intervention length of 6 weeks, to limiting content to 2 articles per week, and to the format of the content journey. However, the main topic of discussion during the consultations was about the order of presentation of the movement behaviors within the content journey articles. Originally, the working group proposed focusing on behaviors in the order presented in the 24HMG tag line of "Move More, Reduce Sedentary Time, Sleep Well" (ie, physical activity, sedentary behavior, and sleep). However, representatives reported that many students are aware that they are not obtaining sufficient physical activity; rather than immediately focusing on a behavior that individuals often perceive as being difficult to perform, it may be more motivating to start with a behavior they may perceive as being easier to achieve. With this feedback, the working group altered the content journey to begin by introducing the 24HMG, then present content focused on the movement behaviors in sequence from sleep, sedentary behavior, light physical activity, to moderate to vigorous physical activity, and finally revisiting the integrated nature of the movement behaviors at the end of the intervention.

Finally, representatives advocated for the removal of the competition component of the intervention. The ParticipACTION app does not offer team communication as

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part of its functionality; given that social connection and support would be important for successful between- and within-campus competition and maintaining participant engagement in competition, the working group agreed to remove this intervention component. See Multimedia Appendix 3 for detailed descriptions of the intervention components (both included and excluded, following representative consultation).

Step 4: Intervention Production (July 2021-August 2021)

Prepare Plans and Draft Protocols and Materials

With the input of our working group and the application of feedback from the consultations conducted in step 3, we moved forward with outlining the participant recruitment protocols and materials for each institution, the resource package, app content articles, and app notifications.

Recruitment Protocol and Materials

Participant recruitment serves as the vehicle of entry for participants into the intervention; thus, recruitment protocol and materials were carefully considered. It was determined that participant recruitment would involve student self-referral to the intervention to limit the burden on recruiters (ie, campus representatives who would be asked to assist with recruitment). At QU and UBC, recruitment avenues included residence advisors or counselors, Student Wellness Services, and undergraduate societies and programs. Recruiters were provided with a 2-page study description as well as posters and preprepared social media posts. Recruiters were asked to place study posters in areas that students were likely to view (eg, student spaces in residences, wellness services, or office bulletin boards) and use preprepared social media posts on their institutional office, service, or society social media accounts (ie, Facebook, Instagram, and Twitter). In addition, instructors of first-year courses at each institution were contacted and provided with a Microsoft PowerPoint slide to add to the beginning of their lecture presentations as well as brief intervention descriptions they could post on their course pages on their institutional course platforms. All developed recruitment materials included links and QR codes for the intervention eligibility screening questionnaire for interested students to complete.

Resource Package

The resource package, a PDF document that would be emailed to participants, was developed by the 24HMG project coordinator (SMF) and research assistant (BT) to include the public facing 24HMG; infographics (ie, tips to "move more, reduce sedentary time, sleep well," benefits of following the 24HMG); and physical activity, sedentary behavior, sleep, and mental well-being resources for campus, community, and web. The resource packages were tailored for each campus and institution city with input from QU Student Wellness Services and UBC Wellbeing.

ParticipACTION App Components

ParticipACTION shared existing app content (ie, evidence-based articles created by ParticipACTION and partners) on the topics of instruction, lifestyle, and behavior change. A research assistant (BT)—a fourth-year undergraduate kinesiology student at QU trained in behavior change theory and practice—reviewed the existing ParticipACTION app content, selected intervention functions, and BCTs (Multimedia Appendix 3) to draft the 12 content journey articles. In total, 12 accompanying push notifications (ie, to notify participants about each new piece of content in the app) and 12 behavior reminder notifications (ie, to remind participants to engage in movement behaviors) were simultaneously drafted to ensure consistent messaging with the content articles.

The developed content articles followed the order of behaviors and behavior strategies defined and selected in step 3 (see Multimedia Appendix 3 for the description of the content articles). Notifications addressing the same movement behavior were scheduled to be staggered across the 6-week period to emphasize the integrated nature of the behaviors. An iterative content review process with the 24HMG project coordinator (SMF) and knowledge translation lead (JRT) was undertaken.

Pretest, Refine, and Produce Materials

Recruitment Materials

The developed recruitment materials were shared with recruiters from QU (Student Wellness Services and Residence Life) and UBC (UBC Wellbeing) for feedback. Minor feedback was provided on the social media posts, suggesting that the amount of text be reduced.

Resource Package

The resource package was sent to QU and UBC campus representatives on the working group who collaborated with colleagues on their end to provide additional suggestions on the developed resources. The final version was reviewed by a subset of the working group and approved for distribution.

ParticipACTION App Components

The developed content journey articles and notifications were reviewed by the 24HMG content experts (ie, researchers involved in the development of the 24HMG recommendations). Incorporated feedback from content experts included (1) making the language less formal, (2) distinguishing more clearly between sedentary time and screen time, (3) hyperlinking to existing ParticipACTION app content (ie, exercise videos) within the content articles, and (4) adding calls to action (eg, "What is your SMART goal?") within the content articles.

Individual and small group consultations were subsequently held with 9 first-year postsecondary students across both institutions, facilitated by the 24HMG research assistant (BT). Students were sent Microsoft Word document drafts of the content articles and notifications in advance of the consultations. During consultations held via Zoom, students were asked to consider whether first-year students would find the content engaging, motivating, exciting, appropriate, and interesting and whether the content was too long or too short. Students were also encouraged to provide feedback on phrasing and whether additional tips or strategies should be included. Feedback from students that was used to refine content included (1) breaking down bigger paragraphs to bullet points for visual appeal, (2) making the content articles read as conversational with the use

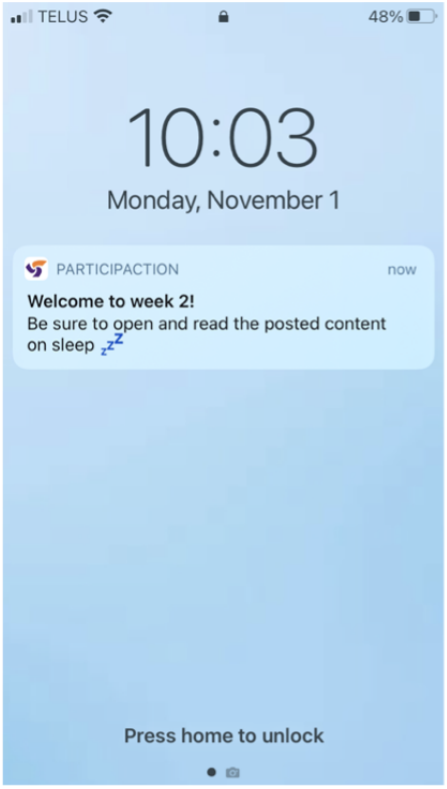
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of rhetorical questions, (3) adding definitions for terms that are less known (eg, sedentary behavior and screen time), (4) adding yoga to the coping planning behavior change strategy article (a popular activity), and (5) breaking down the 150 minutes of moderate to vigorous physical activity into more "manageable" chunks (eg, five 30-minute segments).

Students were also queried about which days of the week and time of day they would prefer to receive app notifications; they reported a preference for push notifications (for content articles) in the mornings and movement behavior reminder notifications in the afternoons. Students agreed with the proposed suggestion of receiving content articles and push notifications on Monday and Wednesday mornings and the movement behavior reminder notifications on Tuesday and Thursday afternoons. These suggested timings were adopted as part of the intervention delivery.

The updated ParticipACTION app content was then reviewed and approved by the entire working group and campus representatives (including first-year students) by email. The content was sent to ParticipACTION staff with expertise in health promotion, knowledge translation, and marketing. The content was reviewed to ensure that ParticipACTION standards, tone, and voice were maintained. Staff edited and formatted the content and returned the content to the knowledge translation lead (JRT), 24HMG project coordinator (SMF), and research assistant (BT), who made the final edits and returned the content to ParticipACTION. Finally, ParticipACTION staff uploaded the content into the ParticipACTION app and prescheduled the delivery of the content articles, push notifications, and movement behavior reminder notifications. Once in the app, the content articles were reviewed by 4 of the working group members (SMF, BT, LMV, and JRT) who suggested final edits relating to formatting and image placement. The final ParticipACTION app content text and images for intervention week 1 can be viewed in Multimedia Appendix 4. Figures 2-5 present examples of students' views in the ParticipACTION app, including examples of notifications, the app home page, and a content article.

Figure 2. A push notification reminding students to view the new article in the ParticipACTION app.



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Figure 3. The ParticipACTION app home page showing user active minutes, steps, and move minutes.

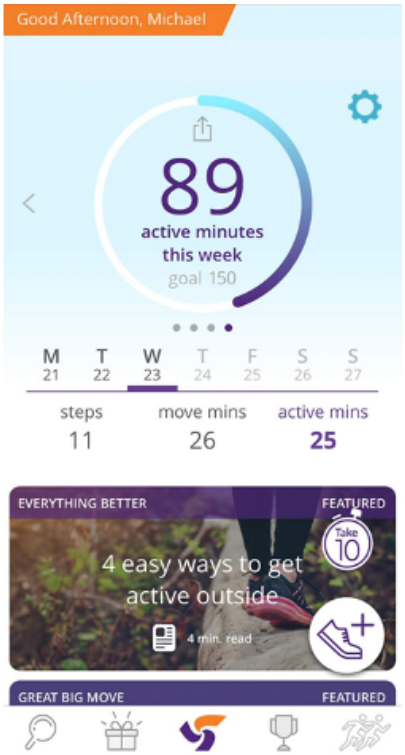
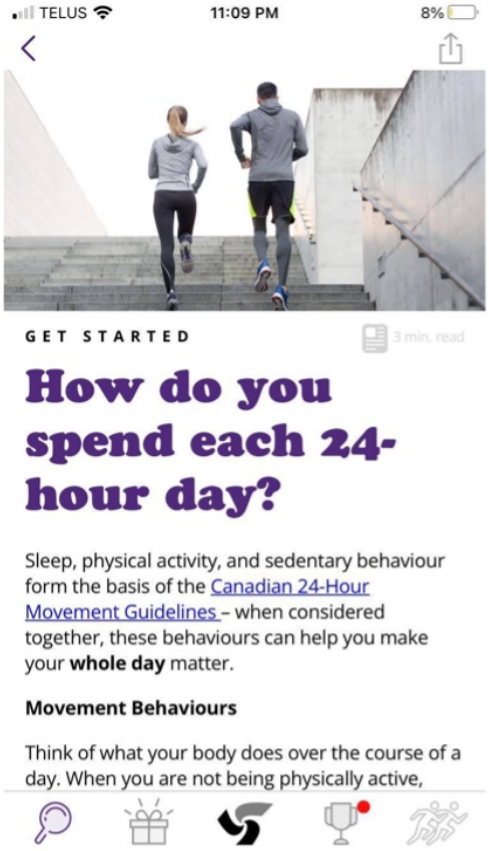
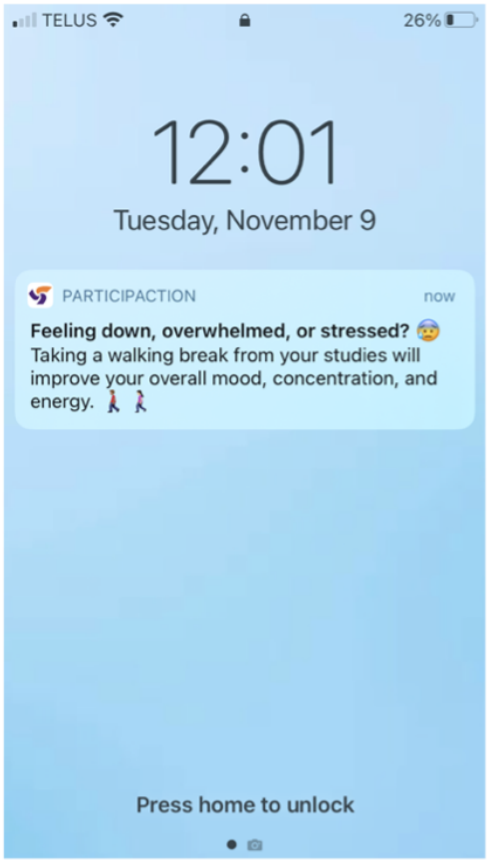


Figure 4. An intervention content article in the ParticipACTION app discussing the 24-Hour Movement Guidelines.



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Figure 5. Movement behavior reminder notification delivered to students—reminders focused on a particular movement behavior or mental well-being.



Step 5: Intervention Implementation Plan (July 2021-September 2021)

To implement and deliver the intervention at the 2 institutions, ParticipACTION staff, recruiters, and study coordinators were required to act as implementers. For this intervention, the adopters were the first-year postsecondary students for whom the intervention was developed.

Implementers

ParticipACTION staff were responsible for formatting and uploading the content articles into the ParticipACTION app and for scheduling the release or delivery of the content and notifications. Recruiters (eg, campus staff and lecturers at UBC and QU) at each institution acted as gatekeepers for the intervention. Their support and recruitment efforts were critical for recruiting students to the intervention. The study coordinators (SMF and JM) were responsible for determining student eligibility for participation in the developed intervention and for participant intake processes.

Adopters

The intervention adopters included first-year undergraduate postsecondary students from QU and UBC. To participate in the intervention, students had to meet the eligibility criteria determined a priori by the working group and refined during consultations with campus representatives (see the section Step 3: Intervention Design [April 2021-July 2021]). Interested students completed an eligibility screening questionnaire via Qualtrics.

The inclusion criteria for eligibility stipulated that students must (1) be first year, full-time, postsecondary students enrolled in an undergraduate program who have just graduated high school or students who graduated high school and took a gap year before enrolling in their current undergraduate degree and have not attended another college or university in the interim; (2) be born in 2003 or earlier (ie, students who will be turning 18 years or older in 2021, as the behavioral recommendations in the 24HMG for adults are applicable to ages 18-64 years); (3) want to make a change in their physical activity, sedentary behavior, or sleep (ie, are contemplators, intenders, or actors); and (4) not be accumulating 150 minutes per week of aerobic moderate to vigorous intensity physical activity (ie, getting <150 minutes per week of moderate to vigorous intensity physical activity); (5) score between 20 and 60 out of 70 on the Warwick-Edinburgh Mental Wellbeing Scale [34], indicating average or low mental well-being; (6) have a smartphone; (7) feel comfortable navigating technology (ie, students were asked if they felt comfortable navigating the ParticipACTION app via their smartphone and were provided with the ParticipACTION app accessibility specifications); and (8) be able to read, speak, and understand English.

The exclusion criteria stipulated that students would be ineligible if they (1) have a physical impairment, as the intervention content focuses on the 24HMG, which was not designed for persons with a physical disability or impairment and therefore may not be appropriate for these individuals; (2) have an acute concussion or symptoms of postconcussion syndrome, as the intervention content was delivered via smartphone and these individuals should avoid screens; or (3) are a QU student

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enrolled in the kinesiology undergraduate degree program or are a UBC student enrolled in any of the following courses: HEAL 100, KIN 300, NURS 180, or NURS 290, as these degrees or courses are confounders for the evaluation (ie, students learn intervention content in these courses).

Screening and Intake Processes

The 24HMG project coordinator (SMF) reviewed the completed eligibility screening questionnaires to determine student eligibility to participate in the intervention. Students were contacted by QU and UBC study coordinators (SMF and JM, respectively) informing them of whether they were eligible to participate in the intervention. Eligible participants were invited to participate in intake meetings conducted by the coordinators (SMF and JM). To ensure anonymity, all participants were given a new Gmail (Google Inc) account, which was used to create ParticipACTION and Fitbit app accounts during their intake meeting. Once logged into the ParticipACTION app, participants were given the ParticipACTION+ code by the study coordinator, enabling intervention content and notification delivery. Both coordinators were provided with the ParticipACTION+ code as well, allowing them to receive intervention content and notifications to confirm intervention fidelity. During intake, participants were provided with their Inspire 2 Fitbit, asked to log into the Fitbit app using their new Gmail account, and showed how to synchronize their Fitbit to both the Fitbit and ParticipACTION apps. Finally, coordinators also provided a clear, verbal outline of the intervention ParticipACTION content journey and walked through what was included in the PDF resource package and emailed participants the PDF document.

Step 6: Evaluation Plan (July 2021-Ongoing)

To complete the iterative Intervention Mapping protocol, a plan for the evaluation of the intervention was developed. A nonrandomized proof-of-concept study was conducted to examine the feasibility, acceptability, and potential impact of the app-based intervention. Note that no a priori criteria were set to assess feasibility and acceptability. Data analysis is ongoing. Full details of the evaluation plan will be published in a forthcoming paper; however, a brief summary of the evaluation plan is described here.

Feasibility will be examined by reviewing the recruitment of students to the intervention (eg, the number of students screened and number of students eligible for participation and enrolled in the intervention), and participant attrition over the course of the intervention. Characteristics of participants (ie, demographics including gender, age, ethnicity, etc) were also collected and will be used to describe who participated in the intervention. The feasibility of evaluation measures will be assessed through the evaluation response rates.

Acceptability of the intervention will be assessed by using the data on ParticipACTION app engagement (eg, percentage of participants clicking and engaging with intervention content articles). Satisfaction with the intervention will be evaluated through analysis of a postintervention questionnaire with items measuring participant agreement on whether the intervention was interesting, useful, easy to participate in, credible, and personally important to them.

The evaluation plan also attempted to establish the potential of the intervention for changes in outcomes between baseline and after the intervention. Outcomes of interest included participants' (1) capability, opportunity, and motivation for the movement behaviors; (2) movement behavior levels; (3) mental well-being; and (4) awareness and knowledge of the 24HMG. Surveys were administered at baseline and after the intervention to assess outcomes 1, 3, and 4. Means and SDs of questionnaire items at each time point and effect sizes between time points will be reported. To assess outcome 2, means and SDs of time spent in each of the movement behaviors before, during, and after the intervention as well as trends in movement behaviors over time will be examined and reported.

Ethics Approval, Informed Consent, and Participation

Ethics approval for the focus groups conducted with first-year postsecondary students was granted by the QU General Research Ethics Board (GSKHS-329-19). Written informed consent was obtained by all focus group participants. Separate ethics approval was sought and granted by the QU General Research Ethics Board (GSKHS-394-21) and UBC Behavioral Research Ethics Board (H21-02741) for the app-based intervention development, recruitment, data collection, analysis, and reporting activities, including all ParticipACTION and Fitbit app–related components. All participants provided written informed consent for the collection, analysis, and storing of their self-reported (ie, survey) data and ParticipACTION and Fitbit app data. All data were deidentified with identifying information stored in separate, password-protected databases on secure, locked servers and not attached to participants' study data. Participants who completed the baseline and postquestionnaire survey were compensated with a CAD $5 (US $3.7) e-gift card for each questionnaire. Participants who participated in the intervention were able to keep the provided Fitbit following the intervention period.

Results

Participant recruitment occurred during September 2021, and the intervention was conducted from October to December 2021. The deadline for completion of the postintervention questionnaire survey by participants was mid-December 2021. We began analyzing the survey, ParticipACTION, and Fitbit data in January 2022, and the publication of the proof-of-concept evaluation is expected in 2023.

Discussion

Summary

Given postsecondary students' suboptimal engagement in the 24HMG behaviors [9], this population is at risk of negative impacts on their physical and mental well-being. In this paper, we describe the application of the Intervention Mapping framework to design and implement an app-based intervention intended to improve first-year postsecondary students' movement behavior and mental well-being.

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Strengths and Limitations

The design and implementation of the intervention followed an iterative process using several frameworks: the Knowledge-to-Action Framework [6], Intervention Mapping [18,19], the TDF [34,35], and the BCW [21,22]. The steps of Intervention Mapping aligned well with the Knowledge-to Action framework, which has been used to guide the overall 24HMG knowledge translation process [7]. Although Intervention Mapping was used to guide a stepwise intervention design and implementation process, the TDF and BCW enabled the working group to categorize barriers and facilitators and to choose intervention functions and BCTs most likely to overcome barriers and leverage facilitators. When used together, these frameworks were well suited to designing an intervention addressing 3 separate movement behaviors, each of which are complex (ie, not a "single incidence" behavior) and occur in multiple contexts and at various times and frequencies. The involvement of a multidisciplinary team helped ensure that the intervention was designed appropriately for the target population [5,52]. Indeed, meticulous efforts were taken to design the intervention content with multiple layers of consultations.

This intervention has several limitations. First, content articles delivered to students in the ParticipACTION app are in a written format; some students may have benefited from the opportunity to view content in alternative formats such as video, which may also increase engagement with the content. In addition, the selected intervention components lacked the elements of social support. Social support can help to facilitate students' performance of the movement behaviors and to improve mental well-being—students identified social support as being an important facilitator for movement behavior change within the needs assessment (Multimedia Appendix 2). However, given the context of the COVID-19 pandemic and the uncertainty of the return of on-campus programing, we chose to not engage interventionist support at the onset of intervention design. This consideration also informed the pragmatic decision to implement individual-level strategies to address behavioral change, even though data from the needs assessment in step 1 suggested that institutional-level strategies (eg, encouraging residences to enforce quiet hours) may also promote performance of the movement behaviors in line with the 24HMG recommendations. Institutional-level strategies need to be explored in future research. Despite these limitations, we developed an intervention that could be scalable to other postsecondary campuses in the future. Finally, prompts and push notifications delivered through the ParticipACTION app may have implications for students' recreational screen time, either through minutes spent on the ParticipACTION app or other unintended app use (eg, students viewing other apps on their phone after being prompted by the ParticipACTION app). However, it is important to consider whether said screen time is considered "productive" or "purposeful" (eg, time spent on the ParticipACTION app may be considered educational as opposed to minutes spent absentmindedly scrolling through a social media app). Although beyond the scope of this study, future work should examine unintended effects of app-based health interventions and recreational screen time and, more broadly, sedentary behavior.

Conclusions

Intervention Mapping, with the use of the TDF and BCW, was a useful approach to combine evidence and theoretical concepts to guide the design and implementation of a ParticipACTION app–based intervention targeting postsecondary students' movement behaviors and mental well-being. This study may be used as an example for other researchers developing multiple behavior change app–based interventions, and should the forthcoming proof-of-concept intervention evaluation demonstrate the intervention's acceptability, feasibility, and potential impact, the intervention may provide a scalable method for improving students' movement behaviors and mental well-being and future behavior change interventions.

Acknowledgments

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Data Availability

Multimedia Appendix 2 includes the complete list of performance and change objectives, with mapping of the combined links between Theoretical Domains Framework domains (ie, determinants of movement behaviors) and Behavior Change Wheel components. After analysis of the data examining the feasibility, acceptability, and potential impact of the intervention (eg, the survey, ParticipACTION, and Fitbit data) is complete, the data sets will be available from the corresponding author upon reasonable request.

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Conflicts of Interest

The following individuals report personal fees or honorariums from the Canadian Society of Exercise Physiology for their role as 24-Hour Movement Guidelines (24HMG) project coordinator, research assistant, study coordinator, ParticipACTION app evaluation expert, Fitbit data collection and analysis expert, and 24HMG knowledge translation methodologist, that is, SMF, BT, JM, GRR, SLS, and MCB, respectively. JRT was the knowledge translation lead for the Canadian 24HMG for Adults.

Multimedia Appendix 1
Details of the student intervention working group constituency.
[DOCX File , 16 KB - resprot_v12i1e39977_app1.docx]

Multimedia Appendix 2
Details of the complete list of performance and change objectives with the combined links between the Theoretical Domains Framework domains (ie, determinants of the movement behaviors) and the Behaviour Change Wheel components.
[DOCX File , 58 KB - resprot_v12i1e39977_app2.docx]

Multimedia Appendix 3
Details of intervention components and descriptions.
[DOCX File , 20 KB - resprot_v12i1e39977_app3.docx]

Multimedia Appendix 4
Description of intervention week 1–ParticipACTION app content text and images.
[DOCX File , 271 KB - resprot_v12i1e39977_app4.docx]

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Abbreviations

24HMG: 24-Hour Movement Guidelines
BCT: behavior change technique
BCW: Behavior Change Wheel
COM-B: capability, opportunity, motivation, behavior
QU: Queen's University
TDF: Theoretical Domains Framework
UBC: University of British Columbia

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Protocol

Designing Practical Motivational Interviewing Training for Mental Health Practitioners Implementing Behavioral Lifestyle Interventions: Protocol for 3 Pilot Intervention Studies

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Abstract

Background: Motivational interviewing (MI) is an evidence-based, patient-centered communication method shown to be effective in helping persons with serious mental illness (SMI) to improve health behaviors. In clinical trials where study staff conducted lifestyle interventions incorporating an MI approach, cardiovascular disease (CVD) risk profiles of participants with SMI showed improvement. Given the disproportionate burden of CVD in this population, practitioners who provide somatic and mental health care to persons with SMI are ideally positioned to deliver patient-centered CVD risk reduction interventions. However, the time for MI training (traditionally 16-24 hours), follow-up feedback, and the coaching required to develop and maintain patient-centered skills are significant barriers to incorporating MI when scaling up these evidence-based practices.

Objective: We describe the design and development of the following 2 scalable MI training approaches for community mental health practitioners: real-time brief workshops and follow-up asynchronous avatar training. These approaches are being used in 3 different pilot implementation research projects that address weight loss, smoking cessation, and CVD risk reduction in people with SMI who are a part of ALACRITY Center, a research-to-practice translation center funded by the National Institute of Mental Health.

Methods: Clinicians and staff in community mental health clinics across Maryland were trained to deliver 3 distinct evidence-based physical health lifestyle interventions using an MI approach to persons with SMI. The real-time brief MI workshop training for ACHIEVE-D weight loss coaches was 4 hours; IMPACT smoking cessation counselors received 2-hour workshops and prescribers received 1-hour workshops; and RHYTHM CVD risk reduction program staff received 4 hours of MI. All workshop trainings occurred over videoconference. The asynchronous avatar training includes 1 common didactic instructional module for the 3 projects and 1 conversation simulation unique to each study's target behavior. Avatar training is accessible on a commercial website. We plan to assess practitioners' attitudes and beliefs about MI and evaluate the impact of the 2 MI training approaches

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on their MI skills 3, 6, and 12 months after training using the MI Treatment Integrity 4.2.1 coding tool and the data generated by the avatar-automated scoring system.

Results: The ALACRITY Center was funded in August 2018. We have implemented the MI training for 126 practitioners who are currently delivering the 3 implementation projects. We expect the studies to be complete in May 2023.

Conclusions: This study will contribute to knowledge about the effect of brief real-time training augmented with avatar skills practice on clinician MI skills. If MI Treatment Integrity scoring shows it to be effective, brief videoconference trainings supplemented with avatar skills practice could be used to train busy community mental health practitioners to use an MI approach when implementing physical health interventions.

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KEYWORDS

motivational interviewing; training; cardiovascular disease; lifestyle interventions; community mental health

Introduction

Background

Addressing inequities in cardiovascular health is a critical public health objective, particularly for persons with serious mental illness (SMI) who experience alarmingly high rates of cardiovascular disease (CVD) risk factors (obesity, hypertension, dyslipidemia, and diabetes mellitus) and risk behaviors (tobacco smoking, physical inactivity, and unhealthy diet) [1-4]. Lifestyle interventions, especially those that adopt a patient-centered approach, have been shown to be effective in helping persons with SMI to improve a wide range of health behaviors, including weight loss management, smoking cessation, and diabetes management [5,6]. A foundational approach for many of these lifestyle interventions is motivational interviewing (MI), which is an evidence-based, patient-centered communication method aimed at evoking patients' motivations for change [7]. MI practitioners adopt a collaborative and empathic attitude, empower patients to act as an equal partner in their disease management, and use specific and core patient-centered communication skills to guide them toward change.

Patients' CVD risk profiles improved significantly in clinical trials in which the study staff incorporated an MI approach to conduct lifestyle interventions among participants with SMI [8-12]. To lessen the disparity of CVD risk experienced by this population on a wider scale, evidence-based programs to improve cardiovascular health need to be implemented in community mental health settings where patients routinely receive their care [13]. Real-world practitioners in these settings need the training not only to deliver the CVD health intervention itself (the requirements of which will likely differ based on education and prior experience) but also for the specific preparation necessary to incorporate an MI approach. Although some mental health practitioners may have had previous exposure to MI, the method involves a complex skill set such that attending a seminar or a traditional 2- to 3-day in-person workshop alone is usually insufficient to build competency [14-16]. A meta-analysis of MI training studies suggested that for learners to gain and sustain MI skills after a workshop training, an average of 3 to 4 coaching sessions with performance feedback from practice sessions over several months were needed [17]. Yet, when scaling up evidence-based practices (EBP) for implementation research, the stated amount of training to deliver patient-centered behavior change lifestyle interventions may be harder to accomplish among practitioners in community mental health settings who have demanding caseloads and limited time for additional training activities [18]. Furthermore, because of the diverse occupational backgrounds of the health care team in these real-world community settings (which often include physicians, nurses, therapists, and frontline day program staff) [19], it is essential to develop MI training that is both tailored and acceptable to a variety of practitioners.

There are a few promising formats to efficiently train busy mental health care practitioners in MI [20]. Synchronous or real-time trainings over videoconferencing can be used to provide learners with a basic introduction to MI. Live videoconferencing, although still requiring coordinating schedules of learners and trainers, can simulate an in-person event. Videoconference trainings may be shorter than standard multiday trainings and can be broken into smaller chunks of time; this may be more appealing to managers and allows learners time to meet their other work demands. This format also allows practitioners the opportunity to reflect on and integrate the concepts they are learning between training sessions.

Web-based self-study programs that include video and workbook activities can be entirely asynchronous or may integrate a *live component* in which learners meet with trainers during scheduled times [21-23]. Both real-time synchronous and web-based training options have the advantage of being able to reach a wider audience of practitioners, including those working in rural settings or where skilled trainers of MI are not available, than in-person events. Both approaches reduce the travel time and cost for trainers and limit the need for learners' transportation, workshop space, and other expenses associated with in-person workshops. When implementing the intervention at multiple locations, videoconference training provides a practical way to reach several sites simultaneously. Constraints around social distancing imposed during the COVID-19 pandemic have created the need for effective options other than traditional in-person trainings for teaching different counseling approaches. Although these modalities have been used more frequently in the past few years, research on the impact of web-based [22] and video trainings in MI remains limited [24].

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Another scalable remote training format for MI involves the use of computer simulations [20,25,26]. SIMmersion [27] offers video-interface trainings; videotaped role-play conversations with human actors give learners the ability to practice and receive coaching and feedback on their recorded responses [20,28]. Avatar-interface programs, by contrast, provide learners with a virtual reality training experience to learn and practice their skills with simulated avatar patients [29,30]. Avatar trainings may involve a human trainer [31] or consist of fully automated, preprogrammed simulations; some platforms also offer coaching and feedback features to learners. Kognito [32] offers several avatar simulations in which the users enter an interactive virtual environment and engage in role-play conversations with emotionally responsive virtual humans on a variety of topics in health care, mental health, and patient-provider communication. Their approach combines the science of learning, the art of conversation, and the power of gaming technology. Avatar-interface programs can be used as stand-alone or as follow-up MI practice opportunities; they have the advantage of allowing learners to practice their skills in a convenient and private environment.

Objective

Despite the many different approaches to training and the demonstrated effectiveness of MI [6], the amount and type of training necessary for real-world practitioners to develop and sustain proficiency in the method is uncertain [24]. In the context of 3 pilot implementation research projects that address weight loss, smoking cessation, and CVD risk reduction among persons with SMI, we aimed to develop scalable training in MI. This paper will provide a brief description of the 3 pilot projects; their corresponding setting and intervention; the design and development of the 2 MI training approaches, real-time brief workshops and follow-up asynchronous avatar training used to implement the EBP; and how we propose to evaluate the impact of the training on practitioners' skills, attitudes, and beliefs about MI.

Methods

Implementation Pilot Studies Overview

The Johns Hopkins ALACRITY Center for Health and Longevity in Mental Illness is a research-to-practice translation center funded by the National Institute of Mental Health that aims to reduce premature mortality from CVD in people with SMI [33,34]. There is an untapped opportunity to develop scalable and generalizable solutions that integrate physical health care into mental health service sectors, which have not historically provided such services. Through the ALACRITY Center, we are conducting 3 pilot implementation projects in community mental health settings to study strategies for the adoption and integration of evidence-based CVD risk reduction interventions related to (1) weight loss; (2) tobacco smoking cessation treatment; and (3) hypertension, dyslipidemia, and diabetes care for people with SMI. This study is a substudy within the ALACRITY Center methods core and focuses on the 2 types of innovative MI training: real-time brief workshop training over videoconferencing and asynchronous avatar training, which span the 3 projects described in the following paragraphs.

ACHIEVE-D (Adapting an Evidenced-based Weight Management Intervention and Testing Strategies to Increase Implementation in Community Mental Health Programs) is a 6-month, 2-arm, weight loss pilot cluster randomized controlled trial (RCT), which is designed to assess the degree to which the implementation strategy, that is, performance coaching, impacts psychiatric rehabilitation program (PRP) coaches' knowledge, self-efficacy, and fidelity to the delivery of the adapted ACHIEVE-D weight loss program curriculum when compared with a standard control group. ACHIEVE-D is a behavioral weight loss program designed for persons with SMI that provides basic weight loss health education using an MI approach, which was adapted from an intervention tested in a previous RCT [10,12,35]. Coaches in PRPs will be provided with the materials, trained on all aspects of the ACHIEVE-D weight loss curriculum, and encouraged to use MI skills in their interactions with the participants.

IMPACT (Promoting Evidenced-Based Tobacco Smoking Cessation Treatment in Community Mental Health Clinics) is a pretest-posttest design–based 12-month observational study that aims to examine the effects of an implementation intervention on mental health providers' delivery of four EBP related to smoking cessation treatment for clients with SMI: (1) assessment of smoking status, (2) assessment of willingness to quit, (3) behavioral counseling, and (4) pharmacotherapy prescribing. Psychiatrists and mental health counselors at 5 community mental health clinics will receive training to implement smoking cessation practices, incorporating an MI style in their interactions with the patients. Counselors and prescribers will be encouraged to use MI to understand their patients' smoking behavior and engage them in smoking cessation treatment.

RHYTHM (A Quality Improvement Process to Support Delivery of Cardiovascular Care in Community Mental Health Organizations) is a pretest-posttest design–based 12-month pilot study examining the effects of an adapted 5-step Comprehensive Unit–Based Safety Program implemented during care coordination aimed at reducing CVD risk for patients participating in behavioral health home programs [36]. Behavioral health home staff will receive the training necessary to implement the program, which will include the use of MI as a way of interacting with patients as they discuss various aspects of their patients' CVD care.

Participants Receiving MI Training

In these pilot implementation projects, we are assessing the use of MI among clinician and staff participants who have been trained to deliver the lifestyle interventions to mental health clients. Practitioners recruited from community mental health settings across Maryland will implement the 3 projects. Only English-speaking adults (aged ≥18 years) who provide informed consent are enrolled. Additional inclusion criteria include willingness to provide baseline data, attend training, implement the study intervention, and participate in follow-up data collection. Exclusion criteria across the 3 projects are minimal and exclude any staff who express an intention to leave the

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facility before project completion. ACHIEVE-D enrolled interested residential staff and employees at the PRP program as coaches. IMPACT participants include community mental health clinic staff (eg, licensed counselors, psychologists, and social workers) and prescribers (eg, nurse practitioners and psychiatrists). RHYTHM participants include PRP staff and health home nurses who are currently employed at the study sites.

Ethics Approval

Approval to conduct the studies and the associated MI trainings was granted by the Johns Hopkins Institutional Review Board (IRB) protocols. ACHIEVE-D study received IRB approval in March 2021 (IRB00247344). IMPACT study received IRB approval in January 2021 (IRB00231836), and RHYTHM study received IRB approval in December 2020 (IRB00269855).

MI Training

MI Training for the ALACRITY Center studies consists of 2 distinct approaches: real-time brief workshop training over videoconferencing and asynchronous avatar training.

Real-time Brief Workshop Training

Overview

Traditional introductory MI training is typically in person and is 16 to 24 hours long. However, based on the preferences expressed by stakeholders at study sites before initiating the projects, we present brief, real-time, and standard introductions to MI over videoconferencing uniquely tailored for each project. The MI trainer (ATD) is an MI practitioner, is a member of the Motivational Interviewing Network of Trainers (MINT), and has extensive experience in training practitioners who treat patients with SMI in the context of health services research. Following the guidelines recommended by MINT members [37], each training session invites the learners to consider why MI is useful in conversations around health behavior change and includes a definition of the method; a discussion of the MI spirit (ie, the accepting, compassionate, collaborative, and empowering style used in MI); an introduction to patient language related to change (change talk and sustain talk); and a brief overview of the following core MI skills: open-ended questions, affirmations, reflections, summaries, and collaborative information exchange [7]. Table 1 presents the real-time training content.

The amount of time devoted to each topic and opportunities for interaction vary by study. To increase the feasibility and acceptability of the workshops, the length of training for each project was negotiated in advance with the site leadership. ACHIEVE-D weight loss coaches will receive 4 hours of MI training. Psychiatrists prescribing smoking cessation pharmacotherapy in IMPACT will receive 1 hour of MI training; mental health counselors who provide the smoking cessation counseling will receive 2 hours of MI training. RHYTHM health home staff who implement the CVD risk reduction program will receive 4 hours of MI training.

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Table 1. Real-time training content.

	Study and the behaviors targeted by participants			
	ACHIEVE-D—weight loss	IMPACT—smoking cessation		RHYTHM—CVD[a] risk reduction
	PRP[b] staff	Prescribers	Counselors and Nurses	Health home staff
Participants, n	• 21	• 35	• 51	• 20
Training length (hours)	• 4	• 1	• 2	• 4
Training agenda	• Why use MI?[c,d] • What does not help?[d] • Righting reflex • Ambivalence • Language of changed • What helps?[d] • MI spirit • Good practice video: MI skills occur with spirit[d,e] • MI skills: OARS[d,e] • Reflections guide the conversationd • Responding to discord • Introduce collaborative information exchanged • Providing feedback • Using leaders guides • MI is not like a recipe • Learning MI • Introduction to the avatar	• Why use MI?[d] • Ambivalence and change talk[d] • What helps?[d] • How MI works: • Good practice video[d] • Brief review of core MI skills • Collaborative information exchanged • What it takes to learn MI • Introduction to the avatar	• Why use MI?[d] • What does not help?[d] • Righting reflex • Ambivalence • Language of changed • What helps?[d] • MI spirit • Good practice video: MI skills occur with spirit[d] • MI skills: OARS[d] • Introduce collaborative information exchanged • MI is not like a recipe • Learning MI • Introduction to the avatar	• Why use MI?[d] • What does not help?[d] • Righting reflex • Ambivalence • Language of changed • What helps?[d] • MI spirit • Good practice video: MI skills occur with spirit[d] • MI skills: OARS[d] • Reflections guide the conversation[d] • Responding to discord • Introduce collaborative information exchanged • Providing feedback • Using leaders guides • MI is not like a recipe • Learning MI • Introduction to the avatar

[a]CVD: cardiovascular disease.

[b]PRP: psychiatric rehabilitation program.

[c]MI: motivational interviewing.

[d]Included an interactive component (eg, chat response, poll, brief discussion, and practice exercise).

[e]OARS: Open-ended questions, Affirmations, Reflections, Summaries

Development

Owing to the advent of the COVID-19 pandemic, all MI trainings were modified from an in-person format to delivery over videoconferencing. Although there is not much known about how best to adapt the content of in-person experiential training workshops for this purpose, MINT members communicated ideas for the transition on the e-forum of their listserve [38]. Additional ideas for modifying training activities were offered during workshops, and a monthly virtual trainers meeting for sharing activities, ideas, and successes is ongoing for any interested MINT member. As a result of participation in these various collaborative conversations, the first author (ATD) modified several training activities for the videoconferencing format. One key consideration was how best to engage participants and encourage them to try different components of the MI method while being observed by others on screen rather than in the privacy of small groups. The trainer incorporates multiple activities, alternating training techniques to keep learners interested, including the use of written transcripts with change talk and sustain talk indicated in different colored fonts and small breakout rooms for practice exercises [39,40]. Efforts are made to switch styles every 20 minutes to best engage learners. Anonymous polling provides low-stakes opportunities for learners to select the most MI-consistent practitioner strategy in response to a vignette (eg, choose an evocative question, select the reflective listening statement, or identify the best example of a collaborative information exchange); the chat function allows the trainees, who may be less comfortable or quick to respond, opportunities to pose questions or respond to trainer requests.

All synchronous, real-time trainings will be held over videoconference and scheduled at a time that accommodates most practitioners at each site. As it is challenging to synchronize participants from multiple sites where the research is being conducted, for anyone unable to attend the real-time meeting, recorded Zoom sessions (Zoom Video Communications) will be made available for viewing. The first author developed a tailored handout resource packet with specific examples of how to use MI when discussing each project's target behavior change; this material will be provided to practitioners to further support their MI skill acquisition during and after training.

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Asynchronous Avatar Training

Overview

The ALACRITY Center partnered with a web-based experiential learning company, Kognito [32], to develop the asynchronous avatar training. This development process with Kognito took approximately 14 months and resulted in the products described in the following sections. After the completion of their real-time MI training, the practitioners are given access to the web platform and are encouraged to register for an account that houses their study-specific avatar training and simulation. The first component is a 12-minute didactic module, "Motivational Interviewing Techniques," which uses an avatar coach to provide an overview of the method. This module is identical for each of the 3 projects and must be completed before the learners move on to the second part of the training, the conversation simulation. The participants are asked to complete their first conversation simulation as soon as possible after the real-time MI training and are prompted to use the platform throughout the study period.

Each study has 1 distinct conversation simulation that addresses the project's respective behavioral target. All conversation simulations involve 3 characters (Figure 1). The avatar practitioner character is played by the study MI learner and discusses weight loss (ACHIEVE-D), smoking cessation (IMPACT), or cholesterol reduction (RHYTHM) with an avatar patient. The avatar patient has speech that is coded to be generated automatically; when the character stops speaking, there are 3 to 4 choices presented to the learner representing options that are more or less effective when using the guiding style of MI. Table 2 shows the learner response choices for the avatar weight loss simulation.

The avatar patient, the character that is not playable or maneuverable by the practitioner, is modeled after an atypical patient with SMI in a community mental health setting. Depending on the study, the avatar patient is obese, smokes tobacco, or has high cholesterol. The avatar patient responds to the practitioner in the way a typical client might respond as the practitioner selects one of the previous MI-consistent or non-MI directive choices. The third avatar character functions as a virtual coach who both narrates the didactic module and, when a response choice is selected by the practitioner, provides on-screen text guidance that either affirms the learner's use of MI or, as needed, provides corrective suggestions to the learner as they engage in the respective conversations about weight loss, smoking cessation, or cholesterol reduction. Learners have the opportunity to undo their selection and pick a different option to see how such a change impacts the conversation flow.

The avatar platform includes several feedback features to assist learners in improving their MI skills. An on-screen meter registers and reinforces practitioners' ability to cultivate change talk, a core skill that is essential in an MI interaction [7]. For example, if the practitioner says, "You're aware of the health effects of smoking and they worry you enough to consider quitting" and the client responds, "Yea, I think about it...I used to smoke right after a shower but now I try to go longer...," then the meter would indicate movement toward cultivating change talk. The simulations also include occasional thought bubbles; that is, a text appears above the avatar patient's head and allows the learners to read the patient's unspoken thoughts from the most recent exchange. This feature is most useful when the patient responds with silence, one-word answers, or if they appear hesitant to voice confusion over what is being discussed. As the learners move through the simulation, the platform keeps a tally of each practitioner's choice; after completing the full simulation, there is a performance dashboard available to the learner on their use of MI spirit and skills. Learners are able to see their scores on the relational components of the MI spirit (partnership and empathy); adherence to the technical aspects of the approach (cultivating change talk and softening sustain talk); and their use of specific core MI skills, questions, and reflections (Figure 2). The participants are encouraged to practice their MI skills with the avatar at least monthly throughout the study.

Figure 1. The avatar characters. MI: motivational interviewing.



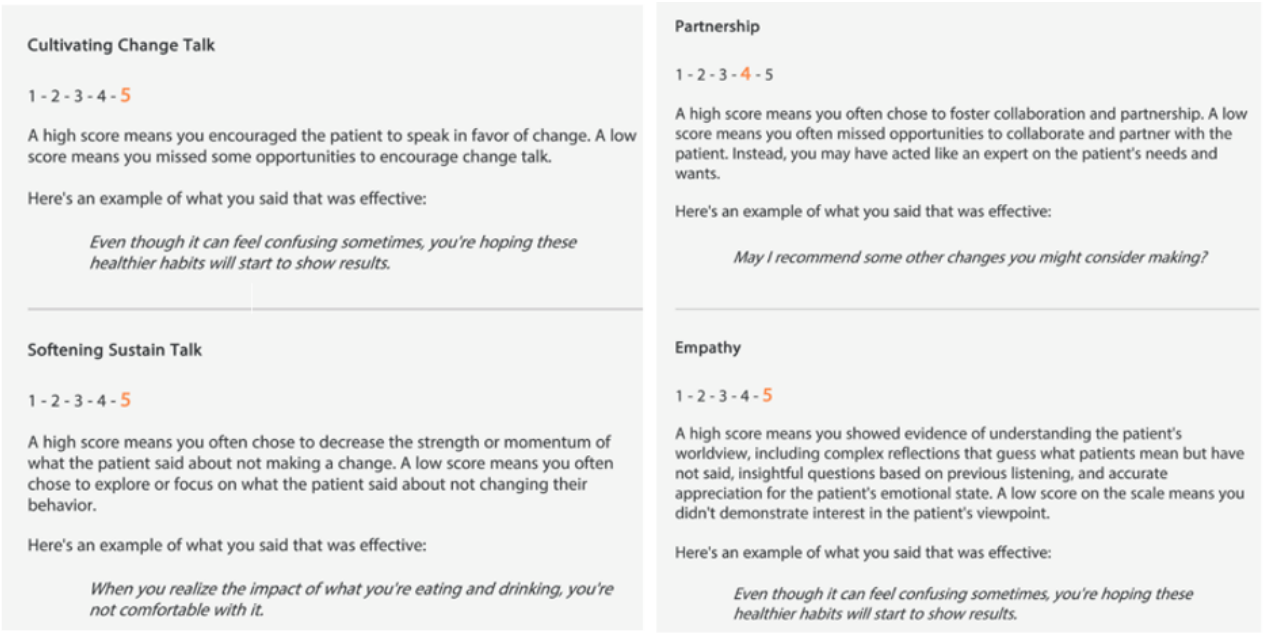
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Table 2. Avatar weight loss simulation learner response choices.

Client statement and practitioner choice options	Practitioner strategy	Effective use of MI[a] approach?
...I'm trying (to lose weight) and nothing's happening!		
Why do you think you can't lose weight?	Question—confrontational	No
You're frustrated that this is so difficult.	Simple reflection of sustain talk	Somewhat
You're frustrated and want to do something that helps you lose weight.	Complex reflection—shifting focus	Yes
I get so tired climbing up all those stairs, my knee flaring' up the whole way, that I just kind of eat whatever I want once I'm up there.		
It sounds like taking those stairs would be a great way to lose weight.	Persuading	No
So, all those stairs are difficult for you.	Simple reflection of sustain talk	Somewhat
Even when you're tired or frustrated, you're still doing what needs to be done. And it makes you realize that you wish you'd eat healthier.	Complex reflection	Yes

[a]MI: motivational interviewing.

Figure 2. The performance dashboard.



Development: The Avatar Characters

Early in the development process, members of the ALACRITY team who were the most familiar with the community mental health program environment provided Kognito with pictures of the study sites and descriptions of practitioners and patients seen at the sites. After a few iterations (eg, adjusting characters' skin tone, patient affect, and voice speed), the project's 3 avatar characters were created. The virtual characters were brought to life with animation, lip-synced speech, and the use of facial and hand gestures to demonstrate their nonverbal emotional responses. The images of the players are the same for each of the studies. The topics of conversation and the names and mannerisms of the virtual patient characters vary by study behavioral focus. The patient avatars were modeled after clients with well-controlled depression (ACHIEVE-D), schizophrenia (smoking cessation), and bipolar disorder (CVD risk reduction) who were seen at the community mental health programs.

Development: The Didactic Module

Kognito's existing MI Techniques module formed the foundation for the product's final didactic training; the first author modified the content to reflect the most current constructs in MI [7]. Clinician and client language tailored to each study's target behavior was incorporated so that the practitioners would find the learning module more relatable. For example, to indicate that the patient was referring to changing their smoking- or weight-related behaviors, we included examples of the patient's change talk statements such as "I need to cut back" or "I'd like to be able to move around more easily."

Development: The Conversation Simulations

To inform the script for each conversation, subject matter experts from the ALACRITY team met with Kognito. Coders then created branching scripts for how the conversations would progress as learners made choices that demonstrated both their use of MI and their options not being aligned with the patient-centered method. Practitioner choices that demonstrated the use of non-MI–adherent strategies, for example, confronting

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the patient's behavior of soda drinking when their weight goes up, were carefully crafted; the MINT member authors (ATD and SM) revised the scripts designed to demonstrate MI skills (eg, asking an open-ended question to learn what the patient knows about lowering cholesterol before giving information) to more closely model effective practitioner responses. Finally, based on our experience during previous clinical trials focused on these CVD risk behaviors [8-11,41], the same authors modified the avatar patient language to better align with more predictable patient responses to each of the practitioner's choices.

The Feedback Mechanisms: On-Screen Coaching

Kognito's platform includes several feedback mechanisms for which ATD and SM provided content expertise. On-screen coaching tips from the virtual coach are available to practitioners as they move through each simulation. For example, if the learner selects the best conversation or target choice, such as, "Well...cutting down smoking, even a little, shows that you're really serious about making changes for your health," the coaching text affirms their effort and identifies the specific MI skill used: "You affirmed specific efforts Danny has made to quit smoking and he told you that in addition to his health, he values spending time with family." If an ineffective choice is selected, such as "So, you know how difficult it is to quit," the coach names the non-MI–adherent tactic and suggests the better or target choice: "By bringing up challenges, you missed an opportunity to affirm the efforts he's already been making. You might have said, 'You were able to cut out your morning cigarette even though you live with people who smoke.'"

The Feedback Mechanisms: The Performance Dashboard

The performance dashboard was designed to help learners know how well they use MI in their simulations. Study MI experts worked with Kognito to modify their existing automated scoring system so that it was better aligned with up-to-date MI training and feedback guidance. This was a multistep and iterative process. First, a careful review of the conversation scripts allowed the study team and Kognito to identify learner pitfalls. A pitfall by definition is when a practitioner selects a conversation strategy that is not likely to be effective when guiding the patient toward the desired behavior change (eg, if a practitioner chooses to ask an information-gathering question when a better response would be to provide a reflection). MI-nonadherent behaviors, such as persuading a patient to take a medication or confronting their lack of willingness to make a change, as well as reflecting on patient sustain talk, missing an opportunity to reflect on change talk, or failing to empathize with the patient, are coded as pitfalls. The team also identified examples of conversation targets for the learner. The targets are defined as the practitioner's conversation choices that are the most consistent with MI in guiding the patient avatar toward the desired behavior change (eg, asking evocative questions, affirming the patient's effort, and seeking collaboration before offering advice).

The study team was interested in having the automated performance feedback align with what is measured by the Motivational Interviewing Treatment Integrity Tool (MITI; version 4.2.1) [42]. MITI is a validated coding system that is used to assess MI skills and provide feedback to learners and is widely accepted as a treatment integrity measure for clinical trials involving MI. The tool has the following 2 components: global scores and behavior counts. Global scores capture the rater's global impression or "gestalt" of the entire interview on 5-point Likert scales for the following 4 dimensions: Cultivating Change Talk, Softening Sustain Talk, Partnership, and Empathy. Because Artificial Intelligence is unable to characterize the "gestalt of a conversation," the study team worked with Kognito to create separate matrices to classify the scoring for each of the MITI global domains. On the basis of the number of targets and pitfalls possible in each conversation type, we determined what combination of pitfalls and targets would comprise the grading criteria for each of the Likert scale scores (1-5). We decided to weight equally hitting the target and avoiding a pitfall. For example, if the domain of Partnership had a total possibility of 4 targets and 5 pitfalls during the weight loss conversation simulation, a *1* on the Likert scale would be assigned if the practitioner missed all the targets and hit every pitfall. A *5* on the Likert scale would be assigned if the practitioner avoided all the pitfalls and hit every target. We used this same mapping process to identify Likert score categories for each global domain for all the 3 conversation types.

MITI behavior counts are tallied instances of 10 specific practitioner behaviors including those that are categorized as MI-adherent (eg, emphasize autonomy, seek collaboration, and affirm) and MI-nonadherent (eg, confront and persuade). The human coder's task is to simply count each instance of the clinician's behavior during the segment being reviewed. The final step in the development of the automated scoring system for this study was to label each practitioner's conversation choice as one of the 5 learner behaviors measured (eg, question, reflection, affirm, persuade, and confront); the automated system as currently developed was not built to provide counts for the 5 additional behaviors measured by MITI (ie, providing complex reflections, persuading with permission, giving information, seeking collaboration, and emphasizing autonomy).

Evaluation of Training Components

Data Collection

Data on the measures as described in the *Measures* section will be obtained from the study practitioners before their MI training and will be collected via telephone, videoconference, or through REDCap (Research Electronic Data Capture; Vanderbilt University) or paper questionnaires. The participants will be compensated for their time to complete all data collection measures; no other financial compensation for participating in the training or implementing the study will be provided. We will use the web-based REDCap survey system or deliver paper questionnaires upon request. We will collect follow-up measures at 3 months and the end of study (at 6 months for ACHIEVE-D) and at 3 months, 6 months, and end of the study (12 months for IMPACT and RHYTHM). Continuing medical education credits will be provided to IMPACT practitioners upon the completion of 3 avatar simulations. Table 3 summarizes data collection items.

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Table 3. Study data collection.

Measure	Time point			
	Baseline (all studies)	3 months (all studies)	6 months (all studies)	12 months (IMPACT and RHYTHM)
Demographic characteristics				
Age	✓			
Gender	✓			
Race or ethnicity	✓			
Length of time at program	✓			
Role in program	✓			
Years at clinic	✓			
Previous formal MI[a] training	✓			
Beliefs about MI questionnaire				
A 7-question survey assessing the extent to which each person agrees with statements about MI	✓	✓	✓	✓
Importance and confidence of using MI				
A 6-question survey assessing the importance and confidence each person has to deliver MI	✓	✓	✓	✓
MITI[b] tool				
Validated tool used to measure fidelity to MI from standardized actor interviews.	✓	✓	✓	✓
Avatar MI performance measurements				
From use of MI techniques in simulated web-based conversations	✓	✓	✓	✓
Perceived usefulness of avatar training questionnaire				
A 6-question survey assessing the extent to which each person agrees with statements about the usefulness of the asynchronous avatar training			✓[c]	✓
Interviews				
Semistructured interviews using a standard protocol that will elicit participants' perceptions of real-time and avatar MI training			✓[c]	✓

[a]MI: motivational interviewing.

[b]MITI: Motivational Interviewing Treatment Integrity.

[c]Applicable to ACHIEVE-D study only.

Measures

We adapted the *Beliefs about Motivational Interviewing* questionnaire [43] to assess participants' beliefs about MI. The original scale asks participants to react to 7 statements about MI on a 5-point Likert scale from "Strongly Disagree" to "Strongly Agree." We included the following two statements in our modified version: (1) "There is strong empirical support for motivational interviewing" and (2) "I am effectively implementing motivational interviewing."

We created a 12-item questionnaire, *Importance and Confidence to Use MI*. The participants are asked about their perspectives on the importance of, and their self-reported confidence to use, MI skills. Example questions include, "Please rate how important is it for you to use motivational interviewing" and "Please rate how confident you are in your ability to use motivational interviewing to elicit behavior change in your patient." Responses are chosen on a 5-point Likert scale from "Not at all" to "Extremely."

We will use the MITI tool to measure clinician fidelity to MI from audiotaped standardized patient (SP) interviews [44-46]. Correlations between practitioners' adherence to MI with real patients and SPs are moderate to large on most indexes of performance [47]. Practitioners will conduct interviews with SP actors playing the role of patients with SMI. SP actors will talk as if they are interested in either weight loss, smoking cessation, or CVD management according to the pilot project their practitioner interviewer is implementing. MITI scores will be determined by blinded, independent coders who were trained by the tool's creators.

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A study staff member blinded to other survey measures will extract data on practitioners' automated scores from the performance dashboard at each data collection time point as another measure of adherence to MI.

Given the novelty of the avatar training, we will also assess participants' perceived usefulness of the avatar platform. Perceived usefulness is a key construct in the literature on technology adoption and use and refers to the extent to which a person believes that using the technology system will enhance their job performance. We adapted the Technology Acceptance Model questionnaire [48,49] to include 6 questions about the perceived usefulness of the avatar on participants' role in the study. Responses are on a 5-point Likert scale presented as 1 ("Strongly Disagree") to 5 ("Strongly Agree"). Example items include "I found the avatar to be useful in my role..." and "Using the avatar enhanced my effectiveness..."

We will track adherence to the following 2 training modalities: attendance at real-time training and frequency of asynchronous avatar use.

At the end of each project, we will collect qualitative data from the interviews and focus groups using a standard protocol to elicit participants' perceptions of both the real-time and avatar MI training.

Analytic Plan

We will examine changes in the MITI from baseline to each subsequent time point to assess the change in practitioners' skills in implementing MI. All SP interviews will be coded. A difference of 1 on a 5-point scale between pre- and posttraining scores for MITI global scores will be considered a clinically significant change in MI skills proficiency and will be used for statistical testing as the relevant effect size [42].

We will use a random 20-minute segment from the audiotaped SP interviews for coding as recommended by the creators of the MITI tool [42]. We will use a random calculator to ensure that the sampling of interviews that are >20 minutes is truly random so that proper inferences about the use of MI can be drawn.

We will examine changes in practitioners' automated scores from completed avatar simulations from baseline to each follow-up time point.

We will also compare the associations of the MITI scores from the SP interviews with the Kognito-automated performance feedback metrics from a conversation simulation completed during the same time as the data collection window.

We will examine changes in participants' beliefs about and the importance of using MI and their confidence to use its components with their patients.

Qualitative data from interviews and focus groups will be audio recorded and transcribed. Using thematic analysis [50], 2 research team members will identify meaningful segments within the responses and assign codes. We will then group these codes into themes, which will be examined by the research team.

Results

The ALACRITY Center was funded in August 2018. Recruitment for the studies started in February 2021. We have enrolled 127 participants. We anticipate the projects will be completed in Spring 2023 and anticipate that the results will be reported in late 2023 or 2024.

Discussion

Overview

The treatment of CVD risk factors is a public health priority for persons with SMI who experience symptoms disproportionally owing to these chronic health conditions. In community mental health practices where patients regularly receive their care, providing physical health interventions using an MI approach has untapped potential [4]. However, practitioners in these facilities already have excessive demands on their time, a challenge exacerbated by staff shortages and turnover, and they may not have the time, energy, or organizational support to learn how to implement patient-centered CVD risk reduction interventions [18,19]. To overcome some of the barriers to wide-scale adoption of MI in these contexts, we have adapted the traditional MI training format and created brief videoconference workshops supplemented by postworkshop avatar-based practice simulations to prepare the practitioners to deliver 3 evidence-based health interventions in community mental health settings. We hope that these formats will be acceptable and lead to an uptake and improvement of practitioners' patient-centered skills.

Strengths

There are several strengths in this study. We created a tailored training that has shorter duration than traditional training as a way to expose busy practitioners to MI. Brief trainings (<8 hours) are more time efficient and have been shown to make some difference in physician consultation behavior [51]. We adapted the real-time training to be delivered remotely in shorter bouts of time. We aim to identify whether the brief trainings provided are adequate to prepare real-world clinicians to perform the EBP and subsequently assess their skill acquisition with a validated measure.

Although technology-based virtual reality training methods have been used in medical and other health professionals' education, the use of avatars and other computer programs that provide interactive learning opportunities is not as common in behavioral health skills training [25,26,30,52-54]. Virtual platforms are a relatively new, potentially promising mode for training in MI and allow busy practitioners to learn the patient-centered counseling approach from expert trainers without having to travel to an off-site location. We incorporated 3 novel avatar conversation simulations tailored for practitioners to practice and receive feedback on their use of MI in simulated discussions about weight loss, smoking cessation, and cholesterol management. We will assess their acceptability to a wide range of practitioners at the end of each project.

We describe the study's training content and development of the avatar simulations as well as 2 methods of measuring

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adherence to MI and assessing change in practice that results from the trainings provided. Research has shown that the immediate skill gains from a workshop training diminish within a few months and that postworkshop follow-up performance feedback with coaching is needed for practitioners to sustain or further improve MI skills [14,16,17,55]. Although our initial training is brief, the automated coaching and feedback offered during the avatar simulations should mirror the role of coaching as a way of providing follow-up training to improve learners' skills. Simulation technology offers the capability to move beyond traditional in-person training and provide skill training through repeated practice and feedback [56].

Limitations

One limitation of the study is that none of the training methods have a comparator condition. The pretest-posttest outcomes are used here to assess the acceptability, feasibility, and effectiveness of the 2 training methods for improving practitioners' MI skills.

Avatar practice requires practitioners to set aside time during their busy workdays. The extra workload and responsibilities of staff during the COVID-19 pandemic may leave little time or motivation for avatar skills practice after their initial exposure to MI, thus potentially decreasing the impact of this component of the training.

Another limitation is that because of the nature of the avatar platform and how the 3 conversations simulations are built, there are limited choice options. Therefore, after a learner has used the platform a few times, they might find it redundant and be less willing to practice. The didactic module and the conversation simulations may be a great opportunity for novice learners to practice their skills; practitioners with more experience in patient-centered counseling may be less interested in using a platform that offers few multiple-choice conversation options.

To overcome the challenges of assessing MI skills in implementation settings, we are using multiple measures, namely, MITI and the automated feedback scores from the avatar simulations. The feedback feature of the avatar simulations was originally designed to assist learners in improving MI skills. The mapping approach we used to create the automated scoring system for each of the global scores may limit the precision of the measure to capture how well the clinician is using MI. In addition, because participants complete the same simulations for training and assessment purposes, scoring from the simulations may not be a valid outcome measure of their MI skills.

This study design was in the context of implementation research and does not allow us to examine the effect of the MI workshop training component alone. However, examining MI in real-world settings is an innovative aspect of the study. Although there are limitations to asking about experiences of the training over a 6- or 12-month period, our qualitative interviews at the end of the study will add detail to the quantitative results.

Although the development of our avatar conversation simulations included multiple iterations between our study experts and the developers of the platform, further advances in virtual training have become available since the study was first conceptualized. Other programs that allow for additional branching conversation scripts could be integrated into future versions of this training to better support virtual learning [57]. Virtual reality programs that create endless iterations of interactive experiences such as those offered by SIMmersion are another option to promote learning. Platforms that use natural language processing with actual recorded patient encounters also have the potential to offer feedback to learners on their MI skills and could be an addition to MI training for busy mental health practitioners [56,58].

Conclusions

This study will help us understand the effectiveness of 2 scalable training strategies on practitioners' use of MI and how these approaches impact practitioners' beliefs about, the importance of, and their confidence to use MI when delivering 3 interventions focused on CVD risk reduction to patients with SMI. The degree of tailoring to specific lifestyle change targets and the amount of real-time interaction needed to garner training effects in MI are not known; this research will contribute to knowledge about the effectiveness of brief videoconferences for training community mental health practitioners in MI. Testing MI skill uptake from videoconference training sessions has not been documented in the literature; this project will be a step forward in filling this gap. The study will also provide information about the perceived usefulness of the avatar as a modality for learning MI. On the basis of our results of this study, a logical next step to determine the most effective scalable training approach would be an RCT that compares different MI training modalities and includes a comparator condition.

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Data Availability

The data sets generated during and analyzed during this study are not publicly available because the study is ongoing but are available from the corresponding author upon reasonable request after the study is completed. Data would be deidentified and provided to researchers whose proposed use of the data has been approved, along with a signed data access agreement and appropriate international review board approval.

Authors' Contributions

ATD and GLD conceived the design of the study. ATD drafted the original version of the manuscript with assistance from GJJ, SM, and CTY. ATD developed the training. SG and SM contributed to the training materials. NYW developed the analytic plan. JG, EM, and TF participated in the recruitment and data collection. All authors read, reviewed, and approved the final manuscript.

Conflicts of Interest

KAG serves as the medical director for the American Board of Obesity Medicine, has a research grant from Novo Nordisk, and is a paid consultant to Eli Lilly.

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Abbreviations

CVD: cardiovascular disease
EBP: evidence-based practices
IRB: international review board
MI: motivational interviewing
MINT: Motivational Interviewing Network of Trainers

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MITI: Motivational Interviewing Treatment Integrity Tool
PRP: psychiatric rehabilitation program
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
SMI: serious mental illness
SP: standardized patient

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Protocol

A Digital Intervention to Improve Mental Health and Interpersonal Resilience in Young People Who Have Experienced Technology-Assisted Sexual Abuse: Protocol for a Nonrandomized Feasibility Clinical Trial and Nested Qualitative Study

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Abstract

Background: No evidence-based support has been offered to young people (YP) who have experienced technology-assisted sexual abuse (TASA). Interventions aimed at improving mentalization (the ability to understand the mental states of oneself and others) are increasingly being applied to treat YP with various clinical issues. Digital technology use among YP is now common. A digital intervention aimed at improving mentalization in YP who have experienced TASA may reduce the risk of revictimization and future harm and make YP more resilient and able to manage distress that might result from TASA experiences.

Objective: In this paper, we describe a protocol for determining the feasibility of the i-Minds trial and the acceptability, safety, and usability of the digital intervention (the *i-Minds* app) and explore how to best integrate i-Minds into existing routine care pathways.

Methods: This is a mixed methods nonrandomized study aimed to determine the feasibility, acceptability, safety, and usability of the intervention. Participants aged between 12 and 18 years who report distress associated with TASA exposure will be recruited from the United Kingdom from the National Health Service (NHS) Trust Child and Adolescent Mental Health Services, sexual assault referral centers, and a web-based e-therapy provider. All participants will receive the i-Minds app for 6 weeks. Coproduced with YP and a range of stakeholders, the i-Minds app focuses on 4 main topics: mentalization, TASA and its impact, emotional and mental health, and trauma. A daily prompt will encourage YP to use the app, which is designed to be used in a stand-alone

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manner alongside routine care. We will follow participants up after the intervention and conduct interviews with stakeholders to explore the acceptability of the app and trial procedures and identify areas for improvement. Informed by the normalization process theory, we will examine barriers and enablers relevant to the future integration of the intervention into existing care pathways, including traditional clinic-based NHS and NHS e-therapy providers.

Results: This study was approved by the Research Ethics Board of Scotland. We expect data to be collected from up to 60 YP. We expect to conduct approximately 20 qualitative interviews with participants and 20 health care professionals who referred YP to the study. The results of this study have been submitted for publication.

Conclusions: This study will provide preliminary evidence on the feasibility of recruiting YP to a trial of this nature and on the acceptability, safety, and usability of the i-Minds app, including how to best integrate it into existing routine care. The findings will inform the decision to proceed with a powered efficacy trial.

Trial Registration: International Standard Randomised Controlled Trial Number Registry (ISRCTN) ISRCTN43130832; https://www.isrctn.com/ISRCTN43130832

International Registered Report Identifier (IRRID): DERR1-10.2196/40539

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KEYWORDS

technology-assisted sexual abuse; digital; young people; abuse; eHealth; mobile health; mHealth; mobile phone

Introduction

Background

Child sexual abuse (CSA) is a major risk factor for many health risk behaviors as well as physical and mental health problems. CSA negatively impacts developmental trajectories, educational attainment, occupational prospects, and communities more broadly, at huge societal and economic costs [1,2]. For young people (YP), using the internet is a routine part of daily life, but it can place them at risk for various forms of CSA. Technology-assisted sexual abuse (TASA) can occur through any device connected to the internet and across multiple platforms and apps. YP can be coerced into sharing sexual images of themselves, taking part in sexual activities via a webcam or smartphone, or having sexual conversations by text ("sexting"). Web-based grooming, abuse, and exploitation may also lead to contact abuse; contact abuse cases increasingly involve web-based elements (eg, the production and distribution of images). Offline and web-based sexual abuse is not mutually exclusive in terms of risk behaviors or harm, but there is evidence of additional risks of TASA afforded by the internet and unique social and psychological harms associated with TASA [3,4].

COVID-19 has led child protection organizations to urge governments, tech companies, educators, and parents to be alert, take urgent measures to mitigate potential risks, and ensure that YP engage in web-based interactions in a safe and positive way. In the United Kingdom, an Online Safety Bill has been published and further consultation will be brought into law in 2022. The bill acknowledged the need for new legislation to make the internet a safer place for everyone, especially children, while protecting their right to freedom of expression on the web. The sharp increase in TASA, even before COVID-19, had already caused increased pressure on health care services, education, and government systems. Recent data show an increase of 34% in the demand for mental health support from YP during the pandemic [5]. The distinctive nature of TASA relative to other forms of abuse is recognized in the current National Institute for Clinical Excellence (NICE) guidelines for responding to child abuse and neglect [1]. The NICE found no evidence-based interventions for improving the mental health and well-being of YP who have experienced TASA (YP-TASA) and recommended further research on the efficacy of interventions aimed at improving well-being and relationships and preventing further harm following internet-facilitated abuse. The efficacy of interventions that could improve well-being and prevent further harm in YP-TASA remains an unmet research need.

Theoretical Framework

Multiple factors are likely involved in vulnerability to being exposed to TASA. A relevant risk factor is a young person's ability to accurately estimate others' intentions and motivations when engaging in a web-based environment. This ability to understand what is going on in our own minds as well as in other people's minds (in terms of thoughts, intentions, desires, and beliefs) is known as mentalization [6]. Mentalization is the ability to attend to and reflect on the mental states in ourselves and in others and consequently understand our own actions and those of others on the basis of intentional mental states. An inverse relationship exists between emotional arousal and mentalization [7]. YP who are distressed or have difficulties with regulation because of being victimized, abused, or exploited on the web may be at the greatest risk of developing difficulties in mentalizing, increasing the likelihood of repeated victimization and harm [8]. Furthermore, social anxiety (often experienced by YP who are groomed on the web) has been found to be associated with mentalization difficulties [9]. People's assumptions about the intentions and motives of others are usually based on the verbal and nonverbal cues of real-life interactions. When we communicate in a web-based environment, signals of empathy and understanding are transmitted more opaquely [10-12], and mentalizing, which is already compromised in vulnerable YP, can be even further affected. Difficulty mentalizing can compromise the evaluation of risk and assumed trust in web-based communications [13] and might therefore represent a valuable target for interventions aimed at reducing risk in YP who have already been exposed

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to TASA. Indeed, difficulties in mentalizing processes have been linked to greater vulnerability to a range of mental health problems that are common among TASA survivors, including depression, anxiety, eating disorders, and shame [14,15].

A recent systematic review [14] has highlighted mentalization-based therapy (MBT), a therapeutic approach that specifically aims to improve mentalizing capacity and consequently affect regulation and psychological distress, as a promising treatment approach across a wide range of clinical presentations, including groups that have previously shown a limited response to psychological therapy (eg, adolescents who self-harm). The efficacy of MBT has been more extensively trialed in adult mental health; however, a growing evidence base is emerging for the efficacy of MBT in YP. For example, in a randomized controlled trial with adolescents who self-harmed, Rossouw and Fonagy [16] found that MBT for adolescents was more effective than treatment as usual, with a recovery rate of 44% in comparison with 17%. A pilot randomized controlled trial conducted by Griffiths et al [17] found that a brief (12 weeks) mentalization-based intervention was acceptable in YP enrolled in Child and Adolescent Mental Health Services (CAMHS) and was associated with significant treatment effects across a range of outcomes, including anxiety, self-harm behaviors, and the ability to regulate distressing emotions. Therefore, improved mentalization capacity following a mentalization-based psychological intervention might result in improvements in two key intervention targets for YP-TASA: (1) reducing the risk of revictimization and future harm and (2) improving the emotional and mental well-being of users who might experience current distress due to TASA experiences.

The Role of Digital Interventions

Although psychological interventions for YP can be delivered across multiple modalities, digitally mediated interventions represent an acceptable way to support YP and overcome some central limitations of traditional clinic-based services. Recent systematic reviews and meta-analyses have demonstrated that digitally mediated psychological interventions represent effective treatment options for improving the mental health and well-being of YP across a range of problems [18], including computerized cognitive behavior therapy targeting depression and anxiety, which have been most commonly examined. Existing feasibility, acceptability, and efficacy studies of digital interventions indicate that they are acceptable across genders [19], impact behavior as well as mood [20], and are safe for vulnerable YP [21]. Long waiting times in CAMHS indicate that there are significant delays in help being offered, preventing timely access to support, potential exacerbation of problems brought about by TASA exposure, and increased risk for repeated victimization in the interim. When effectively integrated within existing care pathways for YP, a digital intervention for YP-TASA has the potential to (1) scale-up access to support and tackle the overwhelming demand for services to provide timely therapeutic input and (2) ensure support can be implemented "in the flow of daily life" and in a format that is both familiar to YP and unconstrained by location and time, allowing access to therapeutic strategies even when traditional means of support are not available.

This Study

The aim of our National Institute for Health and Care Research (NIHR)–funded i-Minds clinical feasibility trial was to assess the feasibility, acceptability, safety, and usability of a theory-driven, coproduced, mentalization-based digital health intervention (the "i-Minds" app) for YP-TASA. This trial represents the third phase in the development and testing of the i-Minds app. In phase 1, we interviewed health care professionals (HCPs) across both Northwest England and Edinburgh, Scotland, to inform them of the content of the i-Minds app and the protocol design of the trial. We explored the following issues: (1) HCPs experiences of adapting face-to-face interventions to a web-based environment, (2) their understanding of TASA and current service approaches to supporting YP-TASA, (3) specific issues HCPs face when working with YP-TASA, (4) previous experience of mentalization approaches in clinical work, (5) advantages and disadvantages of delivering psychological approaches using digital tools, (6) perceived barriers or facilitators to implement digital tools in clinical practice, and (7) uptake of a digital health intervention of this nature with this client group and our proposed trial procedures (results currently being prepared for publication). We also held monthly to bimonthly participatory workshops with a range of stakeholders, including those with lived experience, YP, parents and professionals, and nationally representative stakeholders, to inform the design and functionality of the digital health intervention and our proposed trial procedures. In phase 2, the University of Manchester Digital Health Software (DHS) team built the i-Minds app over an 8-month period of agile development and testing alongside qualitative and participatory design work. In the third phase, using a nonrandomized open trial design, we will test whether the i-Minds app is feasible, acceptable, and safe for YP-TASA.

Regarding consent, where prospective participants expressed an interest in taking part in the study, their clinician obtained the individual's written or verbal consent to pass on their name and contact details to the research team. Once it has been established that a prospective participant is interested in taking part in the study and has given permission to be contacted by the research team, the researcher will contact the prospective participant to explain the study to them in detail and give them the opportunity to ask questions. The researcher will explain that participation is voluntary and that they can withdraw consent at any point during the study without giving a reason, which will not impact them continuing to access standard care within the referring service (as the i-Minds app is designed to be used in addition to, not in place of, standard care) or other sources of support they might access simultaneously.

Personally identifiable data are collected by the local recruitment site, separate from the research database. The research data were deidentified.

YP-TASA participants will be remunerated £40 (US $50) for their time to complete the baseline assessment (£20 [US $25]) and the follow-up (postintervention) assessment (£20 [US $25]). Participants who also participated in the nested qualitative interview study will receive a further £20 (US $25) for their time. This amount was based on NIHR INVOLVE guidelines.

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YP who do not have access to a smartphone will be provided with one, and their data network charges will be covered for the 6-week intervention period. HCPs who participated in the nested qualitative interview study will not receive payment for their participation.

Objectives

The primary study objectives were to determine (1) whether it is feasible to deliver the i-Minds app for YP-TASA, including recruitment and retention to the trial, and identifying primary and secondary outcome measures; (2) whether the i-Minds app is acceptable to users; (3) whether the i-Minds app is usable and safe; and (4) how best to integrate the app into existing National Health Service (NHS) and web-based mental health and sexual abuse service care pathways.

Methods

Study Setting

The trial is funded by the NIHR Health and Social Care Delivery Research program. The study took place across the CAMHS and sexual assault referral centers in Greater Manchester (England) and Edinburgh (Scotland). We also aimed to recruit participants from an NHS-commissioned national (England) e-therapy provider (Kooth).

Ethics Approval

The study was approved by the National Research Ethics Committee (REC) of West Scotland REC 4 (approval number 22/WS/0083).

Study Design

Overview

This was a multicenter mixed methods study comprising two components: (1) a nonrandomized feasibility clinical trial with the aim of recruiting a target sample of 60 YP-TASA across recruitment sites. This sample size was shown to be sufficient to pilot test the feasibility and acceptability of an intervention of this nature. All participants will have access to the app and will be included in all analyses for the feasibility clinical trial. To evaluate who might benefit from using the i-Minds app, we will recruit participants with varied characteristics wherever possible (eg, ethnicity, sexual orientation, gender, TASA experiences); (2) a combination of quantitative data on adoption, uptake and use (aligned with the AMUsED framework [22]), and qualitative data from semistructured interviews guided by the Normalization Process Theory (NPT) with participants (n=approximately 20) and HCPs who referred YP-TASA to the trial (n=approximately 20) and service managers from the referring service provider (n=approximately 10) who referred to the trial will explore the acceptability and usability of the i-Minds app.

Eligibility

The participant inclusion and exclusion criteria are presented in Textboxes 1 and 2, respectively.

Textbox 1. Inclusion criteria.

- Young people (YP) who have experienced technology-assisted sexual abuse (TASA) participants
  - Aged 12 to 18 years
  - Have been exposed to (TASA) and report associated distress
  - Are receiving support from National Health Service Child and Adolescent Mental Health Services, sexual assault referral centers or e-therapy provider (Kooth) and will continue to be actively supported by the provider over the duration of the trial
  - Willing to use an app designed to support YP who have experienced TASA
  - Proficient in speaking and writing in English
  - Capacity to consent
  - Consent to providing their username to the research team (Kooth participants only)
- Health care providers or service manager participants (qualitative interviews)
  - The member of the young person's direct care team who referred the young person to the feasibility clinical trial
  - The manager at the service that referred the YP to the feasibility clinical trial
  - Able to understand and speak English

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Textbox 2. Exclusion criteria.

- Young people who have experienced technology-assisted sexual abuse people participants
  - Insufficient verbal and written command of English
  - Moderate learning difficulties (as assessed by their direct care team)
  - Are at risk of current or recent suicidality
- Health care professional participants
  - None (other than not meeting the inclusion criteria)

Recruitment

Feasibility Clinical Trial

The research team will liaise with the CAMHS and sexual assault referral centers teams and the e-therapy provider Kooth to provide information about the study via presentations at team meetings and study information leaflets, referral and consent to contact forms, and copies of the relevant participant information sheet. Clinical staff will be encouraged to identify potentially eligible participants from their caseload. Participants may also be identified by placing poster advertisements in waiting rooms or via digital spaces (via the digital magazine used by the e-therapy provider Kooth). The advertisement will invite interested prospective participants to ask for information about the study from a member of their clinical team.

After obtaining informed consent, potential participants will be provided with a participant information sheet for reading. Prospective participants aged 12-15 years recruited from the English NHS recruitment site will be provided with a bespoke participant information sheet to give to at least 1 of their parents or caregivers. The parent or caregiver will have the ability to opt their child out of taking part in the study (by contacting the research team or the child's clinical team or by completing an opt-out form), should they not wish their child to take part. Prospective participants aged 12-15 years recruited from the Scottish site will be asked if they would like their parents to be given a participant information sheet.

Nested Qualitative Study: YP-TASA Process

Participants who participated in the feasibility clinical trial and who consented to participate in the qualitative study will be eligible to participate in qualitative interviews, which aim to understand how participants experienced the i-Minds app and its acceptability. Participants will be invited to the qualitative interview study when information is provided, and consent will be obtained for the feasibility clinical trial. Participants will be approached directly by the research team to participate in the interview upon discontinuation from accessing and using the app or completion of using it. Therefore, participants who do and do not complete the feasibility clinical trial in its entirety will be asked to participate in the interview. Participants will be selected according to a sampling framework to capture varied demographics, experiences of TASA, and levels of engagement with the i-Minds app.

Nested Qualitative Study: HCPs or Service Managers

As trial participants start completing postintervention assessments, a research worker will contact and invite a target sample of approximately 20 HCPs who referred YP-TASA to the feasibility clinical trial and 10 service managers from the referring service provider to participate in a semistructured interview (postintervention). A list of referring clinicians or managers will be kept separate from the research data.

Consent

Trained members of the research team will receive consent. In both the quantitative feasibility clinical trial and nested qualitative interview study, fully informed consent will be sought from YP and HCPs or service managers and obtained before data collection and when participants access and use the app. Health Research Authority (HRA)– or REC-approved copies of age-appropriate participant information sheets and consent forms will be used for prospective YP, including those aged 12-15 years and 16-18 years. Prospective participants aged 12-15 years who are recruited in England will be provided with a participant information sheet to give to at least 1 of their parents or caregivers, who will be given the opportunity to opt for their child to not wish their child to take part in the study. Parents or caregivers of 12-15 year olds recruited from our Scottish site will be given a copy of the participant information sheet if the young person wishes. Parents or caregivers of prospective participants aged 12-15 years in Scotland will not be able to opt out of the study if the prospective participant is Gillick competent.

YP are provided with information about both the feasibility clinical trial and the qualitative study in one age-appropriate participant information sheet given to them before taking part in the feasibility clinical trial. They were asked to consent to participate in the qualitative study as part of the consent process for the feasibility clinical trial, but continued consent was checked if they were invited to participate in the interview.

The researcher will explain to all potential participants that participation is voluntary and that they can withdraw their consent at any point during the study without providing a reason. It will be made clear to YP that, as the intervention is not in place of standard care (it is in addition to standard care), withdrawal from the intervention will not impact their ability to continue to access standard care within the referring service or other sources of support they might access contemporaneously. Prospective participants in both the feasibility clinical trial and qualitative study will be given

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multiple options for documenting their informed consent, including (1) a signed hard copy of the consent form by standard mail, (2) returning a digitally signed copy of the consent form by email (encrypted), and (3) recording their consent on an encrypted audio file that will be stored separately from any research data collected from them. The participant's general practitioner or care team will be provided with a letter to inform them that a young person is taking part in the study.

Participants will be given at least 48 hours to decide whether to participate. If a participant who has provided informed consent loses the capacity to consent during the study, the participant will be withdrawn from the study. Identifiable data already collected with consent will be retained and used in the study. No further data will be collected or any other research procedures will be carried out on or in relation to the participant. The withdrawn participants will be referred to their service provider so that appropriate follow-up care and action can take place.

Data Collection and Management

Quantitative and qualitative data were collected through psychometric measures and interviews. The initial interview will involve the completion of self-reported sociodemographic questions, technology use, and clinical or service details. A range of validated self-report scales will measure key intervention targets and outcomes of the intervention both before (week 1) and after using the app (weeks 7-9 post baseline), including reflective function (mentalization), problematic internet use, emotional distress, internet abuse-related distress, emotion regulation, interpersonal sensitivity, attitudes and views toward close interpersonal relationships, and resilience. Multimedia Appendix 1 describes the schedule of the assessments at the 2 assessment time points.

Measures will be completed via the web-based Qualtrics survey system, capturing all the measures in the case record form, or, where this is not possible, a paper or hard-copy version of the case record form will be used. Demographics, clinical, and web-based abuse-related distress measures will be completed with support from the research worker (participants will be given the choice to complete the remaining self-report measures either on their own or with continued support from the researcher). The assessments of reflective function and emotion regulation will be administered next, with the remaining measures completed in a randomized order. All data (ie, demographic data, clinical data, self-report questionnaires, data related to trial administration, and procedures) will be entered and managed on the REDCap (Research Electronic Data Capture; Vanderbilt University) platform [23], a secure clinical trial management system. Data will be stripped of any identifying information and each participant will be assigned a unique participant ID. All information obtained is confidential. Research workers at each participating site will input data collected via Qualtrics (Qualtrics International Inc) into the REDCap database. In the case of paper or hard copy–completed questionnaires, research assistants will (1) scan paper copies for digital preservation of all research completed as part of the study and (2) enter questionnaire scores on the REDCap database.

Qualitative interviews will be audio-recorded for transcription and analytic purposes, using recording devices that enable encryption at the point of data collection. All interviews were anonymized at the time of transcription, and all identifying details were removed. Audio-recorded consent (including participants' names) will be recorded on a separate audio file so that this information cannot be directly linked with the interview transcripts or audio recordings.

Outcomes

Primary Outcome

The primary objective of the trial was to determine the feasibility and acceptability of delivering the i-Minds app for YP-TASA. No formal attempt has been made to test the effectiveness of the intervention which will be conducted.

Feasibility

We will collect detailed recruitment and retention data congruent with all relevant fields of the CONSORT (Consolidated Standards of Reporting Trials) statement for feasibility studies [24], including (1) the number of eligible participants consenting; (2) the total number recruited, including information about recruitment setting to inform the sampling strategy of a future definitive trial; (3) completeness of outcome measures; (4) the number lost to follow-up; and (5) number of services offered the intervention. To evaluate the extent to which YP-TASA engaged with i-Minds, we collected data on the (1) proportion of participants completing the intervention, (2) dropout rates and reason for withdrawal, and (3) platform use and engagement data using Matomo click analytics software [25] with use analysis guided by the AMUsED framework [22].

Acceptability

To understand how the intervention is experienced and how acceptable the app and trial procedures are, we will conduct in-depth qualitative interviews with a proportion of YP-TASA who will be selected according to a sampling framework to capture varied demographics, experiences of TASA, and levels of engagement with the i-Minds app. Interviews will be conducted in rounds of approximately 5 participants to allow for iterative analysis and inform further sampling. Topic guides developed with input from our advisory groups will be used to examine (1) whether i-Minds met expectations; (2) what level of support is needed to facilitate engagement with i-Minds; (3) overall impressions of i-Minds (enjoyable, usability, and satisfaction); (4) what participants liked and did not like about the intervention in terms of content and usability of the platform; (5) how it helped and did not help; (6) what changes they would make; (7) barriers to participation or engagement, including the perceived burden of the research assessment procedures; and (8) acceptability of trial procedures.

To examine barriers and enablers (and unintended consequences) to integration and uptake of the intervention into existing care pathways, we conducted qualitative interviews with a target sample of 20 HCPS who referred to the trial and 10 service managers to examine specific questions around (1) ways in which we can maximize uptake, utility, user experience, acceptability, satisfaction, and reach of the platform; (2) how the platform can be locally adapted and translated into practice;

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(3) HCPs' views on referral routes to a digital intervention within existing care pathways; and (4) strategic perceptions about the relative advantage of the digital platform and its wider transactability (whether it can be scaled up). Before taking part in the interview, HCPs will be asked to complete some brief demographic questions (eg, age, profession, and years of professional experience).

Topic guides were developed in collaboration with our lived experience, parents or caregivers, and professional advisory groups. We anticipate all qualitative interviews to take approximately 1 hour, depending on the extent to which the participant requires breaks or further support or guidance and includes full debriefing.

Secondary Outcomes

The secondary objectives of this trial were to explore whether the i-Minds app brings about clinically meaningful changes in outcomes (described in Multimedia Appendix 1), differences in engagement and attrition, and potential clinical benefits across key demographic groups (eg, lesbian, gay, bisexual, transgender, queer, and others [LGBTQ+] and Black, Asian, and minority ethnic [BAME]), demographics and service differences across recruitment sites (Manchester, Edinburgh, or Kooth), and barriers and enablers to integration and uptake into existing mental health care provider pathways. We will also explore the safety and usability of the app and our trial procedures.

Safety

We will collect detailed adverse event reports using standardized operating procedures in line with our study sponsor and HRA safety reporting procedures.

Any adverse event observed over the course of the research will be documented and reported according to a bespoke standard operating procedure that will fully comply with appropriate HRA safety reporting procedures, sponsor requirements, and local research and development policies of participating NHS organizations. All adverse events will be monitored by an independent Data Monitoring and Ethics Committee (DMEC) that aims to meet on 3 occasions (and more frequently if needed) over the course of the trial period. An adverse event log file will be created to systematically record occurrences with reference to an a priori defined list of anticipated and unanticipated adverse events.

Usability

As this was a feasibility clinical trial, we had no a priori hypotheses or intentions regarding the level of compliance with the app. Rather, we sought to explore and understand how participants used the app and how they used it. Platform use and engagement data collected using secure software analytics while participants use the app will be guided by the AMUsED framework [22]. All interactions with the app are date and time stamped and collected via Matomo click analytics software [25] to help us understand how a participant uses the app; it is open source and is General Data Protection Regulation compliant. All the analytical data were stored securely. The data were stored on a secure server hosted by the University of Manchester. Analytics can be viewed by the researcher using a secure web interface dashboard. Multimedia Appendix 2 provides an overview of the study objectives and time points for the evaluation of each outcome.

The Intervention: i-Minds App

The i-Minds app was developed in phase 2 of the broader program of our work on TASA. It is a modular intervention, underpinned by mentalization principles, and designed to be used as a standalone platform without restrictions. Following the overall structure and content of a mentalization-based manual developed by members of our team in a previous trial [17], the i-Minds app involves several tasks that not only provide psychoeducation about mentalization but also encourage the application of mentalization principles to a range of scenarios presented to YP. For example, we present the story of a young person with lived experience of TASA (called *Mel*) and, in vignette style, invite users to put themselves in *Mel's* shoes and consider a range of questions, such as *How do you think Mel feels at school, at home and in other situations that might remind her of what she went through?* We extend the vignette further throughout the app and invite users to pick out situations that could bring about negative feelings for *Mel* in a range of contexts (school, home, and peer relationships), which we further extended using video material and other interactive exercises.

The aim of the intervention is to help YP-TASA understand the motives of adults and peers more clearly, help protect them from future abuse, and help them feel more confident in ambiguous and challenging interpersonal interactions. The app includes content that aims to introduce the concept of mentalization and relate it to scenarios that YP-TASA might identify with, encourage emotional and cognitive literacy in interpersonal interactions, encourage reflection on interpersonal relationship patterns and their development, and explore how these concepts affect emotional expression, behavior, mental health (eg, anxiety, mood, trauma responses, self-esteem, self-harm behavior), and perspective taking. The content is organized into four modules or topic areas: (1) mentalization, (2) psychoeducation of TASA, (3) emotional and mental health, and (4) trauma. There are links to other areas of the app within each core topic area to maximize interactivity and user experience. In addition to the core topic areas, there is a multimedia repository of available resources that can be accessed from the home screen (Multimedia Appendix 3).

The app can either be downloaded onto a participant's own smartphone or a participant will be loaned a smartphone with the i-Minds app preloaded. The participant can configure certain features of the app themselves during the app "onboarding" session with the researcher, which will either take place in person or remotely, depending on the participant's choice. Participants were required to work through the mentalization module, which is core to the theoretical orientation of the intervention, before all other features of the app can be accessed. There were no limits to how often or when a participant could use the app. That is, we did not restrict how users interacted with the app over the 6-week intervention period.

Consultation with our advisory group indicated that YP would like the app built around a tree metaphor (see Multimedia Appendix 4 for screenshots of the i-Minds app). Topic areas

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are represented by branches of a tree, and subtopics are represented by smaller tree branches. As a user works through a subtopic, a leaf is added to the tree, which begins to flourish as the user works through the content (the branches are bare to start with). As suggested by both our young persons' and professionals' advisory groups, we also included a "progress ring" around each topic area, which shows the user how far they have progressed through each topic. Tapping on a particular topic area opens an introduction screen that includes introductory text on the topic area. Informed by our advisory group, the flow of each topic area thereafter includes text, video material, and interactive exercises exploring the topic areas, as shown in Multimedia Appendix 3.

Daily Prompt

A daily prompt in the form of a standard app notification (similar to a Facebook or Twitter notification) will request the participant to check in with the app. The daily notification is designed to prompt engagement with the app and has been included in response to advisory group feedback and our prior experience with app studies [26]. If a participant could not interact with the app at the time of the prompt, they received a reminder notification 3 hours later. This daily prompt was not sent if the participant had already used the app on that day. Participants can also self-initiate use of the app at any time of the day, as many times as they chose. At midday after each 7-day period, an additional weekly prompt invites the user to reflect on app use in the previous week. A research worker will also call the participant 1 week after the onboarding session to troubleshoot the potential technical difficulties. We include the 1-week phone call, as we know that if any technical issues arise, they will most likely be apparent at this time point.

Onboarding Session

A research worker will meet the participant (either remotely or in person) for a single onboarding session. Here, the research worker will take the participant by configuring the app (eg, including contact details of trusted others), explaining the terms of use in young person friendly terms, demonstrating the features of the app, and demonstrating how to use a smartphone.

Postintervention

At the end of the 6-week intervention period, if the participant had received a loaned phone, the researcher collected the handset at the follow-up assessment. If the app is downloaded onto a participant's own handset, the researcher will either delete the app from the participant's phone so that they can no longer interact with it or the app will automatically stop working no later than 3 weeks after the intervention window. Data network charges will be covered by vouchers and topped up by a member of the research team (if required). Participants will be encouraged to continue receiving support from their health care providers. As participating in this trial does not replace usual care and as all participants will be involved with a clinical service throughout the duration of the trial, participants' posttrial will continue to be supported by the referring health care provider. Participants will be given an information sheet, signposting them for further support if required.

Feature Implementation

We followed an agile development process that supports close collaboration between software engineers, clinical academics, and advisory groups that developed and shaped the content of the intervention, enabling the incorporation of changing requirements throughout app development. In line with this process, the working software was delivered on a regular basis and reviewed by the clinical team and advisory groups who provided interim feedback on the user interface developed, software performance, and usability. Any required changes were then incorporated into the next iteration of platform development and continued until the app was fully functional.

i-Minds was written as a hybrid app (HTML, Cascading Style Sheets, JavaScript) using the ionic or capacitor platform [27]. Phone interactions, such as notifications and alarms, are implemented using the capacitor plug-in framework, which facilitates interactions between JavaScript code and platform-specific phone capabilities. The app uses a secure connection (http secure or SSL) to send data to a server. The only data sent were to indicate progress through each module. Before release, the app is unit, integration and system tested, and then reviewed internally at the University of Manchester before submission to the Google Play and Apple App stores.

The i-Minds app is made available on Apple iPhone Operating System and Android devices and implements best practice guidelines offered by the platform providers (Android App Accessibility Guidelines [28] and Apple Human Interface Guidelines [29]). The app is offered as an app to both Google Play and Apple App stores. This software was developed by the University of Manchester DHS.

The app is not a medical device as it has not been designed to be used for diagnosis, prevention, monitoring, treatment, or alleviation of disease, injury, or handicap.

Accessibility Statement

Accessibility needs of the target audience have been considered when developing accessibility provisions within the i-Minds app, and every effort has been made to ensure that the provision meets the needs of these users. Accessibility needs have been developed in accordance with Public Sector Bodies (web sites and mobile apps) (No 2) Accessibility Regulations 2018 ("Accessibility Regulations" [30]). When using the app on Apple iPhone Operating System and Android devices, users can use the built-in accessibility settings to adjust font sizes, use high contrast settings, zoom in up to 300% with the text staying visible on screen, navigate using only a keyboard or speech recognition software, and use the screen reader. In line with user input, we have made the text in the app as simple as possible to understand to increase its suitability for learners with a wide range of educational backgrounds. Users and research workers can report problems directly to the University of Manchester DHS team email address, which is monitored during the usual working hours. All participants had to accept the end-user license agreement, which is based on a standard template, before they could use the app. A lay version of the end-user license agreement was developed by the research team and was shared and discussed during the onboarding session to

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ensure that participants were making an informed choice about how their data were used.

Testing

We followed a strict user-acceptance testing procedure before the first public test release of the app. This procedure includes a section that specifically encourages researchers to test all accessibility features of their devices and determine which aspects of the app support these features. This procedure highlights any content that is not compliant with the Web Content Accessibility Guidelines 2.1-AA standard. Any noncompliant content that is considered the core functionality of the app or essential to the user experience was addressed at this stage.

Privacy, Security, and Risk

Security measures are robust and fully comply with national policies and relevant data management and information governance policies and procedures of the participating Universities and NHS organizations. All trial investigators and site staff comply with the requirements of the Data Protection Act 2018 or General Data Protection Regulation and the NHS Confidentiality Code with regards to the collection, storage, processing, and disclosure of personal information and will uphold these acts' core principles. The i-Minds app uses the University of Manchester Privacy Notice for Research Participants (available upon request). Once the user has installed it, they are given a unique code. The app will only become functional after the unique code has been given to the researcher, and the researcher will add it to the participant record via the web interface.

The following security features are used: (1) app: Use of the app requires a PIN code on the user's phone, which will be checked and enforced when the app starts. Data collected within the app are sent to the server over http secure using secure ciphers; (2) server: the server is part of the University of Manchester's research virtual machine infrastructure and is secured inside the University's network. Operating system and related security patches are applied on a regular basis to these servers by the University's infrastructure team; and (3) web-based interface: members of the research team are each allocated their own username and password to access the web-based interface. The DHS team has administrative access to the web-based interface to enable it to maintain the system and manage accounts for researchers. All members of this team received their current data protection training.

To minimize security risks, no part of the system will collect identifiable information. A pseudonymized identifier was used to identify each participant. Only the research team knows the link between this identifier and the actual participant. This link will not be stored anywhere in the system, and the software team will only have access to pseudonymized identifiers.

Regarding participant safety and risk, at the point of referral, we will collect the contact details of the participant's general practitioner and key worker from the referring service, who will be our primary point of contact for subsequent liaison with the clinical team or key worker to manage any significant risk. If a participant discloses something that raises serious concerns (eg, historical abuse, current abuse) about their safety or the safety of others or if a research worker becomes distressed themselves, given the topic and nature of the work, we will follow the safeguarding and distress management procedures described in our coproduced and ethically approved detailed standard operating procedure. As a general rule, we signed participants to the appropriate sources of support in their locality.

Withdrawal

A participant will be withdrawn if they express either to a member of the research team or to their key clinical worker that they wish to withdraw from the intervention, the trial, or both. If a participant withdraws from the study, we will complete a withdrawal form, suspend data collection activities, and retain and analyze the anonymized data collected up to the point of withdrawal. If a participant withdraws from the intervention, we will cease their use of the app but still invite them to complete follow-up measures and a qualitative interview to understand their reasons for withdrawal from the intervention (but only if the participant consents to this).

Independent Oversight

Independent oversight of the trial is provided by a project steering committee (PSC) and a DMEC who are independent from the sponsors and investigators and approved by the funder. The PSC comprises an independent chair, statistician, academic, clinician, and patient and public involvement representative and will meet every 6 months over the duration of the project. The PSC is responsible for the independent oversight of the project on behalf of the sponsor and funder and will ensure that the project is conducted according to the rigorous standards set out in the Department of Health's Research Governance Framework for Health and Social Care and the Guidelines for Good Clinical Practice. The DMEC comprises an independent chair, statistician, and digital health expert and is responsible for monitoring ethical issues of consent and confidentiality, data quality and completeness, incidence of adverse events, compliance with the protocol by participants and investigators, and any other issues relevant to the transparent and ethical delivery of the trial. The DMEC aims to meet on 3 occasions over the course of a feasibility clinical trial.

Patient and Public Involvement and Engagement

Our aim was to develop a digital intervention as opposed to an "offline" one that was directly influenced by the views and preferences of YP-TASA. Before our application for funding, we conducted extensive consultations with YP-TASA and a range of stakeholders. In line with NICE [1] research recommendations for developing interventions to improve well-being following TASA, we have continued to seek extensive feedback from YP-TASA, parents, and practitioners via 3 advisory groups, who we will work with for the lifetime of feasibility and nested qualitative studies. The active involvement of YP-TASA, their parents or caregivers, and relevant professionals ensures active input into the development of the intervention, including its content, format, and structure, and linked procedures to ensure participant safety, as well as to

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deliver its evaluation and dissemination of the findings to maximize impact.

Three advisory groups were established. A national stakeholders advisory committee meets every 6 months and comprises professionals from national law enforcement and child protection or safeguarding organizations, academic institutions, TASA support services, and social media organizations. A professional advisory committee meets every 6 months and comprises clinicians from relevant services that provide mental health and web-based sexual abuse or safeguarding support to YP in our recruiting sites. Our lived experience advisory group comprises up to 10 people with TASA experiences who meet monthly to bimonthly over the course of the project. Input was received both through web-based meetings and through individual written feedback on participant-facing documents and app content itself. The lived experience advisory group has already influenced the participant information sheet, for example, explaining that not all sexual experiences on the web are unwanted and some may be wanted but in fact go wrong; as such, we have reflected this important point in our participant-facing documents. Our advisory groups reviewed and entered key trial documents, including our risk management and distress protocols.

In line with the United Kingdom Government User Research guidelines [31], app development was supported by a series of participatory consultations, which enabled end users to influence the design and functionality of the app, leading to the development of an intervention that we hope is more likely to be acceptable, have better uptake, and be effective. By working together, developers and users can learn and optimize platform functionality, with developers being responsible for pointing out technical options and users providing information about their needs, practices, and how they will use the system.

Statistical Analysis Plan

Because hypothesis testing is not the objective of this study, formal power calculations are not appropriate. The proposed sample size is sufficient to establish feasibility and to report response rates, follow-up rates, safety information, and attrition, as well as the clinical characteristics of our study population at the beginning of the study and follow-up.

Appropriate descriptive statistics (mean and SDs for continuous data; counts and percentages for categorical data) will be used to summarize (1) recruitment and retention data in line with CONSORT statement standards and the extent to which services refer to trial, (2) data use patterns (frequencies; data visualization) using secure software analytics in line with the AMUsED framework for analyzing and measuring use and engagement data in digital interventions [22], (3) completeness of study measures, and (4) the number and nature of adverse events observed over the course of the trial. Pre- and postintervention questionnaire data will be analyzed using the Leeds Reliable Change Indicator [32] or other approaches for the evaluation of reliable or clinically significant changes in secondary outcome measures (eg, when conditions for the application of the Leeds Reliable Change Index are not met) to determine the number and proportion of participants who achieved significant improvement on clinical measures and who achieved no significant worsening of clinical measures at posttreatment. To explore how different participants engage with the app, attrition, and clinical benefit across key demographic groups (eg, LGBTQ+ and BAME) and potential service differences across recruitment sites, we will use descriptive analysis to inform future work; we will not test for differences, as the study is not powered for this.

When a participant has completed a questionnaire but has not completed all elements of that questionnaire, we will use validated instruments and will follow the established procedures for calculating overall scores in the presence of partially missing data.

When data are completely missing for a whole questionnaire, we will record the occurrence of this and, if the prevalence of such missing data permits, use multiple imputations assuming these data are missing at random. We may also, if we think these data may be informatively missing, ie, missing not at random, investigate appropriate sensitivity type analyses to see whether our findings are robust to these missing data.

For qualitative data, we used a qualitative framework approach. Analysis of qualitative interviews will occur alongside transcription and data collection so that we can iterate our topic guide. We initially use the framework method to adopt an inductive approach to theme generation. Subsequent theme refinement will be deductive and guided by the NPT. NPT is a widely used [33,34] theory to explain the processes by which an intervention becomes, or fails to become, normalized into routine practice, and offers a framework for assessing the conditions in which interventions become practically workable in health care. NPT comprises 4 constructs (coherence, cognitive participation, collective action, and reflexive monitoring), which are a set of propositions that we will use to explore perceptions, expectations, attitudes, challenges, and unintended consequences of integrating a digital intervention for YP-TASA in existing NHS service and e-therapy provider pathways. This approach enables us to answer our research questions while allowing important insights to be iteratively produced. The coding framework is then applied to the analysis of subsequent transcripts, with ongoing adaptations as new themes emerge. Data will then be charted into a matrix with illustrative extracts and interpretive themes refined through discussions at regular analysis meetings. We will engage a wider research team, our advisory groups, and stakeholders in the analysis process (member checking or participant verification). This peer verification process (together with member checking) is a recognized method for ensuring the trustworthiness of the data and subsequent findings [35]. Records of field notes will be maintained and reflections providing adjunctive data will be used to illuminate and justify interpretative decisions.

Dissemination

We plan to present our findings at academic conferences and publish them in peer-reviewed academic journals. We also developed a project website [36] which we will keep up to date with study progress. Our social media account will also be used to promote the study, update progress, and disseminate high-level findings. The findings will also be disseminated with support from our advisory groups in a multimedia format at, for example, practitioner and public forums, events (eg,

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conferences, meetings, seminars), and via government and policy events. Feedback to participants and clinical services will be provided through coproduced written summaries.

Results

We aimed to collect data from up to 60 YP. This study was registered as a clinical trial (ISRCTN43130832). Recruitment was initiated in May 2022. We expect to report results for feasibility on (but not necessarily limited to) (1) the number of eligible participants consenting; (2) the total number recruited, including information about recruitment setting to inform sampling strategy of a future definitive trial; (3) completeness of outcome measures; (4) the number lost to follow-up; (5) the number of services offered the intervention; (6) the proportion of participants completing the intervention; (7) dropout rates and reason for withdrawal; (8) platform use and engagement data; and (9) safety of the app and our trial procedures. We also expect to report on differences in engagement and attrition and potential clinical benefits across key demographic groups (eg, LGBTQ+ and BAME), the demographics and service differences across recruitment sites, and the barriers and enablers to integration and uptake into existing mental health care provider pathways. We expect the results to be available at the end of 2023 (subject to recruitment targets and funding requirements).

Discussion

Expected Findings

The aim of our NIHR-funded i-Minds trial was to assess the feasibility, acceptability, safety, and usability of the theory-driven, coproduced, mentalization-based i-Minds app for YP-TASA. Specifically, our primary objectives were to determine (1) whether it is feasible to deliver the i-Minds app for YP-TASA, including recruitment and retention to the trial and identifying primary and secondary outcome measures; (2) whether the i-Minds app is acceptable to users; (3) whether the i-Minds app is usable and safe; and (4) how best to integrate the app into the existing NHS and web-based mental health and sexual abuse service care pathways. To the best of our knowledge, this is the first clinical trial of this type in this population worldwide, which is why we chose to conduct a feasibility clinical trial rather than a powered efficacy trial.

To date, we have carried out a series of qualitative interviews and focus groups with HCPs working with YP in secondary care mental health settings, held regular advisory group meetings with our 3 advisory groups, incorporated input and feedback from this work into the development of the app content and user interface, built and tested the app and met all the security standards required for deployment, and commenced recruitment to the clinical feasibility trial. The user-driven design approach we have adopted in this trial is intended to ensure that the intervention is engaging and relevant and reflects the experiences of YP-TASA. For example, Vichta et al [37] used interactive workshops and a web-based survey to gather YP's perspectives on platform integration into mental health care. Venning et al [38] conducted semistructured interviews and focus groups to explore the acceptability of a low-intensity digital computer-based training platform incorporating a virtual coach with university students and HCPs.

If feasibility for the current approach in this population is found, we will use the results from the nested qualitative study about how our approach can be integrated into a model of care (eg, hybrid, stepped, or blended) to inform the design of the next phase trial, should one be indicated.

Limitations

This study targeted young help-seeking individuals accessing clinical services. It is hoped that these findings could also be useful in YP experiencing distress but not necessarily seeking help or support from clinical services. As this was a pilot study, we were unable to conclude whether the intervention brought about a clinically significant change. However, this study design, with its focus on feasibility, acceptability, safety, and usability, will provide valuable insights that will inform parameters for a future definitive trial, should this be indicated. Moreover, feedback from all stakeholders will allow for improvements in the app, trial procedures, and plans for implementation.

Conclusions

This feasibility clinical trial stands to advance the support for YP-TASA, a nascent area for both research and clinical delivery. Exploring the feasibility, acceptability, usability, and safety of the intervention is the first step in creating a more definitive intervention that may be further tested in future studies and implemented to support YP-TASA across a range of settings.

Acknowledgments

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Data Availability

The data set generated in this study is not publicly available owing to ethical restrictions for personal health information; however, limited, deidentified data may be made available from the corresponding author on reasonable request.

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Authors' Contributions

SB, FV, MS, and EQ conceived the study and, along with KC who secured funding and MM, led the development of the i-Minds app. MM is responsible for engineering the i-Minds app. KC and SB drafted the trial protocols. PW led the participatory design work. KC led the Patient and Public Involvement and Engagement work. SB, MS, FV, and EQ led to the development of the app content. JN provided an overview of the trial design. SB and FV reviewed the clinical aspects of Manchester's study. MS and EQ oversaw the clinical aspects of Edinburgh's study. PC and CR oversaw the clinical management of recruiting sites in Greater Manchester and Edinburgh, respectively. VG provides a Patient and Public Involvement and Engagement overview of the study. SB drafted the manuscript. All authors critically revised the manuscript for intellectual content and approved the final version of this protocol.

Conflicts of Interest

Unrelated to this project, SB and PW are directors and shareholders of CareLoop Health Ltd, which develops and markets digital therapeutics for schizophrenia and a digital screening app for postnatal depression. SB also reports research funding from the National Institute for Health and Care Research and Wellcome Trust. PW is also a Director of Prism Life Ltd, a small research and consultancy company, unrelated to this project.

Multimedia Appendix 1
Schedule of quantitative assessments.
[DOCX File , 14 KB - resprot_v12i1e40539_app1.docx]

Multimedia Appendix 2
Overview of the study objectives and time points of evaluation of each outcome.
[DOCX File , 14 KB - resprot_v12i1e40539_app2.docx]

Multimedia Appendix 3
Summary of topic areas and app features.
[DOCX File , 26 KB - resprot_v12i1e40539_app3.docx]

Multimedia Appendix 4
Screenshots of the i-Minds app.
[DOCX File , 481 KB - resprot_v12i1e40539_app4.docx]

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Abbreviations

BAME: Black, Asian, and minority ethnic
CAMHS: Child and Adolescent Mental Health Services
CONSORT: Consolidated Standards of Reporting Trials
CSA: child sexual abuse
DHS: Digital Health Software
DMEC: Data Monitoring and Ethics Committee
HCP: health care professional
HRA: Health Research Authority
LGBTQ+: lesbian, gay, bisexual, transgender, queer, and others
MBT: mentalization-based therapy
NHS: National Health Service
NICE: National Institute for Clinical Excellence
NIHR: National Institute for Health and Care Research
NPT: Normalization Process Theory
PSC: project steering committee
REC: Research Ethics Committee
REDCap: Research Electronic Data Capture
TASA: technology-assisted sexual abuse
YP: young people
YP-TASA: young people who have experienced technology-assisted sexual abuse

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Protocol

An Electronically Delivered Person-Centered Narrative Intervention for Persons Receiving Palliative Care: Protocol for a Mixed Methods Study

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Abstract

Background: In the health care setting, electronic health records (EHRs) are one of the primary modes of communication about patients, but most of this information is clinician centered. There is a need to consider the patient as a person and integrate their perspectives into their health record. Incorporating a patient's narrative into the EHR provides an opportunity to communicate patients' cultural values and beliefs to the health care team and has the potential to improve patient-clinician communication. This paper describes the protocol to evaluate the integration of an adapted person-centered narrative intervention (PCNI). This adaptation builds on our previous research centered on the implementation of PCNIs. The adaptation for this study includes an all-electronic delivery of a PCNI in an outpatient clinical setting.

Objective: This research protocol aims to evaluate the feasibility, usability, and effects of the all-electronic delivery of a PCNI in an outpatient setting on patient-reported outcomes. The first objective of this study is to identify the barriers and facilitators of an internet-based–delivered PCNI from the perspectives of persons living with serious illness and their clinicians. The second objective is to conduct acceptability, usability, and intervention fidelity testing to determine the essential requirements for the EHR integration of an internet-based–delivered PCNI. The third objective is to test the feasibility of the PCNI in an outpatient clinic setting.

Methods: Using a mixed method design, this single-arm intervention feasibility study was delivered over approximately 3 to 4 weeks. Patient participant recruitment was conducted via screening outpatient palliative care clinic schedules weekly for upcoming new palliative care patient visits and then emailing potential patient participants to notify them about the study. The PCNI was delivered via email and Zoom app. Patient-reported outcome measures were completed by patient participants at baseline, 24 to 48 hours after PCNI, and after the initial palliative care clinic visit, approximately 1 month after baseline. Inclusion criteria included having the capacity to give consent and having an upcoming initial outpatient palliative care clinic visit.

Results: The recruitment of participants began in April 2021. A total of 189 potential patient participants were approached via email, and 20 patient participants were enrolled, with data having been collected from May 2021 to September 2022. A total of 7 clinician participants were enrolled, with a total of 3 clinician exit interviews and 1 focus group (n=5), which was conducted in October 2022. Data analysis is expected to be completed by the end of June 2023.

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Conclusions: The findings from this study, combined with those from other PCNI studies conducted in acute care settings, have the potential to influence clinical practices and policies and provide innovative avenues to integrate more person-centered care delivery.

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KEYWORDS

electronic health record; mixed methods; narrative; person-centered care; palliative care

Introduction

Background and Rationale

Health care advances have extended the life span and cured many diseases; however, advanced health care treatments are sometimes discordant with patient preferences, values, and beliefs, which can lead to insufficient symptom control, difficult patient-clinician interactions, and poor psychosocial and spiritual support [1-3]. Furthermore, poor patient-clinician communication contributes to continued unwanted care. A comprehensive palliative care approach improves communication, leading to better quality of life (QoL) for patients [4-6]; however, discordant care continues in part because of knowledge gaps about patients' psychological, social, and spiritual needs [7-10]. Person-centered narrative interventions (PCNIs) can fill these knowledge gaps [11-20], yielding an increased understanding of patients' psychological, social, and spiritual needs, which will help clinicians develop tailored palliative care interventions.

Storytelling (narrative) is an effective way for patients to communicate their cultural values and beliefs. As early as 1542, when Joannes Fernel coined the term physiology, the discussion at that time described the person as a structure of physiological, pathological, and clinical stories [21]. However, in the health care system, patients do not always have the opportunity to share their clinical stories with their clinicians [3,22-26]. Furthermore, even if patients have the opportunity to discuss values, beliefs, and preferences for care, some research has described treatment errors that may occur when clinicians overlook contextual information in a clinic visit. These treatment errors are known as contextual errors [27-29] and are defined as a "decision making error that occurs because of inattention to patient context" [29].

In the health care setting, the electronic health record (EHR) is one of the primary ways of communicating the status of patients; however, most of this EHR information is clinician centered. There is a need to consider the patient as a person and integrate their perspectives into their health record. Incorporating a patient's narrative into the EHR provides an opportunity to communicate patients' cultural values and beliefs to the health care team and has the potential to improve patient-clinician communication [30,31]. However, research on the effective integration of a patient's narrative into the EHR is limited. PCNIs that incorporate cultural values and beliefs are important components of person-centered care [14,31]. Person-centered care includes implementing shared decision-making, providing holistic patient care with respect for patients' preferences and goals, paying attention to nonmedical aspects of care, facilitating communication, knowing the patient as a person, and understanding culture, which influences health behaviors and the meaning of illness [3,14,22-26]. Quality communication is a critical element of person-centered care [3,32,33]. Story theory can be applied to person-centered care because of its foundation in "meaning making" built on promoting intentional dialogue, creating ease, and connecting with self-in-relation [34]. Using the foundation of story theory, patient narratives about illness experiences offer clinicians a view of patients' cultural attitudes about their illness and their psychological, social, and spiritual beliefs and values [14,31]. When a clinician knows more of the patient's narrative, improved quality of communication may occur, which can create opportunities for culturally congruent care with the potential to improve QoL for persons living with serious illnesses [3,32,33]. The PCNI is an example of how story theory might be applied to the fragmented health care system. However, in the current health care environment, limitations on a clinician's time prevent these opportunities to better understand what may or may not improve QoL for persons living with serious illness. A narrative intervention implemented with persons living with serious illnesses can draw together the complexities and varied cultural meanings of illness experiences, and this can improve QoL [3,14,32,33]. Patient participation in narrative interventions has been linked to reduced pain, stress, anxiety, and fatigue and improved psychosocial and QoL outcome measures [15-20].

The integration of the PCNI into the EHR could benefit patients and clinicians interacting in technology-rich environments. Because the EHR is one of the primary modes of communicating health care information about the patient, the integration of patients' narratives into the EHR has the potential to (1) improve person-centered care by incorporating patients' values and beliefs, (2) provide opportunities to enhance patient-clinician communication, and (3) positively impact patients' psychosocial and spiritual well-being. Minimal research has integrated narrative interventions into the EHR in a meaningful and efficient way to test whether the narrative intervention could improve communication between patients and clinicians and impact patients' overall well-being. Our research program investigates innovative ways to integrate patient values, beliefs, and preferences into EHR through PCNIs [14,31]. A *central hypothesis* that guides our research is that the implementation of a PCNI will result in improved patient-clinician communication and care delivery and improve patients' psychological and social well-being. We have conducted prior studies of PCNI in an acute care setting where the intervention was conducted in a face-to-face interaction [14,31]. However,

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owing to the COVID-19 pandemic, there is an urgent need to investigate innovative internet-based–delivered ways to incorporate the patient's narrative into their health care record. In our fragmented health care systems, the lack of personhood in delivery of care has been linked to decreased QoL for persons living with serious illness [32,34-38].

Study Context

We developed a PCNI to address existing gaps in the delivery of person-centered palliative care**.** Our first study on this PCNI used a narrative analysis methodology to elicit illness narratives to aid in understanding patients' psychological, social, and spiritual experiences [37]. This led to a crucial clinical question: how might these person-centered narratives be shared efficiently and effectively with the health care team? Although the use of narratives is an effective way for people to communicate cultural values and beliefs [3,32,33], patients rarely have the opportunity to share such information with their clinicians [4,7,39,40]. Within the health care system, EHR is the primary mode of communicating patient information [30,31]. Thus, incorporating a person-centered narrative into the EHR is an opportunity to share patients' values, beliefs, and preferences, with the potential to improve patient-clinician communication and well-being [14,31,37]. Our second study, a feasibility study, used the Consolidated Framework for Implementation Research (CFIR) [41] to define and refine the integration of the in-person delivery of PCNI into the EHR for persons with serious illness in the inpatient acute care setting [14]. Findings from the second study showed that the PCNI was (1) feasible and acceptable for all 20 hospitalized persons and (2) usable by acute care nurses [14]. Implementation data from our initial feasibility study revealed the ways in which PCNI is valuable and usable for clinicians. The PCNI's added value in nursing care is when the nurse manager of one of the clinical units began reading the person-centered narratives aloud to her entire staff at shift handoffs. We also found value added for the entire health care team when 1 of the person-centered narratives was read during an ethics consultation. The ethics consultation was initiated owing to patient noncompliance and stated the desire to leave treatment against medical advice. Once they heard the person-centered narrative read during the consultation, the health care team realized why the patient was trying to leave before the proposed surgery—he needed to see his 2 daughters, who lived in another state, beforehand. We are currently conducting a third study, a 3-year mixed methods pilot study in the acute care setting [31]. Our long-term goal is to optimize the use of PCNIs by investigating how and in what context they are effective in improving patients' overall well-being and quality of communication with their clinician. A challenge for any biobehavioral intervention is translation across complex health care contexts [42]. Because our in-person–delivered PCNI has been shown to be feasible and to demonstrate preliminary efficacy in the acute care setting, we aim to purposefully enroll participants in the outpatient setting and use an all-internet-based delivery of the PCNI to further evaluate implementation in a new setting and use an all-internet-based delivery—from email recruitment, electronic consent, and Zoom narrative interview to electronically delivered outcome measures.

Objectives

In this protocol, we aim to further develop the continued testing of the feasibility and efficacy of the EHR integration of PCNI in an outpatient setting using an all-internet-based–delivered platform. The first objective of this study is to identify barriers and facilitators of an internet-based–delivered PCNI from the perspectives of persons living with serious illness and their clinicians. The second objective is to conduct acceptability, usability, and intervention fidelity testing to determine the essential requirements for the EHR integration of an internet-based–delivered PCNI. The third objective is to test the feasibility of the PCNI in an outpatient clinic setting.

Methods

Study Design

This study will use a mixed methods design [41,43-45] and collect data from both patient and clinician participants. Our study relies on the CFIR [41,45] to inform the implementation of this single-arm trial across the 2 years of the study. This is a novel approach that documents what affects implementation in a new context of outpatient clinical care with a protocol that is all delivered electronically. The CFIR is a conceptual framework developed to guide multilevel assessment of factors that may influence an intervention's implementation and effectiveness [41,45]. The core CFIR domains are (1) intervention characteristics, (2) inner setting (ie, implementing organization), (3) outer setting (ie, external environment), (4) individual characteristics (ie, knowledge and beliefs of the individuals involved in the implementation), and (5) processes (ie, strategies and tactics used in the implementation [41,45]). Within each domain, specific constructs may influence the implementation. Constructs in the proposed taxonomy of implementation outcomes have the potential to capture clinician attitudes (acceptability) and behaviors (adoption and uptake) as well as contextual factors (system penetration, appropriateness, and implementation).

In this phase of our biobehavioral interventional development, both quantitative and qualitative data give necessary information about acceptability, feasibility, and usability for the optimization of the narrative intervention. Quantitative data include longitudinally measured patient-reported outcomes, and qualitative data include (1) patient and clinician exit interviews for triangulation of the quantitative findings and (2) patients' illness narratives. All data collection and study procedures will be conducted electronically, using secure videoconference, phone, REDCap (Vanderbilt University) [46] surveys, and electronic consent forms. Evaluating the barriers to and facilitators of the implementation of the adapted internet-based delivery of PCNIs is essential for effective translation to practice. Such a design is particularly salient when conducting studies with a palliative care population [47-49] to collect a broad range of data. For example, our qualitative data will provide a deeper understanding of the barriers to and facilitators of the intervention from participants' perspectives not captured through the traditional quantitative measures [50-52]. We will analyze key implementation facilitators and challenges and link these to the outcomes [51]. This work will result in an

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evidence-based set of core functions and forms of this complex intervention into complex health care systems by providing recommendations to guide future PCNI implementation across different health care settings [53-55].

Participants

Purposeful sampling strategies will be used to recruit and enroll 20 patients. The small sample size was chosen to be consistent with both qualitative data analysis techniques [50] and usability data analysis techniques [56,57]. Patient participants (N=20) who are aged ≥18 years (no upper limit), able to read and speak English, and capable of providing informed consent will be enrolled in the study. Owing to the feasibility of this study, we allowed participants to enroll at any stage of illness or symptom acuity. These participants will be newly establishing care at one of the University of Colorado Hospital (UCHealth) outpatient palliative care clinics (Outpatient Palliative Care Clinic and Supportive and Neuro-Palliative Medicine Clinic). The clinician participants (N=10) will be members of the outpatient palliative care interprofessional team, which includes physicians, advanced practice clinicians, registered clinicians, social workers, and a spiritual care clinician. These clinician participants will be included if they are able to confirm verbally that they were involved in the outpatient palliative care of a patient participant.

For the patient participants, the research team will review the outpatient palliative care clinic schedules weekly via the EHR (Epic) to identify persons with upcoming initial new patient visits (NPVs) in the palliative care clinics. These identified persons will receive an initial recruitment email with an institutional review board–approved language and a follow-up email with the initial language approximately 1 week later for those who have not responded. For those who respond to the recruitment email with interest, the research team will arrange a secure videoconference or phone call to discuss the study, review the consent form, and answer questions. When a person opts to participate, the research team will send an email with a link to the electronic consent form (in REDCap) [46] and instructions for completing the consent. It should be noted that persons are contacted approximately 4 weeks before their NPV to facilitate ample time for pre-NPV study activities.

For the clinician participants, the research team will identify the assigned clinician of the enrolled patient participant, once the patient's narrative is uploaded to the EHR. In the same electronic delivery, the research team will contact these clinicians via email to (1) alert them that a narrative was available for one of their newly establishing patients and (2) inquire about their interest in participating in the study using institutional review board–approved language. Because of the nature of the feasibility and usability study, we targeted recruitment efforts to capture the entire interprofessional perspectives of the palliative care clinical team members. For those who respond to the recruitment email with interest, a research team member will arrange a secure videoconference or phone call to discuss the study, review the consent form, and answer questions. When a clinician opts to participate, the research team will send an email with a link to the electronic consent form (in REDCap) [46] and instructions for completing it.

Procedures

Ethics Approval and Data Privacy

All procedures were approved by The University of Colorado Institutional Review Board (Colorado Multiple Institutional Review Board 21-2887), and the approval has been maintained in good standing. REDCap is available as a Health Insurance Portability and Accountability Act–compliant secure research data interface [46]. Web servers routinely use secure socket layer encryption technology and certification authority to ensure the secure transmission of data over the internet. To facilitate secure file sharing between research team members, we will establish internet-based private networks and create sponsored user accounts for all study personnel. All research data files are stored on dedicated, password-protected, access-controlled, and shared drives. Safeguards for protecting participants' anonymity will include creating a master list of names with corresponding numbers assigned to participants at the time of the enrollment. Once assigned, the corresponding numbers will then be used to deidentify the remainder of the participants' personal information and each participant's data. Electronic consent forms, participant identity, and participant data will be securely stored on a password-protected network server. Participants will only be identifiable by an ID number on the server, and only anonymized data will be provided to the data analysis team members. The potential for breach of confidentiality is being addressed through the maintenance of a secure "log-on" system on the secure computer server dedicated to this protocol.

All participants will be compensated for their time. Patient participants will be provided a US $25 electronic gift card after the completion of PCNI and time point 2 and a second US $25 gift card after the completion of time point 3 for a total of US $50 in remuneration. Clinician participants will be provided one US $25 electronic gift card after the completion of the exit interview. In addition to the confidentiality of patient data, there are some minimal physical, social, or psychological risks to the patient participants. Participants could become fatigued during the 60-to-90–minute narrative interview process, the 30-minute exit interview process, outcome measure data collection procedures. In the event of fatigue, the research team members will encourage rest periods or, if necessary, schedule an additional study visit to complete the interview. For the patient participants, there is a minor, moderate, or severe risk of psychological distress because of the sensitive topics of serious illness. Because of the feasibility of the design, we will ensure that the patient participants understand both orally and in writing that they are free to decline participation in any or all study activities at any time based on their own level of distress [58,59]. This could include declining to answer specific questions, refusing participation in the intervention, requesting to speak off the record, or requiring complete withdrawal from the study. We did not apply a specific tool for distress screening; rather, we will give frequent reminders to the participants about the voluntary and autonomous nature of the study, for the participants to determine if the study activities are too distressing for them at any level (mild, moderate, or severe). If any of the interview or psychometric assessment data reveal increased participant distress, dissatisfaction, or any adverse event, the data collection will cease. If the participant exhibits any verbal

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or nonverbal distress, the research team member will allow the participant to stop the interview, reschedule for a return visit to complete the interview, or allow participants to withdraw consent. If moderate distress is exhibited, the research team member will assist in referring participants to emotional support through family, friends, or the health care team for the follow-up related to the participant's distress. If distress is severe, such as suicidal ideation, the research team member will immediately refer the patient for further work-up and care. The research team members will carry a list of contact phone numbers for such referrals. If any moderate or severe distress is noted, it will be reported immediately to the principal investigator to help determine if the event meets the criteria for a reportable adverse event. If deemed a serious adverse event, the institutional review board will be notified, and the participant's involvement in the research study will be discontinued. In a previous study using this methodology, none of the adverse events occurred. Therefore, we anticipate these risks to be rare events, given the nature of the data collection procedures.

The PCNI Procedure

The enrolled patient participants will participate in a narrative interview. These audio-recorded interviews will be conducted by a research team member using an open-ended interview guide. During the interview, patients will be prompted to share their narrative through probing questions or statements such as: tell me about your illness; tell me how your illness has affected your emotions, your relationships, and your spirituality (Textbox 1 lists the interview questions). These probing questions have been field tested in 3 previous studies. As the patient responds, the research team member will take field notes and ask for follow-up or clarification questions as necessary. Using the audio recording and field notes, the research team member will then create a 1-to-3–page metanarrative. Each narrative must meet the following criteria: it must (1) be written in the patient's first-person voice, (2) be nonjudgmental, (3) capture the patient's voice, (4) accurately reflect the content of the interview, and (5) nondiagnostic (not labeling). The patient narrative is then returned to the patient within 48 hours for member checking, the cocreation phase of the PCNI. In this electronically delivered protocol, at the time of member checking, the patient will make any desired changes to the narrative on their own or during a follow-up session with the research team member. These sessions will facilitate the cocreation of the narrative. Once the narrative is approved by the patient, the research team will upload it to the patient's EHR and alert the patient's assigned clinician via email that their patient's narrative is available in the patient's health record. The workflow diagram is depicted in Figure 1.

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Textbox 1. Interview guides for narrative and exit interviews.

Narrative intervention interview guide

- Conversational questions
  - May I call you?
  - What is your illness?
- Conversational probes throughout intervention
  - For example
  - Tell me more about that
  - Anything else?
- Open-ended questions
  - Tell me what it has been like to have _____ (illness).
  - Tell me how your illness has impacted you emotionally, your feelings?
  - Tell me how your illness has impacted your relationships with family, friends, and others?
  - Tell me how your illness has impacted your spirituality? Your faith, beliefs, your values, or your thoughts about a higher power?
- Closing question
  - Is there anything else we have not talked about that you would like to tell me?

Exit interview guide: patient participants

- Describe what you liked about participating in this study.
- Describe what you did not like about participating in this study.
- Did you have the opportunity to discuss your story with anyone other than the research team?
  - *If yes, follow-up questions*
    - Who did you discuss it with?
    - Did you initiate the conversation, or did they?
    - Describe which parts of the story you discussed.
    - How did this discussion make you feel?
  - *If no, follow-up questions*
    - Why do you think others did not discuss it with you?
    - Why did not you discuss it with others?
- Is there anything you would have changed about the study?
- What would you think about participating in a similar intervention in the future?
- Is there anything else you would like us to know?

Exit interview guide: clinician participants

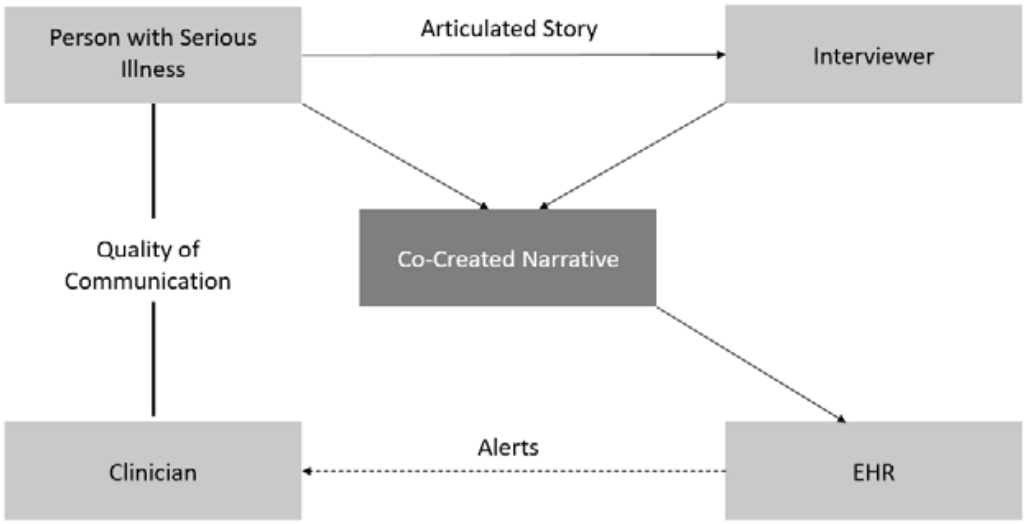
- What did you think about the intervention?
- Were you able to read the patient's story?
- Do you think the study was beneficial to the patients?
- Did you notice any particular patient reactions to the intervention?
- Was the study beneficial to you in any way?
  - *If yes, follow-up questions*
    - Describe what was beneficial to you.
  - If no, follow-up questions

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- Describe what was not beneficial to you.
- What changes could we make to the study for it to be more beneficial to you?

- Do you feel like having the patient's story changed how you delivered care to your patient?
  - *If yes, follow-up questions*
    - Can you provide an example?
  - *If no, follow-up questions*
    - Are there changes we could make that would help with this?
- Did the notification system of the story in the medical record work for you?
  - *If no, follow-up questions*
    - How could the notification system be improved?
- Were there any other study difficulties that you encountered that I have not asked you about?
- Are there improvements to the intervention that you would suggest that we have not already discussed?
- Is there anything else you would like us to know?

Figure 1. Person-centered narrative intervention (PCNI) workflow figure. EHR: electronic health record.



Outcome Evaluations of the PCNI

Usability Testing

Using a human, organization, and technology–fit factor [53] evaluation framework for health information systems, we will collect data across several usability factors. Usability is defined as the relationship between humans and computers [53]. Usability testing [53,56,57,60] focuses on evaluating process measures based on 4 major components: user (clinician), task (use of metanarrative), system (metanarrative in EHR), and environment (outpatient setting). This user-task-system-environment framework of process measures [61] will be incorporated into our usability testing to determine barriers and facilitators from the clinician's perspective, and to help determine the essential requirements for integrating the narrative intervention into the EHR by evaluating information flow, use of information, and system functionality. The process measures collected to determine usability will include (1) chart review and log analysis of the clinical use of the patient's story; (2) time and cost analyses of collecting the story, writing and cocreating the metanarrative, and uploading the final metanarrative into the EHR; and (3) exit surveys and interviews with both patient and clinician participants.

Intervention Uptake and Attrition

We will also analyze the intervention uptake and attrition between baseline and follow-up data collection points [47-49]. Uptake (acceptability) will be assessed using descriptive summaries examining acceptors among people approached for recruitment. The number of dropouts, reasons given, and the

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timing of withdrawals from the study will also be reported. When possible, patient participants who drop out will be provided with a 1-page query about why they left the study. Feasibility will be examined by examining operational issues, namely, staff time spent or issues with recruitment, EHR use, or training. Identified issues will be noted in project logs to guide future studies. These are critical steps for evaluating scalability for the successful implementation of PCNIs in other complex systems. This approach incorporates the human, organization, and technology–fit [53] factors for the successful implementation of PCNIs.

Patient-Reported Outcomes

The primary patient-reported outcome measures for this protocol are the PROMIS (patient-reported outcomes measurement information system)-29 Profile v2.0 form [62] and PROMIS Psychosocial Illness Impact [63]. The PROMIS-29 profile v2.0 form consists of 29 items that assess physiological, social, and psychological outcomes. These biopsychosocial domains include physical function, anxiety, depression, fatigue, sleep, the ability to participate in social roles or activities, and pain interference and intensity. The PROMIS Psychosocial Illness Impact measure consists of 16 items that assess the negative and positive aspects of the illness experience. The PROMIS positive item bank measure (8 items) assesses the positive psychosocial outcomes of illness. Positive psychosocial illness impacts refer to outcomes, such as greater life appreciation, interpersonal relationships, and personal resources, that can occur because of confrontation with one's mortality. The PROMIS negative item bank measure (8 items) assesses the direct negative psychosocial effect of illness, distinct from general emotional distress. All PROMIS measures have established reliability and validity. At baseline, demographic information will also be collected from patient participants, including age, biological sex, gender, race and ethnicity, perceived illness severity, years of education, income, marital status, religion or spirituality preference, and clinical details (to identify comorbidities and severity of illness).

The primary outcome measures for the patient participants will be collected across 3 time points. After enrollment, the research team will generate participant-specific survey links in REDCap [46] and email them to the participants to complete the demographic survey and the baseline (time point 1) outcome measures (Table 1). Outcome measures could also be collected by phone, if preferred by the participant. At a mutually scheduled time, the participant and a research team member will meet on a secure videoconference to conduct and audio record the PCNI interview, as described previously in *The PCNI Procedure*. Within 48 hours after the narrative is uploaded into the EHR, participants will complete time point 2 outcome measures using the same process described for time point 1. Time point 3 will be completed 1 month after the narrative upload and the NPV. Finally, after time point 3, the research team will conduct exit interviews with patient participants at the end of their study participation to collect information about their experience, including suggestions for improvement (Textbox 1 lists the interview questions).

For the clinician participants, the research team will conduct exit interviews with clinician participants within 2 to 4 weeks of their initial appointment with a patient participant to collect information about their experience of having and using the patient narrative before the initial consult. At the end of study enrollment, 1 to 2 audio-recorded focus groups (based on scheduling needs) will be cofacilitated by research team members with all the clinician participants to collect additional information and feedback about their experience and facilitate and record group discussion about their use of the patient narratives in their clinical practice. Interviews will be conducted via a secure videoconference or a phone call and audio recorded. See Table 1 for participant study activities.

Table 1. Participant study activities.

Participant	Outcome	T1: baseline (prenarrative upload)	T2: 24-48 hours after T1 (postnarrative upload to EHR[a])	T3: 1 month after T1
Patient	Biopsychosocial and spiritual well-being	• PROMIS[b]-29-Profile • PROMIS Psychosocial Illness Impact; positive and negative effects	• PROMIS-29-Profile • PROMIS Psychosocial Illness Impact; positive and negative effects	• PROMIS-29-Profile • PROMIS Psychosocial Illness Impact; positive and negative effects
Patient clinician	N/A[c]	• N/A	• N/A	• Exit interviews

[a]EHR: electronic health record.

[b]PROMIS: patient-reported outcomes measurement information system.

[c]N/A: not applicable.

Data Analysis

Quantitative Analysis

Analyses will be performed using SAS software (version 9.4; SAS Institute Inc) [64]. Analyses will be primarily descriptive to determine the feasibility of collecting patient-reported outcome data in this setting (ie, data completeness) and summary statistics and distributional characteristics of those outcomes. Data will be inspected for errors and outliers. Data completeness will be summarized in terms of missing responses across the 3 data collection time points (ie, percent attrition at each follow-up) as well as missing item responses within each measurement period (ie, inspection of item-level missing data patterns). A high level of retention (>90%) across follow-up waves is expected based on previous research in an inpatient setting [14]; however, this will be empirically investigated. Missing responses at the item level are similarly expected to be low, but if present, they will provide information on potential

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response fatigue or problematic items. Baseline demographics and outcome measures at all 3 waves will be summarized using standard descriptive statistics (eg, mean, SD, and range). Preliminary testing of the outcome measures for change from baseline, T2, and T3 will be analyzed in a repeated measures framework (time effect in mixed effect model) to evaluate the effects of the intervention on the individual patient participant's patient-reported outcomes of the PROMIS 29 Profile and PROMIS Psychosocial Illness Impact. This single-arm study is not powered to evaluate the statistical significance of changes in patient-reported outcomes over time; however, distributional characteristics of outcomes and effect size estimates of mean change will be useful for informing a larger-scale randomized trial.

Qualitative Analysis

Qualitative data management software will be used to organize narrative and exit interview data and coding by team members. Notes and transcripts will be collated to provide summaries of patient flow, use of equipment and supplies, perspectives on the PCNI, and ideas about its integration into current practice. A conventional content analysis approach [50-52] will be used to analyze the observations and interviews, and a category system will be created based on the CFIR domains to create a codebook [41,45] (with new codes added if needed). Obtaining data from a variety of interviewees allows for triangulation of data sources to support qualitative rigor. Triangulation of data will also occur between narrative interview data and exit interview surveys to better understand PCNI implementation fidelity and to identify any potential or needed modifications. The research team expects that the outcomes of this analysis will inform the next steps of PCNI integration as we move to implementation at future sites and for future studies. The information gained through this analysis will be used to provide a greater empathetic view of what is currently offered and what matters most to patients and clinicians, as they offer and integrate new evidence-based practices or interventions. We will extract contextual factors (events or statements) from observations (study notes) and interviews to document what facilitates or acts as a barrier to implementation (eg, challenges, resolutions, and the impacts of champions and naysayers). Quantitative data, from patient logs of session completion and the tracking database, will be integrated with qualitative data from observations and transcripts of semistructured interviews with patient participants and nurse participants. Triangulating our data sources will allow us to corroborate the evidence, prevent researcher bias in interpretation, and increase the confirmability of our qualitative data. The first round of coding will be guided by the CFIR domains and constructs [41,45], which include (1) intervention characteristics, (2) inner setting (ie, implementing organization), (3) outer setting (ie, external environment), (4) individual characteristics (ie, knowledge and beliefs of the individuals involved in the implementation), and (5) process (ie, strategies and tactics used in the implementation). Within each domain, specific constructs may influence the implementation. We will also capture emergent themes in the data (the inductive component) [43], which will allow for the discovery of themes not included in a priori CFIR codes. We will follow an iterative process, whereby the analysis will begin at the time of the first observation and will inform the direction and content of future data collection. Research team members will code the data independently and discuss it with other team members. To maximize convergence in coding [43], the team will meet regularly during data collection and analysis to review emerging themes, reconcile differences in coding, and determine whether modifications to the interview guide are needed for the remaining interviews. Discrepant interpretations [43] of the interview data during the coding phase will be resolved by consensus during team meetings. We will maintain an audit trail [50] to document all coding and analytic decisions made during the study. We will conduct between-case analysis to compare cases to look for similarities in processes promoting implementation among similar cases and differences in processes promoting sustainment among different cases [43]. We will analyze coded data by constructing causal diagrams that link the coded elements, logically minimizing the diagrams to produce a parsimonious set of pathways, and using explicit decision rules to guide the analysis [43,55].

Results

The study received funding in January 2021, and ethics approval was received on March 21, 2021. The recruitment of participants began in April 2021. Patient participant recruitment was conducted via weekly screening of the outpatient palliative care clinic schedules for upcoming new palliative care patient visits, and emails were sent to potential patient participants. At this time, some data have been collected and analyzed. A total of 189 potential patient participants were approached via email, and 20 patient participants were enrolled, with data having been collected from May 2021 to September 2022. A total of 7 clinician participants were enrolled, with a total of 3 clinician exit interviews conducted in 2021 and 2022 and 1 focus group (n=5) conducted in October of 2022. Data analysis has been ongoing from the end of data collection in October 2022 to June 2023. Overall, for this feasibility study, we were able to recruit a total of 20 patient participants and 7 clinician participants for data collection. In the initial findings, the electronically delivered person-centered narrative was feasible, acceptable, and usable for both patient and clinician participants. The overall findings are expected to be submitted for publication by the end of June 2023.

Discussion

Overview

Although PCNI is not new [14,31], it has never been studied in an outpatient setting and completed via an all-electronic, internet-based–delivered protocol, a necessity to implement in our postpandemic world. Keeping the safety of all at the forefront in the setting of a continued global pandemic, it was necessary for the PCNI to be evaluated on an electronically and internet-based–delivered platform. In comparison with our previous studies on PCNI [14], the all-internet-based–delivered platform to conduct the study activities and collect person-centered narratives did have some challenges.

Using the CFIR as our framework [41,45], we encountered some implementation challenges. In the CFIR domain of the

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intervention, we did not change any components of the institutional review board–approved person-centered narrative interview conducted in the Zoom app (Zoom Video Communications Inc). We did not change anything from the domain of the inner setting. The entire study was conducted in the outpatient clinic population of persons with serious illnesses who were having an initial palliative care visit. It was feasible to cocreate the PCNI and upload the PCNI before all the initial palliative care visits of patients, with the exception of 1 patient participant. For future studies, there needs to be ample time between narrative interviews and a person's initial visit to the palliative care team. Alternatively, narrative interviews could be conducted at any time of a person's clinical care without the need for the narrative to be uploaded before a patient's initial visit.

In contrast to our acute care studies [14], we did not realize the longer time required to complete the member checking of the cocreated narrative. This process took an average of 5 days versus an average of 48 hours in our acute care studies. This increased time links to the CFIR domain of the outer setting. Persons were not as acutely ill as in the acute care studies of the PCNI. The outpatient participants spent more personal time changing, adding, or adjusting their cocreated narratives. Therefore, the individual characteristics of this outpatient population were distinctly different from those of other patients who are hospitalized in our previous studies. Because these patient participants were also active in their home environments and not hospitalized, additional time was required to obtain the second Zoom app–facilitated session scheduled for the member-checking step of the PCNI review and the approval of their narrative before the narrative was uploaded into the EHR for the clinical team.

In the last CFIR domain of process, we implemented several strategies and tactics for the successful implementation. As we began email recruitment and electronic consenting, we chose not to enroll any patient participant who was noted to have a medical diagnosis of Alzheimer disease or dementia, or terms of cognitive impairment, confusion, or delirium on their problem lists. For this study, this screening excluded 20% of persons with a new patient palliative care visit. At this stage of data analysis, we would suggest that future PCNI programs should consider cognitive impairment. In future studies, the need for a mental capacity screening can be an important consideration. Alternatively, in future studies, the PCNI would need to consider the cognitive capacity of persons who have a serious illness and include a person's support individuals to be a part of a dyadic PCNI. It should be noted that the integration of the PCNI into an outpatient palliative care clinic provides systematically more time for palliative care clinicians to engage with the narrative based on the allowed new palliative care patient visit time allotment of 1 hour. In future studies in other clinical settings that are nonpalliative, the acceptability and usability of the person's narrative will require clinical workflow evaluations of the best strategies for allowing the nonpalliative clinician adequate time to engage with the person's narrative. As in our other PCNI studies, once a patient participant is enrolled, there are limited withdrawals. Only 1 participant reported mild distress with the narrative interview questions that were being asked and made a choice to withdraw from the study.

Finally, although the overall goal of the PCNI is to consider the improvement of the quality of communication in clinical care, for this protocol, the quality of communication is being analyzed by exit interviews with both patient and clinician participants. In our other PCNI study [14], the quality of communication measure has been used [65]. However, in this study, the patient participants were enrolled before NPVs with the palliative clinical team. Therefore, we were unable to quantitatively measure any changes in the quality of communication between the patients and palliative care clinicians. For future studies of PCNIs, the consideration of not timing the PCNI before an NPV should be considered.

Limitations

There are known limitations to our mixed methods single-intervention feasibility study. First, it was conducted in 1 geographic location in 1 health care system. This is an important consideration when considering the contextual complexities of health care systems, their EHRs, and the clinical workflows of clinicians. Second, owing to the nature of the internet-based delivery in this study, this study excluded participants who did not have access to email and technology with an internet connection. During the screening for this study, 11 patients did not have email addresses. Therefore, email should not be the only recruitment method. One would need to add an in-person recruitment approach to capture potential participants who do not have an EHR-listed email. During this in-person session in the clinical setting, one could also verify a person's technology needs and preferences. If the preference or need for technology was identified, the opportunity to conduct the PCNI in person in the outpatient clinical setting could also be used. In this study, participants who expressed less agility with technology were offered more detailed instructions ("click-by-click") or additional phone calls during which the research team member could help them navigate the required systems.

Conclusions

This 2-year feasibility study will provide a site-specific understanding of barriers to and facilitators of the usability and acceptability of the PCNI from the perspectives of both patient and clinician participants. These barriers and facilitators in the setting of a CFIR framework will provide important knowledge about the scalability of the intervention, process-oriented insights, successful implementation strategies, and modifications that are necessary to improve the integration of a person's narrative into the clinical workflow for clinicians. The overall long-term research goal is the creation of a PCNI that could be broadly applicable and sustainable outside of the research setting, with implementation in a variety of health care settings in multiple health systems. The knowledge gained will provide necessary information to evaluate future ways to scale PCNIs, with the goal of implementation across health systems, and will continue to inform the integration of person-centered narratives into the patient's EHR. This feasibility study will provide important information to fully understand the mechanisms of the effects and concurrently contribute to additional knowledge

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of the key factors of implementation. The knowledge gained from this mixed methods study will contribute to key data for the continued development and refinement of PCNIs.

Acknowledgments

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Data Availability

The data sets generated and analyzed during this study are not publicly available owing to patient participant confidentiality but are available from the corresponding author upon reasonable request.

Authors' Contributions

All authors made substantial contributions to the design of the work, participated in revising this document critically, provided final approval of the version to be published, and agreed to be accountable for the work.

Conflicts of Interest

None declared.

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Abbreviations

CFIR: Consolidated Framework for Implementation Research
EHR: electronic health record
NPV: new patient visit
PCNI: person-centered narrative intervention
PROMIS: patient-reported outcomes measurement information system
QoL: quality of life

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Protocol

Sexual Health Outcomes of Adolescent and Young Adult Colorectal Cancer Survivors and Their Partners: Protocol of a Dyadic Mixed Methods Study

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Abstract

Background: Sexual dysfunction represents a critical aspect of quality of life for adolescent and young adult cancer survivors. Studies have consistently documented that adolescents and young adults report greater psychological and physical morbidity than older survivors and healthy peers, including elevated rates of sexual dysfunction, often accompanied by lower satisfaction with sex life and delays in meeting sexual milestones. Moreover, sexual dysfunction, body image concerns, and fertility status affect their confidence in being both physically and emotionally intimate. Despite this evidence, limited research has investigated the influence of psychosocial and interpersonal factors on sexual health outcomes reported by this group. This constitutes a significant gap in the provision of comprehensive sexual health care for adolescent- and young adult–onset cancer survivors, especially since greater emphasis has been recently placed on the biopsychosocial model of sexuality and dyadic approaches to intervention and treatment. In comparison to other cancer types, the incidence of colorectal cancer (CRC) has been increasing at an alarming rate for the adolescent and young adult group. Patients with early-onset CRC experience elevated rates of sexual dysfunction, psychological distress, and social and physical burden, often resulting from issues with bowel control, incontinence, and body image.

Objective: This study uses an explanatory sequential mixed methods approach to (1) characterize sexual function, sexual distress, dyadic coping, infertility-related distress, relationship and mental health outcomes of adolescent and young adult CRC survivors within the first 5 years post diagnosis and their partners; (2) examine the reciprocal influence of sexual function and dyadic coping behaviors on sexual distress; and (3) identify interpersonal or couple characteristics associated with coping with sexual dysfunction and its associated distress.

Methods: Participating couples (n=60) will complete a quantitative web-based survey investigating sexual function, sexual distress, dyadic coping, infertility-related distress, emotional functioning, relationship satisfaction, and body image (cancer survivors only). A subset of 20 couples will participate in an in-depth dyadic interview with 2 members of the research team to further explore couple-based strategies implemented to cope with cancer-related sexual dysfunction and distress.

Results: The study received institutional review board approval. Recruitment and enrollment of couples began in July 2022.

Conclusions: Results will provide a deeper understanding of the challenges couples experience as they navigate sexual intimacy after CRC treatment by highlighting the role of interpersonal processes. These findings will inform a dyadic intervention for young couples at risk of greater sexual distress in the aftermath of CRC.

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KEYWORDS

adolescent and young adult; colorectal cancer; oncology; cancer; couples; dyadic research; dyad; sexual health; sexual dysfunction; reproductive health; infertility-related distress; mixed methods design; mixed method; adolescent; adolescence; young adult; infertility; fertility

Introduction

Background

Cancer-related sexual dysfunction is one of the most common and distressing consequences of the illness, which, if untreated, persists or worsens over time [1-4]. Among adolescents and young adults—individuals aged between 15 and 39 years at diagnosis—a considerable body of research has unveiled unique challenges [5,6] including disruption of normative physical, psychosocial, and emotional development, which can lead to sexual dysfunction [7-13]. Studies have consistently documented that adolescents and young adults report greater psychological [14,15] and physical morbidity [5,6,16] than older survivors and healthy peers, including elevated rates of sexual dysfunction [11,13,17-21] often accompanied by lower satisfaction with sex life [22-26], delays in meeting sexual milestones [21,27,28], and reduced frequency of sexual activity [21,27]. Between 42% and 52% of adolescent and young adult survivors experience 1 or more sexual problems [12,13,29], with one-third of them reporting worse sexual function up to 2 years post diagnosis [13]. Differences exist by sex, with females reporting higher dysfunction scores [30-32]. Young female survivors experience greater problems with pain, lubrication, desire, and sexual satisfaction than healthy peers [22-26,28]. Qualitative studies document that women report pain, lack of desire, and reduced sexual enjoyment, while males experience erectile dysfunction, ejaculation, and arousal problems [12]. While aggregate data from large studies report that the majority of adolescents and young adult survivors were involved in a relationship [12,21], cancer and treatment-related side effects proved to be detrimental to masculinity and perceived closeness with partners [21-27]. Sexual dysfunction, body image concerns, and fertility status may limit the confidence in being both physically and emotionally intimate [29,31,33,34] and contribute to more negative outcomes [29,31,33-35]**.**

In comparison with other cancer types, the incidence of colorectal cancer (CRC) has been increasing at an alarming rate [36-41] for the adolescent and young adult group. Recent reports have projected that by 2030, the largest increase in the incidence of colon (90%) and rectal (125%) cancer will occur for the 20-34–year-old group [36-39,42-45]. Treatments include a combination of chemotherapy, pelvic radiation, and abdominoperineal resection—often with a temporary or permanent ostomy—which negatively impact psychological, sexual, and reproductive health outcomes [46-49]. Patients with early-onset CRC experience elevated psychological distress and social and physical burden, often resulting from issues with bowel control or incontinence and body image [50,51]. Rates of sexual dysfunction are higher than those of other cancer types [51]. Additionally, approximately 48% of young patients with CRC reported that sexual health issues have negatively affected the relationship with their partner [52,53]. Despite the burden associated with the long-term symptoms that accompany this cancer type and elevated rates of impaired functioning, sexual health has been mostly addressed as an individual experience without exploring how young patients with and survivors of CRC cope with sexual distress in the context of their relationship with a partner [10,14,35,54,55].

It is well recognized that the multidimensional distress of cancer affects both patients and partners [3,56-59]. Yet, only a few studies have investigated sexual health outcomes from a couple perspective among adolescents and young adults despite 3 important considerations. First, partners play a critical role in providing emotional, physical, and practical support [56,57,59,60]. Intimate partners also contribute to patients' adjustment to the illness: distress experienced by either partner has been found to directly affect distress levels in the other, with negative outcomes in quality of life, relationship functioning, and mental health for discordant couples [61-64]. Second, integrative models of sexuality place greater emphasis on psychosocial and interpersonal factors [65,66]. This finding supports the notion that greater attention should be placed on the psychosocial experience of both members of the dyad, in terms of shared loss and coordinated strategies to cope with cancer-related sexual dysfunction [3,60,67,68]. Finally, recent findings indicate that interventions addressing both partners' experiences in the context of sexual recovery and treatment are feasible and acceptable and they improve outcomes for both [58,69-76]. Hence, there is a critical need to investigate interpersonal characteristics that influence adolescent and young adult cancer survivors and their partners' experience with sexual dysfunction. This knowledge gap affects the provision of comprehensive sexual health care for adolescent and young adult cancer survivors [12,19,20,35] and the development of interventions tailored to the needs of individuals and couples at higher risk of sexual distress during survivorship.

This paper describes the protocol of the AYA CRC SHARE (ie, Sexual Health And REproductive concerns) project, which investigates sexual and reproductive issues of young adult CRC survivors and their partners within the first 5 years after diagnosis. This study will fill a significant gap in the current body of evidence assessing the long-term consequences of treatments for CRC on sexual health and wellbeing–related outcomes. In addition, this investigation will inform a subsequent intervention to enhance couples' coping and communication skills critical to sexual intimacy.

Theoretical Model

This study is underpinned by a theoretical model that integrates the Biopsychosocial Model of Sexuality after Cancer developed by Bober and Varela [65], with Wittmann's Sexual Recovery Model [67,77,78]. Bober and Varela [65] have outlined an

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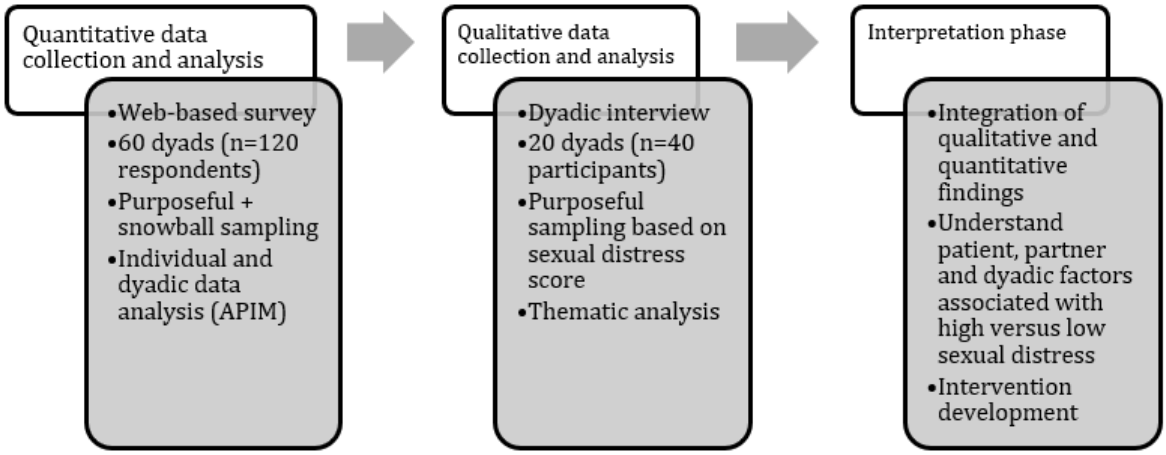
integrative biopsychosocial model, where cancer-related sexual problems exist at the intersection of biological (ie, body image change, fatigue, pain, and loss of sensation), psychological (ie, depression and anxiety), sociocultural (ie, social and cultural norms), and interpersonal factors such as relationship quality, intimacy, and communication [65]. Wittman [74,78] has extended this work, illustrating how changes in sexual functioning after cancer represent a loss for both patients and partners. Their model conceptualizes sexual recovery as a process that shares similarities with the grief experience [67,74,77-79]. Finally, if we consider cancer and the resulting sexual loss as a dyadic stressor, it is possible to postulate that dyadic coping strategies are needed to adjust to this transition. According to the Systemic-Transactional Model [80], dyadic coping includes both partners' strategies to manage their own and their partners' distress as well as coordinated coping behaviors implemented by the dyad in response to stressful situations that may affect the quality of the relationship. Therefore, our work investigates whether dyadic coping behaviors that characterize the exchange within young partners may alleviate the burden associated with sexual distress experienced after cancer.

Methods

Study Design

This study will use an explanatory sequential mixed methods approach [81] to (1) characterize sexual function, sexual distress, body image, fertility concerns, and dyadic coping among adolescent and young adult CRC survivors and their partners using validated measures (n=60 couples); (2) examine the reciprocal influence of each partner's sexual function (model 1) and dyadic coping style (model 2) on self-reported sexual distress; (3) identify interpersonal or couple characteristics associated with their ability to cope with sexual dysfunction; and (4) integrate quantitative and qualitative findings to expand the current understanding of dyadic adjustment to sexual distress (Figure 1).

Figure 1. Overview of the mixed methods explanatory sequential design of the study. APIM: Actor-Partner Interdependence Model.



Inclusion and Exclusion Criteria

The target sample includes 60 dyads composed of young adult CRC survivors and their romantic partners (n=120). A subset of 20 couples (n=40) will complete an in-depth dyadic interview with 2 members of the research team to further explore couple-based strategies implemented to cope with cancer-related sexual dysfunction. Couples will be selected for the qualitative component of the study based on their score on the sexual distress measure (see *Quantitative Web-Based Survey Study Component*). Couples scoring in the highest and lowest 10th percentile will be invited to complete qualitative interviews. Inclusion criteria for cancer survivors consist of (1) having received a diagnosis of CRC (stages I-IV) within 5 years prior to study enrollment; (2) being in a romantic relationship with a partner; (3) being older than 18 and younger than 39 years at the time of diagnosis; and (4) speaking English. Intimate partners are included in the study if they are (1) older than 18 years and (2) able to speak in English. Exclusion criteria are (1) cognitive impairment or severe mental illness that would impede the completion of self-report instruments; (2) attending couples therapy at the time of survey completion; (3) currently receiving end-of-life care; and (4) the partner is not present or unwilling to participate. No exclusions will be made on the basis of gender identity, sexual orientation, ethnicity, or cultural background.

Participant Recruitment and Study Procedure

Multiple recruitment strategies will be implemented to reach the expected sample size of adolescent and young adult couples inclusive of CRC survivors and their partners. Informational flyers and social media scripts will be distributed among advocacy and community-based organizations for individuals with CRC, adolescents and young adults with cancer, and sexual or reproductive health with the help of a CRC survivor and advocate who is a member of the research team (AR). Investigators will also recruit participants at CRC events and conferences. We will work closely with the University of Texas MD Anderson Cancer Center Adolescent and Young Adult Program to promote study recruitment through existing listerves and private social media groups. In addition to active recruitment, study investigators (CA, DW, and MR) will share the study with psychosocial oncology providers and pediatric or medical oncologists to encourage them to refer participants to the study.

Potential participants can self-refer to the study in two ways: (1) by clicking on the URL and QR code, which will link them

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to a web-based study information form and screening questions or (2) by contacting the research team directly via email or telephone. The study information form includes a list of exclusionary criteria, and potential participants can opt out of the study if they present any of the characteristics that would interfere with their ability to qualify for the study activities. To preserve the integrity of the data, a brief telephone screening ascertaining age, cancer diagnosis, and relationship status will be implemented. Upon successful recruitment, participants will receive an individualized link to complete the web-based survey. They will be asked for their permission for the study team to contact their romantic partners, and couple completion of the survey will be monitored through individual and dyadic identifiers. Inclusion in the study is based on both partners' provision of informed consent and completion of study questionnaires. If only one partner completes the study questionnaire or if less than 50% of the survey questions are answered, they will be excluded from the final sample. Two reminders will be sent to the participants and their partners. Additionally, among couples who express interest in participating in the qualitative component of the study while completing the survey, dyadic interviews will be conducted, with 10 couples reporting elevated sexual distress and 10 couples reporting low sexual distress (based on our sample distribution of scores) to appraise strategies implemented to cope with cancer-related sexual dysfunction.

Ethical Considerations

This study will be performed in accordance with the tenets of the Declaration of Helsinki. The University of Houston's institutional review board has reviewed and approved the study protocol (reference number STUDY00003538). Informed consent will be obtained from each participant before commencement of study research activities.

Recruitment and consenting of study participants will occur mostly through web- and internet-based approaches. A cover letter precedes the web-based survey explaining the study aims and procedures. Written information describing the research will be provided to survey participants, and this information will reference the optional interview procedures for a portion of the sample. Upon survey completion, a US $30 Amazon gift card (US $60 per couple) will be distributed via email. Additionally, a US $60 electronic gift card will be provided to each partner after participating in the dyadic interview (US $120 per couple).

Although this is considered a low-risk study, it is possible that answering questions about cancer diagnosis, sexual and reproductive health, as well as cancer-related impact on the couple's relationship may cause participants to experience distress, sadness, or anxiety. The study team will provide participants with resources for cancer-related support in the follow-up thank you message used to disseminate the incentive. Participants can also contact the investigators or let the study team members know about their interest in being referred to community-based organizations. For partners who will participate in the qualitative interview, potential aspects of distress include cancer-related distress, sexual, fertility, and negative relational outcomes. In addition, mental health and suicide risk may emerge in the exchange with the investigators. Both participants (survivor and healthy partner) will receive a copy of the resource list created ad hoc from the research team, which includes the National Suicide Prevention Lifeline link and a 24/7 phone number. Being in an electronic format, the resource list will be attached to the thank you email for the participants, and it can also be shown directly to them upon conclusion of the interview. Other risks include breach of confidentiality or privacy. Efforts will be made to limit the potential for privacy to be threatened by a data breach: first, we made the decision of not pairing data from the web-based survey and the interview with identifying information. When data are downloaded, they will be stored in a password-protected encrypted computer. Each subject's name will be paired with a code number, which will appear on written study material. The list pairing the subject's name to the assigned code number will be kept separate from these materials, and only the study principal investigator will have access to this information.

Participant Safety

Participant safety will be addressed through the implementation of the following strategies. First, survey instruments and study procedures will be reviewed and tested by expert e-patients and young CRC advocates [82] until consensus is achieved. Second, investigators will closely monitor responses to instruments assessing emotional functioning. An ad hoc list of resources in the areas of sexual health, mental health, caregiving, financial toxicity, and oncofertility has been compiled in collaboration with content experts or patient advocates, and it will be distributed to all participants at the end of the study activities. Third, 2 facilitators with expertise in research on sensitive health topics will conduct the interviews to reduce potential harm to participants because of the distress that may be elicited by the topics discussed [83], while affirming the cathartic and empowering aspect of using one's experience to improve quality of care for adolescent and young adult couples. Additionally, to protect the individuals' well-being and couples' functioning, participants may opt to conduct the interview separately.

Study Measures

Quantitative Web-Based Survey Study Component

Survivors and partners will be asked to complete questions about sociodemographic information including current age, sex, gender identity, sexual orientation, race and ethnicity, education, occupational status, insurance status, and income. Relationship characteristics include marital status, length of relationship, cohabitation, and presence of children. Clinical information for adolescent and young adult survivors will include cancer diagnosis, stage of the disease, age at diagnosis, time since diagnosis, and treatment type. Table 1 provides an overview of the sexual and psychosocial measures administered to participants.

Sexual function and satisfaction will be assessed with the Patient-Reported Outcomes Measurement Information System (PROMIS) Sexual Function and Satisfaction Measure version 2.0 Brief Profile (female version: 14 items, and male version: 10 items) [84,85]. The following domains will be answered by females: vaginal lubrication, vaginal pain, vulvar discomfort,

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and clitoral discomfort. The erectile function domain will be completed by male partners and survivors. The brief measure also includes 4 gender-neutral domains: interest in sexual activity, satisfaction with sex life, orgasm ability, and orgasm pleasure. All respondents are invited to complete items related to interest in sexual activity, whereas the remaining domains are to be completed only by respondents who had been sexually active. Per PROMIS network instructions, domain scores will be transformed to a *t* score distribution, where 50 represents the mean for the general US population [24,86]. A cutoff of 1 SD from the mean *t* score distribution of each domain will be used to define sexual dysfunction. The Sexual Function and Satisfaction Measure has shown adequate construct, content, known-groups validity, and test-retest reliability in adults and in groups of adolescents and young adults with cancer [84,85,87]. Because of the focus on young CRC survivors, 2 additional items will explore discomfort in the anus and rectum areas. Participants who do not identify as male or female in their sexual relationships are given the option to complete the General Measure of Sexual Satisfaction [88]. The instrument contains 5 semantic differential items rated on a 7-point scale. The total score, calculated as the sum of each item, ranges from 5 to 35 and higher values indicate greater sexual satisfaction. The instrument has demonstrated strong reliability and validity [88].

Table 1. Overview of the sexual and psychosocial measures included in the web-based survey.

Instruments	Items, n	Psychometrics
Sexual function and satisfaction		
Patient-Reported Outcomes Measurement Information System Sexual Function and Satisfaction Measure Brief Profile	10 for males and 14 for females	Females: α=.89-.95; males: α=.71-.87
Global Measure of Sexual Satisfaction	5	Cronbach α=.96
Sexual distress		
Sexual and Relationship Distress Scale	30	Cronbach α=.95
Dyadic coping		
Dyadic Coping Inventory	37	.68≥Cronbach α=≥.95 for subscales and total score
Perceived infertility-related distress		
Fertility Problem Inventory (Relationship Concern and Need for Parenthood subscales)	10	Relationship Concern: α=.82; Need for Parenthood: α=.84
Emotional functioning		
Patient Health Questionnaire-8	8	Cronbach α=.82
Emotion Thermometers	5	Cronbach α=.90
Relationship satisfaction		
General Measure of Relationship Satisfaction	5	Cronbach α=.96
Body image		
Body Image Scale[a]	10	Cronbach α=.93

[a]Only for colorectal cancer survivors. This scale is not administered to partners.

Sexual distress will be measured with the Sexual and Relationship Distress Scale [89], which consists of 30 items assessing multidimensional (14-factor) individual and relationship distress experienced in the context of sexual difficulties. Each subscale score is calculated by combining the scores on each item, which ultimately determines the resulting total score. The instrument has demonstrated high internal consistency and high convergent and discriminant validity [89], and it has been administered in the context of breast and gynecological cancer survivorship in young adults [90].

Dyadic coping will be assessed using the Dyadic Coping Inventory [71,91-95], a 37-item questionnaire evaluating dyadic coping strategies implemented to cope with the stress of cancer on a 5-point Likert scale from 1="very rarely" to 5="very often." Dyadic coping describes partners' strategies implemented to manage their own and their partners' distress as well as shared coping behaviors enacted by the dyad in response to stressful situations that affect the relationship. Items are organized in multiple subscales: stress communication, supportive, delegate, negative, and common dyadic coping. In addition, respondents are invited to rate their satisfaction with and the effectiveness of the dyadic coping behaviors implemented. Satisfactory psychometrics have been previously reported both for the original version of the instrument [94,95] and the English validated questionnaire [91,96].

Perceived infertility-related distress in cancer survivorship will be measured by administering the Relationship Concern and Need for Parenthood subscales (10 items each) from the Fertility Problem Inventory [97]. Each subscale and the instrument's total score have demonstrated appropriate internal consistency and convergent and discriminant validity, with scores on the selected subscales being associated with marital adjustment.

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Current treatment protocols for CRC have long-term implications for fertility status [98-102], which can represent an additional source of distress for patients and their partners. Participants can opt out of these questions if they have completed their family-building or if the questions are considered not applicable.

Emotional functioning will be assessed with the Patient Health Questionnaire-8 [103,104] and the Emotions Thermometer [105,106]. The Patient Health Questionnaire-8 is a brief measure of depression validated both for the general population and for individuals with cancer [103,104]. Participants rate on a 4-point Likert scale that ranges from 0 to 3 (0="not at all," 1="several days," 2="more than half of the days," and 3="nearly every day") symptoms of depression experienced over the past 2 weeks; for example, feeling tired or having little energy, poor appetite, or overeating. The total score, obtained as a sum of each item, ranges from 0 to 24, with higher scores representing mild, moderate, and severe levels of depression. Excellent psychometric characteristics have been recorded across age and racial and ethnic groups, supporting its application in the context of psychosocial oncology [107-110]. The Emotions Thermometer is a self-report visual analogue tool including 5 domains (distress, anxiety, depression, anger, and need for help) on a scale ranging from 0 to 10. Excellent reliability (Cronbach α=.90), sensitivity (82.4%), and specificity (68.6%) of the instrument have been confirmed in multiple samples [105,106].

Relationship satisfaction will be measured using the General Measure of Relationship Satisfaction to examine the quality of the couple's relationship. This 5-item scale contains five 7-point semantic differentials—"good-bad," "pleasant-unpleasant," "positive-negative," "satisfying-unsatisfying," and "valuable-worthless"—in response to the question, "How would you describe your relationship with your partner?" The scale has shown strong reliability and validity [88] in men (Cronbach α=.96) and women (Cronbach α=.96).

Body image concerns of CRC survivors will be assessed with the Body Image Scale [111,112]. Items assess how patients feel about their appearance and any changes that may have resulted from their disease or treatment ("Have you felt less physically attractive as a result of your disease or treatment?" and "Did you find it difficult to look at yourself naked?"). The 10 items are rated on 4-point response option consisting of "not at all," "a little," "quite a bit," and "very much." Higher scores are indicative of lower body image perception. The scale has demonstrated high reliability (Cronbach α=.93), discriminant validity, and sensitivity to change [111].

Qualitative Study Component

A subset of 20 couples (n=40) will complete an in-depth dyadic interview with 2 members of the research team to further explore strategies implemented by the 2 partners to cope with cancer-related sexual dysfunction and its associated distress. Dyads will be selected for the qualitative section of the study based on their sexual distress score (Sexual and Relationship Distress Scale [83]). Ten couples scoring in the highest and lowest 10th percentile of sexual distress will complete the qualitative interviews. Questions will address participants' experience with sexual dysfunction, sources of sexual distress or concerns; perceived changes and consequences on couples' relationships; and preferences for interventions addressing sexual health issues for patients with CRC and their partners. Couples will be contacted by the research team via email or telephone. Members of the research team will share information about the topics covered in the interviews, how interviews will be conducted, and how data will be collected, stored, and analyzed. Interested participants will be verbally consented at the beginning of the interview, which will be conducted either via telephone or via a Health Insurance Portability and Accountability Act–compliant web-based videoconferencing platform.

Statistical Analysis

Univariate descriptive statistics and graphs will be analyzed to assess variables' distributions. A missing data analysis will be conducted to determine whether list-wise deletion or multiple imputation will be appropriate; this will consider the amount of missingness and viability of the missing at random assumption necessary for multiple imputation [113]. Pearson *r* correlation coefficients will be used to assess the linear relationship among sociodemographic, clinical, and sexual or psychosocial measures, with specific attention to the variables of interest for the study. Comparisons of demographic characteristics between adolescent and young adult CRC survivors and their partners will be conducted using paired samples *t* tests for continuous variables and chi-square tests of association for nominal variables. Correction for multiple tests will be applied to control type I errors.

Then, the Actor-Partner Interdependence Model will be used to examine actor and partner effects of sexual function (model 1) and dyadic coping styles (model 2) on sexual distress of each member of the dyad [114-117]. A patient's score on the predictor variable is expected to affect their own criterion variable scores (actor effect) and those of their partner (partner effect), and vice versa. Thus, it will be possible to determine whether sexual distress results from the score of the patients, partners, or both on the dyadic coping and sexual functioning measure [114,117,118]. Given the small sample size (60 dyads), the pooled regression approach will be used [114,117]. Stata (version 17; StataCorp) [119] will be used for the analysis, as the pooled regression approach is straightforwardly implemented using the *mvreg* command. The reasonableness of regression assumptions will be assessed using diagnostic statistics and plots [120]. Departures from assumptions will be handled using contemporary approaches such as the use of heteroscedasticity-consistent SEs. Power estimates were favorable: with a sample size of 60 dyads, assuming an α level of .05, the power of the regression *F* test to detect a significant model of each partner's sexual function (model 1) and dyadic coping style (model 2) for sexual distress is approximately 0.86 in the presence of a medium effect size [115].

The qualitative phase of the study is designed to further explain quantitative results via purposive sampling of a subset of dyads. Interview recordings (n=20 dyadic interviews) will be transcribed verbatim and analyzed using thematic content analysis [121]. Transcripts will be reviewed for concordance, and discrepancies will be resolved through discussion among

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investigators. Qualitative data will be reviewed iteratively to reach saturation; that is, when no new information emerges during coding [122,123]. Atlas.ti software (ATLAS.ti Scientific Software Development GmbH) will be used to manage and organize qualitative data [124].

Mixed Methods Integration

This study adopts an explanatory sequential mixed methods design, which incorporates quantitative and qualitative approaches as part of 2 consecutive phases [81]. Explanatory designs use qualitative data to explain and achieve greater understanding of the results emerging from the quantitative data [81,125]. In this design, the qualitative component builds on the survey and couples participating in the dyadic interview are selected from the sample that had previously completed the quantitative component. Integration of the 2 strands of data will be presented in a joint display table [126], thus yielding a more comprehensive view of participants' experiences and illustrating interpersonal processes that inform couples' coping with impaired sexual functioning.

Results

Recruitment and data collection started in July 2022, and data collection is expected to be concluded in September 2024. No results are available as of manuscript preparation.

Discussion

This mixed methods study, to the best of our knowledge, will be among the first to apply a relational perspective to the investigation of sexual health outcomes among adolescent and young adult CRC survivors. Conducting research with dyads presents numerous challenges in research design, measurement, and data analysis [96,109-111]. Approaches to recruitment and data collection have been selected on the basis of previous acceptability in similar studies conducted by members of the investigative team (CA and DW) and the existing literature on couple-based research [111-115]. In addition, age-tailored web-based data collection efforts will contribute to the study's feasibility. We consider it a strength of the proposed study that we will integrate survey and qualitative feedback from both partners and from diverse typologies of dyads.

Addressing changes in sexual function and their implications for psychosocial and clinical outcomes is essential to quality cancer care; yet, it is often challenging to translate this knowledge into routine practices inclusive of cosurvivors [20,57]. The expected outcomes of this investigation are to (1) characterize sexual function, sexual distress, and dyadic coping of adolescent and young adult CRC survivors and partners through validated measures; (2) provide a deeper understanding of the challenges couples experience as they navigate sexual intimacy after CRC treatment by highlighting the role of interpersonal processes; and (3) use the findings to develop and test interventions supporting the recovery of sexual intimacy of young couples coping with CRC. Sexual dysfunction and altered intimacy with a partner are salient factors impairing long-term quality of life and emotional well-being [20,69,116]. Through the identification of individual, partner, and relationship-level factors that shape how couples negotiate the loss elicited by the illness and redefine their sexual experience or repertoire, this work will inform the development of a couple-based intervention that promotes intimacy by enhancing coping and communication skills. The results from this study will also contribute to identifying couples who are more vulnerable to poor emotional and relationship functioning, either because of clinical, sociodemographic, or interaction effects. This information can be used to alert the multidisciplinary team and offer timely referral to services.

While the cross-sectional design and the small sample size are limitations of this protocol, this work can lead to further interesting areas of inquiry. Future research will be needed to evaluate sexual health outcomes over time and elicit information about preferred timing, format, and contents of sexual health programs. In addition, investigators can consider integrating momentary ecological assessment approaches and dyadic diaries to better capture antecedents and patterns associated with differential trajectories. Finally, future studies should investigate whether delivering sexual health interventions results in improved quality of life and other psychosocial health outcomes among adolescents and young adults.

In conclusion, sexual health problems are among the most distressing consequences of the disease for young patients with CRC, with recent literature documenting the lack of evidence-based approaches tailored to their experience, preferences, and needs [12,20,55,127]. This study seeks to fill this gap by involving survivors and their partners to generate a dyadic model of sexual functioning and intimacy. In addition, while the literature has often linked addressing sexual health concerns with a higher quality of life, emotional well-being, and relationship functioning [67], these relationships have been minimally examined in this group. This lack of knowledge impairs the range and quality of services, especially considering the impact of sexual dysfunction, body image concerns, and fertility status on physical and emotional intimacy. As growing evidence has documented how the complexity of sexual health issues may hinder providers' capacity and confidence to discuss this topic [127-130], results from this work will provide important recommendations for timely and patient-centered care delivery.

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Data Availability

The data that support the findings of this study will be available from the corresponding author (CA) upon reasonable request. The data are not publicly available due to information that could compromise the privacy of research participants.

Authors' Contributions

CA, DW, and MR conceptualized the study and designed the methodology. CA, DW, MR, and ZG carried out the investigation. CA, DW, MR, and AR procured the resources for the study. CA, LCC, and ZG curated the data. CA drafted the manuscript, and CA, DW, MR, AR, LCC, ZG, and EI reviewed and edited the manuscript. CA and ZG were responsible for the study's administration. CA acquired the funding for the study. All authors have read and agreed to the current version of the manuscript for publication.

Conflicts of Interest

None declared.

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Abbreviations

CRC: colorectal cancer
PROMIS: Patient-Reported Outcomes Measurement Information System

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Protocol

Optimizing the Quality of Clinical Data in an Australian Aged Care and Disability Service to Improve Care Delivery and Clinical Outcomes: Protocol for an Agile Lean Six Sigma Study

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Abstract

Background: In Australia, aged care and disability service providers are legally required to maintain comprehensive and accurate clinical documentation to meet regulatory and funding requirements and support safe and high-quality care provision. However, evidence suggests that poor-quality clinical data and documentation are widespread across the sector and can substantially affect clinical decision-making and care delivery and increase business costs.

Objective: In the Optimizing the Quality of Clinical Data in an Australian Aged Care and Disability Service to Improve Care Delivery and Clinical Outcomes (OPTIMISE) study, we aim to use an Agile *Lean Six Sigma* framework to identify opportunities for the optimization of clinical documentation processes and clinical information systems, implement and test optimization solutions, and evaluate postoptimization outcomes in a large postacute community-based health service providing aged care and disability services in Western Australia.

Methods: A 3-stage prospective optimization study will be conducted. Stage 1 (baseline [T_0]) will measure existing clinical data quality, identify root causes of data quality issues across services, and generate optimization solutions. Stage 2 (optimization) will implement and test changes to clinical documentation processes and information systems using incremental Agile sprints. Stage 3 (evaluation) will evaluate changes in primary and secondary outcomes from T_0 to 12 months after optimization. The primary outcome is the data quality measured in terms of defects per unit, defects per million opportunities, and Sigma level. The secondary outcomes are care delivery (direct care time), clinical incidents, business outcomes (cost of quality and workforce productivity), and user satisfaction. Case studies will be analyzed to understand the impact of optimization on clinical outcomes and business processes.

Results: As of June 1, 2022, stage 1 commenced with T_0 data quality audits conducted to measure current data quality. T_0 data quality audits will be followed by user consultations to identify root causes of data quality issues. Optimization solutions will be developed by May 2023 to inform optimization (stage 2) and evaluation (stage 3). Results are expected to be published in June 2023.

Conclusions: The study findings will be of interest to individuals and organizations in the health care sector seeking novel solutions to improve the quality of clinical data, support high-quality care delivery, and reduce business costs.

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KEYWORDS

aged care; disability; information technology; data; quality; health services

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Introduction

Background

In Australia, aged care and disability service providers are legally required to maintain comprehensive and accurate documentation of the care provided to each client [1,2]. This clinical documentation is crucial to support safe and high-quality care delivery, maintain professional accreditation, and acquire government funding [3-5]. However, widespread clinical documentation and data quality issues have been identified across the sector, with evidence suggesting that most existing clinical data in the aged care and disability services sector are of substandard quality and lack consistency within and across individual organizations [3,6,7].

This problem has been partly because of the absence of national data standards and minimum requirements to guide information collection and documentation processes [3,7]. Therefore, service providers are challenged to collect extensive clinical information to meet multiple funding and regulatory reporting requirements across different and often segregated information systems [3,7]. Existing clinical information systems have also largely used "shrink-wrapped" or off-the-shelf systems owned by external vendors that are modeled on designs from other health care environments, with limited customization to account for the specific environment, workflows, and information requirements of aged care and disability services [8-10].

Investigations of workflow in Australian residential aged care facilities (RACFs) have shown that clinical documentation and information processing are major time-intensive staff activities [9,11]. A study involving 6 RACF sites in New South Wales and Victoria estimated that registered nurses spent a median of 60 minutes on documentation per shift, whereas service managers spent a median of 360 minutes on documentation activities, including filling forms, progress notes, incident reporting, and medication management [9]. Similarly, a second study estimated that RACF support workers spent a mean 14.5% of the total working time per shift on documentation tasks, which is equivalent to approximately 60 minutes for a standard 7.5-hour shift [11].

Although documentation is an essential activity of health care provision, excess time spent on documentation directly reduces the amount of care time spent with residents, which can compromise the quality of care delivery [12]. A survey in the United Kingdom found that 81% of the nurses believed they spent a disproportionate amount of time on record keeping and documentation tasks, which prevented them from providing direct care [13]. Other research has shown that the clinical documentation burden is a major driver of burnout among clinical and care staff [14,15], who believe that time could be better spent attending to residents [16-18], and can negatively impact job satisfaction [17].

Health IT (HIT) has a great capacity to support efficient information processing in aged care and disability services and facilitate high-quality person-centered clinical decision-making at the point of care [19,20]. Research has shown that the overall workforce and management perception of the use of electronic health records (EHRs) in aged care is positive, with widespread agreement that EHRs are beneficial for improving workforce efficiency [21]. However, there is a need to optimize HIT systems based on a detailed understanding of the workflow and requirements specific to aged care and disability services [9]. Several pre-post implementation studies in Australian RACFs have shown that the implementation of electronic systems alone does not automatically lead to greater efficiency [11,12,19] or data quality improvement [22] compared with paper-based systems. Instead, the implementation of suboptimal HIT systems can lead to unintended adverse consequences, including increased documentation time, difficulty in data entry and information retrieval, increased complexity of information management, and increased documentation burden and business costs [23].

Several common issues with EHR systems used in aged care and disability services have been described in the literature. End users have reported that existing systems lack clarity and contain inconsistent data fields, definitions, and terminology that do not match the specific information requirements for aged care and disability services [3,19]. When relevant input fields are unavailable, information is either omitted or recorded elsewhere, meaning that the EHR is often incomplete and does not contain all essential information necessary for the delivery of safe care [24]. Systems have also been reported to be difficult to navigate [25] and lack the structure and organization to guide the workforce to record the required clinical information efficiently [7,20]. A clinical documentation audit study in 7 Australian RACFs showed that although EHRs contained a greater *quantity* of information than paper-based records, information recorded in EHRs had a lower total mean *quality* score [22].

Other research has shown that end users can become reluctant to use EHR systems if they do not easily integrate into their workflow and often revert to using paper-based documentation [3]. This creates further inefficiency with respect to double documentation and the duplication of effort, contributing to a "vicious cycle" [19] of increased documentation burden and poorer data quality [3,9]. One study found that RACF nurses reported an excessive amount of time spent entering the same information across multiple incompatible systems and that double documentation resulted in the omission of important information, inaccuracy, and potential safety concerns [24].

In addition to EHR system–related issues, other complex process-related issues have been described that can contribute to missing, incomplete, inaccurate, or not up-to-date clinical data. In the primary care setting, for example, workload and time constraints [26], workforce attitudes toward documentation tasks, and prioritization of direct care tasks [27] have all been shown to affect the quality of nursing documentation. Well-designed EHR systems can support higher-quality clinical data by guiding the workforce to input the required information more efficiently but may not address all process-related barriers related to clinical documentation.

Ultimately, as organizations become more data mature, important business decisions are increasingly reliant on analytics using administrative, clinical, and other service data [28]. Poor data quality can result in flawed business decisions and increased

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business costs [29]. Therefore, there is a clear need to optimize clinical documentation processes and clinical information systems to support efficient, safe, and quality care delivery and effective business decision-making in aged care and disability services [9].

However, any form of organizational change in systems or processes represents a major cost for service providers, which can be a major barrier to implementation. Therefore, it is important to be able to clearly demonstrate the added value and cost benefits of transformation initiatives to organizational leadership [19]. Currently, few aged care and disability service providers collect benchmarks to routinely evaluate and monitor data quality or its impact on care delivery and organizational efficiency [30]. Implementation without routine evaluation or a control plan can substantially increase business costs, while adding little value to care delivery or operational efficiency.

The Optimizing the Quality of Clinical Data in an Australian Aged Care and Disability Service to Improve Care Delivery and Clinical Outcomes Study

The overarching goal of the Optimizing the Quality of Clinical Data in an Australian Aged Care and Disability Service to Improve Care Delivery and Clinical Outcomes (OPTIMISE) study is to use an integrated Agile *Lean Six Sigma* (LSS) framework [31,32] to (1) identify opportunities for the optimization of clinical documentation processes and clinical information systems, (2) implement and test optimization solutions, and (3) evaluate postoptimization outcomes in a large postacute community-based health service providing aged care and disability services in Western Australia.

Objectives

Specifically, the 3-stage study will include the following:

1. Stage 1 (*baseline*): measure existing clinical data quality, identify the root causes of data quality issues, and generate optimization solutions
2. Stage 2 (*optimization*): implement and test changes to clinical information systems and clinical documentation processes
3. Stage 3 (*evaluation*): evaluate changes in clinical data quality, care delivery, clinical outcomes, and business costs following optimization

Table 1 presents the specific study objectives mapped to the Agile LSS phases (see the *Study Design and Framework section*).

Table 1. Objectives of the Optimizing the Quality of Clinical Data in an Australian Aged Care and Disability Service to Improve Care Delivery and Clinical Outcomes study.

Stage and phase	Objective
Stage 1: baseline	
1.1. Define	Define study goals, scope, outputs, and methodology
1.2. Measure	Measure clinical data quality across aged care and disability services
1.3. Analyze	Identify root causes of data quality issues
1.4. Improve (part 1)	Generate solutions to support optimization of clinical documentation processes and clinical information systems
Stage 2: optimization	
2.1. Improve (part 2)	Implement and test changes to clinical documentation processes and clinical information systems specific for aged care and disability services
2.2. Control	Establish policies and procedures for clinical data governance, collection, and input across care services
2.2. Control	Establish a control plan for routine audit of clinical data quality across care services
Stage 3: evaluation	
3.1. Evaluation	Measure change in primary outcomes (clinical data quality)
3.1. Evaluation	Measure change in secondary outcomes (care delivery, clinical outcomes, business costs, and workforce satisfaction)

Methods

Study Design and Framework

The OPTIMISE study will be a prospective optimization study using an integrated Agile LSS Define, Measure, Analyze, Improve, Control (DMAIC) framework.

Six Sigma is a statistical measurement-based method for process optimization and quality improvement that aims to reduce the number of *defects* in a process to <3.4 defects per 1 million opportunities [33]. *Lean* methodology is focused on reducing *waste* in a process, which is defined as any unnecessary or suboptimal items, actions, tasks, components, materials, systems, or human resources that increase costs and time spent on a process [34]. Therefore, the *Lean Six Sigma* framework aims to reduce both *defects* and *waste* to improve the quality of products and services, improve efficiency, and reduce business costs [35,36]. Originally conceptualized in the manufacturing industry, LSS has been increasingly applied in health care to control rising costs and improve the quality of care delivery [30,36-38].

The strength of LSS is its rigorously structured framework for quality improvement based on statistical measurement. However, this structure can lack flexibility to accommodate changes across the project cycle [32]. *Agile* methodology can complement LSS to increase flexibility and adaptability [39].

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Agile is a popular methodology used in software development that involves the iterative development of a product over short-term incremental cycles called sprints [31]. It is a highly flexible and responsive methodology that allows for product changes during development based on customer feedback. However, this method neglects decision-making based on objective and measurable data, which can compromise quality and efficiency. Therefore, the integration of Agile and LSS frameworks provides a structured methodology for product development, evaluation, and improvement that is simultaneously flexible and responsive to changes over iterative cycles. Hybrid Agile LSS frameworks have been increasingly used in the literature as a more powerful method for quality improvement than single frameworks [39-42].

Study Setting

The study will be undertaken at Brightwater Care Group ("Brightwater"), a large postacute, residential, and community-based aged care and disability service in Perth, Western Australia. Brightwater provides residential and home-based care for approximately 1882 aged care and 522 disability services clients across 10 different programs (Table 2).

Table 2. Overview of aged care and disability services.

Service type and program name	Sites, n	Clients, n	Description
Aged care			
RAC[a]	11	750	Long-term or permanent high care accommodation for people aged >65 years
SDCP[b]	1	31	Long-term or permanent high care accommodation for people with dementia
TCP[c]	2	101	Short-term, posthospital support and active management for older people aged >65 years
AH[d]	—[e]	1000	Home-based support for people aged >65 years
Disability			
TRP[f]	1	53	Specialist neurorehabilitation service for people aged 18-65 years with acquired brain injury
TAP[g]	1	23	Short-term, posthospital support and active management for people aged 18-65 years with disability
SIL[h]	8	71	Long-term and permanent high care accommodation for people aged 18-65 years with disability
CAPB[i]	—	375	Home-based support for people aged 18-65 years with disability and NDIS[j] funding

[a]RAC: residential aged care.

[b]SDCP: Specialist Dementia Care Program.

[c]TCP: Transitional Care Program.

[d]AH: at home.

[e]AH and CAPB services are at-home and community-based care sites.

[f]TRP: Transitional Rehabilitation Program.

[g]TAP: Transitional Accommodation Program.

[h]SIL: Supported Independent Living.

[i]CAPB: capacity building.

[j]NDIS: National Disability Insurance Scheme.

Patient and Public Involvement

Patients or the public were not involved in the design, conduct, reporting, or dissemination plans of our research, as the end product (clinical information system) is not directly used by patients or the public.

Ethics Approval

The study protocol was approved by Brightwater Care Group as a Level 2: Low Risk Study (reference: 2021/BCG2110). This study is classified as an internal service evaluation and does not require ethics approval for research in Australia.

Consent and Participation

Client EHR data will be deidentified before the analysis. Clients provided written consent for their deidentified clinical data to be used for research and service evaluation as part of the conditions of entry into the service. Staff member participation in user surveys and interviews will be voluntary, and nonparticipation will not impact their usual role. All participant data will be deidentified by assigning a randomized numbered code. Participant names will be changed to pseudonyms when referring to qualitative data. When transcribing interviews verbatim, words or statements that could be used to identify participants will be removed to ensure privacy. Audio recordings will be deleted once the transcriptions are complete.

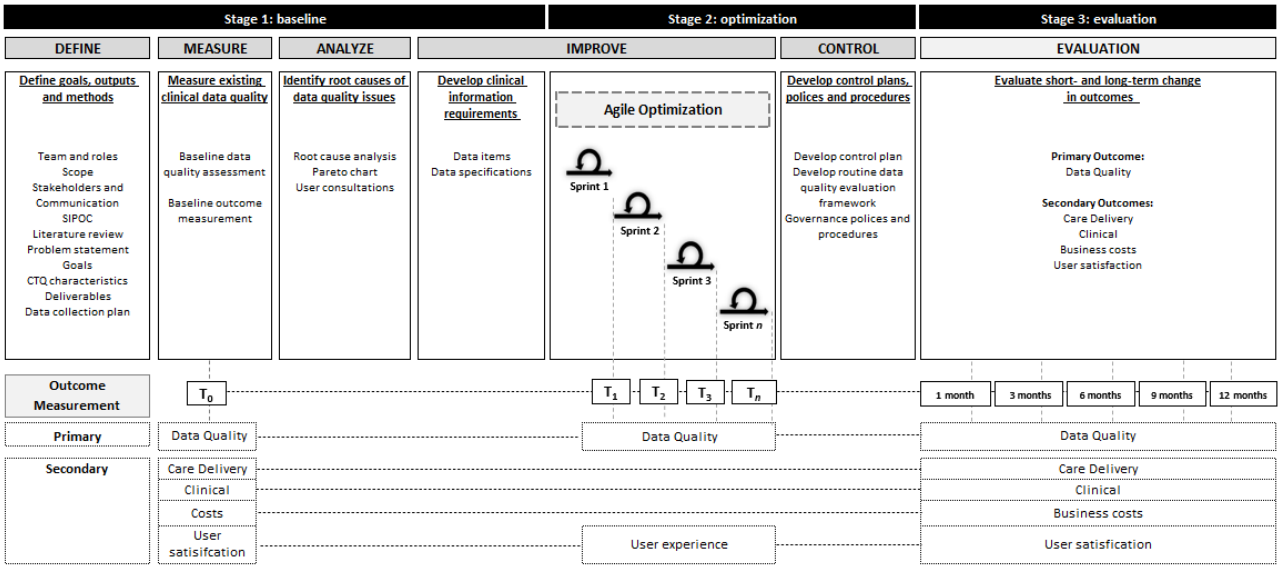
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Study Phases

Overview

Figure 1 outlines DMAIC phases of the study. Stage 1 (*baseline*) will measure existing clinical data quality across services, identify root causes of data quality issues, and generate solutions to directly inform optimization. Stage 2 (*optimization*) will implement and test changes to clinical documentation processes and information systems specific to aged care and disability services. Stage 3 (*evaluation*) will measure the short-term (1-3 months) and long-term (4-12 months) changes in data quality and clinical and business outcomes following optimization.

Figure 1. The Optimizing the Quality of Clinical Data in an Australian Aged Care and Disability Service to Improve Care Delivery and Clinical Outcomes study design. CTQ: critical-to-quality; SIPOC: Suppliers, inputs, process, outputs, customers.



Stage 1: Baseline

Phase 1.1: Define

To execute the study, a multidisciplinary *Six Sigma* project team [43] was formed, consisting of 5 *regular* team members—a project champion (director of research), process owner and expert (technology services manager), project leader (data scientist), project manager and analyst (information systems analyst), and process user (clinical expert). The project leader has >8 years of experience in leading evaluation projects using complex clinical data including hospital, emergency department, general practice, pharmaceutical, Medicare, mortality, aged care, and disability data, whereas the project manager and analyst holds >6 years of experience in project management, policy analysis, and information systems analysis, and both have Black Belt certifications in LSS. The process user is a research-trained occupational therapist with 3 years of experience providing clinical care for residents at 1 of the residential aged care sites involved in the study and was included as a regular team member to provide clinical oversight and expertise as a direct user of clinical information systems.

In addition, 5 executive and senior managers were included as *resource* and ad hoc team members to provide high-level information and process expertise, as needed.

Several different LSS techniques including Voice of Customer; 5 Whys; Specific, Measurable, Achievable, Realistic, and Timely goals; stakeholder analysis; and a Suppliers, Inputs, Process, Outputs, and Customer diagram were used to define study goals, scope, outputs, critical-to-quality (CTQ) characteristics, and methodology [43]. In addition, a Failure Modes and Effects Analysis [44] was conducted to identify the potential risks and failures. Multimedia Appendix 1 provides a brief description of the LSS techniques that appear in this manuscript for readers who are unfamiliar with the LSS framework.

The main component of the define phase was to define the CTQ metrics to be used to measure data quality in the study. CTQ metrics are key factors or attributes determined to be important by an organization and are used to measure the performance of a process [45]. The CTQ metrics for the clinical data were determined using the Delphi consensus method [46]. First, a literature review was conducted to identify data quality metrics commonly used in data quality assessments [47-49]. After review by the project team, a shortlist of the 15 most relevant metrics was circulated to an expert group consisting of 68 key stakeholders in the organization across executives, care services, clinical excellence, quality, technology, business analytics, and research departments, who independently ranked metrics in order of those most critical to clinical data quality in their role. The final CTQ metrics represented the 6 metrics with the highest rankings among the expert group (Table 3).

The define phase was completed in January 2022. The subsequent sections outline the planned protocol for the remaining phases.

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Table 3. Critical-to-quality metrics used to measure clinical data quality.

Rank	Metric	Definition of metric	Measurement method	Defect definition
1	Accuracy	The degree to which EHR[a] data correctly represent a client's personal, medical, clinical, and psychosocial circumstances and care needs	Manual audit of random sample of EHRs compared with original documents (eg, admission documents or medical reports)	Data that do not match the original source of truth
2	Completeness	The degree to which all required data in the EHR are present	Data warehouse audit of all EHRs	Missing data (ie, null or blank fields)
4	Currentness	The degree to which EHR data are up to date and reflect the client's current condition and changes in circumstances and care needs	Data warehouse audit of all EHRs	Data fields not updated within required timeframes as per clinical guidelines
3	Clarity	The degree to which data are presented in a clear format and enable the user to understand a client's care needs without ambiguity	Manual assessment of a random sample of EHRs	Data fields with unclear presentation
5	Compliance	The degree to which EHRs capture all the required information to meet legal, funding, and regulatory requirements and in accordance with best practice clinical guidelines	Manual review of data fields captured in existing systems	Missing mandatory data (ie, null or blank fields)
6	Usability	The degree to which data are presented in a format that allows the information to be directly and efficiently used for primary (eg, care provision) and secondary purposes (eg, reporting, analytics, and evaluation)	Data warehouse audit of all EHRs	Data with limited primary and secondary usability

[a]EHR: electronic health record.

Phase 1.2: Measure

The measure phase will focus on measuring the baseline (T_0) quality of clinical data across services and identifying key data quality issues. T_0 data quality will be measured through an audit of client EHRs using a 6-month lookback period. Data quality will be measured in terms of the *number of defects* present in EHRs, measured using the CTQ metrics identified by the expert group.

Specifically, T_0 data quality will be measured by the number of defects per unit (DPU), defects per opportunity (DPO), defects per million opportunities (DPMO), and the Sigma level (Table 4). T_0 data quality will be measured for each of the 8 programs to allow the identification of any systematic variation between sites and service-specific data quality issues. In addition, the assessment will identify the most common types of defects across services to inform system optimization.

Table 4. *Six Sigma* metrics for measuring defects.

Metric	Formula	Description
DPU[a]		Measures the average number of defects present in a unit (ie, the average number of defects in each client EHR[b])
DPO[c]		Measures the number of defects as a proportion of the total number of data fields (ie, opportunities) present in each client EHR
DPMO[d]		Measures the number of DPO expressed per million
Sigma level	Determined from conversion tables using calculated DPMO	Measures the amount of variability in a process. *Six Sigma* quality performance is defined as 3.4 DPMO.

[a]DPU: defects per unit.

[b]EHR: electronic health record.

[c]DPO: defects per opportunity.

[d]DPMO: defects per million opportunities.

Phase 1.3: Analyze

Following the identification of key data quality issues across services, the analyze phase will focus on understanding the *root causes* of data quality issues. A qualitative research approach will be used to understand the workforce experiences of clinical documentation processes using existing clinical information systems and to identify the root causes of poor data quality.

A purposive sample of the workforce across all 8 programs will be selected to participate in user consultations using either semistructured interviews or web-based surveys (Multimedia Appendix 2). Different functional user groups will be purposively sampled at each site (care staff and clinical, administrative, and service managers) to provide whole-of-organization insight into existing processes, strengths, and gaps. At least 1 site from each program will be selected (a

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minimum of 8 sites). For programs with multiple sites, the sites with the highest, median, and lowest data quality based on the findings mentioned in *Phase 1.2: Measure* will be selected for consultation. In addition, users from the corporate workforce who routinely use clinical data or clinical information systems for reporting and analytics will also be consulted to provide insight into the back-end quality of clinical data.

Data collected through user consultations will be used to generate initial subthemes and themes using an inductive thematic analysis approach [50]. Generated themes and subthemes will then be assembled into a fishbone diagram [51], which is an LSS visualization technique to identify the root causes of poor data quality across services.

Phase 1.4: Improve (Part 1)

In the final phase of stage 1, information collected in the measure and analyze phases will be used to generate solutions to optimize clinical data quality across services. Solutions will address identified process-related issues (eg, deprioritization of documentation tasks and workforce roles and responsibilities) and system-related issues (ie, system design, performance, and usability).

Program-specific *data requirements* and *priorities* will be established to meet funding and regulatory requirements, best practice clinical guidelines, and the specific workflows of each service. In addition, data specifications will be developed to enable efficient and accurate information capture to enable high-quality primary (eg, care delivery) and secondary (eg, reporting, research, and evaluation) uses of data. A solutions selection matrix [43] will be used to propose and rank solutions according to perceived cost benefits and to prioritize recommendations for implementation based on the most urgent needs of the organization.

Stage 2: Optimization

Phase 2.1: Improve (Part 2)

Stage 2 will use Agile methodology to test and implement changes to clinical documentation processes and clinical information systems over a 12-month period.

Program-specific data optimization will be conducted to meet the specific workflows and funding, regulatory, and clinical requirements of each service. *Data requirements* and *priorities* established in stage 1 will determine the order of the Agile sprints (ie, incremental cycles of changes). At the end of each sprint, data quality will be evaluated by calculating DPU, DPO, DPMO, and the Sigma level statistics as mentioned in the *Phase 1.2: Measure* section. User acceptance, experience, and satisfaction will be evaluated through user surveys, and user feedback from each sprint will be directly incorporated into the next Agile sprint. This iterative optimization method ensures a flexible approach that incorporates both user feedback and statistical measurement.

Phase 2.2: Control

At the end of stage 2, governance policies and procedures and a control plan will be developed to allow the process owner to routinely monitor and evaluate the quality of clinical data across the service after implementation.

The control phase is the final phase and a critical part of the LSS DMAIC framework, which ensures that a new or improved process continues to work successfully after its implementation as a regular business process. A *Clinical Data Quality Audit Tool* will be designed to allow the routine evaluation of data quality across services as part of ongoing business practice. Internal policy and procedure documents will be developed, and training will be provided to the relevant departments.

Stage 3: Evaluation

The final stage of the study will evaluate changes in the primary and secondary outcomes in the 12 months following the full optimization (Table 5). Outcomes will be measured at T_0 and at 1, 3, 6, 9, and 12 months after full optimization. Previous studies in Australian RACFs have shown that the time spent on documentation tasks generally increases in the period after the implementation of new or changed systems as users learn the new technology and adjust their workflows [11,12]. Therefore, long-term evaluation is critical for reliably quantifying changes in outcomes and their impact on organizational processes.

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Table 5. Primary and secondary outcomes and data collection plan.

Outcomes and data source or method	Time point								
	Baseline (T_0)	Sprints 1 to n			Follow-up				
		T_1	T_2	T_n	$T_{1\ month}$	$T_{3\ months}$	$T_{6\ months}$	$T_{9\ months}$	$T_{12\ months}$
Primary outcome									
Data quality									
DPU[a]									
EHR[b] audit	✓	✓	✓	✓	✓	✓	✓	✓	✓
DPO[c]									
EHR audit	✓	✓	✓	✓	✓	✓	✓	✓	✓
DPMO[d]									
EHR audit	✓	✓	✓	✓	✓	✓	✓	✓	✓
Sigma level									
EHR audit	✓	✓	✓	✓	✓	✓	✓	✓	✓
Secondary outcomes									
Care delivery									
Direct care time									
Self-report survey	✓				✓	✓	✓	✓	✓
Documentation time									
Self-report survey	✓				✓	✓	✓	✓	✓
Other activities									
Self-report survey	✓				✓	✓	✓	✓	✓
Clinical outcomes									
Pressure injury[e]									
EHR audit	✓				✓	✓	✓	✓	✓
Restraints[e]									
EHR audit	✓				✓	✓	✓	✓	✓
Falls[e]									
EHR audit	✓				✓	✓	✓	✓	✓
Weight loss[e]									
EHR audit	✓				✓	✓	✓	✓	✓
Medication management[e]									
EHR audit	✓				✓	✓	✓	✓	✓
Behaviors of concern									
EHR audit	✓				✓	✓	✓	✓	✓
Choking									
EHR audit	✓				✓	✓	✓	✓	✓
Infection									
EHR audit	✓				✓	✓	✓	✓	✓
Unplanned hospital admission									
EHR audit	✓				✓	✓	✓	✓	✓
Wounds									

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Outcomes and data source or method	Time point								
	Baseline (T_0)	Sprints 1 to n			Follow-up				
		T_1	T_2	T_n	$T_{1\ month}$	$T_{3\ months}$	$T_{6\ months}$	$T_{9\ months}$	$T_{12\ months}$
EHR audit	✓				✓	✓	✓	✓	✓
Business outcomes									
Cost of quality									
Cost analysis	✓								✓
Workforce productivity									
Self-report survey	✓				✓	✓	✓	✓	✓
End user									
User satisfaction									
Self-report survey	✓				✓		✓		✓
User experience									
Self-report survey and interviews		✓	✓	✓					✓

[a]DPU: defects per unit.

[b]EHR: electronic health record.

[c]DPO: defects per opportunity.

[d]DPMO: defects per million opportunities.

[e]National Quality Indicator Program (NQIP) outcome.

Primary Outcome

The primary study outcome is data quality measured using DPU, DPO, DPMO and Sigma level. Improvement in data quality from T_0 to 12 months after optimization will be determined by a reduction in DPU, DPO, and DPMO and an increase in Sigma level. A well-performing process should operate at a Sigma level of 6 and have ≤3.4 DPMO [43].

Secondary Outcomes

Care Delivery

Care delivery will be measured by the proportion of weekly direct care time spent with residents using a self-report version of the Work Measurement Tool developed by Munyisia et al [52], which measures 8 categories of care activities in Australian RACFs, including *direct care*, *medication management*, *communication*, *documentation*, *indirect care*, *personal*, *in-transit*, and *other*. Clinical and care staff will be invited to complete self-report surveys from T_0 to 12 months after optimization to provide a measure of workflow before and after optimization. Self-reported activities will be validated against observer-rated activities for a random staff subsample.

Clinical Outcomes

Under the National Quality Indicator Program, Australian aged care providers are required to undertake mandatory reporting of 5 National Quality Indicator Program indicators as a measure of the quality of clinical services and care provision [53]. These include *pressure injuries*, *physical restraints*, *falls*, *unplanned weight loss*, and *medication management*. In addition, Brightwater routinely measures 5 internal clinical indicators of quality across both aged care and disability services (behaviors of concern, choking, infection, unplanned hospital admission, wounds; Table 5). This study will measure changes in clinical outcomes from T_0 to 12 months after optimization.

Business Outcomes

A cost of quality (CoQ) analysis [54] will be undertaken to compare the operational costs before and after optimization. The CoQ analysis is a critical part of the LSS framework to estimate the ongoing operational costs of optimizing the data or information system and to ensure that the expenses associated with achieving higher data quality are balanced against the costs of poor quality, which is defined as expenses incurred on resources and non–value-added activities to fix poor-quality data. CoQ costs include costs incurred on the optimization, ongoing operation, and maintenance of the data or information system, whereas poor-quality costs include costs incurred on activities such as data cleaning, data quality inspection, and meetings to rectify data inconsistencies. A health economist will be employed to undertake the CoQ analysis.

In addition, workforce productivity will be evaluated before and after optimization in relation to regulatory reporting. Corporate staff will be invited to complete self-report surveys from T_0 to 12 months after optimization to provide an estimate of the number of hours worked to complete regulatory reporting activities before and after optimization.

User Satisfaction

Finally, self-report surveys and qualitative interviews will be used to measure changes in user satisfaction with clinical data systems before and after optimization. Prior research has shown that clinical documentation burden is a major driver of burnout among care staff [14,15] and can negatively impact job

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satisfaction [17]. Therefore, user satisfaction is an important outcome of this study.

Quantitative Analysis

Quantitative analyses will be conducted using STATA (version 16.0; StataCorp LLC) [55]. Multilevel mixed effects regression models will be used to evaluate any change in primary and secondary outcomes from T_0 to 12 months after optimization. For clustered longitudinal data, multilevel modeling recognizes that a change in outcome is affected by a fixed effect (ie, implemented changes) and random effects at both individual and group levels and can explicitly account for this multilevel random variation [56].

An a priori power calculation was performed to determine the minimum number of EHRs required to be evaluated to detect a significant change in our primary outcome (ie, data quality measured using DPU, DPO, DPMO, and Sigma level) from T_0 to 12 months after optimization. First, we used G*Power [57] to compute the required sample size to detect a medium difference (f=0.15) at a Cronbach α level of .05 and a power level of .80 using a linear multiple regression analysis with k=3 fixed predictors (time, program, and the time × program interaction), which returned a required sample size of 77.

This was multiplied by the anticipated *design effect* [58], which is an adjustment factor for clustering in multilevel models. The design effect is calculated as:

$$1 + [(n - 1) \times \text{ICC}] \quad \textbf{(1)}$$

where n is the expected number of subjects per cluster and "ICC" is the intracluster coefficient or the expected correlation within clusters [58]. We defined a cluster as a facility (ie, site) with a median cluster size of 30 clients per facility. With an anticipated moderate intracluster coefficient of 0.10, the design effect is equal to 3.9, giving a required sample size of 77 × 3.9 = 300. On the basis of the occupancy rates and client population size (n=2200) as of January 2022, our primary outcome analysis will have sufficient statistical power.

Qualitative Analysis

Qualitative data from user interviews and surveys will be coded and analyzed using NVivo 12 (QSR International) [59]. An inductive thematic analysis approach will be used to identify and understand key themes, specifically to classify, order, and reassemble data to identify converging and diverging perspectives. A total of 50 interviews are anticipated to reach saturation.

Results

As of June 1, 2022, stage 1 commenced with T_0 data quality audits conducted to identify the current data quality and system strengths and limitations. T_0 data quality audits will be followed by user consultations to identify root causes of data quality issues. Clinical information requirements will be developed by May 2023 to inform optimization (stage 2) and evaluation (stage 3). Results are expected to be published in June 2023.

Discussion

It is anticipated that the study findings will show that optimization of clinical data and documentation will, in turn, have a major impact on care delivery and clinical outcomes and reduce business costs. Although the aim of the OPTIMISE study is to build internal organizational capacity for continuous improvement of clinical data quality, the findings will also be important to individuals and organizations across the aged care and disability service sector, as well as the wider health care sector, which is seeking novel technology solutions to improve the quality of clinical data to support high-quality care delivery and operational efficiency. In addition, the findings will be relevant to researchers and organizations interested in learning the opportunities and limitations of engaging an Agile LSS framework for quality improvement in a health care setting. These findings can stimulate organization-level research to support the development of evidence-based care. The findings will also be disseminated nationally and internationally through industry presentations, scientific conference presentations, and peer-reviewed journal publications.

Data Availability

Data sharing is not applicable for this paper as no data sets were generated or analyzed during this study.

Authors' Contributions

LT designed and leads the study; developed the study framework, methodology, and analysis plan; and leads the evaluation. GT designed the study, developed the study framework and methodology, and performs data collection and analysis. RW performs data collection and analysis. AM designed and leads the study and provides study oversight. MR developed the technology strategy and leads the technology optimization.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Lean Six Sigma techniques.
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Multimedia Appendix 2
Interview schedule.
[PDF File (Adobe PDF File), 542 KB - resprot_v12i1e39967_app2.pdf]

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Abbreviations

CoQ: cost of quality
CTQ: critical-to-quality
DMAIC: Define, Measure, Analyze, Improve, Control
DPMO: defects per million opportunities
DPO: defects per opportunity
DPU: defects per unit
EHR: electronic health record
HIT: health IT
LSS: *Lean Six Sigma*
OPTIMISE: Optimizing the Quality of Clinical Data in an Australian Aged Care and Disability Service to Improve Care Delivery and Clinical Outcomes
RACF: residential aged care facility
T0: baseline

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Protocol

Prehabilitation Before Gastrointestinal Cancer Surgery: Protocol for an Implementation Study

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Abstract

Background: Surgery remains the standard curative treatment for early-stage colorectal and upper gastrointestinal cancer. Reduced preoperative functional capacity, nutritional status, and psychological well-being are associated with poor postoperative outcomes. Prehabilitation aims to improve preoperative functional reserves through physical, nutritional, and psychological interventions. Yet, how it transitions from a trial setting to being integrated into a real-world health setting is unknown.

Objective: The primary aim is to evaluate the implementation of a multimodal (supervised exercise, nutrition, and nursing support) prehabilitation program into standard care for patients with gastrointestinal cancer (colorectal and upper gastrointestinal cancer) scheduled for curative intent surgery. The secondary aim is to determine the impact of a multimodal prehabilitation program on functional capacity, nutritional and psychological status, and surgical outcomes.

Methods: This is an implementation study that will investigate a multimodal prehabilitation intervention, in a nonblinded, nonrandomized, single-group, pre-post design. Patients diagnosed with colorectal and upper gastrointestinal cancer scheduled for potentially curative intent surgery at Concord Repatriation General Hospital, with ≥14 intervention days prior to surgery and are medically cleared to exercise will be eligible. The study will be evaluated using the Reach, Effectiveness, Adoption, Implementation, and Maintenance Evaluation Framework.

Results: The protocol was approved in December 2019 by the Concord Repatriation General Hospital Human Research Ethics Committee (reference number 2019/PID13679). Recruitment commenced in January 2020. In response to the COVID-19 pandemic, recruitment was paused in March 2020 and reopened in August 2020 with remote or telehealth intervention adaptations. Recruitment ended on December 31, 2021. Over the 16-month recruitment period, a total of 77 participants were recruited.

Conclusions: Prehabilitation represents an opportunity to maximize functional capacity and improve surgical outcomes. The study will provide guidance and contribute to the evidence on the integration of prehabilitation into standard care using adaptive models of health care delivery including telehealth.

Trial Registration: Australian and New Zealand Clinical Trials Registry ACTR 12620000409976; https://anzctr.org.au/Trial/Registration/TrialReview.aspx?id=378974&isReview=true

International Registered Report Identifier (IRRID): RR1-10.2196/41101

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(JMIR Res Protoc 2023;12:e41101) doi:10.2196/41101

KEYWORDS

prehabilitation; gastrointestinal; cancer; surgery; exercise; nutrition; telehealth; colorectal; psychological

Introduction

Gastrointestinal cancer is a common type of cancer, with around 28,600 Australians diagnosed each year [1], and incidence rates are expected to increase with our aging population. In Australia alone, colorectal cancer (CRC) is the fourth most diagnosed cancer and the second most common cause of death, with 15,540 new cases and 5295 deaths estimated per year [1]. Upper gastrointestinal (UGI) cancers including esophageal, gastric, hepatic, pancreatic, and biliary represent approximately 12,434 new cancer cases [2] and more than 17% of cancer-associated deaths [1]. Despite improvements in surgical and oncological treatments, morbidity rates remain high, particularly among those with UGI cancer [3].

Surgery remains the best chance of cure for patients with colorectal cancer and upper gastrointestinal cancer. However, even with advances in surgery, anesthesia, and perioperative care, including the application of enhanced recovery after surgery protocols to mitigate the surgical stress response [4,5], postoperative complications still occur in 30%-50% of patients and are associated with higher morbidity and mortality rates, increased health care costs, and reduced quality of life [6-8]. Even in the absence of complications, major gastrointestinal surgery can still result in a 20%-40% reduction in physical and functional capacity, nutritional decline, and delayed recovery [9,10] particularly in the elderly or those with comorbidities, with many not returning to their baseline function or proceeding to their intended oncological treatment.

In the past decade, the focus of optimizing patients in the preoperative period to withstand the upcoming surgical stressor has emerged in a concept known as prehabilitation. Prehabilitation aims to improve preoperative functional reserves through physical, nutritional, and psychological interventions to mitigate the predictable detrimental effects of surgery [11,12]. While early prehabilitation studies focused on the feasibility of singular interventions [12], a multimodal (exercise, nutrition intervention, and psychological support) approach is increasingly favored [13-17]. We previously reported a pilot feasibility study of a short-term multimodal (exercise, healthy eating, and nursing support) prehabilitation program in CRC surgery [18]. In total, 22 participants completed the program, and the median length of the intervention was 14 (range 7-29) days. We found that attendance was excellent (78.5%, mean 3.5 sessions), moderate-intensity aerobic exercise increased from 17 to 73 minutes per week, and functional capacity measured using the 6-minute walk test (6MWT) [19,20] had a clinically significant increase of 48 (from 435 to 483) m. Participant satisfaction was excellent, with all participants strongly recommending prehabilitation.

While the evidence surrounding prehabilitation grows, how it transitions from a trial setting to being integrated into a real-world health setting is less clear. Implementation science frameworks aim to help understand the barriers and facilitators to support the uptake of research findings into routine clinical care [21]. The “RE-AIM” (Reach, Effectiveness, Adoption, Implementation, Maintenance) evaluation framework [22,23] is a theoretical implementation framework that can guide and assess the translation from research into practice at both the individual and organizational levels. The primary aim of this study is to evaluate the implementation of a multimodal (supervised exercise, nutrition intervention, and nursing support) prehabilitation program into standard care for patients with gastrointestinal cancer (CRC and UGI cancer) scheduled for curative intent surgery using the RE-AIM framework. The secondary aim is to determine the impact of a multimodal prehabilitation program on functional capacity, nutritional and psychological status, quality of life (QOL), length of stay at the hospital, and postsurgical outcomes including complications and recovery. We hypothesize that prehabilitation (1) will be feasible, with good participant adherence; (2) will decrease the length of stay at the hospital and postsurgery complications; and (3) improve functional and nutritional status, recovery, and QOL. Here, we outline the trial protocol, including adaptations made to accommodate the COVID-19 pandemic.

Methods

Study Design and Setting

This protocol describes a translational, implementation study that will investigate a multimodal prehabilitation intervention, in a nonblinded, nonrandomized, single-group, pre-post design, in patients with colorectal cancer and upper gastrointestinal cancer undergoing potentially curative intent surgery at Concord Repatriation General Hospital, a tertiary teaching hospital in Sydney, Australia. The study will be evaluated using the RE-AIM Evaluation framework [22,23] (Table 1). Exploratory comparisons of some secondary end points will be made with historical colorectal cancer and upper gastrointestinal patient data obtained from the hospital’s surgical database. The minimum recruitment period will be 12 months. Recruitment commenced in January 2020.

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Table 1. Reach, Effectiveness, Adoption, Implementation, and Maintenance evaluation framework adapted to prehabilitation before gastrointestinal cancer surgery study.

Domain	Description	Data collection instrument
Reach	• The number (and proportion) of eligible patients having gastrointestinal cancer surgery who participated (numerator) and how representative they are of the target population (denominator) of participants and eligible patients who did not consent • Participant characteristics and comparison to nonparticipants	• Patient screening logs • Prehabilitation before gastrointestinal cancer surgery study Research Electronic Data Capture (Vanderbilt University) database including demographics
Effectiveness	• Changes in functionality, nutrition, and well-being from pre- to post intervention	• Participant-reported outcomes (psychological status, and quality of life) and functional assessments (6-minute walk test and 2-minute step test), nutritional status, and body composition, at baseline, before surgery, and 30 days after surgery assessments
Adoption	• For the single site, the number of surgeons who participated versus invited surgeons, characteristics of participating surgeons versus non-participating surgeons, the number of referrals received, referral sources, and barriers to referrals • Clinician and surgeon perceptions	• Number of referring surgeons (numerator) versus total number of surgeons at the site treating colorectal cancer or upper gastrointestinal cancer patients (denominator) • In-house clinician satisfaction surveys
Implementation	• Fidelity of intervention in the real world: consistency of the intervention delivery described in the protocol and adaptations made • Intervention completion rates, defined as the proportion of participants that completed the intervention with reasons for withdrawal described • Participant adherence to the intervention and completion of program evaluation	• Intervention session notes compared with the protocol • Prehabilitation before gastrointestinal cancer surgery study database regarding adherence, completion, and withdrawals • Exercise attendance and support phone call logs • Self-reported exercise and protein diary • Satisfaction surveys and exit interviews
Maintenance	• Setting level: extent of program delivery as part of standard care 12 months after study completion • Standard care program adaptations	• Participant enrolment in the standard care prehabilitation program and delivery as recorded in the medical notes • Multimodal program intervention

Ethics Approval

Ethics approval was granted by Concord Repatriation General Hospital Human Research Ethics Committee under reference number 2019/PID13679, and the study was registered on the Australian and New Zealand Clinical Trials Registry (ACTR 12620000409976). The study will be performed in accordance with the National Health and Medical Research Council National Statement on Ethical Conduct in Human Research (Commonwealth of Australia, 2007 and updates) and the World Medical Assembly (Helsinki 2017 and updates).

Study Population

Patients will be considered eligible if they are 18 years or older, undergoing elective colorectal cancer or upper gastrointestinal cancer resection with curative intent at the Concord Repatriation General Hospital with a minimum of 14 days prior to surgery for the intervention. All participants must be medically fit to exercise as determined by their treating physician, willing to attend supervised exercise sessions at the Sydney Cancer Survivorship Gym Concord Repatriation General Hospital 1-2 times per week, take prescribed high protein oral nutritional supplements, and have Eastern Co-operative Oncology Group performance status of 0-2 [24]. Patients treated with neoadjuvant chemotherapy or radiotherapy are eligible to participate after completion of neoadjuvant chemotherapy or radiotherapy provided there is a 14-day intervention time available before surgery. Patients who do not speak English are eligible and will be provided with a professional health interpreter. Inclusion and exclusion criteria are further outlined in Textbox 1.

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Textbox 1. Study inclusion and exclusion criteria.

Inclusion criteria

- Aged at least 18 years
- Give written informed consent
- Confirmed stage I-III colorectal or upper gastrointestinal cancer or limited stage IV (eg, limited liver metastases planned for curative resection) cancer that is potentially curable with surgery
- Elective surgery scheduled ≥14 days after the time of referral
- Medically cleared to exercise, as determined by the treating physician or Adult Pre-exercise Screening System page 1 V2 (2019) [25]
- Willing to attend supervised exercise sessions at the Concord Repatriation General Hospital Sydney Cancer Survivorship Gym 1-2 times per week until surgery
- Willing to take daily high protein study oral nutritional supplement until surgery
- Eastern Co-operative Oncology Group [24] performance status of 0-2
- Willing to complete patient-reported outcome questionnaires and exercise or dietary logs
- Agreeable to follow-up for 30 days after surgery

Exclusion criteria

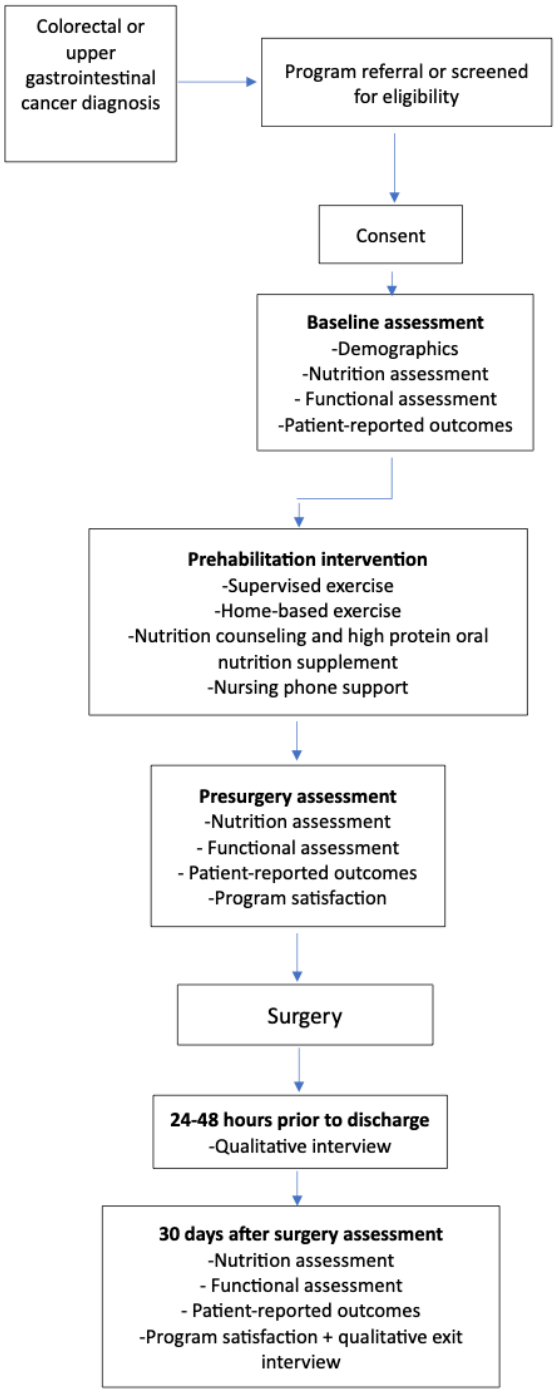
- Unable to exercise or take high protein oral nutritional supplements for physical or medical reasons
- Taking immunonutrition supplements (eg, oral nutritional supplements with immunomodulating ingredients) during the intervention
- Unable to give informed consent or follow instructions due to cognitive difficulties
- Currently receiving chemotherapy or radiotherapy (patients will be eligible providing ≥14 days is still available after completion of neoadjuvant chemotherapy and radiotherapy and before surgery)

Study Procedure

Patients will be referred directly by their surgeon or oncologist or screened in a preadmission clinic for eligibility. Patient flow throughout the study is presented in Figure 1. The study coordinator or cancer nurse specialist will screen and contact eligible patients to explain the study. After consent, a baseline assessment will be conducted in eligible participants within 1-2 days of referral from the surgeon or preadmission clinic visit. Day 1 of the intervention period will be the day of the baseline assessment.

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Figure 1. Study flowchart.

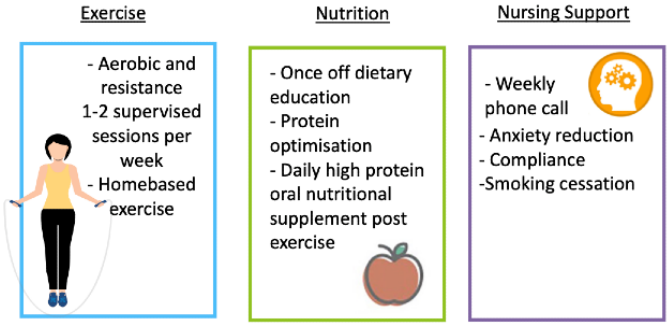


Intervention

The duration of the intervention will vary depending on the scheduled surgery date but will run over 2-4 weeks (minimum of 14 days). The intervention is outlined in Figure 2.

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Figure 2. Multimodal prehabilitation intervention.



Exercise

An accredited exercise physiologist will assess the participant's mobility and exercise capacity during the baseline assessment. Participants must commit to a minimum of one 60-minute weekly supervised session but will be encouraged to attend two 60-minute supervised exercise sessions per week.

Exercise sessions will include both aerobic and resistance exercise training. These sessions will be individually prescribed, facilitated, and monitored by an accredited exercise physiologist at the Sydney Cancer Survivorship Gym, Concord Cancer Centre. Exercise sessions will be delivered either individually or in a small group-based format with other cancer survivors. All participants will complete a warm-up routine consisting of dynamic stretching and a range of motion exercises. Participants will complete 20 minutes of aerobic exercise per 60-minute session with a target intensity of 60%-75% of heart rate reserve. Aerobic exercise may include the use of a cycle ergometer, treadmill, rowing ergometer, elliptical trainer, boxing due to equipment availability, and will be selected depending on participants' preference and capability. The remainder of each session will focus on resistance exercises targeting large muscle groups through multijoint movements and use body weight, hand weights, resistance bands, or cable machine exercises. Participants are assisted in completing 2 sets of 8-12 repetitions for each movement with a target rating of perceived exertion of 13-15, measured using Borg's Rating of Perceived Exertion 6-20 scale [26]. Heart rate and rating of perceived exertion will be recorded throughout each session for safety monitoring and exercise prescription purposes. The exercise volume and intensity will be adjusted by the exercise physiologist in a stepwise fashion.

Participants will be advised to participate in a nonhospital–based aerobic exercise (eg, walk, jog, cycle, swim, and step) program tailored to their baseline ability on at least 5 days per 7-day period. The target duration is a minimum of 30 minutes (continuous or broken into shorter bouts) per day at a self-rated perceived exertion of moderate intensity (13-15). An exercise diary and instructions will be provided to capture the frequency, intensity, time, and type of exercise. During the supervised exercise sessions, the exercise physiologist will provide support to promote program compliance, progression, and adherence.

Nutrition

Nutritional assessments will be completed by an Accredited Dietitian at baseline, before surgery, and 30 days after surgery, using The Patient-Generated Subjective Global Assessment [27]. Other assessments include body composition measured using bioelectrical impedance analysis (The Seca mBCA 515 Analyser) and a diet assessment (calories and protein) using a 24-hour diet recall.

Participants will receive a 200 mL bottle high protein oral nutritional supplement (Fresubin Protein Energy Drink, Fresenius Kabi) containing 20 g protein and 300 kcal per 200-mL bottle to be consumed daily within 60 minutes after exercise to support muscle synthesis [28-30]. Fresubin Protein Energy Drink is taken in addition to normal food and protein intake. Oral nutritional supplement tolerance will be assessed and recorded by the study dietitian. Dietary advice and written material will be provided with the aim of assisting the participant to achieve a protein intake (spread across meals) of 1.2-1.5 g per kg per body weight (or adjusted body weight in participants with obesity) as per the European Society for Clinical Nutrition and Metabolism guidelines [28]. Participants who have additional nutritional support needs (ie, malnutrition or nutrition-impact symptoms: early satiety, altered bowels, nausea, and loss of appetite), will have further individualized nutrition support and have education as a standard of care as determined by the dietitian and their clinical team. Nutrition support after surgery will be determined by the clinical team as per standard practice.

Nursing Support

Participants will be contacted weekly by phone or in person, associated with gym visits, by a cancer nurse specialist to provide support promoting adherence to the exercise and nutritional interventions, reassurance, and to enable participants to discuss any concerns about their upcoming surgery. Participants who are smokers will be strongly encouraged to stop smoking. Sessions are based on semistructured questions developed in association with an experienced oncology clinical psychologist. See Multimedia Appendix 1 for further details. Participants could be referred to a clinical psychologist according to the standard of care if the cancer nurse specialist believed it was required.

Program Satisfaction

Participants will complete an investigator-developed satisfaction survey at completion of the intervention prior to surgery (1-4 days before hospital admission or surgery) and 30 days after surgery (±7 days). A qualitative semistructured exit interview will be conducted 24-48 hours prior to hospital discharge and

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at 30 days after surgery, by an independent researcher face-to-face or over the phone in a subset of participants.

Surgical ward nurses will be requested to complete a survey before the prehabilitation intervention begins and after the completion of the study. Clinical specialists (surgeons and anesthetists) will be requested to complete a web-based evaluation survey after completion of the study.

Study Outcomes

Data will be collected at 3 assessment times: baseline, before surgery (1-4 days before hospital admission or surgery), and 30 days (±7 days) after surgery assessment. Additional data will be collected during the participant's hospital stay. Table 2 gives an overview of all assessments and measurements. The primary end point is related to implementation based on the RE-AIM evaluation framework (Table 1) and will be reported using the following dimensions:

- Reach: number (and proportion) of eligible patients having gastrointestinal cancer surgery who participated among eligible participants and patients who did not consent, and participant characteristics.
- Effectiveness: change in participant outcomes (functionality, nutrition, and well-being) before and after the intervention.
- Adoption: number (and proportion) of surgeons who referred and surgeon characteristics. Total number of referrals, referral sources, barriers to referrals, and clinician and surgeon perceptions.
- Implementation: delivery of the intervention as per the protocol and adaptations made. Overall completion rates, withdrawals and reasons, adherence to exercise sessions, nutrition intervention, and nurse support, and completion of program evaluations.
- Maintenance: status of the program 12 months after study completion and adaptions made.

The secondary end points collected are outlined in Table 2.

Other exploratory end points include the following:

- Participant satisfaction/experience: measured using an investigator-developed questionnaire and qualitative exit interviews.
- Compliance/adherence: measured through attendance logs (exercise and nursing support) and a participant self-reported diary (exercise and high protein oral nutritional supplement consumption).

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Table 2. Assessments and outcomes.

Variables	Timeline
Demographics/history	
• Age • Sex • Smoking history • Background, language spoken, with or without an interpreter • Medical history • Concomitant medications • Cancer diagnosis • Comorbidity index [31,32] • Eastern Co-operative Oncology Group performance status [33]	Baseline, before surgery, and 30 days after surgery
Functional assessment	
• Handgrip strength • 30-second chair stand [34] • 2-minute step test [34] • 3-m timed up and go [35] • 6-minute walk test [19,20] • Activities of daily living [36]	Baseline, before surgery, and 30 days after surgery
Anthropometry	
• Height (cm) (baseline only) • Weight (kg) • Body mass index (BMI) (kg/m^2) • Body composition: fat mass, fat-free mass, skeletal muscle mass, and visceral adipose tissue • Waist circumference (cm)	Baseline, before surgery, and 30 days after surgery
Nutritional assessment	
• Nutritional status using PG-SGA[a] [27] • Total protein intake (diet and oral nutritional supplement): 24-hour diet recall • Patient high protein supplement diary (during intervention)	Baseline, before surgery, and 30 days after surgery
Patient-reported outcomes	
• Exercise behavior—modified Godin's Leisure Time Exercise Questionnaire [37] and Exercise Log/Diary • QoL: EORTC QLQ-C30[b] [33] • FACIT-F[c] subscale [38] • Symptoms of anxiety and depression—HADS[d] [39] • Nutrition/Sarcopenia—PG-SGA. Short form [27] and sarcopenia screening using SARC-F[e] [40] • Distress—National Comprehensive Cancer Network Distress Thermometer (single item) [41]	Baseline, before surgery, and 30 days after surgery
Adverse events	
• Adverse events will be recorded and graded using National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0 (NCI CTCAE v5.0) [42]	Baseline and before surgery
Hospital stay information	
• Surgical complications: intra- and postoperative including Clavien Dindo Grading (I-V) [43] • Length of hospital stay (days) • Discharge information including medically cleared for discharge date, social services required on discharge, discharge destination, and so forth • Length of physiotherapy intervention (days) • Readmission within 30 days of surgery	30 days after surgery
Compliance/adherence	
• Attendance at exercise sessions • Home-based exercise/protein diary (self-reported) • Adherence to nurse calls • Adherence to protein supplement drinks (self-reported)	Before surgery

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Variables	Timeline
Program evaluation	
• Investigator-developed program satisfaction survey • Exit interview	Baseline and before surgery

[a]PG-SGA: Patient-Generated Subjective Global Assessment.

[b]EORTC QLQ-C30: European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire.

[c]FACIT-F: Functional Assessment of Chronic Illness Therapy—Fatigue.

[d]HADS: Hospital Anxiety and Depression Scale.

[e]SARC-F: Strength, assistance with walking, rising from a chair, climbing stairs, and falls.

COVID-19 Adaptations

Assessments and interventions were initially designed to be conducted face-to-face. In response to the COVID-19 pandemic, local lockdowns, reduction in nonurgent face-to-face health care, and cancellation of nonurgent elective surgery with decreased surgery activity, face-to-face recruitment, and intervention delivery were paused in March 2020. The study protocol was adapted to use digital technologies and telehealth methods, and recruitment was recommenced in August 2020. Textbox 2 highlights the key changes.

Textbox 2. Protocol telehealth adaptations to accommodate the COVID-19 pandemic.

- Inclusion criteria
  - Access to internet-based videoconferencing platforms including email address and internet (family members to assist if required)
- Consent
  - Electronically completed consent forms
- Baseline, before surgery, and 30 days after surgery assessments
  - Assessments conducted remotely over videoconferencing or zoom appointments with links emailed to participants
- Nutrition assessment
  - Anthropometric variables self-measured: weight, height, and girths (waist, hip, and midarm; standardized tape measure provided)
  - Body composition analysis omitted
- Exercise assessment
  - Remote functional capacity assessment
    - 6-minute walk test and hand grip test omitted
    - Continuation of 30-second chair stand, 2-minute step test, 3-m timed up and go (to measure cardiovascular fitness)
- Supervised exercise intervention
  - Home-based individualized supervised exercise sessions conducted remotely via videoconferencing or zoom
  - Principles of the original protocol were followed in terms of frequency, intensity, time, and types of exercise
- Nutrition intervention
  - Education material and high protein oral nutritional supplements mailed to participants
- Patient-reported outcome questionnaires
  - Completed by hard copy (mailed out) or web-based or electronically using Research Electronic Data Capture

Statistical Analysis

Sample Size

The sample size is pragmatic, which is based on 2018/2019 surgical and oncology site numbers. We estimate that 50% (n=85) of eligible participants will agree to participate in the prehabilitation program. The study anticipates recruiting 100 participants over a 12-month period. Based on our pilot study adherence and the short-term nature of the intervention, we anticipate attrition will be less than 20% (n=20) of those who complete the baseline assessment, but higher in those who have already undergone neoadjuvant chemotherapy. This gives us sufficient statistical power at the 5% significance level to detect

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an increase of 20 m in the distance walked in the 6MWT from baseline to postintervention based on our pilot study.

Statistical Analyses

The primary outcome based on the RE-AIM evaluation framework will be reported descriptively, with a focus on referral, recruitment, and retention targets.

Secondary end points including baseline characteristics, functional, and nutritional status, will be reported using descriptive statistics, mean (SD) for normally distributed data, or median and IQR for nonnormally distributed data. Counts and percentages will also be used as appropriate. Reported changes in outcome variables from baseline to postintervention (presurgery) and 30 days after surgery will be measured using mixed models and will include all participants with baseline data including those with missing data at follow-up, with adjustment for predictors of dropouts to minimize selection bias. Postsurgery outcome variables will be evaluated using mixed models. Outcomes for UGI cancer and CRC participants will be evaluated separately and combined. Length of hospital stay and postsurgical complications will be compared to historical data from the hospital's surgical 2019 database.

Responses to the investigator-developed questionnaire (participants and clinician) will be presented descriptively using means (SDs) or medians (IQR) and counts and percentages as appropriate. Free text responses will be summarized. The statistical package SPSS (version 24 or the newest release) will be used for quantitative data analysis.

Semistructured interviews regarding participant satisfaction will be transcribed verbatim and undergo qualitative content analysis. Initial transcript sample readings will be carried out. Themes and content will be analyzed descriptively. Coding, linking, and retrieving the qualitative data will be conducted using NVivo software (QSR International).

Data Collection and Management

Participants will be given a unique study number. Deidentified information will be entered into a password-protected project specific Research Electronic Data Capture Database (Vanderbilt University) at Concord Cancer Centre, Concord Repatriation General Hospital. Identifiable information will be stored in a standalone instrument within the Research Electronic Data Capture database and access restricted to a limited number of the research team. In addition, deidentified raw body composition data will be stored on a copy of the manufacturer's secure password-protected computer software (Seca) at the Concord Cancer Centre, Concord Repatriation General Hospital.

Results

The study recruitment commenced in January 2020. Recruitment was paused in March 2020, due to the COVID-19 pandemic, and the protocol was adapted to include a remote or telehealth intervention. Recruitment restarted with the telehealth adaptations in August 2020. Due to ongoing COVID-19 disruptions (restrictions and cancellation of elective surgeries at the hospital), recruitment was extended until December 31, 2021. During the 16-month active recruitment period, a total of 198 (133 CRC and 65 UGI) patients were screened, of which 102 were ineligible. The most common reasons for ineligibility were less than a 14-day intervention time period between screening or referral and scheduled surgery date (n=64), not for surgical intervention (n=12), and not medically cleared to exercise (n=6). In total, 96 patients met the eligibility criteria, and 77 were recruited (64 patients with colorectal cancer and 13 patients with upper gastrointestinal cancer). The results from the study will be analyzed and published in a peer-reviewed journal.

Discussion

Principal Findings

Surgery remains the standard curative treatment for early-stage CRC and UGI cancers. Despite advancements in surgical practices and postoperative care pathways, morbidity and mortality rates remain high [6,7,10]. A reduction in postoperative complications is important. It is well established that the number and severity of postoperative complications are associated with preoperative health status, functional capacity, nutritional status, and muscle strength [44]. While traditional approaches have focused on lifestyle modifications in the postoperative period, recent evidence shows that the preoperative period may be the more appropriate time to intervene [45].

Positive lifestyle practices, including exercise and nutrition, are associated with many health benefits and have been shown to decrease the risk of several common cancers, including CRC and some UGI cancers, and possibly to decrease the risk of cancer recurrence [46,47]. However, only approximately 20% of people diagnosed with cancer are meeting the current exercise guidelines [48-50], and only 37% of patients with gastrointestinal cancer undergo nutrition screening and are offered preoperative nutrition support [51,52]. Recent reviews indicate that optimizing functional capacity with exercise, nutrition interventions, and psychological support strategies in a gastrointestinal surgical population resulted in reduced complications, length of hospital stay, and improved QOL [13-17]. However, few studies have evaluated the integration of prehabilitation practices into standard of care.

This pragmatic prehabilitation program will deliver integrated care, increasing patients' self-management skills to support healthy living during and after a cancer diagnosis. It has the potential to change standard care with a simple, safe, relatively inexpensive coordinated intervention that confers multiple physical and psychological health benefits. This study will determine whether a multimodal (exercise, nutrition intervention, and nursing support) prehabilitation program can be integrated into routine standard care and whether it improves outcomes by reducing postoperative complication rates and length of stay at the hospital. Unique data will be collected on physical activity, nutritional status, dietary intake, and psychological well-being and their influence on surgical outcomes to inform the current evidence base in gastrointestinal surgical oncology preoperative care.

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Prehabilitation adapted to include a telehealth model of care represents a strategy to combat pandemic-related patient and health system challenges. Telehealth initiatives provide an opportunity to minimize health inequalities [53] and improve patient outcomes and access to health care services [54] by offering an alternative delivery method that is not bound by location, especially for those living remotely, or those who have travel difficulties, caregiver or work commitments, or conflicting medical appointments. While telehealth interventions can vary from live consults, electronic monitoring, questionnaires, and support using multimedia platforms, the benefits of education sessions conducted by telehealth have shown to improve the patient's knowledge and satisfaction during cancer treatment [55]. While the evidence in the preoperative setting is limited [56,57], preliminary findings indicate that home-based prehabilitation programs delivered by telehealth are positively received by patients and clinicians.

The hospital system is complex. Engagement from clinicians, administrative personnel, and participants is crucial to the successful implementation of a multimodal intervention. Importantly, the results of this study will identify priority areas regarding the value and feasibility of integrating prehabilitation into routine quality cancer care for patients undergoing major cancer surgery. It has the potential to improve the outcomes of patients undergoing resection for CRC and UGI cancer and deliver better health at a low cost to the Australian and wider communities.

Conclusions

Prehabilitation represents an opportunity to intervene, treat, and prevent physiological and nutritional decline before major gastrointestinal cancer surgery by combining physical, nutritional, and psychological interventions in a multimodal approach. The study will provide new evidence on the integration of prehabilitation into standard care using adaptive models of health care delivery including telehealth, with the secondary aim of improving postoperative outcomes. The intervention could be generalizable to other types of cancer, emphasizing the importance of preoperative optimization to mitigate the surgical stress response and improve patient outcomes. The study outcomes have the potential to change standard care, with a relatively inexpensive intervention delivered either face-to-face or by telehealth especially for those living remotely or with travel or social difficulties, which can improve health-related quality of life and reduce health care costs.

Acknowledgments

Fresenius Kabi supplied the high protein oral nutritional supplements and provided 1-year part-time funding for the study dietitian position. Additional funding was provided by Concord Cancer Centre through a seed research grant to support the part-time exercise physiologist position. Fresenius Kabi and Concord Cancer Centre did not contribute to the study design, data collection, and will not be involved in results analysis, interpretation, or dissemination.

Data Availability

Data will be available from the corresponding author upon reasonable request.

Authors' Contributions

JV is the coordinating investigator and devised the study concept and design. All authors contributed to the study protocol with KLR and JV as the first author and principal investigator, respectively. KLR, SYT, SE, and JV wrote the initial manuscript. All authors read and approved the final manuscript. SE provided statistical analysis support.

Conflicts of Interest

The Concord Repatriation General Hospital Dietetics department and KLR discloses that funding was received for a part-time wage for 1 year from Fresenius Kabi to support the study.

Multimedia Appendix 1
Supplementary material.
[DOCX File , 15 KB - resprot_v12i1e41101_app1.docx]

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Abbreviations

6MWT: 6-minute walk test
CRC: colorectal cancer
QOL: quality of life
RE-AIM: Reach, Effectiveness, Adoption, Implementation, and Maintenance
UGI: upper gastrointestinal

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Protocol

An Interactive Communication Model for Self-Care—Regardless of Health Literacy: Protocol for a Quasi-Experimental Study

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Abstract

Background: Clear dialogue-based (interactive) communication that ensures comprehension and recall becomes more important in patient-provider interactions, especially in relation to patients with chronic diseases, where self-management education and counseling are cornerstones in managing these diseases. If patients with chronic disease experience challenges in obtaining, understanding, and applying health-related information (necessary to make informed health decisions and sufficiently manage their health), clear communication and ensuring comprehension become even more critical in the patient-provider interactions. Furthermore, patient-provider communication has been proposed as a potential pathway through which health literacy might influence health outcomes, especially in individuals with chronic diseases. Hence, adjusting communication to the individual level of health literacy might have a positive influence on health outcomes. On this basis, the authors have developed a web-based interactive communication model that both seeks to accommodate health literacy by allowing tailored communication and ensure comprehension and recall between nurses and patients.

Objective: This study seeks to examine the use of an IT solution that comprises an interactive communication model that seeks to accommodate health literacy in communication and ensure comprehension and recall between nurses and patients.

Methods: A quasi-experimental control group study including full economic evaluation with 6-month follow-up. Based on power calculation, a total of 82 participants will be included. Participants are assigned either the interactive communication model (intervention) or usual nursing care. It will be assessed if the model influences the level of health literacy and participants experience a higher health-related quality of life. Further, cost-effectiveness will be evaluated. Overall, the statistical methods will follow an intention-to-treat principle. Results will be presented in accordance with the Transparent Reporting of Evaluations with Non-randomized Designs guidelines for nonrandomized designs as well as the Consolidated Health Economic Evaluation Reporting Standards.

Results: This paper describes a protocol for a clustered quasi-experimental control study that seeks to evaluate the effectiveness of the interactive communicative model. Most studies in the field of health literacy are epidemiological studies that seek to address the effects of poor health literacy in populations and its potential impact on health inequity. A total of 82 participants, who receive community nursing will be included. The final trial day is May 1, 2022, with the first report of results in the final quarter of 2022.

Conclusions: The results of the trial can create the base for conducting a large-scale study and inspire the conduction of more studies that seeks to create and evaluate interventions aimed at enhancing the level of health literacy and reducing the usage of health resources.

Trial Registration: ClinicalTrials.gov NCT04929314; https://clinicaltrials.gov/ct2/show/NCT04929314

International Registered Report Identifier (IRRID): DERR1-10.2196/37673

(JMIR Res Protoc 2023;12:e37673) doi:10.2196/37673

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KEYWORDS

health literacy; interactive communication; nursing; quasi-experimental study; economic evaluation; economic; cost; rehabilitation; primary care; nurse; communication; health information; patient education; health resource

Introduction

Background

The demographic profile is changing all over the world with a longer life expectancy that yields an increase in the number of people living with chronic diseases [1]. The challenge of meeting the needs of this growing number of people will fall upon already overwhelmed health care services that are struggling to cope with the current demands of changing health care systems [2]. As a result, the role of modern patients is changing from paternalistic models of health care that placed the patient as a passive recipient to more active involvement of patients in their own care [3]. This change in the role of modern patients, however, sets some requirements to their level of patient empowerment and self-management; two concepts wherein health literacy (HL) plays an important role [4]. HL is a relatively new area of research that focuses on the ability to make sensible health choices that promote and maintain good health, based on the individual ability to access, evaluate, and use health-related information [5]. The World Health Organization has defined HL as "the cognitive and social skills which determine the motivation and ability of individuals to gain access to, understand and use information in ways which promote and maintain good health" [6].

The concept of HL includes multiple levels with different requirements to personal skills in relation to health care, making it a very broad and complex concept. In a widely used approach, Nutbeam [7] frames the different levels of HL as follows:

- *A functional level of HL* comprises the basic skills of numeracy, reading and writing that allow an individual to function effectively in a health care setting (eg, by being able to navigate the health care system, take the right dose of medication, and provide an accurate presentation of symptoms).
- *An interactive level of HL* refers to a more advanced level of literacy, that is, social and cognitive skills that allow an individual the capability to understand and retrieve health information. At this level, individuals are also able to engage actively in a dialog about their disease and course of treatment with health care professionals.
- *The critical level of HL* comprises an advanced set of skills that allow the capability to critically analyze health-related information retrieved from the health care system or independently and the ability to act on this information.

According to a Danish study [8], 10%-20% of the Danish population experience difficulties with the ability to understand health-related information sufficiently to act on it and the ability to interact with health care professionals (2 important dimensions of HL). Hence, they do not have the necessary HL competencies to manage their health sufficiently, which incur a higher risk of adverse health effects, including improper use of health care services and medications, poor self-management, and poor health outcomes [9]. On this basis, clear communication and ensuring comprehension and recall become more important in patient-provider interactions, especially in relation to patients with chronic diseases, where self-management education and counseling are cornerstones in managing these diseases. If patients with chronic disease also experience challenges in obtaining, understanding, and applying health-related information (necessary to make informed health decisions and sufficiently manage their health), clear communication and ensuring comprehension become even more critical in the patient-provider interactions [10]. Furthermore, patient-provider communication has been proposed as a potential pathway through which HL might influence health outcomes, especially in individuals with chronic diseases. Hence, adjusting communication to the individual level of HL might have a positive influence on health outcomes [11,12]. Nurses play an essential role in providing education and counseling for patients with a chronic disease through communication—it is considered a core competency in their nursing practice [13]. However, nurses rarely use communication that focuses on comprehension and recall in their interaction with patients [14]. On this basis, this study examines the use of an interactive communication model (ICM) that seeks to accommodate HL in communication and ensure comprehension and recall between nurses and patients.

Objectives

The main objective of this study is to conduct a broad evaluation of a web-based ICM (refers to the interaction between the user [the community nurses in this study] and the recipients [the citizens receiving community nursing in this study]) that both seek to identify knowledge and skills (HL) by enhancing tailored communication and ensure recall and comprehension between patients and nurses. Specific research questions concern whether the ICM improves HL among participants, who receive community nursing care, and whether they experience a higher health-related quality of life. Secondary outcomes include evaluating the cost-effectiveness of the ICM and assessing if it improves the quality of community nursing care, which includes the evaluation of citizens' adherence to care and treatment as well as the community nurses' satisfaction with using the ICM in their care. Finally, how participants, who receive community nursing care from the nurses in the intervention group, experience nursing care prior and after the intervention was assessed.

Methods

Study Design

This trial is conducted as a clustered quasi-experimental control group study with 6-month follow-up. The trial runs from November 2021 to May 2022. This study was originally designed as a 2-armed cluster-randomized controlled trial. However, the randomization protocol was abandoned after several months of unsuccessful recruitment efforts, and the study was redesigned as a quasi-experimental control group

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study. The primary reason for abandoning the randomized controlled trial design was challenges related to recruiting all districts making it difficult to conduct a meaningful randomization. The trial is registered at ClinicalTrials.gov (NCT04929314).

Ethical Considerations

The trial has been presented to the Regional Ethical Committee for Medical Research in North Denmark. The committee determined that no ethical approval was necessary (number 2020-000992-45). The trial has been approved by the Danish Data Protection Agency. Data will be anonymized and stored in accordance with the Danish Data Protection Rules [15].

The investigation conforms with the principles outlined in the Declaration of Helsinki. Potential participants were informed of the content and aims of the study and required to give written, informed consent before enrollment. All participants were informed that the data collected can be used for research purposes, and they were asked to sign an informed written consent form if they wished to participate after thoroughly reviewing the material regarding the study. The informed written consent includes consent for publication. All participants were informed that participation is voluntary, and they can withdraw from the study at any time. The participants did not receive any compensation for their participation in the study.

The Target Sample

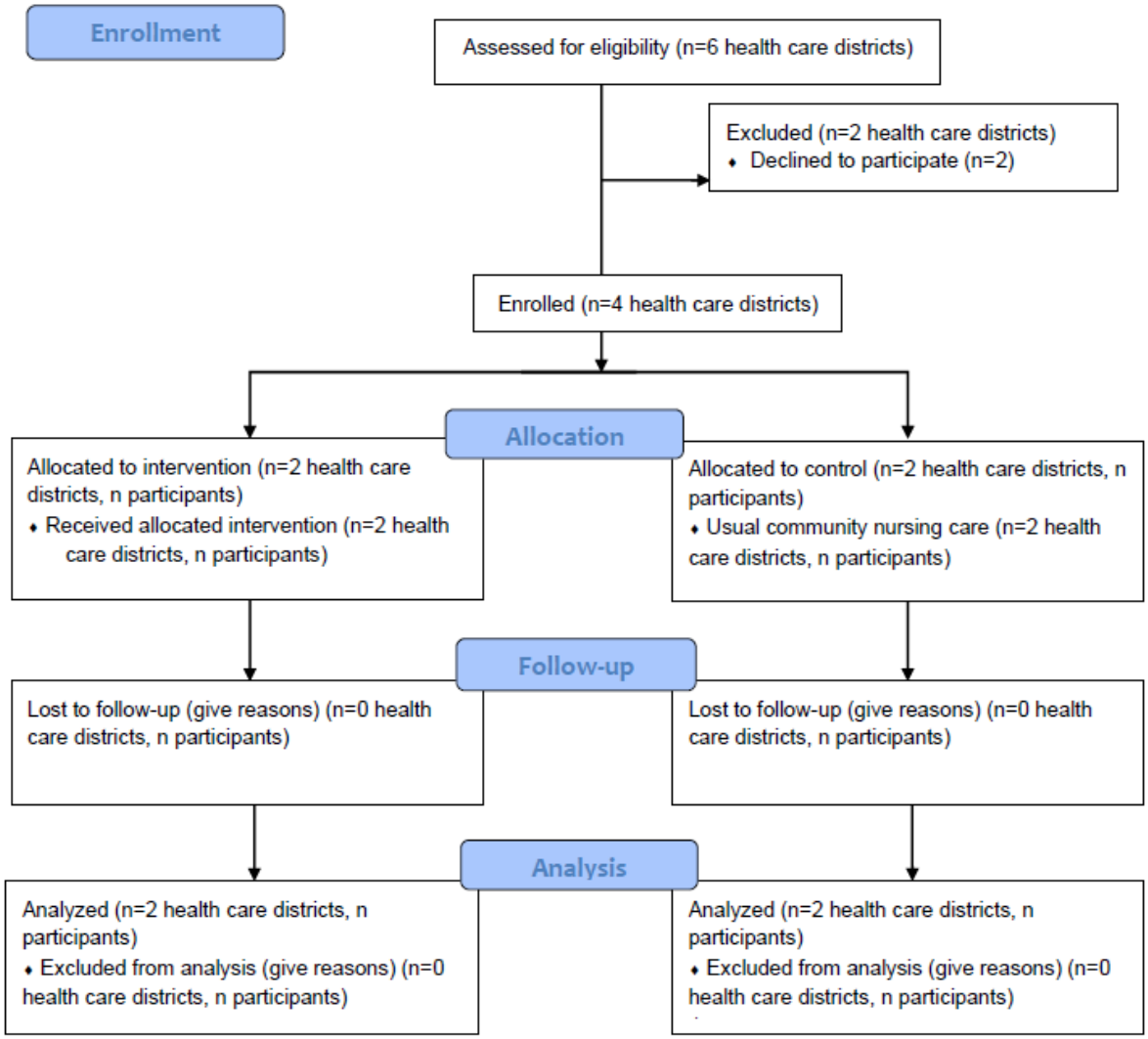
The trial population consists of citizens in 4 districts in the municipality of Aalborg who receive health care services. Participants are eligible for inclusion if they receive home health care (community nursing at least every 2 weeks) in Aalborg Municipality and are older than 18 years at the point of enrollment. Further, participants must receive community health care services for a period of more than 3 months prior to enrollment and be able to speak, read, and write Danish. The participants must also have a fixed residence in Aalborg Municipality. Participants will be excluded from the study if they do not meet the inclusion criteria and if they are terminal or diagnosed with a psychiatric disease, dementia, or other severe cognitive impairments. Participants are also excluded if they are unable to understand and speak Danish (unable to complete study questionnaires).

Recruitment

Recruitment has been ongoing since April 2021 in 4 out of 6 care districts in Aalborg Municipality. The community nurses identify eligible participants (Figure 1) and create a list of potential participants, who have given permission for the researcher to contact them by telephone. The researcher provides further information about the trial, answers questions, and guides them regarding the questionnaires and the written consent form. Subsequently, written information about the study, questionnaires, and a written consent form are sent to eligible participants after receiving oral consent over the telephone. If the participants still wish to participate after thoroughly reviewing the material received, they will return the written consent form and the questionnaires to the community nurse before the date specified in the material. The researcher's contact information is highlighted in the written information, allowing the participants an opportunity to receive support in filling out the questionnaires. Due to the COVID-19 situation, it is attempted to reduce physical contact between the researcher and the participants, and that is why all communication is preferred over the telephone.

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Figure 1. Flowchart diagram representing the design of the study.



The Intervention

Overview

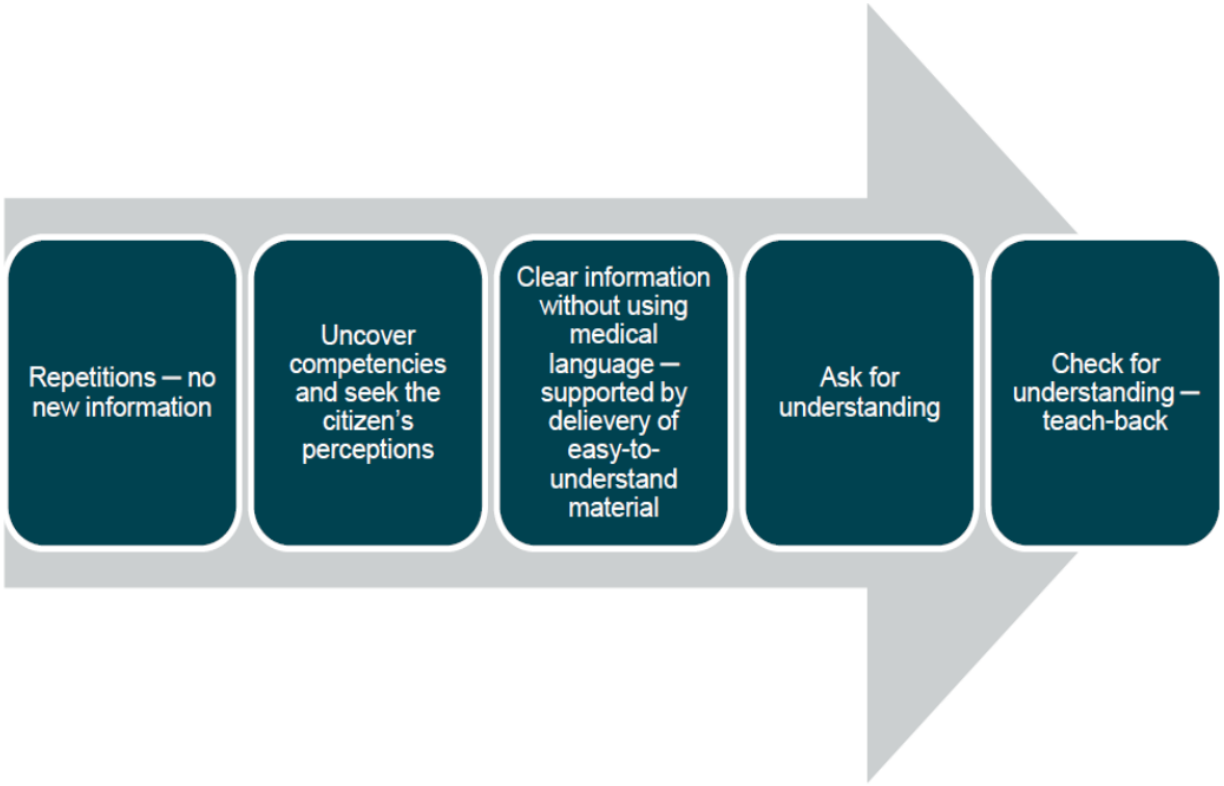
The intervention is based on the research-based knowledge about HL and focuses on interactive communication between community nurses and citizens who receive community nursing care. It seeks to ensure uniform interactive communication from the community nurses to ensure that citizens understand and adapt the information given by nurses, regardless of the level of HL. The intervention is not based on research alone but has been developed in close collaboration with practice (Aalborg Municipality). Almost all community nurses in Aalborg Municipality have participated in a workshop on rehabilitation, self-rehabilitation, and HL. In total, 14 workshops were conducted (a total of 335 community nurses from Aalborg Municipality participated) in the autumn of 2019 as part of a pilot project prior to this research project. A central point of these workshops was to identify challenges related to the more active involvement of citizens (receiving community nursing care) in their own health and disease. Aalborg Municipality puts great emphasis on "self-rehabilitation," where the ambition is to transfer as many health-related tasks (eg, medication administration and dispensing) as possible to the citizens receiving community nursing care and, thus, placing more responsibility on the citizens themselves. The development of the intervention is based on a best-practice approach from the literature combined with solid experience from nursing practice. The involvement of the community nurses in the development of the intervention has also contributed to a sense of ownership among the users (the community nurses in Aalborg Municipality). It should be noted that the community nurses have never seen or used the intervention during the workshops; the workshops contributed to the development of the intervention, as it was identified what community nurses saw as challenges in strengthening self-care among their citizens.

The material from the workshops, in conjunction with relevant research literature, has formed the basis for the development of an intervention containing the following components: (1) a development of competences is related to HL among community nurses in Aalborg Municipality (only those who are responsible for citizens who receive the intervention). The community nurses will receive general education about HL and how to screen for it with the Danish European Health Literacy Survey Questionnaire (HLS-EU-Q-16) [16]. It should be noted that assessing each citizen's level of HL is only being done as part of the study and not as part of standard protocol. (2) The

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community nurses will also receive practical training in systematic and integrative communication using the ICM with integrated teach-back, see Figure 2 for detailed description. The systematic and integrative communication is supplemented by the delivery of easy-to-understand material to the citizen. The material has been developed and evaluated in advance. (3) The community nurses will be introduced to a guide that describes how to document the use of the ICM. This guide seeks to ensure consistency and uniformity in the documentation of nursing care.

Figure 2. Illustration of the elements in the interactive communication model (ICM). The model is inspired by Schillinger et al [17].



Repetitions

The model starts with a repetition of key points (very few sentences) from the last visit or learning session. The community nurse simply repeats key points and provides no new information at this stage. By the first visit, the community nurse cannot perform repetitions, but instead, the citizen is presented with the plan to enhance knowledge and self-care.

Uncover Competencies and Seek the Citizen's Perceptions

This allows the community nurse and citizen to reach a common understanding. Moreover, it helps the community nurse assess how to tailor information and instructions for the citizen.

Clear Information Without Using Medical Language

The community nurse provides information and instructions at a very easy-to-understand level without using medical language. The information and instructions are provided based on predefined material made available to the community nurse on a web page accessible from her working tablet. The information and instructions are supplemented by the delivery of easy-to-understand material to the citizen.

Ask for Understanding

The community nurse asks the citizen directly if they have understood the given information and what has been discussed.

Check for Understanding—Teach-Back

The community nurse uses the teach-back technique to ensure that the citizen understands the information or instructions and what has been discussed. The community nurse asks the citizen to retell (in their own words) the information and instructions provided. This stage may also involve the citizen having to demonstrate the performance of a "task," for example, the community nurse asks the citizen, with chronic obstructive pulmonary disease, to demonstrate their inhalation technique.

The ICM must be an easily accessible and efficient tool for community nurses, and it is therefore created as a web-based IT solution. The IT solution is entitled "personalized support for self-care" and can be accessed from the community nurses' working tablet—direct link on the start page.

The content of the IT solution is selected based on the most prominent diseases and reasons for receiving community nursing in Northern Jutland. People receiving community nursing often have multiple health-related challenges and comorbidities and have a high level of vulnerability, which sets high requirements to their level of HL. The concept is that the ICM (made available in the web-based IT solution) can support community nurses in accommodating citizens' broad range of information and communication preferences. The ICM uncovers what people know about their own health and situation instead of a subjective assumption of what they know; thus, it can be considered a

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more objective approach to accessing knowledge and skills. The IT solution includes a general description of the ICM and how to conduct each individual communicative step in the model. The general description is supported by a graphical illustration of the different steps in the model. There are thorough instructions on how to incorporate the different communicative steps into practice; a "correct" use can promote more interactive communication.

The IT solution also describes how to use the ICM in relation to the most prominent diseases such as chronic obstructive pulmonary disease, diabetes, and cardiovascular diseases. It is thoroughly described how to carry out each individual step in the ICM related to the disease in question—all the way down to how questions should be formulated and asked to uncover citizens' knowledge and level of skills (step 2—ask for understanding) and how information is provided in a concise easy-to-understand manner without medical language (step 3—clear information without using medical language). The idea is that users of the IT solution, containing the ICM, do not have to decide for themselves what easy-to-understand language is because it is provided by the web-based system. The instructions and information formulated in the IT solution, containing the ICM, have been developed in the following manner: information and content about the specific diseases are inspired by an acknowledged national patient–centered web page (sundhed.dk) and use of pedagogical tools that focus on increasing and ensuring the understanding with the recipient [18,19]. The material in the IT solution, containing the ICM, is kept on a readability of sixth- to seventh-grade level and, thus, users provide information and guidance on this level when using the ICM. The material was read thoroughly by independent reviewers to ensure easy-to-understand and concise language not exceeding sixth- to seventh-grade level. It should be noted that the IT solution also provides different links and video material (easy-to-understand that can be used in *step 3—clear information without medical language*) relevant to the specific diseases.

Even though the instructions and information in the IT solution, containing the ICM, serve as a guide to learn the ICM technique, the goal is that users adapt the communication technique into their everyday practice. The IT solution, containing the ICM, is intended to facilitate the use of a very easy-to-understand language and check the understanding of information by the recipient. The community nurses in this study, who are responsible for citizens who receive the intervention, will be instructed to use the IT solution, containing the ICM, at each visit. The web-based IT solution, containing the ICM, has been tested in a small pilot study [20].

The Control: Usual Community Nursing Care

Danish community nursing care combines nursing practice and primary health care in the Danish community setting. Denmark comprises 98 municipalities, which have a specialized role in community nursing care that requires nursing and practical help in the citizens' own homes. Danish community nursing care varies across the municipalities. Community nurses primarily deliver health services, health education, preventive care, rehabilitation, etc, to Danish citizens. Community care nurses in the control group will not receive the special training described earlier, and the participants in this group will receive their usual care and treatment throughout the study period of 6 months.

Allocation

Aalborg Municipality is comprised of 6 health care districts. However, due to practical reasons, a total of 2 districts declined to participate in this study. The remaining 4 districts are matched 1:1 in terms of geographical area (2 rural districts are matched and so are 2 urban), and each pair is then allocated so that one district is in the intervention and the other is in the control group. Coincidently, each pair also matches with the estimated level of social classes (judged by the municipality). Before allocation, all participants must have signed informed consent and conducted baseline measurements.

Outcome Measurements

Primary and Secondary Outcomes

The primary outcome of this study is the change in the level of HL assessed by the HLS-EU-Q-16 questionnaire [16] from baseline to follow-up at 6 months. The HLS-EU-Q-16 measures self-perceived HL and reflects the conformity between individual competencies needed to navigate the health care system and situational complexities. Hence, the HLS-EU-Q-16 reflects the self-perceived level of HL, and this should be taken into consideration when interpreting the survey results. This study hypothesizes that adding the ICM and continuity in documentation to usual community care will lead to a significantly higher level of self-perceived HL for the included participants.

Two secondary outcomes will be reported: first, the between-group difference in health-related quality of life measured by the EQ-5D-3L questionnaire [21] at follow-up after 6 months, and second, the incremental cost-effectiveness ratio representing the total cost per additional HLS-EU-Q-16 point accrued from baseline to follow-up at 6 months. This trial adopts a health- and social sector perspective with the following cost categories: intervention costs, costs associated with all hospital contacts, primary sector costs (ie, general practitioners and other primary care visits), costs associated with home nurse visits, and home care costs due to individual care and practical help as well as individual or group rehabilitation costs. Service cost components will be based on register data, that is, from the Danish National Patient Register (all hospital contacts) [22], the National Health Insurance Service Register (all primary care contacts) [23], and the electronic care register in Aalborg Municipality. All data can be unambiguously linked with the help of a 10-digit social security number that all Danish citizens have.

Additional Outcomes

The quality of nursing care is assessed using a self-constructed questionnaire, which has been used in a previous pilot study by our research group. The quality of nursing care will be evaluated by the community nurses in Aalborg Municipality.

Another additional outcome is to assess how the citizens, who receive community nursing care from the nurses in the

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intervention group, experience nursing care prior to the intervention and after the intervention. Hence, the citizens will be interviewed twice during the study: prior to the intervention and after the intervention. As per the study by Kvale and Brinkmann [24], semistructured qualitative individual face-to-face interviews will be conducted with the citizens in the intervention group in the comfort of the own homes. The interviews will be conducted before the community nurses in the intervention group receive any special training and start using the intervention (prior) and again at follow-up (after). The interviews will be recorded and transcribed by researchers.

It is hypothesized that the ICM will be associated with a larger gain in HL in the intervention group, as the model is expected to increase citizens' control of their own lives as it establishes a more solid knowledge and empowerment of their disease and health [25-27].

Sample Size and Power Calculation

Sample size calculation for the primary outcome was performed in Stata (version 16; StataCorp). The intention is to detect a standardized mean difference in favor of the intervention based on Cohen d>0.8 [28]. Requiring a power of 80% and a significance level (1-sided) of 0.05, with 4 clusters given (2 in each alternative) and assuming a coefficient of variation in cluster size of 0.25 and intracluster correlation equal to 0.05, the required sample size is 37 participants in each arm (or an average of 18.5 participants in each cluster). With an expected loss-to-follow-up of 10%, the total required sample size is 41 in each arm (or an average of 20.5 in each cluster).

Analyses

Overall, the statistical methods will follow an intention-to-treat principle [29]. Results from the trial will be presented in accordance with the Transparent Reporting of Evaluations with Non-randomized Designs guidelines for nonrandomized designs [30] as well as the Consolidated Health Economic Evaluation Reporting Standards [31]. Missing data will be subject to multiple imputations [32]. Data will be analyzed with Stata 16 software.

Between-group differences for both the primary and secondary outcomes of health-related quality of life and cost-effectiveness will be calculated by applying multilevel generalized linear models, and both an unadjusted and adjusted estimate controlling for meaningful baseline differences will be reported. To allow for evaluation of the impact of variability and parameter uncertainty, the economic evaluation will also report the results of one-way and probabilistic sensitivity analysis [33]. The probabilistic sensitivity analysis will be carried out using Excel (Microsoft Inc).

All data from the interviews will be analyzed using NVivo R1 (version 13.0; Lumivero). Inspired by Kvale and Brinkmann [24], the analysis will be conducted according to the following steps: (1) identification of key themes and definitions from theoretical framework, inspired by Braun and Clarke [34]. (2) Review of all data from the interviews to obtain an overall impression of the themes on how the citizens experience their level of HL and self-management, both prior to the intervention and after the intervention. (3) Design of code tree based on key definitions and concepts derived from the theoretical framework and interviews. (4) The researchers will discuss and revise the code tree to ensure intersubjectivity. (5) The first step of the coding process will be centered on gaining an overall understanding of the citizens' perception of their level of HL and self-management, both prior to the intervention and after the intervention. (6) The next step will focus on widening the understanding beyond the citizens' perception. What presents a challenge to their level of HL and self-management and what strengthens it? (7) The final step will be an analysis centered on the citizens' perception of their level of HL and self-management and if this is altered when community nurses use the intervention in their nursing care. (8) Data will be condensed and presented as key themes and findings.

Results

A total of 82 participants, who receive community nursing will be included. The final trial day is May 1, 2022, with the first report of results in the final quarter of 2022.

Discussion

This paper describes a protocol for a clustered quasi-experimental control study that seeks to evaluate the effectiveness of an IT solution that comprises the ICM seeking to enhance more dialogue-based and tailored communication. Most studies in the field of HL are epidemiological studies that seek to address the effects of poor HL in populations and its potential impact on health inequity [35]. There is, however, a call for studies centered on developing interventions aimed at strengthening HL; strengthening HL in populations and making health services more accessible to people with a low level of HL may be a practical strategy to reduce disparities and promote greater equity in health [9,36]. To our knowledge, this is one of the first studies to assess the effectiveness of an intervention that seeks to enhance the level of HL. The strength of this study is that it attempts to illuminate the effects of an intervention centered on interactive communication using a control group design. Another strength is that the study has characteristics like an effectiveness trial, as it evaluates the effects of enhancing knowledge of HL among community care nurses and integrating the use of the ICM in their nursing care.

A limitation of this study is the design as a quasi-experimental and abandoning the original randomization protocol. This means that this study may be subjected to selection bias, as between-group baseline characteristics may differentiate. Another limitation is the relatively short follow-up time, as between-group comparisons can only be made at the 6-month follow-up. This might be problematic since changes in particularly costs and health-related quality of life require behavior change that might take time to occur. However, recent guidance for developing and evaluating complex interventions recommends that broad-ranging evaluations are conducted in the early phases and that they also include economic evaluation. The aim is to identify the scope of cost and different effects that can help decision makers understand the potential of the intervention and decide whether proceeding to a large-scale evaluation is worthwhile [37]. In making this judgment, it is a

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standard health economic practice also to model the joint decision uncertainty surrounding particularly health-related quality of life outcomes and costs [38,39]. Reporting cost-effectiveness (including health-related quality of life, costs, or quality-adjusted life years) with 6-month follow-up specific to the domain of HL has also previously been reported [40,41] and to other interventions aimed at changing behavior [42,43]. The expectation is that the results of the trial therefore can create the base for deciding to conduct a large-scale study and inspire the conduction of more studies that seeks to create and evaluate interventions aimed at enhancing the level of HL and reducing the usage of health resources.

Acknowledgments

This research did not receive any specific grants or funding. Aalborg Municipality (responsible for community care nursing) has contributed significantly to the project in terms of hosting the workshops that has created the basis for the development of the intervention. Aalborg Municipality has further contributed with extensive community nursing hours; the community nurses have helped in the recruitment of citizens and handling clinical practical challenges.

Data Availability

All data will be stored in a secure drive (UCNemDok). Only researchers from the University College of Northern Denmark and Aalborg University will have access to the trial data set.

Authors' Contributions

LKEH conceived, designed, and coordinated the study and drafted the manuscript. OKH contributed to the design of the study and methodological considerations. FWU contributed to the statistical analysis and methodological considerations of the study. All authors read, critically revised, and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

HL: health literacy
HLS-EU-Q-16: European Health Literacy Survey Questionnaire
ICM: interactive communication model

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Protocol

Behind the Scenes of a Technologically Enhanced Intervention for Caregivers of People With Dementia: Protocol for a Feasibility and Acceptability Study

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Abstract

Background: Alzheimer's disease affects 55 million people worldwide. As the disease progresses, these individuals require a devoted caregiver, often a family member, who provides evolving complex care. Caregivers can experience a variety of ongoing stressors, resulting in reductions in caregiver emotional well-being (and other quality-of-life indicators). Information and communication technologies provide an excellent opportunity to train caregivers remotely and help them to manage these stressors and related distress.

Objective: This protocol describes the theoretical rationale, study design, and methods of a new, technologically enhanced psychoeducational skill-building intervention for caregivers of people with dementia that includes a virtual reality component.

Methods: *Through Alzheimer's Eyes* is a 4-week, single-arm, pre-post test pilot study consisting of 4 sessions of 90 minutes each that are delivered by videoconferencing. These sessions include a weekly virtual reality experience characterizing the journey of an older Latina with Alzheimer's disease from her perspective to help caregivers see through the eyes of a person with dementia. The 4 sessions cover the skill-training topics of communication, managing challenging behaviors and unhelpful thoughts, the importance of self-care, and mindfulness—all of which are key components designed to reduce stress and distress in family caregivers. Individual interviews conducted before and after the intervention gather participant insights into the intervention, evaluate its feasibility and acceptability, and assess its impact on key outcomes.

Results: Data collection for the study started in January 2022, and the results are expected to be submitted for publication in the second half of 2023. Twenty caregivers from the United States have completed the workshop to date. Preliminary data gathered from these participants support the intervention's feasibility and acceptability.

Conclusions: *Through Alzheimer's Eyes* leverages existing technology combined with psychoeducational skill building to help caregivers manage their stress, regardless of their location.

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KEYWORDS

Alzheimer's disease; dementia; virtual reality; information and communication technology; ICT; caregivers; pilot study

Introduction

Background

Alzheimer's disease and related dementias (ADRD) are progressive diseases that primarily affect individuals aged ≥65 years. Worldwide, these diseases affect approximately 55 million people [1]; in the United States, 6.5 million people currently live with ADRD. Given the nature of ADRD, devoted family caregivers provide evolving complex care during the disease trajectory, which can amount to as much as 80% to 100% of the care [2]. This constant care translates into ongoing stressors

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for caregivers because they must ensure their loved one's well-being and quality of life. Caregiver tasks include, but are not limited to, aiding the loved one in activities of daily living and instrumental activities of daily living such as bathing, dressing, eating, managing medications, managing problematic behaviors, handling finances, attending physician appointments, and shopping [3]. Caring for people with ADRD can be further complicated by the caregiver's own physical health limitations, mental health concerns, and other stressors (eg, from being housebound to functional impairments, history of depression or anxiety, financial concerns, and employment-related challenges) [3,4]. In addition, the stress associated with family caregiving for loved ones with dementia often translates into deterioration of caregivers' physical and mental health [3,5-8], whether or not caregivers face substantive vulnerabilities or life challenges beyond their caregiver role.

Numerous in-person interventions for caregivers of people with ADRD are available that promote aging in place, caregiver self-care, caregiver burden, and skills training while improving quality of life, relationships, and stress and distress management skills [4,5,9]. A growing number of these interventions have shown effectiveness for decreasing burden, depression, and stress, as well as improving quality of life and one's sense of competence [10,11]. However, in-person interventions present many limitations, especially for caregivers who have scheduling conflicts, work full-time or part-time, live in remote locations, have limited access to transportation, or have a limiting illness [12,13].

Caregiving interventions delivered through information and communication technologies (ICTs) can overcome many of the constraints of in-person intervention delivery and can play a crucial role in reaching out to caregivers of people with ADRD. ICTs are tools and procedures used to acquire and distribute information and enhance communication via technologies such as hardware, software, or the internet. ICTs enable the collection, capture, processing, production, treatment, registry, storing, exchanging, and presentation of information [14,15]. Regardless of their age, many caregivers are willing and eager to incorporate new technological tools into their daily lives [16,17]. However, there are limited studies in the literature that have used ICTs to deliver caregiving interventions to caregivers of people with ADRD. Among the few interventions that have done so, delivery channels have included virtual reality (VR), assistive devices, and internet-based interventions, and all have met with high acceptance [18,19]. Of note, VR is a computer-created interaction-enabled simulation that allows the user to engage in a realistic environment through a specific VR headset [19].

ICT interventions have been successful in training formal (ie, paid professionals and staff) and informal caregivers. Examples of studies include qualitative projects with formal and informal caregivers. One study indicated that the dementia simulation program helped participants to have more empathy for people with dementia as well as enhanced understanding of dementia and risks of developing dementia, to increase their awareness of any changes in the attention and affection they give to people with dementia, and to acquire and reinforce new care strategies and change other strategies such as communication techniques [20]. Another qualitative study with health care providers also highlights that simulation of what it is to have dementia is an insightful, evocative, and convincing immersive experience that takes dementia awareness training to the next level [21]. When the general population interacts with the VR simulation of a person with dementia, results indicate that after the experience, the participants' sense of community is increased. The subscales of the Sense of Community Scale—solidarity and proactiveness as well as reliance on others—also showed a statistically significant positive shift. In addition, participants changed their attitudes toward dementia after the educational program [22].

Two studies are important to highlight when considering projects that use VR to train informal caregivers of people with dementia:

1. The program *Into D'mentia* consists of a 20-minute simulated experience for caregiver participants that focuses on the beginning stages of dementia (primarily of the Alzheimer's disease type). The program helps caregivers to feel the confusion that a person with ADRD might experience when their routine activities cannot be completed as desired. The simulation was followed by a one-on-one conversation with the trainer and a half-day group meeting with other participants. No statistically significant differences were found on key outcomes (eg, empathy, sense of competence, quality of relationship with care recipient, depression, anxiety, and caregiver burden). However, caregivers did report a heightened understanding of dementia and that, after the program, they changed the way they cared for their loved ones. Study limitations delineated by the researchers include the minimal number of simulation and group sessions and a lack of applicability to caregivers whose loved ones have progressed beyond the early stages of dementia [11,23].
2. The *Through the D'mentia Lens 360º* program is a VR adaptation of *Through the D'mentia Lens* scenarios. The experience consists of a 360-degree simulation movie and a self-paced e-course covering topics about dementia and communication. The results indicate that the simulation intervention was user friendly and improved understanding of dementia. Furthermore, the project contributed to improved caregiver empathy on the subscales perspective taking (Interpersonal Reactivity Index questionnaire), proactive competence when caring for a person with dementia as well as resilience (Trust in Own Abilities questionnaire), and more positive interactions with the person with dementia (Dyadic Relationship Scale). Study limitations included the lack of a control group as well as a small sample size and personal circumstances that might have affected the outcome of the study (eg, involvement of professional caregivers or deterioration of the person with dementia), testing effects, sampling bias owing to selection of particular informal caregivers recruited by case managers, using nonvalidated questionaries, and having a large proportion of female participants; in addition, the impact of each component of the intervention was not evaluated individually (rather, the intervention as a whole was evaluated) [24].

Thus, although there are new interventions using ICTs, including simulation or VR for training formal and informal caregivers of people with dementia, there is still a gap in how to implement

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and use new technologies to help educate caregivers about dementia and provide them with different skills to manage behavior challenges and reduce their own stress.

Objectives

To address the paucity of ICT-delivered ADRD caregiving interventions and known limitations, such as the lack of more VR sessions and group meetings, we designed a user-friendly multicomponent ICT-delivered intervention entitled *Through Alzheimer's Eyes*. This intervention is guided by social cognitive theory (SCT), owing to its relevance when learning in a social environment, and cognitive behavioral therapy (CBT) as a model to help caregivers develop and master appropriate skills. Several of the intervention's components are drawn from prior caregiver intervention studies grounded in these theories conducted by Gallagher-Thompson et al [25], Coon et al [26], Belle [27], and Coon [28]. The intervention leverages effective design considerations of previous in-person ADRD caregiving interventions (group format, educational modules and handouts, discussions with participants, home assignments, and individual weekly sessions) to support the participant learning process and promote behavior change. Furthermore, the intervention is designed to prepare caregivers of people with ADRD for their role as caregivers in alleviating stress and distress while improving communication, behavioral management skills, and management of unhelpful thoughts, as well as well-being, with the support of VR. *Through Alzheimer's Eyes* is delivered through the Zoom videoconferencing platform (Zoom Video Communications, Inc) and augmented with VR. In this paper, we describe the theoretical rationale, study design, and methods of a 4-week pilot study designed to evaluate the acceptability and feasibility of the intervention. The aims of the study were to (1) evaluate the feasibility and acceptability of our new ICT-delivered program for caregivers of people with ADRD focusing on VR, educational, and skill-building components; (2) examine patterns of change among key outcomes targeted by the intervention, including communication skills, management of behavioral issues, and management of unhelpful thoughts; and (3) learn about the benefits of the sessions from the participants' perspective. Feasibility and acceptability will be assessed by examining recruitment strategies, participant retention, adherence to the intervention, and participant feedback provided through a postintervention satisfaction survey and one-on-one qualitative interviews. Pre-post intervention changes in key caregiving outcomes will be assessed using validated surveys.

Methods

Study Design and Participants

The study is a 4-week, single-arm, pre-post test pilot study designed to examine the feasibility and acceptability of a technologically enhanced skill-building intervention. The study is ongoing and to date has enrolled 20 adults who are caregivers of people with ADRD. The inclusion criteria are as follows: (1) self-report of being an unpaid primary caregiver of a person with ADRD for at least 6 months, (2) the caregiver and the person with ADRD must live together, (3) the caregiver must be aged ≥18 years, (4) they must be able to speak and read English, and (5) they must have access to a computer or similar device with a camera, speaker, microphone, and reliable bandwidth. Caregivers are not considered for the study if they have (1) vision or hearing impairment that impedes full participation over Zoom or (2) serious memory problems themselves. The research staff consults the principal investigator before determining eligibility if (1) the care recipient has been diagnosed with a severe mental illness before the age of 45 years (as reported by the caregiver), (2) the caregiver reports having memory loss, (3) the caregiver has frequent difficulty comprehending the questions during the screening, or (4) the caregiver is currently participating in a program, study, or workshop for caregivers designed to reduce stress and distress.

Setting

As this is an ICT-delivered intervention, participants can join from any location in the United States. Every participant selects a private location that best meets their needs to connect to the intervention via videoconference. Researchers connect from their preferred location while ensuring privacy and confidentiality.

Ethics Approval

The study protocol for *Through Alzheimer's Eyes* was approved by the Arizona State University institutional review board (STUDY00014856).

Informed Consent

Written informed consent was obtained after initial eligibility screening and before intervention delivery. The consent form contained detailed information about the purpose of the research; intervention details such as assessments to be performed, program schedule, time invested in the intervention, risks, privacy and confidentiality protection, what happens to the information collected for research, funding, cost, and payment (a total of US $25 in the form of eGift cards) for completion of the study's interviews; whom to talk to should the participants have any questions; and a question asking participants whether they are willing to be contacted about participating in future studies (participants did not have to agree to participate in this study).

Privacy and Confidentiality Protection

To ensure privacy and confidentiality, all the records are kept confidential and saved in password-protected secure servers, and any written documentation is kept in locked file cabinets in a secured access research office.

Through Alzheimer's Eyes Intervention

The 4-week intervention includes dementia education and skill-training components on techniques for communicating effectively, managing challenging behavior, controlling unhelpful thoughts, and caring for oneself, which are vital when providing person-centered care [18]. Participants engage with one another and their group leaders through activities facilitated by the group leaders, including mini-lectures, VR experiences, discussions, mindfulness exercises, and other relevant intervention activities, to master the skills. The facilitator has access to the VR set and plays the VR experience for the participants. Participants are divided into two groups: (1)

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immersive VR users and (2) semi-immersive VR users (those who are unable to use the VR headset owing to experiencing cybersickness while using the headset). Semi-immersive VR users will experience what life is like for a person with Alzheimer's disease through visualization on the user's computer via screen sharing.

The semi-immersive VR experience facilitated by Embodied Labs [29] consists of visualizing the journey of "Beatriz," an older Latina with Alzheimer's disease. Participants see through Beatriz's eyes and experience what it is like to have memory challenges, hearing impairments, confusion, and hallucinations, among other limitations associated with the disease.

Intervention Content

The selected topics for the psychoeducational skill-training components of the intervention sessions include not only increasing dementia knowledge but also improving the following skills: (1) communication with the loved one, family, friends, and health care providers; (2) managing challenging behavior; (3) controlling unhelpful thoughts; and (4) mindfulness and other relaxation skills. The goal is to help caregivers manage their most pressing concerns and sources of their stress successfully and understand the changes in the brain associated with Alzheimer's disease and the symptoms their loved one displays [9,30]. The topics were chosen based on existing literature about caregiving's most pressing concerns and sources of stress, as well as past successful psychoeducational interventions such as *Coping with Caregiving* [25,26,31]. Communication, problem-solving, and combativeness (behavioral issues) are topics where caregivers perceive they need the most help. Focusing on skill-building activities with education about the disease helps caregivers manage and decrease their stress. In addition, caregivers often need assistance and reminders about maintaining a healthy lifestyle and relaxation [26,30-32].

Communication skills have been chosen because caregivers need to learn how to communicate effectively with a person with dementia. As the cognition of the person with dementia deteriorates, new ways of communication are encouraged to be implemented to ensure that the caregiver communicates effectively, and the care recipient understands the message. Communication education and skill-training was divided into (1) how to communicate assertively with family and others, as well as the differences between passive and aggressive communication; and (2) how to communicate with the loved one, including verbal and nonverbal tips to deliver messages to their loved ones as the disease progresses. Effective communication helps to increase caregiver and care recipient satisfaction [33,34], and participants from previous interventions considered communication an excellent coping skill [33].

Increasing caregiving skills in managing challenging behavior or combativeness helps the caregiver to provide better and more effective care. Helping the caregiver to find the root or trigger of the challenging behavior decreases their stress [25]. During the intervention, the caregiver learns about the triggers and how to resolve them by helping the care recipient to be calm and helping to decrease the frequency of challenging behavior. Managing these challenges can have a positive impact by improving the quality of the relationship between caregiver and care recipient [5,26].

Learning to control unhelpful thoughts has been chosen as a key skill to help the caregiver change these unhelpful thoughts into productive ones to improve their own well-being [5,25,26]. During the session, participants identify unhelpful thoughts and learn different ways to replace them with more helpful ways of thinking about their loved ones, themselves, and their caregiving situations. Finally, mindfulness skills help the caregiver to be aware of the present moment, such as being aware of unhelpful thoughts when they occur, and offer the opportunity to learn different relaxation techniques to help decrease stress [5,26,27]. The techniques include mindful breathing, mindful eating, and body scan, as well as access to the Calm app for more resources.

Interventionists

A master's prepared social worker and a Doctor of Philosophy candidate in nursing were trained to deliver the intervention under the supervision of the second author, an experienced caregiver intervention researcher and geropsychologist. The main role of the interventionists is to deliver the weekly intervention sessions, guide the weekly individual sessions with the participants, provide extra resources when needed, provide feedback related to the home exercises, and guide the discussions during the sessions.

Intervention Sessions

The intervention will consist of 4 sessions delivered via videoconference (Zoom) over 4 weeks to a group of 5 to 9 family caregivers. Each group session lasts 90 minutes and consists of a new topic, a discussion that includes a review of the previous week's topic, a VR experience, home practice, and mindfulness exercises. The participants join the interventionist individually for a 30-minute discussion to revisit content and work on personalized goals between group sessions. Textbox 1 illustrates the content of both group and individual sessions. Mini-lectures, VR experiences, discussions, mindfulness activities (including options for mindfulness apps), and home exercises or home practice provide excellent opportunities to reinforce the knowledge acquired during the group sessions and facilitate different discussions about the topics covered during these sessions.

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Textbox 1. The intervention's weekly modules, activities, and content.

Week 1

- Weekly topic: learning about Alzheimer's disease, how it affects the brain and symptoms, and communication skills (to decrease challenging behavior)
- Virtual reality (VR) experience 1: focus on early stages of the disease
- Mindfulness: mindful breathing; introduction to mindfulness resources

Week 2

- Weekly topic: problem-solving, managing disruptive and challenging behavior, and applying communication skills
- VR experience 2: focus on middle stages of the disease
- Mindfulness: mindful eating

Week 3

- Weekly topic: controlling unhelpful thoughts; emphasis on actions that can lead the caregiver to have unhelpful thoughts, especially those related to quality of care and future options
- VR experience 3: focus on late stages of the disease
- Mindfulness: mindful walking

Week 4

- Weekly topic: importance of self-care and revision of the covered topics
- VR: experience all 3 VR experiences covering early, middle, and late stages of the disease
- Mindfulness: body scan
- Between sessions
- A 30-minute one-on-one Zoom session with an interventionist
- Review of the materials and work on individual stressors and goals

VR Experience

Participants watch a different VR experience every week. The VR experience facilitated by Embodied Labs consists of 3 modules targeting 3 different stages of the disease: early, middle, and late. The experience portrays the story of Beatriz, an older Latina with Alzheimer's disease, and her journey from the early stages to the late stages of the disease, emphasizing her struggles with communication as visual and hearing impairments affect her activities of daily living and her family. The participant watches the video through the eyes of Beatriz (Figure 1).

Figure 1. Screenshot of a virtual reality scene created by Embodied Labs (reproduced with permission). In this scene, the participant sees the bathroom through Beatriz's eyes and perspective; Beatriz is in the middle stages of Alzheimer's disease. This scene corresponds to when she takes a bath. The participant is experiencing Beatriz's ability to complete daily tasks.



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VR Equipment

The VR equipment includes materials for the instructor as well as for the participants. The instructor VR headset (Figure 2) consists of a laptop computer with the software and a headset connected to the laptop computer. The equipment and software were purchased from Embodied Labs, whose representative provided one-on-one training on the VR software and use of the equipment before its implementation in the intervention. Both the equipment and the software are very user friendly.

The participants have a VR headset adapted for their mobile phones to visualize the experience from their homes. The mobile phone–adapted headset for the participants was bought from a web-based vendor, and the brands used included BNext and Viotek, depending on market availability.

Figure 2. Set-up of the virtual reality equipment (reproduced with permission from Embodied Labs).

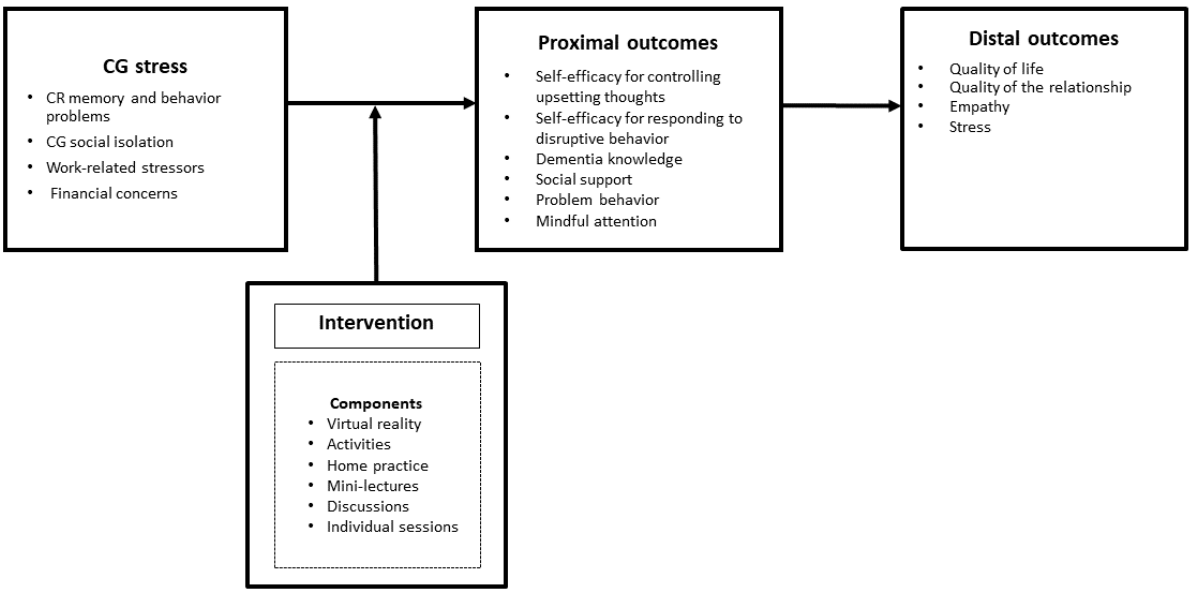


Theoretical Framework

The overall intervention is guided by two main frameworks: (1) SCT, which focuses on behavior change; and (2) CBT to help guide participant training in cognitive and behavioral skills (Figure 3).

SCT is a dynamic, interpersonal behavioral theory. SCT posits that the interaction among the beliefs and attitudes of the person, their behavior, and their social and physical environment influence each other reciprocally and dynamically. SCT explains that acquiring and maintaining new behavior is best achieved when people learn in a social environment while drawing on past experiences [35]. SCT constructs emphasize that learning comes from four sources: (1) mastery experience: acquiring knowledge through obtaining information, (2) vicarious experience: watching others perform an activity, (3) verbal persuasion: learning from feedback, and (4) emotional arousal: learning from past experiences [35,36]. SCT and CBT concepts and intervention components, definitions, relationships among the constructs, outcomes, and scales used to measure the outcomes are described and summarized in Multimedia Appendix 1.

Figure 3. Theoretical framework. CG: caregiver; CR: care recipient.



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The cognitive behavioral skill-building model (based on CBT) is a counseling approach focusing on thoughts and behavior that affect mood. One of the main applications of CBT concerns helping with mental health problems such as anxiety or depressive symptoms, where thoughts and behavior get in the way of a person's mood and functioning [36-38]. CBT is a fundamental component in this intervention, guiding the interventionist to help the caregiver develop cognitive (thought monitoring and restructuring) and behavioral (problem-solving, behavior management, communication, and relaxation) skills [36,37,39].

Feasibility and Acceptability Evaluation

Feasibility and acceptability will be evaluated by examining the different recruitment strategies, adherence to the intervention, and treatment implementation. In addition, individual postintervention Zoom interviews will provide further insight into the benefits and usefulness of the intervention.

Adherence Strategies

To encourage participation over the 4 weeks, strategies include weekly reminders from one session to another, calendar invitations, reminders during the one-on-one videoconference calls, and reminders in emails exchanged during the week. At the end of the study, adherence will be examined by comparing completers with dropouts.

Treatment Implementation

We have chosen the treatment implementation model developed by Burgio et al [40] to evaluate the feasibility and acceptability of the intervention. The treatment implementation model focuses on the 3 components of treatment delivery, receipt, and enactment to monitor activities in the different groups, minimize intervention efficacy bias, and evaluate treatment. The goal is to present the intervention as intended.

Treatment delivery focuses on the interventionists and the consistency of the intervention as delivered in the different groups [40,41]. Strategies to ensure consistency include manuals for the interventionists with a timeline to ensure that the same amount of time is devoted to the intervention activities across the different groups. In addition, a script is available to guide the individual Zoom calls. Weekly monitoring and feedback ensure that the interventionists deliver the sessions consistently.

Treatment receipt records whether the participant has received the intervention and understands the concepts as intended [40,41]. Strategies to evaluate the participant's knowledge include interventionists asking the caregiver about using the different concepts during the individual weekly Zoom calls and whether the caregiver has any questions about the content covered. In addition, during the sessions, the interventionist asks the participants for examples and requests them to share some of the home practices. This measure ensures that participants understand the concepts discussed during the session. The postassessment survey and an individual postintervention Zoom interview also include questions about the caregiver's perspectives of the intervention and their experiences.

Treatment enactment allows us to record and assess the use of skills and knowledge acquired during the different sessions in the participants' daily activities [40,41]. Strategies include recording in the enactment form after each session whether participants completed some written home practice, participated in the discussions, displayed understanding of the content through the question-and-answer sessions, and demonstrated the use of skills in the session, as well as whether they talked about using the skills outside of the intervention sessions.

Perception of Benefit

A 16-item postinterview survey asks participants about the perceived benefits derived from their involvement in the intervention. The survey is drawn from previous research [27,40] with family caregivers, with ratings ranging from *not at all* and *a little* to *a lot*. The survey questions include "Overall, how much do you think you benefited from participating in the program?" "How much did participation in the project help enhance your ability to care for your loved one?" "How much did participation in the program help to control upsetting thoughts?" The findings are expected to help inform whether the intervention meets caregiver needs.

Perceived Changes

The survey on perception of change includes 8 questions [27,40] indicating self-perceived changes in several key areas, including mood, communication, confidence, level of preparation for future care, and physical health. The ratings range from *declined substantially*, *declined minimally*, and *stayed the same* to *improved minimally* and *improved substantially*. The survey questions include "Do you think the communication with others, besides your loved one, has improved, declined, or stayed the same?" "Do you feel your overall confidence that you can provide care for CR has improved, declined or stayed the same?" [27,40].

Pre- and Postintervention Web-Based Surveys

To provide preliminary data on the impact of the intervention, the caregiver participants complete pre-post surveys to assess potential changes in proximal (eg, self-efficacy in responding to disruptive behavior and dementia knowledge) and distal (eg, quality of life and empathy) outcomes. The study's intervention outcomes are assessed with the following scales: Revised Scale for Caregiving Self-Efficacy, Preparedness for Caregiving Scale, Problem-Solving Self-Efficacy Scale, Alzheimer's Disease Knowledge Scale, Negative Interaction and Satisfaction with Social Support, Revised Memory and Behavior Problems Checklist, Mindful Attention Awareness Scale, Quality of Life–Alzheimer's Disease, Kingstone Caregiver Stress Scale, Interpersonal Reactivity Index, and Dyadic Relationship Scale. Table 1 describes each measure used. Sociodemographic information is collected at the screening.

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Table 1. Description of the assessments used to assess changes in key outcomes.

Questionnaire[a]	Subdomain	Cronbach α	*R*	Description
Sociodemographics (specific to study)	N/A[b]	N/A	N/A	Data collected include age, level of education, race and ethnicity, marital status, occupation, and years providing care [42]
Proximal (secondary) outcomes				
Revised Scale for Caregiving Self-Efficacy	Controlling unhelpful thoughts	.800 to .850	0.790	Assesses the confidence of caregivers of chronic individuals to cope with the care recipient's demands and challenges. Selected subdomains focus on efficacy for managing distressful thoughts and managing disruptive behavior [43]
Revised Scale for Caregiving Self-Efficacy	Disruptive behavior	.800 to .850	0.700	Assesses the confidence of caregivers of chronic individuals to cope with the care recipient's demands and challenges. Selected subdomains focus on efficacy for managing distressful thoughts and managing disruptive behavior [43]
Preparedness for Caregiving Scale	N/A	.700 to .800	—[c]	Gauges the ability to perform as a caregiver [44]
Problem-Solving Self-Efficacy Scale	N/A	.830	0.683	Evaluates the caregiver's confidence to perform a skill and solve a problem [45]
Alzheimer's Disease Knowledge Scale	N/A	.710	0.810	Tests knowledge of Alzheimer's disease among the general population and health providers [46]
Negative Interaction and Satisfaction with Social Support	Negative interaction	.873	—	Assesses social support by using 10 items to measure 3 domains of support: received support, satisfaction with support, and negative interactions of support [25,47,48]
Negative Interaction and Satisfaction with Social Support	Satisfaction with support	.878	—	Assesses social support by using 10 items to measure 3 domains of support: received support, satisfaction with support, and negative interactions of support [25,47,48]
Revised Memory and Behavior Problems Checklist	N/A	.840 to .900	—	Evaluates differences in problem behaviors of care recipient and how much it bothered the caregiver [49]
Mindful Attention Awareness Scale	N/A	.800 to .900	—	Assesses mindfulness awareness though a 15-item questionnaire: how attention and sensitive awareness happens while observing the surroundings [50]
Distal (primary) outcomes				
Quality of Life–Alzheimer's Disease	N/A	.860	0.100 to 0.650	Measures physical health, mental health, social and financial domains, and overall quality of life [51,52]
Kingstone Caregiver Stress Scale	N/A	.880	0.880	Monitors stress over time in 3 domains: caregiving, family, and financial issues [53]
Interpersonal Reactivity Index	N/A	.710 to .770	0.610 to 0.710	Evaluates on 4 subscales how the person reacts when observing others' experiences [54,55]
Dyadic Relationship Scale	N/A	.740 to .770	—	Assesses positive and negative aspects of the family relationship [56]

[a]All scales are evaluated before and after the intervention, except for demographics (data gathered during the screening and before the assessment).

[b]N/A: not applicable.

[c]Not available.

Postintervention Qualitative Interviews

After the 4-week intervention and postintervention assessment are completed, an individual postintervention Zoom interview with a research team member (other than the interventionist) gathers additional insight into the usefulness of the intervention and its materials, such as the VR experience, mindfulness activities and apps, and content of the sessions. Examples of questions include "What are your thoughts on the VR experience?" "How did the experience make you feel?" "How useful do you think the communication component is?" "How useful do you think the mindfulness component is?" "How often did you use it?" "How interesting is it for you?"

Study Protocol

Recruitment and Retention

Nonprobability purposive and snowball sampling is used to recruit the maximum number of participants. Purposive sampling allows for selecting caregivers of people with dementia who meet the aforementioned selection criteria [57]. In addition,

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participants are asked to refer other people they know who are in the same situation to participate in the study [58].

The recruitment strategy consists of advertising the intervention via social media platforms such as Facebook, Twitter, Instagram, and TikTok. In addition, flyers and related project information are shared with close professional contacts and other providers at community-based organizations such as the local branch of the Alzheimer's Association and local area agencies on aging, including through invitations to participate sent via email.

To encourage participants to join and complete the workshop, we focus on the following strategies: (1) once a participant contacts the team inquiring about the program, the research team texts, emails, or calls the participants via telephone or videoconference to establish a relationship and offer the opportunity to ask questions before enrolling; (2) provide incentives (eGift cards) after the completion of the pre-post assessments; (3) offer different options of mindfulness and relaxation apps for participants to use; and (4) provide a VR headset compatible with the participant's mobile phone.

Screening

Trained research staff screen participants to determine eligibility via telephone call or Zoom videoconference. Eligible and interested participants complete a second short survey about their fitness to use the VR headset compatible with their mobile phone. This short questionnaire helps to determine whether the participant can safely use VR without physical side effects during the intervention sessions. The questions include "Do you experience motion or car sickness?" "Do you have any conditions where flashing or intense light might affect you, such as epilepsy, migraines, unexplained seizures, recent concussions, or light sensitivity?" If participants answer positively to even one of the questions, they will be deemed noneligible for VR use and asked to visualize the experience through their laptop computers (semi-immersive VR) instead of using the VR headset to avoid potential side effects during the intervention sessions. The questionnaire was determined in coordination with the university institutional review board.

Study Enrollment and Consent

To enroll in the program, eligible participants sign the consent form via REDCap (Research Electronic Data Capture; Vanderbilt University), a Health Insurance Portability and Accountability Act–compliant web-based secure tool to capture and manage research data [56]. The consent form is sent to the participant's preferred email address. In addition, a telephone number is provided to participants in case they need further information or assistance while signing the consent form.

Follow-up Assessment Procedures

Enrolled participants fill in the web-based preassessment survey within 2 weeks before the first day of the intervention sessions via REDCap. Once this survey is completed, participants receive a VR headset compatible with their mobile phone if they are eligible for a VR headset based on the screening about VR tolerance, a binder with the materials, and options for mindfulness apps. As part of the screening process, we identified those who were unable to use the headset because of cybersickness. During the intervention, participants are split into 2 groups: VR and semi-immersive VR (ie, unable to use the headset). However, there is no difference in what the 2 subgroups of participants observe during the VR experience, and the VR experience lasts exactly the same amount of time for both groups during the intervention. Thus, the only difference is during the visualization mode of the VR experience to avoid cybersickness symptoms. As this is a feasibility and acceptability study, we gather feedback about each participant's experience and will be able to comment on differences between the groups as a result. We will explore differences in outcomes across the groups, but as an acceptability and feasibility trial, the study may not have the power to detect differences.

After the intervention, participants fill in the postassessment survey and meet with trained research staff (other than the interventionists) for the individual Zoom interview within 2 weeks after the last web-based check-in. eGift cards are electronically sent to participants who complete each assessment.

Data Analysis

Data analysis will follow the embedded design approach, a type of mixed methods approach, also known as intervention mixed methods framework [59,60]. The study blends elements of quantitative and qualitative research approaches to gain a deeper understanding of a phenomenon—in this case, the experimental intervention. Equal weight will be given to both components because the qualitative results will help to interpret the quantitative results, describe the participants' experiences with the intervention, and refine the intervention for future implementation based on the data gathered [59,61].

Sample Size Considerations

The study objective was to evaluate the feasibility and acceptability of an ICT-delivered intervention for caregivers using a VR component, and 20 caregivers were recruited to date to provide feedback on the VR experience as well as the usefulness of the intervention content. Although the focus is on feasibility and acceptability, the sample will provide us with the opportunity to gather feedback on the project's pre- and postintervention assessments as well as gather preliminary data on changes in key outcomes. The findings will guide the implementation of lessons learned from the project for adaptation of this intervention or the development of new technologically enhanced interventions in the future.

Quantitative Data Analysis Strategies

Variable-oriented data will be entered and analyzed using SPSS software (version 23.0; IBM Corp). Descriptive statistics will help to identify distributions (means and frequencies) for sociodemographic information and feasibility outcomes (perception of benefits and satisfaction survey). Paired 2-tailed *t* tests will be used to explore changes between the pre- and postintervention assessments. Given the focus on feasibility and acceptability, the *P* value for statistical significance will be established at $\alpha<.05$ and 95% CI. Cohen *d*will also be computed to describe the magnitude of each mean change to estimate power for future interventions [61].

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Qualitative Data Analysis

Directed content analysis, which allows for the combining of multiple techniques, will be used to analyze data regarding participant perspectives [62]. Individual postintervention Zoom interviews will gather participants' perceptions of the intervention's critical components, such as the usefulness of including VR or the amount of time devoted to each session. Participants' viewpoints will be audio recorded and transcribed using the Zoom transcription function.

The qualitative analysis will consist of (1) information complementing the quantitative data and (2) thematic analysis to unveil and elaborate on components of the intervention such as participants' views of the VR experience. For data analysis and interpretation, the analytic approach will be based on the indications for coding provided by Miles et al [63], consisting of a first and second cycle of analysis of the transcriptions.

Data Analysis Steps

Overview

The first step of data analysis will be the creation of a codebook with codes and definitions. A list of provisional initial codes will be derived from the research questions and other variables, such as inquiries about the different psychoeducational skill-building components. All the codes will have clear operational definitions.

The anticipated approach for the first cycle of coding will correspond to descriptive coding (1-word summaries), in vivo coding (words used by participants), emotion coding (feelings), evaluation coding (judgments about programs), and theming the data (a phrase that identifies a unit of data). The goal is to create a level 1 code with meaningful units. The first coding cycle will help to identify expected deductive codes (eg, *VR views, communication, challenging behavior, understanding dementia*, and *areas for improvement*). In addition, after a thorough and careful analysis of the data, inductive codes could potentially be identified; therefore, pattern codes will be extracted from the first cycle.

The second cycle of coding will consist of summarizing segments of data using pattern coding, grouping those summaries into a small number of themes (*focused coding*). Codes will be organized in an Excel spreadsheet (Microsoft Corp) using the following format: label used for each code or category, description of the concept or theme the code refers to, samples in the text, notes on how the code relates to others, and quotes. Once data saturation is reached, and the table is populated with all the codes obtained from the interviews, the next step will be to create a tree diagram. The tree diagram will include the main code, subcodes, a second level of subcodes when needed, and quotes that refer to the specific code or subcode. The tree diagram will help to organize and visualize the data, collapsing codes, and explain the relationships among the identified codes. This approach will facilitate interpreting and capturing the main essence of the caregivers' experiences with the intervention, the different components, what they like, suggestions, and other themes [62]. Two team members will revise the downloaded transcriptions to verify the transcription and data analysis accuracy. In case of discordance, a third researcher will intervene. Excel will be a supporting tool to help organize and display the data.

Issues of Trustworthiness

The selected theoretical framework will guide the data analysis process and enable us to draw conclusions. Credibility, dependability, confirmability, transferability, and application will be assessed to ensure trustworthiness. This process will ensure that potential biases affecting the study's design, implementation, and analysis are diminished and affirm that the conclusions are of high quality [58,63,64].

Credibility

To ensure methodological validity (credibility) of the study, we will (1) involve different researchers during the research process, including data analysis, synthesis, and interpretation of the results; (2) revise and discuss the findings with colleagues; and (3) build a logical chain of evidence and present data using illustrations plotting tentative relationships when needed [58,63,64].

Dependability

All the procedures will be documented to demonstrate the consistent use of codes and categories to ensure dependability. The involved colleagues will maintain a diary with their data analysis memos and steps to enhance transparency. Finally, a monitoring plan, including a moderator guide, will be created to help junior researchers interpret data [63,65,66].

Confirmability

To assess confirmability, memos and transcripts can offer a unique opportunity for the reader to evaluate the findings. In this case, a transcript segment will be facilitated in the form of a figure with the coding process to offer visible evidence of the process followed [58,65].

Transferability

The findings will be presented with a rich description of the sample and context, a consistent summary of the findings, and suggestions for new environments to broaden the perspective to ensure transferability [58,59,63].

Application

The data obtained will reach consumers via scientific publications, poster presentations, and oral communications. The findings can bring awareness to policy makers and promote further research [66].

Results

Recruitment began in January 2022, with 20 caregivers across the United States recruited to date. However, recruitment and data collection are still ongoing, and the results are expected to be submitted for publication in the second half of 2023. Preliminary data and feedback from participants support the feasibility and acceptability of the project. All the participants enrolled to date have completed the workshop as well as the pre- and postintervention assessments, including the individual Zoom interview.

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Discussion

Strengths and Limitations

Through Alzheimer's Eyes is a 4-week multicomponent intervention that includes a VR experience in every session. The intervention is designed to decrease the stress and distress of family caregivers of people with memory challenges by improving communication, behavioral management skills, management of unhelpful thoughts, and mindfulness.

A strength of *Through Alzheimer's Eyes* is that it combines VR experiences with different skills-driven components to help caregivers of people with ADRD. VR provides a valuable eye-opening opportunity to experience what it is like to have Alzheimer's disease. The intervention is guided by 2 robust theories: SCT and CBT; this increases the possibility of having a positive impact on participants' behaviors. In addition, the intervention is delivered via Zoom, enhancing the acceptability and feasibility of the intervention because participants can connect from their preferred private location via mobile phone or laptop computer with an internet connection. Connecting from home helps to resolve stressors that arise from in-person interventions (eg, finding respite, transportation, parking fees, and work schedules). This ICT-delivered intervention presents the advantage of reaching individuals living far from the intervention location and allowing caregivers to participate while remaining close to their care recipient, avoiding the hassle of looking for paid caregivers [67-69]. Potential limitations include technical difficulties that can be encountered while using the VR headsets and Zoom, which could affect the timing and flow of the session.

The intervention's novelty includes using VR and connecting remotely to help caregivers cope with stressful situations and better understand ADRD, as well as improve communication skills, manage unhelpful thinking, and increase confidence when providing care. The analysis and synthesis of the results will guide future research by providing information about VR use for learning purposes and promoting behavior change among caregivers of people with dementia.

Conclusions

This innovative study merged technology with psychoeducational and skill-building interventions, addressing a gap in the existing research literature. Interventions using ICTs such as VR present unique advantages [70]. In particular, VR brings the user to a quasi-naturalistic real-life situation where, in a safe environment, they can experience having Alzheimer's disease to help them better understand their loved one and provide holistic care. In addition, ICT-delivered interventions can provide cost savings and be more affordable than traditional in-person interventions [69,71]. By including VR and promoting an ICT-delivered intervention, we aim to reduce the number of caregivers who experience diminished well-being and provide the opportunity for caregivers to better care for their loved ones and themselves while ensuring that their own needs are met [72].

Implications for public health research and health care professionals' education and practice include the opportunity to use technology combined with skill building to (1) broaden awareness of the need to care for the caregiver, (2) advance actions in health care practice that move toward treating the caregiver and care recipient dyad and not focus only on the care recipient's treatment and health care goals, (3) create new training and related resources to promote healthy aging in place at a lower cost to people with ADRD and their family caregivers, (4) offer VR experiences about having Alzheimer's disease to foster understanding for students and professionals serving the older population, (5) reinforce interdisciplinary education and practice to help caregivers better navigate systems when seeking resources, and (6) enhance partnerships among researchers, health systems, and not-for-profit organizations to embed evidence-based technologically enhanced caregiver interventions across providers to fill gaps and more widely distribute resources for caregiving training. If the results are beneficial, they will provide a basis for a future intervention on a larger scale, including a comparison group. A comparison group will help to draw more robust conclusions regarding changes in key outcomes of interest. Improved intervention content based on participant feedback and translation of the lessons learned through piloting this technologically enhanced intervention will also assist in adapting interventions that help caregivers of patients with other chronic conditions to stay healthier and more interpersonally connected. Future studies will offer the sessions in other languages, such as Spanish, to reach the growing Hispanic and Latino communities and bridge health care inequalities. Technologically enhanced interventions hold promise as a tool for training caregivers that can be expanded in the future to serve a wider community.

Acknowledgments

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Data Availability

The data sets generated and analyzed during this study are not publicly available because of ongoing enrollment and future data analyses. However, data generated and analyzed as part of this study will be published in a peer-reviewed journal.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Descriptions of the relationships among the constructs, intervention activities, and outcomes that affect each key social cognitive theory and cognitive behavioral therapy construct.
[DOCX File , 20 KB - resprot_v12i1e42655_app1.docx]

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Abbreviations

ADRD: Alzheimer's disease and related dementias
CBT: cognitive behavioral therapy
ICT: information and communication technology
REDCap: Research Electronic Data Capture
SCT: social cognitive theory
VR: virtual reality

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Protocol

Development of a Conversational Agent for Individuals Ambivalent About Quitting Smoking: Protocol for a Proof-of-Concept Study

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Abstract

Background: Cigarette smoking is the leading preventable cause of disease and death in the United States. Despite the availability of a plethora of evidence-based smoking cessation resources, less than one-third of individuals who smoke seek cessation services, and individuals using these services are often those who are actively contemplating quitting smoking. There is a distinct dearth of low-cost, scalable interventions to support smokers not ready to quit (ambivalent smokers). Such interventions can assist in gradually promoting smoking behavior changes in this target population until motivation to quit arises, at which time they can be navigated to existing evidence-based smoking cessation interventions. Conversational agents or chatbots could provide cessation education and support to ambivalent smokers to build motivation and navigate them to evidence-based resources when ready to quit.

Objective: The goal of our study is to test the proof-of-concept of the development and preliminary feasibility and acceptability of a smoking cessation support chatbot.

Methods: We will accomplish our study aims in 2 phases. In phase 1, we will survey 300 ambivalent smokers to determine their preferences and priorities for a smoking cessation support chatbot. A “forced-choice experiment” will be administered to understand participants’ preferred characteristics (attributes) of the proposed chatbot prototype. The data gathered will be used to program the prototype. In phase 2, we will invite 25 individuals who smoke to use the developed prototype. For this phase, participants will receive an overview of the chatbot and be encouraged to use the chatbot and engage and interact with the programmed attributes and components for a 2-week period.

Results: At the end of phase 1, we anticipate identifying key attributes that ambivalent smokers prefer in a smoking cessation support chatbot. At the end of phase 2, chatbot acceptability and feasibility will be assessed. The study was funded in June 2022, and data collection for both phases of the study is currently ongoing. We expect study results to be published by December 2023.

Conclusions: Study results will yield a smoking behavior change chatbot prototype developed for ambivalent smokers that will be ready for efficacy testing in a larger study.

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KEYWORDS

cigarettes; conversational agent; mhealth; smoking cessation

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Introduction

Cigarette smoking continues to be the leading preventable cause of disease and death globally and in the United States [1]. Cigarette smoking kills more than 480,000 Americans each year and results in more than US $240 billion in health care spending and nearly US $372 billion in lost productivity [2]. Thus, promoting smoking behavior change with the long-term goal of achieving successful cessation is critical to reducing the public health impact caused by tobacco use. Within the United States, the past few decades have seen a groundswell of evidence-based interventions to quit smoking. These have included a wide range of strategies such as mobile health (mHealth) apps [3,4], availability and increased access to effective pharmacotherapy for cessation [5], SMS text messaging support [6,7], evidence-based behavioral counseling [8], and comprehensive state-based programs, such as tobacco quitlines [9,10]. However, despite their widespread availability, less than one-third of people who smoke cigarettes actively avail themselves to cessation strategies [11]. For example, tobacco quitlines—free evidence-based smoking cessation programs providing telephone-based behavioral counseling combined with cessation pharmacotherapy available in all 50 US states—are used by less than 3% of people who smoke [12]. One potential reason for the low uptake of existing services for cessation may be that strategies to promote cessation differ according to an individual's readiness and motivation to quit [13]. Although smokers actively committed to quitting respond positively and engage with cessation services, ambivalent smokers (ie, those not actively seeking treatment) may benefit from approaches that promote modest changes or "behavioral *nudges*" toward smoking behavior change (but not cessation) [14,15]. Most cessation research is focused on those expressing an intention to quit, and research on promoting behavior change in ambivalent smokers (not actively thinking about quitting) is scant.

A conversational agent or "chatbot" is an inexpensive and scalable approach to deliver personalized health information in a human-like manner. Common in the consumer-service sector, chatbots are increasingly being deployed in the health sector to provide education, support, service navigation, and interventions for a range of health issues, from COVID-19 to asthma [16,17]. Human-delivered interventions for smoking behavior change are effective but are resource-intensive, lack scalability, and can be expensive to implement. Chatbots have the intuitive appeal of being low-cost automated interventions that can widely reach ambivalent smokers. Moreover, chatbots can provide "virtual accompaniment" at the frequency and duration preferred by the smoker until the motivation to quit arises, at which time they can be swiftly connected to an existing evidence-based cessation intervention. A few studies on chatbots for smoking behavior change target participants actively intending to quit smoking [18-20] and, while important, only address the tip of the iceberg in terms of reaching the smoking population. Since motivation to quit smoking is dynamic and occurs along a continuum [21], strategies to engage ambivalent smokers may be most helpful if they are tailored to accommodate smokers' changing preferences and are responsive to rapid changes in motivation (eg, connecting smokers to quitlines when ready to quit), while focusing on evidence-based strategies that have been effective for smoking reduction leading to cessation (eg, quit tips, self-monitoring, and tracking savings). Since interventions to assist smokers ambivalent about quitting are in their infancy, little is known about key elements of a chatbot-based smoking behavior change intervention tailored for this target population.

To overcome these gaps in the field, the goal of our study is to test a proof-of-concept of a novel chatbot to support and engage smokers who are not actively engaged in a quit attempt (ambivalent smokers). We propose accomplishing our aims in 2 phases. In phase 1, we will identify the key attributes that will guide the development of the chatbot prototype. We will survey ambivalent smokers to determine their preferences and priorities for a smoking cessation support chatbot. Using conjoint analysis, we will systematically elicit participant preferences for the proposed chatbot prototype (see details below). Grounded in macroeconomic principles [22], conjoint analysis is a quasi-experimental approach that decomposes a product or service into its key attributes, then poses the attributes to patients to understand patient-determined values for each attribute [23,24]. These preferences will be programmed into the chatbot prototype. In phase 2, we will invite participants to use the prototype over a 2-week period to assess the feasibility and acceptability of the developed chatbot prototype.

Methods

Study Overview

To develop the chatbot prototype (phase 1), we will recruit 300 participants who identify as current cigarette smokers to complete a web-based survey. The survey will collect demographics, smoking behavior history, and e-cigarette use, and solicit preferences for the most important features of the proposed chatbot. The top 5 preferred attributes will be used to design and develop the chatbot prototype. In phase 2, 25 participants will be recruited to engage with the developed prototype for a 2-week period. Preliminary acceptability and feasibility data will be collected via validated questionnaires at the end of 2 weeks. For both study phases, participants will be recruited using an established survey panel (Prolific). Study eligibility criteria are as follows: older than 18 years, self-report any smoking in the last 7 days, and no current intention to quit smoking in the next 30 days (score of ≥5 on a 10-point Likert scale assessing likelihood to quit smoking).

Ethics Approval

All study procedures have been approved by the University of South Florida's Institutional Review Board (IRB # 004183). For phase 1, the data are deidentified with participants only providing a prolific ID. For phase 2, participant names and phone numbers will be stored on a password-protected computer only accessible to the study staff. All participants will be identified by a study ID and any identifying information will be removed from interview transcripts prior to beginning qualitative data analysis. Participants will be compensated for both phases of the study. Participants will receive US $6 for completing phase 1 and US $70 for completing phase 2.

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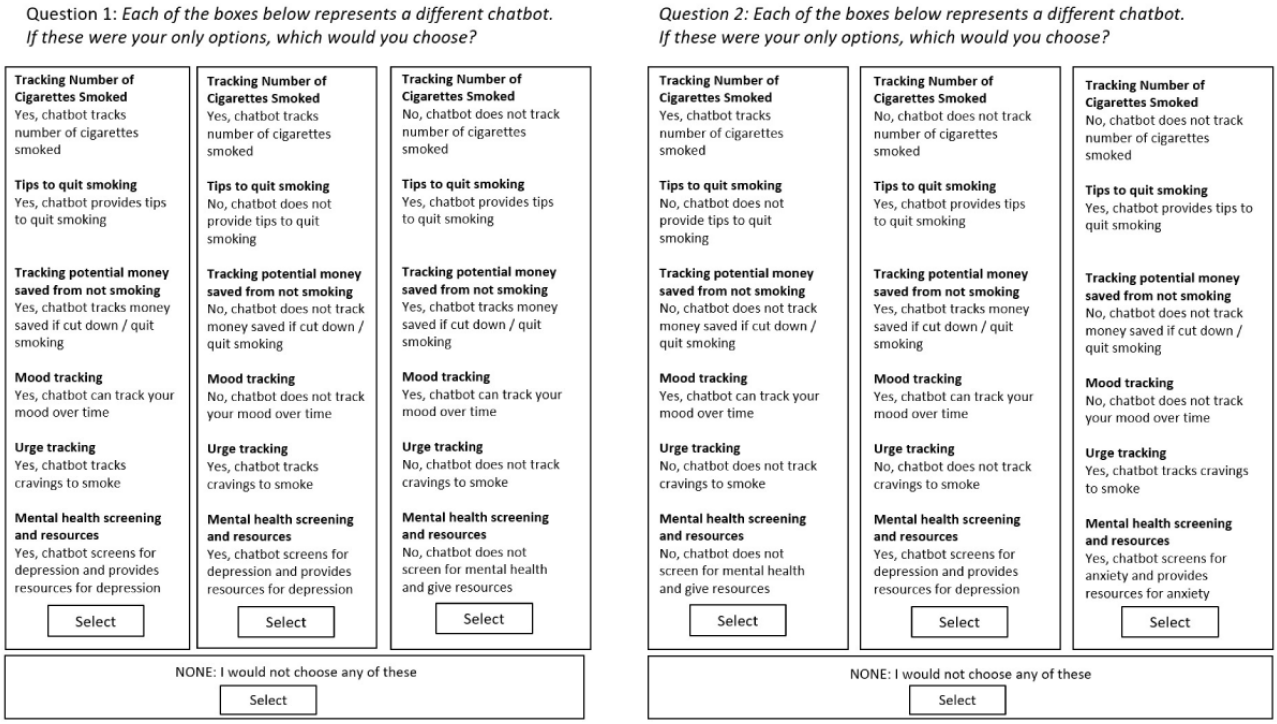
Phase 1: Development of Chatbot Prototype

Overview

This phase is designed as a cross-sectional survey to develop a prototype of the proposed chatbot by assessing preferred attributes in a sample of individuals ambivalent about quitting smoking. To do so, 300 participants have been identified who will be invited to complete a web-based survey. Participants will be recruited using the internet and an established study panel (Prolific). After completing a web-based informed consent, participants will provide information on demographics and smoking history, after which they will be provided with a brief explanation of chatbots (what they are and how they work). They will also be asked about their previous and current experience with chatbots and interest in a chatbot designed to support people who may decide to quit smoking in the future.

Next, we will administer a choice-based conjoint (CBC) analysis experiment to understand participants' preferences for a smoking cessation chatbot. Using Sawtooth Software's web-based choice analytics survey platform, we will construct hypothetical smoking cessation chatbot "scenarios" comprising the following six attributes (ie, potential chatbot features) with varying levels: (1) number of cigarettes smoked per day tracked (yes or no), (2) smoking quit-tips provided (yes or no), (3) money saved by reducing smoking tracked (yes or no), (4) mood tracking (yes or no), (5) smoking cravings tracked (yes or no), and (6) mental health screening and resource provision (only depression screening, only anxiety screening, or no mental health screening). These attributes were chosen a priori based on published smoking cessation literature identifying evidence-based strategies to promote and support smoking behavior change. The sixth attribute, mental health screening, was added given the comorbidity between smoking and mental health [25,26]. In the CBC experiment, participants will be presented with a series of tasks; each task will display 3 different chatbot configurations composed of identical attributes but differing combinations of attribute levels. A total of 10 tasks will be presented to participants. Each question will contain 3 panels that present a combination of the attributes and associated scenarios, and participants will be asked to choose the chatbot configuration they would most prefer (ie, the chatbot that contains the combination of chatbot attribute levels most desired). Participants may also choose "none" if no chatbot configuration presented is desirable. Figure 1 displays examples of the CBC tasks. Finally, the desired frequency of chatbot messages will be assessed, and at the end of the survey, interest in participating in phase 2 will be elicited.

Figure 1. Examples of a conjoint analysis task.



Measures

For phase 1, assessments will include demographics (eg, age, sex, gender identity, and education) and smoking history (age of smoking initiation and number of previous quit attempts in the past year) [27]. Nicotine dependence will be measured by the Fagerstrom Test of Nicotine Dependence [28], which is a validated and ubiquitous instrument assessing dependence on nicotine. Smoking cessation self-efficacy will be measured using the validated Smoking Abstinence Self-Efficacy Questionnaire [29]. This 12-item questionnaire measures an individual's self-reported confidence in resisting the urge to smoke in various settings and conditions. Given the high prevalence of e-cigarette use among individuals who smoke [30], current e-cigarette use will also be assessed [31]. In addition to these measures, we will also collect information on current use and frequency of marijuana or cannabis [32] and alcohol use [33].

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Data Analysis

Summary statistics (mean [SD] or frequency [%]) will be calculated for demographic and smoking characteristics. For the CBC data analysis, also completed using Sawtooth Software [34], utility scores will first be computed to determine the relative desirability of each level within each attribute. These data will inform which of the chatbot feature levels were most desired (eg, whether a cigarette tracking feature is desired). Next, the relative attribute importance scores (ie, the relative impact of each attribute in respondent choices) will be computed; these data will indicate the order of importance of each of the 6 chatbot features (most important to least important). We will also compute the 95% CIs for each of the attribute scores. Finally, CBC data will be examined for variance by select sociodemographic variables (eg, sex, gender, education, and number of quit attempts) to determine possible chatbot preference differences by population segments. The combined data will inform the prioritization of chatbot features programmed into the prototype chatbot tested in phase 2.

Phase 2: Acceptability and Feasibility Testing of the Chatbot Prototype

Overview

For phase 2, 25 eligible individuals expressing interest to participate at the end of phase 1 will be recruited to engage with the developed chatbot prototype. Participants will be contacted by the study staff to explain study procedures and complete informed consent, following which the participant will receive a link to complete a baseline survey. Following completion of the survey, they will be scheduled for an appointment to participate in a 45- to 60-minute interview conducted via secure videoconferencing. During this time, study staff will share a link with the participants to activate the chatbot prototype. An overview of the chatbot will be provided, following which participants will verbalize their thoughts and reactions while interacting with the chatbot, based on the think-aloud usability testing technique [32], and provide initial feedback while interacting with the chatbot. The interview will be audio and video recorded and participant interactions with the chatbot will be observed. At the end of this session, participants will be encouraged to use the chatbot over a 2-week period, engaging and interacting with the programmed attributes and components. To increase retention during this period, data entry and chatbot engagement will be monitored on a frequent basis, and all participants will receive daily reminders to engage with the chatbot. At the end of the 2-week period, participants will complete acceptability and feasibility assessments, provide feedback to open-ended questions to identify any aspect of the chatbot that was confusing, what they liked or disliked, perceived helpfulness of the chatbot, feedback on features they would like included, and aspects that would help keep them engaged with the chatbot. Participants will receive a total of US $70 for phase 2 (US $20 for the interview and US $50 after completion of the follow-up surveys).

Measures

In addition to the measures used in phase 1, phase 2 measures will include intervention acceptability using the Acceptability of Intervention Measure, Intervention Appropriateness Measure, and Feasibility of Intervention Measure [33], as well as intervention usability using Health Information Technology Usability Evaluation Scale [35].

Data Analysis

Quantitative data will be cleaned and analyzed to generate summary tables. We will limit analysis to only include descriptives due to the small sample size, which prevents tests of association. Qualitative data (ie, recorded transcripts from the videos during which participants interact with the chatbot and the qualitative interviews after interacting with the chatbot) will first be transcribed verbatim, resulting in text transcripts. Next, the transcripts will be loaded into the qualitative software, Dedoose [36], and analyzed using a framework analysis approach [37]. Transcripts will be read in their entirety and coded using a preliminary codebook derived from the interview guide, adding de novo codes as new themes are detected. Reports will be generated for all codes and related text extracted into tables for deeper analysis, during which cross-cutting themes will be identified and reported. The COREQ (Consolidated Criteria for Reporting Qualitative Data) checklist [38] will be completed to enhance data rigor and methodological transparency [28-31].

Results

The study was funded in June 2022, and regulatory processes and approval were completed by August 2022. Data collection for the study is currently ongoing, and we anticipate publication of expected outcomes by December of 2023. In phase 1, the methodology described above will result in the identification of key attributes that participants report a preference for in a smoking cessation support chatbot. These data will be used to program a chatbot prototype. Using SmartBot360 [39], a "point-and-click" chatbot development software, a prototype smoking cessation support chatbot will be programmed that contains the top preferences and features as expressed by the participants in phase 1. In addition to the attributes, information on existing evidence-based smoking cessation resources will also be programed to gauge participant preferences for existing evidence-based cessation resources. These will include, but not be limited to, links to sign up for free SMS text messaging services (eg, smokefree TXT) or mHealth quit apps (eg, QuitGuide), connecting to smoking cessation experts (eg, National Cancer Institute's LiveHelp or a state quitline), and information on pharmacotherapy.

At the end of phase 2, we will obtain participant data on chatbot acceptability and feasibility.

Discussion

The goal of our study is to develop and pilot-test for feasibility and acceptability of a novel chatbot prototype to support and engage smokers who are not actively engaged in a quit attempt (ambivalent smokers). The study will test a proof-of-concept of the chatbot, and the anticipated main result of our project is a pilot-tested conversational agent ready to be tested for efficacy in a larger study. To our knowledge, this is the first study to

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develop a conversational agent (chatbot) for ambivalent smokers using a novel methodology.

Interventions to engage individuals ambivalent about quitting smoking are an unexplored area in smoking cessation research [11]. This study will begin an innovative line of research on strategies to optimize and personalize smoking behavior change services for individuals ambivalent about quitting smoking. Of specific mention is the use of conjoint analysis as an innovative strategy to assess and incorporate user preferences in the development of an mHealth intervention. Methodologies to systematically assess and incorporate individual preferences in the delivery of health care services are in their infancy [40], and little is known about the preferences of ambivalent smokers for chatbots as they navigate the motivation to quit continuum. While conjoint analysis has been increasingly used in the health sector, including in the smoking cessation field [41,42], to our knowledge, no mHealth interventions for smoking behavior change have used this methodology for design and implementation. Our investigative team has successfully used conjoint analysis for other health issues, including determining consumer preferences for oral and topical HIV chemoprophylaxis [43,44]. If acceptable in this pilot study, our chatbot could be a low-cost and low-resource intervention that fills a much-needed gap in the field.

The study has a few limitations. First, the study design does not lend itself to testing the effects of the chatbot on smoking behavior change outcomes. However, given the dearth of research in this area, the development of the chatbot and acceptability and feasibility testing are the first steps. At the end of the study, we will have a developed chatbot that will be ready for efficacy testing in a larger randomized controlled trial. Next, our participant recruitment methodology uses a web-based survey panel, which may reduce generalizability. While such survey panels use purposive sampling to gain a representative sample of participants [45], we anticipate using a combination of social media, community-based recruitment efforts, and web-based recruitment panels for larger efficacy trials, which will increase the generalizability of our results.

Our intervention that uses a chatbot to promote smoking behavior change in a sample of ambivalent smokers fills a distinct gap in the field. Our model is a scalable and pragmatic model that can be adopted by cessation services (quitlines) and is designed for easy accessibility to the broader population of individuals who are not actively contemplating quitting smoking. It could additionally serve as a tool for health care providers as they recommend quitting smoking resources to their patients. In the long run, our study design and methodology can be used to develop chatbots that can increase access to other evidence-based interventions within the context of substance use disorders (eg, cannabis and opioids) or compulsive behaviors (eg, eating disorders and gambling).

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Data Availability

The data sets generated and analyzed during this study will be available from the study investigators (USN and JTG) on reasonable request.

Conflicts of Interest

None declared.

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Abbreviations

CBC: choice-based conjoint
COREQ: Consolidated Criteria for Reporting Qualitative Data
mHealth: mobile health

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Protocol

Identification of Patients With Elevated Urine Albumin–to-Creatinine Ratio Levels in a Type 2 Diabetes Mellitus Cohort Based on Data Submitted by Patients via a Smartphone App (SMART-Finder): Protocol for an Observational Study

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Abstract

Background: Despite effective treatment options, chronic kidney disease (CKD) has become a major cause of mortality worldwide due to the ever-increasing number of patients with type 2 diabetes mellitus (T2DM). Guideline-compliant, at least, annual screening of patients with T2DM is crucial to prevent renal disease progression. However, data on the prevalence of CKD in patients with T2DM and on screening frequency are limited. SMART-Finder is the first study to exclusively use data provided directly by patients via an adherence app to collect information on the prevalence of CKD, risk factors, disease management, and quality of life of patients with T2DM in Germany.

Objective: The primary objective of this study is to determine the proportion of patients with T2DM and an elevated urine albumin-to-creatinine ratio (UACR; albumin-to-creatinine ratio stage A2 and A3) at baseline and after 12 (±3) months. Secondary objectives include the proportion of patients who remain in or switch to another albumin-to-creatinine ratio classification category after 12 months, information on quality of life, disease awareness, and adherence rates, as well as the proportion of patients without any UACR-screening data. Recruitment occurs via push notification among MyTherapy app users with T2DM.

Methods: This is a single-arm, retrospective/prospective, observational, digital, patient-centered cohort study, with recruitment and data documentation via a health app. Required routine laboratory data are provided by treating physicians to their patients for data entry. The study population includes adult patients with T2DM documenting their data in the MyTherapy app using their own smartphone or tablet. Study participants are provided with a specifically developed electronic case report form containing questions on demographic and general data, quality of life, disease awareness, and laboratory values including estimated glomerular filtration rate, UACR, hemoglobin 1Ac, and blood pressure. Apart from demographic and general data, all data are collected at baseline and 12 months after the last UACR assessment. An automatically generated push notification reminds participants of the second data entry. The extracted and pseudonymized data are analyzed descriptively.

Results: The enrollment period for this study started in February 2023 and shall end after 12 months or after the enrollment of 5000 patients. An interim analysis is planned 3 months after the inclusion of the first patient and the final analysis after 12 months of follow-up.

Conclusions: Overall, the study will contribute to minimizing the existing data gap on the prevalence of CKD in patients with T2DM in Germany, provide important insights into the current disease management of patients with T2DM in everyday clinical practice in Germany, and support guideline-based care for the participating patients.

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KEYWORDS

app-based documentation; chronic kidney disease; prevalence; MyTherapy; type 2 diabetes mellitus; urine albumin-to-creatinine ratio screening

Introduction

Chronic kidney disease (CKD), a common comorbidity of the ever-increasing number of patients with type 2 diabetes mellitus (T2DM), is a leading cause of death worldwide [1-9]. It is usually characterized by persistently decreased estimated glomerular filtration rate (eGFR) or persistently elevated urine albumin excretion, is often progressive and may finally lead to end-stage renal disease [10-13].

At the same time, effective therapeutic approaches are available, which, if applied early and consistently, can favorably influence or delay the development or progression of kidney damage [9]. According to current recommendations of the Kidney Disease: Improving Global Outcomes Work Group, the treatment of patients with T2DM includes lifestyle measures as an important basic therapy, followed by renin-angiotensin system inhibitors, sodium glucose transport protein 2 inhibitors (SGLT-2i), statins, and metformin as first-line drug therapies. Glucagon-like peptide-1 receptor agonists are recommended if SGLT-2i and metformin do not achieve sufficient glycemic control. For patients at high risk of progression to CKD and cardiovascular events despite standard therapies, a nonsteroidal mineralocorticoid receptor antagonist is recommended in addition to baseline therapy.

In order to effectively implement these therapeutic measures to delay progression, early identification of patients with diabetes at increased risk for renal disease is crucial. National and international guidelines recommend to determine the eGFR on the basis of serum creatinine determination and albuminuria using the urine albumin-to-creatinine ratio (UACR) at least once a year in patients with T2DM [8,9,14-18]. In patients diagnosed with CKD, these parameters should be determined up to 4 times a year, depending on the severity and progression risk [9].

However, data on the prevalence of CKD in patients with T2DM in Germany are sparse. Similarly, data on longitudinally eGRF and UACR measurements are limited, as there are only few studies of patients with T2DM and CKD in a real-world clinical setting [19-21].

A major aim of the study presented here is to minimize the data gap on the prevalence of CKD in patients with T2DM as well as to assess risk factors, satisfaction with treatment management, and quality of life of patients with T2DM over 12 months. SMART-Finder is the first study exclusively using data provided directly by patients via an adherence-supporting app for this purpose.

Methods and Objectives

Objectives

The primary objective of this study is to investigate the proportion of patients with T2DM with elevated UACR levels (albumin-to-creatinine ratio [ACR] stadium A2 and A3) at baseline and after 12 (±3) months. Secondary objectives include investigating the proportion of patients who remain in or switch to another ACR classification category after 12 months as well as the proportion of patients without UACR-screening data, the description of patient characteristics stratified by hypertension and nephrotoxic comedication status, and information on quality of life for patients with T2DM and relevant subgroups. Further secondary endpoints include the description of disease awareness and medication adherence rates among patients with regard to blood pressure control and antidiabetes drugs. Medication adherence is defined as the number of patients who are compliant and persistent during the observation period, that is, who document at least 80% of their planned medication in the MyTherapy app (compliance) and do not stop taking their planned medication during the observation period (persistence).

Study Design

This is a single-arm, retrospective/prospective, observational, digital, patient-centered cohort study in Germany. Both recruitment for this study and documentation of the data are carried out without the assistance of a health care professional (HCP), but as part of the routine use of the MyTherapy app (smartpatient GmbH) by patients with T2DM who document their data in the MyTherapy app using their own smartphone or tablet.

This study is neither intended nor designed to record safety-related data regarding the treatment with T2DM drugs or the use of the MyTherapy app. However, the Diabetes Treatment Satisfaction Questionnaire (DTSQ) questionnaire, which is part of the study electronic case report form (eCRF), captures hypo- and hyperglycemia. Adverse events (AEs) indicative of hypo- or hyperglycemia that may be recorded there, as well as Bayer drug-related AEs recorded in the context of this study, are forwarded from smartpatient, the owner of the MyTherapy app, to the sponsor as a cumulative listing after the end of the study. Furthermore, patients are asked in the patient information of this study to contact HCPs in case of any AEs. For direct reporting, patients are referred to specific web pages [22,23], which is also accessible via an in-app link from the MyTherapy app.

Ethics Approval

Ethics approval for this study was granted by the Ethics Committee of the North Rhine Medical Association (Ärztekammer Nordrhein) on October 13, 2022 (approval number 2022263).

Patient consent for the use of personal data is required for participation in the study. The patient information form explains in detail which data will be used for the study and obtains consent for the use of pseudonymized data.

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Once the eCRF, including questions on UACR, is completed, patients will receive two €10 (US $10.8) vouchers for Shop Apotheke as compensation for their time spent on data documentation, 1 for completed questionnaires at baseline and 1 after follow-up.

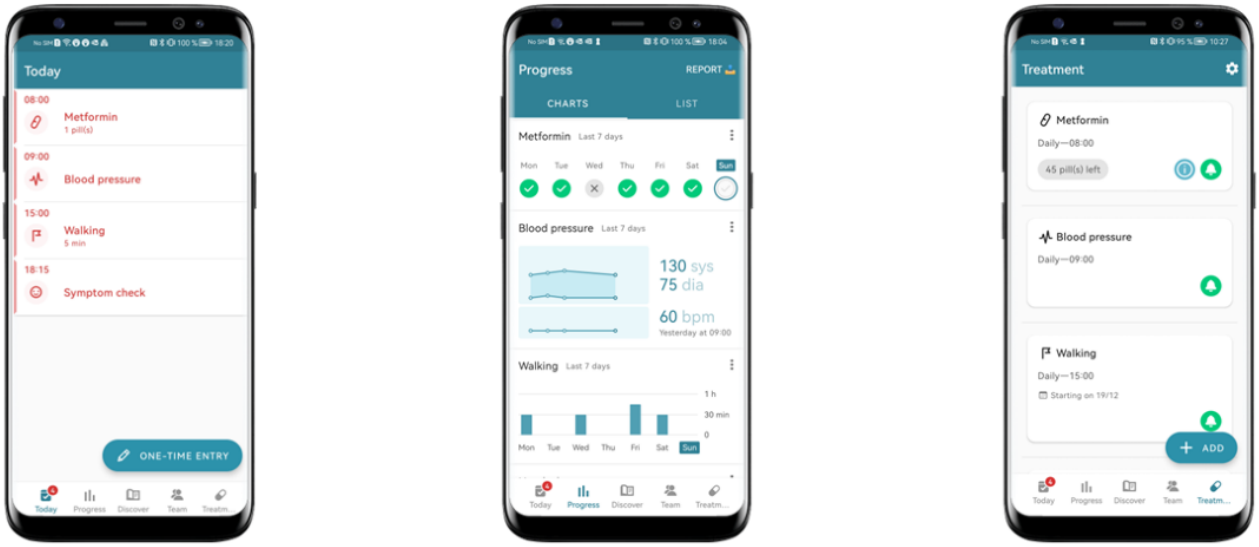
Study Population

The study population consists of adult patients with T2DM in Germany using the MyTherapy app to document their medication intake and monitor adherence. Patients with a self-reported diagnosis of type 1 diabetes mellitus and patients who are treating their diabetes with an insulin pump are not eligible.

MyTherapy App

The MyTherapy app is a widely used medication management app (over 8 Mio Downloads, available in more than 30 languages) that helps patients manage their treatment-related tasks and other health topics, including comorbidities. The application allows the user to track medication intakes and activities and to review them over time. For this purpose, the application translates both simple and complex therapies into a daily list of "To do's," which are either related to "Medication," "Measurement," "Activity," or "Symptom check" (Figure 1). The app then supports the user, by reminding them of their health-related tasks; each user is asked to clear their daily list of "To do's" and is rewarded with a picture of the day afterward. App users can access all tracked events over time in the "Progress" section or request a printable report to be sent to their email address, which can be printed and brought to the next doctor's visit. Studies have already shown that the app strengthens adherence to medication and the doctor-patient relationship in patients with T2DM [24,25].

Figure 1. English version of the MyTherapy app sections "Today," "Progress," and "Treatment.".



The app can also, as in the context of this study, be extended by additional functionalities, such as educational content or surveys. In this case, the user benefits from all features of the basic MyTherapy app, while additionally having access to the extension. For this study, specific content (ie, video, patient information on the study) is provided, users are enabled to give informed consent to participate in the study, and a standardized eCRF is shared with and can be completed by MyTherapy app users who participate in the study.

As the MyTherapy app is routinely used by about 13,000 patients with T2DM in Germany to document their medication adherence and to monitor adherence to self-determined goals [24], it provides a cohort of patients suitable for this study. Therefore, usage of the MyTherapy app enables efficient recruitment of eligible patients and collection of relevant retrospective and prospective data with low operational effort.

Patient Journey and Study Procedure

Recruitment and Study Inclusion

Recruitment for this study is exclusively conducted via the MyTherapy app. All users of the MyTherapy app who have set up reminders for a diabetes medication automatically receive an invitation to participate in this study via push notification during their routine app use as well as a reminder 2 weeks later. An initial question further helps to identify the users with T2DM. In this context, the following medications or medical devices are considered for the initial selection of the target group: metformin, acarbose, dipeptidylpeptidase-4 inhibitor, glucagon-like peptide-1 receptor antagonist, renin-angiotensin system inhibitor, SGLT-2i, basal insulin, nonsteroidal mineralocorticoid receptor antagonist, sulfonylurea, and blood glucose test strips. Interested patients can find a video in German about the etiology of CKD and the importance of regular screening, as well as key information about the SMART-Finder study within the "Discover" section (available as Multimedia Appendix 1). After clicking on the push notification, users access information in German about the background and scope of this study and are able to access, read, and agree to the consent form for participation in this study.

Self-reporting of Data

All data will be entered by the patients themselves via the MyTherapy app, both as part of routine use and on a specifically developed eCRF in German. After completing the patient informed consent, an eCRF including 4 questionnaires is

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provided and can be completed directly within the app: One questionnaire on demographic and general data, 1 on laboratory values, and 2 on quality-of-life aspects. The 2 quality-of-life questionnaires are standardized and validated (EuroQol Five Dimensions Questionnaire [EQ-5D] and DTSQ), both implemented for digital use. Table 1 summarizes variables collected within these 4 questionnaires of the eCRF. Multimedia Appendix 2 provides a detailed description of all variables, including their possible response options and ranges, collected in this study.

Table 1. Listing of variables collected in the electronic case report form.

Questionnaire/topic	Variables
General data	Name, zip code, year of birth, age, gender, weight (kg), height (cm), smoking habit; last systolic blood pressure, and last diastolic blood pressure
Laboratory values	UACR[a], eGFR[b], HbA_{1c}[c], and serum fasting glucose level
QoL I (DTSQ[d])	Satisfaction with current treatment; signs of hypoglycemia, signs of hyperglycemia; feasibility of treatment; satisfaction with the flexibility of actual treatment; satisfaction with own knowledge about the disease; recommendation of own treatment to others; and satisfaction with the continuation of current treatment
QoL II (EQ-5D-5L)	Mobility, self-care, usual activities, pain/discomfort, and anxiety/depression

[a]UACR: urine-albumin-creatinine-ratio.

[b]eGFR: estimated glomerular filtration rate.

[c]HbA_{1c}: hemoglobin A_{1c}.

[d]DTSQ: Diabetes Treatment Satisfaction Questionnaire.

Apart from demographic and general data, all questionnaires should be filled in twice by patients: first at baseline documentation and then 12 (±3) months after the initial UACR measurement ("end-of-observation documentation"). To remind participants of this second data entry, users receive an automatically generated push message.

During the first data entry (baseline documentation), patients are asked to document their most recent available lab values of the last 12 months in the eCRF for UACR, eGFR, HbA_{1c} (hemoglobin 1Ac), and blood pressure. If patients do not know these lab values, they are encouraged to request them from their treating physician. For this purpose, a document is provided via the "Discover" section in the app, which can be shared via email or can be printed to inform the treating physicians about lab values that are required and may still need to be collected.

Overall, laboratory values for baseline documentation can be recorded retrospectively for up to 12 months and prospectively for 3 months after giving informed consent for this study. In addition, patients also have to document fasting blood glucose values, smoking status, and aspects of their quality of life and disease awareness within the other questionnaires of the eCRF as part of this baseline documentation.

The "end of observation documentation" takes place 12 (±3) months after the first documented UACR measurement. Accordingly, the observation period (the period between the 2 UACR screenings) for each patient is 12 (±3) months; however, the period between providing informed consent and the end of observation may be less than 12 months due to the possibility of retrospectively collected UACR baseline data.

Each patient may withdraw from the study at any time and without giving a reason. In this case, no further study data will be collected.

Statistical Considerations

Sample Size

Based on approximately 13,000 MyTherapy app users with T2DM in Germany and recruitment rates from a comparable study focusing on patient adherence and physician-patient relations, participation of up to 5000 patients is expected [24].

Statistical Analysis

All variables are analyzed descriptively with appropriate statistical methods: categorical variables by (absolute and relative) frequency tables, frequencies, and continuous variables by sample statistics (ie, mean, standard deviation, minimum, median, quartiles, and maximum). Continuous variables are described by absolute value and as a change from baseline per analysis time point, if applicable. All analyses are performed for the total study population (overall analysis) and stratified by subgroups (eg, age, gender, and blood pressure), whenever reasonable.

Data Management and Quality

Data sources are limited to the MyTherapy app database including data that have been received from the health records of the treating physicians and documented in the eCRF by the patients. MyTherapy users only participate in the study after having signed study-related informed consent. Data are documented by the participating patients themselves. Data are not queried after data entry, but a check for multiple documented patients is performed.

To avoid free-text entries and queries, and to ensure convenient and accurate data entry, the eCRF is designed with all but 2 fields being checkboxes with suggested response options. Furthermore, incomplete questionnaires cannot be saved but must first be completed. While this may result in a higher dropout rate, it contributes considerably to the completeness of the data sets of study completers.

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With regard to lab values, data entry is only allowed within certain ranges to minimize errors when transferring data (see Multimedia Appendix 2 for detailed information on acceptable ranges per variable). In addition, as described, patients are encouraged to request missing laboratory values from their treating physician and are supported with a document (Multimedia Appendix 2).

Moreover, with regard to the UACR values, patients are given the opportunity to request missing data over a certain period of time: Patients who state "UACR value not yet measured, but have made a doctor's appointment to have my UACR value measured" are informed twice at intervals of 2 weeks via push message that the UACR values are still missing. Subsequently, they must enter a UACR value or select "UACR value not measured." Otherwise, the questionnaire is considered as not answered, and the participant drops out of the study.

The category "value not measured" can only be selected for the lab values UACR, eGFR as well as HbA_{1c} and provides important information on how the guideline-compliant assessment of these lab values is implemented in routine clinical practice.

Smartpatient is assigned with the development of eCRFs and their integration into the MyTherapy app, the quality control of data collection, and the transfer of the pseudonymized study database to the clinical research organization Institute Dr Schauerte, Munich, Germany, which performs data analyses and data transfer to Bayer. Digital implementation of the 2 validated and standardized quality of life questionnaires in MyTherapy was reviewed and approved by their respective providers, that is, EuroQoL Research Association, Rotterdam, The Netherlands (for EQ-5D) and Prof Clare Bradley, Health Psychology Research, University of London, Egham, Surrey, UK (for DTSQ).

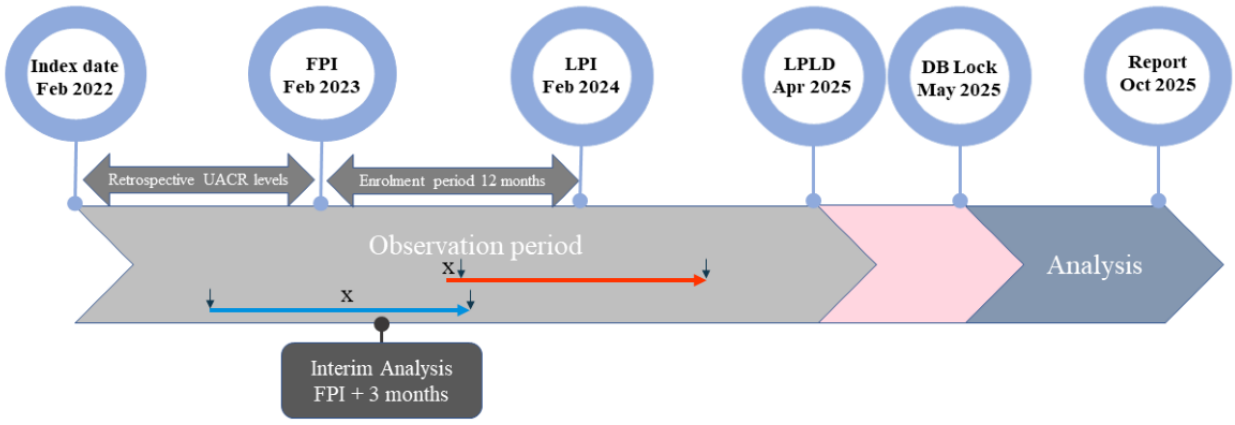
Trial Organization and Regulatory Authorization

This study is sponsored by Bayer Vital GmbH, Leverkusen, Germany. It is performed in collaboration with smartpatient GmbH, Munich, Germany, the provider of the MyTherapy app, a subsidiary of Shop-Apotheke, one of the largest internet-based pharmacies in Germany.

Results

The enrollment period of this study is planned from February 2023 (first patient in) until February 2024 (last patient in). During this period, patients accepting the invitation to participate in the study within the MyTherapy app are consecutively enrolled. Enrollment is stopped, after the target sample size of 5000 patients is reached or at the end of the planned enrollment period. Patients dropping out (eg, withdrawal, lost to follow-up) after the end of enrollment are not replaced. The observation period of each individual patient is 12 (±3) months (last patient last documentation: April 2025). An interim analysis is planned 3 months after the inclusion of the first patient and a final analysis after the study end. Figure 2 illustrates the study time frame.

Figure 2. Study time frame illustrating examples for patients with a retrospectively (blue arrow) and a prospectively (orange arrow) measured first UACR level. FPI: first patient in; LPI: last patient in; LPLD: last patient last documentation: DB, database; x = informed consent; ↓: UACR measurement.



Discussion

The study design presented here is novel, as it uses data exclusively documented by the patients in an app for the first time to collect information on the prevalence of CKD, risk factors, disease management, and quality of life of patients with T2DM. Since recruitment and data entry for this study are carried out via the MyTherapy app, which is routinely used by approximately 13,000 patients with T2DM in Germany, participation of about 5000 patients is expected. This provides a solid database to answer several scientific questions. This study is the first to estimate the proportion of patients with CKD or at high risk of developing CKD among patients with T2DM using UACR data documented exclusively by patients in the app. Also, any change in disease severity over the course of 12 months is identified in this way. In this context, it is a strength of the cohort study design presented here that the required laboratory values and especially UACR values are collected by HCPs and provided to their patients for entry into the app. It is expected that the study will make an important contribution to minimize the existing data gap in Germany regarding the prevalence of CKD in T2DM patients and contribute to a better understanding of its occurrence, severity, and risk of progression.

In addition, this study will also provide key data on the disease management and health care situation of patients with T2DM

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in routine clinical practice in Germany. For example, adherence data of (co-)medications reported by patients in the MyTherapy app as well as the identification of treatment despite contraindication (taking nephrotoxic drugs) will provide important insights into therapy implementation in clinical routine.

Another key aspect is that the proportion of patients with T2DM who receive regular, guideline-compliant UACR and eGFR measurements at least once a year will be determined. To date, only limited data are available in this regard, which suggest a certain discrepancy with recommended annual screening and at least hesitant implementation of guideline-based diagnostics with some potential for improvement. A recent study on adherence to treatment guidelines in Germany, based on combined data from the *Diabetes Patienten Verlaufsdokumentation* and *Diabetes Versorgungsevaluation* databases, showed that only 49.1% of 116,747 patients with T2DM received annual CKD screening measurements [19]. Studies from Finland and Australia indicate similar results [20,21].

Considering that CKD screening in patients with T2DM is not yet universally implemented in clinical practice [19-21], another crucial aspect of this app-based study is the fact that it raises awareness of CKD risk in patients with T2DM and also fosters their self-responsibility and health literacy by pointing out the guideline-recommended UACR and eGRF screening of at least once a year. Furthermore, by providing study participants with a printable document for discussion with their treating physician in case of missing lab values, patients are empowered to take care of their disease themselves to a certain extent. For the future, this study also offers the possibility to establish a systematic, app-based early screening for CKD or other fields or indications.

Overall, the study aims to raise awareness of guideline-based management of patients with T2DM, both among physicians and patients and may help to improve early detection of kidney disease in patients with T2DM—a fundamental prerequisite for timely, guideline-based therapy that can prevent or delay disease progression and help to avoid end-stage renal disease.

Limitations of this study include, first, the fact that UACR values cannot be self-assessed by the patients, as the test strips are only approved for use by a health care professional. Even if a printable document is accessible to support medical consultation, it may still pose a barrier for some patients with T2DM to arrange a medical appointment and ask the doctor to collect this value. Therefore, missing UACR values might be a concern. On the other hand, the number of missing UACR values provides important insights into disease management and guideline adherence in Germany. Second, with a follow-up of 12 months, “digital” attrition, that is, a decreasing adherence to the app, is also to be expected, as its regular use may be challenging and may cause dropouts. Third, potential errors in data transmission are also a limitation as patients document values themselves without the possibility of querying them. However, efforts are undertaken to minimize transmission errors by permitting data entry only within a certain range (see Multimedia Appendix 2 for detailed information on the permitted ranges per variable). Fourth, the study population consists of patients with T2DM routinely using the MyTherapy app to review self-defined health goals and to support their medication adherence—and thus represents a biased subpopulation of health-conscious and technology-savvy patients with T2DM. Accordingly, it may be expected that the UACR screening rate determined in this study may rather represent an overestimation. Nevertheless, it can be assumed that, due to the recruitment and consecutive enrollment among health app users with only very limited exclusion criteria, the study population covered in this study is considerably more “heterogeneous” in terms of health than that in controlled, randomized clinical trials and can therefore provide a more realistic picture of the disease and management situation of T2DM patients in Germany.

In conclusion, it can be assumed that the study will provide important insights into the current disease management of patients with T2DM in everyday clinical practice in Germany as well as into the prevalence of patients with elevated UACR values in this T2DM cohort and will support guideline-based care of the participating patients.

Acknowledgments

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Conflicts of Interest

CM, MS, TN, and UvdO are employees of Bayer Vital GmbH. DW and IvA are employees of smartpatient GmbH. SM received consultancy fees from Bayer Vital GmbH.

Multimedia Appendix 1
Introduction Video presented in MyTherapy app.
[MP4 File (MP4 Video), 134050 KB - resprot_v12i1e44996_app1.mp4]

Multimedia Appendix 2
Variables, including question type, possible response options, and ranges collected in SMART-Finder.

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[XLSX File (Microsoft Excel File), 20 KB - resprot_v12i1e44996_app2.xlsx]

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Abbreviations

ACR: albumin-to-creatinine-ratio
AE: adverse event
CKD: chronic kidney disease
DTSQ: Diabetes Treatment Satisfaction Questionnaire
eCRF: electronic case report form
eGFR: estimated glomerular filtration rate
EQ-5D: EuroQol Five Dimensions Questionnaire
HCP: health care professional
HbA_{1c}: hemoglobin A_{1c}
SGLT-2i: sodium-glucose transport protein 2 inhibitors
T2DM: type 2 diabetes mellitus
UACR: urine albumin-to-creatinine ratio

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Protocol

Wearable Sensor and Mobile App–Based mHealth Approach for Investigating Substance Use and Related Factors in Daily Life: Protocol for an Ecological Momentary Assessment Study

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Abstract

Background: Digital health technologies using mobile apps and wearable devices are a promising approach to the investigation of substance use in the real world and for the analysis of predictive factors or harms from substance use. Moreover, consecutive repeated data collection enables the development of predictive algorithms for substance use by machine learning methods.

Objective: We developed a new self-monitoring mobile app to record daily substance use, triggers, and cravings. Additionally, a wearable activity tracker (Fitbit) was used to collect objective biological and behavioral data before, during, and after substance use. This study aims to describe a model using machine learning methods to determine substance use.

Methods: This study is an ongoing observational study using a Fitbit and a self-monitoring app. Participants of this study were people with health risks due to alcohol or methamphetamine use. They were required to record their daily substance use and related factors on the self-monitoring app and to always wear a Fitbit for 8 weeks, which collected the following data: (1) heart rate per minute, (2) sleep duration per day, (3) sleep stages per day, (4) the number of steps per day, and (5) the amount of physical activity per day. Fitbit data will first be visualized for data analysis to confirm typical Fitbit data patterns for individual users. Next, machine learning and statistical analysis methods will be performed to create a detection model for substance use based on the combined Fitbit and self-monitoring data. The model will be tested based on 5-fold cross-validation, and further preprocessing and machine learning methods will be conducted based on the preliminary results. The usability and feasibility of this approach will also be evaluated.

Results: Enrollment for the trial began in September 2020, and the data collection finished in April 2021. In total, 13 people with methamphetamine use disorder and 36 with alcohol problems participated in this study. The severity of methamphetamine or alcohol use disorder assessed by the Drug Abuse Screening Test-10 or the Alcohol Use Disorders Identification Test-10 was moderate to severe. The anticipated results of this study include understanding the physiological and behavioral data before, during, and after alcohol or methamphetamine use and identifying individual patterns of behavior.

Conclusions: Real-time data on daily life among people with substance use problems were collected in this study. This new approach to data collection might be helpful because of its high confidentiality and convenience. The findings of this study will provide data to support the development of interventions to reduce alcohol and methamphetamine use and associated negative consequences.

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KEYWORDS

alcohol and drug use; alcoholism; digital health; drug use; ecological momentary assessment; ecological momentary intervention; electronic health record; Fitbit; machine learning; mHealth; mobile app; self-monitoring; wearables devices

Introduction

Background

Substance use disorder (SUD) is a major public health concern worldwide. The harmful use of alcohol is responsible for 5.1% of the global burden of disease (7.1% for males and 2.2% for females) [1]. The prevalence of heavy episodic drinking, defined as ≥60 g of pure alcohol on at least one occasion at least once per month, was 18.2% in 2016 among the total population [2]. Alcohol use disorders are more prevalent in high-income countries [2]. About 5.5% of the global population aged 15-64 years had used psychoactive drugs in the previous year, and about 35 million people are estimated to be affected by drug use disorders [3]. However, treatment access has been limited because of the increasing costs of the health care system, patient time demands, and concerns about stigma [4-7]. Additionally, alcohol and other substance use increased during the COVID-19 pandemic [8-10]. The need for accessible and effective health care services has increased.

Ecological Momentary Assessment

Advances in technology have the potential to reduce barriers to treatment services in this field. Broadly known as digital health or mobile health (mHealth), research in these areas uses mobile and computer software apps and wearable biosensor devices to understand and treat health conditions better [11-15]. In the field of SUD, various mobile apps have been developed to provide information on substance use and preventive health care services to continuously track specific health data such as substance use or support chronic condition management. Additionally, mHealth programs can help bridge treatment gaps by allowing patients to communicate with their physician or health care team without meeting face-to-face. One of the typical approaches of mHealth in this area is the ecological momentary assessment (EMA) method. The EMA approach has been developed to explore real-time substance use and motives, cravings, or triggers of substance use in daily life [12,16-19]. EMA has more benefits in capturing data on situations of substance use in the real world than cross-sectional or laboratory setting assessment because substance use is an episodic behavior influenced by immediate environmental factors (eg, external triggers) and internal factors such as stress and craving, which can be difficult to practically and ethically duplicate in an experiment environment [15-17]. Moreover, self-reported substance use can be biased by retrospective recall [20]. In a typical EMA, signaled prompts are sent to participants on a portable device (eg, smartphone) several times per day. The timing of the prompts depends on each study. There are generally the following 3 patterns: random time, fixed time, and event contingent. When participants receive these prompts, they are required to record their current thoughts, behaviors, and feelings on their devices.

Although EMA has advantages in assessing substance use accurately and repeatedly, compliance and missing data are still challenges [18,21]. Participants are likely to be unwilling to complete assessments during work, while studying, or when spending time with friends [22]. In people who use substances, noncompliance may occur because of an unstable life, comorbid psychopathology, and social pathology [17,23]. Missing data, especially systematically missing data (not at random), can lead to low statistical power and biased findings [18,24]. Uncomplicated EMA methods to minimize a participant's engagement with a collection tool are needed to increase compliance with the EMA protocol. Moreover, it is difficult to confirm the validity of the data collected by self-reported assessment [25], even when using EMA methods, because social desirability bias influences subjective judgment when people report situations regarding substance use, especially illicit drug use [26,27].

Wearable Activity Trackers

One of the solutions to the challenges of EMA might be the use of a wearable activity tracker (eg, Fitbit and Apple Watch), which can automatically collect participants' data. Although these products are not specifically made for the data collection on substance use, researchers can repeatedly gather various objective data, such as behavioral data (eg, steps and sleep) and biological data (eg, heart rate, blood pressure, and degree of stress). These devices have been used in observational studies to collect accurate real-time data [28-30], as well as in intervention studies to promote healthy behavior and improve health-related outcomes [31-33]. Also, numerous data collected repeatedly over minutes, hours, or days for a certain period enable the prediction of health outcomes using machine learning methods. For example, acute exacerbation of chronic obstructive pulmonary disease [34], depression [35], movement types [36], sleep stage [37], and COVID-19 symptom exacerbation [38] were detected by analyzing data collected using wearable devices.

If a wearable activity tracker and a self-monitoring tool that records variables related to substance use are combined in a study, researchers can collect behavioral and biological data with minimal reliance on participant input. Moreover, researchers can analyze the data collected by a wearable activity tracker in many ways because these data could be potential predictive factors of substance use or subsequent outcomes following substance use. Daily self-monitored behavioral data along with momentary biological data collected by wearable activity trackers have the potential to bridge important data gaps.

Purpose of This Study

This paper aims to introduce a procedure for implementing wearable tracker technologies as a method of EMA. We describe the methods to analyze data on substance use and psychological

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data using a self-monitoring app and objective behavioral and biological data using a wearable activity tracker (Fitbit). We will develop a predictive model of substance use by analyzing combined data using machine learning methods.

Methods

Materials and Equipment

Wearable Activity Tracker (Fitbit)

Fitbit (a registered trademark of Fitbit LLC) provides devices that offer a range of wearable activity trackers that can automatically track and display a users' daily activity, exercise, and sleep data in real time. Fitbit is designed for use on both Android and iOS smartphones. Its popularity has grown consistently over the years, selling approximately 16 million devices in over 100+ countries in 2019, with an active user community of over 29 million users [39]. The device used in this study was the Fitbit Inspire 2 which uses a combination of a 3-axis accelerometer and optical heart rate monitor in order to track daily steps, calories burned, distance traveled, active minutes, floors climbed, sleep duration and quality, heart rate, and GPS-based information [40].

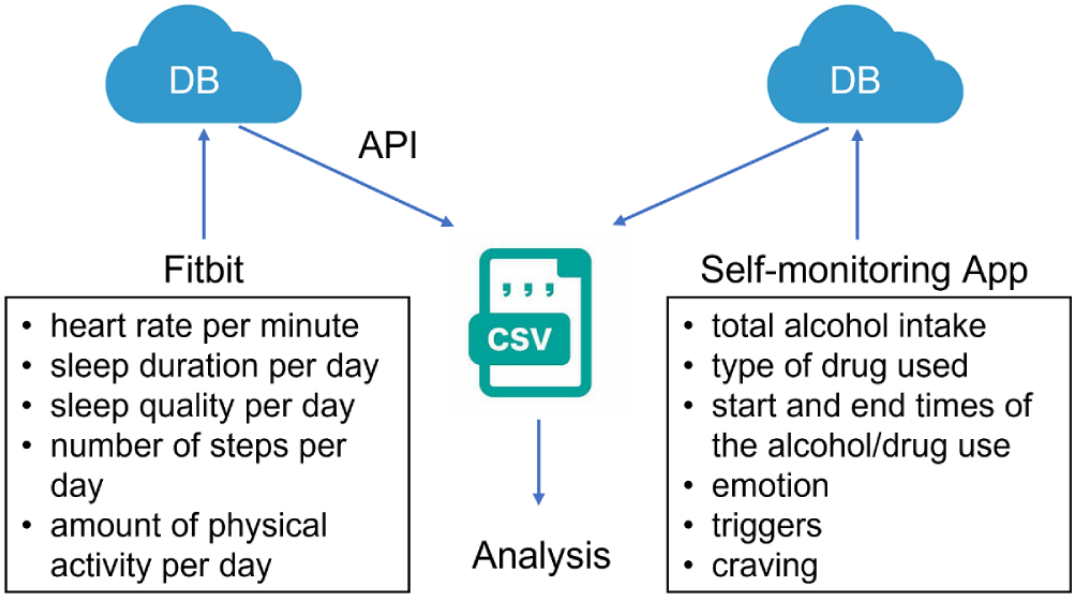
Self-monitoring Apps

Two self-monitoring mobile apps were newly developed for use in this study, depending on whether the participant had mainly alcohol or drug-related problems. Self-monitoring is a widespread approach in mHealth apps in the field of substance use [41]. Moreover, self-monitoring is low-intensive, feasible, and effective for reducing substance use [42]. App content in this study were developed based on previous studies that implemented a web-based relapse prevention program in which treatment effectiveness was already validated [43]. The newly developed self-monitoring apps used validated content and user interfaces from the previous study.

Study Design

This study is an ongoing observational study using a Fitbit and a self-monitoring app (Figure 1). Participants were required to wear the Fitbit for 8 weeks as well as open the Fitbit app every day in order to sync the Fitbit data with their smartphones. Participants were also required to record daily entries in a self-monitoring app for 8 weeks and answer an in-app survey at the time of participation, 1-month, and 2-month follow-up. After the study was finished, participants received the Fitbit along with a gift card as compensation for participating in the study.

Figure 1. Content included in the self-monitoring apps. API: application programming interface; DB: database.



Participants and Recruitment

Participants were outpatients with alcohol or methamphetamine use disorders from 2 psychiatric hospitals in Japan. A psychiatrist specializing in SUD screened potential participants based on inclusion and exclusion criteria, and patients were referred to the study if applicable. General residents with alcohol problems were recruited through a research company. Considering realistic circumstances at each facility and the approximate number of participants required to adequately perform preliminary model testing using machine learning, 20 people with methamphetamine use problems and 40 people with alcohol problems were recruited for this feasibility study. Inclusion criteria were as follows: (1) alcohol consumption with health risks in the past year (Alcohol Use Disorders Identification Test [AUDIT]: 8-19 points) [44,45], or methamphetamine use with health risks in the past year (Drug Abuse Screening Test [DAST]-10: 1-8 points) [46,47]; (2) owning a smartphone (iOS14 or Android 7.0 or later); (3) being able to wear the Fitbit constantly for approximately 8 weeks and record the self-monitoring app daily; and (4) being 20 years of age or older. Exclusion criteria were as follows: (1) not being able to speak or write in Japanese; (2) not being able to access the internet or complete the web-based survey; (3) not being able to participate for the entire 8-week research period, and (4) attending an outpatient clinic and having been deemed unsuitable to participate in the study by their attending physician.

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Measurements

Fitbit Data

The following data were measured while wearing the Fitbit for 8 weeks: (1) heart rate per minute, (2) sleep duration per day, (3) sleep stages per day, (4) the number of steps per day, and (5) the amount of physical activity per day. Data were synced from Fitbit to the Fitbit app every time it was connected to the participant's smartphone. These data were retrieved from the Fitbit servers daily through an application programming interface and stored per user in a secure database created for this study. If there were no records for over 3 days in the past week, an email reminder was sent to the participant by the researcher.

Self-monitoring Data

The following data were measured daily through the self-monitoring app for 8 weeks (Figure 2): (1) total alcohol intake in pure ethanol equivalent format or the presence and type of drug used (depending on whether the participants' main problem was alcohol or drug use), (2) general emotion of the day selected from 4 typical emotion symbols, (3) presence of alcohol or drug use triggers set by the participant, (4) degree of craving selected from a slider scale of 0-10 points, and (5) start and end times of the alcohol or drug use event. Data were retrieved from the self-monitoring app daily and stored per user in a secure database created for this study. Participants were advised to complete the daily entries at the end of each day, but were able to record entries the next day if it was difficult to record an entry before the end of the day.

Figure 2. Framework for data collection using Fitbit and self-monitoring app.



Survey Data

Overview

Surveys were conducted at baseline, 4 weeks, and 8 weeks from the start of participation (Table 1). Alcohol- and drug-related measurements and demographics, as well as treatment history information were collected at the baseline survey. The 4-week survey consisted of the alcohol- and drug-related measurements as well as the usability and satisfaction measures, and the 8-week survey included alcohol- and drug-related measurements. A reminder was sent to the users' registered email addresses when it was time to complete a survey, and a reminder email was sent after 3 days if the survey was not completed.

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Table 1. Overview of measurements for each survey period.

	Baseline	4 weeks	8 weeks
Alcohol- and drug-related measurements			
Amount of alcohol (grams of pure alcohol) or drug consumed per day in the past 7 days	✓	✓	✓
Number of drinking or drug-use days during the observational period	✓	✓	✓
University of Rhode Island Change Assessment Scale	✓	✓	✓
General Health Questionnaire	✓	✓	✓
Short Form-8	✓	✓	✓
Usability and satisfaction			
System Usability Scale		✓	
Client Satisfaction Questionnaire		✓	
Adverse events concerning physical problems or discomfort using the app		✓	
Demographics			
Gender, age, last education, employment status, and marital status	✓		
Primary substance (alcohol or drug)	✓		
Severity of substance use disorder (AUDIT[a] or DAST[b]-10)	✓		
Treatment history	✓		

[a]AUDIT: Alcohol Use Disorders Identification Test.

[b]DAST: Drug Abuse Screening Test.

Alcohol- and Drug-Related Measurements

The amount of alcohol or drug consumed per day (grams of pure alcohol or drug equivalent) in the past 7 days and the number of drinking or drug-use days during the observational period were assessed in this section. Mental health was measured by the General Health Questionnaire abbreviated version with a range of 0-30 points, validated in a Japanese population sample with a cutoff of over 6 points indicating mental distress [48,49]. Health-related quality of life measures were assessed by the Short Form-8, with higher scores indicating higher quality of life, validated in Japanese by previous studies [50,51]. Finally, the degree of behavioral changes was measured by the University of Rhode Island Change Assessment Scale (URICA) [52]. A higher URICA score indicates further progress in behavioral change. URICA was translated into Japanese, and equivalence between the English and Japanese versions was partially confirmed with back translation.

Usability and Satisfaction

The System Usability Scale (SUS), which consists of a total of 10 items, was used to assess the ease of use of the app [53,54]. A higher SUS score means good usability for the self-monitoring app. User satisfaction was measured using the Japanese version of the Client Satisfaction Questionnaire (CSQ) [55,56]. A higher score for the CSQ shows better satisfaction while using the self-monitoring app. Any adverse events concerning physical problems or discomfort using the app were asked in an open-ended question. The validity and reliability of SUS and CSQ have been confirmed in previous studies [54,56].

Demographics and Treatment History

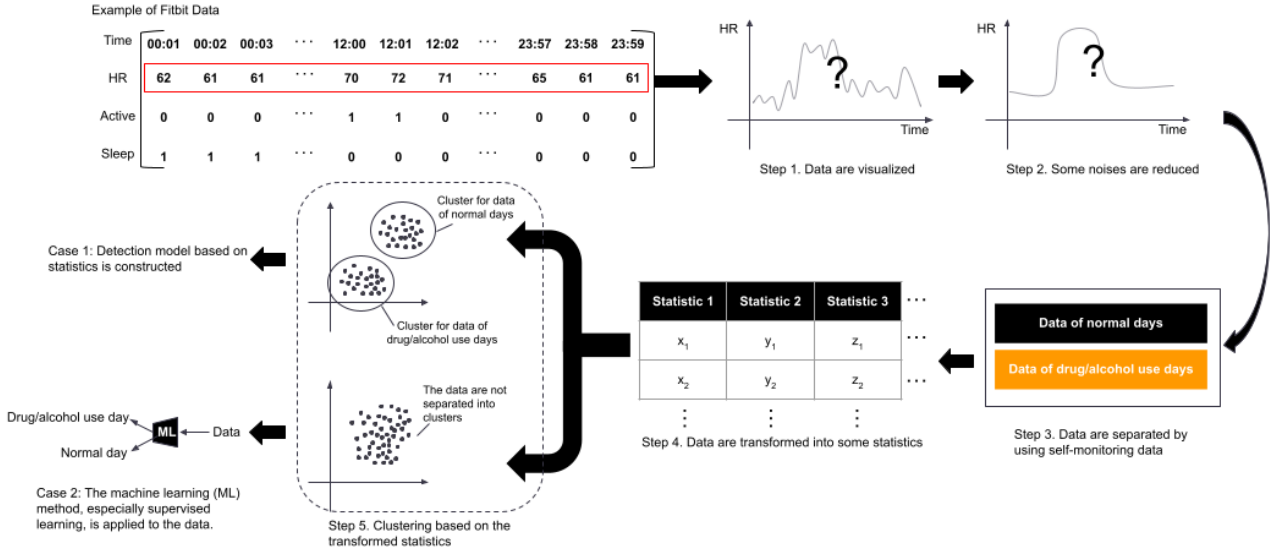
Gender, age, last education, employment status, and marital status were asked as general demographic data. The following were also asked concerning the participants' treatment history: the substance primarily responsible for the problem (alcohol, methamphetamine, marijuana, dangerous drugs, prescription drugs, over-the-counter drugs, organic solvents, or other drugs); the severity of SUD (AUDIT or DAST-10); the frequency of primary substance use in the past year; frequency of primary substance use in the past month (in days); the age of first alcohol or drug use; the age when first recognized an alcohol or drug use problem; the age when first sought medical care for an alcohol or drug use problem; social resources (medical institutions, mental health welfare centers, public health centers, or private addiction rehabilitation facilities); and the presence of comorbid psychiatric disorders and diagnosis.

Data Analysis

Fitbit's application programming interfaces capture data for heart rate per minute, sleep duration per day, sleep stages per day, the number of steps per day, and the amount of activity per day (hereafter referred to as "Fitbit data"). We finished collecting the data in April 2021 and are preparing to conduct data analysis. In order to determine substance use based on the Fitbit data, 3 steps were applied, as shown in Figure 3, and are described in further detail as follows:

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Figure 3. Planned future data analysis. HR: heart rate.



First, the Fitbit data will be visualized to confirm typical Fitbit data patterns for individual users. There are many patterns to detect drug or alcohol use; for example, the heart rate may remain high while drinking alcohol. Accordingly, data visualization is beneficial for confirming such patterns. If, for example, we can detect a typical pattern as mentioned above, signals other than that pattern may be considered noise for this analysis. Subsequently, noise removal methods will be applied to the Fitbit data. For example, average heart rate or heart rate variability may also be influenced by exercise or walking rather than drug or alcohol use. Therefore, we will use step counts or activity amounts on Fitbit data to specifically filter out such movement or workout periods. Other possible methods for noise removal, in terms of signal processing, may include signal smoothing methods, for example, moving average and Gaussian filter. Methods will be chosen to retain typical patterns but remove the other signals.

Second, the Fitbit data will be analyzed by using statistical analysis methods in order to predict drug or alcohol use on a relatively long-term basis, such as within a day or a week. By using self-monitoring data, we can separate the Fitbit data into data reflecting substance use and data from normal activity. Some descriptive statistical methods, for example, averaging, variance, self-correlation, or frequency-domain analysis, will be applied to each parameter in the separated data sets to determine features that include the days a user has declared drug or alcohol use. In this analysis, survey data containing the participants' relation to drug or alcohol use, along with psychological and behavioral data points, may also be added as complements through the descriptive statistics. After transforming the data into its statistics, we would like to apply clustering methods to provide a quantitative evaluation of typical patterns reflecting drug or alcohol use.

There are 2 approaches to determining an optimal detection method for drug or alcohol use. If we can successfully obtain distinctive features by using the above statistical analysis, we will accordingly construct a detection model based on it. However, constructing such a model may be insufficient to isolate use with high accuracy and precision. Therefore, data analysis using both machine learning and statistical analysis methods will be performed in order to create a model that solves the problem as indicated above, based on the combined Fitbit and self-monitoring data. The primary candidate for machine learning methods will be Long Short-Term Memory. Long Short-Term Memory is considered one of the most suitable methods for analyzing time series data, which applies to this study. Meanwhile, other deep learning methods will also be considered to fit the data. The deep learning model will be carefully selected after we perform the statistical analyses, and then this model will be tested based on 5-fold cross-validation. Partitioning data depends on the degree of temporal precision with which drugs and alcohol consumption is estimated. Further preprocessing and machine learning methods will be conducted based on the preliminary results of the validation.

Ethical Considerations

This study was approved by the Ethics Committee of the Faculty of Medicine and Graduate School of Medicine of Tokyo Medical and Dental University (M2020-189) and the Institutional Review Boards of each recruiting hospital. Data collected from the self-monitoring app were automatically stored in a protected database. Fitbit data were archived from the Fitbit server and preprocessed on a cloud-based, protected database without personal information attached. These data were managed by Humanome Lab, Inc. Both self-monitoring data and Fitbit data were then matched using participants' ID numbers. Patients or participants provided their written informed consent in person before participating in this study.

Results

Enrollment for the trial began in September 2020, and the data collection was completed in April 2021. In total, 13 people with methamphetamine use disorder and 36 with alcohol problems participated in this study. Table 2 shows participants' demographics and days of methamphetamine use or drinking. The mean age of the participants was approximately 46 years. In the methamphetamine group, most participants were male, and 5 (38%) were unemployed. In the alcohol group, half of

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them were male, and 26 (72.2%) were employed. The severity of methamphetamine or alcohol use disorder assessed on the DAST-10 or AUDIT-10 was moderate to severe. The resting heart rate measured by Fitbit was 72 in the methamphetamine group and 65 in the alcohol group, whereas the sleep duration per day was 408 minutes in the methamphetamine group and 386 minutes in the alcohol group.

There are 2 main anticipated results in this study. The first is to gain a better understanding of physiological and behavioral data before, during, and after alcohol or methamphetamine use. For example, an extended period of sleep deprivation may lead to a heightened sense of craving, and alcohol or methamphetamine use may increase. On the other hand, sleep quality may decrease due to several days of drinking.

The second anticipated result is to develop more personalized predictive models for alcohol or methamphetamine use. Data gathered through Fitbit are valuable in that it provides longitudinal and sequential data compared to periodic visits to hospitals. Although Fitbit is not a medical device, these data offer a new perspective into the daily life of participants with alcohol or methamphetamine problems. For example, individual participants may drink at night on workdays when stressed, and their heart rate increases to 110 beats per minute during the day.

In the future, understanding physiological and behavioral data and identifying individual patterns of behavior may lead to more effective personalized interventions that support preventive behaviors such as promoting eating or sleeping as a method of harm reduction when there is the detection of continuous levels of high stress and accelerated heart rate. Limitations of previous EMA and wearable tracker studies are still prevalent in this study, as compliance and missing data are still predictable risks. However, along with traditional deterrence methods such as data visualization, rewards, and reminders, this study uses consecutive biological data collected through Fitbit and an extended study period of 8 weeks to supplement missing data.

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Table 2. Demographic characteristics of participants.

	Drug use disorder (N=13)	Alcohol use disorder (N=36)
Sex (male %), mean (SD)	12 (92.3)	18 (50)
Age (years), mean (SD)	46.9 (9)	45.5 (10.7)
Education, mean (SD%)		
Middle school	3 (23.1)	1 (2.8)
Secondary school	4 (30.8)	6 (16.7)
College	1 (7.7)	6 (16.7)
University	5 (38.5)	23 (63.9)
Employment, mean (SD%)		
Employed	5 (38.5)	26 (72.2)
Unemployed	5 (38.5)	3 (2.8)
Other	3 (23.1)	7 (19.4)
Marital status, mean (SD%)		
Married	11 (84.6)	10 (27.8)
Single	2 (15.4)	22 (27.8)
Divorced	0 (0)	4 (27.8)
Age at first drug or alcohol use (years), mean (SD)	21.2 (6.4)	18.8 (2)
Age at first hospital encounter (years), mean (SD)	39.9 (9.3)	—[a]
DAST[b]-10		
Score, mean (SD)	6.9 (1.4)	—
Moderate level (3-5; %), mean (SD)	3 (23.1)	—
Substantial level (6-8; %), mean (SD)	8 (61.5)	—
Severe level (9-10; %), mean (SD)	2 (15.4)	—
AUDIT[c]-10		
Score, mean (SD)	—	13.8 (5)
Low-risk consumption (0-7; %), mean (SD)	—	4 (11.1)
Hazardous consumption (8-14; %), mean (SD)	—	17 (47.2)
Alcohol dependence (15-40; %), mean (SD)	—	15 (41.7)
Days of drug use, mean (SD)		
Did not use	35.9 (17.3)	—
Used primary drug	10.4 (14.9)	—
Used secondary drug	0.3 (0.6)	—
Did not answer	2.2 (5.5)	—
No record	7.2 (12.3)	—
Days of drinking, mean (SD)	—	33.1 (17.8)
Drinking amount per day (g), mean (SD)	—	75.6 (65.5)
State of mind (days), mean (SD)		
Good	20.5 (11.3)	31 (13.9)
Not good	16.8 (13.2)	4.3 (6.3)
Angry	2.8 (3.5)	2 (3.1)
Sad	5.5 (5.5)	3.1 (4.3)
Did not answer	3.1 (5.6)	3.8 (7)

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	Drug use disorder (N=13)	Alcohol use disorder (N=36)
No record	7.2 (12.3)	11.9 (12.8)
Craving (0-10), mean (SD)	4 (3.1)	4.6 (1.9)
Resting heart rate (beats per minute), mean (SD)	72.6 (8)	65.9 (9.4)
Sleep duration per day (minutes), mean (SD)	408.3 (192.8)	386.4 (100)
Sleep stages (minutes), mean (SD)		
Wake	57.7 (35.8)	55.8 (22)
Light sleep	242.9 (128.6)	223.1 (66.8)
Deep sleep	73.8 (40.8)	66.4 (25)
REM[d] sleep	82.1 (49.4)	88.1 (36.5)
Steps per day, mean (SD)	8884.9 (6450.2)	10,277 (5481.2)
Physical activity per day (minutes), mean (SD)		
Lightly active	204.8 (113)	233.7 (100.5)
Fairly active	34.3 (55.6)	19.7 (23.4)
Very active	38.6 (78.8)	28.4 (31.2)

[a]Not available.

[b]DAST: Drug Abuse Screening Test.

[c]AUDIT: Alcohol Use Disorders Identification Test.

[d]REM: rapid eye movement.

Discussion

In this study, we collected data related to substance use and consecutive biological and behavioral information simultaneously using Fitbit and a smartphone app. To the best of our knowledge, this study is the first to collect and analyze real-time data on daily life among people with substance use problems in Japan. Similar to other Asian countries, drug policies in Japan are strict, and there is severe stigmatization against people with substance use problems. The new approach to data collection in this study might be helpful because of its high confidentiality and convenience. We will analyze the data in 2023 and then recruit additional participants based on the results for a more robust analysis.

The use of digital health technologies will be increasingly necessary in the future. In fact, during the COVID-19 pandemic, innovations in cost-effective and user-friendly drug prevention and treatment services, such as internet-based or mobile phone-based services, accelerated to increase accessibility and coverage of services [10]. Accordingly, in future research, based on the findings of this study, we will develop an ecological momentary intervention program to encourage participants to reduce substance use and negative consequences.

Acknowledgments

We wish to thank Dr Kanae Myoenzono for helping us to prepare for the acquisition of Fitbit data. We also thank Mr Junichiro Matsuda and Mr Gen Kikuchi from KANAME Co, Ltd. for the development of the self-monitoring app and for helping us prepare the data analysis. This work was supported by JSPS KAKENHI grant JP20H03977. This study was also partially funded by Revi Co, Ltd. The funders were not involved in the study design, collection, analysis, interpretation of data, writing of this paper, or decision to submit it for publication.

Data Availability

The data sets in this study are not available because we have not obtained the agreement of participants to disclose raw data or the approval of the ethics committee in each institution for data sharing.

Authors' Contributions

AT, MS, MO, and JS were involved in the study design and protocol. AT, KO, KN, YY, and TM were involved in participant recruitment and management of the study. AT, KO, MS, MO, and JS were involved in the preliminary data consideration and analysis, and drafted the manuscript. All authors critically revised the manuscript and approved the final version.

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Conflicts of Interest

Authors MS, MO, and JS are employed by Humanome Lab, Inc. All authors declare no other competing interests.

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Abbreviations

AUDIT: Alcohol Use Disorders Identification Test
CSQ: Client Satisfaction Questionnaire
DAST: Drug Abuse Screening Test
EMA: ecological momentary assessment
mHealth: mobile health
SUD: substance use disorder
SUS: System Usability Scale
URICA: University of Rhode Island Change Assessment Scale

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Protocol

Detection of Atrial Fibrillation Using Insertable Cardiac Monitors in Patients With Cryptogenic Stroke in Japan (the LOOK Study): Protocol for a Prospective Multicenter Observational Study

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Abstract

Background: Paroxysmal atrial fibrillation (AF) is a probable cause of cryptogenic stroke (CS), and its detection and treatment are important for the secondary prevention of stroke. Insertable cardiac monitors (ICMs) are clinically effective in screening for AF and are superior to conventional short-term cardiac monitoring. Japanese guidelines for determining clinical indications for ICMs in CS are stricter than those in Western countries. Differences between Japanese and Western guidelines may impact the detection rate and prediction of AF via ICMs in patients with CS. Available data on Japanese patients are limited to small retrospective studies. Furthermore, additional information about AF detection, including the number of episodes, cumulative episode duration, anticoagulation initiation (type and dose of regimen and time of initiation), rate of catheter ablation, role of atrial cardiomyopathy, and stroke recurrence (time of recurrence and cause of the recurrent event), was not provided in the vast majority of previously published studies.

Objective: In this study, we aim to identify the proportion and timing of AF detection and risk stratification criteria in patients with CS in real-world settings in Japan.

Methods: This is a multicenter, prospective, observational study that aims to use ICMs to evaluate the proportion, timing, and characteristics of AF detection in patients diagnosed with CS. We will investigate the first detection of AF within the initial 6, 12, and 24 months of follow-up after ICM implantation. Patient characteristics, laboratory data, atrial cardiomyopathy markers, serial magnetic resonance imaging findings at baseline, 6, 12, and 24 months after ICM implantation, electrocardiogram readings, transesophageal echocardiography findings, cognitive status, stroke recurrence, and functional outcomes will be compared between patients with AF and patients without AF. Furthermore, we will obtain additional information regarding the number of AF episodes, duration of cumulative AF episodes, and time of anticoagulation initiation.

Results: Study recruitment began in February 2020, and thus far, 213 patients have provided written informed consent and are currently in the follow-up phase. The last recruited participant (May 2021) will have completed the 24-month follow-up in May 2023. The main results are expected to be submitted for publication in 2023.

Conclusions: The findings of this study will help identify AF markers and generate a risk scoring system with a novel and superior screening algorithm for occult AF detection while identifying candidates for ICM implantation and aiding the development of diagnostic criteria for CS in Japan.

Trial Registration: UMIN Clinical Trial Registry UMIN000039809; https://tinyurl.com/3jaewe6a

International Registered Report Identifier (IRRID): DERR1-10.2196/39307

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KEYWORDS

atrial cardiomyopathy; atrial fibrillation; biomarker; cryptogenic stroke; insertable cardiac monitor

Introduction

Stroke is a leading cause of mortality and disability worldwide. A primary goal of stroke management is to clarify the stroke etiology to optimize secondary prevention. Despite standard extensive diagnostic workups, approximately 15%-40% of all ischemic stroke cases are of unknown etiologies and are classified as cryptogenic [1]. Cryptogenic stroke (CS) is heterogeneous in origin, but most cases involve embolic mechanisms. Paroxysmal atrial fibrillation (AF) is suspected to be a major cause of CS, and patients are likely to develop severe cerebral infarction in the absence of anticoagulation therapy. Current guidelines recommend a secondary prevention regimen of antiplatelet agents to prevent stroke recurrence in patients diagnosed with CS and for whom the AF status is unknown. Long-term cardiac rhythm monitoring can reveal occult AF that may otherwise be missed by conventional short-term monitoring [2]. Since September 2016, insertable cardiac monitors (ICMs) for patients with CS have been covered by insurance in Japan.

The term “embolic stroke of undetermined source” (ESUS) has been proposed to describe CS that is not lacunar and is not associated with proximal arterial stenosis or a recognizable cardioembolic source [1]. Two international ESUS trials demonstrated that oral anticoagulants (rivaroxaban and dabigatran) were not superior to aspirin for the prevention of recurrent stroke after ESUS [3,4], although a secondary analysis in the RE-SPECT ESUS (Randomized, Double-Blind Evaluation in Secondary Stroke Prevention Comparing the Efficacy and Safety of the Oral Thrombin Inhibitor Dabigatran Etexilate Versus Acetylsalicylic Acid in Patients With Embolic Stroke of Undetermined Source) study demonstrated that, compared with aspirin, dabigatran was associated with a lower risk of recurrent stroke among Japanese patients with ESUS [5]. In Japan, magnetic resonance imaging (MRI) is widely used in the diagnosis of stroke. The Japanese guidelines indicate that MRI is essential in the selection of candidates with CS eligible for ICM implantation [6]. Branch atheromatous disease (BAD) is a single subcortical infarction larger than lacunar stroke in the territories of deep perforators without relevant arterial stenosis [7]. The Japanese guidelines on the clinical indications for ICMs recommend that BAD should not be considered as an indication because it results from a nonembolic mechanism [6]. These procedural differences between Japan and Western countries may impact the detection rate and predictors of AF in patients with CS. However, available data on Japanese patients are limited to small retrospective studies. Furthermore, additional

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information about AF detection, including the number of episodes, cumulative episode duration, anticoagulation initiation (type and dose of regimen and time of initiation), rate of catheter ablation, role of atrial cardiomyopathy, and stroke recurrence (time of recurrence and cause of the recurrent event), was not provided in the vast majority of previously published studies [8,9].

This study aims to clarify the proportion and timing of AF detection via ICMs in patients diagnosed with CS in Japan. Additionally, we aim to identify risk stratification criteria using real-world data, which could then be used in clinical practice to predict occult AF, identify optimal candidates for ICM implantation, and inform the development of diagnostic criteria.

Methods

Study Design

The LOOK (a multicenter observational study on the detection of AF using insertabLe cardiac mOnitors in patients with cryptOgenic stroKe) registry is an observational, multicenter, prospective registry of patients who have been diagnosed with CS and implanted with an ICM. The Medtronic CareLink Network is being used to remotely transmit the device data.

Ethics Approval

Ethical approval for this study was obtained from the ethics review committee of Nippon Medical School (B-2019-043) and from the relevant ethics committees of all participating centers. Written informed consent is required from all patients or their family members before study participation. This study is registered with the University hospital Medical Information Network (UMIN) Clinical Trial Registry (UMIN000039809).

Patient Population

Patient enrollment for this ongoing study started in February 2020 in 24 medical institutions throughout Japan. The inclusion criteria for this study are as follows: (1) patients who have been diagnosed with CS according to the Japanese diagnostic criteria and have been implanted with an ICM (Reveal LINQ), and (2) patients aged 40-90 years. The main exclusion criterion is the presence of contraindications for MRI. A full description of the inclusion and exclusion criteria is presented in Textbox 1.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Patients of either sex, between 40 and 90 years of age
- Patients diagnosed with cryptogenic stroke and implanted with an insertable cardiac monitor
- Patients (or their legal representatives) who have given written consent

Exclusion criteria

- Patients with a history of atrial fibrillation and atrial flutter
- Patients with permanent contraindications or indications for oral anticoagulants
- Applicable patients with pacemaker or implantable defibrillator implantation
- Magnetic resonance imaging–contraindicated patients
- Patients diagnosed with life expectancy within 2 years due to some disease
- An inappropriate decision made by the investigator

Data Collection

The study data, such as patient background, laboratory data, coagulation test, B-type natriuretic peptide, physiological examination (electrocardiogram [ECG], transthoracic echocardiography, transesophageal echocardiography [TEE], and carotid echocardiography), neuroimaging examination, Mini-Mental State Examination (MMSE), modified Rankin Scale (mRS), and presence of cardiovascular events, gastrointestinal bleeding, and other adverse events, or death (Table 1 and Textbox 2), will be stored on an encrypted website and will be accessible only to study researchers with appropriate training and ethics review board approval. Data monitoring will be performed independently by the study steering committee.

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Table 1. Overview of study schedule.

Survey items	Baseline survey	6 months (±30 days)	12 months (±30 days)	24 months (±30 days)
Consent withdrawal/visit status/health confirmation		✔	✔	✔
Patient background/history	✔			
Blood count, biochemistry, coagulation test, BNP[a]	✔	✔	✔	✔
Physiological examination (ECG,[b] TTE,[c] TEE,[d] carotid echocardiography)	✔			
Brain MRI[e] examination	✔	✔	✔	✔
MMSE[f]	✔		✔	✔
mRS[g]	✔	✔	✔	✔
Presence of cardiovascular events, gastrointestinal bleeding, other adverse events, or death		✔	✔	✔

[a]BNP: B-type natriuretic peptide.

[b]ECG: electrocardiogram.

[c]TTE: transthoracic echocardiography.

[d]TEE: transesophageal echocardiography.

[e]MRI: magnetic resonance imaging.

[f]MMSE: Mini-Mental State Examination.

[g]mRS: modified Rankin Scale.

Textbox 2. Detailed survey items in this study.

Patient characteristics

- Age, sex, body mass index, prestroke modified Rankin Scale (mRS) score, antithrombotic therapy before the index case, previous stroke, hypertension, dyslipidemia, diabetes mellitus, alcohol intake, smoking, peripheral artery disease, history of cancer, education level, and CHA_2DS_2-VASc (Congestive Heart Failure, Hypertension, Age [≥75 years], Diabetes, Stroke/Transient Ischemic Attack, Vascular Disease, Age [65-74 years], Sex [Female]) score

Neuroimaging

- Distribution of infarct lesions, infarct size, number of infarcts, major vessel occlusion, intra-arterial signal signs, susceptibility vessel signs, Diffusion-Weighted Imaging—Alberta Stroke Program Early Computed Tomography Scores, natural recanalization, hemorrhagic transformation, number and location of cerebral microbleeds, old cortical lesions, and recurrence of stroke after magnetic resonance imaging

Electrocardiogram (ECG) and Holter ECG

- Deep terminal negativity of the P-wave V1, P-wave terminal force in lead V1, P axis, PR interval, heart rate–corrected QT interval, and the number and percentage of atrial premature contractions and ventricular premature contractions

Blood examination

- Routine blood biochemistry examinations, including creatinine clearance and measurements of D-dimers, C-reactive protein, brain natriuretic peptide (BNP), and N-terminal prohormones of the BNP

Transthoracic echocardiography and transesophageal echocardiography

- Left atrium diameter, left atrial volume index, valvular disease, right to left shunt, aortic plaque thickness and morphology, spontaneous echo contrast, left atrial appendage filling and emptying velocity, left ventricular ejection fraction, atrial septal aneurysm, and strand readings

Carotid ultrasound

- Max intima-media thickness, plaque morphology, internal carotid artery stenosis as assessed by the European Carotid Surgery Trial method, peak systolic velocity, and end diastolic velocity

Incidence of recurrent stroke or transient ischemic attack

Use and type of oral antithrombotic therapy and antiarrhythmic drugs

Stroke severity assessed using the mRS and the National Institutes of Health Stroke Scale

Cognitive status evaluated through the Mini-Mental State Examination

Cardiovascular events, gastrointestinal bleeding, cancer, other adverse events, or death

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Sample Size

Recent retrospective observational ICM studies have demonstrated that major vessel occlusion (n=84) and frequent premature atrial contractions (n=66) were associated with AF detection after adjustment for risk factors and comorbidities, respectively [8,9]. A subanalysis of the CRYSTAL AF (Cryptogenic Stroke and Underlying AF) study (including 221 patients with a 30% AF detection rate) demonstrated that older age and longer PR interval were associated with an increased likelihood of detecting AF [10]. On the basis of the results of these previous studies, we decided to enroll 200 patients in this observational study to perform statistical analyses, including multivariate regression analysis, with sufficient statistical power.

Data Analysis Plan

Table 1 presents an overview of the protocol schedule for this study. Categorical variables will be expressed as frequencies and percentages, whereas continuous variables will be expressed as mean with SD or median with IQR, as appropriate. Patient characteristics, medical history, vital signs, laboratory data, the CHA_2DS_2-VASc (Congestive Heart Failure, Hypertension, Age [≥75 years], Diabetes, Stroke/Transient Ischemic Attack, Vascular Disease, Age [65-74 years], Sex [Female]) score, neuroimaging characteristics, ECG characteristics, TEE characteristics, MMSE score, mRS score, and stroke recurrence will be compared between patients with AF and patients without AF (Textbox 2). Intergroup differences will be assessed using the chi-square test or the Wilcoxon rank-sum test, as appropriate. The Yates correction or the Fisher exact test will be used if the validity conditions for the chi-square test are not met (theoretical number <5). Furthermore, we will obtain additional information regarding the number of AF episodes, duration of cumulative AF episodes, and time of anticoagulation initiation. We will investigate the rate of initial AF detection within the initial 6, 12, and 24 months after ICM implantation using Kaplan-Meier survival estimates. Cox proportional hazards regression models will be fitted to various baseline characteristics for the prediction of AF. Receiver operating characteristic curve analysis will be performed to assess the predictive accuracy of a variable in AF detection. All analyses will be performed via JMP version 13 (SAS Institute Inc), with $P<.05$ indicating statistical significance.

Study Organization

The LOOK study has been organized by a central coordinating center at the Department of Neurology, Nippon Medical School, and is being conducted at 24 medical centers throughout Japan. A steering committee is managing the trial.

Results

Study recruitment started in February 2020, and thus far, 213 patients have provided written informed consent in May 2021 and are currently in the follow-up phase. The last recruited participant will have completed the 24-month follow-up in May 2023. Data cleanup and analyses are projected to be completed by September 2023, and the results are expected to be submitted for peer-reviewed publication in 2023.

Discussion

Principal Findings

Recent meta-analyses demonstrate that, compared with short-term monitoring, prolonged cardiac rhythm monitoring is associated with higher rates of AF detection, a higher incidence of anticoagulation initiation, and reduced stroke recurrence in patients with CS [11]. However, these studies were mainly conducted in Western countries, and the generalizability of these findings to Asian populations is unclear. We are therefore conducting this study, in which we will recruit patients prospectively and identify the proportion of patients with AF to effectively compare the characteristics and outcomes with respect to the presence and absence of AF in patients with CS in Japan.

Some testing biases are affected by geographic location; for example, brain MRI is used less frequently in European patients with ESUS [12]. However, there is better access to MRI in Japan, and it is often implemented upon hospital admission as well as during follow-ups. Furthermore, MRI is necessary for the selection of candidates for ICMs according to Japanese guidelines [6]. This study is thus investigating detailed MRI findings, such as the presence of lesion patterns, susceptibility vessel signs, hemorrhagic transformation, old cortical lesions, and new asymptomatic lesions, during follow-up.

Recent evidence indicates that atrial cardiomyopathy, diagnosed by the presence of serum or electrocardiographic biomarkers, leads to AF and may result in thromboembolism even before AF manifests [13,14]. In this study, we are investigating not only the left atrial diameter but also the left atrial volume index and P-wave parameters in ECG, including P-wave terminal force in V1. Atrial cardiomyopathy may explain a proportion of ESUS cases, although AF is currently the sole diagnostic criterion for atrial thrombogenic potential. ARCADIA (AtRial Cardiopathy and Antithrombotic Drugs In Prevention After Cryptogenic Stroke) is an ongoing trial investigating whether anticoagulant therapy reduces the occurrence of stroke in patients with atrial cardiomyopathy without known AF [15]. This study will clarify the association among atrial cardiomyopathy markers, AF, and stroke recurrence in patients with CS.

A previous retrospective study reported that plasma brain natriuretic peptide (BNP) levels were elevated in the acute phase of stroke but were substantially reduced in patients with cardioembolic stroke [16]. This suggests that fluctuating levels of BNP or N-terminal prohormone of BNP (NT-proBNP) may be associated with occult paroxysmal AF. However, serial changes in plasma BNP or NT-proBNP levels in patients with CS and ICMs have not been fully investigated. In this study, we will be conducting serial measurements of BNP or NT-proBNP levels.

Conclusions

By conducting this prospective LOOK multicenter study, the characteristics of patients with occult AF detected by ICMs will be clarified in more detail than previously reported by analyzing imaging studies on admission and during follow-up, serial

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measurements of blood markers, and various physiological findings. We hope that our findings will contribute to the identification of markers and enable the development of a risk scoring system with a new and better screening algorithm, which could inform future guidelines for stroke screening in patients with CS as well as the development of comprehensive clinical trials.

Acknowledgments

We would like to thank all collaborators and LOOK investigators for their help with participant recruitment. The LOOK study received funding support from Medtronic Japan Co, Ltd.

Data Availability

Deidentified participant data will be shared on request. Researchers who make the request should include a methodologically sound proposal on how the data will be used. They will also need to sign a data access agreement. The corresponding author can be contacted directly to request data sharing.

Conflicts of Interest

SS reports research funding from the All Japan Coffee Association and Pfizer Co, Ltd, and lecture fees from EISAI Co, Ltd. K Kitagawa reports lecture fees from Daiichi Sankyo Co, Ltd and Kyowa Kirin Co, Ltd, and received research funding from Daiichi Sankyo Co, Ltd. YI reports lecture fees from Bayer Healthcare Co, Ltd, Pfizer Japan Inc, Nippon Boehringer Ingelheim Co, Ltd, Takeda Pharmaceutical Co, Ltd, Otsuka Pharmaceutical Co, Ltd, and Daiichi Sankyo Co, Ltd, outside of the submitted work and research funding from Sanofi Co, Ltd. SF reports lecture fees from Takeda Pharmaceutical Co, Ltd, Bayer Yakuhin Co, Ltd, Otsuka Pharmaceutical Co, Ltd, Bristol-Myers Squibb Co, Ltd, Pfizer Co, Ltd, and Daiichi Sankyo Co, Ltd. KO reports lecture fees from Daiichi Sankyo Co, Ltd. HT received lecture fees from Pfizer Co, Ltd and Daiichi Sankyo Co, Ltd. MK reports research funding from Daiichi Sankyo Co, Ltd and Nippon Boehringer Ingelheim Co, Ltd. MI reports lecture fees from Daiichi Sankyo and EISAI, and grant support from Panasonic, GE Precision Healthcare LLC, Bristol-Myers Squibb, and Shimadzu Corporation. HY reports lecture fees from Stryker Co, Ltd, Bayer Yakuhin Co, Ltd, and Daiichi Sankyo Co, Ltd, and research funding from Bristol-Myers Squibb Co, Ltd. KY reports lecture fees from Daiichi Sankyo Co, Ltd. YU received lecture fees from OHARA Pharmaceutical Co, Ltd, and research funds from Bristol-Myers Squibb. YK reports lecture fees from Daiichi Sankyo Co, Ltd. Bayer Healthcare Co, Ltd, and Medtronic Japan Co, Ltd, and research funding and remuneration from Bristol-Myers Squibb Co, Ltd and Nippon Boehringer Ingelheim Co, Ltd. K Kimura reports lecture fees from Bristol-Myers Squibb Co, Ltd, Nippon Boehringer Ingelheim Co, Ltd, Bayer Healthcare Co, Ltd, and Daiichi Sankyo Co, Ltd, and research funding from Teijin Pharma Co, Ltd, Nippon Boehringer Ingelheim Co, Ltd, and Daiichi Sankyo Co, Ltd.

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Abbreviations

AF: atrial fibrillation
BAD: branch atheromatous disease
BNP: brain natriuretic peptide
CS: cryptogenic stroke
ECG: electrocardiogram
ESUS: embolic stroke of undetermined source
ICM: insertable cardiac monitor
MMSE: Mini-Mental State Examination
MRI: magnetic resonance imaging
mRS: modified Rankin Scale
NT-proBNP: N-terminal prohormone of brain natriuretic peptide
TEE: transesophageal echocardiography

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Protocol

Blood Pressure and Self-management in Black Women With Hypertension: Protocol Revisions to the Brain Relationships Among Information, Neuroprocessing, and Self-Management Study Due to the COVID-19 Pandemic

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Abstract

Background: The COVID-19 pandemic and the halt to in-person research activities beginning in March 2020 brought new challenges to protocol development and implementation. Due to the pandemic, we had to revise our protocol for the Brain Relationships Among Information, Neuroprocessing, and Self-Management (BRAINS) study, which was designed to examine health information behavior, brain activity, diabetes status, and self-management behavior among Black women with hypertension.

Objective: This report outlines 7 steps describing how our research team (1) revised the BRAINS study protocol, (2) implemented a remote method of data collection, and (3) mitigated the challenges we faced.

Methods: Prior to March 2020, Black women with hypertension were invited to participate in the BRAINS study to undergo a functional magnetic resonance imaging scan, complete surveys, have their blood pressure measured, and have their blood drawn. After these measures were collected, participants would receive phone calls from a dietician to complete two 24-hour dietary recalls using the Nutrition Data System for Research. Our revised protocol relied on a web-based, interactive approach. Participants received a study kit that included an Omron automatic home blood pressure monitor and a hemoglobin A_{1c} kit from the DTIL laboratory. In a Zoom meeting with each participant, our team played an introductory video, administered surveys (via Qualtrics), and guided participants through measuring their blood pressure and performing a finger stick to collect a blood sample for hemoglobin A_{1c} testing. We examined cognitive function using the TestMyBrain Digital Neuropsychology Toolkit, as we were unable to access the functional magnetic resonance imaging laboratory to assess brain activity. The 7 steps in revising our protocol were as follows: conceptualizing the move from in-person to remote study activities (step 1); contacting the funders (step 2); submitting changes for Institutional Review Board approval (step 3); preparing to implement the revised protocol (step 4); implementing the study changes (step 5); mitigating challenges (step 6); and evaluating protocol implementation (step 7).

Results: Approximately 1700 individuals responded to web-based advertisements about the BRAINS study. A total of 131 individuals completed our eligibility screener. We conducted our first Zoom appointment in July 2020 and our last Zoom appointment in September 2020. Using our revised strategies, a total of 99 participants completed all study measures within a 3-month period.

Conclusions: In this report, we discuss successes and challenges in revising our protocol and reaching our population of interest remotely, safely, and effectively. The information we have outlined can help researchers create similar protocols to reach and conduct research remotely with diverse populations, such as individuals who are unable to participate in studies in person.

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KEYWORDS

Black; BRAINS; COVID-19 pandemic; eHealth; Facebook; hypertension; protocol; videoconferencing; web-based; women

Introduction

The COVID-19 pandemic complicated the delivery of medical care and the implementation of research studies [1]. While health assessments typically occur in person and include blood pressure readings and other tests conducted by a trained professional, these standards of care were not feasible given the "Stay at Home" orders and imminent dangers of being in-person for routine health care appointments. During the beginning of the pandemic, there was a significant decrease in the "usual care" of preventative screening and monitoring of chronic illnesses [2,3].

Consequently, a shift to self-reported data emerged after March 2020. Although self-reported data has the benefit of being easier to obtain at a smaller expense, there are some considerable drawbacks. These include some participants' inability and willingness to recall and report their measurements [4]. Factors such as age, formal education level, and regular access to health care professionals impact the accuracy of self-reporting, especially self-reporting of hypertension status [5]. Given barriers to accessing health care services at the beginning of the COVID-19 pandemic, the discrepancies related to self-reported data were even more concerning, particularly among vulnerable groups like Black women with hypertension.

Hypertension affects approximately 57.6% of Black women in the United States [6]. Black women who have hypertension are also more likely to have higher blood pressure levels, which increases the risk for other chronic illnesses, such as end-stage renal disease and type 2 diabetes [7]. While hypertension and type 2 diabetes frequently co-occur among all racial and ethnic groups, Black women's odds of this comorbidity are 6 times higher than the odds for White women [8]. Additionally, Black women are the most likely of any racial group to have undiagnosed diabetes [9].

The decrease in usual care at the beginning of the pandemic was even more concerning for individuals who were already part of vulnerable groups, such as Black women with hypertension. Previously, some health care professionals reported difficulty in reaching diverse populations, and this was magnified during the pandemic [10-12]. Prior to the pandemic, previous studies highlighted the barriers to reaching Black individuals with chronic illnesses [10,11]. Not only were Black individuals more severely affected by COVID-19 [12-14], those with chronic illnesses were more likely to have increased difficulty in managing them [15,16]. Previous studies highlight the viability of videoconferencing platforms as tools to meet with patients, but state that additional studies are needed to further assess their utility [17,18].

Prior to the COVID-19 pandemic, we developed an in-person protocol (Brain Relationships Among Information, Neuroprocessing, and Self-Management [BRAINS]) to assess the relationships among health information behavior, brain activity and executive function, diabetes status, and health outcomes among Black women with hypertension. However, to ensure the safety of our participants and our research team, we had to move to remote data collection during the COVID-19 pandemic. In this report, we outline the following seven steps we completed in modifying the BRAINS study: (1) conceptualizing how to move from in-person to remote, (2) contacting funders, (3) submitting Institutional Review Board (IRB) changes, (4) preparing to implement our revised protocol, (5) implementing our protocol, (6) mitigating the challenges we faced, and (7) evaluating our implementation. This study was novel not only because we were able to quickly pivot to remote data collection, but we also were able to reach our diverse population of interest (Black women with hypertension), which is traditionally regarded as a "difficult to reach" group [19]. Future studies can use these guidelines to develop thoughtful, informed, evidence-based, and carefully crafted protocols to reach other diverse or underrepresented populations.

Methods

Study Overview

The BRAINS study aimed to examine relationships among health information behavior, brain activity, diabetes status, and self-management behavior among Black women with hypertension. The study design was descriptive, cross-sectional, and measured concepts using surveys, blood pressure readings, serum testing, and functional magnetic resonance imaging (fMRI) scans (see Textbox 1 for a list of measures). After receiving IRB approval, study recruitment began in June 2020. We used a Facebook campaign to seek individuals who self-identified as Black women. Additional inclusion criteria were being 21-64 years of age, being diagnosed with hypertension by a health care professional, having access to a computer or tablet, and living in the metro Detroit area (determined by zip code).

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Textbox 1. Brain Relationships Among Information, Neuroprocessing, and Self-Management study measures.

Measures:

- Health information behavior [20]
- Neuroprocessing using functional magnetic resonance imaging [21]
- Self-efficacy [22]
- Self-regulation [23]
- Patient activation [24]
- Self-management diet behaviors (Nutrition Data System for Research) [25-27]
- Blood pressure [28,29]
- hemoglobin A_{1c}(HbA_{1c}) [30]
- Quality of life (Patient-Reported Outcomes Measurement Information System) [31]
- Basic cognitive assessment—Montreal Cognitive Assessment [32]

Ethical Considerations

This study was reviewed and approved by the University of Michigan IRB (HUM00138174). Women who were interested in participating in the study reviewed the BRAINS study consent form, then provided informed consent by clicking "Yes, I consent," prior to completing study measures in Qualtrics [33]. Each participant was assigned a study ID number. All study data were deidentified and stored according to study ID. After participants completed all study measures, they received US $75 gift card to compensate them for their time.

In this report, we outline the 7 steps that we completed to revise our BRAINS study from an in-person protocol to a fully remote study.

Steps in Revising the Protocol

Step 1: Conceptualizing the Move From In-Person to Remote Study Activities

The COVID-19 pandemic brought all in-person study activities to a complete halt. We had to decide if we were going to suspend our study activities or pivot to a fully web-based format. We asked the following questions:

(1) *How can we meet safely with our participants?* The first decision we made was to use Zoom, a videoconferencing platform, to meet with our participants [17]. We felt that Zoom would be the best web-based platform where we could send links to surveys and assist participants as needed. We were already using Qualtrics as a platform for our surveys, so we were sure that we could continue to use it remotely by sending participants a link.

(2) *Of the remaining measures, which can be collected remotely and which cannot?* In addition to the surveys we planned to deliver via Qualtrics, we still needed to determine how to collect blood pressure readings, serum testing, and fMRI scans, or find alternative measures. See Table 1 for an overview of the original protocol compared to the protocol changes and revisions.

(i) *Blood pressure measurement*. To obtain participants' blood pressure readings, we selected the Omron 10 series automatic home blood pressure monitor (HBPM). We selected this HBPM for 2 reasons. First, the Omron 10 Series HBPM received satisfactory results during validation testing [34,35]. Second, this HBPM contains a cuff that can accurately obtain blood pressure readings on an arm with a circumference of 9 inches to 17 inches, which is a larger cuff than others included with most HBPM [36]. This allowed for accurate blood pressure readings from a wide variety of participants, and less concern about the diameter of the participant's arm.

(ii) *Blood glucose measurement*. Our team had a previously established relationship with DTIL, a company that packaged and processed at-home hemoglobin HbA_{1c} tests. Therefore, we send their kits to participants to assess their blood glucose levels [30].

(iii) *Measures we were unable to capture*. We did not find at-home alternative measures for high-sensitivity C-reactive protein collection or the fMRI scans. The cost of doing an at-home high-sensitivity C-reactive protein test was not feasible for this study, and there is no replacement for the brain activity data that can be gathered from an fMRI scan. However, we were able to gather data on cognitive function pathways using Harvard University's TestMyBrain, which is a web-based battery of neurocognitive tests [37].

(3) *How will we get the new required supplies to our participants?* We decided to mail participants a study welcome kit that included a welcome letter, a HBPM, and a HbA_{1c} test. We chose to use United Parcel Service to mail the kits because their shipping time estimates were the fastest, and we did not want any delays in getting our supplies to our participants. Our university also had an account preregistered with United Parcel Service that would bill directly to our study's shortcode. All supplies were inventoried before being sent out, and the HbA_{1c} kits were labeled with our study participant ID numbers to make sure that each sample and result would be matched to their other study results.

(4) *How will we obtain informed consent?* We met with our institution's IRB staff to understand how to prepare for and obtain consent remotely. We were advised that we needed to present the consent form to participants in the same format as we usually would, and they would need to read the consent

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themselves. Contact information for the study was given in multiple places, in case potential participants had questions about their participation. At the bottom of the consent page, we asked if participants had thoroughly read and agreed to participate in all study activities. They could either check yes or no. If they checked yes, they were able to complete screening questions to confirm their eligibility for the study. If they checked no, they were routed to a screen that thanked them for their time.

Table 1. The Brain Relationships Among Information, Neuroprocessing, and Self-management (BRAINS) study protocol—original, revised, and additions.

Measure	BRAINS in-person (original protocol)	BRAINS remote (revised protocol)	Additions to revised protocol
Qualtrics surveys	Completed on an iPad, sitting next to a study team member	Completed during a Zoom appointment, with a study team member	Added 7 questions about changes required to blood pressure self-management routine
fMRI[a] scan	Completed in the fMRI laboratory	Unable to conduct	None
Cognitive assessment	MoCA[b]	MoCA	TestMyBrain
Blood pressure	Measured by a study team member	Measured by the participant, with guidance from a study team member	None
HbA_{1c}[c]	Collected by a research nurse	Collected by the participant, with guidance from a study team member	None
High-sensitivity C-reactive protein	Collected by a research nurse	Unable to collect	None
24-hour dietary recall	Collected by a dietician via telephone	Collected by a dietician via telephone	None

[a]fMRI: functional magnetic resonance imaging.

[b]MoCA: Montreal Cognitive Assessment.

[c]HbA_{1c}: hemoglobin A_{1c}.

Step 2: Contacting the Funders

After we conceptualized the changes required and had evidence to support each change, we were able to reach out to the lead investigators who obtained the funds for this study. There were 2 funding sources to support this study; both sources of funding were National Institute of Health center pilot grants (P20 and P30). We wrote a letter to both center directors, briefly describing the challenges we were facing and requesting a meeting to discuss the changes we wanted to implement. During both meetings (Zoom), we displayed PowerPoint slides with our revised study aims and goals for the safety of both participants and members of our team. After meeting with both center directors, we received feedback that our changes were thoughtful and reasonable; therefore, approval to revise the protocol was granted.

Given that we could not access the fMRI lab and complete the fMRI scans, we had an excess of funds to spend. Included in our letter to the center directors was a request to increase the sample size from 50 to 100 participants. We were also able to increase our study incentive to further encourage participation. Both directors agreed that this request made sense and approved it, so we created an IRB amendment to receive their approval as well.

Step 3: Submitting Changes for IRB Approval

We met with a representative from the University's IRB team to receive guidance on revising our protocol. We wanted to make sure that we were aware of all the new requirements related to the COVID-19 pandemic. We asked questions about remote consent, how other studies implemented revisions to their protocols, and how long we could expect before being notified that our revised amendment was approved. This meeting was critical to our success, as we relied on their expertise to complete the revisions in a timely fashion, and we required IRB approval to move forward with the study. We prepared and submitted our IRB amendment, then waited for approval.

Step 4: Preparing to Implement the Revised Protocol

Overview

After receiving IRB approval for our revised protocol, there were several tasks to complete to prepare for the implementation of the study. We had to buy supplies, prepare materials to be mailed, establish a contract with the shipping company, and develop a tracking system to make sure that the correct box got to its intended participant. We purchased boxes and sealable plastic shipping bags. This would keep the study materials protected from physical and water damage during the shipping process. To prepare the materials to be mailed to the participants, all study supplies were inventoried, assigned, and labeled with participant study ID numbers to ensure that the correct supplies went to the correct participant. This was particularly important for the HbA_{1c} kits, as the participant would need to send their prelabeled sample back to the DTIL laboratory.

Each participant's HBPM and HbA_{1c} kit was placed and sealed in a plastic shipping bag and tied with a ribbon to look like a gift. The shipping bags were then placed inside a shipping box that was also labeled with the participant ID number. As participants were enrolled and assigned a study ID number, the assigned box was labeled with a shipping label and the tracking

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number was recorded. We developed a Zoom training protocol for our team to prepare them to meet with participants.

Zoom Meeting Preparation

It was important that the research staff were familiar with and comfortable with Zoom and interacting with participants remotely. Each staff member was sent a HBPM, a HbA_{1c} kit, and a standardized script to follow for the Zoom meetings. Staff meetings were held (via Zoom) to practice instructing participants on how to complete the blood glucose and blood pressure measurements. Each staff member practiced how to instruct participants at least 3 times before they were ready for participant interaction, and everyone received feedback on how to improve their technique and the clarity of their instructions.

After being trained, "mock" Zoom calls were scheduled where staff would guide a participant (another team member) through all of the steps of a study visit. During the mock call, the staff could ask questions and had the option to complete a second mock call if needed. All staff felt comfortable after completing 1 mock call.

Step 5: Implementing the Protocol Changes

While the staff prepared to complete the Zoom calls, we launched our Facebook campaign. Advertisements for the study were displayed on our lab's Facebook page. After viewing the advertisements, individuals who were interested in learning more and potentially participating clicked a link that directed them to a web-based eligibility survey on the Qualtrics platform [33]. The Qualtrics survey contained a study overview, consent document, and eligibility screening questions.

Individuals who provided informed consent to participate in the study and met eligibility criteria were asked to submit their contact information and were contacted by a member of the research team. During a phone call with each potential study participant, the team member verified the information from the Qualtrics screener and administered the Montreal Cognitive Assessment (MoCA) [32]. Given that the test would be administered by phone, the researchers used the blind version of the test that did not incorporate any of the written parts of the traditional MoCA. Participants had to score an 18 or above on the MoCA to be eligible to continue study participation.

Step 6: Mitigating Challenges

There were some issues (technical and shipping) that arose during the implementation of the revised BRAINS protocol.

Technical Difficulties

Participants experienced some technical difficulties participating in the study remotely. Some participants had some difficulty with Zoom, perhaps because of different levels of experience with the platform. Some participants required more assistance than others, but all were able to measure their blood pressure. The TestMyBrain assessment could not be completed with a smartphone, as the participants' reaction time information could not be properly collected. This prevented 5 individuals from participating in the study, as we could only enroll those who could complete the study on a tablet or a computer. Even so, during the study, we also found that the "Amazon Fire tablet" was not compatible with the TestMyBrain website.

Shipping Issues

There were also some issues with mailing the study kits to participants. Occasionally, a participant's study materials would not reach the participant's home in time for their Zoom appointment, which required a research staff member to drive the kit out to the participant and leave it outside to maintain social distancing. The HbA_{1c} tests were sent directly to the DTIL laboratory in Georgia by the participant via the US Postal Service. When the DTIL laboratory contacted our team and stated that a HbA_{1c} test did not arrive, we had to contact participants and ask if they would be willing to retake the test.

Step 7: Evaluating Protocol Implementation

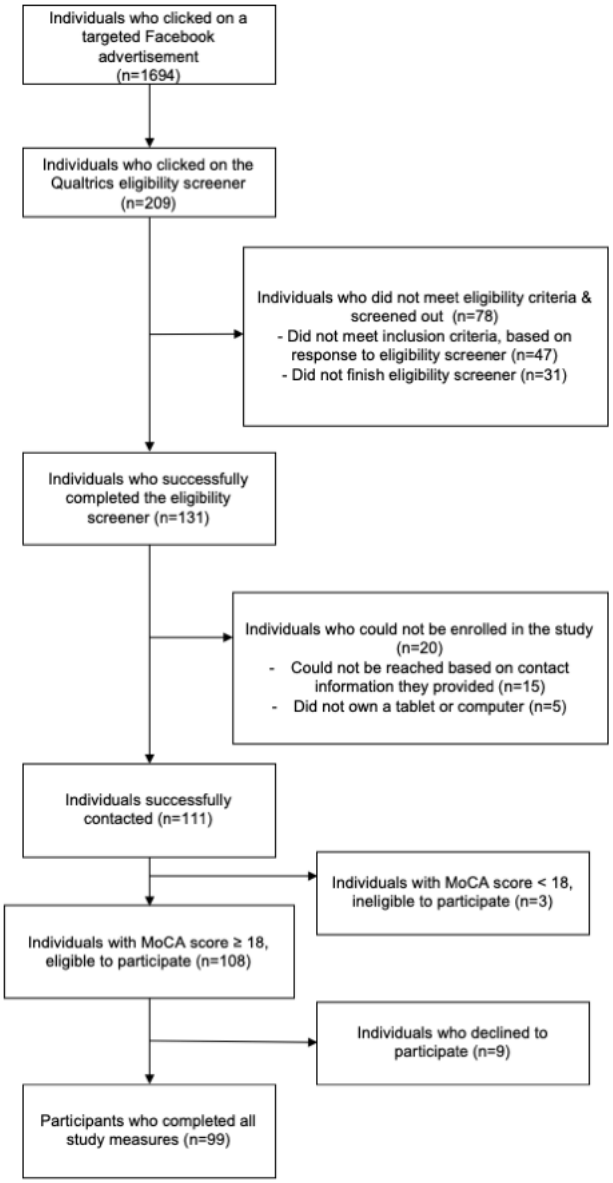
After completing the BRAINS study, we reflected on its implementation to evaluate our processes. There were several successes in this revised protocol. Since we were unable to access the fMRI laboratory, we used the additional funds to increase our sample size. Given that the study was conducted remotely, we were able to reach more women in our population of interest, including those who were potentially unable to come in person to participate in our study. Using Zoom, we were able to meet with our participants in their homes, where they were most comfortable, which gave the study a less "clinical feel." In fact, the principal investigator prepared a 3-minute video thanking participants for joining the study and reminding them how important their participation was. Many of the participants stated that they enjoyed the video and felt at ease after watching it.

Results

In response to our Facebook campaign, 1694 individuals clicked on the link that directed them to an eligibility screener. Of those who clicked, 131 individuals completed the screener and were eligible to participate in the BRAINS study. Figure 1 illustrates participant enrollment. We conducted our first Zoom appointment in July 2020 and completed our last Zoom appointment in September 2020. Despite the challenges that we faced, we were able to obtain all study measures from 99 participants in a 3-month period. A total of 14 of the HbA_{1c} tests were not received by the DTIL laboratory. When we contacted participants to ask if they would retake the HbA_{1c} test, only 8 participants agreed. Therefore, 6 HbA_{1c} results are missing; this is the only measure that is missing from our data set.

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Figure 1. Participant Flow Diagram.



Discussion

Overview

Due to the COVID-19 pandemic, we revised our BRAINS protocol from a study designed to be conducted in person to complete remote data collection. We increased our sample size from 50 to 100 participants and were successful in collecting all study measures from 99 Black women with hypertension. In this report, we highlighted the revisions we completed, described how we moved from in-person data collection to remote data collection, and outlined the challenges that needed to be mitigated to reach our goals.

Most importantly, we were able to safely conduct our study, despite the pandemic and associated challenges of in-person, health-related interactions [1]. We reviewed previous studies that had been conducted remotely with videoconferencing as we revised our protocol [17,18]. We designed the revised study so that we could still meet the study aims while ensuring that there were no in-person interactions between the members of our research team and our participants.

An important part of our protocol was to assess the diabetes status among our participants. Although hypertension and diabetes frequently co-occur [8], there is a gap in the literature regarding when Black women with hypertension are most likely to be diagnosed with type 2 diabetes and possible ways to prevent the transition to a diabetes diagnosis. Our protocol is one of the first that outlines steps to assess diabetes status among Black women with hypertension remotely.

Given concerns about self-reported measures [4,5], it was a top priority for our team to determine how to obtain accurate blood pressure measurements. Previous studies have validated HBPM for use outside of the clinic and patient use [35]. Each member of our research team received a HBPM and training on how to use it correctly to measure their blood pressure. After completing the training successfully, our staff was able to guide our participants in applying the blood pressure cuff and measuring their blood pressure. Additionally, while completing the screener

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to determine eligibility to participate, potential participants had the opportunity to self-report their blood pressure. In our data analysis, we will be able to compare self-reported blood pressure to actual blood pressure measurements.

Some of the measures outlined in the original protocol were unable to be collected remotely. For example, there was no proxy for conducting an fMRI scan, an important part of the original BRAINS protocol. As of this writing, we are inviting participants to undergo an fMRI scan and to repeat some of the original study measures, including the TestMyBrain cognitive assessment, allowing us to examine relationships between the fMRI scan and the neurocognitive battery of tests.

Limitations

As with any research protocol, there were limitations to implementing our protocol that are worth discussing. Some of the measures that we collected required that participants complete them on a tablet or computer rather than a cell phone. This means that participants who did not own the necessary equipment were automatically excluded from participating in the study, creating bias. During 1 Zoom study visit, we learned that the Amazon Fire tablets were not able to load the TestMyBrain software. Additionally, this study was conducted during the COVID-19 pandemic, so participants' habits might have been patterned differently than their usual habits. Despite these limitations, this revised protocol was a unique opportunity to safely reach our population of interest during the pandemic.

Conclusions

The COVID-19 pandemic required revisions of many research protocols for the safety of participants and research staff alike. The pandemic provided a unique opportunity for researchers to gain knowledge about alternate ways of engaging with participants during a "Stay at Home" order. Before the COVID-19 pandemic, the BRAINS protocol was designed so that participants came in person to complete study activities (eg, surveys, serum sample collection, and fMRI). During the COVID-19 pandemic, we pivoted to a completely web-based format to collect survey data, an at-home HbA_{1c} test, and blood pressure measurement. Since we were unable to conduct the fMRI scans, the cost of our research activities dropped drastically, so we were able to enroll additional participants in our study. In addition, working remotely allowed our team to be more flexible with scheduling participants and offer evening and weekend appointments, as we were not subject to the fMRI laboratory's hours. In the future, researchers can use this study as a guide to develop protocols to reach diverse groups, such as individuals who are unable to participate in research activities due to distance, time, or travel constraints.

Acknowledgments

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Data Availability

Data sharing not applicable, as no data were analyzed as of writing this report.

Conflicts of Interest

None declared.

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Abbreviations

BRAINS: Brain Relationships Among Information, Neuroprocessing, and Self-Management
fMRI: functional magnetic resonance imaging
HbA_{1c}: hemoglobin A_{1c}
HBPM: home blood pressure monitor
IRB: institutional review board
MoCA: Montreal Cognitive Assessment

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Protocol

Evaluation of Various Support Intensities of Digital Mental Health Treatment for Reducing Anxiety and Depression in Adults: Protocol for a Mixed Methods, Adaptive, Randomized Clinical Trial

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Abstract

Background: Anxiety and depression are leading causes of disease worldwide, requiring timely access to evidence-based treatment. Digital mental health (dMH) interventions increase accessibility to evidence-based psychological services delivered in a variety of web-based formats (eg, self-help and therapist-assisted interventions). Robust and rigorous studies of adaptive web-based intervention designs are scarce. No identified randomized clinical trial has investigated the efficacy of a 2-stage adaptive design, whereby the program-only condition or *no support* dMH treatment program is augmented by either low or high therapist assistance, if a participant does not improve or engage in the program-only condition.

Objective: The primary objective is to assess whether low or high therapist-assisted support delivered via video chat is more effective in reducing anxiety and depressive symptoms compared with a dMH program–only condition. The secondary objective is to evaluate the role of motivation; self-efficacy; and preferences in participant engagement, adherence, and clinical outcomes (anxiety and depression symptoms) among the 3 treatment conditions (program only, low-intensity therapist assistance, and high-intensity therapist assistance). A mixed methods analysis of factors affecting participant attrition, participant reasons for nonengagement and withdrawal, and therapist training and implementation of dMH interventions will be completed. Qualitative data regarding participant and therapist experiences and satisfaction with video chat assessment and treatment will also be analyzed.

Methods: Australian adults (N=137) with symptoms or a diagnosis of anxiety or depression will be screened for eligibility and given access to the 8-module Life Flex dMH treatment program. On day 15, participants who meet the augmentation criteria will be *stepped up* via block randomization to receive therapist assistance delivered via video chat for either 10 minutes (low intensity) or 50 minutes (high intensity) per week. This adaptive trial will implement a mixed methods design, with outcomes assessed before the intervention (week 0), during the intervention (weeks 3 and 6), after the intervention (week 9), and at the 3-month follow-up (week 21).

Results: The primary outcome measures are for anxiety (Generalized Anxiety Disorder–7) and depression severity (Patient Health Questionnaire–9). Measures of working alliance, health status, health resources, preferences, self-efficacy, and motivation will be used for secondary outcomes. Qualitative methods will be used to explore participant and therapist experiences of video chat assessment and treatment, participant reasons for withdrawal and nonengagement, and therapist training and implementation experiences. Data collection commenced in November 2020 and was completed at the end of March 2022.

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Conclusions: This is the first mixed methods adaptive trial to explore the comparative efficacy of different intensity levels of self-help and a therapist-assisted dMH intervention program delivered via video chat for adults with anxiety or depression. Anticipated results may have implications for the implementation of dMH interventions.

Trial Registration: Australian and New Zealand Clinical Trials Registry 12620000422921; https://tinyurl.com/t9cyu372

International Registered Report Identifier (IRRID): RR1-10.2196/45040

(JMIR Res Protoc 2023;12:e45040) doi:10.2196/45040

KEYWORDS

video chat therapy; therapist assistance; self-help; transdiagnostic; digital intervention; anxiety; depression; comorbidity

Introduction

Background

The Global Burden of Diseases, Injuries, and Risk Factors Study 2019 identified depression and anxiety disorders as the 2 most debilitating mental disorders worldwide [1]. A recent study by Collaborators Cochrane Mental Disorders [2] quantified the global impact of COVID-19 on the prevalence of depression and anxiety disorders. That study estimated, for depression, an international prevalence of 246 million people (increase from 193 million people before the pandemic) and, for anxiety disorders, a prevalence of 374 million people internationally (increase from 298 million people before the pandemic). Such statistics demonstrate that anxiety and depressive disorders are leading diseases on a global scale that become more prevalent during global events such as the COVID-19 pandemic.

Rates of help seeking for a mental health–related service have also increased in light of the COVID-19 pandemic [3]. There has been increased use of digital mental health (dMH) interventions and telehealth services, attributable first to their ability to disseminate and scale quickly and, second, to their utility as an adjunct to existing face-to-face mental health services [4]. However, long wait lists to access psychological treatment via telehealth are reported [5,6], as are substantial costs associated with the delivery of psychological services via telehealth [3].

To ensure access to evidence-based treatment for the wider community, empirical research conducted over the past 20 years has investigated different methods of delivering psychological treatment. As an alternative to the standard in-person, face-to-face model, dMH interventions now have a well-established evidence base for the provision of psychological treatment for anxiety and depression delivered via the internet, in a variety of formats (eg, self-help and therapist-assisted interventions), mitigating the increasing demands for mental health services.

The dMH interventions serve to increase accessibility to evidence-based services within a high-volume, low-intensity treatment model [7]. Low-intensity treatment models have been developed to assist individuals experiencing mild to moderate psychological difficulties and propose that more intensive treatment regimens could then be provided to individuals who do not benefit from less intensive forms of psychological treatment [8]. The dMH interventions can address the evolving needs of consumers by adapting the implementation of treatment such that individuals can be *stepped up* to receive high-intensity treatment if required.

Adaptive intervention treatment designs use decision rules to determine whether and how the delivery of a course of treatment is altered [9]. Stepped care models are identified as a type of adaptive intervention design. Stepped care models incorporate a low-intensity intervention that is increased if certain criteria are fulfilled and can often include augmenting, switching, or maintaining a course of treatment based on some type of consumer characteristic (ie, low engagement levels) or response (ie, symptom severity) [9]. Within a stepped care model, dMH interventions are offered as part of the first step of self-management (eg, self-help web-based program), and if required, an individual's treatment can be increased, whereby a therapist is added to support the dMH intervention.

Previous empirical studies investigating the effectiveness of therapist-assisted dMH interventions for anxiety and depression have largely used telephone, instant messaging, and email assistance. Recent advances in dMH include the use of video chat technology, in which face-to-face synchronous digital communication most closely aligns with the traditional in-person, gold-standard service delivery model in psychology. Empirical investigation into the efficacy of video chat, compared with that of other dMH care models for treating anxiety and depression, is lacking. Most of the research studies completed so far have investigated posttraumatic stress disorder and have compared psychiatric treatment delivered via video chat with that delivered in-person, with comparable outcomes reported [10,11].

Currently, there is a paucity of robust and rigorous studies on the use of video chat methods in dMH interventions. No identified clinical trial has investigated the efficacy of a 2-stage adaptive design offering the *no therapist support* dMH program and augmenting a participant's program with either low or high therapist assistance if they do not improve or engage in the *no therapist support* program-only condition. Within the field of psychology, the literature about dMH is also largely biased toward quantitative research methodology that minimizes the opportunity to more closely investigate factors contributing to the efficacy of various intensities of a dMH treatment program (eg, participant attrition and engagement factors). Therefore, the testing of an adaptive, mixed methods randomized clinical trial design will provide great insight into participant characteristics of engagement; efficacy of video chat as a mode of therapist assistance in dMH interventions; and, overall, improvement of future services delivered via dMH.

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Objectives

The purpose of this study is to present a protocol designed to evaluate various support intensities of a dMH treatment program for anxiety and depression within a mixed methods design. Therefore, the study has the following primary objectives:

1. To compare the efficacy of clinical outcomes (anxiety [Generalized Anxiety Disorder–7; GAD-7] and depression [Patient Health Questionnaire–9; PHQ-9] symptoms) among the 3 treatment conditions (dMH program only, low-intensity therapist assistance, and high-intensity therapist assistance), with particular focus on whether therapist-assisted support produces greater reductions in anxiety and depression severity compared with those produced by dMH program–only support.
2. To examine the role of motivation and self-efficacy on engagement, adherence, and clinical outcomes (anxiety [GAD-7] and depression [PHQ-9] symptoms) among the 3 treatment conditions (dMH program only, low-intensity therapist assistance, and high-intensity therapist assistance) at postintervention (week 9) and follow-up (week 21) assessments, compared with those at preintervention (week 0) assessment.
3. To explore participant and therapist experiences and satisfaction with assessment and therapist assistance delivered via video chat technology, using semistructured interviews; specific areas of focus will include the ability to develop and maintain therapeutic relationships, implementation barriers and facilitators, and identified strengths and limitations of video chat technology for conducting assessments and delivering dMH treatment.
4. To explore therapist training and implementation experiences in the delivery of dMH interventions.
5. To use a mixed methods analysis to examine factors affecting participant attrition in each of the treatment intensities; quantitative examination of preferences, treatment condition allocation (dMH program only, low-intensity therapist assistance, and high-intensity therapist assistance), and attrition rates will be explored; qualitative exploration of participant reasons for withdrawal and nonengagement with therapist support will also be conducted using semistructured interviews.
6. To explore the outcomes of working alliance, health resources, and health status among the 3 treatment conditions (dMH program only, low-intensity therapist assistance, and high-intensity therapist assistance).

Methods

Trial Design

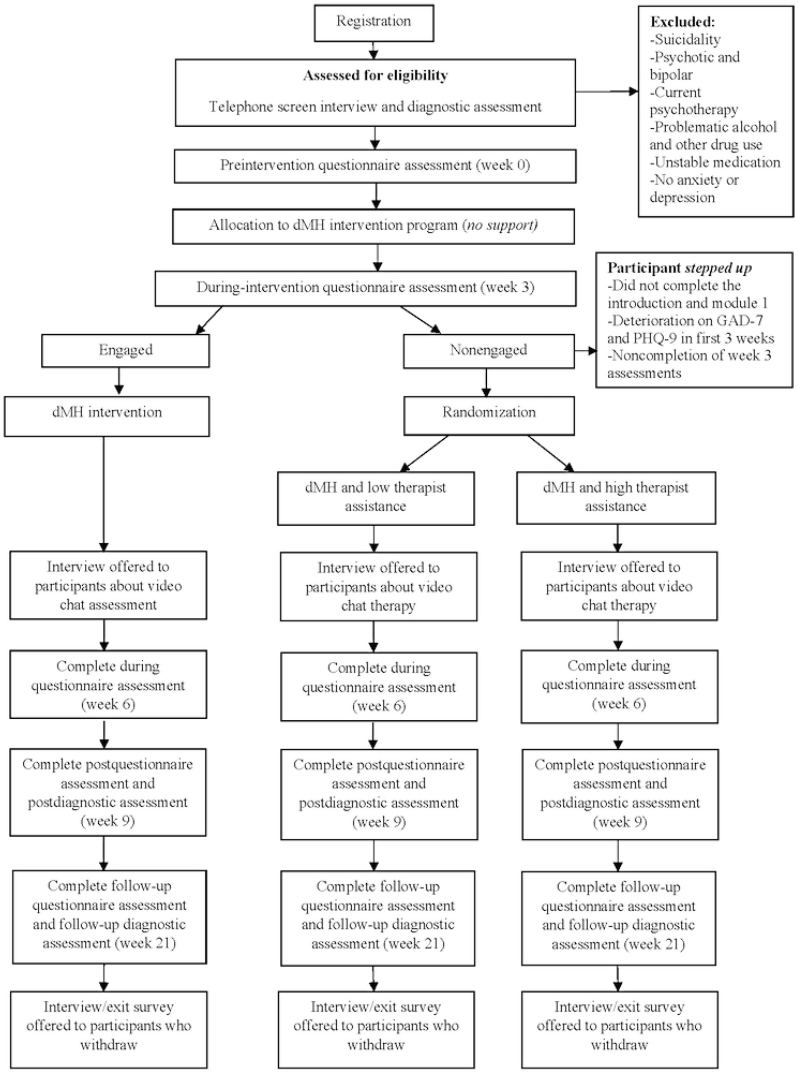
This trial will follow the International CONSORT (Consolidated Standards of Reporting Trials) guidelines and evaluate the conditions using an adaptive randomized clinical trial design [12]. The clinical trial also adheres to SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials; Multimedia Appendix 1). All information will be strictly confidential, yet subject to legal limitations (eg, legal subpoena), and only accessed by the investigators. Data are stored securely using 256-bit encryption Secure Sockets Layer and Transport Layer Security software when information is transmitted. Any hard copy data will be stored securely in lockable filing cabinets at the Federation Community Psychology Services at Federation University.

Eligible participants will be given access to a self-help dMH treatment program (Life Flex) and have their symptoms of anxiety or depression evaluated at day 15 to assess whether they meet the criteria to have their treatment program augmented with therapist assistance. Participants will be considered as eligible to be *stepped up* to a therapist-assisted condition if they meet any of the following criteria: they have not read the introduction module or module 1 of the Life Flex program; have symptoms of anxiety or depression that have deteriorated by >5 points (as assessed by comparison of their baseline depression [PHQ-9] and anxiety [GAD-7] scores against their week-3 scores); show symptom improvement, but their scores remain in a severe range; and are yet to complete the week-3 questionnaire assessment.

Outcomes will be assessed before the intervention (week 0), during the intervention (weeks 3 and 6), after the intervention (week 9), and at the 3-month follow-up (week 21). Results will be disseminated via publication. Figure 1 illustrates the study's design and expected participant flowchart.

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Figure 1. Study design diagram. dMH: digital mental health; GAD-7: Generalized Anxiety Disorder–7; PHQ-9: Patient Health Questionnaire–9.



Participant Recruitment

Eligibility

Participants will be recruited from the Australian community and will be eligible for the trial if they meet the following criteria: aged ≥18 years, are Australian residents, have access to the internet, able to register their interest via the web using an email address, able to read and write in English, and have symptoms or a diagnosis of anxiety or depression (as assessed by the Mini International Neuropsychiatric Interview [MINI] 7.0.2 [13]).

Participants will be excluded if they are currently receiving psychological treatment for their mental health, have moderate to severe levels of alcohol or substance use, have active psychosis or active suicidal intent or plan, have unstable bipolar disorder (as assessed by MINI 7.0.2 [13]), or take unstable doses of medication (ie, eligible participants will need to be on the same doses of their prescribed medications for at least one month before commencing the intervention).

Screening Procedures

Potential participants will register their interest to participate in the study via the completion of a screening contact form on the study's website. Interested participants will be presented with the Plain Language Information Statement before completing the contact form. Consent will be obtained at 2 intervals (upon initial completion of the contact form and again when entered into the trial), whereby participants will be required to click a button, *I agree*, indicating that they consent to the study. After consent is obtained, participants will be invited to participate in a brief telephone screening interview that corresponds with the *Diagnostic and Statistical Manual for Mental Disorders, Fifth Edition* (DSM-5) [14] criteria for generalized anxiety disorder, social phobia, panic disorder, agoraphobia, and major depressive disorder. During the telephone interview, the participants' ability to attend a video chat assessment will be determined. The interview will conclude with exploration of their motivation to improve their symptoms of anxiety or depression.

Eligible participants will be scheduled for a diagnostic assessment. That is, administration of MINI 7.0.2 [13] via video chat technology accessed through the My Digital Health platform of Federation University. This clinical assessment will determine the presence of mental health symptoms (allowing for assessment of the inclusion and exclusion criteria of the study) and assignment of clinical severity ratings for any

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identified disorders. MINI is a short, structured interviewing tool designed to aid DSM-5 diagnosis and monitor the clinical outcomes of the 17 most common mental disorders. It has a mean administration time of 15 minutes, with questions requiring a "yes" or "no" response (eg, "In the past two weeks, were you much less interested in most things or much less able to enjoy the things you used to enjoy, most of the time?"). MINI has been validated against the long Structured Clinical Interview for Diagnostic and Statistical Manual for Mental Disorders diagnoses and has been identified as a more time-efficient diagnostic tool, demonstrating excellent interrater reliability (k=0.88-1) [13]. MINI will be administered before the intervention (week 0); after the intervention (week 9); and 3 months after the treatment, at follow-up (week 21).

Participant Measures

Overview

Eligible participants will be given access to the preintervention (week 0) self-report questionnaire assessment comprising a demographic questionnaire (including age, sex, relationship status, education level, alcohol and other drug use, medication use, and current and past access to mental health services). Participants will also be asked to complete a short questionnaire package at weeks 3 and 6 and outcome measures after the intervention (week 9) and at the 3-month follow-up (week 21). At week 3, participants' questionnaire data for anxiety (GAD-7) and depression (PHQ-9) will be compared against the preintervention outcome data to assess whether the stepped care rules of the trial have been met and whether a therapist is required to be assigned to a participant. Table 1 shows the schedule and frequency of the assessments during the trial for participants.

Table 1. Schedule of enrollment and assessments.

Concepts and measures	Preintervention period (week 0)	Midintervention period (weeks 3 and 6)	Postintervention period (week 9)	Follow-up period (week 21)
Screening				
Anxiety and depression screen (DSM-5[a])	✓			
Diagnosis (MINI[b] 7.0.2)	✓		✓	✓
Primary outcomes				
Anxiety (GAD-7[c])	✓	✓	✓	✓
Depression (PHQ-9[d])	✓	✓	✓	✓
Secondary outcomes				
Working alliance (WAI-S[e])		✓	✓	
Health status (AQol[f])	✓		✓	✓
Health resources		✓	✓	
Moderators				
Motivation (CMOTS[g])	✓		✓	
Self-efficacy (BPSES[h])	✓		✓	
Demographic questionnaire	✓		✓	✓
Treatment				
System Usability Scale		✓		
Preferences questionnaire	✓			
Satisfaction questionnaire			✓	
Semistructured feedback interviews		✓	✓	

[a]DSM-5: *Diagnostic and Statistical Manual for Mental Disorders, Fifth Edition*.

[b]MINI: Mini International Neuropsychiatric Interview.

[c]GAD-7: Generalized Anxiety Disorder–7.

[d]PHQ-9: Patient Health Questionnaire–9.

[e]WAI-S: Working Alliance Inventory–Short.

[f]AQol: Assessment of Quality of Life.

[g]CMOTS: Client Motivation for Therapy Scale.

[h]BPSES: Bipolar Self-efficacy Scale.

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Anxiety

The GAD-7 [15] is a self-report measure that assesses anxiety symptoms over the past 2-week period. Total scores range from 0 to 21, with high scores suggestive of more severe anxiety symptoms. Each item is rated on a 4-point scale, with scores >8 indicative of clinically significant anxiety symptoms, warranting further evaluation. Scores of 5, 10, and 15 represent the cutoff points for mild, moderate, and severe anxiety symptoms, respectively. The GAD-7 is sensitive to changes in generalized anxiety disorder, social phobia, panic disorder, and posttraumatic stress disorder, with a score of >5 points indicative of clinically meaningful change over time [15]. The GAD-7 has strong psychometric properties [15].

Depression

The PHQ-9 [16] is a self-report measure designed to assess symptoms of major depressive disorder over the past 2-week period. Total scores range from 0 to 27, with high scores indicative of great depressive symptoms. Each item is rated on a 4-point scale, with scores >10 used as cutoff to indicate the presence of clinically significant depressive symptoms. Scores of 5, 10, 15, and 20 represent the cutoff points for mild, moderate, moderately severe, and severe depressive symptoms, respectively. The PHQ-9 has strong psychometric properties [16].

Working Alliance

The Working Alliance Inventory–Short (WAI-S) [17] is an abbreviated version of the Working Alliance Inventory based on the theory by Bordin [18] and comprises the following subscales: goal agreement, task agreement, and bond. In this study, the WAI-S is available in a therapist version (10-item scale) and a participant version (12-item scale), with both versions to be used to capture the strength of the therapeutic alliance from both perspectives. Total scores range from 12 to 60, with high scores suggestive of strong therapeutic alliance. Each item is rated on a 5-point scale, and the measure has strong psychometric properties [17]. To assess participants' technological alliance with the self-help dMH program, the wording of the items of the WAI-S have been slightly modified for this study, to capture participant ratings for a dMH program without therapist assistance.

Health Status

The Assessment of Quality of Life (AQol) [19] is a 12-item, self-report measure designed to assess ratings of health-related quality of life in a variety of life areas such as independent living, illness, social relationships, psychological well-being, and physical senses. The AQol can be scored in 2 ways—as a psychometric measure and as a utility measure. As a psychometric measure, scores are used to derive a simple psychometric score for health-related quality of life and provide profile scores on each of the 5 dimensions. When the AQol is scored as a utility measure, it can provide dimension scores and an overall index of the health state, which can be used in economic evaluation and cost analysis. The AQol has been validated across several countries, has been shown to have high degree of internal consistency (Cronbach α=.81), and is deemed an acceptable measure of health-related quality of life.

Health Resources

A Health Care Resource Usage questionnaire for cost-effectiveness has been specifically designed for the study to evaluate participants' primary and secondary health care consultations and admissions, use of antidepressant and antianxiolytic medication, and resource use associated with treatment received in the trial. The treatment received in the trial will encompass the amount of therapist time required, supervisor's time, internet access, and computer use.

Motivation

The Client Motivation for Therapy Scale (CMOTS) [20] is a self-report measure designed to assess the degree to which an individual is motivated for therapy and the impact of a person's motivation on treatment effectiveness and mental health symptoms. The 24 items assess 6 dimensions of the self-determination continuum of motivation proposed by Deci and Ryan [21]: intrinsic motivation, 4 forms of extrinsic motivation (integration, identification, introjection, and external regulation), and amotivation for therapy. The CMOTS obtains subscale scores for each type of motivation, with high scores reflecting high levels of each type of motivation. Each item is rated on a 7-point scale. The CMOTS has strong psychometric properties [20].

Self-efficacy

The Bipolar Self-efficacy Scale (BPSES)–Modified [22] has been slightly modified for use in this study to measure the self-efficacy of participants with anxiety and depressive symptoms opposed to bipolar disorder symptoms. The 17 items of the modified self-report measure of self-efficacy assess how confident an individual feels in performing a range of activities related to their mental health such as taking their medication as prescribed, maintaining regular hours of sleep, and identifying early warning signs of anxiety and depression (as opposed to bipolar symptoms). Each item is rated on a 10-point scale, with high scores indicative of high levels of self-efficacy. The BPSES has strong psychometric properties, with sensitivity to detect change over the course of treatment [22].

Usability

The System Usability Scale [23] is a 10-item measure designed to assess participant perceptions of the usability of a program. The System Usability Scale will be used in this study to assess participants' ease and perceptions about the dMH program's usability (eg, "I thought the program was easy to use"). Each item is rated on a 5-point scale, with high scores reflective of increased system usability.

Preferences

A bespoke preferences questionnaire has been purposively developed to assess participants' preferences for treatment before commencing the trial. Participants are presented with brief information about each of the 3 treatment conditions (dMH program only, low intensity therapist assistance, and high intensity therapist assistance), which they are then asked to rank in order of their preference.

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Satisfaction

A purposively designed 10-item satisfaction questionnaire has also been developed to assess participants' level of satisfaction with the treatment received. Overall, 8 of the 10 items are rated on a 4-point scale. For the other 2 questions, participants are asked to qualitatively share what they believe were the best and worst parts of the dMH treatment program.

Primary Outcomes

The primary outcomes will be participants' level of anxiety (GAD-7 [15]) and depression (PHQ-9 [16]).

Secondary Outcomes

The secondary outcomes being assessed are working alliance (WAI-S [17]), health status (AQol [19]), health resources, self-efficacy (BPSES [22]), and motivation (CMOTS [20]).

Treatment Conditions

Life Flex Program

The primary dMH intervention in each of the 3 treatment conditions is Life Flex, which is one of the dMH programs housed and offered via the My Digital Health platform. Life Flex is a third-wave transdiagnostic biopsychosocial treatment approach that aims to increase psychological flexibility, through cognitive behavior therapy, emotion regulation, and positive psychology principles, for anxiety and depression. The Life Flex program is suitable for individuals with or those without a DSM-5 diagnosis of anxiety or depression.

Life Flex teaches participants biopsychosocial *life skills*. It comprises 6 core modules, along with an introductory module and a booster module. The introductory module provides a rationale for the program, discusses brain plasticity and change processes, includes information about anxiety and depression, and explores factors contributing to motivation for change. Each of the 6 core modules focuses on increasing flexibility within a particular domain, such as biological (eg, breathing, nutrition, and sleep), emotional (eg, increasing emotional awareness), thinking (eg, identifying and challenging unhelpful cognitions), behavioral (eg, increasing pleasurable activities), wellness (eg, loving kindness), and life flexibility (eg, consolidating the life skills learned and goal setting). The booster session focuses on consolidation and reinforcement of learning. Further information about the Life Flex program can be accessed via a forthcoming paper that has recently been accepted for publication in JMIR Formative Research [24].

Each module of the Life Flex program will take approximately 25 minutes to complete. In addition, to reinforce the module-based information, there are 20 to 30 minutes of offline activities each week. Offline activities include applying the concepts and techniques discussed in the modules (eg, self-monitoring depressive and anxiety symptoms), undertaking one of the biological and wellness flexibility intervention strategies, monitoring emotions and thoughts, and undertaking the gradual exposure or behavioral activation activity. Participants will also receive automated emails (eg, to remind them to log in or to complete the questionnaires) and will be asked several questions at the beginning of each module to help gauge their progress. Module features include text, graphics, audio, video, editable forms, interactive games (eg, brain training), and downloads. Modules can be accessed via web, mobile phones, or tablet devices.

Life Flex Program–Only Condition

The treatment in step 1 of the trial will comprise the *program-only* Life Flex treatment program, whereby participants complete the fully automated, self-help program without therapist assistance. If participants do not improve in the *program-only* condition within the first 3 weeks (ie, no change in anxiety or depression symptoms, symptoms remain in the severe range, or noncompletion of the preintervention or week 3 questionnaire) or do not engage with the program (ie, noncompletion of the introduction module or module 1), they will be randomized to augment their program with either *low* therapist assistance (ie, one 10-minute support session per week) or *high* therapist assistance (ie, one 50-minute therapy session per week), delivered via video chat technology by provisionally or generally registered psychologists. Participants who improve or engage with the Life Flex program (program only) within the first 3 weeks maintain their no therapist assistance program. Participants who remain in the *program-only* treatment condition will complete the Life Flex program on a scheduled release design, with a new module being released every week, with the exception of module 4 (participants are given 2 weeks to work through and practice module-4 content).

Life Flex Program and Low-Intensity Therapist Assistance

Participants who are *stepped up* to the low-intensity therapist-assisted treatment condition will complete the same dMH treatment program (Life Flex), with the addition of a 10-minute weekly video chat session with a therapist for support and progress check-in of program content. The role of the therapist in the low-intensity treatment condition is to support the participant's engagement with the Life Flex program by specifically checking participant progress with modules, task reinforcement, providing clarification where required, encouraging reading and skill practice, and ensuring that participants are clear about their between-session module tasks assigned for completion.

Life Flex Program and High-Intensity Therapist Assistance

Participants who are *stepped up* to the high-intensity therapist-assisted treatment condition will complete the same dMH treatment program (Life Flex), with the addition of a 50-minute weekly video chat therapy session with a therapist for individualized tailoring of the program content. Participants in the high-intensity treatment condition will have the opportunity to receive therapist guidance, tailored program content, questionnaire feedback, and support for generalizing skills to daily life and to engage in problem-solving where required.

Therapist assistance in both low-intensity and high-intensity conditions will be offered to participants for a period of up to 7 sessions. To ensure treatment fidelity and standardized treatment, the therapists will be provided with a treatment manual, with random checks of their recorded video chat

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sessions (eg, 20% of the total) by independent raters to determine adherence to the study protocol and treatment fidelity.

Assessors and Therapists

Therapist Training Program

Before commencement of the trial, provisionally and generally registered psychologists will be required to complete and obtain competency in a purposively developed 14-hour, 5-module web-based training program covering an introduction to dMH interventions (specifically video chat technology), diagnostic assessments (covering MINI, anxiety, depressive disorders, and suicidality), qualitative interviewing techniques, and transdiagnostic cognitive behavior therapy principles that underpin the Life Flex dMH treatment program. The training program comprises a 40-item multiple-choice competency assessment, for which therapists are required to obtain a minimum score of 80%. The training program also contains a pre-evaluation and postevaluation survey designed to assess therapists' knowledge about and confidence in the use of dMH interventions before and upon completion of the program and to obtain their satisfaction ratings of the training program.

Outcome Assessors and Trial Therapists

The assessors who complete the diagnostic clinical assessments and the therapists who deliver the low-intensity and high-intensity treatment assistance will be provisionally and generally registered psychologists who are on clinical placement at the Federation Community Psychology Services at Federation University in Ballarat, Victoria, Australia. A new assessor will be assigned for all 3 assessment time points and will differ from any therapist assigned to participants in both the low-intensity and high-intensity therapist-assisted conditions. The assessors will complete and be required to demonstrate competency in diagnostic assessments before administration, and both assessors and therapists will receive training and supervision from an experienced clinical psychologist throughout the trial.

Both assessment and therapist sessions will be audio or video recorded (with participants' permission), so that random checking (eg, 20% of the total) can be completed to ensure adherence to administration, to enable agreement and interrater reliability of diagnoses, and to ensure that adherence to the therapist's role (low or high intensity) is maintained. Adapted versions of the Internet-Delivered Cognitive Behavior Therapy–Therapist Rating Scale [25] and Cognitive Therapy Rating Scale (Multimedia Appendix 2) will be used by supervisors in the review process to ensure treatment fidelity in both treatment conditions. Each therapist will also be required to undertake regular supervision, where any remedial strategies to improve fidelity will be implemented. Remedial strategies will include the provision of constructive feedback, review of the components of treatment in sequence, further practice of skills where drift may have occurred, additional training (if necessary), review of initial fidelity training materials, and extra coaching or supervision.

Participant Interviews

Within the study, there will be 4 different types of interviews offered to participants depending on what is relevant to them: exploration of experiences of assessment via video chat technology, exploration of experiences of therapist assistance delivered via video chat technology, exploration of reasons for nonengagement with therapist assistance, and exploration of reasons for disengagement and withdrawal. Participants will be offered an interview at a suitable time and via their preferred mode: instant message, telephone, video chat, or email. Participants will also have the option to complete a brief exit survey instead of an interview if they withdraw from the study or choose not to engage with the offer of therapist assistance.

Participants who complete a diagnostic assessment or receive at least two therapist-assisted sessions via video chat will be invited to participate in a semistructured interview to reflect upon and share their experiences with the video chat interaction. They will be asked a series of questions focusing on their ability to develop a therapeutic alliance with their assessor and therapist, their views on video chat technology, exploration of any technological issues experienced, and overall strengths and limitations of video chat. The interviews will be conducted by the first author, focusing on asking questions in an open, curious, and reflective manner. If the interview is completed via telephone or video chat, it will be audio recorded (with participants' permission) for qualitative analysis.

Assessor and Therapist Interviews

The provisionally and generally registered psychologists of the study will also be invited for interview to share their experiences with administering diagnostic assessments and delivering treatment via video chat technology and explore their training experiences. Assessors and therapists will be offered an interview at a suitable time and via their preferred mode: instant message, telephone, video chat, or email. They will be asked a series of questions focusing on their ability to develop a therapeutic alliance with their participants; their views about video chat technology; exploration of any technological issues experienced; exploration of implementation barriers and facilitators; and overall reflections about how a service delivered via video chat compares with an in-person, face-to-face service. The interviews will be conducted by the first author, and if completed via telephone or video chat, the interview will be audio recorded (with permission) for qualitative analysis.

Randomization

The process of randomly allocating participants to either the low-intensity or high-intensity treatment groups will comply with CONSORT guidelines. A block randomization design will be used to randomly allocate each participant to either the low-intensity or high-intensity therapist assistance condition throughout the trial. Random allocation will occur when a participant has met the criteria to be *stepped up* to have their Life Flex program augmented with therapist assistance. Participants will be aware of the group they have been randomly allocated to but will remain unaware of the study's objectives. The provisional or general psychologists will not be blinded to the treatment conditions, as they will need to adhere to either the support or the therapist role.

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Sample Size Calculation

Only aggregate data will be used for the main analysis. Assuming a conservative medium effect (ie, GPower f[v] test=0.25), significance set at 5% (P=.05), and power at 80%, 98 cases are required to demonstrate statistical significance in the primary outcome measures. However, allowing for a 30% attrition rate [26], a total target sample size of 137 participants will be required.

Ethics Approval

The trial will be conducted in accordance with the ethical guidelines in the National Statement on Ethical Conduct in Human Research (National Statement on Human Research 2007; updated in 2018). Ethics approval for this project has been granted by the Federation University Australia Human Research Ethics Committee (A19-095), and this clinical trial is registered with the Australian and New Zealand Clinical Trials Registry (12620000422921).

Results

Recruitment began in November 2020 and was completed at the end of March 2022. In total, 240 individuals registered for the clinical trial, of which 113 (47.1%) were assessed as eligible to commence the dMH intervention. At week 3, of the 113 participants, 73 (64.6%) met the stepped care criteria to have the dMH intervention augmented with therapist assistance, whereas 40 (35.4%) remained in the program-only condition. The results of the clinical trial are forthcoming as they have recently been accepted for publication in JMIR Publications [27].

Data will be entered, screened, and analyzed using statistical software. Intention-to-treat analysis will be used for primary outcomes, controlling for baseline differences where appropriate. The primary analysis will be conducted using 2 planned contrasts comparing a change in anxiety (GAD-7) and depression (PHQ-9) scores from preintervention assessment with those of the postintervention (week 9) and follow-up (week 21) assessments, using a mixed model repeated-measure analysis. A mixed model repeated-measure analysis is preferred owing to its ability to include participants with missing data. The study will also investigate whether reliable and clinically significant change has been achieved for participants following the recommendations of Jacobson and Traux [28]. Moderation analyses will be used to determine the role of self-efficacy and motivation in engagement and adherence and their effects on anxiety and depression outcomes in the 3 treatment conditions, and a t test will be used to determine the impact of preferences and treatment allocations on attrition rates.

Data obtained from open-ended questions about intervention satisfaction questionnaires and from interview questions will be transcribed verbatim from audio recordings into text and then analyzed using protocols of thematic analysis to identify common themes. Text transcripts will be read several times to identify emerging themes. Thematic analysis allows for the identification of themes that are driven by the data, using an experiential, bottom-up approach [29]. Close analysis of the data will suggest names for the themes, which are likely to represent something of meaning to participants and therapists, with direct quotes used to further illustrate meaning. Researchers will meet throughout the analysis process to review and discuss the data.

Discussion

Principal Findings

This study protocol presents an outline of the first adaptive intervention trial designed to determine the efficacy of various support intensities (ie, none, low, and high) of a dMH treatment program for anxiety and depression. The primary objective is to compare the efficacy of clinical outcomes (anxiety and depression) among the 3 treatment conditions. Specifically, it is predicted that therapist assistance delivered via video chat will be more effective in reducing anxiety and depression symptoms compared with program-only support. If this hypothesis is supported by the study findings, it will demonstrate that augmenting a dMH intervention with therapist assistance offered via video chat is beneficial for enhancing mental health outcomes within a community mental health treatment setting. The difference between low and high therapist assistance will also be evaluated. If the results indicate that the outcomes of these treatment conditions are similar, support will be provided for the implementation of low-intensity dMH interventions within the community, thus increasing timely community access to evidence-based interventions.

The study also has several secondary objectives that will be assessed. Examination of the role of motivation; self-efficacy; and participant preferences in engagement, adherence, and clinical outcomes among the 3 treatment conditions will be beneficial in improving our understanding of factors affecting participant attrition and engagement within dMH interventions. Qualitative evaluation of participant and therapist experiences and satisfaction with video chat technology is expected to provide further knowledge about the use of video chat for the assessment and treatment of anxiety and depression, specifically, the development of therapeutic relationships, implementation barriers and facilitators, and strengths and limitations of video chat technology. Furthermore, qualitative exploration of therapist training and implementation experiences in the delivery of dMH interventions is likely to improve the future adoption of dMH interventions incorporating video chat technology.

The findings of the trial have the potential to contribute toward the evidence base of adaptive treatment designs for anxiety and depression, with considerable implications for the implementation of stepped care models in dMH. As the study will evaluate outcomes of health resources and health status among the 3 treatment conditions, it is anticipated that the study results will enhance our understanding of participant needs and resources required at the self-help (dMH program only; step 1) and therapist-assisted (low and high therapist assistance; step 2) levels in the context of an adaptive intervention design.

Limitations

Although the current trial is believed to contribute significantly to advancing the field of dMH interventions, the study is likely to have some limitations. Given the widely known high attrition

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rates in dMH treatment and the difficulties that people with depression and anxiety can face, such as avoidance and lack of motivation, participant recruitment and overall engagement may present a challenge. The study protocol has been designed with these considerations in mind, with the overall aim of reducing the impact of these challenges and furthering our knowledge about various support intensities of dMH treatment for anxiety and depression.

Conclusions

This protocol outlines the first adaptive mixed methods clinical trial design investigating the efficacy of a 2-stage adaptive dMH intervention program incorporating both low-intensity and high-intensity therapist assistance delivered via video chat technology, compared with program-only support. This trial adds to the existing studies on dMH interventions and provides further understanding of participant and therapist experiences and satisfaction with video chat assessment and therapist assistance, along with therapist training and implementation experiences. Outcomes are expected to have implications for stepped care models and wide dissemination of dMH interventions for anxiety and depression.

Acknowledgments

The authors thank and acknowledge the Australian Government Research Training Program for supporting BA. The authors want to thank the provisionally and generally registered psychologists who have greatly assisted with this trial and the participants who participated. The authors would also like to acknowledge those who have assisted in the development of the My Digital Health Life Flex program, including Retsim, Rubber Duck, Gasoline Media, Eammon Jones, Jodie Parkinson, Gemma Munro, Rachelle Bridges, and Brett James.

Data Availability

Deidentified aggregate data sets generated or analyzed during this trial may be made available from the corresponding author upon reasonable request and if data sharing is in accordance with the study's ethics approval and general data protection regulations.

Conflicts of Interest

BK was one of the primary creators of the Life Flex digital mental health program. BK receives no personal income from the Life Flex program.

Multimedia Appendix 1
Completed SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist.
[DOC File , 123 KB - resprot_v12i1e45040_app1.doc]

Multimedia Appendix 2
Cognitive Therapy Rating Scale manual.
[PDF File (Adobe PDF File), 309 KB - resprot_v12i1e45040_app2.pdf]

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Abbreviations

AQol: Assessment of Quality of Life
BPSES: Bipolar Self-efficacy Scale
CMOTS: Client Motivation for Therapy Scale
CONSORT: Consolidated Standards of Reporting Trials
dMH: digital mental health
DSM-5: *Diagnostic and Statistical Manual for Mental Disorders, Fifth Edition*
GAD-7: Generalized Anxiety Disorder–7
MINI: Mini International Neuropsychiatric Interview
PHQ-9: Patient Health Questionnaire–9
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
WAI-S: Working Alliance Inventory–Short

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Protocol

Development and Economic Evaluation of a Patient-Centered Care Model for Children With Duchenne Muscular Dystrophy: Protocol for a Quasi-Experimental Study

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Abstract

Background: Duchenne muscular dystrophy (DMD) is a rare progressive muscular disease that primarily affects boys. A lack of comprehensive care for patients living with DMD is directly associated with a compromised quality of life (QoL) for those affected and their caregivers. This disease also has a huge economic impact on families as its treatment requires substantial direct, indirect, and informal care costs.

Objective: This study presents a protocol developed to evaluate the feasibility and efficacy of a patient-centered care (PCC) model for children with DMD. The care model was designed with the aim to empower families, improve QoL, and reduce economic burden on their families.

Methods: This study is planned as a quasi-experimental study that will enroll 70 consecutive families with boys (aged 5-15 years) with DMD visiting a tertiary care center. The study is being conducted in 2 phases (preintervention and postintervention phases, referred to as phase 1 and phase 2, respectively). During phase 1, the patients received routine care. The study is now in phase 2, with the intervention currently being administered. The intervention is based on the PCC model individualized by the intervention team. The model has a comprehensive DMD telecare component that includes teleconsultation as one of its key components to reduce in-person physician visits at the health facility. Teleconsultation is especially beneficial for late-ambulatory and nonambulatory patients. Data on economic burden are being collected for out-of-pocket expenses for both phases during in-person visits via telephone or messaging apps on a monthly basis. QoL data for patients and their primary caregivers are being collected at 3 time points (ie, time of enrollment, end of phase 1, and end of phase 2). Outcome measures are being assessed as changes in economic burden on families and changes in QoL scores.

Results: Participant recruitment began in July 2021. The study is ongoing and expected to be completed by March 2023. The findings based on baseline data are expected to be submitted for publication in 2023.

Conclusions: This paper outlines a research proposal developed to study the impact of a PCC model for patients with DMD in low- and middle-income countries (LMICs). This study is expected to provide evidence of whether a multicomponent, patient-centric intervention could reduce economic burdens on families and improve their QoL. The results of this study could guide policy makers and health professionals in India and other LMICs to facilitate a comprehensive care program for patients living with

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DMD. The economic impact of a rare disease is an important consideration to formulate or evaluate any health policy or intervention related to new treatments and financial support schemes.

Trial Registration: Clinical Trials Registry India (ICMR-NIMS) CTRI/2021/06/034274; https://www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=56650

International Registered Report Identifier (IRRID): PRR1-10.2196/42491

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KEYWORDS

Duchenne muscular dystrophy; patient-centered care; disabilities; quality of life; caregivers; cost of illness; effective; treatment; policy; caregiver; pediatrics; intervention; psychological; disability

Introduction

Background

Duchenne muscular dystrophy (DMD) is an X-linked recessive disease with an incidence of 1 in 3500 to 6000 live male births [1]. It progresses from an ambulatory to a nonambulatory stage, with the child usually becoming wheelchair-bound between 11 and 13 years and death occurring in the late teens or early twenties [2-4]. Even with this short span of life, children with DMD face many challenges, as their progression through various transitional phases impacts not only them but also their families and society at large [5].

The progressive and irreversible damage to the muscles results in weakness, loss of ambulation, breathing issues, and cardiomyopathy. Currently, there is no definitive treatment to halt the disease's progression. Disease management mostly revolves around symptom management and involves a multidisciplinary approach to address various systemic complications [6].

Course of Disease

Boys with DMD usually remain asymptomatic up to 2 years of age and get diagnosed between 4 to 6 years of age. Most of the boys with DMD are limited to assisted ambulation with the help of long leg braces by the age of 10 years. Age of loss of ambulation globally is between 13 and 14 years, whereas in resource-limited settings, it is between 9 and 11 years [4]. There is no study on the prevalence or incidence of DMD in India. However, a study from southern India [7] on 275 genetically confirmed patients with DMD was conducted to study the natural course of motor milestones. Authors reported the mean age of onset of symptoms was 3.7 years, and the mean age at presentation was 8.1 years. During the follow-up period of 15 years, 155 out of 275 (56.4%) children had either become wheelchair-bound or bed-bound or died. The affected children were wheelchairs bound by a mean age of 10.4 years and bed-bound by 11.8 years. Seven boys (2.6%) died during the follow-up period at a mean age of 15.2 years.

DMD requires a multidisciplinary team approach for holistic management. This includes diagnostic services, physical therapy, orthotics, respiratory therapy, corrective orthopedic surgery, ventilation, feeding support, and speech therapy. Muscle degeneration can be slowed down with the use of corticosteroids, while antibiotics may be needed for respiratory infections [8-11]. Occupational therapy, assistive devices, and a wheelchair are also beneficial to the children. Some patients may need a pacemaker for cardiac abnormalities and assisted ventilation for respiratory muscle weakness. Patients diagnosed with DMD should expect to make a successful transition to adulthood, which includes education, health care, and social support to transition smoothly from adolescence to adulthood [12,13].

The DMD Care Considerations Working Group identified eleven components of care: (1) diagnosis, (2) neuromuscular management, (3) rehabilitation management, (4) gastrointestinal and nutritional management, (5) respiratory management, (6) cardiac management, (7) orthopedic and surgical management, (8) psychosocial management, (9) primary care and emergency management, (10) endocrine management (including growth, puberty, adrenal insufficiency, and bone health), and (11) transitions of care across the life span. The mainstay of management is still limited to physiotherapy and glucocorticoids therapy, which help in delaying loss of ambulation, an important milestone of the disease [6,14]. Treatment modalities also have changed, especially with the advent of exon-skipping therapy and gene editing tools. However, these new modalities of treatment have not made a significant clinical impact yet [15].

Empowering Patients and Caregivers

Globally, we are witnessing a new paradigm shift to resolve problems from a mechanistic or Newtonian worldview to a holistic view. This approach involves human values, creativity, and evolution, and it has affected the approach toward understanding human health. Nevertheless, the reductionistic approach dominates the imagination of the scientific fraternity [16]. The biomedical or reductionistic approach sees patients as an isolated problem, whereas we need to understand that a holistic approach (ie, social, economic, sanitary, environmental, and political commitment) is needed to manage a disease.

An inclusive paradigm has two major components: (1) self-empowerment of the patient and (2) holism. Empowering patients involves developing skills, control over resources, ensuring autonomy in decision-making, and taking ownership of their health [17,18].

Empowering patients through an effective health care delivery model has the potential to improve the cost-effectiveness of care, especially for people affected by long-term conditions [19]. Patient-centered care (PCC) increases adherence to disease management, reduces loss to follow-up in the health care system, and, in turn, reduces morbidity and improves quality of life (QoL) for patients [17].

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QoL of Children Living With DMD

With the advancement in medical management, patients with DMD are reported to live longer up to the third decade of life. These require more years to live with functional disability and more years of caregiving. Past studies have reported variable QoL among patients with DMD, with some studies showing poor QoL and others showing no difference between healthy children and those with DMD. Being able to participate in various activities of daily living, like personal care, mobility, social relationships, education, recreation and leisure, spirituality, and community life, are outcomes of health. Physical disability substantially decreases participation and consequently impairs QoL [18]. Studies have reported that only physical participation levels were much lower in patients with DMD, and other participation levels were almost the same.

Bendixen et al [20] compared participation in life activities and perceived QoL between younger and adolescent boys with DMD and age-matched controls. No differences in perceived QoL were observed between the participants with DMD and the healthy controls, but the older adolescent participants with DMD had significantly lower QoL subscales of physical, social, and total composite scores. de Moura and colleagues [21] studied the relationship between physical dependence and QoL of patients with DMD and the QoL and burden of caregivers. Lower QoL was observed in caregivers with increased age and the burden of caregiving. In a review, Landfeldt et al found [22] the informal care of patients with DMD was associated with a substantial burden, and they recommended further research to better understand the relationship between clinical implications and progression of disease and caregiver burden. A cross-sectional study by Jackson et al [23] examined mothers' demographic characteristics and their sons' QoL-related factors to identify which ones contribute to poorer health-related QoL and greater emotional distress. Mothers' perception of their sons' health-related QoL is a significant predictor of their own health-related QoL and emotional distress. In turn, mothers' physical and emotional health influences their social activities. Social activities are important to manage stress among caregiving parents. QoL is a measure used to obtain additional information on the effectiveness of clinical measures, the quality of services they need for health care, the effectiveness of the interventions, and cost-utility analyses. Change in QoL reflects how much a patient is satisfied with his or her treatment or the system of health care delivery [20,24,25].

Economic Burden of Disease

Previous studies have revealed that DMD also has a substantial economic burden on families. Studies have shown that this burden increases markedly with disease progression; however, no such study has been conducted in the Southeast Asian region [22,26].

Health care delivery systems frequently use patient engagement to reduce expenditure and improve health outcomes. When analyzing the health care delivery system in the state of Minnesota, Hibbard et al [27] concluded that patients who were less actively engaged in their treatment had 8 times higher health care costs in the first year, and this was significantly different from patients who were actively engaged in their treatment. Another review by Hibbard and Green [28] on patient engagement concluded that various tailor-made interventions to increase patient involvement in their disease significantly improved health outcomes. Nevertheless, very few studies comment on costs related to disease. Proper allocation of resources is most important for any institution to have sustainable development, and this applies to the health care system as well. Cost-of-illness studies can provide important information to policy makers at both the micro (eg, cost-effectiveness of new interventions) and macro level (eg, fund allocation for further research and prioritization of disease for preventive interventions) [13,29-31].

The Indian Ministry of Health and Family Welfare has begun to address this issue related to rare diseases, as reflected in its 2017 National Health Policy. The Indian government approved the separate National Rare Disease Policy in 2021. This policy recommends a focusing on indigenous research and local production of medicines, searching for low-cost treatments for rare diseases, and screening and early detection. Financial support is sought to be given to the rare diseases classified as Group 1 in the policy under the umbrella of Rashtriya Arogya Nidhi or Pradhan Mantri Jan Arogya Yojana. However, DMD is classified under Group 3, described as "diseases for which definitive treatment is available but challenges are to make optimal patient selection for benefit, very high cost and lifelong therapy" [32]. The policy identified 8 tertiary care centers as Centers of Excellence for managing rare diseases. The hospital-based National Registry of Rare Diseases was created in these centers to ascertain the exact burden of rare diseases.

Accordingly, this study aims to estimate the economic burden incurred by the families of children with DMD seeking care at a government hospital. Next, we aim to develop a PCC model (intervention) to build the capacity of affected families to cope with DMD, thus reducing the financial burden on families. Finally, we aim to compare the impact of intervention with routine care on QoL (caregiver and patient) and economic burden after 6 months of intervention.

Methods

Study Design

This is a longitudinal quasi-experimental study that will be conducted in 2 phases. It is important to note that within the scope of this study, it is difficult to achieve a controlled experimental design. There is no randomization, and the same group of subjects are to be compared before and after the intervention. The experimental condition may be systematically different across the time frame. Considering this limitation, we chose a quasi-experimental design for this study. [33]

Phase 1 of the study is observational, and no intervention is administered. Participants (previously diagnosed and under follow-up as well as new patients) were recruited prospectively from pediatric neurology clinic, department of Pediatrics, Advanced Pediatrics Center, Post Graduate Institute of Medical Education & Research (PGIMER), Chandigarh, India. Detailed information about the study was provided to the children and their caregivers. After providing consent to participate in the

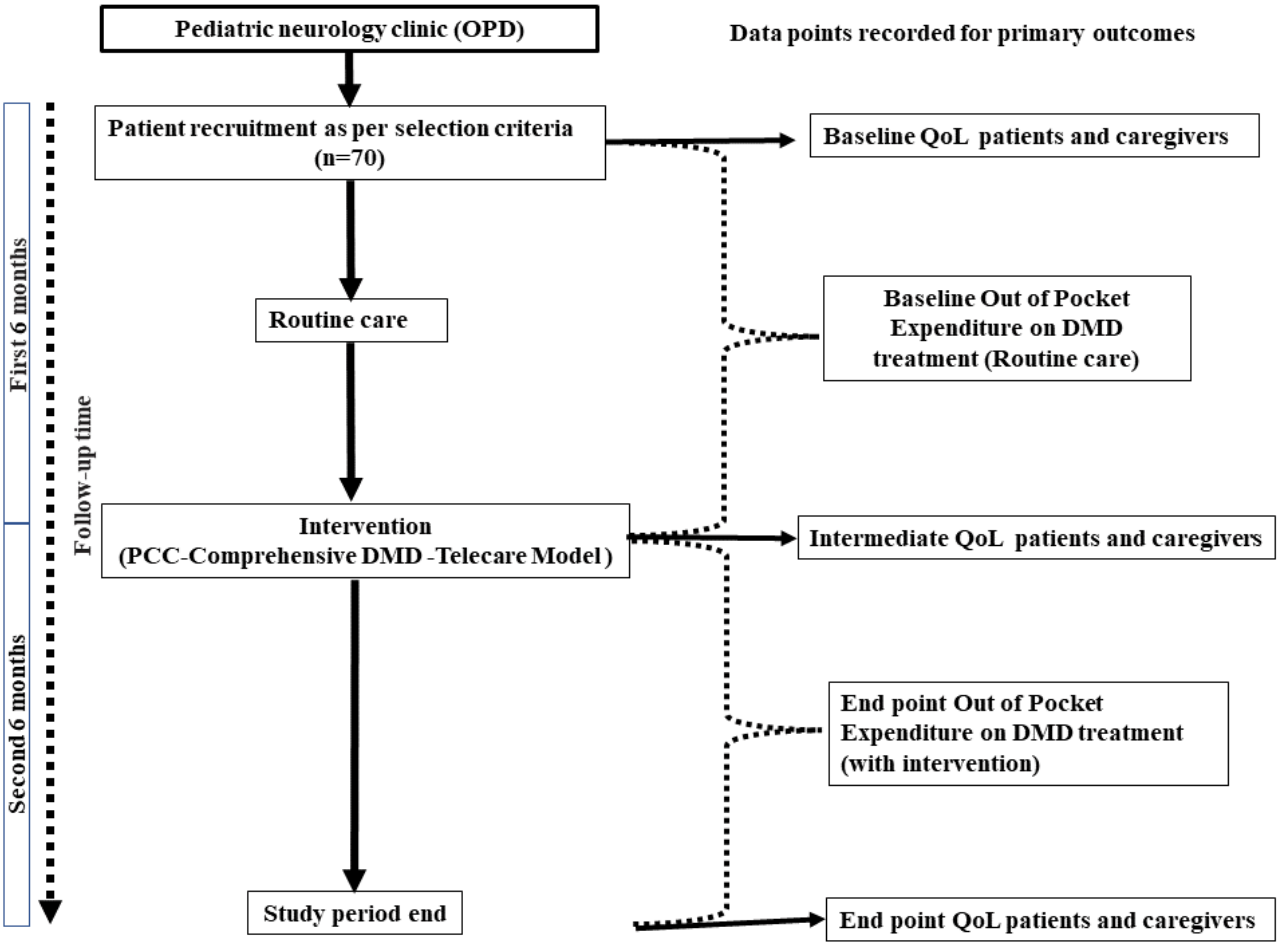
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study, the primary caregivers were interviewed for demographic information, clinical information, and information related to their economic status and financial burden of disease caused by DMD. The QoL of patients and caregivers was assessed with the EuroQoL 5-Dimension 5-Level (EQ-5D-5L) scale and the World Health Organization Quality-of-Life Scale (WHOQOL-BREF), respectively. After recruitment into the study, the patients were followed up for 6 months. Routine treatment as per institutional norms was given during this period. The primary caregiver was contacted via telephone monthly for data collection on economic burden. After the 6 months, the participants entered into the next phase (ie, phase 2).

Parallelly, during phase 1, the PCC intervention model was developed. The rationale behind developing the care model was to provide basic information about DMD and treatment options to the patients and their parents or caregivers so that they could participate effectively in the process of obtaining comprehensive care in a resource-limited setting. The intervention includes information about the disease, an instructional booklet, and a workbook to encourage compliance. This study also includes a teleconsultation with pediatric neurologist and the rehabilitation team. The sessions are designed to facilitate caregivers in decision-making through active participation in every stage of the disease. This set of interventions are collectively referred to as the Comprehensive DMD-Telecare Model.

Phase 2 is the interventional phase of the study, which commences once the patient has completed phase 1 (ie, the first 6 months of the study). During phase 2, patients and their parents or caregivers are given a set of interventions developed during phase 1. The patients are followed up prospectively for the subsequent 6 months (Figure 1), and data on economic burden are recorded telephonically on monthly basis. Children are visiting the health facility just twice during the follow-up period (ie, at the beginning and at the end of phase 2). This reduced the number of in-person visits the patients had to make to the health facility.

Figure 1. Overview of study design. DMD: Duchenne muscular dystrophy; OPD: Outpatient Department; PCC: patient-centered care; QoL: quality of life.



Ethics Approval

Approval for this study was granted from the ethics committees of PGIMER (IEC-01/2021-1884) and Lovey Professional University (LPU/IEC/2021/01/24). The patients and their caregivers were informed about the study and provided consent before recruitment. Information collected from the patients and their caregivers will be anonymized. The study protocol was registered with the Clinical Trials Registry India (CTRI/2021/06/034274).

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Setting and Sample Size Considerations

Patients were recruited prospectively in a consecutive manner from the Pediatric Neurology Clinic of the Advanced Pediatric Center at PGIMER in Chandigarh, India. This institute caters to approximately 7 north Indian states, namely, Punjab, Haryana, Himachal Pradesh, Jammu and Kashmir, Uttarakhand, Bihar, the northwestern part of Uttar Pradesh, and the Union Territory of Chandigarh.

The sample size estimation for the primary outcome was in accordance to changes in patients' health-related QoL (HRQOL) questionnaire scores. The QoL scores were assessed in the observational phase (0-6 months) and compared with the QoL scores in the intervention phase (7-12 months). A clinical meaningful difference based on the minimum important difference from HRQOL was 0.1 [34], along with an SD of 0.2 [35] and an allocation ratio of 1:1. The estimated sample for the study was 126 (63 patient in each phase) to achieve a level of significance of 95% CI at a power of 80%, accounting for a 10% dropout rate. The total sample size was 140, with 70 patients in each phase.

Study Population

The study population comprises families or caregivers with boys aged between 5 and 15 years who were genetically diagnosed with DMD and are seeking consultation at the pediatric neurology clinic of the government tertiary care center. Caregivers defined as the persons who look after the patients in the hospital or at home (parents or family members). This excludes hospital staff and paid workers hired by the family.

Selection Criteria

Boys with DMD presenting to the Pediatric Neurology Clinic were screened for enrollment in the study. The selection of participants was carried out by a pediatric neurologist. Those who fulfilled the inclusion and exclusion criteria were included in the study after providing informed consent. Textbox 1 lists the inclusion and exclusion criteria for this study.

Textbox 1. Inclusion and exclusion criteria for this study.

Inclusion criteria

- Families with boys aged 5 between 15 years who have Duchenne muscular dystrophy (DMD) or Becker muscular dystrophy (BMD) and display clinical symptoms and creatine kinase (CK) levels elevated 10 times or more the normal level
- Laboratory genetic confirmation of DMD or BMD by multiplex ligation-dependent probe amplification (MLPA), polymerase chain reaction (PCR), next-generation sequencing (NGS), or muscle biopsy (showing absence of dystrophin expression on immunohistochemistry)
- Caregivers of the patients with who have access to a smartphone and internet connection

Exclusion criteria

- Caregivers and patients who are unwilling to participate or unable to comply with the study protocol and visits
- Caregivers and patients who did not provide consent to participate

Intervention Program

Routine Care

Boys with clinical symptoms suggestive of DMD were first consulted and evaluated in the pediatric neurology clinic. After detail clinical investigations, a treatment plan for the patient was decided as per the institutional protocol for the management of muscular dystrophies and discussed with the patient. The patient was required to visit the health facility routinely once every 3 months. For multispecialty care, patients visited different subspecialists as required. Physiotherapy and orthosis appointments, along with visits to specialty care units, increase hospital visits, often leading to confusion, treatment nonadherence, and loss to follow-up. The components of routine management are given in Textbox 2.

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Textbox 2. The components of routine management as per institutional protocol (standard operating care).

1. Confirm diagnosis: clinical examination, investigations, confirmation of diagnosis with genetics, and muscle biopsy
2. Family counseling
3. Baseline assessment of motor attributes with the 6-Minute Walk Distance Test, Time Function Test, and Vignos and Brooke scales
4. Baseline cardiac, respiratory assessment, spine, bone health, and endocrine evaluation
5. Oral supplementals of calcium and vitamin D
6. Nighttime ankle-foot orthosis
7. Physical therapy muscles strengthening and stretches to reduce contractures
8. Vaccination (immunization)
9. Steroids as per standard guidelines
10. Dietary advice
11. Advice on play and leisure
12. Three monthly clinical check-ups for disease progression, monitoring for weight, height, blood pressure, ophthalmic evaluation, bone health, and steroid side effects (these visits may be more as per disease progression requirement).
13. Prenatal diagnosis, carrier screening, and genetic counseling

PCC: Comprehensive DMD-Telecare Model

The rationale behind developing the PCC model for patients with DMD was to (1) provide basic information to the patient and their parents or caregivers so that they can effectively understand the disease and participate in the process of obtaining comprehensive care in a resource-limited setting and (2) create awareness about the importance of managing the disease not only pharmacologically but also by improving QoL.

After a systematic review of literature, the intervention designed was based on the Theory of Planned Behavior and tailored to each stage of the study [36]. The conceptual model of PCC is given in Figure 2. The telecare component was added to the model considering the challenges that patients and their caregivers experience when having to travel to the heath care facility frequently, especially in low- and middle-income countries (LMICs). The components of the intervention are provided in Table 1.

The purpose of the intervention is to reduce the number of in-person visits the patient has to make to the clinic. The planned physical follow-up to the health facility during phase 2 is at 6 months. Families are called for physical follow-up only if indicated and instructed by the clinician within 6 months. These visits are recorded.

Protocol material for the Comprehensive DMD-Telecare Model is circulated among pediatricians and pediatric physiotherapists working at the Pediatric Neurology Clinic, School of Public Health experts at PGIMER, and caregivers or parents.

A preliminary version of this package was circulated among specialists for consensus validation and modified according to the feedback received. Thereafter, it was pilot tested among 5 patients and their caregivers. Further corrections were made as needed. Textbox 3 lists the outcomes of the study.

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Figure 2. Overview of patient-centered care (PCC): intervention model. DMD: Duchenne muscular dystrophy; PPT: PowerPoint presentation.

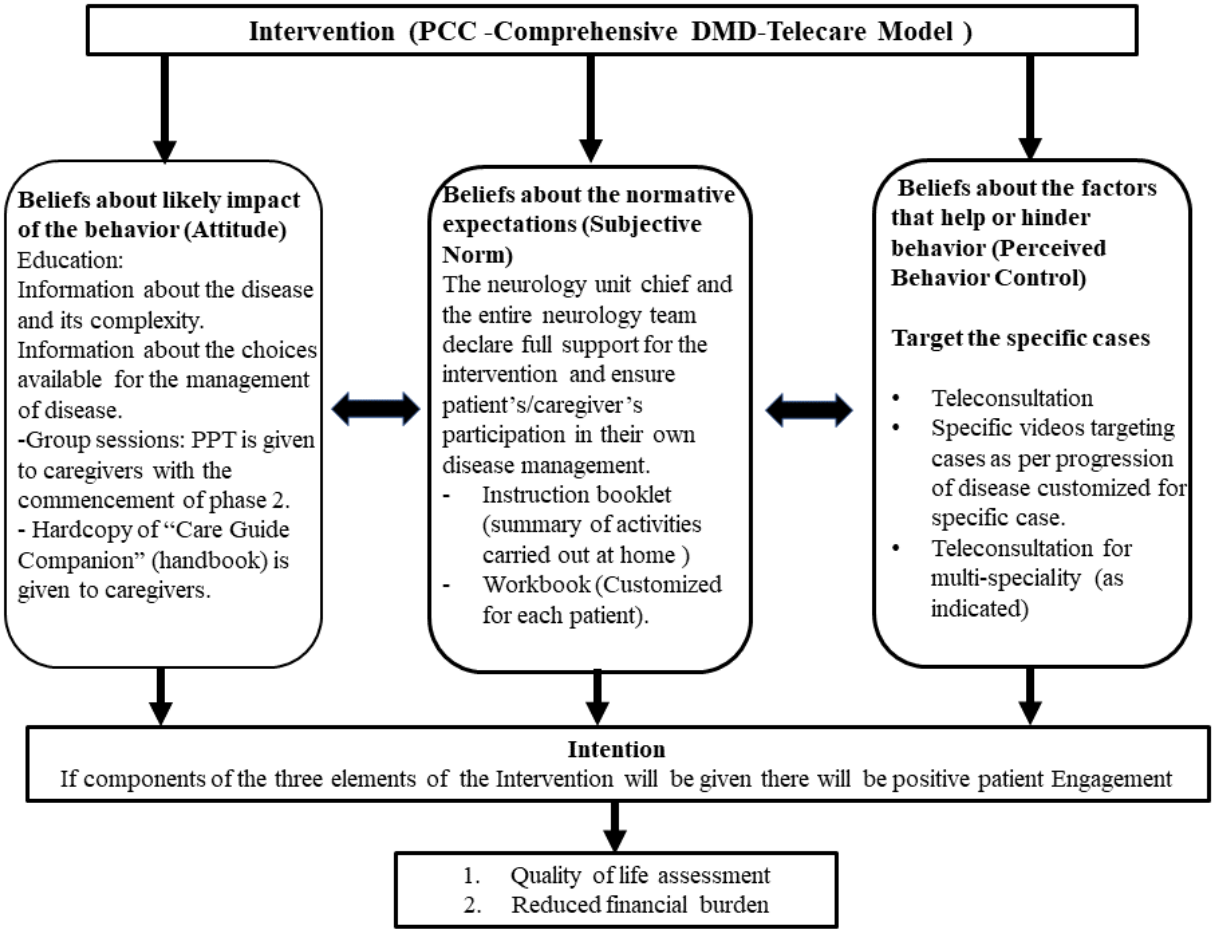


Table 1. Components of the intervention.

Component	Description
Informational session about the disease	Information sessions are carried out via PowerPoint presentation, and a "Care Guide Companion" booklet is provided (both hard copy and digital). The booklet is designed to helping patients and their caregivers participate in decision-making for their treatment. The components of the booklet include (1) basic information related to DMD[a], (2) management of DMD, (3) role of the care provider team, and (4) support groups to help people living with DMD.
Instructions and checklist	Instructions are given to the patients and their caregivers to make them understand all the activities that will be carried out once they enter phase 2 of the study. Audiovisual media and images containing instructions for stretches or physio-therapy and physical activity are provided to the family.
Compliance diary	The patient is expected to comply with the prescribed procedures and medications. A customized daily planner is introduced to each patient in phase 2 to increase their adherence to the protocol. This contains periodic monitoring of weight, height, blood pressure, daily medication (eg, steroids, ACE[b] inhibitors, calcium, and vitamin D), and daily exercise routine. Some clinical evaluations are expected to be performed at home (eg, Gower sign, Vignos score, Brookes scores, etc) which are monitored by the research team over the phone.
Teleconsultation	A total of 3 monthly video teleconsultations are given to the patients by clinicians to provide diagnostic or therapeutic advice electronically. The patient does not have to visit the clinic in person. This is done through: (1) review videos that the family shares with the care team regarding the patient's present state of illness. These videos are recordings of physical activities that the patient can perform at home, which are share with the team for evaluation purposes; and (2) customized videos: As per the clinical requirements, customized videos are shared with patients to address any additional needs.
Multidisciplinary teleconsultation	Not all subspecialists are needed at all ages or stages, but they must be accessible if necessary.

[a]DMD: Duchenne muscular dystrophy.

[b]ACE: Angiotensin-converting enzyme.

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Textbox 3. Study outcomes.

Primary outcomes

1. Difference in quality of life (QoL) with and without the intervention
2. Difference in out-of-pocket (OOP) expenses incurred by patients and their caregivers with and without the intervention
3. Development of patient-centered care (PCC) model known as the Comprehensive Duchenne muscular dystrophy (DMD)-Telecare Model

Primary outcome measures

1. Change in QoL mean scores in phase 1 (0-6 months) and phase 2 (7-12 months) of the study
2. Change in mean OOP expenses incurred by the patients and their caregivers with and without the intervention

Secondary outcomes

1. Socioeconomic determinants of primary outcomes.
2. Feasibility of follow-up via telephone
3. Pattern of health care utilization for different stages of DMD
4. Neuromuscular QoL in the pediatric age group
5. Opinions and experiences related to the challenges faced by stakeholders during the management of DMD (noted verbatim)

Secondary outcome measures

1. Demographic data and socioeconomic status in terms of means and percentages
2. Compliance with telephone follow-up and satisfaction index on Likert scale
3. Mean score of neuromuscular QoL in the pediatric age group
4. Thematic analysis of the qualitative data

Data Collection

At the time of recruitment, primary caregivers are interviewed on their social and demographic characteristics and QoL. Further, after the initiation of phase 1, these caregivers are contacted again prospectively to assess the economic burdens they face by collecting data on out-of-pocket (OOP) expenses incurred during the treatment of DMD. The data on economic burden include information on household consumption expenditure, patient-level expenses incurred on diagnosis and treatment related to DMD, and coping mechanisms for dealing with DMD. A pretested semistructured schedule, adapted from previous studies in similar settings, is used to interview the patients [37-39]. Cost-of-illness (COI) analysis is carried out to assess OOP expenses, which are further classified as direct and indirect expenses [40]. Expenditure on the diagnosis, drugs or consumables, hospitalization, user fee, or procedure fee is considered direct health care expenditure. Transportation, boarding, loading, and food are taken as direct non–health care expenditures. Wage or income loss by the accompanying caregivers during the period of treatment is considered an indirect expenditure.

Information on economic burden is gathered from the caregivers throughout the follow-up period of 12 months. Data are collected during their physical visits as well as telephonically every month.

HRQOL of the patients and their caregivers are gathered at the baseline and then at the completion of phases 1 and 2. QoL of caregivers is also recorded at the 3 data points (baseline, end of phase 1, and end of phase 2). The study design is further explained in Figure 1.

Data Management and Analysis

Primary data are first entered in Epi Info software (version 7; Centers for Disease Control and Prevention). Data will be analyzed using both Epi Info 7 and SPSS software (version 23; IBM Corp). Mean OOP expenditure incurred due to the treatment modalities will be calculated. The OOP expenditure will be reported in Indian rupees. For international comparison, expenses will be converted to US dollars using an appropriate conversion rate. Indirect expenditure will be calculated for the duration of follow-up treatment using a human capital approach by assessing the wage loss of the caregivers [41]. Financial risk will be assessed in terms of catastrophic health expenditure and distress financing. An expenditure on DMD treatment that exceeds the threshold of 40% of nonfood household consumption expenditure is considered a catastrophic health care expenditure [42,43]. Households that had to either borrow money (with or without interest) or sold their assets (such as land, home, cattle, etc) to cope with DMD-related expenditure will be classified as having faced distress financing [38,44,45]. Multiple logistic regression analysis will be performed to examine the risk of catastrophic health expenditure and distress financing with covariates, including age, income status, treatment modality, education, locality, and stage at the time of diagnosis. Sensitivity analysis will be carried out to assess the prevalence of catastrophic expenditure at varying cutoff levels (ie, 20%-50%).

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The HRQOL of the patients will be assessed by the EQ-5D-5L tool. This tool comprises the EQ-5D descriptive system and a visual analog scale (EQ VAS). The EQ-5D-5L descriptive system has 5 dimensions (ie, mobility, self-care, usual activities, pain or discomfort, and anxiety or depression). Each of these dimensions has a response in the form of 5 levels of perceived problems: no problems (level 1), slight problems (level 2), moderate problems (level 3), severe problems (level 4), and extreme problems (level 5). Thus, a unique health state is defined by combining 1 level from each of the 5 dimensions. The EQ VAS records the patient's self-rated health on a VAS, where the end points are labeled as "The best health you can imagine" and "The worst health you can imagine." The analysis of the QoL utility scores based on the EQ-5D-5L tool will be done as recommended in the user guide. Each of the patient's condition or state at a particular time period will be referred to in terms of a 5-digit code. For example, state 11111 implies no problems on any of the 5 dimensions, while state 55555 indicates extreme discomfort in each of the dimensions. Each of these states are further converted into a single index utility value based on the recently generated tariff value set for the Indian population [46,47].

As mentioned earlier in this paper, the self-administered WHOQOL-BREF tool is used to assess the QoL of caregivers. This tool has 26 items describing 4 QoL domains, namely, physical health (7 items), psychological health (6 items), social relationships (3 items), and environmental health (8 items). It also contains items for general QoL and overall health (2 items). The response to each item is recorded in 5 levels and scored from 1 to 5. The raw scores will be converted into transformed scores ranging from 4 to 20. Later, these transformed scores will be converted into main domain scores ranging from 0 to 100, with higher scores indicating better QoL [48].

Correlations of HRQOL in children and QoL of caregivers in all 4 domains at the baseline will be assessed with socioeconomic status (SES), COI, and also with each other. Multiple linear regression analysis will be conducted to address the confounders (eg, age at baseline, family structure, type of disease, family history, family structure, education, and SES).

Economic burden and QOL data will be analyzed as per the study objective, and comparative analysis will be done to justify the hypothesis. Percentage, mean, and SD values will be recorded, and the chi-square test, paired *t* test, and Mann-Whitney *U* test will be carried out for statistical analysis. SPSS software (IBM Corp) will be used for the analyses.

Results

Study enrollment was completed in March 2022 with a total of 100 children with DMD and their caregivers (125% of the target). All 100 patients and their caregivers were followed up for 6 months in phase 1 of the study, which was completed in July 2022. The intervention was administered to 66 patients and their caregivers (94.3% of the target population) in phase 2. The participants were further followed for the subsequent 6 months, and phase 2 ended in December 2022. We are in the process of data entry and data cleaning. Initial data show that the children range in age between 5 and 15 years at enrollment, with a mean age of 8.3 (SD 1.9) years. Most of the children (56/100, 56%) enrolled in this study are in the late ambulatory disease (stage 3), and only 1 (1%) child was in a late nonambulatory stage at the time of enrollment. However, these dynamics changed swiftly with the progression of the disease.

Primary caregivers enrolled (n=100) at the baseline in the study were mostly mothers (58/100, 58%), with fathers comprising 38% (38/100) of the caregivers. Only 57% (57/100) of caregivers had some knowledge about DMD before enrollment. About 75% of the caregivers were educated more than high school, and 8.2% of them did not receive any formal education. More than half (51/100, 51%) the patients were had upper-middle SES, and (3/100, 3%) had lower SES. Because this study is only in the data entry and data cleaning phase, no impact data are available to report on the study objectives, aims, and hypotheses. The findings are expected to be published in 2024.

Discussion

This quasi-experimental study is expected to give baseline data about the economic burden faced by families who have children living with DMD for the first time in the Southeast Asian region. The PCC model (intervention) developed during the study period is based on individual needs and is a part of standard operating care (SOC). The intervention is mainly focused toward nonambulatory patients, as it is difficult for them to travel to health facilities. The health facility is actively approaching these patients to streamline their disease management and reduce loss to follow-up. Later, we also expect to evaluate whether this PCC model (intervention) can help reduce the financial burden faced by caregivers of children with DMD and help increase the QOL of both patients and their caregivers. The intervention has been designed considering the needs of all stakeholders (patients, parents or caregivers, and health care providers) by conducting group discussions, which are essential for the success of any intervention. The effectiveness of the program will be evaluated by collecting postintervention data.

The care required for a rare disease like DMD is not the same as usual medical care. For rare diseases, the patient- or caregiver-physician relationship grows with time, along with an evolution in the knowledge of the disease and its management strategies. As the disease outcomes and management are formative, the health care provider must inform and engage patients and their caregivers as an interactive partner to encourage compliance and adherence to the SOC. Most of the time, treatment seeking by the patients is limited by scarce knowledge about the disease, lack of availability of appropriate multidisciplinary health care, and limited access to treatment modalities [49]. The involvement of multiple disciplines is often overlooked by the health care sector. In addition to medical management, self-care, as well as caregiving by the patients' parents, is very important. Patient engagement when managing a disease is very promising, as the patient takes ownership of his or her health. PCC is one such intervention that ensures patient involvement. Patient or family engagement improves health outcomes and reduces OOP health expenditures. Patient engagement, health outcomes, and health expenditure depend

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on the health care delivery system of the geographical region. The way that the health care delivery system functions depends on preferences, values, cultural traditions, and socioeconomic conditions in a given region [50].

The model will have more geographical coverage through teleconsultation, especially considering the COVID-19 era where travelling is restricted. Once the model is proven successful, it can be replicated for managing other chronic rare diseases. Nevertheless, this study has certain limitations, as out study design is noncontrolled, there is no randomization, and a single group is compared before and after the intervention. The experimental conditions may be systematically different across the study time frame. Our study aims to analyze economic burdens among ambulatory patients with DMD visiting the health care facility and are mostly within the age group of 5 to 15 years. However, previous studies have shown that that the maximum financial burden is faced in the later stages of disease (Stage 5, late nonambulatory), but this group is not covered in this study.

There have been studies conducted on QOL and health expenditure for DMD in Europe and North America, but no such study exists from the Asian region. Therefore, the results from this study will contribute to new scientific evidence on effectiveness of PCC for rare diseases in LMICs, where there is a paucity of research on this topic. The study has public health implications in generating evidence on the effectiveness of the intervention by considering patients' involvement in managing DMD. This can guide policy makers on formulating policies or guidelines for a more patient-centric program to manage a chronic, lifelong rare disease not only in India but also in other LMICs as well.

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Conflicts of Interest

None declared.

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Abbreviations

COI: cost of illness
DMD: Duchenne muscular dystrophy
EQ-5D 5L: EuroQoL 5-Dimension questionnaire
HRQOL: health-related quality of life
LMIC: low- and middle-income country
OOP: out of pocket
PCC: patient-centered care
PGIMER: Post Graduate Institute of Medical Education & Research
QoL: quality of life
SES: socioeconomic status

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SOC: standard operating care
VAS: visual analog scale
WHOQOL-BREF: World Health Organization Quality-of-Life

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Protocol

Effectiveness of a Mobile App (PIMPmyHospital) in Reducing Therapeutic Turnaround Times in an Emergency Department: Protocol for a Pre- and Posttest Study

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Abstract

Background: Delays in reviewing issued laboratory results in emergency departments (EDs) can adversely affect efficiency and quality of care. One opportunity to improve therapeutic turnaround time could be to provide real-time access to laboratory results on mobile devices available to every caregiver. We developed a mobile app named "Patients In My Pocket in my Hospital" (PIMPmyHospital) to help ED caregivers automatically obtain and share relevant information about the patients they care for including laboratory results.

Objective: This pre- and posttest study aims to explore whether the implementation of the PIMPmyHospital app impacts the timeliness with which ED physicians and nurses remotely access laboratory results while actively working in their real-world environment, including ED length of stay, technology acceptance and usability among users, and how specific in-app alerts impact on its effectiveness.

Methods: This single-center study of nonequivalent pre- and posttest comparison group design will be conducted before and after the implementation of the app in a tertiary pediatric ED in Switzerland. The retrospective period will cover the previous 12 months, and the prospective period will cover the following 6 months. Participants will be postgraduate residents pursuing a ≤6-year residency in pediatrics, pediatric emergency medicine fellows, and registered nurses from the pediatric ED. The primary outcome will be the mean elapsed time in minutes from delivery of laboratory results to caregivers' consideration by accessing them either through the hospital's electronic medical records or through the app before and after the implementation of the app, respectively. As secondary outcomes, participants will be queried about the acceptance and usability of the app using the Unified Theory of Acceptance and Use of Technology model and the System Usability Scale. ED length of stay will be compared before and after the implementation of the app for patients with laboratory results. The impact of specific alerts on the app, such as a flashing icon or sound for reported pathological values, will be reported.

Results: Retrospective data collection gathered from the institutional data set will span a 12-month period from October 2021 to October 2022, while the 6-month prospective collection will begin with the implementation of the app in November 2022 and is expected to cease at the end of April 2023. We expect the results of the study to be published in a peer-reviewed journal in late 2023.

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Conclusions: This study will show the potential reach, effectiveness, acceptance, and use of the PIMPmyHospital app among ED caregivers. The findings of this study will serve as the basis for future research on the app and any further development to improve its effectiveness. Trial Registration: ClinicalTrials.gov NCT05557331; https://clinicaltrials.gov/ct2/show/NCT05557331

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International Registered Report Identifier (IRRID): PRR1-10.2196/43695

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KEYWORDS

clinical laboratory information systems; laboratory results; digital technology; emergency department; emergency service; hospital; length of stay; mobile app; mobile health; mHealth; pediatrics; therapeutic turnaround time

Introduction

Background

Emergency department (ED) overcrowding is a global health problem [1], leading to prolonged ED length of stay (ED-LOS). ED-LOS is the time interval between the patient's arrival in the ED for registration or triage to disposition from the ED, either to be admitted to a hospital, discharged home, or transferred to another care setting. ED-LOS is considered as a key indicator of the performance, quality, and operational efficiency of an ED and, more broadly, the entire hospital to which the ED belongs [2]. It also serves as a benchmark metric between institutions. Prolonged ED-LOS, that is, stays exceeding 6 hours (with cutoffs ranging from 4 to 48 hours [3]), can adversely affect efficiency and quality of care, patient outcomes, and patient satisfaction [4].

According to the conceptual input-throughput-output model proposed by Asplin et al [5], ED congestion is partitioned into 3 interdependent components in terms of patient flows into, through, and out of the ED, respectively. The entire laboratory testing process, also known as therapeutic turnaround time (TAT) and part of the throughput component, is a major contributor to prolonging ED-LOS [6,7]. Laboratory tests are ordered in nearly 48% of ED visits [8], and 70% of patient-management decisions are based on these tests [9]. Numerous mitigation strategies to minimize the intralaboratory analytic time, such as laboratory automation and digitalization, have been implemented [10,11]. Yet, it is estimated that up to 96% of the delays that contribute to the therapeutic TAT occur in the pre- and postanalytical phases outside of the central laboratory [12,13]. In the latter case, caregivers' delayed awareness and timely review of available laboratory results have been described as the largest component of perceived therapeutic TAT [11], strongly contributing to prolonged hospital LOS [14]. This delay may be partly related to the fact that busy, multitasking ED physicians and nurses are cognitively distracted from reviewing laboratory results in a timely manner in the absence of individualized, automated real-time prompts. Prompt awareness of results' availability in real time requires health care personnel to regularly access electronic medical records (EMR), leading to incessant and time-consuming trips to computer workstations, thus distracting them from patient care in an extremely challenging and changing environment.

Previous Work

Targeted interventions to reduce the postanalytical TAT phase may contribute to shortening ED-LOS, but mobile digital health solutions to achieve this goal are scarce. In a previous study [15], we described the user-centered development and early technology acceptance evaluation of a mobile app called "Patients In My Pocket in my Hospital" (*PIMPmyHospital*). The app was designed to help ED caregivers obtain relevant information in real time for the patients they care for, including laboratory and imaging results. The app also offers an end-to-end encrypted chat to provide a remote communication channel between caregivers caring for the same patients. In a randomized controlled pilot trial [16], the time required for ED physicians and nurses to review laboratory results after their release was significantly reduced by 92% using the app compared to the usual procedure in a semisimulated model. However, the potential effectiveness of this app in mitigating ED-LOS by taking cognizance of laboratory results in a shorter time frame than usual remains to be evaluated in daily clinical ED practice.

Objectives

In this study, we present the protocol for a pre- and posttest study. Its objective is to evaluate whether the use of the *PIMPmyHospital* app alters ED physicians' and nurses' temporal efficiency to access laboratory results more quickly while actively working in an ED. Temporal efficiency will be assessed by measuring the time between the release of the laboratory results in the clinical information system and their acknowledgment by these clinicians. To our knowledge, no app that can access laboratory results in real time in the ED has been described to date [17]. The study will be structured according to the "Population," "Intervention," "Comparison," and "Outcome" framework as follows: (1) participants: medical and nursing staff working in the pediatric ED; (2) intervention: implementation of the mobile app in the pediatric ED; (3) comparison: remote access to laboratory results in the pediatric ED through the app versus standard access to laboratory results prior to its implementation; (4) outcomes: times to access laboratory results, ED-LOS, technology acceptance, and app's usability among users, and how specific in-app alerts impact on its effectiveness.

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Methods

Study Design

We will conduct an 18-month, single-center, nonequivalent comparison group, pre-post study. We will compare the control and experimental groups on outcome measures before (12-month period) and after (6-month period) the implementation and use of the app. This study protocol adheres to the Standard Protocol Items: Recommendations for Interventional Trials 2013 Checklist [18]. All data will be deidentified. The study will be conducted according to the principles of the Declaration of Helsinki [19] and Good Clinical Practice guidelines [20]. It is our intention to present these at scientific congresses and to publish the results in an international peer-reviewed journal, irrespective of the magnitude or direction of effect. Only deidentified data will be available to researchers for analysis. The study is registered at ClinicalTrials.gov on September 28, 2022 (NCT05557331).

Participants

Eligible participants will be postgraduate residents pursuing a less than 6-year residency in pediatrics, pediatric emergency medicine fellows, and registered nurses from the pediatric ED (aged >18 years). Written informed consent will be obtained from each participant in the experimental group after full information disclosure prior to study participation. On the first day, after completing the informed consent form, participants will be asked to download the app to their personal smartphone through the secure institutional Microsoft Intune portal (Microsoft Corporation). They will then be required to attend a unique standardized 5-minute introduction course to the app and its functionality by the study investigators, but they will not receive specific instructions on how often to use the app. The participants will remain the same throughout the intervention period. No one will be asked to advise on the interpretation of the results.

Setting

The study will take place in the pediatric ED of a tertiary referral and major trauma hospital in Switzerland, with an annual volume of 35,000 visits. This should represent approximately 16,600 visits over the 6-month prospective intervention period, of which approximately one-half could potentially benefit from laboratory tests. The ED has 14 centrally monitored treatment rooms, a resuscitation room, a 5-bed short-term observation room (ie, <24 hours), a plaster room, a hypostimulation room, and a dedicated interview room. The patient population consists of local children from birth to 16 years of age with medical, surgical, and traumatology emergencies, as well as transfer cases from other hospitals in Switzerland or children located in neighboring France.

The usual number of residents is 10 on a monthly basis during a 4-month period. They provide coverage for 6-7 overlapping shifts, which begin at different times, with each shift ranging from 10 hours (9 hours of patient care, 1 hour of recovery) to 12 hours (12 hours of patient care, no recovery time at night) on weekdays and 6 shifts on weekends to cover a 24-hour day (Table 1). During the intervention schedule, residents typically work 3-4 night shifts followed by 72 hours off, then 3-5 consecutive day shifts before 2 days off, followed by 2-day shifts. This pattern repeats throughout the month, with occasional additional days off or vacations. The 14 fellows (some of whom are part-time) work in an irregular combination of 6 overlapping 8-12 hour shifts on weekdays and 3 shifts on weekends (Table 1). Finally, 17 nurses out of a total of 43 cover a 24-hour day. This represents a total coverage of 70-78 hours, 30-48 hours, and 102 hours per day for residents, fellows, and nurses, respectively. The ED uses the Canadian Triage Acuity Scale [21] to guide patient treatment based on medical-surgical urgency. On average, each resident sees about 300 patients per month and fellows 50-70, with a ratio of medicine: surgery-trauma cases of 2/3:1/3. The standard physician-to-patient ratio ranges from 1:5 to 1:7 and varies according to disease acuity and time of the visit. The nurse-to-patient ratio ranges from 1:3 to 1:5. Caregivers see patients on a first-view [22], on-site, 24/7 basis. Whether they work 8-, 10-, or 12-hour shifts, they all work in the same area, have access to the same patient volume, and see the same patient complaints. They have full, secure 24/7 electronic access to laboratory results.

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Table 1. Work shifts by time of day and occupation.

Caregiver and work shift	Count, n	
	Weekdays	Weekend
Residents		
7:45-17:45	1	0
8:00-20:00	1	2
10:00-22:00	1	1
14:00-24:00	1	0
16:00-2:00	1	1
20:00-8:00	1	1
21:00-9:00	1	1
Fellows		
7:30-16:30	1	0
8:00-18:00	1	0
8:00-20:00	0	1
14:00-20:00	1	0
14:30-23:00	1	0
15:30-24:00	1	0
20:00-8:00	1	1
Nurses		
7:00-15:30	5	5
11:30-20:00	1	1
15:00-23:30	6	6
23:00-7:15	5	5

The PIMPmyHospital Mobile App

Information regarding the app has been published previously [16]. In brief, the app was developed iteratively following a user-centered approach starting with the identification of the main functionalities that meet end-user needs [15]. The system operates on a client-server architecture. Four microservices developed on the Java Spring Boot framework ensure (1) transmission of patient information, (2) access to real-time laboratory results, (3) the trigger of push notifications, and (4) exchange of information between caregivers through an instant messaging system. These microservices exchange information with the front end developed in the Angular and Ionic frameworks through a restful app programming interface. Patient medical data are not stored on the app itself, but in the institution's EMR on secure servers to which the app connects. The exchange of data between the app and these servers is secured by the use of JSON web tokens obtained during the authentication of caregivers through a Keycloak identity and access management solution. User authentication on the device relies both on a login password and a specific certificate installed on the user's device. The app runs on Google's Android and Apple's iOS operating systems.

The app's interface features a home page with a personalized view of the patients that each caregiver is taking care of, together with associated information (eg, patient identity, time since admission, and patient's geospatial location within the ED) and clickable actions next to them [16]. In particular, dropdown contextual tabs provide real-time access to laboratory results retrieved from the hospital patient's EMR. Visual push notifications occur as soon as new results are made available. The entire patient management process is available to the caregiver in the palm of their hand and can be accessed at any time while on the go, hence the app's name "Patients in my Pocket."

Procedure and Intervention

This is a pre-post study. Before the implementation of the app, EMR-based data from the past 12 months will be collected retrospectively. These data will include the times (ie, HH:MM:SS) that results issued by the central laboratory were available on the institutional EMR as well as the times at which these results were accessed by caregivers through conventional computerized workstations. After the implementation of the app, data will be collected prospectively over a 6-month period of use. This will include the times (HH:MM:SS) when the results issued by the central laboratory are made available through the app on caregivers' smartphones and access times as well as concurrent or preferred access times on the conventional computerized workstations should this occur. Individual acceptance of the app on the first day (a priori) and then on the last day of the intervention will be evaluated through the Unified

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Theory of Acceptance and Use of Technology (UTAUT) [23]. Usability of the app will be measured by the System Usability Scale (SUS) [24]. Figure 1 shows the study procedure, and Table 2 presents the study schedule. Use of the app will be on a 24-hour basis and at the discretion of participants.

Figure 1. Study procedure. PIMPmyHospital: Patients In My Pocket in my Hospital; SUS: System Usability Scale; UTAUT: Unified Theory of Acceptance and Use of Technology.

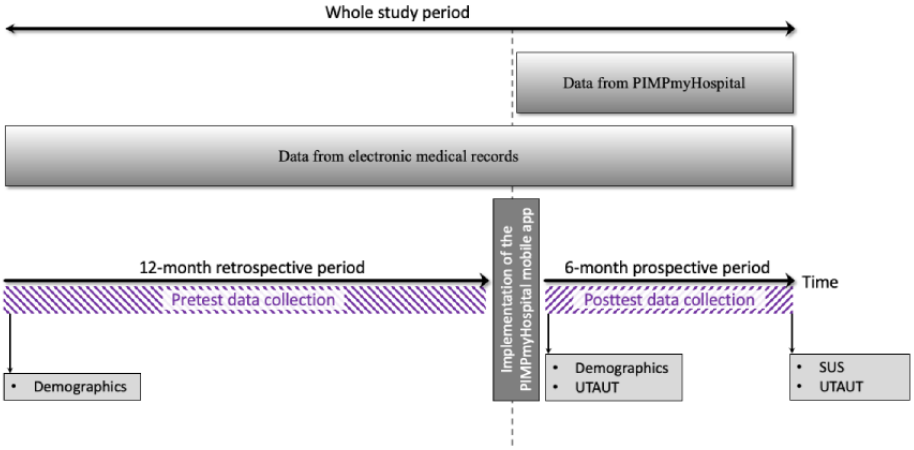


Table 2. Study schedule.

	Study period and time point			
	Pretest ($-t_{12}$)	Enrolment/app implementation (t_0)	Posttest ($+t_6$)	Closeout
Study procedures				
Recruitment		✓[a]		
Eligibility screening		✓		
Informed consent form		✓		
Assessments				
Case report form (demographics)		✓		
EMR[b]-based data	✓	✓	✓	
App-based data		✓	✓	
UTAUT[c]		✓		✓
SUS[d]				✓

[a]✓: Performed.

[b]EMR: electronic medical record.

[c]UTAUT: Unified Theory of Acceptance and Use of Technology.

[d]SUS: System Usability Scale.

Technology Acceptance Terminology and Definition

We use technology acceptance to refer to an initial acceptance of use, as recently defined by Nadal et al [25], to explicitly distinguish between the different temporal stages of technological acceptance. It refers to users' first interactions with the app at the preadoption stage before sustained acceptance of its use in the postadoption stage.

Outcomes and Measures

Primary Outcome: Time to Laboratory Access

The primary outcome will be the mean elapsed time in minutes between the delivery of the laboratory results and the caregiver accessing them, both before and after the implementation of the app.

Secondary Outcome: Technology Acceptance and Usability

The secondary outcomes will be the technology acceptance and usability of the app. The 8-construct, 31-item UTAUT [23] will be used to measure app acceptance and intention to use. This is a 5-point Likert-type scale (1: strongly disagree, 2: moderately disagree, 3: neutral [neither disagree nor agree], 4: moderately agree, and 5: strongly agree). Usability of the app will be measured using the SUS designed by Jordan [24]. According to the International Organization for Standardization, the SUS assesses effectiveness (ie, the ability of users to use the product), efficiency (ie, the effort to use the product), and satisfaction (ie, how the users felt when using the product). It comprises a 10-item questionnaire with 5 response options for each item

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based on their level of agreement, ranging from 1 (strongly disagree) to 5 (strongly agree). According to the scoring system by Jordan [24], for odd-numbered (1, 3, 5, 7, and 9) statements (the positively-worded items), the score contribution is equal to the scale position minus 1 (eg, strongly agree: 5–1=4). For even-numbered (2, 4, 6, 8, and 10) statements (the negatively worded items), the score contribution is equal to 5 minus the scale position (eg, strongly agree: 5–5=0). Each score contribution falls within the range of 0 to 4. Participants' scores for each item are then added up together and multiplied by 2.5 to convert the original scores of 0-40 to 0-100. Although the scores range from 0 to 100, these are not percentages of usability. The higher the score, the better the usability. To obtain a SUS score of 100, the respondent must answer 5 to all odd questions and 0 to all even questions. The original SUS items are presented in Multimedia Appendix 1. When translating the SUS questionnaire from its original version to French [26], we replaced the general term "system" with the specific term *PIMPmyHospital*. Another secondary outcome will be the mean ED-LOS per patient measured from the point when patients are triaged in the ED to discharge from the ED, defined as patients leaving the ED, whether admitted to the intensive care unit or ward, transferred to another hospital for admission, discharged home, or those who left without being seen. These data will be extracted from the hospital administrative electronic database. Finally, we will determine whether specific alerts, such as a flashing icon or sound for reported pathological values of laboratory results, have an impact on the results.

Data Transfer, Safety, and Privacy

Access to the app is controlled through a 2-factor authentication process. An enterprise environment is created on the health care smartphone using the Microsoft Intune software (Microsoft Corp.), for both Android and iOS operating systems. This environment ensures that the app is run in a secure context where only an authorized app can be installed. This environment also enables the installation of a certificate that serves as a second authentication factor, while the first factor is the user's login and password. Access rights are managed by the Active Directory group, which enables access to ED caregivers only. All data collected by the app are transmitted securely through a hypertext secure transfer protocol and stored exclusively on the hospital's secured internal server.

Data Collection

Electronic data will be extracted from the institutional data lake. The data lake stores all data and events from the EMR information system in a database and can be retrieved using Simple Protocol and RDF Query Language (SPARQL) queries. In the preintervention period, the time stamp of the laboratory results on the EMR will be identified as the time of issuance of the said results. Access to these results by the physicians and nurses will be defined by the time stamp of the first access to the laboratory results' viewer on the EMR. Access to results on the app will be computed either by the time stamp of the push notification access or to the dedicated page on the app. No other patient-level data such as identifiers or clinical characteristics will be collected. Collected data will be transmitted to the REDCap database web app (REDCap, Vanderbilt University) hosted by the hospital for analysis.

Blinding

Although neither the participants nor the study investigators can be blinded to the intervention, both will be blinded to the results of the study until their final analysis by the statistician. Participants will be informed only of the overall purpose of the study, which is to evaluate the effects of the app on quality of care, but not about the aim of reducing the time to access laboratory results in order to minimize bias. The statistician will remain blinded to allocation until the final analysis.

Sample Size

Physicians in the pediatric ED see on average 900 patients over 3 months. Assuming an intraclass correlation of 0.1 in time between delivery of the laboratory results and the caregiver accessing them, 5253 individual patients are required to have a 90% chance of detecting, as significant at the 5% level, a decrease in a time difference of 0.5 SD. This represents approximately 18 physicians including 100 patients per month over 3 months. In order to obtain 18 physicians, we will recruit physicians over 2 consecutive rotation periods.

Statistical Analysis

The association of app use with the time between delivery of the laboratory results and their access by caregivers will be assessed using generalized estimating equations with an exchangeable correlation structure to account for the nested structure of the outcome (ie, time) within the physicians. To account for potential differences in case-mix and physician characteristics, we will use multivariable generalized estimating equations. The covariates will be as follows: (1) the triage acuity scale, (2) type of pathology (medical, surgical-traumatological, psychiatric), (3) experience of the caregiver expressed in years since certification, (4) patient age, (5) patient sex, (6) workload represented by the number of patients present in the emergency room, (7) time of day or night, (8) day of the week, and (9) month of the year (seasonal variability). To account for the possible effect of exogenous factors that would impose an asymmetry in the data (skewness on the right) by extending the awareness of laboratory results, we will identify these factors as the study progresses prospectively and take them into account in the final analysis. The same analyses will be performed for the nurses. We will carefully monitor and evaluate through descriptive analyses any differences between nurses' and physicians' frequency access to laboratory results. If the target sample size cannot be reached, we will first extend the prospective data collection period by 3 months (deemed ethically acceptable as not impacting patients) or present only the results of qualitative user experience interviews.

For the technology acceptance self-administered survey questionnaire, scores on the 8 technology acceptance constructs will be described using descriptive statistics. Items on the SUS questionnaire will be described using frequencies. Analyses will be carried out using R software (R Core Team) [27]. All statistical tests will be 2-sided, with an α risk of .05.

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Ethics Approval

The study protocol received a declaration of no objection by SwissEthics on October 18, 2022 (Req-2022-01156), which stated that the need for approval was waived as its purpose was to examine the effect of the intervention on health care providers and thus it does not fall within the scope of the Swiss Federal Law on Human Subject Research, with a waiver of written informed consent.

Data available to research team members will only contain deidentified, coded information. All records that contain personal identifiers, such as consent forms and UTAUT and SUS questionnaires, will be stored separately from study records. Each participant file will be identified by a code number. Study data will not be released to any other individual outside the research team. Only deidentified data will be published and available to researchers for analysis. There will be no financial compensation or incentive for participants.

Dissemination Policy

Only study investigators will have the right to access and analyze the data for dissemination purposes. The principal investigator will oversee dissemination activities to ensure that team members with the necessary subject matter expertise are involved in every aspect of dissemination. We plan to disseminate the results of this study through peer-reviewed publications, conferences, as well as other avenues as appropriate, regardless of the findings.

Results

Retrospective laboratory data will be arbitrarily collected from October 31, 2021, to October 31, 2022. Prospective data will be collected from the start of enrollment on November 1, 2022, through April 30, 2023. We anticipate an analysis of the results by mid-2023 and expect the results to be published in late 2023.

Discussion

Strengths and Perspectives With the Existing Literature

To the best of our knowledge, there are no previous studies describing the effectiveness of a mobile app to provide real-time mobile access to laboratory results in EDs [17]. This study protocol is the first to propose the exploration of the potentially beneficial effect of such an app on the reduction of therapeutic TAT and its acceptance and usability by end users. The study investigators anticipate that implementation of the app will shorten times to consideration of laboratory results among participants who use it compared to those who have not used it previously. We plan to generate a stronger evidence base for a broader implementation of dedicated mobile apps for remote, real-time access to laboratory results in EDs. We also expect good acceptance of the app as well as good usability. One of the strengths of this study is the use of an app whose iterative design and development involved a multidisciplinary end user–centered approach [15]. In addition, the app's ability to reduce the time taken by pediatric ED caregivers to consider laboratory results has already been the subject of a randomized controlled pilot trial in a semisimulated ED environment [16]. This study will attempt to verify its encouraging results in a real environment with its spatial and temporal constraints and inherent human factors.

In terms of implications, the use of dedicated mobile apps could represent a paradigm shift where information would come directly and synchronously to caregivers rather than having to travel to retrieve it. A shorter TAT for the postanalytical phases could be associated with a shorter ED-LOS and thus improve the quality of care and patient satisfaction. Moreover, such a solution could be extended to other care units where the use of mobile apps would make it possible to get rid of the distances and delays to access laboratory results.

Limitations

This study has some limitations. First, participants who agree to be prospectively enrolled may be interested or engaged in digital health promotion in general and mobile technologies in particular, influencing their a priori motivation to use the app. If so, this should be reflected in the UTAUT questionnaire, which is an outcome of interest. Second, the study will be conducted in a pediatric ED, which may limit the generalizability of the findings to adult EDs. For example, the acuity of age-specific diseases may imply a different awareness in the consideration of laboratory results. Other limitations may be identified during the study itself and will be noted after their identification.

Conclusions

Our intervention can serve as a foundation for a broader implementation of supportive mobile apps for in-hospital caregivers to improve the timely availability of EMR-derived results and the efficiency of care by reducing therapeutic TAT and ED-LOS.

Acknowledgments

We are grateful to Rosemary Sudan (freelance technical editor) for providing editorial assistance. This study received no funding.

Data Availability

Data sharing is not applicable to this paper as no data were generated or analyzed during the preparation of this protocol. The final data sets established and analyzed during the study will not be publicly available. An anonymous copy of the final data sets underlying publications resulting from this study will be available from the corresponding author upon reasonable and approved request.

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Authors' Contributions

FE was responsible for the concept and design of the study, responsible for the literature search, and drafted the manuscript. CT and RR contributed to the critical review of its content with the support of RT, AB, and MR. DSC contributed to the design and statistical analysis plan of the study and contributed to the drafting of the manuscript. FE was responsible for the development of the project software with the support of RT, AB, MR, and JNS. FE and JNS oversaw the development of the project software. JNS was the main study coordinator, responsible for the concept and design of the study, responsible for the overall conduct of the study, and drafted and oversaw the writing of the manuscript. All authors have contributed to, seen, and approved the final submitted version of the manuscript and take responsibility for the integrity of the data and the accuracy of the data analysis. The corresponding author (JNS) confirms that he will have full access to participants' data and endorses the final responsibility for the submission. He further affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted, and that any deviations from the study plan will be explained.

Conflicts of Interest

FE and JNS are owners of the PIMPmyHospital app. The app is currently not commercially available. FE, RT, AB, MR, and JNS declare individual intellectual property rights on this app and, as employees of Geneva University Hospitals, indirect institutional rewarding through its potential future commercialization (without personal enrichment). The authors declare no other relationships or activities that could appear to have influenced the submitted work. All authors have completed the International Committee of Medical Journal Editors uniform disclosure form and declare no support from commercial entities for the submitted work, and no financial relationships with any commercial entities that might have an interest in the submitted work in the previous 3 years.

Multimedia Appendix 1
The System Usability Scale. Adapted from Jordan [24].
[DOCX File , 16 KB - resprot_v12i1e43695_app1.docx]

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Abbreviations

ED: emergency department
ED-LOS: emergency department length of stay
EMR: electronic medical record
PIMPmyHospital: Patients In My Pocket in my Hospital
SUS: System Usability Scale
TAT: therapeutic turnaround time
UTAUT: Unified Theory of Acceptance and Use of tTechnology

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Protocol

Exploring the Efficacy of a Set of Smart Devices for Postural Awareness for Workers in an Industrial Context: Protocol for a Single-Subject Experimental Design

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Abstract

Background: In manufacturing industries, tasks requiring poor posture, high repetition, and long duration commonly induce fatigue and lead to an increased risk of work-related musculoskeletal disorders. Smart devices assessing biomechanics and providing feedback to the worker for correction may be a successful way to increase postural awareness, reducing fatigue, and work-related musculoskeletal disorders. However, evidence in industrial settings is lacking.

Objective: This study protocol aims to explore the efficacy of a set of smart devices to detect malposture and increase postural awareness, reducing fatigue, and musculoskeletal disorders.

Methods: A longitudinal single-subject experimental design following the ABAB sequence will be developed in a manufacturing industry real context with 5 workers. A repetitive task of screw tightening of 5 screws in a standing position into a piece placed horizontally was selected. Workers will be assessed in 4 moments per shift (10 minutes after the beginning of the shift, 10 minutes before and after the break, and 10 minutes before the end of the shift) in 5 nonconsecutive days. The primary outcomes are fatigue, assessed by electromyography, and musculoskeletal symptoms assessed by the Nordic Musculoskeletal Questionnaire. Secondary outcomes include perceived effort (Borg perceived exertion scale); range of motion of the main joints in the upper body, speed, acceleration, and deceleration assessed by motion analysis; risk stratification of range of motion; and cycle duration in minutes. Structured visual analysis techniques will be conducted to observe the effects of the intervention. Results for each variable of interest will be compared among the different time points of the work shift and longitudinally considering each assessment day as a time point.

Results: Enrollment for the study will start in April 2023. Results are expected to be available still in the first semester of 2023. It is expected that the use of the smart system will reduce malposture, fatigue, and consequently, work-related musculoskeletal pain and disorders.

Conclusions: This proposed study will explore a strategy to increase postural awareness in industrial manufacturing workers who do repetitive tasks, using smart wearables that provide real-time feedback about biomechanics. Results would showcase a

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novel approach for improving self-awareness of risk for work-related musculoskeletal disorders for these workers providing an evidence base support for the use of such devices.

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KEYWORDS

smart wear; smart health; occupational safety; motion sensing; devices; awareness; posture; fatigue; biomechanics; musculoskeletal disorder; smart device; pressure sensing

Introduction

The agenda for decent work, initially promoted by the World Labor Organization, and recently connected to the sustainable development goals of the United Nations [1], includes safety and security at work as one of its strategic axis [2]. The quest to fulfill this axis also reflects the increased demand from consumers regarding concerns about the development of fair and sustainable products. In the same line of concerns, some companies issue bonds incorporating the fulfillment of objectives related to the reduction of accidents at work [3]. Thus, the opportunities offered by the technological developments of the so-called Industry 4.0 could positively influence the indicators related to this set of objectives and concerns, namely with regard to musculoskeletal injuries. Musculoskeletal disorders (MSDs) are the most prevalent work-related health issues and one of the most critical public health problems worldwide [4,5]. Work-related musculoskeletal disorders (WMSDs) are mainly caused by the execution of work tasks and the environment in which work is performed [4]. In the manufacturing industries, tasks requiring excessive force, poor posture, high repetition, and long duration, which induce fatigue and which are stressful, lead to an increased risk of MSDs [4,6,7]. The consequences of WMSDs have a significant and wide-ranging financial impact on both the social and individual levels [8]. In Europe, about 3 of every 5 workers report MSDs. In assembly and manufacturing workers, the most common types of MSDs reported are back pain (55%) and muscular pain in the neck, shoulder, and upper limbs (47%), followed by the lower limbs (33%) [4]. MSDs are responsible for 15% of the total number of (disability-adjusted) life years. Furthermore, more than half (53%) of the workers with MSDs report work absenteeism. Therefore, a high burden on the economy and health care systems is not surprising. In addition, the individual, coworkers, and families are also affected, directly or indirectly, by the injured workers with an associated decrease in physical and mental health and quality of life [9,10].

Due to the high prevalence of musculoskeletal complaints and diseases, and the high associated burden, a significant effort has been made in the prevention of WMSDs [10]. Assessing exposure to risk factors of WMSDs is among the most successful strategies [11]. One of these emerging approaches is wearable devices [11-14]. These are rapidly developing, fostering the promotion of individual healthier lifestyles. Smart workwear is technology embedded into clothing that contacts the skin. This technology can monitor heart rate and movement delivering holistic information on fatigue and body stress. The real-time feedback of data provided can enhance the monitoring of health status, perhaps enabling earlier diagnosis or, in turn, hastening the integration of injury and illness prevention strategies [13,15]. Thus, comfortable smart workwear with movement and posture monitoring seems an adequate solution for the assessment of WMSDs risk and prevention of WMSDs. Although recent advances have been made in posture assessment and monitoring, few studies focus on compensatory adaptations that provide feedback to the user [16,17]. Injury prevention, due to inadequate posture or muscle fatigue, may be engaged with educational information and biofeedback delivered to the operator in real-time conditions or at strategically selected intervals of time during the work shift. Providing individual feedback to the worker may help decrease the exposure of individual workers to ergonomic risk factors and consequently, injury [18].

Thus, this study protocol aims to detect muscle fatigue related to repetitive activities and to explore a smart wear system for correcting biomechanics and reducing fatigue. The system involves the use of a wearable sensorized jacket and shoes and real-time feedback delivered to the worker. This system was created with the aim of preventing the unconscious development of awkward postures, compensatory movements, and fatigue, predisposing to injuries over time. The system will be tested through a single-subject experimental design with human subjects performing a repetitive task in real industry settings. The development of research in a real context on the factory floor raises different challenges. One of these challenges concerns the interference that investigation activities make in the normal production cycle. Thus, the methodological options should consider the least possible impact for the typical activities carried out there. In this sense, within the range of experimental work options, a single-subject experimental design will be able to contribute to these requirements.

Methods

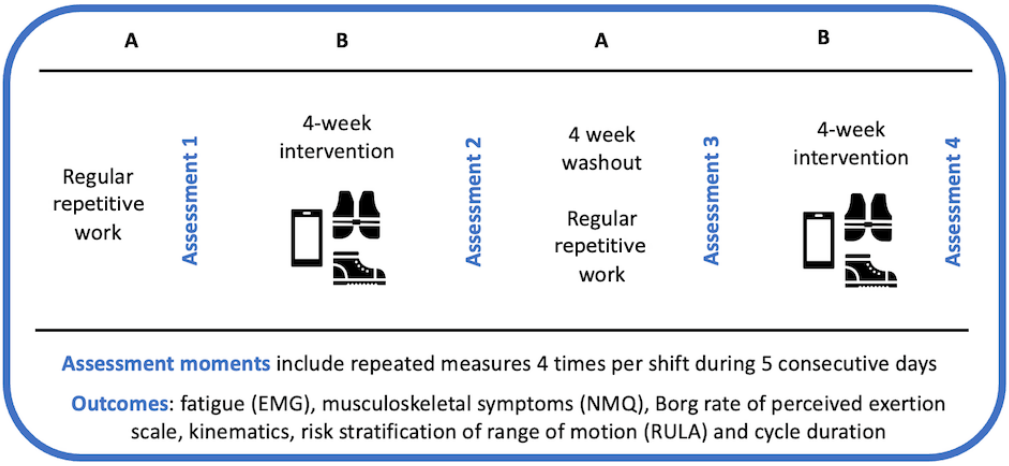
Design and Setting

A longitudinal single-subject experimental design following the ABAB sequence [19] will be developed in a manufacturing industry real context. In the ABAB design, first, a baseline is determined (A), then the intervention is introduced, with the use of the smart wear and real-time feedback to the worker for the first time (B). Next, the intervention is withdrawn, returning to the baseline condition (A). Finally, after baseline stability is reestablished, the intervention is presented (B) for the second time [1,2]. All 4 periods will end with an assessment of the selected outcomes. Figure 1 depicts the study flow. Generally, in this study design, the research is done very thoroughly on 3

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to 5 subjects. The interest is always in the meticulous examination of each participant individually, not in the group's average performance. Multiple single-subject experimental studies also present the opportunity to consider not only the individual variables but also analyze the trial at the environmental level [19,20].

Figure 1. Study flow diagram. EMG: electromyography; NMQ: Nordic Musculoskeletal Questionnaire; RULA: Rapid Upper Limb Assessment.



Ethics Approval and Consent to Participate

All participants will give informed consent to participate. All procedures are handled according to the Declaration of Helsinki and regulatory legislation, which includes approval by an ethics committee. The protocol is under review by the Ethics Committee of the University of Aveiro (17-CED/2023). Data will be processed complying with the European General Data Protection Regulation.

Participants, Eligibility, and Recruitment

This study will include 5 active workers from an industrial manufacturing setting of household appliances in the Region of Aveiro, Portugal. To be included, workers must be aged between 35 and 45 years and have a work experience with the tested workstation for at least 6 months. Exclusion criteria are (1) history of vestibular disorders, (2) neurological, respiratory disease, or spinal surgery, (3) structural spinal problems, (4) medication or a health condition affecting balance, and (5) regular treatments for a musculoskeletal condition.

The workers will be recruited by the occupational health department, which will provide the identification numbers of each selected worker as well as shoe and clothing sizes.

Study Procedure

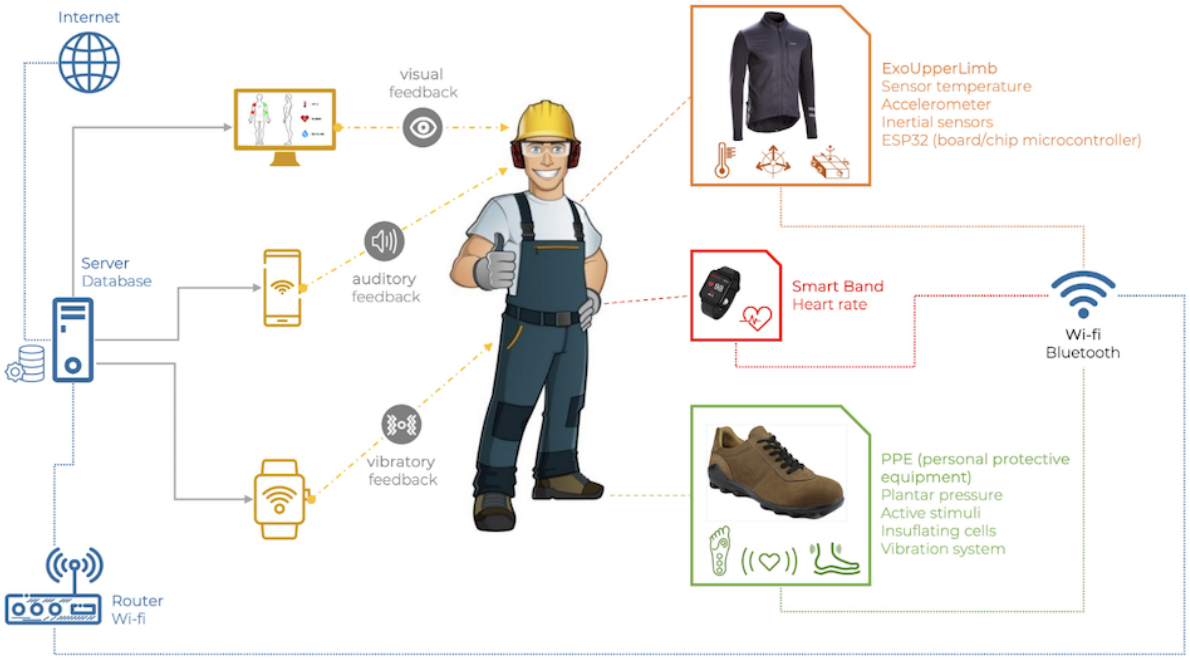
A specific task representing a repetitive movement was chosen. The task consists of the vertical screw tightening of 5 screws in a standing position into a piece placed horizontally. A first assessment period will be executed to analyze baseline repetitive work (A) outcomes. Subsequently, the workers will use the smart wearables and be provided with real-time feedback for 4 weeks (B). A second assessment (assessment 2) will be performed to explore the efficacy of the system. Afterward, the workers will have a washout period of 4 weeks to reestablish baseline repetitive work condition (A), followed by assessment 3. Finally, a second 4-week period of intervention (B) and consequent assessment 4, will take place (Figure 1). Each assessment moment will be accomplished in 5 consecutive days, in 4 periods of the day, which includes measurements for each period of 5 cycles of the performed task in the first 10 minutes after starting the shift (to avoid the warm-up period), 10 minutes before the break time, 10 minutes after the break, and 10 minutes before the end of the day's shift. All tests will be performed guaranteeing that in the anterior 48-hour period each individual did not participate in strenuous physical activities, which may affect the selected outcomes.

Smart Wearable Systems

The smart wearable systems consist of a sensorized jacket, smart footwear, a smart band, and a feedback system provided to the worker. The sensorized jacket aims to monitor the upper limb (shoulder flexion/extension and abduction/adduction and elbow flexion/extension) and trunk (lumbar flexion/extension) with strategically placed inertial measurement unit (IMU) systems and body temperature with a temperature sensor. Smart footwear consists of a shoe equipped with a set of 6 sensors Force Sensitive Resistors (Sensitronics), to map plantar pressures. The sensors have a 30-mm diameter and work in a 0-300–N force range. They were assembled in a custom substrate printed by RokuPrint (RP 2.2, RokuPrint GmbH). A smart band will monitor heart rate. The main system architecture is presented in Figure 2.

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Figure 2. Main system architecture. PPE: Personal Protective Equipment.



Data Collection and Outcomes

The primary outcomes are fatigue and musculoskeletal symptoms. Fatigue will be assessed by electromyography (EMG) and musculoskeletal symptoms by the Nordic Musculoskeletal Questionnaire [21].

Secondary outcomes include perceived effort, assessed by the Borg Rating of Perceived Exertion (RPE), range of motion of the main joints in the upper body and trunk, speed, acceleration, and deceleration of movement, through motion analysis, risk stratification of range of motion of the upper limb and trunk based on limits defined in the Rapid Upper Limb Assessment (RULA) [22], and cycle duration in minutes.

For patient characterization, baseline questionnaires including sociodemographic data, physical activity level, quality of life, anxiety and depression, insomnia and sleep quality, fatigue, and pain and disability will be collected. Table 1 displays the assessment flow.

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Table 1. Assessment flow.

Measurements	Initial measurement	At the start of the shift	During the shift	After the end of the shift
Sociodemographic information and habits	✓			
Quality of life—EUROHIS-QOL-8	✓			
Musculoskeletal pain (NMQ[a]) and adapted NMQ	✓	✓		✓
Physical activity (RAPA[b])	✓			
Anxiety (GAD-7[c]) and depression (PHQ-9[d])	✓			
Subjective fatigue (FACIT-F[e])	✓			
Sleep quality (BaSIQS[f])	✓			
Heart rate			✓	
Joint range of motion			✓	
Ergonomic risk (RULA[g])			✓	
Electromyography			✓	
Perceived exertion (RPE[h])		✓	✓	✓

[a]NMQ: Nordic Musculoskeletal Questionnaire.

[b]RAPA: Rapid Assessment of Physical Activity questionnaire.

[c]GAD-7: General Anxiety Disorder 7-item scale

[d]PHQ-9: Patient Health Questionnaire-9.

[e]FACIT-F: Functional Assessment of Chronic Illness Therapy—Fatigue.

[f]BaSIQS: Basic scale on insomnia complaints and quality of sleep questionnaire.

[g]RULA: rapid upper limb assessment.

[h]RPE: rate of perceived exertion.

Instruments

Electromyography

EMG recording will be conducted using the Cometa EMG wireless portable system (Covidien Kendall) with disposable silver 24-mm surface electrodes. Electrode application will proceed following the recommended procedures of skin preparation: shaving of the area; rubbing and cleaning with alcohol; following a 10-minute resting time to reduce skin impedance [23]. The EMG electrodes will be placed according to manufacturer's recommendations on the upper trapezius, posterior deltoid, triceps medial, biceps brachii, the lumbar portion of the erector, biceps femoris, tibialis anterior, and gastrocnemius. All trials will be visually examined for signal quality and measurement errors. Muscle activity data will be collected with a sampling rate of 2000 Hz. EMG data will be processed with a customized MATLAB script (R2017b, MathWorks), where a fourth-order Butterworth band-pass filter from 10 to 500 Hz will be applied to minimize the appearance of electromyographic artifacts [24]. EMG signal will be normalized using a method that divides each point that constitutes the processed EMG by the peak value acquired from the same EMG. The root-mean-square of the EMG data and the averaged rectified value will be calculated to determine the signal amplitudes. Muscle fatigue will be characterized by median frequency and amplitude.

Motion Analysis

A 3D biomechanical motion analysis for kinetics and kinematics parameters will be recorded with the Vicon-Nexus 3D motion capture system (Vicon Vero, v2.2). Reflective markers (clusters) will be placed on the midpoint between the left shoulder and left elbow, the midpoint between right shoulder and right elbow, the midpoint between the left elbow and left wrist, the midpoint between the right elbow and right wrist, and seventh cervical vertebra and sacral region (midpoint between right posterior superior iliac and left posterior superior iliac) [25]. Additional markers will be placed on the screwdriver (top of the shaft) by the same experienced examiner. 3D marker trajectory data will be collected at 100 Hz with 6 cameras. Before starting the calibration, all reflective objects will be removed from the workspace so that they do not interfere with the recording. Necessary care will be taken to warrant that the worker's clothing is also nonreflective [26]. Prior to the assessment of the subjects, the workstation will be prepared following the recommended procedures of calibration of both optical and video reference cameras according to the manufacturer's recommendations manual. The kinematic variables of interest are the range of motion of the neck, trunk, shoulder and elbow, speed, acceleration, and deceleration. The range of motion will be calculated as the maximum minus minimum joint angle in each selected sample.

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Questionnaires

Overview

For all the questionnaires, the Portuguese-validated version will be used.

Musculoskeletal Symptoms

To assess MSDs and symptoms associated with the working population, the Nordic Musculoskeletal Questionnaire will be used [21]. This questionnaire encompasses 27 questions (3 questions related to the 9 anatomical regions: neck, shoulders, wrists/hands, upper back, low back, hips/thighs, knees, and ankles/feet) with a binary response (yes or no) and a question to rate pain on a numerical scale [21]. This questionnaire presents a good test-retest reliability and good internal consistency [21]. To assess musculoskeletal symptoms before and after the shift on evaluation days, only the first question will be used and adapted for the recall period; instead of the last 12 months, a period of the last 8 hours will be considered.

Perceived Exertion

The Borg RPE scale is a tool for measuring an individual's effort and exertion, breathlessness, and fatigue during physical work and so is highly relevant for occupational health and safety practice. In this scale, 6 corresponds to "No Effort" and 20 corresponds to "Extremely Hard" [27].

Ergonomic Risk

The RULA was selected to assess ergonomic risk in this study. This tool was developed to assess workers' exposure to ergonomic risk work associated with musculoskeletal injuries of the upper limbs, taking into consideration biomechanical and postural load requirements of work task demands on the neck, trunk, and upper limbs. This instrument provides a simple scoring method based on the range of motion, which can identify joints at risk. The output of the RULA assessment tool is the final RULA score, which is a single score that represents the level of MSD risk for the job task being evaluated, ranging from a minimum of 1 to a maximum of 7 points [22].

Physical Activity Level

The level of physical activity will be assessed with the Rapid Assessment of Physical Activity questionnaire (RAPA). This version presents good internal and construct validity [28]. The RAPA evaluates the level and intensity of leisure-time physical activity, as well as strength and flexibility training in a 9-item, self-administered questionnaire [28].

Quality of Life

Participants' quality of life will be assessed with the Portuguese version of the EUROHIS-QOL 8-item index questionnaire [29]. This questionnaire presents a good internal consistency, test-retest reliability as well as construct, discriminant, and convergent validity [29]. In this quality-of-life measure, each of the domains (physical, psychological, social relationships, and environment) is represented by 2 items. The result is a global index, calculated from the sum of the 8 items, with a higher value corresponding to a better perception of quality of life [30].

Depression and Anxiety Symptoms

The Patient Health Questionnaire-9 (PHQ-9) will be used to assess signs of depression [31]. This tool reports to the last 2 weeks and consists of a depression module with 9 items, using a 4-point response scale, ranging from "0" (not at all) to "3" (nearly every day). The PHQ-9 presents good internal consistency, convergent validity, and criterion validity. Total scores of 5, 10, 15, and 20 represent cut points for mild, moderate, moderately severe, and severe depression, respectively [32]. Anxiety-related signs and their severity will be assessed by the General Anxiety Disorder 7-item scale (GAD-7) [33]. The GAD-7 index is obtained by adding the scores from the questionnaire, after having assigned 0 to 3, depending on the severity. The cutoff points 5, 10, and 15 classify the anxiety as none/normal (0-4), mild (5-9), moderate (10-14), and severe (15-21). In general, anyone who scores 8 or above can be considered as having significant anxiety symptoms [34]. This scale presents cultural adaptation, excellent internal consistency, internal validity, and very good reliability [33].

Sleep Quality

The Basic Scale on Insomnia Complaints and Quality of Sleep (ie, BaSIQS) questionnaire is based on a set of 7 questions assessing nocturnal experiences in terms of subjective sleep quality and symptoms of insomnia [35]. Except for the final 2 items, which are scored on a reversed 5-point Likert scale, all items are scored on a scale of 0 to 5, with higher scores indicating poorer sleep. The results on reliability, validity, and accuracy support the use of this questionnaire for research and practical purposes [35].

Subjective Fatigue

Fatigue will be assessed with the Functional Assessment of Chronic Illness Therapy- Fatigue. This 13-item tool measures an individual's level of fatigue during their usual daily activities over the past week. Scoring is based on a 4-point Likert scale (4=not at all fatigued to 0=very much fatigued), with a ranging total score of 0 to 52 (0=worst possible score; 52=best possible score indicating no fatigue) [36]. This questionnaire presents high internal consistency, good convergent and divergent validity, and satisfactory test-retest reliability [37].

Data Management and Monitoring

The collection and data storage will be made in digital format, including those from the questionnaires. The entered data will be checked for completeness, validity, and plausibility by a member of the research team.

Data Analysis

Structured visual analysis techniques will be conducted to observe the effects of the intervention using a Single-Case Visual Analysis package for R. Graphical (RStudio) representations of data for each participant will be plotted considering primary and secondary outcomes on the y-axis and time on the x-axis. The results for each variable of interest will be compared in-between the different time points of the work shift and longitudinally considering each assessment day as a time point.

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For each outcome (primary or secondary) and each moment mean, median, range, and stability envelope will be calculated. The level of change and difference between the first and last values of each period will be compared. The next step includes the calculation trend using the split middle method of trend estimation. After this procedure, percent of data points within the stability envelope (80% of data points between ±25% of median) will be considered. The final step is using the "freehand method" to evaluate data path [38].

Results

Enrollment for the study will start in April 2023. We plan to complete the post assessments of the last worker in April 2023. The results are expected to be available still in the first semester of 2023.

Discussion

Significance of the Study

Given the high prevalence of WMSDs and the associated economic and personal burden, preventive measures such as smart wear for monitoring and providing feedback are crucial. The smart wearables analyzed under this study aim to create awareness of WMSDs risk and empower the worker to reduce the associated risk and have a healthier work environment and higher quality of life. Investing in preventive measures is especially rewarding, since workers in countries and sectors where more preventive measures are in place are less likely to report MSD complaints [10]. Consequently, preventive measures result in an increase in economic benefits for the industries with greater production and worker adherence to these jobs.

The proposed study is, to our best knowledge, one of the first to use devices that provides real-time feedback to industrial workers about posture. This real-time feedback will include the body location at risk, which can lead to the correction of body biomechanics. Posture and movement monitoring technology can help detect and subsequently reduce the compensatory movement patterns, promoting a decrease in fatigue and musculoskeletal symptoms.

Strengths and Limitations

This study is a single-case experimental design. This method design was primarily developed to assess individual behavior. Given the main goal is to develop and test smart wear for reducing fatigue and poor biomechanics, a single-subject approach seems adequate. This design enables the possibility of rapidly determining if the wearables are effective. Immediate changes can be observed firsthand, quickly, and in individual participants. Consequently, adjustments can be rapidly made, if necessary. Contrary to the single-subject approach, a large sample statistical approach will require weeks or months of participant testing, mean calculations, and statistical analyses before the effectiveness may be determined. Conceptually, the treatment condition must influence individual behavior and assure both research intra- and interparticipant replication. Therefore, an ABAB design will be executed, assuring both intra- and interparticipant intervention and control [38]. Graphical analysis of the variability of each outcome, in each of the repeated measures in time, will be performed to explore the possible indicators of fatigue when performing the selected activity.

Conclusions

This proposed study will explore a strategy for reducing fatigue and musculoskeletal symptoms in industrial workers, possibly preventing WMSDs, using smart wearables that provide real-time feedback about biomechanics. Results would showcase a novel approach for improving postural awareness and self-awareness of risk for WMSD providing an evidence-based support for the use of such devices. Further research could explore other health indicators and individualized approaches to prevent similar health risks.

Acknowledgments

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Data Availability

The data sets generated during and analyzed during the current study are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

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Abbreviations

EMG: electromyography
GAD-7: General Anxiety Disorder 7-item scale
MSD: musculoskeletal disorder
PHQ-9: Patient Health Questionnaire-9
RAPA: Rapid Assessment of Physical Activity questionnaire
RPE: rating of perceived exertion
RULA: risk stratification of range of motion
WMSD: work-related musculoskeletal disorder

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Protocol

A Mobile Self-control Training App to Improve Self-control and Physical Activity in People With Severe Mental Illness: Protocol for 2 Single-Case Experimental Designs

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Abstract

Background: Lack of physical activity is a common issue with detrimental consequences for the health of people with severe mental illness (SMI). Existing physical activity interventions show suboptimal effects as they require substantial cognitive skills, including goal setting and writing, whereas cognitive deficits are common in this population. To bolster the effectiveness of physical activity interventions, self-control training (SCT), in which users practice the ability to override unwanted thoughts and behaviors, can be used in addition. Recent research has demonstrated the initial effectiveness of a mobile SCT app, but this has not been studied in psychiatric clinical practice.

Objective: This study aims to evaluate to what extent adding a mobile SCT app designed for and with people with SMI to a mobile lifestyle intervention aimed at increasing physical activity increases physical activity and self-control levels.

Methods: A mixed methods approach incorporating 2 single-case experimental designs (SCEDs) and qualitative interviews was used to evaluate and optimize SCT. Overall, 12 participants with SMI will be recruited from 2 organizations offering outpatient and inpatient care to people with SMI. Each experiment will include 6 patients. SCED I is a concurrent multiple-baseline design across participants that explores initial effectiveness and optimal intervention duration. Using accelerometry and experience sampling questionnaires, participants' physical activity and self-control will be monitored for ≥5 days from baseline, followed by the sequential introduction of Google Fit, the physical activity intervention, for 7 days and the addition of SCIPP: Self-Control Intervention App for 28 days. SCED II is an introduction/withdrawal design in which optimized SCT will be introduced and withdrawn to validate the findings from SCED I. In both experiments, the daily average of total activity counts per hour and the state level of self-control will serve as the primary and secondary outcome measures. Data will be analyzed using visual analysis and piecewise linear regression models.

Results: The study was designated as not subject to the Dutch Medical Research Involving Human Subjects Act by the Medical Research Ethical Committee Oost-Nederland and approved by the Ethics Committee/domain Humanities and Social Sciences of

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the Faculty of Behavioural, Management, and Social Sciences at the University of Twente. Participant recruitment started in January 2022, and we expect to publish the results in early 2023.

Conclusions: The mobile SCT app is expected to be feasible and effective. It is self-paced and scalable and can increase patient motivation, making it a suitable intervention for people with SMI. SCED is a relatively novel yet promising method for gaining insights into whether and how mobile apps work that can handle heterogeneous samples and makes it possible to involve a diverse population with SMI without having to include a large number of participants.

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KEYWORDS

mobile health; mHealth; mobile apps; self-control; physical activity; accelerometry; single-case experimental design; mobile phone

Introduction

Background

Approximately 1% of the world's population lives with severe mental illnesses (SMIs) such as schizophrenia (20 million) or bipolar disorder (46 million) [1]. Although their experiences are diverse, many are faced with multifaceted psychosocial problems in daily life, including difficulties in employment, housing, relationships, and finances and physical health inequalities [2]. An especially poignant problem in this group is the lack of physical activity and increasing sedentary behavior. Compared with healthy controls, people with SMI are more sedentary, less physically active, and less likely to meet physical activity guidelines [3]. This has a broad range of detrimental consequences for the physical and mental health of people with SMI, including reduced quality of life, increased risk of cardiovascular disease, and increased symptom severity [2,4,5]. Fortunately, even minor improvements in physical activity can prevent problems with physical health and deterioration of psychiatric symptoms in people with SMI and, thus, improve their quality of life [2,6,7].

The Role of Self-control in Successful Behavior Change

Clearly, there is an urgent need to improve physical activity in this extremely vulnerable group. However, existing physical activity interventions have several limitations when used in the population with SMI. First, many interventions are delivered by professionals, requiring additional time from already overworked staff [7,8]. For example, behavioral physical activity interventions targeted at people with SMI typically involve biweekly or weekly 60- to 120-minute sessions of counseling [9]. In addition, most physical activity interventions developed for people with SMI are not based on theory [9]. When they are, interventions are often solely underpinned by cognitive and reflective models of behavior change, including the Theory of Planned Behavior, Social Cognitive Theory, and the transtheoretical model [9-11]. Such interventions require substantial cognitive skills, including goal setting, reflecting on behavior, and writing, to produce effects [10]. This makes these interventions especially hard to use for people with SMI because of the vulnerabilities that are common in this target group related to cognitive deficits in memory and attention, low literacy rates, and apathy [12-17]. Finally, although behavioral theories are helpful in predicting behavioral intentions, these intentions do not necessarily relate to accompanying behavior changes, for example, increased physical activity [10,18]. This might explain why there is currently no reliable evidence that physical activity interventions result in better long-term physical health in people with SMI [9]. To address all the aforementioned issues, we need to better target physical activity interventions to vulnerable groups, including people with SMI.

This requires interventions that patients can work on independently; that do not require a high level of cognitive skills; and that target the intention-behavior gap that is common in interventions that are based on cognitive, reflective models. A promising focal point of these interventions is self-control—the ability to prevent or override unwanted thoughts or behaviors in favor of higher-order goals [19]. Studies have shown that self-control plays an important role in a broad range of goal-directed behaviors, including academic achievement, aggression regulation, and healthy eating and physical activity [19]. According to Friese et al [20], the role of self-control can be explained through three interacting components: (1) reflective processes such as personal goals, (2) impulsive processes such as automatic approach and avoidance tendencies, and (3) self-control abilities that allow for the control of impulsive processes and transfer of reflective processes into behavior. Owing to the large body of evidence that shows the relationship between self-control and health behaviors, self-control is an important element of many existing interventions. Even so, these mostly focus on self-control as a reflective process and teach reflective strategies such as goal setting, mental contrasting, and mental transformations [21], whereas interventions that address impulsive processes are underrepresented.

A conceptually different intervention is self-control training (SCT). SCT focuses on improving self-control abilities through repeated practice of self-control. In line with the impulsive processes described by Friese et al [20], individuals practice self-control by suppressing automatic tendencies in low-stakes areas for a predetermined period, often 2 weeks. A common paradigm is the use of the nondominant hand for everyday tasks such as writing or opening doors. This practice is then expected to transfer to behaviors for which self-control matters, such as physical activity. SCT is based on the strength model of self-control [22]. It states that all acts of self-regulation draw from a common, limited resource of self-control. Upon repeated exertion, this common resource becomes depleted, resulting in

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impaired inhibition and goal-directed behavior until the resource is renewed. Although this theory suggests that exerting self-control has negative short-term effects, it also states that the repeated use of self-control strengthens the capacity for self-control in the long run, akin to a muscle.

Traditionally, participants receive face-to-face or written instructions from researchers or health care staff to perform self-control tasks [23,24]. These paper-based versions of SCT consistently show that this practice results in increased self-control [24-26]. As such, SCT has multiple advantages in clinical practice. It is easy to administer, does not require much time and effort from participants, and can be a valuable addition to existing treatment and interventions by means of its focus on the automatic aspect of self-control. However, face-to-face delivery of SCT can take up the precious time of (health care) professionals. To prevent this, delivery of SCT can also be done digitally using either web-based applications or mobile apps.

A mobile app specifically has advantages for the delivery of SCT in clinical practice. First, an app is scalable and easy to implement as it can be accessed by many people without requiring time from already overworked health care staff [27]. Second, design principles such as gamification can be applied to support people who are not that motivated to use SCT. This is especially relevant in populations with low treatment motivation, such as psychiatric patients [28,29]. To involve these target groups, persuasive strategies can be embedded in the design of the app to increase adherence and engagement [30,31]. Adding persuasive features such as rewards, reminders, and personalization to an SCT app can support users in using the intervention as intended, resulting in more positive outcomes. As an app can increase motivation and does not require a high level of cognitive effort, it can be a suitable way to bolster self-control and, thereby, increase the level of physical activity in people with SMI. The first results of using such an SCT app demonstrated that, among 204 healthy young adults who used a mobile SCT app, 10 days of app-based SCT already significantly increased self-control, whereas participants in the control and email conditions showed no improvement [32].

Overall, a large body of research has shown that SCT strengthens self-control [24-26]. However, similar to the effect sizes of cognitive physical activity interventions [33], the effect sizes of SCT alone on behavior are small [25]. Hence, we argue that multiple complementary interventions should be offered that address reflective processes, impulsive processes, and self-control abilities to produce meaningful changes in health behavior. To illustrate, reflective interventions focused on goal setting can be used to create physical activity intentions and directly stimulate behavior change. SCT can be added to these interventions to address the impulsive processes related to self-control, thereby increasing individuals' general self-control capacity and indirectly supporting behavior change. When general self-control capacity is high, individuals are more likely to inhibit the dominant response of remaining sedentary and are expected to instead go for a walk—in other words, they are more likely to put their intention of walking into practice. This suggests that SCT could be added to many existing cognitive interventions to increase participants' self-control and, thus, decrease the intention-behavior gap and bolster the effectiveness of interventions. Surprisingly, despite the large body of evidence showing SCT's potential [24-26,32], it has not been studied in combination with existing cognitive interventions yet. In addition, despite its straightforward nature, SCT has rarely been applied and studied in psychiatric clinical practice.

Study Objectives

Therefore, this study further explores a mobile SCT app and the assumption that it can be used to bolster the effectiveness of existing physical activity interventions. It does so specifically in the vulnerable population of people with SMI. The primary objective is to assess the effect of adding a mobile SCT app to a mobile lifestyle intervention aimed at increasing physical activity (Google Fit) on physical activity levels in people with SMI. The secondary objective is to examine the effect of this combined intervention on self-control directly. Finally, we will explore how long SCT should be offered to produce beneficial outcomes on physical activity and whether and which individual characteristics of patients influence SCT effects.

Methods

Ethics Approval

This study has been designated as not subject to the Dutch Medical Research Involving Human Subjects Act by the Medical Research Ethical Committee Oost-Nederland (approval 2021-13232). Consequently, it has been approved by the Ethics Committee/domain Humanities and Social Sciences of the Faculty of Behavioural, Management, and Social Sciences at the University of Twente (approval 211301) and the research committees of Dimence Groep and GGz Centraal. In addition, this study has been registered at *CCMO Toetsingonline* from the Dutch Central Committee on Research Involving Human Subjects (file NL79450.091.21). This portal will also be used to report (serious) adverse events if they occur.

Study Design

This study will be conducted using a series of 2 single-case experimental designs (SCEDs): a concurrent multiple-baseline design across participants (SCED I) [34,35] and an introduction/withdrawal design (SCED II). SCED is a family of high-quality experimental designs that can be used to draw causal inferences about the relationship between the intervention and the outcome [36,37]. In an SCED, the intervention is systematically manipulated across multiple phases of introduction and withdrawal while the outcome variable is measured repeatedly and frequently [36-38]. In this way, individual patients function as their own controls. An overview of both experiments according to the SCRIBE (Single-Case Reporting Guideline in Behavioral Interventions) guidelines [39] is provided in Table 1.

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Table 1. Single-Case Reporting Guideline in Behavioral Interventions design elements of single-case experimental designs (SCEDs) I and II.

	SCED I	SCED II
Design	• Multiple baselines across participants	• Introduction-withdrawal
Duration	• 52 days	• Approximately 42 days (28-70 days)
Sequence of phases	• A-B-C+follow-up	• B-C-B-C
Description of phases	• Phase A—baseline: 5 days minimum; no intervention, only monitoring of physical activity and self-control • Phase B—Google Fit: 7 days minimum; only Google Fit intervention is administered • Phase C—Google Fit+SCT[a]: 28 days minimum; Google Fit and SCT intervention are administered simultaneously • Follow-up: 3 days minimum; no intervention, only monitoring of physical activity and self-control	• Phase B—Google Fit: 7 days; only Google Fit intervention is administered • Phase C—Google Fit+SCT: 7-28 days minimum; optimal phase length is determined from findings of SCED I; Google Fit and SCT intervention are administered simultaneously
Main outcomes	• Average TACs[b] per hour, measured continuously throughout the trial (at least 5 measures per phase) • Daily self-control, measured twice daily throughout the trial (at least 5 measures per phase)	• Average TACs per hour, measured continuously throughout the trial (at least 5 measures per phase) • Daily self-control, measured twice daily throughout the trial (at least 5 measures per phase)
Randomization	• Baseline duration is randomized with restriction to have at least 5 baseline observation days and 3 measurements	• Not randomized

[a]SCT: self-control training.

[b]TAC: total activity count.

There are several reasons for using SCED to evaluate interventions in people with SMI. First, SCEDs require only a small number of participants—typically 3 to 6. This makes it more feasible to recruit a sufficient number of participants and requires less time and financial resources from both staff and patients. Furthermore, SCEDs can handle heterogeneous samples as participants function as their own controls. This makes it possible to involve the diverse population with SMI, who may present with comorbidities and a broad range of psychosocial problems. Finally, SCEDs enable research into the working mechanisms of SCT, which is required [25] but nearly impossible to achieve through a randomized controlled trial (RCT) as an intervention is treated as a coherent whole, making it hard to open the black box of the studied intervention [40]. Overall, this makes SCEDs very suitable for the evaluation of interventions [41,42] and an excellent and feasible alternative to classic experimental designs such as the RCT.

In total, 2 SCED experiments are used to address different aspects of the overall research aim. SCED I is used to (1) determine the initial effectiveness of the intervention, (2) explore for which patients SCT may be most effective, and (3) determine how long SCT should be offered for optimal effects. The design of SCED I is A-B-C+follow-up, where A refers to the baseline phase, B is the physical activity intervention alone (Google Fit), and C is the combination of physical activity intervention+SCT intervention, followed by a follow-up in which patients are monitored but no interventions are administered. In addition, SCED I uses a mixed methods design incorporating qualitative interviews to provide insights into patients' experiences with both the mobile SCT app and the participation in an extensive longitudinal study. To explore the onset and duration of SCT effects on self-control, SCT is offered for 4 weeks instead of the customary 2 weeks [43]. This information will be used to determine whether SCT should be offered 1, 2, 3, or 4 weeks in SCED II.

The main aim of SCED II is to validate the effectiveness of the optimized intervention—in terms of duration and experience—based on the findings from SCED I. The design of SCED II is B-C-B-C, where, again, B refers to the physical activity intervention alone and C refers to the combination of physical activity intervention+SCT intervention. In both experiments, 6 participants will be monitored for at least one baseline phase and one intervention phase, with each phase lasting at least 5 data points following SCRIBE and What Works Clearinghouse guidelines [36,37,44]. Given that physical activity is measured continuously and self-control is measured twice a day, this will result in at least 28 data points during intervention phase C in SCED I and between 7 and 28 data points during intervention phase C in SCED II.

Randomization and Blinding

We will randomly assign participants to different baseline, intervention phase B, and follow-up durations in SCED I. All are drawn a priori using the web-based random number generator Research Randomizer [45] with the restriction of having at least 5, 7, and 28 baseline observation days, respectively. In SCED II, phase length will not be randomized as the optimal intervention length will be derived from SCED

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I. Phase order will not be randomized in both experiments as we are interested in the additive effect of SCT over Google Fit only.

Owing to the nature of the intervention, in which apps are used by participants, it is not possible to blind participants to the phase. The researchers responsible for supporting participants in transferring between phases will not be blinded to the phase for the same reason. Where possible, researchers only involved in data entry, processing, and analysis will be blinded to the phase to improve the reliability of the findings [36].

Participants

A total of 12 people with SMI will be recruited from the clinics of 2 large Dutch mental health care organizations: Dimence Groep and GGz Centraal. To meet quality standards, an SCED should include at least 3 participants [37,44,46]. To account for the high dropout rates common in the psychiatric population, we will include 6 participants in both SCEDs. Participants will receive €50.00 (US $56.00) for taking part. To promote continued commitment to the longitudinal design, participants will receive €10.00 (US $11.00) at the start, €20.00 (US $22.50) midway, and €20.00 (US $22.50) at the end of the study.

Participants need to meet the inclusion criterion of having an SMI, including but not limited to schizophrenia, bipolar disorder, and major depression, following the Dutch consensus definition of SMI [47]: (1) requires treatment (ie, no symptomatic remission), (2) is associated with severe limitations in social or societal functioning (ie, no functional remission) that result in and are caused by a psychiatric disorder, (3) is not transient (ie, is structural, chronic, or long-term [at least several years]), and (4) requires coordinated care from professional caregivers in care networks to realize the treatment plan.

As the study will be introduced only to people currently receiving care for their SMI at an outpatient clinic or residing in an inpatient clinic, all participants will, on principle, be expected to meet the consensus definition, and no specific diagnosis will be determined. If doubt exists about whether a participant meets this criterion, the health care provider responsible for the patient (Dutch: *persoonlijk begeleider*) will determine whether the participant has an SMI following the consensus definition. In addition, participants must be aged ≥18 years, receive outpatient treatment or reside in an inpatient clinic for at least the data collection period, have sufficient opportunity to be physically active (eg, not be confined to a bed or bedroom), have an intention to improve physical activity as assessed using the single-item assessment of stages of change adapted for healthy behavior [48,49], and provide voluntary consent to participate. Participants are excluded if they do not want to (further) improve their physical activity. This is due to the nature of the SCT intervention—SCT supports putting an existing goal into practice (ie, tackling the intention-behavior gap) but does not support patients who are unwilling to improve physical activity. In a similar vein, SCT is also not expected to be effective for people who already meet their physical activity goals. Participants are also excluded if repetitive behavior may potentially aggravate a patient's disorder or symptoms (eg, obsessive-compulsive disorder) as evaluated by the health care provider or patient. Owning a mobile phone is not an inclusion criterion as participants who do not own a mobile phone will be provided one for the duration of the study.

To recruit participants, the study will be introduced to patients receiving treatment or residing in the clinics via short presentations and flyers distributed by the researchers. We specifically decided to do the initial introduction to the study via researchers rather than the health care provider to avoid any (perceived) role conflicts between health care providers and patients, for example, when the health care provider also makes decisions about patients' leave in a forensic psychiatric context. If patients are interested in the study, they will be able to sign up directly with the researcher (in person or by email), after which we will discuss with their health care provider whether participation is safe, appropriate, and feasible for this patient.

When possible, only 1 patient from each clinic will be selected. This ensures that SCT is tested in different types of patients, staff, and clinics and prevents social comparison effects as patients from the same clinic could challenge each other to be more physically active. Patients not selected will be invited to participate in SCED II or, if not possible, will be offered to use the intervention after the study.

Interventions

The interventions consist of 2 mobile apps designed to improve physical activity. The first is SCIPP: the Self-Control Intervention App, which was specifically designed for this study, and the second is Google Fit, a mobile lifestyle intervention aimed at increasing physical activity.

SCIPP: the Self-Control Intervention App

SCIPP is a mobile app based on the pen-and-paper format of SCT [24-26]. SCIPP is available on Android and provides users with a new daily challenge for 14 days. This daily challenge asks users to perform an everyday activity—such as opening the door or turning on the light—with their nondominant hand. After accepting the challenge, users are reminded of the daily challenge 4 times a day. After 14 days, the app notifies the user that the training has concluded. By restarting the app, the intervention can be used for a longer period—in the case of this study, up to 28 days.

We have previously established the feasibility and preliminary effectiveness of mobile SCT in young adults [32]. This study showed that self-control did improve in participants who used an SCT app, whereas self-control did not increase in participants who received SCT via email and participants in a control group that did not receive SCT. The app was then redesigned with and for people with SMI to meet their cognitive capabilities and preferences following a participatory design study [50]. It meets the following requirements for suitable SCT from the patients' perspective: (1) behavior change is framed as a shared, unpredictable process; (2) visual rewards and explanations are given; (3) the app uses reduced textual and numerical information; and (4) the app provides accessible means for feedback and personal goals. In addition, the app sends reminders throughout the day to remind users of the daily challenge. This was considered specifically important as reminders appeared to be the main advantage of an app over email in the previous study [32]. Participants in the app

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condition of the previous study appreciated the reminders and even requested more, whereas participants in the email condition indicated that they often forgot about tasks and would have liked to have reminders. Finally, the SCT app also incorporates several other persuasive features to promote engagement and adherence [30,51,52], including reduction, self-monitoring, social role, praise, personalization, real-world feel, and liking. Reduction and self-monitoring features reduce complex behavior in simpler, smaller tasks and allow users to track their performance on these tasks. In the SCT app, this means that users monitor daily self-control challenges (Figures 1-2). Social role and praise enable users to form a social relationship with the app, which provides praise when the target behavior is performed. In the SCT app, this is embedded in the virtual coach Scipp (Figure 3). Personalization and real-world feel were incorporated through tangible, personalized goals and feedback (Figure 4), whereas liking refers to the look and feel of the app and is incorporated into the overall minimalist, colorful esthetic used.

Figure 1. Screenshot of daily challenges with reminders in SCIPP: the Self-Control Intervention App. Daily challenges are easily found on the main page and explained visually. Users receive 4 daily reminders of the daily challenge.



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Figure 2. Screenshot of the process page with a winding mountain path in SCIPP: the Self-Control Intervention App. Users self-monitor daily challenges. As behavior change is an unpredictable process, the mountain visualization includes ups and downs, and participants can also report when they were not able to do a challenge.



Figure 3. Screenshot of virtual coach Scipp in SCIPP: the Self-Control Intervention App. Virtual coach Scipp praises users for completing challenges. She also frames behavior change as a shared process and invites users to celebrate success with their broader social network after certain milestones, such as the first successful day of self-control training.



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Figure 4. Screenshot of providing feedback on challenge difficulty in SCIPP: the Self-Control Intervention App. Users can set their own motivation for training self-control and provide feedback on the difficulty of the challenges. Once training is completed, this initial goal is shown to the users and can be adapted if needed.



Google Fit

Google Fit is a freely available mobile health tracking platform developed by Google in collaboration with the World Health Organization and the American Heart Association. Google Fit can be considered a goal-directed, cognitive intervention that incorporates various behavior change techniques to motivate the user to be more active. These include the ability to set a personal activity and step count goal, self-monitor activities in a personal dairy, and receive customized feedback based on health and activity history. To monitor physical fitness activities, Google Fit uses sensors from the user's mobile device or external activity trackers. It translates each minute of moderately intense activity into a Heart Point, and more intense activities result in more points. In addition, the number of steps is tracked. It is available on the Android and iOS operating systems, but in this study, only the Android version will be used.

Google Fit was selected as the physical activity intervention in this study in line with the rationale provided in the Introduction section—it does not require additional support from staff; it is based on reflective processes of self-control (ie, a focus on cognitive processes such as goal setting) and, thus, can be complemented with the novel SCT intervention; and it is likely suitable for the cognitive abilities of people with SMI. The latter was determined based on the assessment of the Regional Public Health Services of the Netherlands, which assessed Google Fit as reliable, theory-informed, secure, and user-friendly, including short, concrete text free of difficult jargon or medical terms [53]. Although no evidence is available regarding the effectiveness of Google Fit in increasing the physical activity of people with SMI, it has been successfully used in people with poor mental health [54].

Material and Measures

Overview

The primary study parameters are daily physical activity and self-control. Daily physical activity will be measured using a wearable accelerometer, the ActiGraph GTX+ [55,56]. Daily self-control will be measured via experience sampling.

Physical Activity

The ActiGraph GT3X+ and ActiLife software (version 6.8.0; ActiGraph) will be used to measure and analyze physical activity. The accelerometer is worn on the right hip and held in place with an elastic strap between 2 belt loops. Patients without belt loops will use a pouch pinned at the same location. The ActiGraph GT3X+ has a high inter- and intra-instrumental reliability [57] and validity [56]. It has been used successfully in previous studies with people with SMI to examine physical activity and sedentary behavior [6,58,59]. None of these studies reported usability, safety, or other issues related to the use of the ActiGraph GT3X+ in this population, which makes it a reliable, valid, and appropriate choice for measuring physical activity in this study.

Physical activity is operationalized as the daily average of total activity counts per hour, which is a continuous and detailed outcome variable of physical activity [6]. More counts indicate a higher level of physical activity. Following existing procedures for valid measurement of physical activity using the ActiGraph

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GT3X+ in this population, a wear time of >6 hours per day for at least 3 days will be used as the criterion for sufficient measurement [6,58].

Daily Self-control

To distribute questionnaires, the mobile survey distribution platform Ethica Data [60] will be used. Ethica is a web-based platform that is designed for researchers to create, modify, and distribute momentary surveys for experience sampling research. It allows researchers to obtain and view the data of the participant in real time to identify possible errors while the study is still running. Furthermore, it amplifies the ecological validity, possibilities, and reliability of frequent data collection [61]. Participants use their smartphones to complete the surveys. This reduces strain on participants as they do not have to carry with them additional study-related materials. Finally, trigger logistics help reduce participant burden by sending automatic reminders to fill out surveys [62].

Daily self-control will be measured using 2 items from the State Self-Control Scale [63] and 2 items specifically developed for this study. Participants use a 5-point slider ranging from 1 (*not at all*) to 5 (*very much*) to reflect on recent self-control experiences. All questions start with "In the past couple of hours..." Participants answer questions about decision-making ("it's hard to make up my mind about even simple things"), subjective feelings of ego depletion ("I had less mental and emotional energy than I normally have"), goal-directed behavior ("I was able to do what I had planned"), and inhibitory control ("I was able to resist temptations"). We have previously used this questionnaire to measure daily self-control in students [64] and rephrased the items for people with SMI to improve clarity and brevity. A small pilot study with 5 patients receiving outpatient psychotherapeutic care showed that the rephrased items had high face validity, feasibility, and comprehension [65].

Trait Self-control and Cognitive Control

Generalization measures assess the intervention effect on untrained tasks and are important to establish the external validity in SCEDs [36]. The SCRIBE guidelines [37] recommend that generalization measures are taken repeatedly, although not as frequently as the main outcome measures. In this study, trait self-control and cognitive control are used as generalization measures and assessed every 5 days (at least once per phase). This combination of measures is used as self-control is a multifaceted construct and it is recommended to use more than one type of measurement instrument to assess it [66].

Trait self-control is measured using the Brief Self-Control Scale (BSCS). The BSCS is a validated, brief, and psychometrically sound measure of individual differences in self-control that consists of 13 items [19,66,67]. The BSCS measures several aspects of trait self-control, including inhibitory and initiatory control [68]. Participants rate the extent to which a statement, for example, "I am good at resisting temptation," matches them on a 5-point Likert scale ranging from 1 (*not at all*) to 5 (*very much*). A total score for self-control will be created by taking the sum of all items after recoding negatively phrased items (Cronbach α=.83-.85 [69]). Higher scores indicate higher levels of self-control, which has a medium effect on behavioral outcomes, showing criterion validity [70].

Cognitive control will be measured using the go/no-go task. This is a well-studied measure of cognitive control and has been used in previous research to assess self-control [32]. In the go/no-go task, participants are instructed to respond to target stimuli but must refrain from responding to nontarget stimuli, which requires suppressing a behavioral response. In this study, we will use average reaction time as the main parameter of cognitive control, with shorter reaction times reflecting more self-control [32,71].

Sociodemographics and Covariates

To describe the characteristics of the participants, we will collect information about their age and gender. To explore possible covariates or moderators of the intervention effect, we will collect data on body weight, height, stage of change, and clinic type (outpatient or inpatient) and monitor intervention use (number of completed challenges and self-reported success of each challenge).

Experience and Feasibility Measures

Once the study is complete, patients' perspectives will be gathered during short semistructured interviews. The interviews will focus on participants' experiences with the SCIPP app, possible points of improvement, and their perceived effectiveness of SCT. This information will be used to optimize digital SCT training as well as understand the feasibility of using SCED methodology in people with SMI.

Procedure

Participants will be visited by a member of the research team 1 day before the start of the experiment. The researcher will help the patient install all necessary apps on the patient's mobile phone. Next, the researcher will fit the accelerometer to the patients' hip or belt and demonstrate how to take it off. Finally, the researcher will help participants fill out the baseline questionnaires.

During the baseline phases, physical activity and self-control will be monitored, but no interventions will be administered. To monitor physical activity, the patient will wear the accelerometer each day from 9 AM to 11:59 PM except when sleeping or during activities that involve water, such as showering or swimming. To measure daily self-control, they will be prompted to fill out a morning survey between 11 AM and 1 PM and an evening survey between 7 PM and 9 PM. Reminders for both surveys will be sent after 30 and 60 minutes.

At the start of intervention phase B, the researcher will visit the patient and help set up Google Fit by entering their activity goals (number of steps and number of Heart Points), wake-sleep schedule, weight, and height. Next, the researcher will demonstrate where to find and how to use the primary functions of Google Fit. This will enable patients to self-monitor their activity and receive personalized coaching. During the withdrawal phases of SCED II, the researcher will also deactivate the SCT app and explain to the patient that this app will not be used for the next phase.

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At the start of intervention phase C, the researcher will visit the patient and help set up SCIPP by entering the personal goal and dominant hand. The researcher will also inquire about their experiences with participation so far and provide additional instructions regarding Google Fit, the accelerometer, or Ethica, if required. The next day, the patient will receive the first self-control challenge and continue to receive and complete challenges throughout the phase. The researcher will return every 7 days to answer questions and, if necessary, reset the app to extend use up to 28 days until the phase is completed.

Follow-up follows the same procedure as the baseline phases. The researcher will visit the patient to disable all apps on the patient's phone except Ethica, which is used for data collection. Once the study is completed, the researcher will make a final visit to collect the accelerometer and reactivate any apps that the patient wishes to continue using. In SCED I, the researcher will also conduct the postintervention interview during this visit.

Data Analysis

Overview

Data analysis will include both visual and supplementary statistical analyses of the time-series data for both SCED I and II [36,42]. Data analysis will be performed using Microsoft Excel (Microsoft Corp), the web-based Tau-U calculator accessible via Single Case Research [72], and R (version 1.4; R Foundation for Statistical Computing) [73] and separately for the primary and secondary outcomes.

To prepare the data for analysis, we will score the primary outcome of physical activity as the daily average of total activity counts per hour. The secondary outcome of daily self-control will be scored as the daily average of the 4 self-control items. Next, we will use the median average deviation to identify and remove outliers. The median average deviation uses the median to identify scores that deviate 3.5 times from the median as outliers using a 95% CI. It is specifically recommended for use in small-sample studies, including SCEDs [74].

As both experiments collect continuous data that are averaged on a daily level, our missing data approach primarily consists of making full use of data that are available. To illustrate, self-control will be measured in the morning and evening. If the morning data are missing, the afternoon data will be used to calculate the level of self-control for that day. If no data are available on a given day, we will use multiple imputation to impute missing data. Multiple imputation methods have recently been developed specifically for use in SCED studies and have several advantages over other missing data approaches, including retention of collected data, maintenance of the design structure of an SCED, reduction of bias, and the ability to capture and communicate uncertainty regarding imputed scores [75].

Visual Analysis

SCED data are primarily interpreted visually [36]. To do so in this study, physical activity and state self-control data will be presented as a time-series graph, with days on the horizontal axis, physical activity or self-control on the vertical axis, and phase changes presented as vertical lines. As recommended by the What Works Clearinghouse guidelines [44,46], we will consider 6 features to examine within- and between-phase data patterns visually: level, trend, variability, overlap, immediacy, and consistency. The phase contrasts to be compared in SCED I are A versus B (baseline with Google Fit only), B versus C (Google Fit only with Google Fit+SCT), and A versus C (baseline with Google Fit+SCT). The phases compared in SCED II are B versus C (Google Fit only with Google Fit+SCT).

Within phases, *level* refers to the mean of all data points in 1 phase and is used to compare changes between phases [36]. *Trend* is the slope of the best-fitting trend line for all data in a phase and is used to determine trends toward (spontaneous) improvement or decline. *Variability* expresses the SD of data about the trend line and is used to calculate the percentage of overlap between data collected in different phases.

Between phases, *overlap* is the proportion of overlap between data from 2 phases, where less overlap indicates stronger intervention effects. The specific nonoverlap index we will use is the Tau-U summary index [76], which is a family of 4 indexes that calculate nonoverlap in relation to the trend. It is expressed by "the percent of data that improve over time considering both phase nonoverlap and Phase B trend, after control of Phase A trend" [76]. Using Tau-U allows for the exploration of, for example, how much the physical activity of a patient has increased after using the SCIPP app while considering a possible increase in physical activity levels that may have already been initiated by Google Fit during the previous phase.

Immediacy compares the extent to which the level, trend, and variability of the last and first 3 data points of subsequent phases are discriminably different. In SCED I, immediacy is used to examine whether SCT effects are immediate or cumulative and to make decisions about the appropriate phase length in SCED II. Finally, *consistency* involves examining whether data patterns (level and trend) are consistent in phases with the same condition, where more consistent patterns provide greater certainty for a causal relationship between the intervention and outcome. This will be used in SCED II to examine whether physical activity reaches similar level and trend effects in both B phases (Google Fit only) and both C phases (Google Fit+SCT).

Piecewise Linear Regression Analysis

To supplement the visual analysis, we will conduct piecewise linear regression analyses (PLMs) using the *scan* package [77]. PLM is an approach to analyzing time-series data that are segmented into phases, including SCEDs [77,78]. The PLM model calculates 4 parameters (intercept, trend, level, and slope) separately for data from each phase, allowing for a comparison between phases. In this case, *intercept* refers to the performance at the start of the study, *trend* effects refer to the continuous increase in the behavior over time, *level* effects refer to the constant and instant effect of the intervention, and *slope* effects refer to the change in continuous increase initiated by the intervention.

Using the PLM, we will construct a linear model for each individual patient, including a *P* value, R^2 effect size, and beta

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weights for trend, level, and slope effects. We will use a cutoff of $P<.05$ to determine significant effects.

In SCED I only, we will also construct a multilevel PLM to aggregate single-case findings across all participants included. Aggregation improves the external validity of the findings by providing overall trend, level, and slope effects and allows for the exploration and quantification of moderation effects using random slopes [77]. First, we will include random slopes in the multilevel PLM to examine whether trend, level, and slope effects differ significantly between participants. If this is the case, we will subsequently consider the interactions between body weight, height, stage of change, clinic type, intervention use, trait self-control, and cognitive control as potential moderators of the effect. As there are no existing hypotheses about moderation, we will not use confirmatory *P* values in this analysis but merely report any findings as preliminary and exploratory.

Reliable Change in Generalization Measures

We will explore individual changes in generalization measures of trait self-control and cognitive control by comparing the means of pre- and postintervention scores obtained during baseline, end of intervention phase C, and follow-up.

Qualitative Analysis of Experience

Interview data will be analyzed inductively using thematic analysis [79] to organize data into overarching themes related to usability and feasibility of the SCIPP app and SCED methodology according to people with SMI.

Results

Funding for this study was obtained in July 2020 by The Netherlands Organisation for Health Research and Development (project 555003023). It was approved by the Ethics Committee/domain Humanities and Social Sciences of the Faculty of Behavioural, Management, and Social Sciences at the University of Twente in November 2021 and the research committees of the participating mental health care facilities in January 2022. Recruitment for the study started in January 2022, and 6 participants have been included as of March 2023. We expect to publish the results in summer 2023.

Discussion

Expected Findings

Earlier studies have shown that SCT using the nondominant hand paradigm can increase self-control in healthy populations [24-26]. Self-control is a key mechanism in translating physical activity intentions into practice [80,81]. Therefore, interventions targeting self-control may be a viable strategy for improving physical activity in people with SMI. Many people with SMI experience poor physical health yet are barely targeted in preventive and health promotion research, leading to large systemic inequality [82]. In addition, people with SMI face a number of social, cognitive, physical, psychological, and sensory impairments, which may make cognitively based physical activity interventions less accessible [83,84]. However, further studies are needed to evaluate the effect of combining SCT and regular physical activity interventions on physical activity in this target group. This study will provide initial insights into whether this is the case.

SCIPP, the SCT app that will be used in this study, is expected to be feasible, effective, and suitable for people with SMI. First, it brings SCT to the digital era as it is delivered via a mobile app. Among other things, an app can be used by patients individually, on their own time, and at their own pace; is scalable; and can increase patient motivation and adherence, making it a suitable instrument to target people with SMI [85]. Previous research has indeed shown that there is a need for well-designed mobile apps to further improve treatment of hard-to-involve patient populations [86]. Second, based on earlier research on SCT and a specific study on an SCT app, it is expected that SCIPP will be effective. We have previously developed and pilot-tested a functioning prototype of an SCT app aimed at students and found that self-control increased after just 10 days [32]. Even though this was studied in a different target group, it still shows the potential of this app to bolster self-control as it is expected that the underlying mechanisms of self-control practice are similar across populations. The findings of this previous study were used to further develop the SCT app, resulting in SCIPP. This study especially highlighted the importance of reminders to ensure that participants did not forget about the SCT tasks throughout their day. Second, SCIPP was specifically designed with and for this target group following a participatory design process in which patients were structurally involved in app development via 3 design workshops. Products designed through a participatory design approach often have a better user experience and usability as they fit more closely with users' needs [84,87]. Indeed, usability tests with 3 patients with SMI who were not involved in the design workshops showed that patients had a high level of satisfaction and intention to use SCIPP. Interventions are expected to benefit from this improved fit in multiple ways, including increased effectiveness [87], adherence [88,89], and adoption. Therefore, we expect that the mobile SCT app will provide an effective and suitable way to train self-control in the population with SMI. This should not be considered a stand-alone psychological treatment, but following this trial, the app could be implemented alongside any intervention aimed at improving the lifestyle of people with SMI to bolster its effectiveness.

To examine SCIPP in concert with Google Fit, we will use 2 SCEDs. The classic RCT is—despite its shortcomings—still the most dominant design for eHealth evaluation [41]. However, assembling the homogeneous population that is required for controlled trials is difficult or even impossible to achieve because of the relatively high number of patients with comorbidities. The fact that people with SMI are considered difficult to involve in larger trials such as RCTs may explain the lack of studies on their physical activity levels. This illustrates a paradox: even though vulnerable populations require more research to improve care, they are very hard to involve in classic study designs, which results in an underrepresentation in scientific literature, which in turn further aggravates inequalities [90]. SCEDs provide a good method to address this paradox as they allow for high-quality experimental research by intensively monitoring a limited number of patients. The

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first studies show that SCEDs are very suitable for the evaluation of eHealth interventions [41,42] and offer an excellent and feasible alternative to more classic experimental designs such as the RCT. However, although SCEDs appear to be a fitting research design, they have not been used to study eHealth physical activity interventions developed for people with SMI. This implies the need for more studies that apply SCEDs. Consequently, this project will apply 2 SCEDs to evaluate the effectiveness of combining a cognitive-based physical activity intervention with a mobile app to train self-control. This study will also explore people with SMI's experiences of being involved in such an extensive longitudinal study. As such, these findings will also allow other researchers to learn the benefits and pitfalls of applying this relatively novel design to the evaluation of other eHealth interventions.

Strengths and Limitations

A major strength of this study is the combination of 2 approaches to SCED: the multiple-baseline design across participants and the introduction/withdrawal design. The first experiment will allow us to demonstrate whether mobile SCT is effective, for whom it may be most effective, and for how long it should be offered for optimal effects. In addition, the qualitative interviews provide insights into how to optimize the mobile SCT app as well as insights into participation in an extensive longitudinal study from the perspective of people with SMI. This knowledge will be directly applied to the second experiment, in which the optimized intervention will be offered to a new set of patients to validate these findings.

Second, the study also uses accelerometry to assess the physical activity of people with SMI objectively. The use of accelerometry data substantially improves the reliability, validity, and level of detail of data on sedentary behavior and physical activity compared with often-used self-reports in which physical activity levels are consistently overestimated [91-93].

The main limitation is that there is no certainty that people with SMI will persist in SCT, faithfully wear the accelerometer, and provide answers to the daily questionnaires for the considerable study duration of 7 weeks. Nonadherence is a major challenge for any longitudinal study, including N-of-1 designs such as SCED [94]. However, it is specifically challenging in people with SMI [95], and studies suggest that low self-control may also further contribute to low adherence [96]. As this study is both longitudinal and will target individuals with SMI (who commonly have lower self-control than the general population [97]), nonadherence may thus be expected. To address this limitation, we will take additional measurements to avoid complete loss of data (eg, 2 daily measures of self-control instead of 1), schedule regular phone calls and visits by the researcher, and offer financial incentives for continued participation in the study, all strategies associated with better adherence [98-100]. Explicitly reporting on the success of these strategies both from a quantitative (eg, use data) and qualitative (eg, patient interviews) perspective will also help other researchers make more informed decisions about the design of SCED studies specifically in the population with SMI.

Acknowledgments

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Data Availability

All data generated during the study will be coded and handled confidentially and anonymously in accordance with the European Union General Data Protection Regulation and the Dutch General Data Protection Regulation Implementation Act. The coded data will be stored at the University of Twente for a period of 15 years. During this period, coded data will be available through the corresponding author upon reasonable request. After the period of 15 years, data will be stored in long-term storage at the Data Archiving and Networked Services by the Royal Netherlands Academy of Arts and Sciences.

Authors' Contributions

TD, HK, SMK, NB-dJ, GDSL, JD, and YB designed the trial. TD, HK, TH, SES, and HK designed the mobile self-control training app. TH, SES, JD, and YHAB will facilitate patient contact and recruitment. TD wrote the manuscript draft. HK provided substantial review, proofreading, and editing. All authors critically revised the manuscript and approved the final version.

Conflicts of Interest

None declared.

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Abbreviations

BSCS: Brief Self-Control Scale
PLM: piecewise linear regression analysis
RCT: randomized controlled trial
SCED: single-case experimental design
SCIPP: Self-Control Intervention App
SCRIBE: Single-Case Reporting Guideline in Behavioral Interventions
SCT: self-control training
SMI: severe mental illness

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Protocol

Upper Airway Assessment in Cone-Beam Computed Tomography for Screening of Obstructive Sleep Apnea Syndrome: Development of an Evaluation Protocol in Dentistry

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Abstract

Background: The upper airways are formed by the nasal cavities, pharynx, and larynx. There are several radiographic methods that allow evaluation of the craniofacial structure. Upper airway analysis in cone-beam computed tomography (CBCT) may be useful in diagnosing some pathologies such as obstructive sleep apnea syndrome (OSAS). OSAS prevalence has increased significantly in recent decades, justified by increased obesity and average life expectancy. It can be associated with cardiovascular, respiratory, and neurovascular diseases, diabetes, and hypertension. In some individuals with OSAS, the upper airway is compromised and narrowed. Nowadays, CBCT is widely used in dentistry by clinicians. Its use for upper airway assessment would be an advantage for screening some abnormalities related to an increased risk of pathologies such as OSAS. CBCT helps to calculate the total volume of the airways and their area in different anatomical planes (sagittal, coronal, and transverse). It also helps identify regions with the highest anteroposterior and laterolateral constriction of the airways. Despite its undoubted advantages, airway assessment is not routinely performed in dentistry. There is no protocol that allows comparisons between studies, which makes it difficult to obtain scientific evidence in this area. Hence, there is an urgent need to standardize the protocol for upper airway measurement to help clinicians identify at-risk patients.

Objective: Our main aim is to develop a standard protocol for upper airway evaluation in CBCT for OSAS screening in dentistry.

Methods: To measure and evaluate the upper airways, data are obtained using Planmeca ProMax 3D (Planmeca). Patient orientation is performed in accordance with the manufacturer's indications at the time of image acquisition. The exposure corresponds to 90 kV, 8 mA, and 13,713 seconds. The software used for upper airway analysis is Romexis (version 5.1.O.R; Planmeca). The images are exhibited in accordance with the field of view of 20.1×17.4 cm, size of 502×502×436 mm, and voxel size of 400 µm.

Results: The protocol described and illustrated here allows for automatic calculation of the total volume of the pharyngeal airspace, its area of greatest narrowing, its location, and the smallest anteroposterior and laterolateral dimensions of the pharynx. These measurements are carried out automatically by the imaging software whose reliability is proven by the existing literature. Thus, we could reduce the possible bias of manual measurement, aiming at data collection.

Conclusions: The use of this protocol by dentists will allow for standardization of the measurements and constitutes a valuable screening tool for OSAS. This protocol may also be suitable for other imaging software. The anatomical points used as reference are most relevant for standardizing studies in this field.

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KEYWORDS

cone-beam computed tomography; three-dimensional image; 3D image; airway obstructions; sleep medicine specialty; dentistry; obstructive sleep apnea; protocol

Introduction

The upper airways are formed by the nasal cavities, pharynx, and larynx. The pharynx (portion most susceptible to collapse) is divided into 3 parts: nasopharynx, oropharynx, and hypopharynx [1,2]. The nasopharynx begins in the choanae (posterior opening of the nasal cavities) and ends on the hard palate. The oropharynx ranges from the uvula to the epiglottis. The hypopharynx spans the area from the epiglottis to the vocal cords, where the trachea begins [1,2].

There are several radiographic methods that allow the evaluation of craniofacial structure. Profile teleradiography, cone-beam computed tomography (CBCT), axial computed tomography (CT), and magnetic resonance imaging are some examples of imaging modalities that allow for this evaluation. Among these auxiliary diagnostic means and comparing those that are available to dentists, CBCT has demonstrated usefulness in 3D evaluation of the airways. For example, the time and radiation exposure in CBCT are considerably shorter than those in CT [1-3]. Profile teleradiography provides a quick 2D assessment of the upper airways but can only depict the 2D morphology and has prone of numerous superimpositions [4-6].

Furthermore, CBCT images are not magnified and are recorded on a 1:1 scale, which permits accurate and direct dimensional measurements [4-6]. Although a radiographic examination, CBCT has a far more favorable risk-to-benefit ratio. It helps determine the total volume of the airways and their area in the different anatomical planes (sagittal, coronal, and transverse) and identify the regions with the highest anteroposterior and laterolateral constriction of the airways [1].

Upper airway analysis in CBCT is useful to help diagnose some pathologies such as the obstructive sleep apnea syndrome (OSAS).

The OSAS is defined by repeated episodes, greater than 5 per hour, of partial or total obstruction of the upper airways during sleep, leading to airway obstruction (apnea) or reduced airflow (hypopnea). An apnea event, by definition, should last at least 10 seconds and is usually associated with sleep or microarousal fragmentation. Hypopnea can be defined as a reduction in ventilation (at least 50%) with an oxygen desaturation of ≥4% [4-11].

This pathology has a relevant negative impact on patients' daily lives and its prevalence has increased significantly in recent decades worldwide, justified by increased obesity and average life expectancy. Benjafield et al [12] estimated that around the world, approximately 1 billion adults aged 30-69 years experience OSAS, of whom more than 45% (425 million) of adults present moderate to severe OSAS requiring treatment [8]. There is a wide geographical variation in the prevalence of OSAS, with some countries having a prevalence above 50%. OSAS is highly underrecognized, and it is estimated that 82% of men and 93% of women with OSAS in the United States are not diagnosed [12-14]. The clinical presentation of OSAS includes fatigue, daytime sleepiness, and snoring. If not treated, it can be associated with cardiovascular (coronary artery disease, arrhythmias, hypertension, congestive heart failure, and stroke), respiratory (exacerbation of asthma, respiratory dysfunction in chronic obstructive pulmonary disease, pulmonary embolism, and pulmonary hypertension), and neurological diseases (frustration, distress, neurocognitive dysfunctions, and attention deficit) and diabetes [4-11].

In OSAS, despite respiratory effort, there is a repetitive total or partial collapse of the upper airways. In normal situations, the genioglossal muscle contracts at each inspiration in order to avoid the posterior movement of the tongue aided by the lift and tensor muscles of the palate, geniohyoid, and stylopharyngeus [4-11]. Together, these muscles ensure continuous air passage through the airways. However, in some individuals, the upper airways are compromised and narrowed as a result of the deposition of adipose tissue in the pharyngeal muscles and parapharyngeal pathways or due to anomalies in the craniofacial structure [4-11].

One of the regions relevant to the pathophysiology of OSAS is the oropharynx. Steffy et al [1] related the constriction value of the oropharynx with the risk of developing OSAS. An area of <52 mm^2 is considered as having a high risk of OSAS; 52-100 mm^2, intermediate risk; and >100 mm^2, low risk [1,10]. Obstruction may arise at different levels of the oropharynx, being more frequent in the retropalatal, retroglossal, and epiglottis areas [10,11].

Due to the severity of this syndrome, multidisciplinary intervention is essential. The role of the dentist in OSAS is essentially 2-fold: contributing to early diagnosis and therapy. This clinician has the possibility to make a direct observation of the palate's soft and oropharyngeal tissues (eg, tonsil region and tongue), can identify breathing difficulties and breathing type (nasal or oral), and has easy access to the cervical region, which helps assess its volume or even measure the cervical perimeter [12]. Furthermore, according to the American Academy of Dental Sleep Medicine, the dentist plays a key role in screening and can help to reduce the number of undiagnosed or untreated patients with OSAS [13].

Currently, CBCT is used in dentistry. Its additional use for upper airway assessment would be an added value for the screening of some abnormalities related to an increased risk of OSAS. Studies on airway measurement methods have revealed that there is no objective and consensual methodology [14,15], which makes it difficult to obtain scientific evidence in this area. There is an urgent need to standardize the protocol and to develop a simple workflow for upper airway measurement, which is the aim of this study.

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Methods

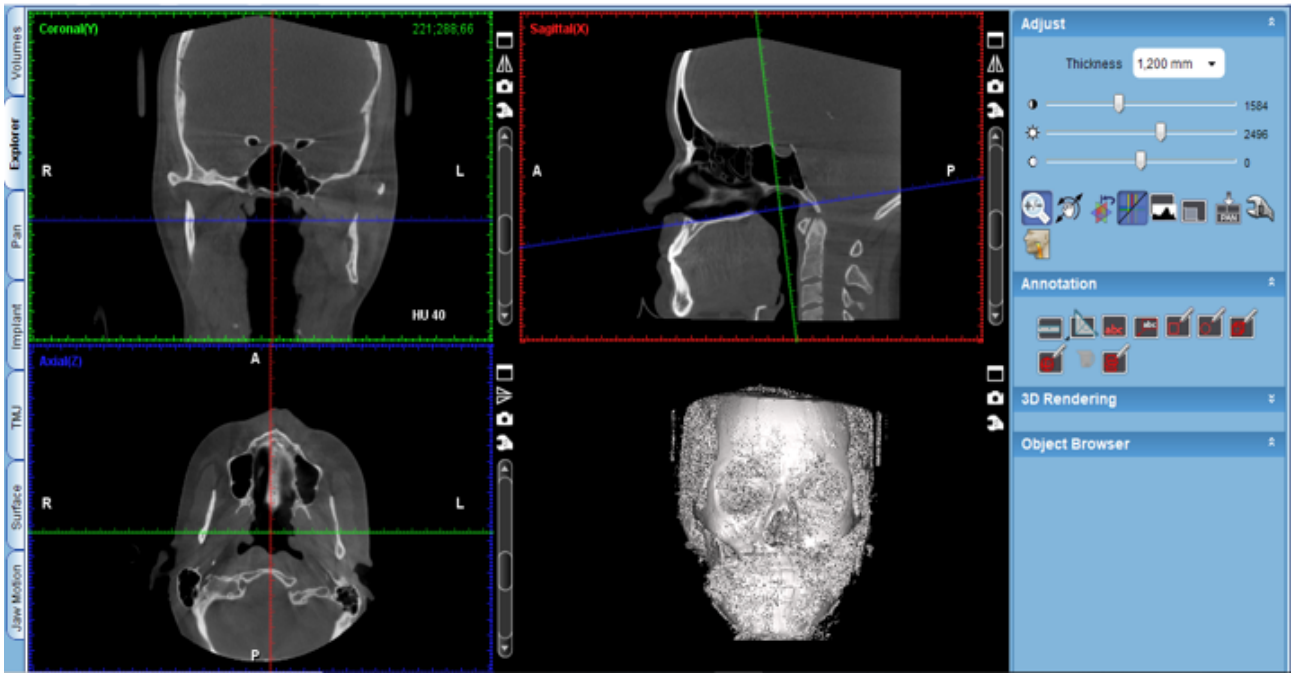
Ethical Considerations

This study was integrated in the project number 27 of the Faculty of Dental Medicine, Catholic University of Portugal, and approved by the Ethics Committee for Health (272022; January 21, 2022). The authors ensured conditions of anonymity and confidentiality that are required for such studies in Portugal.

Data Collection

To measure and evaluate the upper airways, data were obtained using Planmeca ProMax 3D (Planmeca) and in accordance with the manufacturer's indications regarding patient orientation at the time of image acquisition: with the patient standing and with his/her head oriented along 3 vertical references—the facial midline (glabella, subnasal, and mentum), endocant of the eye, and the parietal bone (Figure 1). The patient's head should also be oriented along a horizontal reference—next to the chin. The exposure corresponds to 90 kV, 8 mA, and 13,713 seconds. Others imaging devices can be used to obtain the CBCT image.

Figure 1. Correct orientation of the planes according to the inclination of the airways.



Data collected through CBCT is intended to be used to develop a standard method or protocol for upper airway evaluation.

To develop this protocol, we consulted the radiographic database of the Dental Clinic of the Faculty of Dental Medicine, Catholic University of Portugal, which has a Planmeca ProMax 3D (Planmeca) device. We searched for patients who had complete CBCT (maxilla and mandible) images to perform the analysis.

Data Analysis

The software used for upper airway analysis is Romexis (version 5.1.O.R; Planmeca). The images are exhibited in accordance with the field of view of 20.1×17.4 cm, size of 502×502×436 mm, and voxel size of 400 µm.

The measurements performed for all the CBCT images were as follows: total volume of the pharyngeal airspace, its area and its location, and the smaller dimensions of the anteroposterior and lateral pharynx (these measurements are illustrated in the *Results* section).

The protocol is as follows:

1. Activate the "Extract airways" tool in the box on the right with the title "Adjust" (Figure 2).
2. Then, enlarge the sagittal cut window in the box that appears on the "Airways Tool" screen to keep the threshold at 500 and mark the first point at the level of the posterior nasal spine (Figure 3).
3. Then, continue delimiting the airway following its curvature and mark a last point at the level of the middle of the fourth cervical vertebra (Figure 4).
4. Select, again, the option "Extract airways," and in the box that appears with the name "Airways Tool" adjust the variable that defines the airway limits (a standard adjustment value should be used for all patients so that it is possible to establish adjustments; in this case, the standardized value was 736). Then, the value of the total volume ("airway volume") appears (Figure 5).
5. Place the cursor over the box where the total volume value appears. In the same box will appear the value of the minimum airway area ("min area") (Figure 6).
6. Enlarge the window containing the axial plane and, from the narrowest area of the airway, select in the box on the right with the heading "Annotation" the tool "Measure Length" and measure the anteroposterior and laterolateral dimensions (Figure 7).
7. Record all obtained values.

To ensure the reproducibility of the protocol, all researchers performed the measurements, and patients were categorized into those at risk for OSAS (highest anteroposterior and

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laterolateral constriction of the airways of <52 mm^2 or 52-100 mm^2) or those at no risk (>100 mm^2).

Figure 2. Selection of the tool "Extract Airways" and marking of the points following the curvature of the airways.

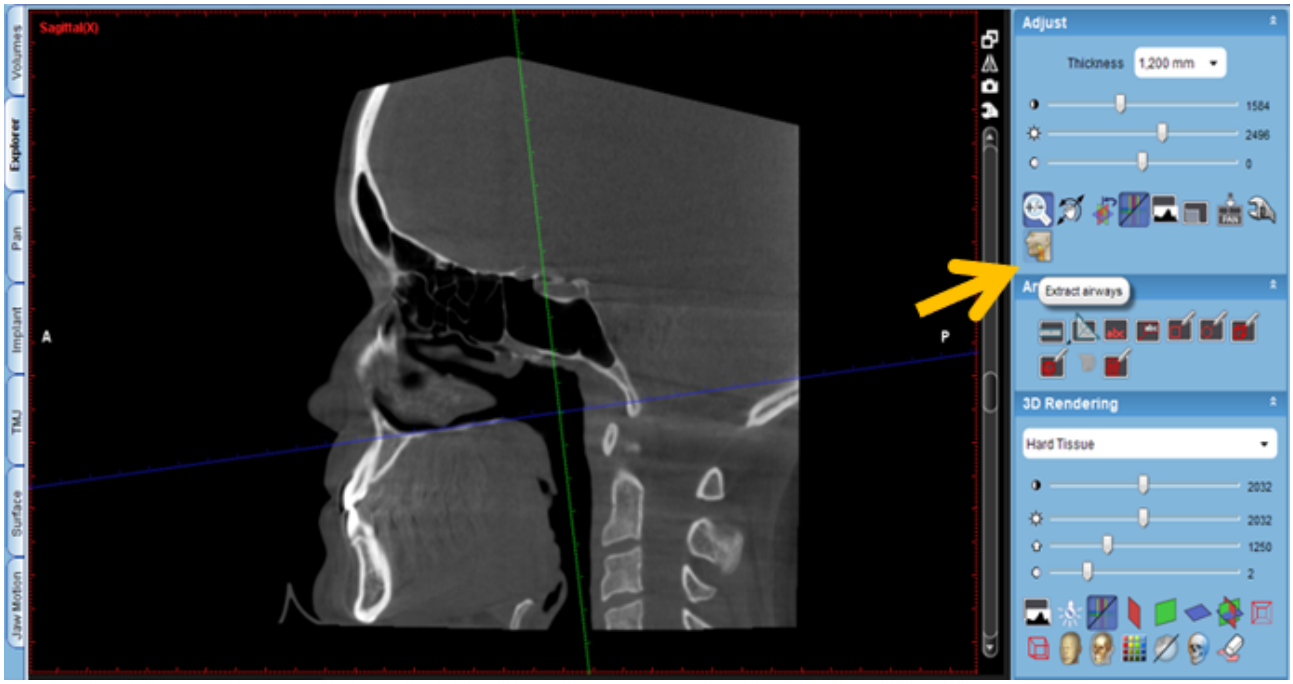
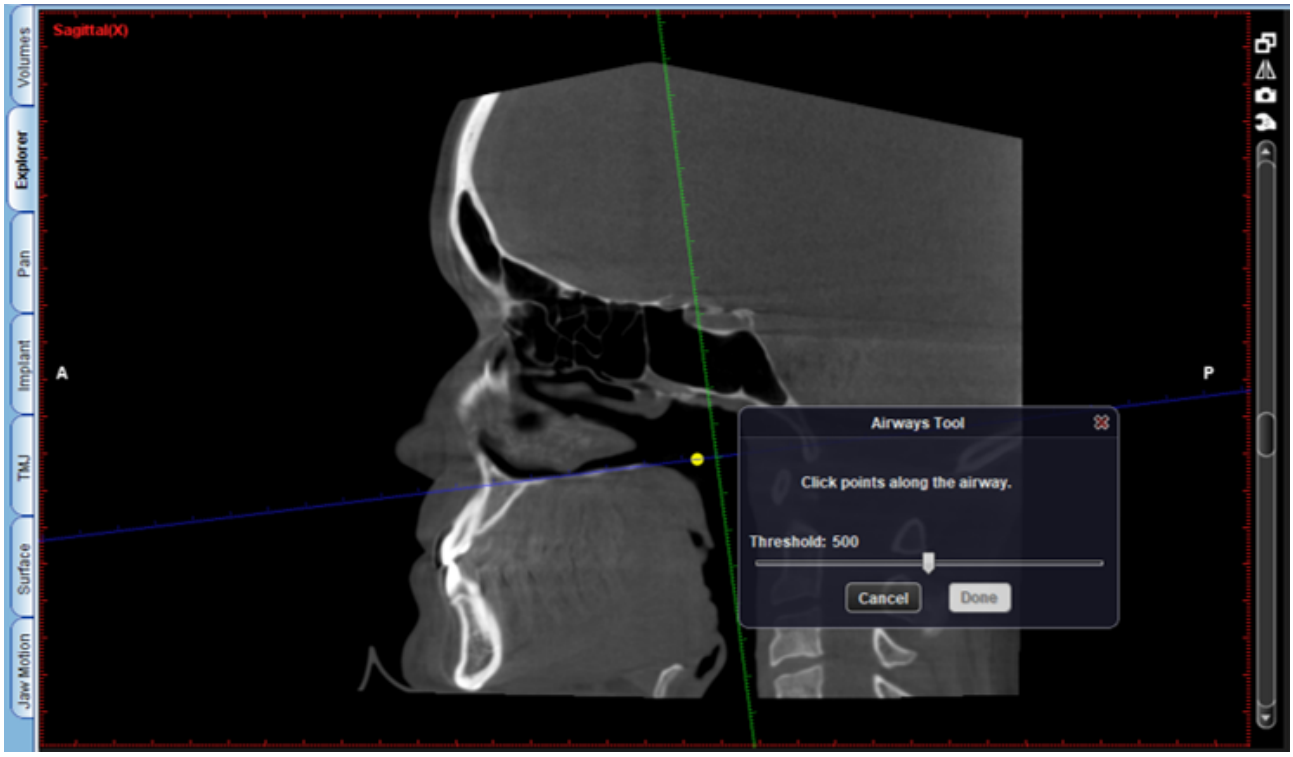


Figure 3. Keeping the threshold at 500 and marking the first point.



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Figure 4. Delimitation of the airway following its curvature.

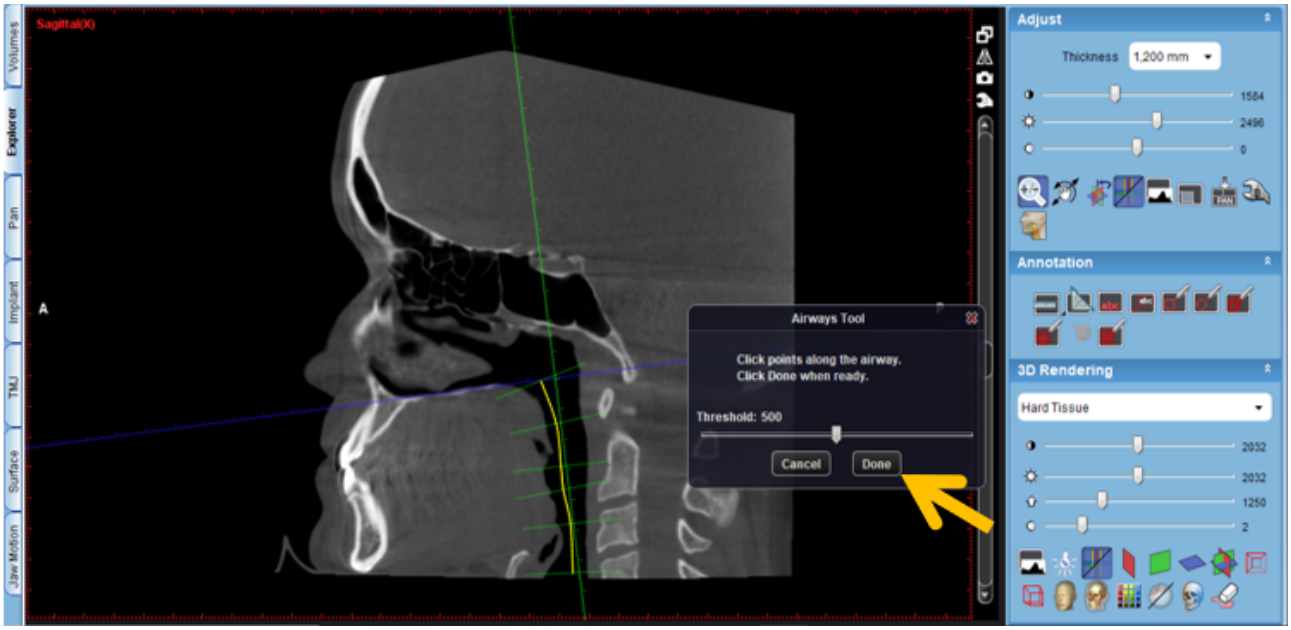
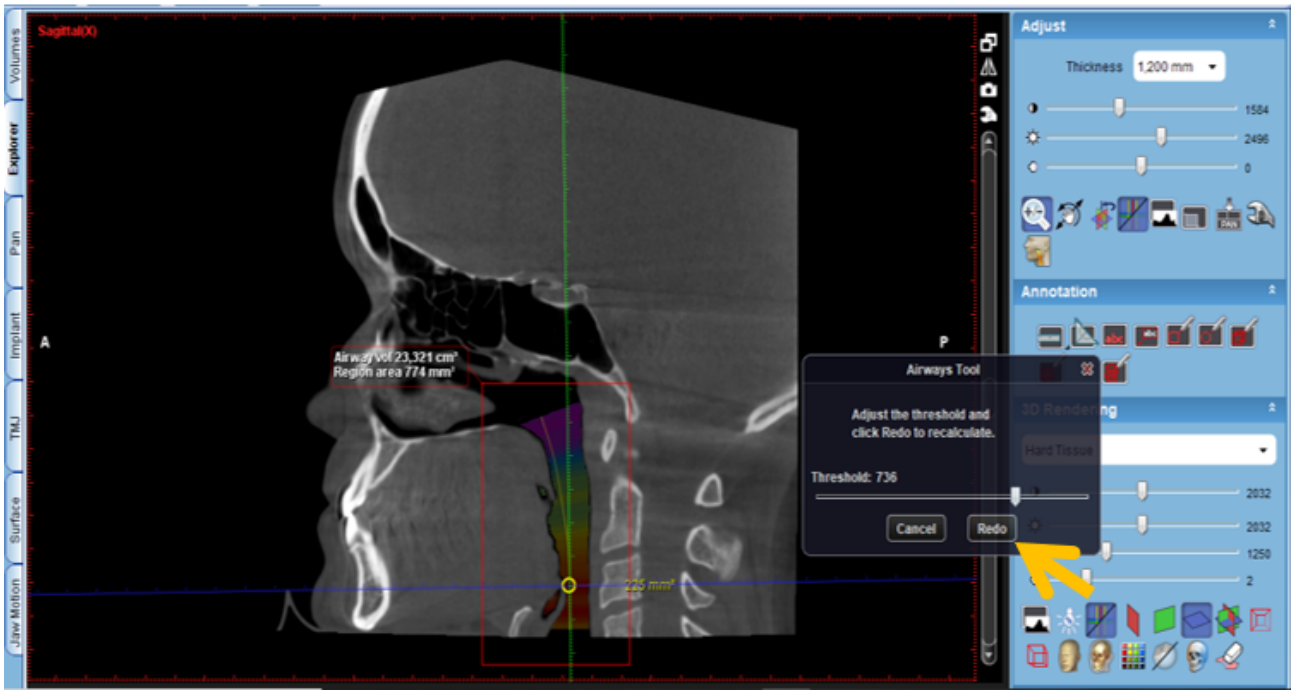


Figure 5. New selection of the option "Extract airways," and in the box that appears with the name "Airways Tool" the variable that defines the image limit is adjusted (standardized value for all patients=736).



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Figure 6. Calculation of the value of the total volume and the value of the minimum airway area ("min area").

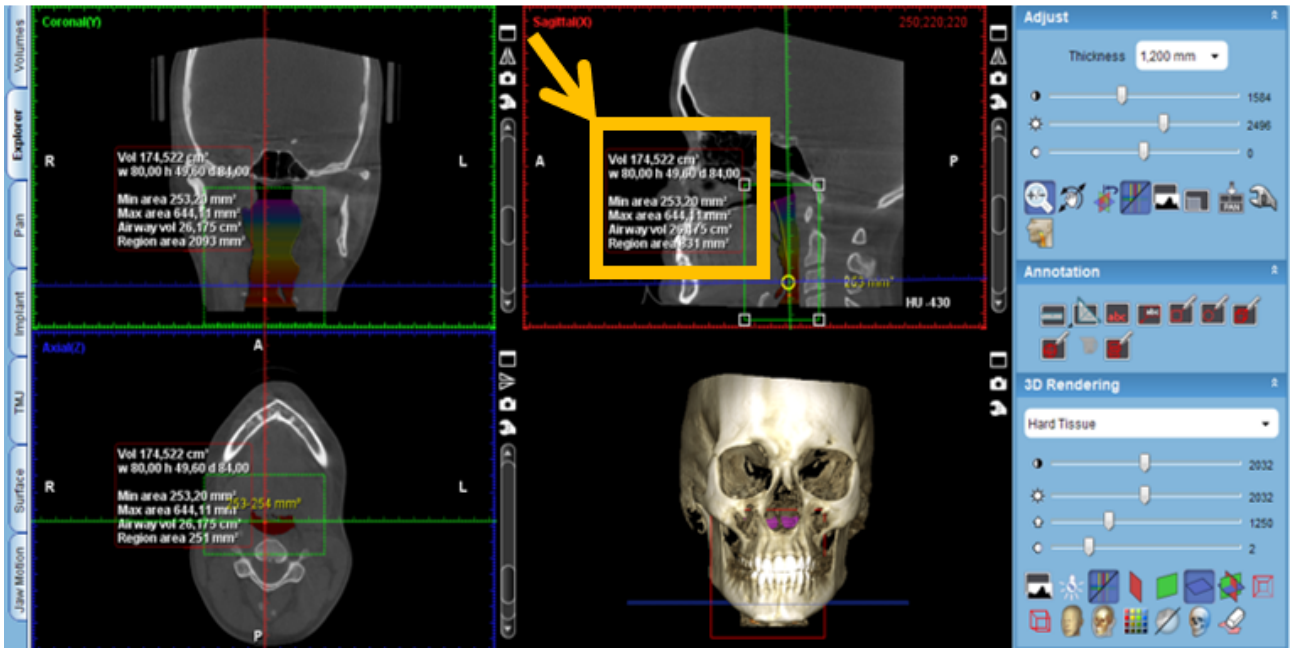
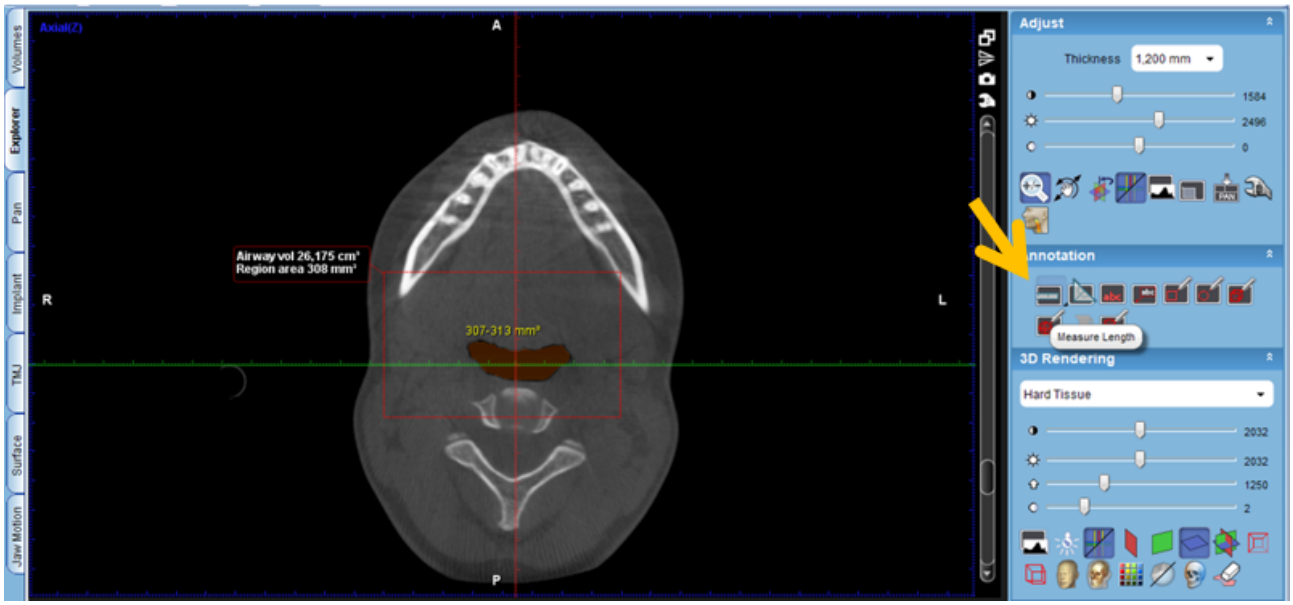


Figure 7. Anteroposterior dimension measurement.



Results

To establish this protocol, CBCT images of 30 patients were used (56% for males and 44% for females), and, in cases where an area of <52 mm^2 or 52-100 mm^2 was detected, the patient was contacted and referred to the hospital for diagnostic confirmation tests.

No differences were found between measurements obtained by the different researchers following the protocol described.

The protocol that the authors suggested for evaluation of the upper airways in CBCT allows for automatic calculation of the total volume of the pharyngeal airspace, its area of greatest narrowing, its location, and the smallest anteroposterior and laterolateral dimensions of the pharynx [15-18]. The measurement is performed automatically by the imaging software whose reliability is proven by the existing literature [16]. Thus, we reduce the possible bias of manual measurement, aiming at data collection.

Discussion

Principal Findings

The literature revealed no consensual and objective methodology for upper airway measurement. The lack of standardization in the definition of anatomical limits makes it impossible to subsequently make comparisons between different studies [19,20]. Recently, with the evolution of software, it is possible to perform upper airway measurement in a fast automatic analysis in an accurate, reproductible, and practical way. Its simplicity and speed allow this analysis to be adopted by all professionals. It is important to note that simplicity is not

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achieved in the detriment of any decrease in viability and reliability in the measurement of airways [16].

The CBCT helps measure the total volume of the pharyngeal airspace, its area of greatest narrowing in 3 different anatomical planes (sagittal, coronal, and transversal), its location, and the smallest anteroposterior and laterolateral dimensions of the pharynx [14-16]. Steffy et al [1] related the constriction value of the oropharynx with the risk of developing OSAS. An area of <52 mm^2 is considered as having a high risk of OSAS; 52-100 mm^2, intermediate risk; and >100 mm^2, low risk [1]. Compared to the other radiographic methods described in the literature, usually available to the dentist, such as profile teleradiography and CT, the CBCT, as previously mentioned, presents more advantages. It is possible to acquire the same or better images with less radiation and less time of exposure. The assessment protocol for CBCT described herein constitutes a valuable screening tool for OSAS, which allows clinicians to refer the patient to the hospital for diagnosis confirmation. To establish this protocol, CBCT images of 30 patients were used, and in cases where an area of <52 mm^2 or 52-100 mm^2 was detected, the patient was contacted and referred to the hospital for diagnostic confirmation tests.

Limitations and Strengths

The protocol's main limitations are related to the position at which this examination is performed. The patient undergoes the examination in a standing position and not in a supine position, which may introduce false negatives here or cause a suspected hypothesis to be discarded. In addition, the step responsible for adjusting the threshold is characteristic of each examination. This threshold adapts the difference between the shades of gray in each voxel of the airway and the rest of the area. However, in general, Zimmerman et al [19] verified, in a systematic review, that most studies measuring the airways have high intraexaminer reliability. Although in this study, no CBCT image was purposely acquired, currently, it is known that it is a comprehensive examination that allows numerous interpretations and simulations from a very low radiation dose. Nevertheless, the ALARA (ie, *As Low As Reasonably Achievable*) principle should be respected, reserving the execution of these examinations for cases in which they are strictly necessary [19,20].

However, despite these limitations and due to the automatic measurements performed by the system, this protocol in CBCT constitutes a good patient screening tool that will help standardize the measurements and ensure that they are performed in a reproductible, accurate, and simple way while the comfort of and benefit for the patients increases.

Conclusions

This protocol provides a new standardized tool to identify patients at the risk of OSAS by using CBCT and contributes to the detection of upper airway–related pathologies, such as OSAS, in patients visiting the dental clinics, using these devices and software. This protocol will have a significant impact in reducing the subdiagnosis of this pathology, contributing to its treatment and subsequently the prevention of serious comorbidities associated with OSAS. Our protocol may also be suitable for other imaging software. The anatomical points used for reference are most relevant for standardizing studies in this field and for software evaluation to reduce bias.

Acknowledgments

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Conflicts of Interest

None declared.

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Abbreviations

CBCT: cone-beam computed tomography
CT: computed tomography
OSAS: obstructive sleep apnea syndrome

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Protocol

Health Status, Quality of Life, Psychosocial Well-being, and Wearables Data of Patients With Active Ulcerative Colitis Receiving Filgotinib Therapy (FilgoColitis Study): Protocol for a Real-world Observational Study

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Abstract

Background: Filgotinib was approved in Germany for treating patients with moderate to severe active ulcerative colitis in November 2021. It represents a preferential Janus kinase 1 inhibitor. The FilgoColitis study began recruiting immediately after approval and aims to assess filgotinib effectiveness under real-world conditions with a particular focus on patient-reported outcomes (PROs). The novelty of the study design is the optional inclusion of 2 innovative wearables, which could provide a new layer of patient-derived data.

Objective: The study investigates quality of life (QoL) and psychosocial well-being of patients with active ulcerative colitis during long-term exposure to filgotinib. PROs related to QoL and psychometric profiles (fatigue and depression) are collected alongside with disease activity symptom scores. We aim to evaluate physical activity patterns collected by wearables as an addition to traditional PROs, patient-reported health status, and QoL in different phases of disease activity.

Methods: This is a prospective, single-arm, multicentric, noninterventional, observational study with a sample size of 250 patients. QoL is assessed with validated questionnaires: the Short Inflammatory Bowel Disease Questionnaire (sIBDQ) for the disease-specific QoL, the EQ-5D for the general QoL, and the fatigue questionnaire (Inflammatory Bowel Disease-Fatigue [IBD-F]). Physical activity data are collected from patients using wearables (SENS motion leg sensor [accelerometry] and smartwatch, GARMIN vívosmart 4).

Results: The enrollment started in December 2021 and was still open at the date of submission. After 6 months of study initiation, 69 patients were enrolled. The study is expected to be completed in June 2026.

Conclusions: Real-world data for novel drugs are important to assess effectiveness outside of highly selected populations represented by randomized controlled trials. We examine whether patients' QoL and other PROs can be supplemented with physical activity patterns measured objectively. Use of wearables with newly defined outcomes represents an additional observational tool for monitoring disease activity in patients with inflammatory bowel disease.

Trial Registration: German Clinical Trials Register DRKS00027327; https://drks.de/search/en/trial/DRKS00027327

International Registered Report Identifier (IRRID): DERR1-10.2196/42574

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KEYWORDS

ulcerative colitis; inflammatory bowel; filgotinib; wearable; eHealth; digital health; quality of life; fatigue; patient-reported outcome; real-world evidence; mobile phone

Introduction

Background

Ulcerative colitis (UC) is a chronic disease, which affects the digestive system and therefore, belongs to inflammatory bowel diseases (IBDs). Worldwide, more than 1.8 billion patients have been diagnosed with UC [1] with an ever-increasing trend [2,3].

UC has a chronic recurrent course of disease. Patients with UC have recurrent diarrhea, abdominal pain, nausea, weakness, or anemia, among other symptoms. As a result, the patients' quality of life (QoL) and well-being can be impaired [4,5].

Currently, there are already many targeted therapies for moderate to severe UC. The use of biologics and other small molecules in patients with UC is increasing. Nevertheless, effectiveness is only approximately 30%. Recently, new modes of action have been introduced. In 2019, tofacitinib became the first Janus kinase (JAK) inhibitor approved in UC. However, as a pan JAK inhibitor, it has elicited some serious adverse events. Due to several Dear Doctor Letters (Rote-Hand-Brief), its acceptance by physicians has declined. Filgotinib is the first oral preferential JAK1 inhibitor, with fewer side effects expected than with a pan JAK inhibitor, approved for UC in Europe as of November 2021. Because pivotal studies with narrow predefined inclusion criteria do not always reflect treatment in routine clinical practice, the FilgoColitis study was established to reflect use under real-world conditions.

The novelty of the study design is the optional inclusion of 2 innovative wearables, which could provide a new layer of patient-derived data. Correlations with disease activity and QoL have been established before [6-8], but the cohort sizes were small and not in a longitudinal setting around targeted therapy. Therefore, real-world studies to assess the effect of digital health tools on disease activity are still needed [9].

Objectives

This study aims to investigate the QoL and psychosocial well-being of patients with UC on filgotinib therapy over the long-term course of different disease phases under routine conditions. Therefore, we aim to use wearables additionally and collect patient-reported outcomes (PROs) related to QoL and psychomotor profiles (fatigue and depression), including physical activity, under real-world conditions.

Using wearables, we aim to investigate whether physical activity data are related to QoL in patients with UC and whether there is an association between physical activity patterns, health status, and QoL, and additionally to define a new outcome in UC treatment. Furthermore, we will evaluate the safety profile of filgotinib therapy considering (serious) adverse events.

Methods

Study Design

The FilgoColitis study is a prospective, single-arm, multicentric, investigator-initiated, noninterventional observational study.

Outcomes

Primary Outcome Measure

The disease-specific QoL of patients with UC during long-term course of therapy is the primary outcome and is assessed with the help of the validated and internationally widely applied Short Inflammatory Bowel Disease Questionnaire (sIBDQ, German version), which contains 4 domains: bowel symptoms, emotional health, systemic systems, and social function [10]. Thereby, the different disease phases will be considered and examined.

Secondary Outcome Measures

As a secondary outcome, the safety profile of the filgotinib treatment will be explored, taking (serious) adverse events into account. Furthermore, clinical parameters such as the disease activity using the partial Mayo Score (pMayo, and additionally PRO2) and the Montreal Classification are assessed. In addition, the therapy deemed necessary and useful for the patient by the physician is recorded. The general QoL using the validated questionnaire EQ-5D-5L (which essentially consists of 2 pages: the EQ-5D descriptive system and the EQ visual analog scale [EQ-VAS]) is documented. The descriptive system comprises 5 dimensions: mobility, self-care, usual activities, pain or discomfort, and anxiety or depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems [11].

Fatigue is highly prevalent among patients with IBD [12]; therefore, the fatigue questionnaire (Inflammatory Bowel Disease-Fatigue [IBD-F]) is used in the study [13]. The scale of the IBD-F questionnaire was developed to be used for the diagnosis of fatigue or monitoring fatigue levels over time. The German version of the questionnaire has been published recently [14].

Additional Exploratory Outcome Measures

Wearables will be given to patients to collect their physical activity data, such as the number of steps per day, pulse rate, calories burned per day, physical activity patterns (day and night), stress, sleep rhythm, and sleep quality. We aim to examine the correlation between physical activity, stress, sleep, disease phases, and the patients' psychosocial impairment. The used wearables are (1) an accelerometry-based sensor (SENS motion, Class 1M medical device), which is attached to the thigh of one leg, and (2) a smartwatch (GARMIN vívosmart 4). The wearables are adapted for German server–based documentation of the physical activity parameters (number of steps per day and speed), pulse rate, calories per day, physical

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activity patterns (day and night), rhythm and quality of sleep, and stress level.

Statistics

Overview

This study is descriptive, and no formal hypotheses are tested. Patient and clinical characteristics are described to capture the baseline situation of patients treated with filgotinib. Descriptive statistics are used to summarize patients' demographics and baseline data. Specifically, for continuous variables, the mean, 95% CI for the mean, SD, median, and IQR are reported. For discrete variables, the frequency and number of missing observations are reported.

In this noncomparative observational study, the primary end point is analyzed as the mean change (the difference in scores between the 2 time points) in sIBDQ values from baseline to week 10 and is presented along with the 95% CI. For sIBDQ scores (total), mean changes from baseline to week 10 (week 52 and week 104) are calculated with a 1-sample *t* test for differences between paired observations (or a nonparametric analog).

Patients' sIBDQ QoL is summarized and compared concerning the following: (1) mean change from baseline to assessment points during the study and (2) at each analysis time point, the number of patients who have completed the questionnaire is reported as a percentage of eligible patients. Data will be collected at visit 1 (ie, at baseline) and then at approximately week 10, and every 6 months up to 2 years.

Repeated Measurements Over Time

Each subject is assumed to have his or her mean response curve that explains how the sIBDQ score changes over time (intraindividual changes). A mixed effects model is used to model individual sIBDQ response curves over time.

Justification of Sample Size

The difference in sIBDQ scores from baseline to week 10 (week 52 and week 104) will be analyzed. The null hypothesis is that the average difference is zero. The alternative hypothesis is that the average difference has a nonzero value. Based on the results of a previous study [15], we aim to demonstrate a difference of 7 points or more with an α of .05, assuming an SD of 12, and assuming that each pair of measurements on the same individual correlates with approximately 0.5. With a sample size of 250 subjects, a power of >90% is achieved to detect the above mean of paired differences with a 2-tailed paired *t* test [16].

Exploratory Data Analysis

As an exploratory data analysis, correlations between the pMayo and exercise data and psychomotor data (such as sleep quality, stress, and fatigue) will be calculated.

Definition of the Study Population

This prospective observational investigator-initiated trial will be conducted with 250 participants at approximately 50 sites all over Germany. The gender ratio will be balanced.

Selection of Study Sites

Sites are IBD-experienced hospitals or gastroenterology practices in Germany. Site selection will be made by the study investigators. By signing the investigator agreement, each site confirms its fulfillment of all formal requirements for inclusion in the study and guarantees its compliance with data privacy laws and any other regulations about the execution of this observational study.

Participant Criteria

The inclusion criteria for the FilgoColitis study include (1) the confirmed diagnosis of UC (according to the current guidelines from the German Society for Gastroenterology, Digestive and Metabolic Diseases and European Crohn's and Colitis Organization), (2) the initiation of therapy with filgotinib at the physician's discretion regardless of potential study participation, (3) age of the patient between 18 and 80 years at inclusion, and (4) in-label use according to filgotinib product information. The exclusion criteria include (1) planned surgical intervention with hospitalization, (2) history of malignant disease (except "nonmelanoma skin cancer"), and (3) contraindications for treatment with filgotinib (according to the product information).

Study-Specific Examinations: The Use of Wearables

Within the scope of the additional examination, the 2 accelerometry-based wearables (SENS motion accelerometry leg sensor, and GARMIN smartwatch) will be provided by the clinical research organization. Participation in the additional examination is voluntary.

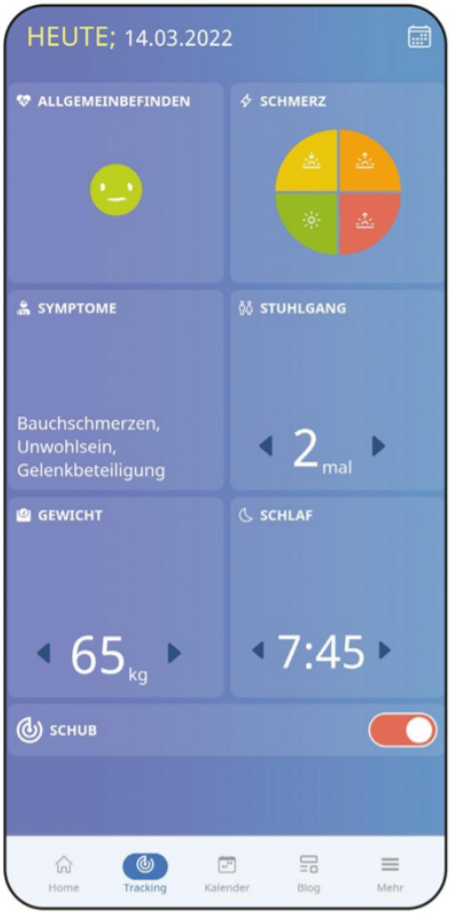
The wearables aim to improve data collection of physical activity behavior. Activity and psychomotor data are recorded by the provided trackers and transmitted to the server via the MyTARGET app.

The MyTARGET app (Figure 1) is a therapy support app for people with IBD. It was developed by the competence network IBD (Kompetenznetz Darmerkrankungen) and the German Association of Gastroenterologists (Berufsverband Niedergelassener Gastroenterologen Deutschlands) in close cooperation with experienced gastroenterologists, physician assistants, and patients to provide the best possible support for patients in their daily lives. The app is freely accessible and can be used by anyone. Within the app, there is a specific FilgoColitis study area, where only study participants have access via a QR code. In this area, patients can connect their wearables to their smartphones via Bluetooth. Once the devices are connected, a secure data transfer of the movement data to the study servers can take place assisted by the MyTARGET app. All data are stored only on the study server and are not passed on to the GARMIN company. The patients also receive a small output of their movement data.

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Figure 1. Homescreen and tracking area of the MyTARGET app.





The GARMIN watch may be worn for the entire study period of 24 months (day and night). If the physician and patient agree, it is desirable to be worn during the 10-week induction phase (day and night) or at least in the following 7 days after the baseline visit. For the follow-up visits, the GARMIN watch, if used, may be worn for 7 days after each follow-up visit (day and night).

If desired by the patient, the SENS motion sensor may be worn from the baseline visit and at each follow-up visit for 7 days (day and night). Both wearables may also be worn 3 days before the start of filgotinib therapy (baseline visit), if applicable. These movement data are not made available to the treating physician in a direct temporal context so as not to influence therapeutic decisions.

Schedule of Visits

Visits at the study site are scheduled at inclusion (baseline visit week 0) and during follow-up (week 10, month 6, 12, 18, and 24). Follow-up visits are not fixed scheduled visits but are to occur when the study participant sees his or her physician as part of routine treatment.

Documentation

Data are recorded using case report forms at the study sites and are transferred to an electronic case report form at the site. Data outlined in Table 1 are recorded during the baseline examination and at follow-up. In addition, each (serious) adverse event is recorded.

The movement data of the additional wearable examination are recorded and stored locally as soon as the patient puts them on (Textboxes 1 and 2). Data are transferred from the wearables to the MyTARGET app on the patient's smartphone via Bluetooth. The patient is given access to the study area via an individual QR code within the app. In this QR code, a digital pseudonym is stored, which enables the assignment of the movement data to the patient's own study number. When the wearables and app are connected via Bluetooth, the data are automatically transferred from the devices to the MyTARGET app on the study participant's cell phone and from there to the study server (Figure 2). There, the movement data are merged with the site-based collected data on the patient's pseudonym.

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Table 1. Clinical data collected in the FilgoColitis study stratified by baseline and follow-up visits.

Variable	Baseline visit	Follow-up visits (week 10, month 6, 12, 18, and 24)
General information		
Date of patient visit	✓	✓
FilgoColitis study number	✓	
Diagnosis of ulcerative colitis	✓	✓
Study participation with wearables	✓	✓
GARMIN Fitness watch	✓	✓
SENS motion ID	✓	✓
Short pseudonym	✓	✓
Demographic data		
Gender	✓	
Date of birth	✓	✓
Height	✓	
Weight	✓	✓
Waist circumference	✓	✓
Smoking status	✓	✓
Zip code	✓	✓
Ethnic origin	✓	
Social status	✓	✓
Highest school qualification	✓	✓
Member in the self-help organization German Crohn's Disease and Ulcerative Colitis Association	✓	✓
Sports activity	✓	✓
Anamnesis		
Date of initial diagnosis (IBD[a])	✓	
First IBD symptoms (retrospective)	✓	
Relatives with IBD	✓	
Hospitalization	✓	✓
Stool frequency previous night	✓	✓
Start of filgotinib therapy (induction phase)	✓	
Proctocolectomy	✓	✓
Cancer diagnosis	✓	✓
Fistula	✓	✓
Stenosis	✓	✓
Comorbidities	✓	✓
Drug intolerances	✓	✓
Current findings		
Montreal classification	✓	✓
Current illness situation	✓	✓
Laboratory parameters (C-reactive protein, fecal calprotectin, and hemoglobin)	✓	✓
Endoscopy	✓	✓
Extraintestinal manifestation	✓	✓
Current medication	✓	✓

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Variable	Baseline visit	Follow-up visits (week 10, month 6, 12, 18, and 24)
Partial Mayo Score	✓	✓
PROs[b]		
General quality of life (EQ-5D-5L)	✓	✓
Disease-specific quality of life (sIBDQ[c])	✓	✓
Fatigue Questionnaire (IBD-F[d])	✓	✓

[a]IBD: inflammatory bowel disease.

[b]PRO: patient-reported outcome.

[c]sIBDQ: Short Inflammatory Bowel Disease Questionnaire.

[d]IBD-F: Inflammatory Bowel Disease-Fatigue.

Textbox 1. Collected data from the wearable GARMIN vívosmart 4 within the additional examination.

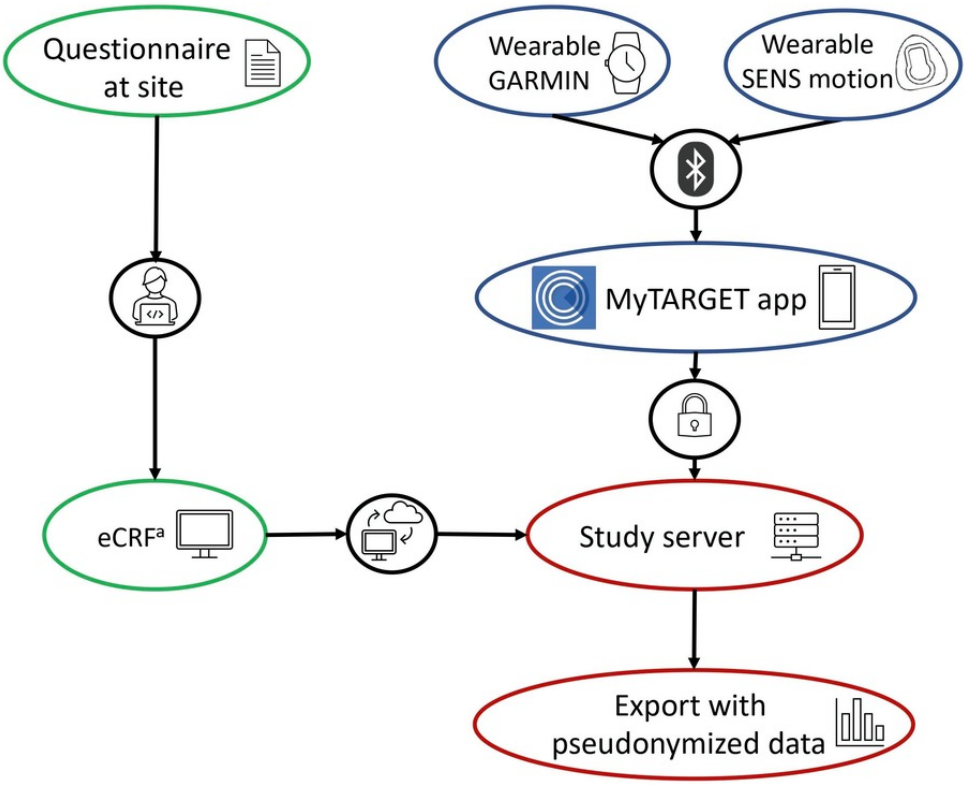
- Steps
- Heart rate
- Stress
  - Recovery
  - Low stress
  - Medium stress
  - High stress
- Sleep duration
- Sleep level
  - Light sleep
  - Deep sleep
  - Rapid eye movement (REM) sleep

Textbox 2. Collected data from the wearable SENS motion within the additional examination. Duration and steps were collected for each movement type.

- Lying or sitting rest
- Lying or sitting movement
- Standing
- Sporadic walking
- Walking
- Moderate intensity
- High intensity
- Cycling

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Figure 2. Transfer of the movement data from wearables to the study server. eCRF: electronic case report form.



Patient Identification

All patient data are pseudonymized. Each patient will be identified by a patient identification number assigned at each study site. The investigator will keep a patient identification list, documenting the patient identification number with the patient's full name, date of birth, sex, and date of informed consent.

The patient identification list is part of the investigator's file and will remain at the site. The patient identification number comprises a 3-digit clinic number and a consecutive 3-digit number of recruited patients per study site.

Study

Start of Patient Participation

Any patient who meets the inclusion and exclusion criteria of the study is a potential candidate. All potential candidates who come to the attention of the investigator will be consecutively informed of the opportunity to participate in the study. Written informed consent will be obtained before the commencement of documentation.

End of Patient Participation

The observation of each patient ends according to the schedule with the last study visit (month 24), after 2 years. A patient's participation in the study will be terminated prematurely if at least one of the following criteria is met: (1) withdrawal of informed consent or death of the patient, (2) change of diagnosis, (3) lack of medical justification for further participation in the study, (4) premature termination of the complete study, or (5) subsequent discovery that not all inclusion criteria are met or that any exclusion criteria are met at baseline. A change in therapy does not result in study dropout. Furthermore, patients may be declared as lost-to-follow-up if they are no longer available and thus could not be documented at more than 2 consecutive visits.

Study Duration

This prospective study is planned for over 3.5 years (including 18 months of recruitment and 24 months of follow-up documentation per patient). The complete study is considered to have ended after all queries from the study coordination center have been answered by each study site, at the latest, 2 months after the last visit of the last patient.

Data Quality, Quality Control, and Assurance

The input fields in the web-based documentation form are stored with an input logic to avoid incorrect entries. In addition, remote monitoring of the data is permanently carried out and, if necessary, corresponding queries are made. Approximately 30% (n=75) of documented cases will be reviewed via in-house or on-site monitoring. Within the on-site monitoring, all study-relevant documents will be inspected and checked for completeness and current validity. In case of missing or implausible data, queries are generated and forwarded to the corresponding study site. This process is described in more detail in the monitoring manual.

Data Collection

Data collection of questionnaires (clinical data) and wearables data will take place on secured web servers based in Germany. The data will be transmitted and evaluated pseudonymously.

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Ethics Approval and Regulatory Aspects

The principal investigators and CED Service GmbH in Kiel are responsible for obtaining the required ethics committee approval as well as compliance with data protection regulations. Approval is obtained from the ethics committee of the medical faculty of the University of Kiel (D 609/21). The German Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte), the "Kassenärztliche Bundesvereinigung," the "Spitzenverbände der Krankenkassen," and the "Verband der Privaten Krankenversicherungen e.V." have been notified of this noninterventional study according to §67 of the German Medicinal Products Act (Arzneimittelgesetz). A final report will be sent to the responsible federal authority after completion of the data collection according to §67 (6) of the German Medicinal Products Act. Furthermore, the study is published in the public German Clinical Trials Register (DRKS00027327).

Before enrollment in the study, the investigator will inform each patient of the nature, significance, risks, and scope of the study and the patient's right to withdraw from the study at any time without prejudice. The patient will be given an informed consent form describing the study in nonscientific and generally understandable language. Each patient must consent in writing to participate in the study. The patient must be given sufficient time to decide and ask questions before signing the consent form.

Results

The enrollment commenced in December 2021 and was still open at the date of submission. The study is expected to complete in June 2026. After 6 months of study initiation, 69 patients were enrolled in FilgoColitis. The median age of patients is currently 41.7 (IQR 28.7-56.0) years; 52% (n=36) of patients were male and had a disease duration of 7.4 (IQR 4.3-14.8) years. In total, 90% (n=62) and 23% (n=16) of patients were pretreated with biologics and small molecules, respectively. Wearables were accepted by 80% (n=55) of patients.

Discussion

The Rationale for the Study

Treatment of moderate to severe UC remains challenging with approximately 30% of patients benefiting from biologics. Further modes of action are therefore needed. JAK inhibitors play a role by inhibiting the Janus kinase/signal transducers and activators of transcription pathway, thereby slowing down the inflammatory process [17].

The first to market in 2019 was a pan JAK inhibitor, tofacitinib. It is hoped to achieve a more specific effect by inhibiting individual JAKs in a more targeted manner: filgotinib is a JAK1 preferential inhibitor, and therefore fewer side effects are expected.

The pivotal SELECTION study [18] showed significantly higher efficacy (clinical remission) in patients receiving 200 mg filgotinib therapy when compared to a placebo in both the induction and maintenance phases. The incidence of serious adverse events was not higher in the filgotinib groups compared to the placebo group.

The safety profile and the effectiveness of objective disease scores as well as PROs under real-world conditions have not yet been studied. Therefore, the FilgoColitis study was initiated shortly after approval in Germany and Europe. The study focuses on PROs, which will be collected both subjectively via questionnaires but also using wearables to provide objective data on activity behavior and psychomotricity. In addition to abdominal pain, fatigue is reported by many patients as a common complication [12]. Therefore, the IBD-F is applied, for which the German version has recently been validated [14]. The scale of the IBD-F questionnaire was developed to be used in the diagnosis of fatigue or to monitor fatigue levels over time. The IBD-F scale consists of 3 sections: section I identifies the level and duration of fatigue, section II assesses the impact of fatigue on daily activities, and section III identifies causes and other factors related to fatigue. The FilgoColitis study will analyze if there is a correlation between the objective movement measures, disease activity, and fatigue.

Justification for Study Design

The study is conducted nationwide and multicentrally with specially selected sites to achieve higher representativeness of the study results for the entire population. Since the study's primary objective is to observe the effects of filgotinib therapy on QoL and psychomotor markers, a single-arm study design is warranted. Furthermore, the study aims to investigate to what extent it is possible to have an additional observational outcome tool for monitoring disease activity in patients with IBD by using wearables.

Wearables

Since exercise and sleep are associated with QoL, 2 wearables are used in this study to enable measurement of the patients' movement and sleep comprehensively. We hypothesize that early changes in wearable parameters (eg, increase of step counts and normalization of heart rate variability) are potentially associated with long-term improvement of QoL. Other studies show similar results. van Langenberg et al [19] reported significantly poorer sleep quality and less physical activity in patients with Crohn disease compared with healthy control subjects, as measured by an accelerometer over 7 days. Similarly, Wiestler et al [6] found significant associations between physical activity and the disease-specific QoL and disease activity in patients with IBD.

In the FilgoColitis study, 2 wearables are used. The leg accelerometry sensor SENS motion is a medical device, whereas the GARMIN smartwatch vívosmart 4 is a simple fitness watch. We aim to show that nonmedical devices can also be used in clinical studies to measure physical activity and can be related to other important outcomes. The advantages of nonmedical devices are higher affordability and easier usability. Thus, we hope to be able to scientifically demonstrate in the FilgoColitis study that less expensive, widely used devices are also suitable for the monitoring of patients with UC. Nevertheless, it must be noted that nonmedical devices can also be less valid and accurate. In an unpublished field study prior to commencement

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of the FilgoColitis study, we successfully showed the comparability of both wearables in an on-site test (data not shown).

To achieve meaningful results from the additional examination, the researchers are dependent on a high level of compliance from the study participants. For the success of the study, patients who voluntarily participate in the additional examination must wear their wearables at the desired times for the desired duration. However, since the FilgoColitis study is noninterventional and due to its voluntary nature in the additional examination, decreasing compliance of study participants must be expected. Because of the longer study duration, patients may forget to put the wearables back on for the visit or to transfer their data. Willingness to wear a watch or leg sensor visibly on the body may also drop over the study course. These assumptions were made based on findings from researchers in other digital studies where a decline in compliance over the course of the study was observed. One review showed that compliance is usually very high at the start of the study and then declines rapidly over the first weeks and months. However, success factors such as user training, health education, and maintaining strong participant motivation were also identified to positively influence compliance [20].

The compliance of the study participants cannot be enforced, but the framework conditions can be designed in the best possible way to achieve the highest possible compliance. Therefore, measures were also introduced in the FilgoColitis study, such as the creation of detailed instructions and web-based tutorials or active technical support by the study team. If the study size is smaller than expected due to low compliance, statistical recalculations must be performed to ensure that the results are still statistically meaningful. Nevertheless, if compliance within additional examination is so low that no meaningful results can be obtained, as a consequence the results can only be examined in relation to the primary and secondary outcome measures. However, due to the measures mentioned above, we hope to achieve the highest possible compliance of the study participants.

The use of new technologies such as smartwatches or leg sensors has many advantages in studies. Examples are higher recruitment rates, faster feasibility of the study, and the collection of a broader range of health data [21,22]. Atreja et al [23] summarize in the review on remote monitoring of patients with IBD that in the near future this rapidly evolving technology will become a mainstream tool in standard patient care practices. Nevertheless, certain obstacles must also be expected. Technical problems may occur at any time, which means that important participant movement data cannot be recorded or transmitted and is therefore lost. In addition, the additional examination is not feasible for everyone. Patients without their own smartphones cannot participate, and certain prior knowledge of smartphone use is also assumed. Due to the partly complicated procedure, older people may be excluded due to excessive demands or lack of knowledge. However, studies show that older people are generally positive about smartwatch technologies for measuring PROs. According to Manini et al [24], the aspect of user-friendliness is one of the most important points that must be given special consideration during design. Therefore, elements such as detailed explanations and descriptions, big visible buttons, and a frequently asked question area were added to the MyTARGET study app. The goal was to create the greatest possible user-friendliness, so that older study participants are also attracted to the additional examination within the FilgoColitis study.

Strengths and Limitations

The FilgoColitis study is the first large real-world study of filgotinib. One strength is the prospective design of the study. In addition, the primary outcome parameter is a PRO, namely QoL. In particular, the assessment of fatigue represents a modern approach in IBD research. Finally, the use of new technologies that objectively measure exercise, sleep, and stress behavior makes the study unique.

The study also has some limitations: a selection bias cannot be excluded in the FilgoColitis study and should also be considered in future analyses. To recruit a broad representative population of study participants and overcome the selection bias, we distributed the study sites all over Germany and included patients with a large age range (18-80 years). In addition, physicians consecutively enrolled eligible patients in the study. Moreover, filgotinib is the first oral preferential JAK1 inhibitor, and its approval has also opened up new strategies for the treatment of patients with UC. Due to the newly emerging treatment opportunities, it can be assumed that mainly last liners, meaning patients who have already taken several biologics without success, will receive the new drug and will be included in the study. Accordingly, it can be assumed that these patients tended to be in poor health prior to study inclusion and have a low QoL. However, the effect that filgotinib may have on QoL can still be well examined by surveying QoL at baseline. Thus, individual improvement or worsening of QoL over the course of the study can be evaluated for all participants without bias regarding the prevailing health status. The selection bias is tried to be avoided accordingly.

In addition, the FilgoColitis study is conducted using written questionnaires completed by the patients and physicians. On the one hand, we do not see limitations with regard to the physicians, since the remote monitoring system allows queries to be asked at any time regarding open or unclear answers. On the other hand, however, there could be omitted questions or illogical answers with regard to the patients, which could negatively influence the analysis of the study objective. To counteract this limitation, however, the attending physicians and the trained study nurses work closely with the patient so that questions can be asked at any time in the event of ambiguities or problems. In this way, as many missings as possible are to be avoided.

Nevertheless, with our efforts to eliminate the mentioned limitations, we aim to use the observational FilgoColitis study to draw significant correlations between the QoL and psychosocial well-being of patients with UC on filgotinib therapy over the long-term course under real-world conditions. With the results of the study, we intent to assist physicians in making future treatment decisions regarding the prescription of filgotinib.

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Conclusions

In summary, in the FilgoColitis study, we aim to find out how the new JAK1 inhibitor filgotinib affects the QoL of patients with UC in clinical practice with real-world conditions and how safe the therapy is. By using wearables, we assume to obtain superior data to assess patients' QoL. We also hope to prove that the use of wearables could be an additional observational outcome tool to monitor disease activity in patients with IBD. With the multicenter approach, large study population, and long study duration, we aim to obtain meaningful and valid data on the safety and effects of filgotinib therapy.

Acknowledgments

This study is supported by Galapagos NV. The authors are grateful to all parties involved in the study, the sites, and the participants.

Data Availability

The data sets generated and analyzed during this study are available from the corresponding author upon reasonable request.

Authors' Contributions

BB, SS, and SPD contributed to the design of the study protocol. All authors were involved in writing the first draft of the manuscript and contributed to the revision of the draft and final approval of the version to be published.

Conflicts of Interest

BB has received consulting fees from AbbVie, MSD, Shire, Ferring, Hospira, Takeda, Movetis, Shield Therapeutics, Pfizer, Biogen, Janssen, Hexal, and Celgene; received financial support for lectures and teaching from AbbVie, Ferring, MSD, Merckle, Falk, HLR, Shield Therapeutics, Pfizer, Celltrion, Takeda, Janssen, and Mundipharma; and received grant and financial support for research from AbbVie and Ferring. SS has received personal fees from Abbvie, Arena, BMS, Biogen, Celltrion, Celgene, IMAB, Gilead, MSD, Mylan, Pfizer, Fresenius, Janssen, Takeda, Theravance, ProventionBio, Protagonist, and Falk.

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Abbreviations

EQ-VAS: EQ visual analog scale
IBD: inflammatory bowel disease
IBD-F: Inflammatory Bowel Disease-Fatigue
JAK: Janus kinase
PRO: patient-reported outcome
QoL: quality of life
sIBDQ: Short Inflammatory Bowel Disease Questionnaire
UC: ulcerative colitis

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Protocol

Usability Testing of a New Digital Integrated Health Ecosystem (PainRELife) for the Clinical Management of Chronic Pain in Patients With Early Breast Cancer: Protocol for a Pilot Study

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Abstract

Background: Chronic pain (CP) and its management are critical issues in the care pathway of patients with breast cancer. Considering the complexity of CP experience in cancer, the international scientific community has advocated identifying cutting-edge approaches for CP management. Recent advances in the field of health technology enable the adoption of a novel approach to care management by developing integrated ecosystems and mobile health apps.

Objective: The primary end point of this pilot study is to evaluate patients' usability experience at 3 months of a new digital and integrated technological ecosystem, PainRELife, for CP in a sample of patients with breast cancer. The PainRELife ecosystem is composed of 3 main technological assets integrated into a single digital ecosystem: Fast Healthcare Interoperability Resources–based cloud platform (*Nu* platform) that enables care pathway definition and data collection; a big data infrastructure connected to the Fast Healthcare Interoperability Resources server that analyzes data and implements dynamic dashboards for aggregate data visualization; and an ecosystem of personalized applications for patient-reported outcomes collection, digital delivery of interventions and tailored information, and decision support of patients and caregivers (PainRELife app).

Methods: This is an observational, prospective pilot study. Twenty patients with early breast cancer and chronic pain will be enrolled at the European Institute of Oncology at the Division of Medical Senology and the Division of Pain Therapy and Palliative Care. Each patient will use the PainRELife mobile app for 3 months, during which data extracted from the questionnaires will

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be sent to the *Nu Platform* that health care professionals will manage. This pilot study is nested in a large-scale project named "PainRELife," which aims to develop a cloud technology platform to interoperate with institutional systems and patients' devices to collect integrated health care data. The study received approval from the Ethical Committee of the European Cancer Institute in December 2021 (number R1597/21-IEO 1701).

Results: The recruitment process started in May 2022 and ended in October 2022.

Conclusions: The new integrated technological ecosystems might be considered an encouraging *affordance* to enhance a patient-centered approach to managing patients with cancer. This pilot study will inform about which features the health technological ecosystems should have to be used by cancer patients to manage CP.

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KEYWORDS

decision-making; decision aid; chronic pain; eHealth; patient electronic health record; clinical; technology; mobile application; pilot study; breast cancer; chronic; patient; cancer; pain

Introduction

Chronic Pain in Patients With Cancer

Chronic pain (CP) and its management are critical issues in the care pathway of patients with breast cancer. Accruing evidence stated that 30% of breast cancer survivors reported CP, which is likely to persist up to 10 years after the end of cancer-specific treatments [1-3]. CP might rise throughout the care pathway due to surgical procedures and chemotherapy-induced toxicities. In particular, in the population of individuals with breast cancer, different causes of pain incidence have been identified: 25%-60% related to postsurgical pain; 47% pertaining to adjuvant hormonal treatments (including aromatase inhibitors); and finally, 58% related to long-term chemotherapy-induced toxicities [4]. The experience of CP interferes with psycho-emotional well-being (eg, increasing anxiety, depression, and fatigue), psychological adaptation to the disease, personal relationships (eg, partners, family members, and colleagues), and then return to work [1,5]. Furthermore, when CP is not promptly recognized, it may alter patients' health-related quality of life, thereby impacting health status, disease, and medication adherence [1,6,7]. Compared to those without CP, patients with breast cancer experiencing CP showed low adherence to anticancer treatments (eg, hormone therapy), with a demonstrated reduction in treatment effectiveness and a 5-year survival rate [1].

Furthermore, compared to hospitalized patients, out-of-hospital patients with cancer have lower pain relief [8]. In particular, patients who live in regions with poor medical resources, an inadequate health system, or low health literacy have an increased risk of experiencing high levels of pain and related disabilities [9]. Besides, this difference in pain management is produced by the fragmented management of cancer survivors [10], causing nonadherence to treatments and follow-ups, poor control of the side effects, and long-term physical and psychological consequences. Thus, the international scientific community has advocated the urgency to introduce interventions that can favor a timely identification of cancer-related CP, which could guarantee continued and tailored management.

Health Integrated Ecosystems for Cancer Chronic Pain Management

Recent advancements in the field of information and communication technology enable the adoption of a novel and challenging approach to care management in the oncological domain throughout the development of integrated ecosystems [11,12]. A growing and consistent series of studies assert that new integrated health technologies have the potential to improve CP management in patients with cancer and overcome current limitations [12-16]. Furthermore, studies suggested that health technology might well manage physical and psychological morbidities associated with pain experience by allowing continuous monitoring [15] of clinical health status in real time and transmitting these data to their health care providers, incorporating them into patients' electronic health records [15,17,18].

Among existing supportive tools for CP, mobile health apps have been increasingly applied [13,14] and they help patients with cancer to monitor and reduce pain experience by promoting self-management skills and improving their quality of life [8,14]. Furthermore, mobile apps, if interconnected with the health technology ecosystem and managed by health care providers, increase the patient's involvement in their care pathway [12]. Overall, this type of technology architecture might achieve different clinical outcomes. First, it monitors the physical and psychological well-being of the patients through self-report questionnaires and momentary ecological assessments (eg, using e-diary), in particular, regular administration of standardized self-report questionnaires and momentary ecological assessments, such as e-diary, effectively track variation in physical and psychological symptomatology, allowing an evaluation of affective instability in CP [15,19]. Second, it favors bidirectional and well-timed communication between health care professionals and patients [7,16], for example, patient-reported outcome measures can be managed by mobile health apps and stored in patients' electronic health records, favoring a fast and direct clinical response to alarm conditions [20]. Third, it permits scheduled clinical follow-ups, reducing the risk of failing continued clinical monitoring during, for example, the survivorship phase [12]. The strategy is meant to improve the quality of care for both outpatients and inpatients.

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This latter statement is coherent with the National Cancer Institute declaration [21] that has remarked on the importance of building a strong and consolidated connection between inpatients and outpatients, reducing the risk that cancer survivors, after the end of active treatment, move out from the care system. Fourth, it boosts patients to be more involved in their treatment decisions, permitting them to achieve a shared decision about their care pathway throughout the implementation of decision aids. According to the American Society of Clinical Oncology international guidelines [21] for pain management, patients with breast cancer can choose between pharmacological and nonpharmacological treatments. Thus, patients with breast cancer experiencing CP have to face a series of preference-sensitive decisions related to the treatments and their consequences in the short, medium, and long term [22,23]. Accruing evidence [24,25] has stressed the critical role of decision aids as an excellent strategy to increase the probability of getting a shared and involved decision. Decision aids are tailored tools designed to deliver evidence-based information on the disease, available treatments, and associated risks; additionally, they may help patients think about the treatment alternatives according to a personal outlook [24,25]. Overall, health technologies are recognized as facilitators of shared decision-making (SDM), reducing decisional conflict and enhancing patient satisfaction.

Implementing SDM models improves patients' knowledge and consolidates the comprehension of their treatment preferences [24,26]. Evidence highlighted that, when implemented on mobile apps, decision aids may support patients by raising awareness of treatment preferences, reducing decisional conflict, and improving adherence to medical treatments [27-30] and SDM [31-33]. We argue that the implementation of the decision aid in clinical practice might be beneficial for patients with early breast cancer in the initial stages of the clinical pathway, that is, immediately after the surgery, when the patients have to face a series of preference-sensitive decisions related not only to the anticancer treatments but also to the management of the pain.

PainRELife Integrated Big Data Ecosystem and Usability Approach

Despite the importance of health technologies in CP management, only some studies have provided integrated technological solutions supporting health care providers in patient management [20]. In addition, available studies have several methodological limitations (eg, small sample size and short follow-up period). Therefore, additional studies are often needed to evaluate the feasibility and usability of such health technology solutions in the clinical practice for supporting patients with CP throughout the care pathway. The evaluation of the user's usability experience is a fundamental prerequisite to increasing the success rate in implementing technologies into routine clinical practice [34] and gives reliable and quantitative information on the quality of e-tools. While the development of new mobile apps should rely on usability testing and patient-centered design process that integrates patients' needs [34], before testing for effectiveness and improving adoption and compliance [35].

This pilot study offers an opportunity to test the patients' usability experience of an integrated technological ecosystem for CP management (PainRELife) in a sample of patients with early breast cancer. Once the usability and effectiveness of PainRELife will be proven, this ecosystem might fill the gap between hospital and home care settings, collecting ongoing, and integrated patient-centered data with the 3-fold future aim to (1) carry out ecological monitoring of the physical and psychological pain experience of the patients; (2) obtain psychoeducational information on pain and available treatments; (3) explore of patients' preferences and support in SDM on pain treatment options between the physicians and the patients.

Methods

Primary End Point

The primary end point of this pilot study is the evaluation of patients' usability experience after 3 months of using a new digital and integrated technological ecosystem (engagement, judgment on usability, aesthetics, quality of given information, personal perception, and perceived impact on behaviors; *Nu* Platform connected with the PainRELife app) for patients with early breast cancer experiencing CP.

Secondary End Points

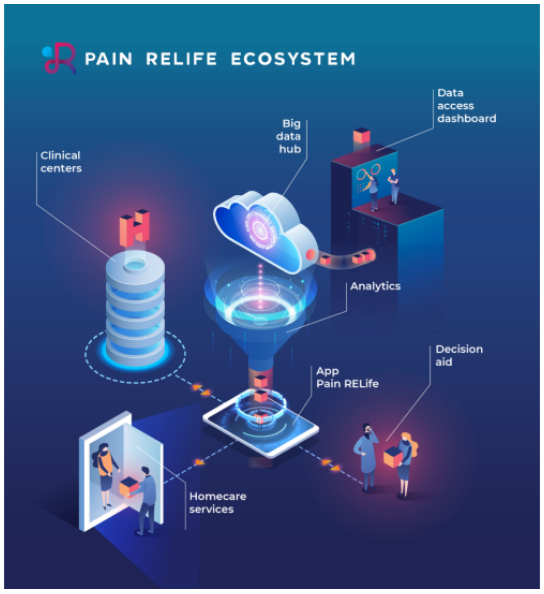
Secondary end points concern the following aspects: (1) assessing the usability of the mobile app in terms of the number of access and usage time; (2) assessing changes in self-efficacy related to CP; and (3) assessing SDM processes between patients and health care professionals.

Study Design

This is an observational, prospective pilot study nested in a large-scale national project named "PainRELife, *Sustainable and integrated big data ecosystem for continuity of care and decision support for patients with pain*" (ID 1173269). The PainRELife project aims to develop a cloud technology platform ("Big data HUB") that is able to interoperate with institutional systems (eg, national electronic health records) and patients' devices to collect integrated health care data (Figure 1).

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Figure 1. Elements involved in the PainRELife ecosystem and their interconnections.



PainRELife Integrated Big Data Ecosystem

The PainRELife is composed of 3 main technological assets integrated into a single digital ecosystem (Figure 1) that were developed during the first year of the project through a collaboration between technical partners and clinical aspects (January 2020 to June 2021).

1. A Fast Healthcare Interoperability Resources (FHIR)–based cloud platform (*Nu* platform) that enables care pathway definition and data collection. The digitized care pathways managed through the *Nu* platform were developed following a consensus procedure that included both the available guidelines and recommendations on CP management and the local experience at the referral centers involved in the project. The digitalized care pathways for pain management became accessible to health care professionals for the data collection on pain, psychological well-being, and decision preferences about treatment options. In particular, the *Nu* platform is the intuitive interface that will be used by health care providers and will permit them to collect and store clinical data (eg, diagnosis, comorbidities, treatments, drugs, pain, anxiety, depression, and emotional distress) and an ongoing monitoring of the patient's health status (from the diagnosis to the follow-ups).
2. A big data infrastructure connected to the FHIR server that analyzes data and implements dynamic dashboards for aggregate data visualization aimed to provide a population-based view for researchers and governance. The dashboards were designed to provide an at-a-glance overview of the population tendencies with respect to the different measures and monitoring procedures. Since these dashboards are not designed for patients, they were not evaluated in this protocol.
3. An ecosystem of personalized apps for patient-reported outcomes collection, digital delivery of interventions and tailored information, and decision support for patients and caregivers (PainRELife app).

The integration of these 3 aspects and the involvement of relevant stakeholders within the CP management process allows the definition of PainRELife as an ”integrated ecosystem.“

Key Features of PainRELife Mobile App

The PainRELife app was developed to interoperate with the *Nu* platform through the FHIR standard, establishing a bidirectional communication channel between health care providers and patients. The PainRELife app has been designed following 3 different steps. First, an extensive and qualitative literature analysis has been performed to define the main issues for patients with breast cancer experiencing CP [36]. In addition, the impact of CP on psychological functioning has been analyzed as the role of the caregivers in the management of the CP experience and how CP impacts different dimensions of the quality of life (sexuality, employment, and returning to work, and psycho-emotional and social determinants). Furthermore, unmet needs in managing CP were evaluated considering multilevel determinants such as sociodemographic, psychological, social, and clinical variables [36]. Finally, the role of technologies in the health care system has been explored to understand the most important aspects that should be considered in the design and development of health technologies. Based on this qualitative analysis, a set of preliminary contents and mock-ups of the mobile app have been developed.

Second, a series of semistructured interviews have been conducted with female patients with breast cancer (N=6) to implement a user-centered design process of the CP mobile app. The semistructured interviews had 3 main goals: evaluating the perceived use of technological support for pain management and the current experience of the patients with the health technologies; evaluating possible interface, contents, functionality, and quality of the mobile app; evaluating a preuser experience of the mobile app through an ad hoc storyboard. Overall, the storyboard is a method used to provide a brief overview of a new mobile app. The storyboard illustrates the main sections of the mobile app and explains the circumstances in which the mobile app should be used.

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Finally, all contents of the mobile app have been revised and discussed by an expert group. The group composed of oncologists, palliative physicians, psychologists, and patients. The obtained suggestions have been integrated into the PainRELife app's last version.

The PainRELife app has been organized into 3 main sections (Figure 2):

1. *Educational Section*: In this section, patients gather evidence-based information on CP and breast cancer. This section aims to improve health literacy using evidence-based information about CP experience during the care pathway (from diagnosis to survivorship). This section contains information on a wide array of topics related to breast cancer diagnosis, cancer pain experience, treatments for CP (pharmacological and nonpharmacological), associated benefits and side effects, and psychological comorbidities. The contents of this section are organized as text, video, and audio files in order to increase the usability rate within different groups of patients with breast cancer.
2. *Pain and Psychological Wellbeing Assessment Section*: It contains a set of self-reported measures evaluating psychological well-being (Hospital Anxiety and Depression Scale; Pain Catastrophizing Scale) [37,38] and pain experience (Brief pain inventory; Visual Analogue Scale [VAS]) [39,40]. This section also includes an e-diary and pain and emotions body mapping exercise. In addition, the e-diary aims to monitor the emotional, cognitive, behavioral, and physical aspects of the CP experience. At the same time, the pain and emotion body mapping exercise request the patients to localize pain and emotions associated using a digital representation of the body (Figure 2). The self-reported measures were implemented with a specific interval time for a total of 3 months with automatic push notifications: Hospital Anxiety and Depression Scale and Pain Catastrophizing Scale monthly; VAS, pain and emotions body mapping exercise, and e-diary each week; and Brief pain inventory 2 times a month. The aim of this section is to (1) permit ongoing monitoring of the patients by health care providers when they are at home and during the follow-up phase and (2) improve the patients' awareness about their own emotional and physical well-being through specific self-monitoring tasks. Overall, the patients will fill questionnaires in the PainRELife app for 3 months. PainRELife app will send an alert to recall the questionnaires.
3. *Decision Aid Section*: It is one of the app's key features (Multimedia Appendix 1). The decision aid comprises 2 parts—profiling patients' preferences and decision tree for CP treatments. In the first part, each patient fills a set of visual analog scales (ranging from 0 to 100) evaluating the general features of the pharmacological and nonpharmacological treatments. The VAS have been designed, considering the key determinants of the patient's treatment decisions suggested by the evidence [41-45]. The pharmacological treatments such as the perception of efficacy, motivation, and general beliefs (3 items); association between drug dosage and tolerability (3 items); the importance of the speed of the effect on pain reduction (1 item); risk of physical dependence (1 item); modality of administration (3 items); side effects tolerability (1 item); the impact of the consumption on cognitive functioning (1 item) are evaluated in detail. On the contrary, the nonpharmacological treatments evaluated efficacy perception, motivation, and general beliefs (3 items); attitude toward interventions that act of mental representations and emotions behind the pain experience (1 item); attitude toward interventions mind-body (1 item); attitude toward interventions that might drive to immediate pain relief (1 item); attitude to short-term interventions (1 item) and that might be implemented autonomously and at-home (1 item); attitude toward interventions that self-administered (active role vs passive role) (1 item); attitude toward interventions that are conducted in a group versus separately (2 items).

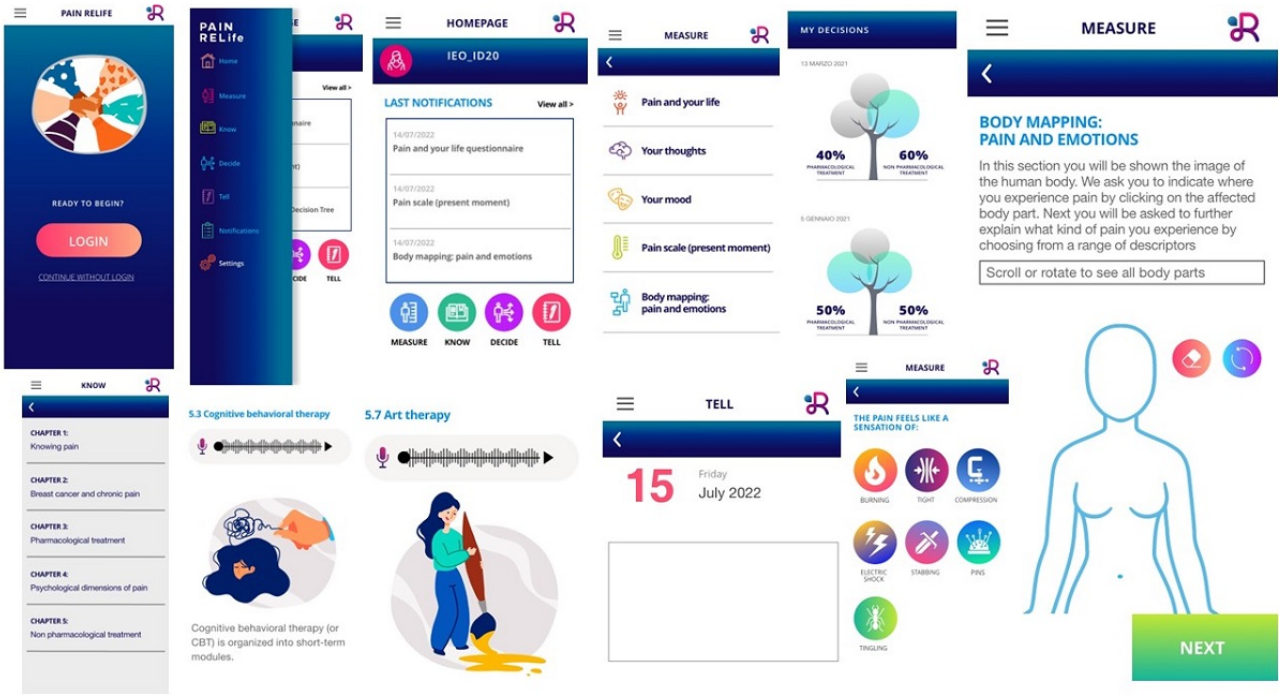
In the second part, patients have to complete a decision tree. A decision tree has been defined as a sort of "abstract structure" able to increase knowledge about the choice that should be performed. The decision tree supports an informed and shared decision [46,47]. Through the decision tree, each patient will compare individual use associated with pharmacological and nonpharmacological treatments. In addition, each patient will identify each option (pharmacological vs nonpharmacological treatments), advantages, and disadvantages. Each of them will be assigned a value ranging from 1 to 10 (advantages-gains) and from −1 to −10 (disadvantages-losses). The total value obtained, given by the sum of the advantages and disadvantages for each option, permit to calculate the individual use associated with each treatment. Each patient is trained to fill the decision aid after 15 days from the discharge to the hospital, at 1 month from surgery, and at 3 months before the clinical follow-ups. The final aim of the decision aid is to support the construction and expression of patients' preferences about current treatments for CP by comparing pharmacological versus nonpharmacological treatments.

Overall, the information collected by the PainRELife app through the self-reported measures and e-diary will be stored in the *Nu* platform and managed by the health care providers (oncologists, nurses, and psychologists) in order to monitor the health and psychological status of the patients and permitting the early identification of at-risk situations. Patients may see the results obtained in each self-reported measure and other tasks of the PainRELife app and are trained to contact the health care professionals for any questions about these issues. The results obtained in the assessment performed through PainRELife app will be discussed in the following clinical consultation.

The PainRELife app will be installed on the patient's mobile phone, and if the patient does not have a personal mobile phone, it will be provided by the researcher (Multimedia Appendix 2). The PainRELife app can run on IOS and Android operating systems. To ensure timely communication with the hospitals and the physicians, relevant contact information will also be explicitly provided to the participants within the PainRELife app.

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Figure 2. English version of the application PainRELife.



Participants

In this study, 20 participants consecutively admitted at Istituto Europeo di Oncologia (IEO) at the Division of Medical Senology and the Division of Pain Therapy and Palliative Care with a diagnosis of breast cancer and CP will be enrolled. Such a sample size is recommended for 1 group [48,49]. Other studies suggested that in order to record a higher percentage of usability errors, it is advisable to enroll a sample of more than 12 participants [50]. Furthermore, within the PainRELife project, a mobile app was also configured for patients experiencing chronic pain post stroke and tested in a referral center for neurological rehabilitation. Thus, a parallel data collection will be conducted on a sample of 20 participants consecutively admitted at Casa di Cura Policlinico. The present protocol refers solely on IEO patients.

Selection Criteria

Inclusion criteria include (1) patients >18 years; (2) having an early breast cancer diagnosis; (3) having undergone surgical intervention for breast carcinoma (quadrantectomy, mastectomy ± lymph node dissection); (4) the presence of postsurgical pain with a score ≥3 in the Numerical Rating Scale (NRS) or VAS; (5) patients with internet access and a personal smartphone; and (6) patients who have read and signed the informed consent.

Exclusion criteria include (1) the presence of primary psychiatric or neurological conditions preventing the ability to use the mobile app and the capacity to express free consent to join the study; (2) the presence of other medical conditions which imply an active antalgic treatment; and (3) patients who refused to sign the informed consent.

Measures

Patient Demographic and Medical Variables

Age, gender, education, marital status, cancer diagnosis, type of surgery, oncological treatments, and comorbid medical disorders were collected through electronic medical records and self-reports.

Pain Self-Efficacy Questionnaire

The PSE is a self-administered questionnaire composed of 10 items rated on a 7-point Likert scale from "*not at all confident*" to "*completely confident.*" The Pain Self-Efficacy Questionnaire (PSEQ) [51,52] measures self-efficacy while performing activities of daily living, despite experiencing pain. The total score of the PSEQ ranges from 0 to 60. The PSEQ has been validated for Italian culture by Chiarotto et al [52] and showed high internal consistency (Cronbach α=.94).

Nine-Item Shared Decision-Making Questionnaire

The 9-item Shared Decision-Making Questionnaire (SDM-Q-9) [53] is a self-administered questionnaire composed of 9 items on a 6-point Likert scale from "*completely disagree*" to "*completely agree.*" The SDM-Q-9 evaluates patients' perception of SDM and their level of involvement during the consultation, as well as the information received on possible treatments and potential risks and benefits of being involved in the decision-making process. The SDM-Q-9 showed high internal consistency in the original validation (Cronbach α=.94).

Mobile Application Rating Scale

The Mobile Application Rating Scale (MARS) [54] is a self-administered questionnaire specifically created to rate the quality of eHealth apps [55], and it is composed of 6 different sections (A, B, C, D, E, and F) for a total of 29 items with 5 possible answers. It assesses the quality of the app according

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to 4 specific dimensions: engagement experienced while using the app (A); functionality (B), aesthetics (C), quality of the information received (D), as well as the subjective perception of app quality (E) and the perceived impact on the app toward knowledge, attitudes, and probability to change user behaviors (F). The MARS showed a high internal consistency (Cronbach α=.90) and good psychometric properties [56].

VAS and NRS

The VAS and NRS [57] are unidimensional assessment scales for evaluating pain intensity. The first one graphically represents the amplitude of perceived pain through a 10-cm predesigned line. The left extremity corresponds to the "*absence of pain*," whereas the right represents the "*worst pain possible*." Next, the patient will be asked to draw a sign on the line representing the level of experienced pain. In the NRS scale, similarly, patients will be asked to verbally specify the number corresponding to their experienced pain, according to the following numerical graduation: (0: "*no pain*," 1-3: "*mild pain*," 4-6: "*moderate pain*," 7-10: "*severe pain*"). The use of the VAS or NRS is determined by the patient's degree of cognitive functioning.

Recruitment and Follow-ups

Patients admitted to the Division of Medical Senology of the IEO will be enrolled by the palliative care physician and a trained psychologist from the Applied Division of Cognitive and Psychological Science. The patients enrolled will have an interview with the psychologist responsible for the data collection. The psychologist will install the PainRELife app and create a personal account. Each patient will use the app for 3 months, during which data extracted from the questionnaires will be sent to the *Nu* platform. Furthermore, at baseline (T0), each patient will fill a set of questionnaires (PSEQ, SDM-Q-9, and VAS or NRS), while at 3 months (T1), each patient will fill the same questionnaires and MARS.

The palliative care physician and the psychologists in charge of data collection will monitor the information transmitted from the PainRELife app to the *Nu* platform for the whole period of testing.

Patients will be informed that neither the platform nor the app will replace the clinical consultation. Furthermore, for any necessity, patients have to get in contact with the pertaining division.

A monthly telephonic interview will be provided to maintain motivation and monitor and detect any psychological, physical, and technical problems. In addition, this program includes 3 calls: 1 at the end of week 4, week 8, and week 12. Each call will last about 10 minutes and address concerns related to the use of the app or their involvement in the pilot study. Data collected through the PainRELife app will be sent to the *Nu* platform and consequently managed by the physician responsible for data collection.

Statistical Considerations

All statistical analyses will be performed through SPSS (version 26; IBM Corp). Data analyzed will be referred to the primary end point, such as usability experience and app quality, which is assessed by the MARS questionnaire. The questionnaire delivers a mean quantitative score for each subscale (A, B, C, D, E, and F), with a mean score from 1 to 5 for the given answers and a total mean score of app quality and the subjective quality perceived by the patients. High mean scores (range 3-5) indicate a good qualitative level of app usability, both considering the global quality and the specific subdimensions [58]. Descriptive statistics of all the questionnaires included in the app will also be processed. Considering the secondary end points, the mean and SD of the PSEQ questionnaire scores will be calculated at T0 (baseline) and T1 (at 3 months) and compared using an appropriate statistic test. PSEQ mean scores will be interpreted according to the established normative reference values [52]. Furthermore, the number of accesses and usage time for each app section will be collected and analyzed. This additional analysis will provide insights into compliance (considering the total number of accesses required by the care pathway) and the perceived usefulness of the educational and decision aid sections.

According to the SDM-Q-9, the questionnaire's total raw score will be obtained by summing all the scale items, ranging from 0 to 45. Since it is more comprehensible, the raw score will be transformed into an interval scale from 0 to 100 (where 0 indicates the lowest possible level of SDM and 200 pinpoints the highest level of SDM) by multiplying the raw score by 20/9. Lastly, bivariate correlations among the questionnaires administered at T1 will be computed. Specifically, a positive correlation between the quality of the app scores (measured by MARS), the perceived self-efficacy despite the presence of pain (measured by PSEQ), and SDM scores (measured by SDM-Q-9) is expected.

Ethics Approval

This pilot study follows the principles stated in the Declaration of Helsinki and subsequent amendments and the Good Clinical Practice Guideline. This protocol was assessed and certified by the ethical board of the European Institute of Oncology (approval number R1597/21-IEO 1701). Informed consent will be obtained from all participants. The informed consent will contain detailed information on the aims and the procedures of the study, as well as on the analysis plan, risks, and benefits for the participants. Participation in the study will be voluntary, and participants will not receive any compensation.

Furthermore, the study data are deidentified. Data will be stored in the IEO databases for 10 years. The study will comply with national and local data protection legislation. Further, all data will be anonymized. Data will be stored in the IEO databases for 10 years.

Results

The recruitment process started in May 2022 and ended in October 2022.

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Discussion

Principal Expected Findings

Considering the complexity of CP experience in the cancer domain, the international scientific community has advocated identifying cutting-edge approaches for CP management. A growing body of studies [8,10,20,31,58] has underlined that health technology solutions might be considered an encouraging and challenging opportunity to enhance patient-centered care and increase patient participation in the care pathway, SDM, and health-related quality of life. This pilot study protocol described here and testing patients' usability experience at 3 months of a digital and integrated ecosystem (PainRELife mobile app and *Nu* platform) for CP in a sample of patients with early breast cancer will permit to achieve of a series of key expected outcomes enriching results obtained from the previous studies.

The *first expected outcome* concerns the possibility of collecting a set of patient-based evidence about the usability experience of the PainRELife mobile app, which will permit to tune of the future version of this type of health technological solutions for patients with chronic pain. More specifically, the results about usability will permit to identify which features (in terms of functionality, aesthetics, and quality of the information provided) a mobile app for CP management should have to be used by patients to manage their care pathway and which are the patient's beliefs about the perceived impact on health behaviors (eg, "*The mobile App will help me to improve health literacy about my pain permitting me to adopt behaviors able to reduce CP*"). A second expected outcome concerns the possibility of overcoming limitations highlighted by earlier studies about health technologies for the patient's clinical management (eg, inadequate sample size or follow-ups) [20]. Indeed, using a pilot study design to evaluate usability experience will inform future studies evaluating effectiveness, thereby increasing the probability of achieving a better implementation of such integrated ecosystem into routine clinical practice and increasing user retention.

A third expected outcome concerns the patient's home monitoring, contributing to reducing barriers to pain management related to poor medical resources, inadequate health system, and low health literacy [9]. In particular, we argue that the direct communication between the *Nu* platform (health care professionals' perspective) and the PainRELife mobile app (patients' perspective) will permit the ongoing tracking of outpatients' physical and psychological health status, allowing physicians to recognize alarm signals promptly. Furthermore, such an integrated ecosystem will permit monitoring clinical follow-ups, reducing the risk of patients' dropout.

Finally, a fourth expected outcome is implementing the decision aid to improve patients' ability to participate in their clinical decision, providing a better portrayal of patient SDM processes in pain management. In addition, we argue that the integration of a decision aid in *the* PainRELife mobile app will allow patients with breast cancer to deal with preference-sensitive decisions by clarifying their needs, values, and expected outcomes associated with the treatment for CP. Also, data collected through the decision aid and shared with the physician will permit us to understand the patient's perspective before the clinical consultation better. This better knowledge about patient perspective will facilitate patient and doctor interaction and consequently will support the achievement of a shared decision about CP care.

Limitations

Despite the innovative clinical and methodological aspects of the current usability study protocol, some limitations should be considered. First, the patient's usability experience of the PainRELife app is evaluated by MARS administration without measuring outcomes related to the care process and the clinical workflow. However, physicians' perspectives and related clinical workflow have been considered in the design phase of the PainRELife *ecosystem*, both for developing the *Nu* platform (the interface used by the physician) and for the PainRELife app (the interface used by the patient). As reported, the digitized care pathways (managed through the *Nu* platform and PainRELife app) were developed following a consensus procedure that included both the available guidelines and recommendations on CP management and the local experience at the referral centers involved in the project (IEO and Casa di Cura Policlinico). This could have contained the risk of implementation bias. Second, a monthly telephonic interview is performed by a trained researcher for the monitoring of usage and concerns to maintain patient involvement in the study, reducing the risk of dropout and increasing the quality of the data collected. Notwithstanding, we have to consider the risk that monthly telephonic interviews are the outcome measures. Indeed, patients might have increased the usage of the PainRELife app to satisfy research expectations (*social desirability effect*) and because the researcher has dedicated attention to the participant (*Hawthorne effect*).

Finally, the last limitation concerns the decision to use a single-group instead a 2-group design for evaluating usability experience according to Julious [49] guidelines for a pilot study. A study design with 2 groups (intervention vs control group) could have also permitted an evaluation of differences in pain management associated with using the PainRELife app. This type of information could have informed a future effectiveness study.

Conclusions

We expect to provide a set of suggestions for the development and implementation of this health technology into routine clinical practice. Data from this pilot study will inform the conduction of full-powered studies testing the efficacy and impact of digital support systems for CP management. Further, the future implementation of this integrated ecosystem will improve CP management in patients with cancer and SDM models through decision aid.

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Acknowledgments

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Data Availability

The data sets generated and analyzed during the current study are available from the corresponding author upon reasonable request.

Authors' Contributions

MM, SFMP, CF, and GP conceived and designed the study. MM and GP coordinated the study; MM and GP acquired legal authorizations; and CF, EF, and ST managed the participants. MM handled the drafting and writing of the manuscript. All authors have read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PainRELife Decision Aid.
[PNG File , 306 KB - resprot_v12i1e41216_app1.png]

Multimedia Appendix 2
Screenshots taken on an iPhone device illustrating the patient interface of the mobile application.
[PNG File , 1023 KB - resprot_v12i1e41216_app2.png]

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Abbreviations

CP: chronic pain
FHIR: Fast Healthcare Interoperability Resources
IEO: Istituto Europeo di Oncologia
MARS: Mobile Application Rating Scale
NRS: Numerical Rating Scale
PSEQ: Pain Self-Efficacy Questionnaire
SDM-Q-9: Shared Decision-Making Questionnaire 9-Item
SDM: shared decision-making
VAS: Visual Analogue Scale

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Protocol

Evaluating the Effectiveness of Rural Digital Social Prescribing in Korea: Protocol for a Cohort Study

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Abstract

Background: The UK National Health Service (NHS) has introduced a digital social prescribing (DSP) system to improve the mental health of the aging population. In Korea, an ongoing pilot social prescribing project has been implemented for older individuals in rural areas since 2019.

Objective: This research aims to develop a DSP program and to evaluate the effectiveness of the digital platform in rural areas of Korea.

Methods: This study was designed as a prospective cohort method for the development and effectiveness evaluation of rural DSP in Korea. The study divided participants into four groups. Group 1 will continuously implement the existing social prescribing program, group 2 implemented the existing social prescribing program but was switched to DSP in 2023, group 3 newly started the DSP, and the remaining group is the control. The research area of this study is Gangwon Province in Korea. The study is being conducted in Wonju, Chuncheon, and Gangneung. This study will use indicators to measure depression, anxiety, loneliness, cognitive function, and digital literacy. In the future, the interventions will implement the digital platform and the Music Story Telling program. This study will evaluate the effectiveness of DSP using difference-in-differences regression and cost-benefit analysis.

Results: This study was approved for funding from the National Research Foundation of Korea funded by the Ministry of Education in October 2022. The results of the data analysis are expected to be available in September 2023.

Conclusions: The platform will be spread to rural areas in Korea and will serve as the foundation for effectively managing the feelings of solitude and depression among older individuals. This study will provide vital evidence for disseminating DSP in Asian countries such as Japan, China, Singapore, and Taiwan as well as for studying DSP in Korea.

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KEYWORDS

digital health; digital social prescribing; elderly health; community health; digital health intervention

Introduction

Globally, those 65 years or older accounted for 10% of the population in 2022. This number is expected to reach 16% worldwide by 2050 and exceed 20% in all high-income countries [1]. The aging of the global population presents the need to introduce various medical systems.

In the era of aging populations, both the physical and mental health of older individuals should be considered. Depression, solitude, and dementia are emerging social problems [2]. Previous studies have shown that an average of 13%-15% of older individuals 65 years or older experience social solitude, and those 80 years or older and in rural areas experience more social solitude [3,4]. In addition, 6%-13% of older individuals 65 years or older experience loneliness [5,6]. These feelings of social solitude and depression among individuals older than 65 years indicate the vulnerability of mental health in this population, which is highly likely to lead directly to suicide risk and deterioration of physical health.

Due to the current era of aging, the health problems of older individuals cause limitations for the medical personnel and resources of primary health care facilities in local communities. They also lead to financial difficulty for national insurance, which increases the medical burden at the national level [7].

The UK National Health Service (NHS) has introduced a social prescribing system to reduce the workload of primary health caregivers. Currently, the United Kingdom's primary health caregivers, accounting for one-third of general practitioners, use social prescribing [8]. This system provides a nonclinical social prescribing program through link workers who have been trained in using community resources rather than the clinical medical system. Representative programs of social prescribing include gardening, dance, music therapy, and social activities. Social prescribing is aimed at improving the health of the local community in particular; however, it aims to reduce and minimize the solitude of older individuals 65 years or older; strengthen the local services, the network of the local community, and the efficiency of medical resources; alleviate the burden on primary care; and improve health and welfare services [2].

Previous studies have reported the effects of social prescribing systems on older individuals in various countries. Gardening, nature-friendly activities, and art activities have been found to positively affect the mental health of older individuals [9-11]. In addition, studies identified the effects of social prescribing in increasing self-esteem, improving mental well-being, reducing loneliness, and decreasing the use of medical services among older individuals 65 years or older who felt social isolation and had severe depression [12,13].

In Korea, a pilot project is being implemented for older individuals in rural areas since 2019. The first social prescribing program was performed for 10 weeks; the 10th social prescribing program was implemented in 2022. The social prescribing programs provided were music storytelling, allotment farming, kalimba music therapy, self-help group, and digital literacy strengthening education. These social prescribing programs in Korea reduced the average depression and loneliness of the participating older individuals and enhanced social participation [14-17].

Various experts emphasize the lack of evidence and research on implementing a sustainable system for the social prescribing system as a limitation [18]. The United Kingdom has developed and operated a digital social prescribing (DSP) system to solve these problems using digital platforms. A representative DSP in the United Kingdom is Elemental Software, now under the name Access Health, Support and Social Care, which is mainly responsible for monitoring, observing, and supporting patients from the time when social prescribing is requested. The DSP platform provides health risk analysis, an attendance tracker, health impact measurement, aggregate reporting, befriending services, web-based home resources, grocery collection and pharmacy delivery services, local food bank access, and NHS app library services. As of October 2022, more than 10,000 social prescribing sites have been registered on this DSP platform, and 160 social prescribing service providers use the platform.

Korea has problems similar to the United Kingdom, such as a lack of primary health care personnel and resources in rural areas and insufficient finances for the National Health Insurance [19]. However, Korea is a digital powerhouse among Organisation for Economic Co-operation and Development (OECD) countries with the highest internet penetration rate of 99.9% as of 2021 [20]. The Korean government launched a digital platform in November 2021 and announced that rural areas will be provided with all services through the digital platform. Therefore, it is imperative to develop and operate the existing rural social prescribing model as DSP.

Therefore, this research aims to develop a Korean rural social prescribing program as DSP and to study the possibility of providing and expanding the digital platform to rural areas in Korea, like the Elemental platform in the United Kingdom. Specifically, the first goal is to conduct an economic evaluation by comparing DSP with existing social prescribing programs. Furthermore, it aims to evaluate the effectiveness of reducing depression and solitude when DSP is provided, as the existing social prescribing program does. Finally, it aims to study scenario modeling that extends to Gangwon Province in Korea.

Methods

Study Design

This study is designed as a prospective cohort method for the development and effectiveness evaluation of rural DSP in Korea. The study period is designed to be 3 years in total. The study framework was divided into stages by year. The study is designed by dividing participants into four groups. Group 1 will continuously implement the existing social prescribing program,

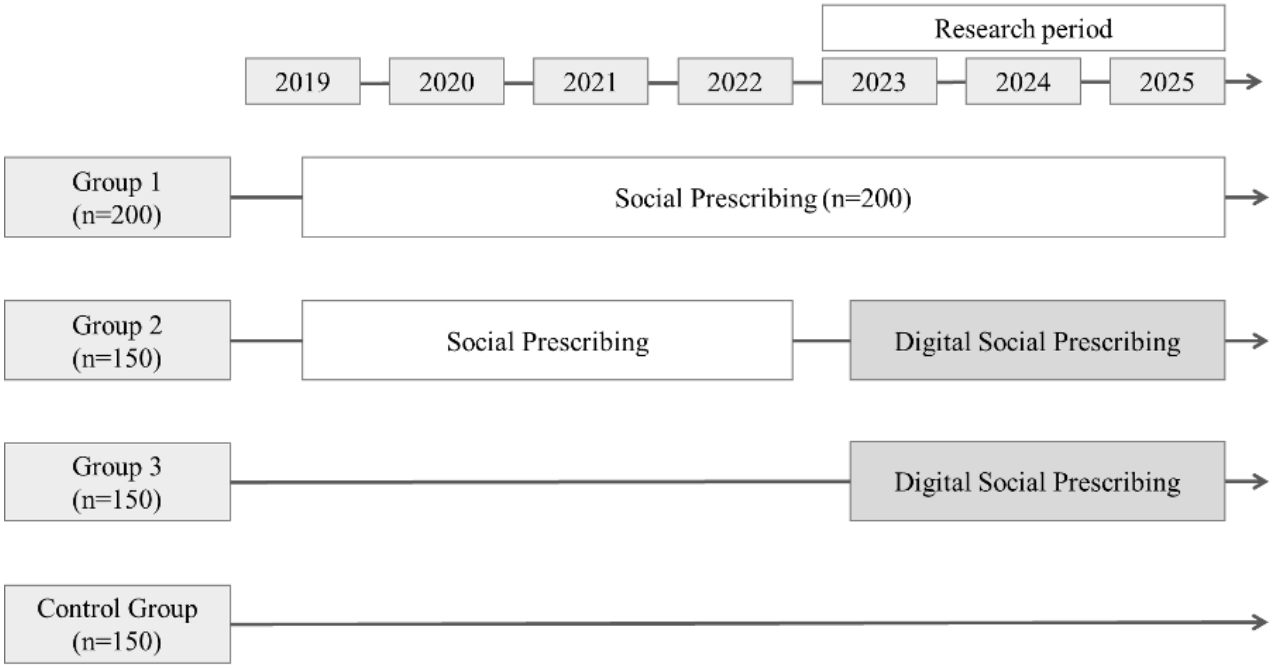
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group 2 implemented the existing social prescribing program but was switched to DSP in 2023, group 3 newly started the DSP, and the remaining group is serving as the control.

Research Area

The research area of this study is the Gangwon Province in Korea. The study was conducted in three cities—Wonju, Chuncheon, and Gangneung—which belong to Gangwon Province (Figure 1). Gangwon Province is one of 16 cities/provinces/districts and is among the major regions of Korea. It has a population of 1,555,876, accounting for 2% of the total population of Korea. The older adult population accounts for 22.2% of this population, making Korea a superaged society with the third-highest aging ratio among the 17 cities/provinces/districts in Korea. Chuncheon, Wonju, and Gangneung are three densely populated cities in Gangwon Province with 361,056 people in Wonju, 361,056 in Chuncheon, and 215,322 in Gangneung. In addition, Wonju, Chuncheon, and Gangneung were selected as research areas because the research team works in these areas.

Figure 1. Research framework.



Study Participants

The participants in this study were older individuals 65 years or older living in Gangwon Province and satisfying the following conditions. Participants had to be older individuals with depression, living alone, and with weak cognitive function. They were recruited after being diagnosed by health care professionals (doctors and nurses) of public health and health service centers. These conditions are the same as those of the existing Korean rural social prescribing model to enable a comparison of the existing model with the DSP model in the future.

Study Instruments

Depression

Older individuals with depression living in rural areas who participate in DSP will be evaluated using the Geriatric Depression Scale Short Form–Korean Version (GDS-K). The GDS is a self-report measurement tool developed by Yesavage [21] to evaluate depression in the older adult population. The GDS-K was developed by modifying and supplementing this measurement tool with expressions that are easy to understand and fit the emotions of older individuals in Korea. Scores range from 0 to 15, with higher scores indicating more severe depressive symptoms. A score of 5 or less is classified as normal, a score of 6-9 as severe depressive symptoms, and a score of 10 or more as depression [22,23].

Anxiety

Anxiety will be measured using the Korean version of the Goldberg Short Screening Scale for Anxiety (GSSA) [24,25]. The GSSA consists of nine items on anxiety. The higher the GSSA score, the higher the anxiety level.

Loneliness

The Revised UCLA Loneliness Scale will be used to measure social loneliness and solitude [26]. This tool consists of 20 items and is scored out of 20 by responding yes or no. The closer to 20 points, the higher the loneliness. A tool will be used that verifies validity and reliability after translating into Korean [27].

Cognitive Function

The Mini-Mental State Examination–Korean Version (MMSE-K) measures overall cognitive function [28]. This tool consists of 30 points, including orientation, memory registration, memory recall, attention and calculation, language skills, and visual composition. A score of 19 or less indicates definitive dementia, a score of 20 to 23 indicates suspected dementia, and a score of 24 or higher is considered normal.

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Digital Literacy

Digital literacy will measure using the eHealth Literacy Scale (eHEALS) [29]. This tool investigates 23 items in five areas—operational internet skill, information navigation, communicational/social internet skill, creative skill, and mobile internet skill—on a 5-point Likert scale.

Ethics Approval

The ethics committee of Yonsei University approved this study (REC No. 1041849-202304-SB-073-01). Written informed consent will be obtained from all participants, and the purpose of this study will be carefully explained to them after their permission.

Results

This study began in October 2022 with support from the National Research Foundation of Korea. The results of the data analysis are expected to be available in September 2023.

Digital Platform: Electronic Medical Record

Existing social prescribing is performed by patients with doctors, link workers, social prescribing sites, and social prescribing programs. Developing a digital platform allows these to be integrated into one platform. This study will develop a platform through which patients can consult doctors, receive a social prescribing program, communicate with link workers and social prescribing sites, and perform the program. Currently, the Elemental Software program is a representative DSP platform in the United Kingdom [30].

Music Story Telling Program

The Music Story Telling (MST) program is a social prescribing program based on the theoretical evidence of music therapy and psychological counseling technology. It received a registration patent for service from the Korean Intellectual Property Office in 2013. The MST program is being provided as one of the rural social prescribing programs in Wonju City in Korea, and its effectiveness has been shown through previous research [15].

Data Analyses

Stata SE 16 (StataCorp) is used for statistical data analysis, and visual analysis will be performed using GraphPad Prism (GraphPad Software, Inc.). We will implement two statistical approaches to understand the effectiveness of rural DSP in Korea. The first tests the effectiveness of DSP, and the second is the economic analysis of DSP.

First, to test the effectiveness of DSP, pre-post comparison for each indicator will be performed using paired *t* test, and the effectiveness of the social prescribing program will be analyzed for each indicator with difference-in-differences regression. In difference-in-differences regression, control variables are input based on the Anderson model to control external factors as much as possible. Statistical significance is analyzed under the significance probabilities of .05, .01, and .001 at the 95% CI. The above statistical method analyzes the intervention effect by dividing it into four research-designed groups.

Second, a cost-benefit analysis is conducted for the economic evaluation of DSP. Cost-benefit analysis is a technique for evaluating input costs and benefits by converting them into monetary values. Costs are estimated as expenses spent on DSP, and benefits are estimated by dividing them into “direct benefits,” which are primary medical costs saved through disease prevention and treatment, and “indirect benefits,” which are incidental results such as improvement in productivity caused by care, prevention, and treatment. The decision indicator for economic evaluation will be finally evaluated based on decision rules using net present value (equation 1) and cost-benefit ratio (equation 2).



Discussion

Expected Findings

As a result of this study, it is expected that an evaluation of the effectiveness of DSP in Korea will be provided. This will include an assessment of the suitability of digital platforms and social prescribing electronic medical records (EMRs) in the Korean context. The study will also aim to propose a model that is appropriate for Korea, taking into account the unique features of the Korean health care system.

Furthermore, by conducting an economic evaluation, this study will provide scientific evidence for expanding the pilot program of social prescribing nationwide in Korea. The results of the economic evaluation will be used to make evidence-based decisions about the allocation of resources and funding for social prescribing initiatives. This will enable policy makers to make informed decisions about how best to invest resources to promote health and well-being in the Korean population.

Overall, this study has the potential to make a significant contribution to the development of social prescribing initiatives in Korea. By providing a comprehensive evaluation of the effectiveness of DSP, as well as proposing a suitable model for digital platforms and social prescribing EMRs, this study will help to ensure that social prescribing initiatives in Korea are evidence based and effective.

DSP Effect

Among the social prescribing programs implemented in rural Korea, MST, allotment farming programs, and self-help groups have already been identified as effective. If MST is developed as a DSP among these social prescribing programs and provided to older individuals in rural areas, it is expected to be effective in improving participants’ digital literacy in the long-term. A previous study on social prescribing in Korea showed that improved digital literacy in older individuals receiving social prescribing effectively prevents cognitive function deterioration [17].

Globally, social prescribing programs are being converted to DSP programs, and studies on their effects are being published. One study showed that DSP reduced the use of medical facilities, including primary health care [31]. Despite the rapidly aging population structure in rural areas of Korea, a shortage of

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medical facilities and personnel remains [32]. Hence, DSP can reduce the need for participating older individuals to visit inadequate medical facilities in rural areas of Korea.

Digital Platform

Korean DSP will be provided by developing and using a digital platform. Although social prescribing programs are continuously being developed and expanded using the digital platform, mainly in the United Kingdom, study cases remain insufficient [33,34]. Elementary Software is a representative example of a digital platform for social prescribing in the United Kingdom [18]. As of August 2022, a cumulative total of 213,757 patients used Elementary Software for social prescribing services [18]. If the study results indicate that DSP is effective, it is expected that digital platforms such as Elementary Software will be widely expanded in Korea. Accordingly, a wide range of big data databases will be automatically collected from the digital platform, and evidence-based DSP studies are expected to be performed.

In terms of the limitations of the existing social prescribing study, there was a significant limitation in data collection to conduct the study on older individuals who participate in social prescribing [35]. Digital platforms will be a cornerstone for developing data-oriented regionally customized programs for older individuals in rural areas participating in social prescribing in the future.

Social Prescribing EMRs

In Korea, 97.3% of hospitals use EMR systems in line with the development of information and communication technology [36]. The EMR system has advantages in that it makes managing patient data easier. Furthermore, it programmatically protects personal information. DSP also establishes social prescribing EMRs through the digital platform, which is used to record hospitals, link workers, and sites that provide social prescribing in the region for each patient. Data are gathered so that sustainable social prescribing can be performed. These data are expected to be evidence for tracking and managing the patient's condition.

Economic Evaluation

Social prescribing programs have been developed, spread, and conducted worldwide, including in Australia, Singapore, Denmark, and Korea, centering on the United Kingdom. A previous study revealed that unnecessary use of primary health care decreased due to social prescribing, thereby reducing unnecessary medical expenses [8]. However, studies on the economic cost-effectiveness of social prescribing programs in the local community are insufficient [31]. There are no cost-effectiveness studies of social prescribing programs in Korea. Therefore, this study plans to conduct an economic evaluation of the social prescribing program in Wonju City, which has been performed since 2019, using cost-effectiveness analysis. The evaluation is expected to prove that the social prescribing program is more cost-effective than the cost of primary health care for older individuals in rural areas in Korea. In addition, an economic evaluation will be carried out cost-effectively when it is developed as a DSP and conducted in rural areas. Accordingly, it will be possible to compare the economic evaluation of existing social prescribing programs and DSP programs, and it is expected to prove the effect hypothesis of digitalized social prescribing.

Limitations

This study has several limitations. First, Korea has a low level of social awareness about social prescribing programs. Hence, there was a limitation regarding asking study participants and stakeholders for insights on this project. Second, because there is no digital platform for social prescribing, most of the study period was used for technology development, making the study period practically insufficient. Third, the digital literacy of Korean older adults in rural areas was low. Thus, when social prescribing is converted to DSP, it is highly likely that the study participants will have difficulty completing the program.

Conclusions

As the aging population grows rapidly in Korea, institutional policies using local community resources are needed to reduce the growing burden on primary health care. A review of the current literature shows that social prescribing, spreading worldwide and mainly in the United Kingdom, is effective in improving depression and solitude in older individuals. Therefore, the pilot project for the social prescribing program in rural Korea is being implemented, and its effectiveness has been identified.

However, the existing social prescribing system lacks sustainability due to the limitations of personnel and resources. Therefore, a social prescribing program is being developed using a digital platform. The platform will be spread to rural areas in Korea and will serve as the foundation for effectively managing the feelings of solitude and depression among older individuals. This study will provide vital evidence for disseminating DSP in Asian countries such as Japan, China, Singapore, and Taiwan as well as studying DSP in Korea.

Acknowledgments

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Data Availability

Data sharing is not applicable to this paper as no data sets were generated or analyzed during this study.

Authors' Contributions

HL, SBK, and HSJ conceptualized the study. All authors were involved in developing the methodology. HL and DHK used the software. HL performed the validation. HL, THL, and DHK conducted the formal analysis. HKN, BZ, SL, and THL performed the investigation. HKN and JAL contributed to the resources and data curation. HL prepared the original draft. All authors reviewed and edited the manuscript. HL contributed to the visualization. HL and HKN supervised the study. HL provided project administration and acquired the funding. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

DSP: digital social prescribing
eHEALS: eHealth Literacy Scale
EMR: electronic medical record
GDS-K: Geriatric Depression Scale Short Form–Korean Version
GSSA: Goldberg Short Screening Scale for Anxiety
MMSE-K: Mini-Mental State Examination–Korean Version
MST: Music Story Telling
NHS: National Health Service
OECD: Organization for Economic Co-operation and Development

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Protocol

Increasing Participation in a TelePrEP Program for Sexual and Gender Minority Adolescents and Young Adults in Louisiana: Protocol for an SMS Text Messaging–Based Chatbot

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Abstract

Background: Sexual and gender minority (SGM) adolescents and young adults (AYAs) are at increased risk of HIV infection, particularly in the Southern United States. Despite the availability of effective biomedical prevention strategies, such as pre-exposure prophylaxis (PrEP), access and uptake remain low among SGM AYAs. In response, the Louisiana Department of Health initiated the LA TelePrEP Program, which leverages the power of telemedicine to connect Louisiana residents to PrEP. A virtual TelePrEP Navigator guides users through the enrollment process, answers questions, schedules appointments, and facilitates lab testing and medication delivery. To increase the participation of SGM AYAs in the program, the TelePrEP program partnered with researchers to develop a chatbot that would facilitate access to the program and support navigator functions. Chatbots are capable of carrying out many functions that reduce employee workload, and despite their successful use in health care and public health, they are relatively new to HIV prevention.

Objective: In this paper, we describe the iterative and community-engaged process that we used to develop an SMS text messaging–based chatbot tailored to SGM AYAs that would support navigator functions and disseminate PrEP-related information.

Methods: Our process was comprised of 2 phases: conceptualization and development. In the conceptualization phase, aspects of navigator responsibilities, program logistics, and user interactions to prioritize in chatbot programming (eg, scheduling appointments and answering questions) were identified. We also selected a commercially available chatbot platform that could execute these functions and could be programmed with minimal coding experience. In the development phase, we engaged Department of Health staff and SGM AYAs within our professional and personal networks. Five different rounds of testing were conducted with various groups to evaluate each iteration of the chatbot. After each iteration of the testing process, the research team met to discuss feedback, guide the programmer on incorporating modifications, and re-evaluate the chatbot's functionality.

Results: Through our highly collaborative and community-engaged process, a rule-based chatbot with artificial intelligence components was successfully created. We gained important knowledge that could advance future chatbot development efforts for HIV prevention. Key to the PrEPBot's success was resolving issues that hampered the user experience, like asking unnecessary questions, responding too quickly, and misunderstanding user input.

Conclusions: HIV prevention researchers can feasibly and efficiently program a rule-based chatbot with the assistance of commercially available tools. Our iterative process of engaging researchers, program personnel, and different subgroups of SGM

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AYAs to obtain input was key to successful chatbot development. If the results of this pilot trial show that the chatbot is feasible and acceptable to SGM AYAs, future HIV researchers and practitioners could consider incorporating chatbots as part of their programs.

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KEYWORDS

chatbot; conversational agent; develop; iterative; messaging; text message; HIV; PrEP; pre-exposure prophylaxis; user testing; rule-based; prevention; eHealth; telehealth; mobile phone; sexual minority youth; gender minority youth; young adult; youth; adolescent; sexual minority; gender minority; gender diverse; gender diversity; SMS; artificial intelligence; patient education; health information; web-based information; user experience

Introduction

Background

Sexual and gender minority (SGM) adolescents and young adults (AYAs) continue to be at increased risk of HIV infection [1]. The stigma of being a sexual or gender minority and the concomitant isolation, rejection, racism, marginalization, and discrimination experienced by these youth contribute to their elevated risk of HIV acquisition [2,3]. Focal points of new HIV cases among SGM are New Orleans and other southern municipalities where 50% of the new HIV cases among SGM are being diagnosed [4]. Biomedical prevention strategies, particularly pre-exposure prophylaxis (PrEP) that reduces the risk of acquiring HIV by 92%-99% [5-9], are highly efficacious. Yet, PrEP uptake is low among SGM AYAs [10]. To realize the full benefits of PrEP, we must increase access and continued engagement in PrEP services by individuals most at risk of acquiring HIV, especially SGM AYAs residing in the South.

In response to this need, the Louisiana Department of Health initiated the Louisiana (LA) TelePrEP Program in 2019. LA TelePrEP provides a novel and convenient way for Louisiana residents 18 years of age or older to access PrEP through telemedicine. A TelePrEP Navigator guides users through the enrollment process, answers questions, schedules virtual medical appointments, and facilitates lab testing and medication delivery. The Navigator also facilitates access to ancillary services including insurance enrollment. The entire enrollment process can be done remotely by completing the self-enrollment form accessible on the LA TelePrEP website [11] or doing so with support from the Navigator. Unfortunately, participation of SGM AYAs in the Program is limited. From 2018 to 2020, only 52 SGM AYAs had contacted the Program, and only 12 were below the age of 21 years. Increasing the reach of the LA TelePrEP services to SGM AYAs is vital to curbing the further spread of HIV in this community. In 2020, the LA TelePrEP Program partnered with researchers from the Adolescent Medicine Trials Network in efforts to increase participation of SGM AYAs in the LA TelePrEP Program. This collaboration aims to extend the Program's current outreach efforts and support the Navigator's functions by developing a chatbot (PrEPBot) and PrEP-focused social media messaging campaign targeting SGM AYAs.

Chatbots for Public Health

A chatbot is an automated system that mimics informal human-to-human conversation [12]. Chatbots can vary greatly in technical sophistication and capabilities. Artificial intelligence (AI)–based chatbots use natural language understanding and machine learning to provide conversational, contextualized responses (ie, human-like) based on input from users. Simpler chatbots can be programmed using rule-based conversations that are scripted but have limited capacity for recognizing free text input. Many companies provide programmable communication tools to develop application programming interface chatbots that can be integrated with various messaging platforms. Chatbots have been widely adopted in education, e-commerce, consumer banking, entertainment, travel, transportation, and logistics, and their use has led to documented benefits for both employers and customers [13]. Chatbots can be accessed around the clock and reduce employee workload by scheduling appointments, setting reminders, answering questions, locating services, and disseminating information. These functions transfer to health care and public health settings [14]. Chatbots have also been used as interventionists. For instance, Woebot is a "talk therapy" chatbot embedded within Facebook Messenger that has been shown to reduce symptoms of depression and anxiety [15,16].

Despite the wide use of chatbots in other public health areas, the migration of chatbots to HIV prevention efforts has been slow [17]. In 2020, The Joint United Nations Program on HIV/AIDS launched Eli [18,19], a chatbot designed to engage youth in text-based conversations focused on issues critical to healthy youth development such as family, relationships, and sexual health. Eli addresses HIV prevention by providing reasons why testing is important, where and how to get tested, and the importance of starting treatment if HIV test results are positive [18]. The initial response suggests that this type of service targets an important need. In the first week alone, over 12,000 users engaged with the service, and Eli answered over 150,000 questions [18,19]. Eli's success supports exploring text-based chatbot options for other prevention strategies, such as PrEP, among SGM AYAs. Chatbots may help overcome the stigma and discrimination often faced by SGM AYAs by providing a medium to communicate sensitive information and connect to prevention services privately [20]. With extensive community engagement, an SGM AYA–targeted PrEPBot could provide concise, high-quality information, respond to requests rapidly, have 24-hour access, and connect interested users with

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either a TelePrEP Program Navigator or the enrollment website to learn more.

Goal of This Protocol

In this paper, we describe the iterative process that we used to develop an SMS text messaging–based chatbot tailored to SGM AYAs that would support Navigator functions and disseminate PrEP-related information. Lessons learned and suggestions that researchers could consider in future application of SMS text messaging–based chatbot technology for HIV prevention efforts were also included. The process we describe in this paper was conducted as part of a parent study designed to increase participation of SGM AYAs in the Louisiana TelePrEP Program. The parent study consisted of a web-based survey and structured focus groups whose findings were used to develop the chatbot and the targeted social media campaign. The institutional review board (IRB) approval for the study included permission to beta-test the chatbot. The testers were not considered to be research participants since their function was to provide recommendations and feedback regarding the functionality of the chatbot. In a separate paper, we will describe the development of the social media campaign and report the findings.

Methods

Phase I—Conceptualization

Prior to chatbot development, the research team met with the TelePrEP Navigator weekly to discuss job responsibilities, program logistics, and interactions with users to identify tasks that would ideally be programmed into the chatbot. The discussions were guided by the following questions: (1) What are your primary responsibilities as a TelePrEP Navigator? (2) What tasks take up most of your time? (3) If you could gain another "human" team member, what would you want them to be able to do? (4) What are the main reasons people contact the TelePrEP Program? and (5) What are the most common questions that people ask you about PrEP and the TelePrEP Program?

Through these conversations, we learned that some of the most time-consuming elements of the navigator's role were discussing PrEP eligibility, facilitating the enrollment process, scheduling appointments, identifying and overcoming PrEP access barriers (eg, insurance), and answering general questions. At our meetings, concerns about the chatbot seeming overly robotic and using inaccessible language that would deter our target population from engaging with the chatbot were also shared.

It was decided that an AI-based chatbot would best meet our functional needs while being "personable." After further investigation, it was realized this type of chatbot required considerable technical expertise, financial resources, and time that were beyond the scope of the project. Instead, we opted to use a rule-based chatbot that was still capable of carrying out all of the functions that would improve Navigator efficiency. A rule-based chatbot was more appropriate for the scope of the project and could be developed using commercially available application programming interface chatbot platforms, such as Twilio [21]. We hired an undergraduate computer science student and proceeded with development using Twilio.

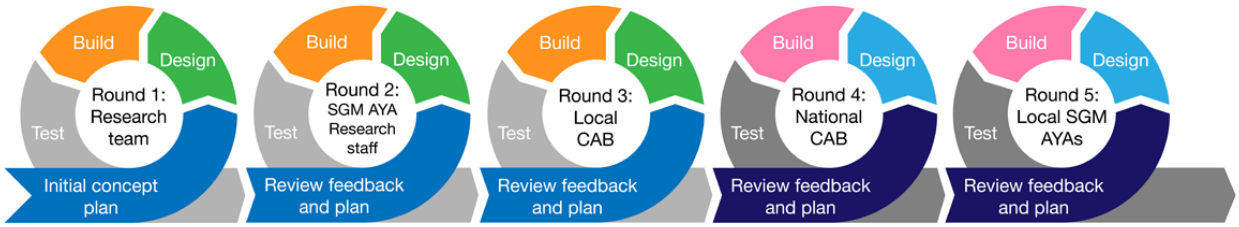
Phase II—Iterative Community–Engaged Development Process

Overall Process

To balance the need to program functions that would support the Navigator while ensuring that the chatbot was user-friendly and accessible to our target population, principles of user-centered design were used to guide our development process [22]. We intentionally engaged Department of Health staff and SGM AYAs within our professional and personal networks. Our iterative process involved multiple stages of testing starting with those directly involved with the project, and each sequential stage approaching real-world conditions to better evaluate the functionality of the chatbot (Figure 1).

In the initial testing phases, we developed unique profiles of hypothetical users from information gathered during the conceptualization phase (see Textbox 1). Each tester was assigned a different profile to use when interacting with the chatbot. Through these conversations, the testers identified areas in need of improvement, technical glitches, typos, and issues with language and terminology.

Figure 1. A diagram of the iterative community–engaged development process. AYA: adolescents and young adults; CAB: community advisory board; SGM: sexual and gender minority.



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Textbox 1. The unique profiles of hypothetical users assigned to testers during the initial testing phase.

Scenario A

- You want to get on pre-exposure prophylaxis (PrEP)
- You’re 18 years old
- You have private insurance
- You’re on your parents’ insurance
- You don't have any questions

Scenario B

- You want to get on PrEP
- You’re 16 years old
- You have public insurance
- You’re on your own insurance plan
- You don’t have any questions

Scenario C

- You want post-exposure prophylaxis (PEP)
- You’re 20 years old
- You were exposed 24 hours ago
- You already have a doctor you see

Scenario D

- You want PEP
- You’re 29 years old
- You were exposed 4 days ago
- You don't have a doctor already

Scenario E

- You want to know if you're eligible for PrEP
- You’re 26 years old
- You're not living with HIV
- You’ve had anal sex recently
- You're unsure of your partner’s status
- You don’t always use condoms
- If you’re eligible, you don’t want to get on PrEP today
- If you’re ineligible, you don't have any more questions

Scenario F

- You have questions about PrEP
- You want to know how PrEP works
- You also want to know if you have to take it everyday

We used 3 groups of testers in the initial testing phase. First, the research team, other HIV research staff, and a local community advisory board (CAB) evaluated the functionality of the prototype chatbot. The research team was comprised of 2 HIV researchers, 1 senior biostatistician, 1 research coordinator, an undergraduate computer science student, and the TelePrEP Navigator. Our second group of testers were 3 SGM AYA research staff who worked on other HIV-focused projects. Third, the prototype was tested by 8 members of a Louisiana-based youth CAB who were identified as SGM AYA and had a working knowledge of the project.

In the later testing phase, SGM AYAs who had no familiarity with the project were engaged. We convened 2 groups to provide

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feedback on the chatbot's functionality. The first was comprised of 8 members of the ATN National CAB, and the second consisted of 5 SGM AYAs recruited from our networks. At the start of each testing session, we provided a brief description of the TelePrEP Program and then instructed the participants to freely engage with the chatbot. No additional instructions were provided. After each iteration of the testing process, the research team met to discuss feedback, guide the programmer on incorporating modifications, and test the chatbot to ensure feedback had been properly integrated.

Initial Development

Our first charge was to create flow diagrams to provide a visual representation of anticipated conversations between the chatbot and potential users. We relied heavily on the navigator's experiences interacting with TelePrEP contacts as the foundation for designing the structure and content of these conversations. We focused our initial efforts on PrEP eligibility, facilitating the enrollment process, scheduling appointments, and identifying and overcoming PrEP access barriers (eg, insurance).

Flow diagrams were created using presentation software (Figure 2) that the programmer would then translate to the Twilio platform using JavaScript coding. Conversation flows were designed based on relevant user characteristics and intent. For example, age and insurance status were important considerations for both program eligibility and addressing privacy implications for those on parents' insurance. In addition to the flow diagram, we created a document to list all conceivable variations of user input in each step of the conversations (eg, yes, yeah, sure, and yup) to minimize the chatbot misunderstanding or misinterpreting communications. We incorporated scheduling appointments with a navigator by inserting a link that directed users to a Calendly calendar [23].

We initiated our iterative testing process as described earlier. After each testing session, the team discussed feedback and proposed solutions that we would route back to the programmer to make the modifications.

Figure 2. Initial chatbot conversation flow diagram. PrEP: pre-exposure prophylaxis.



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Programming Refinements and Ongoing Development

Our initial approach proved efficient for programming straightforward conversations that had limited variation in response options. PrEP eligibility, program enrollment, and scheduling conversation flows were easy to design since users could only respond yes or no. It was quickly realized that dichotomous responses could not be used to answer general program and PrEP-related questions. As we began to program the most commonly asked questions, we noted the nearly infinite ways the questions could be posed and the strong potential for typos, abbreviations, and colloquialisms that, if not entered verbatim, the chatbot would not understand. Furthermore, as the volume of conversation flows became more expansive and iterative changes more frequent, we realized that programming was inefficient and time-consuming. We needed to find an alternative approach for chatbot development.

Twilio tech support advised us to take advantage of additional tools in their platform that did not require a skilled programmer, specifically Studio and Autopilot. Studio is a visual workflow builder that uses drag-and-drop tools as well as custom code for rapid chatbot development. Our research coordinator, who had no experience with programming or chatbots, quickly learned how to navigate Studio and was able to easily make modifications to the chatbot that previously could only be handled by the programmer. We relied on the Autopilot tool to facilitate programming of commonly asked questions. Autopilot is an AI platform that can identify and respond to free text input and could be integrated into our existing rule-based design structure.

Once we incorporated the most common questions and formulated initial responses, we continued our iterative development process by engaging with the National ATN CAB and SGM AYAs in our personal networks. Through this process, the list of questions was expanded, and our responses were revised. This was especially important for colloquial use of certain terms. We could not feasibly integrate all possible questions and variations in wording of preprogrammed questions. Autopilot was able to understand slight variations in question wording and allowed us to program new variations as testers introduced additional ways to pose questions. In the event the chatbot could not understand a question, users would be sent to a frequently asked questions (FAQ) page on the TelePrEP website. Our final round of SGM AYA testers had minimal recommendations for changes and gave overall positive feedback on their experience. Through our highly collaborative and community-engaged process, we successfully created a rule-based chatbot with AI components to improve TelePrEP Navigator efficiency and increase access to the TelePrEP Program among young SGM AYA.

Ethical Considerations

The parent study which included the beta testing described in this paper was approved by the Tulane IRB (2021-207). The role of the testers was to evaluate the chatbot to improve its functionality. They were not considered to be research participants.

Results

Recommendations for Chatbot Development

During our iterative development process, we gained important knowledge that could advance future chatbot development efforts for HIV prevention among SGM AYAs. In this section, we identify issues that hampered the user experience (UX) and describe our strategies for resolving them.

- Sending too many messages for a single response: Testers complained that many chatbot messages were too long, and they preferred concise responses in as few messages as possible. When feasible, it was programmed one response per message ensuring that responses were 160 characters or less, the limit for a single SMS text message.
- Asking unnecessary questions: The conversation flow was streamlined removing redundancies and unnecessary questions or branches. For example, we initially programmed questions that facilitated the enrollment process but were unnecessary to achieve the goal of linking the user to the TelePrEP Program. For instance, we had initially programmed the chatbot to ask the user for their insurance information. However, the user would have to provide this information to the navigator when enrolling, making this question redundant and unnecessary (Figure 2).
- Responding too quickly: Though chatbots are lauded for their ability to immediately respond, testers expressed that receiving responses so quickly was jarring or too robotic. A 5-second delay was programmed to more closely mimic the natural flow of texting conversations.
- Misunderstanding user input: As is common with all chatbots, testers encountered situations in which the chatbot could not interpret user input. In the initial stages of development, the chatbot would continuously ask for clarification when it did not understand a user's input. Users became annoyed when the chatbot continued asking for clarification after a number of failed attempts. We programmed the chatbot to direct the user to the navigator after 2 consecutive failed attempts to understand the user's input.
- Directing users to external links: Directing users to external links discouraged them from continuing to interact with the chatbot. Whenever feasible, the chatbot was programmed to provide information directly to the user. For instance, programming responses to the myriad of possible user questions was overwhelming, so we initially directed the user to our FAQ page. To reduce the number of times users were directed to the FAQ page, responses were programmed that could address multiple questions, and users were only directed when absolutely necessary (see Textbox 2).

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Textbox 2. Using the Autopilot tool within Twilio, similar questions were assigned single responses that could more appropriately answer users' queries.

Question group 1

- Can I stop using condoms?
- How effective is pre-exposure prophylaxis (PrEP) at preventing infection?
- How effective is PrEP at preventing HIV?
- How effective is PrEP?
- Is PrEP effective?
- How well do doctors trust PrEP?
- Does PrEP really prevent HIV?
- Why should I take PrEP?
- Why take PrEP?
- Does it work well?
- How well does PrEP prevent HIV?
- How well does PrEP work?
- How good is PrEP?
- Does PrEP work?

Combined answers 1

- PrEP is highly effective when taken as indicated. The once-daily pill reduces the risk of getting HIV from sex by more than 90%. Among people who inject drugs, it reduces the risk by more than 70%. (Your risk of getting HIV from sex can be even lower if you combine PrEP with condoms and other prevention methods).

Question group 2

- Will hormone replacement therapy interact with PrEP?
- Will my medicine interact with PrEP?
- Will PrEP interact with other pills I take?
- Does Descovy interact with other medicine?
- Does Truvada interact with other medicine?
- Does PrEP interact with other medicine?
- What about poppers?
- Can I use mushrooms while I'm taking PrEP?
- Can I mix cocaine and PrEP?
- Can I use poppers while I'm on PrEP?
- Do poppers interact with PrEP?
- Does molly interact with PrEP?
- Can I take molly while I'm on PrEP?
- Does marijuana interact with PrEP?
- Does cocaine interact with PrEP?
- Can I smoke weed while I'm on PrEP?
- Does PrEP interact with marijuana?
- Does PrEP interact with weed?
- Can I use drugs when taking PrEP?
- Can I do drugs and take PrEP?

Combined answers 2

- Recreational drugs are not known to interact with either Truvada for PrEP or Descovy for PrEP. While PrEP generally has few interactions with prescription medicine, please consult your PrEP provider for information about how PrEP interacts with other medications.

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Discussion

Principal Findings

This project demonstrates that a small team of behavioral researchers and staff can create a functional SMS text messaging–based chatbot to support a state-sponsored TelePrEP Program. We learned that it was important to dedicate sufficient time to the conceptualization process to ensure that the chatbot's functions would address the needs of the Navigator and efficiently link the users to the TelePrEP Program. Our iterative process of engaging researchers, Program personnel, and SGM AYAs to obtain input was key to our success.

We will pilot the chatbot in tandem with the launch of the social media messaging campaign. To evaluate the acceptability of the chatbot, a survey was created based on an existing chatbot evaluation with some modifications [24]. These questions assess users' demographics, intent of engaging with the chatbot, as well as their experiences using the chatbot. Chatbot users will receive a link to the 5-minute Qualtrics survey at the end of a chatbot conversation or, for incomplete conversations, a message with the link will be sent 15 minutes after the last interaction. Participants will be compensated US $5 for completing the survey. We will monitor usage and identify glitches or other unaccounted for issues that can be addressed when refining the chatbot. We will publish the results of this pilot trial and lessons learned in a subsequent manuscript.

Implications

The implementation of chatbots and AI tools within messaging platforms has paralleled the surge of mobile phone use among AYAs [25,26]. However, chatbots are relatively new to the public health arena. A 2022 scoping review assessing the research base for the use of chatbots in public health identified the need for more research describing the development process and evaluating the efficacy and effectiveness of these chatbots [25]. The breadth of information shared in both this paper and an upcoming paper evaluating the feasibility and acceptability of the PrEPBot will begin to address this gap in the literature.

Community engagement was an essential component of our chatbot development process. Community members helped us to refine the chatbot language to be accessible and familiar to the end user as recommended by Barreto et al [27] in their study of chatbots for promoting child health. They also helped us to identify the type of questions users would ask and the information to be provided. With their assistance, we were also able to identify strategies to create a streamlined experience. For example, the number of "failed responses" was limited, so if the system failed to provide a direct answer after 3 attempts, it would automatically triage the user to the navigator [28]. Another important consideration was to ensure that the information provided by the chatbot was reliable and valid [28]. To develop the FAQ section, we drew upon publicly available information from trusted sources, such as the US Centers for Disease Control and Prevention [29] and the San Francisco AIDS Foundation [30]. Participation from the community helped us to incorporate information in the FAQs that resonated with and was relevant to SGM AYAs [27,31].

In developing chatbots for public health, programming and end user fees must also be considered [27]. We opted for SMS text messaging because of its low cost and wide accessibility. A readily available, easily deployable platform was used to program and host our cloud-based, chatbot conversation flow. We also noted that aside from labor, development costs were negligible. There was no charge to use the platform aside from the charges associated with sending and receiving SMS text messages during testing sessions, which cost US $60. We hope the PrEPBot's inherent value as a low-cost SMS text messaging–based chatbot rather than as an independently designed app with a custom UX design will increase accessibility and ease of maintenance.

Limitations

There were factors that limited our chatbot development process. Limited budget and technical expertise did not allow us to create a chatbot with advanced AI and natural language processing capabilities that could enhance the UX and better meet user needs. Though our community-engaged and iterative process was a major strength, we could have incorporated additional stages of testing to further refine the chatbot prior to launch.

Conclusions

Chatbot development tools are accessible, user-friendly, and relatively inexpensive. An undergraduate computer science student and a research coordinator with no prior experience could successfully oversee programming and testing. Our experience proves that HIV prevention researchers can feasibly and efficiently program a rule-based chatbot with the assistance of commercially available tools.

Acknowledgments

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Data Availability

No research data were generated in the development of the chatbot.

Authors' Contributions

MAO, MIF, and WSC conceptualized the project and the methodology. JM participated in all aspects of the development of the project and reviewed the final draft. MAO, MIF, and WRTB participated in all aspects of the development of the project and wrote, reviewed, and edited the manuscript. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

AI: artificial intelligence
AYA: adolescents and young adults
CAB: community advisory board
FAQ: frequently asked question
IRB: institutional review board
PrEP: pre-exposure prophylaxis
SGM: sexual and gender minority
UX: user experience

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Protocol

Assessment of Multidimensional Health Care Parameters Among Adults in Japan for Developing a Virtual Human Generative Model: Protocol for a Cross-sectional Study

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Abstract

Background: Human health status can be measured on the basis of many different parameters. Statistical relationships among these different health parameters will enable several possible health care applications and an approximation of the current health status of individuals, which will allow for more personalized and preventive health care by informing the potential risks and developing personalized interventions. Furthermore, a better understanding of the modifiable risk factors related to lifestyle, diet, and physical activity will facilitate the design of optimal treatment approaches for individuals.

Objective: This study aims to provide a high-dimensional, cross-sectional data set of comprehensive health care information to construct a combined statistical model as a single joint probability distribution and enable further studies on individual relationships among the multidimensional data obtained.

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Methods: In this cross-sectional observational study, data were collected from a population of 1000 adult men and women (aged ≥20 years) matching the age ratio of the typical adult Japanese population. Data include biochemical and metabolic profiles from blood, urine, saliva, and oral glucose tolerance tests; bacterial profiles from feces, facial skin, scalp skin, and saliva; messenger RNA, proteome, and metabolite analyses of facial and scalp skin surface lipids; lifestyle surveys and questionnaires; physical, motor, cognitive, and vascular function analyses; alopecia analysis; and comprehensive analyses of body odor components. Statistical analyses will be performed in 2 modes: one to train a joint probability distribution by combining a commercially available health care data set containing large amounts of relatively low-dimensional data with the cross-sectional data set described in this paper and another to individually investigate the relationships among the variables obtained in this study.

Results: Recruitment for this study started in October 2021 and ended in February 2022, with a total of 997 participants enrolled. The collected data will be used to build a joint probability distribution called a Virtual Human Generative Model. Both the model and the collected data are expected to provide information on the relationships between various health statuses.

Conclusions: As different degrees of health status correlations are expected to differentially affect individual health status, this study will contribute to the development of empirically justified interventions based on the population.

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KEYWORDS

bacterial profiles; body odor; joint probability distribution model; chiral amino acid; skin surface lipid; multidimensional data; mobile phone

Introduction

Background

Advances in information technology such as artificial intelligence and the internet of things enable new approaches to human health care [1-5]. Digital data collected through various measurements can be used together to approximate the current health status of humans. Better approximation allows for more personalized and preventive health care by informing the potential risks and developing appropriate interventions and solutions to achieve predictive, preventive, and personalized medicine [6,7]. Elucidating the modifiable risk factors related to lifestyle, diet, and physical activity will help to ensure optimal approaches for individuals in contrast to populations [6,7].

Big data obtained from the results of health examinations or clinical trials may contain a variety of individual laboratory measurements. Using such data, we can train a generative model that reasonably approximates the joint probability distribution. The resulting generative model may contain undiscovered structures among the data and facilitate a better understanding of the data, estimation of missing or corrupt values, detection of outliers, and prediction of unknown data (eg, patient diagnoses) [8-10]. In addition, a generative model can generate synthetic data for various applications, which alleviates privacy concerns when third parties use health care data.

Recent advancements in generative models, particularly those with deep learning, allow the estimation of a joint probability distribution from a high-dimensional data set. We are training this statistical model, hereafter called a Virtual Human Generative Model (VHGM), by combining a commercially available health care data set containing large amounts of relatively low-dimensional data with the high-dimensional, cross-sectional data set described in this paper. In our first incarnation of the VHGM, we incorporated demographics such as age and sex; anthropometrics; biochemical and metabolic profiles of urine, blood, and blood after a glucose tolerance test; vascular, gait, cognitive, and motor functions; RNA, proteins, and metabolites in skin surface lipids (SSLs) [11]; bacterial profiles of the mouth, skin, intestine, scalp; and body odor of the armpit, sole, and scalp. One of the challenges in developing such a high-dimensional statistical model is obtaining the training data set. Deep learning technologies normally require a large amount of data, typically millions or even billions of records. Such data sets for health care measurements, however, are not available. Constructing a new high-dimensional data set with a sufficiently large sample would require prohibitively high financial resources. Therefore, we aim to create a model by combining a large commercially available health care data set (containing >1 million records but relatively low dimensional) with a smaller high-dimensional, cross-sectional data set containing approximately 1000 records. In this study, we describe the details of the protocol for obtaining this cross-sectional data set. Combining these data sets will be discussed in a separate publication.

Objective

The primary objective of this study is to obtain multidimensional and comprehensive health information to build a data set that will serve as the basis for statistical models such as the VHGM. The secondary objective is to use the same data set to explore the individual relationships among the multidimensional data obtained.

Methods

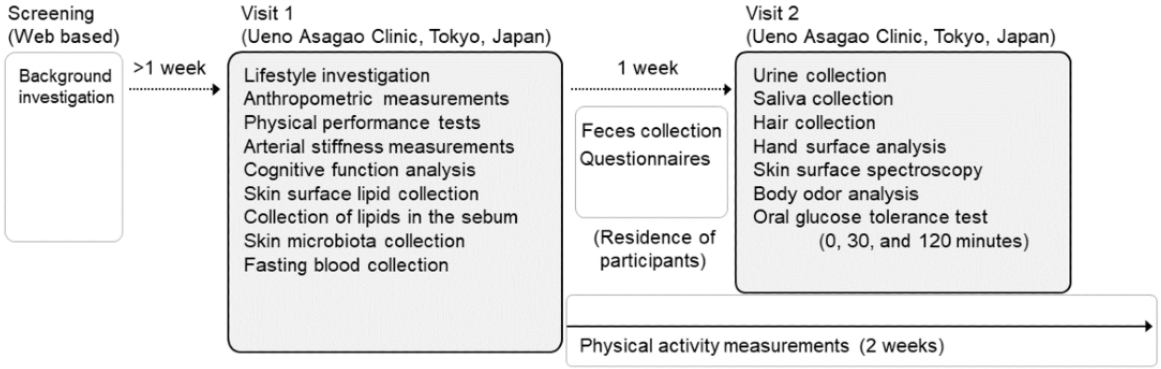
Study Design

A single-center cross-sectional observational study was conducted with adult men and women living in narrowly defined metropolitan areas of Japan (Tokyo, Kanagawa, Chiba, Saitama, Ibaragi, Tochigi, and Gunma prefectures). All measurements were performed by trained research coordinators and medical doctors using standard operating procedures during 2 outpatient visits to the Ueno Asagao Clinic (Tokyo, Japan), 1 week apart

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(Figure 1). The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines were applied according to the study objectives [12].

Figure 1. Experimental scheme. Participants were assessed by an initial screening and 2 visits, with a 1-week interval between visits during which they completed a questionnaire and fecal samples were collected. Daily activity was measured continuously over a 2-week period.



Ethics Approval, Informed Consent, and Participation

The study was approved in October 2021 by the institutional review board (IRB) of the Kao Corporation (Tokyo, Japan; approval #K0023-2108) and the Preferred Network, Inc (Tokyo, Japan; approval #ET22110047). Eligibility was evaluated by asking potential participants a few brief questions. After explaining to potential participants that the data obtained in this study may be published after an anonymization process; that statistical models may be created from the obtained data; and that the created statistical models may be provided to external research institutions, commercial companies, and other third parties, they decided whether to participate. All participants provided written informed consent to participate in this study. The consent form explains in detail which data would be used in the study and obtains consent for the use of anonymized data. Participants of this study were provided with digital points worth approximately US $250, which could be used to alleviate any expenses associated with their participation in this study. This trial is registered with the University Hospital Medical Information Network (UMIN; UMIN000045746).

Participants and Eligibility

Eligible participants were consecutively recruited over a 5-month period from October 2021 to February 2022. The participants were recruited via a website administered by TES Holdings (Tokyo, Japan). We did not perform a formal sample size calculation but set a sample size of 1000 adults to be recruited based on a preliminary calculation that the accuracy of the statistical modeling would not be improved by enrolling >1000 participants. Participants were added and converted to age groups by decade (20-29, 30-39, 40-49, 50-59, 60-69, and >70 years) to evaluate the age of the participants as a numerical value and by sex.

The inclusion criteria were as follows: (1) Japanese men and women aged ≥20 years, (2) individuals who were able to complete the questionnaires and surveys, and (3) individuals who understood the study and could provide written consent. Exclusion criteria were as follows: (1) individuals undergoing hospitalization for serious diseases (diabetes, hypertension, arteriosclerosis, heart disease, malignancy, Alzheimer disease, etc), (2) individuals who could not come to the outpatient unit by themselves, (3) individuals with dementia or suspected dementia, (4) individuals aged ≥60 years who had not received at least 2 doses of the COVID-19 vaccine at least 2 weeks before the visit, (5) individuals who developed symptoms suspicious of COVID-19 infection during the 2 weeks before the visit, (6) individuals who had a pacemaker, (7) individuals who were pregnant or may become pregnant, (8) individuals who had 200 mL of blood drawn within 1 month of the start of this study or >400 mL of blood drawn within 3 months (blood donation, etc) of the start of this study, and (9) individuals whose participation in the study was deemed inappropriate by the study investigators.

Lifestyle Investigation and Questionnaire

Trained physicians or study coordinators collected information about the participants regarding sex; age; years of education; occupation; medical history; diseases under treatment medication use; smoking habits; alcohol consumption habits; and, for participants aged ≥75 years, nursing care requirements. A 3-day food consumption record for each participant as well as information on hygiene, dental hygiene, and bathing habits; health-related attitudes; skin, scalp, and body odor concerns; hair loss awareness; and, in women, menstrual cycle, were collected. During the study period between visits 1 and 2, participants completed a dietary habits survey using the brief-type self-administered diet history questionnaire [13], the international physical activity questionnaire [14,15], a questionnaire for medical evaluation of old-old [16], a dietary habits questionnaire [17], the Athens insomnia scale [18,19], the Oguri-Shirakawa-Azumi sleep inventory middle-aged and aged version [20], the Berlin questionnaire [21], the World Health Organization—Five Well-Being Index [22], the brief job stress questionnaire [23], the Chalder fatigue scale [24], the Center for Epidemiologic Studies Depression Scale [25,26], the fatigue feelings questionnaire [27], the sun exposure questionnaire [28], the 10-item personality inventory [29,30], the Oxford happiness questionnaire [31], the overactive bladder symptom score [32], the international consultation on incontinence questionnaire–urinary incontinence short form [33], the fecal incontinence quality of life scale [34], the neurogenic bowel dysfunction score [35], the Kupperman menopausal index [36], a modified menstrual distress

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questionnaire [37,38], climacteric and senescence scores [39], and the Edinburgh postnatal depression scale for those 3 years post partum [40].

Anthropometric Measurements

Height was measured using a clinical stadiometer. Body weight and body composition, including body fat percentage, body fat mass (kg), lean body mass (kg), total body water (%), and basal metabolic rate (kcal), were measured using a digital bioimpedance scale (InBody 770K, InBody Corp). Visceral fat area and waist circumference were measured using a bioimpedance-type visceral fat meter (EW-FA90; Panasonic Corporation) [41]. Hip circumference was determined using a measuring tape.

Physical Performance Tests

Grip Strength Test and Timed Up-and-Go Test

Grip strength was measured using a Smedley spring-type dynamometer (Grip-D, Takei Scientific Instruments Co, Ltd) [42]. The average value of 2 measurements was recorded. A timed up-and-go test was administered to measure the time required to stand up, walk 3 m, turn, walk back to the chair, and sit down [43].

In-Laboratory Gait Parameter Measurement

In-laboratory gait parameters and foot pressure patterns were determined as described previously [44]. Gait speed was measured using a sheet-type pressure sensor (Anima Corporation) placed at the center of a 6.4-m walkway. The measured gait parameters included the following: general parameters—speed (cm/s) and cadence (steps/min); spatial parameters—step length (%), step width (%), gait angle (degree), and toe angle (degree); and temporal duration parameters—double support phase (%), swing phase (%), and stance phase (%) [45]. An average measurement of the 4 trials was obtained for each participant. The foot pressure patterns were measured simultaneously using the sheet-type pressure sensor. The gait parameters and foot pressure on the left and right feet were recorded bilaterally.

Physical Activity Measurement

Daily physical activity, gait speed, and number of steps were monitored using a triaxial accelerometer (HW-100, Kao Corporation) that allowed for 14 days of continuous recording, as previously reported [44]. Effective days were defined as the days when the accelerometer was worn for at least 10 hours per day and for at least 7 days [46,47]. The participants used the walking speed measurement app (Chami, InfoDeliver Co Ltd) on their smartphones for 14 consecutive days. The smartphone app that measures walking speed uses a step counter and GPS [48,49]. Walking speed data, including the time of measurement, number of steps, and distance walked, were collected on a dedicated server.

Blood Pressure and Arterial Stiffness Measurements

Heart rate, systolic blood pressure, and diastolic blood pressure were measured with the participants in a sitting position using a VS-2500 Vascular Screening System (Fukuda Denshi Co, Ltd). Measurements of the cardio-ankle vascular index and ankle brachial index were obtained while the participants assumed a supine position using the VS-2500 Vascular Screening System with an electrocardiogram, phonocardiogram, and brachial and ankle artery pressures and waveforms [50]. The cardio-ankle vascular index was automatically calculated for the left and right sides, and both values were used for analysis.

Blood, Urine, Saliva, and Hair Collection

Blood samples were obtained from a peripheral vein after overnight fasting or glucose loading. Serum samples were obtained by centrifuging (1500 × g, 15-24 °C, 10 min) blood allowed to stand at room temperature (18-25 °C) for 15 minutes. Plasma samples were obtained by centrifuging (1500 × g, 4 °C, 10 min) blood samples collected in tubes containing EDTA-disodium salt dihydrate or sodium fluoride (glucose). Plasma samples obtained during the oral glucose tolerance test were distributed into tubes containing EDTA-dipotassium salt dihydrate and dipeptidyl peptidase IV inhibitors or sodium fluoride (glucose). Blood samples for ammonia measurements were collected in tubes containing a deproteinizing reagent. Freeze-thaw was performed only once between the collection of biological samples, and all plasma and serum samples were stored at −80 °C until analysis.

Urine samples (4-6 mL) were collected from participants in the morning after overnight fasting for at least 12 hours. All urine samples were stored at −20 °C until laboratory analysis.

Saliva samples were extracted using a standard protocol [51,52]. Saliva samples were obtained from participants seated in a quiet room in the morning between 08:30 AM and 11:30 AM. Participants were asked to accumulate saliva in their mouths and spit into a sterile plastic tube every minute for 20 minutes. The saliva volumes (gram) were weighed in the tube after sample collection [53]. The saliva secretion rate (mL/min) was calculated by dividing the amount of saliva collected by the collection time (20 min). Whole saliva samples were centrifuged at 14,970 × g for 10 minutes at 4 °C, and the supernatant and pellet were stored at −80 °C until analysis. To measure salivary nitrate and nitrite concentrations, the salivary supernatants were mixed with an equal volume of methanol and centrifuged (21,600 × g, 4 °C, 15 min). The supernatants were analyzed using high-performance liquid chromatography (HPLC; ENO-30, Eicom Corp).

All hair samples were collected from the occipital scalp area of each participant. Hair samples were obtained from the edge of each participant's scalp. Hair thickness was measured with a thickness gauge near the root tip for 10 randomly selected hair fibers from each participant (type 547-401; Mitutoyo Corp). The measured thickness usually corresponds to a small diameter when the cross-sectional shape of the fiber is oval. The curvature of the hair fiber was measured by image analysis of a 2D image of each hair fiber [54].

Laboratory Analysis

Hematologic parameters, such as white blood cells, red blood cells, hemoglobin level, hematocrit level, platelet cells, mean corpuscular volume, and mean corpuscular hemoglobin, were measured in whole blood samples using standardized methods.

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The following blood biochemistries and blood electrolytes were measured using standardized methods according to the standard operating procedures of the Health Sciences Research Institute, Inc (Kanagawa, Japan): sodium, potassium, chlorine, calcium, inorganic phosphorus, iron, magnesium, total protein, albumin, albumin:globulin ratio, total bilirubin, aspartate aminotransferase, alanine aminotransferase, γ-glutamyl transpeptidase, alkaline phosphatase, lactate dehydrogenase, creatine phosphokinase, uric acid, urea nitrogen, creatinine, serum triglycerides, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, glucose (plasma), hemoglobin A_{1c}, ammonia, high-sensitivity C-reactive protein, cortisol, triiodothyronine, thyroxine, dehydroepiandrosterone, testosterone, estradiol, progesterone, follicle-stimulating hormone, luteinizing hormone, prolactin, insulin, free fatty acids, total ketones, acetoacetic acid, and 3-hydroxybutyric acid. Plasma inflammation marker levels were measured by Kao Corporation using a Bio-Plex Pro Human Cytokine Screening Test Kit (Bio-Rad Laboratories Inc, Hercules). The following 27 cytokines were quantified: basic fibroblast growth factor, eotaxin, granulocyte colony-stimulating factor, granulocyte-macrophage colony-stimulating factor, interferon-γ, interleukin (IL)-1β, IL-1ra, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12, IL-13, IL-15, IL-17, interferon-γ–induced protein 10, monocyte chemoattractant protein-1, macrophage inflammatory protein-1α, macrophage inflammatory protein-1 β, platelet-derived growth factor, regulated upon activation in normal T cell expressed and presumably secreted, tumor necrosis factor-, and vascular endothelial growth factor.

Glucose, protein, bilirubin, urobilinogen, ketone bodies, creatinine, occult blood reaction, pH, and gravity were measured in the urinary samples.

Salivary oxytocin concentrations were quantified using an enzyme-linked immunosorbent assay kit (Enzo Life Sciences, Plymouth Meeting). Salivary oxytocin concentrations were evaluated in duplicate and determined using the Epoch2 microplate reader (BioTek Instruments, Inc). Bovine serum albumin (Bio-Rad Laboratories, Inc) was used as a standard to calculate the salivary total protein concentration. The salivary oxytocin concentration was normalized by the salivary total protein concentration in each sample (pg/mg protein), as previously described [55].

Oral Glucose Tolerance Test

Other than the participants diagnosed with diabetes or other potentially serious illnesses, all participants underwent an oral glucose tolerance test at visit 2 after fasting overnight. After the fasting blood sample was collected, a 75-gram glucose load was ingested. Blood samples were obtained at 30 minutes and 120 minutes after the glucose load. Glucagon, active glucagon-like peptide-1, total glucose-dependent insulinotropic peptide from plasma, insulin, growth hormone, and insulin-like growth factor 1 from the serum were measured using enzyme-linked immunosorbent assay kits (glucagon: Mercodia; active glucagon-like peptide-1: Immune Biology Laboratories; total glucose-dependent insulinotropic peptide: Merck KGaA; and growth hormone and insulin-like growth factor 1: R&D Systems). Plasma glucose and serum insulin were assessed according to standard procedures at the laboratory at Health Sciences Research Institute, Inc (Kanagawa, Japan).

Liquid Chromatography–Tandem Mass Spectrometry Analysis

Chiral Amino Acid Analysis

According to a previous report [56], human plasma was mixed with an aqueous methanol solution and centrifuged at 2130 × g for 10 minutes at 4 °C to remove proteins. After derivatization using 6-aminoquinolyl-N-hydroxysccinimidyl carbamate, the reaction solution was subjected to chiral tandem liquid chromatography–tandem mass spectrometry (LC-MS/MS).

Lipid Mediator Analysis

Quantification of lipid mediators was performed using LC-MS/MS, as previously described [57,58]. The plasma was mixed with methanol and centrifuged (20,000 × g, 10 minutes, 4 °C), and the solid-phase extraction was carried out using an Oasis hydrophilic-lipophilic balance solid-phase extraction cartridge (Waters Corporation). Lipid mediators were analyzed using an UltiMate3000 liquid chromatography (LC) system (Thermo Fisher Scientific) coupled with a QTRAP5500 triple-quadrupole mass spectrometer (AB Sciex Pte Ltd) equipped with an electrospray ionization source.

Vitamin D Metabolites Analysis

The plasma samples were loaded into Chem Elut S (Agilent Technologies), held for 10 minutes at room temperature and eluted with ethyl acetate. The supernatant was evaporated to complete dryness under a nitrogen stream, and *N*-methyl-1,2,4-triazolinedione solution was added. The reaction solution was subjected to LC-MS/MS. Vitamin D metabolites were analyzed using a QTRAP6500 triple-quadrupole mass spectrometer (AB Sciex Pte Ltd) equipped with a Nexera X2 LC system (Shimadzu). For the quantification of vitamin D metabolites, each peak area of the species was standardized by the peak area of each internal standard.

Polyamine Analysis

Plasma samples were mixed with an internal standard solution containing putrescine-d6, spermine-d20 (C/D/N Isotopes), and spermidine-d8 (Toronto Research Chemicals Inc). Acetonitrile (Kanto Chemical Co, Inc) was added to the plasma, and the precipitate was removed by centrifugation at 20,400 × g for 10 minutes at 4 °C. Amino Tag Wako Borate Buffer, 3-aminopyridyl-N-hydroxysuccinimidyl carbamate (APDS) reagent, and APDS Tag Wako Eluent Buffer (Fujifilm Wako Pure Chemical Corporation) were added to the supernatant. Mass spectrometric analysis of the resulting samples was performed by LC-MS/MS (selected reaction monitoring) using an LC system (ACQUITY Premier System, Waters Corporation) coupled with a Xevo tandem triple-quadrupole-mass spectrometry (MS; Waters Corporation) equipped with a heated electrospray source. For quantification of polyamines, the peak areas of putrescine, spermidine, and spermine were standardized by the peak area of each internal standard.

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Hair Loss Determination

Male-pattern and female-pattern hair loss were determined according to the Japanese Dermatological Association's Guidelines for the diagnosis and treatment of male- and female-pattern hair loss, 2017 version [59]. Male-pattern hair loss was classified by combining the classification method by Norwood [60] and the type II vertex in the classification method by Takashima et al [61], with the type II vertex further divided into 2 groups according to the severity of hair loss. Photographs obtained with a Nikon D5600 from the top of the man's head and hairline observed from the side were used to classify male-pattern hair loss.

To classify female-pattern hair loss, women's thinning hair was determined using a total score (0-20 points) of hair appearance (0-10 points), vellus hair rate (0-5 points), hair shedding (0-2 points), and single hair follicular unit (FU; 0-3 points) [62]. A photograph of the midline of the top of the woman's head was obtained. Using photographs of midline partings, a 5-point scale based on the hair density scale by Sinclair was given a score of 0 to 10 and used to determine thinning of hair in women. An enlarged photograph (20× magnification) of the midline connecting the ears was taken with a digital microscope (KH-7700, Hyrox Co, Ltd), and the numbers of black hairs and gray hairs in a 0.21-cm^2 area and hair diameter were measured using Image-Pro Plus (ver6.1, Hakuto Co, Ltd). Scores of 0 (vellus hair rate <20%) and 5 (vellus hair rate ≥20%) were used to determine thinning of hair in women. To apply these measurements to determine the initial thinning of hair in women, hair shed during washing was collected with a net (draining net stocking type shallow type for drain holes), and the amount of hair shed (from 10 to 750 hairs) was self-evaluated in 6 stages. The number of hairs lost was divided by the time since the previous hair wash, and the amount of hair shedding was determined. Shedding of 10 to 200 hairs was scored as 0, and hair shedding of ≥400 hairs was scored as 2. The ratio of single hair FUs in the 0.21-cm^2 area was measured from a 20× magnification image. Single hair FU ratios were scored for women as follows: <25%, score of 0; ≥25% and <50%, score of 1; ≥50% and <75%, score of 2; and ≥75%, score of 3.

Hand Surface Analysis

Participants were instructed to wash their hands with a commercially available soap [63]. The amount of lactic acid was measured by placing an acrylic cylinder with an inner diameter of 1.5 cm on the hand, adding pure water, and pipetting the mixture. The concentration of l-lactic acid was measured using Lactate Pro 2 (ARKRAY Co Ltd, Inc) with the extracted solution [64]. The measurements were performed twice, and the values were averaged. The skin pH was measured using a multiskin measuring instrument and a skin pH meter (pH 905; Courage+Khazaka Electric GmbH). The surface temperature of the hand was measured using a noncontact thermometer (Shenzhen Hezhizhou Technology Co, Ltd) [65].

Lipids in the Stratum Corneum and Sebum Analysis

Stratum corneum from the forehead were obtained by stripping with adhesive acrylic film (No. 465 #40, Teraoka Seisakusho). According to a previous report [66], ceramides, free fatty acids, cholesterol, and cholesterol sulfate profiles of the stratum corneum samples were determined using reverse-phase LC-MS.

Face sebum was collected from the forehead using 2 pieces of cigarette paper (Blue double, Rizla Ltd). The sebum was extracted using chloroform or methanol for MS analysis. Sebum MS analysis was performed using flow injection analysis coupled with MS with an ultrahigh performance LC system (Vanquish, Thermo Fisher Scientific) containing a Q-Exactive Focus (Thermo Fisher Scientific) equipped with a heated electrospray source. The Fourier transform MS full-scan mode was used.

Body Odor Analysis

Participants were instructed not to use products such as deodorants or antiperspirants on their armpits, scalp, and soles of the feet during the night before collection of the body odor sample. Body odor was analyzed using solid-phase microextraction–gas chromatography–MS (SPME-GC-MS). Scalp odor samples were collected by pressing an oil-blotting film (3M Japan) against the parietal scalp ≤4 times at 6 different places and were then stored in a glass vial, immediately frozen, and stored at −80 °C until analysis. Each scalp odor sample was transferred to a 20-mL clear glass vial with a silicone or polytetrafluoroethylene crimp cap for SPME-GC-MS analysis. To collect samples for axillary odor analysis, a cotton pad (Katte Gauze, Ryugu Co, Ltd) infiltrated with 1.2 mL of distilled water was used to swab a 10-cm^2 area from the armpit at least 10 times for each participant. Foot odor samples were collected from the soles of the feet in the same manner. Each swabbing pad was stored in an aluminum bag with a zipper, immediately frozen, and stored at −80 °C until analysis. Each swabbing pad was centrifuged (6000 revolutions/min, 10 min), and the supernatants were acidified (pH 5.0) with 0.01 N hydrogen chloride and transferred to a 10-mL clear glass vial with a silicone or polytetrafluoroethylene crimp cap for SPME-GC-MS analysis.

Skin Surface Spectroscopy

Advanced Glycation End Product Analysis

The accumulation levels of advanced glycation end products (AGEs) in the skin were measured using an AGE reader (DiagnOptics Technologies) according to the specific protein modifications and fluorescent properties of AGEs [67].

Laser Speckle Blood Flowmetry

Facial skin blood flow was measured using laser speckle flowgraphy (a prototype based on LSFG-ANW, Softcare Co, Ltd) [68]. An industrial digital camera (DFK0818UP1300, The Imaging Source GmbH) with a lens (VS-1300VM, VS Technology Corporation) was used to record a series of moving images at a rate of 30 frames/s.

Cognitive Function Analysis

Cognitive function was assessed using the computer-administered neurocognitive test battery Cognitrax (CNS Vital Signs), for which the validity and reliability have been confirmed [69]. Cognitrax comprises the following battery of tests: a verbal memory test evaluating word learning, word memory, and word recognition, as well as immediate and

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delayed recall; visual memory test evaluating shape learning ability, shape memory, and shape recognition, as well as immediate and delayed recall; finger-tapping test evaluating motor speed and fine motor control; symbol-digit test evaluating complex information processing accuracy, complex attention, visual perceptual speed, and information processing speed; stroop test evaluating simple reaction time, complex reaction time, stroop reaction time, inhibition and disinhibition, and frontal or executive skills; shifting attention test evaluating executive function, shifting sets (rules, categories, and rapid decision-making), and reaction time; and continuous performance test evaluating the ability to maintain sustained attention, choice reaction time, and impulsivity. A composite neurocognitive index and cognitive domain scores were generated on the basis of the 7 tests.

Microbiota Analysis

Intestinal microbiota analyses were performed as previously reported [70,71]. Briefly, the participants were instructed to use an FS-0002 tube kit (TechnoSuruga Laboratory Co Ltd) containing guanidine thiocyanate solution to collect fecal samples and store them in a refrigerator (≤4 °C) between visits. Zirconia beads were added to the samples, milled at 5 m/s for 2 minutes using a FastPrep 24 Instrument (MP Biomedicals), and centrifuged for 1 minute at 2350 × g. Bacteria were identified on the basis of the 16S recombinant DNA V3-V4 region. Fragments of the polymerase chain reaction (PCR) mixtures were purified by electrophoresis on 1% agarose gels, followed by PCR Cleanup Filter Plates (Merck Millipore). Illumina paired-end sequencing was performed using the 2 × 300 cycle paired-end method and the MiSeq system (Illumina).

Skin microbiota were collected from the scalp and cheek. To collect scalp microbiota, the hair was parted with a rubber-gloved hand to expose the frontal area of the scalp, and to collect facial skin microbiota, a custom-made sampling template was used to allow for consistent sampling of 4 cm^2 of the cheek areas. A sterile swab (Nippon Becton Dickinson Company, Ltd) soaked in BBL-prepared saline solution (Becton, Dickinson and Company) was rubbed onto the scalp surface or the designated cheek areas. The head of the swab was cut and placed into a microtube. All samples were frozen at −80 °C until use. The V1-V2 hypervariable region was used as the target for 16S ribosomal RNA (rRNA) gene sequencing. DNA extraction, DNA library preparation, and DNA sequencing were performed by BIKEN Biomics Inc using their standard procedures.

To analyze the saliva microbiota, part of a whole saliva pellet resuspended in sterile water was collected in a 1.5-mL tube and centrifuged for 10 minutes at 15,000 × g at 4 °C. After removing the supernatant, the pellet was stored at −80 °C until the samples were analyzed by Genome Lead Co, Inc. DNA was extracted from each sample using both enzyme treatment and the beads-beating methods (Promega). Then, DNA was extracted from the samples using zirconia beads (EZ-Beads; Promega) and Genfind v2 (Beckman Coulter). The composition of the saliva microbiota was assessed by high-throughput sequencing of the 16S rRNA gene of the V1-V2 region using the Illumina NovaSeq Platform (Illumina). The V1-V2 regions of the 16S rRNA genes from each sample were amplified using primers containing 1 random base sequence at the N position. The 2× KAPA HiFi HotStart ReadyMix (KAPA Biosystems) was used for amplicon PCR and index PCR. Both the PCR products were purified using AMPure XP beads (Beckman Coulter). The amplicon PCR products were purified using AMPure XP beads (Beckman Coulter). NovaSeq sequencing was performed using the NovaSeq 6000 Reagent Kit v1.5 (500 cycles; Illumina) using a 251-bp paired-end sequencing protocol. All 16S rRNA raw sequence data were analyzed using the open-source QIIME2 platform [72], version 2021.2 (qiime2-2021.2).

SSL-RNA Analysis

The SSLs collection and SSL-RNA purification were performed as described previously [11]. In brief, an oil-blotting film (3M Japan) was used to wipe the forehead, cheeks, face line, nose, and chin or parietal scalp and stored in a glass vial at −80 °C until analysis. The oil-blotting film was cut into small pieces and homogenized in 1.45 mL of QIAzol (QIAGEN). The SSLs were extracted by placing the supernatant in a tube, adding chloroform, vortexing the mixture for 10 seconds, centrifuging the mixture at 12,000 × g for 15 minutes at 4 °C, and transferring the upper phase to a fresh tube. A RNeasy Mini Kit and QIAcube (QIAGEN) with concomitant DNase I treatment were used to purify the RNA, following the manufacturer's instructions.

Sequence library preparation was performed using the Ion AmpliSeq Transcriptome Human Gene Expression Kit (Thermo Fisher Scientific), following our previously described modified protocols [11,73,74]. Briefly, the RNA solution was combined with VILO Reaction Mix, SuperScript III enzyme, and T4GP32 (New England Biolabs). The target DNA was amplified using cDNA solution, Ion AmpliSeq HiFi Mix, T4GP32, and the Ion AmpliSeq Transcriptome Human Gene Expression Core Panel with incubation for 20 cycles. We purified the amplified DNA library by binding it to AMPure XP beads (Beckman Coulter), according to the manufacturer's protocol. A High-Sensitivity D1000 ScreenTape on an Agilent 4200 TapeStation was used to assess the quality of the DNA library. After confirming the quality of the DNA library, the purified library solution was combined with the Ion AmpliSeq HiFi Mix, Ion AmpliSeq Transcriptome Human Gene Expression Core Panel, and VILO Reaction Mix to produce the reaction solution. The adapter sequence was ligated to the library by adding Switch solution, Ion Xpress barcode adapters, and DNA ligase to the reaction solution and then incubating the mixture. The libraries were eluted from the beads using Library Amp Mix (Thermo Fisher Scientific) containing Library Amp Primers. An aliquot of the PCR product was purified using AMPure XP beads, and the supernatant was transferred to fresh PCR tubes. The quality of the sequence library was assessed using the High-Sensitivity D1000 ScreenTape on the Agilent 4200 TapeStation. An Ion Library TaqMan Quantitation Kit (Thermo Fisher Scientific) was used to quantify the library. After loading the DNA library in the Ion Chef System (Thermo Fisher Scientific), the template was prepared and the chip was loaded, and the Ion S5 XL System (Thermo Fisher Scientific) was used to perform the RNA sequencing.

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SSL-Protein Analysis

Proteins for SSL-protein analysis were prepared using S-trap micro columns (ProtiFi), according to the partially modified procedure described in the manufacturer's protocol. In this study, sodium deoxycholate and sodium lauryl sulfate were used for the protein solubilization solution. Following the removal of SSL-RNA from the upper layer, 2-propanol was added to the residual solution. After centrifuging at 14,000 × g for 5 minutes, the precipitate was dissolved in a protein solubilization solution and applied to an S-trap column. The eluted tryptic digest was concentrated under reduced pressure and desalted using styrene divinylbenzene polymer GL-Tip (GL Sciences) according to the manufacturer's protocol. The peptide mixtures were subjected to LC-MS/MS. LC separations were performed with a nano-HPLC system Ultimate 3000 (Thermo Fisher Scientific) using an Acclaim PepMap 100 analytical column (Thermo Fisher Scientific). MS detection was performed with a Q-Exactive Plus (Thermo Fisher Scientific) in positive-ion mode and operated in the data-dependent acquisition mode and data-independent acquisition mode. Analysis of the acquired data was performed using Mascot database search (Matrix Science) and DIA-NN software (version 8.1; GitHub) [75].

SSL-Metabolite Analysis

The SSLs for metabolite analysis were collected by wiping oil-blotting paper around the neck below the face line, and the samples were stored in glass vials at −80 °C until use. To extract metabolites, the oil-blotting film was cut into small pieces and placed in a glass vial with methanol. The supernatant was filtered through a DISMIC-13HP 0.45-µm syringe filter (Advantec) and concentrated under reduced pressure until dry. Each sample was redissolved in 80% (volume/volume) methanol and filtered through a DISMIC-13HP 0.45-µm syringe filter. A portion of the filtrate from each sample was mixed in equal volumes to create a pooled quality control sample.

SSL-metabolite analysis was conducted using an ExionLC system (AB Sciex) coupled to an AB SCIEX X500R electrospray-ionization quadrupole time-of-flight high-resolution MS (AB Sciex). The LC system comprises a 2-channel pump, a degasser, a column oven, an autosampler, and a controller. LC was performed by injecting the sample onto an L-column3 C18 reversed-phase column (Chemicals Evaluation and Research Institute).

We used the sequential window acquisition of all theoretical mass spectra. In total, LC-MS analysis was performed in 10 batches. The quality control dilution series was used to confirm the linearity of the metabolites. Data processing, including automatic peak finding, locally weighted scatterplot smoothing normalization, and identification via spectra matching, was performed using MS-DIAL (version 4.7; downloaded from the PRIMe website) [76]. All automatically detected peaks were checked manually, and the linearity of each metabolite was checked using diluted quality controls, excluding peaks with low linearity ($r \leq 0.85$).

Statistical Analysis

Data Management

The data of each participant were managed using an electronic database and case record forms. There were 2 levels of data quality control. The first level of quality control was conducted by the investigators while entering the records into the case record form. For the second level, an independent group conducted data monitoring and validation. An electronic database served as a double-entry system to further ensure accurate data input.

VHGM Analysis

We will construct a generative model to capture the joint distribution among the aforementioned health care attributes. As the attributes comprise both numerical and categorical values, a model that can handle this type of heterogeneity must be selected. To this end, we will use the heterogeneous incomplete variational autoencoder (HIVAE) [8]. The HIVAE is an extension of a variational autoencoder [77] in which a different likelihood function can be selected depending on the attribute type. For example, we will input the normal distribution for weight and height and the categorical distribution for sex (male, female, and other). Given a set of observed attributes as inputs, we can use the trained model to estimate the parameters of the (conditional) probability distribution of each attribute, including the missing ones. The objective function of HIVAE is called the evidence lower bound, which measures the discrepancy between the training data set and the model. We will separate the entire data set into training and testing sets and train the model to minimize the evidence lower bound to fit the training data set.

We will evaluate the performance of the trained model in terms of 2 perspectives: (1) predictability of missing attributes and (2) representability of the empirical distribution. For the first perspective, we will randomly generate missing patterns on the testing set and measure the prediction accuracy. For the second perspective, we will manually compare the joint distribution of the model and the data on several attribute pairs that would have a strong relationship (eg, age and blood pressure) to ensure that there is no notable discrepancy.

Individual Relationships Among the Obtained Multidimensional Data

Normally distributed data will be presented as mean (SD), median (IQR), and number (%), and nonnormally distributed data will be presented as IQR and number (%). The Kolmogorov-Smirnov test will be used to test whether the values of the variables are normally distributed. Analyses of both per-protocol and intention-to-treat groups will be conducted. The areas under the receiver operating characteristic curve (AUCs) and incremental AUCs will be calculated according to the trapezoidal rule from the measurements at each time point during the oral glucose tolerance test. Regression analysis will be used to explore the independent effects of each variable on secondary outcomes. We will examine the relationships among the overall outcomes. Correlations among the overall outcomes will be evaluated using both Pearson correlation coefficient and Spearman rank correlation. In addition, appropriate stratification

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and partial correlation analyses will be performed in the overall interaction analysis. All statistical analyses of the data will be performed using SPSS software (version 21.0; IBM Corp), SAS (version 9.4; SAS Institute Inc), and R software (R Foundation for Statistical Computing).

Results

The study was registered at University Hospital Medical Information Network on October 14, 2021. Recruitment was started on October 19, 2021, and ended on February 25, 2022. A total of 997 participants were enrolled in the study. Sample analysis will be performed from February 2022 to March 2023. Data analysis will be conducted in 2023, and the final report will be available in 2024.

Discussion

Principal Findings

High-dimensional cross-sectional studies are rarely conducted. We believe that there are several methods to use such data sets. We plan to provide the VHGM that we are developing as a commercial service via an application program interface (API) on the internet. Any application program can send a query to the VHGM, such as *what is the mean and variance of systolic blood pressure of Japanese adults? (marginal probability)*; *what is the probable distribution of blood glucose levels given my age, sex, and lifestyle (excursive, drinking, and smoking habits)? (conditional probability)*; and *what would my estimated cognitive function index be if my age were 10 years older (counterfactual inference)*. We are expecting to discover many innovative health care applications using the VHGM API.

Strengths and Limitations

Our exploration of individual relationships among the thousands of variables in the data set is expected to reveal previously unknown relationships, which may lead to a new health care hypotheses and further studies, including those aimed at constructing new intervention tests. Thus, this cross-sectional data set will lead to new discoveries in health care research.

Limitations of this protocol include its cross-sectional study design at a point in time, the fact that recruitment (via a website) was restricted to those who could participate in person to perform the survey. In addition, our sampling methods, such as the study's inclusion criteria and the decision by the responsible physician whether to allow participation, may have introduced a selection bias, making it difficult to generalize our findings to the population. Appropriate weighting can be applied to reduce the impact of selection bias on the estimates. If any modifications to this study design are necessary, we will notify the IRB and submit a study protocol with the necessary changes for IRB review. Thus far, data on preventive medicine and health care have been obtained on an opportunistic and time-consuming basis, using funds as needed. The data obtained from this study have the potential to provide a standardized model for the Japanese population regarding health care and to reveal public health implications. Using a larger sample size would reduce the risk of type II errors.

Conclusions

The results of this study may provide evidence for the future application of a VHGM based on a joint probability distribution model in clinical health care practice.

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Data Availability

The data are not publicly available owing to ethical restrictions. Owing to the nature of this research, the participants of this study did not agree to share their data publicly, and thus, supporting data are not available. The statistical properties of the data are approximated in the model and are available via an application program interface.

Authors' Contributions

M Hibi, S Katada, A Kawakami, KB, and HM designed the trial. S Katada, A Kawakami, KB, and MO were responsible for data curation. S Katada, A Kawakami, KB, MO, KS, T Hasumura, YA, T Fushimi, TA, S Kawano, RK, NC, ZG, KH, KO, YS, SY, and HM analyzed the data. S Katada, KS, NY, YA, T Fushimi, T Fujimatsu, S Kawano, RK, ST, Y Yamamoto, M Haneoka, KK, T Hideshima, ES, JS, A Kirino, TS, YT, MY, S Nagase, T Hirano, RF, Y Yamashiro, YN, and N Ojima performed data acquisition. S Katada, AM, NY, T Hasumura, TA, RK, ST, Y Yamamoto, M Haneoka, ES, JS, A Kirino, HT, S Nakamura, TS, MY, S Nagase, RF, Y Yamamoto, N Ojima, MS, N Oya, YM, and KM were responsible for methodology. S Katada, KS, S Nagase, RF, and Y Yamashiro provided research resources. NC, ZG, KH, KO, YS, and SY were responsible for software. TO supervised the trial. M Hibi and HM wrote the original draft. All authors critically revised the manuscript and approved the final version.

Conflicts of Interest

M Hibi, S Katada, A Kawakami, KB, MO, KS, AM, NY, T Hasumura, YA, T Fushimi, T Fujimatsu, TA, S Kawano, RK, ST, Y Yamamoto, M Haneoka, KK, T Hideshima, ES, JS, A Kirino, HT, S Nakamura, TS, YT, MY, S Nagase, T Hirano, RF, Y

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Yamashiro, YN, N Ojima, MS, N Oya, YM, and KM are employees of Kao Corporation (Tokyo, Japan). NC, ZG, KH, KO, YS, and SY are employees of Preferred Networks Incorporated (Tokyo, Japan). HM is an executive fellow of Kao Corporation and a research fellow of Preferred Networks Incorporated. The other authors have no conflicts of interest to declare.

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Abbreviations

AGE: advanced glycation end product
APDS: 3-aminopyridyl-N-hydroxysuccinimidyl carbamate
API: application program interface
AUC: area under the receiver operating characteristic curve
FU: follicular unit
HIVAE: heterogeneous incomplete variational autoencoder
HPLC: high-performance liquid chromatography
IL: interleukin
IRB: institutional review board
LC: liquid chromatography
LC-MS/MS: liquid chromatography–tandem mass spectrometry
LC-MS: liquid chromatography–mass spectrometry
MS: mass spectrometry
PCR: polymerase chain reaction
rRNA: ribosomal RNA
SPME-GC-MS: solid-phase microextraction–gas chromatography–mass spectrometry

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SSL: skin surface lipid
STROBE: Strengthening the Reporting of Observational Studies in Epidemiology
UMIN: University Hospital Medical Information Network
VHGM: Virtual Human Generative Model

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Protocol

New Web-Based System for Recording Public Health Nursing Practices and Determining Best Practices: Protocol of an Exploratory Sequential Design

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Abstract

Background: Digitalization and information and communication technology (ICT) promote effective, efficient individual and community care. Clinical terminology or taxonomy and its framework visualize individual patients' and nursing interventions' classifications to improve their outcomes and care quality. Public health nurses (PHNs) provide lifelong individual care and community-based activities while developing projects to promote community health. The linkage between these practices and clinical assessment remains tacit. Owing to Japan's lagging digitalization, supervisory PHNs face difficulties in monitoring each department's activities and staff members' performances and competencies. Randomly selected prefectural or municipal PHNs collect data on daily activities and required hours every 3 years. No study has adopted these data for public health nursing care management. PHNs need ICTs to manage their work and improve care quality; it may help identify health needs and suggest best public health nursing practices.

Objective: We aim to develop and validate an electronic recording and management system for evaluating different public health nursing practice needs, including individual care, community-based activities, and project development, and for determining their best practices.

Methods: We used a 2-phase exploratory sequential design (in Japan) comprising 2 phases. In phase 1, we developed the system's architectural framework and a hypothetical algorithm to determine the need for practice review through a literature review and a panel discussion. We designed a cloud-based practice recording system, including a daily record system and a termly review system. The panels included 3 supervisors who were prior PHNs at the prefectural or municipal government, and 1 was the executive director of the Japanese Nursing Association. The panels agreed that the draft architectural framework and hypothetical algorithm were reasonable. The system was not linked to electronic nursing records to protect patient privacy. Phase 2 validated

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each item through interviews with supervisory PHNs using a web-based meeting system. A nationwide survey was distributed to supervisory and midcareer PHNs across local governments.

Results: This study was funded in March 2022 and approved by all ethics review boards from July to September and November 2022. Data collection was completed in January 2023. Five PHNs participated in the interviews. In the nationwide survey, responses were obtained from 177 local governments of supervisory PHNs and 196 midcareer ones.

Conclusions: This study will reveal PHNs' tacit knowledge about their practices, assess needs for different approaches, and determine best practices. Additionally, this study will promote ICT-based practices in public health nursing. The system will enable PHNs to record their daily activities and share them with their supervisors to reflect on and improve their performance, and the quality of care to promote health equity in community settings. The system will support supervisory PHNs in creating performance benchmarks for their staff and departments to promote evidence-based human resource development and management.

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KEYWORDS

community-based activity; evidence-based practice; individual care; information and communication technology; program development; public health nursing; quality assurance; digitalization; eHealth; electronic record

Introduction

Background

Digital technologies promote innovation in health care and nursing [1]. Notably, a previous study categorized different applications of information and communication technology (ICT) in nursing practice into assessment, clinical intervention, health promotion, and service organization [2]. Regarding assessment, nurses have used electronic clinical recording systems [3] to assist in clinical decision-making for individual care [4], meet patients' health needs [5], and reduce overwork time and medical care expenditure [6]. Meanwhile, ICT-based health promotion programs can improve community health [7]. ICT also ensures efficient staffing and supports health workers' decision-making, communication, training, and health system management [1]. Therefore, digitalization and ICT promote effective and efficient care for individuals and communities. However, previous research has primarily focused on hospital- or clinic-based individual care [8]; little work has been done on the function of ICT in public health nursing [2].

Clinical terminology or taxonomy and its framework help visualize the classification of patients and nursing practice and improve health equity in multidisciplinary settings [9-14]. Nursing practices are based on nursing diagnosis systems [11] and interventions [12]. Focusing on patient outcomes is essential to improve nursing care and management quality [13,14]. However, while prior studies examine individual patients, knowledge about public health nursing is scarce. Under each country's different cultures, policies, and health care systems, public health nurses (PHNs) provide a wide range of lifelong care, support at the group level, and community-based activities. They also create policies, programs, projects, and health care systems that meet the needs of each community [15]. Individual care takes up most of a PHN's time [16], making it difficult to perform community-based activities and assessments [17], which are the basis of developing needs-oriented projects. Although these projects are vital for improving health equity in the community [18], evaluating the necessity of these practices and their linkage depends on the PHN's tacit knowledge. Therefore, in this field, assessment items core to clinical reasoning considering sociocultural backgrounds are required.

Given the rapidly changing health care needs that affect services, systems, and staffing [8], digitalization is still recent, especially in PHN [19]. The COVID-19 pandemic has accelerated the shortage of PHNs and digitalization in Japan [20]. Approximately 70% of PHNs in Japan work as prefectural or municipal public servants [21] and work in various departments. As Japan has the world's oldest population and the lowest birth rate, the national government must encourage digitalization and reduce the number of civil servants by half by 2040 [22]. Therefore, the total number of PHNs will potentially be halved by 2040. To ensure the quality of public health nursing, Japan has a national license system for PHNs [23]. Additionally, supervisory PHNs must manage practices in each department [24] while assessing the workloads of their staff and developing their competencies. Owing to the lack of ICT systems, supervisory PHNs may be unable to understand the happenings in each department and the performance and competencies of each staff member. An ICT system is needed to support their management and human resource development.

Furthermore, electronic record systems collect data on nursing care and promote evidence-based management in hospitals [6,10-13,25,26]. The Omaha system also enhances such management for each patient in community settings [14]. In Japan, the national government conducts a public health nursing activities survey every 3 years [27]. To this end, randomly selected prefectural or municipal PHNs gather data on their daily activities and the required hours [27]. However, no study has applied these data to elucidate public health nursing care management. To encourage evidence-based practices and nursing management, PHNs require an electronic recording and management system that identifies health needs and suggests the best public health nursing practices. The system would help PHNs think about their daily activities and share information

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with their supervisors to improve the quality of care and competencies, thus ensuring health equity in the community.

Objective

This study will develop and validate an electronic recording and management system to evaluate the necessity of different public health nursing practices—including individual care, community-based activities, and project development—and to determine their best practices.

Methods

Study Design

This study used an exploratory sequential design, which was conducted in Japan [28]. This design was suitable for exploring unknown questions using qualitative methods and developing a new instrument that can be validated by quantitative research analysis [28]. This study has 2 phases. Phase 1 will include a panel discussion to develop a structure for the electronic recording and management system. Phase 2 will confirm the validity of the proposed items through interviews with expert PHNs and a nationwide survey of PHNs.

Participants

The research team worked in public health nursing, home care nursing, public health, statistics, and computer sciences. This study is divided 2 phases. In phase 1, the research team conducted a literature review and a panel discussion that included 3 supervisors with experience working as prefectural or municipal government PHNs and 1 executive director of the Japan Nurse Association. The criteria for convening the expert panels meeting were to gather their opinions on the draft architectural framework—a hypothetical algorithm to determine the need for practice review; moreover, each item was developed by the research team.

In phase 2, the participants of interviews will be supervisory PHNs in prefectures or municipalities. Additionally, to ensure nationwide representation, we will include supervisory PHNs and midcareer PHNs with experience working in all local governments in Japan except those that completed the interviews. The inclusion criteria of midcareer PHNs have their cases and experience working for 6 to 20 years. The exclusion criteria for them are a managerial position.

Recruitment

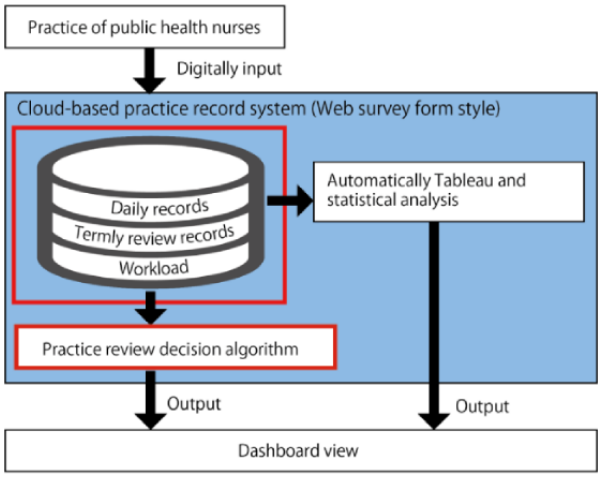
In phase 1, the research team recruited a panel of experts using snowball sampling. In phase 2, they recruited 5 to 10 supervisory PHNs as participants, who worked in prefectures or municipalities to avoid bias in the functions and roles of public health centers. Before starting the nationwide survey, we sent letters, including the study description, to supervisory PHNs. We used a mailing list of all supervisory PHNs from the Ministry of Health, Labour and Welfare to announce the survey by email. We expect approximately 530 local governments to participate based on a collection rate of 30% in a previous study that used a similar survey methodology [29].

Procedures

Phase 1: Develop an Architectural Framework

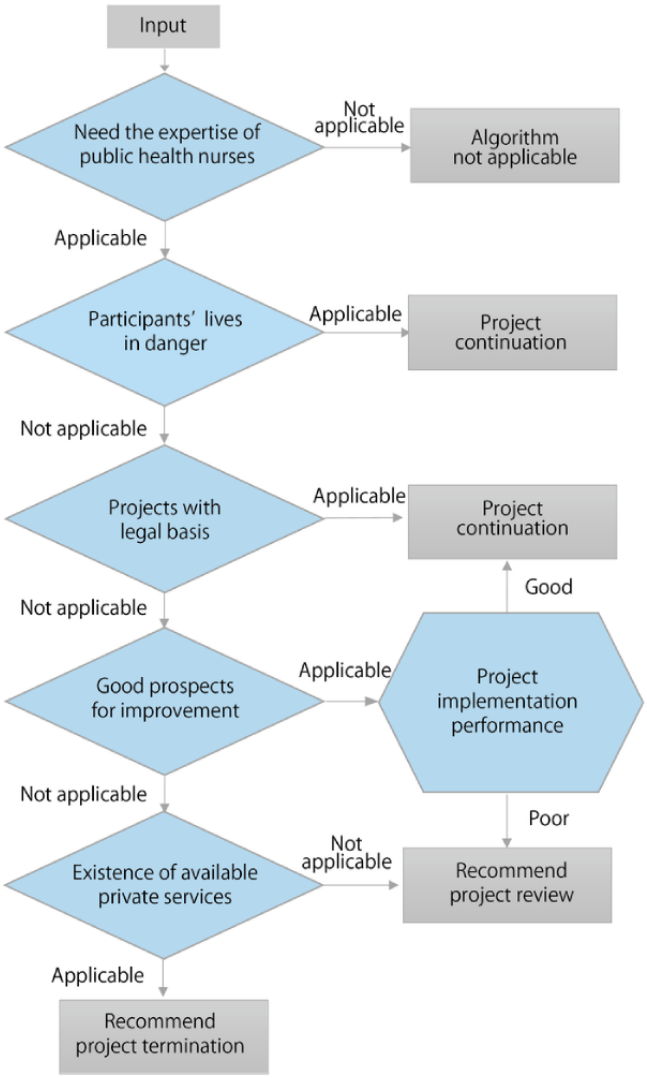
Based on a literature review [6,25-27,30-32] and discussions at 10 meetings, the research team created an architectural framework (Figure 1) for an electronic recording and management system. This study reports the construction of the system in the blue background area, especially the development of the system input items, and the hypothetical algorithm based on the practical experiences in the red frame areas. The data will be stored on a server contracted by the research team. The system can be accessed via a web browser on a touchscreen device or personal computer. We will collect data through a web-based survey form and a cloud-based practice recording system. Statistical analysis will be performed based on the data, and the results will be presented on the dashboard view as tables or graphs. Figure 2 shows the hypothetical algorithm to determine the need for practice review. Based on each PHN's assessment regarding individual care, community activities, and project implementation, an algorithm will suggest appropriate practices and directions for improvement.

Figure 1. An architectural framework for an electric recording and management system.



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Figure 2. A hypothetical algorithm for determining the need for practice review.



Phase 2: Confirming the Validity of the Proposed Items

In phase 2, the validity of the proposed items will be tested using interviews with expert PHNs and a nationwide questionnaire survey of supervisory and midcareer PHNs.

The semistructured interviews with supervisory PHNs will be conducted over a web-based meeting system. We will confirm that the validity of the survey items comprising each unit constructed in phase 2 is relevant to the cases handled by PHNs (ie, to verify that the PHNs will be able to answer the question). We will send the survey items to the interviewees in advance, including the items comprising the unit constructed in phase 1 and a semistructured interview guide. To protect the interviewees' privacy, we will not record the interviews. To ensure the trustworthiness of the qualitative phase and to protect the interviewees' privacy, 2 researchers will conduct the semistructured interviews in pairs, one acting as an interviewer and the other taking notes. After the interviews, we will send a memo of the content to the interviewees over email for confirmation. Based on the results, we will revise each item in the system and finalize it.

The nationwide survey will be conducted using a web-based form, and a URL or QR code for the survey will be distributed to supervisory and midcareer PHNs. We will ask the research participants to (1) select one highly necessary and one less necessary element of individual care, community-based activities, and project development that they have performed within the last month; and (2) enter select cases into our system and summarize them. The level of necessity of each activity will be measured using a 10-point Likert scale from 1 (very unnecessary) to 10 (highly necessary). Additionally, we will ask participants about the importance and incomprehensibility of each item and whether to include any additional items. Responses will be sent directly to the researcher (ie, they will not go through the supervisory PHNs).

Data Analysis

In the qualitative phase, 3 researchers will read the interview transcripts (confirmed by the interviewees) and classify the contents in terms of the survey items using the content analysis method [33]. We will combine expressions with similar meanings into a single concept, whereas contradictory data will be left as is. After consulting with the project's supervisory PHNs, we will revise the survey items. The items for the nationwide survey will be finalized after all the project members confirm their validity.

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The nationwide survey will be conducted through a descriptive analysis of the components of the system and the subjective necessity of PHN practices. In this survey, PHNs will answer based on 2 types of activities: (1) highly unnecessary and (2) highly essential. We want to compare these 2 categories and confirm whether the items will effectively work to help identify the differences between each activity in terms of necessity. We will use Cronbach α to measure the degree of agreement between the importance calculated when the responses were applied to the system developed in phase 1 and the subjective importance expressed by PHN interviewees. We will also perform a decision tree or random forest analysis with the PHN's subjective sense of significance as the outcome and the system configuration items as explanatory variables. The model with the highest prediction accuracy will be compared with the system created in phase 1. Finally, the panels will verify the nationwide survey results to confirm the external validity and consider whether the system may be improved based on the findings.

Ethical Considerations

This study will be conducted following the Declaration of Helsinki. Ethical approval for this study was obtained from the Research Ethics Committee of the Faculty of Medicine of the University of Tokyo, review number ID=2022114NI, 2022114NI-(1), 2022114NI-(2). We will explain the study's purpose and methods to the interviewees and advise them that their privacy will be protected in written form. Informed consent will be obtained from each participant. For the nationwide survey, only those who agree to participate in the study will be asked to respond to the questionnaire.

Results

Overview

This study was supported by the Ministry of Health, Labour and Welfare Japan research grant, which was acquired in April 2022. Interviews for supervisory PHNs were started in September 2022. Additionally, participants in the nationwide survey will be recruited in December 2022. The estimated date of the nationwide survey's completion will be January 2023. The preliminary results will be submitted for publication in December 2023.

Items From a Cloud-Based Practice Record System

In phase 1, the panels agreed that the draft architectural framework and a hypothetical algorithm were reasonable. After meetings with them, we decided that the system should not be linked to electronic nursing records to protect the privacy of each individual case. Items from a cloud-based practice record system are depicted in Tables 1 and 2. The items were divided into 2 domains. The first was a daily record system regarding individual care, community activities, and developing needs-oriented projects, whereas the second was their termly review system. Based on the Omaha system framework [14], we added assessment items from the perspectives of the individual, the family, and the environment, especially for individual care. We used 9 categories regarding a national survey of public health nursing activities [27]: infectious disease, intractable disease, disability, mental health, maternal and child health, health promotion, aging and long-term care, occupational health, and child welfare.

After developing the parts of the system, the researchers entered the data using typical vignette cases based on the national examination level and modified the items based on the results. The expert panels also filled in the items. However, the vignette cases were more straightforward than the actual clients. Therefore, we will ask PHNs to answer each item in the nationwide survey based on their actual cases (see below for more information).

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Table 1. Items from a cloud-based practice record system: individual care.

System, unit, category/domain, and examples of items	Items, n
Daily record system (N=71-89[a])	
Transdomain items (n=69)	
Demographics of the PHNs[b]	5
PHN ID	
Dates	
Districts	
Activity domains	
Time consumed	
Necessity	44
Individual	
Symptom: acute deterioration of medical condition	
ADL[c]: dependent in basic ADLs	
Acceptance: refusal of support, consultation, or treatment	
Treatment: need medical care at home	
Communication: difficulty in communication	
Social support: absence of key persons	
Emergency: risk of self-injury	
Family	
Symptom: family member's poor health	
Acceptance: family member's refusal of support, consultation, or treatment	
Communication: family member's lack of problem awareness and coping skills	
Social support: family member's absence of someone to consult	
Emergency: domestic violence	
Environment	
Housing: unsanitary living environment	
Social resource: lack of social resources available	
Economic: economic deprivation (insufficient income)	
Neighborhood: trouble with neighbors	
Daily review: the problem is worsening or is expected to worsen	9
Activity selection: cooperation of community residents is necessary to solve the problem	6
Task load: how irritated, stressed, and annoyed did you feel during the task?	5
Domain-specific items (N=2-20[a])	
Necessity	
Infectious disease: risk of outbreak	10
Intractable disease: support immediately after diagnosis or discharge	5
Disability: problems in employment or social participation	5
Mental health: disturbance of life rhythm	2
Maternal and child health: caregiver's risk in life history (eg, history of childhood abuse)	5
Health promotion: refusal of specific health guidance	7
Aging and long-term care: behavioral and psychological symptoms of dementia	4
Occupational health: young caregiver	20

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System, unit, category/domain, and examples of items	Items, n
Termly review system (N=14)	
Termly review: imbalance in the number and load of cases per PHN/district	4
Activity selection: accumulation of cases with similar needs	10

[a]Number of items depends on the domain.

[b]PHN: public health nurse.

[c]ADL: activities of daily living.

Table 2. Items from a cloud-based practice record system: community-based activities and project development.

Unit, category/domain, and example of items	Items, n
Daily record system (N=26)	
Demographics of the PHNs[a]	5
PHNs ID	
Dates	
Districts	
Activity domains	
Time consumed	
Necessity: risk to the life and well-being of the participants	4
Daily review: fewer participants in the activity/project than expected	3
Activity selection: people who have interrupted their participation and need individual follow-up	2
Task load: decreased involvement of residents in the operation of activity/project	12
Termly review system (N=57)	
Necessity: data available that support the necessity	12
Termly review	
Prediction and evaluation: initial health issue resolved and low probability of relapse	10
Disparity: inequity in service provision between regions or target groups	3
Substitutability: alternative private services available	5
Institutional issue: end of the year as a subsidized project	2
Resource: lack of cooperation with key persons in the district	8
Aggregated: long-term and large number of PHN inputs determined the project is less necessary	3
Activity selection	
Community-based activities to project development: enactment or amendment of laws related to activities/project	10
Project to community-based activities: necessity to modify the operation of the project depending on the district	4

[a]PHN: Public health nurse.

Daily Record System

The daily record system has 5 units: (1) demographic information of PHNs, (2) assessment of the necessity, (3) daily review, (4) activity selection, and (5) task load [34]. PHNs will enter related data daily, as described below.

1. Demographics of the PHN unit. PHNs will input their IDs, dates of their activities, districts, activity domains, and the time required for each activity.
2. Assessment of the necessity unit. The “necessity unit” determines how necessary each PHN activity is. The necessity of an individual case is determined by checking an applicable option (applicable, not applicable, or unknown) for each of the necessity judgment items in the domain to which each case corresponds to determine clinical urgency and any problems. The level of necessity of community-based activities and project development practices will be determined by checking the transdomain items and recording the number of people—the activity and practice targets.
3. Daily review unit. It evaluates PHN activities to determine whether they are appropriate and worth continuing. Items are distributed across the individual care, community-based activity, and project development subsets.
4. Activity selection unit. It examines movements across the different types of PHN activities. Individual care practices

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include items that speak to or can develop into community-based activities and project development practices.

5. Task load unit. It determines the difficulty level of each activity. Individual care difficulty will be measured using the Japanese version of the National Aeronautics and Space Administration task load index. This considers mental, physical, and temporal demands, level of effort, performance, and frustration [34].

Termly Review System

The termly review system assesses each activity by collecting monthly or semiannual daily reports and inputting additional items, including (1) necessity, (2) the termly review, and (3) activity selection units.

1. Necessity unit. It consists of items that determine the necessity of community-based activities and project development from a long-term perspective. The term review unit in individual care activities is automatically checked based on accumulated daily reports.
2. Termly review unit. The termly review items for community-based activities and project development will be itemized regarding forecasting and evaluation, gaps, substitutability, institutions, and limitations.
3. Activity selection unit. The activity selection unit in the termly reviewed system determines guidelines for the future activities of each PHN. The individual care subsection includes accumulated daily reports and additional items that choose complexity, multiproblematic cases, and rapid changes in social needs. Meanwhile, the community-based activities and project development subsections comprise automatic checks based on accumulated daily reports and items involved in transitions between activity types, such as health crises or government policy changes.

Discussion

Principal Findings

This study will develop and validate an electronic recording and management system to evaluate the necessity of different public health nursing practices and accordingly consider how public health nursing practices may be improved; specifically, the system will focus on practices that fall into the categories of individual care, community-based activities, and project development. This study has several strengths. Validated items will evaluate the necessity of different public health nursing practices, suggest the best ones, and show the clinical reasoning of PHNs. The system will enable PHNs to record their daily activities and share them with their supervisors to reflect on and improve their assessment and the quality of care to promote health equity in community settings.

This study focuses on the links between individual care, community-based activities, and project development to assess the need for continued care. Most studies showed the framework and items of nursing assessment, interventions, and outcomes for individual patients [10-14]. By contrast, PHNs promote health equity and individual, family, and community health through direct care and policy development [15]. However, PHNs are often too busy with individual care to assess community health needs and implement population-wide activities [17]. By offering new insights into PHNs' tacit knowledge, this study can also inform the best practices for them. Additionally, senior and managerial PHNs play a vital role in bridging community needs assessment and grassroots projects in ways that support novice PHNs. Clarifying and translating PHNs' tacit knowledge into explicit knowledge would be essential to developing health care systems [35].

The result of this study will show the required time and burden for PHNs regarding each activity. Health care organizations required help ensuring high-quality care, owing to limited staff and other resources [36]. In this context, it is necessary to optimize human resources in health care. Identifying benchmarks for and measuring staff performance is crucial for effective human resource management and person-centered care [37]. Therefore, supervisory PHNs need to be able to identify the performance of each staff member and the effectiveness of their activities. Our system will support supervisory PHNs in promoting evidence-based human resource development.

Moreover, because the system requires PHNs to record their daily activities, it will enable PHN directors and staff to reflect on their practice periodically. Sharing the results of their daily activities with tier supervisors can help PHNs improve their performance and provide appropriate care for individuals, families, aggregates, and communities. Therefore, this study will improve the quality of care and address community health inequities.

Limitations

This study has some limitations. First, due to the ongoing COVID-19 pandemic, we can only interview a few participants; additionally, we expect the response rate for our nationwide survey to be low. Meanwhile, it is also notable that our study participants will likely be health care workers interested in the study. While we will work to ensure that our sample will be nationally representative by asking all local governments in Japan to participate, this study will still be subject to this selection bias. We will be sure to carefully analyze and interpret the data accordingly.

Conclusions

This exploratory sequential study will attempt to develop and validate an electronic recording and management system to evaluate the necessity of different public health nursing practices and determine best practices. The results will offer insights to develop a system that can help PHNs reflect on their daily routines and create benchmarks that can inform, thus improving on-the-job training by supervisory PHNs. This system will strengthen evidence-based public health nursing practices and management while improving the quality of care to enhance health equities in community settings.

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Acknowledgments

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Data Availability

The data set is not available to protect the participants' privacy; moreover, participants did not provide written consent to share data.

Authors' Contributions

All authors met the criteria forth by the International Committee for Medical Journal Editors (ICMJE) through direct contributions to the design and conduct of this study. All authors significantly revised the draft and confirmed the final version of the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

ICT: information and communication technology
PHN: public health nurse

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Protocol

Testing Behavior Change Techniques to Increase Physical Activity in Middle-Aged and Older Adults: Protocol for a Randomized Personalized Trial Series

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Abstract

Background: Being physically active is critical to successful aging, but most middle-aged and older adults do not move enough. Research has shown that even small increases in activity can have a significant impact on risk reduction and improve quality of life. Some behavior change techniques (BCTs) can increase activity, but prior studies on their effectiveness have primarily tested them in between-subjects trials and in aggregate. These design approaches, while robust, fail to identify those BCTs most influential for a given individual. In contrast, a personalized, or N-of-1, trial design can assess a person's response to each specific intervention.

Objective: This study is designed to test the feasibility, acceptability, and preliminary effectiveness of a remotely delivered personalized behavioral intervention to increase low-intensity physical activity (ie, walking) in adults aged 45 to 75 years.

Methods: The intervention will be administered over 10 weeks, starting with a 2-week baseline period followed by 4 BCTs (goal-setting, self-monitoring, feedback, and action planning) delivered one at a time, each for 2 weeks. In total, 60 participants will be randomized post baseline to 1 of 24 intervention sequences. Physical activity will be continuously measured by a wearable activity tracker, and intervention components and outcome measures will be delivered and collected by email, SMS text messages, and surveys. The effect of the overall intervention on step counts relative to baseline will be examined using generalized linear mixed models with an autoregressive model that accounts for possible autocorrelation and linear trends for daily steps across time. Participant satisfaction with the study components and attitudes and opinions toward personalized trials will be measured at the intervention's conclusion.

Results: Pooled change in daily step count will be reported between baseline and individual BCTs and baseline versus overall intervention. Self-efficacy scores will be compared between baseline and individual BCTs and between baseline and the overall intervention. Mean and SD will be reported for survey measures (participant satisfaction with study components and attitudes and opinions toward personalized trials).

Conclusions: Assessing the feasibility and acceptability of delivering a personalized, remote physical activity intervention for middle-aged and older adults will inform what steps will be needed to scale up to a fully powered and within-subjects experimental design remotely. Examining the effect of each BCT in isolation will allow for their unique impact to be assessed and support design of future behavioral interventions. In using a personalized trial design, the heterogeneity of individual responses for each BCT can be quantified and inform later National Institutes of Health stages of intervention development trials.

Trial Registration: clinicaltrials.gov NCT04967313; https://clinicaltrials.gov/ct2/show/NCT04967313

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KEYWORDS

behavior change techniques; N-of-1; personalized trials; physical activity; behavior change; aging; quality of life; feasibility; acceptability; effectiveness; web-based; intervention; text; email; survey

Introduction

The health benefits of physical activity (PA) are wide ranging, from reducing all-cause mortality and cardiovascular disease risk [1,2] to improving mental health [3]. However, most Americans fail to meet recommended levels of PA, with a prevalence of inactivity increasing as people age [4,5]. This age-related decline in activity is concerning as the benefits of PA are particularly potent as we get older [6]. The development of effective PA interventions such that everyone meets national guidelines remains a central goal, but recent research findings have shown that even small increases in PA offer health benefits [1,2]. Furthermore, a nonlinear dose response exists between PA volume and disease risk reduction, with the greatest drop in risk seen in very inactive older adults who increase PA by even a small amount [2]. Low-intensity PA, such as walking, has been identified as an effective and well-accepted modality, with increases of as little as 1000 steps per day found to lower the risk of mortality [2].

While the evidence demonstrating health benefits for older adults from even small amounts of PA is reassuring [2], questions remain on the most effective ways to encourage any positive change in PA among this population. While there have been numerous PA interventions for older adults, few have shown more than modest improvements [7]. One plausible reason is that many of these studies have been conventional randomized controlled trials (RCTs) with little consideration for active components of behavior interventions, no consideration for heterogeneity of treatment effects, and a mean outcome effect calculated, for example, pre-post change in daily step count for the hypothetical "average" older adult. While between-subjects RCTs are the gold standard of research trials, this design cannot calculate individual heterogeneity of treatment effects, as individuals are only exposed to 1 condition—the single condition to which they were randomized [8]. Even in clinically significant between-subject RCTs, some participants increase in activity, while others show no change or even decrease in activity in response to the intervention.

To address these concerns, some RCT designs focus on within-person behavior change with exposure to multiple interventions. Personalized trial designs, otherwise known as "N-of-1" trial designs, use a within-subject experimental approach to evaluate the outcomes of different interventions specific to that subject [9,10]. For example, a personalized trial can provide a quantitative estimate of the effects of distinct behavioral interventions on a single participant by observing the participant continuously over a given period with the different interventions occurring at scheduled time points. Observing the effects of multiple interventions can determine the quantitative effect of each specific intervention on an individual participant. This means effect sizes for each intervention can be confirmed for that participant rather than relying on aggregate findings that include data from other participants.

Personalized trials have been used to study fatigue, depression, back pain, and preventive behaviors [11,12], but they have not been widely employed in real-world clinical practice because the delivery of such an approach has been perceived as overly burdensome for clinicians and patients [13]. However, with the advent of smartphones, cloud computing, and biometric or activity trackers, platforms can now be developed to conduct N-of-trials more feasibly. N-of-1 trials using this technology can allow researchers to deliver behavioral interventions and obtain real-world data remotely, often in real time.

Extensive research has attempted to untangle those key elements, known as behavior change techniques (BCTs), that contribute to successful changes in behaviors such as smoking, diet, or PA [14,15]. From this body of research, we first focused on those that have been associated with improvements in PA [16] and then narrowed our intervention selection down to 4 BCTs that were most strongly associated with a change in walking and could be delivered effectively using our trial design. The 4 BCTs selected are goal setting, self-monitoring of behavior, action-planning, and feedback on behavior.

This study protocol is designed to evaluate the feasibility and acceptability of a randomized personalized trial that will serially deliver 4 BCTs in random order to promote low-intensity PA. The trial will recruit 60 adults aged 45-75 years. The protocol will integrate wearable technology (ie, Fitbit) capable of measuring participant activity (eg, step count and heart rate) with SMS text messaging and survey delivery via smartphone such that the research team can conduct the study remotely and collect data continuously. The study's primary outcomes will be within-person changes in daily steps and participant satisfaction with personalized trial approach components. Secondary outcomes include self-efficacy for walking and participant attitudes and opinions toward personalized trials.

Methods

Design

The purpose of this study is to determine the feasibility, acceptability and preliminary effectiveness of using personalized or N-of-1 methods to increase low-intensity walking by 2000 steps per day for 5 days each week in a remote research study. Participants can accumulate these additional 2000 steps across the course of the day and do not have to do so in a single bout. The study will recruit Northwell employees aged 45 to 75 years old and use 4 BCTs that have been shown as effective in encouraging increases in PA.

The study design comprises 2 main parts. Part 1 entails a series of 4 phases (see Figure 1) where participants will be recruited to help develop the content and processes for the second main

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part, which is the intervention—a personalized trial series. Up to 60 participants will participate in the initial series of 4 phases undergoing focus groups, interviews, and surveys to elicit feedback concerning the clarity of instructions and convenience of messaging. They will provide feedback on key aspects of study design, including BCT choices, BCT descriptions, materials, and electronic delivery methods such as SMS text messaging and email receipt. Up to 10 of the 60 participants will engage with study materials and procedures as "mock participants," interacting remotely and providing feedback about the ease and acceptability of study procedures to further refine study materials and procedures.

The second main part of the study entails an intervention, where 60 participants (who were not involved in the earlier phases of focus groups and user testing) will be recruited for a 10-week personalized trial assessing the impact of 4 BCTs, assigned in random order, on their walking behavior. Participants will be sent a Fitbit Charge 4 tracker that will monitor the number of steps taken per day. At the end of each 2-week intervention period, participants will complete a survey stating their satisfaction with the specific single BCT delivered during that time. Each BCT will be presented for 2 weeks during the 8-week active intervention in a randomly selected order (see Figure 2). Our study statistician, who is not involved in recruitment, will generate a list of assignments using block randomization, which they will then provide to our project manager. Participants will be assigned a BCT sequence if they complete the baseline and meet all adherence criteria.

At the end of their 10-week trial, participants will receive a detailed summary of their observed data and a final, comprehensive satisfaction survey regarding the overall personalized trial design. The summary will help participants learn more about their responses to each of the 4 BCTs. The satisfaction survey will inform investigators about the feasibility of personalized study design for future research and clinical applications.

Figure 1. Pretrial user testing.

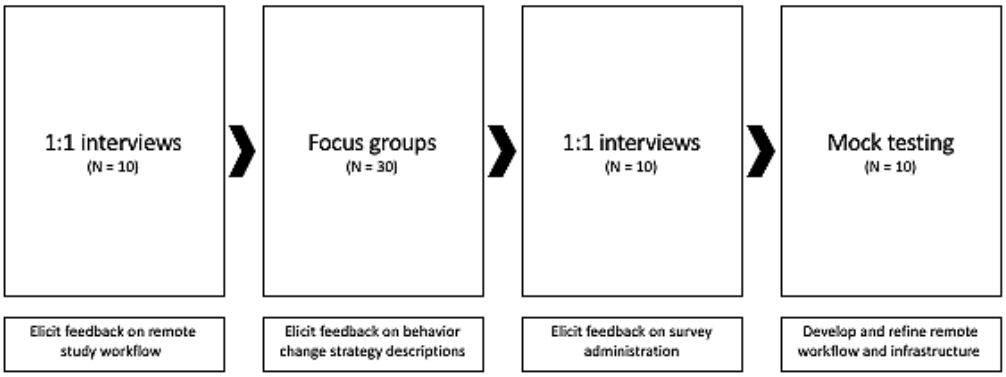


Figure 2. Intervention sequences. AP: action planning; BCT: behavior change technique; FB: feedback on behavior; GS: goal setting; SM: self-monitoring.

BCT 1	BCT 2	BCT 3	BCT 4	BCT 1	BCT 2	BCT 3	BCT 4
2 weeks	2 weeks	2 weeks	2 weeks	2 weeks	2 weeks	2 weeks	2 weeks
GS	FB	SM	AP	GS	FB	AP	SM
FB	GS	SM	AP	AP	SM	FB	GS
FB	GS	AP	SM	GS	SM	FB	AP
FB	SM	GS	AP	GS	AP	FB	SM
FB	SM	AP	GS	GS	SM	AP	FB
SM	GS	AP	FB	AP	FB	SM	GS
AP	GS	SM	FB	GS	AP	SM	FB
SM	FB	AP	GS	SM	AP	GS	FB
AP	FB	GS	SM	AP	GS	FB	SM
AP	SM	GS	FB	SM	AP	FB	GS
SM	GS	FB	AP	FB	AP	GS	SM
FB	AP	SM	GS	SM	FB	GS	AP

Participants, Recruitment, and Screening

Potential participants will be Northwell Health employees who are community residing, 45 to 75 years old, healthy, report that they walk regularly without health and safety issues, and express an interest in participating in a personalized trial to increase their walking.

The study will use Northwell Health's existing employee networks to recruit eligible participants. Potential participants

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may be recruited via the following measures: (1) advertisement emails to those who previously expressed an interest in participating in a personalized trial, (2) flyers circulated within the Northwell Health network, and (3) Northwell Health employee social media sites such as Northwell's employee-only Facebook group.

Interested participants will first be invited to complete a "Screening Survey" where they must respond to inclusion and exclusion criteria. Clinical research coordinators will review these data and determine whether a potential participant is eligible to participate.

Ethics Approval

The protocol and consent processes have been approved by the institutional review board (IRB; 20-1166) at Northwell Health's Feinstein Institutes for Medical Research. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee, Northwell Health Institutional Review Board. The consent document will contain all the elements of informed consent required by applicable federal regulation for the protection of human subjects and elements of authorization required by the Health Insurance Portability and Accountability Act Privacy Rule.

Consent Process

The consent will be presented electronically as an IRB-approved information sheet for the pretrial phases and as a full, IRB-approved informed consent form requiring a digital signature for the intervention. As consent for the intervention will be obtained remotely, the electronic platform will be designed such that the consent form is easy to navigate. We will use interactive, electronic-based technology to present information about the research in a variety of different modalities to facilitate understanding before participants document their consent (eg, print and video formats). The consent document will contain all the elements of informed consent required by applicable federal regulation for the protection of human subjects and elements of authorization required by the Health Insurance Portability and Accountability Act Privacy Rule and will begin with a concise and focused presentation of the key information that is most likely to assist participants in understanding the reasons why they may or may not want to participate in the research. These descriptions will be carefully scripted in language that persons with a sixth-grade education can understand; key information will include a brief description of the participant's proposed involvement, potential risks, and benefits of participation. Voluntary participation affirming participants that they have the right to stop at any time without impact to their employment or care will be emphasized. Potential participants must demonstrate comprehension of the informed consent form by responding to 4 questions about the trial prior to documenting their consent. Their electronic informed consent will be obtained prior to enrollment in the project for those individuals who are eligible. Participants will receive a copy of their signed informed consent form via SMS text message. Since consents are obtained electronically, they will remain in our Research Electronic Data Capture database (Vanderbilt University) indefinitely. The IRB-approved informed consent is included in Multimedia Appendix 1.

Privacy and Confidentiality

Given that study activities involve no more than minimal risks encountered in daily life (ie, increased time spent walking by healthy, working individuals), this study does not require oversight by a Data Safety and Monitoring Committee. Rather, the study has received National Institutes of Health approval for a safety monitor. This safety monitor will be assigned to periodically review and evaluate project data for participant safety, scientific integrity, and trial progress. There is no additional risk with using a Fitbit activity monitor for research as compared to using the device as a consumer, including mild skin irritation (ie, contact dermatitis) which occurs among a small proportion of users. One risk of taking part in this study is the possibility of a loss of confidentiality or privacy. The risk of loss of confidentiality will be minimized by securely storing data including protected health information in a Northwell-approved database and minimizing the use of protected health information.

Participant Compensation

Participant compensation will vary according to the part of the study in which the participant is involved. Participants in the 4 pretrial phases will receive 5000 points credited to their Northwell MyRecognition account (roughly equivalent to US $25) for attending a focus group, participating in an interview, or completing their mock study procedures.

For the intervention, involving 10 weeks of study participation, participants will receive a pay card valued at US $100 for completing all study requirements. Additionally, participants in the intervention will be able to keep their Fitbit, valued at US $150.

Focus Group Procedures

Up to 60 participants will participate in the first 4 pretrial phases of the study. They will be invited to participate in 1-on-1 interviews (up to 20 participants), focus groups (up to 30), or mock testing (up to 10). Participants will provide feedback on key aspects of study design such as BCT descriptions, study workflow remotely (ie, remote screening, informed consent process, and demographic questionnaire), and remote survey administration (ie, satisfaction and self-efficacy surveys).

Participants in the focus groups and 1-on-1 interviews will be presented with study materials and potential aspects of study designs. Participants will then be asked questions on the clarity and readability of that content—for example, IRB-approved questions such as "Do the descriptions make sense?" and "What would motivate someone to participate in this study?" These focus groups and interviews will be conducted by a trained facilitator with a principal investigator and note-taker present. Ten of the 60 participants will engage in mock testing of study materials and procedures, providing feedback to the study team on the acceptability of these procedures. This will allow the study team to develop and refine the workflow and infrastructure remotely.

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Personalized Trial Series Procedures

As noted earlier, an intervention in the form of a personalized trial series will follow the pretrial phases This series will comprise a single trial for each eligible participant that includes a 2-week baseline period and 8 weeks of study intervention, testing 1 BCT at a time each for a 2-week period. During baseline, participants must maintain 80% compliance with Fitbit wear (ie, device is worn a minimum of 10 waking hours on a given day) and responses to questionnaires to be eligible for the intervention period.

Intervention Onboarding

If participants consent, they will receive an "Onboarding Survey" to complete. This form will collect the participant's demographic information and necessary contact information so that the study team can ship the activity tracker and study materials. Once research staff confirm that the participant has completed the required onboarding tasks, an initial study kit, which includes a Fitbit Charge 4 and printed materials to guide the participant through the study, will be shipped to them. The printed materials will instruct participants how to download an app to their personal smartphone so they can use the Fitbit as well as instructions on how to charge and synchronize it. Anonymous study accounts will be created to protect the privacy of the participant.

Intervention Baseline

Participants will be mailed a study kit including a Fitbit Charge 4 device and printed study materials. The study materials will include the participant's start date and instructions on how to download the Fitbit app to their smartphone so they can pair the Fitbit device. All baseline periods will begin on a Monday, and no more than 20 participants will be permitted to begin on the same day.

The baseline period will be 2 weeks in duration. Potential participants will not receive any text message BCT interventions during baseline, but they will be asked to wear their Fitbit all day and night (as tolerated), sync their Fitbit device at least every 2 days, and respond to 1 text message per day to ensure they are receiving communications.

At the end of the baseline period, a clinical research coordinator will review individual adherence to Fitbit wear and responsiveness to the daily surveys. Adherence to Fitbit wear will be defined as having at least 600 minutes (10 hours) of heart rate activity per day. SMS text message adherence will be defined as having responded to the daily message. Baseline participants who do not achieve at least 80% adherence to both Fitbit wear and SMS text message responses during the 2-week baseline period will be withdrawn from the study. Those who maintain at least 80% adherence will be randomized to 1 of 24 sequences of 4 BCTs received 1 at a time, switching every 2 weeks (see Figure 2). Enrollment will continue until up to 60 participants have been randomized.

Main Intervention—BCT Sequences

Participants who successfully complete the baseline period will receive a random sequence of BCT interventions over the next 8 weeks during which a BCT message is delivered daily for a 2-week period. For example, goal-setting messages will be sent for 2 weeks, then self-monitoring prompts for 2 weeks, and so on for action planning and feedback. On the day before each new 2-week period, participants will be sent a message describing which BCT is coming next. BCT messages will be automatically delivered each day, and the participant's own data from baseline and the previous day will be used to generate messages. A description of BCTs employed and sample messages is provided in Table 1.

Participants will also receive a biweekly survey to assess their satisfaction with the BCT intervention sent over those 2 weeks and a self-efficacy survey assessing their confidence in their ability to walk for varying periods of time. Participants may receive additional SMS text messages to those outlined above with reminders to sync their data if needed.

Table 1. Description of behavior change technique intervention content.

Content	Modalities	Sample SMS text message prompt
Goal setting	SMS text message is delivered daily to encourage the participant to set a goal of beating their average daily step count during baseline.	"Is your goal today to walk an extra 2000 steps more than your baseline average?"
Self-monitoring of behavior	Ongoing self-monitoring is prompted by a daily text message delivered each morning. The baseline average is included in the message.	"Check your Fitbit dashboard for yesterday's activity. Did you take an extra 2,000 steps more than your baseline average?"
Feedback on behavior	An SMS text message is delivered each morning stating whether or not the goal had been met on the day prior (Fitbit step data are collected remotely)	"You met your goal yesterday. You walked 2000 steps more than your baseline average." "You did not meet your goal yesterday of walking at least an extra 2,000 steps more than your baseline average"
Action planning	An SMS text message is delivered each morning encouraging the participant to plan for an additional walking session. The baseline average is included in the message.	"Take one minute and plan how, where, and when today you can walk an extra 2000 steps over your baseline."

Postintervention

Upon completion, participants in the intervention will receive an individual report that presents changes in their own walking behavior in relation to their selected BCTs. Participants will also receive a final survey concerning their satisfaction with the personalized trial design and their attitudes and opinions toward personalized trials. After receiving the report, clinical research

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coordinators will notify the participant that they have completed the study, remind them of the US $100 pay card for completing the study, and instruct them to unlink the Fitbit device from the anonymous study account. Participants will also be invited to contact the study team for any remaining questions.

Retention Plans During Intervention

The study has a well-formulated action plan for participant retention: when a participant fails to sync their device or respond to questionnaires for 2 consecutive days, they will receive an automated message notifying them that they have dipped below the benchmark. If improvement is not seen within another 2 days, the clinical research coordinator will reach out to the participant by text/phone/email and troubleshoot issues. Retention rates will be reported in weekly team meetings and, if needed, the study will institute additional incentives such as a weekly regret lottery to ensure compliance with study procedures and retention of study participants. A regret lottery is a method adopted from behavioral economics where participants are entered into a money- or prize-based lottery for which prize receipt is contingent upon participants' achievement of protocol adherence goals [17].

Measures and Analysis: Data Integrity

The study data manager will be responsible for ensuring the integrity of data collected and the preparation of the data for statistical analysis. The data manager is available to provide data to the safety office upon the safety monitor's request in between monthly reports.

Responses from interviews and focus groups in the pretrial phases will be tabulated into documented themes for consideration in the intervention design, such as acceptable levels of participant burden (eg, optimal number of SMS text messages per week) and consensus on design features including the content of messaging.

For missing data, the plan is to invest in collecting data as completely as possible. Given the preliminary work to refine the BCT description and study design prior to the 60 personalized trials, we anticipate minimal missing data in recording participant responses. Intention-to-treat analysis will be used. In the unlikely case of missing data, we will examine the missingness pattern and its association with any phenotypes, thus identifying potential confounders and use multiple imputation approaches.

Primary Outcomes

Within-Person Change in Daily Steps

The Fitbit device continuously collects the number of steps taken by each participant. These data can be examined at a daily level, and the study will aggregate daily step counts for both the baseline and intervention periods [18]. This will allow the research teams to compare the daily step count between each period to see if any change occurs.

Participant Satisfaction With Personalized Trial Components

At the end of the intervention period and after receiving their individual study report, the participant will receive a satisfaction survey comprising nine items with 4-point Likert scales. Each item is preceded by the prompt "How satisfied were you with the following?" and the 4-point scale ranges from "Not at all satisfied" to "Very satisfied."

Secondary Outcomes

Self-Efficacy for Walking

Self-efficacy has been shown to predict longer-term behavior, mediating the relationship between positive experience and PA [19]. At the end of the baseline period and every 2 weeks during the intervention period, participants will complete the Self-Efficacy for Walking Scale [20]. It is a validated 10-item survey assessing the participant's confidence in their ability to walk for a given duration. The phrase "I BELIEVE THAT I CAN WALK" precedes all of the 10 sentences with each one specifying a different amount of time (eg, "For 5 minutes at a moderately fast pace without stopping"). The first item in the survey specifies 5 minutes of walking and the amount increases by 5 minutes with each subsequent item such that the final item specifies 50 minutes of walking. The questions are scored on an 11-point scale, which ranges from "Not at all confident" to "Highly confident" with "Moderately confident" in the middle.

Participant Attitudes and Opinions About the Personalized Trial Implementation

To measure attitudes and opinions about personalized trial implementation, participants will be asked to respond to an 11-item survey on a 7-point scale. This survey is modified from the widely used system usability scale [21]. Each item asks about some aspect of the personalized trial. For example, 1 item reads "The materials I received in the mail were clear and easy to follow" and another reads "I needed to learn a lot of things before I could get going with my personalized trial." These statements will prompt the participant to indicate how much that statement applies to them; on one end of the scale reads, "Strongly disagree," and the other reads, "Strongly agree."

Primary Analyses

Means and SDs for daily steps will be reported for the baseline period and for each BCT intervention period. The effect of the overall intervention relative to baseline will be examined using generalized linear mixed models with an AR(1) (autoregressive order of 1) model that accounts for possible autocorrelation and linear trends for daily steps across time. The overall intervention effect will be tested based on whether the coefficient of the time effect is positive. Additional generalized linear mixed models will be examined to identify the effects of individual BCTs on daily steps. For these AR(1) models, fixed effects will be specified for each BCT intervention and random effects will be specified for each participant. We will adopt a novel Bayesian distributed lagged model to further explore the extent of carryover effects [22]. For participant satisfaction with personalized trial components, responses to the questions will be reported with means and SDs. The distribution of participant responses for each item assessing satisfaction will be displayed using a bar graph.

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Secondary Analyses

Means and SDs for self-efficacy will be reported for the baseline period and for each BCT intervention period. To identify whether self-efficacy for walking mediates the effect of the BCT intervention on daily steps, we will perform the analysis in 3 steps. First, we will estimate the effects of the BCT intervention on self-efficacy. This step will be examined using linear mixed-effects models, which include a random participant effect, fixed effects for the BCT intervention, a fixed time effect, and fixed BCT-time interaction. Next, we will estimate the effect of the BCT intervention on daily steps using linear regression. Finally, we will estimate the indirect effect of the BCT intervention on daily steps via the proposed mediating variable of self-efficacy. This will use natural effects models for effect decomposition into direct effect and indirect effect, mediated by an increase in self-efficacy, relative to baseline [23,24]. Participant attitudes and opinions toward personalized trials will be reported with means and SDs. Bar graphs will be used to display the distribution of participant responses for each item.

Sample Size Justification

Sample size was based on the primary outcome for within-person change in daily steps due to the overall BCT intervention. As this is a feasibility trial, sample size estimates were calculated based on the effect of the overall intervention, not the individual BCT interventions. The effect size is obtained from a previous study [25]. Using a paired *t* test with the effect size of 0.404 and type I error of 0.05 (2-sided), we obtain a power of 80% when comparing the number of steps during BCT period with the baseline period for 50 subjects. We expect a change in step of 2000 between the baseline and BCT periods. We obtained a pooled standard error of 4989.77 from Pinto et al [25], from a SE of 2476 (preintervention period) and 3555 (postintervention period). To achieve a total of 50 participants with complete data, under an assumed 15% attrition, we anticipate randomizing up to 60 participants. This sample size will ensure adequate size to obtain a preliminary assessment of this trial's feasibility, which will be determined by the effectiveness of the overall BCT intervention on PA behavior and participant scores on the satisfaction survey. The number of assessment measures and treatment repetitions per trial are based on expert recommendations by the study statistician and their estimations about the maximal duration of the trial to maintain patient engagement.

Results

The project was funded in 2021, and enrollment was completed in February 2022. Data analysis is currently underway, and the first results are expected to be submitted for publication in June 2023.

Discussion

Principal Findings

This study will evaluate the feasibility and acceptability of a randomized personalized trial to promote low-intensity PA in middle-aged and older adults. Sixty adults aged 45-75 years old will receive 4 BCTs, one at a time, for a 2-week each. The study will be conducted remotely, using automated SMS text messaging and survey delivery, and wearable technology to monitor participant activity. The study's primary outcomes will be within-person changes in daily steps and participant satisfaction with personalized trial approach components. This study's findings will deliver insights into 2 main areas of research interest. First will be the feasibility of delivering a series of individual BCTs in a personalized design to influence PA behavior. Most studies to date have incorporated multiple BCTs in their intervention, which limits our understanding of each BCT's specific impact. Second is the feasibility and acceptability of the personalized trial design as measured by participant satisfaction and completion of trial measures. This approach offers the promise of unique findings that will be used to support later National Institutes of Health stages of intervention development trials. Personalized trials are just one of several innovative trial design approaches being used to address the limitations of classic RCTs. The multiphase optimization strategy and the sequential multiple assignment randomized trial are 2 prominent examples of the many adaptive approaches now being used to facilitate more effective trials and garner greater insights about the component parts that make an intervention successful [26-29]. What is unique about the personalized trial approach is its ability to deliver insights regarding the heterogeneity of effect from a given intervention and support personalized recommendations for each individual [30].

Limitations

There are a number of potential limitations to this study. The first is that there may have been some reactivity to wearing the Fitbit device that could have impacted the baseline step counts. In a future study, where the goal of the study is to examine reactivity to devices and calibrate the effectiveness of commercially available activity trackers like Fitbit, research-grade accelerometers (which do not display steps or other metrics) could be used along with Fitbit devices for a longer duration of time to enhance the data collection. The second limitation is that there is no maximum threshold of activity rather participants will be included if they felt they could benefit from walking more each day. This may lead to the inclusion of participants who are already quite active and could result in a ceiling effect and limit generalizability to less active adults. The third limitation is that the participants may turn on features in the Fitbit app that could deliver additional BCTs (such as adding friends or joining challenges) not part of the intervention. A final limitation is that all participants will be employees at the same health care organization, thus limiting the generalizability of findings.

Conclusions

This remotely delivered study will contribute broadly to the science of PA behavior change in middle-aged and older adults. BCTs are seen as key components of behavior change, but the influence of specific BCTs is not well understood [31,32]. The findings from this study will provide insights into the extent to which individual BCTs are effective in changing PA behavior. Furthermore, it will demonstrate if the influence of BCT on

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walking is consistent across participants or if large individual heterogeneous treatment effects exist [32]. How older adults engage with the technical components of this trial, such as wearable devices and remote onboarding, will inform current practice and offer a foundation for the development of larger personalized trials. In conclusion, this study offers a vision of conducting future series of trials where personalized data derived from wearable sensors, rather than generic guidelines, are used to inform the selection of intervention components for each individual.

Data Availability

This trial was preregistered on ClinicalTrials.gov (NCT04967313) and data will be made available on the Open Science Framework [33].

Conflicts of Interest

None declared.

Multimedia Appendix 1
Example of change in steps across behavior change technique periods.
[PNG File , 58 KB - resprot_v12i1e43418_app1.png]

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Abbreviations

BCT: behavior change technique
IRB: institutional review board
PA: physical activity
RCT: randomized controlled trial

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Protocol

The Impact of Point-of-Care Testing for Influenza on Antimicrobial Stewardship (PIAMS) in UK Primary Care: Protocol for a Mixed Methods Study

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Abstract

Background: Molecular point-of-care testing (POCT) used in primary care can inform whether a patient presenting with an acute respiratory infection has influenza. A confirmed clinical diagnosis, particularly early in the disease, could inform better antimicrobial stewardship. Social distancing and lockdowns during the COVID-19 pandemic have disturbed previous patterns of influenza infections in 2021. However, data from samples taken in the last quarter of 2022 suggest that influenza represents 36% of sentinel network positive virology, compared with 24% for respiratory syncytial virus. Problems with integration into the clinical workflow is a known barrier to incorporating technology into routine care.

Objective: This study aims to report the impact of POCT for influenza on antimicrobial prescribing in primary care. We will additionally describe severe outcomes of infection (hospitalization and mortality) and how POCT is integrated into primary care workflows.

Methods: The impact of POCT for influenza on antimicrobial stewardship (PIAMS) in UK primary care is an observational study being conducted between December 2022 and May 2023 and involving 10 practices that contribute data to the English sentinel network. Up to 1000 people who present to participating practices with respiratory symptoms will be swabbed and tested with a rapid molecular POCT analyzer in the practice. Antimicrobial prescribing and other study outcomes will be collected by linking information from the POCT analyzer with data from the patient's computerized medical record. We will collect data on how POCT is incorporated into practice using data flow diagrams, unified modeling language use case diagrams, and Business Process Modeling Notation.

Results: We will present the crude and adjusted odds of antimicrobial prescribing (all antibiotics and antivirals) given a POCT diagnosis of influenza, stratifying by whether individuals have a respiratory or other relevant diagnosis (eg, bronchiectasis). We will also present the rates of hospital referrals and deaths related to influenza infection in PIAMS study practices compared with a set of matched practices in the sentinel network and the rest of the network. We will describe any difference in implementation models in terms of staff involved and workflow.

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Conclusions: This study will generate data on the impact of POCT testing for influenza in primary care as well as help to inform about the feasibility of incorporating POCT into primary care workflows. It will inform the design of future larger studies about the effectiveness and cost-effectiveness of POCT to improve antimicrobial stewardship and any impact on severe outcomes.

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KEYWORDS

medical records systems, computerized; influenza point-of-care systems; general practice; RSV; implementation; outcome assessment; health care; antimicrobial stewardship; acute respiratory infection; antimicrobial; influenza; primary care; respiratory symptom

Introduction

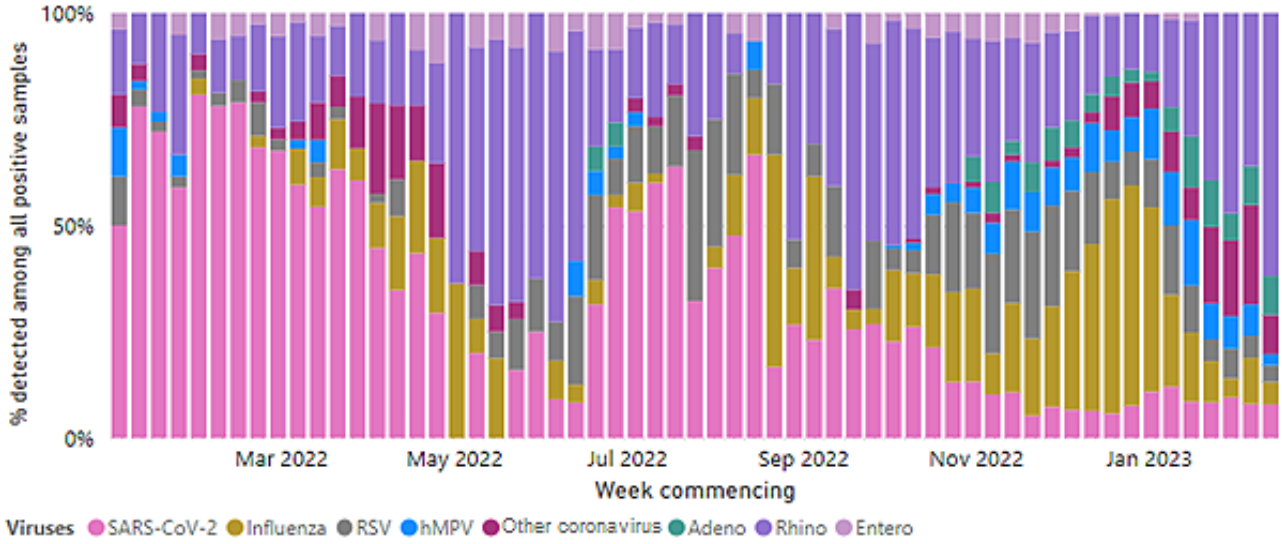
Rapid Testing for Influenza in a Postpandemic Health Service

Measures to limit SARS-CoV-2 transmission during the COVID-19 pandemic coincided with a marked decrease in infections caused by other respiratory viruses [1,2].

After the lifting of COVID-19 containment measures, the robust return of influenza, seasonal coronaviruses, parainfluenza virus, and respiratory syncytial virus (RSV) was observed in many countries including the United Kingdom [3].

Figure 1 and Table 1 show data from the English national sentinel surveillance network as of the end of November 2022. Influenza and RSV were the main circulating respiratory viruses, with SARS-CoV-2 making up only 12.4% (15/121) of the total number of laboratory-confirmed cases.

Figure 1. Swab positivity by week in the English national sentinel surveillance network from March 2022 to January 2023 [4]. hMPV: human metapneumovirus; RSV: respiratory syncytial virus.



In the context of a postpandemic health care service where there are high levels of circulating influenza, accurate, rapid molecular diagnostic test platforms have the potential to (1) improve clinical decision-making regarding the use of antibiotics and antivirals, (2) improve patient outcomes due to the early appropriate use of antivirals, and (3) provide better information to inform sentinel surveillance and clinical research including studies of vaccine effectiveness and real-world trials [5,6].

Specifically, for patients with influenza infection, early diagnosis and administration of antivirals may improve clinical outcomes [7,8]. They may also limit symptom duration and spread to household contacts, and newer antivirals for influenza, such as baloxavir, have been shown to improve the time to resolution of symptoms and reduce complications in high-risk patients [9].

Currently, only a small proportion of patients with respiratory tract infections (RTIs) undergoes diagnostic microbiological testing before receiving treatments in primary care [10], and there is evidence of widespread variations in antimicrobial prescribing practices [11]. This is important, as prescribing in primary care accounts for about 8% of National Health Service (NHS) expenditure, which is equivalent to over £9 billion (US $11.1 billion) per year, with just over £220 million (US $271.5 million) being spent on antimicrobials [12]. Inappropriate prescribing of antimicrobials and unwarranted variation in prescribing can contribute to increase of antimicrobial-resistant strains and patient adverse events in the short and long term [13].

We have previously shown that, in a prepandemic context, it is feasible to undertake point-of-care testing (POCT) for influenza in primary care in the England, with promising impacts on antimicrobial use and estimates of influenza vaccine effectiveness that are comparable with published data [14-16].

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However, its impact on more severe outcomes such as hospitalization and mortality following infection has not been reported.

Recent work on in-pandemic prescribing of azithromycin and doxycycline for RTIs across the sentinel network has shown scope for measures to improve antibiotic stewardship in primary care [17].

With the ending of widespread national testing for SARS-CoV-2 and other RTIs in the United Kingdom in March 2022 [18] and with high levels of circulating influenza in a post-COVID-19 health service during the autumn 2022 compared with 2021, there is a need to revisit questions about the feasibility of implementing rapid diagnosis of influenza during the expected peak of viral circulation this winter (2022-2023) season and its impact on clinical management in terms of improved antimicrobial stewardship and severe outcomes (hospitalization and mortality).

Table 1. Swab positivity by week in the English national sentinel surveillance network between September 2022 and November 2022 (n=818).

Week commencing	Swab positivity					
	Adenovirus (n=54)	hMPV[a] (n=85)	Influenza (n=215)	Other coron-aviruses (n=13)	RSV[b] (n=255)	SARS-CoV-2 (n=196)
9/26/2022 (n=26), n (%)	0 (0)	0 (0)	0 (0)	0 (0)	11 (42.3)	15 (57.7)
10/3/2022 (n=54), n (%)	0 (0)	1 (1.9)	20 (37)	0 (0)	6 (11.1)	27 (50)
10/10/2022 (n=52), n (%)	0 (0)	2 (3.8)	14 (26.9)	1 (1.9)	6 (11.5)	29 (55.8)
10/17/2022 (n=70), n (%)	0 (0)	6 (8.6)	19 (27.1	2 (2.9)	17 (24.3	26 (37.1)
10/24/2022 (n=82), n (%)	0 (0)	6 (7.3)	28 (34.1	0 (0)	30 (36.6	18 (22)
10/31/2022 (n=94), n (%)	9 (9.6)	9 (9.6)	31 (33)	1 (1.1)	24 (25.5	20 (21.3)
11/7/2022 (n=95), n (%)	12 (12.6)	11 (11.6)	16 (16.8)	4 (4.2)	35 (36.8)	17 (17.9)
11/14/2022 (n=122), n (%)	6 (4.9)	18 (14.8)	34 (27.9)	2 (1.6)	42 (34.4)	20 (16.4)
11/21/2022 (n=102), n (%)	12 (11.8)	14 (13.7)	27 (26.5)	0 (0)	40 (39.2)	9 (8.8)
11/28/2022 (n=121), n (%)	15 (12.4)	18 (14.9)	26 (21.5)	3 (2.5)	44 (36.4)	15 (12.4)

[a]hMPV: human metapneumovirus.

[b]RSV: respiratory syncytial virus.

Objectives

This study aims to report the impact of POCT for influenza on antimicrobial prescribing in primary care. We will additionally describe severe outcomes postinfection (hospitalization and mortality) and how POCT is integrated into primary care workflows.

Methods

Study Setting and Population

The impact of POCT for influenza on antimicrobial stewardship (PIAMS) study will take place between December 2022 and May 2023, during the influenza season as defined by the UK Health Security Agency (UKHSA). It is nested within the English national sentinel network managed by the Oxford-Royal College of General Practitioners (RCGP) Research and Surveillance Centre (RSC) at the Nuffield Department of Primary Care, University of Oxford. This network of over 1800 primary care practices is the primary infectious disease surveillance network for England, which is generally representative of the English population [19]. It has been providing weekly infection data for over 50 years that are used to monitor trends in infectious disease and investigate real-world vaccine and treatment effectiveness [20].

All practices that contribute data to the English national sentinel network will be invited to participate in the PIAMS study, and 10 practices will be selected to take part in the PIAMS study. We will prioritize practices within the network with capacity to undertake influenza POCT and who had previously been involved in SARS-CoV-2 POCT through the RAPTOR-C19 study [21]. Those practices that have a history of less than 80% complete data returns during the previous winter season will be excluded.

Each participant practice will receive training about the study, including hands-on training on how to administer a swab test and how to use the POCT analyzers.

Case Definition of Eligible Patients

All patients registered within the PIAMS study practice who do not have an opt-out code on their medical record and are showing symptoms of influenza-like illness (ILI), acute respiratory illness (ARI), or fever of higher than 37.5 °C will be eligible for the study if they consent to participate. We will use the European Centre for Disease Prevention and Control case definitions of ILI and ARI for this study. We will use the following exclusion criteria: (1) patient has an opt-out code on their medical record or (2) no informed consent.

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Face-to-face Recruitment of Eligible Patients and Point-of-care Testing for Influenza

We will undertake opportunistic swab sampling for this study, with potential participants being identified from those registered patients who present to the study practice with respiratory symptoms described in the case definition. No screening nor eligibility assessment will be undertaken. Blinding of participants and researchers will not be undertaken.

Eligible patients or their parent or legal guardian will be approached by a practice general practitioner (GP) or research nurse to explain the study and ask for consent to take part when they present for a face-to-face consultation at the practice.

After obtaining consent, a nasopharyngeal swab will be taken by a suitably qualified and experienced GP or research nurse. For those who do not attend the practice in person, a self-test kit will be sent to their home.

The cobas Liat POCT analyzer, manufactured by Roche Diagnostics International, will be used for this study [22]. This POCT analyzer is an automated multiplex polymerase chain reaction system, with previous studies demonstrating excellent performance comparable with gold standard laboratory assays, with sensitivity and specificity in the region of 100% and 97.1%-100%, respectively, for influenza A and 97.8%-100% and 99.5%-99.7%, respectively, for influenza B when fresh, prospectively collected samples are tested [23,24]. It has CE-marking in the European Union. In the United States, it is Food and Drug Administration–cleared, and it is also Clinical Laboratory Improvement Amendments–waived for use for rapid influenza testing. This study will not assess the accuracy of the POCT analyzer but will use the machine for its approved purpose.

The swab will be inoculated in a test kit and tested on the cobas Liat analyzer as soon as possible after being taken. The results will be available to the clinician in less than 20 minutes.

Antimicrobial prescribing and other study outcomes for those who have been swabbed will be obtained by linking information from the cobas Liat analyzer with data from the patient's computerized medical record in primary care. We will demonstrate the feasibility of reporting antimicrobial stewardship and severe outcomes postinfection. Severe outcomes postinfection such as hospitalization and mortality will be obtained by linking the patient's primary care computerized medical record to secondary care records at the national level including hospitalization and mortality data. A recent study used a linked cohort to study severe outcomes from COVID-19 infection [25].

Virtual Recruitment of Eligible Patients and Home Swabbing of Recruited Patients

We envisage that the majority of eligible patients will be seen face-to-face for this study. Where the eligible patient is not able to attend the practice in person, they will be told about the study remotely, and verbal consent will be taken.

A home swabbing kit will be sent to consented patients who are not able to attend the practice in person. This will include a nasal swab and instructions on how to take a self-test. Further details of our patients self-swabbing at home service have been previously published [26]. Once the nasal swab has been taken, the patient will be asked to place the swab in the included transport container with the manufacturer-approved universal transport media or viral transport media and inform the study practice staff who will arrange collection of the swab sample within 4 hours of being taken for immediate POCT.

Clinical Workflow Integration

Data regarding the utility of the influenza POCT in primary care and the issues and barriers to implementation of influenza POCT in primary care workflows will be collected by ethnographic observation of study practices and by a semistructured survey of clinicians and practice staff at the participating practices. Information will be collected about the following domains previously found to be important to implementation of POCT sampling [27]: usability of the POCT platform, clinical pathways and training, result reporting, clinical governance, costs, monitoring of effectiveness.

The ethnographic observations, semistructured survey, and reported POCT results will be used to assess which practices were more successful at integrating POCTs into their practice processes by comparing business process models of the practices. Business process models are graphical representations of business-oriented processes within an organization. This is helpful to model collaborations and business transactions within health systems. Business processes are typically modeled using Business Process Modeling Notation (BPMN). BPMN can be used to depict the end-to-end flow of a business process. The notation has been specifically designed to coordinate the sequence of processes and the messages that flow between different process participants in a related set of business activities [28,29].

Sample Size Calculation

The primary outcome measure is the proportion of consultations for RTI with all antibiotics prescribed during the winter season. We aim to detect a difference of ≤7% in the proportion of consultations for RTI in which antibiotics were prescribed, which is what we found previously between practices using POCT and the rest of the RCGP network [14,15]. We have assumed that the coefficient of variation between practices within the sentinel network, for the proportion of consultations with antibiotics prescribed, is 0.23 from Ashworth et al [11] with an α of .05 and a power of 80%. To detect a 5% difference in the proportion of consultations at which antibiotics are prescribed, we would need to sample 1023 people with ILI or ARI.

Previous swabbing rates across the network have averaged 6 swabs per practice per week in previous years. Given 10 practices swabbing a maximum of 3 swabs per week for 36 weeks, we would expect to collect up to 1000 face-to-face nasopharyngeal swabs from eligible people with ILI or ARI over the course of the study.

Statistical Methods

We will undertake descriptive analysis of the swabbing rates and swab positivity rates from the study practices. This includes

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analysis of the demographic and clinical characteristics of those presenting with RTI symptoms and those with confirmed influenza infections in primary care. We will also report the number of patients who have also undertaken swabbing for reference laboratory analysis in addition to POCT testing in study practices. In those study practices that also take part in virological surveillance, these reference laboratory swabs are reported to the UKHSA as part of national disease surveillance.

To answer our primary objective, we will calculate the crude odds of antimicrobial prescribing (all antibiotics and all antivirals regardless of type), given a POCT diagnosis of influenza is the probability of antimicrobial prescribing given a particular POCT test result. We will record whether the antimicrobials were given within 7 days of the POCT diagnosis or within 30 days of diagnosis. We will calculate the crude odds ratio by dividing the odds of antimicrobial prescribing in people who receive a positive influenza POCT result by the odds in people who receive a negative test result.

We will also calculate the adjusted odds ratio using a logistic regression model. We will use the following set of covariates that are known to be associated with the severity of influenza and are collected from the routine data extracted from the electronic health record: age, sex, ethnicity (reported in 5 categories: White, Asian, Black, other, or mixed; maximized using an ontology [30]), socioeconomic status (measured using the index of multiple deprivation [31], which is a nationally available measure assigned based on post code), any of these chronic underlying conditions (chronic pulmonary disease, cardiovascular disease, diabetes, liver disease, renal disease, neurologic or neuromuscular conditions, treatment-induced immunosuppression, and disease-induced immunosuppression), number of GP visits in the 12 months prior to the study period describing a study participant's health care–seeking behavior, number of hospitalizations in the 12 months prior to the study period (used as proxy for the severity of the chronic conditions), influenza vaccination in previous influenza seasons (at least one), pregnancy, use of influenza antivirals, and pneumococcal and COVID-19 vaccination status.

To answer our secondary objective, we will select a matched set of practices from the rest of the English national sentinel network based on practice size, average age of registered patients, proportion of registered female patients, and number of GPs employed during the study.

The rates of hospital referrals and deaths related to influenza infection within 30 days of diagnosis will be compared between PIAMS study practices and the rest of the network using the ANOVA test.

Ethical Considerations

The study was approved by the English National Research Ethics Committees (Integrated Research Application System reference: 292961; REC reference: 21/YH/0077).

A practice GP or research nurse will undertake informed consent. This person will be suitably qualified and experienced and have been authorized to do so by the principal investigator. Once an eligible patient is identified, they or their parent or legal guardian will be approached by a practice GP or research nurse. Written and verbal versions of the participant information and informed consent will be presented to the patient or their parent or legal guardian detailing no less than the exact nature of the study, what it will involve for the participant, the implications and constraints of the protocol, and the known side effects and any risks involved in taking part. It will also be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, without affecting their legal rights, and with no obligation to give a reason for withdrawal.

The patient will be allowed as much time as wished to consider the information and provided the opportunity to question the investigator, their GP, or other independent parties to decide whether they will participate in the study. Written informed consent will then be obtained by means of a dated signature and the dated signature of the person who presented and obtained the informed consent. A copy of the signed informed consent will be given to the participant. The original signed form will be retained at the study site.

When the eligible patient is not able to attend the practice in person, they will be told about the study remotely by a trained GP or nurse. The trained GP or nurse will go through the remote consent form with the participant over the phone. Once the participant has provided verbal consent to take part in the study, the researcher will sign a copy of the remote consent form and will provide the participant with a copy via a secure method such as NHS email. The patient will then be sent a swab to take at home and return to the practice within 4 hours of being taken for immediate POCT. Collection of the sample will be arranged by study staff.

For the ethnographic observations, we will verbally inform and orally consent the clinicians, a PIAMS researcher will record the consent process by completing a Record of Consent Form and the form will be signed in the presence of the participant to confirm oral consent. We will also provide information about the PIAMS study on practice posters to notify the patients about the observation activities associated with the nested qualitative study. Their consent will be implied by not opting out. A PIAMS researcher will be available to answer any questions they may have about observations undertaken for the nested qualitative study. Both clinicians and patients have the right to withdraw from participation or to decline to participate at any time without reason.

For the semistructured questionnaire, all survey respondents will complete an informed consent question embedded at the beginning of the anonymous questionnaire. If the participants answer "YES" to the first question of the form, this will imply their consent to participate, and the survey will begin. If the participants answer "NO" to the informed consent question, they will directly exit the current page. No participant will be forced to participate in the survey, and their participation will be based on their agreement, which can be withdrawn at any time.

Pseudonymized information about swab samples from consented patients, including participant ID, site ID, and swab result, will be stored in the POCT machines. These data will be extracted weekly from the machines and sent via an encrypted email to

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the study team to be stored in the research group's secure network.

Data from study practice medical records will be extracted twice weekly from information systems of the RCGP RSC practices by Apollo, part of Wellbeing Software. These records are pseudonymized as close to the source as possible by Apollo using a nonreversible "hash" algorithm. Patients who decline to share their data are excluded from the extraction process.

Data for the study are held on dedicated secure servers at the RCGP data and analytics hub in the Clinical Informatics and Health Outcomes Research Group, University of Oxford. The research group's secure network is located behind a firewall within the university's network; all in-bounded connections are blocked, but out-bounded connections are allowed. Only staff members or associated members of the research group approved by the head of department can access the data from secure workstations or secure laptops with encrypted drive. All staff members of the research group working within the team base work from secure workstations or secure laptops with encrypted drive within the research group's secure network. The use of personal equipment is not permitted and cannot be connected to the secure network. A risk assessment of the physical security of the research group's offices and server room has been conducted by the building and facilities manager, the faculty information technology (IT) service manager, and the research group's information governance lead.

Survey data for the nested qualitative substudy are securely collected using Jisc (online surveys). The university has a license agreement to use this service and has recommended the service for gathering confidential data. Extraction of the survey data is only available to people with a registered Jisc account, which the university has to approve. Only authorized study researchers will be able to export survey data once logged in to Jisc. Once survey data are extracted, the data will be stored within the secure Oxford-RCGP Clinical Informatics Digital Hub (ORCHID) network. Access to your data is strictly controlled. Only authorized study researchers will have access to only pseudonymized research data from within the aforementioned secure ORCHID network.

The university is compliant with the Data Protection Act and UK GDPR and has systems for technical and organizational controls for information security, including a university-level Information Security and Governance Group chaired by the university senior information risk owner. The research group's private network has its own system-level security policy and is tested for vulnerabilities annually.

Study practices are provided with a fee for participating in this study to cover the costs of training staff and hosting the study. A small remuneration is also provided to practices for each swab taken to cover the additional time taken during each consultation to undertake swabbing for this study. Patients are not remunerated for taking part in this study.

Results

The study started in December 2022, and we expect to complete the final analysis for the study by June 2023.

Baseline Data From the English National Sentinel Surveillance Network

In terms of context for this study, currently, the English national sentinel network had grown from just over 500 practices in 2019 to 1879 practices by October 2021. This represents 28.6% of English primary care practices and 31% of the population (N=17,560,196). The sentinel network's population was found to be broadly representative of the national population in terms of age, gender, ethnicity, NHS Region, socioeconomic status, obesity, and smoking habit [19].

Latest data from across the sentinel network, between October 2020 and October 2021, show that practices have collected >8000 virology swab samples for reference laboratory testing [19]. Figure 1 and Table 1 show the latest virology swab positivity by week in the English national sentinel surveillance network prior to the start of the study.

Protocol Amendments

Important protocol amendments will be referred to the English National Research Ethics Committees for ethical approval. Once approved, changes will be communicated directly with the recruiting study practices. The amended protocol will be shared with all relevant parties (eg, investigators and clinical research networks) in a timely manner.

Discussion

Overview

This study will generate data on the impact of POCT testing for influenza in primary care, especially information on its impact on antimicrobial prescribing. Additionally, the study will describe severe outcomes postinfection (hospitalization and mortality) and how POCT is integrated into primary care workflows.

It will be a chance to revisit questions about the feasibility of implementing rapid diagnosis of influenza following the end of widespread national testing for SARS-CoV-2 and other RTIs in the United Kingdom and previous studies about its promising impacts prepandemic [14-16].

Limitations

The nonrandomized design is a limitation of our study. However, we feel that there is still value in examining the objectives within this study using a mixed methods approach as there are many questions about the challenges and barriers to implementation of rapid diagnostic testing in primary care, including the variability of adoption in different practices that are important to understand [15]. Unpacking these factors using a mixed methods design will be important to design a successful experimental study at scale to answer questions related to health outcomes. Additionally, information about influenza subtype is not available from the POCT machines used in this study and will restrict interpretation of our results, especially for calculating influenza vaccine effectiveness. A possible solution to this would have been to ask study practices to send their swabs to the national reference laboratory for additional analysis. However, this would have introduced a further step in the testing procedure in the clinic, which may have increased the risk of

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aerosol generation. Given that the study was originally proposed during the COVID-19 pandemic, we felt it was important to minimize the risk of generating aerosol droplets and thus did not include this in the study.

Strengths

A strength of the study is that it is conducted among practices that are nested in the RCGP RSC English sentinel surveillance network and had also been involved in POCT sampling in previous years. This ensured that practice staff had experience with using rapid diagnostic machines, minimizing the number of spoiled samples. It will also allow comparisons of the performance of practices using POCT for influenza testing with other practices in the sentinel network that participate in the usual virology sampling program conducted by the UKHSA.

Conclusion

Building on previous work showing the promising impacts of rapid, near-patient testing on antimicrobial use in primary care within the context of a prepandemic health service, this study will help inform about the feasibility of incorporating POCT into primary care workflows. It will inform the design of future larger studies about the effectiveness and cost-effectiveness of POCT to improve antimicrobial stewardship and any impact on severe outcomes.

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This collaborative study is funded by Roche Diagnostics through an investigator-initiated grant. The manuscript was also reviewed by Roche Diagnostics before submission.

The University of Oxford sponsored this study and reviewed and proposed edits to the study protocol and study documents prior to submission for ethics approval. The Nuffield Department of Primary Care Health Sciences, University of Oxford is the coordinating center.

Data Availability

Data cannot be shared publicly because the data are owned by the Oxford Royal College of General Practitioners (RCGP) Research and Surveillance Centre (RSC) and its participating practices. Data are available from the University of Oxford Institutional Data Access Committee (contact via ku.ca.xo.chp@nanigsuled.nomis) for researchers who meet the criteria for access to confidential data. The data underlying the results presented in the study are available from [32]. Further enquiries about the RCGP RSC network and data requests can be found at [33] or by emailing ku.ca.xo.chp@seiriuqneecitcarp.

Authors' Contributions

UH, AW, JS, CA, EB, JM, ML, CXX, and SdL contributed to the planning of the study. UH, AW, JS, CA, EB, JM, CO, RB, FF, ML, CXX, MJ, GM, TC, and SdL contributed to the reporting of the study protocol and to the conduct of the study to date.

Conflicts of Interest

SdL is director of the Oxford Royal College of General Practitioners Research and Surveillance Centre. Through his university, he has received funding for vaccine-related research from AstraZeneca, GSK, Sanofi, Seqirus, and Takeda; he has been a member of advisory boards for AstraZeneca, Sanofi, and Seqirus. UH has undertaken continuing professional development podcasts funded by Seqirus and has been a member of advisory boards for Janssen. TC has received grant funding and/or equipment and consumables free of charge for the purposes of independent research from BioFire diagnostics, Biomerieux, QIAGEN and Sherlock Biosciences. They have received speaker fees, honoraria and travel re-imbursement from BioFire diagnostics, BioMerieux, QIAGEN and Janssen. TC has also received consultancy fees from BioMerieux, QIAGEN, Cepheid, Roche, Janssen and Synairgen research. TC has been a member of advisory boards for Cepheid, Roche, Janssen, Shiongi, Sanofi and Seqirus and acted as a member of independent data monitoring committees for trials sponsored by Roche and received remuneration at fair market value for these services. TS is also a member of an independent data monitoring committee for a Roche-sponsored study.

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Abbreviations

ARI: acute respiratory illness
BPMN: Business Process Modeling Notation
GP: general practitioner
ILI: influenza-like illness
NHS: National Health Service
ORCHID: Oxford-Royal College of General Practitioners Clinical Informatics Digital Hub
PIAMS: impact of POCT for influenza on antimicrobial stewardship
POCT: point-of-care testing
RCGP: Royal College of General Practitioners
RSC: Research and Surveillance Centre
RSV: respiratory syncytial virus
RTI: respiratory tract infection
UKHSA: UK Health Security Agency

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Protocol

Co-Design of a Voice-Based Digital Health Solution to Monitor Persisting Symptoms Related to COVID-19 (UpcomingVoice Study): Protocol for a Mixed Methods Study

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Abstract

Background: Between 10% and 20% of people with a COVID-19 infection will develop the so-called *long COVID syndrome*, which is characterized by fluctuating symptoms. Long COVID has a high impact on the quality of life of affected people, who often feel abandoned by the health care system and are demanding new tools to help them manage their symptoms. New digital monitoring solutions could allow them to visualize the evolution of their symptoms and could be tools to communicate with health care professionals (HCPs). The use of voice and vocal biomarkers could facilitate the accurate and objective monitoring of persisting and fluctuating symptoms. However, to assess the needs and ensure acceptance of this innovative approach by its potential users—people with persisting COVID-19–related symptoms, with or without a long COVID diagnosis, and HCPs involved in long COVID care—it is crucial to include them in the entire development process.

Objective: In the UpcomingVoice study, we aimed to define the most relevant aspects of daily life that people with long COVID would like to be improved, assess how the use of voice and vocal biomarkers could be a potential solution to help them, and determine the general specifications and specific items of a digital health solution to monitor long COVID symptoms using vocal biomarkers with its end users.

Methods: UpcomingVoice is a cross-sectional mixed methods study and consists of a quantitative web-based survey followed by a qualitative phase based on semistructured individual interviews and focus groups. People with long COVID and HCPs in charge of patients with long COVID will be invited to participate in this fully web-based study. The quantitative data collected from the survey will be analyzed using descriptive statistics. Qualitative data from the individual interviews and the focus groups will be transcribed and analyzed using a thematic analysis approach.

Results: The study was approved by the National Research Ethics Committee of Luxembourg (number 202208/04) in August 2022 and started in October 2022 with the launch of the web-based survey. Data collection will be completed in September 2023, and the results will be published in 2024.

Conclusions: This mixed methods study will identify the needs of people affected by long COVID in their daily lives and describe the main symptoms or problems that would need to be monitored and improved. We will determine how using voice and vocal biomarkers could meet these needs and codevelop a tailored voice-based digital health solution with its future end

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users. This project will contribute to improving the quality of life and care of people with long COVID. The potential transferability to other diseases will be explored, which will contribute to the deployment of vocal biomarkers in general.

Trial Registration: ClinicalTrials.gov NCT05546918; https://clinicaltrials.gov/ct2/show/NCT05546918

International Registered Report Identifier (IRRID): DERR1-10.2196/46103

(JMIR Res Protoc 2023;12:e46103) doi:10.2196/46103

KEYWORDS

COVID-19; long COVID symptoms; vocal biomarkers; digital health; co-design; mixed methods; mobile phone

Introduction

Context

COVID-19 and Long COVID

The novel SARS-CoV-2 infected >532 million people and caused >6.3 million deaths worldwide as of June 2022 [1].

COVID-19 initial infection can take several forms, from asymptomatic to moderate or severe illness. Common symptoms are fever, cough, dyspnea, fatigue, loss of taste or smell, and gastrointestinal symptoms. Complications include acute respiratory distress syndrome, anemia, or acute cardiac injury [2].

After the acute phase, some people with COVID-19 develop a so-called *long COVID* or *post-COVID condition*. The World Health Organization's definition of this condition is as follows: "Post-COVID-19 condition occurs in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis. Common symptoms include fatigue, shortness of breath, and cognitive dysfunction but also others that generally have an impact on everyday functioning. Symptoms may be new onset, following initial recovery from an acute COVID-19 episode, or persist from the initial illness. Symptoms may also fluctuate or relapse over time" [3,4].

It has been estimated that a mean of 10% to 20% of patients with COVID-19, representing millions of people worldwide, will have persisting or relapsing symptoms >12 weeks after acute infection [5] with complaints such as tachycardia, extreme fatigue, or dyspnea as observed by Rubin [6]. In Luxembourg, we showed that 59% of COVID-19–infected people included in the Predi-COVID cohort study, who completed a detailed 1-year questionnaire, still declared 1 or more persisting symptoms. The number of persisting symptoms increased with the initial disease severity, and the quality of life of these participants was highly affected by sleep disorders (54%) and altered respiratory quality of life (12.9%) [7].

The COVID-19 pandemic accelerated the use of remote patient monitoring in clinical practice or research for safety and emergency reasons, justifying the need for innovative digital health solutions to monitor key parameters or symptoms related to COVID-19 or long COVID. A panel of experts from the National Institute for Health and Care Excellence recommended the development of telemonitoring and encouraged self-management of acute and long COVID symptoms in a tailored and accessible way for each patient [8].

Although long COVID is now a recognized illness in many countries, few dedicated consultations exist, and the awareness and scientific knowledge of this disease are still poor among not only the general population but also general practitioners. For these reasons, many people experiencing persisting symptoms after a COVID-19 infection (confirmed or not) may feel abandoned by or lost in the health care system, with difficulties in obtaining a long COVID diagnosis or obtaining specific support, and there is a demand among them for new monitoring solutions to objectify the symptom evolution and identify causes of symptom degradation. Moreover, people with long COVID experience difficulties in performing daily physical tasks, and many of them cannot engage in the same levels of activity or work as before [9].

Vocal Biomarkers of COVID-19 Symptoms

Using voice is an interesting approach for telemonitoring, as it is easy to collect, quick, and energy efficient, inducing less fatigue on the patients. Moreover, the use of voice-based technologies is increasing swiftly; in 2019, 31% of smartphone users worldwide used voice technology at least once a week, and 20% of queries on Google's mobile app and Android devices were voice searches [10].

Voice is a rich source of health-related information, as many voice features can be related to symptoms or health status [11-14]. In addition, because voice analysis involves highly complex methods for processing audio features, this kind of development might also be capable of detecting subtle changes associated with COVID-19 symptoms [10].

For example, voice features have previously been associated with a COVID-19 infection or a consequence of COVID-19 infection [15,16]. COVID-19 infection or complications can affect the voice through different mechanisms. Indeed, respiratory insufficiency can lead to reduced airflow and thus to changes in voice parameters. Other studies showed that voice quality was reduced in patients with COVID-19 owing to repeated cough, laryngeal or pharyngeal erythema, or sore throat [17-19].

In Luxembourg, participants from the Predi-COVID hybrid prospective cohort study were invited to perform voice recordings at the same time as they completed web-based questionnaires regarding their symptoms and health status. To date, almost 6000 voice recordings from more than >500 patients with COVID-19 have already been collected in the Predi-COVID study [2]. These voice recordings have been

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analyzed, and promising vocal biomarker candidates for fatigue, loss of taste and smell, and symptomatic status in people with a COVID-19 infection have already been identified [20-22].

The question now is to determine how these vocal biomarkers could help and improve the quality of life of people with long COVID and how they could be implemented in a digital health solution such as a smartphone app. For example, people with COVID-19 or long COVID symptoms could record their voice in real-life settings by following basic instructions such as "read a pre-defined text, count from 1 to 20, or say a vowel as long as possible," and the app would analyze voice features and give them back a result for one or several vocal biomarkers. Importantly, to ensure that the developed digital solution using vocal biomarkers is meaningful and useful for the patients, our study involves them at an early stage together with health care professionals (HCPs).

Objectives

The UpcomingVoice project aims to co-design a voice-based digital health solution for screening and self-monitoring of frequently reported COVID-19–related symptoms with its end users, namely, (1) people with persisting COVID-19–related symptoms, with or without a long COVID diagnosis confirmed by an HCP, and (2) HCPs involved in the care of people with long COVID. The goal of this study is to develop a digital health solution that really matters and helps people with long COVID in their daily lives and could be a complementary support in addition to the medical care that they could benefit from.

To achieve this main objective, the UpcomingVoice study will (1) explore the impact of long COVID in the everyday lives of people with long COVID and the needs of people with long COVID to improve their quality of life and manage their symptoms; (2) explore the extent to which the use of voice and, in particular, vocal biomarkers could propose a solution to the patient's needs (ie, we will investigate the expectancies, acceptability, fears, barriers, and leverages regarding using voice to self-monitor or screen for long COVID symptoms); and (3) define the specifications that such a mobile app should meet so that it could be recommended to patients by HCPs and be considered acceptable and useful by its intended users in terms of technological aspects (ie, type of device, type of voice recordings, etc), frequency of use, design, etc.

As a secondary aim, we will also assess the transferability potential of the results of this study in the context of COVID-19 to other diseases (eg, monitoring fatigue could also be used in the context of cancer).

Methods

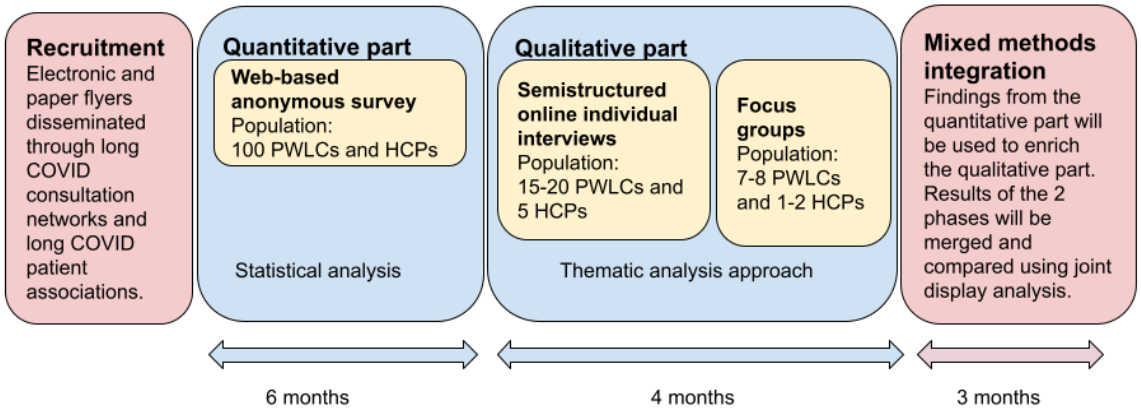
Study Design

This cross-sectional study is based on a mixed method sequential explanatory design. It consists of 2 successive phases: a quantitative phase (descriptive approach), followed by a qualitative phase (inductive pragmatic approach). The study design is summarized in Figure 1. The research questions addressed in the 2 phases of the study are listed in Table 1.

A conceptual framework of the key areas of daily functioning will be elaborated based on the literature review, the survey, and individual interview results as previously described [23], and the framework will be used to identify the most relevant use cases of the digital health solution. The general design of the digital health solution will be defined using the survey results, and its specific items and response modalities will be further elaborated during the qualitative phase.

To study the transferability potential of the digital health solution that will be developed, we will provide an extensive description of our study population and their daily life concerns to identify other populations, diseases, or conditions with similar characteristics (in terms of impact on quality of life, main symptoms, and intensity of symptoms) that could also benefit from a voice-based technology. Subsequently, we will use the APEASE (Affordability, Practicability, Effectiveness, Acceptability, Side Effects, and Equity) criteria and other relevant checklists previously described for the evaluation of transferability of health technology assessments [24,25] to assess the potential transferability of each use case or the main characteristics of the solution identified in the 2 phases of the study to the other fields.

Figure 1. Study design. HCP: health care professional; PWLC: people with long COVID.



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Table 1. Research questions (RQs) addressed in phase 1 and phase 2.

Study phase and objectives	Measure instrument	RQs	Questions of HCP[a] survey	Questions of PWLC[b] survey
Phase 1 (quantitative phase)				
To understand the needs of PWLC and to assess acceptability, expectancies, and fears regarding the use of voice to meet these needs	Web-based anonymous survey (different questions for PWLC and HCPs)	• 1. What are the demographic and sociodemographic characteristics of the participants?	• 1-3	• 1-3
To define the general specifications of the digital health solution based on vocal biomarkers	Web-based anonymous survey (different questions for PWLC and HCPs)	• 2. What is the acceptance rate of the use of voice for symptom monitoring? • 3. What proportion of participants already heard about the notion of vocal biomarker? • 4. What are the most important LC[c] symptoms to be monitored? • 5. What are the needs, fears, expectations, and use cases for PWLC and HCPs regarding the use of voice for symptom monitoring? • 6. What are the main specifications of a smartphone app based on VB[d] (engagement, functionalities, esthetics, information content, and subjective items) • 7. What are the most important aspects of the smartphone app? • 8. Should such an app be reimbursed or be paid by the patient? What cost would be acceptable? • 9. To what extent do COVID-19 infection and vaccination have an impact on the opinions and needs regarding the use of voice for symptom monitoring?	• 5[e] • 4[f] • 11-12[g] • 6-10; 14[h] • 19-35[i] • 13[j] • 15-18[k]	• 17[e] • 16[f] • 24-25[g] • 18-27[h] • 32-57[i] • 26[j] • 28-31[k] • 4-15[l]
Phase 2 (qualitative phase)				
To further clarify PWLC's needs and their expectations and fears regarding voice-based technologies	Individual semistructured interviews with PWLC and HCPs	• 10. What are the needs and problems of PWLC in their everyday lives and how could the use of vocal biomarkers bring a solution to these problems?	N/A[m]	N/A
To define the specifications of the voice-based digital health solution	Individual semistructured interviews with PWLC and HCPs	• 11. What are the detailed specifications of a smartphone app based on VB (engagement, functionalities, esthetics, information content, and subjective items)? • 12. What are the best app items and response options?	N/A	N/A
To develop a smartphone app prototype	2 focus groups with a panel of 8-10 PWLC and HCPs together	• 13. How is the smartphone app prototype perceived? • 14. What are the improvements suggested by PWLC and HCPs?	N/A	N/A

[a]HCP: health care professional.

[b]PWLC: people with long COVID.

[c]LC: long COVID.

[d]VB: vocal biomarkers.

[e]Survey questions related to RQ2.

[f]Survey questions related to RQ3.

[g]Survey questions related to RQ4.

[h]Survey questions related to RQ5.

[i]Survey questions related to RQ6.

[j]Survey questions related to RQ7.

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[k]Survey questions related to RQ8.

[l]Survey questions related to RQ9.

[m]N/A: not applicable.

Phase 1 (Quantitative)

The first phase, the quantitative phase, consists of a web-based anonymous survey.

The objective of this survey is to define the main aspects of daily life impacted by long COVID and the needs of people with long COVID and to assess the acceptability and expectancy toward the use of vocal biomarkers for the symptom monitoring of long COVID. The general outline of the digital health solution based on vocal biomarkers will be defined based on these results.

The following dimensions adapted from the user version of the Mobile Application Rating Scale (uMARS) [26] will be covered by different questions: engagement, functionality, aesthetics, information, and subjective items ("Would you recommend," "Would you be interested in," etc).

People With Long COVID

In addition to the above-mentioned items, the survey for people with long COVID has been designed to further identify the most impairing symptoms for their quality of life, to assess whether the severity of their initial infection or of their long COVID symptoms or their vaccination status has an impact on their opinions and needs regarding a new health technology based on voice, and to assess how the use of vocal biomarkers could be of interest for the management of their symptoms. The detailed questionnaire for people with long COVID is provided in Multimedia Appendix 1.

HCP Survey

The HCP survey is focused on assessing the needs of their patients with long COVID in their daily lives and how they foresee the use of vocal biomarkers of long COVID symptoms in the management of their patients and in the health care system. The detailed HCP questionnaire is provided in Multimedia Appendix 2. Completing the survey will take a maximum of 20 minutes to ensure a high acceptability rate, particularly in people with long COVID who frequently experience fatigue and trouble concentrating. The participants are expected to complete the survey once.

Web-based survey data will be collected and managed using REDCap (Research Electronic Data Capture; Vanderbilt University) tools hosted at the Luxembourg Institute of Health (LIH) [27].

Phase 2 (Qualitative)

The second phase is based on qualitative methods and consists of semistructured individual interviews and focus groups. Participants in this phase will have either participated in the web-based survey or not.

Individual interviews will be conducted to deeply understand the impact of long COVID on daily life, the needs of people with long COVID, and the potential interest in using vocal biomarkers to meet these needs, and define use cases for the digital health solution. The maximum duration for the interview will be 60 minutes.

Following the individual interviews, 2 successive focus groups (maximum duration of 90 minutes) will be organized with a panel comprising people with long COVID and HCPs. During the first focus group, the objective is to present 1 or 2 prototypes of the digital health solution and to collect users' comments and suggestions. The prototype or prototypes will be improved according to the collected comments and validated during the interaction with the second focus group.

The individual interview and focus group guides will be elaborated based on the insights obtained from the survey in phase 1. The questions will be asked in a general manner to ensure the identification of the most relevant aspects for people with long COVID in their daily lives and to minimize the expectancy and confirmatory bias.

Using teleconferencing software, interviews and focus groups will be conducted by a qualified interviewer and a moderator, respectively, both trained in qualitative methods.

Patient Public Involvement

The INVOLVE recommendations [28] will be followed to involve people with long COVID and HCPs in the most efficient way during the entire course of the project. First, we contacted a representative of a long COVID association and an HCP in charge of people with long COVID and presented them with the study aims and the participation procedures. They were then invited to review the study protocol, participant documents, and questionnaires before the study implementation.

Second, we will also follow the framework of core principles for selecting and developing measurements in digital health developed by Manta et al [29]. The 4 levels of this framework to evaluate the meaningfulness of digital biomarkers for patients are the Meaningful Aspect of Health, the Concept of Interest, the Outcome to be measured, and the End point.

In this perspective, the UpcomingVoice study design is a co-design process that will continuously involve patients with long COVID and HCPs.

At each step, the participants will receive feedback on the results from the previous step: during individual interviews, feedback on survey results will be given, and during the first focus group, results from the individual interviews will be provided and discussed.

Finally, participants with long COVID and HCPs willing to be even more deeply involved in our research will be invited to coauthor the scientific articles presenting the results of this research and to promote the results of the study to the lay audience.

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Study Participants

Inclusion Criteria

Participation in the study will be proposed to adults (men and women) with persisting COVID-19–related symptoms, with or without a long COVID diagnosis, and to HCPs in charge of patients with long COVID (doctors, nurses, psychologists, physiotherapists, etc).

All participants must be aged >18 years, have a sufficient level of speaking and comprehension in French, and have internet access to participate in the web-based survey and the web-based individual interviews and focus groups.

Seeking a representative sample of people is not part of qualitative research aims [30]; however, to increase the variations in our study population, the inclusions in the qualitative phase will be monitored to obtain an equal representation of different age and gender categories.

Recruitment and Enrollment

Before starting each part of the study, pilot phases will be performed to correct potential technical issues and ensure that the time for the completion of the survey and the interviews and focus groups do not exceed the expected duration (20 minutes for the survey and 60 and 90 minutes for individual interviews and focus groups, respectively).

The recruitment of participants will be based on electronic and paper flyers disseminated via social media, long COVID consultations, and long COVID patient associations in Luxembourg and neighboring countries (eg, France). Participation will also be proposed to participants from the Predi-COVID cohort study [2] who declared persisting symptoms at 1 year.

Flyers present information about the study and contain a direct link to the web-based survey so that interested persons can directly participate. The contact details of the study assistant at the LIH are also provided so that people can contact her directly if they are interested in participating in the qualitative part of the study.

People who expressed their interest in participating in the second part of the study, either after the survey completion or by contacting us directly, will be contacted by the study assistant. The study assistant will provide additional information regarding the second part of the project, and if the person confirms his or her interest in participating, an electronic ethical information notice and consent form will be sent to the participant. After signing the electronic consent form, the participant will be able to download a copy of the document. The study assistant will contact him or her to organize the individual interview. Electronic informed consent will be obtained before any data collection for the second part of the study.

Once the study assistant has received the notification that the participant has a valid signed consent, they will contact her or him to organize the web-based individual interview.

When all the individual interviews are completed, a panel comprising 7 to 8 people with long COVID and 1 to 2 HCPs will be constituted among the participants who expressed their willingness to participate in the focus group sessions.

When all individual interviews and focus groups are conducted, a restitution meeting will be organized. Everyone who has expressed an interest in this project will be invited.

Sample Size Calculation

For the quantitative part of the study, a formal size calculation was not feasible, given the exploratory nature of the study. The quantitative data from the survey will be exclusively used for descriptive purposes and to evaluate the different topics' importance for the participants.

For the qualitative part, no gold standard for the "right" sample size exists and depends closely on the nature and aims of the study [31]. Qualitative studies do not aim to estimate magnitudes or generalize the results to a larger population but evaluate patterns in a data set. Participants will be sampled until data saturation is reached, which can be formalized as the point at which new data repeat what were already collected [32,33]. A recent systematic review showed that data saturation was achieved with a mean of 9 to 17 interviews but with high disparities between studies [34]. The ideal size for focus groups is estimated to be between 6 and 10 persons, particularly when including participants with high knowledge of the problem, which is the case for people with long COVID and HCPs [35].

To achieve data saturation, at least 15 people with long COVID and 5 HCPs involved in the management of patients with long COVID will participate in the individual semistructured interviews. However, these are estimations, and we will recruit participants until data saturation is reached.

A maximum of 7 to 8 people with long COVID and 1 to 2 HCPs will participate in 2 successive focus groups with an iterative co-design objective. Participants in the focus groups may be the same as those in the individual part, but this is not mandatory.

Data Analysis

Phase 1: Quantitative Part

Quantitative data from the web-based survey will be analyzed using descriptive statistics methods. Continuous variables will be presented as means with SDs. Discrete numeric variables and ordinal variables will be presented as medians with IQRs. Nominal and categorical variables will be presented as proportions. Standard statistical methods will be followed.

Phase 2: Qualitative Part

Qualitative data from the semistructured interviews and focus groups will be audio recorded and transcribed verbatim. Transcripts will be checked for accuracy to ensure data quality and analyzed by using the thematic analysis approach [36]. This is the most commonly used method in qualitative research and allows one to identify, analyze, and report patterns within the data through the following five major steps:

1. Compiling: during this step, the recorded interviews are transcribed and organized.

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2. Disassembling to allow for the creation of meaningful codes by identifying themes, concepts, or ideas. The coding process will be iterative and based on grounded theory [37].
3. Reassembling to further dive into the themes and creating subthemes. The coding process will be iterative until saturation.
4. Interpreting: thematic maps or code clusters will be created to analyze the relationship between the themes and thus answer the research question.
5. Concluding: conclusions are not generalizable to the population; they are merely an analytical generalization—a guide to assess how the findings can be transferred and applied. Indeed, qualitative research typically aims for in-depth understanding rather than statistical generalizability.

The MAXQDA software (VERBI Software GmbH) will be used for the transcription of the audio files, for coding and qualitative analysis.

Data analysis will be performed by the study investigators. In particular, coding will be performed by 2 researchers, including an experienced qualitative researcher.

On the basis of the data, the codes and the overall coding structure will be created by the researchers themselves, which is justified because the analysis will be based on grounded theory. Common themes and subthemes from the qualitative data will be identified using a thematic analysis. The first step will be performing coding from scratch. To facilitate coding, we will also create memos. We will clearly define each code that both researchers should approve. The 2 researchers will also have regular meetings to decide whether to merge or exclude codes (data reduction). The themes will be created by grouping similar codes. Subsequently, each theme will be revised to ensure a good definition that aligns with the required codes and to avoid redundancy or missing themes. In addition, we will define themes automatically, using nonsupervised machine learning algorithms (natural language processing using topic modelling R package [R Foundation for Statistical Computing]).

We will assess the intercoder reliability by double-blinded coding performed by 2 independent researchers. The Intercoder Agreement function from the MAXQDA software will be used to compare the coding of the 2 researchers involved in the coding process.

Mixed Methods Integration and Analysis

The integration of the quantitative and qualitative data will be done twice. First, in the design of the qualitative phase of the study: the findings from the quantitative phase will be used to develop the semistructured interview guide that is to be used for the qualitative phase. In particular, the most important topics raised by the survey will be addressed first in the discussions.

Second, after the end of the qualitative phase, the results from the 2 phases will be integrated to triangulate the findings.

Ethics Approval, Informed Consent, and Participation

This study was approved by the National Research Ethics Committee of Luxembourg (study number 202208/04) in August 2022. Interested persons can participate either in the 2 parts of the project or only in 1 part.

In the first part (quantitative web-based survey), each person who receives the link can participate. Detailed information on the survey is provided before acceding to the survey. Informed consent is not required, as this part is anonymous.

An extensive electronic information and informed consent form will be sent to people interested in participating in the qualitative part of the study. Electronically signed informed consent will be collected before any data collection for the second part of the study. REDCap will be used to manage the electronic consent forms.

Participants enrolled in the qualitative part may terminate their participation at any time by contacting the study assistant, and they will not be required to provide reasons for the decision. The assistant will complete the withdrawal form for our own records to ensure that the participant has declared whether LIH may continue to use the information that was already collected or if it should be destroyed (if applicable).

Participation in the individual interviews and the focus groups may tire some participants, particularly people with long COVID. To prevent this risk, regular pauses will be proposed during the interviews and focus groups, and the maximum duration of 60 and 90 minutes, respectively, will be strictly respected. The interviewer and the moderator will be the investigators trained in qualitative research methods and confidentiality.

There will be no financial incentive for participation in one or both parts of the study. Participants will be informed that they will not have any direct benefit but will contribute to a research effort that could make an impact not only in the care of patients with long COVID but also that of patients with other chronic diseases in the following years.

Data Management—Confidentiality

The personal data of participants will be protected according to the *Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation)*. The participants will receive detailed information on data privacy and protection in the information sheets from both parts of the study. In particular, they will be informed of how the data will be collected and stored, what security measures will be in place, and who will be authorized to access the data. They will also be asked to give their consent for the potential secondary use of their data for other research projects and will be informed that in case they agree, only their anonymized data will be shared with other researchers. Participants in the anonymous survey will be informed that their data will potentially be used for other research studies and shared with other researchers. The participants will be informed that they can contact the institution's data protection officer if they have questions related to data privacy and protection. The contact details of the data protection officer are provided in the electronic information and consent form.

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The survey will be anonymous and accessible by following a direct link to the web-based survey platforms (no application to download).

No account, log-in, or password will have to be created by the participants. There will be no link between the email addresses collected after the survey completion from people interested in the second part of the study and the survey answers.

The data collected from the qualitative part will be pseudonymized. Participants who express their interest in participating in the second part of the project will receive a unique link to access the electronic consent form. After the completion of the electronic consent form, a unique study number will be assigned to them.

Data collected during the individual interviews and focus groups will never be linked to a participant's name or email address. A nickname will be used to refer to each participant during the exchanges. Interviews and focus groups will be recorded and transcribed using a transcription tool. All records will be destroyed directly after the transcription. The interviewer will be responsible for audio transcription and destruction.

The nominative data collected via the consent form will be stored on LIH internal servers, separated from the pseudonymized data from the interviews and focus group notes. All data stored on the LIH servers will be encrypted using the Transport Layer Security (TLS) encryption protocol. Access to the data will be restricted by user accounts and will be provided by the principal investigator of the study to a limited number of people. Access logs will be implemented to control data accesses and ensure high data security.

The contact data (email address and identification data) of the participants will be deleted 2 years after the individual interview. The pseudonymized data will be anonymized after 2 years by deleting the correspondence table and deleted after 10 years according to the LIH standard procedure for archiving.

LIH internal procedures will be followed to ensure data destruction after the retention period ends.

Results

The web-based survey was launched in October 2022. The individual interviews and focus groups will start after the end of the survey in March 2023. The end of data collection is expected in September 2023, and the results will be published at the end of 2023 or in 2024.

Discussion

This paper presents a protocol for a mixed methods study that aims to codevelop a digital health solution based on vocal biomarkers to monitor long COVID symptoms and conditions with its potential end users, namely, people with long COVID and HCPs in charge of patients with long COVID.

Expected Findings

Long COVID is a complex disease with a high impact on the daily life and quality of life of affected people [38,39]. Patients often feel abandoned by the health care system and demand for support and new tools to track their symptoms and relapses. This could be helpful to identify the potential causal factors of symptom exacerbation and relapses to improve pacing and prevention. In particular, postexertional symptom exacerbation is a well-known problem in long COVID and can be defined as the worsening of symptoms following a physical or mental activity [40]. Postexertional symptom exacerbation needs to be carefully monitored, for example, to ensure a safe rehabilitation program or to personalize the daily activities to prevent symptom degradation.

HCPs also recognize that there is a need for more integrated health care structures to manage patients with long COVID. Additional tools to ensure an efficient and safe rehabilitation would also be helpful for both people with long COVID and HCPs, as some patients with long COVID experience postexertional malaise [40] and may need a tailored rehabilitation program. Moreover, with new therapies and drugs currently in development for long COVID treatment, this tool might also be used as a companion tool to monitor the health status of people with long COVID during clinical trials.

The use of vocal biomarkers to monitor long COVID symptoms seems of high interest because voice samples are noninvasively collected and are easy to collect compared with the completion of tedious self-reported questionnaires. They could also objectify a subjective condition such as fatigue or mental health and facilitate the communication between patients and HCPs [10,41]. Moreover, audio recordings may be more adapted and accurate than traditional paper questionnaires for people with neuropsychological disorders or other patients who are chronically ill with reduced functioning [42,43].

Vocal biomarkers of several symptoms related to COVID-19 and long COVID have been identified previously and need to be integrated into a digital health solution before being used in daily life or clinical practice. We recently proposed an optimal pipeline and recommendations to achieve the successful implementation of vocal biomarkers in practice, with their potential benefits and limitations in the context of long COVID [41]. The identification of the problem and the symptoms to be monitored and the involvement of the end users as soon as possible in the development process are key points. The protocol of the study described in this paper is based on these recommendations.

The findings of this study will have several potential implications. First, we will take advantage of combining quantitative and qualitative data in a mixed methods design to describe the needs of people with long COVID in depth and understand how the use of vocal biomarkers in a voice-based digital health solution could solve their problems. The visualization of the results in the digital health solution will also be discussed and tailored to best fit its end users. The tool will be developed with an interoperability objective to ensure its future dissemination to a maximum number of people.

Second, the findings could potentially be transferred to other diseases, and this is of the highest importance for the future of vocal biomarkers and voice-based health technologies to understand the extent of transferability.

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Finally, the concrete output of the study will be a voice-based digital health solution that will provide support to people with long COVID in their daily lives and improve their quality of life.

Strengths and Limitations

One of the strengths of this study is that patients with long COVID and HCPs in charge of patients with long COVID have been involved in the study design and will be involved in the entire study course.

The use of a mixed methods design, using quantitative and qualitative approaches, will provide an extensive description of the future user's expectancies, barriers, and leverages regarding the use of vocal biomarkers in a digital health solution and will provide the specifications of a digital health solution optimally designed with and for its end users.

The results will reveal the transferability potential of the use of vocal biomarkers for other diseases and contribute to the expansion of this recent technology.

This study has some limitations. First, the fully web-based format of the study may limit the participation of some population categories (such as people with low eHealth literacy) but by contrast, may also facilitate the participation of people who are geographically distant or experience more impacting symptoms.

Another potential limitation is that even if the chosen sample size should ensure achieving data saturation, it may probably not represent all different subpopulations with long COVID. However, this is not the objective of this mixed methods study. The opinions collected should be varied enough to ensure the development of a digital solution that provides help and support to all patients with long COVID.

Finally, mixing people with long COVID and HCPs in the focus groups may induce conformity, dominance, and shyness biases. However, people with long COVID are highly involved in the management of their disease and generally interact easily with HCPs. The moderator's role will also be crucial in minimizing the risks of bias during focus groups by communicating from the start the objectives of the discussions and by ensuring that each participant receives the same amount of speaking time. The cultural bias will also be reduced by the inclusion of participants from different countries.

Conclusions

This mixed methods study will identify the needs of people affected by long COVID in their daily lives and describe the main symptoms or problems that would need to be monitored and improved. We will determine how the use of vocal biomarkers in a digital health solution could meet these needs and further describe the end user's expectations and barriers regarding the use of this new digital technology to monitor COVID-19–related symptoms. Finally, our study will ensure the development of a digital health solution that will match the actual needs of people with long COVID by involving them in the design process from the beginning. The study will also provide important insights into the transferability of the results to other diseases and contribute to the deployment of vocal biomarkers in general.

Publication Plan

The study results will be disseminated at the end of 2023 in a scientific article submitted to an international peer-reviewed journal, to long COVID patient associations, and through social media communications to the lay audience.

Acknowledgments

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Data Availability

The data sets generated during this study are available from the corresponding author upon reasonable request.

Authors' Contributions

AF, GAA, and GF contributed to the study design, literature review, and drafting of the manuscript. PO, LM, and CB contributed to the study design and reviewed the study documents. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Detailed questionnaire for people with long COVID.
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Multimedia Appendix 2
Detailed health care professional questionnaire.
[DOCX File , 20 KB - resprot_v12i1e46103_app2.docx]

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Abbreviations

APEASE: Affordability, Practicability, Effectiveness, Acceptability, Side Effects, and Equity
HCP: health care professional
LIH: Luxembourg Institute of Health
REDCap: Research Electronic Data Capture
TLS: Transport Layer Security
uMARS: user version of the Mobile Application Rating Scale

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Protocol

A Technology-Enriched Approach to Studying Microlongitudinal Aging Among Adults Aged 18 to 85 Years: Protocol for the Labs Without Walls Study

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Abstract

Background: Traditional longitudinal aging research involves studying the same individuals over a long period, with measurement intervals typically several years apart. App-based studies have the potential to provide new insights into life-course aging by improving the accessibility, temporal specificity, and real-world integration of data collection. We developed a new research app for iOS named Labs Without Walls to facilitate the study of life-course aging. Combined with data collected using paired smartwatches, the app collects complex data including data from one-time surveys, daily diary surveys, repeated game-like cognitive and sensory tasks, and passive health and environmental data.

Objective: The aim of this protocol is to describe the research design and methods of the Labs Without Walls study conducted between 2021 and 2023 in Australia.

Methods: Overall, 240 Australian adults will be recruited, stratified by age group (18-25, 26-35, 36-45, 46-55, 56-65, 66-75, and 76-85 years) and sex at birth (male and female). Recruitment procedures include emails to university and community networks, as well as paid and unpaid social media advertisements. Participants will be invited to complete the study onboarding either in person or remotely. Participants who select face-to-face onboarding (n=approximately 40) will be invited to complete traditional in-person cognitive and sensory assessments to be cross-validated against their app-based counterparts. Participants will be sent an Apple Watch and headphones for use during the study period. Participants will provide informed consent within the app and then begin an 8-week study protocol, which includes scheduled surveys, cognitive and sensory tasks, and passive data collection using the app and a paired watch. At the conclusion of the study period, participants will be invited to rate the acceptability and usability of the study app and watch. We hypothesize that participants will be able to successfully provide e-consent, input survey data through the Labs Without Walls app, and have passive data collected over 8 weeks; participants will rate the app and watch as user-friendly and acceptable; the app will allow for the study of daily variability in self-perceptions of age and gender; and data will allow for the cross-validation of app- and laboratory-based cognitive and sensory tasks.

Results: Recruitment began in May 2021, and data collection was completed in February 2023. The publication of preliminary results is anticipated in 2023.

Conclusions: This study will provide evidence regarding the acceptability and usability of the research app and paired watch for studying life-course aging processes on multiple timescales. The feedback obtained will be used to improve future iterations of the app, explore preliminary evidence for intraindividual variability in self-perceptions of aging and gender expression across the life span, and explore the associations between performance on app-based cognitive and sensory tests and that on similar traditional cognitive and sensory tests.

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KEYWORDS

life-course aging; longitudinal research; subjective age; gender; cognition; sensory function; app; mobile app; eHealth; mobile health; mHealth; measurement burst design; ecological momentary assessment; health information technology; personalized health; mobile phone

Introduction

Background

Longitudinal aging research involves studying the same individuals over a long period, typically with measurement intervals several years apart. Although this approach can inform long-term developmental processes, it cannot capture processes that fluctuate on multiple—sometimes acute—microlongitudinal timescales. This project aims to contribute to the contemporary theories of life-course aging and gender by establishing a novel methodology for examining their daily experiences, known as the Labs Without Walls research app. We seek to evaluate the feasibility and usability of the app and a paired Apple Watch (Apple Inc) for studying the microlongitudinal processes of aging among a life-course sample of Australian adults. The validity of the app-based administration of common cognitive and sensory tasks will also be explored.

Benefits of App-Based Approaches for Longitudinal Aging Research

Recent data suggest that 91% of Australians aged 18 to 75 years own a smartphone, and 58% use a smartphone or smartwatch device to monitor their health or well-being [1]. The rise in the popularity of smartphone devices has been accompanied by a commensurate rise in app-based studies of health and well-being. However, it is notable that many of these studies are designed for younger cohorts or specific clinical populations [2,3]. Few studies have examined processes that may differ across the life course [4].

App-based approaches to research offer a number of benefits for conducting longitudinal research [5] that may provide new insights into many factors that may be associated with developmental changes across the human life span, which we term *processes of life-course aging*. First and foremost, research apps remove the physical barriers to participation that are a feature of more traditional life-course aging studies. Apps can be accessed from anywhere with an internet connection, and this opens participation opportunities to adults living remotely or experiencing mobility restrictions that would otherwise prevent travel to urban research centers. Apps can be convenient for both participants and researchers, as they can allow participants to configure their testing and alert schedules to times that suit their daily routines and reduce researcher workloads associated with in-person testing sessions. Well-designed apps can also be interactive and engaging. This may be particularly important for studies that require participants to provide regular, intensive data.

Smartphones and paired wearable devices also include a range of sensors that provide new opportunities to noninvasively study complex microlongitudinal processes. For example, mobile apps can be designed to collect high-quality passive data (including physical activity metrics, heart rate, location data, and noise exposure), which can help researchers obtain more accurate and detailed data than possible using other methods. These data can be collected and integrated in real time, which can be useful for studying dynamic or rapidly changing phenomena and improving the ecological validity of research.

Finally, although substantial investment is often required in the development stage of bespoke research apps, app-based research can be a cost-effective option, as they can reduce the need for in-person research sessions and specialized equipment and leverage free-to-use open-source cognitive, sensory, and behavioral testing resources for research, such as those provided by the Apple ResearchKit framework (Apple Inc) [6].

This Study: Capturing Day-to-Day Subjective Experiences of Age and Gender

Age and gender are 2 defining characteristics used in nearly all human studies. The perceptions and expressions of each are influenced by social, biological, and environmental determinants, and people's subjective experiences of age and gender have been vastly understudied. Self-perceptions of aging (SPA) is a multidimensional construct involving the personal evaluation of age-related changes experienced in various life domains, irrespective of chronological age [7]. Subjective age is a form of SPA and refers to how young or old individuals experience themselves to be. SPA is associated with numerous health outcomes, including mortality [8], mental health [9], and functional health [10]. SPA changes over the life course. Previous research has shown that adolescents perceive themselves as older than their chronological age (age in years from the date of birth), potentially reflecting increased perceptions of maturity [11]. This changes in early adulthood, when people usually hold younger subjective ages. The discrepancy between the chronological and subjective age increases across the life span [11,12]. Life-course variability in SPA may reflect psychosocial changes experienced at different life stages; however, there is yet to be a study exploring SPA among a life-course sample. Despite strong evidence of long-term variability in SPA, limited data exist on how SPA fluctuate on microtimescales, that is, hours, days, or weeks. Existing day-to-day variability in measures of subjective age, an area of SPA, suggests fluctuations in multiple domains [13]. The measurement timescale may greatly alter the perceived relationship between variables [14] and could help elucidate intraindividual variability in SPA and the interplay between SPA and other time-varying constructs, such as mood, stress, and physical activity.

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Gender, similar to many other social constructs, can change and evolve over time [15]. Gender is often conflated with sex, although they are distinct constructs. *Sex* commonly refers to a person's biological status as male, female, or another variation of sex characteristics. Indicators of biological sex can include sex chromosomes (XX and XY), hormones, internal reproductive organs, and external genitalia [16]. In research practice, sex is usually reported as male or female based on the sex recorded at birth. *Gender* is a dynamic social construct that refers to the psychological, social, and cultural factors that shape attitudes, behaviors, stereotypes, and knowledge. In research practice, gender is typically treated as a fixed, binary variable despite substantial variations in the real world [17]. Such an approach does not take into account the multidimensional nature of gender, which includes gender norms (spoken and unspoken rules within the family, community, institution, or culture), gender relations (power relations between individuals with different gender roles and identities), gender identity (how individuals and groups perceive and present themselves within specific cultures), and gender expression (the outward expression of one's gender identity, including physical and behavioral dimensions) [16], nor does such an approach allow for an understanding of gender as dynamic [15]. Indeed, gender dynamism can be seen in at least 3 aspects: the meaning of gender has changed over time; there are substantial cultural differences in the meaning of gender; and one's own gender and relationship with it can change, evolve, weaken, and galvanize across the lifetime [15]. There is also likely to be heterogeneity in gender dynamism at the individual level and between and within age and sex-at-birth groups, which has not been the subject of study to this point.

Theoretical accounts of socioemotional aging suggest that intraindividual variability in gender expression may be greatest during early adulthood—when broad social networks and diverse social interactions are used to help craft an individual's self-concept—and decrease at older ages when interactions with diverse identities are reduced and one's sense of self is more clearly defined [18]. This study seeks to understand the factors that impact daily variability in gender expression across the life span and how variability may differ between male participants and female participants. Research has not explored the variability in SPA and gender expression and its relationships with both stable and variable personal, social, and environmental factors. Improving the understanding of life-course variability in self-perceptions may help identify complex relationships among self-perceptions, health, and the environment.

Aims of This Study

Technology has enabled vast improvements in app-based research that have yet to be used to study SPA or gender expression across the life course. Therefore, the aim of this study is to evaluate the feasibility and usability of the newly developed Labs Without Walls research app and a paired Apple Watch for studying life-course aging among male and female participants from different age groups. We hope to disentangle processes that may vary across microtimescales, including SPA and gender expression. The study also aims to validate the app-based administration of common cognitive and sensory tasks for use among Australian life-course samples.

Hypotheses

We hypothesize the following:

Hypothesis 1: Participants aged 18 to 85 years will be able to successfully provide e-consent, be able to input survey data through the Labs Without Walls research app, and have passive data collected using an Apple Watch over 8 weeks.

Hypothesis 2: The user experience of the Labs Without Walls research app and Apple Watch will be rated as acceptable by research participants aged 18 to 85 years.

Hypothesis 3: Data collected on multiple timescales using the Labs Without Walls research app will enable the exploration of variability in SPA and how SPA may be affected by personal characteristics, environmental conditions, physical health, resilience, fatigue, stress, and mood.

Hypothesis 4: Data collected using the Labs Without Walls research app will also allow for the exploration of stability and variability in gender expression and how gender expression may be affected by personal characteristics, physical health, resilience, mood, stress, and fatigue.

Hypothesis 5: Cognitive and sensory assessments delivered through the Labs Without Walls research app will be comparable with the traditional face-to-face versions of the assessments.

Methods

Participants

We aim to recruit a total of 240 Australian adults stratified by sex (male and female) and age group (18-25, 26-35, 36-45, 46-55, 56-65, 66-75, and 76-85 years).

Power

Sample size calculations for the full sample and the face-to-face validation subsample were estimated using the following criteria: threshold probability for rejecting the null hypothesis (2-tailed =.05) and the probability of failing to reject the null hypothesis under the alternative hypothesis (=.20). This pilot study is exploratory in nature. However, based on a previous meta-analysis [19], the odds ratio of subjective age impacting overall health is estimated to be 1.57. Using the aforementioned criteria, G*Power [20] was used to calculate the minimum sample size of 129 participants for the full study, which was well below our target. To allow for the addition of multiple covariates in statistical models and potential cases of missing data or attrition across the 8-week study period, we aim to recruit a total sample of 240 participants.

For the face-to-face validation subsample, a minimum sample size of 29 participants is required to detect a moderate correlation of r=0.50 between the performance on app-based cognitive and sensory tasks and that on face-to-face cognitive and sensory tasks, based on α (2-tailed)=.05 and β=.20 [21]. We aim to oversample to a total of 40 participants to account for possible missing data or the withdrawal of consent across the study.

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Recruitment

Between May 2021 and January 2023, research volunteers will be recruited from the general Australian population using email, social and professional media call outs, and the Neuroscience Research Australia (NeuRA) Healthy Research Volunteer Registry. Participants will be invited to read the study information on the web via the study website. Web-based recruitment materials include a link to the study website, where those who are interested enter their contact details and preferred method of contact (phone, email, or text) for the research team to conduct eligibility screening.

Eligibility

To be eligible to participate in this study, adult volunteers must be living in Australia, be aged 18 to 85 years, be a current iPhone (Apple Inc) user, be willing to use their iPhone to download free research apps, be proficient in English, be able to access a home Wi-Fi connection for the duration of the study, not be reliant on text-to-speech services to use their iPhone, be willing to wear the Apple Watch during the study period and use headphones to complete hearing tasks, be willing to provide informed consent and comply with the study protocol, and agree to return the loaned study equipment (Apple Watch and headphones) at the end of the study.

As noted earlier, approximately 40 participants who join the study and are located in metropolitan Sydney will be invited to attend a 2-hour onboarding session either at the NeuRA or their homes to complete the traditional face-to-face versions of cognitive and sensory measures to assess validity across face-to-face and app-based administration methods.

Materials and Devices

iPhones

Study participants will use their own iPhones (model 6S or newer, supporting iOS 13 or later) in the study.

Apple Watches

Participants can join the study with their own Apple Watch or can elect for the study team to post them an Apple Watch Series 5 GPS for use during the study period. In this study, Apple Watches will be used to collect a range of health and behavioral data (as outlined in Table 1). In addition, Apple Watches will be used to deliver task reminders to the participants.

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Table 1. Brief description of the app- and laboratory-based cognitive and sensory tasks administered in the Labs Without Walls Study.

Format and task name	Source	Expected duration (minutes)	Construct or constructs measured	Description
App-based testing				
Trail Making Task A	[6]	2	Sequencing, visual search, and processing speed	The participant uses their finger to connect a series of labeled circles presented on their phone screen, in order. The circles are labeled with sequential numbers (1, 2, 3, etc).
Trail Making Task B	[6]	2	Cognitive flexibility, alternating attention, sequencing, visual search, and processing speed	The participant uses their finger to connect a series of labeled circles presented on their phone screen, in order. The circles are labeled with alternating numbers and letters (1, a, 2, b, 3, c, etc).
Spatial Memory Task	[6]	2	Visuospatial memory and executive function	The participant is asked to observe and then recall pattern sequences of increasing length in a game-like environment.
Stroop Task	[6]	3	Cognitive flexibility and inhibitory control	The participant is shown a series of words that are displayed in color and must select the first letter of the color's name.
Tapping Speed	[6]	2	Motor function, tapping speed, tapping accuracy, and tapping rhythm	The participant rapidly alternates between tapping 2 targets on the touch screen. The task is repeated for the left and right hands.
Tower of Hanoi	[6]	2	Problem solving	The participant is asked to solve a puzzle in a minimum number of moves. To solve the puzzle, the participant must move the entire stack to the highlighted platform in as few moves as possible.
Reaction Time	[6]	2	Reaction time	The participant shakes their iPhone (Apple Inc) in response to a visual cue on the screen.
9-Hole Peg Test	[6]	2	Hand dexterity	The participant uses 2 fingers to touch on an on-screen peg and drag it into an on-screen hole and across a line. Both hands are tested.
dB HL Tone Audiometry task	[6]	6	Hearing ability	The participant listens through ear pods (provided by the research team) to a series of tones and taps the left or right button on the screen when they hear each tone. These tones are of different audio frequencies and play on different channels (left and right), with the volume being progressively increased until the user taps one of the buttons.
Amsler Grid	[6]	1	Visual problems, such as macular degeneration	The participant observes an on-screen grid while closing 1 eye for any anomalies and marks the areas that appear distorted using their finger.
16-Plate Ishihara Colour Deficiency Test	Adapted for mobile from the original 25-plate Ishihara colour deficiency test [22]	3	Red-green color deficiency	The participant is shown 16 images depicting a circle made of smaller red and green dots. Each circle is presented on a single screen. Within each circle, numbers appear in alternating colors. The participant must enter the number shown within each circle using an on-screen keyboard.
Face-to-face testing				
Trail making task A	[23]	3	Sequencing, visual search, and processing speed	The participant is presented with a sheet of paper that contains numbers randomly scattered throughout. The task is to connect the numbers in sequential order as quickly as possible.
Trail Making Task B	[23]	5	Cognitive flexibility, alternating attention, sequencing, visual search, and processing speed	The participant is presented with a sheet of paper that contains both numbers and letters randomly scattered throughout. The task is to connect the numbers and letters in alternating, sequential order as quickly as possible. For example, the participant would connect 1 to A, then A to 2, then 2 to B, and so on.
WMS-III[a] Spatial Span (forward span)	[24]	5-10	Visuospatial memory	The participant is shown of a series of spatial locations, typically marked by a set of blocks or cubes, arranged in a particular order on a board or table. The examiner then points to each location in sequence, and the participant being tested is required to touch or point to each location in the same order.

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Format and task name	Source	Expected duration (minutes)	Construct or constructs measured	Description
Victoria Stroop Task	[25]	5-10	Cognitive flexibility and inhibitory control	The participant is asked to read aloud a list of color names, such as “red,” “green,” and “blue,” as quickly and accurately as possible. The participant is then presented with a list of color words that are printed in an incongruent color, such as the word “red” printed in blue ink and is instructed to name the color of the ink, not the word itself, as quickly and accurately as possible.
SHOEBOX dB HL Tone Audiometry Test	[26]	10-20	Hearing ability	The participant wears headphones. A series of pure tone sounds are presented at different frequencies and loudness levels, and the participant is asked to respond each time they hear the sound. The test typically begins at a frequency of 1000 Hz and progresses to higher and lower frequencies.
25-plate Ishihara Colour Deficiency Test	[22]	5-10	Red-green color deficiency	The participant is shown a series of plates with colored dots or patterns arranged in a specific way to form a number. The participant must identify the number on each plate.

[a]WMS-III: Wechsler Memory Scale-III.

Headphones

Participants will be posted a new pair of Apple in-ear wired EarPods with a lightning connector (model number MMTN2FE/A) for use during hearing tasks.

Labs Without Walls Research App for iOS

Labs Without Walls was developed to provide a means of conducting life-course aging research outside traditional research laboratories. It was conceived and developed by the investigators. The app is primarily built in Swift (Apple Inc), using XCode (Apple Inc) as the development environment. Objective-C (Apple Inc) is used for enhancements to the Apple ResearchKit framework [6]. Apple’s ResearchKit is used to provide functionality, including consent, questionnaires, prebuilt active tasks, and graphs. The app uses read-only access to the local health store on the participant’s iPhone via Apple’s HealthKit interface, subject to the participant’s consent. Data will be collected continuously throughout the study period from both the worn Apple Watch and the participant’s iPhone. The app fully supports light and dark mode presentations throughout.

Backend

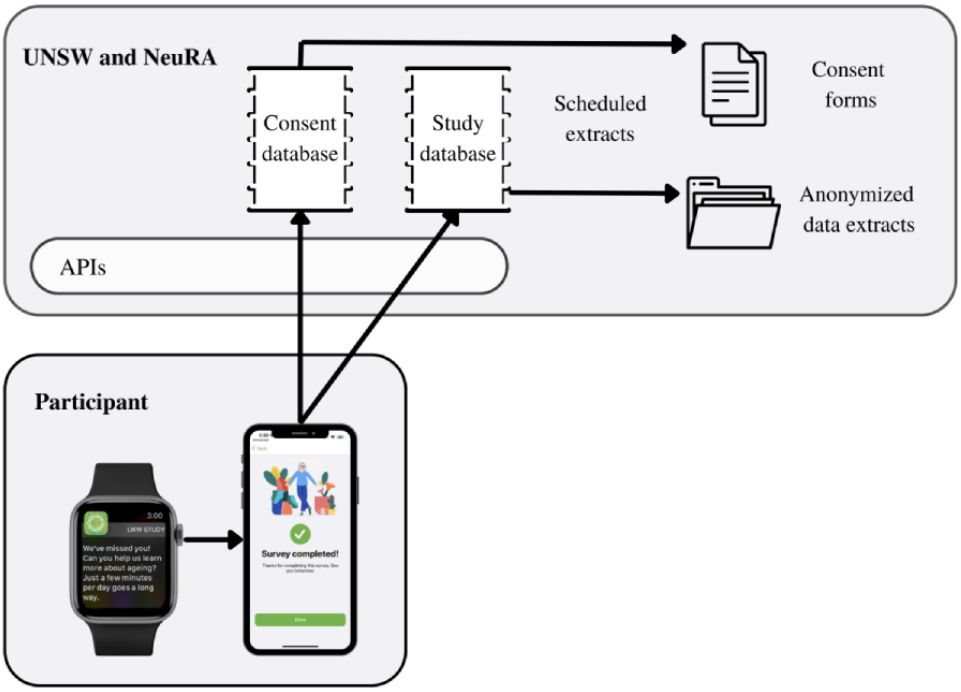
A backend, hosted on the Amazon Web Services (AWS) platform, will be used to collect study data securely. The AWS offers a range of security measures to protect data stored in the cloud, including industry-standard encryption algorithms to protect data in transit and at rest. Data cannot be accessed without the appropriate decryption key, and access is restricted to only essential research staff approved by the ethics committee. Two-factor authentication will be implemented, and 6-month audits of data access will be conducted.

Technical Architecture

The technical architecture of the Labs Without Walls study is summarized in Figure 1.

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Figure 1. Technical architecture of the Labs Without Walls research study. API: application programming interface; NeuRA: Neuroscience Research Australia; UNSW: University of New South Wales.



The technical architecture of the app is designed to separate consent forms and other identifiable information from deidentified study data. The consent details provided, including those in the signed e-consent form, will be transmitted by secured application programming interfaces to an AWS backend, where they will be stored in the stand-alone consent database. All other study data collected from participants (including data from questionnaires and cognitive and sensory tasks and health data) will be initially stored on the iPhone and transmitted to the backend when the app is running and has an active internet connection.

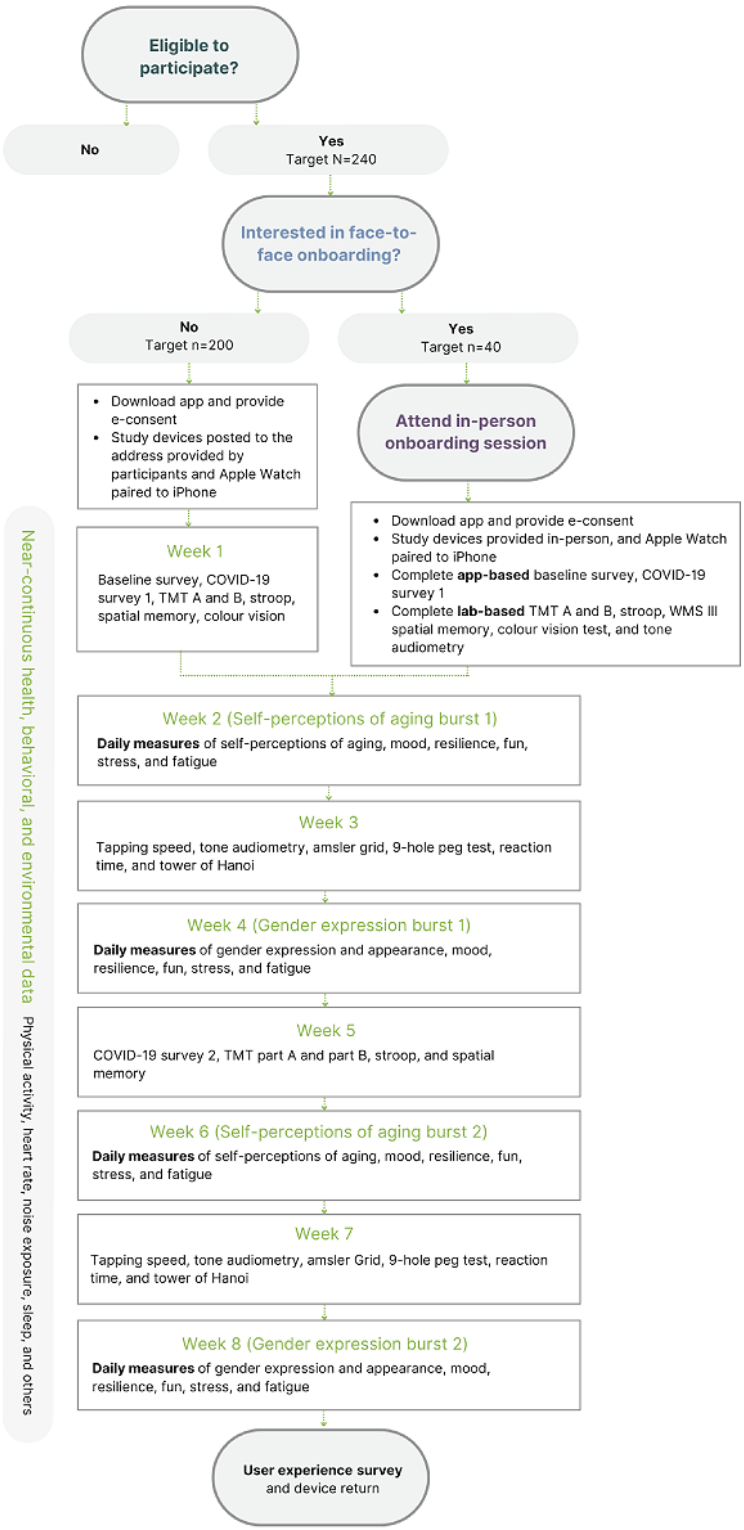
Two sets of data extracts will occur on a periodic basis. First, consent forms will be extracted to a secured location (S3 bucket), accessible to a limited number of members of the study team. These will be retained as a record of informed consent. Second, the collected study data will be extracted for analysis. These extracts will be anonymized to remove personally identifying information. These will be extracted to a separate secured location (S3 bucket) and will be accessible only to a limited number of members of the study team. Data extracts will be stored and handled according to an approved University of New South Wales Research Data Management Plan.

Procedure and Study Design

This project uses a multitimescale measurement burst design [27,28] to collect single–time point, near-continuous, and repeated-measure data from participants using the Labs Without Walls research app and an Apple Watch. Participants will complete a total of 31 short surveys and 14 active tasks using the research app. The completion of tasks is staggered across the 8-week period. The study procedure is summarized in Figure 2. The time commitment for each day will not exceed an average of 5 to 10 minutes. At the end of the study, after completing a user satisfaction questionnaire, participants will be asked to return any borrowed devices (Apple Watch and headphones) using a supplied prepaid mailing box. Participants may also choose to leave the study early from within the app and specify whether they consent to the data previously collected from them being used in the study. Participants will not receive payment for joining the study. However, participants who attend the NeuRA for face-to-face cognitive and sensory testing will be offered a voucher worth Aus $20 (US $13) to assist with travel costs.

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Figure 2. Flowchart summarizing the Labs Without Walls study procedure from eligibility screening to user experience feedback. TMT: Trail Making Task; WMS-III: Wechsler Memory Scale-III.



Ethics Approval

Ethics approval was obtained from the University of New South Wales Human Research Ethics Committee (HC200792).

Participant App Experience

Joining the Study

Eligible participants will be given a link to download the Labs Without Walls app from the Apple's public App Store and install it onto their existing iPhone. Alternatively, as the app is publicly visible in Australia, participants can search for it using the App Store app on their device. Each participant will be issued a

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unique 1-time invitation code to allow them to join the study within the app. Once their invitation code is accepted, the user can proceed to the study consent process within the app.

e-Consent

The e-consent process obtains and records the consent of the participant within the app before they participate in the study.

The Labs Without Walls e-consent flow, summarized in Figure 3, is presented in Textbox 1.

Figure 3. Summary of the Labs Without Walls in-app consent flow.



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Textbox 1. Labs Without Walls e-consent flow.

- An introductory page will appear.
- Multiple pages presenting essential study information will appear.
- A consent quiz to check the participant's understanding of key consent concepts will be administered. The participant needs to complete the quiz correctly to proceed (can retry as required).
- A review page with an Agree button, which the participant can tap on to proceed further, will appear.
- When the participant taps on Agree, a confirmation message will be shown.
- If the participant confirms their agreement, then they will be taken to a signature capture page, to obtain their signature.
- A page where the participant can allow access to their health data and choose which measures are to be accessible (refer to the *Health Data Collection* section) will appear.
- Contact information will be collected to allow for device mail-out.
- Pages where the participant can provide optional consent for the use of anonymous data by other approved researchers, contact for further studies, and contact for media events will appear.
- A completion page will appear.

Once consented, participants will be posted an Apple Watch (if not joining with their own device) and Apple EarPods for use during the study. Once participants pair the watch with their phones, they will begin the 8-week study period.

Study Tasks

Task List

At any time, the list of available tasks to complete will be displayed on the home tasks screen. Tasks will remain in the task list for 3 days after the scheduled date, and the date of completion will be recorded in the data file. Tasks beginning the following day will also be shown in the task list, although not accessible until the scheduled date. Tapping on a task will start the task. A task can be a survey, cognitive task, or physical or sensory task. These are described in the subsequent section.

Survey Measures

Much of the study data will be collected from participants in the form of short surveys. The Labs Without Walls research app includes one-off surveys (eg, baseline), surveys administered twice (COVID-19 experiences), and daily diary–style repeated-measure surveys (eg, SPA, gender expression, mood, and resilience). A list of the in-app surveys and their measurement frequencies is provided in Table 2. Composite scores—which can be automatically computed within the app—will be created according to the published guidelines for existing measures. The typical survey flow consists of an introductory page, multiple pages of questions, and a completion page (Figure 4).

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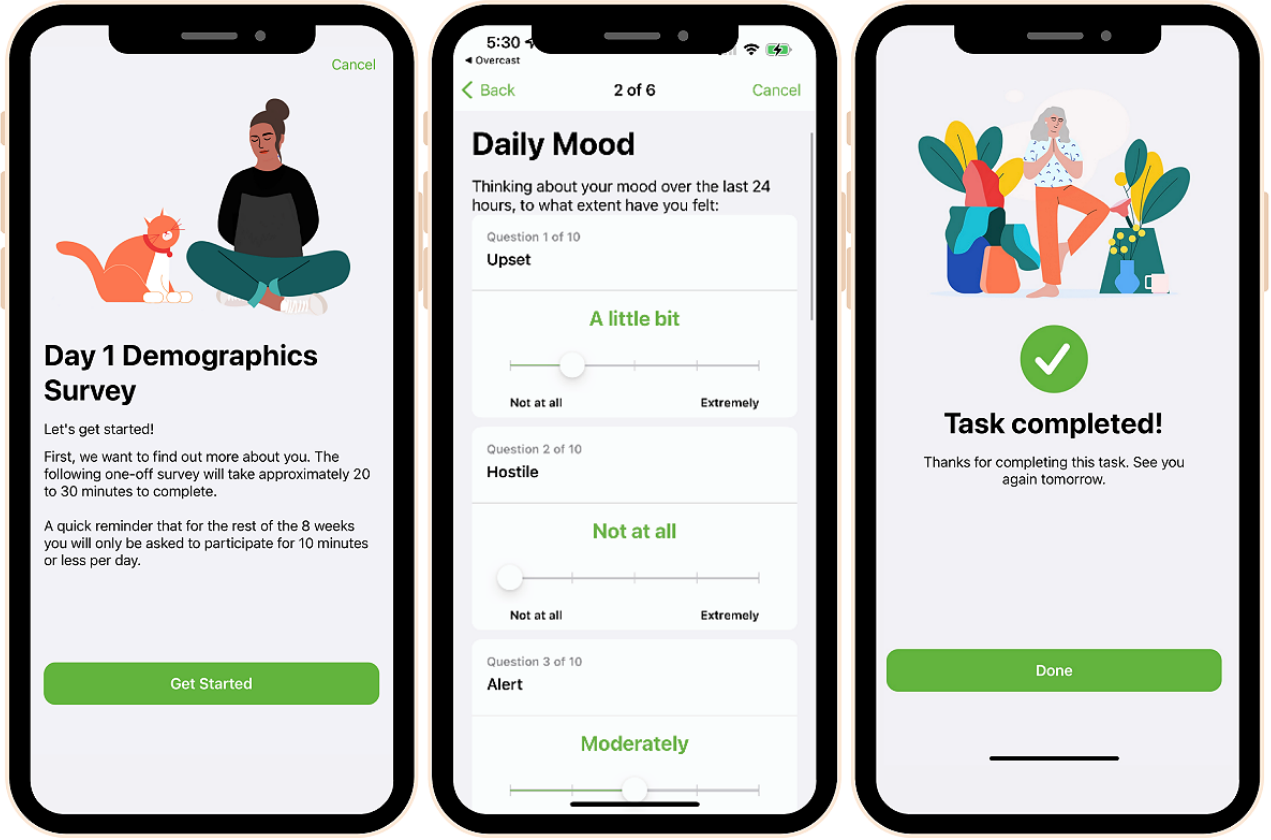
Table 2. Surveys included in the Labs Without Walls research app and their measurement frequencies.

Construct of interest	Measure description	Items, n	Administration day or days
Age	Years	1	1
Ethnicity	Ethnic group or groups identified with	1	1
Relationship status	Married, in a relationship, or single	1	1
Education	Years of education by education stage (primary, secondary, technical college, university, or other)	5	1
Household income	Weekly average household income before tax	1	1
Employment	Employed, unemployed, or retired	1	1
Self-rated health	Physical and mental health measured by the SF-12[a] version 2 [29]	12	1
Sex	Self-reported sex at birth	1	1
Gender identity	Self-reported gender identity	1	1
Childhood gender role nonconformity	Subset of items from the Recalled Childhood Gender Identity and Gender Role Questionnaire [30]	3	1
Genders in childhood home	Balance of genders in childhood home	1	1
Sexuality	Sexual orientation	1	1
Menopause	Self-reported female reproductive status (administered only to those assigned female at birth)	1	1
HRTs[b]	Currently taking HRTs	1	1
Smoking	Currently smoke	1	1
Vaping	Currently vape	1	1
Alcohol	Frequency of consumption and amount per occasion	2	1
Resilience	CD-RISC2[c] [31]	2	1
Chemical intolerance	BREESI[d] [32]	3	1
Perceptions of air quality	Perceived in-home air quality and perceived impact of quality on health	2	1
Future time perspective	Short-form FTP[e] scale [33,34]	5	1
Expectations regarding aging	ERA-12[f] [35]	12	1
Social isolation	UCLA[g] Loneliness Scale [36]	3	1
Digital technology use	Weekday use of digital and internet technologies and impact of use	6	1
COVID-19 experiences	COVID-19 experiences and impact questionnaire	37	4 and 30
Subjective aging (daily)	Felt age, look age, behave age, mental performance age, interests age, and ideal age	6	1, 8-14, and 36-42
Mood (daily)	Adapted 10-item Positive and Negative Affect Scales [37]	10	8-14, 22-28, 36-42, and 50-56
Resilience (daily)	Adapted CD-RISC2	2	8-14, 22-28, 36-42, and 50-56
Fun (daily)	Original items measuring fun, laughter, and excitement in the past 24 hours	3	8-14, 22-28, 36-42, and 50-56
Gender expression (daily)	Gender appearance and expression adapted from the study by Wylie et al [38]	2	22-28, and 50-56
Stress (daily)	Original items measuring daily stress about work, finances, relationships, global events, and COVID-19	5	8-14, 22-28, 36-42, and 50-56
Fatigue and vitality (daily)	SF-36[h] vitality subscale [39]	4	8-14, 22-28, 36-42, and 50-56
User satisfaction	Multifaceted feedback on the app and watch user experience	9	56

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[a]SF-12: 12-Item Short Form Survey.
[b]HRT: hormone replacement therapy.
[c]CD-RISC2: 2-item Connor-Davidson Resilience Scale.
[d]BREESI: Brief Environmental Exposure and Sensitivity Inventory.
[e]FTP: Future Time Perspective.
[f]ERA-12: 12-item Expectations Regarding Aging Scale.
[g]UCLA: University of California, Los Angeles.
[h]SF-36: 36-Item Short Form Survey.

Figure 4. Sample introductory page, survey page with slider response options and completion page from the Labs Without Walls research app.



Feasibility and Acceptability Data

The feasibility and acceptability of the app and paired Apple Watch will be assessed in a number of ways. First, we will look at the number of successful consents—including successful completion of the 3-item consent quiz—as an indicator that the e-consent process is clear and reliable. The study retention rate will be examined as an indicator of how many participants remained in the study for the entire 56 days. Survey and task completion rates will be examined to look for potentially systematic gaps in the data or frequently incomplete surveys or tasks across participants. Participant-reported acceptability of the app will be assessed using 3 items: "Was the assessment schedule *manageable* in the context of your daily life? (Yes or No)," "How *user-friendly* did you find the mobile technology? (1=Not at all to 5=Extremely)," and "How much did you *enjoy* using the mobile technology? (1=Not at all to 5=Extremely)." Participants will be asked to provide feedback on alert frequency by responding to the item "What do you think about the frequency of alerts?" using a 9-point scale ranging from "too few" (1) to "just right" (5) to "too many" (9). Participant-reported acceptability of the watch as a study device will be assessed using 4 items: "How difficult did you find the watch setup process? (1=Not at all to 5=Extremely)," "How much did you enjoy wearing the watch? (1=Not at all to 5=Extremely)," "How comfortable did you find the Apple watch? (1=Not at all to 5=Extremely)," and "How difficult was it to charge the watch? (1=Not at all to 5=Extremely)." Participants will also be asked the question "What impact do you think the watch had on your physical activity?" to which they can respond using a 5-point scale ranging from "increased activity a lot" to "decreased activity a lot." Participants will also be invited to provide general feedback by responding to the question "Do you have any other feedback on the research app that you would like to share with us?" using free text.

Cognitive Tasks

Several different cognitive tests will be conducted during the study, and in some cases, they will be repeated during the course of the study. App-based measures are a variety of active tasks, including the Trail Making Task (parts A and B), Spatial Memory, Stroop Test, Tapping Speed, Tower of Hanoi, Reaction Time, and 9-Hole Peg sourced from the Apple ResearchKit framework [6]. Laboratory-based cognitive measures include

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the Wechsler Memory Scale-III (WMS-III) Spatial Span (forward span) [24], Victoria Stroop Task [25], and the pen and paper version of the Trail Making Task (parts A and B) [23]. More information regarding the cognitive tasks is provided in Table 1.

Sensory Tasks

Several different sensory tests will be conducted during the course of the study, and in some cases, they will be repeated during the course of the study. We will use the dB HL Tone Audiometry task to assess hearing thresholds and the Amsler Grid to detect potential visual problems, sourced from the ResearchKit framework [6]. Our research team also developed an app-based version of the Ishihara Colour Deficiency Test [22]. Laboratory-based sensory tasks include a dB HL Tone Audiometry test administered using SHOEBOX Audiometry software (SHOEBOX Ltd) [26] and the 25-plate Ishihara Colour Deficiency Test. More information regarding the sensory tasks is provided in Table 1.

Alerts and Progress Reminders

As new tasks are available for completion, notifications will be sent to the participant via both the iPhone and Apple Watch (subject to them allowing notifications on their phone). The notification time of day is user configurable in the app. Repeated notifications will be sent if the participant misses completing tasks for 1 day and 3 days, as shown in Figure 5. Tapping on a notification on their iPhone will take the participant to the task list page of the app. The task list page also includes a progress ring that displays the number of days completed and the number left to be completed. A balloon animation will be displayed to participants as they complete the project milestones (eg, week 1 complete and week 2 complete).

Figure 5. Sample task reminder alerts from the Labs Without Walls (LwW) research app on an iPhone and Apple Watch.



Health Data Collection

As noted, a range of health data measures will be collected throughout the study. These will be accessed from the health app on the participant's iPhone, with their explicit on-device consent (see the *e-Consent* section). These data will be collected from the participant's iPhone and a paired Apple Watch as appropriate (if worn). Participants can change their consent at any time using phone settings. Requested health measures are presented in Table 3.

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Sleep data will be collected whenever the participant wears an Apple Watch while sleeping. For 1 week during the study, the participant will be asked to do so each night and will receive reminders to charge the watch in advance and put it back on before going to bed.

Table 3. Daily health, behavioral, and environmental data collected during the Labs Without Walls pilot study using an iPhone (Apple Inc) and an Apple Watch (Apple Inc).

Domain and measure	Input device	Are the data visible to participants in the app?
Energy used		
Active energy (kJ)	Apple Watch	Yes
Basal energy (kJ)	Apple Watch	Yes
Activity		
Exercise (minutes)	Apple Watch	Yes
Stand time (minutes)	Apple Watch	Yes
Hours with at least 1 minute standing (number)	Apple Watch	Yes
Step count (number)	Apple Watch	Yes
Walk and run distance (km to 3 decimal places)	Apple Watch	Yes
Flights of stairs climbed (number)	Apple Watch	Yes
Hours the Apple Watch is worn (hour, to nearest quarter hour)	Apple Watch	Yes
Heart rate		
Resting (beats per minute)	Apple Watch	Yes
Walking (beats per minute)	Apple Watch	Yes
Maximum (beats per minute)	Apple Watch	Yes
Variability (SD of the interbeat [RR[a]] interval between normal heart beats)	Apple Watch	No
Mobility		
Walking speed (km per hour)	iPhone and Apple Watch	Yes
Walking step length (cm)	iPhone and Apple Watch	Yes
6-minute walk: meters (to a maximum of 500 m)	iPhone and Apple Watch	No
Stair speed (up and down; km per hour)	iPhone and Apple Watch	No
Gait—double support time (percentage of total walk time)	iPhone and Apple Watch	No
Gait—walking asymmetry (percentage of total walk time)	iPhone and Apple Watch	No
Noise exposure		
Environmental (average and maximum)	Apple Watch	Yes
Headphones (average and maximum)	iPhone	Yes
Sleep		
Hours slept (number)	Apple Watch	Yes

[a]RR communicates the time between 2 successive heartbeats.

Data Analysis Plan

Statistical Models

To answer hypothesis 1, aggregate data and summary statistics will be reported on the number of successful consents, retention rate, survey and task completion rates, app and watch usability, feedback on alert frequency, and hours of watch wear. To answer hypothesis 2, qualitative data on usability will be analyzed using thematic analysis, and quantitative data will be collected via Likert-type scales and analyzed using summary statistics (eg, mean and range). To answer hypotheses 3 and 4, the variability in SPA and gender will be analyzed using multilevel modeling. Random coefficient regression models will be used to analyze time-varying covariates. To answer hypothesis 5, correlation analysis will be used to establish the validity of the app-based versions of cognitive and sensory tests against laboratory-based tests. Log transformations will be used for any nonnormal data needed for parametric testing. In general, categorical variables will be coded numerically from low to high (eg, low=1 and high=5). The threshold probability for rejecting the null hypothesis will be set as (2-tailed)=.05, unless otherwise specified, and 95% CIs will be reported.

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Data Exclusion and Missing Data

The data collected from the Apple Watch will be validated against the number of hours it has been worn each day. If the watch has been worn for <10 hours within a 24-hour period, data from that day will be excluded from the analyses. The average time taken to complete the surveys and tasks will also be checked for any outliers using box and whisker plots. Listwise or pairwise deletion or multiple imputation will be used to account for missing data where feasible and depending on what is most appropriate for the variables under consideration.

Results

Recruitment began in May 2022. Data collection was completed in February 2023. The main project outputs will be (1) peer-reviewed publications, (2) conference presentations, and (3) research briefs that explain the study outcomes in a shorter format designed for a general audience. The publication of the preliminary results is anticipated in 2023.

Discussion

Expected Findings

There is a scarcity of studies that have examined the feasibility and acceptability of app- and smartwatch-based research technologies among life-course samples. This study aims to fill this gap by demonstrating the validity of these technologies among adults aged 18 to 85 years recruited from the general population of Australia. On the basis of previous research indicating high ownership and use rates of smartphones and smartwatches in Australia [1], it is expected that Labs Without Walls will prove to be acceptable, usable, and engaging for the life-course sample in this study.

This study aims to provide the first evidence for daily variability in multidimensional SPA from an Australian life-course perspective. SPA has been shown to be associated with mortality, mental health, and functional health [8-10]. Although long-term variability in SPA is well evidenced [11,12], far fewer studies have explored variability in SPA on shorter timescales. The findings of this study could shed light on intraindividual variability in SPA and the interplay between SPA and other time-varying constructs, such as mood, stress, and physical activity.

In addition, this study is expected to be the first to explore stability or variability in gender expression across time, as well as the degree to which gender expression is impacted by other factors such as age and sex at birth. In research practice, gender is typically treated as a fixed, binary variable despite significant variations in the real world [17], where gender dynamism can be seen in at least 3 aspects: the meaning of gender has changed over time; there are significant cultural differences in the meaning of gender; and one's own gender and relationship with it can change, evolve, weaken, and galvanize across the lifetime [15]. This study aims to provide initial evidence exploring the degree of heterogeneity in gender dynamism at the individual level and between and within age and sex-at-birth groups.

The study also seeks to explore the cross-validity of app-based and laboratory-based administrations of common cognitive and sensory tests. Previous research has provided initial support for remote digital cognitive assessments in the context of cognitive aging [40] and psychiatric disorders [41]. The findings could add to the evidence base for remote digital cognitive assessments in the context of cognitive aging and psychiatric disorders.

Overall, the anticipated results of the Labs Without Walls study will inform the development of future iterations of the research app, aiming to answer ambitious questions regarding aging. We are interested in exploring the utility of other yet-to-be-used capabilities of the Apple Watch and iPhone in future studies. For example, GPS data collected using the Apple Watch or Apple smartphone can provide interesting insights into an individual's "life-space," which has been linked to well-being [42], mobility, and health [43,44]. Emerging behavioral and linguistic digital biomarkers of cognitive function are also promising [45,46]. By pilot-testing a Labs Without Walls approach, this study hopes to provide evidence for a platform that drives innovation in life-course aging research in Australia and beyond.

Strengths and Limitations

This study has several limitations. Owing to budget restrictions, the Labs Without Walls app is built only for iPhones and is not available to Android users. Although iPhones are by far the most commonly used smartphones in Australia [47], we acknowledge that there is a selection bias inherent in the restricted availability of the app. We also acknowledge that the pilot version of the Labs Without Walls app does not include the functionality to enable adults with vision impairment to interact with it. In addition, app-based research can raise ethical concerns, such as the potential for privacy violations and the use of sensitive personal data. As detailed earlier, the research team has taken measures to protect the rights of participants, including their data security. Overall, the potential benefits of app-based approaches for conducting more accessible, convenient, and enjoyable research that also deliver more complex longitudinal data warrant dedicated efforts to develop apps that overcome (to the greatest extent possible) potential shortcomings.

Conclusions

App-based studies have the potential to radically improve our understanding of processes that vary over microlongitudinal timescales. This study will provide evidence regarding the feasibility, acceptability, and usability of the Labs Without Walls research app and a paired Apple Watch for conducting research among a life-course sample of Australian adults. The feedback obtained will be used to improve future iterations of the app, explore preliminary evidence for intraindividual variability in SPA and gender expression across the adult life span, and explore the associations between the performance on app-based common cognitive and sensory tests and that on traditional common cognitive and sensory tests.

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Acknowledgments

The research team would like to thank the research volunteers who have joined the Labs Without Walls study from around Australia. This project received assistance for the design and setup of the backend data storage architecture from University of New South Wales Sydney Research Technology Services. Research Technology Services also partially supported the cost of hosting the backend storage of the study data via their cloud pilot scheme. Apple Watches were provided by Apple Inc, following a successful application to their Investigator Support Program [48]. Apple is not involved in the conduct of the research. This project is funded by the University of New South Wales Ageing Futures Institute. BB, LZ, and KJA are supported by the Australian Research Council Laureate Fellowship (FL190100011). SZ is supported by an Australian Government Research Training Program scholarship and the Australian Research Council Centre of Excellence in Population Ageing Research (project number CE170100005).

Data Availability

Study data sets and analytic codes will be deposited in publicly available repositories (where available and appropriate), as dictated by our funders, or presented in the main paper or additional supporting files whenever possible.

Authors' Contributions

BB contributed to conceptualization, methodology, software (review), resource accumulation, writing—original draft, writing—review and editing, supervision, and project administration. SZ contributed to methodology, software (review), resources, writing—review and editing, project administration, and data curation. LZ contributed to methodology, software (review), resources, writing—review and editing, and project administration. DA contributed to methodology, software (lead), resources, writing—review and editing, and data curation. RE contributed to writing—review and editing, project administration, and funding acquisition. MHH contributed to methodology and writing—review and editing. KJA contributed to conceptualization, methodology, software (review), resources, writing—review and editing, supervision, project administration, and funding acquisition.

Conflicts of Interest

None declared.

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Abbreviations

AWS: Amazon Web Services
NeuRA: Neuroscience Research Australia
SPA: self-perceptions of aging
WMS-III: Wechsler Memory Scale-III

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Protocol

Digital Outpatient Services for Adults: Development of an Intervention and Protocol for a Multicenter Non–Randomized Controlled Trial

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Abstract

Background: Health care services are being challenged by an increasing number of patients and limited resources. Hence, research investigating options to reduce costs and increase effectiveness is warranted. Digital outpatient services can provide flexible and tailored follow-up, improve patients' health literacy, and facilitate the identification of adverse courses of disease. However, previous research largely focused on disease-specific contexts and outcomes. Therefore, research on digital services investigating generic outcomes such as health literacy is warranted.

Objective: This article aims to describe the "digital outpatient service" intervention and present the protocol for an ongoing multicenter, nonrandomized trial evaluating this intervention.

Methods: Based on previous experiences and evidence-based knowledge, we developed this intervention through patient-journey maps in collaboration with each clinical specialty. The patients gain access to a mobile app for self-monitoring and patient-reported outcomes and a chat for contact between the patients and health care workers. The health care workers' dashboard includes a traffic light system to draw attention to the most urgent patient reports. In this multicenter, non–randomized controlled trial, patients are allocated to the control group receiving standard care or the 6-month intervention. Eligible patients are aged 18 years or older who receive outpatient care at the neurology, lung, pain, or cancer departments at 2 university hospitals in Norway. Our evaluation will include patient-reported outcomes, qualitative interviews, and clinical measures. The primary outcome will be health literacy using the Health Literacy Questionnaire. A sample size of 165 participants is split into a 1:2 ratio in favor of the intervention. We will analyze quantitative data in SPSS (IBM Corp) using descriptive statistics and logistic regression, and qualitative data using thematic analysis.

Results: This trial started in September 2021, and the intervention started in January 2022. Recruitment has ended, with 55 patients in the control group and 107 patients in the intervention group. Follow-up is expected to end in July 2023, with results expected to be obtained in December 2023.

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Conclusions: This study will evaluate an intervention facilitated by an already certified digital multicomponent solution, with intervention content based on patient-reported outcomes, health literacy, and self-monitoring. The intervention is specifically tailored to each participating center and the needs of their patients using patient journey maps. The comprehensive and generic evaluation of this digital outpatient service intervention is a strength as it targets a heterogeneous sample of patients. Thus, this study will provide important knowledge about the applicability and effects of digital health care services. As a result, patients and health care workers will gain a new, evidence-based understanding of whether and how digital tools may be used in clinical care.

Trial Registration: ClinicalTrials.gov NCT05068869; https://clinicaltrials.gov/ct2/show/NCT05068869

International Registered Report Identifier (IRRID): DERR1-10.2196/46649

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KEYWORDS

cancer; complex pain; digital solution; epilepsy; health literacy; interstitial lung disease; mHealth; outpatient; patient-reported outcome measures; remote monitoring; self-monitoring

Introduction

While advanced medicine contributes to prolonged life expectancy, the number of patients increases, and health service resources remain limited [1]. The reduction in hospital overnight capacity often increases the number of outpatient consultations. There is a risk of suboptimal resource use in current health services as these do not sufficiently meet individuals' needs for understandable health information [2,3]. Digital health solutions, which have emerged over the last decades, are embraced and called for by health authorities [4,5], and the recent COVID-19 pandemic has led to a fast, large-scale adoption [6]. Systematic reviews provide some evidence about the effects of digital solutions [7-9], but the extent to which digital services can improve patient outcomes or resource use has not been firmly established [10].

Any implementation of digital health solutions requires patients' and health care workers' understanding of why and how the digital possibilities are used [11,12]. Thus, it is necessary to attain a certain level of health literacy, defined as "the cognitive and social skills that determine the motivation and ability of individuals to gain access to, understand, and use information in ways which promote and maintain good health" [13]. Health literacy is closely related to patients' self-management and decisions related to their health [14], and eHealth literacy is linked to the use of digital solutions for health [12]. Low health literacy is associated with poorer health outcomes [15], lower self-management, and less use of digital health solutions [2,16]. It is reasonable to expect that better health literacy will improve self-management and the ability to benefit from digital health solutions [12]. The paucity of systematic reviews supports research focusing on the possibilities of digital interventions on health literacy [12,16].

Digital health solutions have embraced the use of patient-reported outcome measures (PROMs), allowing patients to subjectively report their health, pain, symptoms, and other relevant parameters [17]. PROMs allow health care workers to individualize patient care, although it has been challenging to demonstrate clinical effects in research [18]. However, effect evaluations should be part of studies on how PROMs are used in a clinical setting, and explanatory factors should be identified [19-21]. When routinely used, PROMs may support self-management and communication between patients and health care workers [17,19].

Allowing patients to digitally engage, self-monitor, and share data with health care workers has some obvious advantages and challenges [16,20,22,23]. From both the patient's and the health care worker's perspectives', digital solutions must be usable, clinically relevant, convenient, and evidence based. Patients rely on health care workers to assess their data; likewise, health care workers depend on patients to report the assigned health parameters without under- or overreporting symptoms [24]. Digital solutions in outpatient care may contribute to the prevention of complications or exacerbations by promoting contacts between patients and health care workers, allowing the latter to intervene earlier and to act according to clinical needs [25]. A recent systematic review found that using digital solutions increased patients' engagement in the technical usability of the solutions that affected their everyday lives [26]. Patients were also found to report more confidence in and knowledge of their own conditions and increased autonomy. These findings support those of earlier research on patients' engagement and the impacts of digital solutions [27].

There is limited research regarding the development and impacts of multicomponent digital solutions that include PROMs, remote monitoring, patient notifications, alerts for health care workers, asynchronous chats, and video consultations. An evaluation of a heterogenous range of digital health interventions found some positive effects on coping, quality of life, and pain in cancer treatment [28], as well as alleviation of both pain and functional disabilities in disorders associated with musculoskeletal pain [29]. Primary research in home monitoring of symptoms enables detection of exacerbations and progression in patients with interstitial lung disease (ILD) [30], but there is a need for evidence to support new ILD interventions [31]. There has been wide adoption and positive effects of mobile apps for patients with epilepsy, although less so in collaboration with health care workers [32]. The need to study homogeneous, static, and standardized interventions with a high level of fidelity [33] might explain why research on digital solutions is rarely conducted despite the frequency of their application in clinical care. Furthermore, clinical challenges remain, particularly regarding the integration of electronic health records into

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existing platforms [22]. There is limited knowledge about how digital systems fit current workflows and about how data and PROMs should be standardized to best generate registry data of value for other clinical sites and researchers [16,23]. Altogether, there is a paucity of empirical studies on the implementation and impacts of digital health solutions on outpatient care.

The purposes of this article are to (1) describe the digital outpatient service intervention and how it promotes digital outpatient care, and (2) present a multimethod protocol for a multicenter, nonrandomized trial to evaluate the intervention.

Methods

In the following, the development of the digital outpatient service intervention is presented before the details of the planned trial. The aim of the planned trial is to evaluate whether this intervention can have positive impacts on outcomes, including health literacy, health-related quality of life (HRQL), digital health literacy, satisfaction, and use of health service resources. Qualitative interviews will provide in-depth knowledge about the intervention from the perspectives of patients and health care workers. Furthermore, possible care pathways that ensure the quality of care and efficiency of remote monitoring in digital outpatient care will be investigated. The reporting of the intervention was guided by the Template for Intervention Description and Replication (TiDiER) [34], the protocol is reported according to the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) [35], and the PROMs are reported according to the SPIRIT PRO extension [36].

Development of the Digital Outpatient Service Intervention

Participants in the Development of the Intervention

The intervention was developed through collaboration among researchers from the Oslo University Hospital (OUH) intervention center, product managers at Dignio Connected Care, and health care workers and health care researchers from each participating department. These include the Department of Respiratory Diseases, the Department of Neurology, and the Department of Pain Management at OUH, as well as the Department of Cancer at the University Hospital of North Norway (UNN). To achieve an intervention suitable for patients' needs and available staffing resources, each department tailored the intervention to their patient group and organizational structure.

Patient and Public Involvement

Representatives from the Norwegian Cancer Society contributed to the project's development. Furthermore, the intervention for the neurology department is based on content developed together with patients and stakeholders. Health care workers are included as they constitute significant users in this project. The MyDignio app has been through several patient reviews before the current version.

Essential Elements and Aim of the Intervention

At the core of the intervention in all 4 departments is increased access to outpatient services. On the digital platform, patients can respond to PROMs and self-monitor parameters relevant to their conditions and have asynchronous, easy-access contact with health care workers. Designated health care staff will assess these data and act accordingly. These elements may facilitate flexible patient follow-up, building on a conceptual model that explains associations between health literacy and health outcomes, such as access to services, use of services, interactions between patients and health care workers, and patient self-care [37]. Patients can have an increased influence on their care and their contact with health care services through self-reported subjective experiences related to their care needs and their wishes for follow-up, in combination with their reports of objective measures such as blood pressure or oxygen saturation. This may facilitate timely contacts between patients and health care workers, where patients can receive guidance based on their questions, and likewise enable health care workers to identify patient struggles more accurately.

The Digital Platform for the Intervention: Dignio Connected Care

The platform for the digital outpatient service intervention is Dignio Connected Care [38], consisting of the multicomponent cloud-based system Dignio Prevent for health care workers and the MyDignio patient app. It is CE (Conformité Européenne: French for "European conformity") marked, satisfies all regulatory requirements for privacy and information security, and has been used in various clinical settings in Norway [39-41], the United Kingdom [42], and China [38]. The digital platform can be tailored to the needs of individual patients in consultation with their health care workers. Components can be added to individualize follow-ups (Tables 1 and 2) and will vary depending on the treatment at any given time. Examples of the interface are given in the Multimedia Appendices 1 and 2.

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Table 1. Patient-reported components used in the digital outpatient service.

Dignio component	Short description	Center using the component in its intervention
Patient-reported outcome measures (PROMs)	Standardized and individualized PROMs with numerical scales, single and multiple-choice answers, and free text.	• Cancer: Edmonton Symptom Assessment System (ESAS-r) [43], Eastern Cooperative Oncology Group (ECOG) scale assessing functional level [44], PROM version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) [45] and items on side effects of chemotherapy. The frequency of administration is per individual needs. • Lung: King's Brief Interstitial Lung Disease questionnaire (K-BILD) [46] assessing self-reported health every 12th week, and items on side effects (vomiting, rash, dizziness, abdominal pain, or diarrhea), administered every 4th week. • Neuro: PRO-EPI: A multidimensional epilepsy PROM with items on seizures, medication, living with epilepsy, and need for health services developed by clinicians and the Norwegian Epilepsy Network for health care workers [47,48], administered every 11th week. • Pain: Items on pain on a visual analog scale, intensity, location, side effects (constipation, sweat, anxiety, etc), compliance with current treatment and need for health services, administered per medication plan when changes to this plan are made.
Physiologic measures		
Blood pressure	Bluetooth devices or BYOD[a]	• Cancer, on clinical indication
Body temperature	Bluetooth devices or BYOD	• Cancer, on clinical indication
Body weight	Bluetooth devices or BYOD	• Lung, weekly
Spirometry values	Bluetooth device	• Lung, weekly
Oxygen saturation	Bluetooth device	• Lung, weekly
Pulse	Bluetooth devices or BYOD	• Lung, weekly

[a]BYOD: bring your own device.

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Table 2. Functionality for remote monitoring and communication.

Dignio component	Brief description
Tasks	• Health care workers can specify tasks for patients, such as performing daily activities, registering measures taken with the patients' own devices, or watching patient videos.
Thresholds	• Health care workers can define thresholds. The limit values are set, based on each patient's baseline, and follows the traffic light model, with green, yellow, and red alerts.
Notifications and triage	• When measures are outside defined thresholds, health care workers are notified. Deviating values, responses, and unanswered messages from patients are captured by an overview of patients in Dignio Prevent, where they are sorted by degree of urgency or severity (traffic light model). If the patient does not perform the defined tasks at the specified time, a warning is triggered. This can admittedly be turned off if desired.
Reminders	• Reminders can be sent to the patients as push-notifications in MyDignio, through email or SMS texts. When the task or measure is done, the reminders stop.
Messages or chat	• Patients and health care workers can send messages to each other and have an asynchronous dialogue when it is best for both parties. • Lung: patients are asked to upload photos of the results of any laboratory tests conducted and the results of a 6-minute walking test conducted at their local hospital every 12th week. • Neuro: patients are allowed to upload photos of seizures whenever relevant.
Video consultations	• A video consultation can be arranged if needed. A video room is created with an encrypted connection where the patient and health care worker can meet.
Information pages	• MyDignio has an information page that can be updated by health care workers from the web portal Dignio Prevent. It is possible to create an individual information page, create templates, and send updates to several patients.
Efficacy tools (templates)	
Templates for patient care	• Templates can be developed to facilitate a standardized follow-up at given times, allowing health care workers to monitor any changes in a timely manner.

Patient Journey Maps

In collaboration with each department, patient journey maps have been drawn [49] to target the potential for a digital outpatient service and assess how the use of digital tools may affect patient outcomes, patient flow, and health care workflow. Common challenges, visualized through the red exclamation marks (Figures 1 and 2), include limited health care worker resources, an overwhelming number of patients, time-consuming telephone calls, and the challenge of contacting patients at risk (see Multimedia Appendix 3 for further examples). Patients may have a limited overview of their parameters, including PROMs and clinical data, compromising their health literacy and self-monitoring.

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Figure 1. Patient journey map from the neurology department: as-is.

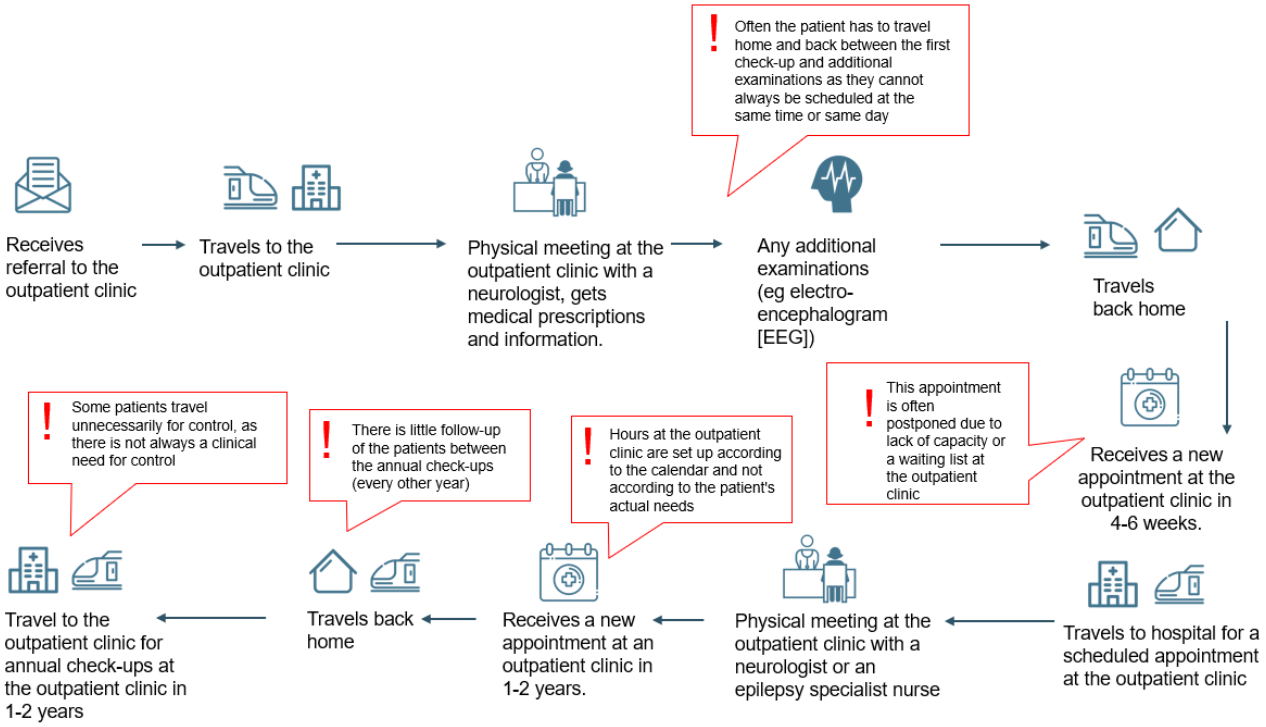
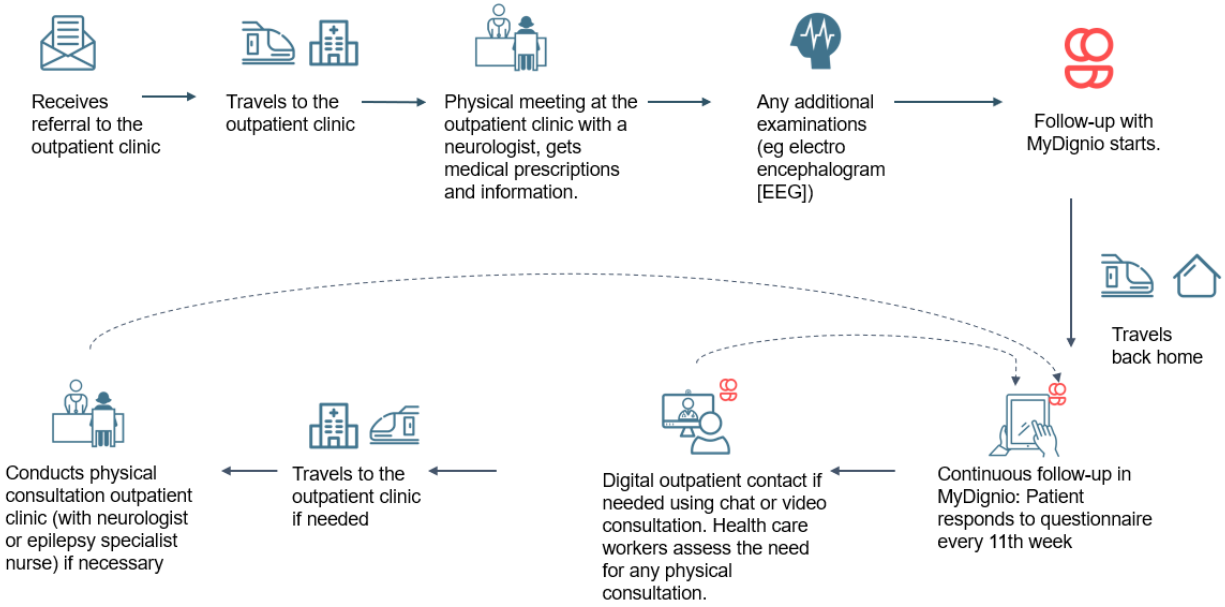


Figure 2. Patient journey map from the neurology department: to-be.



Information and Training

The patients receive a brief introduction and digital user manuals for the app. Patients using technical equipment such as spirometers are instructed to ensure correct technique and synchronization with MyDignio. Patients in the intervention group can contact their health care worker or a researcher for technical inquiries.

Most of the health care workers are familiar with the platform as they are involved in the development of the individual interventions at each center. All new health care workers receive training by the Dignio personnel or the assigned administrator at their center, and the training will be repeated upon request.

Training in interpreting scores reported by the patients is provided within each department based on the needs of the health care workers. For the majority of the involved health care personnel, the PROMs applied are already used paper-based in the clinics; thus, a dialogue between the programmers from Dignio Connected Care and the health care workers has facilitated the use of already standardized cutoffs.

Implementation is secured through the involvement of dedicated health care workers within each department that contributed to the development of the intervention, the summarizing of the "as-is," and the potential and suggestions of the "to-be" that had received training in the digital platform. In addition,

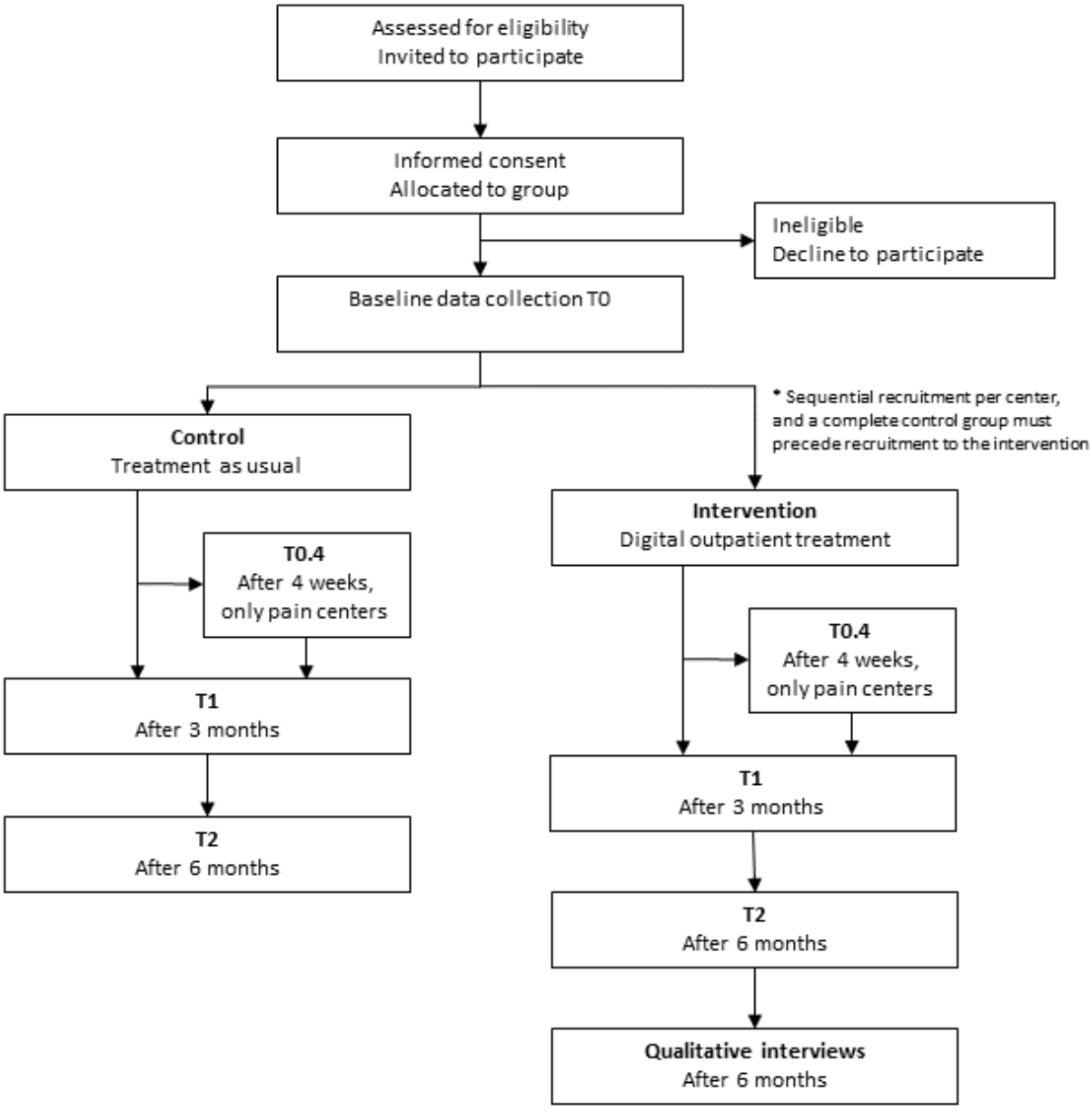
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designated health care workers were compensated for 10%-20% of their time to contribute to the intervention.

Study Design for the Planned Trial to Evaluate the Intervention

The study is a multicenter, non–randomized controlled trial with 2 treatment arms and a 6-month follow-up (Figure 3). The comprehensive evaluation is based on the method for assessment of telemedicine (MAST) [50], including elements regarding the purpose and maturity of the technology, how the health problems align with the technology, safety, clinical effectiveness, patient perspectives, economic aspects, organizational, and sociocultural, ethical, and legal aspects, followed by an assessment of cross border between countries, transferability, and generalizability to other contexts. The relevance of MAST lies in its thorough assessment of the preceding conditions and its multidisciplinary assessments. Patients are currently allocated to 1 of the 2 arms. At each department, recruitment to the control arm will be completed before inclusion in the intervention arm. The control arm will receive follow-up *per the* routines at each department, largely as described in the patient journey maps labeled "as-is" (Figures 1 and 2, and Multimedia Appendix 3). The intervention arm will receive our digital outpatient service. Quantitative measures are collected longitudinally, and qualitative interviews are conducted postintervention.

Figure 3. Flowchart of the multicenter non–randomized controlled trial.



Patient Participants and Recruitment

Patients at the Department of Respiratory Diseases, the Department of Neurology, and the Department of Pain Management at OUH, as well as the Department of Cancer at UNN, are eligible for participation in the study if they are 18 years of age or older, home-based, and able to fill out Norwegian questionnaires (Table 3). Both newly diagnosed or newly referred patients, those with a diagnostic history, and those already in outpatient care are eligible for inclusion.

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Eligible patients are identified through an outpatient consultation or through patient lists. All patients receive written and oral information about the project from a nurse or physician before giving their consent. The patients are not regarded as consenting participants until they have signed the consent form and filled out the baseline questionnaire. To reduce contamination in the intervention arm, patients must consent and fill out the baseline questionnaire before accessing the digital intervention.

The recruitment of patients to the qualitative interviews after the intervention is based on their consent to receive information regarding the interviews. Purposive sampling is applied to reach a heterogeneous sample with a balanced diversity in age, gender, and use of the intervention. Thus, in-depth knowledge can be obtained from both high and low users.

Table 3. Eligibility criteria for patients.

Patient groups	Inclusion criteria	Exclusion criteria
Patients with cancer	• Cancer • Receiving active treatment	• Life expectancy: less than 6 months • Expected need for follow-up: less than 6 months
Patients with interstitial lung disease (ILD)	• ILD	• Very low degree of function with risk of cognitive influence
Patients with epilepsy	• Epilepsy	• Complex causes of epilepsy • Severe comorbidity • Other planned or ongoing assessment and treatment, including assessment of unexplained illness or testing of medication
Patients with long-term, complex pain	• Drug testing, adjustment, and dose reduction • Self-administering medication	• Comorbidity that directly affects the drug adjustment • Interference with other ongoing treatment • Cognitive impairment • Not living at home

Health Care Personnel Participants

Health care workers in the hospital departments are eligible for the qualitative interviews if they are affiliated with the included departments and have had a role in this project. This group includes leaders and health care workers, such as nurses and physicians, with hands-on management of patient follow-up through the intervention.

Randomization and Blinding

This is a non–randomized controlled trial without blinding. Both patients and health care workers are familiar with the treatment arm to which the participants belong during the study.

Outcomes to be Measured

Overview

The study will consider the elements affected by both external factors in the health care services and internal factors held by the patient. Patients will self-report on the questionnaires (Tables 4 and 5). Clinical parameters and information on the use of resources will be collected from electronic medical records. The primary outcome is the health literacy questionnaire (HLQ) domain 9 “understanding health information well enough to know what to do” [51]. This domain encompasses health actions relevant for a digital service, such as basic reading and understanding of health information, following instructions from health care workers, and the ability to fill out forms correctly. The secondary outcomes are health literacy, eHealth literacy, HRQL, and acceptability of the digital intervention (Table 4).

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Table 4. Outcome measures for health literacy, health-related quality of life, digital health literacy, satisfaction, and COVID-19.

Measures, domains, and variables	Response options	Scale	Interpretation	Time point		
				T0	T1	T2
Health literacy						
Health literacy questionnaire (HLQ) (5 of 9 domains)						
• Feeling understood and supported by health care providers (4 items) • Having sufficient information to manage my own health (4 items) • Actively managing my own health (5 items)	All items have the same response options: strongly disagree, disagree, agree, or strongly agree	1-4	A higher score indicates a higher level of health literacy	✓	✓	✓
• Ability to actively engage with health care providers (5 items) • Understanding health information well enough to know what to do (5 items)	All items have the same response options: cannot do or always difficult, usually difficult, sometimes difficult, usually easy, or always easy	1-5	A higher score indicates a higher level of health literacy	✓	✓	✓
eHealth literacy						
eHealth literacy questionnaire (eHLQ; 7 of 7 domains)						
• Using technology to process health information (5 items) • Understanding health concepts and language (5 items) • Ability to actively engage with digital services (5 items) • Feel safe and in control (5 items) • Motivated to engage with digital services (5 items) • Access to digital services that work (6 items) • Digital services that suit individual needs (4 items)	All items have the same response options: strongly disagree, disagree, agree, or strongly agree	1-4	A higher score indicates a higher level of eHealth literacy	✓	✓	✓
Health-related quality of life (HRQL)						
RAND 12 (2 of 2 domains)						
• Physical health composite (6 items)	All items have their individual scoring, and the physical composite score is based on the following 6 items: • General health (excellent, very good, good, fair, or poor) • Moderate activities, and • Climb several flights of stairs, are scored on: limited a lot, limited a little, or not limited at all • Accomplished less (physical), and 5. Limited in any kind of work, are scored on yes or no • Pain interference (not at all, a little bit, moderately, quite a bit, or extremely)	0-100	A higher score reflects good physical health.	✓	✓	✓

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Measures, domains, and variables	Response options	Scale	Interpretation	Time point		
				T0	T1	T2
• Mental health composite-12 (6 items)	• Accomplished less (emotional) (yes or no) • The following items have the same scoring: (all of time, most of the time, a good bit of the time, some of the time, a little of the time, or none of the time) • Did work less careful • Calm and peaceful • Energy • Downhearted and blue • Social limitations (time)	0-100	A higher score reflects good mental health.	✓	✓	✓
Service User Technology Acceptability Questionnaire (SUTAQ; intervention arm only)						
SUTAQ (5 of 5 domains)						
• Perceived benefit (9 items) • Kit as a substitute (3 items) • Satisfaction (3 items)	• All items have the same response options: completely agree, moderately agree, mildly agree, mildly disagree, moderately disagree, or strongly disagree	1-6	A higher score reflects higher satisfaction.		✓	✓
• Privacy and discomfort (4 items) • Care personnel concerns (3 items)	• All items have the same response options: completely agree, moderately agree, mildly agree, mildly disagree, moderately disagree, or strongly disagree	1-6	Reversed scale, thus higher score reflects a higher concern.		✓	✓
Satisfaction in general						
• Satisfaction with the outpatient service in general (3 items)	All items have their individual scoring. • Satisfaction with treatment (very satisfied, satisfied, neither satisfied nor dissatisfied, dissatisfied, or very dissatisfied) • 2. Benefit from treatment (much better, somewhat better, stayed the same, somewhat worse, or much worse)	1-6	A higher score reflects higher satisfaction.	✓	✓	✓
• Satisfaction with the outpatient service in general (3 items)	• Safer with digital outpatient services (Yes; Feel free to elaborate/ No; Feel free to elaborate)	Y/N	Yes–safer	✓	✓	✓
COVID-19						
• Perceived safety related to the COVID-19 pandemic (2 items)	• Previously infected (yes or no)	Y/N	Yes–previously infected	✓	✓	✓
• Perceived safety related to the COVID-19 pandemic (2 items)	• Fear of COVID-19 (never, seldom, sometimes, often, or almost always)	1-5	A higher score reflects more fear	✓	✓	✓

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Table 5. Background variables and clinical outcomes.

Variables	Response options	Time point		
		T0	T1	T2
Background variables				
Gender	Male, female, or unwilling to answer	✓		
Marital status	Unmarried, married, cohabitant, widow or widower, divorced, separated, registered partner, divorced partner, or surviving partner	✓		
Education	No education or preschool education, elementary school, high school without diploma, high school with diploma, bachelor's degree or university or college lower level, master's degree or university or college higher level, or PhD or researchers training	✓		
Employment status	Full-time, part-time, home-employed, pursuing further education, unemployed, disabled, or retired	✓		
Lifestyle habits (3 items)	(1) Smoking (yes or no), (2) snuff (yes or no), and (3) alcohol consumption (yes, no, and if yes, how often)	✓		
Digital skills (3 items)	(1) Use of smartphone (yes or no), (2) use of tablet (yes or no), and (3) use of computer (yes or no)	✓		
Use of mobile health apps	Yes or no–if yes, specify which apps	✓	✓	✓
Clinical variables (from the medical record)				
Primary diagnosis		✓		
Time since diagnosis or start of condition	Duration of condition	✓		
Medication	Current treatment and any changes	✓	✓	✓
Comorbidities	Number of comorbidities	✓		
Use of health care resources (from the medical record)				
Contact with the outpatient clinic	Contact type (physical consultation, video consultation, telephone call, or other), planned or acute, and number of each			✓
Use of the digital service (dose of intervention)	Contact type (PROM[a] response, task, chat, video, or other) and the number of each			✓

[a]PROM: patient-reported outcome measure.

Health Literacy

The HLQ is a multidimensional measure of health literacy, with 44 questions across 9 domains. The HLQ is validated for adults using various modes of administration, including computer-based [51,52]. The HLQ was developed in Australia, translated into Norwegian, and used in studies on chronic diseases [51,52]. To reduce overlap with the domains of the eHealth literacy questionnaire (eHLQ), 5 of the HLQ domains (domain 1,2,3,6, and 9) that represent all 3 levels of the Nutbeam model have been included in this study [14]. Domains 2 and 9 are at the basic level; domains 1, 3, and 6 are at the communicative level, while domain 3 is at the critical level of health literacy [51].

eHealth Literacy

The eHLQ is multidimensional with the same origin as the HLQ, assessing people's interactions with digital services based on the eHealth literacy framework [53]. The eHLQ contains 35 questions over 7 domains, and the full questionnaire is applied in this study. Although the eHLQ is translated into Norwegian and used in Norway, it is not yet validated. Validation in Denmark shows good psychometric properties [53].

HRQL

To assess HRQL, the patients fill out the RAND-12 [54,55], an abbreviated version of its predecessor, the SF-36. The 12 items are summarized into 1 physical and 1 mental health composite. The RAND-12 is validated in Norwegian [56].

Acceptability of the Digital Intervention

To assess acceptability among the participants assigned to the intervention arm, the patients fill out the service user technology acceptability questionnaire (SUTAQ). Acceptability refers to whether a system is good enough to satisfy users' needs and requirements. The SUTAQ also assesses the importance of having contact with health care workers and whether this may affect patients' acceptance [57,58]. The SUTAQ has 22 items across 5 domains. The participants are instructed to keep the digital outpatient service intervention in mind when responding. The SUTAQ has been translated into Norwegian, psychometrically tested [58], and is used in Norway for patients with type 1 and type 2 diabetes.

Qualitative Evaluation Measures

Individual qualitative interviews will be conducted following the same structure for patients in the intervention group and the health care workers. The interviews will explore the

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interviewees' perceived satisfaction with the digital outpatient service, and security in and beyond pandemic situations. The semistructured guide has been developed by the research team, inspired by topics on innovation assessment [59] and is added as a Multimedia Appendix 4. The aim of the qualitative interviews is to gain in-depth knowledge about the components of the intervention, how they are used, and whether and how they are perceived as useful. The interviews are also intended to obtain in-depth knowledge about how the digital intervention differs from traditional consultations and how these differences are perceived. In line with the primary outcome of health literacy obtained from the quantitative measures, any experiences of improved or otherwise affected health literacy will be investigated. Accordingly, the same guide will be applied to health care workers, tailored to their profession.

Sample Size

An *a priori* sample size calculation was conducted to estimate the number of patients from all departments necessary to recruit based on changes from the baseline to the 6-month follow-up in the generic primary outcome "understanding health information well enough to know what to do" (HLQ domain 9) [51]. Previous research was summarized to find the most fitting SD. No similar studies were identified. Thus, an SD of 0.6 was applied in this study's calculations based on 3 identified studies: one study on patients with epilepsy, reporting an SD of 0.77 after 18 months of follow-up [60], and studies reporting an SD of 0.42 in patients after kidney transplant [61] and an SD of 0.025 in the Danish norm data [62]. With no previous description of a minimally important difference for this exact domain, a 10% change on this scale of 1-5 was calculated, ending in a 0.5-unit difference between the groups. The analysis was based on a power of 0.90, an SD of 0.6 from the outcome measure, and a 2-sided significance test. The effect size was a 0.5-unit difference between the groups on a scale of 1-5, with a 20% dropout and an opportunity to perform controlled analyses. With a 1:2 recruitment ratio, this study must have a minimum of 55 participants in the control group and 110 participants in the intervention group. This is equivalent to a total sample size of 165 participants. When divided among the 5 departments, each department must recruit 33 participants. However, the total sample size is a shared goal. The intention was a 1:1 allocation of participants; however, to provide a more efficient recruitment when recruitment was slow, a statistician was consulted, suggesting an alternation in the allocation to ensure a sufficient sample size in favor of both groups.

For the qualitative interviews, this study needs a sample of 12-15 patients from the intervention group [63] and 12-15 health care workers or stakeholders that have experience with the tailoring of, or patient follow-up, using the digital outpatient intervention.

Analysis

Statistical Analysis

The baseline and follow-up variables will be presented descriptively. Continuous variables will be analyzed using the mean and the SD for normally distributed data and the median and the range if the data are skewed. Categorical data will be presented as counts and percentages. The mean change will be estimated by subtracting the baseline score from the follow-up score, both at 3 months and 6 months. Differences in mean changes in short-term and long-term variables will be modeled using a one-way ANOVA. To adjust for possible confounders, logistic regression models will include age, gender, education, and hospital department. Missing data will be handled according to the syntax and protocol of the standardized instruments, such as HLQ, eHLQ, SUTAQ, and RAND-12. The missing data in terms of dropout has been accounted for in the power analysis.

Qualitative Analysis

Individual interviews with patients and health care workers will be audio-recorded, transcribed verbatim, and analyzed using thematic analysis [64], with the following steps: (1) familiarize with the data; (2) generate initial codes; (3) search for themes; (4) review themes; (5) define and name the themes; and (6) produce the report. Examples of data extracts and codes will be presented alongside the final thematic analysis results. Patient interviews will be analyzed by 2 researchers (HH and EF), while health care worker interviews will be analyzed by HH, EF, and an associated member of the research team. Any conflicts during the analysis will be resolved through discussion as a natural part of the analysis process. Preliminary findings will be presented to the project group to add reflections and nuances not already addressed.

Data Security

Digital consent and digital responses to the questionnaires are collected using a service for sensitive data developed at the University of Oslo. The service for sensitive data is designed for storing and processing sensitive data in compliance with the Norwegian "Personal Data Act" and "Health Research Act." The questionnaires are sent to the participants through the pretty good privacy-encrypted version of the University of Oslo web-questionnaire service "Nettskjema" which demands a governmental ID portal for login and allows secure data harvesting. A personal, secure link to the follow-up questionnaires is sent to the participants' email or mobile phone, with 1 reminder after 6-7 days in the case of unanswered questionnaires, followed by a phone call if they still have not filled out the pending questionnaire after 1 more week.

Ethics Approval

The regional ethical committee (REC) in Norway prereviewed the protocol and judged the project as outside its mandate according to the Norwegian Health Research Act (REC south-east reference number 252051). The project was reviewed by the institutional data protection officer at UNN regarding the cancer department (reference number 2021/4942) and the data protection officer at OUH regarding the remaining departments (reference number 21/06826); both granted approval.

Results

Trial Status

Recruitment started in September 2021, and as of December 14, 2022, a total of 55 patients had been enrolled in the control

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group, and 101 patients had been enrolled in the intervention group. It is expected that the recruitment will be completed by the end of December 2022 and that the 6-month follow-up for all participants will end by June 2023. Qualitative interviews will be conducted successively as the participants complete their 6-month assessments. All study results are expected to be ready by the end of 2023.

Deviations From the First Registration in Clinical Trials

Initially, this study was a 2-arm trial with a 1:1 recruitment ratio. Recruitment was planned in 4 departments, and the department of pain management aimed at recruiting both patients with chronic pain as well as acute postoperative pain. However, due to unforeseen challenges, the recruitment of patients with postoperative pain was terminated in March 2022. Thus, a new power analysis was performed with reduced heterogeneity. Additionally, the follow-up period was shortened from 12 months to 6 months due to the lengthy process of the risk and vulnerability assessment before the use of the digital outpatient service in the hospital setting, which had not been done before this study.

Discussion

Evidence regarding the need for multicomponent digital outpatient services and their possible effects on outcomes in a real-life setting remains scarce [12,16]. Therefore, this study will likely provide valuable knowledge as it aims to assess the impact and acceptability of digital outpatient services and their effects on health literacy, HRQL, and the acceptability of the digital intervention. The analyses will also address how the digital outpatient intervention is used. In-depth perspectives gathered from the qualitative interviews with patients and health care workers will add value to the qualitative findings. This study will provide important knowledge about the applicability and effects of digital health care services. As a result, patients and health care workers will gain a new, evidence-based understanding of whether and how digital tools may be used in clinical care.

The described intervention will be delivered through a multicomponent digital platform (Dignio) that has been implemented and studied in various health care settings in recent years. This way, digital usability is considered ready for evaluation on a larger scale in specialized outpatient care services. By collaborating with the clinical environment and the patient's journey to identify the best potential for the digital intervention, the relevance of the intervention is increased. Likewise, complementing the digital platform with PROMs and clinical measures based on the expected needs according to the patient's diagnosis will likely facilitate use among patients and health care workers. Together, these will add value to this study's evaluation of health literacy, HRQL, and the acceptability of the intervention.

This intervention will support and enhance patients' understanding of health information well enough to know what to do, make them feel understood and supported by health care workers, ensure that they have sufficient health information, support their feeling of actively managing their health, and improve their ability to interact with health care workers. These actions are directly transferable to the HLQ and this study's outcome domains [51]. Additionally, the intervention will support patients' use and understanding of digital solutions for health and thus their engagement, as well as ensure their access to digital solutions that work, suit their needs, and keep their health data secure, all of which are transferable to digital health literacy [12,53]. Altogether, this intervention will target and measure the domains of health literacy skills at the basic, communicative, and critical levels [14]. This study will also consider factors that are affected by external factors in health care services and the internal factors held by the patient. As this intervention will be individualized according to each patient's needs, it can facilitate health actions and lead to an increase in health literacy.

This study describes how the digital outpatient service intervention will be explored in a multicenter, nonrandomized controlled trial with 2 treatment arms and a 6-month follow-up. The strengths of the current trial include its focus on patient-reported health literacy in a digital health intervention that targets a diverse sample of outpatients. Previous interventions have tended to focus on a single component, target a very specific sample, and primarily use clinical end points. Whether or not a patient chooses to use a digital intervention perhaps relies more on their health literacy and motivation to self-monitor, and a positive change in clinical end points may primarily be perceived as a potential result of their health literacy levels and self-monitoring. Moreover, the multimethod design inspired by the MAST [50] will provide quantitative data on the effects of the intervention on health literacy and in-depth qualitative knowledge on the acceptability of the intervention among patients and health care workers. Overall, the proposed trial will evaluate the effects while providing an understanding that can facilitate lasting changes in how outpatient specialty health services use digital solutions.

The proposed trial is designed as a nonrandomized trial, which inherently includes some risk of bias. Thus, differences may occur between the control group and the intervention group. The groups will therefore be compared at baseline to detect any imbalances that would need handling in the statistical analysis. Changes in outcome measures will be calculated based on the change from baseline to follow-up, thus handling the fact that individuals might have a different baseline score. Further, we did not pilot the intervention within each group before the full trial, which could have revealed weaknesses relevant to the full trial. Lastly, the outcomes measured by standardized questionnaires have not been used to screen for any need for a more tailored intervention. That is, it could have been relevant to tailor the intervention based on the participants' scores in health literacy or digital health literacy. Individual health care workers have individualized patient follow-up based on the patients' needs, but not through systematic screening. Also, we do not have data on the occurrence of any comorbidities in the sample, which could have been a relevant confounder added to the already described ones. No patients were specifically involved in the development of this intervention or the design of this trial. However, the intervention toward patients with

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epilepsy was developed alongside user representatives before this study.

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Data Availability

Data sharing is not applicable to this paper as no data sets were generated or analyzed during this study. Future data collected as part of the study described in this protocol will be made available from the corresponding author upon reasonable request.

Authors' Contributions

All authors had a substantial contribution in the development of the intervention. HH drafted and revised the manuscript and has the responsibility for data collection in the ongoing trial. HH wrote the PRO specific content of the protocol. CE, AMH, TKK, and LSL are responsible for local recruitment and intervention. CE, LPG, AMH, TKK, LSL, TML, and EF commented and revised on versions of the draft, and all approved the final manuscript. The funding proposal was written by EF, TKK, Dignio, and other partners.

Conflicts of Interest

None declared.

Multimedia Appendix 1
DignioPrevent screenshot.
[DOCX File , 122 KB - resprot_v12i1e46649_app1.docx]

Multimedia Appendix 2
MyDignio.
[DOCX File , 122 KB - resprot_v12i1e46649_app2.docx]

Multimedia Appendix 3
Patient journey maps from all departments.
[PDF File (Adobe PDF File), 381 KB - resprot_v12i1e46649_app3.pdf]

Multimedia Appendix 4
Interview guides.
[DOCX File , 24 KB - resprot_v12i1e46649_app4.docx]

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Abbreviations

CE: Conformité Européenne
eHLQ: eHealth literacy questionnaire
HLQ: health literacy questionnaire
HRQL: health-related quality of life
ILD: interstitial lung disease
MAST: method for assessment of telemedicine
OUH: Oslo University Hospital

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PROM: patient-reported outcome measure
REC: regional ethical committee
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
SUTAQ: service user technology acceptability questionnaire
TiDiER: Template for Intervention Description and Replication
UNN: University Hospital of North Norway

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Protocol

Financial Health of People Living With Dementia and Their Informal Care Partners: Protocol for a Mixed Methods Study

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Abstract

Background: There is a growing body of academic literature focusing on the significant financial burdens placed on people living with cancer, but little evidence exists on the impact of rising costs of care in other vulnerable populations. This financial strain, also known as financial toxicity, can impact behavioral, psychosocial, and material domains of life for people diagnosed with chronic conditions and their care partners. New evidence suggests that populations experiencing health disparities, including those with dementia, face limited access to health care, employment discrimination, income inequality, higher burdens of disease, and exacerbating financial toxicity.

Objective: The three study aims are to (1) adapt a survey to capture financial toxicity in people living with dementia and their care partners; (2) characterize the degree and magnitude of different components of financial toxicity in this population; and (3) empower the voice of this population through imagery and critical reflection on their perceptions and experiences relating to financial toxicity.

Methods: This study uses a mixed methods approach to comprehensively characterize financial toxicity among people living with dementia and their care partners. To address aim 1, we will adapt elements from previously validated and reliable instruments, including the Comprehensive Score for Financial Toxicity and Patient-Reported Outcomes Measurement Information System, to develop a financial toxicity survey specific to dyads of people living with dementia and their care partners. A total of 100 dyads will complete the survey, and data will be analyzed using descriptive statistics and regression models to address aim 2. Aim 3 will be addressed using the process of "photovoice," which is a qualitative, participatory research method that combines photography, verbal narratives, and critical reflection by groups of individuals to capture aspects of their environment and experiences with a certain topic. Quantitative results and qualitative findings will be integrated using a validated, joint display table mixed methods approach called the pillar integration process.

Results: This study is ongoing, with quantitative findings and qualitative results anticipated by December 2023. Integrated findings will enhance the understanding of financial toxicity in individuals living with dementia and their care partners by providing a comprehensive baseline assessment.

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Conclusions: As one of the first studies on financial toxicity related to dementia care, findings from our mixed methods approach will support the development of new strategies for improving the costs of care. While this work focuses on those living with dementia, this protocol could be replicated for people living with other diseases and serve as a blueprint for future research efforts in this space.

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KEYWORDS

avoiding care due to cost; care rationing; cost; delayed care due to cost; dementia; economic strain; financial burden; financial distress; financial hardship; financial strain; financial stress; financial toxicity; MCI; mild cognitive impairment; out-of-pocket costs; out-of-pocket spending

Introduction

There are significant financial burdens placed on people living with chronic, complex medical conditions and their care partners. The growing body of evidence primarily focuses on people with cancer and the subsequent adverse effects of financial hardship due to the unchecked rising costs of cancer care [1,2]. This treatment-related financial strain of cancer care for people diagnosed and their family members has been coined financial toxicity. Financial toxicity can impact multiple domains of life, including behavioral (eg, rationing medications or medical care due to costs), psychosocial (eg, depression associated with medical costs), and material (eg, bankruptcy, loss of income, and debt) [3-5]. It can take the form of both direct costs (eg, copays for appointments and medication) and indirect costs (eg, lost income from a patient or care partner's inability to work).

There is mounting evidence that people living with dementia and their care partners face limited access to health care, employment discrimination, income inequality, and higher burdens of disease [6]; however, the majority of evidence surrounding financial toxicity has focused on the population with cancer [7]. Previous research highlights the high cumulative financial burden of dementia (particularly in the final years of life) [8-10]. Other studies have quantitatively examined the relationship between financial difficulty and care partner mental health [11]. Yet few studies have combined qualitative and quantitative methods to examine the complex behavioral, psychosocial, and material impacts of dementia and dementia-related care costs. There remains limited knowledge surrounding how these domains of financial toxicity are experienced by people living with dementia and their families, this knowledge is essential to inform system-level solutions. The Comprehensive Score for Financial Toxicity (COST) measure is a reliable screening tool within the cancer space, but a similar metric does not exist within the dementia space [12].

The purpose of this study is to comprehensively characterize the financial burdens experienced by people living with dementia and their care partners using a mixed methods approach. This study is guided by the following aims: (1) adapt a survey to capture financial toxicity in dyads of people living with dementia and their care partners, (2) characterize the degree and magnitude of different components of financial toxicity among people living with dementia and their care partners (eg, out of pocket expenses, financial stress, and retirement savings), and (3) empower the voice of people living with dementia and their care partners through images and critical reflections of their perceptions and experiences related to financial well-being and hardship due to dementia using "photovoice," a creative, qualitative method. Results of this study will support the identification of primary drivers of financial toxicity for potential system-level solutions to mitigate patient burden.

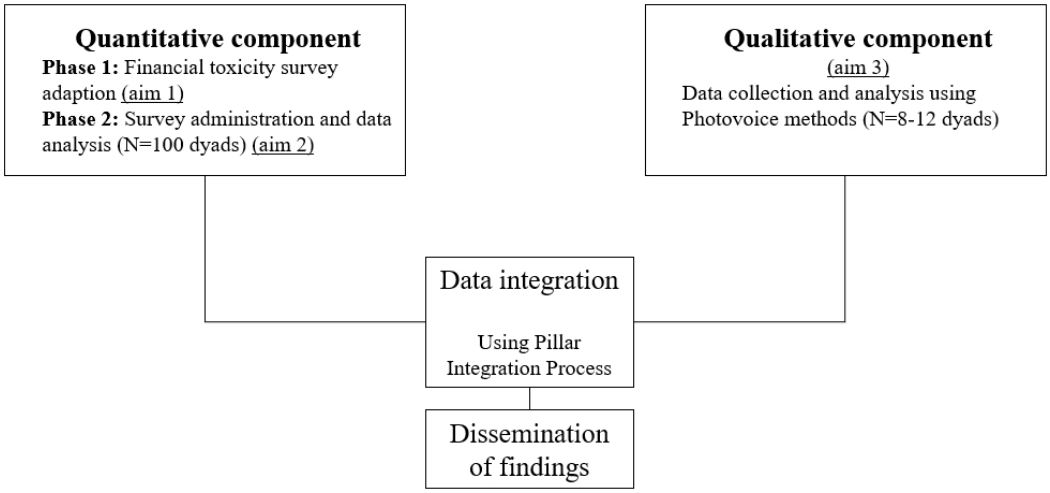
Methods

Study Design

This study will use a convergent mixed methods design to comprehensively characterize financial toxicity among people living with dementia and their care partners. Quantitative methods include survey adaptation (aim 1) and administration and analysis (aim 2). Qualitative photovoice methods will be used to address aim 3. Quantitative and qualitative data will be collected concurrently within a similar time frame, analyzed independently, and then integrated using a validated, joint display table approach called the pillar integration process (PIP) [13]. (See Figure 1 for an overview visualization of quantitative and qualitive component data integration)

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Figure 1. Quantitative and qualitative components and data integration overview.



Quantitative Methods

A financial toxicity survey will be adapted to capture sociodemographic data, out-of-pocket expenses, and cost-coping strategies of the people living with dementia and their primary care partners. Adapted elements from validated instruments include the Patient-Reported Outcomes Measurement Information System (PROMIS) [14], COST [12], the Institute for Medical Technology Assessment Productivity Cost Questionnaire (iPCQ) [15], and the Cost of Care Index [16]. (See Table 1 for adapted elements from validated instruments included in the survey)

The survey will then be administered to 100 participant dyads of people living with dementia and their care partners. The study includes a projected sample size of 100 dyads (200 total participants). We chose a sample size of 200 for our survey study based on a power analysis conducted to detect even a small effect size (Cohen *d*=0.2) with low to moderate variability of SD 0.5-1.0. The power analysis indicated that a sample size of 200 would be sufficient to detect this small effect size with 80% power at a significance level of .05 (See Table 2 for power analysis and sample size calculations).

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Table 1. Concepts, measurement instruments, psychometric properties, and references.

Concept and measurement instruments	Psychometric properties	References
• General health of person living with dementia and care partner: Perceived General Health (Likert scale; 1 item) • Mental health of person living with dementia and care partner: Perceived Mental Health (Likert scale; 1 item)	• Internal consistency: Cronbach α of .73-.81 have been reported for physical and mental health reporting items [17] • Test-retest reliability: ICCs[a] were greater than 0.85 for physical and mental health scores [18]. • Construct validity: physical function measures have high correlations with conceptually related measures ranging from 0.43 to 0.82, demonstrating strong convergent validity [19]. • Discriminant validity: Patient-Reported Outcomes Measurement Information System physical function measures show weak correlations with dissimilar domains, indicating good discriminant validity. [20]	Patient-Reported Outcomes Measurement Information System Questionnaire [14]
• Financial toxicity for dyad: Perceived Likelihood of Various Financial Costs (Likert scale; 5 items)	• Internal consistency: Cronbach α of .73-.86 have been reported for general financial situation and impact of illness on financial situation items [21] • Test-retest reliability: cost measures have been reported to have ICC of 0.80 [12] • Construct validity: the Comprehensive Score for Financial Toxicity measures of financial toxicity are shown to have good predictive validity and be multidimensional in a sample of individuals with chronic conditions [22] • Discriminant validity: discriminant validity has been reported as acceptable when compared to the Financial Index of Toxicity and Breast Cancer Finances Survey Inventory [23]	Comprehensive Score for Financial Toxicity tool [12]
• Amount of missed work for the person living with dementia and for the care partner: Perceived Missed Work (Likert scale; 1 item)	• Internal consistency: interitem correlation has been reported to range from 0.42 to 0.62 for productivity cost items, including absenteeism [24]. • Test-retest reliability: ICCs for absenteeism have been reported as greater than 0.88, indicating overall good reliability [24]. • Construct validity: confirmatory factor analysis found a 3-component solution accounting for 82% of the total variance, similar to the original study of the Institute for Medical Technology Assessment Productivity Cost Questionnaire [24] • Discriminant validity: discriminant validity has been reported as acceptable when included in a comprehensive questionnaire [25]	Institute for Medical Technology Assessment Productivity Cost Questionnaire [15]
• Financial toxicity of dementia care for dyad: Perceived Likelihood of Various Financial Costs (Likert scale; 5 items)	• As the Cost of Care Index is not a specific instrument, it does not have standardized psychometric properties such as reliability or validity. It is primarily used to compare the relative cost of living and health care expenses in different geographies.	Cost of Care Index [16]

[a]ICC: intraclass correlation coefficient.

Table 2. Power analysis and sample size calculations.

	Low variability (SD 0.5)	Moderate variability (SD 1.0)	High variability (SD 1.5)
Small (Cohen *d*=0.2)	125	252	405
Medium (Cohen *d*=0.5)	32	64	102
Large (Cohen *d*=0.8)	14	28	43

Eligible participants with dementia will (1) be at least 40 years old and (2) have a diagnosis of dementia of any type (determined by self- or proxy-report by caregiver). The age range of 40 years and older was chosen, as it provides a more inclusive view of the population with dementia and has been shown to be a critical, but less understood time period in dementia-related pathology [26,27]. Eligible care partners must (1) be at least 21 years old; (2) identify as the primary care partner of the person with dementia; and (3) be able to read and speak English. Dyads must live together in the same household and will be excluded if they reside in an assisted living home, nursing home, or other long-term care setting. The survey can be completed by the dyad together or by the caregiver on behalf of the family unit.

Dyads will be recruited through several local, regional, and national dementia- and caregiver-specific community support organizations, including the Duke Dementia Family Support Program, Dementia Inclusive Durham, Durham Center for Senior Life, Family Caregiver Alliance, and the National Council of Dementia Minds. Study information and flyers will be shared through web-based and in-person events offered by these organizations. Study information will also be shared

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through a national social media campaign using Facebook and Reddit. Interested individuals will be able to access the eligibility screening electronically using a link or QR code or contact the study team directly to determine eligibility. Our social marketing plan was developed with guidance and support from the Duke Clinical and Translational Science Institute Recruitment Innovations Center. We will use an adaptive recruitment method and review recruitment and enrollment every week through weekly team meetings. Changes will be made to recruitment strategies as necessary to reach our projected samples.

If eligible, participants will complete the survey electronically through REDCap's survey distribution platform or by hardcopy depending on their preference. Participant responses will auto-populate to the study's REDCap database. All participants will review a study informed consent form embedded in the electronic survey, or as a hardcopy. Completion of the survey will be considered implied consent to participate in the study.

Data Analysis

The data analysis for this survey will involve both descriptive and inferential statistical analysis. Descriptive statistics will be used to summarize the background demographics and qualitative responses about financial hardship. Inferential statistics, such as the Wilcoxon rank-sum test, logistic regression, and correlation analyses will be used to examine the relationships between financial health, demographic variables, and additional survey elements. Results will be reported with appropriate measures of central tendency and dispersion, and statistical significance will be determined at an α level of .05. Stata (StataCorp) will be used to manage, analyze, and create graphical presentations of data.

Qualitative Methods

Photovoice is a highly creative, participatory research method that involves photography, reflection, and in-depth discussion to capture the lived experience and empower the voice of participants [28]. Photovoice methods were selected for this study as reflection on photos and photo-elicitation is an important approach to more actively engage people living with dementia by allowing them more opportunities to share their lived experiences using verbal communication, as well as visual cues [29,30].

The qualitative component of this study will engage 8-12 dyads of people living with dementia and their care partners recruited through the same channels as the quantitative component. The same eligibility criteria will be used for the qualitative component as is used for the quantitative survey with two additions: (1) participants with dementia in the qualitative component must also be able to express themselves verbally in English and (2) dyads must have access and ability to use a phone or internet. Dyads who complete the quantitative survey can also participate in the qualitative component, provided they meet the eligibility criteria. A study informed consent form will be sent to all participants and verbal consent will be obtained by telephone from all dyads before data collection.

All consenting dyads will attend a series of 6-8 group discussion sessions using the photovoice participatory research approach. The photovoice methodology includes taking photos, discussing these photos with a group, selecting photos to caption, and grouping photos and captions thematically (Table 3) [31,32]. Photovoice was chosen as the preferred qualitative research method because people living with dementia may be limited in their ability to engage verbally, and photos can allow them to communicate aspects about their self and daily living [33]. Given that financial changes can be mundane and ingrained into everyday life, photos may be well-positioned to capture the topic of financial toxicity. Furthermore, photo elicitation also has been shown to enable caregivers of individuals living with dementia to share a more nuanced look into their own experience [34]. Participants will be encouraged to use their own cell phones or digital cameras to take photos. Disposable cameras will be provided to participants without phones or cameras. No photos will be kept by the study team without written permission from participants. Ownership and copyright of the photos will remain with the participants, and media release forms will be obtained as needed for the dissemination of findings. Qualitative analysis occurs through interactive and iterative group discussions throughout the photovoice process. Data analysis will occur in the following ways:

- Coding selected photographs and calculating a summary frequency count by theme.
- Visual analysis of selected photographs, involving (1) descriptions of photo production techniques, for example, spontaneous or planned photography, existing photos, and photos taken by someone other than the participant; (2) thematic analysis of how the subject matter, caption content, or photo group themes relate to the broader topic [35]; and (3) structural narrative analysis of the photo and caption together to understand how participants make sense of their realities and experiences through photography [35].

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Table 3. Overview of photovoice sessions and procedures. Procedures achieved through each session may vary depending on the group's process. This table is meant to provide an overview and preliminary plan but may be adapted throughout the study.

Photovoice group sessions	Description
1	The research team will introduce participants to the overall photovoice process and the group will broadly discuss the meaning of financial health and well-being.
2	The research team will introduce the ethics of photo taking for research purposes and basic photography skills. As a group, participants and the research team will brainstorm ideas for photos that participants could take in their daily lives to capture financial well-being and hardship.
Between sessions 2 and 3	People living with dementia and care partners will take photographs between sessions to document their own experiences with financial well-being and financial hardship. From the photos taken, dyads will select 3-5 for group discussion.
3 and 4	People living with dementia and care partners will be asked to share and discuss their photos. They will be asked to describe how each photo relates to financial well-being and hardship, what it was like to take each photo, and what it feels like to reflect on the photo through group discussion. Sharing and discussion of photos will occur 1-on-1 with a study team member, in small groups, or with the larger group. A trained research team member will take detailed notes on these discussions. Post-group summaries will be prepared after each group by a trained research team member.
5	Participants will work with the research team to write or dictate narrative captions and titles for each photo they shared.
6 and 7	As a group, participants and research team members will group photos into themes that cluster together conceptually. The team will analyze photos, titles, captions, previous session notes, and postgroup summaries to identify emergent themes. Consensus on final themes and theme titles will be achieved through in-depth discussion.
7 and 8	Participants and research team members will work together to prepare materials to present photovoice findings through a public exhibit of photographs and captions. This exhibit will be designed to engage broad audiences to encourage dialogue among people living with dementia and their families, researchers, community leaders, health care professionals, policymakers, decision-makers, and others.

Data Integration Process

Quantitative and qualitative data will be analyzed independently and then integrated using a validated mixed method, joint display table approach called PIP. The PIP includes 4 stages to integrate mixed methods data after it has been analyzed independently (See Table 4, Table 5, and Textbox 1 for stage descriptions, exemplar, and emergent pillar themes) [13]. The PIP is designed to not only verify or illustrate discrepancies between quantitative results and qualitative findings, but also expand findings through identification of emergent pillar themes. Pillar themes emerge by rigorously comparing and contrasting quantitative results and qualitative findings.

Table 4. Pillar integration process stages.

Pillar integration process stages	Description
Stage 1: Listing	Raw data and coded or grouped data are listed in a joint display table (Table 5) in the quantitative data and categories columns, or the qualitative codes and qualitative categories columns.
Stage 2: Matching	Quant data and qualitative codes that reflect similar content, patterns, or qualities are horizontally aligned to match quantitative results to qualitative findings.
Stage 3: Checking	Data cross-checked for completeness and appropriate matching.
Stage 4: Pillar building	Findings in the quantitative and qualitative columns are compared and contrasted, and gaps are identified to analyze patterns, insights, and emergent findings to build inferences from the findings as a whole, then added to the pillar building themes column.

Table 5. Pillar integration process exemplar table. Concept: health-related financial hardship among people living with dementia and their care partners; goal: illustrate points of convergence in quantitative results with qualitative findings, identify discrepancies and gaps, and expand findings to elucidate potential strategies to reduce financial hardship among dyads living with dementia

Quantitative data	Quantitative categories	Pillar building themes	Qualitative categories	Qualitative codes
Raw data (percentages, frequencies, means, cross-tabulations)	Coded or grouped data abstracted from raw data (categories abstracted from raw data)	Integrated themes identified through the pillar building process	Coded or grouped data (themes and categories)	Raw data (narratives, captions, individual photographs, notes)

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Textbox 1. Pillar integration process data and emergent pillar themes.

Hypothesized example of PIP data and emergent pillar theme

- 30% of lower-income dyads report that they do not have enough money in savings, retirement, or assets to cover the costs of the partner living with dementia care, compared to 10% of higher-income dyads.
- Higher use of savings to pay for care for lower-income dyads.
- Targeted strategies are needed that include alternatives to using savings to pay for dementia related-care for families in lower income brackets.
- Unanticipated use of savings.
- Caption of a photo taken by photovoice participant with dementia of a hospital bill: "Not my plan for retirement savings."

Dissemination of Findings

Findings will be disseminated through scholarly outlets (eg, abstracts, manuscripts, symposiums, and presentations), as well as to the broader public through news and social media. A web-based or in-person photovoice exhibit will be held to raise awareness of financial toxicity in this population. The exhibit's intent will be to inspire discussion and actionable solutions to improve the lived experiences of people living with dementia and their care partners. Further brainstorming sessions may be planned, depending on the interest of attendees.

Ethics Approval

This study protocol was reviewed and approved by the Duke Health Institutional Review Board (PRO00111170).

Consenting Procedures

Quantitative Component

In place of written or verbal consent, participants will be asked to review a study information sheet embedded at the beginning of the survey. The study information sheet indicates participation is voluntary and that participants can stop the survey for any reason at any time. Completion of the survey implies voluntary consent. The study information sheet will include contact information that participants can use to contact the study team with any additional questions.

Qualitative Component

All participants will provide their consent verbally to participate in the photovoice project. Potential participants will review a study consent form with a research team member by phone who will assess participants' understanding of participation and answer any questions that participants have regarding the study. After reviewing the consent form, participants will be asked verbally if they wish to participate in the study. Both members of the dyad must provide verbal consent. Date of verbal consent and staff member who received consent will be documented. The research team member obtaining consent will let participants know that they can ask questions regarding consent or withdraw participation at any time throughout the study.

Understanding of Participation

To demonstrate a sufficient understanding of study participation, a trained research team member designated to obtain consent will use the teach-back method [36], where they will ask potential participants to recall or explain topics that were discussed in the study information sheet, using their own words. These questions are meant to prompt a discussion [36]. The designated research team member will ask the following questions to assess comprehension of informed consent: (1) "This is a research study, do you have to participate?" (2) "What would you do if you change your mind about participating in the study?" (3) "There are some risks involved in this study. Can you tell me about the risks discussed?" (If they do not remember, they are prompted to review them again), and (4) "Do you still want to participate after hearing all the details?" If the person living with dementia or the care partner participant cannot demonstrate comprehension of study participation or necessary cognitive ability for study participation or both as assessed by the research team member, the dyad will not be included in the study.

Confidentiality

To protect participants' confidentiality, we will limit the amount of protected health information and identifiable information that is collected. Data management will strictly adhere to the Duke University Health System Institutional Review Board guidelines and federal privacy regulations. All participant data (eg, questionnaires, photos, captions, discussion notes, themes, and categories) will be deidentified, where each participant will receive a 3-digit identification number that will be used to label their data materials. Only the study principal investigators will have access to the key linking identification numbers to participants' names. No identifiers will be used in reports, materials, or presentations that originate from this study. For publication purposes, only group data will be published. All data will be stored in a secure Duke University manner (secure drives, identifiers separate). More specifically, all recorded information will be documented in an electronic format. All electronic data files will be stored only on a password-protected secure file server (located behind a firewall) using a Duke University secure file server, or on a secure REDCap study database. Nonelectronic files will be immediately entered into the study database upon receipt, then shredded.

Compensation

Dyads that complete the survey will be able to follow a separate link at the end of the survey to provide their contact information to receive a US $25 gift card as compensation. These responses will not be linked to the finance survey responses. Participant dyads in the photovoice component will receive a US $100 check for compensation.

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Results

Quantitative Component

This study is ongoing with survey data collection anticipated to be completed by December 2023. Quantitative results from survey analysis are expected to describe the extent to which dyads experience financial toxicity and correlation across sociodemographic identities, out-of-pocket expenses, and cost-coping strategies.

Qualitative Component

The study team anticipates a comprehensive collection of photographs and narrative captions from each photovoice session, compiled into a poster for exhibition. Anticipated results from the data integration process are emergent themes pertaining to potential strategies to reduce financial hardship among dyads living with dementia (see Table 5) [13]. Emergent themes will be highlighted in the photovoice exhibit and used to spark discussion among the research team and attendees.

Discussion

Overview

Financial toxicity has garnered more of the limelight in recent years; however, the academic and policy focus has centered on people diagnosed with cancer. While rising financial costs and associated financial burden on health systems are frequently studied, there remains a dearth of evidence on the impact these costs might have on the individual level. Longitudinal and chronic diseases have rarely found a place in the academic literature, especially with regard to the financial impact on the patient and their family. Dementia is one particularly important chronic disease process with an estimated prevalence of 7 million people living with dementia in the United States, and the number is projected to rise to 12 million by 2040 [37]. Our study would be one of the first to use a mixed methods approach to characterize financial toxicity in individuals living with dementia and their care partners.

This study must be considered in the context of its potential strengths and limitations. The strengths of this study center on its novel methodological approach of integrating both qualitative and quantitative methods. In particular, the use of photovoice allows us to richly capture the “patient voice,” which is frequently missing in financial studies that use retrospective, claims-based, and even validated financial questionnaires. Potential limitations include difficulty ascertaining individual insurance plans which impact out of pocket health care expenditures and therefore the degree of financial toxicity. Because recruitment for this study was primarily through partner organizations and social media campaigns, additional limitations may include a bias toward participants of higher socioeconomic positions.

The results of this study have important implications for health care professionals, policymakers, and leaders going forward. Policymakers, including the Center for Medicare and Medicaid Services and Center for Medicare and Medicaid Innovation, have emphasized a focus on addressing affordability of care for people in their strategic vision [38]. However, a major roadblock in developing new care models or policies to improve affordability is robust financial data for people with chronic diseases like dementia. Our study would provide a baseline assessment of the financial well-being of people living with dementia and their care partners to support the development of new strategies for improving costs of care. Furthermore, as new treatments and high-cost drugs are potentially incorporated into the care pathways for those with dementia, this financial baseline will become increasingly important to understand the financial impact these medications and treatments could have. Importantly, understanding financial health at the individual level provides an important foundation for improving health equity. While this work will start with those living with dementia, this protocol could potentially be replicated for people living with other diseases as well and serve as a blueprint for future research efforts in this space. Insights gleaned from this study can also support education and training materials for health care professionals regarding financial resources available for people living with dementia. Gaining a better understanding of the financial challenges that people living with dementia and their caregivers face can inform the creation of pathways to assist families in navigating the financial journey after diagnosis.

Conclusions

The issue of financial toxicity is an increasingly prevalent problem for people living with chronic conditions and their care partners. Despite considerable evidence for the financial burdens of cancer care, there is little known about financial toxicity’s impact on people living with dementia and their families. This study will use an adapted survey and photovoice interviews as quantitative and qualitative methods to comprehensively characterize financial toxicity in dementia dyads. Study results will enhance the understanding of financial toxicity in individuals living with dementia, provide insights into the primary drivers of financial burden, and explore potential solutions to mitigate this issue. Findings from this study can be used to inform payment reform efforts, lead to improved health outcomes for people living with dementia and increase support for their families.

Acknowledgments

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Data Availability

Data sharing is not applicable to this paper, as no data sets were generated or analyzed during the current study.

Conflicts of Interest

None declared.

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Abbreviations

COST: Comprehensive Score for Financial Toxicity
iPCQ: Institute for Medical Technology Assessment Productivity Cost Questionnaire
PIP: pillar integration process

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PROMIS: Patient-Reported Outcomes Measurement Information System

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Protocol

User-Initiated Symptom Assessment With an Electronic Symptom Checker: Protocol for a Mixed Methods Validation Study

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Abstract

Background: The national Omaolo digital social welfare and health care service of Finland provides a symptom checker, Omaolo, which is a medical device (based on Duodecim Clinical Decision Support EBMEDS software) with a CE marking (risk class IIa), manufactured by the government-owned DigiFinland Oy. Users of this service can perform their triage by using the questions in the symptom checker. By completing the symptom checker, the user receives a recommendation for action and a service assessment with appropriate guidance regarding their health problems on the basis of a selected specific symptom in the symptom checker. This allows users to be provided with appropriate health care services, regardless of time and place.

Objective: This study describes the protocol for the mixed methods validation process of the symptom checker available in Omaolo digital services.

Methods: This is a mixed methods study using quantitative and qualitative methods, which will be part of the clinical validation process that takes place in primary health care centers in Finland. Each organization provides a space where the study and the nurse triage can be done in order to include an unscreened target population of users. The primary health care units provide walk-in model services, where no prior phone call or contact is required. For the validation of the Omaolo symptom checker, case vignettes will be incorporated to supplement the triage accuracy of rare and acute cases that cannot be tested extensively in real-life settings. Vignettes are produced from a variety of clinical sources, and they test the symptom checker in different triage levels by using 1 standardized patient case example.

Results: This study plan underwent an ethics review by the regional permission, which was requested from each organization participating in the research, and an ethics committee statement was requested and granted from Pirkanmaa hospital district's ethics committee, which is in accordance with the University of Tampere's regulations. Of 964 clinical user–filled symptom checker assessments, 877 cases were fully completed with a triage result, and therefore, they met the requirements for clinical validation studies. The goal for sufficient data has been reached for most of the chief symptoms. Data collection was completed in September 2019, and the first feasibility and patient experience results were published by the end of 2020. Case vignettes have been identified and are to be completed before further testing the symptom checker. The analysis and reporting are estimated to be finalized in 2024.

Conclusions: The primary goals of this multimethod electronic symptom checker study are to assess safety and to provide crucial information regarding the accuracy and usability of the Omaolo electronic symptom checker. To our knowledge, this will be the first study to include real-life clinical cases along with case vignettes.

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KEYWORDS

triage; symptom assessment; self-care; health service accessibility; telemedicine; health service research; internet; validation study; primary health care; clinical studies; telehealth

Introduction

Background

Seeking information online regarding medical symptoms is a common and well-known phenomenon worldwide [1-4]. According to a study in the United States, more than one-third of the surveyed adults regularly used the internet for self-diagnosis [5]. In another study, on average, 15% of the people queried on general-purpose search engines about symptoms associated with their conditions before receiving a proper medical diagnosis [6]. However, self-diagnostic web-based sources may be of varying quality, with misleading information and possibly false advertising [7,8].

To address these problems, health care digital applications have been introduced online, including self-diagnosing tools and symptom checkers. Based on users' input of their symptoms, applications such as Babylon GP at Hand, K Health, Isabel, Symcat, Everyday Health, Ada, and WebMD use algorithms to help identify the relevant medical condition. An evaluation study of GP at Hand found that healthier individuals use e-services more than others [9]. Studies have also found that younger, highly educated people, and those with a higher socioeconomic status use eHealth services more actively [10-12]. Evidence on user behavior when using symptom checkers indicates that 3 in 4 users in a sample of nearly 500 users comply and follow electronic symptom checker recommendations, regardless of the urgency level [13]. One study [14] found that users are overcautious in deciding whether they require medical care at all and they miss identifying a considerable portion of emergencies. Further, women may be more risk averse than men in both types of decisions. However, users have mostly been satisfied with the electronic symptom checkers they use [10,15-18].

As with clinical decision-making in general, symptom checker questionnaires and algorithms used are based on research evidence, probabilities, and expert opinions as to whether the condition described is mild and self-limiting or whether it requires the intervention of a health care professional. In terms of urgency, an assessment is made on how soon the condition would worsen without treatment. For an accurate diagnosis, the user provides information that is required, complemented by clinical examinations, various diagnostic tests, and potential consultations with other medical personnel [19,20].

Previous studies have evaluated the accuracy of electronic symptom checkers for diagnosis and triage by using clinical case vignettes [21-30]. Vignettes appear to be a valid and comprehensive method that directly focuses on the process of care provided in actual clinical practice [31]. Under experimental conditions, the diagnostic accuracy of clinicians has been shown to be superior to that of electronic symptom checker tools in both primary and specialized health care [21-23].

Studies have shown that there are risks and room for error in digital triage. Users diagnosed with electronic symptom checkers may be referred to self-care even if they need professional help, and users for whom self-care would be sufficient are referred to professionals [21-23]. Specifically, self-care guidance should be limited to situations where it is safe and appropriate. A study to the point used data on more than 150,000 patient interactions with a web-based triage tool and found that the urgency of patients' intended level of care decreased in more than 1 in 4 of the cases and increased in 1 in 20 cases, with the remaining patients remaining at the same level [32].

When comparing physicians' and computers' diagnostic accuracy by using case vignettes, physicians listed the correct diagnosis first more often than symptom checkers (72.1% vs 34%, respectively) [22]. There is limited evidence of patient safety hazards associated with the use of electronic symptom checkers [10,22,23,33]. However, a study comparing artificial intelligence and human doctors for the purpose of triage and diagnosis found that the artificial intelligence system was able to provide users triage and diagnostic information with a level of clinical accuracy and safety comparable to that of human comparators [34,35]. Electronic symptom checkers are, on average, more sensitive at recommending more urgent care than is actually needed [21,23,29,36]. Triage performance of symptom checkers has, on average, not improved over the course of 5 years [30].

In clinical practice, triage assessment and guidance are usually performed by health care professionals either during telephone contact or face-to-face, for example, at a health care center. In England, there were 1,678,880 calls made to National Health Service 111 in March 2021. Out of these calls triaged, 12% were referred to ambulance service, 11% to accident and emergency, 54% were recommended primary care, 8% advised to attend another service, and 14% were deemed not to need another service, that is, suitable for self-care [37].

Triage takes a lot of professional time and is of varying quality. In health care organizations, therefore, the goal is to unify triage and digitalize it with the help of symptom checkers. This is expected to increase service uniformity and efficiency as well as free up working hours [10,38].

Study Objectives and Outcomes

The goal of this study was to ensure that the symptom checker is sensitive enough to recommend urgent care when it is needed and that it is specific enough to avoid unnecessary use of health care services. This is a mixed methods validation study of the Omaolo symptom checker (Table 1, Table 2, and Textbox 1). The focus of this study is on the usability of this tool, reliability of the assessments, and user safety [37-41]. The first part consists of comparing the Omaolo symptom checker assessment with an assessment made by an experienced primary care triage nurse to see how well they match. The second part complements

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the first by using patient case vignettes for the validation of the Omaolo symptom checker.

Table 1. Overview of the Omaolo symptom checker studies.

Characteristics	Substudy 1	Substudy 2
Study type	Quantitative clinical validation study	Validation with case vignettes study
Study objectives	Differences and similarities between the nurse's and symptom checker's (n=15) triage in real-life settings	To test if recommendations are safe on rare and acute cases, which could not be tested extensively in a real-life setting Case vignette accuracy is determined by comparing case vignette–filled symptom checker surveys with expert panel's assessment (gold standard)
Study design and setting	Comparison of nurse's triage to symptom checker's triage	Comparison of symptom checker's triage to triage nurse, general practitioner, and gold standard
Outcome	Triage frequencies, proportions of matches, symptom checker safety, specificity, and sensitivity	Case vignettes to complement the real-life assessment of the symptom checker

Table 2. Research questions for the clinical and case vignettes validation study.

Substudy	Research question
Clinical validation study: differences between the nurse's and symptom checker's triage in real-life settings	• Are the recommendations of the symptom checker safe to use? • In what proportion (% and 95% CIs for an estimate) of the assessments do the experienced nurse's triage and the recommendation of action given by the symptom checker correspond or differ before the nurse has seen the recommendation of action given by the symptom checker? • Are the recommendations of the symptom checker specific and sensitive enough to prevent unnecessary use of primary health care services? • Does an experienced nurse change his or her assessment after seeing the recommendation for action by the symptom checker? • What are the key factors that lead an experienced nurse's triage to differ from the symptom checker's recommendation? • How many cases are there and to which symptom checker do they relate to wherein a triage nurse would refer the user to a heavier service than that recommended by the symptom checker (2 levels lighter is considered as unsafe recommendation for a symptom checker)? • How many assessments can be found and to which symptom checker they relate to wherein the triage nurse would refer the user to a lighter service than that recommended by the symptom checker (2 levels heavier is considered as overconservative recommendation for a symptom checker)? • Analysis of the content for the reasons given by the participants that influenced their triage when the individual assessments differed
Validation with case vignettes study: performance between nurses' and symptom checker's triage in case vignettes compared to expert panel assessment (gold standard)	• In what proportion (% and 95% CIs for an estimate) of the assessments do the experienced nurse's triage and the recommendation of action given by the symptom checker correspond to or differ from case vignette's predetermined (assesses by expert panel) triage? • Does an experienced nurse change his or her assessment after seeing the recommendation for action by the symptom checker? • How many cases are there and to which symptom checker do they relate to wherein a triage nurse would refer the user to a heavier service than that recommended by the symptom checker (2 levels lighter is considered as unsafe recommendation for a symptom checker)? • How many assessments can be found and to which symptom checker they relate to wherein the triage nurse would refer the user to a lighter service than that recommended by the symptom checker (2 levels heavier is considered as overconservative recommendation for a symptom checker)? • Analysis of the content for the reasons given by the participants that influenced their triage when the individual assessments differed • Sensitivity, specificity, positive and negative predictive values of the symptom checker and nurse assessments compared to expert panel assessments

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Textbox 1. Questions presented in the research forms specifically for triage nurses.

Questions

- How old are you?
- How much work experience do you have in assessing the need for care (triage) ? ____ years
- How did the user arrive at the reception? (walk-in or via telephone contact)
- Did you consult a doctor to assess the user's need for treatment (triage)?
- Choose where the user should be referred according to the terms of the electronic symptom recommendation action guide (based on your own evaluation, triage)
- What was the most significant thing (observation, symptom, or discovery) that influenced your decision-making?
- Do you feel the need to change your assessment of need for treatment (triage) after seeing the responses and recommendation in the electronic symptom checker? (Yes/No)
- If yes, then why did you change the assessment of the need for treatment (triage) after seeing the responses and recommendation in the electronic symptom checker?
- If you feel it is necessary to change your triage assessment, reselect where the user should be referred to according to the classification terms of the electronic symptom checker's recommendation.

Intervention

Development of the Omaolo Symptom Checker

The clinical validation process of the Omaolo symptom checker proceeded at a national level and it complies with the European Union and Finnish medical device requirements with a CE marking (risk class: IIa) [42-45]. The Omaolo management team selected the topics to be included in the symptom checker on the basis of the most popular searches made on the evidence-based medicine guidelines (decision support for health care professionals by Duodecim Medical Publications Ltd), considering the most common reasons for visiting health centers and joint emergency services [46]. The Omaolo symptom checker is intended for users older than 15 years. There is no upper age limit, except for the symptom checker for urinary tract infections, which is intended for women aged 18-65 years.

The reasoning of each symptom assessment consists of 1 algorithm, which uses a common function library as an aid. All traffic goes through the engine of the evidence-based medicine decision support device, the application programming interface and related filters and conversions, and data processing. However, the algorithm that has the most central effect on reasoning can be separated from each individual symptom assessment within the symptom checker.

Description of the Omaolo Symptom Checker

Omaolo is a national web-based service for social welfare and health care. The purpose of Omaolo is to promote the health and well-being of citizens. Omaolo supports self-care and helps people to contact public health care professionals, if necessary. Omaolo is a medical device with a CE marking, manufactured by government-owned DigiFinland Oy founded in the year 2017. Omaolo meets the requirements set for medical devices.

The aim of the Omaolo symptom checker (Textbox 2) is to identify, based on the assessment of alarm symptoms and other pre-existing conditions, situations that require immediate or urgent assessment and to conduct follow-up examinations and treatment without delay in situations where conservative treatment may lead to complications. Both the questionnaire for the user and the algorithm that the symptom checker uses are based on research evidence (Multimedia Appendix 1), especially on the need to treat different combinations of symptoms and in other respects on medical experience (Textbox 2) [42-50].

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Textbox 2. List of symptoms selected for the Omaolo symptom checker (n=15) and sources of medical knowledge and regulations applied in creating them [42-50] (full detailed references are listed in Multimedia Appendix 1).

Omaolo symptom checker

- Anal region symptom
- Cough
- Diarrhea
- Discharge from the eye, watery or reddish eye
- Headache
- Heartburn
- Knee symptom or injury
- Lower back pain or injury
- Oral health
- Painful or blocked ear
- Respiratory tract infection
- Sexually transmitted disease
- Shoulder pain, stiffness, or injury
- Sore throat or throat symptom
- Urinary tract infection

Regulations

- Regulation (European Union) 2017/745 of the European Parliament and of the Council of April 5, 2017, on medical devices [42]
- Finnish Health Care Equipment and Supplies Act [43]
- New requirements and operational implications of medical devices (Finnish) [44]

Sources of medical knowledge

- Cochrane Database of Systematic Reviews [45]
- Articles in the DynaMed Plus; database produced by the EBSCO (Elton B Stephens CO) community [46]
- Finnish administrative sector of the Ministry of Social Affairs and Health publication “Basics of Emergency Care” [47]
- Finnish Current Care Guidelines [48]
- Evidence-Based Medicine Guidelines (Duodecim Medical Publications Ltd) [49]
- City of Helsinki Assessment of the Need for Urgent Care in Adult Patients (2014) [50]
- Preliminary studies investigating the likelihood of different combinations of symptoms and associated conditions requiring treatment

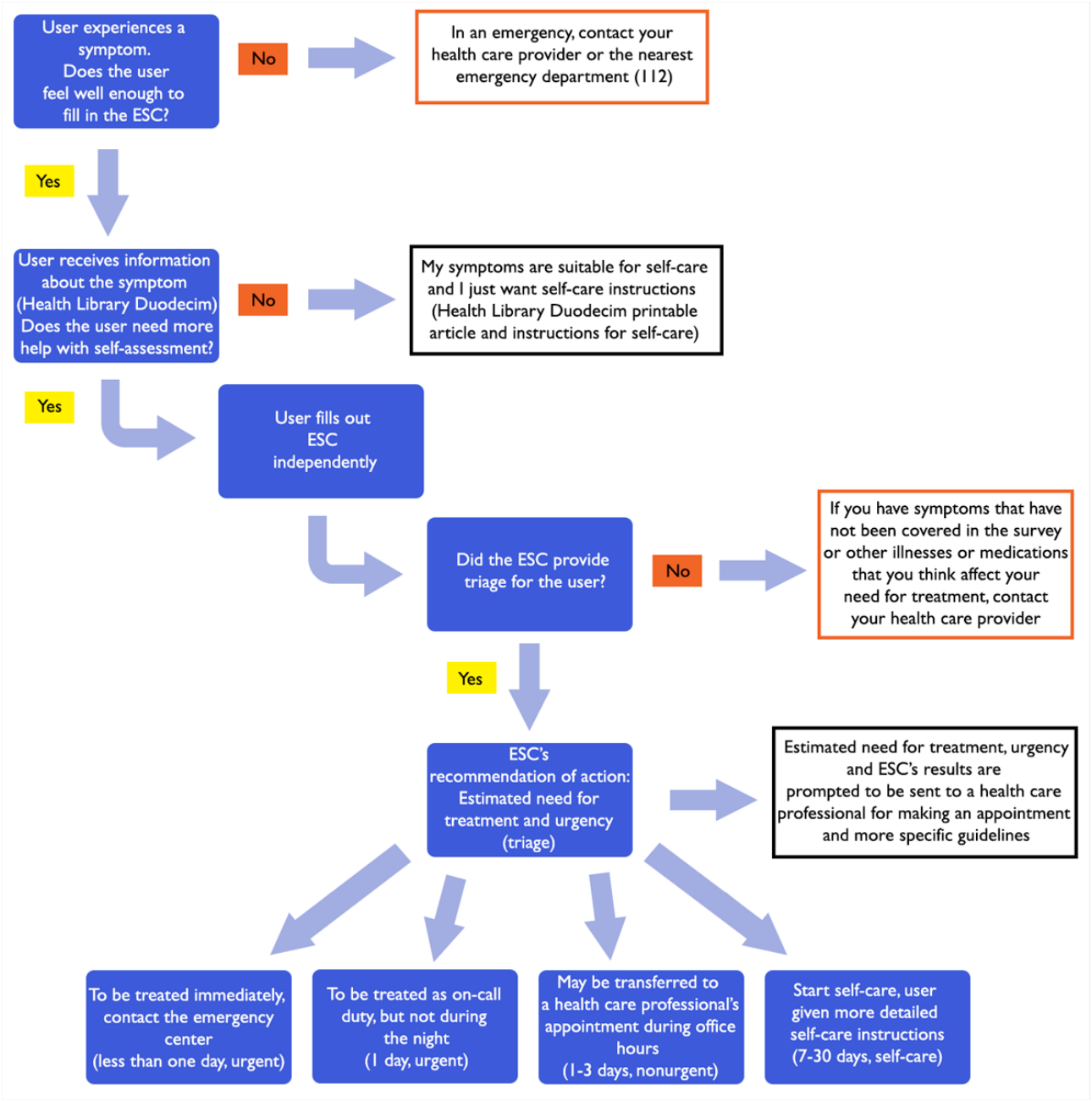
The symptom checker can only assess symptoms based on the information provided by the user. As with clinical decision-making in general, assessments of the need for treatment are based on the likelihood that the condition described is mild and self-limiting or that action by a professionally trained health professional is likely to be required to treat or prevent its worsening. In terms of urgency, the available information is used to assess whether and how quickly the condition is likely to worsen without treatment.

The symptom checker makes a general assessment and then recommends a course of action based on medical knowledge. It gives the user an idea of the quality and urgency of the treatment (triage) likely required. The user will be recommended to either treat their symptoms and their health problems themselves or be prompted to contact a health care professional who can provide a professional assessment of the situation and appropriate treatment, if necessary [39-41].

The use of the Omaolo symptom checker is intended to be as simple as possible (Figure 1): the user initially receives reliable information about the symptom (articles in the Health Library Duodecim) with a short summary, helping the user in assessing their condition. If, however, the user is still unable to decide on the treatment, they can next answer the relevant symptom checker questions. These will, in turn, result in a recommendation by the checker on course of action and urgency. The checker does not result in a diagnosis.

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Figure 1. Flowchart for using Omaolo services and the decision tree of the symptom checker. ESC: electronic symptom checker.



The first priority of the symptom checker is to seek to identify any alarming symptoms that should prompt immediate contact to an emergency department. The aim is then to identify situations where a professional assessment is necessary and to determine the urgency of the assessment. For example, these include situations where antibiotic treatment may be necessary or situations where the symptom of the infection can be associated with an exacerbation of another disease. The combinations of symptoms are used to draw conclusions about the likely nature of the situation and to provide an appropriate recommendation. The successfully answered questions are saved, and the user can have it sent to a health care professional through the Omaolo symptom checker [39-41].

The user is encouraged to access the Duodecim Medical Library articles on the subject, which open as links in the questionnaire introductory text and feedback, since not all possible real-life situations can be covered. The user is also encouraged to consider whether they have other symptoms not covered by the questions of the information provided. To help with this, the following is displayed to the user at the end of the query: "If you have symptoms that have not been covered in the survey or other illnesses or medications that you think affect your need for treatment, contact your health care provider or, in an emergency, the nearest emergency department" [39-41].

Methods

Inclusion Criteria

To be eligible for the study, users had to be older than 18 years and experience some of the symptoms listed in the Omaolo symptom checker when participating. There is no upper age limit, except for the symptom checker of urinary tract infection,

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which is intended for women aged 18-65 years. The experienced nurses had to have at least 2 years of triage experience.

Exclusion Criteria

The only exclusion criterion was refusal of the user to participate in this study.

Pilot Study

The purpose of this pilot study was to examine the functionality of the study design of the symptom checker validation. The pilot was conducted at the Espoonlahti Health Center in July 2018. The pilot complied with the research plan and was performed to test the feasibility of the study design and the questionnaires. The pilot was conducted by collecting symptom checker assessments of 50 users with several symptoms at the same time. More than 200 users (Table 3) were interviewed to participate in this study, but only 50 symptom checker assessments were completed. The pilot caused minor changes mainly to question the formulations of the data collection documents and details of collecting the data.

Table 3. Reported reasons for users not taking part in the pilot study.

Reason for not participating in the study	Users (n=234)
Skeptical toward digitalization and e-services	33
Polite refusal without further explanation	76
Already has a reserved appointment time	41
On a matter regarding a family member's well-being	10
Severity of symptoms hinders participation	29
User's experienced symptoms are not found in the symptom checker	35
Fear of losing their place when waiting in the queue to meet the nurse	10

Study Design and Setting

The study setting is Finnish Primary Health Care, with 13 participating health care organizations nationwide. Each participating organization provided the study space where it is practically possible for the users to complete Omaolo symptom checker and triage by an experienced nurse. The organization also ensures that the target population of the study remains unscreened. Study users are recruited in units that use the walk-in model in primary health care settings, where clients come to a health center without prior contact (Figure 2).

The validation with case vignettes (virtual clinical patient cases) will be used to complement the assessment of triage accuracy of some of the questions of the Omaolo symptom checker (Figure 3). Vignettes are either obtained from previous studies or produced for this study from a variety of clinical sources, including material used in medical education examinations. For example, an outcome that has been reached in a patient case in the educational environment is considered when creating a virtual patient case vignette [21-24]. Patient case vignettes are also produced from standardized clinical patient cases and panel-decided materials [22]. Panel-decided patient case vignettes and standardized patient case vignettes are a common method for developing and training health care professionals in their diagnostic ability to make treatment decisions [21].

The panel in our study aims to consist of 3-5 independent clinician general practitioners (GPs) and another 3-5 triage nurses. We will apply a modified Delphi procedure [51]. For the creation of clinical vignettes, the GPs are required to have over 5 years of primary care and emergency department experience. These GPs are not to be directly involved with Omaolo creation. In case of the vignette validation process, the panel first assesses the triage for case vignettes (gold standard). Second, the panel-decided triage is then compared with the nurse's and GP's triage and the symptom checker's recommendation of action (this is possible in simulated cases where conditions are constant) (Figure 2). Case vignettes test the symptom checker and compare their performance with other providers in different triage levels by using standardized patient case examples [21-24]. Individual patient case vignettes are formed according to urgency classifications. Case vignettes also include common and rare diseases. The focus of this study will be on rare and acute cases, which cannot be tested extensively in real-life settings, for example, the number of cases collected for diarrhea and heartburn symptom checker is small (Table 4). Some of the vignettes will be derived from established sources [22].

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Figure 2. Study design for the clinical validation study.

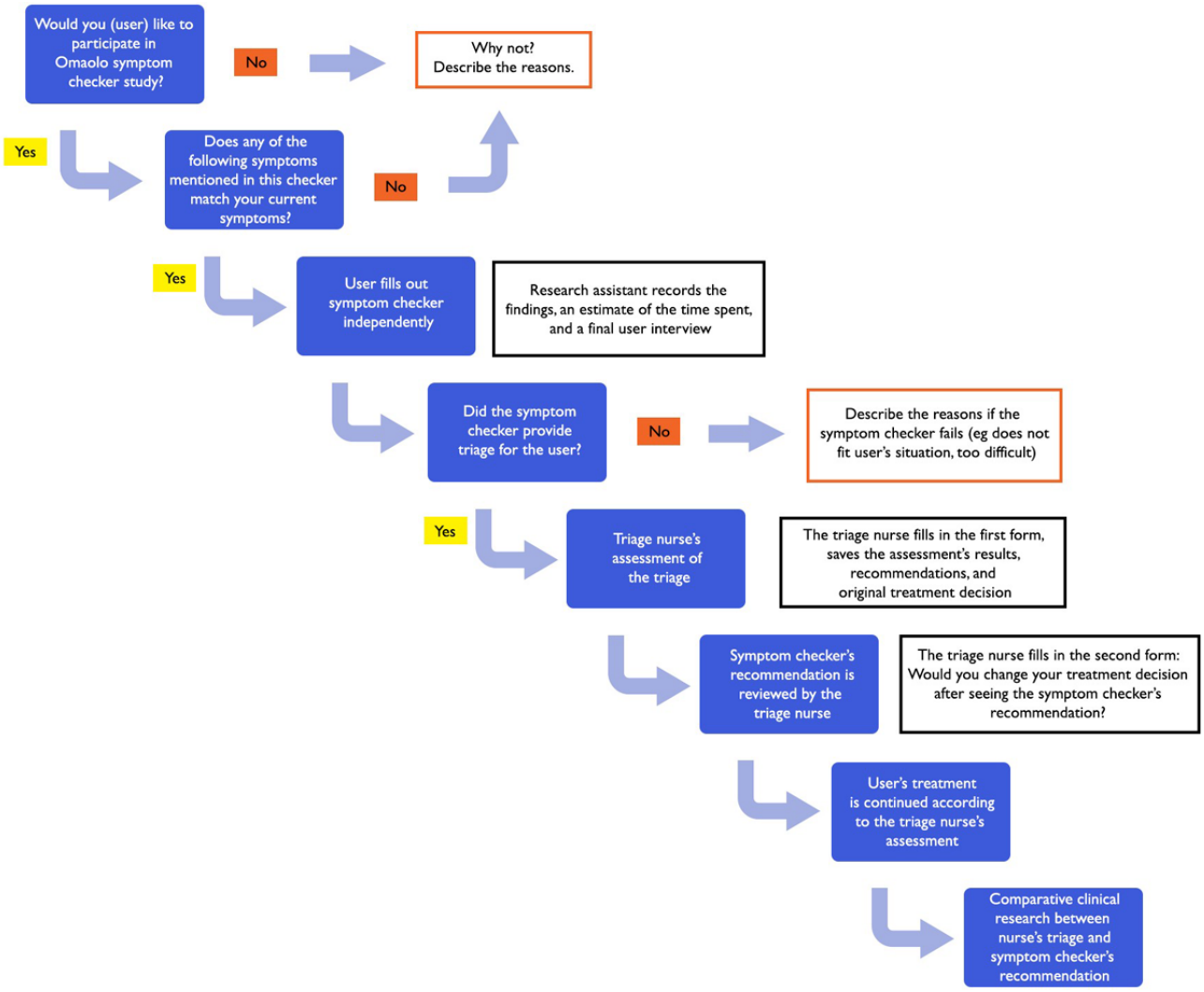
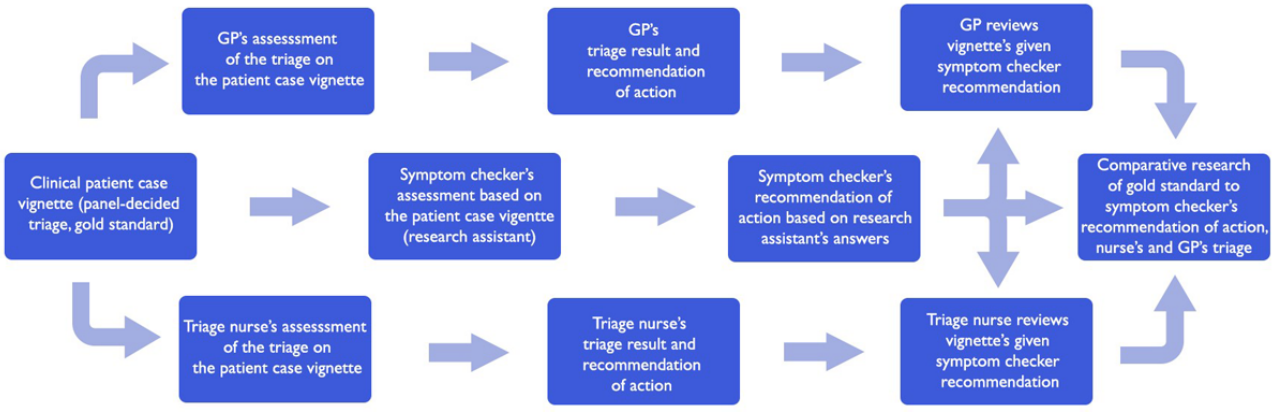


Figure 3. Study design for validation with case vignettes study. GP: general practitioner.



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Table 4. Data of the collected clinical user cases across the symptom checker.

Symptoms in Omaolo symptom checker	Approved assessments for clinical validation (n=877), n	Approved assessments for usability study (n=964), n
Anal region symptom	41	39
Cough	71	87
Diarrhea	21	23
Discharge from the eye, watery or reddish eye	65	64
Headache	41	45
Heartburn	24	19
Knee symptom or injury	55	56
Lower back pain or injury	65	69
Oral health	62	69
Painful or blocked ear	81	83
Respiratory tract infection	104	121
Sexually transmitted disease	39	30
Shoulder pain, stiffness, or injury	47	50
Sore throat or throat symptom	101	117
Urinary tract infection	60	60

Sample Size Calculations

In a study performed by Gilbert et al [22], triage levels of 7 different symptom checker apps were tested and the mean percentage of safe advice provided by the apps was found to be 90.1% (SD 7.4%). Furthermore, a symptom checker app was found and defined to be safe to use if the particular app had safe advice performance within 1 SD compared to the GP's (mean) percentage of given safe advice. The GP's percentage of safe advice was 97% (SD 2.5%) [22]. For our study, hypothesis 1 (α) is that the Omaolo symptom checker is safe to use in the defined study settings (Table 1).

For the study group in the clinical validation study, we accept a safe performance of 97% when directly comparing symptom checker's recommendation of action to nurse's triage of the same user that has filled in the symptom checker successfully. We estimate the required sample size by assuming the given range of safe advice at 97% and by using a 95% confidence level, and we compute the confidence interval estimate for the true proportion of safe-filled symptom checker assessments (Figure 2). For each symptom, we aim to collect as many completed symptom assessments as possible.

For the study in validation with the case vignettes study, we assume that the Omaolo symptom checkers' performance is similar to that of symptom checker apps defined as safe as described by Gilbert et al [22]. This includes that the suggested safe advice performance marginal and size of the difference between the study groups is acceptable (Figure 3).

Data Analysis

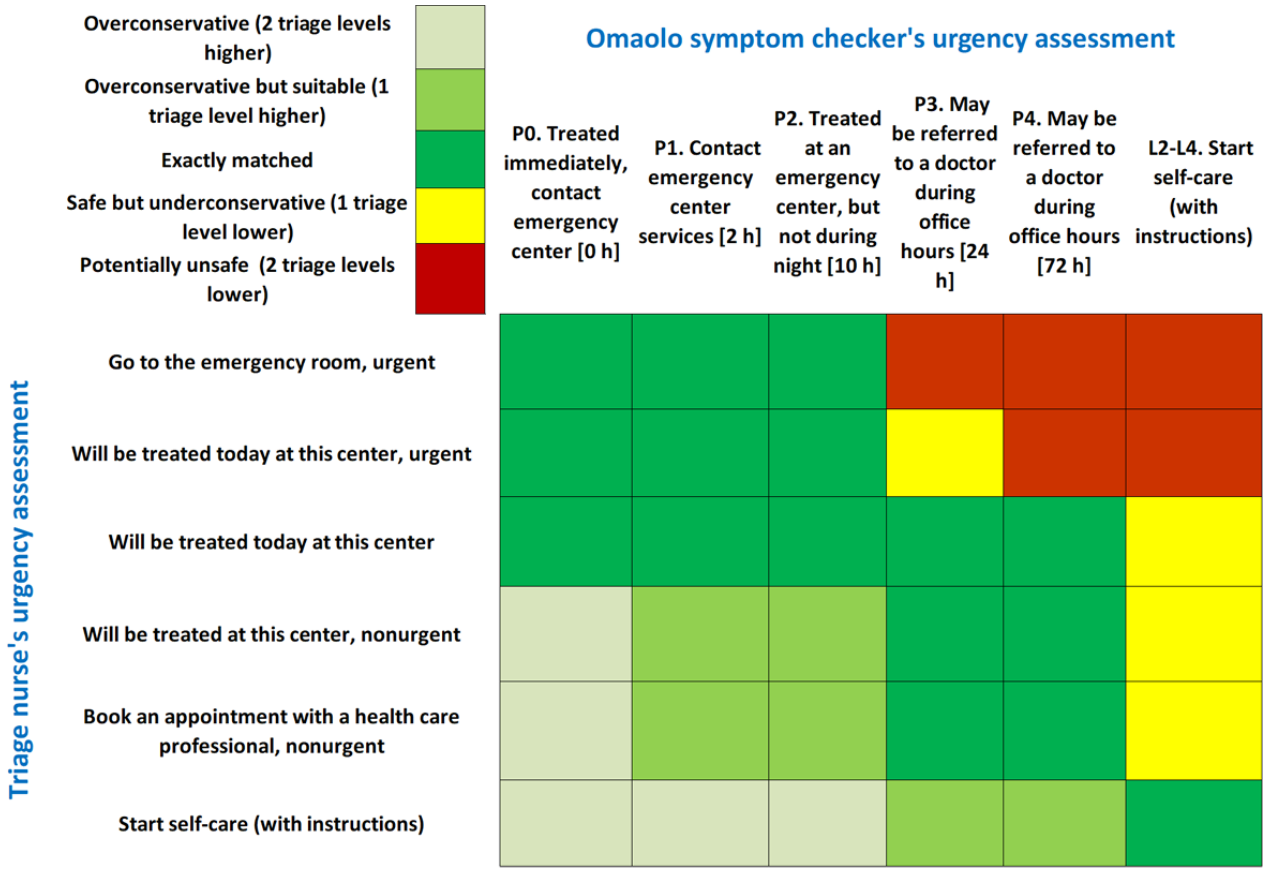
The qualitative assessment of the study data from the open-ended questions of the survey was analyzed by qualitative inductive content analysis [52]. In this approach, the codes and themes derived from the data were suggested by the data rather than by a theoretical framework. The steps that we used for our analysis were iterative processes to familiarize ourselves with the qualitative data and to identify quotations with common concepts, code formation, grouping of codes into subthemes and themes, and creation of an explanatory thematic summary.

The quantitative analysis in the clinical and vignette validation studies includes the results and findings of individual users, nurses, and study assistants being analyzed based on individually completed study forms. The results of the electronic symptom assessments compared to the assessment of an experienced nurse and case vignettes will be presented regarding each symptom checker individually. Possible differences in triage levels, including "overconservative," "overconservative but suitable," "exactly matched," "safe but underconservative," and "potentially unsafe," for all symptom estimates will be reported (Figure 4) [22]. We will calculate the percentages of matches for each individual symptom checker and the 95% CIs.

A case is to be defined as safe if the conflict condition is not met and the recommendation for action given by the symptom assessment is at most 1 degree of urgency less urgent than the triage assessment of the same case. The definition of a conflict is as follows: cases assessed by the nurse as urgent/on-call duty but assessed by the electronic symptom checker as nonurgent/self-care.

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Figure 4. An example of a triage comparison chart with matched color coding differences in triage levels. Matching rows (triage nurse) to their respective columns (symptom checker) results in a safety assessment. P1-4, Finnish Ministry of Social Affairs and Health Classification of emergency care criteria; L2-4, referral urgency classes of Finnish Institute for Health and Welfare coding service.



Ethics Approval

This study plan underwent an ethics review by the regional permission, which was requested from each organization participating in the research, and in addition to this, an ethics committee statement was requested and granted from Pirkanmaa hospital district's ethics committee (ETL-Code:R18126), which is in accordance with the University of Tampere's regulations. When recruiting participants for this study, the research assistant informs the user about the study, distributes the study information sheet, and then asks if the user is willing to participate in the study. If, after being informed, the user is willing to participate in the study, they are asked to sign a consent form in which the user acknowledges that they have received sufficient information about the study and agree to participate in it. The user is given an information sheet about the study, which contains information about the study and contact information in case the user wants to ask more about the study. The user was paid no amount of compensation. The user's consent form is not connected to the response form with a personal identification code, that is, the users are anonymized. No medical record data are collected or combined with research forms. The users can withdraw their consent to the study at any time, but the completed forms cannot be destroyed after the data collection, because the consent form, which contains personal data, does not have an identification code that could be used to link the consent to other study forms. The most significant ethical issue related to the research setting is that the user's participation in the research does not affect their chances of receiving timely treatment. In connection with the research protocol, all users who fill out the symptom checker will be forwarded to an appointment with an experienced nurse. Denial of treatment for users who refuse to participate in the study is strictly prohibited.

Results

Data (Table 4) for this study were collected between June 1, 2018, and December 31, 2020, when users filled in electronic symptom checker questionnaires on arrival at the health centers (they also signed an informed consent form). The version of the Omaolo.fi symptom checker of 2019 was used. Few user cases were collected for diarrhea and heartburn in the clinical validation part of the study. In the supplementary case vignette validation study, the use of virtual clinical patients will be used to support the triage accuracy of chief symptom assessments with a small number of approved assessments for clinical validation (heartburn, diarrhea) in the Omaolo symptom checker. The focus will be on rare and acute cases, which cannot be tested extensively enough in real-life settings. Data collection was completed in September 2019, and the first feasibility and patient experience results were published by the end of 2020 [33]. Further results and publications are expected in 2023-2024. It is estimated that the analysis and reporting will be finalized during 2024.

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Discussion

Principal Findings

This multidimensional study will be the first to assess both the usability and safety of the Omaolo symptom checker in the Finnish primary health care context. In addition, this research might provide information to help evaluate the reliability and possible shortcomings of this service. This information can then be used to support the further development of the service entity and thus improve the usability of the Omaolo service. The real benefit and safety of this service can be gauged from the written feedback of users who use the symptom checker in real clinical trial environments [53].

Strengths and Weaknesses

The real-life setting is both a strength and a potential weakness of this study. A strength of this study is the large number of real-life users with real-life symptoms and real-life triage performed by a nurse. The first potential concern is the selection bias of the symptoms experienced when users fill the symptom checker questionnaires in health center waiting rooms, while in real-life settings, the symptom checker questionnaire is filled at home. The Omaolo symptom checker is designed for users older than 15 years, but in this study setting, only users older than 18 years are recruited. Second, the potential selection bias results from excluding users who are not able to complete the symptom checker questionnaire independently (inability to use the provided computer mouse or tablet devices). Further, users presenting with symptoms at the extremes of the spectrum may be problematic. Cases of mild self-care symptoms may be excluded, and users with serious acute symptoms may be rare in this setting. The symptom checker service does prompt users to contact health care services urgently when unable to fill in the questionnaire due to severe symptoms. The lack of urgent cases for some symptoms (eg, heartburn, diarrhea) in real-life settings is considered to be supplemented by virtual user cases, that is, case vignettes. The focus of validation with the case vignette study will be on rare and acute cases, which cannot be tested extensively enough in real-life settings. More common and less urgent situations can be covered even with the vignette study. Finally, although the production of research data was slowed down by the COVID-19 pandemic [54,55], the number of individual users of mobile medical apps and Omaolo.fi grew exponentially during the pandemic [56-58].

Acknowledgments

This research was carried out in addition to the work of primary health care centers, municipalities, health care district–based health care organizations nationwide, Omaolo project employees, and Finnish Medical Society Duodecim employees.

Data Availability

The forms concerning individual users in the database are anonymized and cannot be combined with the user's identification code to personal data. The information in the questionnaires is coded electronically and transferred to an electronic folder. The names or personal information of the users are not shown in this electronic file but only the user's identification code. Paper forms with identification codes are stored in a locked cabinet. The consent form containing the user's name and signature is kept in a separate locked cabinet. All paper forms are stored in the University of Tampere. The forms are disposed of with a shredder 10 years after the end of the study. The electronic data sets generated during and analyzed in this study are available from the corresponding author on reasonable request.

Conflicts of Interest

MK is the President of Finnish Medical Society Duodecim. THK has worked as a salaried part-time editor for Duodecim Medical publications up to year 2018.

Multimedia Appendix 1
Sources of medical knowledge applied in creating the Omaolo electronic symptom checker.
[DOCX File , 25 KB - resprot_v12i1e41423_app1.docx]

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Abbreviations

GP: general practitioner

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Protocol

A Wearable Artificial Intelligence Feedback Tool (Wrist Angel) for Treatment and Research of Obsessive Compulsive Disorder: Protocol for a Nonrandomized Pilot Study

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Abstract

Background: Obsessive compulsive disorder (OCD) in youth is characterized by behaviors, emotions, physiological reactions, and family interaction patterns. An essential component of therapy involves increasing awareness of the links among thoughts, emotions, behaviors, bodily sensations, and family interactions. An automatic assessment tool using physiological signals from a wearable biosensor may enable continuous symptom monitoring inside and outside of the clinic and support cognitive behavioral therapy for OCD.

Objective: The primary aim of this study is to evaluate the feasibility and acceptability of using a wearable biosensor to monitor OCD symptoms. The secondary aim is to explore the feasibility of developing clinical and research tools that can detect and predict OCD-relevant internal states and interpersonal processes with the use of speech and behavioral signals.

Methods: Eligibility criteria for the study include children and adolescents between 8 and 17 years of age diagnosed with OCD, controls with no psychiatric diagnoses, and one parent of the participating youths. Youths and parents wear biosensors on their wrists that measure pulse, electrodermal activity, skin temperature, and acceleration. Patients and their parents mark OCD episodes, while control youths and their parents mark youth fear episodes. Continuous, in-the-wild data collection will last for 8 weeks. Controlled experiments designed to link physiological, speech, behavioral, and biochemical signals to mental states are performed at baseline and after 8 weeks. Interpersonal interactions in the experiments are filmed and coded for behavior. The films are also processed with computer vision and for speech signals. Participants complete clinical interviews and questionnaires at baseline, and at weeks 4, 7, and 8. Feasibility criteria were set for recruitment, retention, biosensor functionality and acceptability, adherence to wearing the biosensor, and safety related to the biosensor. As a first step in learning the associations between signals and OCD-related parameters, we will use paired *t* tests and mixed effects models with repeated measures to assess associations between oxytocin, individual biosignal features, and outcomes such as stress-rest and case-control comparisons.

Results: The first participant was enrolled on December 3, 2021, and recruitment closed on December 31, 2022. Nine patient dyads and nine control dyads were recruited. Sixteen participating dyads completed follow-up assessments.

Conclusions: The results of this study will provide preliminary evidence for the extent to which a wearable biosensor that collects physiological signals can be used to monitor OCD severity and events in youths. If we find the study to be feasible, further studies will be conducted to integrate biosensor signals output into machine learning algorithms that can provide patients, parents, and therapists with actionable insights into OCD symptoms and treatment progress. Future definitive studies will be tasked with testing the accuracy of machine learning models to detect and predict OCD episodes and classify clinical severity.

Trial Registration: ClinicalTrials.gov NCT05064527; https://clinicaltrials.gov/ct2/show/NCT05064527

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International Registered Report Identifier (IRRID): DERR1-10.2196/45123

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KEYWORDS

machine learning; signal processing; wearable biosensor; obsessive compulsive disorder; oxytocin; children; adolescents; family accommodation; psychiatric symptoms; clinical practice; automatic assessment tool; psychotherapy; mental health

Introduction

Background

Up to 3% of children and adolescents suffer from obsessive compulsive disorder (OCD) [1], which is characterized by repetitive, intrusive thoughts about threats of contamination, harm to self or others, loss of esteem, and committing moral transgressions, accompanied by repetitive or ritualized behaviors that can be time consuming, such as cleaning, checking, and ordering [2]. These obsessive thoughts and compulsive behaviors lead to marked distress, avoidance, and negative emotion (eg, anxiety and disgust) [2]. To regulate OCD-related distress, youths (individuals below the age of 18 years) may avoid situations that trigger obsessions and compulsions, perform rituals to neutralize feelings of incompleteness or magically remove the threat, or seek reassurance and help from others such as parents [3]. Parents are biologically primed to be sensitive to distress signals from their children [4,5]. Thus, parents may become distressed when their children are distressed. Interactions between parents and youths with OCD can be conflictual when parents refuse to accommodate their children's symptoms [6]. Youths may coerce or use verbal and physical aggression to elicit accommodation or parents may voluntarily provide family accommodation to regulate their own or their children's distress [7]. Family accommodation refers to ways in which parents help their children with OCD perform rituals, avoid stimuli that trigger symptoms, and change their own routines because of their children's OCD symptoms [8]. This reciprocal coordination of parent-child behavior is reflected in the parent's and child's physiology and may in part be facilitated by the oxytocin system [9]. In short, OCD is characterized by distress, negative emotions, and behavioral repertoires in individual youths and their parents that can be directly observed or indirectly detected in behavior, facial expressions, speech patterns, and physiological signals.

Automatic, continuous detection of these OCD signals would facilitate close monitoring of patient treatment progress and allow for more targeted interventions. The first-line treatment for OCD is cognitive behavioral therapy with exposure and response prevention (ERP) [10,11]. Continuous monitoring of distress levels and the function of distress during the treatment is essential for optimizing ERP [12]. Currently, patients are asked to rate their level of distress throughout an ERP task. Machine learning (ML) models that detect distress levels would automate distress monitoring and enable passive collection of objective measures allowing therapists to adjust exposures accordingly. Automatic, continuous distress detection may also facilitate the monitoring of treatment response across therapy sessions as well as monitoring disorder progression in individuals with subclinical symptoms. Finally, an important part of therapy is increasing awareness of the connections between thoughts, emotions, behaviors, and bodily sensations [13]. ML models that detect changes in mental states would facilitate increasing awareness of these connections.

Previous studies have demonstrated that ML models can detect physiological, behavioral, and speech signals that may be relevant to youth with OCD and thus aid in developing objective, intelligent monitoring tools that will enable timely actionable insights and interventions supporting psychotherapy in and outside of the clinic. A previous study demonstrated that ML models using 3 minutes of physiological data from a wearable biosensor worn by 20 youths could predict aggressive behaviors in youths with autism spectrum disorders 1 minute prior to their occurrence with relatively high accuracy [14]. Another study linked behavioral synchrony between 15 fathers and their 2-5–year-old children with Down syndrome to synchrony in the dyads' electrodermal activity (EDA) measured with wearable biosensors during a play session [15]. Using speech features as input, ML models have classified the severity of depression [16] and differentiated between children with and without internalizing disorders [17]. ML models that use speech features as input have also been utilized to gauge the quality of interpersonal interactions in a psychotherapy setting [18]. Finally, ML models (ie, computer vision models) are also capable of analyzing data from videos to track movement; infer emotion from facial expressions; and estimate visual attention, engagement, and interpersonal interaction from gaze-tracking information [19,20]. A systematic review showed that computer vision studies have sample sizes as low as 2 participants, often in the range of 10-20 and with more than 50 participants in rare cases, to demonstrate the capabilities of computer vision as a clinical tool [19]. To date, no artificial intelligence (AI) tools for monitoring clinically relevant parameters of OCD in youth are available and validated. Thus, Wrist Angel aims to develop AI tools capable of predicting OCD episodes, related (mal)adaptive parent behavior, and continuously monitoring OCD-related distress in youths and parents.

Goal of This Study

The purpose of this protocol is to provide a detailed account of our study design and methods for data collection. The primary aim of the Wrist Angel pilot study is to test the feasibility of using a wearable biosensor to detect OCD-related events and monitor clinical severity in children and adolescents. Ultimately, we aim to develop algorithms for detecting OCD-relevant parameters using physiological, audio, and visual signals as input and assess their accuracy. Thus, important information from the pilot study will be whether it is feasible to collect enough data to develop such algorithms. Specifically, we will test the feasibility of recruiting and retaining participants for brief experiments in the clinic and an 8-week observational

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study during which youths and parents wear a biosensor in their everyday lives. Feasibility will also be assessed in terms of biosensor safety and functionality, participant acceptance of the biosensor, and participant adherence to wearing the biosensor. We also explore methods for collecting ecological momentary assessments (EMAs) for labeling data collected in the 8-week observational study, including a mobile app for data collection. Our primary hypothesis is that the study protocol will demonstrate sufficient feasibility to support subsequent larger studies.

Biosensors are worn by youths and one of their parents, as OCD causes distress in youths with the diagnosis as well as their parents. Furthermore, efficacious psychotherapy approaches for OCD in youth intervene by working either exclusively with the child [13] or the parent [21]. We also include measurements of oxytocin levels and response in youths and parents, as oxytocin may hold important information about how family dynamics interact with OCD symptoms and the optimal type of psychotherapy to address these interactions [22].

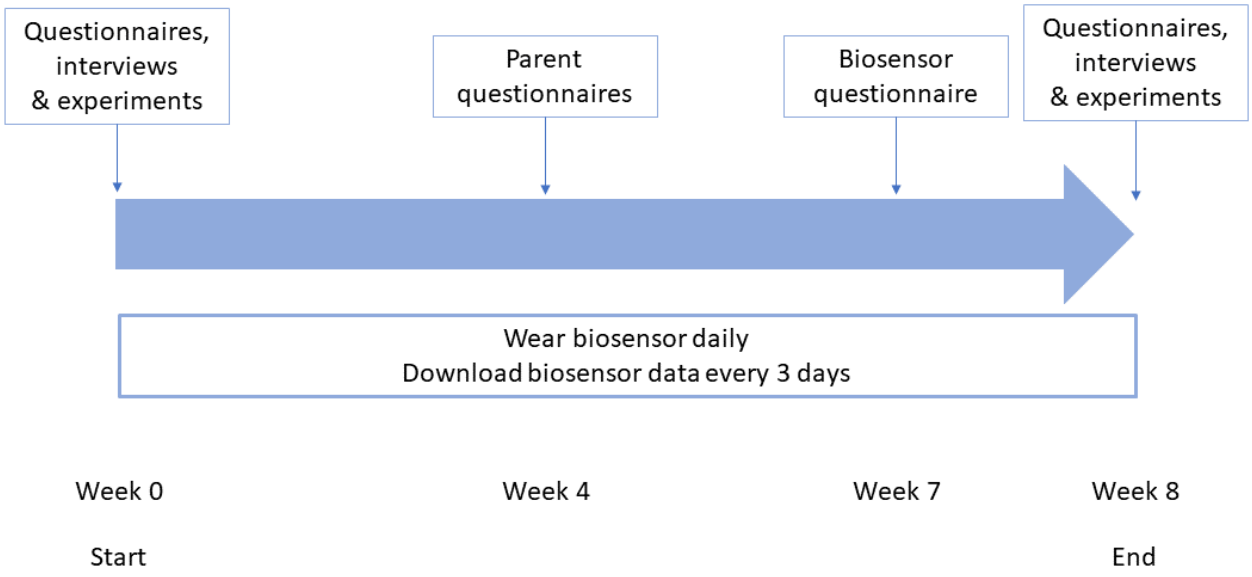
Methods

Design

The reporting of this protocol follows the recommendations for reporting protocols of pilot and feasibility trials [23]. We used the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2013 checklist for interventional trials [24] ignoring nonapplicable items, supplementing with relevant items from the CONSORT (Consolidated Standards of Reporting Trials) extension to pilot trials [25] and making relevant modifications according to the guidelines for reporting nonrandomized pilot and feasibility studies [26] (see Multimedia Appendix 1).

This is a nonrandomized, longitudinal pilot study, which includes a case-control comparison and repeated experiments. Youths and their participating parent are asked to wear a biosensor daily during waking hours for 8 weeks. In comparison, previous studies have collected data from 7 hours to 10 days [14]. To better understand these *in-the-wild* signals, we collect physiological signals and additional audio and visual signals under controlled conditions in the clinic. Figure 1 depicts the study design.

Figure 1. Design of the Wrist Angel pilot study. Lab visits were performed at week 0, or the start of the study (baseline), and at week 8. Participants completed self-rated questionnaires at weeks 0, 4, 7, and 8. Participants wore the biosensor for up to 8 weeks.



Setting

This pilot study is being conducted at a public child and adolescent mental health center within a psychiatry department of a university hospital in Denmark, covering the geographical area of the Capital Region.

Participants

We aim to enroll 10 patient-parent dyads and 10 healthy control-parent dyads. A small sample size was chosen for practical and economic reasons to establish proof of concept. We aim to collect a larger number of observations for each individual (8 weeks) compared to previous studies (less than 2 weeks) to assess feasibility within subjects in contrast to across subjects. The inclusion and exclusion criteria are summarized in Textbox 1.

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Textbox 1. Participant inclusion and exclusion criteria.

Patient inclusion criteria

- 8 to 17 years old (both inclusive)
- Primary or secondary diagnosis of obsessive compulsive disorder (OCD; International Classification of Diseases [ICD]-10 F42) [27] as set by a child and adolescent psychiatric team
- Primary psychiatric diagnosis that a psychiatrist determined is eligible for care within psychiatry
- Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS) [28] entry total score >7 points
- Normal intellectual functioning as indicated by parent or youth report, clinical observation, and/or the appropriate full-scale Wechsler Intelligence Scale (for Children-Fifth Edition or Wechsler Adult Intelligence Scale-Fourth Edition) [29,30] (Intelligence Quotient>70)
- Signed informed consent from legal guardian(s)

Patient exclusion criteria

- Disorders that contraindicate study participation, including substance dependence syndrome (ICD-10 F1x.2), schizophrenia/paranoid psychosis (ICD-10 F20-25 and F28-29), mania or bipolar disorder (ICD-10 F30 and F31), depressive psychotic disorders (ICD-10 F32.3 and F33.3), intellectual disorder (ICD-10 F70-79), pervasive developmental disorder (ICD-10 F84.0-84.4 and F84.8-84.9), not including Asperger syndrome [27]
- Any condition (eg, allergies, eczema, hypersensitivity associated with Asperger syndrome) that would prevent the child or parent from wearing a wristband biosensor
- Current participation in other OCD trials

Control participant inclusion criteria

- 8 to 17 years old (both inclusive)
- Lives in the catchment area of the study site during the study
- Normal intellectual functioning as indicated by parent or youth report, clinical observation, and/or the appropriate full-scale Wechsler Intelligence Scale (for Children-Fifth Edition or Wechsler Adult Intelligence Scale-Fourth Edition) [29,30] (Intelligence Quotient>70)
- Signed informed consent from legal guardian(s)

Control exclusion criteria

- Any current or previous psychiatric or intellectual disorders according to ICD-10 criteria, as assessed by Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL) [31] at the time of screening
- Current participation in other OCD trials
- Any condition (eg, allergies, eczema) that would prevent the youth from wearing a biosensor on the wrist

Parent inclusion criteria

- Has a child participating in the current study
- Signed informed consent

Parent exclusion criteria

- Any condition (eg, allergies, eczema) that would prevent them from wearing a biosensor on the wrist

Concomitant Care

There are no prohibited forms of care or interventions. Patients could be on wait lists, in any form of psychotherapy, or taking any form of pharmacological treatment.

Recruitment

Patient participants are recruited from patients referred to the child and adolescent mental health center with probable OCD symptoms or a set OCD diagnosis. Potential patient participants' journals are first screened for eligibility. Case workers then ask patient families if our research group may contact them about our research project. The control group is recruited from the control group of the Treatment Effects of family based Cognitive Therapy in children and adolescents with Obsessive compulsive disorder (TECTO) trial [32] and schools in the catchment area. After obtaining permission from the school administration, flyers are posted in the school or the school intranet.

Psychologists, medical doctors, and masters-level medical and psychology students screen and assess potential participants. For previous TECTO participants, we use their clinical information from the TECTO trial to determine eligibility. Potential control participants who contact us are screened for intellectual disability and psychiatric diagnoses using the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL) criteria [31].

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The recruitment period ranged from September 15, 2021, until December 31, 2022.

Ethical Considerations

Approval and Consent

The Ethics Committee of the Capital Region of Denmark approved this study on June 17, 2021 (H-18010607-79689). This study is registered at ClinicalTrials.gov (NCT05064527; October 1, 2021). The interdisciplinary team of principal investigators (the authors) are responsible for the design and conduct of the study and preparation of the protocol and revisions. The principal investigators at the hospital are responsible for recruitment and monitoring participants. Any major modifications or protocol deviations are discussed with the other principal investigators during weekly meetings. Any major protocol modifications are reported to the Ethics Committee and amended on ClinicalTrials.gov.

After families assent, we inform the families about the project verbally, in person or over the telephone, and send written participant information via secure email. After receiving verbal and written information about the study, youth and parents are given 24 hours to deliberate. A psychologist or medical doctor obtains signed consent forms from legal guardians of youth and their participating parent along with assent from participants before participating in the study. A model consent form is available in Multimedia Appendix 2.

Safety

We are not aware of any major risks or safety issues associated with participation. Adverse reactions to the biosensor are monitored throughout the study (see Multimedia Appendix 1). Any serious adverse events will be reported to the sponsor and The Ethics Committee of the Capital Region of Denmark. Participants have the right to submit complaints and seek compensation for injuries or unsatisfactory treatment related to the study.

Compensation

Child and parent participants receive a DKK 600 (~US $90) gift card upon completion of their participation and return of the biosensor.

Withdrawal/Discontinuation From the Study

A participant who no longer wishes to participate in the study can withdraw their informed consent at any time without explanation nor consequences for their treatment. Consent can be withdrawn from parts of the study. For example, participants can consent to biosensor data collection and withdraw their consent for video data. Participants are also allowed to withdraw from parts of the pilot study such as the experiments, the 8-week observation period, and completion of measurements. We withdraw participants if they experience an untenable adverse reaction related to the biosensor or data collection procedures, they consistently do not attend data download meetings, the child participant receives a diagnosis included in our exclusion criteria, or we otherwise deem continued participation to be unsafe. We modify measurement requirements in the case of nonserious adverse events (eg, skin irritation at the site of the biosensor) and reduce burden of measurements if they are too frequent for the participant or found to be incomprehensible to the participant.

Data Management

Data collection, storage, and security adhere to the regulations set by The Knowledge Centre on Data Protection Compliance in The Capital Region of Denmark and follow the General Data Protection Regulation of the European Union. Signed data processing agreements between The Capital Region of Denmark and the Technical University of Denmark allow our interinstitutional research team to share data for analysis. Participating child-parent dyads are identified using a unique identification number with each dyad's data linked to the unique identifier.

Original electronic, paper, and relevant medical records are source documents. The research team will ensure that all data entered in the central database represent a true record of events. Study data are collected and managed using Research Electronic Data Capture (REDCap) electronic data capture tools hosted at The Capital Region of Denmark [33,34]. REDCap is a secure, web-based software platform designed to support data capture for research studies, providing (1) an intuitive interface for validated data capture, (2) audit trails for tracking data manipulation and export procedures, (3) automated export procedures for seamless data downloads to common statistical packages, and (4) procedures for data integration and interoperability with external sources.

Empatica, the manufacturer of the E4 biosensor, is also a data processor. Physiological signals recorded by the E4 biosensor are stored on a central database managed by Empatica. Anonymized biosensor data, which can only be traced to our research group, are transferred to Empatica's E4 Connect via a secure Amazon Web Service server. E4 Connect stores physiological signals under unique device identifiers. Our research group then downloads and stores physiological signal data on a logged drive of The Capital Region of Denmark where the data are connected to the unique participant identification number.

Wearable Biosensor

Prior to the experiments at baseline, we instruct participants on how to use and care for the biosensor, which the youth and parent then place on their nondominant hand. Following the manufacturer's manual, we inform the participants that they should not look directly at the light-emitting diode lights, that the biosensor tolerates splashes of water during handwashing and rain but not submersion, and that the biosensor should be stored at room temperature and out of direct sunlight. Participants are asked to charge the biosensor at night. We demonstrate how to put on the wristband, how to turn it off and on, how to tag events, and how to click the charging cradle on and off the wristband. All participants received an abridged user manual that we translated into Danish.

The E4 (Empatica, Milan, Italy) wristband is a US Food and Drug Administration (FDA)-approved Class II device for adults and children (FDA 2018, 2019) and a European Union Class IIa device denoting that it is a noninvasive monitoring device [35]. The E4 battery can last over 48 hours and can store up to

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60 hours of data. The E4 wristband contains a photoplethysmographic (PPG) sensor, an EDA sensor, a 3-axis accelerometer, and an optical thermometer. PPG uses infrared light to measure changes in blood volume (ie, blood volume pulse) calculated by an algorithm that uses light signals during red and green exposure, sampled 64 times per second, as input [36]. The interbeat interval timings and heart rate are computed using the blood volume pulse signal as input to algorithms [36]. Under conditions of slight movement (<30% of the time), it is possible to use the interbeat interval to compute heart rate variability. The EDA sensor measures skin conductance sampled 4 times per second [37]. The accelerometer measures movement on three axes at a sampling rate of 32 times per second. The optical thermometer measures skin temperature at a sampling rate of 4 times per second [37].

Data Collection

Assessments

The assessment time of each measure is outlined in Multimedia Appendix 3.

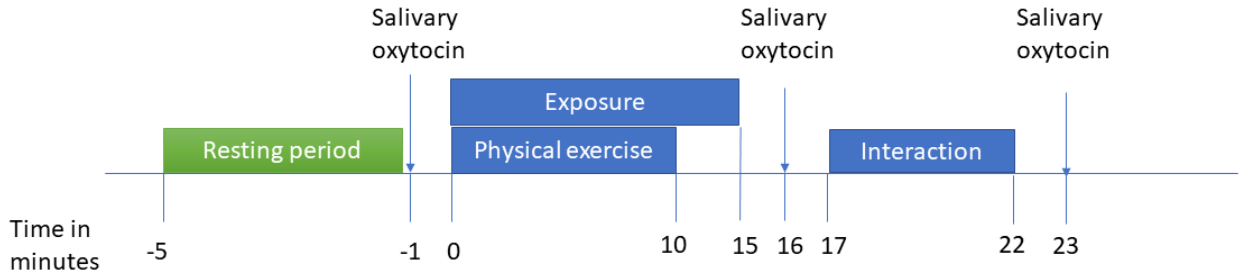
After recruitment (baseline assessment), we obtain information about mental health treatment history for the patients by asking the youths and parents and checking the youths' medical journals. Medical journals are also used to obtain patient multiaxial diagnoses. During baseline testing, we ask participating parents to report probable or confirmed psychiatric diagnoses in the youths' first-degree relatives, and we ask youths about their current stage of puberty using the Tanner stages [38]. After baseline testing, participating families are asked to complete a set of questionnaires online to provide demographic information and baseline measures of youth quality of life, family dynamics, and parent symptoms of affective disorders. The demographic questionnaire includes questions about age, sex, and country of origin for the youths and parents as well as parents' highest attained level of education. Youths and parents also complete a questionnaire that includes questions about menstruation, hormone medication use, pregnancy, and breastfeeding. Information about hormones and puberty are collected as these are factors that may influence salivary oxytocin levels. Parents are also asked to complete the KIDSCREEN-52 [39], Parental Stress Scale (PSS) [40], Depression, Anxiety and Stress Scale (DASS) [41], and the Family Environment Scale [42]. Youths receive the KIDSCREEN-52 [39]. Parents of patients are also asked to complete a modified version of the Family Accommodation Scale–Parent Rated (FAS-PR) [43,44].

At the 8-week follow-up, patients' OCD severity is assessed with the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) before the experiments. After the experiments, all youth-parent dyads are interviewed for a maximum of 30 minutes about their experiences with the biosensor and their opinions about potentially using an app for data collection. Patient interviews are video- and audio-recorded. All participant answers are paraphrased and recorded in the REDCap database during the interview.

Experiments

Before the experiments at the beginning (week 0) and end (week 8) of the study, a researcher interviews patients about their current OCD symptoms using the symptom checklist from the CY-BOCS and the distress level associated with each endorsed symptom on a scale from 0 to 10. The timeline for the experiments is depicted in Figure 2.

Figure 2. Experiment design. Participants complete experiments during lab visits at week 0 and 8. Before providing the first saliva sample, participants rest for 5 minutes. Afterward, patients complete an exposure task for up to 15 minutes and controls are physically active for about 10 minutes. All participants complete a parent-child interaction task that lasts for 5 minutes. Saliva samples are collected again, before and after the interaction task.



The experiment starts with a 5-minute resting period, in which the youth and parent are left in a room and are asked to relax and refrain from speaking and touching each other for 5 minutes. Patients complete an exposure task for up to 15 minutes led by a mental health professional in the research team in the presence of the parent unless the patient prefers to complete the exposure without the parent. The preparation and delivery of the exposure exercise were inspired by a treatment manual for youth with OCD [45] (page 73). The clinical researcher delivering the exposure provides psychoeducation about OCD and explains the procedure and rationale behind the exposure. During this ERP preparation phase, patients are asked to report their expectation for what will happen to their distress level during ERP with a multiple-choice question: (1) distress will increase until it is unbearable, (2) distress will remain the same, (3) distress will decrease over time. Throughout the exposure, patients are asked to report their level of distress.

Control dyads complete a physical activity task, in which they are shown an exercise dance video lasting approximately 10 minutes. The participants are not required to follow the video, but are asked to move their bodies in a way that increases their heart rate for the duration of the task. The physical activity task allows us to examine the performance of the biosensor under

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intense movement and measure salivary oxytocin reactivity following physical stress. In the final controlled condition, patient and control dyads complete a parent-child interaction task, in which they are asked to plan their best warm-weather (baseline) and cold-weather (follow-up) vacation together, inspired by previous work [46,47]. Saliva samples are collected from the youth and the parent after the resting period, exposure task, physical activity, and the parent-child interaction task.

For behavioral coding, the exposure and parent-child interaction tasks are video- and audio-recorded. Human coders will code the videos for interlocutor positive and negative affect, anxiety, arousal, affective touch, and synchrony, as well as parent sensitivity and youth engagement using the Coding Interactive Behavior manual [48].

Exposure sessions will also be coded for youth distress, avoidant/approach behavior, reassurance and proximity seeking, as well as parent accommodating behavior and discouraging avoidance, using items from the Exposure Rating Scale for Exposure and Response Prevention [49] and the Exposure Process Coding System [12,50]. Parent acceptance statements and confidence statements will be coded based on definitions in a treatment manual for OCD and anxiety disorders in youth targeting parents [51].

Observation Period (Weeks 1-8)

We ask participating youths and parents to wear the biosensor during their daily routines for 8 weeks from the time they wake up until the time they go to sleep.

Patients are asked to push the event tag button every time they feel stressed by their OCD symptoms. Their parents are asked to tag every time they notice their child is distressed by their OCD symptoms. Control youths are asked to push the button when they feel very scared. Control parents are asked to push the button when they notice that their child feels very scared. Researchers meet with participants up to twice a week during the 8 weeks of continuous data collection to exchange biosensors full of data with empty biosensors. A byproduct of having up to two weekly in-person meetings with participants to download biosensor data securely throughout the observation period is an implicit reminder to wear the biosensor.

Ecological Momentary Assessment

We are developing mobile apps for EMAs of child and parent emotional states to produce more data labels during the observation period. The Copenhagen Center for Health Technology Research Platform, on which the apps are built, is a research tool for data collection [52]. The child and parent apps contain information about the study and versions of the Positive and Negative Affect Questionnaire [53,54] that are triggered at random times during the day to offset the potential negative focus on OCD and anxiety symptoms from tagging these emotional events on the biosensor. In addition to reporting their emotional state, children and parents report whether they are in the company of the other, other family members, or friends to establish the context of EMA data, similar to previous studies [55]. The patient app also includes daily guided exposure tasks to help patients practice ERP outside of the clinic and a weekly form for reporting OCD symptoms and their severity.

Study End Points

Defining Feasibility

The following study-specific feasibility criteria were developed: recruitment; retention rate; biosensor functionality; acceptability of the biosensor; compliance with wearing the biosensor; safety related to the biosensor; and physiological, audio, and visual markers of OCD. These are defined in Table 1.

Table 1. Operationalized feasibility success criteria.

Feasibility indicator	Criteria for success
Recruitment: consenting invited families (%)	>30% of invited families consent
Retention rate (%)	>80% retention
Biosensor functionality: unfixable malfunctions (N)	<10% irreparable malfunctions
Acceptability of biosensor: user experience questionnaire	>85% positive attitudes
Compliance	
Days participants wear biosensor (N)	Biosensor worn >30% of days in study
Tagged events, falsely tagged events, missed events (N)	False events identified; >70% accurately tagged events
Safety: adverse reactions to biosensor[a]	No major injuries or worsening of symptoms reported
Comparison of physiological signals as measured by the wearable biosensor; audio or visual signals; and reported, observed, or biochemical endpoints as markers of clinically relevant obsessive compulsive disorder parameters	>70% accuracy or high correlation with relevant endpoint

[a]Adverse reactions are defined as any negative effects of the biosensor. Investigators monitor adverse reactions at in-person visits, and they can be reported by parents, youths, or case workers.

Biosensor Experience

Children's and parents' level of physical (dis)comfort of wearing the biosensor, degree of satisfaction with the design, concerns of stigmatization, and data security as well as usability are assessed with a questionnaire in week 7. There are 13 multiple-choice questions answered on a 4-point scale (0=disagree a lot to 3=agree a lot) and one open-ended question. The English versions of the patient questionnaire and experience

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of biosensor questionnaire are provided in Multimedia Appendix 4.

Participants and parents are interviewed together after the experiments in week 8 about their experiences with the biosensor. They are also asked about their thoughts on the convenience and data security of using a mobile app for data collection (see Multimedia Appendix 4). At the end of the interview, participants are also asked whether they have any feedback about any aspect of their participation in the study.

Biosensor Compliance

Compliance to wearing the biosensor will be measured separately for youths and parents. Signals from the biosensor indicate whether the biosensor was worn while turned on. For the experiments, compliance is a binary outcome: either the participant wore the biosensor for the experiments or not. We will provide reasons for noncompliance (eg, discomfort or technical problems with the biosensor). For the observational period, we will count the number of days the participants wore the biosensor and define adherence as more than 30% of days (1 day=at least 3 hours) in 1 month of participation. The biosensor provides time data per recording session in hours, minutes, and seconds, and provides the dates on which the sessions were recorded. We will also report total time in hours that each participant wore the biosensor.

OCD Markers

Distress

During the lab visits, OCD distress is rated by youths in two ways. First, OCD distress related to each current OCD symptom is rated before ERP sessions on a symptom hierarchy on a scale from 0 (no distress) to 10 (maximum distress). During ERP sessions, the clinical researcher asked youths to rate their current distress levels after 1, 3, 5, 7, 10, and 15 minutes on the same scale as the symptom hierarchy. When OCD distress is rated during an ERP session, it is called subjective units of distress (SUDs) [56].

During the in-the-wild observational period, OCD distress is a binary measure, with patients and their parents marking events of OCD distress. Control dyads mark occurrences of youth fear to compare clinical to subclinical distress.

ERP Quality

Two major theories for mechanisms of change in ERP include emotional processing theory and inhibitory learning theory. According to emotional processing theory, ERP works by replacing an association between a stimulus and a feared outcome with a new harmless association [57,58]. Here, quality ERP sessions require habituation, defined as sessions in which distress levels decrease from the first measurement until the last measurement, and the decrease in distress occurs in the absence of avoidance, reduced task difficulty, and accommodation as defined previously [12]. This theory also assumes that there is an optimal level of distress that is neither too low nor too high for conducting effective exposures [59]. As subjective distress may not correspond to physiological levels of arousal, we will use both measures. Using SUDs and physiological measures of arousal, we will categorize low, medium, and high distress.

Alternatively, the inhibitory learning theory states that successful exposures are characterized by reduction in expectancy of an aversive outcome by creating alternative harmless associations that compete with the feared expectations [60]. A therapeutic expectancy violation occurs when an anticipated negative outcome fails to actualize and a benign or positive outcome occurs instead [60,61]. We will calculate distress-related expectancy violations in the baseline and follow-up exposure sessions in three ways. First, an expectancy violation occurs when the patient's expected distress trajectory as reported in the multiple-choice question before an ERP does not match the actual distress trajectory during ERP. Another way that we will define expectancy violation is by subtracting the actual maximum distress level during ERP by the distress level reported prior to an ERP session on the symptom hierarchy [62]. The final way that we will define an expectancy violation is by subtracting the distress level reported prior to ERP on the symptom hierarchy by the actual distress level at the end of an ERP session [62].

OCD Symptom Severity

The CY-BOCS, the gold-standard semistructured clinical interview for assessing OCD symptom severity in youths on a scale from 0-40 [63], is completed at baseline and at week 8 of follow-up. Items 1-10 are summed to obtain a total OCD severity score, with higher scores indicating higher severity. Items 1-5 can be summed to obtain an obsession severity score and items 6-10 can be summed to obtain a compulsion severity score. Change in OCD severity is calculated by subtracting the week 8 CY-BOCS score from the baseline CY-BOCS scores. Remission is defined as a 30% or greater reduction in the CY-BOCS score from baseline to follow-up. The CY-BOCS also contains information about types of OCD symptoms, such as those marked by anxiety or disgust. We expect these two mental states to have different effects on physiological signals as previously found [64].

Quality of Life

KIDSCREEN-52 is a parent- and child-rated questionnaire of child (8-18 years) health-related quality of life [39]. Higher scores indicate a better quality of life. In this study, we are particularly interested in the following subscales: psychological well-being, mood and emotions, autonomy, and parent relation and home life. These subscales provide information about the internal states of patients and controls as well as family dynamics.

Family Interactive Processes

The FAS-PR is completed by parents of patients and asks parents to rate how often they modify their routines due to their children's OCD and how frequently they help their children complete OCD rituals [43]. One item assesses how much distress the parents experience because of their accommodating behavior. Three items ask parents to rate how unhappy, anxious, angry, or violent their children become if not accommodated [44].

To obtain insight into the family interactive characteristics of patients and controls, we ask all parents to complete the following subscales on the FES-PR: cohesion, expressiveness,

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conflict, independence, organization, and control. The FES-PR assesses the rater's current perception of their family environment [65].

The PSS contains 18 items that ask parents to rate how stressful they experience parenting their participating child [40]. Parents rate the extent to which they disagree or agree on a 5-point scale (1=highly disagree to 5=highly agree) to statements about their role as parents.

Parent Affective Symptoms

Parents report their symptoms of depression, anxiety, and stress on the 42-item DASS [41,66,67]. These internal states of parents will likely affect their physiological signals.

Oxytocin

Oxytocin levels are measured in youths and their parents before and after the controlled conditions during lab visits, as described in the Experiments section above. Salivary oxytocin response is defined as a change in oxytocin levels measured before and after a condition (physical activity, exposure, parent-child interaction). We ask participants to refrain from eating 2 hours and drinking 30 minutes before collecting the first saliva sample. To collect one saliva sample, participants are asked to chew on a Salivette (Sarsted, Rommelsdorf, Germany) for 60 seconds. The saliva samples are frozen at –20°C. At the biochemistry laboratory, the samples are centrifuged twice with a 2-day interval at 4°C at 1500 ×*g* for 20 minutes. The obtained liquid samples are lyophilized at –80°C/0.02 mbar overnight and stored at –20°C. On the day of the assay, the freeze-dried samples are reconstituted with assay buffer. The factor depends on the amount of saliva before freeze-drying. Samples are concentrated three times. The immunoassay is performed with the Enzo (NY, USA) oxytocin kit or a kit of comparable detection sensitivity. Measurements are performed twice, and the sample concentrations are calculated using WorkOut version 2.5 software that is provided with the enzyme-linked immunoassay reader according to relevant standard curves.

Measuring oxytocin in saliva is a noninvasive and easy way of estimating peripheral oxytocin levels [68]. Salivary oxytocin is sensitive to manipulations of stress and social interaction, as demonstrated by increases in oxytocin levels after 10 minutes of physical exercise [69], anticipation of and engagement in a socially stressful condition [70], and a 7-minute parent-child interaction task [71]. Higher oxytocin levels have been associated with parental synchrony and affect synchrony between parents and infants [72]. Higher oxytocin levels have also been linked to lower heart rate [69,73].

Synchrony

Synchrony is operationalized as two processes that are or become correlated above chance levels [74]. We will calculate synchrony between youth and parent affect, behavior, oxytocin, and physiological signals.

Data Analysis

Analysis Plan

We will summarize the demographic and clinical characteristics of the patients, control youths, parents of patients, and parents of control youths at baseline. At baseline, week 4, and week 8, we will summarize parental stress for patients and controls and family accommodation for patients in plots. At baseline and week 8, we will summarize child quality of life for patients and controls and OCD severity for patients in plots. We will also summarize physiological signals, accelerometer data, facial emotion recognition, movement, speech, and observational codes under the controlled conditions (rest, exercise, exposure, parent-child interaction) separately. Physiological and accelerometer data collected in the wild will be summarized in a plot with time on the x-axis, separately for patients and controls. Means with SDs will be reported for continuous variables and frequencies and proportions will be reported for categorical variables. We will not perform imputations of missing data. Data will be analyzed on an intention-to-treat basis regardless of protocol violations.

Model Development and Testing

Detailed statistical/ML analysis plans will be published separately. Table 2 provides an overview of the primary prediction targets and the hypothesized associations among signals and clinical endpoints. As a first step in learning the associations between signals and OCD-related parameters, we will plot the progression of endpoints (responses for future paired *t* tests) and use mixed effects models with repeated measures to assess associations between oxytocin, individual biosignal features, and outcomes such as stress-rest and case-control comparisons. Confounding factors and important interactions will be included to the extent possible. These initial statistical results will mainly serve to estimate sample sizes for future studies. Substudies will focus on assessing automating behavioral observations using audio and video data from parent-child interactions and exposure sessions.

We will test the feasibility of developing AI tools that use signals from a wearable biosensor and audio and video recordings of human interactions. Audio and video recordings are collected at two time points for each participant dyad, which will increase power of these analyses. Furthermore, the exposure tasks last for over 20 minutes and will be sliced into different events: ERP preparation, ERP, ERP debrief. These events will be segmented in 5-minute slices for analyses, which will increase the number of observations.

We will use ML models for classification and prediction of OCD-related and physical stress, as well as prediction of in-the-wild distress episodes. We will use a double-loop cross-validation for model selection and to assess model accuracy within and across subjects. Differences in accuracy within and across subjects can provide information on the needed number of observations for developing robust models in the future. We will use pretrained speech emotion recognition models and computer vision models to estimate behavioral labels from audio and video, respectively.

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Table 2. Overview of clinically relevant parameters and hypothesized associations among signals and clinical endpoints.

Prediction target	Definition	Physiological signals	Paralinguistic signals	Linguistic signals	Visual/behavioral signals	Biochemical signals	Ground truth/validation
OCD[a] distress (youth)	Stress, fear, worry, disgust, embarrassment, shame, anger, sadness caused by obsessions/compulsions	Change in HR[b] depending on emotion; increased EDA[c] and temperature	High activation; negative valence	Negative emotion statements	Negative emotion facial expression; increased movement	Low oxytocin	Biosensor tags; (SUDs[d]); child negative emotions (CIB[e]); avoidance (ERP[f]); child stress (FAS[g]); consequences (CY-BOCS[h])
OCD severity	Time spent on, interference, and distress caused by obsessions/compulsions; resistance of and control over obsessions/compulsions	Change in HR depending on emotion; increased EDA and temperature	High activation; negative valence	Negative emotion statements	Negative emotion facial expressions	Low oxytocin	Symptom hierarchy; child negative emotions (CIB); avoidance (ERP); mood and emotion (KIDSCREEN-52)
OCD distress (parent)	Stress, embarrassment, worry, shame, anger, sadness caused by youth's OCD	Change in HR depending on emotion; increased EDA and temperature	High activation; negative valence	Distress statements	Negative emotion facial expressions	Low oxytocin	Biosensor tags; parent negative emotions (CIB); parent stress (FAS); parental stress (DASS[i])
Overdemanding parenting [51]	Expecting youth not to feel distressed despite lived experience [51]	HR, HRV[j], EDA; lower resting HRV; asynchrony	High activation; negative valence; asynchrony; interruptions	Example: "You must…"	Negative emotion facial expressions	Low oxytocin; low concordance between parent and child	Intrusiveness, criticism, low validation (CIB); conflict (FES[k]); low demand (FAS, item 5)
Overprotective parenting [51]	Cognitions/behaviors aimed at protecting child from distress or harm [51]	HR, HRV, EDA; lower resting HRV; asynchrony	Positive valence; asynchrony	Protective statements	Proximity; affective touch	Low oxytocin; low concordance between parent and child	Accommodation (ERP); participation and modification (FAS); autonomy (KIDSCREEN-52)
Supportive parenting [51]	Nonjudgmental, emotional and cognitive, empathy and conviction that child can cope [51]	Higher resting HRV; HR, HRV, EDA; synchrony	Positive valence; entrainment [18]	Accepting and confidence statements [51]	Movement synchrony	High oxytocin; high concordance between parent and child	Youth engagement, parent sensitivity (CIB), synchrony (ERP); discourage avoidance (FAS low score); cohesion (FES); parent relation (KIDSCREEN-52)

[a]OCD: obsessive compulsive disorder.

[b]HR: heart rate.

[c]EDA: electrodermal activity.

[d]SUD: subjective unit of distress.

[e]CIB: coding interactive behavior [48].

[f]ERP: exposure and response prevention.

[g]FAS: family accommodation scale [43,44].

[h]CY-BOCS: Children's Yale-Brown Obsessive Compulsive Scale.

[i]DASS: depression anxiety and stress scale [41].

[j]HRV: heart rate variability.

[k]FES: family environment scale [42].

Feasibility Outcomes

Study-specific feasibility criteria are defined in Table 1. Where appropriate, we will provide 95% CIs. Feasibility outcomes are binary: "success" indicates that the a priori feasibility criteria have been met, whereas "revise" indicates that the criteria have not been met. "Success" will indicate that no or small changes are needed before proceeding with a larger study and "revise" will indicate the need for major changes before proceeding.

We will also identify the clinical measures needed to validate the AI tools. Measures will be retained for further studies if they are comprehensible to the participants, do not overburden participants, and can be practically delivered to participants without overburdening research staff. EMAs about emotions should not exceed 60 seconds to complete. Questionnaires and

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semistructured interviews about participant experiences with the biosensor will be used to generate hypotheses that can be tested in a larger study and, if relevant, to improve researcher scripts for introducing the biosensor to participants. We will report frequencies of responses to the user experience questionnaires.

Dissemination

Study results will be released to participants and referring clinicians upon request. Results will be published in scientific journals and conferences targeting mental health professionals and researchers within computer science. We follow authorship guides set by the National Academies of Sciences, Engineering, and Medicine [75] and the International Committee of Medical Journal Editors [76].

Results

The first participant was enrolled on December 3, 2021, and recruitment closed on December 31, 2022. Nine patient dyads and nine control dyads were recruited. Sixteen participating dyads completed follow-up assessments. We expect to submit results of our study by the summer of 2023.

Discussion

Study Overview and Significance

One percent of children and adolescents will be diagnosed with OCD before their 18th birthday [77]. Today, diagnosis and severity ratings depend on self-report and clinical observation, and no objective measures exist for OCD symptoms. ML models that detect distress levels would automate clinical severity monitoring and passively collect objective measures allowing therapists to adjust exposure treatment accordingly. Automatic, continuous distress detection may also facilitate the monitoring of treatment response across therapy sessions as well as monitoring disorder progression in individuals with subclinical symptoms. Finally, ML models that detect changes in mental states would facilitate increasing awareness of connections between thoughts, emotions, behaviors, and bodily sensations, forming an essential part of effective therapy [13].

In this protocol, we present the study design and methods of a pilot study that will evaluate the feasibility of using a commercially available wearable biosensor to monitor symptoms of OCD in youth from physiological signals. Embedded in our pilot longitudinal, case-control study are substudies of audio/visual signals and actively collected biochemical parameters from youths and parents with the goal of detecting and predicting episodes of OCD-related distress.

Potential feasibility issues involve recruiting and retaining participants, biosensor safety and functionality, participant adherence to wearing the biosensor, and logistics of collecting and processing data. The size and design of the biosensor and the lack of a substantial clinical intervention may deter participation. User experience questionnaires and interviews explore themes of stigma attached to wearing a biosensor. A previous study demonstrated that a group of 16 youth, aged 10 to 17 years, participating in a study of similar length wore a similar biosensor for an average of 11 out of 30 days and one child managed to wear the wristband 5 days per week [78]. The study aimed to develop a personalized weight management program with the E3 wristband and asked youths to wear the biosensor for at least 5 days per week for 3 months [78]. No technical difficulties were reported for the wristband [78]. Youth in the wristband condition reported a similar level of (dis)comfort as youth in the control condition [78]. Nonetheless, the researchers speculated as to whether the youths did not wear the wristband due to concerns that it would attract unwanted attention from peers [78]. Some participants expressed concern of being surveilled by the biosensor [78]. To address potential concerns in our participants, we will thoroughly explain what the wristband is and is not capable of and coach the participants in informing others about their new accessory. The E4 wristband has been used to monitor arousal in 15 children as young as 2 years with Down syndrome during 7-minute parent-child interaction sessions [15]. EDA data from children were deemed useable (90% of interactions tracked) for 27 out of 30 interactions; from parents, EDA data were useable for 23 out of 30 interactions [15]. Missing data were due to 7 instances of software malfunctions [15].

A byproduct of having up to two in-person meetings with participants to download biosensor data securely throughout the observation period may be an implicit reminder to wear the biosensor. We will examine whether participants were more likely to wear the biosensor on data collection days. Asking youths with obsessions, compulsions, and safety behaviors to tag OCD-related events may interact with or become a symptom. This theme is also explored in the user experience interview.

Strengths and Limitations

The strengths of the protocol include the ecological validity of in-the-wild passively collected physiological signals; collecting physiological signals under repeated controlled conditions; the case-control design; and supplementing with multimodal signals from audio, video, and biochemistry. One limitation of the protocol is the small sample size. The sample size limits generalizability of the statistical and ML results. The ML models risk producing false-positive predictions. In the case of high individual variation, false negatives will also be a risk. Nonetheless, we have enough observations to evaluate the feasibility of making the proposed predictions. We have up to 8 weeks of physiological signal data per participant. Moreover, previous studies indicate that these physiological signals are sensitive to strong sustained stressors [75] such as those experienced in OCD.

Conclusion

If the findings of this pilot study support our hypotheses of sufficient feasibility, subsequent larger studies will further develop and test ML models that can detect and predict OCD severity, distress, and related family processes that maintain OCD. Ultimately, these innovations will contribute to increasing knowledge about objective markers of OCD severity and OCD-related, clinically relevant family processes. Furthermore, the AI tools we aim to develop have the potential to assist in validation of assessments of the severity of psychiatric disorders and inform treatment decisions. Such AI tools would enable

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monitoring disease and treatment planning. For example, automatic clinical severity classification models could be applied in the therapy room or in the patients' everyday lives while youths are on treatment wait lists to monitor symptoms or between therapy sessions to monitor and support treatment progress.

Acknowledgments

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Data Availability

After results are published, we will strive to make a depersonalized data set publicly available in a legally compliant way. We will open-source the machine learning code where relevant in conjunction with publications.

Authors' Contributions

All authors made substantial contributions to the conception and design of the work. NNL and LKHC drafted the manuscript. All authors revised the work critically for important intellectual content, approved the final version, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT Checklist.
[PDF File (Adobe PDF File), 121 KB - resprot_v12i1e45123_app1.pdf]

Multimedia Appendix 2
Model consent form.
[PDF File (Adobe PDF File), 59 KB - resprot_v12i1e45123_app2.pdf]

Multimedia Appendix 3
Assessment timeline.
[PDF File (Adobe PDF File), 27 KB - resprot_v12i1e45123_app3.pdf]

Multimedia Appendix 4
Sample questionnaires and interviews.
[PDF File (Adobe PDF File), 194 KB - resprot_v12i1e45123_app4.pdf]

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Abbreviations

AI: artificial intelligence
CONSORT: Consolidated Standards of Reporting Trials
CY-BOCS: Children's Yale-Brown Obsessive-Compulsive Scale
DASS: Depression Anxiety Stress Scales
EDA: electrodermal activity
EMA: ecological momentary assessment
ERP: exposure and response prevention
FAS-PR: Family Accommodation Scale- Parent Rated
FDA: Food and Drug Administration
K-SADS-PL: Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version
ML: machine learning
OCD: obsessive compulsive disorder
PPG: photoplethysmography
PSS: Parental Stress Scale
REDCap: Research Electronic Data Capture
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
SUD: subjective unit of distress
TECTO: Treatment Effects of family based Cognitive Therapy in children and adolescents with Obsessive compulsive disorder

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Protocol

The National Coordinated Citrien eHealth Program to Scale Up Telemonitoring: Protocol for a Before-and-After Evaluation Study

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Abstract

Background: Sustainable implementation of telemonitoring in health care is challenging, especially if one aims to scale up telemonitoring initiatives nationwide. The National collaborative eHealth program in the Netherlands is supporting the nationwide upscaling of telemonitoring in 3 clinical domains by implementing telemonitoring in all Dutch university medical centers (UMCs). The chosen telemonitoring concepts are (1) telemonitoring solutions in the domain of cardiology, (2) telemonitoring solutions providing care from a distance in obstetrics, and (3) telemonitoring solutions monitoring vital functions in hospital wards.

Objective: The aim of this study is to evaluate the upscaling of telemonitoring in Dutch university hospitals in order to gain a better knowledge of the process, methods, and outcomes of nationwide upscaling strategies. Our hypothesis is that by the completion of the Citrien program's scale-up, telemonitoring will be operational in all UMCs but not normalized in routine care.

Methods: A before-and-after study will be conducted to assess upscaling. The theoretical frameworks used are the framework for nonadoption, abandonment, scale-up, spread, and sustainability; the Normalization Process Theory; and a project management tool Project Canvas. The primary outcome of the study is the degree of normalization to which health care providers at UMCs consider telemonitoring a part of their routine practice, measured using the Normalization MeAsurement Development tool (NoMAD). Our secondary outcome is the uptake of telemonitoring at the Dutch UMCs, using management data from UMCs' business intelligence systems query.

Results: Data will be collected between May 2020 and December 2022. Results were retrieved in June 2023. UMCs' business intelligence systems are queried for data for the secondary outcome measures. There is a risk that the UMCs will not be able to provide this management information. The laws and regulations governing telemonitoring in the Netherlands are changing, with the Electronic Data Exchange in Health Care Act (Wet elektronische gegevensuitwisseling in de zorg) and the European Health Data Space Act expected to positively influence implementation and upscaling.

Conclusions: The Citrien program is a nationally coordinated change management program that is scaling up telemonitoring across contexts and settings. This study will produce original data on the uptake and upscaling of telemonitoring at Dutch UMCs. Future initiatives to implement eHealth in the health care sector may be guided by the wide range of success factors, obstacles, and experiences collected through this program. The network itself may be of great value impacting future acceleration of eHealth initiatives.

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KEYWORDS

study protocol; implementation; upscaling; telemonitoring; telemedicine; e-health; eHealth; healthcare; health care

Introduction

Telemonitoring in health care can be defined as the use of IT to monitor a patient's status remotely [1-3]. Telemonitoring includes the collection, transmission, evaluation, and communication of individual health data from a patient to their health care provider from outside a hospital to the hospital record using technology [3]. Telemonitoring may not only benefit health outcomes [4-6] but also reduce workload for clinical staff and save health care resources. [7]

Significant advantages for patients, the economy, and society could result from widespread telehealth adoption [8]. For example, using a digital platform for blood pressure and symptom monitoring in antenatal care for high-risk women is related to lower costs and equal health outcomes in conventional care [9].

Hence, sustainable adoption, implementation, and subsequent upscaling of telemonitoring initiatives in hospital settings remains challenging nationwide [10-12]. Although there are systematic reviews on adopting digital care [13,14], to our knowledge, little has been published on national implementation programs or national scale-up. A scoping review on nationwide upscaling of telemonitoring revealed heterogeneity in describing nationwide uptake. According to this study, there are 89 factors influencing nationwide upscaling [10].

Implementation of telemonitoring in the Dutch medical landscape is still rather limited, focusing on use in pilots and research settings [15,16]. To date, only 19% of the Dutch medical specialists report the use of telemonitoring in their daily practice [17]. Ten percent of the Dutch medical specialists claim that the COVID-19 pandemic has increased their use of telemonitoring [18]. Only 6% of Dutch patients have reported sharing their health data with their own hospital-based physician, and only 3% of them reported sharing their health data with their hospital-based nurse for the purpose of telemonitoring [17,19].

In the Netherlands, the Ministry of Health, Welfare and Sports (HWS) has called upon the university medical centers (UMCs) to take the lead in shaping the digital health landscape, ensuring sustainable health care [20]. Over the last decade, the Ministry of HWS continues to advocate this role for UMCs [21-23], and recent policy papers continue to do so [24]. From 2014, Dutch UMCs collaborated within the "Citrien" eHealth program, which was founded by ZonMw—a health research and development organization in the Netherlands [25]. The Citrien program is now in its second term. In the first term, the Citrien program was themed "Evidence-Based eHealth." In this program, the effectiveness of eHealth was jointly studied [26]. This resulted in an increased focus on specific eHealth topics including monitoring and insights into the positive contribution of eHealth in health care and a nationwide eHealth vision [27-29]. Despite valuable projects and scientific evidence in the first term of the program (2014-2018), nationwide upscaling of these projects was not in scope. Therefore, a follow-up program was implemented, called "Citrien Implementation and Upscaling." This is the current term of the Citrien program running between 2018 and 2022 [23,30]. At this time, the Citrien program aims at scaling up 3 telemonitoring concepts in a collaborative effort at all Dutch UMCs, including many of their partnering hospitals and systems.

The UMCs in the Netherlands—8 in 2019 and 7 at the moment—act as a knowledge and network partner for nonuniversity hospitals. An effective scaling up of telemonitoring (and obtained knowledge regarding scaling up) at UMCs could affect roughly 70 additional nonuniversity hospitals in the Netherlands. Within this program, a strong implementation network has emerged, aiding UMCs in being more successful in jointly scaling up telemonitoring with other hospitals and care settings [31].

The aim of this study is to evaluate the upscaling of telemonitoring in Dutch university hospitals in order to gain a better knowledge of the process, methods, and outcomes of nationwide upscaling strategies.

Our hypothesis is that by the completion of the Citrien program's scale-up, telemonitoring will be operational at all UMCs, although it has yet to become normal practice among health care providers.

Methods

Study Design

To evaluate the success in scaling up of 3 telemonitoring concepts across settings, flexibility in vendor and concept selection is deemed necessary. This is required to better adapt to existing variations in hospital settings from a technical, organizational, financial, and cultural perspective while simultaneously safeguarding outcome end goals. A before-and-after study will be conducted to assess the degree of successful upscaling.

Theoretical Frameworks

In order to describe essential elements of the Citrien program—including the intervention, target group, application design, and implementation choices—the framework for nonadoption, abandonment, scale-up, spread, and sustainability (NASSS) will be used [32]. The NASSS framework consists of 7 domains and is designed to identify activities such as those performed by Citrien within a complex context from local adoption to sustainable national scale-up. This framework is considered to be a good fit, as it intends to be used reflexively to guide conversations and help generate ideas about barriers and facilitators [33]. The NASSS framework is intended to evaluate unfolding technology programs in real time and, in particular, to identify and manage their emergent uncertainties and interdependencies. In our study, the NASSS framework

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guides the estimation of the complexity of implementation and subsequent scale-up.

Given that this protocol describes the scaling up of 3 telemonitoring projects at 8 university hospitals, the descriptions of all of its essential elements are very lengthy. We, therefore, have appropriately explained the analysis of key elements in accordance with the NASSS framework in Multimedia Appendices 1-3.

Whether end users (health care providers and patients) integrate telemonitoring into daily care (normalization) is a socio-technical issue. An implementation framework such as the NASSS does not provide sufficient insight. To measure normalization, we, therefore, have used the Normalization MeAsurement Development (NoMAD) questionnaire, which is based on Normalization Process Theory (NPT). According to the NPT, a normalization process is a result of individual and group behaviors and entails the embedding and integration of health care innovations into everyday treatment.

According to the theory, 4 constructs play a central role in generating the work of implementation:

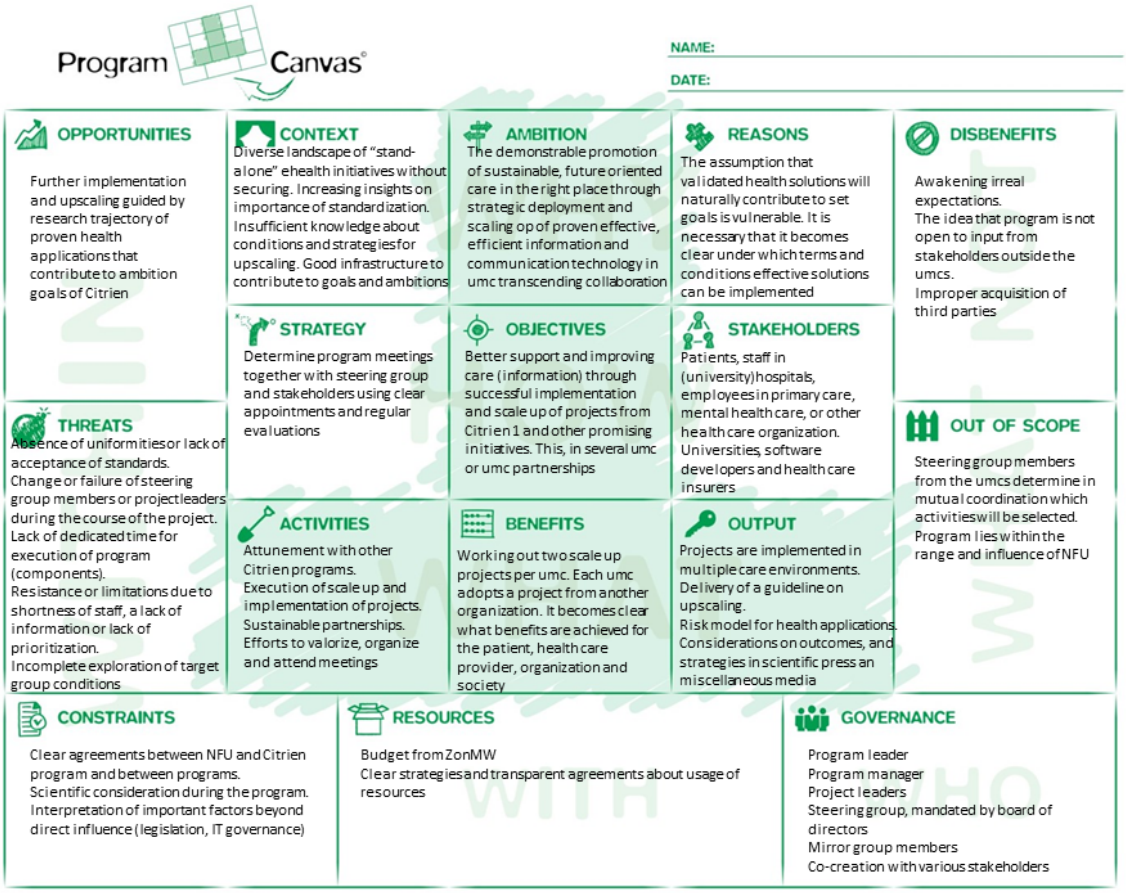
- Coherence of the innovation with the goals of daily routine
- Cognitive participation as a process of enrollment and engagement of individual participants and groups
- Collective action by individuals and groups to apply the innovation in daily routine
- Reflexive monitoring through which participants in the implementation process evaluate and appraise the use of the innovation in practice

The NPT successfully aids in the conceptual understanding of implementation processes and outcomes across a wide variety of health care settings [34].

The brief self-report NoMAD questionnaire was designed in accordance with the general approach of the NPT for the goal of detecting factors likely to influence normalization processes [35]. The questionnaire aims to (1) facilitate the evaluation of normalization progress over time in an implementation project and (2) facilitate the comparison of normalization (progress or outcomes) among sites in multicenter studies. The NoMAD questionnaire has been translated to Dutch [36]. Therefore, the NoMAD questionnaire seems suitable as a tool for tracking the progress of implementation for telemonitoring in our Citrien program.

A project-based approach (Program Canvas; Figure 1), advocated by the Netherlands Federation of University Medical Centres, was chosen as the management template for the Citrien program. Program Canvas, and the associated Project Canvas, is a simple model consisting of 16 elements from which a program is built. Project Canvas provides a universal technology to design and initiate new projects. The Canvas has been particularly created for teams involved in interdisciplinary projects, who aim at developing a common ground in an early stage of the project [37].

Figure 1. Citrien program canvas [37].



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Settings and Intervention

In 2020, a total of 1,200,000 patients were treated in all of the UMCs in total [38]. The telemonitoring concepts aim to encourage and foster adoption of (1) telemonitoring solutions in the domain of cardiology, (2) telemonitoring solutions providing care from a distance in obstetrics, and (3) telemonitoring solutions monitoring vital functions in hospital wards. In a prior Citrien initiative, these telemonitoring concepts were developed and evaluated [9,29,39-43].

The Citrien program was structured such that each UMC appointed a tripod of a steering group member, a deputy steering group member, and a project leader. Members are all professionals working at the UMCs, with expertise in the field of eHealth. The steering group members were formally appointed by their hospital boards, and the other members of the tripod were subsequently chosen by the steering group members. All members are in a key position or a management role to guide implementation within their organization. The Citrien program characteristics are outlined in Textbox 1 and Figure 2.

Textbox 1. Outline of the Citrien program.

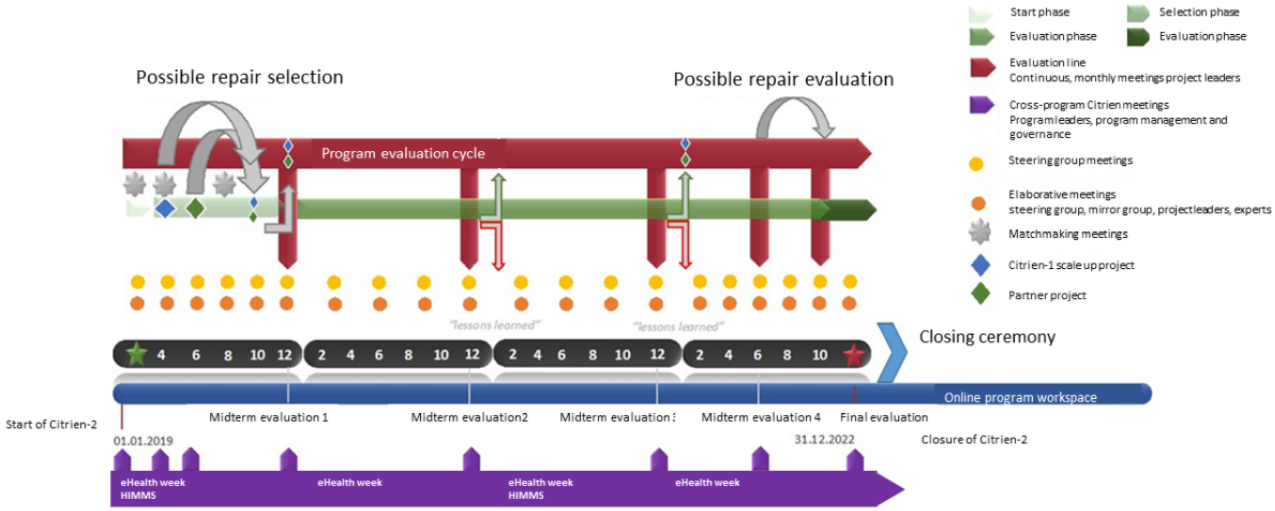
The Citrien eHealth Program

The Citrien eHealth program focuses on nationwide upscaling of telemonitoring by actual implementation at university medical centers (UMCs) in the Netherlands. The diverse concept of telemonitoring among cardiology patients, high-risk pregnancies, and for in-patients undergoing continuous monitoring of vital signs using wearables is implemented and researched. For all concepts chosen, differences in the target population or chosen technology (or both) may exist to fit the existing infrastructures and hospital strategy. In the Netherlands, different electronic health records (EHR) are in use by the UMCs. To facilitate interoperability, different requirements must be met to accommodate upscaling of the concepts. UMCs were free to opt for stand-alone solutions, although embedding technology into the existing EHR is a well-known enabler for implementation. Although the technology supply model is open to UMCs, the participating UMCs had to comply to the vision of the Citrien program, choosing trusted suppliers with validated, reliable, secure, and scalable solutions.

Collaboration within the Citrien program supported the project leaders in preparing a business case for their own organization. To analyze barriers and enablers for scaling up telemonitoring locally, UMCs used methodologies they were most experienced with. The Citrien program supported the analysis and drafting of implementation strategies by exchanging best practices among project leaders.

This Citrien program is aligned with relevant initiatives such as information standards and regulations on secure exchange of health data. Part of the program's strategy is to strengthen and foster cooperation within the UMCs and to foster cross-UMC partnerships while implementing various telemonitoring initiatives. Overarching issues related to scaling up such as reimbursement, screening new technologies for viability and suitability, procurement of devices, and privacy aspects were tackled by the UMCs in a joint effort. Typical of the Citrien program was the monitoring of change over a period of 2 years. Project leaders kept track of progress every month during their meetings.

Figure 2. Program planning and characteristics. HIMMS: Healthcare Information and Management Systems Society.



Outcomes and Data Collection

Overview

Upscaling of telemonitoring is operationalized as the actual use (uptake) and normalization of telemonitoring. Effectiveness is expressed in the degree of uptake and normalization of the use of telemonitoring at the UMCs. Data will be aggregated in a protective collaborative web-based environment created for this purpose and managed by the chair of the steering group (MS) and the principal investigator (HG).

Primary Outcome

The primary outcome is the degree of normalization to which health care providers consider telemonitoring to be a part of their routine practice, as measured by the NoMAD questionnaire [36]. The NoMAD questionnaire has high internal consistency and has been validated in heterogeneous examples in different languages and settings [35,36].

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Recruitment of Respondents

We make a pragmatic choice for a purposeful sample of respondents without performing a power calculation. Citrien program project leaders within each UMC recruited participants for each telemonitoring project to take part in the survey. The local project leader within each UMC sent a standardized invitation email to 10 self-selected health care professionals involved in the adoption of a telemonitoring project, containing the objective of the study and a link to a web-based survey. We aimed for a total of 10 respondents per project and consequently 30 respondents per UMC. This is a pragmatic choice because project leaders have noted at this stage of the scale-up that not more than 10 care providers are involved in the telemonitoring projects. Three reminders were sent. The local project leaders and the researcher were both unable to determine who had filled out the questionnaire. The questionnaire did not collect any email or IP addresses. The questionnaire responses could not be linked to specific individuals.

Secondary Outcome

The secondary outcome is the uptake of telemonitoring in Dutch UMCs, as measured by (1) the absolute number of patients using telemonitoring within each UMC and (2) the percentage of patients using telemonitoring compared to the number of patients eligible for telemonitoring.

These data are management data or business intelligence data. Patients are not actively being included. This study observes the nationwide coordination of implementation and scale-up practices carried out on a daily basis.

Statistical Analysis

The results will be presented as a summary of the outcome measures sorted by UMC and telemonitoring project, using frequencies, medians, and percentages for categorical factors and means and SDs for continuous measures in order to have as much information as possible available for exploration and nonparametric analysis. For evaluation of NoMAD data, we will use the Wilcoxon signed-rank test. To evaluate the secondary outcome measures within each UMC, we will use a 2-tailed paired *t* test. All statistical analyses will be conducted using SPSS software (version 28.0, 2021 release; IBM Corp).

Ethical Considerations

The primary outcome measure is a questionnaire administered to health care professionals. It is a nonburdensome questionnaire that is completed voluntarily and anonymously. Health care professionals are not subjected to any actions, nor are any behavioral rules imposed.

The secondary outcome measure is management information collected retrospectively. No data are collected from patients, and no actions or behavioral rules are imposed on patients. The use of telemonitoring is always and only in the context of patient care. The reason for monitoring is not different but only the method of delivery is in a digital manner.

The Medical Ethics Review Committee Amsterdam UMC exempted this study from ethical review. The study protocol is registered on the Open Science Framework [44].

Results

The baseline assessment was carried out from May 2020 to January 2021. Data on scaling up are collected quarterly. The final results were retrieved in June 2023. Data collection will be carried out under governance of the project leaders at every UMC. The findings are likely to be available in the second half of 2023.

Discussion

Anticipated Findings

This study will define the degree of uptake of telemonitoring at Dutch UMCs and elucidate how it is normalized in the daily routine of health care professionals. This protocol is important as it describes the theoretical framework that will be used and activities that will be performed. Evaluating the implementation of 3 telemonitoring projects at all university hospitals of the Netherlands provides the opportunity to provide a better understanding of the process, methods, and outcomes of a nationwide implementation of strategies.

Limitations

While launching this initiative, we thoroughly analyzed the scale-up's challenges and created tailored implementation plans and strategies for each UMC. However, we are unable to completely control all variables and influences in this real-world evaluation study. This implies that there remains a degree of uncertainty about the effectiveness of the scale-up program. If unforeseen circumstances arise despite carefully planned implementation actions and plans, the effect of the Citrien program may be underestimated. Thus, maybe the impact of the Citrien program could be overestimated if there are favorable changes in the health care environment that are unrelated to the Citrien program and accelerate the scale-up of telemonitoring. Nonetheless, it is interesting to evaluate this in a systematic approach.

Although not likely, limitations may also occur as a result of data collection; for example, when too few responses are received for the primary outcome measure. We can send additional reminders and request project leaders to exercise leadership in this situation.

The UMCs' business intelligence systems are queried for data for the secondary outcome measures. Although the outcome measures are actual fundamental parameters, there is a risk that the UMCs will not be able to provide this management information. It is crucial to acknowledge this and communicate the lesson that has been taught if this happens.

Nationwide upscaling of telemonitoring in different target groups requires a range of technologies and suppliers. The Citrien program aims to contribute to important preconditions, such as writing a business case, providing insight into barriers and enablers, and designing implementation strategies. With a pragmatic approach, Citrien aims to provide insight in, and solutions for, various barriers such as interoperability, reimbursements, adjustments in care paths, privacy policies, and procurement policies. These initiatives were carefully and

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purposefully developed in light of the variables that affect nationwide upscaling, which were identified in a recent scoping review on upscaling telemonitoring [10].

The laws and regulations governing the use of telemonitoring in the Netherlands are subject to change. The legal responsibility in monitoring patients remotely was still unclear at the start of this program. From 2023, the Electronic Data Exchange in Health Care Act (Wet elektronische gegevensuitwisseling in de zorg) mandates digital data exchange among health care providers. This also affects the processing of telemonitoring data. In the near future, European Health Data Space Act will also be enacted [45]. These regulations are expected to positively influence implementation and upscaling.

Finally, there are other eHealth scale-up initiatives in the Netherlands. In order to encourage eHealth activities outside of hospitals, the government has incentive regulations for eHealth in primary care [46]. A coalition of patients, health care professionals, health insurers, and suppliers was formed by the Netherlands Patient Federation in order to advance digital care [47]. Although these programs are not aimed at UMCs, the Citrien program will include similar strategies.

Conclusions

The Citrien program is a nationally coordinated change management program in the eHealth domain, now scaling up telemonitoring across situations and settings. We expect that this study will yield unique evidence about the use and upscaling of telemonitoring in Dutch UMCs. This study protocol could serve as inspiration for others who would like to implement a similar programmatic intervention for nationwide scale-up of applications, such as a digital ward or artificial intelligence–driven decision support. The success factors, barriers, and experiences collected in this program could guide future projects that aim to implement eHealth in the health care sector. The Citrien network itself may be of great value impacting future acceleration of eHealth initiatives.

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Data Availability

The data set that will be generated during this study are available from the corresponding author upon reasonable request.

Authors' Contributions

HG conceived the study with the involvement and advice of MS and TvdB. All authors participated in the writing and reading of the manuscript and approved the final version.

Conflicts of Interest

None declared.

Multimedia Appendix 1

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NASSS framework analysis of telemonitoring in cardiac diseases. NASSS: nonadoption, abandonment, scale-up, spread, and sustainability.
[DOCX File , 36 KB - resprot_v12i1e45201_app1.docx]

Multimedia Appendix 2
NASSS framework analysis of telemonitoring in antenatal care. NASSS: nonadoption, abandonment, scale-up, spread, and sustainability.
[DOCX File , 36 KB - resprot_v12i1e45201_app2.docx]

Multimedia Appendix 3
NASSS framework analysis of telemonitoring vital signs. NASSS: nonadoption, abandonment, scale-up, spread, and sustainability.
[DOCX File , 36 KB - resprot_v12i1e45201_app3.docx]

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Abbreviations

HWS: Health, Welfare and Sports
NASSS: nonadoption, abandonment, scale-up, spread, and sustainability
NoMAD: Normalization MeAsurement Development
NPT: Normalization Process Theory
UMC: university medical center

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Protocol

Creation of a Laboratory for Statistics and Analysis of Dependence and Chronic Conditions: Protocol for the Bages Territorial Specialization and Competitiveness Project (PECT BAGESS)

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Abstract

Background: With the increasing prevalence of chronic diseases, partly due to the increase in life expectancy and the aging of the population, the complexity of the approach faced by the structures, dynamics, and actors that are part of the current care and attention systems is evident. The territory of Bages (Catalonia, Spain) presents characteristics of a highly complex ecosystem where there is a need to develop new, more dynamic structures for the various actors in the health and social systems, aimed at incorporating new actors in the technological and business field that would allow innovation in the management of this context. Within the framework of the Bages Territorial Specialization and Competitiveness Project (PECT BAGESS), the aim is to address these challenges through various entities that will develop 7 interrelated operations. Of these, the operation of the IDIAP Jordi Gol-Catalan Health Institute focuses on the creation of a Laboratory for Statistics and Analysis of Dependence and Chronic Conditions in the Bages region, in the form of a database that will collect the most relevant information from the different environments that affect the management of chronic conditions and dependence: health, social, economic, and environment.

Objective: This study aims to create a laboratory for statistical, dependence, and chronic condition analysis in the Bages region, to determine the chronic conditions and conditions that generate dependence in the Bages area, in order to propose products and services that respond to the needs of people in these situations.

Methods: PECT BAGESS originated from the Shared Agenda initiative, which was established in the Bages region with the goal of enhancing the quality of life and fostering social inclusion for individuals with chronic diseases. This study presents part

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of this broader project, consisting of the creation of a database. Data from chronic conditions and dependence service providers will be combined, using a unique identifier for the different sources of information. A thorough legal analysis was conducted to establish a secure data sharing mechanism among the entities participating in the project.

Results: The laboratory will be a key piece in the structure generated in the environment of the PECT BAGESS, which will allow relevant information to be passed on from the different sectors involved to respond to the needs of people with chronic conditions and dependence, as well as to generate opportunities for products and services.

Conclusions: The emerging organizational dynamics and structures are expected to demonstrate a health and social management model that may have a remarkable impact on these sectors. Products and services developed may be very useful for generating synergies and facilitating the living conditions of people who can benefit from all these services. However, secure data sharing circuits must be considered.

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KEYWORDS

chronic disease; multiple chronic conditions; primary health care; diffusion of innovation; health data; data sharing

Introduction

The prevalence of chronic diseases has increased worldwide over recent decades and is no longer a characteristic of developed countries [1,2]. These types of diseases tend to be long-lasting, generally slow to progress, and noncommunicable among people [1,3,4]. Life expectancy has increased as a result of social progress and advances in health [4]. However, this has led to an increased risk of chronic multimorbidity, especially among older adults [2,4,5].

As a result, an increase in the burden of noncommunicable and chronic diseases is being described globally [1,4,6,7]. Consequently, there is an increase in years lived with disability and eventually in situations of dependence. Altogether, this poses a challenge from multiple perspectives. Health systems, and especially primary care, must adopt a complex approach in terms of detection, care, and follow-up of cases of chronic conditions or chronic multimorbidity, in addition to the costs involved [2,4,8]. There is also a direct impact on the loss of quality of life of people with these conditions and the emerging needs they develop [2,4,5]. At the same time, the circumstances of chronic conditions increase the fragmentation and burden of care, as well as the burden on family relationships and carers [5,9-13].

The difficulty of dealing with chronic diseases often lies in the complexity of the structures, dynamics, and actors involved in care, beyond the clinical complexity that care for these conditions may entail. Given the diversity of chronic diseases and their impact on the people who have them, management that takes into account a multiplicity of factors is necessary. This requires patient identification, comprehensive needs assessments, management of needs and resources, coordination between health and social agents that can influence an optimal care response, ensuring round-the-clock care, minimizing potentially avoidable hospitalizations, and accompanying people at the end of their life trajectory when appropriate [4].

The Catalan health system (integrated within the Spanish national health system) is intended to provide universal care and is financed by citizens' taxes, based on a public model centered on personal care and a comprehensive approach to health [14]. In this context, primary care plays an important role in the clinical management of chronic diseases and cases of patients with complex conditions. Thus, the system allows for continuity and longitudinality of care, together with other levels of care (emergency, specialist consultations, and hospital admissions) [4,15]. In parallel, sociohealth and social structures provide care focused on aspects derived from clinical conditions (eg, home care and formal care) [10]. Together, the various health and social agents make it possible to respond to a series of needs of the group most affected by chronic conditions and situations of dependence [14,16].

Despite the existence of an integrated health and social system, there are shortcomings in relation to the diversity of cases for which the system is unable to respond. These include informal care and the burden on family members [9,12,17]; the impact on the quality of life of patients with chronic diseases [2,5]; the differential impact of chronic conditions according to sex and gender [18,19]; barriers to access to health or social services [20,21]; and, finally, a lack of coordination within the network of actors involved who are sometimes unaware of the extent to which all the needs are being met [20].

The population of the Bages region (Central Catalonia) shows a sustained increase in population aging and overaging [22], which favors a high prevalence of chronic diseases. Although chronic conditions are present in various stages of life, they become more complex to manage as age advances and there are more cases of multimorbidity and dependence. It is therefore crucial to have data and information on the needs of people affected by these conditions, their environment, and the services they require.

The Bages region, primarily a rural area, spans a surface of 1092 km^2 and is characterized by the presence of only 2 urban centers [23]. As of 2021, the total population of the region was 179,770 [22]. Situated within Central Catalonia, the Bages region is 1 of the 7 regions that form the Catalan health system. The Catalan Health Institute (ICS) serves as the main health care provider in the area, covering approximately 85% of the population of Bages [24].

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According to data from the Central Catalonia Territorial Management of the ICS [25], the prevalence of various chronic diseases grew between 2018 and 2021 (ICS, unpublished data, 2023). The most prevalent diseases were hypertension (40.2%), chronic pulmonary diseases (26.3%), and type 2 diabetes (16.1%). At the same time, the most prevalent mental disorders were anxiety (42.6%) and depression (18.3%), which also corresponded with the continued increase in chronic conditions and as one of the most common comorbidities. At the same time, the data showed differences by age and sex in the burden of chronic conditions, which reinforces the need to differentiate the approach by taking into account a sex and gender perspective [18,26-28].

Despite the availability of this information, mainly of a clinical nature, the ICS system does not have information on the needs of people with chronic and dependent conditions. It should be considered that the Bages area has a structure of health and social health services and providers included in the public system other than the ICS [14]. At the same time, social services depend on local public administration, which is governed by different legislation from the health sector [29]. Therefore, there is a lack of a procedure to bring together all these institutions and actors that provide care to people with chronic conditions and dependence across the board.

Given these conditions, in 2019, the Territorial Specialization and Competitiveness Project-Big Data, Analytics, Management and Strategy in Health and Social (Proyecto de Especialización y Competitividad Territorial – Big Data, Analytics, Gestión y Estrategia en Salud y Social [PECT BAGESS]) project was born. It was formed by several agents of the health and social system, public administration, technological sector, and university and research sector in the Bages region. The objective of the project is to address the problems and needs arising from dependence and chronic conditions and their impact on the health and social spheres, developing solutions, products, and services that can also become opportunities for economic growth.

This protocol presents one of the operations of the PECT BAGESS, which corresponds to the creation of a Laboratory for Statistics and Analysis of Dependence and Chronic Conditions in Bages. This will serve as the basis for coordinating information from all project entities. It will also make it possible to define the chronic conditions and conditions that generate dependence in the Bages area; identify their prevalence, incidence, and main associated factors; and propose products and services that can respond to these needs.

The PECT BAGESS project is currently being developed by 7 partners, with funding from the Generalitat de Catalunya [30], and 4 collaborating entities without funding. The coordination of the project is led by Manresa Town Hall.

Methods

Theoretical Approach

In order to address such a complex challenge as the one posed by the PECT BAGESS project, the Bages Shared Health and Social Agenda was drawn up. The Shared Agendas are initiatives promoted by different agents in the area with the aim of implementing a coordinated approach to complex challenges linked to the Sustainable Development Goals and the problems and opportunities arising from them [31].

The Bages Shared Agenda aims to bring together the relevant main actors in the area who will adopt a proactive approach to the challenge. In this way, objectives, resources, and structures can be shared, and collaborative and multidisciplinary solutions can be generated. In short, it is structured to satisfy the need for applying enabling technologies in this highly complex ecosystem relating to dependence and chronic conditions, placing the person living with these types of conditions and the needs arising from their health circumstances at the center. The main actors in the area who participate in the Shared Agenda are part of the health and social sector, both from the public administration, research centers, universities, and health care centers at all levels (eg, from primary care, specialized consultations, acute care, and chronic diseases).

The structure of the Shared Agenda, and consequently the PECT BAGESS project, in this environment of chronic conditions and dependence is framed within the strategy promoted by the Research and Innovation Smart Specialization Strategy (RIS3) of the Generalitat de Catalunya in the RIS3CAT 2030 edition. This commitment to transformative and responsible research and innovation is based on shared agendas as the main drivers to guide Catalonia toward a greener, digital, resilient, and fairer socioeconomic model [32]. In addition, the use of technology and a quadruple helix structure (4H) are promoted: patients and the population, health and social system, science and technology, and business. The joint work of these sectors and agents in the region will make it possible to provide a united response to the needs associated with the chronic conditions and population with dependencies in Bages, to export the dynamics and solutions generated to other regions of Catalonia once the project is completed.

The PECT BAGESS project seeks to improve the quality of life and promote the social inclusion of people with dependence and chronic diseases, making them active agents of their own health. Furthermore, it also wants to drive the economic transformation of the county with a focus on the digital transition of the health and social sector, both public and private, to make it a more competitive, sustainable, resilient, and quality service.

To this end, one of the operations to be carried out is the definition and detection of the needs of people in these circumstances. For this reason, mechanisms need to be established for sharing data and information among the different actors involved in the project, especially among those providing direct health care or population health care. The availability of real data on chronic conditions and dependence will make it possible to go deeper into the other aspects of the project, as well as to offer subsequent analyses and evaluations in greater depth.

As part of the study, data from supplier entities will be combined. In order to have information corresponding to a single person, the data will be merged using a unique identifier for any of the provider entities. This strategy ensures that the combined data are accurate in terms of ownership, although the

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problem in its implementation lies in the existence of a common unique key (Table 1).

Table 1. Characterization of the data sets involved in the combination process.

Characteristics	Health data	Social services data	Context data
Unique identifier	Personal identification code (PIC), personal ID	Personal ID	Personal ID
Additional information	Sex, age, municipality, nationality	Sex, age, municipality, nationality	Sex, age, municipality, nationality
Thematic data	Diagnosis	Problem, dependence	Income, living conditions

The utilization of a unique patient identifier is a complex yet essential aspect of the data merging process. Its purpose is to prevent duplication and ensure a comprehensive understanding of regional requirements and attributes. Recent literature delves into the discussion surrounding data sharing and provides insights into the implementation of unique patient identifiers [33-35], highlighting the complexities associated with integrating data, particularly personal data, from diverse sources. Furthermore, it is essential to address the legal implications before creating the database, as outlined in the "Ethical Considerations" section.

Project Partners

The collaboration of various entities in the area, through research and implementation of comprehensive and innovative digital solutions, make the PECT BAGESS project possible. Among the partners (entities receiving funding) are Manresa Town Hall, as project coordinator; Sant Andreu Salut Fundació; Althaia Xarxa Assistencial de Manresa Fundació Privada; Fundació Eurecat; Institut Universitari d'Investigació en Atenció Primària-Institut Català de la Salut de la Catalunya Central (IDIAPJGol-ICS); Fundació Universitària del Bages-UManresa; and, finally, Fundació Ampans.

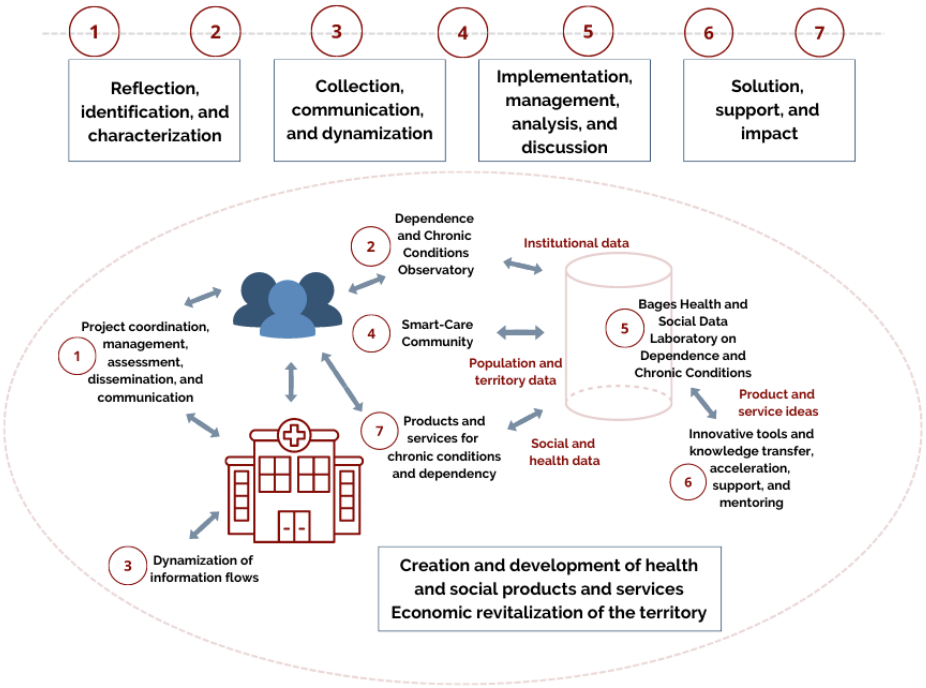
Also collaborating are the Regional Council of Bages, the Unió Consorci Formació, the Associació Catalana d'Entitats de Base Associativa, and the Fundació TIC Salut Social.

Project Structure and Interconnection Between Operations

Overview

The various entities involved in the project are key players in the 4 phases defined by the PECT BAGESS: (1) reflection, identification, and characterization; (2) collection, communication, and dynamization; (3) implementation, management, analysis, and discussion; and (4) solution, monitoring, and impact. These 4 phases group 7 operations, which are determined by the performance of each partner entity in each of them (see Figure 1).

Figure 1. Structure of the Proyecto de Especialización y Competitividad Territorial-Big Data, Analytics, Gestión y Estrategia en Salud y Social (PECT BAGESS) and interconnection of operations.



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Operation 1: Coordination, Management, Evaluation, Dissemination, and Communication of the PECT BAGESS

Manresa Town Hall is leading the transverse coordination operation. This allows one to have an overall view of the rest of the operations, facilitate their management, and ensure that the project is on schedule. It also supports each individual entity in terms of administrative and economic justification, while acting as a liaison between the entities and the General Directorate of Local Administration.

Operation 2: Observatory of Dependence and Chronic Conditions in Bages

Developed by Sant Andreu Salut, the objective of this operation is to manage the information generated about chronic conditions and dependence, both for the affected person and his or her family and carer. The observatory aims to be a tool for sharing needs and resources for this group, as well as gathering new actions and relevant information in this regard.

Operation 3: Dynamization of Information Flows

Althaia, responsible for the management and dynamization of information flows, seeks to incorporate the use of technologies to contribute to the transformation of the health care model, promoting a better patient-professional relationship and improved coordination among professionals. Using support tools, shared among the different health and social care providers, the aim is to contribute to better patient stratification and predictive medicine, thus minimizing acute cases and, consequently, regulating the need for health care resources. In this way, the quality of life of patients with chronic diseases is improved, and their care is made more efficient.

Operation 4: Smart-Care Community

Eurecat develops information and communication technology (ICT) tools for the integrated care of patients with chronic diseases, in a global context that takes into account the patient, caregivers, and health care environment. The center uses technologies based on artificial intelligence and human-machine interaction interfaces. This operation involves co-designing, implementing, and validating various management, learning, and support tools for the patient-professional care and social system. Eurecat also conducts 2 pilot tests in cardiac rehabilitation and mental health (schizophrenia), which are implemented in coordination with agents using these tools.

Operation 5: Statistical and Intelligent Analysis Laboratory

The collection of chronic condition and dependence data and their analysis are carried out at IDIAP JGol-ICS Catalunya Central through the Laboratory of Statistics and Intelligent Analysis. With the legal requirements to do so, with the completion of a legal study and an impact assessment, this operation makes it possible to gather all the existing data in terms of health and social data to detect the problems and needs of people with chronic conditions and dependence and their environment. Similarly, this operation serves to validate the interventions proposed by health care institutions, as well as the products and services of companies in the sector, and to propose new solutions based on the scientific evidence identified by the analysis.

Operation 6: Transformative and Knowledge Transfer, Acceleration, Support, and Monitoring Tools

The Fundació Universitària del Bages-UManresa focuses on the creation of a platform for entrepreneurship and support for health and social initiatives (eHealthinking) in the process of developing products and services in this sector, providing expertise in this type of process from a position of knowledge of existing structures. Both initial financing (Business Angels network) and support from the business network with expertise in the health-social field (Health and Social Innovation Cluster) will be provided.

Operation 7: Dependence Products and Services

The latest operation is led by Fundació Ampans, with the aim of creating a product that offers people with chronic conditions and dependence and in need of support solutions and tools that empower and facilitate the management of their daily reality. In the form of a technological tool (mobile app and back end platform), this product will enable the concerned person to find specialized professional social and health care services for their condition. Additionally, it will provide them with access to a library of resources, tools, and knowledge from collective experiences and enhance social relationships by finding specific recreational activities. This technological solution seeks to build change, fostering empowerment, quality of life, and person-centered care and focusing on meeting the needs of the dependent population.

Creation of a Laboratory for Statistics and Analysis of Dependence and Chronic Conditions in Bages

In light of the project's overarching framework outlined previously, we will now proceed to describe the implementation of the operation assigned to IDIAPJGol-ICS, which corresponds to operation 5. This consists of the following 2 elements: (1) description of the procedures associated with the laboratory and (2) description of the implementation proposal to be carried out.

Procedures Associated With the Laboratory

The procedures for operation of the laboratory are as described in the following paragraphs.

First, data collection in the health, social, and contextual areas covers the data life cycle from its contribution by users at the time of access to services including the generation of new services in the area of chronic conditions and dependence by the economic fabric (Figure 2).

Second, data that contribute to performing operations 4 and 6 of the PECT BAGESS project are transferred. One of the first uses of the data obtained by the statistics laboratory is to deliver data to the ICT tools developed in the context of operations 4 and 6 of the PECT BAGESS project (Figure 3).

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Figure 2. Procedure 1: collection, combination, and publication of chronic condition and dependence data.

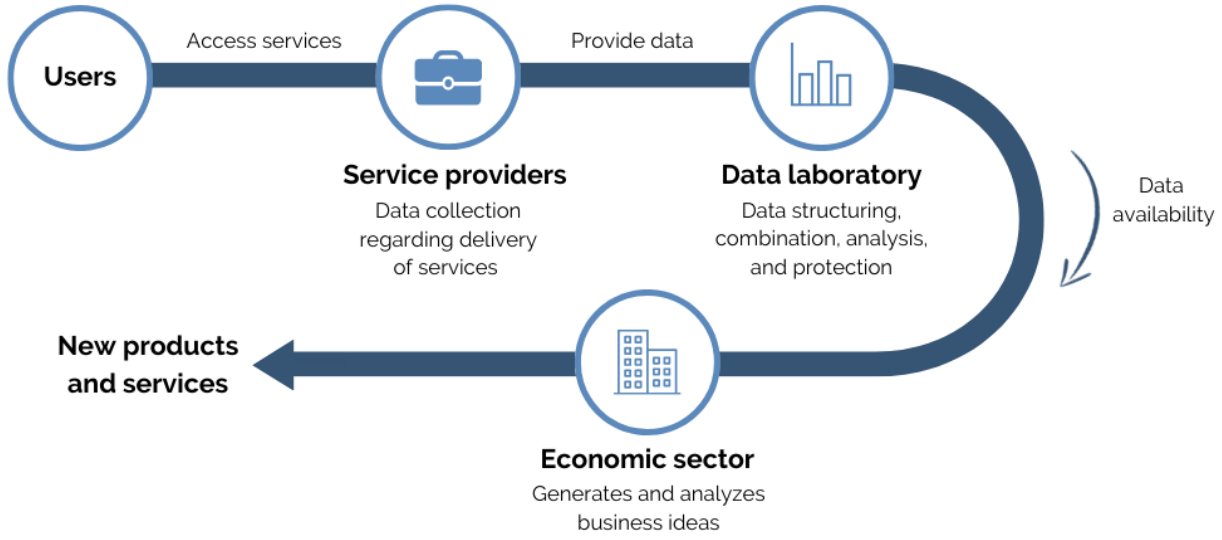
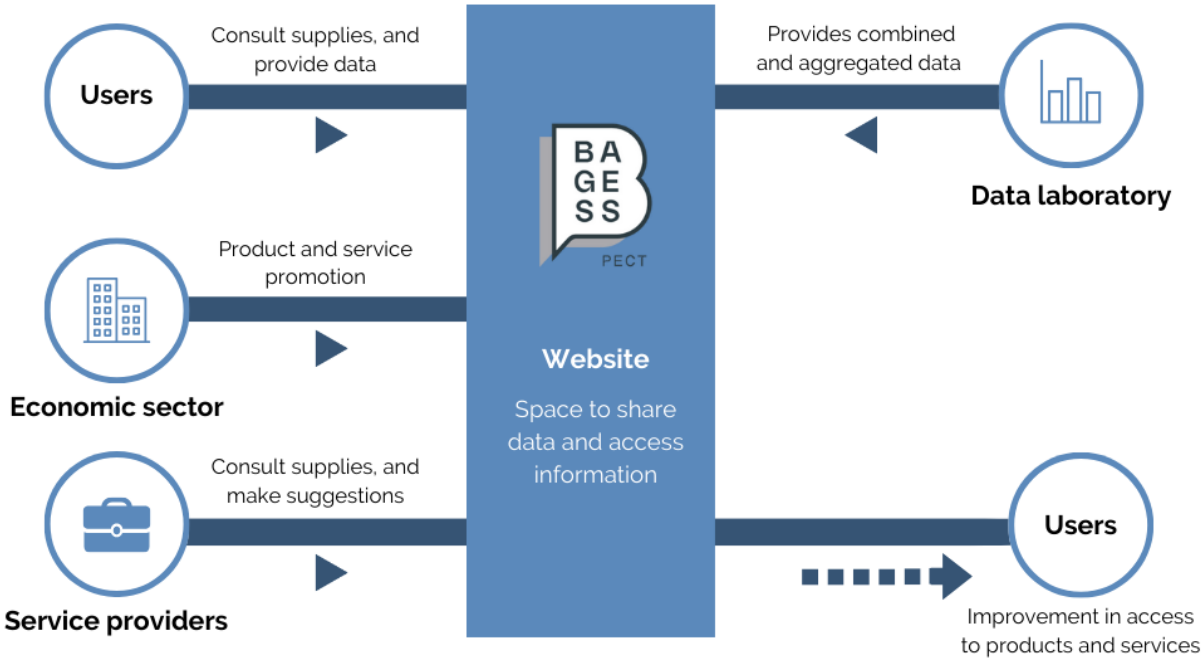


Figure 3. Procedure 2: transfer of data to contribute to the implementation of operations 4 and 6 of the Proyecto de Especialización y Competitividad Territorial-Big Data, Analytics, Gestión y Estrategia en Salud y Social (PECT BAGESS) project.



Description of the Implementation Proposal

In accordance with the previous paragraphs, the proposal involves creating the chronic condition and dependence laboratory with the implementation characteristics described in the following paragraphs.

First, the combination of the data will be carried out by combining 2 strategies: (1) use of pseudonymized data in which a unique identifier (personal ID) is used as the basis for the generation of the pseudonym combined with the person's date of birth for the combination of health and social data and (2) use of general demographic data for the combination of contextual data.

Second, IDIAPJGol separates the functions in its project according to the following 2 blocks: (1) technical block, which is part of the process of pseudonymization, combination of data, creation of the data repository, obfuscation, and aggregation and preparation of data for dissemination to third parties, and (2) research block, which involves data analysis tasks and review of scientific evidence, needs assessment, and proposal of products and services.

Third, the pseudonymization process is carried out in a distributed manner both in the generation of the pseudonym and in the custody of the translation dictionaries and consists of the following entities: (1) pseudonymization neutral point that is in charge of obtaining the hash by applying the algorithms (SHA256 hash with a fixed salt not specified in the database and a pepper of 3 characters in length) and of keeping the resulting pseudonym values and of the entity making the request and (2) provider entities that are in charge of keeping the translation dictionary of the entity's own pseudonyms.

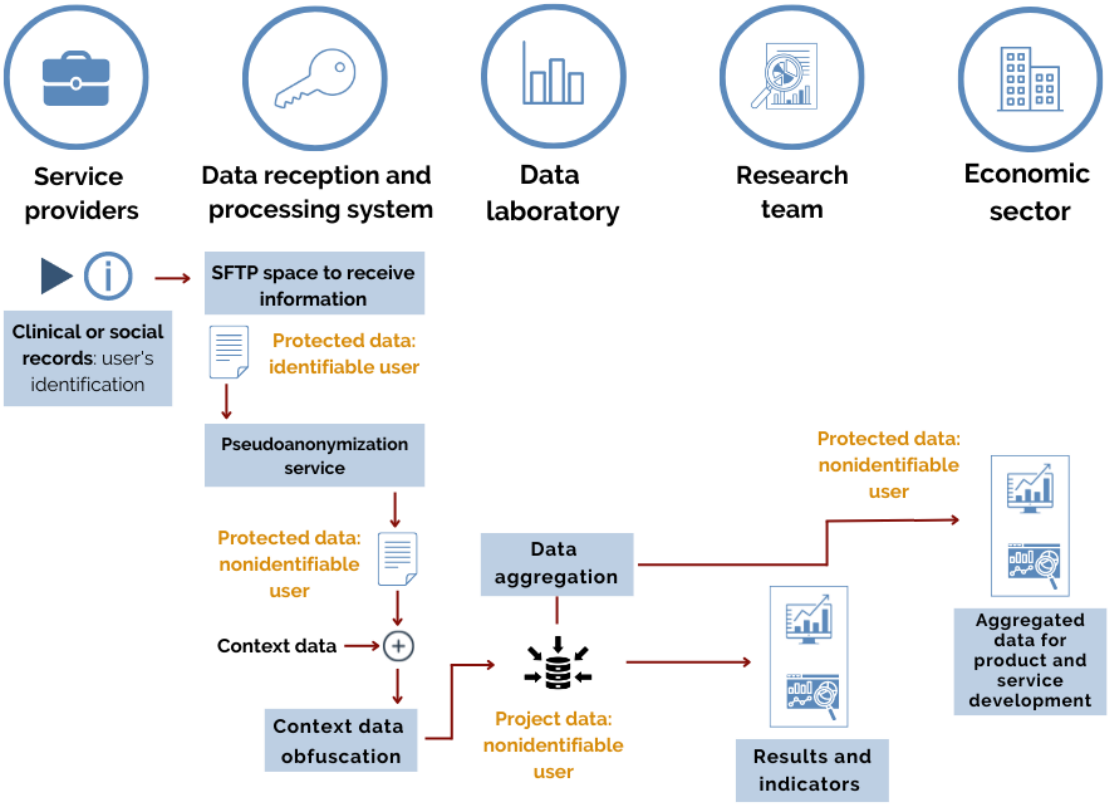
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Going into more detail on the operation, it is necessary to describe the agents involved in the process and their main function in relation to the process (except for the service users, who are not considered even though they are the ones providing the data, since they do not perform interactions at the information system level), which are as follows:

- Entity providing health or social services, which provides the data and keeps the pseudonym dictionaries of its own users
- Pseudonymization neutral point (IDIAPJGol-technical), which performs the pseudonymization process and the keys to obtain it
- Statistical laboratory (IDIAPJGol-technical), which prepares and keeps the pseudonymized data
- Research team (IDIAPJGol-research), which analyzes the pseudonymized data
- Economic fabric, which is the recipient of the aggregated data containing specially protected data but in which the individual is not identifiable

The overall model that would emerge from this description can be seen in Figure 4.

Figure 4. Global model proposed by the creation of the laboratory. SFTP: secure file transfer protocol.



Monitoring and Assessment

Monitoring will be done in cooperation with the various partners involved in the project. The various operations will be evaluated by each entity, through process and results indicators, in order to meet the project's objectives. Quality measures of the activities carried out will also be provided, assessing whether the objectives are being met and their impacts, always taking into account new needs that may arise throughout the process. The evaluation will be shared with all the participants regularly involved.

Communication and Dissemination

The results of the project will be disseminated through the following different strategies led by the various entities participating in the project:

- PECT BAGESS website and social networks
- Observatory of Dependence and Chronic conditions (operation 2)
- Citizen science meetings and events
- Elaboration of a Policy Brief that includes recommendations for better care and prevention of the needs derived from chronic conditions and dependence, based on the experience of Bages
- Reports, presentations, and meetings with policy makers, health and social professionals, and other relevant stakeholders and organizations
- Scientific publications
- Presentations at local and national conferences

Ethical Considerations

This project has been reviewed and approved by the Ethics Committee of IDIAPJGol (22/068-P). All activities carried out within the framework of this study will be conducted in accordance with existing ethical guidance, as indicated in the Universal Declaration on Bioethics and Human Rights adopted by UNESCO (19/10/2005); the Council of Europe Convention for the Protection of Human Rights and Dignity of the Human

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Being with regard to the Application of Biology and Medicine (1997) and its Additional Protocol on Biomedical Research (2005); the Declaration of Helsinki (2013) and relevant European Union laws (Directive 2001/20/EC of the European Parliament and of the Council); the Spanish Law on Biomedical Research (14/2007); and the Spanish Law on Personal Data Protection (3/2018). This analysis was also carried out considering the legislative aspects in the field of health and social services provision, as well as those related to the protection of personal data.

With regard to general ethical aspects, the following have been considered: social and scientific value of research, equitable search in relation to the resources of the population, use of widespread informed consent, processing of data from vulnerable groups.

Regarding the social and scientific value of research, the aim of the study is to obtain combined data on chronic conditions and dependence of the population of Bages. From the data obtained, it will be possible to better characterize the needs of the population (regardless of their characteristics), and as a result of the new products and services that can be defined by the economic fabric, the health and well-being of people will be improved.

Regarding the equitable search in relation to the resources of the population, the result of the research should make it possible to cover the analysis of the global population regardless of its context and based on the propensity to need access to products and services linked to social and health services.

Regarding the use of widespread informed consent, in this phase of the research and under current data protection regulations, consent of the interested parties in the data processed is not obtained for its implementation.

Regarding the processing of data from vulnerable groups, the aim of the research is focused on the group of users benefiting from social and health services who, according to the definition of the project itself, are or may be in a situation of vulnerability. In this respect, the research is aimed at achieving new services to reduce the effects and, if possible, the presence of these situations of vulnerability.

In any case, one of the most relevant aspects is the one related to the processing of service users' personal data, which are combined to obtain the statistics laboratory. These specially protected data are subject to the provisions of Law 21/2000 on the rights to information concerning health and patient autonomy and clinical documentation, the basic Law 41/2002 regulating patient autonomy and rights and obligations regarding information and clinical documentation, Law 12/2007 on social services, Eropean Union Regulation 2016/679 General Data Protection Regulation, and Organic Law 3/2018 on the protection of personal data and guarantee of digital rights, General Health Law 14/1986.

To ensure that the activities to be carried out in the project are conducted in accordance with the law, prior consultation was held with the Catalan Data Protection Agency. The authority's response indicated that the project was covered by current data protection regulations, provided that it was part of a research project and worked with anonymized data, guaranteeing technical and functional separation of pseudoanonymization and the conduct of the research. Considering all the aforementioned information, the data will be stored in an ICS server, and the IDIAPJGol research team will be responsible for data processing.

Results

With project start-up in 2021, all PECT BAGESS operations have been initiated and are in progress. As of June 2023, the operation corresponding to the creation of the Laboratory for Statistics and Analysis of Dependence and Chronic Conditions reached the legal study stage, which covers the suitability of use and combination of the data necessary to create the database.

Since the laboratory will primarily consist of personal data provided by various entities offering health and social services in the region, ensuring data protection is of paramount importance. Considering that processing personal data involves the use of special data categories and entails high risk, a data protection impact assessment (DPIA) was carried out following the WP248 guide of Article 29 of the Working Party of the European Data Protection Board.

IDIAPJGol carried out this DPIA through data protection, analyzing the typology of the data included in the new treatment, collection, integration, and data processing procedures, as well as technical and organizational measures applied, in order to minimize the risk associated with their treatment. As a result of the implementation of the planned measures, the final impact of the data processing involves a low level of risk, and therefore, no additional measures are necessary. Thus, the data processing resulting from the creation of the laboratory was deemed feasible from the point of view of personal data protection.

At the same time, coordination with the rest of the operations includes monthly meetings between entities and the organization of various communication events open to the authorities and the public of the Bages region, which have made it possible to publicize the work being done within the framework of this project.

Discussion

This paper presents the project for the creation of the Laboratory for Statistics and Analysis of Dependence and Chronic Conditions in the Bages region, as part of the PECT BAGESS. As an ongoing project, the authors anticipate an improved data sharing process among partners that will be key to move toward a better understanding of the chronic conditions and dependent needs of the population in this area. This project should also provide a foundation for the scalability of this model in other regions.

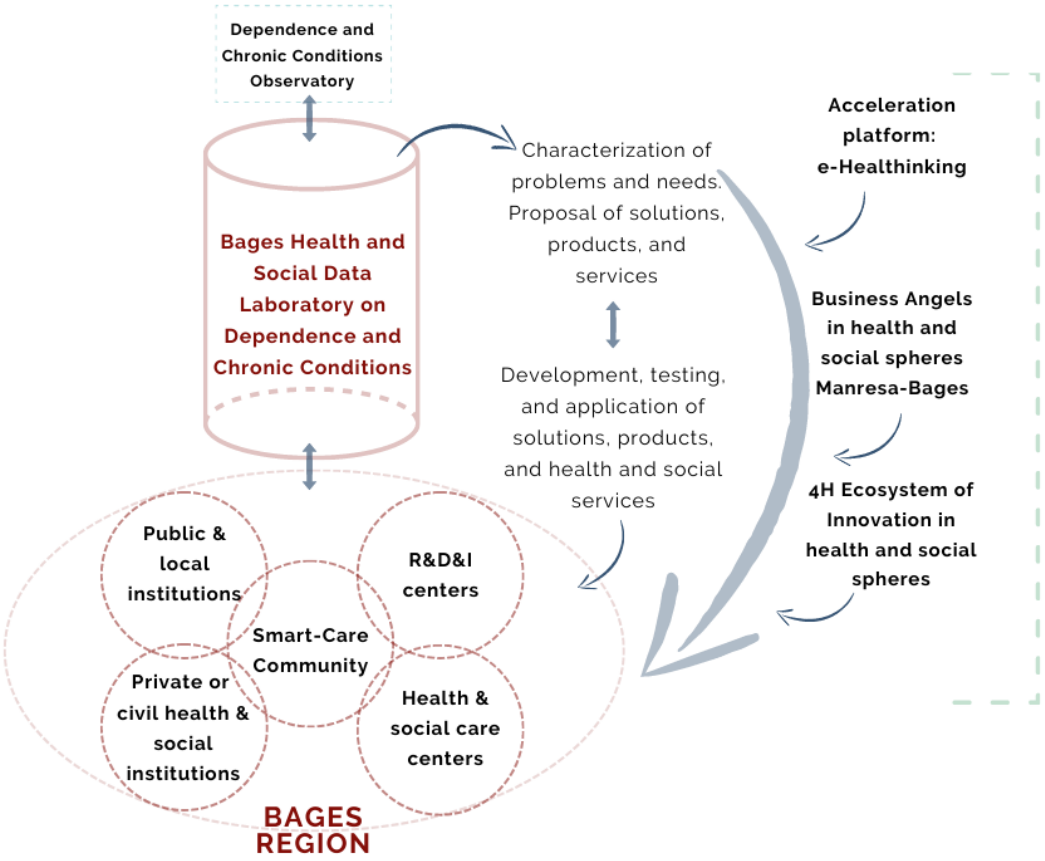
The authors and agents involved in this project expect that the resulting organizational dynamics and structures will allow for a model of health and social management that may have a remarkable impact on these sectors. Products such as the Observatory of Dependence and Chronic Conditions, the "eHealthinking" entrepreneurship platform, the Bages-Catalonia

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Central Business Angels organization, the Smart-Care Community citizen participation platform, or the Health and Social Innovation Cluster, as well as the websites and applications to be developed may be very useful for generating synergies and facilitating the living conditions of people who can benefit from all these services. In relational terms, the project seeks to culminate in interaction and collaboration in other health and social projects, whether they have an impact on research, innovation, or economic development (Figure 5).

To facilitate these dynamics, the backbone of the BAGESS project lies in the Health and Social database, which is fed by the different communication strategies and the information available from each entity, both from health care and other organizations related to dependence and chronic conditions. From the analysis of data from the Laboratory of Statistics and Analysis, it will be possible to extract the information that the Observatory of Dependence and Chronic conditions will collect to offer a more precise characterization of problems and needs related to dependence. As a result of these analyses, it will be possible to propose solutions, products, and services that will be shared with the BAGESS community, accompanied by research and innovation entities, and developed as business projects. These will contribute to the dynamization of the health and social structure and to the economic acceleration of the area. Previous experiences with similar projects can be found in southern Catalonia, where an integrated care model called Salut + Social was implemented. This model aimed to enhance coordination among professionals from health and social services, with a specific focus on addressing the needs of patients with chronic diseases and dependencies [36]. The program received positive acceptance among professionals and high satisfaction among users, improving the efficiency of care and preventing duplication of tasks [37]. Despite not covering the scope of the PECT BAGESS (which also includes economic and technologic agents), this experience confirms the benefits of joining forces to look after a population with potentially high health and social care needs.

Figure 5. Relationship schemes, information flows, and management of the Big Data, Analytics, Gestión y Estrategia en Salud y Social (BAGESS) project, once the Proyecto de Especialización y Competitividad Territorial (PECT) has been passed. 4H: quadruple helix structure; R&D&I: research and design and innovation.



We acknowledge, however, that this study presents several limitations. The potential risks of the implementation of this project will be detected at the time of implementing this management model, as well as the limitation of database maintenance, which will require resources beyond those that have been developed for this project, although several options are currently being considered and coordinated by the Generalitat de Catalunya. Moreover, the commitment and availability of the entities involved in taking on the current tasks and the possible continuation of the tools and products derived from the project must be taken into account, although, so far, the coordination and communication between them have been very positive. Finally, there is a risk arising from the nature of the information with which we work, since it refers to personal health and social data; therefore, it is very necessary to adhere to the corresponding regulations in order to maintain its confidentiality. Being aware of the latter, we developed a legal study within the framework of the operation presented in this

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protocol, in order to rely on the necessary legal support to develop the project.

In conclusion, the proposal discussed in this study emphasizes the importance of finding a balance between the needs of the population and the protection of data privacy. Implementing secure data-sharing models in health and social care systems can lead to improved efficiency and satisfaction among both professionals and the population. It also presents an opportunity to foster synergies and develop new products and services that cater to the specific needs of individuals with chronic diseases and dependencies. Additionally, the creation of comprehensive databases plays a crucial role in generating evidence and facilitating research in these areas of increasing prevalence. However, it is essential to adhere to frameworks and regulations that ensure the secure transmission and handling of data, whether at the local or international level. By establishing robust and protected circuits, the potential benefits of data sharing can be realized while maintaining the privacy and confidentiality of individuals' personal information.

Acknowledgments

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Data Availability

Access to the data used in this article is limited to the Catalan Health Institute due to the sensitive nature of personal data and the requirements set forth by Spanish and European regulations. As a result, the data cannot be openly shared. However, the results mentioned in the Introduction section will be presented in a forthcoming manuscript by Pujolar et al titled "A Gender-Based Approach to Chronic Conditions in Central Catalonia (Spain): A Descriptive Cross-Sectional Study" (in preparation as of 2023).

Furthermore, the creation of the laboratory outlined in this protocol aims to facilitate broader access to data within the established legal and ethical frameworks.

Authors' Contributions

This paper is based on a funded grant proposal, which was conceived and developed collaboratively by the authors and all members of the PECT BAGESS Group. GPD and JVA conceptualized the study, performed the investigation, wrote the original manuscript draft, and reviewed the final manuscript. AF, EDS, and JB reviewed the final manuscript.
The members of PECT BAGESS Group are M Lluïsa Sort-Garcia, Jullieth Suarez-Guevara, Gemma Cuberas, Juanjo Martín, David Marí, Maria Bosch Gall, Jordi Mir, Carles Clotet Vilalta. They reviewed and edited the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

4H: quadruple helix structure
DPIA: data protection impact assessment
ICS: Institut Català de la Salut (Catalan Health Institute)
ICT: information and communications technology
IDIAPJGol: University Institute for Research in Primary Health Care Jordi Gol i Gurina
PECT BAGESS: Territorial Specialization and Competitiveness Project-Big Data, Analytics, Management and Strategy in Health and Social (Proyecto de Especialización y Competitividad Territorial-Big Data, Analytics, Gestión y Estrategia en Salud y Social)
RIS3: Research Innovation Strategies for Smart Specialization

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Protocol

Promoting Healthy Behaviors Among Adolescents and Young Adults With Intellectual Disability: Protocol for Developing a Digital Intervention With Co-Design Workshops

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Abstract

Background: Intellectual disability (ID) is a neurodevelopmental disorder associated with a poorer health profile and higher mortality. Young people with ID have more sedentary lifestyles than their typically developing peers. Consequently, this group is at significant risk of developing lifestyle diseases (ie, noncommunicable diseases) later in life. Increasing physical activity and eating a healthier diet have been argued to be effective ways to improve the health of adolescents and young adults with ID. Digital interventions are a viable option for improving health behaviors.

Objective: This research protocol describes a co-design approach using workshops to develop a digital intervention that promotes healthy behaviors, including increasing physical activity and eating a healthier diet, among adolescents and young adults with ID.

Methods: A participatory design using a co-design approach will be applied as a strategy to include potential users of the digital intervention and other stakeholders in the research process, comprising research design, data collection, and data analysis. A total of 7 to 10 workshops will be conducted aimed at developing a digital intervention and will include procedures for assessing needs; facilitators and barriers to health promotion; physical, mental, and social well-being; participation; and relationships. The workshops will include 12 to 18 stakeholders with experience of clinical practice and research related to young people with ID, including relatives, as well as adolescents and young adults (aged 16-25 years) with mild to moderate ID. Participants will perform a mixture of individual and group work using whiteboards, sticky notes, felt-tip pens, cards, balls, stickers, and wireframe templates. Data analysis will take place concurrently with data collection as an iterative process. Transcribed data from the audio and video recordings of the groups' discussions will be analyzed following a qualitative methodological procedure.

Results: This study protocol provides a systematic record of the scientific methodologies used when developing the digital intervention and provides insights into the potential practical solutions and challenges when following a co-design approach in which relatives and professionals, as well as adolescents and young adults with ID, are included as research partners. Recruitment of participants started in April 2023. Data collection, analysis, and reporting will be completed in December 2023.

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Conclusions: This study will explore the effectiveness of workshops at gathering rich, reliable, and valid data in a co-design approach with participants. The results will provide increased knowledge in how to use technology to develop novel, evidence-based, and scalable interventions that adolescents and young adults with ID can and want to use to motivate physical activity and a healthier diet. The project will provide a simple and cognitively accessible digital solution for promoting lifestyle behaviors tailored to the needs of adolescents and young adults with ID.

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KEYWORDS

intellectual disability; lifestyle behavior; eHealth; co-design; digital intervention; lifestyle; adolescents; young adult; healthy diet

Introduction

Health of Adolescents With Intellectual Disabilities

Intellectual disability (ID) is a neurodevelopmental disorder with onset during childhood [1]. In Sweden, about 1% to 3% of the population is diagnosed with ID. ID differs from person to person but always impacts conceptual, social, and practical skills [2]. The ability of people with ID and the support they therefore need varies, as the severity of ID can be mild, moderate, or severe [1]. ID is associated with more health problems, poorer health profiles, and higher mortality rates [3]. People with ID are more likely to have a chronic illness, such as cardiovascular and respiratory disease [4] or mental illness [5,6]. Adolescence is a time of change, marking the transition from childhood to adulthood, and it is a critical life period when health-related behaviors often are set for adulthood [7]. Adolescents with ID have, in general, a more sedentary lifestyle, a less healthy diet, and greater social isolation compared to adolescents in the general population [3,8]. Consequently, this group is at significant risk of developing lifestyle diseases (ie, noncommunicable diseases), such as type II diabetes, hypertension, obesity, heart disease, stroke, and cancer later in life [4,9-11]. A recent population-based longitudinal cohort study of adolescents and young adults in Sweden found that premature mortality was significantly increased in those with ID [12].

Digital Interventions to Promote Lifestyle Behaviors

As in the general population, lifestyle behaviors have a strong impact on health for this group [13]. Establishing healthy behaviors is often easier and more effective during adolescence than trying to change unhealthy behavior during adulthood [7]. Increasing physical activity and eating a healthy diet have been argued to be the most effective ways to improve the health of adolescents with ID [14]. However, few studies have investigated health promotion interventions that target this group [13]. One viable option for improving health behaviors is to use digital interventions, called eHealth, which is defined as the use of information and communication technologies for health and can include the use of email, text messages, push notifications, websites, and mobile apps [15]. Previous systematic reviews [16,17] and our own previous randomized controlled trials (RCTs) [18-20] have shown that eHealth provides a wide range of possibilities for health-behavior promotion among young people in the general population. Digital interventions may also be useful for adolescents and young adults with mild to moderate ID, but there is a lack of such studies. Research comparing the internet use of adolescents with ID with a reference group of adolescents without ID shows that 70% of adolescents with ID have a smartphone and use the internet for entertainment purposes, compared to over 95% among adolescents without ID [21]. This is in line with other research and provides the knowledge that digital devices and internet activities are used in this target group [22-24]. Although Johansson et al [25] reported that there is a disability digital divide related to cognitive understanding and language difficulties, there is a possibility to design usable and accessible digital interfaces by using simple and logical interaction, clear design, and easy-to-understand written and audiovisual language combined with the use of clarifying icons and symbols. Digital interfaces can also be constructed to be adaptable to personal needs [26] and interoperable with personal assistive technology [27]. Combined, these measures can create a cognitively accessible digital intervention [28,29]. However, few studies have examined the feasibility or effectiveness of eHealth interventions to promote healthy behaviors (eg, a healthy diet and physical activity) in adolescents with ID. Furthermore, few studies have examined the possibility of co-designing eHealth interventions together with, rather than for, adolescents and young adults with ID. Only one protocol study for an RCT [30] has used a digital intervention to encourage youth with ID to increase their physical activity, and that study also targeted adults with ID. Clearly, there is a need to develop and design interventions that promote healthy behaviors tailored to the needs of adolescents and young adults with ID.

Participatory Design With a Co-Design Approach

The World Health Organization's Global Strategy on Digital Health (2020-2025) [15] prioritizes the development and adoption of appropriate, acceptable, and scalable health solutions to promote health and well-being worldwide. Participatory design [31] with a co-design approach [32,33] is crucial for successful development of digital interventions, as it is an effective method to understand the context, culture, attitudes, behaviors, needs, and expectations of those for whom the digital intervention is being designed. Previous research, including our own studies targeting adolescents and lifestyle behaviors [18-20,34-36], has consistently shown that the active participation of stakeholders and end users throughout the design of digital interventions supports the development of an intervention that meets the needs of its intended users. The development of a complex intervention requires several phases, although these phases do not follow a linear sequence [37]. The

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developers and designers of eHealth interventions targeting people with ID should be aware that this group might have the same needs to stay or become healthy as anyone, but they will have special prerequisites to consider due to their intellectual challenges, and there will be special requirements on how to design and promote such an intervention [38,39]. Through the co-design process, all included persons are given the possibility to become active partners at different stages in the development process [31].

Objective

The objective of this research protocol is to describe a co-design approach using workshops to develop a digital intervention that promotes healthy behaviors among adolescents and young adults with ID.

Methods

Study Context

This study is part of a larger research project that aims to develop and evaluate a digital intervention to promote healthy behaviors among adolescents and young adults with ID. To accomplish the purpose of the research project, we have established an ID research forum together with adolescents and young adults with ID; stakeholders, such as professionals within the social welfare, health care, and school systems; relatives; other relevant partners; and researchers. The development of the digital intervention will be based on a review of the literature and existing evidence and will be centered on insights of stakeholders and adolescents and young adults with ID gathered through specially adapted workshops [40].

Study Design

A participatory design approach using co-design [41] will be applied, in which research is conducted together with participants instead of on them. Co-design will be applied as a strategy to include potential users of the digital intervention and other stakeholders in the research process, including research design, data collection, and data analysis. The work draws from value sensitive design [42], a theoretically grounded approach that includes ethical and moral values in the design of technology. Value sensitive design allows stakeholders to have a voice in the design process and uses a tripartite method to perform conceptual, empirical, and technological investigations. Adolescents and young adults with ID; stakeholders within the health care, social service, and school systems; designers; accessibility experts; and researchers will form a design team. The design team will use an iterative and nonlinear process to design solutions to complex and prespecified problems. Every co-design activity will be carefully planned to fit the need to involve adolescents and young adults with ID.

Workshops provide a platform that can aid researchers in identifying and exploring relevant factors in a given domain by providing a way to understand complex work and knowledge processes that are supported by technology; an example of this is eHealth [43]. Workshops have a 3-fold purpose and focus within research: as a means, as a practice, and as a research methodology [44]. This study focuses on the workshop as a means to do co-design and develop the process for participation and as a research method to generate and collect data.

Setting, Recruitment, and Participants

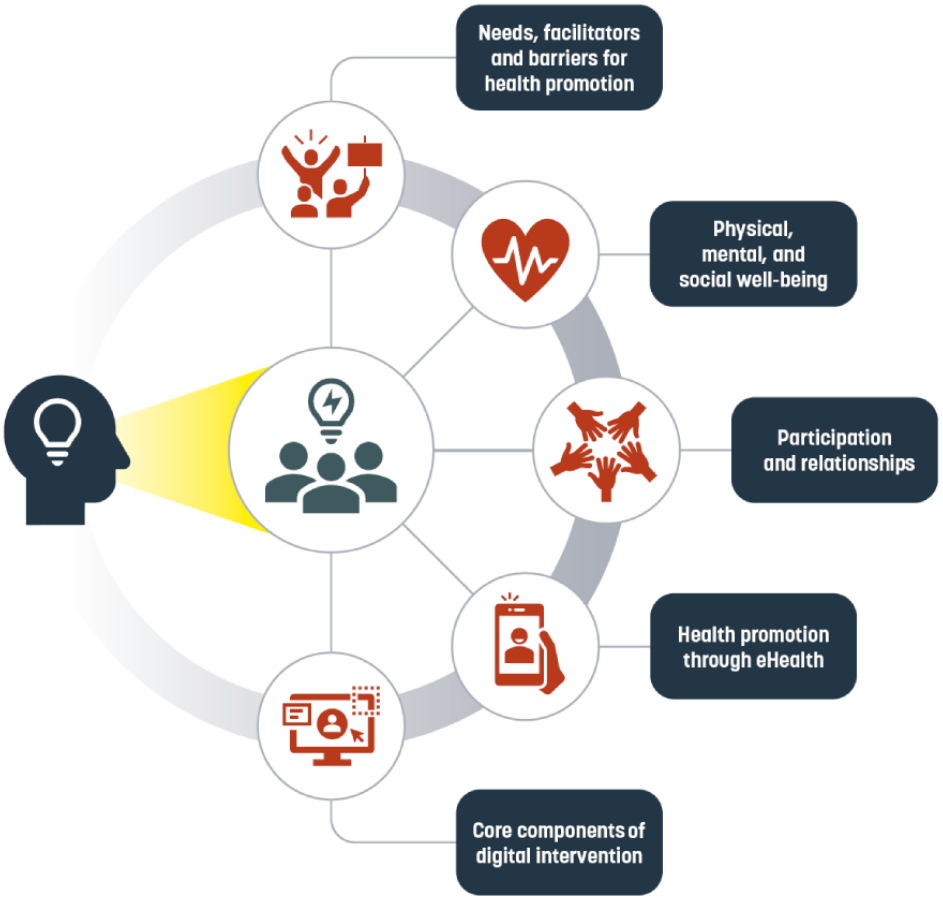
Adolescents and young adults with ID, as well as stakeholders living in Östergötland, Sweden, will be invited to workshops. The inclusion criteria for taking part in workshops for adolescents and young adults with ID will be as follows: (1) diagnosis of mild to moderate ID; (2) age between 16 and 25 years; (3) frequent use of either smartphones, tablets, or computers, that is, digital literacy, since we want them to use that experience in designing a digital intervention; (4) willingness to participate in a workshop; and (5) ability to provide informed consent. An equal mix of genders will be sought. Workshops with stakeholders will be divided into 2 groups with the following participants: group 1, including professionals from the areas of social welfare, health care, and the school system, and group 2, including relatives and representatives from the disability organizations. The inclusion criteria for the stakeholders will be as follows: (1) experience with clinical practice or other experiences related to adolescents with ID; (2) willingness to participate in a workshop; and (3) ability to provide informed consent. All participants will be geographically located in the region of Östergötland. Participants will be recruited with purposeful sampling to provide a representative sample of all relevant areas in collaboration with research partners in Östergötland and already established networks of the authors.

Data Collection

In total, 7 to 10 workshops [43] will be conducted between May and August 2023. Young adults and adolescents with ID will participate in a series of 3 workshops. The co-design process with specially adapted workshops will be used to gather rich, reliable, and valid data involving all participants. An overview of the included themes in the workshops is presented in Figure 1. The following themes will be included in all workshops: needs; facilitators and barriers to health promotion; physical, mental, and social well-being; participation and relationships; health promotion through eHealth; and core components of digital intervention. All workshops will be conducted in a meeting room at Linköping University or at rooms close to where young people with ID go to school or after-school clubs. The workshops will be organized in rooms with a whiteboard, internet connection, and wall surfaces suitable to tape up sheets of paper or sticky notes. Each workshop will produce rich data material, including design artifacts such as sketches, wireframe templates, screenshots of participants' phones, and lists of technological barriers and enablers. The workshops will also be documented with video and audio recordings and field notes, allowing participants to revisit important discussions and ideas. All collected data will be used in an iterative analytical process. The data will be used to evaluate the workshop as a tool for co-designing together with people with ID and to design the digital intervention for promoting a healthy lifestyle. Each workshop will last approximately 2 hours, including breaks.

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Figure 1. An overview of the included themes in the co-design workshops.



Structure and Activities of the Workshops

A structure of the workshops has been outlined. The workshop phases, including preparation, introduction, the main act, and evaluation, as well as planned activities, are presented in Table 1 and further described below. Workshops with relatives and representatives from disability organizations and professionals will be initially conducted once per group of stakeholders. Adolescents and young adults with ID will take part in 3 consecutive workshops.

Table 1. Structure and activities of the workshops.

Phase	Structure and activities
Preparation	• Provide information to participants (information videos, information letters, informed consent forms) • Prepare workshop management (moderator, notetaker, video documenter) • Construct the workshops (structure, content, and length) • Prepare workshop materials (sticky notes, felt-tip pens, balls, wireframe templates of a mobile phone, stickers, colored cards) • Prepare the use of assistive technology (devices for time management, taking turns, and recording) • Prepare surveys
Introduction	• Joint meal • Presentations given by participants • Moderators introduce the workshop and the timetable • Notetaker and video documenter present assistive devices
Main act	• Moderator introduces the topics to discuss and to work with • Individual and group work (using whiteboards, sticky notes, felt-tip pens, cards, balls, stickers) • Identifying core components using own devices and wireframe templates • Tasks using colored cards to indicate agreement on suggestions (green, yellow, red) • Survey on demographic variables and expectations on participating in co-design workshops (only for participants with intellectual disability)
Evaluation	• Qualitative evaluation of the participants' perceptions of their experiences taking part in the workshop • Quantitative evaluation survey: demographic variables and perceptions of participation in the co-design process (only for participants with intellectual disability)

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Preparation

The workshops will be carefully planned in line with the aim of the study. In preparation for participation in the workshops for adolescents and young adults with ID, a short video will be produced by the researchers in cooperation with relatives and representatives from the disability organizations. The video will be shown to the participants to explain the aim of the research project and ethical issues. All participants will be informed that the purpose of the workshops is to address barriers and facilitators to health promotion and to co-design components of a digital intervention. To avoid dropping out caused by, for example, issues with time management or memory issues, we will reach out and contact participants to remind them of the upcoming workshop. Workshop management will be organized to divide roles (eg, moderator, notetaker, and video documenter) between researchers. Workshop materials and assistive technology will be prepared, including cognitive adaptation to involve adolescents and young adults with ID.

Introduction

The workshops with participants with ID will be executed according to set procedures to make them cognitively accessible: start the workshop by establishing a convivial tone, present the agenda and the upcoming tasks, and present the rules for collaboration. Furthermore, to respect the timetable for the workshop, we will find a good pace and rhythm for the work, allow room and space for everyone to participate (while respecting participants who temporarily want to be silent), and give all participants time to think and reflect; we will stop and explain things that participants do not understand. We will start all workshops with a meal together to equalize differences in social status, get to know each other, and make participants feel comfortable. The participants will also give presentations. All participants (adolescents and young adults with ID; professionals from the areas of social welfare, health care, and the school system; and relatives and representatives from the disability organizations) will give oral presentations, preferably incorporating their own drawings. Moderators will introduce the workshops, including their length, schedule, and breaks. The notetaker and video documenter will explain the assistive devices.

Main Act

The moderators will present the proposed topics to discuss and work with during the workshop. The topics are (1) the health and well-being of young people with ID, (2) support for health-related activities and behaviors, and (3) the core components to include in a digital intervention to promote health behaviors. The co-design process will be implemented by giving all included participants the possibility to become active partners in all parts of the main act phase of the workshop. The goal is to both discuss the topics and create new outputs (ideas, concepts, and designs), as well as to evaluate special aspects of interest, such as drawing upon ideas for the design of a digital intervention prototype to promote healthy behaviors. Throughout the workshop, participants will make use of graphical arrangements along with verbal exchanges to express their ideas and to discuss proposals. Participants will perform a mix of individual and group work using whiteboards, sticky notes, felt-tip pens, cards, balls, and stickers. The selection of the specific materials and tools will be made in order to facilitate all participants to express themselves and hence to ensure a rich selection of data. The method of using a mix of individual work and group work encourages less talkative participants to have as much influence as more talkative participants. Additionally, the design team (ie, participating individuals and researchers) will use their own devices to discuss the apps they use that day. We will also use wireframe templates of a mobile phone for identifying core components of a digital intervention to promote health behaviors. Participants with ID will use stickers to prioritize what they perceive to be the most important components to include in a digital intervention and use green, yellow, and red cards to indicate if they agree with upcoming suggestions. An initial survey on demographic variables and expectations on participating in a co-design workshop will be provided to participants with ID.

Evaluation

The workshop will end with an evaluation of the participants' perceptions of their experiences of taking part in the workshop. In line with the co-design process, all included participants will be active oral partners in a qualitative evaluation process. Further, during the last of the 3 workshops, participants with ID will also be provided with a quantitative survey on demographic variables, their perceptions of the co-design process as implemented in the workshops, and their interest in continued participation in our research.

Data Analysis

Inspired by Sanders and Stappers [32], we use the following definition of co-design: "Co-design in a broader sense [refers] to the creativity of designers and people not trained in design working together in the design development process." In co-design, roles are diversified and potential end users are given the position of "experts of his/her experiences" and play a central role in knowledge development, idea generation, and concept development. In order for them to take on this role, appropriate tools for ideation and expression are necessary [32], which in this study will be provided throughout the co-design workshops. Co-creation will be applied across the whole span of a design process. Data analysis will be performed together and take place concurrently with data collection. By striving for concurrent data collection and data analysis, we will start the joint analysis simultaneously during the workshops. The co-design process will be an iterative process between ideation and visualizing the ideas as frameworks for a preliminary prototype of the intervention. Data collection and data analysis are, in other words, seen as an intertwined back-and-forth process used by the design team. This process draws from methods adapted from the participatory action research and participatory design approach presented by Johansson [45] and will follow the double diamond design process with discovery, define, develop, and delivery phases [46]. The discovery phase will focus on understanding relevant phenomena and discussing the prerequisites for health promotion through a digital intervention. The define and develop phases will narrow the ideas down to those that will be developed in this project. The delivery phase will end with the framework for a preliminary

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prototype that the design team will use to move forward, but we will also work in iterative loops, going back and forth to co-design the prototype. This will be done by, for example, checking with participants, reflecting on feedback, and examining the processes of the included activities together with the participants. Preanalysis of quantitative aspects, for example, summarizing the colored-dot stickers, will be performed together by counting the dots and analyzing the results.

In order to analyze the workshop as a method for co-designing together with people with ID, transcribed data from the audio and video recordings of the groups' discussions will be analyzed in an approach inspired by inductive program theory development [47] following a qualitative methodological procedure [48]. As suggested in literature describing participatory design methods from process to outcome [49], we will strive to follow an approach that creates space for all partners to draw on their different, yet complementary, experiences and skills and to determine their respective analytical roles and responsibilities. Analyses of the transcribed data will therefore be led by the first author (UM) and performed together with the researchers and representatives from the design team. Given the time and skills required, the transcribed data will be analyzed initially by the researchers. The evaluation survey will be analyzed using descriptive statistics. The representatives of the participating stakeholders will be actively engaged in determining the meaning of the results and their implications for action. By capturing visual details from the filmed workshops, this analytical approach will allow us to review not only what we said, but how we expressed it and in what situations. Systematic analyses will follow a prescribed sequential process [50].

Ethical Considerations

All participants will receive written and oral information about the study, including information that participation is voluntary and that they are allowed to ask questions and leave the study at any time without giving reasons as to why. Informed consent will be obtained from all participants before participation in either written form or orally during audio recording. The study data will be deidentified before publication. Young adults and adolescents with ID will receive a diploma and a gift card of 100 SEK (US $9.77) for their participation. All procedures were approved by the Swedish Ethical Review Agency (Dnr 2022-06682-01).

Results

Recruitment of participants started in April 2023 through initial contacts with schools, after-school clubs, community-based services, and social services. The recruitment continued until the end of June 2023. Initial workshops were planned for May 2023. Data collection and analysis are planned to be completed in September 2023. The main contribution of this protocol article is a detailed description of how to conduct and analyze co-design workshops to develop a digital intervention that promotes healthy behaviors among adolescents and young adults with ID. Full results from the workshops are expected to be published in December 2023.

Discussion

This research protocol describes a co-design approach using workshops to develop a digital intervention that promotes healthy behaviors, such as physical activity and a healthy diet, among adolescents and young adults with ID. In this study protocol, we set out to describe a co-design approach using workshops to develop a digital intervention that promotes health-related activities and behaviors among adolescents and young adults with ID, who are a group that is often marginalized in society and in research regarding aspects of their own lives. However, research with the involvement of people with ID has proven to be plausible [51]. Through the co-design process, all included persons will be given the possibility to become active partners at all different stages in the development process. A description of how the participants will be involved in the co-design process has been presented. In this study protocol, needed adaptations are described and will be continuously redesigned to improve the involvement of people with ID in the co-design process.

It is well known that young people with ID have a more sedentary lifestyle compared to their typically developing peers. Specifically, they are less physically active, have a poorer diet, and are more socially isolated [3,8]. These health conditions are more prevalent due to lack of knowledge of their effects, reduced physical and behavioral skills, and lack of motivation attributed to ID [52]. As little evidence-based knowledge is available about how to promote physical activity, a healthy diet, and social participation for this group, this proposed study will identify needs, as well as facilitators and barriers to health promotion activities enabled through digital interventions. Furthermore, since few studies have examined the effectiveness of eHealth interventions to promote healthy behavior (eg, a healthy diet and physical activity) among adolescents and young adults with ID, our research aims to develop an eHealth intervention that targets this often-marginalized group. Including young individuals with ID in trials can involve challenges in many aspects of the research process. Common challenges in trials involving these individuals include informing the individuals with ID about the research process, obtaining informed consent, arranging transportation to research sites, and ensuring that instructions are followed [53]. Hence, it is particularly important to plan and conduct intervention studies for this group carefully. Therefore, by using a co-design approach when developing the intervention, we believe that we also will optimize participation in the trial and the potential uptake and reach of the digital tool.

This research project will develop an eHealth intervention that is specifically designed to address the needs of adolescents and young adults with ID. The digital intervention will be complex, especially given the variety of the intervention components needed, the degree of flexibility required, and the ability to adapt to the contextual, social, and practical skills of the individual. This research protocol describes a participatory design in order to develop a digital intervention to promote healthy behaviors. First, this protocol provides a systematic record of the scientific methodologies used when developing the intervention to enhance transparency of research and ensure

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research rigor. Second, the protocol provides insights into potential practical challenges and solutions when following a co-design approach in which relatives, professionals, and adolescents and young adults with ID are included as research partners. Third, this protocol provides procedural considerations on how to use workshops as a means and research method when developing digital interventions. The protocol describes how data will be collected and analyzed in cooperation with stakeholders and adolescents with ID. We hope this study will contribute to and inspire new approaches to develop effective interventions for lifestyle behaviors for young people with ID. Further studies will examine the effectiveness of our individually tailored digital intervention to support healthy lifestyle behaviors among adolescents and young adults with ID. If successful, the project will provide a simple and accessible digital solution for promoting physical activity and a healthy diet. Hence, our research has potentially important implications for both this target group and their support networks. Since it is necessary to engage stakeholders for widespread clinical implementation, this study will also be valuable during the later stages of our project. We have established networks through our ID research forum that include adolescents and young adults with ID, stakeholders (ie, professionals within the social welfare, health care, and school systems), relatives, other relevant partners, and researchers.

Several procedures will be performed to fulfill the quality criteria (ie, credibility, transferability, confirmability, dependability) for qualitative research to verify trustworthiness [54] when designing, analyzing, and reporting the processes related to the video-recorded workshops. The research process will be clearly described and documented. The Consolidated Criteria for Reporting Qualitative Research (COREQ) 32-item checklist [55] will be followed to create a clear audit trail. Data will be analyzed in accordance with the steps following indicative program theory development [47] and qualitative methodological procedures [48] to facilitate a rigorous and systematic process. The sample size will be based on data saturation [56], and data collection will accordingly be finalized when the data reach satisfactory depth and complexity to answer the aim with sufficient confidence. Trustworthiness will be further enhanced by the use of a guide [48] during all workshops. Video recordings will yield more details and secure high accuracy since the recorded data can be reviewed indefinitely [57]. Moreover, video recordings can help guard against researcher bias because they can be analyzed by researchers other than those who led the workshops [43]; hence, researcher triangulation will be used [48]. A possible limitation of the study design is that the transferability of the forthcoming results to other study contexts may vary depending on how the care is organized. However, we consider that the results from the study will be relevant and applicable to the development of digital interventions in similar settings. We expect that the results from this study will be valuable for the development of eHealth interventions in young adults with ID.

Acknowledgments

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Data Availability

The data sets generated during and/or analyzed during this study are not publicly available due to Swedish ethical review guidelines but are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

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Abbreviations

COREQ: Consolidated Criteria for Reporting Qualitative Research
ID: intellectual disability
RCT: randomized controlled trial

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Protocol

Internet-Delivered Cognitive Behavioral Treatment for Chronic Pain in Adolescent Survivors of Childhood Cancer: Protocol for a Single-Group Feasibility Trial

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Abstract

Background: There are over 500,000 survivors of childhood cancer in North America alone. One in 4 survivors experiences chronic pain after treatment has been completed. Youths with chronic pain report increased anxiety, depression, activity limitations, and sleep disturbances. An 8-week web-based cognitive behavioral treatment for chronic pain (Web-Based Management of Adolescent Pain [WebMAP]) has demonstrated a reduction in pain in youths but has not yet been explored in survivors.

Objective: The objectives of this study are to (1) test the feasibility and acceptability of WebMAP for a sample of survivors with chronic pain and their parents; (2) assess the acceptability of WebMAP using qualitative interviews; (3) assess WebMAP's effect on activity limitations, pain intensity, depression and anxiety symptoms, and sleep disturbances; and (4) assess WebMAP's effect on parent pain catastrophizing and parental response to their child's pain.

Methods: A single-arm mixed methods pre-post intervention study design will be used. Participants will be 34 survivors and at least one of their parents or caregivers. Inclusion criteria are (1) a cancer history, (2) current age of 10-17 years, (3) >2 years post treatment or >5 years post diagnosis, (4) pain present over prior 3 months impairing >1 area of daily life and occurring >1 time per month, and (5) computer access with broadband internet. Survivors will complete a pretreatment questionnaire, which will include the following: the Child Activity Limitations Interview, the pain intensity Numerical Rating Scale, Patient-Reported Outcomes Measurement Information System (PROMIS)–Pain Interference, Anxiety, Depression, Insomnia Severity Index, and Adolescent Sleep Wake Scale. Parents will complete the Pain Catastrophizing Scale–Parent Version and the Adult Responses to Child Symptoms. Upon completion of pretreatment questionnaires (T0), survivors will begin WebMAP. After the 8-week intervention, survivors will complete the same measures (T1), and at 3-month follow-up (T2). Posttreatment interviews will be conducted to determine acceptability. Feasibility will be assessed via recruitment and retention rates. Treatment engagement will be measured by number of modules completed. Pre-post outcome data will be assessed using linear mixed models. Qualitative data will be analyzed using thematic analysis. Patient partners will be involved in study design, recruitment, interpretation of results, and knowledge translation.

Results: This study has been funded in January 2022. Data collection started in May 2022 and is projected to end in August 2023. We have enrolled 10 participants as of December 2022.

Conclusions: Investigating whether WebMAP is useful to survivors will be an important step in improving pain management in this population.

Trial Registration: ClinicalTrials.gov NCT05241717; https://clinicaltrials.gov/ct2/show/NCT05241717

International Registered Report Identifier (IRRID): DERR1-10.2196/45804

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(JMIR Res Protoc 2023;12:e45804) doi:10.2196/45804

KEYWORDS

pediatric oncology; chronic pain; cognitive behavioral therapy; eHealth; intervention; late effects; cancer survivorship; pediatric cancer; youth; mental health; psychological difficulties; chronic health conditions; pain management; intervention; cancer survivor

Introduction

Currently, there are over 500,000 survivors of pediatric cancer in North America alone [1]. Unfortunately, two-thirds of survivors of childhood cancer will experience late- and long-term effects from their cancer and its treatments, such as subsequent chronic health conditions and psychological difficulties [2]. Our previous work demonstrated that approximately 1 in 4 survivors of childhood cancer experiences chronic pain after treatment completion and 1 in 5 experiences moderate to severe chronic pain problems, reporting high pain intensity and interference in activities [3]. We also found survivors living with chronic pain reported significantly worse depressive and anxiety symptoms and poorer quality of life than survivors without chronic pain [3,4].

Survivors of childhood cancer are already at risk for worse mental health than their healthy peers as a result of cancer and its often toxic treatments [2], and pain could exacerbate these outcomes. Importantly, pain among survivors of childhood cancer has been shown to persist into adulthood, which among noncancer adolescents has been linked to lower educational and social attainment and poor vocational functioning in young adulthood [5]. With the growing number of survivors of childhood cancer, improving long-term follow-up care will help improve health care for these vulnerable youths by reducing their risk of continued pain and poor health into adulthood.

Chronic noncancer pain in childhood is associated with negative developmental outcomes in young adulthood including a higher likelihood of dropping out of high school, a lower likelihood of graduating from university, poor vocational functioning, and social impairments [6]. A large, longitudinal study demonstrated that chronic pain in adolescence conferred risk for lifetime anxiety and depressive disorders [6].

According to the United Nations Office on Drugs and Crime's most recent World Drug Report, approximately 585,000 people experienced drug-related deaths and the majority of these deaths could be attributed to opioids [7]. Importantly, there is little evidence for the efficacy of prescription opioids for the treatment of chronic pain, and long-term opioid use for the treatment of chronic pain can cause adverse effects such as overdose, cardiovascular events, and motor vehicle accidents [8,9]. Chronic pain is also a significant financial burden on families, society, and the health care system, costing up to CAD $60 billion (US $46.99 billion) per year in Canada [10], and is one of the most common reasons for seeking health care [11,12]. According to a recently proposed developmental model of chronic pain, strategies for pain prevention and management should begin in childhood and should leverage psychological interventions in order to prevent pain-related morbidities and promote better overall well-being in adulthood [13]. Thus, research on nonpharmacological pain management strategies is needed in general, particularly in this underserved population.

While the prevalence of pain is high in survivors of childhood cancer, no evidence-based interventions for pain are available for youth survivors of childhood cancer [14]. Most promising for this population may be cognitive behavioral therapies, as they can effectively target activity limitations, depression and anxiety symptoms, and sleep disturbances related to pain. Cognitive behavioral therapies are effective in reducing the burden of pain in youths with chronic noncancer pain conditions [15]; however, there are also significant barriers to participation in clinic-based cognitive behavioral therapy programs. For example, parents may have to take time off work and take their children out of school to visit a psychologist (the professionals most often trained and competent to deliver cognitive behavioral therapy), a psychologist may not be affordable, or there may not be a psychologist available in some areas.

In response to these limitations and barriers, internet-delivered cognitive behavioral therapy (CBT) can address these significant barriers and has demonstrated feasibility and efficacy in youths with chronic pain [16]. An 8-week web-based cognitive behavioral therapy program called web-based management of adolescent pain (WebMAP) has been rigorously developed and tested in children and adolescents with various chronic pain conditions, and is feasible and acceptable for this group, demonstrating clinically significant reductions on primary targets including activity limitations and pain intensity [17,18]. In addition, previous trials with WebMAP have shown economic benefits for both intervention and education groups, demonstrating a significant decrease in health care–related expenditures from the year before participating in the trial to the year after [19]. In other populations, WebMAP has demonstrated feasibility and acceptability in adolescents with sickle cell disease and their parents, with no indication that the program needed to be significantly tailored for those with sickle cell disease [20].

Treatment for chronic pain in youths is enhanced by the inclusion of parents, given the developmentally important role they play in their child's life. For example, unique social factors exist related to parent and family influences on pediatric chronic pain and disability such as parental responses to child pain behavior, parenting style, family environment, and overall family communication and functioning [21]. Parent pain catastrophizing has also been shown to play an important role in their child's pain interference [22,23]. Parent protectiveness is also related to important child-level outcomes (eg, child functional disability) in trials assessing family cognitive behavioral therapy for adolescents with chronic pain [24]. WebMAP includes a parent component in which parents complete modules in parallel with their child in order to target these factors. In WebMAP, parents are taught various operant strategies to respond to their child's pain behaviors. In previous

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trials with WebMAP, parent distress, and parent protective behaviors predict child functional disability trajectories 6- and 12-months post treatment [25], and parent engagement in the program may also be predictive of treatment outcomes [26]. Thus, the inclusion of parents in psychological intervention trials for youths with chronic pain is recommended.

WebMAP has never been tested on a sample solely comprised of youths with a history of cancer. Thus, the primary objective of this study is to test the acceptability and feasibility of WebMAP for survivors of childhood cancer living with chronic pain and their parents, using a single-arm, pretest-posttest mixed methods design with semistructured interviews. Objective 1 will test the feasibility and acceptability of WebMAP for a sample of survivors with chronic pain and their parents. We hypothesize that the intervention will be feasible, that families will be engaged in the treatment and it will be safe. Objective 2 will assess the acceptability of WebMAP using qualitative interviews. Objective 3 will assess WebMAP's effect on activity limitations, pain intensity, depression and anxiety symptoms, and sleep disturbances. We hypothesize that survivors of childhood cancer participating in WebMAP will report significantly reduced activity limitations, pain, anxiety and depressive symptoms, and sleep disturbances from before to after the intervention. Finally, objective 4 will assess WebMAP's effect on parent pain catastrophizing and parental response to their child's pain. We hypothesize that parents participating in WebMAP will report significantly reduced catastrophizing about their child's pain, distress, and reduced protective parental responses to their child's pain. This study protocol follows the Standard Protocol Items: Recommendations for Interventional Trials Checklist for recommended items to address in a clinical trial protocol [27].

Methods

Study Design

This study will use a single-arm, mixed methods, pre-post design. Survivors of childhood cancer with chronic pain will participate in an 8-week internet-delivered cognitive behavioral therapy intervention (WebMAP). Assessment questionnaires will be collected before the intervention (T0), immediately following the intervention (T1), and 3-months after intervention completion (T2). Individual interviews will also be conducted upon completion of the intervention.

Participants

Sample Size

Based on an audit of sample sizes of combined feasibility and pilot trials in similar populations, median sample sizes ranged from 30 to 36 [28]. A sample of 34 will be sufficient to detect an effect size (Cohen *d*) of 0.4 with our preliminary outcomes with 80% power and α at .05. Therefore, we will aim to recruit a total sample of 38 to conservatively account for 10% attrition over the study duration.

Eligibility Criteria

Inclusion criteria for participation are (1) history of any cancer diagnosis; (2) current age 10-17 years; (3) >2 years posttreatment or completed treatment and >5 years post diagnosis; (4) pain present over prior 3 months that impairs at least one area of daily life and occurs >1 per month; and (5) computer access, internet, and literacy. Survivors wishing to participate without a parent will not be excluded but will still require parental consent.

Patient Engagement

Patient engagement is an important component of health research. One systematic review found that across studies, engaging patients as partners in research increases enrollment and retention rates, and improves dissemination of results to be more meaningful and digestible for patient audiences [29]. The Canadian Institutes of Health Research Strategy for Patient Oriented Research Patient Engagement Framework [30] is a roadmap on how to engage patients as partners in health research, with the goal of improving health outcomes and creating a more enhanced health care system. The framework provides guiding principles (inclusiveness, support, mutual respect, and cobuilding of ideas), tools, and resources for researchers to use throughout their projects. It highlights that patients should be included from the start of the research project and that they should collaborate with the researchers as equal members of the team.

In this study, 3 patient partners were involved in the study design and will be involved in recruitment, interpretation of results, and knowledge translation for this study. More specifically, the patient partners have been consulted on the study protocol where they provided feedback and have approved the final version to be submitted to the institutional ethics committee. We started a group on Slack (Slack Technologies, Salesforce Inc), a web-based communication platform that allows us to share communications and materials all in 1 place. Patient partners will help with the creation and dissemination of recruitment materials, using their own connections with advocacy groups and Canadian cancer advocacy groups. Similar to previous experiences, we will discuss findings with patient partners in order to seek their interpretation of the results and how to communicate them. This work will foster inclusiveness, support, mutual respect, and cobuilding of ideas [30].

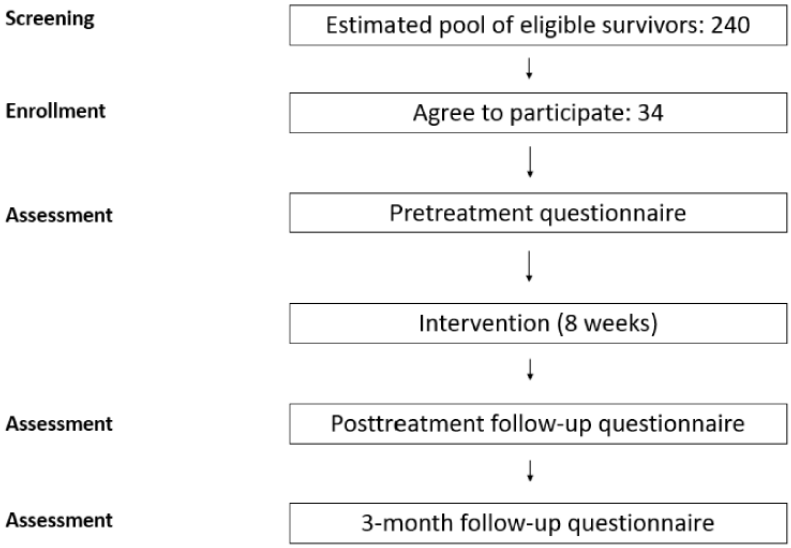
Procedures

Recruitment

Survivors will be recruited from the Long-Term Survivors Clinic at the Alberta Children's Hospital in Calgary, Alberta, Canada. The participant flowchart is in Figure 1. The study team will contact potentially eligible survivors by phone or email. Approximately 700 survivors receive follow-up care at ACH, and an estimated 240 of these survivors may be experiencing chronic pain based on our research [3]. Approximately 94% of Canadians have internet access at home [31] and recruitment rates from our previous pain-related research were 70% [3]. Conservatively, we expect 40% of these survivors to meet our inclusion and exclusion criteria, leaving a possible sample of 70. Meeting our targets would require a participation rate of 49% (34/70).

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Figure 1. Participant recruitment flowchart.



Data Collection

Upon enrollment and completion of informed consent, survivors and their parents will complete pretreatment questionnaires (T0) and be given access to WebMAP. Upon treatment completion (T1), survivors and parents will complete the same questionnaire battery plus the Treatment Evaluation Inventory—Short Form [32]. In addition, we will conduct posttreatment interviews to gather feedback on the program. Patient and caregiver partners will be involved in creating the interview questions and conducting a portion of the interviews. Interviews will be recorded and transcribed. Finally, survivors will be administered the same questionnaire battery at 3 months post intervention (T2) to assess longer-term effects of the intervention. Questionnaires will be completed over internet via Research Electronic Data Capture (REDCap) tools hosted by the University of Calgary Clinical Research Unit. REDCap is a secure, web-based application designed to support data capture for research studies, providing (1) an intuitive interface for validated data entry, (2) audit trails for tracking data manipulation and export procedures, (3) automated export procedures for seamless data downloads to common statistical packages, and (4) procedures for importing data from external sources. The investigator leading the trial (MP) and the sponsor (FS) will have access to the final trial data set (Table 1).

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Table 1. World Health Organization trial registration data set.

Data category	Information
Primary registry and trial identifying number	ClinicalTrials.gov NCT05241717
Date of registration in primary registry	February 4, 2022
Sources of monetary or material support	Alberta Children's Hospital Trainee Small Research Grant[a]
Primary sponsor	Fiona Schulte, PhD[a], fsmschul@ucalgary.ca
Contact for public queries	Fiona Schulte, PhD, fsmschul@ucalgary.ca
Public title	Internet-delivered cognitive behavioral treatment for adolescent survivors of childhood cancer with chronic pain
Scientific title	Internet-delivered cognitive behavioral treatment for adolescent survivors of childhood cancer with chronic pain: A pilot feasibility trial
Countries of recruitment	Canada
Health conditions or problems studied	Cancer, chronic pain
Intervention	
Active comparator	Internet-delivered cognitive behavioral therapy
Key inclusion and exclusion criteria	
Ages eligible for study	10-17 years
Sexes eligible for study	Any
Accepts healthy volunteers	No
Inclusion criteria	History of any cancer diagnosis, >2 years post treatment or completed treatment and >5 years post diagnosis, pain present over prior 3 months that impairs at least one area of daily life and occurs >1 per month, computer access and literacy.
Study type	Interventional study; intervention model: single arm; primary purpose: pain management; phase II
Date of first enrollment	May 24, 2022
Target sample size	34
Recruitment status	Currently recruiting
Primary outcomes	Feasibility, satisfaction
Key secondary outcomes	Pain intensity, activity limitations, anxiety symptoms, depressive symptoms, pain interference, insomnia symptoms, parent catastrophizing about child's pain, parent distress, parent responses to child's pain behaviors

[a]The funders will not contribute to any aspects of study design or management. The sponsor will be responsible for overseeing the study, interpretation of data, and the decision to submit the report for publication.

Intervention

Upon completion of the pretreatment questionnaires, survivors will receive access to the WebMAP program, an 8-week web-based cognitive behavioral therapy program with weekly modules including (1) education about chronic pain, (2) recognizing stress and negative emotions, (3) deep breathing and relaxation, (4) implementing coping skills at school, (5) cognitive skills, (6) sleep hygiene and lifestyle, (7) staying active, and (8) relapse prevention.

WebMAP is built using a responsive framework so that it can be easily viewed on any internet-enabled device (eg, smartphone and laptop). The program makes use of multimedia components (eg, audio and video) and interactive exercises. Support is provided through a message center, which allows asynchronous messaging with a coach over the internet. The study coach will be a member of the research team (MP) and is a clinical psychology doctoral student trained in cognitive behavioral therapy. The study coach will have access to a previously developed web-based coach's manual to standardize responses to participants in the message center. The WebMAP backend system monitors the completion of modules so treatment progress can be recorded.

Survivors will be asked to complete 1 module per week, which is approximately 20 minutes in length. Survivors and parents will be asked to spend approximately 4.5 hours each over the course of the intervention on WebMAP including 4 hours to complete the modules and 30 minutes total corresponding with a coach.

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Each week, survivors will be instructed to log in to WebMAP to learn a new skill and practice that skill for 1 week to allow time for skills acquisition. WebMAP consists of 2 separate, password-protected programs including 1 for children and adolescents and 1 for parents.

Parents will also be given access to their own web-based program with weekly modules including (1) education about chronic pain, (2) recognizing stress and negative emotions, (3) operant strategies I (using attention and praise to increase positive coping), (4) operant strategies II (using reward to increase positive coping and strategies to support school goals), (5) modeling, (6) sleep hygiene and lifestyle, (7) communication, and (8) relapse prevention. The parent version of WebMAP uses the same type of multimedia and interactive elements as the teen version including access to the message center.

Measures

Clinical and Demographic Information

We will collect clinical and demographic information from parents including survivor's date of birth, gender, race, ethnicity, and household income. We will also ask about the survivor's previous medical issues (excluding cancer) including major injuries, illnesses, or surgeries as well as current or past history of pain treatments (behavioral or pharmacological). Upon receiving consent, we will also collect clinical information from electronic medical records including survivor sex, diagnosis date and description, and treatment received.

Objective 1

Feasibility

Feasibility will be assessed by considering rates of: (1) recruitment, (2) retention, (3) treatment engagement, (4) acceptability, and satisfaction. "Recruitment" will be measured by the number of survivors enrolled or consented divided by the total number of survivors invited to participate. Based on previous trials of similar nature [17], a 50% recruitment rate of eligible survivors will be used as the benchmark to determine this factor of study feasibility. "Retention" will be measured by the number of survivors who complete the study defined as those who complete the intervention and all assessments from enrollment (T0) to 3-month follow-up (T2) divided by the total number of survivors who enrolled in the study. Survivors will be considered to be enrolled in the study when they have read and signed the informed consent form. Based on previous pilot trials [17], an 80% retention rate will be considered "feasible." "Treatment engagement" will be measured by number of modules completed by survivors and parents. Based on similar trials [17], the goal to determine treatment engagement will be at least 75% of survivors completed at least 6 of the 8 modules, and the mean number of modules completed by the sample being at least 6. We hypothesize that >75% of survivors will complete assessment measures across the 3 specified time points. "Acceptability" will be measured using the Treatment Evaluation Inventory—Short Form (TEI-SF) [32], a 9-item self-report measure of acceptability of treatment, completed by both survivors and parents. The TEI-SF was originally designed to measure parents' acceptability of a treatment for children with problem behaviors but has been adapted to assess the acceptability of WebMAP in previous studies [17]. Responses are scored on a 5-point Likert scale and summed to create a total score. Higher scores represent better acceptability. Moderate to high acceptability, defined as a score of 27 or higher, has been considered sufficient for trials of similar nature [17,33]. The TEI-SF has good reliability and validity across various child treatments [32]. This study will use the adapted version and will be completed by survivors and parents.

Satisfaction

A survey including open-ended questions will be created with patients to elicit feedback on specific modules. These questions will ask about what information was helpful and what may need to be adjusted to better serve youths with a history of cancer for both patients and parents. The satisfaction survey will be completed as part of the posttreatment questionnaire by survivors and parents.

Qualitative Interviews

Semistructured interviews will be conducted with survivors and parents separately upon treatment completion to assess feasibility, acceptability, and satisfaction with the program. Patient partners will be involved in creating an interview guide. The interview guide will include open-ended questions about participants' experience with the program to facilitate self-reflection and open discussion around important aspects of their experience. Interviews will be audio-recorded and transcribed verbatim.

Objective 2

Pain Intensity

Daily surveys, administered to survivors through REDCap, will be used to assess the daily presence of pain and pain intensity for 7 days at the beginning of each assessment period (T0, T1, and T2). Pain intensity will be assessed with an item asking about the magnitude of pain experienced answered on an 11-point numerical rating scale (0=no pain, 10=worst pain). This measure of pain intensity has demonstrated to be a reliable and valid measure of pain in many populations of children 8 years and older [34-37], including those with chronic cancer pain [38].

Activity Limitations

The Child Activity Limitations Interview (CALI-9) [39] is a measure of children's perceived difficulty in completing typical daily activities because of pain. The CALI will be collected from survivors for 7 days at the beginning of each of the study timepoints (pretreatment, posttreatment, and 3-month follow-up). Survivors will choose from a list of 9 activities (eg, running, doing a hobby, playing with friends, sports, going to school), and will be asked each day whether the activity occurred and how difficult the activity was to perform because of their pain. Total scores range from zero to 100, where higher scores indicate greater functional limitations. Average daily limitation scores across each assessment period will be computed. The CALI has demonstrated reliability and validity in school-age children and adolescents with chronic pain, including those referred to pain clinics from hematology departments [40].

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Anxiety and Depressive Symptoms and Pain Interference

The Patient-Reported Outcomes Measurement Information System (PROMIS) Anxiety and Depression instruments [41] (8-item short form) will be administered to survivors to screen for current symptoms of anxiety and depression. Survivors will complete the self-report instrument corresponding to their age (child: aged 8-17 years; adult: aged 18 years or older). Items (eg, "I felt worried") are rated on a 5-point scale (1=never, 5=always). Higher scores signify greater severity of symptoms. Pain interference will be assessed using the 4-item PROMIS interference scale for survivors 8-17 years of age, and the 7-item PROMIS interference scale for survivors over 18 years of age [42]. The PROMIS pediatric measures have been validated for use in pediatric oncology [42].

Insomnia

Insomnia Severity Index (ISI) is a 7-item self-report questionnaire assessing the nature, severity, and impact of insomnia [43,44] and will be administered to survivors. Items are rated on a 5-point Likert scale (0=no problem; 4=very severe problem). The scale is scored using a total sum ranging from 0 to 28 and cut scores are interpreted as such: absence of insomnia (0-7), subthreshold insomnia (8-14), moderate insomnia (15-21), and severe insomnia (22-28). The ISI is a reliable and valid measure used to detect cases of insomnia in a population sample and is sensitive to treatment response in patients presenting with sleep difficulties [43].

Catastrophizing About Child's Pain

The Pain Catastrophizing Scale–Parent Version [45] is a 13-item measure used to assess parents' catastrophic thoughts and feelings about their child's pain and will be administered over the internet via REDCap. Parents rate statements about their child's pain on a 5-point Likert scale (ie, "When my child has pain, I can't keep it out of my mind"). Items are summed to yield a total score and can also be summed to provide scores on 3 subscales: rumination, magnification, and helplessness. Lower scores indicate less catastrophizing. This scale has been found to have good reliability in parents with children who experience pain.

Parental Responses to Child's Pain Behaviors

The Adult Responses to Children's Symptoms [46,47] measures parental responses to their child's pain behaviors and will be administered over the internet via REDCap. This study will only use the Protect subscale, which assesses parents' responses that either positively or negatively reinforce pain complaints. Parents' responses are rated on a 5-point scale (0=never, 4=always). Subscale scores represent an average of the items, with higher scores indicating more frequent use of that behavioral style. This scale has demonstrated reliability and validity for use with parents of children with chronic pain [46,47].

Parent Distress

The Kessler Psychological Distress Scale [48] will be administered to parents and is a 6-item measure used to assess nonspecific psychological distress representing diagnoses of major depression and generalized anxiety disorder and also contains a positive affect domain. The measure has good precision in the 90th-99th percentile range of the population, and has solid psychometric properties across major sociodemographic populations distribution in the United States and Canada [48]. It also strongly discriminates between meeting and not meeting diagnostic thresholds for psychological disorders [48].

Data Analysis

Quantitative Data Analysis

To address objective 1, we will use frequencies and descriptive statistics to describe recruitment and retention rates, treatment adherence, and acceptability. To address objectives 2 and 3, primary efficacy end points of the study will be calculated as within-person changes in outcome measures using Cohen *d* effect sizes from T0 to T1 and T2. Outcome data will be analyzed using paired samples *t* tests in order to assess changes in outcome variables over time. Treatment effect sizes (Cohen *d*) will be calculated for changes in means, standardized by the pooled SD. All quantitative analyses will be conducted using SPSS (version 27; IBM Corp).

Qualitative Data Analysis

Qualitative data will be coded independently by 2 study team members and analyzed using reflexive thematic content analysis, consistent with Braun and Clark's thematic analysis guide [49]. Team members will first familiarize themselves with the data by reading the transcripts multiple times. The data will then be coded independently using a hybrid deductive-inductive approach whereby codes will be inductively derived from the data and codes will be deductively generated from existing literature [50]. Afterward, the 2 coders and the principal investigator (MP) will meet to discuss the codes and iteratively generate themes and subthemes. Additional team members will be invited to offer critical reflections and insight on the interpretations. Several strategies will be used throughout the data analysis to enhance rigor including having clear and extensive descriptions around the research setting and process, member checking, providing thick descriptions of themes, regular debriefing meetings, data triangulation with the quantitative analysis, and having the authors actively practicing reflexivity through notes and meetings [51].

Ethics Approval

Ethics approval was obtained from the Health Research Ethics Board of Alberta Cancer Committee (HREBA.CC-21-0272). Any changes to this protocol will be made through this ethics board. Potential survivors will be contacted and informed of study details such as the voluntary nature of participation, confidentiality, and risks and benefits of participating. Once survivors are fully informed, they will be given the opportunity to provide written consent and enroll in the study. Survivors will provide assent and will require parental consent to participate. Parents will provide consent for their own participation. WebMAP is known to be safe and previous trials reported no adverse events directly related to study participation [17]. Data will be collected using participant identification numbers to protect confidentiality. Names and corresponding identification numbers will be kept in a separate, password-protected document. Potential benefits of participating

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in the intervention include a reduction in pain and an improvement in mental health.

The results will be disseminated to a range of stakeholders such as survivors of childhood cancer, parents of survivors of childhood cancer, health care practitioners, and researchers. Dissemination efforts will be made through national and international conference presentations, social media posts (eg, Twitter and Facebook), peer-reviewed academic journal publications, and cancer advocacy group newsletters (eg, Kids Cancer Care).

Results

This study was funded in January 2022. Data collection started in June 2022 and is projected to finish by August 2023. As of December 2022, we have recruited 10 participants, with zero participants completing all aspects of the protocol.

Discussion

The primary objective of this study is to assess the feasibility and acceptability of a well-studied internet-based psychological intervention developed for adolescents with chronic pain in a population of youths with a history of cancer. The strength of the study is the usage of a mixed methods design, which will provide both quantitative and qualitative information regarding the feasibility, acceptability, and potential efficacy of the intervention. Additionally, 3 patient and caregiver partners with lived experience of cancer and chronic pain will inform the study from the beginning. The web-based intervention will also be accessible for survivors who would not otherwise be able to access CBT with a psychologist. This may prove to be more inclusive for survivors living in rural or remote areas and survivors of families with low household incomes.

The proposed study has limitations. Participants for previous studies were recruited from tertiary pain clinics, which serve the most severe cases of chronic pain. One limitation of this study is that the participants may not experience a severe chronic pain problem compared to participants from other studies, though screening criteria require that they have chronic pain that affects at least one area of their daily life, similar to previous studies. This limitation may lead to smaller effects of the pain intervention on participants with mild to moderate chronic pain problems, and may also affect motivation to engage in the program if participants are generally functioning with pain. Another limitation is that the study will be conducted at a single location, in which the feasibility and acceptability of the study may not be generalizable to survivors across Canada.

The Obesity-Related Behavioral Intervention Trials (ORBIT) Model for Behavioral Treatment Development [52] is a framework for increasing the number of optimized evidence-based behavioral trials to prevent and treat chronic diseases. The ORBIT model includes several phases that serve as a roadmap for conducting behavioral intervention research in a systematic way that ensures quality and cost-efficient methods. This dynamic framework begins with a significant clinical question. This study proposes that while chronic pain is a prevalent issue in survivors of childhood cancer, no interventions to date have been empirically tested on this population. Phase I in the ORBIT Model represents the Design phase, where the goal is to design essential features of the intervention or to adapt to an existing treatment [52]. This phase has already been completed in that the intervention has been designed, refined, and tested on a different population [17]. Phase II represents the Preliminary Testing phase, where the goal is to test the ability of a fixed intervention to produce a clinically significant improvement on a behavioral risk factor [52]. While this phase has already been completed in previous studies [17], this intervention has never been tested on adolescents with a history of cancer, and thus this study aims to complete this phase. Should survivors not find the study helpful and adjustments are warranted, the trial will move back to phase I to be tailored for youths with a history of cancer. If the study finds WebMAP to be feasible and acceptable with promising preliminary efficacy, the trial will move to a phase III efficacy trial in future studies. This study will provide valuable information about the potential usefulness of WebMAP for survivors of childhood cancer with chronic pain.

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Data Availability

Data and materials will be available upon request of the corresponding author after data have been collected.

Authors' Contributions

All authors participated in research conceptualization, study design, and revising drafts of the protocol. The first author (MP) completed the literature review and wrote the first protocol draft.

Conflicts of Interest

None declared.

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Abbreviations

CALI: Child Activity Limitations Interview
CBT: cognitive behavioral therapy
ISI: Insomnia Severity Index
ORBIT: Obesity-Related Behavioral Intervention Trials
PROMIS: Patient-Reported Outcomes Measurement Information System
REDCap: Research Electronic Data Capture
TEI-SF: Treatment Evaluation Inventory—Short Form
WebMAP: web-based management of adolescent pain

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Protocol

An mHealth Intervention to Improve Guardians' Adherence to Children's Follow-Up Care for Acute Lymphoblastic Leukemia in Tanzania (GuardiansCan Project): Protocol for a Development and Feasibility Study

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Abstract

Background: Cancer is a leading cause of death during childhood and in low- and middle-income countries survival rates can be as low as 20%. A leading reason for low childhood cancer survival rates in low- and middle-income countries such as Tanzania is treatment abandonment. Contributing factors include poor communication between health care providers and children's guardians, insufficient cancer knowledge, and psychological distress.

Objective: Our aim is to respond to Tanzanian guardians' poor adherence to children's follow-up care after treatment for acute lymphoblastic leukemia with the help of mobile health (mHealth) technology. Our goal is to increase guardians' adherence to children's medications and follow-up visits and to decrease their psychological distress.

Methods: Following the Medical Research Council framework for developing and evaluating complex interventions, we will undertake the GuardiansCan project in an iterative phased approach to develop an mHealth intervention for subsequent testing. Public contribution activities will be implemented throughout via the establishment of a Guardians Advisory Board consisting of guardians of children with acute lymphoblastic leukemia. We will examine the acceptability, feasibility, and perceived impact of Guardians Advisory Board activities via an impact log and semistructured interviews (study I). In phase 1 (intervention development) we will explore guardians' needs and preferences for the provision of follow-up care reminders, information, and emotional support using focus group discussions and photovoice (study II). We will then co-design the mHealth intervention with guardians, health care professionals, and technology experts using participatory action research (study III). In phase 2 (feasibility), we will examine clinical, methodological, and procedural uncertainties associated with the intervention and study procedures to prepare for the design and conduct of a future definitive randomized controlled trial using a single-arm pre-post mixed methods feasibility study (study IV).

Results: Data collection for the GuardiansCan project is anticipated to take 3 years. We plan to commence study I by recruiting Guardians Advisory Board members in the autumn of 2023.

Conclusions: By systematically following the intervention development and feasibility phases of the Medical Research Council Framework, and working alongside an advisory board of guardians, we intend to develop an acceptable, culturally appropriate, feasible, and relevant mHealth intervention with the potential to increase guardians' adherence to children's follow-up care after

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treatment of acute lymphoblastic leukemia, leading to a positive impact on children's health and chances to survive, and reducing distress for guardians.

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KEYWORDS

childhood cancer; eHealth; feasibility; guardians; intervention development; low- and middle-income countries; Tanzania; mHealth; mobile health; public contribution; public involvement; mHealth intervention; leukemia; psychological distress

Introduction

Overview

Cancer is a leading cause of death during childhood [1,2]. In high-income countries over 80% of children are cured [3], whereas in low- and middle-income countries (LMIC) survival rates can be as low as 20% [4]. If childhood cancer treatment inequalities are not addressed, it is estimated that 11.1 million children will not survive childhood cancer between 2020 and 2050, with 9.3 million (84%) of these cases living in LMIC [5]. Avoidable deaths from childhood cancer in LMIC result from factors including lack of diagnosis, misdiagnosis or delayed diagnosis, financial barriers, lack of essential chemotherapy, drug toxicity, poor survivorship care, reliance on traditional and complementary medicine, and treatment abandonment [4-8]. Deficiencies in pediatric cancer care are particularly pronounced within sub-Saharan Africa [9].

A major reason for low survival rates in LMIC is treatment abandonment, which is defined as failure to start (refusal) or continue curative treatment for 4 or more consecutive weeks [10-12]. Commonly reported factors contributing to treatment abandonment include dissatisfaction with health care providers' communication, guardians' lack of knowledge about cancer, preferences for traditional and complementary medicine, and psychological distress alongside limited access to psychological support [13,14]. In a Kenyan study, parents of children receiving treatment for leukemia reported anxiety, shock, fatigue, and economic challenges, which were associated with heightened family tension and increased need for emotional support [15]. Our research in Tanzania has identified that guardians report poor communication between themselves and health care providers, insufficient cancer knowledge, and emotional concerns [16], with findings suggesting that guardians have unmet needs related to health provider communication, information about childhood cancer, and emotional support. Importantly, these unmet needs can have negative consequences for guardians' adherence to the child's follow-up care, for example, medication adherence and follow-up appointments, which can have an impact on the child's health and chances of survival. However, research from Malawi suggests receiving information about treatment duration, reasons for and frequency of medical procedures, and the positive outcome in many cases of common childhood cancers can reduce treatment abandonment [17].

Mobile health (mHealth) interventions may represent a solution to address guardians' unmet needs, reduce treatment abandonment, and ultimately improve childhood cancer survival rates. Specifically, mHealth interventions may provide guardians with follow-up treatment reminders, educational information about cancer and treatment, and emotional support. Across sub-Saharan Africa, national-level digital health strategies and architectures are being implemented and are endorsed by the United Nations and the World Health Organization [18]. mHealth interventions have shown promise in improving treatment adherence among patients with tuberculosis in Tanzania [19] and young people living with HIV in sub-Saharan Africa [20]. A recent systematic review of the use of 2-way SMS text message interventions to improve appointment attendance and medicine adherence in sub-Saharan Africa found improvements in medicine adherence in comparison to standard care, but not appointment attendance. However, effectiveness differed between clinical conditions [21]. While an mHealth intervention represents a promising solution to improve adherence to the child's follow-up care, more knowledge is needed regarding the relationship between different types of mHealth interventions (eg, apps or SMS text messaging) and different outcomes including appointment attendance and medicine adherence. In addition, although mHealth technology has been piloted in many sub-Saharan African countries for various clinical and public health interventions, most of these interventions have not been scaled up due to poor design, limited stakeholder involvement, and neglecting to consider the implementation context [22].

mHealth interventions could also provide emotional support to guardians. mHealth apps using cognitive behavioral therapy (CBT) principles are effective for common mental health difficulties [23], and we have successfully used internet-administered CBT to improve depression and anxiety in Swedish parents of children during [24,25] and after [26] cancer treatment. An mHealth intervention informed by CBT principles that supports guardians' unmet emotional needs may facilitate their adherence to the child's treatment and follow-up care. In addition to the uncertainties regarding which type of mHealth intervention should be used, and how to integrate CBT principles to target emotional needs, mHealth interventions should also be tailored to the target population [19]. Tailoring includes careful consideration of the population's needs and preferences, attitudes toward mHealth interventions, and perceived barriers and facilitators to intervention use. Potential barriers related to the technology, the health care system, and community factors, such as households sharing mobile phones, should also be carefully considered [27]. In addition, the acceptability and feasibility of the intervention and trial methods should be explored before undertaking a definitive randomized controlled trial (RCT) [28]. This paper describes the design of

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the GuardiansCan project in which we aim to respond to Tanzanian guardians' poor adherence to children's follow-up care after treatment for acute lymphoblastic leukemia (ALL) with the help of mHealth technology.

Overall Aim and Specific Goals

Our goal is to increase guardians' adherence to children's medications and follow-up visits and, second, to decrease their psychological distress. Our overall objectives are to (1) implement public contribution activities throughout the GuardiansCan project via the establishment of a Guardians Advisory Board (GAB) and to examine the acceptability, feasibility, and perceived impact of GAB activities (study I); (2) to explore guardians' needs and preferences concerning the provision of follow-up care reminders, information, and emotional support (study II); (3) to co-design an mHealth intervention providing guardians with follow-up care reminders, relevant information, and emotional support (study III); and (4) to examine clinical, methodological, and procedural uncertainties associated with the intervention and study procedures to prepare for the design and conduct of a future definitive RCT of the mHealth intervention (study IV).

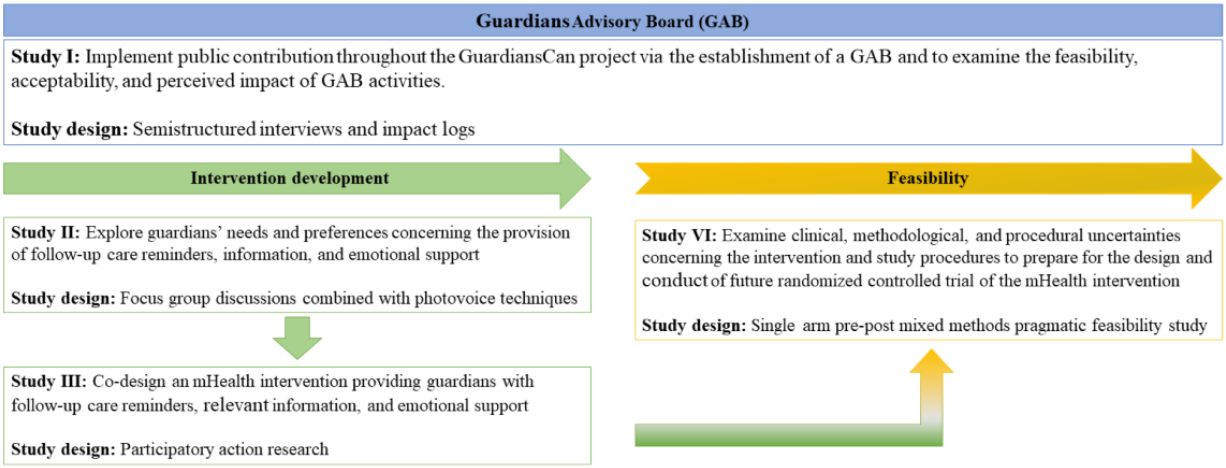
Methods

Overview

Following the revised United Kingdom Medical Research Council (MRC) framework for developing and evaluating complex interventions [29], we will undertake the GuardiansCan project in an iterative phased approach to develop an mHealth intervention for subsequent testing. The GAB will contribute to the project [30-32] and follow a study-focused framework [33] with public contribution activities planned at the managing and undertaking, analysis and interpretation, and dissemination phases of the project. As GAB members will be involved in designing the detailed research protocols for studies II-IV, we provide here an overview of the methods and study procedures as planned for now, to be further informed via GAB contribution.

The GuardiansCan project is divided into two main phases in accordance with the MRC Framework: (1) intervention development and (2) feasibility, with data anticipated to be collected over a 3-year period. We will follow published guidance to conduct the intervention development phase, paying attention to involving stakeholders, reviewing published evidence, developing a program theory, and considering future real-world implementation [29,34], and the feasibility phase regarding the design and reporting of feasibility trials [35] and supplementary guidelines for nonrandomized feasibility studies [36]. An overview of the GuardiansCan project can be seen in Figure 1.

Figure 1. Overview of the GuardiansCan project. mHealth: mobile health.



Setting

The GuardiansCan project is an international collaboration between Tanzania and Sweden. Uppsala University (Sweden) is the responsible academic institution with research primarily coordinated from Muhimbili National Hospital (MNH), a National Referral and University Teaching Hospital located in Dar es Salaam, Tanzania. MNH provides basic and advanced medical and surgical treatments, and is a strategic center for the implementation of eHealth aligning with the Tanzania National Road map of eHealth Investment 2017-2023 [37]. MNH is the main hospital for the treatment of pediatric cancer in Tanzania and the center for the pediatric oncology network that established a pediatric oncology unit at MNH in 2013 with collaborative support from the government, nongovernmental organizations, and other donors. The pediatric oncology unit includes "Upendo children's cancer ward" and the "Ujasiri house," a hostel for families. Around 100 children are diagnosed annually with ALL at the unit.

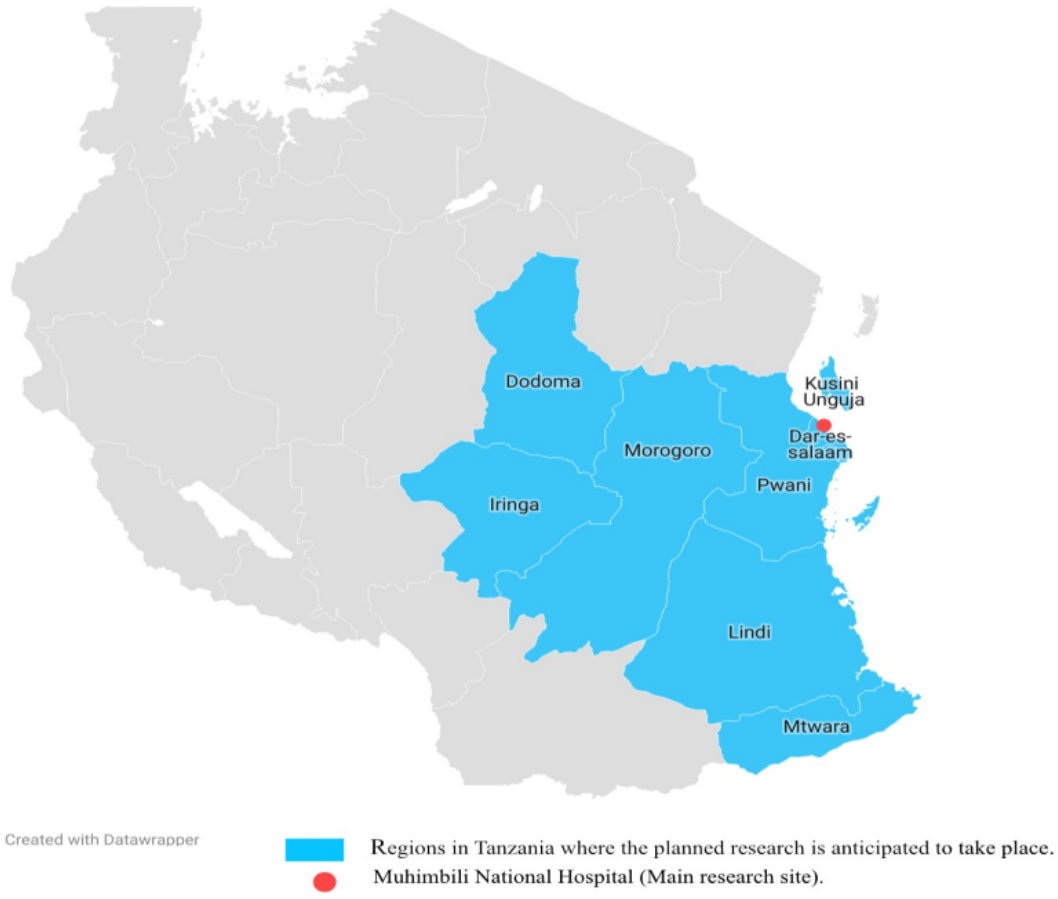
Regarding general access to mobile phones, Tanzania's mobile subscription rate per 100 population is 85%, with Android (Google) being the dominant operating system [38,39]. A study among guardians of children with cancer showed that 85% had mobile phones; however, out of these, only 9% reported having smartphones [40].

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Recruitment

For each planned study, we intend to recruit guardians from 7 regions in Tanzania including Dar es Salaam, Dodoma, Iringa, Lindi, Morogoro, Mtwara, and Pwani, and the island of Zanzibar (a semiautonomous state and part of the United Republic of Tanzania). The regions represent urban and rural areas in Tanzania and have been selected to facilitate including guardians with different cultural backgrounds and accessibility to Dar es Salaam (see Figure 2). Recruitment will be conducted in collaboration with pediatric oncologists or pediatric oncology nurses at the pediatric oncology unit at MNH. Oncologists or nurses will identify potential participants for each study via MNH records. An oncologist or a nurse will call identified guardians to explore inclusion criteria and their initial interest in each study. Subsequently, a member of the research team will call interested guardians to provide more study information, undertake screening procedures, and obtain informed consent. The detailed recruitment strategy for study I will be published elsewhere. An overview of planned recruitment procedures is presented for studies II-IV as planned for now; however, recruitment strategies are subject to change via collaboration with the GAB.

Figure 2. Map of regions in Tanzania where the planned research is anticipated to take place.



Public Contribution in Research

Guardians Advisory Board: Study I

Aims

We aim to involve guardians of children treated for ALL in the managing and undertaking, analysis and interpretation, and dissemination phases of the GuardiansCan project, and examine the acceptability, feasibility, and perceived impact of GAB members' contribution to the GuardiansCan project from the perspective of GAB members and public contribution coordinators.

Methods

The full public contribution plan for the GuardiansCan project will be published elsewhere. We aim to recruit 6 to 8 guardians of children treated for ALL at MNH, representing different genders and coming from rural and urban communities, into the GAB. Workshops will be held with GAB members, facilitated by public contribution coordinators who are Kiswahili speakers with GAB members contributing to the undertaking and managing, analysis and interpretation, and dissemination phases of the GuardiansCan project. Examples of public contribution activities include, but are not limited to, designing detailed study protocols for studies II-IV, assisting in writing participant information sheets and consent forms, data collection (eg, cofacilitating or observing focus groups), data interpretation and sense-making of findings, developing a dissemination plan, and helping to distribute findings within community settings.

Data Collection

Public contribution activities will be recorded in an impact log [41] immediately after each GAB workshop. Workshop discussions will be held in Kiswahili and will be audio-recorded; however, audio-recordings will not be transcribed and only made to ensure impact log accuracy. Semistructured interviews

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will also be conducted to explore the acceptability, feasibility, and perceived impact of GAB activities from the perspective of GAB members and public contribution coordinators 6 months after GAB has been formed and at the end of studies II-IV. Semistructured interviews will be conducted in Kiswahili and audio-recorded.

Data Analysis

Researchers in our group who are not involved in public contribution activities and conversant with Kiswahili will read impact logs, with impacts (eg, anticipated and unanticipated changes to the research process and potential benefits and harms) extracted and summarized. Summaries of impacts will be presented for discussion with GAB members and public contribution coordinators to aid sense-making and interpretation of results. Two members of the research team who are not involved in GAB activities will analyze semistructured interviews using manifest content analysis [42]. Descriptions of subcategories and categories will be presented for discussion with GAB members and public contribution coordinators to aid in sense-making and interpretation of results.

Phase 1: Intervention Development

Intervention Program Theory

Following the MRC Framework [29] throughout the intervention development phase we will use findings iteratively to develop and refine an intervention program theory [34]. The program theory will describe: (1) how we expect the mHealth intervention to increase guardians' adherence to children's medications and follow-up visits; (2) pathways predicted to drive the change; and (3) under what conditions the change is expected to occur [43]. The program theory will be presented diagrammatically, in the form of a logic model. Cumulative information from the intervention development phase will be used to identify intervention program inputs, activities, outputs, and the context in which they operate to deliver short- and long-term outcomes of interest [44]. We will continue to iteratively build the program theory and logic model throughout intervention development and later test and refine the developed program theory during the feasibility phase [34].

Focus Group Discussion and Photovoice: Study II

Aims

We aim to explore (1) perceived needs and preferences concerning the receipt of follow-up care reminders, information, and emotional support; (2) attitudes toward mHealth interventions; and (3) perceived barriers and facilitators of mHealth intervention use.

Study Design

An explorative qualitative design with data collected via focus group discussions combined with photovoice techniques will be used [45-47]. Photovoice is a qualitative research method whereby participants are engaged actively in the research process, using photographs or pictures to facilitate discussion and generate knowledge around a particular research topic, with an overall aim to reach policy makers to generate societal change concerning an important community issue [47,48].

Inclusion Criteria

Participants will be guardians of the children treated for ALL at MNH and health care professionals (eg, nurse practitioners, pediatric oncologists, pediatric oncology nurses, pediatricians, pharmacists, and social workers) working at the pediatric oncology unit at MNH. We will include guardians who meet the following inclusion criteria: (1) are at least 18 years of age; (2) whose child has been discharged within the last 3-36 months from MNH after receiving main treatment for ALL (ie, completion of the induction phase of treatment); (3) are able to speak Kiswahili; (4) have completed primary school education (International Standard Classification of Education [ISCED] level 1 to postsecondary nontertiary education ISCED level 4), but not tertiary education; (5) can provide written informed consent via ink signature; and (6) are able to travel to attend focus group discussions.

Recruitment

A member of the research team will speak to interested health care professionals working at the pediatric oncology unit at MNH face-to-face or over the telephone to provide more study information. Those who wish to participate will be provided with a study information sheet and consent form. Written informed consent or alternatively verbal recorded consent over the telephone or via a secure videoconferencing system will be obtained. After provision of informed consent, background and sociodemographic characteristics will be collected, that is, age, gender, profession, length of time in profession, professional qualifications, and length of time working with pediatric oncology.

An oncologist or a nurse will call identified guardians to explore inclusion criteria and their initial interest. A member of the research team will call guardians who fulfill the inclusion criteria and are interested in participation to provide more detailed verbal study information. Guardians interested in participating will be invited to the first focus group discussion. We will provide guardians with (1) a study information sheet and (2) consent form and written informed consent (via ink signature) will be obtained prior to data collection.

Data Collection

A series of 2 focus group discussions with health care professionals (n≈6-8) at MNH will be held in Kiswahili. We will hold a series of 6 focus group discussions combined with photovoice with guardians (n≈3-4 females and n≈3-4 males). We plan to conduct focus groups in Dar es Salaam at a venue where participants can share their thoughts and feelings in privacy. It is anticipated that guardians will meet approximately once every 2 weeks for a 12-week period with each focus group lasting approximately 3 hours. However, the exact venue, frequency, and duration of focus group discussions will be planned in collaboration with the GAB.

Focus groups with guardians will be combined with photovoice techniques [45-47]. We will predevelop topics for each focus group in collaboration with GAB members and they will be conducted in Kiswahili. During the first focus group with guardians, we will present study aims and participants will be trained in photovoice procedures, how to use a camera, and in

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ethical considerations [49]. Next, we will introduce the topic for the subsequent focus group discussion and participants will take 3 photographs based on the topic prior to the subsequent planned focus group. During each of the focus group discussions, photographs will be used to elicit discussions around each preplanned topic. At the end of each focus group, the topic for the subsequent focus group will be introduced.

Focus group discussions will be moderated and notes taken with the assistance of an observer, a GAB member who will help facilitate discussions. We will audio-record focus group discussions and they will be transcribed verbatim by a person conversant in Kiswahili. An external translation company will translate transcripts to English and back-translate it to Kiswahili to facilitate analysis by the whole research team. Transcripts will be anonymized.

Data Analysis

Data will be analyzed using manifest content analysis [42]. Two members of the research team will individually code transcripts and perform categorization of codes into categories and subcategories. Subsequently, categories and subcategories will be discussed in the wider research team to facilitate interpretation. Descriptions of subcategories and categories will be presented for discussion with GAB members to aid sense-making and interpretation of results. Visual data from photographs will be used as supplementary data sources. Trustworthiness of the analysis will be established in accordance with a trustworthiness checklist for content analysis [50] and by adopting procedures including an audit trail, case analysis for deviant cases, and peer examination.

Participatory Action Research: Study III

Aims

We aim to identify: (1) intervention content informed by findings from study II, behavioral change techniques [51-53] and evidence-based CBT principles [23,54], and may include audio, visual, and written elements; (2) acceptable methods of intervention delivery within the health care context (eg, 1-way SMS text messaging, automatic voice message reminders, 2-way SMS text messaging, or via artificial intelligence methods, or a basic or smartphone app) which are suitable for urban and rural environments; (3) intervention delivery preferences, for example, technical elements [55,56] such as reminders and personalization and whether a professional group is needed to support intervention delivery; and (4) potential technical support and training needs of guardians and health care professionals.

Study Design

A qualitative design based on principles from participatory action research (PAR) will be used [57,58], placing key stakeholders at the center of the research process.

Inclusion Criteria

Participants include guardians of the children treated for ALL at MNH, meeting the same inclusion criteria as study II, and health care professionals working in pediatric oncology care, and technology experts, including mobile operator technicians.

Recruitment

We anticipate identifying health care professionals and technology experts via in-person networks and guardians via MNH patient records, following the same recruitment procedures used in study II.

Data Collection

Approximately 8 face-to-face PAR iterative meetings will be held in Kiswahili at a venue where participants can share their thoughts and feelings in privacy. Each meeting is anticipated to last approximately 3 hours, including a refreshment break. Before the first meeting, background and sociodemographic characteristics from participants will be collected. Some meetings will only include guardians or health care professionals and technology experts, and some meetings will be combined.

Each meeting will have a predefined theme to focus the discussions and we will predevelop topics in collaboration with GAB members. PAR meetings will be conducted in iterative cycles and each meeting will involve cycles of collaboration, discussion, reflection, and evaluation. At the beginning of each meeting, we will present the agenda and participants will be encouraged to add items to the agenda. Action plans related to the topic will be developed collaboratively and at the end of each meeting, participants will individually reflect on the group discussions by answering open-ended questions and will be encouraged to provide suggestions for the upcoming meeting [58]. An initial intervention prototype will be drafted after 6 meetings. We will discuss the initial prototype in combined meetings and come up with the proposed intervention to be tested in the feasibility phase.

PAR meetings will be facilitated and notes taken with the assistance of an observer, who will be a GAB member. Meetings will be audio-recorded and will be transcribed verbatim by a person native in Kiswahili. An external translation company will translate transcripts to English and back-translate to Kiswahili to facilitate analysis by the whole research group. Transcripts will be anonymized. Participants' input at meetings and on action plans will be discussed by meeting facilitators, the research team, and the GAB who jointly plan further actions.

Data Analysis

Data will be analyzed (meeting notes, action plans, and transcripts) using manifest content analysis [42] in a "recursive" process to reach a collaborative understanding of the data. Two members of the research team including a Tanzanian national will individually code transcripts and perform the categorization of codes into categories and subcategories. Subsequently, categories and subcategories will be discussed in the wider research team to facilitate interpretation. The analysis will be presented for discussion with GAB members to aid sense-making and interpretation of results. Trustworthiness of the analysis will be established in accordance with a trustworthiness checklist for content analysis [50] and by adopting procedures including an audit trail, case analysis for deviant cases, and peer examination. We will develop a full prototype of the mHealth intervention describing the type of intervention, information to be provided, and mode and frequency of delivery for feasibility testing.

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Phase 2: Feasibility

Single-Arm Pre-Post Mixed Methods Pragmatic Feasibility Study: Study IV

Aims

We aim to determine (1) intervention acceptability from the perspectives of guardians and health care professionals; (2) feasibility of the intervention; and (3) feasibility and acceptability of study methods and procedures.

Study Design

We will undertake a single-arm pre-post mixed methods pragmatic feasibility study [35,36,59].

Inclusion Criteria

Participants will be guardians (1 per child) whose child has been discharged from MNH after receiving main treatment for ALL (ie, completion of the induction phase of treatment) with the inclusion or exclusion criteria informed by studies II and III findings and GAB member involvement.

Recruitment

Exact recruitment procedures will be informed by GAB member involvement. It is anticipated the recruitment period will take 6 months. To examine recruitment feasibility, the study invitation materials will include the possibility for guardians who decline participation to provide reasons for nonparticipation and consent to take part in an interview to explore potential decisions not to participate. Written informed consent (via ink signature) will be obtained prior to data collection and being provided with access to the intervention. In addition to the intervention, guardians will receive care from health care professionals as per normal clinical practice.

We anticipate recruiting a sample of between 20 and 40 participants, following recommendations for feasibility studies [60] and, as in other single-arm pragmatic feasibility studies [61], to provide information on feasibility outcomes and inform the sample size for a future definitive RCT [62].

Data Collection

We plan to collect data at screen, baseline, and posttreatment follow-up (12 months post intervention). In line with our feasibility objectives [35], we will collect the following outcomes: (1) intervention acceptability from the perspectives of guardians and health care professionals (eg, intervention acceptability, intervention usability, and indications for usage such as number of opened messages); (2) feasibility of delivering the intervention (eg, number of successfully delivered messages); and (3) feasibility and acceptability of study methods and procedures (eg, number of guardians eligible and enrolled, data collection completeness, and feasibility of data collection procedures). Progression criteria and stopping rules will be defined [63] to inform progression to an RCT. The exact progression criterion and stopping rules will be developed in accordance with our feasibility objectives, existing relevant literature, and input from a broad range of relevant stakeholders, including GAB members and researchers external to the research team who have relevant expertise in conducting similar research [64].

To examine the feasibility of data collection, the following clinical data will be collected: (1) adherence to child's medications as per discharge instructions (eg, amount of medication taken and successful prescription refill); (2) attendance of follow-up visits at MNH or another hospital as per discharge instructions; (3) number and types of complications after discharge, number of readmissions after discharge, and progress of children's cancer; and (4) psychological distress as measured with the Kiswahili adaptation of the Kessler Psychological Distress scale [65], cancer knowledge, and quality of life [66]. We will examine the feasibility of collecting economic data to inform a future cost-effectiveness evaluation, for example, provider costs pertaining to direct financial costs of delivering and maintaining the intervention and personnel costs [67]. Semistructured interviews at posttreatment will be conducted in Kiswahili to explore intervention acceptability, relevance, impact (eg, on medication adherence, attendance at outpatient follow-up visits, guardians' psychological distress, cancer knowledge, and child's well-being), and barriers and facilitators to intervention use. All guardians included in the study will be invited to participate in the interviews until data saturation is met. We will also interview health care professionals involved in the intervention to explore experiences of the intervention and perceived impact on guardians.

Data Analysis

Participant flow will be illustrated in accordance with the CONSORT (Consolidated Standards of Reporting Trials) diagram for feasibility and pilot studies [35]. We will calculate the percentages of participants (1) consenting, (2) screened, (3) meeting eligibility criteria, and (4) enrolled calculated with 95% CIs. Reasons for ineligibility, ambiguities regarding eligibility criteria, and reasons for nonparticipation at each stage will be reported. We will calculate follow-up rates, and the numbers of missing items relating to outcome measures are calculated with 95% CIs. We will report descriptive statistics (means and SDs or proportions with 95% CIs) for each clinical outcome at eligibility screen, baseline, and posttreatment (eg, adherence to child's medications, attendance of follow-up visits, number and types of complications and readmissions, psychological distress). We will also report frequencies of intervention activity relating to intervention adherence and use. We will analyze semistructured interviews using manifest content analysis [42] and establish the trustworthiness of the analysis in accordance with a trustworthiness checklist for content analysis [50] and by adopting procedures including an audit trail, case analysis for deviant cases, and peer examination. Quantitative and qualitative data will be analyzed separately, with findings integrated following a triangulation protocol at the participant level to explore potential relationships between mHealth intervention implementation, intervention acceptability and perceived impact, and changes in adherence to medication and follow-up visits and psychological distress. Joint displays will be used to compare quantitative and qualitative findings [68,69]. We will present the analysis for discussion with GAB members to aid sense-making and interpretation of results.

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Reporting

We will report: (1) GAB activities and perceived impact of activities following the GRIPP2 (Guidance for Reporting Involvement of Patients and the Public) checklist [70]; (2) qualitative results in accordance with the SRQR (Standards for Reporting Qualitative Research) checklist [71]; (3) intervention development in line with GUIDED (Guidance for Reporting Intervention Development Studies in Health Research) [44]; (4) intervention content following the TIDieR (Template for Intervention Description and Replication) checklist [72] and the mERA (mHealth Evidence Reporting and Assessment) checklist [73]; and (5) feasibility study results in accordance with the CONSORT extension for reporting randomized pilot and feasibility [35].

Data Management

We will process data in accordance with the Swedish Patient Data Act (2008:355), the General Data Protection Regulation (EU 2016/679), and the Tanzania National Institute of Medical Research policy [74]. Tanzanian and Swedish members of the research group will have access to collected data and will be involved in data management and analysis. We will develop a detailed data management plan for each study that will be made available on DMPonline. In summary, research data will be pseudonymized and a list linking ID number and identifiable personal information (ie, participant name and contact details) will be kept separately from research data. Data will be stored on password-protected USB sticks kept in a locked fireproof cabinet at MNH and stored in ALLVIS, a secure web-based data portal used by Uppsala University for the confidential storage of research data, accessible by both Tanzanian and Swedish members of the research group. A Data Transfer Agreement will be completed between Uppsala University and MNH.

Ethical Considerations

The GuardiansCan project will be conducted in accordance with the Declaration of Helsinki [75]. Informed consent (via ink signature) will be obtained from all GAB members and study participants. We will obtain ethics approval for all studies from the Swedish Ethical Review Authority, MNH Ethics Review Board, and the Tanzania National Research Ethics Committee; and research permits for foreign researchers will be sought from the Tanzania Commission for Science and Technology for study IV. Given the iterative nature of the planned research and involvement of the GAB, ethics approval will be obtained for all 4 studies in a stepwise manner, with ethics approvals initially obtained for study I.

Members of the GAB (study I) will receive reimbursement for their contribution, which includes travel and living cost and an allowance equivalent to the government daily subsistence allowance for ISCED level 4 personnel: 75,000 Tanzanian Shillings (≈US $31). Guardians participating in study II will receive mobile phones to facilitate the use of photovoice techniques. Guardians participating in studies II-IV will also receive reimbursement for any travel and living costs incurred.

Results

Data collection for the GuardiansCan project is anticipated to take 3 years. We plan to commence study I by recruiting Guardians Advisory Board members in the autumn of 2023.

Discussion

Principal Findings

The development of interventions to address childhood cancer treatment inequalities and avoidable deaths from childhood cancer in LMIC is a high public health priority. To the best of our knowledge, this is the first study to seek to increase guardians' adherence to children's medications and follow-up visits after treatment for ALL, decrease guardians' psychological distress via the use of mHealth, and represents an opportunity to increase childhood cancer survival rates in LMIC such as Tanzania.

Despite the piloting of mHealth interventions across sub-Saharan African countries, mHealth interventions are seldom scaled-up due to factors such as lack of stakeholder involvement and consideration of the implementation context [22]. To overcome these limitations, robust methods will be adopted systematically following the intervention development and feasibility phases of the revised MRC complex interventions research framework [29], developing program theory, and involving wider stakeholder groups throughout the intervention development phases. In addition, we will implement public contribution throughout the GuardiansCan project by working alongside an advisory board of guardians with lived experience to enhance the quality and relevance of the GuardiansCan project, ensuring local applicability and acceptance, and a feasible and sustainable solution to a significant health care challenge. Consequently, important data will be generated to facilitate the development of an acceptable, culturally appropriate, feasible, and relevant intervention, as well as maximize the success of a future definitive RCT. Significant stakeholder involvement and consideration of context and future real-world implementation will enhance the future implementation potential of the intervention should it later be demonstrated to be clinically and cost-effective. In addition, we will use our developed program theory to inform future process evaluations of the intervention.

Limitations

We did not involve guardians as public contributors when developing the overall research plan, limiting our ability to plan study procedures in advance that maximize acceptability and feasibility for guardians. However, we plan to overcome this limitation by embedding public contribution via the GAB throughout the GuardiansCan project, including activities related to the managing and undertaking, analysis and interpretation, and dissemination phases of the project. As planned currently, we will only recruit guardians from 7 geographical regions of Tanzania. Therefore, results may not be generalizable to guardians located in other regions of Tanzania, including guardians located at very long distances from the pediatric oncology unit at MNH. We will not include guardians who have not completed at least primary school; therefore, the proposed

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mHealth intervention may not be suitable for guardians who have not attained primary education.

Conclusions

The proposed mHealth intervention and research have significant potential to promote equitable and sustainable care for families struck by ALL in Tanzania, adding to the capacity building of health care services in Tanzania. Our research may have a positive impact on children's health and chances to survive, and guardians' ability to provide for the family as a result of reduced costs for treatments, transportation, and long periods of hospitalization. The mHealth intervention also has significant potential to be a clinical and cost-effective solution, optimally prepared alongside key stakeholders for the implementation and a real-world clinical impact. The project, and the novel and robust methodological approach being taken, will also add to the existing evidence base concerning how mHealth interventions should be developed and tested, which may be of benefit to patients and informal caregivers for a variety of different conditions and unmet needs.

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Authors' Contributions

FSC contributed to the writing of the original draft and visualization. JW contributed to the methodology, writing of the original draft, visualization, supervision, and project administration. GM contributed to the writing of the original draft and visualization. DAR contributed to the methodology, review and editing, and supervision. VS contributed to review and editing. LvE contributed to the conceptualization, methodology, review and editing, supervision, project administration, and funding acquisition.

Conflicts of Interest

None declared.

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Abbreviations

ALL: acute lymphoblastic leukemia
CBT: cognitive behavioral therapy
CONSORT: Consolidated Standards of Reporting Trials
GAB: Guardian Advisory Board
GRIPP2: Guidance for Reporting Involvement of Patients and the Public
GUIDED: Guidance for Reporting Intervention Development Studies in Health Research
ISCED: International Standard Classification of Education
LMIC: low- and middle-income countries
mERA: mHealth Evidence Reporting and Assessment
mHealth: mobile health
MNH: Muhimbili National Hospital
MRC: Medical Research Council
PAR: participatory action research
RCT: randomized controlled trial
SRQR: Standards for Reporting Qualitative Research
TIDieR: Template for Intervention Description and Replication

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Protocol

Implementation of a Surveillance System for Severe Acute Respiratory Infections at a Tertiary Care Hospital in Austria: Protocol for a Retrospective Longitudinal Feasibility Study

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Abstract

Background: The risk of a large number of severe acute respiratory infection (SARI) cases emerging is a global concern. SARI can overwhelm the health care capacity and cause several deaths. Therefore, the Austrian Agency for Health and Food Safety will explore the feasibility of implementing an automatic electronically based SARI surveillance system at a tertiary care hospital in Austria as part of the hospital network, initiated by the European Centre for Disease Prevention and Control.

Objective: We aim to investigate the availability of routinely collected health record data pertaining to respiratory infections and the optimal approach to use such available data for systematic surveillance of SARI in a real-world setting, describe the characteristics of patients with SARI before and after the beginning of the COVID-19 pandemic, and investigate the feasibility of identifying the risk factors for a severe outcome (intensive care unit admission or death) in patients with SARI.

Methods: We will test the feasibility of a surveillance system, as part of a large European network, at a tertiary care hospital in the province of Lower Austria (called Regional Hospital Wiener Neustadt). It will be a cross-sectional study for the inventory of the electronic data records and implementation of automatic data retrieval for the period of January 2019 through the end of December 2022. The analysis will include an exploration of the database structure, descriptive analysis of the general characteristics of the patients with SARI, estimation of the SARI incidence rate, and assessment of the risk factors and different levels of severity of patients with SARI using logistic regression analysis.

Results: This will be the first study to assess the feasibility of SARI surveillance at a large 800-bed tertiary care hospital in Austria. It will provide a general overview of the potential for establishing a hospital-based surveillance system for SARI. In addition, if successful, the electronic surveillance will be able to improve the response to early warning signs of new SARI, which will better inform policy makers in strengthening the surveillance system.

Conclusions: The findings will support the expansion of the SARI hospital-based surveillance system to other hospitals in Austria. This network will be of use to Austria in preparing for future pandemics.

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KEYWORDS

severe acute respiratory infection; SARI; Austria; influenza; European Union; COVID-19; respiratory; data retrieval; information retrieval; electronic health record; EHR; health records; health record; surveillance; risk; database structure; incidence; data collection

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Introduction

Globally, there has been an increase in acute respiratory infections, which are considered among the major causes of morbidity and mortality across all age groups [1]. Annually, over 4 million people die from acute respiratory infections, and the majority are due to lower respiratory tract infections [1]. Mortality is high in infants, children, and older people, especially in low- and middle-income countries [2]. Therefore, public health surveillance is an essential tool for monitoring population-level changes in the incidence and burden of respiratory infectious diseases, which is essential for their prevention and targeted control [3].

The COVID-19 pandemic has shown the importance of routine syndromic surveillance of respiratory infections, especially new cases of severe acute respiratory infection (SARI) [4,5]. Currently, there is a need to invest more into systematic data collection on SARI, including the identification of risk factors associated with the SARI cases, which is going to guide policy makers in tailoring appropriate interventions to reduce the SARI public health burden.

Currently, a total of 27 countries in the European Union and 3 countries in the European Economic Area are part of a SARI surveillance network, in collaboration with the European Centre for Disease Prevention and Control (ECDC) and the World Health Organization [6]. The countries using the SARI surveillance network report to the ECDC about the population under their surveillance. This includes persons of all ages living in the catchment areas of the hospitals participating in the national surveillance systems (also, the target population tends to be representative of the general population) [6].

There is concern about the acute emergence of a large number of severe infectious cases, which can overwhelm the health care capacity and cause several deaths. Therefore, in 2022, the ECDC took the initiative to establish a hospital network sustainable infrastructure to conduct enhanced surveillance of SARI, including the performance of studies on the impact and burden of diseases. Thus, it is becoming important and crucial to have at the EU level a hospital-based surveillance system for the monitoring of incidence trends and an early detection system for epidemics, including the identification of the risk groups for severe diseases to measure the impact of these diseases [7].

Austria is participating in this network and is initiating such SARI hospital-based surveillance for the first time. In this feasibility study, we aim to investigate the availability of routinely collected inpatient health record data pertaining to respiratory infections and the optimal approach to use such data for a systematic automated surveillance of SARI. Furthermore, we aim to describe the characteristics of patients with SARI before and after the beginning of the COVID-19 pandemic. Additionally, we investigate the feasibility of identifying risk factors for a severe outcome (intensive care unit [ICU] admission or death) in patients with SARI at a tertiary care hospital in Austria.

Methods

Study Design and Setting

This will be an investigative feasibility and cross-sectional study at an 800-bed tertiary care hospital (Regional Hospital Wiener Neustadt) in the federal state of Lower Austria. The analysis will include the inventory of electronic data records and the implementation of automatic data retrieval between January 2019 and December 2022.

For inclusion, we will include all cases that meet the SARI case definition based on the ECDC surveillance definition; we will also include all patients regardless of their address of residence (ie, either inside or outside Austria). Patients not meeting the SARI case definition will be excluded.

Setting

The Federal State of Lower Austria

The Regional Hospital Wiener Neustadt is located in the federal state of Lower Austria, which is the largest federal state in Austria (area size of 19,174 km^2 and a population of over 1.6 million) [8]. The health care system in Austria is financed through health insurance subsidies provided to hospitals at the federal, regional, and municipal levels [8]. Lower Austria is the only Austrian federal state where all hospitals are legal entities of one single health care provider, the Niederösterreichische Landesgesundheitsagentur (NÖ-LGA), which offers clinical health care services, from basic to specialist, including the handling of the operative management of the hospitals.

Lower Austria is located in the northeast of Austria, where its borders are adjacent to two neighboring countries (Czech Republic and Slovakia). Since 2008, the federal state of Lower Austria has initiated six cross-border health care projects. Additionally, in 2017, The Lower Austrian Health and Social Fund launched a so-called “Initiative Health Across,” which combines all cross-border health care activities in Lower Austria. The aim of this project is to facilitate optimum and equitable usability of the health care services for the population living in the border areas through close cooperation of the health service providers in a simple and uncomplicated way [8].

Hospital

The Regional Hospital Wiener Neustadt is an 804-bed tertiary care facility located 60 km south of the Austrian capital Vienna. The hospital provides all major fields of medicine and surgery to large parts of eastern Austria, including the border regions near Slovakia and Hungary, and in Styria to the south. The Regional Hospital Wiener Neustadt is an acute and specialist tertiary referral center with 21 anesthesiology ICU beds, 14 medical intermediate care unit beds, and 21 stroke unit beds, which cares for approximately 35,000 inpatients and 390,000 outpatients, and performs more than 21,000 surgical procedures annually. The medical and nursing staff of the hospital cares for both pediatric and adult patients with respiratory tract infection.

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Austrian Agency for Health and Food Safety

The Austrian Agency for Health and Food Safety (AGES) is a government-owned agency attached to the Austrian Federal Ministry of Social Affairs, Health, Care and Consumer Protection and the Austrian Federal Ministry of Agriculture, Regions and Tourism. AGES executes several federal tasks, including public health issues and research in the areas of infectious diseases (in addition to other areas, eg, agriculture, food and feed safety, veterinary medicine, radiation protection, medical devices, and pharmaceuticals). In Austria, certain infectious diseases fall under the category of mandatory reporting. Therefore, these diseases are registered in a national registry called the Epidemiological Reporting System (EMS), which is used by laboratories located at the hospitals. The EMS has a central national registry, which is hosted at the Austrian Federal Ministry for Social Affairs, Health, Care and Consumer Protection and maintained under the Institute of Surveillance and Infectious Diseases Epidemiology at AGES [9].

Data Sources and Variables: Hospital Data Management System

We will be using the data from the EMS together with medical data stored in the local hospital information system. We will include the following information from the clinical records about the patients: the *International Statistical Classification of Diseases, Tenth Revision* (*ICD-10*) code; district of residency; gender (man/woman); date of birth; SARI date onset; bronchoalveolar lavage; tissue from biopsy or autopsy, other, or unknown/not specified; clinical symptoms; existing underlying conditions (yes/no); asthma (yes/no); diabetes (yes/no); cancer (yes/no); immunocompromised (yes/no); heart (yes/no); kidney (yes/no); lung (yes/no); liver (yes/no); neurological (yes/no); obesity (no, BMI 30-40, BMI>40, clinically obese); pregnancy (yes/no); pregnancy trimester (first trimester, second trimester, third trimester); vaccination status related to SARI organisms (yes/no); antiviral prophylaxis (yes/no); antiviral treatment (yes/no); respiratory support (no, oxygen, ventilation, extracorporeal membrane oxygenation [ECMO]); pneumonia diagnosis (no; yes, clinical/abnormal chest x-ray or raised C-reactive protein level), tuberculosis (no history of tuberculosis, history of tuberculosis, positive test during hospital visit); influenza test (not performed, polymerase chain reaction, culture, immunofluorescent assay, other—not specified—test); test result (negative/positive); influenza type (A/B); influenza A subtype (A[H1N1]pdm09, A[H3N2]); ICU admission; outcome (discharged alive/death); and cause of death (not influenza, influenza as a primary cause, influenza as a secondary cause). Only cases with available data will be included in the final analysis, and we will report the proportion of variables with missing data.

Ethical Considerations

Ethical clearance will be obtained from the Ethics Committee of Lower Austria. A waiver will be requested pertaining to informed consent for this retrospective study. All data will be anonymized to ensure the privacy and confidentiality of patients' personal information, with each participant assigned a unique identifier.

No compensation is given to the participants.

Statistical Analysis

The statistical analysis will be conducted, pending the feasibility of the data quality, through the following four steps. In step 1, we will assess the existing database structure, including the exploration of the optimal methods for data retrieval. In step 2, we will conduct a descriptive analysis of the general characteristics of the patients with SARI. The percentage will be calculated by using the total number of patients identified with an underlying condition divided by the total number of patients included in the data set. In step 3, we will calculate the estimation of the SARI incidence rate by using the available data. In step 4, we will then assess the association between the risk factors and different levels of severity of patients with SARI (only cases with available data will be included in the final analysis).

The outcome will be defined as follows: patients with SARI that were discharged alive and not admitted to the ICU, patients with SARI that were discharged alive post admission to the ICU, patients with SARI that died, and patients with SARI with any severe outcome (eg, intensive care, respiratory support, ECMO). We will conduct a logistic regression analysis (backward method) to identify the risk factors associated with a severe outcome. All variables showing an association with a severe outcome at a statistical significance level of $P<.15$ will be included in the multivariable logistic regression analysis. The final variables with a statistical significance of $P<.05$ will be defined as the significant variables. R software (version 4.2.1; R Foundation for Statistical Computing) will be used for the statistical analysis [10].

Results

The main purpose and objective of this study will be to assess the feasibility of the SARI surveillance system at one of the largest tertiary care hospitals in Austria. The SARI case definition will be defined based on the ECDC SARI protocol. The sources of the SARI surveillance data will include the following: new SARI cases during the calendar week, new SARI cases in which specimens were collected during the reported week, the total number of new hospital admissions to wards under the SARI case definition, the list of *ICD-10* that were used with the number of cases per *ICD-10*, and other specimen and epidemiological data.

Discussion

As part of a first-time established European SARI hospital-based surveillance network, we will evaluate the feasibility at one of the largest tertiary care hospitals in Austria. We will explore the existing tools to gather data and evaluate the data used in the surveillance reporting and monitoring of SARI, including COVID-19 cases and influenza A. The importance of routine syndromic surveillance of respiratory infections, especially new cases of SARI, became of high importance due to the lessons learned during the COVID-19 pandemic [4,5]. We have conducted a review of the literature and identified that there are no universally agreed standards on the topic of SARI

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surveillance (El-Khatib Z, unpublished data, June 1, 2023). Therefore, this study and the newly established European network will be useful for the improvement of the preparedness for upcoming pandemics, so we can recommend directions for the future evaluation of SARI surveillance systems.

As shown by the COVID-19 pandemic, early warning and access to relevant data is imperative to act appropriately to ensure the safety of the public from infectious hazards. This study will foster the alertness of public health agencies regarding future respiratory health threats. Therefore, we will be able to improve the response to early warning signs of new SARI signs and eventually better inform policy makers on strengthening the surveillance system. Finally, we should share a potential limitation of this study. The findings of this hospital may lack representativeness at the national level. We may identify additional limitations, pending the data quality, but we could not comment on it at this stage, as the data collection has not started.

The findings of this study will support expansion to other hospitals in Austria and including them in the SARI hospital-based surveillance system. Eventually, such a network will be of use to Austria in preparing for future pandemics.

Acknowledgments

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We would like to thank all staff of the hospital and the Austrian Agency for Health and Food Safety that are providing support for this study.

Data Availability

Data sharing is not applicable to this paper, as no data sets were generated or analyzed during this study.

Authors' Contributions

All authors conceptualized the study. ZEK and OA wrote and prepared the original draft. All authors reviewed and edited the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

AGES: Austrian Agency for Health and Food Safety
ECDC: European Centre for Disease Prevention and Control
ECMO: extracorporeal membrane oxygenation
EMS: Epidemiological Reporting System
ICD-10: *International Statistical Classification of Diseases, Tenth Revision*
ICU: intensive care unit
NÖ-LGA: Niederösterreichische Landesgesundheitsagentur
SARI: severe acute respiratory infection

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Protocol

Stimulating the Uptake of Preconception Care by Women With a Vulnerable Health Status Through mHealth App–Based Nudging (Pregnant Faster): Cocreation Design and Protocol for a Cohort Study

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Abstract

Background: Women with a low socioeconomic status often have a vulnerable health status due to an accumulation of health-deteriorating factors such as poor lifestyle behaviors, including inadequate nutrition, mental stressors, and impaired health literacy and agency, which puts them at an unnecessary high risk of adverse pregnancy outcomes. Adequately preparing for pregnancy through preconception care (PCC) uptake and lifestyle improvement can improve these outcomes. We hypothesize that *nudging* is a successful way of encouraging engagement in PCC. A nudge is a behavioral intervention that changes choice behavior through influencing incentives. The mobile health (mHealth) app–based loyalty program *Pregnant Faster* aims to reward women in an ethically justified way and nudges to engage in pregnancy preparation by visiting a PCC consultation.

Objective: Here, we first describe the process of the cocreation of the mHealth app *Pregnant Faster* that aims to increase engagement in pregnancy preparation by women with a vulnerable health status. Second, we describe the cohort study design to assess the feasibility of *Pregnant Faster*.

Methods: The content of the app is based on the eHealth lifestyle coaching program Smarter Pregnancy, which has proven to be effective in ameliorating preconceptional lifestyle behaviors (folic acid, vegetables, fruits, smoking, and alcohol) and an interview study pertaining to the preferences of the target group with regard to an mHealth app stimulating PCC uptake. For moral guidance on the design, an ethical framework was developed based on the bioethical principles of Beauchamp and Childress. The app was further developed through iterative cocreation with the target group and health care providers. For 4 weeks, participants will engage with *Pregnant Faster*, during which opportunities will arise to earn *coins* such as reading informative blogs and registering for a PCC consultation. Coins can be spent on small fun rewards, such as folic acid, fruits, and mascara. *Pregnant Faster*'s feasibility will be tested in a study including 40 women aged 18 to 45 years, who are preconceptional or <8 weeks pregnant, with a low educational level, and living in a deprived neighborhood. The latter 2 factors will serve as a proxy of a low socioeconomic status. Recruitment will take place through flyers, social media, and health care practices. After finalization, participants will evaluate the app through the "mHealth App Usability Questionnaire" and additional interviews or questionnaires.

Results: Results are expected to be published by December 2023.

Conclusions: *Pregnant Faster* has been designed through iterative cocreation with the target group and health care professionals. With the designed study, we will test *Pregnant Faster*'s feasibility. If overall user satisfaction and PCC uptake is achieved, the app will be further developed and the cohort will be continued with an additional 400 inclusions to establish effectiveness.

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(JMIR Res Protoc 2023;12:e45293) doi:10.2196/45293

KEYWORDS

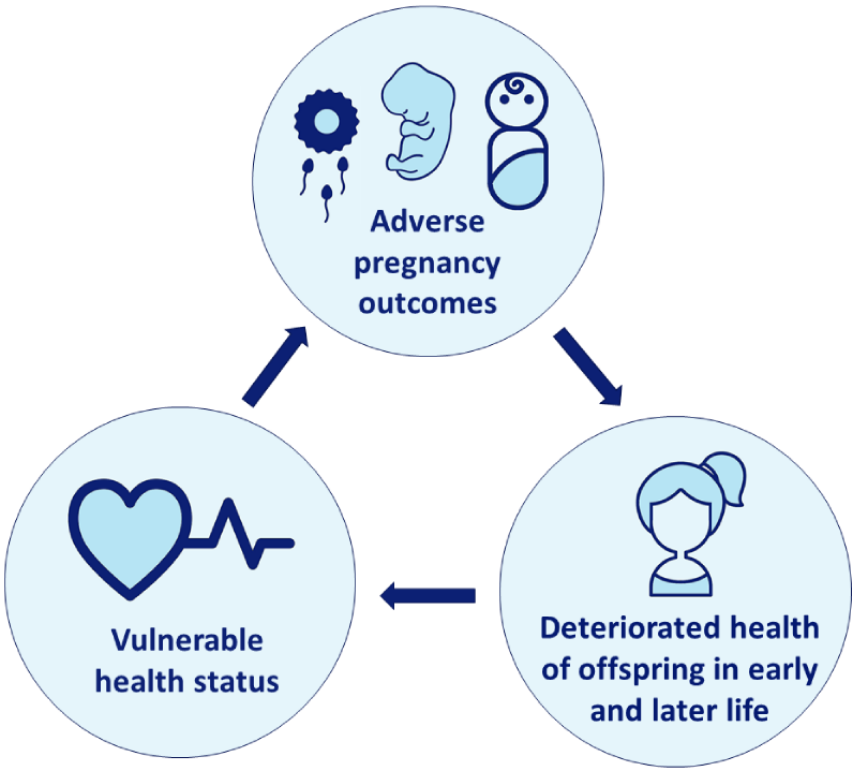
preconception care; periconception; health inequality; socioeconomic status; lifestyle; ethics; mobile health; mHealth; mental stressor; pregnancy; mobile phone

Introduction

Background

Although decreasing, perinatal morbidity and mortality rates are still relatively high in the Netherlands, especially among women who live in deprived neighborhoods and have a low socioeconomic status (SES) [1-3]. These women, who represent up to 45% of the total population in the 4 largest cities in the Netherlands [4], are more likely to have adverse pregnancy outcomes based on the accumulation of health-deteriorating risk factors such as poor lifestyle behaviors (eg, smoking, alcohol consumption, and sedentary lifestyle), inadequate nutrition (consumption of unhealthy food or insufficient intake of healthy food), mental stressors, and impaired health literacy and agency [5-7]. These risk factors, some of which are modifiable, can detrimentally influence the pregnancy course and outcome in the periconceptional phase comprising the preconceptional period of gametogenesis and the first 3 months of embryogenesis and placentation [8]. Complications that occur later in pregnancy are also more common among these women, such as preeclampsia and low birthweight [9-11]. These outcomes result in increased perinatal morbidity and mortality that has its origin in the periconceptional period. Furthermore, there is an increasing body of evidence showing that these pregnancy complications increase the risk of noncommunicable diseases in mothers and their infants during their life course, such as obesity, cardiovascular disease, and diabetes [12,13]. Therefore, we categorized these women with a low SES as women with a vulnerable health status. In short, the vulnerable health status of women with a low SES leads to an increased risk of adverse pregnancy outcomes, which in turn leads to deterioration of the offspring's health, causing them to have a vulnerable health status as well, impacting the health and lives of generations (Figure 1).

Figure 1. Generational impact of the vulnerable health status in women with a low socioeconomic status.



Most clinical manifestations of adverse pregnancy outcomes, such as hypertension or fetal growth restriction, are terminal features of a cascade of events that originate in the periconceptional period (ie, the 14 weeks before conception up to the first 10 weeks of pregnancy) [14]. During this period, on which the focus is limited in research as well as in clinical practice, modifiable poor lifestyle behaviors are known to be common risk factors for subfertility and adverse pregnancy course and outcomes [15-17]. For example, ≥80% of women who are contemplating pregnancy have at least one modifiable behavior associated with adverse pregnancy outcomes, such as not taking folic acid supplements, low vegetable and fruit intake, and smoking [18,19].

Preconception care (PCC) focuses on improving women's health, including lifestyle behaviors, before pregnancy and plays an essential role in encouraging healthy lifestyle behaviors in preparation for pregnancy. Therefore, it reduces the risk of

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adverse pregnancy outcomes and improves health outcomes in mothers and their children now and later in life [20,21]. PCC is usually delivered face-to-face, for example, at midwifery practices or hospitals. However, web-based PCC has been gaining popularity, which are delivered through video consultations or even combined as blended care [22].

The low uptake of PCC by the general population in the Netherlands is associated with women's perceived absence of risks and lack of awareness of PCC [23]. The delivery of PCC for women with a vulnerable health status faces even more obstacles, as these women are more difficult to reach and more difficult to motivate to engage in PCC [24]. These obstacles may lead to an ethically unjustifiable inequality in the health outcomes and life prospects of mothers and children from different socioeconomic backgrounds [24].

To encourage pregnancy preparation, our research group developed the web-based mobile health (mHealth) platform *Smarter Pregnancy* [19], an internet-based, tailored coaching platform that supports women who wish to become pregnant (and possibly their partners) to adopt healthy lifestyle behaviors (such as folic acid supplement use, adequate intake of vegetables and fruits, and cessation of smoking and alcohol consumption) before and during pregnancy. Previous research on the effectiveness of *Smarter Pregnancy* has shown that these healthy behaviors increase by at least 30% and that the chance of an ongoing pregnancy after fertility treatment increases by more than 50% [19,25,26]. Furthermore, *Smarter Pregnancy* has proven to be effective and highly valued by women from deprived neighborhoods [27]. This shows the potential of tailor-made mHealth for women with a vulnerable health status and underlines the importance of customizing an intervention that aims to overcome the obstacles associated with reaching and motivating women with a vulnerable health status to engage in PCC.

Changing behavior and lifestyle habits is challenging for all but even more so for women with a low SES, as they often endure stressful situations and deprived circumstances [28,29]. Therefore, it is advisable to offer this group more support in changing their behavior, which also follows the demands of social justice [30]. One way to support behavioral change is through *nudging*. Nudges are a class of interventions that change people's choice behavior by influencing their incentives, thereby stimulating beneficial, healthy behaviors that individuals themselves value [31]. This could be, for instance, offering fruit instead of chocolate bars at checkout counters to increase fruit consumption and lower refined sugar intake. Previous research has shown that nudging is a promising intervention to encourage the improvement of healthy eating behaviors [32]. Another example of nudging is loyalty programs, in which people can gather rewards by making healthy choices. Nudging via a smartphone app, especially designed for women with a vulnerable health status, may be very suitable to motivate them to engage in PCC due to the current wide availability of smartphones, as well as among women with a vulnerable health status.

Hypothesis

We hypothesized that nudging via the app *Pregnant Faster* is a feasible way to encourage pregnancy preparation and increase PCC uptake in women with an SES-related vulnerable health status. We expect that this will eventually lead to improved maternal health and pregnancy outcomes as well as improved health of the offspring in early and later life.

Aims

In this paper, we aimed to describe in detail the cocreation design process of the mHealth app *Pregnant Faster*, a loyalty program embedded in an app, based on the tailored mHealth lifestyle coaching platform *Smarter Pregnancy*. Furthermore, we aimed to develop a cohort study protocol to test the feasibility of *Pregnant Faster*, comprising overall user satisfaction; the number of booked and visited PCC consultations; and the course of practical conduction with regard to the inclusion process, reward allocation, and finalization. The general goal of *Pregnant Faster* is to encourage women with a vulnerable health status, in an ethically justified way, to adequately prepare for pregnancy by visiting a PCC consultation.

If the results of this study indicate that *Pregnant Faster* is appreciated by the participants and stimulates the uptake of PCC, we aim to continue this proposed study with an updated version of *Pregnant Faster* and an extended cohort, to establish the effectiveness of increasing the uptake of PCC in women with an SES-related vulnerable health status.

Our ultimate goal is to contribute to the reduction of inequalities in the health of women before and during pregnancy by (1) creating awareness regarding women's own influence on the course of their pregnancy and an increased uptake of PCC, (2) reducing perinatal morbidity and mortality, and (3) improving the long-term physical and mental health of mothers and their children.

Methods

The Cocreation Process

Preparation

The preparation of the design process of *Pregnant Faster* can be subsumed under 3 pillars. First, we have developed an ethical framework to assess the ethical justifiability of developing a loyalty program to stimulate PCC uptake among women with a vulnerable health status. An ethical framework can be viewed as a guideline that offers guidance on the moral permissibility of an intervention and provides suggestions on how to avoid ethical pitfalls, such as exposing susceptible participants to stigmatization based on their SES. This framework was developed by performing a literature search to identify records broadly relevant to the subject of using nudges to stimulate healthy lifestyle behaviors and extracting ethical dilemmas and pitfalls from these records. On the basis of these extracted dilemmas and pitfalls, criteria were set up to which an incentive-based intervention encouraging pregnancy preparation in susceptible women must comply to be morally justifiable. These criteria were subdivided under the 4 ethical principles of Beauchamp and Childress [33]: (1) respect for autonomy, (2)

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beneficence, (3) nonmaleficence, and (4) justice. By addressing all 4 principles, an attempt was made to address as many ethical pitfalls as possible without overlooking any major aspects. This *principlist* approach is ideally suited for the topic of nudging women with an SES-related vulnerable health status because it allows for balancing between the duty to improve their and their children's health and well-being and the duty to respect them and treat them as free and equal persons.

Second, we conducted semistructured interviews with 15 women from the target group, which allowed us to gain insight into how they regard loyalty programs; which type of loyalty program they prefer; and which rewards are considered most legitimate, attractive, and effective [34]. The interviews were analyzed using a framework approach and thematic content analyses of five themes: (1) "usefulness of an app as an integral information source," (2) "permissibility and effects of offering rewards," (3) "preferences regarding content," (4) "preferences regarding the type of rewards and system of allocation," and (5) "barriers." Involving the target group in the design of the app, thereby respecting their autonomy and preferences, is an imperative criterion of the ethical framework.

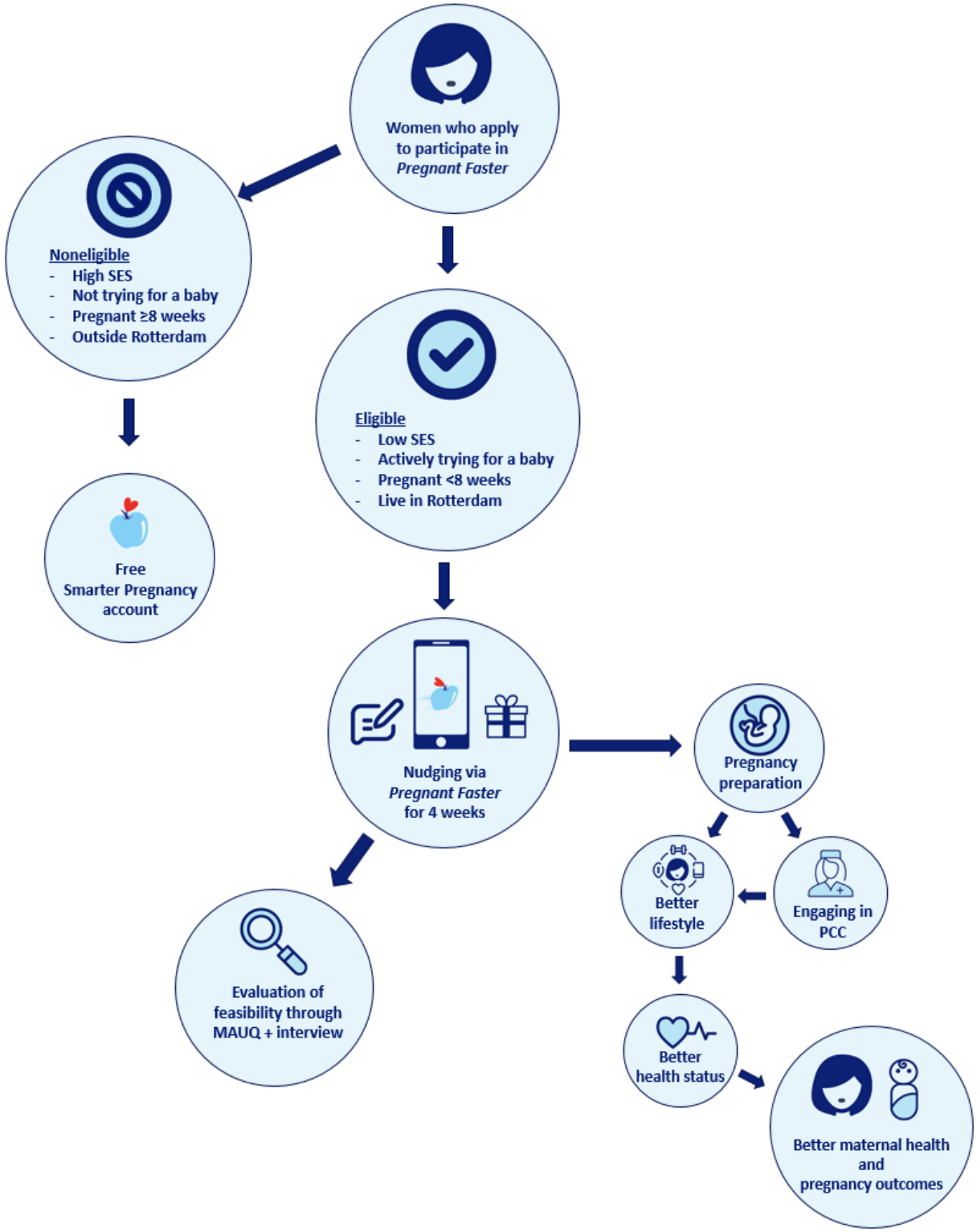
Third, we based the lifestyle-related content of the app on the tailored mHealth lifestyle coaching platform *Smarter Pregnancy*. *Smarter Pregnancy* has previously proven to be effective in ameliorating preconceptional health and lifestyle behaviors and is based on over 30 years of research and the expertise of this research group regarding the influence of nutrition and lifestyle on reproduction and pregnancy course and outcome [25]. The main focus of *Smarter Pregnancy* lies in the amelioration of nutrition, including folic acid supplement use, and supporting healthy lifestyle behaviors such as reaching a healthy weight, smoking and alcohol cessation, and sufficient physical activity. The knowledge gained through these 3 pillars was combined into a first design of the app *Pregnant Faster*. The choice to develop this loyalty program as a nudge was based on the fact that women are known to wish for a healthy baby when they want to become pregnant [23,35]. Thus, the definition of nudging is that a nudge always aims to help the *nudgee* reach a goal they themselves wish for and value [31]. In addition, a nudge may not harm the nudgee. This description complies with the aforementioned biomedical ethical principles.

Iterative Cocreation

Subsequently, we conducted a strategic work session with professionals in this field (5 midwives, 2 gynecologists, and 2 general practitioners) in which we discussed our findings regarding moral permissibility, the wishes and preferences of the target group, and the first design of the app. The professionals asked to participate were known to practice in low-income areas, providing them with experience in caring for the target group of women with a vulnerable health status. The strategic work session was led by an external communication bureau specialized in transforming these types of sessions and the yielded insights into practical reports. These insights were then implemented in the app, leading to the design of a new and improved version of the app, adhering to the ethical framework. Through an iterative process (Figure 2), adjusted versions of the app were discussed by the communication bureau multiple times with 10 women in the target group who had previously participated in the interview study [34] and the aforementioned professionals, until all were satisfied with the design of the app and the app was considered morally permissible. The resulting app-based nudge *Pregnant Faster* can be viewed as an *umbrella* or a *macro-level* nudge, containing multiple *micro-level nudges*.

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Figure 2. Overview of the intervention. MAUQ: mHealth App Usability Questionnaire; PCC: preconception care; SES: socioeconomic status.



Cohort Study Protocol

Overview

This study was set up as an open cohort to reflect the real-life situation, and it aims to assess the feasibility of the mHealth app–based nudge that stimulates PCC uptake in women with an SES-related vulnerable health status.

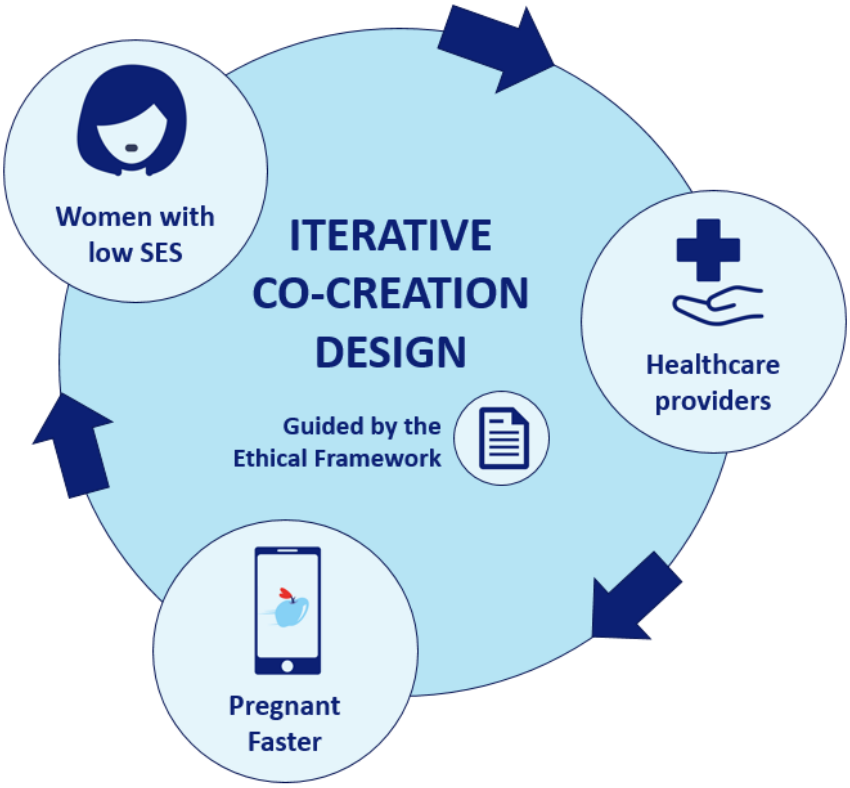
After inclusion (T0), the women start the intervention, consisting of using the app daily. The total duration of the intervention will be 4 weeks per participant, as we deemed a short period of active engagement more feasible than a longer period and did not expect additional engagement in pregnancy preparation or PCC consultations after 4 weeks of using the app.

After the intervention (T1), participants fill out the "mHealth App Usability Questionnaire" (MAUQ), assessing the app, as well as partake in an interview in which they may state their

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opinions regarding the content of the app and how they rate their experience. At T1, we will assess the uptake of PCC as well (Figure 3). The results of this study will provide further insights to enhance the final design of the nudge and the app and can be viewed as another round in the iterative process, implementing the opinions and experiences of the target group into the final design. After this proposed cohort study, we aimed to update *Pregnant Faster* and plan to establish its effectiveness in a cohort of 400 women. Originally, the sample size of 400 was based on a power calculation for a randomized controlled trial with 2 groups using the app: one with and one without the allocation of rewards. However, the choice was made to convert the planned controlled trial to a cohort study due to the nature of this intervention and the possible disappointment women would feel if they would be randomized in a nonreward group, which could lead to disengagement and biased outcomes.

Figure 3. Iterative cocreation of Pregnant Faster. SES: socioeconomic status.



This research group has previously experienced difficulty in including women with a vulnerable health status in an interview study [34]. Although we believe that the nature of the intervention *Pregnant Faster* might encourage more women to participate, we consider these previously obtained experiences. Therefore, for this pilot study, we chose to aim for a sample size of 40 participants (10% of the larger planned cohort study), which we deemed sufficient to provide the first insights supporting further development of *Pregnant Faster*.

Participants

To be eligible, participants must meet all the following inclusion criteria: assigned female at birth, 18 to 45 years of age, living in the municipality of Rotterdam (the Netherlands), currently trying to conceive or planning to actively try within 3 months, or pregnant with a gestational age below 7+6 weeks, and having a vulnerable health status. In this study, having a vulnerable health status is defined as having a low SES based on the combination of a low to intermediate educational attainment (prevocational or vocational education) and living in a deprived neighborhood based on the zip code's median income [36].

A potential participant who meets any of the following exclusion criteria will be excluded from participation in this study: insufficient proficiency in Dutch, not in possession of a smartphone or tablet suitable for the app, living outside of the municipality of Rotterdam, refusal to fill out the questionnaires, or refusal to participate in the interview.

The choice to only include citizens of the municipality of Rotterdam is based on the plan to deliver the rewards per bike, car, or public transport.

Recruitment and Inclusion

Women from the target population will be recruited not only through midwifery practices, hospitals, and general practitioner practices but also directly through the distribution of flyers and posters and through social media, specifically Instagram and Facebook. Social media campaigns will be directly targeted at specific areas and populations, which fit our inclusion criteria. Recruitment will take place in collaboration with the Regional Consortium Pregnancy & Childbirth of the Southwest Netherlands, in particular with 5 midwifery practices located in or near deprived neighborhoods of Rotterdam. Women may enroll themselves in the study or they can be enrolled by a health care provider.

When women receive the flyer or are informed about the study by a health care provider, they may fill in their email on the

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website *Getting Pregnant Faster* [37]. The researcher receives their email address and sends them a screening survey with questions regarding the inclusion criteria. This information will allow for the selection of women who fit the target group. If a potential participant is eligible, the researcher will contact her via telephone and email to provide further information about the study. If the woman is interested in participating, informed consent will be sent via email.

If women are eligible and have signed the informed consent form, they will be asked to download the app and start the intervention. If women are not eligible for participation, they will be provided with a free 26-week subscription to our mHealth coaching platform *Smarter Pregnancy*.

Randomization and Blinding

Owing to the nature of the intervention, all participants will receive the same intervention. Therefore, this section is not applicable. Blinding of the participants is not possible. Neither the participants nor the researchers will be blinded.

Intervention

The intervention consists of using the app *Pregnant Faster* (Dutch: *Sneller Zwanger*), which can be viewed as a macrolevel nudge containing a multitude of microlevel nudges. All nudges are aimed at encouraging participants to adequately prepare for pregnancy by making healthy nutrition and lifestyle choices and visiting a PCC consultation.

Outcome Measures

The main objective of this study design is to establish the feasibility of the app *Pregnant Faster* as a nudge that encourages pregnancy preparation by stimulating the uptake of PCC. Feasibility in this study pertains to overall user satisfaction, the number of booked and visited PCC consultations, and the course of practical conduction with regard to the inclusion process, reward allocation, and finalization. The outcome will be assessed in multiple ways: (1) through the number of women who registered for this study, which indicates the effectiveness of the methods used to reach women; (2) the number of women eligible to participate, which indicates the effectiveness of these methods in reaching the target group; (3) the number of participants who were included and the number who actually started the intervention, which may reveal possible barriers between inclusion and conduction; (4) the number of participants completing the intervention, which offers information on how engaging the app is; and (5) the frequency with which certain rewards are chosen that indicates which rewards are deemed the most desirable and motivating. Furthermore, the usability of the app will be assessed using the MAUQ, a validated 18-item questionnaire on user satisfaction, information arrangement, and usefulness based on a 7-point Likert scale (strongly disagree, disagree, somewhat disagree, neither agree nor disagree, somewhat agree, agree, and strongly agree) as presented in Multimedia Appendix 1 [38].

To further investigate how participants have experienced using the app, the first 10 participants will be interviewed in a semistructured manner to explore the answers they give on questions such as how often they opened the app and if this was according to how often they would have liked to open the app. A topic list and additional information on this interview is present in Multimedia Appendix 2. This topic list and participants' answers will be converted into a questionnaire offered to the remaining 30 participants. To include the first 10 participants in this questionnaire, the first author will fill in the questionnaire based on the participants' answers in the interview. The MAUQ and the interview or additional questionnaire will be offered 4 weeks after a participant has started the intervention (T1).

The number of PCC consultation requests and confirmed visits will be registered during the study period and in the aforementioned questionnaires, women will be asked why they registered (or did not register) for a PCC consultation and if they changed their lifestyle behaviors due to using the app. Descriptive statistics will be used for these outcomes, and the results will be reported in a narrative and tabular form.

Sample Size

The aim of this study is to test the feasibility of *Pregnant Faster* and explore the barriers that might be encountered. On the basis of our previous experiences with including the described target group, we are confident that 40 participants will be sufficient to reach our aim.

Ethics Approval

This study was assessed and approved by the Medical Ethical Committee of the Erasmus University Medical Center, Rotterdam, The Netherlands (MEC-2020-0974). Considering the low risk of this study, composing a Data Safety Monitoring Board was deemed unnecessary.

Results

The App Design

The name *Pregnant Faster* serves as a first microlevel nudge to join the study because most women who wish to have a baby often hope to become pregnant quickly. Using the app and its various components, all of which form microlevel nudges, will lead to earning so-called *coins*. Earning coins functions as a microlevel nudge because it stimulates participants to use the app.

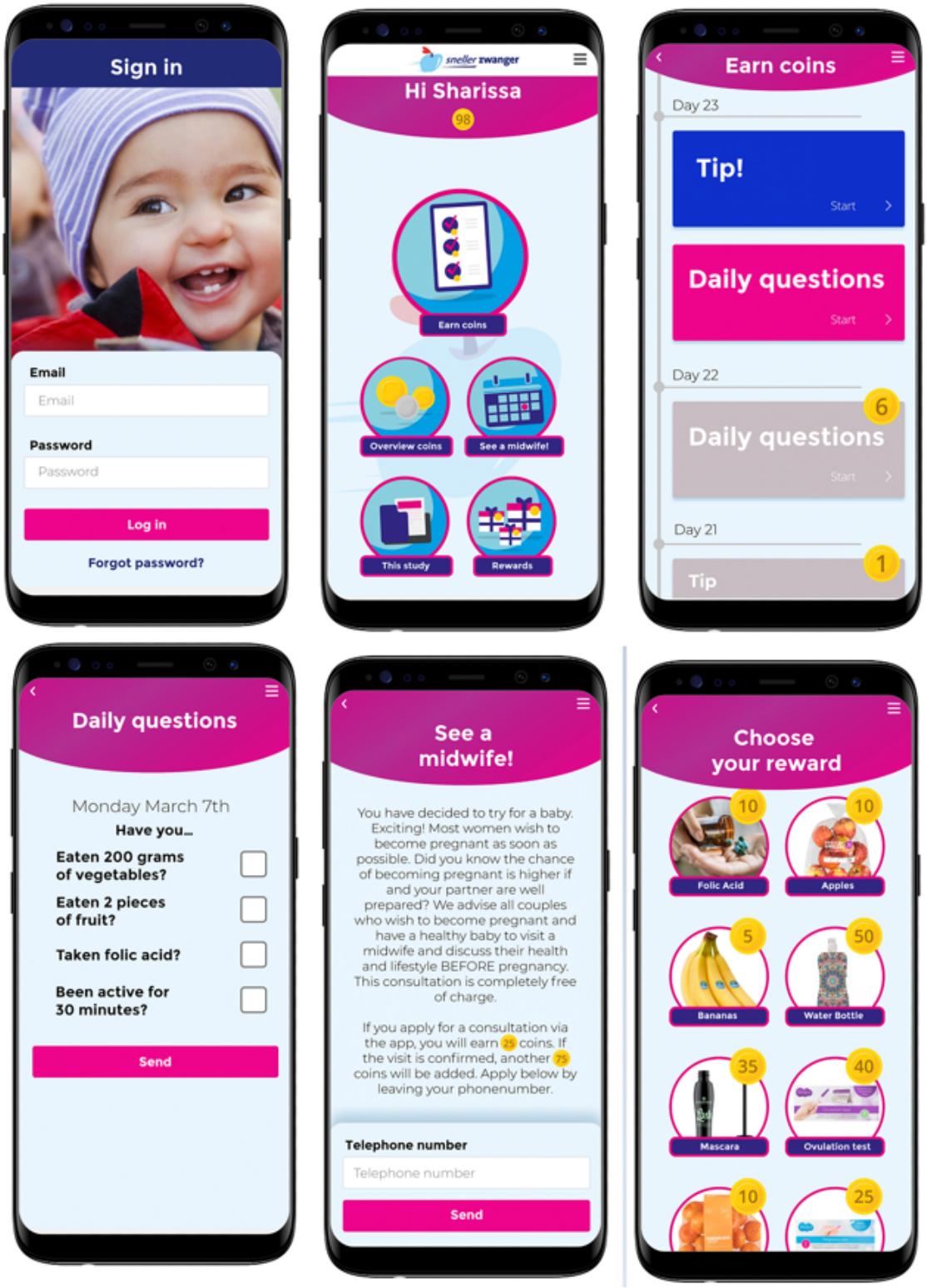
Participants log-in with their email address and a password that yields 1 coin per day. The first log-in yields 50 coins to immediately stimulate the participants to engage with the app. After log-in, a dashboard appears, containing five buttons: (1) Earn coins, (2) Overview coins, (3) See a midwife! (4) This study, and (5) Rewards (Figure 4).

Button 1, "Earn coins," leads to a timeline in which new information appears daily in blogs or tips. Reading these yields 4 to 8 coins depending on the reading time and reading difficulty. Earning coins acts as a microlevel nudge to engage in reading relevant information about how to adequately prepare for pregnancy and ameliorate lifestyle and preconceptional health. Putting pregnancy preparation into the participant's focus stimulates active thought on this topic, which in turn may lead to increased motivation for pregnancy preparation and healthier choices. In the same timeline, a daily questionnaire

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appears in which participants can tick off if they have eaten enough fruit and vegetables, exercised, and taken their folic acid supplements. Each ticked-off point yields 2 coins. This questionnaire also acts as a microlevel nudge because it serves as a reminder and motivator, which may lead to performing the behavior that can be ticked off.

Figure 4. Screenshots of the mobile health app Pregnant Faster.



Button 2, “Overview coins,” displays when and how coins have been earned and how many coins have been spent on which products. Having saved or spent a certain number of coins may nudge women to try and earn more coins, leading them back to the timeline in which they learn about properly preparing for pregnancy.

Button 3, “See a midwife!” contains information regarding what PCC entails and for whom it is meant. Here, we try to encourage participants to sign up for a consultation with a midwife in their

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vicinity and offer an easy way to sign up for a consultation in their neighborhood by filling in their phone number, which yields 25 coins immediately and an additional 75 coins after the visit has been confirmed. Minimizing the effort required to register for a PCC consultation serves as a microlevel nudge by lowering the threshold to engage in PCC.

Button 4, "This study," contains information about the study itself, the researchers, and where to find additional information and contact details for questions, help, or complaints.

Button 5, "Rewards," contains a list of rewards accompanied by images that participants can spend their coins on. Participants can choose from a variety of rewards such as folic acid supplements, fruits, nail polish, mascara, ovulation or pregnancy tests, newborn clothing, water bottles, and other healthy or fun rewards that may contribute to preconceptional health.

In our earlier ethical research and interview study [34], it became apparent that adequately respecting participants' autonomy and preferences is imperative when it comes to increasing motivation for certain behaviors. Women wanted to have the option to either save up for a large reward or spend their coins on multiple smaller rewards. When participants choose their rewards freely, this will automatically lead them to choose the timing and type of reward that motivates them the most. In other words, being able to freely choose supports the app in stimulating women with different preferences regarding the timing and types of rewards to engage in pregnancy preparation and visit a PCC consultation. To satisfy this requirement, the app contains multiple types of rewards of varying value.

Another microlevel nudge lies in the varying value of the coins. One coin represents a monetary value of €0.06 to €0.26 (US $0.06 to US $0.26). By making healthy rewards, such as folic acid supplements and fruits, relatively cheap, we steer participants toward picking healthy products over luxury goods, while still allowing them to choose luxury goods if that is what stimulates them most to earn coins and engage in PCC. For instance, the mascara and folic acid supplements are of equal monetary value and cost €3.00 (US $3.00). However, the folic acid supplements can be ordered for 10 coins whereas ordering the mascara will cost the participant 35 coins.

Participants of our previously conducted interview study [34] mentioned that it might be painful for them if they could only choose pregnancy and baby-related products, in case of not getting pregnant quickly. To take this into account, we have included rewards in the app that are not relatable to pregnancy or babies, such as water bottles, a book voucher, and resistance bands for physical exercise.

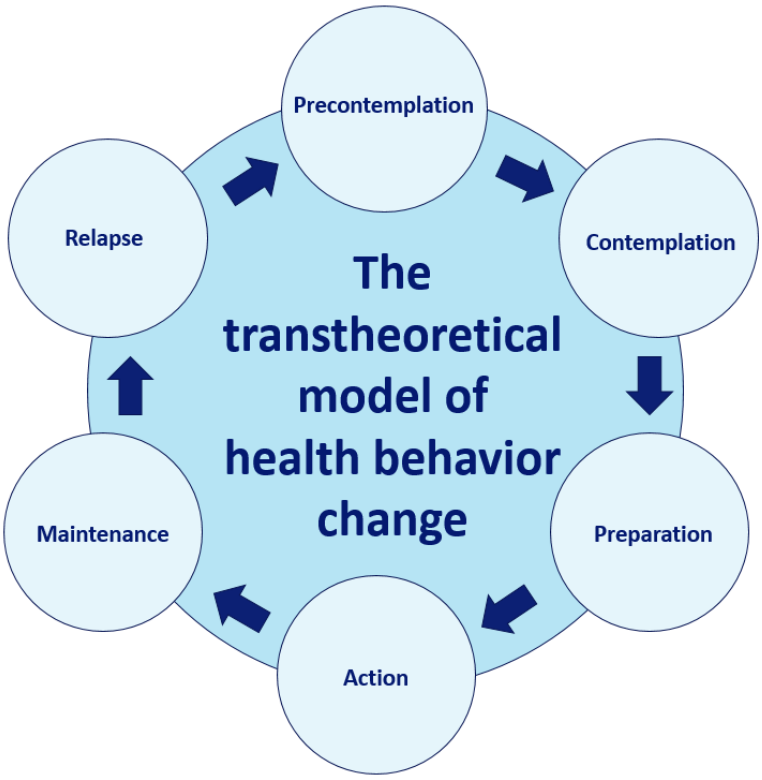
The design of *Pregnant Faster* makes the app suitable for all women because it automatically matches participants' personal preferences and their current level of motivation to prepare for pregnancy and engage in PCC. This is done by allowing participants to freely choose the type and timing of their rewards and by matching their current "Stage of Change," as described by Prochaska and DiClemente [39].

The transtheoretical model of behavior change by Prochaska and DiClemente [39] describes the different and subsequent stages of changing a certain behavior: precontemplation, contemplation, preparation, action, maintenance, and relapse (Figure 5). Each stage requires a different type of approach [40]. For instance, if a woman has an unhealthy diet and is currently in the precontemplation stage, is not aware of a problem, and is not willing to change, helping her set up a detailed healthy eating plan may lead to her feeling overwhelmed or rejecting the idea that a healthy diet is important, which results in resistance and noncompliance. The first step for this specific woman would be to help her discover why a healthy diet is important to her and which benefits it could possibly yield for her. This will help her acknowledge that her current diet may be problematic and requires a change: the contemplation stage. However, if the woman has been contemplating improving her diet for a while, helping her set up a practical plan may be the exact nudge she needs to help her reach the next stages of change: preparation and action. The choice to use this model was based on the fact that it is widely used and taught in medical education and health care professions, as it provides solid instructions on how best to approach the patient or client to encourage and support them in changing unhealthy behaviors, in addition to the available evidence regarding its effectiveness [41,42] and the amount of experience of the authors in the application of this model.

It is clear that the most effective approach differs by stage and that the current stage of change is very personal. However, we chose not to assess the participants' current stage of change to minimize what participants could deem *fruitless engagement*—spending time in the app without being rewarded for it, which could diminish interest in the app. Therefore, *Pregnant Faster* was designed to passively match all possible stages, as described by Prochaska and DiClemente [39]. If a participant is currently not preparing for pregnancy and is not interested in doing so (precontemplation), it is still attractive to read the information *Pregnant Faster* offers because of the coins she can earn and spend on rewards to her liking. The blogs and tips in *Pregnant Faster* focus on conveying that healthy choices and PCC may help to have a healthy baby sooner, a goal that many women strive for. This may cause a participant to start contemplating if she too could get pregnant faster by actively preparing for pregnancy and visiting a midwife for PCC. She might even start to plan how she could take action (preparation). If a participant is already preparing for pregnancy by, for instance, eating more vegetables (action or maintenance), reading about the benefits of this behavior in the timeline of the app will act as a stimulant to maintain this behavior or maybe even make a plan to also eat 2 pieces of fruit per day (preparation). For women who already have a healthy diet and lifestyle, and are currently in the maintenance stage, the app will serve as a stimulant to sustain healthy behavior and may help to prevent a relapse (maintenance). In conclusion, the app appeals to women in each stage of change by either encouraging new healthy behavior or the continuation of preexisting healthy behavior.

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Figure 5. The transtheoretical model of health behavior change by Prochaska and DiClemente [36]. (1) Precontemplation: unaware of the need for change and unwilling to change. (2) Contemplation: aware of the problem but not yet committed to change. (3) Preparation: believes change is good, intent on taking action, and planning to start. (4) Action: actively changing behavior or creating new habits. (5) Maintenance: behavior has changed, committed, and resolved; must be aware of the possibility of relapse. (6) Relapse: relapsing into old behavior; may skip precontemplation in the next cycle.



Participants in any stage of change may choose to register for a PCC consultation as the reward is high and the required action (filling in their phone number) is relatively small. This was decided consciously to meet the main objective of *Pregnant Faster*, stimulating pregnancy preparation by visiting a PCC consultation provided by a health care provider. These face-to-face consultations allow health care providers to directly apply motivational conversation techniques [43] and actively match the participant's current stage of change on the topics that are most relevant for them, for instance, smoking cessation, an unhealthy diet, or a sedentary lifestyle. Having an engaging, live conversation in which the participant can ask questions and feels heard and supported may be the greatest encouragement or nudge to engage in adequate pregnancy preparation and make healthy choices. Furthermore, a live consultation allows for relevant referrals (eg, for smoking cessation) without relying on the participant to take the first step.

This intervention is completed after 4 weeks. If women still have coins left by the end of the intervention, they will be able to exchange these for rewards within 2 weeks after the completion date or 2 weeks after their PCC consultation. The app and timeline will continue to be available for participants, so they can access its information and register for a PCC consultation whenever they please, but they will no longer be able to earn or spend coins by using the app.

The iterative developmental process has led to the detailed design of the app *Pregnant Faster*, which we have built in cooperation with the event agency Improve in Delft, the Netherlands, and the mobile app manufacturer TJIP The Platform Engineer. *Pregnant Faster* is an app of 5.2 MB and is currently only available in the research setting for Android by a download link and for iPhone through the Apple store. The app has a modern, colorful interface (Figure 4) inspired by the preferences of the target group. Overall, the app was designed to fit the user's needs and preferences concerning the content of the app as well as easy and intuitive operating.

Cohort Study

Results are expected to be published by December 2023.

Discussion

Principal Findings

In this paper, we have described the iterative cocreation design process of the app *Pregnant Faster*, an mHealth app–based nudge specifically designed for women with a vulnerable health status based on their SES who have a higher risk of adverse pregnancy outcomes. In addition, we have described the protocol of the cohort study aimed at establishing the feasibility of using *Pregnant Faster* to encourage these women, in an ethically justified way, to adequately prepare for pregnancy by engaging in PCC and making healthy nutrition and lifestyle choices.

In this proposed study, women will be nudged through an app that rewards them to encourage them to make healthy choices. The nature of an incentive-based intervention, or nudge, is such that its aim is to *influence* the participant's behavior. There is a fine line to tread between nudging and manipulation, which

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we consider in this protocol. Nudging entails that alternative choices are never taken away or obstructed, and choosing differently does not require significant extra effort or create a great sense of loss, as this would count as coercion. This study does not force women to prepare for pregnancy or engage in PCC. Using the app or registering for a consultation is optional, and the offered rewards are of such value that they will not coerce participants into actions they do not value or wish to perform.

Furthermore, the aim of the nudge must be beneficial to the target group and must align with their own preferences and aims. In this case, the intervention aimed to adequately prepare women with a vulnerable health status for pregnancy to reduce the chance of adverse pregnancy outcomes. This aligns with the preferences and aims of the participants as they want to give birth to a healthy baby. For manipulation to be prevented, transparency concerning the aim of this study is crucial. Therefore, proper explanation, obtaining informed consent, and ensuring that the participant consents to being influenced is of utmost importance.

van der Windt et al [22] established that blended care is an effective method to improve lifestyle and nutrition choices. In this study, we will use an mHealth app to offer an intervention that aims to encourage women to learn about healthy pregnancy preparation via an app and visit a face-to-face PCC consultation. In other words, it aims to provide blended care while still offering important information to women who are not yet ready to engage in a face-to-face consultation.

The use of smartphones is widespread, even among women with a low SES [44]. This means that *Pregnant Faster* as an app-based nudge will be widely available and easily accessible for the target group, allowing them to use the app privately and at a time that suits them best, which reduces the burden of participating in the study. The attractive interface and overall positive outlook applied in the app are aimed at further reducing any negative feelings that may result from learning about necessary lifestyle behavioral changes, resulting in an app that is fun to have and use. A foreseen possible limitation of the app design lies in the fact that it cannot yet be altered to best suit the participant's personal situation regarding her gestational age or how long she has been trying to become pregnant. However, even though *Pregnant Faster* does not specifically target women with difficulty conceiving, it does address the experiences associated with subfertility, which means that this group may also benefit from using the app. For example, the offered information aligns with the nutrition and lifestyle advice given to couples in the fertility outpatient clinic of the University Medical Center where this study has taken place. Furthermore, attention is paid to which factors influence the chance to become pregnant and have an ongoing pregnancy, specifying which factors are within and outside one's own control. By providing clarity on what can and cannot be influenced, including the size of the expected effects, we aim to encourage healthy lifestyle behavior without possibly burdening participants with the idea that they themselves would be responsible for (possible) subfertility or miscarriage cessation. Furthermore, within the blogs and tips, advice is given on when and how to find support when trying for a baby takes longer than expected, considering women's age and medical history in line with Dutch General Practitioner guidelines on referral for fertility treatments. In addition, the stress that may accompany trying to get pregnant is acknowledged and tips are provided to cope with these experiences.

With regard to the study design, the outcomes comprising *Pregnant Faster's* feasibility allow for practical evaluation, which will form solid stepping stones to further develop the app. The design of the app is such that we aim to continue its development throughout the coming years and possibly explore its use in different target groups, with and without rewards. A possible limitation in the study design pertains to the interviews with the first 10 participants that have been used to develop the additional questionnaire on user experiences. To evaluate the group of 40 women as one, these interviews will be used to fill out the developed questionnaire. It might be more prudent to qualitatively analyze these interviews and view these 10 participants as a separate group. However, as this feasibility study mainly aims to provide holdfasts for further development of *Pregnant Faster*, we believe that this method will suffice.

A potential risk of using *Pregnant Faster* may be that providing rewards can "crowd out" intrinsic motivation to make healthy choices [45,46]. In other words, the healthy behavior that women value and display before the start of the intervention, diminishes or vanishes after the intervention ends, and rewards are no longer provided. For example, if women went to the gym before the intervention, they could maintain this habit and receive rewards for it. This influences the way they view and value this behavior by shifting their focus from health-related rewards, such as strength and fitness, to material rewards. When the intervention ends and going to the gym no longer leads to material rewards, these women might be less inclined to exercise than they were before they participated in the intervention. This is caused by increasing extrinsic motivation for a behavior at the expense of intrinsic motivation.

If a nudge only appeals to extrinsic motivation, the healthy behavior "dies out" as soon as the intervention ends [46]. However, scaffolding intrinsic motivation leads to a more sustainable change because it focuses on health-related rewards. Overall, women who want to become pregnant wish to have a healthy baby. Educating them about the control they may exercise on their pregnancy outcomes by taking up PCC and making healthy nutrition and lifestyle choices fits their wish to have a healthy baby and may increase their intrinsic motivation to make healthy choices. This cancels out the *crowding out* effect and allows for continuation of healthy behavior because the focus is not placed on limited material rewards but on continued health-related rewards, making the behavioral changes more sustainable.

Another potential risk lies in how the app makes women feel. It is known that mHealth apps may evoke feelings of guilt, shame, and stress and even discouragement when participants fail to meet the app's goals [47]. It is paramount that the tips and blogs in *Pregnant Faster* convey that small steps are worth celebrating and that women are not obliged to strive for a perfect lifestyle to have a healthy baby. Furthermore, the app must also contain information on the fact that a healthy lifestyle increases

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the chance of a healthy baby but offers no guarantees. It must be stated that not all adverse outcomes can be prevented and that an adverse pregnancy outcome does not mean that the woman (or her partner) is to blame.

When this pilot study has been conducted, we expect to have obtained valuable information on how to further adjust *Pregnant Faster* to best fit the needs of women with a vulnerable health status and encourage PCC uptake in this group. In other words, this proposed study can be viewed as yet another phase of the iterative process, and the outcomes will be used to update and alter the app to further develop the design of *Pregnant Faster*. Furthermore, practical information on, for example, the number of registrations of eligible and noneligible women will provide guidance on our methods to reach the target group and evaluation of the rewards, and the frequency of allocation will provide more insight into which rewards are deemed most desirable. Finally, any barriers encountered during this pilot study will be assessed to avoid such barriers in the future.

Conclusions

We have developed an mHealth app (*Pregnant Faster*)–based nudge that aims to encourage women with a vulnerable health status to engage in pregnancy preparation by taking up PCC, to improve the high incidence of adverse pregnancy outcomes in this group.

The risks and burdens of participating in this study will be minimal, whereas the benefits for both the mother and (unborn) child are potentially substantial. Furthermore, we designed a study protocol to establish the feasibility of *Pregnant Faster*. If the results of this study indicate that using *Pregnant Faster* to increase the uptake of PCC in women with a vulnerable health status is feasible, we will implement the obtained insights and further develop the app. For example, if a specific barrier in joining the study or registering for a PCC consultation is encountered, we will attempt to overcome these barriers to improve inclusion rates and increase PCC consultation requests and continue this study with an updated version of the app and an additional 400 inclusions, thus attempting to establish the (cost) effectiveness of *Pregnant Faster* with regard to increasing the uptake of PCC.

Finally, we aim to investigate the possibility of offering *Pregnant Faster* without rewards to all women who wish to become pregnant, regardless of their health status. Earning material rewards forms just one of the multiple microlevel nudges in this macrolevel nudge and is meant to attract women with little knowledge of, or headspace or motivation for, pregnancy preparation. However, many women look for information on how to become pregnant quickly and healthily. For these women, the knowledge and motivation provided by *Pregnant Faster* may also be valuable and help them adequately prepare for pregnancy.

Acknowledgments

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Data Availability

As this paper concerns a design process and proposed study, no pilot study data are available to share as yet. However, the design process of *Pregnant Faster* and the proposed pilot study are based on earlier research conducted by this group. Articles about *Smarter Pregnancy* and its development and testing have been published previously [19,26], as has the interview study on the preferences of susceptible women regarding a loyalty program [34]. Due to the ethical framework currently being submitted, we are unable to provide its data, as that would be in conflict with the conditions of submission. Further inquiry with regard to the ethical framework and reports of the strategic work session (which are written in Dutch) can be provided by the authors at reasonable request.

Authors' Contributions

RPMS-T conceived the study and provided funding. RPMS-T, SMS, and BB initiated the study design. SMS wrote the original draft and BB and RPMS-T reviewed and edited the original draft. BB, RPMS-T, HIM, and MHNS supervised this study. All authors contributed to the refinement of the study protocol and approved the final manuscript.

Conflicts of Interest

RPMS-T is an initiator and developer of the mobile health app Smarter Pregnancy. The funder had no role in the design of the study, writing of the manuscript, or decision to publish the protocol.

Multimedia Appendix 1
The mHealth App Usability Questionnaire.
[DOCX File , 22 KB - resprot_v12i1e45293_app1.docx]

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Multimedia Appendix 2
Topic list—user experiences Pregnant Faster.
[DOC File , 82 KB - resprot_v12i1e45293_app2.doc]

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Abbreviations

MAUQ: mHealth App Usability Questionnaire
mHealth: mobile health
PCC: preconception care
SES: socioeconomic status

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Protocol

Using Presurgical Biopsychosocial Features to Develop an Advanced Clinical Decision-Making Support Tool for Predicting Recovery Trajectories in Patients Undergoing Total Knee Arthroplasty: Protocol for a Prospective Observational Study

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Abstract

Background: Following total knee arthroplasty (TKA), 10% to 20% of patients report dissatisfaction with procedural outcomes. There is growing recognition that postsurgical satisfaction is shaped not only by the quality of surgery but also by psychological and social factors. Surprisingly, information on the psychological and social determinants of surgical outcomes is rarely collected before surgery. A comprehensive collection of biopsychosocial information could assist clinicians in making recommendations in relation to rehabilitation, particularly if there is robust evidence to support the ability of presurgical constructs to predict postsurgical outcomes. Clinical decision support tools can help identify factors influencing patient outcomes and support the provision of interventions or services that can be tailored to meet individuals' needs. However, despite their potential clinical benefit, the application of such tools remains limited.

Objective: This study aims to develop a clinical decision tool that will assist with patient stratification and more precisely targeted clinical decision-making regarding prehabilitation and rehabilitation for TKA, based on the identified individual biopsychosocial needs.

Methods: In this prospective observational study, all participants provided written or electronic consent before study commencement. Patient-completed questionnaires captured information related to a broad range of biopsychosocial parameters during the month preceding TKA. These included demographic factors (sex, age, and rurality), psychological factors (mood status, pain catastrophizing, resilience, and committed action), quality of life, social support, lifestyle factors, and knee symptoms. Physical measures assessing mobility, balance, and functional lower body strength were performed via video calls with patients in their home. Information related to preexisting health issues and concomitant medications was derived from hospital medical records. Patient recovery outcomes were assessed 3 months after the surgical procedure and included quality of life, patient-reported

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knee symptoms, satisfaction with the surgical procedure, and mood status. Machine learning data analysis techniques will be applied to determine which presurgery parameters have the strongest power for predicting patient recovery following total knee replacement. On the basis of these analyses, a predictive model will be developed. Predictive models will undergo internal validation, and Bayesian analysis will be applied to provide additional metrics regarding prediction accuracy.

Results: Patient recruitment and data collection commenced in November 2019 and was completed in June 2022. A total of 1050 patients who underwent TKA were enrolled in this study.

Conclusions: Our findings will facilitate the development of the first comprehensive biopsychosocial prediction tool, which has the potential to objectively predict a patient's individual recovery outcomes following TKA once selected by an orthopedic surgeon to undergo TKA. If successful, the tool could also inform the evolution rehabilitation services, such that factors in addition to physical performance can be addressed and have the potential to further enhance patient recovery and satisfaction.

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KEYWORDS

biopsychosocial; total knee arthroplasty; prospective; recovery trajectories; patient-reported outcomes; predictive clinical decision tool; clinical decision support; knee arthroplasty; rehabilitation; psychosocial; patient-reported outcome; quality of life; patient recruitment; presurgery; patient stratification

Introduction

Background

Total knee arthroplasty (TKA) is a well-established and effective treatment for end-stage osteoarthritis [1]. The number of TKA procedures performed is increasing annually, both locally and globally. In both Australia [2] and the United States [3], it is projected that the number of TKAs undertaken will rise by 276% and 181%, respectively, by 2030, placing an increased burden on health care services. Surgical success rates are high and are currently based on a range of objective medical outcomes including survival, prosthesis performance, and revision rates [4]. However, despite this, there are consistent reports that up to 20% of patients report dissatisfaction with the outcomes of the procedure, reflected by enduring pain, limited function, and diminished quality of life [5-7].

Rehabilitation is an important factor that improves recovery from this surgery. However, no clinical guidelines are currently available to inform the recovery pathways. This is because there is no evidence to suggest who may benefit from rehabilitation, when and where this service should be delivered, and what services should be provided. Consequently, some patients receive inpatient (7-10 days) rehabilitation or at home rehabilitation through exercise monitoring (up to 10 weeks), whereas others are not referred to any form of rehabilitation, depending on the surgeon and the clinic. This inconsistent approach to rehabilitation may be because of the general lack of data demonstrating the effectiveness of any specific pathway. For example, a recent study demonstrated no difference in patient mobility at 26 weeks after the surgery when comparing inpatient rehabilitation with home-based monitoring [8]. Furthermore, a systematic review concluded that the setting did not significantly influence the outcomes [9].

During rehabilitation programs, the primary emphasis is on assisting patients in regaining muscle strength, enhancing joint stability, improving range of motion, restoring neuromuscular function, and recovering proprioception [10]. The approaches taken and outcomes vary widely among therapists, and to date, no clear guidelines exist for the most effective therapeutic strategies to be applied [9]. In addition, several psychological factors have also been reported to be linked to recovery following knee replacement or have the potential to impact recovery [11,12]. This includes psychological "vulnerability factors," such as depression, anxiety [13-15], and pain catastrophizing [16,17], and "protective factors," including resilience and committed action. However, despite their potential impact on recovery, quality of life, and satisfaction [12], these factors are not routinely reviewed in patients before surgery and remain overlooked in rehabilitation referral and ongoing clinical decision-making.

Determining whether rehabilitation programs are effective is also complicated by the use of inconsistent measures of "success." Many studies to date have used a single traditional outcome measure, such as a physician's or patient's report of functional mobility, pain, or quality of life [18]. Although surgical success has been characterized by a number of objective medical outcomes, including survival, prosthesis performance, and revision rates [4], there has been increasing interest in considering and combining longer-term outcomes of success, such as patient satisfaction and social integration, with these other traditional measures. Over the last decade, the integration of patient-reported outcome measures (PROMs) in the evaluation of the success of TKA has become more widespread [19]. However, the impact of PROMs on clinical practices remains limited. Although there are clear benefits of assessing the patient's perspective of recovery, including their symptoms, functional status, and quality of life [20,21], there remains a lack of consensus regarding the appropriate measures to be used, together with concerns of the cost-effectiveness involved in their application [22].

Regardless of the adopted outcome definition, no consistent set of factors that predict a successful surgery outcome have been identified. Individual studies have identified some factors associated with long-term outcomes. These include BMI, radiological arthritis severity (Kellgren-Lawrence score), mood status (eg, anxiety and depression), quality of life, and functional

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mobility [18,23,24]. Nevertheless, it is important to note that the collective predictive value of these metrics has not been externally validated, nor has their generalizability been demonstrated across various settings and populations [25].

Mounting evidence suggests that it may be possible to predict, via the use of a model, which patients could benefit from a more multifaceted approach to rehabilitation, which could encompass a broad range of biopsychosocial parameters, and how this can be precisely tailored to address each patient's individual needs [26]. Importantly, if such a prediction model can be developed and validated, it would be extremely useful to guide the future provision of rehabilitation services to support superior outcomes for each patient. In a recent systematic review, we demonstrated that the number of clinically meaningful, well-validated prediction tools for recovery following total knee replacement is limited [26]. Several clinical and lifestyle factors have been linked to poor outcomes and dissatisfaction following a variety of surgical procedures, including TKA, such as female sex, obesity [27,28], lower social support level [29], and comorbidity status [15]. Indeed, predictive models have demonstrated that age and sex can predict improvement in knee function [30] and satisfaction [31]. However, few studies have reported the inclusion of psychological parameters in their model development. Moreover, many of the models developed have limited predictive success and lack external validation, which limits their implementation in routine clinical use. There are also constraints when predictive models repurpose existing data sets owing to the limitations of data quality and completeness [32].

To date, there is an unmet need for the development of a clinical tool based on a comprehensive range of parameters that can assist in determining individual recovery trajectories following TKA, which can be easily adopted in the clinical setting. Through the identification of factors influencing patient recovery trajectories across a range of success outcomes, rehabilitation pathways will be better informed regarding the tailoring of services to meet patients' individual needs. This has the potential to improve long-term outcomes and satisfaction by addressing a broader range of pre- and postoperative parameters.

Aims and Objectives

The major aim of this study is to develop a clinical tool that can be used in the prediction of recovery trajectories, which can inform rehabilitative services regarding the nature of potential interventions and the timely delivery of the right services to each individual patient. Our approach will be to look beyond the impact of biomedical features alone on patient outcomes by adopting a biopsychosocial approach. The biopsychosocial model of health systematically considers biological, psychological, and socioenvironmental factors and their complex interactions in understanding illness, health, and health care delivery. It encompasses a more holistic approach to understanding illness and wellness than a purely biological vision. The tool will be constructed by assessing the predictive capacity of a comprehensive battery of biopsychosocial factors on a number of patient outcomes following TKA, including improvements in knee symptomology, quality of life, and satisfaction. This approach has the potential to facilitate the allocation of rehabilitation resources toward a more holistic approach to recovery following surgery and could improve the effectiveness of TKA across a range of success outcomes, including patient satisfaction. By supporting the delivery of rehabilitative interventions that are precisely targeted to patient needs, this clinical decision-making tool could also improve the efficiency of health care resource delivery.

Methods

Study Setting

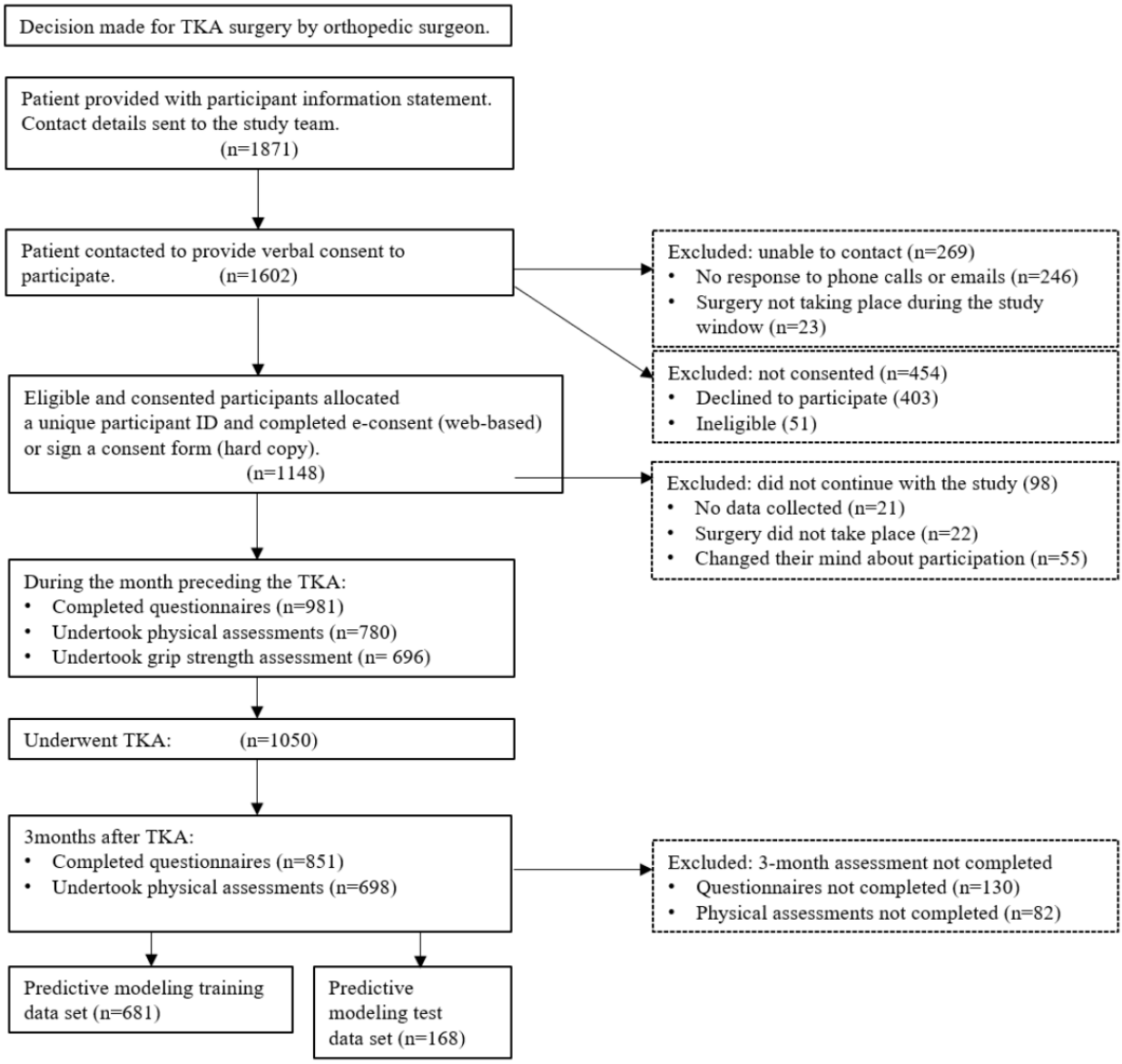
This study was undertaken with patients who underwent TKA surgery between November 2019 and June 2022 across 4 participating Ramsay Health Care facilities in New South Wales (NSW), Australia, including Lake Macquarie Private Hospital, Gateshead; Kareena Hospital, Caringbah; Baringa Hospital, Coffs Harbour; and Wollongong Private Hospital, Wollongong. Surgical procedures were performed by 11 collaborating orthopedic surgeons.

Study Design

This study had a prospective observational design. Participants were involved in the study for a duration of 4 months, with data collection taking place at 2 time points during this period: within the month preceding their scheduled TKA and 3 months (12 weeks) following the TKA procedure. Figure 1 outlines the participants' timeline for this study and the number of participants recruited and excluded at each stage.

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Figure 1. Participant timeline. TKA: total knee arthroplasty.



Study Population and Eligibility

All patients identified by the participating orthopedic surgeons as requiring a total knee replacement and who fulfilled the eligibility criteria were invited to participate in the study. Patients were included as eligible if they were aged ≥18 years, could complete the PROMs questionnaires, and confirmed to require a primary total knee replacement (bilateral or unilateral procedure). Patients were excluded from participating if they were receiving a primary total knee replacement owing to trauma, had undergone previous knee surgery within the past 6 months, were planning to undergo additional knee surgery within the next 12 months, or did not have the capacity to provide informed consent to the research.

Sample Size

For machine learning modeling, the standard required sample size used should ensure at least 10 events for each included predictor parameter [33]. In this study, we have a total of 39 input variables and 76 input events when applying the conversion of categorical variables to numerical data (one-hot-encoding). Applying the standard approach, we would require 390 participants for models without one-hot encoding and 760 participants when using one-hot encoding.

Recently, Riley et al [34] have developed a more refined calculation of the required sample size, which depends not only on the number of candidate predictor parameters but also on the total number of participants, the outcome proportion (incidence) in the study population, and the expected predictive performance of the model. Applying the method proposed by Riley et al [34] to our classification modeling with an aim of 90% accuracy and an outcome proportion of 20% (ie, 20% of participants were not expected to meet the minimal clinically important difference [MCID] improvement threshold), a predicted R^2 of 0.5, and shrinkage of 0.85, returns a required sample size of 864.

In this study, we aimed to recruit at least 1000 patients undergoing total knee replacement. This will ensure sufficient data for inclusion in our machine learning predictive modeling

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analyses and allow for 13.6% (136/1000) of data to be nonevaluable owing to missing data fields.

Recruitment and Enrollment Procedures

Eligible participants were contacted by the study team through a follow-up phone call made after they received the study Patient Information Sheet from their surgeon. Eligible participants who chose not to participate when they received the Patient Information Sheet from their surgeon were not contacted. If the participant verbally agreed to participate in the study, they were provided access to study materials either on the web or by post, and if they consented to undertaking physical assessments of mobility via a video call, a time for this appointment was made at a time convenient to the participant.

If patients opted to have their study questionnaires accessed via the study-specific web-based platform, they were provided with a copy of the Patient Information Sheet when they accessed this system via a participant-specific log-in. Following a review of the Patient Information Sheet, they were asked to acknowledge their consent to participate in the study and provide electronic consent on the Electronic Letter of Consent Form. Questionnaire templates were not accessible to the participants until the consent field on this form had been completed. Participants also had the option to consent to all study assessments being undertaken or to only complete the study questionnaires.

If patients opted to have their study questionnaires posted to them, a copy of the Patient Information Sheet and Letter of Consent were included in the posted package. The participants were asked to sign the consent form before completing the questionnaires. The completed consent form and questionnaires were subsequently posted back to the study team.

Participation in this study was voluntary. Patients had the option to decline participation at any time point during the study and were informed that this would not impact their ongoing medical care. If patients decided to withdraw from the study, they could specify whether their data were to be removed from the study or if they were willing for it to be used as part of the analysis.

Data Collection Tools and Procedures

Web-Based Data Collection Platform and Centralized Data Repository

Data were entered and stored on the secure electronic platform Vision Tree Optimal Care (VTOC) developed by VisionTree Software, Inc. This platform enables the direct entry of data by participants when completing study documents and serves as a centralized data repository. The addition of an e-consent form, as the first item viewed and completed by participants when accessing the study-specific platform, enabled consent to be obtained before the collection of study data. Participants accessed the site via a unique encrypted link sent to their email. Using the encrypted link, the participants also validated their identity by entering their initials on the platform.

The electronic site is 256-bit Secure Sockets Layer (SSL) encrypted to protect the privacy of the participants. The VTOC meets all Health Insurance Portability and Accountability act of 1996 security and compliance standards, which include physical, technical, and procedural safeguards to help protect personal information. Using Thawte as a third-party encryption service, all reminders or messaging are 256-bit SSL encrypted.

The participant log-in links are encrypted using Advanced Encryption Standard-256 encryption. The participant internal identification number, only known to the VTOC application, is included in the encrypted payload, thus ensuring that it is unique to the participant. Advanced Encryption Standard is a symmetrical-key algorithm, meaning the same key is used for both encrypting and decrypting the data.

The platform can be viewed by any modern browser, whether a tablet, mobile, or computer-based system. No data were housed on the device at any point; therefore, if a device gets lost, there was no exposure of any of the data within the platform or data being collected.

VisionTree's security technologies include an F5 Load Balancer and Cisco Firewall. Software technologies include 256-bit SSL, third-party verification, command line and basic virus scanning, audit logs, and secured biometric access to the data centers. The VTOC platform firewall was OSCI level 4 compliant.

Patient Deidentification and Study Code Allocation

Unique study code or ID numbers were automatically and randomly assigned to each participant within the VTOC. Reports were available from the system using deidentified data, that is, study code or ID numbers. Members of the study team involved in data management, processing, and analysis only have access to the data that have been deidentified. Identifiable data can be accessed by study team members who need to make direct contact with participants during study visits or for the entry of additional data.

Study Questionnaires

Overview

Consented participants were asked to complete the study questionnaires either on the web using the VTOC platform or on a posted hard copy. Questionnaires were disseminated for completion at 2 distinct time points: within 4 weeks before their scheduled TKA and at 3 months after their TKA. These questionnaires are validated self-report tools that are used to measure a variety of biopsychosocial parameters associated with recovery following TKA.

Biopsychosocial measures and self-report tools used to derive each measure and administration time points are shown in Table 1. Psychosocial variables were selected following a thorough literature review that was conducted to determine the types of constructs that had demonstrated associations with outcomes that were relevant to the outcomes of interest in this study. Many of the selected variables were supported by systematic review–level and meta-analytic–level evidence. In addition, because of the innovative nature of the proposed tool, we also wanted to explore the role of other factors that had good face validity with respect to their potential to enhance or hinder someone's behavioral engagement in rehabilitative activities or general restoration of functioning [12]. Measurement tools were selected based on their psychometric properties and length (shorter scales were selected where possible to reduce the strain on participants).

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Participants were also asked before their TKA if they had experienced any falls or unexpected weight loss within the last 12 months. In addition to measuring biopsychosocial parameters before surgery, participants were asked about their expectations about surgical outcomes, enabling them to perform specific activities, as well as their expectation of experiencing a reduction in knee pain.

Table 1. Biopsychosocial measures and administration time points.

Measure	Tools	Before TKA[a]	3 months after TKA
Knee symptomology	Western Ontario and McMaster University Osteoarthritis Index [35]	✓	✓
Mood status (depression, anxiety, and stress)	Depression Anxiety and Stress Scales-21 [36]	✓	✓
Pain catastrophizing	Pain Catastrophizing Scale [37]	✓	
Resilience	Brief Resilience Scale [38]	✓	
Committed action	Committed Action Questionnaire-8 [39]	✓	
Capacity to succeed in achieving goals	Valued Living Scale [40]		✓
Quality of life	Short Form-12 version 2 [41]	✓	✓
Social support	Medical Outcome Study Social Support Survey, 6 item [42]	✓	
Employment status	—[b]	✓	
Physical activity	University of California, Los Angeles Activity Scale [43]	✓	✓
Sleep quality	Extract from the Pittsburgh Sleep Quality Index [44]	✓	✓
Nutrition status	Starting the Conversation tool [45]	✓	
Alcohol consumption	The Alcohol Use Disorders Identification Test-Consumption [46]	✓	
Smoking behavior	—[b]	✓	✓
Concomitant medical conditions	Charlson Comorbidity Index [47]	✓	✓

[a]TKA: total knee arthroplasty.

[b]As reported by the participant.

Knee Symptomology

We implemented the Western Ontario and McMaster University Osteoarthritis Index (WOMAC) [35] to evaluate the level of knee function limitation, pain, and stiffness symptom severity. The WOMAC is a validated and widely used self-administered questionnaire [48] developed to provide a means of standardizing self-report health status and activities relevant to patients. It consists of 24 items: 5 relating to pain, 2 to stiffness, and 17 function items with ratings provided using a 5-point Likert scale. Lower scores are indicative of lesser symptoms, and higher scores are indicative of worse symptomology. The global score is the sum of the scores for all the items combined. In this study, participants were asked to complete the WOMAC before their TKA and at 3 months after their surgery.

Mood Status

The mood status of the study participants was assessed using the Depression Anxiety Stress Scales (DASS)–21 [36]. Higher scores are indicative of higher levels of depression, anxiety, and stress. All scores derived from the 21-point scale were multiplied by 2 to enable comparison with the full 42-point DASS and to determine clinical cut-offs for symptom severity. The full DASS and abbreviated DASS-21 have been validated to measure the 3 negative emotional states (ie, depression, anxiety, and stress) in research and clinical settings, but is not considered a diagnostic tool or a replacement for a comprehensive clinical interview [49]. Each of the DASS-21 subscales contains 7 items. The Depression scale assesses dysphoria, hopelessness, devaluation of life, self-deprecation, lack of interest or involvement, anhedonia, and inertia. The Anxiety scale assesses autonomic arousal, skeletal muscle effects, situational anxiety, and the subjective experience of anxious affect. The Stress scale is sensitive to levels of chronic nonspecific arousal. It assesses difficulty relaxing; nervous arousal; and being easily upset or agitated, irritable or overreactive, and impatient. Participants are asked to use a 4-point severity or frequency scales to rate the extent to which they have experienced each state over the past week. The scores for depression, anxiety, and stress are calculated by summing the scores for the relevant items. In this study, participants were asked to complete the DASS-21 before their TKA and at 3 months after their surgery.

Pain Catastrophizing

We used the Pain Catastrophizing Scale (PCS) [37] to measure the level of catastrophic thinking related to pain before TKA. PCS is one of the most widely used instruments for measuring pain catastrophizing and has been used extensively in clinical practice and research settings [50]. The self-report form consists of 13 items describing thoughts and feelings that patients may experience when they are in pain. Respondents provided ratings for each item on a 5-point Likert scale ranging from 0 (“not at all”) to 4 (“all the time”). Higher scores are associated with

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higher amounts of pain catastrophizing, with scores >30 associated with a high risk of chronic pain.

Resilience

We assessed participants' resilience before their TKA using the Brief Resilience Scale (BRS) [38]. This scale assesses an individual's ability to recover from stressful events (level of resilience), and has demonstrated relationships with positive postsurgical health, satisfaction, and pain outcomes [12]. The BRS contains 6 items, including 3 positively and 3 negatively worded statements (reverse scored). Respondents rated their responses using a 5-point Likert scale ranging from 0 ("strongly disagree") to 4 ("strongly agree") for each statement. Raw scores are calculated by summing the item scores and range from 6 to 30. The BRS-weighted score is calculated by dividing the summed item scores by the number of items and ranges from 0 to 5. Higher scores are indicative of greater resilience.

Committed Action

Committed action is a component of "psychological flexibility" and is defined as a person's capacity to flexibly engage in effective and adaptive behaviors, guided by personally held values, even in the presence of challenges and discomfort [39,51]. We assessed committed action in our study cohort before their TKA because of the role this psychological process has been shown to play in an individual's health outcomes and their management of pain [12]. We used a shortened form of the Committed Action Questionnaire-8 [39], which comprised 8 statements. Respondents rate the extent to which each item applies to them, ranging from 0 ("never true") to 6 ("always true"). The total scores are calculated by summing the item scores, with a maximum score of 48. Higher scores denote greater committed action.

Capacity to Succeed in Achieving Goals

The Valued Living Scale assesses a person's goal importance, success, and confidence with respect to 8 value domains [40]. The scale was used to assess a person's rating of the importance of each of the 8 goals, their confidence in achieving these goals, and their success in achieving them following TKA.

Quality of Life

To evaluate participants' quality of life before and after TKA, we used the Short Form-12 (SF-12, version 2) quality of life questionnaire [41]. This tool is a 12-item self-administered measure of general quality of life that is widely used and has been validated in an Australian population [52]. It is a shortened and modified version of the original 36-item form [53]. Scores are transformed to generate 2 weighted summary scores for physical health, PCS, and mental health, the Mental Component Scale. Scores range from 0 to 100, with higher scores indicating a better health state. In this study, the participants completed the SF-12 before their TKA and at 3 months after their TKA.

Social Support

The amount of social support available to patients has been reported to influence physical and mental well-being [54] as well as being a key determinant of the suitable location of postsurgical rehabilitation services (ie, inpatient vs community based). The level of social support that participants felt they had available to them before their TKA was assessed using the Medical Outcomes Study Social Support Survey, 6 item [42]. The survey captures information related to perceived psychological and material support derived from interpersonal relationships. Scores ranged from 6 to 30, with higher scores indicative of higher levels of perceived support.

Physical Activity

Recent activity levels of the participants were determined using the University of California, Los Angeles Activity Index, which was developed to assess activity levels in patients undergoing joint replacement [43]. Participants were asked to indicate which of the 10 activity levels provided best reflected their current level of activity. The activity levels included being inactive (1 and 2), undertaking mild activities (3 and 4), moderate activities (5 and 6), active events (7 and 8), and impact sports (9 and 10). Activity status was evaluated before the TKA and at 3 months after the TKA.

Sleep Quality

To assess sleep quality in our study cohort, we used the sleep quality question extracted from the Pittsburgh Sleep Quality Index [44]. Participants were asked to rate their current sleep quality on a Likert scale ranging from 1 ("very bad") to 4 ("very good") on 2 occasions: before their TKA and at 3 months after the TKA.

Nutrition Status

The dietary habits of participants before TKA were assessed using the Starting the Conversion Score [45]. The Starting the Conversion Score is a validated 8-point screening tool used to evaluate dietary habits. The participants rate the frequency of ingesting a range of 8 different food types over the past few months. The total scale ranges from 0 to 16, with higher scores associated with worse dietary habits.

Alcohol Consumption

Alcohol consumption before TKA was evaluated using a modified version of the Alcohol Use Disorders Identification Test [55] related to alcohol consumption only (Alcohol Use Disorders Identification Test-Consumption) [46]. Participants were asked 3 questions related to their average alcohol consumption over the last 12 months, with a maximum total scale score of 12. Total scores <5 indicated low-risk consumption and scores >5 indicated hazardous or harmful consumption.

Smoking Behavior

Before and 3 months after the TKA, we asked participants to indicate their smoking status. Smokers were asked to provide details regarding smoking frequency.

Concomitant Health Conditions

The Charlson Comorbidity Index provides a weighting to concomitant health conditions based on the nature of the condition and age of the individual and is used to predict 1-year mortality. The higher the score, the higher the mortality risk [56]. We applied the same 10 medical conditions and weightings used by Chaudry et al [47]. Participants were asked to indicate whether they experienced any of the 10 medical conditions provided before their TKA and at 3 months after TKA.

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Outcome Recovery Measures—3 Months After TKA

Table 1 shows the PROMs questionnaires completed by the participants 3 months after TKA and the parameters measured. Questionnaires related to knee symptomology (WOMAC), quality of life (SF-12), mood status (DASS-21), and lifestyle (physical activity, sleep, and smoking behavior) were also repeated at the 3 months post-TKA time point. This allowed us to evaluate changes or improvements in these factors at 3 months after TKA compared with levels measured before surgery. The primary outcome measure in our study is the improvement in quality of life 3 months after TKA (changes in SF12 physical and mental health scores).

Secondary outcome measures include knee symptomology (changes in WOMAC scores), satisfaction with the surgery, and mood status (changes in DASS-21 scores) 3 months after TKA.

We also asked questions related to satisfaction in achieving specific activities, the level of knee pain reduction, and overall satisfaction with the surgery. Information related to the type of rehabilitation they undertook and health care services used following their surgery were also collected.

Study Participation Evaluation Survey

A study participation evaluation survey was included to enable the participants to provide the research team with feedback regarding the assessments they were asked to undertake and the overall conduct of the study. It also allowed the study cohort to share their suggestions for future research areas they considered important to be addressed in the recovery from TKA surgery. The results from this survey will inform our team's future research endeavors in similar cohorts.

Physical Assessments

Overview

When participants were contacted by phone regarding their potential involvement in the study, they were also asked if they consented to undertake 2 physical tests in their home, taking 15 minutes, that enabled measurements of their mobility, balance, and strength. These assessments were undertaken via a video call between the participants in their home and a member of the study team in their office. To participate in these calls, the participant needed to have the following:

- Sufficient internet access and a mobile phone, tablet device, or computer with a movable camera
- Someone to be at home with them during the call, to assist with holding the device during the call and be there for safety support if the participant stumbles or falls during the assessments
- A dining chair or a similar chair with a firm seat and arm rests to perform assessments
- A 4-m length floor space with uniform flooring and no trip hazards to perform assessments

Physical assessments were conducted on 2 occasions during the study, within 2 weeks before their scheduled TKA and at 3 months after the TKA.

In our original protocol, we planned to conduct face-to-face physical assessments with participants at each of the 4 study sites. As these activities were restricted by the COVID-19 pandemic, we adopted the approach to undertake these measures via video calls with participants in their home. This approach enabled these assessments to be performed despite social distancing regulations being implemented at the time of the study. It also enabled the study to be managed from a central location and still involve participants located across a large geographical range.

The physical measures applied in this study were selected following a thorough literature review that was conducted to determine the types of assessments used to assess joint function, mobility, and knee; were extensively validated; and were used to assess improvements or changes associated with total knee replacement surgery. As these assessments needed to be undertaken via video calls between participants and study staff, they also needed to have the capacity to be accurately measured without supervision by a physiotherapist and, if possible, not require specialized equipment.

Timed Up and Go Test

The Timed Up and Go test is a simple, reliable, and valid test of functional mobility that can be used to monitor clinical changes over time [57]. It enabled an evaluation of the participants' capacity to engage in simple daily activities involving walking and getting up from a chair. We performed the Timed Up and Go test before the TKA and at 3 months after the TKA. On each occasion, the test was performed twice, with the fastest time for each individual to get up from a chair, walk to a 3-m mark, turn around, and come back and sit down recorded. Therefore, the shorter the time taken to perform the test, the better the performance.

30-Second Sit-to-Stand Test

The 30-second Sit-to-Stand (30 s-STS) test is a reliable and valid measure of lower extremity strength [58]. We performed the Sit-to-Stand test on 2 occasions, before the TKA and 3 months after the TKA. On each occasion, the total number of completed chair stands achieved over a 30-second period was recorded. A larger number of stands is indicative of better performance. The test is a general measure of the strength and endurance of a person's legs and is sensitive to change when a person's knee pain and function changes.

Presurgery Hand Grip Strength Assessment

Hand grip strength measures the maximum amount of static force that a person can apply by their hand while gripping a handheld dynamometer. It is a reliable proxy for overall strength and is related to the risk of frailty, falls, functional capacity, morbidity, and mortality [59,60]. Hand grip strength was assessed before the surgery. As this assessment requires the use of a calibrated dynamometer (Jamar Plus+ Hand Dynamometer, Jamar Diagnostics), a device was provided to each study site. The hospital site staff received training from a member of the research team before the start of the study to conduct these assessments.

Demographic and Clinical Information

To reduce the data collection strain on study participants, we extracted demographic data from patient hospital records at

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each study site. In addition, medical data related to knee pathology diagnosis and medications were also collected from the hospital records. The scope of additional patient data used in this study is shown in Textbox 1.

Textbox 1. Demographic and medical data derived from patient hospital records.

Demographic and lifestyle behavior

- Age at the time of surgery
- Sex
- Nationality
- Suburb or postcode (rurality)
- Working status

Medical

- BMI
- American Society of Anesthesiologists score
- Surgery type (unilateral or simultaneous bilateral)
- Diagnosis
- Concomitant medications (were >5 different medications taken before surgery? What type of medications were taken before surgery?)
- Anesthetic and analgesic agents
- Length of hospital stay

Data Analysis

Overview

For prediction modeling, we are interested in whether a combination of presurgery measures can predict the change in physical (WOMAC subscores) and quality of life (SF-12 subscores) for participants at 3 months after surgery. Both the absolute improvement and whether a patient reported an MCID in improvement between the preoperative and postoperative stages will be predicted, requiring the implementation of regression and classification prediction models, respectively. The distribution-based MCID for each outcome measure will be determined according to the method outlined by Carender et al [61]. Every measure conducted before the surgery, including those from PROMs, physical measures, and medical records, will be considered as potential inputs (predictors) for the model. The data will be divided into 2 sets: a training set, consisting of 80% (840/1050) of the cohort chosen at random, and a test set, consisting of the remaining 20% (210/1050) of the cohort.

Data Cleaning

Although the web-based forms required each question set to be answered completely before the next was commenced, some participants used paper-based forms, and questions may have been missed. Moreover, some participants were unable to attend the video calls for the measurement of physical parameters, and in some cases, their medical records were incomplete. Any inputs with low variance or with >30% missing data will be discarded from the analysis. To deal with missing information in the remaining inputs, we will use multiple imputation, whereby missing measurements are replaced with the population mean (or the population mode for categorical measures). Imputation will be conducted independently on the training set without reference to the test set.

Models

We will consider standard linear models for prediction (ie, multivariable linear regression) with and without regularization and will also consider nonlinear models (decision trees, random forest, gradient boosting, neural networks, and Bayesian soft decision trees). Models will be trained both with and without one-hot encoding for the categorical variables.

Training

Models will be trained using 5-fold cross validation on the training set. The metric used to select the best classification model will be accuracy (ie, the percentage of patients classified correctly).

For each model, we will use a grid search for hyperparameter optimization. For example, a decision tree model will be trained for a range of depths and a range of minimum number of samples required at the leaf nodes, and the combination that returns the best model will be the chosen hyperparameters. We will also consider the subset of inputs used to train a model as a hyperparameter and will use exhaustive search to find the best input subset (ie, to find the best model that uses only 7 predictors; every possible combination of the 7 predictors will be tested). This avoids training a model using a “greedy” algorithm, which is not guaranteed to find the best combination of inputs.

Validation

The performance results of the chosen models will be validated on the test set containing the remaining 20% (210/1050) of the cohort. The root mean square error, R^2, and error rate will be reported on the training set, and plots showing the predicted

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versus measured outputs will be included in the supplementary materials in future papers. Where the model type allows it, we will also report CIs for the parameters and predictions.

We will then apply a common post hoc method to establish if the sample size is sufficient for the reported error rate for each model as follows: taking an increasingly large subset of the data, we will train the model, calculate the error, and plot the error as a function of the number of observations in the subsample. Fitting a power law curve, will establish an estimate of the sufficient sample size. Where the model type allows it, we will also report CIs for the parameters and predictions.

All machine learning methods will be conducted using the Python programming language. The *pandas* and *numpy* packages will be used for data cleaning, with the *scikit-learn* package used for training with standard machine learning models and techniques, and custom Python code will be used for training the Bayesian soft decision trees.

Ethics Approval

This research methodology was peer-reviewed and approved by the School of Medicine and Public Health at the University of Newcastle, NSW, Australia, in accordance with the Australian Code for the Responsible Conduct of Research. This study was conducted in accordance with the National Statement on Ethical Conduction in Human Research (2007). Ethics approval was granted by the University of Newcastle Human Research Ethics Committee (approval H-2019-0109) on June 21, 2019. Approval for each study site's participation was reviewed and approved by the Ramsay Research and Governance Office in NSW, Australia (RHC RG-2019.008).

Results

This study was funded by the Ramsay Hospital Research Foundation in September 2018. Recruitment for this study occurred between November 2019 and June 2022. Data collection was completed in September 2022. The study results will be available within 12 months of the final data collection on completion of the machine learning data processing of the predictive models (ie, final results are expected by September 2023).

During the recruitment phase, 1871 individuals requiring TKA were identified by the collaborating orthopedic surgeons across all 4 study sites, with a total of 1050 eligible, consented patients undertaking at least 1 of the pre-TKA study assessments in the study cohort (Figure 1). Participants for whom a complete data set was collected (ie, responses to all study questionnaires at both time points) were included in the machine learning data processing for predictive model development (n=851). Participants were randomly allocated for analysis into 2 groups, such that 80% (681/851) were included in the model training data set and 20% (170/851) were included in the model test data set.

Discussion

Expected Findings

This study responds to an unmet clinical need to address factors that can improve outcomes in patients undergoing total knee replacement. With a substantial increase in the number of TKA procedures expected to take place over the next decade, there is the potential for a significant number of patients to be dissatisfied with their surgical outcomes, unless the issue can be effectively addressed.

We anticipate the development of a clinical predictive tool that has the potential to improve patient-centered TKA outcomes. The uniqueness of the model being used is the inclusion of a comprehensive assessment of modifiable psychological, resilience, and clinical factors that have been linked to TKA recovery outcomes.

Comparisons With Prior Work

The approach adopted in this protocol builds on existing research demonstrating the involvement of factors influencing recovery of patients following total knee replacement and the inclusion of these factors in predictive modeling of postsurgery outcomes. We are unaware of any published predictive models of patient outcomes following TKA that include such a comprehensive battery of biopsychosocial parameters as those being evaluated in our study protocol. Our systematic review of predictive models for TKA outcomes [26] and those undertaken by others [32] revealed that the most consistently used presurgical parameters included clinical and medical factors such as age, sex, BMI, and concomitant health conditions, whereas psychological factors were incorporated to a lesser extent and, when applied, were restricted to measures of mood status (depression and anxiety) or mental health quality of life. There have been several specific modifiable psychological factors, including pain catastrophizing [18,62] and resilience [63], which have been associated with recovery following TKA and could inform the optimization of patient outcomes. However, their predictive capacity for patient outcomes after TKA has not been widely explored.

Previous limitations of predictive models are associated with using data derived from existing registries or retrospectively collected data sources [26]. Such approaches can be problematic because of the need for data imputation caused by missing values or limitations in predicting specific outcomes owing to insufficient presurgery variables collected. The prospective collection of specific variables of interest, as we propose in this study, enables the collection of specific input data that have been associated with specific outcomes. This approach has the potential to inform appropriate rehabilitation interventions to improve patient outcomes.

Potential Impact and Clinical Implementation

If successful, this project will provide a tool that can help guide health professionals with respect to comprehensive rehabilitation decisions individualized to each patient. The tool will underpin and support the identification of biopsychosocial risk factors for poor postoperative holistic outcomes and facilitate the development of biopsychosocial prehabilitative and

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rehabilitative interventions, which could lead to improved overall outcomes. In addition, the tool will enable efficient patient stratification according to identified individual needs, which allows a vastly more targeted service provision, maximizing the potential for impact. Currently, patients are infrequently evaluated using formal, standardized assessments for the type of rehabilitative service they would most likely need and benefit from. This project will provide a means of stratification of patients in a clinical setting, identification of "at risk" individuals early in their recovery journey, and support appropriate follow-up services to be implemented.

The scope of the factors influencing decision-making will be evolved. Typically, when patient information is collected, it generally focuses on selected medical or targeted joint parameters [64] and does not take consider parameters such as patient anxiety, stress resilience, quality of pain, social support, and sense of purpose, all of which have recently been shown to be associated with patient outcomes [12]. The model used in this study will explore the influence of these additional parameters on recovery and well-being following TKA, thereby providing evidence for a more comprehensive therapeutic strategy.

Strengths and Limitations

In this study, we are collecting data prospectively, which enables the scope of features that may impact patient outcomes to be extended beyond that routinely collected in existing data sets and provide a focus on the biopsychosocial parameters of interest. The development of a clinical decision tool that is focused on a broader scope of patient features affords the opportunity for a more holistic approach to be taken in rehabilitation programs that extend beyond physical recovery strategies alone. The design of the study has attempted to reduce surgeon and hospital bias by including patients who underwent TKA by 11 different orthopedic surgeons across 4 different hospitals. These facilities were located across a large geographical range and enabled the inclusion of participants residing in metropolitan and rural communities to take part in the study. This was further enhanced by the capacity to collect data on the web and via video calls, which enabled the study to be managed at a central location and include participants across a large geographical area.

Although the planned study will evaluate the predictive capacity of a comprehensive battery of biopsychosocial parameters on TKA patient outcomes and offer significant contributions to the existing literature, there are potential limitations. In this study, we are assessing the predictive capacity of presurgical parameters on recovery outcomes assessed at 3 months after TKA. This may be considered early on in a patient's recovery journey. It has been demonstrated that the maximal changes in patient-reported knee symptomology occur rapidly within the first 3 months, with subsequent improvements continuing, albeit at a slower rate, up to 12 months after surgery [65,66]. It is possible that the impact of psychological factors on patient outcomes may differ at later time points, as patients' circumstances and needs change, and as such, predictive modeling developed in this study may be limited to early recovery outcomes.

We recognize that our study protocol does not encompass all factors that could potentially influence outcomes after TKA. Our analyses do not include surgical factors known to impact outcomes, including factors such as the surgeon or hospital, prosthesis type, and surgical procedures [67], and radiological factors, such as the Kellgren-Lawrence score [23]. Therefore, it is important to note that our predictive models are unlikely to account for 100% of the variability in patient outcomes that we observe. Instead, they will provide insight into the extent to which the presurgical biopsychosocial factors assessed in our model contribute to the observed variance.

Future Directions and Concluding Comments

As per the data analysis plan for this study, a rigorous internal validation of the predictive models generated will be performed. Ongoing external validation of the models will also enable the suitability and specificity of the findings to be applied to a wider clinical setting than that included in this study. In addition, through future engagement with key stakeholders, including clinical care teams (surgical and rehabilitation specialists), health care providers, and patient advocates, we will develop the predictive models to optimize their clinical implementation and usefulness.

The classification models proposed will facilitate the evaluation of intervention studies, whereby biopsychosocial risk factors are identified, targeted interventions are provided, and the benefits to postoperative outcomes are evaluated. This will enable the determination of whether targeting these factors in an individualized manner leads to improved satisfaction and PROMs.

In conclusion, the findings of this study will contribute to the development of a comprehensive biopsychosocial clinical decision–predictive tool. Such a tool will have the potential to inform clinical care teams regarding individual patient outcomes, enable the stratification of potentially "at risk" individuals, and inform the evolution of rehabilitation services through the identification of potential interventions, all of which could lead to an improvement in patient outcomes and satisfaction following TKA.

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Authors' Contributions

KR and SJ wrote the manuscript. All authors provided input for the study protocol design and reviewed the manuscript. SJ, AW, and JC provided insight into the machine learning and data processing for the protocol; ED provided consultation regarding psychological outcomes; TF provided insights regarding protocol design and assessments to be undertaken; GM provided guidance on the application of physical measures; and FRW, MP, and MN provided guidance on the scope and clinical aspects of the protocol. MN is overseeing the project.

Conflicts of Interest

None declared.

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Abbreviations

BRS: Brief Resilience Scale
DASS: Depression Anxiety Stress Scales
MCID: minimal clinically important difference
NSW: New South Wales
PCS: Pain Catastrophizing Scale
PROM: patient-reported outcome measure
SF-12: Short Form-12
SSL: Secure Sockets Layer
TKA: total knee arthroplasty
VTOC: Vision Tree Optimal Care
WOMAC: Western Ontario and McMaster University Osteoarthritis Index

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Protocol

Delivery of the HIV Service and Telemedicine Through Effective Patient-Reported Outcomes (+STEP) Intervention to Increase Screening and Treatment of Mental Health and Substance Use Disorders for People Living With HIV in Alabama: Protocol for an Effectiveness-Implementation Study

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Abstract

Background: The syndemic of mental health (MH) and substance use disorders (SUDs) is common among persons living with HIV and jeopardizes HIV treatment adherence, engagement in care, and viral load suppression. Electronic patient-reported outcomes (ePROs), completed through tablet or computer, and telemedicine are evidence- and technology-based interventions that have been used to successfully increase screening and treatment, respectively, a model that holds promise for persons living with HIV. To date, there is limited guidance on implementing ePROs and telemedicine into HIV clinical practice even though it is well known that these evidence-based tools improve diagnosis and access to care.

Objective: To address this, we aim to conduct a multicomponent intervention for persons living with HIV, including the delivery of HIV services and telemedicine through effective ePROs (+STEP), to increase screening and treatment of MH and SUD in Ryan White HIV/AIDS Program (RWHAP)–funded clinics in Alabama.

Methods: Through this intervention, we will conduct a readiness, acceptability, and accessibility assessment and implement +STEP to improve the diagnosis and treatment of MH and SUD at RWHAP clinics in Alabama. To describe implementation strategies that address barriers to the uptake of +STEP in RWHAP clinics, we will conduct qualitative interviews in years 1 (early implementation), 2 (scale up), and 4 (maintenance) with patients and key staff to evaluate barriers, facilitators, and implementation strategies. Our Results will enable us to modify strategies to enhance +STEP penetration over time and inform the implementation blueprint, which we will develop for both RWHAP clinics in Alabama and future sites. We will assess the impact of implementing

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+STEP on diagnoses, referrals, and health care use related to MH, SUD, and HIV by comparing clinical outcomes from patients receiving these interventions (ePROs and telemedicine) with historical controls.

Results: The first study site began implementation in April 2022. A total of 2 additional sites have initiated ePROs. Final results are expected in 2026. The results of this study will provide a foundation for future research expanding access to ePROs for improved diagnosis linked to telemedicine access to accelerate patients along the continuum of care from MH and SUD diagnosis to treatment.

Conclusions: Achieving the end of the HIV epidemic in the United States necessitates programs that accelerate movement across the MH and SUD care continuum from diagnosis to treatment for persons living with HIV. Scaling these services represents a path toward improved treatment outcomes with both individual health and population-level prevention benefits of sustained HIV viral suppression in the era of undetectable=untransmittable (U=U). This study will address this evidence gap through the evaluation of the implementation of +STEP to establish the necessary systems and processes to screen, identify, and better treat substance use and MH for people living with HIV.

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KEYWORDS

clinics; diagnosis; engagement; HIV; implementation science; intervention; interview; mental health; patient reported outcomes; protocol; screening; substance use; telemedicine; treatment; USA; viral

Introduction

Almost 10 million people in the United States are estimated to have both substance use and mental health (MH) disorders [1]. In Alabama, the burden of MH is higher than the national average with nearly 1 in 4 people meeting criteria for any depressive disorder compared to the national average of under 20% [2]. Additionally, approximately 8% of Alabama residents are diagnosed with a substance use disorder (SUD) each year [3]. The syndemic of MH and SUDs is common among persons living with HIV, with estimated prevalence rates of 39% and 48%, respectively [4,5]. This syndemic jeopardizes HIV treatment adherence, engagement in care, and viral load (VL) suppression [6]. Specifically, MH and SUD are associated with reduced antiretroviral treatment (ART) adherence, high viral load levels, and increased mortality [7,8]. persons living with HIV with MH and SUD may be reluctant to report these conditions due to stigma, medical mistrust, or social desirability bias, but diagnosis is an essential first step toward management of these comorbidities [6,9]. Following diagnosis, improving access to MH and SUD treatment has the potential to reduce HIV transmission risks by fostering sustained viral suppression.

Treating MH conditions and reducing drug use improves ART adherence and VL suppression [10-12]. Thus, MH and SUD should be monitored often and addressed rapidly, a process facilitated by real-time electronic patient reported outcome (ePRO) data. A recent Cochrane review of 116 randomized control trials demonstrated that ePROs are a successful mechanism to improve patient-provider communication, diagnosis, and disease control [13]. While there is currently insufficient evidence that ePROs improve distal clinical outcomes, research shows ePROs can improve the process of care by collecting information directly from patients, minimizing potential for judgment and social desirability bias [14-16]. ePROs completed on a laptop or tablet using validated tools, such as the Patient Health Questionnaire-9 (PHQ-9), are replicable and provide longitudinal monitoring of the overall health of persons living with HIV [6,17-19]. This evidence-based screening mechanism enables clinics to respond with individualized counseling and education, allowing resource-limited clinics to prioritize scarce resources to those with active psychosocial barriers that may impair ART adherence and VL suppression.

Alabama is 1 of 7 states with the greatest rural HIV burden nationally, and the rural, resource-limited region poses additional barriers in treating psychosocial comorbidities in persons living with HIV. Challenges include a lack of providers, especially MH and addiction treatment providers, long commutes across rural settings to clinics, and a lack of public transportation. Lack of Medicaid expansion substantially widens this treatment gap [9,20-22]. Telemedicine offers an opportunity to overcome barriers to treatment in southern and rural states, such as lack of transportation, time away from work and childcare, costs, and stigma [22,23].

There is a need for programs that improve and accelerate the diagnosis and management of MH and SUD among persons living with HIV and promote the individual health and population level prevention benefits of sustained HIV viral suppression in the era of undetectable=untransmittable (U=U). ePROs, completed through tablet or computer, and telemedicine are evidence- and technology-based interventions that have been used to successfully increase screening and treatment, respectively, a model that holds promise for persons living with HIV [24,25]. To date, there has been a lack of consensus in the field on the implementation of ePROs, with specifically limited guidance on how to implement ePROs and telemedicine into HIV clinical practice. A majority of existing implementation recommendations are for integration into clinical practice generally and are not specific to HIV settings [14,26-28]. Additionally, implementation studies to date were not based in the Deep South, where at-risk populations face unique barriers to MH, SUD, and HIV care [14,26-29]. Given that ePROs improve diagnosis and access to care, additional recommendations specific to the integration of ePROs into clinical HIV settings are necessary to improve the

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implementation and dissemination of this evidence-based tool to address the HIV epidemic [6,30]. To address limited guidance specific to HIV clinical settings, we are conducting a multicomponent intervention for persons living with HIV, delivery of HIV services, and telemedicine through effective ePROs (+STEP), to increase screening and treatment of MH and SUD in Ryan White HIV/AIDS Program (RWHAP)-funded clinics in Alabama. The aims of this study are the following:

- Aim 1: to conduct readiness, acceptability, and accessibility assessments through qualitative interviews and a quantitative survey followed by the implementation of +STEP to improve the diagnosis and treatment of MH and SUD at RWHAP clinics in Alabama.
- Aim 2: to describe implementation strategies that address barriers to uptake of +STEP in RWHAP clinics. We will conduct qualitative interviews in years 1 (early implementation), 2 (scale up), and 4 (maintenance) with patients and key staff to evaluate barriers, facilitators, and implementation strategies. Results will enable us to modify strategies to enhance +STEP penetration over time and inform the implementation blueprint, which we will develop for both RWHAP clinics in Alabama and future sites.
- Aim 3: to measure the impact of implementing +STEP on diagnoses, referrals, and health care use related to MH, SUD, and HIV by comparing clinical outcomes from patients receiving these interventions (ePROs and telemedicine) with historical controls. We will complete a quantitative assessment of clinic-level diagnoses (MH and SUD) and patient-level indicators (screening, reporting, and treatment for MH and SUDs) relative to historical RWHAP reports using segmental regression (previous 3 years).

This will be the first study to evaluate integrated implementation of 2 effective evidence-based technologies—ePROs and telemedicine—in serving people living with HIV in Alabama. The results of this study will provide a foundation for future research expanding access to ePROs for improved diagnosis linked to telemedicine access to accelerate patients along the continuum of care from MH and SUD diagnosis to treatment.

Methods

Setting

+STEP is being implemented in RWHAP-funded clinics in Alabama. RWHAP-funded clinics provide medical care, medications, and essential support services to low-income persons living with HIV. In addition to providing essential care to persons living with HIV, these clinics aim to improve HIV-related health outcomes and reduce HIV transmission in their local communities [31]. Of the 9 RWHAP-funded clinics in Alabama, a total of 5 have agreed to participate in the study.

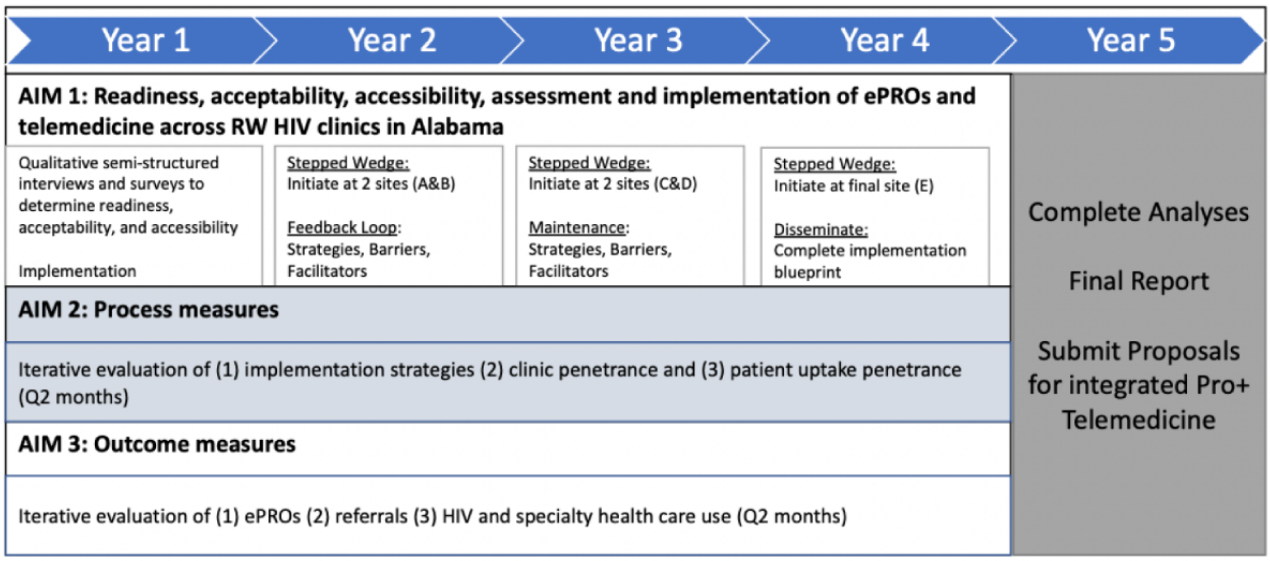
Study Design

We will conduct a stepped-wedge hybrid implementation-effectiveness type 1-design study, allowing the testing of implementation strategies while simultaneously evaluating the impact of the intervention on clinical outcomes of +STEP. Key staff from the participating sites, including clinic leadership, patient representatives, and clinicians (social workers, nurses), will participate in clinic-level trainings and assessments. Each site will identify key staff and patients who will be invited to join the advisory board. Implementation outcomes will be assessed using Proctor's Implementation Framework [32].

For aim 1, we will conduct qualitative, semi-structured interviews and surveys with key staff to assess organizational readiness and existing protocols. Specifically, interviews will explore each clinic's current resources and protocols, team structure, screening procedures, and barriers to telehealth. Surveys will measure organizational readiness. We will also survey patients with personal MH or SUD experiences to determine the accessibility and acceptability of ePROs and telehealth. We will then implement a multicomponent intervention with ePROs, targeted training to frontline providers, and telemedicine. We will assess fidelity and process measures, including clinic adoption and patient participation, as part of routine care in community-based RWHAP clinics. For aim 2, we will use the Consolidated Framework for Implementation Research (CFIR) to conduct a qualitative evaluation of implementation strategies, barriers, and facilitators to +STEP uptake. [33] Thus, Aim 2 will allow us to develop and refine an implementation blueprint. For Aim 3, we will evaluate the intervention impact on patient and clinic outcomes using patient-reported data (eg, MH, ART adherence), use of services (ie, clinical encounters and telemedicine), and retention in care, a proximal measure of VL suppression. A timeline for implementation of this study can be found in Figure 1.

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Figure 1. Study timeline of specific aims. ePRO: electronic patient reported outcome; RW: Ryan White; Q: quarter.



Intervention

+STEP will combine 3 components in a novel, multicomponent intervention**:** ePROs, targeted knowledge to frontline providers and staff, and telemedicine services for the management of MH and SUD. The intervention will include ePRO surveys adapted at the clinic level based on the results of the readiness, acceptability, and accessibility assessments. The ePROs will include validated surveys of MH and SUD, and final instruments will be selected following key staff meetings in order to ensure that they meet the needs and preferences of sites. Key staff from the participating sites, including clinic leadership, patient representatives, and clinicians (social workers, nurses), will participate in clinic-level trainings and assessments. The intervention will also include ongoing targeted trainings for frontline staff emphasizing the importance of diagnosis and evidence-based treatment of MH and SUD [30,34]. We will educate participants on the role of stigma and language as barriers to MH and SUD treatment [35]. With input from clinic-level key staff, we will design training on how to respond to ePRO results, including evidence of MH and suicidal ideation, according to clinic-specific policies and procedures. Telemedicine from the University of Alabama at Birmingham (UAB) eMedicine Center allows persons living with HIV to leverage UAB's telemedicine experience and infrastructure in 55 out of 57 counties across Alabama. Patients referred to telemedicine will have access to a central contact at UAB's eMedicine Center who will arrange an appointment at the closest referral site.

Implementation strategies: we will identify and train a +STEP champion at each clinical site who will receive additional hands-on training on the +STEP protocols, technology, and troubleshooting [36]. Implementation champions are an established implementation strategy to influence and facilitate change within their organization [37]. +STEP champions will be identified at each site before implementation and join regular meetings with the +STEP research team to discuss ongoing challenges and successes. Additional implementation strategies to improve implementation will be identified and used during the evaluation of +STEP implementation and as additional sites initiate the intervention.

Study Population

Participants include staff at RWHAP-funded clinics in Alabama and the persons living with HIV receiving care at these clinics. All adult (18 years of age or older) patients will be included in the analysis regardless of race, ethnicity, insurance status, and time in HIV care based on HIV clinic use.

Recruitment

Aim 1

Clinics will identify a convenience sample of 5 staff members to participate in qualitative interviews and complete surveys at each of the 5 sites. The interviewed staff will include key staff such as the nursing supervisor, physicians, social workers, and administrators. At the conclusion of the interviews, staff participants will be sent a Qualtrics Software (Provo) survey to complete. Additionally, 5 patients, identified by key staff for their experience with MH and SUD, from each clinic will be recruited to complete an anonymous survey through Qualtrics.

Aim 2

We will work with each of the clinics to identify 3 patients and 5 key staff members in years 2, 3, and 5 of the study for individual interviews (45 patients and 75 key staff participants will be selected using purposive sampling with maximum variation to ensure diversity in perspectives. We expect representation of persons living with HIV of different races, ages, duration of engagement in HIV clinical care, education level, socioeconomic status, and insurance status. Unique patients and staff will be selected at each time point. Recruitment for each participant group will take place at each time point (years 1-4) until thematic saturation is reached.

Aim 3

Patients will be recruited to +STEP by their clinic staff. Participating patients will complete ePROs at least once per year. Their ePRO records and historical clinical data will be used for both process and clinical outcomes. The target sample

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size for is 4000 participants across sites, which would allow us to detect for an odds ratio of 1.29.

Data Sources

For aim 1 of this study, we will collect data using a patient telephone survey, a staff survey, and qualitative interviews with key staff to understand current capacity and infrastructure to inform implementation. The patient survey measured the acceptability and accessibility of ePROs and telehealth services. The key staff survey included the organizational readiness to implement change instrument to determine perceived institutional readiness [38]. Interviews with key staff explored technological capacity and organizational readiness for change using the CFIR. Additional methodological details for aim 1 have been published in BMC Health Services Research [39]. The Implementation data will be abstracted from scheduling logs, training logs, and the electronic medical record (EMR) at each clinic site every 2 months to characterize the clinic and patient adoption and penetration of +STEP. We will supplement these reports with manual chart abstraction if needed to understand any gaps in the data. For aim 2, patients and staff who meet eligibility criteria will be invited to participate in an hour-long qualitative interview. All interviews will be designed to elucidate (1) perceptions of implementation strategies and (2) anticipated and observed barriers and facilitators to +STEP delivery. These data will be used to refine implementation over time. Research staff with expertise in qualitative research and program evaluation will lead in-depth interviews using standardized interview guides. Interview guides will elucidate contextual factors and will be informed by constructs from the 5 domains of CFIR, predominantly intervention characteristics and the inner setting domains, and the associated implementation strategies designed to target those factors. These factors may influence clinics' ability to implement and sustain +STEP and ultimately improve outcomes. In addition, the interviews will evaluate the acceptability of +STEP, a key component of Proctor's Implementation Framework [32]. For aim 3, clinical data will be extracted from the EMR, scheduling data, and training logs. Historical controls will be the percentage of MH and SUD diagnoses among patients and will be collected at the start of the study. We will extract ePROs, referrals for clinical encounters, visits attended and missed, and other HIV care continuum outcomes (eg, VL). We will quantify the proportion of participants with ePROs indicative of MH and SUD, and suboptimal ART adherence. We will quantify the number and proportion of clinical encounters scheduled and attended related to HIV, MH, substance use, social services, case management, and telemedicine visits.

Outcomes

Targeted outcomes for this study are outlined in Table 1.

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Table 1. Outcomes including units, evaluation metrics, data source, and timing for aim 1, 2, and 3.

Outcome, concept, and unit	Evaluation metrics	Data source	Timing
Aim 1			
Outcome: readiness, acceptability, and accessibility			
Concept: organizational readiness			
Unit: key staff			
	Interviews to understand capacity and infrastructure	Interviews with key staff	Preimplementation
	Survey of organizational readiness to implement change instrument	Key staff survey	Preimplementation
Concept: acceptability and accessibility			
Unit: patients			
	Survey of acceptability and accessibility of ePROs[a] and telehealth services	Patient survey	Preimplementation
Outcome: fidelity			
Concept: degree to which an intervention is delivered as intended			
Unit: clinics			
	Review of use of intervention and implementation strategies	Implementation team	Every 2 months
Unit: patients			
	Use of implementation strategies, consistency of ePROs, telemedicine uptake	EMR[b] and ePRO data, scheduling data	Quarterly as part of reports
Outcome: process			
Concept: clinic penetration			
Unit: clinics			
	Percentage of staff taking CME[c] training, percentage of ePROs delivered and percentage generating response, number of referrals to services, number of telemedicine referrals	Implementation team, EMR, ePRO scheduling data	Every 2 months
Concept: patient penetration			
Unit: patients			
	Percentage of patients enrolled; percentage completing ≥1 ePRO report; average number of PROs completed per patient; number of MH[d], SUD[e], or telemedicine visits	EMR, ePRO, scheduling data	Quarterly as part of reports
Aim 2			
Outcome: implementation			
Concept: facilitators, barriers, and perception of implementation strategies			
Unit: patients and staff			
	Patient and staff perspective of implementation, as framed by CFIR[f]	Patient and staff interviews	Annually
Aim 3			

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Outcome, concept, and unit	Evaluation metrics	Data source	Timing
Outcome: ePROs			
Concept: MH and substance use			
Unit: patients			
	Percentage of patients reporting MH, alcohol and illicit drug use, including OUD[g]; low ART[h] adherence	ePRO data	Every 6 months
Concept: ART adherence			
Unit: patients			
	Association between ePRO, intervention, and ART adherence	ePRO data	Every 6 months
Outcome: referrals for services			
Concept: counseling, psychiatry, addiction medicine, and rehabilitation			
Unit: patients			
	Referrals to specialty care	Training logs, EMR and scheduling data	Every 6 months
Outcome: use of services			
Concept: counseling, social work, MH, and addiction services			
Unit: patients			
	Percentage of patients with clinical encounters with counselor, social work, MH, addiction services	Training logs, EMR and scheduling data	Every 6 months
Outcome: telemedicine encounters			
Concept: MH and substance use			
Unit: patients			
	Percentage of encounters completed through telemedicine	Training logs, EMR and scheduling data	Every 6 months

[a]ePRO: electronic patient reported outcome.

[b]EMR: electronic medical record.

[c]CME: continuing medical education.

[d]MH: mental health.

[e]SUD: substance use disorders.

[f]CFIR: consolidated framework for implementation research.

[g]OUD: opioid use disorder.

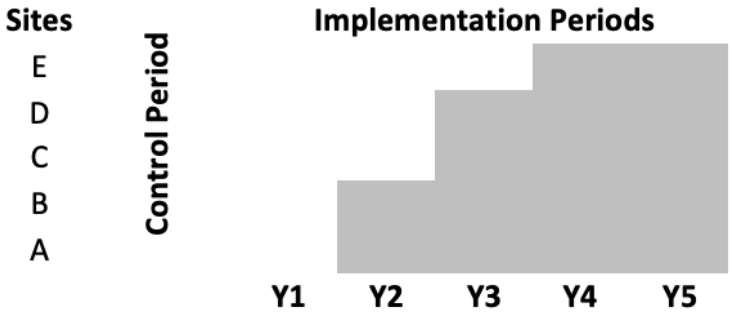
[h]ART: antiretroviral treatment.

Analysis Plan

The analysis process will align with a stepped-wedge study design and each aim of the study (Figure 2). Aim 1 is to conduct readiness, acceptability, and accessibility assessment and implement +STEP. Data collected during the readiness, acceptability, and accessibility assessment will be analyzed using descriptive and frequency statistics for the staff and patient survey and by a rapid qualitative analysis of qualitative interviews with key staff members from the 5 participating sites. The team will use a data reduction analysis method by coding and summarizing each transcript by code before integrating the themes across all interviews [40]. This process will elucidate each clinic's protocol for completing annual screening and reporting of MH and SUD, clinic procedures for psychosocial service provision, including on-site services and details of referral options in the community and beyond, and the use of telemedicine if applicable.

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Figure 2. The stepped-wedge study design in which the intervention (patient-reported outcomes) is introduced at sites across 3 years of the study (Years 2-4). Y: years.



Aim 2 is focused on describing implementation strategies addressing barriers to uptake of +STEP in 5 RWHAP clinics using CFIR. The analytic strategy for aim 2 is framework-guided rapid qualitative analysis (F-RQA) of interview transcripts [40]. We will develop an interview guide informed by the domains and constructs of CFIR and using the recommended CFIR interview questions. In alignment with F-RQA, a preliminary summary table will be developed to correspond to the domains and constructs reflected in the interview guide. Once both processes are complete, the research team will independently extract relevant data from a single transcript, including pertinent quotes, and organize them in the draft summary table. Draft summary tables from these team members will be compared to resolve discordance. A modified summary table will then be used on a second interview before finalizing the summary table, which will be used for data analysis of all subsequent interview transcripts. This analytic process will provide an in-depth understanding of implementation as it is ongoing and will allow us the opportunity to share this information with clinics during quarterly meetings with participating clinics [41].

Aim 3 includes the measurement of the impact of implementing +STEP on diagnoses, referrals, and health care use related to MH, SUD, and HIV by comparing clinical outcomes from patients receiving these interventions (ePROs and telemedicine) with historical controls. This analytic process will begin with descriptive analyses to illustrate characteristics of patients, including age, race, gender, sex, and time in HIV care for each site and overall. Historical control data will be compared to the prospectively collected ePRO data and percentages. As it will be difficult to identify certain historical values, we will note any uncollectable data and present descriptive statistics for +STEP patients alone. For all other outcomes, we will perform generalized linear mixed effects models to account for the within-clinic correlation. These models will be performed with and without covariate adjustment to determine if any potential patient population changes (eg, more persons living with HIV newly engaged in care receiving +STEP) confound the effect of STEP+ on the identification of MH diagnoses, referral to services or actual service use. We will determine if random effects are necessary and if they can be ignored, we will use logistic regression models for each outcome. For each model, all assumptions will be verified, and goodness-of-fit will be assessed.

Ethics Approval

This study received approval from the UAB's institutional review board (300005613).

Results

In 2021, at the initiation of the study, the participating RWHAP-funded clinics provided care to a total of 4065 persons living with HIV (Table 2). The number of patients at each clinic ranged from 200 to 1819 (Table 2). These clinics are situated in the some of the most disadvantaged regions of Alabama based on the area deprivation index (Figure 3). The sociodemographic traits of persons living with HIV who are receiving care at RWHAP clinics in Alabama are as follows: median age of 47 years; 2622 (76%) cisgender men; 2273 (65%) non-Hispanic Black; 372 (10%) with unstable housing or homelessness. In 2019, there were 4065 persons living with HIV receiving care at one of the participating +STEP sites.

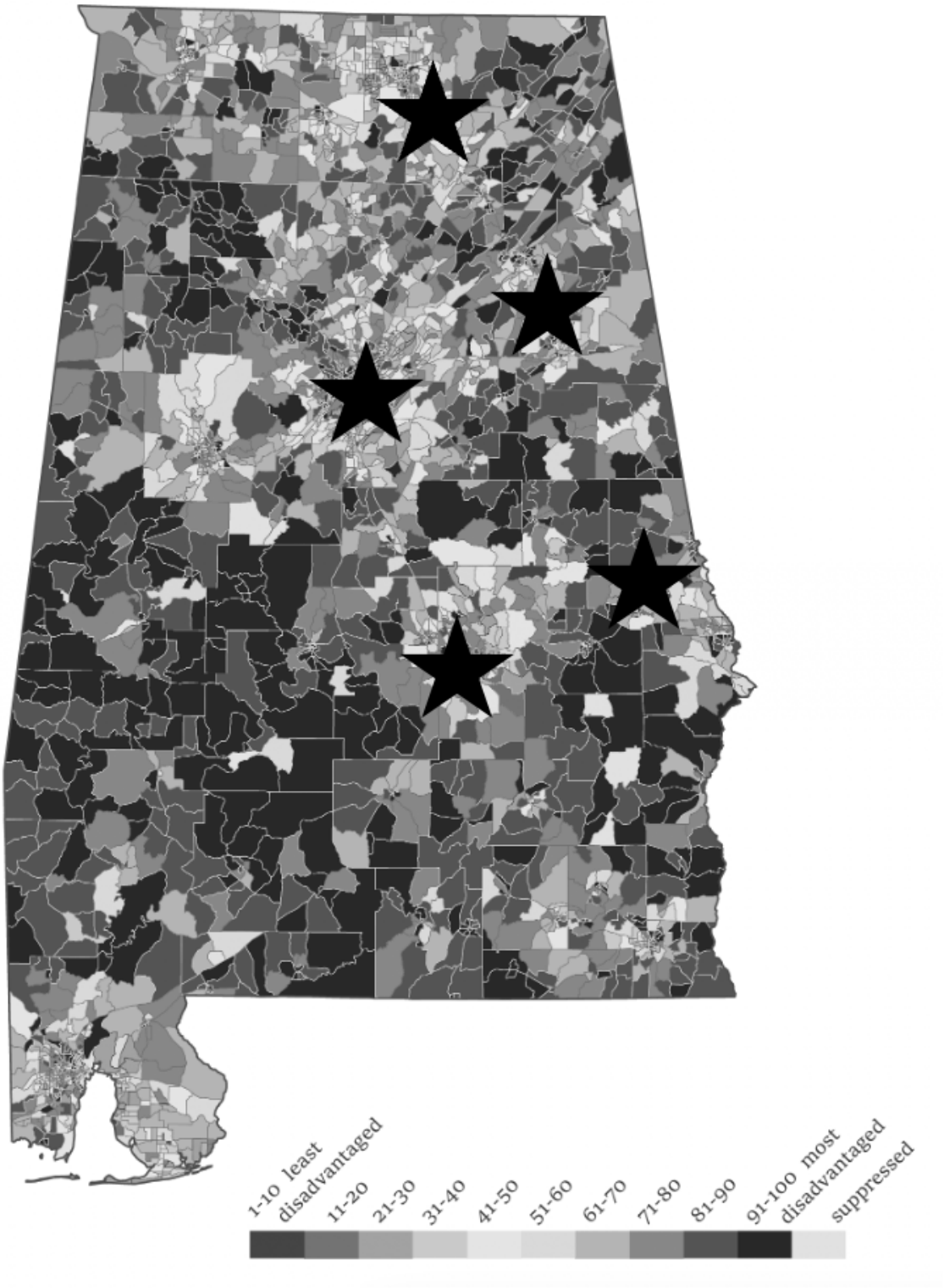
Table 2. Summary of sites participating in +STEP (N=4065).

Sites	Persons living with HIV, n (%)
Ryan White Funded Clinics in Alabama[a]	
University of AL Family Clinic	300 (7.38)
Thrive Federally Qualified Health Services Center	956 (23.52)
Health Services Center	562 (13.83)
Medical Advocacy and Outreach	1819 (44.75)
Unity Wellness Center	428 (10.53)

[a]Data from 2020; 2021 data unavailable for this site.

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Figure 3. Stars indicate the location of RWHAP (Ryan White HIV/AIDS Program) clinics. Zip codes are shaded in accordance with the level of disadvantage based on the Area Deprivation Index, with White being the least disadvantaged and Black being the most disadvantaged.



Initial findings from aim 1 of this study are available at BMC Health Services Research [42]. Using data from patient surveys and key staff members' qualitative interviews, this study found that all participating RWHAP-funded clinics were ready and willing to implement and integrate ePRO screening for MH and SUD followed by telehealth services as part of their treatment strategy. Patients reported comfort with technology, such as smartphones and computers, and telehealth; however, patients expressed concerns around not having a physical examination and less in-person interaction.

Future results of this study will be collected in alignment with the study timeline (Figure 1). As part of aim 2, we anticipate the results will be used to iteratively refine the formal implementation blueprint, which includes barriers and facilitators to +STEP delivery in routine care. Results will be instructive for the continued implementation of +STEP at

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RWHAP clinics and future sites. We anticipate that the results of aim 3 will demonstrate that +STEP will improve the diagnosis and treatment of MH and SUDs. We expect that +STEP will result in an increased number of referrals for evidence-based care of these conditions, an increased proportion of patients in treatment for both psychosocial comorbidities and HIV, and an increased quality of data used to monitor persons living with HIV in care at RWHAP clinics at the individual and clinic levels.

Discussion

Principal Findings

This will be the first study to evaluate the integrated implementation of 2 effective evidence-based technologies—ePROs and telemedicine—in serving people living with HIV in Alabama. We hypothesize that this study will provide foundational evidence demonstrating ePROs as an effective intervention to increase routine screening, referrals, and treatment for MH and SUDs. The results of this study will also include a refined blueprint for the implementation of ePROs at HIV clinics based on participant study–team meetings and evaluation of implementation over the course of the study.

Comparison to Previous Work

A systematic review of ePRO randomized control trials identified consistent methodological limitations in the existing literature [14]. These limitations included lack of consensus on the structure of ePRO interventions, including how questionnaire results were provided to clinical providers, limited provider training on the interpretation of ePRO results, and a disconnect between ePROs and targeted outcomes, such as exploring the impact of ePROs on distal clinical outcomes in lieu of proximal process outcomes [14,43-45]. This study will address the existing limitations by including provider training on ePROs among persons living with HIV and the measurement of process outcomes to inform an implementation blueprint for ePROs to identify MH and SUDs in HIV clinics.

Future Directions

The results of this study will provide evidence for future research expanding access to ePROs for improved diagnosis linked to telemedicine access to accelerate patients along the continuum of care from MH and SUD diagnosis to treatment. We will also use study findings to tailor future implementation research to the needs of African American communities, rural residents, historically marginalized communities, and those affected by intersectional stigmas, including gay men, transgender communities, and people who use drugs. These findings will have applicability in RWHAP-funded clinics in other parts of the Deep South and regions identified as priority sites for ending the HIV epidemic, which is a national initiative to scale up science-based strategies to diagnose, treat, prevent, and respond to HIV [46]. Implementing evidence-based services to support the mental and substance use needs of persons living with HIV is foundational to accelerating overall well-being and individual and population level viral load suppression.

Limitations

This study is not without potential limitations. The initiation of this study took place during the COVID-19 pandemic, which affected community partners capacity to fully engage in the early stages of the study. However, COVID-19 has increased patients' experience and comfort with telemedicine, aiding in the transition to ePROs and telemedicine for this study. Notably, during COVID-19, several clinics developed their own telemedicine programs out of necessity rather than waiting for the +STEP implementation. This means that many clinics are already providing MH services virtually, but few, if any, are using telehealth for addiction treatment services. Additionally, our community partners participate in others research studies and may have experienced study fatigue. Further, 1 site declined participation after the study was funded, citing COVID-19–related concerns and clinical capacity issues. Issues with clinic research saturation and COVID-19–related barriers will be monitored throughout the implementation of this study to try to mitigate overburdening our partners with research tasks when possible.

Conclusions

Achieving the end of the HIV epidemic in the United States necessitates programs that accelerate movement across the MH and SUD care continuum from diagnosis to treatment for persons living with HIV. Scaling these services represents a path toward improved treatment outcomes with both individual health and population-level prevention benefits of sustained HIV viral suppression in the era of undetectable=untransmittable (U=U). This study will address this evidence gap through the evaluation of the implementation of +STEP to establish the necessary systems and processes to screen, identify, and better treat substance use and MH for people living with HIV.

Data Availability

Since this is an ongoing study, data are not yet publicly available, but may be available upon request to principal investigator EE at eeaton@uabmc.edu.

Conflicts of Interest

GB has received honoraria from Med-IQ for medical education, and their institution has received grant funds on their behalf from Eli Lilly and Merck Foundation.

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Abbreviations

ART: antiretroviral treatment
CFIR: consolidated framework for implementation research
EMR: electronic medical record
ePRO: electronic patient reported outcome
F-RQA: framework-guided rapid qualitative analysis
MH: mental health
PHQ-9: Patient Health Questionnaire-9
RWHAP: Ryan White HIV/AIDS Program
SUD: substance use disorders
U=U: undetectable=untransmittable
UAB: University of Alabama at Birmingham
VL: viral load

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Protocol

Evaluation of the Effectiveness of Assistive Technology for Executive Function Support for People With Acquired Brain Injury: Protocol for Single-Case Experimental Designs

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Abstract

Background: Executive function, including prospective memory, initiating, planning, and sequencing everyday activities, is frequently affected by acquired brain injury (ABI). Executive dysfunction necessitates the use of compensatory cognitive strategies and, in more severe cases, human support over time. To compensate for the executive dysfunction experienced, growing options for electronic mainstream and assistive technologies may be used by people with ABI and their supporters.

Objective: We outline the study protocol for a series of single-case experimental designs (SCEDs) to evaluate the effectiveness of smart home, mobile, and/or wearable technologies in reducing executive function difficulties following ABI.

Methods: Up to 10 adults with ABI who experience executive dysfunction and have sufficient cognitive capacity to provide informed consent will be recruited across Victoria and New South Wales, Australia. Other key inclusion criteria are that they have substantial support needs for everyday living and reside in community dwellings. On the basis of the participant's identified goal(s) and target behavior(s), a specific electronic assistive technology will be selected for application. Both identification of the target behavior(s) and selection of the assistive technology will be determined via consultation with each participant (and their key support person, if applicable). The choice of SCED will be individualized for each participant based on the type of technology used in the intervention, the difficulty level of the behavior targeted for change, and the anticipated rate of change. For each SCED, repeated measurements of the target behavior(s) during the baseline condition will provide performance data for comparison with the performance data collected during the intervention condition (with technology introduced). Secondary outcome measures will evaluate the impact of the intervention. The protocol includes 2 customizable Microsoft Excel spreadsheets for electronic record keeping.

Results: Recruitment period is June 2022 through March 2024. Trial results for the individual participants will be graphed and analyzed separately using structured visual analysis supplemented with statistical analysis. Analysis will focus on important features of the data, including both within- and between-phase comparisons for response level, trend, variability, immediacy, consistency, and overlap. An exploratory economic evaluation will determine the impact on formal and informal support usage, together with quality of life, following the implementation of the new technological intervention.

Conclusions: The study has been designed to test the cause-effect functional relationships between the intervention—in this case, electronic assistive technology—and its effect in changing the target behavior(s). The evaluation evidence gained will offer

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new insights into the application of various electronic assistive technologies for people who experience executive dysfunction following ABI. Furthermore, the results will help increase the capacity of key stakeholders to harness the potential of technology to build independence and reduce the cost of care for this population.

Trial Registration: Australian New Zealand Clinical Trials Registry (ANZCTR) ACTRN12622000835741, https://www.anzctr.org.au/ACTRN12622000835741.aspx

International Registered Report Identifier (IRRID): DERR1-10.2196/48503

(JMIR Res Protoc 2023;12:e48503) doi:10.2196/48503

KEYWORDS

acquired brain injury; assistive technology; clinical research protocol; economic evaluation; executive function; single-case experimental design

Introduction

Overview

Acquired brain injury (ABI) refers to damage to the brain that occurs after birth and includes traumatic brain injury, stroke, infection, anoxia or hypoxia, and brain cancer to name the most common [1]. Cognitive impairments, including damage to higher-order executive functions, are frequently observed after ABI. Common executive function impairments include issues with prospective memory, flexibility, judgment, insight, planning and organization, and initiation of functional tasks [2]. Executive impairments can have a significant impact on functional outcomes and adversely affect participation in areas such as employment, leisure pursuits, relationships, and independent living [3-5].

Assistive Technology for Executive Function Support

A growing range of electronic assistive technologies is available, which may compensate for a number of challenges to participation. For instance, smartphones and tablets used by the wider population are emerging as useful tools for developing independence and participation after ABI [6-9]. To date, most studies evaluating the efficacy of assistive technology in providing support to compensate for executive impairments have focused on prospective memory compared with other components of executive function. The strongest evidence to date has come from a small number of randomized controlled trials testing the efficacy of delivering reminders to reduce prospective memory failures through text messages or other auditory cues delivered by personal digital devices or mobile phones [10,11]. To date, few studies have investigated the efficacy of assistive technology in supporting other areas of executive function, such as supporting goal-directed behavior to undertake functional therapy [12,13] or enhancing executive monitoring of daily intentions [14].

As the assistive technology field has been rapidly evolving, there are growing platforms and means for delivering support for executive functions. For example, home hubs constitute a more specialized type of multifunctional device. One example of such devices is “Sofihub,” which provides home-based movement sensing, audio-prompting technology (similar in principle to “Alexa” or “Google Home”). Sofihub was designed and marketed for people with disabilities, including those with cognitive impairment [15]. Fernando et al [15] provided preliminary evidence of the effectiveness of Sofihub in augmenting human support for people with executive dysfunction, including impaired initiation. The system provided prerecorded verbal prompts to participants at set times or triggered by sensors detecting movement. The verbal prompts targeted self-care activities (eg, showering, teeth cleaning, and medication administration), household tasks (eg, cleaning and putting out garbage), and reminders to take necessary items (eg, phone, keys, and hearing aids) when leaving the house.

In Australia, the National Disability Insurance Agency has identified that assistive technology offers the potential to reduce the lifetime care costs of people with severe disabilities [16]. Nevertheless, to date, there is limited published evidence regarding the use of technology in the delivery of support to people with ABI in a range of community settings [17]. Specific to electronic personal assistive devices, there is insufficient evidence to recommend any practice standards [18]. This limits the capacity of people with ABI and their supporters, including family, carers, and health professionals, to effectively implement and harness emerging technologies within community living.

Objectives

This paper outlines the study protocol for a series of single-case experimental designs (SCEDs) to evaluate the effectiveness of smart home, mobile, and/or wearable technologies for executive function support following ABI. The findings from the Sofihub trial [15] and other published evidence identify SCED as the principal methodology used to evaluate technological solutions for people with ABI [18]. The rigorous methodology of SCED enables it to test for cause-effect functional relationships between the intervention—in this case, smart home, mobile technology, or wearable technologies—and its effect in changing a behavior (eg, an increase in the number of steps in a specified task completed following a prompt from smart devices and a corresponding decrease in the number of verbal cues required from a support person) [19-21]. However, to date, many SCEDs have been of low scientific quality [22,23], and therefore, there is a need for more methodologically rigorous, evidence-based research to better understand the benefits of the introduction of technological aides [24]. The aim of this paper is to present a study protocol that will examine the efficacy of assistive technology (including home-based, mobile, and wearable technologies) in reducing executive function difficulties and care needs experienced by people with ABI.

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Methods

Study Design

A series of SCEDs will be used to evaluate the effectiveness of the intervention technologies. The choice of design will be individualized for each participant based on the type of technology used in the intervention, the difficulty level of the behavior targeted for change, and the anticipated rate of change. It is expected that the most common design will be a withdrawal A_1-B_1-A_2-B_2 design (where A denotes the baseline phase and B denotes the intervention phase). However, multiple baseline, alternating treatments, changing criterion, and combination designs may also be used [25]. Decisions regarding the design to be implemented will be made on a case-by-case basis by the research team.

Each SCED will be planned using the Risk of Bias in N-of-1 Trials Scale [26,27] to maximize internal and external validity and will be conducted over approximately a 12-month period. The Risk of Bias in N-of-1 Trials Scale is a 15-item critical appraisal tool that evaluates the methodological quality of intervention studies using a single-case methodology. It comprises 2 subscales: internal validity and external validity and interpretation.

The report of each case will be prepared in accordance with the SCRIBE (Single-Case Reporting Guideline in Behavioral Interventions) statement [28] using a customized Microsoft Excel spreadsheet (Multimedia Appendix 1) to enable electronic record keeping. The SCRIBE is a 26-item reporting guideline developed in the CONSORT (Consolidated Standards of Reporting Trials) tradition to facilitate clear, complete, and transparent reporting of the study.

Ethics Approval, Informed Consent, and Participation

The study design, recruitment, and data collection procedures were approved by the South Western Sydney Local Health District and Monash University Human Research Ethics Committees (Project IDs 2019/ETH14038 and 27923). The trial has been registered with the Australian New Zealand Clinical Trials Registry (ACTRN12622000835741). All participants will provide written informed consent before participating in the study. Each phase of the study will be monitored closely, and—as detailed in the procedures section—a customized Microsoft Excel spreadsheet (Multimedia Appendix 1) will be used to document and manage any adverse events or harms.

Participant Eligibility

The inclusion criteria are as follows: participants will be aged ≥18 years, experience executive dysfunction following ABI, have substantial support needs for everyday living, reside in community dwellings, and have sufficient cognitive capacity to provide informed consent (determined by a review of any available neuropsychological assessment and/or in consultation with their treating allied health professionals). Participants will not be excluded based on their living location (metropolitan vs regional) or living situation (alone or with others). Exclusion criteria included people with current severe mental health problems or challenging behaviors.

Standardized clinical measures will be used to screen for eligibility. The instruments are described in Multimedia Appendix 2 [29-39]. The Frontal Systems Behavior Scale (FrSBe) [40] will be used to screen for executive dysfunction and the Care and Needs Scale [41] will be used for support needs. The Health of the Nation Outcome Scale—Acquired Brain Injury [42] will be used to identify severe mental health problems, and the Overt Behavior Scale–Adult [33] will be used for challenging behaviors.

Setting

All data collection and assistive technology interventions of consenting participants will be carried out in the community, either their place of residence or work environment.

Measures and Materials

Overview

All screening and outcome measures are described in Multimedia Appendix 2, along with two contextual measures: (1) Assessing Needs and Supports in Relation to Assistive Technology (A-AT; an unpublished semistructured interview) and (2) the World Health Organization Disability Assessment Schedule [34]. These will be administered to better understand participants' functions, goals, and use of assistive technology. All published instruments have been used extensively in previous research in the field of ABI.

Primary Outcome Measure

Measures of Target Behavior(s)

In consultation with each individual participant, target behavior(s) will be identified based on their personal goal(s) for executive function support and/or participation in activities within home and community settings. The target behavior(s) will be tailored to each participant, and, as such, the measurement of the behavior will vary among participants. Target behaviors will be very specific, for example, frequency of occurrence or duration of a behavior, number of steps of an activity completed, or number of prompts from a support person. The frequency of measurement of the target behavior(s) will vary depending on the nature of the target behavior(s), but they will be measured, as appropriate, continuously throughout the baseline and intervention phases.

Goal Attainment Scaling

The Goal Attainment Scaling will be used to evaluate the level of goal attainment linked to the identified target behavior. Personalized evaluation scales ranging from +2 to −2 will be developed based on the framework of Krasny-Pacini et al [43] to ensure that the scales are a valid, reliable, and meaningful outcome measure.

Secondary Outcome Measures

The reason for including secondary measures is for the purpose of generalization and to determine whether the intervention has had effects on broader aspects of the participant's functioning. The secondary outcome measures are as illustrated in the following sections.

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Community Integration Questionnaire-Revised

The Community Integration Questionnaire-Revised [44] is an 18-item scale, which will be used to measure changes in community integration across four domains: (1) home integration (eg, meal preparation and housework), (2) social integration (eg, shopping, visiting friends, and leisure activities), (3) productive activity (eg, full-time vs part-time work, school, and volunteer activities), and (4) electronic social networking enabled social integration.

EuroQol-5 Dimensions Instrument

The self-complete (participant rated) and/or proxy (completed by a family member or paid support person(s) (ie, support worker, house manager, and allied health professional) versions of the EuroQol-5 Dimensions Instrument (EQ-5D-5L) [45] will provide a profile of health-related quality of life for the participant. The questionnaire has two components: (1) health state description and (2) evaluation. In the description section, they will be asked to rate 5 dimensions of health (mobility, self-care, usual activities, pain or discomfort, and anxiety or depression). In the evaluation part, they will be asked to indicate their overall health status ("TODAY") using the visual analog scale from 0 to 100 with the end points labeled "the worst health you can imagine" to "the best health you can imagine," respectively.

Psychosocial Impact of Assistive Devices Scale

The Psychosocial Impact of Assistive Devices Scale [46] will be used to measure the psychosocial effects the assistive technology device has had on the participant. It is a 26-item questionnaire, which will be used to measure the impact the assistive device has had on the participants' sense of competence, adaptability, and self-esteem in daily life.

Quebec User Evaluation of Satisfaction With Technology

The Quebec User Evaluation of Satisfaction with Assistive Technology, version 2.0 [39], is a 12-item scale that will be used to measure the participants' satisfaction with a technology device and its related services. This includes physical properties (eg, size, weight, ease of use, and effectiveness), and, if applicable, service delivery, maintenance, and follow-up services. The final part of the measure asks participants to choose the 3 assistive technology satisfaction items that are most important to them from a total of 12 items.

Disability Support Use and Cost

If agreed by the participant as part of the consent process, disability support costs will be sourced from an administration database of their funding organization to ascertain whether the assistive technology intervention impacted disability support use and cost. These data will be augmented with discussions with the participants (and/or their proxy) using a Participant Economic Evaluation Questionnaire (Multimedia Appendix 3) to ensure that all cost data, including informal supporter costs, have been accurately captured. Data will be gathered preintervention and after the second intervention. Where costs are not available for disability support through the funding organization, market rates will be applied, with the cost of informal care based on the Australian minimum wage [47]. All costs will be inflated to 2022-2023 by applying the Consumer Price Index [48].

Blinding

Blinding in SCEDs refers to whether the participant, practitioner, and assessor are blind to the phase of the experiment. Blinding of participants will usually not be possible, given the nature of the intervention. However, the intervention is delivered by an assistive technology device, without the need for human involvement, thus eliminating human error and minimizing the risk of bias. Hence, for all intents and purposes, the "practitioner" (ie, the technology) can be considered blind to phase. Similarly, for each participant, the assessment data will be generated automatically from the assistive technology device, without the need for human involvement. Thus, the "assessor" (ie, the technology) can be considered blind to phase. In addition, data analysis will be performed by a statistician who will not be involved in discussions with the research group. The statistician will be blinded to all aspects of the intervention, including the specific phases in which data were collected.

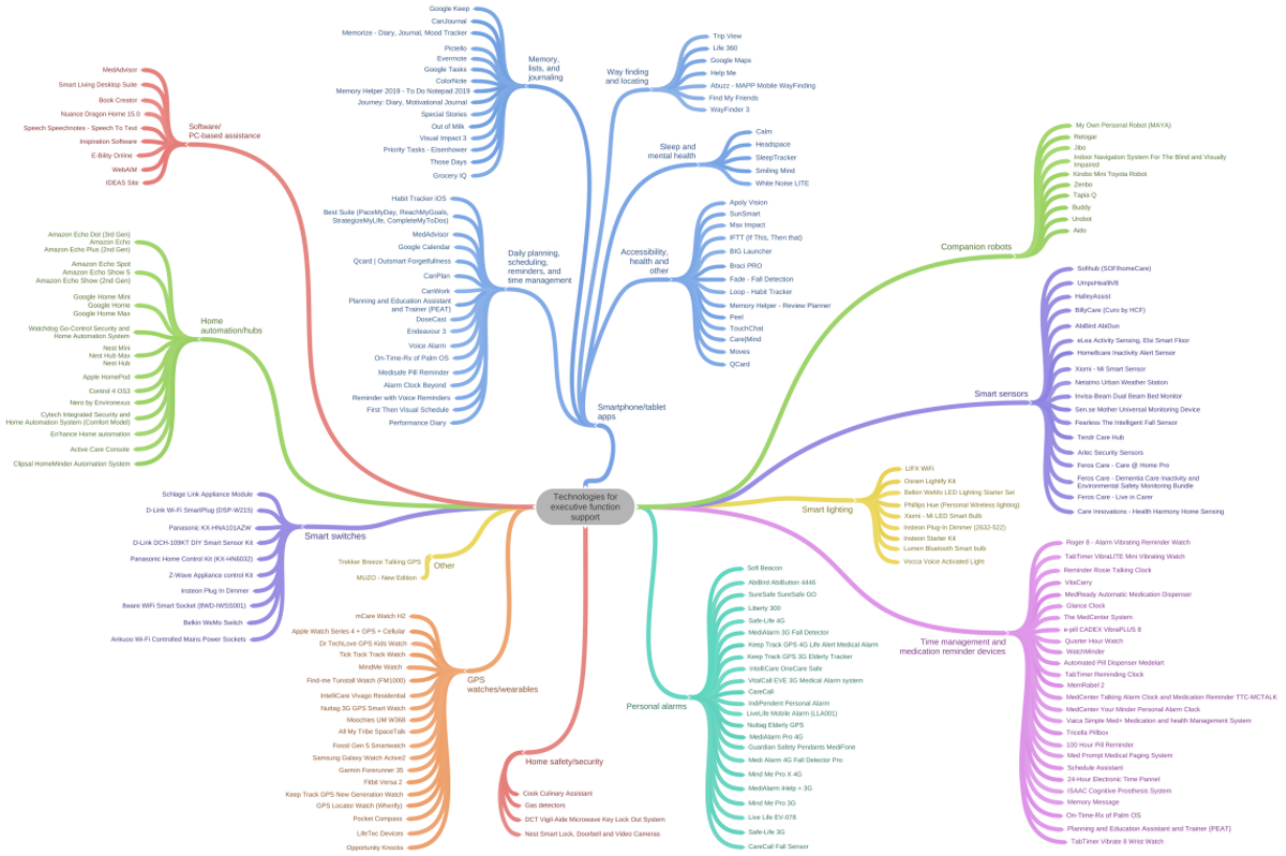
Intervention

Electronic Assistive Technology

A scoping review identified a wide range of technologies (eg, apps, wearables, home sensors, and smart lights) appropriate for use in executive function support [49]. These are shown in Figure 1 and will be used to shortlist electronic assistive technology appropriate for addressing the individual participant's target behavior(s). The shortlist will be discussed with each participant, and through consultation with the participant and/or their proxy, assistive technology will be chosen for application and purchased using research funds.

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Figure 1. Technologies identified for use in executive function support.



Customized Orientation and Training Tool

Depending on the selected electronic assistive technology, there may be a need to develop a customized orientation and training tool in either a paper or digital format. The tool will include a step-by-step guide and/or video demonstration on how to navigate to prioritized function(s) that may be controlled by electronic assistive technology. Digital information will be saved to the smartphone or tablet that the participant currently uses, and written information will be left in a prominent location in the participants' place of residence or work environment. This will ensure that they (or, where appropriate, a family member or other support person) can refer back to it if and when required.

Procedures

Initial Study Setup

The initial study setup phase with the individual participants will involve several tasks, as described below. To ensure anonymity, a pseudonym will be allocated to each participant, and no identifying information (eg, residential address) will be recorded.

Recruitment

A third-party recruitment strategy will be used to recruit up to 10 adult participants across Victoria and New South Wales in Australia. A single-page information sheet about the study, including inclusion criteria, and a "consent to contact" form will be prepared and distributed (in hard copy or via email) to community-based allied health professionals, with the request to pass the information sheet to potentially eligible clients. The consent to contact form asks whether the individual is willing to provide their own name and phone number and the contact details of the allied health professional(s) who work with them. If the individual agrees to provide contact information, the completed form can be posted or a copy emailed to the research group. Once returned, a member of the research group will make contact to invite the individual (and/or their proxy) to a face-to-face meeting to discuss their potential participation in the research.

Consent to Participate

At the first meeting, a plain English information sheet of the study and consent form will be provided and explained verbally to the participant (and/or their proxy), as will the screening process, to ascertain eligibility. The individual can either choose to review the explanatory statement and consent form during that meeting and provide written consent at that time or later. If they wish to decide later, a member of the research group will email or call the individual (and/or their proxy) within 2 weeks of the meeting to see if they would like to consent to participate. This is the only follow-up contact made with the individual unless they request additional time to make their decision.

Screening for Eligibility

Individuals who consent to participate in the study will attend a further appointment to complete the screening assessment. Except for 1 proprietary measure (FrSBe), responses to the other measures will be recorded on a Microsoft Excel spreadsheet (Multimedia Appendix 4). Measures consist of the semistructured interview (A-AT), a clinician-rated contextual

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measure of functional ability (World Health Organization Disability Assessment Schedule 2.0), and 3 clinician-rated and 1 proxy-rated measures to ensure participants meet the clinical threshold (as detailed in Multimedia Appendix 2) in terms of executive function (FrSBe), have high support needs (Care and Needs Scale), and do not have mental health issues (Health of the Nation Outcome Scale—Acquired Brain Injury) or severe levels of challenging behavior (Overt Behavior Scale–Adult). Individuals who do not meet the study inclusion criteria will be thanked for their interest and time but have no further participation in the study.

Identification of Goals, Target Behaviors, and the Intervention

Overview

Several sessions will be spent working with the participants (and their proxy) to identify the goal(s), target behavior(s), and intervention to be trialed in the study. As recommended, goal(s) and target behaviors will be specific, measurable, attainable, realistic, and time limited (SMART) [50,51]. Details regarding the primary outcome (target behavior) measures will be recorded on the SCRIBE checklist: Electronic Version of Selected Items (5-21; Multimedia Appendix 1). The checklist is an interactive, fillable Excel document containing 17 of the 26 items (items 5-21) detailed in the SCRIBE guidelines [28]. A total of 2 SCRIBE items were expanded from the original SCRIBE checklist by the authors of this paper: Item 14 (measures) has added Goal Attainment Scaling (which is commonly used in neurorehabilitation) to the target behaviors to measure progress toward the goal(s); item 21 (adverse events) was slightly modified to incorporate a plan or procedure to manage adverse events. A video demonstrating the use of the SCRIBE Checklist: Electronic Version of Selected Items (5-21) is available from the authors on reasonable request.

If agreed by the participant as part of the consent process, a member of the research group will take photographs of the participant's home or work environment. The photographs will be used to help with discussions with the research team about the potential considerations regarding the layout of the house or work environment for possible technology use. A shortlist of potential assistive technologies that are appropriate to address the target behavior(s) will be developed and chosen in consultation with the participant (and/or their proxy) and the research group.

Phase 1: Baseline (A) Phase

Preintervention (secondary) measures will be administered (Multimedia Appendices 2 and 4). In addition, disability support costs will be sourced (Multimedia Appendix 3). During the baseline phase, the target behavior(s) will be measured repeatedly before implementing the intervention. Accordingly, this phase will serve as the control condition and include a minimum of 5 data points. For some technologies, it may be possible to use system-generated log reports to generate the target behavior data during the baseline (and intervention) phases. As such, the technology will be set up or installed (but during the baseline phase, it will not be activated, ie, for reminders or prompts) by either the occupational therapist to the research group or an external provider. If system-generated log reports are not possible, behavioral recordings of the target behavior(s) will be used.

Phase 2: Intervention (B) Phase

The technology will be installed, worn, and/or activated by an occupational therapist in the research group or an external provider. If required, participants (and/or their proxy) will receive a single 1-hour orientation and training session by a member of the research group on how to use the technology. Any barriers to technology use will also be identified and ameliorated if possible. The target behavior will be measured continuously throughout the intervention phase, with a minimum of 5 data points.

Depending on the specific study design for each participant, there will be subsequent phases (for A-B-A-B withdrawal designs), subphases of the intervention (for changing criterion designs), staggered introduction of the intervention across multiple target behaviors (for multiple baseline designs), or alternating interventions in rapid succession (for alternating-treatment designs). Combination designs can also be used for this purpose.

Postintervention Assessment

Following the completion of the intervention, the secondary outcome measures will be readministered (Multimedia Appendices 2 and 4). In addition, the disability support costs will be sourced (Multimedia Appendix 3). The occupational therapist in the research group will also discuss with the participant whether they wish to continue or cease using the technology following trial completion. If the participant chooses to cease using the technology, the occupational therapist will either uninstall the technology or organize for an external provider to do so at a mutually convenient time.

Results

Recruitment began in June 2022 but has been impacted by the unprecedented COVID-19 pandemic. The data collection is expected to be completed by March 2024. Only data from participants who complete all baseline and intervention phases of the study will be included in the analyses; however, reasons for withdrawal will be documented (eg, hospitalization due to deteriorating health).

Participant raw data from the publicly available contextual, secondary outcome, and screening measures will be entered into a Microsoft Excel spreadsheet (Multimedia Appendix 4). The spreadsheet contains formulas and calculations that automatically calculate scores and subscores (as per author guidelines for each measure). Test booklets will be used to enter and score the participant data from the FrSBe.

The target behavior data collected during the baseline and intervention phases will be entered or imported into SPSS statistical software (version 29; IBM Corp). Data for each participant will be evaluated separately using both structured visual analyses and statistical techniques suitable for within-subject, time-series data. Structured visual analysis will use the standard protocol of Kratochwill et al [52]. It will focus

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on important features of the data making both within- and between-phase comparisons for response level, trend, variability, immediacy, consistency, and overlap. The Tau-U technique [53] or another suitable technique (depending on the individual data patterns) will be used to statistically quantify the overlap and generate effect sizes. The results will offer new insights into the application of various electronic assistive technologies for executive function support following ABI.

The SCED data analysis will be coupled with an exploratory economic evaluation analysis using Microsoft Excel (version 2306) and SPSS Statistics, delivered under the supervision of a health economist from the research team. This analysis will be completed by comparing a new intervention (ie, the assistive technology product applied during the intervention phase) against an alternative or comparator. In this study, the comparator is an intervention that would usually apply to the care of the population of interest in the absence of new technology, often referred to as standard care (ie, baseline phase). In addition, to ascertain whether the intervention had an impact on quality of life, changes in quality-adjusted life years (QALYs) will be compared between baseline and follow-up for both the participants and/or their informal support person.

The exploratory economic evaluation will determine both the incremental effect and incremental costs of the new technology intervention over those of the comparator state for each single case (each participant). The incremental costs will be presented as a "return on investment," with the return referring to the change in cost for care needs and the investment referring to the cost of the assistive technology. The incremental effect will be presented as QALYs, derived from the baseline and follow-up EuroQol-5 Dimensions Instrument utility indices. The cost difference between the "return" and "investment," together with the QALYs, will produce an individual incremental cost-effectiveness ratio for each participant.

Discussion

Expected Findings

This protocol for a series of single-case experiments delivered across 2 states of Australia (Victoria and New South Wales) offers digital tools, including the SCRIBE checklist: Electronic Version of Selected Items (5-21; Multimedia Appendix 1), a semistructured interview schedule (A-AT), and a customizable Microsoft Excel spreadsheet of screening tools and outcome measures (Multimedia Appendix 4). The single-case experiments will rigorously test the effectiveness of a suite of smart home, mobile, and wearable technologies and deliver high-quality evidence regarding technology interventions. Furthermore, an exploratory economic evaluation will determine the impact on formal and informal support use and quality of life.

This study extends the work of the Sofihub trial [15] and has been strategically designed to test the cause-effect functional relationships between the intervention (in this case, smart home, mobile technology, or wearable technologies) and its effect in changing the target behavior(s). Consequently, the results will address the current evidence and knowledge gaps for people with ABI who experience executive function issues, their formal and informal support networks (including health professionals), technology developers, smart home designers, and funders of disability services. Furthermore, the findings will be translated into a suite of freely available digital, written, and face-to-face educational resources to increase the capacity of key stakeholders to harness the potential of technology to build independence and reduce the cost of care for people who experience executive dysfunction following ABI. Dissemination of the study will also be undertaken by publishing results in peer-reviewed journals, presenting them at relevant conferences and in a final report provided to the 2 project sponsors.

Limitations

This study has some potential limitations. First, the study is limited to English-speaking participants, which limits the generalizability of the findings to culturally and linguistically diverse groups. Second, people with severe mental health problems or challenging behaviors will be excluded from participating in the study, so it will not be possible to determine the potential application of various electronic assistive technologies for executive function support following ABI in those populations.

Conclusions

The digital tools developed and made available as part of this protocol may be useful for other researchers to consider, or draw upon, when designing single-case experiments. Evaluation evidence gained from a series of SCEDs will offer new insights into the application of various electronic assistive technologies for people who experience executive dysfunction following ABI. Furthermore, the results will help increase the capacity of key stakeholders to harness the potential of technology to build independence and reduce the cost of care for this population.

Acknowledgments

The authors would like to acknowledge the support received to undertake this work through funding from the Transport Accident Commission (Victoria) and icare New South Wales (project reference T012).

Data Availability

The data sets generated during this study are not publicly available, as the study is still ongoing and analysis has not yet taken place.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
SCRIBE (Single-Case Reporting Guideline in Behavioral Interventions) checklist: Electronic Version of Selected Items (5-21).
[XLSX File (Microsoft Excel File), 68 KB - resprot_v12i1e48503_app1.xlsx]

Multimedia Appendix 2
Summary of measures and data collection procedures.
[PDF File (Adobe PDF File), 110 KB - resprot_v12i1e48503_app2.pdf]

Multimedia Appendix 3
Participant Economic Evaluation Questionnaire.
[DOCX File , 65 KB - resprot_v12i1e48503_app3.docx]

Multimedia Appendix 4
Screening tool and outcome measures.
[XLSX File (Microsoft Excel File), 393 KB - resprot_v12i1e48503_app4.xlsx]

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Abbreviations

A-AT: Assessing Needs and Supports in Relation to Assistive Technology
ABI: acquired brain injury

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CONSORT: Consolidated Standards of Reporting Trials
FrSBe: Frontal Systems Behavior Scale
SCED: single-case experimental design
SCRIBE: Single-Case Reporting Guideline In BEhavioural Interventions
SMART: specific, measurable, attainable, realistic, and time limited

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Protocol

Deferring Postoperative Follow-Up Visits up to 4 Weeks After Uneventful Cataract Surgery in a Tertiary Level Eye Hospital: Protocol for a Prospective, Quantitative, Experimental Control Study

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Abstract

Background: Routine examination after cataract surgery, including a refraction test 4 to 6 weeks after surgery, is mandatory in most hospitals. In recent years, there has been growing interest in exploring alternative approaches to postoperative follow-up in cataract surgery patients due to the increasing number of cataract surgeries being performed, the limited availability of health care resources, and the need to optimize the use of health care services.

Objective: We aim to compare postoperative visual outcomes after a day 0 examination in patients with 2 follow-ups, one on day 7 and other on day 30, and patients with a single ophthalmic follow-up between days 25 to 30.

Methods: A prospective, quantitative, experimental control study will be carried out in Reiyukai Eiko Masunaga Eye Hospital, located in Banepa, Kavrepalanchok, Nepal. All patients undergoing cataract surgery meeting the inclusion and exclusion criteria irrespective of the type of surgery (small-incision cataract surgery or phacoemulsification) will be included in the study. The patients will be randomly assigned to 1 of 2 groups. Patients in group 1 will be examined on day 1, day 7, and day 30, whereas patients in group 2 will be examined on day 1 and once between days 25 to 30. The minimum clinically important difference (MCID) in our study will be set according to the improvement in the Snellen visual acuity chart.

Results: The study is expected to be completed within 6 to 8 months from the start of the project. Data analysis and report writing will be carried out in a 2-month period. Best-corrected visual acuity will be compared between the 2 groups to determine if the MCID is achieved. The cost-effectiveness of the new approach will also be analyzed.

Conclusions: We aim to conclude that we can safely defer the 1-week postoperative follow-up visit in patients undergoing uncomplicated cataract surgery and that, moreover, we can reduce the patient load at the hospital and decrease patient expenses by decreasing the frequency of hospital visits.

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KEYWORDS

cataract surgery; operational research; SICS; small-incision cataract surgery; postoperative visits; cataract; follow-up visit; postoperative care; surgery

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Introduction

Background

Cataract is the leading cause of blindness and visual impairment in lower- and middle-income countries [1,2]. Surgery is the only available treatment that is highly cost-effective and capable of significantly improving visual function [3,4]. Cataract surgery often achieves an excellent visual outcome with low rates of complication [5,6]. Routine examination after cataract surgery, including a refraction test a few weeks after surgery, is mandatory in most hospitals [7,8].

Limburg et al [9] investigated the benefits of postoperative follow-up in India and concluded that visual acuity at hospital discharge was not representative of visual acuity several weeks after surgery [10]. However, a study by Congdon et al [11] concluded that early vision assessment of all patients and a follow-up assessment only for patients who return to the clinic without prompting were adequate to ensure the quality of cataract surgical services. This is again countered by a study by Gupta et al [12], who presented evidence of substantial changes between visual acuity on the first postoperative day and at subsequent follow-up. Postoperative complications and uncorrected refractive errors are 2 major issues that lead to poor visual outcomes [5,13-16]. Both issues can be wholly addressed by promoting and ensuring postoperative follow-up at the designated time [17-20]. As per the National Programme of Control of Blindness, Vision 2020: Right to Sight, the recommended postoperative follow-up visit schedule is a first follow-up on the first postoperative day by the surgeon (mandatory), a second follow-up between day 7 and day 10, and a third follow-up (with refractive correction) between day 30 and day 45 [21]. Saeed et al [22] and Tinley et al [23] concluded that postoperative follow-up visits can be safely deferred up to 2 weeks after cataract surgery, thereby enhancing the efficiency of day care units. Meltzer et al [24] performed a study using data from the PRECOG (Prospective Review of Early Cataract Outcomes and Grading) trial and reported that visual acuity immediately after cataract surgery was highly correlated with visual acuity after 40 days, suggesting that for the purposes of quality assessment, follow-up of all patients is not needed. A study by Deshpande et al [25] concluded that visual outcomes after uneventful cataract surgery were comparable between patients followed up on days 3 to 7 and days 25 to 30 in comparison to patients directly followed up on days 25 to 30. Additionally, it was observed that the first follow-up visit could be safely deferred until 4 weeks after uneventful cataract surgery, including phacoemulsification or small-incision cataract surgery (SICS), in patients with no preexisting ocular or systemic comorbidity [25]. The purpose of this study is to evaluate, from a safety perspective, altering the standard postoperative management guidelines after cataract surgery so that the first follow-up visit at 1 week is deferred in patients with no significant preexisting ocular or systemic comorbidity and no intraoperative surgical complications or immediate postoperative complications at the time of discharge from the hospital.

General Objective

The general objective is to reduce follow-up visits in cataract surgery patients.

Specific Objectives

The specific objectives are (1) to compare postoperative visual outcomes after a day 0 examination in patients with either 2 follow-up visits, one on day 7 and the other on day 30, or 1 ophthalmic follow-up visit between day 25 and day 30; (2) to assess the safety of deferring the first follow-up visit at 1 week; and (3) to perform a cost-benefit analysis of the intervention.

Methods

Study Design, Setting, and Participants

This will be a prospective, quantitative, experimental, noninferiority control study of health services use. Selected patients undergoing cataract surgery at Reiyukai Eiko Masunaga Eye Hospital irrespective of the type of surgery (SICS or phacoemulsification) will be included in the study.

All enrolled patients will undergo an examination on the first postoperative day conducted by an ophthalmologist who is unaware of the patient's group assignment. Subsequently, the patient will proceed to the counselor's office, where a unique identification number will be generated and the patient will be randomized into either group 1 or group 2.

In group 1, patients will be instructed to attend follow-up visits at 1 week and 1 month postoperatively. In group 2, patients will be instructed to attend a follow-up visit at 1 month postoperatively only. During the visit, the patients will receive detailed guidance on the appropriate use of medications and be educated about the signs and symptoms they should be vigilant for. The specific date of the postoperative visit will also be communicated.

At each follow-up visit, the patient will directly visit the counselor's office. Upon arrival, they will be provided with a blank sheet of paper containing the unique identification number assigned to them on the first postoperative day. Visual acuity testing will be conducted by a blinded optometrist, while slit lamp biomicroscopy will be performed by a blinded ophthalmologist. Before leaving the hospital, the patient will return the paper to the counselor, who will then enter the necessary information into the patient's file.

Inclusion Criteria

Patients undergoing uncomplicated cataract surgery at Reiyukai Eiko Masunaga Eye Hospital irrespective of the type of surgery (SICS or phacoemulsification) will be included in the study.

Exclusion Criteria

Patients will be excluded if (1) there are complications during the surgery that warrant more frequent follow-up visits (eg, premature entry, posterior capsular rupture, zonular dialysis, postoperative hyphema, toxic anterior segment syndrome, or postoperative fibrin in the anterior chamber); (2) the surgery is for complicated cataract, traumatic cataract, ocular hypertension, or if the patient has drug allergies; (3) the patients has a history

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of diseases that might affect postoperative visual outcomes, such as uveitis, glaucoma, viral keratitis, corneal scarring, hypertensive retinopathy, diabetic retinopathy, central retinal vein occlusion, branched retinal vein occlusion, or age-related macular degeneration; (4) the patient is unwilling to participate or does not provide written consent; and (5) the patient misses the follow-up visits.

Sample Size and Sampling Technique

Sample size is calculated as follows: $2[Z\alpha + Z1 - \beta] 2 \times (sd2/d2) = 2 [1.96 + 1.645] 2 \times [(0.1125)2/(0.025)2] = 263$ for one group, where reference mean values for postoperative visual outcomes are taken from the study conducted by Deshpande et al [25]. The number of participants in intervention group will be 263 and the number of participants in the control (reference) group will be 263. We will use a random sampling technique and computer-generated random numbers to assign patients to the intervention or control group. We generated randomized numbers with a commonly used method [26]. The assignment will be done by the counsellor on the first postoperative day. The researchers will be masked as to randomization at all postoperative visits.

Data Collection Technique and Tools

A proforma will be developed for data collection. A questionnaire will be prepared; counselors will ask the questions and the information will be recorded in a register. This information will be transferred to an Excel (Microsoft Corp) sheet on a daily basis.

Plan for Supervision and Monitoring

The study will be carried out by a team of investigators. The principal investigator will provide orientation for the involved staff 1 week prior to participant enrollment. The issues that might arise during the course of data collection will be resolved by mutual discussion between the investigators. The study will be supervised remotely by the Seva team.

Plan for Data Management and Analysis

Study records that identify the patients will be kept confidential, as required by law. All records pertaining to the patients' involvement in this research study will be stored in a locked file cabinet in the hospital. A case number will indicate the patients' identity on these records. This information will only be accessible to the authors.

Expected Outcome of the Research Results

We expect to determine whether we can defer the 1-week cataract surgery follow-up visit of patients to the hospital.

Primary Outcome

Visual acuity measurements serve as the most important primary outcome. This includes assessing the level of visual improvement or stability achieved by patients during the 4-week follow-up period. Visual acuity outcomes can provide insights into the effectiveness of deferring follow-up visits for achieving comparable visual outcomes to the standard practice of early postoperative visits.

Secondary Outcome

The results of the cost-benefit analysis can be considered a secondary outcome. Conducting a cost-effectiveness analysis allows for the assessment of the economic implications and potential cost savings associated with deferring postoperative follow-up visits. This outcome provides insights into the financial feasibility and efficiency of implementing the deferred follow-up strategy.

We will perform a cost-benefit analysis to compare the economic status of the intervention group and active control group. For this we have to collect financial data on direct and indirect costs. Data on direct costs will be retrieved from the hospital record system, because this is the money paid directly by patients for their treatment after the surgery is recorded, including payments for consultation, medicine, and investigation (if required) at each follow-up visit.

Data on indirect costs, that is, costs incurred to the patient in the process of coming to the follow-up visit, include the following: (1) lost productivity costs (how much money the patient could have earned if the patient hadn't come to the hospital follow-up visit), (2) transportation costs (the cost incurred while travelling), and (3) companion costs (patients will definitely have a companion, for whom we also have to calculate both costs above (lost productivity and transportation). Data on indirect costs will be obtained from interviews with the patients. We will calculate the average cost per visit, which will ultimately reveal the costs and benefits of the new approach, because the suggested new regimen will eliminate one follow-up visit.

Plan for Use of Research Findings

Research findings will be disseminated through the Reiyukai Eiko Masunaga Eye Hospital newsletter. Donors will be also informed. Results will be published in high-impact journals for better coverage.

Ethical Considerations

Ethical Approval

The Declaration of Helsinki will be adequately addressed. Ethical approval for this study has been obtained from the ethical review board of the Nepal Health Research Council (428/2022 P).

Consent

Participants will be provided with detailed information about the study, including the deferral of postoperative visits, as well as potential risks, benefits, and alternatives. A written informed consent form will be provided to all participants.

Privacy and Confidentiality

Study data will be collected and stored in a manner that ensures the anonymity or deidentification of participants. Personally identifiable information such as names, addresses, and social security numbers will be removed from the data set. Each participant will be assigned a unique identifier that is used instead of their personal information.

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Results

More than 526 participants will be enrolled in the study, with a minimum of 263 assigned to the intervention group (deferred follow-up visits) and a minimum of 263 to the comparison group (standard practice of early postoperative follow-up visits). The sample will have diverse demographics, ensuring a representative population.

Visual acuity measurements will be obtained for both groups during the follow-up period. We will be able to statistically compute whether the deferred follow-up visit group demonstrates comparable visual acuity outcomes to the comparison group. This will be inferred if there are no statistically significant differences between the two groups in terms of visual acuity outcomes (P>.05).

Among the participants in the deferred follow-up visit group, the number of patients who experience postoperative complications during the 4-week follow-up period will be compared with the group with the 1-week follow up visit.

We will also determine if participants in the deferred follow-up visit group report high levels of satisfaction with the extended recovery period and reduced travel burden. The number of participants who express that deferring follow-up visits provided them with convenience and comfort during the recovery phase will be mentioned.

We will determine if reduction in early postoperative visits allows health care providers to allocate their time and expertise more efficiently, focusing on patients with immediate needs or complex postoperative care requirements.

Discussion

Expected Findings

The proposed study will investigate the feasibility and potential benefits of deferring postoperative follow-up visits up to 4 weeks after uneventful cataract surgery in a tertiary level eye hospital in Kavrepalanchok.

Deferring postoperative follow-up visits will allow patients to recover in the familiar environment of their homes, reducing the need for immediate travel and associated costs. This can have a positive impact on patient satisfaction and comfort during the recovery period. By avoiding unnecessary trips to the hospital, patients may experience reduced anxiety and stress, leading to an improved overall experience.

By spacing out follow-up visits, health care providers can optimize resource allocation within the tertiary level eye hospital. This approach will allow health care personnel to allocate their time and expertise more efficiently, focusing on patients who require immediate attention or complex postoperative care. Moreover, it can potentially reduce the burden on health care facilities, as fewer appointments are scheduled during the early postoperative period.

Deferring follow-up visits may also improve access to care, particularly for patients residing in remote areas. Traveling to health care facilities shortly after surgery can be challenging, especially for individuals with limited mobility or limited access to transportation. By extending the follow-up period, patients from distant locations can receive necessary care without the immediate need for travel, increasing the likelihood of their adherence to follow-up appointments.

One major concern related to deferring follow-up visits is the potential delay in detecting postoperative complications. Early postoperative visits allow health care providers to closely monitor patients for any signs of infection, inflammation, or other adverse events. When extending the follow-up period, it is crucial to educate patients regarding the signs and symptoms of postoperative complications so that they can visit the hospital, if required, on time. Patients should receive comprehensive information about self-care, potential warning signs, and instructions on when to seek medical attention. This will empower patients to actively participate in their own recovery and promote a sense of responsibility for their eye health.

Limitations and Challenges

There are potential challenges associated with deferring postoperative follow-up visits. It is important to carefully consider the selection criteria for eligible patients to ensure that only those with a low risk of complications are included in the study. Additionally, proper communication channels must be established to ensure patients have access to health care providers in case of emergency concerns or complications during the extended follow-up period.

Conclusion

The proposed study on deferring postoperative follow-up visits up to 4 weeks after uneventful cataract surgery in a tertiary level eye hospital in Kavrepalanchok will offer several potential benefits for patients, health care providers, and health care facilities. By prioritizing patient convenience, optimizing resource use, and ensuring appropriate support and education, this approach has the potential to improve access to care and overall patient satisfaction. However, careful consideration should be given to the selection criteria and establishment of effective communication channels to address potential challenges and ensure patient safety. The findings of this study will contribute valuable insights to the delivery of eye care services and may have implications for similar settings.

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Data Availability

The data sets generated during and/or analyzed during this study are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

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Abbreviations

PRECOG: Prospective Review of Early Cataract Outcomes and Grading
SICS: small-incision cataract surgery

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Protocol

Developing a Core Outcome Set for Prognostic Research in Palliative Cancer Care: Protocol for a Mixed Methods Study

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Abstract

Background: Studies exploring the impact of receiving end-of-life prognoses in patients with advanced cancer use a variety of different measures to evaluate the outcomes, and thus report often conflicting findings. The standardization of outcomes reported in studies of prognostication in palliative cancer care could enable uniform assessment and reporting, as well as intertrial comparisons. A core outcome set promotes consistency in outcome selection and reporting among studies within a particular population. We aim to develop a set of core outcomes to be used to measure the impact of end-of-life prognostication in palliative cancer care.

Objective: This protocol outlines the proposed methodology to develop a core outcome set for measuring the impact of end-of-life prognostication in palliative cancer care.

Methods: We will adopt a mixed methods approach consisting of 3 phases using methodology recommended by the Core Outcome Measure in Effectiveness Trials (COMET) initiative. In phase I, we will conduct a systematic review to identify existing outcomes that prognostic studies have previously used, so as to inform the development of items and domains for the proposed core outcome set. Phase II will consist of semistructured interviews with patients with advanced cancer who are receiving palliative care, informal caregivers, and clinicians, to explore their perceptions and experiences of end-of-life prognostication. Outcomes identified in the interviews will be combined with those found in existing literature and taken forward to phase III, a Delphi survey, in which we will ask patients, informal caregivers, clinicians, and relevant researchers to rate these outcomes until consensus is achieved as to which are considered to be the most important for inclusion in the core outcome set. The resulting, prioritized outcomes will be discussed in a consensus meeting to agree and endorse the final core outcome set.

Results: Ethical approval was received for this study in September 2022. As of July 2023, we have completed and published the systematic review (phase I) and have started recruitment for phase II. Data analysis for phase II has not yet started. We expect to complete the study by October 2024.

Conclusions: This protocol presents the stepwise approach that will be taken to develop a core outcome set for measuring the impact of end-of-life prognostication in palliative cancer care. The final core outcome set has the potential for translation into clinical practice, allowing for consistent evaluation of emerging prognostic algorithms and improving communication of end-of-life prognostication. This study will also potentially facilitate the design of future clinical trials of the impact of end-of-life prognostication in palliative care that are acceptable to key stakeholders.

Trial Registration: Core Outcome Measures in Effectiveness Trials 2136; https://www.comet-initiative.org/Studies/Details/2136

International Registered Report Identifier (IRRID): DERR1-10.2196/49774

(JMIR Res Protoc 2023;12:e49774) doi:10.2196/49774

KEYWORDS

core outcome set; palliative care; end-of-life; prognosis; advanced cancer; systematic review; interviews; Delphi study

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Introduction

Background

Palliative care is a service provided to patients with life-limiting illnesses, such as advanced cancer, focusing on improving quality of life and symptom management through the early identification, assessment, and treatment of pain and other ailments [1,2]. It can also enable patients to understand their choices for treatment while providing physical, psychological, social, and spiritual support to patients and their families or informal caregivers alike.

Prognostication is broadly defined as the process of making predictions about the future, such as the likely outcome or course of a disease and the chance of recovery or recurrence. This research is specifically concerned with prognostication of survival, or end-of-life (EOL) prognostication. Prognostication of EOL is a vital component of patient management and decision-making in palliative care [3,4]. An accurate prognosis of the EOL allows patients and their families or informal caregivers adequate time to prepare, such as making financial plans and identifying their preferences for place of death [5]. Medically, an accurate prognosis can allow clinicians to identify appropriate treatment strategies based on individual patients' prognostic factors and symptoms [4].

Currently, there is no gold standard for prognostication of EOL. Many prognostic methods rely on clinician-estimated prognosis [5]. However, clinicians' survival predictions are often inaccurate, inconsistent, and overoptimistic [6,7]. Various prognostic tools have been validated for use in palliative cancer care, and they may provide better accuracy, consistency, or other benefits in comparison with clinicians' predictions [5]. However, the impact of such prognostic algorithms has yet to be established, and inconsistency in outcome reporting among prognostic studies makes it difficult to compare results.

Rationale for Core Outcome Set Development

The selection of appropriate primary and secondary outcome measures is an essential component of study design; a study is only as credible as its end points [8]. However, researchers may select outcomes that do not reflect meaningful end points for all stakeholders, namely patients and informal caregivers or clinicians [9,10]. Inconsistency in end points across a particular area of research can be a barrier to comparing study findings, reducing the feasibility of meta-analysis, and perpetuating outcome reporting biases [10]. Heterogeneity of outcomes has been noted in palliative care research. Previous studies have often focused on outcomes deemed important by experts, namely academics and clinicians, thereby overlooking patients' and other stakeholders' opinions and experiences and hindering the translation of findings into clinical practice [11-14].

A core outcome set (COS) promotes consistency in outcome selection among studies within a particular population, such as palliative cancer care, by providing a consensus-based, agreed minimum set of clinically meaningful outcomes to be measured and reported in all clinical trials of a specific population [15]. The Core Outcome Measures in Effectiveness Trials (COMET) initiative provides guidance for COS developers planning to construct a COS [15]. First, it is recommended that outcomes in existing published and ongoing studies be identified. Interviews with patients, informal caregivers or family, and other stakeholders can then be performed to ascertain outcomes important to them and assist research teams in understanding why particular outcomes are important [16]. Next, a Delphi process is advised, where key stakeholders such as patients, informal caregivers, and those who design and use research rank all the outcomes identified in the previous 2 phases until consensus is reached on which ones are the most important. The result is an agreed set of core outcomes.

There is as yet no consensus on which outcomes should be used to assess the impact of EOL prognostication in palliative cancer care. This study will develop a COS to assess prognostic impact, which will assist in preparing for future impact studies.

Scope of the COS

Palliative care can be provided to people living with a variety of disease types and chronic illnesses, including but not limited to cancer, cardiovascular diseases, chronic respiratory disease, diabetes, and acquired immunodeficiency syndrome [1]. This study will focus on palliative care in patients with a life-limiting, advanced, or progressive cancer to avoid confounding outcomes that might arise from including all such a wide range of illnesses. This will be the first study to investigate and define a COS for prognostic research in palliative cancer care. For the purpose of this study, the term *palliative cancer care* will be defined as treatment, care, and support provided to those with a life-limiting, advanced, or progressive cancer that cannot be cured [1,2]. This is a working definition, in that this definition has been chosen for the purpose of this study, and we recognize that it may not fully conform with established or authoritative definitions of *palliative cancer care*. Informal caregivers will include family members, friends, or other individuals who provide a wide range of unpaid assistance for someone with whom they have a personal relationship, including but not limited to physical and psychological support [17,18].

The intervention of interest in our study is EOL prognostication, defined as any process of estimating and communicating the likelihood of survival (ie, how long an individual has left to live) [5].

Aim and Objectives

This study aims to create a COS for measuring the impact of EOL prognostication in palliative cancer care.

The objectives for the whole study are as follows:

1. To develop a list of outcomes relevant to the impact of EOL prognostication in palliative cancer care.
2. To prioritize outcomes for measuring the impact of EOL prognostication in palliative cancer care that are important to relevant stakeholders, namely, patients, informal caregivers, and clinicians.
3. To achieve consensus on a minimum set of relevant outcomes to assess the impact of EOL prognostication in palliative cancer care.

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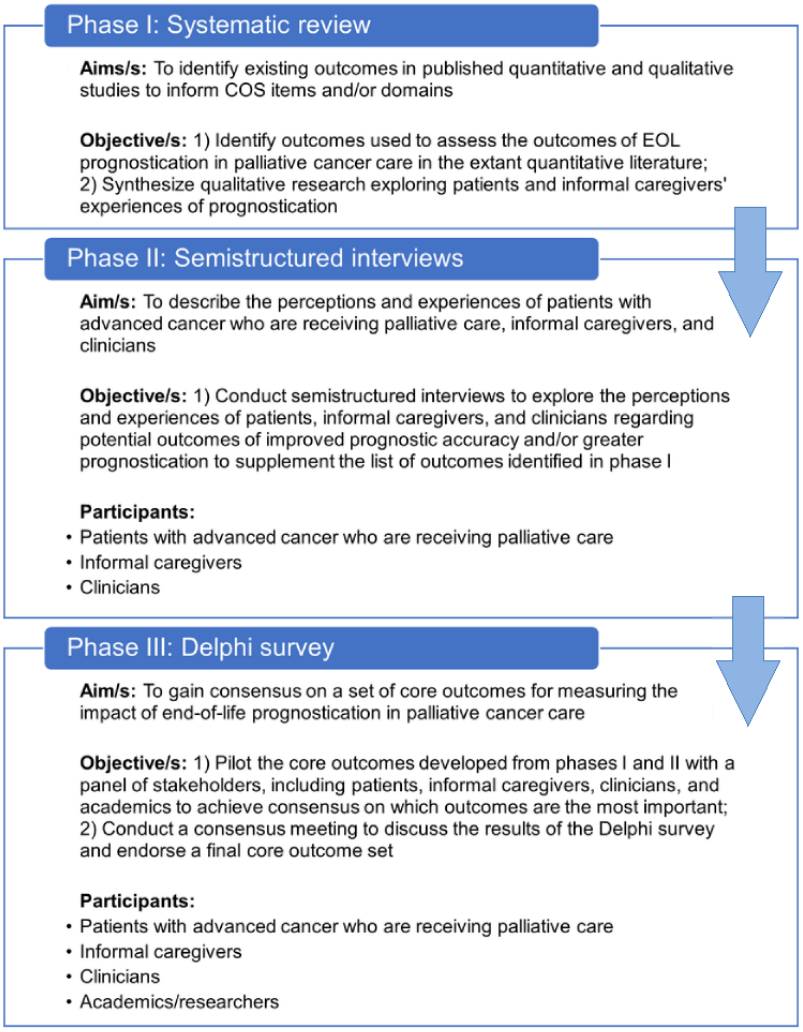
Methods

Design

This study will adopt a multiphase, mixed methods approach suggested by the COMET guidelines [15] and will adhere to the Core Outcome Set—STAndards for Development (COS-STAD) recommendations to support the development, implementation, and evaluation of the COS [19]. This study protocol was written following the Core Outcome Set—STAndardized Protocol Items (COS-STAP) guidelines for reporting protocols of COS development [20].

The study will consist of three phases: (1) a systematic literature review of relevant outcomes reported in extant quantitative and qualitative literature to measure the impact of EOL prognostication in palliative cancer care; (2) semistructured, qualitative interviews to explore the views and experiences of patients, informal caregivers, and clinicians; and (3) a Delphi study to prioritize outcomes derived from phases I and II. Figure 1 shows a summary of the study design.

Figure 1. Phases of developing a core outcome set (COS) for the impact of end-of-life (EOL) prognostication in palliative cancer care.



Stakeholders and Setting

This study will involve four stakeholder groups: (1) patients with advanced cancer who are receiving palliative care, (2) informal caregivers, (3) clinicians, and (4) academics or researchers. We will recruit patients, informal caregivers, and clinicians through palliative care services from 3 sites in London, United Kingdom, including 2 National Health Service trusts and 1 hospice. We will begin recruitment to the study by placing posters advertising the study in public spaces of the participating sites to recruit patients (both inpatients and outpatients), informal caregivers, and clinicians simultaneously. These posters will include the researchers' contact information so that interested individuals can contact them for further details regarding the study, to ask questions, or to express their interest in participating.

Where possible, a researcher (CS) will also attend weekly multidisciplinary team meetings within the sites and be available on site to encourage clinical staff to identify patients who are eligible to participate and who are physically and mentally capable. The researcher will only attend multidisciplinary team meetings at a time point agreed with the clinical team (ie, at the beginning or the end) to discuss the study and will leave before any confidential patient information is discussed. A member of the patient's direct clinical care team (ie, someone who is currently treating them) will make the first approach to potential participants to ask them if they would be interested in participating in the study, and if so, whether they give

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permission for the clinical team to provide the minimum, necessary information (name and contact details) for the researcher to approach them. The researcher will only approach participants who have consented (ie, verbally) for them to do so. The researcher or clinical staff will provide such patients with a participant information sheet and the researchers' contact information. If present at the time, informal caregivers will also be asked if they would be interested in participating in the study.

An invitation email, participant information sheet, and researcher contact information will be shared with palliative care clinicians at participating sites. We will also contact relevant organizations, such as the Association for Palliative Medicine of Great Britain and Ireland and the European Association for Palliative Care, to recruit national and international palliative care clinicians. We will ask the group or association chair to forward an email to group members that contains the participant information sheet and a link to the first round of the survey.

We will identify academics or researchers through opportunity sampling. We will ask colleagues and other contacts to suggest potential participants who have the relevant experience and are able to read and write in English. To encourage participation from a wide geographical area, we will screen academic profiles on UK and international university websites to identify individuals who have conducted relevant work. Heads of palliative care research departments may also be contacted and asked whether any members of their team have conducted research within the field of palliative care and would be willing to put us in contact. Additionally, the reference list of any relevant reviews will be searched to identify academics who have published research in the palliative care settings, and the authors who have cited relevant papers will also be screened for eligibility.

For phase II, we estimate that we will need to recruit 8 to 10 participants per group (patients, informal caregivers, and clinicians), making a total of 24 to 30 participants. This sample size is based on a previous COS study's recommendations, as well as the research team's experiences of qualitative research [21]. However, data collection will continue until data saturation is reached. Data saturation will be determined to have occurred when no new themes are being identified in analysis. Data collection will occur concurrently with recruitment to minimize attrition.

There is currently no consensus on how to determine the sample size for a Delphi survey. Balancing the sample size in a Delphi survey is crucial for achieving meaningful consensus; larger sample sizes may present challenges in terms of communication and follow-up, leading to lower response rates, whereas smaller sample sizes can restrict the scope and reliability of the survey results [22-24]. When considering sample size, it is also important to consider attrition that is likely to occur between each round. Therefore, based on previous studies' recommendations [25,26], we took a pragmatic decision to recruit a minimum of 10 participants to represent each stakeholder group, with a minimum of 40 participants in total. For pragmatic reasons, and to ensure that we include a range of perspectives, we aim to recruit a minimum of 10 international experts. For the consensus meeting, we will recruit approximately 4 participants from each stakeholder group. Maintaining a balance between stakeholder groups is important to ensure that certain voices are not overpowered. This group size will be manageable for a web-based meeting, while still permitting a range of perspectives to be heard.

Phase I: Systematic Literature Review

Phase I of the study was completed in June 2023. The complete protocol for this systematic literature review, including the search strategy and study selection criteria, was submitted for registration on PROSPERO (the International Prospective Register of Systematic Reviews) on March 29, 2022, and was subsequently published on the PROSPERO website on April 1, 2022 (CRD42022320117). This review was conducted according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 statement [27].

The aim of this systematic literature review was to identify existing outcomes to inform COS items and domains. Retrieved papers were analyzed in two subsets: (1) quantitative studies (clinical trials and observational studies), seeking to identify the outcomes used in previous research to measure the impact of EOL prognostication in palliative cancer care, and (2) a systematic review and thematic synthesis of qualitative studies exploring patients' and informal caregivers' experiences of EOL prognostication in palliative cancer care.

We carried out searches using the following electronic databases from inception to September 2022: Ovid MEDLINE, Ovid Embase, Ovid PsycINFO, CINAHL, and the Cochrane Library (both the Cochrane Controlled Register of Trials and the Central Register). We also extended searches to gray sources and adopted snowballing techniques to identify additional papers and ensure literature saturation. Search terms included keywords related to prognostication, palliative care, advanced cancer, and outcomes and cognate terms. Search limits were applied to restrict results to a human, adult population, and studies published in English language only due to limitations in resources. Eligibility criteria included (1) patients with advanced cancer, or their informal caregivers; (2) prognostication, defined as any process of estimating and communicating the length of survival of an individual's disease; (3) quantitative studies that reported outcomes of prognostication; and (4) qualitative studies that explored experiences and perceptions of prognostication.

The search results from each database were imported and deduplicated in the Rayyan software [28]. The titles and abstracts of the studies were screened by 4 independent reviewers using the above-mentioned eligibility criteria. Those that met the inclusion criteria for either review question were read in full by at least 2 authors. Discrepancies were resolved through discussion between authors. If no consensus could be reached, a third author was consulted.

Methodological quality was assessed using the Mixed Methods Appraisal Tool [29]. A narrative approach was used to undertake the quantitative synthesis, along with tables of outcomes, their descriptions, and measures. Outcomes were categorized using the taxonomy for COS recommended by COMET [30]. For the qualitative analysis, the analysis was guided by Thomas and 'Harden's [31] framework for thematic synthesis, with 3 stages.

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The COMET taxonomy was used as an external framework to support the development of analytical themes and facilitate the combination of the results of both the quantitative and qualitative studies. A narrative description of each theme in relation to the review question was provided.

The results of the review have been accepted for publication in an academic journal and will be taken forward for consideration for inclusion in the COS.

Phase II: Semistructured Interviews

The second phase of this study will be a qualitative study using semistructured interviews to explore the perceptions and experiences of patients, informal caregivers, and clinicians regarding the potential outcomes and impact of EOL prognostication.

Participants

We will use purposive, maximum variation sampling to capture a range of patients, informal caregivers, and clinicians with the characteristics shown in Textbox 1. To achieve this, we will collaborate closely with staff at participating sites and seek to identify a diverse sample, accounting for characteristics such as age, gender, ethnicity, socioeconomic status, education level, cancer diagnosis, relationship to the person with cancer, and professional role. This will enable us to ensure that our study includes a broad spectrum of perspectives and experiences, making our research findings more comprehensive and representative. For pragmatic reasons related to resource availability, we will only be able to recruit participants who are able to communicate in and understand written and spoken English.

Textbox 1. Eligibility criteria for phase II.

Inclusion criteria

- Patients
  - Aged ≥18 years
  - Receiving palliative cancer care as per the prespecified definition [1,2]
- Informal caregivers
  - Aged ≥18 years
  - Identifies as an informal caregiver, as per the prespecified definition [17,18]
  - Have provided such care within the last 12 months before study recruitment, irrespective of survival (in cases where the informal caregiver is bereaved, they will be contacted no less than 6 months after bereavement out of respect and concern) [32]
- Clinicians
  - A registered health care professional (eg, a physician, nurse, or allied health professional) employed in the palliative care services at one of the participating sites, who routinely estimates and provides end-of-life (EOL) prognostic predictions

Exclusion criteria

- Patients
  - Children (aged <18 years)
  - Individuals who, in the opinion of their treating clinician, would not be appropriate to participate in this research
  - Individuals who have previously expressed a wish not to be involved in research
  - Individuals who lack capacity to give informed consent
- Informal caregivers
  - Young informal caregivers (aged <18 years)
  - Informal caregivers who, in the opinion of the clinician gatekeeper, would be inappropriate to approach about enrollment in the study due to physical or mental illness
  - Individuals who lack capacity to give informed consent
- Clinicians
  - Clinicians whose role in palliative care is undertaken exclusively outside of the United Kingdom (to avoid varying, potentially confounding practices)
  - Clinicians who do not routinely estimate and provide EOL prognostic predictions in palliative cancer care

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Data Collection

Participants will be invited to take part in one semistructured interview, which will be conducted by one researcher (CS) with individuals either face-to-face, via video call, or via telephone, depending on practical considerations, participant preferences, and any prevailing COVID-19 restrictions. Interviews are anticipated to last between 30 minutes and 1 hour and will be conducted in a quiet environment, at a convenient time for the participant. From our experience, people with advanced cancer may only be willing or able to be interviewed for 30 minutes at a time, so we will be flexible in meeting their needs and will either continue for longer if they are comfortable or take a break. Before the interview starts, the interviewer will explain the concept of the COS and the importance of measuring the impact of prognostication in palliative care. Participants will also be asked to provide basic demographic information for descriptive reasons only.

The interviews will be semistructured using a topic guide. The main topics covered will be consistent across the interviews, but the specific phrasing of questions and when they are posed during the interview will vary depending on how the conversation develops throughout the interview. Interviews will be audio-recorded with the participant's consent.

Data Analysis

Interview transcripts will be analyzed thematically using a framework analysis approach. Audio recordings will be transcribed verbatim. A researcher (CS) will independently read the transcripts and generate initial codes. A second researcher (BV) will independently read a sample set of interviews to provide a second, independent perspective and ensure that all codes capture the range and depth of data. The 2 researchers will develop initial proposals for themes and then meet to discuss and agree broad themes. CS will then review and construct a final set of themes. The data from these interviews will be analyzed alongside the data from phase I, so as to identify outcome domains to be included in the long list of core outcomes to be taken forward into phase III. Descriptive statistics will be used to present demographic information.

Phase III: Delphi Survey

Once a list of core outcomes has been developed from phases I and II, we will carry out a Delphi survey and consensus meeting to achieve consensus between disparate stakeholders, including patients, informal caregivers, clinicians, and academics or researchers, about which of these outcomes are most important. An international sample of clinicians and academics or researchers will be sought to widen the generalizability of the final COS.

Participants

The goal is to have representation of different perspectives about which are the important outcomes to include in the COS. The Delphi panel members should reflect the population that is intended to use the COS or who will be involved in subsequent research studies that use the COS [33]. Therefore, the participant panel will comprise 4 key stakeholder groups: patients, informal caregivers, clinicians with clinical experience in palliative care, and academics or researchers with research experience in palliative care. We will use convenience sampling, as well as opportunity and snowball sampling to achieve a maximum variation sample by including people with the characteristics shown in Textbox 2.

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Textbox 2. Eligibility criteria for phase III.

Inclusion criteria

- Patients
  - Aged ≥18 years
  - Receiving palliative cancer care as per the prespecified definition [1,2]
- Informal caregivers
  - Aged ≥18 years
  - Identifies as an informal caregiver, as per the prespecified definition [17,18]
  - Have provided such care within the last 12 months before study recruitment, irrespective of survival (in cases where the informal caregiver is bereaved, they will be contacted no less than 6 months after bereavement out of respect and concern) [32]
- Clinicians
  - A registered health professional (eg, a physician, nurse, or allied health professional) with experience in estimating and providing end-of-life (EOL) prognostic predictions in palliative care and who is currently or was recently clinically employed (ie, not retired for >12 months or dismissed from clinical work)
  - Palliative care experience can be within the United Kingdom or international
- Academics or researchers
  - Academics or researchers who have published research, written or supervised a thesis, or contributed to a book chapter on the topic of prognostication in palliative care
  - Research experience can be within the United Kingdom or international
  - These experts may also be clinicians; however, this will not be a requirement

Exclusion criteria

- Patients
  - Children (aged <18 years)
  - Individuals who, in the opinion of their treating clinician, would not be appropriate to participate in this research
  - Individuals who have previously expressed a wish not to be involved in research
  - Individuals who lack capacity to give informed consent
- Informal caregivers
  - Young informal caregivers (aged <18 years)
  - Informal caregivers who, in the opinion of the clinician gatekeeper, would be inappropriate to approach about enrollment in the study due to physical or mental illness
  - Individuals who lack capacity to give informed consent
- Clinicians
  - Clinicians who are not clinically employed in the last 12 months (ie, retired or dismissed from clinical work)
  - Clinicians who do not routinely estimate and provide EOL prognostic predictions in palliative cancer care
- Academics or researchers
  - Academics or researchers whose experience lies within the generic topic of palliative care without any specific experience in prognostication

Data Collection

The Delphi survey will comprise multiple web-based surveys that will be answered anonymously by stakeholders until consensus is achieved about which outcomes should be included in the COS. The outcomes resulting from the systematic review and the semistructured interviews will be prioritized by the participants in up to 3 of these web-based Delphi rounds via secure, web-based software (REDCap; Vanderbilt University) [34,35].

In round 1, participants will be asked to grade the importance of each outcome on the long list relative to the other outcomes in terms of how important they think they are in measuring the impact of improved prognostication. A 9-point Likert scoring

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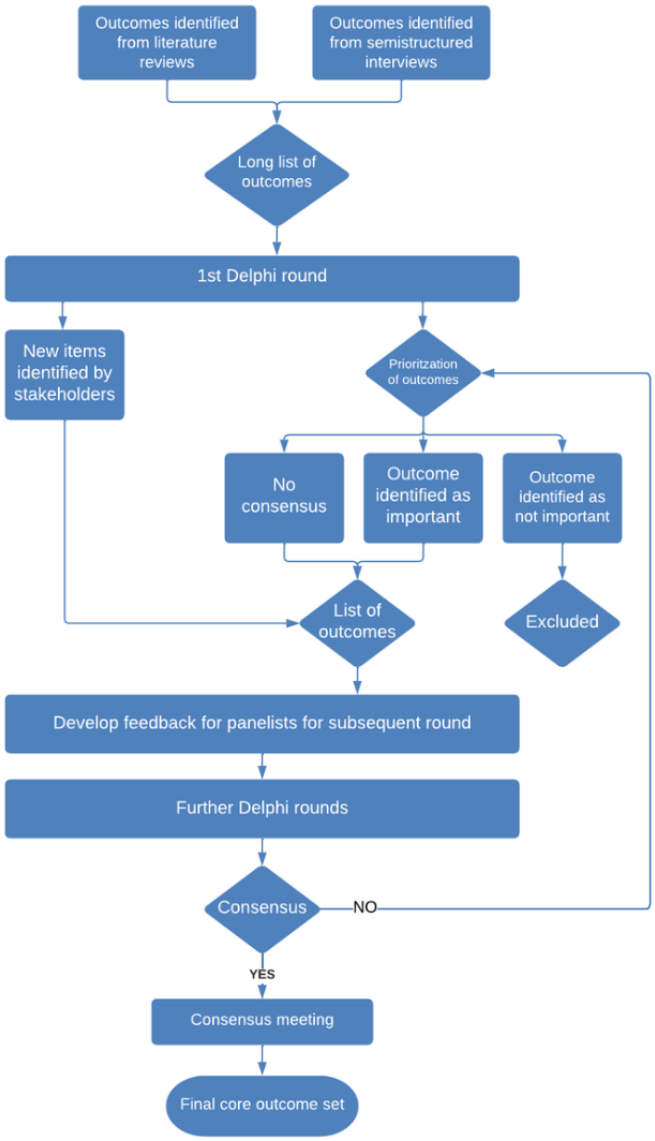
system will be used, where a score of 1 to 3 denotes "low importance," 4 to 6 is "important, but not critical," and 7 to 9 is "critical," as per the GRADE (Grading of Recommendations Assessment, Development and Evaluation) scale [36]. Participants will also be provided with an "unable to score" response if they consider themselves unable to rate any of the outcomes, as well as a free textbox to provide any comments.

It is anticipated that each survey will take approximately 30 minutes to complete. Participants will be given 2 weeks to respond to the survey. Participants will also have the opportunity to identify any outcomes that they think are relevant from their perspective, but which were not included in the initial list. This will facilitate the inclusion of outcomes that may be relevant but were not obtained in phases I and II of the study.

The group's ratings will be analyzed together, and outcomes removed or included depending on the group consensus. The survey will be repeated (with modifications) up to 3 times. Group descriptive statistics and a summary of comments will be generated after each round and sent to the participants during the next round of the survey. All comments and ratings shared will be anonymous.

If after 3 rounds, items remain without consensus, the Delphi survey will be terminated and the outcomes with no consensus, alongside those with consensus for inclusion and exclusion, will be presented at the consensus meeting where a final decision will be made. The aim of this meeting will be to discuss the results of the Delphi survey and vote on the final COS. Participants for the consensus meeting will be purposefully selected from the Delphi survey participants. The consensus meeting will be conducted via a web platform for practical reasons, allowing for the inclusion of international participants and accommodating any prevailing COVID-19 restrictions. This remote format is generally adopted in COS consensus meetings as it ensures accessibility, safety, and global representation, promoting a more inclusive and fruitful discussion during the meeting [37]. The panel will be asked to confirm whether they agree (or not) with the inclusion or exclusion of the outcomes in the COS. The result of this will be the final, consensus-agreed COS. Figure 2 summarizes the Delphi process proposed in this study.

Figure 2. Flow chart of the Delphi process.



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Data Analysis

To determine which items should be included in the final COS, the thresholds recommended by the COMET initiative will be used [10]. Consensus for inclusion or "consensus in" will be defined as ≥70% of all participants rating the outcome as "critical" (GRADE score 7-9) and ≤15% of all participants rating the outcome as of "low importance" (GRADE score of 1-3). Consensus for exclusion or "consensus out" will be defined as ≥70% of the participants rating the outcome as of "low importance" and ≤15% of all responses rating the outcome as "critical." Outcomes meeting consensus for "not important for inclusion" will be removed and the remaining outcomes carried forward to the next round. Outcomes that are rated as "critical" or of "low importance" by one panel will be carried forward to the next Delphi round. For example, outcomes rated <70% by informal caregivers, clinicians, and academics, but with a patient rating of >70%, will be considered "patient-important" and included in the next round.

The same definitions for "consensus in" or "consensus out" will be applied to the consensus meeting.

Patient and Public Involvement

We advertised the opportunity to be involved in this research project as part of a patient and public involvement (PPI) advisory group through the National Institute for Health Research "People in Research" website and the Marie Curie Research Voices Group. Our advisory group included members of the public with experience of talking about prognosis, either as someone with advanced cancer or as one caring for someone with advanced cancer, who reviewed the protocol and all participant-facing documents. They advised on how the protocol could be adapted to ensure that the research study meets the needs and preferences of those taking part. They also made suggestions for how the documents might be made more suitable for participants, particularly for those receiving palliative care, to ensure that sensitive language was used.

In the future, we will consult this PPI advisory group regarding the format of the Delphi survey, before distributing it to participants, to ensure that it is easy to understand, access, and use. Specifically, the group will be requested to review and streamline the extensive list of outcomes intended for inclusion in the Delphi survey. We recognize that lengthy lists can be daunting for Delphi participants, potentially impacting their engagement. The PPI advisory group's expertise will be invaluable in identifying and addressing this risk, guiding us in minimizing the occurrence of overly lengthy lists and ensuring that the Delphi survey is well received and productive. We will also ask the group to review and propose outcome names and plain-language descriptions for each outcome. This step aims to ensure that all participants interpret the concepts as intended, reducing the potential for misunderstandings and enhancing the overall clarity of the survey.

During the data analysis, we will ask members to comment on the plain-language presentation of findings to ensure that this is understandable and relevant. We will also seek input from members of the PPI advisory group when disseminating results of the study to ensure that we communicate the study in a way that is appropriate for the general public.

The involvement of the PPI advisory group in these crucial aspects of the study has already made, and will continue to make, a considerable contribution to the success and impact of our research. In particular, this facilitates more meaningful participation and the likelihood of gaining valuable insights from participants.

Ethics Approval and Informed Consent

Ethical approval was obtained for this study from the London-Camberwell St. Giles Research Ethics Committee and the Health Research Authority on September 6, 2022 (reference 22/LO/0469).

Written, informed consent will be obtained from participants taking part in face-to-face interviews, the first round of the Delphi survey, and consensus meeting. Verbal, recorded consent will be obtained from participants being interviewed over the telephone or via a web platform. Participation in sequential rounds of the Delphi survey will be considered indicative of consent.

Dissemination

Promoting the uptake of the COS is paramount in preventing research waste and involves engaging key stakeholders, raising awareness, and demonstrating its value and relevance [38]. To achieve this, we will aim to disseminate findings to academic and research community audiences via publications in peer-reviewed journals and as presentations or posters at regional, national, and international palliative care conferences. After the finalization of the COS, further research will be necessary to identify the most suitable outcome measures or instruments for each core outcome. Subsequently, we will conduct a comprehensive evaluation of their quality and feasibility. To encourage adoption, we will collaborate with relevant journals and funding bodies, urging them to incorporate the COS in their guidelines for researchers and authors. Furthermore, we will actively seek feedback from researchers who pilot the COS in their studies. Being open to updates and revisions based on emerging evidence and feedback, we will continually improve the COS, ensuring its continued relevance and value over time.

The findings will be disseminated to participants in the form of plain-language summaries at the end of the study. To reach wider public audiences, plain-language newsletters, tweets, or blog posts will be published. Professional and clinical groups will also receive the findings as research summaries for participants and by engaging with palliative care representatives such as the palliative care team at the participating sites.

The final COS will be shared with the expert panel so they can verify the changes made and review what the project produced.

Results

As of July 2023, we have completed and published the systematic review (phase I) and have started recruitment for phase II. So far, we have recruited 5 patients, 10 informal caregivers, and 10 clinicians. We are still recruiting patients for

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phase II. Data analysis for phase II has not yet started. We anticipate that the recruitment for the Delphi survey will begin in January 2024. We expect to complete the study by October 2024 and publish the results by June 2025.

Discussion

Anticipated Study Findings and Potential Impact

This study protocol presents what will be the first study that aims to develop a COS to measure the impact of EOL prognostication in palliative cancer care. The objective of this COS is to involve various stakeholders in its development and reach a consensus on the essential outcomes that hold significance for this population. Developing a COS for measuring the impact of EOL prognostication in palliative cancer care is an important step to improve patient care and communication of EOL prognoses. By addressing the inconsistent outcome measurement in existing studies and aligning the outcomes with those that are important to stakeholders, our COS has the potential to help standardize and improve prognostic research in palliative cancer care, such as the development of prognostic algorithms. Furthermore, the findings from this study have the potential to ensure that outcomes measured in future prognostic impact studies will reflect what is important to such stakeholders and ultimately facilitate the translation of the findings into clinical practice [39-41]. Once the COS is finalized, further research will be required to establish which outcome measures or instruments are most appropriate for each of the core outcomes, followed by an evaluation of their quality and feasibility.

Comparison With Existing Literature

Currently, research on the impact of EOL prognostication in palliative cancer care faces a significant challenge because of the measurement of different outcomes across various studies. Academic and clinical interests often dominate the selection of outcomes, potentially neglecting their meaningfulness to patients or informal caregivers [9,10]. Consequently, some studies might employ outcomes that do not resonate with those directly impacted by prognostic information. Moreover, the lack of uniformity in outcome measurement across studies hampers the ability to compare or combine results, leading to research wastage. A COS will address these issues. This COS aims to integrate the perspectives and experiences of patients and other personally affected stakeholders. By doing so, it is expected to enhance the translation of research findings into clinical practice and foster comparability in future prognostic research in palliative cancer care. Ultimately, this harmonized approach will optimize the use of research efforts and promote more effective advancements in the field.

Strengths and Limitations

This will be the first COS specifically focused on measuring the impact of EOL prognostication in palliative cancer care. The development of the COS will involve a rigorous and systematic search to gather the views and opinions of patients and other key stakeholders. Engaging with these groups will not only ensure that their perspectives are considered but will also enhance the overall relevance and applicability of the COS. By making the protocol for the COS publicly available, we will ensure the transparency and replicability of our study.

The inclusion of only adult English-speaking participants in this study might potentially limit the generalizability of the findings. Nevertheless, to mitigate this limitation, we will actively seek the involvement of international participants in the Delphi survey. Additionally, in phase I of the study, the systematic review considered international publications to minimize the risk of selection bias.

It is essential to acknowledge that conducting the Delphi survey using a web-based software may lead to underrepresentation of certain groups, particularly those who lack digital skills and access. To address this concern, we will explore alternative methods of data collection to ensure broader representation if it becomes apparent that our sample is significantly biased.

Recruiting and retaining participants may pose a challenge in our study, especially given the nature of the target population, who may face health deterioration or bereavement. To minimize attrition during phase II, we will conduct interviews concurrently with recruitment, aiming to interview participants shortly after enrollment to reduce dropouts. If a participant or caregiver cannot proceed with the interview, we will document their reasons for withdrawal and continue recruiting until reaching our desired number of interview participants or research data saturation, whichever occurs first. Attrition in Delphi surveys is a common challenge, resulting from both participant factors and reduced interest over time during multiple rounds [42]. Although we will send regular reminders and strive for timely rounds, it is challenging to minimize attrition resulting from external circumstances. Furthermore, the survey's anonymity prevents us from knowing specific reasons for dropouts or withdrawals. Despite this limitation, we will openly acknowledge its impact in any published results.

Employing stakeholder meetings to determine the final COS carries the risk of bias based on the opinions expressed by those present. To counteract this, we will make diligent efforts to encourage participation from all stakeholder groups. Despite our efforts, there remains a possibility of underrepresentation for a particular stakeholder group, and we will be transparent about this potential limitation in our study.

Conclusions

The necessity for a COS to measure the impact of EOL prognostication within palliative cancer care arises from the need to enhance outcome measurement and reporting. This COS has the potential to make a substantial impact on the field by advancing prognostication practices and aligning outcome measures with the preferences and requirements of patients and other important stakeholders. As a result, it will enable more precise comparisons and better synthesis of evidence across various prognostic studies.

The overall promise of this study lies in its potential to elevate the quality of care and decision-making for patients facing EOL care in the context of palliative cancer care. By standardizing and improving the measurement and reporting of prognostic outcomes, the COS will play a vital role in optimizing patient

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outcomes and enhancing the overall care experience for those in need.

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Data Availability

The data sets generated during and/or analyzed during this study are not publicly available due to the sensitive nature of the information, and participants' consents for public data sharing were not obtained in this study.

Authors' Contributions

PS, BV, NW, and CS contributed to the design of the review and protocol development. CS led on drafting of the manuscript. All authors contributed to revisions and approved the final version.

Conflicts of Interest

None declared.

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Abbreviations

COMET: Core Outcome Measures in Effectiveness Trials
COS: core outcome set
COS-STAD: Core Outcome Set—STAndards for Development
COS-STAP: Core Outcome Set—STAndardized Protocol Items
EOL: end of life
GRADE: Grading of Recommendations Assessment, Development and Evaluation
PPI: patient and public involvement
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO: The International Prospective Register of Systematic Reviews

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Protocol

Wellness in Nursing Education to Promote Resilience and Reduce Burnout: Protocol for a Holistic Multidimensional Wellness Intervention and Longitudinal Research Study Design in Nursing Education

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Abstract

Background: The United States faces a nursing shortage driven by a burnout epidemic among nurses and nursing students. Nursing students are an integral population to fuel the nursing workforce at high risk of burnout and increased rates of perceived stress.

Objective: The aim of this paper is to describe WellNurse, a holistic, interdisciplinary, multidimensional longitudinal research study that examines evidence-based interventions intended to reduce burnout and increase resilience among graduate and undergraduate nursing students.

Methods: Graduate and undergraduate nursing students matriculated at a large public university in the northeastern United States are eligible to enroll in this ongoing, longitudinal cohort study beginning in March 2021. Participants complete a battery of health measurements twice each semester during the fourth week and the week before final examinations. The measures include the Perceived Stress Scale, the Satisfaction with Life Scale, the Oldenburg Burnout Inventory, the Brief Resilience Scale, and the Pittsburgh Sleep Quality Index. Participants are eligible to enroll in a variety of interventions, including mindfulness-based stress reduction, mindful eating, fitness training, and massage therapy. Those who enroll in specific, targeted interventions complete additional measures designed to target the aim of the intervention. All participants receive a free Fitbit device. Additional environmental changes are being implemented to further promote a culture that supports academic well-being, including recruiting a diverse student population through evidence-based holistic admissions, inclusive teaching design, targeted resilience and stress reduction workshops, and cultural shifts within classrooms and curricula. The study design protocol is registered at Open Science Framework (DOI 10.17605/OSF.IO/NCBPE).

Results: The project was funded on January 1, 2022. Data collection started in March 2022. A total of 267 participants have been recruited. Results will be published after each semester starting in December 2023. WellNurse evaluation follows the Rapid Cycle Quality Improvement framework to continuously monitor ongoing project processes, activity outcomes, and progress

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toward reducing burnout and increasing resilience. Rapid Cycle Quality Improvement promotes the ability to alter WellNurse interventions, examine multiple interventions, and test their effectiveness among the nursing education population to identify the most effective interventions.

Conclusions: Academic nursing organizations must address student burnout risk and increase resilience to produce a future workforce that provides high-quality patient care to a diverse population. Findings from WellNurse will support evidence-based implementations for public baccalaureate and master's nursing programs in the United States.

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nursing workforce; academic performance; burnout; resilience; wellness; nursing; education; nursing education; protocol; nursing students; students; holistic; implementation; workforce

Introduction

Background

The COVID-19 pandemic exacerbated already prominent feelings of burnout and stress among nursing students in the United States. Nursing students experienced high levels of perceived stress elicited by numerous interpersonal, intrapersonal, and community factors [1]. Nursing students' stress contributes to less academic engagement [2], and over 55% of nursing students report increased stress and worsened health after entering nursing school [3]. During the COVID-19 pandemic, economic strain, academic workload, and isolation from peers accelerated nursing students' stress and well-being [4]. Students cite limited clinical experiential learning and adjustment to web-based learning as prominent barriers influencing their intention to join the nursing workforce [4]. McKee-Lopez et al [5] found that adverse childhood experiences also contribute to mental health status among the nursing population, with nursing students experiencing a higher prevalence of adverse childhood events. Adverse childhood events have been associated with higher rates of burnout and depression among undergraduate nursing students [5]. Urban et al [6] found that nursing undergraduate students reported significantly higher stress levels than their nonnursing major peers. Moreover, COVID-19 can be seen as an adverse experience faced by all new incoming nursing students. A total of 60% of nurses younger than 35 reported an emotional, traumatic, or stressful event related to COVID-19 [7]. Nursing students are a critical component of the future nursing workforce. Currently, 55% of the nursing workforce experiences symptoms of burnout [8], contributing to an alarming acceleration of nurse turnover and shortages nationally. Stress does, in fact, predict nurses' job satisfaction and turnover intention [9]. In total, 25% of nurses left the profession in 2022 compared with 20% in 2020, and the average hospital turned over 95% of its nursing staff in the past 5 years [10].

Personal resilience, or the capacity to adjust positively to adversity to limit negative impacts, has been correlated with reduced burnout [6]. As the United States faces a critical shortage of nurses confounded by high rates of burnout and stress, nursing schools must develop interventions and strategies to reduce burnout and promote resilience among nursing students. Stress reduction interventions could promote improved stress management and mitigate burnout among students [2,3,11], which can support nursing student retention, on-time graduation, and resilience when students transition to the nursing workforce.

The health care profession's burnout crisis prompted the National Academy of Sciences to convene a committee and create a report that promotes the collective urgency to address burnout and resilience among health professionals, including nurses and students. Their vision includes a thriving health care workforce that provides high-quality care to patients in an environment that fosters their well-being [8]. The research study and project presented in this paper align with five of the seven priorities outlined by the academy: (1) create and sustain positive work and learning environments and culture; (2) invest in measurement, assessment strategies, and research; (3) support mental health and reduce stigma; (6) institutionalize well-being as a long-term value; and (7) recruit and retain a diverse and inclusive health workforce. There is a lack of substantive research that applies longitudinal analysis, large sample sizes, or randomization to support effective interventions that reduce burnout and promote resilience among nursing students [12], which this study aims to address.

WellNurse (Wellness in Nursing Education to Promote Resilience and Reduce Burnout) is a longitudinal research study implemented at a public nursing school in the northeastern United States to reduce burnout and increase resilience among nursing students. This multidimensional study examines the effect of various interventions on burnout, resilience, perceived stress, and academic performance. This paper aims to describe the comprehensive and holistic interventions and measures provided to nursing students at a public university in the northeast offering BSN and MSN education.

WellNurse Project Goals

The project's overarching purpose is to reduce burnout and increase resilience among nursing students at a public university in the northeast. Several objectives were implemented to achieve this aim, including (1) providing access to evidence-based mindfulness-based stress reduction (MBSR) to nursing students, faculty, and staff within a 3-year time frame; (2) providing evidence-based physical fitness, nutritional, and peer mentor training and support to all nursing students, faculty, and staff; (3) establishing a resilience and stress management curriculum to sustain program activities after the grant period with a credit-bearing course; and (4) creating an environment and

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culture that embraces resilience, wellness, diversity, equity, and inclusion. The study design protocol is registered at Open Science Framework [13].

Methods

Participant Recruitment

Matriculated graduate and undergraduate nursing students, faculty, and staff older than 18 years who complete a web-based consent form are eligible to participate in the study. The initial phase of the study occurred from March to May 2022, and recruitment is ongoing as new students and faculty will enter the program through December 2024.

The recruitment strategy involves the WellNurse research team visiting various in-person and remote nursing classes and hosting meetings with administrative staff and faculty. The team also posts recruitment messages on the school's social media pages. Participants are offered a free Fitbit and enrollment in various interventions described below and can choose whether or not they consent to the evaluation aspect of the project. Some academic courses provide course credit, extra credit, or clinical hours to students who agree to participate. Faculty and staff are provided work time to participate in the interventions.

Measures

Comprehensive Wellness Survey

After completing a web-based consent form, participants complete a comprehensive health behavior survey. This survey is distributed during week 4 and again during week 14 (the week before finals week) in the fall and spring semesters. Week 4 was selected based on the typical nursing student's academic loads and stress. Examinations and competency testing begin each semester's third to fourth week, accelerating stress during those periods. Participants complete the comprehensive health behavior survey during designated class or work time. Additional measures are collected before specific engagement in targeted study interventions. Participants' answers are tracked through the project using unique ID codes. As listed below, several variables are assessed to capture the health of nursing students. The comprehensive measurement strategy aligns with Priority Area 2 from the National Academy of Sciences [8], which recommends the longitudinal use of valid and reliable measurements of burnout and factors that mitigate burnout to drive effective interventions and data-driven decision-making at the organizational level.

Demographics

Participants are asked several sociodemographic questions, including gender identity, sexuality, and ethnicity. Participants also provide their grade point average. Student progression status is also tracked to determine how various interventions influence retention and on-time graduation.

Perceived Stress Scale

The Perceived Stress Scale (PSS) is used to measure perceived stress. The scale includes 10 items that address experiences of distress related to "how unpredictable, uncontrollable, and overloaded respondents find their lives" [14]. Example items include "In the last month, how often have you felt that you were unable to control the important things in your life?" and "In the last month, how often have you felt difficulties were piling up so high that you could not overcome them?" The PSS demonstrates reliability and validity among healthy college populations [14].

Satisfaction With Life Scale

The Satisfaction with Life Scale is used to measure satisfaction with life. The 5-item Satisfaction with Life Scale [15] uses Likert scale responses ranging from "strongly agree" to "strongly disagree." An example item is "The conditions of my life are excellent." The measure demonstrates strong validity and reliability in past research [16,17].

Oldenburg Burnout Inventory

The Oldenburg Burnout Inventory is a 16-item measurement tool that measures the concepts of disengagement and exhaustion to assess burnout. Participants rank statements such as "When I work, I usually feel energized," with Likert responses ranging from "strongly agree" to "strongly disagree." The Oldenburg Burnout Inventory is a valid and reliable measure of burnout related to work and academics [18].

Brief Resilience Scale

The Brief Resilience Scale is a 6-item scale that measures resilience and one's ability to bounce back and recover from stress. The Brief Resilience Scale is a valid and reliable measure of resilience [19].

BMI

BMI screens for weight categories that may be associated with health problems and reflects a person's weight in kilograms divided by the square of height in meters [20]. Participants were asked to self-report their height and weight, and a BMI for each participant was derived accordingly.

Pittsburgh Sleep Quality Index

Sleep quality is measured using the 2-item Pittsburgh Sleep Quality Index [21], which assesses participants' estimated average hours of sleep per night and overall perception of sleep quality within the past 7 days. This survey has demonstrated acceptable validity and reliability in past research [21].

Nutrition Assessments

WellNurse participants have an opportunity to engage in a mindful eating cooking workshop conducted by a registered dietitian nutritionist. Before attendance, participants are required to complete a web-based registration form and relevant assessments. The assessments involve multiple health and nutrition behavior surveys, described below.

Mindful Eating Questionnaire

The Mindful Eating Questionnaire was developed to measure mindful eating, which can be described as nonjudgmental awareness of physical and emotional sensations associated with eating [22]. This 28-item scale comprises several subdomains, including disinhibition, awareness, external cues, emotional response, and distraction. Scores range from 0 to 4, with higher scores indicating greater mindful eating skills. This scale has been previously validated in adult populations [22].

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Food Preparation Experience and Confidence Survey

This survey measures cooking self-efficacy and frequency of use of 13 different cooking styles (eg, boiling, baking, and microwaving). Participants are asked to rate their perceived confidence of each cooking method, ranging from confident, to uncertain, to not confident. This survey has been validated among young adults [23].

Body Appreciation Scale

Body appreciation reflects positive body image and has been previously associated with higher levels of self-esteem and lower levels of coping by avoidance. The Body Appreciation Scale is composed of 13 items, to which participants are asked in a Likert format the frequency to which they exhibit each statement [24]. Examples of statements on the questionnaire include "I respect my body" and "I do not focus a lot of energy being concerned with my body shape or weight." Scores range from 1 to 5, with higher scores indicating higher levels of body appreciation. This scale has been validated among young adults [24].

Weight Satisfaction

Weight satisfaction is measured using 3 items. The first asks, "Which of the following are you trying to do about your weight?" This gives respondents the ability to state that they are trying to lose weight, gain weight, stay the same weight, or that they are not doing anything about their weight. The second item measures how they feel about their current weight, with responses including "happy," "upset," or "don't care." The third item inquires about their desired weight in pounds. Weight satisfaction is then determined using the formula: [(actual weight – desired weight)/actual weight × 100].

Short Healthy Eating Index

Diet quality is measured using the Short Healthy Eating Index, validated in college populations [25]. Higher scores indicate greater adherence to the Dietary Guidelines for Americans, 2020-2025 [26].

Physical Activity Assessments

WellNurse participants have an opportunity to engage in physical fitness training to prepare for a 5K walk or run. Before and after the training, participants complete a comprehensive measure of physical activity.

International Physical Activity Questionnaire

The International Physical Activity Questionnaire measures participants' frequency of physical activity [27]. This 4-item instrument provides an overall estimate of physical activity levels over a week. The measure is valid and reliable in assessing college students' physical activity [28].

Fitabase Data Collection

Participants also have an opportunity to receive a free Fitbit Versa 2 (Fitbit). Because various health indices can be derived from ongoing data collection metrics within the Fitbit, participants complete an in-person consent form separate from the WellNurse consent form before receiving their device. The WellNurse research team connects each Fitbit to the web-based database, *Fitabase*. Fitabase tracks a multitude of movement and health-related behaviors, including steps taken per day, distance traveled, calories burned per day, heart rate variability (sedentary-very active minutes, logged physical activity, floors, basal metabolic rate, and resting heart rate), and sleep behavior (minutes in light sleep, deep sleep, and rapid eye movement sleep).

Mindfulness-Based Stress Reduction

Participants who sign up to participate in MBSR complete additional pre- and postintervention measures.

Five Facet Mindfulness Questionnaire

Mindfulness is measured using the Five Facet Mindfulness Questionnaire. This survey is composed of 39 questions and five subscales, including (1) observing, (2) describing, (3) acting with awareness, (4) nonjudging, and (5) nonreactivity. This survey has demonstrated good validity and reliability in past research [29].

Positive and Negative Affect Scale

Participants are asked to complete the 20-item Positive and Negative Affect Scale, which measures underlying experiences of positive or negative feelings of mood or emotion. This survey has demonstrated excellent validity and reliability in past research [30].

Massage Therapy

Short Form PSS

The Short Form PSS is a 4-item perceived stress survey that demonstrates validity and reliability [31]. Participants who receive a massage are invited to complete the Short Form PSS before the massage session and again 1 week later. Additionally, they have an option to complete a qualitative question on the follow-up survey, "Describe how massage therapy has affected your stress, anxiety, or happiness. Use specific examples if possible."

Attendance Records

When participants attend any additional workshop or activity, such as an exercise class, massage, or use of the WellNurse room, they sign in to track attendance.

Interventions Under Investigation

Holistic and comprehensive interventions are under investigation that align with 4 of the National Academy of Health's priorities areas: Priority 1: create and sustain positive work and learning environments and culture; Priority 3: support mental health and reduce stigma; Priority 6: institutionalize well-being as a long-term value; and Priority 7: recruit retain a diverse and inclusive health workforce [8].

Environmental and System Interventions

Diversity, Equity, and Inclusion

According to the United States Census Bureau [32], individuals from ethnic and racial minority groups accounted for 40% of the population in 2022. Nursing programs have a responsibility to recruit and retain a more diverse student body and more diverse faculty and staff to build a vibrant nursing workforce that reflects the diversity of the population it serves [33].

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Therefore, several institutional changes were implemented and are ongoing to promote a culture that embraces diversity, equity, and inclusion (DEI).

A DEI committee was established at the school in 2021. An extensive holistic admission review training was provided to the faculty and staff who interface with the admission process. A holistic admission review process was implemented that includes objective and relational admission measures. Training and workshops about diverse populations were implemented as part of routine team meetings and class presentations. Curricular experts offered courses and programming to promote faculty transforming their courses to align with Inclusive Teaching Design. Inclusive teaching is being responsive to the diversity of the class and designing learning environments that include all students while allowing students to be engaged in an equitable learning environment and feel a sense of belonging [34]. The design begins with a clear syllabus outlining tools needed for success in a course, and transparent assignment frameworks highlighting what the learner needs to do, why they need to do it, how they should do it, and how their work will be evaluated. Faculty also include an intersectionality statement in the syllabus to state their commitment to the collective diversity learners bring to the learning environment.

Classes also include a *Getting-to-Know-You Survey* before the first class meeting that identifies learner preferences and perceived barriers to learning for early intervention. The survey is used for targeted student outreach, with an initial email offering resources specific to their concerns and a frequently asked question response to all students for commonly asked questions. Building community is a focus of the first class meeting. Students introduce themselves and share pictures from their life on the learning management software discussion board. Faculty share their social identities with the class and discuss the contexts that impact learning and teaching. Vulnerability and reflexivity are essential to breaking down real and exaggerated power differentials in the course. Ground rules are discussed and published on the learning management system during the first class. A reflection prompt completed in the first meeting allows learners to consider how they manifest their nurse role. Establishing purpose with a sense of belonging and self-confidence is threaded throughout the class meetings. Holistic admissions practices and inclusive teaching strategy training from experts are incentivized among faculty and staff and ongoing.

The faculty who teach Psychiatric Mental Health Nursing implemented wellness and resilience strategies in their classrooms. Faculty provided students with several mindfulness and wellness classroom options, such as guided meditations; mindful movement and stretching; and information about campus resources before class, during times of transition, or after emotionally taxing lecture content such as suicide. Faculty also implemented short meditations before examinations and provided extra credit to engage in any of the WellNurse programming.

WellNurse Room

A conference room in the School of Nursing was converted to a WellNurse room. The WellNurse room signals an institutional and systemic investment in supporting the resilience of incoming students, faculty, and staff. The renovation also promotes recruitment into the MBSR program by raising the profile of these activities with dedicated space for practice.

Participants are invited to attend free workshops that aim to promote healthy behavior change through evidence-based practices. Each workshop is designed and led by an interdisciplinary member of the research team. Advertisements for upcoming workshops are posted to the School of Nursing's social media pages and through email blasts. Attendance is optional. Workshops address various topics of concern, including the role of diet quality, sleep, and navigating test anxiety. Health behavior workshops are held monthly, both remote and in-person. Recordings are available to participants upon request.

Classroom Enhancements

Faculty integrate selected WellNurse interventions into their classes by offering extra credit or providing assignments attached to interventions. Additionally, faculty use class time to implement short periods of mindfulness either through guided meditations, outdoor walks, or open discussion about how students might embrace mindfulness and self-care during a rigorous schedule.

Wellness and Resilience Social Media Presence

A graduate student was hired to promote WellNurse activities and interact with students on social media. These posts highlight brief research findings about resilience, stress, and well-being among nurses and students. They also guide students through time management, test-taking strategies, community-building activities, and more.

Mindfulness-Based Stress Reduction

MBSR is an 8-week experiential program including 2.5-hour weekly class sessions and a 1-day silent retreat. MBSR engages participants in simple evidence-based mindfulness practices, including meditation, mindful walking and movement, cognitive reframing, and communication strategies. Pioneered in 1979 by Dr Jon Kabat-Zinn at the University of Massachusetts Medical Center, MBSR includes didactic and experiential training that teaches participants to cultivate self-awareness by redirecting attention away from past or future concerns and focusing instead on the present moment. With regular practice, participants learn to change habitual stress reactivity patterns and instead more flexibly respond to stress with adaptive coping. As a result, participants learn to avoid internalizing stress in reactive patterns of negative emotion [35] and, thus, reduce distress and prevent negative health and mental health outcomes.

WellNurse partnered with the University of California San Diego School of Medicine Center on Mindfulness and Brown University Mindfulness Center to provide remote, 8-week MBSR courses via Zoom and intensive week-long, in-person MBSR courses. MBSR was offered as an elective course to count toward the students' elective requirements for Nursing. Additionally, faculty and staff were provided work time to participate in the program. Selected WellNurse project personnel including faculty, staff, and graduate students completed a

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multiyear teacher training certification process through the University of California San Diego and Brown University Mindfulness Center to develop a group of certified MBSR teachers to support long-term project sustainability.

MasterChef: Nursing Edition

This monthly workshop is innovative in combining gamified learning, cooking self-efficacy, mindful eating, and nutrition education for prelicensed nursing students. The course outline consists of (1) mindful eating concepts, (2) nutrition education, (3) participants designing their own healthful and accessible recipe, (4) participants mindfully eating and voting on their favorite meal, and (5) discussion and application to clinical practice. Participants are also encouraged to do 2 "homework" assignments per week, each emphasizing healthy eating or mindfulness behaviors. Participants also receive ingredients for recreating their healthful recipe at home and a "dorm-friendly" recipe book developed by a registered dietitian nutritionist. All students, staff, and faculty are encouraged to join, but students in designated courses receive credit for attendance.

Fitness Interventions

Participants are eligible to receive a free Fitbit Versa 2. Fitness trainers provide weekly 5K training in the fall and spring semesters to prepare participants for a 5K walk or run. Additionally, the campus recreation center offers nursing-specific fitness courses such as yoga and full-body workouts to promote a fitness community. Faculty are integrating fitness step challenges using the Fitbit devices as part of class assignments.

Ethics Approval

The University of Maine institutional review board reviewed and approved the WellNurse research project procedures (02-05-2-2022).

Results

Overview

The project was funded on January 1, 2022. Data collection started in March 2022. A total of 267 participants have been recruited. Results will be published after each semester starting in December 2023.

The primary study variables will be analyzed 4 times per year to track population outcomes and changes. Regression analysis will be conducted to examine the relationship of students' on-time progression, stress, resilience, and burnout with physical and emotional health variables and on-time progression. Subanalysis will be conducted for unique groups such as first and fourth year students, faculty and staff, and graduate students, as well as students from historically underrepresented populations such as first-generation college students and racial and ethnic minorities. Additionally, program retention, on-time graduation, and faculty and staff retention will be tracked over time. The cost of implementing MBSR, massage therapy, MasterChef, and fitness events will be tracked to determine cost per student. Additionally, feasibility will be measured using qualitative focus group interviews with students who complete specific interventions along with attrition rates for completing specific interventions such as MBSR and MasterChef.

MBSR Analysis

Quantitative evaluation of MBSR outcomes will be conducted by comparing MBSR participants with matched control participants at selected intervals with regard to key study variables (eg, stress, burnout, and mindfulness skills). Participants enrolled in MBSR are assessed immediately before their first MBSR session and immediately after completing the final MBSR session. Matched controls are identified for each MBSR participant by randomly selecting nonenrolled individuals from the WellNurse participant pool on the basis of identical gender identity, birth year, and role (faculty, staff, and student). Controls are assessed at the same intervals as MBSR participants.

Statistical analysis will test whether MBSR participants differ significantly from controls with regard to postintervention levels of each outcome variable, controlling for preintervention levels. ANOVA models will be used to conduct initial comparisons. With time, larger samples, and thus more statistical power and more complex models (eg, multilevel modeling), can be tested to evaluate the potential impact of instructor, delivery modality (in-person vs remote), duration (1 week vs 8 weeks), and dose (number of sessions attended), as well as individual participant characteristics (eg, gender identity and role). Ongoing assessments for all WellNurse participants will allow for longer term follow-up of MBSR and control participants with regard to distal outcomes of interest (eg, academic retention). We expect significant differences between MBSR and control participants; immediate postintervention effects may be strongest, with somewhat weaker longitudinal effects observed over time. Analyses will also be able to test whether those participants who engage in ongoing mindfulness practice after formal MBSR training may experience improved outcomes as compared with those individuals who discontinue regular practice.

Physical Activity Analysis

Data logs generated from Fitbit devices will be collected from the Fitabase platform [36], a partner to Fitbit, and raw data will be preprocessed, including merging the data of all participants in the study and purging the data set from empty cells or invalid data. The privacy-respected data set, besides participants' ID and event date, involves information on 3 major categories—sleep, activity, and wearing time—with each category covering more information in their respective parameters for a duration of fall and spring academic semesters. The sleep category provides information ranging from sleep minutes in rapid eye movement, deep, light, and total asleep minutes to sleep efficiency. The activity category is reporting time and distances traveled in very active, moderately active, lightly active, and sedentary modes, alongside calories, basal metabolic rate, and approximated heart rate levels. Analysis of the data set is done using the Python language [37] and the Scikit-learn [38], Pandas [39], Numpy [40], Matplotlib [41], and Seaborn [42] packages by applying the multiple linear regression method and also generating a heatmap of the parameters.

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MasterChef Analysis

MasterChef will be evaluated initially for feasibility through a qualitative focus group design along with an expert content analysis. After modifications to the program based on feasibility analysis, the intervention will be evaluated using a matched-based cohort design with the non-MasterChef control group selected based on gender, ethnicity, and year in college matched-based design, with a focus on gender, ethnicity, and year in college. Descriptive and frequency statistics were used to analyze the sample's baseline and demographic data. A 2-way repeated-measures analysis will be used to assess significant changes in baseline and postintervention outcomes within the experimental group and as a comparison with the control. Participants will complete the aforementioned nutrition measures before the week-long Fall 2023 program delivery, directly after the program, and again at the end of the semester. A control will be recruited through a matched-based design. A 2-way repeated-measures ANOVA will be used to identify significant changes between baseline data, postintervention data, and follow-up data between the intervention and control group. The program will also be implemented in the format of monthly workshops. A multivariate ANOVA will be used to compare health outcomes between curriculum formats. Multiple linear regressions will be used to identify predictors of diet quality using the combined fall and spring samples. Significance levels will be set at $P<.05$.

Discussion

Principal Findings

Stress and burnout among nurses and students is not a new phenomenon. However, the COVID-19 pandemic has exacerbated the challenge and demonstrated the urgency in mitigating stress to improve well-being and resilience and reduce burnout. As the United States faces a looming nursing shortage and burnout crisis, more research that includes large sample sizes and longitudinal studies is needed to determine and implement resilience-building and stress reduction interventions within nursing programs [12]. Interventions that demonstrate effectiveness at improving student retention, reducing the risk of burnout, and improving resilience and well-being will be infused into a course, which will be embedded as part of the standard nursing curriculum.

Comparisons With Prior Work

WellNurse Room

Effective strategies to promote resilience and reduce burnout require system and environmental interventions [43]. The room contains floral murals, live plants, aromatherapy, meditation cushions, light therapy, coloring books, and tactile engagement. The WellNurse room is stocked with meditation cushions and a massage therapy table. Weekly mindfulness sessions are offered to support MBSR practices. A licensed massage therapist provides complimentary massage therapy in 15- to 30-minute sessions. Aromatherapy and massage therapy have shown stress-reducing effects [44,45]. This study aims to understand how environmental changes may influence nursing students' resilience, stress, and well-being.

Mindfulness-Based Stress Reduction

Extensive literature supports MBSR as an effective intervention in reducing burnout among nurses [46-52].

MBSR, meditation, and mindful movement are further effective in treating posttraumatic stress disorder and depression symptoms [35], preventing substance use relapse, and curbing binge-eating behavior [53-55]. MBSR has demonstrated better outcomes for binge-eating than cognitive-behavioral therapy [56] and is as effective as anxiolytic medication in managing anxiety disorders [57].

College students with mindfulness training have been able to better resist the negative impact of stress during challenges [58], and mindful movement and meditation are both recommended as nonpharmacologic interventions to reduce stress and anxiety among college students [43]. Among medical students, these practices were found to improve happiness, self-confidence, endurance, and patience [59]. Systematic reviews have demonstrated that MBSR decreases stress and burnout and increases resilience, coping, and job satisfaction among nurses [60,61]. Given MBSR's significant benefits with regard to physical and mental health and its demonstrated impact in nursing and college student populations, this evidence-based intervention was an ideal fit for the WellNurse nursing students. This study aims to examine the effect of MBSR on graduate and undergraduate nursing students', faculty's, and staff's resilience, perceived stress, mindfulness, and burnout.

Nutrition

Nursing students report poor diet quality and dietary behaviors elicited by high levels of perceived stress, peer influence, and academic workload [62]. The impact of mindful eating may mediate this relationship [63]. Mindful eating describes applying mindfulness practices to internal hunger and satiety cues and incorporating a nonjudgmental, self-compassion–led viewpoint in navigating dietary choices [64]. Mindful eating interventions effectively improve several health behaviors, including reducing extreme dieting behaviors, improving portion control, and weight reduction within some populations [65,66]. This study aims to examine the effect of the newly developed program, MasterChef Nursing Edition, on nursing students' diet quality, resilience, burnout, and well-being.

Fitness

Physical activity reduces stress and anxiety [67-70], and stress and anxiety are associated with increased burnout and decreased resilience among nurses [52]. A review of 37 studies on Fitbit-based interventions demonstrated the effectiveness of this wearable technology for physical fitness support; wearing a Fitbit significantly increased daily step counts and moderate to vigorous physical activity and significantly decreased weight [69]. Although students have access to healthy food and physical fitness environments, nursing programs do not systematically integrate support systems that promote physical well-being [12,71-74]. The aim of this study is to examine the effect of fitness interventions on nursing students', faculty's, and staff's burnout, resilience, fitness, and well-being.

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Conclusions

WellNurse aims to examine multiple resilience-building and stress-reducing strategies while creating a culture that promotes student, faculty, and staff well-being in concert with academic and clinical preparedness and job satisfaction. Dissemination of findings will be released as they are available with an anticipated release date of initial findings in 2024.

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Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during this study.

Conflicts of Interest

None declared.

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Abbreviations

DEI: diversity, equity, and inclusion
MBSR: Mindfulness-Based Stress Reduction
PSS: Perceived Stress Scale

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Protocol

A Digital System (YouXin) to Facilitate Self-Management by People With Psychosis in China: Protocol for a Nonrandomized Validity and Feasibility Study With a Mixed Methods Design

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Abstract

Background: Psychosis is one of the most disabling mental health conditions and causes significant personal, social, and economic burden. Accurate and timely symptom monitoring is critical to offering prompt and time-sensitive clinical services. Digital health is a promising solution for the barriers encountered by conventional symptom monitoring approaches, including accessibility, the ecological validity of assessments, and recall bias. However, to date, there has been no digital health technology developed to support self-management for people with psychosis in China.

Objective: We report the study protocol to evaluate the validity, feasibility, acceptability, usability, and safety of a symptom self-monitoring smartphone app (YouXin; Chinese name 佑心) for people with psychosis in China.

Methods: This is a nonrandomized validity and feasibility study with a mixed methods design. The study was approved by the University of Manchester and Beijing Anding Hospital Research Ethics Committee. YouXin is a smartphone app designed to facilitate symptom self-monitoring for people with psychosis. YouXin has 2 core functions: active monitoring of symptoms (ie, smartphone survey) and passive monitoring of behavioral activity (ie, passive data collection via embedded smartphone sensors). The development process of YouXin utilized a systematic coproduction approach. A series of coproduction consultation meetings was conducted by the principal researcher with service users and clinicians to maximize the usability and acceptability of the app for end users. Participants with psychosis aged 16 years to 65 years were recruited from Beijing Anding Hospital, Beijing, China. All participants were invited to use the YouXin app to self-monitor symptoms for 4 weeks. At the end of the 4-week follow-up, we invited participants to take part in a qualitative interview to explore the acceptability of the app and trial procedures postintervention.

Results: Recruitment to the study was initiated in August 2022. Of the 47 participants who were approached for the study from August 2022 to October 2022, 41 participants agreed to take part in the study. We excluded 1 of the 41 participants for not meeting the inclusion criteria, leaving a total of 40 participants who began the study. As of December 2022, 40 participants had completed the study, and the recruitment was complete.

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Conclusions: This study is the first to develop and test a symptom self-monitoring app specifically designed for people with psychosis in China. If the study shows the feasibility of YouXin, a potential future direction is to integrate the app into clinical workflows to facilitate digital mental health care for people with psychosis in China. This study will inform improvements to the app, trial procedures, and implementation strategies with this population. Moreover, the findings of this trial could lead to optimization of digital health technologies designed for people with psychosis in China.

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KEYWORDS

psychosis; self-management; digital; smartphone app; eHealth; mHealth; China

Introduction

Background

Psychosis is one of the most disabling mental health conditions and causes significant personal, social, and economic burden [1], which increases the risk of physical health problems and reduces life expectancy by around 20 years [2]. Within 5 years after the first episode, 80% of people with psychosis will have at least one relapse [3]. The prevalence of schizophrenia in China is the highest in the world [4]. A recent Chinese national survey showed that the lifetime prevalence rate of schizophrenia and other psychotic disorders was 0.7% [5], and schizophrenia accounted for 13.7% of all mental and substance disorder disability-adjusted life years in 2019 [6].

Accurate and timely symptom monitoring is arguably one of the essential components of quality clinical services. Conventional symptom monitoring approaches in mental health services face several practical and methodological challenges. First, conventional methods rely on clinical interviews or comprehensive assessment batteries, which can be carried out only by trained professionals and require service users to attend an in-person meeting with their health provider. However, a lack of resources means that access to in-person services is limited; the wait times between referral and assessment can range from 4 weeks to 6 months or longer [7]. Meanwhile, organizational barriers (eg, financial availability, transportation) and attitudinal barriers (eg, stigma, reluctance to seek help) prevent people with mental health problems from attending appointments regularly [8]. Moreover, accessing in-person services has been further hindered by the COVID-19 pandemic, since clinic visits have been restricted to mitigate virus transmission [9,10].

Second, the conventional approach to assessing symptoms lacks ecological validity; current methods for assessing service users' difficulties, broadly speaking, capture cross-sectional information rather than continuous information over a certain period of time [11,12]. Clinical visits tend to be scheduled mostly, at best, monthly, which means health care providers only get a snapshot of service users' conditions every 2 weeks to 6 weeks. However, clinically meaningful symptom fluctuation, such as mood or hallucinations, may occur on a daily basis [13], which conventional methods struggle to capture.

Third, recall bias has long been identified as a limitation of conventional clinical assessment methods [11,14]. Service users, especially people with severe mental health problems for which cognitive impairments are common [15], may have trouble accurately recalling their thoughts, feelings, and behaviors over a preceding period of time, making recall experiences at a granular level challenging [16]. Therefore, to optimize the quality of assessment and capture symptom fluctuation in a real-time, real-world granular manner, more ecologically valid assessment methods are needed.

The aforementioned barriers affect countries worldwide [14], even high-income countries with sophisticated mental health service systems (eg, the United Kingdom and the United States) [17,18], and China has been no exception to these challenges.

Mental Health Services in China

China has invested substantial resources to reform its mental health system to improve the accessibility and quality of mental health services in the past 15 years; however, the effort has only been partially successful, and the mental health treatment gap remains significant [19,20]. The estimated shortage of mental health professionals in China was 40,000 relative to the population need [21]. According to the WHO Global Health Observatory, as of 2015, there were only 2.20 psychiatrists, 5.42 mental health nurses, and 0.07 mental health hospitals per 100,000 population in China [22]. In contrast, in the United States, there are 10.54 psychiatrists, 4.28 mental health nurses, and 0.19 mental hospitals per 100,000 population [22]. Moreover, since the Chinese health care system is designed as hospital-centered care [23], most well-trained mental health care professionals (ie, psychiatrists, mental health nurses, and psychologists) are concentrated in psychiatric hospitals located in urban areas, which makes it difficult for people in rural or remote communities to access care [24,25].

In China, mental health services are primarily delivered through psychiatric hospitals [26-28]. Compared with other settings (ie, general hospitals and community-based settings), tertiary psychiatric hospitals are best placed to provide quality mental health services, which results in service users overwhelmingly concentrated in tertiary psychiatric hospitals causing long wait times and reduced service quality [26].

The Role of Digital Health

Digital health is a promising solution to address both the barriers encountered by the conventional symptom monitoring approach [14] and China's health care system that has a shortage of mental health care resources [29,30]. The ubiquitous accessibility of digital technologies (eg, smartphones) provides unprecedented potential to scale-up service provision. Smartphone ownership

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rates in China have reached 96% [31]. Previous studies showed that smartphone ownership by people with psychosis was comparable with that of the general population [32]. More specifically, the internet access rate reached 90.9% of people with a diagnosis of schizophrenia in Hong Kong [33], and people with mental health problems in China in general were willing to accept mobile health interventions and considered them helpful [34]. Integrating digital health technologies (DHTs) into clinical workflows provides the potential to augment evidence-based care, support shared decision-making, and increase continuity of care [35]. These potential benefits are true for all countries worldwide and arguably even more so for countries with less sophisticated mental health care systems such as China. We conducted a systematic review on digital mental health in China and found that DHTs were generally feasible and acceptable among people with mental health problems, including people diagnosed with schizophrenia [29].

Among different types of DHTs, smartphones are the most advantageous tool for symptom monitoring given their ability to generate a plethora of data through active and passive monitoring methods [14]. Active monitoring is typically defined as the user self-reporting data (eg, psychological, behavioral, physiological) by ecological momentary assessment or other ambulatory assessment methods [12]. Passive monitoring refers to using the smartphone and its embedded sensors or a wearable device to measure the user's behavior pattern (eg, app usage, activity log) or contextual information (eg, location) via passive user data collection [36]. By combining active and passive monitoring, smartphone-based monitoring has the potential to provide a more dynamic, personal, and valid representation of a person's emotional and behavioral state [16,37]. Additionally, studies have shown that active self-monitoring of symptoms can reduce positive psychotic symptoms in people with recent-onset psychosis [38].

Smartphone-based symptom monitoring for people with psychosis has proved to be feasible in the Western context [39]; however, only 1 study conducted in non-Western, low and middle-income countries tested a digital platform with a symptom monitoring element [40]. To date, no smartphone-based symptom monitoring tool has been developed and evaluated for people with psychosis in China [29].

Study Objectives

The aims of this study are to evaluate the validity, feasibility, acceptability, and safety of a symptom self-monitoring smartphone app (YouXin) for people with psychosis in China.

Methods

Ethical Considerations

The study was approved by the University of Manchester (Ref: 2022-13262-24297) and Beijing Anding Hospital (Ref: [2021] Research No.58) Research Ethics Committee. The study was conducted in full conformance with all relevant legal requirements and the principles of the Declaration of Helsinki, Good Clinical Practice, and the UK Policy Framework for Health and Social Care Research 2017. Potential participants were given a participant information sheet to read. The detailed informed consent procedure is described in the Recruitment section. Participants were informed that they are free to withdraw from the study at any time and for any reason. Withdrawal from the study did not impact participants' access to standard care at Beijing Anding Hospital. The delivery of the intervention did not affect any form of clinical care participants received, and they continued to be actively supported by the hospital during their participation in the study. Study data are anonymous and were managed according to the data management plan described in the Data Management section. Participants were given a ¥100 (US $13.76) gift voucher for each completed assessment. For participants who took part in the interview, at the end, they were given a ¥100 (US $13.76) gift voucher as a thank you for their time and to cover any costs incurred as a result of their participation. This information was included in the participant information sheet and was provided to participants before they entered the study.

Study Setting

The study took place at Beijing Anding Hospital of Capital Medical University, which is one of the largest tertiary psychiatric hospitals in the Beijing metropolitan area. The hospital has 800 beds, an average 5000 inpatient admissions per year, and over 1200 daily outpatient visits.

Study Design

The study uses a mixed methods design consisting of a nonrandomized feasibility study and a nested qualitative acceptability study. The study was designed according to the Consolidated Standards of Reporting Trials (CONSORT) statement extension for pilot and feasibility studies [41]. We recruited 40 people with psychosis at a tertiary-level psychiatric hospital in Beijing, China. This number is in line with other feasibility studies and sufficient to report on response rates, follow-up rates, safety information, and attrition, as well as the clinical characteristics of our study population at the beginning of the study and at follow-up [42]. Formal power calculations for treatment effects are not appropriate for a study primarily aimed at establishing feasibility. This sample size means a monthly recruitment target of 10 participants. Moreover, monitoring the recruitment target is part of the feasibility outcomes.

Eligibility Criteria

Eligibility criteria were deliberately inclusive to fully assess feasibility and validity of the app and to reach generalizable conclusions for a wide range of service users with psychosis. Due to the limited resources, the research team could not provide devices to participants who did not own a smartphone. However, according to a recent survey study in China, 83.2% of service users and family members reported owning and frequent use of mobile devices [34]. Participant inclusion and exclusion criteria are presented in Textbox 1.

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Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria:

- Diagnosed with schizophrenia spectrum according to DSM-5 (F20-F29) or met the criteria for being at clinically high risk for developing psychosis according to the Structured Interview for Prodromal Syndromes (SIPS)
- Aged 16 years to 65 years
- Receiving care from Beijing Anding Hospital and will continue to be actively supported by the hospital over the next 5 weeks (ie, the duration of the project's participant enrollment period)
- Own and able to use a smartphone

Exclusion criteria:

- Diagnosed with organic or substance-induced psychosis
- Lack of capacity to provide informed consent
- Unsafe to participate in research as viewed by their treating clinician (ie, clinically unstable or at risk for self-harm or harm to others)

Recruitment

Participants were recruited from Beijing Anding Hospital, which is a major tertiary psychiatric hospital located in Beijing, China. Participants were initially approached by a clinician working at the hospital to introduce the project and assess the willingness and potential eligibility of the potential participant to participate in the study. If participants appeared to be eligible and willing to participate, they were referred to the principal researcher who confirmed their eligibility. When eligible, potential participants were given a participant information sheet to read, and their contact details were obtained by the researcher with their consent. The principal researcher followed up with a phone call to the potential participant after at least 48 hours to explain the details of the study and answer any questions that the potential participant had about the study. If the potential participant was still interested in taking part, a face-to-face meeting was arranged to obtain written consent to participate using a hard copy consent form prior to conducting the baseline assessment at the same meeting. Participants were recruited until the recruitment target was met (n=40).

Study Intervention and Procedures

YouXin is a smartphone app designed to facilitate symptom self-monitoring for people with psychosis. The app is adapted from the ClinTouch app [13], a self-monitoring app for psychosis validated against the Positive and Negative Syndrome Scale (PANSS) and the Calgary Depression Scale for Schizophrenia (CDSS) items. The PANSS and CDSS have been translated and validated in Chinese and have been widely used in practice in China [43,44]; however, app-based versions of these measures among people with psychosis have not been validated in Chinese. In this study, we translated the ClinTouch-based PANSS and CDSS items into Chinese and combined these items with passively collected data to develop the YouXin app to be tested in the Chinese context. Screenshots of the YouXin app are shown in Figure 1.

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Figure 1. Screenshots of the app prototype: (A) log-in page, (B) user center, (C) assessment module.

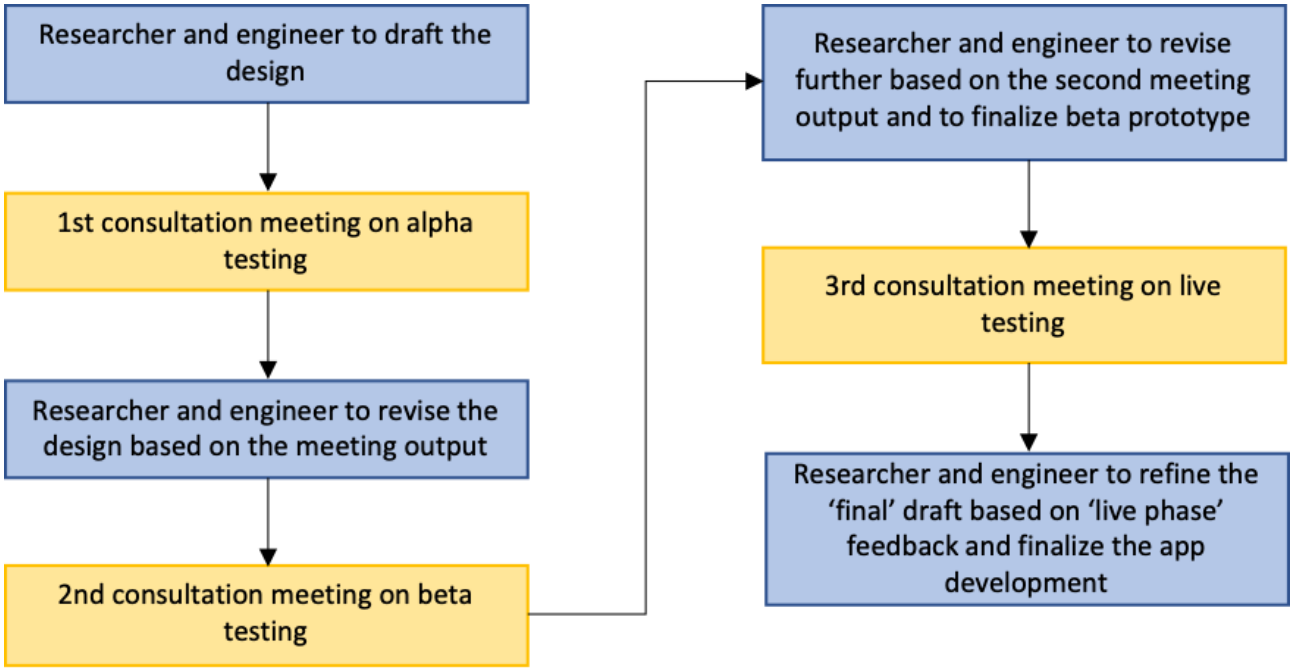


The YouXin development team consisted of experts from various disciplines, including academics, clinicians, software engineers, and experts by experience. The principal researcher led the development of the app and was supported by members of the research team who are academic clinicians at the University of Manchester (a Professor of Clinical Psychology and a Professor of Adult Psychiatry). A psychiatrist at Beijing Anding Hospital assisted the development of the app to ensure the content reflected the Chinese context. A technology team led by a computer scientist at Beijing Jiaotong University supported software development.

To maximize the usability and acceptability of the app for end users (ie, service users and clinicians), the development process utilized a systematic coproduction approach. A series of coproduction consultation meetings was conducted by the principal researcher with service users and clinicians at Beijing Anding Hospital. We used an iterative approach to coproduction, which means the outputs of a previous meeting formed the content of subsequent consultation meetings. The framework for coproduction (shown in Figure 2) was inspired by the process of development used for the Actissist app [45,46], a cognitive behavioral therapy–informed app designed to support people in the early phase of psychosis, and the UK government user research guidelines [47]. A series of participatory design consultations involving 3 phases (alpha, beta, and live phases) was held with service users with severe mental health problems and clinicians. As the YouXin app is adapted from the ClinTouch app, we skipped the discovery phase, which is normally used to generate ideas and hypotheses for a completely new product. The remaining 3 phases are described in Textbox 2.

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Figure 2. The coproduction process.



Textbox 2. The phases of the coproduction process.

Alpha:

- The alpha phase aims to understand the end users' (clinicians and service users) needs for using digital tools to monitor symptoms and demonstrate the preliminary design with users (the ClinTouch app and the user interface prototypes of the YouXin app). The design, contents, and functions of the app were further developed based on the feedback from users.

Beta:

- The principal researcher and software engineer integrated the feedback and delivered a functional prototype that users could install on their phones. During the meeting, users tested the app and provided feedback.

Live:

- A fully developed digital platform was presented to users (3 clinicians and 3 people with psychosis) to try out for a week. This meeting focused on evaluating the usability and acceptability of the app and any major issues regarding implementation.

YouXin has 2 core functions: active monitoring of symptoms (ie, smartphone survey) and passive monitoring of behavioral activity (ie, passive data collection via embedded smartphone sensors). The app is available for both Android and iOS platforms. The active monitoring uses a time-contingent design. To minimize participant assessment burden and increase compliance, in accordance with a previous similar study [38], prompts were set to alert at 2 pseudorandomized timepoints per day, during a 12-hour interval from 10 AM to 10 PM, 7 days a week for 4 weeks. A minimum 1-hour increment was set between each prompt on a particular day to avoid clustering of responses. Participants could either snooze (5 minutes or 30 minutes) or decline answering the prompt. Based on previous works by the research group, on average, it takes 70 seconds to complete each prompt. Smartphone sensors passively collected GPS data every 5 minutes. According to a recent systematic review [39], passive sensing was feasible for measuring negative symptoms; specifically, GPS indicators were associated with apathy, avolition, asociality, and anhedonia [48,49]. All collected data were uploaded to a secure server at Beijing Anding Hospital.

Participants were given a training session by the principal researcher to help them navigate the app after they consented to take part. During the training, the principal researcher helped the participant download the app onto their smartphone and gave a demonstration of the app. Participants had the opportunity to practice using the app and ask questions during the process; they had access to the app from the training session until the 4-week timepoint. An opt-out approach was applied to give participants autonomy to switch on or off the passive sensing section during the study.

The principal researcher provided technical support as needed during the study; no clinical care was provided by the research team (clinical care continued as usual from the service). The participant was referred to their treating clinician for appropriate mental health care should any clinical issues be raised to the research team. Participants were informed at the training sessions that the app is not suitable for seeking urgent medical care while in any emergency circumstance.

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Data Collection

The timeline of outcome assessments is summarized in Figure 3. Participants were assessed in an in-person meeting at baseline, 1 week after baseline, and 4 weeks after baseline. To assess the validity of the remote monitoring, PANSS and CDSS were assessed at 1 week to calculate the association between the active and passive monitoring results and relevant domains of the clinical assessment. To determine which outcomes are sensitive to change in this population, participants were asked to complete an assessment of relevant outcomes of the self-monitoring intervention at baseline and the 4-week timepoint. The assessor is a clinician, has been trained in the assessment measures used, and has rich experience in conducting assessments in clinical trials. Semistructured qualitative interviews were conducted after the 4-week timepoint to explore the acceptability of the app.

Figure 3. Timeline of data collection. CDSS: Calgary Depression Scale for Schizophrenia; MINI: Mini International Neuropsychiatric Interview; PANSS: Positive and Negative Syndrome Scale; PHE-S, Patient Health Engagement Scale; PSP, Personal and Social Performance; QFQ: quantitative feedback questionnaire; SIPS: Structured Interview for Prodromal Syndromes.

Time point	Enrollment	Baseline	1-week follow-up	4-week follow-up
Eligibility screening	X			
Informed consent		X		
Training session		X		
Intervention				
Smartphone monitoring		←	—	→
Assessments				
MINI	X			
SIPS	X			
PANSS		X	X	X
CDSS		X	X	X
PHE-S		X		X
PSP		X		X
EQ-5D		X		X
Sociodemographic characteristics		X		
Clinical characteristics		X		
QFQ				X
Qualitative interview				X
Electronic health record				
Number of hospitalizations		←	—	→
Time at first onset		X		
Number of episodes		←	—	→
Medication(s) or therapy used		←	—	→

Outcome Measures

Sociodemographic and Clinical Characteristics

Sociodemographic characteristics including age, gender, education level, marriage status, average income, accommodation and living situation, employment status, and ethnicity were collected. We also collected data regarding digital literacy and mental health literacy.

Data From Service Users' Electronic Health Records

Number of hospitalizations, time at first onset, number of episodes, and medication(s) or therapy used before and during the study were collected from service users' electronic health records (EHRs). At Anding Hospital, the EHR is used in both outpatient clinics and inpatient units and is shared within the hospital. All records are kept in the EHR system using

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computers, and no records are written by hand; service users receive a hard copy of their record following each appointment.

Clinical Measurements

The Chinese version of the Mini International Neuropsychiatric Interview [50,51] was used to determine the DSM-5 diagnosis.

The Chinese version of the Structured Interview for Prodromal Syndromes [52,53] was used to assess the risk for psychosis.

Psychotic symptoms were rated using the Chinese version of the PANSS [54,55], a 30-item scale that assesses positive symptoms, negative symptoms, and general psychopathology. The Chinse version is comparable to the original version and has good internal consistency reliability (Cronbach α=.87) [43].

Mood symptoms were assessed using the Chinese version of the CDSS [56,57], a 9-item scale designed specifically for assessing depression for schizophrenia. The Chinese version [44] has good reliability (Cronbach α=.798-.810) and is significantly correlated with the Hamilton Depression Scale (r=0.76) and PANSS-G6 (r=0.70).

Service user engagement was measured using the Chinese Version of the Patient Health Engagement Scale [58], a self-report scale assessing service users' attitudes toward engagement in health care.

Social functioning was rated using the Chinese version of the Personal and Social Performance scale (PSP) [59,60], a 100-point single-item rating scale assessing 4 main areas of functioning, including socially useful activities, personal and social relationships, self-care, and disturbing and aggressive behaviors.

Quality of life was evaluated using the Chinese version of the EQ-5D-5L [61], a self-report questionnaire designed to assess health status and health-related quality of life. The EQ-5D-5L consists of 5 questions that assess 5 health dimensions and a visual analog scale to assess the overall current health judged by the individual respondents.

Smartphone Monitoring

Active Monitoring

Active monitoring consisted of the following 3 sections: psychotic symptoms, mood symptoms, and contextual information. The psychotic and mood symptom items were translated into Chinese from the ClinTouch app and were compared against the Chinese version of the PANSS and CDSS. Contextual questions were added to understand the context of participant responses and to validate GPS data. Examples of the items are shown in Table 1.

Table 1. Examples of the active monitoring items.

Domain	Item	Response items	Format
Psychotic symptoms	"I have heard voices."	1-7	Likert scale
Mood symptoms	"I have felt sad."	1-7	Likert scale
Contextual questions	"Where were you?"	At home; at work; at school or other educational setting; in hospital; in vehicle; in a convenience store, supermarket, or shopping mall; outside walking; inside other; outside other	Check box

Passive Monitoring

Passive monitoring used collected GPS data to measure mobility and activity level of users. GPS mobility indicators measured on the smartphone, including home time, distance travelled, and location clusters, will be extracted following the procedures by Müller et al [62]. Briefly, locations will be clustered as "unique" if a person spent at least 30 minutes within a 200-meter radius. Home location will be determined by selecting the mode of location clusters during the night (ie, 9 PM to 6 AM). Distance travelled will be computed by aggregating the distance changes between 2 successive GPS data points; however, distance changes of GPS data points in the same location cluster will be considered as zero. Time spent at each location, including time at home, will be calculated by summing the differences of the time stamps of 2 successive GPS data points in the location cluster.

Validity

The validity of active monitoring items will be assessed against relevant clinical assessments (ie, PANSS and CDSS) using Spearman correlation. An exploratory analysis will also be conducted to understand the association between mobility indicators, corresponding contextual questions in active monitoring, and PANSS negative symptom scores. We define a moderate statistically significant correlation (ie, Spearman rho>0.35) as the validity threshold.

Feasibility Parameters

To assess the feasibility of the study, we collected detailed recruitment and retention data accordant with the CONSORT statement for feasibility studies [41], including (1) number of eligible participants consenting; (2) completeness of outcome measures; (3) number of participants lost to follow-up; and (4) reason for withdrawal. We defined Green (>80%; ie, feasible and no changes needed), Amber (60%-80%; ie, additional elements required to increase feasibility), and Red (<60%; ie, not feasible) categories to indicate the levels of feasibility for the above parameters. We will explore app usage and engagement data guided by the Analyzing and Measuring Usage and Engagement Data framework [63].

Acceptability

The quantitative feedback questionnaire (QFQ) was given to participants at the 4-week timepoint to collect quantitative information regarding acceptability. The QFQ is a 27-item questionnaire designed to assess the acceptability of utilizing smartphone app interventions for service users. It has been used in previous digital mental health studies for people with psychosis [64,65].

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Qualitative interviews were conducted to explore their experiences using Youxin including (1) overall impressions of YouXin, (2) positive and negative aspects of the app in terms of content and usability, (3) how it helped or did not help, (4) what changes they would make, (5) barriers and facilitators to engagement, and (6) views on the training session.

Safety

To evaluate the safety of the app, detailed adverse events and serious adverse events were collected and reported using standardized operating procedures in line with National Institute for Health and Care Research and Health Research Authority Safety Reporting procedures.

Safety Considerations, Adverse Events, and Risks

We did not expect participating in the study would cause any significant risks. Although the study involves people with severe mental health problems, the eligibility criteria for the study require the participants to be stable and at low risk for self-harm or harm to others, as judged by a clinician. There is the potential for participants to report elevated levels of distress because of taking part in assessments and digital self-monitoring. This may include the potential for increasing awareness of one's own symptoms. Participants were informed during the recruitment process that they may encounter such situations, and they were encouraged to discuss this with the research team if they feel distressed during the study.

Statistical Analysis Plan

All quantitative analyses will be performed using R (version 4.0.5) [66]. Feasibility data and safety data including (1) recruitment and retention data, (2) app usage data, (3) completeness of study measures, and (4) the number and nature of adverse events will be analyzed using appropriate descriptive statistics (mean and standard deviations for continuous data; counts and percentages for categorical data). Logistic regression and linear regression analyses will be used to explore sociodemographic and clinical characteristics and device attributes as predictors of feasibility (eg, dropouts, app usage).

The active monitoring will generate 3 levels of data, with the data entered for each "beep" as level 1, nested within the level 2 "day" level, which is nested within the level 3 subject level. Because the PANSS and CDSS measure participants' symptoms for the past week, and to minimize the impact of missing data, the subject level mean score of the first week will be used to calculate the association between active monitoring items score and relevant symptom domain scores of the PANSS and CDSS at the week 1 follow-up assessment to evaluate validity. The significance level for the study will be set to .05. Cronbach alpha will be used to calculate the internal consistency reliability of the sets of the items of active monitoring. To account for the nested structure of the data, multilevel models will be used to explore the instability of the different constructs across time and patterns of missing data.

The GPS mobility indicators will be extracted from passive monitoring data. The convergent validity of passive monitoring will be calculated by the correlation between GPS mobility indicators and the PANSS negative symptom score. Discriminant validity of passive monitoring will be demonstrated by low correlation between GPS mobility indicators and positive symptoms measured by PANSS.

Qualitative data will be transcribed verbatim in Chinese and then translated to English by the principal researcher. A framework analysis approach will be used based on the protocol by Braun and Clarke [67], which consists of the following 6 phases of thematic analysis: familiarization, transcription, generating initial codes, searching for themes, reviewing themes, and defining and deciding on meaningful themes. Nvivo software (version 12) [68] will be used to manage the qualitative data.

Data Management

Names and contact information are password-protected and stored electronically and separately with anonymous questionnaire responses in a secure, password-protected folder on the principal researcher's university drive and are kept for the purposes of contacting participants during the study. All quantitative data are stored as an anonymous electronic file and stored on the principal researcher's university drive for the purpose of analysis. Data generated from the smartphone app are stored on a secure server at Beijing Anding Hospital. The server is managed by the IT department of Beijing Anding Hospital according to the Chinese government's data protection regulations. Only the IT staff can access the data stored on the server. The principal researcher applied to download the raw data at the end of the study data collection.

Qualitative interview data recordings were anonymized as soon as practical after the interview, and anonymous transcripts were prepared by the principal researcher. Personal information was removed from the final transcripts or replaced with pseudonyms where appropriate. The file name was saved with the date of transcription and allocated a number to protect confidentiality and ensure no file names are the same (ie, DD_MMM_YYYY_SU_1). For the publication write-up, quotations may be used for which the participants will be given a pseudonym (ie, "service user1," which will be representative of the allocated number of the saved document name); however, they will not be identifiable by the research team at this point.

Results

Recruitment for the study was initiated in August 2022. Of the 47 participants who were approached for the study from August 2022 to October 2022, 41 participants agreed to take part in the study. Reasons for not participating included concerns that answering app questions would be a burden (n=1) and family member concerns that answering app questions might be triggering for the participant (n=1). Another 4 participants declined to participate without giving any reason. We excluded 1 participant for not meeting the inclusion criteria, leaving a total of 40 participants taking part in the study. As of December 2022, 40 participants had completed the study. We expect to report the validity of the app-based monitoring and results for feasibility on the (1) number of eligible participants consenting, (2) completeness of outcome measures, (3) number of participants lost to follow-up, and (4) reasons for withdrawal.

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We also expect to report participants' overall impressions of YouXin, positive and negative aspects of the app in terms of content and usability, perceived helpfulness of the app, barriers and facilitators to engagement, and views on the training session.

Discussion

This study aims to test the validity, feasibility, acceptability, usability, and safety of the YouXin smartphone app for people with psychosis in China to self-monitor symptoms. To the best of our knowledge, this study is the first to develop and test a symptom self-monitoring app specifically designed for people with psychosis in China. Therefore, a feasibility study is necessary to determine if a DHT like this will be appropriate to facilitate self-management for this population.

We conducted a systematic review and series of surveys and qualitative interviews with people with severe mental health problems and mental health staff in China to facilitate the development of the app. Based on our previous findings, DHTs were generally feasible and acceptable among people with mental health problems in China [29], and mental health professionals were willing to implement such technologies in clinical practice [30]. In addition, DHTs developed in China have rarely used the coproduction approach [29]; we coproduced the app to maximize the chance it meets end user needs.

One of the concerns of utilizing DHTs is the risks related to data security and privacy, which may hinder the implementation of DHTs [69-71]. To tackle these issues, we designed and developed the app to meet the standard required by China's Data Security Law. Additionally, we discussed these issues with both the service users and mental health staff in the coproduction process, and the feedback from the coproduction process indicated that, as long as the app was designed and developed according to data security regulations, both staff and service users felt safe using it. Moreover, we conducted postintervention interviews with participants to have an in-depth understanding of their concerns and how data security and privacy issues may impact their usage of the app.

If YouXin is feasible, acceptable, and safe and brings clinical benefit, a potential future direction is to integrate the app into clinicians' workflows to facilitate a digitally enabled care pathway to support timely mental health care for people with psychosis in China. This could include a remote symptom monitoring system [38] or a more comprehensive integrated digital clinic [35]. According to views collected from mental health staff during the coproduction workshops, staff expressed positive attitudes toward implementing digital mental health care in practice and considered digital health to be the future of mental health care.

In summary, this study will provide valuable insights for evaluating the feasibility, safety, acceptability, trial procedures, and implementation strategies of a DHI with this population in the Chinese context. Moreover, the findings of this trial have the potential to inform the development of digital solutions for China's mental health services in general, and, more specifically, it could lead to optimization of DHTs designed for people with psychosis in China.

Acknowledgments

The development of the YouXin smartphone app is funded by Beijing Anding Hospital of Capital Medical University. The authors would like to thank the service users and professional advisory groups for their help developing the app.

Data Availability

The data sets generated during or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

XZ and SB designed the study. XZ drafted the protocol and led the development of the app. SB and SL supervised the design of the trial and the app development. LAC provided oversight of the methodology section of the trial design. XZ drafted the manuscript. All authors revised the manuscript critically for intellectual content and approved the final version of this protocol.

Conflicts of Interest

SL is the Academic Lead of Mental Health at Health Innovation Manchester. SL and SB are Directors and shareholders of CareLoop Health Ltd, a company spun out from the University of Manchester to develop and market digital solutions for remote monitoring using smartphones for mental health conditions, currently schizophrenia and postnatal depression. SB also reports research funding from the National Institute for Health and Care Research and the Wellcome Trust.

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Abbreviations

CDSS: Calgary Depression Scale for Schizophrenia
CONSORT: consolidated standards of reporting trials
DHT: digital health technology
DSM: diagnostic and statistical manual of mental disorders
EHR: electronic health record
PANSS: Positive and Negative Syndrome Scale
QFQ: quantitative feedback questionnaire

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Protocol

The Australian Genetic Heart Disease Registry: Protocol for a Data Linkage Study

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Abstract

Background: Genetic heart diseases such as hypertrophic cardiomyopathy can cause significant morbidity and mortality, ranging from syncope, chest pain, and palpitations to heart failure and sudden cardiac death. These diseases are inherited in an autosomal dominant fashion, meaning family members of affected individuals have a 1 in 2 chance of also inheriting the disease (“at-risk relatives”). The health care use patterns of individuals with a genetic heart disease, including emergency department presentations and hospital admissions, are poorly understood. By linking genetic heart disease registry data to routinely collected health data, we aim to provide a more comprehensive clinical data set to examine the burden of disease on individuals, families, and health care systems.

Objective: The objective of this study is to link the Australian Genetic Heart Disease (AGHD) Registry with routinely collected whole-population health data sets to investigate the health care use of individuals with a genetic heart disease and their at-risk relatives. This linked data set will allow for the investigation of differences in outcomes and health care use due to disease, sex, socioeconomic status, and other factors.

Methods: The AGHD Registry is a nationwide data set that began in 2007 and aims to recruit individuals with a genetic heart disease and their family members. In this study, demographic, clinical, and genetic data (available from 2007 to 2019) for AGHD Registry participants and at-risk relatives residing in New South Wales (NSW), Australia, were linked to routinely collected health data. These data included NSW-based data sets covering hospitalizations (2001-2019), emergency department presentations (2005-2019), and both state-wide and national mortality registries (2007-2019). The linkage was performed by the Centre for Health Record Linkage. Investigations stratifying by diagnosis, age, sex, socioeconomic status, and gene status will be undertaken and reported using descriptive statistics.

Results: NSW AGHD Registry participants were linked to routinely collected health data sets using probabilistic matching (November 2019). Of 1720 AGHD Registry participants, 1384 had linkages with 11,610 hospital records, 7032 emergency department records, and 60 death records. Data assessment and harmonization were performed, and descriptive data analysis is underway.

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Conclusions: We intend to provide insights into the health care use patterns of individuals with a genetic heart disease and their at-risk relatives, including frequency of hospital admissions and differences due to factors such as disease, sex, and socioeconomic status. Identifying disparities and potential barriers to care may highlight specific health care needs (eg, between sexes) and factors impacting health care access and use.

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KEYWORDS

data linkage; genetic heart diseases; health care use; cardiomyopathies; arrhythmia; cardiology; heart; genetics; registry; registries; risk; mortality; national; big data; harmonization; probabilistic matching

Introduction

Genetic heart diseases are a significant cause of cardiac morbidity and mortality in the youth and are characterized by distinct variability in the onset and severity of symptoms [1]. The most prevalent is hypertrophic cardiomyopathy (HCM), which affects up to 1 in 500 people [2]. They are generally inherited as autosomal dominant traits, conferring a 50% risk to first-degree relatives. A diagnosis relies on clinical investigations with a cardiologist and, in some cases, genetic testing, which is ideally conducted in a multidisciplinary clinic [3].

Disease symptoms can be variable ranging from asymptomatic to episodes of unexplained syncope, palpitations, and chest pain to the most serious outcomes of heart failure and sudden cardiac death (SCD). Accordingly, some individuals with a genetic heart disease require life-saving medical intervention via emergency department presentation and hospitalization. Treatment options may include prescription medication, cardioversion, and surgeries such as implantable cardioverter-defibrillator insertion, pacemaker insertion, septal reduction therapies (eg, alcohol septal ablation and septal myectomy), or heart transplant. The implantable cardioverter defibrillator is the only proven therapy to prevent SCD in individuals with a genetic heart disease [4]. The frequency with which these individuals interact with the health care system is unknown, including for noncardiac reasons [5].

Routinely collected health data are data collected for purposes other than research or without specific a priori research questions developed before collection [6]. These data provide both population- and person-based information, meaning we can examine common patterns of health care for the population [7,8]. In jurisdictions with universal health care such as Australia, we can observe an individual's interaction with hospitals and emergency departments over time and link them to mortality data. Studies that have used routinely collected data to investigate genetic heart diseases, or their consequences such as SCD, focus predominantly on mortality data and may restrict to specific subpopulations such as infants or children [9-11]. There are limitations in correctly identifying individuals with a genetic heart disease in these data collections due to insufficient International Classifications of Diseases (ICD) codes [5], inadequate recognition of these diseases outside of specialized settings, and infrequent interaction with health facilities for many patients who remain largely well and are generally managed via outpatient clinics.

Here we report a protocol for the linkage of Australian Genetic Heart Disease (AGHD) Registry participants [12,13] with state-wide hospitalization, emergency department and mortality registries, and the national mortality registry to establish a rich and comprehensive data resource to examine the health care use of individuals with a genetic heart disease and their families for the first time.

Methods

Study Setting, Design, and Population

This is a retrospective cohort study of people in New South Wales (NSW), Australia, enrolled in the AGHD Registry from 2007 to 2019. The AGHD Registry operates nationally and has actively recruited participants since 2007 [12,13]. The goal of the AGHD Registry is to enroll every individual in Australia with a genetic heart disease and their at-risk relatives to understand and improve diagnosis, prevention, and treatment options. Eligibility criteria include a confirmed diagnosis of any inherited cardiomyopathy (HCM, dilated cardiomyopathy, arrhythmogenic cardiomyopathy, and restrictive cardiomyopathy), left ventricular noncompaction, or primary arrhythmia syndromes (long QT syndrome, Brugada syndrome, or catecholaminergic polymorphic ventricular tachycardia; Table 1) or at-risk relatives of those with a confirmed diagnosis.

Participant demographic, clinical, and genetic information (provided by the AGHD Registry data custodian) was linked with whole-population routinely collected health data, specifically hospital admissions (NSW Admitted Patient Data Collection), emergency department presentations (NSW Emergency Department Data Collection), and in the event of death, mortality registry data (NSW Registry of Births, Deaths, and Marriages; Australian Coordinating Registry Cause of Death Unit Record File; Table 2). Although the AGHD Registry is an ongoing registry, linkage to the routinely collected data is not continuous and only occurs on application to the data custodians with ethics approval.

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Table 1. Classification and description of genetic heart diseases included in the AGHD[a] Registry.

Genetic heart disease type and specific condition	Definition	Diagnostic tests
Inherited cardiomyopathies		
Hypertrophic cardiomyopathy	Abnormal thickening of the heart muscle on either the left or right ventricle	Electrocardiogram, echocardiogram, cardiac magnetic resonance imaging (MRI), and Holter monitor
Dilated cardiomyopathy	Enlargement of the left ventricle of the heart affects the ability of the heart to pump blood effectively	Electrocardiogram, echocardiogram, cardiac MRI, and Holter monitor
Arrhythmogenic cardiomyopathy	A disease of the heart muscle where the normal heart muscle cells on either the left or right ventricle are replaced by fat and scar tissue. This change can lead to heart rhythm abnormalities, or the affected ventricle may become enlarged and not pump blood effectively	Electrocardiogram, echocardiogram, cardiac MRI, and Holter monitor
Left ventricular noncompaction	Characterized by deep trabeculations (finger-like projections) in the heart muscle wall of predominantly the left ventricle, but may also appear in the right ventricle	Electrocardiogram, echocardiogram, and cardiac MRI
Primary arrhythmia syndromes		
Long QT syndrome	Characterized by abnormal electrical activity in the heart that often presents in children and teenagers	Electrocardiogram, echocardiogram, and exercise or stress test
Catecholaminergic polymorphic ventricular tachycardia (CPVT)	CPVT is a rare condition often present in children and teenagers. A cardiac event can occur during periods of high emotion or exercise as these situations cause the body to release adrenalin or noradrenalin. These persons have an abnormal response to adrenaline, which causes the heart to beat fast and irregularly	Electrocardiogram, echocardiogram, exercise or stress test, and Holter monitor
Brugada syndrome	A rhythm disorder that causes the ventricles to beat abnormally fast, affecting the ability of the heart to pump blood effectively	Electrocardiogram, echocardiogram, and drug infusion study

[a]AGHD: Australian Genetic Heart Disease.

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Table 2. Data sets included in the Australian Genetic Heart Disease (AGHD) Registry data linkage study.

Data set	Purpose	Description	Variables
AGHD Registry	Cohort definition and linked data	National registry collecting clinical and genetic data of patients with genetic heart disease and their families	Demographics • Sex • Birth date (mm/yyyy) • Ethnicity (based on the Australian Standard Classification of Cultural and Ethnic Groups [14]) • Vital status (alive or deceased) • Postcode • Disease status (definite, possible, or at-risk) • Smoker status Clinical history • Clinical diagnosis • Age at diagnosis • Reason for diagnosis • Genetic status (likely pathogenic, pathogenic variant identified, or not identified) • Sudden cardiac events ever • Heart failure ever • Syncope ever • Nonsustained ventricular tachycardia ever • Atrial fibrillation ever • Left ventricular outflow tract obstruction ever • Interventions (implantable cardioverter defibrillator, pacemaker, ablations, myectomy, and heart transplant) • Family history Investigations • Echocardiography parameters • Electrocardiography parameters
NSW[a] Admitted Patient Data Collection	Linked data	Records all admitted patient services provided by NSW public hospitals, private hospitals, and private day procedure centers	Demographics • Sex • Birth date (mm/yyyy) • Country of birth • Residential statistical local area (SLA) at admission • Health insurance on admission Episode of care • Episode start date • Episode end date • Condition onset flag • Diagnosis codes ICD-AM[b] (up to 50) • Australian Refined Diagnosis-Related Group • Hours in intensive care unit • Hours on mechanical ventilation • Mode of separation • Procedure codes ICD-AM (up to 50) • Procedure date • Service-related group Facility information • Hospital type • Local health district (LHD) • Facility identifier • Facility transferred to • Facility transferred from

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Data set	Purpose	Description	Variables
NSW Emergency Department Data Collection	Linked data	Provides information about patient presentations to the emergency departments of public hospitals in NSW	Demographics • Sex • Birth date (mm/yyyy) • Country of birth • Residential SLA at admission • Health insurance on admission Episode of care • Episode start date and time • Episode end date and time • Diagnosis code ICD-AM (up to 50) • Type of visit • Mode of separation • Referred to on departure Facility information • LHD • Facility identifier
NSW Registry of Births, Deaths, and Marriages	Linked data	Includes death registrations	• Birth date (mm/yyyy) • Death date (mm/yyyy) • LHD at death
Australian Coordinating Registry Cause of Death Unit Record File	Linked data	Includes death registrations	• Death date (mm/yyyy) • Death age • Place at birth • State/territory of usual residence • Sex • Place of occurrence for external cause of death • Underlying cause of death ICD code • Contributing cause of death ICD codes (up to 20 comorbidity codes)

[a]NSW: New South Wales.

[b]ICD-AM: International Statistical Classification of Diseases and Related Health Problems, Australian Modification.

Aims

Our objective is to characterize AGHD Registry participants using routinely collected whole-population health data sets to investigate the health care use of individuals with a genetic heart disease and their at-risk relatives (Figure 1). We will also examine the concordance between data sources to see whether diagnoses, interventions, and outcomes match those recorded in the AGHD Registry. In our analyses, we will determine if patterns of care vary according to patient demographics such as age, sex, level of residential, and relative socioeconomic disadvantage of patient residence (Figure 2). We will evaluate episodes of care for any medical condition or reason.

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Figure 1. Aims of the Australian Genetic Heart Disease (AGHD) Registry data linkage study. NSW: New South Wales.

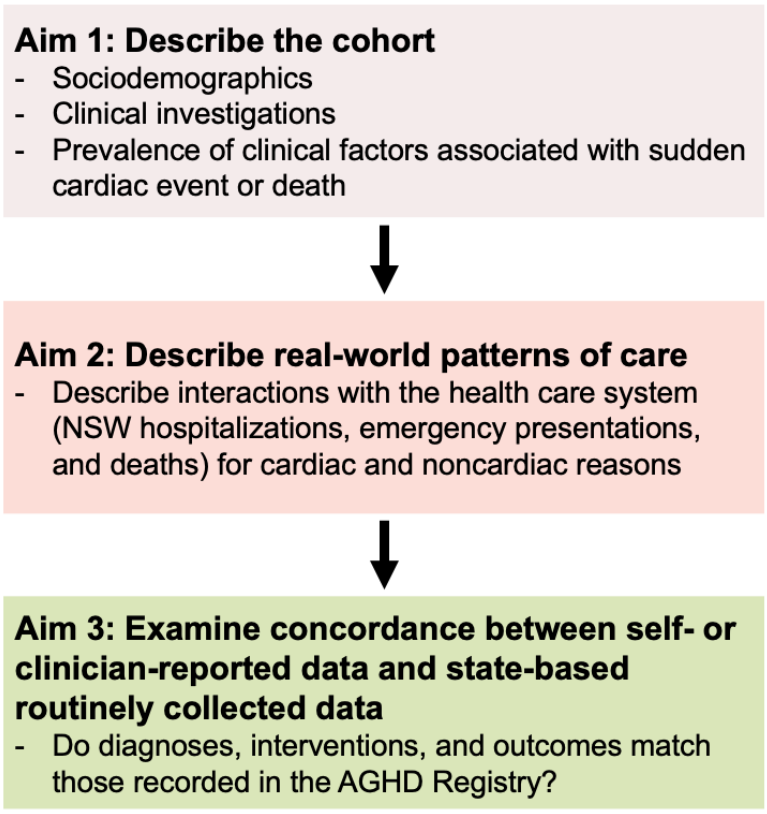
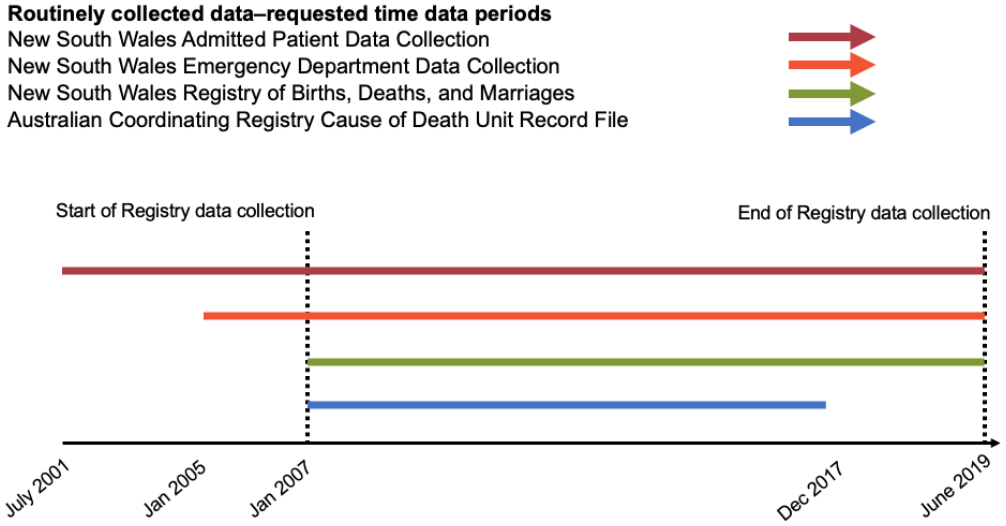


Figure 2. Period of data requested per routinely collected health data set.



Recruitment and Consent

Participants have been recruited to the AGHD Registry since 2007. Two recruitment methods were used for the data linkage aspects of the study:

1. For participants enrolled in the AGHD Registry between 2007 and April 2017, an opt-out approach was coupled with a waiver of consent. This involved sending a letter to all AGHD Registry participants outlining the study and asking them to contact us if they wish to withdraw their consent for this study. If the participant did not contact us, then the waiver of consent was applied.
2. An amendment to include permission for access to linked data sets was made to the participant information and consent form. Every person enrolled in the AGHD Registry from May 2017 provided written, informed consent for their data to be linked to the administrative data collections mentioned herein.

As part of the AGHD Registry recruitment process, extensive demographic, clinical, and genetic information was collected from the individuals and their cardiologist.

Although participants can withdraw their consent at any time for the AGHD Registry, data already included in the linkage

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before their withdrawal of consent cannot be removed as all extracted data held by the researchers are deidentified.

Data Sources and Variables

Table 2 lists and describes the data sets used in this study. The AGHD Registry was used for cohort definition and linking variables with the routinely collected health data. We linked to the following data sets.

NSW Admitted Patient Data Collection

The Admitted Patient Data Collection collates information on all admitted patient services provided by NSW public (including psychiatric hospitals and multipurpose services) and private hospitals (including day procedure centers) [15]. Data include patient demographics (ie, sex, birth date, country of birth, and statistical local area of residence at admission), episodes of care (ie, date and time of admission and separation [the completion of treatment for an admitted patient because of death, discharge, or transfer to another facility or care type], referral source, diagnoses, procedures, and service referred upon discharge), and facility information (ie, hospital type, facility, and local health district [LHD]). Up to 50 relevant diagnoses and procedures were included. These are coded according to standardized codes from the International Statistical Classification of Diseases and Related Health Problems, Australian Modification and the Australian Refined Diagnosis-Related Group.

This study included data on admissions between July 1, 2001, and June 30, 2019 (Figure 2). When linked with the AGHD Registry data, this period allowed us to examine patterns of care before and after a genetic heart disease diagnosis. The requested variables will allow us to examine the frequency and type of interactions and care received during hospitalizations.

NSW Emergency Department Data Collection

The Emergency Department Data Collection provides information about patient presentations to the emergency departments of public hospitals and contracted private hospitals in NSW [15]. Each record represents a presentation to an emergency department for emergency care and treatment. Data include demographics (same as Admitted Patient Data Collection), episodes of care (eg, date of arrival and separation, diagnoses, and status at separation), and facility information (eg, facility identifier and LHD). Up to 50 relevant diagnoses are included and are coded according to standardized codes from the International Statistical Classification of Diseases and Related Health Problems, Australian Modification.

Data for the Emergency Department Data Collection were available from January 1, 2005, to June 30, 2019 (Figure 2). By combining the hospital data with the AGHD Registry data, we can analyze the emergency department episodes before and after their diagnosis during this period. These data will allow us to explore the frequency and reason for an emergency department presentation for any medical reason.

Mortality Data

Two data sets contain mortality information for deaths occurring in NSW: the NSW Registry of Births, Deaths, and Marriages death registrations and the Australian Coordinating Registry Cause of Death Unit Record File [15]. All deaths are certified by a medical practitioner or coroner (if a coronial inquiry is required) and registered by the NSW Registry of Births, Deaths, and Marriages. Details of all registered deaths are forwarded to the Australian Coordinating Registry. Details include the date of death, underlying cause, and up to 20 contributing causes of death. The causes of death are coded using the ICD, Tenth Revision, international coding system rather than the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification used in Australian hospitals. The Australian Coordinating Registry Cause of Death Unit Record File data are finalized considerably later than the NSW Registry of Births, Deaths, and Marriages death registration data because of the time needed to confirm details on the death certificate.

Data from the NSW Registry of Births, Deaths, and Marriages were available from January 1, 2007, to June 30, 2019, and data from the Australian Coordinating Registry Cause of Death Unit Record File were available from January 1, 2007, to December 31, 2017 (Figure 2). These variables will allow us to determine the reasons and causes of death.

Data Linkage Methods

Linkage of each AGHD Registry participant's demographic, clinical, and genetic information with whole-population routinely collected health data was conducted by the Centre for Health Record Linkage (CHeReL). The AGHD Registry data custodian (the individual responsible for the registry data and any related activities) provided CHeReL with 2 separate files. To protect privacy, identifier information, including given names, last names, and current and past residential addresses (street, suburb, postcode, and state), was separated from the content information (registry clinical and genetic information). The 2 files from each data set were stored and handled separately. CHeReL's data linkage unit applied a combination of matching methods to the identifier data to identify and distinguish between individuals. The identifier data belonging to each individual were then assigned an arbitrary person number, which replaced the name, address, and other identifying details. Using an encrypted version of the arbitrary person number, CHeReL's data integration unit created a research project-specific person number (PPN). This PPN was used to join the AGHD Registry content data to the NSW state-wide Admitted Patient Data Collection, Emergency Department Data Collection, and the mortality registries (Registry of Births, Deaths, and Marriages and Australian Coordinating Registry Cause of Death Unit Record File). Once linkages were complete, the data sets were released to the research team in a fully deidentified form, ensuring the privacy and confidentiality of all individuals. The AGHD Registry custodian does not have access to the linked data to ensure that the linked data cannot be reidentified. These deidentification measures preclude the withdrawal of any individuals included in the data linkage study after the linkage takes place. Access to the deidentified linked data is only provided to individuals named in the approved ethics protocol. The PPN combines records for the same person across different data sets.

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Statistical Analysis

All data harmonization and analyses will be conducted using the R software (version 4.2.3; R Foundation for Statistical Computing). Harmonization of the data sets will involve systematic identification and removal of any duplicate records, checking for a consistent number of person-level records across the data sets, consistency across variables (eg, admission dates before discharge dates), checking for outliers, and identification and flagging of missing or invalid data. We will analyze and report each data set using descriptive statistics, including mean, median, SD, IQR, and sample size (number). We will also conduct descriptive analysis stratified by factors including age, sex, relative socioeconomic disadvantage, and advantage of patient residence and LHD of facility using the Australian Bureau of Statistics Socio-Economic Indexes for Areas [16] and genetic status (likely pathogenic or pathogenic gene identified vs no gene identified). Additionally, Cox regression models will be developed to identify independent factors associated with adverse outcomes, such as heart failure, atrial fibrillation, stroke, and death.

Patient and Public Involvement

Patients and the public have not and will not be involved in the study design.

Ethics Approval

Technical feasibility for the study was granted by the CHeReL, NSW Ministry of Health (ID#2016.38). Ethical approval has been granted by the NSW Population and Health Services Research Ethics Committee (2019/ETH0153) and Sydney Local Health District (Royal Prince Alfred Hospital zone) Human Research Ethics Committee (2020/ETHO00220). The current approval permits data storage at the Garvan Institute of Medical Research. We will disseminate project findings at scientific conferences and in peer-reviewed journals.

Results

Currently, the research team has received all deidentified data from CHeReL. The record linkage occurred in November 2019. A total of 1384 NSW-based AGHD Registry participants have been linked with 11,610 hospital records, 7032 emergency department records, and 60 death records. Data assessment and cleaning processes have been undertaken, with descriptive data analysis underway. Initial results are expected to be published by early 2024.

Discussion

This study represents the first in Australia to provide a comprehensive clinical data set on health care use patterns of individuals with a genetic heart disease and their at-risk relatives. It overcomes the limitations of previous studies, which rely on ICD codes to identify patients, by linking data from the AGHD Registry with routinely collected health data in NSW. The study will shed light on health care use among individuals with a genetic heart disease in Australia, examining hospitalizations, emergency department presentations, and mortality rates over approximately 20 years, stratified by clinical diagnosis, age, sex, socioeconomic status, and genetic status. We will investigate the impact of these factors on patterns of care, including interactions with health care providers and on disease severity and outcomes. Overall, we aim to improve the diagnosis, prevention, and treatment options for individuals with a genetic heart disease by providing a better understanding of their health care use and identifying areas for improvement in health care provision. Ultimately, the study's results will have a significant impact on the care of individuals with a genetic heart disease and their at-risk relatives.

Routinely collected data are commonly used in patterns of care studies. These studies are prolific when investigating cancer populations [17], as they provide the opportunity to describe a patient population and common treatment, as well as examine potential differences such as sex [18] and residential location [19]. In relation to cardiovascular diseases, patterns of care studies have predominantly focused on coronary heart disease or heart failure [18-22]. However, the population of individuals diagnosed with genetic heart diseases differs from those with these conditions, often being younger at diagnosis, with different risk factors and lifestyle constraints such as exclusion from high-level and competitive sports [23]. Therefore, studies such as that described here are needed to examine the unique genetic heart disease population.

By linking the AGHD Registry to routinely collected health data sets, we have overcome a significant limitation of previous studies that relied exclusively on the ICD diagnosis coding system to identify patients with genetic heart diseases [5]. A previous systematic review by our team found that for countries such as Australia, only 3 of the 12 genetic heart diseases included in the search strategy had an explicit ICD diagnosis code [5]. Codes that best match the other 9 genetic heart diseases being investigated were broad descriptive diagnoses (such as other cardiomyopathies used to describe arrhythmogenic cardiomyopathy), which also encompasses other genetic heart diseases. Additionally, the ICD diagnosis coding system fails to explicitly identify rare diseases, with only 500 of the 6000 rare diseases having an ICD diagnosis code [24].

Procedure codes may provide a little more information with specific codes for implantable cardioverter-defibrillator implantation and other interventions and surgeries associated with genetic heart diseases. However, as not all individuals undergo surgical procedures because of their condition, these codes also cannot identify all patients with a genetic heart disease. Because of these coding issues, studies to date have largely focused on those genetic heart diseases where discrimination from linked data sets is possible, that is, HCM and Marfan syndrome.

The clinical course for many patients with a genetic heart disease can be mild, meaning interactions with hospital and emergency departments could be infrequent or not required. However, when hospitalization is necessary, these patients often require urgent and potentially life-saving medical intervention. To date, there is limited research available regarding the health care system interactions of individuals with causative variants, and only one paper has used linked primary care hospital and mortality records in patients with HCM. Our study aims to address these

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gaps in knowledge and provide answers to these important questions. We will be able to observe the interaction of individuals with less severe clinical course who may never require treatment at a hospital or emergency department for genetic heart disease but present for other reasons.

Because of the absence of studies exploring care patterns associated with genetic heart diseases, it remains unclear whether care varies based on specific factors. Previous studies examining nongenetic cardiac conditions have found that patient factors, such as age, sex, and residential location, impact care patterns [15,18,20,25]. It is vital to examine the impact of socioeconomic factors, as the AGHD Registry contains a significant proportion of patients seen at specialist genetic heart diseases clinics in NSW, which have been shown to overrepresent socioeconomically advantaged individuals [26]. We will be able to investigate if patterns of care or outcomes vary based on the location of the facility and the relative socioeconomic disadvantage of that location. For instance, we will examine whether areas with a relatively high disadvantage have fewer implantable cardioverter defibrillator surgeries than other facilities, as observed in other countries [27].

Among studies using more than one data source, validating the agreement between data types such as self-reporting and routinely collected health data is important. Multiple studies have examined the concordance between these data types for many medical conditions including cardiac diseases [18-21,28-31]. One study found that the agreement between self-report data and health records was substantially lower for persons with heart failure than for other chronic illnesses such as diabetes, hypertension, myocardial infarction, and stroke [28]. Patient factors associated with discordance include sex, age, education level, and socioeconomic status [30,32]. However, no studies have investigated the concordance in individuals with a genetic heart disease between self-reported and routinely collected health data.

There are limitations in coding accuracy, especially for the Emergency Department Data Collection, which could affect the validity of the data collected. The study relies on AGHD Registry participants who are predominantly from a single tertiary center, which has been shown to lack socioeconomic diversity [29]. We will be unable to ascertain the prevalence and incidence of genetic heart diseases accurately as the AGHD Registry does not include all patients in NSW with a genetic heart disease. However, even if our sample is not representative, the relationships between variables are still valid [33].

This study aims to provide valuable insights into the health care use patterns of individuals with a genetic heart disease and their at-risk relatives. By linking data from the AGHD Registry with routinely collected health data in NSW, this study has established a comprehensive clinical data set that can identify reasons for hospitalization and emergency presentation, with the potential to reveal disparities based on disease, sex and sociodemographic status, and opportunities for preventive care. Overall, this study's findings may have a significant impact on the care of individuals with a genetic heart disease and their at-risk relatives, with the potential for better outcomes and quality of life.

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Data Availability

The NSW Health data sets generated during and analyzed during this study are not publicly available as they contain sensitive health information and an application must be made to the data custodians to use this data (through the Centre for Health Record Linkage). The Australian Genetic Heart Disease Registry data are available from the Registry custodian (A/Prof Jodie Ingles) on reasonable request.

Conflicts of Interest

JI receives research grant support from Bristol Myers Squibb. All remaining authors have nothing to disclose.

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Abbreviations

AGHD: Australian Genetic Heart Disease
CHeReL: Centre for Health Record Linkage
HCM: hypertrophic cardiomyopathy
ICD: International Classification of Diseases
LHD: local health district
NSW: New South Wales
PPN: project-specific person number
SCD: sudden cardiac death

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Protocol

Technology-Enabled Intervention to Enhance Mindfulness, Safety, and Health Promotion Among Corrections Professionals: Protocol for a Prospective Quasi-Experimental Trial

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Abstract

Background: Correction professionals are a highly stressed workforce with heightened risks for depression, suicide, obesity, cardiovascular disease, and injury. These professionals, largely hidden from view, have received little study concerning means to improve their safety, health, and well-being. In other settings, mindfulness has resulted in lowered stress, along with other benefits. We hypothesized that a program that promoted mindfulness combined with more typical health and safety components could uniquely benefit corrections professionals.

Objective: This project will assess a novel scalable, self-administered program to enhance the mindfulness, safety, and health of a vulnerable worker group.

Methods: In partnership with the Oregon Department of Corrections, we are conducting a prospective quasi-experimental trial of a safety, health, and mindfulness program among 100 corrections professionals from 2 institutions. Survey and physiologic data will be collected at enrollment, upon weekly program completion (3 months), and at 9 months after enrollment. Primary outcome behaviors promoted by the program are being mindful, healthier eating, more physical activity, and greater restorative sleep. Secondary downstream benefits are anticipated in stress level, mood, positive feelings about the organization, vascular health, and cellular aging, along with job performance, injuries, and economic costs. Participants will meet in-person or in a Zoom-type meeting as 3- to 5-member coworker groups during their usual work hours for 30-minute sessions once a week for 12 weeks. The program uses self-guided web-based learning modules that include brief mindfulness practice, and it is accessible by smartphone, tablet, or laptop. Daily mindfulness practice is encouraged between sessions, which is facilitated by the study website and group format. The modules' structure emphasizes prerequisite knowledge, peer support, skill practice, self-monitoring, and enhancing self-efficacy for change. The program continues through self-directed use of the Headspace app following the 12 weekly sessions.

Results: Participants are being enrolled, and the intervention is ready to launch.

Conclusions: Although mindfulness training has gained traction for worker well-being, its usual format requires a skilled trainer, an initial retreat, and weekly 2-hour meetings for several weeks. The content is limited to mindfulness without safety or health promotion aspects. The need for skilled trainers and time commitment limits the scalability of the usual mindfulness interventions. The planned program is an innovative combination of technology, e-learning, and a group format to add mindfulness to a safety and health curriculum. If acceptable and effective, the format would facilitate its widespread use.

Trial Registration: ClinicalTrials.gov NCT05608889; https://classic.clinicaltrials.gov/ct2/show/NCT05608889

International Registered Report Identifier (IRRID): PRR1-10.2196/45535

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KEYWORDS

corrections professionals; mindfulness; total worker health; occupational safety; digital; health promotion; safety; depression; suicide; obesity; cardiovascular disease; well-being; stress; survey; healthy eating; physical activity; mood; vascular health; injury; cop; police; security; undercover; remand; detention; prison; state correctional; state corrections; correction; penitentiary

Introduction

Background and Rationale

Those working in correctional facilities experience high stress levels, which negatively impact their mental and physical health [1-5]. The US Department of Justice published a review that highlighted the many sources of stress in corrections work, such as hypervigilance, constant threats of violence, media scrutiny, a closed work environment, understaffing, organizational issues, and work or family conflicts [1]. These workers have high rates of depression [6], suicidality [7], obesity, and other cardiovascular disease risks [4]. Corrections professionals also experience twice the rates of injury, sick leave, and health care costs than other government employees [8,9]. These professionals, largely hidden from view, have received little study concerning means to improve their safety, health, and well-being.

We are conducting a prospective proof-of-concept acceptability and initial efficacy trial of a scalable, technology-enabled worksite mindfulness, safety, and health promotion program specifically designed for corrections professionals. The unique program adds to our prior worker health and safety programs [10-12] by adding mindfulness. Mindfulness is especially applicable because of its ability to mitigate the effects of stress [13-15]. Our prior National Institutes of Justice-funded work with this population provided a basis for stress mitigation in corrections [16,17]; in that project, we surveyed corrections professionals and measured their perceived stress using the Perceived Stress Scale (PSS-4 Short Form). Using a linear mixed effects regression model, we found that perceived stress increases with increased work-related stress (P=.02), work hours (P=.03), work-life imbalance (P=.002), and lack of procedural justice (P=.03) [16]. Those findings helped inform this program's content. We also stratified participants by their stress level, and the higher and lower stress subgroups completed brain functional magnetic resonance imaging assessment of decision-making under emotionally charged conditions [17]. It is known that decision-making is affected by stress [18], and the ability to make quick, thoughtful decisions particularly is relevant for corrections work. We found that the officers who have higher stress needed significantly more top-down cognitive control, suggesting that their decision-making may be impaired in certain situations. Similar alterations in executive function have been found among young adults with a history of chronic stress [19,20].

Those detrimental effects on cognitive function, as well as other stress-related mental and physical adverse effects, can be mitigated by mindfulness [14]. A 2023 systematic review of mindfulness interventions among law enforcement identified 8 studies demonstrating promising benefits on reducing stress [21]. Several years ago, the Oregon Department of Corrections (DOC) used mindfulness training within a subset of corrections professionals [22]. However, as in most worksite studies, mindfulness training required a major time commitment and skilled trainers [15]. For example, the Oregon DOC program involved 2, day-long workshops plus 2 months of 2 hours per week for its trainer-led sessions. We sought to use a new format for mindfulness training, using a strategy that would be more scalable.

We are adding mindfulness to a program that is designed to promote Total Worker Health (TWH) [23]. The term Total Worker Health, trademarked by the US Centers for Disease Control and Prevention, refers to the combination of policies, programs, and practices that integrate protection from work-related health hazards with the promotion of illness prevention. As the founding members of the National Institute for Occupational Safety & Health-funded Oregon Healthy Workforce Center, we have been at the forefront of TWH efforts and have developed programs that positively impacted first responder groups and home health care workers [10-12].

Mindfulness generally is not a component of TWH programs, and our challenge was to design a scalable TWH program that added mindfulness training. The program is called Next Level, taking the traditional TWH program up a notch with mindfulness. We also recognize that many TWH programs have not been used outside of their study setting [24], and to further maximize dissemination potential, outcome data go beyond participant behaviors and include indices of compensable injuries and work performance [25].

Objectives

Our overarching aim is to create a scalable and effective program of mindfulness and TWH for corrections professionals. We hypothesized that the intervention would result in beneficial effects related to primary outcomes of dispositional mindfulness, as well as behaviors favoring health promotion and health protection.

Design

This study will use a quasi-experimental pre-post design to compare values of outcome measures at 3 times points: baseline, immediately post intervention (3 months after baseline), and follow-up (9 months after baseline). Randomization of the intervention by site or individual is not feasible due to personnel movement and contamination effects within and across correctional facilities. An advantage of the pre-post design is that each participant will act as their own control, increasing the power of the study [26]. Each of the 2 participating corrections facilities will be enrolled sequentially and will be a new wave of the project to allow managing activities across the 2 dispersed sites.

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The theoretical underpinnings of the intervention are based on our validated model of effective behavior change [27]. In establishing that model, we combined mediation analyses across our prospective randomized behavior change trials with different populations and established that effective programs included prerequisite knowledge, normative beliefs, and self-efficacy for change. Each of those features was built into this program.

Practicing mindfulness will be addressed similarly to other behaviors, such as healthy eating and achieving regular physical activity. However, unlike eating and exercise, mindful meditation will be a new ability for many participants requiring skill acquisition and practice. Accordingly, mindfulness practice is included in each session with a focus on its relationship to that session's safety or health topic. The program also emphasizes behavioral self-monitoring and peer norms to reinforce Social Cognitive Theory's tenant that observing progress toward objectives can enhance self-efficacy [28,29].

Methods

Setting and Participants

Eligible participants are corrections professionals working on units from the Oregon State Correctional Institution and Coffee Creek Correctional Facility. Corrections professionals are security and nonsecurity staff working for pay at the facility. Enrollment criteria include being employed for at least 6 months, with the exclusion criteria of not planning to leave or retire during the next 9 months. The total number of eligible participants is estimated to be approximately 600, with a budget for 100 participants. Following informational meetings with the administration hierarchy and union officials, we will use existing communication channels to inform potential participants and personally meet with them at their preshift group meetings, when information concerning the prior shift is shared. Individuals will not be directly compensated but will receive release time to participate. Enrollment is on a first-come, first-serve basis, and we expect to reach our 100-participant goal during a 6-month recruitment window. We have used similar strategies successfully in our prior studies of first responders [10,11]. We will carefully track all enrolled participants using the CONSORT (Consolidated Standards of Reporting Trials) guidelines [30].

Ethics Approval

The Oregon Health & Science University (OHSU) institutional review board (IRB; #24303) has approved the study and its procedures.

Confidentiality

The OHSU IRB requires an explicit safety and monitoring plan, and it supervises project safety and reporting of any adverse events. All data and all participant responses will be confidential and stored securely. All participants will be assigned a unique, nonmeaningful identifying code number, necessary for longitudinal participant tracking that will correspond to their Headspace participant identification number, to allow merging Headspace website analytics with other data. The study data will be collected and managed using Qualtics and REDCap (Research Electronic Data Capture; Vanderbilt University) electronic data capture tools [31,32]. Qualtrics offline surveys is an application that allows securely administering surveys on a mobile device without an internet connection. REDCap is a secure web-based software platform designed to support data capture for research studies. Both are approved by the OHSU IRB for data collection. Audio files of focus groups will be recorded on OHSU password-protected devices and downloaded to an OHSU password-protected secure site. Hard copies of observation information will be stored in a locked file cabinet at OHSU. No identified individual data will be presented or published. Individual data may be shown without identifying the participant to illustrate scientific principles.

Intervention

The intervention will be delivered during twelve 30-minute weekly meetings among coworkers. The Oregon DOC supports the project by providing paid time during participants' usual work days to participate. The sessions are built using Articulate 360, which is a well-established subscription platform for e-Learning course development [33]. It includes access to authoring apps and a library with thousands of course assets. For example, it has hundreds of potential dynamic components, such as interactive games, quizzes, and reveals. It provides a consistent learner experience across all devices (desktop computer, smartphone, or tablet).

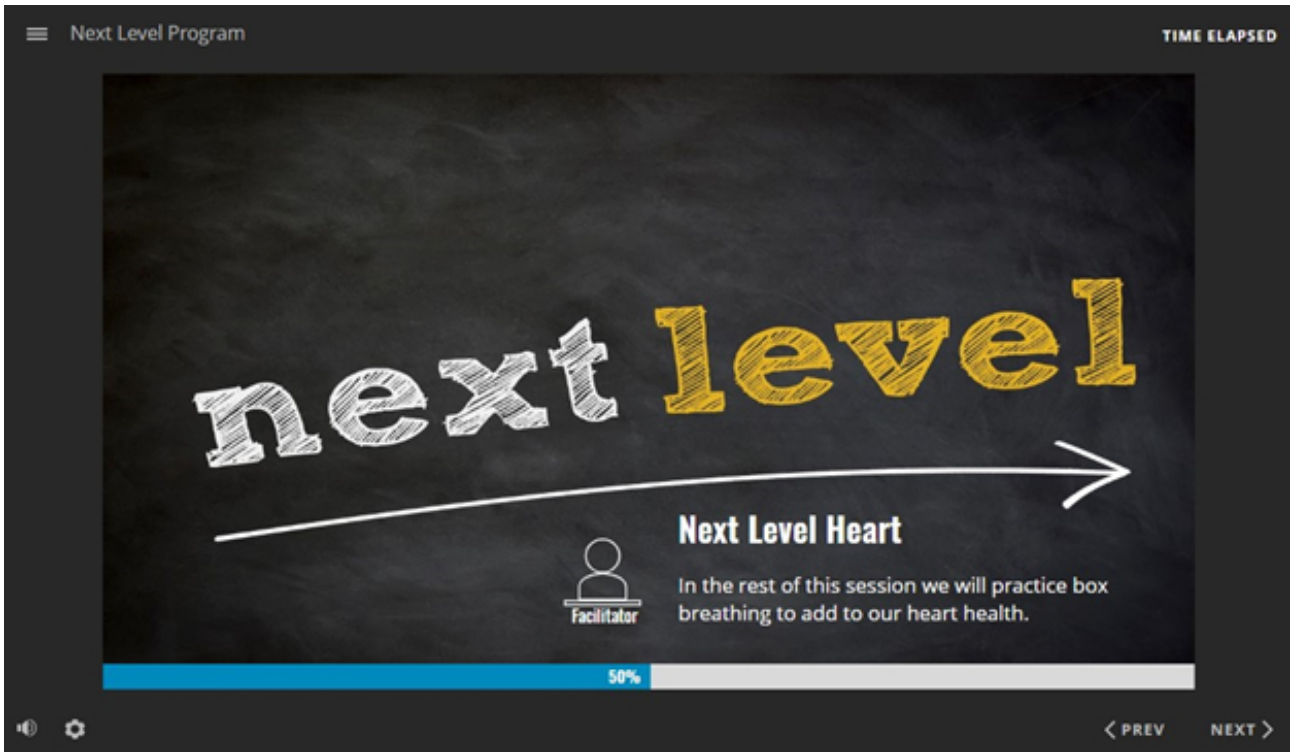
Each of the sessions contains approximately 20 wireframes. The wireframes are the baseline structure to which features (eg, games, quizzes, reveals, matching, videos, and links to other content) can be attached. Each module follows a similar format. The sessions are done with 3 to 6 coworkers positioned around a large video screen or sharing a screen when meeting in a Zoom-type meeting. Early in each session, there is a 5-minute follow-up on behavioral objectives (or practice opportunities) from the prior session (Figure 1). This provides a forum to problem-solving challenges, enhance self-efficacy for efforts, and engage in social support. Next, foundational knowledge for that session's content is presented and actively processed by completing quizzes, reading reveals, or watching a 2-minute video. The session transitions to mindfulness with a "Next Level" wireframe (Figure 2). During the second half of the session, participants either practice a seated meditation or a new mindfulness skill related to that session's topic. For example, in Healthy Heart, they learn and practice box breathing (Figure 3). The session wrap-up presents daily mindfulness practice objectives for the coming week, which will be revisited in the following session (Figure 4).

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Figure 1. Shared reflection on prior session's objectives.



Figure 2. Transition to add mindfulness to traditional Total Worker Health topic.



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Figure 3. In-session introduction to a skill that is followed by video-led skill practice.

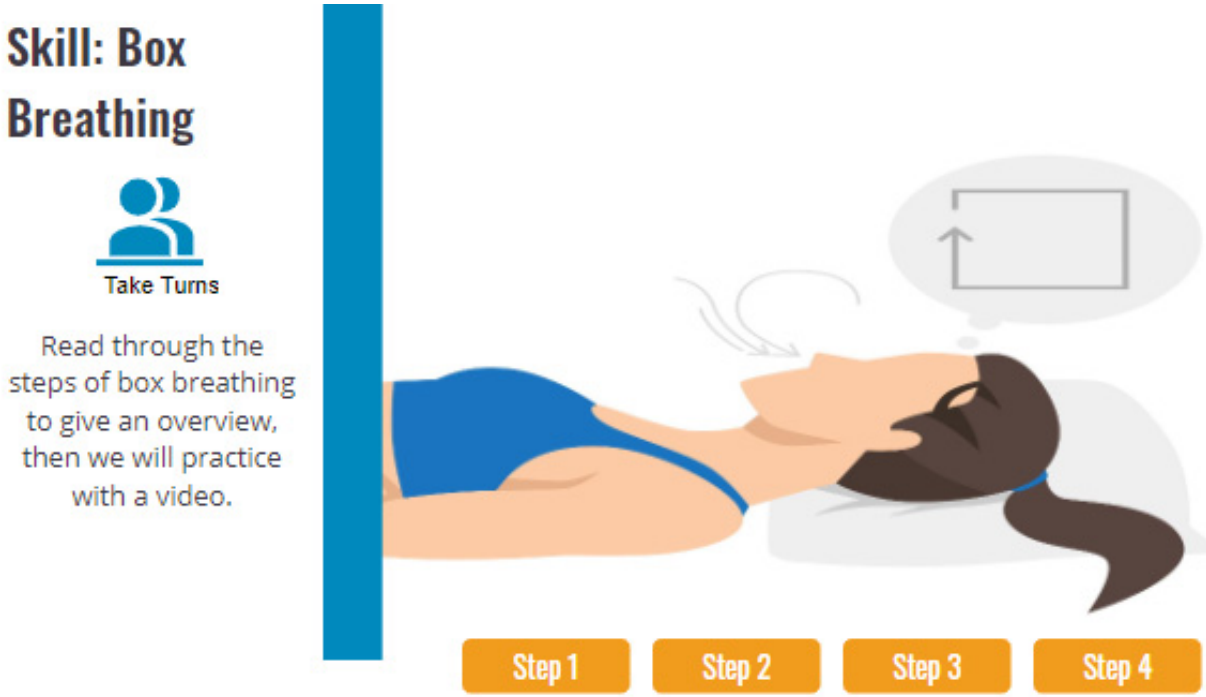
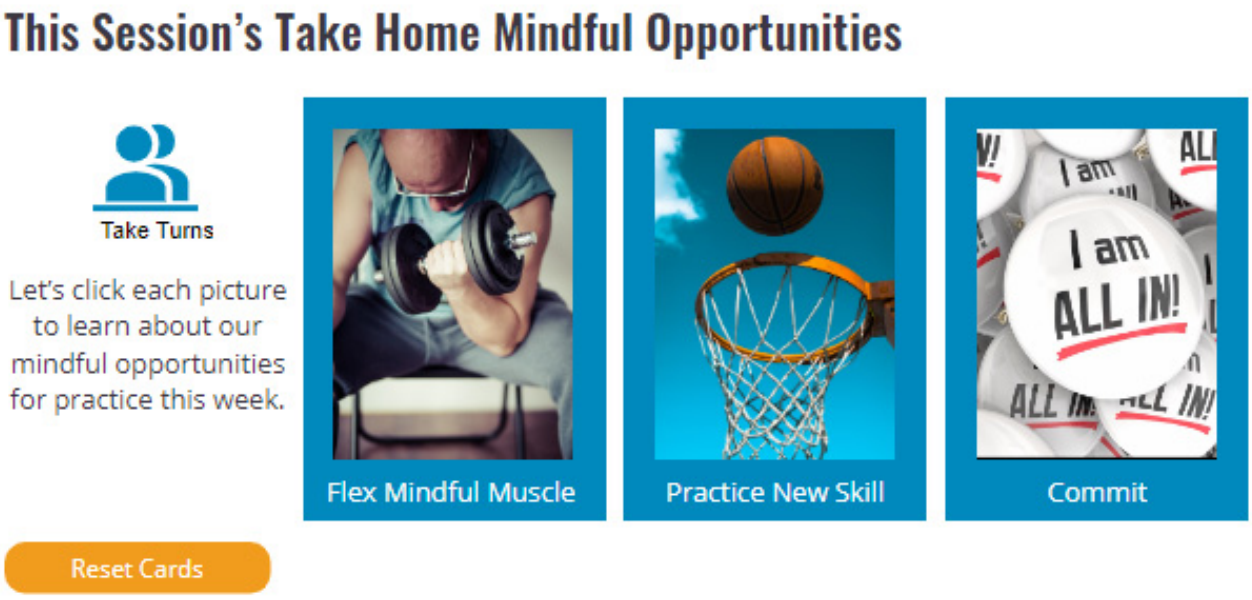


Figure 4. Participants click on each picture and read the opportunities (goals) for mindfulness practices for that week.



Our experience and the literature [34] emphasize that corrections professionals feel that their unique stressors require an authentic understanding of their issues, and accordingly, the content is specifically related to their profession. In addition, we believed that corrections professionals frequently lacked a background or intrinsic interest in mindfulness [35]. Consequently, the initial 2 sessions were designed to build motivation by providing background relevance, a scientific basis for mindfulness, and testimonials from corrections professionals, as well as an overview of the program's content, process, and how they will run the sessions. These sessions involve a series of videos and voiceover wireframes. Beginning in session 3, on-screen icons guide participants to run the session themselves, with 1 of them as the designated facilitator for that session. The scope and sequence of the twelve, weekly 30-minute sessions are shown in Table 1.

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Table 1. Next-level scope and sequence.

Session	Content	Mindful in-session practice	Take home daily practice
1	Background and motivation building	Two-minute guided meditation	Daily 2-minute meditation+explore the website
2	Format for and running the sessions	Two-minute guided meditation	Daily 2-minute meditation+explore the website
3	Healthy heart	Box breathing	Daily 3-minute meditation+box breathing twice this week
4	Physical fitness	Three-minute guided meditation	Daily 3-minute meditation+walking meditation twice this week
5	Healthy eating	Mindful eating	Daily 3-minute meditation+mindful eating three times this week
6	Mental fitness	Three minute-gratitude meditation	Daily 3-minute meditation+gratitude meditation at least twice this week
7	Halfway check-in	Three-minute guided meditation	Daily 3-minute meditation+watch introduction Headspace video
8	Sleep	Body scan	Daily 5-minute meditation+bedtime body scan twice this week
9	Injury prevention	Three-minute guided meditation	Daily 5-minute meditation+visit Headspace app
10	Resilience	Three-minute guided meditation	Daily 5-minute meditation+visit Headspace app
11	Medical check-up	Three-minute guided self-compassions meditation	Daily 5-minute meditation+at least 2 self-compassion meditations
12	Wrap-up and next steps for next level	Three-minute guided meditation	Daily 5-minute meditation+visit Headspace app

The program does not require a trained instructor. The coworkers, guided by icons on the screen, are responsible for running the sessions. The initial session has videos and voice-over wireframes, and during session 2, the group-managed format is presented. The group is directed to identify 1 member as the designated facilitator, who follows those icons' directions. However, being the facilitator requires no preparation or special expertise and other group members can easily assume that role if that individual is not present.

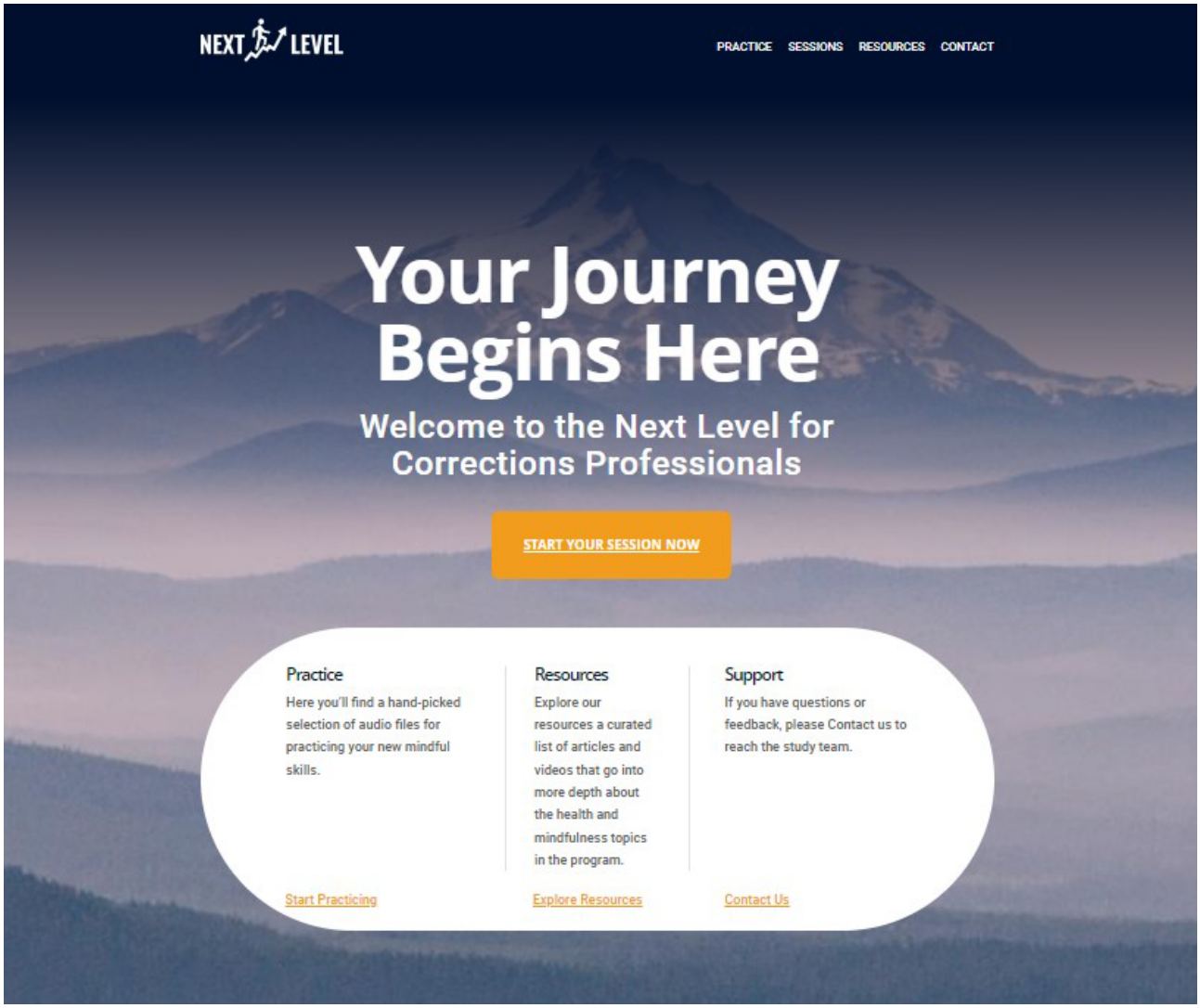
We have used similar coworker-led sessions successfully with other occupational groups [10-12]. We particularly wanted to avoid a hierarchical pedagogic structure of "teaching to" corrections professionals. Peer-led programs have documented efficacy and may be as effective as professionally delivered formats [36,37]. Peers also reduce expenses, promote a sense of shared norms, enhance social support, and augment material with credible examples and personal experiences [38].

To provide a longitudinal program component, we partnered with Headspace, an established effective mindfulness app. In a recent review of mindfulness training apps, Headspace received the highest rating [39]. Individuals will have continuous access to the Headspace app beginning at enrollment for a total of 12 months. Transitioning to more Headspace use is incorporated in the latter weekly sessions to maintain mindfulness once completing the weekly sessions tailored to corrections professionals.

The program is accessible from a simple website portal designed specifically for corrections professionals. It functions on all operating systems. While corrections professionals often do not have their smartphones with them on duty, they do have access to the meeting and breakrooms with computers, tablets, and internet access. A mockup of that the website landing page is shown in Figure 5. Menu pages include (1) the sessions, (2) audio files of guided mindfulness meditations for use during their daily practice, (3) resources with PDFs and links to videos of interest and related to session topics, and (4) Headspace information. For each session, there is a link to play the session, along with buttons to review the video used in that session, and a restatement of the take-home practice opportunities for that session.

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Figure 5. Landing page for the Next Level website.



Outcomes

Three types of outcome data will be collected at baseline, immediately after the 12-week intervention, and at 9 months (6 months following the intervention's conclusion): (1) Surveys using validated self-report measures for demographic variables, mindfulness indices, current (if any) mindfulness practices, healthy behaviors (nutrition, physical activity, sleep, and safety actions), work-life balance, mental health, perceived stress, and perceptions of the organization or worksite; (2) biomeasures: blood pressure, height, weight, vascular reactivity, and blood work for cellular senescence; and (3) economic outcomes: missed days, overtime, sick days, injuries, incidents, and workmen's comp claims.

These variables along with citations to the validated instruments are shown in Textbox 1.

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Textbox 1. Outcome measures.

Primary outcomes

- Mindfulness (Mindful Attention Awareness Scale [40,41] and Facet Mindfulness Questionnaire [42])
- Self-compassion [43]
- Gratitude [44]
- Eating habits [11]
- Mindful eating [45]
- Physical activity [46]
- Mindful physical activity [47]
- Sleep [48,49]

Secondary outcomes

- Perceived stress [16]
- Centers for Disease Control and Prevention health days [50]
- Feelings about the organization [16]
- Mood [51-53]
- Other biometrics (height, weight, and blood pressure)
- Vascular reactivity [54]
- Telomere length [55]
- Health care costs (overtime, days missed, injuries, incidents, and worker compensation claims)

Other

- Session observations for fidelity, dose, and reach
- Application metrics
- Follow-up focus groups

The primary outcomes relate to behaviors directly promoted by the program: being mindful; healthier eating; more physical activity; and greater restorative sleep. Secondary downstream benefits are anticipated in perceived stress; negative affect; greater positive feelings about the organization; vascular health or cellular aging; and job performance/injuries/economic costs. All survey constructs have established validity, and many have been used in prior studies. In addition, the baseline survey will include demographic and work history items. The post intervention survey also will include items related to intervention usability, acceptance, enjoyment, and whether they would recommend the program to other corrections professionals.

We will track injury counts, absenteeism (used as a proxy for productivity), worker's compensation claims, and costs associated with illness and injury. We will collect data on individuals' reported illness, injury (slips, trips, falls, exposures, and incident interactions) before enrollment and prospectively during and for 2 months following the study. We will use 2-month data for participants, including 2 months prior to enrollment, months 3 and 4 after beginning the program, and a third 2-month interval after completing the study. Absenteeism will be indexed with the Institution Staff Deployment System. We will track pre- and postprogram unusual incident reporting, which is a DOC method of tracking the activity of consequence to the good order, such as inmate self-injury, uses of force, blood and bodily fluid exposure, contraband, and individual or group disturbances.

There are 2 unique biomeasures used in this study: digital thermal monitoring and markers of cellular senescence. Digital thermal monitoring is a cost-effective test of vascular reactivity and endothelial function. It is well correlated with Framingham Risk Score, Coronary Artery Calcium Score, and computerized tomography angiography. It is measured with the Endothelix DTM system, which is approved by the US Food and Drug Administration, noninvasive, and easy to use (VENDYS, Endothelix Inc). With that system, a blood pressure cuff occludes arm arterial flow for 5 minutes. Following cuff deflation, reactive hyperemia is largely dependent on endothelial cells. The healthier the artery, the larger the hyperemic response. This assessment can show changes in response to health promotion interventions and provide a proximal index of positive cardiovascular effects.

We also will assess cellular senescence. This is a measure known to be accelerated by stress and reversed by effective wellness interventions [56-58]. Changes in senescence are associated with a heightened risk for disease and mortality. At present, there is no "gold standard" for cellular senescence. We will use a combination of methods to assess cellular aging: cellular staining for senescence-associated β-gal (Senescence Cells Histochemical Staining Kit, Sigma); the presence of

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senescence-associated proteins using Western blot; and senescence marker antibody sampling kits to stain for p16, p21, phospho-histone H2AX, Lamin B1, HMGB1, matrix metalloproteinase 3, cytokine interleukin 6, and tumor necrosis factor α. We also will determine the telomerase activity in cell extracts through its ability to synthesize telomeric repeats onto an oligonucleotide substrate, which is amplified by polymerase chain reaction, using the TRAPEZE RT Telomerase Detection kit (Sigma). The relative quantification of gene expression will be determined using the $2^{-\Delta\Delta Ct}$ method with control RNAs appropriate for blood, and a comprehensive senescence phenotype profile will be obtained using the Human Cellular Senescence array (SA Biosciences).

Fidelity and Adherence

We will observe approximately half of the sessions and use the session's wireframes as a checklist for fidelity, as well as note taking during session observations concerning participation, engagement, and any deviations from the planned format. When possible, observations will done be in person, and we also will join group Zoom-type meetings. We will assess fidelity (the extent to which the intervention is delivered as intended), dose (how much is delivered), and reach (the proportion of intended recipients participating). A simple email check-in will be a final session component, where participants self-report attendance and indicate session duration. In addition, participants' visits and time on the Headspace app will be tracked with that app's analytics.

Qualitative Data Collection

Following the intervention, we will conduct focus groups concerning program use and outcomes. We will offer partaking in a focus group to all participants. When possible, we will have individuals who went through the sessions together also be together in a focus group. These will last 45 to 60 minutes and will use a trained facilitator and interview guide designed to explore the study outcomes and session observations. The focus group roadmap or interview guide is included in Multimedia Appendix 1. A scribe will take notes and track participant comments.

Power and Sample Size

We expect a sample size of 100 participants from 2 facilities. We first estimated an approximate dropout rate of 20%, leaving 80 participants. For the 4 primary outcome constructs, we adjusted the α level using Bonferroni corrections by dividing .05 by 4 giving us an α level of .0125 to account for multiple testing. In order to power the change in outcomes from baseline to post intervention (3 months), we used paired *t* tests. We estimate that this sample size has 90% power to detect a moderate effect size. We estimate (Cohen *d*=.41), 85% power to detect (*d*=.43), and 90% power to detect (*d*=.46). All power analyses were conducted using PASS 2019 (NCSS, LLC). For qualitative data, rather than a specified number of groups, data gathering will continue until saturation, when no new information is obtained.

Data Analysis

Preliminary analyses will include careful examination of descriptive statistics and distributions for variables at each time point. This will include counts and proportions for categorical variables and means, SDs, and range for continuous variables, as well as 95% CIs for all proportions and means.

Primary Outcomes

Our primary criterion for determining intervention efficacy will be differences in changes in the primary outcomes listed in Textbox 1. Our primary hypothesis is that the intervention will be associated with an improvement in each of those outcomes. Repeated measures linear mixed effects models will be used to determine whether the outcome measures improved from baseline to post intervention. Models will include terms for the time points T_3 (0 vs 3 months) and T_9 (0 vs 9 months), and nested random effects for individuals within sites. Primary analyses will test the significance of the terms to determine whether outcome measures change from baseline to post intervention. Models will adjust for age and gender and follow a purposeful selection strategy to determine which other background characteristics to include. Mixed effects models have the advantage that participants do not need complete data for all 3 time points to be included in the analyses. If after data inspection it is decided to dichotomize some measures, logistic mixed effects models will be used instead.

Secondary Outcomes and Associations

Secondary outcomes will be analyzed similarly using repeated measures mixed effects models with linear or logistic links depending on whether the outcomes are continuous or binary. We will furthermore analyze whether the changes in primary outcomes are associated with changes in other selected measures. In particular, we hypothesize that (1) reduced stress and healthier behaviors (eg, nutrition, physical activity, and sleep) are associated with improvements in vascular reactivity and cellular senescence and (2) reduced stress and improved perceptions of the organization are associated with reduced injuries and incidents.

Qualitative Outcomes

We are experienced in mixed methods, having used them successfully in understanding program outcomes [48,59,60]. Analyses of the focus groups following the intervention will involve reiterative pattern analysis of comments, which avoids the substantive bias inherent in a priori categorization. Instead, we will adapt the more inductive constant-comparative method typical of grounded theory [61]. This analysis approach increases the transparency and reproducibility of qualitative research. Our aim is to further explore the findings observed in the primary and secondary outcomes, beginning with a roadmap of questions and exploring the responses. Barriers and enhancements to program impact will be sought within the dynamic contexts of actual experience. Construction of themes and interpretations rather than bounding interpretation with a prespecified list of categories for coding avoids the substantive bias inherent in a priori categorization. Instead, we will use an adaption of the more inductive constant-comparative method [62,63]. Following the identification of themes, the data set will be subjected to

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microreview in a search for both confirming and disconfirming data. Quotations will be selected to exemplify and elaborate themes, support findings, and illuminate contexts, promoting reader understanding and facilitating. We will use applicable items from the COREQ (Consolidated Criteria for Reporting Qualitative Research) checklist to document and communicate our methods [64]. In addition to providing a deeper understanding of outcomes, the qualitative findings should allow the development of case studies that may be useful in sharing findings with the corrections community.

Results

As of December 2022, this study is enrolling participants and finalizing the web-based curriculum and website. We anticipate beginning the intervention in early 2023, with data collection to be completed by November of 2023.

Discussion

Fifty years ago, Kabat-Zinn et al [65] used Mindfulness-based Stress Reduction to lessen stress and distress for those with chronic pain [65]. MBSR takes time and generally includes a day-long retreat, weekly 2.5-hour classes for 2 months, and daily activities including around 40 minutes of meditation. Although its effectiveness is well established [66], its time commitment is a hurdle. Work-related stress is estimated to result in losses of up to US $300 billion annually in the United States [67]. Mindfulness training has gained some traction in the worksite setting [68,69] but still has limited use, partially due to the need for a significant time commitment and an experienced trainer. The innovative format described in this protocol overcomes 3 challenges: time, tailoring, and TWH incorporation. It is delivered in a 30-minute once-a-week, self-directed format and designed specifically for corrections professionals. Importantly, it is incorporated in a TWH context. Mindfulness and TWH are rarely combined. A literature search for TWH and mindfulness yielded only a single citation. Some evidence suggest that mindfulness training may be more effective when combined with other components [70].

Our outcome findings will include three main dimensions: (1) implementation acceptability, observations for fidelity, and adherence; (2) pre- to postsurvey measures of targeted behaviors and in particular dimensions of mindfulness along with measures of inflammation and cellular senescence, in addition to human resource data on missed work, injury claims, and incident reports; and (3) postparticipation survey items relating to program acceptability and focus group interviews concerning for a deeper understanding of practical issues, social validity, and suggestion to improve the program and its use.

The 3 listed dimensions reflect 3 components of this protocol. The first dimension relates to whether we crafted a program that was easy to use and engaging enough to sustain participation, especially in the context of the stressful and generally understaffed context of corrections. The second dimension relates to changes in behaviors with an emphasis on instruments used to assess mindfulness following the usual longer form of mindfulness interventions. The focus group aspect of the third dimension will allow a more thorough understanding of the program, as well as provide suggestions for improvement.

We recognize that each correctional system has its unique structural, organizational, and personnel factors and that our findings may not generalize to corrections professionals in other settings. In addition, this is the first evaluation of the peer-led, technology-enabled weekly session and self-directed practice format to increase mindfulness, hence the emphasis on observing sessions and formative qualitative feedback in debriefing after the trial. In addition, participants are not a random sample of these workers. However, we have site-wide data from our previous work [16], and we will be able to compare participants with other corrections professionals from these sites. Despite limitations, the innovative aspects of the program will provide outcome numbers that could inform a subsequent larger randomized controlled trial of the program in this and other settings.

Acknowledgments

We are grateful for the cooperation of the Oregon Department of Corrections. This study was funded by the National Institute of Justice (#2020_R2-CX-0006).

Data Availability

The data sets generated and analyzed during this study will be available in the National Archive of Criminal Justice Data repository.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Focus group interview guide.
[PDF File (Adobe PDF File), 472 KB - resprot_v12i1e45535_app1.pdf]

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Abbreviations

CONSORT: Consolidated Standards of Reporting Trials

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COREQ: Consolidated Criteria for Reporting Qualitative Research
DOC: Department of Corrections
IRB: institutional review board
PSS-4: Perceived Stress Scale
OHSU: Oregon Health & Science University
REDCap: Research Electronic Data Capture
TWH: Total Worker Health

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Protocol

Decision Trade-Offs in Ecological Momentary Assessments and Digital Wearables Uptake: Protocol for a Discrete Choice Experiment

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Abstract

Background: Ecological momentary assessments (EMAs) and digital wearables (DW) are commonly used remote monitoring technologies that capture real-time data in people's natural environments. Real-time data are core to personalized medical care and intensively adaptive health interventions. The utility of such personalized care is contingent on user uptake and continued use of EMA and DW. Consequently, it is critical to understand user preferences that may increase the uptake of EMA and DW.

Objective: The study aims to quantify users' preferences of EMA and DW, examine variations in users' preferences across demographic and behavioral subgroups, and assess the association between users' preferences and intentions to use EMA and DW.

Methods: We will administer 2 discrete choice experiments (DCEs) paired with self-report surveys on the internet to a total of 3260 US adults through Qualtrics. The first DCE will assess participants' EMA preferences using a choice-based conjoint design that will ask participants to compare the relative importance of prompt frequency, number of questions per prompt, prompt type, health topic, and assessment duration. The second DCE will measure participants' DW preferences using a maximum difference scaling design that will quantify the relative importance of device characteristics, effort expectancy, social influence, and facilitating technical, health care, and market factors. Hierarchical Bayesian multinomial logistic regression models will be used to generate subject-specific preference utilities. Preference utilities will be compared across demographic (ie, sex, age, race, and ethnicity) and behavioral (ie, substance use, physical activity, dietary behavior, and sleep duration) subgroups. Regression models will determine whether specific utilities are associated with attitudes toward or intentions to use EMA and DW. Mixture models will determine the associations of attitudes toward and intentions to use EMA and DW with latent profiles of user preferences.

Results: The institutional review board approved the study on December 19, 2022. Data collection started on January 20, 2023, and concluded on May 4, 2023. Data analysis is currently underway.

Conclusions: The study will provide evidence on users' preferences of EMA and DW features that can improve initial uptake and potentially continued use of these remote monitoring tools. The sample size and composition allow for subgroup analysis by demographics and health behaviors and will provide evidence on associations between users' preferences and intentions to uptake EMA and DW. Limitations include the cross-sectional nature of the study, which limits our ability to measure direct behavior. Rather, we capture behavioral intentions for EMA and DW uptake. The nonprobability sample limits the generalizability of the results and introduces self-selection bias related to the demographic and behavioral characteristics of participants who belong to web-based survey panels.

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KEYWORDS

digital wearables; discrete choice experiment; ecological momentary assessment; mHealth; mobile health; remote monitoring technology

Introduction

Ecological momentary assessments (EMAs) and digital wearables (DWs) are exemplars of remote monitoring technologies that afford us the ability to monitor the individual and their environment around the clock [1]. Remote monitoring technologies are a hallmark of precision medicine, whereby medical and health decisions can be tailored to the individual based on their unique and up-to-date data [2]. Specifically, EMA is an approach where people's experiences and behaviors are repeatedly captured through brief self-report surveys [3]. DWs are electronic devices that repeatedly collect, process, store, and transmit data either directly through an internet connection or indirectly through a smartphone [4]. EMAs and DWs capture momentary contextual, sociopsychological, physiological, and behavioral data in the wild (ie, in real time and in a person's natural environment), which improves the accuracy, granularity, and ecological validity of the measurements [5].

User-generated data on behavioral and medical conditions from EMAs and DWs can be used for diagnostic, management, and treatment purposes [1]. Examples include (1) detection of smoking and alcohol use episodes and lapses [6-8] and of various medical conditions [9] (eg, seizures [10] and atrial fibrillation) [11,12]; (2) management of diabetes [13], hypertension [14], physical activity, and diet [15-18]; and (3) treatment of cigarette smoking [19], sleep [20], and mood disorders [21] by intervening whenever and wherever support is needed. Data from EMAs and DWs can improve health and clinical outcomes through various mechanisms. EMAs and DWs capture events and behaviors, their determinants, and their effects. These data relate to several cognitive processes (eg, self-monitoring) underlying the self-regulatory mechanism that motivates and guides proactive and purposeful actions [22]. Additionally, data from EMAs and DWs represent feedback information to their users that is used to form and assess self-views and goals [23], thereby reinforcing desired behaviors [24]. Indeed, evidence shows that EMA and DW use is associated with improved health outcomes [25,26] (cf [27,28]).

Real-time EMA and DW data are the foundation of intensively adaptive health interventions and personalized medical care. Intensively adaptive interventions use ongoing information about the user to disseminate (or not) an appropriate treatment type and dose at the right time and place, relying on predefined decision rules that accommodate between- and within-user characteristics and other tailoring factors (eg, intrapersonal state and contextual cues) that change by the day, hour, or second over the course of an intervention [29,30]. For example, in Text2Quit, an interactive text messaging smoking cessation intervention, users' data are periodically updated throughout the intervention (eg, number of cigarettes smoked) and subsequently integrated in pre- and postquit support messages [19]. In Sense2Stop, users wear chest and wrist DWs and answer smoking- and mood-related EMAs, both of which trigger digital prompts for users to engage in exercises to manage stress, a known antecedent of smoking lapse [31]. Although evidence on the efficacy and effectiveness of intensively adaptive interventions is largely based on pilot studies [32], they often outperform nonadaptive interventions [33]. Similarly, in clinical settings, continuous input from remote monitoring tools can be integrated into a patient's electronic health record, which subsequently informs medical decision-making and improves clinical outcomes [34,35].

To reap the benefits associated with the use of remote monitoring technology, end users must uptake and continually use these digital tools. Uptake refers to the likelihood that an individual is willing to take part in an EMA or use a DW [36]. Continued use refers to the likelihood that an individual consistently completes the EMAs or uses DWs as prescribed [37]. Rates of EMA and DW uptake and continued use are frequently low or variable. For example, health and fitness mobile apps have a mere 3.7% retention rate 30 days post installation [38] and a third of DW owners stop using their devices within 6 months [39]. When reported, EMA completion rate varies across studies, between 20% and 90% in substance use studies [8] and between 44% and 96% in diet and physical activity studies [16]. Compounding these issues, the operationalization of uptake and continued use is often absent or inconsistent across research studies. For example, some studies report percentages of participants who engage in an activity or a previously set threshold of that activity, while others report averages or the exact number of times or number of days participants engage in a given activity [40]. Researchers have documented some of the facilitators of and barriers to the uptake and continued use of EMAs and DWs. Facilitators of use include perceptions of utility, usefulness, ease of use, usability, and having the motivation and ability to use the technology, to name a few [40]. Barriers include technical (eg, technology malfunction and incompatibility) and nontechnical (eg, digital literacy and cost) factors [40].

Uptake and continued use may be improved when the features of EMAs and DWs match the preferences of potential users. However, there is scarce evidence on the relative importance of different attributes and attribute levels of EMAs and DWs that might affect uptake and potentially continued use, although uptake and continued use are driven by different factors [4]. Indeed, the design of EMAs varies greatly regarding key attributes. For instance, the length of EMA studies ranges from 1 to 182 days, with a median of 7 days, whereas the number of daily prompts ranges from 1 to 42 [41]. Additionally, user preferences for specific attributes are rarely examined across sociodemographic and behavioral subgroups, despite well-documented differences in uptake and continued use of remote monitoring technologies between these groups [41,42]. There is also little evidence on the relationship between EMA and DW preferred attributes and intentions to use remote monitoring technologies.

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Using a discrete choice experiment (DCE) [43], this study aims to identify the optimal attributes of EMAs and DWs that may increase uptake and continued use. A DCE is a quantitative survey-based methodology that elicits preferences by presenting participants with alternatives and asking them to make a choice. The process is repeated with different combinations of attributes, and the resulting data are used to calculate the relative importance each participant places on each attribute [44]. In previous studies, this method has been used to elicit preferences for health mobile apps [45-47], sharing health data [48,49], and health interventions [50]. In this study, 2 DCEs will elucidate preferences for EMAs and DWs, examine how these preferences vary across demographics (ie, sex, age, and race and ethnicity) and behaviors (ie, substance use, physical activity, dietary behavior, and sleep duration), and assess whether specific preferences are associated with attitudes toward or intentions to use EMAs and DWs in the future.

Methods

Aims

This study aims to (1) quantify the relative importance of 5 EMA attributes (ie, prompt frequency for surveys, number of questions per prompt, prompt type, health topic, and assessment duration) and 30 DW features centered around 6 domains (ie, device characteristics, effort expectancy, social influence, and facilitating conditions related to technical, health care, and market factors); (2) identify the relative importance of EMA and DW attributes within demographic (ie, sex, age, and race and ethnicity) and behavioral (ie, those who meet vs who do not meet predefined criteria or guidelines for a given behavior) subgroups; and (3) examine the associations between users' preferences and EMA and DW uptake intentions.

Design

The focal point of the study is 2 DCEs (Multimedia Appendix 1). Each participant will complete only 1 DCE.

The first DCE will assess EMA preferences using a choice-based conjoint design [51,52] in which 5 attributes (eg, number of surveys per day) are presented as a package. Each attribute is assigned one of several levels (eg, 2-3 surveys or 6 or more surveys). Participants choose between 2 packages or neither package. Attributes and levels (Table 1) were selected from previous research on EMAs [15,16,18,41,53]. Collectively, over 1500 unique packages can be constructed from these attribute levels. However, a balanced fractional factorial design will be implemented in Qualtrics so that each participant only needs to repeat the task 9 times and evaluate 18 packages.

The second DCE will measure DW preferences using a maximum difference scaling design [54,55] in which participants view a subset of 4 features from a larger set of 30 features (Table 2). Participants choose which feature in the subset they value the most and which they value the least. The attributes and corresponding statements were adapted and developed from previous research on DWs [4,56-60] and digital health tools more broadly [40,46,48,50,61-65]. Attribute domains correspond to constructs derived from technology acceptance theoretical frameworks [66]. The attributes and corresponding statements center around effort expectancy, defined as the level of ease in using the technology; social influence, defined as the level of support the user of the technology receives from important others; and facilitating conditions related to technical infrastructure, health care, and market factors that can prohibit or support the technology use [66]. We also include device characteristics as an external factor associated with technology acceptance [59]. Although over 24,000 combinations of attributes are possible, each participant will only be required to complete the task 23 times.

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Table 1. Attributes and attribute levels in an ecological momentary assessment discrete choice experiment.

Attributes and attribute levels	Descriptions
Prompt frequency	
0-1 per day	None or only 1 survey
2-3 per day	2-3 surveys
4-5 per day	4-5 surveys
≥6 per day	6 or more surveys
Number of questions per prompt	
1 question	1 question
2-3 questions	2-3 questions
4-5 questions	4-5 questions
≥6 questions	6 or more questions
Prompt type	
Event-contingent	Self-initiated when a predefined event has occurred (eg, smoking a cigarette, snacking between meals, or being in a specific location such as a bar)
Signal-contingent	At random times
Time-contingent	On fixed times
Mixed	Combination of random and fixed times
Health topic	
Nicotine or tobacco use	Nicotine or tobacco use
Alcohol use	Alcohol drinking
Marijuana use	Marijuana use
Physical activity	Exercise
Nutrition	Diet or nutrition
Sleep	Sleep
Assessment duration	
≤1 month	1 month or shorter
>1 but <6 months	More than 1 month but less than 6 months
≥6 but <12 months	More than 6 months but less than 1 year
≥1 year	1 year or longer

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Table 2. Attributes examined in the digital wearables discrete choice experiment.

Domains and attributes	Statements
Device characteristics	
Type	• The device collects nonmedical data (eg, steps) • The device collects medical data (eg, blood glucose)
Point of contact	• I must wear the device on my chest or ankle
Battery life	• The device must be charged every 48 hours
Display	• The device has a touchscreen interface
Memory	• The device has a memory chip to prevent data loss
Cellular data	• The device must be always connected to the internet
Personalization	• I can personalize the device to my individual goals and preferences • I can change the look and feel of the device (eg, by using different strap styles and colors)
Added features	• The device provides information in languages other than English (eg, Spanish) • The device allows me to interact with other users if I want to
Effectiveness	• The accuracy of the device has been proven in scientific studies
Effort expectancy	
Ease of use	• The device is easy to use
Data sync	• The device syncs automatically with a smartphone
Comfort	• The device fits with my lifestyle and daily activities • The device can cause skin irritations
Social influence	
Peer recommendation	• A friend or family member recommended the device to me
Facilitating technical factors	
Compatibility	• The device is compatible with all smartphones (eg, Android and Windows) • The device is compatible with popular health apps
Data security and privacy	• I can enable or disable location tracking on the device • I get to choose when and how the device shares data • My data are encrypted • My data will be sold to third parties for profit
Facilitating health care factors	
Insurance	• The device is covered by health insurance
Doctor recommendation	• My doctor recommended the device to me
Data exchange	• I can share the data with my doctor
Facilitating market factors	
Costs	• The device is under US $150
Customer reviews	• The device has a high customer rating
Warranty	• The device comes with a 2-year warranty
Customer service	• There is a number I can call if the device stops working

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Sample

A nonprobability sample of 3260 US adults, 18 years and older, will be recruited nationwide to participate in a web-based survey. The sample will be equally split across biological sex, age groups, and race and ethnicity to allow comparisons of users' preferences within demographic subgroups (Table 3). Sample size calculations were performed using standard DCE formulas [67,68]. A sample of 333 participants is required for the EMA DCE based on the formula n≥1000(x)/yz, where *x* is the maximum number of levels of any attribute, *y* is the number of choices per task excluding the option none, and *z* is the number of times the task is completed per participant [ie, 1000(6)/(2 × 9) = 333]. A sample of 163 participants is required for the DW DCE based on the formula n≥500(w)/yz, where *w* is the number of features and *y* and *z* are defined identically to the previous formula [ie, 500(30)/(4 × 23) = 163]. However, the minimum sample for the DW DCE will be set at 300 participants in accordance with recommended guidelines [68]. Based on these calculations, the study should be well powered even when the sample is further stratified by demographic and behavioral subgroups.

Table 3. Target sample characteristics (N=3260).

Characteristics	Participants, n (%)
Sex	
Female	1630 (50)
Male	1630 (50)
Age (years)	
18-29	815 (25)
30-44	815 (25)
45-59	815 (25)
≥60	815 (25)
Race and ethnicity	
Non-Hispanic American Indian, Alaska Native, Native Hawaiian, or Pacific Islander	652 (20)
Non-Hispanic Asian	652 (20)
Hispanic or Latino	652 (20)
Non-Hispanic Black	652 (20)
Non-Hispanic White	652 (20)

Recruitment

Through its research panels, Qualtrics will send an invitation email to individuals with demographic characteristics that match the target sample. The email includes links to 2 identical surveys: the first has the EMA DCE, and the second has the DW DCE. The email also includes an estimated time to complete the survey and the incentive offered. Qualtrics will compensate participants and distribute the incentives at a rate equivalent to surveys of similar scope, burden, and duration. Data collection will continue until the desired sample size and composition are reached.

Procedures

Participants will consent before proceeding to any survey questions. Consenting participants will respond to inclusion and exclusion questions. To be included in the study, participants must be adults residing in the United States. Inclusion questions include zip code, age, biological sex, and race and ethnicity. The latter 3 questions are the basis of built-in hidden quotas for sample characteristics (Table 3). When a quota is met (eg, 50% females already recruited), participants who belong to that subgroup will not be allowed to take the survey. The only exclusion criterion is when participants respond yes to "Do you use any fitness tracker, smartwatch, or electronic medical device to monitor or track your health?" [69]. Participants who use a DW are excluded to improve inferences about preferences among nonusers. Ineligible participants receive a thank you message and are not allowed to proceed any further. Eligible participants will proceed to the remainder of the study questions. Except for completing 1 of the 2 DCEs, all instructions and questions are identical for all participants. The survey will take about 30 minutes to complete.

Measures

We will collect sociodemographic (ie, zip code, biological sex, age, race and ethnicity, sexual orientation, education, household income, employment, marital status, and English language proficiency) [69,70] and health (ie, weight and height [69], general health [71], emotional health [72], perceived susceptibility to disease [73], underlying health conditions [70], having a regular health care provider [69], and health insurance [69]) data. We also collect behavioral data on nicotine and tobacco use [74,75], marijuana use [76], alcohol use [77], fruit and vegetable intake [69], physical activity [69], and sleep [69], all of which are risk factors for chronic conditions and are thus the focus of health and medical interventions. These behavioral data allow comparisons of users' preferences within behavioral subgroups. Where each participant can demonstrate any number of the 6 behaviors examined in the study, we follow public

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health guidelines to group each participant into 1 of 2 groups, one where participants do (vs do not) meet those guidelines and thresholds for each behavior as follows: (1) Nicotine and tobacco use is defined as current use of any nicotine or tobacco product [78]. (2) Marijuana use is defined as current use of marijuana or cannabis [78]. (3) Alcohol misuse is defined as daily consumption of >1 drink per day for women and >2 drinks per day for men, or as total consumption of >7 drinks per week for women and >14 drinks per week for men [79,80]. Alcohol use questions are asked only of participants 21 years or older. (4) Insufficient physical activity is defined as <150 minutes or 2.5 hours of physical activity per week [81]. (5) Inadequate fruit and vegetable intake is defined as <5 servings of fruit and vegetables total per day [79]. (6) Insufficient sleep is defined as <7 hours of sleep per night [82].

We also collect data on digital technologies access and use [69,83]; phone affinity [84]; previous use of [69], attitudes toward [85], and satisfaction with health applications [86]; attitudes toward wearable devices [85]; technology acceptance [59,87-89]; and willingness and intentions to use EMAs and DWs.

Data Analysis

Data from both DCEs will be analyzed using hierarchical Bayesian multinomial logistic regression models [90,91]. These models will generate subject-specific utilities quantifying the relative importance of each attribute to each participant. EMA and DW attribute preferences will be characterized among all participants and within subgroups defined by sex (female or male), age group (18-29 years, 30-44 years, 45-59 years, or 60 years or older), race and ethnicity (Non-Hispanic American Indian, Alaska Native, Native Hawaiian, or Pacific Islander; Non-Hispanic Asian; Hispanic or Latino; Non-Hispanic Black; or Non-Hispanic White), or health behavior (meeting vs not meeting established public health guidelines for each behavior). Differences between subgroups will be evaluated using *t* tests, analysis of variance, or linear regression, as appropriate. The association between each utility and each measure of attitude toward or intention to use EMAs and DWs will be depicted in correlation matrices generated from data comprising all participants or data from specific demographic or behavioral subgroups. A latent profile analysis [92,93] of individual-level utilities will be performed to detect segments of individuals who share common preferences. The extent to which demographics or behavioral characteristics predict membership in these segments will be quantified using the 3-step method [94,95]. The Bolck, Croon, and Hagenaars method [96] will evaluate whether specific segments are associated with specific attitudes or intentions.

Ethical Considerations

The study was deemed exempt on December 19, 2022, under category 2: research that only includes interactions involving educational tests, survey procedures, interview procedures, or observation of public behavior [§45 CFR 46.10(d)(2)], National Institutes of Health Institutional Review Board (001208).

Results

Data collection started on January 1, 2023, and concluded on May 4, 2023. Data analysis is ongoing.

Discussion

This protocol outlines a survey-based DCE to identify attributes that are associated with the uptake of EMAs and DWs. EMAs and DWs are remote monitoring technologies that capture real-time data in users' natural environments that are foundational to precision medicine. These data-driven approaches to health and medical care are the face of an increasingly digital ecosystem and align with the emphasis on person-centered care [97].

The study will generate insights on the optimal attributes and features that users value to maximize the uptake of EMAs and DWs. Such insights have significant health and medical implications given the ubiquitousness of mobile technologies. In 2021, smartphone ownership was at 85% in the United States [98] and there were approximately 100,000 health care apps on the Apple App Store and Google Play Store [99,100]. As of 2022, wearables penetration was at 25.3% among US adults [101] and is forecast to reach 628.3 million devices globally by 2026 [102]. Additionally, mobile health technologies enjoy acceptance and demand from users and patients [103]; interest of commercial, research, and health care entities [104,105]; and support of national and international policies and initiatives [106,107]. These technologies have given rise to terms like digital biomarkers, digital diagnostics, digital therapeutics, and digital treatments [1]. They are becoming common in medical research as well as available directly to users who can engage in self-care within (eg, electronic health records) [108] or outside (eg, faith organizations) [109] the traditional health care system. This is especially relevant given the prevalence of chronic conditions (eg, heart disease) and associated modifiable risk factors (eg, tobacco use) that are suited for remote monitoring [110]. Programs for the integration of telemonitoring in clinical and medical care for managing and treating chronic conditions in patients are developed and piloted [26,34], providing a far-reaching platform for health care delivery that can benefit underserved populations such as those with limited access to health care or those who disproportionally bear the highest burden of disease and risk factors [111].

The study has several limitations. Participants belong to web-based survey panels, rendering the results nongeneralizable to the US population and raising concerns about self-selection bias. The Qualtrics platform does not permit the inclusion of 2 DCEs in the same survey. Accordingly, participants received an invitation email with links to both surveys but were permitted to take only one. Although current use of a wearable device is an exclusion criterion for this study, the sample can include ex-users of wearables who may hold preexisting attitudes toward DWs based on previous experiences. Because of the cross-sectional nature of the survey, we capture behavioral intentions rather than EMA and DW use behavior. To avoid survey burden, we limited the number of EMA attributes and DW features. The study has several strengths, including a robust

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sample size that allows for subgroup analysis by sociodemographic and behavioral groups. The study also examines the preferences-intentions relationship that provides actionable information to increase the uptake of EMAs and DWs, especially among at-risk or disadvantaged populations.

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Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during this study.

Authors' Contributions

SE conceptualized the study and drafted the manuscript. JP developed the statistical analysis plan. GZ and PH built and tested the web-based surveys. All authors approve the manuscript as submitted.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Discrete choice experiment tasks.
[DOCX File , 15 KB - resprot_v12i1e47567_app1.docx]

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Abbreviations

DCE: discrete choice experiment
DW: digital wearable
EMA: ecological momentary assessment

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Protocol

Feasibility Study of Virtual Reality–Based Cognitive Behavioral Therapy for Patients With Depression: Protocol for an Open Trial and Therapeutic Intervention

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Abstract

Background: The clinical usefulness of cognitive behavioral therapy (CBT) for patients with depression who do not remit with pharmacotherapy has been recognized. However, the longer time burden on health care providers associated with conducting CBT and the lack of a system for providing CBT lead to inadequate CBT provision to patients who wish to receive it.

Objective: We aim to evaluate the feasibility of introducing virtual reality (VR) into CBT for patients with depression.

Methods: This is a single-center, interventional, exploratory, single-arm, nonrandomized, open, pre-post–comparative feasibility study of an unapproved medical device program to evaluate the acceptability, preliminary efficacy, and safety of the study device. Eligible patients meet the diagnostic criteria of the DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, 5th Edition) for major depressive disorder, have a 17-item Hamilton Depression Rating Scale (HAMD-17) score of ≥12, and are aged 18-65 years. The sample will comprise 12 patients. VR-based CBT (CBT-VR) sessions will be conducted once a week in an outpatient setting. CBT-VR has been developed in accordance with 6 stages and 16 sessions in the current CBT therapist manual. VR contents and other components correspond to the themes of these 16 sessions. The flow of CBT-VR treatment is similar to that of normal CBT; however, this product replaces the in-person portion of CBT. The primary end point will be the change in the HAMD-17 score from baseline up to 16 sessions. Secondary end points will be treatment retention; psychiatrist consultation time; satisfaction with the equipment or program; ease of use; homework compliance; change in the HAMD-17 score from baseline up to 8 sessions; change in Montgomery-Åsberg Depression Rating Scale (MADRS), Quick Inventory of Depressive Symptomatology Self-Report (QIDS-SR), EQ-5D-5L, and Clinical Global Impressions (CGI) scores from baseline up to 8 and 16 sessions; and change in remission and response rates and HAMD-17, MADRS, QIDS-SR, and EQ-5D-5L scores from baseline to 3 and 6 months post intervention (or discontinuation). CBT-VR's feasibility will be assessed at baseline, after 8 sessions, after 16 sessions, or treatment discontinuation, by measuring the time required for testing and medical care during each session and with a patient questionnaire. After intervention discontinuation, a follow-up evaluation will be conducted unless the patient withdraws consent or otherwise discontinues participation in the study after 3 and 6 months.

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Results: Participant recruitment started on November 30, 2022, and data collection is ongoing as of September 2023.

Conclusions: This study is the first step in testing the acceptability, feasibility, and preliminary efficacy and safety of CBT-VR for patients with depression without controls in an open-label trial. If its feasibility for depression treatment is confirmed, we intend to proceed to a large-scale validation study.

Trial Registration: Japan Registry of Clinical Trials jRCTs032220481; https://jrct.niph.go.jp/en-latest-detail/jRCTs032220481

International Registered Report Identifier (IRRID): DERR1-10.2196/49698

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KEYWORDS

depression; cognitive behavioral therapy; virtual reality; CBT; feasibility study; open trial; VR

Introduction

Depression is a common disorder, with a lifetime prevalence rate of over 10% [1,2].

It is generally treated with antidepressant medication. However, some patients with depression do not respond to those medications, and depressive symptoms may persist for a long period without adequate improvement [3], resulting in a significant emotional and financial burden on the patients and their families [4-6].

Cognitive behavioral therapy (CBT) is a structured psychotherapy that modifies cognitive biases and assists problem-solving since mood is influenced by how one perceives and acts. CBT comprises several components: cognitive restructuring, behavioral activation, assertion, problem-solving, and relaxation [7,8]. CBT for patients with depression consists of 16-20 sessions of at least 30 minutes each, mainly through face-to-face sessions.

The efficacy of CBT for patients with depression who do not remit with pharmacotherapy has been tested in a randomized controlled trial in Japan [9]. Eighty patients with drug-resistant major depressive disorder were randomized to CBT or no-CBT groups. The change in the 17-item Hamilton Depression Rating Scale (HAMD-17) score from baseline to 16 weeks later was compared, with a significant improvement in the HAMD-17 score in the CBT group compared to that in the no-CBT group (between-group difference: –5.4 points; $P<.001$). Although the clinical usefulness of CBT has been recognized and insurance coverage is available when performed by a physician or nurse, the provision of CBT to patients who wish to receive it is currently inadequate. This can be attributed to the prolonged time burden on health care providers when performing CBT and the lack of a system to provide CBT. Therefore, developing a delivery system that uses information and communication technology is a challenge that must be overcome to enable the widespread use of CBT.

Web-based CBT has the same content as face-to-face CBT; however, it is more flexible and cost-effective treatment than face-to-face therapy for depression. Web-based CBT significantly improved patients' depressive symptoms and quality of life, similar to face-to-face CBT [10]. Mixed treatment integrating face-to-face CBT and web-based CBT has also been shown to be effective in treating patients with depression [11]. CBT can also be delivered through virtual reality (VR), a technology that immerses users in a computer-generated virtual world [12]. VR is considered a powerful educational tool because it allows people to experience, rather than merely perceive, what they need to learn [13].

However, several previous studies of VR interventions for mental health have focused on treating anxiety disorders [12,14], pain distraction [15,16], and relaxation [17,18], with surprisingly few VR interventions for depression [19].

In a joint study conducted in 2020 by the National Center for Cognitive Behavioral Therapy, Jolly Good Inc, and the National Center of Neurology and Psychiatry, the impact on depressive symptoms and safety of VR technology in providing CBT for patients with depression were evaluated (University hospital Medical Information Network [UMIN] Clinical Trials Registry; UMIN000040864). As a result, 4 of 7 patients included in the study had improvements in 2 or more Beck's Depression Inventory-II depression rating scale severity categories. One of 7 patients showed an improvement in 1 severity category compared to the previous treatment. No adverse events were observed, suggesting that using VR technology during CBT for patients with depression is well tolerated. However, this previous study has yet to be published. This previous study aimed to increase positive emotions in 7 patients with depression. The VR content comprised images of landscapes, animals, and a woman laughing, but not the CBT content.

The newly developed VR-based CBT (CBT-VR) uses VR to deliver CBT content to patients with treatment-resistant depression. CBT-VR for depression in this study aims to help patients acquire CBT skills, become aware of their own automatic thought patterns through the examples of others, and guide them toward solutions. Therefore, the VR content in this study is different from that in the previous study.

The newly developed CBT-VR follows the 16-session agenda in the therapist's manual and is intended to treat patients with depression in the same way as current CBT. CBT-VR can replace a part of the CBT conducted face-to-face by a health care provider and reduce the longer time burden. It is expected to expand opportunities for the treatment of depression and improve patient benefits through CBT.

In this study, we will evaluate whether it is possible to reduce the intervention time of medical personnel while retaining the effects of CBT by replacing part of the CBT conducted in person with VR and videoconferencing, using information terminals. By incorporating VR into CBT, patients can learn CBT skills

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and become aware of their own automatic thought patterns through the examples of others. Changing one's mindset is important in CBT for depression, and the advantage of VR is that it provides an immersive experience that puts one in another person's shoes. The CBT-VR system to be used in the study is an unapproved medical device program under development by Jolly Good Inc, which intends to apply for the relevant manufacturing and marketing approvals in collaboration with Teijin Pharma Limited.

This study aims to evaluate the feasibility of introducing VR into CBT for patients with depression. In this study, 16 sessions of CBT-VR will be conducted, its acceptability will be assessed, and its efficacy and safety will be preliminarily examined by measuring and collecting data on the participants' usability and the time required for psychiatrist consultation.

If the feasibility of CBT-VR for depression is demonstrated in this study, we may proceed to a confirmatory study. In addition, if further work shows that CBT-VR is effective, it may provide a new option for patients who do not respond adequately to conventional treatment and have not had the opportunity to receive CBT.

Methods

Study Design

This is a single-center, interventional, exploratory, single-arm, nonrandomized, open, pre-post–comparative study involving a feasibility study of an unapproved CBT-VR device intervention to evaluate its acceptability, preliminary efficacy, and safety among patients with depression.

Participant Selection Criteria

Inclusion Criteria

Patients who meet all the following criteria will be enrolled in the study: (1) those who meet the DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, 5th Edition) diagnostic criteria for major depressive disorder; (2) those with a HAMD-17 score of ≥12 at screening; (3) those who do not respond adequately to ≥1 antidepressants or are unsuitable for pharmacotherapy due to intolerance, comorbidity, pregnancy, or refusal of medication; (4) those who are aged between 18 and 65 years when consent is obtained; and (5) those who provide written informed consent.

Exclusion Criteria

Patients meeting the following criteria will be excluded from the study: (1) those with comorbid or preexisting manic, hypomanic, or psychotic episodes; personality disorders or posttraumatic stress disorder; or alcohol or substance use disorders; (2) those with active suicidal ideation; (3) those who have not responded to CBT in the past; (4) those who have difficulty using VR devices and applications; and (5) those deemed inappropriate for this study by the principal investigator.

Sample Size Determination

The sample size will be 12 patients. This sample size was not determined on the basis of the distribution of any end point or statistical power.

In order to evaluate the acceptability of CBT-VR in this study, it is necessary to obtain data on use and satisfaction from a wide range of patients (based on parameters such as sex, age, and severity). In addition, a certain number of patients is necessary to evaluate efficacy and safety. A similar pre- and postintervention comparative study of CBT using VR for patients with depression (UMIN000040864) was conducted with 12 patients, and the number of patients was deemed to be sufficient for feasibility evaluation.

Study Outline

Screening tests will be performed for patients who have obtained consent to participate in the study, and baseline testing will be performed for eligible participants before the start of the intervention. In principle, 16 CBT-VR sessions will be administered weekly in an outpatient setting. The feasibility of CBT-VR will be assessed by testing at baseline, at the end of 8 sessions, at the end of 16 sessions, or treatment discontinuation, and by measuring the time required for testing and medical care during each session and by patient questionnaire. The duration of the intervention, including allowance, will be a maximum of 24 weeks, with no interruption of more than 8 consecutive weeks from the end of each session to the implementation of the next session. In addition, no more than 1 session will be conducted on the same day. If a patient is hospitalized during the intervention period, participation in the study will not be discontinued if it is possible to continue. After the intervention is terminated, follow-up assessments will be conducted unless the patient withdraws consent or otherwise discontinues participation in the study. After 16 sessions or after the intervention is terminated, patients will be treated as usual; however, they will continue to view the VR and use the application for 6 months during the follow-up period.

Information on Drugs, Medical Devices, and Treatments to be Used in the Study

A CBT-VR device (Jolly Good Inc) will be used in this study. CBT-VR is an unapproved medical device program developed to support CBT for patients with depression.

The system structure of this product is shown in Table 1. This product is a system that integrates 6 components consisting of VR contents installed on general-purpose commercial VR goggles, 3 applications used by patients or health care providers, and progression support tools with CBT-VR content management system in the cloud.

CBT-VR has been developed in accordance with 6 stages and 16 sessions described in the current CBT therapist manual, and the VR contents and other components correspond to the themes of each of these 16 sessions. The treatment flow using CBT-VR is similar to that of the normal CBT protocol; however, this product replaces a part of the CBT conducted face-to-face by a health care provider with VR and videoconferencing. The homework app will be downloaded to the patients' smartphone.

Adverse events anticipated from CBT-VR include pain in the area where the VR goggles are worn and discomfort from viewing the VR images (VR sickness), both of which are expected to be mild and tolerable.

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Table 1. List of names and functions of each component, equipment, and users.

Name	Main functions	Equipment used	User
Viewer application	Content playback, choice operation, and choice data acquisition	VR[a] goggles	Patient
Homework app	Homework implementation and scheduling	Smartphone	Patient
Manager application	Content control	Tablet terminal	Health care provider
My Page	Patient information registration and data viewing	PC or tablet device	Health care provider
VR contents	Video and audio of CBT[b] sessions	VR goggles	Patient
Progression support tools	Manual for health care providers and manual for patients	Tablet terminal or printed matter	Health care provider and patient
CBT-VR[c] CMS[d]	System integration of VR goggles, the Viewer application, the Homework app, the Manager application, My Page, and Progression support tools	Cloud server	Jolly Good Inc

[a]VR: virtual reality.

[b]CBT: cognitive behavioral therapy.

[c]CBT-VR: virtual reality–based cognitive behavioral therapy.

[d]CMS: content management system.

Dosage and Administration of Drugs, Applications, or Equipment Used in This Study

In this study, 16 sessions of CBT-VR will be conducted once a week in an outpatient setting. The flow of each session of CBT using this product is described in Table 2.

When participants arrive at the clinic, they will review their homework using the progression support tool and experience the theme by viewing the VR content corresponding to each session. While using the progression support tool again, they will use the VR experience as a guide to practice the themes. The participant will then interact with the physician and conduct homework at home using the Homework App and the progression support tool [20,21].

If depressive symptoms exacerbate and require hospitalization after each session, the principal investigator will decide whether or not to continue the treatment.

Table 2. The flow of each session.

Session	Progress of the session	Components	Implementor
1	Introduction	Progression support tools	Patient
2	Theme experience	VR[a] goggles (includes content and other programs)	Patient
3	Theme practice	Progression support tools	Patient
4	Dialogue on the theme (medical treatment by a physician)	Progression support tools	Physicians and patients
5	Homework (conducted at home)	Homework app and Progression support tools	Patient

[a]VR: virtual reality.

Rules for Concomitant Medications and Concomitant Therapy

The type and dosage of concomitant antidepressants will not be changed during the intervention period from baseline to the examination at the end of the 16 sessions or at the end of the intervention. Dosage and administration will be in accordance with the package insert of each antidepressant. If no concomitant antidepressants are used, no new antidepressants will be initiated during the intervention period. No structured psychotherapy, repetitive transcranial magnetic stimulation, or electroconvulsive therapy will be administered during the intervention period, and treatment will not be restricted during the follow-up period after 16 sessions or after discontinuation of the intervention.

End Points and Evaluation Methods

The primary end point is a change in the HAMD-17 score from baseline to the end of 16 sessions. The secondary end points are the treatment continuation rate (ie, the proportion of participants who completed 16 sessions); the time required for psychiatrist consultation; patient satisfaction and usability of the equipment and programs and compliance with homework; change in the HAMD-17 score from baseline to the end of 8 sessions; change in the Montgomery-Åsberg Depression Rating Scale (MADRS), Quick Inventory of Depressive Symptomatology Self-Report (QIDS-SR), EQ-5D-5L, and Clinical Global Impressions (CGI) scores from baseline to the end of 8 and 16 sessions; remission rates (ie, the proportion of participants with a HAMD-17 score of ≤7 and a <ADRS score of ≤10); response rates (ie, the proportion of participants with

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a ≥50% reduction in the HAMD-17 and MADRS scores from baseline); change in HAMD-17, MADRS, QIDS-SR, EQ-5D-5L, and CGI scores from baseline to 3 and 6 months post intervention (or discontinuation); the proportion of participants with a decrease in the number of prescriptions or doses of psychotropic drugs from baseline to 3 and 6 months post intervention (or discontinuation); adverse events; and equipment failures.

For the safety evaluation, pain, discomfort from wearing or viewing VR, manic and hypomanic episodes (meeting the DSM-5 criteria), and suicidal ideation will be assessed during the intervention and observation periods. Suicidal ideation will be assessed using HAMD-17, MADRS subitems, and clinically. The interviewer will check for the presence and worsening of suicidal ideation at each session.

Observation and Examination Items

The following items will be collected per schedule: patient background (age, sex, height, weight, comorbidities, medical history, educational history, employment experience, and VR viewing experience); depression treatment history (date of diagnosis, number of previous episodes, duration of the current episode, number of antidepressant failures due to Antidepressant Treatment History Form, and history of CBT treatment); concomitant therapy (including medications, repetitive transcranial magnetic stimulation, and electroconvulsive therapy, and whether they were hospitalized); satisfaction with CBT-VR, feeling of use, and compliance with homework; time required for consultation by health care providers; HAMD-17, MADRS, QIDS-SR, EQ-5D-5L, and CGI scores; adverse events; and equipment failures.

The observation schedule is shown in Figure 1. In total, 16 CBT-VR sessions will be performed weekly in an outpatient setting. The intervention period will be a maximum of 24 weeks, including allowance, with no interruption of more than 8 consecutive weeks between the end of each session and the implementation of the next session. No more than 1 session will be conducted on the same day. The day of the week will not be fixed, and only 1 session will be carried out per week. If a session is held on Friday, the next session will be held on any day from Monday to Friday the following week. Therefore, the minimum interval between sessions will be 2 days (Friday to Monday).

Figure 1. Observation and inspection schedule. Combined therapy during the 6-week tracking period after 3 and 6 months post intervention include continuous use of VR or applications. CGI: Clinical Global Impressions; HAMD-17: 17-item Hamilton Depression Rating Scale; MADRS: Montgomery-Åsberg Depression Rating Scale; QIDS-SR: Quick Inventory of Depressive Symptomatology Self-Report; VR: virtual reality.

	Before start (2 weeks)	Intervention period (~24 weeks)					Tracking period (6 weeks)	
		1-7 sessions	8 sessions	9-15 sessions	16 sessions	Abortive	After 3 months	After 6 months
Obtaining consent	✓							
Patient background	✓							
History of depression treatment	✓							
HAMD-17	✓		✓		✓	✓	✓	✓
MADRS	✓		✓		✓	✓	✓	✓
QIDS-SR	✓	✓	✓	✓	✓	✓	✓	✓
EQ-5D-5L	✓		✓		✓	✓	✓	✓
CGI	✓		✓		✓	✓	✓	✓
Combined therapy	✓	✓	✓	✓	✓	✓	✓	✓
Satisfaction feeling of use					✓	✓		✓
Compliance with homework		✓	✓	✓	✓	✓		
Psychiatrist consultation time		✓	✓	✓	✓	✓		
Adverse events and failure	←							→

Statistical Analysis

The study objective is purely descriptive. We do not intend to decide the efficacy and safety of CBT-VR based on statistical tests.

Population for Efficacy and Safety Analysis

The population for efficacy analysis includes all participants who have used CBT-VR at least once and at least 1 end point is measured. The population for safety analysis consists of all participants who have viewed CBT-VR at least once.

Analyses

Baseline characteristics will be assessed using descriptive statistics.

As a primary analysis, original scores and changes in the score on the HAMD-17 from baseline to the end of 16 sessions will be summarized, the latter depicted as mean and 95% CI values. A 1-sample *t* test against the null hypothesis that the mean change in score equals 0 will be performed. The threshold for statistical significance will be set at 5%, and multiplicity will

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not be adjusted since this study is exploratory by nature. Missing data will be imputed using the previous measurement.

As secondary analyses, original scores and changes in the scores on the HAMD-17 from baseline to other time points will be summarized, and mean and 95% CI values will be estimated. The same analyses will be performed for changes in MADRS, QIDS-SR, EQ-5D-5L, and CGI scores. The frequency and proportion of the patients in remission at each measured point and those with a decreased number or dose of psychotropic medications will be summarized. The frequencies and proportions of the patients who completed the 16 sessions, patient satisfaction, and usability (the Japanese version of Client Satisfaction Questionnaire-8 and other answers to questions) will be summarized for feasibility assessment. The time required for psychiatric consultation and the number of homework assignments done will be tabulated and summarized for each session. In addition, missing data will be excluded from the analysis at each measured point.

Detailed definitions for classification will be determined on the basis of the distribution before data fixation. The stratification variables for subgroup analyses are as follows: sex, duration of the current episode (<2 years and ≥2 years), age, work experience, previous CBT treatment, baseline HAMD-17 score, concomitant medications, homework compliance, time spent at the doctor's office, continued viewing of VR content and use of applications (during follow-up).

As a safety analysis, the frequency of adverse events and failures will be tabulated for each event.

Ethical Considerations

The clinical study will be conducted in compliance with the Clinical Trials Act. It was registered with the Japan Registry of Clinical Trials (trial ID jRCTs032220481) and approved by the Japan Certified Clinical Research Review Board. The study's details will be fully explained to all patients, and face-to-face informed consent will be obtained before starting the study. After obtaining informed consent, the participants' data will be deidentified before analysis.

If the obtained data are used in the future for purposes other than those indicated in this study, the following conditions will need to be met: (1) the study will be reviewed again and approved by the center's ethics committee or clinical research review committee, and (2) the willingness of the participants to cooperate in the study will be confirmed through reconsent or information disclosure regarding the conduct of another study.

Results

This study was registered with the Japan Registry of Clinical Trials (trial ID jRCTs032220481). Informed consent will be obtained before enrollment in the study. Participant recruitment started on November 30, 2022, and data collection is ongoing as of September 2023. The results will be published in a peer-reviewed academic journal, presented at scientific conferences, and communicated to the participants and patient organizations. International Committee of Medical Journal Editors criteria on contributorship and authorship are applied.

Discussion

This study is a first step toward testing the acceptability, feasibility, and preliminary efficacy and safety of introducing CBT-VR to patients with depression.

The efficacy of CBT for patients with depression who do not remit with pharmacotherapy has been verified in randomized controlled trials in Japan [3]. However, the provision of CBT to patients who wish to receive it is currently inadequate due to the large time burden on health care providers when conducting CBT and the lack of a system to provide CBT. In this study, we will evaluate whether it is possible to reduce the intervention time of health care providers while maintaining the therapeutic effects of CBT by replacing a portion of CBT conducted in person with VR and videoconferencing, using information terminals.

If this study confirms the feasibility of CBT-VR for depression, we may proceed to a confirmatory trial. Furthermore, if a future trial confirms that CBT-VR is effective, it may provide a new option for patients who have not had an adequate response to conventional treatment and have not had the opportunity to receive CBT.

As a limitation, the study will have a small number of cases, is not blinded, and will have no controls. In a future study, we would like to conduct a randomized controlled trial with appropriate controls.

Treatment options for CBT are expanding to include face-to-face, web-based, and VR components. Future developments may lead to new techniques, increasing access to CBT for more patients.

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This study will be conducted as joint research between Jolly Good Inc and Teijin Pharma Limited, with research funding and equipment, including unapproved medical device programs, to be used in the research provided by the manufacturer, Jolly Good Inc.

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Data Availability

The data sets generated or analyzed during this study will not be publicly available but will be available from the corresponding author upon reasonable request.

Authors' Contributions

SK contributed to this study's conceptualization, protocol development, and project management. AI and FH contributed to this study's design and the manuscript's preparation. MSO made significant contributions to the protocol of this study, especially in the statistical analysis section. AK and AM contributed to the development and design of the CBT-VR. All authors participated in reviewing and revising the manuscript and approved the final manuscript.

Conflicts of Interest

AK and AM are employees of Jolly Good Inc.

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Abbreviations

CBT: cognitive behavioral therapy
CBT-VR: virtual reality–based cognitive behavioral therapy
CGI: Clinical Global Impressions
DSM-5: Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
HAMD-17: 17-item Hamilton Depression Rating Scale
MADRS: Montgomery-Åsberg Depression Rating Scale
QIDS-SR: Quick Inventory of Depressive Symptomatology Self-Report
UMIN: University Hospital Medical Information Network
VR: virtual reality

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Protocol

Identifying and Addressing Barriers and Facilitators for the Implementation of Internet of Things in Distributed Care: Protocol for a Case Study

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Abstract

Background: The internet of things (IoT) is recognized as a valuable approach to supporting health care to achieve quality and person-centered care. This study aims to identify the facilitators and barriers associated with implementing IoT solutions in health care within a Scandinavian context. It addresses the pressing need to adapt health care systems to the demographic changes occurring in Scandinavia. The vision of "Vision eHealth 2025," a long-term strategic direction for digitalization in Sweden, serves as the background for this project. The implementation of IoT solutions is a crucial aspect of achieving the vision's goal of making Sweden a global leader in using digitalization and eHealth opportunities by 2025. IoT is recognized as a valuable approach to supporting health care to achieve quality and person-centered care. Previous research has shown that there is a gap in our understanding of social and organizational challenges related to IoT and that the implementation and introduction of new technology in health care is often problematic.

Objective: In this study, we will identify facilitating and hindering factors for the implementation of IoT solutions in social and health care.

Methods: We will use an explorative design with a case study approach. The data collection will comprise questionnaires and qualitative interviews. Also, a literature review will be conducted at the start of the project. Thus, quantitative and qualitative data will be collected concurrently and integrated into a convergent mixed methods approach.

Results: As of June 2023, data for the review and 22 interviews with the stakeholders have been performed. The co-design with stakeholders will be performed in the fall of 2023.

Conclusions: This study represents a unique and innovative opportunity to gain new knowledge relevant and useful for future implementation of new technology at health care organizations so they can continue to offer high-quality, person-centered care. The outcomes of this research will contribute to a better understanding of the conditions necessary to implement and fully use the potential of IoT solutions. By developing cocreated implementation strategies, the study seeks to bridge the gap between theory and practice. Ultimately, this project aims to facilitate the adoption of IoT solutions in health care for promoting improved patient care and using technology to meet the evolving needs of health care.

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KEYWORDS

barriers; digital health; facilitators; health care; implementation; internet of things; IoT solution; older people; person-centered care; technology

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Introduction

Overview

There is a growing movement toward distributed care, wherein health care services are increasingly offered in the home environment to foster a close and person-centered approach to health care delivery. In addition, an increasing number of older adults often live longer at home, even with cognitive and physical disabilities [1,2], and extensive support is usually required to maintain autonomy and independence in daily life [3]. The increase in the older population and their health care needs has put health care under extra pressure. For example, increased costs and a shift from the traditional single-disease paradigm to a more holistic patient-centered approach are considered among the greatest challenges for society in this century [4]. At the same time, personnel and financial constraints may reduce health care services or the quality of care for older adults. Due to this, there is a need to use technology to provide more efficient health care services. IT can support health care organizations in providing high-quality, person-centered care [5-7]. Information technology can reduce the burden on health care and its resources, enable better health care and cost savings, support more care at home, and thus reduce costs [8,9]. Examples of such technologies are the Internet of Things (IoT) and wearable technologies that could offer promising solutions for the care of older people. It also has the potential to improve the quality of life of older adults and allow them to maintain their independent lifestyles [10]. In addition, IoT is suggested to be crucial in transitioning care and rehabilitation from the hospital to care and rehabilitation at home [11]. IoT technology can also contribute to health promotion initiatives, reducing the need to provide treatment and hospitalization [12,13]. The implementation of IoT is a vital aspect of Sweden's Vision eHealth 2025, which aims to make Sweden a global leader in digitalization and the opportunities provided by eHealth.

There is no unified definition of IoT, and many suggestions are put forth in the literature. One definition that is useful for our project is that IoT is "a network that connects uniquely identifiable devices (or things) to the internet, enabling them to collect, send, store, and receive data" [12]. From a technical point of view, an IoT architecture consists of several "layers." Again, there is no unified agreement describing the IoT architecture, and the number of layers varies. For example, Nord et al [14] propose three layers: (1) sensing layer, (2) network layer, and (3) application layer, while Kashani et al [10] propose four layers: (1) perception layer, (2) network layer, (3) middleware layer, and (4) application or business layer. This means that in an IoT architecture, first, there is the "thing" that collects data; then, the data are sent somewhere via the internet; and lastly, the data are analyzed and used in or by some kind of application. IoT approaches can also be divided into the following five categories depending on their technological focus: (1) sensor-based IoT (eg, wearable sensors and environmental sensors), (2) resource-based IoT (eg, scheduling and resource allocation), (3) communication-based IoT (eg, technological approaches and algorithmic approaches), (4) application-based IoT (eg, monitoring systems and recommender systems), and (5) security-based IoT (eg, privacy, access control, and confidentiality). The definition of IoT in this research project is a network that connects uniquely identifiable sensor-based things to the internet, enabling them to collect, send, store, and receive data, as shown in Figure 1.

Figure 1. Illustration of how Internet of Things is defined in this study.



Previous research shows that most IoT-related research within the health care domain has a technological focus. Dantu et al [15] analyzed keywords for IoT research in the health care domain in a systematic literature review. They found 5 topic clusters: security and privacy, data, application, wireless network technologies, and cloud and smart health. The authors found

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that the social and organizational challenges (eg, factors related to users, health care professionals, and health care organizations) of IoT within health care have received little to no attention in existing research. They conclude that there is a gap in our understanding of social and organizational challenges related to IoT.

These are important perspectives when an IoT product is to be implemented in an ongoing business. Nord et al [14] have conducted a study of factors that influence IoT implementation. In that study, they state that theories related to IoT adoption and implementation appear to be nonexistent [14]. This can be troublesome when previous research has shown that implementing and introducing new technology in general in health care is often problematic [16,17]. However, there may be factors at several different levels that prevent or facilitate implementation. Flottorp et al [18] systematically reviewed factors that hinder and facilitate implementation in health care. They identified factors at seven different levels that influence implementation in health care: (1) innovation, (2) health care staff, (3) patients, (4) professional interaction, (5) incentives and economics, (6) capacity for organizational change, and (7) the surrounding society [18]. Venter et al [19] found several factors that hinder the implementation of welfare technology, such as (1) high costs, (2) lack of competence and knowledge of available solutions, (3) organizational issues, (4) resistance to change, (5) communication and cooperation across stakeholders, (6) legal complications, and (7) technological problems. As is visible in these studies, most of the factors influencing implementation are nontechnical. In line with this, Kashani et al [10] argue that one of the biggest challenges around IoT in health care right now is its implementation in the health care environment, thus underlining the need for research on these aspects.

Identifying and addressing factors that influence implementation is, however, only the first stage of actually implementing new solutions such as IoT and, through this, improving care. The factors will tell us what should be changed or addressed to achieve implementation. In order to make use of the factors, they need to be connected with relevant implementation strategies, that is, methods that target specific factors and aim to change these or underlying behaviors [20]. For instance, if health care practitioners do not use IoT solutions because they forgot, then a suitable implementation strategy would focus on forgetting and improving conditions to remind them to use the solution [21]. To our knowledge, studies on IoT have not examined or focused on implementation strategies. However, existing research on implementation in health care has identified a multitude of implementation strategies that fit with specific factors at the individual, organization, and system levels [20]. Technology-related factors do not have their own strategies as the technology is often given, allowing only slight local adjustments, and thus one should target other levels such as the individual's interaction with the technology and the organizational fit of the technology. Still, on many occasions, connecting factors with suitable implementation strategies is rare [22], and the usual approach has long been to study factors and implementation strategies independently from each other, which implies that our knowledge of effective implementation strategies is incomplete [23].

Furthermore, we can state that a cocreation between researchers and concerned personnel in developing strategies for how new solutions should be implemented creates good conditions for the strategies to be well adapted and implemented [24]. We use this fact in this research project and intend, as a part of the project, to cocreate with staff to develop strategies based on the researched insights and the staff's knowledge of the local context.

Aim and Research Questions

The aim of the project is to contribute to an increased ability to use the potential of IoT solutions in society. In this study, we will identify facilitating and barrier factors for the implementation of IoT solutions in health care, including home care. To contribute to this aim, the study intends to answer the following two questions:

1. Research question 1: What are the barriers and facilitators when implementing IoT solutions within distributed care?
2. Research question 2: How to address barriers and facilitators when implementing IoT solutions within distributed care?

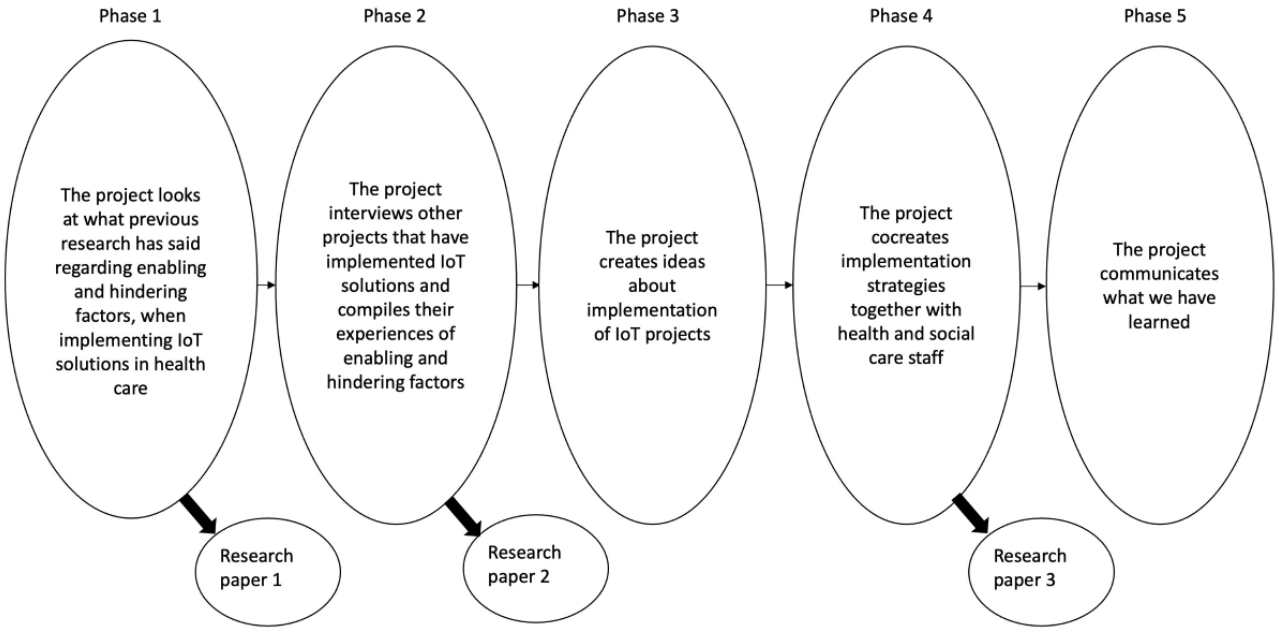
Methods

Design

The study will be performed in 5 phases (Figure 2). The aim of the first phase is to identify and categorize existing knowledge about barriers and facilitators for the implementation of IoT solutions in health care, including home care. The first phase will build on a systematic review. In the second phase, we will broaden the empirical base with more experiences from facilitating and barrier factors when implementing IoT solutions in Sweden. This will be done through a qualitative data collection from ongoing implementation projects of IoT solutions in care in Sweden. In the third phase, the project will analyze and draw conclusions from phases 1 and 2 and, based on this, formulate recommendations to strengthen facilitators and mitigate barrier factors when implementing IoT solutions in health care. In the fourth phase, these recommendations are to be applied in 2 implementation cases within the framework of ongoing safety-creating technology development. In this phase, there will also be a compilation of what we learned from these 2 implementation projects. In the fifth phase, the project will work on the use and dissemination of the generated results.

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Figure 2. The 5 phases of the research process. IoT: internet of things.



The knowledge generated by this project has the potential to benefit the fulfillment of Vision eHealth 2025. An important prerequisite, however, is that the knowledge generated by the project be communicated and used. Therefore, in phase 5, the researchers will collaborate with municipalities, regions, and the Swedish Association of Local Authorities and Regions to communicate results. Throughout the project, learning and experiences are shared through regular project meetings where new knowledge and experiences are shared between the project participants. Furthermore, new knowledge and experiences from a work package are applied and used in subsequent work packages. Experience is gained within the project's parties by holding internal seminars and meetings where the project participants' colleagues can take part in the experiences gained and the new knowledge that is developed within the project.

Context

Many health care providers in Sweden realize that they face major demographic and resource challenges. To a certain extent, there is high confidence that digital solutions will help deal with these challenges. There is therefore relatively big support within municipalities and health care provider organizations for carrying out research promoting the implementation of IoT solutions. At the same time, several of the private companies that work on developing new IoT solutions perceive that there are major challenges in making use of their solutions. All in all, this means that the organizational context is expectant and generally positively disposed to this type of research project.

To run this research project, a research project committee has been created. The committee consists of researchers at the Department for Industrial Engineering and Management at Uppsala University; researchers at the School of Health and Welfare at Dalarna University, the Division of Assistive Technology in Council Regional Dalarna Healthcare Administration, Dalarna Science Park, and Falun's and Rättvik's municipalities; and a representative for producers of goods and services within IoT. The majority of these are also represented in a regional steering group for digitization and welfare technology in Dalarna.

Data Collection

Data Collection to Respond to Research Question 1

We will conduct a systematic literature review to study what has already been written about implementing IoT technology. We will search for relevant articles in 4 databases: CINAHL, PubMed, Web of Science, and Scopus. A combination of Medical Subject Headings terms and keywords in titles and abstracts will be used, such as IoT and health care.

Data will also be collected from stakeholders' experiences of implementation challenges, facilitators, and barriers in implementing IoT solutions in health care, including home care. Data are collected from ongoing projects on the implementation of IoT solutions. Empirical data are collected from IoT projects aimed at the implementation of IoT solutions in Sweden in health care, including home care. Interviews will be conducted with stakeholders involved in the implementation project. In total, it is estimated that between 20 and 30 respondents will be interviewed. Data collection takes place through semistructured interviews. The interviews are planned to take place digitally. Audio recording will be used if respondents accept this and then transcribed.

Data Collection to Respond to Research Question 2

To answer this question, conclusions will be drawn from research question 1. On the basis of these conclusions, support will be developed to create implementation strategies for IoT solutions within 2 pilot projects. These implementation strategies will be developed in cocreation with employed health and social

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care staff within the county Dalarna and municipalities in Dalarna within the 2 pilot projects. These pilot projects will be selected during the work on answering research question 1. The criteria for selecting pilot projects are that they must consist of projects offering health or social care and be ready to implement IoT-based solutions in accordance with this project's definition of IoT. Data will be collected through a participative study in workshops for the development of implementation strategies and through interviews with representatives of key stakeholders involved in the implementation of the IoT solutions.

Data Analysis

The following analysis method will be used to answer both research question 1 and research question 2.

Bibliometric and content analysis of previous literature will be used in the systematic literature review.

The analysis of barrier and facilitating factors from previous research will constitute the analytical framework in the research process, which means that the identified barrier and facilitating factors will be deductively categorized on the basis of existing research. Previous implementation research has generated a spectrum of perspectives that focus on barrier and facilitating factors for implementation, for example, Flottorp et al's [18] previously identified seven different groups of barrier and facilitating factors: (1) guidelines, (2) care staff (eg, current knowledge), (3) patients (eg, preferences), (4) professional interaction, (5) incentives and finances (eg, remuneration), (6) capacity for organizational change (eg, mandate), and (7) society (eg, laws).

The categorization of the empirical data will be made on the basis of Flottorp et al's [18] framework. The analysis also takes into account unique contextual conditions for implementation, which means that the analysis allows the identification of new factors and strategies that can complement previous research. The deductive approach is thus complemented by an inductive approach.

Relation to Sustainable Development

The project contributes to Sustainable Development Goal (SDG) number 3 by increasing the ability to implement IoT-based technology, which creates better conditions for a continued or increased cost-effective health service to citizens. The project contributes to SDG number 5 by focusing on IoT solutions that create conditions for both men and women to enjoy good, individualized care. The project contributes to SDG number 9 by taking place in collaboration with industrial stakeholders working with developing products and services within IoT technology. The project is expected to contribute with an increased ability to develop products, test them, and implement solutions.

Ethical Considerations

The Helsinki Declaration will be followed. The most overriding ethical issue in this type of research is of an integrity-infringing nature, as the researcher, during an interview, asks employees' own thoughts about barriers and facilitators. Issues that may be discussed, such as fears, concerns, and difficulties related to barriers and facilitators, may be perceived as personal and private. The results will not be reported so that the respondents' age, gender, profession, and other characteristics can function as identity markers. When presenting individual quotations, the research group will not use quotations where identity markers or other information are named or mentioned in such a way that the respondent risks being identified.

An application about the need for ethical review of the research has been submitted to the Swedish Ethical Review Authority. The authority has announced that ethical review is not necessary in this research, given that the questions do not regard any personal data.

Results

As of June 2023, data for the review and 22 interviews with the stakeholders have been collected. The co-design with stakeholders will be performed in the fall of 2023. All data will be analyzed and disseminated during 2024.

Discussion

Overview

As one of the first studies to identify facilitators and barriers for implementing IoT solutions in health care in a Scandinavian context, we hope this project will contribute to better conditions to implement and thus use the potential of IoT solutions to contribute to the changes that need to take place in health care given the demographic changes we see in Scandinavia.

Sweden has a vision for digitalization in health care, Vision eHealth 2025. The vision sets out a long-term strategic direction for the digitalization area. It constitutes a joint collaboration platform between the Swedish Association of Local Authorities and Regions and the governmental stakeholders in the field. The vision is that by 2025, Sweden will be the best in the world at using the opportunities of digitalization and eHealth. Complementing the vision, there is also a national 3-year strategy for implementing it. The implementation is largely about developing new working methods and learning how new technology can be used operationally. In this context, implementing IoT solutions is an upcoming major issue.

Therefore, we hope that this research project will not just identify facilitators and barriers but also make use of those findings in cocreative workshops with health and social care staff in order to develop cocreated implementation strategies. The study will give insight into how knowledge from former implementation projects can be integrated into new implementation projects. Namely, we contribute knowledge about how a process for developing a strategy can be performed based on the experiences of other projects. In other words, we can also learn from what is easy and what is difficult in the transformation from gained insights into concrete actions in a new context.

Strengths and Limitations

This project has a strong design with several phases that build on each other, validating and expanding the knowledge gained in previous phases. Additionally, the study includes 2 pilot cases in real-world health care settings, providing valuable insights

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into the implementation of IoT. While patients and older adults at home (end users) are important for understanding the full impact of IoT, they are not included in the sample as their perspectives are beyond this project's scope. Future research needs will indeed include end users.

Conclusions

This study represents a unique and innovative opportunity to gain new knowledge that is relevant and useful for implementing new technology in municipalities and health care organizations. By identifying and understanding the barrier and facilitating factors associated with implementing IoT solutions in health care, including care and service at home, the study can provide valuable insights into the challenges that need to be overcome and the strategies that can be used to facilitate successful implementation. The study can also help identify best practices and key success factors that can be used to guide future implementation efforts. Additionally, the study can contribute to developing person-centered care by using new technology in municipalities and health care organizations.

Data Availability

The data sets generated during this study are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

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Abbreviations

IoT: Internet of Things
SDG: Sustainable Development Goal

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Protocol

Evaluating a Novel Infant Heart Rate Detector for Neonatal Resuscitation Efforts: Protocol for a Proof-of-Concept Study

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Abstract

Background: Over 10 million newborns worldwide undergo resuscitation at birth each year. Pediatricians may use electrocardiogram (ECG), pulse oximetry (PO), and stethoscope in determining heart rate (HR), as HR guides the need for and steps of resuscitation. HR must be obtained quickly and accurately. Unfortunately, the current diagnostic modalities are either too slow, obtaining HR in more than a minute, or inaccurate. With time constraints, a reliable robust heart rate detector (HRD) modality is required. This paper discusses a protocol for conducting a methods-based comparison study to determine the HR accuracy of a novel real-time HRD based on 3D-printed dry-electrode single-lead ECG signals for cost-effective and quick HR determination. The HRD's HR results are compared to either clinical-grade ECG or PO monitors to ensure robustness and accuracy.

Objective: The purpose of this study is to design and examine the feasibility of a proof-of-concept HRD that quickly obtains HR using biocompatible 3D-printed dry electrodes for single-lead neonatal ECG acquisition. This study uses a novel HRD and compares it to the gold-standard 3-lead clinical ECG or PO in a hospital setting.

Methods: A cross-sectional study is planned to be conducted in the neonatal intensive care unit or postpartum unit of a large community teaching hospital in Toronto, Canada, from June 2023 to June 2024. In total, 50 newborns will be recruited for this study. The HRD and an ECG or PO monitor will be video recorded using a digital camera concurrently for 3 minutes for each newborn. Hardware-based signal processing and patent-pending embedded algorithm-based HR estimation techniques are applied directly to the raw collected single-lead ECG and displayed on the HRD in real time during video recordings. These data will be annotated and compared to the ECG or PO readings at the same points in time. Accuracy, F_1-score, and other statistical metrics will be produced to determine the HRD's feasibility in providing reliable HR.

Results: The study is ongoing. The projected end date for data collection is around July 2024.

Conclusions: The study will compare the novel patent-pending 3D-printed dry electrode–based HRD's real-time HR estimation techniques with the state-of-the-art clinical-grade ECG or PO monitors for HR accuracy and examines how fast the HRD provides reliable HR. The study will further provide recommendations and important improvements that can be made to implement the HRD for clinical applications, especially in neonatal resuscitation efforts. This work can be seen as a stepping stone in the development of robust dry-electrode single-lead ECG devices for HR estimations in the pediatric population.

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KEYWORDS

newborn; electrocardiogram; ECG; dry electrode; heart rate; pediatric; resuscitation; infant; vital signs; neonatal

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Introduction

Background

Each year, over 10 million newborns require resuscitation worldwide, representing more than 10% of all global births [1]. Neonatal resuscitation is the set of interventions at the time of birth to support the establishment of breathing and circulation. These interventions include providing warmth to the infant using a heat source, placing the head in a sniffing posture with neck flexion and upper cervical extension (a position to open the airways), drying the infant, and simulating breathing. Multiple metrics—respiration, infant color, and heart rate (HR)—are measured every 30 seconds to ensure successful neonatal resuscitation [2]. Out of these indicators, HR is identified as the most important for an effective resuscitation process [3]. HR guides decision-making and escalation of care, including positive pressure ventilation, endotracheal intubation, chest compressions, and administration of epinephrine.

Despite the importance of HR in neonatal resuscitation, HR determination is challenging due to a lack of evidence regarding the most rapid and accurate method to assess it. Clinically accepted methods of HR assessment include pulse palpation (umbilical, brachial, and femoral), auscultation with a stethoscope, pulse oximetry (PO) monitoring, and 3-lead electrocardiogram (ECG) monitoring [2]. It is important to note that neonatal resuscitation efforts should be performed within the first minute of life, known as the "golden minute," to ensure a high success rate and avoid neurodevelopmental disorders and hypoxic injury [4].

A systematic review compared these different methods in terms of expense, intermittent or continuous HR assessment, and other strengths and weaknesses. Auscultation and pulse palpation are rapid and easily accessible approaches due to their low cost. However, both approaches are highly inaccurate and unreliable, resulting in errors of omission, which causes failure or delay in resuscitation steps and commission through inappropriate intervention [5]. Auscultation requires a pause in resuscitative efforts, which can disrupt the flow of resuscitation and result in a delay in stabilization of the newborn. This method is the most used approach compared to other HR determination approaches, due to its quick and easy accessibility as well as its cost-effectiveness. However, auscultation accuracy is reliant on health care professional experience and can be inconsistent from one practitioner to the other, resulting in inequitable care [6]. On the other hand, PO is relatively inexpensive and noninvasive, and it displays continuous HR and oxygen saturation to the entire team in the delivery room. However, a pulse oximeter can be inaccurate due to motion artifact, ambient light, or poor tissue perfusion, and it takes several minutes to apply and achieve the first data display, potentially delaying resuscitative efforts [4,5].

Current guidelines suggest a 3-lead ECG monitor as the gold standard for HR determination in neonates due to its high speed and accuracy and because of its capabilities to provide continuous visual and auditory data compared to the other modalities, such as PO and auscultation. However, 3-lead ECG has its disadvantages. Errors in the placement of the 3 leads can yield inappropriate ECG signals that cannot be used for HR detection [7]. Additionally, similar to PO, wet electrode ECG placement takes time to apply, surpassing the golden minute of life [5]. ECG adhesive wet electrodes can cause skin damage to premature infants. Moreover, motion artifacts may be present with ECG leads. In rare scenarios, ECG-derived HR may fail to correspond with the effective mechanical contraction of the heart [8]. Most importantly, both PO and 3-lead ECG require additional equipment, which needs to be purchased and maintained, accumulating significant expenses for health care systems [7,8]. Both technologies may not be feasible or accessible in areas with limited health care resources [9].

Recent rapid scientific advancement in sensing technology have driven the development of novel technologies to assess HR, including camera-based photoplethysmography, reflectance PO, laser Doppler technology, capacitive sensors, piezoelectric sensors, electromyography, and electronic or digital stethoscope (DS) [10]. Although a systematic review of these novel technologies concluded that none are ready for widespread clinical adoption, DS offers the greatest potential [10]. Currently, DS is at the forefront in the field of "computer-aided auscultation," as advances in acoustic sensor design, digital signal processing and filtering, auditory enhancement, and machine learning can enable automated diagnoses of cardiac dysfunction [10,11]. In neonates, DS used for HR measurement is more accurate than auscultation or pulse palpation and faster than PO in "time to first HR display"; DS also correlates appropriately with ECG HR in noncrying infants [10-12]. Furthermore, DS is most similar to existing smart device technologies that are rapidly adopted, in both high- and low-resource settings. These technologies include smartphones, wearables, and other devices in the Internet of Medical Things. Although DS represents a significant improvement in neonatal resuscitation HR monitoring, further refinement and evaluation is necessary before clinical implementation, along with optimization of the existing technologies in a user-centric manner [13]. DS has severe disadvantages, including short battery life, low clinical adoption due to training requirements [14], and its nonstandardized variable sensor technologies, such as the differences between Littman Eko DUO with an ECG module, Littman CORE with analog and digital amplification, and Thinklabs' One DS with a nonstandard headphone jack. It is important to note that none of the current DS technologies take neonatal ECG into consideration during their development.

It is evident there is a lack of cost-effective and fast signal acquisition technology that uses the gold-standard ECG for quick HR measurements and display in newborns. This study focuses on the deployment of a single-lead ECG handheld monitor capable of using dry-electrode ECG for signal acquisition and HR measurements in a quick and efficient manner. The following protocol study is structured as follows: the study significance, its impact on the current technologies in single-lead ECG devices for neonatal HR monitoring, and the objectives of this study. The Methods section is presented next, and it covers an in-depth look into the ethics-approved protocols through Study Design, Study Personnel, Recruitment, Inclusion and Exclusion Criteria, Ethical Considerations, and Study Procedures sections. Study Procedures section includes the

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subsections of Data Collection, Debrief, Data Management, Data Analysis, and Data Maintenance and Security. These sections are followed by the Results section, which offers the current progress of this study. Lastly, the final section provides a brief discussion of the protocol and the limitations of the current study, providing future steps to further improve neonatal single-lead ECG monitoring.

Study Significance and Impact

Given that no single method of HR assessment is clearly superior to others, finding the optimal method to delineate HR within the golden minute after birth remains elusive. Pediatric guidelines recognize this knowledge gap and identify the opportunity to develop new technologies for the rapid, accurate assessment of HR after birth, ideally integrating newborn ECG. Currently, there are no novel medical devices that have been specifically developed to provide rapid and accurate HR immediately after birth. The proposed research study will address several gaps in the scientific study of device development, vital signs measurement and monitoring, and neonatal resuscitation. Recent advances in biomedical sensors and wireless communication technologies have enabled us to develop a novel HRD, targeted to outperform the traditional HR assessment in neonatal resuscitation. The rapid application, measurement, and display of HR on a device located on the neonate addresses significant gaps in the provision of optimal neonatal resuscitation. The HRD is undergoing rigorous design and development, and this study aims to assess its feasibility in quickly detecting accurate HRs in infants using 3D-printed dry electrodes. This early proof-of-concept HRD study will establish the basis for using 3D-printed dry electrodes and determine whether novel HR estimation algorithms are appropriate for neonatal HR applications.

Objectives

The overall aim of this research study is to evaluate a novel HRD that may enable timely and appropriate neonatal resuscitation. This study is being completed using a phased sequential user-centered approach. We completed the first phase of this research to determine end-user requirements and preferences for HR assessment in neonatal resuscitation. This phase resulted in the current design and features of the HRD.

The second phase outlines the creation of the HRD conceptual design and proof-of-concept prototype to be used in the final phase of feasibility mentioned in this study.

In the final phase, the focus of this proof-of-concept research study is to examine the functionality, speed, robustness, and reliability of the prototype HRD.

Specific research questions to be answered through this phase are the following:

- How long does it take to place the HRD on an infant?
- Can the prototype HRD detect the HR of newborns?
- How fast can the prototype detect the HR of newborns?
- How accurate is the HR detection when compared to PO or ECG?

Methods

Study Design

A prospective observational study will be used to measure the performance of the HRD prototype, as shown in Figure 1, in terms of time required to place it on an infant, its ability to detect HR, the speed of detection, and its reliability (accuracy) in comparison with clinical HR monitors. Given the paucity of data on infants regarding the HRD, there is insufficient evidence to support the feasibility and performance of a randomized controlled trial. The study setting will be in the postpartum unit (PPU) and neonatal intensive care unit (NICU) of a large community teaching hospital in Toronto, Canada. Specifically, the study will take place within 2 physical settings at the hospital: PPU and NICU. As shown in Figure 2, a digital camera will be used to record the HRD concurrently with either an ECG or PO monitor, depending on their availability at the time, for 3-minute durations per newborn. It is important to note that although both 3-lead ECG or photoplethysmogram technology are compared to single-lead dry-electrode ECG, both clinical devices are considered acceptable for neonatal resuscitation efforts, which is the targeted use of the HRD in later versions and research studies.

The HRD uses two 3D-printed dry electrodes to collect 3-minute single-lead neonatal ECG signals with a 500 Hz sampling rate. The HRD's electrodes are placed approximately in the V1 and V2 locations on the newborn's chest, as shown in Figure 3. The electrodes are developed using conductive polylactic acid filaments (Proto Pasta) and a 3D printer with printing settings of nozzle temperature at 215 °C, print speed of 35 mm/s, heated bed temperature of 60°C, and a design fill ratio of 100% [15]. These settings are chosen as specified under the datasheets provided for the conductive polylactic acid filament. As shown in Figure 4, the electrodes are connected to an ECG analog front-end circuitry, which provides analog signal processing and filtering. A 3-48 Hz analog bandpass filter is applied to attenuate the powerline and electromagnetic interference noise in the 50-60 Hz range [15]. The single-lead ECG signal is later transmitted to a microcontroller, where patent-pending embedded heart estimation techniques are used to calculate HR. HR is displayed on an OLED screen on the HRD. At the same time, the HR and raw ECG information are transmitted using Bluetooth to a nearby computer interface for data storage.

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Figure 1. Heart rate detector (HRD) prototype. (A) The front side of the HRD with an OLED display to present heart rate in real time; (B) the backside of the HRD with two 3D-printed dry electrodes for single-lead neonatal electrocardiogram acquisition.

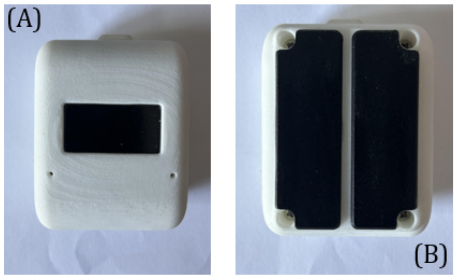


Figure 2. Data collection setup. (A) A digital camera is used for 3-minute video recordings; (B) a pediatrician holding the heart rate detector (HRD) to the newborn's thorax; (C) electrocardiogram monitor and (D) pulse oximetry, present in the video recordings with HRD for comparison.

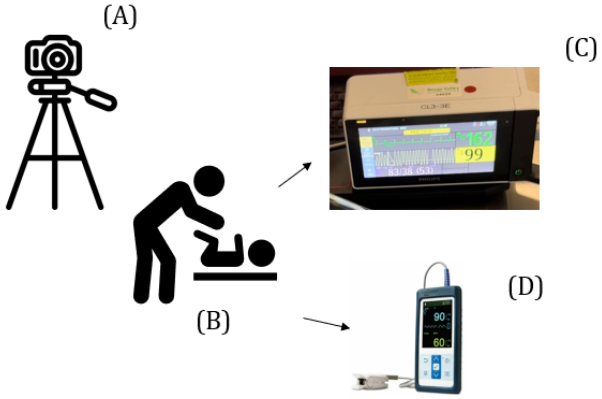


Figure 3. The placement of heart rate detector's dry electrodes on the newborn's chest. HRD: heart rate detector.

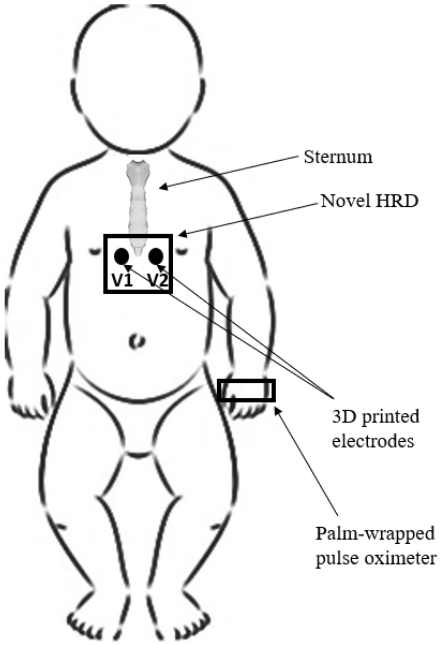
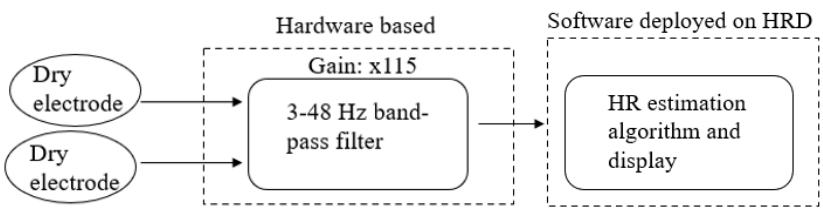


Figure 4. The hardware and software components of the heart rate detector (HRD).



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Study Personnel

A pediatrician and graduate student will be conducting all the study tasks.

Recruitment

All Infants admitted to the PPU after routine delivery, regardless of method, and all infants admitted to the NICU will be eligible if their clinical status is stable and not at high risk of deterioration. In total, 50 newborns will be recruited based on previous accepted research studies that focused on examining long-term neonatal ECG and HR monitoring applications using proof-of-concept novel ECG acquisition devices [14-19].

The two groups of infants are identified as follows:

1. Infants admitted to the PPU who are at least 24 hours of age and are undergoing routine critical congenital heart disease (CCHD) screening with PO.
2. Infants admitted to the NICU who are routinely placed on 3-lead ECG or PO monitors.

Recruitment steps include the following:

Infants will be identified by a pediatrician for eligibility 5 days a week (Monday to Friday) between 8 AM and 8 PM. Recruitment on Saturday and Sunday will be done if feasible. Recruitment will happen on random days when a pediatrician is available and time permits.

Once an infant is identified based on eligibility (ie, inclusion and exclusion criteria), mentioned below, the pediatrician will ask the bedside nurse to ask the parents if they would be willing to speak to the pediatrician as shown in the recruitment script in Multimedia Appendix 1.

The pediatrician will then meet the parents in a face-to-face meeting to discuss the study, provide the written consent form, and potentially obtain consent. The parents will be given at least 15 minutes to review the consent form prior to being asked to sign it. When the parents are not available at the bedside, the pediatrician will inquire the nurse about a suitable time for the parents to meet. The infants will not be under the care of the researcher pediatrician as their primary admitting health practitioner to avoid a conflict of interest.

Inclusion Criteria

The inclusion criteria for the PPU infants are as follows:

- Corrected gestational age (35 weeks + 0 days)
- Infants undergoing routine CCHD screening with PO at 24 hours of life or later
- Stable clinical status
- Parental consent

For the NICU infants, the inclusion criteria are as follows:

- Corrected gestational age (30 weeks + 0 days)
- Infants undergoing routine 3-lead continuous ECG monitoring or PO
- Infants with at least 24 hours of life
- Stable clinical status, as defined by the following: stable requirement for supplemental oxygen and stable respiratory rate on at least 2 measurements, a respiratory rate <70 breaths per minute, HR <180 beats per minute, oxygen supplementation <0.5 L/min via nasal prongs, and not being on heated high-flow oxygen
- Parental consent

Exclusion Criteria

The exclusion criteria include high-risk clinically unstable newborns who might show unstable requirements for supplemental oxygen and unstable respiratory rates, congenital malformations that interfere with the placement of the HRD, and nonconsent.

The criteria mentioned above are standardized points used in multiple studies pertaining to neonatal noninvasive physiological monitoring. These criteria have undergone rigorous ethics review, as specified in the approved ethics proposals.

Ethical Considerations

The study was approved by the research ethics boards of the Toronto Metropolitan University (2023-070) and Scarborough Health Network (PED-21-025) in April and June of 2023, respectively. Parents will complete a detailed written informed consent prior to infant enrollment. Recruitment procedures are described under the Recruitment subsection in Methods. A number of measures will be taken to protect the rights of eligible infants, including the following: (1) using an intermediate approach—a neutral person, a bedside postpartum or NICU nurse, will seek initial permission to approach potential participants about the study; (2) ensuring anonymity, privacy and confidentiality of the participant's information; and (3) proceeding through the formal ethical review process at both the participating hospital and the university conducting the collaborative research. As per institutional policies, consent forms will be kept in a secured location, with access provided to only the primary principal investigator and then shredded. Finally, participants will be assured that the study reports, video recordings, and paper-based data collection forms will not contain identifying information in keeping with the Canadian privacy legislations—Personal Information Protection and Electronic Documents Act and Personal Health Information Protection Act.

Study Procedures

The PPU infants will be placed in the supine (face up) position. The conventional PO will be connected to the right hand as per the device's instructions and CCHD screening protocol. In the usual standard of care for CCHD screening, PO is placed on the right hand and right or left foot for 1 to 2 minutes. The change in the standard of care will include the data collection protocol during the time of CCHD screening, which includes video recording of the HRD and PO simultaneously. The HRD will be held in place by a pediatrician on the thorax for 3 minutes. This will prolong CCHD screening by an additional 1-3 minutes. On the other hand, as per the usual standard of care, NICU infants will be placed in the supine (face up) position prior to their usual feeding time; they will be unbundled and have their diaper changed. An already attached conventional 3-lead ECG will be placed on the infant's chest, as per the conventional 3-lead ECG device's instructions. The change in this standard of care will involve the thorax to be exposed, if

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not already exposed, and the HRD will be held in place by a pediatrician on the thorax for 3 minutes during simultaneous video recording of the HRD and the 3-lead ECG monitor. It is important to note that the 3-lead ECG electrodes will not be in contact with the HRD's dry electrodes.

The displayed HR from the HRD will be compared to 1 or 2 reference monitors, depending on the infant's clinical setting (PPU or NICU). The PPU uses a conventional PO (Nellcor Portable SpO2 Patient Monitoring System; Medtronic) with an accompanying sensor wrap, while infants in the NICU are attached to a conventional 3-lead gel electrode ECG (Intellivue Bedside Patient Monitor; Koninklijke Philips) monitor. In both clinical-grade devices, PO and ECG biosensors and algorithms detect and display HR based on pulse peak or QRS peak detection. An internal algorithm in each device designed by the manufacturer determines how pulse or QRS peak detection is transformed into the HR displayed on the screen. Depending on the sensing technology—PO (a light-emitting diode-based pulse detection) or the 3-lead ECG (an electric activity sensing transducer that detects electrical heart activity)—a different HR may be displayed. Differences in the PO and ECG algorithmic HR estimation techniques may also influence the HR displayed on both devices. However, both technologies are known as clinical-grade HRDs and are used extensively in medical settings, which justifies their use as the ground truth state in this HRD proof-of-concept study.

Data Collection

The displayed HR from the HRD and the PO or ECG monitor will be video recorded for 3 minutes within the same video frame, as shown in Figure 1. Video recording will take place using a dedicated research digital camera mounted on a stand. Video recording will start once the infant is settled and the PO or ECG readings are stable. Stable readings are defined based on the device's instructions on waiting for an appropriate amount of time after sensor placement for clinical HR determination. The HRD will then be placed on the infant's chest until a consistent HR is displayed for 3 minutes, at which point video recording will start. After 3 minutes, the HRD will be removed, and then, the recording will be stopped. After the recording is completed, the entire HRD, including electrodes, will be wiped down with a surface disinfectant towelette (CaviWipe; Metrex). HRD device failure will be considered if no HR is displayed on the HRD within 60 seconds of application to the thorax.

Debrief

After video recording has concluded, parents will be asked of their perceptions of the HRD, and their answers will be written by the primary researcher on a paper data collection form, as shown in Multimedia Appendix 2.

Data Management

Video recordings will be individually analyzed by 2 health professional researchers to determine the time it takes to apply the HRD to the thorax and the time from HRD placement to a steady HR display. Each researcher will review and record the HR from the HRD and PO or ECG at 2-second intervals for 3 minutes, providing approximately 90 HR notations per device per patient. For 50 newborns, the total number of HR annotations will be approximately 4500 data points. This will result in multiple HR data points to compare. To avoid human error in the annotation process, discrepancies in the HR of more than 5 beats per minute between the 2 researchers will lead to a reexamination of the video recordings until a consensus can be reached regarding the correct HR. The annotations from the 2 researchers will be averaged for the subsequent analyses.

Additionally, the HRD will record raw ECG signals for the duration of the device being in contact with the infant. Raw ECG data will be collected at 500 Hz sampling rate and transmitted to a research-dedicated laptop. The raw ECG and HR information from the HRD will be stored on different CSV files with a randomized identification number.

Data Analysis

HR and raw ECG data will be analyzed using MATLAB (the MathWorks). Infant demographics will be analyzed using summary statistics. Continuous variables will be expressed as mean (SD) values, and categorical variables will be expressed as numbers (percentages), unless otherwise stated. The HR from HRD will be compared to PO or ECG using a paired *t* test. The Bland-Altman method will be used to compare the HR derived from each device—the HRD and the PO or ECG monitor, used as reference. The correlation between devices will be assessed using Pearson *r* statistic. Data will be first analyzed using all data points available, and outliers will be defined as 20 beats per minute rate difference between the methods. These discrepancies will be further analyzed to find the likely reason for deviation, including reexamination of the video recordings.

Data Maintenance and Security

Each infant will be assigned a participant identification number using a random number generator [20]. No personally identifying demographic information, such as name or parents' names, will be collected. Confidentiality will be maintained throughout the study, in accordance with the Personal Health Information Protection Act. Paper-based data collected will be electronically transcribed into a CSV file. The paper-based data collection form will then be disposed in a confidential document bin at the hospital. The data, video recordings, CSV files with raw ECG data, the CSV files with infant demographics and characteristics as well as parental perceptions will be downloaded to a research-dedicated laptop for analysis. The data will be stored in a password-protected folder and will not be emailed nor transmitted on the web. Data transfer among the research team (the primary researchers) will occur through an encrypted flash drive, if necessary. The laptop will be stored in a locked cabinet in a locked room in the research lab at the university, with access provided to only the primary research investigators. All the study investigators will have access to all the data, except the consent forms, which will be only accessible by the principal investigator.

Results

The study is currently ongoing. The projected end date for data collection is around July 2024.

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Discussion

This paper discussed a research protocol for conducting accurate and reliable HR estimation using a novel real-time HRD based on 3D-printed dry-electrode single-lead ECG signals. Recent advances in biomedical sensor and wireless information and communication technologies have enabled us to develop a novel HRD, aimed at potentially disrupting the traditional assessment of HR in neonatal resuscitation efforts. The rapid application, measurement, and display of HR on a device mounted directly on the neonate addresses significant gaps in the provision of optimal neonatal resuscitation. The main objective of this study is to examine the novel HRD's ability and feasibility in obtaining an accurate HR in newborns, using dry electrodes, and comparing it to the state-of-the-art clinical-grade HR monitors at the hospital.

However, this study is limited to the feasibility of HR detection on a healthy population of newborns using dry electrodes, and it does not cover in-depth analytical metrics of ECG and HR for disease diagnosis. It is apparent that further studies should focus solely on ECG abnormalities in neonates, including bradycardia, pulseless electrical activity, and long QT syndrome. The work is also limited to the use of certain 3D-printed conductive plastic-based dry electrodes for single-lead ECG acquisition, limiting its applicability when ECG quality is compared to other dry-electrode materials, such as stainless steel and textiles. Furthermore, the proposal does not include clinical-grade ECG acquisition for comparison with the HRD's raw ECG signals due to the restraints in obtaining access to HR monitor raw ECG information. In addition, the use of algorithms on clinical-grade devices cannot be accessed, limiting this work to the examination of HR information between the HRD and clinical HR monitors. However, the raw ECG obtained through the HRD can be used to derive novel hand-crafted features that assist in quick HR estimation and prediction using artificial intelligence.

Ideally, this study will lead to critical improvements in the HRD prototype's accuracy and speed of detection, ensuring its robustness prior to further clinical testing. This preliminary work is essential to form the foundation of a larger programmatic endeavor to transform this HRD into a relevant and robust novel medical device for neonatal resuscitation efforts. It is critical that new clinical technologies be evaluated with methodologic rigor to help inform clinicians and parents on the reliability, feasibility, and ultimately, the effectiveness of new technologies. This is an early proof-of-concept study to assess the reliability of the value behind this HRD and its goals of ultimately saving infant lives through widespread clinical adaptation and implementation.

Acknowledgments

This study was conceptualized by AA, SK, and NM. AA and SK are involved in the heart rate detector (HRD) prototype design and production. AA and NM are involved in direct data collection. All authors contributed to the writing and obtaining of the ethics-approved proposals. All authors read and approved the final manuscript.

Data Availability

The anonymized data pertaining to this study will be available upon request from the corresponding author, except for video recordings, which are not available in accordance with the ethics approvals of the participating hospital and academic institution.

Conflicts of Interest

SK is the founding Chief Scientific Officer of Nanu Health, the company involved in commercializing the infant heart rate detector prototype discussed in the paper. He is also a coinventor of a patent application under review for the prototype discussed in the paper. NM is the cofounder of and owns stock in Nanu Health.

Multimedia Appendix 1
Recruitment script.
[PDF File (Adobe PDF File), 18 KB - resprot_v12i1e45512_app1.pdf]

Multimedia Appendix 2
Data collection form.
[PDF File (Adobe PDF File), 55 KB - resprot_v12i1e45512_app2.pdf]

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Abbreviations

CCHD: critical congenital heart disease
DS: digital stethoscope
ECG: electrocardiogram
HR: heart rate
HRD: heart rate detector
NICU: neonatal intensive care unit
PO: pulse oximetry
PPU: postpartum unit

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Protocol

Recruiting Sexual and Gender Minority Veterans for Health Disparities Research: Recruitment Protocol of a Web-Based Prospective Cohort Study

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Abstract

Background: The *Health for Every Veteran Study* is the first Veterans Health Administration–funded, nationwide study on lesbian, gay, bisexual, transgender, queer, and other sexual and gender minority (LGBTQ+) veterans' health that relies exclusively on primary recruitment methods. This study aimed to recruit 1600 veterans with diverse sexual and gender identities to study the mental health and health risk behaviors of this population. A growing body of literature highlights the health inequities faced by LGBTQ+ veterans when compared with their heterosexual or cisgender peer groups. However, there is little to no guidance in the health disparities literature describing the recruitment of LGBTQ+ veterans.

Objective: This paper provides an overview of the recruitment methodology of *Health for Every Veteran Study.* We describe the demographics of the enrolled cohort, challenges faced during recruitment, and considerations for recruiting LGBTQ+ veterans for health research.

Methods: Recruitment for this study was conducted for 15 months, from September 2019 to December 2020, with the goal of enrolling 1600 veterans evenly split among 8 sexual orientation and gender identity subgroups: cisgender heterosexual women, cisgender lesbian women, cisgender bisexual women, cisgender heterosexual men, cisgender gay men, cisgender bisexual men, transgender women, and transgender men. Three primary recruitment methods were used: social media advertising predominantly through Facebook ads, outreach to community organizations serving veterans and LGBTQ+ individuals across the United States, and contracting with a research recruitment company, Trialfacts.

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Results: Of the 3535 participants screened, 1819 participants met the eligibility criteria, and 1062 completed the baseline survey to enroll. At baseline, 25.24% (268/1062) were recruited from Facebook ads, 40.49% (430/1062) from community outreach, and 34.27% (364/1062) from Trialfacts. Most subgroups neared the target enrollment goals, except for cisgender bisexual men, women, and transgender men. An exploratory group of nonbinary and genderqueer veterans and veterans with diverse gender identities was included in the study.

Conclusions: All recruitment methods contributed to significant portions of the enrolled cohort, suggesting that a multipronged approach was a critical and successful strategy in our study of LGBTQ+ veterans. We discuss the strengths and challenges of all recruitment methods, including factors impacting recruitment such as the COVID-19 pandemic, negative comments on Facebook ads, congressional budget delays, and high-volume surges of heterosexual participants from community outreach. In addition, our subgroup stratification offers important disaggregated insights into the recruitment of specific LGBTQ+ subgroups. Finally, the web-based methodology offers important perspectives not only for reaching veterans outside of the Veterans Health Administration but also for research studies taking place in the COVID-19-impacted world. Overall, this study outlines useful recruitment methodologies and lessons learned to inform future research that seeks to recruit marginalized communities.

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KEYWORDS

lesbian, gay, bisexual, transgender, queer, and other sexual and gender minority; LGBTQ+; veteran; recruitment; health disparities

Introduction

Background

People who identify as lesbian, gay, bisexual, transgender, queer, and other sexual and gender minority (LGBTQ+) make up a sizable portion of US military service members and veteran populations. As of 2015, it has been estimated that 6.1% of current US military personnel have an LGBTQ+ identity [1]. This is a higher proportion than the overall US population; in the same year, 3.9% of US adults identified as part of the LGBTQ+ community [2]. Among male veterans, 1.9% were identified as gay, 2% as bisexual, and 0.5% as transgender. Among female veterans, 7% were identified as lesbian, 9.1% as bisexual, and 1.2% as transgender [1]. Both lesbian and bisexual women and transgender people have been shown to be overrepresented in military and veteran populations compared with the general population [3,4]. LGBTQ+ people join the military for a number of reasons, many of which may be similar to non-LGBTQ+ service members. However, LGBTQ+ people may be more likely to face violence, lack of acceptance from family, or socioeconomic challenges, leading them to choose the military as a career path [5,6].

These statistics are likely an underestimate, given the rising numbers of LGBTQ+ identification in the general population and the impact of homophobia, transphobia, and sexism in and out of the military [1,2,6]. In particular, “Don’t Ask, Don’t Tell,” established in 1994, prevented a generation of nonheterosexual service members from serving openly [6]. Over 14,000 service members were less-than-honorably discharged due to the policy until its repeal in 2011 [6]. LGBTQ+ veterans still face the aftereffects of the policy, continued attacks against transgender service members, and other forms of structural stigma [6]. Given the pressure to hide their identities, there could be more veterans identifying as LGBTQ+ than the current statistics describe.

A growing body of literature has highlighted the health inequities faced by LGBTQ+ veterans, both in comparison with their fellow veterans and the general population. LGBTQ+ veterans as a group demonstrate disparities in suicide mortality, depression, alcohol use, posttraumatic stress disorder, intimate partner violence including sexual violence, chronic obstructive pulmonary disease, asthma, stroke, and physical health [6-14]. Disparities can be found within specific LGBTQ+ subgroups. Research indicates that compared with non-LGBTQ+ female veterans, LGBTQ+ female veterans were more likely to feel unwelcome or unsafe within the Veterans Health Administration (VA) health care system and miss needed care [15]. A national study of transgender veterans found that 46% reported delaying medical care and that 36% delayed mental health care in the past year when they thought they needed it [16]. However, there has been limited research on more detailed subgroups. LGBTQ+ veterans are a diverse group across sexual orientation and gender identity, and research is still needed to identify additional physical and mental health disparities, as well as the causal pathways for these inequities. In particular, structural stigma in the form of homophobic and transphobic policies, practices, and norms plays a significant role in causing health disparities among LGBTQ+ populations [17].

Therefore, it is crucial to better understand how to reach and recruit LGBTQ+ veterans in health research. As with other marginalized populations, LGBTQ+ veterans’ unique social contexts and lived experiences are shaped by their intersecting identities. However, there is little to no guidance in the health disparities literature describing the recruitment of LGBTQ+ veterans.

VA electronic medical records (EMRs) do not yet have readily accessible self-identified fields for sexual orientation or gender identity [18]. Although this is starting to change, it has been difficult for researchers studying LGBTQ+ veterans to monitor target populations for research or clinical care purposes through administrative records, as is often done for other groups, such as women [18]. Past research with transgender veterans has relied on the International Classification of Disease, 9th and 10th Revisions diagnosis codes in EMR data, rather than self-identified gender [19-21]. Such data can be obtained through

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VA EMRs [22]. Although these diagnostic codes have shown concordance with self-identification [20], they also rely on terms or diagnoses that may be outdated, stigmatizing, or misaligned with how transgender patients identify [23]. As such, veterans may choose not to disclose their gender identity to their VA providers. In addition, these diagnosis codes are specific to gender identity, meaning that sexual minority veterans cannot be identified using EMR data. Moreover, recruitment methods that rely solely on VA EMR data exclude veterans who are not connected with VA care. Veterans who were dishonorably discharged are not eligible for VA health care benefits, and others may choose not to enroll. LGBTQ+ veterans may decide not to engage with VA because of their previous experiences with discrimination in the military, VA, or other health care settings. Anticipation or fear of such experiences may also prevent LGBTQ+ veterans from connecting with the VA. As such, EMR-based recruitment methods for research are not yet sufficiently inclusive for the recruitment of a diverse sample of LGBTQ+ veterans.

In civilian communities, the recruitment of LGBTQ+ populations for health research often occurs through community-based sites [24] and social media [25]. Historically, emphasis has been placed on men who have sex with men, with less information on the recruitment of sexual minority women and other groups [24,26]. For instance, a systematic review of the psychology literature on LGBTQ+ populations found that sexual minority women comprised only 4.8% of the study samples [26]. Therefore, the civilian LGBTQ+ health research recruitment literature may also have limited applicability for researchers hoping to recruit a wide range of LGBTQ+ veterans in health research. Literature on the web-based recruitment of gay and bisexual men describes the use of social media websites (eg, Facebook), gay news sites, and dating and sexual networking mobile apps [25]. Web-based recruitment has also been paired with in-person community-based recruitment at places targeted toward gay and bisexual men [25]. The literature on recruiting transgender people into health research also describes the use of social media ads, in addition to partnering with transgender individuals with similar lived experiences as the desired study population to conduct outreach [27,28].

Finally, race and ethnicity are other dimensions of identity that are important for researching the health of LGBTQ+ veterans. Little research exists on the recruitment of participants across the intersection of these identities (race, ethnicity, sexual orientation, gender identity, and veteran status). Structural racism and the ways in which it intersects with homophobia, transphobia, and sexism affect health [29-31]. As such, it is important to recruit LGBTQ+ racial and ethnic minority veterans into health disparities research, who have lived experiences with these intersectional forms of discrimination both in and out of military service.

Thus, gaps remain in the health research literature regarding the recruitment of individuals at the intersection of LGBTQ+ and veteran identities. Further knowledge is needed to effectively reach veterans in and out of the VA and across sexual orientation and gender identity; this paper addresses these gaps. To our knowledge, no previous study has focused on the recruitment of people who identify as LGBTQ+ *and* as veterans. In addition, we have described the efforts to recruit LGBTQ+ racial and ethnic minority veterans. By more effectively recruiting a diverse group of LGBTQ+ veterans, researchers can conduct health research that informs targeted interventions, treatments, and prevention strategies tailored to the specific needs of this population.

Objectives

The *Health for Every Veteran Study* is one such study that aims to better understand the health of LGBTQ+ veterans (VA Health Services Research & Development Study, Investigator Initiated Research 17-089). This is the first VA-funded nationwide study on LGBTQ+ veteran health that relies exclusively on primary recruitment methods, meaning that the data were collected directly from individuals prospectively. The *Health for Every Veteran Study* offers a unique opportunity to learn more about the recruitment of LGBTQ+ veterans for health research, particularly through web-based methods.

This paper describes the following: (1) the recruitment methodology of the *Health for Every Veteran Study*, (2) demographic characteristics of the enrolled cohort, (3) challenges faced during recruitment, and (4) considerations for recruiting LGBTQ+ veterans in health research.

Methods

Overall Recruitment Methodology

The *Health for Every Veteran Study* is a web-based, national, VA-funded, prospective cohort study on health disparities among LGBTQ+ veterans. The objectives of this study are as follows: (1) identify the extent of sexual orientation and gender identity disparities in mental health problems (eg, depression, posttraumatic stress disorder, anxiety, nonimminent suicidal ideation or attempt) and health risk behaviors (eg, alcohol misuse and smoking) among veterans; (2) examine risk and protective factors associated with these outcomes guided by a conceptual model informed by the minority stress theory and the self-medication hypothesis; and (3) assess LGBTQ+ veterans' experiences with and preferences for treatment, including VA health care use, barriers to access, and preferences for tailored care. This study aims to include a wide range of veterans, including those who are and are not enrolled in VA health care.

Recruitment was conducted over 15 months, from September 2019 to December 2020, with the goal of enrolling 1600 veterans evenly split among 8 subgroups (200 veterans/subgroup): cisgender heterosexual women, cisgender lesbian women, cisgender bisexual women, cisgender heterosexual men, cisgender gay men, cisgender bisexual men, transgender women, and transgender men. Male and female heterosexual cisgender participants are included as comparison groups to assess the disparities. The transgender groups include veterans of all sexual orientations because splitting those groups further by sexual orientation was not seen as feasible due to sample size concerns, budget, and timeline. Although not explicitly targeted in recruitment efforts, several interested participants indicated a gender identity not represented by the above groups. As such, an exploratory subgroup comprising nonbinary and genderqueer

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veterans and veterans with other gender-diverse identities was added after the recruitment had begun.

Three primary recruitment methods were used in this study: (1) social media advertising conducted by staff, predominantly through Facebook ads; (2) outreach to community organizations serving veterans and LGBTQ+ individuals across the United States; and (3) contracting with a research recruitment company, Trialfacts.

Social Media Advertising

On the basis of previous research on recruitment experience using social media to reach female and transgender veterans [32,33], the study team created several ad sets for use on social media platforms. Facebook was the primary social media platform used; Google and Instagram ads were tested for 6 and 12 weeks, respectively, but were discontinued for cost-effectiveness reasons.

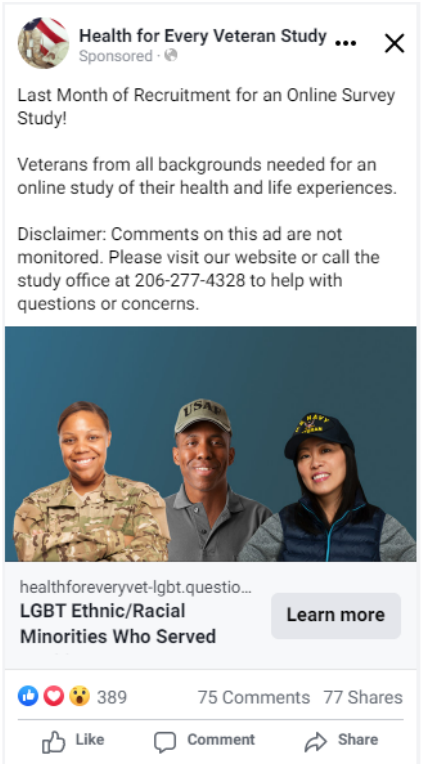
Several Facebook ad sets were created by the study staff and approved by the VA Puget Sound Institutional Review Board (IRB), each with targeted images and language carefully selected to reflect the various recruitment subgroups (Figures 1-4). The staff selected photos for ads from Adobe stock photos, and the VA Medical Media Department assisted in editing and tailoring images for certain subgroups, such as LGBTQ+ racial and ethnic minority veterans.

Although the Facebook policy does not allow for the explicit targeting of users by sexual orientation or relationship status, other audience parameters were used to reach the target population. For instance, gender, military service, and affiliation with LGBTQ+ and military organizations were used to further target the individuals through ads.

The most successful ads, determined by the number of views and clicks, were shown more often as part of Facebook's ad-optimization algorithm. The use of separate ad sets also allowed the study staff to fine-tune the budget on a given ad set to adjust to the study's changing recruitment goals across subgroups. This gave staff the opportunity to prioritize a larger percentage of the study's budget toward harder-to-reach subgroups such as bisexual veterans. Geographic parameters of audience viewers were also adjusted to improve representativeness across geographic regions (eg, limiting ad audiences to underrepresented states in the study sample).

Facebook ads were initially placed as right-column ads and were later expanded to newsfeed ad placements to reach both desktop and mobile app users. Due to the VA Puget Sound IRB policy, direct interactions with veterans on social media were prohibited. Commenting cannot be disabled on newsfeed ads; therefore, an IRB–approved disclaimer was included on those ads to inform viewers that all questions or concerns should be relayed to the study staff directly by phone. Comment sections on all ads were monitored for influxes of negative and derogatory comments. Filtering tools available on Facebook were used, and manual staff reviews were conducted daily to block or hide all comments.

Figure 1. Facebook ad created by study staff for the *Health for Every Veteran Study* aimed toward lesbian, gay, bisexual, transgender, queer, and other sexual and gender minority veterans who also identify as racial and ethnic minorities.



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Figure 2. Facebook ad aimed toward transgender veterans created by study staff for the *Health for Every Veteran Study*.

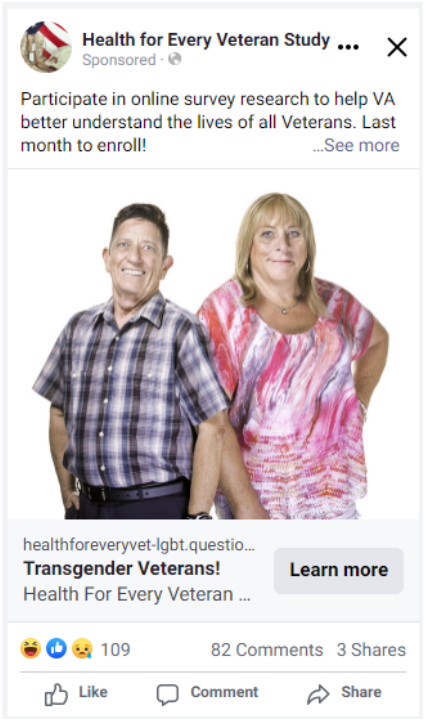
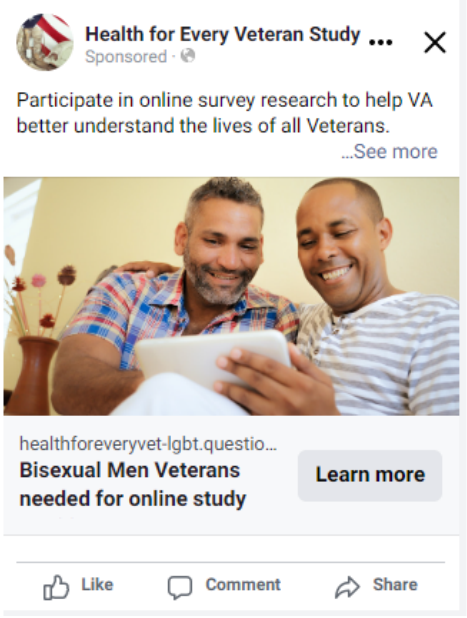
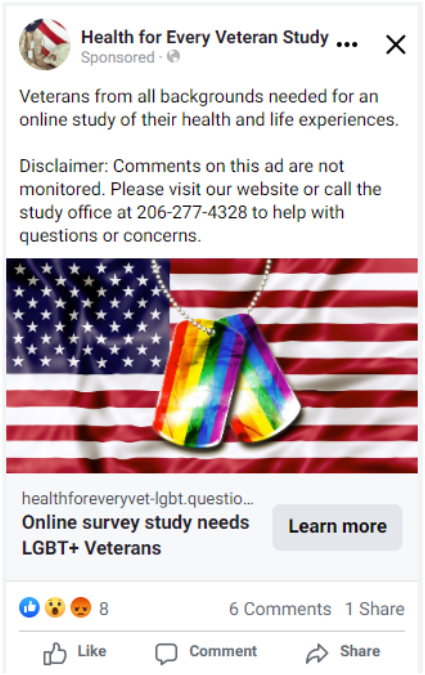


Figure 3. Facebook ad aimed toward bisexual male veterans created by study staff for the *Health for Every Veteran Study*.



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Figure 4. Facebook ad aimed toward lesbian, gay, bisexual, transgender, queer, and other sexual and gender minority veterans created by study staff for the *Health for Every Veteran Study*.



Community Organization Outreach

The community organization outreach recruitment method served two purposes: (1) to reach veterans who do not regularly use social media and (2) to establish more trust with populations who may otherwise not feel comfortable participating in research. For this recruitment method, the study staff created a database of community organizations serving veterans and LGBTQ+ individuals across the United States. Community organizations were identified through internet searches by the study staff, and their information was added to the study recruitment database. These community organizations included nonprofit, grassroots organizations and other community-based organizations at the national, state, and local levels. For instance, organizations that shared the study advertisements included the Modern Military Association of America, a nonprofit dedicated to LGBTQ+ service members, veterans, and their families, and SPART*A, an organization of transgender (including nonbinary and gender nonconforming) service members and veterans. Local organizations across all 50 states were included, as were organizations representing various subgroups (eg, transgender groups and bisexual groups). The search ultimately expanded to LGBTQ+ and veteran groups at universities, community colleges, and large employers (eg, Microsoft, Starbucks, and health care companies).

The size, demographics (age, race, ethnicity, sexual orientation, gender identity, etc), and locations of these organizations were intentionally diversified. In particular, a concerted effort was made to recruit veterans who identified as racial and ethnic minority veterans in the study. Organizations serving racial and ethnic minority veterans, whether LGBTQ+ focused or not, were included in the internet search and contact process. Nonveteran groups serving LGBTQ+ veterans, racial and ethnic minority veterans, and LGBTQ+ racial and ethnic minority veterans were also included in recruitment efforts in recognition that civilian groups may also include veteran members.

The final database included 2942 community organizations. Staff sent initial emails to the main contact listed for each of these organizations by using “mail merge,” which is an email feature that allows users to send personalized emails to large batches of recipients by uploading spreadsheets with appropriate contact information. After the first email contact, up to 4 follow-up reminders were sent via email if there was no initial response. Those who agreed to participate were recontacted at future time points and asked to reshare study information and tailored ads.

The initial email message shared background information about the study, with a request to directly share study ads and contact information with members via email distribution lists, bulletin boards, the organization’s social media platforms, or other communication methods regarding their preferences. The email messages and ads were tailored to the community organization’s membership base. For instance, the language of a contact email to an organization serving transgender veterans was adjusted to highlight how the study sought to better understand the experiences of transgender veterans, and ads designed for transgender veterans were attached with the email.

Ultimately, 10.47% (308/2942) of the organizations responded to the study staff and agreed to share the study information with their membership bases. Organizations that assisted with the recruitment were publicly acknowledged on the study website with their permission. After the completion of the full study, the participating organizations will receive an update on the study findings.

Given the nature of community outreach, there were, at times, high-volume surges of interested participants from a single organization. These surges occurred after large organizations sent out study information to their membership bases, resulting

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in many members completing the web-based screener. All high-volume surges were manually reviewed, and screening decisions were discussed by the study team and documented to ensure that the study sample was not biased by a single organization or geographic region. When surges occurred, the study's current enrollment profile was reviewed, and subgroups requiring additional participants were prioritized. Oftentimes, surges were comprised of predominantly White cisgender male heterosexual veterans. Therefore, LGBTQ+, female, and racial and ethnic minority veterans were prioritized for screening.

Trialfacts

In the first 9 months of recruitment, enrollment numbers had not yet reached the target goals. Therefore, in May 2020, the study team decided to contract with an outside company to bolster its recruitment efforts by the study team. Trialfacts, a company that specializes in recruitment services for the clinical trial industry [34], was chosen due to its due diligence process and prior success with recruiting veteran populations.

Trialfacts was paid to use Facebook advertising to reach potential participants, as well as reaching out to a pool of participants from previous Trialfacts recruitment efforts in their internal database. These Facebook ads were run by Trialfacts employees, who were able to use their marketing and social media expertise to monitor and optimize ads consistently. The study team shared ad images and language that were shown to be successful in the study team's own social media ads, and Trialfacts also created their own IRB–approved ads with staff input and guidance.

Typically, Trialfacts guarantees a minimum number of participant referrals when contracting with study teams. However, Trialfacts had no prior experience of specifically recruiting LGBTQ+ veterans. As a result, Trialfacts proposed approaching this study as a pilot program. As such, the study team worked closely with the Trialfacts staff during the recruitment process. In addition to cocreating ads, the eligibility of Trialfacts referrals was relayed back to Trialfacts on a regular basis to help Trialfacts fine-tune its recruitment methods.

Trialfacts helped recruit participants across all study subgroups, although certain subgroups were prioritized in the study budget based on recruitment needs. In particular, the study team requested Trialfacts to focus on the recruitment of bisexual female and male, transgender male, and racial and ethnic minority veterans. In addition, Trialfacts used geotargeting and other advertising strategies to increase overall demographic diversity, with the goal of increasing the national representativeness of the enrolled sample.

Screening and Enrollment

Interested participants who were recruited via staff social media ads, community outreach, and Trialfacts were directed to an information landing page hosted by QuestionPro. These landing pages were tailored based on the ads on which the interested participant clicked; unique language and images were displayed based on the tailored subgroup for that ad. For example, ads for LGBTQ+, female, and general veteran audiences would link to LGBTQ+, women, and general landing pages, respectively (Figures 5-7). These landing pages contained relevant information about the *Health for Every Veteran Study* for interested participants, including benefits of participation, number of follow-ups (every 9 mo for 27 mo), and a description of the study team.

If participants indicated that they were interested in participating, they would then be directed to the study information statement, screening consent form, and the study screener (which were all the same across participants and hosted in QuestionPro) to determine eligibility. The eligibility criteria mandated that the veteran must be aged ≥18 years; be currently nonincarcerated; and have prior service in the US military, US residence, routine internet access, valid contact information, and willingness to answer questions about key demographics. Individuals recruited through Trialfacts underwent the same screening procedures, although the landing pages and study screeners were housed and conducted by Trialfacts.

All prospective participants underwent a manual review to gauge veteran "insider knowledge" to ensure authentic veteran status. In this manual review, the study staff reviewed responses to questions regarding military branches, job fields and acronyms, and rank to determine the validity of the prospective participant's veteran status. In addition, a statement was also included on the screener as a deterrent to falsifying responses saying the following: "Per the Stolen Valor Act of 2013, it is a federal crime to obtain money or other benefits by falsely representing prior military service." Additional screening precautions are detailed in our paper elaborating the baseline results [35]. Those who did not pass the screener or manual review were deemed ineligible and provided with a link to a detailed resource page that included contact information for emergency crisis services, mental health services, sexual assault and domestic violence support, substance use support, organizations serving specific populations such as female and LGBTQ+ veterans, and information on VA benefits.

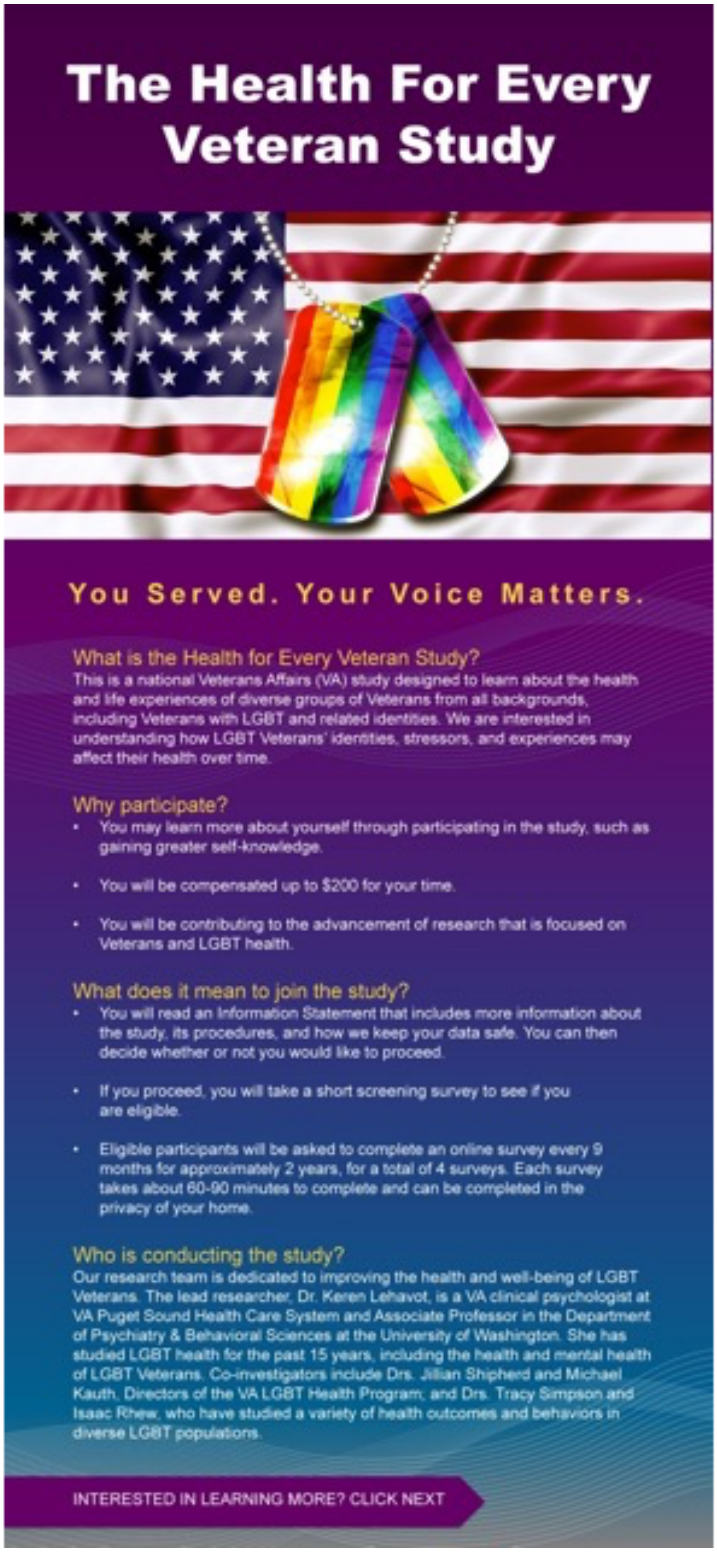
Eligible participants were emailed a link to the 60- to 90-minute web-based baseline survey to be completed on a website developed by the VA Cooperative Studies Program. If completed, the participants were considered to be enrolled and compensated US $30. Additional compensation was provided for follow-up surveys as follows: US $35 for the 9-month follow-up, US $40 for the 18-month follow-up, US $45 for the 27-month follow-up, and an additional US $50 bonus for the completion of all surveys. As such, participants could earn up to US $200 for their time. According to the VA policy, payments were issued by the Department of Treasury via physical checks or electronic fund transfers.

Weekly reporting of screening and enrollment was conducted by the study team to track the recruitment process. Screened and enrolled participants were examined by the subgroup and demographics to better understand the enrollment needs and tailor recruitment strategies across all recruitment methods. Demographic characteristics from national research surveys, such as the Behavioral Risk Factor Surveillance Survey, National Epidemiologic Survey on Alcohol and Related Conditions-III, and Millennium Cohort, were reviewed and compared by demographics (ie, age, race, marital status, education, income, and geographic region) to improve national

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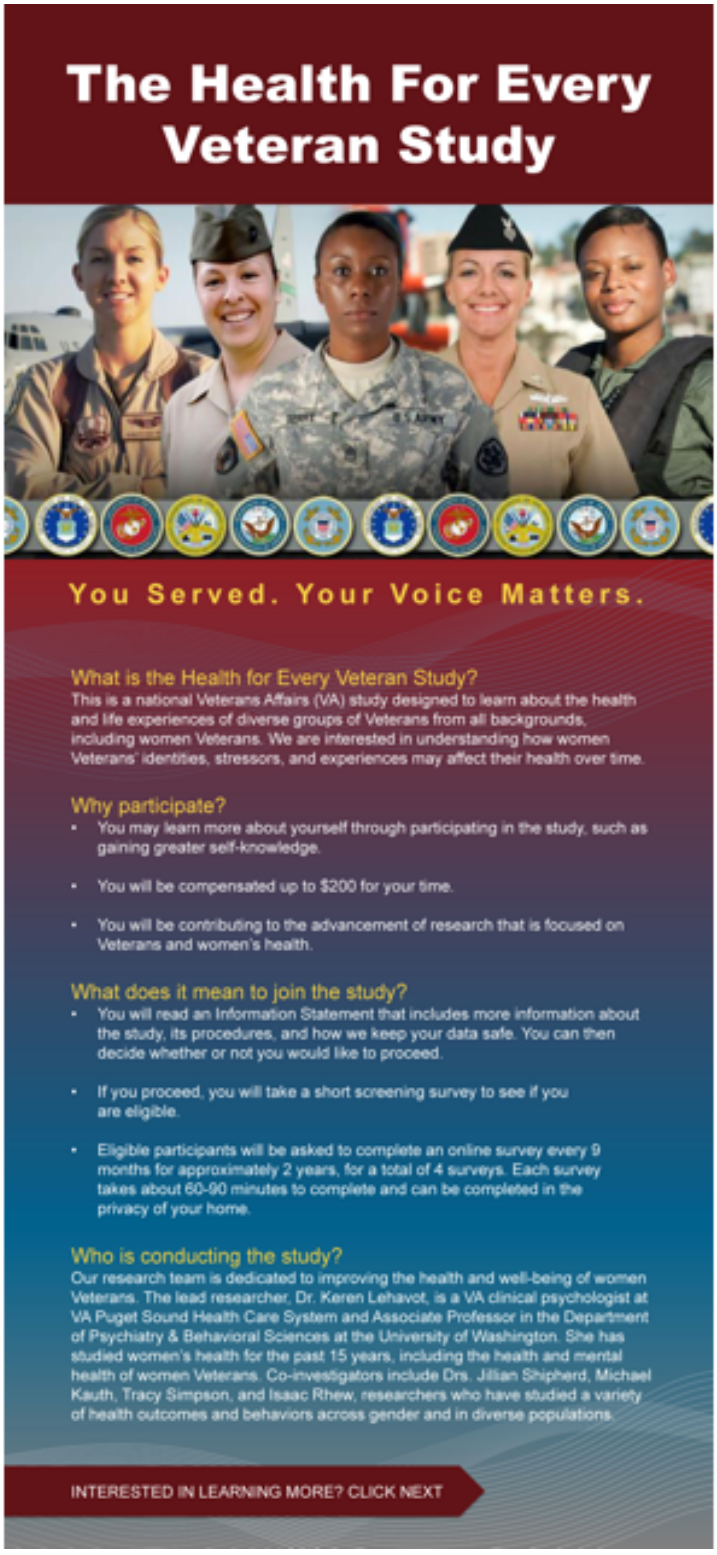
representativeness. Additional strategies were used to optimize validity, such as not including study compensation amounts in advertising and monitoring for duplicate identifying information.

Figure 5. *Health for Every Veteran Study* information landing page for lesbian, gay, bisexual, transgender, queer, and other sexual and gender minority populations.



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Figure 6. *Health for Every Veteran Study* information landing page for female veteran populations.



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Figure 7. *Health for Every Veteran Study* information landing page for general veteran populations.



Ethical Considerations

This study was approved by the VA Puget Sound Health Care System IRB (01672) and granted a waiver for the documentation of informed consent. Potential participants were provided with an information statement comprehensively describing the nature of the study as well as its risks and benefits upon visiting the study website. All study data in this paper have been deidentified to protect the privacy and confidentiality of the participants.

Results

Enrollment in the *Health for Every Veteran Study* concluded in December 2020. A total of 3535 participants accessed the study information statement to begin the screening process, and 1819 (51.46%) participants passed screening; of these 1819 participants, 1062 (58.38%) completed the baseline survey to enroll. The CONSORT (Consolidated Standards of Reporting Trials) diagram [36] demonstrates the flow of recruitment, from

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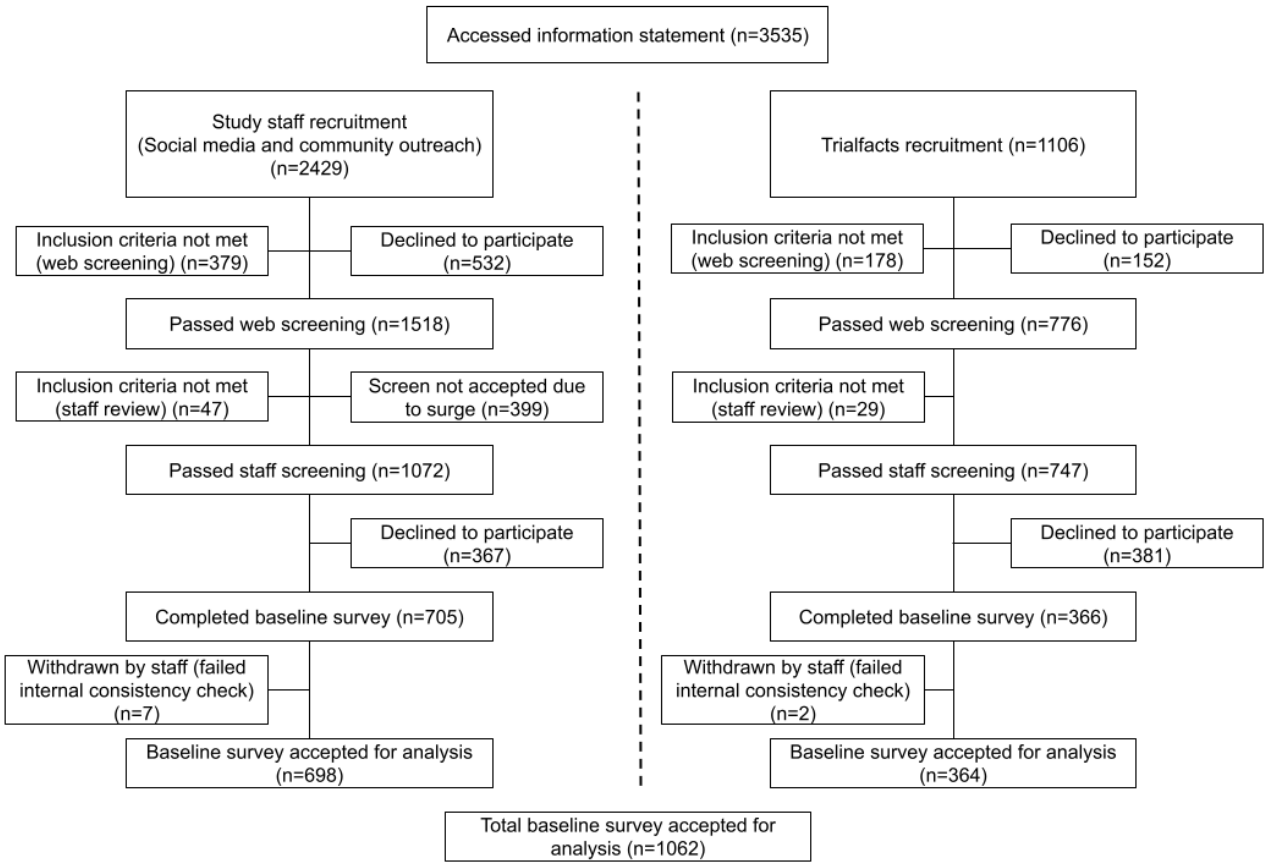
screening to enrollment, divided across study staff recruitment methods (ie, social media advertising and community outreach) and Trialfacts recruitment (Figure 8). All descriptive results were calculated using R (R Foundation for Statistical Computing) [37].

Of the enrolled participants (n=1062), 25.24% (n=268) were recruited from staff Facebook ads, 40.49% (n=430) from community outreach, and 34.27% (n=364) from Trialfacts. Trialfacts proved to be instrumental for the study, providing one-third (364/1062, 34.27%) of the participants despite being initiated 9 months after the recruitment had begun. Notably, all 3 methods of recruitment contributed to substantial portions of the enrolled cohort, indicating that a multipronged approach was a critical and successful strategy for the recruitment of hard-to-reach populations in our study of LGBTQ+ veterans.

Of the 8 subgroups targeted for recruitment, 5 subgroups neared the target recruitment goal of 200 participants per subgroup: cisgender gay men, cisgender heterosexual women, cisgender heterosexual men, cisgender lesbian women, and transgender women. However, cisgender bisexual men, cisgender bisexual women, and transgender men did not reach recruitment goals. Table 1 describes the enrollment by subgroup, including the percentage of the target enrolled. Of note is the subgroup of gender-diverse veterans; although they were not an a priori recruitment group, they were enrolled as an exploratory group after recruitment began to be inclusive of the experiences of veterans not encompassed by the other a priori subgroups.

Table 2 demonstrates the demographic breakdown of the study sample by recruitment method. Various recruitment methods were effective at recruiting different subgroups; however, it should be noted that the methods were tailored to target specific subgroups based on needs at various points of the recruitment period. For instance, because community outreach methods were extremely successful in recruiting cisgender heterosexual male and cisgender female veterans (at times resulting in recruitment surges; see the *Discussion* section), only a small fraction of Trialfacts ads focused on these populations. Instead, Trialfacts purposefully focused on the recruitment of cisgender bisexual men, cisgender bisexual women, and transgender men. This proved critical; 68% (42/62) of cisgender bisexual men were recruited through Trialfacts, compared with 11% (7/62) through Facebook and 21% (13/62) through community outreach (Table 2). Similarly, Trialfacts recruited 48% (29/61) of cisgender bisexual women and 49% (22/45) of transgender men (Table 2). To speak to the broader demographic representativeness of participants gleaned from each recruitment method, information on age, race, ethnicity, education, income, and marital status of the enrolled sample by recruitment method is also included in Table 2.

Figure 8. *Health for Every Veteran Study* CONSORT (Consolidated Standards of Reporting Trials) diagram demonstrating study staff recruitment and Trialfacts recruitment.



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Table 1. Enrollment by recruitment subgroup.

Gender identity and gender and sexual orientation	Target enrollment (N=1600), n (%)	Enrolled (n=1062, 66.4%), n (%)[a]
Men		
Cisgender gay men	200 (12.5)	189 (94.5)
Cisgender bisexual men	200 (12.5)	62 (31)
Transgender men	200 (12.5)	45 (22.5)
Cisgender heterosexual men	200 (12.5)	169 (84.5)
Women		
Cisgender lesbian women	200 (12.5)	154 (77)
Cisgender bisexual women	200 (12.5)	61 (30.5)
Transgender women	200 (12.5)	144 (72)
Cisgender heterosexual women	200 (12.5)	172 (86)
Gender-diverse (eg, nonbinary, gender nonconforming, and genderqueer) individuals	N/A[b]	66 (33)

[a]Percentage of the target enrollment achieved (n=200).

[b]N/A: not applicable; not an a priori group.

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Table 2. Demographics of enrolled sample by recruitment source.

	Facebook (n=268, 25.2%), n (%)[a]	Community outreach (n=430, 40.5%), n (%)[a]	Trialfacts (n=364, 34.3%), n (%)[a]	Overall (N=1062), n (%)[b]
Study subgroup				
Cisgender heterosexual men	43 (25.4)	111 (65.7)	15 (8.9)	169 (15.9)
Cisgender gay men	49 (25.9)	64 (33.9)	76 (40.2)	189 (17.8)
Cisgender bisexual men	7 (11.3)	13 (21)	42 (67.7)	62 (5.8)
Transgender men	8 (17.8)	15 (33.3)	22 (48.9)	45 (4.2)
Cisgender heterosexual women	68 (39.5)	96 (55.8)	8 (4.7)	172 (16.2)
Cisgender lesbian women	34 (22.1)	53 (34.4)	67 (43.5)	154 (14.5)
Cisgender bisexual women	18 (29.5)	14 (23)	29 (47.5)	61 (5.7)
Transgender women	34 (23.6)	44 (30.6)	66 (45.8)	144 (13.6)
Gender-diverse individuals	7 (10.6)	20 (30.3)	39 (59.1)	66 (6.2)
Age group (years)				
20-25	0 (0)	10 (40)	15 (60)	25 (2.4)
26-35	38 (21.8)	46 (26.4)	90 (51.7)	174 (16.4)
36-45	49 (22.9)	74 (34.6)	91 (42.5)	214 (20.2)
46-55	57 (27.3)	75 (35.9)	77 (36.8)	209 (19.7)
56-65	64 (28.6)	94 (42)	66 (29.5)	224 (21.1)
>65	60 (27.8)	131 (60.6)	25 (11.6)	216 (20.3)
Race and ethnicity				
Black and non-Hispanic	18 (36.7)	25 (51)	6 (12.2)	49 (4.6)
Hispanic	20 (22)	35 (38.5)	36 (39.6)	91 (8.6)
White, non-Hispanic	212 (25.3)	333 (39.8)	292 (34.9)	837 (78.8)
Other race, non-Hispanic	5 (18.2)	12 (54.5)	5 (22.7)	22 (2.1)
Multiracial, non-Hispanic	13 (20.6)	25 (39.7)	25 (39.7)	63 (5.9)
Education				
12th grade	16 (34)	14 (29.8)	17 (36.2)	47 (4.4)
Vocational or training >12th grade	15 (35.7)	10 (23.8)	17 (40.5)	42 (4)
Some college	87 (24)	127 (35.1)	148 (40.9)	362 (34.1)
College graduate	47 (20.7)	91 (40.1)	89 (39.2)	227 (21.4)
Some graduate or professional	18 (20.7)	43 (49.4)	26 (29.9)	87 (8.2)
Master’s degree	67 (28.3)	112 (47.3)	58 (24.5)	237 (22.3)
Doctoral degree	17 (29.3)	32 (55.2)	9 (15.5)	58 (5.5)
Missing	1 (50)	1 (50)	0 (0)	2 (0.2)
Income (US $)				
<15,000	13 (25)	13 (25)	26 (50)	52 (4.9)
15,000 to ≤20,000	10 (29.4)	11 (32.4)	13 (38.2)	34 (3.2)
20,000 to ≤25,000	12 (25)	16 (33.3)	20 (41.7)	48 (4.5)
25,000 to ≤30,000	8 (18.6)	14 (32.6)	21 (48.8)	43 (4)
30,000 to ≤40,000	22 (22.4)	38 (38.8)	38 (38.8)	98 (9.2)
40,000 to ≤50,000	34 (31.5)	36 (33.3)	38 (35.2)	108 (10.2)
50,000 to ≤60,000	21 (21.4)	37 (37.8)	40 (40.8)	98 (9.2)
60,000 to ≤70,000	18 (21.4)	32 (38.1)	34 (40.5)	84 (7.9)

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	Facebook (n=268, 25.2%), n (%)[a]	Community outreach (n=430, 40.5%), n (%)[a]	Trialfacts (n=364, 34.3%), n (%)[a]	Overall (N=1062), n (%)[b]
70,000 to ≤80,000	27 (26.2)	42 (40.8)	34 (33)	103 (9.7)
80,000 to ≤90,000	16 (26.2)	28 (45.9)	17 (27.9)	61 (5.7)
90,000 to ≤100,000	14 (29.8)	19 (40.4)	14 (29.8)	47 (4.4)
≥100,000	71 (25.5)	138 (49.6)	69 (24.8)	278 (26.2)
Missing	2 (25)	6 (75)	0 (0)	8 (0.8)
Marital status				
Married or domestic partnership	141 (25.9)	240 (44)	164 (30.1)	545 (51.3)
Never married	53 (25.6)	76 (36.7)	78 (37.7)	207 (19.5)
Separated	5 (15.2)	6 (18.2)	22 (66.7)	33 (3.1)
Divorced	58 (25.6)	85 (37.4)	84 (37)	227 (21.4)
Widowed	9 (27.3)	14 (42.4)	10 (30.3)	33 (3.1)
Other	2 (12.5)	8 (50)	6 (37.5)	16 (1.5)
Missing	0 (0)	1 (100)	0 (0)	1 (0.1)
Region				
Northeast	30 (25.6)	52 (44.4)	35 (29.9)	117 (11)
South	109 (25.1)	165 (37.9)	161 (37)	435 (41)
Midwest	52 (24.8)	81 (38.6)	77 (36.7)	210 (19.8)
West	76 (25.5)	131 (44)	91 (30.5)	298 (28.1)

[a]Percentage of subgroup enrollment by recruitment source.

[b]Percentage of overall enrollment by subgroup.

Discussion

Recruitment Methods

The Health for Every Veteran Study is the first study to specifically recruit a diverse sample of LGBTQ+ and heterosexual cisgender veterans nationwide to examine health disparities among these subgroups of veterans. Recruitment results indicated that all 3 recruitment methods, namely, Facebook ads, community outreach, and contracting with a recruitment company, were crucial for the recruitment and enrollment success. Each method contributed to at least a quarter of the enrolled participants.

In addition to the number of participants recruited, the study staff found unique benefits and costs for each method. Because recruitment strategies were continuously adjusted to best meet the study needs, all final recruitment numbers (both overall and for specific subgroups) should be interpreted within the context of this study's time period, population, and aims. However, lessons learned from the study's recruitment methodology and strategies can be applied to a wide range of researchers who work with hard-to-reach populations. To capture this, Table 3 describes various strengths and challenges of all 3 recruitment methods based on the study team's experience.

In particular, a company that specializes in recruitment strategies for research may be an attractive option for researchers with limited abilities or staff resources to manage or optimize social media ads. Despite launching this partnership 9 months after recruitment had begun, Trialfacts brought in 34% of the enrolled participants. Using Trialfacts at the start of the study recruitment period may have allowed the study to achieve full enrollment. However, researchers should consider whether they wish to have a single source for recruitment or whether a diversified recruitment strategy is desired. Depending on the study's aims and the desired target population, different strategies and methods may be beneficial.

Notably, each VA health care system has a designated LGBTQ+ Veteran Care Coordinator (VCC). VCCs serve as the point persons for LGBTQ+ veteran affairs at their respective sites. However, we intentionally chose not to engage with VCCs for recruitment to reduce bias that would have been introduced had we recruited veterans who were already engaged in VA services. For other researchers, connecting with VCCs for recruitment may be an ideal option for the recruitment of LGBTQ+ veterans.

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Table 3. Strengths and challenges of study recruitment methods.

Recruitment method	Strengths	Challenges
Facebook ads	• Reach those not affiliated with the VA[a] or connect with wider audience • Can target audience by some parameters to optimize reach • Can adjust ads and targeting in real time, improves cost-efficiency, and can follow recruitment needs for specific subgroups • Provides a variety of metrics to track performance, such as reactions to and engagement with ads	• Takes experience to get audience parameters correct • Negative comments need frequent monitoring; negative comments and hate speech can have negative impacts on study staff as well as on potential study participants • Not able to reach those not on Facebook • Little to no direct customer service if ads were deemed to violate Facebook policy • Takes significant staff time to optimize • Learning platform requires time and research • Requires thoughtful budgeting due to varied and somewhat unpredictable costs and efficacy of ads
Community outreach	• Reach those not affiliated with the VA or connect with wider audience • Can reach those not on social media • Establish trustworthiness and credibility with leaders of community organizations who hold closer personal relationships with organization members	• Little control to how or when organizations shared study information • High-volume surges of interested participants to manage; surges may cause recruitment bias by geographic region or demographic group • May be biased toward those involved with community groups (eg, those who publicly identify as LGBTQ+[b] vs those who do not) • Some organizations may be hard to reach or may not have up-to-date contact information • Researching, compiling, contacting, and following up with organizations may require significant time and energy • Some relevant local groups may be missed if study team is not connected or familiar with the region
Trialfacts or similar recruitment service company	• Expertise and resources solely dedicated to recruitment and social media advertising • Reduces burden on study staff • Typically offers a recruitment number guarantee—will prorate a refund if numbers are not achieved • Familiarity with institutional review board protocols • Affordable or cost-efficient for this study • Provides a tailored recruitment plan and study timeline	• Can be expensive • Less control over advertisements • Requires establishing secure information exchanges with Trialfacts to meet all VA information security guidelines • May lack content area expertise for specific populations, such as LGBTQ+ veterans • Difficulty recruiting some subgroups • Quality checks needed to review data or reports • May overlap in reach if study is already conducting separate social media recruitment • Not able to reach those not on social media

[a]VA: Veterans Health Administration.

[b]LGBTQ+: lesbian, gay, bisexual, transgender, queer, and other sexual and gender minority.

Population Subgroups

Despite the overall success in recruiting LGBTQ+ veterans in this longitudinal study, there were areas where the recruitment underperformed. In particular, the number of bisexual veterans of any gender and transgender male veterans recruited was lower than the study aims. The reasons for underrecruitment likely differed between the groups.

Transgender men appear to be less prevalent in the veteran population compared with transgender women, although more accurate population estimates are needed [3,38]. This may be one reason why the study team had greater difficulty reaching a target goal of 200 for transgender men compared with other LGBTQ+ subgroups. In addition, transgender men face the barriers of stigma and invisibility [39,40]. For instance, a national study of transgender men found that 14.1% of participants were refused care by a provider due to their gender identity, and 32.8% delayed needed care due to fear of discrimination because of their gender identity [39]. These obstacles may reduce participation in health research.

Difficulties in recruiting bisexual veterans into research studies may be due to biphobia within and outside the LGBTQ+ community. Although bisexual people represent a large proportion of the LGBTQ+ community among both veterans and civilians [41], structural, interpersonal, and internalized biphobia may result in the exclusion of or decreased sense of belonging among bisexual people from the LGBTQ+ community [41,42]. This may make it difficult to recruit bisexual veterans through broadly targeted LGBTQ+ ads or through LGBTQ+ community groups. In addition, changes in sexual orientation identity labels over time also mean that veterans with same-gender or different-gender attractions do not necessarily identify as bisexual. Although the screening survey included other sexual identity options (eg, pansexual), the screener also required the selection of a single sexual orientation that best represented the interested participants' sexual identity (choosing from 1 of the following: gay or lesbian, bisexual, or

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heterosexual) for study stratification purposes. Ultimately, improved methods for recruiting bisexual veterans and other veterans with both same-gender and different-gender partners in health research deserve further investigation. This is particularly important because the literature indicates that bisexual community members, especially bisexual women, experience health inequities in mental and physical health compared with lesbian and heterosexual women [43,44].

Notably, the study enrolled 66 gender-diverse veterans (a category that included nonbinary, gender nonconforming, and genderqueer veterans and veterans of other gender identities with any sexual orientation) despite not being an a priori recruitment category. This indicates a promising future area of research and engagement. There is limited research on the health of gender-diverse populations in general. Current literature shows that gender-diverse individuals face a number of inequities in health and social determinants of health, including increased risk of poverty, uninsurance, homelessness, discrimination in the health care system, suicide attempts, and psychological stress [45] compared with their cisgender peers.

Finally, racial and ethnic minority veterans were difficult to recruit across the subgroups in the study. The enrolled sample was less racially diverse compared with the overall veteran population, with 21.4% of the study sample identifying as racial and ethnic minority people compared with 26% in the wider veteran population [46]. Racial and ethnic minority veterans were intentionally included in targeted recruitment efforts, including through representation in ad images, outreach to community organizations specifically centering on racial and ethnic minority veterans, and Trialfacts' advertising strategies. It is possible that a deeper community-based partnership building ahead of study recruitment would improve the perceived trustworthiness of the study and increase outreach to racial and ethnic minority veterans, particularly those within the LGBTQ+ community. Generally, the multiple layers of marginalization experienced by LGBTQ+ racial and ethnic minority veterans may add structural and interpersonal barriers. For example, racism within LGBTQ+ and veteran communities may also result in further marginalization of LGBTQ+ racial and ethnic minority veterans from both communities, resulting in fewer chances to hear about or less desire to participate in this study. In addition, recruitment for this study occurred during the COVID-19 pandemic and a wave of ongoing violence and racism against Asian American, Black American, and other racial and ethnic minority individuals. This could have made it more difficult for racial and ethnic minority veterans to hear about or participate in research studies, even with study compensation.

Other Recruitment Challenges

It is impossible to know whether the COVID-19 pandemic increased or decreased participation in the study and for whom. Potentially eligible veterans may have been prevented from participating due to COVID-19–related stressors, such as physical, mental, emotional, and social health needs, as well as socioeconomic stressors such as lost work, housing instability, childcare responsibilities, financial uncertainty, and loss of access to internet or technology. By contrast, the entirely web-based nature of the *Health for Every Veteran Study* may have facilitated participation during a time of social distancing and stay-at-home orders, particularly compared with other research studies requiring in-person recruitment and enrollment.

Other factors that impacted the study recruitment process were as follows: (1) US congressional budget delays impacting VA research processes, (2) high-volume surges of heterosexual participants from community outreach, and (3) negative comments on Facebook ads. Congressional budget delays caused 2 pauses in social media advertising during the study recruitment period: from October 5, 2019, to October 25, 2019, and from October 1, 2020, to October 5, 2020.

On several occasions, the study team experienced high-volume surges of screeners from interested participants, which primarily occurred when conducting community outreach with large veterans' organizations. This resulted in large numbers of heterosexual veterans completing the initial screener, which necessitated manual screening by staff to reduce bias in the sample toward one particular community organization (see the *Methods* section). Underrepresented subgroups in the sample were prioritized for enrollment, including women, LGBTQ+ subgroups, and racial and ethnic minority veterans. This may have introduced sampling bias, including for racial and ethnic minority, cisgender, and heterosexual veterans, who had a greater likelihood of being enrolled. However, this type of manual review was necessary to create a balanced study sample, reduce overall bias, and meet enrollment goals.

Finally, the study staff encountered a large volume of negative and derogatory comments on Facebook ads, up to dozens per day. These comments were predominantly anti-LGBTQ+ and often expressed opposition to the content of the ad images. Automatic filters allowed the study staff to hide comments immediately with certain keywords and phrases. In addition to these filters, the staff monitored the ad accounts throughout the day to manually hide the comments to minimize any potential negative impact on the LGBTQ+ study participants. Unfortunately, it is possible that some potential participants may have been exposed to and adversely affected by negative and derogatory comments before the study staff members were able to manually delete them. Filters and monitoring also served to discourage commenting in general, keeping recruitment in line with the VA institutional review board protocols, which do not allow direct social media interactions between the study team and veterans. Some ad images were adjusted based on constructive criticism shared in comments (most commonly, viewers criticized any images that altered the standard US military uniform). In addition, recognizing that health disparities research may attract scholars and study staff who hold one or more marginalized identities, it was important for the study team to build support mechanisms around social media monitoring. The study team regularly discussed recruitment topics in weekly meetings, which included conversations about the emotional and cognitive labor involved in monitoring derogatory Facebook comments. The team decided to rotate the task of moderating Facebook ads to ensure that a single person would not be overwhelmed by regular exposure to hate speech.

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Limitations and Strengths

There are limitations to this study, one of which is generalizability. To some extent, our processes and experiences were influenced by VA regulations, which reduces generalizability to non-VA researchers. Although we made concerted efforts to improve the national representativeness of our enrolled cohort, there were participant characteristics that we did not collect (eg, rurality) and could not be used to fine-tune our recruitment methods.

Importantly, our specific study design and subgroup stratification affected the recruitment methodology described in this paper. Because different recruitment strategies were used to attract different subgroups of participants, it was not possible to analyze which subgroups responded best to various types of recruitment methods. Consequently, it is difficult to draw concrete conclusions on whether specific methods are favored by certain subgroups. Overall, the nonprobability manner of recruitment is a significant limitation of this study. Therefore, the study results may not be generalizable to other populations. However, the lessons learned and general recruitment methodology are pertinent to a wide variety of research. In addition, our subgroup stratification still offers important disaggregated insights into the recruitment of specific LGBTQ+ subgroups.

The completely web-based methodology of the study served as both a strength and a limitation. Crucially, web-based recruitment allowed the recruitment to continue, even when the COVID-19 pandemic began. As such, this study offers tested recruitment options for other health research studies that will begin or continue recruitment during the pandemic or for other studies using solely web-based methods. However, the recruitment methodology could also have resulted in selection bias in the sample, as there are veterans who may not use social media and who may not be connected with community organizations. In addition, the social media platforms used may also have caused selection bias based on the user base (eg, age of users). However, our widespread community-based organizations targeted veterans across a variety of age ranges and other demographics.

Overall, this study contributes to the current literature on both LGBTQ+ and veteran health research recruitment. In the LGBTQ+ recruitment literature, this study offers insights into the recruitment of multiple LGBTQ subgroups. In addition, we add to the current literature on web-based recruitment through social media. Uniquely, we used community outreach in a completely web-based manner, offering opportunities for community-based recruitment efforts when face-to-face recruitment is not feasible. We add to the veteran recruitment literature by relying on methods that do not use VA administrative or EMR data. This improves the study's generalizability by using recruitment methods that are inclusive of veterans outside the VA health care system.

Conclusions

We share our descriptions and findings of the recruitment process of the *Health for Every Veteran Study* to convey the lessons learned during the web-based recruitment of LGBTQ+ veterans. As the first study to recruit a large and diverse group of veterans that varies across gender identity and sexual orientation, important insights were gathered that have implications for the web-based recruitment of LGBTQ+ veterans and potentially other hard-to-reach populations. The multipronged recruitment plan that consists of social media advertising, outreach to community organizations, and partnering with a recruitment company offers 3 viable options for researchers who plan to conduct web-based recruitment for health research studies.

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Data Availability

The data sets generated and analyzed during this study are available from the corresponding author upon reasonable request.

The views expressed in this paper are those of the authors and do not necessarily reflect the position or policy of the funders, institutions, the Department of Veterans Affairs, or the United States Government.

Conflicts of Interest

None declared.

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Abbreviations

CONSORT: Consolidated Standards of Reporting Trials
EMR: electronic medical record
IRB: Institutional Review Board
LGBTQ+: lesbian, gay, bisexual, transgender, queer, and other sexual and gender minority
VA: Veterans Health Administration
VCC: Veteran Care Coordinator

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Protocol

Digital Phenotyping for Monitoring and Disease Trajectory Prediction of Patients With Cancer: Protocol for a Prospective Observational Cohort Study

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Abstract

Background: Timely recognition of cancer progression and treatment complications is important for treatment guidance. Digital phenotyping is a promising method for precise and remote monitoring of patients in their natural environments by using passively generated data from sensors of personal wearable devices. Further studies are needed to better understand the potential clinical benefits of digital phenotyping approaches to optimize care of patients with cancer.

Objective: We aim to evaluate whether passively generated data from smartphone sensors are feasible for remote monitoring of patients with cancer to predict their disease trajectories and patient-centered health outcomes.

Methods: We will recruit 200 patients undergoing treatment for cancer. Patients will be followed up for 6 months. Passively generated data by sensors of personal smartphone devices (eg, accelerometer, gyroscope, GPS) will be continuously collected using the developed LAIMA smartphone app during follow-up. We will evaluate (1) mobility data by using an accelerometer (mean time of active period, mean time of exertional physical activity, distance covered per day, duration of inactive period), GPS (places of interest visited daily, hospital visits), and gyroscope sensors and (2) sociability indices (frequency of duration of phone calls, frequency and length of text messages, and internet browsing time). Every 2 weeks, patients will be asked to complete questionnaires pertaining to quality of life (European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire [EORTC QLQ-C30]), depression symptoms (Patient Health Questionnaire-9 [PHQ-9]), and anxiety symptoms (General Anxiety Disorder-7 [GAD-7]) that will be deployed via the LAIMA app. Clinic visits will take place at 1-3 months and 3-6 months of the study. Patients will be evaluated for disease progression, cancer and treatment complications, and functional status (Eastern Cooperative Oncology Group) by the study oncologist and will complete the questionnaire for evaluating quality of life (EORTC QLQ-C30), depression symptoms (PHQ-9), and anxiety symptoms (GAD-7). We will examine the associations among digital, clinical, and patient-reported health outcomes to develop prediction models with clinically meaningful outcomes.

Results: As of July 2023, we have reached the planned recruitment target, and patients are undergoing follow-up. Data collection is expected to be completed by September 2023. The final results should be available within 6 months after study completion.

Conclusions: This study will provide in-depth insight into temporally and spatially precise trajectories of patients with cancer that will provide a novel digital health approach and will inform the design of future interventional clinical trials in oncology. Our findings will allow a better understanding of the potential clinical value of passively generated smartphone sensor data (digital

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phenotyping) for continuous and real-time monitoring of patients with cancer for treatment side effects, cancer complications, functional status, and patient-reported outcomes as well as prediction of disease progression or trajectories.

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KEYWORDS

cancer; digital phenotyping; biomarkers; oncology; digital phenotype; biomarker; data collection; data generation; monitor; monitoring; data collection; predict; prediction; model; models; mobile phone

Introduction

Cancer continues to be the leading cause of morbidity and mortality worldwide and a serious public health challenge [1-3]. Early cancer detection as well as increased effectiveness and availability of novel treatment approaches such as immunotherapy and targeted therapies have resulted in a steadily growing number of cancer survivors [4-7]. Continuous monitoring of patients undergoing treatment for cancer and cancer survivors is important for timely identification of cancer treatment complications and cancer progression that is important for optimized long-term prognosis [8]. Therefore, there is an urgent need for developing widely available, automated, and evidence-based monitoring systems of patients with cancer [9].

The COVID-19 pandemic continues to be a serious public health challenge [10]. Patients with cancer are vulnerable to SARS-CoV-2 infection due to immunosuppression, frequent hospital visits [11,12], and lower efficacy of the COVID-19 vaccines [13]. The mortality risk of patients with cancer infected with SARS-CoV-2 was greater than that of the general population and was shown to exceed by 33% among patients with thoracic and hematologic malignancies [14-16]. A meta-analysis of 52 studies and 18,650 patients estimated the probability of death at 25.6% in patients with cancer infected with COVID-19 [17]. Furthermore, the COVID-19 pandemic caused major delays and interruptions in cancer treatments [18,19], and they are estimated to have caused over 15% increase in additional cancer deaths [20]. Finally, patients with cancer were vulnerable to adverse mental health and quality of life sequalae during the COVID-19 pandemic [21,22].

Although there is no standardized definition for mobile health (mHealth), the World Health Organization defines mHealth as "medical or public health practice that is delivered with the support of mobile phones, patient monitoring devices, and other wireless devices." mHealth encompasses the use of mobile phones and other wireless technologies for health care and is a promising approach for improving health monitoring and delivery of health interventions [23-25]. The adoption of telehealth and mHealth solutions is growing [26]. The number of digital health apps currently exceeds 300,000, with hundreds of apps being introduced every day [27]. The market size of digital health apps will grow exponentially in the coming decade [27]. However, the adoption of digital health apps in clinical practice is limited due to numerous obstacles such as unclear clinical value because they are often not developed by health care professionals and not tested in clinical environments [28]. Thus, there is an urgent need to develop evidence-based personalized telehealth or mHealth solutions and test them in real-word clinical environments that would allow evidence-based monitoring of vulnerable patients with cancer and would ideally consider the clinical, functional, and patient-reported health outcomes [29-31].

Digital phenotyping allows continuous and spatially and temporally precise quantification of individual's phenotype in his or her natural environment by using passively harnessed data from personal digital devices, including smartphone sensors [32,33]. Digital phenotyping approaches have been increasingly tested across mental health and somatic conditions [34], including amyotrophic lateral sclerosis [35], multiple sclerosis [36], posttraumatic stress disorder [37], depression [38], schizophrenia [39], sleep disorders [40], and spine disorders [41]. There is a growing body of evidence that passively generated data can allow identification of treatment complications and disease trajectories of patients with cancer. For example, the Helping Our Patients Excel study of 10 patients (mean age 60 [SD 11] years and mean Eastern Cooperative Oncology Group performance status of 1 [SD 0.66]) with gynecological cancer undergoing palliative chemotherapy found that passively acquired accelerometer data using wearable devices enabled the identification of high-risk patients and complications [42]. In another prospective observational study, 62 individuals undergoing elective cancer surgery were followed up using a smartphone app for a median of 147 (IQR 77-179) days after the surgery [43]. They found that exertional physical activity in patients who experienced postoperative events (27%) was lower than that in those who did not experience postoperative events, suggesting that this approach can allow to quantify recovery after cancer surgery [43]. However, these studies are limited by small to moderate sample sizes and consideration of a snapshot of cancer journey. Numerous barriers remain for implementing mobile-sensing data into the care of patients with cancer due to ongoing challenges related to raw data analysis and interpretation as well as integration of results in the clinical workflow [44]. Interpretation of passively collected data within clinical contexts requires multidisciplinary collaboration to identify potential clinical values of the mobile-sensing data. The analysis of passively harnessed sensing data is another important challenge, and it has been shown that deep learning approaches can be used to anticipate complications of patients undergoing treatment for hematologic malignancies [45]. Therefore, future studies are warranted to better understand the potential clinical values of mobile sensing data in oncology.

The aim of our study is to evaluate the usefulness of passively generated smartphone sensor data streams (as in digital phenotyping) for monitoring patients with cancer. We will evaluate if novel cancer trajectory biomarkers that integrate

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high-resolution passively acquired data streams from smartphone sensors with actively collected data can enable real-time data analytics and monitoring of patients with cancer in their natural environment. We will (1) develop and adapt a monitoring system tailored for patients with cancer that integrates passively and actively acquired data streams, (2) investigate if continuous monitoring of patients with cancer using passively collected data acquired through personal smartphones correlates with objective and patient-reported health status and therefore can be used as actionable digital phenotype, and (3) develop prediction models anticipating disease trajectories as well as functional and reported outcomes of patients with cancer. This study will allow to better understand the potential clinical value of passively generated smartphone sensor data (digital phenotyping) for continuous and real-time monitoring of patients with cancer for treatment side effects, cancer complications, functional status, and patient-reported outcomes, as well as prediction of disease progression or trajectories.

Methods

Study Design

This is a prospective observational cohort study with a 6-month follow-up of patients diagnosed with cancer who will use a smartphone app to acquire continuously generated data from smartphone sensors (passively generated data) and deploy questionnaires (actively generated data). This study is conducted at the Department of Oncology, Hospital of Lithuanian University of Health Sciences, Kaunas, Lithuania, in collaboration with Vytautas Magnus University, Kaunas, Lithuania, and ProIT, Vilnius, Lithuania.

Patient and Public Involvement

Patient involvement in this study will last for the duration of the study and will include continuous collection of smartphone sensor data, actively collected questionnaire data via LAIMA app, and 3 in-person visits. The patients and the public were not involved in the design of this study.

Recruitment

The study inclusion criteria are (1) diagnosis of cancer, (2) current active treatment (radiation therapy, chemotherapy) for cancer or surveillance, (3) ability to comprehend Lithuanian, (4) ownership of a smartphone device (Android or iOS platform) that can support the smartphone apps, (5) age of 18 years or older, and (6) ability to provide informed consent. Patients will be excluded if they have cognitive, visual, or functional impairment or any other clinically significant medical condition that in the opinion of the study investigators could affect participant safety, preclude evaluation of responses, or interfere with the ability to comply with the study procedures.

Ethics Approval

Ethics approval was obtained from the Kaunas Regional Bioethics Committee on April 14, 2022 (protocol BE-2-31). All participants will provide informed consent before inclusion in this study. Identifying data will be available for the study oncologists and will be deidentified for other members of the research team. Patients will not receive compensation for participating in this study.

Sample Size

The sample size was calculated using the Digital Phenotyping Power Calculator tool [46]. We plan to recruit 200 patients diagnosed with cancer undergoing active treatment and actively follow-up with them for at least 3 months, with expected missing data of <50% that will allow to achieve power (type 1 error .05) of .971 at effect size (β_1) of .03 and power of 1 and effect sizes (β_1) of .05 and .07.

Primary Outcome

We will examine changes in each of the collected digital biomarker data streams during the 6-month follow-up period in relation to progression-free survival. Cancer progression will be defined based on clinical, laboratory, and radiological data in accordance with guidelines and criteria for the specific cancer type. Cancer progression will be determined by the treating oncologist according to relevant clinical guidelines.

Secondary Outcome

We will examine temporal changes in questionnaire data trajectories collected using the LAIMA app and will examine the association of passively harnessed digital biomarkers with actively collected questionnaire data. We will also examine the association of passively acquired digital biomarker data with clinically relevant outcomes of patients with cancer, such as overall survival, cancer-related complications (type of complication, unexpected presentation to emergency department or hospital admission), and cancer treatment–related adverse events. The precision of digital biomarker data to identify and predict clinically relevant outcomes of patients with cancer will be examined.

Digital Data

Data will be collected using the LAIMA app that was developed by the researchers based on the open-source Beiwe platform [47]. The LAIMA app is supported by iOS and Android operating systems. We also developed a corresponding digital platform that is linked with the smartphone app and will be used for patient registration and remote monitoring by the study investigators.

The LAIMA app and digital platform will be used to collect and integrate (1) passively generated data streams from smartphone sensors that will be uploaded to the LAIMA platform and integrated with questionnaires and clinical data, (2) actively collected questionnaire data that study participants will be prompted to answer in predefined days at 2-week intervals after inclusion in this study, and (3) sociodemographic and clinical data that will be entered by the study investigators at initial and follow-up study visits. In this study, we will include questionnaires that are commonly used for clinical and cancer research and were validated in Lithuanian as well as clinical data that are relevant for patients with cancer. The data will be uploaded to the server and aggregated. We utilize cloud services for secure data storage as well as data preparation and predictive modeling using generated data. The LAIMA platform has several data preparation methods such as classification,

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clustering, regression, and ranking. The platform also has a built-in artificial intelligence algorithm function. The LAIMA app and platform are compliant with the European Union General Data Protection Regulation requirements [48]. Continuously and passively generated data from smartphone sensors will be collected during the course of this study that will take from 3 to 6 months for each patient included in this study. The following smartphone sensor data will be considered for this study:

1. Mobility data will include continuous collection and aggregation of passively generated data streams from the accelerometer (mean time of active period, mean time of exertional physical activity, distance covered per day, duration of inactive period), GPS (places of interest visited daily, hospital visits), and gyroscope.
2. Sociability indices will include continuous capture and aggregation of frequency of duration of phone calls, frequency and length of text messages, and internet browsing time.

Questionnaires

Eastern Cooperative Oncology Group Questionnaire

The Eastern Cooperative Oncology Group questionnaire will be used for the assessment of the functional status of patients with cancer during their clinic visits [49]. It is a widely used measure of the functional status of patients with cancer in clinical practice and in clinical trials.

European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire

The European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30) will be used for the assessment of quality of life of the study participants [50,51]. The EORTC QLQ-C30 will be deployed during study visits and via the LAIMA app. The EORTC QLQ-C30 consists of 9 multi-item functional scales and 6 single-item symptom scales that evaluate global health status, functional status, role functioning, emotional functioning, cognitive functioning, social functioning, fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties. Scores are linearly transformed to a scale ranging from 0 to 100, with higher scores indicating better health-related quality of life on global health status and functional status scales and worse health-related quality of life on symptom scales.

Patient Health Questionnaire-9

The Patient Health Questionnaire-9 (PHQ-9) will be used for the assessment of depressive symptom severity during study visits and via the LAIMA app [52,53]. The PHQ-9 consists of 9 symptoms of depression that respondents rate based on their severity during the preceding 2 weeks, with a greater score indicating greater depressive symptom severity and with scores of 10 or greater indicating moderate to severe depressive symptoms.

General Anxiety Disorder-7 Questionnaire

The General Anxiety Disorder-7 (GAD-7) scale will be used for the assessment of anxiety symptom severity during the study visit and via the LAIMA app [54,55]. The GAD-7 includes 7 questions pertaining to generalized anxiety disorder, with higher scores indicating greater anxiety symptom severity.

COVID-19 Fears Questionnaire

The COVID-19 Fears Questionnaire for chronic medical conditions will be used for evaluating fears related to the COVID-19 pandemic [56,57]. This questionnaire includes 10 items. Respondents are asked to select the response that reflects how much each statement describes their experience on a typical day in the last week on a 5-point numerical scale ranging from 1 (not at all) to 5 (extremely). The total score is the sum of all items and ranges from 10 to 50, with higher scores reflecting greater COVID-19 fear. The questionnaire has been validated in Lithuania [56] and will be administered during the study visits.

Questionnaire Administration

The Eastern Cooperative Oncology Group questionnaire, EORTC QLQ-C30, PHQ-9, GAD-7, and the COVID-19 Fears Questionnaire for chronic medical conditions will be administered by trained clinicians. Deidentified data will be entered into a database, and hard copy documents are kept on-site under lock and key. EORTC QLQ-C30, PHQ-9, GAD-7 will also be deployed via the LAIMA app to study participants in predefined 2-week intervals via text messages and a secure link to the website. Participants will have 2 days to complete each questionnaire. The data will be uploaded to the LAIMA digital platform and integrated with other data sources for each patient.

Sociodemographic Data

We will consider patients' age at the time of cancer diagnosis and study inclusion, gender, education, job, and marital status. The type of smartphone device and operating system (Android, iOS or other) will be recorded.

Clinical Data

Information about cancer diagnosis, cancer location, presence of distant metastases, and tumor, node, metastasis stage at time of study inclusion, date of cancer diagnosis, and pathology results, including relevant molecular data, will be recorded at the initial study visit. We will record information regarding currently active cancer treatment(s), including radiation therapy (dose, target, and number of fractions) and chemotherapy (chemotherapeutic agent and dose and treatment start and finish dates). We will also gather information about all previous cancer treatments (surgery, radiation therapy, and chemotherapy), including their date, radiation dose, and chemotherapeutic agent(s). Information about comorbidities and currently used medication will be considered.

At 2 follow-up visits that will take place at 1-3 months and 3-6 months after patient inclusion in the study, we will record information pertaining to cancer treatment (chemotherapy, radiation therapy, and other) that is ongoing or that the patient has received during the follow-up period. Disease progression

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and its date will be evaluated using standard clinical assessment studies and relevant criteria. Treatment complications (date and description) and unanticipated visits to the emergency department (date and description) will be recorded for all study patients. Disease progression and complications of patients who will not be able to attend the follow-up visit will be evaluated by reviewing medical records or via phone interviews. All clinical and sociodemographic data will be recorded and entered into the LAIMA platform by the study investigators who are board-certified oncologists.

Detailed Procedure

Baseline Visit

At the baseline visit, the study investigator will inform the patients about the study and procedures, and informed consent will be obtained. Participants will complete a battery of questionnaires that will be administered by the study investigators (Table 1). The LAIMA app will be installed into the participant's personal smartphone device, and an account will be created. Participants will be provided with a personal password and informed about the procedures in case he or she decides to withdraw from the study. The study investigators will ensure that the passively acquired data are being properly collected from a smartphone device by registering in the LAIMA platform.

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Table 1. Study protocol.

	Visit 1 (month 0)	Data collected using smartphone app	Visit 2 (months 1-3)	Visit 3 (months 3-6)
Data collected only at initial visit				
Informed consent	✓			
Installation of mobile app	✓			
Demographic and sociodemographic data	✓			
Clinical data	✓		✓	✓
Treatment complications and adverse events	✓		✓	✓
Functional status (Eastern Cooperative Oncology Group)	✓		✓	✓
Health-related quality of life (EORTC QLQ-C30[a])	✓		✓	✓
Symptoms of depression (Patient Health Questionnaire-9)	✓		✓	✓
Symptoms of anxiety (General Anxiety Disorder-7)	✓		✓	✓
COVID-19 Fear (COVID-19 Fear Questionnaire)	✓		✓	✓
Questionnaire data collected using smartphone app (every 2 weeks)				
Health-related quality of life (EORTC QLQ-C30)		✓		
Symptoms of depression (Patient Health Questionnaire-9)		✓		
Symptoms of anxiety (General Anxiety Disorder-7)		✓		
Passively collected data using smartphone app (continuous)				
Accelerometer		✓		
Gyroscope		✓		
GPS		✓		
Phone on or off		✓		
Phone calls		✓		
Phone calls		✓		
Text messages		✓		
Internet browsing time		✓		

[a]EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Core Quality of Life questionnaire.

Follow-up Visits

All study patients will complete follow-up visits at months 1 to 3 and months 3 to 6 after the study inclusion. Follow-up visits will take place during routine clinical visits or via telephone encounter. We anticipate that most follow-up encounters will take place during in-person clinic visits. At follow-up visits, patients will complete the study questionnaires, and relevant clinical, laboratory, and imaging data will be reviewed for assessment of disease progression and treatment-related adverse events (Table 1). Given the observational nature of this study, patients will undergo clinical, laboratory, and imaging evaluation as clinically indicated and per appropriate guidelines because we will include patients with different cancer diagnoses undergoing different treatments. At the end of month 6 of the study or in case of patient death, the app will be remotely uninstalled from the device. Monitoring of passively generated data via smartphone sensors and actively collected questionnaire data via LAIMA app collection and upload in the platform will be conducted daily. Patients without passively generated or uploaded data for 3 days or more will be contacted by the study investigators, and problems will be resolved.

Data Analysis

Data cleaning will be performed on both active and passive data. The main cleaning tasks will be removing errors,

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identifying outliers, and filling the missing data. Moreover, data will be transformed using aggregation and normalization methods. Missing data from smartphone sensors will be restored using data recovery extension (Firebase Cloud Messaging). For small numbers of missing observations, the missing values will be inputted using linear or polynomial interpolation methods (data imputation will not be used for mixed effects regression models). Cases with more than half of the smartphone sensor data missing will be excluded from the analyses. Missing answers in a questionnaire will not be considered in the analyses, and data imputation will not be performed as it could skew the results of the analyses. A descriptive analysis (mean, SD, median, relative frequencies for qualitative variables) of all the variables will be performed. To investigate associations among digital, clinical, and patient-reported health outcomes, χ^2 test (qualitative characteristics) or 2-sided *t* test or Mann-Whitney (quantitative characteristics) *U* test will be conducted. To visualize data, boxplots, bar plots, and heatmaps will be used. In the initial exploratory analyses, we will analyze each digital biomarker separately that will be followed by their aggregation to identify the most informative biomarkers and their sets for different clinical and patient-reported outcome measures of patients with cancer. Mixed effects regression models will be used for the analysis of longitudinal data obtained from smartphone sensors. For all hypotheses, statistically significant differences will be evaluated at a significance level of .05, and multiple comparison adjustments will be performed. Statistical analysis will be employed using SPSS software (version 27; IBM Corp) and RStudio (version 2022.12.0+353; Posit, PBC).

Results

Patient recruitment and data collection are expected to be completed by September 2023. As of July 2023, we have reached the planned recruitment target, and patients are undergoing follow-up. The final results of this study should be available within 6 months after the study completion.

Discussion

In this prospective observational cohort study, 200 patients with cancer will be followed up for 6 months by using (1) continuously and passively generated data from sensors (accelerometer, gyroscope, GPS) of smartphone devices (digital phenotyping) and (2) actively collected data using questionnaires for assessment of quality of life, symptoms, depression, anxiety, and COVID-19 fear. Disease progression and treatment complications will be evaluated during clinic visits. This study will allow to better understand the potential value of passively generated data from smartphone sensors for remote real-time monitoring of patients with cancer and anticipation of disease progression or trajectories, treatment complications, and unfavorable patient-reported outcomes.

Digital phenotyping is a promising approach in oncology that enables utilization of data that are passively generated by patients in their natural environments. It is a user-friendly approach because it uses personal digital devices, thus causing limited interruption of daily routine and device use habits. High and growing adoption of smartphones across age groups underscores the scalability of digital phenotyping approaches [58]. However, the barriers for deploying and integrating the digital phenotyping approach in oncology workflow should be considered and addressed, including data privacy and security concerns and participant willingness to share data. Caveats of analysis of passively generated data and its integration with routinely collected clinical and patient-reported data should be overcome to provide clinically meaningful digital biomarkers that can provide additional clinical value above and beyond the standard of care of patients with cancer. Emerging evidence suggests that this approach can be promising to predict the complications of cancer treatment [42,43]. However, it remains largely unclear if this approach can accurately prognosticate disease and treatment trajectories of patients with cancer. Our findings will allow us to better understand the potential clinical value of digital biomarkers for the prediction of clinical and patient-centered trajectories of patients with cancer.

The limitation of this study is the inclusion of patients with different cancer diagnoses and undergoing various treatments that can have a direct impact on the digital biomarkers included in this study. However, this will allow us to better understand which patients could potentially benefit the most from such a monitoring approach. The use of sensors of personal smartphone devices will provide real-world data with regard to patient behavior in their natural home environment but is subjected to individual differences of smartphone use habits. We hope that our study will provide further insights regarding the value of digital biomarkers and will be used to inform the planning and implementation of interventional clinical trials in oncology.

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Data Availability

Data will be available 6 months after study completion.

Conflicts of Interest

None declared.

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Abbreviations

EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire
GAD-7: General Anxiety Disorder-7
mHealth: mobile health
PHQ-9: Patient Health Questionnaire-9

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Protocol

An eHealth App (CAPABLE) Providing Symptom Monitoring, Well-Being Interventions, and Educational Material for Patients With Melanoma Treated With Immune Checkpoint Inhibitors: Protocol for an Exploratory Intervention Trial

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Abstract

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Background: Since treatment with immune checkpoint inhibitors (ICIs) is becoming standard therapy for patients with high-risk and advanced melanoma, an increasing number of patients experience treatment-related adverse events such as fatigue. Until now, studies have demonstrated the benefits of using eHealth tools to provide either symptom monitoring or interventions to reduce treatment-related symptoms such as fatigue. However, an eHealth tool that facilitates the combination of both symptom monitoring and symptom management in patients with melanoma treated with ICIs is still needed.

Objective: In this pilot study, we will explore the use of the CAPABLE (Cancer Patients Better Life Experience) app in providing symptom monitoring, education, and well-being interventions on health-related quality of life (HRQoL) outcomes such as fatigue and physical functioning, as well as patients' acceptance and usability of using CAPABLE.

Methods: This prospective, exploratory pilot study will examine changes in fatigue over time in 36 patients with stage III or IV melanoma during treatment with ICI using CAPABLE (a smartphone app and multisensory smartwatch). This cohort will be compared to a prospectively collected cohort of patients with melanoma treated with standard ICI therapy. CAPABLE will be used for a minimum of 3 and a maximum of 6 months. The primary endpoint in this study is the change in fatigue between baseline and 3 and 6 months after the start of treatment. Secondary end points include HRQoL outcomes, usability, and feasibility parameters.

Results: Study inclusion started in April 2023 and is currently ongoing.

Conclusions: This pilot study will explore the effect, usability, and feasibility of CAPABLE in patients with melanoma during treatment with ICI. Adding the CAPABLE system to active treatment is hypothesized to decrease fatigue in patients with high-risk and advanced melanoma during treatment with ICIs compared to a control group receiving standard care. The Medical Ethics Committee NedMec (Amsterdam, The Netherlands) granted ethical approval for this study (reference number 22-981/NL81970.000.22).

Trial Registration: ClinicalTrials.gov NCT05827289; https://clinicaltrials.gov/study/NCT05827289

International Registered Report Identifier (IRRID): DERR1-10.2196/49252

(JMIR Res Protoc 2023;12:e49252) doi:10.2196/49252

KEYWORDS

eHealth; melanoma; fatigue; quality of life; intervention; pilot study; QoL; cancer; oncology; HRQoL; fatigue; symptom; symptoms; monitoring; adoption; acceptance; patient education; digital health; immune checkpoint inhibitors; immunotherapy

Introduction

In recent years, the introduction of immunotherapy with immune checkpoint inhibitors (ICIs) has significantly improved the clinical outcome of patients with melanoma and has become the standard of care [1-4]. However, treatment with ICIs is associated with short- and long-term immune-related adverse events (AEs) [5-7], most commonly fatigue [7,8], and a deteriorated health-related quality of life (HRQoL) [6,9,10]. Some studies have reported that inadequate symptom monitoring and reporting (eg, under detection) can lead to worsening of AEs and more frequent emergency department visits and hospitalizations [11-13]. Therefore, enhanced symptom monitoring in the general cancer population as well as in this specific patient population is necessary. Furthermore, enhanced symptom monitoring is associated with improved clinical outcomes (eg, survival and adverse event management) and improved HRQoL in patients with cancer treated with chemotherapy [14-17].

One approach to monitoring symptoms and potentially enhancing patient-centered care can be the periodic collection of symptom information through patient-reported outcome measures by using eHealth tools [18,19]. Results from several studies show that web-based symptom monitoring tools are also beneficial for patients with cancer receiving ICIs [20-22]. However, in one study specifically, the use of an electronic patient-reported outcomes tool alone in patients with melanoma treated with ICIs could not reduce the number of severe AEs. Despite there being no impact on reducing the number of severe AEs, the intervention group had significantly better HRQoL outcomes compared to the control group as measured by the utility scores of the EQ-5D (P=.05) [22,23]. Furthermore, home monitoring by biometrical sensors could have the potential to detect symptoms (complementary) and monitor physical activity in outpatient oncology settings, although this has not been extensively researched [24,25].

As cancer-related fatigue (CRF) is the most common symptom experienced by patients with melanoma during and after ICIs [8] and a common problem in patients with cancer in general [26,27], much effort has been made to develop interventions to address this, as CRF negatively impacts HRQoL [26,28]. Current recommendations for all patients with cancer suggest encouraging physical exercise and providing psychosocial interventions and psychoeducation [28]. Multiple studies investigating these interventions have shown a decrease in fatigue and an increase in HRQoL [29-34]. Furthermore, mindfulness-based clinical interventions and yoga appear to be feasible interventions, and beneficial effects have been reported on several physical and psychosocial symptoms in patients with cancer, such as patients' psychosocial adjustment to their disease and improvement of biomarkers of stress, inflammation, and immune function [35-37]. Encouraging physical exercise, psychoeducation, mindfulness-based interventions, and yoga have therefore been included in web-based programs and eHealth apps targeting CRF, with promising results [38-41].

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eHealth apps may also contribute to addressing the unmet care and information needs of patients [42,43]. Patients with melanoma during and after targeted therapies or ICIs have extensive needs for supportive care, information provision, and symptom management, specifically with regard to clinical- and self-management topics, CRF management, and available supportive care services [43]. By providing remote monitoring and information provision through an eHealth tool, patients believe this will positively affect their HRQoL and symptom burden [43].

This study will investigate the extensively pretested (manuscript in preparation) CAPABLE (Cancer Patients Better Life Experience) eHealth app providing information and supportive care, symptom monitoring, and well-being interventions (as part of the European Union's Horizon 2020 research and innovation program under grant agreement number 875052). CAPABLE functionalities are accessible for patients through a mobile app, connected to a smartwatch, and available for health care professionals (HCPs) through a web portal. In this pilot study, we will explore the effect of using CAPABLE on HRQoL outcomes such as fatigue and physical functioning and patients' acceptability of using a system like CAPABLE. The results of this pilot trial will be compared with a historical prospective cohort of patients with the same characteristics but without CAPABLE. We hypothesize that patients using the CAPABLE app will have a reduced increase in fatigue in the first 3-6 months of treatment compared to patients in the control cohort.

Methods

Overview

The CAPABLE study is a prospective, exploratory pilot study in which we compare an exploratory cohort that receives the CAPABLE smartphone app and a multisensory smartwatch (intervention) to a historical prospective cohort that did not receive the CAPABLE app and smartwatch (control group). The control group (NL75996.031.20) consists of patients with the same inclusion criteria and self-reported data collection as the intervention group but receives standard care without the CAPABLE app (eg, the patient calls the hospital when a symptom is experienced and has a blood analysis and follow-up appointment with a nurse practitioner before every ICI infusion). The initial plan of the CAPABLE consortium was to perform a randomized trial, but due to time constraints in the project, development issues, and the COVID-19 pandemic, we were not able to set up a randomized study and include the needed number of patients because of the limited numbers of patients with melanoma in the restricted and foreseen time period. No data safety monitoring board is in place due to the low risk of the intervention, as assessed by the internal data security team. The results of the study will be published in international peer-reviewed journals.

Study Population

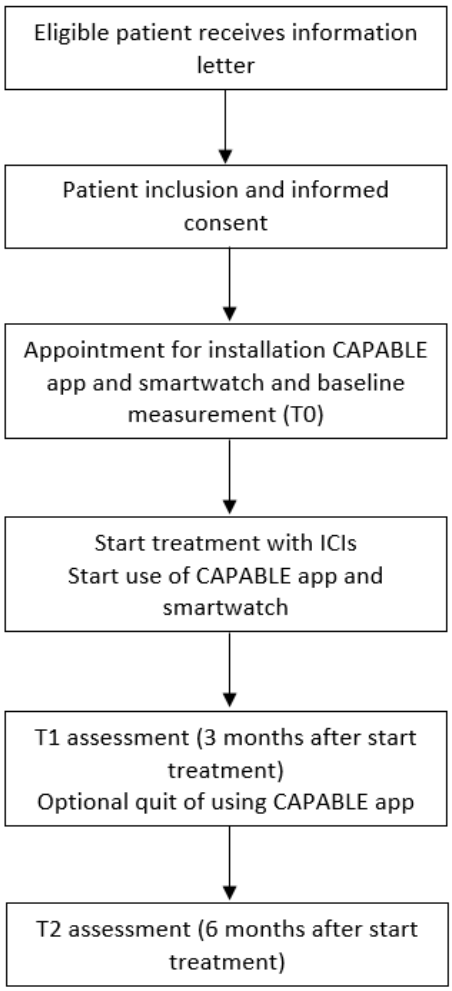
This study aims to include 36 patients with histologically confirmed stage III or IV melanoma eligible for starting treatment with ICIs (anti-PD1 or anti-CTLA4) according to standard clinical practice. In order to be eligible to participate in this study, a subject must be >18 years of age, have a sufficient understanding of the Dutch language, and be able to use a smartphone. Patients are excluded if they are included in an experimental clinical trial.

Recruitment and Data Collection

Patients will be recruited over a period of 6 months at the Netherlands Cancer Institute (NKI) in Amsterdam, a comprehensive cancer center. Eligible patients will be invited to participate in the study by their treating physician approximately 2 weeks before the start of treatment during an outpatient visit. Patients will then receive an information letter about the study from the physician or coordinating researcher. After receiving written informed consent from the patient, the patient will be enrolled in the CAPABLE system. Consenting patients will have an intake appointment with the research team before their first ICI infusion to install and set up the CAPABLE app and smartwatch. Furthermore, patients will receive a verbal explanation and an instruction manual on how to use the CAPABLE app. Patients will be asked to use the smartphone app for a minimum of 3 to a maximum of 6 months after the start of ICI treatment. In case the patient is not using the system or is not wearing the smartwatch for at least 2 weeks, the research team will contact the patient to assess possible technical issues or drop out for other reasons. Research data are collected at the intake appointment at baseline (T0), 3 (T1), and 6 months (T2) after the start of treatment (Figure 1). Data will be extracted from medical records and validated questionnaires. The patient will receive a link to a digital platform (ALEA, FormVision) through email to fill out the questionnaires. Reminders will be sent to patients' emails if the questionnaires are not completed after 2 weeks or if they are asked to fill them out during a follow-up visit in the hospital. Clinical data (eg, staging, treatment details, and demographics) will be extracted from the medical record during the study. Data will be coded and only accessible by the NKI research team on a secured server. Patient recruitment and data collection started in April 2023 and are currently ongoing.

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Figure 1. CAPABLE study flowchart. CAPABLE: Cancer Patients Better Life Experience; ICI: immune checkpoint inhibitor.



CAPABLE Intervention

Overview

CAPABLE is an eHealth tool consisting of front end and backend components (mobile app and smartwatch for patients, web-based dashboard for HCPs) that users interact with and that provide functionality related to decision support and coaching. CAPABLE monitors treatment-related symptoms and well-being and provides patients with extensive educational material and nonpharmacological evidence-based interventions called Virtual Capsules (VCs). VCs are developed using Fogg behavioral model [44] to help patients turn the proposed interventions into healthy habits. CAPABLE consists of several components that run on the backend of the system. Patient-reported information is made available to HCPs through the physician web dashboard, which can only be accessed by users in the private network of the hospital using personal credentials to login. Around 15 HCPs (medical oncologists and nurse practitioners in training) involved in the treatment of enrolled patients have access to the CAPABLE dashboard. Compared to usual clinical care, the CAPABLE dashboard is checked daily by the HCPs to see new alerts for entered symptoms or questionnaires. Besides this, existing care structures stay in place and symptom management is the same as in usual care. Figure 2 shows the overall structure of the CAPABLE system. CAPABLE will be connected 1-sided to the electronic health record (EHR), meaning the CAPABLE system can extract EHR data but cannot write back data into the EHR. Each component of the CAPABLE system will be deployed on a Virtual Machine provided by the hospital. Access to the Virtual Machines for the CAPABLE software developers will be possible through dedicated virtual private networks set up by NKI's information technology staff.

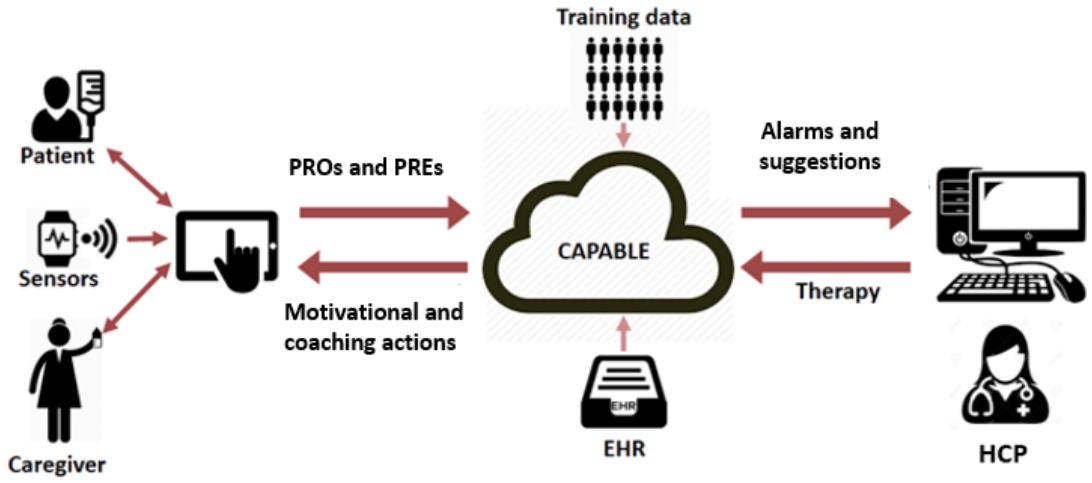
During the use of the CAPABLE system, the patient will be able to perform the following set of activities through the smartphone app:

- Report symptoms using a self-developed 130-item list derived from and based on the National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5 [45] and the Patient-Reported Outcome version of the CTCAE (PRO-CTCAE) standard term lists [46], which are considered self-reportable by the CAPABLE clinical expert team;
- Tracking and viewing activities and vital signs when wearing the smartwatch;
- Answer to periodic questionnaires concerning mental well-being;
- Work on well-being goals (eg, sleep improvement, improving physical or mental well-being, accepting the cancer journey) through interventions delivered by VCs;

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- Access evidence-based educational material regarding disease, treatments, side effects, lifestyle, well-being interventions, supportive care, and links to peer support.

Figure 2. Overall structure of the CAPABLE system; the CAPABLE backend (depicted as a cloud) is shown in the middle and connects to the mobile app on the patient side and the web-based dashboard on the HCP's side. CAPABLE: Cancer Patients Better Life Experience; EHR: electronic health record; HCP: health care professional; PRE: patient-reported experience; PRO: patient-reported outcome.



Symptom Monitoring

The CAPABLE smartphone app facilitates patient symptom reporting at any moment in time, based on when a symptom occurs for this patient. Patients can access their app, choose a symptom from the symptom list, and select the symptom description that matches their experience of the symptom. For each symptom, the patient can select the symptom description that matches the patient's experience of the symptom in terms of severity and impact on activities of daily living. These descriptions allow the CAPABLE app to get specific information about the experienced symptom and give appropriate feedback and advice to the patient and HCPs. Since the NCI's CTCAE grading system is intended for use by HCPs, it cannot be directly exploited as a symptom reporting system for patients. Furthermore, NCI's PRO-CTCAE list was not considered fully suitable for the purposes of CAPABLE. Therefore, we created a symptom list based on the full CTCAE list, from which we removed AEs that were not detectable by a patient or his or her caregiver, used a priority scoring system of involved HCPs, and made the remaining symptom list patient-friendly, when possible exploiting the PRO-CTCAE descriptions. The descriptions were constructed by following the structure of the PRO-CTCAE monitoring, namely, defining the symptom severity as "mild," "moderate," "severe," or "very severe" and defining interference with usual or daily activities as "a little bit," "somewhat," "quite a bit," and "very much." In addition, the CTCAE terms of the symptoms and information from the CTCAE grades were incorporated in the symptom description to help the patient distinguish between a "mild," "moderate," "severe," or "very severe" symptom. Symptoms can be mapped to grades in CTCAE version 5.

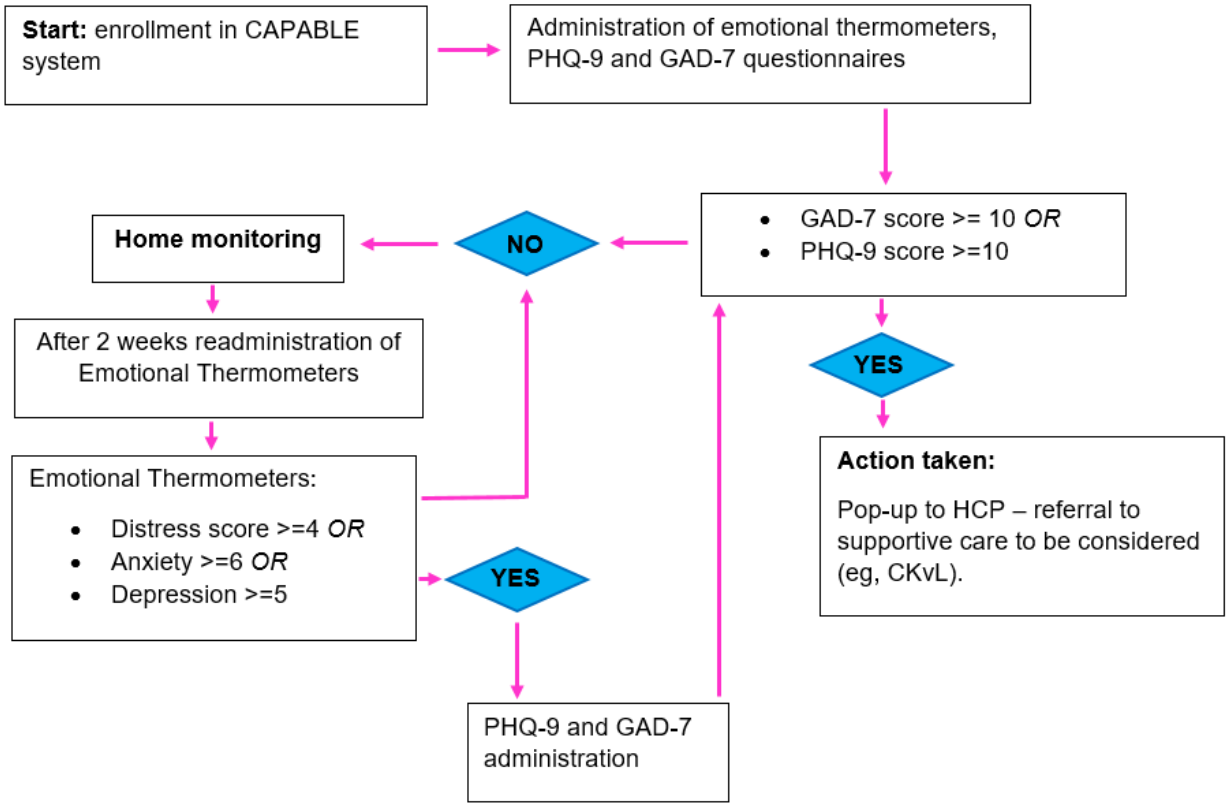
After a patient reports a symptom, the CAPABLE clinical decision support system provides feedback that is based on implemented computer-interpretable clinical guidelines for immunotherapy toxicity management (based on CTCAE version 5) and contact levels defined by participating clinicians. For example, the CAPABLE system can assign self-care instructions to the patient after reporting low-grade skin toxicity and will also send an alert to the HCP [5]. After clinical assessment of the entered symptom, the HCP can further decide how to manage the symptom [5]. The HCP will be able to report symptoms after seeing the patient during an outpatient visit. The list of symptoms provided to HCPs on the dashboard includes the full list of CTCAE terms and the related grading. Furthermore, the HCP receives specific recommendations related to the management of the reported symptoms. The dashboard is checked every workday by the HCPs. During the weekends, patients are instructed to call the hospital in cases of severe symptoms.

Monitoring Mental Well-Being

Besides the symptoms related to immunotherapy, the CAPABLE app also facilitates home monitoring of mental well-being through Distress (Emotional) Thermometers [47] and 2 protocolled and validated questionnaires: the Patient Health Questionnaire-9 (PHQ-9) [48] and Generalized Anxiety Disorder-7 (GAD-7) scale [49]. The management of the questionnaire outcomes is also performed by the CAPABLE clinical decision support system and is based on clinical cutoffs [49,50]. The management strategies have been thoroughly discussed with support consultants in the hospital and will allow a possible earlier referral to supportive care in the Center for Quality of Life in the hospital for further follow-up. The complete workflow for psychological follow-up is shown in Figure 3.

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Figure 3. Psychological workflow in the CAPABLE system. CAPABLE: Cancer Patients Better Life Experience; CKvL: Center for Quality of Life; GAD-7: Generalized Anxiety Disorder-7; HCP: health care professional; PHQ-9: Patient Health Questionnaire-9.



Educational Material

In a previous study, we identified unmet information needs in patients with melanoma treated with ICIs and how this could be integrated into an eHealth tool [43]. Based on this study, we have developed a content list of information that should be provided in the CAPABLE app as educational material [43]. In more detail, the content of the educational material in the CAPABLE app consists of extensive information on the following topics:

- General melanoma content (diagnosis, diagnostic methods, causes, and prevention)
- Treatment with ICIs (information on the different immunotherapies)
- Side effects of ICIs (detailed descriptions per side effect)
- Experiences from fellow patients and peer support
- Supportive care options
- Nutrition
- Work and cancer
- Intimacy, sexuality, and cancer
- Adolescence and young adult care
- Other relevant topics (with links to external resources)

The content is created from evidence-based information leaflets already offered by the hospital and the European Society for Medical Oncology. Medical specialists and supportive care consultants from the hospital checked all content that was embedded in the CAPABLE mobile app.

Well-Being Interventions

CAPABLE offers patients a set of functionalities to set goals to work on various aspects of mental, physical, and social well-being at home. The interventions added to the CAPABLE system are nonpharmacological, evidence-based interventions that have been shown to improve the mental and social well-being of patients with cancer, as well as other stress-related conditions such as sleep problems and fatigue. The process works by setting specific goals for the patients (eg, sleep improvement) and selecting specific interventions to achieve those goals. Goal setting and intervention selection will be done together by the patient and HCP during the intake appointment, which facilitates shared decision-making. Interventions can serve multiple goals at once. It is always possible for the HCP to contraindicate an intervention for the patient if the conditions to perform the related activity are not met. The interventions available in the CAPABLE app and their related goals are listed below:

- Thai Chi (goals: improve sleep and insomnia, mental well-being, physical well-being) [51]
- Yoga Hatha or Nidra (goals: improve sleep and insomnia, mental well-being, physical well-being) [28]
- Walking in nature (goals: improve sleep and insomnia, mental well-being, physical well-being) [28]
- Breathing exercises and mindfulness (goals: improve sleep and insomnia, mental well-being)
- Imagery meditation (goals: improve sleep and insomnia, mental well-being) [52]

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- Photo diary (goals: mental well-being, accepting the cancer journey) [53]
- Gratitude journal (goals: mental well-being, accepting the cancer journey) [54,55]

Smartwatch

Patients will also be provided with a smartwatch (the ASUS VivoWatch 5 HC-B05), which will be set up during enrollment. To ensure proper communication with the ASUS Life cloud platform (OmniCare), an additional app (OmniCare Hub, provided by ASUS Life) needs to be installed on the patients' smartphones. The smartwatch will collect data on heart rate and blood pressure, sleep (stages, hours, and performance), physical activity, and stress. However, data from the smartwatch is treated as ancillary data and will not be used for symptom monitoring or diagnosis.

Study End Points

Primary Outcome

The primary end point of this study is the change in fatigue between baseline and 3 and 6 months, as measured by The European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) [56]. The changes in fatigue over time in the intervention cohort will be compared to the changes in fatigue over time in the control cohort. Fatigue is constructed out of 3 questions: "Did you need to rest?" "Have you felt weak?" "Were you tired?" Responses range from 1 (not at all) to 4 (very much) and are linearly transformed into a fatigue scale ranging from 0 to 100, with higher scores representing more experienced fatigue.

Secondary Outcomes

Secondary end points of this study are changes in physical symptoms and functioning scales [56], melanoma-specific HRQoL [57], utilities used for establishing quality-adjusted life years [58], anxiety and depression [59], patient-reported immune-related AEs and information needs [60] (Table 1). Furthermore, we will assess feasibility and patient-reported usability outcomes [61-63] at different time points (Table 1). Additionally, component-specific technical end points (clicks or completion of content in the patient app, accepted recommendations or clicks in the HCP dashboard), referrals to additional care, and the number of emergency visits will be measured.

HCPs using the CAPABLE system will retrieve extensive self-developed usability questionnaires consisting of questions about expectations, overall satisfaction, perceived impact, technical errors, ease and usefulness, efforts and resources, and the validated System Usability Scale (SUS) [64]. HCPs will receive these questionnaires after the first patient enrollment, after 1 month of using the system, and at the end of the study. They are covered in a different approved study protocol (P23CAP; IRBd23-012).

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Table 1. Study end points and corresponding questionnaires.

Description of outcome	Assessment	T0	T1	T2
Sociodemographic data, disease, and treatment characteristics	Sociodemographic and clinical data will be abstracted from medical records or reported by the patient through the CAPABLE application[a]	✓	✓	✓
Primary end point				
PROMs[b]				
Fatigue	EORTC QLQ-C30 [56][c,d]	✓	✓	✓
Secondary end points				
PROMs				
Physical-, social-, emotional-, cognitive- and role functioning, symptoms, and overall HRQoL[e] (summary score)	EORTC QLQ-C30 [56]	✓	✓	✓
Melanoma-specific HRQoL	Functional Assessment of Cancer Treatment-Melanoma (FACT-M) [57][f]	✓	✓	✓
Self-rated health and economic evaluation	EQ-5D-5L [58][g]	✓	✓	✓
Anxiety and depression	Hospital Anxiety and Depression Scale (HADS) [59][h]	✓		✓
Immune-related adverse events	Immunotherapy-specific questionnaire (EORTC item bank)[i]	✓	✓	✓
Information needs and satisfaction	EORTC QLQ-INFO25 [60][j,k]	✓		✓
Usability				
User friendliness and usability	System Usability Scale (SUS) [61]		✓	
Patient trust to health service	Patient Trust Assessment Tool (PATAT) [62]		✓	
Quality of mobile health apps	User Version of the Mobile Application Rating Scale (uMARS) [63]			✓
Feasibility				
Recruitment rate	Percentage of patients included in the study out of the eligible patients	✓	✓	✓
Patient compliance	Percentage of patients completing the questionnaires	✓	✓	✓
Patient retention	Percentage of patients adhering to the app	✓	✓	✓

[a]CAPABLE: Cancer Patients Better Life Experience.

[b]PROM: patient-reported outcome measure.

[c]EORTC: European Organization for Research and Treatment of Cancer.

[d]QLQ-C30: Quality of Life Questionnaire-Core 30.

[e]HRQoL: health-related quality of life.

[f]Of the FACT-M, we use the Melanoma Subscale and the Melanoma Surgery Subscale, items specific to quality of life in patients with melanoma. High scores show a high quality of life. Testing has shown that the FACT-M is a reliable and valid instrument to assess quality of life in patients with melanoma.

[g]The EQ-5D is a standardized 5-level, 5-dimensional multi-attribute utility questionnaire that measures mobility, self-care, usual activities, pain/discomfort and anxiety/depression, using a five dimension scale.

[h]Psychological distress will be assessed with the Hospital Anxiety and Depression Scale (HADS). The HADS, a 14-item questionnaire, assesses symptoms of mood disturbance, yielding separate scale scores for anxiety and depression, as well as a total score.

[i]Immunotherapy-specific questionnaire. In assessing quality of life in patients with cancer, it is recommended to use a generic and cancer-specific measure of quality of life plus a treatment-specific questionnaire. However, to date the available validated measurements do not include the problems and symptoms of immunotherapy. Therefore, we identified, based on literature and expert opinion, 19 symptoms and created a symptom list based on items of the EORTC item Library.

[j]Fulfilment of information needs will be measured by the EORTC QLQ-INFO25 questionnaire. This validated 25-item questionnaire incorporates four information provision subscales: perceived receipt of information about the disease, medical tests, treatment and other care services.

[k]QLQ-INFO25: Quality of Life Questionnaire-Information 25.

Sample Size Calculation

As this is an exploratory study, a rough sample size calculation was performed based on preliminary changes in fatigue in the control cohort and feasibility parameters. In the control cohort (currently composed of 70 patients with melanoma that started with ICIs), an increase of 15 points in fatigue is shown in the first 3 months of treatment (nonpublished data). When providing the CAPABLE system to patients in the pilot study, we expect

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significantly less worsening of patients' fatigue levels (by 5 points less increase in fatigue). With a 10-point difference and an SD of 20, the selected effect size is 0.5. Since the inclusion period is restricted to 6 months due to project obligations, we use an enrollment ratio of 0.3 (two-third of the control cohort and one-third of the CAPABLE cohort). Together with a 2-sided α of .05 and an accepted power of 70%, the needed sample size would be 139 patients, of whom 107 will be enrolled in the control cohort and 32 will be enrolled in the CAPABLE pilot study. We anticipate a dropout rate of 5%-10% because of unforeseen rapidly progressive diseases that might occur in this patient population. Questionnaire dropouts are considered minimal because the research team will see the patient around their 3- and 6-month follow-up at the patient's hospital appointments. A compliance rate of 60% to participate in and use the CAPABLE system is considered feasible and clinically acceptable, meaning 36 patients have to be included to meet this feasibility end point. Therefore, we need to have 60 eligible patients in the 6-month inclusion period.

Statistical Methods

Descriptive statistics will be calculated to provide information about the patient population. The mean scores of fatigue and other questionnaire outcomes will be calculated using algorithms in the existing literature, and these scores will be used as end points for analyses. Summarizing and visualizing methods such as line graphs will be used to make the data more interpretable. Effect sizes will be calculated using standard statistical procedures. The difference in fatigue (improvement or worsening) over time (baseline and follow-up moments) will be analyzed either using a linear mixed model or generalized estimating equation analysis. We will adjust for baseline patient-reported outcome scores and other covariates such as sociodemographic variables, disease, and treatment characteristics. To compare the mean fatigue scores between the group receiving the CAPABLE intervention and the control group at each individual time point, we will use *t* tests or Mann-Whitney U tests. Patients will be individually matched on sex, age, tumor staging (stage III or IV), and treatment (mono- or combination therapy). For differences in fatigue between the groups over time, we will use repeated measures ANOVA. A *P* value of <.05 will be seen as statistically significant; however, according to Cocks et al [65], a mean difference in change scores (per subdomain) can be seen as clinically relevant even if this is not statistically significant. Therefore, statistical and clinically meaningful differences will be analyzed. However, as this is an exploratory study, analysis will mostly consist of descriptive statistics, as *P* values are expected to render most outcomes nonsignificant.

Missing items from the questionnaires will be imputed according to the corresponding guidelines. The scale scores of the EORTC QLQ-C30 will be set to missing if fewer than half of the items on a given scale are answered. Where at least 50% of the relevant scale scores will be present, the missing values can be replaced by the mean of the present values. Statistical analyses will be done using R (R Core Team) [66].

Patient and Public Involvement

One of the CAPABLE consortium members is an Italian patient association that was involved in the development of the CAPABLE app. Furthermore, the development of CAPABLE went through multiple research phases. Patient and clinician interviews were held to establish baseline needs and wish for the CAPABLE system (P20CAP; IRBd20-085), of which a paper is published [43]. HCPs provided valuable input for the clinical validation of the implemented guidelines. Furthermore, multiple patients and HCPs provided their valuable input to enhance the quality of the system during the development of the CAPABLE app through multiple usability testing rounds (P21CAP; IRBd21-139). The results of the study will be communicated to participants if wish.

Ethics Approval

Ethical approval was granted by the Medical Ethical Committee of NedMec (Amsterdam, The Netherlands) under reference number 22-981/NL81970.000.22. Any amendments will be reviewed by this Medical Ethical Committee. CAPABLE is registered as a medical device trial according to the Medical Device Regulation, article 62. The trial is prospectively registered at ClinicalTrials.gov (NCT05827289). Original informed consent signed by patients allows for the analysis of the primary and secondary outcomes of this study. In case additional data needs to be analyzed, additional informed consent will be asked. Subject data will be pseudonymized and key-coded. No compensation is provided to participating patients. This study is conducted in accordance with the principles of the Declaration of Helsinki, version 9, October 2013, and the Medical Research Involving Human Subjects Act (WMO), including International Organization for Standardization (ISO) 14155 (medical device use).

Results

Inclusion in this trial started late in April 2023 and is currently enrolling. We expect to finalize inclusion by the end of August 2023. The expected last follow-up measurement will be collected in February 2024, after which data cleaning and data analysis will start. Preliminary data analysis will be carried out in December 2023 due to a project deliverable deadline by the end of December 2023.

Discussion

In this pilot study, we will explore the effect of using the CAPABLE app immediately after melanoma diagnosis in 36 patients, providing symptom monitoring, education, and well-being interventions during their first phase of treatment with ICIs, on 3- and 6-month HRQoL outcomes such as fatigue and functioning, and the patient acceptability of using a system such as CAPABLE. Since treatment with ICIs is becoming standard therapy for patients with high-risk and advanced melanoma, more and more patients experience treatment-related AEs. One of the most common symptoms of this treatment is fatigue. Consequently, a decrease in short- and long-term HRQoL can occur in these patients. An approach to improving symptom control and HRQoL outcomes is to use an eHealth

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tool. eHealth apps may contribute to improving HRQoL by addressing the unmet supportive care and information needs of these patients by enabling autonomy and self-management. Moreover, eHealth tools have shown promising results in improving fatigue by stimulating physical exercise, psychoeducation, mindfulness-based interventions, and yoga. However, previous studies focused on eHealth apps providing either symptom monitoring or interventions targeting fatigue.

It is hypothesized that the CAPABLE intervention will limit the increase in fatigue in patients with melanoma receiving ICIs by 10 points at 3 months after the start of treatment compared to a similar patient group receiving standard care. Furthermore, it is hypothesized that the system will be feasible to implement during ICI treatment in clinical practice. This system will be evaluated by 36 patients for 3-6 months from the start of their ICI treatment. End points of the study will be measured at baseline, 3 months, and 6 months after the start of treatment.

Several limitations of this pilot study should be noted. First, the intervention period will be 3 to maximally 6 months due to the limited number of well-being interventions in the mobile app and information provision focusing on the first period of treatment. Therefore, we will not be able to evaluate the long-term effects of the CAPABLE mobile intervention. Second, the inclusion period will be restricted to 6 months, as the time frame of the study is limited by project restrictions and available funding. Third, the control group is collected before the intervention group (ie, the CAPABLE cohort). Because of time restrictions in the project and the limited number of patients available in the hospital, it was necessary to create 2 separate prospective cohorts instead of using a randomized design. Moreover, the control group was collected during the COVID-19 pandemic, and this might have negatively influenced the HRQoL outcomes. Furthermore, we chose the short EORTC QLQC30 fatigue scale to measure our primary outcome, as we already use this questionnaire in our daily clinical routine, facilitating future implementation. As it is short, it minimizes patient burden. Furthermore, it was previously shown that there was no difference in chronic fatigue as measured by the EORTC QLQ-C30 and the validated Fatigue Assessment Scale (FAS) in Hodgkin lymphoma survivors [67]. Lastly, this pilot study does not include the possible relevance of supportive care provided for patient's informal caregivers. It is well-known that informal caregivers or relatives of patients with cancer experience high caregiver burden and distress [68]. eHealth interventions could offer a convenient approach for providing support to the informal caregivers of individuals facing cancer [69]. Future studies with the CAPABLE app should focus on including support for informal caregivers.

Nevertheless, this pilot trial has several strengths, including the prospective study design of the CAPABLE group and the control group. Furthermore, both study groups are collected from a population receiving standard care and do not participate in experimental trials. The CAPABLE smartphone app is developed following user-centered design principles and in close collaboration with patients, app developers, component developers, and technical and clinical staff. Initial prototypes were built after content-generating interviews with patients and HCPs, following 3 rounds of user experience and user interface testing in both target populations. Consequently, the content offered in the CAPABLE app is of high quality and reviewed by the local medical staff in collaboration with patients. Last, although not primarily focusing on evaluating the change in care structures, it is worth mentioning that an eHealth tool such as CAPABLE may lead to earlier intervention for immune-related AEs and psychological complaints. A future and larger trial should focus on the impact of the implementation of such tools and their effect on existing care structures.

In conclusion, the CAPABLE pilot study will provide preliminary evidence about the effect, usability, and feasibility of the CAPABLE system, which may encourage further studies with this eHealth app. A similar pilot trial with the same CAPABLE system but for another population is currently enrolling patients in an Italian hospital. These studies will be the first to provide a system containing symptom monitoring, information provision, and well-being interventions in one eHealth tool. When positive results are generated on the primary outcome, outcomes should be validated in a larger randomized controlled trial, keeping end points for possible implementation in mind. Adding the CAPABLE system to active treatment is hypothesized to decrease fatigue in patients with high risk and advanced melanoma during treatment with ICIs compared to a control group receiving standard care.

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Data Availability

The data sets generated during or analyzed during this study are not publicly available due to the sensitive information of patients in this data set, but are available from the corresponding author on reasonable request.

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Conflicts of Interest

SW reports serving on an advisory board for Eisai, Bristol-Myers Squibb, Pfizer, Novartis and Pierre Fabre (paid to institution). DG is an employee of and shareholder in Deontics Ltd, the company that provided the Computer Decision Support platform used in the study.

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Abbreviations

AE: adverse event
CAPABLE: Cancer Patients Better Life Experience
CRF: cancer-related fatigue
CTCAE: Common Terminology Criteria for Adverse Events
EHR: electronic health record
EORTC: The European Organization for Research and Treatment of Cancer
FAS: Fatigue Assessment Scale
GAD-7: Generalized Anxiety Disorder-7
HCP: health care professional
HRQoL: health-related quality of life
ICI: immune checkpoint inhibitor
ISO: International Organization for Standardization
NCI: National Cancer Institute
NKI: Netherlands Cancer Institute
PHQ-9: Patient Health Questionnaire-9
PRO-CTCAE: Patient-Reported Outcome version of the Common Terminology Criteria for Adverse Events
QLQ-C30: Quality of Life Questionnaire-Core 30
SUS: System Usability Scale
VC: Virtual Capsule
WMO: Medical Research Involving Human Subjects Act

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Protocol

Identification of Psycho-Socio-Judicial Trajectories and Factors Associated With Posttraumatic Stress Disorder in People Over 15 Years of Age Who Recently Reported Sexual Assault to a Forensic Medical Center: Protocol for a Multicentric Prospective Study Using Mixed Methods and Artificial Intelligence

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Abstract

Background: Sexual assault (SA) can lead to a range of adverse effects on physical, sexual, and mental health, as well as on one's social life, financial stability, and overall quality of life. However, not all people who experience SA will develop negative functional outcomes. Various risk and protective factors can influence psycho-socio-judicial trajectories. However, how these factors influence trauma adaptation and the onset of early posttraumatic stress disorder (PTSD) is not always clear.

Objective: Guided by an ecological framework, this project has 3 primary objectives: (1) to describe the 1-year psycho-socio-judicial trajectories of individuals recently exposed to SA who sought consultation with a forensic practitioner; (2) to identify predictive factors for the development of PTSD during the initial forensic examination using artificial intelligence; and (3) to explore the perceptions, needs, and experiences of individuals who have been sexually assaulted.

Methods: This longitudinal multicentric cohort study uses a mixed methods approach. Quantitative cohort data are collected through an initial questionnaire completed by the physician during the first forensic examination and through follow-up telephone questionnaires at 6 weeks, 3 months, 6 months, and 1 year after the SA. The questionnaires measure factors associated with PTSD, mental, physical, social, and overall functional outcomes, as well as psycho-socio-judicial trajectories. Cohort participants are recruited through their forensic examination at 1 of the 5 participating centers based in France. Eligible participants are aged 15 or older, have experienced SA in the last 30 days, are fluent in French, and can be reached by phone. Qualitative data are gathered through semistructured interviews with cohort participants, individuals who have experienced SA but are not part of the cohort, and professionals involved in their psycho-socio-judicial care.

Results: Bivariate and multivariate analyses will be conducted to examine the associations between each variable and mental, physical, social, and judicial outcomes. Predictive analyses will be performed using multiple prediction algorithms to forecast PTSD. Qualitative data will be integrated with quantitative data to identify psycho-socio-judicial trajectories and enhance the prediction of PTSD. Additionally, data on the perceptions and needs of individuals who have experienced SA will be analyzed independently to gain a deeper understanding of their experiences and requirements.

Conclusions: This project will collect extensive qualitative and quantitative data that have never been gathered over such an extended period, leading to unprecedented insights into the psycho-socio-judicial trajectories of individuals who have recently

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experienced SA. It represents the initial phase of developing a functional artificial intelligence tool that forensic practitioners can use to better guide individuals who have recently experienced SA, with the aim of preventing the onset of PTSD. Furthermore, it will contribute to addressing the existing gap in the literature regarding the accessibility and effectiveness of support services for individuals who have experienced SA in Europe. This comprehensive approach, encompassing the entire psycho-socio-judicial continuum and taking into account the viewpoints of SA survivors, will enable the generation of innovative recommendations for enhancing their care across all stages, starting from the initial forensic examination.

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KEYWORDS

sexual violence; posttraumatic stress disorder; functional outcomes; risk factors; artificial intelligence; trajectory; longitudinal; mixed methods; sexual assault; mental health; cohort study; PTSD; innovative

Introduction

Background

In recent years, sexual assault (SA), defined by French law as any form of sexual abuse involving violence, coercion, threats, or surprise, and occurring without clear and explicit consent, has gained recognition as a public health issue. Research indicates high prevalence rates of SA [1] and highlights its association with numerous negative outcomes, including effects on physical, sexual, and mental health; social life; financial stability; and overall quality of life [2]. It is recognized as one of the most traumatic events [3-5]. However, not everyone who experiences SA will necessarily develop negative functional outcomes. Various protective and risk factors can influence their psycho-socio-judicial trajectories. One of the most comprehensive models for categorizing these factors is the ecological model developed by Campbell, Dworkin, and Cabral [6]. This model is based on Ecological Theory [7], which classifies factors according to the environment in which they develop in relation to the individual.

Although there is a growing body of literature on the characteristics associated with negative outcomes and the utilization of medical, social, and legal resources, the precise manner in which these characteristics influence trauma adaptation remains unclear and does not enable the prediction of psycho-socio-judicial trajectories. Following an ecological framework, this project aims to advance research in this area using mixed longitudinal data and artificial intelligence (AI) to delineate the 1-year psycho-socio-judicial trajectories of individuals who recently experienced SA. Additionally, it seeks to identify predictive factors for the development of posttraumatic stress disorder (PTSD). Furthermore, it serves as an exploratory study of the needs and experiences of people who experienced SA and the available resources for them in France.

Sexual Assaults and Negative Functional Outcomes

Data from the Global Burden of Disease study revealed that the global prevalence of SA in 2017 was 11.6% for men and 27.5% for women [1]. However, prevalence rates vary greatly depending on the definition of SA adopted by researchers, the research settings, and the study populations. A review of literature on SA prevalence outside of North America since 2010 revealed that past-year prevalence rates ranged from 0% to 59.2% for women, 0.3% to 55.5% for men, and 1.5% to 18.2% for individuals identifying as lesbian, gay, bisexual, and gender-diverse [8].

The literature demonstrates that SA can have a substantial impact on the quality of life and functional outcomes, affecting physical and sexual health, behaviors, financial stability, social life, as well as psychological and psychiatric well-being [2,9-11]. Among the various outcomes of SA, psychological and psychiatric effects have been extensively studied, with a particular focus on PTSD due to its strong association with SA. Indeed, US and international population–based studies indicate that the lifetime prevalence of PTSD ranges from 4% to 7% among individuals who have experienced any type of traumatic event [3-5]. However, for those who have endured rape and other forms of SA, these lifetime prevalence rates vary significantly, ranging from 17.4% to 65% [3-5], highlighting SA as one of the most profoundly traumatic experiences.

Factors Associated With SA Negative Outcomes

Functional outcomes can vary considerably and are influenced by a multitude of protective and risk factors. Campbell, Dworkin, and Cabral [6] developed a framework to examine the diversity of these factors [6]. This framework is based on Bronfenbrenner's Ecological Theory [7], which states that human development "evolves as a function of the interplay between person and environment" [7]. The authors adapted this framework to comprehend "how factors at multiple levels of the social ecology contribute to (...) deleterious mental health effects" [6]. It is one of the most comprehensive models to date as it classifies protection and risk factors into 7 levels depending on the environment in which they interact with the person. Using the same levels as defined by Campbell, Dworkin, and Cabral [6], we included in this review factors associated with negative mental health outcomes, overall recovery, and quality of life.

Individual-level factors represent the intrinsic characteristics of individuals that can affect their mental health and recovery after SA [6]. These are sociodemographic factors [6,11-16], preexisting mental health conditions and family history of mental health problems [6,17-19], and coping strategies [6,20-23]. Coping strategies encompass both positive strategies such as religious coping [24,25] and maladaptive strategies such as self-blame, which is related to more PTSD and depressive symptoms [6,20,26]. Campbell, Dworkin, and Cabral [6] conceptualized this last factor as a meta-construct, arguing that

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it transcends any single level of the model as it is influenced and enhanced by factors across all other levels.

Characteristics of the assault, such as the perceived life threat during the assault and the perceived dangerousness of the assailant, have been linked to negative mental health outcomes, as evidenced by research on SA [6]. These factors are also associated with general trauma [18,19]. Peritraumatic factors, including peritraumatic distress and dissociation, may also serve as moderate to strong predictors of PTSD, especially in cases of interpersonal violence [18,19], although documentation of these factors is relatively scarce.

The microsystem level is defined as the "face-to-face interactions and interrelations between individuals and others in their immediate setting" [6,7]. It encompasses factors such as a lack of social support, which is considered one of the most important risk factors for mental disorders [18,19,27]; and negative reactions following disclosure, which can severely impede recovery [6,27] and are associated with posttraumatic distress [28] and self-blame [29]. By contrast, positive social reactions are shown to lower psychological distress [6] and are associated with positive life changes [28].

The meso/exosystem level, as defined, involves interactions with the formal system [6]. This encompasses both positive formal support and instances of secondary victimization within the legal, medical, and mental health systems, as well as within the advocacy community. Perceptions of social reactions from formal responders have been associated with psychopathology [6,27]. However, results are not always consistent between studies: the only study to our knowledge to compare formal and informal support showed that reactions from formal providers, regardless of whether the reaction was positive or negative, were not associated with more general psychological distress; however, positive reactions were associated with benefits in the aftermath of trauma [28]. Regarding various forms of formal support, the literature indicates that the legal system tends to have the most adverse impact on mental health due to the prevalence of questions blaming the impacted individual. Additionally, the medical system has been shown to exacerbate PTSD symptoms [6,30]. By contrast, the mental health system and the advocacy community have been found to be supportive and beneficial for individuals who have experienced SA, especially those who have had negative experiences with the legal and medical systems. These entities can help mitigate the adverse effects of such experiences [6].

The macrosystem level is defined as "consistencies, in the form and content of lower-order systems (…) that exist, or could exist, at the level of the subculture or the culture as a whole, along with any beliefs systems or ideology underlying such consistencies" [7]. It includes sociocultural factors such as race/ethnicity when explored from a sociocultural perspective [6,15]. Given that the definitions of "victim," "survivor," and "trauma" are influenced by societal imaginaries or representations [31], we have placed the impact of labeling individuals who have experienced SA as "victim" or "survivors," and the SA event itself as "trauma," within the macrosystem. Research has demonstrated that such labeling can have detrimental effects on their social life and their sense of self [32-35].

The chronosystem level examines "the cumulative effects of multiple sequences of developmental transitions over the life course" [6]. Research has shown that a prior history of SA and a history of other forms of violence exposure and reexposure are related to more negative psychological outcomes, which may be cumulative [6,36]. Besides, it is well-established that a history of trauma is a predictive factor for PTSD, regardless of the type of trauma experienced [18,19].

The multitude of factors and their complexity could explain the heterogeneity observed in the trajectories of individuals who have experienced SA [6,19].

Limits of the Current Literature

Despite a growing body of literature, how these characteristics impact adaptation to trauma remains unclear [36,37] and does not provide us with the means to characterize psycho-socio-judicial trajectories [38]. Similarly, some factors remain unexplored, such as the impact of formal support on mental health outcomes [19,27,36,37]. Consequently, given that the conventional approach of predicting the development of PTSD using bivariate analyses and traditional multiple regression analysis has shown limited success, it is pertinent to investigate new predictive methods, such as AI. There are several reasons why AI might outperform conventional regression analyses: it automates the identification of hidden interactions and nonlinearities among features, enables the handling of larger and more complex data sets, and facilitates the integration of information from highly diverse sources. Additionally, it reduces the likelihood of overestimating prediction performance when dealing with numerous highly correlated independent variables [39,40]. Moreover, AI statistical algorithms represent an inductive approach, in contrast to traditional approaches that are hypothesis driven [41]. This makes AI useful for discovering unknown mechanisms [41] and uncovering relationships between data that may not be discernible through traditional statistics [39].

To date, fewer than 100 studies have used AI for predicting PTSD following a traumatic event using clinical and biological data. These studies have demonstrated a good predictive ability, with area under the curve values ranging from 75% to 98% [42,43]. However, to the best of our knowledge, only 1 study [44] has specifically included adults who experienced SA in its sample, and it reported poor predictive ability (area under the curve 64%). Moreover, other useful indicators, such as sensitivity (ie, the capacity to give a positive result when the hypothesis is verified) and specificity (ie, the capacity to give a negative result when the hypothesis is not verified), appear necessary to judge the usefulness of AI algorithm in routine clinical practice but seem to be missing in these studies, hindering the interpretation of the results and evaluation of relevance. It is therefore necessary to explore in more detail the utilization of AI to predict the onset of PTSD for people who experienced SA and to measure its usefulness for forensic services.

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Furthermore, there has been minimal research conducted on the accessibility and effectiveness of support services, including psychiatric and psychological follow-ups, legal assistance, and support from associations, in Europe [38]. Thus, conducting an assessment of the functionality and quality of available resources in France is essential to describe psycho-socio-judicial trajectories accurately and to offer services that are better aligned with the needs of individuals who have experienced SA.

Study Objectives and Aims

This study is structured into 3 major components, each fulfilling a distinct primary objective. Our first objective is to delineate the 1-year psycho-socio-judicial trajectories of individuals who have recently encountered SA and sought consultation with a forensic examiner. We hypothesize that there exist several typical psycho-socio-judicial trajectories among individuals who have recently experienced SA and sought assistance from a forensic practitioner in France. However, we also believe that a multitude of individual and contextual factors and circumstances play a crucial role in conjunction with the characterization of these trajectories [19,30].

Our second objective is to use AI to identify predictive factors for the development of PTSD. We posit that AI may be a more effective method for this prediction compared with traditional statistical methods such as multiple regression analysis [39]. A secondary goal within this primary objective is to develop an algorithm capable of screening for PTSD symptoms based on clinical criteria that are accessible during the initial forensic examination.

Our third objective is to examine the concepts of "victim" and "trauma" and enhance the understanding of SA from the perspective of individuals who have experienced it. We hypothesize that the significance and representation associated with the terms "victim" and "trauma" are either socially imposed on individuals who have experienced SA or ascribed by those involved in their recovery. However, these representations are expected to differ significantly and qualitatively from the perceptions held by the individuals directly affected by them [31,34]. Additionally, this investigation will enable us to assess the functioning and quality of available resources.

Methods

Overview

The research team consists of 14 professionals with expertise in forensic sciences, anthropology, psychiatry, law, criminology, and data sciences. Together, they are involved in the development and execution of our research project, named "Intelligence Artificielle, Dépistage et trajectoires psychosociojudiciaires des victimes de Violences Sexuelles" (IADViSe), which translates to "Artificial Intelligence, Screening, and Psycho-Socio-Judicial Trajectories of Sexual Violence Victims".

Overall Study Design

Our study is a longitudinal multicentric cohort study that uses mixed methods. Quantitative data will be gathered through repeated questionnaires administered over the course of up to a year following the SA. Qualitative data will be obtained through semistructured interviews conducted with members of the cohort, individuals who have experienced SA but are not part of the cohort, and professionals involved in their psycho-socio-judicial care. Similar to many medical and epidemiological studies [2], and given that our primary sample comprises individuals who have reported recent SA and have been referred to a medical practitioner for a formal examination, our study focuses solely on nonconsensual sexual acts that involve physical contact. This includes the legal concepts of SA (sexual contact committed by force, coercion, threats, or surprise without the clear and explicit consent of the person) and rape (SA with penetration), but excludes harassment and exhibitionism.

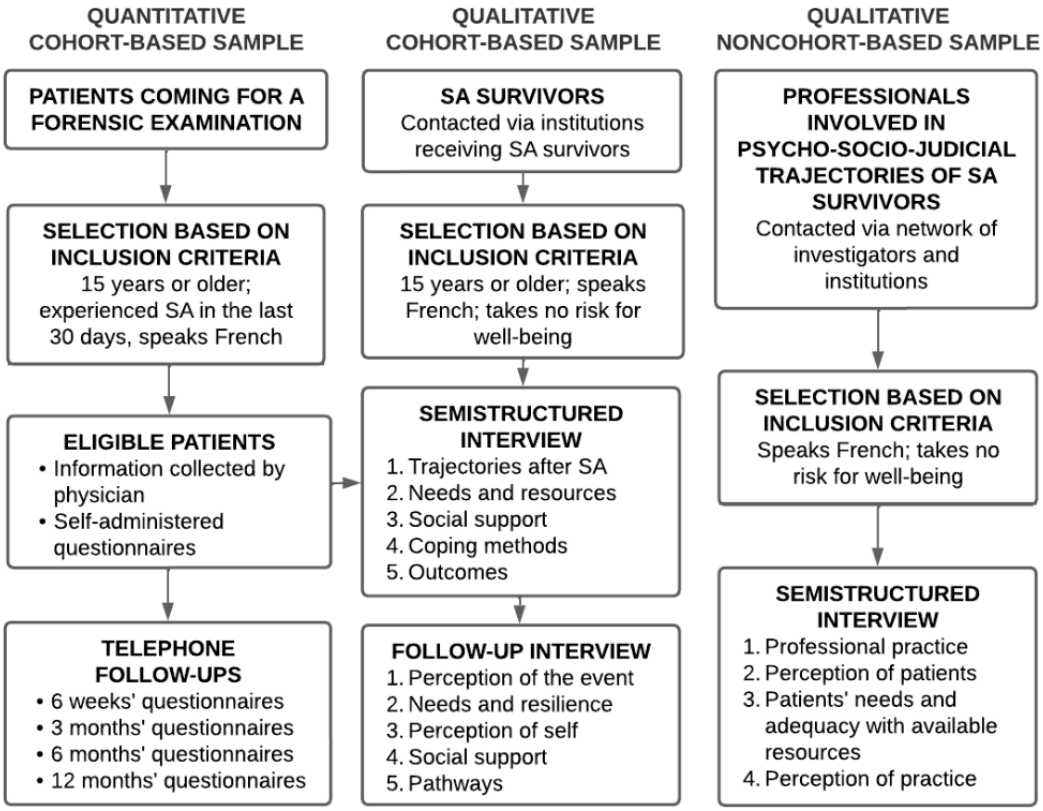
Participants

Cohort Participants

An integral component of our project involves establishing a cohort of individuals who have recently experienced SA and have undergone a forensic examination, whether it was court ordered or not. This cohort will serve as the source for longitudinal quantitative and qualitative data collection (Figure 1).

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Figure 1. Inclusion and follow-ups stages of participants. SA: sexual assault.



Participant Recruitment

Participants are being recruited during their examinations for recent SA by physicians at 1 of the 5 participating forensic medical centers or medico-legal units in Île de France, which include Hotel-Dieu Hospital in Paris, Jean Verdier Hospital in Bondy, the Inter-communal Hospital Center of Créteil, the Sud Francilien Hospital in Corbeil-Essonnes, and the Versailles Hospital Center. During these examinations, physicians provide patients with consent forms that outline the purpose and methodology of the research. If patients choose to sign the consent form, their initial information and contact details are shared with one of the investigators (EF, VT, TS, or JO) responsible for follow-ups at 6 weeks, 3 months, 6 months, and 1 year after the SA. Additionally, participants are asked if they are willing to participate in interviews. If they agree, we arrange 1-3 meetings in a private setting of their choice to review the responses provided in the questionnaires and to discuss any other topics they wish to address, including their self-representations and perceptions of the SA.

Inclusion Criteria

We will include all individuals who undergo an SA forensic examination at 1 of the 5 forensic centers where the study is conducted, provided they consent to participate, are aged 15 or older, and have experienced SA within the last 30 days. The 30-day limit is set because one of our main objectives is to investigate the onset of PTSD, which can be formally diagnosed if symptoms persist for more than 1 month, in accordance with criterion F of the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders [45].

Exclusion Criteria

We will exclude individuals for whom callbacks are challenging or impossible and those who do not possess sufficient proficiency in French to independently complete the questionnaires.

Feasibility

The potential number of participants to be included will vary depending on the clinical activity of each forensic center where the study is conducted. When considering all participating centers, there is the potential to include between 500 and 650 individuals annually. As participation in this study is entirely voluntary and offers no immediate benefits to the patients, we anticipate that not everyone will choose to participate. As a result, our recruitment period is expected to extend over a minimum of 2-3 years.

Noncohort Participants

Overview

The data gathered from the cohort are supplemented with qualitative interviews involving individuals outside the cohort (Figure 1). These interviews include individuals who have experienced SA but were recruited through alternative methods, as well as professionals engaged in the psycho-socio-judicial care of SA survivors.

Participants Recruitment

We are recruiting noncohort participants through the networks of our investigators and by promoting our study in various organizations that assist individuals who have experienced SA, such as survivor support associations, police stations, forensic

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centers, regional psychotrauma centers, and more. In each organization, our designated contact person is responsible for disseminating a recruitment poster containing the investigators' contact details, both within the organization and throughout its network where applicable. This information is shared via their website, mailing lists, in their offices, or on their social media platforms. Individuals who are interested can then reach out to the investigators to arrange a meeting. We will continue to add participants until we reach saturation.

Inclusion Criteria

To be eligible for participation, individuals must be aged 15 or older, have a history of experiencing SA or work closely with individuals who have experienced SA, provide their consent to participate in the research, and possess sufficient proficiency in French to be interviewed without requiring a translator.

Exclusion Criteria

Individuals who are unable to arrange a face-to-face or video meeting in a location that ensures their privacy and does not jeopardize their well-being will be excluded from participation.

Ethical Considerations

All procedures, including the process of obtaining informed consent, underwent a thorough ethical review and received approval from the Research Ethics Committee of Paris Cité University (institutional review board approval number: 00012022-14, date: April 5, 2022). All experiments and methodologies are conducted in strict accordance with the principles outlined in the Declaration of Helsinki**.**

Informed consent is obtained from all study participants through the signing of a printed consent form. This form explicitly outlines the study's objectives, methodology, and associated risks. The consent process is facilitated either by the physician during the forensic examination or by one of the investigators at the commencement of the first interview for noncohort participants. Physicians and investigators are readily available to address any questions or concerns that participants may have regarding the study. Furthermore, participants are informed of their right to withdraw from the study at any point in time.

Participants may be experiencing latent psychological distress, with or without PTSD, either in the usual aftermath of the events or potentially triggered during the forensic examination or telephone contacts and interviews. However, most of these risks are not attributable to the research project itself. The security of participants during the forensic examination is the responsibility of the medical examiner, who follows the safety guidelines required by their department. To ensure the security of participants during and between follow-ups, investigators, all of whom are trained in dealing with people who have been exposed to SA, remind participants that some questions may be triggering, emphasize their right to stop their participation at any moment and ensure that participants are not in distress at any time during the call. As they are already part of an identified medical and psychological care system, participants will be asked to contact the forensic medical center where they were received if necessary. A list of professionals and resources is also provided to all participants for information and guidance. Participation is voluntary and does not include compensation, but it can be beneficial to participants who need to discuss their experiences.

Each participant is assigned an inclusion number to anonymize the database entries and questionnaires. Physicians or investigators record identifying and contact information in tables outside the database, allowing each participant to be linked to their inclusion number and recontacted. The audio of the interviews is recorded, transcribed, and anonymized with the same embedding code where applicable. All documents allowing the identification of the participants are securely stored and located in each participation center and will be destroyed as soon as the data collection is completed. After the data collection is completed and the database is appropriately anonymized and cleaned, the data and all necessary materials for their use will be uploaded to a public archive, such as HAL (Hyper Article en Ligne, which translates to Online Hyper Article), under a CC (creative commons) license, in compliance with the FAIR (Findable, Accessible, Interoperable, Reusable) principles and GDPR (General Data Protection Regulation) regulations.

Quantitative Measures

Quantitative measures at each time point are presented in Table 1. Initial data are collected during the forensic examination. The physician completes a questionnaire (see Multimedia Appendix 1) based on information that forensic practitioners routinely collect for their report to the criminal justice system. The questionnaire is adapted from a previously constructed questionnaire [46], which is still in use today by forensic practitioners in the Department of Forensic Medicine at the Jean Verdier Hospital (Bondy, France). Participants are also asked to complete 2 self-assessment questionnaires on peritraumatic dissociation and distress. Investigators contact the participants again at 6 weeks, 3 months, 6 months, and 1 year after the SA so that they can answer follow-up questionnaires regarding their health, support, and the status of their judicial proceedings. These follow-up sessions do not exceed 40 minutes.

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Table 1. Characteristics and outcome measures and time points at which they are collected.

Variable category and variables	Measure	Timeline				
		Baseline (30 days maximum)	6 weeks	3 months	6 months	1 year
Individual characteristics						
Sociodemographic variables[a]	Bespoke measures	✓	✓			
Medical and psychiatric history and treatment	Bespoke measures	✓				
Coping	Brief-COPE (French version)		✓	✓	✓	✓
Substance misuse	HSI[b], CAGE[c], CAST[d] (French versions), and ECAB[e]		✓	✓	✓	✓
Assault characteristics						
Aggressor and aggression information[f]	Bespoke measures	✓				
Microsystem						
Received social support	RNAE-22[g]		✓	✓	✓	✓
Exosystem (formal support)						
Use of services	Bespoke measures		✓	✓	✓	✓
Quality of contact	Bespoke measures	✓	✓	✓	✓	✓
Perceived negative support	From Campbell and Raja [30]		✓	✓	✓	✓
Secondary victimization	Bespoke measures		✓	✓	✓	✓
Chronosystem						
Childhood history of violence and exposition to domestic violence	Bespoke measures	✓				
Prior assault history	Bespoke measures	✓				
Sexual violence reexposure	Bespoke measures		✓	✓	✓	✓
Functional outcomes						
Peritraumatic distress	PDI[h] (French version)	✓				
Peritraumatic dissociation	PDEQ[i] (French version)	✓				
Physical and psychological state at examination	Bespoke measures	✓				
Posttraumatic stress disorder symptoms	PCL-5[j] (French version)		✓	✓	✓	✓
Quality of life	SF-12v2[k] (French version)		✓	✓	✓	✓
Impact on daily life	WHODAS 2.0[l] (French version)		✓	✓	✓	✓

[a]Sociodemographic variables are age, gender identity, marital status, employment status, level of education, sexual identity, and race/ethnic identity.

[b]HSI: Heaviness of Smoking Index.

[c]CAGE: Cut Annoyed Guilty Eye-Opener.

[d]CAST: Cannabis Abuse Screening Test.

[e]ECAB: Echelle Cognitive d'Attachement au Benzodiazépine (Benzodiazepine Cognitive Attachment Scale).

[f]Aggressor and aggression information includes the number of aggressors, their gender, age, their relation to the impacted individual, alcohol or substance use from the aggressor and the impacted individual, the impacted individual's physical reaction of defense, impacted individual's amnesia, suspicion of chemical submission, the location of the sexual assault, types of sexual assault, and associated violence.

[g]RNAE-22: Questionnaire sur les réactions nuisibles et aidantes de l'entourage lors d'un dévoilement de violences à caractère sexuel – Version francophone adaptée

[h]PDI: Peritraumatic Distress Inventory.

[i]PDEQ: Peritraumatic Dissociative Experience Questionnaire.

[j]PCL-5: Posttraumatic Stress Disorder Checklist for DSM-5.

[k]SF-12v2: Short Form 12-item version 2 Health Survey.

[l]WHODAS 2.0: World Health Organization Disability Assessment Schedule 2.0.

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Individual Factors

Sociodemographic Variables

Sociodemographic data are first collected during the initial examination. These include participants' age (in years) and gender (1=female, 2=male, and 3=other), the name of the forensic center in which the examination took place, the anonymized identity of the practitioner, and the time between the assault and the examination (in hours). Complementary sociodemographic variables are collected during follow-ups. These include marital status (0=never married, 1=married, 2=separated, 3=divorced, 4=widowed, and 5=cohabitation) and employment status (1=employee, 2=independent worker, 3=unpaid worker, 4=student, 5=housewife/husband, 6=retired, 7=unemployed due to health reasons, 8=unemployed for another reason, and 9=other), which are based on sociodemographic information measured in the World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2.0) questionnaire [47]. The level of education (from 0=no diploma to 10=master's degree; and 11=other) is based on the sociodemographic questions in the 2019 Health Barometer Study [48]. Sexual identity (1=heterosexual, 2=gay or lesbian, 3=bisexual or pansexual, and 4=other) is based on an item recommended by the University of California (UCLA) Sexual Minority Assessment Research Team (SMART) team [49]. We created an item to collect information about gender diversity identification (0=no and 1=yes). The last sociodemographic variable collected is ethnicity/race (1=White, 2=Black, 3=Middle Eastern, 4=Hispanic/Latinx, 5=Asian, and 6=other) and is based on the recommendation from Public Health Ontario [50] and adapted to a French context.

Medical and Psychiatric History and Treatments

We will collect data recorded by the practitioners during the initial examination, including a history of serious or chronic diseases, personal and familial psychiatric history, and current medical treatments that could impact psychological well-being (eg, mood stabilizers, anxiolytic, hypnotic, antidepressant, neuroleptic, analgesic drugs).

Coping

Coping strategies are measured at each follow-up (6 weeks, 3 months, 6 months, and 1 year) using the French version [51] of the Brief-COPE [52]. This 28-item instrument measures the frequency with which an individual uses different positive and maladaptive coping strategies on a 4-point Likert scale ranging from 0=not at all to 3=a lot. The Brief-COPE and the COPE inventory are widely used tools for assessing coping strategies and have been translated and validated in at least seven languages, facilitating international replication and comparisons [51]. The French version of this instrument demonstrates good psychometric properties [51].

Follow-Up Substance Use

Tobacco, alcohol, delta-9-tetrahydrocannabinol, and benzodiazepine use since the assault is assessed at each follow-up (6 weeks, 3 months, 6 months, and 1 year) by inquiring whether participants use each substance and whether their consumption has increased or decreased since the assault [53]. If participants report using these substances, follow-up questionnaires are administered to assess whether their use of each substance is problematic. This assessment is performed using the 2-item simplified Fagerström test [54], a French version of the Heaviness of Smoking Index (HSI) [55], the French version of the Cut Annoyed Guilty Eye-Opener (CAGE) test (Diminuer Entourage Trop Alcool; DETA) [56], the French version of the Cannabis Abuse Screening Test (CAST) [57], and the Echelle Cognitive d'Attachement au Benzodiazépine (Benzodiazepine Cognitive Attachment Scale; ECAB) [58]. All of these instruments are validated and recommended by the French High Authority for Health.

Assault Characteristics

Standard consultation information about the assailant (ie, number, gender, age, relation to the impacted individual, and alcohol or substance use), the aggression (ie, location of the assault, types of violence, and context of the assault), and the impacted individual (ie, physical defense reaction, amnesia, chemical submission, and substance or alcohol use) is collected during the initial forensic examination as part of the physicians' routine screening.

Microsystem (Informal Support System)

We will assess social support during follow-ups at 6 weeks, 3 months, 6 months, and 1 year using the *Questionnaire sur les réactions nuisibles et aidantes de l'entourage lors d'un dévoilement de violences à caractère sexuel – Version francophone adaptée* (RNAE-22) [59]. This questionnaire is a French version of the Social Reaction Questionnaire–Short (SRQ-S) [60] adapted to be applicable to all genders. This instrument measures the frequency of positive and negative social reactions to an SA disclosure on a 5-point Likert scale ranging from 0=never to 4=always. Items are split into 3 subscales describing the behavior of people receiving the disclosure: Turning against, Unsupportive acknowledgment, and Positive support, which have been validated in their original [60] and French versions [59].

Exosystem (Formal Support System)

Use of Judicial, Medical, Mental Health, and Community Services

The use of different formal services (judicial, medical, psychological, and community) is measured at each follow-up (6 weeks, 3 months, 6 months, and 1 year) with questions built by the research team based on empirical findings and the perspective of care providers and legal professionals, such as "Have you filed a complaint with the police department?" We inquire about the evolution of medical, psychological, and community care, as well as the progress of the legal procedure at each follow-up.

Quality of Contact With the Exosystem

The quality of the contact between the physician and the patient is initially measured during the initial examination, where the physician is asked to rate it on a scale ranging from 0=very bad to 6=excellent. Participants are subsequently asked to evaluate the quality of their contact with each formal system during follow-ups, including their interactions with the medical system.

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Negative Perceived Social Support by the Exosystem

The participant's negative perceived support from each formal service they used is assessed at each follow-up (6 weeks, 3 months, 6 months, and 1 year) using 5 items adapted from a study by Campbell and Raja [30]. These items examine various negative feelings the participant may have experienced after their interaction with each system, including guilt, depression, anxiety, distrust, and reluctance to seek further help.

Secondary Victimization

We will assess secondary victimization at each follow-up (6 weeks, 3 months, 6 months, and 1 year) by inquiring whether participants have experienced any guilt-inducing or unhelpful behaviors from justice system officials. Examples of such behaviors are "being pressured to withdraw your complaint" or "questioning your words." The list of these secondary victimization behaviors was developed by the research team, drawing from empirical findings and insights from legal system professionals.

Chronosystem

History of Violence During Childhood

We will measure participants' history of psychological, physical, and sexual violence exposure (by the same aggressor or by another); history of intrafamilial psychological, physical, and sexual violence exposure; and instances of witnessing domestic violence in their childhood. These questions are administered during the initial forensic examination.

Sexual Violence Reexposure

We will assess instances of physical, psychological, and sexual violence reexposure at each follow-up point (6 weeks, 3 months, 6 months, and 1 year) by inquiring whether the participant has experienced any of these forms of violence, by the same assailant or another, since the initial assault.

Functional Outcomes

Peritraumatic Distress

Peritraumatic distress is measured during the forensic examination using the French version of the Peritraumatic Distress Inventory (PDI) [61]. This instrument measures the frequency with which participants experienced various negative feelings, such as "feeling helpless" or "feeling like dying" during or directly after the assault, on a 5-point Likert scale ranging from 0=not at all to 4=extremely, and shows good psychometric properties [61].

Peritraumatic Dissociation

Peritraumatic dissociation is measured during the forensic examination using the French version of the Peritraumatic Dissociative Experience Questionnaire (PDEQ) [62]. This instrument measures 10 symptoms of dissociation during and immediately after an event on a 5-point Likert scale ranging from 0=not at all to 4=extremely and shows good psychometric properties [62].

State at the Time of Examination

We will gather information on physical complaints and injuries, the participant's psychological state, and the duration of "total or temporary work incapacity" (a legal term used in France to evaluate the severity of the SA) as reported by the physician during the consultation.

PTSD Symptoms

We will assess PTSD symptomatology at each follow-up (6 weeks, 3 months, 6 months, and 1 year) using the French version of the Posttraumatic Stress Disorder Checklist for DSM-5 (PCL-5), which has been validated both in French and in its original version [63]. This 20-item instrument evaluates the PTSD symptoms experienced by participants during the past month. It uses a 5-point Likert scale ranging from 0=not at all to 4=extremely. A total score of 31-33 or higher suggests that the participant may meet the criteria for PTSD and could benefit from PTSD treatment.

Quality of Life

The Short Form 12-item version 2 Health Survey (SF-12v2) [64] will be used to assess the physical, mental, and social quality of life during the past month. This survey is administered at each follow-up (6 weeks, 3 months, 6 months, and 1 year). Each item contributes to the scores of the Physical and Mental Component Summary. Both indexes are converted to a scale from 0 to 100, and the mean score of the sample can be compared with the national norm (where the national mean is 50 with an SD of 10).

Impact on Daily Life

We will assess the impact of the assault on daily life, including personal activities, social activities, and work, at each follow-up (6 weeks, 3 months, 6 months, 1 year) using the WHODAS 2.0 questionnaire [47]. This 12-item instrument measures the extent of these impacts on a Likert scale ranging from 0=none to 4=extremely.

Qualitative Interviews

Semidirective interviews are conducted with both cohort participants and individuals who have experienced SA in the past but are not part of the cohort (see Multimedia Appendix 2). These interviews will complement our quantitative data collection. The initial 1-hour semidirective interview covers topics such as the individual's perception of the event, formal and informal support, coping methods, and the event's impacts. After establishing a good rapport between the participant and the interviewer, additional interviews (second or third) can delve deeper into topics discussed in previous sessions. These interviews explore the participant's value system, their integration of the event into their life course, and their perceptions of themselves and the SA in relation to the concepts of "trauma" and "victim."

Other semidirective interviews are conducted with professionals involved in the pathways of people who have experienced SA (see Multimedia Appendix 3). These interviews cover various aspects: first, professionals discuss their practice and the needs of their patients or clients; second, they share their perceptions of the help they provide, the adequacy of available resources,

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and the needs of SA survivors; finally, they provide insights into their definitions of the notions of "trauma" and "victim," and discuss the utility of these terms in their field and for SA survivors.

Statistical Analysis Planned: Quantitative Analysis

Descriptive analyses of participant characteristics will be conducted. The total population initially included and the follow-up cohort will be compared to understand the differences between patients who abandon their participation and those who complete their follow-up.

Bivariate and multivariate analyses, including trajectory analyses, will be conducted to examine the associations between each variable and mental, physical, social, and judicial outcomes at 6 weeks, 3 months, 6 months, and 1 year after the SA. Results regarding the presence or absence of PTSD will serve as the basis for our predictive analyses.

We will conduct predictive analyses using multiple prediction algorithms, such as meta-learners and support vector machines, to predict PTSD at the initial examination. The testing phase will be carried out in a subsequent study to validate the algorithms using a subset of our cohort. Initially, we will select relevant variables automatically, either through feature selection or manual selection based on the results of multivariate analyses. We will assess the internal validity of the prediction model through cross-validation. To quantify the performance of the algorithms, we will use metrics such as precision (accuracy and area under the precision-recall curve), sensitivity, specificity, positive predictive value, and negative predictive value. Additionally, we will explore tools for visual explanation, feature relevance explanation, and explanation by example [65] to provide elements of explainability.

Qualitative Analysis and Data Integration

Interviews conducted with individuals who have recently experienced SA, with those who have experienced SA in the past, and with professionals will be transcribed before performing coding and thematic analysis. The results of interviews with recent SA survivors included in the cohort will be integrated with the quantitative data, following best practices for mixed methods research [66]. This integration will enable us to add or enhance existing variables to be used in constructing our predictive model for PTSD using AI. Furthermore, it will provide more comprehensive information on the 1-year psycho-socio-judicial trajectories of participants, allowing for a more precise characterization of these trajectories, particularly concerning the judicial aspect and the role of the exosystem (formal support system), which have not been extensively analyzed in quantitative literature.

The data concerning the perceptions of the significance and utility of the concepts of "trauma" and "victims" will be analyzed separately to gain deeper insights into the representations and definitions of SA and individuals who have experienced it. This data will be conducted from the perspectives of recent SA survivors (cohort participants), those who have experienced SA in the past, and professionals who provide assistance to individuals impacted by SA (noncohort participants).

Results

Data collection commenced in September 2022 and is anticipated to conclude by 2026. Data analysis will commence before the conclusion of data collection, with several articles expected to be prepared and submitted for publication between 2023 and 2026.

Discussion

Anticipated Findings

Our first 2 study objectives involve delineating the psycho-socio-judicial trajectories over 1 year of individuals who undergo forensic examinations after a recent SA and using AI for early detection of those at risk of developing PTSD. Third, using mixed methods and conducting interviews with both individuals who have recently experienced SA and those with nonrecent experiences, in addition to professionals engaged in their care, we aim to assess the functionality and attributes of the available resources in France. This approach will contribute to a deeper understanding of SA, its integration into the life course, and the perceptions of "victim" and "trauma" as perceived by those who have experienced it.

Limitations

Our study has certain limitations. In France, the majority of forensic centers require a court order to admit patients, and this order is typically granted once the alleged impacted individual files charges. However, only 7%-8% of people who experience SA choose to press charges [67], and it is possible that this small percentage may not accurately represent the experiences of all individuals who have been subjected to such violence. As a result, individuals who undergo a forensic examination following SA represent a specific subset of individuals and types of assaults. In our study, the forensic center at Jean Verdier Hospital is the only one that does not require patients to have a court order for examination. Consequently, only a small portion of our cohort sample will consist of individuals who have not pressed charges. This limitation could potentially affect the representativeness of our sample.

Furthermore, our specific age and temporal criteria necessarily exclude individuals under the age of 15 years and those whose experience of SA occurred more than 30 days ago. This exclusion limits the participation of individuals who have experienced certain types of sexual violence, such as incest or child sexual abuse. This criterion is necessary to study the onset of PTSD, which typically occurs 1 month after the trauma according to DSM-5 criterion F [45]. Additionally, it facilitates the inclusion of participants, as individuals aged 15 years and older can provide consent for matters related to their sexual health. However, this criterion introduces a potential selection bias, as it excludes individuals under the age of 15 years.

There is also a potential for interviewer bias in the qualitative part of the study. However, several measures have been put in place to minimize interviewer bias. These include using a standardized interview guide for all participants, predesigning codes based on the framework used, ensuring the interviewer is trained in qualitative interviews with crime offenders and

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impacted individuals, adopting an inductive approach, maintaining long-term monitoring of participants to enable reflexivity on practice, and allowing for reformulation of hypotheses and material as the fieldwork progresses. Additionally, inclusions are based on specific criteria and are not made by the interviewer but by different forensic practitioners, further enhancing reflexivity and limiting this bias.

Lastly, it is important to note that part of our study involves the use of AI, which can be more complex to implement and manipulate compared with standard statistical methods [39]. Previous research has highlighted several challenges associated with the integration of AI into studies on psychiatric disorders and its application in clinical settings. These challenges include issues related to model validation; computational resources; data quality; multimodal data; nonstationary data distributions; the heterogeneity of clinical diagnoses; the interpretability of AI models; conservative health care funding practices; and ethical concerns such as data privacy, anonymity, and the potential impact of predictive models on individuals [68].

Despite these limitations, this study plays a crucial role in filling knowledge gaps concerning the psycho-socio-judicial consequences of recent SA, the development and progression of PTSD symptoms, and the requirements of individuals who have experienced SA.

Strengths and Expected Implications

On the quantitative aspect of the project, the systematic data collection process across multiple forensic medicine centers, each with its own unique practices and recruitment patterns, will offer unparalleled insights into individuals seeking consultation for SA across various dimensions, as well as into the practices of professionals involved in these cases. This will enable us to monitor the emergence of significant psychological disorders, including PTSD, and assess their consequences on the life trajectories and functional outcomes of the participants. Furthermore, our quantitative design uses well-established and commonly used scales to assess psychological trauma and the functional consequences of trauma, facilitating comparisons with other national and international research.

Another significant quantitative advantage of our study is its emphasis on predicting the development of PTSD through the application of AI. Indeed, the data gathered during the initial forensic examinations will serve as the foundation for developing initial AI algorithms to identify individuals at risk of developing PTSD. This study will serve as the foundation for a second study, which will be integrated into the project, aimed at investigating the contribution of AI in the early detection of PTSD, as well as the reception and integration of this tool by medico-social services. We hope to develop tools to better guide individuals who have experienced SA from their initial forensic examination, particularly in terms of psychotrauma. This could potentially yield novel findings, as there is promising evidence that AI can be of great assistance in medical services [42,43], although it has not, to our knowledge, been tested in the context of forensic examinations following SA.

Regarding the qualitative aspect of the project, it stands as one of the few endeavors exploring the characteristics and challenges of French infrastructures and the requirements of individuals who have experienced SA in France. This will enable us to map the existing, accessible, and deficient resources within their paths. It is also uncommon in medical and public health research to longitudinally follow individuals who have experienced SA while placing them at the center of the study, enabling us to redefine the representations of their experiences. We aspire to gain a deeper understanding of the individuals seeking help after experiencing SA, their perceptions, and the appropriateness of the support services available to them across various contexts and timeframes. By comprehensively examining how individuals who have experienced SA perceive and incorporate this event into their life course, we can gain valuable insights into their needs and work toward enhancing their support and care. This involves considering the entire medico-social infrastructure in France and its capabilities to address these needs effectively.

Conclusions

This project will allow us to collect numerous data never before collected over such long periods in medical sciences not only in France but also globally. The wealth of data collected is expected to yield unprecedented insights and findings. First, our project will advance research on the impact of risk and resilience factors on trauma adaptation and the characterization of trajectories using innovative methods and extensive quantitative and qualitative longitudinal data. Second, it is a first step toward a functioning AI tool for early diagnosis of PTSD, which will enable us to prevent the chronicization of PTSD and provide better guidance to individuals during their first forensic examination. Third, this study will help bridge the existing gap in the literature regarding the accessibility and effectiveness of support services for individuals who have experienced SA in Europe by comprehensively mapping the currently available resources while also identifying areas where resources may be lacking. This assessment will be based on the needs and perspectives of individuals who have experienced SA, considering the impact of the events on their lives. Furthermore, this innovative research, which encompasses the entire psycho-socio-judicial chain, places a central emphasis on the perspectives of those who have experienced SA. This approach will enable the formulation of novel recommendations aimed at improving the quality of care and support provided at all levels of the system, commencing with the initial forensic examination.

We hope our approach may fuel further research to investigate psycho-socio-judicial trajectories via the creation of cohorts of people who experienced SA in other settings to have a more representative view of all people who have been sexually assaulted. Future research should also continue to focus on the use of AI to help medical examiners refer their patients toward more adapted services by testing the algorithms that will be developed in this project on several samples with different sociodemographic and trauma characteristics.

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Availability of Data and Materials

Data and materials will be available on an open-access archiving platform such as the UK Data Archive once the data collection is completed.

Authors' Contributions

EF was involved in the study conception, design and investigation, original draft preparation, and review and editing. TS, VT, and JO were involved in the study conception, design and investigation, and in the review and editing of the manuscript. TL was involved in the study conception, design, investigation and supervision, and in the review and editing of the manuscript. TF was involved in the study conception and design and review and editing. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Forensic examination questionnaire of the IADViSe study.
[PDF File (Adobe PDF File), 112 KB - resprot_v12i1e46652_app1.pdf]

Multimedia Appendix 2
Semi-directive interview guide for participants who experienced sexual assault.
[PDF File (Adobe PDF File), 53 KB - resprot_v12i1e46652_app2.pdf]

Multimedia Appendix 3
Semi-directive interview guide with professionals.
[PDF File (Adobe PDF File), 51 KB - resprot_v12i1e46652_app3.pdf]

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Abbreviations

AI: artificial intelligence
CAGE: Cut Annoyed Guilty Eye-Opener
CAST: Cannabis Abuse Screening Test
CC: creative commons
DSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth edition
ECAB: Echelle Cognitive d'Attachement au Benzodiazépine (Benzodiazepine Cognitive Attachment Scale)
FAIR: Findable, Accessible, Interoperable, Reusable
GDPR: General Data Protection Regulation
HAL: Hyper Article en Ligne, which translates to Online Hyper Article
HIS: Heaviness of Smoking Index
IADViSe: Intelligence Artificielle, Dépistage et trajectoires psychosociojudiciaires des victimes de Violences Sexuelles (Artificial Intelligence, Screening, and Psycho-Socio-Judicial Trajectories of Sexual Violence Victims)
MRA: multiple regression analysis
PDEQ: Peritraumatic Dissociative Experience Questionnaire
PDI: Peritraumatic Distress Inventory
PTSD: posttraumatic stress disorder
SA: sexual assault
SF-12v2: Short Form 12-item version 2 Health Survey
SRS-Q: Social Reaction Questionnaire–Short
WHODAS 2.0: World Health Organization Disability Assessment Schedule 2.0

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Protocol

Enabling Expedited Disposition of Emergencies Using Telepsychiatry in Israel: Protocol for a Hybrid Implementation Study

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Abstract

Background: Telepsychiatry is the use of virtual communication, such as a video link, to deliver mental health assessment, treatment, and follow-up. Previous studies have shown telepsychiatry to be feasible, accurate compared with in-person practice, and satisfying for psychiatrists and patients. Telepsychiatry has also been associated with reduced waiting times for evaluation and, in some studies, lower admission rates. However, most previous studies focused on using telepsychiatry in community settings and not on involuntary admission.

Objective: The aim of this study is to examine the effectiveness and implementation process of patient assessment for involuntary admissions in the psychiatric emergency department (ED) using a video link.

Methods: This type 1 hybrid implementation study will examine telepsychiatry effectiveness and the implementation process, by comparing telepsychiatry (n=240) with historical controls who had a face-to-face evaluation (n=240) during the previous, usual care period in 5 psychiatric EDs in Israel. A temporary waiver of the standing policy requiring in-person evaluations only, for the purpose of research, was obtained from the Israeli Ministry of Health. During the telepsychiatry phase, clinical staff and patients will join a video call from the ED, while the attending physician will log in elsewhere. The Promoting Action on Research Implementation in Health Services (PARIHS) framework will guide the evaluation of the telepsychiatry implementation process in the ED. PARIHS has the following 3 constructs: (1) *evidence*: staff's opinions regarding the innovation's viability and practicality, their satisfaction levels with its use, and patients' perceptions of the change; (2) *context*: level of approval of new strategies in the ED, decision-making processes, and the manner in which clinical teams converse and work together; (3) *facilitation*: adequacy of the facilitation efforts using champions reports. Primary clinical outcomes include ED length of stay and violent incidents obtained from medical records.

Results: This study received Helsinki approval from the Ethics Committee of Abarbanel Mental Health Center (174; March 13, 2023), Jerusalem Mental Health Center (22-21; November 6, 2022), Lev-Hasharon Mental Health Medical Center (LH12023; February 12, 2023), Tel-Aviv Medical Center (TLV-22-0656; January 3, 2023), and Sha'ar Menashe (1-4-23; April 18, 2023). Data collection began in July 2023 in 2 study sites and will begin soon at the others.

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Conclusions: Telepsychiatry could have significant benefits for patients in the psychiatric ED. Examining telepsychiatry effectiveness in the ED, in addition to identifying the facilitators and barriers of implementing it in different emergency settings, will facilitate better policy decisions regarding its implementation.

Trial Registration: ClinicalTrials.gov NCT05771545; https://clinicaltrials.gov/study/NCT05771545

International Registered Report Identifier (IRRID): DERR1-10.2196/49405

(JMIR Res Protoc 2023;12:e49405) doi:10.2196/49405

KEYWORDS

eHealth; telepsychiatry; digital health service; emergency department; mental health; implementation science; Promoting Action on Research Implementation in Health Services; organizational innovation

Introduction

Telepsychiatry is the use of email, chats, telephone, or video link for mental health assessment, treatment, and follow-up [1,2]. In this paper, we focus exclusively on 2-way communication using a real-time video link. There is evidence for the feasibility and effectiveness of telepsychiatry in certain settings, including for children and adolescents [3], adults and older adults [4], postpartum depression [5], developmental disorders like autism [6], and bipolar disorder [7]. Telepsychiatry can be used in different cultures [8] and health settings [9].

Although telepsychiatry is feasible and effective in various situations [1,9], there is less evidence and experience regarding its use for decisions about involuntary admission. Such decisions require the input of an attending psychiatrist, who may currently be required to physically come to the hospital for a face-to-face assessment. Making the patient wait until the attending psychiatrist arrives may increase the risk of additional decompensation, as the patient is already in a vulnerable state. This waiting period and possible decompensation may contribute to violent incidents and worsen the patient's condition.

In this paper, we discuss the use of telepsychiatry to streamline this process. By allowing an expedited assessment via video link, even when the attending physician is away from the hospital, telepsychiatry can facilitate quicker decisions about involuntary hospitalization. This protocol outlines the evidence supporting a research project to examine this issue empirically and the methods we plan to use.

Although previous studies have discussed the basic conditions to support telepsychiatry in other settings, it does require certain conditions to work well [3]. To conduct a 2-way video conference, one must have adequate internet speed, video and audio quality, and video meeting software [3,10]. It is important to address the security of the video link to prevent malicious intrusions or loss of confidentiality [11]. Both the psychiatrist and patient must be able to operate a computer, join a conference, and operate basic functions such as mute and unmute [3]. Quiet and private rooms must be arranged for both [3,10,11]. Videoconferencing also requires patients to be more active and cooperative than during face-to-face meetings, especially if they are in an unsupervised setting, including home [11,12]. The need for an active and cooperative patient should be considered, especially for patients with cognitive impairment, substance abuse [11], or active psychosis [13]. In our study, a trained staff member, usually a psychiatry resident or a nurse, will be physically present with the patient to support the video chat [3].

Those who wish to use telepsychiatry should be convinced of its accuracy. In fact, a narrative review of 134 articles, mostly from community settings, showed that telepsychiatry can be just as accurate as in-person meetings [9]. However, we are aware of only 2 studies that examined the accuracy of telepsychiatry in emergency settings. In one study from 2014, the authors examined the concordance between clinical impressions via telepsychiatry or in-person evaluation of 73 patients in the psychiatric emergency department (ED) in the United States. A second psychiatrist was present in the room with the patient and completed the assessment independently. In that study, there were no significant differences between raters regarding the recommended disposition, strength or confidence of the disposition recommendation, provisional diagnosis, or the rating of dangerousness [14]. In 2022, our research group published a study of 38 Israeli patients who were referred to the ED for possible involuntary admission. All patients were evaluated both face to face and by video link by 2 different clinicians. The main finding was that there was an extremely high degree of concordance between impressions arrived at under the 2 conditions, especially regarding the need for involuntary admission [15].

In addition to being convinced that telepsychiatry is accurate, one also must be convinced that it is feasible. The question of feasibility can be divided into whether it is feasible for patients as well as for health care providers. For patients, previous work has shown that telepsychiatry is acceptable and highly satisfying in community-based settings [2,9] and in the ED [15-17]. Regarding health care providers, the evidence for feasibility is also generally positive, although more limited. In one study, health care providers had mixed feelings about telepsychiatry before using it [18]. In other studies, after using telepsychiatry, they perceived it to be acceptable [1,17].

In addition to this generally positive impression by clinicians, telepsychiatry has advantages for the health care system. Several studies have documented positive system effects. For example, the use of telepsychiatry contributed to decreased waiting times for patients awaiting psychiatric input in clinical setting (EDs and community clinics), reducing workloads [9,19], and reducing medical costs [20].

In addition to using telepsychiatry in the ED, some studies have examined professionals' impressions of the process of

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implementing telepsychiatry in the ED. Saurman et al [21] evaluated the perceptions of hospital staff regarding a new telepsychiatry program at a rural ED in Australia. The staff reported that they were satisfied with the program, felt confident in managing patients' cases, and valued the accessibility to mental health experts, which they otherwise would not have in such a remote location. An additional study examined the views of 17 staff members from Canadian EDs, and participants reported that telepsychiatry can improve patient experience and expedite service but can also introduce challenges for an already overloaded ED [22]. According to a 2009 report for the California Health Care Foundation, providers and patients who participated in ED telepsychiatry programs reported high satisfaction from the video meetings and stated that, in their opinion, patient outcomes, such as hospital admission or length of stay, were improved using this method [16].

One study that is worth noting was not conducted in an ED setting but does support the use of telepsychiatry for psychiatric emergencies. A university hospital in Norway developed new telepsychiatry services for emergencies in rural areas that lack psychiatric service availability. The findings showed that having access to experts through telepsychiatry was beneficial for patient involvement, reduced nurses' uncertainty, and served as a safety net for the health care team [23].

Unfortunately, previous studies regarding the feasibility of using telepsychiatry in an ED setting have limitations. These studies examined the practical implementation of telepsychiatry in relatively few settings and with relatively small samples and only characterized a relatively limited range of process outcomes. Additional information about the feasibility of using telepsychiatry in ED settings and the outcomes of patients managed using telepsychiatry would help support decisions by policymakers to adopt this strategy.

Although the previous literature has important gaps, we do already know that there are some barriers to the increased use of telepsychiatry. For example, Cowan et al [19] found that health care providers noted technological challenges, the need for guidance and training on how to use this method, and concerns regarding patients' privacy and safety. Other studies documented the unequal degree of comfort with the use of telepsychiatry by patients, with some patients adapting to the new technology relatively easily and others having more difficulty [24]. Last, several studies documented legal or procedural challenges with using telepsychiatry [3,12].

In some cases, restrictive laws may make it difficult or impossible to use telepsychiatry. In Israel, for example, it is the law that, before they can be hospitalized involuntarily, patients must be evaluated in person by a senior psychiatrist [25]. It is worth noting that such policies were created before it was possible to evaluate patients by video link. Although policy is difficult to modify, a number of jurisdictions around the world found ways to change these rules during COVID-19 lockdowns. This led to a rapid expansion of the use of many kinds of telemedicine, including telepsychiatry [26,27].

Although most previous efforts to use telepsychiatry have been in the relatively low-stress setting of delivering outpatient care, the use of telepsychiatry for ED triage could have great benefits, at least theoretically. Patients with acute psychiatric decompensation may pose a danger to themselves and those around them [28]. Their vulnerable state is complex, as they may be agitated and have poor reality testing [28]. Decompensation is more likely to happen when psychiatric patients are staying in settings that are not well-suited to their needs, such as the ED [29]. The ED is a relatively uncomfortable environment for any patient but is even more stressful for patients with psychiatric emergencies [28]. This can result, ironically, in the patient's condition worsening, violent incidents directed toward medical staff, and starting the hospitalization with precisely the reverse of the intended therapeutic benefit [29]. To the extent that incorporating telepsychiatry could help move such patients out of the ED faster, this could decrease the strain on the patients, bringing them to a quiet and controlled environment sooner, where they can begin to heal. Thus, introducing telepsychiatry in this setting, although possibly challenging, could also have great benefits.

Although the idea of using telepsychiatry in triage decisions is not entirely novel, relatively few studies on patients' outcomes have been published in this setting. A national survey in the United States in 2016 examined the extent to which telepsychiatry is already in use in some ED settings. The study found that 20% of the EDs used telepsychiatry, with the most common use being to decide which patients to admit and which to send home [30]. Additional studies examined patient outcomes with telepsychiatry in the ED. Narasimhan et al [31] examined 7261 patients who arrived at the ED and underwent a real-time video visit with a remote psychiatrist. Compared with a matched control group, the telepsychiatry group had significantly more outpatient follow-up care and fewer hospitalizations. This, in turn, was associated with a significant reduction in hospital costs. An additional study from the United States examined the use of telepsychiatry in the pediatric ED. The findings showed a significant reduction in patients' length of stay for nonhospitalized patients (ie, for those sent home from the ED) [32].

Previous studies described the use of telepsychiatry in an ED setting but did not specifically examine its use for the purpose of deciding which patients require involuntary admission. In fact, only 1 observational study examined involuntary admissions to the ED via telepsychiatry [33], but this study did not directly compare patient outcomes between telepsychiatry and face-to-face approaches.

To broaden our understanding of successful telepsychiatry implementation in the ED, further studies guided by implementation science frameworks are needed. One example of an implementation science framework is the Promoting Action on Research Implementation in Health Services (PARIHS) framework [34]. PARIHS posits that successful implementation (SI) is a function of 3 inputs: *evidence*, *context*, and *facilitation* [35]. SI is the extent to which the innovation is completely implemented and adopted as part of standard practice, as opposed to being incompletely adopted or resisted. *Evidence* refers to end users' assessments of the strength of the evidence for the innovation, including their expectations that it will be feasible to use in their setting. *Context* refers to the factors in the environment that support (or resist) the

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implementation of changes in practice. *Facilitation* refers to the efforts of the research team or champions within the clinical team to promote the change.

Our study will examine the implementation of telepsychiatry in Israeli EDs for involuntary admissions using the PARIHS framework, with attention to characterizing which aspects of *evidence*, *context*, and *facilitation* contributed to SI, or the lack thereof. We will also examine the impact of telepsychiatry on patient outcomes and health care utilization, compared with historical controls managed without telepsychiatry.

Methods

Ethics Approval

Our study is being performed in accordance with all relevant guidelines and regulations. Helsinki approval was obtained from the Ethics Committees of Abarbanel Mental Health Center (174; March 13, 2023), Jerusalem Mental Health Center (22-21; November 6, 2022), Lev-Hasharon Mental Health Medical Center (LH12023; February 12, 2023), Tel-Aviv Medical Center (TLV-22-0656; January 3, 2023), and Sha'ar Menashe (1-4-23; April 18, 2023). Any changes in the study protocol will be promptly communicated to the ethic committees, and if necessary, approval for the change will be obtained. Patients will provide verbal assent for telepsychiatry evaluation.

Since the care provided during the study will be the same standard of care for all patients, at least for the duration of the study, it was not deemed necessary to have a data safety monitoring committee. The most easily foreseeable adverse consequences of the change in practice are being measured by the study, and the duration of the intervention period (4 months) is brief. In addition, study data are being collected via chart review and not necessarily contemporaneously within the study period itself. There is not sufficient time during this brief study period to conduct interim analyses. Following an analysis of the study outcomes, a policy decision will be made on the part of Israel's Ministry of Health whether to continue or end the change in practice. There are no formal plans to compensate patients for any harms that may occur during the study, which are likely to be similar to whatever harms could occur under usual care.

Study Design

We will implement a multisite study in 5 Israeli EDs to evaluate the use of telepsychiatry compared with the regular face-to-face method. Under the Mental Health Act regarding involuntary hospitalizations in Israel, all involuntary hospitalizations require an in-person evaluation by the attending psychiatrist [25]. Our study received a limited waiver of this policy for the purposes of research, after which the results of our study will be used to re-evaluate whether the current policy should be changed.

In our study, there will be clinicians, including psychiatry residents and nurses, physically present. However, using the innovation, the attending physician will evaluate the patient via video link, with the conversation facilitated by another provider who is physically present. This has numerous potential advantages, in that the patients may enter a calmer environment (ie, the psychiatry ward) or be sent home sooner if they are not admitted. Less time spent in the ED has the potential to reduce violent incidents and improve the patient's hospital course, by minimizing exposure to a noxious stimulus.

Our study will be a type 1 hybrid implementation study. Hybrid implementation studies aim to shorten the process of translating clinical innovations into practice by simultaneously collecting data about effectiveness as well as the implementation process [36]. A type I hybrid study emphasizes the collection of effectiveness data, often because there is limited previous evidence of effectiveness. However, the team also collects information regarding the contextual factors that supported or impeded implementation, with an eye toward improving the future implementation of this strategy.

Our study will compare the innovation with historical controls. During the pre-intervention period, we will collect data about patient outcomes during a period of 4 months when attending physicians continue to evaluate patients in person, as they have been doing (usual care). During the intervention period, attending physicians will evaluate the patients and make decisions based on a video link. Seasonality would be one possible threat to study validity [37]. To address this, we will collect data using the same 4 months of the year, both in the pre-intervention and intervention periods.

Evaluation of process implementation will be guided by the PARIHS framework [34]. We will characterize the extent to which staff members believe that the innovation will be effective and will be feasible to use in their context and how this belief contributes to SI [34]. We will characterize how the context, including relationships among staff, styles of administrative leadership, and organizational attitudes toward change and quality improvement, at each of our 5 medical centers contributes to or detracts from SI. Finally, we will characterize how the efforts of champions within the clinical staff, known as internal facilitators, did or did not help promote SI [35].

Study Settings

The study will be conducted in 5 psychiatric EDs in Israel. One of the study sites is a general hospital, so psychiatric emergency patients are evaluated and treated in a special section of the general ED. The other 3 hospitals are dedicated psychiatry hospitals, meaning that the ED is only used for psychiatric emergencies. All sites are located in the densely populated center of Israel, in or near Tel Aviv and Jerusalem, where most of the country's population lives [38]. All 5 hospitals are moderate to large in size.

Participants

This study will include 2 population groups: patients and hospital staff.

Patients

We anticipate that our 5 hospitals will collectively evaluate at least 60 patients per month for involuntary admission. Given that each hospital will have a 4-month pre-intervention period and a 4-month intervention period, we plan to enroll at least 240 patients in each study period. To be included, patients must be 18 years or older and arrive during hours when the attending physician is not at the hospital (evening and night shifts). Due

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to the waiver we received for this study and the limitations that were placed on the waiver, we will exclude patients who are brought for evaluation by police after being detained or charged with a crime. Only patients needing an attending assessment under the Mental Health Act regarding involuntary hospitalizations will be included. Patients will provide verbal assent to be evaluated by video link; patients who do not agree will be evaluated in person. Although we will endeavor to support patients who have difficulty participating in a video link, there may be some patients who are unable to communicate adequately by video link, and we will exclude them from the study. To maximize study generalizability, no other exclusion criteria exist.

With an anticipated 240 patients in the control arm and 240 patients in the intervention arm (4 X 60), we will have statistical power to show a relatively small effect size for most outcomes. For example, we will be able to show a difference of as little as 15 minutes of ED time.

Hospital Staff

We will collect data about implementation from all those who are involved with administrating, supervising, or staffing the psychiatric ED. Key staff will include the hospital director, department director, unit director, service manager, senior physicians, psychiatry residents, and nursing staff.

Clinical Outcomes

Clinical outcomes are explained in detail in Table 1. Data will be collected in the same manner from the medical record both before and during the intervention. Baseline patient variables will include sex, age, marital status, city of residence, ethnic group (Jewish or Arab), and known psychiatric diagnoses. We will also collect information about the patient's arrival at the ED, including mode of arrival, legal status, violent incidents pre-arrival, and chronic medications. The primary outcomes for the ED stay, for patients who are admitted involuntarily and for those discharged home, will include time in the ED and violent incidents. Secondary outcomes will include the psychiatric diagnosis given by ED staff, psychiatric status (eg, judgment intact or not intact), and legal status upon release. For patients admitted to hospital, we will also collect information on hospitalizations reversed within 72 hours, which implies that the hospitalization was not necessary, and length of hospital stay. For patients discharged home, we will collect information on those admitted within 7 days, which implies that the patient should have been hospitalized.

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Table 1. Planned collection of outcome variables for a 6-month pilot study comparing telepsychiatry with usual care (historical outcomes during the pre-intervention period) in the emergency department (ED) setting, for assessment of the need for involuntary admission.

Variable	Data collection method
Background characteristics	Patient sex, age, family status, residence, ethnic group, known psychiatric diagnosis; as well as, for both ED arrival and hospitalization: involuntary arrival or by police or emergency services, legal status, violence incidents pre-arrival, and prescribed medications and dosages
Primary outcomes	
ED length of stay	Measured from the time of arrival in the ED until the patient physically leaves the ED to go home or for hospitalization
Violent incidents in the ED	As recorded by ED staff and adjudicated by blinded review of the chart by a senior psychiatrist; violent incidents defined as one of the following: (1) degree of restlessness: calm, moderate restlessness, severe agitation, or catatonia; (2) violence type: verbal violence, violence toward property, violence toward others (eg, escort, staff member, other patients)
Duration of hospitalization (hours)	From the time of ED release until the time of leaving the hospital
Violent incidents in the ward	As recorded by the hospital staff and adjudicated by blinded review of the chart by a senior psychiatrist
Secondary outcomes	
Psychiatric diagnosis in the ED and hospitalization in case of admission	Psychiatric diagnosis categorized as one of the following: (1) neurodevelopmental disorders, (2) schizophrenia spectrum and other psychotic disorders, (3) bipolar and related disorders, (4) depressive disorders, (5) anxiety disorders, (6) obsessive-compulsive and related disorders, (7) trauma and stressor-related disorders, (8) somatic symptom and related disorders, (9) substance-related and addictive disorders, (10) neurocognitive disorders, (11) personality disorders, (12) adjustment disorder, (13) diagnosis deferred
Psychiatric status in the ED and hospitalization in case of admission	Psychiatric status to include the presence or absence of the following: (1) disturbed thinking, (2) disturbed perception, (3) disturbed judgement, (4) dangerousness
Release from the ED and hospitalization in case of admission	Release from the ED and hospitalization in case of admission to include one of the following: (1) discharge to home, (2) discharge to the institution from which the patient came, (3) hospitalization in a general hospital, (4) hospitalization in another psychiatric hospital, (5) police, (6) runaway, (7) other place
Legal status upon release from the ED and hospitalization in case of admission	Legal status upon release to include one of the following: (1) with consent, (2) compulsory follow-up visits in a community clinic, (3) involuntary hospitalization order, (4) other
Reversal of admission	Unnecessary admission: involuntary admission that is reversed within 72 hours; measurement of the proportion of admissions reversed within 72 hours
Admission within 1 week of ED discharge	A patient sent home from the ED without being admitted, who is then admitted within 1 week and should have been admitted the first time
Implementation process outcomes	
Evidence construct	
SHEMESH[a] questionnaire	A validated tool to evaluate organizational change and identify its barriers; evaluation of the evidence construct achieved via 4 online questions administered to the medical and nursing staff about the strength and feasibility of psychiatric assessment via video link at the ED and how preferable it is compared with the face-to-face method; items rated from 1 (strong disagreement) to 5 (strong agreement)
Patient satisfaction with ED course	As they are leaving the ED, patients asked to rate their overall satisfaction with 4 items (overall ED experience, interactions with nurses, interactions with residents, interactions with the attending physician), rated using a visual analog scale from 1 (very dissatisfied) to 5 (very satisfied)
Staff satisfaction with the ED work	Medical and nursing staff asked to rate their overall satisfaction with their work in the ED on a scale from 1 (very dissatisfied) to 5 (very satisfied)
Medical staff confidence with evaluation	Medical staff asked to rate their overall confidence with evaluating patients sufficiently well to make appropriate decisions about whether they need to be admitted on a scale from 1 (very uncertain) to 5 (very confident)
Context construct	
SHEMESH	Evaluation of the context construct achieved via 6 online questions administered to the medical and nursing staff about the acceptability of initiatives, the way decisions are made, and the way medical and nursing teams are communicating and collaborating in the ED; items rated from 1 (strong disagreement) to 5 (strong agreement)
Measurement of successful implementation	
Staff's impression of the implementation process	Measured via an open-ended questionnaire to all staff members at the conclusion of the intervention period, to gather their thoughts on the advantages and the challenges of using telepsychiatry; its fit for a variety of patient groups; and in their opinion, the necessary conditions for the use of telepsychiatry

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Variable	Data collection method
Feedback from clinical champions	Solicitation of ongoing feedback from clinical champions located within each site who are responsible for promoting the intervention; feedback to be recorded in a research diary by the researchers and include their impression of success and failure of the implementation process, what would help improve it, and how fully the innovation is being adopted

[a]SHEMESH: acronym of "SHE'elon Muchanut Ergunit le'SHinuy" in Hebrew, translated from the English name of "Organizational Readiness to Change Assessment."

Implementation Outcomes

Evaluation of the implementation process of telepsychiatry will be guided by the PARIHS model. We will collect information on SI and the 3 factors that contribute to it: *evidence*, *context*, and *facilitation*. SI will be assessed according to feedback from site champions at each of the 5 sites, who will share impressions with our team about what is going well or less well in the implementation effort. This feedback will also be used to support tailoring of the intervention across each of the 5 sites. SI will also be investigated by open-ended questionnaires administered to all staff members to understand providers' impressions of which parts of the intervention succeeded and which should be modified.

The *evidence* construct includes staff perceptions of the strength and feasibility of psychiatric assessment via video link at the ED, how preferable it is compared with the face-to-face method, and psychiatrist confidence in the accuracy of admission decisions made using video link. The *context* construct includes the acceptability of initiatives in the ED, the way decisions are made, and the way medical and nursing teams are communicating and collaborating in the ED. Information on the *facilitation* construct and the adequacy of our facilitation efforts will come mostly from the site champions.

Data Collection

Data collection will include patient outcomes and implementation outcomes. Patient outcomes will be collected through hospital medical records using trained assessors. Process outcomes will be collected using questionnaires. The Organizational Readiness to Change Assessment survey is a validated tool created to evaluate organizational change and innovation and identify the barriers through the prism of the PARHIS framework [35]. For the purpose of this study and initially for the use of others, our group developed and validated the Hebrew version of this questionnaire, named "SHE'elon Muchanut Ergunit le'SHinuy" (English: Organizational Readiness to Change Assessment) and abbreviated as SHEMESH. The SHEMESH will examine medical and nursing staff perceptions about the evidence of telepsychiatry and its implementation in the ED context. The SHEMESH has high Cronbach alpha scores for the 2 scales (total of 10 items on a 5-point Likert scale): *evidence* (4 items): α=.887; *context* (6 items): α=.852 [39]. The questionnaire will be administered online once before implementing telepsychiatry and again 3 months after the implementation. Staff will be asked to rate their overall agreement with statements on a scale from 1 (strong disagreement) to 5 (strong agreement).

Data about the *evidence* construct will be also collected through the following questionnaires: patient satisfaction questionnaire, staff satisfaction survey, and medical staff confidence in psychiatric evaluations survey.

The patient satisfaction questionnaire will be used to compare the patient experience under usual care with that under the intervention condition. ED patients will be asked 3 questions about their overall experience at the ED and their interactions with medical and nursing staff. Patients will be asked to rate the questions using a visual analog scale from 1 (very bad) to 5 (very good). During the telepsychiatry phase, they will also be asked about their satisfaction with the video link.

The staff satisfaction survey will be administered online for all ED medical and nursing staff, once before implementing telepsychiatry and 3 months after the implementation. Staff will be asked to rate their overall satisfaction with their work in the ED from 1 (very dissatisfied) to 5 (very satisfied)

The medical staff confidence in psychiatric evaluations survey will be administered online before the telepsychiatry implementation and 3 months after the implementation. Staff will be asked to rate their overall confidence in patients' evaluations from 1 (very uncertain) to 5 (very confident) for admission decisions.

Data regarding the SI outcome will be collected using an open-ended questionnaire administered to all staff members at the end of the intervention phase. Staff will be asked about the advantages of and challenges with using telepsychiatry in the ED, its fit for patients from different backgrounds, and their opinion of the necessary conditions for the use of telepsychiatry.

All data collected during the research will be anonymized, entered, and stored in password-protected files on a researcher's (LS) computer.

Data Analysis and Dissemination of Results

All data will be analyzed using SPSS (version 27.0). Baseline characteristics will be compared between the intervention and historical controls to ensure that the 2 groups are balanced. All normally distributed data will be analyzed using *t* tests or ANOVAs. Data found to be non-normally distributed will be analyzed using Mann-Whitney *U* tests or Kruskal-Wallis *H* tests. Comparisons of percentages between different groups will be analyzed using chi-square tests. Close-ended questions using Likert scale responses will be grouped as negative (1-2), neutral (3), or positive (4-5).

The results of the study will be disseminated to the public via published manuscripts in the peer-reviewed literature, and we also plan to brief the Israeli Ministry of Health on our study findings. Authorship will include all study investigators, including, at a minimum, all site principal investigators and likely others who participated in collecting data. Manuscripts

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and reports will be written by study investigators, and we will not rely on medical writers. The study protocol is being published with this manuscript, and we intend to share the statistical code with those who request it. Data from the study cannot be made available due to the terms of our study approvals by the relevant research ethics committees of the hospitals involved.

Results

This study has been funded by the Israel National Institute for Health Policy Research (grant number 2021/77). Data collection began in July 2023 in 2 study sites and will begin soon at the others. Data collection for the pre-period will be performed from the previous year, to match the months during which the pilot program was implemented at that site.

Discussion

Overview

We propose an innovative approach to evaluate the impact of telepsychiatry on involuntary admissions, as well as the barriers and facilitators to implementing this method in the ED. Using telepsychiatry for ED assessment is currently not allowed as part of standard Israeli practice. With a waiver of the usual policy from the Ministry of Health, for the purpose of evaluation, we will implement telepsychiatry in 5 EDs throughout Israel. We will examine the effectiveness and implementation of telepsychiatry for involuntarily committed cases. We will compare administrative and clinical outcomes from the implementation phase with those from historical controls, as well as evaluate process outcomes using questionnaires. This study provides an opportunity to understand the feasibility of using this approach, as well as the impact of using this method on patients' outcomes. Our results will also help to provide policymakers with data to reassess the current policy.

This study is a response to the lack of evidence for telepsychiatry use in the ED. Other studies have examined telepsychiatry effectiveness in the outpatient setting [1,9]. There are some mixed studies from community and emergency settings examining telepsychiatry's effectiveness [40] or its implementation process [24]. To date, there are no studies that evaluate the use of telepsychiatry specifically for clinicians to evaluate the need for involuntary commitment. The issue of involuntary commitment involves some of the most vulnerable patients in the entire medical system, and there is a strong impetus to evaluate these patients promptly and help them reach a quieter and more stable environment more quickly. To the extent that telepsychiatry may help accomplish this goal, the study we present in this paper is crucially important to the telepsychiatry field.

This study has the potential to directly impact patient care and welfare as well as health systems. Our proposed study could improve patient safety and well-being by preventing long waits and, thus, opportunities for decompensation. We expect to show that this approach allows patients to be put in a safer place faster and spend less time in uncontrolled settings. We hypothesize that this will be expressed as fewer violent incidents and shorter hospital stays. There may also be an impact on ED crowding, which we will not directly measure. Patients may also receive direct therapeutic benefit. Telepsychiatry may be used to initiate psychiatric evaluation faster, reduce the length of the ED wait, and reduce decompensation. In turn, implementing telepsychiatry in the ED could reduce the costs and workload in the ED by moving patients out quicker. To the extent that we are able to show such an outcome, this will constitute a compelling argument for its widespread adoption.

Limitations

This study has several potential challenges. There may be barriers to implementation, such as difficulty using video equipment or software, adequacy of Wi-Fi, or inability to reach the attending physician. There may also be resistance to change, as could occur with any change in practice. Since this is a “real world” study, another challenge is matching telepsychiatry to a variety of patients' backgrounds and contexts. Since motivation and intention are required on behalf of the patient in a video session [11,12], the ability of patients to fully cooperate may be an issue, especially since these are patients in the midst of a psychiatric emergency. By conducting this study, we will be able to identify such gaps and address them accordingly, or at least to quantify them.

Conclusions

The implementation of telepsychiatry in the ED setting has the potential to improve care for patients. Although its efficacy has been noted in community settings, its application in emergency contexts remains largely uncharted territory. This study aims to shed light on the effectiveness of telepsychiatry for evaluations of involuntary commitment in the ED, as well as exploring the facilitators and barriers to its implementation in this setting. If our hypotheses are confirmed, it will not only demonstrate the accuracy of telepsychiatry but also pave the way for a more patient-centered and efficient approach in the psychiatric ED.

Acknowledgments

This is work is supported by the Israel National Institute for Health Policy Research (grant number 2021/77). No generative AI was used in any portion of the manuscript writing.

Data Availability

The data sets that will be used and analyzed during the current study will be available from the corresponding author on reasonable request.

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Authors' Contributions

LS was involved in study planning, study design, and drafting the manuscript. MB, GL, KA, SR, and OL were involved in the study planning and reviewing the manuscript. RE and AJR initiated the study and were involved in study planning, intervention design, and reviewing the manuscript. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

ED: emergency department
PARIHS: Promoting Action on Research Implementation in Health Services
SI: successful implementation

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Protocol

A Mindfulness-Based Resiliency Program for Caregivers of Patients With Severe Acute Brain Injury Transitioning Out of Critical Care: Protocol for an Open Pilot Trial

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Abstract

Background: Caregivers of patients with severe acute brain injuries (SABI) that lead to coma and require intensive care unit (ICU) treatment often experience chronic emotional distress. To address this need, we developed the Coma Family (COMA-F) program, a mindfulness-based resiliency intervention for these caregivers.

Objective: We will conduct an open pilot trial of COMA-F (National Institutes of Health Stage IA). Here we describe our study protocol and proposed intervention content.

Methods: We will enroll 15 caregivers of patients with SABIs during their loved one's hospital course from 3 enrollment centers. A clinical psychologist will deliver the COMA-F intervention (6 sessions) over Zoom (Zoom Video Communications, Inc) or in person. We will iterate COMA-F after each caregiver completes the intervention and an exit interview. English-speaking adults who have emotional distress confirmed by the clinical team and are the primary caregivers of a patient with SABI are eligible. The adult patient must have been admitted to the neuro-ICU for SABI and (1) have had a Glasgow Coma Scale score below 9 while not intubated or an inability to follow meaningful commands while intubated at any point during their hospitalization for >24 hours due to SABI; (2) will be undergoing either tracheostomy or percutaneous endoscopic or surgical gastrostomy tube placement or have already received one or both; and (3) have a prognosis of survival >3 months. We will identify eligible caregivers through screening patients' medical records and through direct referrals from clinicians in the neuro-ICU. During the intervention we will teach caregivers mind-body and resilience skills, including deep breathing, mindfulness, meditation, dialectical thinking, acceptance, cognitive restructuring, effective communication, behavioral activation, and meaning-making. Caregivers will complete self-report assessments (measures of emotional distress and resilience) before and after the intervention. Primary outcomes are feasibility (recruitment, quantitative measures, adherence, and therapist fidelity) and acceptability (treatment satisfaction, credibility, and expectancy). We will conduct brief qualitative exit interviews to gather feedback on refining the program and study procedures. We will examine frequencies and proportions to determine feasibility and acceptability and will analyze qualitative exit interview data using thematic analysis. We will also conduct 2-tailed *t* tests to explore signals of improvement in emotional distress and treatment targets. We will then conduct an explanatory-sequential mixed methods analysis to integrate quantitative and qualitative data to refine the COMA-F manual and study procedures.

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Results: This study has been approved by the institutional review board at 1 of the 3 enrollment centers (2023P000536), with approvals at the other 2 centers pending. We anticipate that the study will be completed by late 2024.

Conclusions: We will use our findings to refine the COMA-F intervention and prepare for a feasibility randomized controlled trial.

Trial Registration: ClinicalTrials.gov NCT05761925; https://clinicaltrials.gov/study/NCT05761925

International Registered Report Identifier (IRRID): PRR1-10.2196/50860

(JMIR Res Protoc 2023;12:e50860) doi:10.2196/50860

KEYWORDS

severe acute brain injury; coma; caregiver; resilience; mindfulness; brain injury; emotional distress; decision-making; emotional support; intervention; support; self-report assessment; mental health

Introduction

Background

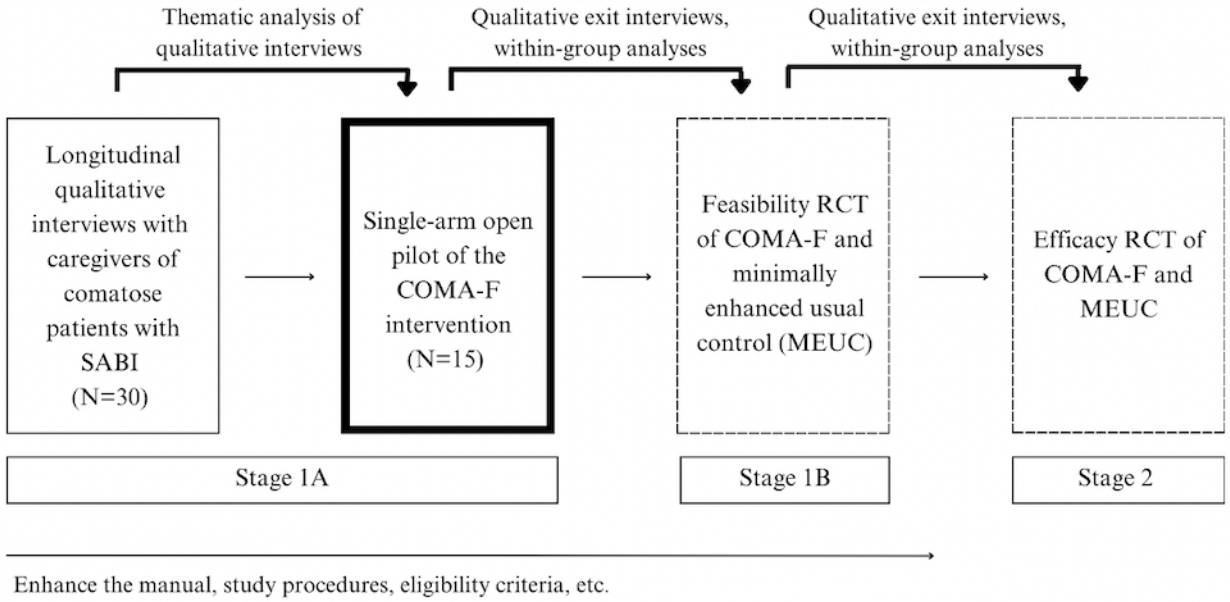
Severe acute brain injuries (SABI) such as ischemic stroke, hemorrhagic stroke, traumatic brain injury, or hypoxic-ischemic encephalopathy are sudden catastrophic events for both patients and their families [1]. The majority of patients with SABI cared for in an intensive care unit (ICU) are incapacitated, and many are comatose [2]. Caregivers of patients with SABI who survive their ICU admission nevertheless experience high rates of emotional distress, which, if untreated, becomes chronic [1,3]. These caregivers grapple with the uncertainty of their loved one's long-term prognosis, the stress of making decisions on their loved one's behalf, grief over their loved one's loss of neurological function, and the stress of managing their own life outside of the ICU [1,3,4]. While the stay in an ICU itself can be quite lengthy, ultimate recovery from SABI can be prolonged and uncertain, and caregivers often endure these stressors beyond the acute hospitalization [5,6].

Caregivers of hospitalized patients with SABI have unmet needs for emotional support. Prior work shows that they feel overwhelmed, underprepared for caregiving, unable to manage basic self-care, isolated, and lonely, and that they deal with ambiguous loss [5-8]. Despite these needs, a recent systematic review found that among 22 interventions for caregivers to general ICU patients, none led to long-term improvements in emotional distress, and many actually increased caregiver burden [9]. Further, there are few interventions specific to the needs of SABI caregivers. Those that do exist focus mainly on crisis management and decision-making during the initial 48 hours of admission [3,10,11] rather than addressing prolonged uncertainty, grief, and stress. Taken together, there is a critical need for effective interventions for caregivers of surviving patients with SABI that extend into the period following the ICU stay.

Our team has followed the National Institutes of Health (NIH) Stage Model for behavioral intervention development [12] to develop the Coma Family Program (COMA-F), a mindfulness-based resiliency program for caregivers of patients with SABI transitioning out of the ICU (Figure 1). We developed preliminary COMA-F content based on adaptations of our intervention for patients and caregivers hospitalized in the neuro-ICU (Recovering Together) [13] and from qualitative interviews of caregivers of surviving patients with SABI. For the latter, we conducted longitudinal qualitative interviews with 30 caregivers across 14 ICUs in the United States to better understand their stressors, coping methods, and treatment preferences [14,15]. Nearly all caregivers discussed using avoidance or distraction as initial coping strategies [14]. They also expressed a desire to learn adaptive coping skills, learn communication skills for interacting with the patient's care team and other family members, and for support with making difficult decisions (Hwang et al, "Psychosocial support needs and preferences among family caregivers of ICU patients with severe acute brain injury: a qualitative thematic analysis," manuscript under review). We have used this feedback and adapted content from Recovering Together to develop the first version of the COMA-F intervention. We plan to deliver COMA-F through a single-arm open pilot trial outlined in this paper (N=15 caregivers). We will use the findings from the open pilot to iteratively refine COMA-F. We will then conduct a feasibility randomized controlled trial (RCT) of COMA-F versus minimally enhanced usual control (MEUC).

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Figure 1. Iterative stages of the development of a mind-body resiliency program for caregivers of patients with severe acute brain injury (the COMA-F program). The open pilot trial described in this protocol is outlined in bold. The subsequent feasibility RCT and efficacy RCT are outlined by dashed lines. COMA-F: Coma Family program; MEUC: minimally enhanced usual control; RCT: randomized controlled trial; SABI: severe acute brain injury.



Objectives

Here we describe our procedure and delivery of the COMA-F open pilot trial. We will explore the preliminary feasibility and acceptability of COMA-F. Further, through exit interviews at the end of the intervention, we expect to elicit feedback on program procedures (hybrid in-person and Zoom format), treatment manuals, support from study staff, and expectations of the program. We will use this feedback to inform each iteration of COMA-F. After completion of the open pilot trial, we will then proceed to test the feasibility of the refined COMA-F program versus the MEUC.

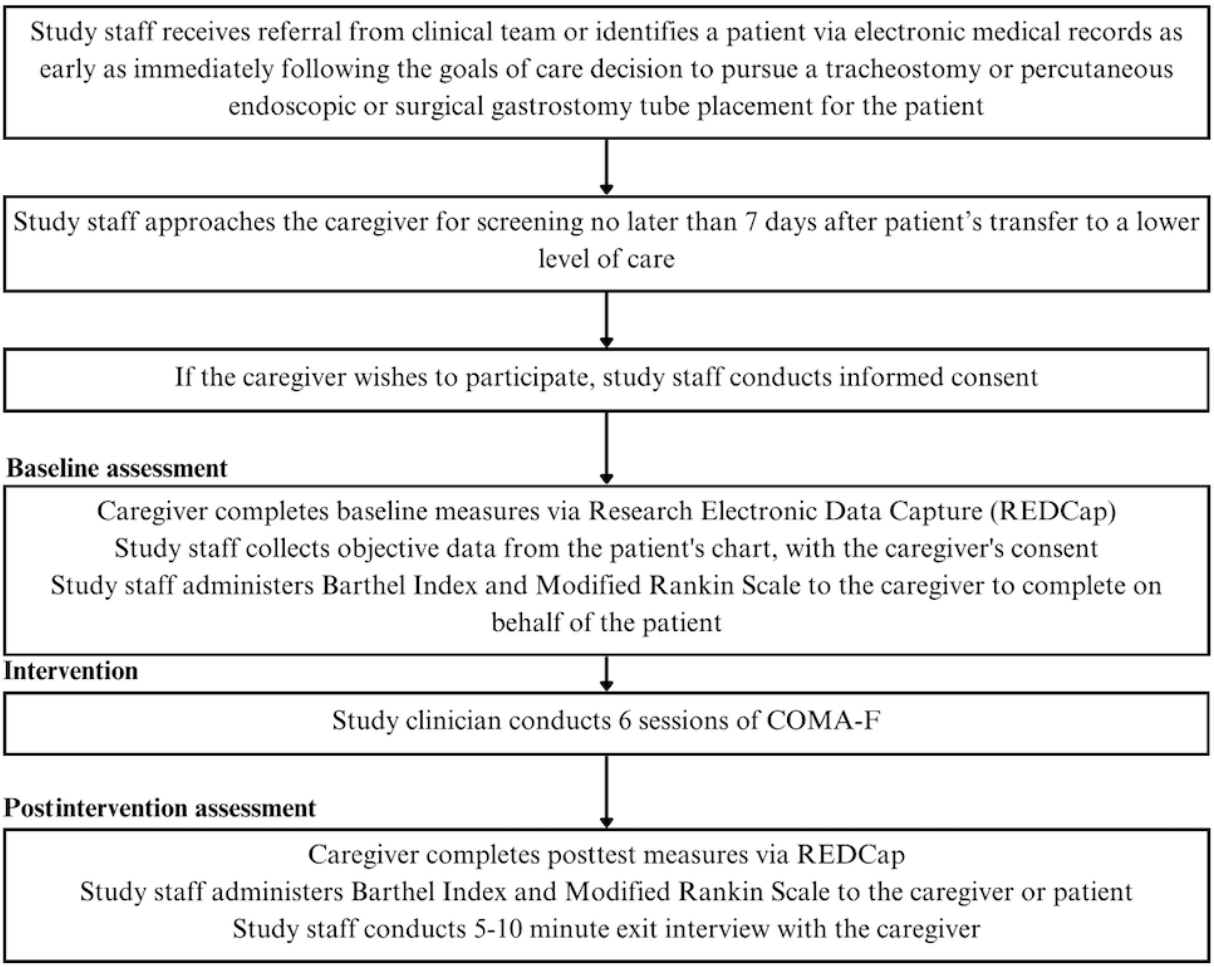
Methods

Study Design and Setting

We will deliver our open pilot of COMA-F for caregivers of comatose patients with SABIs enrolled from 3 academic medical centers in the United States. If we encounter recruitment challenges, we will also plan to enroll from collaborators' institutions in the northeastern and mid-Atlantic regions of the United States. We present our study design and procedure in Figure 2.

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Figure 2. Open pilot trial design and procedure for the development of a mind-body resiliency program for caregivers of patients with severe acute brain injury (the COMA-F program). COMA-F: Coma Family; REDCap: Research Electronic Data Capture.



Ethics Approval

This study has been approved by the institutional review board at 1 of the 3 enrollment centers (Mass General Brigham Institutional Review Board, 2023P000536), with approvals at the other 2 centers pending. We will conduct informed consent with all caregivers enrolled in the study. We will deidentify all data and provide subject ID numbers to participants. We will compensate participants US $20 via check for completing baseline assessments and US $40 via check for postintervention assessments, for a total of US $60 per participant.

Recruitment and Screening

Overview

We present our study inclusion criteria in Textbox 1. We will recruit caregiver subjects through 2 concurrent mechanisms.

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Textbox 1. Open pilot trial inclusion criteria for the development of a mind-body resiliency program for caregivers of patients with severe acute brain injury (the Coma Family program).

- Age 18 years or older
- English-speaking
- Screens for emotional distress on either depression or anxiety subscales (>7) of the Hospital Anxiety and Depression Scale
- Confirmed by the primary clinical team as the primary caregiver for a patient who has the following characteristics:
  - Age 18 years or older
  - Admission to the intensive care unit with a severe acute brain injury for one of the following: ischemic stroke, intracerebral hemorrhage, subarachnoid hemorrhage, traumatic brain injury, or hypoxic-ischemic encephalopathy
  - Glasgow Coma Scale score below 9 (in the judgment of the medical team) while not intubated or an inability to follow meaningful commands while intubated at any point during their hospitalization course for more than 24 consecutive hours due to the brain injury itself and not a confounding factor (ie, sedation and seizures)
  - Still alive in the intensive care unit at the time that the clinical team approaches the primary caregiver about possible recruitment
  - Either will be undergoing tracheostomy and percutaneous endoscopic or surgical gastrostomy tube placement or has already received one or both
  - Has a prognosis for survival of greater than 3 months and does not have a concurrent diagnosis of a terminal illness or injury, as judged by the clinical team

Referrals From the Clinical Team

ICU medical and nursing team members who are caring for patients with SABIs will identify eligible caregivers and notify the study team, as they currently do in 1 of our enrollment centers for our ongoing Recovering Together trial of patients and caregivers in the neuro-ICU [13]. Notably, COMA-F will capture caregivers of patients with SABI as described in Textbox 1, whereas Recovering Together exclusively focuses on dyads of caregivers and patients who are cognitively intact.

Study Staff Screening

We will conduct daily prescreening of electronic health record admission reports to identify patients that meet the SABI criteria discussed below. Study staff will then inquire with the clinical team if the identified patients have a caregiver that meets inclusion criteria.

Enrollment

Once a potential caregiver has been identified and approved by the clinical team, a member of the study team will approach the caregiver in person or call them via phone no later than 7 days after the patient's transfer to a lower level of care.

Caregivers who wish to participate will complete consent. During the consent process we also inform caregivers that we will collect patient data from the medical record (eg, demographics, diagnosis, and procedures). Prior to the intervention, caregivers will complete self-report baseline assessments through Research Electronic Data Capture (REDCap) either in person on a tablet, or they will be emailed a link to the REDCap survey. We plan to enroll 15 caregivers.

COMA-F Intervention Content

The intervention will have 6 sessions and be presented as a hybrid program. Caregivers will have the option for any number of initial sessions to be delivered in person within the hospital (until the patient is discharged). If the patient is discharged at any point in the intervention, the remaining sessions will be delivered via live video using Zoom. We will also give caregivers the option of completing the intervention completely over Zoom. Zoom is a free and secure internet-based videoconferencing software program that is currently used to provide care for patients at each of the recruiting centers.

Sessions focus on developing mindfulness-based resiliency skills to cope with and manage caregiver-related stressors. The sessions were developed based on caregiver feedback in our qualitative interviews [14,15] and from adapted Recovering Together content [13]. Caregivers will choose 6 modules from a selection of 7 modules. The 7 modules are presented in Table 1.

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Table 1. Session outline for the COMA-F[a] program. The program will be delivered to caregivers of patients with severe acute brain injuries. The program will take place over 6 weeks.

Session	COMA-F topic	COMA-F skills and session content
1	Coping with the here and now	Deep breathing, mindfulness, 24-hour block, and mindfulness meditation
2	Coping with uncertainty	Dialectics, hands as worries, and support with difficult decisions
3	Adjusting to new roles	Identify the distress spiral and challenge unhelpful thoughts
4	Engaging social support	Effective communication with other family members and friends and care team
5	Engaging with positive activities	Behavioral activation, using social support, and setting daily goals
6	Managing fear and worry	Observing fear and worry and acceptance and change
7	Making meaning from our experiences	Making meaning: finding purpose and meaning in new caregiving role

[a]COMA-F: Coma Family.

Feasibility and Acceptability Outcomes

The feasibility and acceptability markers are presented in Table 2.

Table 2. Feasibility and acceptability outcomes for our open pilot trial of a mind-body resiliency program for caregivers of patients with severe acute brain injuries. Outcomes will be assessed at the end of the program.

Outcome	Definition
Feasibility (>70% acceptable; >80% excellent)	
Recruitment	Percentage of eligible caregivers who participate
Assessments	Percentage of enrolled caregivers with no measures missing
Adherence	Percentage of caregivers that complete 4 of 6 sessions
Therapist fidelity	After randomly selecting 20% of sessions, percentage of sessions with 100% of content delivered
Acceptability (>70% acceptable; >80% excellent)	
Treatment satisfaction	Percentage of caregivers who score above the midpoint on the Client Satisfaction Questionnaire-3 [16]
Credibility and expectancy	Percentage of caregivers who score above the midpoint on Credibility/Expectancy Questionnaire [17]
Adverse events	Mild adverse events reported in <10% of caregivers; no adverse events linked to program participation

Assessments

We selected quantitative measures based on those collected in Recovering Together and from our qualitative interviews during COMA-F development (Textbox 2). We will administer the same measures at baseline and after the intervention.

Textbox 2. Quantitative measures administer at baseline and after the intervention.

Emotional distress

Hospital Anxiety and Depression Scale—measures anxiety and depression symptoms [18]; Posttraumatic Stress Disorder Checklist–5—measures posttraumatic stress symptoms [19].

Resiliency factors

Measure of Current Status Part A—measures adaptive coping abilities [20]; Cognitive and Affective Mindfulness Scale Revised—measures inclination toward acting mindfully [21]; Toronto Mindfulness Scale–Trait—measures trait mindfulness [22]; ENRICHD Social Support Instrument—measures perceived availability of social support [23].

Functional status of patient

Barthel Index—measures functional independence in activities of daily living [24]; Modified Rankin Scale—measures level of disability in patients after a SABI [25].

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Exit Interview Procedures

Caregivers will complete the postintervention measures listed above immediately after the end of session 6. We will then conduct a brief 5-10 minute exit interview. We will ask caregivers to provide feedback on the program procedures, hybrid in-person and Zoom format, treatment manuals, support from study staff, and expectations of the program. We will also ask caregivers to discuss their responses on the pre- and postintervention assessments.

Data Analysis

For quantitative data, we will calculate frequencies and proportions of the feasibility and acceptability outcomes. We will also conduct exploratory analyses to examine differences in emotional distress outcomes and feasibility or acceptability outcomes by the sex of the caregiver. For qualitative data, we will examine exit interviews using thematic analysis following the Framework Method [26]. We will then conduct mixed methods analysis using an explanatory-sequential design which will allow us to integrate quantitative and qualitative data to refine the COMA-F manual and study procedures. Specifically, we will use the exit interviews to explain the quantitative findings and to elicit feedback on the program.

Results

We have received funding by the Neurocritical Care Society to begin recruiting in January 2024. Based on our recruitment data from our qualitative interviews [14,15] we expect to enroll 15 caregivers by November 2024. Following this timeline, our last enrolled caregiver would complete the program in December 2024.

Discussion

Scientific Contribution

Chronic emotional distress is common in caregivers of comatose patients with SABIs, which in turn undermines their caregiving ability and the patient's own health and recovery [27,28]. As novel neurocritical care interventions seek to pursue exciting and more aggressive measures to "cure coma," [29-31] caregivers of more patients may potentially endure lengthy periods of uncertainty and distress. As such, the COMA-F program is timely, aiming to prevent the development of chronic distress in these caregivers by teaching them mindfulness-based resiliency skills. These skills will help caregivers manage the severity of their distress.

This protocol provides the framework of our open pilot trial of COMA-F. The intervention is novel and flexible, offering hybrid delivery methods to bypass geographical barriers to participation. Following the NIH Stage Model for behavioral intervention development [12], we will use the open pilot results to refine the program and inform a future feasibility RCT of COMA-F versus MEUC.

Limitations

Our pilot trial has limitations that we hope to address in future iterations and adaptations of COMA-F. First, our recruitment will be restricted to the demographic distribution of our 3 enrolling centers. In our future feasibility RCT we will focus specifically on recruiting a representative racial and ethnic sample of the United States. Second, we are targeting caregivers caring for patients who are undergoing prolonged life-supporting therapy as opposed to transitioning patients to comfort care only. In future trials, we do plan to adapt COMA-F to be offered to caregivers potentially transitioning their loved ones to comfort measures.

Conclusions

We will use the results from this open pilot trial to inform the development of a mind-body resiliency program for caregivers of patients with SABIs. Our study will provide quantitative and qualitative data that we will use to refine the current iteration of the program. We will then test the refined intervention in a feasibility RCT.

Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during this study.

Conflicts of Interest

None declared.

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Abbreviations

COMA-F: Coma Family
ICU: intensive care unit
MEUC: minimally enhanced usual control
NIH: National Institutes of Health
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
SABI: severe acute brain injury

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Protocol

Cultural Adaptation of the Actionable Health App Evaluation in Japan: Protocol for a Web-Based Modified Delphi Expert Consensus Study

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Abstract

Background: With an increase in both the number of mental health disorders people are experiencing and the difficulty in accessing mental health care, the demand for accessible mental health care services has increased. The use of mobile devices has allowed people to receive care in their daily lives without restrictions on time or location. However, the majority of publicly available mobile health apps are not evidence-based, and the top-rated apps are not always safe or user-friendly and may not offer clinically beneficial results.

Objective: This study aims to create a cultural adaptation of the American Psychiatric Association's comprehensive app evaluation framework in Japan using a web-based modified Delphi expert consensus.

Methods: A web-based modified Delphi study includes developing the Japanese version of the comprehensive app evaluation framework and 3 Delphi rounds. In the first round, our working group sends a questionnaire to the panelists, who then complete it. In the second and third rounds, the working group sends a questionnaire and a summary of the panelists' answers based on each of the previous rounds. The panelists answer the questionnaires based on this summary. The summarization procedure is automated to help reduce the biases that can be generated when panelists' answers are summarized and when the panelists receive them. The working group sends only the result of the summarization with the next round's questionnaire. All interactions between the working group and the panelists will be conducted on Qualtrics (Qualtrics Japan LLC), a questionnaire platform. To culturally validate the comprehensive mental health app evaluation framework, participants from the following three categories will be recruited in Japan: (1) researchers, (2) practitioners, and (3) app developers.

Results: This study received funding from a crowdfunding campaign in Japan (April 2023). The Delphi study began in January 2023 and will be completed in December 2023. We had already completed the translation of the 105 original app evaluation item questions by December 2022.

Conclusions: While the need for treatment using mental health apps is increasing, no framework that can be used to develop a centralized database for health apps is available or accessible, and no consensus has been reached among stakeholders in Japan about an appropriate framework. The results of the web-based modified Delphi method presented in this paper may provide direction for the development and use of mental health apps in the future among the relevant stakeholders. Furthermore, this study will enhance recognition of the framework among researchers, clinicians, mental health app developers, and users, in addition to devising new instruments to help users or practitioners efficiently choose the right app for their situations.

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KEYWORDS

mobile; eHealth; mHealth apps; mobile health; modified Delphi study; Japan

Introduction

Problems with mental health, such as mental health disorders, affect people internationally. According to the Global Burden of Diseases, Injuries, and Risk Factors Study, the 2 most disabling mental disorders, depression and anxiety disorders, ranked among the top 25 leading causes of burden worldwide in 2019 [1]. In addition, the COVID-19 pandemic has had an enormous impact on mental health. For example, the World Health Organization [2] indicated that there was a remarkable increase in mental health problems in the general population; loneliness and a positive COVID-19 diagnosis increased the risk of suicidal thoughts. The COVID-19 pandemic led to a 27.6% increase in cases of major depressive disorders and a 25.6% increase in cases of anxiety disorders in 2020 [3]. Furthermore, COVID-19 has made it more difficult for people facing mental health problems to access outpatient mental health services [2].

With the rise of mental health problems and the increasing difficulty in access to in-person mental health care services, the demand for accessible mental health care services has significantly increased. The use of mobile devices, which are now owned by a majority of people, has made it possible for individuals to access care in their daily lives without being restricted by place and time [4-6]. As of 2017, more than 318,000 health apps existed worldwide; this is twice as many as were available in 2015. Of 318,000 health apps, 490 apps targeted mental health and behavioral disorders [7]. In Japan, a systematic search of the Google Play Store and Apple App Store between June 4 and June 11, 2021, found that 172 mental health apps are available [8]. Moreover, a previous study of Japanese university students found that the mobile health (mHealth) apps usage rate was 32.1% [9]. Considering that 36% of adults who owned smartphones or tablets in a national sample of the United States [10] had mHealth apps on their devices, the usage rate of mental health apps in Japan is estimated to be about the same as in other countries.

Recent reviews have found that mHealth apps could be effective in reducing symptoms of depression and anxiety in adults and youth [11,12]. Unfortunately, some of the apps available are unreliable or harmful. Most publicly available mHealth apps are not evidence-based, and top-rated apps on the app store are not always safe or user-friendly and may not offer clinically beneficial results [13,14]. Similar problems have been reported in Japan [15].

It is difficult for service users (eg, clinical therapists, patients, the general public, and those without mental health concerns) to ensure that apps are safe, evidence-based, usable, and offer clinically beneficial results [16]. Multiple scales and frameworks have been developed to evaluate mHealth apps [17,18]. These scales and frameworks include scales for evaluating the quality, safety, usability, and importance of apps [19]. However, the majority of scales have been developed for app developers to evaluate their own apps [19], and more inclusive tool apps are necessary to help users select the right app based on their conditions and preferences.

The App Evaluation Model framework proposed by the American Psychiatric Association (APA) is useful for addressing this issue [20]. This framework was constructed via a 6-step process that involved harmonizing the 961 app evaluation questions included in 45 existing app evaluation frameworks, removing duplicate, redundant, and nonrelevant questions, and then grouping the remaining 357 questions into 5 priority levels: background information, privacy and security, evidence-based, ease of use, and data integration [21]. Even then, there was no centralized database where users can glance at how various health apps perform when assessed via the framework. Therefore, Lagan et al [16] translated APA's framework for evaluating apps into a set of objective questions that can be published on the internet; the questions from the APA model were operationalized into the 105 objective questions that are either binary or numeric. The 105 objective questions are aligned with the levels of the APA framework, with the 5 levels arranged in a pyramid format to reinforce the need to first consider access, safety, and privacy. There were some additions and alterations to several questions to reflect ongoing feedback from stakeholders after a 2-day summit in December 2019 [16]. The main difference between the user version of the Mobile App Rating Scale, which is the most used mHealth apps evaluation scale, and the app evaluation model is that the app evaluation model does not score questions or produce summary scores about the quality of app safety, usability, etc, but instead allows the user to judge what is important and a good match for them.

Currently, no framework that can be used to develop a centralized database for health apps is available and accessible, and no consensus has been reached among experts and clinicians in Japan about an appropriate framework. The aim of this paper is to describe the study protocol that will be used to validate the adaptation of the 105 objective questions in Japan and develop a Japanese version of the framework among stakeholders involved in mental health apps. In the absence of empirical evidence to reach such a consensus, various methods can be used to synthesize opinions based on expertise and scientific background. In this study, we will use the Delphi method, which ensures anonymity and allows opinions to be expressed without group pressure. The Delphi method has been used to formulate various guidelines and models [22,23]. Our Delphi study is conducted to examine whether the 105 objective questions are comprehensive, content-appropriate, and relevant to this domain as criteria for evaluating mental health apps. The target audience for this framework includes people involved in the research, clinical practice, and app development of health apps throughout Japan. The reason for targeting these people whose native language is Japanese is also to identify difficulties in understanding items that were not noticed during the Japanese translation process.

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Methods

Ethical Considerations

Participation in this study is voluntary. The emailed Delphi survey invitation includes the following information for potential panelists: presentation of the researcher responsible for the study, description of the study, reasons for the selection of the expert, procedures to be followed to participate, estimation of the time required, expectations regarding the expert (including the importance of participating in all rounds of the consultation), the promise of anonymity and participation recognition, and rewards for participation (payment of 20,000 JPY [approximately US $143] at the end of the study). Before participation in this study, informed consent was obtained from all panelists.

Design

This research procedure is planned with reference to the Conducting and Reporting Delphi Studies (CREDES) guidelines [24] and reviews of the Delphi study [25,26]. The classic Delphi techniques have the following characteristics [27]: (1) a working group organizes the Delphi study; (2) the working group recruits a panelist's group of individuals with some expertise on the topic; (3) the group compiles a questionnaire with a list of statements that the experts rate for agreement; (4) the group collects responses from the panelists using the questionnaire; (5) the group gives anonymous feedback to each panelist about how their responses compare to the rest of the panelists; (6) each panelist is able to revise their responses to the questionnaire after receiving the feedback; and (7) responses converge across rounds of questionnaires, with some statistical criterion being used to define consensus. Since developing a Japanese version of the comprehensive app evaluation framework serves as a starting point for the modified Delphi technique, we refer to our Delphi study as a modified Delphi study. The expected duration of the study is 12 months, which began in January 2023. To culturally validate the comprehensive mental health app framework in Japan, Japanese participants will be recruited from three categories: (1) researchers, (2) practitioners, and (3) app developers.

Procedure of the Web-Based Modified Delphi Study

Table 1 shows the procedure of developing the Japanese version of the comprehensive app evaluation framework. The Delphi method includes 3 rounds, with evaluation panelists answering anonymously in each round. In each round of the Delphi survey, the working group will pilot the round with 1 researcher, 1 practitioner, and 1 app developer prior to initiation. The individuals who participate in the pilot will not participate in the Delphi process. In the first round, our working group will send a questionnaire to the panelists, who will complete it within 4 weeks. If any panelist does not complete the evaluation within 4 weeks and does not respond to communications from the working group, the panelist would be considered to have dropped out of the study and will be excluded from the analysis. In the second and third rounds, the working group will send a questionnaire and a summary of the panelists' answers based on each previous round. The panelists answer the questionnaires based on this summary. The summarization procedure is automated to reduce biases that may occur when summarizing panelists' answers and providing those summaries to the panelists. The working group sends the result of the summarization with the next round's questionnaire. Each round's summary includes the following: the quantitative result for each item's question and explanation, the qualitative comments and explanation for each evaluation, and suggestions for modifying (revising, removing, and adding) items. When the panelist suggests revision or addition of items, the working group members will review the proposals within 3 weeks after the panelists' response. The working group would discuss the items and judge whether each revised or added item's expression is adequate. An independent liaison from the working group will make contact with the panelists, and the information about the panelists will be masked to the working group members who are participating in the discussion. These discussions will be conducted by 2 or more members.

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Table 1. Steps of the study process.

	Working group	Panelist
Preparation		
Step 1 (completed)	• Developing the app evaluation items Japanese version	N/A[a]
Step 2 (completed)	• Defining the inclusion and exclusion criteria for panelists	N/A
Step 3	• Sampling the Delphi round's panelists	Determine whether or not to participate in this study
Step 4	• Developing the Delphi questionnaire	N/A
Delphi round		
First round	• Conducting the pilot study • Analysis	Evaluating the appropriateness of items in the final version of the 105 objective questions and suggesting notations for each item
Second round	• Conducting the pilot study • Providing feedback to panelists on the summary of the first round • Analysis	Judging the appropriateness of items in the final version of the 105 objective questions and suggesting notations for each item
Final round	• Conducting the pilot study • Providing feedback on the summary of the second round • Final analysis and publication	Judging the appropriateness of items in the final version of the 105 objective questions and suggesting notations for each item

[a]N/A: not applicable.

Develop Questionnaires

The 105 original evaluation items were translated in accordance with the guidelines provided by the International Society for Pharmacoeconomics and Outcomes Research task force [28]. First, forward translation from English to Japanese was performed independently by 2 of the authors (KY and HNT). Then, a professional English translator who was English-Japanese bilingual and blinded to the 105 objective questions translated the provisional app evaluation item back into English. The 2 English versions of the app evaluation item questions (ie, the original and back-translated versions) were reconciled by KY, HNT, and John Torous (original 105 objective questions' author), and only minor discrepancies were found. These discrepancies were discussed until a consensus was reached. The original author (John Torous) evaluated the finalized English version of the app evaluation item questions and confirmed that the original meanings of the items, instructions, and responses had been maintained throughout the translation procedure.

Administer Questionnaires

Panelists will complete evaluations in a 2-stage structure (the 105 items and the 11 key levels). The 105 objective questions are constructed by the following key levels: app origin, functionality, app store attributes, accessibility, privacy and security, inputs, outputs, clinical foundation, features, engagement style, and interoperability and data sharing. At the beginning of each key level, the questionnaire explains the key level, and panelists will be asked to assess the appropriateness of the item that comprises the key level. At that time, we will ask panelists to suggest additional items if needed. After the evaluation of key level, panelists will assess 105 objective questions and descriptions. Panelists will be asked to respond on a 9-point scale (1=not at all appropriate to 9=quite appropriate) regarding whether the item is appropriate to evaluate apps. When the panelists assign a score of 1-5, they will be asked to provide free-text feedback that includes suggestions for changing the wording.

Synthesize Answers

In keeping with the described methods, satisfactory agreement for each round will require both (1) all responses >5 (ie, no participant disagreement) and (2) 60% (n=31) participation in voting in each round. These criteria were conservatively set with reference to several previous studies [29,30]. In addition, satisfactory consensus for each round will require the following: the smaller the IQR, the greater the consensus; an IQR of 0 or 1 indicates a very strong consensus, while an IQR of 2 indicates a strong consensus [31]. IQR includes the difference between the 75th percentile (third quartile) and the 25th percentile (first quartile). The items that meet these criteria will be removed for the next round of the Delphi. In addition, for free-text feedbacks, 2 or more people of the working group would discuss the panelists' responses regarding the addition or modification of items, whether to adopt the responses in the next round, and in case of adoption, how the items should be added or modified. If no conclusion is reached through discussion, the working group members who were not able to participate on the discussion day will be asked for their opinions. For this reason, the discussions will be recorded on video and via the minutes of the meeting.

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Elaborate Selection Criteria for Evaluation Panelists

Overview

The panelists will consist of 51 researchers, practitioners, and app developers. Inclusion and exclusion criteria of the panelists in each category are as follows.

Researchers who have experience contributing to at least 1 study for psychological assessment or treatment with mHealth apps will be included. The number of relevant publications, the manner in which they contribute to the research, and the degree of contribution are not required; however, if they are involved in assessment, treatment, development, usability or feasibility studies, protocol studies, reviews, preprints, conference papers, etc, they will be considered candidates for panelists.

Any practitioner who has experience with at least 1 app that assists in the treatment of procedure to a patient or client who is facing mental health issues will be considered a candidate. Practitioners include psychiatrists and clinical psychologists. Clinical experience related to mental health care is not required. Given the state of app development in Japan, we anticipate that the panelists would be limited, which would undermine their inclusiveness. Therefore, we include those who have used an app for patients for treatment or assessment purposes, regardless of the mental health app.

For app developers, candidates must have experience developing at least 1 app related to mental health care. There is no minimum requirement for years of experience in mental health app development that must be met. However, panelists who participated in the development of mental health app items will be excluded.

Make a List of Panelists

Panelists will be recruited based on the inclusion and exclusion criteria that will be considered in the primary list. Subsequently, snowball sampling will be conducted to expand the pool of panelists.

Dissemination

The preponderant involvement of various stakeholders throughout the study will offer the possibility of disseminating the results and progress of this study during the conduction of this study. Following that, diverse activities will take place to transfer knowledge. For example, scientific papers will be published, and conferences will be held to share the results with researchers. These activities could include working with the media to produce commentary papers, features, and stakeholder interviews on research findings. Workshops will be organized with professionals. A podcast will also be available for people interested in delving deeper into the results and related topics and listening to interviews and discussions with experts. Public lectures for citizens are also planned to disseminate the results of the study and explain how to use the app evaluation items to the general public. These activities will be conducted both on-site and on the internet, and records of the activities will be made available through the website and social networking sites developed for the study.

Results

We have already completed the translation of the 105 original app evaluation item questions in December 2022. We compiled a list of panelists willing to participate in the Delphi study. We anticipated the first Delphi round to commence in January 2023, and that all Delphi rounds will be completed by December 2023. Finally, the results of each Delphi round will be anonymously reported, and the report will be distributed among all panelists who participated in the Delphi study. This report will include an indication of the distribution of panelists' ratings, including their comments and suggestions. The results will be presented both quantitatively and qualitatively. We expect this study to be published in a peer-reviewed journal and presented at national and international conferences.

Discussion

Principal Considerations

While the need for treatment using mental health apps and the development of mental health apps to meet this need are increasing [32], no framework which can be used to develop a centralized database for health app is available and accessible, and no consensus has been reached among stakeholders in Japan about an appropriate framework. The web-based modified Delphi method presented in this paper aims to reach a consensus on an app framework, and thus ensure the direction of use and development of mental health apps in the future.

We expect that this web-based modified Delphi method will incorporate many different stakeholders involved in mental health apps (researchers, clinicians, and mental health app developers), facilitate the application of the comprehensive app evaluation framework in Japan, and provide valuable insights that will contribute to future developments in this field.

Furthermore, we expect that this work will raise awareness of the framework among some stakeholders involved in mental health apps, in addition to leading to the development of tools that will enable users or practitioners to efficiently choose the right app for their situations.

Strengths and Limitations

The majority of studies aiming at cultural adaptation of a survey have thus far failed to follow the CREDES guidance. This study is the second CREDES-based cultural adaptation of a scale in Japan. Furthermore, the panelist group in this Delphi study includes clinical experts, researchers, and developers to use diverse perspectives. This limitation will be due to the diversity of panelists, as there will be only 51 panelists in total, which is 17 participants for each domain. The CREDES prefers 50 participants for Delphi studies; therefore, the planned number of participants is acceptable. On the other hand, since this study plans to conduct the first round for 51 panelists at the time of study participation, it is possible that the number of panelists will decrease over time.

Conclusions

This study will develop the Japanese version of the comprehensive app evaluation framework that has reached a

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consensus among some stakeholders involved in the mental health app. It will generate useful insights for people involved in research, clinical practice, and app development regarding mental health apps throughout Japan and suggest the direction of use and development of mental health apps in the future. Furthermore, this study will enhance recognition of the framework among researchers, clinicians, mental health app developers, and users, in addition to developing new instruments to help users or practitioners efficiently choose the right app for their situations.

Acknowledgments

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Data Availability

Data sharing is not applicable to this paper as no data sets were generated or analyzed during this study.

Conflicts of Interest

KY received personal fees from a for-profit company promoting integrated resorts in Japan and abroad, domestic tobacco companies, and CureApp Inc. YT received personal fees from CureApp Inc, emol Inc, and Kaijyu Campany Inc. SM received personal fees from CureApp Inc.

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Abbreviations

APA: American Psychiatric Association

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CREDES: Conducting and Reporting Delphi Studies
mHealth: mobile health

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Protocol

A Guided Web-Based Intervention Targeting Procrastination in College Students: Protocol for an Open Trial

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Abstract

Background: Academic procrastination is a widespread problem among college students. It is linked to poor academic performance and increased college dropout intentions, as well as several mental health problems such as depression, anxiety, and stress. Guided web-based interventions can help reduce procrastination. However, guidance by professional clinicians draws upon valuable and limited societal resources, and a more efficient, scalable form of guidance is needed. Guidance by trained clinical psychology students has not yet been examined.

Objective: The aim of this open trial is to examine the feasibility and acceptability of a web-based procrastination intervention for college students under the guidance of student digital coaches (e-coaches).

Methods: We developed a single-arm trial of a guided web-based intervention targeting procrastination for the Dutch student population. Guidance is delivered by trained clinical psychology students asynchronously in the form of textual feedback on intervention progress, with the aim of supporting and motivating the participant. Participants are recruited at 7 Dutch universities. Primary outcomes are intervention satisfaction, usability, and adherence, which are assessed by the Client Satisfaction Scale (CSQ-8), System Usability Scale (SUS-10), and number of completed modules, respectively. The primary outcomes will be examined by calculating descriptive statistics. Secondary outcomes are e-coach satisfaction and changes to procrastination, depression, stress, and quality of life from pre- to posttest and follow-up.

Results: The project was funded in 2019, and recruitment began in January 2021. As of May 2023, a total of 985 participants were enrolled, of which 372 had completed the posttest and 192 had completed the follow-up. The expected date of analysis and publication of the results is 2024.

Conclusions: The results are expected to contribute to the body of literature regarding eHealth in 3 ways. First, we will examine whether students who procrastinate adhere to and are satisfied with an eHealth intervention targeting this problem. Second, we will explore whether an intervention targeting procrastination can also decrease depression and stress. Lastly, we will investigate whether trained psychology students can effectively guide their peers in web-based interventions. Given the shortage of licensed psychologists, exploring alternative sources of guidance is much needed in order to provide students with the mental health support they need.

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KEYWORDS

eHealth; feasibility; guidance; online intervention; procrastination; protocol

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Introduction

Academic procrastination is a widespread problem among college students, with studies reporting prevalence rates ranging from 29% to 67% [1-4]. Procrastination, which is defined as the tendency "to voluntarily delay an intended course of action despite expecting to be worse off for the delay" [5], is linked to poor academic performance [6] and increased college dropout intentions [7]. Procrastination is also associated with several mental health problems, such as depression [8], anxiety, stress [9,10], maladaptive coping, and low self-esteem [11]. Negative long-term consequences associated with procrastination include poorer overall health, difficulties with social relationships, financial struggles, and limited career opportunities [10,12,13].

Effective treatments to target procrastination are available. A recent meta-analysis reports that psychological treatments are effective in reducing procrastination [14]. When comparing different types of treatment, cognitive behavioral therapy (CBT) was found to be the most effective in reducing procrastination when compared with self-regulation training, strengths training, and acceptance-based behavior therapy [15].

Still, it is uncommon for students to seek or receive help for mental health complaints due to several barriers. The most common barriers are the perception that help is not needed, as students view their problems as minor or temporary, and a perceived lack of time. Other barriers include a preference for self-management, a fear of stigmatization, and low awareness of available resources [16,17]. Lastly, the detection and treatment of students with mental issues in general is hampered by limited available resources and a limited number of available student psychologists or student counselors, resulting in long waiting lists [18]. One solution to several of these barriers may be eHealth interventions, consisting of web-based treatments such as CBT. They offer quick access to treatment, anonymity, flexibility, and improved cost-effectiveness compared to face-to-face treatment [19,20]. These interventions are effective in improving mental well-being for a wide range of psychological complaints such as depression, anxiety [21,22], and stress [23]. Guided eHealth and face-to-face treatment have been found to be equally effective in treating depression and anxiety [24,25].

Studies examining the effectiveness of eHealth interventions targeting procrastination specifically show that eHealth is also effective in reducing procrastination [26-28]. When comparing eHealth to traditional treatment, chat-based counseling and face-to-face counseling resulted in a comparable decrease in procrastination [29]. Similarly, a group intervention and self-guided internet-based treatment produced comparable levels of improvement for procrastination behavior after the treatment period [30].

However, there are also drawbacks to eHealth. An often-mentioned reason for a lessened intervention effect is the problem of nonadherence, meaning participants do not make optimal use of the intervention [31-33]. For procrastination specifically, the problem of nonadherence could be exacerbated, as individuals with procrastination tendencies can struggle to adhere to the treatment [28].

Adding therapist guidance to eHealth interventions could offer a solution to this problem. Meta-analytic evidence suggests that guidance from professionals increases eHealth treatment effectiveness when compared with unguided treatment [24,34]. This may be explained by the positive effect guidance has on motivation, engagement, and adherence [35-37]. However, the addition of professional guidance in eHealth draws upon valuable and limited societal resources, and there is a scarcity of properly trained professionals.

The question arises whether there is a more efficient, scalable form of guidance without lowering therapy effectiveness. There is evidence suggesting guidance by nonclinicians (eg, peers, research assistants, or other laypeople) has comparable effects compared to guidance by clinicians in eHealth interventions [38]. What has not specifically been examined yet is whether guidance by trained clinical psychology university students can be equally effective. Were this to be the case, it could greatly reduce the load on the health care system as trained clinical psychology students could offer eHealth guidance for significantly lower costs compared to clinicians. Finally, most clinical psychology students welcome the opportunity to gain hands-on experience guiding real clients during their studies.

The main objective of this study is to evaluate the acceptability and feasibility of a new eHealth intervention targeting procrastination in college students that is guided by clinical psychology students by assessing its usability, adherence, and client satisfaction. The secondary objectives are to explore differences between pre- and posttests for procrastination, depression, stress, and quality of life.

Methods

Study Design

This study is a single-arm open trial of a guided eHealth intervention (GetStarted) aimed at decreasing procrastination in college students. It uses a single-group pretest (T0), posttest (T1), and follow-up (T2) design in which T1 and T2 are administered 4 weeks and 6 months after T0, respectively. The study is conducted within the Caring Universities consortium, a Dutch project that is part of the World Mental Health International College Student Initiative (WMH-ICS) of the World Health Organization (WHO) [39].

Participants and Recruitment

Participants are undergraduate, graduate, or PhD students enrolled in the abovementioned 7 universities across the Netherlands. These 7 universities are situated in 10 cities across the Netherlands and have a combined total of approximately 190,000 domestic and international students. Participants may be both domestic and international students.

The aim of this study is to recruit a minimum of 50 students, and recruitment is conducted in 3 ways. Firs, through a yearly web-based survey of the WMH-ICS. This survey canvasses the mental well-being of students and is sent by email to all the students of the participating universities. At the end of the survey, students who want to receive feedback are provided feedback on their mental health. Students who show increased procrastination tendencies (ie, a score >28 on the Irrational

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Procrastination Scale; IPS) are invited to sign up for the Caring Universities procrastination program. Second, marketing activities are conducted on the web through social media and on campus through posters, flyers, and other advertisements. Third, we recruit participants through the staff at participating universities. Staff members who work directly with students, such as student psychologists, study advisors, and lecturers, are informed of the program and can recommend it to students who might be interested.

Students are not offered compensation for participation.

Eligibility Criteria

Participants will be included if they meet the following criteria: (1) being aged 16 years or older; (2) being enrolled as a bachelor, master's, or PhD student; and (3) having given informed consent.

The sole exclusion criterion is suicidal risk. Participants will be asked if they have had thoughts of killing themselves or made plans to kill themselves in the past 12 months. If they answer yes, the follow-up question, "How likely do you think it is that you will act on this plan in the next 12 months?" is asked. Participants that respond to this question with "somewhat likely" or "very likely" are excluded from the intervention.

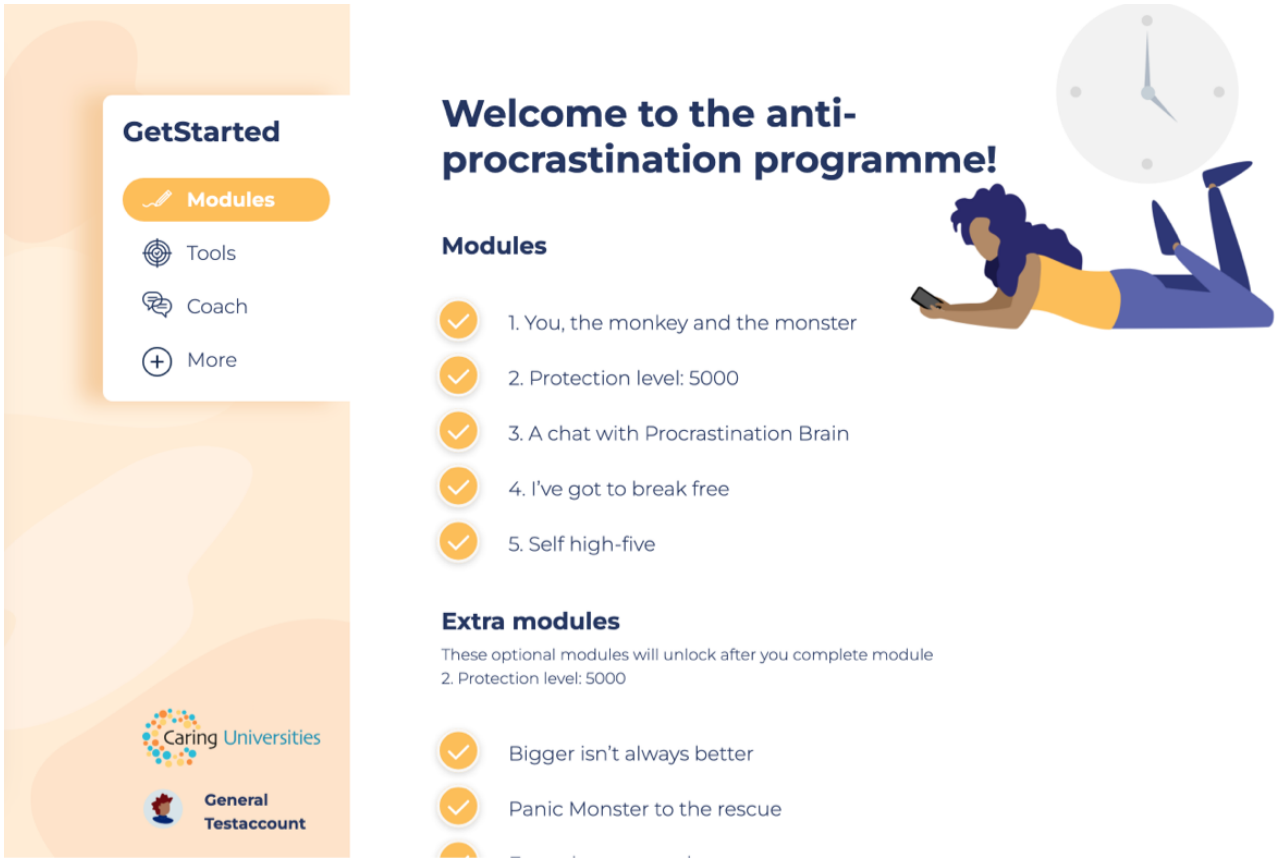
Intervention

The guided eHealth program aimed at reducing procrastination behavior (GetStarted) is developed based on the principles of CBT. Students are involved in the development of the program by giving their opinions and feedback on the program content as well as the layout of the website that contains the program. The feedback is implemented to ensure that GetStarted meets students' needs and preferences.

GetStarted (Figure 1) consists of 9 modules, of which 5 are mandatory main modules and 4 are optional modules. The modules consist of psychoeducation, reflective questions, interactive exercises, and homework assignments. The content is delivered both textually and visually, including through the use of pictures, infographics, and videos. Each module takes approximately 30 to 45 minutes to complete, and students are advised to complete 1 main module a week. The duration of the program will therefore be approximately 4-5 weeks, though students are allowed to go at their own pace and can access the intervention for 2 years. Students will be able to access the program from any device that allows internet access.

The first module offers an introduction to the program and its contents. Students are recommended to continue with the second module right away, which covers information on the psychological processes behind procrastination. The third module will allow students to identify the negative thoughts and feelings that accompany certain tasks, causing them to procrastinate. The fourth module will contain a cognitive restructuring exercise in which they will challenge their negative thinking patterns. The fifth and final main module will let the student reflect on their progress, prepare for the future, and include a summary of all the modules.

Figure 1. Screenshot of GetStarted, an eHealth intervention targeting procrastination.



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In addition to the main modules, students will be able to choose to do 1 or several of 4 optional modules. The topics of the optional modules will be (1) breaking a big task into smaller parts; (2) creating and sticking to a plan; (3) motivational techniques; and (4) increased productivity. All optional modules will become available upon completion of the second main module.

The intervention will be created based on the following principles of optimized user interface [40] in collaboration with a user experience designer: a menu containing several main sections, presentation of content in small chunks, stepwise exercises with separate instructions at each step, examples presented in expandable containers, and showing responses given by the participant in previous exercises when relevant.

Digital Coaches

During the registration process, participants select a digital coach (ie, e-coach) to support them during the program. The e-coach provides asynchronous, textual feedback through the platform after the completion of every module by the participant. While doing the intervention, participants respond to questions about the subject of procrastination. The e-coaches read these answers, which form the basis of the textual feedback. In this feedback, e-coaches respond to the participant's answers, show empathy, encourage the participant to apply the techniques, and ask reflective questions with the aim of deepening the participant's understanding of their procrastination. The feedback contains the following elements:

- an opening statement containing positive feedback for the participant's completion of the module;
- selecting 2 to 3 points of note in the participant's answers to provide empathy, encouragement, reiterate the goal of the module, or ask a follow-up question; and
- a closing statement regarding the next module.

Writing feedback for a single module takes around 30 minutes on average, and e-coaches provide feedback within 3 working days of a module being completed by the participant. E-coaches also send reminders about the intervention to participants who have been inactive for a while. E-coaches who cannot provide feedback within 3 working days due to a short temporary absence (such as a holiday) write an explanatory message to the participants explaining the absence and informing them of a return date. In the event that an e-coach cannot adequately perform their duties in the long term, the participant is assigned a different available e-coach. The reason for the change, as well as an apology, are provided to the participant by the new e-coach. A member of the research team monitors the e-coaches and the quality of the coaching.

E-coaches are (research) master students in clinical psychology and third-year clinical psychology bachelor students who meet a number of requirements in the area of low-intensity treatments for common mental health problems. E-coaches are recruited by making third-year bachelor and master students aware of the opportunity to coach as an (extracurricular) internship. They can apply for the position with their curriculum vitae and motivation. Based on their previous experience and motivation, certain students are then invited for an interview with the research team, and selected students are offered the position. These students complete 6 hours of coach training before starting their coaching activities and are required to attend weekly 1-hour intervision meetings, which are supervised by the research team.

Possible Harms

Several meta-analyses show that internet-based programs might be beneficial for college students [41] and that there are no indicated risks to internet-based programs. Moreover, individual patient data meta-analyses showed that participants who received an internet-based program for depression had a lower risk of clinical deterioration when compared with the control group [20,42]. These findings seem to indicate minimal to no risk of possible harm. However, in the event that a participant shows signs of more severe mental health problems, which include but are not limited to self-harm or suicidality, in their responses to the questions in the intervention, the protocol for (emerging) crisis situations will be applied: the e-coach (under the supervision of and in collaboration with a certified mental health care psychologist) will reach out and assess the student's current situation in more detail through the platform. In cases of mild to moderate risk of a worsening of psychological symptoms, we will advise the student to seek professional help aside from participating in the study. In cases of high risk, we advise the student to seek out professional help and resolve the current situation before continuing participation in the study.

Platform

The intervention is embedded within the Caring Universities platform. This platform was developed by Caring Universities specifically to deliver eHealth interventions to college students. The platform allows researchers to create interventions, add and arrange the contents (eg, text and visuals), and add questionnaires. Students of participating universities can freely register for the intervention by creating an account on their device (eg, computer or mobile phone). Participants can log into the platform to view its contents 24-7 for a total duration of 2 years, even upon completion of the program. During registration, each participant is presented with a random selection of 3 e-coaches out of all available coaches to choose from based on a name, short biography, and profile picture. Within the platform, participants and e-coaches can interact using textual messages. The platform complies with the General Data Protection Regulation (GDPR) guidelines.

Assessment Measures

Primary Outcomes

Satisfaction With the Intervention

To measure participants' satisfaction with the overall intervention, the Client Satisfaction Questionnaire–8 (CSQ-8) [43] is used. The CSQ-8 is commonly used to measure satisfaction with web-based interventions. It consists of 8 items on a 4-point scale with a total score ranging from 8 to 32, where a higher score indicates greater satisfaction. The CSQ-8 showed high reliability and validity for web-based interventions [44]. Similar properties were found in the Dutch translation of the CSQ-8 [45].

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Usability

The System Usability Scale–10 (SUS-10) [46] is used to measure the usability of the intervention. It consists of 10 items on a 5-point Likert scale, with a total score ranging from 0 to 40. Total scores are then multiplied by 2.5 to achieve a total score of 0 to 100, where a higher score indicates greater usability. The SUS-10 has become the most widely used standardized questionnaire to assess perceived usability and has shown good psychometric properties (reliability and validity) [47]. The Dutch translation of the SUS-10 has previously been used [48], though publications on its specific psychometric properties could not be found. However, several other translations of the SUS-10 were found to have similar psychometric properties as the English version [47].

Adherence

Adherence refers to "the degree to which the user followed the program as it was designed" [32]. This study measures adherence by dividing the number of main modules completed by a participant at the time of posttest by the total number of main modules in the program and multiplying this by 100. The resulting percentage will indicate the completion rate. Participants who have not completed a single module will be excluded from these analyses as they did not start the treatment.

Secondary Outcomes

Procrastination Tendencies

The IPS is used to assess procrastination tendencies [49,50]. This scale contains 9 items on a 5-point Likert scale. The scale aims to assess the extent to which participants procrastinate. Higher scores indicate higher levels of procrastination. The IPS is used to assess the changes from pre- to postscores. The IPS showed good internal consistency (Cronbach α=.91) [50] as well as a high level of reliability (r_{pm}=0.58-0.74), and good content, structural, and substantive validity [51].

Depressive Symptoms

Depression is assessed with the Patient Health Questionnaire–9 (PHQ-9) [52]. It consists of 9 items on a 4-point Likert scale, with a total score ranging from 0 to 27. Higher scores indicate higher levels of depression. The scores of 0-4, 5-9, 10-14, 15-19, and 20-27 are indicative of no depression, mild depression, moderate depression, moderately severe depression, and severe depression, respectively [52]. The PHQ-9 was found to have high sensitivity (0.71-0.84), specificity (0.90-0.97), internal consistency (Cronbach α=.86-.89), test-retest reliability (r=0.84), and validity [53,54].

Perceived Stress

Stress levels are assessed using the Perceived Stress Scale–10 (PSS-10) [55,56]. This self-report scale consists of 10 items on a 5-point Likert scale with a total score ranging from 0 to 40, where a higher score indicates higher perceived stress. The PSS-10 was found to have high validity, internal consistency (Cronbach α=.74-.91), and test-retest reliability (r=0.74-0.88) [56,57].

Quality of Life

Quality of life was measured using the Mental Health Quality of Life questionnaire (MHQoL) [58]. It contains 7 items on a 4-point Likert scale that cover the dimensions of self-image, independence, mood, daily activity, physical health, relationships, and future. The total score ranges from 0 to 21, where a higher score indicates a better quality of life. The MHQoL was found to have good validity, test-retest reliability (r=0.85), and internal consistency (Cronbach α=.85) [58].

Digital Coach Evaluation

The Working Alliance Inventory for guided Internet interventions (WAI-I) [59] is used to evaluate participants' satisfaction with the e-coach. The WAI-I consists of 12 items on a 5-point Likert scale with a total score ranging from 12 to 60, where higher scores indicate higher satisfaction. The psychometric characteristics of the WAI-I yielded adequate results [59].

Additional Measures

The following sociodemographic information is collected to examine sample characteristics: age, gender, marital status, nationality, attending university, faculty, education level (bachelor, master's, or PhD), and whether psychotherapy and medication are received.

Assessments

An overview of the assessments can be seen in Table 1.

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Table 1. Measures and assessment points.

Measures	Assessment points		
	T0[a]	T1[b]	T2[c]
Sociodemographic	✓		
Client Satisfaction Questionnaire (CSQ-8)		✓	
System Usability Scale (SUS-10)		✓	
Irrational Procrastination Scale (IPS)	✓	✓	✓
Perceived Stress Scale (PSS-10)	✓	✓	✓
Patient Health Questionnaire (PHQ-9)	✓	✓	✓
The Mental Health Quality of Life Questionnaire (MHQoL)	✓	✓	✓

[a]Pretest.

[b]Posttest (4 weeks).

[c]Follow-up (6 months).

Sample Size

There is no clear method to calculate the sample size of an open feasibility study. Studies have suggested sample sizes ranging from at least 12 participants [60,61] to 35 or more participants [62]. In this study, no power calculation was conducted to determine the sample size, as the main focus is on the feasibility and acceptability of the intervention. Based on these rules of thumb and similar previous studies [63], we anticipate that a minimum of 50 participants will be sufficient to examine our main objectives. However, as the intervention will remain accessible to students for several years as part of the service offering of the Caring Universities project, we anticipate more than 50 participants will make use of the intervention. We will analyze the data of all participants who have used the intervention at the time of data analysis to be able to draw stronger conclusions.

Statistical Analysis

Participants' satisfaction with the intervention, usability, and adherence will be examined by calculating descriptive statistics.

Satisfaction

Each of the 8 items on the CSQ-8 has 4 answering options, of which 2 indicate dissatisfaction (scored 1 or 2) and the other 2 indicate satisfaction (scored 3 or 4). Our goal is for participants to be satisfied or very satisfied with the intervention, meaning a score of 3 or 4 per item. This corresponds with an average total score between 24 and 32. We will consider the intervention a success if average CSQ-8 scores reach a minimum of 24.

Usability

Bangor et al [64] have found that SUS-10 scores above 70 are passable, with scores above 90 indicating superior products. We will consider the intervention a success if average SUS-10 scores reach a minimum of 70.

Adherence

A recent meta-analysis looking at internet interventions for mental health among university students found dropout rates between 11.84% and 50.33% [65]. Given the nature of procrastination, dropout is expected to be on the higher side. We will consider the intervention a success if adherence reaches 50%.

Secondary Outcomes

We will conduct 2-tailed paired *t* tests using a significance level of α=.05 to assess changes in the scores of IPS, PHQ-9, PSS-10, and MHQoL. Average WAI-I scores will be calculated to assess satisfaction with the digital coach.

Ethical Considerations

This study protocol was approved by the Scientific and Ethical Review Board of all universities that participate in Caring Universities on May 15, 2020 (Vrije University, Leiden University, Maastricht University, Utrecht University, Erasmus University, University of Amsterdam, and Inholland University of Applied Sciences; reference number 2020.088). Participants in the study provide informed consent to the collection, storage, and viewing of their personal data. If the researchers want to use the data later for further research and scientific education, or if interim interventions require new data to be processed or used in other ways than for which they were originally collected, this will be communicated to the participants, and permission will be asked again. Research data are collected by the platform, which complies with GDPR guidelines. These are then coded and shared with Vrije Universiteit Amsterdam, which will be responsible for the data processing. Identifying information, such as name and contact information, is stored separately from all other data that are collected. Each participant is assigned an ID code to which the collected data are linked. This ID code is stored separately and is only accessible to the researcher if it is necessary for linking data for contact or permission. The coded data will be analyzed within the study.

Results

This study was funded in 2019, and recruitment began in January 2021. As of May 2023, a total of 985 participants were enrolled, of which 372 had completed the posttest and 192 had completed the follow-up. The expected date of analysis and publication of the results is 2024.

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Discussion

Overview

This study aims to examine the feasibility and acceptability of a new, guided web-based intervention for procrastination in college students. The main outcomes are client satisfaction, usability, and adherence to the intervention. In addition, we will explore any changes in the secondary outcomes of procrastination, depressive symptoms, stress levels, and quality of life from pretest to posttest. We expect the intervention to be perceived as feasible and acceptable by college students. An improvement in the secondary measures upon receiving the treatment is also expected, though not all may reach significance.

Strengths and Limitations

eHealth interventions targeting procrastination for students show promising results [26-30]. Guidance from professionals seems to increase the effectiveness of eHealth treatment when compared with unguided treatment [24,34]. However, to our knowledge, research on guidance by clinical psychology students in eHealth interventions is scarce in the literature. Therefore, it is our belief that this study will be informative in the development and implementation of eHealth interventions targeting procrastination among students in the Netherlands.

There are some limitations to be taken into consideration. First, the recruitment method must be mentioned. The main recruitment channel will be through a yearly web-based mental health survey of the WMH-ICS, which is a voluntary survey that is sent out to all students of participating universities. This may result in a selection bias, as not all students are equally likely to fill out the survey and subsequently participate in a voluntary web-based intervention. The sample in this study may therefore not be entirely representative of the Dutch student population. However, it is important to note that participants are not offered course credits or any other form of compensation. As a result, this study will provide an opportunity to examine the real-life demand and use of the intervention by students in 7 different universities across the Netherlands. While the sample may not be representative of the Dutch student population, it is still likely a good representation of students that seek help and are open to eHealth solutions.

Second, this study is a feasibility and acceptability study without a control group. As a result, any findings on the secondary measures of procrastination, depression, stress, and quality of life cannot be directly attributed to the intervention. Further research and randomized controlled trials will be necessary to draw conclusions on intervention effectiveness.

Lastly, nonadherence is a known problem in eHealth, which may be exacerbated by the nature of procrastination [28,31-33]. To increase adherence to the intervention, participants will receive guidance from trained clinical psychology students. This is expected to increase engagement, motivation, and adherence to the intervention [35-37].

There are also several strengths of this study. First is the design of the intervention, which is done in collaboration with students. The visual style of the intervention as well as its contents are discussed with students during the development. Student feedback is implemented to ensure that the intervention meets the needs of the student population. To further promote engagement and adherence, we design the intervention based on principles of optimized user interface [40] and work closely with a user experience designer. This resulted in a highly user-friendly platform, which is expected to promote students' satisfaction and engagement with the intervention. Lastly, we include automated reminders as well as personal ones by the e-coaches to increase adherence [66].

The comprehensiveness of assessment is a second strength. While this study examines the acceptability and feasibility of a new eHealth intervention targeting procrastination, extensive secondary outcomes are also measured. Procrastination is linked to many mental health issues, such as depression, social anxiety, stress, and low self-esteem [8-11]. In this study, we will explore any changes in procrastination, depression, stress, and quality of life, as well as assess the main outcomes of adherence, client satisfaction, and usability. In doing so, we will gain a more comprehensive understanding of the intervention. It also allows us to explore potential moderators and mediators of intervention adherence and effectiveness.

Finally, we believe the use of trained clinical psychology students is a strength of this study. Guidance by nonclinicians such as peers, research assistants, and laypersons has been found to be equally effective as that by clinicians [38]. To our knowledge, no studies have been conducted on guidance by trained clinical psychology students. The use of student coaches is highly cost-effective, as clinical psychology students are often required to gain work experience through extracurricular internships during their studies. Therefore, student coaching would be a more scalable form of guidance. If student guidance in eHealth interventions was found to be feasible and acceptable, it could greatly reduce the load on the health care system and offer more timely access to mental health support to those in need.

Conclusions

This study aims to examine the feasibility and acceptability of an eHealth intervention for procrastination specifically designed for college students and under the guidance of clinical psychology students. The results are expected to contribute to the body of literature regarding eHealth in several ways. First, the nature of procrastination might intensify the known problems of eHealth, such as nonadherence. This study examines whether students who procrastinate will adhere to and be satisfied with eHealth interventions targeting this problem. Second, this study explores whether an intervention targeting procrastination can also decrease depression and stress. Lastly, this pilot investigates whether trained psychology students can effectively guide their peers in web-based interventions. Given the shortage of licensed psychologists, exploring alternative sources of guidance is much needed in order to provide students with the mental health support they need.

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Acknowledgments

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Data Availability

The data sets generated during and/or analyzed during this study are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

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Abbreviations

CBT: cognitive behavioral therapy
CSQ-8: Client Satisfaction Scale–8
GDPR: General Data Protection Regulation
IPS: Irrational Procrastination Scale
MHQoL: Mental Health Quality of Life questionnaire
PHQ-9: Patient Health Questionnaire–9
PSS-10: Perceived Stress Scale–10
SUS-10: System Usability Scale–10
WAI-I: Working Alliance Inventory for guided Internet interventions
WHO: World Health Organization
WMH-ICS: World Mental Health International College Student Initiative

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Protocol

A Web-Based Mindfulness-Based Cognitive Therapy for Couples Dealing With Chronic Cancer-Related Fatigue: Protocol for a Single-Arm Pilot Trial

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Abstract

Background: Chronic fatigue is a common symptom among patients who have been treated for cancer. Current psychosocial interventions typically target the patient alone, despite growing evidence suggesting that a couples' approach can increase and broaden the efficacy of an intervention. Therefore, based on an existing web-based mindfulness-based cognitive therapy for patients, the couple intervention COMPANION was developed.

Objective: The primary objectives of this study are to determine the acceptability of COMPANION and its potential efficacy in reducing fatigue in patients with cancer. Our secondary objectives are to examine the feasibility of the trial procedures and the potential working mechanisms of the couple intervention.

Methods: We will conduct a single-arm pilot trial for couples (ie, patients with cancer with chronic fatigue and their partners). All couples are allocated to the web-based couple intervention that consists of psychoeducation, mindfulness, and cognitive-behavioral exercises. The 9 sessions of the intervention are supervised remotely by a trained therapist. Patients and partners will complete questionnaires before starting the intervention (T0), 2 weeks after completing the intervention (T1), and 1 month after T1 (T2). They will also fill out weekly diaries during the intervention period. A subsample of patients (n≈5) and partners (n≈5) as well as all the therapists providing COMPANION will participate in the final focus groups. Benchmark values have been defined to determine the acceptability (ie, ≥60% of couples complete the intervention and/or ≥70% of the participants are satisfied with the intervention) and potential efficacy (ie, a significant improvement in fatigue and/or a clinically relevant improvement in fatigue in 45% of the patients between T0 and T1) of the intervention. The trial procedures are deemed feasible if an average of at least three couples are included per recruiting month and/or adherence to the assessments is at least 65% for T1 and the diaries and 60% for T2. To establish potential working mechanisms, changes in affect, sleep, catastrophizing, partner communication and interactions, self-efficacy, mindfulness, and closeness will be examined. Quantitative outcomes will be interpreted along with the results from the focus groups.

Results: Data collection is expected to be completed by March 2024.

Conclusions: This pilot trial will test the first web-based mindfulness-based cognitive therapy for couples targeting chronic cancer-related fatigue. Findings will indicate whether proceeding with a randomized controlled trial is warranted.

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Trial Registration: ClinicalTrials.gov NCT05636696; https://clinicaltrials.gov/study/NCT05636696
International Registered Report Identifier (IRRID): DERR1-10.2196/48329

(JMIR Res Protoc 2023;12:e48329) doi:10.2196/48329

KEYWORDS

acceptability; cancer; chronic cancer-related fatigue; couple intervention; eMBCT; fatigue; feasibility; partners; pilot trial; web-based mindfulness-based cognitive therapy

Introduction

Background

Chronic cancer-related fatigue (CCRF) is a common symptom among patients treated with curative [1-4] as well as palliative intent [5-7]. It can persist for many years and has a profound negative impact on patients' quality of life [2,8,9]. Its etiology is likely multifactorial and includes several biological pathways [10,11]. According to the cognitive-behavioral model of CCRF, cancer and its treatment initially trigger fatigue, while cognitive-behavioral variables (eg, negative cognitions about fatigue and disrupted activity patterns) explain its persistence after completion of treatment [12-14]. Based on this model, cognitive-behavioral and mindfulness-based therapies have been developed to address CCRF. While these and other interventions have been shown to effectively alleviate patients' fatigue [15-19], they are directed at the patient with cancer alone, despite growing evidence for the importance of involving patients' partners in the treatment of CCRF (ie, a couples' approach to treatment).

CCRF is experienced in the context of patients' close relationships in multiple ways. First, the way patients and their partners interact in daily life is related to patients' fatigue outcomes. For example, a daily diary study among survivors of cancer and their partners showed that partners' facilitative reactions (eg, encouragement to be active) were related to better fatigue outcomes, while solicitous reactions (eg, taking over the patient's chores) as well as ruminative conversations—fueled by patients and their partners maladaptive cognitions—were related to worse outcomes during the day [20,21]. This suggests that interventions encouraging adaptive daily interactions between couple members have the potential to contribute to better fatigue outcomes for the patient. Second, the degree to which patients benefit from cognitive behavioral therapy for fatigue appears to be related to partner and relationship variables. That is, a recent study [22] among patients with chronic fatigue syndrome showed that relationship dissatisfaction among patients and high fatigue in their partners are associated with less improvement in fatigue severity after therapy. Third, ample research shows that the cancer experience also impacts intimate partners. In particular, partners have been shown to experience substantial distress [23,24], which is positively related to patient fatigue [25,26], suggesting that an effective fatigue intervention can also benefit partners. Fourth, the aforementioned diary study [20] suggests that the way a partner deals with fatigue in the couple's daily life is not only related to fatigue outcomes but also patients' relationship satisfaction, with solicitous and facilitative responses being related to higher relationship satisfaction. Jointly, the evidence suggests that targeting the couple instead of the patient alone has the potential to increase the intervention's effect on patient fatigue and broaden its impact to alleviate partner distress and benefit the couple's relationship.

Based on this and studies indicating beneficial effects of interventions for couples coping with cancer in general [27-30], the study team has developed a couple intervention for dealing with CCRF called COMPANION (Dutch: Samen Minder Moe). The intervention is based on a web-based mindfulness-based cognitive therapy (eMBCT) that has been shown to be effective in reducing patient fatigue [31].

Research Aims

Given the relative novelty of this interventional approach, conducting a pilot trial is warranted. The primary aims of this pilot trial are (1) to determine the acceptability of the couple intervention and (2) to investigate its potential efficacy in reducing patient fatigue. Secondary aims are (3) to examine the feasibility of the trial procedures and (4) to determine the potential working mechanisms of the couple intervention.

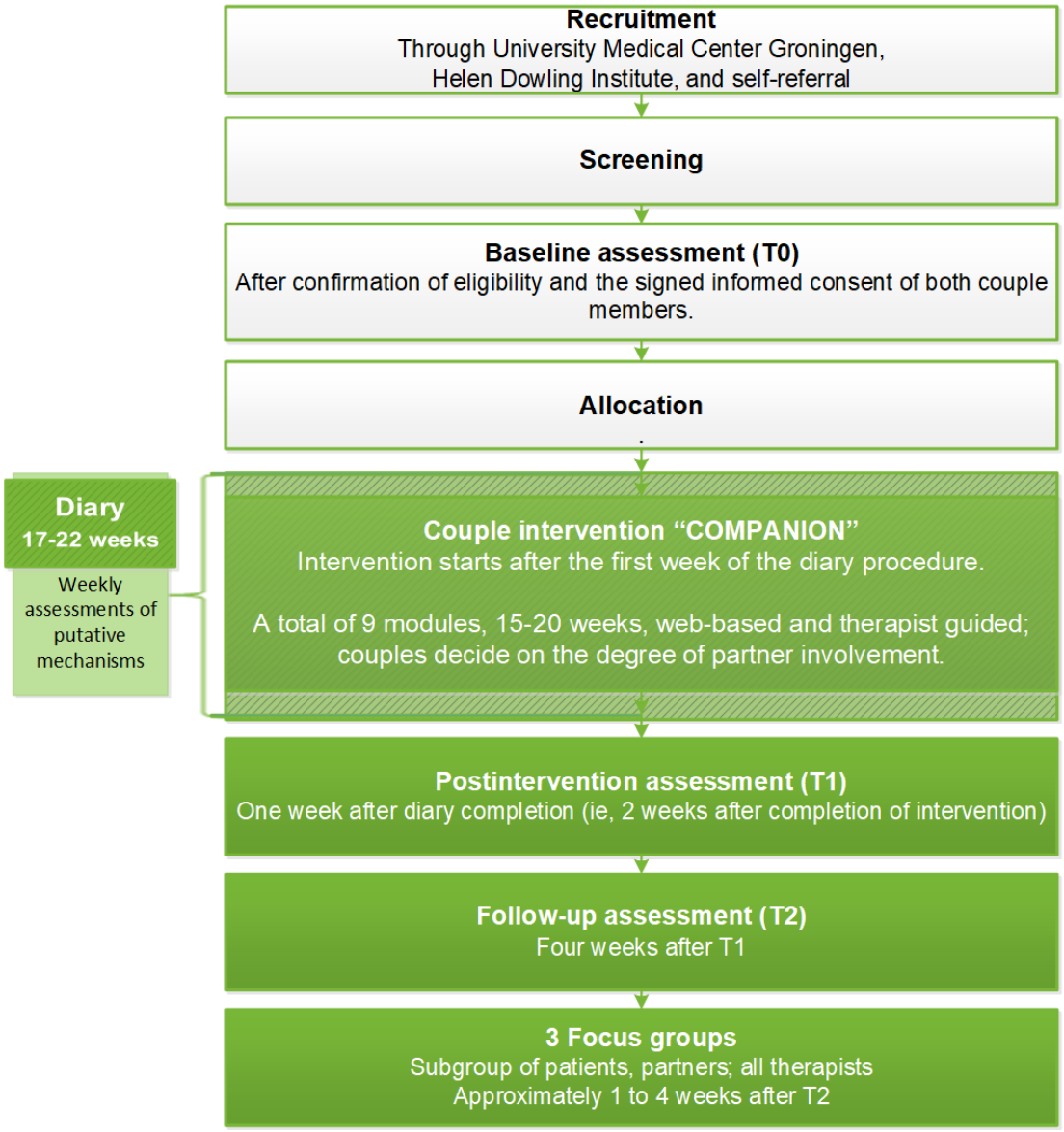
Methods

Design

This study is a single-arm pilot trial among patients with cancer with CCRF and their partners. All included couples will be allocated to receive the COMPANION intervention, with a planned duration of 15-20 weeks. Couples will complete questionnaires and weekly diaries. Trial participation is estimated to take 6-8 months in total. Figure 1 presents a flowchart of the study.

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Figure 1. The study flowchart.



Participants

Eligible participants are couples in which one member was diagnosed with cancer, completed cancer treatment for at least 3 months (excepting hormone therapy), and has been experiencing severe fatigue for at least 3 months. See Textbox 1 for an overview of all inclusion and exclusion criteria.

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Textbox 1. Inclusion and exclusion criteria for the study.

Inclusion criteria

- The patient has received a cancer diagnosis (all malignancies are included).
- The patient completed cancer treatment with either curative or palliative intent ≥3 months earlier. Patients who currently receive hormone therapy are eligible.
- The patient experiences severe levels of fatigue (a score of ≥35 on the Checklist Individual Strength, subscale fatigue severity) at the screening.
- The patient has been experiencing severe fatigue for ≥3 months (as self-reported by the patient).
- The patient was 18 years of age or older at disease onset.
- The partner is 18 years of age or older.
- Both couple members live together.
- Both couple members have good command of the Dutch language (checked implicitly during registration).
- Both couple members have adequate computer literacy and have access to an internet-connected computer, laptop, or tablet (based on self-report).
- Both couple members agree to participate in the research.

Exclusion criteria

- The patient is currently following an evidence-based therapy for chronic cancer-related fatigue (ie, cognitive behavioral therapy, mindfulness-based therapy, exercising, or physiotherapy) as self-reported at the telephone screening.
- The patient has a condition that can explain his or her fatigue and is potentially treatable (eg, anemia).
- The therapist decides, based on information collected during the intake session, that the intervention is not suitable for the couple. Criteria that will be considered include, but are not limited to:
    - The presence of severe psychiatric morbidity such as suicidal ideation or psychosis (as assessed by the therapist at the intake session). Mild depression is not an exclusion criterion. A score of ≥20 on the hospital anxiety and depression scale at T0 is considered indicative of depression [32]. Therefore, if the patient or the partner scores ≥20, the therapist will determine at intake whether the participant has suicidal ideation or has another severe psychiatric morbidity. A participant (and thus the couple) will be excluded if, according to the therapist, that is the case.
    - The presence of substance abuse, except for smoking.

Recruitment

Recruitment will take place at the University Medical Center Groningen (UMCG), the Helen Dowling Institute (HDI), and through self-referral. At the UMCG, patients will be invited to the study by their oncologist or nurse, either at a follow-up appointment or during a phone call. Couples who indicate interest will be contacted by the research assistant. At the HDI, the research assistant will contact patients who are on the waiting list to receive patient-centered eMBCT and have given permission to be contacted for research purposes. Recruitment through self-referral will be encouraged by social media posts, newspaper articles, the panel of Kanker.nl [33], and flyers to be distributed at psychosocial care centers for people affected by cancer (Dutch: IPSO centra). Interested couples will be directed to the project website [34], where they can register.

Screening

The research assistant will schedule a web-based call with all interested couples to further inform them about the study and screen their eligibility. During the screening process, reasons for ineligibility and decline of participation will be recorded in the recruitment log as they inform our secondary aim (ie, feasibility of trial procedures). Upon obtaining informed consent from the patient with cancer and their partner, the patient will receive a link through email to a survey to confirm fatigue- and cancer-related eligibility criteria.

Assessments

Participants will complete questionnaires before starting the intervention (T0), 2 weeks after completing the intervention (T1), and 1 month after T1 (T2). Patients and their partners will also complete weekly diaries, starting 1 week before the intervention and ending 1 week after the intervention is completed. All questionnaires and diaries will be provided on the web through a secure, web-based application called REDCap (Research Electronic Data Capture) [35]. Patients and their partners will receive a link sent to their personal email and will be encouraged to respond independently from each other. In the event of nonresponse to the questionnaire, participants will receive a reminder email after 7 days and a second reminder after another 7 days of nonresponse. In case a diary assessment is missed, participants will receive a reminder the next day, and if 2 consecutive diaries have not been responded to, the assistant will call the participant to discuss possible problems. Therapists will also keep a therapist log to register data on intervention delivery, and the research assistant will keep a recruitment log to register data on recruitment and study adherence. A subsample of 5 patients with cancer and 5 partners (anticipated sample sizes), as well as all therapists providing the COMPANION intervention, will be invited to participate in separate focus groups. Patients and partners will be sampled purposefully (ie, based on high vs low levels of adherence or

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intervention satisfaction) and can be invited independently from each other.

Sample Size Calculation

The study is powered to test the potential efficacy of the couple intervention in reducing patient fatigue (ie, the second primary research aim). Patients' baseline (T0) and postintervention (T1) scores on the Checklist Individual Strength, subscale Fatigue Severity (CIS-fatigue) will be analyzed with a 1-tailed matched pairs *t* test. G*Power analysis indicated that 27 patients are required to detect a medium effect (0.5) with an α of .05 and a power of 0.8 (1-tailed). We expect CIS-fatigue scores at T1 to be significantly lower than CIS-fatigue scores at T0. We will conduct a 1-sided test given the gain in power as compared to a 2-sided test and evidence that an increase in mean fatigue is unlikely to occur [31]. Based on the drop-out rate in our previous trial [31] and a recent review of the attrition rate in couple-based interventions for cancer [36], we assume a 20% drop-out rate. Hence, we will aim to include a total of 34 couples.

Intervention

COMPANION is a couple intervention developed from an evidence-based patient-centered eMBCT that aims to change the patient's behavioral and cognitive reactions to cancer-related stressors, including fatigue [31]. Like the patient-centered eMBCT, COMPANION is web-based and guided remotely by a trained therapist. However, COMPANION also involves the patient's partner in the treatment. The intervention consists of 9 sessions, which take approximately 15 to 20 weeks to complete (ie, the intervals between sessions are flexible to accommodate holidays and other commitments). Patients will have access to a secure web-based platform where they will receive written information about a specific theme for each session. Partners will have access to these materials through the patient. Table 1 provides an overview of all 9 sessions. Participants will be provided with audio files to practice different mindfulness-based cognitive-behavioral exercises each session. Patients will document their experiences in their personal log and perform exercises for approximately 30 minutes, 6 days a week. The exercises comprise topics such as relaxation, eating with awareness, moving with awareness, 3-minute breathing exercises, or meditation. Apart from the video call consultations, communication with the therapist will be mostly asynchronous, meaning that the therapist reads the experiences in the logs and provides feedback once a week. Adaptations compared to the patient-centered version were based on the findings from the preceding needs assessment among patients, partners, and therapists (van Dongen et al, unpublished data, 2023). These adaptations mainly concerned: 3 video call consultations between patient, partner, and therapist; psychoeducation for the partner; additional exercises for patient and partner (to be performed together or independently); and an extra session focused on the couple's mutual relationship and mindful communication about fatigue. Together with their therapist, couples can decide how and to what extent their partner will be involved.

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Table 1. Modules of COMPANION.

Theme of module	Web-based psychoeducation	Exercises
Module 1: Fatigue and the automatic pilot	• Automatic pilot • Coping with fatigue • Patients formulate treatment goals	• Practice relaxation and awareness of the body with an audio file "bodyscan" • Register experiences with the "bodyscan" • Register experiences with eating with awareness
Module 2: Practice being open-minded	• Coping with pain and fatigue • Handling thoughts during breathing exercise • Tips for better sleep quality	• "Bodyscan" with muscle tension • Breathing exercise • Register experiences with these exercises • Register awareness during a specific activity • Register awareness during pleasant moments
Module 3: Dealing with boundaries	• Awareness of handling physical and emotional boundaries • Cultivating acceptance	• Moving with awareness and a 3-minute breathing exercise, alternated with previous exercises • Register experiences with these exercises • Register awareness about what happens when meeting boundaries
Module 4: Dealing with stress	• Patience • Recognizing automatic negative cognitions • Recognizing daily stress-inducing experiences and their emotional impact	• Using the senses (hearing, seeing, and feeling) with awareness • Alternating with previous exercises
Module 5: Communication	• How to communicate about cancer-related fatigue • How to communicate mindful of your own and others' thoughts and feelings	• Mindful communication exercise • Alternating with previous exercises
Module 6: Dealing with feelings	• Accept things as they are • Coping with negative emotions through acceptance	• Allowing intense feelings by focusing on present awareness of sensations in the body • Alternating with previous exercises
Module 7: Dealing with thoughts and anxiety	• Dealing with thoughts and fears • Interaction between thoughts, emotions, and behaviors • Physiology of fear	• Becoming aware of automatic negative thinking • Making a list of these thoughts • Alternating with previous exercises
Module 8: Self-care	• Self-care	• Compose own practice schedule by choosing from previous exercises • Making a list of helpful cognitions
Module 9: From stress and fatigue to strength	• Patients continue practice with their own practice schedule	• Writing about what helps their practice • Formulation of potential pitfalls in the future and composition of self-management strategies

Therapist Training and Treatment Integrity

Therapists at the HDI will deliver COMPANION. They all fulfill the criteria established by the United Kingdom Mindfulness-Based Teacher Therapist Network Good Practice Guidelines for teaching mindfulness-based interventions [37]. They will be trained in providing the couple intervention by an experienced therapist and a researcher from the COMPANION project team. This training starts with a preparatory self-study assignment using the web-based COMPANION treatment environment (a web portal for therapists). Next, therapists participate in an interactive training session addressing the content of the new therapy, the role of the therapist within this new therapy (including exercises and suggestions for involving the partner and giving therapeutic feedback [38]), and the design and procedures of the COMPANION pilot trial. All information is documented in a detailed written manual for therapists. Regular supervision will take place during the pilot trial, led by a member of the COMPANION project team who is a registered supervisor at the Dutch Society for Cognitive Behavioral Therapy. This supervisor has 15 years of experience in psycho-oncology, including 12 years of work experience with the patient-centered eMBCT for CCRF.

Measures

Table 2 provides an overview of all the constructs to be assessed. For conciseness, we have only described the key measures. Where possible, we chose validated and widely used instruments

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in the field. Table 2 provides references for measures not described here.

Table 2. Overview of instruments, questionnaires, and assessment time points. Unless otherwise indicated, both patients and their partners complete questionnaires, and they report on their own health, perception, and state. Partner version of scales are own adaptations.

Construct	Instrument or type of assessment	Assessment time points				
		Screening[a]	T0[b]	T1[c]	T2[d]	FG[e]
Personal characteristics						
Demographics	Standard items	✓	✓			
Cancer-related characteristics[f]	Standard items	✓	✓			
Fatigue onset[f]	Developed item	✓				
Fatigue duration[f]	Developed item	✓				
Current CCRF[g] care use[f]	Developed item	✓				
Primary and secondary outcomes						
Intervention completion	Developed items, self-report and therapist log			✓		
Intervention satisfaction	Developed items based on [39,40]			✓		
Intervention experiences	Not applicable					✓
Partner involvement	Developed item, self-report and therapist log			✓		
Fatigue severity[h]	CIS-fatigue[i]	✓	✓	✓	✓	
Potential mediators: mindfulness- and cognitive-behavioral variables						
Self-efficacy	SES[j] or SES partner version		✓	✓		
Catastrophizing	J-FCS[k] or J-FCS partner version		✓	✓		
Mindfulness	FMI[l]		✓	✓		
Other relevant measures						
Emotional well-being	HADS[m]		✓	✓	✓	
Relationship satisfaction	MMQ-marital satisfaction[n]		✓	✓	✓	
Caregiver burden regarding patient fatigue[o]	ICQ[p], partner version		✓	✓		
Perceived change in fatigue[f]	Developed item based on [41]			✓		
Adverse events	Developed items based on [41], self-report and therapist or recruitment log			✓		
Supportive care use for mental health issues	Developed items based on [41]		✓			

[a]Some screening items will be assessed verbally on the phone (eg, relationship status), others through a questionnaire (eg, fatigue items).
[b]T0 is baseline.
[c]T1 is 2 weeks after completion of the intervention.
[d]T2 is 1 month after T1.
[e]FG: focus group.
[f]Patient only.
[g]CCRF: chronic cancer-related fatigue.
[h]For partners at baseline and T1 only.
[i]CIS-fatigue: Checklist Individual Strength, subscale Fatigue Severity [42,43].
[j]SES: Self-Efficacy Scale [44].
[k]J-FCS: Jacobsen Fatigue Catastrophizing Scale [45].
[l]FMI: Freiburg Mindfulness Inventory Short Form [46].
[m]HADS: Hospital Anxiety and Depression Scale [47,48].
[n]MMQ: Maudsley Marital Questionnaire, subscale Marital Satisfaction [49,50].
[o]Partner only.
[p]ICQ: Illness Cognition Questionnaire [51].

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Demographic characteristics will be assessed at the screening and T0 and include self-reported age, sex, level of education, occupational status, relationship status and duration, cohabitation status and duration, and comorbidities.

Patients' cancer-related variables are self-reported and include cancer type, prognosis, presence of metastasis, treatment received, time since diagnosis, and time since treatment completion.

Intervention adherence will be assessed at T1, as self-reported by the patients and as registered by the therapists in their therapy log. The item used reads: "Did you/your client complete all sessions of the COMPANION therapy?" Answer categories are (1) "Yes, I/my client completed all sessions of the intervention" and (2) "No, I/my client stopped after session ____ (fill in the blank)." Reasons for stopping can be recorded in a free text field. By design, partners' involvement in the intervention is flexible, as this was an important requirement derived from the preceding needs assessment study (van Dongen et al, unpublished data, 2023). We consider receiving 6 sessions to be the minimal therapeutic dose. Therefore, intervention completion is achieved when a patient receives ≥6 out of 9 sessions, as reported by the patient at T1 and/or in the postintervention therapist log, and the partner did not drop out from the intervention.

Intervention satisfaction will be assessed with items based on those of other pilot trials for patients and their loved ones [39,40]. For both patients and partners, a total of 2 items will be used to assess satisfaction with the intervention overall (ie, "Overall, how satisfied are you with the COMPANION therapy?") and satisfaction with the couple approach (ie, "How satisfied are you with the possibility of jointly participating in the COMPANION therapy?"). Additional items assess satisfaction with specific aspects of the intervention. Items are scored on a 7-point Likert scale; scores 5 to 7 represent (high) satisfaction.

Fatigue severity will be assessed using the CIS-fatigue. A total of 8 items assess fatigue severity during the past 2 weeks (eg, "I feel tired") and are scored on a 7-point Likert scale, ranging from (score 1) "Yes, that is true" to (score 7) "No, that is not true." A higher sum score indicates more severe fatigue (range 8-56), with a score of ≥35 indicating severe fatigue in patients with cancer [42,43]. A clinically relevant change is operationalized as a difference of 6 points [52].

Recruitment rates: the research assistant will complete a recruitment log. The following information will be collected: (1) number of patients approached for recruitment (through the UMCG and HDI); (2) number of participants (ie, patient and/or their partner) interested in participation; (3) number of included couples; and (4) number of couples dropping out from the intervention and study. Along with these rates, reasons will be recorded. The recruitment rate is defined as the average number of couples included per month.

Adherence to the study protocol will be recorded by the research assistant in the recruitment log in terms of the number and percentage of questionnaires completed. Completion is defined as having responded at least to the items assessing the outcome measures.

Potential mechanism variables will be assessed in the weekly diary and include affect, sleep, catastrophizing, partner communication, partner interactions, self-efficacy, mindfulness, and closeness. Items are based on and adapted from a daily diary study among survivors of cancer and their partners [20,21,53] and existing scales. Table 3 provides an overview of the items.

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Table 3. Concepts assessed with the diary method. Participants complete weekly diaries starting the week before the intervention, during the course of the intervention, and the week following the end of the intervention (ie, a total of 17-22 weeks) to assess potential working mechanisms of COMPANION.

Constructs	Items and instruments	Time frame
Outcome variables		
Fatigue severity[a]	1 item, as in [20,21,53]	Momentary[b]
Fatigue severity[c]	4 items based on SFQ[d]	Last week[e]
Intervention adherence	1 developed item	Last week
Partner involvement	2 developed items	Last week
Potential mechanism variables		
Affect	5 items, shortened from [53]	Momentary
Sleep	2 items, as in [53]	Last night[f]
Catastrophizing	4 items, as in [21,53]	Last week
Partner communication	3 items, based on [21]	Last week
Partner interactions	6 items, shortened from [20]	Last week
Self-efficacy	3 items, based on the SES[g]	Last week
Mindfulness	4 items, based on the FMI[h]	Last week
Closeness	2 developed items	Last week

[a]Patient only.

[b]Items ask the participants to report their current state (eg, "How fatigued do you feel right now?").

[c]Partners report on their perception of patients' fatigue.

[d]SFQ: Short Fatigue Questionnaire [54].

[e]Items ask the participants to report their state from the previous week.

[f]Items ask the participants to report their state from the previous night.

[g]SES: Self-Efficacy Scale [44].

[h]FMI: Freiburg Mindfulness Inventory Short Form [46].

Weekly fatigue severity in patients will be assessed with the 4-item Short Fatigue Questionnaire (SFQ) [54], a shortened version of the CIS-fatigue. The time frame has been adapted from the original past 2 weeks to the previous week, and items are formulated in the past tense (eg, "I felt tired").

Current fatigue severity will be assessed in the weekly diaries with 1 item, "How fatigued do you feel right now?" that is scored on an 11-point Likert scale ranging from (score 0) "not at all" to (score 10) "as fatigued as I could be" [20,21,53].

Analyses

Analyses will be conducted in SPSS (IBM Corp) and Mplus (Muthén & Muthén).

Descriptive Statistics

Descriptive statistics will be presented in a table. Data for patients with cancer and their partners will be presented separately (with the exception of couple characteristics such as relationship status). A study flowchart will show the number of couples screened, eligible, and included, as well as reasons for noneligibility and dropout.

Benchmark and Critical Values

This pilot trial is designed to assess the acceptability, potential efficacy, and potential working mechanisms of COMPANION and to determine the feasibility of trial procedures. To establish whether a subsequent randomized controlled trial (RCT) is justified, we have set benchmarks and critical values. Benchmark values represent the lower values of what we deem desirable to achieve. Critical values are defined as half of the benchmark values and represent potential problems with the outcome assessed. These benchmarks and critical values are based on comparable literature and our clinical and research experience. As each trial is unique (eg, in terms of study design, target population, intervention content, and duration), benchmark values are set rather conservatively (ie, similar to or lower than in comparable studies). The benchmark and critical values will not serve as definitive thresholds to determine whether a larger RCT is justified but will be interpreted along with the other outcomes, focus group data, and the recruitment log. Table 4 provides an overview of the key outcomes, their operationalizations, benchmark, and critical values.

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Table 4. Overview of outcome measures, their operationalizations, benchmark, and critical values.

Outcome	Operationalization	Data	Benchmark values	Critical values
Acceptability of COMPANION				
Intervention adherence	Percentage of couples in which the patient completed the intervention, that is, followed at least 6 out of 9 sessions, and the partner did not drop out	T1 (patients) and/or therapist log	≥60% of couples completed the intervention	<30% of couples completed the intervention
Intervention satisfaction	Percentage of patients and partners responding to T1 who are satisfied with the couple approach and the intervention overall (score ≥5 on a 7-point Likert scale)	T1 (patients and partners)	≥70% of patients and ≥70% of partners are satisfied with the intervention overall and/or the couple approach	<35% of patients and <35% of partners are satisfied with the intervention overall and/or the couple approach
Potential efficacy for patient fatigue				
Significant change in patient fatigue	Statistically significant decrease from CIS-fatigue$_{T0}$[a] to CIS-fatigue$_{T1}$ (intention-to-treat).	T0 and T1 (patients)	Significant improvement in patient fatigue (P<.05, intention-to-treat)	N/A[b]
Clinically relevant improvement	Percentage of patients in which CIS-fatigue$_{T0}$–CIS-fatigue$_{T1}$≥6.	T0 and T1 (patients)	≥45% of patients improved (intention-to-treat)	<23% of patients improved (intention-to-treat)
Feasibility of trial procedures				
Rates related to the recruitment procedure	Recruitment rate: average per month, averaged across recruitment strategies.	Recruitment log	≥3 couples included per month	<1.5 couples included per month
Adherence to the T1 and T2 questionnaires	Percentage of patients and partners completing and returning T1 and T2.	T1 and T2 (patients and partners), recruitment log	≥65% of patients and partners completed T1 and ≥60% of patients and partners completed T2	<33% of patients and partners completed T1 and <30% of patients and partners completed T2
Adherence to the diary protocol	Percentage of diaries completed by patients and partners.	Diary (patients and partners), recruitment log	≥65% of diaries completed by patients and partners	<33% of diaries completed by patients and partners
Potential working mechanisms				
Changes in fatigue and potential mechanisms over time	Co-occurrence of time slopes of potential mechanisms with time slope of fatigue.	Diary (patients)	Targeted cognitions and behaviors improve (ie, time slopes are significantly different from 0); improvements co-occur with improved fatigue (standardized covariance is significant, P<.05)	N/A

[a]CIS-fatigue: Checklist Individual Strength, subscale Fatigue Severity.

[b]Not applicable.

Primary Aims

Acceptability of the couple intervention will be determined in terms of adherence to and satisfaction with the couple intervention. The benchmark value for adherence is based upon the rates of the trial that tested the patient-centered intervention (ie, 38% of intervention dropout [31]) and on comparable web-based couple interventions [55,56]. Couples will not be considered in cases where the investigator decides to withdraw the couple or a change in health status occurs that interferes with participation. The benchmark value for satisfaction is based upon the couple intervention trial by McDonnell et al [40], in which acceptability with different intervention components ranged between 75% and 100% for patients and family members.

The potential efficacy of the couple intervention will be determined in terms of a statistically significant decrease and a relevant improvement (≥6-point decrease on CIS-fatigue) in patient fatigue between T0 and T1. Both intention-to-treat analyses (ie, including all couples allocated) as well as per-protocol analyses (ie, including only couples who completed COMPANION as defined above) will be performed. The benchmark value for the percentage of clinically relevant improvement is based on our previous trial, in which 49% of the patients allocated to patient-centered eMBCT benefitted in terms of reduced fatigue (intention-to-treat; using a stricter criterion to define improvement as used here) [31].

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Missing values will be replaced with multiple imputations using chained equations. The imputation model will include demographic and clinical variables as assessed at baseline. In sensitivity analyses, completer analyses will be performed (ie, including only cases with nonmissing CIS-fatigue$_{T0}$ and CIS-fatigue$_{T1}$ values). Of note, the study evaluating the patient-centered intervention included only curatively treated patients. It might be that the formulated benchmark values for efficacy are too strict for patients with cancer recurrence or reinitiation of treatment. If applicable, we will therefore calculate the efficacy outcomes with and without these patients included.

Secondary Aims

The feasibility of the trial procedures will be determined in terms of the recruitment rate. In our trial testing patient-centered eMBCT, on average, a total of 6 patients were included per month [31]. Given the known challenges in recruiting dyads for interventional research [36,57-59], the benchmark value is set lower, even lower than the number required (ie, 3,8) to reach our target sample size within the planned 9-month recruitment period.

The feasibility of the trial procedures will also be assessed in terms of adherence to the study protocol. In our previous trial, 73% of patients completed T1 and T2 [31]. In this trial, the follow-up period is shorter than in comparable trials (ie, 4 weeks). Still, given the intensity of the diary assessments (ie, up to 22 diaries), we set our benchmark value for completion of both assessments conservatively. In our observational diary study among fatigued survivors of cancer and their partners, compliance with the evening diary exceeded 90% [21]. While assessments in this study were also performed in the morning and noon, the diary period lasted only 2 weeks. It seems likely that the completion rate in this study is lower as the diary procedure is embedded in intensive treatment and the diary period covers several months; a study that had a diary duration of 6 months had a completion rate of 69% [60].

Based on the cognitive-behavioral model of fatigue and previous research [20,21,53,61], the potential mechanism variables are affect, sleep, catastrophizing, partner communication, partner interactions, self-efficacy, mindfulness, and closeness. A variable is established as a potential working mechanism of the couple intervention if its change (ie, improvement) over the course of the diary period covaries with decreases in weekly fatigue. Multilevel growth curve analysis will be applied to model the time slopes of the potential mechanisms and weekly fatigue over the entire diary period. We will explore both linear and nonlinear time trends and consider modeling random intercepts and random slopes. An improvement in fatigue and maladaptive constructs such as catastrophizing is indicated by a decrease over time. An improvement in adaptive constructs such as self-efficacy and mindfulness is indicated by an increase over time. For mechanism variables pertaining to partner communication and partner interactions, an improvement might be indicated by a decrease or increase. For some couples, talking (temporarily) more about fatigue is adaptive, while for others, talking (temporarily) less is adaptive. Covariances between the time slopes of the presumed mechanisms and the time slope of daily fatigue will be estimated to identify whether the temporal changes co-occur. A variable is established as a potential working mechanism in case the standardized covariance between the slope change factor for the outcome and that of the presumed mediators is significant (using a *z* test where ±1.96 is significant at the .05 level). Models will be run for weekly fatigue as well as weekly-reported momentary fatigue.

Explorative Analyses

First, we will explore whether there are differences between couples with low versus high partner involvement. A comparison will be performed on personal and couple characteristics. Second, we will explore whether the degree of partner involvement is related to the potential effect on patient fatigue, intervention adherence, and satisfaction. Please note that in cases of little variation in partner involvement, we might not be able to conduct these analyses. Third, we will explore the potential efficacy for fatigue severity as assessed at T2. For these analyses, the scores from the T0 and T2 assessments will be used for the statistical test (ie, CIS-fatigue$_{T0}$ and CIS-fatigue$_{T2}$). Fourth, we will explore whether the couple intervention had a positive effect on cancer patients' and partners' well-being (as assessed with the Hospital Anxiety and Depression Scale [HADS]) and on couples' relationship outcomes (as assessed with the subscale marital satisfaction of the Maudsley Marital Questionnaire [MMQ]) at T1 and T2. Lastly, we will explore whether the diary data of partners also show the expected improvement in targeted variables and partner outcomes over time.

Analysis of Focus Group Data

Focus groups are held to assess participants' experiences with following the intervention (patients and their partners) and delivering the intervention (therapists). Barriers and facilitators, as well as ideas for improvement of the intervention and trial procedures, are discussed. The data will be analyzed following the principles of thematic analysis, using open, axial, and selective coding [62]. A total of 2 researchers will independently familiarize themselves with the transcripts of the focus groups and identify initial codes (open coding). These initial codes will be collated into potential themes, described in relation to the coded extracts, and organized into a preliminary coding scheme (axial coding). Emergent themes will subsequently be reviewed and organized according to the main themes, resulting in a final coding scheme (selective coding). Using the constant comparative method [63], we will compare intervention experiences and ideas for improvement both between and within groups (ie, patients, partners, and therapists). Codes, themes, and their interpretations will be regularly discussed within the project team. The qualitative data will be interpreted along with the quantitative data.

Monitoring

This study is subject to on-site monitoring based on the risk classification "negligible."

Ethical Considerations

This study has been approved by the medical ethics committee of the University Medical Center Groningen (registration

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number 2022/203, NL80201.042.22). The study is registered on ClinicalTrials.gov (NCT05636696). Written informed consent will be obtained from all participating patients with cancer and partners. A separate consent form will be signed by those who participate in the focus groups.

Results

Data collection is expected to be completed by March 2024.

Discussion

This pilot trial is designed to assess the acceptability, potential efficacy, and potential working mechanisms of COMPANION, a web-based couple intervention targeting CCRF. The feasibility of the trial procedures will also be determined. Together with qualitative data, a priori benchmarks and critical values for the key outcomes will inform whether conducting a future RCT to test the efficacy of COMPANION as compared to a control condition is warranted. If all or most benchmark values are achieved and qualitative data are reflective of this, progression to a larger RCT without adjustment to the intervention and/or trial is indicated. In the case of less positive results, progression with some adjustments to the intervention and/or trial procedures might be indicated. If few or no benchmark values are reached and qualitative data are reflective of this, it may be decided not to progress to an RCT.

Interventions directed at patients with cancer and their close relatives are becoming increasingly common. However, of those relevant to the proposed pilot study, most either apply a couple's mindfulness-based approach [64,65] or target cancer-related fatigue [66]. To the best of the authors' knowledge, there is not yet a mindfulness-based intervention for couples that primarily targets fatigue. There is 1 mindfulness-based (ie, yoga) intervention for patients and their family members that focuses on symptom reduction, with 1 outcome being fatigue reduction [40]; yet, due to the pilot design and small sample size, no conclusions about change in fatigue can be drawn. This lack of studies examining mindfulness-based interventions for couples that primarily target fatigue is surprising given the large evidence base supporting the efficacy of patient-centered mindfulness-based interventions for reducing cancer-related fatigue [16-19,67]. Therefore, the main strength of the proposed pilot trial is that it is the first to test a couple mindfulness intervention primarily targeting CCRF. This couple intervention is based on a patient-centered mindfulness-based intervention that also primarily targets CCRF and has been shown to be effective in reducing it. Further, the adaptation of the patient-centered intervention to the couple was performed with input from relevant stakeholders. Therefore, we expect that the intervention will likely meet the needs of patients and partners. Moreover, the intervention is web-based. Patients, and to a varying degree, their partners, walk through the sessions themselves while being guided remotely by their therapist. This delivery format facilitates the scalability of the intervention due to reduced participant burden and therapist time.

Another strength pertains to the collection of diary data. By measuring potential mechanism variables throughout the treatment, we make the first step toward understanding through which processes the expected beneficial effect may be reached. With this knowledge, the intervention could be made more efficient in the future. Another strength pertains to the collection of qualitative data. These data will be helpful in interpreting quantitative findings and, if needed, providing insight into how the intervention and trial procedures could be improved for a subsequent RCT. Furthermore, applying different recruitment strategies allows us to estimate the most effective ways of including couples. Lastly, we also include patients treated with palliative intent (provided they completed treatment ≥3 months ago; reinitiation of treatment after inclusion is not an exclusion criterion) and we do not exclude participants with comorbidities (barring cases as outlined in Textbox 1), increasing the external validity of the trial.

Several limitations of the pilot trial need to be mentioned. It is a single-arm, uncontrolled trial. Accordingly, results regarding the potential efficacy of COMPANION on patient fatigue and exploratory outcomes will need to be interpreted with caution. Furthermore, due to time constraints, the T2 follow-up assessment is planned only 4 weeks after T1. In a subsequent RCT, a longer follow-up period is needed to assess whether the expected treatment effect will be sustained over time. Adherence to the T2 assessment in this pilot study will therefore likely overestimate adherence to the long-term follow-up in a subsequent RCT.

The authors hope that COMPANION has the potential to positively contribute to CCRF care and benefit patients as well as their partners.

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Data Availability

The data sets generated and analyzed during this study are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

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Abbreviations

CCRF: chronic cancer-related fatigue
CIS-fatigue: Checklist Individual Strength, subscale Fatigue Severity
eMBCT: web-based mindfulness-based cognitive therapy
HADS: Hospital Anxiety and Depression Scale
HDI: Helen Dowling Institute
MMQ: Maudsley Marital Questionnaire
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
SFQ: Short Fatigue Questionnaire
UMCG: University Medical Center Groningen

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Protocol

A Framework to Guide Implementation of AI in Health Care: Protocol for a Cocreation Research Project

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Abstract

Background: Artificial intelligence (AI) has the potential in health care to transform patient care and administrative processes, yet health care has been slow to adopt AI due to many types of barriers. Implementation science has shown the importance of structured implementation processes to overcome implementation barriers. However, there is a lack of knowledge and tools to guide such processes when implementing AI-based applications in health care.

Objective: The aim of this protocol is to describe the development, testing, and evaluation of a framework, "Artificial Intelligence-Quality Implementation Framework" (AI-QIF), intended to guide decisions and activities related to the implementation of various AI-based applications in health care.

Methods: The paper outlines the development of an AI implementation framework for broad use in health care based on the Quality Implementation Framework (QIF). QIF is a process model developed in implementation science. The model guides the user to consider implementation-related issues in a step-by-step design and plan and perform activities that support implementation. This framework was chosen for its adaptability, usability, broad scope, and detailed guidance concerning important activities and considerations for successful implementation. The development will proceed in 5 phases with primarily qualitative methods being used. The process starts with phase I, in which an AI-adapted version of QIF is created (AI-QIF). Phase II will produce a digital mockup of the AI-QIF. Phase III will involve the development of a prototype of the AI-QIF with an intuitive user interface. Phase IV is dedicated to usability testing of the prototype in health care environments. Phase V will focus on evaluating the usability and effectiveness of the AI-QIF. Cocreation is a guiding principle for the project and is an important aspect in 4 of the 5 development phases. The cocreation process will enable the use of both on research-based and practice-based knowledge.

Results: The project is being conducted within the frame of a larger research program, with the overall objective of developing theoretically and empirically informed frameworks to support AI implementation in routine health care. The program was launched in 2021 and has carried out numerous research activities. The development of AI-QIF as a tool to guide the implementation of AI-based applications in health care will draw on knowledge and experience acquired from these activities. The framework is being developed over 2 years, from January 2023 to December 2024. It is under continuous development and refinement.

Conclusions: The development of the AI implementation framework, AI-QIF, described in this study protocol aims to facilitate the implementation of AI-based applications in health care based on the premise that implementation processes benefit from being well-prepared and structured. The framework will be coproduced to enhance its relevance, validity, usefulness, and potential value for application in practice.

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KEYWORDS

artificial intelligence; AI; health care; implementation; process models; frameworks; framework; process model

Introduction

Artificial intelligence (AI) has the potential to revolutionize health care delivery [1]. AI refers to the simulation or approximation of human intelligence in machines, such as perception, reasoning, and decision-making [2]. It can be used for a variety of applications in health care, for example, diagnosis, treatment planning, disease prediction, and personalized medicine [3-5]. AI can analyze large amounts of data quickly and accurately. This can be especially useful in health care for screening and diagnosis; AI can identify patterns and anomalies in medical images or laboratory results that human clinicians might miss or overlook [6]. AI can also be used to predict disease progression and recommend treatment options based on a patient's individual characteristics and medical history [7]. AI can also be useful in the development of digital tools and interventions in health care [8]. AI-powered mobile apps and wearables such as smartwatches can provide patients with personalized health recommendations, monitor vital signs, and alert health care providers to potential problems. This can help to reduce the burden on health care systems and improve patient outcomes by enabling more proactive and personalized care.

Expectations for the use of AI-based applications to improve health care delivery and efficiency are high. However, this sector has been slow to make use of AI compared with other sectors of society, such as banking, transport, and retail [9-12]. The implementation of AI in health care has encountered various technological, individual, social, and organizational barriers. These barriers have been classified in different ways, for example, data related, methodological, technological, regulatory or policy related, human factor related, environmental, and organizational [13-15]. Several studies have concluded that the implementation of AI-based applications tends to be unstructured [16,17]. Research on strategies to overcome these barriers or how to best implement AI-based applications in health care is scant [17].

Research in implementation science on the introduction and use of technological innovations and other new practices has shown that implementation is often suboptimal [18]. Implementation tends to be a complex and challenging process because it requires changes in existing behaviors, practices, and routines, many of which are well established or ingrained [19]. There may also be competing priorities or resource constraints that make it difficult to prioritize the implementation of new practices. To address these challenges, implementation science emphasizes the importance of planning for implementation from the outset to create conditions conducive to implementation and carrying out implementation processes in a structured, well-planned, and orderly way [20]. Process models are a key tool in implementation science, providing guidance for well-prepared and structured implementation by describing the key considerations and activities that are important to take into account during the implementation process [21]. These models help to ensure that implementation proceeds in a way that is systematic and focused on achieving the desired outcomes.

Interest in using AI in health care has increased in recent years, but there is a lack of knowledge to guide the process of implementing various AI-based applications in this setting. Therefore, the aim of this protocol is to describe the development, testing, and evaluation of a framework ("Artificial Intelligence-Quality Implementation Framework"; AI-QIF) intended to guide decisions and activities related to the implementation of various AI-based applications in health care. The target group of the framework are those who make decisions about, lead, or are involved in change processes in connection with the implementation of AI-based applications in health care.

Methods

Overall Design

This project will use a cocreation design [22] to develop, test, and evaluate a framework to guide the implementation of AI-based applications in health care. This will be carried out in 5 phases by Halmstad University researchers in collaboration with various stakeholders (Table 1). Cocreation involves collaboration between researchers and stakeholders for a creative problem-solving process, from design, production, and implementation to evaluation of solutions [22]. Cocreation has been found to improve the quality, usability, and social acceptance of new solutions [23]. In this project, participants with different roles in relation to AI implementation will offer diverse insights by means of interviews and informal conversations. The aim of the cocreation approach is to obtain a more holistic view of the form, content, and potential value of the framework that will be developed and to ascertain its usability in health care practice.

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Table 1. The 5 phases of the project to develop, test, and evaluate the AI-QIF[a].

Phase and time period	Aim of the phase	End product of the phase	Data collection	Data analysis	Cocreation aspects
I: January to June 2023	To produce an AI[b]-adapted version of QIF[c]	A preliminary version of a Swedish-language AI-QIF (AI-QIF 1.0)	Inspection of the Swedish QIF version developed by the Public Health Agency of Sweden; consultations with QIF experts at the Public Health Agency of Sweden.	No formal analysis. Discussions in the research team regarding the adaptation of QIF for AI purposes.	QIF experts at the Public Health Agency of Sweden
II: June to December 2023	To enrich a preliminary version of AI-QIF and to make sure it is grounded in empirical AI research	An initial version of a Swedish-language AI-QIF (AI-QIF 1.2) presented as a mockup of a web-based application	Secondary data in the form of published studies concerning AI implementation and transcripts of 120 interviews conducted by Halmstad University researchers.	Deductive mapping of information to the 14 steps of QIF.	Managers, practitioners, and developers from health care as well as individuals from academia and the business sector with AI knowledge
III: September to December 2023	To incorporate organization- and management-relevant AI aspects	A prototype AI-QIF with an intuitive user interface (AI-QIF 1.3)	Individual interviews with managers in Region Halland involved in AI-relevant decision-making, national AI experts, and patients. Estimated interviews, n=20.	Qualitative content analysis.	Managers in Region Halland involved in AI-relevant decision-making and national AI experts
IV: January to June 2024	To investigate the usability of an AI-QIF prototype under real-world conditions	A proposed final version of the framework (AI-QIF 2.0)	Individual interviews with managers and AI-users in Region Halland involved in 3 AI cases. Estimated interviews, n=20.	Qualitative content analysis.	Managers and AI users involved in 3 AI cases in Region Halland
V: August to December 2024	To evaluate the real-world use of the final AI-QIF and investigate barriers and facilitators to using the AI-QIF when implementing various AI applications	A description of the development of the AI-QIF and guidelines for its use in practice based on the key barriers and facilitators to its use in routine practice that have been identified	Individual interviews with approximately 20 users of the AI-QIF in 5 regions in Sweden.	Qualitative content analysis, inductive and deductive, the latter based on Capability-Opportunity-Motivation-Behaviour.	Users of AI-QIF in 5 regions

[a]AI-QIF: Artificial Intelligence-Quality Implementation Framework.

[b]AI: artificial intelligence.

[c]QIF: Quality Implementation Framework.

Quality Implementation Framework as the Basis for the Initial Development of the Framework

The AI implementation framework will be based on the Quality Implementation Framework (QIF), a process model in implementation science aimed at guiding implementation processes. The QIF describes a number of activities and considerations that should be undertaken when implementing new practices. It was developed by Meyers et al [24] to achieve an improved understanding of "the nature of the implementation process." Meyers et al [24] posited that "quality implementation" is "putting an innovation into practice in such a way that it meets the necessary standards to achieve the innovation's desired outcomes." In total, 25 theories, models, and frameworks across multiple research and practice areas were examined. A synthesis of the frameworks yielded 14 activities (referred to as steps) to be carried out in the implementation process. These steps are clustered into a 4-phase temporal sequence [25].

The first phase of the QIF is an initial consideration regarding the host setting, with work focusing primarily on making sure there is a fit between the innovation and the host setting. The second phase involves creating a structure for implementation and emphasizing the importance of creating an organized structure to oversee the implementation process. This can involve, for example, having a clear plan for implementing the innovation and identifying a team of qualified individuals who will take responsibility for the process. The third phase is aimed at creating an ongoing structure once implementation begins, for example, providing required technical assistance, coaching and supervision, and creating supportive feedback mechanisms for the users of the innovation. The fourth phase is aimed at learning from the implementation of the innovation to improve future applications [25].

The QIF has many strengths that were important for choosing this process model as a starting point for the AI-QIF. It has been widely used and shown to be feasible in many different types of settings, for example, studies on the implementation of a

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primary health care system improvement initiative in South Africa [26], electronic medical records for clinical and research purposes in Malaysia [27], an oral screening tool for pediatric cardiologists in the United States [28], and a mindfulness-informed social and emotional learning program in elementary schools in England [29]. The flexible application of the QIF underscores the model's adaptability and usability. Furthermore, the QIF has a broad scope and is not restricted to any specific "implementation object." Rather, the "object" can be any practice (innovation, intervention, program, routine, service, etc) that is introduced into an organization. Other process models in implementation science have a considerably narrower scope, for example, focusing on how research findings are used by nurses in their everyday practice [21].

The QIF is comprehensive, yet it provides fairly detailed guidance concerning important activities and considerations for successful implementation. This is in contrast to many other process models in implementation science that provide considerably more generic guidance, for example, describing an overarching process of how research is transformed into action [21]. A further strength of the QIF is that it has been translated into Swedish and used in Swedish health care by the Public Health Agency of Sweden [30]. The agency is an expert state authority under the Government's Ministry of Social Affairs with national responsibility for public health issues. The agency aims to protect the population against communicable diseases and other health threats, developing general guidelines and recommendations [31]. Agency staff tasked with developing an updated Swedish version of the QIF have recently collected feedback from QIF users in various settings, which they have used for some modifications to the Swedish version.

Phase I: Repurposing the QIF for Use in an AI Implementation Context

The first phase is aimed at verifying the validity of the QIF process model as the starting point for producing the first version of an AI-adapted version of the Swedish-language AI implementation process model (AI-QIF 1.0). This work is similar to the psychometric investigation of content validity and face validity that is done for various assessment instruments [32]. This preliminary version will be collated from the original QIF (in English) and current Swedish versions of the QIF.

Data will be collected in 2 ways. First, we will examine the Swedish QIF translation developed by the Public Health Agency of Sweden, comparing and contrasting the original QIF with the Swedish version item by item. Potential differences will be discussed with representatives of the team at the Public Health Agency of Sweden, who developed the Swedish version.

Second, we will draw on feedback documented by the Public Health Agency of Sweden from testing of the QIF by Region Dalarna and 15 municipalities in Dalarna. The framework is also used by other regions, but the Public Health Agency has not yet received feedback from them. Comments and suggestions for revisions have been collected by the team (n=3) at the agency who are in charge of the QIF. We will consult with QIF-knowledgeable experts in this team concerning lessons learned from this hands-on use of the QIF, for example, in terms of potential difficulties in interpreting items or whether important aspects were perceived to be missing from the Swedish QIF model.

Phase II: Developing a Mockup of the AI-QIF

The aim of the second phase is to enrich the preliminary version of the Swedish-language AI-QIF and to make sure it is grounded in empirical AI implementation research. The work is largely similar to face and content validity evaluation that is part of instrument development [32]. This is achieved by accounting for and integrating empirical findings from two sources: (1) AI implementation cases described in studies identified through literature reviews [17,33] and (2) interview studies involving various stakeholders involved in or affected by the implementation of AI applications in health care [34]. The end product of phase II will be an adapted version of a Swedish-language AI-QIF (AI-QIF 1.1) presented as a mockup of a web-based application.

First, we will examine AI literature of relevance for the AI-QIF by identifying AI implementation cases in studies identified in literature reviews of AI implementation studies [17,33] and examining the studies in question. This will enable us to identify overlap between the AI-QIF and existing knowledge about barriers and strategies concerning the implementation of AI in health care as well as possible differences and other aspects to take into account when implementing AI in health care.

Second, we will draw on a secondary analysis of 120 interviews conducted with stakeholders such as managers, practitioners, and developers from health care as well as academia and business sector individuals with AI knowledge [34]. The interviews will focus on, among other AI applications, mortality prediction in the emergency department, prevention of mental health problems among young adults, digital triage in primary care, and reducing the risk of readmission of heart failure patients. The purpose of analyzing these interviews is to identify AI-specific implementation barriers and strategies that might be relevant to integrate into the framework. The interviews address experiences and perceptions held by stakeholders concerning the implementation of AI in general and various specific AI-based applications.

Findings from the 2 sources (ie, AI implementation cases in the literature and interviews) will be combined and analyzed in a deductive mapping process [35] to the contents of the 14 steps of the first version of the AI-QIF (from phase I). In the first step of the analysis, an inductive approach will be undertaken to identify barriers and strategies for the implementation of AI in practice. In the second step, a deductive approach will be undertaken to map these barriers and strategies to the 14 steps in the AI-QIF. If deemed necessary, parts of AI-QIF can be adjusted to fit the needs of stakeholders by adjusting, adding, or removing steps or changing the wording in the framework to fit AI implementation. All authors will be involved in the entire analysis process, thus enabling a variety of interpretations of the material before consensus is reached among all authors.

Third, the results of phase II will be used to further adapt the Swedish-language AI-QIF (AI-QIF 1.2) and will be presented as a mockup of a web-based application.

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Phase III: Developing a Prototype of the AI-QIF

The aim of phase III is to incorporate organization- and management-relevant AI aspects based on input from national AI experts and health care managers in Region Halland who are involved in AI-relevant decision-making and deployment of AI-based applications in health care in this region (regions are responsible for the provision of health care in Sweden). The goal is also to achieve a comprehensive face-validity check [32] of an intuitive and user-friendly prototype of the AI-QIF (AI-QIF 1.3).

We will develop an interview guide and conduct interviews with AI experts and managers on usability and feasibility issues around the potential use of the AI-QIF in practice. Purposive sampling will be used to identify and select individuals who can provide rich information to achieve the objective of developing the AI-QIF prototype. Approximately 20 interviews are tentatively planned, but the actual number of interviews will be guided by the information power principle [36], meaning that the larger information the sample holds relevant for the study, the lower amount of interviews is needed, and vice versa. The interviewees' experiences and perceptions will improve the fit of the framework within the context in which it will be used. The interviews will potentially function as a needs assessment, thus adding to our understanding of which organizational actors could be involved in the implementation of AI.

The interviews will also cover which terminology is experienced as appropriate, clear, and concise enough for users in these organizational capacities. The interviews will also invite participants to highlight their preferred order of the steps, which AI-QIF steps are perceived as more or less important, and which steps might be missing or redundant.

The interviews will be analyzed using qualitative content analysis [35], and the information from the interviews will be applied to the development of the prototype, which will be tested and verified iteratively with the informants to ensure that consensus is reached on how the steps should be understood and acted upon.

Phase IV: Usability Testing of the AI-QIF Prototype

Phase IV involves usability testing of the prototype of the AI-QIF developed in phase III [37]. The aim is to investigate experiences from and functionality of its use under real-world conditions. Usability testing at the prototype stage presents opportunities to check the user experiences and functionality before a final version is developed. The end product of phase IV will be the proposed final version of the framework (AI-QIF 2.0) for investigation in phase V.

For this purpose, 3 real-world AI implementation cases will be selected in close collaboration with relevant managers in Region Halland to ascertain that appropriate cases are chosen to enable timely testing of the framework before implementation starts. The following cases are planned: (1) optimized work practices and patient flows for improved care of patients with heart failure based on the implementation of an AI-based application that enables prediction of readmission risk; (2) new tools for documentation, follow-up and optimization of care flows, and management of patients with long-term wounds based on an AI-based application for analysis of and guidance for optimization of individualized wound care; and (3) introduction of interventions and resources for increased accessibility to primary care and specialist mental health care for young individuals with mental health problems based on AI-based applications for health monitoring, identification of risk groups, and mediation of care.

Key informants in each AI case will be recruited for structured interviews focusing on usability issues [38], with both Region Halland managers and users involved in any of the 3 selected cases. The aim is to investigate their experiences of using the prototype framework when implementing AI-based applications in health care. Approximately 20 interviews (managers and users) are tentatively planned, but sampling will be based on the information power principle [36]. The interviews will be analyzed using qualitative content analysis [35]. Information from these interviews will provide input for potential modifications of the framework and the prototype for the digital web application.

Phase V: Evaluating the Use of the AI-QIF

The aim of the final phase is to evaluate the real-world use of the final version of the AI-QIF and to investigate barriers and facilitators to using the AI-QIF when implementing various AI applications. The users will be asked to reflect on how they used the AI-QIF. The end product of phase V will be a description of the development of the framework and guidelines for its use in practice based on the key barriers and facilitators to its use in routine practice that have been identified.

A qualitative explorative design will be used based on individual semistructured interviews with a sample of approximately 20 framework users in 5 regions. The regions will be purposively selected with regard to geographical location (regions in different parts of Sweden) and size in terms of populations (small and large regions). A combination of conventional (inductive) and directed (deductive) approaches to qualitative content analysis will be used [35]. The deductive analysis will use 3 predefined categories of the widely used implementation determinant framework, COM-B (Capability-Opportunity-Motivation-Behaviour). COM-B posits that behavior (B), for example, using the AI-QIF, is influenced by the person's capability (C), opportunity (O), and motivation (M) to perform that behavior [38].

Ethical Considerations

The study conforms to the principles outlined in the Declaration of Helsinki [39] and will fulfill the following requirements for research: information, consent, confidentiality, and safety of the participants, guided by the ethical principles of autonomy, beneficence, nonmaleficence, and justice. Ethical approval by the Swedish Ethical Review Authority (2020-06246, 2023-02581-02) is available for required parts in phases I and II. Ethical approval will be applied for the work to be conducted in phases III, IV, and V. All participants will receive written and oral information about the studies in which they are directly or indirectly involved. Participants will also be given information about the voluntary nature of the studies,

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confidentiality, and the ability to withdraw their consent at any time without having to justify why. All personal data will be registered according to the General Data Protection Regulation (GDPR2016/679), and the data will be stored in accordance with the Archive Act in Sweden (SFS1990:782). The results will be communicated to the participants and partners, and key findings will be fed back to participants and study sites to enable refinement of the developed framework. The results will be disseminated via publications in peer-reviewed journals and presentations at national and international conferences.

Results

This project will be conducted within the frame of a research program "Toward Successful Implementation of Artificial Intelligence in Health Care Practice" [34] with the overall objective of developing theoretically and empirically informed frameworks to support AI implementation in routine health care. The program was launched in 2021 and has carried out numerous research activities, including scoping reviews, mapping of different stakeholder perspectives, and initiation of several case studies. Thus, the development of AI-QIF as a tool to guide the implementation of AI-based applications in health care will draw on knowledge and experience acquired from these activities.

The development process of the AI-QIF started in January 2023 (phase I) through collaboration with the Public Health Agency of Sweden, and the plan is to finish the tool in December 2024. The AI-QIF is under continuous development and refinement. Reporting will be done through scientific papers and various formats for more practical application in health care and in national efforts on promoting and supporting AI implementation in health care.

The insights gained during the development and refinement of the framework will be used as the foundation for parallel investments in regional capacity to increase the practical resources, competencies, partnerships, and organizational structures required to facilitate the implementation of AI-based applications. This work will be carried out in collaboration with representatives from academia, strategic partners from the business sector, and political and operational leaders and teams from the regional and municipal health care systems. The framework will be an integral part of a strategy toward the use of AI in health care (described as a "roadmap"), which is planned with strategic investments to support AI implementation and quality improvement in clinical health care practice [34].

Discussion

There is little doubt that AI will play an important role in the future of health care, yet research has documented that the use of AI in health care faces many challenges in the "last mile" of the AI research and development process, that is, the introduction and routine use of AI-based applications in health care settings [40,41]. Numerous barriers to the implementation of AI in health care have been identified [9-14,17]. The AI-QIF described in this study protocol aims to facilitate the implementation of AI-based applications in health care based on the premise that implementation processes benefit from being well-prepared and structured [42]. We have not been able to identify any AI-related studies that have investigated how or to what extent the quality of the implementation process influences the outcomes.

The starting point for the AI-QIF is the QIF, a widely used process model in implementation science. Process models have been developed in this field to facilitate implementation processes [21]. There are many process models, but most share key characteristics with the QIF. To some extent, process models present an ideal view of implementation processes as a structured, linear process that proceeds stepwise in an orderly fashion. Process models aim to create favorable conditions for implementation processes [21]. However, researchers behind many models emphasize that the actual process is not necessarily sequential. The researchers behind the QIF [24] observed that "quality implementation does not always occur in the exact sequence of [the steps]."

The importance of planning ahead of the actual implementation is evident in the QIF; 10 of the 14 steps described in this model are to be carried out before the actual implementation begins. Another common feature of process models is the recognition that context matters; hence, there is a need for adaptation of implementation to local conditions and circumstances [21]. The AI-QIF does not describe specific solutions or pinpoint particular actions. The focus of the framework is on "what" should be done and considered, not on exactly "how" this should be done. Contextual conditions and the characteristics of various AI-based applications are likely to differ considerably, making it difficult to provide a cookbook-style guide.

Following on from repurposing the QIF for use in an AI implementation context (phase I), 2 development phases (phases II and III), and pilot-testing of a prototype (phase IV), we will investigate the barriers and facilitators to using the AI-QIF under routine conditions in health care (phase V). Numerous studies have documented barriers to AI implementation, but we have not identified any studies exploring how AI implementation processes can be supported by using a framework such as the QIF. The use of the QIF can be seen as an implementation strategy intended to facilitate the implementation. Strategies in implementation science are defined as "methods or techniques used to enhance the adoption, implementation and sustainability of a clinical program or practice" [43]. There is wide recognition in implementation science that successful implementation requires efficient strategies to support implementation processes [18].

The development of the AI-QIF will be guided by cocreation principles to create new value together with stakeholders [30] and by incorporating lessons learned from cases of AI implementation in health care practice. The development of the AI-QIF will involve stakeholders such as QIF experts (phase I), health care practitioners and developers (phase II), AI experts (phase III), health care managers (phases II and III), and presumptive health care users of AI-based applications (phases IV and V).

The cocreation process of the project will draw on both research-based and practice-based knowledge. Research-based

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knowledge is explicit, primarily articulated in different types of text, with the aim of achieving improved understanding or explanation of problems. Practice-based knowledge, on the other hand, tends to be tacit, gained through experience, and expressed through action rather than words, with finding solutions to problems an important aim [44]. Research-based knowledge makes it possible to move beyond the specific "here-and-now" circumstances of a current situation, for example, AI implementation in health care. At the same time, practice-based knowledge is important to account for practical judgment and contextually adapt solutions, for example, the AI-QIF, thus facilitating flexibility and usability. Integrating the 2 forms of knowledge makes it possible to challenge taken-for-granted assumptions, thus broadening the views and enabling unexpected, creative solutions [44].

Some methodological considerations must be accounted for. The framework development is based on data from Sweden, which might negatively affect the generalizability of the results to other countries. Furthermore, much of the development of AI-QIF will take place in the regional setting of Region Halland by researchers from Halmstad University, potentially further restricting the generalizability of the framework. However, national AI and health care developers and experts will be involved in phase III, while phase V is based on the use of AI-QIF in 5 regions in Sweden, thus increasing the generalizability in a Swedish context. In addition, the framework development will be carried out by an experienced multidisciplinary research team, which will strengthen the feasibility of the study and ascertain a comprehensive and robust process. It is also a strength that AI-QIF will be based on the existing and widely used and versatile QIF process model. Cocreation is a guiding principle in the project that will benefit the development since research has shown that cocreation tends to improve the quality, usability, and social acceptance of new solutions [23]. However, there are also challenges with cocreation processes. The literature on the implementation of new technologies in health care suggests that the complexity of technologies can slow down cocreation processes [22,23].

In conclusion, the AI-QIF described in this study protocol aims to facilitate the implementation of AI-based applications in health care based on the premise that implementation processes benefit from being well-prepared and structured. The framework will be coproduced to enhance its relevance, validity, usefulness, and potential value for application in practice.

Acknowledgments

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Data Availability

The data sets generated during or analyzed during this study are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

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Abbreviations

AI: artificial intelligence
AI-QIF: Artificial Intelligence-Quality Implementation Framework
COM-B: Capability-Opportunity-Motivation-Behaviour
QIF: Quality Implementation Framework

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Protocol

Progressive Transition From Supervised to Unsupervised Robot-Assisted Therapy After Stroke: Protocol for a Single-Group, Interventional Feasibility Study

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Abstract

Background: Increasing the dose of therapy delivered to patients with stroke may improve functional outcomes and quality of life. Unsupervised technology-assisted rehabilitation is a promising way to increase the dose of therapy without dramatically increasing the burden on the health care system. Despite the many existing technologies for unsupervised rehabilitation, active rehabilitation robots have rarely been tested in a fully unsupervised way. Furthermore, the outcomes of unsupervised technology-assisted therapy (eg, feasibility, acceptance, and increase in therapy dose) vary widely. This might be due to the use of different technologies as well as to the broad range of methods applied to teach the patients how to independently train with a technology.

Objective: This paper describes the study design of a clinical study investigating the feasibility of unsupervised therapy with an active robot and of a systematic approach for the progressive transition from supervised to unsupervised use of a rehabilitation technology in a clinical setting. The effect of unsupervised therapy on achievable therapy dose, user experience in this therapy setting, and the usability of the rehabilitation technology are also evaluated.

Methods: Participants of the clinical study are inpatients of a rehabilitation clinic with subacute stroke undergoing a 4-week intervention where they train with a hand rehabilitation robot. The first week of the intervention is supervised by a therapist, who teaches participants how to interact and train with the device. The second week consists of minimally supervised therapy, where the therapist is present but intervenes only if needed as participants exercise with the device. If the participants properly learn how to train with the device, they proceed to the unsupervised phase and train without any supervision during the third and fourth weeks. Throughout the duration of the study, data on feasibility and therapy dose (ie, duration and repetitions) are collected. Usability and user experience are evaluated at the end of the second (ie, minimally supervised) and fourth (ie, unsupervised) weeks, allowing us to investigate the effect of therapist absence.

Results: As of April 2023, 13 patients were recruited and completed the protocol, with no reported adverse events.

Conclusions: This study will inform on the feasibility of fully unsupervised rehabilitation with an active rehabilitation robot in a clinical setting and its effect on therapy dose. Furthermore, if successful, the proposed systematic approach for a progressive transition from supervised to unsupervised technology-assisted rehabilitation could serve as a benchmark to allow for easier comparisons between different technologies. This approach could also be extended to the application of such technologies in the home environment, as the supervised and minimally supervised sessions could be performed in the clinic, followed by unsupervised therapy at home after discharge.

Trial Registration: ClinicalTrials.gov NCT04388891; https://clinicaltrials.gov/study/NCT04388891

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International Registered Report Identifier (IRRID): DERR1-10.2196/48485

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KEYWORDS

technology-assisted rehabilitation; unsupervised therapy; self-directed therapy; stroke; neurorehabilitation; neurocognitive rehabilitation; robot-assisted therapy; rehabilitation technology; robot.

Introduction

Stroke survivors often do not entirely recover upper limb function [1], which severely impacts independence and quality of life as remaining upper limb impairments may limit their ability to perform activities of daily living. Increasing evidence shows that therapy dose is a key factor contributing to sensorimotor recovery and that administering a higher dose of upper limb therapy to people after stroke could improve their functional outcome even long after stroke [2,3].

However, due to factors such as unfavorable therapist to patient ratios [4], high rehabilitation-related costs, and the overall frailty of health care systems (as highlighted, for example, by the COVID-19 pandemic [5,6]), increasing the dose of high-quality therapy for both inpatients and outpatients is challenging as long as it relies on hospital visits and supervised therapy.

Unsupervised technology-assisted rehabilitation, defined here as patients training with rehabilitation technologies without any supervision by an external person, is a promising solution to increase therapy dose without dramatically weighing on the health care system [7]. Relying on novel digital approaches, such as wearable sensors or robotic tools, offers new ways to promote motivation and engagement for specific therapy exercises. It promises to go beyond the conventional set of exercises prescribed for patients to train independently, which may lead to low adherence [8,9]. A range of upper limb rehabilitation technologies have been tested in unsupervised settings, such as the home environment, with varying results regarding acceptance, satisfaction, success, and amount of use [10-15]. Besides the use of different technologies, these outcomes may also be influenced by the different methods applied to teach the patients how to use a rehabilitation technology in an independent way. A key step for the successful and safe use of a rehabilitation technology without supervision is the progressive transition toward unsupervised use, where users first learn how to correctly use a technology. This becomes especially critical in the case of active technologies, such as rehabilitation robotics, whose use without any external supervision has rarely been reported.

Unfortunately, most existing studies only report little information on these methodological steps or use very different protocols (eg, from multiple training sessions in supervised settings [11] to a single explanation session directly at home [12]). Similarly, there is a lack of agreement on objective measures to evaluate and document the feasibility and success of unsupervised training.

In this protocol paper, we report on the study design of a single-group, interventional clinical study to test the feasibility of fully unsupervised therapy with an active hand rehabilitation robot in patients with subacute stroke. More specifically, we describe in detail a study protocol with the following aims: (1) to evaluate the feasibility of unsupervised therapy assisted by an active rehabilitation robot and a standardized approach for the progressive transition from supervised to unsupervised use based on a set of well-defined and objective criteria, (2) to investigate the effect of unsupervised therapy on achievable therapy dose during rehabilitation, and (3) to evaluate user experience as well as the usability of the rehabilitation technology.

The secondary objective of this study is to identify patient-related parameters (eg, age, cognitive abilities, level of impairment) that might influence the ability of a user to transition to unsupervised therapy and the dose of self-administered therapy.

Methods

Study Population and Recruitment

For this study, we aim to recruit patients in the subacute phase after stroke that are currently undergoing rehabilitation (inpatients). To be eligible for the study, patients must fulfill all the following inclusion criteria: (1) be between 18 and 90 years old, (2) be within 6 weeks from stroke onset, (3) have a prestroke Modified Rankin Score [16] ≤1, (4) have a National Institutes of Health Stroke Scale [17] score ≥1 in at least one of the items concerning motor or sensory function and ataxia, and (5) have provided informed consent as documented by a signature.

Patients are excluded if one of the following exclusion criteria is present: (1) moderate to severe aphasia (Goodglass-Kaplan scale [18] <3), (2) moderate to severe cognitive deficits (levels of cognitive functioning-revised [19] <8), (3) functional impairment of the upper limb due to other pathologies, (4) severe pain in the affected arm (visual analogue scale [VAS] for pain ≥5), (5) other pathologies that may interfere with the study, (6) pacemakers and other active implants, and (7) a modified Ashworth Scale [20] >2 for one or more of the following muscles: shoulder adductors, forearm pronator and supinator, and flexors and extensors of the elbow, wrist, and fingers.

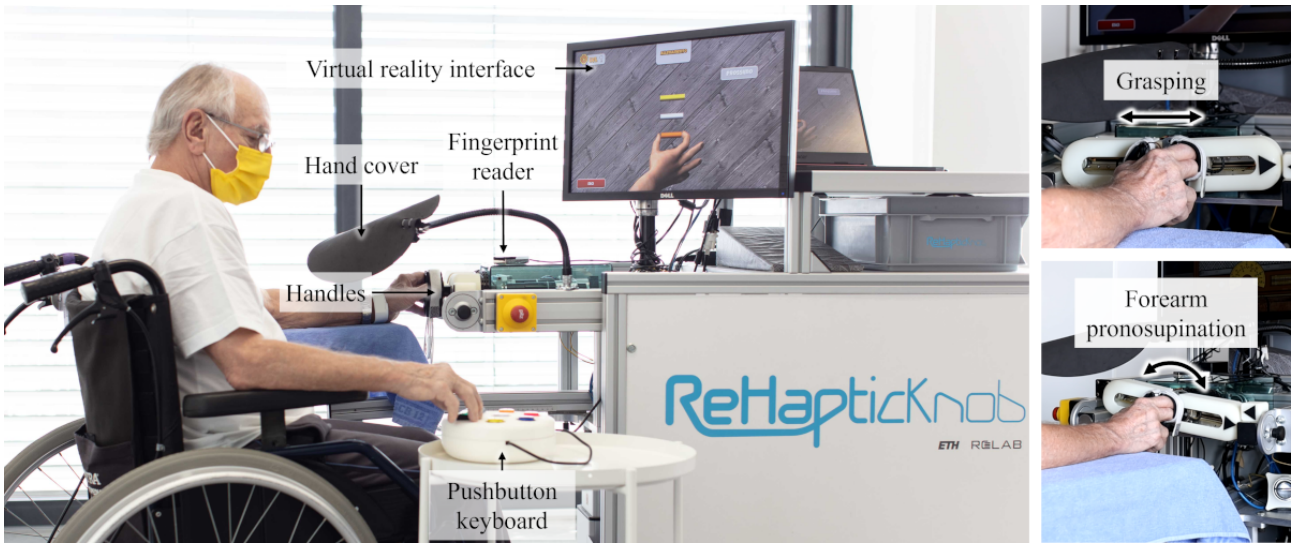
The study is recruiting inpatients with stroke from the Clinica Hildebrand Centro di Riabilitazione Brissago, a rehabilitation clinic in Switzerland where the rehabilitation technology used in the study is available. One of the medical doctors of the rehabilitation clinic involved in the study proposes to patients potentially meeting the eligibility criteria to participate in the study, explains the protocol, and obtains informed consent from them. Compensation is not provided.

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The ReHapticKnob

The rehabilitation technology used in this study is the ReHapticKnob (RHK; Figure 1), which consists of a haptic device for the rehabilitation of hand sensorimotor function after stroke with 2 active degrees of freedom, allowing for hand opening and closing and forearm pronosupination [21].

Figure 1. A patient with stroke performing an exercise with the ReHapticKnob. During a therapy session with the device (left), users first log in to their personal therapy account with a fingerprint reader; then, when performing the exercises, they place their fingers on the handles and interact with the virtual reality interface by using a colored pushbutton keyboard. As the exercises implemented on the ReHapticKnob require the user to solve tasks by relying on the sensorimotor information coming from the impaired limb and not on visual information, view of the impaired hand is blocked with a hand cover. The ReHapticKnob allows for grasping (top right) and forearm pronosupination (bottom right) movements.



The rehabilitation exercises implemented on the RHK follow the neurocognitive therapy approach [22-24] and promote motor learning by focusing on sensorimotor integration, as they require patients to use kinesthetic and proprioceptive information from their impaired upper limb and cognitively process it to solve the therapy tasks in the correct way. Assessment-driven exercises ensure an optimal difficulty level from the beginning while ensuring dynamic difficulty adaptation based on the user's performance [25]. Therapy with the RHK was previously shown to be as efficient as dose-matched conventional therapy [26] when performed in supervised settings.

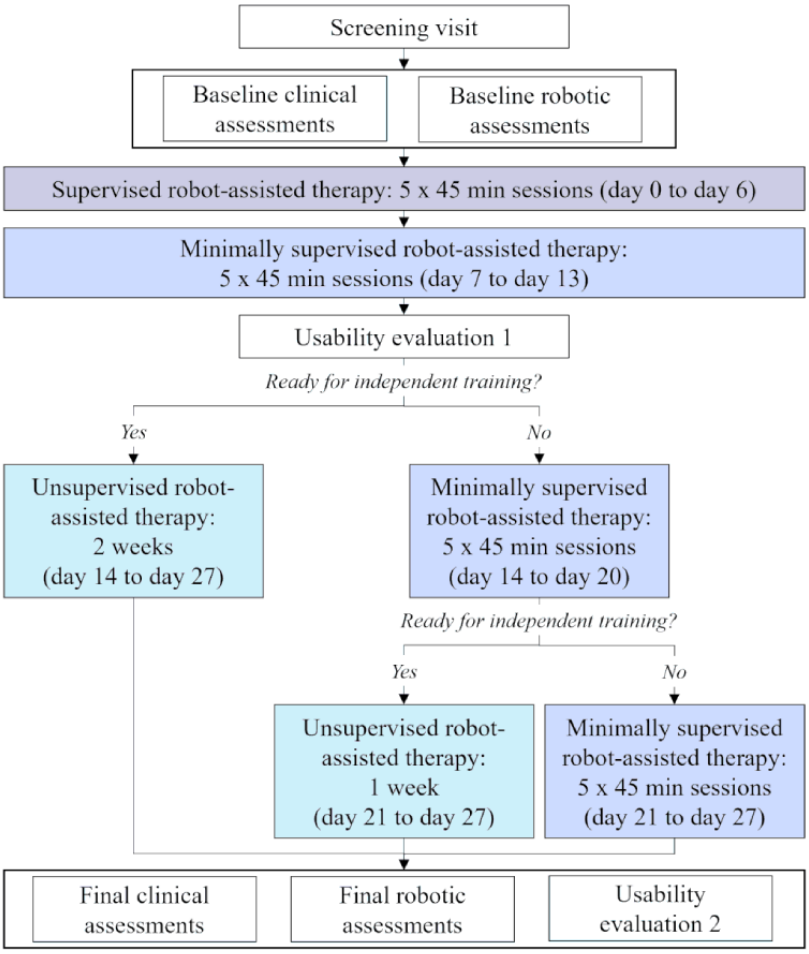
To make the device suitable for unsupervised use, design changes, such as the implementation of a new graphical user interface and pushbutton keyboard to allow direct interaction between the user and the device, were implemented and tested in a previous usability study [24]. Building on that work, the usability of the platform was further improved by implementing minor graphical changes and audio instructions for the exercises. Furthermore, the platform was improved by integrating clinically inspired algorithms to automatically monitor, control, and adapt therapy in a personalized way [27,28]. This set of algorithms was evaluated in a pilot study with 5 patients with subacute stroke, demonstrating its ability to guide them through several therapy sessions with the RHK and to automatically adapt the difficulty level of the exercises to keep therapy challenging.

Intervention

This trial is a single-group, interventional clinical study. The study protocol lasts for about 4 weeks for each patient (Figure 2), which is compatible with the duration of an inpatient stay at the rehabilitation clinic and comparable to our previous studies with the RHK [26]. The data collected and procedures performed at each time point are listed in Table 1.

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Figure 2. Design of the interventional study for each of the study participants. All participants undergo a screening visit, baseline assessments, 1 week of supervised therapy, and 1 week of minimally supervised therapy. After the first week of minimally supervised therapy, the therapist checks whether the patient properly learned how to use the technology and is ready for unsupervised training. If yes, the patient proceeds to 2 weeks of unsupervised use. If no, an additional week of minimally supervised therapy is performed. At the end of this second week, the therapist checks again whether the patient can train independently. If yes, the patient proceeds to 1 week of unsupervised therapy. If no, an additional week of minimally supervised therapy is performed. In total, each patient performs 4 weeks of technology-assisted rehabilitation. At the end of the protocol, the clinical and robotic assessments as well as the evaluation of the user experience and usability are repeated for all patients.



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Table 1. Data collected and procedures (marked with an "X") performed at each time point of the clinical trial, with primary (PO) and secondary (SO) outcomes indicated. Day 0 corresponds to the first supervised robot-assisted therapy session. The time range indicates how far a procedure can be advanced (–) or postponed (+) for organizational reasons from the precise time point at which it should be performed.

	Screening visit	Baseline clinical assessment	Baseline robotic assessment	Robot-assisted therapy sessions		Usability evaluation 1	Robot-assisted therapy sessions		Final clinical assessment	Final robotic assessment	Usability evaluation 2
Time point	Day –2	Day –1	Day –1	Day 0-6	Day 7-13	Day 13	Day 14-20	Day 21-27	Day 27	Day 27	Day 27
Time range (days)	–4 to +1	±2	±1	—[a]	—	±2	—	—	±2	±2	±2
Enrolment											
Informed consent	X	—	—	—	—	—	—	—	—	—	—
Eligibility criteria	X	—	—	—	—	—	—	—	—	—	—
Demographics[b]	X	—	—	—	—	—	—	—	—	—	—
Medical data[c]	X	—	—	—	—	—	—	—	—	—	—
Myo-relaxant drugs	X	X	—	—	—	—	—	—	X	—	—
Assessments											
VASp[d]	X	X	—	—	—	—	—	—	X	—	—
BBT[e]	—	SO	—	—	—	—	—	—	SO	—	—
MESUPES[f]	—	SO	—	—	—	—	—	—	SO	—	—
FMA-UE[g]	—	SO	—	—	—	—	—	—	SO	—	—
mAS[h]	X	SO	—	—	—	—	—	—	SO	—	—
ABILHAND	—	SO	—	—	—	—	—	—	SO	—	—
Robotic assessments	—	—	SO	—	—	—	—	—	—	SO	—
Checklist	—	—	—	—	X	—	(X)[i]	(X)	—	—	—
Usability											
SUS[j], PSSUQ[k], TLX[l], NPS[m], CSAT[n]	—	—	—	—	—	SO	—	—	—	—	SO
VAS-smiles[o]	—	—	—	SO	SO	—	SO	SO	—	—	—
Intervention											
Supervised therapy	—	—	—	X	—	—	—	—	—	—	—
Minimally supervised therapy	—	—	—	—	X	—	(X)	(X)	—	—	—
Unsupervised therapy	—	—	—	—	—	—	X	X	—	—	—
Others											
Robotic therapy data[p]	—	—	—	PO	PO	—	PO	PO	—	—	—
Conventional therapy data[q]	—	—	—	X	X	—	X	X	—	—	—
Adverse events	X	X	X	X	X	X	X	X	X	X	X
Device deficiencies	—	—	X	X	X	—	X	X	—	X	—

[a]Not applicable.

[b]Demographics include gender, age, year of birth, and hand dominance.

[c]Medical data include stroke onset, lesion type and side, and impaired hand.

[d]VASp: visual analogue scale for pain.

[e]BBT: Box and Blocks Test.

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[f]MESUPES: Motor Evaluation Scale for Upper Extremities in Stroke Patients.

[g]FMA-UE: Fugl-Meyer Assessment for upper extremities.

[h]mAS: modified Ashworth Scale.

[i](X): Performed only for patients who are not ready to train without supervision. These will continue with 5 additional minimally supervised therapy sessions. In this case, the checklist is repeated during the fifth session.

[j]SUS: System Usability Scale.

[k]PSSUQ: Post-Study System Usability Questionnaire.

[l]TLX: raw Task Load Index.

[m]NPS: Net Promoter Score.

[n]CSAT: Customer Satisfaction Score.

[o]VAS-smiles: 5-point visual analogue scale represented by different emoticons used to answer the question "How was your therapy session today?"

[p]Robotic therapy data includes, for example, time of logging in and out, duration of sessions and breaks, number of task repetitions, correct answers, difficulty level of the exercises, and muscle tone data.

[q]Conventional therapy data includes the number and type of standard therapy sessions performed by the patient while participating in the clinical trial.

Before starting the intervention, patients undergo a screening visit with a medical doctor at which the eligibility criteria are checked and demographic and medical data relevant for patient characterization are collected. At the beginning and end of the study, patients undergo a visit with an experienced therapist where clinical assessments are performed to characterize upper limb sensorimotor deficits. Before the first robot-assisted therapy session and at the end of the study, robotic assessments are performed. The baseline robotic assessments are used to tailor the initial difficulty level of the therapy exercises. As robotic therapy is an addition to conventional therapy and this protocol does not comprise a control group, functional recovery is not used to evaluate the efficacy of unsupervised robot-assisted therapy, as it is not possible to infer how much of the recovery is due solely to the addition of robotic therapy, but rather to investigate the possible relation of different impairment profiles on the observed increase in therapy dose.

During the first week of intervention (ie, the supervised phase), a therapist familiarizes the participants with the therapy platform and teaches them how to perform the therapy exercises. During the second week (ie, the minimally supervised phase), participants try to perform the therapy exercises with the device by themselves. A therapist is still present in the room but intervenes only upon request or if deemed to be needed. The first 2 phases consist of 5 sessions of about 45 minutes each, performed on consecutive days (weekends excluded). These sessions are an addition to standard therapy. Therefore, during the study, participants are allowed to fully follow the conventional interdisciplinary rehabilitation program provided by the clinic.

During the last session of the minimally supervised phase, a checklist (Multimedia Appendix 1) is used by the therapist to record whether participants learned how to correctly perform each assigned therapy exercise. The checklist is also used to assess the patient's functional independence in ambulation and in positioning in front of the device and to decide if the patient meets the requirements to train with the technology in a safe and effective way without supervision. If the requirements are met, the participant can proceed to the unsupervised phase, which lasts for 2 weeks. During the unsupervised phase, patients can independently exercise with the rehabilitation platform during their free time, during dedicated sessions indicated on their therapy schedule, as well as after 5 PM and during the weekend. Specific guidelines on how much to train are not provided. Even though a possible time to train with the device is suggested on the patient's daily therapy schedule during weekdays, patients are clearly told that they do not necessarily need to attend the session but can rather freely decide when to seek additional therapy within the offered slots or whether to go at all (ie, as a way to simulate home settings).

If, at the end of the first week of minimally supervised therapy, the patients do not meet the requirements to transition to the unsupervised phase, they continue with minimally supervised therapy for an additional week. At the end of the second minimally supervised week, the checklist is performed again. If the patients are now ready for unsupervised training, they can proceed to 1 week of unsupervised therapy; if they are not ready, they undergo a third week of minimally supervised sessions (Figure 2).

During the entire study, the device is placed in an open-access room and an emergency call system is available next to it. Trained personnel of the clinic turn on the device in the morning and turn it off in the evening. If needed, patients are taken to the device by the personnel of the clinic responsible for patient transportation. The personnel might also help patients to position themselves in the correct way in front of the device but do not help with placing the patient's hand on the handles or operating the device.

The usability of the platform and user experience during robot-assisted therapy is rated a first time at the end of the first week of minimally supervised therapy and a second time at the end of the study. The difference in the ratings between the 2 time points is used to investigate the effect of unsupervised training (ie, of the therapist's absence) on the perceived usability of the therapy platform and on the user experience during technology-assisted rehabilitation.

Adverse events and device deficiencies are monitored throughout the whole study protocol. The intervention can be discontinued after consultation with medical doctors and therapists or if the participant decides to quit.

For each patient, attendance to the robot-assisted therapy sessions is registered. As attendance to robot-assisted therapy is one of the study outcomes, strategies to increase adherence are not implemented. Reasons for nonattendance are registered

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a posteriori for each missed supervised or minimally supervised session as well as if patients train for less than 50% of the possible days (ie, less than 7 of 14 days when the patient undergoes 2 weeks of unsupervised therapy or less than 4 of 7 days in cases where the patient undergoes only 1 week of independent training) during the unsupervised phase.

Outcome Measures

Primary Outcomes

The primary outcomes of this study are the feasibility of the proposed protocol, the dose of unsupervised robot-assisted therapy performed by participants, and the difference between usability and user experience between the phases where a therapist is present (ie, supervised and minimally supervised phases) and the unsupervised phase.

Feasibility is measured as the number of patients who could transition to the unsupervised phase out of the total number of tested patients, attendance during the unsupervised phase, and safety of use. Attendance is defined as the percentage of days out of the total number of offered days where the patient trains with the device at least once, while safety is defined as the number of adverse events and device deficiencies throughout the entire protocol.

The different metrics used to characterize therapy dose are therapy duration in minutes, number of task repetitions (ie, the number of target movements performed), and percentage change in physical therapy time with respect to the conventional therapy program. Total conventional physical therapy time is estimated from the sum of the duration in minutes of the physiotherapy (without differentiating between upper limb and lower limb) and occupational therapy sessions regularly performed by each patient at the clinic.

Platform usability is assessed with the System Usability Scale [29], the raw Task Load Index [30], and the Post-Study System Usability Questionnaire [31]. User experience during robot-assisted therapy is assessed with the Net Promoter Score [32] and the Customer Satisfaction Score, as well as by evaluating the reasons (if any) for not attending the therapy sessions with the device.

The results of the checklist used to define which patient can proceed to unsupervised therapy are also used to identify specific aspects of the platform that might need to be further improved.

Secondary Outcomes

The difference in intensity (ie, number of task repetitions per minute) and task performance during supervised or minimally supervised therapy and unsupervised therapy is used to evaluate if the content of the therapy varies when the therapist is no longer present. A task repetition corresponds to the target action that the patient must perform in a given exercise (eg, a movement or combination of movements, such as one opening and closing of the hand or interacting with one virtual object rendered by the robot). A third metric to evaluate the difference in therapy content is the ratio of effective therapy time (ie, net therapy time without breaks) to total duration of a therapy session during supervised or minimally supervised therapy and unsupervised therapy.

Functional recovery, assessed as the difference between the baseline and final scores in the clinical and robotic assessments, is another secondary outcome. Clinical assessments comprise the Fugl-Meyer Assessment for upper extremities [33], ABILHAND [34], the Box and Block Test [35], the Motor Evaluation Scale for Upper Extremities in Stroke Patients [36], and the modified Ashworth Scale [20]. Robotic assessments comprise active range of motion, hand proprioception, and haptic perception (A1-A3 in [25]).

The scores of the cognitive assessments performed during the screening visit (Goodglass-Kaplan scale and levels of cognitive functioning-revised) are used to gain more insights into the effect of cognitive function on the ability to transition to the unsupervised phase.

Other parameters possibly influencing therapy dose or attendance are also evaluated. These comprise age, baseline assessment scores, functional recovery, the number of total conventional therapy sessions, and functional independence and mobility, as assessed with the Barthel index [37] and custom questions every time the checklist is performed (ie, at the end of each week of minimally supervised therapy).

Sample Size

The study includes 13 patients; 10 patients are expected to be sufficient to perform a feasibility study and gather information on the potential of unsupervised therapy to plan a subsequent larger study targeting efficacy, and a dropout rate of around 20% is accounted for based on our previous studies [26]. The selected sample size guarantees the execution of the study within a relatively short time (ie, 2 years) such that improvements to the device, if needed, can be implemented in a timely manner for follow-up studies. Furthermore, this sample size is comparable to previous studies performed by our group with the RHK and to other studies with similar goals [10,11,15].

Data Collection, Management, and Confidentiality

All the data listed herein are collected by trained personnel. For withdrawn participants, the clinical and robotic data collected until withdrawal are kept, and no further clinical or robotic evaluations are performed after that. A specific follow-up phase is not needed.

At the beginning of the study an ID is assigned to each patient and the saved data are coded according to this ID. Study data are reported on a paper case report form (CRF), 1 for each patient, and then entered in an electronic CRF with the help of an electronic database, namely Research Electronic Data Capture (REDCap) [38,39], hosted on a secure server at the Swiss Federal Institute of Technology Zürich. REDCap promotes data quality via functions and settings, like audit trails, field type restriction, range checking, and definitions of required fields. Data automatically saved by the RHK are stored on the connected laptop. Backups of the data saved on the laptop and of the electronic CRF are saved monthly on the protected server of the sponsor institution. To promote security, the laptop is password protected and participants can only access the therapy interface. The data will be archived for a minimum of 10 years after study termination or premature termination of the clinical trial.

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Data Analysis

Descriptive statistics will be used to describe the study population (eg, demographics, initial clinical scores, and changes in clinical scores, such as functional recovery), attendance and therapy dose in the unsupervised phase, user experience, and platform usability.

Normal distribution of the data will be checked with the Shapiro Wilk test. For each usability metric, a paired *t* test (normal distribution) or a paired samples Wilcoxon test (for data not normally distributed) will be performed to compare the data collected during the usability evaluation 1 and usability evaluation 2 sessions.

To evaluate the content of unsupervised therapy, 1-way repeated measures ANOVA or its nonparametric version (Friedman test) with post hoc tests will be run to compare intensity (average block intensity for each patient), performance, and ratio of effective therapy time to total session duration during supervised, minimally supervised, and unsupervised therapy. The same tests will be used to compare the answers to the VAS-smiles, a 5-point VAS represented by different emoticons, performed at the end of each therapy session during the 3 phases. For these comparisons, we expect therapy content and VAS-smiles not to vary significantly depending on the level of supervision, as ideally the absence of the therapist should not impact these outcomes. Patients who did not reach the unsupervised phase will be excluded from this analysis.

Linear mixed-effects models will be used to investigate parameters (eg, demographics and baseline data) possibly influencing the achieved dose of unsupervised therapy.

Relevant qualitative data will be summarized and reported accordingly.

Data analysis will be performed with MATLAB R2021b (MathWorks).

Monitoring

Monitoring is performed by a study nurse employed at the sponsor institution. An initiation visit on-site is performed to check the suitability of the infrastructure and staff. Routine monitoring is then performed through on-site or web-based visits depending on the needs of the investigators (eg, on request or for safety reasons). A close-out visit is performed after the completion of the study. Interim analysis is not foreseen.

Observed or spontaneously reported adverse events are collected and assessed by one of the medical doctors involved in the clinical study and recorded on the CRF. Adverse events are then reported in the annual safety report and final report. Serious adverse events are reported to the ethics committee and to the competent authority within 7 days.

Auditing may be conducted at any time by the ethics committee or the competent authority, both independent from the sponsor and investigator. The study documentation, CRF, and informed consent are accessible for auditing.

Ethical Considerations

This study protocol follows the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) reporting guidelines [40]. The study follows the guidelines on good clinical practice and the Declaration of Helsinki. The protocol (Version 2, 17.03.2020) has been approved by the cantonal ethics committee (“Comitato etico cantonale Ticino,” CE TI 3577) and by the Swiss Agency for Therapeutic Products (Swissmedic, 102681300) and was registered at ClinicalTrials.gov (NCT04388891) and on the portal for clinical trials in Switzerland (SNCTP000003850). Substantial amendments have to be submitted and approved by the cantonal ethics committee and Swissmedic before being implemented and distributed to the study staff both orally and in writing.

Ancillary and post-trial care is not needed. An insurance was stipulated to compensate for eventual harm from trial participation.

The sponsor and investigators will have access to the final trial data set. The study results will be presented among the collaborators of the Clinica Hildebrand Centro di Riabilitazione Brissago and of the sponsor institution. Results are planned to be published in peer-reviewed journals or conferences. The use of a professional writer and public access to the data set and statistical code is not foreseen.

Results

Recruitment started in November 2020. As of April 2023, 13 patients were recruited and completed the protocol. Data analysis is ongoing, and publication of the results is expected for 2023.

Discussion

This paper describes the details of a single-group, interventional clinical study investigating the feasibility of unsupervised robot-assisted therapy of hand function in inpatients with subacute stroke and its effect on the dose of therapy. In particular, we propose a systematic approach for a progressive transition from supervised to unsupervised use of an advanced rehabilitation technology.

Unsupervised technology-assisted rehabilitation is seen as a promising avenue to increase therapy dose for stroke survivors without increasing the workload for therapists. As opposed to most telerehabilitation interventions, whose development was fueled, for instance, by the COVID-19 pandemic and the need for neurorehabilitation services to decrease reliance on hospital presence (eg, by proposing remotely supervised physiotherapy sessions [41,42]), robot-assisted therapy may not rely on the presence of a therapist [7]. Such a fully unsupervised approach to neurorehabilitation might therefore provide a more sustainable answer to the unfavorable patient to therapist ratio [4,43].

The absence of supervision during rehabilitation certainly raises challenges with respect to adherence and motivation to train, understanding of tasks to be achieved, and safety. We expect that an initial standardized training procedure can help patients to learn how to use a rehabilitation technology in a controlled way so that the risk of adverse events during unsupervised

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therapy is reduced and patients feel comfortable and motivated in using the technology on their own. Despite the many feasibility studies describing unsupervised technology-assisted rehabilitation, there exists no consensus on how to optimally achieve the transition from supervised to unsupervised use of such technologies, nor is there an agreement on how to define and evaluate feasibility. The systematic approach outlined in this protocol paper provides a way for patients to progressively transition from supervised to unsupervised use of a rehabilitation technology based on objective data (ie, a checklist). Furthermore, it allows for the collection of information on the feasibility of unsupervised therapy and its effect on therapy dose, user experience, and the usability of the rehabilitation technology used. We expect this systematic approach to allow patients to transition to unsupervised use of a rehabilitation technology in a safe and comfortable way, meaning that usability and user experience do not drop during unsupervised use. High perceived usability and user experience are essential and increasingly investigated aspects [11,24,44] as they may increase adherence, and therefore, therapy dose, in the unsupervised phase, potentially leading to an improvement in functional outcomes.

While designed here for a specific robotic technology (ReHapticKnob), the proposed methodological approach could be generalized to other rehabilitation technologies with minor adjustments, such as the goals reported in the checklist, which need to be adapted to the specific rehabilitation platform as they depend on the practical actions that users need to learn to use a given technology. Furthermore, depending on the complexity of the technology, the number of supervised and minimally supervised sessions might be adapted. All other outcome measures, such as the usability and user experience questionnaires, adverse events, device deficiencies, and clinical assessments, can be collected independently from the technology used. Outcomes used to characterize therapy dose, namely, therapy duration in minutes or the number of repetitions, should be parameters that most rehabilitation technologies automatically record, as one or both of them are already reported by many research groups working in the field [13,45-47]. Given its generalizability, the proposed methodological approach could serve as a benchmark to allow for better and easier comparisons between different technologies for unsupervised rehabilitation.

The proposed interventional study of patients with subacute stroke aims to demonstrate the feasibility of fully unsupervised robot-assisted rehabilitation in a clinical setting. While no supervision is provided during the use of the device in the unsupervised phase of the study, the fact that it takes place in a clinical environment may still influence adherence and the achieved dose. However, if successful in terms of feasibility, the approach outlined in this paper could, as a next step, also be applied to the home setting. For example, the supervised and minimally supervised (and even the unsupervised) phases can be implemented in the clinic, and after discharge, the patient could continue training with the technology in an unsupervised way at home. The purpose of the progressive transition approach we propose here would be to guarantee that enough training in the use of the device is provided before discharge to later allow for safe and high-quality unsupervised use of the robot at home, which could help keep patients engaged in rehabilitation and maintain or even further increase functional recovery.

Acknowledgments

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Data Availability

This paper describes a research protocol and does not report collected data. The data sets generated during the study detailed here will later be presented in the related main manuscript describing the results of the study and will be available from the corresponding author upon reasonable request.

Authors' Contributions

All authors contributed to the development of the described study protocol. GD wrote the manuscript with the help of RR and OL. All authors reviewed the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Checklist used by the therapist to record whether participants learned how to correctly perform each assigned therapy exercise, the patient's functional independence in ambulation and in positioning in front of the device, and to decide if the patient meets the requirements to train with the technology in a safe and effective way without supervision.
[PDF File (Adobe PDF File), 282 KB - resprot_v12i1e48485_app1.pdf]

Multimedia Appendix 2
Checklist for SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines.

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[PDF File (Adobe PDF File), 128 KB - resprot_v12i1e48485_app2.pdf]

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Abbreviations

CRF: case report form
REDCap: Research Electronic Data Capture
RHK: ReHapticKnob
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
VAS: visual analogue scale

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Protocol

Clinical Prediction Models for Hospital-Induced Delirium Using Structured and Unstructured Electronic Health Record Data: Protocol for a Development and Validation Study

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Abstract

Background: Hospital-induced delirium is one of the most common and costly iatrogenic conditions, and its incidence is predicted to increase as the population of the United States ages. An academic and clinical interdisciplinary systems approach is needed to reduce the frequency and impact of hospital-induced delirium.

Objective: The long-term goal of our research is to enhance the safety of hospitalized older adults by reducing iatrogenic conditions through an effective learning health system. In this study, we will develop models for predicting hospital-induced delirium. In order to accomplish this objective, we will create a computable phenotype for our outcome (hospital-induced delirium), design an expert-based traditional logistic regression model, leverage machine learning techniques to generate a model using structured data, and use machine learning and natural language processing to produce an integrated model with components from both structured data and text data.

Methods: This study will explore text-based data, such as nursing notes, to improve the predictive capability of prognostic models for hospital-induced delirium. By using supervised and unsupervised text mining in addition to structured data, we will examine multiple types of information in electronic health record data to predict medical-surgical patient risk of developing delirium. Development and validation will be compliant to the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) statement.

Results: Work on this project will take place through March 2024. For this study, we will use data from approximately 332,230 encounters that occurred between January 2012 to May 2021. Findings from this project will be disseminated at scientific conferences and in peer-reviewed journals.

Conclusions: Success in this study will yield a durable, high-performing research-data infrastructure that will process, extract, and analyze clinical text data in near real time. This model has the potential to be integrated into the electronic health record and provide point-of-care decision support to prevent harm and improve quality of care.

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KEYWORDS

big data; machine learning; data science; hospital-acquired condition; hospital induced; hospital acquired; predict; predictive; prediction; model; models; natural language processing; risk factors; delirium; risk; unstructured; structured; free text; clinical text; text data

Introduction

Background

Hospital-induced delirium, defined as any episode of acute decline or fluctuation in attention, awareness, or other cognitive function, affects up to 56% of hospitalized older adults [1-3]. The experience of delirium can result in higher likelihood of hospital mortality, increased length of hospital stays, greater risk of 1-year mortality after discharge, functional decline, and increased caregiver burden [2-4]. The costs of hospital-induced delirium have ranged from US $16,000 to over US $64,000 per patient hospitalization, resulting in an estimated US $152 billion in national direct annual expenditures [5].

Clinicians, aging experts, patient advocates, and federal policymakers agree that there is a need to enhance the safety of hospitalized older adults through identification and reduction of iatrogenic conditions (ICs), such as hospital-induced delirium [6-8]. Advances in computing technology and availability of electronic health record (EHR) data—both structured, such as billing codes, and unstructured, such as clinical notes—present opportunities to assist health care systems and providers in more accurately identifying ICs and at-risk older adults [6,9,10].

Automated identification of conditions from EHR or other health data is not straightforward, even when biomedical ontologies such as the World Health Organization's International Classification of Diseases (ICD) or the Systemized Nomenclature of Medicine–Clinical Terms are used [11,12]. Previous studies have shown that ICD code data captures a low percentage of delirium cases [13-16]. The notion of "computable phenotype" has been introduced to provide standardized, automated algorithms that make use of both structured and unstructured health data to identify conditions [11,12]. Automated methods, such as text mining, have shown promise for medical record reviews and retrospective identification of ICs, including delirium [17-23].

Computable phenotypes are vital to identification of conditions that can be used as "dependent variables" or "targets" for prediction models to discern high-risk patients. The use of clinical notes, such as nurses' notes, has been shown to improve both computable phenotyping and prediction modeling [24]. There has been discussion about the importance of appropriately defining the outcome when developing a prognostic model for delirium; training a model to identify patients with a diagnostic code, as opposed to all patients with a condition, can result in a biased model. Researchers have suggested that incorporating clinical notes would increase the accuracy of a computable phenotype for delirium and improve a prediction model [25-27].

Registered nurses' (RNs) progress notes, a type of clinical note, often contain important contextual factors and information related to patient safety that are not found in structured data fields [28]. The ability to process and analyze text data can fill gaps in practice-based evidence, provide contextual information, and improve the accuracy of prediction models [22,29,30]. The development of a research-data infrastructure that supports the use of both structured data and text data is critical for a learning health system aimed at improving care and patient outcomes [20,22].

Despite the value in text data, few hospital-induced delirium prediction models have included nurse-generated data, such as assessments and progress notes [2]. Prior studies have also emphasized patient factors which are not mutable, such as age and gender, even though clinical interventions can only be implemented with regard to variables that can be changed. Moreover, existing prediction models tend to have a high risk of bias, and the predictive value and generalizability of these models have rarely been validated using an external data source [31,32].

Objective

Our long-term objective is to enhance the safety of hospitalized older adults by reducing ICs through a reliable and efficient learning health system. This will involve optimization of text and structured electronic data in a way that increases the reuse of clinical and administrative data for aging research, risk identification, and ultimately development of point-of-care technologies; and identification of the best ways to process and analyze text data generated by RNs to inform prospective identification of ICs in real or near–real time.

In this study, we will develop prediction models for hospital-induced delirium. In order to accomplish our objective, we will need to create a computable phenotype for hospital-induced delirium to be used as our outcome measure, design an expert-informed traditional logistic regression model to be used as a baseline model, leverage machine learning techniques to generate a model using structured data, and use machine learning and natural language processing (NLP) to produce an integrated model with components from both structured data and text data.

Building on our previous work with hospital-acquired falls [33,34], our study constitutes the first research effort to generate automated risk models of hospital-induced delirium by integrating RN-generated text data with existing structured patient, clinical, and administrative data.

Methods

Study Design

The study will use data from 2 academic medical centers in North Florida. Leveraging data from 2 medical centers will allow us to use data from 1 center for training and data from the other center for testing. Specifically, 1 medical center has

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about 1095 beds and 54,757 admissions per year, and the other medical center has about 603 beds and 23,685 admissions per year. We will include older adult (≥65 years) admissions to a medical-surgical unit between January 2012 and May 2021. We will obtain the data from the Integrated Data Repository (IDR).

The IDR was created to serve as a common source of information for clinicians, executives, researchers, and educators. The IDR enables new research discoveries as well as patient care quality and safety improvements through a continuous flow of information between the clinical enterprise and research community. The IDR currently consists of a clinical data warehouse that aggregates data from various clinical and administrative information systems, including the Epic electronic medical record. The clinical data warehouse contains demographics, inpatient and outpatient clinical encounter data, diagnoses, procedures, lab results, medications, select nursing assessments, comorbidity measures, and select perioperative anesthesia information system data.

IC Task Force

We will develop a nurse-led IC task force whose purpose is to provide relevant clinical and technical expert knowledge to translate the use of electronic clinical data. In addition to focusing on delirium, members of the IC task force will also be involved in evaluating the expanded research-data infrastructure.

Outcome

We aim to develop a computable phenotype that has greater sensitivity to identify patients with hospital-induced delirium than ICD codes alone. Along with using ICD code and medication data, we will incorporate nursing assessment documentation from structured data fields as part of our phenotype. Examples of the different types of data we will use include the ICD-10 code F05, the medication haloperidol, and the nursing assessment "observed/expressed feelings: agitated." Expert clinicians will validate the phenotype; after evaluating performance, we will iteratively refine the phenotype and use it as our outcome measure.

Structured Data Modeling

We will develop a clinical model to predict hospital-induced delirium, as defined by the (validated) computable phenotype.

We will compile a list of structured data variables to be used as candidate predictors of hospital-induced delirium, on the basis of a systematic review of the literature regarding model development and validation studies [32].

Clinical experts from our IC task force will help to select which predictors to use in a logistic regression model. We will also use machine learning methods, including decision tree, bagging, random forest, and adaptive boosting, to develop prediction models of hospital-induced delirium [35-39]. We will compare the performance of the models from machine learning techniques with our expert-informed logistic regression model. We are going to evaluate both discriminative ability and calibration; measures will include area under the receiver operating characteristic curve, balanced accuracy, sensitivity, specificity, and Brier score. We are going to use 1 admission event (encounter) per patient in order to avoid corelated instances.

Text Mining

Supervised and unsupervised text mining approaches will be used to identify concepts related to risk factors, signs, and symptoms of delirium. For risk factors, we will be reviewing and adapting NLP pipelines developed to extract concepts related to risk factors for hospital-acquired falls. To identify and extract signs and symptoms of delirium, we will start by creating a reference thesaurus of keywords and phrases (ie, n-grams and sequence of consecutive keywords) thought to indicate signs and symptoms of delirium based on domain expertise and review of the literature. New themes that emerge from the data will be added to the reference thesaurus, which will be used to develop a guide for the manual annotation process. In total, 2 practicing bedside nurses will be trained as annotators to review progress notes and label phrases related to signs and symptoms of delirium. The entire process will be overseen by text-mining experts and clinicians.

We will use clinical named entity recognition (NER) to identify text patterns and attributes related to the signs and symptoms of delirium. The NER approaches are based on conditional random fields (CRF), a statistical method of sequence modeling [40,41]. The NER identifies the boundary (start and end positions) and semantic type for each clinical concept (eg, whether the concept is a laboratory finding, a medical condition, or something else). To develop the NER system, we will recruit annotators to manually identify the signs and symptoms of delirium from clinical notes as the gold standard. We will divide the annotations into a training set and a test set. The training set will be used to train the NER model and the test set will be used for performance evaluation. The performance of the NER model will be evaluated based on measures of precision and recall, including the F-measure. The model will also become a component of a text-mining pipeline to automatically extract and analyze RNs' progress notes.

We will also develop a semiautomatic (unsupervised) method to discover previously unknown terms related to delirium from RNs' progress notes using topic modeling which can support the generation of new hypotheses of risk factors or early signs of hospital-induced delirium. A topic refers to a cluster of similar words; for example, "confused, agitated, disoriented" could emerge as a cluster with the label "patient mental status." We will apply latent Dirichlet allocation (LDA), a state-of-the-art topic modeling method which represents text files or documents as a collection of topics and assumes that each word is contained within one of these topics [42]. This probability-based approach will allow us to determine the optimal number of topics based on metrics of model performance. We will train an LDA model using the full collection of RN progress notes from one of the medical centers. The team will review the clusters of words generated by the LDA model and assign a clinical topic label based on the most frequently occurring words (this will allow us to organize the results and facilitate interpretation). Additionally, the results will be the foundation of an LDA model in our delirium text-mining pipeline. We will then generate a composite model of text and structured predictors by leveraging the structured data prediction modeling portion of our study.

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In case more than 1 model has similar performance, the most parsimonious will be chosen. In order to integrate text data and structured data into 1 model, we will translate text into vectors (ie, a numerical representation) using Word2Vec models [43]. Word2Vec is a collection of models developed and widely tested to process a large body of text to produce a vector space, with each unique text attribute being assigned a corresponding vector in that space [43]. This mathematical representation enables the inclusion of text patterns in statistical and machine learning predictive models.

Finally, we will prepare a single data set that contains the converted textual data, and significant empirical and clinical factors from the structured data modeling. We will assign a vector value to each of the unstructured text variables. This way, the structured data variables and the text attributes will all be represented in the same format and can be fitted into the same vector space for prediction model development. We will then apply logistic regression methods with a LASSO (least absolute shrinkage and selection operator) feature selector and machine learning approaches including naive Bayesian classification, decision trees, and support vector machines. Interpretability and clinical significance are critical to understand the impact of different attributes on the overall prediction and clinical translation and will be carefully considered in choosing the best fitting model [44]. The performance of the prediction models will be evaluated by calculating sensitivity, specificity, and area under the curve using 10-fold cross-validation. To minimize false negatives (ie, failing to identify a person that truly is at risk of developing hospital-induced delirium), we will prioritize sensitivity; we will also aim to maintain a specificity of at least 0.9.

Once an integrated model is developed, we will externally validate it using a sample of patients hospitalized from January 2012 to May 2021 at the medical center which was not used for training the model. All work will be completed and results will be reported in accordance with the rigorous reporting and validation standard, the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) statement, and its 22 associated items [45].

Pipeline Infrastructure

We will integrate the clinical text pipelines by adding and linking them into existing components of the IDR. To evaluate the text-mining pipelines, we will carry out a testing procedure with two phases: (1) “white-box” testing—evaluating code coverage or the internal structures of modules within the research-data infrastructure, and (2) “black-box” testing—evaluating the functionality and scalability of the research-data infrastructure. For “white-box” testing, we will examine whether branch, path, and statement programming in the expanded IDR infrastructure is functional and error free. For “black-box” testing, RN members of the IC task force (see section above) will be asked to complete a series of tasks that involve querying clinical text data in the IDR instance of the Informatics for Integrating Biology and the Bedside (i2b2) computerized platform. These tasks might include identifying patients at high risk for delirium or patients with signs or symptoms of delirium. Tasks could focus on pulling data from structured EHR data fields, structured data derived from the NLP, or both. To assess functionality, we will measure perceived ease of use, processing speed, and errors reported. To determine scalability, we will assess memory usage and processing time of all “black-box” testing to identify bottlenecks or problem areas that could increase system load at scale-up. We will use an iterative testing approach to refine the integration of the text-mining pipelines until processing speed, memory use, and error reporting have reached acceptable levels.

Ethics Approval

This project was approved by the University of Florida Institutional Review Board on February 11, 2019 (IRB201900208).

Results

Work on this project will take place through March 2024. For this study, we will use data from approximately 332,230 encounters of 170,868 patients, including 6,980,470 narrative notes; these encounters took place from January 2012 to May 2021. We will create and validate a computable phenotype for hospital-induced delirium, develop prediction models for hospital-induced delirium using structured data and unstructured text data, and integrate text pipelines into the IDR. In addition, we will identify important nursing structured EHR data, curate data, and bring these data elements into the IDR to make them available for other future research projects.

Research findings will be disseminated through scientific conferences and peer-reviewed journals. Dissemination of the results and future studies (informed by this project) may expand practice-based evidence of hospital-induced delirium, which will improve clinical decision–making by clinicians and improve patient care in hospitals.

Discussion

In this study, we will use both structured and unstructured EHR data to develop computable phenotype and prognostic models for hospital-induced delirium. By leveraging nurse-generated data, including structured fields from flowsheets and text from notes, we will identify more robust and accurate predictor and outcome measures, resulting in a highly accurate prediction model with less risk of bias than those from prior studies [31,32].

Creating multiple models will allow us to assess which data and modeling techniques make an appreciable difference. There are challenges associated with using text data, and not all EHRs contain easily accessible clinical notes. In our study, by comparing our structured data model with our integrated text and structured data model, we will be able to determine whether the text data significantly helps to predict which medical-surgical patients are at high-risk of developing hospital-induced delirium. Since the model with both unstructured and structured data will include the structured data model, we can use nested model criteria to compare their performance on the test set.

In addition, we will be able to compare our expert-informed traditional logistic regression model with models developed

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using machine learning methods. Even though models developed using machine learning techniques may be more accurate, they are also more difficult to interpret [44]. We will attempt to discern whether gain in performance is appreciable and if it outweighs the loss in interpretability.

Our study has some limitations; for instance, EHR data often has issues with completeness, accuracy, and complexity [11]. We will regularly consult with members of our IC task force so that we can better understand where and how clinicians usually document relevant data items in the EHR.

Findings from this study should allow us to develop and test a research-data infrastructure to support ongoing research on hospital-induced delirium, determine the scalability of our research-data infrastructure to OneFlorida, a state-wide PCORNet, and create synergistic relationships to test and translate our work in other health systems. This study will be a model for health care organizations to increase safe, effective care for the millions of older adults hospitalized every day.

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Authors' Contributions

SES drafted this paper; KS contributed to paper preparation; UAS contributed to paper preparation; MP contributed to the study design and paper preparation; YW contributed to the study design and paper preparation; TM contributed to the study design and paper preparation; RIB conceptualized the study and contributed to paper preparation; RJL conceptualized the study and contributed to paper preparation.

Conflicts of Interest

None declared.

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Abbreviations

EHR: electronic health record
IC: iatrogenic condition
ICD: International Classification of Diseases
IDR: Integrated Data Repository
LASSO: least absolute shrinkage and selection operator
LDA: latent Dirichlet allocation
NER: named entity recognition
NLP: natural language processing
RN: registered nurse
TRIPOD: Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis

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Protocol

Telehealth Diabetes Prevention Program for Adults With Prediabetes in an Academic Medical Center Setting: Protocol for a Hybrid Type III Trial

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Abstract

Background: Diabetes is a costly epidemic in the United States associated with both health and economic consequences. These consequences can be mitigated by participation in structured lifestyle change programs such as the National Diabetes Prevention Program (DPP) led by the Centers for Disease Control and Prevention. Mississippi consistently has among the highest rates of diabetes and prediabetes nationally. Implementing the National DPP through large health care systems can increase reach and accessibility for populations at the highest risk for diabetes. Translational research on the National DPP in Mississippi has not been studied.

Objective: This study aims to evaluate the implementation and impact of the National DPP delivered using telehealth modalities at the University of Mississippi Medical Center in Jackson, Mississippi.

Methods: An effectiveness-implementation hybrid type III research design is proposed. The study design is guided by the Reach, Effectiveness, Adoption, Implementation, and Maintenance framework and the Practical, Robust Implementation and Sustainability Model. Participants are being recruited via provider referral, and the DPP is being delivered by trained lifestyle coaches. Study participants include adult (≥18 years) patients eligible for the DPP with at least 1 encounter at 1 of 3 ambulatory clinic specialties (lifestyle medicine, family medicine, and internal medicine) between January 2019 and December 2023. The National DPP eligibility criteria include a BMI ≥25 kg/m^2 and hemoglobin A_{1c} between 5.7% and 6.4%. The University of Mississippi Medical Center criteria include Medicare or Medicaid beneficiaries. The University of Mississippi Medical Center's a priori implementation plan was developed using the Consolidated Framework for Implementation Research and includes 23 discrete strategies. The primary aim will use an embedded mixed method process analysis to identify and mitigate challenges to implementation. The secondary aim will use a nonrandomized quasi-experimental design to assess the comparative effectiveness of the DPP on health care expenditures. A propensity score matching method will be implemented to compare case subjects to control subjects. The primary outcomes include patient referrals, participant enrollment, retention, engagement, the incidence of diabetes, and health care resource use and costs.

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Results: At baseline, of the 26,151 patients across 3 ambulatory clinic specialties, 1010 (3.9%) had prediabetes and were eligible for the National DPP. Of the 1010 patients, more than half (n=562, 55.6%) were aged 65 years or older, 79.5% (n=803) were Medicare beneficiaries, 65.9% (n=666) were female, and 70.8% (n=715) were obese.

Conclusions: This is the first translational study of the National DPP in Mississippi. The findings will inform implementation strategies impacting the uptake and sustainability of the National DPP delivered in an academic medical setting using distance learning and telehealth modalities.

Trial Registration: ClinicalTrials.gov NCT04822480; https://clinicaltrials.gov/study/NCT03622580

International Registered Report Identifier (IRRID): DERR1-10.2196/50183

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KEYWORDS

prediabetic state; prevention; preventive medicine; Centers for Disease Control and Prevention; Medicare; telemedicine; telehealth; behavioral science; implementation science; implementation; research evaluation; cost-benefit analysis; diabetes; diabetic; cost; costs; economic; prevention; design; engagement; use; distant learning

Introduction

Background

Type 2 diabetes mellitus (herein referred to as diabetes) is a costly epidemic in the United States responsible for significant morbidity and mortality. In 2019, over 37.1 million (14.7%) adults (≥18 years) were diagnosed with diabetes [1]. Diabetes is a metabolic derangement characterized by insulin insensitivity resulting from insulin resistance, reduced insulin production, and eventual pancreatic beta-cell failure, leading to hyperglycemia. Prediabetes is often a precursor to diabetes, a condition with plasma blood glucose levels higher than normal (hemoglobin A_{1c} [HbA_{1c}] 5.7%-6.4%) but not high enough to be characterized as diabetes (HbA_{1c} ≥6.5%) [2]. An estimated 96 million (38%) adults had prediabetes in 2019 [1].

In 2017, diabetes was estimated to impose a US $327 billion annual economic burden, including US $237 billion in direct medical costs [3]. A retrospective study of claims data from 2010 to 2014 among a commercially insured adult (18 to 64 years) population showed patients with newly diagnosed diabetes spent US $10,000 or more than their nondiabetic counterparts over the 5 years leading up to the diagnosis [4]. Annual medical expenditures are nearly one-third higher for those who subsequently develop diabetes relative to those who do not transition from prediabetes to diabetes, with an average difference of US $2671 per year [5]. At that cost differential, the 3-year return on investment (ROI) for diabetes prevention was estimated to be as high as 42% [5].

In 2010, the Centers for Disease Control and Prevention (CDC) introduced the National Diabetes Prevention Program (DPP) to mitigate the transition from prediabetes to diabetes [6-8]. In 2018, the Center for Medicare and Medicaid Services launched the Medicare DPP offering an unprecedented opportunity to reach the estimated 48.3% (25.9 million) of older adults with prediabetes [9]. Despite macrolevel policy support for disseminating lifestyle change programs (LCPs) such as the Medicare DPP, significant challenges hinder translation. There are gaps in program accessibility and population reach and challenges to community and organizational uptake and sustainability of LCPs [9-15]. A recent review by Ackermann and O'Brien [16] found that more than 1500 organizations had reached about 300,000 people with the DPP nationally, representing a mere 1% of the target population. In another review of Medicare DPP supplier organizations, Ritchie and Gritz [17] found 126 unique suppliers across 601 sites nationally (1 site per 100,000 beneficiaries), and the estimated reimbursement to cover program delivery was US $661 per beneficiary. The National DPP is less available to residents in rural locales [18], in counties with higher diabetes incidence, and among socioeconomically disadvantaged groups relative to their respective counterparts [19]. Furthermore, program attrition rates are the highest among racial and ethnic minority populations [14]. Efforts are needed to increase the overall detection, diagnosis, and referral of patients with prediabetes to an LCP such as the DPP, and tailored approaches for vulnerable populations are needed to ensure equity.

Hybrid implementation-effectiveness trials are particularly well suited to identify strategies to address these gaps. Blended designs study the translation of evidence-based interventions within a real-world context to foster more rapid translation over conducting these studies independently [20]. Curran et al [21] proposed 3 types of hybrid designs. Type I designs prioritize effectiveness testing and, secondarily, the gathering of contextual information for implementation. In type II designs, clinical and implementation aims are tested simultaneously, and type III designs prioritize implementation. Type III designs are specifically recommended when implementing an evidence-based practice or program such as the DPP in a new setting or population. Damschroder et al [10] used a type III design to study the implementation of LCPs to veterans through the Veterans Health Administration while comparing the effectiveness of the National DPP with the MOVE! weight management program [10]. The findings demonstrated that large health care systems have the potential to fill gaps in advancing equity in diabetes prevention through improved reach among priority populations and support for uptake in large health care systems. Critical implications included the need for buy-in among systems and local leaders, disseminating evidence-based findings to referring clinicians who may question the overall effectiveness of LCPs for diabetes prevention, and allocating sufficient time and resources for staff training. Conducting hybrid trials in regions with the highest rates of diabetes and disparities is a priority; however, in states such as Mississippi,

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where diabetes rates are persistently among the highest, no translational studies of the National DPP have been conducted.

Aims

The primary aim of this study is to evaluate the implementation of the National DPP and Medicare DPP LCPs in 1 large health care system. The RE-AIM (Reach, Effectiveness, Adoption, Implementation, and Maintenance) framework [22] will guide a mixed methods process evaluation to understand how and why the DPP LCP worked, for whom, in what settings, and at what intensities. The secondary aim is to use a nonrandomized quasi-experimental design to assess the comparative effectiveness of the DPP on reducing diabetes risk, health care cost savings, and health care use. An overview of the study research questions is provided in Table 1.

Table 1. Research questions by measures of the Reach, Effectiveness, Adoption, Implementation, and Maintenance framework.

Measure	Research question
Reach	• What percent of potentially eligible patients were excluded and participated? • How representative were the participants of the target population?
Effectiveness	• What impact did the intervention have on all participants who began the program?
Adoption	• What percent of clinical sites and providers participated in the intervention?
Implementation	• To what extent were the intervention components delivered as intended?
Maintenance	
Organizational	• To what extent was the intervention continued? • How were the implementation strategies adapted? • To what extent was the intervention modified? • Can the institution maintain delivery of the LCP[a]? • What is the cost-benefit of delivering versus not delivering the LCP to patients with prediabetes?
Participant	• What was the attrition rate? • What was the representation of participants not completing the intervention? • How did attrition impact conclusions about effectiveness?

[a]LCP: Lifestyle Change Program.

Methods

Study Design

This study uses a hybrid type III research design [21] and follows the Standards for Reporting Implementation Studies (StaRI) [23]. StaRI guidelines were developed to promote the translation of implementation studies. The 27-item checklist ensures the transparent reporting of implementation strategies and the effectiveness of the intervention that is being implemented. The proposed study will be the first to comprehensively evaluate the translation of the National DPP and Medicare DPP in Mississippi.

Ethics Approval

This study was reviewed by the institutional review board at the University of Mississippi Medical Center (2020V0327). This trial is registered with ClinicalTrials.gov (NCT04822480).

Implementation Context

Setting

Mississippi is consistently ranked among the states with the highest rates of diabetes (n=326,420, 14.4%) and prediabetes (n=814,000, 35.6%) in the United States [24]. It is also the only state where every county is included in the Diabetes Belt, a cluster of counties in the Southeastern United States where obesity and physical inactivity account for one-third of all diagnosed diabetes cases [25]. Mississippi has the highest percentage of Black (n=1,111,340, 37.8%) populations of any state in the United States and persistently has higher rates of poverty (n=570,371, 19.4%) and a lower median household income (US $49,111) compared to national statistics (n=38,661,356, 11.6% and US $69,021, respectively) [26]. The exceedingly high rates of poverty contribute to Mississippi having the highest Federal Medical Assistance Percentage in the nation (77.27%) [27]. It is the nation's fourth most rural state [20], where 65 (79.3%) of the 82 counties are considered rural areas. According to the Health Resources and Services Administration [28], every one of Mississippi's 82 counties is designated a medically underserved area [28].

Implementation Site

The University of Mississippi Medical Center (UMMC) in Jackson, Mississippi, is the state's only academic medical center. Annually, UMMC physicians conduct over 535,000 clinical visits; 195,000 outpatient and 135,000 emergency room encounters; and 31,000 hospital admissions serving pediatric and adult patients statewide. The UMMC is a minority-serving and research-intensive health care organization with a state mandate to provide no less than 50% of its services to indigent persons (Miss. Code Ann. § 37-115-27; 2017).

The UMMC is also home to 1 of only 2 telehealth centers of excellence in the country funded by the Health Resources and Services Administration (6-U66RH31459-04-01). In partnership

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with telehealth, the UMMC launched its DPP program in 2020. Implementing the National DPP LCP through health care systems, such as the UMMC, has the potential to increase program reach and accessibility for residents who are among those at the highest risk for diabetes in the most medically underserved communities; however, no studies of the translation of the DPP have been conducted in Mississippi. The proposed study will be the first to comprehensively evaluate the translation of the National DPP and Medicare DPP in Mississippi.

Implementation Strategy

The implementation plan was developed using the CFIR (Consolidated Framework for Implementation Research) [29]. The CFIR is a determinants framework for navigating the contextual factors that affect the uptake of innovations by health care institutions. The framework is comprised of 39 constructs across 5 complex interacting domains such as intervention characteristics, organizational inner setting context, outer setting context, characteristics of individuals involved with implementation, and implementation processes. The 4 interrelated processes include planning, engaging, executing and reflecting, and evaluating. The processes interact dynamically to achieve organizational (eg, UMMC health care system) and individual (eg, UMMC clinical providers) level use of an intervention as intended (eg, use of electronic health record system for screening and referral of patients at risk for diabetes). The UMMC's a priori implementation plan includes 23 [24] discrete strategies described in Table 2 [30]. One strategy is taking a phased approach to implementation. Thus, in phase 1 of implementation, 3 clinical specialties were targeted based on provider buy-in including family medicine (n=8 clinical sites), lifestyle medicine (n=1 clinical site), and internal medicine (n=5 clinical sites).

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Table 2. Discrete implementation strategies according to the Consolidated Framework for Implementation Research domains and taxonomy.

Domain	Strategy
Implementation processes	
Evaluative and iterative strategies	1. Conduct a needs assessment to support the need for diabetes prevention LCP[a] 2. Develop a formal blueprint that defines goals and strategies 3. Access various organizational aspects to determine their degree of readiness to implement, barriers that may impede implementation, and strengths that can be used in the implementation effort 4. Stage implementation scale-up by starting with demonstration projects and gradually moving to a system-wide rollout 5. Collect and summarize clinical performance data to monitor, evaluate, and modify provider behavior 6. Obtain and use patient feedback on LCP to enhance program use and uptake
Adapt and tailor to context	1. Involve, hire, and consult experts to inform management on the use of data generated by implementation efforts 2. Tailor strategies to address barriers and leverage facilitators
Inner setting	
Financial strategies	1. Secure external funding to support implementation and dissemination 2. Explore innovative models of bundled payments
Change infrastructure	1. Change and adapt the location of clinical service sites to increase access 2. Change records systems to allow better assessment of implementation or clinical outcomes 3. Develop and implement tools for quality monitoring
Individuals	
Develop relationships	1. Identify early adopters to learn from their experiences 2. Inform providers identified as opinion leaders to serve as DPP[b] Champions, influence other providers, and contribute to an organizational climate that values prevention through lifestyle change
Provider engagement	1. Meet with providers in their practice settings to teach them about the DPP with the intent of increasing referrals to the DPP 2. Plan for and conduct continuous training 3. Develop and disseminate informational materials to educate about the DPP and how they can refer their patients
Support clinicians	1. Create a new clinical team by adding an operations manager and integrating trained lifestyle coaches into the clinical team 2. Develop reminder systems designed to help clinicians recall information and prompt them to use the clinical innovation
Outer setting	
Patient engagement	1. Develop strategies with patients to encourage adherence and problem-solving barriers 2. Prepare patients to be active participants in preventing diabetes
Develop multilevel and interdisciplinary partnerships	1. Identify and strengthen external partnerships and collaborations centered on diabetes prevention

[a]LCP: Lifestyle Change Program.

[b]DPP: Diabetes Prevention Program.

Intervention Characteristics

National DPP

The National DPP is a 12-month LCP delivered in a group setting by a trained lifestyle coach. The core 16 sessions are delivered weekly in the first 6 months of the program. In the maintenance phase, a minimum of 6 sessions are delivered monthly. The evidence-based program aims to develop behavior change skills leading to increased physical activity (150 minutes per week) and modest weight loss (7% reduction in total body weight), which are proven to prevent or delay diabetes in adults [7]. The DPP LCP is a clinical service of lifestyle medicine in the Department of Preventive Medicine in both the School of Medicine and John D. Bower School of Population Health at the UMMC. The LCP achieved full recognition from the CDC within the first year and, in 2020, became the third Medicare-approved DPP provider in Mississippi.

Interventionists

Lifestyle coaches are UMMC employees and include registered dietitians, project coordinators in population health, and community health workers. All interventionists completed a CDC-recognized lifestyle coach training, have a registered

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National Provider Identifier, and completed continuing education units. Newly trained lifestyle coaches shadow an experienced coach prior to leading an independent cohort of patients.

Delivery

Group-based sessions are delivered using BigBlueButton, an open-source web-based classroom software [31]. This educational platform provides a unique link to connect participants using videoconferencing. Participants click a homeroom link, type their names, and enter the room. Weekly weight is tracked using digital body weight scales (developed by BodyTrace, Inc) equipped with cellular connectivity. Weekly physical activity minutes are reported to the lifestyle coach via phone call or email before or immediately following each session. Participant attendance, weight, physical activity, and billing (Medicare-eligible participants only) are tracked in patients' electronic medical records in Epic (Epic Systems Corporation).

Eligibility Criteria

UMMC adult patients (≥18 years) who are overweight (BMI≥25 to 29.9 kg/m^2) or obese (BMI≥30 kg/m^2), have an HbA_{1c} between 5.7% and 6.4%, and are Medicare or Medicaid beneficiaries are recruited for the LCP by physician electronic referral. Using the Healthy Planet coordinated care management tool in Epic [32], physicians are prompted at the patient encounter by Best Practice Alert to diagnose, inform, and refer patients with prediabetes to the LCP. Epic is a patient-centered, cloud-based electronic health record software program comprised of multiple systems to facilitate patient care. Patients with 1 or more of the following are excluded: <18 years; pregnant or planning to become pregnant within the next 12 months; a primary or secondary diagnosis of diabetes, including all International Classification of Diseases, Tenth Revision (ICD-10) codes with a prefix of E11; or end-stage renal disease (ICD-10 code N18.6). Patients with a diabetes diagnosis and an HbA_{1c} value above 6.4% will be excluded.

Given that the LCP is delivered in a telehealth setting, it is preferred that patients have their own computer, tablet, or smartphone equipped with a camera and connected to a reliable Wi-Fi network. However, in a largely rural and underresourced state, this is not a realistic expectation. Thus, participants are eligible to participate if they own or have access to a computer, tablet, or smartphone connected to a reliable Wi-Fi network, have a mobile or landline phone to call into group sessions, or agree to use a study-provided tablet equipped with Wi-Fi and cellular connectivity. Study-provided tablets have restricted use and are provided to participants for the duration of the LCP and must be returned to the study team at the end of the program.

Recruitment, Retention, and Engagement

Electronic referrals to the LCP were extracted from Epic monthly between 2019 and 2021. In 2022, a dedicated LCP staff person was hired, and referrals have since been extracted from Epic twice weekly. Prior to making contact, the coordinator confirms the patient's eligibility. Medical records of ineligible patients are updated, and they are referred to the Lifestyle Medicine clinic rather than being contacted. Among those eligible, up to 3 attempts are made to contact each patient including phone calls, voicemails, and emails. The date, time, type and outcome of contact, and the staff person's name are documented. At a failed third attempt to make contact, the contact attempt details are recorded in the patient's medical record and the referral is closed. Patients declining participation are also noted in their respective medical records and the referral is closed. Interested patients are added to a cohort and provided with information to attend session 0, an informational session.

Following session 0, interested participants are enrolled in the LCP and begin session 1 the following week. Scheduling cohorts consider patient preference and lifestyle coach availability. All session dates over the 12-month intervention period are determined prior to session 0, and participants receive the 12-month schedule at the start of the program. Makeup sessions are provided as needed but participants are encouraged to attend regularly scheduled group sessions. There is no limit to the number of participant makeup sessions. Up to 2 reminder contacts are made with each participant prior to each session. All participants with an email address are contacted via email, followed by a reminder phone call at which point participants are asked to report their weekly weight and physical activity minutes. For participants who do not have an email address, up to 2 phone call contacts are made. These procedures are consistent across participants and cohorts. In addition, when a participant misses 2 consecutive sessions, the project coordinator attempts to make contact to offer support in overcoming barriers and re-engaging them in the program. After 4 consecutive missed sessions and failed attempts to make contact, the participant is excluded from the program.

Implementation Outcomes

Overview

Implementation outcomes are mapped across the 5 domains of the RE-AIM framework (Table 2). The evaluation seeks to determine the intervention reach among patients at risk for diabetes, clinic and provider adoption, implementation fidelity, intervention effectiveness in preventing diabetes, and the organizational and patient uptake of the intervention. Implementation outcomes, research questions, measures, and methods are outlined in Table 3. Data sources will include electronic medical records, session notes provided by lifestyle coaches, intervention cohort and delivery details, meeting notes, and evaluation of DPP sessions conducted by an external reviewer.

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Table 3. Implementation outcomes following the Reach, Effectiveness, Adoption, Implementation, and Maintenance framework.

Outcomes and measure	Methods
Reach	
Eligibility	• Number and proportion of patients eligible among the total number of patients in an ambulatory setting
Enrollment	• Number and proportion of patients enrolled among the total number of referred patients • Descriptive characteristics of patients enrolled
Exclusion	• Number and proportion of patients excluded among the total number of patients referred • Descriptive characteristics of patients excluded • Reasons why patients are excluded
Conversion rate	• Number and proportion of patients referred, eligible, and enrolled among those referred and eligible
Effectiveness	
Incidence of diabetes	• The ratio of the number of diabetes cases to the total time at risk among the LCP[a] participants compared with control-matched nonparticipants
Adoption	
Clinical sites	• Number and proportion of clinical sites making referrals among sites eligible to make referrals
Providers	• Number and proportion of providers making referrals among providers eligible to make referrals • The mean number of referrals made among the top 3 providers making referrals
Implementation	
Fidelity	• Organizational recognition status awarded by the CDC[b] • Barriers, solutions, and facilitators to program delivery • Observation of randomly selected DPP[c] sessions
Intervention costs	• Microcosting: time, training, and program materials
Maintenance	
Organizational	• Number of new clinical sites making referrals • Number of new providers making referrals
Participant engagement	• Number and proportion of sessions attended
Participant retention	• Duration of participation in days from first to last session within the 12-month program • Number of patients completing the 12-month LCP compared to the number of patients enrolled

[a]LCP: Lifestyle Change Program.

[b]CDC: Centers for Disease Control and Prevention.

[c]DPP: Diabetes Prevention Program.

Reach

The extent to which the target population is exposed to the intervention or population reach will be determined by the number of eligible patients referred to and enrolled in the LCP, yielding the appropriate referral to enrollment conversion rate. The a priori conversion rate goal is 50%. Reasons for exclusion and participant refusal to participate will be documented where possible. Descriptive characteristics such as age, sex, race, ethnicity, and BMI be explored and compared between patients eligible for the program who were referred and not referred.

Effectiveness

The LCP effectiveness will be determined by the differential incidence of diabetes. Diabetes will be defined by diagnosis code or HbA_{1c} values greater than 6.4%. Data will be extracted from patient medical records and reviewed biannually. The a priori reduction in diabetes diagnosis among the intervention compared with the control group is 50%.

Adoption

The adoption of the LCP will be defined as the number and proportion of clinical sites with referring providers making referrals to the LCP, and the number and proportion of eligible providers making referrals. Data will be extracted from medical records and reviewed quarterly. The a priori adoption clinical and provider addition rates are 70%.

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Implementation

Implementation fidelity and costs will be evaluated. Fidelity will be based on the UMMC's recognition category by the CDC. The CDC standards consider participant recruitment, retention, attendance, the proportion of participants meeting the LCP 7% weight loss goal, the proportion of participants achieving 150 minutes or more of physical activity per week, and reductions in HbA_{1c}. Barriers, solutions, and facilitators will be documented by the project coordinator and lifestyle coaches in a weekly session log, during quarterly lifestyle coach meetings, and in strategic planning meetings with UMMC leadership and the American Medical Association Improving Health Outcomes team.

Maintenance

Ongoing organizational and participant engagement in the LCP will provide a robust measure of program maintenance. Longitudinal changes in the number of clinical sites and providers making referrals will be extracted from Epic quarterly, including data to monitor referral maintenance across sites and providers. Attendance and retention in the LCP will provide a measure of maintenance among participants. The a priori participant retention rate is 60%.

Economic Outcomes

The secondary aim of this study is to use a nonrandomized quasi-experimental design to assess the comparative effectiveness of the LCP on cost savings. The primary outcome will be health care expenditures (Table 4). For economic measures, trends in per capita medical expenditures will be tracked among a panel of case (LCP participant) and control (non-LCP participant) subjects. To compare variations in spending, the differences in the arithmetic mean, compound annual growth rates, and propensity score matching models will be implemented to compare case and control subjects. The investigators may also record data from those with prediabetes who are later diagnosed with diabetes and individuals with prediabetes who are not later diagnosed with the condition. These estimates of spending differentials and evidence of DPP participation and engagement rates will further enhance the estimates of potential cost savings and ROI if diabetes is prevented or delayed in the at-risk population who participate in the LCP.

Table 4. Economic outcomes.

Outcomes and measure	Method
Health care use	
Medical encounters	• Number and type of medical encounters extracted from electronic medical records • Types of CPT[a] codes at each medical encounter extracted from electronic medical records
Medical cost	
Medical expenditures	• Dollar amount billed per encounter
Condition or problem	• ICD-10[b] code or CPT codes per encounter

[a]CPT: Current Procedural Terminology.

[b]ICD-10: International Classification of Diseases, Tenth Revision.

Allocation

Overview

Study participants are identified in Epic using the eligibility criteria. Patients are placed in the intervention or comparison group based on natural selection. Each participant is assigned a study identification number that is matched to their medical record number. There is no interaction between study personnel and participants.

Intervention Group

The intervention group includes eligible patients referred to and enrolled in the LCP. Once a participant is enrolled in the study, they are assigned a study identification number.

Comparison Group

The comparison group includes patients meeting the inclusion criteria who are not enrolled in the LCP. Once a patient is enrolled in the DPP, they are no longer included in the control group. These participants include patients with and without a referral. Patients referred to the LCP, deemed ineligible based on insurance type, and referred to lifestyle medicine are excluded from the comparison group. Participants in the comparison group are matched to their intervention counterparts for final effectiveness and cost-benefit analyses. Participants enrolled in the comparison group are assigned a study identification number.

Study Period

The baseline period is January 2019 to December 2019. The study period is from September 2020 (the start of the first DPP patient cohort) through December 2023.

Statistical Analyses

Implementation Analysis

An embedded mixed method process analysis is being conducted to identify and mitigate challenges to implementation. Quantitative data are extracted from Epic and reviewed quarterly to inform reach and adoption. Quarterly data are used to adapt questions to further understand the quantitative data using qualitative methods. Qualitative data are subsequently analyzed using a narrative realist analytic approach. Meeting minutes,

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observation notes, and lifestyle coach feedback are compiled and analyzed in Word (Microsoft Corp) documents twice annually. Solutions to challenges are framed in the context of what is acceptable and appropriate to patients and providers and what is feasible within the context of the health care system (inner setting) and outer setting conditions, policies, and funding [33]. Findings are used in the ongoing planning process to continuously adapt, implement, and evaluate. Similar complex mixed methods designs have been used for evaluating the implementation of lifestyle interventions within new populations and settings [34-38].

Economic Analysis

Arithmetic means will be calculated overall and for specific sectors of health care between the 2 groups. Compound annual growth rates in per capita expenditures will be calculated to track the geometric progression ratio and estimate the rate of growth in spending time. A propensity score matching method will be implemented to compare case subjects to control subjects. The model takes the form of $P(X)=Pr(D=1|X)$, where $D=1$ indicates DPP participation and matches on the probability of participation instead of attempting to create a match for each participant with the same value of X. This model aims to account for unobservables and obtain an unbiased and accurate measure of costs. Matched control subjects who do not participate in a DPP must be similar to the case subjects who did participate such that the only difference is attributed to the disease. The matching model in this analysis will control for the following: patient age; sex; race; ethnicity; zip code; and prevalence of other conditions such as but not limited to hypertension, chronic obstructive pulmonary disease, congestive heart failure, cancer, and metformin use in all years of the data. Differences in spending will be compared between individuals with prediabetes who participate in a DPP and those individuals who do not compute net savings and ROI (if any) of program participation. A similar methodology may be applied to compare individuals who progress to diabetes relative to those who do not progress for more in-depth cost savings and ROI analysis. Given this is the first time the DPP will be implemented at the UMMC, the sample size will be determined based on the convenience sample or the number of participants enrolled based on the proposed recruitment and retention strategies.

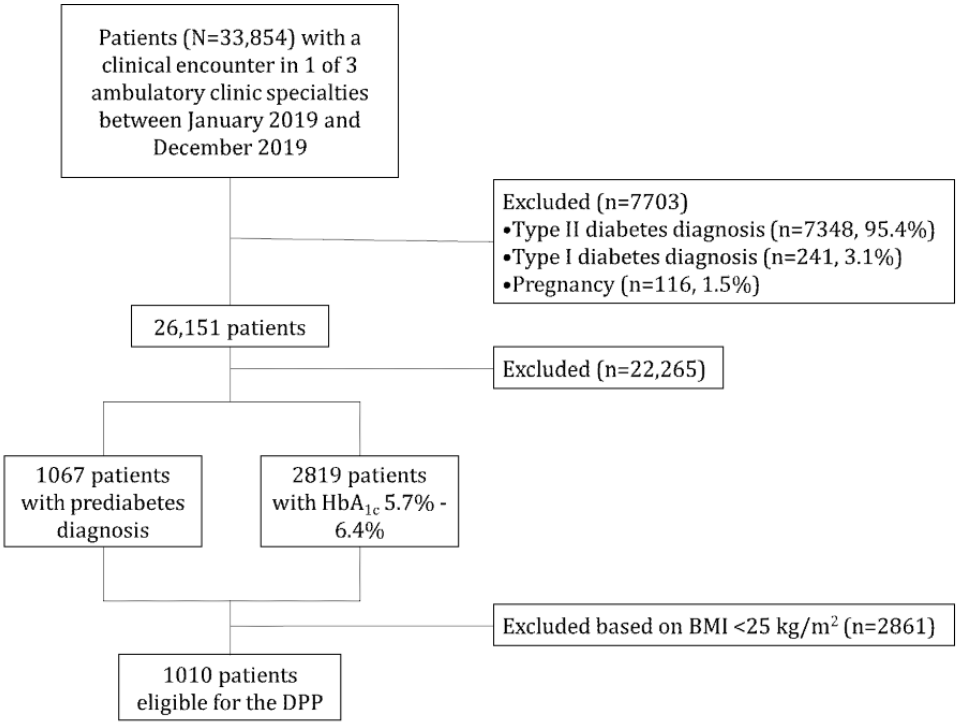
Data Security and Quality Assurance

Data will be exported from Epic and stored in password-protected computerized files. All data are deidentified at extraction. Data files are stored on the UMMC secure server and shared with the American Medical Association via a secure file transfer process and password protection.

Results

The baseline recruitment is depicted in a flow diagram in Figure 1. In 2019, a total of 33,854 adult patients had at least 1 clinic encounter at 1 of 3 UMMC specialty sites (lifestyle medicine, family medicine, or internal medicine). More than half (n=19,631, 58%) were non-Hispanic Black and 64.2% (n=21,744) were female. The mean HbA_{1c} was 6.4% (SD 1.69%), 49.7% (n=16,812) were obese, and 25.7% (n=8698) had a BMI between 25 and 30 kg/m^2. About 1 in 5 patients had diabetes (n=7348, 21.7%) and 467 (1.4%) had end-stage renal disease.

Figure 1. Baseline recruitment. DPP: Diabetes Prevention Program; HbA_{1c}: hemoglobin A_{1c}.



Of the 33,854 patients, 7703 (22.7%) patients were excluded based on diabetes diagnosis (7348/7703, 95.4%), type I diabetes mellitus diagnosis (241/7703, 3.1%), or pregnancy (116/7703, 1.5%).

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Among the remaining 26,151 patients, 1067 (4.1%) patients had a prediabetes diagnosis (n=1067, 4.1%), and 2819 (10.8%) had an HbA_{1c} between 5.7% and 6.4%. After applying the BMI eligibility criterion, 1010 (3.9%) patients were eligible for the National DPP. Baseline characteristics for those patients are described in Table 5. Future outcomes will be published in peer-reviewed implementation science journals and presented at national, regional, and state professional meetings and conferences.

Table 5. Baseline characteristics of patients eligible for the National Diabetes Prevention Program.

Characteristics	Values (n=1010)
Age group (years), n (%)	
18-24	16 (1.6)
25-44	104 (10.3)
45-64	328 (32.5)
≥65	562 (55.6)
Sex, n (%)	
Female	666 (65.9)
Male	344 (34.1)
Race, n (%)	
Non-Hispanic Black	677 (67)
Non-Hispanic White	302 (29.9)
Other	31 (3.1)
Hemoglobin A_{1c}, mean (SD)	5.93 (0.31)
Weight status, n (%)	
Overweight	295 (29.2)
Obese	715 (70.8)
Insurance type, n (%)	
Medicare	803 (79.5)
Medicaid	207 (20.5)

Discussion

This is the first implementation study of the National DPP LCP in Mississippi. Iterative findings and adaptations will elucidate strategies to successfully improve access to the National DPP, improve awareness of prediabetes and LCPs, and meet physician and patient needs for diabetes prevention.

The hybrid study design is a strength of the proposed study. Limitations to the sample size as recruitment strategies are tested and refined may be a limitation of this study; however, outcomes from this study will be used to calculate a robust sample size for testing in phase 2 of implementation, which will include additional clinical sites and providers.

The implementation strategies from this study can be scaled and findings replicated to measure the impact of diabetes prevention efforts within other health care systems. In addition, given the relatively recent introduction of the Medicaid DPP and reimbursement models for Medicaid agencies, a longitudinal study, such as this, may be relevant to other large health systems seeking to quantify the impact of their diabetes prevention efforts in Medicare and Medicaid populations.

Acknowledgments

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AmeriGroup Mississippi of Anthem, Inc; the Department of Health Resources and Administration; the National Institutes of Health; and the University of Mississippi Medical Center.

Data Availability

The data sets generated during this study are not publicly available due to their containing information that could compromise the privacy of research participants but are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

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Abbreviations

CDC: Centers for Disease Control and Prevention
CFIR: Consolidated Framework for Implementation Research
DPP: Diabetes Prevention Program

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HbA1c: hemoglobin A1c
ICD-10: International Classification of Diseases, Tenth Revision
LCP: Lifestyle Change Program
PRISM: Practical, Robust Implementation and Sustainability Model
RE-AIM: Reach, Effectiveness, Adoption, Implementation, and Maintenance
ROI: return on investment
StaRI: Standards for Reporting Implementation Studies
UMMC: University of Mississippi Medical Center

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Protocol

Predicting Obsessive-Compulsive Disorder Events in Children and Adolescents in the Wild Using a Wearable Biosensor (Wrist Angel): Protocol for the Analysis Plan of a Nonrandomized Pilot Study

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Abstract

Background: Physiological signals such as heart rate and electrodermal activity can provide insight into an individual's mental state, which are invaluable information for mental health care. Using recordings of physiological signals from wearable devices in the wild can facilitate objective monitoring of symptom severity and evaluation of treatment progress.

Objective: We designed a study to evaluate the feasibility of predicting obsessive-compulsive disorder (OCD) events from physiological signals recorded using wrist-worn devices in the wild. Here, we present an analysis plan for the study to document our a priori hypotheses and increase the robustness of the findings of our planned study.

Methods: In total, 18 children and adolescents aged between 8 and 16 years were included in this study. Nine outpatients with an OCD diagnosis were recruited from a child and adolescent mental health center. Nine youths without a psychiatric diagnosis were recruited from the catchment area. Patients completed a clinical interview to assess OCD severity, types of OCD, and number of OCD symptoms in the clinic. Participants wore a biosensor on their wrist for up to 8 weeks in their everyday lives. Patients were asked to press an event tag button on the biosensor when they were stressed by OCD symptoms. Participants without a psychiatric diagnosis were asked to press this button whenever they felt really scared. Before and after the 8-week observation period, participants wore the biosensor under controlled conditions of rest and stress in the clinic. Features are extracted from 4 different physiological signals within sliding windows to predict the distress event logged by participants during data collection. We will test the prediction models within participants across time and multiple participants. Model selection and estimation using 2-layer cross-validation are outlined for both scenarios.

Results: Participants were included between December 2021 and December 2022. Participants included 10 female and 8 male participants with an even sex distribution between groups. Patients were aged between 10 and 16 years, and adolescents without a psychiatric diagnosis were between the ages of 8 and 16 years. Most patients had moderate to moderate to severe OCD, except for 1 patient with mild OCD.

Conclusions: The strength of the planned study is the investigation of predictions of OCD events in the wild. Major challenges of the study are the inherent noise of in-the-wild data and the lack of contextual knowledge associated with the recorded signals. This preregistered analysis plan discusses in detail how we plan to address these challenges and may help reduce interpretation

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bias of the upcoming results. If the obtained results from this study are promising, we will be closer to automated detection of OCD events outside of clinical experiments. This is an important tool for the assessment and treatment of OCD in youth.

Trial Registration: ClinicalTrials.gov NCT05064527; https://clinicaltrials.gov/study/NCT05064527

International Registered Report Identifier (IRRID): DERR1-10.2196/48571

(JMIR Res Protoc 2023;12:e48571) doi:10.2196/48571

KEYWORDS

machine learning; obsessive-compulsive disorder; children; teens; adolescents; OCD; AI; artificial intelligence; mental health; Empatica E4; prediction; physiological signal; mental health care; wearable; monitoring; obsessive compulsive disorder

Introduction

Increased heart rate and electrodermal activity (EDA) are associated with mental phenomena such as fear, anxiety, anger, contamination disgust, embarrassment but also happiness [1]. Decreased heart rate and increased EDA are associated with sadness and mutilation-related disgust [1]. These negative emotions are seen in obsessive-compulsive disorder (OCD). Several types of OCD symptoms are linked with specific emotional profiles (eg, fear of contamination and contamination disgust, fear of harming or violating others, and guilt and shame), which could be detected using affective computing. Thierfelder et al [2] showed that an increase in heart rate and a decrease in heart rate variability (HRV) are indicative of an increase in stress during OCD events. Heart rate and HRV show distinctive patterns of anxiety when patients are exposed to fearful situations and relief when performing compulsive behavior. These patterns were found to be highly different between individuals but useful for distinguishing between cognitive stress, exposure and response prevention (ERP) episodes, and physical activity.

OCD is a burdensome psychiatric disorder that affects up to 3% of youths (individuals younger than 18 years) [3-5]. Obsessions are repetitive and intrusive thoughts that cause negative emotions such as anxiety, disgust, embarrassment, shame, guilt, and feelings of incompleteness, that is, marked distress [6]. Compulsions are repetitive or ritualized behaviors or actions the patient feels compelled to perform, despite their sometimes nonsensical nature [7]. Distress can arise from performing compulsions and when prevented from performing compulsions.

First-line treatment for OCD is cognitive behavioral therapy with ERP [8,9]. In the context of OCD treatment, ERP refers to approaching OCD symptom–triggering stimuli (exposure) and refraining from performing rituals and compulsions (response prevention). During ERP, patients are asked to intermittently report their level of distress [10]. This information helps the therapist adjust the interventions. Awareness of distress trajectories within and across ERP sessions is also a tool used to increase therapeutic learning [11,12]. Therefore, monitoring distress levels during exposure is important for optimizing ERP and measuring the severity of symptoms in OCD. Similarly, when collected over time, distress can provide information about the progression and improvement of the condition [13].

Many symptoms of OCD are directly related to specific objects or situations that cannot be realistically reproduced in clinical settings. Automatic, continuous detection of these OCD signals would facilitate close monitoring of patient treatment progress and allow for more targeted interventions and evaluation of treatment in the real world [14,15]. Ideally, distress would be objectively and affordably assessed in a noninvasive manner.

Recently, machine learning methods applied to data collected using smartwatches have demonstrated success in classifying stress levels [16,17], recognizing emotions [18,19], detecting panic attacks [20], and detecting hand washing—a common compulsion in individuals with OCD [15]. Thierfelder et al [2] demonstrated that recordings of heart rate and HRV using wearable devices may also be used to identify distress in patients with OCD caused by exposure during ERP sessions. Additionally, relief through compulsive behavior is reflected in the recorded heart rate and HRV, but the results also suggest that a change in the environment or simple distractions may reduce anxiety.

This paper aims to assess the possibility of using machine learning models for the detection of OCD events in the wild based on signals from wrist-worn devices. Automatic detection of OCD events will allow targeted interventions in the real world to improve OCD treatment. To the best of our knowledge, this is the first study of this kind. We aim to investigate the relationship between personalized and generalized predictive models by comparing the predictive performance of models trained on each participant individually and models trained on a sample of participants. In this paper, we also weigh our methodological decisions. Our research questions may be summarized as follows: (1) Is it feasible to collect enough data (physiological signals and tags) from individual participants to evaluate the feasibility of developing models? (2) To what extent do participants adhere to wearing the biosensor? (3) Is the number of event tags associated with OCD severity? (4) Do features extracted from physiological signals during OCD episodes in the wild resemble features during controlled ERP sessions in the clinic? (5) Can OCD episodes in the wild be predicted using physiological signals from a wearable biosensor? and (6) To what extent do predictive models generalize to newly recorded data from the same subjects or new subjects?

Methods

Overview

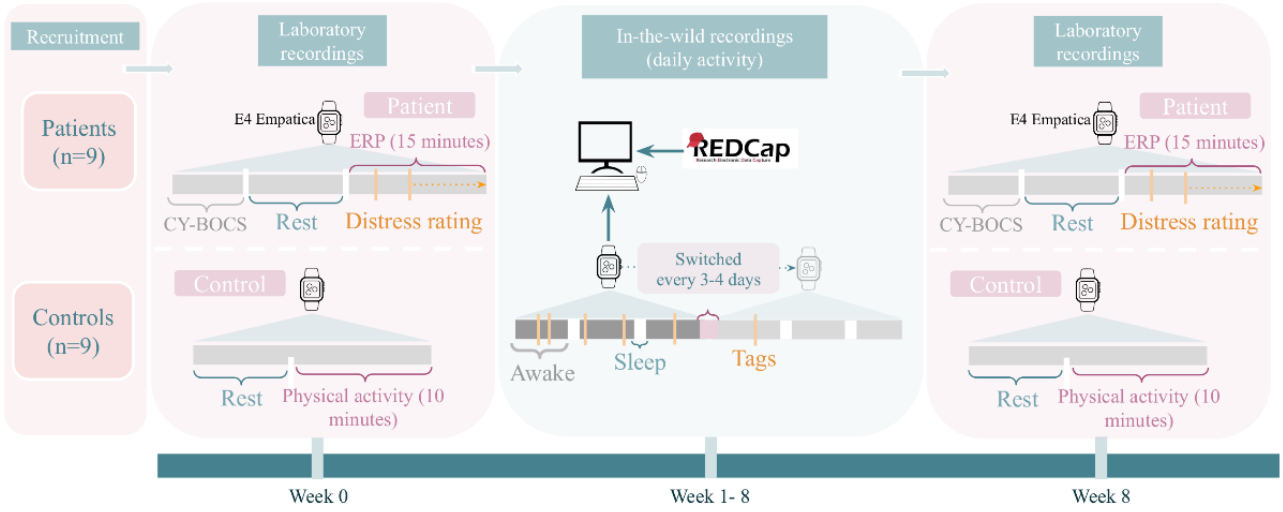
A complete description of the study design, recruitment, and data collection procedures are reported in the Wrist Angel study protocol, which was submitted for publication prior to the collection of data from the last participant [21].

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Participants

A total of 18 youths aged 8 to 16 years and their parents were included in this study, and data were collected for 8 weeks. Nine participants had an OCD diagnosis (patients) and 9 youths presented without a psychiatric diagnosis (controls). Other studies have predicted aggressive behavior from wearables worn by 20 youths in 87 hours (10 consecutive days) or behavioral synchrony between father and their child with Down syndrome from wearables worn by 12 families in a 7-minute free play [22,23]. Although the number of participants is low, we followed each participant for 8 weeks, and we argue it will be enough for a feasibility study of prediction possibilities (as a minimum within individuals). Additionally, we are targeting a high emotional response, facilitating a stronger correlation between biosignals and emotional response. We present a brief description of the data acquisition illustrated in Figure 1 using the E4 wristband (Empatica) [24].

Figure 1. Design of the study and data collection procedure. Before and after an 8-week data collection period, all participants take part in a clinical recording session in the lab. Participants with an OCD diagnosis complete a clinical interview that assesses OCD severity and an ERP session. Participants with no psychiatric diagnosis engage in physical activity. During the in-the-wild recordings, participants wear the Empatica E4 biosensor daily during waking hours for 8 weeks and are asked to tag events of distress related to their OCD symptoms for patients, whereas nonclincal participants tag events of intense fear. Researchers meet with participants approximately every 3 days to switch wristbands. The collected biosignal data is then transferred to the hospital server. CY-BOCS: Children's Yale-Brown Obsessive Compulsive Scale; ERP: exposure and response prevention; OCD: obsessive-compulsive disorder; REDCap: Research Electronic Data Capture.



Ethical Considerations

This study was approved by the ethics committee of the Capital Region of Denmark on June 17, 2021 (H-18010607-79689). Participants received written and verbal information about the study and the plan for disseminating results before they or their legal guardians signed the consent forms. We were not aware of any major risks or benefits for participants associated with participation. Adverse reactions to the biosensor throughout the study were monitored.

Laboratory Recordings

Before (week 0) and after (week 8) data acquisition, each participant partook in laboratory experiments to obtain recordings of physiological signals in a controlled environment. Physiological signals were collected using the Empatica E4 wristband under rest and stressful conditions. During the rest period, participants were asked to sit still and quietly, without talking or touching each other, and to relax to the best of their ability. To simulate stressful conditions, control participants engaged in physical activity for approximately 10 minutes, while patients completed an ERP exercise. During the ERP task, patients approach OCD symptom–provoking stimuli and refrain from compulsions for up to 15 minutes led by a mental health professional in the presence of their participating parent. Patients provided subjective units of distress, that is, they rated their level of distress on a scale from 0 (no distress) to 10 (extreme distress), every few minutes.

In-the-Wild Recordings

The youth and 1 of their parents were asked to wear the Empatica E4 biosensor daily during waking hours for 8 weeks. Patients were asked to press the event tag button when they felt stressed by their OCD symptoms. Parents of patients were asked to tag every time they noticed their child was distressed by their OCD symptoms. Control youth were asked to push the button when they felt very scared, and control parents were asked to push the button when they noticed that their child felt very scared. Researchers met with participants up to twice a week during the 8 weeks to exchange biosensors full of data with empty fully charged biosensors.

Measures

Physiological Signals

The E4 wristband contains a photoplethysmographic (PPG) sensor, an EDA sensor, a 3-axis accelerometer, an optical thermometer, and an event tag button that records a point in time when pressed. PPG uses infrared light to measure changes in blood volume, that is, blood volume pulse (BVP). BVP is sampled 64 times per second and can be used to calculate the timings of the interbeat interval (IBI) and the heart rate [25]. Under conditions of slight movement (<30% of the time), it is

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possible to use the IBI to compute HRV. However, this constraint is often too rigid and results in the removal of entire signals, making this approach impractical for robust data acquisition in the wild. The EDA sensor measures the skin conductance sampled 4 times per second. The accelerometer measures movement on 3 axes at a sampling rate of 32 times per second. The optical thermometer measures skin temperature at a sampling rate of 4 times per second.

Clinical Measures

Participants were assessed with the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) [26] before the start of the observation period. The CY-BOCS is the gold standard measure of OCD symptom severity [26]. Ten items (five items each for obsessions and compulsions) are summed to a total severity score [26]: (1) How much time is spent on obsessions and compulsions? (2) To what extent do obsessions and compulsions interfere with normal functioning? (3) How much distress do obsessions and compulsions (or not performing compulsions) cause? (4) To which extent are you able to resist obsessions and compulsions? and (5) To which extent do you have control over obsessions and compulsions? Five obsession or compulsion items can be summed to obtain obsession or compulsion severity scores, respectively. The CY-BOCS severity score has demonstrated high internal consistency and convergent and discriminant validity [10].

The CY-BOCS also includes a checklist for common symptoms, which are presented in 15 categories. These include seven obsession categories: (1) contamination, (2) aggressive, (3) sexual, (4) superstitious, (5) religious or moral, (6) hoarding, and (7) miscellaneous, and the eight categories for compulsions include (1) cleaning or washing, (2) checking, (3) repeating, (4) counting, (5) hoarding, (6) superstitious behaviors, (7) involving others in rituals, and (8) miscellaneous. Meta-analysis supports the existence of a 4-factor structure of OCD symptoms representing the following factors: symmetry, forbidden thoughts, cleaning, and hoarding [27]. Symmetry includes thoughts about symmetry and counting, ordering, and repeating compulsions. Forbidden thoughts include thoughts of an aggressive, sexual, and religious nature. The cleaning category covers contamination, somatic obsessions, and cleaning behaviors. Finally, the hoarding factor includes obsessions about losing or saving things and saving compulsions. We will accumulate the number of endorsed items belonging to each category to produce a category score as previously done in factor structure studies [28].

Analysis Plan

Overview

This work will focus on the in-the-wild recordings obtained from the youth participants only. We will treat marked OCD events as binary targets and design predictive models of these targets. We will limit the data to physiological signals and marked events from youth and only consider data recorded in-the-wild during the 8 weeks.

Assessing the Feasibility of In-The-Wild OCD Event Prediction

Continuous data acquisition as described previously presents several practical issues and barriers whose effects must be evaluated for wide-scale use. Even though the Empatica E4 wristband is generally considered a nonintrusive device, some patients might consider it a conspicuous piece of hardware and fear strangers might judge them on a potentially sensitive problem. Additionally, participants might need to adjust to wearing the bracelet and learn to tag events at the appropriate time, not forget to tag events, or even wear the wristband over time.

We qualitatively evaluate the potential issues and barriers based on feedback and comments from participants and their parents during data collection approximately every 3 days. We associate the number of days the wristband has been worn; the number of recorded hours and tagged events per day as a function of time to the CY-BOCS severity and type, number; and the severity of OCD symptoms from the preobservation period clinical interviews.

Preprocessing of Signals and Feature Extraction

We examine the length and end time of each recording session to verify that participants only wear the Empatica E4 wristband during waking hours. In the case where participants wear the wristband during sleep, we intend to manually exclude these recordings.

We extract features from the heart rate, skin temperature, EDA, and BVP signals recorded by the Empatica E4 wristband. The preprocessing of the signals is outlined as follows:

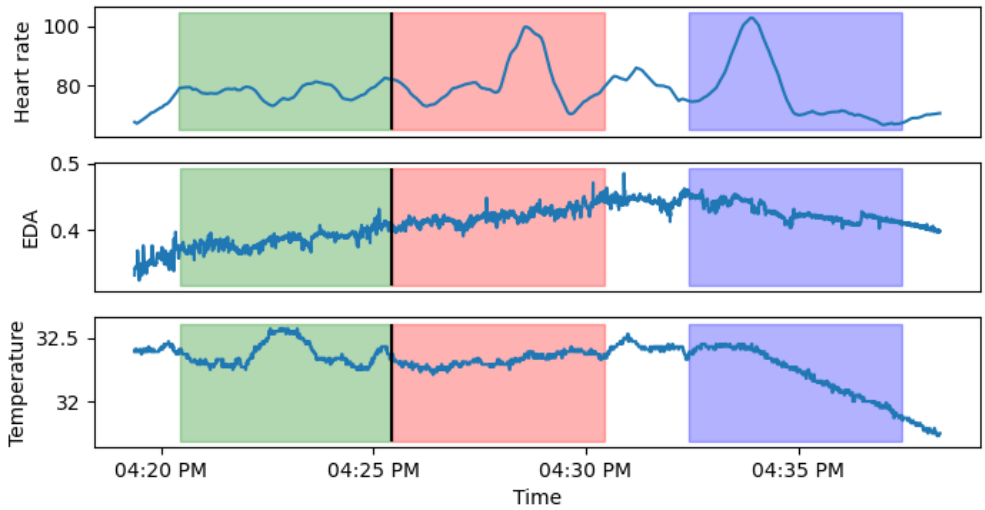
1. The skin temperature is processed using a sixth-order Butterworth low-pass filter with a cutoff frequency of 1 Hz.
2. The heart rate is extracted using the PPG sensor in the Empatica E4 wristband using a proprietary Empatica algorithm. The recordings of the heart rate are used as is and require no further preprocessing.
3. As discussed previously, the E4 wristband only provides the IBI signal in periods of low movement. Therefore, this signal is highly discontinuous and may not be useful for extracting the HRV during short time windows. Instead, the recorded BVP signal is segmented using a rolling window of 5 seconds with a time step of 1 second [29]. For each segment, we determine the noise level based on the skew and kurtosis [30]. If the kurtosis is less than εk=–0.5 and the magnitude of the skew is less than s=1, the segment is deemed a low-noise segment and included in the segmenting process. Features are extracted from each selected segment and then averaged to obtain the final features.
4. Features extracted from the EDA signal have previously been found to be good predictors of stress [31,32]. However, the EDA signal is also affected by physical activity and environmental factors, leading to expected participant and temporal variations unrelated to the stress level. The EDA signal is first processed using a sixth-order Butterworth low-pass filter with a cutoff frequency of 1 Hz. The signal

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is then normalized to the interval [0,1] to reduce the effects of subject and temporal variations. The normalized signal was decomposed into its tonic and phasic parts using the *NeuroKit2* library [33] for Python (Python Software Foundation). The tonic part is a slowly varying baseline conductivity, and the phasic part is a series of event-related high-frequency peaks. The unnormalized EDA signal is retained for feature extraction as the normalization may inadvertently remove explanatory features related to the level of the signal.

For feature extraction, we apply a window strategy around each tagged OCD event, as shown in Figure 2. We use the 5-minute period before each tag as positive observations. The 5 minutes after each tag is removed is a buffer period to avoid event contamination in nonevent windows. Nonevent windows of equal temporal length are sampled randomly from the remaining time periods as negative observations. By increasing the number of randomly sampled negative observations, we investigate the performance differences between models trained on class-balanced data sets and models trained using more but imbalanced data.

Figure 2. Illustration of the windowing strategy around each tagged OCD event (black). Positive cases are sampled from the period leading up to the tagged event (green) and a buffer period of 5 minutes is applied after the event from which no observations can be sampled (red). Negative cases are sampled randomly from the remaining time periods (blue). EDA: electrodermal activity.



Within each extracted window, we compute the features tabulated in Table 1.

1. We compute the following time domain features of each used signal: mean (SD), minimum, maximum, and gradient of a least square regression. For the BVP signal, we also compute the minimum, maximum, and average of the slope fitted in each segment. For the heart rate and EDA signal where the level is expected to carry some explanative power, we also compute the quartiles and IQR.
2. From the BVP signal, we detect systolic peaks using the *NeuroKit2* library [33] within each low-noise segment. These peaks are used to calculate the interbeat interval and the successive differences of this interval. We then compute the final features as the average of the IBIs and the root mean square of the successive differences calculated in all low-noise segments.
3. For the phasic component of the EDA signal, we compute the number of peaks as well as the average peak amplitude and response time.
4. For the EDA signal, we compute the power of the frequency bands: ultralow frequency (0.01-0.04 Hz), low frequency (0.04-0.15 Hz), high frequency (0.15-0.4 Hz), and ultrahigh frequency (0.4-1.0 Hz). These frequency bands are computed for the unnormalized EDA signal and the phasic component.
5. For the BVP signal, we compute the mean (SD), median, IQR, minimum, maximum, and sum of the frequency content. These values are further separated into real and imaginary parts.

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Table 1. Features extracted from each used signal.

Feature	Heart rate	Temperature	EDA[a]	BVP[b]
Mean and SD	μ_{HR}, σ_{HR}	μ_{TEMP}, σ_{TEMP}	μ_{sig}, σ_{sig} sig ∈ {EDA, Phasic}	μ_{BVP}, σ_{BVP}
Median	p^{50}_{HR}	—[c]	p^{50}_{sig} sig ∈ {EDA, Phasic}	p^{50}_{BVP}
25th and 75th quartiles	p^{25}_{HR}, p^{75}_{HR}	—	p^{25}_{sig}, p^{75}_{sig} sig ∈ {EDA, Phasic}	—
IQR	p^{75}_{HR}-p^{25}_{HR}	—	$p^{75}_{sig} - p^{25}_{sig}$ sig ∈ {EDA, Phasic}	—
Minimum and maximum	min_{HR}, max_{HR}	min_{TEMP}, max_{TEMP}	min_{sig}, max_{sig} sig ∈ {EDA, Phasic}	min_{BVP}, max_{BVP}
Slope	δ_{HR}	δ_{TEMP}	δ_{Tonic}	μ_{BVP}^{δ}, min_{BVP}^{δ}, max_{BVP}^{δ}
Average RR intervals	—	—	—	μ_{RR}
RMSSD[d] RR interval differences	—	—	—	$RMSSD_{RR}$
Number of peaks	—	—	$\#_{Phasic}$	—
Average peak amplitude and response time	—	—	μ_{Phasic}^{Amp}, μ_{Phasic}^{t}	—
Power in ULF[e], LF[f], HF[g], and UHF[h] components	—	—	f_{sig}^{x} x ∈ {ULF, LF, HF, UHF} sig ∈ {EDA, Phasic}	—
Mean (SD) of real and imaginary frequency component	—	—	—	RE (μ_{BVP}^{f}), RE (σ_{BVP}^{f}), IM (μ_{BVP}^{f}), IM (σ_{BVP}^{f})
Median of real and imaginary frequency component	—	—	—	RE ($p^{50}_{BVP,f}$), IM ($p^{50}_{BVP,f}$)
IQR of real and imaginary frequency component	—	—	—	RE ($p^{75}_{BVP,f}$-$p^{25}_{BVP,f}$), IM ($p^{75}_{BVP,f}$ -$p^{25}_{BVP,f}$)
Minimum and maximum of real and imaginary frequency component	—	—	—	RE (min_{BVP}^{f}), RE (max_{BVP}^{f}), IM (min_{BVP}^{f}), IM (max_{BVP}^{f})
Sum of real and imaginary frequencies	—	—	—	RE (Σ_{BVP}^{f}), IM (Σ_{BVP}^{f})

[a]EDA: electrodermal activity.

[b]BVP: blood volume pulse.

[c]Not applicable.

[d]RMSSD: root mean of successive square differences.

[e]ULF: ultralow frequency.

[f]LF: low frequency.

[g]HF: high frequency.

[h]UHF: ultrahigh frequency.

Machine Learning Modeling

To address the feasibility of predicting OCD events from in-the-wild recordings from a machine learning point of view, we make a principal component analysis decomposition of the extracted features from recordings obtained from different known settings. We compared recordings that precede tagged OCD events in the wild during clinical ERP sessions of patients with OCD, the resting phase of patients with OCD, and the physical activity of the control group.

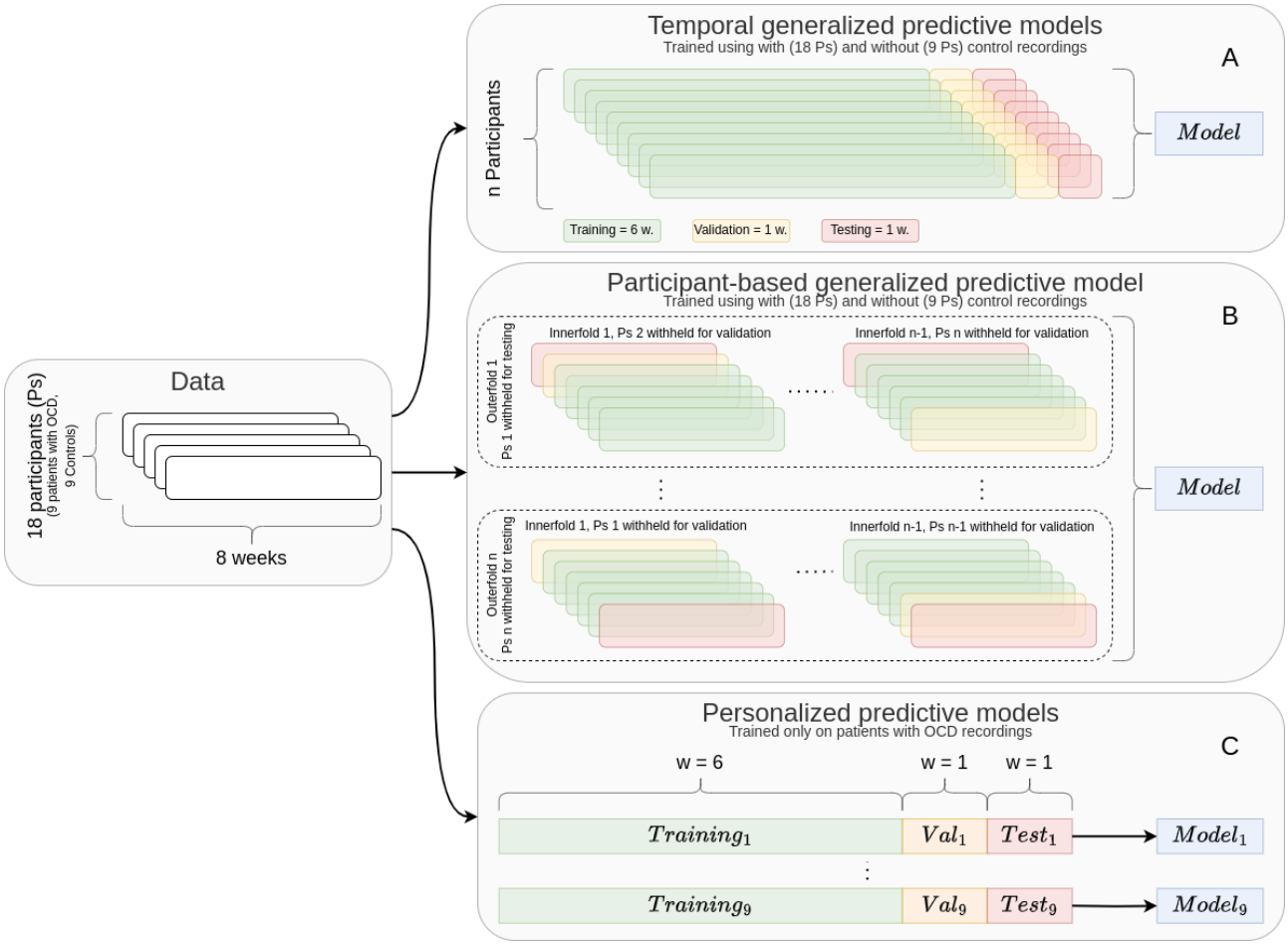
We will consider the prediction of OCD events a binary classification problem. Each time window is considered an independent observation and will be labeled according to the window strategy outlined above. We apply a 2-layer

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cross-validation strategy with each layer being a random 10-fold cross-validation.

We then consider 2 subproblems to study the generalization capabilities of OCD event prediction: generalized predictive models and personalized predictive models as shown in Figure 3. For each subproblem, we apply a 2-layer cross-validation strategy designed to evaluate the generalization across participants and time, respectively. The outer loop estimates model performance by the accuracy, F_1-score, and area under the receiver operating characteristic. The inner loop selects the model and hyperparameters that perform best according to accuracy among logistic regression, random forest, feed-forward neural networks (NNs), and mixed-effect random forest [34].

Figure 3. Design of the cross-validation strategies. Temporal generalized predictive models (A) and personalized predictive models (C) use a leave-last-week-out strategy, while participant-based generalized predictive model (B) uses a leave-one-subject-out strategy. OCD: obsessive-compulsive disorder.



Generalized Predictive Models

In generalized predictive models, we will train models to predict OCD events across patients and for new time periods. We compare the performance of models trained on data solely consisting of patients with OCD and models with data from both patients with OCD and controls.

In participant-based generalized models, we apply 2-layer cross-validation where both the inner and outer layers are leave-one-subject-out. That is, the models are trained on all available participants, except 1 participant who is withheld for testing purposes.

In temporal generalized models, the model is trained and tested on recordings from all participants. The recordings of each participant are divided into 3 data sets for training, validation, and testing. The test data consists of the last week of recording from all participants, and the validation set consists of the recordings from week 7 from all participants.

Personalized Predictive Models

Personalized predictive models are trained using the same schema as the temporal generalized models except a different model will be trained for each participant. That is, models are trained and tested on recordings from the same participant. For each participant, the type of model and hyperparameter values are selected using the training and validation data, and model performance is evaluated using the test set.

Exploring Deep Learning Models

Once a baseline model based on feature extraction within sampled windows is established, as described above, we will explore the feasibility of deep learning models as a secondary study. In particular, we will consider recurrent NNs [35] or 1D convolutional NNs [36,37]. Feng et al [35] use a combination of 1D convolutions and long short-term memory as feature

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extractors for stress detection on the WESAD [17] data set, improving the performance over traditional machine learning methods. Chen et al [38] use 1D convolution of 3 physiological signals for automatic emotion recognition. Yu and Sano [37] propose an AutoEncoder-based semisupervised method for stress detection using physiological signals and self-reported stress tags. A benefit of long short-term memories and 1D convolutions is that they can be applied to the recorded time series with little need for preprocessing. We will use the same validation strategies as above. Considering data are limited, we consider this an exploratory proof-of-concept study, and we do not expect results from this study to directly generalize to other studies.

Results

Participants were included between December 2021 and December 2022. Participants included 10 female and 8 male participants with an even sex distribution between groups. Patients were between the ages of 10 and 16 years, and adolescents without a psychiatric diagnosis were between the ages of 8 and 16 years. Most patients (8/9, 89%) had moderate (CY-BOCS total score between 14 and 24 [39]) to moderate-severe OCD (CY-BOCS total score of 25-30 [39]), except for 1 patient with mild OCD (CY-BOCS total score below 14 [39]).

Discussion

Principal Findings

Here, we present a predefined plan for how data will be preprocessed, analyzed, and presented in the publication. If the artificial intelligence tools show promising results, this preregistered analysis plan helps reduce interpretation bias.

We will investigate the predictive generalization of models to newly recorded data and new individuals. Good generalization to new data is required for real-world applications where models are trained on historical data and then expected to perform well on new data recorded in real time. Similarly, if models are found to generalize well to new unseen individuals, they can be applied immediately to new patients without the need for recording data for fine-tuning. This would significantly expedite the application of models on new patients.

The relatively small number of participants In this study could raise issues regarding the generalization of the trained models, especially considering that the data distribution between participants is expected to be very imbalanced. To assess how much data are needed to train predictive models with acceptable performance, we will include a power analysis that compares models trained on different amounts of the available data and estimate the required number of observations to achieve a given performance level using the inverse power law.

As physiological signals may differ heavily from person to person, there is a risk that models trained using multiple people will perform worse than models trained using only 1 person. We assess this issue by comparing the predictive performance of models personalized for each participant and generalized models trained using multiple participants. If personalized models are found to be superior to generalized models, a natural following question is how much labeled data are needed to build such a personalized model and predict OCD cases. Ideally, the data collection period should be as short as possible. For this purpose, it could be interesting to study whether recordings from clinical sessions are sufficient to fine-tune models previously trained on data from a larger corpus.

Models trained solely on patients with OCD are prone to false positives and risk predicting OCD events in individuals without OCD. In future work, we will assess this risk by comparing predictive differences between models trained solely on data recorded from known patients with OCD and models trained using combined patient and control data.

Physiological signals recorded from in-the-wild wearable devices inherently contain high levels of noise and artifacts from the environment, motion, or reflection or absorption properties of different skin tones. This is discussed in van Lier et al [40], using a standardized assessment of the Empatica E4 EDA and BVP measurements compared with established clinical reference devices on multiple levels. Features extracted from the EDA signal using Empatica E4 are found to have significant nonsystematic differences from the same features using the reference device. However, they are still useful in detecting stressful events expected to substantially increase skin conductivity. Moreover, van Lier et al [40] speculate that the "cool-down" period following a stressful event is longer using the E4 than the reference device. This might be problematic for OCD detection as periods following an OCD event could have inflated feature values and be falsely classified as positives. This highlights the need for our proposed block of 5 minutes following each tagged event. For the BVP signal, van Lier et al [40] found a good agreement with the reference device for features related to the heart rate and root mean of successive square differences. However, they also conclude that the E4 has too much data loss due to noise to be useful for prediction of stressful events but argue that the events in their study might not induce enough stress or be of too short duration. The experiments of van Lier et al [40] were conducted in a stationary clinical setting. As such, the issues of data loss must be expected to only increase using in-the-wild data. To combat this issue, we apply the previously explained segmentation strategy to find low-noise segments in the BVP that are suitable for feature extraction.

In this initial study, we discard the parent recording and limit our data to the youth recordings. It is important to understand the relationship between the child tags and the child signals, and we wish to keep the analysis as simple as possible to assess the feasibility. However, in future work, we wish to incorporate data from the parents as well. Children often seek help or reassurance from their parents, which might increase the stress levels of the parent. Thus, we would expect some degree of synchrony between the physiological signals between child and parent. How well the patients cope with their stress levels is expected to be affected by the extent to which the parent accommodates or refuses to accommodate the patient's symptoms. Refusal to accommodate symptoms or overly accommodating behavior can both increase the stress of the parent at the expense of the patient's treatment. Additionally,

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parents may notice stress triggers before the child and attempt to avoid the trigger. Such events can increase the stress of the parent but not the patient. Thus, physiological signals from the parent could be used for parent-focused interventions to ensure the proper supportive treatment. Additionally, the parent tags and signals may also provide insight into how their children's OCD affects the parents' peripheral autonomic nervous system responses. This is interesting independently of the children's signals.

Potential Clinical Implications

Automated detection of OCD events in the wild may help clinicians assess and monitor the clinical severity of patients waiting for or in treatment. Monitoring distress during ERP and in between sessions allows for data-informed therapy. Automatic feedback will help to increase the patient's awareness of physiological reactions and the connection between thoughts, feelings, sensations, and actions—a goal of cognitive behavioral therapy [41]. Furthermore, automated detection of OCD events during the build-up phase may serve as a tool for individually tailored ecological momentary interventions, which use upcoming stress events to prompt just-in-time interventions to prevent maladaptive behavior and promote adaptive coping strategies [42]. However, this poses significant requirements to the precision of the predictive models as this function itself could evolve into a source of stress for some patients. Additionally, if the signal characteristics indicating an OCD event are not unique to OCD, it could contribute to an overexaggeration of OCD symptoms if not implemented carefully. This would give clinicians a wrong assessment of the severity of patients and could result in wrong treatment plans. However, comparison with other conditions is outside the scope of this initial feasibility study and left for further research.

Limitations

In this initial study, we implement a simple windowing approach. We do not have knowledge of whether OCD events were tagged leading up to, during, or after a distress event. For this reason, we consider fairly large time windows to ensure a complete event is captured within each window. Larger time windows were found to increase performance in stress detection in a previous study [16]. The inherent risk associated with large windows is the reduction of the signal-to-noise ratio and the potential overlap of multiple events. Yet, others found that, overall, the window size had little effect on the task of detecting negative emotions using physiological signals in the wild [43]. However, window length was found to affect personalized predictive models differently. As OCD symptoms often differ from patient to patient, we similarly expect that window length will affect participants differently. Therefore, adaptive windowing based on each participant for personalized models might give some knowledge of whether this is an appropriate course to pursue. However, considering the small number of patients included in this initial study, we do not expect conclusive evidence regarding the generalizability of window size. Therefore, a detailed discussion of the relation between window length and symptom type is outside the scope of this study. In future work, we might consider comparing different window lengths for each patient, similar to Gjoreski et al [16].

Event tagging comes with inherent uncertainty. Patients might forget to tag events completely or tag events minutes later after remembering. Moreover, tags might happen by accident or the same event might be tagged multiple times. These issues might lead to falsely labeled positive and negative cases, thereby negatively impacting model training, evaluation, and quality. To circumvent this, Gjoreski et al [16] recommend also labeling windows adjacent to tagged events as positive cases. They argued that an anticipated stressful event might cause physiological arousal leading up to the event as well. However, as OCD events are entirely unplanned, this phenomenon is not expected in our data. On the contrary, falsely labeling windows earlier than the OCD event as positive cases would expectedly negatively impact model precision. In some cases, patients reported that they accidentally tagged events during data collection but could not report the exact time, allowing us to filter such wrong labels. However, these reports in combination with our practical feasibility study might give some insight into the extent of the false labels and allow us to gauge the impact on the model assessment. In the end, a ground truth is required for model training and the best source for internal private processes, such as obsessions or the discomfort caused by obsessions or compulsions, is the person experiencing them. Even if this is sensitive to the problem of human error.

The simple windowing approach ignores the temporal dependence between observations, which may cause false detection of windows in proximity to a labeled OCD event. Future work will investigate a time series–based approach to detect events in the biosignal time series. This could potentially be paired with some of the deep learning methods mentioned in the section "Exploring Deep Learning Models." A time-series approach may also be useful to address the issues related to the timing of the tags described above. Our current windowing approach treats each tag as an independent event. This may be a fair assumption for events separated by a longer period of time than the cool-down period of 5 minutes. However, for events less than 5 minutes apart, this assumption may not be valid. Patients were asked to tag events when they were bothered by their OCD, which can be interpreted in several ways. When an obsessive thought enters the patient's mind, the patient tags an event and the first obsessive thought triggers another obsessive thought. Should the patient tag a new event or is this still the same event? A potential prospective future work is to investigate how often tags appear and how dependent they are. Each tag could be used to define a new time series describing the probability of an OCD event currently taking place. At the time of a tag, this probability would be one and then slowly taper off during the period before the tag. This tapering would allow for more uncertainty than the binary tags.

Initially, we disregard recordings from the accelerometer built into the E4 wristband. Acceleration is not expected to be an explanatory signal for the prediction of OCD events. However, as previously discussed, explanatory signals such as EDA and BVP are expected to experience motion artifacts. In previous works, accelerometer data have been used to exclude periods of high movement (see Taylor et al [44], Sarker et al [45], and Hovsepian et al [46]). Initially, we were not interested in excluding periods of high movement as we wish to assess the

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predictive performance of OCD events during periods of high movement. We intend to study this qualitatively using physical activity and ERP sessions in the clinical setting. Thierfelder et al [2] found that general movement energy increases with higher stress levels; however, that does not mean there is a causality. Thierfelder et al [2] also argue that some compulsive tasks may result in unique frequency spectra. However, this is not common to all compulsive tasks and requires the need for an accelerometer on both hands to look for asymmetric movements. If motion artifacts are found to resemble the changes in physiological signals due to OCD events, we suspect this will result in an increase in type 1 errors (false positives). Gjoreski et al [16] found that an activity context obtained from accelerometer data may reduce the number of false positives. In future work, we will use the laboratory recordings to obtain an understanding of how physiological signals (eg, EDA and BVP) are affected by physical motion compared to OCD events. If these studies find that motion artifacts resemble OCD events, we will aim for an end-to-end solution that explicitly includes the data from the accelerometer in the modeling to reduce the number of false positives.

Conclusions

In this work, we have discussed the data acquisition and planned analysis for a feasibility study of the prediction of OCD events in the wild using physiological signals recorded from smart wristbands. The current predefined analysis plan will help limit bias for reported results in future publications. We have discussed in detail the potential issues and sources of uncertainty as well as how we plan to address these issues, such as interparticipant and temporal differences, the window length used for feature extraction, event labeling, noisy recordings, and movement-based artifacts. Additionally, we discuss ideas for future work which will improve the understanding of how these limitations affect the problem of predicting OCD events in the wild. If the obtained results from this analysis plan are promising, we will be a step closer to automated detection of OCD events outside of clinical experiments. This is an important tool for the assessment and treatment of OCD in youth.

Acknowledgments

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Data Availability

The data sets generated and analyzed during this study are not publicly available due to the sensitive nature of the data and General Data Protection Regulation (GDPR) concerns but are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

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Abbreviations

BVP: blood volume pulse
CY-BOCS: Children's Yale-Brown Obsessive Compulsive Scale
EDA: electrodermal activity
ERP: exposure and response prevention
HRV: heart rate variability
IBI: interbeat interval
NN: neural network
OCD: obsessive-compulsive disorder
PPG: photoplethysmography

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Protocol

Home-Based Treatment for Chronic Pain Combining Neuromodulation, Computer-Assisted Training, and Telemonitoring in Patients With Breast Cancer: Protocol for a Rehabilitative Study

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Abstract

Background: Chronic pain is a disabling symptom frequently reported in patients with breast cancer with a prevalence ranging from 25% to 60%, representing a major health issue. It has negative consequences on health status, causing psychological distress and affecting quality of life. Furthermore, the clinical management of chronic pain is often inadequate, and many patients do not benefit from the administration of pharmacological treatments. Alternative therapeutic options have been implemented to improve the psychophysical well-being of patients, including neuromodulation and complementary interventions.

Objective: We aimed to investigate the effectiveness of a home care strategy combining computerized rehabilitation, transcranial direct current stimulation (tDCS), and remote telemonitoring via a web-based platform in patients with breast cancer suffering for chronic pain.

Methods: A web-based structured survey aimed at monitoring chronic pain and its effect on psychological functions will be delivered to patients with breast cancer through social media and email. In total, 42 patients with breast cancer affected by chronic pain will be recruited during the medical screening visit. The patients will be randomly divided into 3 treatment groups that will carry out either tDCS only, exercise therapy only, or a combination of both over a 3-week period. All the treatments will be delivered at the patients' home through the use of a system including a tablet, wearable inertial sensors, and a tDCS programmable medical device. Using web-based questionnaires, the perception of pain (based on the pain self-efficacy questionnaire, visual analogue scale, pain catastrophizing scale, and brief pain inventory) and psychological variables (based on the hospital and anxiety depression scale and 12-item short form survey) will be assessed at the beginning of treatment, 1 week after the start of treatment, at the end of treatment, 1 month after the start of treatment, and 3 months after the start of treatment. The system's usability (based on the mobile app rating scale and system usability scale) and its involvement in the decision-making process (based on the 9-item shared decision-making questionnaire) will be also evaluated. Finally, at the end of the treatment, a digital focus group will be conducted with the 42 patients to explore their unexpressed needs and preferences concerning treatment.

Results: The study project is scheduled to start in June 2023, and it is expected to be completed by August 2025.

Conclusions: We expect that the combination of tDCS and telemedicine programs will reduce pain perceived by patients with breast cancer and improve their mental well-being more effectively than single interventions. Furthermore, we assume that this home-based approach will also improve patients' participation in routine clinical care, reducing disparities in accessing health care processes. This integrated home care strategy could be useful for patients with breast cancer who cannot find relief from

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chronic pain with pharmacological treatments or for those who have limited access to care due to poor mobility or geographical barriers, thus increasing the patients' empowerment and reducing health care costs.

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KEYWORDS

telemedicine; chronic pain; breast cancer; tDCS; transcranial direct current stimulation; home care treatment; home care; care; training; pain; cancer; quality of life; rehabilitation; telemonitoring; web platform; exercise; therapy

Introduction

Background

Chronic pain is related to a multitude of pathological conditions, with a prevalence of 20% to 30% in Europe, and it is considered one of the major health and social problems that our society is facing [1,2]. This disabling symptom is frequently reported in patients with cancer, who often have to deal with pain during their illness. For this reason, the term "chronic cancer-related pain" has recently been used to identify chronic pain caused by the primary cancer itself, metastases, or treatment [3].

In particular, chronic pain has been specifically investigated in patients with breast cancer, with a prevalence that varies from 25% to 60% of patients [4]. Chronic pain has a significant negative impact on the health status of patients with breast cancer that tend to experience higher levels of perceived stress and greater anxiety and depressive symptoms [5,6], thus compromising medical treatment adherence [7].

Moreover, chronic pain has a detrimental impact on daily activities by negatively affecting patients' quality of life and can cause high degrees of disability as well as the possible onset of psychiatric problems [2]. It can even compromise the ability to work, especially for the younger patients with breast cancer that face a constellation of complex responsibilities, such as family caregiving, professional duties, and financial uncertainty [4,8].

The clinical management of chronic pain is often inadequate since it is still frequently hidden by patients with breast cancer and often neglected by health care professionals [6]. In addition, many patients report several unmet clinical needs and are often referred to multiple specialists without being effectively taken care of by the health system [2,9-12]. Furthermore, it is important to highlight that in many cases, patients suffering from chronic pain do not benefit from the administration of pharmacological treatments. For this reason, alternative therapeutic options have been implemented, including neuromodulation and complementary interventions aimed at improving psychophysical well-being, such as cognitive-behavioral therapy, occupational therapy, physical treatment, and thermotherapy and cryotherapy [13-19]. Indeed, the implementation of complementary interventions can reduce pain intensity and psychological distress by improving the individual's ability to cope with and manage their pain [13-15,18].

The term "neuromodulation" refers to stimulation techniques that modify the activity of brain circuits [20]. Neuromodulation techniques are now considered an essential tool of precision medicine, and in recent years it has been greatly used in chronic pain management [21-25]. One of the most adopted approaches during clinical trials [26] is transcranial direct current stimulation (tDCS), a noninvasive neuromodulation procedure that uses a low-intensity current capable of modifying the excitability of the cerebral cortex [27].

The restrictions imposed by the COVID-19 pandemic and the mobility limitations that patients face due to chronic pain conditions have brought about awareness of the need to develop new health services based on digital technologies (ie, eHealth). To address these needs, the use of "telemedicine" has been implemented. Telemedicine is a subset of telehealth that uses communications networks for the delivery of health care services and medical education from one geographical location to another, primarily to address challenges like uneven distribution and shortage of infrastructural and human resources [28]. Among other advantages, it has allowed the provision of remote services directly in the homes of patients [29,30].

The development of computerized rehabilitation protocols at home in combination with noninvasive neuromodulation and monitoring by the clinical team could represent an innovative tool for improving the quality of life and life expectancy of patients at a relatively low cost [29]. It has been observed in patients with chronic pain that the improvement of monitoring through a telemedicine-oriented approach capable of guaranteeing continuous and effective communication with health care professionals [31] and an interaction with the patient community can lead to a significant increase in the effectiveness of treatments [32]. eHealth applications appear to be facilitators of the implementation of shared choice processes between doctor and patient, reducing decision-making conflicts and improving patient satisfaction with the treatment process [33].

The growing use of protocols combining neuromodulation techniques and cognitive behavioral interventions through telemedicine, and the possibility of using them in diversified clinical populations, has led to the search for technological ecosystems capable of guaranteeing more personalized treatment approaches [34,35]. Accordingly, a previous project developed an integrated platform, including customized applications and educational and telemonitoring tools for the management of patients with chronic pain [36,37].

Aims

This protocol is part of the Technopain project aimed at evaluating a new home care strategy combining computerized training rehabilitation, noninvasive neuromodulation, and remote telemonitoring via a web platform. In this study, the use of

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telemedicine will allow the assessment of psychosocial and physical symptoms related to chronic pain in patients with breast cancer and the identification of its impact on patients' quality of life and on decision-making related to their own clinical care. In addition, this study aims to investigate the acceptance of the technological approach and the related ethical challenges in order to define a framework of reliability and trust for future therapeutic application.

Methods

Procedure

In a first stage, patients will be invited to participate in a mixed method study through social media and email. The delivery and self-administration of questionnaires will take place through a structured survey that can be filled in on a smartphone, tablet, or computer via a web-based platform (Qualtrics). After completing a web-based consent to data processing, participants will receive a link, which will allow them to access a web-based questionnaire aimed at monitoring the repercussions of chronic pain on psychological functions and on the performance of daily life activities. All data will be collected, anonymized, and stored in a password-protected electronic format.

Subsequently, patients who have previously completed the questionnaires will be identified at a screening visit by the doctor and selected according to the eligibility criteria shown in Textbox 1.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria:

- Diagnosed with breast cancer (stage I, II or II)
- Aged ≥18 years
- Undergoing oncological treatments (postconservative or nonconservative surgery)
- Visual analogue scale score >4
- Completed and signed the informed consent form after a detailed explanation of the task and the tools used in the study
- Possess sufficient cognitive skills to support a rehabilitation process mediated by an electronic device
- Montreal cognitive assessment score >15.5 (adjusted for age and years of education) [38]

Exclusion criteria:

- Started new pharmacological treatments or changed current therapies that act on pain within the last month
- Have a bone marrow stimulator or intrathecal drug delivery pump
- Have respiratory, cardiac, metabolic, or other conditions incompatible with at least 30 minutes of light or moderate intensity exercise as assessed by a specialist
- Have severe cognitive impairment
- Have aphasia, dementia, or a psychiatric comorbidity interfering with communication or rehabilitation program compliance
- Have blindness or severe vision problems that may interfere with the use of the tablet
- Possess insufficient knowledge of the Italian language or inability to understand verbal and written instructions
- Concomitant participation in another study or clinical trial involving rehabilitation therapy or administration of an investigational drug

Questionnaires

Each patient enrolled in the study will be provided with a tablet on loan for use, which will allow the collection of some symptomatologic manifestations and behavioral characteristics relating to the presence of chronic pain. Table 1 describes the questionnaires that will be digitally administered to investigate the perception of pain, the psychological variables, and the patient's decision-making within the treatment path.

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Table 1. List of questionnaires administered to each patient with chronic pain.

Questionnaires	Description
Pain	
PSEQ[a]	Measures the perception of self-efficacy in carrying out daily activities, despite the presence of pain [39,40]
VAS[b]	A 1-dimensional rating scale of pain intensity [41]
PCS[c]	Investigates catastrophic thinking resulting from the perception of chronic pain [42]
BPI[d]	Evaluates the severity of the patient's pain and its impact on daily functioning [43,44]
Anxiety and depression	
HADS[e]	Investigates the presence of anxious and depressive disorders and evaluates their severity [45]
Health status	
SF-12[f]	Measures the patient's perception of their health status [46]
Decision-making	
SDM-Q-9[g]	Measures the sharing of decisions between doctor and patient [47]
Usability tools	
MARS[h]	Investigates the quality of the app according to engagement, functionality, aesthetics, and information [48]
SUS[i]	Evaluates the usability of the pain monitoring system [49]

[a]PSEQ: pain self-efficacy questionnaire.
[b]VAS: visual analogue scale.
[c]PCS: pain catastrophizing scale.
[d]BPI: brief pain inventory.
[e]HADS: hospital and anxiety depression scale.
[f]SF-12: 12-item short form survey.
[g]SDM-Q-9: 9-item shared decision-making questionnaire.
[h]MARS: mobile application rating scale.
[i]SUS: system usability scale.

Randomization

All patients who have signed the informed consent form will be assigned an alphanumeric identification code through which they will be registered in a management software. Randomization is an integral part of the patient registration process and will take place automatically through an integrated randomization block with a 1:1 ratio, and each participant will be randomly assigned by the use of "RAND" formula in Excel (Microsoft Corp) to 1 of the 3 treatment groups described in Table 2.

Table 2. Description of the experimental groups.

Treatment group	Description
Group A (tDCS[a])	Patients will be treated with only tDCS 3 times a week for 3 consecutive weeks.
Group B (exercise therapy)	Patients will be treated exclusively with exercise therapy for 2 or 3 days a week for 3 consecutive weeks, depending on the patient's characteristics.
Group C (combined therapy)	Patients will be treated by combining tDCS with exercise therapy. They will be subjected to a cycle of tDCS 3 days a week for 3 consecutive weeks. On the days between 1 stimulation and another, the patients will carry out exercise therapy sessions.

[a]tDCS: transcranial direct current stimulation.

Treatment With tDCS

The delivery of tDCS will be administered through a programmable medical device called "HDCkit" (Newronica). This kit has been specifically designed for both research and clinical use and allows the administration of tDCS for use at home. The HDCkit comprises an "HCDstim" that delivers the tDCS treatment, a touch screen liquid crystal display "HDCprog" that is connected to the HDCStim and controls stimulation settings, and a "Mindcap" that guarantees the correct placement of the electrodes and the reproduction of the appropriate setup when the tDCS treatment is dispensed at home [50]. In the application, the tDCS consists of very low–intensity electric currents that are barely perceptible (1-2 mA) through

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2 electrodes (an anode and a cathode) in electroconductive rubber with an area of about 25 cm^2 integrated inside sponges soaked in physiological solution to facilitate the flow of current.

Kari System

Patients who plan to undergo exercise therapy will be provided with the kari system (Euleria Health), a CE class 1/m medical device [51], on loan for use. The kari system comprises a tablet with its charger (supplied to all patients), a wearable inertial sensor (IMU) with its magnetic charging cable, a dedicated app that guides the patient through the exercise therapy program, and a kit of 7 elastic bands to facilitate easily positioning the inertial sensor on the body. The IMU is a noninvasive methodology used to collect motion data related to the body section where it is worn. It allows the clinical team to recognize the physical exercise and to verify the accuracy of the movements performed by the patients.

A member of the clinical team will educate each patient individually on the use of the kari system upon delivery of the same so that everyone acquires familiarity and independence in its safe use.

The tablets will also be used for the periodic compilation of questionnaires and rating scales by patients. The data will be saved locally on the device at the end of each training session and then transmitted to the web management system. Once transferred to the web management system, the data are immediately available for consultation by clinical staff.

The results of the clinical and functional evaluations will be collected anonymously on the patient data collection form.

Intervention

Patients in groups B and C will carry out exercise therapy sessions involving the use of the kari system at home for about 30 minutes a day under the remote supervision of the clinical staff via the web management system. This device allows researchers to remotely configure, customize, and quantitatively monitor an exercise therapy path for patients. A dedicated app guides the rehabilitation patient through the exercise therapy program configured by the professional. Monitoring is guaranteed by the integrated chat and video call functions, as well as by a web application accessible remotely by the therapist in which various quantitative factors related to the therapy can be monitored, such as adherence and program effectiveness.

Patients assigned to groups A and C will receive tDCS treatment, where stimulation parameters will be personalized on the basis of the patients' clinical characteristics, according to 1 of the methods described in Table 3.

Table 3. Description of transcranial direct current stimulation treatment typologies.

Type of stimulation	Description
Spinal stimulation	The active electrode will be placed on the spine in the median position in correspondence with the 10th thoracic vertebra with the reference on the right arm or in correspondence with the somatosensory area [52]. A stimulation intensity of 2.5 mA will be provided for 20 minutes.
Cerebellar stimulation	The active electrode will be placed in correspondence with the cerebellum with the reference on the right arm [53]. A stimulation intensity of 2.0 mA will be provided for 20 minutes.
Brain stimulation	The active electrode will be placed on the left motor cortex with the reference on the right arm or in correspondence with the contralateral supraorbital cortex [54]. A stimulation intensity of 2 mA will be provided for 20 minutes.
Dorsolateral prefrontal stimulation	The active electrode will be placed on the left dorsolateral prefrontal cortex with the reference on the contralateral area [55]. A stimulation intensity of 2 mA will be provided for 20 minutes.

To explore psychological variables and the individual impact of perceived pain, patients will be evaluated and receive a link with the questionnaires described in Table 1 at the following specific time points: before starting any treatments, 1 week after the start of the treatment, at the end of the 3 weeks of treatment, 1 month after the start of the treatment, and 3 months after the start of treatment. Furthermore, at the end of the treatment, each patient will be asked to answer questionnaires aimed at evaluating the usability of the system.

Finally, a focus group will be conducted with all the patients who took part in the study. The patients will be divided into groups of 14 participants based on the treatment group to which they were assigned. The aim of this investigation is to analyze the unexpressed needs, expectations, and preferences related to the home-based treatment. The focus groups will be conducted starting from a list of questions concerning the experience of the disease by the study participants, the relationship between the painful symptoms and the psychological significance, the expectations with respect to the treatment, and any difficulties encountered during the use of the technologies adopted during the rehabilitation program.

Focus Group Meetings

A telematic platform will be used to carry out the focus group meetings at the end of the treatment. The duration of the focus group meetings will be between 60 and 90 minutes, and breaks will be provided every 45 minutes to avoid tiring the patients. Audio and video will be recorded from every meeting and subsequently analyzed using T-Lab software, which comprises several linguistic and statistical tools [56].

Sample Size

At least 42 patients with breast cancer will be recruited for the study. The patients will be divided into 3 experimental groups, each consisting of 14 patients, based on the type of treatment performed (tDCS only, exercise therapy only, or combined treatment). In case of dropouts, the recruitment of patients will continue until 42 participants complete the treatment.

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Since the present study is the first to evaluate the effects of tDCS in patients with different types of chronic pain over a 3-week period, to estimate the expected difference between the effect of tDCS and combined therapy (tDCS and exercise therapy), for the calculation of the sample size we relied on a recently published study [54] of 45 patients with fibromyalgia to calculate the sample size. The published study compared the effects of tDCS and exercise therapy if carried out individually or in combination for 1 week. The improvements observed in the 3 treatment groups are shown in the Table 4.

Table 4. Mean visual analogue scale (VAS) scores of the different treatment groups.

Treatment group	Baseline VAS	Improvement (%)	VAS at 1 week after treatment	ΔVAS (beginning of treatment vs 1 week after treatment)
tDCS[a]	7.2	18	5.904	1.296
Combined therapy	7.3	40	4.4019	2.8981
Exercise therapy	6.8	24	5.202	1.598

[a]tDCS: transcranial direct current stimulation.

The sample number for each individual clinical center was calculated to demonstrate the difference between the change in the visual analogue scale (VAS) value at the beginning of treatment and after 1 week of treatment between the group of patients receiving tDCS and that receiving combined therapy. A Wilcoxon-Mann-Whitney test was performed using G*Power V3 software [57] with an effect size of 1 and assuming the following parameters: a VAS change of 1.3 in the tDCS treatment group and 2.9 in the combined therapy group, as reported by Mendonca et al [54] in the evaluation after 1 week of treatment; an SD of 1.27 in both groups; a type 1 error of 0.05; and a power of 80%. A sample of the same size is adequate to demonstrate the difference in VAS between the exercise therapy group and the combined therapy group (based on data from Mendonca et al [54]).

Statistical Analysis

To evaluate the efficacy of the treatments, a statistical analysis will be conducted on the clinical scales, functional tests, and questionnaires using a dedicated software. Data distribution will be evaluated using Shapiro-Wilk tests. In the case of a normal distribution, statistical significance will be evaluated by applying parametric *t* tests and ANOVA for repeated measures. In case the assumption of a normal distribution is not supported, a nonparametric Wilcoxon-Mann-Whitney test will be used. Statistical analysis will be performed on all participants who complete the treatment required by the protocol. Participants who do not complete all phases of the study (ie, dropouts) will be excluded from the data analysis. Furthermore, as suggested by recent scientific literature, Bayesian statistics will also be applied using JASP open-source software in order to better estimate the possible absence of an effect of therapeutic strategy [58]. In particular, intragroup comparison analysis will be assessed using repeated measures ANOVAs (within subjects, time factors). Comparison of the subgroups (n=14 per group) will be performed using parametric or nonparametric hypothesis tests depending on the normality of the data distribution and corrections of type 1 errors. Finally, correlations will be performed between the VAS, patient demographics, and clinical data. All secondary outcomes will be evaluated by descriptive statistical analysis. Analysis will be carried out using SPSS Statistics (version 27; IBM).

Ethical Considerations

This protocol was approved by the ethical committee of the Istituti di Ricovero e Cura a Carattere Scientifico European Institute of Oncology (April 2023). Written and verbal information will be provided and informed consent will be obtained from all participants. Participation in the study is voluntary and free. No additional fees will be charged to the participants, and no payments will be made.

All the methodologies mentioned in the study protocol will be carried out according to the relevant guidelines and regulations.

Data Protection

Patient data will be treated as strictly confidential and subject to anonymity so that it cannot be associated in any way with the individual. For this purpose, at the beginning of the study, the study doctor will assign to the participants a code with which they will be identified during all subsequent phases of the study. The data relevant to the study, with the exception of patients' names, will be recorded, processed, and stored together with this code and all clinical data relating to the state of health. Only the physician and authorized parties will be able to link this code to the patients' names.

This information will be treated as strictly confidential in accordance with EU Regulation 679/2016, Legislative Decree 196/2003 as amended (Processing of Personal Data) and will only be used for research purposes in connection with this study.

Results

The project, Technopain, is scheduled to start in June 2023, and it is expected to be completed by August 2025. Results will be available following data analysis in the subsequent months.

This innovative approach will contribute to furthering our understanding of the neurophysiological mechanisms of chronic pain and the related psychosocial and physical symptoms. Additionally, the suitability of the telemedicine approach for patients and clinicians will favor the application of new technologies able to improve patients' well-being and access to care.

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Discussion

Projected Impact

The present study protocol represents an innovative approach to the management of chronic pain in patients with breast cancer without the adoption of pharmacological treatments. Consistent with previous studies [15,59-62], we expect that the implementation of combined therapeutic interventions can directly produce a relevant improvement on pain relief.

Considering the beneficial effects of tDCS in increasing emotional well-being in psychiatric and neurological patients [63-65], we also assume that tDCS combined with telerehabilitation programs will reduce psychological distress and improve mental wellness in patients with breast cancer with chronic pain. Moreover, this interactive approach may motivate patients to increase treatment compliance, thus favoring better clinical outcomes.

Another key objective of this integrated home care strategy will focus on limiting the impact of physical and psychosocial symptoms associated with chronic pain on patients' daily lives [4,7]. They represent significant barriers that can affect the ease of travel to health facilities and cause difficulties in accessing care treatments, with consequent economic and organizational impacts [66]. We hypothesize that the introduction of a home-based approach directly and continuously monitoring patients at home will allow us to assess disease progression and improve patients' participation in routine clinical care, thus reducing disparities in accessing health care. Moreover, we expect to significantly optimize the rehabilitation session in terms of time and efficacy, thus reducing the direct and indirect health care and social costs.

Finally, the project aims to support patients affected by chronic pain through decision aids during critical moments of the therapeutic journey [67]. Telemonitoring of remote patients throughout the care process allows the evaluation of both clinical outcomes and patients' reported opinions. Furthermore, the focus groups will allow a greater exchange of the preferences and perceptions of the treatment received by patients with breast cancer, highlighting the strengths and barriers that could have influenced their psychoemotional well-being and their overall experience with chronic pain [68]. We expect that focus group sessions will also contribute to examine adherence, identifying patients who need more personalized pain management strategies, and contextualizing the problem of unrelieved pain.

Clinical Implications

It is possible to hypothesize several advantages following the application of this treatment. First, we expect a reduction in pain perceived by patients, since noninvasive brain stimulation methods and exercise therapy have been shown to have beneficial effects on the management and treatment of chronic pain in previous studies [15,17,18]. Furthermore, the information obtained may also be useful in the future for other people suffering from chronic pain, allowing us to determine which treatment among those investigated in the study will be more appropriate.

Additionally, we expect that the implementation of a home-based care system can facilitate patient adherence by reducing travel costs and establish a more direct and continuous exchange of information between patients and health care professionals.

Study Limitations

A main limitation of the present study could be the personal use of the home care strategy. Despite the many advantages of this technological approach, some patients may find it difficult to use the equipment without direct assistance from a health care professional. The self-management of the home care strategy could also have a negative influence on treatment adherence, causing possible dropouts during the study phases. For these reasons, it will be necessary to monitor patients' motivation during treatment to prevent patients from neglecting rehabilitation.

Patients should also be adequately informed of the possible risks linked to the administration of the treatments to reduce concerns about the occurrence of possible adverse effects of tDCS. In particular, adverse events could involve the appearance of local effects of the stimulation consisting of a slight burning sensation or skin redness. Nevertheless, it should be noted that participation in a trial involves strict control by the experimenter to limit any problems that may arise.

Furthermore, the initial recruitment via social media and email could orient the sample toward younger and technologically experienced patients. However, we adopted this instrument to promote the recruitment of patients throughout the country to overcome geographical barriers related to the access to health care. Additionally, due to the use of digital devices during the rehabilitation program proposed in this study protocol, the enrollment of technologically savvy patients with breast cancer could facilitate the use of the home-based treatment.

Finally, given the importance of subjective perception on the classification of pain, we chose to adopt several self-report tools to assess the personal experience of the patients with breast cancer. However, these instruments have limitations, as it is not possible to obtain objective information. When drawing conclusions, it will therefore be necessary to consider that the data may be influenced by various personal factors.

Conclusion

The Technopain protocol is a new home care strategy that combines computerized training rehabilitation, noninvasive neuromodulation, and remote telemonitoring via a web platform for the treatment of psychosocial and physical symptoms related to chronic pain in patients with breast cancer. In particular, this approach will evaluate the impact of chronic pain on patients' quality of life and will offer a rehabilitation program that can favor the treatment of the greatest number of patients through home delivery. This trial will primarily evaluate the fluctuation of perceived pain by patients during and after treatments, evaluating which of the different types of treatments is the most effective between the single treatments or their combination. In particular, we expect that this study will provide a useful treatment for all patients who cannot find relief from chronic pain with pharmacological treatments. Our ultimate aim is to

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encourage the development of personalized telemedicine, which can provide daily clinical assistance to patients, eliminating the economic and geographical barriers related to the use of health services.

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Data Availability

Data sharing is not applicable to this protocol as no data sets have yet been collected or analyzed.

Authors' Contributions

LC and CM wrote the protocol manuscript. LC, CM, RG, RF, AP, FM, and FR contributed to the design of the intervention. LC, CM, and RG drafted the original version of the manuscript. GP coordinated the study. All the authors have critically reviewed the entire manuscript and have read and approved the final version of the manuscript.

Conflicts of Interest

RF, AP, and FM are stakeholders for Newronika SPA.

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Abbreviations

tDCS: transcranial direct current stimulation
VAS: visual analogue scale

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Protocol

Internet-Delivered Therapy for Parents With Health Anxiety by Proxy: Protocol for a Single-Case Experimental Design Study

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Abstract

Background: Health anxiety (HA) by proxy is described as parents' obsessive worries that their child is severely ill although this is not medically confirmed. Research on HA by proxy suggests that it is highly distressing for the parent and that the child may be at risk of developing maladaptive symptom coping strategies. No targeted treatment for this group exists. We developed PROXY, an 8-week psychological internet-delivered treatment for parents with HA by proxy. The treatment components of PROXY are informed by cognitive behavioral therapy as well as acceptance and commitment therapy, and it was developed in collaboration with parents experiencing HA by proxy and clinical experts.

Objective: This paper describes the protocol for a study investigating the potential effects of PROXY on parents' worries about their children's health using a single-case experimental design (SCED).

Methods: Five parents clinically evaluated as experiencing HA by proxy will be included. A replicated randomized SCED study will be conducted in which each participant will be randomized to receive treatment after a baseline period of between 7 and 26 days (phase A). The treatment phase duration is 8 weeks for all participants (phase B), followed by a follow-up phase lasting between 14 and 33 days (phase C), ensuring that all participants remain in the study for 96 days. Participants will report daily anxiety level by SMS text message throughout the study. They will also answer self-report questionnaires, including questions on HA by proxy and own HA, 4 times during the study. Data will be submitted to structured visual analysis to inspect anxiety level, the variability of anxiety, trends, the overlap of data points among phases, when effects occur, and the consistency of data patterns across participants. Furthermore, randomization tests will be conducted for each participant to test the null hypothesis that PROXY will have no effect on participants' anxiety.

Results: The recruitment of parents began in June 2022. As of March 2, 2023, a total of 4 parents have been included in the study. Data collection was expected to cease in April 2023.

Conclusions: To the best of our knowledge, this protocol describes the only study of treatment for HA by proxy. As the prevalence of this condition is still unknown, a SCED was chosen because this method allows the inclusion of very few participants while still providing information on effects and treatment courses. Conducting the study with a replicated randomized phase design enables methodologically sound testing despite the inclusion of very few participants. The results will inform researchers on individual treatment courses and effects, which may direct future research in terms of the possible mechanisms of change, ideas for how to refine the treatment content, and how the treatment may be offered to patients in the future.

Trial Registration: ClinicalTrials.gov NCT04830605; https://clinicaltrials.gov/study/NCT04830605

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KEYWORDS

health anxiety by proxy; health anxiety; internet-delivered treatment; single-case experimental design; SCED; protocol

Introduction

Background

Health anxiety (HA) by proxy is defined as parents' excessive fear that their child is experiencing a serious illness although this is not confirmed by a medical professional [1]. It is characterized by obsessive rumination about the health of one's child and is often accompanied by control or avoidance behavior, such as facilitating repeated medical evaluations of the child or avoiding all information about child illnesses [2]. More severe cases may be observed in parents diagnosed with HA [3], but milder cases on the continuum are also likely to be recognized by health professionals working in pediatric settings.

A recent qualitative study investigating the lived experiences of parents with HA by proxy found that these parents experience significant distress as a result of their anxiety, and they struggle with finding the right balance in worrying about their child's health [4]. Furthermore, the parent's relationships with their child, other parent, and health professionals are affected [4].

HA by proxy may also have consequences for the child. Evidence suggests that HA symptoms in parents with health worries and increased focus on somatic concerns play a significant role in HA symptoms in children [5]. Furthermore, the parent's response to the child's health concerns [6] and how the parent copes with their own symptoms have been found to influence the health attitudes and behaviors of the child [7-10]. This risk may be especially high in HA by proxy because the child is exposed to a particular parental preoccupation with symptoms and fear of illness.

The members of the research team behind this study have previously investigated the assessment of HA by proxy by developing the Health Anxiety by Proxy Scale (HAPYS) with promising results [2]. Now that parents with excessive worries over their child's health can be identified, the next important step is to develop effective treatment. Existing treatments do not specifically address HA by proxy. A treatment program has already been developed to target parents with anxiety to prevent anxiety in their offspring [11], and effective psychological treatments for HA also exist in both face-to-face and internet-delivered formats [12-14]. Specifically, a recently developed treatment program for HA based on the principles of acceptance and commitment therapy (ACT) and delivered over the internet (iACT) [15] has shown promising results [14,16] and was usable as a template for the development of specialized treatment for parents with HA by proxy.

Developing an Internet-Delivered Treatment Program for HA by Proxy (PROXY)

PROXY is inspired by the existing iACT program for HA and uses the same web platform [17]. The treatment content for PROXY was developed de novo in several steps by 4 of the authors: 3 psychologists (KI, DHF, and LF) and a child and adolescent psychiatrist (CUR) with clinical and research experience with HA. Furthermore, 2 of these authors (LF and CUR) are also trained specialists in cognitive behavioral therapy (CBT). The development process included a number of steps. First, ideas for content, themes, exercises, videos, and audio files were brainstormed. These were presented as sketches to 3 parents diagnosed with HA and with worries about their children's health who subsequently provided group feedback.

Next, the treatment manual went through several rounds of feedback from the project group. Further written feedback on the text manual was provided by 2 (67%) of the aforementioned 3 parents with individual comments in Microsoft Word document format. These 2 parents also participated in patient videos about living with HA by proxy, how to involve relatives, and how to speak to their children about their anxiety. Finally, the content was programmed on a web platform with close collaboration between the project group and web developers.

Usability Test

The thinking-aloud method was used to test the usability of specific selected parts of PROXY. The method involved participants verbalizing their thoughts *while* using the web-based program [18,19]. A male layperson aged 25 years without prior knowledge about the treatment and a female patient aged 47 years with HA by proxy and prior ACT group treatment of HA explored how they experienced (1) navigating the treatment and (2) potential technical issues, as well as (3) how they understood the program. Generally, they navigated the platform easily. Minor adjustments to the instructions, navigation, the choice of wording, and models were made.

Final Version of PROXY

PROXY is an 8-week therapist-supported internet-delivered program containing written psychoeducation, audio files, behavioral exposure exercises, homework, and videos distributed in 8 modules (Textbox 1). The therapist answers questions and provides feedback every week using an embedded secure message system.

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Textbox 1. Overview of module content.

Week 1

- Gain knowledge about health anxiety (HA) by proxy (module 1)
  - Helper: knowledge
  - Aim: for the parent to obtain knowledge about having HA on behalf of their child and explore how they can begin to understand their own anxiety
  - Exercises: (1) write own story of anxiety and (2) fill in the anxiety spiral
  - Videos and audio: (1) parent videos about having HA by proxy, (2) psychoeducation about HA by proxy, and (3) introduction video to the treatment
  - Homework: pay attention to when and where anxiety arises
- Learn about values (module 2)
  - Helper: values
  - Aim: to help the parent identify their own values as a parent and motivate them to start coping differently with their anxiety
  - Exercises: (1) consequences of the anxiety, (2) reflections on being a good parent, and (3) own values as a parent
  - Videos and audio: audio with focus on identifying values
  - Homework: practice putting off worries and set aside a specific time of day to worry

Week 2

- Look at the anxiety from the outside (module 3)
  - Helper: defusion
  - Aim: introduction to anxiety-related control and avoidance strategies, followed by exercise to investigate own behaviors; learning how to defuse from thoughts and feelings; the process of coping differently with the anxiety is initiated
  - Exercises: (1) “Don’t think about the ice cream,” (2) behavior analysis, and (3) defusion exercise
  - Videos and audio: audio with defusion exercise
  - Homework: practice putting off control and avoidance behavior

Week 3

- Practice acceptance (module 4)
  - Helper: acceptance
  - Aim: to practice accepting and holding the anxiety as a new way of coping
  - Exercises: (1) stop, breathe, observe inner states, and prioritize
  - Videos and audio: (1) audio with acceptance exercise and (2) audio with body scan
  - Homework: practice having more breaks during the day, and practice acceptance with mindfulness audio files

Week 4

- Challenge the anxiety (module 5)
  - Helper: exposure
  - Aim: to motivate parents to gradually expose themselves to their anxiety; focus on letting personal values direct choices instead of control and avoidance strategies
  - Exercises: (1) exposure exercise with pictures of sick children, (2) drafting their anxiety hierarchy, and (3) exposure work sheet
  - Videos and audio: none
  - Homework: practice exposure
  - Extra: a module for relatives is introduced with the aim of providing information on HA by proxy and how to be supportive during treatment, including exposure exercises

Week 5

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- Practice self-compassion (module 6)
  - Helper: self-compassion
  - Aim: show the connection among one's expectations, stress, and anxiety, along with how one can be more kind to oneself and practice self-compassion
  - Exercises: (1) "How would you treat a friend?" (2) working with own conditional assumptions
  - Videos and audio: audio on self-compassion
  - Homework: do something nice for oneself and practice exposure

Week 6

- Use your network (module 7)
  - Helper: parents' network
  - Aim: to help parents use their close network for support and provide tools to talk about their anxiety with others, including their child
  - Exercises: (1) How is the anxiety affecting own close relations? (2) talk about the anxiety with a friend and partner, and (3) talk about the anxiety with child and or write a letter to child
  - Videos and audio: (1) parent videos about talking to their children about their anxiety and (2) parent video about family support
  - Homework: talk to child about anxiety and practice exposure

Weeks 7 and 8

- Your path further (module 8)
  - Aim: to recap the treatment content, emphasize why it is important to continue working with acceptance, values and exposure, and how to prevent relapse; furthermore, advice about how to handle future child symptoms and physician visits is provided
  - Exercises: (1) continued work and insights from the treatment and (2) strategies to apply in the event of setbacks
  - Videos and audio: none

The content framework is based on a combination of ACT [15] and CBT [20]. ACT aims to create greater psychological flexibility that allows (1) full awareness of here-and-now experiences, with an attitude of openness and curiosity; and (2) conscious and deliberate decisions inspired by core values, that is, deepest desires for who one wants to be and what one wants to stand for in life [15,21]. Thus, PROXY targets parents' maladaptive anxiety-driven behaviors toward their child with focus on their gradual exposure to the things or situations that trigger their anxiety. This means that the CBT concept of exposure is urged to be based on the patient's personal value. Furthermore, practicing acceptance helps to reduce the influence and impact of the painful thoughts and feelings that arise during the exposure.

Each of the first 7 modules in PROXY offers a *helper*, which is a treatment component (eg, awareness of values, acceptance, and self-compassion) that will help the patient move in a value-based direction in life instead of being trapped trying to control and avoid anxiety (Textbox 1).

Aims

In patient groups in which the prevalence of a health condition is low or unknown, as is the case with HA by proxy, randomized controlled trials are either not possible or unlikely to succeed [22]. Single-case experimental design (SCED) studies are used in clinical psychology to determine whether an effect of an intervention at an individual level has occurred [23-25]. Thus, a SCED study allows testing the effect of treatment for parents with HA by proxy in a small sample size while still controlling for external factors and upholding internal validity [26].

Consequently, this paper aims to describe the design for the first testing of PROXY using a SCED. The study investigates the potential effect of PROXY on parents' worries about their children's health. We hypothesize an initial increase in worries and anxiety, followed by a delayed and gradual reduction.

Methods

Study Design

A SCED study implies control of the independent variable (here, PROXY) while measuring the dependent variable (here, parental worries about their child's health) repetitively and often [24]. SCEDs should be distinguished from both case studies, which are not experimental but descriptive, and designs based on group comparisons where the experimental unit is the participant and where participants are assigned to different groups [27]. In a SCED, the experimental units are the repeated measures of a specific variable under investigation. Various types of SCEDs exist, but only the replicated randomized single-case AB phase design type will be elaborated here [23,27].

The project was registered on ClinicalTrials.gov on April 2, 2021 (NCT04830605).

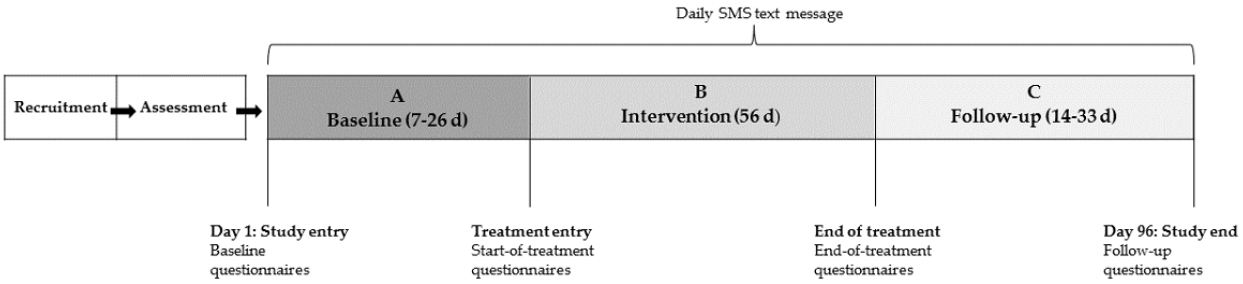
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A Replicated Randomized Single-Case ABC Phase Design

This study will apply a replicated randomized single-case AB phase design for testing the treatment effects. AB designs are particularly useful when testing a psychological treatment that cannot be subjected to withdrawal or to repeated reversal between treatment and baseline. By adding a randomization feature and a replication feature to this basic design, both the internal and external validity are strengthened [27-29]; for example, potential confounding variables related to time, such as natural changes in the participants' anxiety level or events that may affect anxiety, are statistically controlled for when the time point for the introduction of the intervention is randomized. In addition, replicating the design adds to the generalizability.

Specifically for this study, the intervention is randomly introduced after 7 to 26 days in the baseline phase (phase A). After the intervention (phase B), a follow-up phase (phase C) lasting between 14 and 33 days, depending on when the intervention was introduced, ensures that every participant has the same number of daily measurement points throughout the study (96 in total; Figure 1).

Figure 1. Study flowchart for the single-case experimental design (refer to Table 1 for specifics on questionnaires).



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Table 1. Overview of outcome measures, instruments, and distribution time points.

Outcome	Instrument	Time point						
		D[a]	W[b]	Re[c]	BL[d]	Start[e]	EoT[f]	FU[g]
Primary outcome								
Symptoms and effect on daily life of health anxiety by proxy	SMS text message	✓						
Secondary outcomes								
Health anxiety by proxy	HAPYS[h]			✓	✓	✓	✓	✓
Illness behavior when a child has symptoms	ARCS[i]			✓	✓	✓	✓	✓
Catastrophic thinking about child's symptoms	PCS-P[j]			✓	✓	✓	✓	✓
Illness worry	WI-6-R[k]			✓	✓	✓	✓	✓
Depression and anxiety	SCL-12[l]			✓	✓	✓	✓	✓
General well-being	WHO-5[m]			✓	✓	✓	✓	✓
Feasibility outcomes								
Experience of treatment	ESQ[n]						✓	
Negative effects of treatment	NEQ-20[o]						✓	
Experience of internet-delivered treatment	IEUQ[p]						✓	
SMS text message evaluation	Selected items							✓
Feasibility measures	Free writing		✓				✓	
Other								
Suicide risk	Single item from the SCL[q]		✓					
Bodily symptoms	BDS[r] checklist			✓				

[a]D: daily.
[b]W: weekly.
[c]Re: questionnaire filled in at self-referral.
[d]BL: baseline.
[e]Start: start of treatment.
[f]EoT: end of treatment.
[g]FU: follow-up after 96 days from study entry.
[h]HAPYS: Health Anxiety by Proxy Scale.
[i]ARCS: Adult Response to Children's Symptoms.
[j]PCS-P: Pain Catastrophizing Scale–Parent version.
[k]WI-6-R: Whiteley Index-6 Revised.
[l]SCL-12: Symptom Checklist-12.
[m]WHO-5: World Health Organization-5 Well-Being Index.
[n]ESQ: Experience of Service Questionnaire.
[o]NEQ-20: Negative Effects Questionnaire-20.
[p]IEUQ: Internet Evaluation and Utility Questionnaire.
[q]"Thoughts of ending your life."
[r]BDS: bodily distress syndrome.

Participants

Five parents assessed with HA by proxy using the HAPYS [2] will be recruited for the study. No more than 3 participants may be allocated to a baseline duration of between 7 and 10 days to ensure that the participants will have different start times. The specific inclusion and exclusion criteria are presented in Textbox 2.

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Textbox 2. Inclusion and exclusion criteria.

Inclusion criteria

- Parents aged >18 y
- Assessed with health anxiety by proxy
- At least 1 child aged <18 y
- Read, write, and speak Danish

Exclusion criteria

- Comorbid diagnoses of substance abuse, bipolar disorder, psychotic disorders (International Classification of Diseases, Tenth Revision [ICD-10], codes: F20-29), or autism spectrum disorder
- Suicidal risk
- Recently started taking psychotropic drug therapy (within the last 2 mo)
- Child with severe health problems requiring care in hospital setting

Recruitment

Participants are recruited in two ways: (1) participants self-refer to the project through the secure email system at the Research Clinic for Functional Disorders and Psychosomatics (hereinafter the Research Clinic), Aarhus University Hospital, and complete the project questionnaire (Table 1) in Research Electronic Data Capture (REDCap; Vanderbilt University), which includes written consent to assessment [30,31], and, after a diagnostic interview, they are included in the project, if eligible; and (2) participants are recruited at their ordinary assessment for HA at the Research Clinic if they are also clinically assessed as experiencing excessive worries about their child's health.

Assessment

Participants are assessed using a short standardized diagnostic interview based on schedules for clinical assessment in neuropsychiatry (SCAN) [32,33] and supplemented with an assessment of HA by proxy using the HAPYS.

Ethical Considerations

All participants receive written and verbal information about the project before signing the consent to participate. The project has been approved by the Danish research ethics committee (1-10-72-296-20) and registered with the Danish data protection agency (1-16-02-921-17).

Outcome Measures

Primary Outcome

The primary outcome measures of HA by proxy are answered through a link in an SMS text message sent to the participants every day during the study period. The measures contain 3 items selected from the HAPYS [2] (1-3), 1 impact questionnaire (4), and 1 de novo formulated item on committed action (5). All items are answered on a scale ranging from 1 to 10 (Textbox 3; coded as 0-9 for analyses). A daily score is summed for items 1 to 3 (range 0-27), and items 4 and 5 are assessed individually (range 0-9). The 3 items from the HAPYS were selected by the project group based on the following considerations: items that have excellent face validity as evaluated by clinical experts (2 psychologists and 1 child and adolescent psychiatrist) and items indicative of high sensitivity to change as evaluated by looking at the sensitivity to change on similar items from the Whiteley-7 scale [34] using data from a randomized controlled trial of internet-delivered ACT for HA [14].

Textbox 3. Questions sent via SMS text message.

"On a scale ranging from 1 to 10, how well do the following statements describe your day? 1='does not describe it at all' and 10='describes it very well.'"

- "I have had persistent worries about my child's health."
- "I have been worried that my child suffers from a serious physical illness."
- "I have had the need to reassure myself by seeking a physician, examining my child, Googling symptoms, or something else."
- "My anxiety for my child's health has influenced my time together with my child."
- "I have done something in the past 24 hours that was important to me in spite of my anxiety."

Secondary Outcomes

The secondary outcome measures are full questionnaires answered 4 times during the study period. An overview of measures and data collection is presented in Table 1.

HAPYS Questionnaire

The HAPYS is a 26-item self-report questionnaire assessing HA by proxy, including an impact section with an additional 6 items [2]. The items are rated on a 5-point scale (0=not at all or never, 1=a little or rarely, 2=some or sometimes, 3=quite a lot or often, and 4=a lot or most of the time; range 0-104; higher

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scores indicate more anxiety), except for the impact section, which is rated on a 4-point scale (0=no; 1=yes, a little bit; 2=yes, quite a bit; and 3=yes, a great deal; range 0-18; higher scores indicate more impact). The HAPYS has shown good psychometric properties [2].

Adult Response to Children's Symptoms–Protect and Monitor Subscales (Revised)

The Adult Response to Children's Symptoms scale measures parental behavior in relation to the child having abdominal pain and consists of 4 subscales: protect, monitor, minimize, and distract [35]. For this study, a revised Danish version of the protect (13 items) [36] and monitor (4 items) subscales are used, replacing *abdominal pain* with *feels unwell*. The monitor subscale was translated into Danish for this study following World Health Organization (WHO) guidelines [37]. Both scales are measured on a 5-point scale ranging from 0=never to 4=always, averaged to a total score of 0 to 4, with higher scores indicating more protective and monitoring parental behavior. The original scale and the subscales present with satisfactory psychometric properties [38-40].

Pain Catastrophizing Scale–Parent Version

The Pain Catastrophizing Scale–Parent version consists of 13 items assessing parents' thoughts and feelings when their child has pain symptoms (rated on a scale ranging from 0 to 4, with 0=not at all and 4=extremely; range 0-52; higher scores indicate more catastrophizing) [41]. Psychometric investigation has demonstrated a 3-factor model and good internal consistency [41]. The Danish version was translated following WHO guidelines [37] and showed good face validity after cultural adaption [42].

Whiteley Index-6 Revised

HA and illness worries are assessed using the Whiteley Index [34,43]. In this study, we use the Whiteley Index-6 Revised, where items concerning somatic symptoms were eliminated, and an item about obsessive illness rumination was included ("Recurrent thoughts about being ill that are difficult to put out of your mind"), resulting in strengthened psychometric properties [44]. The scale consists of 6 items with scores ranging from 0=not at all to 4=a great deal and a summed score of 0 to 24, with higher scores representing higher levels of illness worry.

Symptom Checklist

Parents' levels of distress, anxiety, and depression are screened by the Symptom Checklist-12, which are subscales from the Symptom Checklist-90-Revised [45] that have shown satisfactory sensitivity and specificity in detecting depression and anxiety and general distress in relation to emotional psychiatric disorders [46,47]. The scales are scored from 1=not at all to 5=extremely, and the summed scores are divided by the number of items to yield a mean score (range 1-5).

WHO-5 Well-Being Index

The WHO-5 Well-Being Index is a 5-item rating scale measuring subjective well-being on a scale ranging from 0 to 5. The raw score ranging from 0 to 25 is multiplied by 4, providing a final score ranging from 0 to 100, where a lower score represents worse well-being [48]. This scale has demonstrated high validity and is considered a good outcome measure for wanted and unwanted treatment effects [48].

Feasibility Outcomes

Experience of Service Questionnaire

The Experience of Service Questionnaire measures parents' experience with the treatment they have received [49,50]. In this study, a modified version will be used where all questions related to physical settings are removed, and 7 questions about impact on the parent, child, and their interaction are added from the Danish revised version developed and used by the Department of Psychology and Behavioral Sciences, Aarhus University [51]. The 14 statements are scored as 0=not true, 1=partly true, and 2=true (range 0-28).

Negative Effects Questionnaire-20

The Negative Effects Questionnaire-20 measures 6 factors related to the negative effects of psychological treatment: encompassing symptoms, hopelessness, failure, stigma, dependency, and quality [52]. Each negative effect is rated on a scale ranging from 0=not at all to 4=extremely and attributed to either "The treatment I received" or "Other circumstances." The 20-item version has demonstrated satisfactory psychometric properties [52].

Internet Evaluation and Utility Questionnaire

The Internet Evaluation and Utility Questionnaire will be used to evaluate the experience of receiving internet-delivered treatment. Using 15 items, this instrument measures the usability and utility of an internet-delivered treatment program with questions answered on a 5-point rating scale [53].

SMS Text Message Evaluation

Three questions evaluating SMS text message data collection will inquire about how the participants experienced answering an SMS text message every day, whether it had any influence on their daily life, and whether their answers were affected by the fact that they had to do this every day. The questions are answered in free writing and will inform the researchers about the experience of this type of self-monitoring.

Evaluation of Modules

After each module, the participants are asked about the content of the modules answered in free writing.

Analyses

Analysis of Primary Outcome Measure

Visual Analysis

First, the data collected daily will be submitted to visual analysis, with the scores of the dependent variable on the y-axis and the measurement times on the x-axis. Six main features are visually examined using the guidelines provided in the study by Lane and Gast [54]: anxiety level in the phases, the variability of data points both within and among phases, trends in data, the immediacy of effect, the overlap of data points among phases, and the consistency of data patterns across participants [54,55]. As we have predicted a delayed treatment effect, we will explore the duration of the delay and whether this delayed effect is

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consistent across participants, instead of testing immediate effects as proposed by Ledford et al [55]. Data patterns will be analyzed in detail in all 3 phases.

Randomization Tests

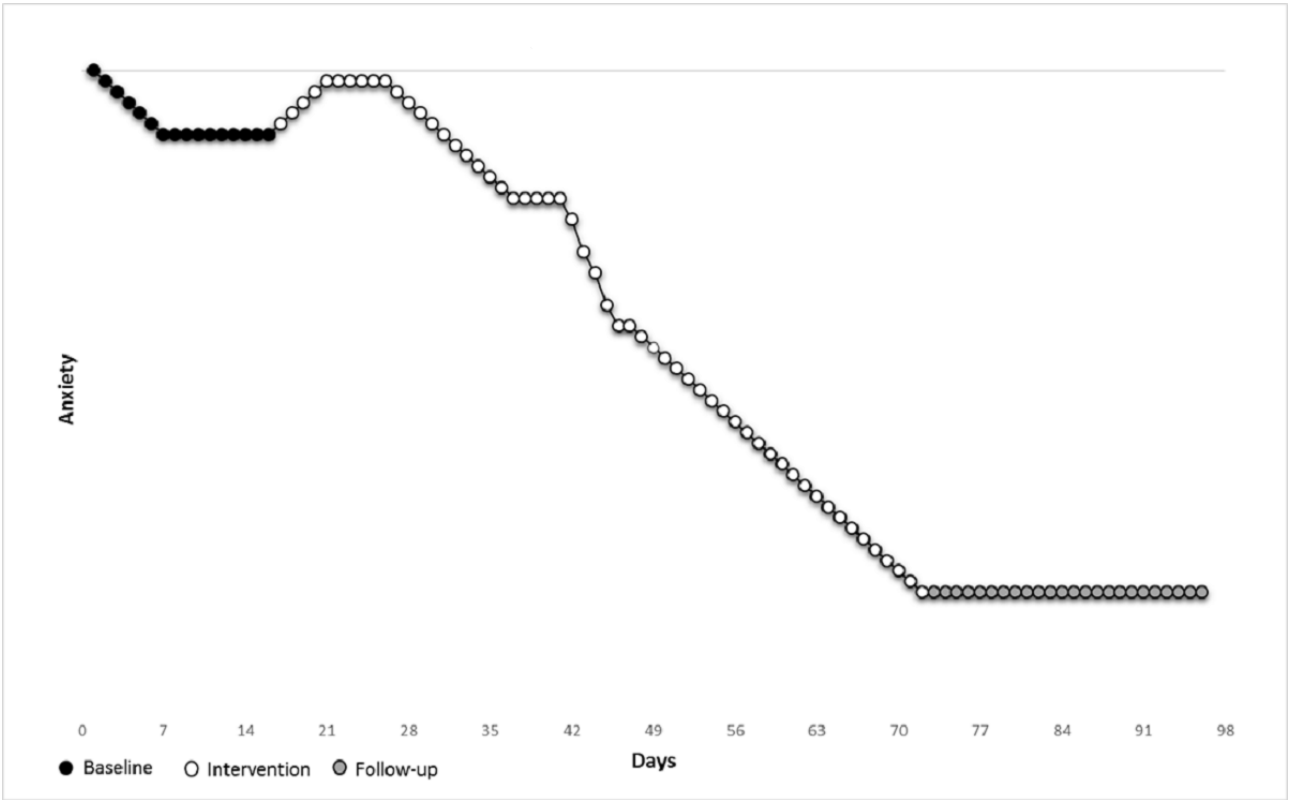
Randomization tests will be conducted for each participant to test the null hypothesis that PROXY will have no effect on the participants' anxiety [56-59]. A randomization test for a randomized single-case phase design uses the data in the order they were obtained and is based only on the randomly determined moment in time where the intervention is introduced. Two different test statistics will be used, as follows:

1. Primary test statistic: a mean comparison of phase A and BC will be carried out to investigate mean anxiety levels before and after treatment entry (mean A − mean BC = test statistic). As the starting point of phase B (intervention) is randomly determined and the follow-up phase does not include any new intervention methods, phases B and C are combined. As a mean comparison does not take into account the expected gradual and delayed effect of treatment, we also use a secondary test statistic.
2. Secondary test statistic: response functions [60] will be used to test the hypothesis of delayed and gradual reduction in anxiety (see the Aim section). Informed by previous research on internet-delivered treatment and exposure, we hypothesize that (1) assessment will have a positive effect on participants' anxiety level; (2) there will be an increase in anxiety at the beginning of treatment, followed by a gradual decrease that becomes steeper after exposure is introduced in module 5; and (3) the effect will be permanent throughout follow-up [14,61,62]. The response function predicted for participants in PROXY is illustrated in Figure 2. Importantly, this is not a prediction of exact anxiety scores but a predicted pattern. The absolute distance between the observed response pattern and the predicted response pattern is used as a test statistic.

As the exact course of treatment effect and the exact scores of anxiety are not known a priori, a multiverse approach will be followed exploring different response functions [60]. These different response functions will follow the same overall response pattern but with variations in the timing as well as the gradient of the response. The multiverse approach entails checking the degree to which the predicted response functions agree or converge with the collected data [63].

We will calculate the primary test statistic as well as the secondary test statistic for each possible randomization scenario of the treatment start using the obtained data. The proportion of test statistic values that are as extreme as, or more extreme than, the test statistic of the true treatment starting point is the *P* value of the randomization test [27,57-59]. This procedure is repeated with data from all 5 participants, and *P* values are combined using the additive method formulated by Onghena and Edgington [64].

Figure 2. Response function for participants in PROXY.



Effect Size Measure

In addition to the randomization tests, effect size measures will be calculated for each participant. An effect size measure is a standardized indicator that can be compared across studies and is not used as a test statistic in this study. Parker et al [65] recommend using the nonoverlap method Tau-*U* for SCED studies. Tau-*U* is particularly good if data show a baseline trend [65,66]. In addition, the effect sizes will be summarized across

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all 5 participants by calculating common descriptive statistics (median and range).

Analysis of Secondary Outcome Measures

The secondary outcome measures will be analyzed using descriptive statistics because data from only 5 participants will be included.

Results

The recruitment of parents began in June 2022. As of March 2, 2023, a total of 4 parents have been included in the study. Data collection was expected to cease in April 2023. The project was funded in September 2019. Results are expected to be published in 2024.

Discussion

Summary

HA by proxy is a novel research area where much still remains to be investigated. Recent studies suggest that parents experiencing this type of anxiety struggle with how to cope with their health-related worries about their child [4]. When a parent directs special attention toward bodily symptoms and demonstrates health worries regarding their child, research suggests negative consequences for the child, such as negative illness perception and maladaptive symptom coping [5,6,67,68]. Together, this underlines the need for the development and testing of more specific treatment options. Therefore, we developed the first systematic treatment program for HA by proxy, named PROXY.

In this study protocol, we described the treatment components of PROXY and how these components were established in the web-based treatment program. It is a collaboratively developed treatment program that involved clinical experts, web developers, and users in the process. PROXY received positive feedback from patients during development, and it seems to be a usable treatment program. Conducting this first testing and having patients receive treatment in the program may shed light on how to further improve the treatment content of PROXY.

The SCED approach was chosen for the first testing of PROXY because it is particularly useful when testing novel treatments for smaller patient groups [22]. It enables us to measure potential effect with a limited number of participants and to investigate treatment courses for each participant.

Strengths and Limitations

The randomization and replication across participants are important methodological strengths of this SCED study. By using randomization and randomization tests, confounding factors that are time related are statistically controlled for [27-29]. The external validity is strengthened when this procedure is repeated for several participants [69]. This accommodates the criticism against the standard single-case AB phase design of having low internal validity and a lack of multiple phases without data collected concurrently [70,71].

The selected test statistics for the randomization test are mean comparison and predicted response functions. Using test statistics based on predicted response functions for SCED studies is a newly described framework with the purpose of offering statistical analysis for data with nonlinearity and delayed or gradual changes to the primary outcome measure, as is often seen in psychological treatment [60]. The advantage of response functions is the ability to test very specific developmental trajectories—this is central when testing therapeutic interventions where the introduction of therapeutic techniques can be hypothesized to cause sudden and temporary increase or decrease in symptoms (eg, exposing oneself to feared stimuli may initially increase one's anxiety symptoms). However, the great specificity of the trajectory described by a response function also means that there is a high risk of failing to reject the null hypothesis. Therefore, primary analyses include visual analysis. Furthermore, using the multiverse approach enables the testing of whether slight adaptations of the characteristics of the trajectory are more fitting.

Importance of This Study

As the treatment for patients with HA by proxy has not been previously examined, this study is particularly important in terms of describing the treatment development and content as well as the research protocol for using a SCED for the first testing of PROXY. Applying a SCED provides us with the opportunity to investigate the effect of the treatment in a small sample and explore individual treatment courses in detail. Furthermore, the detailed visual analysis provides implicit tests of treatment mechanisms. This has relevance in clinical practice and can potentially be used to inform larger studies on the mechanisms of change and when and how the treatment may be offered to patients in the future [22]. In addition, this study may help to further refine the treatment content of PROXY.

Acknowledgments

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Data Availability

Data sharing is not applicable as this is a protocol paper where no data sets were generated or analyzed.

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Conflicts of Interest

None declared.

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Abbreviations

ACT: acceptance and commitment therapy
ARCS: Adult Response to Children's Symptoms
CBT: cognitive behavioral therapy
ESQ: Experience of Service Questionnaire
HA: health anxiety
HAPYS: Health Anxiety by Proxy Scale
iACT: internet-delivered acceptance and commitment therapy
PCS-P: Pain Catastrophizing Scale–Parent version
REDCap: Research Electronic Data Capture
SCAN: schedules for clinical assessment in neuropsychiatry
SCED: single-case experimental design
SCL: Symptom Checklist
WHO-5: World Health Organization-5 Well-Being Index

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Protocol

Caries Detection in Primary Teeth Using Intraoral Scanners Featuring Fluorescence: Protocol for a Diagnostic Agreement Study

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Abstract

Background: Digital methods that enable early caries identification can streamline data collection in research and optimize dental examinations for young children. Intraoral scanners are devices used for creating 3D models of teeth in dentistry and are being rapidly adopted into clinical workflows. Integrating fluorescence technology into scanner hardware can support early caries detection. However, the performance of caries detection methods using 3D models featuring color and fluorescence in primary teeth is unknown.

Objective: This study aims to assess the diagnostic agreement between visual examination (VE), on-screen assessment of 3D models in approximate natural colors with and without fluorescence, and application of an automated caries scoring system to the 3D models with fluorescence for caries detection in primary teeth.

Methods: The study sample will be drawn from eligible participants in a randomized controlled trial at the Royal Children's Hospital, Melbourne, Australia, where a dental assessment was conducted, including VE using the International Caries Detection and Assessment System (ICDAS) and intraoral scan using the TRIOS 4 (3Shape TRIOS A/S). Participant clinical records will be collected, and all records meeting eligibility criteria will be subject to an on-screen assessment of 3D models by 4 dental practitioners. First, all primary tooth surfaces will be examined for caries based on 3D geometry and color, using a merged ICDAS index. Second, the on-screen assessment of 3D models will include fluorescence, where caries will be classified using a merged ICDAS index that has been modified to incorporate fluorescence criteria. After 4 weeks, all examiners will repeat the on-screen assessment for all 3D models. Finally, an automated caries scoring system will be used to classify caries on primary occlusal surfaces. The agreement in the total number of caries detected per person between methods will be assessed using a Bland-Altman analysis and intraclass correlation coefficients. At a tooth surface level, agreement between methods will be estimated using multilevel models to account for the clustering of dental data.

Results: Automated caries scoring of 3D models was completed as of October 2023, with the publication of results expected by July 2024. On-screen assessment has commenced, with the expected completion of scoring and data analysis by March 2024. Results will be disseminated by the end of 2024.

Conclusions: The study outcomes may inform new practices that use digital models to facilitate dental assessments. Novel approaches that enable remote dental examination without compromising the accuracy of VE have wide applications in the research environment, clinical practice, and the provision of teledentistry.

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KEYWORDS

dental caries; diagnosis; oral; technology; dental; image interpretation; computer-assisted; imaging; 3D; quantitative light-induced fluorescence; diagnostic agreement; intra oral scanners; oral health; teeth; 3D model; color; fluorescence; intraoral scanner; device; dentistry

Introduction

Background

Dental caries is the most prevalent chronic disease in childhood [1]. It causes mineral loss within the dental hard tissue, which results in visual changes in the enamel in the initial stages [2]. With increasing severity, demineralization advances into the dentine-pulp complex, and a cavity can develop [2]. More severe caries can result in pain, difficulty eating, and infection, and its management is more invasive and costly from an individual and public health perspective. In contrast, managing early caries is noninvasive, and damage to the tooth surface is reversible [3]. Epidemiological research should use methods that enable early disease detection to better target caries prevention and timely intervention programs during the early years.

Dental Caries Detection in Epidemiological Research

In epidemiological research, visual examination (VE) is the standard method for detecting dental caries on visible tooth surfaces. VE can be subjective, particularly for early disease detection and monitoring. Validated indices, such as the International Caries Detection and Assessment System (ICDAS), improve the accuracy of VE for early caries detection [4-6]. ICDAS classifies caries based on severity, and a strong correlation exists between ICDAS and histological caries depth [7,8]. Studies using ICDAS report good inter- and intraexaminer reliability. Training and calibration improve examiner accuracy and reliability and are essential for standardizing examiners [9-11].

Epidemiological research, particularly multisite studies, requires the presence of multiple qualified dental examiners to undertake VE at the time of data collection, which is time and resource intensive. Digital photography has been suggested as an alternative to VE in these settings, where images are taken and assessed by trained and calibrated examiners. Boye et al [12] demonstrated high examiner agreement (weighted kappa, κ_w>0.9) between VE and remote assessment of 2D images. High accuracy for caries detection has been reported using 2D images compared to a gold standard examiner; however, the threshold used for disease detection in these studies is mostly tooth cavitation. Such thresholds cannot inform and drive early disease management strategies. Novel methods that facilitate the remote assessment of dentitions without compromising accuracy relative to VE for early disease detection would have broad applications in the research setting and beyond. Intraoral scanning technology provides such a method, yet its performance for caries detection in children's primary teeth has yet to be established.

Intraoral Scanners for Dental Caries Detection

Intraoral scanners (IOSs) are handheld devices that create 3D digital models of the teeth and surrounding structures [13]. Digital representation of the teeth is achieved using specialized hardware (to scan the teeth) and software (to combine the data received and create 3D models). Scanners shine light onto a tooth region, and the distance between the area of interest and the scanner sensor is calculated via optical triangulation, confocal imaging, or active wave front sampling [14,15]. Numerous data points regarding tissue geometry are generated and used to construct a 3D model [14]. Red, green, and blue signals received from the tissues are applied to the model as color texture. Recently, light-induced fluorescence technology has been incorporated into the hardware of a commercially available IOS to enhance early caries detection (TRIOS 4 and 5) [16].

Light fluorescence technology is suitable for detecting and quantifying early carious lesions [17]. Exposure to blue-violet wavelength light causes sound dental tissue to auto-fluoresce green and demineralized carious dental tissue to appear darker [17]. The diagnostic capability of light fluorescence is enhanced because porphyrins, a metabolite of bacteria associated with dental caries, emit red fluorescence when exposed to light at this wavelength [18].

The interpretation of light fluorescence can be subjective, as it depends on the skill and experience of the dental practitioner. A study investigating occlusal caries detection of permanent teeth with and without fluorescence found no difference in accuracy between on-screen assessment and VE, suggesting that on-screen assessment of 3D models could be used for early caries detection and as a potential alternative to VE [19]. To our knowledge, there are no studies that have investigated the validity of on-screen assessment of 3D models for caries detection in primary teeth.

Recent advances have seen the development of computational methods as a more objective measure to quantify dental caries and support clinical diagnosis. TRIOS has developed an automated caries scoring system for their software that can automatically classify caries on occlusal surfaces based on color and fluorescence changes (TRIOS Patient Monitoring [TPM]; version 2.3; 3Shape TRIOS A/S) [16]. When comparing the diagnostic performance as quantified by the area under the curve (AUC), early in vitro and in vivo validation studies suggest that the automated score is comparable to VE at the early (AUC VE

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0.71 vs 0.76) and moderate disease thresholds (AUC VE 0.90 vs 0.90), based on a histological reference standard for permanent teeth [20]. A separate investigation into the validity of this algorithm in primary teeth concluded it had comparable performance (AUC 0.88) to VE (AUC 0.96) for caries detection of primary tooth occlusal surfaces [21]. The latter was a small in vitro feasibility study; consequently, results should be interpreted cautiously and not generalized to the clinical setting. The in vivo performance of automated assessment of 3D models for caries detection in primary teeth has yet to be established.

One of the problems with investigating early caries detection methods in realistic settings is the choice of a reference standard for method comparison, as histological or operative references are rarely feasible or ethical. It is argued that when VE alone is used as a gold standard, measures of diagnostic accuracy (sensitivity and specificity) may overestimate the true accuracy of the caries detection method under investigation [22,23]. Instead, reporting on the diagnostic agreement has been suggested to be more appropriate. Diagnostic agreement quantifies the similarity between methods in detecting the outcome of interest to be used interchangeably [24].

This study describes the protocol and statistical analysis plan for determining the diagnostic agreement between VE, on-screen, and automated caries detection methods using 3D models in children.

Methods

Aims and Objectives

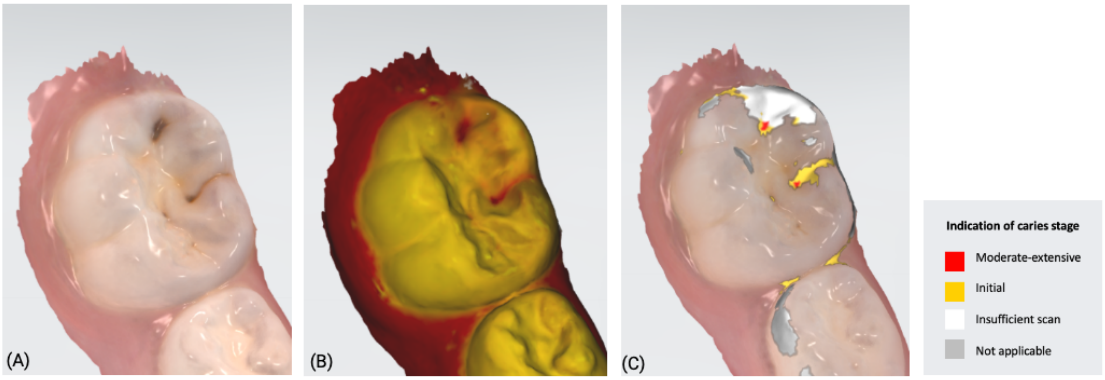
The specific study objectives are to, first, determine and compare the diagnostic agreement between VE and on-screen visual assessment of 3D models in approximate natural colors with and without fluorescence to detect and classify carious lesions on visible tooth surfaces in primary teeth. The second objective is to determine the diagnostic agreement between VE and the automated caries scoring system for detecting and classifying occlusal carious lesions in primary teeth. Finally, the third objective is to explore the impact of caries threshold, tooth surface examined (smooth vs occlusal), and enamel defects' presence on the reported agreement estimates between caries detection methods.

Study Design

This is a diagnostic agreement study, as VE is not considered a gold standard in this setting [23]. Dental caries in this study is defined as primary coronal caries. Data sources (age at dental visit, sex, VE data, and 3D models) will be retrospectively sourced from a sample of children who underwent VE using the ICDAS and intraoral scanning with the TRIOS 4 to produce 3D digital models.

The 3D models for each eligible participant will be subject to an on-screen assessment by 4 qualified dental practitioners. Each practitioner will examine all 3D models at 2 separate time points. An on-screen assessment of 3D models based on tissue geometry and approximate natural colors (excitation to visible white light) will take place first (Figure 1A), followed by an on-screen assessment with the addition of fluorescence texture (excitation to light at 415 nm; Figure 1B). An interval of at least 4 weeks will follow to minimize recall bias before the on-screen assessment process is replicated. Occlusal surfaces of primary molars will be examined using the automated caries scoring system at a single time point only (Figure 1C). Examiners will be blinded to all clinical examination data and automated caries scores when scoring the 3D scans.

Figure 1. Caries detection methods based on 3D models obtained using an intraoral scanner.



Study Setting and Participants

The study sample will be drawn from eligible participants in an existing randomized controlled trial, the Melbourne Infant Study Bacille Calmette Guérin (BCG) for Allergy & Infection Reduction (MISBAIR; ClinicalTrials.gov NCT01906853; for a complete description of the trial, please refer to the MISBAIR study protocol) [25]. English-speaking immunocompetent pregnant women scheduled for birth at hospitals servicing Werribee, Ballarat, Geelong, and Melbourne in Victoria, Australia, from mid-2013 to mid- to late 2016 provided consent for their infants to participate in a longitudinal and randomized controlled trial to determine if BCG immunization within the first 10 days of life prevents the development of allergy and infection in early childhood. Infants were excluded if they had any conditions at birth that would contraindicate the use of live vaccines. The MISBAIR trial included a 5-year-old study visit where a clinical assessment (including dental assessment) was undertaken (219/536, 40.9% remaining MISBAIR participants). All study visits occurred between January 31, 2021, and March 31, 2022, at the Murdoch Children's Research Institute in Melbourne.

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Participant Eligibility Criteria

MISBAIR participant data will be included for analysis in this study if participants meet the following criteria: (1) attended the 5-year-old study visit for MISBAIR (target age 4-6 years), (2) completed of a VE during the 5-year-old study visit, (3) acquired an intraoral scan at the same time as the VE, and (4) provided informed consent for the analysis of dental data and on-screen assessment of 3D models.

Tooth Surface Inclusion Criteria

For each participant, a tooth surface will be eligible for on-screen assessment if it (1) has been examined as part of the dental exam, (2) is from a primary tooth, and (3) is visible on the 3D model.

Tooth Surface Exclusion Criteria

Tooth surfaces will be excluded from on-screen assessment if (1) they have a sealant, direct or indirect restoration; (2) the tooth surface visibility on the 3D model is impeded by calculus, debris, or plaque; and (3) less than one-third of the surface is visible due to insufficient or missing scan data.

Tooth surfaces will be excluded from the application of the automated caries scoring system if they (1) have a sealant, direct or indirect restoration; (2) have an enamel defect; (3) are not a primary molar occlusal surface; and (4) less than one-third of the surface is visible due to insufficient or missing scan data.

Dental Examination Protocol at the 5-Year-Old Study Visit

VE Protocol

VEs occurred with participants in a semisupine position on an adjustable examination bed. The examiner stood to the side of, or behind, the participant. A portable LED light (220 lumens NÄVLINGE clamp spotlight IKEA) and a dental mirror were used and positioned to provide maximum illumination and visibility of the oral cavity without magnification. Cotton rolls and swabs were used to dry teeth and remove plaque. Compressed air was not used. Universal infection control standards and additional COVID-19 precautions were adhered to for all examinations.

Dental examinations were conducted by trained and calibrated registered dental practitioners (BJ and Jennifer Copley) with experience and prior training in using the ICDAS index in research settings. Examiner BJ is an oral health therapist with 13 years of clinical experience, and examiner Jennifer Copley is an oral health therapist with 5 years of clinical experience. Before commencing VEs, both examiners had participated in the web-based ICDAS and International Caries Classification and Management System (ICCMS) e-learning modules [26]. Additionally, a senior researcher and pediatric dentist (MS) with experience in conducting surveys using ICDAS and enamel defect indices facilitated a presentation on ICDAS using the ICDAS or ICCMS examiner training materials and training materials for the use of a modified molar incisor hypomineralization (MIH) index to assess for enamel defects (with permission from the author) [27]. A 2-hour calibration session on the application and interpretation of the indices, followed by a computer-based calibration exercise, took place. The computer-based calibration exercises were repeated until both examiners reached an intra- and interexaminer agreement of κ_w>0.8.

Dental caries experience was recorded for each tooth surface using the 2-digit ICDAS criteria [28]. Code 01 could not be scored for smooth surfaces due to a lack of compressed air. Enamel defects were recorded using a modified MIH index describing each surface's clinical presentation and the extent of the defect [29]. All tooth surfaces were examined using a systematic approach. The score given was the most severe of the 2 clinical presentations if multiple lesions were present on the same tooth's surface.

All dental examination data were collected and managed using Research Electronic Data Capture (REDCap; Vanderbilt University) tool hosted at Murdoch Children's Research Institute [30,31]. REDCap is a secure, web-based software platform designed to support data capture for research studies.

Intraoral Scanning

Immediately following the VE, intraoral scanning took place using the TRIOS 4 scanner. This generation scanner has a high accuracy and fast acquisition time relative to other scanners on the market for complete arch scanning [32]. It also has specialized fluorescence technology built into its hardware which exposes teeth to 415-nm light during scanning. Light emitted from the teeth passes through a filter in the scanner (which filters out blue light) to be received by the scanner sensor. The fluorescence signal overlays onto the 3D models as green fluorescence and red fluorescence texture, aided by commercial software (TPM; version 2.3, Dental Desktop and TRIOS; 3Shape TRIOS A/S).

The clinical examiners were trained to use the 3Shape TRIOS software interface and intraoral scanning protocols. Before scanning, the dental lamp was switched off, and the window blinds were closed to limit external light during the scanning process as per manufacturer instructions [33]. Teeth were dried with gauze or cotton rolls, and the manufacturer-recommended scanning strategy was followed. The scanning procedure was considered adequate when the software had obtained sufficient information about tooth color and fluorescence for the region of interest. If the scan was incomplete, the reasons why the scanning procedure was inadequate were documented. The reasons for insufficient scan data included the scanner tip being too big to accommodate, gag reflex, and behavioral or developmental issues that limited cooperation with the scanning procedure. Both complete and incomplete 3D models were saved with the participant's unique identifier in the dental desktop software.

Dental Examination Protocol for 3D Models Obtained From an IOS

On-Screen Assessment

3D models will be examined in postprocessed formats on a laptop with a 15-inch monitor (Alienware, DELL). On-screen assessment in approximate natural colors and featuring fluorescence will occur using a noncommercial software

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(developed by 3Shape) that allows for visualization of the 3D models similar to the commercially available TPM software but permits faster examination of multiple models, making the viewing process more efficient for this study. 3D models will be viewed in rooms with natural lighting following a standard operating procedure. Examination periods will be at most 3 hours without breaks, and each 3D model will be viewed for less than 15 minutes to avoid examiner fatigue. The viewing time for each scan will be recorded.

Each model will be viewed first with color and then without color to inspect tissue geometry and possible surface cavitation. Dental caries experience for on-screen assessment of 3D models in color will be recorded using a merged ICDAS index. Codes 01 and 02 will be combined as "initial caries" because the 3D models cannot be dried, and codes 05 and 06 will be combined as "extensive caries" as discriminating between these latter categories is not of interest for this study (Table 1). These merged ICDAS categories still provide sufficient information about caries depth to support clinical decision-making [8,9,34].

Table 1. Caries classification criteria for on-screen assessment of 3D models obtained with TRIOS intraoral scanners.

Caries extent	Merged ICDAS index: on-screen assessment—color		Merged modified ICDAS index: on-screen assessment—fluorescence	
Sound (ICDAS 0)	Sound tooth surfaces which show no evidence of visible caries		Sound surfaces (yellow-green fluorescence) with no visible fluorescence change (no red fluorescence)	
Initial (ICDAS 1-2)	First or distinct visual changes in enamel seen as carious opacity or visible discoloration (white spot lesion and brown carious discoloration) not consistent with clinical appearance of sound enamel and which show no evidence of surface break down or underlying dentine shadowing		First or distinct visual changes in enamel seen with orange-red fluorescence and altered green fluorescence not consistent with the appearance of sound enamel and which show no evidence of surface breakdown or underlying red fluorescence from dentine	
Moderate (ICDAS 3)	A white or brown spot lesion with localized microcavitation of enamel without visible dentine exposure		Lesion with localized enamel breakdown with a distinct fluorescence change (usually intense red and reduced green), without visible dentine exposure. Usually, poorly delineated fluorescence change is seen	
Moderate (ICDAS 4)	Obviously discolored dentine or dark shadow visible through apparently intact or microcavitated enamel, which has originated on the surface being evaluated		Lesion with or without enamel breakdown and poorly delineated distinct fluorescence change (intense red fluorescence and significantly reduced green fluorescence which appears almost black), deriving from dentine	
Extensive (ICDAS 5-6)	A distinct cavity in opaque or discolored enamel with visible dentine		Distinct cavity with visible fluorescence changes and exposed dentine	

3D models will then be viewed with the addition of fluorescence texture and dental caries will be recorded using a merged ICDAS index previously described by Ferreira Zandoná et al [35], where each scoring criteria has been modified to incorporate fluorescence features (Table 1). This index enables a consistent approach to classifying carious lesions using fluorescence and has been previously validated for the on-screen assessment of 3D models [19]. If multiple lesions are present on the same tooth's surface, the caries classification will be the more severe of the 2 clinical presentations, per VE protocol. Data will be recorded using REDCap.

A total of 4 examiners will undertake on-screen assessment. Before commencing on-screen assessment, all examiners will undergo a 2-hour training workshop followed by calibration exercises. Training will focus on applying a merged and modified ICDAS criteria to a data set of 3D models with fluorescence. A dentist and expert in using modified ICDAS to interpret 3D models (SM) will facilitate training. To establish interrater agreement, each examiner will independently undertake an on-screen assessment of a training-calibration data set of 200 examination sites. This data set includes carious lesions and sound surfaces which have been validated histologically as part of a previous study [16,20]. Examiners

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will repeat this calibration exercise 2 weeks after the initial assessment to establish an intrarater agreement. Examiners will repeat the calibration process until the agreement exceeds κ_w>0.7.

Automated Caries Scoring System

The automated caries scoring system will be applied to the occlusal surfaces of primary teeth and visualized using the commercially available software (TPM version 2.3; 3Shape TRIOS A/S) on a laptop with a 15-inch monitor (Alienware, DELL). Using a predefined logistic regression function, this software identifies a healthy reference standard per tooth and compares regions of interest to the healthy reference, to quantify fluorescence changes [16]. The automated system classifies a region of interest as caries based on the predefined cut offs which have been validated using permanent tooth histology as a reference standard, to indicate relative caries depth. The software classifies a surface as sound, initial caries (ICDAS 01/02) or moderate-extensive caries (ICDAS>03), and this is indicated on the 3D models as a yellow or red overlay respectively (Figure 1). The automated classification will be recorded using REDCap.

Sample Size

This is a retrospective study drawing all eligible participants from the MISBAIR trial who underwent the dental assessment at their 5-year-old study visit.

Outcome Measures

For agreement analyses, ICDAS and modified ICDAS codes will be collapsed for each surface into four categories labeled sound surface (0), initial caries (1), moderate (2), and extensive caries (3). A binary dental caries variable will be created for each surface, and the detection threshold will be initial caries (0 vs 1, 2, and 3).

Statistical Analysis

Data checking and cleaning will take place before analysis. Descriptive statistics for patient characteristics such as age, sex, caries prevalence, and the proportion of children with enamel defects will be reported. The total number of tooth sites included in the analysis will be reported.

Descriptive characteristics for the rater population will be reported, including qualification, clinical background, years of experience, and training results for each rater. Interrater and intrarater reliability for on-screen assessment of 3D models based on color and fluorescence using the intraclass correlation coefficient will be reported for all examiners. These estimates will be obtained from a multilevel model fitted to the surface-level data, accounting clustering (see below), and zero inflation.

To assess agreement among methods, we will undertake both surface-level and individual-level analyses. At the surface level, caries data naturally have 3 levels with surfaces clustered within a tooth, which are clustered within an individual. Therefore, for this analysis, we will use multilevel logistic regression to estimate method agreement while accounting for clustering for the tooth. Specifically, separate multilevel models will be fitted to compare VE with each of the alternative methods by including the variable method (VE vs on-screen assessment of 3D models in approximate natural colors, on-screen assessment of 3D models in approximate natural colors featuring fluorescence, and automated system) as the fixed effect. The coefficient estimates for the variable method will be used to indicate the level of agreement. The multilevel model will be fitted with a zero-inflated binomial distribution.

At the individual level, a numerical variable representing the number of lesions per individual will be generated and analyzed with 2 approaches. First, Bland-Altman method agreement analysis will be performed using a regression approach. Specifically, a model will be constructed to regress the difference between each pair of methods on their average [36]. The analysis will be repeated for each possible pair of methods. Second, for each possible pair of methods, an intraclass correlation coefficient will be estimated from a multilevel model fitted to the paired data consisting of the 2 measures for each individual obtained from the 2 methods, fitted with a zero-inflated Poisson distribution.

A sensitivity analysis will explore the impact of the diagnostic threshold used on agreement estimates. Analyses will be repeated with the caries data dichotomized at alternative thresholds: the moderate and extensive thresholds. In the analysis of the moderate threshold, sound and initial surfaces will be labeled caries absent (0) and all remaining categories (moderate-extensive) will be labeled caries present (1). In the analysis of the extensive threshold, sound, initial, and moderate caries will be combined and labeled as caries absent (0) and only teeth with extensive caries will be marked as caries present (1). To evaluate if the surface location and presence of enamel defects impact the diagnostic agreement estimates, these variables will be included as additional variables in the regression models for the surface-level analyses, including interaction terms with the method. The surface location variable will have 3 levels for each visible tooth surface (occlusal, smooth, and proximal). Enamel defects will be a binary variable, defined as present or absent per person. The sensitivity analysis to compare the agreement between on-screen assessment of 3D models in approximate natural colors and on-screen assessment of 3D models in approximate natural colors featuring fluorescence will include additional variables, rater and timing, as fixed effects.

Ethical Considerations

The MISBAIR trial has ethical and governance approval from Mercy Health Human Research Ethics Committee (HREC, No. R12-28) and Royal Children's Hospital (RCH) HREC (HREC No. 33025). Informed consent to participate in the study and to share dental data to validate and develop intraoral scanning technology for dental health assessment was obtained from participants' parents or guardians. Participant records sourced have a unique identifier and are not reidentifiable to the dental team. This diagnostic agreement study has ethical approval from the RCH HREC (RCH HREC No. 88321). It will be conducted according to the principles outlined in the Declaration of Helsinki. This protocol has registration with the Australian New

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Zealand Clinical Trials Registry (ANZCTR; registration ACTRN12622001237774p).

Results

As of October 2023, automated caries scoring of primary molar occlusal surfaces on the 3D models for 213 eligible participants has been completed. Data are currently being analyzed, with expected results to be published within 6 months' time. On-screen assessment of 3D models based on color and fluorescence has commenced and is expected to be completed in March 2024, with results disseminated by December 2024.

The results of this study will be reported per the Guidelines for Reporting Reliability and Agreement Studies [37].

Discussion

This protocol aims to fill a knowledge gap by describing an approach for determining the diagnostic agreement between VE using ICDAS and on-screen assessment of 3D models featuring fluorescence obtained with an IOS.

Intraoral scanning is increasingly being adopted in dentistry as it offers improved clinical workflows for patient assessment and treatment planning, particularly in the disciplines of prosthodontics, orthodontics, and periodontics [13,38,39]. The role of scanning technology in supporting clinical diagnostics is an emerging research area [19,20,40-43]. There is paucity in the literature describing on-screen assessment of 3D models as a method for caries detection.

A strength of our study is the consideration of different approaches to analyze agreement. Our use of multilevel generalized linear regression models to analyze surface-level dental caries data has several strengths. First, caries from the same individual are more correlated than those between individuals. If this clustering is ignored, the estimated variance may be misleadingly small [44]. We will use multilevel models that account for clustering. Second, the multilevel regression approach allows for estimating method agreement while accounting for variability due to the influence of the rater and timing of assessment [45]. Finally, because all eligible primary teeth surfaces will be analyzed the high proportion of sound surfaces will result in zero-inflated outcome data. We will address this by fitting a generalized linear regression framework allowing the use of a zero-inflated binomial distribution; whereas traditional agreement methods, such as the κ statistic, are limited in this context [46]. A limitation of the statistical approach is that the coefficient estimates derived from the multilevel model do not quantify absolute agreement. As an alternative analysis, we will analyze the total caries at the individual level with a regression-based Bland-Altman agreement analysis [36]. The excess of zeros and, hence, the nonnormal distribution of the data precludes the calculation of the limit of agreement estimates that are clinically interpretable. Consequently, we will use the intraclass correlation coefficient derived from a multilevel model fitted with a zero-inflated Poisson distribution, acknowledging that this is influenced by the variability in the population.

Further limitations include the retrospective study design, as multiple raters did not undertake VE over multiple time points, so we cannot account for the effects of this in the analysis. The prospective design of the onscreen assessment is a strength, as it has been designed to capture these effects.

The study results will inform whether 3D models can be used interchangeably with VE for detecting and classifying dental caries. This work serves as a proof of concept for performing dental examinations digitally. Study outcomes may change existing practices for data collection in children for epidemiological research. The findings may also provide insight into how scanners can be used more broadly in the provision of teledentistry services and to improve the access of young children to comprehensive dental examinations.

Acknowledgments

We thank the Melbourne Infant Study Bacille Calmette Guérin for Allergy and Infection Reduction participants and their families for participating in the dental assessments. We thank examiner Jennifer Copley for her support with data collection. Figures were created with BioRender [47]. Images in Table 1 were adapted from 3Shape TRIOS A/S training materials with permission from 3Shape TRIOS A/S and coauthor SM, and the images in Figure 1 were obtained from the TRIOS Patient Monitoring Software. BJ's PhD stipend is funded by 3Shape TRIOS A/S fund according to an industrial PhD agreement with Murdoch Children's Research Institute. MS is funded by a Melbourne Children's Clinician-Scientist Fellowship. MMB is funded by the Australian Government NHMRC Investigator Grant (ID 2009572).

Data Availability

The data sets generated and analyzed during this study are not publicly available due to consent not obtained from participants for public sharing of data but are available from the corresponding author on reasonable request.

Authors' Contributions

BJ was responsible for conceptualizing the study, developing the research questions, study design, and protocol development. MS, CV, DB, NK, and SM contributed to supporting study conceptualization and development of the research questions, protocol, and study design as members of the research team. TC and MMB contributed to developing the statistical analysis plan. BJ was

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responsible for drafting this study. MMB and TC helped draft the statistical analysis section of this study. All authors provided feedback and comments on the drafts and have read and approved the final version.

Conflicts of Interest

Coauthor CV is employed at 3Shape TRIOS A/S. SM was employed at 3Shape TRIOS A/S when this study was drafted. The remaining authors declare no competing interests.

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Abbreviations

ANZCTR: Australian New Zealand Clinical Trials Registry
AUC: area under the curve
BCG: Bacille Calmette Guérin
HREC: Human Research Ethics Committee
ICCMS: International Caries Classification and Management System
ICDAS: International Caries Detection and Assessment System
IOS: intraoral scanner
MIH: molar incisor hypomineralization
MISBAIR: Melbourne Infant Study-Bacille Calmette Guérin for Allergy & Infection Reduction
RCH: Royal Children's Hospital
REDCap: Research Electronic Data Capture
TPM: TRIOS Patient Monitoring
VE: visual examination

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Protocol

Prolonged mHealth-Based Arrhythmia Monitoring in Patients With Hypertrophic Cardiomyopathy (HCM-PATCH): Protocol for a Single-Center Cohort Study

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Abstract

Background: Patients with hypertrophic cardiomyopathy (HCM) are at increased risk of sudden cardiac death (SCD) due to ventricular arrhythmias and other arrhythmias. Screening for arrhythmias is mandatory to assess the individual SCD risk, but long-term electrocardiography (ECG) is rarely performed in routine clinical practice. Intensified monitoring may increase the detection rate of ventricular arrhythmias and identify more patients with an increased SCD risk who are potential candidates for the primary prophylactic implantation of an implantable cardioverter-defibrillator. To date, reliable data on the clinical benefit of prolonged arrhythmia monitoring in patients with HCM are rare.

Objective: This prospective study aims to measure the prevalence of ventricular arrhythmias in patients with HCM observed by mobile health (mHealth)–based continuous rhythm monitoring over 14 days compared to standard practice (a 24- and 48-h long-term ECG). The frequency of ventricular arrhythmias in this 14-day period is compared with the frequency in the first 24 or 48 hours for the same patient (intraindividual comparison).

Methods: Following the sample size calculation, 34 patients with a low or intermediate risk for SCD, assessed by the HCM Risk–SCD calculator, will need to be recruited in this single-center cohort study between June 2023 and February 2024. All patients will receive an ECG patch that records their heart activity over 14 days. In addition, cardiac magnetic resonance imaging and genetic testing data will be integrated into risk stratification. All patients will be asked to complete questionnaires about their symptoms; previous therapy; family history; and, at the end of the study, their experience with the ECG patch-based monitoring.

Results: The Hypertrophic Cardiomyopathy: Clinical Impact of a Prolonged mHealth-Based Arrhythmia Monitoring by Single-Channel ECG (HCM-PATCH) study investigates the prevalence of nonsustained ventricular tachycardia (ie, ≥3 consecutive ventricular beats at a rate of 120 beats per minute, lasting for <30 seconds) in low- to intermediate-risk patients with HCM (according to the HCM Risk–SCD calculator) with additional mHealth-based prolonged rhythm monitoring. The study was funded by third-party funding from the Department of Cardiology and Intensive Care Medicine, University Hospital Ostwestfalen-Lippe of Bielefeld University in June 2023 and approved by the institutional review board in May 2023. Data collection began in June 2023, and we plan to end the study in February 2024. Of the 34 patients, 26 have been recruited. Data analysis has not yet taken place. Publication of the results is planned for the fall of 2024.

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Conclusions: Prolonged mHealth-based rhythm monitoring could lead to differences in the prevalence of arrhythmias compared to 24- and 48-hour long-term ECGs. This may lead to improved identification of patients at high risk and trigger therapeutic interventions that may provide better protection from SCD or atrial fibrillation–related complications such as embolic stroke.

Trial Registration: Deutsches Register Klinischer Studien DRKS00032144; https://tinyurl.com/498bkrx8

International Registered Report Identifier (IRRID): DERR1-10.2196/52035

(JMIR Res Protoc 2023;12:e52035) doi:10.2196/52035

KEYWORDS

hypertrophic cardiomyopathy; nonsustained ventricular arrhythmia; sudden cardiac death; implantable cardioverter-defibrillator; long-term ECG; digital medicine; long-term electrocardiography

Introduction

Cardiac arrhythmias, especially nonsustained ventricular tachycardia (nsVT) and atrial fibrillation (AF), are important comorbidities of hypertrophic cardiomyopathy (HCM) [1,2]. In particular, nsVT is a predictor of sudden cardiac death (SCD) [3,4]. A well-established risk assessment is the HCM Risk–SCD calculator, which queries, among other parameters, the occurrence of nsVT. It is used for recommendations regarding the primary prophylactic implantation of an implantable cardioverter-defibrillator (ICD) [4].

Therefore, adequate screening for nsVT in patients with HCM is highly relevant. It must be assumed that more intensive monitoring can increase the detection rate of cardiac arrhythmias. For example, in one study, a 14-day long-term Holter electrocardiography (ECG) detected nsVT in up to 75% of intermediate-risk patients with HCM. In the same group, a 48-hour long-term ECG revealed nsVT in only 34% of patients [5,6]. In addition, a trial of 100 patients with HCM in Spain showed a 62% rate of nsVT during 30 days of monitoring compared to 8% in the first 24 hours [7]. In another study, 24- to 48-hour long-term Holter ECGs showed at least one AF episode in 23% of patients with HCM [8]. It can be speculated that prolonged ECG monitoring may increase AF detection, leading to the earlier introduction of oral anticoagulants to prevent embolic complications. Patients with HCM with AF have an exceptionally high risk of embolic complications [1].

The feasibility of mobile health (mHealth)–based screening for arrhythmias has not yet been thoroughly investigated in patients with HCM. Holter long-term ECGs and implantable loop recorders are established in everyday clinical practice. Whereas prolonged Holter monitoring is associated with patient discomfort, implantable devices are expensive, have some limitations concerning specificity in arrhythmia detection [9], and carry a risk of surgical intervention for implantation and explantation. More recently, mHealth ECG recorders have become increasingly available, and thus, it should be investigated to what extent mHealth-based prolonged ECG monitoring is feasible and accepted by patients.

In addition to the HCM Risk–SCD calculator, there is increasing evidence that the presence of late gadolinium enhancement and its extent is associated with an increased SCD risk in patients with HCM [10,11]. Furthermore, genotyping is recommended for patients with HCM by the current European Society of Cardiology guidelines since 60% of patients have mutations in cardiac sarcomere protein genes, which have been associated with an increased SCD risk [1,12]. Therefore, we aim to correlate the occurrence and frequency of nsVT associated with late gadolinium enhancement on cardiac magnetic resonance imaging (cMRI) or evidence of a pathogenic mutation. The extent of late gadolinium enhancement on cMRI will be graded as mild (<5%), moderate (5%-15%), or severe (>15%) using a semiquantitative score based on the standard left ventricular 17-segment model.

Prolonged monitoring for cardiac arrhythmias may have relevant implications for clinical decisions, such as primary prophylactic ICD implantation for nsVT and anticoagulation or rhythm-control measures for AF. The extent to which noninvasive prolonged rhythm monitoring through an mHealth ECG patch impacts the detection of cardiac arrhythmias and clinical decisions has not been investigated.

Methods

Study Design

The Hypertrophic Cardiomyopathy: Clinical Impact of a Prolonged mHealth-Based Arrhythmia Monitoring by Single-Channel ECG (HCM-PATCH) study aims to investigate the association between the occurrence of cardiac arrhythmias with detected gene mutations and the extent of late gadolinium enhancement in cMRIs. This single-center prospective cohort study will be conducted at the Department of Cardiology and Intensive Care Medicine at the University Hospital Ostwestfalen-Lippe (OWL), Campus Klinikum Bielefeld in Germany. The trial is registered under clinical trial number DRKS00032144 (DRKS-ID).

Recruitment

According to the sample size calculation (see Statistical Analysis section), recruiting 34 patients will be sufficient for the statistical analysis. Study participants will receive an echocardiography at rest and during exercise (bicycle ergometry) and a cMRI. In addition, their symptoms, family history, and premedication are collected, and their HCM Risk–SCD calculator score will be calculated. According to this score, patients are allocated to three risk groups: low risk (<4%), intermediate risk (4%-6%), and high risk (>6%) of SCD within 5 years. An ICD is generally recommended in the high-risk group, should be considered in the intermediate-risk group, and is not indicated for the low-risk group [1]. For this study, it is planned to recruit 17 patients with

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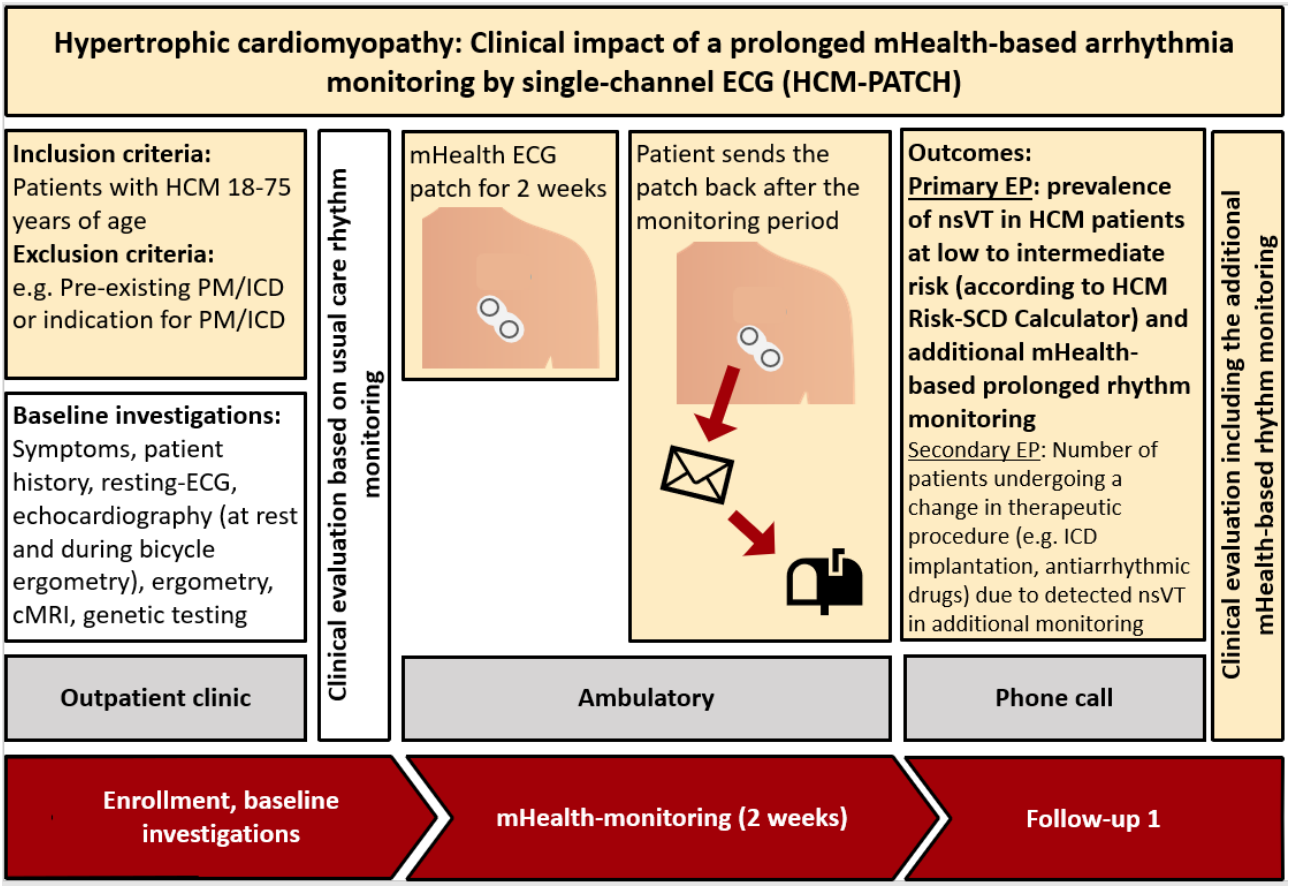
low and 17 with intermediate risk scores. All these patients will receive the 14-day ECG patch.

Patients with HCM between the ages of 18 and 75 years will be included if they have not yet undergone implantable loop recorder, pacemaker, or ICD implantation and if their estimated 5-year SCD risk according to the HCM Risk–SCD calculator score is <6%. A maximum age of 75 years was set as the upper limit, as SCD in patients with HCM mainly occurs at a young age [13]. Patients with a pre-existing cardiac implant (pacemaker, ICD, or implantable loop recorder) or an already accepted indication for it; Morbus Parkinson disease with relevant tremor; a transcoronary ablation of septal hypertrophy procedure in the last 4 weeks; inability to give informed consent; and current symptoms or a history of skin cancer, rash from skin adhesive, or dermatoses (contraindication to wearing the patch) are excluded.

A therapeutic procedure is established for the patient based on the information available to date. Afterward, an ECG patch is applied to the chest to continuously monitor the heart rhythm over 14 days. After completing the 14-day wearing period, patients should return the ECG patch. Any arrhythmias recorded will then be documented, and the therapeutic procedure will be re-evaluated with a recalculation of the HCM Risk–SCD calculator score.

An overview of the study process can be seen in Figure 1.

Figure 1. Overview of the study process. cMRI: cardiac magnetic resonance imaging; ECG: electrocardiography; EP: endpoint; HCM: hypertrophic obstructive cardiomyopathy; ICD: implantable cardioverter-defibrillator; mHealth: mobile health; nsVT: nonsustained ventricular tachycardia; PM: pacemaker; SCD: sudden cardiac death.



Questionnaires

At the beginning of study recruitment, various data such as the patient's family history, previous syncope or rhythm abnormalities will be collected. In addition, secondary causes for left ventricular hypertrophy, such as arterial hypertension, will be queried. At the beginning and after monitoring completion, we will also ask patients if they have any questions, concerns, or requests they want to address with us. After completion of the 14-day monitoring period, the patient's perception of the mHealth measure will be evaluated through a questionnaire (Multimedia Appendix 1). This questionnaire is based on the System Usability Scale by Brooke [14], a standardized questionnaire for evaluating utensils.

Electrocardiogram Device

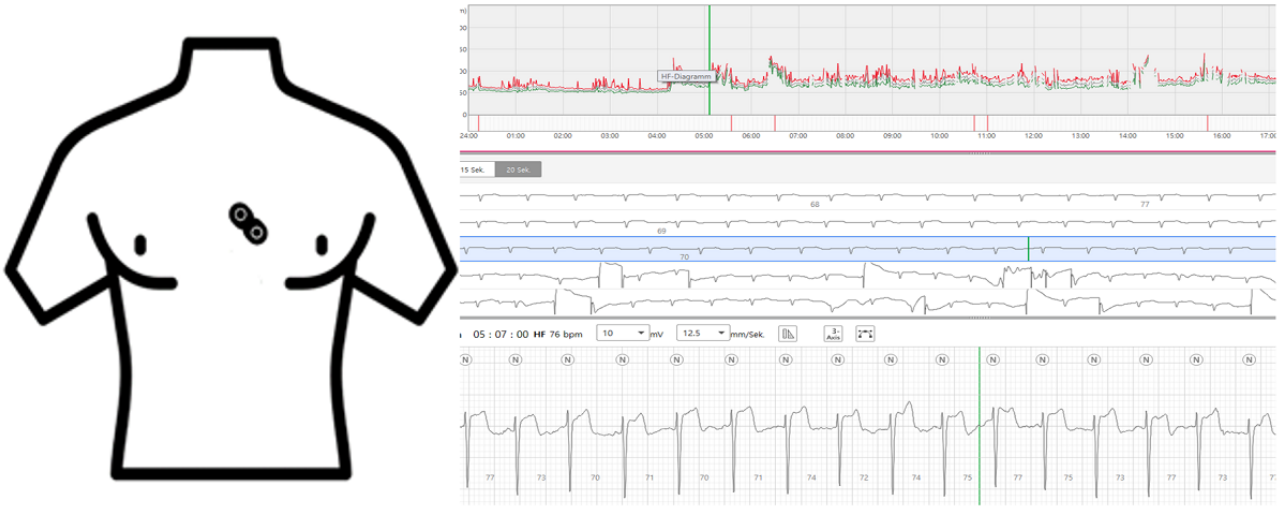
The ECG patch used is the AT-Patch from ATsens Co, Ltd (Seongnam-si, Republic of Korea), which is a single-channel ECG. The AT-Patch carries the CE mark as a registered medical device and is available for sale in the European Union. It can easily be attached to the chest and continuously records the heart rhythm for 14 days. During monitoring, patients can observe their ECG via an app (AT-Note) and may indicate symptoms (eg, dizziness or palpitations) via this app. Live tracking by the study physician is not possible. The ECG patch is light and compact and meets the grade of being showerproof (IP44/IP57). At the end of the monitoring period, the patient sends back the patch for rhythm evaluation. The detected

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arrhythmias are documented and adjudicated by two independent physicians.

Figure 2 shows a schematic representation of the ECG patch on the chest and an example rhythm analysis of the accompanying app.

Figure 2. Single-channel electrocardiography system in situ and sample screen of the accompanying app.



Outcomes

The rate of nsVT detection in the first 24 and 48 hours of monitoring versus the whole 14-day monitoring period will be compared. In addition, the prevalence of AF and other arrhythmias will be examined. Moreover, the results of the cMRI and, if applicable, the results of the genetic examination will be considered. The HCM Risk–SCD calculator score will be recalculated if new findings have occurred.

nsVT is defined as ≥3 consecutive ventricular beats at a rate of 120 beats per minute, lasting for <30 seconds [1]. AF is defined as atrial tachyarrhythmia lasting for >30 seconds [15]. The diagnosis of HCM is based on echocardiography; septum hypertrophy ≥15 mm in the absence of other causes of myocardial hypertrophy or septal or posterior wall thickness ratio >1.3 is required.

At the patients' request, they will be informed about the rhythm-monitoring results and the resulting therapy changes after the ECG patch has been returned.

Statistical Analysis

The sample size has been planned in collaboration with the Department of Biostatistics and Medical Biometry at the Medical School OWL, Bielefeld University. Patients should be divided into low- or intermediate-risk groups according to their HCM Risk–SCD calculator score, and both groups should be of equal size. Based on the prevalence of nsVT, an assumption was made for the group of low-risk patients based on the publications of Magnusson and Mörner [16] and Sakhi et al [17], where the prevalence after a 24- to 48-hour long-term ECG ranged from 7% to 42%. For case-finding purposes, the assumption was made that a similar increase (ie, a doubling) would be expected after 14 days in the intermediate-risk group. Therefore, a prevalence of 25% after 14 days is assumed. In the intermediate-risk group, a prevalence of 75% is expected [6]. Using a χ^2 test, the total number of cases is 30, corresponding to 15 patients per group (α=0.05, power=0.8). In addition, a dropout probability of 10% was considered. This would result in 34 cases (17 per group).

After data collection, a statistical analysis will be conducted concerning the primary and secondary end points. Since this is a cohort study, all analyses will be adjusted for confounders, including, for example, age and sex. Potential confounders will be assessed from a clinical point of view before the statistical analysis is performed. A Poisson regression will be applied to analyze the primary end point (rate of nsVT detection). Furthermore, we will conduct a negative binomial regression as a sensitivity analysis. The same will be done for the secondary end points measured as the number of patients that experience specific events during the study period. Secondary end points regarding the prevalence of cardiac arrhythmias will be analyzed using logistic regression.

Data Protection of Study Participants

The single-lead ECGs generated by the device are stored in the hospital network without external access. A patient identification list is kept in the Department of Cardiology, in which patient identification numbers are linked to the full patient names of the participants. This list allows later identification of participating patients. It will be kept confidential and archived for at least 10 years after the end of the study. The patient identification list will be stored separately from the documentation records on a computer using appropriate rights management and access monitoring. Subsequently, all patient-related data will be pseudonymized so that it is no longer possible for outsiders to identify individual patients. Passing on the pseudonymized data to external parties is expressly prohibited.

Dropout

If the patient wishes to discontinue participation in the study during the 14 days of wearing the device, this is possible at any time and without any disadvantages for the patient. In addition, according to patients' preferences, they may not be informed about rhythm observations. The study physician should be

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informed about this and discontinuation. If a patient does not return the patch after the 14 days, this will be counted as a dropout.

In addition, a minimum duration of 288 hours has been established. If the ECG patch is worn for less than this time, exclusion from the study will occur. How long the patch has been worn can easily be determined based on the duration that ECG data is available.

Ethical Considerations

Each patient is informed about the nature, relevance, objectives, potential risks, expected benefits, implications, and other aspects of the clinical trial through a discussion between the investigator and the patient. The patients receive written patient information. The investigator makes sure that the patient has understood the information. After the information session, each patient is given sufficient time and opportunity to clarify any unanswered questions and to decide on their participation.

The study will be conducted following the ethical principles originating in the Declaration of Helsinki and the recommendations of Good Clinical Practice and Good Scientific Practice. In addition, the study was approved by the ethics committee of the Ärztekammer Westfalen-Lippe (2023-262-f-S).

The devices were partially purchased by our department and partially sponsored by the company ATsens. None of the manufacturers were involved in the study design, and they will not participate in the data collection, statistical analysis, or manuscript writing. There are no other financial contributions. Participation in the study is free of charge for all study participants.

Results

The primary study objective and primary end point is the prevalence of nsVT in patients with HCM at low to intermediate risk (according to the HCM Risk–SCD calculator) and additional mHealth-based prolonged rhythm monitoring. We will also explore the following secondary end points:

- Number of patients undergoing a change in therapeutic procedure (ICD, antiarrhythmic drugs, etc) due to detected nsVT in additional monitoring
- Number of patients with detection of AF (duration >30 sec) by prolonged monitoring
- Number of patients who experience a change in therapeutic procedure (anticoagulation, antiarrhythmic drugs, catheter ablation, etc) due to detected AF
- Prevalence of cardiac arrhythmias in patients with positive cMRI findings (>5% late gadolinium enhancement)
- Prevalence of cardiac arrhythmias in patients with positive genetic diagnosis (detection of HCM-typical gene mutations)

Patient recruitment began in June 2023 and is expected to be completed in February 2024. Data analysis has not yet started. An example table listing patient characteristics and outcomes is provided in Multimedia Appendix 2.

Discussion

This prospective study aims to measure the prevalence of nsVT in 34 patients with HCM observed by mHealth-based continuous rhythm monitoring over 14 days compared to standard practice (a 24- and 48-h long-term ECG). Thereby, the frequency of ventricular arrhythmias in the 14 days is compared with the frequency in the first 24 or 48 hours for the same patient (intraindividual comparison). We will evaluate whether the prolonged rhythm monitoring detects nsVT and AF more often compared to conventional 48-hour monitoring and to what extent these findings can induce changes in therapeutic management. It may be speculated that, especially in patients with intermediate HCM Risk–SCD calculator scores, prolonged monitoring may identify patients at high risk, who may potentially benefit from a prophylactic ICD, with higher accuracy. If no rhythm abnormality is detected during the 14-day monitoring, this will not likely occur in everyday life and ICDs can be avoided due to a sufficiently low risk. In addition, a higher diagnostic yield for previously undetected AF may also improve decision-making regarding the need for early anticoagulant therapy.

We set an upper age limit of 75 years because it is known that especially young patients with HCM especially have a higher risk of SCD [13]. Nevertheless, a residual risk remains, so no upper limit for ICDs is defined in the European Society of Cardiology guidelines. Several years ago, the DANISH (The Danish Study to Assess the Efficacy of ICDs in Patients With Nonischemic Systolic Heart Failure on Mortality) study demonstrated no survival benefit from an ICD in patients older than 75 years in a sample of patients with systolic heart failure [18]. We have followed this age limit despite the different patient samples.

We hypothesize that prolonged rhythm monitoring will detect more arrhythmias than 24- or 48-hour monitoring. In a study with prolonged rhythm monitoring by Holter ECG over 14 days, 75% of patients with HCM had nsVT, compared with only 16.9% of patients in the first 24 hours [6]. However, it remains unclear if all these patients with nsVT should now receive an ICD. Previous studies have shown that patients who present with nsVT during 24-hour monitoring show it more frequently if monitoring is prolonged. Patients who showed nsVT later in the subsequent 14 days usually had only one episode [7]. Thus, it can be speculated that the detection of nsVT in a 24-hour monitoring period indicated more frequent spells of nsVT overall, with an associated higher SCD risk. Moreover, the rate and duration of nsVT vary, suggesting that longer and more rapid nsVT episodes indicate a higher SCD risk [6]. Prolonged monitoring may allow for the identification of patients with more frequent nsVT episodes, also taking into account the rate and duration of nsVT.

In addition, a correlation with late gadolinium enhancement load on cMRI will be investigated. If patients with high late gadolinium enhancement load show increased nsVT, these scar areas detected on cardiac MRIs could be identified as possibly pathogenic for the arrhythmias, and appropriate therapy (eg,

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ICD fitting) should be performed. This has so far not been investigated, so the results are needed.

In addition, the mHealth ECG patch method used here offers opportunities for other diseases as well. For example, patients with a stroke of unclear origin can be screened for AF over an extended period. It is also possible to capture intermittent subjectively perceived cardiac arrhythmias with the help of such an ECG patch, as this is often not possible with normal long-term ECGs.

In summary, prolonged mHealth-based rhythm monitoring will be used to investigate arrhythmia burden in patients with HCM. Increased detection of arrhythmias compared with 24-hour long-term ECG monitoring can be expected. It is essential to individually consider the rhythm monitoring results and optimize therapy accordingly. Findings of prolonged rhythm monitoring might be helpful in cases of borderline risk. A thorough discussion of the findings and possibly individual reassessment using the risk calculator could be an approach.

Acknowledgments

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There was no generative artificial intelligence used in any portion of the manuscript writing.

Data Availability

The data sets generated or analyzed during this study are not publicly available due to patient data protection but are available from the corresponding author upon reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
The questionnaire to be used in the study.
[DOCX File , 15 KB - resprot_v12i1e52035_app1.docx]

Multimedia Appendix 2
Characteristics of patients with hypertrophic cardiomyopathy eligible for participation in the Hypertrophic Cardiomyopathy: Clinical Impact of a Prolonged mHealth-Based Arrhythmia Monitoring by Single-Channel ECG (HCM-PATCH) cohort study.
[DOCX File , 18 KB - resprot_v12i1e52035_app2.docx]

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Abbreviations

AF: atrial fibrillation
cMRI: cardiac magnetic resonance imaging
DANISH: The Danish Study to Assess the Efficacy of ICDs in Patients With Nonischemic Systolic Heart Failure on Mortality
ECG: electrocardiography
HCM: hypertrophic cardiomyopathy
HCM-PATCH: Hypertrophic Cardiomyopathy: Clinical Impact of a Prolonged mHealth-Based Arrhythmia Monitoring by Single-Channel ECG
ICD: implantable cardioverter-defibrillator
mHealth: mobile health
nsVT: nonsustained ventricular tachycardia
OWL: Ostwestfalen-Lippe
SCD: sudden cardiac death

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Protocol

The Ability of Austrian Qualified Physiotherapists to Make Accurate Keep-Refer Decisions and to Detect Serious Pathologies Based on Clinical Vignettes: Protocol for a Cross-sectional Web-Based Survey

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Abstract

Background: The recognition of serious pathologies affecting the musculoskeletal (MSK) system, especially in the early stage of a disease, is an important but challenging task. The prevalence of such serious pathologies is currently low. However, in our progressing aging population, it is anticipated that serious pathologies affecting the MSK system will be on the rise. Physiotherapists, as part of a wider health care team, can play a valuable role in the recognition of serious pathologies. It is at present unknown how accurately Austrian qualified physiotherapists can detect the presence of serious pathologies affecting the MSK system and therefore determine whether physiotherapy management is indicated (keep patients) or not (refer patients to a medical doctor).

Objective: We will explore the current ability of Austrian qualified physiotherapists to recognize serious pathologies by using validated clinical vignettes.

Methods: As part of an electronic web-based survey, these vignettes will be distributed among a convenience sample of qualified Austrian physiotherapists working in a hospital or private setting. The survey will consist of four sections: (1) demographics and general information, (2) the clinical vignettes, (3) questions concerning the clinical vignettes, and (4) self-perceived knowledge gaps and learning preferences from the perspective of study participants. Results will further be used for (1) international comparison with similar studies from the existing literature and (2) gaining insight into the participants' self-perceived knowledge gaps and learning preferences for increasing their knowledge level about keep-refer decision-making and detecting serious pathologies.

Results: Data collection took place between May 2022 and June 2022. As of June 2022, a total of 479 Austrian physiotherapists completed the survey. Data analysis has started, and we aim to publish the results in 2023.

Conclusions: The results of this survey will provide insights into the ability of Austrian physiotherapists to make accurate keep-refer decisions and to recognize the presence of serious pathologies using clinical vignettes. The results of this survey are expected to serve as a basis for future training in this area.

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KEYWORDS

red flags; clinical reasoning; physiotherapy; screening; referral; musculoskeletal

Introduction

We live in an aging society. The forecasted increase in the number of people older than 65 years from currently 34.4% to 59.2% by 2070 for the entire area of the European Union will pose great challenges for the health care systems of the European Union member states [1]. A very high increase in health care expenditure is to be expected [1]. In view of the challenges of an aging society, measures are being sought to cope with the increased pressure on the health care system in the future. One measure to relieve the burden on hospitals and to be able to provide the most efficient care for patients, the establishment of primary care units, is currently being propagated in Austria [2]. The core idea of primary care units is that patients are managed in a team consisting of general practitioners and different nonphysician health care professionals (such as nurses, physiotherapists, speech therapists, and occupational therapists) [2]. The expansion of primary health care in Austria is in line with the recommendations of the World Health Organization, which highlights that even though some musculoskeletal (MSK) conditions may require more specialist or surgical management, most conditions of the MSK system can readily and effectively be managed in a primary care setting [3].

MSK conditions that often present with pain and restricted mobility are highly prevalent within the general population [3]. In 2016, low back pain, for instance, was the leading cause of years lived with disability for men in 133 of 195 countries and for women in 104 of 195 countries [4].

Recent data from Denmark demonstrated that the overall prevalence of serious pathologies affecting the MSK system is at present comparatively low (2.3%) [5]. For instance, the prevalence of malignant neoplasms affecting the MSK system was 1.13% [6]. These figures are consistent with those from previous studies that reported a prevalence of metastatic spinal cancer as a serious cause of low back pain below 1% in primary care [7-10]. Another example is osteoporotic spinal fractures. The prevalence of osteoporotic fractures as a cause of vertebral pain in primary care ranges between 0.13% and 0.7% [5,9] but can be as high as 5% in a predominantly older study population [10]. In a progressively aging society, the number of people developing a serious pathology is likely to rise in the future. There is a clear link between advanced age and many cancers [11] such as prostate, lung, bowel, and breast cancer [12,13]. The significance of prostate, lung, thyroid, kidney, and breast cancer is that they account for 80% of all osseous metastases [14]. In addition, 80% of all fractures in women older than 50 years are caused by osteoporosis. One in 2 women and 1 in 5 men over the age of 50 years will experience an osteoporotic fracture [15].

The recognition of serious pathologies affecting the MSK system especially in the early stage of a disease is a challenging task [16]. However, early diagnosis is essential because this significantly improves prognosis and outcomes [16]. It is well known that especially in early stages (prodromal period), there are (if any) few or very vague/nonspecific signs and symptoms of a serious pathology [17]. However, as the disease progresses, these signs and symptoms become more obvious. Physiotherapists work very closely and sometimes over a prolonged period with their patients. They are therefore well suited to monitor the clinical situation of their patients (watchful waiting) [18] and repeatedly screen them for the occurrence or presence of specific signs and symptoms (red flags) that might indicate the presence of a serious pathology. Red flags can become apparent during the interview, physical examination, or treatment of a patient.

To analyze clinical decision-making abilities of medical and other health professionals, researchers make use of clinical vignettes that are concise paper-based or electronic descriptions of actual clinical situations [19]. Vignettes simulate real patients with various ailments and a wide range of different, sometimes complex, symptoms. Based on the clinical descriptions within such vignettes, clinicians are asked to decide about either examination procedures, (differential) diagnosis, or possible treatment options [20]. An additional advantage of vignettes is that they can be easily distributed among a large number of clinicians even with different educational backgrounds or from divergent health care settings [20,21].

Previous cross-sectional studies on qualified physiotherapists in the United States [22-26], Germany [27], Switzerland [28], Denmark [6], on Doctor of Physical Therapy students in the United States [29], and on European final year undergraduate physiotherapy students [30] have raised some concern about the physiotherapists' ability to decide when physiotherapy is indicated (keep), or not (refer), and their ability to accurately detect the presence of serious pathologies based on clinical vignettes. Having said this, numerous case studies and case series within the literature highlight that physiotherapists can become key in the detection of serious pathologies in a clinical setting [31,32].

The ability of Austrian qualified physiotherapists to accurately detect serious pathologies and to determine if a patient is suitable for physiotherapy, or rather needs a more comprehensive medical workup, has not yet been explored. Considering the above-outlined changes to the Austrian health care sector and challenges of an increasingly aging society, this knowledge gap needs to be addressed. To fill this knowledge gap, we propose a cross-sectional web-based survey using validated clinical vignettes [6].

The overall aim of this study is to assess the ability of Austrian qualified physiotherapists to make accurate keep-refer decisions and their ability to detect serious pathologies affecting the MSK system based on 12 clinical vignettes. In addition, we want to explore potential knowledge gaps and learning preferences to acquire more expertise in making keep-refer decisions from the perspective of study participants.

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Methods

Overview

The Methods, Results, and Discussion sections will adhere to the CHERRIES (Checklist for Reporting Results of Internet E-Surveys) statement [33].

Ethics Considerations

The project was formally examined by the Commission for Scientific Integrity and Ethics of the Karl Landsteiner Private University, and it was found that in accordance with the set criteria, a further review by the commission was not required (project number: 1021/2022, date April 20, 2022). There were no medical ethical concerns about the conduct of the project.

Eligibility Criteria

To be included in this study, prospective participants need to (1) be registered as qualified physiotherapists with the Austrian Health Professions Registry and (2) work in a hospital or private setting in Austria. Physiotherapists who have not actively treated patients during the last 12 months will not be eligible for this study.

Recruitment Process

The email addresses of physiotherapists registered on the Austrian Health Professions Registry and with a publicly available email address have been collected. The recruitment process will be divided into the recruitment of physiotherapists working in a private setting and physiotherapists working in a health institution.

In the first part, physiotherapists who are working as private physiotherapists will be sent an email with an explanation of the study and a link to take part in the survey. If needed, after 2 weeks, the email will be re-sent to remind physiotherapists of the study.

In the second part, the multidisciplinary team leaders (n=44) of each health institution in Austria will be sent an email with information about the study and will be asked to provide information on the number of physiotherapists currently working for the institution and indicate if they are interested in taking part in the study. If interested, a new email will be sent to the multidisciplinary team leaders containing a link to forward to the physiotherapists to take part in the study.

When the link is activated, the physiotherapists will be taken to a website on the Unipark platform. Information regarding the research aim, eligibility criteria, and the anonymous nature of the study will be available. Consent will be given when participants accept the consent form and click on the “next” button.

Sample Size Calculation

On March 15, 2022, a total of 16,991 physiotherapists were registered on the Austrian Health Professions Registry. Given this population, 376 physiotherapists need to be recruited to retain a 95% CI with a margin of error of 5% [34].

Data Collection Tool

The survey will be constructed on the internet using the web-based survey tool Unipark. It will take 15 to 20 minutes to complete the whole survey. A copy of the survey, except the 12 translated vignettes, is provided in Multimedia Appendix 1.

The survey consists of four sections:

1. Demographic features of participants, for example, age, sex, working experience, and educational level.
2. Twelve vignettes, translated from English to German. After reading each clinical vignette, participants will be asked to decide if this is (a) an MSK condition, which does not need referral to a medical doctor (keep); (b) a noncritical medical condition, which needs referral to a medical doctor, while the patient can be treated by a physiotherapist (keep-refer); and (c) a critical medical condition, which needs immediate referral to a medical doctor and treatment by the physiotherapist should be stopped (refer). The vignettes (used with permission) have been validated by a panel of medical doctors and expert physiotherapists [6].
3. Feedback will be sought from participants on the 12 vignettes. Questions will be asked on
   - how difficult (on a Likert scale from 1 to 5) it is to make keep-refer decisions based on the information presented in the vignettes,
   - the relevance of the vignettes for everyday work (on a Likert scale from 1 to 5), and
   - possible missing information within the vignettes for making accurate keep-refer decisions (open-ended question).
4. Exploration of knowledge gaps and learning preferences to acquire more expertise in making keep-refer decisions and detecting serious pathologies from the perspective of study participants. Questions will be posed on
   - the confidence of participants to conduct clinical examination procedures (such as cranial nerve testing, reflex testing, and auscultation of blood vessels)
   - if participants are interested in learning more about keep-refer decision-making
   - suggestions for content and format of future training sessions to acquire more expertise in keep-refer decision-making (such as learning medium and environment/setting, teaching contents, and educational strategies)
   - any further suggestions and comments (open-ended question).

Pilot Testing

The first draft of this survey was sent to 5 physiotherapists and 4 medical doctors. Participants were asked to comment on their general understanding of the questionnaire and the appropriateness, comprehensibility, and proper sequencing of individual questions. In addition, the participants in the pilot could suggest additional questions that they deemed valuable. For an example, one participant suggested adding a question where future participants will be asked about their confidence in conducting clinical examination procedures (eg, cranial nerve testing) that might be relevant for clinical and keep-refer

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decision-making. Another suggestion was to add a question that could aid with the inclusion and exclusion criteria. Participants were therefore, right at the beginning of the survey, asked if they have treated patients during the last 12 months. If the participants answer this question with "no," they will be thanked for their interest and then will automatically be prevented from continuing with the survey. The validity of some of the vignettes in the Austrian health care system was also questioned; therefore, after elaborate discussions, the originally envisioned vignettes by Jette et al [23] were replaced by the more current vignettes of Budtz et al [6]. The feedback from the pilot was collected and incorporated into the existing survey.

Data Management and Analysis

The survey will be constructed online, and progression through the 12 vignettes will be mandatory so that an answer must be entered before one being able to continue. This will allow only completed clinical vignettes to be included in the analysis. Completed surveys will be automatically sent back to the online survey tool Unipark. The data will be stored at the QuestBack server park in Bremen, Germany. After the data collection is completed, the raw quantitative data will then be downloaded onto an SPSS file (IBM SPSS Statistics 28.0). The qualitative data will be exported to a Word document and then imported to a MAXQDA project (MAXQDA 2020). All data will be stored on a secure OneDrive folder to which only the researchers have access through their password protected laptops. The survey will be designed to be completely anonymous; however, there is a small risk that participants will share personal data in the open-ended question in the last section of the survey. If this happens, these data will be anonymized by a member of the research team.

Individual participants' responses for each of the 12 vignettes will be classified as either being correct (Yes) or incorrect (No). Replicating previously used methodology [6,23,25,27-30], definitions of correct answers are as follows:

- For the MSK vignettes: treat the patient without the need for medical referral (keep) or treat the patient with additional medical checkup (keep and refer, also called watchful waiting).
- For the medical noncritical vignettes: choose to start physiotherapy with additional medical evaluation (keep and refer) or refer the patient without physiotherapy management (refer).
- The sole correct answer for medical critical vignettes is sent the patient for medical evaluation without physiotherapy management (refer).

Once the data collection period is finished, the quantitative data will be checked for completeness and outliers. Missing data will be labeled. The Shapiro-Wilk test will be used to examine if the data are normally distributed. If values are normally distributed, the mean (with SD) will be calculated; if not, the median (with IQR) will be calculated. All descriptive statistics, such as age, sex, years of experience as a physiotherapist, and type of expertise, will be collected as categorical data, and the percentage for each category will be calculated.

In the clinical vignettes, the mean percentages (plus SD) of correct keep-refer decisions and actual numbers as well as percentages of participating physiotherapists who manage to accurately answer all vignettes from a specific category will be calculated (MSK vs medical noncritical vs medical critical) [6,23,25,27-30]. If it is not normally distributed, the median percentages with IQR will be presented.

The questions concerning the feedback from study participants on the 12 vignettes, such as "how sure the participants were when answering the clinical vignettes?" and "how relevant the vignettes were for the participants?" will be calculated as percentages for each category.

The questions concerning learning about red flags, such as interest for red flags training, medium of training, and interest of specific assessment techniques, will also be listed as percentages for each category.

The 2 open-ended questions concerning missing information in the clinical vignettes and any other remarks will be analyzed deductively using framework analysis [35] in MAXQDA. The predefined codes were in line with the diagnostic physiotherapeutic process [36]: referral, medical history, and physical examination. Recurrent remarks on additional information, which could help the participants with their clinical decision-making, will be coded and combined into categories to inform the next phase of the study: the development of educational clinical case studies for physiotherapists.

Results

The distribution of the survey took place between May 2022 and June 2022. As of June 2022, a total of 479 Austrian physiotherapists completed the survey. It is anticipated that data collection, analysis, and writing up for a potential publication in a peer-reviewed journal will take 4 to 6 months.

Discussion

Study Strengths

A major strength is that our methodology is in line with previously published studies [6,23,25,27-30]. In addition, we use validated clinical vignettes (with permission) that have already been used in previous research [6,23,25,27-30]. This will give us the opportunity for international comparison.

To the best of our knowledge, this is the first study that examines the ability of Austrian physiotherapists to make accurate keep-refer decisions and to recognize the presence of serious pathologies using clinical vignettes. Moreover, this is the first attempt to explore potential knowledge gaps and learning preferences to acquire more expertise in making keep-refer decisions and recognizing the presence of serious pathologies from the perspective of Austrian qualified physiotherapists. These results will be used to inform future training in this field and should help advance patient safety and interdisciplinary collaboration within the Austrian health care system.

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Study Limitations

During the preparation of the study the aim was to collect the email addresses of all physiotherapists currently registered to work in Austria. However, from the private physiotherapists not all email addresses were retrievable on the internet, and 50% of the population will not be contacted. This could have implications on the generalizability of the study.

The limitations of clinical vignettes as a sole instrument for examining clinical decision-making strategies of health care professionals have previously been highlighted [37-39]. However, vignettes have the advantage that they can be distributed to a large pool of potential participants relatively quickly and at low cost. Our approach is in line with previous research using similar methodology [6,22,23,25,27-30]. The participants in this study will have the opportunity to provide feedback on the vignettes, which will be used to develop vignettes validated for the Austrian context.

Acknowledgments

The project team would like to thank the Gesellschaft für Forschungsförderung Niederösterreich m.b.H. (GFF) for the funding provided to carry out the project.

Data Availability

We are aiming to deposit the quantitative data in a GitHub repository.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Red Flags survey.
[PDF File (Adobe PDF File), 190 KB - resprot_v12i1e43028_app1.pdf]

Multimedia Appendix 2
External peer-review from Life Science Call 2020 - Gesellschaft für Forschungsförderung Niederösterreich m.b.H. (GFF).
[PDF File (Adobe PDF File), 17 KB - resprot_v12i1e43028_app2.pdf]

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Abbreviations

CHERRIES: Checklist for Reporting Results of Internet E-Surveys
MSK: musculoskeletal

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Protocol

Detection of Motor Cerebral Activity After Median Nerve Stimulation During General Anesthesia (STIM-MOTANA): Protocol for a Prospective Interventional Study

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Abstract

Background: Accidental awareness during general anesthesia (AAGA) is defined as an unexpected awareness of the patient during general anesthesia. This phenomenon occurs in 1%-2% of high-risk practice patients and can cause physical suffering and psychological after-effects, called posttraumatic stress disorder. In fact, no monitoring techniques are satisfactory enough to effectively prevent AAGA; therefore, new alternatives are needed. Because the first reflex for a patient during an AAGA is to move, but cannot do so because of the neuromuscular blockers, we believe that it is possible to design a brain-computer interface (BCI) based on the detection of movement intention to warn the anesthetist. To do this, we propose to describe and detect the changes in terms of motor cortex oscillations during general anesthesia with propofol, while a median nerve stimulation is performed. We believe that our results could enable the design of a BCI based on median nerve stimulation, which could prevent AAGA.

Objective: To our knowledge, no published studies have investigated the detection of electroencephalographic (EEG) patterns in relation to peripheral nerve stimulation over the sensorimotor cortex during general anesthesia. The main objective of this study is to describe the changes in terms of event-related desynchronization and event-related synchronization modulations, in the EEG signal over the motor cortex during general anesthesia with propofol while a median nerve stimulation is performed.

Methods: STIM-MOTANA is an interventional and prospective study conducted with patients scheduled for surgery under general anesthesia, involving EEG measurements and median nerve stimulation at two different times: (1) when the patient is awake before surgery (2) and under general anesthesia. A total of 30 patients will receive surgery under complete intravenous anesthesia with a target-controlled infusion pump of propofol.

Results: The changes in event-related desynchronization and event-related synchronization during median nerve stimulation according to the various propofol concentrations for 30 patients will be analyzed. In addition, we will apply 4 different offline machine learning algorithms to detect the median nerve stimulation at the cerebral level. Recruitment began in December 2022. Data collection is expected to conclude in June 2024.

Conclusions: STIM-MOTANA will be the first protocol to investigate median nerve stimulation cerebral motor effect during general anesthesia for the detection of intraoperative awareness. Based on strong practical and theoretical scientific reasoning from our previous studies, our innovative median nerve stimulation–based BCI would provide a way to detect intraoperative awareness during general anesthesia.

Trial Registration: Clinicaltrials.gov NCT05272202; https://clinicaltrials.gov/ct2/show/NCT05272202

International Registered Report Identifier (IRRID): PRR1-10.2196/43870

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(JMIR Res Protoc 2023;12:e43870) doi:10.2196/43870

KEYWORDS

intraoperative awareness; brain-computer interfaces; median nerve stimulation; electroencephalography; general anesthesia

Introduction

Unexpectedly awakening during surgery is a terrifying experience for patients, who fear it, but also for the medical staff, who are worried that the situation may occur under their supervision [1]. This type of phenomenon is called an accidental awareness during general anesthesia (AAGA) [2]. Although its origin is still debated, the reasons and factors favoring AAGA are being studied. This phenomenon appears if the depth of anesthesia, induced by the concentration of anesthetic used, is not deep enough to compensate for all the surgical stimuli related to the operation in progress. The role of the anesthetist is to succeed in inducing an altered state of consciousness, which is complexly intertwined with analgesia and amnesia. Indeed, if the anesthesia is too light, it may result in recovery of consciousness and volitional movement during the operation, which would be very dangerous for the patient [3]. Conversely, if too much anesthetic agent is given, it increases the depth of anesthesia but may lead to problems such as adverse cardiovascular effects, postoperative delirium, and cognitive impairment, increasing the probability of mortality during surgery [4]. Finally, an anesthetic overdose may also increase the symptoms of postoperative nausea and vomiting and thus delay the patient's discharge from the hospital [5].

The rate of AAGA in high-risk practices (eg, obstetric, cardiac, and thoracic) varies from 1% to2% [6]. Considering that hundreds of millions of general anesthesia are performed each year worldwide, new solutions to better prevent this phenomenon are needed [7,8]. AAGA can also cause physical pain [2] and lead to psychological sequelae called posttraumatic stress disorder [1-3], which can last for several years and have severe psychological effects leading to suicide [9,10]. From the economic impact perspective, AAGAs generate direct costs because it is one of the top 3 causes of complaints against hospitals (>US $43,000 per claim) [2,3,11] and indirect costs from the expenses related to the follow-up and psychological support of the patient who has experienced an AAGA. There are currently 2 procedures to monitor the depth of anesthesia based either on the observation of the clinical features (eg, heart rate, temperature, blood pressure, and movement) or electroencephalographic (EEG) analysis. Unfortunately, the first one does not prevent AAGA during surgery may be because such clinical signs observations remain a very indirect way of monitoring the patients' cerebral state not always enabling the anesthesiologist to predict an AAGA before it occurs [12]. Although new devices based on frontal EEG activity indexes are already in use, the studies demonstrating the superiority compared to clinical surveillance or end-tidal anesthetic gas [13-16] are not conclusive. Moreover, several studies consent to the use of BIS as it has been shown that the predictive accuracy is decreased when using neuromuscular blockers [1].

The patients' testimonies show that the first reaction during an AAGA is usually to move to alert the medical staff [2,17]. Unfortunately, during most surgeries, the patient is curarized, which causes neuromuscular block and prevents any movement. Detecting movement intention (MI) is possible by analyzing EEG signals from the motor cortex with a brain-computer interface (BCI). This is based on previous evidence demonstrating that simple MIs are characterized by power spectrum variations (ie, event-related (de)-synchronization called ERD/ERS) in the EEG mu (7-13 Hz) and beta (15-35 Hz) bands over the motor cortex [18] and that electrical stimulation of the median nerve also induces changes in the cortical activity [19,20], which are visible in the EEG signal and which are similar to an MI [21,22]. Interestingly, our preliminary results suggested that when a hand MI coincides with median nerve stimulation (MNS), the ERD/ERS is considerably reduced, and thus the MI can be detected much better by machine learning techniques than an MI without MNS [23-26]. The originality of this BCI paradigm is to exploit this MNS-induced phenomenon to accurately detect the patient's motor intention during an AAGA. Based on these previous results, we envisage a routine procedure where the anesthetized patient is stimulated by electrical pulses delivered at the median nerve position at the wrist, while a BCI device analyzes the ERD and ERS modulations over the motor cortex to detect the intention of movement of the patient. Our previous clinical trial (MOTANA protocol [23]) also includes a condition with MNS and another with MNS accompanied by MI for 3 concentrations of propofol (0, 0.5 µg/mL, and 1 µg/mL). The preliminary results (n=15) highlighted the advantage of a BCI based on MNS from both a functional and an accuracy point of view. First, MNS intrinsically provides a trigger to know when to analyze the signal. Second, the classification accuracy of an MNS-based BCI appeared to be way better than that of a BCI aiming to discriminate a motor imagination from a resting state. More precisely, an MNS-based BCI detected the MI state 15% more accurately. For several subjects, the use of MNS improves performance by more than 20% compared to a standard method [22,25].

These preliminary results also showed that propofol sedation (at 0.5 µg/mL and 1 µg/mL) has no negative impact on the ability of an MNS-based BCI to detect MI. Concretely, at relatively low concentrations, ERD/ERS patterns are still present in the sensorimotor cortex [26]. From these encouraging results, we intend now to verify that the oscillatory activity generated by the MNS remains present during general anesthesia with higher concentrations of propofol. This is in line with the existing literature, suggesting that the detection of MNS under general anesthesia can be achieved as somatosensory cortex maintains a certain activity confirmed by the presence of evoked potentials during sleep or general anesthesia-induced unconsciousness [27]. The cortical regions may still be receptive to information, but their ability to communicate with other regions may be altered during general anesthesia [28]. According to our knowledge, no study has investigated the way in which the cerebral motor activity was modulated with peripheral nerve

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stimulation over the sensorimotor cortex during general anesthesia. The aim of this study is to verify that ERD/ERS following MNS is still present and detectable under high doses of propofol with the EEG technique. Such new knowledge will enable the design of an innovative BCI specialized in the detection of intraoperative awareness during general anesthesia.

The first objective of this study is to verify that ERD and ERS patterns induced by MNS can be detected in the cortical motor EEG signal under various concentrations of propofol corresponding to the anesthetic doses required for general anesthesia. The secondary objective is to characterize and understand how the ERD and ERS generated after each MNS will be altered according to each concentration of propofol at the effect site. These results will be discussed in relation to previous results obtained from a protocol investigating the effect of light propofol sedation on EEG signals in the motor cortex. The third objective is to analyze EEG signals offline and try to detect MNS under propofol with new machine learning algorithms. Complementary, the short and middle latency components of the somatosensory evoked potentials (SEPs) will be analyzed for different propofol concentrations. Finally, the long-term goal is to design a BCI that can detect intraoperative awareness during general anesthesia.

Methods

Study Design

The study will be held in an approved location in the operating theaters, at the University Hospital of Bruxelles-Brugmann (Belgium). An anesthetic evaluation will be performed by the study investigator (DS) within 1 month prior to surgery. During this consultation, the study protocol will be explained to the patient, and the different explanatory documents will be given. Only eligible subjects will be enrolled (inclusion and exclusion criteria are listed). Participation is completely voluntary and withdrawal will be always possible at any time without affecting the level of care that will be received. There will be no financial compensation for this study. Each voluntary patient recruited for the study will benefit from the standard of care before, during, and after the surgery. On the day of surgery, and as recommended, the anesthetist will check that there are no current contraindications to perform general anesthesia (ie, failure to fast, fever, occurrence of other medical conditions or disease, unusual blood sample, etc).

Recording a patient's baseline EEG during MNS without an anesthetic drug administered is a prerequisite for the proper functioning of the BCI. It will take place before surgery in a specific quiet room in the postanesthesia care unit. The estimated time to set the EEG headset is 25 minutes, and the estimated time for baseline EEG monitoring is 20 minutes (see Table 1). Painless discontinuous stimulation of the median nerve and recording of the patient's EEG signal will take place throughout the operation. The anesthesia protocol will be left at the discretion of the anesthesiologist, except for obtaining hypnosis, which will have to be performed with propofol using a target-controlled infusion (TCI) pump with the Schnider pharmacokinetic model at the effect site [29-31]. If necessary, neuromuscular blocker agents will be used and monitoring will be performed. Data collection of the propofol site effect target administered to the patient will be directly recorded on a computer. After the surgery is completed, sedation will be discontinued allowing the patient to recover and be monitored afterward in the postanesthesia care unit.

Table 1. Schedule of enrollment, interventions, and assessments.

Action	Anesthesia	Preanesthetic visit	Presurgical visit	During surgery
Location	Consultation office	Hospital room	Specific room	Operation room
Timeliness	(−50 days; −5 days)	(−1 day)	(d-day)[b]	(d-day)
Consent collection	N/A[a]	N/A	N/A	N/A
Consent confirmation	N/A	N/A	✓	N/A
Providing information documents	✓	N/A	N/A	N/A
Checking inclusion and exclusion criteria	✓	N/A	✓	N/A
Medical interview	✓	✓	✓	N/A
Clinical examination	✓	✓	✓	✓
Electroencephalographic recording	N/A	N/A	✓	✓
Electromyography recording	N/A	N/A	N/A	✓
Median nerve stimulation	N/A	N/A	✓	✓
Adverse event collection	N/A	N/A	N/A	✓

[a]N/A: not applicable.

[b]d-day: day of experimentation.

Table 1 shows the registration, intervention, and evaluation schedule.

Considering the SEP stimulation, we consider that nonpainful stimuli will consist of square electrical pulses of 0.2 milliseconds of duration, generated by Micromed device Sd Ltm Stim Energy (Micromed) and delivered through a pair of grass gold cup

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electrodes (cathode [−] placed proximally) to the right/left median nerve at the wrist [32]. The intensity will be adjusted for eliciting visible small thumb twitches and without exceeding 50 mA.

Study Population

In this clinical protocol, a total of 30 patients who require scheduled surgery under general anesthesia will be enrolled. For the recruitment of this study, we have designed a flyer that will be disseminated through different media channels. Participation in this experiment will not be remunerated. Patients will be exposed to the same risks of general anesthesia limited to propofol. The doses used in this clinical protocol are the same as those that induce loss of consciousness during conventional surgery.

The inclusion criteria include patients (1) who have received full details of the research organization and have signed our informed consent, (2) aged between 18 and 81 years, (3) scheduled for surgery with the use of total intravenous sedation with propofol, and (4) who are affiliated to a social security regime in Belgium. We shall exclude patients who (1) are allergic to propofol or its ingredients, (2) have a history of an anaphylactic reaction during anesthesia, (3) are female due to the impossibility of checking pregnancy status, (4) are deprived of liberty by a judicial or administrative decision, (5) are under psychiatric care, (6) are unable to give consent and without being subjected to a legal protection measure, (7) refuse to participate in the study, (8) have a BMI below 20 or above 35 kg/m², (9) require surgery for less than an hour, (10) have a pathological history related to the right median nerve, and (11) have any drug addiction.

Ethical Considerations

This research was officially approved by an ethical committee from Belgium (CHU Brugmann, CE 2021/225) and was registered at EUDRACT (2021-006457-56). The study protocol was also registered on ClinicalTrials.gov (NCT05272202). This protocol will follow the principles of the Declaration of Helsinki and the Medical Research Involving Human Subjects Act [33]. Informed written consent will be obtained from all patients before study inclusion. Because involvement of patients is voluntary, the study can be stopped at any time.

EEG Data Acquisition

Motor EEG signals will be collected through the OpenViBE software platform with eego mylab system (ANT neuro) 64-EEG channels, covering the entire scalp at 16,000 Hz and 1 external channel placed on the dorsum of the contralateral hand to the electric stimulation, by means of an adhesive surface electrode. All offline analyses will be performed using the EEGLAB toolbox [34] and Matlab2016a (The MathWorks Inc). The findings will be additionally investigated by applying a Laplacian filter and a mastoidal re-referencing [35]. Then, the EEG signals will be resampled (128 Hz) and epoched into 6-s windows (1 second before and 5 seconds after the MNS). We will compute the ERD/ERS% using the “band power method” [36]. Additionally, SEP will be calculated by averaging epochs extracted from 0.25 to 0.5 with respect to the electric shock.

Statistics

The data processing methods will be similar to those described in the MOTANA protocol [23]. For each patient and each MNS, the maximal value of ERD and ERS max will be, respectively, selected in (0.25;0.5) seconds and (2;4) seconds after stimulation, in accordance with the literature [24,37]. An average over the ERDs max and ERSs max will be performed for each concentration. These 2 values will be, respectively, compared with average ERDs max and ERSs max obtained in the preoperative rest condition with a Student t test (P<.05). To visualize the event-related spectral perturbations with the EEGLAB toolbox, a surrogate permutation test will be used (P<.05; 2000 permutations). In addition to the permutation test, we will apply a false discovery rate correction to show the difference in MNS effect during different concentrations of propofol.

In addition to the event-related spectral perturbation analyses, we will apply 4 different offline machine learning algorithms to detect the MNS at the cerebral level. To do this, these algorithms are based on 4 classification methods in a 4-fold cross-validation scheme. The classification score will be computed for the MNS versus the rest class. Each trial will be segmented into a motor task time window and a resting time window, both lasting 2 seconds. The motor task time window will begin 0.5 seconds after the MNS, and the resting phase time window will begin 3 seconds before the MNS. The first classification method is a linear discriminant analysis method using a common spatial pattern [38] (referred to as common spatial pattern+linear discriminant analysis). For the next 3 classifiers, we will use classifiers that are based on Riemannian geometry. Riemannian geometry-based methods have the advantage of being immune to linear transformations and to be particularly efficient for the detection of motor intentions. For the statistical differences in the latency and topographic voltage of the SEP components, similar permutation tests and post hoc tests will be applied.

Study Duration

The duration of the participation is from 45 minutes before surgery (installation of the EEG cam and the median nerve stimulator) until the end of surgery.

The expected overall duration of the research, including the time required for the completion of the data analysis, is 4 years. The promoter (CHU Brugmann) reserves the right to stop the research (1) if serious, there are significant procedural deviations in the protocol that could impact the statistical analysis of the data, (2) if recruitment of subjects is not adequate, or (3) if a significant issue regarding the safety and rights of the subjects arises.

Data Collection

Data will be collected with a case report form and patient data will be anonymized (ie, a unique study number will be assigned to each individual). The case report form will contain demographic information of the patient, undesirable events which may be experienced during the study, the anesthesia chart will be photocopied at the end of the procedure and anonymized,

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and EEG data stored electronically under the supervision of the principal investigator.

Patient and Public Involvement

A total of 30 patients will be involved in the STIM-MOTANA protocol. Patients, patient advisors, and the public were not involved in the development of the research questions or in the design of the study. Patient involvement in the study includes answering survey questionnaires at baseline and at each follow-up. Summaries of study results will be disseminated to study participants via email or mail. The results will be published in international peer-reviewed journals, and summaries will be provided to the funders and patients.

Results

Evaluation Criteria

Primary End Points

A total of 30 patients will be involved in the STIM-MOTANA protocol. We will compute the amplitude of ERD/ERS modulations before and after each MNS during the different phases of anesthesia at 2 different times: when the patient is awake before surgery and under general anesthesia. The primary evaluation end point will be the amplitude of the ERD. According to the Pfurtscheller method, ERD/ERS modulations will be calculated using a baseline taken before each stimulation [36]. The changes in ERD/ERS during MNS according to the various propofol concentrations will be continuously monitored. To compare the motor EEG signal before and after injection of the anesthetic product, we will apply paired statistical tests (Student *t* test).

Secondary End Points

In this project, we need to reach the highest MI EEG detection accuracies as possible, which is necessary in the context of a surgery for which we need a very high true positive rate (ideally all AAGAs are detected) as well as a very low false positive rate (ideally no false alarm). To do so, we will build BCI classifiers based on Riemannian geometry [22,24] a framework in which EEG signals are represented as covariance matrices, which are directly analyzed and classified.

Trial Status

When the manuscript was initially submitted, recruitment had not started. The recruitment began in December 2022. The current protocol version is version 1 and was previously accepted by the ethical committee of the CHRU Brugmann Hospital.

Discussion

Principal Findings

STIM-MOTANA is an interventional study aimed at designing an innovative BCI-based EEG-motor brain activity, which would detect the intention to move of a patient during general anesthesia. STIM-MOTANA is the first study to investigate cerebral motor activity modulations following peripheral nerve stimulation during general anesthesia.

AAGA can occur unexpectedly and is therefore a complication that cannot be easily anticipated and that is only retrospectively diagnosed. The STIM-MOTANA protocol proposes to detect intraoperative awareness reliably by analyzing, in real-time, brain motor activity under general anesthesia with a BCI based on MNS and new machine learning methods. Designing such a BCI presents us with 2 challenges. The first one is to detect the MI of a person who is a victim of AAGA without any time marker presented to the subject (ie, asynchronously) since, during AAGA, it is impossible to ask and know exactly when the patient will intend to move. Unfortunately, the literature clearly shows insufficient classification accuracies and high false positive rates with asynchronous BCI [22]. The second challenge is, therefore, to obtain a high level of accuracy (>90%—the minimum required accuracy according to the clinical application) to ensure a reliable BCI device that can be used in hospitals. To satisfy these 2 requirements, our objective is to design a robust MNS-based BCI. Based on strong practical and theoretical scientific reasoning from our previous studies, our innovative MNS-based BCI would provide a way to detect intraoperative awareness during general anesthesia. The primary limitation of this study is that ERD/ERS habitually generated by media nerve stimulation without anesthetic may disappear for deep levels of anesthesia.

Conclusions

STIM-MOTANA will provide the first protocol study to investigate MNS cerebral motor effect during general anesthesia for the detection of intraoperative awareness. Based on strong practical and theoretical scientific reasoning from our previous studies, an innovative MNS-based BCI used in this study would provide a way to detect intraoperative awareness during general anesthesia.

Acknowledgments

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Data Availability

The datasets generated and analyzed during the current study will be available from the corresponding author on request. Records of all patients will be kept separately in a secure place in the CHU-Brugmann.

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Authors' Contributions

SR conceived the idea and rationale for this study. DS and PG are the principal investigators of this study. SR, JL, DS, CM, AMCA, GC, and PG contributed to the design and protocol of this study, and are responsible for the collection and analysis of the data. SR, JL, DS, CM, AMCA, SJB, GC, and PG were responsible for drafting and critically revising the manuscript. All authors have read and approved the final version of this manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review report by Fonds de la Recherche Scientifique (FNRS) / National Funds of Research of Belgium - SVS-3 Sciences de la Vie et de la Santé - 3 (Brussels, Belgium).
[PDF File (Adobe PDF File), 150 KB - resprot_v12i1e43870_app1.pdf]

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Abbreviations

AAGA: accidental awareness during general anesthesia
BCI: brain-computer interface
EEG: electroencephalography
ERD: event-related desynchronization
ERS: event-related synchronization
MIL: movement intention
MNS: median nerve stimulation
SEP: somatosensory evoked potential
TCI: target-controlled infusion

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Protocol

Development of an Individualized Responsive Feeding Intervention—Learning Early Infant Feeding Cues: Protocol for a Nonrandomized Study

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Abstract

Background: Responsive infant feeding occurs when a parent recognizes the infant's cues of hunger or satiety and responds promptly to these cues. It is known to promote healthy dietary patterns and infant weight gain and is recommended as part of the Dietary Guidelines for Americans. However, the use of responsive infant feeding can be challenging for many parents. Research is needed to assist caregivers recognize infant hunger or satiety cues and overcoming barriers to using responsive infant feeding.

Objective: The Learning Early Infant Feeding Cues (LEIFc) intervention was designed to fill this gap by using a validated coaching approach, SS-OO-PP-RR ("super," Setting the Stage, Observation and Opportunities, Problem Solving and Planning, Reflection and Review), to promote responsive infant feeding. Guided by the Obesity-Related Behavioral Intervention Trials model, this study aims to test the feasibility and fidelity of the LEIFc intervention in a group of mother-infant dyads.

Methods: This pre-post quasi-experimental study with no control group will recruit mothers (N=30) in their third trimester (28 weeks and beyond) of pregnancy from community settings. Study visit 1 will occur prenatally in which written and video material on infant feeding and infant hunger and satiety cues is provided. Demographic information and plans for infant feeding are also collected prenatally via self-report surveys. The use of responsive infant feeding via subjective (survey) and objective (video) measures is recorded before (study visit 2, 1 month post partum) and after (study visit 5, 4 months post partum) intervention. Coaching on responsive infant feeding during a feeding session is provided by a trained interventionist using the SS-OO-PP-RR approach at study visits 3 (2 months post partum) and 4 (3 months post partum). Infant feeding practices are recorded via survey, and infant weight and length are measured at each postpartum study visit. Qualitative data on the LEIFc intervention are provided by the interventionist and mother. Infant feeding videos will be coded and tabulated for instances of infant cues and maternal responses. Subjective measures of responsive infant feeding will also be tabulated. The use of responsive infant feeding pre-post intervention will be analyzed using matched *t* tests. Qualitative data will be examined to guide intervention refinement.

Results: This study initially began in spring 2020 but was halted because of the COVID-10 pandemic. With new funding, recruitment, enrollment, and data collection began in April 2022 and will continue until April 2023.

Conclusions: After refinement, the LEIFc intervention will be tested in a pilot randomized controlled trial. The long-term goal is to implement LEIFc in the curricula of federally funded maternal-child home visiting programs that serve vulnerable populations—those that often have infant feeding practices that do not align with recommendations and are less likely to use responsive infant feeding.

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KEYWORDS

responsive feeding; infant growth; infant nutrition

Introduction

Infant feeding practices, which include what and how infants are fed, contribute to infant growth and development, and thus, lifelong health [1]. Specifically, healthy infant feeding practices contribute to a healthy weight gain trajectory, which has been associated with decreased obesity later in life [2,3]. Healthy infant feeding practices include not only *what* infants are fed but also *how* infants are fed. The introduction of breastfeeding, breastfeeding until at least 6 months of age, introduction of complementary foods around 6 months and not before 4 months of age, and avoidance of juice and sugar sweetened beverages are recommended examples of *what* infants should be fed [1,4].

The responsive feeding approach is recommended for *how* infants should be fed and has been associated with healthy infant weight gain trajectories [4].

Responsive feeding occurs when a parent (or other caregiver) learns and recognizes the infant's cues of hunger and satiety (Textbox 1) and responds promptly to these cues [5]. Responsive feeding is thought to promote the ability to recognize and respond to internal cues of hunger and satiety [6-10]. This ability to recognize these internal cues and self-regulate intake in response to physiologic need is associated with healthy weight gain during infancy as well as dietary behaviors later in life [8,11]. For these reasons, it is important that parents use the responsive feeding approach when feeding their infant.

Textbox 1. Hunger and satiety cues in infants less than 6 months [5,7].

Hunger signals

- Wakes up and increased alertness
- Moves around
- Smacks lips
- Sucks on fist and fingers
- Cries or fusses
- Opens mouth wide
- Response to rooting reflex

Satiety signals

- Seals lips
- Turns head away
- Decreases or stops sucking
- Spits out nipple
- Falls asleep
- Decreased muscle tone

Three things must be in place for responsive feeding to occur: (1) the child signals hunger; (2) the caregiver recognizes cues and responds promptly; and (3) the child experiences a predictable response to hunger [5]. For this process to occur, caregivers must read their child's nonverbal cues and respond contingently. The degree to which a caregiver responds contingently to a child's communication, whether it is to a child's hunger cues or to bids for social interaction, is widely known to predict a child's language development [12-14]. As such, coaching caregivers to respond to feeding cues could impact overall caregiver responsiveness to their child's communication bids, which could support the child's early language development by extension.

Interventions to promote responsive feeding have shown benefit in preventing rapid infant weight gain and promoting healthy dietary patterns in infants and young children [15-22]. Despite the correlation between responsive feeding and healthy infant weight gain, the successful use of responsive feeding by caregivers is still lacking [23]. Caregivers report that recognition of hunger and satiety cues in their infant is challenging [24,25]. Infant cues can be subtle, and it can be difficult for parents to differentiate reflexive movements such as hand to mouth and rooting. Additionally, recent literature has identified maternal characteristics such as infant feeding beliefs, age, mental health, and the mother's own eating behavior as contributing to the use of responsive feeding [26-29]. Infant temperament and support from health care professionals and family and friends also play a role [23,26]. Therefore, more research is needed to find ways to assist caregivers in recognition of hunger and satiety cues and to overcome additional barriers to promote the use of responsive feeding during infancy.

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The Learning Early Infant Feeding Cues (LEIFc) intervention was designed to fill this gap by using a validated coaching approach with the mothers of new infants to promote responsive feeding. The proposed study aims to test the feasibility and fidelity of the LEIFc intervention in a group of mother-infant dyads. We aimed to (1) develop, refine, and test a responsive feeding intervention that can be used within real-world settings to serve mother-infant dyads in the community and (2) design the model with a primary emphasis on responsive feeding, but with a secondary focus on early communication to help caregivers understand the dual benefit of noticing and responding to infant cues.

Methods

Ethics Approval

The institutional review board at Florida State University approved this study (STUDY00002895).

Theoretical Framework

The Obesity-Related Behavioral Intervention Trials (ORBIT) model is used to guide the proposed study [30]. The ORBIT model uses an iterative process and was chosen because the LEIFc intervention is behavioral in nature, in the early stage of development, and focused on prevention of a chronic disease [30]. Testing fidelity and feasibility of the LEIFc intervention study falls into phase I of the ORBIT model as the intervention has been designed but needs to be refined based on preliminary testing. The findings from this initial study will provide the foundation to move to phase II and conduct a proof-of-concept trail.

Study Design and Intervention

This study uses a pre-post quasi-experimental design with no control group to examine the feasibility, fidelity, and social validity of the LEIFc intervention. The intervention was developed based on existing literature regarding enablers and barriers to the use of responsive feeding by caregivers and communication cues present early in life. The multicomponent LEIFc intervention involves maternal education on responsive feeding practices and mother-infant communication while using a family-guided caregiver coaching approach called SS-OO-PP-RR (“super,” Setting the Stage, Observation and Opportunities, Problem Solving and Planning, Reflection and Review) during feeding sessions [31,32]. The SS-OO-PP-RR approach was developed based on adult learning theory and has been successfully used with parents and childcare providers to promote development across domains in infants and young children [31-33]. For the LEIFc intervention, SS-OO-PP-RR was modified to be specific to communication during feeding to promote responsive feeding (Textbox 2). It is used as a guide for the interventionist during the coaching session but will also be used to evaluate the fidelity of the intervention. The objective measure of responsive feeding will occur through video recording of feeding sessions between mothers and infants. Videos will be coded before the intervention and then after 2 coaching sessions between the interventionist and the mother during a feeding session. The subjective measure of responsive feeding will be collected via a self-report questionnaire completed by mothers before and after the intervention study visits.

Textbox 2. The “super,” Setting the Stage, Observation and Opportunities, Problem Solving and Planning, Reflection and Review intervention.

Setting the Stage (SS)

- Asks the caregiver to update how responsive feedings have been going since the last visit—listens, encourages caregiver reflection, and sets up problem-solving as needed
- Shares information related to responsive feeding—connects strategies to the child’s long-term health, well-being, and communication development
- Clarifies responsiveness strategies to use during the session (watching for hunger and fullness cues, using talk and touch during feeding, and stopping when the baby is full)

Observation and Opportunities to Embed (OO)

- Observes the caregiver-child interaction in feeding routine—provides feedback and builds on dyad strengths
- Uses coaching strategies (guided practice, direct teaching, demonstration, and caregiver practice) to help the caregiver embed responsiveness strategies into the feeding routine
- Provides general and specific feedback on caregiver and child behaviors and interactions (links caregiver strategy to child response)

Problem-Solving and Planning (PP)

- Problems solved with the caregiver about appropriate responsive feeding strategies
- Supports the caregiver to identify opportunities to help other caregivers use the strategies (other parents, childcare, and grandparents)

Reflection and Review (RR)

- Asks questions and comments to promote caregiver reflection and review of the feeding routine—identifies what worked for the caregiver and child
- Engages the caregiver to lead development of a “best plan of action” for using responsiveness strategies between visits

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Setting and Participants

Mothers of any parity will be recruited from community settings during the third trimester (28 weeks and beyond) of a healthy pregnancy. To be eligible, mothers need to be aged 18 years or older, able to read and speak English, and agree to video recording of an infant feeding in their home. Any medical or congenital condition in the fetus that would interfere with infant feeding or growth (ie, Down syndrome or cleft lip or palate) will be excluded. Mothers will be enrolled in the third trimester and then screened again after the birth of the infant to ensure that mother and infant remain eligible to participate.

An interventionist will be recruited to deliver the LEIFc intervention in the homes of new mothers. He or she will ideally have a background in maternal-child health and may be a nurse, social worker, speech-language pathologist, dietician, or early child development specialist. The interventionist will be trained on the SS-OO-PP-RR approach and the LEIFc protocol. Because the purpose of this study is to test the fidelity and feasibility of the intervention, feedback from the interventionist will be sought as part of the research protocol.

Procedures

Eligible mothers will be identified through community settings such as obstetrician offices, prenatal parenting or birth classes, social media forums that pregnant moms may frequent, and word of mouth. If eligible and interested in the study, study personnel will consent mothers for the study. Once enrolled in the study, the interventionist will implement each study visit (Table 1). Study visit 1 is conducted when the mother is in the third trimester of pregnancy. Written material on infant feeding and infant cues of hunger and satiety is provided. Additionally, 2 short videos, one on infant hunger cues and the second on infant satiety cues, are watched with the interventionist and the mother. Any questions on feeding or communication are answered by the interventionist. Study visit 2 is conducted when the infant is approximately 1 month old. At this visit, a video recording of a feeding session between the mother and the infant is taken with no interaction with the interventionist. The feeding can be from the breast or from the bottle (with breastmilk or formula). Study visits 3 (at infant age of 2 months) and 4 (at infant age of 3 months) are the intervention study visits. At each visit, the interventionist will use the SS-OO-PP-RR tool to coach the mother through the feeding to identify hunger and satiety cues and discuss ways to respond. Each of these visits is also video recorded. The final study visit is at infant age of 4 months when another video recording of the infant feeding session is taken with no coaching from the interventionist.

At study visit 1, demographic data are collected along with the mother's prenatal plans for infant feeding. At study visit 2, birth history is collected along with infant feeding practices, and the mother completes the Infant Feeding Questionnaire (IFQ). During study visits 3 and 4, infant feeding practices are collected. At study visit 5, the mother completes the IFQ and provides feedback on the study itself through a series of qualitative questions.

Table 1. Timing of study visits and procedures.

Study visit	Timing of visit	Components of the visit	Visit location
1	Prenatal (28 weeks or beyond of gestation)	• Education provided on communication with your baby during feeding—videos and written material	Video conferencing platform (Zoom)
2	Infant age approximately 1 month	• Complete Infant Feeding Questionnaire • Video record the mother and baby during a feeding with no coaching • Collect current infant feeding practices	Family home
3	Infant age approximately 2 months	• Video record the mother and baby during a feeding • Provide coaching to the mother during the feeding • Collect current infant feeding practices	Family home
4	Infant age approximately 3 months	• Video record the mother and baby during a feeding • Provide coaching to the mother during the feeding • Collect current infant feeding practices	Family home
5	Infant age approximately 4 months	• Video record the mother and baby during a feeding with no coaching • Complete Infant Feeding Questionnaire • Collect current infant feeding practices	Family home

Outcome Measures

The primary outcome in this study is the use of responsive feeding. This will be measured before (study visit 2) and after (study visit 5) intervention. Data are obtained subjectively through evaluation of the IFQ and objectively through a video review. The IFQ will provide a subjective measure of responsive feeding. This 20-item self-report tool has been validated for use in mothers of infants [29,34,35]. Likert-type scoring is used; higher scores indicate a stronger measure of the construct. Three subscales will be used to measure responsive feeding: use of food to calm, use of food to soothe, and awareness of infant cues.

The objective measure of responsive feeding will be collected via coding of the video session before and after intervention. The research team developed a coding scheme to capture both mother and infant behaviors during the feeding interactions. The coding scheme was adapted from the Responsiveness to Child Feeding Cues Scale [36] to define specific, discrete

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maternal behaviors that relate to responding to infant hunger and satiety cues as well as early infant communication acts. Infant behaviors are coded for hunger, satiety, and early communication acts. Research assistants will be trained on the coding scheme and will use existing videos to code with a goal of at least 85% agreement achieved to confirm inter-rater reliability. The coding scheme developed by the team will be used to code the feeding interactions for study visits 2 and 5. Videos will be coded for the number and rate of maternal utterances directed toward the child and responsiveness to the child's vocalizations using the Noldus Observer XT software. The percentage of the interactions spent jointly engaged between the mother and the infant will also be coded.

Infant feeding practices, demographic characteristics (ie, maternal age, marital status, education level, and race and ethnicity), and maternal depression will be considered as covariates. Initiation and duration of breastfeeding and age at complementary food introduction will be extracted from data and tabulated into variables: duration of breastfeeding (any and exclusive) calculated in weeks and age at complementary food introduction calculated in weeks. Demographic data are collected at study visit 1, infant feeding practices at study visits 2 through 5, and maternal depression (via the Patient Health Questionnaire-9) at study visits 2 through 5.

Statistical Analyses

Power analysis for the matched-pair *t* test was conducted. With the lower limit of the medium effect size of 0.5 [37], sample sizes of 27 and 36 provided 80% and 90% power, respectively, under 1-sided directional null hypothesis and the nominal significance rate of .05. We will aim to enroll 30 participants for this feasibility and fidelity study.

Once data are clean, descriptive statistics will be computed and examined. For the primary outcome, benefit will be determined by an increase in responsive feeding codes pre-post SS-OO-PP-RR coaching sessions (visits 2 and 5). IFQ subscale scores will be analyzed using matched sample *t* tests for pre-post coaching sessions to determine the benefit of the intervention. If the assumptions of statistical tests are not clearly met, the Mann-Whitney *U* test would be considered as an alternative. In a future pilot randomized controlled trial (RCT), analysis of covariance (ANCOVA) will be conducted where the difference between treatment and control groups for the postmeasure is examined with the premeasure as a covariate. The use of ANCOVA provides a statistical control in addition to the design control for the premeasure via random assignment in the RCT.

Results

This study was initially designed to begin recruitment in the spring of 2020. Because of the COVID-19 pandemic, all research activities ceased from March to September 2020. The research team modified the protocol to conduct this study with socially distanced measures in place (ie, using videoconferencing platforms for data collection) and began recruitment in October 2020. Two enrolled participants were unable to complete study visits as scheduled, and data collection was unsuccessful. New funding was sought and obtained; recruitment began again in April of 2022 and data collection soon after. It is anticipated that data collection will be complete in April of 2023.

Discussion

Anticipated Findings

Although data collection for this study is ongoing, it is anticipated that the LEIFc intervention will be feasible to implement with and socially acceptable to mother-infant dyads by a trained interventionist. Additionally, it is hypothesized that fidelity of the intervention would need to be refined to better meet the needs of mother-infant dyads, especially those from high-risk populations (ie, minority groups and low socioeconomic status). Qualitative data collected from mothers (visit 5) and from the interventionist (visits 3 and 4) will be used to refine the intervention. Finally, it is hypothesized that there may be a change in responsive feeding before or after intervention; however, it cannot be attributed to the intervention until tested with a control group, in the future planned RCT.

Implications

Childhood obesity rates continue to rise. Data from the National Health and Nutrition Examination Survey (NHANES) found that between 2017 and 2020 (prepandemic), 19.7% of children aged 2-19 years in the United States had obesity [38]. This is up from the previous NHANES data reporting 18.5% of children with obesity [39]. This rise in childhood obesity percentage suggests that efforts in recent years are not enough and more strategies are needed to halt this epidemic. Additionally, there are a higher percentage of children who are non-Hispanic Black, Hispanic, or from families living below the poverty line with obesity (24.8%, 26.2%, and 25.8%, respectively) [38]. Children with obesity are at risk for lifelong cardiometabolic conditions such as hypercholesterolemia, hypertension, and type 2 diabetes [40,41]. Children with obesity are also more likely to have mental health disorders (ie, depression and anxiety) and complications of the pulmonary, orthopedic, and gastrointestinal systems [1,42,43]. The first 1000 days of life, from conception to age 2 years, is a critical period for the development of habits that contribute to one's weight status later in life, such as dietary preferences and behaviors [3,44-46]. Therefore, interventions implemented during the first 1000 days and targeting infants from high-risk groups (those of minority race and ethnicity and low socioeconomic status) have potential to decrease one's obesity risk and subsequent complications. The promotion of responsive feeding is one such intervention that could be used to promote healthy infant weight gain and prevent obesity.

Outcomes

Education on and promotion of responsive feeding should begin prenatally and evolve with the developmental of the child [5]. Research has demonstrated that responsive feeding during infancy helps an individual learn to eat in response to their own internal cues opposed to eating on a schedule [8-10]. The development of this eating pattern early in life may promote healthy eating behaviors lifelong, thus contributing to healthy weight status and prevention of cardiometabolic complications [41]. In addition, this early support for maternal-child

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communication may enhance language development during infancy. Infants' earliest communication acts relate to signaling hunger cues, and maternal responsiveness to a child's cues has long been established as an important predictor of later language outcomes [14]. As such, the LEIFc intervention has the potential to support 2 positive outcomes in children—healthy weight gain and positive communication outcomes.

Infant feeding in the first months after birth often occurs in the home, making this an ideal environment to promote responsive feeding [44,46]. Should the LEIFc intervention be successful, implementation in maternal-child home visiting programs would be sought. Maternal, infant, and early childhood home visiting programs, such as Early Head Start and Healthy Start, provide services to families from pregnancy up to the age of 5 years in at-risk communities [47,48]. These programs serve families from low socioeconomic backgrounds that often include those of minority status. Children from these families have higher rates of childhood obesity, cardiometabolic complications, and language delays [38,43]. The implementation of a responsive feeding intervention in these programs has potential to prevent several complications in children who receive this support, making implementation of the LEIFc intervention an important component to maternal-child home visiting program curricula.

Conclusions

The current funded study will test the feasibility and fidelity of the LEIFc intervention in a group of mother-infant dyads. The intervention has potential to promote 2 childhood outcomes: healthy weight gain and early language development. The results of this feasibility study will allow the researchers to refine the intervention and move to phase IIa of the ORBIT model, testing proof of concept of the intervention. If successful, the LEIFc intervention would be expanded to include vulnerable mother-infant dyads enrolled in maternal-child home visiting programs. Once implemented into the curricula of such programs, application and sustainability would be strong.

Acknowledgments

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Data Availability

Data are available from the corresponding author upon request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
External peer review comments from Florida State University College of Nursing.
[PDF File (Adobe PDF File), 449 KB - resprot_v12i1e44329_app1.pdf]

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Abbreviations

ANCOVA: analysis of covariance
IFQ: Infant Feeding Questionnaire
LEIFc: Learning Early Infant Feeding Cues
NHANES: National Health and Nutrition Examination Survey
ORBIT: Obesity-Related Behavioral Intervention Trials
RCT: randomized controlled trial
SS-OO-PP-RR: "super," Setting the Stage, Observation and Opportunities, Problem Solving and Planning, Reflection and Review

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Protocol

Home Care in the Daily Lives of Older People: Protocol for an Ethnographic Two-Year Longitudinal Study

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Abstract

Background: Research on eldercare has been dominated by a provider-oriented perspective, concerned with the conditions and views of care providers. There are striking differences compared with the field of disability studies, where help is framed as part of a larger project of having a daily life and being included in society. Pilot interviews indicate that older people develop active strategies to make care work. These include *practical* preparations, *emotional* activities such as showing an interest in staff members' lives, or *rhetorical* skills in asking for help.

Objective: The aim of this project is to develop empirical and theoretical knowledge of eldercare as a relational practice, accomplished by older people in their daily lives. This perspective will also offer an alternative to ongoing attempts to reduce the user perspective to an issue about older people acting as customers in a market.

Methods: The project will map, investigate, and follow up on care use from the perspective of care users. The project has an ethnographic 2-year longitudinal approach. Data consist of interviews and participant observations with 35 persons (home care users and cohabitating partners) and a diary study with additional 10 care users. Inclusion criteria are people 65 years or older with home care provided by needs assessors. It is preferred that they have had home care between 6 months and 2 years in order to follow a progression in roles, identities, and strategies within home care use.

Results: Between May and October 2022, 25 interviews with home care users were conducted. Data collection with follow-up interviews and observations, analysis, and reporting of findings will be completed by December 2024.

Conclusions: By studying care use in the context of older people's lives the project will add important knowledge about the strategies and adjustments older people apply to make care arrangements work. A user-oriented perspective will further the understanding of how power relations play out in home care over time in relation to the formal rights, categorical belongings, and established norm systems that place the user in superior or subordinate positions.

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KEYWORDS

eldercare; user perspective; home care; theory of care use

Introduction

Background

Care has been studied as a relational practice, but above all as a practice for those who *provide* care. This project will shift focus to go beyond the casting of older people as either passive objects or active consumers to provide the empirical and theoretical base for a third route. The point of departure is that older persons act and reason in specific ways to make home care work for them and to ensure that help is provided without friction. This entails thoughts, deliberations, and a range of actions that for older people with home care are part of everyday life:

- Waking up early to prepare the home for visiting care staff

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- Learning the home care organizations' technical vocabulary
- Working out which care staff will take out the rubbish as they leave, even if this service is not officially included
- Showing an interest in the personal lives of the care staff and finding common interests
- Deciding whether to go grocery shopping in person or to adapt to buying food online
- Deciding to buy in tax-deductible cleaning and laundry services privately to supplement council-provided home care. (Tax deduction on household services or RUT (rengöring, underhåll, och tvätt [cleaning, maintenance, and washing] were introduced in Sweden in 2007, and RUT service companies increasingly use the term "eldercare" to promote their services.)

Research on home care and other forms of eldercare has been dominated by a provider-oriented perspective, which revolves around the organization, conditions, views, and activities of those who provide the care. This perspective has been developed in theories that define care as a moral, relational practice by which the caregiver interprets the needs of the dependent person [1-6]. Studies of the everyday realities of home care have comprised both providers and users, but as in the excellent thesis by Szebehely [7], the analytical focus and the theorization of eldercare have usually been directed toward the provider side of the relationship. This perspective has also dominated studies of the coordination of care efforts, informal care, and its nexus of formal care [8,9]. Even approaches in the "person-centered" care paradigm share this focus; one review found that most models measured staff members' views [10]. Although the provider-oriented perspective has enlarged our knowledge of the everyday realities of care, few studies have considered the care users' perspectives. The absence of a user-oriented perspective is significant when compared with the field of disability studies. In a review of Swedish research, Erlandsson [11] noted that of 26 Swedish theses about "non-old" people with disabilities, the sole focus of 11 was the person being helped and 2 focused on the provider. By contrast, of the 25 Swedish theses about care for older people, none focused only on the user, whereas the sole focus of 12 was the care provider. The provider-oriented perspective in eldercare is strikingly different from approaches in disability studies. One reason for this is that help for "non-old" people is framed as part of a larger project of daily life and being included in society [11-13]. The provider perspective is crucial in any care situation, but too strong an emphasis on providers plainly risks discounting aspects such as social rights and undermining attempts to resist ageism and exclusion.

This project will address the need for a user-oriented perspective as part of a larger mission to develop a theory of care use. A user-oriented perspective will further the understanding of how power relations play out in home care over time, in relation to the formal rights, categorical belongings, and established norm systems that place the user in superior or subordinate positions. The perspective will also offer an alternative to ongoing attempts to make sense of the meaning of eldercare in a new landscape, where new cohorts of older people become care users, and where marketization has been presented as both a solution and a threat to the welfare state's ambitions [14-16]. Critical approaches have provided valuable knowledge, but in the attempt to combat unrealistic forms of marketization [17], there is an evident risk of downplaying the capabilities of older care users. An alternative route is needed that acknowledges the importance of relations, skills, and adjustments over time.

The project will use qualitative interviews, participant observations, and a diary study to investigate understanding, strategies, and adjustments of older people who use home care, thereby providing a type of knowledge that has so far not been devoted sufficient attention.

Aim and Research Questions

The aim of the project is to develop empirical and theoretical knowledge of home care as a relational practice, as interpreted, accomplished, and negotiated by older people in their daily lives, as part of the formal and informal services available to them:

- RQ1: How do older people navigate, coordinate, and fit care arrangements and other forms of help into their home contexts, daily activities, long-term plans, and social relations?
- RQ2: What practical, emotional, and rhetorical strategies do older people apply in their interaction with care staff?
- RQ3: What types of identities, categorizations, and roles are played out when older people receive home care, and what is the bearing on power relations?
- RQ4: How are users' needs formulated as part of their experience of the eldercare system and their relations with home care staff over time?

The Context of Studies

The studies of the project are situated within several fields of research and investigations, internationally and in the Nordic countries.

A comprehensive body of research theorizes and investigates eldercare, with a strong tradition and prominent research environments in Sweden, Denmark, Finland, and Norway [3,5,18-20]. The research has concentrated on the provision of formal eldercare as part of the social policy of the Nordic welfare states, with studies of the everyday realities, organization, working conditions, needs assessments, and relations between formal and informal care. Research and theories that use this provider-oriented perspective will serve as a backdrop to the project.

A second type of research that informs the project consists of studies that gauge care users' opinions when defining quality of care. The National Board of Health and Welfare's large annual user survey "Vad tycker äldre om äldreomsorgen?" (What do older people think about eldercare?) is the most prominent study from a Swedish horizon [21]. It should be noted that such studies have been criticized for the way they translate quality into numbers. Internationally, qualitative and mixed methods have been used to investigate how the quality of care is measured or the broader issue of quality of life from the perspective of the care user [22].

A third type of research that will feed into the project consists of studies of user participation, originally developed to empower

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older people who use health care or social care. This research tradition is anchored in Arnstein's [23] paradigmatic article on the ladder of participation and includes studies of decision-making, power sharing, and the influence of formal interest groups [24]. Notably, however, that participation is usually constructed in eldercare as involvement in care (such as helping get dressed, and sometimes with the aim to achieve help to self-help), whereas the disability field focuses on participation in society and how society's support makes that possible [11].

For the project, the state-of-the-art research builds on what Lloyd [25] calls the personalization agenda, also described as a relational-political interpretation of the capability approach [26]. Acknowledging the relevance of structural conditions and care policies, this research has included studies of power and control over services, relations, time, and the home and its artifacts, and shows that home care can be both enabling and restrictive [27,28]. The approach has also included studies with a phenomenological approach that relate the experience of receiving home care to the meaning to older individuals of home, body, dependence, and relations [29]. Several studies have focused specifically on how older people view, evaluate, and work to establish such relations [30]. Studies using this approach have also addressed the shift to marketization and show that older care users' choices play out in ongoing care and not just at the point when a particular care provider is chosen [31-33].

Drawing on theories in disability studies, the knowledge gained from the project will be used to develop a theory of care. The fact that the nexus of disability and ageing is attracting greater interest, and that concepts such as social rights, discrimination, and exclusion are now being used in policies on ageing, will facilitate the use of a disability lens in the study of home care [11,12,34], bringing a fresh focus on the way home care services enable older people to fully participate in society, or, where relevant, to regard services as restrictive and therefore ageist, with all that the concept of ageism means for the project findings.

The project will take a longitudinal approach. Increased needs frequently entail help from ever-larger numbers of providers, and pilot interviews reveal the efforts made to navigate what is on offer from different providers. Previous studies show that care users adapt their habits to (restrictive) arrangements that they consider to be the conditions of care, but that they also learn what demands and questions to put to care providers, and they try to develop relations that work against and between what is formally granted by the organization [27,28]. The project will provide a unique understanding of how relations, loyalties, skills, and adaptations develop within home care.

Methods

Overview

To address its stated aim and questions, the project will map, investigate, and follow up on care use from the perspective of care users. The mapping will be done with structured interviews with users and in some instances with information from their cohabiting partners and is inspired by existing network studies [35]. The main part of the project will be based on interviews and participant observations. Finally, care use will be followed up using the project's chosen longitudinal approach [36]. This phase of the project will also include a study of care users' diary notes. In its qualitative and longitudinal approach, the project will provide knowledge beyond satisfaction ratings and so will contribute to a well-grounded understanding of eldercare as negotiated by older people in their daily lives, with developing relations and adaptations. By including cohabiting partners, knowledge will be gained about how they too fit care arrangements into their daily lives, and possibly must take on new roles when interacting with home care staff.

Care always occurs within a broader social context of established policies, here in the context of the Nordic welfare state. Policy is realized in everyday practices, and thus a microsociological understanding is crucial when theorizing care use. The project will be theoretically anchored in symbolic interactionism and will use an ethnographic study design to reveal meaning-making, interaction, and the negotiation of identities. The point of symbolic interactionism is that people act toward things based on the meaning those things have for them, and meaning is created in an interpretive process derived from social interaction [37]. In the data analysis, we will make use of theories and concepts developed for the understanding of human service work [38,39] and care work [1,40]. These theories and concepts will be adapted to the care users' positions and perspectives, and the analysis will focus on categorization work (users' categorizations and their evaluations of care staff), empathy, and emotion work, whereas impression management will be studied at the point when older people encounter human service organizations and their representatives (the care staff). This redirecting of analytical focus will be facilitated by the types of comparison to the field of disability studies suggested above.

The theories that the project is designed to develop will increase the understanding of home care use as a *position* and *practice*, anchored in a broader social context but realized in older people's everyday lives. This way of theorizing care could potentially be developed as part of a broader paradigm of help-receiving and care-receiving that reflects people's everyday conditions.

Studies that use a symbolic interactionist approach typically have 2 overarching stages: exploration and investigation [37]. Below, we will first describe how the exploration stage has proceeded, to be followed by the investigation stage, which falls into 3 phases. During the investigation, concepts will become fixed as part of the findings and theory development.

Exploration

The exploration stage has been initiated and conducted through pilot interviews and various contacts with partners for collaboration in the field. The pilot interviews (financed by Helsingborg Council for December 2020 to October 2021) indicate that care users engage in a continuous form of "work"—emotional, practical, and rhetorical activities. Care users use these activities to prepare staff and guide the provision of care, to defend the privacy of their relations and homes, and to avoid depersonalization. Some users carefully prepare their homes and themselves to ensure that care activities run

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smoothly. They may display an emotional interest in staff members' personal lives to make themselves visible as individuals. Some users describe rhetorical strategies to adopt the correct organizational and technical vocabulary to get the help they want, to avoid the response "We don't do that," and to develop relations with staff that affect the character of care.

From the exploration stage's pilot interviews and literature review, we have so far identified four themes to be used as sensitizing concepts.

1. Enablement (goals in everyday life, achieved with home care and the navigation and coordination of services)
2. Relations and loyalties (in and beyond the home care tasks)
3. Power and control (over services, space, time, and categorizations)
4. Identity (as affected by receiving care and used to interpret the meaning of care)

The investigation will fall into 3 phases, including empirical studies, collaboration with users and other actors outside academia, and dissemination. The studies of the project are described below, whereas the other activities are described elsewhere in this application.

Stakeholder Involvement During the Exploration Stage

Contacts with members and stakeholders of the field studied are an essential part of the exploration stage, and in the project, such contacts take the form of user involvement and collaboration with actors outside academia. The project uses a model for collaboration and user involvement that focuses on purpose, actor, magnitude, and process [41]. This PAMP (Purpose, Actor, Magnitude, and Process) model (SAPO in Swedish) will guide the development of the project, and below we describe the way the initial stage has proceeded. The purpose of this involvement is to identify relevant questions and sensitizing concepts for further studies, a process similar to what Greenhalgh et al [42] call priority-setting.

Two stakeholder panels have been set up, and additional collaboration has been established with a panel of stakeholder organizations.

Panel 1: Stakeholders With Home Care and Cohabitating Partners

Throughout the project, a user panel of 5 older people with several years of experience of home care will provide feedback on the research process, analysis, and dissemination of results. The panel members have already been involved in the exploration stage, developing research questions and provided valuable feedback on how to strengthen the project's user orientation. Members of the user panel will be part of the project for the entire period (except the dissemination phase) and will be able to influence findings by their validation at regular meetings. The panel consists of persons from the pilot interviews, the current ethnographic study, and professional and personal contacts. Participants have been informed that participation in the panel is voluntary and based on interest to discuss the type of questions that the project investigates. The plan is to have 2 annual meetings. A first meeting was held in May 2022 and a second in November 2022. A lesson so far concerns the frailty of the panel, with a need to recruit new members in case of severe illness or death.

Panel 2: Senior Stakeholders

Throughout the project, a panel of 6 older persons who are interested in the topic of the project will provide feedback on the research process, analysis, and dissemination of results. They will be recruited among senior citizen organizations as well as professional contacts in order to get a balanced distribution of senior citizens. Participants have been informed that participation in the panel is voluntary and based on interest to discuss the type of questions that the project investigates. The plan is to have 2 annual meetings, and the meetings were held in April 2022 and October 2022.

Panel 3: Organizations as Stakeholders

Contact has been established with 3 collaboration partners to act as members of a reference group during the projects. These partners are representatives of Helsingborg Council's eldercare provision; regional and local representatives of the 2 pensioners' organizations, PRO (Pensionärernas riksorganisation, the Swedish national pensioners' organization) and SPF (SPF-Seniorerna, the Swedish association for senior citizens); and representatives of Seniorval (lit. Seniors' choice), a national private provider of information and guidance for older people who apply for home care. During the investigation and dissemination stage, the external partners will be invited for discussions on how to translate our findings into information and programs that are useful for older people who use home care.

The purpose of involving representatives of a local authority and a provider of information—Seniorval—is to achieve direct impact by developing routines and information based on the findings of the project. These actors will be consulted at regular meetings.

Investigation

Phase 1: Mapping Care Arrangements and Investigating Care as a Relational Practice

The first core study will map out the different kinds of care arrangements in older people's everyday lives. Research on informal care has shown that relatives provide a type of managerial care that includes the planning and coordination of help efforts [9], and it has been noted that also older home care users themselves and their cohabiting partners engage in such coordinating efforts [28].

Study 1 will be based on semistructured, qualitative interviews with 25 care users and 10 cohabiting partners, in which the research questions will serve as nodal points for the questions in the interview guide. The first part of each interview will be devoted to a structured mapping of help from the perspective of the care user (including cohabiting partners' perspectives on the help provided in their shared home).

Phase 2: Home Care as Accomplished, Coordinated, and Fitted Into Everyday Life

The second core study will be the most extensive, to be based on interviews and participant observations on several occasions.

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Researchers will be present in the users' homes on 2 separate occasions when care staff visit. During these "stay-along observations" (inspired by go-alongs [43]; see also [28]) we will observe and engage in informal field-based interviews with users, staff, and (where present) cohabitating partners. This method will allow us to observe users' preparations and interactions, matched with a fine granularity in the details of care for the necessary contextual understanding of the users' and cohabiting partners' interpretations and strategies.

Study 2 will be based on the interviews conducted in study 1 and on 2 participant observations in the homes of the 25 care users within a month of the first interviews. Instead of accompanying home care staff as they visit various users, we will be present in the users' homes on 2 separate occasions when home care staff visit.

Phase 3: Care Use and Change Over Time

The third stage of the project will follow up on care use using the project's chosen longitudinal approach [36]. On the basis of interviews with care users and additional observations, this approach will provide knowledge of how the user's strategies, perceived needs, and relationships with care staff change. A second study with the same objective will collect data in the form of older care users' diaries. Diary methods can offer a more comprehensive understanding of an individual's everyday activities and thoughts, and the data provided are likely to give a different insight compared with conventional interview approaches [44]. It is also a means of identifying important but seemingly mundane practices, which may be overlooked when relying on "snapshot" approaches such as interviews and surveys.

The follow-up study is based on interviews with all available care users, conducted 16-22 months after study 1. The objective is to gauge how perceptions, relations, and strategies change over time, especially in relation to any alteration in the users' needs and degree of dependence. A total of 10 participants will be chosen for a final round of participant observations.

Diary data will be collected from approximately 10 care users. Each participant will be asked to complete and return a weekly diary for 20 weeks.

Data Collection

Approximately 25 care users from three Swedish local authorities will be included in the project. Additional interviews will be conducted with 10 cohabiting partners. Out of the 35 total respondents, data will thus consist of 60 (25 + 25 + 10) interviews plus 60 (25 + 25 + 10) stay-along observations and diary notes from 10 home care users. The following selection criteria will be used to identify participants: the care user should be 65 years or older and have home care at least twice a week. The project will strive to achieve diversity in the level of care, gender, socioeconomic aspects, and length in experience of living with home care. As part of the effort to map services from a user perspective, 10 participants will be chosen who have home care and combine it with private help through the RUT.

Approximately 10 older people will participate by writing diary notes about their experiences of home care and other forms of care over 20 weeks. The following selection criteria will be used: the care user should be 65 years or older, have home care at least twice a week, and be interested in formulating their experiences in writing. Participants will be recruited through the website Seniorval, where the researchers will advertise for home care users with an interest in documenting their experiences and reflections in diary format.

Home care users with cognitive disorders (dementia) will not be included in the project studies, but the project will develop theory that may be used in future studies of persons with such disorders.

The types of data that are generated are recorded and transcribed interviews, field notes from observations, and diary entries.

Data Analysis

The project will produce a range of findings and is designed to develop a theory of care use. Data will be coded using the NVivo software package, and the steps of qualitative content analysis [45] will be used in the different project studies. Following the tradition of symbolic interactionism, findings will be grounded in the data, guided by the research questions of the project and by the sensitizing concepts identified during the exploration stage. Theories of care work and categorizations that relate to the tradition of symbolic interactionism will inspire the analysis and development of the theory. See also the section on theoretical foundations and guiding tools above.

Ethics Approval

The project plan has been approved by the Swedish authority of ethics approval (2022-00829-02).

The project will focus on how older people interpret and negotiate home care in their daily lives. Thus, it will likely generate sensitive personal data on health. This will be the case, for instance, if interviewees comment and elaborate on illness, disability, dependency, and well-being. The principal investigator and co–principal investigator are familiar with the content and procedures for such applications and the proper procedures that follow ethical approval. Research participants will be provided with written and verbal information about the project's studies, they will be informed that participation is voluntary, and they will be asked to sign a consent form. Data will be anonymized, and publications will not contain information that makes it possible to identify individuals.

The members of the research team have extensive experience in interviewing older people and observations in sensitive contexts. Our experience is that project information and informed consent should be treated as continual practices throughout the research process. Given the project's longitudinal approach, researchers will ask for informed consent at each of the 4 visits. Prior to each "stay-along observation," the researcher will ask research subjects about potentially sensitive situations and how these should be handled. Researchers will not observe situations that are ethically problematic, such as toilet visits and dressing or undressing.

The knowledge gained will benefit older people in a broad sense by shedding light on the everyday realities of those who receive home care. Hitherto, the absence of a true user perspective is

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striking. The project is not expected to cause any harm or inconvenience to the research subjects but will hopefully lead to improvements in the long run for older people with home care.

Results

Members of panel 2 participated in a meeting with representatives of the project in April 2022, with the aim to introduce the project. A meeting with panel 1 was held in May 2022, where members of the group provided feedback on an interview guide, through meta-discussions and direct responses to some of the questions. A second meeting with the 2 panels was held in October and November 2022, with the aim to present preliminary findings in order to discuss their validity and relevance.

Between May and October 2022, the first round of interviews (n=25) was finalized. Interviews with partners will be finalized in January 2023, and the first round of observation is expected to be finalized by March 2023. Data collection with follow-up interviews and observations, analysis, and reporting of findings will be completed by December 2024.

Discussion

Principal Findings

The expected main findings of this ethnographic study on home care from the user perspective are that older people use their agency to navigate and fit home care into their daily lives, and that home care enables aging in place but has a number of restricting features that concern the control of time and place.

A user-oriented perspective on eldercare will have an important role in the new landscape of eldercare. This landscape has a theoretical and administrative ambiguity about the content and meaning of eldercare. A revision of the Social Services Act [46] in 2018 allows local authorities to grant older persons home care without an assessment of individual needs. This reform is likely to push the assessment of needs toward the actual meeting between the care user and the care provider, a development at odds with the emphasis on professional needs assessments according to the International Classification of Functioning, Disability and Health–based tool IBIC (Individens behov i centrum [the Individual's needs in center]), previously introduced by Socialstyrelsen [47]. The emphasis on the actual meeting or interaction between the user and provider is also evident in the government white paper [48], according to which older home care users should be offered a personal contact person (*omsorgskontakt*) who is responsible for providing support and managing the personalization of care. However, the actual nature of the position of *omsorgskontakt* is left open. Should it be a member of the professional team that coordinates services for the user, or should it be a care worker who is chosen by the user to perform most services based on their relation and trust? This role ambiguity is also connected to the ongoing marketization of eldercare. Should care be provided by certified, professional care staff, as has been suggested in a government investigation [49] or should Sweden's system for tax deductions for domestic services (RUT), which is increasingly being used and sometimes labeled as "eldercare," be further developed for the category of older people [50]? This system has made it cheaper for older people with higher incomes to buy help and personal care or to top up needs-assessed home care [15]. This development may cause increased social inequality and the exploitation of unskilled workers—private care is now the backbone of eldercare in several European countries. Within the heated debate on marketization, there is even a risk that researchers stress the inability and incompetence of older people as care users to question the relevance of choice models [17]. The third route that the project will develop is needed as part of the ongoing development of eldercare.

Strengths and Limitations

The project has a qualitative multimethod approach using semistructured interviews, observations, and diary notes. A strength in method diversification is a prediction of each capturing different aspects of the subjective experience. An interview is more likely to prime a respondent to evoke stories of critical or otherwise noteworthy events, mostly because of role expectation. The collection of diary notes aims to capture more mundane observations from an older person that may not have made it into an interview answer. The added strength of a period of diary note taking is that the older person will likely be more observant for a period of time. The observations complement the other methods, in that the researchers observe what is happening and prompt a series of short field-based interviews [51] right after a home care visit, which is expected to give slightly different answers when the memory and possibly affect are fresh. The mapping aspect has the strength of combining older persons' experiences with more structured questions from the researcher, contrasting the older persons' subjective experience with references of comparative needs [52].

The main limitation of the project concerns recruitment and inclusion criteria. For the selection of the first 35 older persons for interviewing, the municipal home care managers are needed in order to gain access according to plan. By having municipal managers and home care staff as gatekeepers, there is a risk that older persons who are most likely to have a positive attitude toward home care will be asked to participate. This risk is particularly present when organizations represent fear that the project aims to evaluate the organization and its co-workers rather than exploring the experience of everyday life with home care. Representatives will therefore be informed about the aims of the project and that data will be anonymized when presented in publications. Alternative forms of recruitment based on advertising and snowball sampling will be used as complement, but it should be acknowledged that these methods are likely to result in an overrepresentation of persons being particularly critical. Finally, persons living with dementia and mental illness are excluded from the project for ethical reasons, unless they appear in interviews with cohabiting partners. This excludes an important part of the population who uses home care. These problems of representations will be continuously discussed among members of the research team and presented as limitations in publications of the project.

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Conclusions

In this ethnographic 2-year study on home care from a user perspective, we will interview older persons on 2 occasions, conduct participant observations and ask care users to write home care diaries.

By studying care use in the context of older people's lives the project will add important knowledge on the strategies and adjustments older people use to make care arrangements work. A user-oriented perspective will further the understanding of how power relations play out in home care over time, in relation to the formal rights, categorical belongings, and established norm systems that place the user in superior or subordinate positions. The project is expected to contribute empirical and theoretical knowledge on care and is anticipated to have a societal impact on 3 different levels.

First, the quotes and discussions that will be cocreated by respondents and researchers can serve as important consultative data for policy makers. The unique value from a policy design perspective is that the research goes beyond a user-satisfaction focus and gives an older person perspective on how the current welfare delivery is received, interpreted, and negotiated.

The second dimension of contribution is that this research can be read by providers of home care. It may act as consultative data in terms of how the scheduling, staffing patterns, and "the doing" are perceived and how the elderly use their agency to make it fit their life plans. More importantly, it can be used by care staff and other providers of care in order to develop a deeper understanding of everyday practices from the perspective of those receiving help.

The third dimension of the societal impact is an emancipatory one, given that older people who use home care can take part in other persons' stories in order to make sense of their own experiences as well as finding legitimacy, comfort, and courage in knowing that others share aspects of their subjective experiences. A long-term secondary outcome may be a contribution toward mobilization and gaining leverage in maneuvering a quasi-market of welfare provision.

Acknowledgments

The project is based on a pilot study funded by the city of Helsingborg. The project is funded by Swedish Research Council for Health, Working Life and Welfare (FORTE 2021-00506).

Data Availability

All data are qualitative and no data sets have been used. According to the project plan's ethics approval, the transcribed interviews are available to the responsible research team.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review report by Forskningsrådet för hälsa, arbetsliv och välfärd / Swedish Research Council for Health, Working Life and Welfare (FORTE).
[PDF File (Adobe PDF File), 44 KB - resprot_v12i1e42160_app1.pdf]

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Abbreviations

RUT: Rengöring, underhåll och tvätt (cleaning, maintenance, and washing)

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Protocol

Health System–Level Barriers to Living Donor Kidney Transplantation: Protocol for a Comparative Case Study Analysis

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Abstract

Background: Living donor kidney transplantation (LDKT) is the best treatment option for patients with kidney failure and offers significant medical and economic advantages for both patients and health systems. Despite this, rates of LDKT in Canada have stagnated and vary significantly across Canadian provinces, the reasons for which are not well understood. Our prior work has suggested that system-level factors may be contributing to these differences. Identifying these factors can help inform system-level interventions to increase LDKT.

Objective: Our objective is to generate a systemic interpretation of LDKT delivery across provincial health systems with variable performance. We aim to identify the attributes and processes that facilitate the delivery of LDKT to patients, and those that create barriers and compare these across systems with variable performance. These objectives are contextualized within our broader goal of increasing rates of LDKT in Canada, particularly in lower-performing provinces.

Methods: This research takes the form of a qualitative comparative case study analysis of 3 provincial health systems in Canada that have high, moderate, and low rates of LDKT performance (the percentage of LDKT to all kidney transplantations performed). Our approach is underpinned by an understanding of health systems as complex adaptive systems that are multilevel and interconnected, and involve nonlinear interactions between people and organizations, operating within a loosely bounded network. Data collection will comprise semistructured interviews, document reviews, and focus groups. Individual case studies will be conducted and analyzed using inductive thematic analysis. Following this, our comparative analysis will operationalize resource-based theory to compare case study data and generate explanations for our research question.

Results: This project was funded from 2020 to 2023. Individual case studies were carried out between November 2020 and August 2022. The comparative case analysis will begin in December 2022 and is expected to conclude in April 2023. Submission of the publication is projected for June 2023.

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Conclusions: By investigating health systems as complex adaptive systems and making comparisons across provinces, this study will identify how health systems can improve the delivery of LDKT to patients with kidney failure. Our resource-based theory framework will provide a granular analysis of the attributes and processes that facilitate or create barriers to LDKT delivery across multiple organizations and levels of practice. Our findings will have practice and policy implications and help inform transferrable competencies and system-level interventions conducive to increasing LDKT.

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KEYWORDS

transplantation; living donor kidney transplantation; health systems; barriers; resource based theory; complex adaptive systems

Introduction

End-stage renal disease represents a major public health burden. Patients needing dialysis have extremely poor survival rates when compared with the general population [1,2]. This is because these patients have a higher cardiovascular disease burden, greater susceptibility to infections, and demonstrate a decreased response to vaccination [3-6]. The intrusiveness of dialysis can significantly impede normal facets of life, such as work, vitality, and freedom to travel [7].

Kidney transplantation, in particular living donor kidney transplant (LDKT), is widely regarded as the best therapeutic option for patients with kidney failure. When compared with patients undergoing dialysis, those who have undergone kidney transplantation experience a 64%-75% lower risk of death by the first year following transplantation [8-13]. LDKT is a surgery that involves a healthy individual donating one kidney to a patient (recipient) with kidney failure. Given that there is a finite pool of deceased donors in any given year, and that the demand for organs far exceeds its supply [11,14], pursuing LDKT can narrow this gap and provide early access to a transplant. There are also many medical benefits to LDKT. The median survival of a kidney transplant from a living donor is longer than that from a deceased donor [8-11]. Those with LDKT also experience lower rates of acute rejection, spend less time on dialysis, and have an improved quality of life [10,15-21]. Thus, there is considerable interest in increasing the rate of LDKT [15].

Despite its significant benefits, LDKT rates in Canada have stagnated over the past decade and continue to average around 12-14 living donors per 1 million population. This is despite national efforts to increase LDKT, such as the paired kidney exchange program [1,10,22,23]. There are also significant interprovincial variations across provinces. For example, in Quebec, Ontario, and British Columbia, Canada's most populous provinces, <15%, 30%-40%, and 50%-60% of kidney transplants performed annually are from living donors, respectively [11]. Similar trends are noted when comparing the living donor rates per million population across these provinces [1,10,23,24]. The reason for this significant disparity in a country with universal health care is not known.

Currently, the impetus of finding living donors is largely placed on the patient, and much of the present work to increase LDKT focuses on patients and addressing these microlevel barriers [25]. We conducted a qualitative study, exploring the perspectives of health professionals on the provision of LDKT [26,27] and identified poor communication between treating teams, absence of consistent guidelines, and lack of resources as barriers. Notably, some of these barriers were more prominent in provinces of Canada that have lower rates of LDKT. This work alluded to the existence of systemic attributes that impede the effective delivery of LDKT, thus driving the need to understand the factors driving these differences to inform system-level interventions to increase LDKT.

As such, the objective of the study described in this protocol is to generate a systemic interpretation of LDKT by identifying the attributes and processes that facilitate the delivery of LDKT in a provincial health system and those that create barriers. We also aim to identify the differences between these attributes and processes by comparing higher- and lower-performing systems. These objectives are contextualized within our broader goal of increasing rates of LDKT in Canada, particularly in lower-performing provinces. Our primary research question is the following: what are the attributes and processes of provincial health systems that account for variability in LDKT rates?

Methods

Research Approach

This study takes the form of a comparative case study analysis as described by Yin [28,29] and illustrated in Figure 1. Case study research is an in-depth, noninterventional examination of a single case over time to investigate a contemporary phenomenon in its natural context [29,30]. Case studies have been identified as the preferred methodology for examining high-performing health systems [31-39]. As quantitative data concerning rates of LDKT across provinces have been well-documented elsewhere [40-4], our study follows a qualitative design to investigate *how* and *why* these differences in performance exist. Qualitative methods have established relevance to answering these questions in health research [43]. Understanding the system as an integrated whole lies in understanding the patterns and relationships between its levels and key players [44]. Our qualitative design will investigate these real-world behaviors and perspectives at multiorganizational levels, in order to understand full system function. Thus, our case study analysis will be explanatory because it will explore and connect how certain attributes and processes of a provincial health system are linked to the provision of LDKT [28]. It will be inductive—that is, allowing

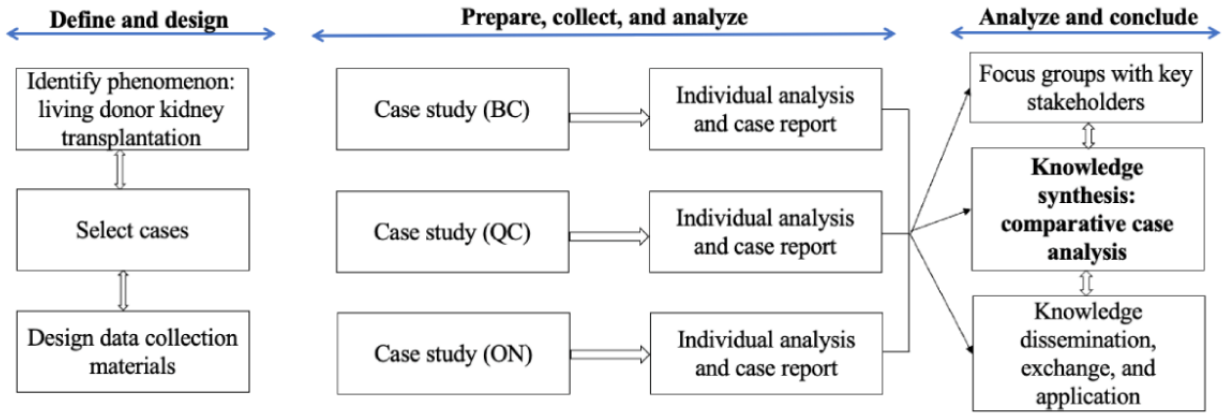
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themes and explanations to be derived primarily from a close reading of the data—without trying to fit it into a priori concepts.

Conceptually, our approach is underpinned by an understanding of health systems as complex adaptive systems (CASs). The concept of CAS stems from the complexity theory and takes a dynamic systems approach. A CAS is "an entity composed of many different parts that are interconnected in a way that gives the whole capabilities that the parts don't have on their own" [45]. A provincial health system that delivers LDKT can be understood as a CAS, in that, it is a multilevel, interconnected system that involves nonlinear interactions between people and organizations, operating within a loosely bounded network. CAS approaches have been used increasingly as an analysis and research development tool in health care, with favorable results [44,46,47].

There also exists a tight fit between a CAS approach and case study methodology [44]. Researchers have identified that multiple methods that are often used in case study research lend themselves to understanding emergent elements and system dynamics [44]. Complexity theory also suggests that comparing the best to the worst in multiple case comparison can be a fruitful way of understanding the source of new structural arrangements and patterns of behavior [44,48]. Accordingly, our comparative method entails the comparison and synthesis of the similarities, differences, and patterns across multiple cases that share a common goal [39,49].

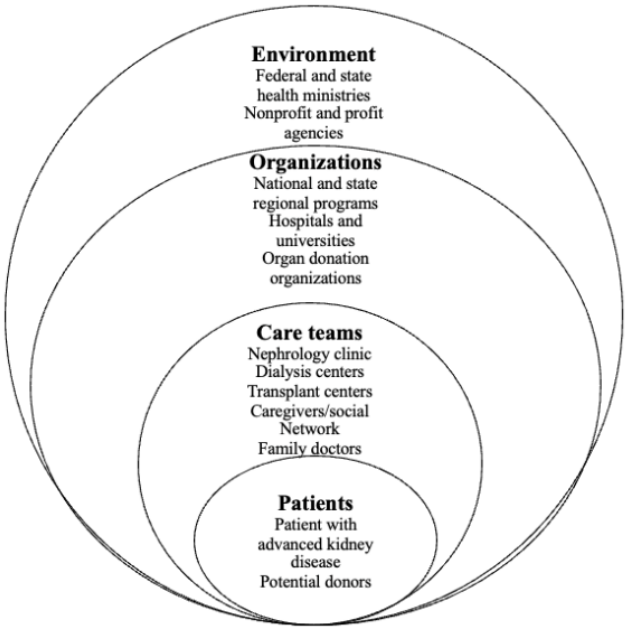
Figure 1. Comparative case study analysis design (adapted from Yin's [28,29] methods of case study research). BC: British Columbia; ON: Ontario; QC: Quebec.



Case Definition

In accordance with the CAS theory, we defined each provincial "case" as the health system involved in facilitating LDKT. Adapted from the 4-level model proposed by leading agencies [50] we mapped a whole-system model of LDKT, composed of macro-, meso-, and microlevels of practice that are interconnected, dynamic, and nested, with the patient at its core (Figure 2) [51]. These levels include organizations, service providers, recipients, and donors, representing the human and nonhuman agents that are implicated in the delivery of LDKT and thus form the elements for our analysis.

Figure 2. Envisioning the health system that delivers living donor kidney transplantation to patients as a complex adaptive system (adapted from the 4-level model proposed by the National Academy of Engineering [United States] and Institute of Medicine [United States] Committee on Engineering and the Health Care System).



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Case Selection

We will conduct a comparative case study between British Columbia, Ontario, and Quebec, which represent respectively high, moderate, and low performance in LDKT as defined by the percentage of LDKTs to all transplantation performed annually [11]. These three provinces represent 75% of Canada's population, and over 70% of the patients with end-stage renal disease reside in these provinces. Thus, performance in these provinces significantly influences the country's overall transplant results. Additionally, since these provinces have low, moderate, and high rates of LDKT, we have an ideal case mix to facilitate interprovincial learning, as well as for theoretical replication, reliability, and external validity [28].

Design

Our study follows sequential stages of data collection and analysis (Figure 1). We have conducted independent case studies of the health systems in British Columbia, Ontario, and Quebec using the data collection methods discussed below. Following data collection and independent analysis in all 3 provinces, we have recently conducted focus groups with stakeholders from across Canada, asking their opinions and experiences of the themes derived from the preliminary analysis of these cases. We will now conduct a comparative case study of British Columbia, Ontario, and Quebec. We will use the focus group data to develop and refine the themes from our comparative case study to form a final analysis.

Participants

Participants from different levels of the health system, as shown in Figure 2, were recruited for interviews. As LDKT is organized largely by each province, representatives from federal bodies were invited to participate in focus groups, where we discussed and refined the national relevance of our findings. Table 1 shows a breakdown of participants invited for an interview. The composition of interviewees seen in Table 1 comprises an approach to "studying through," tracing relations among actors, institutions, and discourses across spaces through interview data [52,53]. In accordance with our CAS approach, our participants represent macro-, meso-, and microlevels of practice. As the organizations implicated in LDKT vary among British Columbia, Ontario, and Quebec—for example, Quebec does not have a provincial renal program—the list of participants invited was adjusted accordingly.

Table 1. Types of participants and the numbers that were targeted in each category in each province.

Participant category	Number for each province
Ministry of Health representative	1-2
Organ Donation Organization representatives	2-3
Renal program representatives	2-3
Health care professionals at transplant centers	8-10
Health care professionals at nephrology clinics or dialysis centers	8-12
Living donor kidney transplant recipients	2-4
Living donors	2-4

Recruitment

To recruit participants, purposive criterion sampling was used to invite key leadership at organ donation organizations, provincial renal programs, and transplant centers. Participants were considered to have key leadership roles if they held decision-making authority with interorganizational impact. Thereafter, snowball sampling was used to recruit providers from kidney care clinics and dialysis centers [52,55]. Data gathering continued until data saturation was reached; that is, when new interviews and document reviews did not provide additional information [56].

Data Collection Methods

Semistructured Interviews

Semistructured interviews were conducted to understand the dynamic organization, governance, and care entailed in LDKT delivery and the interdependencies between the elements of each provincial health system. We also sought to understand what aspects of the system variously promoted or hindered patient access to LDKT. Interview guides for professional participants addressed their involvement in facilitating LDKT for patients, their interactions with other professionals in this process, their attitude toward LDKT, and which phenomena helped and which ones posed challenges in their work. Interview guides for donors and recipients of LDKT focused on their experiences of LDKT, their perception of care, and what helped and hindered their care path. Distinct interview guides with open-ended questions were developed for each category of participant with the combined expertise of our research team and preliminary document review (see sample guide in Multimedia Appendix 1). We followed an iterative approach whereby issues or ideas identified by participants were discussed with subsequent participants to enable further definition and refinement of themes [57]. Interviews were conducted remotely in English or French by our bilingual research coordinator (AH). All interviews were digitally recorded and transcribed. Participants were compensated with a CAD $50 (US $37.57) gift card following their participation in the interview.

Document Review

Document review served as complementary data collection to inform our understanding of programs, policies, and resources concerning LDKT in each province and as means of triangulation with interview data [58]. Documents for review were identified in consultation with our collaborators in each province, during interviews, and using web searches of

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governmental, organ donation organizations, renal programs, and hospital platforms. Documents were included if they were a policy, guideline, resource, program outline, presentation, announcement, or report pertaining to LDKT. Searches were conducted in both English and French.

Focus Groups

Following data collection in all 3 provinces and the initial coding of individual case studies, we conducted 4 focus groups remotely with the purpose of gleaning opinions about our preliminary themes from key stakeholders (Table 2). Focus groups comprise a small group of people brought together to discuss a particular issue, under the direction of a facilitator [59]. They are widely used in health research and are recognized to produce considerable information in a short space of time [59]. We recruited previous interview participants for focus groups, as well as patients, patient partners, and professionals from other provinces of Canada. In these focus groups, we presented themes from our preliminary analysis of the 3 case studies to participants and asked them about their opinions and experiences. Focus group guides were developed from our initial data analysis and reviewed by the research team. Each focus group lasted approximately 60 minutes, comprised 5-13 participants, and was conducted by the research team experienced in facilitating discussions in this setting (AH and KL). The focus groups were audio-recorded and transcribed. Participants were compensated with a CAD $50 (US $37.57) gift card following their participation in the focus group.

Table 2. Types of participants who were identified for participation in the focus group.

Focus group	Approximate number of participants	Participant types	Language of conduct
1	10-12	A health care professional working in transplantation or nephrology; or a representative from a provincial renal program, organ donation organization, or provincial health ministry, who has previously participated as an interviewee in this study	English
2	4-6	A health care professional working in transplantation or nephrology; or a representative from a provincial renal program, organ donation organization, or provincial health ministry, who works in a province outside of British Columbia, Ontario, and Quebec	English
3	4-6	An LDKT[a] recipient or living donor who has experienced LDKT in the last 7 years and whose preferred language of conduct is English	English
4	4-6	An LDKT recipient or donor who has experienced LDKT in the last 7 years and whose preferred language of conduct is French	French

[a]LDKT: living donor kidney transplantation.

Data Analysis

Individual Case Studies

Data from each case study were analyzed using inductive thematic analysis [43]. Thematic analysis involves identifying and analyzing patterns of meaning [60], and mapping regularities and variations across different accounts [59,61]. It is best suited to studying the processes and attributes of a system because it provides a "map" of the content and patterns across a data set [59], preserving our whole-system approach to understanding LDKT delivery [44]. Interview transcripts were analyzed independently by 2 research associates experienced in qualitative research (AH and KL). NVivo (version 12; QSR International) was used to support data management and analysis.

Transcribed interview data were read and highlighted line-by-line to openly derive preliminary codes that emerged iteratively from the data set. These codes were organized into categories and subcodes to form an initial coding scheme. Codes were then compared across the data set for regularities and divergences and modified accordingly. Through this process of inductive analysis, a coding scheme evolved, which retained strong links with the original data set [62]. The resultant codebooks for each individual case study have been retained as the basis for cross-comparative analysis. Coding, emerging themes, links between themes, and any disagreements between the 2 research associates were discussed at regular research team meetings. Our analytic procedure of documents entailed appraising and synthesizing the data contained in documents, followed by clustering the documents thematically [58]. The 2 research associates compared interview data to verify and corroborate findings from each case study. Analyses from each province are being published as individual case studies as the research progresses.

Comparative Case Analysis

Our comparative analysis will operationalize the resource-based theory (RBT) to compare case study data and generate explanations for our research question. The RBT is a strategic management theory that provides a framework for explaining and predicting the basis of an organization's competitive performance and advantage [63]. RBT involves a broad classification of resources as tangible and intangible assets and aims to assess how resources create strategic advantage by examining how they are combined and managed [64,65]. It is a framework with established relevance in health systems and health management research to understand problems of high organizational complexity [66]. Thus, there is a high level of theoretical congruence between the complexity theory and the RBT, as the RBT engages with the social complexity of how resources—physical, human, and organizational—are combined [67]. The importance of network competence, dynamic capabilities, and strategic alliances between organizations is also well-recognized in this framework for achieving strategic advantage [67-69]. This is particularly pertinent for the study of the CASs that provide LDKT, where management is

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distributed between organizations and interorganizational relationships [69]. As such, the RBT provides relevant and useful concepts to understand the full-system function of LDKT, as well as identify the attributes and processes that characterize a high-performing system. Our analysis will follow the principles of RBT, with an emphasis on collaborative organizational relationships, in order to understand and compare the whole-system function of LDKT provision.

Following inductive coding and individual analysis of data collected from British Columbia, Ontario, and Quebec, we will use an RBT framework to analyze and compare our case study data and generate explanations for our research question. To do this, we will organize codebooks from each province into capabilities identified from the RBT literature, following questions stemming from these capabilities to guide our organization (Table 3). According to the RBT, a capability is what can be done as a result of resources working together [70]. We will therefore delineate and compare the attributes and processes from each province that determine their capabilities to deliver LDKT. The same 2 research associates who coded individual case studies will go through codebooks from each case study to extract information about the RBT capacities identified above and assign existing codes to the relevant RBT capability, to build themes. Through an iterative process, we will assign codes to emerging themes, create new themes where needed, and merge themes if they replicate each other until saturation is reached. We will then compare and contrast the themes in each RBT capability among provinces to identify "distinctive competencies" [71]; that is, attributes and processes that exist in certain provinces and not in others. We will compare our focus group data (analyzed using inductive thematic analysis, following the same process described above [43]) to themes from the comparative analysis, adding these data to existing themes where it is concurrent and creating new themes where it diverges. This process will deepen our understanding of the attributes and processes we have identified, and their relevance to other Canadian provinces. Following this approach, we will develop explanations for how resources in each province are deployed to achieve strategic advantage and to explain one province's strategic advantage relative to others in LDKT performance. We will contextualize these capabilities in characteristics described by interviewees that operate externally from the provincial organization of LDKT, which influence delivery. We will situate our analysis in a discussion of these external dependencies.

Table 3. Resource-based theory capacities for comparative analysis.

Capacity	Guiding questions
Resources	What, where, and how are resources deployed in LDKT[a] delivery?
Competition for resources	What competition exists for resources to facilitate LDKT?
Organizational capacity	What are the organizational capacities of the organizations involved in LDKT delivery?
Collaborative capacity	What collaborative capacities exist in and between organizations?
Value creation	What activities create value for LDKT?
Dynamic capabilities	What are the dynamic capabilities of organizations?

[a]LDKT: living donor kidney transplantation.

Ethics Approval

Ethics approval for this study was obtained from the McGill University Health Centre Research Ethics Committee (MP-37-2021-7126/LDKT Case Study). This study is being conducted in accordance with the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (2014), and the Declaration of Istanbul.

Results

This project was funded by a grant from a Gift of Life Institute, a Clinical Faculty Development Research Grant from the American Society of Transplantation from 2020 to 2021, and by a Health Research Grant from the Kidney Foundation of Canada. Individual case studies of British Columbia, Ontario, and Quebec were carried out between November 2020 and August 2022. The individual case study findings of LDKT delivery in British Columbia have been published [72,73]. Focus groups were carried out between June and November 2022. The comparative case analysis began in December 2022 and is expected to conclude in April 2023. Writing up of our findings is projected for May 2023, and manuscripts are expected to be submitted for publication by July 2023. A patient partner from Quebec was consulted regarding participant selection, study materials, and analysis and was involved in the publication of the case study [73].

Discussion

Expected Findings

This study aims to produce a system-level understanding of LDKT delivery in Canada's 3 most populous provinces that have variable rates of LDKT, presenting a unique opportunity for comparative analysis. Informed by quantitative data [11], we are using qualitative methods to explain these differences. We want to identify the attributes and processes that facilitate or create barriers to LDKT using the RBT. Our preliminary findings suggest that barriers to effective LDKT delivery exist at different organizational levels of the health system and, critically, in the relationships between these organizations. LDKT delivery is aided by supportive governance organizations with a provincial overview, which increase the collaborative capacities of the system, boost organizational capacity, and

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generate value for LDKT across the different organizations involved [72,73].

To our knowledge, a comparative case analysis approach has not been used in the field of nephrology or kidney transplantation. Our approach has implications in these disciplines where there exists a poor understanding of system-level factors leading to inferior outcomes, inequities in access to therapy, and fractured transitions of care. This work also has global implications as LDKT is the main way to obtain a transplant in many countries that lack infrastructure for deceased donation. Based on our preliminary results and background work, we believe that to make significant improvements to LDKT delivery, interventions must target the dynamic relationships between different elements of a system. Much of the current work has focused on microlevel interventions to improve LDKT delivery [25,51], missing the important influence of meso- and macropractices and the dynamic interdependencies that exist between these levels of a health system [51]. Our findings will build on other studies that focus on implementing interventions to improve patient education and comfort on LDKT [16,74-78], and will help reenforce it by informing effective implementation strategies that encompass all levels of a health system.

Limitations

The following limitations to our study may apply. First, our data collection largely pertains to 3 provinces of Canada and our findings may not be applicable to other regions and countries. Nonetheless, it should be noted that Quebec, Ontario, and British Columbia are Canada's most populous provinces and represent 75% of the Canadian population, and our focus group data also go some way to establish the pertinence of our findings to other provinces. Our data also lay the foundations to extend our work across Canada and to other countries. Second, our research will not comprehensively explore the system-level factors leading to disparities in LDKT, such as gender and sex disparities and low rates of LDKT in Indigenous and other vulnerable populations. However, the data collected in this study will inform future systematic approaches needed to address this complex issue.

Another limitation may pertain to the challenge of delineating the "boundaries" of the health systems that form the basis for our cases. Identifying the unit of analysis for case study research has long been identified as a challenge [79], and in the complex field of health care, it may be difficult to differentiate between organizational and system boundaries and their environments [80]. We have delineated our cases by drawing on the extensive expertise of our team and collaborators, many of whom are practitioners in this field, as well as following a snowballing technique to iteratively identify the actors and organizations implicated in LDKT delivery. However, some perspectives may have been missed in this process, for example, family physicians who are primarily involved in living donor care for and may exercise influence over the LDKT process. To mitigate this challenge, we will situate our analysis in a detailed discussion of factors external to the boundaries of our case, which impact LDKT delivery. Where relevant, we will highlight areas for further research. Relatedly, there is some variation in our sample size and organizational representation between cases, given the heterogeneity in how care is structured in different provinces. This may have some impact on how we are able to compare across provinces. Our analysis will include an in-depth discussion of the structural differences in renal care among British Columbia, Ontario, and Quebec to situate our findings. Finally, though we believe our document review serves as useful complementary data collection and triangulation with interview data, we acknowledge that it may not be exhaustive.

Conclusions

LDKT is the optimal treatment option for patients with kidney failure; yet, rates of LDKT have stagnated in Canada and vary significantly across provinces. There is a need to better understand how health systems deliver LDKT to patients. Following our prior work that has suggested system-level differences contributing to variability in LDKT performance, we will generate a systemic interpretation of LDKT delivery by identifying the attributes and processes that facilitate or create barriers to the delivery of LDKT. We will also identify the differences between these attributes and processes by comparing higher- and lower-performing provincial health systems. This qualitative comparative case study analysis is informed by CASs, and data analysis will be carried out in accordance with the RBT. Our findings will have practice and policy implications and help inform specific strategies, regulations, and infrastructure that are transferrable competencies and conducive to promoting the service delivery of LDKT.

Acknowledgments

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Data Availability

The data sets generated and analyzed during this study are not publicly available, as informed consent to share transcribed data for secondary use beyond this research was not obtained from the participants.

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Authors' Contributions

SS conceived, designed, and conceptualized the study. PN, AH, KL, and MCF advised on the methodology, design, and theoretical frameworks. IM, GK, LG, MC, DL, and MP helped with the methods and design and facilitated data collection. AH is the research coordinator and conducted interviews. AH and KL conducted focus groups and are conducting data analysis. AH wrote the first draft of the manuscript. SS contributed to the development of the paper and provided comments for improvement. All authors read and approved the final manuscript.

Conflicts of Interest

SS has received a grant from Amgen Canada to increase living donor kidney transplantation.

Multimedia Appendix 1
Peer-review report by La Fondation Canadienne du rein / Kidney Foundation - 2021 Kidney Health Scientific Committee (Montréal, Canada).
[PDF File (Adobe PDF File), 3244 KB - resprot_v12i1e44172_app1.pdf]

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Abbreviations

CAS: complex adaptive system
LDKT: living donor kidney transplantation
RBT: resource-based theory

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Original Paper

Acceptance and Commitment Therapy Wellness Program for Latine Adults Who Smoke and Have Psychological Distress: Protocol for a Feasibility Study

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Abstract

Background: Tobacco smoking is a major independent risk factor for chronic disease, and the prevalence of smoking among people with behavioral health disorders is 2-fold in comparison with the general population. Smoking rates remain high for various subgroups within the Latine community, the largest ethnic minority group in the United States. Acceptance and commitment therapy (ACT) is a theoretically sound and clinically validated therapeutic approach for several behavioral health conditions with growing evidence of its effectiveness for smoking cessation. Unfortunately, the evidence of ACT effectiveness for smoking cessation among Latine individuals is scarce, and none of the existing studies have tested a culturally targeted intervention for this population.

Objective: This study aims to address the co-occurrence of smoking and mood-related challenges among Latine adults via the development and testing of a culturally tailored ACT-based wellness program: Project PRESENT.

Methods: This study entails 2 phases. Phase 1 consists of the intervention development. Phase 2 entails the pilot testing of the behavioral intervention along with the administration of baseline and follow-up measures to 38 participants. Primary outcomes include feasibility of recruitment and retention, and treatment acceptability. Secondary outcomes are smoking status and depression and anxiety scores at end of treatment and 1-month follow-up.

Results: This study received institutional review board approval. Phase 1 outputs were the health counselors' treatment manual and participant guide. Recruitment was completed in 2021. Phase 2 outcomes will be determined after project implementation and data analyses are complete, which are expected by May 2023.

Conclusions: Findings from this study will determine the feasibility and acceptability of an ACT-based, culturally relevant intervention for Latine adults who smoke and have probable depression and/or anxiety. We expect feasibility of recruitment, retention and treatment acceptability, and reductions in smoking status, depression, and anxiety. If feasible and acceptable, the study will inform large-scale trials, which will ultimately contribute to narrowing the gap between research and clinical practice for the co-occurrence of smoking and psychological distress among Latine adults.

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KEYWORDS

acceptance and commitment therapy; Hispanic or Latine; smoking; telehealth

Introduction

Tobacco smoking is a major independent risk factor for chronic disease [1,2]. Although the number of smokers in the United States has declined over the past decades, smoking prevalence remains disproportionately high among individuals with behavioral health disorders [3-5]. For instance, depressive and anxiety syndromes are more prevalent among smokers than nonsmokers [6,7], and smokers with these conditions are more likely to be nicotine dependent [4,8]. Considerable research has assessed the impact of depression and anxiety on cessation outcomes, with a number of studies reporting that depression and anxiety place smokers at increased risk for cessation failure [9-14], with other studies suggesting that the evidence is inconclusive [6,15-18]. Additionally, given the high comorbidity between depression and anxiety [19], the independent contribution of each disorder to smoking cessation remains unclear [11,20,21]. The *Treating Tobacco Use and Dependence Clinical Practice Guideline: 2008 Update* concluded that the evidence is insufficient to determine whether smokers with psychiatric disorders benefit more from tobacco use treatment tailored to their disorder than from standard treatments [22].

Given the link between behavioral health issues and smoking, it would be ideal to identify an intervention that might be especially appropriate for people with behavioral health issues who smoke. Acceptance and Commitment Therapy (ACT) belongs to what is known as "third wave" cognitive behavioral therapy and is positioned as a form of "contextual cognitive behavioral therapy" [23]. An important and unique assumption underlying ACT's treatment approach is that, through conditioning processes, humans learn to avoid thoughts and their accompanying feelings, images, and physical sensations as they would avoid the event itself [24]. This avoidance of aversive private events, called experiential avoidance, is assumed to underlie much of people's suffering, and emotional dysregulation arises from attempts to avoid and alter private experiences that are judged to be aversive [25].

Unfortunately, experiential avoidance often results in an increase in the frequency or intensity of the avoided thoughts and feelings [26] and can generate mood disturbances, including depression and anxiety. An important component of ACT is helping individuals abandon efforts to change their thoughts and feelings and instead engage in an active process of experiencing emotions simply as a constellation of physiological sensations, which have no intrinsic power to harm or hold one back. The goal is the removal of experiential avoidance as a barrier to pursuing valued outcomes (ie, quitting smoking and improving mood).

With respect to substance abuse, behaviors like tobacco smoking are often negatively reinforced via attempts to regulate and control internal, negative experiences [27]. In ACT-based models for the treatment of tobacco use disorders [28], individuals are helped to identify subtle signals of negative affect and to understand that efforts to control or avoid internal experiences are linked to their tobacco use behavior. They are then taught to develop acceptance and willingness to remain in the presence of withdrawal symptoms and aversive internal states associated with triggers to smoke tobacco.

ACT has increasingly shown its effectiveness for treating smoking, depression, and anxiety [23,29-31], and its applicability to diverse populations [32]. However, research on the usefulness of ACT approaches for Hispanic or Latine (hereafter *Latine*, a gender-neutral term) populations, the largest ethnic minority group in the United States [33,34], is limited. Although there are some ACT-related studies that include a considerable proportion of Latine people in their samples [29,35], there is only 1 published study specifically focused on Latine individuals in the United States [36]. However, this study is a secondary data analyses of treatment engagement and efficacy from an ACT treatment not culturally tailored to the population. Moreover, no published studies have specifically addressed smoking cessation among Latine individuals with depressive and anxiety symptomatology.

These gaps in the literature illustrate the need for an ACT smoking cessation treatment that is appropriate for Latine individuals with behavioral health issues. ACT represents a coherent theoretical framework from which to address many of the factors that may present barriers to smoking cessation among Latine individuals with depression and anxiety symptomatology. Hence, the proposed study (ie, PRESENT Wellness Program) aims to improve the health of the Latine community by developing and pilot-testing a culturally relevant ACT-based wellness program addressing smoking, depression, and anxiety among Latine adults.

Methods

Phase 1: Intervention Development: The PRESENT Wellness Program

The PRESENT Wellness Program consists of the ACT-based behavioral treatment component with a participant's guide and nicotine replacement therapy (NRT).

Behavioral Treatment Component and Participant Guide

The techniques used in ACT target the following six main processes [37]: (1) *acceptance*—willingness to experience the natural flow of thoughts, feelings, and sensations (not trying to suppress them); (2) *cognitive defusion*—ability to recognize thoughts and images as just words and pictures, not as real events; (3) *beingpresent*—focus on the present in a nonjudgmental way; (4) *self-as context*—exposure to experiential processes to promote awareness of one's own flow of experiences without attachment to them; (5) *values*—awareness and clarification of personal values and goals; and (6) *committed action*—willingness to behave in line with values and goals, even in the presence of discomfort.

The baseline behavioral treatment was developed using an ACT-based smoking cessation protocol described in existing publications on ACT and smoking cessation [38-40]. This

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baseline treatment protocol was then adapted to also address depression and anxiety and to be culturally appropriate for Latine adults. The behavioral health and cultural adaptations were informed by an existing framework for adaptation [41,42], the first author's training on the ACT therapeutic model, and expert consultation. A literature review informed changes to content and to the frequency and duration of sessions.

Adaptations of the baseline protocol to address co-occurring depression and anxiety entailed the proactive inclusion of emotional dysregulation discussions and experiences as part of the treatment. Regardless of participants' initiative to share their experiences with mood management, the health counselor proactively inquires about the person's psychological distress, validates their pain, and highlights that facing discomfort is an inevitable human experience oftentimes necessary for valued living. ACT works to enhance an individual's ability and willingness to experience undesirable or adverse thoughts and feelings, which is expected to assist individuals in developing broader alternatives to mood management. Adaptations of the baseline protocol to be culturally appropriate for Latine individuals started with the labeling of the treatment. For instance, given Latine individuals' stigma related to seeking behavioral health help [43], we chose to call the treatment a "wellness program" so it could be better received by the Latine community. Similarly, we use the terms "health counselor" and "health counseling" to refer to the therapist and the treatment sessions, respectively, to increase openness to the program. Adaptations were also based on the ideas of cross-cultural communication [44,45] as well as the integration of Latine values (eg, familism, personalism, and collectivism) and context (eg, heritage group, acculturation, and enculturation) [46].

The treatment manual includes overall training modules that cover the ACT model, tobacco dependence, depression, anxiety, Latine cultural values, and a session-by-session guideline that includes the core aspects of ACT and their applications for treatment of tobacco dependence and depression or anxiety. The participant's guide mirrored the counselors' treatment manual content in a more simplified manner and includes practice exercises.

The treatment protocol consists of 8 one-hour individual sessions. *Session 1* entails the contextual interview (focused on smoking and psychological distress) and offers didactic information about the effectiveness and use of NRT. The contextual interview is organized around valued domains of living (ie, relationships, health, work, education, and leisure) and the functionality of smoking. Sessions 2-7 focus on each one of the 6 core ACT processes [23,37]. *Session 2* focuses on clarifying participants' overall values and those involved in quitting smoking, as well as the discrepancies between current behaviors and values. *Session 3* focuses on discussing and demonstrating what SMART goals are (ie, specific, meaningful, adaptive, realistic, and timebound) and the development of a preliminary plan to stop smoking, including setting a quit date. *Session 4* introduces participants to mindfulness and helps them notice their internal and external triggers as they occur and to recognize the link between connecting with emotions and the ability to act on them. *Session 5* aims to increase participants' willingness to accept cravings and withdrawal symptoms as a typical experience of the quitting process and develop motivation and skills to deal with them without smoking. *Session 6* helps participants identify and defuse (or to get "unhooked") from thoughts that limit their achievement of quitting smoking and mood-related behavioral goals. In this context, defusion is to see thoughts simply as thoughts rather than as a literal truth that can control one's behavior. *Session 7* guides participants to connect with a transcendent sense of self that is separate from their own internal experience but provides a safe place to observe them. *Session 8* focuses on overall experiences during the wellness program as well as the creation of an individual self-care plan for the future, including value-based actions. All sessions include experiential exercises and metaphors tailored to the participant's situation. Latine-specific issues are incorporated into each session. Participants are instructed to engage in value-based actions as homework assignments between sessions. Table 1 below shows a summary of the session-by-session content with focal exercises [47].

Table 1. Summary of session-by-session content.

Session	Overview of the session	Experiential exercise
1	Contextual interview, explanation of the ACT[a] model and overall wellness program, and didactic information about NRT[b]	Life path
2	Values identification	Bull's eye
3	Goal setting and committed action (quit day is encouraged)	Establishing SMART[c] goals
4	Contact with the present moment	Mindful breathing
5	Acceptance and willingness	The ball in the pool metaphor
6	Cognitive defusion (getting unhooked!)	Hands as thoughts metaphor
7	Self as context (also called perspective taking)	The stage show metaphor
8	Integration and maintenance	Miracle question and Passenger on the bus metaphor

[a]ACT: acceptance and commitment therapy.

[b]NRT: nicotine replacement therapy.

[c]SMART: specific, meaningful, adaptive, realistic, and timebound.

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Health counselors with at least a master level degree in clinical or counseling psychology are trained to provide the PRESENT Wellness Program. Specifically, the health counselors undergo about 100 hours of specialized training in tobacco dependence treatment and ACT, including didactic, experiential, and applied training. Before engaging with study participants, health counselors role-play the treatment sessions and have to demonstrate ACT competency, measured by the ACT Core Competency Rating Form [37].

Guideline for NRT Use

NRT is offered as part of the PRESENT Wellness Program. The selected NRT is the nicotine patch because it is frontline therapy for smoking cessation, is safe, well-tolerated, and available over the counter [22]. Also, the nicotine patch has proven effective among smokers with depression and anxiety symptomatology [48]. Participants are given 6 weeks of nicotine patches and are told to start using them 1 week before the quit day, which is encouraged on Session 3. Participants smoking more than 10 cigarettes per day are given 4 weeks of 21-mg patches, 1 week of 14-mg patches, and 1 week of 7-mg patches. Participants who smoke 5-10 cigarettes per day are given 4 weeks of 14 mg patches and 2 weeks of 7 mg patches.

Phase 2: Pilot Testing: Study Design and Participants

This is a longitudinal, 1-arm pre-post feasibility study. A total of 38 participants will be enrolled in the study. The inclusion criteria are ≥18 years of age; self-identify as Latine (of any national group); current smoker (average of >5 cigarettes per day for the past year and carbon monoxide [CO] >6 ppm); motivated to quit within next 30 days; screened positive for probable depression and/or probable anxiety (via a score of >10 in the Patient Health Questionnaire [49-51]; at least marginal health literacy; functioning telephone number; ability to speak English; and physicians' release to participate if taking psychotropic medications. Of note, we chose to recruit only English-speaking Latine participants because it facilitates the supervision of sessions and preparation of materials in only 1 language, maximizing the feasibility of completing the study within the time frame and available resources. The exclusion criteria are contraindication for use of nicotine patch; current use of tobacco cessation medications; current participation in counseling for depression, anxiety, or smoking cessation; being pregnant or nursing; having other current psychiatric disorder that would limit ability to participate; and having a household member enrolled in the study.

Procedures

Recruitment and Screening

Participants are mainly recruited through community outreach, social and print media (eg, local newspaper), flyers, and the ResearchMatch platform [52]. To determine eligibility criteria, interested people complete a phone screening with project staff or complete a self-screening accessed via a QR code located in the study flyer. Individuals who are ineligible or decline participation are given self-help materials and referrals to other cessation programs. Eligible individuals are scheduled for their first appointment.

Baseline Visit

During the in-person baseline visit, study personnel provide a detailed description of the study, answer questions, and obtain informed consent. Enrolled participants complete web-based baseline questionnaires, biochemical verification of smoking status (via a CO test), and their first health counseling session.

Treatment Procedures and Fidelity

The health counseling component consists of 8 one-hour individual sessions (1 in person and 7 by phone) completed within a 3-month period. The initial 2-week nicotine patch is dispensed at the first face-to-face visit and then sent biweekly by regular mail. Participants receive only the number of patches necessary to last 2 weeks, plus several extra patches should a patch fall off or become torn.

Treatment fidelity refers to the extent to which an intervention is delivered as planned. To ensure treatment fidelity, all sessions are recorded and a random sample of at least 15% are coded using the following two forms: (1) an investigator-developed checklist to track fidelity to treatment content per session and (2) the ACT Core Competency Rating Form to determine adherence to an ACT therapeutic approach [37]. The checklist entails a list of all session components (per session), which are marked as covered or not covered. The rating is calculated by assigning 10 points to each component marked as covered and dividing by the maximum number of components in that particular session (see the Multimedia Appendix 1). In the ACT Core Competency Rating Form, the rater evaluates the counselor's competency in ACT on a scale of 1-7, from "never true" to "always true." The supervisor provides written feedback based on the ratings of the rated sessions. Low treatment adherence is addressed by additional training and repeated assessment of adherence on additional cases. Treatment fidelity is attained when 85% or more (ie, ≥8) of the session components were covered and when receiving an overall rating of adequate or above adequate delivery (eg, ≥5) of the ACT essential components.

Follow-up Assessments and Treatment Evaluation

After the final health counseling session, participants attend 2 in-person follow-up visits, at 1-week and 1-month posttreatment, in which they complete a CO test as well as web-based questionnaires about tobacco use, depression, anxiety, and ACT-related constructs. At the 1-month visit, participants rate the degree of acceptability and helpfulness of each ACT component and their satisfaction with the PRESENT Wellness Program.

Financial Compensation

Participants are compensated in the form of gift cards for each of the in-person visits in which they complete assessments (ie, US $30 for baseline and 1 week after end of treatment; and US $40 for 1-month posttreatment follow-up). Thus, participants could receive a maximum total of US $100/person for the completion of assessments and health counseling sessions.

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Measures

Primary Outcomes

The primary outcomes of the study are feasibility of recruitment, feasibility of retention, and treatment acceptability. The feasibility of recruitment will be measured by the proportion of participants who consented to participate and attended the baseline session out of the number of individuals who were eligible. The feasibility of retention will be measured by the number of health sessions completed and the rate of follow-up visit completion. Treatment acceptability will be measured by the Program Acceptability Questions (see the Multimedia Appendix 2), an investigator-developed questionnaire rating the degree of acceptability and helpfulness of the PRESENT Wellness Program. The questionnaire contains 7 items categorized on a 5-point Likert scale ranging from "Completely Disagree" to "Completely Agree." Higher scores indicate higher acceptability. A sample item is "This program has helped in my acceptance of my physical cravings, emotions, and thoughts that cue my smoking."

Secondary Outcomes

Smoking Abstinence

Seven-day point prevalence and continuous abstinence will be reported following the Society for Research on Nicotine and Tobacco guidelines [53,54]. *Seven-day point prevalence* abstinence is defined as a self-report of no smoking during the previous 7 days and a CO level of less than 6 ppm. *Continuous abstinence* is defined as a self-report of no smoking since the quit date and biochemically confirmed abstinence at all follow-ups up to and including that time point.

Probable Depression

Probable depression is measured by the Patient Health Questionnaire [49,50], which evaluates symptoms for the last 2 weeks. Items range from not at all (0) to nearly every day (3). The scores for each item are summed to produce a total score between 0 and 24 points. Higher scores indicate higher depressive symptoms. Probable depression is determined by a total score of 10 or above, indicating at least moderate symptoms [50].

Probable Anxiety

Probable anxiety is measured by the Generalized Anxiety Disorder Scale [51], which evaluates symptoms for the last 2 weeks. Items range from not at all (0) to nearly every day (3). The scores for each item are summed to produce a total score between 0 and 21 points. Higher scores indicate higher anxiety symptoms. Probable anxiety is determined by a total score of 10 or above, indicating at least moderate symptoms [51].

Data Analyses

Data analyses in the context of a pilot study are not hypothesis-driven but serve to provide information regarding feasibility and acceptability of the intervention [55]. As such, data analyses will include descriptive statistics (eg, mean tests and proportions) about screening, recruitment, retention, process assessments, and treatment acceptability. We will use descriptive analysis techniques to present participants' characteristics, as well as their scores on secondary outcome measures at the 3 different time points (baseline, 1 week after end of treatment, and 1-month posttreatment).

Ethics Approval

The first author and principal investigator of the study received institutional review board approval from her academic institution, the University of Houston (#00001007).

Results

The outputs of the intervention development (phase 1) were (1) a treatment manual, which guided the health counselors' training, and (2) the participant's guide. Recruitment was completed in 2021. After project implementation and data management and analyses are conducted, the outcomes of the pilot study (phase 2) will be published in a separate paper. Dissemination of outcomes from phase 2 is slated for May 2023.

Discussion

Despite the availability of evidence-based interventions for smoking cessation, there is still a need for interventions focused on individuals with behavioral health challenges, given their high smoking rate and difficulty quitting. Similarly, culturally appropriate interventions for the Latine community, the largest ethnic group in the United States, are greatly needed. To address these gaps, the innovation of the PRESENT Wellness Program lies in the adaptation and testing of an ACT smoking cessation intervention for Latine smokers with clinically significant depression and anxiety symptomatology. This entails refinements and new applications of an existing theoretical and evidence-based clinical approach (ie, ACT) for understudied comorbid conditions (ie, depression, anxiety, and smoking) among an underserved and understudied ethnic minority group (ie, Latine). Besides adaptations in content, the proposed protocol is delivered in a hybrid format, with 1 session in person and the rest by phone, which is expected to address common treatment barriers for Latine individuals (eg, childcare and transportation). All these aspects are strengths of the study.

The implementation of the PRESENT Wellness Program will provide data on the feasibility and acceptability of the intervention as well as preliminary data on the impact of the intervention on decreasing smoking, anxiety and depression, and addressing ACT-related constructs. As primary outcomes, it is expected that recruitment and retention into the intervention is feasible and that the provided treatment is acceptable. For secondary outcomes, it is expected that there is an increase in participants' smoking abstinence and a decrease in depression and anxiety symptoms at the end of treatment and 1-month posttreatment. Our findings will help inform large-scale ACT-based smoking cessation studies for Latine adults with psychological distress and may contribute to a growing body of evidence of the importance of culturally relevant interventions. Findings will be disseminated via professional forums as well as community-accessible venues, such as our laboratory website, social media, and newsletters.

Of note, this pilot study was focused on English-speaking Latine individuals mainly for pragmatic reasons related to study budget

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and the feasibility of conducting the intervention and related supervision in only one language. Nonetheless, we acknowledge this is a limitation as excluding Spanish-preferring individuals will reduce the generalizability of findings and the reach of the intervention. We believe there is an urgency to reach Spanish-speaking Latine individuals who smoke and, as such, will work on the translation and linguistic adaptation of the intervention as a next step in this line of research.

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Data Availability

Data sharing is not applicable to this research protocol paper as no clean data sets have been generated for data management or analyses in this study.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Treatment Fidelity: Checklist Sample.
[DOCX File , 15 KB - resprot_v12i1e44146_app1.docx]

Multimedia Appendix 2
Program Acceptability Questions.
[DOCX File , 14 KB - resprot_v12i1e44146_app2.docx]

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Abbreviations

ACT: acceptance and commitment therapy
CO: carbon monoxide
NRT: nicotine replacement therapy
SMART: specific, meaningful, adaptive, realistic, and timebound

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Protocol

Characterizing Symptoms and Identifying Biomarkers of Long COVID in People With and Without HIV: Protocol for a Remotely Conducted Prospective Observational Cohort Study

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Abstract

Background: Living with HIV is a risk factor for severe acute COVID-19, but it is unknown whether it is a risk factor for long COVID.

Objective: This study aims to characterize symptoms, sequelae, and cognition formally and prospectively 12 months following SARS-CoV-2 infection in people living with HIV compared with people without HIV. People with no history of SARS-CoV-2 infection, both with and without HIV, are enrolled as controls. The study also aims to identify blood-based biomarkers or patterns of immune dysregulation associated with long COVID.

Methods: This prospective observational cohort study enrolled participants into 1 of the following 4 study arms: people living with HIV who had SARS-CoV-2 infection for the first time <4 weeks before enrollment (HIV+COVID+ arm), people without HIV who had SARS-CoV-2 infection for the first time within 4 weeks of enrollment (HIV−COVID+ arm), people living with HIV who believed they never had SARS-CoV-2 infection (HIV+COVID− arm), and people without HIV who believed they never had SARS-CoV-2 infection (HIV−COVID− arm). At enrollment, participants in the COVID+ arms recalled their symptoms, mental health status, and quality of life in the month before having SARS-CoV-2 infection via a comprehensive survey administered by telephone or on the web. All participants completed the same comprehensive survey 1, 2, 4, 6, and 12 months after post–acute COVID-19 symptom onset or diagnosis, if asymptomatic, (COVID+ arms) or after enrollment (COVID− arms) on the web or by telephone. In total, 11 cognitive assessments were administered by telephone at 1 and 4 months after symptom onset (COVID+ arms) or after enrollment (COVID− arms). A mobile phlebotomist met the participants at a location of their choice for height and weight measurements, orthostatic vital signs, and a blood draw. Participants in the COVID+ arms donated blood 1 and 4 months after COVID-19, and participants in the COVID− arms donated blood once or none. Blood was then shipped overnight to the receiving study laboratory, processed, and stored.

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Results: This project was funded in early 2021, and recruitment began in June 2021. Data analyses will be completed by summer 2023. As of February 2023, a total of 387 participants were enrolled in this study, with 345 participants having completed enrollment or baseline surveys together with at least one other completed study event. The 345 participants includes 76 (22%) HIV+COVID+, 121 (35.1%) HIV−COVID+, 78 (22.6%) HIV+COVID−, and 70 (20.3%) HIV−COVID− participants.

Conclusions: This study will provide longitudinal data to characterize COVID-19 recovery over 12 months in people living with and without HIV. Additionally, this study will determine whether biomarkers or patterns of immune dsyregulation associate with decreased cognitive function or symptoms of long COVID.

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KEYWORDS

HIV; SARS-CoV-2; COVID-19; long COVID; post–acute COVID-19 syndrome; postacute sequelae of SARS-CoV-2 infection; prospective observational cohort study; remote study; remote participation

Introduction

Background

SARS-CoV-2, the virus that causes acute COVID-19, rapidly spread throughout the world and caused a global pandemic, leading to >6 million confirmed deaths since late 2019 [1]. In early 2020, people with persistent symptoms and new health complications after known or suspected SARS-CoV-2 infection began gathering in online forums and support groups. Working both independently and together, they sounded an alarm in the media for a new, often debilitating, post–COVID-19 syndrome called long COVID [2]. Many other terms for long COVID have been used, including *post-COVID condition*, *long-haul COVID*, *post–acute COVID-19*, *and postacute sequelae of SARS-CoV-2 infection* [3]. Long COVID and related terms generally describe a syndrome encompassing a wide range of symptoms or health conditions that occur after confirmed or suspected SARS-CoV-2 infection that can wax, wane, or persist and can last from weeks to years [3,4].

People with long COVID with interest and skills in research advanced the research agenda by conducting and publishing the first large surveys characterizing the symptoms and time course of long COVID [5]. Dozens of symptoms and sequelae of long COVID have been described since then in survey-based and electronic medical record studies. Commonly reported long COVID symptoms include fatigue, postexertional malaise, difficulties with concentration or thinking (also referred to as “brain fog”), sleep disorders, headache, dyspnea, chest pain, heart palpitations, joint or muscle pain, body aches, anxiety, full or partial loss of taste or smell, among many others. [5-12].

People living with HIV are at a higher risk of severe acute COVID-19 outcomes compared with people without HIV [13-15]. Among people with HIV, those with lower absolute CD4 T cell counts or unsuppressed HIV viral load are at a higher risk of poor acute COVID-19 outcomes [15-17]. However, it is unknown whether living with HIV is a risk factor for long COVID. In addition, it is unknown whether the symptoms, sequelae, or time course of long COVID may differ in people living with HIV compared with people without HIV. People living with HIV are eager to learn the full picture of the risk for long COVID. Although the exact pathophysiological mechanisms contributing to long COVID are currently unclear, some researchers hypothesize that chronic inflammation or immune dysfunction may contribute [18,19]. Chronic inflammation and immune dysfunction are well described in people living with HIV on effective antiretroviral therapy [20]. Whether preexisting inflammation predisposes people living with HIV to long COVID or distorts its presentation needs further investigation. Moreover, some symptoms in individuals with long COVID, such as cognitive symptoms, may overlap with conditions common in people living with HIV, such as HIV-associated neurocognitive disorders.

To investigate long COVID in people living with HIV, we designed a prospective observational cohort study to characterize symptoms, sequelae, and cognitive function formally and prospectively in the 12 months after first SARS-CoV-2 infection in people living with HIV as compared with people without HIV, and as compared with people with no history of SARS-CoV-2 infection both with and without HIV. Because identifying and enrolling a sizeable population of individuals living with HIV with first SARS-CoV-2 infection within the previous 4 weeks would be challenging at any 1 location, and to ensure a study population representative of the demographic and geographic diversity of people living with HIV in the United States, we designed this study to be entirely remotely conducted to allow for enrollment and study participation from any location within the continental United States. Surveys are completed by telephone or on the web, cognitive assessments are administered by telephone, and blood and vital signs are collected via a mobile phlebotomy company. Mobile phlebotomists contracting for this company can meet participants at any location of their choice, for example, home or office.

Study Objectives

This study aimed to characterize symptoms, sequelae, and cognition formally and prospectively in the 12 months following first SARS-CoV-2 infection in people living with HIV as compared with people without HIV at 1, 2, 4, 6, and 12 months after acute COVID-19 symptom onset or after diagnosis if asymptomatic. In addition, people living with and without HIV with no history of SARS-CoV-2 infection were enrolled as controls and completed study events on a similar timeline. The study also aims to identify blood-based biomarkers or patterns of immune dysregulation that are associated with symptoms or sequelae of long COVID.

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Other objectives of this study are as follows:

1. To determine baseline host factors correlated with symptoms and sequelae of long COVID.
2. To understand the impact of SARS-CoV-2 infection on quality of life, sleep, fatigue, cognition, mental health, respiratory function, and behavior in the 12 months following infection in people living with and without HIV.
3. To determine whether abnormal orthostatic vital signs are associated with long COVID.
4. To characterize the host response to SARS-CoV-2 infection in people living with and without HIV, including innate and acquired immune responses and circulating levels of immune signaling molecules.
5. To develop a specimen biorepository that includes data and specimens from people living with and without HIV and with and without prior SARS-CoV-2 infection.

Methods

Ethics Approval and Informed Consent

This study was reviewed and approved by the Johns Hopkins University School of Medicine institutional review board (IRB00278774). Written informed consent in English or Spanish was obtained from all participants using either paper consent forms or DocuSign.

Study Design Overview

This study is a prospective, observational cohort study enrolling people living with and without HIV within 4 weeks of first SARS-CoV-2 infection. The study also enrolled people with and without HIV who believed they never had SARS-CoV-2 infection as controls. The study collected health information and specimens from participants at predetermined time intervals through questionnaires, cognitive assessments, and blood draws (Figure 1). This study was designed to enroll participants soon after SARS-CoV-2 infection so that the time course of postacute symptoms and sequelae in the first 12 months could be prospectively investigated and because biomarkers or immune markers of long COVID may only be present early in the postacute period [21]. The study recruited people into the following 4 study arms:

1. HIV+COVID+ arm: people living with HIV with first SARS-CoV-2 infection within the previous 4 weeks.
2. HIV−COVID+ arm: people without HIV with first SARS-CoV-2 infection within the previous 4 weeks.
3. HIV+COVID− arm: people living with HIV who believed they never had SARS-CoV-2 infection.
4. HIV−COVID− arm: people without HIV who believed they never had SARS-CoV-2 infection.

Figure 1. Schedule of study events. *Optional for HIV−COVID− participants; **Only for COVID+ participants.

	Entry	Month 1	Month 2	Month 4	Month 6	Month 12
Surveys	X	X	X	X	X	X
Neurocognitive assessments		X		X		
Blood, height, weight, and orthostatic vitals		X*		X**		

Study Eligibility

We recruited people with and without HIV, who either had first SARS-CoV-2 infection within the previous 4 weeks or who believed they had never had SARS-CoV-2 infection. Adults aged ≥18 years living in the 48 contiguous United States who had the ability to provide consent, who believed they could complete the study events, and who could communicate by telephone in either English or Spanish were eligible. Further eligibility criteria are presented in Table 1.

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Table 1. Participant inclusion and exclusion criteria.

Criteria	HIV+COVID+ arm	HIV−COVID+ arm	HIV+COVID− arm	HIV−COVID− arm
Inclusion	• Self-reported HIV infection • Ability to furnish proof of SARS-CoV-2 infection or reasonable certainty that they had SARS-CoV-2 infection • First COVID-19 symptoms or first positive diagnostic COVID-19 test (if asymptomatic) occurred within 28 days before enrollment	• Self-reported HIV-negative status[a] • Ability to furnish proof of SARS-CoV-2 infection or reasonable certainty that they had SARS-CoV-2 infection • First COVID-19 symptoms or first positive diagnostic COVID-19 test (if asymptomatic) occurred within 28 days before enrollment	• Self-reported HIV infection • Never tested positive for SARS-CoV-2 and does not believe they have ever had SARS-CoV-2 infection[b]	• Self-reported HIV-negative status[a] • Never tested positive for SARS-CoV-2 and does not believe they have ever had SARS-CoV-2 infectionb
Exclusion	• A first or only diagnosis of SARS-CoV-2 infection >28 days before contact with study	• A first or only diagnosis of SARS-CoV-2 infection >28 days before contact with study	• Have tested positive for SARS-CoV-2 or believe that they have had SARS-CoV-2 infection at some point in the past regardless of whether they were tested	• Have tested positive for SARS-CoV-2 or believe that they have had SARS-CoV-2 infection at some point in the past regardless of whether they were tested

[a]HIV antigen and antibody test was performed on all participants in this group as part of the study to confirm HIV-seronegative status.

[b]SARS-CoV-2 antinucleocapsid antibody testing was performed as part of this study and must be negative for inclusion in the analyses.

Recruitment

Participants living with HIV came to know about this study through health care providers, social media, and peers in a number of ways. The study coinvestigators and study team emailed and called HIV clinic directors across the 48 contiguous United States and requested permission to hang study flyers in their clinics. The study principal investigator (PI) and coinvestigators established a network of academic investigators and other people interested in HIV and COVID-19 across the United States and kept them abreast of updated flyers and recruitment updates through regular contact. HIV providers who were colleagues of these people were informed about the study by emails or announcements at provider meetings. Emails were sent to the United States HIV Medicine Association and the Infectious Diseases Society of America's Exchange listserves (primarily subscribed to by infectious diseases physicians and providers) every 2-4 months with updated flyers and information about the study to increase study referrals. HIV providers who had heard about the study informed their patients with recent SARS-CoV-2 diagnosis about the study and sought permission for the study team to contact them. This study also reached out to established HIV and substance use study cohorts with information on this research study to disseminate to their study cohort participants. Importantly, this study and people living with HIV aiding this study engaged people living with HIV in the community in numerous ways including social networks, email, and social media. The study worked with the Network for Long COVID Justice to amplify dissemination efforts around this study to several social media sites and web-based media sites popular among people living with HIV. The study worked with several community members to disseminate information about this study through social media channels. The study staff asked the participants who were enrolled to ask their friends and contacts who were eligible to contact our study if they were interested; there was no compensation for this recruitment. Advertisements for the study were posted on Facebook and Grindr. Finally, the study investigators received permission to identify people living with HIV with recent positive SARS-CoV-2 tests within the Johns Hopkins Health System via weekly electronic medical record reports. The study staff called these people with an invitation to hear more about the study.

Participants without HIV heard about this study in a number of ways. Advertisements for the study were posted on Facebook and Grindr. The study worked with several community members to disseminate information about this study through social media channels. Participants were recruited through the Johns Hopkins Institute for Clinical and Translational Research recruitment registry, Hopkins Opportunity for Participants Engagement (HOPE) registry. The HOPE registry is a centralized, institutional review board–approved database that contains the name and contact information of people who have taken a SARS-CoV-2 test within the Johns Hopkins Health System and have expressed interest in participating in research studies. The registry is housed in Research Electronic Data Capture (REDCap; Vanderbilt University), and people who have consented to participate in the registry enter their own data into the registry's web-based intake form, or they have their data collected by recruitment navigators via telephone and entered into the database by HOPE registry navigators. Eligible participants are then matched to each participating study based on the information they have provided and study eligibility criteria. This study's staff then reached out to the people matched to this study to assess their willingness and eligibility for this study. Physical flyers were posted on the Johns Hopkins medical campus.

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A study website was developed to provide information for interested people to self-refer via a web-based REDCap Health Insurance Portability and Accountability Act (HIPAA)–compliant form or by contacting the study directly (via email or phone). This website was advertised on social media platforms such as Facebook (including special interest groups such as for lesbian, gay, bisexual, transgender, queer, and others [LGBTQ+] communities in different cities) and Grindr.

Consent

A study coordinator based at Johns Hopkins University held a consent conversation with potential participants by telephone or video call, and consent was signed using DocuSign or paper consent forms. All consent activities were conducted in either English or Spanish. The DocuSign process was approved by the institutional review board and is 21 Code of Federal Regulations Part 11–compliant to obtain a secure electronic signature. This process involved sending the consent form to the participant via an email from DocuSign and providing a participant-specific access code that was required when the participant accessed and signed the consent form. Participants were given adequate time to consider the study and ask questions before signing the consent form. When ready to sign, each participant entered their code, verifying that the person signing the consent was the person whom we spoke with previously, and signed the consent within the DocuSign system. Once the participant had electronically signed, the study team member obtaining informed consent would be notified that the electronic form was ready for their signature. Once signing was completed by all parties, both the study team and the participant could download the signed consent as a PDF. The study team also had access to the audit log and the Certificate of Completion. Documentation capturing details of the consent process was maintained on REDCap.

In instances where DocuSign could not be executed or the potential participant declined to use it, the consent conversation happened in person or by telephone or video call and a paper consent was signed. In these cases, participants were provided with a copy of the paper consent document before the consent conversation either via email, fax, mail, or in person. After the consent conversation, the participants were given adequate time to consider the study and ask questions. The participant would sign, date and time the paper informed consent document. The document was then handed, mailed, emailed, or faxed to the consent designee for their signature, and a copy of the double-signed consent document was handed, mailed, emailed, or faxed back to the participant.

Surveys

Multimedia Appendix 1 [22-48] and Multimedia Appendix 2 provide detailed information about the surveys and the timing of study events. At enrollment, participant demographics, social history, substance use, medical history, medication use, SARS-CoV-2 vaccination status, and HIV history (for people living with HIV only) were recorded. Participants in the COVID+ arms also completed a comprehensive survey on symptoms, mental health, and quality of life via telephone or on the web in the month before having SARS-CoV-2 infection. At each time point after COVID-19 diagnosis (for the COVID+ arms) or after enrollment (for the COVID− arms), participants completed a comprehensive symptom, mental health, and quality of life survey (Multimedia Appendix 1). This survey consisted of several validated tools, which are detailed in the following paragraphs.

Participants indicated the presence and severity (on a scale of "Not at all," "A little bit," "Somewhat," "Very much," or "Quite a bit") of 49 long COVID symptoms. Overall, 34 symptoms derive from the FLU-PRO Plus, and 15 additional symptoms were added based on their frequency of report in a Long COVID Patient Led Research Collaborative survey with input from the patient-researcher authors [5,22]. Dyspnea was assessed using the Modified Medical Research Council (mMRC) Dyspnea Scale, which is used to assess the degree of baseline functional disability because of dyspnea [23]. The Breathless, Cough, and Sputum Scale (BCSS) was used to evaluate the respiratory symptoms common in COVID-19 [24]. The survey also included the Insomnia Severity Index (ISI), which is a 7-item questionnaire assessing the participant's perceived insomnia symptoms and resulting disruption to their lives [25,26]. Participants self-reported the average daily sleep duration in the previous week. Participants completed the Fatigue Severity Scale (FSS), a 9-item questionnaire assessing their perception of the impact of fatigue on their quality of life and activities of daily living [27]. The FSS global fatigue question was used to measure the participants' global fatigue. At each study event, the participants were asked whether they had received a COVID-19 vaccine or had a new infection with SARS-CoV-2 since the previous study event.

The survey included the Patient Health Questionnaire Depression 8-item (PHQ-8) and Generalized Anxiety Disorder-7 (GAD-7) tool to assess the severity of depressive and anxiety symptoms, respectively [28-30]. Participants also completed the computerized adaptive testing for mental health (CAT-MH), which draws upon a bank of >1000 test items aligned with the Diagnostic and Statistical Manual of Mental Disorders (DSM)-5 criteria.[31-33]. The modules completed included the computerized adaptive diagnostic test for major depressive disorder (CAT-MDD; screener for major depressive disorder), the computerized adaptive diagnostic test–Depression Inventory (CAT-DI; assesses depression severity), and computerized adaptive diagnostic test–Anxiety Inventory (CAT-ANX; assesses anxiety severity). The survey also assessed self-reported cognitive problems using the self-assessment section of the General Practitioner Assessment of Cognition (GPCOG). This tool consists of 6 yes or no items relating to participants' perceived difficulty with certain activities owing to cognitive limitations compared with a prior time point [34]. We asked participants to evaluate their current ability to complete the tasks compared with their ability before they had COVID-19 or before enrollment.

Quality of life was assessed using the Short Form Survey (SF-36) and the EuroQuol EQ-5D-5L. The SF-36 contains 36 Likert and binary items relating to the participant's activities and perceptions of health status [35,36]. The EQ-5D-5L assesses general quality of life through 5 dimensions that include mobility, self-care, usual activities, pain and discomfort, and

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anxiety and depression [37]. The EQ-5D-5L includes a general health question that asks the participant to provide 1 number from 0 to 100 on a visual analog scale representing their overall health [37]. The Brief Resilience Scale was used to assess the perceived ability to bounce back or recover from stress [38]. Stressor-related questions were also asked to assess general stress levels from daily life during the COVID-19 pandemic (Multimedia Appendix 1).

Participants in the COVID+ arms were administered an additional acute COVID-19 survey at 1 or more months after COVID-19 diagnosis in which the participant was asked to recall the presence and severity of the same 49 COVID-19 symptoms described earlier within the first 14 days of symptom onset or positive testing (if asymptomatic). The survey also queried the type of COVID-19 test taken, sample source, COVID-19 exposure, treatment for acute COVID-19, and whether hospitalization or oxygen was required during acute COVID-19. Reinfection was not uncommon in this cohort, and each participant was asked about reinfection (COVID+ arm) or new SARS-CoV-2 infection (COVID− arm). Each individual with a new SARS-CoV-2 infection since enrollment was administered the same acute COVID-19 survey described earlier one or more months after COVID-19 diagnosis to collect information on the acute course of COVID-19. Further information about the surveys used in the study can be found in Multimedia Appendix 1.

Neurocognitive Assessments

Participants in all arms underwent a telephone-based neurocognitive assessment at 1 and 4 months after acute SARS-CoV-2 symptom onset or diagnosis (COVID+ arm) or after enrollment (COVID− arm). Telephone assessment has been shown to be feasible and provides a valid assessment of cognitive function relative to in-person neurocognitive testing [49-51]. This telephone assessment has been successfully implemented in diverse patient populations, including post–COVID-19 populations [52-54].

A total of 11 cognitive assessments were administered in this study. The Hopkins Verbal Learning Test–Revised (HVLT-R) is a test of new auditory-verbal learning (VL), verbal memory (VM), and recognition discrimination memory (RM) [39,40]. The Oral Trail Making Test part A (OTMT-A) and Oral Trail Making Test part B (OTMT-B) are brief motor-free tests of mental processing speed (part A) and executive functioning requiring sequential set shifting (part B) [39-41]. The Wechsler Adult Intelligence Scale–Fourth Edition (WAIS-IV) Digit Span Forward (DSF) and Digit Span Backwards (DSB) assessments test auditory attention (forward) and working memory (backward) [42-44]. The Calibrated Ideational Fluency Assessment (CIFA) assesses letter-cued and category-cued verbal fluency (VF). Category-cued VF assesses rapid access to semantic information, and letter-cued VF assesses speeded word retrieval in response to phonetic cues [45-47]. The WAIS-IV Information (WAIS-IV IN) test assesses the general fund of knowledge and was only administered once in this study [42-44]. Performance on the WAIS-IV IN is relatively resistant to neurological damage, and scores correlate highly with overall IQ, thereby allowing scores to serve as a proxy for lifelong intellectual functioning [48].

Mobile Phlebotomist Visits and Clinical Laboratory Testing

Participants in the COVID+ arms had mobile phlebotomy visits at a location of their choice at 1 and 4 months after post–acute COVID-19 symptom onset (or after diagnosis if asymptomatic). Participants in the HIV+COVID− arm had 1 mobile phlebotomy visit at either month 1 or 4, provided that they had not had SARS-CoV-2 infection before the visit. Participants in the HIV−COVID− arm could optionally undergo specimen collection at either month 1 or month 4, provided that they had not had SARS-CoV-2 infection before the visit. Anti–SARS-CoV-2 nucleocapsid immunoglobulin G was measured in all participant specimens, and data from participants in the COVID− arm were excluded from analyses if their specimens tested positive for antinucleocapsid antibodies and they were unaware of SARS-CoV-2 infection.

A mobile phlebotomy company that operates in every state of the United States was engaged to (1) measure participant height and weight, (2) measure orthostatic vital signs, and (3) draw ≤50 mL blood. A blood draw kit was shipped to the participants before the date of the blood draw. The kit included a vital sign sheet, a sodium citrate tube, serum separator tubes, EDTA tubes, and a PAXgene blood RNA tube. All tubes were plastic and labeled with the participant identifier and a space for the date and time of collection. In addition, absorbent sleeves to separate tubes, approved shipping materials including an outer cardboard box, and an inner 95-kPa specimen transport bag with appropriate biohazard labeling were included in the blood draw kit.

For the measurement of orthostatic vital signs, the participants were asked to lie down for 5 minutes before the first blood pressure and heart rate measurement. Participants were then asked to stand up, and after 1 and 3 minutes, additional heart rate and blood pressure measurements were recorded. After the measurement of orthostatic vital signs, blood was drawn from the participant by the phlebotomist. After filling, all tubes were inverted gently 6-8 times. The serum separator tubes were kept upright for 30-60 minutes before centrifugation for 15 minutes at 1100-1300 g by the mobile phlebotomist. The tubes were placed in absorbent sleeves and were shipped overnight using International Air Transport Association–approved procedures to the study laboratory (Rush Clinical Retrovirology Research Laboratory, Chicago). When specimens arrived at the laboratory, designated specimens were sent to the study Clinical Laboratory Improvement Amendments of 1988 (CLIA)–certified testing laboratory (Rush Medical Laboratories, Chicago) for testing. If unforeseen shipping delays occurred and blood was received >48 hours after collection, then some of the clinical testing was not performed owing to stability issues (eg, CD4, complete blood count, lipid panel, and D-dimer). The remaining blood was processed on the same day, and serum, plasma, peripheral blood mononuclear cells (PBMCs), and the PAXgene blood RNA tubes were appropriately frozen and stored. An inventory of the biorepository was created and maintained by the study laboratory using the Laboratory Data Management System

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(Frontier Science) [55]. The Johns Hopkins REDCap team developed a novel method to directly input biorepository inventory files from the Laboratory Data Management System into the study's REDCap database for seamless and rapid updating of the biorepository in the central database.

Biospecimen Testing

The CLIA-certified study testing laboratory ran the following panel of tests: SARS-CoV-2 antinucleocapsid IgG (Abbott Architect), complete blood count with differential, high-sensitivity C-reactive protein, creatine phosphokinase, D-dimer, lipid panel, HIV fourth-generation antigen and antibody testing (for those who self-reported as HIV-seronegative), and CD4 T cell percentage and absolute count (for those who self-reported as living with HIV). Plasma, PBMCs, and serum were also obtained from all samples. If the blood sample was received by the Rush Clinical Retrovirology Research Laboratory >48 hours after collection, the sample was not sent for complete blood count, CD4 panel, lipid panel, or D-dimer according to the clinical laboratory protocol. The blood sample was still processed for plasma and PBMCs, but in cases where the sample did not separate, plasma and PBMCs were not saved. However, serum was obtained from these samples.

Coronavirus antibodies and select hormones and cytokines were quantified in a subset of specimens. The panel of coronavirus antibodies that were quantified included HCoV-229E Spike, HCoV-HKU1 Spike, HCoV-NL63 Spike, HCoV-OC43 Spike, SARS-CoV-1 Spike, SARS-CoV-2 Nucleocapsid, SARS-CoV-2 NTD. SARS-CoV-2 RBD, SARS-CoV-2 Spike, AY.4, B.1.351, BA.2, BA.2+L452M, BA.2+L452R, BA.2.12.1, BA.3, BA.4, BA.5, and CoV-2 Spike. The hormones and cytokines that were tested were based on what might be important in long COVID from the current literature at the time: interferon (IFN)-β, interleukin (IL)-1RA, IL-1α, IFN-λ1, IL-5, IL-8, interferon gamma-induced protein-10 (IP-10), chemokine (C-X-C motif) ligand 9 (CXCL9), macrophage inflammatory protein (MIP)-1β, vascular endothelial growth factor (VEGF), alpha-1-acid glycoprotein 1 (ORM1), MIP-5, T cell immunoglobulin and mucin-domain containing (TIM)-3, Factor D, lipocalin 2 (LCN2), glial fibrillary acidic protein (GFAP), pentraxin 3 (PTX3), Cortisol, IFN-λ2, transforming growth factor (TGF)-β1, ADAMTS13, complement component 5a (C5a), IFN-γ, IL-1β, IFN-λ3, IL-6, C-C motif chemokine ligand 20 (CCL20), C-C motif chemokine ligand 23 (CCL23), and tumor necrosis factor (TNF)-α [21,56-59]. Most of these analytes were measured with validated assays using commercial plates manufactured by Meso Scale Discovery. Results were analyzed using Discovery Workbench (version 4.0.12; Meso Scale Discovery). The antibody kits were provided by the company.

Data Collection and Management

Database services were provided by the Johns Hopkins University REDCap, a secure, HIPAA–compliant web application for building databases and managing web-based data for research [60]. Almost all data were collected by Johns Hopkins University study staff. A limited number of data points were generated by the mobile phlebotomy company (eg, orthostatic vital signs, height, weight, and status of collection and shipment) and by the study laboratories at Rush University (eg, clinical laboratory test results, status of shipment receipt, and status of sample processing and storage). Study staff at Johns Hopkins University or Rush received data from the mobile phlebotomy company via the phlebotomy secure internet portal and entered it into the REDCap database. The PI of the study was notified of grossly abnormal vital signs or laboratory results and about moderate to high depression or anxiety PHQ-8 and GAD-7 scores. The PI was also notified if the mobile phlebotomist noted any concerning event during the mobile phlebotomy visit. In each case, the PI reached out to the participant to provide basic health advice and guidance and resources for referral to the appropriate health provider.

Outcomes

Primary Outcomes

1. *Time to return to usual health and time to return to usual activities* will be measured using the FLU-PRO Plus instrument where we will assess the days taken to return to usual health and activities after COVID-19 or enrollment.
2. *Fatigue, severity of fatigue, and its effect on activity level* will be measured using the FSS (on a scale of 9-63) and the FSS global fatigue score (on a scale of 0-10) at 1, 2, 4, 6, and 12 months after COVID-19 or enrollment.
3. *Dyspnea* will be measured using the mMRC instrument (on a scale of 0-4) at 1, 4, and 12 months after COVID-19 or enrollment.
4. *Cognitive impairment* will be assessed using age-standardized scores from the 11 cognitive assessments and the GPCOG (on a scale of 0-36) at 1, 4, and 12 months after COVID-19 or enrollment.
5. *Number of symptoms* experienced will be measured using the FLU-PRO Plus instrument and the 11 additional long symptoms in the domains of neuropsychiatry, cardiovascular, and skin (on a scale of 1-5) at 1, 2, 4, 6 and 12 months after COVID-19 or enrollment.

Secondary Outcomes

1. *Orthostatic hypotension and orthostatic tachycardia* will be assessed at 1 and 4 months after COVID-19 or enrollment.
2. *Mental health* will be measured via self-reported measures of depressive symptoms and anxiety using the PHQ-8 and GAD-7 assessments at 1, 2, 4, 6, and 12 months after COVID-19 or enrollment and the CAT-MH at 1 and 4 months after COVID-19 or enrollment.
3. *Quality of life* in the domains of physical functioning, physical limitation of role fulfillment, emotional limitation of role fulfillment, energy and fatigue, emotional well-being, social functioning, pain, and general health will be assessed using the SF-36 and the EuroQuol EQ-5D-5L. The *RAND* 36-Item Health Survey 1.0 scoring method will be used to convert these questions into scores of the 8 QoL domains at 1, 4, and 12 months after COVID-19 or enrollment [61,62].
4. *Insomnia* (presence, severity, and patterns of insomnia) and its interference with daily functioning will be assessed by the ISI (on a scale of 0-28) at 1, 2, 4, 6, and 12 months after COVID-19 or enrollment.

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Compensation

All participants were offered compensation for their time and efforts in participating in the study. A compensation of US $25 was offered per blood draw and US $25 per cognitive assessment completed, for a total of up to US $100 (for COVID+ arm) or US $75 (for COVID− arm) if all study events were completed. Participants were compensated in the form of an Amazon or VISA gift card.

Power Calculation

The target enrollment was as follows: 105 participants in the HIV+COVID+ arm, 105 participants in the HIV−COVID+ arm, 45 participants in the HIV+COVID− arm, and 50 participants in the HIV−COVID− arm. This resulted in a total target sample size of 305 participants overall, 210 of whom would be in the post–COVID-19 arms. Using a 2-tailed α of .05 and 10% estimated proportion of persistent symptoms in the comparator group, we estimated that there was 80% power to detect a difference of 15% in new or worsened symptom prevalence between people living with and without HIV after SARS-CoV-2 infection using a chi-square test of proportions.

Statistical Analysis

First, we will calculate the prevalence of persistent symptoms across the entire cohort and new or worsening symptoms compared with pre–COVID-19 symptoms in the 2 COVID-19 recovery arms. We will calculate mean and SD as well as median and IQR of the participant symptom score and quality of life by domain, reporting the statistic that is most reflective of the underlying distribution of the data. We will perform a time-to-event analysis to examine the return to baseline health using a Kaplan-Meier curve to graphically demonstrate COVID-19 recovery. To screen for unanticipated clinical syndromes related to COVID-19, we will also perform an exploratory analysis examining the proportion of participants reporting an abnormality in each item on the symptom checklist. In addition, we will perform cross-sectional cluster analyses at each time point to determine how each symptom relates to the others in each study arm at each time point.

After performing the descriptive analyses for each of the comparator arms, we will compare outcomes between the study arms. For binary outcomes such as new or worsened symptoms, we will report an unadjusted prevalence ratio. For symptom score and quality of life domain scores, we will perform unadjusted linear regression. For return to health, we will perform a time-to-event analysis and use a Cox regression model to estimate hazard ratios. In the next stage of the analysis, we will repeat these models but adjust for covariates including potential confounders (age, sex, race, ethnicity, etc) and effect modifiers (vaccination status and severity of illness).

Finally, we will make comparisons between individuals in each study arm with and without persistent symptoms—we will compare various biological analytes outlined in the *Biospecimen Testing* section among people living with HIV with and without persistent symptoms and among people without HIV with and without persistent symptoms and also describe these analytes among people living with and without HIV who have not had SARS-CoV-2 infection.

Results

The project was funded in early 2021, and recruitment began in June 2021. Data analyses are expected to be completed by summer 2023, and the primary study results are expected to be submitted for publication in 2023. As of February 2023, 387 participants enrolled in this study, 345 of whom completed enrollment and baseline surveys together with at least one other completed study event at month 1, 2, 4, 6, or 12. The 345 participants include 76 (22%) HIV+COVID+, 121 (35.1%) HIV−COVID+, 78 (22.6%) HIV+COVID−, and 70 (20.3%) HIV−COVID− participants.

Discussion

Expected Findings

This study will objectively characterize cognition, symptoms, and sequelae in the 12 months after first SARS-CoV-2 infection in people living with and without HIV. We aimed to replicate the demographic and geographic diversity of people living with HIV in the United States by opening enrollment to people who speak English or Spanish living anywhere in the 48 contiguous United States. As the demographics and medical histories of people living with HIV differ in important ways from people without HIV, we will compare post–COVID-19 cognition, symptoms, and sequelae with postenrollment cognition, symptoms, and sequelae in people living with and without HIV who have never had SARS-CoV-2 infection. We anticipate that people living with and without HIV will have broadly overlapping symptoms and sequelae after COVID. However, given that people living with HIV are more likely than people without HIV to have neurocognitive disease, we anticipate that people living with HIV will be more likely to have subjective and objective cognitive difficulties after COVID than people without HIV [63].

The pathophysiology of long COVID is currently not well defined. Proposed mechanisms include perturbations of immune and inflammatory responses during acute COVID-19, persisting reservoirs of SARS-CoV-2 in tissues, reactivation of latent pathogens such as Epstein-Barr virus, alterations of microbiota, autoimmunity and priming of the immune system from molecular mimicry, microvascular blood clotting, endothelial dysfunction, and dysfunctional signaling in the brainstem [18,19,21,56-58,64-72]. This study will be able to provide evidence to support or refute mechanisms that involve immune dysfunction and persistence of SARS-CoV-2 in plasma by testing samples for cytokines and coronavirus antibody and T cell responses. A central biorepository was created with samples from this study, which could be tested in the future for evidence of the reactivation of latent pathogens, complement activation, and autoimmunity.

Research on the relationship between HIV and long COVID is limited. A US-based electronic medical record preprint using data from TriNetX demonstrated that people living with HIV are more likely to report symptoms and sequelae ≥1 months following COVID-19 compared with propensity score–matched HIV-negative individuals [73]. A moderate-sized cohort study in San Francisco found that HIV is a risk factor for neurological

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long COVID [71]. By contrast, a study in South Africa found that people living with HIV were as likely as HIV-negative individuals to report symptoms 6 months after hospitalization for COVID-19 [74]. Studies like ours that have the ability to link symptoms, sequelae, and objective measures such as cognitive testing to biological analytes are needed to help the field understand why people living with HIV might be more likely to develop long COVID symptoms and sequelae.

Strengths

This study was designed to meet the needs of people potentially experiencing long COVID who may be juggling fatigue and other symptoms and sequelae with life, work, and family responsibilities. The major strength of this study is its remote and participant-centric design. Participants could complete every study event from any location of their choice, including their home. This also allowed for the recruitment of a diverse participant population from around the United States who spoke either English or Spanish. In addition, the development of a central biorepository for specimen sharing will serve as a resource for investigators interested in the intersection of HIV and long COVID. Another strength of the study was that our surveys were developed in consultation with patient researchers who were experiencing long COVID.

Limitations

Limitations of the study include study dropout given the extended period of follow-up. To limit dropout, the study staff regularly reminded participants to complete the study events through phone calls, text messages, and emails. Unfortunately, shipping interruptions owing to weather and shipping company errors delayed the delivery of a percentage of specimens and affected which clinical tests could be performed. The survey asking participants to recall symptoms and quality of life in the month before SARS-CoV-2 infection was subject to a recall bias. In addition, as many participants completed the survey on the web in the context of other similar surveys asking about the present time, participants may have reported current rather than pre–COVID-19 symptoms. Questions on alcohol and substance use may have been subject to social desirability bias.

We aim to disseminate results from this study to participants via emails and at least 2 internet calls (with phone numbers and names anonymized by study staff to protect identifying information) so that participants can learn about study findings, ask questions, and provide feedback. We aim to disseminate the results from this study to affected communities by reaching out through the same networks used to advertise the study (social media, community advisory boards, activist groups, informal and formal newsletters, and magazines), ensuring that affected communities hear about science relevant to them.

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Data Availability

The data sets generated or analyzed during this study are not publicly available because of the presence of patient identifying information but are available from the corresponding author upon reasonable request pending institutional review board approval.

Conflicts of Interest

Under a private license agreement, TDV is entitled to a share of royalty from the sales of the products described in this study. The terms of this arrangement are being managed by the Johns Hopkins University in accordance with its conflict-of-interest policies. No other authors declare a conflict of interest.

Multimedia Appendix 1
Additional information about surveys used in the study.
[DOCX File , 81 KB - resprot_v12i1e47079_app1.docx]

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Multimedia Appendix 2
Peer-reviewer report from amfAR, The Foundation for AIDS Research (USA).
[PDF File (Adobe PDF File), 107 KB - resprot_v12i1e47079_app2.pdf]

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Abbreviations

BCSS: Breathless, Cough, and Sputum Scale
CAT-ANX: Computerized Adaptive Diagnostic Test–Anxiety Inventory
CAT-DI: Computerized Adaptive Diagnostic Test–Depression Inventory
CAT-MDD: Computerized Adaptive Diagnostic Test-Major Depressive Disorder
CAT-MH: Computerized Adaptive Test-Mental Health
CIFA: Calibrated Ideational Fluency Assessment
CLIA: Clinical Laboratory Improvement Amendments of 1988
DSB: Digit Span Backwards
DSF: Digit Span Forward
DSM: Diagnostic and Statistical Manual of Mental Disorders
FSS: Fatigue Severity Scale
GAD-7: Generalized Anxiety Disorder-7
GFAP: glial fibrillary acidic protein
GPCOG: General Practitioner Assessment of Cognition
HIPAA: Health Insurance Portability and Accountability Act
HOPE: Hopkins Opportunity for Participants Engagement
HVLT-R: Hopkins Verbal Learning Test–Revised
IFN: interferon
IL: interleukin
ISI: Insomnia Severity Index
LGBTQ+: lesbian, gay, bisexual, transgender, queer, and others
MIP: macrophage inflammatory protein
mMRC: Modified Medical Research Council
OTMT-A: Oral Trail Making Test part A
OTMT-B: Oral Trail Making Test part B
PBMC: peripheral blood mononuclear cell
PHQ-8: Patient Health Questionnaire Depression 8-item
PI: principal investigator
REDCap: Research Electronic Data Capture
RM: recognition discrimination memory
SF-36: Short Form Survey
TGF: transforming growth factor
TIM: T cell immunoglobulin and mucin-domain containing
TNF: tumor necrosis factor
VF: verbal fluency
VL: verbal learning
VM: verbal memory
WAIS-IV IN: Wechsler Adult Intelligence Scale–Fourth Edition Information test
WAIS-IV: Wechsler Adult Intelligence Scale−Fourth Edition

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Protocol

Optimal Dosing and Timing of High-Dose Corticosteroid Therapy in Hospitalized Patients With COVID-19: Study Protocol for a Retrospective Observational Multicenter Study (SELECT)

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Abstract

Background: In hospitalized patients with COVID-19, the dosing and timing of corticosteroids vary widely. Low-dose dexamethasone therapy reduces mortality in patients requiring respiratory support, but it remains unclear how to treat patients when this therapy fails. In critically ill patients, high-dose corticosteroids are often administered as salvage late in the disease course, whereas earlier administration may be more beneficial in preventing disease progression. Previous research has revealed that increased levels of various biomarkers are associated with mortality, and whole blood transcriptome sequencing has the ability to identify host factors predisposing to critical illness in patients with COVID-19.

Objective: Our goal is to determine the most optimal dosing and timing of corticosteroid therapy and to provide a basis for personalized corticosteroid treatment regimens to reduce morbidity and mortality in hospitalized patients with COVID-19.

Methods: This is a retrospective, observational, multicenter study that includes adult patients who were hospitalized due to COVID-19 in the Netherlands. We will use the differences in therapeutic strategies between hospitals (per protocol high-dose corticosteroids or not) over time to determine whether high-dose corticosteroids have an effect on the following outcome measures: mechanical ventilation or high-flow nasal cannula therapy, in-hospital mortality, and 28-day survival. We will also explore biomarker profiles in serum and bronchoalveolar lavage fluid and use whole blood transcriptome analysis to determine factors that influence the relationship between high-dose corticosteroids and outcome. Existing databases that contain routinely collected electronic data during ward and intensive care admissions, as well as existing biobanks, will be used. We will apply longitudinal modeling appropriate for each data structure to answer the research questions at hand.

Results: As of April 2023, data have been collected for a total of 1500 patients, with data collection anticipated to be completed by December 2023. We expect the first results to be available in early 2024.

Conclusions: This study protocol presents a strategy to investigate the effect of high-dose corticosteroids throughout the entire clinical course of hospitalized patients with COVID-19, from hospital admission to the ward or intensive care unit until hospital discharge. Moreover, our exploration of biomarker and gene expression profiles for targeted corticosteroid therapy represents a first step towards personalized COVID-19 corticosteroid treatment.

Trial Registration: ClinicalTrials.gov NCT05403359; https://clinicaltrials.gov/ct2/show/NCT05403359

International Registered Report Identifier (IRRID): DERR1-10.2196/48183

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KEYWORDS

COVID-19; corticosteroid; infectious diseases; virology

Introduction

Background

The emergence of SARS-CoV-2 in Wuhan caused a global COVID-19 pandemic, with a high mortality and morbidity rate worldwide [1]. Over the past years, many efforts have been made to unravel the underlying complex pathophysiological mechanisms and explore various treatment options. Substantial variation exists in systemic and alveolar levels of inflammation between patients, contributing to the heterogeneous clinical course of the disease. This ranges from asymptomatic infection to life-threatening hypoxemic pneumonia. Corticosteroid therapy has the potential to inhibit disease progression and decrease the severity of clinical symptoms and is first-line immunosuppressive therapy in patients with COVID-19 with hypoxia [2].

The main reason for hospitalization of patients with COVID-19 is the requirement of supplemental oxygen therapy because of hypoxemia. In some patients, ground glass opacification and the beginning of consolidations on pulmonary CT scan are observed [3], accompanied by increased parameters of inflammation and coagulation in bronchoalveolar lavage fluid (BALF) and the systemic compartment [4,5]. In case of progressive respiratory failure, patients with COVID-19 will be admitted to the intensive care unit (ICU). These patients have a significantly decreased partial pressure of oxygen in arterial blood–fraction of inspiratory oxygen concentration ratio and frequently fulfill the Berlin criteria of moderate and severe acute respiratory distress syndrome (ARDS) [6]. Analysis of their inflammatory profiles shows a further elevation of proinflammatory cytokines, which is associated with increased mortality [7,8].

For decades, corticosteroids are given to treat patients with non–COVID-19 ARDS because of their strong anti-inflammatory effects [9]. Among patients with COVID-19, the Randomized Evaluation of Covid-19 Therapy (ie, RECOVERY) study showed that low-dose dexamethasone reduces mortality in patients requiring supplemental oxygen therapy or invasive mechanical ventilation but not in patients without respiratory support [10]. Current COVID-19 guidelines recommend a dose of 6 mg of dexamethasone per day for 10 days when oxygen therapy is required, regardless of the level of inflammation or severity of the disease [2]. Unfortunately, a proportion of patients still show progressive deterioration despite this treatment.

In these dexamethasone-unresponsive patients with COVID-19, corticosteroid therapy is sometimes escalated to a much higher dose. However, large heterogeneity in the type, timing, and

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dosing of escalated corticosteroid therapy exists [11]. High-dose corticosteroids are mainly administered during the late phase of the clinical course and in patients with the most severe disease, while earlier administration could be beneficial in preventing disease progression. However, the results of the studies on high-dose corticosteroid treatment for critically ill patients with COVID-19 are contradicting [12-15]. A recent meta-analysis compared high-dose corticosteroids versus low-dose corticosteroids in hospitalized patients with COVID-19 and reported no difference in mortality. Given the low level of evidence, inconclusive trial sequential analysis, and substantial heterogeneity, the authors stress the importance of future research to improve the certainty of evidence [16].

Treatment with high-dose corticosteroids may come at the cost of complications, such as secondary infections due to the immunosuppressive effects. To better predict the response to high-dose corticosteroids prior to therapy, additional diagnostic tools such as serum and BALF biomarker determination and whole blood transcriptome analysis could be helpful [17]. Implementation of these tools may result in a more precise and individualized approach to corticosteroid dosing in clinical practice.

Overall, the optimal dosing and timing of high-dose corticosteroids in hospitalized patients with COVID-19 remains uncertain. Here, we present the study design and methodological considerations of the SELECT (Steroids in Hospitalized Patients with COVID-19 in The Netherlands) study, a multicenter study that aims to study the most optimal dosing and timing of corticosteroid therapy to reduce the morbidity and mortality of hospitalized patients with COVID-19. In addition, we aim to provide a basis for personalized corticosteroid treatment regimens by exploring the predictive value of biomarkers and whole blood transcriptome analysis. We hypothesize that the effect of corticosteroid therapy on outcome is determined by the dosage and timing of administration, as well as the patient's underlying inflammatory state.

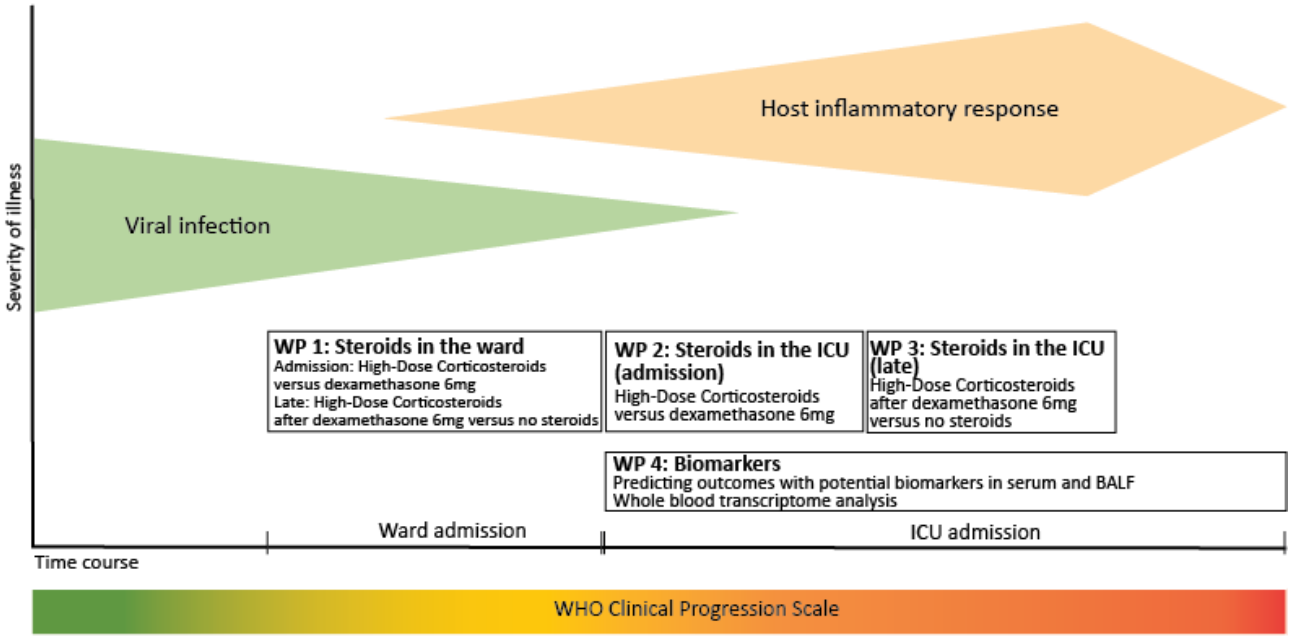
Study Aims

Work Package 1: High-Dose Corticosteroid Treatment in the Ward

Work package 1A (WP1A) is used to investigate whether initial treatment with high-dose corticosteroids compared to treatment with 6 mg dexamethasone per day for 10 days, or an equivalent corticosteroid, improves patient outcomes in the ward (Figure 1).

WP1B is used to investigate whether treatment with high-dose corticosteroids compared to no corticosteroids, after treatment with 6 mg dexamethasone per day for 10 days, improves patient outcomes in the ward.

Figure 1. Integration of work packages in the Steroids in Hospitalized Patients with COVID-19 in The Netherlands (SELECT) study. On the y-axis, the viral and host inflammatory response are depicted. On the x-axis, the admission to the ward or intensive care unit (ICU) is shown, and below that, the World Health Organization (WHO) clinical progression scale is displayed as a measure of supplemental oxygen therapy. steroids: corticosteroids; HDS: high-dose corticosteroids; WP: work package.



Work Package 2: High-Dose Corticosteroid Treatment in the ICU

Work package 2 (WP2) is used to investigate whether initial treatment with high-dose corticosteroids compared to treatment with 6 mg dexamethasone per day for 10 days, or an equivalent corticosteroid, improves patient outcomes in the ICU.

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Work Package 3: High-Dose Corticosteroid Treatment After Standard Corticosteroid Treatment in the ICU

Work package 3 (WP3) is used to investigate whether treatment with high-dose corticosteroids compared to no corticosteroids, after treatment with 6 mg dexamethasone per day for 10 days, improves patient outcomes in the ICU.

Work Package 4: Biomarker Profiles and Whole Blood Genome Transcriptomes in High-Dose Corticosteroid Treatment

Work package 4a (WP4a) is used to investigate whether biomarker profiles in serum and BALF act as response predictors for high-dose corticosteroids on the outcome.

WP4b is used to investigate whether whole blood transcriptome analysis acts as a response predictor for high-dose corticosteroids on the outcome.

Methods

Definition High-Dose Corticosteroids

High-dose corticosteroids are defined as every treatment with dexamethasone >6 mg daily or an equivalent corticosteroid (Table 1). Regarding prior and continuing use of corticosteroids for other conditions, corticosteroids are considered as part of the COVID-19–related intervention when the high-dose threshold is passed.

Table 1. Equivalent corticosteroids and dosages (total daily dosing)[a].

Drug	Equivalent dose (mg)	Low-dose (mg)	High-dose (mg)
Dexamethasone	0.75	≤6	>6
Cortisone	25	≤200	>200
Hydrocortisone	20	≤160	>160
Prednis(ol)one	5	≤40	>40
Methylprednisolone	4	≤32	>32
Bethamethasone	0.75	≤6	>6

[a]This table shows the equivalent corticosteroids and dosages. The equivalent dose is derived from Farmacotherapeutisch Kompas [18].

Study Design and Setting

The SELECT study is a retrospective cohort study with data from 22 hospitals in the Netherlands, including 4 academic and 18 nonacademic hospitals (Figure 2). Other hospitals may be included as the study progresses and we will use routinely collected electronic data from the participating hospitals. The data sets will contain data on hospitalized patients with COVID-19 from the date the first patient was admitted to the hospital in the Netherlands (March 1, 2020) until data transfer (expected May-December 2023). We will use the heterogeneity in therapeutic regimens in time (ie, first, second, and third epidemiological wave), centers (per protocol high-dose corticosteroids or not), and individual patients in the initial databases to address our aims. In a subpopulation of patients, we will use biobank material collected within the Collaboration on Identification, Understanding and Improved Management of patients with infectious diseases study of the Erasmus MC or collected at the Amsterdam University Medical Center (UMC) within the MERMAIDS-ARI, VIS cohort study or the Amsterdam UMC COVID-19 biobank.

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Figure 2. Participating hospitals of the Steroids in Hospitalized Patients with COVID-19 in The Netherlands (SELECT) study. UMC: University Medical Center. MC: Medical Center; OLVG: Onze Lieve Vrouwe Gasthuis.

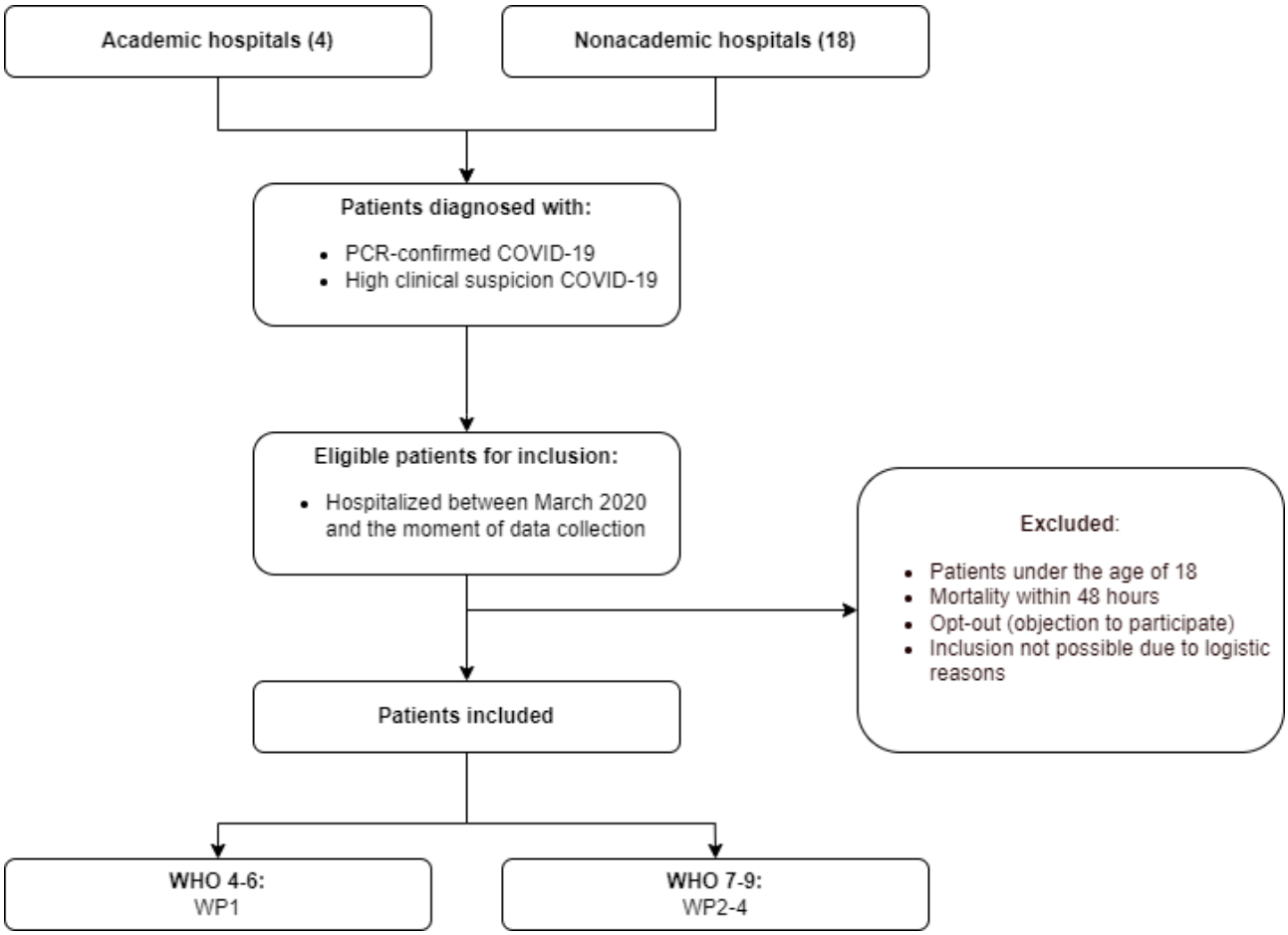


Patient Selection and Inclusion Criteria

Adult patients (≥18 years) hospitalized with polymerase chain reaction–confirmed COVID-19 or high clinical suspicion of COVID-19 will be included (Figure 3). Pregnant patients and patients receiving corticosteroids for other conditions during or prior to hospital admission are eligible, although a prespecified sensitivity analysis excluding these patients will be performed. Patients who die within 48 hours after admission or patients who object to participate will be excluded from the study. In WP1 and WP4, we will include patients from all SARS-CoV-2 epidemic waves, and in WP2-3, we will include patients from the first and second waves only. Specific inclusion and exclusion criteria for each work package will be applied. In WP1A, patients will be included who are admitted to the ward with a World Health Organization clinical progression scale class of 4-5 [19] (ie, no oxygen or oxygen therapy via a cannula or [non-rebreather] mask). WP1B includes patients who have progressed to the World Health Organization clinical progression scale class of 5-6 (ie, noninvasive oxygen therapy, including conventional oxygen via cannula [non-rebreather] mask, high-flow nasal cannula, noninvasive continuous positive airway pressure, and noninvasive bilevel positive airway pressure) after in-hospital treatment with 10 days of 6 mg per day dexamethasone. The study population for WP2-4 consists of patients admitted to the ICU for a period exceeding 48 hours, who received invasive mechanical ventilation via an endotracheal tube, a tracheostomy, or extracorporeal membrane oxygenation during their ICU stay.

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Figure 3. Patient inclusion. World Health Organization (WHO) classification: 0=uninfected, 1=asymptomatic; viral RNA detected, 2=symptomatic; independent, 3=symptomatic; assistance needed, 4=hospitalized; oxygen by mask or nasal prongs, 5=hospitalized; oxygen by mask or nasal prongs, 6=hospitalized; oxygen by noninvasive ventilation or high flow, 7=intubation and mechanical ventilation partial pressure of oxygen in arterial blood–fraction of inspiratory oxygen concentration (PaO2/FiO2) ratio of ≥150, 8=mechanical ventilation PaO2/FiO2 ratio of <150 or vasopressors, 9=mechanical ventilation PaO2/FiO2 ratio of <150 and vasopressors, dialysis or extracorporeal membrane oxygenation, 10=dead. PCR: polymerase chain reaction; WP: work package.



Ethics Approval and Consent to Participate

The study will be conducted according to the principles of the Declaration of Helsinki (64th World Medical Association General Assembly, Fortaleza, Brazil, October 2013) and in accordance with Erasmus MC Research code, Netherlands Code of Conduct for Research Integrity, General Data Protection Regulation, Code of Conduct for Health Research (not subjected to the Medical Research Involving Human Subjects Act [non-WMO]), Code of Conduct for Responsible Use of Human Tissue (Non-WMO), and Medical Treatment Contracts Act. The study was approved by the Medical Research Ethics Committee from Erasmus University Medical Center (MEC-2022-0297) and the local review boards of all other participating centers. Regarding informed consent procedure: within the Erasmus MC, a consent waiver was provided by the Medical Research Ethics Committee for research including patients with COVID-19 due to the pandemic (exception due to emergency situation). Therefore, an opt-out informed consent procedure will be used in the participating centers, and subjects with registered objections to participate will be excluded from the study. This opt-out registration method was approved by the Medical Research Ethics Committee from Erasmus University Medical Center (MEC-2022-0297). Each center is responsible for appropriate informed consent procedures, which are covered in the data transfer agreements. Regarding the biobank data, only biobank material collected within the Collaboration on Identification, Understanding and Improved Management of patients with infectious diseases study of the Erasmus MC (METC number primary application: 2017-0417 and amendment 2020-0222) and samples collected at the Amsterdam UMC within the MERMAIDS-ARI (NL54834.018.15), VIS cohort study (NL73759.018.20), and the Amsterdam UMC COVID-19 biobank will be used.

Data Collection

In WP1, variation in corticosteroid treatment protocols on the ward between centers is evaluated via questionnaires and extraction of data from the electronic patient record. The focus lies on collecting data from centers that use high-dose corticosteroids on the ward directly after admission and subsequently collecting data from centers with low-dose regimens as a comparison. For the data collection of ICU patients (WP2-3), a collaboration with 2 large COVID-19 study groups is started: the Practice of Ventilation in COVID-19 study (ie, PROVENT-COVID) study and the “Practice of Adjunctive Treatments in Intensive Care Unit Patients with Coronavirus Disease 2019” (PROACT-COVID) study [20,21]. The data of

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interest will be collected in Castor EDC [22], and it will be imported from each center via a secured data transfer system. Corticosteroid data will be collected on a daily basis including type, dose, and administration route. Regarding biobank WP4, a number of serum biomarker levels were already determined during standard COVID-19 care. In case of missing measurements, the stored samples (Tempus tubes) in the biobank can be used. The BALF was collected during routine COVID-19 care in the Amsterdam University Medical Centers and saved in aliquots at −80 °C for further analysis. SARS-CoV-2 viral load will be measured in BALF by using an in-house reverse transcription polymerase chain reaction. Subsequently, other commercially and generally available biomarkers might be determined in serum and BALF later by using a multiplex assay, such as Luminex. For the whole genome transcriptomes analysis, material was collected and saved in blood RNA Tempus tubes.

Interventions

Patients were administered with >6 mg dexamethasone or an equivalent corticosteroid for a minimum of 3 consecutive days (Table 1). Our study permits the use of other general concurrent interventions, such as venous thromboembolism prophylaxis, fever and glucose control, fluid management, antibiotics, and antiviral drugs. The use of other immunomodulatory agents such as baricitinib, JAK inhibitors, and interleukin 6 pathway inhibitors, as well as antiviral drugs such as remdesivir, is allowed as part of a clinical trial or hospital policy. However, a sensitivity analysis will be performed excluding these patients.

Outcomes

Primary Outcomes

Several outcome parameters will be studied for the different work packages based on the available data. In WP1A, the primary outcome of interest is hospital mortality in patients who do not receive high-flow nasal canule or invasive mechanical ventilation due to restrictions in care, either on medical grounds or advance directives of the patient. In patients who do not have restrictions in care, the need for high-flow nasal canule or invasive mechanical ventilation will be the primary outcome of interest (WHO severity 6-9). In WP1B, WP2, and WP3, 28-day survival and 28-day need for invasive mechanical ventilation will be studied as primary outcomes. In WP4, we will study the response to corticosteroids using the same outcomes.

Secondary Outcomes

Secondary outcomes for the ICU work packages include ICU mortality; in-hospital mortality; hospital length of stay (the number of days from the date of ICU admission to date of ICU discharge or death); mechanical ventilation duration (total duration of mechanical ventilation in days); and ventilator-free days, and alive at day 28. In all 4 work packages, we will evaluate the incidence of general systemic complications during the hospital stay as a secondary outcome, including myocardial infarction, deep venous thrombosis, pulmonary embolus, hyperglycemia, acute kidney injury, and sepsis. The definition of the various general systemic complications is shown in Table S1 in Multimedia Appendix 1.

Statistical Analysis

Data will be analyzed on a convenience sample. No sample size calculations are considered for the study nor will they be provided post hoc [23]. The use of high-dose corticosteroids will be defined as a dichotomous variable (yes or no) in primary analysis and as a continuous variable in secondary analysis.

To study between-center variation in corticosteroid dosing strategy, the proportion of individuals who received high-dose corticosteroids will be compared across hospitals. Determinants of receiving high-dose corticosteroids will be evaluated using a multivariable logistic regression model with study center forced in the model. Whether the effects of significant determinants are different across centers will be tested through a determinant × center interaction term added for each determinant, separately.

In WP1, WP2, and WP3, several statistical analysis approaches will be considered to determine the association between high-dose corticosteroids and outcome, and statistical analyses will depend on the structure of the available data. A multivariable logistic regression model will be used with high-dose corticosteroids as exposure and survival at day 28 as an outcome. Covariates used for adjustment will include age, gender, BMI, smoking status, prior administration of corticosteroids during admission, comorbidity, sequential organ failure assessment score, oxygen saturation, partial pressure of oxygen in arterial blood–fraction of inspiratory oxygen concentration ratio, C-reactive protein, procalcitonin, ferritin, interleukin 6, D-dimer, lactate dehydrogenase, platelet count, lymphopenia, and level of respiratory support. Covariates can be added or removed based on insights from the data set or from the literature. A model might be constructed in which patients are matched on a propensity score based on their probability to receive high-dose corticosteroid treatment. Propensity scores will be determined using a logistic regression model with high-dose corticosteroids as a dependent variable and determinants of high-dose corticosteroids as independent variables. After matching, survival and mortality at day 28 and other outcome parameters will be compared between matched groups using logistic regression. A Cox proportional hazards model might be performed to determine the effect of high-dose corticosteroids on time to death while taking into account the days of administration using time-dependent covariates. Other approaches involving censoring weights for differential loss to follow-up (eg, marginal structural models) or competing risks (eg, joint models) might be explored.

Furthermore, we will use clinical and biological data to perform latent class analysis to search for subphenotypes, which respond more favorably to corticosteroid treatment. This heterogeneity of treatment effect will be evaluated by including the latent class analysis-derived subphenotype, corticosteroid exposure, and an interaction term of the 2 as c-variate in the above-described survival models. Heterogeneity of treatment effect is considered to be present if the interaction term has a *P* value of <.05.

Regarding WP4, patients are randomly selected and cases will be patients treated with high-dose corticosteroids, whereas controls will be patients who were not treated with high-dose

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corticosteroids. In WP4a, inverse probability treatment weighting and inverse probability of censoring weights will be used together in a marginal structural model. After we have analyzed the effect of high-dose corticosteroids on mortality and the other outcome measures, we will use this model to determine if the listed biomarkers modify the effect of high-dose corticosteroids on mortality.

In WP4b, we will identify transcriptome features that are differentially altered between cases and controls. Mean transcriptome levels will be compared using an unpaired *t*-test and *P* values will be adjusted for false-discovery rate using the Benjamini-Hochberg procedure. The $\log_2$ mean fold change of levels between cases and controls will also be calculated for each transcriptome. We will define transcriptome features as those with an adjusted *P* value of <.05 and a >2.0 or <–2.0 $\log_2$ mean fold change in level.

Results

The study was funded in December 2021. As of April 2023, data have been collected for a total of 1500 patients, with data collection anticipated to be completed by December 2023. We expect the first results to be available in early 2024.

Discussion

The SELECT study is a retrospective multicenter observational cohort study that aims to determine the most optimal dosing and timing of high-dose corticosteroid therapy in hospitalized patients with COVID-19 and to provide a basis for personalized treatment regimens using biomarkers and whole transcriptome analyses. Increasing insight in the pathophysiological pathways that underlie SARS-CoV-2 infection and the efficacy of high-dose corticosteroid therapy could lead to more precise targeting of high-dose corticosteroid therapy, and as a result, could improve patient outcomes.

The necessity of exploring this matter is underlined by the fact that there is currently no consensus regarding the administration of high-dose corticosteroid therapy in patients with COVID-19.

This study design has several strengths. First, no studies have been performed that evaluate the effect of high-dose corticosteroids throughout the entire clinical course of hospitalized patients with COVID-19. Our study will evaluate the effect of high-dose corticosteroids from hospital admission to the ward or ICU, until hospital discharge. Furthermore, our exploration of biomarker and gene expression profiles for targeted corticosteroid therapy represents a first step toward personalized corticosteroid therapy in COVID-19. By using existing research databases and biobanks, successful data collection is assured, and we will be able to include a large number of patients, which increases the generalizability of the results.

Due to the retrospective study design, some methodological considerations require further discussion. A major issue for any observational study is the fact that treatment modalities are not randomly assigned, but rather likely given based on specific patient characteristics or within-center protocols. This nonrandomized assignment is prone to bias by indication. To correct this bias, our initial analysis step will be the identification of factors that contribute to the allocation of corticosteroid treatment. Subsequently, we will examine several statistical approaches, such as the use of propensity scores at the patient level to minimize treatment indication bias.

The findings of this study could support COVID-19 guidelines and hospital protocols regarding the management of hospitalized patients with COVID-19. Thus far, the translation of predictive biomarkers and whole transcriptome analysis into an applicable bedside tool is highly challenging. We expect to provide valuable tools to guide the dosing and timing of high-dose corticosteroid therapy. Furthermore, the answers to our research questions might be extrapolated to patients with non–COVID-19 ARDS, as the use of high-dose corticosteroids is still a matter of debate in this group of patients. The mortality rate of non–COVID-19 ARDS is even higher than that of COVID-19 ARDS [24], emphasizing the need for improved treatment strategies. Nonetheless, more efforts are required to determine similarities and differences between patients with COVID-19 ARDS and those with non–COVID-19 ARDS to determine whether extrapolation from one group to the other is possible.

In conclusion, our study protocol presents a strategy to gain a better understanding of the optimal dosing and timing of high-dose corticosteroid therapy in hospitalized patients with COVID-19 and thereby improve patient outcomes.

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Elting; AA Esmeijer; M Gama de Abreu; AR Girbes; MJ de Graaff; DM Go; RL Goossen; HJ Hansen; JJ Haringman; L Hol; MW Hollmann; PL van der Heiden; J Horn; LE van Ingen; NP Juffermans; MA Kuiper; LJ Kuipers; E Koornstra; A Lokhorst; SG Nijbroek; I Martin–Loeches; G Mazzinari; S Myatra; F Paulus; M Offermans; T Pisters; A Prins; P van Oosten; J Pillay; IM Purmer; AS Rezaee; TCD Rettig; O Roca; NM Rosenberg; N Schavemaker; AA Sciascera; MJ Schultz; A Serpa Neto; G Shrestha; ME Sleeswijk; W Stilma; AC Strang; PE Spronk; PR Tuinman; AM Tsonas; CMA Valk; M Verboom; AP Vlaar; FL van der Ven; WH van der Ven; P van Velzen; EJ Verhoef; TD Vermeulen; P van Vliet; JJ Voorham; PH van der Voort; M van der Woude; Weiner; N Yaali; JM Zandvliet; AR van Zanten; TZ van Zijl; and SA Zonneveld. The SELECT study received an unrestricted research grant from ZonMw (grant number 0430102110010). The funders of this study did not play any role in the design of the study, nor in the writing of this manuscript or the decision to publish.

Data Availability

The data sets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Authors' Contributions

HE, JS, LDJB, and AB designed the study and arranged funding. AB outlined the statistical analysis. KD, JAH, and VASHD drafted the manuscript. All authors critically revised and approved this final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Definition of general systemic complications.
[XLSX File (Microsoft Excel File), 12 KB - resprot_v12i1e48183_app1.xlsx]

Multimedia Appendix 2
Peer-review report by the COVID-19 Program - The Netherlands Organisation for Health Research and Development / ZorgOnderzoek Nederland (ZON) and the area Medical Sciences (MW) (ZonMw, Netherlands).
[PDF File (Adobe PDF File), 1304 KB - resprot_v12i1e48183_app2.pdf]

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Abbreviations

ARDS: acute respiratory distress syndrome
BALF: bronchoalveolar lavage fluid
ICU: intensive care unit
SELECT: Steroids in Hospitalized Patients with COVID-19 in The Netherlands
UMC: University Medical Center
WP: work package

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Protocol

Capturing and Documenting the Wider Health Impacts of the COVID-19 Pandemic Through the Remember Rebuild Saskatchewan Initiative: Protocol for a Mixed Methods Interdisciplinary Project

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Abstract

Background: In the Canadian province of Saskatchewan, the global COVID-19 pandemic appeared amidst existing social health challenges in food insecurity, housing precarity and homelessness, poor mental health, and substance misuse. These chronic features intersected with the pandemic, producing a moment in time when the urgency of COVID-19 brought attention to underlying shortcomings in public health services.

Objective: The objectives of the program of research are (1) to identify and measure relationships between the pandemic and wider health and social impacts, namely, food insecurity, housing precarity and homelessness, and mental health and substance use in Saskatchewan, and (2) to create an oral history of the pandemic in Saskatchewan in an accessible digital public archive.

Methods: We are using a mixed methods approach to identify the impacts of the pandemic on specific equity-seeking groups and areas of social health concern by developing cross-sectional population-based surveys and producing results based on statistical analysis. We augmented the quantitative analysis by conducting qualitative interviews and oral histories to generate more granular details of people's experiences of the pandemic. We are focusing on frontline workers, other service providers, and individuals within equity-seeking groups. We are capturing digital evidence and social media posts; we are collecting and organizing key threads using a free open-source research tool, Zotero, to trace the digital evidence of the pandemic in Saskatchewan. This study is approved by the Research Ethics Board at the University of Saskatchewan (Beh-1945).

Results: Funding for this program of research was received in March and April 2022. Survey data were collected between July and November 2022. The collection of oral histories began in June 2022 and concluded in March 2023. In total, 30 oral histories have been collected at the time of this writing. Qualitative interviews began in April 2022 and will continue until March 2024. Survey analysis began in January 2023, and results are expected to be published in mid-2023. All data and stories collected in this work are archived for preservation and freely accessible on the Remember Rebuild Saskatchewan project's website. We will

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share results in academic journals and conferences, town halls and community gatherings, social and digital media reports, and through collaborative exhibitions with public library systems.

Conclusions: The pandemic's ephemeral nature poses a risk of us "forgetting" this moment and the attendant social inequities. These challenges inspired a novel fusion among health researchers, historians, librarians, and service providers in the creation of the Remember Rebuild Saskatchewan project, which focuses on preserving the legacy of the pandemic and capturing data to support an equitable recovery in Saskatchewan.

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KEYWORDS

COVID-19; Saskatchewan, Canada; mixed methods; interdisciplinary; mental health and substance use; food insecurity; housing precarity; archive

Introduction

Background

On March 11, 2020, the World Health Organization declared a global pandemic caused by a new virus, SARS-CoV-2. Due to the uncertainties about the virulence of COVID-19, the disease caused by SARS-CoV-2, and the need to mitigate the expected demand on the health care system, the federal and provincial governments of Canada imposed strict public health restrictions that limited population movement. These new policies helped to slow the spread of COVID-19, but they also had significant social consequences, such as the pivot to remote work and learning and the closure of many small businesses.

In Saskatchewan, a province in central Canada with a population of just under 1.2 million people, the provincial government introduced public health measures with the intention of dampening the initial wave of the pandemic. The transmission of the virus in Saskatchewan was slow during the first 6 months of the pandemic, and the province reported far fewer cases and deaths due to COVID-19 (58.75 and 0.85 per 100,000) than the Canadian average (180.42 cases and 15 per 100,000 deaths) in that time [1]. Like other regions in Canada, Saskatchewan experienced an economic downturn during the first 6 months of the pandemic, losing 5% of its gross domestic product and recording a 5% increase in unemployment [2].

COVID-19 in Saskatchewan

By 2021, COVID-19 cases and deaths in Saskatchewan were trending upward, surpassing the Canadian average in January and remaining above the national rates throughout 2022 [1]. In November 2022, Saskatchewan reported the third-highest death rate among Canadian provinces, with 142 deaths per 100,000, exceeding the national average of 123 deaths per 100,000. Despite high rates of transmission and deaths per capita, the Government of Saskatchewan progressively eliminated public health restrictions, arguing that these protocols hindered economic growth and personal freedom [3]. Subsequently, Saskatchewan became one of the first Canadian provinces to relax all pandemic-related restrictions, first doing so in July 2021 and then again comprehensively easing restrictions during the Omicron wave in February 2022 [3,4].

The 2022 policy reversals coincided with a reduction in pandemic-related data collection and reporting, resulting in limited access to publicly available data and the capacity for the public to understand and interpret the ongoing effects of the pandemic [5]. Beyond prioritizing economic issues over public health, the decision to stop sharing COVID-19 data publicly made the province of Saskatchewan stand apart from other provinces and territories. This, in part, made it an ideal case study for further examination. This shift in priorities during the pandemic also exacerbated preexisting public health needs, namely food insecurity, housing precarity and homelessness, mental health, and substance use.

Since March 2020, the urban centers of Regina and Saskatoon have experienced an increased surge in social service usage [6-8], homelessness, and housing precarity [9-11]. Saskatchewan residents also reported higher rates of food insecurity [12], mental distress, and illness [13-16], and the province experienced a drastic increase in substance use-related deaths [17]. Moreover, the government's decision to stop releasing health data in 2022 led to only a partial understanding of how COVID-19 influenced wider health trends across Saskatchewan.

Remember Rebuild Saskatchewan: A COVID-19 Project

This protocol paper presents our innovative mixed method protocol for a program of research entitled "Remember Rebuild Saskatchewan." This, in turn, consists of 2 constituent federally funded projects: "Build Back Better: Data and equity needed to drive postpandemic recovery in Saskatchewan," funded by Canadian Institutes of Health Research (operating grant 478277), and "Saskatchewan's COVID-19 public archive," funded by Social Sciences and Humanities Research Council of Canada Partnership Development (grant 356339). The objective of the program of research is to identify and measure relationships between the pandemic and wider health and social impacts, namely, food insecurity, housing precarity and homelessness, and mental health and substance use in Saskatchewan. We also aim to identify how the pandemic affected service providers and service users across the province as they navigated (or attempted to navigate) the COVID-19 pandemic. The overall goal is to preserve data and stories in a digital archive and use them, alongside social media and web archives, to create a social history of the COVID-19 response in Saskatchewan, Canada. The findings from this multidisciplinary and community-focused research model will be used to develop policy, programming,

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and practice recommendations for policy makers and community-based human service agencies.

Methods

Study Setting and Design

This program of study is set in the province of Saskatchewan, Canada. Our interdisciplinary team blends the expertise of many disciplinary experts, for example, epidemiologists, population health researchers, digital humanists, and medical historians, with the expertise and lived experience of community-based partners to create knowledge and build and share a record of the implications of COVID-19 for the province of Saskatchewan. We use a mixed methods study design, including quantitative survey data collection, qualitative engagements with service providers and individuals from equity-seeking groups through interviews and oral histories, as well as social and digital media record collection and analyses. Our interdisciplinary and mixed methods approach allows us to use diverse and complementary techniques for data collection and analysis and to illuminate the impacts of the pandemic in a multifaceted and evidence-informed manner.

Patient and Public Involvement

The Remember Rebuild Saskatchewan project is heavily community-involved. Because of the limited pandemic-related data in Saskatchewan, we use a bottom-up approach to highlight the impacts and trends of the pandemic and to compare community experiences against a broader provincial population survey. We have partnered with community-based organizations working in food insecurity, housing precarity and homelessness, mental health, and substance use; a task force formed to harmonize a community response to the pandemic; and public sector unions representing nurses and teachers. Community-based organizations and union leaders joined each project as research partners during the initial project conceptualization and aided in the study design through consultation on the development of the public archive and during the Build Back Better survey development. Community partners have shared their stories for the archive, which aids us in the recruitment of frontline staff and people who access services to participate in oral histories and qualitative interviews. Citizens have shared their stories with us, for instance, about those they lost to COVID. We engage community partners quarterly with formal project updates and further consult as needed as the projects progress. Furthermore, partners will be engaged in community events focused on collaborative analysis and knowledge mobilization.

Project: Build Back Better

Overview

Our health research teams are collecting both quantitative and qualitative data to assess the impacts of the pandemic on 4 interrelated areas: food insecurity, housing precarity and homelessness, mental health, and substance use. Given Saskatchewan's huge geographical landscape and the importance of rural and northern communities in addition to its 2 major cities, Saskatoon and Regina, and several midsized urban centers, the team also relies on stratified regional analysis to ensure the relevance of the multiple interacting components of this work across the province. The survey also enables an analysis of how access to services has differed for equity-seeking groups across the province. For our study, we define equity-seeking groups as women; Indigenous populations; youth and older adults; 2-spirited, lesbian, gay, bisexual, transgender, and queer/questioning (2SLGBTQ+) persons; immigrants and refugees; those living in remote and rural or underserved areas; and those living with mental health or disabilities. Our mixed methods approach enables the project to connect survey results with qualitative research analyzing the impacts of the pandemic on service provision by affected frontline workers and health, human, and social service organizations.

Quantitative Methods

Overview

Quantitative data were collected through a population-based cross-sectional web-based survey administered between July and November 2022 (Multimedia Appendix 1). The survey inclusion criteria for the study were the following: (1) a minimum age of 18 years, (2) residing in Saskatchewan, and (3) English language proficiency. We selected the study population for the survey through random probability sampling from the following panels of target populations: the Saskatchewan Community Panel from the Canadian Hub for Applied and Social Research, the Probit Panel from EKOS Research Associates, Inc, and a convenience sample from Voxco's omnichannel cloud. Quotas were implemented to closely approximate the sample to the Saskatchewan population with respect to gender, age, and geographical location; however, postsurvey weights were also calculated and applied to ensure our study sample aligns with provincial demographics.

The survey data address the following research questions: (1) what is the prevalence of adverse mental health status, substance use, home evictions and housing precarity, and food insecurity in Saskatchewan? How has the prevalence of these challenges changed during the pandemic and compared to that before the pandemic? (2) Has the pandemic differentially affected people in equity-seeking groups (Indigenous groups, visible minority or newcomers, 2SLGBTQ+, people with disabilities, etc) and for those with the greatest social and economic needs (unemployed or underemployed and low-income)?

The web-based survey began with general information about the study, resources for support, and an informed consent form for participation. After providing consent, participants were directed to complete the web-based questionnaire. Participants, on average, took 20 minutes to complete the survey. Upon completion, participants were given the option to enter a draw to win one of fifteen grocery store gift cards valued at CAD $100 (US $73.48) each. The survey included 6 sections: demographics, impacts of the pandemic, food insecurity, housing precarity, mental health, and substance use. Measures included in the survey were taken from or adapted from other validated and reliable instruments to ensure consistency and validity of findings, or they were self-drafted collaboratively by the interdisciplinary team.

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Demographics

Our survey asked demographic questions to ascertain participants' age, gender and sexual identity, ethnicity, location, immigrant status, disability, and household composition. We asked respondents about their highest levels of education attained. We also queried whether they are engaged in full-time or part-time employment, unemployed, looking for work or not, stay-at-home parenting, retired, studying, unable to work due to disability, and others. If participants indicated employment, they were asked to specify their area of work for their primary job, which included 22 job areas. We also asked whether participants worked in a frontline position to assess the impacts specific to frontline workers during the pandemic.

Impacts of the COVID-19 Pandemic

We measured the impact of the pandemic on participants' health and well-being (both personal and socioeconomic). First, we assessed the current state of health through self-rated physical and mental health questions, positive COVID-19 tests, the severity and duration of COVID-19 symptoms, and the receipt of COVID-19 vaccines and boosters. Participants' personal well-being was assessed through self-rated questions on the quality of life and ability to perform day-to-day activities. We also assessed the pandemic's impact on households' socioeconomic well-being through 6 indicators drafted by the research team, including changes to individual and household employment, income, household finances, and access to financial or community support. In addition, we measured individual and household coping strategies to mitigate economic challenges through 5 indicators adapted from the Canadian Housing Survey [18].

Food Insecurity

We assessed household food insecurity through the Household Food Security Survey Module derived from the Canadian Community Health Survey [19]. Originally developed by the United States Department of Agriculture, the Household Food Security Survey Module is an 18-item standardized and validated module to be used in Canada, consisting of an adult scale (10 items) and a child scale (8 items). These 18 items capture households' experiences of food insecurity over the 12 months preceding the survey, including the quantity, quality, and affordability of food items. Two other questions were developed to assess the quality of the diet and the accessibility of healthy food during the pandemic.

Housing Precarity

Housing precarity was primarily measured by adapting 5 indicators from the Canadian Housing Survey and 8 indicators from the University of California survey of students' basic needs [18,20]. We asked respondents to select any challenges they experienced managing housing finances (rent and mortgage payments) and whether they were due to the pandemic. The survey also captured respondents' precarious housing or homelessness experiences by asking about knowing where to sleep, unsafe sleeping arrangements, and shared accommodations such as CouchSurfing or shelter stays. These indicators also included financial challenges to meet housing needs, such as the inability to pay for housing or utilities, taking on debts to pay for housing costs, or cutting back on other expenses to cover housing costs. If an affirmative response was received to any of these questions, a follow-up question was presented to find out if these challenges were partly or entirely due to financial challenges arising from the pandemic. Our survey also included 7 new questions on moving or finding new housing, reasons for moving, including eviction, and if housing challenges arose from the pandemic.

Mental Health

We measured participants' anxiety, depression, stress, and health-seeking behavior for each mental health condition. Anxiety was assessed using the Generalized Anxiety Disorder 7 diagnostic scale, and depression was assessed using the Patient Health Questionnaire 9 scale [21,22]. In addition, we adapted questions from the Mental Health Commission of Canada and the Canadian Centre of Substance Use and Addiction Leger Questionnaire to assess pandemic-driven stressors (18 questions), ability to handle stressful situations (2 questions), and overall mental health (1 question) [21]. Finally, drawing on questions from the Mental Health Commission of Canada, the Canadian Centre of Substance Use and Addiction Leger Questionnaire, and the Mental Health Research Canada's Mental Health and COVID Tracker poll, we assessed participants' health-seeking behavior through their access to and attitudes about opting for treatments or supports for mental health concerns [21,22]. Questions included whether participants sought treatment from a trained professional, the ease (or difficulty) of accessing these services and reasons for not accessing them, mental health diagnoses from a medical or psychological professional, and the time of receiving a diagnosis. We also included 2 self-drafted questions about participants' feelings about needing help with mental health and for what purpose they sought help or treatment.

Substance Use

We measured participants' substance use in 5 categories: alcohol, tobacco or nicotine, cannabis, prescription medication (opioids, sedatives [benzodiazepines and non-benzodiazepines] and barbiturates, stimulants, and cannabis), and other drug or substance use; self-rated impacts of the pandemic on use of each substance; and substance use concerns, treatments, and supports. We assessed participants' use of each substance using indicators either taken or modified from the Mental Health Commission of Canada and the Canadian Centre on Substance Use and Addiction Leger Questionnaire [21], the Canadian Alcohol and Drugs Survey [23], and the Canadian Nicotine and Tobacco Survey [24] or were self-drafted. We asked about frequency, quantity, and preferences or modes of use for each substance category, where applicable, and these indicators were primarily taken or adapted from the above instruments. We measured the self-rated impacts of the pandemic on substance use through self-drafted questions. We modified an indicator from the Mental Health Commission of Canada and the Canadian Centre on Substance Use and Addiction Leger Questionnaire to measure self-rated concern of use for each substance. If participants indicated some level of concern for one or more of the five substance categories, we asked about seeking treatment or support services from a trained professional, the ease (or

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difficulty) of accessing these services, reasons for not accessing services, substance use disorder diagnoses from a medical or psychological professional, and when a diagnosis was received.

Following the closing of the survey, we checked and cleaned the data for outliers to identify if it was skewed in a certain direction. We checked variables with a significant proportion of missing values to see if there was any systematic pattern in the missing data. We conducted a multiple imputation analysis and imputed data for the following variables: location of the residence (5.4%), sex (1.6%), age (3.2%), ethnicity (2.4%), education (3.0%), employment status (1.8%), income (7.1%), and housing insecurity (13.7%).

The final data set, deidentified and cleaned, was shared with the core research team members. Preliminary analyses have been conducted to identify the impact of the pandemic on the overall study population. We presented the findings as frequencies and percentages for categorical variables with associated confidence intervals and means and standard deviations for continuous variables. In addition, we use graphs and maps to present our findings to community partners for ease of understanding key results. Next, we will perform multivariable linear and logistic regression analyses to investigate the risk factors that have intensified households' experiences of food insecurity, housing precarity and homelessness, mental health, and substance use.

Qualitative Methods

The surveys help to provide important quantitative indicators of a broader range of impacts of the pandemic on other public health services, but we also recognize the need to connect the numbers with the stories of how people have experienced this historical moment. We are collecting qualitative data to answer the following research questions: (1) what role have frontline human services agencies played in helping people deal with the challenges of the pandemic? What barriers have hindered access to services? What makes services effective? (2) What do people who access services and service providers believe the priorities for policy and practice implementation should be in the 4 interrelated study areas?

We are collecting data through open-ended interviews with two categories of respondents: (1) service providers from partner agencies (Multimedia Appendix 2) and (2) people who access services within partner agencies (Multimedia Appendix 3). For service providers, we will interview 5 service providers working in agencies in the 4 focus areas (n=20). For people who access services, we will interview 8-10 people per focus area (n=24-32). Interviews last between 30 and 60 minutes, and we provide an honorarium of CAD $25 (US $18.37) to people who access services at participating agencies to compensate for their time and contribution to the project. Service providers will not receive an honorarium as their interviews will be related to their employment at partner agencies, and thus they will be compensated for their time through their workplaces. After the initial interviews, we will consult partner organizations to expand participant recruitment in Regina, midsized urban centers, and rural regions in the province.

Interviews take place in locations that are best suited to individual participants in one of 3 options: in-person at partner or host organizations from which they were recruited; remotely over Zoom, where participants decide where is most advantageous; or remotely over Zoom at partner or host organizations from which they were recruited. Not all people who access services have access to technology for virtual interviews, and some are not comfortable doing interviews in person; thus, we work with host organizations to facilitate an ideal setting for each participant. To further ensure the safety of participants, interviewers completed Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans certification and will complete trauma-informed care training prior to recruiting people who access services.

The analysis of qualitative interview data will begin with the first interview and continue throughout the data collection period. Both inductive and deductive methods of data coding will be used. Reflection on the quantitative data and engagement with the community partners will help us identify the initial coding framework. We will use thematic analysis to identify initial codes in the first rounds of data analysis across the 4 focus areas and begin conceptualizing broad themes [25]. Subsequent iterative rounds of analysis will sharpen our coding into more specific themes. We will also be analyzing for saturation and adapting and updating codes to ensure extracted data reflect participants' contributions as interviews progress. Moreover, we will consult community partners throughout the process. For the data retrieved from people who access services, we will extract common themes across the 4 focus areas as well as stratified thematic analysis for themes specific to equity-seeking groups and other characteristics as the research team identifies emerging themes. For service providers, we will extract themes across the 4 focus areas as well as a broader thematic analysis illuminating common experiences faced by those working in human services during the pandemic.

We use both quantitative and qualitative data to gain a broad understanding of the impact of the COVID-19 pandemic on people's lives and well-being in Saskatchewan. The quantitative data help us identify specific groups of people and areas of concern that are generalizable to the province and comparable with national data sources, and the qualitative data helps to provide a more granular level of detail about impacts on individuals. The qualitative approach allows us to emphasize the intersectionality of the pandemic and other public health needs that are not necessarily readily parsed into categories when it comes to how they were experienced in real time. By allowing participants to describe their encounters in their own words, we seek to enrich our understanding of qualities that include elements of pacing or timing of decisions, to better understand how providers and clients made decisions that prioritized health and economic needs in real time, and how they reflect on the impact of the pandemic and government policies on meeting their basic needs. In combining quantitative and qualitative approaches, we enhance our understanding of the wider impacts of the pandemic, generating a wide range of evidence that is crucial for policymaking in postpandemic recovery.

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Project: Saskatchewan's COVID-19 Public Archive

Historians on the team are collecting and analyzing a large archive of academic, oral history, and social and digital media sources to develop a unique digital community archive. The project began as a response to the concern that COVID-19 risked being another forgotten pandemic because of the ephemeral nature of web-based primary sources. We have expanded the project to incorporate new digital methods to increase the capacity to collect digital materials and lay the foundation for writing a social history of the COVID-19 pandemic in Saskatchewan [26]. We began in March 2020 by setting up an Archive-It repository to automatically record a web archive of government, organizations, and media reports related to the COVID-19 pandemic in Saskatchewan. We took inspiration from other jurisdictions engaged in COVID-19 archiving and drew from examples of archives established to capture "disaster responses" that include public memorialization to remember events like Hurricane Katrina in the United States and the 9-11 attacks [27]. Remembering—including analyzing and learning from—COVID-19 requires new theoretical and methodological approaches that capture and preserve the experience for future generations.

We began collecting oral histories in 2020, interviewing local business owners, reporters, and a prominent retired doctor. The new funding and formal partnerships with community organizations allowed us to expand the interviews in the summer of 2022 as we collected perspectives from vaccine scientists, intensive care unit doctors and nurses, frontline workers, employees at a safe consumption site and food banks, justice-involved individuals, and other marginalized racial and ethnic groups of residents. Interviews are conducted using an open-ended interview guide. We plan to expand the scope of these interviews, both by supporting the qualitative research interviews led by the Build Back Better team with at-risk populations and by continuing to seek out oral history interviews with as wide a range of people as possible with unique experiences during the pandemic.

Exploring the Archive-It collection in partnership with the Archives Unleashed project [28], we quickly recognized that we had captured the important institutional experiences via their websites in the province but missed a lot of the social media discussion. We are working to archive large sections of Twitter and Facebook to preserve this public debate. Twitter's application programming interface provides free access to academics, allowing us to record millions of tweets related to the pandemic starting in 2020. We collected every post made by the premier of Saskatchewan during the pandemic, along with all the replies to his tweets, the conversations using the #COVID19SK hashtag, and conversations involving numerous other COVID-19 influencers in the province. Facebook does not provide an application programming interface and actively blocks web crawling software. As a result, it requires manual scrolling of content on the platform. We, therefore, restricted our archiving efforts to focus on the public Facebook page and public posts from a small number of influential accounts commenting on the public health measures. One of these accounts has since been removed from the platform, reminding us again of the ephemeral nature of this material.

Finally, while the Archive-It collection holds thousands of web pages from news outlets, they are not cataloged and are difficult to navigate. To create a more user-friendly repository, we are using citation database software Zotero (Corporation for Digital Scholarship, George Mason University) to catalog stories on the pandemic in Saskatchewan. The collection includes 3200 stories and hundreds of documents generated by community-based organizations responding to community needs during the pandemic. Research assistants work on assigned topics, including homelessness, substance use, nursing, or the start of the COVID-19 pandemic in Saskatchewan. Our research assistants clean the metadata and add keyword tags, including the people mentioned in the news stories, the places discussed, and the main topics and periods of the pandemic, such as "Fourth Wave." The tag categories are carefully managed and edited to avoid using synonyms or the proliferation of tags to the point they become useless. The Zotero database, which includes the HTML code from the original stories, provides another means to preserve web-based content and creates opportunities for text-mining approaches that will help us navigate the much larger Archive-It collection.

Ethics Approval

This study is approved by the Research Ethics Board at the University of Saskatchewan (Beh-1945) and is being conducted in accordance with the guidelines and stipulations of the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans [29]. Changes to the protocol will be submitted for approval through amendment requests to the Research Ethics Board. Participation in either project is completely voluntary.

Results

The "Build Back Better" and "Saskatchewan's COVID-19 Public Archive" projects received federal funding in March and April 2022, respectively. Survey data were collected between July and November 2022 and are being analyzed with results expected to be published in the fall of 2023. Qualitative interview data were collected between March and June 2023, and 19 interviews have been completed. Qualitative data are being analyzed, with results expected to be published in winter 2024. Initial oral histories and archival data collection began in June 2022 and will conclude in the summer of 2023. Thirty oral histories have been completed. The archive will be continuously updated. On the 3-year anniversary of the first COVID-19 case in the province, we released a new feature on the website: a digital memorial to the lives lost to COVID-19 called "Remember Lives Not Numbers." After reviewing publicly accessible obituaries and media stories about COVID-19 deaths in the province, we created a web-based memorial featuring over 100 entries that honor the lives lost in the province due to COVID-19. This digital memorial includes a public portal, which allows for continued submissions to the site to help expand the reach of this memorial to the hundreds of cases that were not covered in the news media or explicitly mentioned in published obituaries.

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Discussion

The global COVID-19 pandemic has been a significant crisis that catalyzed both immediate and long-term changes, prompting collective responses across and within nations, the effects of which are still unfolding (in May 2023). The Remember Rebuild Saskatchewan project has a wide impetus to illuminate what we have learned—both what went wrong and what worked well in our collective responses—and to preserve this legacy for future health crises and events. Our innovative and collaborative program of research harnesses community-engaged research and showcases the strengths of different health, social sciences, and humanities disciplines, and we will produce relevant and accessible quantitative and qualitative findings.

Within "Build Back Better," we expect findings from our general population survey to illuminate disparities in outcomes in the 4 focus areas (food insecurity, housing precarity, mental health, and substance use) in Saskatchewan, where groups such as youth, newcomers, Indigenous peoples, 2SLGBTQ+ individuals, people with low income, or people living with disabilities experience higher rates of negative outcomes. In addition, we expect to elucidate the dual experiences of outcomes during the COVID-19 pandemic—namely, poor mental health and problematic substance use, housing precarity, and food insecurity—which are often experienced together, adding complexity and vulnerability to people's lives.

Our survey design limits our understanding of the depth and intensity of the disruption and negative effects caused by the pandemic, though it captures well the prevalence, scope, and factors associated with these negative effects. We expect our qualitative interview analysis to reveal the depth and intensity of the disruption and negative effects. First, service-providing organizations in Saskatchewan were greatly impacted by the pandemic through modified service provision in accordance with public health guidelines and increased service demand and usage in each of the 4 focus areas. Additionally, we expect interview analysis to reveal that people accessing services in Saskatchewan faced increased barriers to accessing services, such as less access due to shutdowns and public health restrictions, which exacerbated negative health outcomes across the 4 focus areas.

Our COVID-19 public archive is a legacy product and will host the findings from all aspects of our research and outreach, as well as maintain a voluntary submission feature. The Remember Rebuild Saskatchewan findings exist in a freely accessible web-based repository, available on the project website [30]. Creating a public archive enables us to recognize the diversity of the pandemic experience and provides the foundation for future research on the changes we need to implement to build resilience as we prepare for a future with more public health crises. Findings will be available in various formats, such as academic knowledge translation outputs from Build Back Better, the oral his or her or their-stories of various Saskatchewan residents, social and digital news media stories, and audiovisual and creative contributions such as artwork or music. The archive, inclusive of the different components of each project, will be promoted widely to the public at a community event through collaboration with the Saskatoon Public Library in early 2024 and interviews with digital and social media journalists. These events help raise awareness of the projects in addition to facilitating contributions to the archive as the collection continues. We have prepared media releases and policy briefs to further engage the public, media, and policy makers.

We will compile project findings into various academic outputs, including journal articles, research posters, technical reports, conference presentations, and infographics, which will also be stored in the archive. We will additionally host academic contributions from other pandemic-related projects from the Remember Rebuild Saskatchewan team and other research contributions on the province's COVID-19 experience beyond those from the team. In this way, the archive will also act as a research hub for the pandemic in Saskatchewan, offering a repository for data and evidence documenting the multifaceted impacts of the pandemic in Saskatchewan.

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Data Availability

Data and stories collected in this work are archived for preservation and freely accessible on the Remember Rebuild Saskatchewan website [30].

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Authors' Contributions

NM, ED, and JC conceived, designed, and drafted the research protocols and acquired funding. JD drafted the protocol manuscript. PC, SDG, and members of the Remember Rebuild Saskatchewan Team DA, SB, RE-S, IF, BF, BJ, EM, J McCutcheon, TM, MM, NN, GN, and YP-C critically reviewed the protocols and manuscript for methodological and academic content. CC-C and Remember Rebuild Saskatchewan Team members GA, KD, SK, J Macleod, LO, LU (community partners), CB, J McCutcheon, AP, DH, IR, and LS (knowledge users) contributed content expertise and community knowledge. PC, JD, SDG, and Remember Rebuild Saskatchewan Team member EM will implement the research under the supervision of NM, ED, and JC.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Build Back Better Questionnaire.
[PDF File (Adobe PDF File), 1295 KB - resprot_v12i1e46643_app1.pdf]

Multimedia Appendix 2
Build Back Better--Service provider interview guide.
[PDF File (Adobe PDF File), 162 KB - resprot_v12i1e46643_app2.pdf]

Multimedia Appendix 3
Build Back Better--People accessing services interview guide.
[PDF File (Adobe PDF File), 209 KB - resprot_v12i1e46643_app3.pdf]

Multimedia Appendix 4
Peer review report (CIHR).
[PDF File (Adobe PDF File), 155 KB - resprot_v12i1e46643_app4.pdf]

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Abbreviations

2SLGBTQ+: 2-spirited, lesbian, gay, bisexual, transgender, and queer/questioning

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Protocol

Leptospirosis in Aotearoa New Zealand: Protocol for a Nationwide Case-Control Study

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Abstract

Background: In Aotearoa New Zealand, 90% of patients with notified leptospirosis (a zoonotic bacterial disease) have been men working in agricultural industries. However, since 2008, the epidemiology of notified cases has been gradually changing, that is, more women are affected; there are more cases associated with occupations traditionally not considered high risk in New Zealand; infecting serovars have changed; and many patients experience symptoms long after infection. We hypothesized that there is a shift in leptospirosis transmission patterns with substantial burden on affected patients and their families.

Objective: In this paper, we aimed to describe the protocols used to conduct a nationwide case-control study to update leptospirosis risk factors and follow-up studies to assess the burden and sources of leptospirosis in New Zealand.

Methods: This study used a mixed methods approach, comprising a case-control study and 4 substudies that involved cases only. Cases were recruited nationwide, and controls were frequency matched by sex and rurality. All participants were administered a case-control questionnaire (study 1), with cases being interviewed again at least 6 months after the initial survey (study 2). A subset of cases from two high-risk populations, that is, farmers and abattoir workers, were further engaged in a semistructured interview (study 3). Some cases with regular animal exposure had their in-contact animals (livestock for blood and urine and wildlife for kidney) and environment (soil, mud, and water) sampled (study 4). Patients from selected health clinics suspected of leptospirosis also had blood and urine samples collected (study 5). In studies 4 and 5, blood samples were tested using the microscopic agglutination test to test for antibody titers against *Leptospira* serovars Hardjo type bovis, Ballum, Tarassovi, Pomona,

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and Copenhageni. Blood, urine, and environmental samples were also tested for pathogenic *Leptospira* DNA using polymerase chain reaction.

Results: Participants were recruited between July 22, 2019, and January 31, 2022, and data collection for the study has concluded. In total, 95 cases (July 25, 2019, to April 13, 2022) and 300 controls (October 19, 2019, to January 26, 2022) were interviewed for the case-control study; 91 cases participated in the follow-up interviews (July 9, 2020, to October 25, 2022); 13 cases participated in the semistructured interviews (January 26, 2021, to January 19, 2022); and 4 cases had their in-contact animals and environments sampled (October 28, 2020, and July 29, 2021). Data analysis for study 3 has concluded and 2 manuscripts have been drafted for review. Results of the other studies are being analyzed and the specific results of each study will be published as individual manuscripts..

Conclusions: The methods used in this study may provide a basis for future epidemiological studies of infectious diseases.

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KEYWORDS

leptospirosis; Leptospira; case-control study; New Zealand; mixed methods; protocol; Indigenous health; public health; One Health

Introduction

Background

Leptospirosis is a neglected zoonotic disease that causes severe febrile illness, renal and hepatic failure, and death [1]. Globally, 1.03 million cases and 58,900 deaths occur annually [2], with a loss of 2.90 million disability-adjusted life years [3]. However, the burden is underestimated [4]. Adding to the disease burden, approximately 30% of patients have symptoms that persist for several years [5,6].

The disease is caused by bacteria of the genus *Leptospira*, which includes >71 species [7] and >300 serovars worldwide [8]. Pathogenic species of *Leptospira* colonize the kidneys of mammals, as well as birds, amphibians, and reptiles [9], and this leads to intermittent urinary shedding. High-risk populations vary spatially and temporally and include those in contact with infected animals (livestock or wildlife) or contaminated environments (water, mud, or soil) [4].

In Aotearoa New Zealand, leptospirosis is a notifiable disease, and its incidence peaked in 1971 with dairy farmers, abattoir workers, and pig farmers identified as a high-risk population [10]. At that time, cattle were the recognized maintenance hosts for serovar Hardjo type bovis and pigs for serovars Pomona and Tarassovi [10,11]. In the early 1980s, cattle vaccines against serovars Hardjo type bovis and Pomona and pig vaccines against serovars Pomona and Tarassovi were developed, and vaccination programs were implemented. Guidelines on the operation of dairy farms were developed, including minimum approved distances between livestock, pigs, and poultry [12]. Awareness campaigns resulted in the increased use of personal protective equipment (PPE) among agricultural workers. Although the guidelines, vaccinations, and PPE appeared to substantially reduce the disease risk in humans [13,14], these preventative measures are only partially effective. Leptospirosis animal vaccines offer strain-specific protection; however, current vaccines do not cover all strains, and noncommercial farmers are often not aware of industry guidelines. In addition, the use of protective equipment does not necessarily prevent infection [15].

Analysis of notification data from 1999 to 2017 showed a decline in leptospirosis cases attributed to serovars Hardjo type bovis and Pomona but an increase in cases attributed to serovars Ballum and Tarassovi [16]. From 1999 to 2017, leptospirosis notifications in abattoir workers were almost exclusively attributed to serovars Hardjo type bovis and Pomona, whereas leptospirosis notifications in dairy farmers were predominantly attributed to serovars Hardjo type bovis and Tarassovi. Occupationally acquired leptospirosis in New Zealand is covered by the Accident Compensation Act 2001. The Accident Compensation Corporation is the Crown entity responsible for enactment of the provisions set out under this Act and manages personal injury including economic, social, and personal costs [17]. However, workplace compensation for leptospirosis cases is challenging for some claimants because of reliance on serological testing and the limited range of automatically eligible occupations [18].

Notification data from 1999 to 2017 also showed that serovar Ballum cases were largely associated with occupations that were not agriculturally based [19]. Our pilot work suggests that wildlife sources [20] and environmental pathways [21] may be increasingly important in disease transmission. A longitudinal survey of wildlife on a coastal dairy farm and bordering forest conducted in autumn and spring for 2 years (from spring 2016 to autumn 2018) determined that the overall prevalence of serovar Ballum in mice, rats, and hedgehogs was 46% (95% CI 39%-52%); 44% (95% CI 26%-62%); and 27% (95% CI 11%-50%), respectively [22]. Metabarcoding of 24 enriched environmental cultures from water, soil, and mud samples taken from the same study site identified pathogenic *Leptospira* in all cultures [21].

Objectives

On the basis of the changes in serovar predominance in the at-risk occupations, as well as an increase in cases with occupations that are not agriculturally based, we hypothesize a change in the epidemiology of leptospirosis in New Zealand. This identified the need to update risk factors and sources of infection, the protocol of which is outlined in this manuscript. The overall aim of this research is to improve the evidence base

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to inform effective policies and practices to lower the incidence, health impact, and burden of leptospirosis in New Zealand. The specific aims are as follows:

1. Assess risk factors for leptospirosis in New Zealand, with a focus on activities associated with livestock, wildlife, and pets, as well as environmental and recreational exposure.
2. Assess the effect of preventative measures such as the use of PPE, animal vaccinations, and hygiene practices during high-risk activities.
3. Describe the burden of the disease including the duration, frequency, and severity of symptoms, costs incurred, and support needed by patients.
4. Explore the barriers associated with workplace compensation for occupationally acquired leptospirosis.
5. Assess the potential sources of infection from in-contact animals and environments.
6. Identify the strains of Leptospira causing disease in New Zealand.
7. Establish a cohort of patients for a long-term follow-up study.

Methods

Study Design

This manuscript describes the design and methods of the study titled, "Emerging sources and pathways for leptospirosis—a paradigm shift," an investigator-initiated project that was peer reviewed and funded by the Health Research Council of New Zealand (Multimedia Appendices 1-4).

The key study design is a nationwide frequency-matched case-control study with 4 substudies involving cases only. Studies comprise questionnaire-based investigations (studies 1 and 2), semistructured interviews with a few open questions (study 3), and laboratory-based investigations with testing in our research laboratory (studies 4 and 5):

- Study 1: Case-control survey for all participants (aim 1)
- Study 2: Follow-up survey of all cases (aims 2-4)
- Study 3: Semistructured interviews with a subset of cases who worked in agricultural industries at the time of diagnosis (aims 2-4)
- Study 4: Serological investigations of blood and molecular investigations of blood, urine and kidney samples from in-contact animals and environments of a subset of cases who had regular animal and environmental exposure at the time of diagnosis (aim 5)
- Study 5: Serological and molecular investigations of blood and urine samples from a subset of patients suspected of leptospirosis (aim 6)

Study Location and Period

This is a nationwide study in which the participant recruitment was expected to last for 18 months with the aim of recruiting 150 notified cases starting from July 22, 2019. However, the recruitment period was extended until January 31, 2022, as the New Zealand government–imposed restrictions to manage the COVID-19 pandemic [23] slowed the recruitment process. The extension of the recruitment period allowed an adequate number of cases to be recruited to have sufficient statistical power.

Cases

Case Definition

The case definition for those recruited between July 22, 2019, and October 14, 2020, was the Ministry of Health definition for a confirmed or probable case, that is, a clinically compatible illness with laboratory evidence from a diagnostic laboratory [24].

The case definition given in Textbox 1 was subsequently modified for 2 reasons that became apparent during the conduct of study 5. First, the microscopic agglutination test (MAT) requires 2 blood samples, an acute and a convalescent sample, 2 to 3 weeks apart [25], and 77% (10/13) of the patients did not return to provide the convalescent sample, despite consent to enrollment in the study. Most serological samples are prescreened with an immunoglobulin M (IgM) test and forwarded for MAT only if IgM is positive. Given the case number attrition associated with paired blood samples, case definitions were modified to include those that were IgM positive or equivocal at diagnostic laboratories. This occurred from October 15, 2020, until study completion. Second, 9 of the 10 patients suspected of leptospirosis that did not return to provide the second serology sample, tested positive by the polymerase chain reaction (PCR) analysis performed in the research laboratory. Thus, from January 28, 2021, until study completion, the case definition was further broadened to include cases who tested positive for the tests listed in Textbox 1, and the tests were performed at the research laboratory at Massey University.

Textbox 1. Laboratory evidence for confirmed or probable case as per the Ministry of Health definition.

Confirmed case

- Isolation of leptospires from a clinical specimen
- Detection of leptospiral DNA from a clinical specimen using the polymerase chain reaction
- Detection of a ≥4-fold rise in serology titers between acute and convalescent sera using the microscopic agglutination test (MAT)
- Detection of a single raised titer of ≥400 using MAT

Probable case

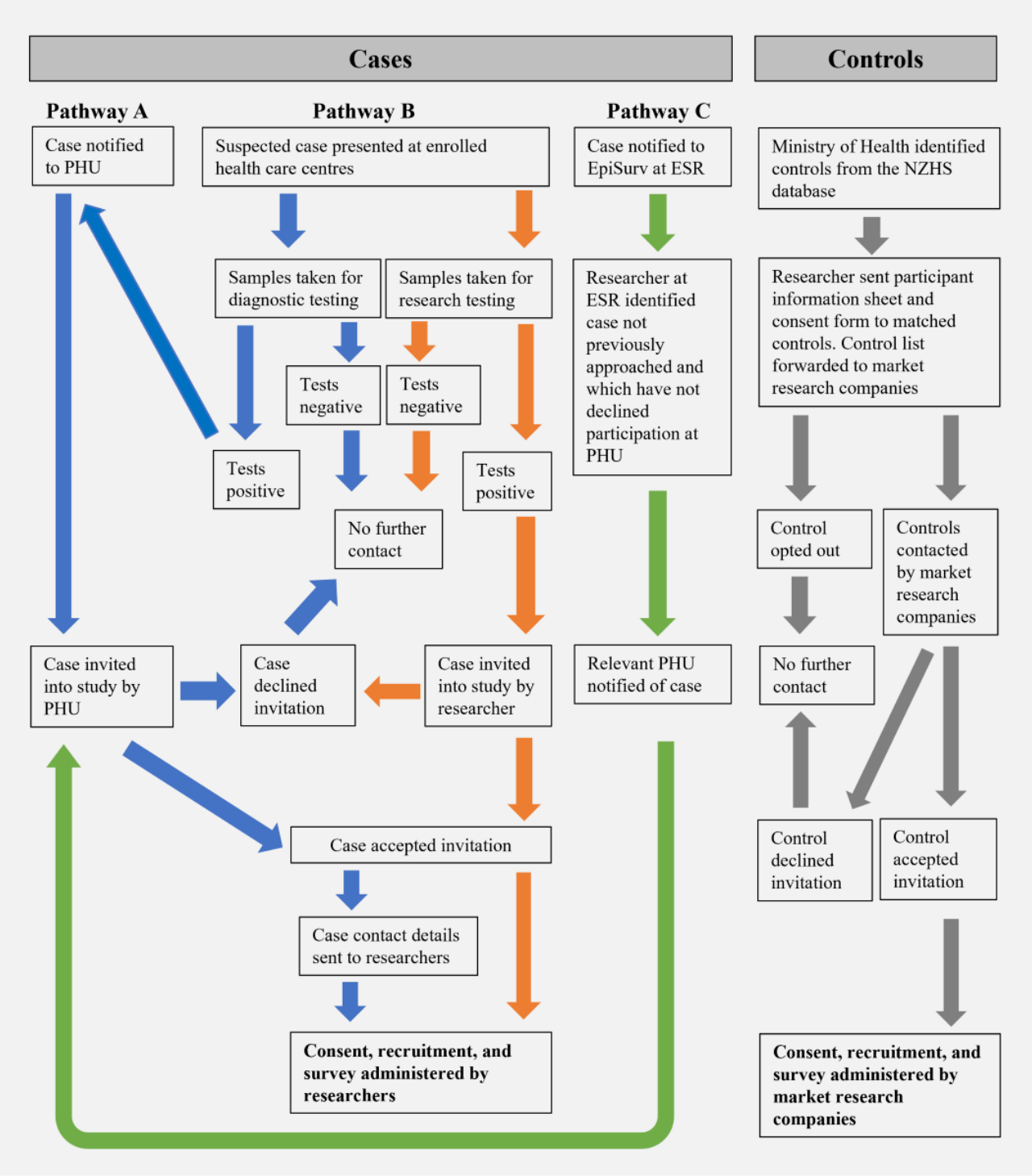
- Detection of a single raised titer of <400 using MAT

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Case Selection

Cases were identified via 3 pathways (A, B, and C) to ensure that all notified cases were given an opportunity to participate in the study (Figure 1).

Figure 1. Study flow diagram of participant selection and recruitment for a case-control study on risk factors for leptospirosis in New Zealand. ESR: Environmental Science and Research; NZHS: New Zealand Health Survey; PHU: Public Health Unit.



1. Notified leptospirosis cases were identified by 12 Public Health Units that represented 20 District Health Boards in New Zealand. Public health officers called all leptospirosis cases to capture demographic and epidemiological data as part of their routine surveillance program for notifiable diseases. This call usually occurred 2 to 4 weeks from when cases first became ill, but the exact time was dependent on the diagnostic tests requested by the attending clinician [26]. Cases who were diagnosed by MAT were called nearer to 4 weeks or later after first becoming ill, because MAT requires 2 samples 2 to 3 weeks apart. At the end of their routine surveillance calls, public health officers informed cases of the study and asked for consent to share contact details with the research team. Cases who did not wish to participate were noted to ensure that they were not contacted again about the study via pathway C.

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2. Patients suspected of leptospirosis were identified by clinicians at selected North Island health care facilities. Health care facilities were sampled for convenience based on prior links that had been established between researchers and facility staff and because they were based in regions with a high incidence of leptospirosis, that is, Northland, Waikato, and Hawke's Bay [16]. To increase recruitment of Māori cases (New Zealand's Indigenous population), from January 20, 2021, until the end of the study, an additional health care facility in Hawke's Bay where 76% of service users are Māori was included. Clinicians informed the patients of the study at the time of suspicion of leptospirosis and sought consent to share the patients' contact details and samples with the research team (Multimedia Appendix 5). A scanned copy of the written consent form was kept with patient notes at the clinic, and the original written consent form was sent to the researchers with the patient's samples. In addition to the research samples, samples from these patients were sent to the diagnostic laboratories for standard testing.
3. Recruitment of notified cases from pathway A and suspected cases from pathway B was complemented by monthly check-ins with EpiSurv [27], the notifiable disease surveillance database managed by the Institute of Environmental Science and Research on behalf of the Ministry of Health. These check-ins identified notified cases from pathway A who had not already declined to participate and who were not already enrolled and suspected patients from pathway B who met the case definition after diagnostic testing. The local Public Health Units were informed of these cases and requested to contact them to invite them to participate in the study.

Case Consent and Recruitment

All consenting cases from pathways A, B, and C who met the case definition were sent a participant information sheet and consent form (Multimedia Appendix 6) via either post or email. The researchers called the cases over telephone at least 1 week after sending the information sheet to go through it. Once the researchers had answered cases' queries, they requested and documented verbal consent from them for the following parameters:

- Participation in a
  - case-control survey
  - follow-up survey 6 months after the case-control survey
  - semistructured interview if cases worked in an agricultural industry
- Access to cases'
  - physician's notes associated with leptospirosis
  - leptospirosis diagnostic test results
  - diagnostic DNA samples
- Sampling cases' in-contact animals and environments if cases had regular animal exposure that was not at an abattoir
- Keeping cases' contact details to invite them for the long-term follow-up study

Case Exclusion Criteria

All participants who were aged <16 years were excluded from the study.

Controls

Control Definition

Frequency matching of controls was considered a suitable approach to reasonably ensure that cases and controls were drawn from the same source population. The frequency was based on the distribution of sex and rurality of leptospirosis notifications from January 1, 2014, to December 31, 2018 [27]. During this time, 89.2% (403/452) of cases were males and 63.6% (204/321) lived rurally. However, only 16.29% (766,060/4,699,755) of the New Zealand population lives rurally [28]. Thus, controls were frequency matched as 90% male and 65% rural dwelling, and a 2:1 ratio of controls to cases was planned. Rurality was determined by home address according to the most recent urban or rural classification method by Stats New Zealand [29].

Control Selection

The control population was selected from a database of 18,954 New Zealand Health Survey (NZHS) [26] participants who agreed to be approached for future surveys (Figure 1). This database from the 2016-2017 and 2017-2018 survey periods was provided by the Ministry of Health [30]. The NZHS participants included the usually resident population, that is, they had lived in New Zealand for at least 1 year, with a residence visa or citizenship. Exceptions included the prison population, those who live on small New Zealand islands, and people who have been away from their households for >4 weeks during the NZHS recruitment period.

Control Consent and Recruitment

An invitation letter endorsed by the Ministry of Health and Massey University, together with the participant information sheet and consent form (Multimedia Appendix 7), was posted by the researchers to 1715 NZHS participants that matched our sex and rurality criteria. There was an option to opt out by contacting the research team if they desired. A total of 1613 people who received the invitation for the study and did not opt out of the study had their details sent to the market research companies, Up Market Research and Infield International, who conducted the control surveys.

The market research companies contacted potential controls 6 times during the study period via telephone, verified control eligibility, and obtained verbal consent for participation in the study. Controls were only invited to participate in a telephone survey for the case-control survey (study 1).

Control Exclusion Criteria

The NZHS participants who were aged <16 years and who had an influenza-like illness in the 4 weeks before the control survey were excluded.

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Substudy Populations

Study 2: Selection of Cases for the 6-Month Follow-up Survey

All cases were invited to complete a follow-up questionnaire at the time of the case-control survey. The follow-up survey of cases was planned to occur at least 6 months after the case-control survey.

Study 3: Selection of Cases for the Semistructured Interview

Occupational data were collected from all cases who participated in the case-control survey. Participants identified as working in agricultural industries (specifically abattoir workers and farmers) and who were recruited as cases between July 22, 2019, and July 23, 2021, were selected for semistructured interviews. Māori participants were prioritized because they are proportionally overrepresented in the group of people affected by leptospirosis [16].

Study 4: Selection of Cases for In-contact Animal and Environmental Sampling

Animal and environmental exposure data were collected from all cases as part of the case-control survey. Participants identified as having regular non–abattoir-associated animal contact were invited to have their in-contact animals (livestock, pets, and wildlife) and environments sampled.

Study 5: Selection of Patients for Sampling

Biological specimens from patients for research testing at Massey University were acquired in two ways.

1. All patients suspected of leptospirosis who were recruited at selected health care facilities (study 5 or pathway B detailed in case selection) provided blood and urine samples to be tested at both diagnostic laboratories and the research laboratory.
2. All cases who met the case definition and agreed to participate in the case-control study provided consent for the researchers to access their diagnostic samples through the diagnostic laboratories. Only DNA extracted from blood, urine, cerebrospinal fluid, and plasma to test for leptospirosis with PCR testing was requested from the diagnostic laboratories.

Data Sources, Collection, and Storage

Overview

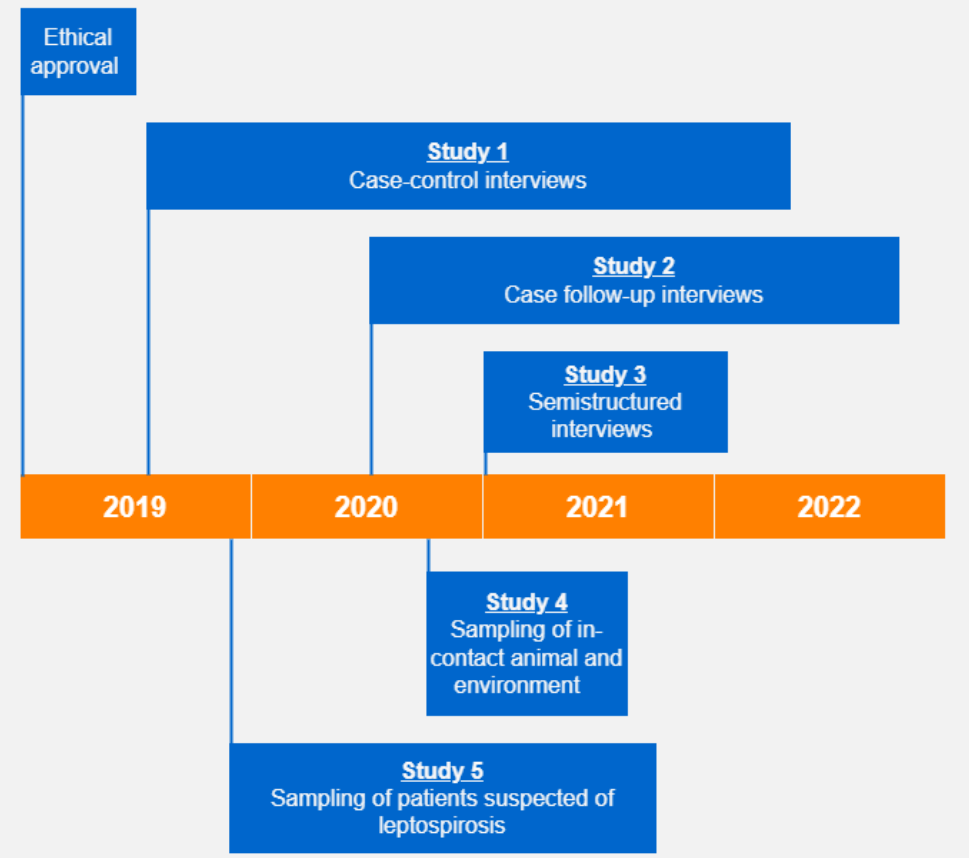
Data for this study were sourced from:

- Quantitative telephone interviews using questionnaires (case-control and follow-up)
- Selective transcripts of semistructured interview approved by interviewees
- Physician’s notes
- Biological specimens collected from patients, patients’ in-contact animals, and patients’ in-contact environments. Specimens were processed and tested in the research or diagnostic laboratory.

All data were sourced between July 25, 2019, and October 25, 2022 (Figure 2). Study-specific source documents containing identifiable data were maintained either with a restricted access or in a password-protected network shared drive hosted by Massey University. Information pertaining to the identity of the cases was censored from databases and biological samples and was replaced using unique participant codes. Biological samples were stored frozen at −80 °C.

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Figure 2. Study timeline of the 5 studies described in this protocol. Cases in study 1 were asked if they were interested in participating in studies 2 to 4 if they met the study selection criteria. Cases took part in study 2 at least 6 months after partaking in study 1. Cases took part in study 3 after they finished study 1 and study 2 interviews. Study 4 was conducted after study 1 at the earliest convenience. Study 5 participants were enrolled from health care facilities upon presentation.



Study 1: Case-Control Questionnaire

Eligible cases and matched controls answered a case-control questionnaire delivered over the telephone (Multimedia Appendices 8 and 9). The case-control questionnaire was developed to obtain data on exposures. Care was taken during questionnaire content development, via the review of other studies and questionnaire contents, to ensure that appropriate variables and exposures were incorporated. The questionnaire included the following:

- Leptospirosis case report forms used by the Institute of Environmental Science and Research [27] and the Waikato District Health Board [31]
- Questionnaires used in the study of leptospirosis exposure and risk factors in farmers [32], abattoir workers [33], veterinarians [34], veterinary students [35], and livestock [36] in New Zealand
- Questionnaires used for leptospirosis research in Sri Lanka [37], Nepal [38], and Tanzania [39]
- Case-control questionnaires used for other diseases in New Zealand, including campylobacteriosis [40], acute rheumatic fever [41], Legionnaires' disease [42], and Shiga toxin–producing *Escherichia coli* [43]

The case questionnaire also contained additional items including clinical course and outcome, sick leave, and sick leave entitlements as well as emotional well-being questions that were followed up in the substudy surveys. The researchers received training on the delivery of sensitive questions such as the Kessler Psychological Distress Scale (K10) [44] and risk assessment and management skills for interviewing sensitive people.

The case questionnaire was pilot tested by the researchers in 3 cases (patients who had leptospirosis before this study commenced). After piloting, changes were made to the survey questions to remove ambiguities.

Case interviews were conducted by the research team from July 25, 2019, to April 13, 2022, at a time that suited the participants and as soon as convenient after the initial contact. All cases were asked about their exposures in the month before they became ill. Data were collected using the electronic version of the questionnaire and transferred to the database, and 10% of the surveys were checked for data integrity.

All control interviews were conducted by the market research companies: UMR Market Research between October 19, 2019, and February 28, 2021, and Infield International between May 1, 2021, and January 26, 2022. The control questionnaire was pilot tested by the UMR Market Research on 12 controls (participants of the NZHS). The control surveys were conducted in 6 batches, with 50 controls interviewed in each batch. Batched control interviews were conducted in October and November 2019; January and February 2020; January and February 2021; May 2021; August 2021; and January 2022. The lack of control interviews between March 1, 2020, and December 31, 2020, was due to a delay in research during the COVID-19 pandemic.

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All controls were asked about their exposures in the month preceding the interviews. Data from the market research companies were received in emails with password-protected Microsoft Excel spreadsheets and transferred to the database, and 10% of the surveys were checked for data integrity.

Study 2: Follow-up Questionnaire

The follow-up questionnaire (Multimedia Appendix 10) was designed to expand on some of the questions from the case-only items in the case questionnaire and to introduce some new items. Follow-up interviews were conducted between July 9, 2020, and October 25, 2022. All symptoms identified in the case questionnaire were further quantified with symptom duration, frequency, and severity scores of 1 to 5, where 1 was mild and 5 was severe. Participants were also asked if they had any new symptoms that they attributed to leptospirosis since their previous interviews. Other questions included following up on current occupation, updates on sick leave, sick leave entitlements, and a repeat of the K10 questions. New items included the costs associated with leptospirosis treatment and support from the workplace, family, and friends during the illness. The follow-up interviews were administered to the cases at least 6 months after the case-control interview and by the same research team. The follow-up questionnaire was pilot tested by the researchers on 4 people who had leptospirosis before this study commenced. Data were collected using the electronic version of the questionnaire and transferred to the database, and 10% of the surveys were checked for data integrity.

Study 3: Semistructured Questionnaire

The semistructured questionnaire (Multimedia Appendix 11) was designed to collect patient experience data to inform the work of 3 groups of professionals: medical professionals (doctors and nurses); public health policy makers (Ministry of Health and Accident Compensation Corporation); and stakeholders in agricultural industries (managers, workers, industry boards, and workers' unions). Semistructured interviews were conducted between January 26, 2021, and January 19, 2022. Cases were asked to share their experiences of the disease; the financial implications; and their advice to workmates, employers, and their community. The semistructured interviews were conducted by the research team that received specific training for this interview. The semistructured questionnaire was pilot tested by the researchers on other researchers in the team who role-played as patients. This helped the researchers to upskill their rapport-building and prompting skills.

Face-to-face interviews were carried out before the COVID-19 pandemic–related movement restrictions were implemented, after which distance interviews using telephone or video calling were used. Data were recorded using Dictaphone for in-person interviews or Zoom (Zoom Video Communications) for distance interviews. Selective transcripts were made from the recordings and sent to the respective interviewees for review and editing with a request to return the transcript within 2 weeks.

Study 4: In-contact Animal and Environmental Sampling

Farm Animal Samples

All farm animal samplings were conducted between October 28, 2020, and July 29, 2021. All live animals were sampled for blood and urine by either the case's veterinarian or a veterinarian serving the area the farm was in. When animals were culled as part of normal farming practices (eg, prime cattle), kidney samples were also collected from the abattoir. On the basis of our earlier studies on leptospirosis in animals, up to 40 livestock of each relevant species were sampled; this allowed the detection of *Leptospira* infection or exposure for a prevalence as low as 15% for any herd or flock size with an error of 5% [45,46] and the isolation of leptospires, assuming a shedding prevalence of 35% and a success rate for isolation of 20% [47].

- Cattle were sampled while restrained in a race or milking shed. Cattle serum was collected from the jugular vein or tail vein with a 20 g needle with a volume not exceeding 10 mL. Urine from cattle was either an opportunistic free catch or collected by perivulval stimulation.
- Sheep were sampled while restrained by hand in a race or a yard. Sheep serum was collected from the jugular vein with a 20 g needle, with the volume not exceeding 10 mL. Urine from sheep was opportunistic free-catch urine or collected by a partial smothering technique. The partial smothering time was restricted to 15 seconds.
- Dogs were sampled while they were restrained by hand. Dog serum was taken from the cephalic or jugular vein with 23 to 22 g needles with the volume not exceeding 5 mL. Urine collection in dogs was by free catch, with an option for the veterinarian to use diuretics.

The samples were sent chilled to the laboratory at Massey University. Approximately 100 µL of urine was cultured in Ellinghausen-McCullough-Johnson-Harris (EMJH) medium, and cultures were kept at 28 °C with shaking and monitored for 13 weeks [48] before being discarded. The rest of the urine was centrifuged at 3000g for 20 minutes, with the supernatant removed [45], and the pellet stored at −80 °C and batch tested. All kidney samples were homogenized in an equal weight/volume of phosphate-buffered saline (PBS); the slurry was then centrifuged at 3000g for 20 minutes, and most of the supernatant was removed, leaving behind 1 mL of liquid [47], which was stored at −80 °C and batch tested. All serum samples were centrifuged at 3000g for 20 minutes, and the supernatant was stored at −80 °C and batch tested [49].

Wildlife Samples

Attempts were made to capture wildlife from farms that provided farm animal samples if the farmers were able to support this work. Wildlife was captured in kill traps, and necropsies were performed by the farmers who were provided with instructions by the researchers. Both kidneys were collected, bagged separately, and frozen upon collection by the farmer. The kidneys were then sent to the research laboratory at Massey University in 1 batch. Kidneys were thawed upon receipt and homogenized in equal weight/volume of PBS; the slurry was centrifuged at 3000 g for 20 min, and most of the supernatant

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was removed, leaving behind 1 mL of liquid that was stored at −80 °C and batch tested.

Environmental Samples

Attempts were made to obtain environmental samples from the farms that provided farm animal samples. Where possible, 10 sites (eg, farm dam, muddy paddock) that the participants identified as having contact with during the month before they became ill were sampled. Participants were sent materials and methods outlining how to collect environmental samples from the identified sites. Where possible, a 50-mL specimen bottle was filled with soil, mud, and water from each site. All samples were sent to the research laboratory at Massey University at room temperature and processed within 3 days of receipt. The soil and mud samples were resuspended in 50 mL of PBS, and the supernatant was collected for processing. Soil and mud supernatant and water samples were centrifuged at 3000g for 20 minutes, and most of the supernatant was removed, leaving behind 1 mL of liquid of which 50 µL was cultured in EMJH culture medium, while the rest was stored at −80 °C and batch tested with PCR [21].

Study 5: Human Samples

Samples from patients suspected of leptospirosis were obtained at the patients' usual phlebotomy centers between November 6, 2019, and September 29, 2021. Research samples were collected at the same time as the diagnostic samples and included whole blood, serum, and urine samples. Approximately 100 µL of whole blood and urine was inoculated into the EMJH medium at the laboratories serving the phlebotomy centers. The culture medium and culture protocol were provided to these laboratories by the researchers as part of this study. The rest of the urine was centrifuged at 3000g for 20 minutes; the supernatant was removed, and the pellet was resuspended in RNAlater (Ambion). A total of 5 tubes containing blood culture, urine culture, serum, whole blood, and urine pellets in RNAlater were sent to the research laboratory at Massey University at room temperature. Blood and urine cultures were kept at 28 °C with shaking and monitored for 13 weeks before being discarded. Serum samples were centrifuged at 3000g for 20 minutes, and the supernatant was kept at −80 °C and batch tested. The urine pellet and whole blood were kept at −80 °C and were batch tested. Diagnostic laboratory results for all notified cases in the study were collected from EpiSurv to identify cases that were tested with a diagnostic PCR and to identify the diagnostic laboratories that ran these PCRs. The researchers then acquired the diagnostic sample (DNA) from the respective diagnostic laboratories to perform a research PCR.

Ethics Approval

This study received human ethics approval from the Health and Disability Ethics Committee (reference number 19/STH/80). In addition, this study received locality agreements together with local Māori consultations from 20 District Health Boards. The study received animal ethics approval from the Massey University Animal Ethics Committee (reference number Protocol 19/11).

Data Analysis Plan

Sample Size and Statistical Power

For common exposures (prevalence 30%-70%, such as exposure to flooded paddocks) [35], 150 cases and 300 controls provide more than 80% power for odds ratios (ORs) as low as 1.8, whereas for less common exposures (15%, such as wild deer on or near the farm) [32], this provides 80% power to detect ORs as low as 2.1.

Missing Data

Our approach to handling missing data was to design the answers to the survey questions with contingencies. For sensitive questions such as date of birth, participants could either provide their date of birth, age, or an age range. In addition, the category *unsure* was available to interviewers if participants were asked about the vaccination status of the animals they worked with or the treatment of their work water supply, as employees may not necessarily have this information. The *unsure* category was included in the data analysis.

Study 1: Risk Factors

Descriptive statistics consisted of comparing cases and controls (eg, percentage of respondents within strata and their CIs) according to the demographics and exposure factors present in the questionnaire. Contingency tables were drawn to compare dichotomous and ordinal variables. When applicable, 2 × 2 tables and Fisher exact test were used to calculate the crude ORs and CIs. Ordinal, discrete, and continuous variables with nonnormal distributions were compared using the nonparametric Mann-Whitney-Wilcoxon rank sum test. Boxplots were used to compare discrete and continuous variables. Comparison of independent variables and collinearity was determined using Pearson correlation coefficients. Timelines were plotted to analyze temporal trends and compare interviews of cases and controls.

Multivariable logistic regression models were used to calculate the ORs and CIs. Both crude and adjusted ORs were calculated for each exposure, with adjustment for potential confounders and matching variables. Variables were added in a stepwise manner forming precursor models; this was done separately for each main category of exposure variables, for example, wildlife. Subsequently, the different category precursor models were combined before running a further stepwise backward selection. To assist the decision of variable inclusion or exclusion, the following methods were used: relevance of the exposure in the literature and expert opinion, the Akaike Information Criterion of the model, and sensitivity analysis. Risk factors were initially estimated from a model without occupation, while adjusted for the matching factors (rurality and sex) and other confounders. To provide insight into the effect of occupation, a second analysis was conducted with occupation included.

Study 2: Follow-up of Cases

The proportion of cases with different symptoms at several time points after the onset of symptoms and up to the time of the follow-up interview was calculated. Kaplan-Meier survival curves were used to graphically display the time until symptoms were no longer present [50]. Multivariable logistic regression

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models were used as described for the analysis of risk factors to identify possible factors associated with the persistence of symptoms, and crude and adjusted ORs and 95% CIs were calculated.

Descriptive analyses using means, frequencies, and percentages were used to explore how living with leptospirosis had impacted patients' activity participation, ability to cope, capability to return to usual daily activities, and support received from family and friends for recovery.

The K10 scores will be categorized using the method described in the NZHS [51]. Each of the 10 questions was scored from 0 to 4, and for NZHS reporting, psychological distress meant having a score of ≥12. This analysis will allow case K10 scores at both time points from the acute and follow-up surveys to be compared with those of NZHS participants. To assess changes in K10 scores over time, a mixed model repeated measures ANOVA will be used as described previously [52].

Study 3: Semistructured Interviews of Cases

Anonymized selective transcripts were made from the recordings of the semistructured interviews by the interviewer, leaving in what the interviewer considered to be the essential answers to inform the work of 3 groups of professionals. Selective transcripts were used as raw data for content analysis [53]. In this analysis, 3 important choices were made. First, the content analysis focused on *what was said* without the exploration of *what was meant*. Second, the content analysis was inductive, and recurring themes were identified as they emerged from the transcripts. Finally, an issue was considered a recurring theme when approximately one-third of the interviewees mentioned it [54-56].

Studies 4 and 5: Sources of Infection

Attempts to identify the strains of *Leptospira* in human, animal, and environmental samples were as follows:

- Genotyping pure *Leptospira* cultures: DNA extractions from cultures were subjected to *LipL32* quantitative PCR [57] and *glmU* conventional PCR [21] for the detection of pathogenic *Leptospira*. All *glmU* PCR amplicons were sequenced to identify the species and serovars of *Leptospira*. Any culture-negative samples for the pathogenic PCRs were subjected to a 16s PCR [58] to identify saprophytic or intermediate strains of *Leptospira*.
- Genotyping samples: all samples stored at −80 °C from humans (blood, urine, cerebrospinal fluid and serum); animals (urine and kidneys); and the environment (water, soil, and mud) were subjected to DNA extraction and to *LipL32* and *glmU* PCRs as described in the previous paragraph. Samples positive for *glmU* PCR were sent for amplicon sequencing to identify species and serovar of *Leptospira*.
- Serotyping via MAT: all serum samples were serially diluted from 1/24 to 1/3072 and subjected to a MAT assay against 5 serovars belonging to 2 species: *Leptospira borgpeterseneii* serovars Hardjo type bovis, Ballum, and Tarassovi and *Leptospira interrogans* serovars Pomona and Copenhageni. Seropositivity for humans was defined as per the case definition for cases (Textbox 1). Seropositivity for animals was defined as a MAT titer of ≥48, whereas titers of ≥384 indicated likely current or recent infection [59].

Culture media, cultivation of cultures, DNA extraction method, primers, and PCR protocols were as published previously [21].

Results

All participants in this study were recruited between July 22, 2019, and January 31, 2022, and data collection for the study has completed. During this period, a total of 220 cases were notified to ESR, of which 139 were forwarded to us from the Public Health Units; 12 (8.6%) of whom declined to participate, 24 (17.3%) did not meet the case definition, and 7 (5%) were unable to be contacted; thus, 95 (68.3%) cases met the case definition, agreed to participate in the study, and were interviewed. All case interviews were conducted from July 25, 2019, to April 13, 2022. A total of 300 controls were recruited and interviewed: 150 (50%) from UMR Market Research and 150 (50%) through Infield International. Control interviews were conducted from October 19, 2019, to January 26, 2022. A total of 91 cases participated in the follow-up interviews that were conducted between July 9, 2020, and October 25, 2022, and 13 cases participated in the semistructured interviews that were conducted between January 26, 2021, and January 19, 2022. Semistructured interviews were conducted after the participants completed the case (study 1) and follow-up (study 2) interviews. Data integrity checks showed that all responses to the questions in the case-control and follow-up surveys were recorded because of the contingencies put in place to account for missing data. In-contact animal and environmental samples were collected from 4 farms (1 dairy farm, 1 sheep farm, and 2 beef farms) between October 28, 2020, and July 29, 2021. Samples were collected from cattle (16 kidney, 186 serum, and 193 urine samples); sheep (40 urine and 40 serum samples); dogs (12 serum samples); possums (28 kidney samples); rats (6 kidney samples); wild pigs (3 kidney samples); wild rabbits (3 kidney samples); and environmental sources including water (n=10), mud (n=11), and soil (n=15). A total of 20 samples were collected from patients suspected of leptospirosis between November 6, 2019, and September 29, 2021.

Data analysis for the semistructured interviews has concluded, and 2 manuscripts have been drafted for review. Results of the other studies are being analyzed and the specific results of each study will be published as individual manuscripts. All animal and human samples have been tested, and the results returned to farmers and patients by their veterinarians or clinicians, respectively.

Discussion

Principal Findings

This study is the first in New Zealand to quantify the association between leptospirosis and a range of risk factors including contact with livestock, wildlife, and pets; exposure to soil, mud, and water; and the use of PPE and animal vaccination. The identification of risk factors will enable us to design effective intervention strategies to reduce exposure to these factors and thus reduce the disease burden in New Zealand (study 1). Our

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assessment of the disease burden for patients is novel, as we included the potential difficulties associated with compensation for occupationally acquired cases. This information may be used to update the compensation policies to adequately support future leptospirosis cases (study 2). The successful follow-up survey of 91 cases and 13 cases from agricultural occupations who shared their experiences in a semistructured interview will provide a new and detailed understanding of the postleptospirosis experience and its burden on individuals and households. This information will help identify the appropriate measures, including social, financial, and emotional measures, to support leptospirosis cases (studies 2 and 3). Furthermore, the data from patients' in-contact animals and environments will provide information on pathways for infection previously not considered important in New Zealand, such as pests or flooding, which will inform (and have informed) health messaging (study 4). Finally, this study identified a large underascertainment of cases, as 70% of patients did not return to provide a second blood sample and did not receive a diagnosis (study 5).

Limitations

It is important to acknowledge the limitations of this study. Case-control studies are generally prone to biases, particularly differential recall, and selection biases. To reduce the impact of recall bias on the findings of this study, both cases and controls were given similar memory aids during the interview and close-ended questions were prioritized over open-ended questions at the analysis stage. Selection bias was reduced by matching only 2 variables (sex and rurality), the major known confounders, to ensure that controls were representative of the case population, as 90% of leptospirosis cases were males and 65% lived in rural areas of New Zealand. By focusing on notified cases, albeit with some broadening of the case definition, the issue of underascertainment, which has previously been estimated at 3-fold where mild cases do not seek medical attention and thus do not receive a diagnosis or get notified [60], was not directly addressed; however, the inclusion in our protocol to (1) enroll and test patients suspected of leptospirosis with a range of research tests (culture, PCR, and serology) and (2) test diagnostic samples with a research PCR will shed light on this hidden burden.

Strengths

One of the strengths of this study was ensuring that all notified cases were given an opportunity to participate in the study by using 3 pathways to identify these cases nationwide (Figure 1). This effort is crucial for a disease uncommon in New Zealand (approximate incidence risk of 2 per 100,000 people) [16] and ensures that the results from this study will provide nationally valid data.

Future Work

Future research goals include following the cohort of patients established in this study (aim 7) in a long-term follow-up study. Furthermore, the underascertainment of cases owing to the requirement of 2 tests identified in study 5 has led us to collaborate with human diagnostic laboratories to develop a PCR test that will require 1 sample for diagnosis and will subsequently be able to type the strain of *Leptospira*.

Conclusions

The dissemination of the study results will occur through scientific and stakeholder channels including publications in international peer-reviewed journals and presentations at international and national meetings. Our stakeholders in the community such as the Meat Industry Association, NZ Meat Workers Union, Department of Conservation, Dairy Women's Network, WorkSafe NZ, Rural Women New Zealand, and district and regional councils will use their websites, social media channels, and publications to deliver key messages. We held a leptospirosis forum in March 2019 that socialized the study with stakeholders and in September 2022 with stakeholders and patients to disseminate the findings of the study. The researchers have summarized the key findings of the study and circulated them to Public Health Units, District Health Board research offices, Māori Health teams, and all participants. These summaries will also be more widely disseminated to the community.

Acknowledgments

The investigators thank the following for their assistance and support with this study: study participants; the Health Research Council of New Zealand for funding this study (reference ID 18/239); medical officers of health from the District Health Boards that worked with us to obtain locality agreement and Māori consultations; Public Health Officers for recruiting cases, clinicians, nurses, and practice managers who assisted with recruitment and sampling of suspected cases; Institute of Environmental Science and Research for allowing monthly surveillance of cases from EpiSurv and for providing diagnostic tests results; laboratory staff in Whangarei Hospital; Waikato Hospital laboratory and Hastings laboratory for specimen collection and processing before transport to the research laboratory; Canterbury Health laboratory and Waikato Hospital laboratory for providing the research laboratory with patient DNA samples used for diagnosing leptospirosis cases in the study, Northland Regional Council for providing traps for trapping wildlife on patient farms; and the Ministry of Health for providing the New Zealand Health Survey database.

Data Availability

The data sets generated during this study are not publicly available, as they are currently unpublished data. Data sets may be available from the corresponding author when they are published on reasonable request.

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Authors' Contributions

JB conceived and developed the study design with assistance from SN, JC-E, JM, EV, GP, JD, MGB, DAW, JW, MH, and TQ. MH provided expertise on Māori codes of practice. AF managed the electronic databases. SL managed the laboratory data, and PY provided peer supervision and training on the delivery of sensitive questions. All authors contributed to the drafting and revising of the manuscript. All authors have read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review comments from the Health Research Council of New Zealand—Reviewer #11.
[PDF File (Adobe PDF File), 132 KB - resprot_v12i1e47900_app1.pdf]

Multimedia Appendix 2
Peer review comments from the Health Research Council of New Zealand—Reviewer #48.
[PDF File (Adobe PDF File), 135 KB - resprot_v12i1e47900_app2.pdf]

Multimedia Appendix 3
Peer review comments from the Health Research Council of New Zealand—Reviewer #73.
[PDF File (Adobe PDF File), 136 KB - resprot_v12i1e47900_app3.pdf]

Multimedia Appendix 4
Peer review comments from the Health Research Council of New Zealand—Reviewer #97.
[PDF File (Adobe PDF File), 134 KB - resprot_v12i1e47900_app4.pdf]

Multimedia Appendix 5
Suspected patient information sheet.
[DOCX File , 139 KB - resprot_v12i1e47900_app5.docx]

Multimedia Appendix 6
Case information sheet.
[DOCX File , 131 KB - resprot_v12i1e47900_app6.docx]

Multimedia Appendix 7
Control information sheet.
[DOCX File , 108 KB - resprot_v12i1e47900_app7.docx]

Multimedia Appendix 8
Case questionnaire.
[DOCX File , 177 KB - resprot_v12i1e47900_app8.docx]

Multimedia Appendix 9
Control questionnaire.
[DOCX File , 56 KB - resprot_v12i1e47900_app9.docx]

Multimedia Appendix 10
Follow-up questionnaire.
[DOCX File , 133 KB - resprot_v12i1e47900_app10.docx]

Multimedia Appendix 11
Semistructured questionnaire.
[DOCX File , 112 KB - resprot_v12i1e47900_app11.docx]

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Abbreviations

EMJH: Ellinghausen-McCullough-Johnson-Harris
IgM: immunoglobulin M
K10: Kessler Psychological Distress Scale
MAT: microscopic agglutination test
NZHS: New Zealand Health Survey
OR: odds ratio
PBS: phosphate-buffered saline
PCR: polymerase chain reaction
PPE: personal protective equipment

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Protocol

Intergenerational Reminiscence Approach in Improving Emotional Well-Being of Older Asian Americans in Early-Stage Dementia Using Virtual Reality: Protocol for an Explanatory Sequential Mixed Methods Study

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Abstract

Background: After a dementia diagnosis, Asian Americans experience anxiety, feelings of shame, and other negative effects. Emotional well-being is not only an important aspect of mental health, but also a quality of resilience that helps people bounce back faster from difficulties. However, few studies have addressed issues in developing, implementing, and testing intervention strategies to promote emotional well-being among older adults. Intergenerational solidarity between grandparents and grandchildren has been emphasized in Asian families and is beneficial for the health of persons with dementia. Reminiscence and life review have been identified as potentially effective intervention strategies for helping depression and emotional well-being for older adults.

Objective: This proposed study aims to develop and implement an intergenerational reminiscence approach and evaluate its potential feasibility and effectiveness in improving the emotional well-being of older Asian American adults who have a recent dementia diagnosis.

Methods: An explanatory sequential mixed methods design will be used in which quantitative data will first be collected and analyzed to identify subsamples of participants who report the greatest and least change in emotional well-being; then, these subsamples will be interviewed to further understand why or why not this intervention works for them. Older adults will receive 6 sessions of life review with grandchildren in virtual reality (VR; 1-1.5 hours each week for 6 weeks), aided by pictures and virtually traveling to important places in their life using Google Earth to look around at those places and remember important times. Quantitative survey data will be collected pre- and postintervention and at a 3-month follow-up. Qualitative interviews with selected participants will also be integrated into the study design. The quantitative data from the surveys will be entered into SPSS (IBM Corp) and analyzed using descriptive analyses, Pearson chi-square tests, nonparametric Friedman tests, or nonparametric Wilcox signed-rank tests (2-tailed). The qualitative data will be transcribed by research assistants, coded by the investigators independently, and analyzed with guidance from content analysis software (Atlas.ti; Atlas.ti Scientific Software Development GmbH).

Results: The project was delayed due to the COVID-19 pandemic. Data collection started in late 2021, and 26 participants were recruited as of December 2022. While we are still cleaning and analyzing the quantitative data, the qualitative interviews showed promising results of this intergenerational reminiscence approach in improving emotional well-being among older Asian American adults who have cognitive impairment.

Conclusions: Intergenerational reminiscence provided by grandchildren is promising in improving the emotional well-being of grandparents. VR technology is likely to be accepted by older adults. Future research may consider scaling up this pilot into

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a trackable, replicable model that includes more participants and develops a more rigorous study design with control groups to test the effectiveness of this intervention for older adults with dementia.

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KEYWORDS

intergenerational reminiscence; grandparent-grandchild; dyad; emotional; well-being; Asian American; older adults; dementia; virtual reality; VR

Introduction

Background

The Asian American population in the United States nearly doubled between 2000 and 2019. Asians now make up about 7% of the nation's overall population, and their numbers are projected to surpass 46 million by 2060, nearly four times their current total [1]. Older Asian immigrants often immigrate to the United States at a late age [2] and experience many challenges related to migration, such as low acculturation, limited English language proficiency, ineligibility for entitlement and welfare programs, family or generational conflicts, and social isolation [3,4]. Older Asian American adults also face numerous challenges and physical, psychological, and mental health problems [5], as well as racial discrimination on a regular basis, especially after COVID-19 [6,7]. As the US population becomes older and more diverse, programs and interventions on how to improve mental health of older immigrants are sorely needed.

In addition, if older immigrants are diagnosed with dementia, they face triple adversity: immigration, aging, and dementia. Immigration is a life-changing event that is often accompanied by elevated stress and adversity; aging adds an additional layer of adversity to immigration, and dementia can lead to experiencing further adverse events. This triple jeopardy poses a trauma risk to older Asian American adults, creating a pressing need to understand how to best restore and preserve their resilience. After a dementia diagnosis, people often experience anxiety, negative impacts on self-esteem, preoccupation with the diagnosis, and hyper-vigilance, which can precipitate a crisis [8]. Asian Americans also report feelings of shame and weakness after a dementia diagnosis; however, they seek fewer formal services for support compared to Whites [9-11], leading to negative emotional and mental health outcomes [12]. Despite vulnerabilities among this population, Asian Americans often attract less research attention, in part due to the "model minority" myth [13].

Despite their overall better physical health, older Asian immigrants have worse mental health outcomes than their White counterparts [14-16]. People who are emotionally well (ie, are satisfied with life, have a positive affect, and find purpose or meaning in life) have a quality of resilience and are able to bounce back faster from difficulties [17]. While there are some studies that have specifically looked at emotional well-being among adults and adolescents [18], few studies have examined emotional well-being among older adults. Prevention and interventions to improve emotional well-being among aging populations have attracted special attention because of its strong correlation with health [19]. Reminiscence and life review have been identified as potentially effective intervention strategies for helping depression and increasing emotional well-being among older adults [20-23]. The literature also asserts the positive impact of an intergenerational approach in achieving positive mental health and emotional well-being among older adults [24-26]. Intergenerational solidarity between grandparents and grandchildren has been emphasized in Asian families [27] and is beneficial for the health of persons with dementia [28,29]. When reminiscence and life review strategies are combined with the intergenerational approach, the mental health benefits for older adults are even clearer and more significant [30]. This approach may also help grandchildren gain more historical and cultural understanding of their grandparents' lived experiences, positively change their views of aging, and increase their bonding with grandparents.

Using technology to help enhance the well-being of older adults is a growing research and practice trend. One recent technological advancement is audiovisual virtual reality (VR), which creates a 3D computer-generated environment to provide an immersive and interactive personal experience [31]. Emerging technologies that allow older adults to socialize across geographic boundaries using a head-mounted display paired with a smartphone have been well accepted by older adults [32]. Studies have also shown the potential of social VR as a powerful reminiscence tool to challenge stereotypes of aging and promote the well-being of older adults [33].

Aims and Research Questions

This proposed study aims to develop and evaluate the potential feasibility and effectiveness of an intergenerational reminiscence approach in improving the emotional well-being of older Asian American adults who have a recent dementia diagnosis. This pilot study is the first to develop and test how social VR can help older Asian Americans improve their emotional well-being and cope with the stress and adversity of having been diagnosed with dementia. It is hypothesized that the resiliencies of family through grandchildren, reminiscence, and technology together will help older adults develop better emotional well-being, which will help them withstand difficulties in the journey of dementia and have better mental health outcomes. The study addresses three specific aims: (1) develop 6 intervention sessions based on the reminiscence and life review theory using VR technology; (2) quantitatively test the effectiveness of this intervention in improving emotional well-being; and (3) qualitatively evaluate the usefulness of this intervention.

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Methods

Study Design

An explanatory sequential mixed methods design [34] will be used, involving first collecting quantitative data and then analyzing this data to identify subsamples of participants who report the greatest and least change in emotional well-being. Next, we will conduct qualitative interviews among these subsamples. For the intervention, a single-arm trial will be used in which all the recruited participants are given the intervention and then followed over time to observe their response. This design is used when the objective of the trial is to obtain preliminary evidence of the efficacy of the intervention, but it is not generally used for confirmation of efficacy [35]. Such a design may be desirable when the available participant pool is limited; thus, it is not optimal to randomize many participants to a control arm [35].

Recruitment

Participants in this study will be recruited from immigrant Chinese, Korean, Vietnamese, and Indian families since they are the top 4 minority Asian groups in the greater urban area of Dallas, Texas [36]. The eligibility criteria of the older adult participants include (1) self-identification as Chinese, Korean, Vietnamese, or Indian American and living in the greater Dallas area; (2) age 65 years or older; (3) a dementia diagnosis in the past 12 months (self-reported); and (4) at least one grandchild aged 18 years or older. When both an eligible older adult and his or her grandchild agree to participate in the study, the grandparent-grandchild dyad will be included in the study. The dyads will be recruited through multiple ways, including referrals from facilities or community agencies, flyers posted in Asian grocery markets, announcements posted on Facebook and Twitter, and local churches that service these Asian American groups. Eight dyads from each of the 4 Asian groups are proposed to be recruited (64 total participants).

Procedure

After participants sign the informed consent form, both the older adults and their grandchildren will be offered a VR headset. Training on how to use the VR headset will be offered to grandparents and grandchildren by the research team before the intervention starts. If the grandchildren do not reside locally, Microsoft Teams–based training will be offered. Then, older adults will receive 6 sessions of life review with their grandchildren in VR (1-1.5 hours each week for 6 weeks). The themes will include (1) major turning points in life, (2) family history, (3) life and career accomplishments, (4) history of loves and hates, (5) experiences of suffering or stressful experiences, and (6) meaning and purpose of life. A manual of interaction guidelines will be prepared for the grandchildren to lead the interactions with their grandparents based on the intervention manual proposed by Watt and Cappeliez [37,38] and others, which will outline the implementation of integrative and instrumental reminiscence interventions that promote acceptance of self, conflict resolution and reconciliation, a sense of meaning and self-worth, recalling how one coped with past problems, and drawing from past experience to solve present problems.

The process is a series of discussions using the above themes of major moments in the participants' lives, aided by pictures and virtually traveling to important places in their lives with Google Earth to look around these places and remember important times. Information on important pictures and places will be collected by the grandchildren before the session by asking the grandparents' spouses, their own parents, or the grandparents' caregivers or legally authorized representatives (LARs). Both the grandparents and their grandchildren will participate in the intervention remotely. The VR intervention process is linked to YouTube 360 slideshows, an application that enables 2 or more people to communicate verbally while seemingly in the same shared space despite being physically apart. Participants open the YouTube app and select the video we have created. The videos are slideshows using 360-degree scenery that fits with their personal history and the images provided by their family members. The subjects speak over a speakerphone, talking about their memories, while viewing the same video. The intervention through VR linked to YouTube is not recorded, and the private family account set up for this study does not publicly list any scenery video and is thus private to the participants (grandparents and grandchildren), the older participants' caregivers or LARs, and the research team. Mobile Oculus Quest headsets will be mailed to each participant in the dyads. These headsets do not require a computer and enable an immersive video chat–like experience where participants can do activities together in a virtual world. Some older adults with dementia may need some help from their caregivers or LARs if needed. An eyeglass spacer (a rubber border) comes with every headset provided to the subjects. The interaction process via VR will offer older adults audio as well as visual perceptions and thus increase interactions and engagements while overcoming the limitations of geographical distance between the 2 generations. Pretest, posttest, and 3-month follow-up tests will be performed. Qualitative interviews with selected participants will also be integrated into the study design.

Measurement

The primary outcomes of the study will be the social and emotional well-being of grandparents, and the secondary outcomes are the benefits to the grandchildren.

Primary Outcome Measurements

Primary outcomes among the grandparents include satisfaction with life, emotional well-being, subjective happiness, resilience, depression, and grandparent-grandchild bonds; these are assessed via culturally appropriate standardized instruments before and after the intervention. Demographic information for each dyad, such as age, gender, education, geographic proximity, and self-rated health, are also collected in the pretest survey.

Satisfaction with life is measured by the Satisfaction with Life Scale (SWLS) [39], a 5-item scale designed to measure global cognitive judgments of one's life satisfaction as a whole. Participants indicate how strongly they agree or disagree with each of the 5 items using a 7-point scale that ranges from 7 (strongly agree) to 1 (strongly disagree). The SWLS has shown good reliability and validity and thus has been recommended as a complement to scales that focus on psychopathology or

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emotional well-being because it assesses individuals' conscious evaluative judgment of their life by using their own criteria [40].

Emotional well-being will be measured by the Warwick-Edinburgh Mental Wellbeing Scale (WEMWBS) [41], which consists of 14 items that describe participants' experience over the past 2 weeks. The WEMWBS covers positive affect (feelings of optimism, cheerfulness, and relaxation), satisfying interpersonal relationships, and positive functioning (energy, clear thinking, self-acceptance, personal development, competence, and autonomy). Each item is measured using a 5-point Likert scale ("none of the time," "rarely," "some of the time," "often," and "all of the time). Sum scores were calculated with a range of 14 to 70, with a higher score indicating a higher level of mental well-being. The WEMWBS has shown good reliability and validity [41].

The Subjective Happiness Scale (SHS) [42] is a global subjective assessment of whether a person is happy or unhappy. The SHS consists of 4 items, each measured on a 7-point Likert scale ranging from 1 to 7. Sum scores of the 4 items are calculated, yielding a range from 7 to 28. The SHS has been translated to different languages and has shown good reliability and validity.

Resilience of older adults will be measured by the Brief Resilience Scale (BRS) [43,44]. The BRS is one of the best and most highly recommended [44] resilience scales and has shown high reliability and validity in the literature [43,45,46]. Six items are used, each ranging from 1 (low resilience) to 5 (high resilience). After reverse coding 3 items, sum scores are calculated for the final analysis, with a higher score indicating more resilience.

The Geriatric Depression Scale (GDS) [47] short form consists of 15 questions that ask participants to answer yes or no in reference to how they felt over the past week. Of the 15 items, 10 indicate the presence of depression when answered positively while the rest indicate depression when answered negatively. The GDS-15 has been tested and used extensively with the older population and is easy to administer (it takes about 5 to 7 minutes to complete).

Grandparent-grandchild bonds will be measured by 3 questions assessing the quality of their relationship using a scale adapted from the Intergenerational Solidarity Inventory [48]. The 3 questions are as follows: (1) "Taking everything into consideration, how close do you feel to this grandchild?" (2) "How much do you feel that this grandchild would be willing to listen when you need to talk about your worries and problems?" and (3) "Overall, how well do you and this grandchild get along together?" For each question, scores range from 0 to 2 (0="not at all," 1="somewhat," 2="very"). An additive emotional cohesion score was computed, ranging from 0 to 6, with higher scores representing a closer grandparent-grandchild relationship.

Usability of virtual reality technology will be measured by adapting the System Usability Scale (SUS) [49]. The SUS provides a "quick and dirty" but reliable tool for measuring usability. It consists of a 10-item questionnaire with 5 response options (from "strongly agree" to "strongly disagree"). The SUS allows researchers to evaluate a wide variety of products and services, including hardware, software, mobile devices, websites, and applications [50]. In this study, we added "VR" to the 10 statements. In addition, 3 separate questions are asked to evaluate participants' subjective feelings on VR technology (whether they find it comfortable, satisfactory, and effective), with "yes", "no," and "unsure" answers for each question.

Secondary Outcome Measurements

Secondary outcome measurements for the grandchildren include emotional well-being, attitude toward aging, the grandparent-grandchild relationship, and the usability of VR technology. Except for the attitude toward aging, all measurements for the grandchildren will be the same as those for the grandparents.

The young adult volunteers' attitude toward aging will be measured with the Fraboni Scale of Ageism (FSA), which was developed by Fraboni et al [51] and revised by Rupp et al [52]. Participants will be asked to respond on a 4-point Likert scale to 29 statements (1="strongly disagree" to 4="strongly agree"). The FSA has been extensively used among college students and has shown high internal consistency and strong validity [53,54]. Sum scores will be calculated for the final analysis, with higher scores indicating more ageism.

Other Outcomes

Follow-up qualitative interviews are also conducted to explore participants' experience with VR technology and their overall experience and feelings regarding the proposed intervention. We will select 3 dyads from each group for further qualitative interviews (12 dyads total). Each generation's experiences, perspectives, challenges, and suggestions with this intervention will be determined with in-depth interviews (in person or via a phone call lasting for about 45 to 60 minutes). In general, we will use the following probe questions for the in-depth interviews with older adults: (1) "In general, what did you share with your grandchild in the past few weeks?" (2) "Can you describe how your emotional well-being has changed as a result of the intervention program? Please provide a few examples, especially on what part of the intervention helped you most or least when improving your well-being" (3) "How did you feel about the weekly talk with your grandchild?" (4) "How do you feel about the virtual reality technology in this intervention program?" and (5) "What suggestions or advice do you have for this project? Or any suggestion or advice for improving your emotional well-being?" For the grandchildren, we will use the following questions: (1) "In general, what did you talk with your grandparent in the past few weeks? Or what contents did you share with each other?" (2) "Can you describe how your grandparent's emotional well-being has changed as a result of the intervention program? Please provide a few examples, especially what part of the intervention helped you most when improving your well-being" (3) "How did you feel about the weekly talk with your grandparent? Challenges? Ways to overcome?" (4) "How do you feel about the virtual reality technology in this intervention program?" and (5) "What suggestions or advice do you have for this project? Or any suggestion or advice for improving the emotional well-being of your grandparent?"

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Statistical Analysis

The quantitative data from surveys will be entered into SPSS (IBM Corp) and analyzed using descriptive analyses, Pearson chi-square tests, Friedman tests, or nonparametric Wilcox signed-rank tests (2-tailed). The qualitative data will be transcribed by research assistants, coded by the investigators independently, and then analyzed with the guidance of content analysis software (Atlas.ti; Atlas.ti Scientific Software Development GmbH).

Ethical Considerations

Prior to commencing the study, all members of the research team successfully completed the Human Subject Protection training and acquired the necessary certification. The study adheres strictly to the guidelines outlined in the Declaration of Helsinki and received approval on July 14, 2020, from the University of Texas at Arlington (UTA) institutional review board (2020-0210). Before conducting the interviews, the participants were provided with clear and comprehensive information regarding the purpose of the study, the procedures involved, the potential risks and benefits associated with participation, the use and anonymization of research data, and the maintenance of confidentiality. Furthermore, the participants were explicitly informed, both initially and through reminders, that their involvement was completely voluntary and that they could withdraw from the project at any point without facing any penalties. The study officially commenced only after participants signed the consent form. The consent form included the contact details of the principal investigator and the institutional review board office, and each participant received a signed copy for their records. Each participant who successfully completes the study is provided compensation in the form of a $110 Walmart gift card.

Each participant is given an ID number. The data obtained for this study has been carefully collected to exclude any personal identifiers. All data files are securely stored in password-protected and encrypted formats on laptops provided by the UTA. These UTA-issued laptops also adhere to encryption protocols mandated by the UTA Office of Information Technology. The encrypted data files will be stored using an approved UTA storage tool, such as OneDrive, to ensure their secure preservation. The utmost priority is given to safeguarding the privacy of the participants involved. A list containing participant names will be maintained securely using author LX's authorized and protected OneDrive account. In the final report, only deidentified data will be included, ensuring anonymity. The data will be retained for a period of 3 years following the conclusion of the study's protocol.

Results

This study was funded by the Rutgers University Asian Resource Centers for Minority Aging Research Center under the National Institutes of Health/National Institute on Aging (grant P30-AG0059304) for a project duration of April 4, 2020, to June 30, 2023. The project was delayed due to the COVID-19 pandemic. Data collection started in late 2021. As of December 2022, 26 participant dyads were recruited, for a response rate of approximately 72% (we approached 36 potential dyads). Among the 26 grandchild participants, 11 were Chinese American, 8 were Vietnamese American, 5 were Indian American and 2 were Korean American. Data for the grandparents at baseline and after the intervention were collected by phone calls by trained bilingual research assistants. Individual grandchild participants entered the data in QuestionPro (Survey Analytics LLC), a centrally supported online survey research tool. The data collected were checked for correctness by means of cross-validation.

After the intergenerational reminiscence intervention was completed, 11 dyads were selected for further qualitative interviews. However, the majority of the dyads interviewed were from Chinese American families. We are currently in the stage of entering, cleaning, and analyzing the quantitative and qualitative data.

Discussion

Principal Findings

The objective of this study is to create and implement a 6-session intervention using VR technology and the reminiscence approach targeting grandparents and grandchildren in Asian American families. By gathering both qualitative and quantitative data, this study aims to assess the effectiveness of the intervention in enhancing the emotional well-being of grandparents and strengthening intergenerational bonds. The research will contribute valuable and up-to-date data to address existing research gaps, particularly by focusing on reminiscence and life review content, incorporating VR technology, and including Asian grandparents who experience cognitive impairment.

Given the various physical, psychological, and mental health issues and instances of discrimination faced by Asian American families [5-7], this study holds significant importance. By focusing on the emotional well-being of older Asian adults, it aims to enhance their life satisfaction, positive emotions, and sense of purpose, all of which contribute to resilience and faster recovery from adversities [17], including the challenges associated with dementia diagnosis. Consequently, this study makes a valuable contribution to the limited existing literature on emotional well-being among older adults, particularly within the context of Asian American families.

Moreover, this research incorporates an innovative approach that combines the positive practice of reminiscence and life review [20-23] with an intergenerational perspective [24-26]. While intergenerational approaches involving younger and older generations have been documented in the literature [24-26], it is worth noting that no previous studies, to the best of the authors' knowledge, have applied this approach specifically to grandparents and grandchildren. This grandparent-grandchild approach holds special significance for Asian Americans, as it aligns with the emphasis placed on intergenerational solidarity between grandparents and grandchildren within their culture. By engaging in this approach, grandchildren can gain a deeper understanding of their immigrant grandparents' lived experiences, from both a historical and cultural perspective. This, in turn, has the potential to positively reshape their

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perceptions of aging and strengthen their bonds with their grandparents.

Strengths and Limitations

This mixed methods study is the first to develop and examine an intergenerational reminiscence-based intervention to improve the well-being of older adults in Asian American families with the aid of VR technology. Intergenerational reminiscence provided by grandchildren is a promising approach to improving the emotional well-being of grandparents, as VR technology is likely to be accepted by older adults. This study will help increase intergenerational closeness between grandparents and grandchildren. Findings from this study will also help health or human service providers develop programs to help Asian American families in general.

Limitations of this study include its small sample size and the absence of a control group. Future research may consider scaling up this pilot into a trackable, replicable model that includes more participants and has a more rigorous study design with a control group to test the effectiveness of this intervention for older adults with dementia. In addition, because there are wide differences between different Asian-American groups, it would be better to focus on only one Asian ethnic minority for one research project and compare the differences within that ethnic Asian group. Lastly, this protocol is proposed for in-person interactions between grandparents and grandchildren. Due to the risks and feasibility of conducting an in-person intervention during COVID-19, this project had to be tailored to a telephone-based approach. Future studies may consider comparing the effectiveness of interventions delivered as in-person meetings versus those that use a telephone-based approach.

Conclusions

Intergenerational reminiscence programs have the potential to foster social connection and engagement between grandparents and grandchildren within Asian American families. These programs also serve as a means for grandchildren to gain a deeper understanding of the life experiences of older adults both before and after immigration. By specifically focusing on intergenerational reminiscence between grandparents and grandchildren, a valuable avenue is opened for strengthening generational bonding and relationships. This, in turn, has the potential to enhance the psychological well-being, particularly the emotional well-being, of older Asian immigrant adults residing in the United States. Furthermore, this study will contribute valuable evidence to support future research exploring the feasibility and effectiveness of using VR in interventions or programs designed for older adults with cognitive impairments.

Acknowledgments

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Data Availability

The data sets generated during and/or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

LX and AH contributed to conceptualization, methodology, and original draft preparation; LX contributed to validation, formal analysis, investigation, resources, data curation, supervision, and project administration. All authors contributed to review and editing and funding acquisition. All authors have read and approved the final version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review reports from the Rutgers Institute for Health, Health Care Policy and Aging Research, The State University of New Jersey (United States).
[PDF File (Adobe PDF File), 234 KB - resprot_v12i1e48927_app1.pdf]

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Abbreviations

BRS: Brief Resilience Scale
FSA: Fraboni Scale of Ageism
GDS: Geriatric Depression Scale
LAR: legally authorized representative
SHS: Subjective Happiness Scale
SUS: System Usability Scale
SWLS: Satisfaction with Life Scale
UTA: University of Texas at Arlington
VR: virtual reality
WEMWBS: Warwick-Edinburgh Mental Wellbeing Scales

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Protocol

Homeownership While Aging—How Health and Economic Factors Incentivize or Disincentivize Relocation: Protocol for a Mixed Methods Project

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Abstract

Background: Many factors influence housing choices among older adults, but far from all have been identified. There is little systematic analysis that has included economic factors and virtually no knowledge about the interplay among perceived costs of moving, health status, and the mobility rate of older homeowners. It is currently unclear whether economic factors influence older adults' willingness to move, and the effects of economic policies on their actual behavior in the housing market are largely unknown.

Objective: The overarching objective of the AGE-HERE project is to develop knowledge of the relationship between health and economic factors that incentivize or disincentivize relocation during the process of aging.

Methods: This project uses a mixed methods convergent design across 4 studies. The initial quantitative register study and subsequent qualitative focus group study will nurture the evidence base and the development of a national survey. The final study will synthesize and integrate the results of the entire project.

Results: Ethical approval for the register study (DNR 2022-04626-01) and focus group study (DNR 2023-01887-01) has been obtained. As of July 2023, data analyses (register study) and data collection (focus group study) are currently being conducted. The first paper based on the register data is expected to be submitted after the summer of 2023. Three meetings have been held with the nonacademic reference group. The qualitative data will be analyzed in the autumn. Based on the results of these studies, a survey questionnaire will be developed and distributed nationally during the spring of 2024, followed by data analyses in the autumn. Finally, the results from all studies will be synthesized in 2025.

Conclusions: Results from AGE-HERE will add to the knowledge base for research on aging, health, and housing and can play a critical role in guiding future policy decisions aiming to balance the housing market. Such developments may lower related social costs and support older adults to maintain active, independent, and healthy lives.

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KEYWORDS

housing market; aging-in-place; housing policy; healthy aging; mobility; housing preferences

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Introduction

Background

The aging population increases the demand for housing adapted to diverse needs that facilitates active and healthy aging [1]. However, this demand is far from met because older adults face a challenging housing market with few choices available [2]. In Sweden, the supply of newly built homes has not kept pace with the increasing demand, and municipalities experience housing shortages [2], which has a major impact on individuals as well as on economic growth. Reforms have been implemented, and further reforms have been discussed. However, the housing policy debate has largely been based on increasing housing construction rather than finding ways to make better use of the existing housing stock.

According to the public debate, older homeowners are concerned about the costs associated with moving (eg, higher rental costs, a monthly association fee, and bank policies) [3]. At the same time, the housing market is experiencing insufficient residential mobility and inefficient relocation chains [2]. However, studies on housing and health in later life seldom incorporate economic factors [4], and how such factors influence older adults' willingness to move is currently unknown. A better understanding of these relationships can play a critical role in guiding future policy decisions aiming to balance the Swedish housing market, which in turn may lower associated economic and social costs as well as support older adults to maintain active, independent, and healthy lives.

Older adults spend more time at home compared to other age groups, and therefore, it is important that the home environment is adapted to suit their needs and preferences. Thus, as people age, housing is associated with health outcomes [5-8]. For example, accessibility problems in the home may lead to injuries and social isolation, which in turn have negative health effects [9]. Yet, research on factors that contribute to residential mobility for those who wish or need to move is sparse [8]. Given that older adults represent a group with varying housing preferences and needs [10,11], more knowledge is needed to support the development of future housing policies that accommodate this heterogeneity.

Recent international research has primarily focused on relocation to residential care facilities [12-14], with disabilities and frailty as predictors of relocation [15]. Situational circumstances such as strong community ties and individual or family health, in combination with social and economic conditions, make housing decisions complex in older age [16]. Thus, negotiating relocation is described as a long process until turning points emerge [17,18]. While these studies primarily focus on the very old, a recent study using register data from the United States showed that factors such as a change in income, years living in the community, and degree of social support are important characteristics for predicting relocations among persons in early retirement age [10]. Adding to this, qualitative research from Sweden suggests that older adults start to have more active reflections regarding their future housing choices and relocations around retirement age [19]. While some studies indicate that retirement triggers actual moves [10,20], we do not know whether economic issues encourage this younger group of older adults to stay in privately owned houses longer, even though those no longer suit their needs and preferences. This knowledge is crucial, especially during times of economic uncertainty and rapid social change, as it can assist policymakers in making informed decisions that support older adults in making suitable housing choices and enhancing their overall well-being.

Turning to the economic situation on a national level, macroeconomic trends such as booms or recessions, usually measured by gross domestic product growth, are likely to influence individuals' behavior in the housing market. This might be especially true for homeowners, as they often have most of their savings invested in the house and can therefore be affected by changes related to the housing market, such as house prices and interest rates [21]. Yet, the majority of studies on this topic focus on the entire population [22] rather than specific age strata, such as older adults. One exception is a study conducted in the United States evaluating lock-in effects due to the financial crash in 2008 and a subsequent major decrease in housing prices. The authors found that the probability of downsizing for adults aged 55 years and older was higher among people with a higher loan-to-value ratio (measured by mortgage loans or value of the house) compared with owners with a lower ratio [23]. Hence, it is likely that economic fluctuations influence households differently, but how such associations develop over time and emerge in a Swedish context remains unknown.

Housing Policy Context

The AGE-HERE project focuses on homeowners aged 55 years and older. In Sweden and most other Organisation for Economic Co-operation and Development (OECD) countries, the most common form of tenure among this age group is single-family home ownership [24,25]. This age group often has most of their savings invested in their house, and other available assets are limited [21], which makes them more vulnerable to changes related to the housing market, such as interest rates or housing prices. As to other economic factors, several have been suggested to encourage this population segment to stay in their current home rather than move. The 2008 Swedish property tax reform lowered the yearly property tax on especially highly assessed property by introducing a low maximum amount, but the capital gains tax was raised from 20% to 22%. Taken together, these changes increased the incentives to stay in large houses rather than moving to smaller ones. In addition, rent control has reduced the supply of apartments, which increases the price of other types of housing, such as owner-occupied housing [3]. Hence, it is likely that the way housing is taxed influences people's relocation behavior, which calls for more research in this area.

Study Objective and Research Questions

AGE-HERE aims to develop new knowledge on relationships between economic factors and health that incentivize or disincentivize relocation among homeowners from an early stage of the aging process (55 years and older). The specific research questions are as follows:

- How did macroeconomic events during the period 1970-2016 affect relocation patterns across time for older

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homeowners of different ages? Are there different patterns of relocation depending on civil status and sex?
- In what way did the tax reform of 2008 affect the probability of moving among older homeowners?
- What economic factors predict relocation to different types of housing (eg, condominiums, owner-occupied housing, and rental apartments), taking health factors into account?
- What economic and health factors do older homeowners perceive as important when considering relocation?
- What are older homeowners' preferences and beliefs regarding the economic factors that disincentivize or incentivize relocation?
- To what extent do older homeowners report that economic factors are an important part of the relocation decision process?
- How are economic factors and health related to decisions to move among older homeowners?
- How are the questions above affected by regional differences and housing market structures?

Framework

As a starting point, we will use a framework developed by Roy and coauthors [4] to conceptualize and examine the complexity of factors associated with housing decisions in older age. Covering 6 dimensions—socioeconomic and health, built and natural environment, social, time and space, psychological and psychosocial, and housing economics—this framework is a useful tool to build ties between different research fields [26]. With this framework as the starting point, we will combine several bodies of theories used in research investigating housing decisions in older age: environmental press, migration theory, residential normalcy, and control [4].

Deciding to relocate or not is influenced by individual health factors such as functional limitations and environmental factors [4], which is in line with the environmental press theory stating that the relationship between a person and their environment (social, environment, policy) affects their well-being and behavior [27,28]. Additionally, migration theory covers several domains described by Roy et al [4] and is important to elucidate the place- and people-based push and pull factors that influence older adults' decisions to relocate, particularly after retirement [29]. For example, while investment and housing value may be important for the decision to remain in a current home, stressors such as poor health, safety concerns, mortgages, and tenure status might manifest as push factors leading to a decision to relocate. In parallel, we will draw upon theories relating to the concepts of space (ie, housing, the physical dwelling) and place (ie, a home, with personal meanings) [28]. Thus, the meaning assigned to a home impacts the decision to relocate, and moving into a new home initiates a process of recreating meaning in the new place through living there [28]. These are important aspects in the time and space dimensions as well as in the psychosocial dimension of Roy et al's [4] framework. From an economic perspective, we will use the life cycle hypothesis, which predicts that households favor smooth rather than uneven consumption over their life cycle. In line with the economic factors (eg, mortgages, relocation costs, and taxes) described as important in the framework, the life cycle hypothesis implies that older adults who view their property as part of their retirement savings would sell their property in favor of renting or moving to a smaller, less costly home (ie, to increase the possibility to consume). In addition, tax theory, specifically the principles of tax neutrality and economic efficiency [30], is relevant. For taxes to be efficient, they should be designed so they do not influence behavior (eg, consumption and investments) [30], but when diverse types of housing are taxed differently (as in Sweden), taxes will steer behavior toward types of housing with beneficial taxation. That is, in contrast to the prediction of the life cycle hypothesis described above, the Swedish tax system may disincentivize relocation, so older adults remain in their homes even if that is not what they prefer.

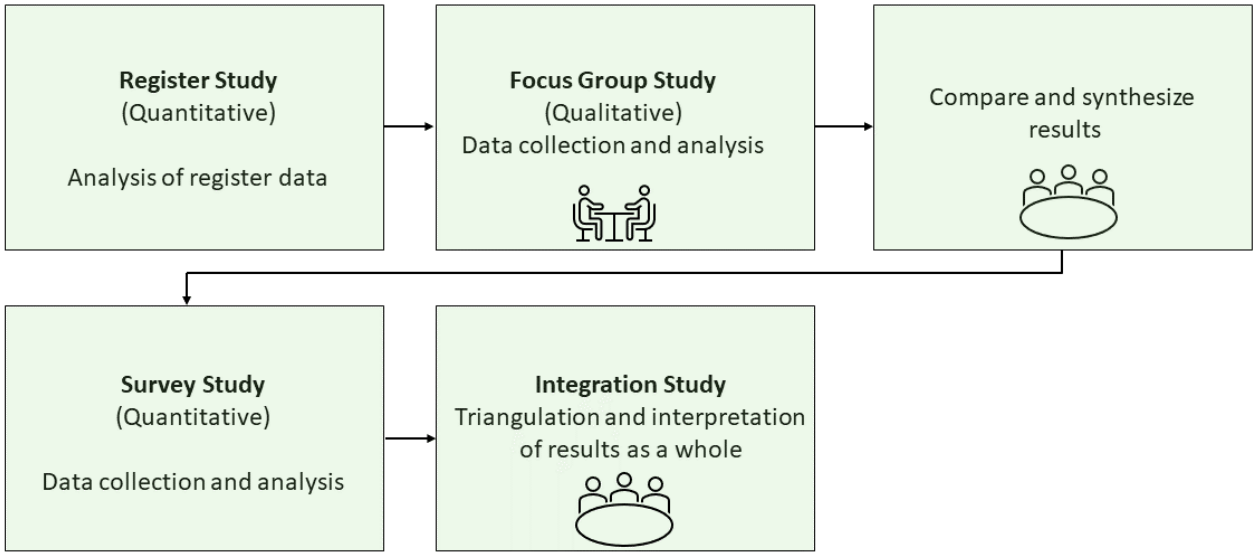
Methods

Overview

AGE-HERE has 4 parts (Figure 1): a register study, a qualitative focus group study, a national survey study, and an integration study. The project is conducted in collaboration with a reference group consisting of nonacademic partner representatives (eg, housing market experts and senior citizen organization representatives) who will provide their input and reflections throughout the research process.

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Figure 1. AGE-HERE project design; mixed methods convergent design.



Study Design

AGE-HERE has a mixed methods approach in a convergent design [31]. Results from the initial quantitative and qualitative studies will be used to develop a quantitative national survey. The final study will synthesize and integrate the results of the entire project (Figure 1).

Register Study

To investigate how macroeconomic events and taxes on property and capital gains affect relocation patterns for older homeowners, we will use data from several registers such as the Longitudinal Individual Data Base, a longitudinal database with a representative sample of the population in Sweden (N=300,000) from 1968 to 2016, and the income and taxation register, which provides information related to taxation and income for the entire population of Sweden. To analyze different factors, we will link data from the Longitudinal Individual Data Base and the income and taxation register to register data on health and housing, for example, from the property register, the population register, and the patient register.

Analysis

Tax Reform 2008

Differences-in-difference analysis [32] will be used to study the effects of the tax reform of 2008. Detailed information about taxes and income sources, as well as types of housing and socioeconomic variables, will be used to compare households that were affected to a large extent by the tax reform, that is, those living in highly assessed properties (high exposure group), with those that were less affected, that is, those living in properties worth less (low exposure group). The differences in the number of moves between the high and low exposure groups 2 years prior to the reform (2006) with the differences in the number of moves in the same groups 2 years after the reform (2010) will be compared. As this is not a randomized experiment, 3 methods to adjust for potential systematic differences between the groups will be used. First, we will control for variables such as income, education level, and place of residence that may affect the 2 groups differently. Second, we will use a propensity score matching technique [33] to determine a matched comparison group. Third, we will use a regression discontinuity design to evaluate the effect of the 2008 tax reform. Because the 55 years and above age group is heterogeneous, we will investigate whether different groups are more or less sensitive to economic factors. More specifically, we will compare different subgroups such as age cohorts, retired or working, have been or are receiving sickness payments, marital status, and sex.

Macroeconomic Trends and Health Factors

To evaluate historical trends in the relocation patterns of older adults, descriptive statistics will be used. Means will be described over time for different groups of individuals, depending on age and macroeconomic characteristics for the specific year of the relocations.

To analyze how health factors influence relocation, we will use descriptive and inferential statistics such as odds ratios, mean comparisons, and multivariate regression analyses.

Focus Group Study

To explore how older homeowners reason about their current housing situation in relation to future needs and opportunities to move and what financial and health-related factors they perceive as important in such a decision-making process, data will be collected from a series of focus groups [34] in 4 municipalities across Sweden.

Selection of Municipalities and Recruitment of Participants

Four heterogeneous municipalities have been selected based on demographics (ie, proportion of older adults), local housing market structure (eg, range of housing types, price, rent levels, and new production of housing that matches the needs of older adults), and geographic location.

Participants will be recruited via senior citizens' organizations [19] and through advertisements on social media. The selection of interested participants will be based on similarities dictated by the purpose of the study [34] and heterogeneity among them

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(eg, sex, age, and living situation) to explore various perspectives. A total of 64 people will be recruited into 8 groups (ie, 2 focus groups per municipality), with 8 participants in each.

Data Collection

The interview guide will be developed based on findings from the register study, theories underpinning the project, relevant literature, and current media discourse. The groups will meet twice each, and the preliminary results from the first sessions will be used to adapt the interview guide for the second session to allow deeper exploration of the themes that emerge. If a need to contrast different perspectives emerges in the analysis, the participant constellations may change during the second session. Two moderators will lead each group: one will lead the discussions, and one will observe group interactions and listen to the discussions [34]. Sessions will be audio-recorded and last approximately 2 hours. The observing moderator will take field notes on settings and group dynamics as well as pose clarifying questions. At the end of each session, the observing moderator will give a brief summary of the core issues discussed and allow participants to comment and suggest amendments.

Analyses

We will use a constant comparative analytic framework as described by Krueger and Casey [34]. After round 2, audiotapes will be transcribed verbatim. The moderators will read the transcripts and listen to the recordings to get a feel for the dynamics of the discussions and independently code the data. This includes identifying patterns in the data and relationships among concepts. NVivo (Lumivero) will be used as it promotes transparency and validation of coding. To further enhance trustworthiness and reduce potential bias, peer debriefing meetings with all coauthors will be held throughout the analysis process [35].

Survey Study

Overview

The survey study will include a random sample of homeowners aged 55 years and older living across Sweden. In Sweden, approximately 3.71 million people are aged 50 years or older. Within this group, 2.8 million (70%) live in privately owned accommodations: 2.13 million in houses and 710,000 in condominiums [36]. Because men own their homes to a greater extent than women of older age, participants will be stratified by sex and randomly selected from the Swedish national population registry. Using a 95% CI and a margin of error of 4, we estimate a total sample size [37] of 3600 to be representative. We expect a 40%-50% response rate and will therefore draw an initial sample of 7200.

Survey Data Collection Procedures

Results from the register study and focus group study will be used to develop the survey questions in an iterative process involving the nonacademic reference group. The reference group will provide input to ensure the survey length is reasonable, the questions and response choices are clear and understandable, and the items cover the content identified in the previous studies. Sociodemographic questions and established self-rating scales on quality of life, independence, participation, and health will be integrated into the survey to explore the relationships between personal factors, health, and economic factors in decisions to relocate. The survey will be tested in a pilot with a sample drawn from the target population for the main study (n=25), and questions and procedures will be modified based on the results.

A professional survey company will be contracted for the data collection [19]. Potential participants will be sent a postal invitation, which includes a detailed description of the study and instructions for how to opt out. Participants will be able to complete the survey via the internet, using a paper form, or via telephone. Those who have not completed a web-based survey or requested a paper survey after 2 weeks will be contacted by trained interviewers who can conduct the survey using a computer-assisted telephone interview protocol. Data collection will continue until the target sample size is reached.

Analyses

Descriptive statistics will be used to analyze the demographics of each stratum and compare them with national population statistics. If results differ from the population, sample weights to match the population will be created. Weighted sample statistics will be used to describe the prevalence of reported economic incentives or disincentives, and a 2-tailed *t* test will be used to identify sex differences. Univariate and multivariate linear and logistic regression models will be used to assess associations between economic factors, health, and sociodemographic variables.

Integration Study

As a final step, toward the end of the project (in 2025), the results will be merged and interpreted as a whole [31]. The purposes are triangulation (ie, validation based on corroboration between data sets), complementarity (ie, different methods to answer related questions), and expansion (ie, data sources address different aspects of answering questions raised by other data sets) [38,39]. Using an interactive merging strategy, narrative integration and weaving, presenting qualitative and quantitative data together, and forming connections based on specific topics will be used [40]. Analysis meetings involving the reference group will be an integral part. Emerging themes will be explored and developed based on Roy et al's [4] framework, the theoretical underpinnings, relevant international or national reports, policy documents, and legislation.

Ethics Approval

Ethical approval for the register study (DNR 2022-04626-01) and focus group study (DNR 2023-01887-01) has been obtained from the Swedish Ethical Review Authority. We will adhere strictly to the Helsinki Declaration's requirements for research involving humans. Because a systematic examination of ethical considerations is also needed in the survey study, an additional ethical approval will be sought. We will make sure that project staff are trained and supervised on ethical issues, with specific attention to collecting data from older adults. In case participants have questions, contact information of the responsible researchers will be provided for the focus group study and the survey study. In the information letter to study participants, they will be informed about confidentiality and their right to withdraw from the study at any time. Informed consent will be

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obtained first after the participants have been given written and oral information on the study's purpose and what participation would entail. All data will be collected and stored in compliance with the requirements of the Ethical Review Authority and the European General Data Protection Regulation.

Results

Ethical approval for the register study and focus group study has been obtained (DNR 2022-04626-01, DNR 2023-01887-01 respectively). Data analyses (register study) and data collection (focus group study) are currently being conducted (July 2023). The first paper based on the register data is expected to be submitted during the summer of 2023. Three meetings have been held with the nonacademic reference group. The qualitative data will be analyzed in the autumn. Based on the results of these studies, a survey questionnaire will be developed and distributed nationally during the spring of 2024, followed by data analyses in the autumn. Finally, the results from all studies will be synthesized in 2025.

Discussion

Principal Findings

This project sets out to investigate how economic and health aspects influence the decision to relocate or not among older adults. By integrating theory and methods from economics and gerontology, we will identify the most influential factors in older homeowners' housing decisions. We expect that economic policies play an important role in the decision to remain in single-family homes even when the home no longer supports older adults with declining health. Furthermore, we expect this decision to also be related to a lack of affordable housing with good accessibility in the Swedish housing market. Although we specifically focus on Sweden, the project has broader geographical implications. Hence, findings can be used to inform the allocation of resources and policy decisions concerning the living arrangements and housing choices of older adults in countries where comparable housing policies are being implemented or intended.

Aging in place has become the norm for most older adults in Sweden as well as in other Western countries, which is supported by society as it is considered less costly to provide home care than care in institutions [41]. Even so, most research on housing and aging does not consider factors that incentivize or disincentivize relocation within the ordinary housing stock; instead, the focus is on people aging with disabilities or frailty, with growing needs for special forms of housing and housing adaptations [14]. Given that aging in place is far from supportive for all older adults [42], future research and policy initiatives should focus on the diverse needs of the heterogeneous aging population [43] and consider aging in the right place [44]. This is important because, with population aging, the share of older adults living with functional limitations and age-related diseases will increase [45], implying that the housing stock needs to be adapted and developed to fit the needs and preferences of this substantial population segment. The dwellings older homeowners tend to live in often have a high prevalence of environmental barriers, and older adults aging with functional limitations experience accessibility problems, which can hinder daily activities and have negative consequences for health and quality of life [9,46,47]. From a societal economic and public health perspective, it is therefore important that municipalities comply with their housing provision responsibility and create conditions for everyone to be able to live in adequate housing [48].

Most older adults in Sweden live in dwellings they purchased much earlier in their lives and are now reticent about selling [49]. This trend is similar to the majority of OECD countries [25]. For example, in the United States, homeownership rates remain unchanged after the age of 55 years [50], and this trend has been relatively stable despite the economic recession and the housing market crash in 2007 [44]. The reluctance to sell contradicts the life cycle hypothesis, which says that older homeowners would sell their property in favor of renting or moving to a smaller, less costly home to start "consuming" or using their equity to support their living costs [50]. While many factors can explain why older homeowners are reluctant to move (eg, attachment to a place), concerns about the associated costs have gained little attention. This has been highlighted by Sweden's largest senior organization, showing that every fifth senior household in Sweden has decided not to move because of the capital gains tax [49]. This means that a substantial number of moves do not happen, which in turn slows down relocation chains and reduces the housing supply for young families who are in need of a larger home.

While there are other recent reports highlighting this issue [51], no scientific efforts have so far been made in Sweden or internationally to understand this complexity in depth. Overall, there is a paucity of studies investigating associations between taxation and decisions to move. Previous studies are based on US conditions and aggregated data [52], where the property tax is local and used to finance local public services and therefore affects the choice to move. As such, the AGE-HERE register study represents a novel approach compared to existing research, as we will study the impact of taxes on housing decisions in older age using high-quality register data. The design of the Swedish property tax, which is national rather than local (and therefore does not interfere with the choice to move), allows us to test this empirically in a valid way. By linking registers with data on taxes, income, and health and using a framework based on a systematic literature review [28], we will be able to analyze a large range of factors. Adding to this, we will observe the number of relocations among older adults historically, which will provide unique knowledge on housing decisions depending on the state of the economy across time.

Turning to the focus group study, previous research conducted in 6 European countries (the United Kingdom, Germany, the Netherlands, Ireland, Italy, and Hungary) has shown that housing choices among older homeowners are highly dependent on the local housing market situation [53], which is seldom considered in research. Our approach in AGE-HERE to collect data in 4 different municipalities across Sweden will provide valuable insights related not only to the range of possible factors that influence older homeowners' decisions to move but also to the role played by preconditions in local housing markets. Local housing markets are heterogeneous and need to be considered

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by housing policymakers. For example, in some municipalities, almost the entire housing stock consists of single-family houses, which limits the possibility of moving to a smaller dwelling when needs and preconditions change. In contrast, other municipalities have a large variety of smaller dwellings, both rentals and condominiums. In terms of new production, especially forms of housing that are aimed at the older population, some municipalities have many completed and ongoing projects while others have few. It is not farfetched to believe that such diverse situations will be a huge challenge in the coming years as the share of older people will increase substantially in all municipalities. That is, housing needs will change with population aging, and therefore policymakers need to relate to this diversity of prerequisites when planning for the future.

By better understanding the living conditions of older people from their own diverse perspectives, we can promote a positive development of social relations and enhance full participation in society on an individual level. Additionally, a better functioning housing market would have positive spillover effects on the labor market because relocation chains would function better and on the financial markets because real estate prices would be adjusted, which in turn would affect households' debt levels [3]. Altogether, a better-functioning housing market will enhance not only health and well-being but also the economic performance of society.

Limitations and Strengths

AGE-HERE is conducted in Sweden, but the knowledge gained from the project is expected to be relevant for the development of housing and policies internationally. Hence, population aging is a global phenomenon, and most countries will need to adapt their housing markets to fit diverse needs and expectations.

The data collection for the AGE-HERE focus group and survey studies will be conducted against the backdrop of the COVID-19 pandemic, during a time of high energy prices and inflation. How such periodic effects may influence the data collected will be considered and discussed in all parts of the project.

Conclusions

Results from AGE-HERE can inspire future research and play a critical role in guiding policy decisions aiming to balance the housing market, which in turn may lower related social costs and support older adults to maintain active, independent, and healthy lives.

Acknowledgments

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Data Availability

The data sets generated and analyzed during the register and survey studies are not publicly available due to a data agreement between Lund University and a third party but are available from the corresponding author or data holder on reasonable request.

Authors' Contributions

MK generated the project idea, designed the project, and wrote the proposals for funding in close collaboration with all coauthors except DD. MK wrote the manuscript, assisted by SMS and DD, with critical reviews from all coauthors. DD and ÅH provided details regarding the register study. All coauthors approved the final version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review report from Länsförsäkringar.
[PDF File (Adobe PDF File), 442 KB - resprot_v12i1e47568_app1.pdf]

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Abbreviations

OECD: Organisation for Economic Co-operation and Development

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Protocol

Effects of Interventions to Prevent Work-Related Asthma, Allergy, and Other Hypersensitivity Reactions in Norwegian Salmon Industry Workers (SHInE): Protocol for a Pragmatic Allocated Intervention Trial and Related Substudies

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Abstract

Background: Workers in the salmon processing industry have an increased risk of developing respiratory diseases and other hypersensitivity responses due to occupational exposure to bioaerosols containing fish proteins and microorganisms, and related allergens. Little is known about effective measures to reduce bioaerosol exposure and about the extent of skin complaints among workers. In addition, while identification of risk factors is a core activity in disease prevention strategies, there is increasing interest in health-promoting factors, which is an understudied area in the salmon processing industry.

Objective: The overall aim of this ongoing study is to generate knowledge that can be used in tailored prevention of development or chronification of respiratory diseases, skin reactions, protein contact dermatitis, and allergy among salmon processing workers. The main objective is to identify effective methods to reduce bioaerosol exposure. Further objectives are to identify and characterize clinically relevant exposure agents, identify determinants of exposure, measure prevalence of work-related symptoms and disease, and identify health-promoting factors of the psychosocial work environment.

Methods: Data are collected during field studies in 9 salmon processing plants along the Norwegian coastline. Data collection comprises exposure measurements, health examinations, and questionnaires. A wide range of laboratory analyses will be used for further analysis and characterization of exposure agents. Suitable statistical analysis will be applied to the various outcomes of this comprehensive study.

Results: Data collection started in September 2021 and was anticipated to be completed by March 2023, but was delayed due to the COVID-19 pandemic. Baseline data from all 9 plants included 673 participants for the health examinations and a total of 869 personal exposure measurements. A total of 740 workers answered the study's main questionnaire on demographics, job characteristics, lifestyle, health, and health-promoting factors. Follow-up data collection is not completed yet.

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Conclusions: This study will contribute to filling knowledge gaps concerning salmon workers' work environment. This includes effective workplace measures for bioaerosol exposure reduction, increased knowledge on hypersensitivity, allergy, respiratory and dermal health, as well as health-promoting workplace factors. Together this will give a basis for improving the work environment, preventing occupational health-related diseases, and developing occupational exposure limits, which in turn will benefit employees, employers, occupational health services, researchers, clinicians, decision makers, and other stakeholders.

Trial Registration: ClinicalTrials.gov NCT05039229; https://www.clinicaltrials.gov/study/NCT05039229

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KEYWORDS

allergy; bioaerosols; exposure-response; health promotion; hypersensitivity; occupational asthma; occupational skin disease; psychosocial work environment; salmon processing industry

Introduction

Overview

This paper describes the protocol for an ongoing comprehensive study in the salmon industry, comprising collection of information on bioaerosol exposure and health outcomes, as well as health-promoting factors among salmon processing workers. It includes the description of an intervention trial and several substudies.

Background and Previous Research on Salmon Industry Workers

Current knowledge is sufficient to conclude that workers in the fish processing industry have increased risk of developing respiratory diseases and other hypersensitivity responses due to occupational exposure to bioaerosols (ie, bioactive molecules, including fish allergens, enzymes, microorganisms, and endotoxins) [1-3]. We previously reported on an exposure-response relationship between total protein exposure and cross-shift lung function, as well as respiratory symptoms among exposed workers [4]. In addition, we described a case of hypersensitivity pneumonitis caused by proteins from salmon muscle [5]. Impaired respiratory status has also been reported by Douglas et al [6] and Dahlman-Høglund et al [7], and the prevalence of allergy is reported to be 2%-8% [6,8]. Avoidance or reduction of hazardous exposures at the workplace is well established as a key principle for the primary prevention of occupational diseases. For individuals who have developed occupational asthma or hypersensitivity pneumonitis, delayed diagnosis and prolonged exposure may lead to further aggravation and chronification of the disease [9,10]. Early diagnosis with identification of trigger allergens is therefore of great importance.

Hand eczema, representing either an irritant or allergic contact dermatitis, is common in occupations with prolonged use of gloves and wet work [11], and such risk factors are substantial also within salmon processing [12]. Further, contact with fish products after direct contact or deposition of bioaerosols on skin may cause development of irritant contact dermatitis and protein contact dermatitis. Nevertheless, literature concerning skin symptoms within the fish processing industry is scarce [12-14].

As described above, identifying risk factors is a core activity in disease prevention at the workplace. However, there is a growing awareness of the importance of factors influencing well-being at work [15,16]. This implies a shift in focus toward health promotion and more specifically the identification of contributing psychosocial factors. That is, the individual's experience of health-promoting working conditions. To our knowledge, very few studies have so far examined the occurrence of such factors in the working environment in this industry [17].

Background on Salmon Processing and Bioaerosol Exposure

Slaughtering and processing, as well as cleaning and waste handling, generate bioaerosol exposure [4,7,13]. When entering the processing plant, the salmon is stunned before it is killed by cutting the gill arches and transferred to a water tank for exsanguination. Afterward, it is degutted and cleaned of internal organs with a scraper. The salmon is individually assessed and graded according to size and quality. Further on, it is either packed whole in boxes on ice, frozen, or transported to the fileting department. During fileting, the head and backbones are removed. Filets are processed further, depending on the desired end product, for example, removal of skin and cutting to portion sizes. The removed by-products are usually gathered and used for lower-grade foods, such as animal feed or extracted oil.

During salmon processing, bioaerosols are generated along the entire production line outlined above, for example, when water beams hit the fish or surfaces with organic matter. The amount of water used is high in order to meet hygiene requirements and to ensure good workflow. Bioaerosol exposure levels of workers depend on different factors, such as the amount of water used, production activity (number of fish per time unit), distribution mode of water (eg, type and number of water nozzles, jets, spray, high vs low pressure), techniques (manual vs mechanical), type of equipment (open or closed), and shielding for water spray.

It is important to note that fish processing workers are exposed to components that are usually removed from edible parts of the fish before they reach the consumer. Therefore, the importance of specific proteins and epitopes causing allergic sensitization or inflammatory reactions in the occupational setting may be different from what we know from food allergies,

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where many proteins are denaturized through food preparation and digestion [18].

Rationale of the Study

Total avoidance of exposure to bioaerosols during salmon processing is not feasible; thus, reduction of exposure is considered the best approach. This is in accordance with the recommendation from the Fifth International Fishing Industry Safety and Health Conference (IFISH5) in 2018 [19] that seafood processing activity that generates excessive bioaerosols must be reduced. To our knowledge, no intervention studies aiming at reducing bioaerosol exposure have been carried out in the salmon industry.

Control measures that aim at reducing bioaerosol generation or increasing bioaerosol elimination are interventions assumed to be efficient in decreasing bioaerosol exposure. Accordingly, the arms of the intervention study that will be described later represent different intervention categories.

Proper exposure assessment, including characterization of bioaerosols, is a prerequisite for establishing preventive measures. Lack of data on the associations between exposure levels and health outcomes has so far prohibited the establishment of occupational exposure limits. A recent European Academy of Allergy and Clinical Immunology (EAACI) position paper [2] addresses the lack of concentration-response data to set internationally accepted occupational exposure limits for airborne food allergens. Also, the progression from allergen exposure to hypersensitivity responses and development of lung diseases, contact dermatitis, and protein contact dermatitis involves a continuum of measurable molecular events, including nonspecific inflammation and immunological responses. More knowledge on mechanisms behind the exposure-induced health outcomes might provide an opportunity for future applications, such as biomarkers for early prediction of disease.

Knowledge on which indicators of health-promoting work environments are present in processing plants in the salmon industry, as well as demographic differences in the perception of health-promotion factors, is lacking. This knowledge is needed both to increase the awareness of and support future health-promoting strategies in this industry.

Aims of the Study

The overall aim is to identify effective and feasible interventions to reduce the exposure to airborne bioaerosols, thereby preventing the development or chronification of respiratory diseases, skin diseases, and allergies among salmon processing workers. Substudies aim to identify and characterize clinically relevant exposure agents, to identify determinants of exposure, and to measure the prevalence of work-related symptoms and disease. Also, the exposure-response relationship between the exposure to individual bioactive agents in bioaerosols and the prevalence of airway symptoms, altered lung function, skin symptoms, and immunological responses indicating hypersensitivity will be investigated. Finally, substudies that aim to identify factors that contribute to a healthy psychosocial work environment in the different processing plants will be conducted.

The data collection will serve multiple stakeholders, ranging from employees, employers, and occupational health and safety personnel to researchers, clinicians, decision-makers, and authorities. Bioaerosol-reducing measures will be assessed, and the most effective approach will be recommended to the industry. In addition, data on exposure characterization, development of better diagnostic tools, follow-up of health examination and symptoms, and the perceived work environment will give new knowledge to basic, clinical, and translational research.

Methods

Study Setting and Study Personnel

The study population comprises salmon processing workers from 9 processing plants along the Norwegian coastline, 3 in each of the included geographical areas. The plants are situated in rural areas in western Norway (surrounding area of up to 110 km from Bergen), mid-Norway (up to 190 km from Trondheim) and northern Norway (up to 400 km from Tromsø). The processing plants vary in size, production volume, technology, and number of departments. In some plants the processing line is localized in 1 building, while in other plants the processing steps are separated and localized in several buildings. This can affect both ventilation and other technical solutions which in turn can affect generation and removal of bioaerosols. In some of the factories the processing workers tend to be specialized in specific parts of the processing line (eg, slaughtering, degutting, fileting, and packing), while in others the workers take part in all processes. Shift plans vary in terms of duration of work and breaks. A detailed description of the individual plants, job categories, and tasks will be published in a separate paper.

Study personnel for the fieldwork to gather exposure and health data comprise personnel from the university hospitals and universities of Bergen, Trondheim, and Tromsø. They are competent in occupational hygiene, medicine, nursing, biotechnology, biomedical laboratory science, or sociology, and mainly participate in fieldwork at plants within their own geographical region. Those carrying out health examinations underwent specific training according to study protocols that had been developed within the project group in collaboration with external clinical specialists and in line with national and international guidelines and recommendations. In order to minimize variability in testing techniques, individual study personnel are dedicated to 1 type of health examination whenever possible, and we aim to keep the same personnel within the geographical region and between baseline and follow-up fieldwork.

Data

Overview

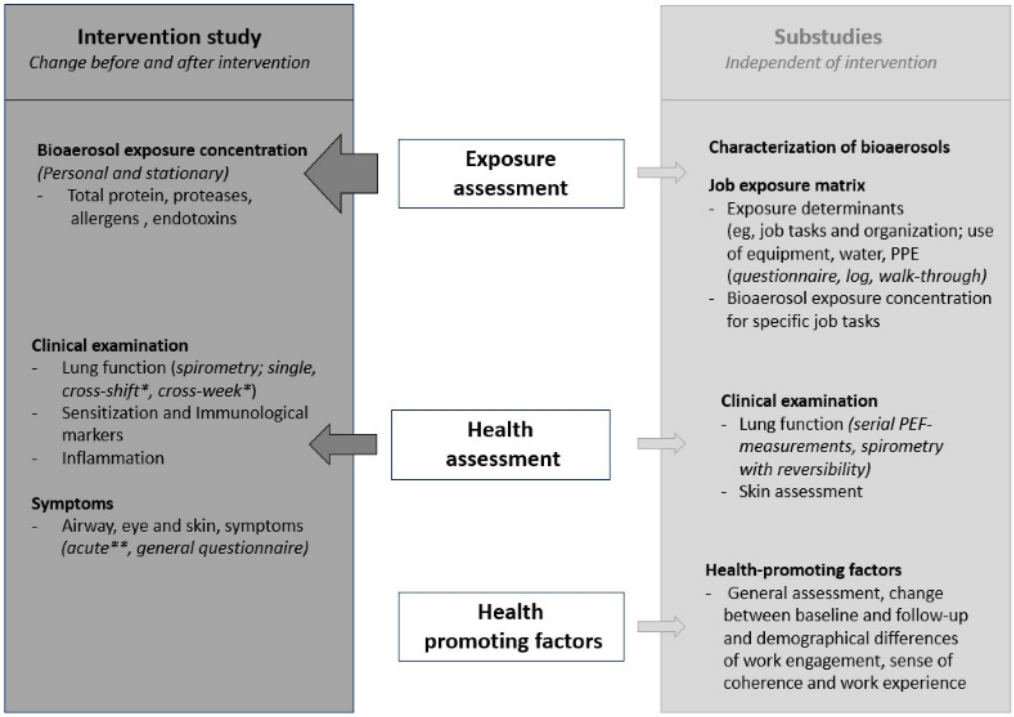
This study consists of an intervention trial and related substudies. It will gather extensive information about bioaerosol exposure, health, and work environment for workers in the salmon industry. Fieldwork is carried out at 2 time points that are related to the intervention study: a baseline visit (T_1) and a follow-up visit (T_2). The visits include exposure measurements,

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questionnaires, and health examinations, described in more detail below.

For an overview of this comprehensive study, see Figure 1.

Figure 1. Overview of the study with its core, the intervention trial (left side), and its substudies (right side), covering the main topics (middle). Change in health-promoting factors are not part of the intervention study. *Cross-shift and cross-week examinations to be carried out with the same individual before and after shift on Monday and after shift on Thursday; **acute questionnaires to be filled out by the same individual before and after their shift, registering possible symptoms before and during their shift, as well as work tasks. PEF: peak expiratory flow; PPE: personal protective equipment.



Exposure Assessment of Bioaerosols

Sampling Strategy

Full shift personal exposure measurements of airborne bioaerosols are collected in the workers' breathing zone at both T_1 and T_2. Workers are selected based on their work tasks with the aim of covering different areas of the production process. Within each plant, we aim to include 5 job groups in the exposure assessment: workers from slaughtering, fileting, packing, the laboratory or technical department, and the central control room or administration. For the cross-week measurements, 12 workers carry a backpack with personal measuring equipment on Monday and Thursday containing 3 pumps, each connected to a filter containing a sampling head in the workers' breathing zone. The filters are analyzed for inhalable protein, inhalable protease enzymes, fish allergens, and endotoxins. On Tuesday and Wednesday, 12 other workers carry 2 pumps whose filters are analyzed for inhalable protein, inhalable protease enzymes, and fish allergens. Workers register work tasks performed while wearing the backpack, in addition to breaks and other time away from the production area.

Stationary exposure measurements for bioaerosols are performed on Tuesday and Wednesday for a minimum of 6 hours during production. Sampling pumps are placed in plastic containers close to one of the following 3 work stations: cutting of gill arches, degutting, and trimming of filets in plants with filet departments. The filters are analyzed for inhalable protein, inhalable protease enzymes, fish allergens, and endotoxins.

Culturable bacteria and fungi are collected using a microbiological air sampler adjusted to sample 100 L and 250 L or 250 L and 500 L of air. This is done on Tuesday in close proximity to the 3 locations in each plant where the stationary bioaerosol measurements are located.

Temperature and relative humidity are registered every 15 minutes in selected areas of the processing plant throughout the week of data collection using direct reading instruments. The instruments are placed centrally in rooms with salmon production, away from sources of heat or cold.

Analysis of Bioaerosols

Personal and stationary bioaerosol samples are collected and analyzed for inhalable total protein (μg/m^3), inhalable protease enzymes (ng/m^3), fish allergens (as total dust; ng/m^3), and endotoxins (as total dust in endotoxin units; EU/m^3).

Inhalable protein will be quantified by bicinchoninic acid (BCA) assay [20]. Inhalable enzymes will be quantified by zymographic assay [21]. The amount of allergen will be monitored using targeted proteomic analysis using a high-throughput Q Exactive liquid chromatography–mass spectrometry (LC-MS) system [22]. Endotoxin samples will be analyzed using recombinant factor C (rFC) assay [23]).

To identify known and novel allergens, extracts from these filters will be separated by sodium dodecyl-sulfate polyacrylamide gel electrophoresis (SDS-PAGE) and subjected to immunoblotting using sera from workers with immune

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globulin E (IgE) reactivity to salmon (>0.1 kU/L). Antibody binding will be graded and presented in allergograms.

Identification of microorganisms to species level will be collected from area sampling on growth media. Quantification and identification of bacteria and fungi will be performed using matrix-assisted laser desorption and ionization-time of flight mass spectrometry (MALDI-TOF MS) as described by Madsen et al [24].

Determinants of Exposure

Determinants of exposure are factors that directly or indirectly affect the environmental concentration of the agent of interest. To register relevant information on potential determinants of exposure to bioaerosols (inhalable protein, allergen, enzymes, and endotoxins) a walk-through survey and meetings with the management during fieldwork to gather technical and process-related information will be performed. In addition, workers carrying the sampling devices will be asked about job tasks performed, number and duration of breaks, and any incidences thought to affect exposure.

Questionnaires

There are 2 types of self-administered questionnaires. The main questionnaire includes questions on demographics, background data regarding health and previous job history, smoking habits, department and job tasks, exposure determinants, respiratory and skin symptoms, allergies, and health-promoting factors. All employees present at work during the T_1 and T_2 visits are intended to be invited to answer this form. Repeated short questionnaires regarding work tasks and acute symptoms from the airways, nose, eyes, and skin will only be filled out by workers carrying out personal exposure measurements.

Questionnaires are available in Norwegian, English, Polish, Lithuanian, Slovakian, and Romanian. A Russian version of the main questionnaire is made available at T_2. Validated questions were used whenever possible. For further information, see the “Health Assessment” section.

Distribution of main questionnaires is done either by study personnel, contact persons, or other plant staff, depending on the plant. Those who participate in health examinations usually receive their questionnaire at this time point.

Health-Promoting Factors

Health-promoting factors in the salmon processing industry are assessed in the main questionnaire using a compilation of standardized questionnaire-based instruments, including the Utrecht Work Engagement Scale (UWES) [25], Work-related Sense of Coherence Scale (Work-SOC) [26-28], and Work Experience Measurement Scale (WEMS) [29,30].

Health Assessment

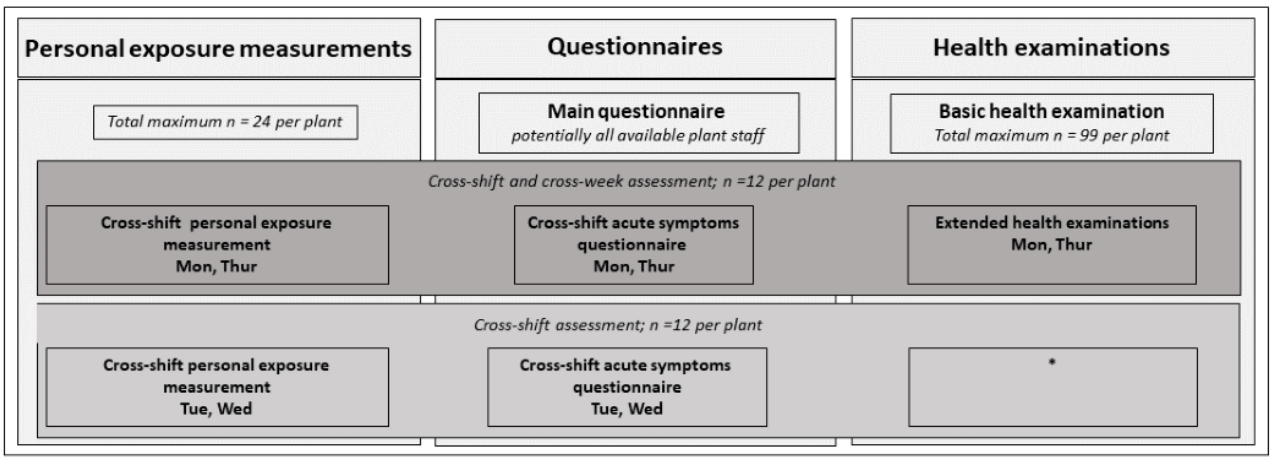
Due to logistical constraints, a maximum of 99 workers at each processing plant are invited to participate in health examinations. They are prioritized based on their work tasks, with production workers being the main focus. For the T_2 measurements, the plants are asked to aim at recruiting workers that participated in the first round when possible. Before the health examinations, participants are to fill out a form ruling out contraindications to examinations and to register their postal address so that pathological findings can be sent directly to the participant.

Health Examinations

Overview

The basic health examinations include skin prick test, spirometry, and blood samples. Workers participating in personal exposure measurements on Monday and Thursday undergo extended health examinations with cross-shift and cross-week assessments that include repeated spirometry, extended and repeated blood samples, and short questionnaires regarding acute symptoms (see Figure 2). Workers participating in personal sampling on Tuesday and/or Wednesday can or cannot undergo basic health examinations, depending on their preference. Health assessments are described in more detail in the following sections.

Figure 2. Overview of the different modes of data collection for both baseline and follow-up visits. Main questionnaires are to be filled out by all available plant staff, whereas exposure measurements and health examinations are restricted in number. All individuals carrying out cross-week exposure measurements on Monday and Thursday also undergo basic health examinations. *These staff carry out cross-shift exposure measurements on Tuesday and Wednesday; they can or cannot undergo basic health examinations.



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Lung Function

Spirometry, including forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC), is performed as recommended in the American Thoracic Society and European Respiratory Society guidelines [31]. In one of the geographical areas, it is intended to perform a reversibility test in a subsample of participants with abnormal lung function at T_2. In addition, subsamples of about 80 participants with work-related lower respiratory symptoms and 20 participants with no respiratory symptoms from 6 plants are asked to perform serial peak expiratory flow (PEF) measurements for 4 weeks at least 4 times a day. The PEF data will be interpreted with the Occupational Asthma System (OASYS) software [32].

Respiratory Symptoms

Information on symptoms from the lower and upper airways in general, during the past week, or during the past 12 months are collected through the questionnaires comprising standardized questions on respiratory symptoms, allergic status, and malaise from the European Community Respiratory Health Survey (ECRHS). Participants wearing bioaerosol sampling equipment also answer questionnaires on acute symptoms from eyes, upper and lower airways modified from Wasserfallen et al [33] before and immediately after ending the work shift [34].

Hand Eczema and Urticaria

Symptoms of hand eczema and urticaria are assessed through the Nordic Occupational Skin Questionnaire (NOSQ-2002). In 1 of the 3 geographical areas, scoring of hand eczema using the Hand Eczema Severity Index (HECSI) [35] is carried out, and skin barrier function (degree of hydration) is assessed measuring transepidermal water loss (TEWL) [36].

Immunological and Inflammatory Markers

Blood samples are collected for determination of high-sensitive c-reactive protein (CRP), total IgE, as well as specific IgE in a pooled screening test of common inhalant allergens (1 for birch, timothy grass, mugwort, alternaria, and cladosporium, and 1 for cat, horse, dog, mites, and rabbit), as well as IgE against salmon, cod, *Anisakis simplex*, and shrimp. As part of the extended health examinations, peripheral blood leukocytes (total and differential count of lymphocytes, eosinophils, and neutrophils), and CRP are assessed cross-shift and cross-week (Monday and Thursday).

Skin prick tests are performed, including commercial tests for seafood components as well as in-house study-specific extracts from salmon components, to map immunological responses to common seafood components that workers are exposed to. The 10 substances tested comprise commercial cod and salmon with its positive and negative controls, as well as study-specific extracts made in the Tromsø laboratory (2 negative controls, raw muscle, mucous from skin, skin, and cooked muscle).

Figure 2 summarizes the different modes of data collection during fieldwork. For questionnaires and registration cards, see Multimedia Appendix 1. More details on different analytical methods and health assessments will be described in detail in future publications regarding the specific topics.

Specifics for the Intervention Trial

The core of the study is a pragmatic parallel group, 3-arm nonrandomized multicenter superiority trial with a 1:1:1 allocation ratio (ClinicalTrials.gov NCT05039229).

Eligibility and Exclusion Criteria for Individual Participants

All workers employed in, and present at, the processing plants at baseline (T_1) and follow-up (T_2) are eligible for answering the self-administered questionnaire. The numbers of invitees for health examinations and individual exposure assessments are limited to a maximum of 99 and 24, respectively, per plant, owing to logistical, financial, and time constraints.

Pregnant participants are excluded from skin prick testing and spirometry, while persons with a history of heart attack or surgical interventions in the eye, stomach, or chest within the preceding 3 months are excluded from carrying out spirometry testing.

Intervention Groups and Content of Intervention Follow-Up

Overview

While the control group will not receive any intervention, there are 2 different intervention arms that imply measures with the potential to reduce bioaerosol exposure for the employees. These intervention arms represent a general intervention category in which details for the actual intervention are to be developed in collaboration with the factory management and staff. Their involvement ensures local knowledge, including local-specific characteristics, specific location of intervention, other ongoing projects, operation plans, or other aspects that are important to achieve a high effect of intervention measures.

The following sections describe possible alternatives for interventions.

Nozzles Intervention

Nozzles intervention (NZ) is a technical intervention targeting alteration of nozzle types, numbers, or nozzle function along the production line, for example, by manipulation of nozzle dimensions, alteration of operating pressure, or shielding of the nozzle's output stream.

Cleaning of Surfaces Intervention

Cleaning of surfaces intervention (CS) is a behavioral or technical intervention related to cleaning of the workers' personal operating areas (work benches and part of production lines) during work operations or while cleaning floor areas during production hours. This can include increased use of swabbing instead of flushing with water hoses or alterations in use of water hoses for cleaning. Examples for the latter are a reduced flushing frequency, reduction of number of employees executing the work, alterations of hose dimension, or nozzles on hoses.

Control Group

For the control group work is to be carried out as usual without any intervention measures.

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Interventions in the NZ and CS groups were to be started between 5 and 8 weeks after baseline measurements at time point T_1. The weeks between T_1 and T_2 are hereafter called "intervention weeks." All 3 arms are followed up in the same way between T_1 and T_2. This includes regular contact by phone or email and 1 physical meeting in intervention weeks 31-36. This midway meeting has a scheduled agenda addressing evaluation of baseline fieldwork, suggestions and input for follow-up fieldwork, status of potential technical changes in the plant, as well as assessment of adherence and employees' experiences of the intervention and study participation.

Adherence to the Trial Protocol and Concomitant Activities

Regular contact, midway meetings, and postintervention measurements are one way of increasing adherence in the intervention groups. Local staff involvement in the eventual design of the intervention also has the potential to increase adherence, especially when behavioral changes are part of the intervention.

Although it was expressed to the plants' management that it is desirable to not engage in any other technical or behavioral changes that could affect the study, there are no restrictions regarding concomitant activities during the study period.

Recruitment of Processing Plants and Individual Participants

Participating plants were recruited through earlier collaboration and by establishing new contacts based on regional knowledge about existing factories.

Each plant has a designated contact person from their own staff who helps with recruitment of individual participants and organization and logistics related to fieldwork at T_1 and T_2; this person keeps in contact throughout the intervention period.

Timeline

Participating factories were recruited during time of funding application. A visit at time point 0 (T_0), 1-3 weeks before baseline measurements at T_1, was used for detailed mapping of the specific factory's infrastructure, a walk-through of the facilities, and for recruiting individual participants through information meetings and distribution of information material. Allocation of intervention groups was done based on this mapping and communicated to the factories in a meeting with company, employee, and safety representatives during the week of baseline measurements at T_1. The companies then had time to discuss details of the intervention activities internally until the expected implementation period (intervention weeks 5-8).

Individual participants are enrolled with individual consent forms for both health examinations and questionnaires. T_1 and T_2 measurements were scheduled within 1 working week (Monday through Thursday). The interval between T_1 and T_2 is set to be 12 months (plus or minus 2 weeks).

Table S1 in Multimedia Appendix 2 gives an overview of the timeline of the intervention study.

Assignment of Intervention

Randomization of intervention arms was not feasible because of different premises of plant infrastructure. The participating plants were therefore allocated to the study arms by the project group, based on meetings and discussion with the local staff and management, and aiming at covering all 3 study arms in each region. Criteria that were taken into account for allocation to a specific arm were prestudy status of awareness and compliance of bioaerosol-reducing behaviors and technical installation, such as use of swabbing; flushing of work areas during work shifts; number, type, and shielding of water nozzles; water pressure; ventilation system; and plans for any alteration of these factors within the study period.

Allocation concealment and blinding was not relevant for obvious reasons.

Data Collection and Management

Database

Study data are collected and managed using REDCap electronic data capture tools hosted at the University Hospital of North Norway (UNN) [37,38]. REDCap is a secure, web-based software platform designed to support data capture for research studies; it provides (1) an intuitive interface for validated data capture; (2) audit trails for tracking data manipulation and export procedures; (3) automated export procedures for seamless data downloads to common statistical packages; and (4) procedures for data integration and interoperability with external sources. The main questionnaire and the questionnaires on acute symptoms are filled out in a self-administered paper form and consecutively scanned into the REDCap database. Analysis results on occupational exposure, inflammation markers (blood), skin examinations, skin prick tests, and spirometry will be put into the system by import or manual plotting.

We use the automatic quality check inherent in REDCap, including checking that critical variables have been entered, checking that the participant has consented, and performing range checks and inspection of outliers. Visual data checks are performed for 10% of the manually plotted data in order to identify transcription errors (skin prick tests and lung function measures). Exposure measurements, differential counts, CRP, and IgE are visually checked (100%) after transfer to Excel (Microsoft Corp) sheets. Excel sheets are imported into RedCap and 10% are checked after this process. In addition, 10% of the main questionnaires that are scanned and directly imported into REDCap will be visually inspected and adjudicated.

The database is administered at UNN and will comprise all the original data from T_1 and T_2, in addition to metadata and syntaxes (statistical coding) for generated variables. Only a limited number of researchers will have access to the data, as well as have permission to do data entries and corrections.

Biobank

Biological specimens (serum and plasma) are transferred and stored in a pseudonymized form in a project specific biobank at UNN for later analyses.

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Data Management Group

The project has established a data management group comprising of the principal investigator and leaders of the 6 work packages (WPs). If not covered by the group of WP leaders, each center is represented by up to two other researchers. The data management group will ensure that the publication plan covers the research questions in the protocol, handle applications of data and biomaterial, and make sure that the data management in the project is in compliance with the approvals from the ethical board and General Data Protection Regulation (GDPR). A data management plan further describes data security issues and ethics regarding data management.

Ownership and Use of Data

As this project is a multicenter study, an agreement of ownership and use of data has been completed among the 3 study centers. Agreements between the 3 study centers and the participating plants, ensuring mutual commitment to its collaboration, have also been signed. All data will be archived for 10 years after study termination. Extension of data archives beyond 10 years must seek special approval by the Norwegian ethical committees.

Data Access

The participant-level data set will not be available for public access owing to the GDPR. Metadata and statistical codes (syntaxes) beyond those reported in publications will be available upon reasonable request.

Ethics Approval

This research is carried out in compliance with the Helsinki Declaration of 1975 as revised in 2000, and has been approved by the Regional Committee for Medical Research Ethics North Norway (REK Nord No. 175081). Written, informed consent is obtained from each participant before participation. The consent forms emphasize the right to withdraw from the study at any time without explanation, and that the participants may at any time request that their biological material be destroyed. Information about the study was given orally in an information meeting at T_0 and orally and in written form during fieldwork (T_1 and T_2), with the opportunity to ask questions on-site. Personally identifiable data are entered and analyzed in pseudonymized form by replacing the name with a project-specific identification code, ensuring personal confidentiality. Only the principal investigator and co–principal investigator are given access to a code key that is stored electronically with 2-factor authentication on a safe server at UNN. All personal data will be handled in accordance with GDPR.

The project protocol will ensure that findings reported back to the participants will be analytically valid, clinically significant, and actionable [39,40]. Abnormal lung function measurements, positive skin prick tests, and IgE for salmon-related proteins, and white blood cell count substantially outside the normal range, as well as abnormal white blood cell distribution will be reported back to the participants.

There are ethical concerns related to the common use of workers from outside Norway hired from temporary staff recruitment agencies, as workers with occupational health issues discovered in the project may be lost to follow-up. We will try to avoid this by giving appropriate information at a personal level. All data collection and result analyses will be performed or supervised by experienced investigators trained in good ethical research practices. Scientific and popular scientific publishing will follow the ethical standards for coauthorship and publishing.

Statistical Analysis

Sample Size and Power Analysis

Statistical power was estimated according to the primary outcomes of the project: the change in exposure to inhalable total protein in the breathing zone before T_1 and after T_2 and implementing exposure-reducing interventions in the participating salmon processing factories. A previous study in the Norwegian salmon industry reported a geometric mean exposure of total protein in the processing areas of 2.7 (range 0.76-12.62) μg/m^3 [4]. The study was based on 273 exposure measurements, making it the most extensive study available on assessment of the concentration of total proteins in the salmon processing workers' breathing zone. The crude data allowed us to estimate the corresponding arithmetic mean exposure of total protein (10.0, SD 5.8 μg/m^3). Based on these data we estimated that with a significance level of .05 there is a power of 80% of finding a 40%, 30%, and 20% reduction of exposure in 1 intervention arm if we include 34, 59, and 133 measurements in each of the groups, respectively. Since baseline measurements are performed at all sites before intervention, there will be an even higher statistical power given that we can adjust the exposure levels after intervention for mean baseline values at each site. Based on these calculations, we aimed at including 24 workers with 2 repeated measurements in each of the intervention groups (144 measurements in each group equals a total of 432 measurements) both at baseline and after intervention.

Analysis of Data

Detailed description of statistical analyses will be found in the respective scientific publications. In general, for parametric data displaying a normal distribution, results will be presented as arithmetic means with SDs. For data showing a skewed distribution, as is commonly found for exposure measurement data, the results will be presented as geometric means with geometric SDs. Categorical data will be presented as percentages. In case of missing variables, omission or imputation will be performed depending on the type of data.

In general, risk estimates for the various outcomes with 95% CIs will be estimated using a regression model being appropriate for the analysis in question. The estimates will be adjusted for covariates identified as potential confounders, effect modifiers, and mediators. Tests are considered statistically significant at a *P* value of .05.

Analyses related to the intervention study will be performed according to intention-to-treat, regardless of protocol adherence. Results will be reported in line with CONSORT (Consolidated Standards of Reporting Trials) guidelines.

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Intervention Outcomes

The primary outcome, outcome measure (OM) 1, is to evaluate the effect of the interventions (control measures) on reducing salmon processing workers' personal exposure to airborne inhalable total protein (μg/m^3) from T_1 to T_2. Differences in mean concentration of full shift measurements (8 hours) between intervention groups and between intervention groups and control groups will be analyzed.

The secondary outcome measures are the changes from T_1 to T_2 for a range of other exposure and health outcomes. Differences between intervention groups and between intervention groups and control groups will be analyzed. The following secondary outcomes will be assessed:

OM 2: Change of concentration of salmon processing workers' personal exposure to proteases (ng/m^3).

OM 3: Change in total protein (μg/m^3, inhalable aerosol fraction) from stationary measurements in relevant areas of the salmon production line.

OM 4: Change of salmon processing workers' personal exposure to airborne fish allergens, measured by concentration of total aerosol fraction of fish allergens (ng/m^3).

OM 5: Change of salmon processing workers' personal exposure to airborne endotoxins (EU/m^3).

OM 6: Change in salmon processing workers' self-reported symptoms from the upper airways.

OM 7: Change in salmon processing workers' self-reported symptoms from the lower airways.

OM 8: Change in salmon processing workers' self-reported eye symptoms.

OM 9: Change in salmon processing workers' lung function at group level (FEV_1 in percentage of predicted value).

OM 10: Change in salmon processing workers' lung function at individual level (FEV_1/FVC ratio).

OM 11: Change in salmon processing workers' cross-shift lung function (FEV_1).

OM 12: Change in salmon processing workers' cross-week lung function (FEV_1).

OM 13: Incidence of salmon processing workers' sensitization to salmon assessed by serum IgE specific to salmon proteins.

OM 14: Change in salmon processing workers' self-reported skin symptoms.

For more details regarding the intervention study, please see ClinicalTrials.gov NCT05039229.

Other Outcomes of Interest (Substudies)

In addition to outcome measures related to the intervention study itself, substudies will investigate the following:

1. Characterization of airborne bioaerosols from the work environment with respect to inhalable protein, protease enzymes, microorganisms, and microbially derived agents, as well as known and possible novel fish allergens.
2. Development of improved test extracts for seafood allergy diagnostics
3. Exposure-response relationship between bioaerosol exposure and indicators of respiratory health effects, markers of inflammation, and sensitization.
4. Identification of factors that can explain the variation in bioaerosol exposure (determinants of exposure).
5. Evaluation of prevalence and determinants of respiratory work-related symptoms and disease.
6. Evaluation of prevalence of work-related asthma by assessment of respiratory symptoms and work-related airflow limitation by serial measurements of PEF.
7. Cross-shift and cross-week changes in acute symptoms from airways and eyes, as well as inflammatory biomarkers.
8. Status of markers of inflammation and sensitization among salmon processing workers.
9. Presence of indicators of health-promoting working environments in the salmon processing industry, demographical differences in perception, and their consistency through a 1-year follow-up.
10. Evaluation of prevalence and determinants of dermatological work-related symptoms and disease.
11. Objective evaluation of hand eczema and skin barrier function.
12. Investigation of which indicators of health-promoting working environments are present in the salmon processing industry, and whether these are consistent through a 1-year follow-up.
13. Associations between employment conditions and health among migrant workers.

Participant and Public Involvement

Participants and the public have been involved in the design of and recruitment for the study by personal contact and through the reference group. They will be further involved in dissemination activities to ensure that information is given in a way that is clear and easy to understand for the different stakeholders.

Reference Group

The reference group's mandate is to ensure that the project is relevant for the salmon processing workers, is professionally sound and anchored within the industry, and that it is practically feasible and adequately prioritized. Its main role is to give advice in terms of planning, executing, and possibly adjusting the project. The group's purpose it to ensure good collaboration with those who can profit from the project's results, to root the project in the participating factories, as well as to give advice in terms of communication. The reference group does not have any responsibility for the project's progression, goal achievement, or formalities; neither does it have any authority to take decisions. It consists of members of the employer organization the Norwegian Seafood Federations (Sjømat Norge), the employee organization Norwegian Food and Allied Workers Union (Norsk Nærings- og nytelsesmiddelarbeiderforbund), the Norwegian Labour Inspection Authority, an occupational health service, 1 plant

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representative from each of the 3 geographical regions, 1 researcher from each of the project group's locations (Tromsø, Bergen, Trondheim), and the principal investigator.

Results

The study was originally planned to begin in fall 2020 but was delayed to September 2021 due to the COVID-19 pandemic. The pandemic further influenced both data gathering and company access due to access restrictions and short-notice sick leaves or quarantines. Among other consequences, this led to delays in baseline measurements, especially in the plants in mid-Norway that had carried out their baseline measurements (T_1) between March and June 2022, 3 months behind schedule.

As the study is still ongoing and data quality checking is not finished, we only have preliminary results from the baseline measurements at T_1. The main questionnaire at T_1 was answered by 740 participants. Due to uncertainties in numbers of distributed questionnaires, it was not possible to calculate a precise response rate, but we estimated its average to be 61% with a range between about 48 (31%) out of 155 and 134 (91%) out of 147. A total of 673 workers participated in the baseline health examinations. Calculating the participation rate is futile, because in several plants there was a much higher number of potential participants than there was capacity to carry out health examinations.

Exposure measurements were undertaken, resulting in over 700 personal measurements (400, 203, and 122 for protein, allergens, and endotoxins, respectively), as well as almost 150 stationary measurements (59, 51, and 34 for protein, allergens, and endotoxins, respectively).

Due to a long time frame of about 2 years between the companies' original consent to participate in the trial and the actual start of the study, technical adjustments were done in several factories before the study start. Thus, the original plan to allocate 3 plants per intervention group was not feasible. One plant planned adjustments to the ventilation system during the intervention period and was therefore not allocated to any of the original intervention groups at T_0. This left only 2 groups for the CS arm, while 3 plants each were allocated to the NZ and control group arms.

Discussion

Preliminary Principal Findings

The response rate could not be calculated precisely as the project group did not have the opportunity to distribute questionnaires personally in all plants. Also, the seafood industry is an industry heavily relying on short-time and temporary labor, making it difficult to keep track of which employees are available for inclusion at any given time, as well as to supply questionnaires in the correct language. Difficulties in calculating exact response and participation rates is a known problem in research concerning occupational health in the seafood industry [41,42], and our average is in line with earlier studies with questionnaires in the Norwegian seafood industry [43].

In general, response or participation rates have been declining steeply over the past decades. It has been suggested to report several types of rates together with careful explanations about how they were calculated, rather than reporting single numbers, in order to give a more nuanced picture of the specific study [44].

Strengths and Limitations

To our knowledge, this is the largest study on a salmon processing worker population assessing exposure to bioaerosols and its associations with respiratory and skin outcomes. Further, it is the first study to strategically test different measures of intervention for reducing bioaerosol levels.

The main strengths of the study include (1) its prospective design, with measurements of bioaerosol exposure and a range of health effects before and after implementation of exposure-reducing measures; (2) its multicenter design and provision of study material in 6 relevant languages, thereby covering a large and representative proportion of workers in the Norwegian salmon processing industry; (3) the large population size, with repeated sampling over consecutive work shifts and with a 1-year interval between measurements, which allows us to assess what affects the variability in exposure; and (4) extensive collection and analysis of active components in the bioaerosols, such as fish allergens, enzymes, and endotoxins, which will allow us to investigate which bioactive molecules and microbial agents are commonly present in bioaerosols produced during salmon processing, as well as respiratory and dermal health and health-promoting factors among salmon industry workers. The repeated measurements design allows analyses of paired samples, reducing the interindividual variation in samples assumed to show small changes in assumed healthy workers.

A special trait of the study is the combination of the assessment of work-related risk factors and work-related health-promoting factors which has so far not been done in the salmon processing industry.

For the health examinations, we cannot rule out a certain selection bias, as participation was restricted due to capacity reasons, as well as because it was voluntary. The latter could result in workers with existing health problems being more prone to participate, in order to find out more about their health, but it could also lead to refusal due to a fear of losing their job. The latter was addressed in the consent form and information meetings, emphasizing that employers of plant staff will not be informed about individual health findings. In any case, it is impossible to say in which direction this possible bias would influence results.

The lack of randomization to interventional categories is in part a weakness, but at the same time a necessary approach in order to make the study feasible. The seafood industry is in constant change and has to react quickly to challenges on the market. Therefore, it is unlikely to meet stable conditions over a longer time period, as this study confirmed. Also, as each plant's infrastructure and needs are so different, it is not feasible to allocate the plants to predefined detailed interventions. Due to limited capacity, it will only be possible to include some of the

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participants in the different health examinations, and this will hamper the interpretation of associations between the different outcomes to a varying extent.

Another weakness is the pandemic-related delay in baseline measurements at 3 of the plants, which moved the period under study forward to a timeframe with a potentially lower production rate, warmer weather, and higher probability of pollen exposure outdoors, which could affect exposure measurements, as well as symptoms in the airways and skin. In order to keep circumstances somewhat similar, follow-up measurements at T_2 are planned to be performed around the same time of the year.

All abovementioned factors will be further discussed in future publications for data from this study.

Dissemination Plan

Trial results will be disseminated to participants, the salmon processing industry, researchers, health personnel, authorities, and other interested parties through scientific conferences, publications, reports, and public dissemination measures. There are no publication restrictions, and the results will be disseminated regardless of the magnitude or direction of the effect. Authorship eligibility is determined according to the International Committee of Medical Journal Editors criteria for manuscripts submitted for publication. There is no intention to use professional writers. Data presentation will be performed in a way that ensures confidentiality for individual or workplace-specific data.

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Authors' Contributions

BEB conceived the study. All authors contributed to the design, planning, and fieldwork of the study, especially BEB, BEH, MRT, ACH, TEE, and MG as work package–leaders of the study. ACH and JK wrote the first draft of the manuscript, supported by the remaining authors.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Main questionnaire, pre- and postshift questionnaire.
[PDF File (Adobe PDF File), 264 KB - resprot_v12i1e48790_app1.pdf]

Multimedia Appendix 2
Timeline of participants and data gathering.
[DOCX File , 19 KB - resprot_v12i1e48790_app2.docx]

Multimedia Appendix 3
Peer-review reports from the Research Council of Norway (Norway).
[PDF File (Adobe PDF File), 21 KB - resprot_v12i1e48790_app3.pdf]

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Abbreviations

BCA: bicinchoninic acid
CONSORT: Consolidated Standards of Reporting Trials
CRP: c-reactive protein
CS: cleaning of surfaces intervention
EAACI: European Academy of Allergy and Clinical Immunology
ECRHS: European Community Respiratory Health Survey
EU: endotoxin units
FEV_1: forced expiratory volume in 1 second
FVC: forced vital capacity
GDPR: General Data Protection Regulation

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HECSI: Hand Eczema Severity Index
IFISH5: Fifth International Fishing Industry Safety and Health Conference
IgE: immune globulin E
LC-MS: liquid chromatography–mass spectrometry
MALDI-TOF MS: matrix-assisted laser desorption and ionization-time of flight mass spectrometry
NOSQ-2002: Nordic Occupational Skin Questionnaire
NZ: nozzles intervention
OASYS: Occupational Asthma System
OM: outcome measure
PEF: peak expiratory flow
rFC: recombinant factor C
SDS-PAGE: sodium dodecyl-sulfate polyacrylamide gel electrophoresis
T1: time point 1 of intervention trial (baseline)
T2: time point 2 of intervention trial (follow-up)
TEWL: transepidermal water loss
UNN: University Hospital of North Norway
UWES: Utrecht Work Engagement Scale
WEMS: Work Experience Measurement Scale
Work-SOC: Work-related Sense of Coherence Scale
WP: work package

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Protocol

Identifying the Characteristics of Responders and Nonresponders in a Behavioral Intervention to Increase Physical Activity Among Patients With Moderate to Severe Asthma: Protocol for a Prospective Pragmatic Study

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Abstract

Background: Previous research has suggested that most adults improve their asthma control after a short-term behavioral intervention program to increase physical activity in daily life (PADL). However, the characteristics of individuals who respond and do not respond to this intervention and the medium-term response remain unknown.

Objective: This study aims to (1) identify the characteristics of adult responders and nonresponders with asthma to a behavioral intervention to increase physical activity and (2) evaluate the functional and clinical benefits in the medium term.

Methods: This prospective pragmatic study will include adults with moderate to severe asthma who enroll in a behavioral intervention. All individuals will receive an educational program and an 8-week intervention to increase PADL (1 time/wk; up to 90 min/session). The educational program will be conducted in a class setting through group discussions and video presentations. Behavioral interventions will be based on the transtheoretical model using counseling, incentives, and individual feedback aiming to increase participation in physical activity. Motivational interviewing and guidelines for overcoming barriers will be used to stimulate individuals to reach their goals. Pre- and postintervention assessments will include the following: PADL (triaxial accelerometry), body composition (octopolar bioimpedance), barriers to PADL (questionnaire), clinical asthma control (Asthma Control Questionnaire), quality of life (Asthma Quality of Life Questionnaire), anxiety and depression levels (Hospital Anxiety and Depression Scale), and exacerbations. “Responders” to the intervention will be defined as those who demonstrate an increase in the number of daily steps (≥2500).

Results: In December 2021, the clinical trial registration was approved. Recruitment and data collection for the trial is ongoing, and the results of this study are likely to be published in late 2024.

Conclusions: The intervention will likely promote different effects according to the clinical characteristics of the individuals, including asthma control, age, anxiety and depression levels, obesity, and several comorbidities. Identifying individuals who respond or do not respond to behavioral interventions to increase PADL will help clinicians prescribe specific interventions to adults with asthma.

Trial Registration: ClinicalTrials.gov NCT05159076; https://clinicaltrials.gov/ct2/show/NCT05159076

International Registered Report Identifier (IRRID): DERR1-10.2196/49032

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(JMIR Res Protoc 2023;12:e49032) doi:10.2196/49032

KEYWORDS

asthma; behavioral intervention; physical activity; responders

Introduction

According to the Global Initiative for Asthma (GINA), asthma is a heterogeneous disease characterized by chronic airway inflammation [1]. Asthma is defined by the history of respiratory symptoms, such as shortness of breath, wheezing, chest tightness, and cough, which can vary over time and in intensity, together with variable expiratory airflow limitation [1]. Asthma is a global health problem that affects all age groups. For example, in 2019, about 262 million people were diagnosed with asthma, and 461,000 died from this disease [2]. Moreover, its prevalence is increasing, affecting up to 18% of the population in some countries [1].

Several treatments, both pharmacological and nonpharmacological, are involved in the control of asthma. A supervised, structured exercise program is a nonpharmacological treatment known to improve asthma control [3]. However, despite the proven benefits of exercise, several barriers, such as the lack of space, limited access to pulmonary rehabilitation programs, and decreased motivation to remain physically active after the completion of such programs [4], make interventions to increase physical activity in daily life (PADL) an attractive and viable option [5].

Despite the known benefits of being physically active that have already been shown in this population, individuals with asthma are less physically active than control populations [6]. For instance, a previous study demonstrated that physical inactivity and a sedentary lifestyle are the only extrapulmonary factors associated with asthma exacerbation [7]. In addition, higher levels of physical activity positively impacted the clinical outcomes in this group [6]. Consequently, it is important to develop strategies to modify behavior to increase physical activity and reduce sedentary activities in this population.

The World Health Organization (WHO) recommends that adults perform 150 to 300 minutes of moderate-intensity aerobic physical activity weekly to achieve certain health benefits [8]. In addition, international guidelines [9] and GINA [1] classify, with A-level evidence, people with asthma who engage in regular physical activity to reduce cardiovascular risk and improve their quality of life [1]. A previous study found that a behavioral intervention to increase PADL improves clinical asthma control, sleep quality, and anxiety symptoms in adults with moderate to severe asthma [5]. However, 17% of the individuals did not improve their physical activity level, and 25% did not improve their clinical control after the intervention. Individuals with other chronic respiratory [10], cardiac [11], musculoskeletal [12], and neurological diseases [13] have also been classified as better or worse responders to specific interventions.

Thus, despite the benefits obtained by behavioral intervention aimed at increasing PADL in adults with asthma [5], it is necessary to know the characteristics of responders and nonresponders to guide the management in a more personalized approach. Moreover, the effects of this intervention were only assessed in the short term (immediately after the intervention), and the medium-term effects remained unknown. We hypothesize that the intervention might cause different effects according to the clinical characteristics of the individuals, including asthma control, age, anxiety and depression levels, obesity, and several comorbidities. Therefore, the main objective this prospective cohort study will be to identify the characteristics of adult responders and nonresponders with moderate to severe asthma to a behavioral intervention to increase PADL and evaluate the functional and clinical responses in the short and medium terms.

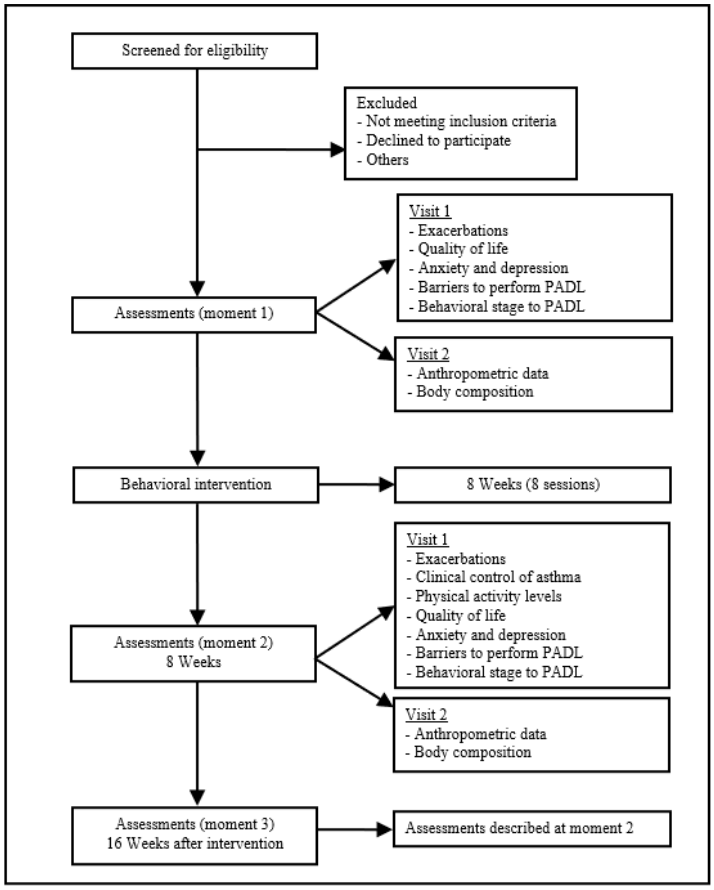
Methods

Study Design

This prospective cohort study will be conducted at a university hospital that provides specialized asthma treatment. The study protocol was developed following the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist guidelines [14], and the trial was registered at ClinicalTrials.gov (NCT05159076). The study design is illustrated in Figure 1. Individuals with asthma will be enrolled in the trial after a routine medical consultation. Baseline lung function will be checked from the medical records. Eligible participants will undergo an 8-week behavioral intervention protocol to increase PADL and reduce sedentary behavior. First, all included individuals will receive an educational program, followed by an intervention aimed at increasing physical activity. All individuals will be assessed before and after the 8-week intervention and then 16 weeks later. The outcomes assessed will include anthropometric variables, clinical asthma control, health-related quality of life, physical activity levels, anxiety and depression symptoms, exacerbations, body composition, barriers to performing PADL, and physical activity behavioral stages (Figure 1).

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Figure 1. Study design. PADL: physical activity in daily life.



Participants

The study will include both male and female adults aged 18 to 65 years with moderate to severe asthma [1] who are not physically active (<150 min of moderate to vigorous physical activity/wk [15] or ≤7500 steps/d) and have partially controlled or uncontrolled asthma (Asthma Control Questionnaire [ACQ] score ≥0.75) [16]. In addition, the following inclusion criteria will be considered: diagnosis of asthma based on the recommendations established by GINA [1], outpatient medical treatment for at least six months, and a stable clinical status for at least 30 days (no hospitalizations, visits to emergency services, or medication changes) [17]. Pharmacotherapy will be maintained throughout the intervention period. After being informed about the possible risks and benefits of the study, participants will be instructed to sign an informed consent form.

Ethics Approval

This study will be performed in accordance with the Declaration of Helsinki. Ethics approval has been granted by the Research Ethics Committee of the Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (#51929221.7.0000.0068).

Consent to Participate

Written informed consent will be obtained by researchers from all study participants.

Analysis of the Population

Exclusion criteria will include participation in another research study, difficulty understanding any questionnaires, and pregnancy or psychiatric problems that make it difficult to understand the questionnaires and study protocol. If a patient misses any session, they will be contacted by telephone to confirm the reason, and the session will be rescheduled. Attending a total of 6 sessions will be considered the cut-off point to establish patient compliance [18-20]. An intention-to-treat analysis will be performed using the patient's most recent assessment in the case of withdrawal from the study or the absence of data. The intervention will be conducted by a trained physiotherapist who is not otherwise directly involved in the assessments. In case of possible injuries occurring during the intervention period, the individuals will be referred for appropriate treatment.

Procedures

Interventions

The intervention proposed here has been previously performed for individuals with asthma [5]. All individuals will participate in a brief asthma education program with 2 sessions, each lasting approximately 90 minutes. The educational program will be conducted in a class setting in the form of group discussions and video presentations. Educational topics will include asthma pathophysiology, medication and peak flow meter use, self-monitoring symptoms, environmental hygiene [1,21], and physical activity recommendations and benefits [15].

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Behavioral interventions will be based on the transtheoretical model using counseling and incentives to increase the practice of physical activity [22,23]. Motivational interviewing, feedback, and guidelines for overcoming barriers will be used to stimulate individuals to reach their goals. Furthermore, individuals will receive a commercially available smartwatch activity monitor (Mi Band 5; Xiaomi) with an alarm that vibrates when the recommended daily number of steps is achieved and if the individual remains sedentary for 60 minutes. The main objective of the behavioral intervention will be to increase the level of PADL at any intensity, and the secondary objective will be to reduce sedentary time. The program will include 8 weekly face-to-face individual sessions, lasting up to 90 minutes each. At the beginning of the protocol, the motivational interview will identify the behavioral stage for physical activity practice using an appropriate questionnaire [24]. In addition, individuals will be asked to complete a daily physical activity diary and sign a contract with the health professional.

The data referring to the respective weeks of use will be reviewed for each behavioral intervention session. Each individual will receive advice based on their smartwatch data. Each session will address different topics related to physical activity practice and sedentary behavior, and individuals will be motivated and encouraged to make behavioral changes. In the last session, a motivational interview will be conducted to identify the individual's behavioral stage, goals achieved, benefits gained, strategies used to overcome the most significant barriers, and proposed attitudes to keep themselves physically active in the long term. The schedule and content of each session are detailed in Table 1. The protocol of Freitas et al [25] will be modified by only changing the activity smartwatch monitor used during the intervention (Mi Band instead of Fitbit) [25].

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Table 1. Description of the behavioral change intervention sessions. Reproduced from Freitas et al [25] under CC-BY License [26] . In this study, Mi Band 5 replaces Fitbit Flex 2.

No. Week	Topics covered
Week 1: Lifestyle choices	• Motivational interview to establish an educational diagnosis • Identify the behaviour stage regarding physical activity • Raise awareness of physical activity benefits • Provide the Fitbit Flex 2 and ask them to wear it for at least 3 days each week
Week 2: Why become physically active?	• Raise awareness of the physical activity international recommendations • Deepen the knowledge about the physical activity benefits for patients with asthma • Review Fitbit Flex 2 data of the past week and set one smart weekly goal (number of steps) • Establish the action planning (goal) and sign a contract • Evaluate the confidence of patients in achieving the goal (self-efficacy) • Explain about the use of the workbook, diary and vibration alert
Week 3: Sedentary behaviour	• Raise awareness of the risks of prolonged uninterrupted periods of sitting • Ask them to start monitoring their sitting time (diary in a workbook) • Discuss strategies to stand up/break up the sedentary time, according to the Fitbit Flex 2 vibration function • Review achievement (using the diary and Fitbit Flex 2 data) of the current goal • Discuss progress of the current goal • Set one smart weekly goal (number of steps)
Week 4: Dealing with barriers	• Dealing with barriers (as part of action and coping planning) • Brainstorm the main barriers and possible solutions/modifications • Discuss preferred activities • Invite participants to come up with ideas for walking (progression in duration/intensity) • Congratulate patients on any success (positive reinforcement) and ask them to reflect on any difficulties • Review achievement (using the diary and Fitbit Flex 2 data) of the current goal • Progress the current smart goal (number of steps and sedentary behaviour)
Week 5: Self-control	• Facilitate self-control (how to self-monitor the negative and positive behaviours regarding PA) • Identify the benefits acquired with the lifestyle change and reinforce the commitment to change • Invite participants to come up with ideas to break up the sedentary time • Review achievement (using the diary and Fitbit Flex 2 data) of the current goal • Progress current goal(s) as able/required
Week 6: Setting additional goal	• Review initial goal and discuss the progress of this goal (challenges) • Evaluate the confidence about achieving the new goal (self-efficacy) • Reinforce the health benefits of increased participation in PA and of breaking up sedentary time • Congratulate any success and reflect on any difficulties • Review achievement (using the diary and Fitbit flex 2 data) of the current goal • Set a new smart goal as able/required
Week 7: Being rewarded	• Identify the behaviour stage regarding physical activity • Discuss the change (or not) that was achieved, as well as the benefits acquired with the new lifestyle • Discuss positive reinforcement • Review achievement (using the diary and Fitbit flex 2 data) of the current goal • Set a final goal (number to steps)
Week 8: Goal balance	• Final motivational interview (goal setting, benefits acquired and strategies to overcome barriers) • Reinforce the importance of following through with these changes • Establish a long-term goal to stay physically active

Participant Timeline

The schedule of enrollment, interventions, and assessments is outlined in Table 2. The recruitment of the study participants began in May 2022.

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Table 2. Content for the schedule of enrollment, interventions, and assessments.

	Time point				
	Enrollment	Allocation	Postallocation		
	$-t_1$	0	Baseline	8 Weeks	16-Week follow-up
Enrollment					
Eligibility screen	✓				
Informed consent	✓				
Allocation					
Interventions:					
Behavioral intervention				✓	
Assessments:					
Lung function			✓		
PADL[a] and sedentary behavior	✓			✓	✓
Asthma Control	✓			✓	✓
Asthma exacerbations			✓	✓	✓
Quality of life			✓	✓	✓
Anxiety and depression			✓	✓	✓
Barriers to perform PADL			✓	✓	✓
Behavioral stage for PADL			✓	✓	✓
Anthropometric data			✓	✓	✓
Body composition			✓	✓	✓

[a]PADL: physical activity in daily life.

Outcome Measures

The primary outcome will be PADL (the number of steps per day) using an activity monitor (by actigraphy). Secondary outcomes will include clinical asthma control, quality of life, body composition and anthropometric data, anxiety and depression levels, asthma exacerbations, physical activity barriers, and behavioral stages for physical activity. This will be a single-blinded (outcome assessor) study in which assessments will be performed before, immediately after, and 16 weeks later.

Primary Outcome: PADL

PADL will be objectively assessed using an activity monitor (ActiGraph GT9X), a device that monitors frequency, intensity, and duration [27] in real time and is considered a sensitive and reliable method [28,29]. This triaxial monitor provides measurements of the amount and intensity of PADL and the monitoring of posture [27,30] through variations in acceleration. The "counts" obtained in a given period of time are linearly related to the intensity of the patient's physical activity in this period [29]. Individuals will be instructed to use the accelerometer, attached to the hip using an elastic belt, for 7 consecutive days. All accelerometers will be initialized to collect data in 60 "epochs" on the 3 axes using ActiLife (version 6.9.5; ActiGraph) software. The following data will be later analyzed using the same software: the number of daily steps and the time spent in sedentary, light, moderate, and vigorous states of activity. Moderate to vigorous physical activity will also be evaluated. Sedentary behavior will be assessed using the same activity monitor.

Secondary Outcomes

Asthma Clinical Control

Clinical asthma control will be assessed using the ACQ, a reliable and validated tool [16,31] that comprises 7 questions [16]. Five questions are related to asthma symptoms (waking up at night, activity limitation, shortness of breath, and wheezing), 1 question is related to rescue medication (short-acting β_2-agonist use), and 1 question is related to lung function (forced expiratory volume prebronchodilator, in percentage of predicted). The questions are scored on a 7-point scale ranging from 0 (no limitation) to 6 (maximum limitation), and the total score is the average of the 7 items, ranging from 0 (totally controlled) to 6 (severely uncontrolled). A cut-off value ≥1.5 indicates poorly controlled asthma, 0.75-1.5 indicates partially controlled asthma, and ≤0.75 indicates fully controlled asthma [16]. A change of at least 0.5 points in the ACQ score is considered clinically significant [32].

Asthma-Related Quality of Life

Health-related quality of life will be evaluated using the Asthma Quality of Life Questionnaire (AQLQ) [33,34]. This questionnaire consists of 4 domains that assess the last 2 weeks: activity limitation, symptoms, emotional function, and environmental stimulation. The AQLQ score ranges from 0 to

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7; the higher the score is, the better the quality of life. A difference of 0.5 points is considered clinically significant [35].

Body Composition and Anthropometric Indexes

Octopolar InBody 720 equipment (Biospace) will be used. The weight, fat mass, fat-free mass, visceral adiposity area, and skeletal muscle mass will be calculated. The InBody 720 uses 8 electrodes to assess body composition according to total body water, proteins, minerals, and fat mass. The contact points to connect the electrodes will be cleaned with an electrolytic cloth, according to the manufacturer's instructions. Data will be electronically imported into Microsoft Excel using Lookin'Body 3.0 software (Biospace). Anthropometric data, including height, body weight (Filizola), abdominal, waist, and hip circumference, and waist-to-hip ratio will be measured according to standardized protocols [36,37]. BMI will be calculated by dividing body weight (in kg) by height (in m^2) [38].

Anxiety and Depression

The Hospital Anxiety and Depression Scale (HADS) will be used to assess anxiety and depression symptoms [39]. The HADS is composed of 14 questions divided into 2 subscales, anxiety and depression (7 questions each). Each question ranges from 0 to 3, with a maximum score of 21 points for each subscale. In this study, a cut-off score (≥8) will be used to classify the presence or absence of symptoms of anxiety or depression [40].

Asthma Exacerbations

Asthma exacerbation is defined as an event in which a patient requires urgent action and needs to change the pharmacological treatment [41]. During this study, at least one of the following criteria will be used to define an exacerbation: the use of ≥4 puffs of rescue medication per 24 hours during a 48-hour period, a need for the administration of systemic corticosteroids, an unscheduled medical appointment, and either a visit to the emergency room or hospitalization [21,25,41].

The Behavioral Stage for Physical Activity

The assessment of "readiness to change" will be graded using a questionnaire to evaluate the following behavioral stages for physical activity: *Precontemplation*, *Contemplation*, *Preparation*, *Action*, and *Maintenance* [24,42]. The data will be presented in frequencies.

Barriers to Performing Physical Activity

Barriers to PADL practice will be assessed using a questionnaire that contains the most common barriers in adults [43,44]. The options to answer each question included: never, rarely, sometimes, almost always, and always, and each item score varies from 0 to 4. Higher scores indicate higher barriers.

Sample Size Calculation

A minimum number of 17 individuals in at least one of the groups (responder or nonresponder) was established to detect a difference of 2500 (SD 2500) steps [45] in the primary outcome (α=5%, 1 – β=80%). A sample of 100 participants was established, considering the percentage of nonresponders (17%) as previously observed [5]. Clinical improvement in the ACQ score (≥0.5) [3,32] will be considered a secondary outcome.

Statistical Analysis Planning

Individuals will be stratified as "responders" and "nonresponders" based on an increase of ≥2500 steps [45]. The Kolmogorov-Smirnov test will be used to assess data normality. Cluster analysis will be used to characterize the groups according to individual characteristics. Cluster analysis will be carried out in 2 stages: hierarchical analysis using the Ward method to determine the number of clusters and k-means analysis to group the clusters [46]. Comparisons of clinical, anthropometric, and psychosocial data obtained in the responder and nonresponder groups will be conducted using the 2-tailed *t* test or Mann-Whitney *U* test for continuous variables and the chi-square test for categorical variables. To determine the independent factors associated with the level of PADL (dependent variable, considering clinical control, smoking, obesity, anxiety, and depression as independent variables), multiple linear regression analysis (stepwise forward) will be used. The intra- and between-group comparison at baseline, short term, and medium term will be assessed using the 2-way ANOVA with repeated measures test. The significance level will be adjusted to 5% (P<.05) for all tests. If necessary, intention-to-treat analysis will be performed, as described earlier. SPSS Statistics (version 22.0; IBM Corp) will be used for statistical analysis. Data integrity will be monitored by regularly scrutinizing data files for omissions and errors. Participants will be given an anonymous study ID to protect confidentiality, and only study investigators will have access to the final trial data set.

Results

In December 2021, the clinical trial registration was approved. Recruitment and data collection for the trial is ongoing, and the results of this study are likely to be published in late 2024.

Discussion

Potential Impact and Significance of the Study

The role of exercise training in individuals with moderate to severe asthma has been widely studied in recent years [47,48]. Aerobic exercise training improves physical fitness, health-related quality of life, asthma control, and lung function in this population [46,49]. However, despite the beneficial effects of exercise training, little is known about the behavioral modifications needed to achieve a more active lifestyle [4], and studies have been conducted to address behavioral interventions. Very recently, it was demonstrated that a behavioral intervention aimed at increasing PADL modified the behavior of patients with asthma, resulting in an increase in PADL and improvement in symptoms of the disease [5]. This protocol was developed to identify the characteristics of individuals who respond and do not respond to this type of intervention, which may help guide clinical practice.

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Strengths and Limitations of the Study

In addition to the potential to identify the characteristics of responders and nonresponders, this study will also follow up 4 months after training, considered the medium term. These results will allow us to determine if behavioral changes are maintained in the responders over time. The assessment of PADL using accelerometers as a primary outcome is a study strength because it is an objective outcome measure, thus decreasing the risk of bias. The fact that the study will be performed in only 1 hospital center can be considered a limitation.

Contribution and Clinical Applicability

To our knowledge, this will be the first study to assess the characteristics of responders and nonresponders to a behavioral intervention aimed at increasing PADL in adults with asthma. Therefore, the results obtained in the proposed protocol may provide vital information for health care professionals to refer patients with asthma to more specific intervention approaches (behavioral or otherwise) based on their profile as potential responders or nonresponders. Furthermore, this study may clarify whether the potential gains obtained in the short term after the intervention are maintained in the medium term in individuals with moderate to severe asthma.

Conclusion

The behavioral intervention to increase PADL may promote different effects according to the clinical characteristics of the individuals, including asthma control, age, anxiety and depression levels, obesity, and several comorbidities. Furthermore, identifying individuals who respond or do not respond to behavioral interventions to increase PADL will help clinicians prescribe specific interventions to adults with asthma.

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The study funders (FAPESP and CNPq) are public research foundations and do not have any influence on the study's results, including data collection; the management, analysis, and interpretation of data; or writing of the manuscript.

Table 1 was reproduced from from Freitas et al [25], which is published under Creative Commons Attribution 4.0 International License [49].

Data Availability

The data obtained in this study will be available from the corresponding author (CRFC) upon reasonable request.

Authors' Contributions

FFdL and CRFC contributed to the writing of this study protocol. FFdL and DHAP are involved in recruiting and collecting data. FFdL, ACL, and CRFC will conduct the analyses. ACL, DHAP, RMCP, RS, PGB, and RCA contributed to the review and commented on all versions of this study protocol. All authors approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

ACQ: Asthma Control Questionnaire
AQLQ: Asthma Quality of Life Questionnaire
GINA: Global Initiative for Asthma
HADS: Hospital Anxiety and Depression Scale
PADL: physical activity in daily life
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
WHO: World Health Organization

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Protocol

Fear of Reprisal and Change Agency in the Public Health and Social Service System: Protocol for a Sequential Mixed Methods Study

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Abstract

Background: Since they are key witnesses to the systemic difficulties and social inequities experienced by vulnerable patients, health and social service (HSS) professionals and clinical managers must act as change agents. Using their expertise to achieve greater social justice, change agents employ a wide range of actions that span a continuum from the clinical (microsystem) to the societal (macrosystem) sphere and involve actors inside and outside the HSS system. Typically, however, clinical professionals and managers act in a circumscribed manner, that is, within the clinical sphere and with patients and colleagues. Among the hypotheses explaining this reduced scope of action is the fear of reprisal. Little is known about the prevalence of this fear and its complex dynamics.

Objective: The overall aim is to gain a better understanding of the complex dynamic process leading to clinical professionals' and managers' fear of reprisal in their change agent actions and senior administrators' and managers' determination of wrongdoing. The objectives are (1) to estimate the prevalence of fear of reprisal among clinical professionals and managers; (2) to identify the factors involved in (a) the emergence of this fear among clinical professionals and managers, and (b) the determination of wrongdoing by senior administrators and managers; (3) to describe the process of emergence of (a) the fear of reprisal among clinical professionals and managers, and (b) the determination of wrongdoing by senior administrators and managers; and (4) to document the legal and ethical issues associated with the factors identified (objective 2) and the processes described (objective 3).

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Methods: Based on the Exit, Voice, Loyalty, Neglect model, a 3-part sequential mixed methods design will include (1) a web-based survey (objective 1), (2) a qualitative grounded theory design (objectives 2 and 3), and (3) legal and ethical analysis (objective 4). Survey: 77,794 clinical professionals or clinical managers working in the Québec public HSS system will be contacted via email. Data will be analyzed using descriptive statistics. Grounded theory design: for each of the 3 types of participants (clinical professionals, clinical managers, and senior administrators and managers), a theoretical sample of 15 to 30 people will be selected via various strategies. Data will be independently analyzed using constant comparison process. Legal and ethical analysis: situations described by participants will be analyzed using, respectively, applicable legislation and jurisprudence and 2 ethical models.

Results: This ongoing study began in June 2022 and is scheduled for completion by March 2027.

Conclusions: Instead of acting, fear of reprisal could induce clinical professionals to tolerate situations that run counter to their social justice values. To ensure they use their capacities for serving a population that is or could become vulnerable, it is important to know the prevalence of the fear of reprisal and gain a better understanding of its complex dynamics.

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KEYWORDS

change agency; fear; professional practice; retaliation; social justice

Introduction

As they are in regular contact with patients who are vulnerable or at risk of becoming vulnerable, health and social services (HSS) professionals are often the first to see the systemic difficulties and social inequalities these patients encounter. These professionals are then called upon to act to defend the rights and promote the social inclusion of these patients, in other words, to assume the role of change agent [1-6]. From both a professional [1-6] and an ethical [7] perspective, this role is not optional, it is an obligation. Clinical managers (eg, department heads and coordinators), who are usually HSS professionals [8], also take on this role. In times of uncertainty (pandemic and disaster), it is all the more critical to act as a change agent because of increasing inequities, including in HSS [9,10]. The COVID-19 pandemic revealed or exacerbated existing social and health inequities in populations at risk of increased vulnerability, including seniors and people with disabilities, chronic illnesses, or mental health issues [9,10]. Using their expertise and influence to achieve greater social justice [7], change agents employ a wide range of actions that span a continuum from the clinical (microsystem) to the societal (macrosystem) sphere and involve actors both within and outside the HSS system [11]. To increase social inclusion and justice for people with heightened vulnerability, however, the clinical actions typically mobilized (such as advocating for a patient's choices in a team meeting) are not enough [12]. In light of the systemic issues that persist in HSS, including ableism, ageism, and racism [13], social actions such as advocating to policy-making bodies, serving in an official capacity within an advocacy organization, or speaking out in public [11] are also necessary to stimulate positive systemic change.

Typically, HSS professionals and clinical managers act as change agents in a circumscribed manner, at the clinical level and with patients and colleagues. For example, in a quantitative cross-sectional study [14], the change agency practice of occupational therapist practitioners and clinical managers included little social action (such as public speaking) and rarely targeted higher level actors in their institution (eg, senior administrators or senior managers) or outside it (eg, senior government officials and elected officials). One of the hypotheses suggested to explain the lack of action outside the clinical sphere is the fear of reprisal. This fear emanates from a risk of retaliation, whether this risk is real or not [15]. Reprisals are "action[s] taken by an individual or group to inflict physical, economic, or other harm in response to an action taken by another" (free translation [16]). They include but are not limited to formal sanctions. Instead of taking action, fear of reprisal may lead clinical professionals and managers to tolerate situations that run counter to their social justice values [12]. In an interpretive qualitative study with change agents recognized as such by their peers, participants reported that having a system that "supports" the agency of professionals is one of the essential elements for carrying out change actions [17]. Thus, to ensure they are using their capacities as agents to serve a population that is or could become vulnerable, HSS professionals and clinical managers should not fear reprisals for their actions to improve social inclusion and justice for their patients; rather, they should feel supported in their change efforts.

Some authors [14,18] suggest that a fear of negative repercussions may be rooted in part in how professionals and their managers interpret the duty of loyalty to their employer [19]. Other potential causes associated with the duty of loyalty include the confidentiality agreement that new employees must sign in some HSS settings, disciplinary proceedings for professional misconduct (eg, Carolyn Strom in Saskatchewan [20]), and disciplinary action taken by the employer (eg, nurses suspended without pay [21]). To our knowledge, no empirical study has specifically examined the fear of reprisal associated with change agents' actions, or sought to understand when and under what conditions this fear arises. Some studies that focused on the change actions of professional practitioners and managers did, however, document part of this reality. In particular, an exploratory qualitative study [22] examined the actions of 39 nurses who were politically engaged in their hospital practice setting. Fear of retaliation by colleagues and managers was reported as a barrier to change actions in the clinical setting. Among the types of retaliation used, participants described

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"various forms of harassment, violence (often public), confrontation, intimidation or threats, loss of privilege, and abandonment by colleagues...increased monitoring...sudden deterioration of relationships with their superiors, ongoing tensions, and more frequent sanctions such as 'going to [the superior's] office'... [use of] disciplinary notes, various forms of coercion, such as suspensions and dismissal" [22]. Participants spoke of fear-based management to explain their reluctance to voice their opinions within the HSS system. By analyzing 597 anonymous whistleblower reports from outside the HSS system at the beginning of the COVID-19 pandemic, Perron et al [18] were also able to identify retaliation against nurses, including intimidation, threats, and sanctions. These 2 studies shed light on nurses' perceptions of potential or actual retaliation for acting as change agents. However, it is not clear if this view is shared by all HSS professionals and clinical managers. Moreover, since they are also concerned about a fear of reprisal, the perspective of senior administrators and senior managers regarding what constitutes an improper change agent action must be considered. To date, nothing is known about this perspective.

In "professionalizing" HSS university programs, professional competencies, including those related to the change agent role, are being developed and fostered by a longitudinal, gradual, and explicit deployment of learning activities [23]. This deployment takes place in authentic professional situations [24] involving high ecological validity and increasing complexity [23], drawing on transformational learning [25] and critical consciousness [26], and combined with formative (eg, providing feedback) and summative assessments of competencies through programmatic or longitudinal approaches [27]. Both ecological validity and increasing complexity optimize the preparation of future professionals for their actual practice conditions. This preparation is associated with an increased sense of competence in practice [28] and consequently a greater motivation to act [29]. Further, by increasing their critical awareness [30], authentic educational experiences open up learners to professional transformation [31,32] and allow for reflexivity [33], which may assist in developing skills leading to patient advocacy and participation in social justice initiatives in partnership with community stakeholders. To ensure the ecological validity and increasing complexity of authentic educational activities related to the change agent role in HSS university programs, it is important to gain a better understanding of when and under what conditions fear of reprisal and determination of wrongdoing occur, respectively, in professional practitioners and clinical managers and in senior administrators and senior managers. Knowledge of these processes is crucial to better prepare future HSS professionals to incorporate the change agent role in their practices, and hence support high quality, compassionate, and equitable health and social care. Eventually, professionals trained in this way will help to increase social inclusion and justice for people with heightened vulnerability.

Methods

Objectives and Design

The aim of this study is to gain a better understanding of the complex dynamic process leading to clinical professionals' and clinical managers' fear of reprisal in their change agent actions and senior administrators' and senior managers' determination of wrongdoing. More specifically, the objectives are (1) to estimate the prevalence of fear of reprisal among clinical professionals and managers, overall and by profession and practice setting; (2) to identify the factors involved in (a) the emergence of this fear among clinical professionals and managers, and (b) the determination of wrongdoing by senior administrators and managers; (3) to describe the process of emergence of (a) the fear of reprisal among clinical professionals and managers, and (b) the determination of wrongdoing by senior administrators and managers; and (4) to document the legal and ethical issues associated with the factors identified (objective 2) and the processes described (objective 3).

We will use a 3-part sequential mixed methods design [34]. In the first component, a survey, the prevalence of fear of retaliation in the population under study, that is, clinical professionals and managers in HSS in Québec (Canada), will be estimated (objective 1). This type of design has already been used successfully to estimate the prevalence of this fear among Canadian workers according to different types of occupational health and safety advocacy actions [35]. The aim of the second component, a qualitative grounded theory design, will be to identify the factors involved in the emergence of this fear among clinical professionals and managers and in the determination of a wrongful action by senior administrators and managers in HSS in Québec (objective 2) as well as to describe the process of emergence of this fear among clinical professionals and managers and of this determination by senior administrators and managers (objective 3). Finally, in the third component, a legal and ethical analysis, the legal and ethical issues associated with the factors identified and the processes described will be documented (objective 4). Thus for components 2 and 3, there will be 2 study populations in HSS in Québec: clinical professionals and clinical managers, on the one hand, and senior administrators and senior managers, on the other.

Theoretical Background

This study is based on the *Exit, Voice, Loyalty, Neglect* (EVLN) model [36], which presents 4 possible employee responses to unsatisfactory working conditions. This model is relevant to this study because professionals' ability to act to improve social inclusion and justice for their patients is a function of their practice and thus of their working conditions. In the EVLN model, exit induces the professional to leave his or her job while voice leads him or her to speak up to improve the situation. Loyalty reflects his or her decision to wait. Finally, in neglect, the professional gives up trying to improve the situation and disengages or obstructs. The concept of interest here, namely fear, can be met with silence (nonaction; [37]). Depending on the reason for the professional's "silence" [38], the silence will fall under loyalty (expectation) or negligence (disengagement). For example, as a strategy or due to resignation or fear, the

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professional may choose not to act (remain silent). The nature of silence can thus vary according to the characteristics of the situation and the moment [39]. Examples of characteristics and moments are the intensity and immediacy of the fear and the person with whom the professional is dealing (eg, senior manager). This finding is independent of the status of the professional (could be a department head); relatively high status workers are affected [40]. Even among workers hierarchically equivalent to clinical managers, actions may vary depending on the severity of retaliation, the coping strategy chosen, the relative organizational statuses of those involved, and the person's gender. All of these contextual elements will be considered in the development of data collection tools for components 1 and 2. The EVLN model will also enrich the interpretation of the results of the 3 components.

Study Components, Data Collection, and Analysis

Component 1: Survey

Overview

Given the common challenges they face, such as labor shortages [41], waiting lists, and wait times [42-44], as well as the at-risk vulnerable populations they serve, nurses, occupational therapists, physical therapists, social workers, and speech therapists working in the public HSS system will be the target population. In fact, these challenges and patient populations may increase the likelihood of acting or intending to act as change agents. To estimate the prevalence of fear of reprisal (objective 1), we will survey this entire population using a web-based self-administered questionnaire that we will develop.

Development, Validation, and Pretesting of the Questionnaire

To develop the questionnaire, we will use 3 alternative sources of information combined with the EVLN model. This will give us recent examples of situations involving fear of reprisal that are highly relevant to our target population. *Source 1:* we will conduct a review of papers citing fear of reprisal by HSS professionals in the Québec media from January 2015 (last HSS reform) to May 2022 using 2 databases: Eureka and the Canadian Business & Current Affairs Database. The former contains papers from Canadian news media, including periodicals, newspapers, and television and radio transcripts; the latter contains news stories, and radio and television transcripts. *Source 2:* We will collate case law from employment and professional tribunals concerning formal sanctions against HSS professionals and clinical managers from January 2015 to May 2022 from the 2 leading legal databases in Québec, CanLII, and Soquij. This source will provide examples of situations that may cause concern. *Source 3:* We will conduct 4 open-ended exploratory interviews, 2 with 2 union representatives and 2 with 2 association representatives, about their experiences with the relevant situations. For all 3 data sources, we will conduct a summative content analysis [45]. This type of analysis leads to an interpretation of the contextual meaning of specific terms or types of content. Supported by the EVLN model, we will then triangulate the distinctive elements of the reported situations, including change agency actions and manifestations of fear of reprisal. Based on these elements, we will develop survey questions focusing on change agent actions that were considered or carried out and the occurrence of fear of reprisal for these actions. The questionnaire will consist mainly of Likert scale questions (4 levels; from 0: not at all, to 3: completely) and closed multiple choice questions. For example, for actions, 1 question could be: "I have thought about making a claim or I made a claim to a manager regarding a situation of concern for my patients." For the associated fear, 2 questions could be "When I thought about advocating or when I advocated to a manager about a concern for my patient, I feared retaliation" and "If you checked 1 to 3, choose which of the following retaliations you feared." The Delphi method will be used to ensure content and face validity of the questionnaire [46,47]. Further, 10 content experts from various fields (law, management, industrial relations, and HSS) will be consulted during (content validity) and after (face validity) construction of the questionnaire. This systematic method of consultation is particularly useful when empirical knowledge is poor [48]. The consultation will be conducted by email and in successive rounds until a consensus of 80% (n=8) of experts for each question is reached. To characterize the profile of participants, a sociodemographic section (eg, occupation, background, and years of experience) will be added to the validated questionnaire as well as an invitation to participate in component 2 of this study. The questionnaire will then be pretested with 5 graduate students in health or management who have experience as a health professional or clinical manager, respectively.

Data Collection

As recommended by Dillman et al [48], the entire target population will be contacted. Our connections and credibility in the professional community (1 researcher from each profession) will facilitate recruitment. To be recruited, individuals will need to hold a professional or clinical management position, be a member of 1 of the 5 relevant professions, understand French, and have at least 6 months' experience in the public HSS system. From their membership lists, 2 unions (one representing nurses and the other representing occupational therapists, physical therapists, social workers, and speech therapists) will send an email invitation to participate in this study and a link to the survey hosted on LimeSurvey (LimeSurvey GmbH). This strategy will also reach clinical managers. A total of 77,794 clinical professionals or clinical managers working in the public HSS system will be reached: 4125 occupational therapists, 2142 speech-language pathologists, 8895 social workers, 2489 physiotherapists (O Dallaire-Turmel, personal communication, August 13, 2021), and 60,143 nurses [8]. Considering the participation rate for recent surveys of the target population (eg, references [49,50]), we estimate that we will obtain a minimum participation rate between 30% (n=23,338)and 45% (n=35,007).

Analyses

To estimate the prevalence of fear (objective 1) and describe the participants, descriptive statistics (means, SD, frequencies, and percentages) will be used, overall by type of participant, and then by setting, profession, and position (professional or managerial). The data will be analyzed in Excel (Microsoft Corp) and SPSS (IBM Corp) and the analyses will be validated

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by all team members. The results will shed light on the elements to be studied in greater depth in component 2.

Component 2: Qualitative Grounded Theory

Overview

We will use a qualitative grounded theory design based on a constructivist perspective [51] with 3 types of participants: clinical professionals, clinical managers (department heads, coordinators), and senior administrators and managers. This type of design enables the exploration and definition of a little-known process (fear of reprisal and determination of reprehensible change agent actions) by taking into account all of the factors involved.

Recruitment and Sampling

To recruit our 3 types of participants, we will use three main recruitment strategies: (1) contact with component 1 participants who have indicated an interest in participating in component 2 (clinical professionals and clinical managers); (2) an email invitation from the *Association des gestionnaires des établissements de santé et de services sociaux* (managers) and the *Association des cadres supérieurs de la santé et des services sociaux* (senior managers); and (3) word of mouth through participants already recruited (clinical professionals, clinical managers, and senior administrators). *Association des gestionnaires des établissements de santé et de services sociaux* represents almost three-quarters of all managers in the HSS system [52] and all senior administrators and senior managers automatically become (unless voided) members of *Association des cadres supérieurs de la santé et des services sociaux* [53]. For clinical professionals and managers to participate in this study, the same inclusion criteria will apply as in component 1. In addition, they must have experienced a situation in which their change agency's actions, either planned or carried out, led to a fear of reprisal. For managers to be included, they will have to hold a management position, understand and speak French, and have at least 6 months' managerial experience in the public HSS system. For individuals recruited by convenience sampling and for each type of participant, we will then use a theoretical sampling technique to vary the heterogeneity of the personal characteristics and situations experienced by the participants. This will be done in successive phases with 2 or 3 participants, according to criteria guided by data analysis needs [54]. We estimate that a theoretical sample of 15 to 30 people will be needed for each of the 3 types of participants to achieve theoretical saturation, that is, the point at which data do not add any new properties to the theoretical concepts identified [55]. This saturation is fostered by comparing and contrasting emerging theoretical concepts with different empirical contexts [54,55].

Data Collection

Each participant will be met digitally on a secure platform (Teams) for a 60-90 minute semidirected, audio-recorded, and transcribed interview. This approach will help to recruit participants from across Québec, offer greater flexibility in the timing of interviews and ensure confidentiality. Based on the results of component 1 and the EVLN model, a semistructured interview guide will be developed for each type of participant, validated by 4 methodological experts (grounded theory) and content experts (health and management) and pretested with 3 graduate students in health and management. To promote theoretical saturation, the guides will be refined following the analysis of each interview. To characterize their profile, participants will also complete the sociodemographic section of the web-based questionnaire in component 1. Throughout data collection, memos (collection and analysis notes) will be used to (1) record preconceived notions (logbook), (2) clarify methodological choices (audit trail), and (3) outline emerging concepts and categories (data source). Memos will thus be used as a source and tool for analyzing the data and interpreting the results [51,54].

Tools

Semistructured interview guides will use open-ended questions to address change agent actions reported, factors involved in the emergence of fear of reprisal (clinical professionals and managers) or determination of wrongdoing (senior administrators and managers), and how that fear or determination emerged (process). For example, questions might be "What actions caused you to fear retaliation?" "Describe what led you, as a result of [this action], to determine that it was wrong"; "You told me that [this factor] led you to fear retaliation. What other [factors], if any, contributed to your fear? Explain"; "What actions did you determine to be objectionable? Explain." These questions will elucidate the specific experience of participants while avoiding the use of preconceived categories [51]. Each guide will be developed according to the principles of Vermersch's [56] explicitation technique. This interview technique aims to make participants' experience of actions explicit, which reduces the risks of post hoc rationalization inherent in the retrospective nature of the method used in this study. Thus, respecting explicitation technique principles adds rigor to the chosen design and increases the credibility of the results.

Analyses

The analyses will be carried out independently for each type of participant. Sociodemographic data will be analyzed using descriptive statistics. Data from interviews will be transcribed using the Teams transcription function and transcripts will be verified against the audiotapes. All the data collected will be analyzed according to the constructivist perspective of grounded theory [51] and, to enrich the analysis [57], in relation to the EVLN model. This flexible and open-ended method makes it easier to understand complex processes [54] such as fear of reprisal and the determination of wrongdoing. The data will be analyzed using a constant comparison process [51]. The strategies used are (1) simultaneous data collection and analysis, (2) coding (open and then selective), (3) comparative analysis methods, (4) use of memos to facilitate analysis of the concepts under study, (5) theoretical sampling to refine theoretical constructs and saturate data, and (6) integration of theoretical structure (ie, updating conceptual links) to facilitate the emergence of a process model. Further, 3 models will be developed initially. The 2 models of the fear of reprisal process will then be compared to identify points of convergence and divergence, leading to an integrated model of fear of reprisal. The points of divergence and convergence between the

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integrated model of fear and the integrated model of determination of wrongdoing will also be documented to provide a comprehensive picture of these interrelated processes and form a final integrated process model.

Component 3: Legal and Ethical Analysis

To document the legal and ethical issues associated with the factors identified and the 2 processes described (objective 4), the situations described by the participants in the 3 groups will be analyzed from both a legal and an ethical viewpoint. Specifically, the legal analysis will include a collection of applicable legislation as well as jurisprudence from specialized labor and employment tribunals (notably arbitration awards) and disciplinary bodies (decisions of disciplinary committees and the Professions Tribunal) from the 2 leading legal databases (CanLII and Soquij). From an analysis of the circumstances in which courts and tribunals have concluded that the employer's or the professional association's sanctions were justified, it will be possible to identify situations in which fear of reprisal is legally founded. To understand the role played by the actors' understanding or misunderstanding of the applicable law, these situations will then be compared to the factors involved in the emergence of fear of reprisal among clinical professionals and managers and the determination of wrongdoing among senior administrators and managers. On the ethical front, we will first analyze the same situations using Swisher and Royeen's [58] model. This model aims to conceptually organize a situation's ethical issues into 5 categories: dilemma, ambiguity, distress, temptation, or silence. The issues identified can then be deepened by mobilizing deductive ethical theories (deontology and consequentialism) and inductive ethical theories (ethics of care and axiology) using the Quadripartite Ethical Framework [59,60]. The results of this in-depth ethical analysis of situations mentioned by participants will provide clues to the ethical tools to be developed to improve how practicing and future professionals are trained.

Ethical Considerations

The research protocol has been approved by the Research Ethics Board of the Université de Sherbrooke (Comité d'éthique de la recherche – Lettres et sciences humaines; #2022-3473/Carrier). All participants will be required to provide free and informed written consent [61]. Participants will be able to withdraw from this study at any time without any repercussions. They will also be informed of the confidential nature of the data collected and the procedures followed to ensure confidentiality and anonymity. The data collected, both electronically and on paper, will be secured (on a password-protected computer or in a locked fireproof filing cabinet at the Research Centre on Aging) and only the research assistant, research trainee, and principal investigator will have access to them. To ensure they are not lost, electronic data will also be stored on the Université de Sherbrooke's secured institutional platform accessible only through institutional identification and password by the same team members.

Results

This ongoing study began in June 2022 and will be conducted according to an optimal but realistic 5-year timeline that takes into account the uncertain context related to the COVID-19 pandemic (Table 1). Components 1 and 2 will be completed within a 4-year time frame (2022-2026) while component 3 will be completed in the final year. To ensure rapid knowledge mobilization, dissemination strategies will be employed by the entire team throughout this study.

Table 1. Tasks and timeline by component. This table describes the tasks and timeline for each component (C) of the 3-part sequential mixed-method design research over a 5-year period.

Task	C1[a]		C2[b]		C3[c]
Year	1	2	3	4	5
Ethics and C1 survey (quantitative)					
Ethical approval	✓	N/A[d]	N/A	N/A	N/A
Development of the questionnaire (collection from 3 sources; analysis, validation by Delphi, and pretest)	✓	N/A	N/A	N/A	N/A
Recruitment, data collection, and analysis	N/A	✓	N/A	N/A	N/A
C2 qualitative grounded theory					
Development of interview guides	N/A	N/A	✓	N/A	N/A
Recruitment, data collection, and analysis	N/A	N/A	✓	✓	N/A
C3 legal and ethical analysis					
Analysis of situations	N/A	N/A	N/A	N/A	✓
Dissemination and mobilization strategies	✓	✓	✓	✓	✓

[a]C1: component 1.

[b]C2: component 2.

[c]C3: component 3.

[d]N/A: Not applicable.

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Discussion

Strengths and Limitations

Building on established and new collaborations, the research team has all the interdisciplinary expertise required to conduct this study successfully and ensure effective and relevant dissemination and mobilization of the knowledge developed. In fact, a conscious effort has been made to secure complementary expertise and professional networks. Each profession concerned is represented, and each member has a high degree of credibility in his or her profession and strong ties to organizations related to that profession or to senior administrators and managers. This will undeniably facilitate the recruitment of participants, which is the main challenge of this study. The results should lead to a fleshed-out understanding of the fear of reprisal associated with change agent actions, a phenomenon that is apparently growing in HSS.

Broad Implications

Using a sequential mixed-method design, this study will first establish the prevalence of fear of reprisal among clinical professionals and managers in the public HSS system who are particularly involved with the vulnerable population: nurses, occupational therapists, physical therapists, social workers, and speech therapists. Second, this research will identify the factors involved in the emergence of this fear among clinical professionals and managers and in the determination of wrongdoing by senior administrators and managers. Third, the emergence process of this fear among clinical professionals and managers and this determination by senior managers will be described. Finally, this study will document the legal and ethical issues associated with the factors identified and the processes described. This will provide a better understanding of the complex dynamic process leading to professionals' and clinical managers' fear of reprisal in their change agency actions and senior managers' determination of wrongdoing.

The scientific knowledge developed in this study will help to prepare practicing and future professionals to work in real-world settings. In addition, this knowledge will be useful for university programs both in Québec and globally. These results will also be of interest to professional regulatory boards and associations, unions, and management associations, all of which are concerned with their members' continuing education and quality of practice. Moreover, knowledge mobilization strategies will include the organization of forums (eg, training) to encourage the emergence of actions. Finally, the interest of researchers studying other public services potentially affected by fear of reprisal, such as education and the environment, will also be stimulated.

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Data Availability

The research team abides by the Research Data Management Plan of the *Université de Sherbrooke*.

Authors' Contributions

AC drafted the French and English versions of this paper. FB, NDC, FM, AH, MEC, AD, and MB helped draft and extensively revised this paper. All authors approved the final paper and are willing to take responsibility for appropriate portions of the content.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review report by Social Sciences and Humanities Research Council of Canada (SSHRC). 435-23A (Multidisciplinary or interdisciplinary social sciences).
[PDF File (Adobe PDF File), 866 KB - resprot_v12i1e48400_app1.pdf]

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Abbreviations

EVLN: Exit, Voice, Loyalty, Neglect
HSS: health and social service

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Protocol

The Effects of Suicide Exposure on Mental Health Outcomes Among Post-9/11 Veterans: Protocol for an Explanatory, Sequential, Mixed Methods Study

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Abstract

Background: The toll associated with suicide goes well beyond the individual who died. This study focuses on a risk factor for veteran suicide that has received little previous empirical attention—exposure to the suicide death of another person.

Objective: The study's primary objective is to describe the mental health outcomes associated with suicide exposure among veterans who served on active duty after September 2001 ("post-9/11"). The secondary objective is to elucidate why some veterans develop persistent problems following suicide exposure, whereas others do not.

Methods: This is an explanatory, sequential, mixed methods study of a nationally representative sample of post-9/11 veterans enrolled in Department of Veterans Affairs (VA) health care. Our sampling strategy was designed for adequate representation of female and American Indian and Alaska Native veterans to allow for examination of associations between suicide exposure and outcomes within these groups. Primary outcomes comprise mental health problems associated with trauma and loss (posttraumatic stress disorder and prolonged grief disorder) and suicide precursors (suicidal ideation, attempts, and planning). Data collection will be implemented in 3 waves. During wave 1, we will field a brief survey to a national probability sample to assess exposure history (suicide, other sudden death, or neither) and exposure characteristics (eg, closeness with the decedent) among 11,400 respondents. In wave 2, we will include 39.47% (4500/11,400) of the wave-1 respondents, stratified by exposure history (suicide, other sudden death, or neither), to assess health outcomes and other variables of interest. During wave 3, we will conduct interviews with a purposive subsample of 32 respondents exposed to suicide who differ in mental health outcomes. We will supplement the survey and interview data with VA administrative data identifying diagnoses, reported suicide attempts, and health care use.

Results: The study began on July 1, 2022, and will end on June 30, 2026. This is the only national, population-based study of suicide exposure in veterans and the first one designed to study differences based on sex and race. Comparing those exposed to suicide with those exposed to sudden death for reasons other than suicide (eg, combat) and those unexposed to any sudden death may allow for the identification of the common and unique contribution of suicide exposure to outcomes and help seeking.

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Conclusions: Integrating survey, qualitative, and VA administrative data to address significant knowledge gaps regarding the effects of suicide exposure in a national sample will lay the foundation for interventions to address the needs of individuals affected by a suicide death, including female and American Indian and Alaska Native veterans.

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KEYWORDS

veterans; suicide; death; posttraumatic stress disorder; bereavement; health services

Introduction

Background

Suicide is a public health problem that disproportionately affects US veterans. Veterans are 1.5 times more likely to die by suicide than members of the general population, after adjusting for age and sex [1]. Adjusting for age, female veterans are 2.1 times more likely to die by suicide than female nonveterans [1]. Suicide rates are particularly high in the year following military separation and may remain elevated for at least 6 years following separation [2,3].

Groups at increased risk of suicide may also be at increased risk of *suicide exposure*, defined as knowing someone who has died by suicide. It has been estimated that for each person who dies by suicide, 135 others may be exposed, and up to 50% of them may be intimately and directly affected [4,5]. Those exposed to a suicide death are at increased risk for psychiatric disorders, disordered grief, physical disorders, impaired social functioning, and their own fatal and nonfatal suicide behavior compared with those who are unexposed [6-9]. Consequently, suicide prevention strategies recommend *postvention*, which is the provision of services and support to those affected by a suicide death to facilitate their healing [10]. This study characterizes the postvention needs of veterans during the first 6 years after military separation.

Suicide exposure among military populations is an understudied risk factor for suicide. A scoping review of studies based on military samples identified 6 empirical studies of exposure to suicide death and one study of exposure to suicide attempts [11]. Suicide exposure ranged from 47.1% in a sample of 931 veterans living in Kentucky [12] to 65.4% in a sample of 971 active-duty National Guard personnel in Utah and Idaho [13]. Consistent with studies based on civilian samples, studies of suicide exposure in military samples reported high frequencies of mental health disorders, including posttraumatic stress disorder (PTSD) and disordered grief; suicidal ideation; and suicide attempts among those exposed to suicide compared with those who were unexposed [11].

These studies established that suicide exposure is all too common among military populations. However, they leave unanswered questions foundational to preventing and treating mental health and psychosocial problems among those affected by a suicide death. The studies of suicide exposure in military populations were based on geographically distinct or small samples that did not include a sufficient number of female and racial and ethnic minority individuals to examine potentially critical differences based on sex and race. American Indian and Alaska Native individuals serve in the US military at the highest rate per capita compared with other US racial groups and have the highest suicide death rate, yet American Indian and Alaska Native veterans are not represented in these studies [14,15]. Another limitation is regarding the comparison group selected for extant studies in military samples. With 1 exception [16], studies of suicide exposure based on military samples have compared service members or veterans who knew someone who died by suicide with those who did not. Therefore, the comparison group included individuals who were unexposed to any type of sudden death and those exposed to sudden death from other causes such as natural events (eg, cardiac arrest) or unnatural events (eg, combat and vehicular crashes). An understanding of how a suicide loss differs from other sudden and traumatic losses is needed for the design of postvention interventions [17].

There is also an absence of studies of modifiable moderators that could be targeted to promote healing among those affected by a suicide death. Studies of risk factors following suicide exposure has primarily examined sociodemographic variables, such as family and personal history of psychiatric disorders and suicidal behavior, relationship with the decedent (eg, kinship and perceived closeness), and the number of trauma exposures, none of which are modifiable [7,18]. An additional knowledge gap is that we know almost nothing about help seeking following a suicide death and whether the received services and supports (eg, support groups for suicide death survivors) facilitate healing. The 1 study to examine the effect of suicide exposure on mental health treatment seeking in veterans was based on a small university sample [19].

In summary, the numbers of veterans needing intervention following suicide exposure, the types of problems they are experiencing, and the services and supports that might most benefit them are all unknown.

This Study

This paper describes the protocol for a US Department of Veterans Affairs (VA) Health Services Research and Development–funded study on suicide exposure among veterans within 6 years of military separation. Veterans who have served on active duty since September 2011 are known as “post-9/11” veterans. The study’s primary objective is to describe the mental health outcomes associated with suicide exposure among post-9/11 veterans within the first 6 years of military separation, when their risk for suicide is elevated [1,2]. Our sampling strategy aims for adequate representation of female and American Indian and Alaska Native veterans to allow for the examination of associations between exposure and outcomes

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within these groups. Our secondary objective is to elucidate why some veterans develop mental health problems following suicide exposure, whereas others do not. Consistent with the socioecological model of suicide prevention, risk and protective factors are grouped at individual, relational, community, and societal levels [20]. We will include 2 comparison groups—those exposed to sudden death for reasons other than suicide (eg, combat) and those unexposed to any sudden death—to identify the common and unique contribution of suicide exposure to health outcomes and help seeking.

Methods

Study Objectives, Design, and Aims

This is a 4-year, explanatory, sequential, mixed methods study of a nationally representative sample of post-9/11 veterans enrolled in VA health care. The study starts with quantitative data collection and analysis (which is the priority of the study), followed by qualitative interviews. Textbox 1 presents the study aims and hypotheses. Primary outcomes comprise mental health problems associated with trauma and loss and suicide precursors (suicidal ideation, attempts, and planning).

Textbox 1. Study aims and hypotheses.

Aim 1 (1 of the 2 primary aims of the study)

- Aim 1 is to evaluate differences in the prevalence of posttraumatic stress disorder; prolonged grief disorder; and suicidal ideation, attempts, and planning among veterans exposed to suicide compared with those exposed to other causes of sudden death and with unexposed veterans. We will also assess whether prevalence differs based on sex and race.

Hypothesis 1

- The prevalence of posttraumatic stress disorder; prolonged grief disorder; and suicidal ideation, attempts, and planning will be high in veterans exposed to suicide compared with veterans exposed to other sudden deaths and with unexposed veterans, after controlling for closeness with the decedent and other covariates.

Aim 2 (1 of the 2 primary aims of the study)

- Aim 2 is to identify the modifiable moderating factors for the association between suicide exposure and negative outcomes and the modifiable moderating factors for the association between suicide or sudden death exposure and negative outcomes relative to those with neither exposure.

Hypothesis 2

- Social support will buffer, whereas stigma will worsen, the effects of suicide exposure on health outcomes after controlling for closeness with the decedent and other covariates.

Aim 3 (exploratory)

- Aim 3 is to describe the treatment experiences, reported suicide attempts, and patterns of Department of Veterans Affairs service use among those exposed to a suicide death compared with veterans exposed to other sudden deaths and with unexposed veterans. We will also explore differences based on sex and race.

Aim 4 (explains and illustrates aim 2 findings among those exposed to suicide)

- Aim 4 is to contextualize the quantitative findings from aim 2 through interviews with a purposive sample of veterans exposed to suicide. The interviews will focus primarily on modifiable factors at each level of the socioecological model of suicide prevention to better understand the targets for intervention for people affected by a suicide loss.

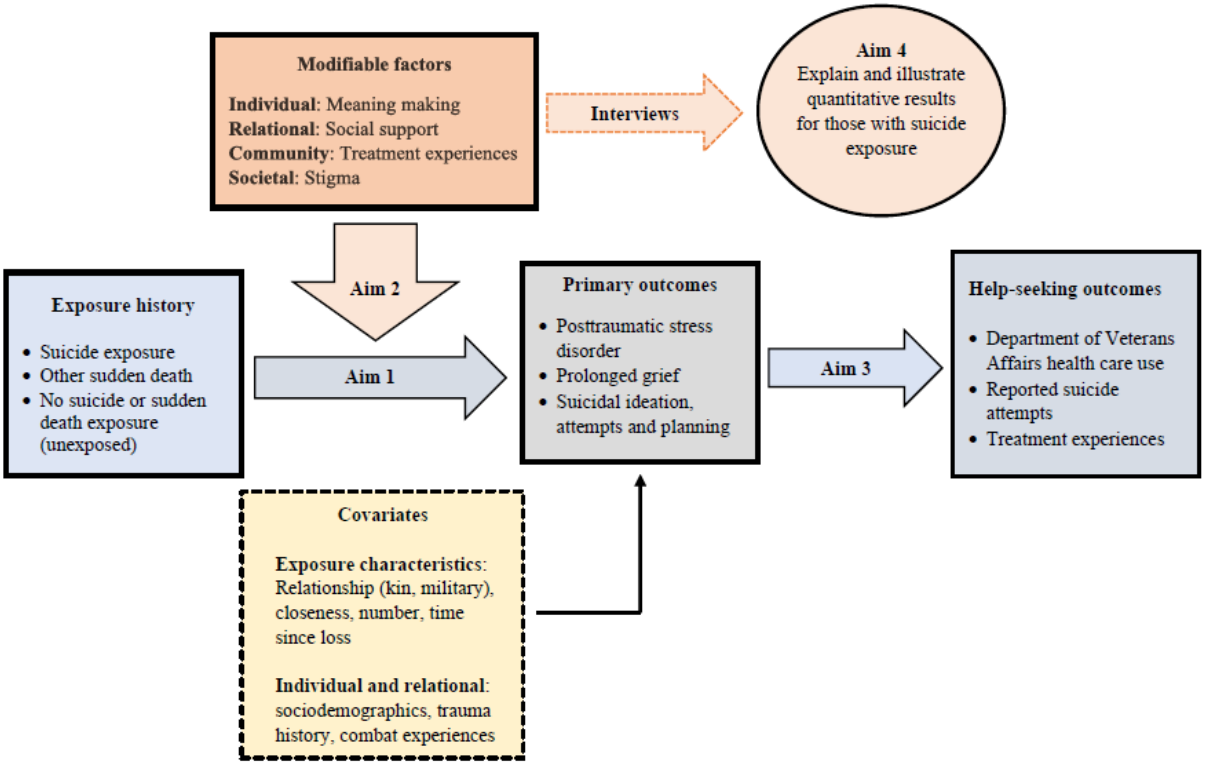
Primary data collection will be implemented in 3 waves. During wave 1, we will field a brief survey to a stratified random sample drawn from the population of post-9/11 veterans to assess exposure history (suicide, other sudden death, or neither) and exposure characteristics (eg, time since exposure and closeness with the decedent; N=11,400 participants). This will provide prevalence estimates for suicide exposure among post-9/11 veterans. During wave 2, we will survey a stratified random sample of wave-1 participants (4500/11,400, 39.47%) to assess health outcomes, covariates, and moderators. Female and American Indian and Alaska Native veterans will be oversampled in both surveys. During wave 3, we will interview a purposive subsample of 32 participants with a history of suicide exposure to understand how and why potential moderators affect outcomes. We will supplement the surveys and interviews with VA administrative data identifying diagnoses, reported suicide attempts, and health care use.

Conceptual Framework

Figure 1 presents the study's conceptual framework. Aim 1 examines differences in outcomes based on exposure history (suicide exposure, other sudden death exposure, or neither), controlling for covariates. Aim 2 examines the moderating effect of modifiable factors, again adjusting for covariates. Aim 3 explores interventions and supports received for identified mental health problems and whether they differ based on exposure history. Aim 4 will help explain and illustrate aim 2 findings for those affected by a suicide loss to further inform interventions.

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Figure 1. Conceptual model.



Participant Selection and Recruitment and Data Collection

Study Population

The study population consists of post-9/11 veterans within 6 years of military separation, who are enrolled in VA medical care.

Self-Administered Surveys

The wave-1 survey assesses suicide and other sudden death exposure history and willingness to consider participating in a follow-up web-based survey. We used data from the VA's data repository, the Corporate Data Warehouse (CDW), to identify the study population, their sex, and their race and to obtain their contact information. The only exclusion criterion is an invalid US mailing address. Veterans in the study population with a valid US mailing address will be stratified based on sex (male or female) and whether they are American Indian or Alaska Native (yes or no).

To allow time for recruitment following sample identification, the recruitment pool includes post-9/11 veterans within 5 years of military separation. As of February 2023, there were 619,216 post-9/11 veterans who were within 5 years of military separation enrolled in VA health care. Of these, 96.82% (599,522/619,216) had valid US mailing addresses. Of those with a valid mailing address, 19.09% (114,424/599,522) were female (gender is inconsistently reported in VA databases and will be assessed as part of this study) and 1.49% (8939/599,522) were classified as American Indian and Alaska Native. We will oversample female and American Indian and Alaska Native veterans, so that female veterans comprise approximately 30% and American Indian and Alaska Native veterans collectively comprise approximately 12% (4% American Indian or Alaska Native female veterans and 8% American Indian or Alaska Native male veterans) of those recruited. The recruitment pool will be updated every 3 to 6 months.

Wave-1 recruitment material will be sent through the US postal service and include a letter that describes the study, a 2-page questionnaire, a postage-paid return envelope, and a pen and note pad as nonconditional incentives. We will append bright-colored Post-it notes to the survey to encourage participation [21]. The notes will be customized for the 4 demographic strata (American Indian or Alaska Native female individuals, American Indian or Alaska Native male individuals, female individuals from other racial groups, and male individuals from other racial groups). The survey coversheet will include a shortened URL and a QR code that recipients can scan if they prefer to complete the survey on the web and a phone number to call if they prefer to complete it over the phone. We will use repeat mailings, emails, and phone calls to encourage participation among nonresponders. The survey can be completed in <10 minutes, as demonstrated by members of the veteran engagement group who provided feedback about the study material. A sample of 11,400 wave-1 participants should provide a sufficiently large pool of veterans in each exposure group for the wave-2 survey. Although we hope to achieve a response rate >50%, response rates to a survey about suicide exposure in this population are not known and will be evaluated over the course of this study.

The wave-2 survey assesses outcomes, covariates, moderators, and experiences of getting help and support for the suicide, sudden death, or another significant loss. Inclusion criteria are responding to the first survey, having a valid email address (provided on the wave-1 survey or identified though CDW), and indicating willingness to consider participating in the

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wave-1 survey. Those who meet these criteria will be stratified based on exposure history (suicide, sudden death unrelated to suicide, or neither) and, within exposure history group, sex and whether they have been identified as an American Indian or Alaska Native so that we can monitor wave-2 survey participation rates based on these characteristics and evaluate the possibility of adjustment in our sampling plan or recruitment strategy. We plan to randomly select 1500 participants with suicide exposure, 1500 participants with sudden death exposure but no suicide exposure, and 1500 participants with neither suicide exposure nor sudden death exposure from the eligible wave-1 survey respondents to participant in the wave-2 survey. The selection within each arm will match the sex and race composition targets of the wave-1 survey.

We will recruit those who meet the above mentioned inclusion criteria through email. The email will include information about the study, a hyperlink to the study website with pictures and information about the study incentives, and a URL for the web-based survey. Nonresponders will receive reminder emails, a postcard, and outreach calls. Participants will be able to choose an incentive valued at approximately US $20 after completing the survey. On average, members of the veteran engagement group completed the wave-2 survey in 45 minutes. The target sample size for the wave-2 survey is 4500 participants, with the goal of approximately even distribution across the 3 exposure history groups. The feasibility of achieving that goal will depend on the prevalence of suicide and sudden death exposure and response rates.

We will use Qualtrics Federal Risk and Authorization Management Program electronic survey software (Qualtrics XM) for the web-based surveys. Participants will access the website using a secure, shortened URL link and unique personal identification number assigned to them; protected health information will be kept behind the VA firewall. The Qualtrics surveys use branching logic, required fields, and pop-up warnings to reduce missing data. Participants' survey responses are stored in a web-based database as the participant progresses through the survey.

Interviews

We will conduct qualitative interviews with a subsample of at least 32 of the participants who have been exposed to suicide. Veterans who indicated on the first survey that they were at least somewhat close to a person who died by suicide within the past 5 years will be eligible for inclusion. The 5-year criterion will help ensure that participants can remember the help they received after the suicide loss.

Veterans will be purposively selected for interview after quantitative data collection and preliminary analyses [22]. Half of the interview subsample will be veterans with clinically significant symptoms based on our primary outcomes; the other half will have no clinically significant symptoms. Our purposive sampling strategy will ensure a demographically diverse group of participants in terms of sex, race, ethnicity, and relationship (family member, fellow veteran, friend, etc) with the decedent. Half of the sample will be women (as self-reported in the wave 2 survey) and at least half will be from racial and ethnic minority groups, with oversampling of American Indian and Alaska Native veterans.

We will use mail and email to initiate the recruitment of our interview sample. The study team will call veterans within 1 week of sending the recruitment material to discuss participation and will repeat attempts to contact those selected for recruitment. We anticipate contacting approximately 64 of the wave-2 responders who meet our interview inclusion criteria, to achieve the target sample size of 32 interview participants.

We will conduct semistructured interviews with participants over the phone or through an approved videoconference platform. A team member will conduct the interview while another manages the logistics and takes notes. The interview will focus on the modifiable factors included in the study's conceptual model and measured quantitatively in the second survey. Veterans will also be asked for recommendations that could help other veterans after a suicide loss. Consistent with the explanatory, sequential, mixed methods design, we will use the quantitative findings to inform the content of the qualitative interviews. The semistructured interview guide will be further refined based on feedback from veterans participating in the study's veteran engagement group and from professional experts in postvention and trauma participating in our advisory panel. Interviews are anticipated to last up to 60 minutes.

Stakeholder Engagement

This study has 2 stakeholder engagement panels to ensure that the work is meaningful and useful to the target population, build trust in the study findings and results, and accelerate the uptake and translation of the study findings into clinical practice [23,24]. The first is a veteran engagement group with experience in consulting to researchers about research projects. At the time of proposal development, the veteran engagement group consisted of 10 veteran members varying in health status and personal backgrounds, including 5 female individuals, 4 post-9/11 veterans, 5 racial and ethnic minority individuals (1 American Indian or Alaska Native, 2 African American, 1 Pacific Islander, and 1 Asian), and 1 Hispanic or Latinx veteran. The veteran engagement group provided feedback about the topic and recruitment material during grant development. During the project, they will meet with the research team at least 3 times to provide feedback about the recruitment materials, survey content, and dissemination to veterans. The second panel comprises staff with roles in VA's suicide prevention program, the Mental Illness Research Education and Clinical Center for suicide prevention, and the National Center for PTSD and an expert in prolonged grief disorder (PGD) from outside the VA. This professional advisory panel provided consultation about the topic and its relevance for VA health care, the study-specific risk management protocol, and the survey measures to assess treatment experiences. They will ensure that the study team is aware of relevant policies and initiatives and assist with dissemination to health care system–level stakeholder groups (clinicians, program managers, and operations leaders), as relevant.

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Risk Management

Resources are provided to enhance safety and access to mental health resources for all veterans recruited for participation. For example, the recruitment material and surveys include information (either written instructions or a hyperlink) to access the Veterans Crisis Line. Furthermore, the study team will implement a detailed protocol if participants exhibit concerning behavior or express thoughts of self-directed or other-directed violence in written content on surveys or during phone calls or interviews. This protocol includes administration of the Columbia–Suicide Severity Rating Scale Adult Screener for Primary Care [25] and a warm handoff to the Veterans Crisis Line for a positive screen when possible elevated acute risk is identified.

Measures

Factors considered in measure selection were reliability and validity, use in related studies (to facilitate comparison across studies), veteran engagement panel feedback about relevance and acceptability, and participant burden. Secondary and exploratory measures are included to develop a more comprehensive understanding of the effects of suicide exposure and inform future studies.

Exposure History and Characteristics

Questions assessing suicide exposure history and exposure characteristics were drawn from the Military Suicide Research Consortium recommendations for common data elements and modified for clarity based on recommendations from the study's veteran engagement group.

Suicide exposure will be assessed using the question, "Did you personally know anyone who has died by suicide?"

Other sudden death exposure will be assessed using the question, "Did you know anyone who died suddenly from something other than suicide?" The latter question is followed with an explanation, "By 'suddenly' we mean the death was not expected or occurred within a few days. Causes of sudden death include natural disaster, medical illness (such as cardiac arrest or stroke), combat, car crashes, accidents or homicide."

For each exposure type, we will ask 6 questions. Questions 1 and 2 ascertain the number of exposures and year of the most recent exposure. As individuals may have multiple exposures and closeness to the decedent is related to outcomes [26], the remaining 4 questions ask participants to think of the person with whom they were closest who died by suicide or other sudden death while rating closeness to the decedent (5-point Likert scale ranging from "not close at all" to "very close"), perceived impact of the death (5-point Likert scale ranging from "the death had little effect on my life" to "the death had a significant or devastating effect on me that I still feel"), relationship with the decedent (eg, family member or fellow service member), and year of the death of the person with whom they were closest.

Primary Outcomes

PTSD in the past month will be assessed using the PTSD Checklist version 5, a validated 20-item self-report measure to assess the Diagnostic and Statistical Manual of Mental Disorders–Fifth Edition (DSM-5) symptoms of PTSD, with scores ranging from 0 to 80 [27,28]. Participants will be asked to complete the PTSD Checklist version 5 with respect to "the very stressful experience" that is on their mind and bothers them the most, as assessed using the measure of trauma history described in the following section. At the time of protocol development, a score ≥33 was considered to be indicative of probable PTSD [29].

PGD will be assessed using the 10 items from the Prolonged Grief-13–Revised (PG-13–R) that assess DSM-5 Text Revision symptoms of PGD on a 5-point Likert scale, with total scores ranging from 10 to 50 [30]. PG-13–R is a reliable and valid measure of maladaptive grief response consistent with the new diagnosis of PGD. Participants are asked to complete PG-13–R with respect to the "the death that was the most difficult." Following completion of the measure, participants indicate the cause of the death, year of the death, and relationship with and closeness to the decedent. Those who indicate that the cause of death was suicide or other sudden death will not be prompted to indicate closeness to and relationship with the decedent, as both were assessed in the wave-1 survey. A score ≥30 is indicative of probable PGD [30].

Suicide ideation, *attempts*, and *planning* will be assessed using the 4-item Suicidal Behavior Questionnaire–Revised [31], a measure recommended for population-based surveys because of its utility, appropriateness, and psychometric properties [32]. Item 1 assesses lifetime suicide ideation and attempts, item 2 assesses past-year suicidal ideation, item 3 assesses the threat of suicide attempt, and item 4 evaluates the self-reported likelihood of suicidal behavior in the future. We added an item to identify the person to whom participants communicated the threat of suicide attempt (item 3). Response to each item will be used to evaluate the prevalence of lifetime and past-year suicidal ideation, attempts, and planning. We will also compute total scores (range 3-18). Scores >7 are indicative of possible suicide risk in nonclinical samples [31].

Secondary Outcomes of Functioning

Community reintegration will be assessed using the Military to Civilian Questionnaire, a 16 - item self - report measure of reintegration difficulty across 5 domains of functioning [33]. Items are rated on a 5-point Likert scale ranging from "no difficulty" to "extreme difficulty." Total scores range from 0 to 4, with high scores indicating more reintegration difficulty. The scale's factor structure and association with theoretically related measures support construct validity. We are piloting the inclusion of 2 additional items to assess financial difficulty and housing instability or homelessness.

Physical and mental health–related quality of life will be assessed using the Veterans Rand–12 item health survey, an adaptation of the 36-item Medical Outcomes Study health survey that has been extensively validated in outpatient VA populations [34]. Veterans Rand–12 physical component and mental component summary scores are comparable with 36-item versions and standardized to the US population. Scores range from 0 to 100 (mean 50, SD 10).

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Secondary Clinical Outcomes

Depression will be assessed using the 8-item Patient Health Questionnaire, a screening measure to assess the prevalence and severity of depression in epidemiological studies that has strong psychometric properties [35]. Total score ranges from 0 to 24, with scores ≥10 indicative of current depression and scores ≥20 indicative of severe depression.

Anxiety will be assessed using the Generalized Anxiety Disorder 7-Item [36,37]. This scale is based on the diagnostic criteria for generalized anxiety disorder described in the Diagnostic and Statistical Manual of Mental Disorders–Fourth Edition, but there is evidence supporting its reliability and validity as a measure of anxiety in the general population [37]. Scores range from 0 to 21, with scores between 10 and 14 indicating moderate anxiety and scores between 15 and 21 indicating severe anxiety. A score ≥10 will be used to identify probable anxiety disorder [36].

Exploratory Clinical Outcomes

Exploratory clinical outcomes are other known risk factors for suicide among veterans [38].

Sleep disturbance and *impairment* will be assessed using the Patient-Reported Outcomes Measurement System Short Form Sleep Disturbance and Sleep-Related Impairment scales. These two 4-item scales (8 items in total) are rated on a 5-point Likert scale and yield total scores that range from 4 to 20 and can be converted to *t* scores, with high scores indicating great sleep disturbance or impairment [39].

Probable alcohol and *drug problems* will be assessed using the Two-Item Conjoint Screen [40]. This screen was included in the Department of Defense Post-Deployment Health Reassessments. A cutoff score of 1 had 0.80 sensitivity and specificity in patients in primary care.

Pain intensity and interference in the past week will be assessed using the 3-item Pain, Enjoyment of Life, and Activity scale. This scale has been found to have good reliability and construct validity [41]. Participants will also indicate the main causes of their pain (eg, a combat injury or a chronic health problem).

Covariates

Sociodemographics assessed using VA administrative data include sex, age, race, time since military separation, VA disability ratings, psychiatric diagnoses, medical diagnoses, and zip code of home residence. Medical diagnoses will be used to compute the Charlson Comorbidity Index scores using International Classification of Diseases–10th Revision codes [42,43]. Zip code will be used to determine region and rurality, which is associated with suicide risk [44]. These measures are available for responders and nonresponders and will be used to adjust for response bias.

Sociodemographics assessed using self-report include marital status, number of times married, education, employment, sexual orientation, and parental status. We will identify race, ethnicity, and gender identity because these variables are incomplete in administrative data. Those identifying as American Indian or Alaska Native will be asked to specify their nation or tribal affiliation, whether they reside in their reservation homeland, and whether they receive health care through the Indian Health Service. We will assess age of entry into the military, military branch and component, rank, and number of combat deployments. We will use single-item questions to assess mental health treatment history (eg, age of first mental health treatment and receipt over the past 12 months). Those who received mental health care within the past 12 months will be asked to indicate the location of care (VA or non-VA).

Trauma history will be assessed using a modified version of the Trauma Screen from the PTSD Diagnostic Scale for DSM-5. Participants indicate the very stressful events that they have experienced or witnessed at any time in their lives from a list of 8 categories (eg, assault, sexual trauma as adult, or child abuse) [45]. A follow-up question asks which of the endorsed "very stressful experiences" is on their mind and bothers them the most.

Combat experiences will be assessed using the 13 items designed to capture experiences commonly encountered during Iraq and Afghanistan deployments that are included in the Millennium Cohort Study, the largest population-based, prospective study of health and well-being in US military history. Items will be summed (range 0-26), and combat severity will be categorized as no combat (0 items), low combat (1-3 items), medium combat (4-7 items), and high combat (8-13 items), as done in previous studies [46].

Potentially Modifiable Factors

Social support will be assessed using the Postdeployment Social Support Scale from the Deployment Risk and Resilience Inventory-2 [47]. This scale measures the extent to which family, friends, coworkers, employers, and community provide emotional and instrumental support. Each of the 10 items is scored on a 5-point Likert scale, with responses ranging from "strongly disagree" to "strongly agree." Total scores range from 10 to 50. The scale has high internal consistency, and associations with mental health outcomes support its construct validity.

Perceived stigma will be assessed using the 10-item version of the stigmatization subscale from the Grief Experience Questionnaire [48]. Items (eg, "feel like the death somehow reflected natively on you or your family") are rated on a 5-point Likert scale, with responses ranging from "never" to "almost always" and total scores ranging from 10 to 50. Consistent with previous studies [48,49], we modified the stem to elicit reactions following the suicide or sudden death of the closest contact identified in the first survey. Those who have had both suicide and sudden death will be asked to select the death that was most difficult for them. Participants in the unexposed group will not complete this measure.

Meaning making will be assessed using the 6-item Integration of Stressful Life Experiences Scale–Short Form [50]. High scores indicate more adaptive meaning made following a loss. The measure has good internal consistency, test-retest reliability, and convergent validity with scales for psychiatric and bereavement distress. A total score ≤20 may be used as a cutoff for indicating problems with meaning made of loss [51]. We

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modified the stem to elicit reactions following the suicide or sudden death of the closest contact identified in the first survey. Those who have had both suicide and sudden death will be asked to select the death that was most difficult for them. Participants in the unexposed group will not complete this measure.

Everyday discrimination, an exploratory measure associated with suicide risk [52], will be assessed using the Everyday Discrimination Scale–Short Version [53]. This scale assesses frequency of exposure to 5 types of discrimination in "day to day life" rated on a 5-point scale ("never" to "at least once a week"). An additional item assesses the main reasons (eg, gender, race, and religion) for discrimination experienced at least "a few times a year."

Help-Seeking Outcomes

Treatment experiences for the loss or losses will be assessed using 14 items developed for this study based on the UK survey by Pitman et al [54] for help seeking and support following suicide and other sudden death exposure and recommendations from the study's advisory panel. Participants indicate whether they received interventions or supports after the loss from a checklist (yes or no) and, if received, how helpful it was to them on a 5-point scale ranging from "not at all helpful" to "extremely helpful." They are asked to describe other types of assistance or support they wish they had received and whether they have participated in "an event or gathering to increase awareness of suicide and suicide loss." Participants are instructed to complete this measure with respect to the suicide or sudden death of the person closest to them, as reported in wave 1, or the loss that was most difficulty for them, as identified for PG-13–R. We will derive four binary outcomes from these questions to indicate (1) receipt of any intervention from a medical professional (eg, therapist or physician), (2) receipt of any support from clergy or spiritual leaders, (3) receipt of any informal support or interventions (eg, community members, elders, friends, and family), and (4) receipt of any support or intervention rated as at least "somewhat helpful."

VA Health Care Use

We will extract CDW data about service use for the 12 months before wave-2 survey completion. Service use will be classified as mental health, primary care, and specialty care. We will use procedure codes to classify outpatient mental health care as individual psychotherapy, group psychotherapy, or other. We will use pharmacy data to identify psychiatric medication prescriptions (eg, antidepressant, antipsychotic, lithium salts, prazosin, and benzodiazepines). We will use data from templated notes to identify the use of evidence-based psychotherapies for PTSD, depression, and insomnia among those who meet the survey criteria for these conditions. Outcomes will be binary (yes vs no for each type of service) and continuous (number of appointments per service category and inpatient length of stay over the preceding 12 months).

Suicide attempts reported to VA clinicians will be extracted from the CDW, based on data automatically generated from the Comprehensive Suicide Risk Evaluations and Suicide Behavior and Overdose Report, either of which VA requires for reporting suicide behavior. We will identify nonfatal events using the self-directed violence classification of suicide attempt with injury or suicide attempt without injury, based on self-directed violence classification guidelines developed by the Centers for Disease Control and Prevention and adopted by the VA.

Analysis

Power

The anticipated wave-2 sample size (n=4500) will provide >90% power for a global likelihood ratio test and for pairwise comparisons for a range of considered differences between exposure history groups in the distribution of a binary outcome (hypothesis 1). The configurations considered for the trio of outcome rates in these calculations comprised differences between the middle rate and each of the lower and higher rates corresponding to approximately half of the middle rate. Among female veterans (anticipated n=900), the study should have >82% power. Among American Indian and Alaska Native veterans (anticipated n=540), the global comparisons will have >82% power. Power for the pairwise comparisons will be limited for comparisons involving an exposure history group with very low representation of American Indian or Alaska Native veterans. Power to detect moderation (hypothesis 2) is determined by sample size, prevalence of the exposure history classification, prevalence of the moderator within each group, and outcome rates for the different combinations of exposure and moderator measures. Under different plausible scenarios for these measures, power to detect the interaction ranges from 0.81% to 0.87%.

As discussed previously, little is known about the response rates of veterans to surveys regarding suicide exposure. The study population is sufficiently large that obtaining ≥10,000 respondents for the wave-1 survey is highly likely by sufficiently increasing the selected sample for this aim. The precision of the estimation of exposure rates among this population then will be less affected by sample response rates and sample size than response bias. For wave 2, we may find that those with no exposure are less willing to participate and that the cohort of wave-1 respondents willing to participate in wave 2 is shifted toward those with suicide or other sudden death exposure. In this event, we will likely need to alter the planned analysis to focus on comparing the suicide and other sudden death exposure groups. However, we would expect that the power available for the analyses will be comparable with or larger than the power discussed previously for analyses within female and American Indian and Alaska Native veterans.

Preliminary Analyses

We will construct nonresponse-adjusted, sample inclusion probability–weighted estimates of the prevalence of suicide exposure, sudden death exposure, and the combination of exposures (exposure to suicide and other sudden death) and the prevalence of the study outcomes. We will use administrative data together with the survey sampling strata to develop logistic regression models for the probability of survey response for each survey. We will then adjust the initial survey weights based on the estimated probability of survey response to generate weights for use in analysis. If there is <3% of missing data for

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the survey items required for a particular analysis, we will further adjust the weights within classes of individuals with similar response propensities from the same stratum to address missing data. If the amount of missing survey items exceeds 3%, we will use the available survey and administrative data in a chained sequence of regression analyses to impute missing survey items [55]. We will then use the imputed data to implement the weighted analyses described in the following section.

Aims 1, 2, and 3

For aim 1, we will use nonresponse-adjusted, sample inclusion probability–weighted logistic regression analyses for the outcomes with sampling strata and exposure categories as explanatory measures. We will conduct global Rao-Scott likelihood ratio tests to assess the differences in prevalence of the primary outcomes between exposure history groups followed by tests for pairwise differences between groups (hypothesis 1). To assess whether associations between exposure and outcomes persist when adjusting for covariates, we will expand these models to include closeness to the decedent or decedents, an interaction between exposure history group and closeness, and the sociodemographic and trauma history covariates. If there does not appear to be an interaction, we will simplify the model. We will also expand the analyses to include interactions of exposure history group with number of death exposures, time since exposure, and time since military separation to examine whether associations vary with these covariates. We will summarize the differences between exposure history groups using model-estimated odds ratios and CIs.

To assess whether the differences between exposure history groups vary with sex and race, we will use similar Rao-Scott likelihood ratio tests to compare weighted logistic regression models incorporating exposure history, sex or race, the respective interaction with exposure, closeness of decedent, and sociodemographic and trauma history covariates with models that do not include the exposure by sex or exposure by race interaction. Additional analyses will examine the differences in total scores (continuous measures) for the outcomes, modifying the abovementioned analyses to use weighted multiple linear regression models. Similar likelihood ratio tests will be used and the differences between exposure history groups will be summarized with model-estimated least square mean differences and corresponding CIs. We will also conduct a similar set of analyses to explore whether the prevalence of the outcomes differ based on the use of VA services (any and mental health) in the previous year.

For aim 2, we will add the potential modifying factor (eg, social support or stigma for hypothesis 2) and the interactions with exposure history and with decedent closeness to the model developed for aim 1. We will use Rao-Scott likelihood ratio tests to assess whether the association between exposure history and a given outcome varies across levels of the moderating factor or across levels of exposure and decedent closeness. If we obtain significant results for a test of an interaction between exposure and a moderator, model-estimated associations between the moderator and the outcome within exposure history groups and additional pairwise contrasts between exposure history groups conditional on the various values of the moderator will be examined.

For our exploratory aim 3, we will create summary measures of treatment experiences, reported suicide attempts, and VA service use and then, similar to aim 1, construct weighted estimates of the prevalence of these treatment measures, along with 95% CIs, in the exposure history groups and compare these using weighted logistic regression analyses with Rao-Scott likelihood ratio tests. Within exposure history groups, among those we have identified as meeting the survey criteria for the clinical conditions, we will estimate the population rates of receiving VA mental health care (yes, no, number of sessions, type of therapy, and report of attempt) during the year before the survey using finite population sampling domain estimation methods. We will then assess whether these vary based on sex and race.

Aim 4 Qualitative Analysis

We will use a qualitative data management software package to facilitate the coding and retrieval of qualitative themes. Coders will apply a priori–determined, first-level codes that correspond to the interview domains (eg, social support, professional help, and stigma). We will use a constant comparative analysis approach in which we begin to review data as soon as the first interviews are conducted to permit the identification of emerging issues to be included where appropriate in the ongoing interviews. We will review all proposed codes in weekly meetings to derive an initial codebook. We will elaborate upon the codebook and adjust content as each interview is reviewed, through practice coding and interview reviews until we have finalized the code list. Before independent coding, we will practice coding as a team until we reach consensus and record all decisions to create an audit trail. In addition, we will double code at least 20% of the transcripts, ensuring that each coder codes at least one of the transcripts of each of the other coders and ensure acceptable interrater reliability. Discrepancies will be resolved in team meetings. After coding is complete, we will produce code reports that include all subcodes for each selected first-level code and by veteran mental health status (clinical vs nonclinical interview groups). We will use the code reports to synthesize patterns of responses related our domains of inquiry into larger themes.

For aim 4, interpretation will involve the identification of differences in modifiable factors across our clinical and nonclinical groups. For example, we will examine whether veterans who differ in outcomes describe differences in how people in the community supported them or in their treatment experiences. We will examine convergence and expansion across the quantitative and qualitative data [56].

Ethical Considerations

The Minneapolis VA Health Care System Insitutional Review Board (IRB) granted this protocol (reference number 1676462) an exempt determination under category 2 (research that involves surveys or interview procedures) subparts 2 (disclosure would not be harmful) and 3 (IRB conducts limited review to make the required determination that there are adequate provisions to protect the privacy of participants and to maintain

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the confidentiality of data). The IRB also granted a Waiver of Health Insurance Portability and Accountability Act Authorization for all study procedures involving the collection or use of protected health information. The overseeing Research and Development Committee has reviewed and approved all amendments or modifications to study procedures and materials.

Results

This project began on July 1, 2022. The study team includes experts in suicide exposure, suicide prevention, traumatic stress, epidemiology, survey development and methods, statistics, programming, and VA administrative data. A veteran engagement group and an advisory panel of professional experts provide additional guidance throughout the study. Milestones so far include the identification of the sampling frame, implementation of the first phase of the stratified random sampling plan, refinement and preparation of the recruitment material and surveys, and piloting of survey methods in a sample of approximately 800 veterans to identify and resolve challenges before scaling up. Pilot enrollment began on May 1, 2023.

The study's funding period will end on June 30, 2026. The veteran engagement group will help us identify the findings that are most important to veterans, including study participants and dissemination vehicles (eg, the study website, publications for service members and veterans, and veterans service officers). We will collaborate with the professional advisory panel to disseminate key findings to VA operational stakeholders and clinicians. Findings will be disseminated to the scientific community through publications and presentations.

Discussion

Summary

This is the only national, population-based study of suicide exposure in veterans and the first one designed to study differences based on sex and race. It is an initial, crucial step in addressing the dearth of studies of suicide risk in American Indian and Alaska Native veterans and fills the knowledge gaps identified by the US National Alliance for Suicide Prevention, including the need for reliable and valid estimates of suicide exposure and the impact of exposure to suicide [17]. This information is needed to identify postvention strategies and interventions that address the needs of those affected by suicide loss or combinations of suicide, other losses, and trauma and whether these needs differ based on sex and race.

We are prioritizing outcomes associated with trauma and loss. However, the rich data set this study creates may yield novel information about the effect of suicide exposure on health and functioning that have not been hypothesized. Analyses involving secondary and exploratory measures and VA health care use may pave the way for full understanding of the effects of suicide loss and help identify those at risk for being most affected. As such, we anticipate that this data set will lay the foundation for studies that go beyond the aims of this project. Possibilities for future studies include epidemiologic studies of outcomes beyond those we are able to examine as part of this project (eg, the longitudinal course of physical and mental health effects of suicide loss and other sudden death) and, alternatively, studies that prioritize qualitative data collection and analysis to obtain a more complete understanding of risk and protective factors following exposure to suicide or other sudden and traumatic death.

A challenge for studies in this area is that veterans may have been exposed to >1 suicide or other sudden death from combat or other reasons [9,16]. Consistent with previous studies, we are asking participants to focus on the suicide and sudden death of the person with whom they were closest because this is the loss that is likely to have the most significant effect on them [26]. Relatedly, participants may have PTSD owing to the suicide exposure or another stressor, and they may have PGD owing to suicide exposure or another death. To provide more clarity regarding the sources of their symptoms, we are asking participants to specify and use as a referent the trauma and death that was the most difficult for them. However, participants may have difficulty in separating their response to 1 loss or trauma from their responses to others. In our analyses, we will examine the timing, number, and combinations of exposures in an effort to better understand how multiple losses and trauma of different types interact to affect outcomes.

We are assessing exposure history through survey because we are not able to ascertain exposure history through medical records. Challenges associated with survey data collection include the possibility that response rates may be lower than expected and vary based on exposure history, sex, or race. In anticipation of these potential problems, we will recruit in batches, closely monitor participation rates, and adjust the recruitment methods and the sampling plan in an effort to approximately achieve the desired number of wave-1 and wave-2 responders per stratum. In the analysis, we will use inverse probability weights to help account for differential responses and weigh estimates back to the population. We will also report all results with CIs as measures of precision, irrespective of *P* values, so that our results can still lay a foundation for future studies.

We also recognize that the prevalence of suicide exposure, other sudden death exposure, and neither may be different than expected based on previous studies with veterans from earlier service eras [12]. If the wave-1 survey does not provide an adequate number of veterans in each exposure history group for our second survey, we may have to adjust our analysis plan. This may occur if, for example, the proportion of post-9/11 veterans unexposed to either suicide or sudden death is very low.

This study does not allow us to examine the longitudinal course of symptoms in our exposure history groups, an important topic with clinical implications. Unfortunately, additional waves of data collection would not be feasible within the funding mechanism's budget cap. We will, however, be able to evaluate the effect of time since exposure in our analyses. A limitation associated with our sampling strategy is the lack of inclusion of post-9/11 veterans who are not enrolled in VA health care and are at high risk for suicide [1]. However, as not all enrolled veterans use service regularly, we will be able to compare those

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who have with those who have not used VA health care in the previous year.

Despite these limitations, this study addresses knowledge gaps and will direct VA and the field toward an understanding of the most critical outcomes among veterans exposed to suicide and the mechanisms that may lead to deleterious outcomes and lay a foundation for the development and implementation of effective postvention interventions.

Conclusions

This study addresses an understudied risk factor for suicide—suicide exposure. Integrating survey, VA administrative, and qualitative data to address significant knowledge gaps regarding the effects of suicide exposure will lay the foundation for interventions to address the needs of post-9/11 veterans affected by a suicide death, including female and American Indian and Alaska Native veterans. By advancing the scientific understanding of suicide loss compared with other sudden deaths, findings have the potential to also inform postvention research and interventions more broadly.

Acknowledgments

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review of grant material from the HSR-4 Mental and Behavioral Health, Health Services Research Parent IRG, Office of Research & Development, HSR4 (USA).
[PDF File (Adobe PDF File), 135 KB - resprot_v12i1e51324_app1.pdf]

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Abbreviations

CDW: Corporate Data Warehouse
DSM-5: Diagnostic and Statistical Manual of Mental Disorders–Fifth Edition
IRB: institutional review board
PG-13–R: Prolonged Grief-13–Revised
PGD: prolonged grief disorder
PTSD: posttraumatic stress disorder
VA: Department of Veterans Affairs

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Protocol

Adaptation in Young Military Recruits: Protocol for the Advancing Research on Mechanisms of Resilience (ARMOR) Prospective Longitudinal Study

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Abstract

Background: Military services provide a unique opportunity for studying resilience, a dynamic process of successful adaptation (ie, doing well in terms of functioning and symptoms) in response to significant adversity. Despite the tremendous interest in positive adaptation among military service members, little is known about the processes underlying their resilience. Understanding the neurobiological, cognitive, and social mechanisms underlying adaptive functioning following military stressor exposure is essential for enhancing the resilience of military service members.

Objective: The primary objective of the Advancing Research on Mechanisms of Resilience (ARMOR) longitudinal study is to characterize the trajectories of positive adaptation among young military recruits in response to basic combat training (BCT), a well-defined, uniform, and 10-week period of intense stress (aim 1), and identify promotive and protective processes contributing to individual variations in resilience (aim 2). The secondary objective is to investigate the pathways by which neurobehavioral markers of self-regulation assessed using electroencephalography and magnetic resonance imaging contribute to adaptive trajectories (aim 3).

Methods: ARMOR is an ongoing, prospective longitudinal cohort study of young military recruits who recently joined the National Guard but have not yet shipped out for BCT. Participants (N=1201) are assessed at 5 time points over the initial >2 years of military service beginning before BCT (baseline) and followed up at 2 weeks and 6, 12, and 18 months after BCT. Participants complete web-based questionnaires assessing vulnerability and protective factors, mental health, and socioemotional functioning at each time point and a battery of neurocognitive tests at time 0. A subset of participants also complete structured diagnostic interviews and additional self-report measures and perform neurobehavioral tasks before and after BCT during electroencephalography sessions and before BCT only during magnetic resonance imaging sessions.

Results: This UG3/UH3 project was initially funded in August 2017, with the UG3 pilot work completed at the end of 2018. The UH3 phase of the project was funded in March 2019. Study enrollment for the UH3 phase began on April 14, 2019, and ended on October 16, 2021. A total of 1201 participants are enrolled in the study. Follow-up data collection for the UH3 phase is ongoing and projected to continue through February 2024. We will disseminate the findings through conferences, webinars, open access publications, and communications with participants and stakeholders.

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Conclusions: The ARMOR study provides a rich data set to identify the predictors and mechanisms of resilient and nonresilient outcomes in the context of military stressors, which are intended to empirically inform the development of prevention and intervention strategies to enhance the resilience of military trainees and potentially other young people facing significant life challenges.

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KEYWORDS

study protocol; military personnel; longitudinal studies; resilience; adaptive behavior; stress; adversity; mechanisms; protective factors

Introduction

Background

Across the military career life cycle, service members are at a considerable risk for exposure to stressors that may impact their health, well-being, and performance [1-3]. Extensive research has identified factors that contribute to the risk for psychopathology (eg, posttraumatic stress symptoms and depression) following combat exposure and other military-related stressors [4-6]. However, mounting evidence suggests that most individuals show resilience, adapting successfully to risk and adversity [7,8]. Understanding the neurobiological, cognitive, and social mechanisms underlying successful adaptation following military stressor exposure is essential for designing prevention and intervention strategies to enhance resilience in military populations [9]. However, the mechanisms and processes that facilitate resilience following military stressors remain poorly understood.

Most studies on resilience within the military context have operationalized resilience as a static, trait-like attribute or have relied on cross-sectional designs [10]. One-time assessments of adaptation, adversity exposure, and resilience, particularly through self-report questionnaires, provide very limited insights into risk and protective processes and their influence on later mental health outcomes. There is now a growing consensus that resilience is a multidimensional and dynamic process that unfolds over time in response to a challenge [11-14]. We define resilience as the capability of a system to adapt successfully through multiple processes to challenges that threaten the system function [12]. In addition, the resilience of an individual draws on support from systems beyond the individual, including supportive relationships, such as battle buddies or a supportive unit [15,16]. Variations in the nature and timing of adversity exposure also influence how individuals adapt, and it is ideal to assess adaptive functioning before, during, and following exposure to well-described uniform stressors. Basic combat training (BCT) provides a systematic and relatively uniform challenge with known timing, so assessments of adversity, potential vulnerabilities, and protective influences, as well as adaptive functioning, can be performed before, during, and following a well-described period of challenge. Therefore, our approach to operationalizing resilience calls for a prospective, longitudinal study that tracks the adaptation of military service members over time with assessments before and after BCT and related, well-defined challenges.

A growing body of longitudinal research with military populations has identified distinct latent classes (groupings) of service members demonstrating similar trajectories of adaptation over time [7,8,17]. This literature suggests that there is significant heterogeneity in people's responses to comparable stressors. However, these studies have generally examined trajectories following deployment and across the transition from military to civilian life [18,19]. Little research has focused on young military recruits from the outset of their military careers. During the initial years of military service, recruits are faced with numerous challenges (eg, moving away from home, separation from family and friends, dramatic changes in the living environment, and intense military training) as they are encultured into military life. Moreover, for most recruits, this transition from civilian to military life occurs within the context of the transition from adolescence to emerging adulthood [20]. Identifying potential contributing factors linked to risk and resilience early in military service may be particularly useful for effectively intervening in service members during this key developmental transition. Longitudinal studies have also examined a limited number of outcomes in isolation (eg, posttraumatic stress disorder [PTSD], depression, and alcohol use). Our conceptualization of resilience as a multidimensional process in which a person may show successful adaptation within some domains but not others [21] calls for research that assesses multiple outcome domains (eg, internalizing symptoms, externalizing problems, and social-occupational functioning) over time. Finally, prior research has investigated the role of demographic characteristics (eg, age and gender), psychological factors (eg, neuroticism and self-efficacy), and environmental factors (eg, social support and subsequent life stressors) in differentiating individuals who manifest resilience from those who exhibit maladaptive trajectories [8,18,19]. Few studies have integrated neurobehavioral paradigms into longitudinal cohort studies [7,22], so the neurobiological, cognitive, and behavioral processes contributing to trajectory membership remain largely unknown.

Drawing on the aforementioned literature, the Advancing Research on Mechanisms of Resilience (ARMOR) study was established at the Minneapolis Veterans Affairs Health Care System (MVAHCS) and the University of Minnesota-Twin Cities (UMN) [23]. The overarching goal of this prospective, longitudinal cohort study with an embedded laboratory substudy is to develop a comprehensive, multilevel model of resilience to guide the development of prevention and intervention

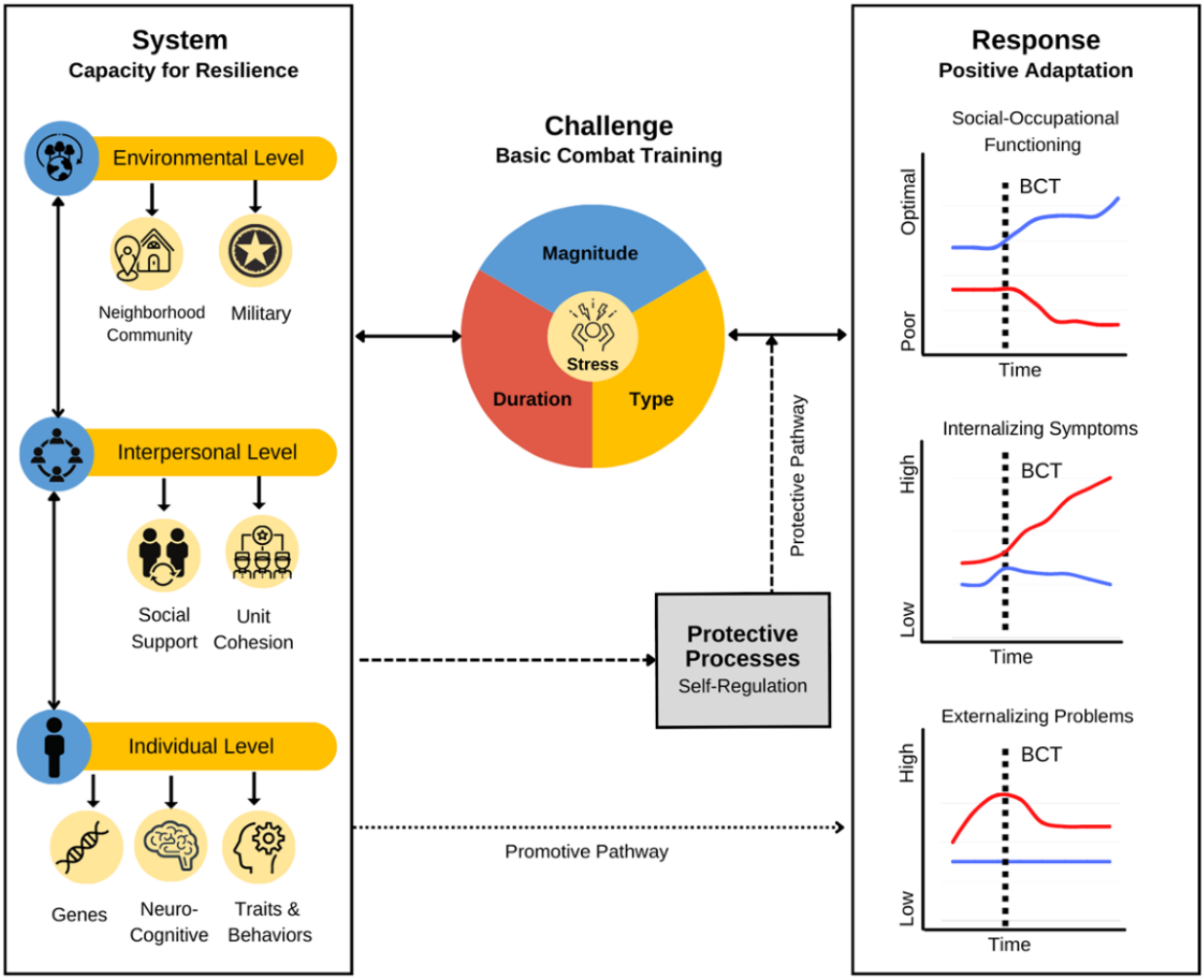
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strategies for military trainees and potentially other young people facing significant life challenges.

Figure 1 presents the basic conceptual model guiding this study [24]. It recognizes that individuals are embedded within a complex system of risk and protective factors that span multiple levels, from individual neurobiological and behavioral factors to social and broader environmental factors. This multisystemic perspective acknowledges the dynamic and reciprocal relationships among these influences and their joint impact on resilience [25]. The model also emphasizes potential pathways to risk and resilience in the face of adversity (shown as blue and red lines in response to BCT). Challenging life experiences in the past and at present, including childhood adversity or trauma and exposure to military training, can heighten the risk of developing psychopathology. As illustrated by the dotted line in Figure 1, promotive factors, such as cognitive ability and social support, directly contribute to positive adaptation, regardless of the risk level. The dashed line in Figure 1 illustrates how protective factors can act as buffers against the detrimental effects of adversity. In the ARMOR study, the focus is on investigating self-regulation as a key protective process contributing to resilience.

Self-regulation comprises 3 distinct but interrelated neurocognitive processes involving affect, behavior, and cognition, which together can facilitate adaptive responding to adversity [26]. Attentional control involves the ability to concentrate and sustain attention despite distractions, inhibitory control refers to the regulation of maladaptive behavior in favor of goal-directed actions, and behavioral flexibility enables the adaptation of behavioral strategies to meet environmental demands. Previous studies using laboratory-based paradigms have identified significant associations among these self-regulatory processes and measures of trait resilience, implying their potential as stress-buffering mechanisms [27]. However, few studies have examined neurobiological, cognitive, and behavioral processes in relation to resilience trajectory membership [7].

Figure 1. Integrated multilevel model of resilience for military service members. Conceptual model of resilience as a dynamic process in response to the challenges of basic combat training (BCT). Risk and protective factors across multiple levels (individual, social, and environmental) are depicted in the box on the left. Promotive and protective pathways are depicted with dashed and dotted lines, respectively. Positive (blue) and negative (red) responses to the challenges of BCT are shown in the graphs in the box on the right. This figure is from the study by Polusny and Erbes [24] and used under Creative Commons CC-BY) license.



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Objectives

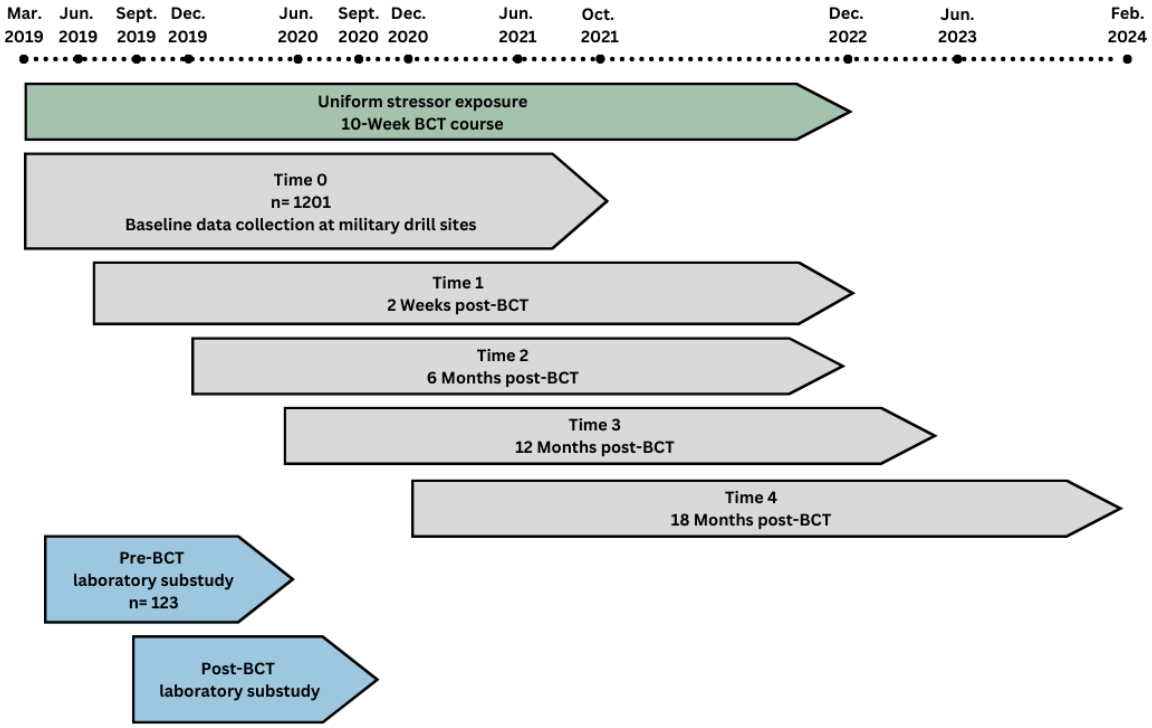
The primary objective of the ARMOR study is to characterize the trajectories of adaptation among young military recruits in response to BCT over the first 2 years of military service (aim 1) and identify promotive factors and protective processes contributing to individual variations in adaptation (aim 2). The secondary objective is to investigate whether neurobehavioral markers of self-regulation are predictive of resilient and nonresilient trajectories (aim 3).

Methods

Study Design

ARMOR is a prospective, longitudinal cohort study of young military recruits, including those aged 17 years at study entry, that investigates the mechanisms contributing to manifested resilience across multiple levels of analysis (neural, cognitive, behavioral, and social). The study includes the following two components: (1) a web-based longitudinal survey component, including self-report measures presented via Qualtrics (Qualtrics International Inc) and neurocognitive tests administered using the Penn Computerized Neurocognitive Battery (PCNB); and (2) a laboratory substudy component consisting of clinical diagnostic interviews, additional self-report questionnaires, and a series of performance-based tasks involving electroencephalography (EEG) and magnetic resonance imaging (MRI) assessments. We aimed to enroll a cohort of at least 1200 young military recruits who recently enlisted in the Minnesota Army National Guard. Participant recruitment began on April 14, 2019, and ended on October 16, 2021. Data collection is ongoing and is expected to continue into 2024. As shown in Figure 2, participants were assessed at baseline (time 0) before exposure to a uniform military challenge (BCT) and are currently being followed up at 4 time points (study is ongoing): 2 weeks following return from BCT (time 1) and at 6 months (time 2), 12 months (time 3), and 18 months (time 4) after BCT. A subset of participants from the longitudinal cohort (123/1201, 10.24%) completed the laboratory substudy procedures before shipping out for BCT (before BCT) and after returning from the training (after BCT).

Figure 2. Advancing Research on Mechanisms of Resilience (ARMOR) study timeline. BCT: basic combat training.



Context and Setting

This study aims to investigate mental health and adaptive functioning among young military recruits before and immediately after BCT and beyond, offering a unique opportunity to study resilience in response to a well-defined, naturally occurring, and uniform military stressor. BCT is a mandatory, intensive, and 10-week training course that all military recruits must successfully complete. The training environment is highly structured and characterized by low personal autonomy, with strict discipline enforced by drill instructors [28]. One distinctive aspect of BCT is the deliberate introduction of numerous stressors into the training environment, designed to prepare recruits for the challenges they will face in future military life [29]. These challenges include prolonged separation from family and friends, dramatic changes in the living environment, extreme physical demands, mental challenges, and simulated combat. This process is believed to foster unit cohesion and cultivate a strong sense of mental and physical toughness known as the *warrior ethos*. Previous research has shown that BCT has positive effects on cognitive performance, mood, and physical fitness [30-34], and it is associated with increased unit cohesion over time, which, in turn, leads to reduced psychological distress and improvements in tolerating training stressors [35].

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Although most military recruits successfully adapt to the challenges of BCT, some recruits experience it as highly stressful. A considerable percentage (approximately 20%) of National Guard recruits fail to complete BCT [36]. This suggests that although BCT is a uniform stressor experienced by all recruits, its impact and perceived stressfulness vary among individuals. A study of Swiss Armed Forces recruits participating in a 21-week BCT course found that higher perceived stress at the beginning of the training was associated with greater mental distress and poorer military performance at later stages [37]. Previous studies focusing solely on BCT completers have overlooked valuable data from a significant minority of individuals who exhibit reduced resilience.

To comprehensively understand how BCT influences adaptive functioning and study resilience processes over time, we use a prospective, longitudinal research design with data collection before and after the relatively uniform stressor of BCT. This design makes it possible to capture changes within participants over time and allows us to test the temporal order of variables. Longitudinal designs permit stronger inferences about causal effects, although not with the rigor of a randomized controlled trial. Our design also provides insights into the underlying mechanisms contributing to individual variations in resilience and lays the groundwork for studying the impact of unforeseen events, such as the COVID-19 pandemic and military deployments, on resilience trajectories. By evaluating the perceived frequency and intensity of stressor exposure during BCT, we capture the individual experiences of military recruits. Furthermore, our focus on young, healthy participants at the beginning of their military careers, *before* significant exposure to military stressors, enables us to take a developmental approach to studying resilience within a military context. Finally, the integration of a laboratory substudy within our research design provides an opportunity to conduct in-depth, multilevel assessments of a subset of the cohort. This laboratory substudy allows us to investigate neurobehavioral markers of self-regulation that may predict resilience trajectories, enhancing our understanding of the underlying mechanisms associated with resilience in the context of military training.

Participants and Recruitment

The enrollment of participants in this study was based on specific inclusion criteria. Individuals aged ≥17 years who were newly enlisted members of the National Guard and had been assigned a ship date to complete BCT during the study period were eligible for participation. Exclusion criteria included a history of prior military service or any previous experience with BCT.

To recruit participants, a consecutive approach was used within designated National Guard Recruitment Sustainment Program (RSP) units across the state until the target sample was reached. The research team recruited participants between April 2019 and October 2021 using briefing presentations held during drill events at military posts. The relevant Army National Guard command provided the research team with a list of all potentially eligible military service members. During the briefings, interested individuals were provided with a study packet, which included a consent or assent letter, a "Help Us Keep in Touch" locator form, a "What to Expect Next" card illustrating the study design in layperson's terms, and a randomly generated unique study ID number. Throughout the recruitment process, detailed documentation was maintained. This included recording the total number of eligible military service members approached as well as the number of participants enrolled, those who refused to participate, and those found to be ineligible based on the inclusion and exclusion criteria.

Ethical Considerations

This study was reviewed and approved by the institutional review boards of the UMN (STUDY00004470) and the MVAHCS (VAM-18-00334/1594664). All study procedures were also approved by the relevant military command. All participants provided informed consent. Participants were provided with a letter that explained all the procedures, risks, and benefits. This information was verbally presented during the briefings, and participants indicated their consent to take part in the survey component by entering a unique study ID number to begin the web-based survey. A waiver of the requirement to document consent for the survey component of this study was granted. The survey component of this study was also provided an approval to include individuals aged <18 years under 21 CFR 50.51/45 CFR 46.404. From the subset of participants aged ≥18 years taking part in the laboratory substudy, written informed consent was obtained before participation in any laboratory study procedures. Participants in the longitudinal survey component of the study will be compensated up to US $150 for the completion of all the currently planned survey waves (US $25 for the time-1 survey, US $35 for the time-2 survey, US $40 for the time-3 survey, and US $50 for the time-4 survey). Owing to military regulations, articipants were not compensated for participating in the baseline (time 0) survey. Participants in the laboratory component were compensated up to US $400 for the completion of both the pre-BCT and post-BCT visits.

Survey Data Collection Procedures

For the web-based survey component conducted at baseline (time 0), participants were asked to complete a battery of self-report questionnaires on Qualtrics as well as select tests from the PCNB. Time-0 data were collected using study Chromebooks (Google LLC) in classrooms at local armories. Participants were instructed to log into a secure web-based Qualtrics platform using their unique study ID for authentication. Most participants completed the baseline data collection procedures within 90 to 120 minutes.

As exposure to BCT is required for continued follow-up, participants are monitored over the course of the study and retrospectively excluded if they are discharged before exposure to BCT. Participants' exposure to BCT is verified before the initial follow-up wave (time 1), and those eligible to continue study participation are invited to complete the battery of self-report questionnaires at each follow-up time point. All follow-up assessments are completed outside the drill training. Participants complete either a confidential web-based survey of the battery of computerized self-administered questionnaires linked to the participants' study ID or a paper-and-pencil version of questionnaires marked with the participants' study ID.

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To ensure the continuity of follow-up assessments, we adapted the longitudinal retention model developed by Scott and colleagues [38] to engage and maintain contact with participants from enrollment to the final follow-up time point. During enrollment, participants were asked to provide detailed contact information, BCT ship and return dates, and full contact information for 3 alternate contacts who can help the study team locate the participant if needed. Study engagement will be maintained between follow-up waves through periodic communication (ie, newsletters and greeting cards), and survey nonrespondents will be contacted to encourage survey completion.

Measures

Self-Report Variables

Table 1 lists the self-report questionnaires administered via Qualtrics at baseline and at each follow-up time point. This battery of measures assesses 8 domains (internalizing symptoms, externalizing problems, social-occupational functioning, health, self-regulation processes, supportive relationships, personality, and vulnerability or risk factors). Although most questionnaires are repeated across all time points (time 0 to time 4), as they are critical for tracking outcome trajectories and resilience processes, some are completed only at time 0 (ie, personality) or time 1 (ie, BCT stressor exposure), as they do not require repeated assessment.

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Table 1. Self-report measures administered over time in the Advancing Research on Mechanisms of Resilience longitudinal study.

Outcome domains and measures	Items, n	Time 0[a]	Time 1[b]	Time 2[c]	Time 3[d]	Time 4[e]
Internalizing symptoms						
PROMIS[f]-Depression 4 Scale [39]	4	✓	✓	✓	✓	✓
PROMIS-Anxiety 4 Scale [39]	4	✓	✓	✓	✓	✓
PROMIS-Anger 5 Scale [39]	5	✓	✓	✓	✓	✓
Primary Care PTSD[g] Screen for DSM-5[h] [40]	6	✓	✓	✓	✓	✓
Externalizing problems						
Behavioral Report on Rule-Breaking Questionnaire [41]	18	✓	✓	✓	✓	✓
Alcohol Use Disorders Test [42]	10	✓	✓	✓	✓	✓
Drug Abuse Screening Test [43]	10	✓	✓	✓	✓	✓
Social-occupational functioning						
PROMIS–Role Satisfaction Scale [44]	4	✓	✓	✓	✓	✓
PROMIS–Social Participation Scale [44]	4	✓	✓	✓	✓	✓
Couple Satisfaction Inventory [45]	4	✓	✓	✓	✓	✓
Revised Conflict Tactic Scale [46]	2	✓	✓	✓	✓	✓
Health and Work Performance Questionnaire [47]	12	✓	✓	✓	✓	✓
Utrecht Work Engagement Scale [48]	9	✓	✓	✓	✓	✓
Health						
Patient Health Questionnaire-15 [49]	15	✓	✓	✓	✓	✓
Graded Chronic Pain Scale-Revised [50]	6		✓	✓	✓	✓
Self-regulatory processes						
Difficulties in Emotional Regulation Scale-16 [51]	16	✓	✓	✓	✓	✓
Multidimensional Experiential Avoidance Questionnaire-30 [52]	30	✓	✓	✓	✓	✓
Attention Control Scale [53]	20	✓	✓	✓	✓	✓
Flexible Regulatory Emotional Expression Scale [54]	16	✓	✓	✓	✓	✓
Identity Coherence Scale [55]	12	✓	✓	✓	✓	✓
Response to Stressful Experiences Scale [56]	22	✓	✓	✓	✓	✓
Supportive relationships						
PROMIS-Emotional Support 4 Scale [57,58]	4	✓	✓	✓	✓	✓
PROMIS-Informational Support 4 Scale [57,58]	4	✓	✓	✓	✓	✓
PROMIS-Instrumental Support 4 Scale [57,58]	4	✓	✓	✓	✓	✓
DRRI-2[i] Unit Support Scale [59]	12	✓	✓	✓	✓	✓
Personality						
Multidimensional Personality Questionnaire-Brief Form [60]	155	✓				
Triarchic Psychopathy Measure [61]	58	✓				
Vulnerability or risk factors						
Adverse Childhood Experiences Questionnaire [62][j]	17	✓			✓	
DRRI-2 Prior Stressors Scale [59]	18	✓				
DRRI-2 Adapted Postdeployment Life Stressor Scale [59]	14		✓	✓	✓	✓
Suicidal Ideas and Behaviors Questionnaire [63]	6	✓				
Basic Training Stressors Scale [23]	14		✓			

[a]Baseline, before basic combat training.

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[b]2 weeks after basic combat training.

[c]6 months after basic combat training.

[d]12 months after basic combat training.

[e]18 months after basic combat training.

[f]PROMIS: Patient Reported Outcomes Measurement Information System.

[g]PTSD: posttraumatic stress disorder.

[h]DSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.

[i]DRRI-2: Deployment Risk and Resilience Inventory-2.

[j]Adverse Childhood Experiences Questionnaire adapted for youths at time 0.

Outcomes

Primary outcomes include trajectories of internalizing symptoms, externalizing problems, social-occupational functioning, and global adaptive functioning. Secondary outcomes are self-reported self-regulatory processes, neurobehavioral markers of self-regulation, and ecologically valid markers of functioning extracted from administrative military records.

Neurocognitive Measures

Table 2 lists the neurobehavioral functions and major cognitive domains assessed by tests from the PCNB administered at baseline. Neurocognitive tests measure performance accuracy (eg, proportion of correct responses) and speed (eg, median correct response time) in major cognitive domains [64].

Table 2. Neurobehavioral functions and domains assessed using tests from the Penn Computerized Neurocognitive Battery at baseline in the Advancing Research on Mechanisms of Resilience longitudinal study.

Neurobehavioral Function	Domain	Test
Executive control	Attention	Penn Continuous Performance Test
Complex cognition	Language reasoning	Penn Verbal Reasoning Test
Episodic memory	Face memory	Penn Facial Memory Test
Social cognition	Emotion differentiation	Penn Emotion Differentiation Test

Laboratory Substudy Procedures

A subsample of the longitudinal cohort (123/1201, 10.24%) was recruited for a laboratory visit, both before and after BCT. Laboratory participants were selected based on their responses to baseline self-report measures and a predictive algorithm developed in the pilot UG3 phase of this project (details reported elsewhere; S Noorbaloochi et al, unpublished data, 2023). This strategy was intended to provide a subsample enriched with participants at a relatively high risk of maladaptive functioning (~72/123, 58.5%) compared with a low-risk group (~48/123, 39%). Participants were briefly screened via phone call, and those reporting contraindications to MRI due to the potential presence of metal in the body (eg, participants employed as a metal worker or participants with implanted medical devices) or due to problems with being in enclosed places were excluded.

Data for the laboratory substudy were collected during an 8- to 9-hour combined pre-BCT laboratory visit to the MVAHCS and UMN Center for Magnetic Resonance Research and during a 4- to 5-hour post-BCT laboratory visit at the MVAHCS. During the pre-BCT and post-BCT laboratory visits, participants completed a structured clinical interview (1-2 hours) with a trained master's level assessor under the supervision of a licensed clinical psychologist (CRE or PAA). The Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) was used to diagnose lifetime mental disorders and determine whether the disorder is "current" [65]. The Clinician-Administered PTSD Scale for DSM-5 was used to diagnose PTSD [66]. Participants also completed a battery of self-report measures assessing constructs related to self-regulation (Table 3).

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Table 3. Self-report measures administered in the Advancing Research on Mechanisms of Resilience laboratory substudy before and after basic combat training (BCT).

Measure	Items, n	Pre-BCT laboratory visit	Post-BCT laboratory visit
Patient Health Questionnaire-9 [67]	9	✓	✓
Beck Depression Inventory-II [68]	21	✓	✓
Depressive Symptom Index-Suicidality Subscale [69]	4	✓	✓
State Trait Anxiety Inventory [70]	40	✓	✓
Positive and Negative Affect Schedule [71]	20	✓	✓
Multidimensional Experiential Avoidance Questionnaire [72]	62	✓	✓
Anxiety Sensitivity Index [73]	16	✓	✓
Intolerance of Uncertainty Scale-Short Form [74]	12	✓	✓

Participants were asked to complete an EEG session to measure resting-state neural function as well as brain responses during cognitive tasks. We used electrodes embedded in an elastic cap to record electrical activity from 128 scalp sites. The precise physical location of the electrodes was recorded in 3D space with respect to auricular and nasion landmarks so that EEG recordings could be integrated with the corresponding structural MRI data. To measure eye movements for the detection of bioelectrical artifacts, vertical electro-oculograms were recorded from above and below the right eye, and horizontal electro-oculograms were recorded from near the outer ocular canthi. Left and right forearm electromyographs and electrocardiograms were recorded to identify and reduce artifacts and quantify the aspects of muscle contraction associated with button presses. EEG signals were digitized at the rate of 512 Hz with 0.5-200 Hz low frequency and 200 Hz high frequency bandpass filters. Each participant completed assessments of visual acuity and handedness as well as provided information about medications, alcohol consumption, caffeine consumption, and sleep in the last 24 hours. Self-report ratings of emotional state were assessed before and after EEG recording sessions using the Positive and Negative Affect Scale [71].

At the pre-BCT laboratory visit only, MRI data were collected at the UMN's Center for Magnetic Resonance Research on a 3T (Siemens) Prisma scanner using a 32-channel birdcage head coil with foam pads to minimize head movements. Sequences included T1-weighted Magnetization Prepared-Rapid Gradient Echo, T2-weighted Sampling Perfection with Application optimized Contrast using different flip angle Evolution, diffusion-weighted MRI, resting-state functional MRI (fMRI), and task-based fMRI.

Neurobehavioral Assessments

Overview

During the EEG session at the pre- and post-BCT visits, participants were asked to perform a series of neurobehavioral tasks applying paradigms to assess attentional control (dot-probe paradigm) [75,76], emotional inhibitory control (go or no-go paradigm) [77,78], and feedback processing (gambling decision paradigm) [79]. In addition, participants were asked to complete a video game–based task applying the Pavlovian-instrumental generalization paradigm [80] to assess adaptive versus maladaptive avoidance in the face of a physical threat.

Dot-Probe Task

Attentional bias is assessed using the dot-probe task [75,76]. Participants passively inspect rapidly presented face pairs with neutral, happy, or angry and threatening expressions. The face pairs disappear and are replaced by a blank space on one side of the screen and an asterisk (target probe) on the other. Participants are instructed to respond as quickly as possible to indicate the side on which the target probe appeared.

Emotional Go or No-Go Task

Inhibitory control is assessed using the emotional go or no-go task [77,78]. Participants view a series of rapidly presented visual targets and nontargets. Participants are instructed to press a response button for each target presented ("go trials") and to avoid pressing the button for each nontarget ("no-go trials"). Errors (response to no-go trials or failure to respond to go trials) are accompanied by visual (red bar in the center of the screen) feedback. The task is completed in 3 blocks with adaptive response timing windows to increase task difficulty based on performance. Participants are provided with visual feedback on task points earned or lost, which is displayed on the screen every 20 trials. During the second block, time windows are shortened to increase the task's difficulty just beyond what is feasible for participants. Points awarded during the second block for correct responses are also significantly reduced.

Gambling Decision Task

Error and performance monitoring is measured using the gambling decision task [79]. For each trial, participants are presented with 2 adjacent squares, each enclosing a number (5 or 25). Participants are instructed to choose between the 2 squares and then receive feedback (the chosen box turns red or green to signify either a win or a loss, with the winning and losing colors counterbalanced across participants). Winning and losing squares are preprogrammed in a randomized manner such that participants must make guesses and will be unable to detect a true pattern using the task feedback. Thus, the task assesses participant biases toward risk-taking following the experience of loss.

Farmer Task

While in the MRI environment, participants completed the farmer task [80]. In this gamified task, the participant is asked to take on the role of a farmer whose task is to travel between

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a shed and garden to harvest crops. Two different roads connect the shed to the garden: (1) a short road and (2) a long road. Traveling the short road is perilous (contingently associated with an electric shock; 3-5 mA for 100 ms) but allows the farmer quick travel from shed to garden, thereby assuring a successful harvest. Conversely, traveling the long road is always safe (never associated with shock) but often prevents the farmer from arriving at the garden before "wild birds" eat the crop.

Before each trial, a stimulus is presented to the participant that they learn can indicate whether the short road will deliver the electric shock. Specifically, participants learn, through fear conditioning, that shock is predicted by a visual ring of extreme size (conditioned danger cue: CS+) but not by rings of the smallest size (conditioned safety cue: CS–) displayed on the screen. During the game, rings of intermediary sizes, presented in the absence of a shock, serve as generalization stimuli. The task captures fear generalization and subsequent instrumental avoidance by assessing task-based behaviors in response to generalization stimuli that are similar (but not identical) to CS+. Decisions to "unnecessarily" avoid during safe cues is considered *maladaptive* because danger (threat of shock) is not a realistic possibility, and avoiding unnecessarily compromises performance on the task. Adaptive responding is operationalized by higher rates of decisions to push through (ie, low levels of avoidance) when encountering safe yet danger-resembling cues.

DNA Samples

All participants enrolled in the longitudinal study were asked to provide a DNA saliva sample at baseline, which is stored for future analysis. Participants in the laboratory substudy are also asked to provide a blood sample to be stored for future research.

Administrative Data

The study team will work with the local National Guard to extract administrative data capturing sociodemographic and service-related variables (ie, Armed Forces Qualification Test score, training dates, and military discharge). Administrative data from military records will be deidentified and matched by participant ID.

Sample Size and Power Analysis

Sample size was calculated based on the primary objective of the study (aims 1 and 2) using structural equation models of various hypothesized structures (nested and longitudinal). This demand resulted in a sample size that could provide sufficient power to test such hypotheses across varying df. Control of root mean square error of approximation (RMSEA) was the criteria used for our sample size and power calculations. According to MacCallum and colleagues [81], RMSEAs of 0.01, 0.05, and 0.08 indicate excellent, good, and mediocre fit, respectively. Table 4 presents the required sample sizes and the corresponding powers for df=2 and df≥5, assuming a null RMSEA of 0.05 and an α of .05. Assuming a retention rate of 65% to reach an effective sample size of 780, we needed to recruit 1200 participants. Note that for n=780, structural equation models with df≥5 would have an expected power of at least 0.909. The column for df=2 demonstrates that for df smaller than 5, the power for our feasible sample size drops below conventional 0.80.

Table 4. Power estimates (chi-squared test for root mean square error of approximation=0.05).

Sample size	Estimate (*df*)	Estimate (*df*)
700	0.567 (2)	0.878 (5)
800	0.619 (2)	0.916 (5)
1000	0.707 (2)	0.961 (5)
1200	0.776 (2)	0.982 (5)

Data Management

Data collected via the web-based survey platform (Qualtrics) administered at the UMN will be downloaded securely into the study databases stored on a shared server at the MVAHCS, with access limited to authorized study personnel. Qualtrics includes a complete suite of features to support Health Insurance Portability and Accountability Act compliance, including a full audit trial, user-based privileges, and integration with the institutional Lightweight Directory Access Protocol (LDAP) server. Hard copy surveys will be double entered and checked for consistency. Laboratory substudy data (ie, neuroimaging and EEG data) will be stored in secure databases held on servers at the UMN and will be available only to lead investigators of each substudy component and the principal investigator. Administrative data will be transferred directly from the Minnesota Army National Guard to a secure server at the MVAHCS via secure data transfer. At the MVAHCS, the data will be accessible by a named Center for Care Delivery and Outcomes Research (CCDOR) Data and Statistics Team member. This individual will deidentify the personal information, match records with the study ID number, and transfer them to a shared server for the study. The study ID numbers will be used for data transfer, communication, and analysis purposes to protect confidentiality. Participant contact information linked with the study ID number will be stored in an SQL server database that will be created on internal Department of Veteran Affairs (VA) web servers. Only individuals with a need to access the data, as vetted by the principal investigator, will be granted access. Access to contact information will be obtained through Windows authentication (ie, personal identity verification card and password for the network).

Statistical Methods

Aim 1 will characterize adaptation among young military recruits over the first 2 years of service. Consistent with a hierarchical concept of the structure of resilience, we will use latent growth mixture modeling to identify the latent trajectories of adaptation and its indicators. We will apply latent growth

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mixture modeling at the level of internalizing symptoms, externalizing problems, and social-occupational functioning as well as an overall model that simultaneously embeds all 3 domains into a model of adaptive functioning. We hypothesize that at least three trajectories (one showing resilient adaptive functioning or low pathology and the other two showing new-onset and chronic distress) will emerge for each domain assessed (internalizing symptoms, externalizing problems, social-occupational functioning, and global adaptive functioning).

Note that all remaining analyses for aims 2 and 3 will be conducted on the trajectory class membership data for each of these 4 domain outcomes to test for the specificity of resilience mechanisms**.**

Aim 2 will identify the promotive factors and protective processes contributing to individual variations in adaptation. We will apply structural equation modeling and Bayesian network analysis to detect and identify the latent constructs and the dependency structure between different domains. We will also examine the effects of protective and vulnerability factors on membership in different trajectory classes. We propose to investigate this in 2 complementary ways. First, in our structural equation modeling, we will augment the measurement submodels of the most parsimonious latent growth structural mixture models accepted in aim 1 with the indicators of protective and vulnerability measurements (Tables 1 and 2) and evaluate the change in the relationships (coefficients) that indicators have with the latent trajectories. We will treat potential predictors as moderators or mediators, depending on their hypothesized role in the model, and we will test their contribution to the model by change in model fit indices using the Akaike information criteria (AIC), the Bayesian information criteria (BIC), root mean squared error (RMSE), and goodness-of-fit (G^2) also known as the likelihood ratio test. Second, the trajectory class membership assignment in aim 1 will be used as dependent variables (resilient vs nonresilient or distressed trajectories), and protective and vulnerability factors will be used as predictors in random intercept multinomial logistic mixed models that will provide a quantitative picture of the unique contribution of these measures. We hypothesize that the risk factors listed in Tables 1 and 2 will predict membership in nonresilient or distressed trajectory classes, whereas protective or promotive factors will predict membership in the resilient or nondistressed trajectory classes. All analyses will be estimated within the propensity classes that adjust for any possible lack of imbalance and will be performed on both complete cases and 5 imputed data sets.

Aim 3 will investigate whether neurobehavioral markers of self-regulation assessed using a series of performance-based tasks involving EEG and fMRI assessments are predictive of resilient and nonresilient trajectories. EEG recordings will be put through an independent component analysis–based processing pipeline to isolate and remove noisy time segments, signal artifacts (eg, eye movements), and bad electrodes. Recording epochs centered around the onset of task stimuli will be extracted for the analysis of event-related potentials and time-frequency energy. Given that this study focuses on conflict monitoring and bottom-up covert attention, we plan to examine brain responses at midline frontal (eg, FCz) and lateralized posterior electrodes (eg, PO7 and PO8), respectively. We will quantify brain response metrics such as feedback-related negativity and θ-band (4-8 Hz) oscillations, which we predict will be associated with trajectory class membership. fMRI data collected during the farmer task will be analyzed using an event-related design to model blood oxygenation level dependent (BOLD) fluctuations due to stimuli onsets using Analysis of Functional Neural Images software [82]. Functional activation maps will be computed by regressing each voxel's fMRI response time course onto an ideal response function for 5 stimulus types: the danger cue, 3 classes of safety cues with parametrically varying levels of perceptual similarity to the danger cue, and a control condition including a safety cue with no perceptual similarity to the danger cue [83]. We will focus particularly on fMRI responses to these stimuli in brain areas associated with fear reactivity (anterior insula and dorsomedial prefrontal cortex) and fear inhibition (ventromedial prefrontal cortex and anterior hippocampus). Fear-related brain activations to safety cues resembling danger cues (relative to safety cues without danger-cue resemblance) will be used as predictors of maladaptive avoidance (costly or unnecessary avoidance of safe cues perceptually resembling danger cues). Finally, these brain and behavioral responses, as well as their moderation by protective (eg, social support, military cohesion, and self-regulation) and vulnerability factors (eg, BCT stressors and anxiety traits), will be used as predictors of trajectory class membership.

Handling of Missing Data

Every effort will be made to maximize the completion of data and responding across waves in the longitudinal survey (aims 1 and 2). However, the data collected at each wave will be subject to various random missingness. At the end of each wave, the mechanism of missingness for each measured variable will be assessed, and an imputation model appropriate to that variable (predictor, response, or adjustor covariate) will be identified. Appropriate imputation methods based on variable characteristics (eg, linear regression for continuous variables, multinomial logit models for categorical models, and propensity matching based on multiple predictors) will be used. After selecting a relevant model and, more importantly, deciding on the predictors of missingness, 5 imputed data sets will be constructed for each wave. The relevant analyses will then be based on the combined inferences derived from these 5 imputed data sets.

Results

This UG3/UH3 project was reviewed by the National Institutes of Health (Multimedia Appendix 1) and initially funded in August 2017. The UG3 pilot phase for establishing the feasibility of the larger prospective longitudinal study was conducted between August 2017 and December 2018 and is reported elsewhere [23]. The UH3 phase of the project was funded in March 2019. Study enrollment began on April 14, 2019, and ended on October 16, 2021. A total of 1201

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participants are enrolled in the study; follow-up data collection is ongoing and projected to continue through February 2024.

Discussion

Aims of the Study

ARMOR targets a gap in resilience research by providing a rich longitudinal database to assess resilience as a dynamic process of successful adaptation in response to significant adversity and identify the processes underlying resilience. Specifically, this study will characterize the trajectories of adaptation (ie, resilient vs nonresilient) among young US Army National Guard recruits in response to BCT beginning at career onset and spanning 2 subsequent years (aim 1) and identify promotive factors and protective processes contributing to individual variations in adaptation (aim 2). ARMOR will also investigate whether neurobehavioral markers of self-regulation are predictive of resilient versus nonresilient trajectories (aim 3).

Strengths and Limitations

This study takes a longitudinal, multilevel approach to examine the mechanisms underlying individual variations in resilience trajectories. Through the assessment of recruits before BCT and follow-up across 4 time points after BCT, the design provides an opportunity to map individual trajectories in response to exposure to a naturally occurring, uniform military challenge. Although previous research has identified numerous resilience factors, most existing longitudinal studies have relied almost entirely on self-report. This study uses an embedded laboratory substudy design that integrates novel laboratory-based experimental paradigms for assessing dynamic self-regulatory processes into a large, prospective, and longitudinal study. This approach will enable us to explore whether neurobehavioral markers of self-regulation assessed using a series of performance-based tasks involving EEG and fMRI assessments are predictive of resilient versus nonresilient trajectories. A final strength is the involvement of military stakeholders in the study design. Beginning at the early planning stage, members of the local National Guard command were involved in the research process, providing feedback on relevant research questions and consultation on the feasibility of the study methods. The selection of the outcome measures was informed by their priorities and military experience. The local National Guard command also facilitated the study team's access to military personnel and allocated training time for the investigators to present information about the study to potential participants and collect baseline data.

Despite these strengths, ARMOR has several limitations. The nature of our study design, incorporating in-person laboratory visits for a subset of the cohort, required that participants reside within a limited geographical area. Therefore, it was necessary to limit the recruitment of participants to the National Guard of a single state. Although we will investigate the influence of demographic characteristics on our findings, the results may not be generalizable to all military service members from other states or to all military branches.

Although we attempt to be exhaustive in our assessment of the risk and protective processes relevant to resilience in the context of military stress, it is possible that some relevant variables may not be assessed. For example, we recognize that collecting data from other informants, such as peers, commanders, or family members, would provide information on the influence of environmental factors on resilience. However, collecting such data would be prohibitive in terms of cost and time given the number of participants we are studying. However, we obtained permission from military service members to access military and VA administrative records so that these sources of information (eg, ecologically valid markers of functioning from administrative military records) can be accessed and analyzed in the future.

A key challenge for any longitudinal study is the retention of participants over time. This can be particularly difficult when participants are both young and highly mobile, as is the case in this study. We have taken steps to ensure a satisfactory response rate so that the study will be adequately powered to detect small effects in analyses testing our major hypotheses. Although follow-up survey data collection continued throughout the COVID-19 pandemic, all in-person research activities, including participant recruitment, baseline data collection, and laboratory visits, were suspended from March 2020 to early August 2020. During this period, some participants returned from BCT but were unable to complete in-person laboratory visits.

As of March 2020, over half (755/1201, 62.86%) of the ARMOR participants had been recruited and assessed at baseline before the pandemic outbreak. All remaining participants were enrolled and completed baseline measures after the pandemic outbreak between August 2020 and October 2021. This presents a rare opportunity to conduct a "natural experiment" in which recruits who have completed the stressful but potentially resilience-enhancing BCT before the pandemic can be compared with those who have not. For details outlining the collection of additional COVID-19–focused surveys through supplemental funding from the National Center for Complementary and Integrative Health, see the Multimedia Appendix 2 [1,31,38,44,45,48,84-127].

Conclusions

The ARMOR study provides a rich data set to identify the predictors and mechanisms of resilient and nonresilient outcomes in the context of military stressors. Understanding the neurobiological, cognitive, and social mechanisms underlying adaptive functioning following military stressor exposure is essential for enhancing the resilience of military service members. The findings from our study will facilitate the understanding of the mechanisms underlying self-regulatory processes implicated in resilience and thus provide a foundation for the development of prevention and intervention strategies that help to promote positive adaptation and resilience among young military recruits. Specifically, the findings of this study may support the optimization of mindfulness-based interventions, which focus on increasing the awareness of one's thoughts, emotions, and actions to improve specific aspects of executive functioning, including attention, cognitive control, and emotion regulation.

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Acknowledgments

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Data Availability

Data sharing is not applicable to this paper, as it does not report on any data generated or analyzed during this study.

Authors' Contributions

MAP was responsible for the overall conception and design of the study and led manuscript writing. CAM made substantial contributions to the acquisition of data and critical revision of the manuscript. MH made substantial contributions to the acquisition of data for the study and review of the manuscript. EHC made substantial contributions to the analysis and interpretation of data and the review of the manuscript. PAA made substantial contributions to the acquisition of data and critical revision of the manuscript. NDD made substantial contributions to the acquisition of data and critical revision of the manuscript. KOL made substantial contributions to the acquisition of data and critical revision of the manuscript. SL made substantial contributions to the development of the Farmer Task, acquisition of data, and critical revision of the manuscript. JDS made substantial contributions to the critical revision of the manuscript. SRS made substantial contributions to the acquisition of data and critical revision of the manuscript. ASM contributed to the conception and design of the study and critical revision of the manuscript. SN contributed to the conception and design of the study, analysis and interpretation of data, and critical revision of the manuscript. All authors have provided final approval of the manuscript for submission.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Summary statement from National Institutes of Health review.
[PDF File (Adobe PDF File), 137 KB - resprot_v12i1e51235_app1.pdf]

Multimedia Appendix 2
Advancing Research on Mechanisms of Resilience (ARMOR) study COVID-19 supplemental protocol.
[PDF File (Adobe PDF File), 3581 KB - resprot_v12i1e51235_app2.pdf]

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Abbreviations

AIC: Akaike information criteria
ARMOR: Advancing Research on Mechanisms of Resilience
BCT: basic combat training
BIC: Bayesian information criteria
BOLD: blood oxygenation level dependent
CCDOR: Center for Care Delivery and Outcomes Research
DSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
EEG: electroencephalography
fMRI: functional magnetic resonance imaging
G^2: goodness-of-fit
LDAP: Lightweight Directory Access Protocol
MRI: magnetic resonance imaging
MVAHCS: Minneapolis Veterans Affairs Health Care System
PCNB: Penn Computerized Neurocognitive Battery
PTSD: posttraumatic stress disorder
RMSE: root mean squared error
RMSEA: root mean square error of approximation
RSP: Recruitment Sustainment Program
UMN: University of Minnesota-Twin Cities
VA: Veteran Affairs

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Protocol

Repeated Human Exposure to Semivolatile Organic Compounds by Inhalation: Novel Protocol for a Nonrandomized Study

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Abstract

Background: Semivolatile organic compounds (SVOCs) comprise several different chemical families used mainly as additives in many everyday products. SVOCs can be released into the air as aerosols and deposit on particulate matter during use by dispersion, evaporation, or abrasion. Phthalates are SVOCs of growing concern due to their endocrine-disrupting effects. Human data on the absorption, distribution, metabolism, and excretion (ADME) of these compounds upon inhalation are almost nonexistent.

Objective: The goal of this study is to develop a method for repeated inhalation exposures to SVOCs to characterize their ADME in humans.

Methods: We will use diethylhexyl phthalate (DEHP), a major indoor air pollutant, as a model SVOC in this novel protocol. The Swiss official Commission on Ethics in Human Research, Canton de Vaud, approved the study on October 14, 2020 (project-ID 2020-01095). Participants (n=10) will be repeatedly exposed (2 short daily exposures over 4 days) to isotope-labeled DEHP (DEHP-d4) to distinguish administered exposures from background exposures. DEHP-d4 aerosols will be generated with a small, portable, aerosol-generating device. Participants will inhale DEHP-d4-containing aerosols themselves with this device at home. Air concentrations of the airborne phthalates will be less than or equal to their occupational exposure limit (OEL). DEHP-d4 and its metabolites will be quantified in urine and blood before, during, and after exposure.

Results: Our developed device can generate DEHP-d4 aerosols with diameters of 2.5 µm or smaller and a mean DEHP-d4 mass of 1.4 (SD 0.2) µg per puff (n=6). As of May 2023, we have enrolled 5 participants.

Conclusions: The portable device can be used to generate phthalate aerosols for repeated exposure in human studies.

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KEYWORDS

DEHP; diethylhexyl phthalate; healthy participants; inhalation exposure; phthalates; portable aerosol-generating device; protocol; semi-volatile organic compounds; SVOCs; toxicokinetics study; toxicology

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Introduction

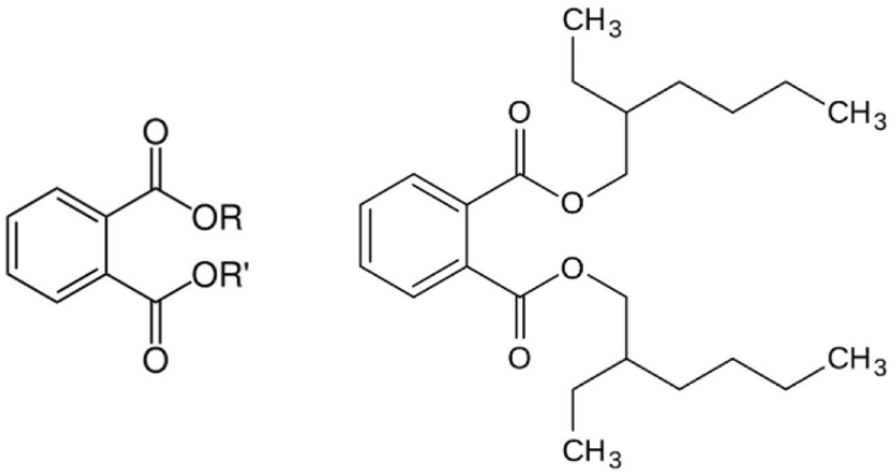
The general population is exposed every day to semivolatile organic compounds (SVOCs) through inhalation [1-4], but few data exist on the internal (eg, blood) concentrations of these compounds when inhaled. One reason for this lack of data is the absence of a device to aerosolize SVOCs for controlled human exposure over several days. These compounds cannot be tested in common devices used for volatile chemicals such as solvents in whole-body exposure chambers. SVOCs are found in the air as liquid aerosols and deposited onto solid particles that are easily resuspended in the air and directly available through inhalation [5]. They are used as active ingredients in pesticides, cleaning agents, and personal care products, as well as additives in materials such as plastics, floor coverings, furnishings, and electronic components [4]. More than a thousand SVOCs are high-production-volume chemicals (HPVCs) [6]. Many of these have been associated with adverse health effects and have since been removed from commercial use [7,8]. Some are presumed (category 1B) endocrine-disrupting chemicals (EDCs) [9,10], including, among others, phthalates [11-14], brominated flame retardants [15], bisphenol A [16], nonylphenol [17], and some pesticides [18]. SVOCs are found in higher abundance indoors than outdoors [19,20] and are detected in both blood and urine collected from the general population [21]. This confirms the omnipresent and concurrent body burden.

Phthalates are a specific family of SVOCs used to impart flexibility to polymer plastics (ie, plasticizers) [22]. Phthalates are not covalently bound to the polymer matrix. Therefore, they can migrate to the surface and be slowly released into the air [21-24]. Phthalates with short alkyl chains, such as diethyl phthalate (DEP), have the highest vapor pressures and can also be released in the air in the vapor phase. Phthalates with long alkyl chains, such as diethylhexyl phthalate (DEHP), have lower vapor pressures and tend to adsorb to aerosol particles or dust [23] (Figure 1). DEHP has been reported to be the most abundant phthalate in house dust, with measured concentrations up to 5.3 mg/g [24,25].

Children and adults living in industrialized countries are estimated to spend around 17-19 hours and 21 hours per day indoors (ie, at home and in the working environment), respectively [26]. There is considerable concern regarding phthalate exposures because several epidemiological studies have shown associations between exposures to some phthalates and retarded male reproductive development [11,12], altered semen quality [13,14], endometriosis [27,28], and respiratory diseases in children [29]. When inhaled, phthalates can reach the alveoli, be absorbed into the blood, and then be distributed to potential target tissues, where they may trigger an effect. Therefore, absorption rates (ie, rate at which the molecule enters blood), internal doses (ie, parent compound concentrations in blood), as well as metabolic and elimination rates (ie, rate of metabolites' formation and elimination, usually in urine), are important toxicokinetic parameters to accurately determine the total exposures in the human body and, thus, potential risks to the population. Although urinary metabolite ratios were reported to be different between humans and animals [30-34], these toxicokinetic parameters have not been studied in humans exposed to phthalates through inhalation as a single exposure route. The few human toxicokinetic studies conducted with phthalates were mainly after ingestion [35-38]. A total of 2 human studies have been conducted on phthalates, including simultaneous exposure through the skin and inhalation routes [39,40]. These studies only provided estimated toxicokinetics (absorption, distribution, metabolism, and excretion [ADME]) for the inhalation route. Since inhalation is considered a significant indoor route of exposure for some phthalates [41], toxicological studies need to be performed to understand phthalates' ADME through this exposure route. However, a procedure to expose healthy participants to SVOCs is lacking due to the absence of devices for human studies with SVOCs through inhalation. We aim to fill these gaps by describing the required steps to obtain human ADME data after inhalation. The SVOC selected in this study is DEHP, a model SVOC due to its major presence in the indoor environment (air and dust) and human populations (urine). This study is divided into 2 parts. Part I describes the dosing procedure and how to generate aerosols at environmentally relevant phthalate concentrations with a device suitable for chronic inhalation exposure. Airborne phthalate aerosols will be produced based on the technology of commercially available "electronic nicotine delivery systems" (ENDS), which have proven efficacy in generating aerosols for human use [42,43]. ENDS are generally used to generate nicotine or flavored aerosols from highly viscous liquids such as glycerol (viscosity=1412 mPa·seconds) making this technology suitable for viscous chemicals such as some phthalates. Part II provides the study protocol for participants exposed to ring-deuterated DEHP for several days. Unisanté has strong expertise in toxicological studies with healthy participants and has adapted its protocols for repeated, at-home exposure. We will show the results of the first participant here as proof of concept.

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Figure 1. Generic chemical structure of phthalates, where R and R' are alkyl or aryl moieties (left), and chemical structure of diethylhexyl phthalate (DEHP) (right).



Methods

Part I: Dosing Protocol

Portable Dosing Device

The commercial ENDS "Endura T20-S" (Innokin) was chosen as the portable dosing device for participants' exposure to DEHP. ENDS consists of a battery-powered heated coil that functions as a thermal atomizer, a mouthpiece, and an e-liquid tank. Generally, the e-liquid is mainly composed of nicotine, flavoring agents, and ethanol in a base of propylene glycol (PG) and vegetable glycerol (VG). Base composition can vary from a PG/VG ratio of 20/80 to 70/30 and is typically 50/50. When the user activates the heated coil by pressing a button on the ENDS, the e-liquid is vaporized, releasing a flavored nicotine-containing aerosol called a "puff." The user inhales this aerosol through the mouthpiece.

E-Liquids

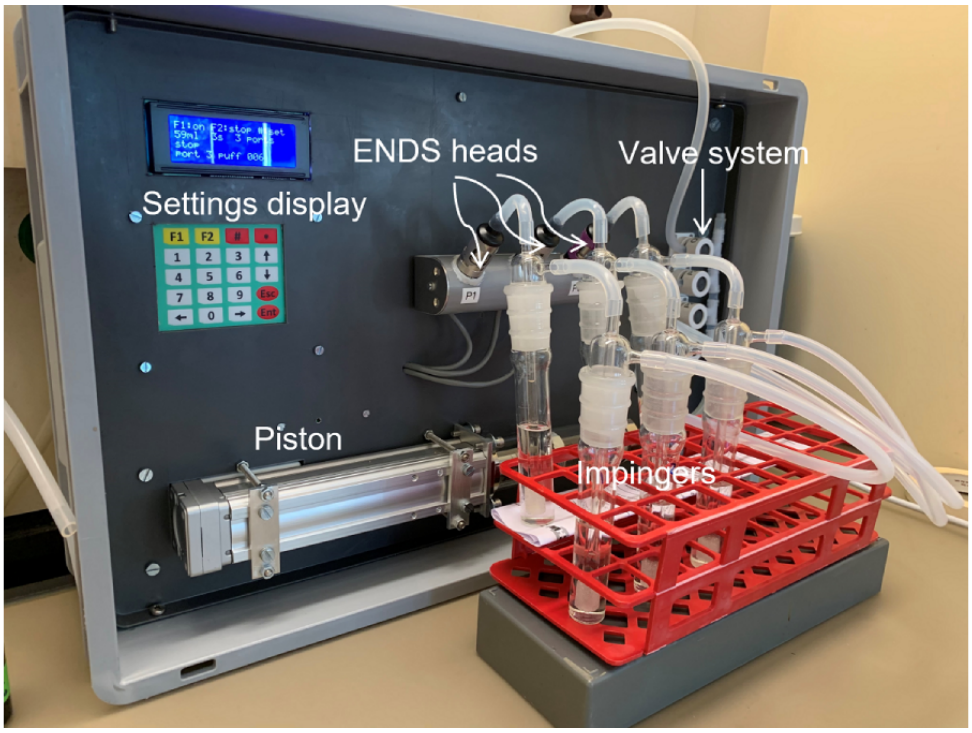
Aerosols generated by ENDS are complex mixtures containing volatile and semivolatile gases (mainly PG and glycerol) and nonvolatile particles (mainly glycerol, PG, and nicotine) [44,45]. The e-liquid formulated in this study is composed of glycerol (purity 99.5%, Hänseler Swiss Pharma), PG (PG 0 mg/mL nicotine, Revolute), ethanol (absolute for analysis EMSURE, Supelco, Merck), and DEHP. Ring-deuterated DEHP (DEHP-d4, CAS# 93951-87-2, Sigma Aldrich) is used to differentiate exposures generated in our experiment to environmental and laboratory DEHP contaminations.

Aerosol Generation and Vaping Machine

To adapt the ENDS to generate DEHP aerosols at controlled concentrations, we used a vaping machine that was developed in the Unisanté laboratory in collaboration with the University Centre of Legal Medicine of Lausanne (CURML) [46]. The purpose of the vaping machine was to replicate the puffing behavior of an individual using an ENDS according to the method n°81 recommended by the Cooperation Centre for Scientific Research Relative to Tobacco (CORESTA) [47]. This method describes the requirements for the generation and collection of e-cigarette aerosols for analytical testing purposes and led to an ISO (International Organization for Standardization) standard (20768:2018). Our vaping machine included 3 ports, each for an ENDS head (e-liquid tank, atomizer, and mouthpiece), a power supply, a piston syringe, a pinch-valve system, and silicon tubing (Figure 2). The machine was equipped with its own power supply, which replaced the individual ENDS batteries. This provided a steady-state power of 12 W throughout all experiments. The replacement of the ENDS battery by the machine's power supply precisely controlled puff duration during the experiments. The piston, in combination with the pinch valve system, controlled the puff volume, that is, the volume leaving the ENDS. Puff volumes were trapped by n-hexane in subsequent glass impingers (with P1 porosity fritted nozzle tip, joint connection NS 29/32, Bistabil, Sigma Aldrich) for analytical analysis. Puff duration (3 seconds per puff), volume (55 mL per puff), and frequency (30 second between puffs) were set up as per CORESTA criteria. Tests were carried out in triplicates. Control tests served to verify that the entire setup was not contaminated by DEHP-d4. A total of 3 ENDS with 0.8-ohm atomizers were used for all the experiments. New atomizers were used in each experiment.

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Figure 2. Aerosol generation tests with our vaping machine. A total of 3 electronic nicotine delivery systems (ENDS) heads were directly screwed onto the vaping machine. Each ENDS head was attached to 2 sampling bottles (impingers) in series by silicon tubes. The impingers were attached to the valve system of the vaping machine and could be set to a specific vaping volume, duration, and frequency through the display at the top left.



E-Liquid Formulation and Testing Conditions Optimization

A first series of tests was carried out on the vaping machine to optimize the e-liquid formulation for generating stable aerosol concentrations as well as trapping conditions. We prepared several formulations with different PG/VG ratios (from 0/100 to 50/50), different ethanol amounts (0%-10%), and different DEHP amounts (0.002%-0.3%, w/w) to determine e-liquid formulations that allowed DEHP to be dissolved in the e-liquid and aerosolized by the atomizer. For each ENDS, DEHP-d4 was quantified in the n-hexane of all impingers. The number of impingers (2 and 3), impinger volume (20 and 100 mL), and n-hexane volume in each impinger (13, 50, 75, and 80 mL) were tested for optimal DEHP-d4 trapping conditions.

DEHP-d4 Mass Balance and Aerosols Concentrations

We carried out a second series of experiments with the vaping machine to determine mass balance and confirm DEHP-d4 concentration in the aerosols. DEHP-d4 was quantified in the n-hexane of all impingers, in the e-liquid before and after the experiment, and in an acetone/ethanol (50/50 v/v) mixture (acetone, suitable for high-pressure liquid chromatography [HPLC] ≥99.9%, Sigma Aldrich) that was used to extract DEHP-d4 from disassembled ENDS parts at the end of the experiment by the Central Environmental Laboratory of the Ecole Polytechnique Fédérale of Lausanne (EPFL).

DEHP-d4 Stability in E-Liquid

The stability of the DEHP-d4 concentration in e-liquid was an important control step for the participants' safety and to avoid any exposure concentration variability between the participants. The stability test for DEHP-d4 in the e-liquid was performed on the e-liquid stored at room temperature for 1 week and frozen at –20 °C for 2 weeks.

Aerosol Particle Mass Distribution in E-Liquid

A portable optical particle counter (aerosol spectrometer, model 1.109, GRIMM) was used to determine the mass distribution of e-liquid particles in the aerosols and assess deposition in the respiratory system [48,49]. Aerosols were generated by equipping the vaping machine with ENDS. The e-liquid used for these tests was composed of a PG/VG ratio of 50/50 with 1% ethanol and was not spiked with DEHP-d4. A total of 6 puffs of aerosol (55 mL×6=330 mL) were diluted in ambient air in a 3 L sampling bag (Tedlar sampling bag, Nutech Instruments Inc). The dilution in ambient air simulated the aerosol dilution in inhaled air by an individual puffing, assuming a 55 mL puff and a 500 mL tidal volume (330 mL/3000 mL=55 mL/500 mL). The particle size distribution profile was then measured. A control test was performed with ambient air.

DEHP-d4 Exposure Concentration

The concentration of DEHP-d4 in the e-liquid (percentage by weight) was set at a value that produced DEHP-d4 concentrations for participant exposures (C_{exp}, mg/m^3) at or below the Swiss occupational exposure limit (OEL) for DEHP (2 mg/m^3) [50]. The OEL is set at concentrations that, based on available scientific data, should not produce health effects in workers exposed to a substance in the air every day for a workweek throughout their working lifetime (in Switzerland: 8 hours per day, 5 days a week, for 40 years). C_{exp} was calculated based on the following equation:



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where M_{puff} was the mass of DEHP-d4 in the aerosols generated in a puff by ENDS coupled with the vaping machine (µg per puff), p was the number of puffs per minute that an ENDS user would consume per minute (puff per minute), V_{tidal} was the human mean tidal volume (0.5 L of air per inhalation [51,52]), and IE was the number of inhalations/exhalations per minute.

Part II: Human Toxicological Study Protocol

Participant Sample Size and Selection

A maximum of 10 participants (N=10) will be recruited for repeated exposure to DEHP. Participants who are interested in the study will be checked for eligibility through a short general health questionnaire. These questions are about smoking status, age, BMI, alcohol consumption, general health status, and current job (to exclude the possibility of exposure to phthalates at work). The eligibility criteria are described in Textbox 1.

Textbox 1. Inclusion and exclusion criteria approved by the Ethical Committee. The inclusion criteria "able to understand the procedure" mean the presumed ability of the participants to understand or discern the written and oral explanations during the first visit. This capability will be assessed as follows: by asking the participants to repeat what they understood about the study; by asking questions to the participants and assessing their answers (eg, studied molecules, number of visits, right to accept or reject participation in the study, etc).

Inclusion criteria

- Aged between 18 and 65 years old.
- Men and nonpregnant women (negative pregnancy test).
- Nonsmoker (vaping is authorized).
- Not under a medical regime.
- BMI between 18 and 25.
- Not exposed to phthalates at work.
- Able to understand the procedure.
- Has signed the consent form for research project participation.

Exclusion criteria

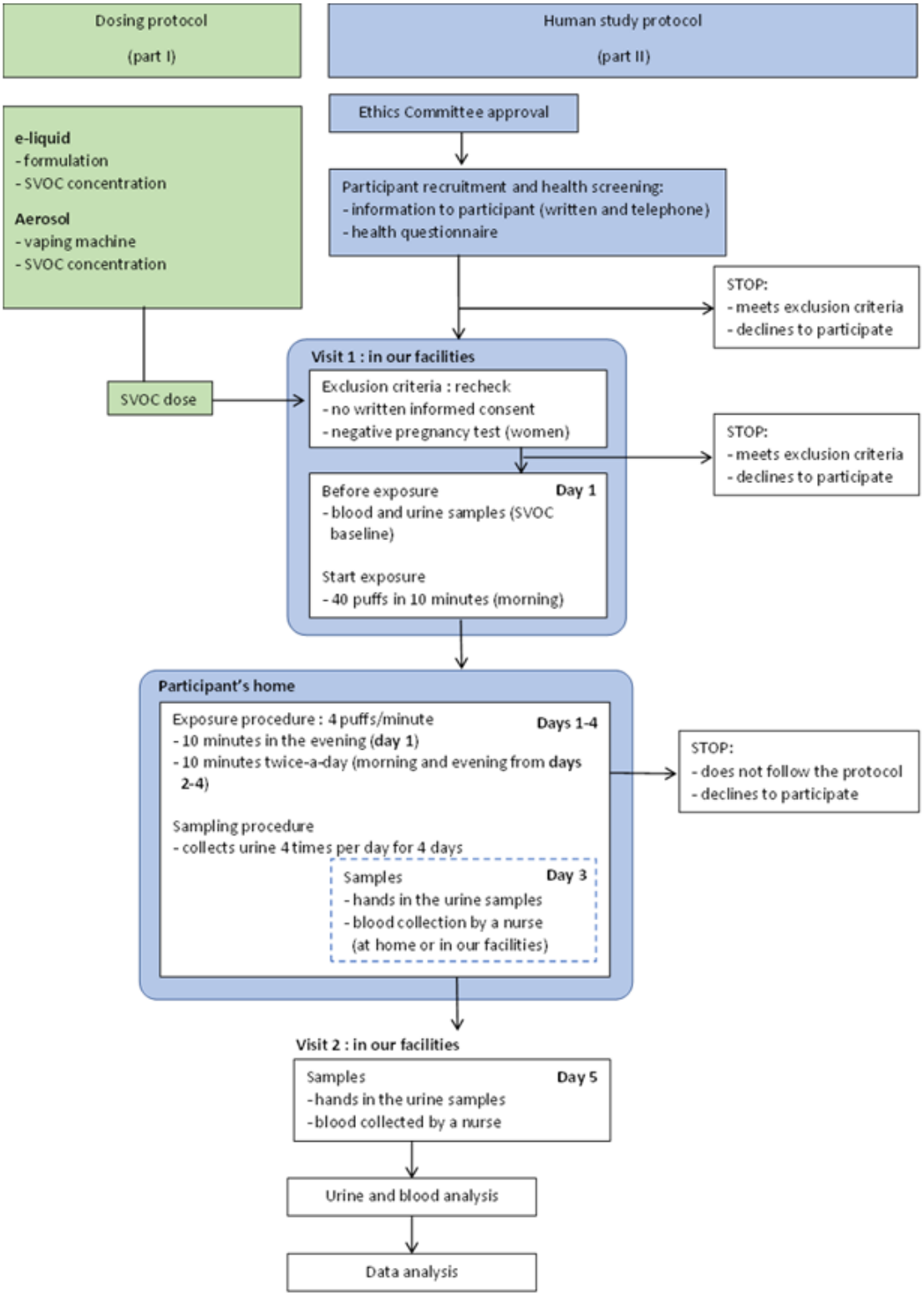
- Aged 18 years or younger.
- Pregnant women.
- Smoker (cigarette, pipe, and cigar smoker).
- Under a medical regime.
- BMI below 18 or greater than 25.
- Exposed to phthalates at work.
- Not capable of understanding the procedure.
- Has not signed the specific consent form for research project participation.

Participant Timeline

The flowchart in Figure 3 shows the steps from participant screening and visits through exposure periods until data analysis. Briefly, an initial contact with the participant will be established by email to explain the study and obtain informed consent. Then, a phone call will be made to check if the inclusion and exclusion criteria are met and to get answers for a short general health questionnaire. If the inclusion criteria are met, the participant will be invited for a first visit. At this visit, the participant will sign the written informed consent. Women of reproductive age will also undergo a pregnancy test. Then, the participant will be given an aerosol-forming device and, after being instructed on how to use the device, will undergo the first inhalation exposure under the supervision of a research team member (see "Participant Exposure" section). A blood and urine sample will be collected before the first exposure (baseline) and will serve as baseline concentrations (control). Blood will be drawn again 30 minutes after the first exposure. Then, participants will follow the expected vaping schedule with DEHP-d4-spiked e-liquid and collect spot urine samples 4 times throughout the day (morning, midday, evening, and night) for the 4 days of exposure. Blood and urine collecting times are shown in Multimedia Appendix 1.

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Figure 3. Flowchart of recruitment, screening, visits, interventions, sampling, and analysis. SVOC: semivolatile organic compound.



Blood and Urine Analysis

The Laboratory of Clinical, Forensic, and Environmental Toxicology, University Hospital of Liege, will determine DEHP-d4 and its metabolites concentrations in blood. The quantified metabolites will be deuterated mono(2-ethylhexyl)phthalate (MEHP-d4), deuterated mono(2-ethyl-5-hydroxyhexyl)phthalate (5OH-MEHP-d4), and deuterated mono(2-ethyl-5-oxohexyl)phthalate (5oxo-MEHP-d4). The Institute for Prevention and Occupational Medicine of the German Social Accident Insurance, Institute of the Ruhr-Universität Bochum (IPA), will quantify DEHP-d4 metabolites in urine, as described in Koch et al [53]. The metabolites quantified by the IPA laboratory will be MEHP, 5OH-MEHP, 5oxo-MEHP, and mono(2-ethyl-5-carboxypentyl)phthalate (5cx-MEPP).

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Participant Exposure

Participants will use the portable aerosol-forming device themselves, first in our facilities (day 1) and then at home (days 1-4). The e-liquid will have a PG/VG ratio of 50/50 with 1% (w/w) ethanol and 0.02% (w/w) DEHP-d4. The participants enrolled in the study will press a button on the ENDS battery. The coil will heat the e-liquid, generating an aerosol with DEHP concentrations less than or equal to the OEL.

The e-liquid will be prepared in advance for DEHP-d4 quantification analysis and will be stored at room temperature during the exposure week. A fraction of the e-liquid will be sent to the analytical laboratory of EPFL to confirm the DEHP-d4 concentration in the e-liquid, and the rest will be frozen at –20 °C until use. On the day of the first exposure to DEHP, the e-liquid will be defrosted. A vial with a weighted amount of e-liquid sufficient for 1-week exposure (ie, reserve) will be prepared for each participant. This vial will be stored at room temperature at the participant's place, where they will use it to refill the ENDS e-liquid tank when needed. Therefore, a stability test is required to verify DEHP-d4 concentration after several days of storage at room temperature. This step is also important for the relevance of the study. On day 5, the participant will return the ENDS and the e-liquid vial, which will be weighed to calculate the exact amount of e-liquid puffed by the participant, hence the amount of puffed DEHP-d4.

Statistical Analysis

Standard descriptive statistics (ie, scatter plots, box plots, means, and SD) will be performed to describe the within-participant evolution of parent compound and metabolite distribution and elimination over time. Absorption and elimination rates will be estimated for each of the participants using standard nonlinear regression methods (hockey plots, piecewise linear regression models, or exponential models). These rates will be compared while accounting for potential effect modifiers (eg, age and gender) using mixed models.

Ethical Considerations

This study protocol has been approved in Switzerland by the official ethics committee of the Canton de Vaud for research studies with humans (Commission cantonale d'éthique de la recherche sur l'être humain, CER-VD, October 14, 2020, project ID 2020-01095). This study will be carried out at the Department of Occupational and Environmental Health at Unisanté, Lausanne (Switzerland).

This study is in compliance with the Declaration of Helsinki [54], the Swiss legal requirements for scientific research involving human beings [55,56], the Human Research Ordinance (HRO) [57], and the legislation relative to data protection (Swiss Biobanking Platform [SBP]). The Cantonal Ethics Committee of Vaud (CER-VD) approved the first version of the study on October 14, 2020 (project ID 2020-01095). The protocol described in this study is Version 8 of September 14, 2021.

The study is presented to any subjects who contact us for recruitment by phone and through a written participant information sheet. Participants also receive 2 consent forms, one for this study and one for possible future studies. If they agree to participate in the study, they need to sign the informed consent form before being exposed. The information sheet and the consent forms have been approved by the CER-VD.

All health information and biological samples related to this study will be part of a biobank that follows the current Swiss legal requirements for data protection and will be performed according to the Swiss HRO, Article 5. The SBP approved the study on January 21, 2021 (Vita Label N° Unisante_2101_1).

The results from this study will be communicated at scientific meetings and submitted for publication in peer-reviewed journals.

Results

Here we will present results for the portable aerosol-forming device (Part I) and anticipated results with the participants (Part II).

Part I: Dosing Protocol

E-Liquid Formulation and Testing Conditions Optimization

The optimized e-liquid formulation had a PG/VG ratio of 50/50 with 1% (w/w) ethanol and 0.02% (w/w) DEHP-d4. Ethanol was necessary to dissolve DEHP-d4 and then create a homogeneous solution with PG/VG. The mean recovery in impingers was 89% (SD 5%) of the mass of aerosolized DEHP-d4 (n=5). The optimized number of impingers, impinger volume, and n-hexane volume in each impinger were 3 mL, 125 mL, and 80 mL, respectively. The number of puffs per experiment (n=36) was set to produce 2 dm^3 of aerosol, a volume that generated quantifiable amounts of DEHP-d4, and that was a submultiple of 1 m^3 (the volume used to define the OEL), which simplified calculations.

DEHP-d4 Mass Balance and Aerosol Concentrations

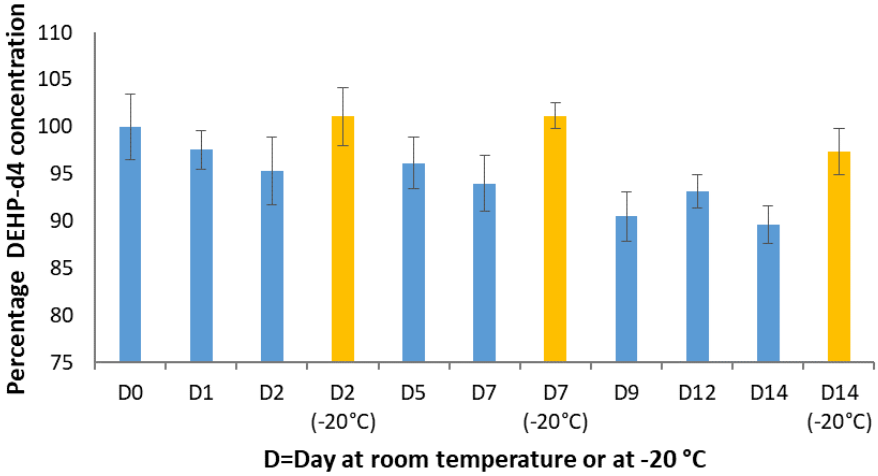
Total DEHP-d4 mass mean recovery for e-liquids, ENDS heads, and impingers was 100% (SD 22%; n=4). A DEHP-d4 concentration of 0.02% (w/w) in the e-liquid was confirmed by chemical analysis and produced aerosols containing 25.4 (SD 3.4) mg/m^3 DEHP-d4 (median 26 mg/m^3), corresponding to a mean of 1.4 (SD 0.2) µg DEHP-d4 per puff (n=6).

DEHP-d4 Stability in E-Liquid

The results of the stability test (Figure 4) showed a decrease in DEHP concentration of about 10% when the e-liquid was stored at room temperature. This loss may be explained by slight adsorption of the DEHP to the recipient wall or analytical error (up to 10% is considered in the error range of the analytical method). Therefore, the concentration of DEHP was stable when the e-liquid was stored in the freezer at –20 °C.

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Figure 4. Percentage of isotope-labeled diethylhexyl phthalate (DEHP-d4) concentration over 14 days of storage at room temperature (blue) and at –20 °C (yellow). Note that the y-axis starts at 75%.



Aerosol Particle Mass Distribution in E-Liquid

The aerosol particle size distributions are shown in Figure 5. Table 1 lists the particle means expressed in terms of environmental (PM10, PM2.5, and PM1) and occupational (inhalable, thoracic, and respirable) mean mass concentrations. Most of the particles in the diluted ENDS-generated aerosols were at the respirable mass fraction level, with a diameter of 2.5 µm or smaller.

Figure 5. Mean (n=48) particle counts per cubic meter of air measured in ENDS-generated aerosol containing propylene glycol/vegetable glycerol (PG/VG=50/50), 1% ethanol, 0.02% DEHP-d4 (blue line with diamond marks). Gray line and squared marks represent the control (ambient air). Error bars represent the ± SD. Particles with diameters larger than 3 µm were 0.0003% of total counts.

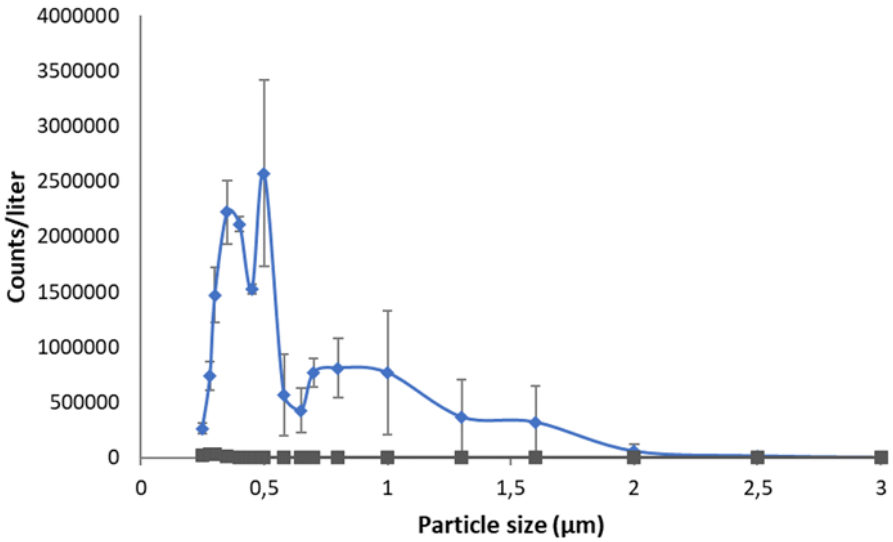


Table 1. Mean mass concentrations (µg/m3) corresponding to the aerosol fractions of PM10, PM2.5, and PM1 (PMX: 50% of particles exhibit an aerodynamic diameter below the indicated numbers 10, 2.5, and 1 microns, respectively) as well as the inhalable, thoracic, and respirable fractions (50% of particles exhibit an aerodynamic diameter below the indicated numbers 100, 10, and 4 microns, respectively) as per European Standard EN 481:1993 definitions.

	PM10 (µg/m^3)	PM2.5 (µg/m^3)	PM1 (µg/m^3)	Inhalable (µg/m^3)	Thoracic (µg/m^3)	Respirable (µg/m^3)
Diluted aerosol, mean (SD)	6325 (4363)	6192 (4213)	2634 (728)	6325 (4363)	6325 (4363)	6217 (4245)
Control, mean (SD)	4 (1)	4 (1)	4 (1)	4 (1)	4 (1)	4 (1)

DEHP-d4 Exposure Concentration

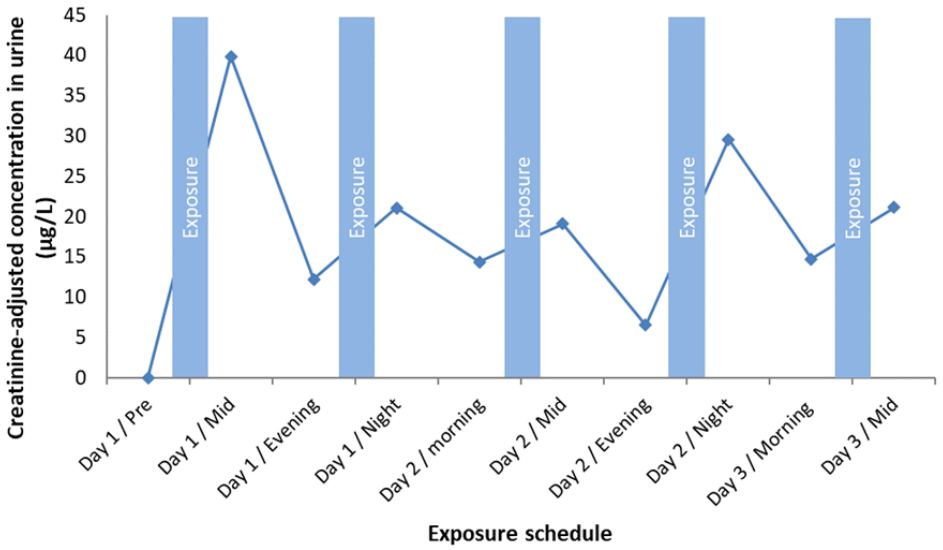
We observed that on average, an individual puffs 4 times per minute and inhales and exhales 12 times per minute (data not shown). Therefore, a 0.02 % (w/w) DEHP-d4 concentration in the e-liquid generating an aerosol with 1.4 µg per puff of DEHP-d4 led to an estimated exposure concentration C_{exp} of 0.9 mg/m^3 over a 10-minute exposure, which was below the OEL. Assuming that a participant puffed 40 times on average

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over the 10-minute exposure duration twice a day (80 puffs per day), the predicted DEHP-d4 dose for a week of exposure was 0.45 mg.

Our first participant could not complete the exposure week because some e-liquid leaked out of the ENDS, preventing our control of the puffed dose. Therefore, results for this participant are shown in Figure 6 as proof of concept. Our results from our first participant showed quantifiable amounts of DEHP-d4 in this participant's urine. DEHP-d4 was quantified in the e-liquid by chemical analysis before participant exposure (0.019%, w/w). The participant was asked to puff 40 times over 10 minutes twice a day. After five 10-minute exposure periods over 3 days and minor leaking, 2.52 g of e-liquid were used, corresponding to 0.47 mg DEHP-d4. This amount was in line with the DEHP-d4 predicted dose and led to exposure concentrations lower than the OEL but still sufficiently high to quantify DEHP in urine and to elucidate the urinary elimination kinetics. However, C_{exp} led to concentrations below our limit of quantification (LOQ) for blood.

Figure 6. Urinary concentration of the sum of isotope-labeled diethylhexyl phthalate (DEHP-d4) metabolites (MEHP-d4, 5OH-MEHP-d4, 5oxo-MEHP-d4) quantified for 1 participant.



Part II: Human Toxicological Study Protocol

As of May 2023, we have enrolled 5 participants. Following the whole protocol, participants will be able to generate aerosols with controlled DEHP concentrations using the ENDS and the prepared e-liquid at home for several days.

Discussion

We developed a method to generate aerosols containing controlled concentrations of SVOCs of toxicological relevance (ie, DEHP in this study) for controlled human exposure studies. Aerosols were generated by a portable and easy-to-use device (ENDS). Our results showed that DEHP in the e-liquid was stable for the duration of the study and that ENDS-generated aerosol particles were in the respirable range. Therefore, DEHP was likely to reach the alveoli, be absorbed, and enter the systemic circulation. Knowledge of human toxicokinetics after SVOC aerosol inhalation exposures will help regulatory agencies set new exposure limits and new requirements for toxicity reporting from manufacturers or suppliers because the data are human data instead of animal data. Some e-liquid leaking occurred with our first participant. This will be prevented by asking the next participants to keep the ENDS at home in a vertical position.

In the near future, our portable aerosol device will be used to study biomarkers of phthalate exposure in humans and the influence of these chemicals on a panel of readouts related to human health. We believe that this protocol with a take-home device has an easy approach, and we therefore anticipate that participant compliance rates to the exposure protocol will be high. The potential limitations of this protocol are the risks of missing part of the dose in blood and urine because only DEHP metabolites, not the parent compound, are quantified in these fluids, and participants are asked for spot urine samples, not 24-hour urine collection for every day of exposure. We hope this protocol will help other researchers design human inhalation studies of environmental substances that can contribute to the large data gap that exists today.

The results of this study will add new and important human data on the toxicokinetics of SVOCs such as DEHP upon repeated, inhalation-only exposures. Understanding phthalate toxicokinetics upon repeated exposure will help researchers understand possible phthalate accumulation in the body (if any) and improve models estimating internal exposures from external exposures, as well as interpret biomonitoring results from the general population, where urine is often collected at different times.

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Authors' Contributions

ER contributed with conceptualization, methodology, investigation, validation, writing the original draft, and visualization; NBH contributed with conceptualization, methodology, writing, review, and editing; FB contributed with validation, resources, methodology, and formal analysis; DG contributed with validation, resources, methodology, and formal analysis; CP contributed with resources and validation; CC contributed with resources and validation; HMK investigation, resources, writing, review, and editing; AB contributed with methodology, conceptualization, resources, writing, review, and editing; GS contributed with methodology, conceptualization, writing, review, and editing; MB contributed with conceptualization, methodology, visualization, supervision, project administration, funding acquisition, writing, review, and editing.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Blood and urine sampling design. The exposure period is shown in grey. On day 1, blood and urine will be taken to provide baseline data (controls). Then, the first exposure starts and will be repeated twice a day, in the morning and in the evening. On day 3, participants return to our facilities to hand out day 1 to day 3 urine samples and for blood sampling. The last exposure is on day 4. On day 5, participants hand out urine samples from day 4 and the morning of day 5; a postexposure blood sample is collected at our facilities.
[PNG File , 18 KB - resprot_v12i1e51020_app1.png]

Multimedia Appendix 2
SCAHT_Experts_Outcome.
[PDF File (Adobe PDF File), 464 KB - resprot_v12i1e51020_app2.pdf]

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Abbreviations

5cx-MEPP: mono(2-ethyl-5-carboxypentyl)phthalate
5OH-MEHP-d4: mono(2-ethyl-5-hydroxyhexyl)phthalate
5oxo-MEHP-d4: mono(2-ethyl-5-oxohexyl)phthalate
ADME: absorption, distribution, metabolism, and excretion
CER-VD: Cantonal Ethics Committee of Vaud
CORESTA: Cooperation Centre for Scientific Research Relative to Tobacco
CURML: University Centre of Legal Medicine of Lausanne
DEHP: diethylhexyl phthalate
DEHP-d4: isotope-labeled diethylhexyl phthalate
DEP: diethyl phthalate
EDC: endocrine-disrupting chemical
ENDS: electronic nicotine delivery systems
EPFL: Ecole Polytechnique Fédérale of Lausanne
HPLC: high-pressure liquid chromatography
HPVC: high-production-volume chemical
HRO: Human Research Ordinance
IPA: Institute of the Ruhr-Universität Bochum
ISO: International Organization for Standardization
LOQ: limit of quantification
MEHP-d4: mono(2-ethylhexyl)phthalate
OEL: occupational exposure limit
PG: propylene glycol
SBP: Swiss Biobanking Platform
SVOC: semivolatile organic compound
VG: vegetable glycerol

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Protocol

Resilience-Informed Community Violence Prevention and Community Organizing Strategies for Implementation: Protocol for a Hybrid Type 1 Implementation-Effectiveness Trial

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Abstract

Background: Community violence is a persistent and challenging public health problem. Community violence not only physically affects individuals, but also its effects reverberate to the well-being of families and entire communities. Being exposed to and experiencing violence are adverse community experiences that affect the well-being and health trajectories of both children and adults. In the United States, community violence has historically been addressed through a lens of law enforcement and policing; the impact of this approach on communities has been detrimental and often ignores the strengths and experiences of community members. As such, community-centered approaches to address violence are needed, yet the process to design, implement, and evaluate these approaches is complex. Alternatives to policing responses are increasingly being implemented. However, evidence and implementation guidance for community-level public health approaches remain limited. This study protocol seeks to address community violence through a resilience framework—Adverse Community Experiences and Resilience (ACE|R)—being implemented in a major US city and leveraging a strategy of community organizing to advance community violence prevention.

Objective: The objective of this research is to understand the impact of community-level violence prevention interventions. Furthermore, we aim to describe the strategies of implementation and identify barriers to and facilitators of the approach.

Methods: This study uses a hybrid type 1 effectiveness-implementation design. Part 1 of the study will assess the effectiveness of the ACE|R framework plus community organizing by measuring impacts on violence- and health-related outcomes. To do so, we plan to collect quantitative data on homicides, fatal and nonfatal shootings, hospital visits due to nonaccidental injuries, calls for service, and other violence-related data. In Part 2 of the study, to assess the implementation of ACE|R plus community organizing, we will collect process data on community engagement events, deliver community trainings on community leadership and organizing, and conduct focus groups with key partners about violence and violence prevention programs in Milwaukee.

Results: This project received funding on September 1, 2020. Prospective study data collection began in the fall of 2021 and will continue through the end of 2023. Data analysis is currently underway, and the first results are expected to be submitted for publication in 2024.

Conclusions: Community violence is a public health problem in need of community-centered solutions. Interventions that center community and leverage community organizing show promise in decreasing violence and increasing the well-being of community members. Methods to identify the impact of community-level interventions continue to evolve. Analysis of outcomes beyond violence-specific outcomes, including norms and community beliefs, may help better inform the short-term and proximal impacts

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of these community-driven approaches. Furthermore, hybrid implementation-effectiveness trials allow for the inevitable contextualization required to disseminate community interventions where communities drive the adaptations and decision-making.

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KEYWORDS

ACEs; community organizing; community violence; implementation-effectiveness trial; resilience

Introduction

Community violence is a persistent problem impacting public health. Community violence impacts the overall mental and physical health of neighborhoods, towns, and collective spaces. Risk factors associated with violence and community trauma include community poverty, community disadvantage, and disorganization [1]. Research framed through social disorganization theory, sometimes referred to as "broken windows theory," has suggested that disorder within a community can impact mental health and contribute to stress in individuals [2]. Among youths and adolescents, the impacts of community violence are particularly strong [3]. Violence, including experiencing physical violence and being a witness to violence, is considered an adverse childhood experience that can significantly impact children's future physical and behavioral health [4]. Different types of violence against youths, such as child abuse and neglect and community youth violence, often share the same risk and protective factors [5].

Protective factors, contrasted with risk factors, are increasingly seen as key to effective community-level violence prevention interventions. In taking a strength-based approach, which highlights protective factors, there is an opportunity to center the role of community members and their experiences while moving away from risk-framing approaches [6]. Strength-based approaches to community violence prevention are those that consider community relationships as a positive, protective factor against violence. Resilience theories, along with constructs of collective efficacy and social cohesion, have allowed for an expanded understanding of how to consider structural-level interventions leveraging protective factors to address community violence [7].

Interventions conducted at the community level can impact multiple individuals, particularly youths, at once [8]. Community-level interventions can interrupt patterns of violence at the structural level, preventing exposure to violence at an early age, and can move beyond school-based approaches commonly targeting youth [9]. Furthermore, community-level interventions developed through an asset-based framework, rather than deficits, have gained wider understanding and evidence. One community-level primary prevention strategy that has been explored in the context of community resilience is community organizing [10]. Community organizing can be defined as a process in which people affected by common concerns aim to build their power together and identify solutions for those shared concerns by mobilizing [11,12]. Community organizing, in the context of community violence prevention, seeks to address issues of social cohesion and isolation by building up relationships within communities and having communities lead the violence prevention strategies. Community organizing has been incorporated into interventions seeking to address domestic violence [13], as well as a way to empower youth in the violence prevention space [14,15].

It is difficult to implement community-level interventions and measure their effects, because of the complexity of intermingled contextual and temporal factors. Community-level interventions are often not broadly disseminated nor scaled up because they are developed according to the unique demographic characteristics of the community, as well as the unique characteristics of the practitioners or other persons leading implementation. Community-level interventions may also occur at a particular moment in time that cannot be easily incorporated into statistical models to determine intervention impacts. Hybrid trials seek to address these problems by allowing for implementation-related data collection to be incorporated into the study design [16]. Thus, this study uses a hybrid type 1 implementation-effectiveness trial; these are typically conducted early in the intervention development process and have the primary aim of evaluating the effectiveness of an intervention while allowing for the collection of implementation-related data to improve dissemination and intervention uptake.

Adding to the complexity of researching community-based interventions is the appropriate selection of statistical approaches to analyze community-level outcomes captured as interrupted time series data. Statistical decisions include the choice of analytic model (eg, autoregressive integrated moving average vs regression), if and how to account for autocorrelation and seasonality, if and how to correct for a small sample size, and aligning the statistical strategy with the available data, such as the number of time points. Reporting the planned analytic strategy a priori in protocol papers is important for avoiding bias due to a selected approach, as well as engendering confidence in the results [17].

Promising structural interventions that account for these methodological and implementation issues to address community violence have emerged in recent research. Cure Violence, a violence prevention intervention adapted from "Chicago Ceasefire" that was developed in the mid-1990s, framed violence as a communicable disease [18]. Through adaptations and implementations in multiple cities over the last 3 decades, the impacts of Cure Violence have been mixed [19]. The research has allowed for an evolved understanding of the importance of changing community norms around violence, in addition to the physical acts of violence [20,21]. Another study building on Chicago Ceasefire, the CeaseFire 365 intervention, effectively reduced gun violence in Baltimore while identifying the importance of measuring nonviolence-related outcomes to

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determine impact. The intervention included weekend "ceasefires" in which community events and public meetings sought to communicate a stop to violence during specific times [22].

Building on previous experiences and challenges of Cure Violence and similar community violence prevention interventions, the Prevention Institute (PI) and the University of California San Francisco, developed the Adverse Community Experiences and Resilience (ACE|R) framework as a community-level approach to violence prevention. The ACE|R framework uses community-specific data combined with an underlying evidence-based understanding of how adverse childhood experiences impact adolescents and communities [10]. In 2016, PI introduced the ACE|R framework to over 150 community partners and residents in Milwaukee during a time when the Milwaukee Blueprint for Peace—a call to action for violence prevention—was in development. The PI partnered with the Milwaukee Office of Violence Prevention (OVP) to facilitate the development of the Milwaukee Blueprint for Peace using the ACE|R framework, including having residents identify the leading risk and resilience factors related to violence in Milwaukee. These factors were solicited through community conversations, roundtable discussions, and web-based surveys. Residents and community organizations shared input on the emerging vision and principles in alignment with the ACE|R framework through those same forums. Through this citywide organizing and mobilization approach to comprehensive planning, a shared set of goals, strategies, and indicators was identified and formally launched in 2017 as the Blueprint for Peace.

The primary objective of this study is to assess whether community organizing and mobilizing residents to act on the Blueprint for Peace increases the effectiveness of the ACE|R framework to reduce community-level measures of child abuse and neglect and youth violence in 4 select communities, compared with having no community organizing in the 6 remaining select communities. The secondary objective is to explore the barriers to and facilitators of implementing community organizing as a strategy for increasing support for the sustainability of the Blueprint for Peace and the reduction of community-level violence in Milwaukee.

Methods

Study Design

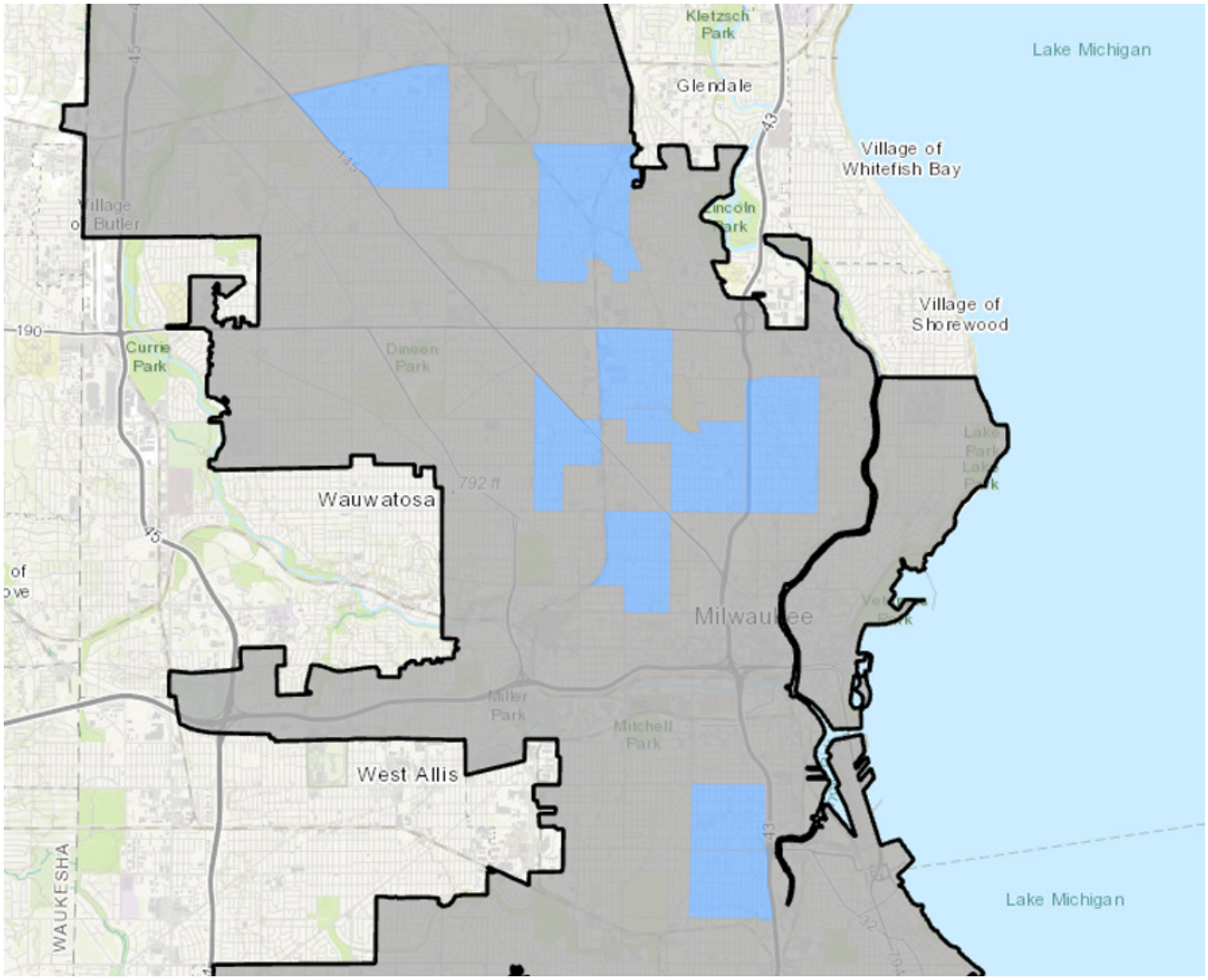
To meet the objectives of this study, the proposed research design is a hybrid type 1 effectiveness-implementation design using a mixed methods approach, leveraging both quantitative and qualitative methods to measure the effect of the ACE|R plus community organizing on communities and collect data on the implementation of community organizing. We present the details of the proposed study in two parts: part 1 describes the proposed study to measure the effectiveness of the ACE|R plus community organizing, and part 2 describes how we will measure the implementation of the ACE|R plus community organizing.

Setting

This proposed study will take place in Milwaukee, Wisconsin, where the Blueprint for Peace was first launched in 2017. Blueprint for Peace participants in the development process selected 10 communities as the neighborhoods to prioritize and focus on violence prevention efforts (Figure 1). This study focuses on 4 of the 10 selected communities, hereafter referred to as the "select communities."

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Figure 1. Map of Milwaukee, with the 10 communities where the Blueprint for Peace Initiative has been implemented highlighted in blue.



Intervention—Blueprint for Peace and the Resident Leadership and Advocacy Training

The proposed study uses the ACE|R framework plus community organizing as a strategy to directly address the need for community-level action to prevent child abuse and neglect and youth violence. Intervention communities will receive training and technical assistance that integrates the ACE|R framework, community organizing and mobilization, and operational knowledge of the Milwaukee Blueprint for Peace**.** The goal of this intervention element is to prepare residents and other interested parties in the community (eg, community-based organizations and faith-based organizations) to understand and be prepared to act on (organize or support) structural community-level change in support of the Blueprint for Peace. The ACE|R plus community organizing trainings (hereafter referred to as “resident leadership and advocacy training”) consist of 5 modules that ground participants in the knowledge of systemic trauma and then cover ways to address neighborhood violence through community-designed solutions. The details of each of the training modules are presented in Table 1.

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Table 1. Content details for the 5 modules that make up the resident leadership and advocacy training.

Module	Module title	Module objective	Example content
1	Systematic and Historical Trauma (Adverse Community Experiences and Resilience)	Learn about systematic and historical trauma through the recognition that the impact is cumulative and reverberates across neighborhoods for generations	• Defines adverse childhood experiences • Defines trauma
2	Social Determinants of Health and THRIVE[a]	Explore community factors—people, places, and equitable opportunities—that influence health, safety, and well-being in their neighborhoods	• Defines the social determinants of health inequities and describes how socioeconomic factors and neighborhood characteristics shape behaviors • Identifies strategies to address community-level factors and move toward health equity • Discusses the role of neighborhood, home, and work environments in determining health and the quality of life
3	Addressing and Preventing Community Trauma and Healing	Learn ways to address community trauma through healing	• Healing as a starting point for community and system transformation, including activities to explore opportunities for healing and identify strong examples of how community healing is already taking place in the neighborhood • Strategies for healing • Strategies to address community trauma
4	Building Resident Leadership and Voice, Navigating Systems from Civic Engagement to Movement Building	Identify the steps of effective community action, including needs and issue assessment and strategic planning	• Defines key components of a toolkit specific to Milwaukee city and county processes • Outlines opportunities for shifting power by elevating community ownership, creating community change, such as shifting policy, and influencing decision makers. • An overview of the Blueprint for Peace and the goal areas, including discussion and activities, to map how it is connected to existing neighborhood efforts and neighborhood goals that support the blueprint
5	Resident Leadership in Action—Needs and Opportunity Assessment	Identify actions they will take to implement community action	• Readiness assessment designed to guide and support communities in determining capacity-building needs • Readiness assessment to build a plan for community mobilization of assets that accelerates community-level violence norms change and collective action toward a public health approach to violence prevention

[a]THRIVE: Tool for Health & Resilience in Vulnerable Environments.

Part 1: Effectiveness of the ACE|R Framework Plus Community Organizing

To define and determine the effect of a community violence prevention intervention, the first part of this study will be an effectiveness study of the ACE|R framework plus community organizing. This part will include using an idiographic clinical trial research design that captures within-community changes to analyze the Blueprint for Peace–related activities and outcomes, including child abuse and neglect, youth violence, and other violence-related outcomes (Textbox 1).

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Textbox 1. Key measures to evaluate the implementation and effectiveness of Adverse Community Experiences and Resilience (ACE|R) plus community organizing through outcome constructs.

Outcome constructs and tracked measures

- Increased community organizing
  - Events led by individuals trained in community organizing
- Long-term development of safe and healthy communities
  - Homicides
  - Nonfatal shootings in select neighborhoods
  - Fatal shootings in select neighborhoods
  - Firearm-related injuries
  - Arrests due to violence among youths younger than 18 years
  - Arrests due to child maltreatment
  - Calls for service in selected communities
  - Nuisance, vacant, and blighted properties abated in select neighborhoods
  - Poverty rate in select neighborhoods
- Reduced adverse childhood experiences
  - Children hospitalized for confirmed and suspected child abuse or violence-related injury
  - Children at the emergency department for confirmed and suspected child abuse or violence-related injury
  - Home removals
- Reduced child abuse and neglect
  - Child protective services referrals
  - Child maltreatment reports
  - Rate of child victims per 1000 children
- Increased social cohesion
  - Block clubs in select neighborhoods
  - Resident-led events in select neighborhoods
- Increased awareness of violence prevention strategies
  - Neighborhood perceptions of safety, resilience, and access to resources and services
  - Awareness of neighborhood assets, resources, and programming among neighborhood residents

Unlike randomized controlled trials, which use large samples and randomization to control confounding influences, the idiographic clinical trial will manage differences by collecting control data and treatment data from the same community. Differences between control and treatment phases are quantified as change at treatment onset (ie, phase intercepts) and change over time (ie, phase slopes). Blueprint for Peace activities include events, workshops, and trainings that provide communities with strategies and resources to reduce violence. Counts and descriptions of Blueprint activities will be collected in the 4 select communities monthly. The 4 selected communities are defined by geographically bounded areas that city government agencies provided to the research team (Figure 1). Milwaukee is a safe and resilient city where the lives of all residents are valued, promoted, and protected. Outcome measures were derived from the following six overarching goals of the Blueprint for Peace [23], (1) stop the shooting, stop the violence; (2) promote healing and restorative justice; (3) support children, youth, and families; (4) promote economic opportunity; (5) foster safe neighborhoods; and (6) strengthen capacity and coordination of violence prevention efforts.

Data Analysis

Primary analysis of outcome measures will use intensive hierarchical modeling with maximum likelihood estimation, a multilevel linear model that has evolved for use in small-sample clinical trials [24]. This approach can capitalize on both change from baseline (preintervention) to treatment phases of time series data and differences between communities that do and do not receive an intervention.

Recent developments in intensive hierarchical modeling for small samples allow for evaluation models that (1) control for

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biases due to small samples, (2) estimate intervention impacts that are quantified in terms of phase "jumps" and slopes, (3) use thorough power analysis using Monte Carlo simulation, and (4) have the ability to model and test complex causal inferences [24,25]. For intensive hierarchical modeling of the ACE|R plus community organizing impacts, time series data are clustered within communities; the effect of community organizing is quantified at level 1 as change over time, with aggregate models across communities being analyzed at level 2. Corrections to statistical testing and parameter estimates (to account for small sample sizes) will include the Satterthwaite degrees of freedom [26] and use full information maximum likelihood estimation for statistical testing of parameters but estimate model parameters using restricted maximum likelihood.

Differences between baseline and treatment phases will be estimated within the 4 select communities; community-level factors that may enhance or attenuate the impact of resident leadership and advocacy training will be explored using between-select communities fixed effects. An additional contrast will be to compare the changes in the 10 select communities to matched communities in Milwaukee outside the study.

Part 2: Implementation of the ACE|R Framework Plus Community Organizing Strategy

To address the objective of improving the research-to-practice gap, the second part of the study is the collection of data on the implementation of community organizing, as well as neighborhood perceptions of safety, resilience, and access to resources and services. This includes awareness of neighborhood assets, resources, and programming among neighborhood residents. Data sources include community members and resident leaders who have received training on how to deliver training on ACE|R and Blueprint for Peace activities. Data collection activities include focus groups and surveys.

Recruitment

Recruitment of community residents will occur in collaboration with PI, OVP, and community organizations including neighborhood associations in the 10 select neighborhoods. Materials for recruitment will be cobranded to reach community residents in venues like community centers, food pantries, flea markets, and social service organizations. Social media outreach will take place on the web through Instagram and Facebook. In addition to recruitment in the broader community, those participants who have completed the resident leadership and advocacy training will be referred to the community resident focus groups.

Focus Groups With Community Members

We plan to conduct focus groups within the select communities every 6 months to better understand the implementation of the Blueprint for Peace and community organizing as a strategy. At least 1 focus group in each select community will occur, with community residents recruited through convenience sampling, resident advisory committees, and local advertisements.

Those who agree to participate in the focus groups will undergo informed consent procedures and receive a US $40 gift card (their choice between Walmart, Amazon, or 2 local Milwaukee vendors) as part of their participation. Focus groups with community participants will be conducted through Zoom or in person in private or semiprivate spaces convenient for the participants (eg, community center) by research staff trained in qualitative methods. Focus groups will be digitally recorded and transcribed verbatim using a third-party service. Once the transcript is returned, it will be autocoded in NVivo (version 12; QSR International). Theme identification will occur for each question on the focus group transcripts.

Trainings and Community Events

In addition to focus groups with community members, we plan to collect data on the resident leadership and advocacy training conducted by the PI and the events delivered by those trained on resident leadership and advocacy, as well as events hosted by the city of Milwaukee as part of the Blueprint for Peace. Data will be collected through information provided by those trained (through surveys), as well as regular monthly meetings with the Milwaukee OVP.

Guided by the Consolidated Framework for Implementation Research (CFIR), we will use the data from these trainings and community events to better understand key CFIR domains: outer setting, inner setting, intervention characteristics, and process. These data will allow for the definition of specific strategies for improving intervention implementation (Table 2).

Table 2. Data sources informing implementation of Adverse Community Experiences and Resilience (ACE|R) plus community organizing through the use of the Consolidated Framework for Implementation Research (CFIR).

CFIR domain	Domain description	Goal	Data source
Outer setting	Characteristics outside the program and program delivery staff (eg, OVP[a] and PI[b])	Identify elements external to the program (eg, media) that might shape implementation barriers and facilitators	Community outreach event log
Intervention characteristics	Elements of the program that might cause barriers to implementation and sustainability	Facilitate adaptations of the program and program delivery	PI training tracking
Process	Actions taken during the implementation and delivery of the program that can be defined	Develop strategies that facilitate the implementation of the intervention	Community outreach event log and PI training tracking

[a]OVP: Milwaukee Office of Violence Prevention.

[b]PI: Prevention Institute.

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Ethical Considerations

There is strong evidence that the trauma of community violence impacts those living in these communities, including health effects on youth and adolescents [27]. Importantly, those who are both in the community and engaging in intervention delivery are also greatly impacted [28]. Given these considerations, we will engage community members through focus groups and surveys on trainings to better understand the norms of violence as well as the mental and physical impacts. We will make every effort to support those participating in the study and provide mental health support, as requested. This study has been approved by the institutional review board of Advarra (#0217719). The proposed study will be performed in accordance with the Declaration of Helsinki.

Informed consent will be obtained from all the participants or legal guardians of participants for the community focus groups through signing a digital consent form. Those who attend the focus group will receive a US $40 gift card (participants may choose between Walmart, Amazon, or 2 local Milwaukee vendors). For the community focus groups, the audio of each of the focus groups will be recorded, transcribed, and anonymized. All data are securely stored on the RTI International server, and all electronic files containing identifiable information are password protected, with access limited to study staff. Only aggregate data will be shared with study partners. Focus group recordings will be destroyed as soon as the project is completed.

Results

This project received funding on September 1, 2020. Prospective study data collection began in the fall of 2021 and will continue through the end of 2023. Data analysis is currently underway, and the first results are expected to be submitted for publication in 2024.

Discussion

Expected Findings

This study aims to understand the impacts of a community-centered violence intervention. Our goal is not only to determine the impact of community organizing on community violence prevention but also to determine the feasibility and acceptability of such a strategy. This intervention centers the community, leveraging community member strengths, experiences, knowledge, and wisdom.

A key strength of this study is the engagement with government and community partners, along with the use of existing community infrastructure. Using the ACE|R framework plus community organizing to identify approaches to strengthen the city's implementation and impacts of the Milwaukee Blueprint for Peace engages resident leaders within an existing policy initiative. We will use our findings to further build the evidence for this approach, including identifying the barriers to and facilitators of implementation as faced by the community and its partners.

The first limitation of this study is the impact of COVID-19 on staffing, recruitment, and data collection. Labor markets have shifted widely during the pandemic; as such, identifying research support staff in Milwaukee may prove difficult. Such impacts are also being seen by other nonprofit organizations and government agencies. Because of our partnerships with the Milwaukee OVP, we may see impacts on its structure and the OVP-led community engagement activities. Recruitment at in-person events is difficult because, despite relaxed COVID-19–related restrictions, there continues to be less in-person interaction; remote events are also challenging as recruiting avenues because of scheduling conflicts and a lower engagement than at in-person events. Because conducting focus groups remotely is difficult, we aim to incorporate in-person focus groups once local Milwaukee officials have determined that it is safe to do so.

Beyond the impacts of COVID-19, an additional limitation with a community-level intervention is the possibility of contamination bias—that is, bleeding of the intervention into control communities. With extensive reporting and regular team meetings with the OVP, the PI, and our community partners, we hope to account for this bias but recognize that it cannot be completely avoided.

Conclusions

Our hope is that this approach will further strengthen the evidence that not only should community violence be viewed as a public health problem but also that there are ways to address it as such with a community-level approach that centers communities as agents of community transformation. How to implement these types of programs and the methods of measuring their impact remain mixed. The role of resident leaders is pivotal for understanding the effects of the intervention on community violence and the impacts on the leaders themselves in delivering and implementing the intervention. Results from this study will provide a road map for how other communities can implement community organizing within the ACE|R framework and further community violence prevention efforts.

Acknowledgments

We wish to thank our community partners—including the Milwaukee Office of Violence Prevention, Safe & Sound, and the Medical College of Wisconsin—and the broader Milwaukee community for all their support. This study was funded by the National Center for Injury Prevention and Control, Centers for Disease Control and Prevention (5R01CE003191-03). The funders had no role in the design of the study or the writing of the manuscript.

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Data Availability

The data from this study are not publicly available as data collection is ongoing and the results have not been analyzed. Materials for data collection are available from the corresponding author upon reasonable request.

Authors' Contributions

PG is the principal investigator and drafted the preliminary protocol. Funding for this research was obtained by PG, AY, DFJ, SR, and TAR. NAB drafted the initial manuscript for publication, and SR, MD, CW, NK, and PG provided input on the methods. SR, MD, CW, and PG have critically revised the manuscript. All authors have read and approved the final manuscript. All authors agreed to be personally accountable for their own contributions.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review from the National Center for Injury Prevention and Control, Centers for Disease Control and Prevention (USA).
[PDF File (Adobe PDF File), 138 KB - resprot_v12i1e50444_app1.pdf]

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Abbreviations

ACE|R: Adverse Community Experiences and Resilience
CFIR: Consolidated Framework for Implementation Research
OVP: Office of Violence Prevention
PI: Prevention Institute

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Protocol

Built Environments to Support Rehabilitation for People With Stroke From the Hospital to the Home (B-Sure): Protocol for a Mixed Method Participatory Co-Design Study

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Abstract

Background: A global trend is to move rehabilitation closer to people's neighborhoods and homes. Still, little attention has been given to how the built environment outside the hospital setting might impact rehabilitation and recovery for stroke survivors.

Objective: The overarching objective of this project is to develop conceptual models of built environments that support stroke rehabilitation and recovery outside the hospital setting. Specifically, the project will explore factors and characteristics of the built environment that support people with stroke and their families and identify innovative built environments that can be designed for local health care. The project will examine facilitators and obstacles for implementing built environmental solutions and evaluate the potential benefits, feasibility, and acceptability.

Methods: The project uses a mixed methods design approach with 3 phases. In phase 1, factors and characteristics of the built environment for rehabilitation will be identified. Based on the results from phase 1, phase 2 will involve co-designing prototypes of environments to support the rehabilitation process for people with stroke. Finally, the prototypes will be evaluated in phase 3. Qualitative and quantitative methods will include a literature review, a concept mapping (CM) study, stakeholder interviews, prototype development, and testing. The project will use multidimensional scaling, hierarchical cluster analysis, descriptive statistics for quantitative data, and content analysis for qualitative data. Location analysis will rely on the location-allocation model for network problems, and the rule-based analysis will be based on geographic information systems data.

Results: As of the submission of this protocol, ethical approval for the CM study and the interview study has been obtained. Data collection is planned to start in September 2023 and the workshops later in the same year. The scoping review is ongoing from January 2023. The CM study is ongoing and will be finalized in the spring of 2024. We expect to finish the data analysis in the second half of 2024. The project is a 3-year project and will continue until December 2025.

Conclusions: We aim to determine how new environments could better support a person’s control over their day, environment, goals, and ultimately control over their recovery and rehabilitation activities. This “taking charge” approach would have the greatest chance of transferring the care closer to the patient's home. By co-designing with multiple stakeholders, we aim to create solutions with the potential for rapid implementation. The project’s outcomes may target other people with frail health after a

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hospital stay or older persons in Sweden and anywhere else. The impact and social benefits include collaboration between important stakeholders to explore how new environments can support the transition to local health care, co-design, and test of new conceptual models of environments that can promote health and well-being for people post stroke.

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KEYWORDS

stroke rehabilitation; built environment; person-centered; participation; self-efficacy; meaningful activities; accessibility; participatory co-design; good quality and local care

Introduction

Overview

The Built environments to support rehabilitation for people with stroke from the hospital to the home (B-Sure) initiative aims to create conceptual models of environments designed specifically to support the rehabilitation of stroke patients, from hospital settings to their homes. The project addresses the fundamental transformation of health care to provide care and rehabilitation close to the person or at home, that is, good quality and local health care [1-3]. Exploring how the built environment can support these new care policies is important to enhance a person's potential to live an active life. Surprisingly, little consideration has been given to how the built environment might influence rehabilitation and recovery for people with stroke. Developing new, more supportive environments may be a crucial factor in the success of local health care innovation.

Background

Stroke is a highly prevalent and debilitating brain injury that causes disability in adults [4,5]. In Sweden alone, an estimated 25,000 people are affected annually [6], while globally, stroke affects over 15 million people yearly, resulting in over 5 million deaths [5]. People with stroke often have long-lasting rehabilitation needs, and recovery is known to be complex, with several care providers involved [7-9]. The effects of stroke can be profound and lead to a range of activity and participation limitations [9-11], such as reduced quality of life, social isolation [12-14], and adverse events such as falls [9,15]. Many patients and families describe the support provided poststroke as poor and not patient-centered [16-18] and report poor engagement in their care and treatment decisions [7,19]. In addition, the role and importance played by the built environment to support rehabilitation outcomes have been largely ignored, especially when patients return home [20,21].

Rehabilitation aims to restore a person's functional capacity and societal participation after injury [22]. Effective health care services support a person's independence, participation, and self-directed capacity as people return to the community after a stroke. Recovery after a stroke is best supported when the person and their family or care network feel empowered to take responsibility for their rehabilitation, recovery goals, and activities [22,23].

There is a general need for improvements in the rehabilitation environments. Hospital environments, even specialized rehabilitation hospitals, make patients feel bored and lonely and inhibit independence and control [24-26]. These shared experiences can influence recovery and disempower individuals from leading or engaging in meaningful recovery. Studies show that patient outcomes vary between rehabilitation facilities [27], possibly partially due to the differences in the built environment [28,29]. The design of rehabilitation environments may impact the recovery of people with a stroke, affecting their function in the long term [30]. For society, this can increase disability expenditure and reduce productivity by hampering people's ability to participate fully [26,30]. It is worth noting that in most design strategies in rehabilitation, the built environment has not undergone empirical testing or evaluation.

New Places for Health Care

Moving care and rehabilitation to peoples' neighborhoods and in the home is a global development [1]. In Sweden, the reform, "good quality and local health care" is described as a new service [3] with more outpatient care and less but highly specialized inpatient care. This requires an empowered, more self-directed patient with control over their care and rehabilitation. The care must be person-centered and needs to switch from traditional 1-way expert providers to shared decisions with the patient [31,32]. Health care is far from fulfilling the demands of person-centered care and shared decision-making [33,34]. The Swedish government argues that the reform has implications for the building sector as they must be involved in policy discussions to avoid the risk when expensive new inpatient hospital building projects with large climate footprints are realized. At the same time, care and rehabilitation should move closer to patients or into their homes [3].

Developing local health care systems will require innovative approaches to living environments and care provision. These approaches must prioritize providing safe and dignified care, healthy working environments for health care staff, and support for continued independent living despite disability [35]. To achieve these goals, new models of care that promote health and rehabilitation in alternative settings may be necessary, such as rehabilitation hotels, small recovery homes, and day rehabilitation environments. Web-based care and technology, such as telerehabilitation, may also be critical in creating effective transition pathways between different care environments [36-38]. To achieve this, it will be important to develop simple systems for monitoring progress and requesting appointments with health care teams, which can be embedded into the built environment of these care settings.

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Our starting point was to ask whether the alternative care environments, between hospital and home, might better support people with rehabilitation needs and avoid the current negative effects of hospital-based rehabilitation. While rehabilitation at home may suit some more mildly affected individuals with stroke and their families, it is impossible for others. Our goal is to explore built environment solutions for individuals who require more support or for individuals unable to readily or immediately go home. This direction aligns with the 2030 Agenda for Sustainable Development to ensure cities are inclusive, safe, resilient, and maintainable and promote well-being for all [39]. We believe the design and development of built environments can support recovery for people with stroke but also benefit others with similar needs and functional challenges, for example, multiple sclerosis or Parkinson and those sensitive to obstacles in their environment, including older people.

Despite the growing trend of rehabilitation at home, earlier research has neglected the role of the environment in this transformation, creating a significant knowledge gap [40]. This gap undermines the effectiveness of rehabilitation at home. There is a pressing need for an in-depth exploration of the environmental factors that impact rehabilitation outcomes, including innovative methods and solutions. An integrative mixed methods approach and participatory design can offer a comprehensive understanding of the importance of the environment for rehabilitation at home. By using these approaches, it will be possible to generate robust evidence on the impact of environmental factors on rehabilitation outcomes, inform the development of guidelines and policies for local care and rehabilitation, and enhance the effectiveness of rehabilitation at home.

Objectives and Research Questions

B-Sure aims to explore the essential factors in a built environment that supports stroke survivors and their families during rehabilitation. The specific research questions include (1) what are the most important factors in a built environment that supports people with stroke and their families in their rehabilitation process? (2) What do innovative built environments for local health care and rehabilitation look like? (3) What are the significant facilitators and obstacles for implementing various built environmental solutions? (4) How do stakeholders evaluate different built environment solutions regarding their potential benefits, feasibility, and acceptability?

Theoretical Framework

We will use several theories and frameworks to conceptualize and explore the interaction between a person and the environment. For example, the Person-Environment-Occupation model [41] and the International Classification of Functions [42] show that the environment comprises many facilitating or hindering factors external to the person. These factors include features of the built environment (eg, stairs and doors), natural environment (eg, surfaces outdoors), and objects. The models describe that a good fit between a person's (P) functional abilities and the demands of environmental factors (E) leads to positive outcomes such as increased independence and overall well-being [43-45]. Hence, to optimize rehabilitation outcomes, it is important to use a person's environment and be aware of facilitating and hindering factors.

B-Sure is also based on theoretical components of self-efficacy in which the person is seen as capable, with unique experiences, expectations, needs, and resources. Self-efficacy is a key construct from Bandura's theory of social cognition [46]. It is defined as "people's beliefs about their capabilities to produce designated levels of performance that influence events that affect their lives." Self-efficacy beliefs can determine how people feel, think, motivate themselves, and behave concerning their health. For example, self-efficacy influences motivation and health behaviors by determining people's goals, how much effort they invest in achieving them, and their resilience when faced with difficulties or failure.

In addition, B-Sure is based on the framework of Living-Lab and co-design [47], that is, a close collaboration between stakeholders in the design development process. One of the major challenges in planning and architectural practices today is the communication gap between the design team, the various levels of user groups, and the wide array of specialized consultants in the process.

Methods

Study Design

B-Sure has a mixed methods approach [48], including participatory co-design [49,50]. The project has 3 phases. In phase 1 a literature review, concept mapping (CM), and interviews will be done. In phase 2 the results from phase 1 will be used to co-design prototypes of environments to support the rehabilitation process for people with stroke. Finally, phase 3 will evaluate the prototypes obtained with the co-design process. The process will be iterative, enabling knowledge accumulation and increased common understanding between stakeholders and researchers, and contributing to solid knowledge production.

Phase 1: Identify Factors

Overview

Phase 1 involves 3 primary methods of data collection. First, a rapid scoping review [51] will be conducted to synthesize relevant knowledge of essential environmental factors. Second, a participatory mixed methods approach called CM [52] will engage stakeholders in mapping conceptual areas related to the built environment's importance for home rehabilitation. This process will involve collecting qualitative and quantitative data through generated statements, which will then be synthesized and sorted. Finally, interviews with diverse stakeholders will be conducted, covering sociodemographic data and open-ended questions related to identifying crucial factors for promoting the rehabilitation process of people with stroke and their families within the built environment.

Participants

Participants from five stakeholder categories will be recruited for the CM and the interviews: (1) people with stroke; (2) relatives or significant others; (3) health care staff; (4) government, including officials responsible for the operation of health care environments and stroke rehabilitation in the

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region and municipalities; and (5) industry practitioners, including architects and other designers working within the health care contexts and home environments. We will strive to recruit 20 individuals from each category for the CM study and 3-5 people from each category for the in-depth interviews.

People who have had a stroke and their relatives will be recruited locally and regionally through advertising on several portals: hospital notice boards, stroke units, outpatient wards, the STROKE National Association's website, and social media. Participants meet the criteria to participate if they are willing to give written informed consent, have a diagnosed stroke, are 18 years of age and older, or care for someone who has had a stroke. We will use a strategic selection procedure with maximum variation to ensure we get a broad description of experiences from the participants regarding age, gender, time since stroke, ethnicity, and geographical location. Staff with clinical experience in rehabilitation after a stroke will be recruited through the research group's contacts, email lists, and targeted personal emails. We will strive to have a balance between different professionals and regional distribution. We will also recruit representatives from the region, municipality, and real estate owners through our network and collaborators.

Analysis

We will use multidimensional scaling analysis and hierarchical cluster analysis for the CM of quantitative data [53] and qualitative content analysis [54] for the interviews and CM. The NVivo software (QSR International) [55] will be used to aid the qualitative analyses and promote the validation and transparency of the coding.

Phase 2: Co-Design Prototypes or Models of Environments

Overview

This aspect of the research will be carried out within the framework of a Living Lab [47] using an iterative and learning co-design approach to engage stakeholders. Building on Phase 1, we will use the well-established Double Diamond method [56] as a guide for the workshop, previously used by the research group [57]. The method includes a three-step process: (1) idea generation, (2) modeling a prototype, and (3) testing and discussing. The research team will facilitate the sessions. Each co-design session is scheduled to continue the work of the previous session. The sessions will be combined with meetings with an advisory committee to guide the progression of the developing prototype. We will use tools and techniques that combine narratives, creativity, and imagination (scenario planning, group discussions, world cafe, individual work, collective sessions, and mock-ups) to ensure we reach all participants based on their characteristics and to guarantee that power is shared within the group.

We will be running 2 co-design processes, 1 in a dense city area and 1 in a rural area. The process will consist of 5 co-design sessions of 3 hours, which will take place over 6 months.

In this process, we will also use a geographic information system (GIS) method [58]. Through the analysis, we can visualize optimal places with the highest possible accessibility for the population. To perform the analysis, we will collect network data for transport systems, information about the population, government thresholds, and rules. Sensitivity analysis of optimal places will be done where the population's place patterns alternate (according to gender, socioeconomic status, and health status). Furthermore, a rule-based modeling method will be used to work out the optimal places where the identified needs from the literature study and the interviews will be used as criteria and matched with environments in the urban area and in the rural area.

Participants

Participants from five stakeholder categories (not included in phase 1) will be recruited: (1) persons with stroke; (2) relatives or significant others; (3) health care staff; (4) government, including officials responsible for the operation of health care environments and stroke rehabilitation in the region and municipalities; and (5) industry practitioners, including architects and other designers working within health care contexts and home environments. We will strive to have at least 2-4 people from each group. They will be recruited in the same way as in phase 1.

Data Collection

The data will be obtained from (1) notes taken by the team, (2) prototypes produced by each group, and (3) notes taken after the working sessions via a meeting with the research team to share their impressions.

Analysis

A qualitative content analysis [54] supported by using NVivo software [55] will be used. To enhance the mixed methods approach of CM a qualitative GIS method [58,59] will be used to spatially analyze and contextualize the CM results. Open access Swedish spatial data (ie, street network files and geocoded health services) will be triangulated with the CM results using qualitative GIS methods to provide a layered, grounded theory understanding of the meaning and experiences of the stakeholders. A qualitative GIS approach offers a deeper understanding of the context and meaning of the situations that influence person-place interactions and the social factors that relate to the perception and interactions.

Phase 3: Evaluation of the Prototypes

Overview

The third phase will evaluate the different prototypes or models of different environmental solutions according to benefits, feasibility, and acceptability. This is a matter of observing future user and stakeholder discussions when confronted with the prototypes, aiming to identify possibilities and challenges with the prototypes.

A combination of think-aloud and focus group interviews will be used. The think-aloud method is frequently used to reveal views from users when they encounter potential solutions [60]. In general, this method aims to capture a systematic process of thinking aloud and analyze this process to gain a deeper understanding of the feasibility of the developed models or prototypes. The sessions will be filmed to allow for transcription

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of the communications and permit us to associate them with the prototypes.

Participants

A sample of potential users and stakeholders will be recruited. We will base the sample on the 5 stakeholder groups and recruit 2-3 people from each group.

Analysis

The transcriptions will be coded to identify possibilities and challenges with the prototypes and content analysis will be used [54].

Patient and Public Involvement

B-Sure study aims to achieve active engagement and empowerment of persons with stroke, health care professionals, decision makers, and other stakeholders by developing partnerships that emphasize equal power while acknowledging different roles and responsibilities. The collaborative nature of the research design supports a strong patient and public involvement approach. We are actively working in collaboration with stroke organizations and stroke units where the research questions for the study have emerged. This ensures that the research aligns with the needs and perspectives of stroke survivors, their families, and the wider community. During the initial phase, individuals with stroke, family members, and relevant stakeholders, including representatives from stroke organizations and stroke units, will contribute their insights and lived experiences to identify key factors and characteristics of the built environment for rehabilitation. The co-design phase will adopt a participatory approach, actively involving stroke survivors, their families, stakeholders, and representatives from stroke organizations and units as partners in developing prototypes for rehabilitation-supportive environments.

To generate and disseminate knowledge, an iterative Integrated Knowledge Translation approach will be used, with participants and researchers functioning as cocreators. Practical implications of cocreators include the terms “knowledge user” and “stakeholder,” as defined by the International Association for Public Participation Spectrum of Public Participation [60]. The study will evaluate the level of participation using this framework [61].

Dissemination

Our participatory approach involves engaging knowledge users and researchers as partners throughout the study. We will create knowledge products that feature the review results, interviews, and co-design process. These products will include recommendations for improvements in stroke care and presentations for health care leaders, clinical teams, and policy makers. Additionally, we will produce traditional academic outputs like conference presentations and publications.

Ethical Considerations

The study has ethics approval from the Swedish Ethical Review Authority (2023-02337-01 and 2022-04231-01). The project will adhere to ethical guidelines outlined in the Helsinki Declaration. Informed consent will be obtained. Written and oral information on the study purpose and what participation would entail will be given before the informed consent. They will also be informed about confidentiality and their right to withdraw from the study at any time. The design of B-Sure is inherent, iterative, and dynamic. This means participants will be able to keep discussions about ethical issues along the way.

Results

The B-Sure is a 3-year project which started in January 2022 and is planned to continue until December 2024. The project was funded in November 2022, ethical approval was obtained in March 2023. Data collection is planned to start in September 2023, and the workshops later in the same year. The scoping review is ongoing from January 2023. The CM study is ongoing and will be finalized in the spring of 2024. We expect to finish the data analysis in the second half of 2024.

Discussion

Principal Results and Social Benefit

We aim to determine how new environments could better support a person’s control over their day, environment, goals, and ultimately control over their recovery and rehabilitation activities. This “taking charge” [22] approach would have the greatest chance of transferring the care closer to the patient's home. By co-designing with multiple stakeholders, we aim to create solutions with the potential for rapid implementation. The project’s outcomes may be scaled up and target other persons with frail health after a hospital stay or older persons in Sweden and elsewhere.

B-Sure will provide knowledge about how buildings and environments in society can support the new care landscape with more care and rehabilitation outside the hospital. The project can thus contribute to improved, strategic, and maintainable planning of environments in society. We will examine this issue from the perspective of the needs of people with stroke in their recovery and rehabilitation phases. Stroke is common, and the affected individuals have complex health needs. As acute care shortens, rehabilitation and recovery will increasingly happen in the community or at home.

We will use Living-Lab and participatory co-design, where the users (patients, relatives, and professionals) and other key stakeholders such as decision makers in the health service and municipalities, architects, and building planners will be involved. There is a need for collaboration between the users, the building sector, health care, regions, and municipalities to develop innovative and maintainable environments that can support the transition to local health care. Overall, there is a great need for investments in health care environments, which affects the resource space for care. Poor design that is not supportive of the end users, entails significant costs for the patients, the government, and health care and risks contributing to large climate footprints as the buildings reduce the chance of being maintainable. In addition, we know that traditional planned building projects are often stuck in conventional thinking and risk cementing old care structures and obstacles between the care providers while innovative solutions are needed.

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It is still uncommon for more developed, innovative collaboration between the stakeholders when planning and developing facilities [62]. The Swedish government has drawn attention to this [63]. It intends to map and analyze how these investment projects related to the ongoing development of health care at a national level and how facilities can contribute to the national development of health care and increased socioeconomic efficiency.

We expect that the knowledge produced by B-Sure is critical to fill this gap. The impact and social benefits include (1) Collaboration between important stakeholders (patients, health care, and building sector) to explore how new environments can support the transition to local health care. (2) Co-design and test new conceptual models of environments that can promote health and well-being of people poststroke. (3) Conduct a participatory design process that can create conceptual models where the built environment is included as an important part of rehabilitation. (4) Stimulate the establishment of a strong national network that can strengthen the development of high-quality rehabilitation environments.

With the B-Sure approach, new knowledge and results will be disseminated locally, nationally, and internationally by our broad stroke rehabilitation and architecture network. We will initiate and participate in knowledge transition activities such as conferences and seminars. Most importantly, we have designed the project to include persons with stroke, relatives, staff, and actors from society, enabling rapid user feedback and the spread of results to a wider public. We will initiate and be involved in knowledge transition activities such as conferences and seminars as contributing to a collaboration between health care, region, and municipalities is the goal to generate knowledge and bilateral development.

Strengths and Limitations of This Study

The study aims to examine the specific requirements of individuals with subacute stroke during their recovery and rehabilitation phases, emphasizing the crucial role of built environments in facilitating innovative care approaches beyond the hospital setting.

This project will foster collaboration among key stakeholders, including stroke survivors, health care professionals, the building sector, and policymakers. This collaborative effort will explore how the built environment can effectively support the transition toward the new health care landscape with local health care, thereby driving the development of optimal rehabilitation environments.

The research findings will not only enhance the knowledge base for individuals with stroke, health care providers, building sectors, policymakers, and educational institutions but also underscore the critical significance of the built environment.

These findings will pave the way for introducing groundbreaking solutions in health care services and communities. Although implementing these solutions may encounter challenges, the research team ensures maximum buy-in by actively involving key representatives from relevant institutions and units as integral research team members. This approach ensures a comprehensive and well-rounded perspective in addressing the complexities of optimizing the built environment for stroke rehabilitation.

Acknowledgments

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Data Availability

The data sets generated and analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

ME, MK, SMS, JB, RLS, HPR, and TS drafted the study design and applied for the funding of Built environments to support rehabilitation for people with stroke from the hospital to the home (B-Sure). ME, MK, SMS, JB, RLS, HPR, and TS planned the detailed study design and study protocol. JS planned the detailed design of the scoping review. ME, MK, and LdV drafted the study and revised it based on comments from all authors. All authors approved the final version of the study.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review report by Formas, Sweden.
[PDF File (Adobe PDF File), 50 KB - resprot_v12i1e52489_app1.pdf]

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Abbreviations

B-Sure: Built environments to support rehabilitation for people with stroke from the hospital to the home
CM: concept mapping
GIS: geographic information system

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Protocol

HIV Prevention and Care Among Black Cisgender Sexual Minority Men and Transgender Women: Protocol for an HIV Status–Neutral Cohort Study Using an Observational-Implementation Hybrid Approach

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Abstract

Background: Black cisgender gay, bisexual, and other sexual minority men (SMM) and transgender women (TW) continue to be heavily affected by HIV. Further research is needed to better understand HIV prevention and care outcomes in this population. In particular, there is a need for research examining the impact of substance use and sleep health on HIV prevention and treatment outcomes among Black SMM and TW.

Objective: This paper outlines the study methods being used in the recently launched follow-up study to the Neighborhoods and Networks (N2) study, which we refer to as N2 Part 2 (N2P2). N2P2 aims to address this gap in the literature, build off the findings of the original N2 study, and identify socioenvironmental determinants of health, including whether neighborhood and network factors mediate and moderate these relationships.

Methods: Building on the N2 cohort study in Chicago from 2018 to 2022, N2P2 used a prospective longitudinal cohort design and an observational-implementation hybrid approach. With sustained high levels of community engagement, we aim to recruit a new sample of 600 Black SMM and TW participants residing in the Chicago metropolitan statistical area. Participants are asked to participate in 3 study visits across an 18-month study period (1 visit every 9 months). Four different forms of data are collected per wave: (1) an in-person survey, (2) biological specimen collection, (3) a daily remote ecological momentary assessment for 14 days after each study visit, and (4) data from electronic health records. These forms of data collection continue to assess

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neighborhood and network factors and specifically explore substance use, sleep, immune function, obesity, and the implementation of potential interventions that address relevant constructs (eg, alcohol use and pre-exposure prophylaxis adherence).

Results: The N2P2 study was funded in August 2021 by the National Institute of Drug Abuse (R01DA054553 and R21DA053156) and National Heart, Lung, and Blood Institute (R01HL160325). This study was launched in November 2022. Recruitment and enrollment for the first wave of data collection are currently ongoing.

Conclusions: The N2P2 study is applying innovative methods to comprehensively explore the impacts of substance use and sleep health on HIV-related outcomes among an HIV status–neutral cohort of Black SMM and TW in Chicago. This study is applying an observational-implementation hybrid design to help us achieve findings that support rapid translation, a critical priority among populations such as Black SMM and TW that experience long-standing inequities with regard to HIV and other health-related outcomes. N2P2 will directly build off the findings that have resulted from the original N2 study among Black SMM and TW in Chicago. These findings provide a better understanding of multilevel (eg, individual, network, and neighborhood) factors that contribute to HIV-related outcomes and viral suppression among Black SMM and TW.

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KEYWORDS

HIV; cisgender sexual minority men; transgender women; Black; African American; cannabis; sleep; stimulants; substance use; alcohol

Introduction

Background

Black cisgender gay, bisexual, and other sexual minority men (SMM) and transgender women (TW) continue to be heavily affected by HIV, with both groups at increased vulnerability for HIV acquisition [1-8]. Despite accounting for <1% of the US population, Black SMM constituted 28% of newly diagnosed HIV cases in 2020 [1]. Black TW also experience disparately high rates of HIV prevalence, with a recent systematic review estimating HIV prevalence to be 14.1% among TW, overall, and 44.2% among Black TW, in particular [9]. Despite these long-standing inequities, much of the research on HIV among SMM and TW has been conducted among racially and ethnically diverse samples, and, in some instances, focused on comparing Black and White populations. In contrast, this study focuses exclusively on Black SMM and TW as a more intentional, effective, and efficient research approach that recognizes the nuanced challenges faced by these communities.

Within this context, intersectionality theory provides a framework for understanding and examining the ways in which intersecting societal oppressions have multiplicative effects on health outcomes among multiply marginalized people. Indeed, in a society structured by White supremacy, cisnormativity, and heteronormativity, Black SMM and TW experience multilevel, interrelated oppressions that directly impact their life experiences, including factors related to HIV prevention and care [10-13]. It is important to recognize that Black SMM and TW experience these oppressions in distinct ways [14]. However, in certain local contexts (eg, Chicago), there is also a significant overlap of social and sexual networks as well as neighborhood-related factors between Black SMM and TW [15-17]. Given the long-standing health inequities experienced by Black SMM and TW [4,9,18,19], such as those related to HIV prevention, care, and its determinants, research to further understand salient issues in the lives of these multiply marginalized populations is urgently needed.

Current research on HIV prevention and care should be responsive to a dynamic biomedical landscape. Specifically, HIV pre-exposure prophylaxis (PrEP) represents an unrealized yet potentially critical tool for ending the HIV epidemic (EHE) [20] and reducing inequities [21-28]. Although PrEP awareness and use have been increasing [29-32], there has been limited uptake of PrEP among marginalized populations, especially Black SMM and TW [33-38]. For example, in 2020, among those for whom PrEP is recommended, only 9% of Black individuals were on PrEP (as opposed to 66% of White individuals) [39]. Similar levels of suboptimal PrEP uptake have been noted in TW populations as well [26]. Antiretroviral therapy (ART) is another critical tool for EHE as it functions to maintain undetectable levels of HIV viral load among people living with HIV [40]. Achieving sustainable levels of effective ART adherence is critical for HIV prevention and treatment, as research demonstrates that viral load is associated with onward HIV transmission [41], such that no HIV transmission events occur when viral loads are below a certain threshold (eg, undetectable=untransmissible) [42]. However, evidence indicates that many Black SMM and TW face challenges in achieving sustained viral suppression, including factors such as stigmatizing experiences, depression, anxiety, intimate partner violence, and financial stressors [43-48].

Further research is needed to better understand HIV prevention and care outcomes among Black SMM and TW, including the impact of prevalent behaviors such as substance use. Recent findings indicate that cannabis use, including heavy cannabis use, is highly prevalent among Black SMM and TW. For example, in the Neighborhoods and Networks (N2) study among Black SMM and TW in Chicago (mainly the south side of Chicago) [49], two-thirds of participants currently use cannabis (past month), half of whom use cannabis daily [50], similar to other studies among Black SMM and TW [48,51,52]. Cannabis use also likely increased during the COVID-19 pandemic [53,54], including for Black SMM and TW [50]. Thus far, however, there have been mixed findings as to whether cannabis use impacts HIV-related outcomes [55,56]; although among

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Black SMM and TW, studies have shown that cannabis use is associated with HIV acquisition [51], being connected to an HIV transmission cluster [57], and decreased HIV testing [58]. The impact of cannabis use on the PrEP care continuum has not been studied as much, although initial results suggest that there may be an association [55,59-61], including a few studies on Black SMM [59,60]. Additional substance use behaviors among Black SMM and TW (beyond cannabis use) are also potentially relevant to understanding HIV-related outcomes. Alcohol misuse, including heavy drinking and binge drinking, is prevalent and has been shown to negatively impact HIV-related outcomes, including in Black SMM and TW [62-64]. Increasing methamphetamine use among Black SMM and TW is also a growing concern [65,66], especially given its negative impact on HIV prevention [67,68], the acquisition of other sexually transmitted infections (STIs) [69-71], and HIV treatment outcomes [72,73].

There are critical gaps in our understanding of substance use among Black SMM and TW, including identifying its socioenvironmental determinants as well as its impacts on HIV-related outcomes. Further research into whether substance use impacts HIV-related outcomes should also focus on potential mechanisms (eg, biological vulnerability [74-79] and neurocognitive impacts [80-82]), which will help identify potential intervention points along causal pathways and enhance external validity, which can also help inform future intervention and implementation strategies [83]. When studying HIV prevention and care among Black SMM and TW, it is also critical to take contextual factors into account [84,85], particularly those operating at multiple socioecological levels [86]. Neighborhood and social factors have been shown to be associated with HIV-related outcomes in general populations as well as among intersectional minoritized populations, such as Black SMM and TW [87]. One especially important issue is policing and police brutality, as research has demonstrated that Black SMM and TW frequently encounter law enforcement [88,89], and the presence of police has been linked to be various HIV-related outcomes, including among Black SMM [90].

Sleep health is another salient factor in the lives of Black SMM and TW, as studies have found a high prevalence of sleep problems (eg, excessive or short sleep) [91,92], and this has worsened during the COVID-19 pandemic [93]. Sleep health has been found to be associated with HIV-related outcomes in the general population [94] as well as in samples of sexual and gender minority groups [95,96]. Research regarding the relationship between sleep and HIV outcomes among Black SMM and TW is scant, although 1 study from our team has demonstrated that poor sleep health is associated with lower PrEP adherence among Black SMM [93].

Generally, there have been limitations to the collective research that has been conducted, thus far, on substance use, sleep health, and their impacts on HIV-related outcomes among Black SMM and TW. First, most studies used cross-sectional data and relied on self-reporting (which are subject to social desirability bias). Studies that use objective measures, such as biological specimens and data from electronic health records (EHRs), allow researchers to assess the accuracy of self-report data and minimize self-report bias. Furthermore, most studies have used retrospective measures, which summarize across periods and are subject to recall bias [97]. Prospective data, especially granular data, can be collected using innovative methods such as ecological momentary assessment (EMA) [97,98], which captures day-to-day and event-level variation of experiential, spatial, and behavioral data in real time. Longitudinal studies that include objective, prospective, and granular measurement of relevant constructs and that evaluate mechanisms and context will allow us to better study these complex constructs and how they interrelate among Black SMM and TW.

Objectives

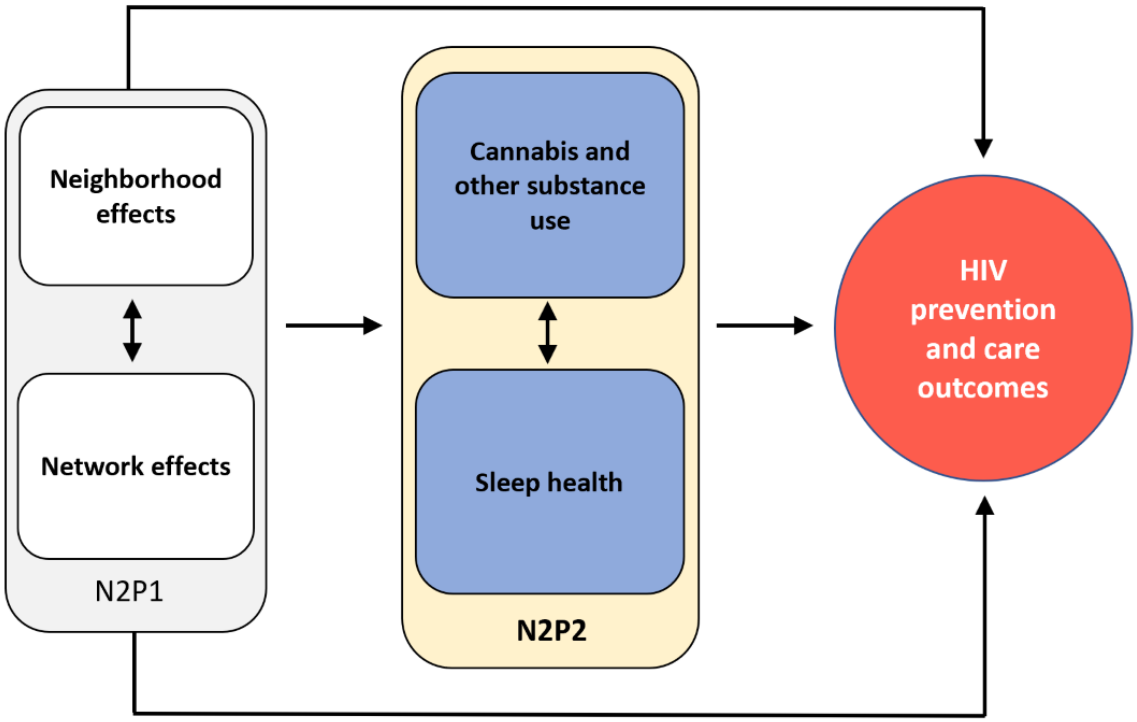
To overcome these limitations, we are conducting a prospective study to explore the impact of substance use and sleep health on HIV-related outcomes among a well-characterized HIV status–neutral cohort of Black SMM and TW in Chicago, Illinois. The study objectives are conceptualized in Figure 1, and the primary objectives are summarized as follows:

1. Determine the causal effects of substance use (eg, cannabis use and stimulant use) and sleep health on HIV outcomes, including acquisition, prevention (eg, HIV testing, PrEP uptake, and PrEP adherence), and care outcomes (eg, retention in care and viral suppression).
2. Assess whether associations between substance use, sleep health, and HIV prevention and care outcomes vary by contextual characteristics (eg, individual-, network-, and neighborhood-level constructs) and are mediated by relevant constructs (neurocognitive impacts and biological vulnerability).

To prioritize the potential expedited translation of study findings into public health impact, which is of critical importance among populations such as Black SMM and TW that experience long-standing health inequities, we will use an innovative observational-implementation hybrid approach [99]. The observational-implementation hybrid approach prioritizes the collection of implementation data while conducting observation research. This paper outlines the study methods being used in the recently launched follow-up study to the N2 study [49], which we refer to as N2 Part 2 (N2P2).

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Figure 1. Conceptual model for the Neighborhoods and Networks Part 2 (N2P2) study. Originally looking at the neighborhood and network factors of HIV-related outcomes in the Neighborhoods and Networks Part 1 (N2P1) study, we have now launched the N2P2 study to expand our understanding of substance use, sleep, and HIV-related outcomes.



Methods

Study Design

Building on the N2 cohort study in Chicago, which was completed between January 2018 and June 2022 (N=412), the N2P2 study uses a prospective longitudinal cohort design and aims to recruit a sample of 600 Black SMM and TW participants residing in the Chicago metropolitan statistical area (MSA). Following updated recommendations for labeling hybrid studies [100], we will apply an observational-implementation hybrid approach in the context of the cohort study design [99]. Following an initial baseline assessment (conducted in person), participants are asked to participate in 2 subsequent in-person visits every 9 months, totaling 3 visits across an 18-month study period. The participants are also asked to participate in a daily remote EMA survey occurring for 14 days after the in-person study assessment. As has been our long-standing practice for work with this heterogeneous community in Chicago, we are using an HIV status–neutral approach with Black SMM and TW to increase inclusivity and minimize the risk that participation in the study could disclose HIV status [101]. The HIV status–neutral approach (also known as an integrated continuum) is a person-centered approach that uses the same treatment approach for all individuals, regardless of HIV serostatus. This approach has been noted as a strategy that works toward achieving health equity among marginalized populations and is in line with ongoing calls for prioritizing the social determinants of health in health equity research [101,102]. Relatedly, all study procedures are identical for participants regardless of their HIV serostatus.

Hybrid Observational-Implementation Approach

As part of the observational-implementation hybrid approach, we are preparing to conduct multiple activities as part of N2P2 that will provide data on implementation constructs related to evidence-based interventions that address salient health issues impacting Black SMM and TW. For example, we are currently collecting data that will inform how to improve the delivery of evidence-based interventions to reduce alcohol use among Black SMM and TW who could benefit from reducing their drinking. Specifically, we are developing a Discrete Choice Experiment (DCE) [103,104] to determine preferences for alcohol interventions among N2P2 participants who have an Alcohol Use Disorders Identification Test-Consumption score ≥4 [105,106]. DCE's are a preference elicitation method that asks participants to complete multiple-choice tasks (eg, paired comparisons of profiles A vs B) with different levels and combinations of questions to compare various attributes (ie, key intervention design features). The DCE that we are currently developing will ask N2P2 participants for their preferences regarding the delivery of several evidence-based alcohol interventions, including pharmacotherapy [107,108], behavioral therapies [109,110], and mobile health interventions [111,112]. Attributes that will be included in the DCE tasks include type of intervention, person delivering the service, delivery settings, and communication platforms. We will consult with the N2P2 community advisory board as part of the formative work for

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refining the DCE, and it will be incorporated into the second wave of N2P2 data collection using a logic step in the survey.

In addition to the DCE on preferences for alcohol intervention delivery, we will also apply a human-centered design approach [113] to a subsample of N2P2 participants to create journey maps of Black SMM and TW experiences as they access HIV prevention and care settings. We are also using the same approach to understand the experiences of health care providers as they deliver HIV prevention and care services to Black SMM and TW. These data will then be used to inform how to tailor alcohol interventions to be more contextually informed to better suit the needs of Black SMM and TW and how to integrate them into community-based and clinical HIV prevention and care service settings. In subsequent waves of data collection, we plan to explore the collection of data on implementation constructs related to evidence-based interventions that address cannabis use, such as cognitive behavioral therapy. In addition, as recruitment settings for N2P2 seeds include HIV testing and substance use treatment facilities, and referral participants are likely to have accessed these services as well, we will also collect data from N2P2 participants about their experiences with these interventions. Collectively, these data can be used to better understand the implementation of evidence-based interventions and related determinants.

Recruitment

Soft-launch recruitment for N2P2 commenced in September 2022. Respondent-driven sampling (RDS), a systematic form of snowball sampling that leverages existing social networks, is being used for recruitment [114]. RDS has previously been used to sample marginalized populations [115], including Black SMM and TW [49,116]. A total of 60 nonrandomly selected "seed" participants will be recruited from a variety of community sources with attention paid to diversity in geography and prior involvement in research and substance use (eg, recruiting seeds who use methamphetamine) [117,118]. In the cohort before N2, uConnect (n=612), we achieved a representative sample using approximately 60 seeds, which generated a large sample (n=620) [119]. Although a diverse sample was generated, homophily was achieved across several demographics in fewer waves (including some nonproductive seeds) given the inclusion criteria based on race, geography, and age. We hope to replicate a successful RDS in N2P2. Study facilitators will monitor the recruitment process and track referrals along recruitment threads. During recruitment, participants will receive a flyer with a unique identifier code, allowing them to be added to the study, which will also be used to indicate who referred them. For each additional individual that a participant successfully recruits to the study, the participant will receive US $30 compensation (up to a maximum of 6 additional participants) via cash or an electronic money transfer service of their choice (eg, PayPal, Cash App, and Venmo). Recruitment materials were developed to increase awareness of the study among the community, including the development of an N2P2 study logo (Figure 2).

Eligibility criteria for inclusion in the N2P2 study include (1) assigned male sex at birth, (2) identify as being Black or African American, (3) aged 18 to 34 years, (4) report of at least 1 sexual encounter with another man or transgender woman within the past year, and (5) currently residing in the Chicago MSA with no plans to move or relocate during the proposed study period. Individuals who are unable to provide informed consent are excluded from participating in the study. Individuals who screen eligible will then be scheduled for an appointment at the study site, the Village, the Chicago Center for HIV Elimination's, off-campus community service and research space that has served Chicago's South Side community for over a decade and that specializes in HIV prevention and care services [120].

Regarding the eligibility criteria, we made a conscious decision to be inclusive in the N2P2 study and engage Black TW as well as Black SMM. There are multiple reasons for this decision. First, the environments in Chicago in which both Black SMM and TW predominantly live include hyper-segregated neighborhoods that create similar exposures that are major drivers of HIV [121-123]. In addition, networks are often similar and overlapping with social networks including members of the house or ball community and sexual networks including many SMM. Indeed, research has shown that Black SMM and TW are members of social and sexual networks that are associated with HIV-related outcomes in nuanced ways [15-17,124-127]. In addition, many Black TW transition later than their White counterparts, and they identify at younger ages as SMM [128-130]. The reasons for this are complex, but the situation is likely not helped by most adolescent gender programs across the United States (including in Chicago), which underuse gender-affirming hormone therapy [131,132]. Finally, the decision to intentionally include both Black SMM and TW in the N2P2 study was made with community input, including from participants in the original N2 study, and with the understanding that social and sexual networks among Black SMM and TW in Chicago significantly overlap [126,133]. Importantly, community input highlighted increasing inclusivity, with particular attention needed to ensure that survey materials, procedures, and protocols are culturally tailored and gender affirming, with appropriate skip patterns and language to ensure that community members feel included and respected.

We recognize that transgender individuals describe themselves in a variety of different ways; for the purposes of our study and in congruence with established research on TW with HIV [134,135], we define TW as individuals who were assigned male sex at birth and have a feminine gender identity. We acknowledge that it is important to note that Black SMM and TW are distinct populations that experience unique social contexts and challenges related to substance use, sleep health, and HIV-related outcomes [14,136]. Indeed, studies have demonstrated that compared with Black SMM, Black TW experience substantially higher rates of financial instability, incarceration, and HIV and STIs [137,138].

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Figure 2. Neighborhoods and Networks Part 2 (N2P2) study logo.



Procedures and Measures

Assessments are conducted every 9 months for 3 waves. Assessments are conducted in person in private interview rooms at an off-campus research and service space, The Village, which is located in the same building that has been engaging Black sexual and gender minority community members for >20 years. Four different forms of data are collected at each assessment: (1) a self-report survey, (2) biological specimen collection, (3) the administration of a daily remote EMA survey, and (4) extraction of EHR data. The prospective design of N2P2 enables the study team to alter and expand future surveys based on preliminary findings, including measuring relevant implementation issues, as per the hybrid observational-implementation approach [99]. After completing the survey, blood samples are drawn by trained study staff and screened for HIV antibodies to determine participant HIV serostatus. To encourage engagement with community members from all backgrounds, reduce barriers to entry, and increase accessibility, participants have the option to complete assessments remotely on Zoom (Zoom Video Communications), thus reducing the in-person requirement of participation to only collection of the biospecimens, which are scheduled at a separate date and time following survey completion. At the end of the assessment, survey technicians confirm contact information, schedule follow-up visits, provide instructions on completing the daily EMA survey, and disburse compensation for completion of the survey (US $100) and provision of biological samples (US $50) in cash or other preferred mechanism for compensation. Finally, as we did for the original N2 study [139], we continue to seek permission to access EHR data and health department data of each participant via release of information forms and subsequently link these data with the participant's study identification number. Details on each type of data collection are described in the following sections.

Self-Report Survey

Overview

The self-report survey was developed by the study investigators in tandem with the University of Chicago Survey Laboratory. Of note, certain constructs from N2 Part 1 continue to be used in this N2P2 study, allowing for robust longitudinal analyses. Trained survey technicians obtain written informed consent before participants complete a survey using computer-assisted participant interview (CAPI) technology. Self-report survey measures assessed using CAPI technology are described by construct in the paragraphs below and summarized in Table 1.

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Table 1. Neighborhoods and Networks Part 2 measures assessed via computer-assisted participant interview.

Construct	Measurement	Reliability (Cronbach α)
Demographics (age, sex assigned at birth, height, weight, gender identity, sexual orientation, sexual attraction, history of incarceration, housing status, education, employment, income, and health insurance status)	Sociodemographic questionnaire	N/A[a]
Potential moderating and mediating variables		
Neighborhood factors	Neighborhood preferences: questions adapted from the Belgian Environmental Physical Activity Study [140]	N/A
Neighborhood factors	Neighborhood disorder and violence scales [141,142]	.70 [141] and .913-.921 [142]
Network factors	Network composition*:* questions adapted from the Chicago Community Adult Health Study [143]	.85
Network factors	Network size and PrEP[b] use*:* questions adapted from the National HIV Behavioral Surveillance System [144]	N/A
Obesity	Sociodemographic questionnaire	N/A
Anxiety and depression	Patient Health Questionnaire-4 [145]	.85
Self-efficacy	Sherer Self-Efficacy Scale [146]	.71-.86
Race-based harassment	Black Men's Experiences Scale [147]	.86
Intersectional discrimination	Intersectional Discrimination Index [148]	.70-.72
Interpersonal violence	Questions adapted from the original Neighborhoods and Networks cohort study	N/A
Social support	Medical Outcomes Study Social Support Scale [149]	.91-.96
Loneliness	Loneliness Scale for Emotional and Social Loneliness [150]	.70-.76
Implementation data		
Preferences for alcohol interventions	Discrete choice experiment [103,104]	N/A
Exposures		
Cannabis use	Daily Sessions, Frequency, Age of Onset, and Quantity of cannabis use inventory [151]	.69-.95
Cannabis use	Cannabis Use Disorders Identification Test-Revised [152]	.73
Cannabis use	Marijuana Motives Measure: Cannabis Coping Motives Subscale [153]	.80-.89
Cannabis use	Questions adapted from The International Cannabis Policy Study [154]	N/A
Alcohol use	Alcohol Use Disorders Identification Test [106]	.88
Other substances	Questions adapted from the 2020 National Survey on Drug Use and Health [155]	N/A
Other substances	Drug Abuse Screening Test [156]	.71-.94
Sleep	*Sleep duration and quality:* Pittsburgh Sleep Quality Index [157]	.83
Sleep	*Sleep-related problems:* Functional Outcomes of Sleep Questionnaire [158]	.87
Primary outcomes		
Antiretroviral therapy adherence	Wilson self-report scale [159]	.83
Retention in HIV care	Missed visit proportion	N/A

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Construct	Measurement	Reliability (Cronbach α)
PrEP uptake	PrEP uptake: questions adapted from the National HIV Behavioral Surveillance System [144]	N/A
PrEP Adherence	PrEP adherence: Wilson self-report scale [159]	.87
Secondary outcomes		
Sexual behaviors	Questions adapted from the National HIV Behavioral Surveillance System [144]	N/A

[a]N/A: not applicable.

[b]PrEP: pre-exposure prophylaxis.

HIV Care

Self-reported HIV care outcomes include ART adherence and linkage to HIV care, which are assessed using validated measures [144,159].

PrEP Cascade of Care

To assess self-reported PrEP outcomes, we are providing participants with an adapted description of PrEP used successfully with samples of SMM and TW vulnerable to HIV [160]. The PrEP cascade of care measures include *current PrEP use* [144], *PrEP modality* (pill or injection), *PrEP initiation and discontinuation, and PrEP adherence* [159].

Cannabis Use and Other Substance Use

Cannabis use is being assessed via multiple validated and reliable measures that describe the frequency of use [151], modes of use [151], timing of use [151], risk of disordered use [152], motivations for cannabis use [153], and reasons for seeking cannabis treatment (if sought out by participants) [154]. The use of other substances such as alcohol, stimulants, heroin or opiates, and nicotine is also assessed and described in terms of frequency, method of consumption, and risk of disordered use [105,155,156].

Sleep

Sleep health outcomes include the self-reporting of sleep duration [157], sleep quality [157], and sleep-related problems (eg, apnea and trouble falling asleep or insomnia) [158].

Sexual Behavior

We are measuring partnered sexual behavior in the past 3 months [161], including characteristics of sexual partners (eg, gender, relationship type, HIV status, PrEP use, and undetectable viral load), sexual acts, and condom use.

Moderating Variables

Additional relevant individual-, network-, and neighborhood-level characteristics will be assessed as moderators of the impact of cannabis use on PrEP outcomes. Individual-level characteristics will include sociodemographics, reasons for using cannabis, cannabis use expectations, intersectional discrimination [148], and race-based harassment [147]. Obesity will also be assessed as a potential moderator for analyses involving sleep health as an exposure variable. Social and sexual network characteristics will include the racial and ethnic composition of network members, network size, network substance use, and network PrEP use. Neighborhood-level characteristics will include socioeconomic disadvantage, racial and ethnic composition, and locations of dispensaries. Many of these measures were captured in the original N2 study. Whenever feasible, preexisting N2 data will be used.

Covariates

Data are being collected on the following relevant sociodemographic variables: age, ethnicity, sexual orientation, sexual attraction, socioeconomic status (eg, education, income, and employment), current living situation (eg, housing instability), nativity, relationship status, mental health, history of incarceration, health insurance status, and existing or recent STIs (eg, chlamydia, gonorrhea, and syphilis).

Biological Specimen Collection

Collected blood samples are screened on site for HIV and syphilis, after which the plasma from each sample is objectively measured for quantitative levels of cannabis metabolites via liquid chromatography–tandem mass spectrometry [74]. These metabolites will also be measured using solid-phase extraction and gas chromatography–negative ion chemical ionization mass spectrometry [162]. The detection of cannabis metabolites in plasma will be used to confirm self-reported cannabis use by the study participants. In addition, we will explore the utility of using plasma levels of tetrahydrocannabinol to stratify participants into cannabis use groups (eg, heavy user or moderate user) [163]. Cytokine and chemokine levels are also assessed in the systemic circulation (plasma samples) using the Human Inflammation Panel via the LEGENDplex assay (BioLegend, Inc), which measures 13 different cytokines or chemokines, including those relevant to HIV infection [164].

After instruction by study staff, the participants also self-administer 3 rectal swabs and 1 oral swab. The 1 oral swab and 1 of the 3 rectal swabs are tested on site for chlamydia and gonorrhea nucleic acid amplification tests [165]. The remaining 2 rectal swabs are evaluated for the levels of proinflammatory cytokine and chemokine in the rectal mucosal secretions. Finally, participants are asked to provide a urine sample, which is used to conduct on-site toxicological screening of marijuana, methamphetamine, opioids, and cocaine as well as chlamydia and gonorrhea nucleic acid amplification tests. Participants who test positive for HIV or STIs or who are interested in PrEP, primary care, or substance use treatment are linked to care with services available in the same building as the data collection. A summary of the biological measures is presented in Textbox 1.

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Textbox 1. Biological data in Neighborhoods and Networks Part 2 data collection.

Constructs and measurements

- Cannabis use
  - Biological presence in blood or urine samples
- Other substances
  - Biological presence in blood or urine samples
- Sexually transmitted infections
  - Biological data for chlamydia, gonorrhea, or syphilis in urine, blood, saliva, or rectal mucosa samples
- Inflammation
  - Biological data on cytokine and chemokine levels in systemic circulation and rectal mucosa

EMA Survey

The EMA survey is administered over a 2-week period following the in-person assessment. If participants are unable to complete the EMA survey using their personal phone, the study team sends the EMA survey via email. Participants receive a daily notification through their cell phones at the same time each day asking to complete the brief survey. The participants have 2 hours to complete the survey. Participants receive an additional reminder notification 1 hour before the survey expires as well as personalized reminder text messages from the study staff. Daily assessments (rather than more frequent assessments) were chosen to minimize participant burden, based on feedback from community members who participated in the original N2 study. Participants receive US $2 for each daily survey completed within the first week and US $3 for each daily survey completed during the second week. The participants also receive a US $5 bonus if all 14 days are completed. The EMA survey includes multiple measures regarding policing, substance use, HIV outcomes, and mental health. Example questions and response options from the EMA survey are listed in Table 2.

Table 2. Ecological momentary assessment survey measures in Neighborhoods and Networks Part 2 data collection.

Measure	Example question	Example response options
Policing	"In the past 24 hours, did you encounter someone in law enforcement that:"	"(Select all that apply) Pushed or grabbed you?; Followed you?; Made you feel unsafe?; etc."
HIV outcomes	"In the past 24 hours, did you take a daily PrEP[a] pill"	"Yes; No"
Cannabis use	"In the past 24 hours, how many times did you use cannabis?"	"(Numerical drop-down selection) 1-7+"
Other substance use	"In the past 24 hours, did you use any of the drugs listed below?"	"Heroin (Smack, Junk, Dope); Fentanyl (China White, China Girl, Tango); Benzos; Methamphetamine (Speed, Meth, Crystal, Crystal Meth, Ice, Crank); Cocaine (Coke, Snow, Crack, Rock); Prescription opioids; Unknown combination of opioids; Other; None of the above"
Alcohol use	"In the past 24 hours, how many drinks of alcohol did you have?"	"(Numerical drop-down selection) 1-7+"
Anxiety and depression [145]	"In the past 24 hours how often were you bothered by the following problems (if at all)?"	"Not at all; Several times throughout the day; More than half the day; Nearly all day"

[a]PrEP: pre-exposure prophylaxis.

EHR Data

Overview

As we did for the original N2 study [139], we continue to seek permission to access the EHR data of each participant via release of information forms from a local partnering health clinic and surveillance data from the health department and subsequently link these data with the participant's study identification number. The outcomes described in the following subsections will be extracted from participants' EHRs (Textbox 2).

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Textbox 2. Electronic health record data in Neighborhoods and Networks Part 2 data collection.

Constructs and measurements

- Viral suppression
  - Biological viral load
- Retention to HIV care
  - Missed visit proportion
- Pre-exposure prophylaxis (PrEP) outcomes
  - PrEP persistence and type of PrEP product

Viral Suppression

Viral suppression data will be obtained from the participants' EHRs. Viral suppression is defined as having a viral load of ≤200 HIV RNA copies/mL.

Retention to HIV Care

Retention to HIV care is measured by calculating a missed visit proportion, or the proportion of total scheduled visits (eg, nonacute appointments with an ART-prescribing provider) that are missed across the 27-month follow-up period [166,167]. Appointment and visit history to calculate the missed visit proportion will be collected from each participant's EHR. To permit longitudinal analyses, we will divide the 27-month follow-up period into three 9-month sections and record, for each participant, whether they completed or missed their scheduled appointment during that section.

PrEP Outcomes

Several PrEP-related outcomes will be obtained from the participants' EHR data, including PrEP persistence, which will be measured in several ways (eg, number of dedicated PrEP visits and number of prescriptions for PrEP) [168]. The type of PrEP product will also be collected, although we expect limited uptake of long-acting injectable PrEP in this community owing to a number of social and structural barriers; notably, these barriers are repeatedly observed with each new biomedical advance purportedly developed for community members classified as most vulnerable [169,170].

Data Management

Each N2P2 participant receives a unique study identification number, which is used to link all 3 forms of the primary data into a centralized database in the same manner as our original N2 study [139]. Data will be analyzed with the aim of maintaining participant anonymity. Access to the participant identification number, which links data to unique identifiers, will be restricted to designated members of the research team. All survey, biological, EMA, and EHR data will be uploaded to the encrypted University of Chicago servers and will be backed up on a weekly basis.

Data Triangulation

For data triangulation, objective measures will be prioritized, using previously validated decision rules for combining objective biomarker data with self-reported measures, an approach that has been used in other studies with regard to substance use [171,172] and that we will adapt as needed. This approach will allow us to account for the limitations of respective measures (eg, inaccuracy of self-report [173] and varying rates of metabolizing substance use [174]) and also allow us to identify relevant categories, as has been done in other studies [74,175]. Using multiple measures to assess constructs, particularly those regarding sensitive topics, is superior to relying on a single method [176].

Statistical Analyses

The longitudinal design of N2P2 will allow researchers to evaluate changes in constructs over time as well as cross-sectional, series cross-sectional, and longitudinal associations between exposures and outcomes [177]. We will use generalized linear models to evaluate the associations between relevant exposures and outcomes. These models will include the appropriate time-invariant and time-varying covariates to adjust for confounding of each exposure-outcome relationship. In addition, we will apply generalized estimating equations to account for repeated measures within individuals across study visits. For analyses that assess mediation, we will use statistical tests that leverage the latest statistical methodological advances in the causal inference field and that test for and estimate the effect of mediation (ie, the natural indirect effect). Our inferences will support a causal mediation interpretation if the covariates effectively control for confounding in 4 key relationships: the impact of the candidate exposure on the outcome, the effect of the candidate exposure on the candidate mediator, the influence of the candidate mediator on the outcome, and if the candidate exposure has no impact on any confounding variables related to the effect of the candidate mediator on the outcome. We recognize that this approach is among various mediation analysis methods, and we will also consider other commonly applied approaches [178]. To assess effect modification, we will conduct regression analyses by adding 2-way interaction terms (eg, cannabis use × moderator) to the previously described generalized linear models. We also plan to evaluate cross-level interactions to determine whether our 2-way interaction analyses vary by other variables in the associations between our candidate exposures and outcomes. We further plan to use additional modeling approaches, including egocentric analysis, mesolevel sociometric analysis, multilevel (affiliation network) modeling, 2-mode person or place network modeling, synergistic place or network models, and spatial autocorrelation regression modeling. In

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some analyses, moderating variables that are considered confounders will be adjusted for as covariates.

Power Calculations

We have adequate power to address our primary study aims. With a planned baseline sample size of 600 Black SMM and TW with 80% attrition over the study period and assuming α=.05 and power=0.80, we estimate that we will have 80% power to detect Cohen *d* effect sizes of 0.40 in differences of continuous HIV-related outcomes (based on distributions of those outcomes in N2 baseline data) in the highest versus lowest quintiles of exposure in the cohort. This is a conservative calculation, as it does not account for the adjustment of covariates, which can serve to increase power. To maximize the sample size and minimize potential selection bias as a result of loss of participants who do not attend all follow-up waves, we will use a pooled analysis approach and include participants who attend at least 1 of the 3 waves over the study period. A total of 600 participants will contribute 1800 potential observations across waves. This approach has been used in our prior work and in other cohort studies to efficiently maximize analytic capabilities [179]. Moderation analyses may not be optimally powered, especially to examine cross-level interactions. Mediation analyses may also not be optimally powered. However, to mitigate power issues, we plan to dichotomize sociodemographic characteristics when possible and appropriate [180]. Moreover, the potential mechanisms linking study exposures to HIV-related outcomes will be the focus of future research proposals (ie, adequate power will be prioritized).

Governance and Organizational Study

Research strategies and protocols for the N2P2 study were developed using a community-based participatory approach [181] where study staff members regularly meet with the community advisory board to guide the study. These meetings involve receiving community feedback on survey assessments and protocols, presenting progress reports on the study, discussing preliminary data, and determining the best practices for dissemination to community members and policy makers. In addition, 1 staff member who is from the Chicago Black SMM and TW community further guides community engagement through periodic social events and social media development. Moreover, we have also created a scientific advisory board to provide expert feedback on the overall study design and methodology of N2P2, thereby supporting the collection and analyses of high-quality data.

Ethical Considerations

This study was conducted in accordance with the guidelines of the Declaration of Helsinki. The N2P2 study protocol has been approved by the institutional review board (16-1419) of the University of Chicago (institutional review board of record), and a reliance agreement has been established with Columbia University. Written informed consent is required from all participants before participation in the study. Benefits to participation in the study include sharing the results of HIV serostatus and STI testing at multiple time points as well as referral to relevant health services when necessary (substance use treatment and mental health).

Results

The N2P2 study was funded in August 2021 by the National Institute of Drug Abuse (R01DA054553 and R21DA053156) and National Heart, Lung, and Blood Institute (R01HL160325), and approved by the institutional review board in September 2022. Data collection was launched in November 2022. As of manuscript submission, 431 participants have been enrolled. Recruitment and enrollment for the first wave of data collection are currently ongoing.

Discussion

Expected Findings

In summary, the N2P2 study applies innovative methods to comprehensively explore the impact of substance use and sleep health on HIV-related outcomes among an HIV status–neutral cohort of Black SMM and TW in Chicago. This study applies an observational-implementation hybrid design to prioritize the expedited translation of findings into public health impact, a critical priority among populations such as Black SMM and TW that experience long-standing inequities with regard to HIV and other health-related outcomes owing to systemic racism, homophobia, and transphobia. N2P2 directly builds on the findings of the original N2 study among Black SMM and TW in Chicago. These findings contribute to a better understanding of how multilevel (eg, individual, network, and neighborhood) factors are associated with HIV prevention and care outcomes among Black SMM and TW [139,182,183]. Relatedly, the N2 COVID-19 study contributed additional findings related to factors associated with PrEP and ART use, among other health outcomes and health behaviors, at the initial peak of the COVID-19 pandemic [50,184-186].

A major goal of the N2P2 study is to inform the implementation of evidence-based practices that already exist to address many of the issues that we are studying. For example, we observed a high prevalence of heavy drinking in the original N2 study, which aligns with other studies among Black SMM and TW [187]. We also observed from the N2 COVID-19 study that alcohol use increased among Black SMM and TW during the pandemic [50], as it did among the general population [188,189]. However, very few individuals who could benefit from alcohol treatment receive it [190,191], despite the availability of multiple evidence-based interventions [107], indicating a clear implementation gap. Therefore, in this observational cohort study, we are working to incorporate elements of implementation science related to evidence-based interventions that address alcohol use. We have named this the *hybrid observational-implementation approach*, and we have previously described how this practical approach can be applied to observational epidemiologic research to make it more consequential by contributing more directly to the growing implementation science movement [99]. This may also help to make the research pipeline more efficient and faster [192] and help observational research achieve its intended public health impacts, an innovation that is especially important for health

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equity research. In future waves of the N2P2 study, we intend to expand this work to address other salient health issues, particularly those that we learn about through findings from the existing N2 study data, or in the upcoming waves of N2P2 data collection.

In addition, given the longitudinal nature of our data collection, we are able to continue examining COVID-19 as well as recently emerged STI threats (eg, mpox [193]), evolving STI epidemics such as syphilis, and other infections that disproportionately impact these communities (ie, meningococcus). This can be an important extension for future N2P2 waves, as it is known that there are clear racial and ethnic differences in new and emerging infectious disease epidemics, including among Black SMM and TW [194,195].

Maintaining meaningful community engagement at each step of the research process and enhancing those efforts are top priorities in the N2P2 study, an approach used in the original N2 study. For example, community members provided iterative feedback that has informed this study's design. In addition, the study team organized several community dinners and social events (eg, study relaunch event at the Village) to share the findings of the original N2 study and further strengthen community trust and inclusion. We aim to continue prioritizing shared decision-making and using innovative community-based research approaches (eg, crowdsourcing and human-centered design) as the N2P2 study progresses forward [196].

Relatedly, many papers from the original N2 study were led by trainees and early-stage investigators (eg, postbaccalaureate research coordinators, master's-level students, PhD students, and postdoctoral fellows), including those who hold minoritized identities, particularly trainees who hold the same intersectional identities as those in the N2 study. This has enhanced our ability to situate interpretations of data in the community context and obtain high-quality data. For example, because many research coordinators hold similar intersectional identities as N2 study participants, we were able to build trust with the community. This hopefully will contribute to less misclassification in self-reported measures and a greater willingness to adhere to study protocols. In N2P2, we plan to continue this work, especially because we recognize the harms that can arise from power differentials between researchers and study participants [197]. We view this component of our work as part of our intersectional and health equity–focused research program, which aims to ultimately achieve better health outcomes among Black SMM and TW [198,199].

Finally, we note that the N2P2 study currently does not have funding for recruitment in the Southeastern United States, which was a component of the original N2 study. We are actively working to acquire funding to study Black SMM and Black TW in the Southeastern sites included in N2, including New Orleans and Baton Rouge, given that the burden of the domestic HIV and AIDS epidemic is heaviest among Black SMM and TW living in that part of the country [200].

Strengths and Limitations

The N2P2 study has some limitations. First, our sample of Black SMM and TW is sampled exclusively from the Chicago MSA and may have limited generalizability to other geographic contexts, such as smaller cities or rural areas. We decided to continue our focus on the Chicago MSA as >80% of the US population lives in urban settings [201]. Chicago shares similar contextual and environmental characteristics with many other hyper-segregated EHE jurisdictions in the United States, such as Houston and Detroit. In addition, owing to the duration of the cohort, our study's ability to assess causality may be limited by participant loss to follow-up. This limitation is particularly significant for minoritized populations such as Black SMM and TW because of the structural barriers that these groups experience. For example, in the original N2 study cohort, 70% of the participants had an annual income of <US $25,000 and 35% reported unstable housing. These structural barriers have also been shown to be related to HIV-related outcomes [48], and they also serve as barriers to participation in research. To mitigate this challenge, participant retention is prioritized within the study's community integration efforts as well as through protocol-based approaches such as recording participant contact information and consistent efforts to connect with participants and remind them of their engagement with the study. Moreover, owing to social desirability bias, it is possible that substance use, sexual behaviors, and PrEP and ART nonadherence are underreported. We aim to reduce the effects of this bias by obtaining objective biomarker data and using CAPI to collect potentially sensitive information. Finally, we recognize heterogeneity in Black SMM and TW and the importance of meaningful intersectional analyses; however, because we are not intentionally focusing on this heterogeneity, we may have limited power for subgroup analyses such as by ethnicity and socioeconomic status. For example, in the original N2 study, although we have variation in socioeconomic status, only 6.6% of the sample reported being Latinx or Hispanic ethnicity. We are also making efforts to ensure variability in other factors that are related to health, such as our intentional geographical sampling approach, and collect data on experiences that are relevant to Black SMM and TW, such as membership in the house or ball community and other queer family structures.

Conclusions

These limitations are offset by many notable strengths. In N2P2, we are using a unique and innovative approach to simultaneously explore multiple salient questions about what potentially drives the long-standing HIV-related inequities experienced by Black SMM and TW [1,9]. Combining resources to conduct a comprehensive study, such as N2P2, marks a potentially more efficient use of resources, one that may reduce the logistical challenges associated with establishing independent cohorts to address each of these topics independently. The inclusive HIV status–neutral approach minimizes potential stigmatization and enhances the potential to connect participants with relevant HIV prevention and treatment services. Furthermore, the multiple innovative methods that are being used to collect primary data in N2P2, including EMA, biobehavioral overlap, preference elicitation, and human-centered design, will allow a more holistic understanding of how substance use, sleep, and HIV-related outcomes interrelate. Similarly, because of the pressing need for additional research on the HIV epidemic, specifically within Black SMM and TW communities, the study

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findings from N2P2 may have a substantial potential public health impact. As such, the N2P2 study provides a pivotal opportunity to better understand the impact of substance use and sleep on HIV among Black SMM and TW, which may inform the development of future evidence-based culturally relevant interventions and policy approaches.

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Data Availability

Once data are collected, they will be stored in a public repository hosted by Data Commons. In addition, investigators can obtain data via an email request to the Neighborhoods and Networks Part 2 staff.

Authors' Contributions

JRK, JAS, and DTD were responsible for conceptualization of the project. The methodology was developed by JRK, JAS, and DTD. Formal analysis was conducted by EA, AH, and CM. JRK, JAS, DTD, IM, MD, HH, and EA. Resources were provided by JAS. Data curation was conducted by HH, EA, and AH. JRK, BD, TM, and DTD prepared the original draft of this manuscript and IM, MD, HH, EA, AH, JP-B, Y-TC, DE, JM, JR, CM, BM, GJ-L, HJR, SSM, CG, DSH, AWC, SS, JAS, and DTD revised and edited the manuscript. JRK, JAS, and DTD supervised the project with project administration by IM, MD, HH, and JAS. Funding acquisition done by JRK, JAS, and DTD.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-reviewed reports from NIH.
[PDF File (Adobe PDF File), 352 KB - resprot_v12i1e48548_app1.pdf]

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Abbreviations

ART: antiretroviral therapy
CAPI: computer-assisted participant interview
DCE: Discrete Choice Experiment
EHE: ending the HIV epidemic
EHR: electronic health record
EMA: ecological momentary assessment
MSA: metropolitan statistical area
N2: Neighborhoods and Networks
N2P2: Neighborhoods and Networks Part 2
PrEP: pre-exposure prophylaxis
RDS: respondent-driven sampling
SMM: sexual minority men
STI: sexually transmitted infection
TW: transgender women

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Protocol

Efficient Generation of Chondrocytes From Bone Marrow–Derived Mesenchymal Stem Cells in a 3D Culture System: Protocol for a Practical Model for Assessing Anti-Inflammatory Therapies

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Abstract

Background: Chondrocytes are the primary cells responsible for maintaining cartilage integrity and function. Their role in cartilage homeostasis and response to inflammation is crucial for understanding the progression and potential therapeutic interventions for various cartilage-related disorders. Developing an accessible and cost-effective model to generate viable chondrocytes and to assess their response to different bioactive compounds can significantly advance our knowledge of cartilage biology and contribute to the discovery of novel therapeutic approaches.

Objective: We developed a novel, streamlined protocol for generating chondrocytes from bone marrow–derived mesenchymal stem cells (BMSCs) in a 3D culture system that offers significant implications for the study of cartilage biology and the discovery of potential therapeutic interventions for cartilage-related and associated disorders.

Methods: We developed a streamlined protocol for generating chondrocytes from BMSCs in a 3D culture system using an "in-tube" culture approach. This simple pellet-based 3D culture system allows for cell aggregation and spheroid formation, facilitating cell-cell and cell–extracellular matrix interactions that better mimic the in vivo cellular environment compared with 2D monolayer cultures. A proinflammatory chondrocyte model was created by treating the chondrocytes with lipopolysaccharide and was subsequently used to evaluate the anti-inflammatory effects of vitamin D, curcumin, and resveratrol.

Results: The established protocol successfully generated a large quantity of viable chondrocytes, characterized by alcian blue and toluidine blue staining, and demonstrated versatility in assessing the anti-inflammatory effects of various bioactive compounds. The chondrocytes exhibited reduced inflammation, as evidenced by the decreased tumor necrosis factor-α levels, in response to vitamin D, curcumin, and resveratrol treatment.

Conclusions: Our novel protocol offers an accessible and cost-effective approach for generating chondrocytes from BMSCs and for evaluating potential therapeutic leads in the context of inflammatory chondrocyte–related diseases. Although our approach has several advantages, further investigation is required to address its limitations, such as the potential differences between chondrocytes generated using our protocol and those derived from other established methods, and to refine the model for broader applicability and clinical translation.

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KEYWORDS

chondrocytes; bone marrow–derived mesenchymal stem cell; BMSC; tumor necrosis factor-α; TNF-α; vitamin D; curcumin; resveratrol; enzyme-linked immunosorbent assay; ELISA; inflammation; anti-inflammation; proinflammation; 3D culture system

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Introduction

Background

The burgeoning field of regenerative medicine has placed a considerable focus on the differentiation of bone marrow–derived mesenchymal stem cells (BMSCs) into chondrocytes [1,2]. This area of research is critical for advancing our understanding of cartilage repair and regeneration and for developing novel therapeutic strategies [3]. Therefore, it is essential to consider the optimal environment for these sophisticated cellular processes. Although cell culture plates have been the standard for differentiation experiments, recent evidence suggests that using tubes for differentiation may better simulate the native chondrocyte habitat and foster more accurate cell-cell and cell–extracellular matrix (ECM) interactions [4]. Consequently, research has shifted its focus toward tube-based, 3D culture systems that more accurately simulate native tissue conditions [5].

Several studies have highlighted the superiority of tube-based culture over conventional 2D cell culture plates. A comparative analysis is presented in Table 1. The rationale behind this innovative approach lies in the unique characteristics of the chondrocyte ECM and the intricacies of cartilage tissue formation. By using tubes for differentiation, we can create a 3D environment that better mimics the native milieu of chondrocytes, fostering improved cell-cell and cell-ECM interactions. This shift in methodology not only enhances our understanding of chondrogenesis but also has the potential to accelerate the development of novel therapeutic strategies for cartilage repair and regeneration.

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Table 1. Comparison of 2D and 3D cell culture methods.

	Type of cell culture		Key references	Advantage of tube-based cell culture used in this protocol[a]
	2D	3D		
Cell-cell interactions	Limited	Enhanced	Breslin and O'Driscoll [6]	Enhanced cell-cell interactions
Cell–extracellular matrix interactions	Restricted	More accurate	Cukierman et al [7]	Improved mimicry of in vivo conditions
Spatial organization	Flat and monolayer	Complex and multilayered	Edmondson et al [8]	Better representation of tissue architecture
Cell polarization	Mostly absent	Prominent	Théry [9]	Improved cell polarity and functionality
Cell signaling	Altered and oversimplified	More realistic	Bissell and Radisky [10]	More accurate signaling pathways
Cell migration and invasion	Less accurate	Closer to in vivo	Friedl and Alexander [11]	Improved evaluation of cell migration and invasion
Cellular morphology	Flattened and simplified	More in vivo–like	Ravi et al [12]	Enhanced representation of native morphology
Stiffness	High stiffness (approximately 3×10^9 Pa)	Low stiffness (>4000 Pa)	Krausz et al [13]	Low stiffness reduces durotaxis, augmenting cell growth and proliferation and reduction of cellular stress, which may alter gene expression
Gene expression	Altered	More physiologically relevant	Duval et al [14]	Improved gene expression profile
Cellular functions and responses	Limited and oversimplified	More complex and accurate	Edmondson et al [8]	Better simulation of in vivo functionality
Differentiation and stem cell maintenance	Reduced fidelity	Enhanced fidelity	Hockemeyer and Jaenisch [15]	Improved maintenance of cell identity
Cell viability and proliferation	Unreliable representation	More accurate representation	Langhans [16]	Better assessment of cell growth and survival
Drug sensitivity	Less predictive	More predictive	Imamura et al [17]	More accurate drug sensitivity when compared with the 2D system but not as superior when compared with complex 3D techniques such as organoids and scaffold-based systems
Drug exposure	Nonphysiological	Closer to in vivo	Badr-Eldin et al [18]	Improved drug exposure over the 2D system; but when it comes to in vivo mimicry, it may not be as superior as complex 3D techniques such as organoids and scaffold-based systems
Ease of imaging	Enables simple imaging owing to their monolayer structure	Requires sophisticated imaging protocol owing to the complex and multilayered structure	Temple et al [19]	Ease of imaging is high in 2D over 3D cell culture systems, although in-tube–based 3D cell culture systems involving a single type of cell, imaging is relatively easy with high replicability over complex 3D techniques such as organoids and scaffold-based systems
Technical complexity	Low	Higher and varies according to the type of 3D culture system being used	Cacciamali et al [20]	In this protocol, complexity is moderate when compared with a 2D culture system

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	Type of cell culture		Key references	Advantage of tube-based cell culture used in this protocol[a]
	2D	3D		
Scalability	High	Variable and technique dependent	Fang and Eglen [21]	Depends on the 3D cell culture technique but is relatively high for tube-based 3D cell culture techniques. Scalability is especially restricted in scaffold and matrix and microfluidic 3D models
Reproducibility	High	Variable and technique dependent	Duval et al [14]	Typically higher than other 3D cell culture techniques
Cost of experimentation	Low	High—varies with technique	Khalil et al [22]	Typically higher than 2D cell culture techniques, varies with technique but lower when compared with scaffold or matrix, organoid, and microfluidic 3D models
Cost of maintenance	Low	High—varies with technique	Raic et al [23]	Typically higher than 2D cell culture techniques, varies with technique but lower when compared with scaffold or matrix, organoid, and microfluidic 3D models.

[a]The 3D tube-based method for culturing chondrocytes demonstrated in this protocol offers advantages over 2D culture plates, such as enhanced cell-cell interactions, improved extracellular matrix production, and more physiologically relevant cellular responses. Although this tube-based approach is relatively simple compared with other 3D methods such as scaffold-based systems, hydrogels, and organoids, it still possesses many benefits of 3D cell culture systems.

Furthermore, investigating the response of the differentiated chondrocytes to proinflammatory stimuli such as lipopolysaccharide (LPS) is a vital aspect of understanding the intricate mechanisms of cartilage tissue degeneration and inflammation. By creating a proinflammatory model using LPS with the differentiated chondrocytes, we can delve deeper into the cellular and molecular responses that occur during inflammatory conditions such as osteoarthritis. This knowledge is crucial for the development of targeted therapies to mitigate inflammation and promote cartilage regeneration.

Objective

In this concise research protocol, we outline an uncomplicated approach to differentiate BMSCs into chondrocytes within a 3D culture system. Subsequently, we establish a proinflammatory model using the differentiated chondrocytes for further investigation. This succinct research protocol not only provides a valuable contribution to the field of cartilage tissue engineering but also offers a practical foundation for researchers seeking to explore the potential therapeutic applications and underlying molecular mechanisms in chondrocyte-based proinflammatory models.

Methods

Reagents and Equipment

The different reagents and equipment that were used in this study are presented in Textbox 1 in the form of a list for ease of use and reference by researchers.

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Textbox 1. Reagents and equipment used in this study.

Cell culture

- Reagents
- Human BMSC line (Addexbio, United States [24])
- Complete MesenCult-ACF Chondrogenic Differentiation Medium (Stem Cell Technologies, Canada [25])
- Phosphate-buffered saline (PBS; Gibco, United Kingdom [26])
  - Mesenchymal stem cell growth media (MSCM; Himedia, India [27])
  - Fetal bovine serum (Himedia, United States [28])
  - Penicillin-streptomycin solution (Himedia, India [29])
  - Trypsin and ethylenediaminetetraacetic acid solution (Himedia, India [30])
- Equipment
  - Automated cell counter (DeNovix, Cell Drop, United States [31])
  - Microfuge 20 centrifuge [32]

Histological section of pellets

- Reagents
  - Dimethyl sulfoxide [33]
  - Neutral-buffered formalin (TissuePro, United States [34])
- Equipment
  - Microtome (Leica RM2255, Germany [35])

Staining of chondrocytes

- Reagents
  - Toluidine blue ($C_{15}H_{16}N_3S^+$; Abcam, United States [36])
  - Alcian blue ($C_{56}H_{68}C_{14}CuN_{16}S_4$; Abcam, United States [37])
- Equipment
  - Olympus BX63 microscope (Japan [38])

Creation and evaluation of proinflammation model

- Reagents
  - LPS (Thermofisher Scientific, United States [39])
  - Vitamin D (calcitriol; 1,25-dihydroxyvitamin D3 [1,25(OH)2D3]; Abcam, United States [40])
  - Curcumin (MedChem Express, Ukraine [41])
  - Resveratrol (MedChem Express, Ukraine [42])

Cytokine expression study

- Reagents
  - Tumor necrosis factor-α (TNF-α) enzyme-linked immunosorbent assay (ELISA) kit (Abcam, United States [43])
- Equipment
  - Microplate reader (Hidex, Finland [44])

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Ethical Considerations

In this study, we conducted experimental procedures exclusively using in vitro methodologies with commercially available cell lines. The absence of animal models or samples, patient samples or data, and the recruitment of human participants ensured minimal risk associated with our research. As such, this study falls under 1 of the exempt review categories defined by the institutional review board regulations of Mohammed Bin Rashid University. For further information and clarification, the institutional review board of the Mohammed Bin Rashid University can be reached at irb@mbru.ac.ae.

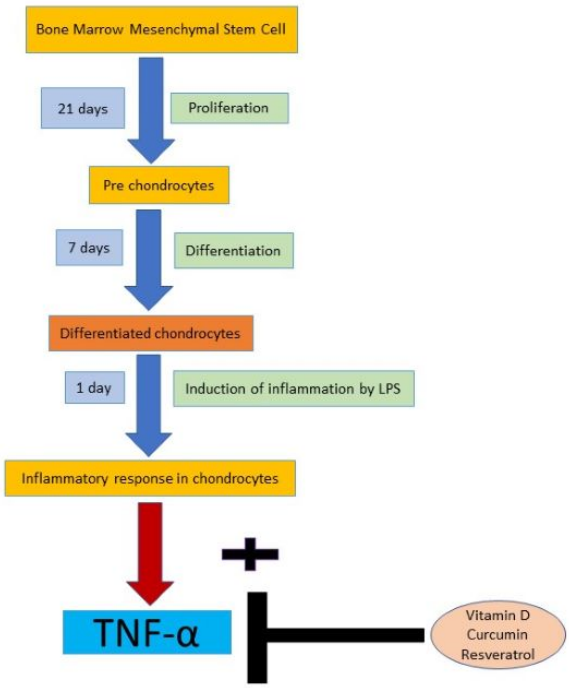
As our experiments were conducted using commercially purchased cell lines and did not involve human participants, there was no requirement for informed consent or the inclusion of minors, eliminating the need for parental or guardian consent. In addition, our study did not involve the use of medical records or archived samples. As no human participants were involved, the need for a language waiver was not applicable.

In summary, our study focused on in vitro experiments using commercially available cell lines, negating the involvement of human participants. Consequently, no participant consent was required, and the need for consent, as well as a language waiver which is often required for addressing a form or an agreement while obtaining consent, was waived by the ethics committee. This study complies with human subject research ethics review, exemptions, and approvals, although it primarily involves observations of public behaviors or secondary analyses of research data.

As this study did not involve human participants, the privacy and confidentiality protection descriptions for human participants research, such as statements about data anonymity or deidentification, were not applicable. In addition, because our research did not involve human participants, there was no compensation type or amount provided for human participants research.

The workflow underlying the proof-of-concept study is shown in Figure 1.

Figure 1. Workflow of this study. LPS: lipopolysaccharide; TNF-α: tumor necrosis factor-α.



Preparation of Human Bone Marrow Mesenchymal Stem Cell Line for Cell Culture

Upon receiving the human BMSC line in liquid nitrogen, they were immediately washed with PBS to ensure that the cells were free from the cryoprotectant dimethyl sulfoxide. The washed cells were then cultured in MSCM supplemented with 10% fetal bovine serum and 1% penicillin-streptomycin antibiotic solution. After the addition of MSCM, the cells were kept in an incubator at 37 °C and 5% carbon dioxide. The cell culture medium was replaced with fresh medium at an interval of 3 days, and their confluency was appraised. Once the cells reached 90% confluence, the proteolytic enzyme trypsin was added to dislodge the adherent cells from the culture flask. Trypsinization was performed using trypsin and ethylenediaminetetraacetic acid solution. The detached cells were subcultured for further growth in MSCM.

Cell Culture

In this study, we cultured cells as pellets in 15-mL tubes, instead of using a monolayer culture. Although we did not use a matrix gel or scaffold, our cell culture system can be categorized as a "simple 3D cell culture system." In this pellet culture system, cells are aggregated and allowed to form spheroids or clusters, promoting cell-cell and cell-ECM interactions that more closely resemble the in vivo cellular environment compared with traditional 2D monolayer cultures [45].

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This pellet culture system has several advantages over the 2D cell culture system. First, the 3D cell culture system provides a more physiologically relevant environment for the cells, allowing for better simulation of in vivo conditions, including nutrient diffusion, oxygen gradients, and cell signaling (Table 1) [8]. Second, cell behavior, morphology, and gene expression profiles are often more representative of in vivo conditions in 3D culture systems compared with 2D monolayers (Table 1) [14]. As a result, the pellet culture system may provide more accurate insights into cellular responses to various stimuli, such as drug treatments or the presence of inflammatory molecules, which can be beneficial for therapeutic development and disease modeling.

It is worth noting that although the pellet culture system described in this study represents a simple form of 3D cell culture, more complex 3D culture systems using scaffolds or matrix gels can further enhance the recapitulation of the in vivo microenvironment and may provide additional benefits for various applications [46].

After 5 passages of subculture (passage 5), the BMSCs were used for chondrogenic differentiation. For chondrogenic differentiation, 2×10^6 BMSCs (estimated using an automated cell counter) were pelleted in 15-mL polypropylene tubes after centrifugation at 1000 rpm for 10 minutes. In total, 2 mL of complete MSCM chondrogenic differentiation medium was added to the cell pellet, from which 0.5 mL of the cell suspension was added to each 15-mL polypropylene tube (4 in total) for "in-tube" differentiation. Each of these tubes was centrifuged at 1000 rpm for 10 minutes at 25 °C. Caps of the tubes were gently loosened, and the tubes were incubated at 37 °C in the presence of 5% carbon dioxide to ensure that there were no alterations in the pH of the cell culture media. After 3 days of incubation, 0.5 mL of complete MSCM chondrogenic differentiation medium was added to the tubes, followed by incubation at 37 °C in the presence of 5% CO_2 for 3 days. After incubation, the cell culture medium was carefully aspirated from each tube, and 0.5 mL of fresh MSCM chondrogenic differentiation medium was added. The tubes were further incubated at 37 °C in the presence of 5% CO_2 for 21 days, with intermittent replacement (at 3-day intervals) of cell culture medium with fresh MSCM chondrogenic differentiation medium. After each change of cell culture medium, the differentiating cell pellets were gently "flicked" to ensure that the pellets did not adhere to the tube surfaces. After 21 days of incubation, the cell pellets, which were at the stage of chondrogenic differentiation to prechondrocytes, were further incubated for 7 days.

Cryopreservation of Differentiated Chondrocytes

Chondrocytes intended for cryopreservation were centrifuged at 1000 rpm for 10 minutes. The cells were then resuspended in the freezing medium and transferred into suitable sized cryovials. The pellets were kept at −80 °C overnight, followed by storage in a liquid nitrogen tank for long-term use.

Preparation of Histological Section From Cell Pellet

The pellet was transferred to a histology cassette, followed by fixation in 10% neutral-buffered formalin for 24 hours. The cassette along with the pellet were then transferred to 70% ethanol, followed by dehydration in graded ethanol series (25%, 50%, 75%, 90%, 95%, and 100% for 3 minutes each). The clarification steps were carried out in xylene and embedded in paraffin, following a standard embedding protocol. Cell pellets containing chondrocytes were sectioned (6 µm) using a microtome. The sections were mounted on slides. The sections were deparaffinized in 3 changes of xylene, followed by rehydration of the slide sections using a decreasing alcohol series (100%, 95%, 90%, 75%, 50%, and 25% for 3 minutes each), followed by a final rinse with deionized water for 5 minutes.

Toluidine Blue Staining

Toluidine blue solution was prepared by dissolving 0.1 g of toluidine blue in 100 mL of deionized water. The pH of the solution was adjusted to 4. Following the preparation of slides (as described in detail in the *Preparation of Histological Section From Cell Pellet* section), the slides were stained with toluidine blue and kept for 2 minutes at room temperature. The slides were carefully rinsed with water for 1 minute, followed by dehydration in a graded ethanol series (25%, 50%, 75%, 90%, 95%, and 100% for 3 minutes each). The slides were incubated in xylene for 5 minutes to improve visibility by removal of impurities, and mounted in mounting solution. The slides were then observed using a microscope.

Alcian Blue Staining

The alcian blue solution was prepared by dissolving 1 g of alcian blue in 3% acetic acid. The pH of the solution was adjusted to 2.5. The preprepared slides (as described in detail in the *Preparation of Histological Section From Cell Pellet* section) containing 6-µm sections of the pellet were placed in 3% acetic acid solution for 3 minutes. The slides were placed in a 1% solution of alcian blue for 30 minutes. The slides were then washed with running water for 1 minute, followed by dehydration in a graded ethanol series (25%, 50%, 75%, 90%, 95%, and 100% for 3 minutes each). The slides were incubated in xylene for 5 minutes to improve visibility by removal of impurities, and mounted in mounting solution. The slides were then observed using a microscope.

Microscopic Analysis

The Olympus BX63 microscope was used to analyze the staining protocol. The microscope is equipped with Olympus DP80 camera (resolution of 4080 × 3072 pixels and pixel size of 6.45 × 6.45 µm) with Cell Sens Dimension 2.3 software (Olympus Soft Imaging Solutions GmbH). Images were acquired with 20X (numerical aperture 0.45; 1920 × 1200 pixels; 465.079-nm/pixel resolution in both x-axis and y-axis) and 40X (numerical aperture 0.6; 1920 × 1200 pixels; 232.54-nm/pixel resolution in both x-axis and y-axis) objective lenses.

Creation and Evaluation of the Proinflammation Model

LPS was used to stimulate inflammation in the differentiated chondrocytes to create the proinflammation model. LPS was administered at 10 µg/mL concentration to the differentiated chondrocytes to induce inflammation. The cells were incubated in an incubator at 37 °C and 5% CO_2 concentration for 1 day.

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To validate our proinflammation model, we evaluated the anti-inflammatory effects of vitamin D, curcumin, and resveratrol by their dose-dependent inhibition of TNF-α. After 1 day of LPS treatment, LPS-treated chondrocytes were treated with various doses of vitamin D (calcitriol) at 0, 0.01, 0.02, 0.12, and 0.25 µM. Curcumin and resveratrol were used at various concentrations (0, 25, 50, 75, and 100 µM). Following treatment with these nutraceutical leads, the cells were incubated at 37 °C and 5% CO_2 concentration for 1 day.

Cytokine Expression Study

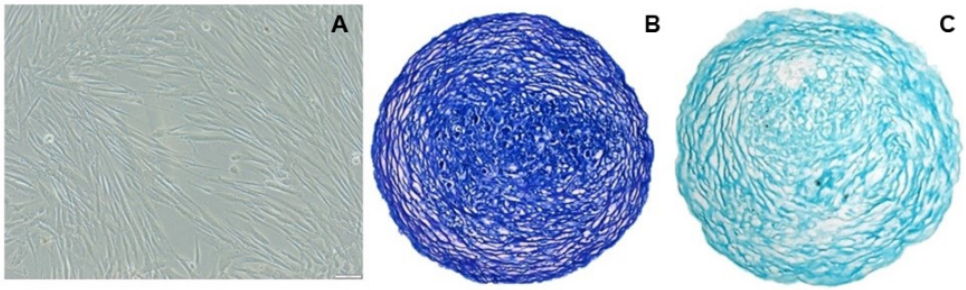
Expression of TNF-α was assessed in LPS-treated chondrocytes with or without vitamin D, curcumin, and resveratrol. The chondrocyte supernatants were collected by centrifugation at 5000 rpm for 10 minutes. Concentrations of TNF-α were determined through the use of a commercially available ELISA kit. The assay was performed in accordance with the manufacturer's guidelines. The plates were precoated with human TNF-α. TNF-α levels were measured using a microplate reader at 450 nm, with a reference wavelength of 620 nm. All experiments were performed independently 3 times. All data were reported as mean (SD).

Results

Qualitative Evaluation of Differentiated Chondrocytes

Chondrocytes successfully differentiated from human BMSCs (Figure 2A) after culturing in a chondrogenic differentiation medium. The quality of the differentiated chondrocytes was assessed histologically using 2 different dyes: toluidine blue (Figure 2B) and alcian blue (Figure 2C).

Figure 2. Qualitative analysis of the differentiated chondrocytes. (A) Differentiated chondrocytes obtained from bone marrow–derived mesenchymal stem cells after 28 days; (B) differentiated chondrocytes stained with toluidine blue, and (C) differentiated chondrocytes stained with alcian blue.



Qualitative assessment of successful chondrogenic differentiation of BMSCs was pursued using toluidine blue staining, where the cationic dye specifically binds to the sulfate groups of proteoglycans. A well-differentiated chondrocyte will stain purple owing to the presence of proteoglycans in the ECM, as observed in this study (Figure 2B). The expression of proteoglycan (aggrecan), type II collagen and type X collagen after 21 days of differentiation, was confirmed in the chondrocytes by alcian blue staining (Figure 2C).

Creation of Proinflammatory Chondrocyte Model and Its Evaluation

Following the generation of high-quality chondrocytes from BMSCs, inflammation was induced in the chondrocytes to generate a "proinflammation model." Inflammation was induced using LPS, a biomolecule of predominant abundance in the outer membrane of gram-negative bacteria, which is a key pathogenic stimulator for the dysfunctions. During septicemia, circulating LPS, as a pathogen-associated molecular pattern (PAMP) stimulates the innate immune system, leading to local or systemic inflammatory responses. It has also been shown that LPS also stimulates nonimmune cells and initiates the severe inflammatory responses through dedicated receptors. In particular, the innate LPS–pattern recognition receptor, that is, the Toll-like receptor 4 (TLR4), is extensively expressed in cardiomyocytes, which leads to a severe LPS-induced inflammatory response in cardiomyocytes irrespective of the involvement of immune cells [47,48]. TLR4 is also extensively expressed in chondrocytes [49]. Building upon this foundation, we postulated that LPS can trigger proinflammatory reactions in differentiated chondrocytes independent of immune cell participation.

To assess inflammation, the levels of TNF-α in LPS-treated chondrocytes versus LPS-naive chondrocytes (control) were investigated. TNF-α holds particular significance in comparison with other cytokines, with respect to inflammation in chondrocytes. This is primarily because of its well-established role as a key mediator of inflammatory processes in various cell types, including chondrocytes. Several studies have demonstrated the crucial involvement of TNF-α in the pathogenesis of cartilage degradation and osteoarthritis [50-52].

First, TNF-α has been shown to directly promote the production of other proinflammatory cytokines, such as interleukin-1β (IL-1β) and interleukin-6, which subsequently contribute to the inflammatory cascade in chondrocytes [50,53,54]. This amplification of the inflammatory response highlights the central role of TNF-α in this process.

Moreover, TNF-α has been found to induce the expression of matrix metalloproteinases (MMPs) in chondrocytes [55]. MMPs are enzymes responsible for the degradation of the ECM in cartilage tissue, thereby playing a crucial role in cartilage breakdown and the progression of osteoarthritis [56].

In addition, TNF-α can inhibit the synthesis of cartilage matrix components, such as aggrecan and type II collagen, further impairing the structural integrity and function of the cartilage [57,58]. This effect on cartilage homeostasis further underscores the importance of TNF-α as a marker for assessing inflammation in chondrocytes.

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In light of these findings, focusing on TNF-α as a marker for evaluating inflammation in chondrocytes is well justified, as it serves as a reliable indicator of the extent of cartilage degradation and the inflammatory status of chondrocytes in various pathological conditions.

Following the addition of LPS, differentiated chondrocytes were incubated for 24 hours, following which the level of TNF-α was assessed by ELISA. LPS-treated chondrocytes expressed 40% more TNF-α, when compared with the LPS-naive chondrocytes (control population of cells treated with PBS instead of LPS).

Investigating the Effects of Vitamin D, Curcumin, and Resveratrol on Chondrocytes Derived From the "In-Tube" Culture System

After successfully establishing a proinflammatory chondrocyte model, we evaluated its applicability for characterizing potential therapeutic candidates. In this context, we investigated the impact of vitamin D, curcumin, and resveratrol in ameliorating the expression of TNF-α in the proinflammatory chondrocyte model (Table 2).

Table 2. Anti-inflammatory response of vitamin D, curcumin, and resveratrol at different doses in the generated proinflammatory chondrocyte model. (Note: Increasing concentrations of the bioceuticals attenuate tumor necrosis factor-α [TNF-α] expression, although vitamin D exhibits the highest potency of inhibition).

Doses (μM)	Percentage of TNF-α expression, mean (SD)	TNF-α expression reduction at max assessed dose (%)
Vitamin D		66.1
0	100 (0.2)	
0.01	88 (2.3)	
0.02	72 (1.7)	
0.12	58 (1.9)	
0.25	33.9 (0.9)	
Curcumin		61.9
0	100 (0.8)	
10	88.4 (2.9)	
25	72.9 (5.8)	
50	59.7 (1.2)	
75	44.3 (6.4)	
100	38.1 (2.4)	
Resveratrol		45.3
0	100 (1.9)	
10	92.3 (2.4)	
25	88.2 (6.8)	
50	76.2 (3.7)	
75	63.0 (5.9)	
100	54.7 (3.0)	

Although the effects of vitamin D on TNF-α are well described in the literature, our study focuses on the unique "in-tube" 3D culture approach for differentiating BMSCs into chondrocytes. This novel method offers significant advantages over traditional 2D culture systems (Table 1), such as improved cell-cell interactions, increased ECM production, and more physiologically relevant cellular responses. Given the unique nature of the "in-tube" culture system, it is essential to verify whether the well-known anti-inflammatory effects of vitamin D on TNF-α are maintained. Using vitamin D in our protocol, we aim to assess the reproducibility and consistency of its effects in an innovative 3D chondrocyte model.

Moreover, the inclusion of vitamin D serves as a positive control to validate the effectiveness of our proinflammatory chondrocyte model, as its effects on TNF-α reduction are well established. By demonstrating that vitamin D effectively reduces TNF-α levels in our "in-tube" culture system, we can confirm the suitability of the model for investigating other potential therapeutics, such as curcumin and resveratrol.

In summary, the use of vitamin D in our protocol is justified by the need to validate the "in-tube" 3D culture system's ability to replicate well-known anti-inflammatory effects as well as to provide a positive control for evaluating the effectiveness of other nutraceuticals, such as curcumin and resveratrol. The inclusion of vitamin D, along with curcumin and resveratrol, expands our understanding of the potential therapeutic leads for inflammatory chondrocyte–related diseases in the context of our unique 3D culture model.

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Vitamin D, specifically its active form, 1,25-dihydroxyvitamin D3 (1,25(OH)2D3), has been shown to exert anti-inflammatory effects in various cell types, including chondrocytes. It modulates the production of proinflammatory cytokines, such as TNF-α and IL-1β, and suppresses the expression of MMPs, which are involved in cartilage degradation [59]. In addition, vitamin D promotes chondrocyte differentiation and enhances the synthesis of ECM components such as type II collagen and aggrecan [60]. Thus, vitamin D can be used to assess the effectiveness of anti-inflammatory agents in a proinflammatory chondrocyte model.

Curcumin, the bioactive component of turmeric, has demonstrated potent anti-inflammatory, antioxidant, and chondroprotective properties [61]. Studies have shown that curcumin can inhibit the expression of proinflammatory cytokines, including TNF-α, IL-1β, and interleukin-6, as well as MMPs in chondrocytes [62-64]. Furthermore, curcumin suppresses the activation of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), a key transcription factor involved in the regulation of inflammation and cartilage destruction [63]. Therefore, curcumin is an ideal candidate for assessing the efficacy of anti-inflammatory interventions in a proinflammatory chondrocyte model.

Resveratrol, a polyphenol found in grapes, red wine, and other plant sources, exhibits strong anti-inflammatory and antioxidant properties. Research has shown that resveratrol can attenuate inflammation in chondrocytes by inhibiting the production of proinflammatory cytokines and reducing oxidative stress [65]. Moreover, resveratrol suppresses the activation of NF-κB and the expression of MMPs, which are implicated in cartilage degradation [63]. Given its well-documented anti-inflammatory and chondroprotective effects, resveratrol is an appropriate choice for evaluating the performance of anti-inflammatory agents in a proinflammatory chondrocyte model.

In summary, vitamin D, curcumin, and resveratrol possess anti-inflammatory and chondroprotective properties, which make them suitable for assessing the effectiveness of potential therapeutic interventions in a proinflammatory chondrocyte model.

Chondrocytes treated with LPS were exposed to varying concentrations of vitamin D, curcumin, and resveratrol. Each of these nutraceuticals effectively mitigated inflammation, as evidenced by the inverse relationship observed between TNF-α levels and the administered doses of vitamin D, curcumin, and resveratrol (Table 2). This finding has significant implications, as it highlights the potential therapeutic utility of these bioactive compounds in alleviating inflammation and promoting cartilage health in the context of inflammatory chondrocyte conditions. Furthermore, the successful demonstration of the anti-inflammatory effects of vitamin D, curcumin, and resveratrol in this model validates their utility for screening and evaluating other potential therapeutics.

Discussion

Principal Findings

In summary, we have described a straightforward and efficient protocol for generating a large quantity of viable chondrocytes derived from BMSCs in a simple pellet-based 3D culture system. This approach, although not using a matrix gel or scaffold, allows for cell aggregation and spheroid formation, facilitating cell-cell and cell-ECM interactions that better mimic the in vivo cellular environment compared with 2D monolayer cultures. However, it is important to note that the pellet culture system is a simple form of 3D cell culture. More complex 3D culture systems using scaffolds or matrix gels can further improve the recapitulation of the in vivo microenvironment, providing additional benefits for various applications.

This approach can also be used to evaluate the effects of potential therapeutic agents on the inflammatory response of chondrocytes. Importantly, this protocol is accessible to all laboratories, including those without readily available patient samples. Furthermore, this “proinflammatory model” can be used to investigate therapeutic targets for diseases involving chondrocytes, such as osteoarthritis.

A notable aspect of this model is its versatility, as it has been effectively used to assess the anti-inflammatory effects of various bioactive compounds such as vitamin D, curcumin, and resveratrol (Table 2). This adaptability allows researchers to explore a wide range of potential therapeutic leads in the context of inflammatory chondrocyte–related diseases, ultimately expanding our understanding of these compounds’ mechanisms of action and their potential for clinical application.

The established model offers several advantages over the existing methods reported in the literature. First, unlike some chondrogenesis models that recommend the use of synthetic or hybrid scaffolds [66], this model does not require scaffold presence. For instance, Sofu et al [67] demonstrated chondrogenesis using a hyaluronic acid scaffold. The incorporation of scaffolds not only adds multiple steps to the experimental process but also increases costs.

Second, our novel chondrogenic differentiation protocol uses an “in-tube” culture system, which reduces the need for cell splitting. Consequently, this minimized the cells’ exposure to degradative enzymes, ensuring the production of higher-quality cells (Figure 2).

Third, by significantly reducing the number of cell-splitting steps, our protocol minimizes human intervention in the chondrogenic differentiation process. This reduction in intervention subsequently decreases the risk of bacterial contamination, genetic alterations, and phenotypic instabilities [68]. Overall, the proposed protocol offers an accessible, cost-effective, and efficient method for generating chondrocytes and for assessing potential therapeutic leads in the context of inflammatory chondrocyte–related diseases.

The chondrocytes derived through this “in-tube” protocol also have diverse applications:

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- Tissue engineering and regenerative medicine: The derived chondrocytes can be used for the development of engineered cartilage constructs for cartilage repair and regeneration, particularly in conditions such as osteoarthritis and focal cartilage defects.
- Drug screening and development: The chondrocytes can serve as an in vitro model for evaluating the efficacy and safety of novel therapeutic compounds targeting cartilage-related disorders, potentially accelerating the drug discovery process.
- Disease modeling: The derived chondrocytes can be used to establish in vitro models for investigating the molecular and cellular mechanisms underlying various cartilage-related diseases, providing valuable insights into disease pathogenesis and progression.
- Personalized medicine: By generating patient-specific chondrocytes from autologous BMSCs, our protocol could facilitate the development of personalized treatment strategies tailored to individual patients' needs, thereby improving therapeutic outcomes and reducing the risk of adverse effects.

Limitations

Nevertheless, certain aspects of the developed model warrant further investigation. One of the limitations of our proposed protocol is the potential difference between chondrocytes generated using our method and those derived from other established protocols or directly isolated from humans or laboratory animals. Although our simple 3D cell culture system facilitates cell-cell and cell-ECM interactions that more closely resemble the in vivo cellular environment compared with traditional 2D monolayer cultures, it is important to recognize that this system is not as advanced as more complex 3D culture systems using scaffolds or matrix gels. These more sophisticated systems can further improve the recapitulation of the in vivo microenvironment and provide additional benefits for various applications.

Another aspect to consider is the use of single-cell transcriptomics to compare the gene expression profiles of chondrocytes generated using our protocol with those isolated directly from humans or laboratory animals. This analysis would help to validate the methodological strength of our approach and provide valuable insights into the similarities and differences between the generated chondrocytes.

Another limitation of our protocol is that the pellet culture system, although beneficial for cell aggregation and spheroid formation, may not be suitable for all cell types or for studying specific cellular behaviors. Certain cell types may not adhere or proliferate well in this system, and the lack of a defined matrix or scaffold may limit the ability to investigate cell-matrix interactions and cellular migration.

In addition, our protocol has not been extensively tested for scalability, which could be a concern when attempting to generate large quantities of chondrocytes for applications such as tissue engineering or regenerative medicine. Further optimization of the protocol may be required to ensure that the system can be effectively scaled up to meet the demands of these applications.

Moreover, in response to an inflammatory microenvironment, chondrocytes adapt their physiology by modulating the expression of cell surface proteins, collectively referred to as the "surfaceome" [69], and the assortment of transporters and ion channels, known as the "channelome" [70]. It is crucial to determine whether the chondrocytes obtained using this new protocol exhibit surfaceome and channelome profiles consistent with those found in physiological conditions.

In addition, other potential limitations of this study should be acknowledged. For instance, further research is necessary to validate the long-term stability and functionality of the generated chondrocytes in both in vitro and in vivo settings. Moreover, it would be beneficial to explore the effects of other inflammatory mediators on the chondrocytes derived from this protocol to determine their applicability in a broader range of inflammation-driven scenarios. Finally, a comprehensive assessment of the safety and efficacy of the tested bioactive compounds is essential before transitioning to clinical applications. By addressing these limitations, the model used in this study can be refined and expanded to provide a more robust foundation for future research on inflammatory chondrocyte–related diseases.

Conclusions

In conclusion, the development of our novel, streamlined protocol for generating chondrocytes from BMSCs in a 3D culture system offers significant implications for the study of cartilage biology and the discovery of potential therapeutic interventions for cartilage-related disorders. The "in-tube" culture approach not only allows for the efficient production of viable chondrocytes but also provides a versatile platform for evaluating the anti-inflammatory effects of various bioactive compounds, as demonstrated by the decreased TNF-α levels following treatment with vitamin D, curcumin, and resveratrol. This accessible and cost-effective model holds promise for advancing our understanding of chondrocyte function in cartilage homeostasis and its response to inflammation, which is critical for unraveling the progression of cartilage-related diseases and identifying novel therapeutic strategies. Although our findings contribute to the growing body of knowledge in the field, further investigation is needed to address the limitations of the model used in this study, refine its applicability, and facilitate its translation into clinical practice. By doing so, this innovative approach may ultimately pave the way for the development of more effective and targeted therapies for a range of cartilage-related disorders, ultimately improving patient outcomes and quality of life.

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Acknowledgments

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Conflicts of Interest

None declared.

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Abbreviations

BMSC: bone marrow–derived mesenchymal stem cell
ECM: extracellular matrix
ELISA: enzyme-linked immunosorbent assay
IL-1β: interleukin-1β
LPS: lipopolysaccharide
MMP: matrix metalloproteinase
MSCM: mesenchymal stem cell growth media
PAMP: pathogen-associated molecular pattern
PBS: phosphate-buffered saline
TLR4: Toll-like receptor 4
TNF-α: tumor necrosis factor-α

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Protocol

Adapting and Scaling a Digital Health Intervention to Improve Maternal and Child Health Among Ethnic Minority Women in Vietnam Amid the COVID-19 Context: Protocol for the dMOM Project

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Abstract

Background: Due to interconnected structural determinants including low maternal health knowledge, economic marginalization, and remoteness from low-capacity health centers, ethnic minority women in remote areas of Vietnam face severe maternal, newborn, and child health (MNCH) inequities. As ethnic minorities represent 15% of the Vietnamese population, these disparities are significant. mMOM—a pilot mobile health (mHealth) intervention using SMS text messaging to improve MNCH outcomes among ethnic minority women in northern Vietnam—was implemented from 2013-2016 with promising results. Despite mMOM's findings, exacerbated MNCH inequities, and digital health becoming more salient amid COVID-19, mHealth has not yet been scaled to address MNCH among ethnic minority women in Vietnam.

Objective: We describe the protocol for adapting, expanding, and exponentially scaling the mMOM intervention *qualitatively* through adding COVID-19–related MNCH guidance and novel technological components (mobile app and artificial intelligence chatbots) and *quantitatively* through broadening the geographical area to reach exponentially more participants, within the evolving COVID-19 context.

Methods: dMOM will be conducted in 4 phases. (1) Drawing on a review of international literature and government guidelines on MNCH amid COVID-19, mMOM project components will be updated to respond to COVID-19 and expanded to include a mobile app and artificial intelligence chatbots to more deeply engage participants. (2) Using an intersectionality lens and participatory action research approach, a scoping study and rapid ethnographic fieldwork will explore ethnic minority women's unmet MNCH needs; acceptability and accessibility of digital health; technical capacity of commune health centers; gendered power dynamics and cultural, geographical, and social determinants impacting health outcomes; and multilevel impacts of COVID-19. Findings will be applied to further refine the intervention. (3) dMOM will be implemented and incrementally scaled across 71 project communes. (4) dMOM will be evaluated to assess whether SMS text messaging or mobile app delivery engenders better MNCH outcomes among ethnic minority women. The documentation of lessons learned and dMOM models will be shared with Vietnam's Ministry of Health for adoption and further scaling up.

Results: The dMOM study was funded by the International Development Research Centre (IDRC) in November 2021, cofacilitated by the Ministry of Health, and is being coimplemented by provincial health departments in 2 mountainous provinces. Phase 1 was initiated in May 2022, and phase 2 is planned to begin in December 2022. The study is expected to be complete in June 2025.

Conclusions: dMOM research outcomes will generate important empirical evidence on the effectiveness of leveraging digital health to address intractable MNCH inequities among ethnic minority women in low-resource settings in Vietnam and provide

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critical information on the processes of adapting mHealth interventions to respond to COVID-19 and future pandemics. Finally, dMOM activities, models, and findings will inform a national intervention led by the Ministry of Health.

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KEYWORDS

mobile health; digital health; Vietnam; maternal health; maternal, newborn, and child health; MNCH, health equity, ethnic minority; maternal and child health; child health; ethnography; coronavirus; COVID-19; perinatal; antenatal; woman; mother; pregnancy; newborn; infant; baby; ethnic; ethnicity; visible minority; culture

Introduction

Maternal, Newborn, and Child Health Inequities Among Ethnic Minority Women in Vietnam

Despite Vietnam's remarkable progress in improving maternal, newborn, and child health (MNCH) outcomes during the era of the Millennium Development Goals, increasing evidence demonstrates that ethnic minority communities living in remote areas have not benefited equally from this progress—MNCH inequities between the Kinh (ethnic majority group in Vietnam) and ethnic minority communities have in fact widened [1-3]. There are 54 ethnic groups in Vietnam, with the Kinh majority representing 85% (98 million) of the national population and 53 ethnic minority groups representing the remaining 15%. In Vietnam, as in other Southeast Asian countries, the term "ethnic minority" is commonly utilized by government bodies for populations who may elsewhere be classified as Indigenous peoples. As government authorities in Vietnam do not recognize Indigenous identity in programs or reports, this paper utilizes the terminology "ethnic minority."

Among ethnic minority populations, 75% live in 13 provinces in the northern mountain and central highlands regions, which are known for high concentrations of poverty [3]. Ethnic minority populations in Vietnam have higher total fertility rates, adolescent birth rates, and infant and child mortality rates and lower life expectancies [1,4,5]. An analysis of data from 4 recent censuses of Vietnam showed that at all survey time points (2000, 2006, 2011, 2014), the proportions of women who received skilled antenatal care and who gave birth with assistance from skilled staff were significantly higher among Kinh, higher economic status, and urban populations, highlighting clear structural inequities in health access for ethnic minority women in remote settings [2]. Vietnam's overall progress on MNCH indicators obscures severe disparities among marginalized ethnic minorities: in 2020-2021, 95% of all live births in Vietnam were delivered by a skilled birth attendant, yet this figure was only 37.7% among Hmong minority women [4]. Data from the same 2020-2021 national survey show that the percentage of women who received at least four antenatal care visits during pregnancy was 88.2% among the Kinh and Hoa, 62.3% among the poorest quintile, and 10.6% among the Hmong [4].

Shaped by decades of structural deprivation and social exclusion, specific factors contributing to the profound MNCH disparities faced by ethnic minority populations are limited access to education, economic marginalization, remote and rural residence (where there are fewer and lower capacity health centers and a documented shortage of health workers [5,6]), limited access to MNCH information, low reproductive health knowledge, language barriers, and poor access to and uptake of perinatal care services [2,3,5,7,8]. A 2021 study found that economic marginalization and living over 5 km from the nearest health facility were associated with having fewer than 4 antenatal care visits [7]. Importantly, documented inequities along ethnic lines in health care seeking and utilization, MNCH, nutrition, and oral health and hygiene suggest that minority ethnicity alone is a critical determinant impacting health outcomes [9]. Taken together, this evidence highlights how the confluence of ethnic minority status and related facets of socioeconomic exclusion has shaped severe and intractable MNCH inequities among ethnic minority women in Vietnam.

mMOM 2013-2016

To address MNCH disparities among ethnic minority women in remote areas, the "mMOM" project (2013-2016) piloted and evaluated a low-cost mobile health (mHealth) intervention in Thai Nguyen province, northern Vietnam. mMOM was developed by the Institute for Population, Health and Development in Hanoi (PHAD) and Simon Fraser University (SFU) in Vancouver and funded by the International Development Research Centre (IDRC) from Canada. The project aimed to determine whether integrated use of an electronic health information system, low-cost mobile technology, a user-provider interaction model, and behavior change communication (BCC) via SMS text messaging could improve access to MNCH information and services among perinatal ethnic minority women and their families. Developed using templates from the Mobile Alliance for Maternal Health [10] and adapted for local acceptability, mMOM administered 2 SMS text messaging programs for pregnancy and postpartum periods, featuring information, education, and communication (IEC); reminder; and BCC messages designed to support maternal health and to promote deeper interaction between ethnic minority women and the health care system. Participants were registered in mMOM according to their specific week in pregnancy/new motherhood and received tailored information on healthy fetal and infant development 2-3 times weekly via SMS text messaging. Additional details about the mMOM project development and protocol are available elsewhere [11,12].

Between 2013-2016, the mMOM intervention built and implemented an integrated mHealth platform, which sent timely IEC, reminder, and BCC text messages to 961 participating women in 8 communes in Thai Nguyen toward stimulating ethnic minority women's demand for quality perinatal care. In

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midterm and final qualitative evaluations assessing mMOM's acceptability and impact involving over 60 participants, women expressed satisfaction with the intervention's quality, timeliness, and convenience, and health workers reported increased efficiency and quality of care [12]. The mMOM project increased care seeking from ethnic minority women and promoted increased contact and strengthened relationships between participants and health providers, demonstrating the potential of mHealth to address the marginalization of ethnic minority women from the health system in this setting [12].

Need for the Current Study

Broader Geographic Area

Despite these findings and mMOM's promise in promoting MNCH among structurally marginalized ethnic minority women, the intervention's impacts were limited due its pilot nature and implementation in only 8 communes in a single province in Vietnam. Implementing an adapted and scaled version of the intervention across a broader geographic area, thus reaching more participants, is necessary to generate robust empirical evidence on the potential of mHealth to improve MNCH health equity in Vietnam and to build models that can be replicated and utilized for country-level mHealth projects.

SMS Text Messaging Versus Mobile App

Despite the high penetration of mobile services in Vietnam (143 mobile subscriptions for every 100 people in 2020 [13]), the application of mHealth for MNCH in Vietnam remains limited, with the exception of a current notable study examining a mobile app to promote early initiation and exclusive use of breastfeeding [14]. In alignment with this current research, given the rapid expansion of telecommunication technology and coverage of 4G network ever since mMOM was completed in 2016 and extensive smartphone uptake and usage even in remote areas [15], the potential impacts of mobile app–based MNCH delivery (rather than SMS text messaging based) among ethnic minority women must also be investigated and compared.

COVID-19, Exacerbated Health Inequities, and the Salience of mHealth

Current gaps in mHealth research and utilization in Vietnam were rendered even more salient by COVID-19, which exacerbated existing inequities in health access and outcomes globally—particularly for communities already marginalized from health systems including ethnic minority populations, women, immigrants, refugees, and people in rural/remote areas [16-20]. The pandemic underscored the urgency of research and development surrounding digital health interventions in the context of physical distancing restrictions and overloaded health facilities to maintain health access and prevent deepening health disparities amid COVID-19. The pandemic impacts have also been gendered and intersectional: globally, perinatal women represent a vulnerable population who have faced poorer maternal health outcomes and increased mental health concerns including heightened postpartum depression amid COVID-19 [21,22], and these disparities have been shaped by economic and class status, ethnicity, and geographic location [17,19,22-26]. This emerging evidence and calls for virtual and digital health programming to support perinatal women during the pandemic [21] suggest an urgent need for mHealth interventions that support maternal mental health and broader MNCH in Vietnam through the evolving COVID-19 crisis and beyond.

Objective

Despite mMOM highlighting the potential of mHealth to promote MNCH among ethnic minority women in Vietnam, existing severe MNCH inequities among ethnic minority women, and digital health approaches becoming even more salient amid COVID-19, mHealth has not yet been leveraged or scaled to address MNCH in Vietnam. Thus, the objective of this paper is to describe the protocol for adapting, expanding, and exponentially scaling the mMOM intervention *qualitatively* through the addition of COVID-19–related MNCH guidance and novel technological components (a mobile app and the use of artificial intelligence [AI]) and *quantitatively* through its expansion over a broader geographical area to reach exponentially more participants. This protocol details the adaptation of the 2013-2016 mMOM intervention (SMS text messaging intervention reaching 8 communes in 1 district with 900 participants) to the dMOM intervention (SMS text messaging, mobile app, and AI intervention reaching 71 communes in 5 districts with 9000+ participants), within the unique pandemic context.

Methods

Overview

The dMOM project will be conducted in 4 phases: (1) updating, adapting, and expanding the mMOM intervention; (2) scoping study and rapid ethnographic fieldwork; (3) dMOM intervention implementation and incremental scaling; and (4) intervention evaluation and documentation of lessons learned. A series of smaller studies conducted through project phases 2-4 will gather evidence on different dMOM facets and models to inform replication and scaling at the country level.

Phase 1: Updating, Adapting, and Expanding the Intervention

For phase 1, the mMOM project components will be (1) updated and adapted to respond to COVID-19 and its impacts and (2) expanded to include a mobile app and AI chatbots to more deeply engage participants. To adapt the intervention to serve perinatal women's unique vulnerabilities and needs through the pandemic and beyond, a literature review of publications on MNCH amid COVID-19 will be undertaken by a multidisciplinary team. Institutional and governmental guidelines on pregnancy during COVID-19 as well as peer-reviewed manuscripts, conference abstracts, and case studies will be screened and reviewed, with relevant information extracted to inform, revise, and update the original mMOM intervention content. As a result, the IEC, reminder, and BCC messages in the SMS text messaging packages and the mobile app content will include critical information (i.e., on COVID-19 risk awareness, testing, vaccinations, and maternal mental health) to support healthy pregnancies and newborn care during the pandemic and postpandemic contexts and ensure that the dMOM intervention reflects international and country-level

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institutional guidance on MNCH during COVID-19. Particular attention will be paid to emerging evidence and institutional guidelines surrounding COVID-19, mental health, and postpartum depression among perinatal women [21,22,27]. Finally, the mMOM BCC messages will be updated to target not only ethnic minority women and women living in remote mountainous areas, but also perinatal women in less remote areas, given the novel constraints in MNCH care accessibility and isolation from health services engendered by the pandemic.

To offer participants a more nuanced, customizable, and lower-cost avenue for engaging with the intervention, the dMOM app will be developed in partnership with computing science consultants to leverage smartphone capabilities and provide a more complex variety of functions to improve MNCH access and health outcomes among perinatal ethnic minority women. Similar to the mMOM SMS text messaging intervention, the dMOM mobile app will provide person-centered, tailored, and timely information according to women's specific stage of pregnancy/new motherhood. However, the dMOM app will feature more information per message/interaction (messages will not be subject to SMS text messaging character limits); photo, audio, and video messages to increase engagement with participants; and audio-photo messages as an important accessibility consideration for women with limited literacy and/or disabilities. The dMOM app also will reduce the cost of project participation (there are no associated costs after app installation, unlike SMS text messaging fees) and support health promotion activities among village health workers through the digitalization of traditional, familiar, and culturally acceptable IEC materials (i.e., MNCH posters and educational cartoons) and their inclusion in the app to reach a broader audience.

An assessment of how AI chatbots (automatic dialogue system) can be leveraged in dMOM to promote MNCH care and support project scalability and sustainability will be conducted through a literature review and consultation with AI experts who are members of the research team, and relevant components of existing uses of AI for MNCH will be extracted and adapted for use in the dMOM app. AI chatbots will be developed and piloted, with information collected to train AI models to correct SMS text messages, assess MNCH risks, and provide advice that is responsive to women's inquiries and enables them to quickly act in a health emergency situation requiring expertise from a health professional. dMOM will utilize the richer technological capacities offered by a mobile app and AI chatbots and evaluate their effectiveness in improving the quality of MNCH BCC.

Phase 2: Scoping Study and Rapid Ethnographic Fieldwork

For phase 2, a broad scoping study using mixed methods and rapid ethnographic fieldwork will be conducted at the project outset to involve key stakeholders in the intervention's codevelopment from its initial stages. The scoping study will begin with preliminary engagement meetings with the Ministry of Health, provincial and district health departments, women's health service providers, community advocacy groups for women and ethnic minority populations, local authorities, village chiefs, and individual women to ensure that the intervention is shaped by key institutional and community voices.

The scoping study will apply mixed research methods including in-depth interviews; focus group discussions led by trained project staff; and survey questionnaires with pregnant and postpartum ethnic minority women, family members, and health workers at diverse levels. It will assess (1) unmet MNCH needs among ethnic minority women and their newborns; (2) roles of husbands, family members, and broader community members as well as their gendered power dynamics impacting MNCH care; (3) existing MNCH communication mechanisms, gaps, and MNCH health service utilization; (4) the extent of mobile phone use of ethnic minority women in the new districts in Thai Nguyen and Dien Bien provinces (i.e., districts not covered in the mMOM project) and social and cultural factors impacting phone ownership and usage; (5) literacy and language barriers to receiving SMS text messages and using apps; (6) technical capacity of commune health workers and health centers surrounding mHealth utilization and technical constraints (i.e., power outages and mobile network coverage); and (7) long-term, multilevel impacts of COVID-19 on MNCH access and outcomes, ethnic minority health, and broader socioeconomic status of remote communities. The study will also include a rapid ethnographic review of gendered determinants; ethnicity-based barriers; and other key social, cultural, economic, and political factors that may hinder or facilitate project outcomes, as well as in-depth interviews with other potential stakeholders (i.e., corporate and technological institutions and government bodies) at district and provincial levels to explore partnership opportunities and policy constraints to project implementation and scaling up.

Within the broader scoping study, 2 smaller intersectionality and digital health uptake studies will take place. The intersectionality study will explore ethnicity, gendered power relationships, geographical and social distancing, and other interconnected determinants of MNCH outcomes and mHealth applicability, not in isolation but how they interact dynamically with one another to shape severe health disparities among ethnic minority women in northern Vietnam [28,29], particularly as impacted by COVID-19. This intersectionality study will utilize a participatory action research and people-centered approach—identified as critical contributing factors to the uptake and success of mMOM [12]—toward codeveloping and continually refining the intervention in interaction with community members to ensure that it is culturally sensitive, sustainable, and responsive to community needs [30]. The digital health uptake study will explore digital health accessibility and acceptability in geographically and/or socially remote settings, especially among ethnic minority women. Given current research gaps on digital health preferences among ethnic minority groups, the study will investigate participants' preferences for either the mobile app or SMS text messaging intervention; factors at individual, family, and societal levels informing their preferences; and potential solutions to increase uptake among ethnic minority women in remote areas toward reducing digital health inequity.

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Ethics Approval

Trained commune health staff will obtain oral informed consent from focus group and in-depth interview participants prior to their participation in the scoping study. The study has been approved by an institutional review board at PHAD, which is registered with and uses ethical protocols of the Office for Human Research Protections of the United States Department of Health and Human Services (2023/PHAD-DMOM-01). Project data are subject to privacy and security protocols of the Office for Human Research Protections. Participants in the focus groups and in-depth interviews will be remunerated 100,000 Vietnamese Dong (~US $4.20) for their expertise, time, and travel.

The scoping study's findings will be used to refine the scope of work, project activities (e.g., modifying the research design, updating intervention content, and selecting additional ethnic minority languages), and timeline in alignment with implementation capacities at the village and commune health center levels. The study's involvement of stakeholders in shaping the dMOM intervention from the project outset is expected to increase their interaction with the project and empower and strengthen ethnic minority women and their families' increased engagement in MNCH care [30]. It will also provide a critical opportunity for stakeholders to express COVID-19–related concerns regarding the intervention's operation so that these concerns may be accounted for and mitigated.

Phase 3: Intervention Implementation and Incremental Scaling

Upon completion of the first 2 study phases (updating and adapting the intervention content, developing the mobile app, and undertaking the scoping study), for phase 3, the dMOM intervention will be implemented and incrementally scaled. As the project plan will be informed by, updated, and revised based on the scoping study to ensure the intervention's accessibility and acceptability to the target population, the below protocol represents only a general guideline. Implementation will be initiated with project staff conducting a training-of-trainers activity to (1) train commune health workers as dMOM project implementors including on health management information system operations and dMOM integration and (2) enable them to train village health workers in the intervention's routine operation (i.e., registering participants, using the mobile app, and operating and monitoring the dMOM system). First, the updated SMS text messaging intervention will be implemented in Dinh Hoa, Thai Nguyen (the original mMOM intervention site) to initiate the intervention and troubleshoot potential challenges related to human resources, project staff training, and health management information system operation. This initial implementation period limited within 1 district will also provide critical ongoing engagement and continuity of the intervention while the dMOM app is being developed and ease the introduction of the dMOM app. Subsequently, the dMOM mobile app will be piloted in Dinh Hoa and 2 new districts in Thai Nguyen province (one remote and one urban district—Vo Nhai district and Song Cong city) and 2 districts (Muong Cha district and Dien Bien Phu city) within the even more remote and mountainous Dien Bien province, where ethnic minorities constitute 82.6% of the population [31]. To compare the relative acceptability, uptake, and MNCH impact of the dMOM mobile app to the SMS text messaging intervention, an equal number of communes in each district will be randomly assigned with the use of either the dMOM app or mMOM SMS text messaging to assess each component's feasibility among participants. Although the 2013-2016 pilot mMOM intervention reached 961 perinatal women across 8 communes in 1 district, the dMOM intervention will be implemented across 71 communes in 5 districts of 2 provinces, aiming to reach approximately 9000 women participants over a 30-month period.

Phase 4: Intervention Evaluation and Documentation of Lessons Learned

For phase 4, dMOM will be evaluated to assess whether SMS text messaging delivery or mobile app delivery engenders the most improved MNCH health-seeking behaviors and outcomes among ethnic minority women. The dMOM evaluation will involve data collection via multiple channels. Demographic and socioeconomic data will be collected by commune health staff at the intervention onset intervention when participants are registered. Monitoring and evaluation indicators on health-seeking behaviors and pregnancy and birth outcomes will be collected via automatic individual data collection and questions posed to participants within the dMOM app. The SMS text messaging and app systems will also be mined for back-end information regarding user statistics. Finally, qualitative in-depth interviews and quantitative survey questionnaires will be administered online or in-person, depending on COVID-19–related factors and feasibility. Data from these sources will be analyzed using thematic analysis in NVivo for qualitative data and regression models in Stata (StataCorp) or R (R Foundation for Statistical Computing) for quantitative data and triangulated to examine how they expand upon one another and explore both intended and potential unexpected outcomes of the intervention, aiming to improve the credibility, integrity, and utility [32] of the research to multilevel policy institutions in Vietnam and internationally. The documentation of lessons learned will be conducted and shared with Vietnam's Ministry of Health and the public for adoption and further scaling up; upon project completion, the models developed and refined in dMOM will inform a national mHealth project led by the Ministry of Health, representing a scaling of components of the dMOM project to the country level.

During the evaluation phase, a smaller scalability study will draw on the data collected as part of all dMOM components and assess different scenarios associated with several scaling-up strategies. This study will identify factors that may facilitate or constrain effective and ethical scaling of dMOM models and will investigate the potential of the private sector as a financing mechanism to sustain a broader mHealth intervention for MNCH.

Results

The dMOM study was funded by the IDRC in November 2021, cofacilitated by the Ministry of Health, and is being coimplemented by provincial health departments in the 2

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mountainous provinces of Thai Nguyen and Dien Bien. The intervention received approval from and completed a memorandum of understanding with Vietnam's Ministry of Health in May 2022. Phase 1 (literature review and updating, adapting, and expanding intervention components) was initiated in May 2022, and phase 2 (scoping study and rapid ethnographic fieldwork) is planned for December 2022. The entire study is expected to be complete at the end of June 2025.

Discussion

Expected Findings

This paper describes the protocol for adapting and exponentially scaling the mMOM intervention *qualitatively* through the addition of novel technological components (i.e., mobile app and the use of AI chatbots); *quantitatively* through its expansion over a broader geographical area; and in its *scope* through deep, ongoing engagement with the Ministry of Health toward the replication of the dMOM models at the country level. This protocol details the expansion of the pilot mMOM SMS text messaging intervention in 8 communes with 900 participants to an SMS text messaging, mobile app, and AI intervention in 71 communes reaching 9000+ participants.

This research will contribute to bridging current gaps in mHealth research and utilization in Vietnam, which were rendered even more salient by COVID-19 and exacerbated existing inequities in health access particularly for ethnic minority populations and people in rural/remote areas globally [16-20]. Our protocol and study aim to respond to research calls for virtual and digital health programming to support perinatal mental health and broader MNCH in Vietnam through the evolving COVID-19 crisis and beyond [21]. Through the dMOM intervention's development, implementation, and evaluation of a mobile app for MNCH amid COVID-19, the project aims to contribute to urgently needed evidence on the application of digital health during the pandemic context, particularly in maintaining health access and promoting health equity among women, ethnic minority populations, remote communities, and other intersecting populations globally who are the most vulnerable to the negative socioeconomic and health impacts of pandemics.

Limitations

Although this study will be conducted within a broader geographical area than the pilot mMOM study, it will only involve ethnic minority populations who are in contact with the health system, as commune health workers will only recruit women who present at the health center. As such, it is possible that the project may exclude members of the target population who are not known to health workers due to extremely remote residence, poverty, or language barriers.

Study Implications

The outcomes and findings of the dMOM study will be relevant to future research on the applicability and use of mHealth and AI for MNCH for ethnic minority communities and for improved MNCH and health-seeking behaviors among other structurally marginalized populations and populations living in remote settings.

Conclusions

This paper outlines the development of the dMOM intervention and its planned expansion and scaling amid the COVID-19 context. The dMOM research outcomes will generate important empirical evidence on the effectiveness of leveraging digital health to address intractable MNCH inequities among ethnic minority women and women living in remote areas and low-resource settings in Vietnam, build models for utilization and replication in country-level mHealth projects, and provide critical information on the processes of adapting mHealth interventions to respond to COVID-19 and other future pandemics.

Data Availability

Data sharing is not applicable to this article, as no data sets were generated or analyzed during the current protocol study.

Conflicts of Interest

None declared.

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Abbreviations

AI: artificial intelligence
BCC: behavior change communication
IDRC: International Development Research Centre
IEC: information, education, and communication
mHealth: mobile health
MNCH: maternal, newborn, and child health
PHAD: Institute for Population, Health and Development
SFU: Simon Fraser University

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Protocol

mHealth to Improve Experience, Adherence to Pharmacological Treatment, and Positive Mental Health in Patients Diagnosed With Femur Fractures: Protocol for a Quasi-Experimental Study

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Abstract

Background: Considering the prognosis of femur fractures worldwide, the ageing of our society, and the problems in adherence to treatment found in these patients, it is believed that mobile health can have a positive impact on the process and quality of care.

Objective: We aim to evaluate the effectiveness of a pharmacological educational nurse intervention with Myplan app with regard to knowledge, adherence to pharmacological treatment, and positive mental health of patients with femur fractures.

Methods: A nonrandomized, quasi-experimental study will be carried out with a pretest-posttest control group. It will include 278 older patients diagnosed with femur fractures, with a Glasgow Coma Scale of 15 and access to mobile devices. Patients with psychological pathologies and cognitive impairment or patients treated in isolation will be excluded. Study variables are as follows: sociodemographic variables (AdHoc Form), patient experience (Patient Experience Questionnaire-15), adherence to pharmacological treatment (Morisky-Green questionnaire), and positive mental health (Positive Mental Health questionnaire). The measurements will be taken 24 hours after admission, upon discharge, and 25 days after discharge.

Results: Enrollment commenced in October 2022. Data collection will be completed in April 2023.

Conclusions: The results of this study will offer evidence of the effectiveness of a pharmacological educational nurse intervention by means of a free smartphone app. If its efficacy is demonstrated and the results are acceptable, it could mean an improvement in the care of patients with femur fractures, and this technology could be used to guide other training interventions in patients with other pathologies.

Trial Registration: ClinicalTrials.gov NCTT05669040; https://clinicaltrials.gov/ct2/show/NCTT05669040

International Registered Report Identifier (IRRID): DERR1-10.2196/45856

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(JMIR Res Protoc 2023;12:e45856) doi:10.2196/45856

KEYWORDS

education; patient experience; medication adherence; mental health; nurse; mHealth; mobile health; protocol; prognosis; pharmacological treatment; femur fracture; femur; diagnosis; quality of care; care; psychological; efficacy; training; pathology

Introduction

Overview

The estimated amount of femur fractures by 2050 is 6 million worldwide. Due to the increase in life expectancy, the incidence of femur fractures in people older than 65 years is close to 4-6 cases per 1000 inhabitants per year in Spain, Catalonia, being the region with the highest incidence of femur fractures [1]. It has been shown that the population experiencing this type of fracture exhibits a high degree of complexity, causing an increase in morbidity, mortality, and subsequently, health care expenditure [2]. It is, therefore, necessary to establish an adequate health care quality, where the affectivity of the treatment and the safety of the patient are guaranteed [3].

There is evidence of the relationship between a good patient experience and both direct and indirect clinical results, which leads to better prognosis, faster discharges, and lesser use of medication [4,5]. Another important factor is the relationship between positive mental health and capacity for self-care. The more positive patients' mental health is, the better their ability for self-care will be, and vice versa [5-7]. Another key factor, as the literature indicates, is health education for patients regarding their illness and its treatment. The more knowledge they have, the better their health and ability for self-care will be [8,9]. We usually find education studies focused on patients diagnosed with chronic diseases [10], but we rarely find studies that evaluate the effectiveness of education and information in relation to medication adherence.

When informing patients about medication, the term "10 rights" [11] regarding the safe administration of medication should also be mentioned—inform the patient about the medication that is being used, how it must be taken, what it is being used for, and what secondary effects or adverse reactions may derive from its use. The importance of this point stands out in two aspects: (1) the patient's health education regarding all the medications they take, so they understand everything related to the care of their illness; and (2) the potential detection of errors on the patient's part, acting as the last filter just before the administration of the drug by the nurse. This point is so important that not informing patients is considered a medication error in some studies [12].

Prescription of medication is one of the most common interventions in clinical practice [13], and it has a significant repercussion in the time used by nurses in administrating medicines, which takes up a substantial part of their workday. Cleveland Hospital applies one of the innovative strategies in administration of medicines, named the Ask3/Teach3 initiative [14]. In this strategy, the patient is informed about the medicine, but its secondary effects are also inserted into that same conversation with the patient.

Studies in medical literature describe that the introduction of educational tools related to medication in health care organizations is linked to a decrease in hospitalization, admissions into emergency rooms, and readmissions [15]. Patients nowadays have a very close relationship with technology, as has been shown in various published studies that prove the use of apps improves health management [16,17]. Mobile health (mHealth) has opened the doors to new forms of relationships between nurses and patients, providing numerous benefits for both parties with regard to accessibility and optimization of time in office and improvement of therapeutic adherence. The mass use of web-based devices by patients older than 65 years (ie, the population sector with the highest probability of requiring medical care) has had a very positive influence in this regard [18].

It is described that there is a lack of adherence due to the complexity of the treatment, its secondary effects, lack of trust in the treatment, and the relationship between health care professionals and patients [19]. The lack of adherence can lead, firstly, to a lack of treatment effectiveness, and secondly, to a potential increase in the secondary effects of the treatment, a problem that affects 50%-60% of patients with chronic diseases. It is estimated that 20%-50% of patients do not take their medication as prescribed [20]. The index of medication adherence in these patients is only 50% [21]; therefore, improving medication adherence would result in a decrease in morbidity, mortality, and expenditure in medical care [22]. Treatment adherence is also linked to patients' emotional well-being, the mental strength with which they face the situation, and ultimately, their level of positive mental health [23,24]. It has been observed that interventions are needed to improve lack of treatment adherence [25]. No studies have been found in medical literature on the subject of pharmacological adherence and patients with femur fractures.

One of the tools developed to complement patient education is mHealth, described by the World Health Organization (WHO) in its 2015 Global Observatory for Health report (reviewed in 2016) [26] as the use of mobile devices, such as smartphones, personal digital assistants, and patient monitoring devices, in medical practice and public health.

The WHO believes that mHealth can contribute to achieving coverage of health care at a global level, making it accessible to remote populations and communities with health service deficits. This is one of the strategic lines of the government of Catalunya. At the same time, the WHO recognizes that it is not very costly to supply these areas with mobile technology infrastructures [27].

Based on this evidence, this study proposes to respond to the needs raised so far, with the development and evaluation of a pharmacological educational nurse intervention based on a smartphone app (MyPlan app) and with regard to knowledge,

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pharmacological treatment adherence, and positive mental health of postoperative patients with femur fractures.

Objectives

The primary objective of this study is to evaluate the effectiveness of a pharmacological educational nurse intervention with MyPlan app in the experience of medical assistance, pharmacological treatment adherence, and positive mental health of patients with femur fractures at the Hospital Clínic de Barcelona. We also intend to compare the pre-post intervention effectiveness in the study variables 24 hours after admission, upon discharge, and 25 days after hospital discharge.

Methods

Study Context

This study aims to test the nurse intervention with the added support of mHealth by creating personalized medical care and a 3-stage follow-up plan to improve the patient's experience, adherence, and positive mental health.

Scope of Study

This project estimates the application of this approach in the Institute of Traumatology and Orthopedics of the Hospital Clínic de Barcelona between October 2022 and April 2023.

Design

This protocol describes a nonrandomized, quasi-experimental study with a pretest-posttest control group.

Participant Selection and Recruitment

Eligible participants will be identified in the hospitalization unit through the observation of a census by the principal investigator (PI) with a nonprobabilistic sample (according to the patients' willingness to participate).

The sample calculation will be made by taking into account the total number of patients treated in the traumatology service for a femur fracture diagnosis during 2020. Approximately 494 patients are admitted annually with a femur fracture diagnosis. GRANMO software (version 7.12; IMIM Medical Informatics Unit) will be used with a 95% CI and a maximum indeterminacy of P=.5, accounting for a 15% loss, for a final recommended sample of 278 subjects to ensure a sufficient sample size for the analysis of the different variables.

Inclusion and Exclusion Criteria

The criteria for inclusion are as follows: (1) femur fracture diagnosis, (2) 18 years of age or older, (3) knowledge of Spanish language, (4) 24-hour admission into the traumatology unit, (5) awareness level of 15 on a Glasgow scale, (6) access to mobile devices, (7) ability to participate in the pilot study, and (8) ability to provide written informed consent personally or to obtain consent via a legal representative. Criteria for exclusion are as follows: (1) presence of psychological pathologies or cognitive impairment and (2) treatment in isolation during hospitalization.

Ethics Approval

This study has been approved by the Regional Health Research Ethics Committees of the Hospital Clínic de Barcelona (HCB/021/0341).

All questionnaires are confidential, and all patients must sign the informed consent according to the current Spanish legislation. In compliance with the current law on data protection and guarantee of digital rights, no data will be shared without express authorization, preserving patients' confidentiality and anonymity of their identity at all times. Their participation will be voluntary, and their anonymity will always be preserved. This will be achieved by anonymizing the names or any personally identifiable information.

Intervention

The final app is named MyPlan. it is based on a platform developed by the nonprofit organization Trilema, with the support of Amgen laboratory. The app is user-friendly and intuitive, and it allows patients to see their updated medication plan on their mobile phones at all times in a safe and private environment (Figure 1). One of its main functions is the daily (Figure 2) and monthly (Figure 3) calendar, and it also features reminders and allows adding programmed activities (eg, medication times, check-ups, and appointments). MyPlan is also a tool that supports treatment, allowing patients to plan and validate individual medication intake (Figure 4).

To ensure that the intervention works as expected and patients are able to access the app, the PI has a private area in MyPlan (Figure 5), where every individual patient is registered with a personal username and password. The PI will also add their individual medication plans so that patients are able to view them on the app.

The nursing pharmacological education intervention will be performed by a single nurse (an employee of Hospital Clínic de Barcelona) and the PI. This intervention consists of 4 sessions (Figure 6). First, the nurse will introduce themselves to the patient as the professional who will carry out the training session. Subsequently, patients will be informed about the intervention and its objectives. They will be introduced to MyPlan app, which will be downloaded on their smartphone, and a username and password will be generated for them (30 minutes). Then, the prescribed treatment and any questions from the patient about it will be discussed and reviewed (20 minutes). Finally, the session itself will be evaluated (10 minutes), using the Morisky-Green scale, as well as the PI's review of the patient's use of MyPlan during the admission, making sure they have pressed "OK" at the time they were taking the medication according to the prescription.

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Figure 1. MyPlan app; medication plan.

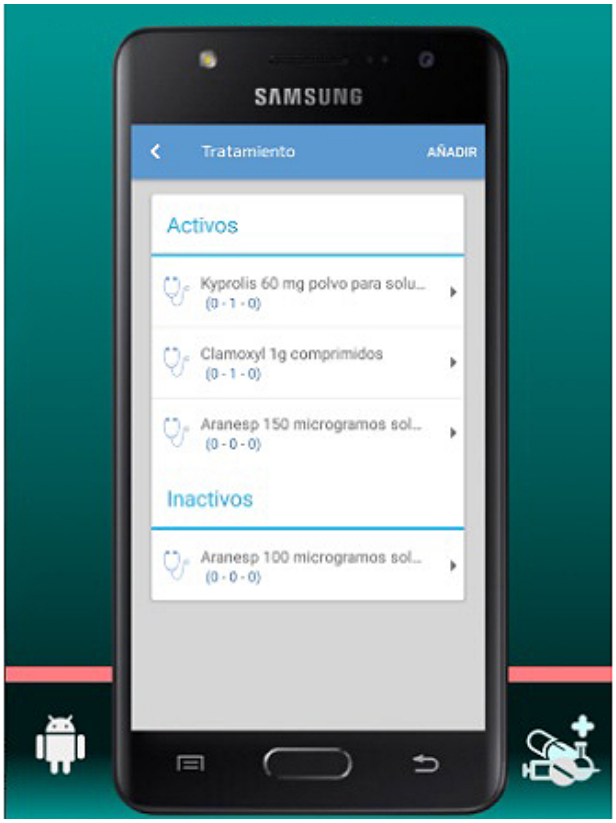


Figure 2. MyPlan app; daily calendar.



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Figure 3. MyPlan app; monthly calendar.

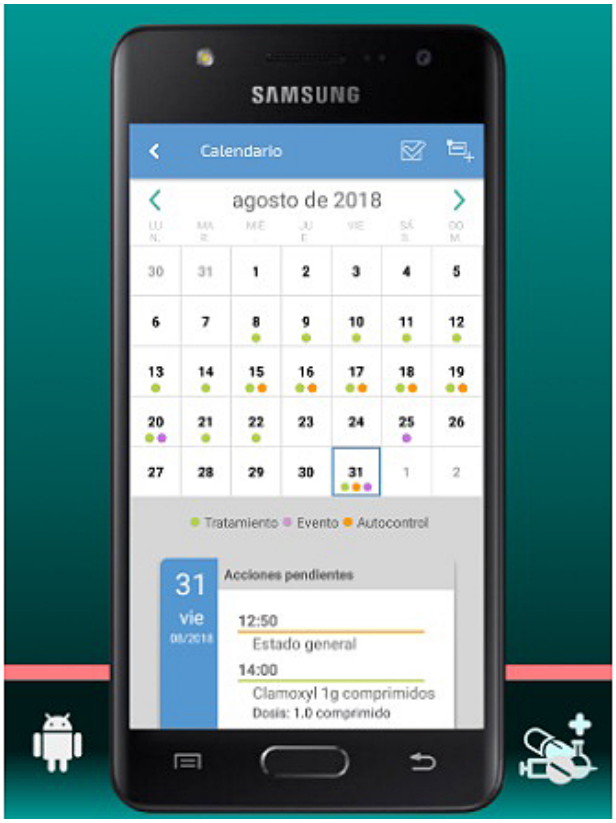


Figure 4. MyPlan app,; individual medication.



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Figure 5. MyPlan app; private area.

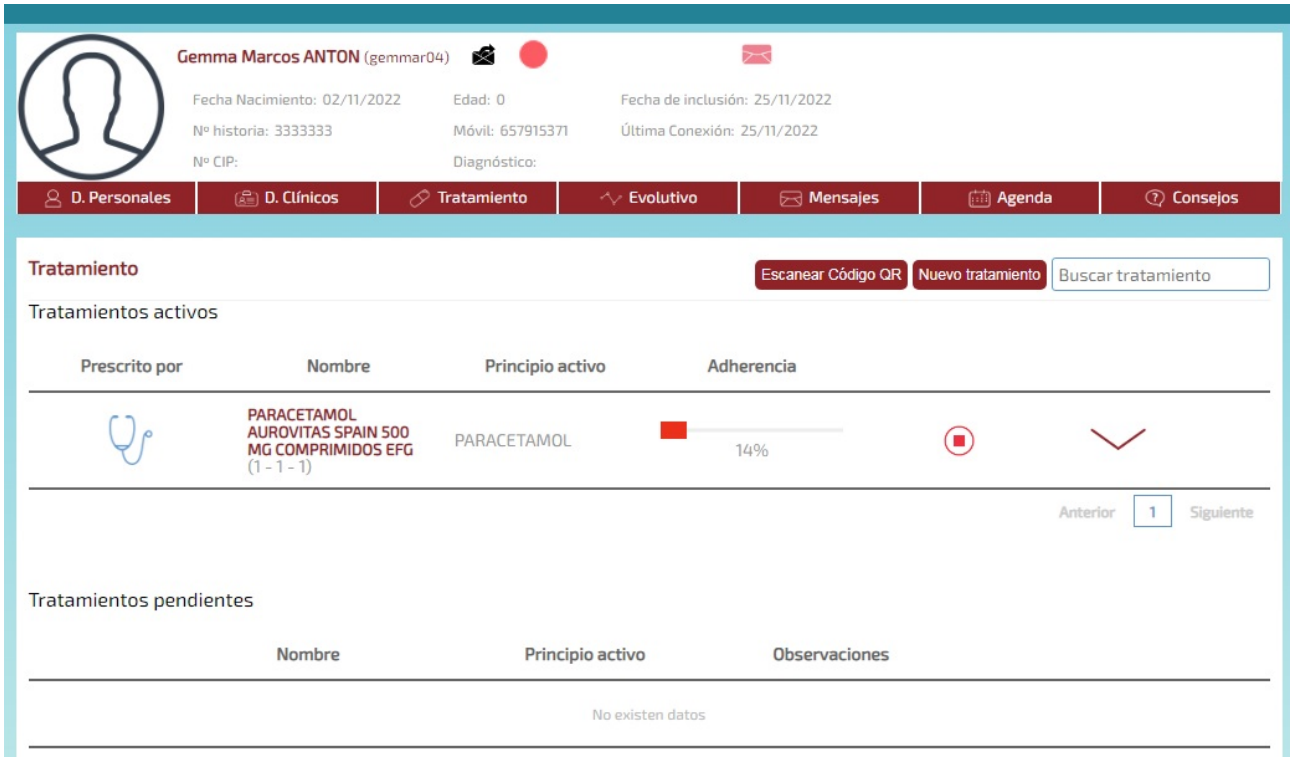
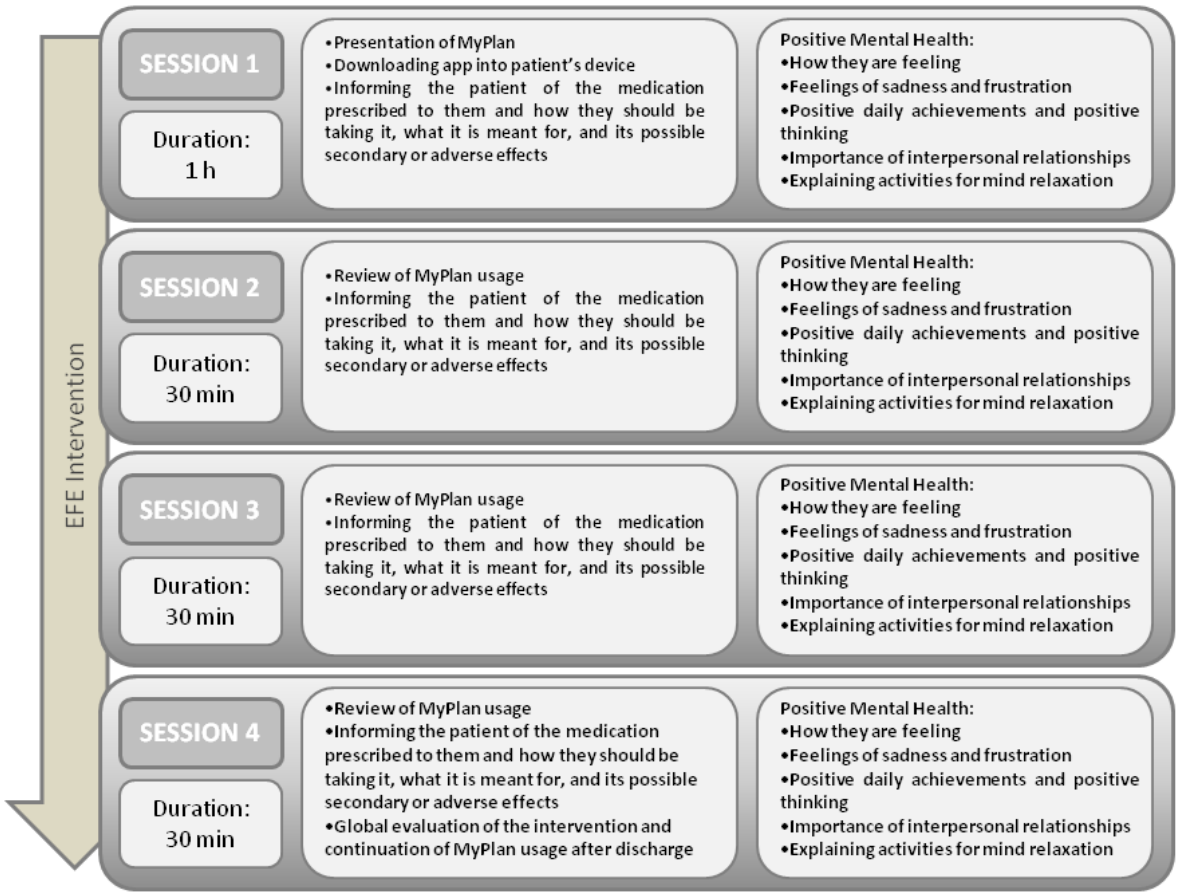


Figure 6. The nursing pharmacological education intervention (EFE).



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Positive mental health will be promoted in every session by giving patients the opportunity to explain how they are feeling, telling them that it is normal to feel sadness and frustration during hospitalization, but also encouraging them to think about the small daily achievements like decrease in pain or improvement in mobility. If the negative feelings persist, the patient will need to ask for help. The nurse will constantly encourage the patient to try to maintain a positive mindset and think that the final outcome will be good. The patient must value the positive things they have in life and cultivate interpersonal relationships. They will receive help in trying to find activities that will help them achieve a state of mental relaxation. This action will be evaluated by using the Positive Mental Health questionnaire.

The patient's experience will be measured with the Patient Experience Questionnaire-15. These tools have been added into MyPlan, making it agile to fill them out and export their data.

Procedure

Following the inclusion and exclusion criteria defined in the study, the patient will be requested to answer the different questionnaires described in the "measurement tools" section.

The PI will download the MyPlan app for the patient and explain its function to them. The PI will also manually transcribe the treatment that has been prescribed for the patient's hospitalization time. The medication that must be administered to the patient and the medication schedule will be added into the app. The PI will also carry out a basic training session for each medicine prescribed to the patient, including what the drugs are for and their possible adverse effects.

During hospitalization, the same procedure will be repeated every day from Monday to Friday. A minimum of 4 sessions, as described above, will be held to educate the patient and improve their knowledge in pharmacology and autonomy upon discharge. The PI will maintain an individual registry in a Microsoft Excel spreadsheet that will contain all adverse drug reactions notified in the patient's clinical history. These data will be extracted from the information in the Systems Applications and Products in Data Processing bed chart (there is a shortcut icon for adverse drug reactions notifications), which is filled in by the medical professionals in charge of any given patient during hospitalization when applicable. As soon as the patient has been deemed fit to be discharged, the treatment prescribed for the time after discharge will be explained to them using the app (we will restrict the explanations to those pertaining to the treatment specified in the discharge report). It will be explained to them that they can use the app during the 30 days following discharge, as long as their primary care doctor does not make modifications to the treatment. For this reason, the patient's history will be reviewed daily by the PI to make sure there have been no consultations that have resulted in a change in the medication; 25 days after discharge, the PI will contact the patient via the MyPlan app to ask them to fill out the questionnaires and remind them that the study will end 5 days later (ie, 30 days after discharge). A message will be sent to the patient via the app 30 days after discharge to thank them for participating in the study, and their access to the app will be blocked, considering that the intervention has concluded.

Demographics and Baseline Functioning

Background data about the participants will be collected in the first session of the nursing pharmacological education intervention with the objective of evaluating any significant differences in the results after completion of the test. This background data will include age, gender, nationality, level of education, cohabitation status, caregiver, treatment, time of hospitalization, number of previous hospitalizations, evaluation of own health, and adverse effects.

Pilot Study

A pilot study will be carried out for the duration of a month with 20 subjects. The objective will be to evaluate the questionnaires' complementarity, clarity, and understandability. The patients selected for the pilot study will meet the criteria for inclusion. Once the pilot has concluded, modifications to the questionnaires will be made if necessary. The possibility to create a leaflet for the handling of the MyPlan app and the time frame for patient assistance via the app will be discussed.

Measurement Tools

The following measurement tools have been validated:

- Patient Experience Questionnaire-15, adapted and validated for Spanish language [28,29]: this questionnaire will allow us to explore patients' perception with regard to the educational process and their participation in the decision-making processes during their hospitalization.
- Morisky-Green Questionnaire [30]: this questionnaire will allow us to evaluate patients' treatment adherence. It is comprised of 4 binary questions that will reflect the degree of compliance in patients as well as information regarding the causes of noncompliance.
- Positive Mental Health Questionnaire [31]: this scale evaluates mental health from a positive viewpoint. It is comprised of 39 items, which are distributed across 6 categories: personal satisfaction, prosocial attitude, self-control, autonomy, problem-solving and self-actualization, as well as interpersonal relationship skills. Their measurement is made via Likert-type answers with the following range: "always or almost always," "frequently," "sometimes," and "never or almost never." It is validated among the general population in favorable psychometric values, with global reliability of 0.88 and variance of 45%.
- Forms for collection of sociodemographic and clinical variables.

Data Analyses

The statistical analysis will be made using Stata (version 15; StataCorp). It will consist of obtaining the differences between different data collections (24 hours after admission, upon discharge, and 25 days after discharge) for every variable considered in this project as a performance measurement of the intervention. Efficacy, effectiveness, and efficiency indicators will be based on the study of change from before the intervention to after the intervention (ie, before the intervention; upon discharge; and the last control, 25 days after discharge at home). These will be based on relative indexes (ie, change percentages) and reliable change indexes (ie, Jacobson-Truax coefficient as

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well as alternative indexes, such as Tsu, Hagerman-Arrindell, and Speer-Greenbaun indexes). The difference in quantitative measurements in different phases will be based on factorial analysis (ANOVA). These will provide the main effects of change for all different phases. They will also provide the reliability intervals of the averages and the differences of proportion as measures to be assessed, as well as that of standardized indexes, such as Cohen *d*.

Results

Enrollment was initiated in October 2022 and will be completed in April 2023.

The main contribution of this protocol is a detailed description of a nursing intervention with the support of a smartphone app that will generate knowledge about patients' experiences, their adherence, and their positive mental health. The protocol is registered with ClinicalTrials (NCTT05669040).

Discussion

Expected Findings

One of the strong points of this study is the linear evaluation of the intervention (ie, 24 hours after admission, upon discharge, and 25 days after discharge), which can demonstrate the effectiveness of assisting the patient throughout the process. Another important finding may be related to the impact of the intervention on the quality of care because it could contribute to early detection and prevention of medication errors, minimizing both the associated complications that these patients may have and hospital re-admissions. Finally, another potential strength of the study is that the intervention can be extrapolated to different specialties in the hospital, which would contribute to the improvement of care for all patients.

The main result will be to generate a change in the medication administration process, implementing the nursing pharmacological education intervention. The secondary result will be related to the patient's hospital experience, the increase in treatment adherence, and the improvement of positive mental health. The expectation is to generate patient empowerment and a reduction in the number of consultations and hospital admissions derived from some adverse effects of the pharmacological treatment.

Potential Limitations and Implications

The main limitation of this study is that the sample is not randomized. Another limitation presented is the selection of patients included in the study according to the level of awareness and cognitive capacity as well as the ability to understand and use the MyPlan app.

The training nurse's time availability to train and educate patients in their pharmacological treatment is another limitation to take into consideration.

Conclusions

The results of this study will offer evidence of the effectiveness of a nursing pharmacological educational intervention that uses a free smartphone app. If its efficacy is demonstrated and the results are acceptable, it could mean an improvement in the care of patients operated for femur fractures and guide other training interventions in patients with other pathologies.

Acknowledgments

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Data Availability

The data confidentiality and availability disclaimer is included in the information sheet that is distributed to study participants and is explained to them prior to signing the informed consent form.

Authors' Contributions

All authors contributed to the design and writing of this article, and they all read and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

PI: principal investigator
mHealth: mobile health
WHO: World Health Organization

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Protocol

A Technology-Enhanced Intervention for Violence and Substance Use Prevention Among Young Black Men: Protocol for Adaptation and Pilot Testing

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Abstract

Background: Black boys and men from disinvested communities are disproportionately survivors and perpetrators of youth violence. Those presenting to emergency departments with firearm-related injuries also report recent substance use. However, young Black men face several critical individual and systemic barriers to accessing trauma-focused prevention programs. These barriers contribute to *service avoidance*, the exacerbation of violence recidivism, substance use relapse, and a revolving-door approach to prevention. In addition, young Black men are known to be digital natives. Therefore, technology-enhanced interventions offer a pragmatic and promising opportunity to mitigate these barriers, provide vital life skills for self-led behavior change, and boost service engagement with vital community resources.

Objective: The study aims to systematically adapt and pilot-test Boosting Violence-Related Outcomes Using Technology for Empowerment, Risk Reduction, and Life Skills Preparation in Youth Based on Acceptance and Commitment Therapy (BrotherlyACT), a culturally congruent, trauma-focused digital psychoeducational and service-engagement tool tailored to young Black men aged 15-24 years. BrotherlyACT will incorporate microlearning modules, interactive safety planning tools for risk assessment, goal-setting, mindfulness practice, and a service-engagement *conversational agent* or chatbot to connect young Black men to relevant services.

Methods: The development of BrotherlyACT will occur in 3 phases. In phase 1, we will qualitatively investigate barriers and facilitators influencing young Black men's willingness to use violence and substance use prevention services with 15-30 young Black men (aged 15-24 years) who report perpetrating violence and substance use in the past year and 10 service providers (aged >18 years; any gender; including health care providers, street outreach workers, social workers, violence interrupters, community advocates, and school staff). Both groups will be recruited from community and pediatric emergency settings. In phase 2, a steering group of topic experts (n=3-5) and a youth and community advisory board comprising young Black men (n=8-12) and service providers (n=5-10) will be involved in participatory design, alpha testing, and beta testing sessions to develop, refine, and adapt BrotherlyACT based on an existing skills-based program (Achieving Change Through Values-Based Behavior). We will use user-centered design principles and the Assessment, Decision, Administration, Production, Topical, Experts, Integration, Training, and Testing framework to guide this adaptation process (phase 2). In phase 3, a total of 60 young Black men will pilot-test the adapted BrotherlyACT over 10 weeks in a single-group, pretest-posttest design to determine its feasibility and implementation outcomes.

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Results: Phase 1 data collection began in September 2021. Phases 2 and 3 are scheduled to start in June 2023 and end in September 2024.

Conclusions: The development and testing of BrotherlyACT is a crucial first step in expanding an evidence-based psychoeducational and service-mediating intervention for young Black men involved in violence. This colocation of services shifts the current prevention strategy from telling them *why* to change to teaching them *how*.

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KEYWORDS

youth; violence; adolescent health; mindfulness; digital health; usability; Black; African American; men; mobile app

Introduction

Background

Youth violence and substance use co-occur as a public health double threat. Youth violence encompasses a range of behaviors, including dating violence, actual or threatened violence, physical fighting, web-based and school bullying, threats and assault with weapons, homicide, and firearm-related and gang-related violence [1,2]. Similarly, substance use is linked to violent incidents, even as persistent substance use (of marijuana and alcohol) is associated with youth violence perpetration and victimization [3,4]. Although the evidence is conflicting [4,5], youth violence and substance use share transdiagnostic risk and protective factors [4,6] and underlying mechanisms that cross-cutting preventative measures can address. Moreover, these socially costly issues are linked to multiple adverse physical, social, and health effects, such as low quality of life, subpar academic and social functioning, mental health disorders, and suicide risk [4].

Young Black men and boys from disinvested communities are disproportionately survivors, perpetrators, and witnesses of youth violence and homicide [7-9]. Recent Centers for Disease Control and Prevention data reports homicide as the primary cause of death for Black boys and men (aged 10-24 years), and firearms were involved in 94% of these incidents [9-11]. During the pandemic, firearm homicide rates in the United States rose to its highest level since its peak in 1994 [12]. Black boys and men aged 10 to 44 years saw the largest increase in these adjusted rates from 2019 to 2020, followed by Native American individuals, aged 25 to 44 years [7,12]. Consequently, Black youth are 14 times more likely and Hispanic youth are 3 times more likely than White youth to die from firearm-related violence [12].

More than 700,000 urban youths (aged 10-24 years) present to emergency departments (EDs) each year with nonfatal assault-related injuries [4,13,14]. Approximately 20% of these youths report substance use within 3 hours of an assault-related injury [3,14,15]. Despite this, service gaps continue to hamper violence and substance use prevention efforts for underserved, urban, and low-income youth. Outside the juvenile and criminal justice systems, racial and ethnic minority youth report critical barriers to obtaining behavioral health services across the continuum of prevention, treatment, and recovery. These barriers include but are not limited to neighborhood disadvantage, racism, homelessness or temporary housing, unemployment, discrimination, peer and gang pressures, transportation issues, program fees, the lack of culturally relevant services, and competing demands on time to attend clinic or group-based rehabilitation sessions [16-18].

Similarly, violence prevention programs in hospital EDs, schools, juvenile justice facilities, child welfare systems, faith-based and street outreach initiatives continue to have substantial wraparound effects in reducing violence [19,20]. However, in resource-limited communities, these programs lack 24/7 staff coverage, follow-up services, and trauma-informed training and report high employee turnover [16-18,21]. Furthermore, injured young Black men perceive hospital violence intervention programs—and other formal institutions—as places of interface with law enforcement and thus avoid using these services [16,22-24], even though EDs are increasingly recognized as a critical intervention venue for youth at risk for future violent injury [4].

Similar to contexts where these services exist, sociostructural barriers can also impede youth willingness to use them. These barriers include and are exacerbated by experiences of police bias and violence, treatment stigma [16,17,25-27], racial trauma, and a historic mistrust of legal and medical systems linked to the systemic discrimination and overt criminalization of Black men and boys [16,28-30]. In addition, the language (and culture) of formal therapy centering on Western-centric curricula [31] and gender norms that frame help-seeking as a *weakness* have also been identified by young Black men as impediments to service use despite the high prevalence rates of trauma exposure among these underserved groups [32,33].

These barriers have created substantial service gaps [17]. In addition, they have exacerbated treatment inequities, leaving young Black men involved in violence in underserved communities to adopt ineffective coping techniques, such as service avoidance or *opting out* [22]. Service avoidance takes the form of deliberate attempts to avoid or disengage from formal treatment or rehabilitation programs perceived to be associated with *feds* or that place them *in the system* [22], whereas *opting out* from preventative programs can manifest as early dropouts, noncompliance, nonparticipation, tardiness, and absenteeism even when the court system mandates program completion. Consequently, persistent service-avoidant behaviors contribute to violence recidivism, substance use relapse, and a revolving-door approach to prevention. Therefore, improving youth access to and trust in existing violence and substance use prevention interventions is critical.

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Technology-Enhanced Interventions to Reduce Barriers to Co-occurring Violence and Substance Use Prevention

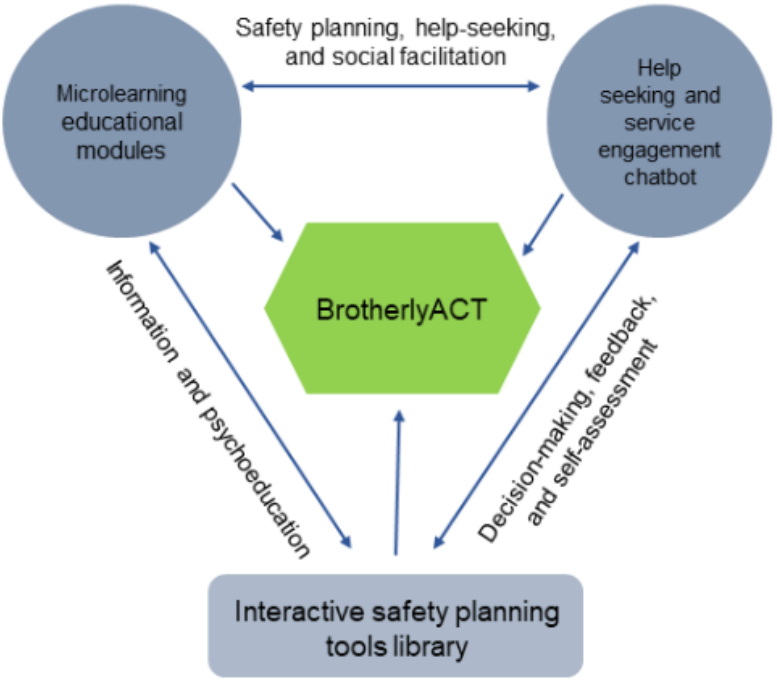
Technology-enhanced interventions can empower underserved and low-income youth to overcome some of these barriers [18]. Studies show that young Black men favor digital interventions as digital natives in a *tech-saturated* world [34-37]. Even after controlling for age, parent education, and family composition (single vs 2-parent households), Black youth have higher cell phone ownership rates and internet use (ie, hours per day) than Hispanic and White adolescents [36]. Therefore, technology-enhanced interventions can simultaneously mitigate these barriers and broaden the access to trauma-focused therapies. From a prevention science standpoint, engaging at-risk young Black men in this digital landscape—by meeting them where they are—is a promising and pragmatic approach to early prevention of substance-related violence [37-39]. This strategy can potentially reduce service avoidance while boosting the availability, accessibility, and personalization of evidence-based interventions [37-39]. Notably, technology-enhanced interventions can serve the "treatment curious" (those at early risk who have not sought out formal services but who can benefit from a low-stakes digital tool that highlights the risks and consequences of youth violence) and the "treatment veterans" (or returning citizens who are chronically involved *in the system* and familiar with violence and substance use services). Innovative public health and equity-focused interventions promoting health equity and positive service engagement for at-risk and underserved young Black men are needed to address the gaps and barriers identified previously.

This study aimed to systematically adapt and pilot-test Boosting Violence-Related Outcomes Using Technology for Empowerment, Risk Reduction, and Life Skills Preparation in Youth Based on Acceptance and Commitment Therapy (BrotherlyACT), a culturally congruent, trauma-focused digital intervention tailored to Black boys and men aged 15 to 24 years. BrotherlyACT will incorporate microlearning modules, interactive safety planning tools for risk assessment, goal-setting, mindfulness practice, and a service-engagement *conversational agent* or chatbot to connect young Black men to relevant services.

Overview of BrotherlyACT

To address these gaps and barriers, we developed a protocol for adapting and pilot-testing BrotherlyACT. It is envisioned as a multilevel, multicomponent, web-delivered, and app-delivered intervention to promote psychoeducation, safety planning, and service-engagement self-efficacy to reduce the risk and effects of co-occurring youth violence and substance use among low-income Black boys and men (aged 15-24 years). BrotherlyACT will comprise three main components (as depicted in Figure 1): (1) microlearning psychoeducational modules (or brief lessons framed as learnable *life skills* in an interactive curriculum) organized around the 6 fundamental acceptance and commitment therapy (ACT) principles (intrapersonal focus); (2) a safety planning tools library with resources to facilitate risk assessment, goal-setting and tracking, and mindfulness practice (interpersonal focus); and (3) an SMS text messaging–styled service-engagement chatbot or *conversational agent* to promote help-seeking, self-advocacy, and access to a curated list of national and local violence and substance use prevention programs and services (interactional focus). The need for these three components emerged out of interest from young Black men and service providers working with teens involved in violence to help them (1) develop self-efficacy to practice help-seeking while accessing trusted services on their own, (2) create a supportive motivational climate for underserved youth to feel comfortable seeking help, and (3) identify safe people and resources in their communities.

Figure 1. Boosting Violence-Related Outcomes Using Technology for Empowerment, Risk Reduction, and Life Skills Preparation in Youth Based on Acceptance and Commitment Therapy (BrotherlyACT) components.



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Theoretical Rationale

BrotherlyACT is based on several theoretical and conceptual models. The intervention's psychoeducational modules will adapt an existing theory-driven and skills-based manualized intervention (Achieving Change Through Values-Based Behavior [ACTV]) with motivational, informational, and behavioral activation strategies [40-45]. These brief or microlearning psychoeducational modules will cover topics on help-seeking, substance use, conflict resolution, nonretaliation, healthy relationships, gun and gang refusal skills, mindfulness (putting a *brake* on emotional reactivity), and positive future orientation and coping.

The original ACTV curriculum comprises 5 modules designed for violence reduction with incarcerated men and women using group sessions [38-44]. In addition to feedback from young Black men and service providers, the other components of BrotherlyACT were informed by the Capability, Opportunity, and Motivation to Change Behavior model [46], which proposes 3 elements that are vital to sustainable behavior change: capability, opportunity, and motivation [46]. *Capability* refers to an individual's abilities and skills, such as physical, cognitive, or technical skills, and considers situational and background risk factors that precipitate youth violence. *Opportunity* refers to the presence or availability of resources and opportunities that enable the individual to engage in a particular behavior, such as access to information, social support, or resources, and practice self-direction and decision-making. *Motivation* refers to the individual's desire or willingness to engage in the behavior, which may be influenced by factors such as attitudes, beliefs, values, or goals. Capability and opportunity jointly influence motivation [46], contributing to lasting behavior change. Taken together, the Capability, Opportunity, and Motivation to Change Behavior model helped to clarify individual, community, and structural risk factors (eg, service avoidance and emotional avoidance) that may be targeted by BrotherlyACT.

We hypothesize that through improved behavioral and cognitive skills and service-engagement self-efficacies, BrotherlyACT can reduce key psychological avoidant mechanisms (emotional avoidance and service avoidance) and increase motivation, capability (eg, self-efficacy to create and use a safety plan), and opportunity (eg, knowledge about service options). These improved conditions will, in turn, reduce the risk and effects of violence and co-occurring substance use among low-income young Black men involved in violence.

ACTV Approach

ACTV is an evidence-based psychotherapy based on ACT [47-52]. ACT is a third-generation cognitive behavioral therapy (CBT) based on the philosophy of functional contextualism and Relational Frame Theory [53]. ACT differs from other CBT-based approaches because it is based on a unified model of human behavior change and psychological growth. It is focused on helping individuals develop a different relationship with their thoughts and emotions instead of trying to change them directly. For example, CBT aims to help individuals identify and change negative or irrational thoughts, whereas ACT holds that pain and discomfort are a fact of life—something we must become comfortable with if we wish to live a happy, fulfilled life. ACT aims to increase *psychological flexibility* or "the process of contacting the present-moment fully as a conscious human being and persisting or changing behavior in the service of chosen values" and reduce *emotional avoidance* (unwillingness or perceived inability to remain in contact with difficult internal experiences and efforts to delay gratification and live a value-based lifestyle) [47-52]. Therefore, ACT encourages flexibly responding with openness and acceptance of our thoughts and emotions rather than trying to directly change their form or frequency and then shifting our attention (with practice) to what is most important in our lives. Of note, >20 meta-analyses and >900 randomized trials, with 12,477 participants, have shown that ACT is effective for a wide range of target conditions, with effect sizes ranging from small to medium for depression, anxiety, substance abuse, and chronic pain and small to large effects for increasing psychological flexibility in general [53,54].

ACTV was developed by a coauthor (AZ) and has been rigorously tested in multiple randomized effectiveness trials, feasibility studies, and pilot studies in collaboration with the Iowa Department of Corrections [38-44]. A series of effectiveness trials compared ACTV with the traditional Duluth or CBT model. A 1-year postintervention comparison of community-based ACTV vs the Duluth and CBT models (widely used globally in rehabilitation programs for abusive men) found that ACTV significantly reduced new charges, domestic assault charges, and violent charges for men who were mandated to complete a domestic violence intervention program (N=3474) at 12 months after treatment [42]. In addition, this effect was maintained for both program completers and dropouts [40]. A recent 5-year survival analysis of ACTV participants corroborated a previous study with 1-year outcomes, showing ACTV participants being less likely to acquire new violent or domestic abuse charges at year 5 (χ^2_1=6.8, *P*=.009) but with no difference in general criminal charges between ACTV and Duluth or CBT participants (χ^2_1=0.3, *P*=.60) [40]. In addition, control participants acquired new charges faster than intervention participants [40]. Although effective for reducing partner and criminal violence, ACT (and ACTV) has not been adapted for cross-cutting violence and substance use prevention with at-risk youth or for digitally enhanced delivery.

However, trauma-focused therapies, such as ACTV, remain inaccessible to youth who are economically disadvantaged and belong to a racial and ethnic minority group (eg, Black and Latinx youth) [54]. These interventions are typically developed, adapted, and evaluated with White, high-income populations [55-57]. In addition, White youth who are involved in violence are more likely than their non-White counterparts to be diverted to rehabilitative therapy [58]. In comparison, young Black men who are involved in violence are substantially more likely to be transferred to more punitive alternatives (eg, transferred to adult court) or other forms of detention [58]. Interventions addressing these issues similarly use Western-centric theories for individualistic violence prevention and emphasize racial and socioeconomic distinctions between treatment facilitators,

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program curricula, and men referred to these programs, resulting in a *therapeutic mismatch* [31].

User-Centered Design for Technology-Enhanced Interventions

User-centered design (UCD) is a general term for design methodologies in which end users are involved in the iterative process to shape the design of an intervention and contexts for its implementation [59-61]. UCD strategies can be put into practice quite fast, enabling us to swiftly determine user needs and create appropriate interventions to address these needs.

UCD methods are important, as they can uncover new information that is not revealed by conventional techniques, improve user experience, and ensure that we obtain representative participant response to match a predetermined usability requirement. In addition, users develop a sense of ownership for the product [59]. Contextual interviews, think-aloud protocols, cognitive walk-throughs, semistructured cognitive interviews, and acceptability or feasibility surveys are some of the UCD techniques we will use with key stakeholders as we develop BrotherlyACT.

The development of BrotherlyACT using UCD principles reimplements the design and adaptation methodologies from our previous studies with young men who are involved in violence and affected by trauma [34,62]. In more recent studies, we have used UCD methods in the design of a mobile clinical decision support app for urinary tract infection in long-term care [63,64] and in understanding the usability and function of consumer-grade wearable devices [65].

Several iterations of BrotherlyACT will be produced and tested for usability. Early studies indicate a need for cross-cutting interventions for violence co-occurring with other risky behaviors. Young men in these studies confirmed the suitability of, and the potential to explore further, the use of digital methodologies as a primary prevention tool [34]. Participants listed the following as intervention *must-haves*: individualized feedback, compelling firearm injury testimonials, inspiring tales of other young men who have successfully avoided violence and substance use, humanlike chat capabilities, actual stories and violence-related testimonials, pictures and videos of people similar to them, and mechanisms to monitor behavior change. This feedback substantially informed the proposed BrotherlyACT intervention [34].

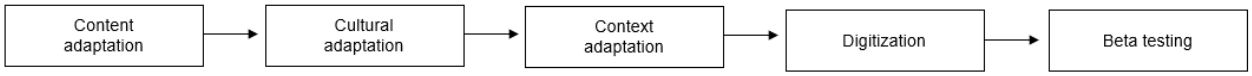
Methods

Overview

The development of BrotherlyACT will occur in 3 phases. In phase 1, we will collaborate with Black boys and men (aged 15-24 years) and service providers (aged >18 years; any gender) to identify social and structural barriers and motivators influencing youth violence and substance use prevention. Black boys and men (aged 15-24 years; n=25-30) and their service providers (n=10) will be recruited from clinical (pediatric ED) and community-based settings in the West and South sides of Chicago—2 areas with historically high violence burden and persistent economic disadvantages, but with much promise and a wealth of community-based programs [66-69]. Sessions will include participatory focus groups, in-depth one-to-one interviews, and wish listing activities (ie, listing intervention must-haves).

In phase 2, we will use content and cultural adaptations of the ACTV curriculum using the 8-stage Assessment, Decision, Administration, Production, Topical, Experts, Integration, Training, and Testing (ADAPT-ITT) framework [70,71]. Finally, in phase 3, we will assess the feasibility and acceptability of BrotherlyACT. Overall, 60 young Black men (not part of phase 1 or 2) will remotely pilot-test BrotherlyACT for 10 weeks to determine feasibility and implementation outcomes. An outline of the study stages is shown in Figure 2.

Figure 2. Outline of study phases.



Ethics Approval

All study phases have been approved by the Rush University Medical Center institutional review board (IRB; Office of Research Affairs number 21122902-IRB01). In addition, we have received recruitment-only IRB approval from the Stroger Cook County Hospital (study 22-087R). Each participant will provide informed consent before recruitment into the study and receive a copy of the signed form as a PDF. They will also be informed that their participation is voluntary and that they may withdraw from the study at any time. Furthermore, permission will be sought to audio-record and take notes during the interviews. All study data will be deidentified and kept confidential according to IRB protocols at designated study sites, with Rush IRB being the primary study site.

Study Design, Participants, and Recruitment

Phase 1—Risk and Needs Assessment

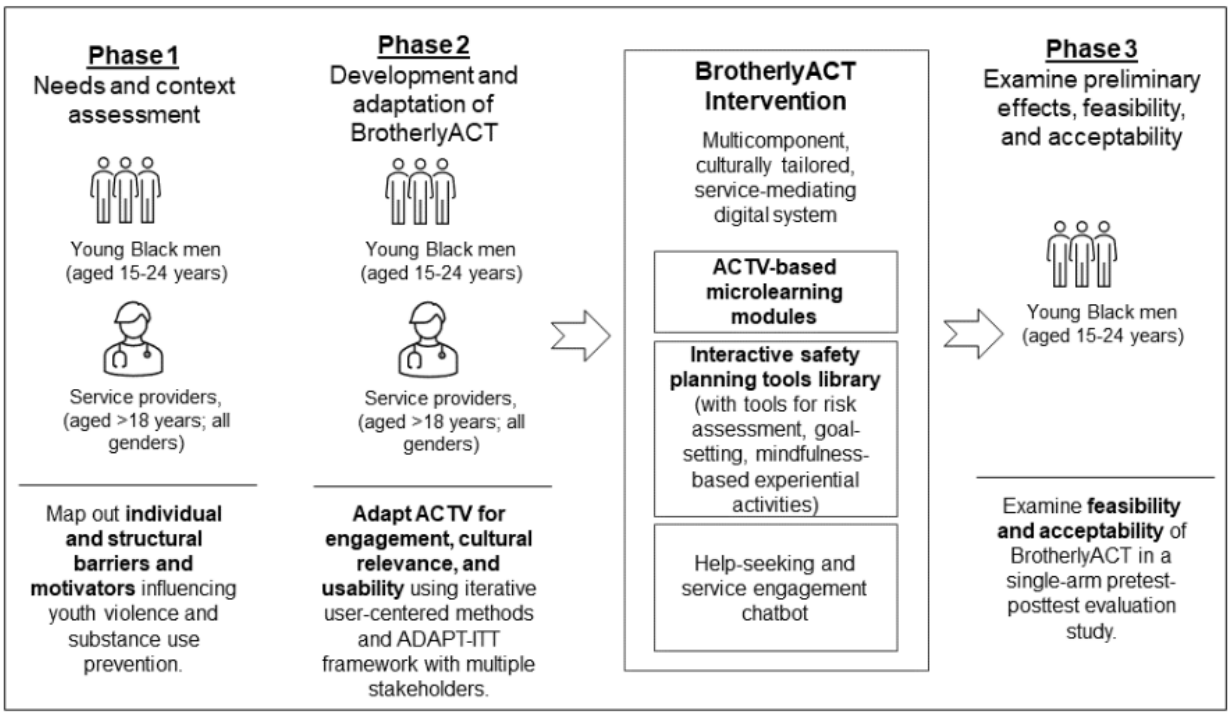
Overview

This phase will involve formative, qualitative research using individual web-based interviews and focus group discussions with key informants (young Black men and service providers). This needs elicitation phase will identify social and structural barriers and motivators influencing youth violence and substance use prevention services among Black boys and men (aged 15-24 years) and their service providers (including but not limited to health care providers, street outreach workers, social workers, violence interrupters, community advocates, and school staff). In separate focus groups and individual interviews, we will include community barrier mapping and graphic facilitation sessions (ie, displaying ideas expressed during meetings on a

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whiteboard with text and imagery). Young Black men and service providers will describe (1) sociostructural targets to improve young Black men engagement with violence prevention services, (2) culturally salient needs, (3) knowledge of existing resources (eg, where, how, and why young Black men seek assistance), and (4) preference for digital behavior change interventions. In addition, we will age-stratify all interviews (15-17 years and 18-24 years) to account for differences in risk taking, peer culture, developmental age, and self-identity. The service providers and young Black men will not interact in the same sessions. Instead, separate sessions will be scheduled for service providers so that young Black men may openly communicate their experiences and account for developmental, background, and age differences without bias. Sessions will be conducted in person, via phone, or via secure video chat (Zoom; Zoom Video Communications Inc). The outline of the study design is shown in Figure 3.

Figure 3. Outline of study design. ACTV: Achieving Change Through Values-Based Behavior; ADAPT-ITT: Assessment, Decision, Administration, Production, Topical, Experts, Integration, Training, and Testing; BrotherlyACT: Boosting Violence-Related Outcomes Using Technology for Empowerment, Risk Reduction, and Life Skills Preparation in Youth Based on Acceptance and Commitment Therapy.



Study Setting

Study sessions will occur concurrently, with Zoom, phone (phases 1 and 2), and in-person options for participation (phase 3). Only in Chicago, where the study researchers are based, will participants be able to undergo in-person procedures in pediatric EDs and community-based centers, if they prefer. We have chosen to start with young Black men in 1 major high-risk city (Chicago) to establish proof of concept before expanding to other cities with a high violence burden (Detroit, Baltimore, Camden, and Oakland) in the future.

Consent and Assent Process

Black boys aged 15 to 17 years will assent, and Black men aged 18 to 24 years will consent. Participants can electronically assent or consent on a Health Insurance Portability and Accountability Act–compliant e-consent platform. The informed e-consent form will include information about the study's aim, procedures, confidentiality, and risks and benefits of participation and the safety and risk mitigation protocols. Alternatives for contacting the study team (ie, text, calls, and emails) will accommodate participant needs and account for digital divides, internet bandwidth issues, and digital health equity concerns (eg, privacy and data safety concerns). We will not collect written documentation of youth assent and consent to safeguard the participants' confidentiality. We will waive parental consent as this study poses low risk, according to federal laws (45 Code of Federal Regulations 46), Section 116 (d) [72]. Waiving parental consent does not affect the rights and welfare of our participants. Low rates of young Black men enrollment when parental consent is mandated have impeded previous studies.

Moreover, young Black men with low risk (less substance use; little to no violent history) are oversampled when parental consent is mandated (individuals with high risk or great use of violence and substances are less likely to join owing to this reason). Waiving parental consent may reduce sampling biases and dishonest reporting by participants, as adolescent participants may fear their parents discovering their participation in the study. Ineligible participants will be redirected to the end of the survey, where they will find resources (eg, crisis helplines and suicide hotlines) to help young Black men obtain the needed services. In addition, once the e-consent form is submitted, participants can print or save a copy of the informed assent and consent form before moving on to the web-based survey. Importantly, there is no more than minimal risk involved in completing the brief web-based sociodemographic questionnaire, and the participants' responses will remain completely

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anonymous (no IP addresses will be automatically logged in REDCap [Research Electronic Data Capture; Vanderbilt University]).

Consent Process for Service Providers

Service providers will be required to verbally consent at the beginning of each session. Service providers will be informed about the voluntary nature of this study, that all questions are optional, and that the session will be audio-recorded. As a part of the consenting process, service providers will be informed that they will not have access to any young Black men's data, even if they come from the same organization.

Data Analysis for Phase 1

Focus groups and interviews will be audio-recorded and transcribed verbatim by an independent transcriptionist. Transcripts from the study sessions will be recorded (with permission after informed consent), transcribed verbatim, and analyzed by 2 research team members using qualitative description, low-abstraction, and low-inference approach to closely interpret the data [73-75]. Qualitative description is ideal for describing phenomena of the participants' experience and language and is well suited for needs and risk assessment with susceptible populations [73-75]. After sorting, rearranging, and comparing codes, we will form categories and subcategories by pooling codes based on commonality, divergence, and logical parsimony [60,61,76]. Primary themes will be identified based on data generalizations and supplemented by participant excerpts [73,74]. Qualitative analysis software will be used to develop codes and a codebook. Approximately 10% of all transcripts will be double coded as pilot transcripts and reviewed for intercoder reliability or consistency to ensure high coder agreement (κ>0.80). In addition, *wish list* data will be analyzed according to a multilevel content analysis using an inductive six-phase process [76]: (1) coding of data sources (ie, focus group and interview transcripts), (2) reflexive note taking and bracketing, (3) cross-examination to discern similarities and variations in data, (4) observing commonalities and differences among the data, (5) identifying stable generalizations from the data, and (6) comparison of results with established literature.

Inclusion and Exclusion Criteria

Black boys and men invited to participate are eligible if they identify as male, irrespective of sexual orientation; identify as Black or African American; are aged between 15 and 24 years (inclusive); report having internet access; and are able to assent or consent to participation. We have received an IRB waiver of parental consent, as this study presents minimal risk. Those who are actively suicidal or homicidal, not medically stable, intoxicated during recruitment, and cognitively unable to provide informed consent; have impairments (such as emergent injuries); or are in police custody or incarcerated during the study enrollment will be excluded. Service providers will be adults (1) aged >18 years (all genders), (2) with experience in working with racial and ethnically diverse youths, (3) of any race or ethnicity, and (4) who are able to speak and read in English.

Recruitment Plan

Recruitment will be based on the Strategies to Recruit, Engage, and Retain Children in Behavioral Health Risk Factor Studies (REACH) model [77]. Strategies will include distributing flyers in high-traffic areas frequented by adolescents (eg, youth-serving agencies, festivals, churches, not-for-profit organizations, sports centers, reentry resource fairs, and barbershops). Our partner organizations will assist in recruitment using channels they deem appropriate for reaching the youth they serve. Partner organizations include The Urban Male Network and the Chicago Black Therapists Network (a network of 140 Black therapists). Both programs support underserved Black youth with mentoring and mental health services. We will also recruit through clinical research platforms, such as ResearchMatch (funded by the National Institutes of Health) [78] and The New Normal. We will work with 2 urban pediatric EDs: John H Stroger, Jr Hospital of Cook County (IRB approved), a level-1 trauma hospital that treats approximately 120,000 adults and children annually; and the 62-bed pediatric ED at Rush University Medical Center. Social media will support broadcast recruitment (via Instagram and Facebook advertisements). Service providers will be recruited via direct email to relevant organizations, word of mouth, and snowballing. Study materials will refer to the *Youth Health and Safety Study*.

A community champion familiar with the West and South sides of Chicago will advise and facilitate recruitment in these communities. Similarly, clinical research assistants in each ED or in-patient trauma unit will enroll participants presenting with assault-related or violence-related injuries who meet our eligibility criteria. All study staff will be trained in research compliance, motivational interviewing, trauma-informed research and data collection, and sensitivity training. After obtaining consent, young Black men will complete a survey on REDCap to assess their eligibility. Participants' compensation will be graded, ranging from US $25 to US $40, with the amount increasing for each study session completed. Service providers will receive US $50 for each session they complete.

Retention Plan

Similarly, we will use the REACH model [77] to maximize participant retention. These strategies will include the following: (1) obtaining the names, phone numbers, and email addresses or SMS text messages of several (at least 3) individuals (ie, friends, parents, and siblings) as alternate safe contacts to keep in touch with participants; (2) after each study communication, the participant will be provided with study contact information; (3) gift card compensation and train or bus passes will be provided for in-person meetings; and (4) a secured database for organizing follow-up contacts. When the app is developed and ready for testing (ie, phase 3), retention plans will include offering participants access to a password-protected study website with instructions on how to safely use the app and maintaining periodic contact throughout the study to assess for safety and confirm planned or unplanned changes to contact information.

Phase 2—Adapt and Optimize BrotherlyACT

Overview

Pertinent themes from phase 1 will inform the adaptation of the ACTV curriculum into a microlearning format in BrotherlyACT. This stage will be focused on iteratively

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developing all 3 components of BrotherlyACT tailored to young Black men affected by violence and substance use. The microlearning modules will draw on the evidence-based ACTV intervention by adapting, modifying, or adding modules directly relevant to young Black men's unique experiences in noninstitutionalized contexts. UCD principles and the 8-stage ADAPT-ITT framework will guide this adaptation process. The ADAPT-ITT framework is an 8-stage sequential guide to intervention adaptation, particularly in resource-poor settings [70,71]. Overall, 2 phases of stakeholder adaptations will occur at this stage. Stage 1 will focus on content and cultural adaptations and alpha testing. Then, stage 2 will comprise context adaptations and beta testing. UCD efforts will be informed and guided by our previous study using this methodology.

Stage 1

Overview

This phase of adaptation and optimization will involve *content* and *cultural* adaptations (ie, ADAPT-ITT stages 1-5; refer to Table S1 in Multimedia Appendix 1) and will conclude with alpha testing with topic experts and a multidisciplinary steering group (n=8-10; including the codeveloper of ACTV). This steering group will alpha test using semistructured cognitive interviews and several acceptability and feasibility questionnaires, including the 10-item System Usability Scale (SUS) [79]. The SUS can heuristically capture the perceived ease of use of BrotherlyACT (usability) and learnability (the ease with which users understand the intervention curriculum and layout). The SUS score is stable, with as few as 5 participants testing it. The SUS score must average at least 68 out of 100 (68 is the universal average acceptable score) [79,80]. The SUS is highly reliable (Cronbach α=.90), with scores >70 indicating *good* usability [80].

Content Adaptation

In sessions lasting 60 to 90 minutes, adaptation will focus on altering the noncore components of the ACTV curriculum, including language; simplifying ACTV modules while retaining its therapeutic values; and providing examples, case studies, and metaphors relevant to young Black men. Adaptation will also refine BrotherlyACT to determine which core components must be maintained or excluded (eg, therapeutic jargon). Specifically, we will systematically adapt ACTV skills-based modules into a paper-based microlearning curriculum (draft 0) that will be evaluated and refined independently.

Participants will be taught and will read each of the modules in the ACTV curriculum. Following each module, debriefing sessions will be completed to assess acceptability. Participants will then discuss and recommend (1) vital components to be retained, excluded, emphasized, or condensed to ensure that the adapted curriculum is appropriate for young Black men based on age, context, and community setting; (2) how to structure the module's learning objective in line with Bloom Taxonomy (to improve knowledge, life skills self-efficacy, and motivation to learn); (3) the modules' voice, tone, and pacing; (4) engaging formats for lesson practice and rehearsal (eg, true or false factoids, card sorting exercises, multichoice questions, and quizzes); and (5) module length. The paper-based curriculum will be drafted based on this feedback using Microsoft Word.

Next, adaptation plans will focus on how BrotherlyACT's clinical goals (eg, life skills self-efficacy) will map to BrotherlyACT's other in-app components and pragmatic features (safety planning toolkit and service-engagement chatbot). Overall, curriculum adaptations will consider logistical issues, such as intervention workflow, and what point-of-care organizational and community capacities are required for BrotherlyACT to be successfully implemented.

Cultural Adaptation

This step is vital, as identity, racial socialization, and culture are central themes in minority youth decision-making to seek and use prevention services and to facilitate great sustained engagement in treatment. Culturally adapted interventions must consider racial socialization messaging, beliefs, cultural values, contexts, and racial barriers that affect young Black men. We will also plan to incorporate culturally salient factors (ie, spirituality, Black masculinity, family support, fatherhood, a community, or *village mentality*) into draft 0. These factors influence help-seeking among young Black men [81]. In addition, we will incorporate relevant media (eg, videos of reformed young Black men), providing cultural and community icons as role models, and positive ethnic pride messaging (eg, messages countering the myth that Black boys are prone to violence). Cultural adaptation will necessitate modifying elements of draft 0 based on 8 cultural domains (language, contexts, symbols, metaphors, content, concepts, goals, methods, and context) through the lens of the Ecological Validity Model [82].

Stage 2

This phase of adaptation and optimization will include *context* adaptations, digitization, and *beta testing* of BrotherlyACT by a youth and community advisory board (YCAB).

Context Adaptation

The paper-based curriculum (*draft 0*) will be optimized into a digitized curriculum (ie, interactive web-accessible and app-accessible format) as part of BrotherlyACT (*draft 1*). Using UCD principles that incorporate youth needs [59-61,72,83], the YCAB (young Black men [n=8-12] and service providers [n=5-10]) will alpha test draft 1 for contextual acceptability, esthetics, understandability, relevance, and cultural salience. This wireframe version will not have color or graphics and will concentrate on content flow, functionality, and priority using sketches and layouts of interfaces with clickable components, buttons, and dropdowns. This stage of adaptation will increase BrotherlyACT's suitability to be digitized.

Next, our technology partner (Hekademeia Research Solutions [84,85]) will build a prototype of BrotherlyACT (*draft 2*), beginning with the adapted curriculum. This version will be functional and reflective of the final intervention. The original ACTV is a standardized manual in a predetermined sequence of modules across 24 weeks, which may restrict its flexibility in digital format. Therefore, BrotherlyACT will allow for the nonsequential deployment of interactive micromodules (that can be completed in 5-7 minutes) in response to the urgency of

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youth violence and the immediate skills needed and to fulfill real-world needs in high-violence, high-vigilance contexts. We will reconvene confirmatory focus groups with our YCAB to inform a finalized version of BrotherlyACT (*draft 3*—a high-fidelity prototype).

Beta Testing

The YCAB will beta test draft 3 in 2 consecutive sessions (broken into 2 rounds to reduce the cognitive load on participants) and build on findings from iterative sessions. Each session will last 30 to 90 minutes to identify usability problems early, quickly, and economically to find areas for improvements and to recommend content and features to retain or remove (ie, with sufficient features and functionality for testing). The YCAB will click portions (eg, buttons on the interface) on study iPads or personal phones. They will observe, rate, and clarify content tone and esthetic issues using a semiscripted usability protocol, including *cognitive walk-throughs* (to identify content and phrases not understood or interpreted as intended in modules and app pages) based on scripted cognitive tasks. *Theater testing* will be used to clarify their cognitive processes as they react to questions about content ("what comes to mind when the app asks you if you want to redo a module?"), paraphrase or summarize app-related elements (eg, text), and identify technical issues (eg, glitching or slow-loading pages) [71].

Phase 3—Clinical Trial

Overview

Overall, 60 young Black men (not part of phases 1 and 2) will be recruited to a single-group, pretest-posttest study of the finalized version of BrotherlyACT. This pilot test will determine its early feasibility outcomes (the feasibility of recruitment and retention methods; feasibility of module co-design with youth by observing fidelity to and deviations from the study protocol; completion of outcome measures; and satisfaction, appropriateness, cultural relevance, feasibility, and acceptability of the intervention). We will also ascertain the implementation outcomes for a large trial (ie, adherence, sustainability, and usability).

Assessments will be taken at baseline (T0) and after the intervention (T1) at 10 weeks, with SMS text message prompts to complete modules and study sessions. Given the exploratory nature of this study and its focus on feasibility, acceptability, and implementation outcomes, phase 3 data analyses will not be designed to have a specified level of statistical power. Nonetheless, with sample size of N=60, pretest-posttest correlation of 0.60, and α^2 (tailed)=.05, we estimate 80% power to detect a pretest-posttest change of Cohen $d \geq 0.33$ (a small to medium effect). We will use mean imputation on the missing items in the event of participant loss. Participants who leave the study will be compared with those who stay to identify any differences in baseline and follow-up data for descriptive purposes and to determine if data are missing at random.

Data Analysis for Phase 3

Pretest and posttest scores will be compared to see if participants improved, stayed the same, or deteriorated on each outcome scale. Data will be checked for missing data patterns, distributions of outliers, and variable distributions to ensure that they meet the assumptions of planned analyses. For baseline characteristics, descriptive statistics will be generated. We are limited in attributing postintervention change without a control group to the intervention. Thus, the effects observed are preliminary. All statistical analyses will be conducted using SAS. Initial data analysis will be performed to check for data quality, including allowable ranges and errors.

Generalized linear models will analyze the pretest and posttest survey measures using repeated measures analysis. As this pilot study is exploratory, we will use a P value <.05 to denote significant findings but not adjust for multiple tests, given the pilot nature of the study. Exploratory analyses will examine differences in rates of pretest-posttest change by baseline characteristics, including recruitment site (pediatric ED vs community). To test such moderation effects, terms for the moderator and for the moderator × time (before and after) interaction will be added to the models described previously. Significant interactions will be graphed to aid interpretation. At the end of the 10-week study period, participants will complete exit interviews via the web individually and will complete the SUS. Additional open-ended process interview questions will focus on young Black men's perceptions of BrotherlyACT and the research experience. As part of this study, responses to exit interview questions will be recorded with permission and thematically analyzed in a qualitative phase before being combined with pretest and posttest findings.

Results

Phase 1 data collection began in September 2021. Phases 2 and 3 are scheduled to start in June 2023 and end in September 2024. The entire study is expected to be completed by the end of 2025.

Discussion

Expected Findings

Using a mixed methods study format, subjective and objective feasibility and acceptability data will be compared. This will ensure that survey data can be quantified and contribute to our qualitative understanding of the curriculum's practicality and acceptability.

Few antiviolence technology-enhanced interventions exist, and even fewer studies have studied the acceptability, usability, and engagement of a life skills and mindfulness coaching intervention for co-occurring youth violence and substance use among young Black men. The extent to which existing technology-enhanced interventions are used for violence prevention has been limited to supporting the work of street outreach workers [86]. We expect that BrotherlyACT will prove to be acceptable and usable by young Black men affected by violence. Furthermore, findings from the development of BrotherlyACT will be useful for a future definitive trial. This trial will validate an expanded version of BrotherlyACT across clinical and community-based settings for young Black men in Chicago and other cities with a high prevalence of youth violence. Clinical outcomes will be determined after we evaluate how well BrotherlyACT works (ie, reduction in violence and

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substance use, perceived likelihood of involvement in violence and problematic behaviors, self-efficacies to plan for a positive future, use of ACT and life skills, and likelihood of using service options). The success of this intervention in different deployment contexts (eg, in a hospital vs a community setting or web-based vs face-to-face setting) will be evaluated as part of the implementation analysis. BrotherlyACT will be tested (1) with referred (vs recruited) young Black men, (2) with an organic deployment by service providers (vs research staff), and (3) in comparison with conventional care in future effectiveness trials.

On the basis of previous application of qualitative methods [34] and UCD [34,59,62], we anticipate that our study will highlight the benefits of technology-enhanced modalities for addressing motivation and self-efficacy to reduce and prevent co-occurring violence and substance use among at-risk young Black men. Studies so far support an association between substance use and violence [4,5], with a consensus that substance use can increase both the frequency and severity of violence [4-6]. A common substance implicated in violent experiences when misused is alcohol, with the suggestion that eliminating hazardous drinking would reduce general violence by 44% [5]. Such findings have led many researchers to focus on developing integrated intimate partner violence and substance use interventions [4-6].

However, this study is the first stage in developing and evaluating a technology-enhanced intervention for reducing co-occurring violence and substance use among Black boys and men aged 15 to 24 years in a high-violence setting. We are using an existing theory-driven and evidence-based intervention (ie, ACTV) that has been proven to reduce violence. This approach eliminates the need for expensive additional investments in developing a new intervention from other data sources, which may face significant feasibility issues and require considerable time. Extending ACTV to noninstitutionalized juvenile samples exposed to youth violence is a logical next step. Addressing our research objectives squarely will drive innovation in violence prevention and identify settings, conditions, and limitations for situations where digital solutions are inapplicable or even detrimental.

Furthermore, crime prediction technologies, digital surveillance tactics, and facial recognition software have all been known to target and penalize Blackness [86]. Therefore, we approach this study through a transformative justice lens, mindful of how technology affects Black communities. We hold ourselves and our team accountable in our quest for ethical and dignified technology-enhanced interventions. We remain responsible to young Black men, who will support this process and, eventually, use BrotherlyACT.

Strengths and Limitations

This study and our approach have some limitations. As our study only includes young Black men, we cannot generalize our results to other groups of young men (such as Hispanic; tribal; and lesbian, gay, bisexual, transgender, queer, and more youth) who are disproportionately affected by violence and substance use. Furthermore, using a single sample group for pretest and posttest will not infer causative relationships and will limit the causal attribution related to the proposed intervention. However, our goal at this stage is to develop and pilot-test BrotherlyACT for preliminary feasibility and acceptability. We have evaluated the power of our sample size using suggestions and guidelines for conducting pilot studies contained in the existing literature.

Nevertheless, it is possible that our sample size is very small, which could influence the results we receive. Regarding cultural adaptation of the intervention to young Black men, it can be challenging to present diverse groups with a unified view of *culture*. Some participants may find that traditional values conflict with their convictions or that generic cultural values may not adequately capture the particulars of their own cultural experience. Therefore, we intend to develop BrotherlyACT's architecture to be adaptable to user requirements and capable of rapid, iterative adjustments. Moreover, young Black men who have perpetrated violence and use illicit substances are a self-selecting population that may not feel comfortable reporting their substance use and histories of violence, thus necessitating the use of novel recruitment tactics.

Conclusions

At the individual level, studies show that life skills are a vital tool and coping strategy for adolescents in high-trauma contexts. Life skills have been used for decades to prevent violence and aggression in adolescents, particularly those in their early to middle adolescence. However, there is compelling evidence that low-income urban youth have few opportunities to observe, learn, or practice the actionable skills required to deal with the heightened levels and severity of the stressors they face. Accordingly, there is a need for combining multilevel strategies, such as psychoeducation and safety planning (at the individual level), with service engagement at the community level. There is also a dire need for easily accessible and youth-endorsed interventions that allow young people to acquire and practice these abilities as they plan for a values-based life. Improving Black adolescents' access to skill-building resources and connecting them to already existing and trusted services is a critical and urgent public health need, the absence of which has resulted in a revolving-door approach to youth violence and substance use prevention.

Acknowledgments

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Data Availability

Study data sets will be deposited in publicly available repositories (where available and appropriate), as dictated by our funders, or presented in the main paper or additional supporting files whenever possible. Using a community-engaged approach ensures that the research findings are owned by the community, sustainable, and widely disseminated. Therefore, the dissemination of results in the community will be considered along with community input on how Boosting Violence-Related Outcomes Using Technology for Empowerment, Risk Reduction, and Life Skills Preparation in Youth Based on Acceptance and Commitment Therapy can be integrated into existing violence prevention programs, policies, and resources for schools, clinics, and community-based settings serving young Black men. Furthermore, service providers can use the adapted Boosting Violence-Related Outcomes Using Technology for Empowerment, Risk Reduction, and Life Skills Preparation in Youth Based on Acceptance and Commitment Therapy curriculum (paper or digital version) as a brief intervention resource to help at-risk and underserved adolescents in various contexts.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Assessment, Decision, Administration, Production, Topical, Experts, Integration, Training, and Testing framework.
[DOCX File , 19 KB - resprot_v12i1e43842_app1.docx]

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Abbreviations

ACT: acceptance and commitment therapy
ACTV: Achieving Change Through Values-Based Behavior
ADAPT-ITT: Assessment, Decision, Administration, Production, Topical, Experts, Integration, Training, and Testing
BrotherlyACT: Boosting Violence-Related Outcomes Using Technology for Empowerment, Risk Reduction, and Life Skills Preparation in Youth Based on Acceptance and Commitment Therapy
CBT: cognitive behavioral therapy
ED: emergency department
IRB: institutional review board
REACH: Strategies to Recruit, Engage, and Retain Children in Behavioral Health Risk Factor Studies
REDCap: Research Electronic Data Capture
SUS: System Usability Scale
UCD: user-centered design
YCAB: youth and community advisory board

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Protocol

Digital Health App to Address Disparate HIV Outcomes Among Black Women Living in Metro-Atlanta: Protocol for a Multiphase, Mixed Methods Pilot Feasibility Study

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Abstract

Background: Cisgender Black women in the southern United States are at heightened risk for HIV and adverse sexual and reproductive health outcomes. Mobile health interventions that target HIV risk while being adapted to the needs and lived experiences of Black women are remarkably limited.

Objective: The study aims to refine *SavvyHER*, a mobile app for HIV prevention, with Black women residing in high HIV incidence areas of Georgia and evaluate the feasibility, acceptability, and usability of *SavvyHER*. This paper describes the procedures implemented to conduct this research.

Methods: Community-based participatory research tenets guide this multiphase study to finalize the development of what we hypothesize will be an effective, sustainable, and culturally relevant HIV prevention and optimal sexual health and reproductive wellness app for Black women. This multiphased, mixed methods study consists of 3 phases. The first phase entails focus groups with Black women to understand their preferences for the functionality and design of a beta prototype version of *SavvyHER*. In the second phase, an app usability pretest (N=10) will be used to refine and optimize the *SavvyHER* app. The final phase will entail a pilot randomized controlled trial (N=60) to evaluate the app's feasibility and usability in preparation for a larger trial.

Results: Findings from preliminary focus groups revealed educational content, app aesthetics, privacy considerations, and marketing preferred by Black women, thus informing the first functional *SavvyHER* prototype. As we adapt and test the feasibility of *SavvyHER*, we hypothesize that the app will be an effective, sustainable, and culturally relevant HIV prevention, sexual health, and reproductive wellness tool for Black women.

Conclusions: The findings from this research substantiate the importance of developing health interventions curated for and by Black women to address critical HIV disparities. The knowledge gained from this research can reduce HIV disparities among Black women through a targeted intervention that centers on their health needs and priorities.

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KEYWORDS

Black women; CBPR; community-based participatory research; HIV; human centered design; mhealth; pilot usability study

Introduction

Black women in the United States are disproportionately affected by HIV. In fact, this group accounts for 60% of new HIV infections among women in the nation, despite only making up 15% of the female population [1-6]. A total of 8 out of 10 states with the highest incidence of HIV diagnoses are located within the southern region of the United States (hereinafter called "the South") [7] and regrettably, Black women also comprise 67% of all HIV diagnoses in this area. Numerous barriers contribute to the increased risk of HIV among Black women which have been well cited in the literature. These barriers often include structural barriers (eg, income inequality, housing insecurity, incarceration, low health care access, and medical racism), social and environmental barriers (eg, small sexual networks, community stigma, intimate partner violence [IPV], and social support), and personal barriers (eg, low knowledge of and access to pre-exposure prophylaxis [PrEP], low self-perceived HIV risk, stigma toward HIV, and medical mistrust). While research often focuses on addressing HIV risk among Black women of lower socioeconomic status, the risk of HIV extends beyond this sub-group. College-educated Black women and Black women of higher socioeconomic status remain at higher risk of HIV due to factors such as limited partner availability, small sexual networks, and health care provider bias. However, they are oftentimes not represented in HIV prevention and larger sexual and reproductive health (SRH) studies [8-10].

Reducing the burden of HIV among Black women requires innovative methods that acknowledge and address the multiple interrelated social and structural factors that promote HIV susceptibility among Black women. PrEP offers an HIV prevention method for women that is discreet, minimizes the need for partner consent, and has no adverse effect on contraception or conception [11-13]. While there is a plethora of PrEP awareness and adoption research that focuses on men who have sex with men (MSM), Black women are overlooked in PrEP literature [14,15]. Studies that have investigated PrEP attitudes exclusively among women have found that while most women have low PrEP knowledge and awareness, they generally respond positively to the idea of using PrEP for HIV prevention [16,17]. Black women's willingness to consider PrEP depends greatly upon social understandings—whether it is seen as an effective, healthy, and socially acceptable HIV prevention strategy—in addition to cultural and structural factors [18-20]. The heightened risk of HIV acquisition among Black women living in the South combined with the lack of PrEP awareness among Black women confirms the need for innovative, affordable, accessible, and tailored HIV interventions for this group.

Previous research highlights the benefits of using mobile health (mHealth) technology to promote sexual and reproductive health [21-23]. A growing body of literature has reported Black women's acceptability toward mHealth interventions, including the use of smartphones for health promotion among Black women of reproductive age [19,24-26]. Although Black women are engaged by mobile apps, little to no mobile apps have been developed for the purpose of HIV prevention in Black women [27,28]. Therefore, our research team is developing an mHealth intervention entitled *SavvyHER* (Sexual/HIV Health Electronic Empowerment Resource), a mobile app developed for Black women by Black women which addresses HIV prevention and SRH among Black women living in the South.

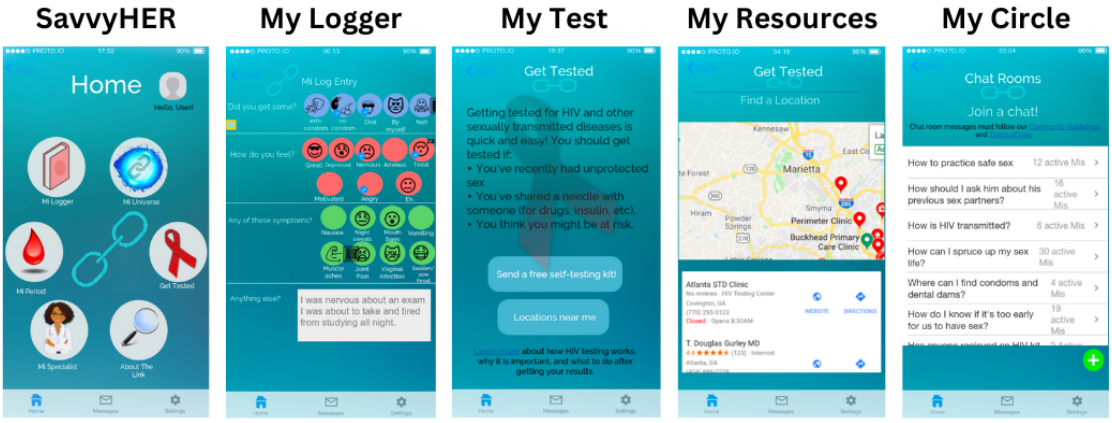
Methods

Formative Work

SavvyHER has been developed based on formative work conducted with Black women living in a high-priority region of the South [19]. We solicited input about the most relevant social inequities hindering or prohibiting HIV prevention through focus groups with Black women. This work gathered Black women's preferences for the functionality, format, and design of a mobile HIV prevention app tailored for Black women. Black women in our formative work specified the following: (1) lack of access to culturally targeted and gender-considerate health care; (2) gender-based power differentials in couple relationships that limit women's ability to negotiate HIV-protective actions with their male sex partners (eg, condom use); (3) unreliable HIV prevention education and limited access to HIV prevention resources; and (4) susceptibility to other sexually transmitted infections (STIs) and chronic illnesses. Women desired content pertaining to women's sexual and reproductive health, including HIV prevention, comprehensive health information relative to the health disparities of the Black community, and linkage to women of color health care providers. Preliminary wireframes were developed using findings from our formative work (Figure 1). In addition, the research team conducted a separate study evaluating perspectives from health care providers regarding challenges and facilitators to PrEP initiation among Black women. This work has helped to guide message framing within the preliminary *SavvyHER* app [18].

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Figure 1. Early depictions of *SavvyHER* features. *SavvyHER*: Sexual/HIV Health Electronic Empowerment Resource.



Theoretical Frameworks

Social Cognitive Theory of Mass Communication

The *SavvyHER* study is grounded in the Social Cognitive Theory of Mass Communication (SCT-MC) [29]. This theoretical framework has been successfully used as a foundation for computer-assisted and internet-based health promotion interventions. SCT-MC applies the SCT to technologically based interventions, postulating that critical mechanisms for behavior change can occur through mass media technology [30]. The constructs of SCT-MC include cognitive factors, situational (ie, environmental) factors, and behavioral factors, with an emphasis placed on symbolic modeling and the notion that people's perceptions of reality depend upon the media's symbolic environment, which can contribute to new ways of thinking. Symbolic modeling exerts greater influence in populations that look to media-based images to discern what is and is not reality [31]. SCT-MC also posits that experiences (real or vicarious) facilitate the expansion of knowledge and awareness of causal relationships. Thus, SCT-MC is ideally suited to guide mobile-based interventions focused on behavioral knowledge, behavioral acceptance, and the cultivation of supportive social networks. We will operationalize the SCT-MC to address the health communication priority of using media to improve women's sexual and reproductive health outcomes, focusing on HIV prevention behaviors. As SCT-MC has been used in numerous studies to explore the behavioral acceptance of communications interventions among minority communities, the case can be made for using SCT-MC to evaluate feasibility within a group that has been relatively understudied. Research guided by this framework has identified the benefits of using mobile apps to deliver evidence-based health messaging and training [32,33].

Community-Based Participatory Research

This study uses community-based participatory research (CBPR) principles to promote the efficacy, sustainability, and cultural relevance of *SavvyHER* as an HIV prevention app. CBPR is well-suited for addressing health disparities within historically marginalized communities, as it reduces the power dynamic between researchers and participants and fosters shared learning. As a result, CBPR empowers individuals to voice their needs and concerns and facilitates shared learning between researchers and participants [30,34,35]. In order to establish trust and build capacity in our priority community, we ensured that our study team was composed of researchers who identify as Black women to reflect the community we serve. Literature highlights the effectiveness of insider research, or rather, research conducted inside a community to which the researcher also belongs, as a means of "challenging existing structures of power and creating opportunities for the development of innovative and effective solutions to the problems facing society" [36]. In addition to well-established CBPR practices, our team draws on 4 principles of Black feminist epistemology: (1) lived experiences; (2) dialogue; (3) the ethics of caring; and (4) personal accountability [37]. By centering Black women in this project, *SavvyHER* is curated *for and by* Black women to effectively meet this group's needs [38]. In following CBPR principles, we have assembled a community advisory board (CAB) to steer project priorities, implementation, and dissemination. The multidisciplinary CAB has a total of 8 members and includes HIV clinicians, SRH advocacy representatives, social workers, educators, and nonprofit organizations consisting of Black women.

SavvyHER App Design and Development

Industrial and technology designers have used human-centered design (HCD) to facilitate innovation [39-41]. Key principles of HCD are the following: (1) the design is driven and refined by user-centered evaluation; (2) the process is iterative; (3) the design addresses the whole user experience; and (4) the design team includes multidisciplinary skills and perspectives. Although not explicitly a research methodology, HCD employs qualitative and quantitative research methods and encourages health innovators to design technology by focusing on how users can, want, and need to use it. This process begins with the identification of health needs, rapid prototyping, and iterative design and development. Once a prototype is created, it is tested and refined based on the user's experience. The purpose of this approach is to move away from traditional methods of involving users during the latter phases of the prototype and instead regard users as active contributors from the beginning of the design process.

Like other health interventions, mobile health apps face challenges in terms of uptake, engagement, efficiency, and confidentiality. These challenges can be mitigated by ensuring that the intervention content is developmentally appropriate, comprehensible, and comfortable to use. We have chosen an HCD approach to increase the usefulness and use of the app,

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encourage HIV protective behavior, and promote optimal HIV prevention practices. Additionally, there may be potential risks of abuse during discussions in the app's virtual peer support communities. The research team will designate chat room moderators to be trained to monitor for abuse. Abuse will be defined in the app-use policies conveyed to participants in the orientation. Examples of these policies might include: no sending of identifying information such as phone numbers or addresses; no posting of links; etc. These policies will be drafted with the CAB. Another potential risk is that women may experience psychological and emotional distress while recounting sexual experiences or discussing sensitive health topics. The research team includes clinicians with experience counseling patients on sensitive health topics. The research team will follow institutional review board (IRB) reporting procedures in the instance that participants experience psychological and emotional distress and will refer participants to local SRH clinicians for support services as needed.

The current version of *SavvyHER* was derived using recommendations from the CAB and based on our preliminary studies [19,42,43]. The app uses text, video, still frames, and other features to convey tailored health messages. The interactive portions of *SavvyHER* are primarily click and swipe functions. Our research team ensured the readability of the app content is no higher than sixth grade level, using the Flesch-Kincaid readability score [44]. *SavvyHER* contains a variety of app features, reflective of the SCT-MC constructs, that were developed based on our formative work with Black women (see Table 1).

Table 1. *SavvyHER* mobile app's features informed by SCT-MC (Social Cognitive Theory of Mass Communication) constructs.

SCT-MC constructs and their descriptions and functions	App feature	Addresses barriers to HIV prevention services
Personal		
Reliable resource for health resources and tools tailored for Black women; addressing Black women's priority SDOH[a] issues	*My Resources*	Unreliable or unknown health information sources; HIV risk perception; resource insecurities characterized as SDOH
HIV prevention plan; health promotion; Health communication messaging	*My Logger*	HIV risk perception: global prevention information that is perceived to be irrelevant to Black women
Maintain interaction with the user; self-monitoring	*My Logger* *My Resources*	Not the focus of HIV prevention efforts
Environmental		
Digital expertise through conversational interface providing consult regarding reproductive health concerns. Health communication messaging	*My Resources*	Stigma; cultural representation and sensitivity; choice of information dissemination modality, resource accessibility
GPS locator and geofencing for HIV and women's health resources; at-home testing for convenience and destigmatizing the sexual health needs of Black women	*My Tests*	Neighborhood health care services; PrEP[b] providers don't prescribe to women; stigma
Behavioral		
Messaging, modeling, and learning community	*My Circle*	Social support; subjective norms
Personalized health messaging based on participant inputs like symptoms, sex behaviors, social stability information (eg, housing and employment status)	*My Logger*	PrEP knowledge and attitudes; HIV testing knowledge and attitudes; and HIV risk perception

[a]SDOH: social determinants of health.

[b]PrEP: pre-exposure prophylaxis.

My Logger integrates a self-tracking and preventive health messaging feature that incorporates symbolic modeling, behavioral knowledge, behavioral acceptance, and the cultivation of supportive social networks. Participants are encouraged to journal about any sexual or reproductive health encounters, appointments, indicators of social instability associated with HIV risk behaviors (eg, IPV [45,46] and changes in employment and housing), and descriptive anecdotes in the journal section of *My Logger* [47].

My Test consists of two components: (1) a GPS locator for HIV testing and PrEP clinics; we leveraged the existing application programming interface (API) of the HIV.gov testing locator to provide a centralized place for identifying testing and prevention sites; and (2) to make commodity ordering available to participants. Participants can order condoms and STI testing kits through an in-app widget.

My Resources gives participants access to a multimedia resource kit consisting of videos, current events, news feeds, podcasts, and support groups related to women's health, reproductive health, and HIV prevention. In addition, the study team has and will continue to generate health messages, like 1- to 2-minute video clips and infographics.

My Circle is a digital environment for women to connect, extending opportunities for peer modeling, learning, and support. In the moderated web-based groups, women share sexual health goals they are pursuing in the app, use messaging features to provide support around these goals and in their lives more broadly, and share insights they have found meaningful through

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the educational messaging components of the app to support peer learning (eg, through buttons that let them easily share information gained through the *My Logger* and *My Resources* features).

Study Design

The pilot feasibility trial will consist of 3 distinct phases in which data collection, analysis, and interpretation will occur separately for each phase. The procedures were modeled after other successfully implemented HIV app development procedures [48-50]. The first phase included qualitative focus group discussions (FGDs) with participants; the second phase involved a pilot of the *SavvyHER* app with a select number of participants; and the final phase will consist of a randomized controlled trial in which participants will be randomized to either the *SavvyHER* intervention arm or the control arm. At the time of this manuscript, phases I and II were complete. Phase III will be initiated during second quarter of 2023. This design approach was deemed appropriate as it allows for further refinement of the *SavvyHER* app using the data obtained from phase I and phase II before the randomized controlled trial in phase III.

Recruitment and Eligibility

Eligibility criteria are consistent throughout all phases of the study. Participants must meet the following inclusion criteria: (1) be 18-45 years of age; (2) self-identify as Black and African American; (3) be assigned female sex at birth and identify as female; (4) PrEP-qualified based on CDC criteria for residence in high HIV incident areas—reside in Fulton, Cobb, Gwinnett, or Dekalb counties; (5) sexually active within the last 6 months; (6) HIV-negative; and (7) own a smartphone. While the *SavvyHER* app is designed by Black women for Black cis women, we anticipate the unique needs of transgender women. The first iteration of the *SavvyHER* app focuses on cis women; future iterations of the app will incorporate the needs of trans women.

A combination of both passive and active recruitment approaches is used to achieve study enrollment goals for all phases. Passive recruitment involves the distribution of flyers through local SRH organizations, clinics, and social media. Active recruitment efforts incorporate the assistance of SRH clinicians who will refer eligible patients to the study as well as targeted advertisements. All digital and print recruitment communications encompass a QR code—a scannable barcode—that guide interested participants to a web-based questionnaire and a brief description of the study [51]. If eligible, participants provide their contact information (eg, by calling or texting the study phone) for a research team member to contact them to establish an intake meeting for the completion of the baseline assessments and group assignment.

Phase I: Focus Group Discussions

Phase I of the study consisted of qualitative data collection through web-based FGDs on Zoom. FGDs were structured in which participants were shown the app and guided through the app's content and features. After demonstrating the app, participants were asked questions regarding the preferences of each of the *SavvyHER* features, along with questions inquiring about the design of the overall app and features, navigability, and usability.

Phase II: App Usability Pretest

Phase II, or the app usability pretest, involved a 1-month pilot test of the *SavvyHER* app with 10 Black women. During a web-based enrollment session, study staff used a checklist to walk participants through procedures for downloading and using the app. Participants were encouraged to use all *SavvyHER* app components over the pilot period, including the HIV and STI test kit ordering feature. Participants completed a weekly questionnaire to provide feedback on the functionality, technical performance, errors encountered, feasibility, acceptability, and overall experience of using *SavvyHER*. Upon completion of the 1-month pretest, participants completed an exit interview through Zoom. Interviews provided further context in regard to the quantitative survey findings to obtain rich insight on app acceptability, feasibility, usability, concerns and challenges in using *SavvyHER*. Exit interviews were audio-recorded and are being transcribed for analysis by the research team. Findings from the app usability pretest will then be used to inform the final version of the *SavvyHER* app for the pilot feasibility trial in phase III.

Phase III: SavvyHER Pilot Feasibility Trial

After the *SavvyHER* app is refined and optimized using feedback from phase II under the guidance of the CAB, we will evaluate the feasibility, acceptability, and usability of the *SavvyHER* app through a pilot feasibility trial in phase III. This intervention will include a total of 60 Black women who will be recruited and randomized into the intervention group (N=30) or the control group (N=30). The sample size was determined based on feasibility objectives and measures and general guidelines for path analysis, which recommend a sample size of 10-20 participants per study concept while accounting for attrition. Interested participants will provide their contact information, and a research team member will follow up with a baseline assessment and group assignment. After baseline assessments are completed, participants will be randomized 1:1 to either intervention or control using a randomization schedule generated by our statistician using a permuted block procedure [52]. Allocation concealment will be employed before the randomization of participants. Once participants are assigned to groups, blinding will occur, in which researchers involved in data analysis will be blinded to the groups in which participants are enrolled to reduce observer bias and bias in data analysis and interpretation [53]. To restrict access to the *SavvyHER* app to the intervention group, participants will be provided with a single-use registration code that will need to be entered to gain access to the app. Study team members will teach participants how to download the app and navigate app features such as reminders.

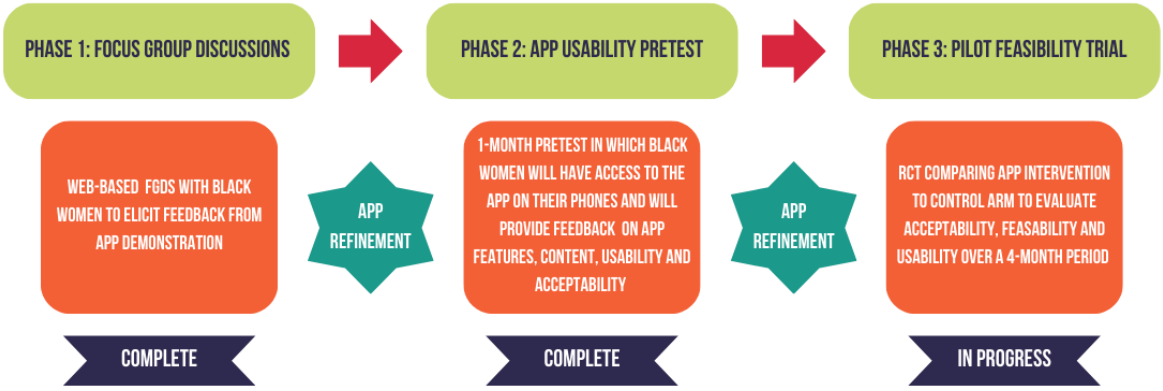
Each participant will have 4 months to engage with the app, with e-reminders at time intervals preferred by the participants (a minimum of 3 times per week) through push notifications. We will ask that participants schedule reminders during their peak times of cell phone use. Participants will also be prompted to take a weekly survey to provide app feedback similar to the weekly survey in phase II. Research staff will complete 2-month

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check-ins through phone call or video chat with participants in both the intervention and control conditions. At month 4, all participants will complete an endline survey in addition to an exit interview. Procedures for exit interviews are the same as those used in phase II. Participants will be remunerated for completion of the baseline assessment and for completion of the endline survey and exit interview. Furthermore, the CAB will review all feedback given and deliberate on what improvements or changes should be made to the *SavvyHER* app.

The control condition will be a 1-time web-based women's health counseling session with a health care provider. Participants will be given information on (1) STI and HIV prevention; (2) family planning; and (3) general health promotion (eg, exercise and diet). The control condition provides access to HIV prevention materials that are publicly available but that do not offer the dynamic and individually customized features of the health communication and new media research approach proposed herein. The control group will not have access to the *SavvyHER* app until after the study has concluded. See Figure 2 for a visual depiction of *SavvyHER* study procedures.

Figure 2. *SavvyHER* study procedures. FGD: focus group discussion; RCT: randomized controlled trial; *SavvyHER*: Sexual/HIV Health Electronic Empowerment Resource.



Data Collection

All assessments are taken through REDCap, a secure platform for constructing web-based surveys and databases [54]. Participant data is stored under a unique study ID number to ensure security and privacy. In order to inform intervention testing, we collect data on the number and yield of screened participants enrolled, recruiting sources that generated the largest number of enrolled individuals, effective recruitment used for successful enrollment, elapsed time from first contact to enrollment, amount of app interactions, and technological challenges or glitches. Feedback on content and delivery is elicited through REDCap surveys and focus group sessions or interviews, which both undergo qualitative data analysis, also known as coding. Additionally, we collect data on participants' ownership of smartphones and preferred app formats. These measures will help determine the time, resources, and workload necessary for implementing the HIV prevention mobile app for Black women. Moreover, with this data, we can assess whether users perceived the app as beneficial and whether alternatives (in app content and delivery) can be determined.

All participants provide demographic information through REDCap surveys. Primary outcome measures focus on the feasibility, usability, and acceptability of the *SavvyHER* app in addition to the control group procedures. Feasibility metrics will be determined by meeting predefined benchmarks specific to retention, screening, and interaction with app features. Examples include the number of weekly app sign ins, time spent using the app, and its features. Usability and acceptability will be assessed with the system usability scale (SUS) and a 30- to 45-minute exit interview that queries participants' experience with study procedures [55]. Because this is a feasibility study, we do not propose a statistical analysis of changes in behavior (eg, PrEP initiation, HIV testing) among users of the *SavvyHER* mobile app. Secondary measures collected in phase III include information on social determinants of health (eg, health care access near her location, employment status, housing status, transportation access, and social support), sexual health history and knowledge, self-perceived discrimination, mental health status, experiences of intimate partner violence, PrEP stigma, racism, and discrimination, personal media and technology use, as well as web-based health information seeking. The completion of the end line survey will also indicate the feasibility of study procedures (eg, retention). A summary of primary and secondary measures is displayed in Table 2.

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Table 2. *SavvyHER* study outcome measures.

Measure	Questionnaire or survey	Weekly survey	Baseline or end line survey
Demographics	• Name, age, race and ethnicity, gender identity, county of residence, relationship status, education, household income	✓	✓
Social determinants of health and women's sexual health history	• Your current life situation [56,57] • Protocol for responding to and assessing patients' assets, risks, and experiences (PRAPARE) [58] • A guide to taking a sexual history [59]		✓
Primary outcomes			
Usability/acceptability	• System Usability Scale (SUS) [60,61]	✓	✓
Feasibility	• Average number of app sign ins per week; number of minutes spent using the app weekly; sexual health tracking entry, home test kit ordering, number of app glitches; 40% of participants using My Logger, My Test, My Resources and My Circle		✓
Secondary outcomes			
HIV knowledge	• Human Immunodeficiency Virus- Knowledge Questionnaire (HIV-KQ AG) [62]		✓
HIV risk	• PrEPa information and self-screening tool for women [63]		✓
HIV and PrEP stigma, PrEP intention or initiation	• Brief HIV PrEP stigma scale (HPSS) [64]		✓
Self-reported racial/ethnic discrimination	• Everyday racial/ethnic discrimination scale [65]		✓
Depression	• Patient health questionnaire-2 (PHQ-2) [66] • The patient health questionnaire (PHQ-9) [67]		✓
Self-reported social media use and technology use; attitudes toward technology use	• The media and technology usage and attitudes scale (MTUAS) [68]		✓
Information seeking	• Web-Based Health Information Seeking [69]		✓
Usability assessment of *SavvyHER*	• Health information technology usability evaluation scale (Health-ITUES) [70]		✓
User experience of *SavvyHER*	• User experience questionnaire [71] • User experience questionnaire short from (UEQ-S) [71]		✓

[a]PrEP: pre-exposure prophylaxis.

Data Analysis Plan

Quantitative Analysis

Data will be downloaded from REDCap into STATA (StataCorp). Exploratory and descriptive analyses will be conducted for all study variables. Variables will be examined for normality in addition to means, SD, range, and medians. The literature on effect size estimates, from pilot studies and National Institutes of Health (NIH) recommendations, confirms that attempting to obtain valid estimates of effect sizes cannot be statistically justified [72-78]. We have identified feasibility and acceptability as the primary outcomes of this pilot. We have indicated target metrics that will substantiate feasibility, and we will use both quantitative survey and qualitative interview data to determine the acceptability of both the mobile app and the control condition. For all outcome measures (eg, PrEP knowledge), a mean score and 95% CI will be calculated, and distributional assumptions will be assessed. The mean change in outcome measure scores between pretest (T0) and posttest (T1) will be compared (paired samples *t* test) for trends in the expected direction or no change. A paired samples *t* test will be conducted to evaluate the mean change in outcome measure scores between pretest (T0) and posttest (T1) within groups. *t* Tests will also be used to compare variables before the intervention among the 2 groups. To compare differences between intervention and control groups, a 2-way analysis of covariance (ANCOVA) will be used in which covariates will be controlled for. All statistical tests will be performed at a 95% CI with an alpha of .05.

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We will use mobile app analytics (eg, Google Analytics) to assess trends in app engagement, such as duration and number of app/module/social media forum engagement, clicks, modules viewed/completed, GPS solicitation, and correct or incorrect responses to questions. Analytics data will be collected as categorical and continuous variables. Continuous variables will be transformed into categorical variables, and multivariable logistic regression will be conducted to evaluate the relationship between usage characteristics and primary outcomes using STATA.

Qualitative Analysis

All interviews will be audio-recorded and transcribed using Otter.ai software. Transcribed interview data will be reviewed for overall impressions of the content, materials, activities, and delivery of the *SavvyHER* app. Once transcribed, transcripts will be transferred into Dedoose, a qualitative and mixed methods data analysis platform [79,80]. Our analytic strategy employs a hybrid approach involving concept-driven coding as well as open coding, thus combining the deductive and inductive coding methodologies [81]. Deductive coding denotes the curation of premade codes or themes that are applied to raw data as a means of categorizing quotes for interpretation [82]. Our initial codebook will consist of feedback themes we want to capture regarding the *SavvyHER* app, such as feasibility, acceptability, and usability. Research team members will apply the preset codes to the interview transcripts in an iterative process. Simultaneously, research team members will be creating new codes inductively, or rather, allowing new themes to emerge from the data itself for further analysis [83].

Ethics Approval

Ethical approval for this study was obtained through Emory University's IRB (STUDY00002857). Before enrolling in the study, the research team will discuss the purpose of the study, study procedures, and risks and benefits with participants. Participants who agree to participate in the study will provide informed consent to a member of the research team. For the quantitative portion of the study, written informed consent will be obtained from participants. For the qualitative phase, oral informed consent will be obtained. Participants will be provided a unique study ID upon enrollment, and all data will be deidentified to maintain confidentiality. Survey data is also password protected in REDCap. Focus group transcripts and recordings are password protected in digital files. Only study team members on the IRB will have access to data files. Participants will receive compensation for completion of the baseline assessment (US $50) and for completion of the exit interviews (US $80) for a total of US $130.

Results

Numerous works discuss the gap between scientific discovery and real-world application [84-88]. Literature points to the lack of cultural competency in translational public health research as the source of this gap [88-91]. Our research team and community stakeholders will center on culturally sound, reciprocal knowledge translation, otherwise known as 2-way translation of knowledge. Two-way translation of knowledge involves the creation and distribution of information from academia to the public as well as from the public to academia [91]. In adhering to CBPR approaches, our research team will copresent findings from this project to study participants and other community stakeholders. Disseminating results will not occur for the sole purpose of reporting outcomes but to empower community members to take part in the contextualization of the study findings that guide the development of the *SavvyHER* app. Thus, fostering social action toward mitigating HIV disparities among Black women. The outcomes of the analysis for phase I and phase II will be reported in a future manuscript.

This study was funded in August 2021; data collection is ongoing (we had several phases, and we are currently starting our pilot randomized controlled trial phase now).

The numbers recruited as of submission of the manuscript for this study: a total of 17 participants were recruited for the focus group discussions from December 2021 to March 2022 and met the eligibility criteria to participate. A total of 13 Black cisgender women participated in focus group discussions (phase I). A total of 10 participants enrolled in the study's single-arm "technology usability pretest." Among the participants, 8 completed the quantitative and qualitative analyses, which were all components of phase II. We are currently recruiting for phase III, the pilot randomized controlled trial. We aim to recruit 60 (30 in the intervention arm and 30 in the control arm of the study).

The data analysis for the single-arm "technology usability pretest" is currently completed and under review for publication. Furthermore, the data for the pilot randomized controlled trial will be analyzed once the study has concluded. We project that results will be published in the fall of 2024.

Discussion

Overview

Although Black women are a priority population concerning HIV in the southern United States, few public health interventions are curated for prevention and treatment among this group. Black women experience some of the highest rates of HIV acquisition due to broader social forces and systems embedded in discrimination. In order to mitigate the disproportionate impact of HIV among Black women, novel and effective strategies must support Black women's capacity to protect their own health [92]. We anticipate that the *SavvyHER* intervention will address barriers in HIV prevention and broader SRH disparities among Black women by providing access to culturally responsive resources, educational materials, and health services that otherwise would be difficult to acquire given the limited awareness and extensive structural barriers that this community faces. Several studies have begun to explore the benefits of digital platforms in addressing HIV burdens at local and global levels. A review conducted by Cao et al [93] indicated that digital health interventions have demonstrated feasibility in increasing PrEP uptake and optimizing clinical interventions for target communities. It is critical, however, for such interventions to be adequately adapted toward demographic profiles including age, gender identity, sexual orientation, race, and ethnicity [94-96]. As reported by Budhwani et al [97],

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acceptability testing and adaptation that are underpinned by user feedback significantly increase the likelihood of intervention relevance, satisfaction, and acceptability in new populations of interest. As previously described in our methods, our team will be conducting this study in various phases to ensure that *SavvyHER* is adapted to ensure a strong fit between the intervention and the community being targeted [98,99]. To date, several studies have described the benefits of CBPR in the literature, particularly in creating interventions that reflect community priorities and perceived needs [96-98]. The research teams' approach of including a diverse array of community stakeholders through CBPR practices, coupled with involving community stakeholders throughout all phases of the research process, can greatly aid in generating awareness and buy-in toward the app on a larger scale [96-98]. Previous literature highlights the need for centering Black voices as a means for discovering knowledge and developing innovative pathways toward advancing health equity [100,101]. The *SavvyHER* mHealth study is spearheaded by Black women for Black women given that they are underrepresented in public health studies as participants and as researchers [102]. By substantively integrating feedback from Black women at the various phases of this study, our team is continuously refining the *SavvyHER* app to ensure that the content, design, and navigation are effective for HIV prevention and treatment among Black women.

Strengths and Limitations

We have developed a rigorous plan to explore the feasibility, usability, and acceptability of an HIV prevention app for Black women and a strong control comparison. However, potential problems could occur, such as technological glitches, feature imbalances, infirm backend support, irrelevant content, and low engagement, which may be limitations to this study. We have built in questions about all procedures for the focus groups and alternative methods to deal with problems that might arise during the study. This study has low external validity given the randomized controlled trial design and the fact that it is limited to Black cisgender women in the metro-Atlanta area. Therefore, generalization to Black women residing in other areas of Georgia or women of other racial or ethnic identities is limited. This study is strengthened through ensuring that researchers are blinded to which participants are assigned to the intervention and control arms. Thus, observer bias will be mitigated, which will help maximize the validity of the results. Another limitation is the potential for social desirability and recall bias during data collection. Qualitative interviewers will be trained to reduce the likelihood of these biases occurring. While the surveys that will be used contain items from previously validated surveys, the overall survey itself has not been validated, which may contribute to some measurement bias. Measurement bias will be reduced, however, through administering surveys at various time points and coupling Google Analytics data with survey data. Lastly, there may be retention issues with the app; however, we have employed reminders and intrinsic motivation strategies to counter this potential issue.

Future Directions

Future directions for the *SavvyHER* app involve the integration of mHealth and telemedicine. mHealth solely allows for self-health monitoring, in which app users can take charge of overseeing their health without the guidance of a health care clinician [103,104]. Incorporating telehealth into *SavvyHER* permits not only patient self-monitoring but also clinician-to-patient and clinician-to-clinician interactions. The telehealth structure authorizes the electronic exchange of personal health information that can be used for full-spectrum remote patient care [105,106]. Previous research notes that clinician-level factors affect uptake, as does the adherence support that patients receive [17,107-109]. In forthcoming iterations of *SavvyHER*, we will create clinician-specific functions and coaching that address culturally relevant SRH concerns for Black women. Testing would comprise of a 3-arm study that would assess a control group, a mobile app user-only group, and a group where *SavvyHER* has a health clinician and patient interaction feature.

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Synergistic Sisters in Science is a research team that investigates how digital health innovations can be designed to support the wellbeing of women, with a particular focus on effecting equitable outcomes in women's reproductive, sexual, and maternal health. We are a group of synergistic researchers from Georgia Tech, Morehouse School of Medicine, and Emory University. Please visit our website to learn more: https://sites.gatech.edu/womenshealthequity/. Additionally, if you are interested in learning more about Sexual/HIV Health Electronic Empowerment Resource (Savvy HER) study or how to get involved please visit our website: https://www.savvyher.me/about.

Data Availability

As this study is currently ongoing, data are not yet publicly available. The authors will make the data available upon request to the corresponding author once the study is completed.

Conflicts of Interest

None declared.

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Abbreviations

ANCOVA: analysis of covariance
API: app programing interface
CAB: community advisory board
CBPR: community-based participatory research
FGD: focus group discussions
HCD: human-centered design
IPV: intimate partner violence

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IRB: institutional review board
mHealth: mobile health
MSM: men who have sex with men
NIH: National Institutes of Health
PrEP: pre-exposure prophylaxis
SavvyHER: Sexual/HIV Health Electronic Empowerment Resource
SCT-MC: Social Cognitive Theory of Mass Communication
SRH: sexual and reproductive health
STI: sexually transmitted infection
SUS: system usability scale

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Protocol

Epidemiological Modeling of the Impact of Public Health Policies on Hepatitis C: Protocol for a Gamification Tool Targeting Microelimination

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Abstract

Background: Hepatitis C is a disease with a strong social component, as its main transmission route is via blood, making it associated with lifestyle. Therefore, it is suitable to be worked on from the perspective of public health policy, which still has a lot of room to explore and improve, contrary to diagnoses and treatments, which are already very refined and effective.

Objective: An interactive gamified policy tool, designated as Let's End HepC (LEHC), was created to understand the impact of policies related to hepatitis C on the disease's epidemiology on a yearly basis until 2030.

Methods: To this end, an innovative epidemiological model was developed, integrating Markov chains to model the natural history of the disease and adaptive conjoint analysis to reflect the degree of application of each of the 24 public health policies included in the model. This double imputation model makes it possible to assess a set of indicators such as liver transplant, incidence, and deaths year by year until 2030 in different risk groups. Populations at a higher risk were integrated into the model to understand the specific epidemiological dynamics within the total population of each country and within segments that comprise people who have received blood products, prisoners, people who inject drugs, people infected through vertical transmission, and the remaining population.

Results: The model has already been applied to a group of countries, and studies in 5 of these countries have already been concluded, showing results very close to those obtained through other forms of evaluation.

Conclusions: The LEHC model allows the simulation of different degrees of implementation of each policy and thus the verification of its epidemiological impact on each studied population. The gamification feature allows assessing the adequate fulfillment of the World Health Organization goals for the elimination of hepatitis C by 2030. LEHC supports health decision makers and people who practice patient advocacy in making decisions based on science, and because LEHC is democratically shared, it ends up contributing to the increase of citizenship in health.

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KEYWORDS

hepatitis C; modeling; public health policies; patient advocacy; mobile phone

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Introduction

Background

Hepatitis C virus (HCV) is 1 of 6 oncogenic viruses, as established by the World Health Organization (WHO) [1]. Its transmission occurs primarily through infected blood, with which one may come in contact through injection drug use, unsafe injection practices, unsafe health care, and the transfusion of unscreened blood and blood products [2]. Estimates indicate that approximately 20% to 30% of the patients initially infected manage to control the acute infection, whereas approximately 75% develop chronic hepatitis C (CHC) [1,3-5].

Hepatitis C is recognized as a major public health concern, with an estimated 58 million people having CHC infection worldwide [1]. A substantial proportion of chronically infected individuals eventually develops cirrhosis or liver cancer. Approximately 190,000 people die annually from hepatitis C–related events, mostly cirrhosis and hepatocellular carcinoma (HCC) [1].

The introduction of new direct-acting antiviral (DAA) drugs dictated a paradigm change in the treatment of hepatitis C. These new drugs are much more effective and safer than their predecessors, achieving cure rates of ≥95% [6,7]. This paradigm change enabled the contemplation of disease elimination.

In May 2016, the World Health Assembly adopted the first "Global Health Sector Strategy on Viral Hepatitis, 2016-2021" [8]. The strategy encompassed a vision of eliminating viral hepatitis as a public health problem. This is encapsulated in the global targets of reducing new viral hepatitis infections by 90% and reducing deaths due to viral hepatitis by 65% by 2030 [8]. The strategy includes raising awareness; promoting partnerships; mobilizing resources; formulating evidence-based policy and data for action; preventing transmission; and scaling up screening, care, and treatment services [8]. However, in each country, several obstacles must be overcome to accomplish the WHO's goals, many of which are related to the implementation of health policies on hepatitis C [9-12].

The effective means to eradicate hepatitis C already exist (eg, therapeutics, national health services financing therapeutics, harm-reduction services, and hepatitis C health care services), but it is still necessary to persuade decision makers by providing robust policy-relevant information that allows the implementation of necessary measures.

An interactive gamification policy tool, designated as Let's End HepC (LEHC), was created to help stakeholders understand how different political decisions may affect the evolution of hepatitis C in their country. The objective was to create an easy and intuitive high-level communication tool to support decision-making with the aim of formulating hepatitis C eradication policies.

Currently, the tool is fully functional in Portugal, Spain, Austria, Romania, and Bulgaria and is being implemented in other countries. The policy tool is based on an epidemiological model that allows assessing the impact of the degrees of implementation of 24 public health policies (PHPs) on the evolution of hepatitis C epidemiology over time, throughout the cure cascade. The system allows for consultation in cross-platforms, such as computers, smartphones, and tablets. Several health outcomes were defined, and it is possible to observe the impact of the degree of implementation of each policy or set of policies on these health outcomes (eg, hepatitis C incidence, hepatitis C prevalence, diagnosed individuals, individuals linked to care, individuals on treatment, cured individuals, individuals with compensated cirrhosis and decompensated cirrhosis [DC], individuals with HCC, individuals requiring liver transplants [LTs], and individuals with liver-related deaths) and consequently to eliminate hepatitis C by 2030. The model contemplates the evaluation of 5 population groups at risk and the total country's population (the sum of all populations at risk). Some policies are specific to a particular population group, thus impacting only that specific group. Therefore, the policy tool may prove to be a useful resource to support evidence-based policy-making by the involved countries' national health authorities.

Hepatitis C Modeling

In the past decades, several studies have developed mathematical models, including Markov chains, related to the natural history of hepatitis C, such as the work of Salomon et al [13,14]. The focus has been the modeling of incidence and prevalence rates, transmission routes, disease burden, and other factors that could be fundamental to the determination of when elimination could be achieved in different countries. Modeling in this area gained momentum with the introduction of DAA as a new effective treatment for hepatitis C in 2014 and the WHO's targets for the elimination of hepatitis C by 2030.

Razavi et al [15] calculated the total number of individuals infected with HCV, including those newly infected with HCV, those diagnosed with HCV infection, and those cured of HCV infection, in 2013 among 16 countries. They also assessed disease burden by forecasting the disease progression and the total number of individuals at each stage of liver disease in each of the 16 countries between 1950 and 2030. Hatzakis et al [16] developed a mathematical model focused on characterizing the population infected with HCV and deaths due to hepatitis C during the same period.

In 2015, the Polaris Observatory HCV Collaborators developed hepatitis C disease burden models for 100 countries [17], with 59 models being approved by experts in each country. Using the Markov chain component in these models, which analyzed hepatitis C prevalence and genotype distribution studies published after 2013, it was possible to calculate both disease burden and disease prevalence in each country.

In 2017, Scott et al [18] conducted research on when Iceland could achieve the WHO's elimination targets. This research was done by developing a mathematical model with a dynamic compartmental nature and performing liver disease assessment related to hepatitis C progression. The model's targeted indicators were injecting drug status, age, and position of the individual in the HCV cascade of cure. This model comprised the analysis of hepatitis C policy implementation in the country while identifying key targets for elimination and factors that could hinder the WHO's objective.

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Chhatwal et al [19] described the importance of components for the mathematical modeling of hepatitis C, such as demographic features, the natural history of the disease, and incidence. This was illustrated for the forecast of hepatitis C burden in the United States, with the comparison of different approaches and strategies to achieve the elimination of the disease by 2030.

Models of hepatitis C have also been developed in Catalonia and applied to PHPs focused on primary health care [20], including a model involving the national health system [21].

In 2019, Tordrup et al [22] modeled the costs of resources and interventions necessary to attain the elimination goal for viral hepatitis in 67 low-income and middle-income countries.

More recently, Razavi et al [23] used Markov chains to forecast the different outcomes related to hepatitis C incidence, prevalence, diagnosis, and treatment, among others, in 45 high-income countries in relation to their progress toward the WHO hepatitis C elimination goal.

Methods

Inputs

For the construction of the LEHC model, the following elements were reviewed, discussed, and validated: (1) each PHP; (2) the acceptable fluctuation ranges of the PHP impact on epidemiology; (3) the application scales on which each PHP would be measured; (4) the identification of national specificities of each country where LEHC would be implemented and necessary adaptations for the modeling process; (5) the discussion of the main sources of published or unpublished statistical data and their qualification; (6) the explanation of the adaptive conjoint analysis (ACA) and its importance as an individual response; and (7) the creation of channels of permanent communication between the national researchers, scientific partners, and National Advisory Board (NAB) and the scientific coordination team of the LEHC model.

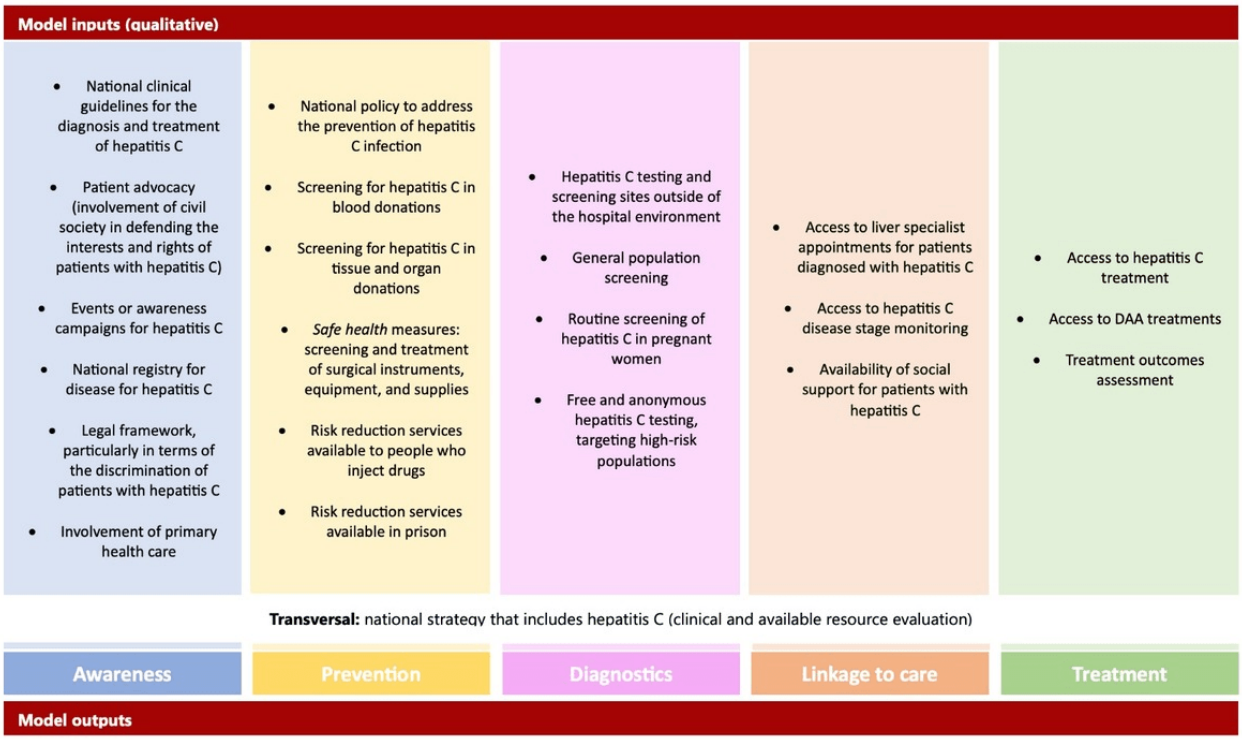
The PHP pool used in the LEHC model was obtained through literature review and in-depth interviews with experts in hepatitis C and the reviewed articles' authors. Three subsequent deliberation sessions of 4 hours each, followed by decision-making, were held with the Portuguese NAB on February 22, 2017, to have an in-depth discussion of the final PHPs to be included in the model. According to a cure cascade reading, a total of 24 PHPs and their application scales were selected.

First, the scientific coordination team of the LEHC model application met with the scientific partners of each country involved in the project in a first moment to discuss the PHPs. Second, there was a meeting with the NABs of each country selected by the corresponding country's scientific partner.

In sum, the epidemiological model considers 24 PHPs and corresponding scales that may impact HCV-related health outcomes in each population group being studied and discussed by approximately 50 national experts in hepatitis C.

Five groups of policies were defined based on the literature review and expert opinion (Figure 1): awareness, prevention, diagnostics, linkage to care, and treatment.

Figure 1. Final qualitative policies of the public health tool and respective outcomes. DAA: direct-acting antiviral.



Each policy was classified into 1 of these 5 groups, thus having a direct positive impact on specific outcomes (Figure 1). Owing to their importance and relevance across the cure cascade, some policies were considered transversal, impacting all the outlined

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outcomes. Each policy has several possible degrees of implementation, ranging from not being available in the country to being available but not fully to being fully available. Each of these degrees results in a different impact on the model outcomes.

Tool Outputs and Outcomes

The impact of the implementation degree of the 24 health policies can be assessed by analyzing 3 groups of indicators: hepatitis C cure, disease stages, and disease elimination within the tool.

The first group comprises the distribution of individuals throughout the cure cascade, in terms of incidence (number of new hepatitis C–positive cases), prevalence (total number of hepatitis C–positive cases), number of diagnosed individuals, number of individuals linked to specialized care, number of individuals on treatment, and number of cured individuals.

The second group comprises the distribution of individuals through the disease stages, number of individuals with compensated cirrhosis, number of individuals requiring LTs, number of individuals with HCC, and number of individuals with liver-related deaths.

The third group comprises the disease elimination (considering cutoffs of 90% in new CHC infections and 65% in mortality) [24].

These outcomes can be evaluated over time (from 2015 to 2030) for a country's total population and each of the population segments considered in the model: (1) individuals who receive blood products, (2) prisoners, (3) people who inject drugs, and (4) individuals who are infected through vertical transmission and the remaining population (total population excluding the other 3 population groups).

Core Model

One of the principal components of the model is an adaptation of the Markov model for the natural history of CHC infection and the impact of treatment, as published by Salomon et al [14]. This model, including stages of Metavir fibrosis and long-term complications such as compensated cirrhosis, DC, HCC, and LT, is widely adopted in the international literature on the cost-effectiveness of hepatitis C treatment and screening.

To be able to calculate the impact of different health policies on the epidemiology of CHC within a population, the aforementioned Markov model was augmented by a cascade of infection, diagnosis, and treatment (referred to as the cure cascade in the remainder of the manuscript). This cascade further divides the population into uninfected individuals, individuals who are infected but not diagnosed, individuals who are diagnosed but not retained in care, individuals who are retained in care but not treated, individuals who are treated but do not achieve subsequent sustained virologic response (SVR), and individuals who are treated and achieve subsequent SVR.

On the basis of these 2 main linked components, all individuals of a particular population subgroup (stratified by age and gender) can be represented in a set of mutually exclusive states through which individuals move over time, much in line with the auxiliary epidemiological model reported in the study by Salomon et al [14].

The impact of different policy measures on the epidemiology of hepatitis C was determined through ACA. For each of the policy measures and their implementation levels, the relative weight was determined based on the total impact on the different steps of the cure cascade.

ACA has proven to be a powerful health decision-making tool because it can go further than the traditional conjoint analysis: the computer adjusts the question following the respondent's previous answer, instead of having hard cards; determines the relative importance of attributes; and associates the preference of choice to its importance [25], as safety procedures are set in place, defined by International Society for Pharmacoeconomics and Outcomes Research. There are 10 International Society for Pharmacoeconomics and Outcomes Research health use safety criteria [25], which were followed in this study. Multiple ACA applications have been developed in recent years in the health field: quality-adjusted life year studies [26], clinical decision-making [27], and choice of prescription [28].

Macrolevel Description of the Conceptual Modeling Framework

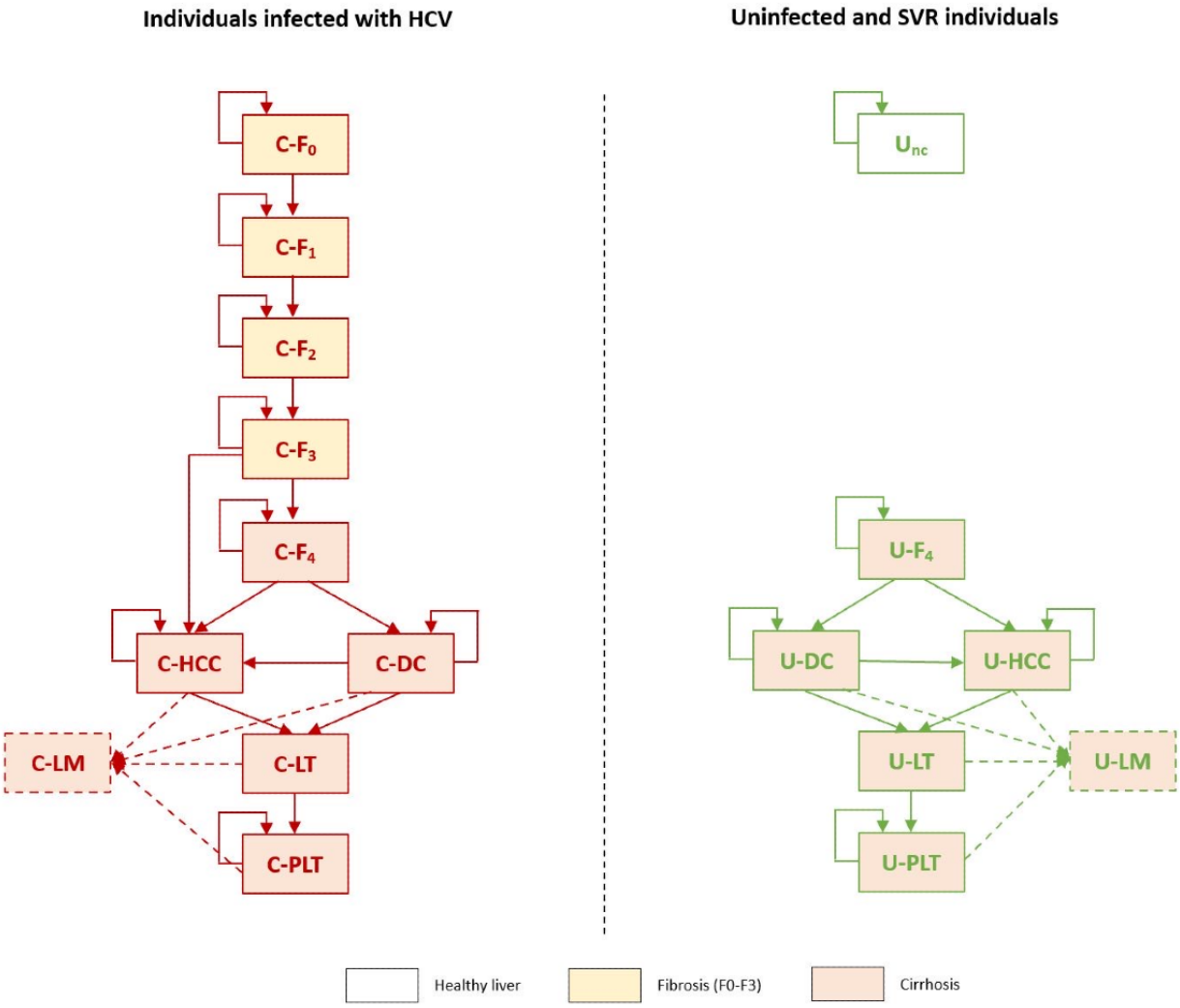
CHC Disease Progression

In terms of CHC disease progression, the population is divided into 2 similar, but distinct, sets of health states with different transition probabilities between their respective states:

1. The first set of health states (left side of Figure 2) corresponds to individuals infected with HCV. This set represents the natural progression of CHC for untreated individuals (or individuals treated but without SVR).
2. The second set of health states (right side of Figure 2) corresponds to uninfected individuals and includes states for cirrhosis's natural progression in individuals with SVR.

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Figure 2. Schematic of the Markov model for the progression of chronic hepatitis C. C: chronically infected; DC: decompensated cirrhosis; HCC: hepatocellular carcinoma; HCV: hepatitis C virus; LM: liver-related mortality; LT: liver transplant; nc: noncirrhotic; PLT: post–liver transplant; SVR: sustained virologic response; U: uninfected.



For the natural progression of CHC, mutually exclusive health states for Metavir fibrosis stages (F_0-F_4) and long-term complications (DC, HCC, and LT) are considered. Individuals progressing to LT pass through a tunnel state representative of the year of transplant, after which they move to a post-LT (PLT) for the remainder of their life. Possible transitions between the health states are identified by arrows (Figure 2).

The health state U_{nc} represents individuals who have never been chronically infected or attained SVR before reaching compensated cirrhosis (F_4). Individuals who attained SVR after reaching compensated cirrhosis, although technically cleared of the virus, are considered to have had irreversible damage to the liver and face disease progression states similar to those faced by individuals chronically infected with cirrhotic (Figure 2).

No explicit health state for acute HCV infection was considered, as it was deemed not to add extra value to the model. For the same reason, no explicit health states for individuals with SVR in Metavir fibrosis stages F_0 to F_3 were considered. Generally presenting with reversible damage to the liver, these individuals are assumed to eventually clear fibrosis [29].

Irrespective of the health state, all individuals experience an age- and gender-dependent general mortality risk [30]. Individuals in the DC, HCC, and LT or PLTs are targeted by liver-related mortality in addition to general mortality.

The annual probabilities of transition between the different health states were obtained from the international literature and are listed in Table 1.

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Table 1. Annual probabilities of transition between the different health states mentioned in Figure 2.

Stage from which transition occurs	Stage to which transition occurs	*P* value	Bibliographic reference
Natural progression			
C[a]-F0[b]	C-F1	.12	Thein et al [31]
C-F1	C-F2	.09	Thein et al [31]
C-F2	C-F3	.12	Thein et al [31]
C-F3	C-F4	.12	Thein et al [31]
C-F3	C-HCC[c]	.008	Younossi et al [32]
C-F4	C-DC[d]	.04	Westerhout et al [33]
C-F4	C-HCC	.02	McEwan et al [34]
C-DC	C-HCC	.08	McEwan et al [34]
C-DC	C-LT[e]	.03	McEwan et al [34]
C-HCC	C-LT	.02	Westerhout et al [33]
C-DC	C-LM[f]	.28	Westerhout et al [33]
C-HCC	C-LM	.51	Westerhout et al [33]
C-LT	C-LM	.15	Westerhout et al [33]
C-PLT[g]	C-LM	.05	Westerhout et al [33]
With sustained virologic response (cirrhotic population only)			
U[h]-F4	U-DC	.005	Westerhout et al [33]
U-F4	U-HCC	.008	Westerhout et al [33]
U-DC	U-HCC	.04	Calculated
U-DC	U-LT	.009	Calculated
U-HCC	U-LT	.02	Assumed to be the same as that for C-HCC to C-LT
U-DC	U-LM	.28	Assumed to be the same as that for C-DC to C-LM
U-HCC	U-LM	.51	Assumed to be the same as that for C-HCC to C-LM
U-LT	U-LM	.15	Assumed to be the same as that for C-LT to C-LM
U-PLT	U-LM	.05	Assumed to be the same as for that C-PLT to C-LM

[a]C: chronically infected.

[b]F0-F4: Metavir stages.

[c]HCC: hepatocellular carcinoma.

[d]DC: decompensated cirrhosis.

[e]LT: liver transplant.

[f]LM: liver-related mortality.

[g]PLT: post–liver transplant.

[h]U: uninfected.

It should be noted that for individuals with SVR, the probabilities of transition from HCC to LT and from DC, HCC, LT, and PLT to liver-related mortality were assumed to be the same as those for the natural progression of the disease because no evidence was found to contradict the natural history of hepatitis C by Salomon et al [13,14]. However, scientific evidence suggests that the transition probabilities from DC to HCC and from DC to LT reduce after achieving SVR. Therefore, these transition probabilities were calculated by applying the same ratio found between the transition probabilities of the corresponding stages for patients without SVR [35].

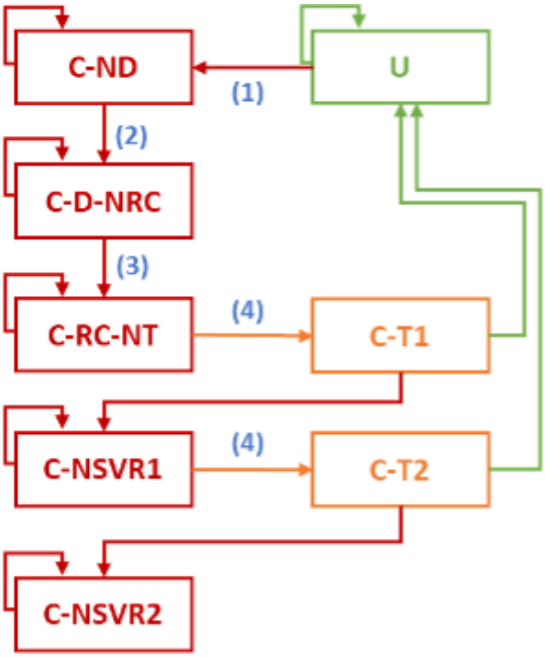
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Cure Cascade

Concerning the cure cascade, the population was further divided into individuals who are uninfected, individuals who are chronically infected but not diagnosed, individuals who are diagnosed but not retained in care, individuals who are retained in care but not treated, individuals who are treated but do not achieve subsequent SVR, and individuals who are treated and achieve subsequent SVR (ie, uninfected). For the ease of modeling retreatment, the key to distinguishing the pre-DAA era from the post-DAA era, individuals without SVR after the first course of treatment are eligible for a second course of treatment.

In Figure 3, possible transitions between the different states of the cure cascade are identified by arrows.

Figure 3. Schematic of the Markov model for the cure cascade of chronic hepatitis C. C: chronically infected; D: diagnosed; ND: not diagnosed; NRC: not retained in care; NSVR1: no sustained virologic response after first treatment course; NSVR2: no sustained virologic response after second treatment course; NT: not treated; RC: retained in care; SVR: sustained virologic response; T1: first treatment course; T2: second treatment course; U: uninfected (including individuals with sustained virologic response); 1: annual incidence; 2: annual probability of diagnosis; 3: annual probability of being retained in care; 4: annual probability of treatment.



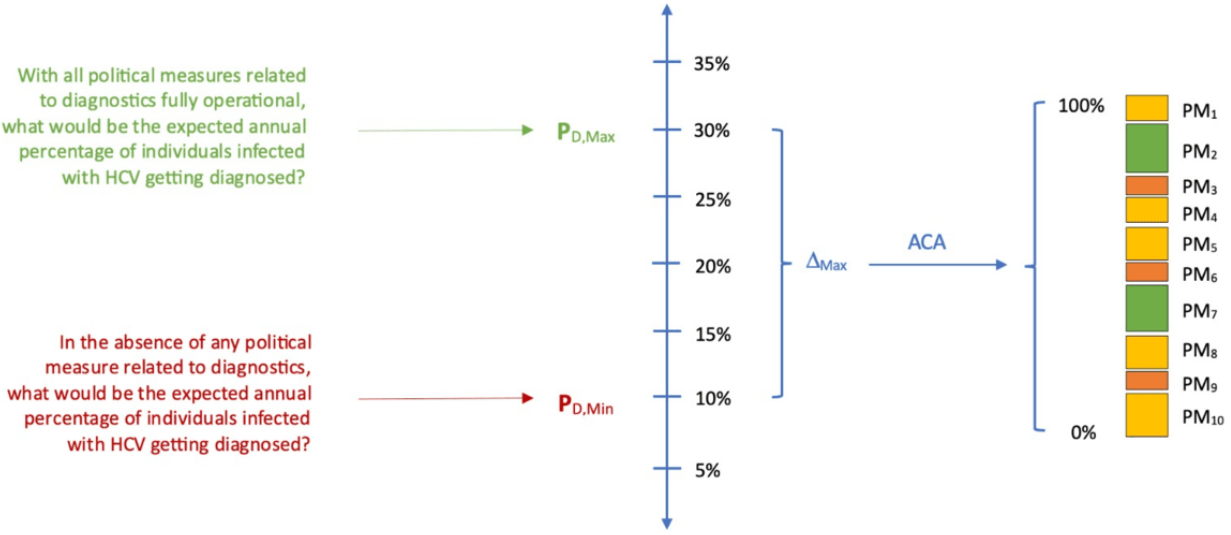
The distribution of individuals across the different states of the cure cascade is highly dependent on the annual incidence of CHC infection (transition 1 in Figure 3), the annual probability of being diagnosed (transition 2), the annual probability of being retained in care (transition 3), and the annual probability of being treated (transition 4). These probabilities are considered variable from country to country or from population subgroup to population subgroup and are impacted by the modeled policy measures.

Impact of Policy Measures

The policy measures considered in the LEHC health policy tool are of a qualitative nature. Their impact on the CHC cure cascade was quantified via a 2-step process. For example, the policy measures' impact on the annual probability of diagnosis will be considered (Figure 4). The quantification of the policy measures' impact on the remaining steps in the cure cascade followed equivalent steps.

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Figure 4. Conceptual model behind the quantification of individual policy measures' impact on the cure cascade (exemplified with the annual probability of diagnosis). ACA: adaptive conjoint analysis; HCV: hepatitis C virus; PMi–ith policy measure.



In the first step, an expert panel was asked to address 2 important questions:

1. In the absence of any policy measure related to diagnostics, what would be the expected annual percentage of individuals infected with HCV getting diagnosed ($P_{D,Min}$)?
2. With all political measures related to diagnostics fully operational, what would be the expected annual percentage of individuals infected with HCV getting diagnosed ($P_{D,Max}$)?

The difference between these 2 values defines the maximum impact ($\triangle_{Max}$) the policy measures can have on the annual probability of diagnosis (Figure 4).

In the second step, each policy measure's contribution to the maximum impact was determined. A simple solution could be to assume that this amount is equally distributed across the policies in question. In the case of 10 policy measures impacting diagnostic rates, this would mean that each policy measure's implementation would add one-tenth of $\triangle_{Max}$ to the annual rate of diagnosis starting at $P_{D,Min}$. However, it is highly unlikely that policy measures related to patient advocacy will have the same impact on annual diagnosis rates as those related to general population screening.

Conjoint analysis techniques were used to determine a more realistic relative weight of each policy measure (and their level of implementation) on the maximum possible impact. These techniques are ideally suited to quantify the relative importance of different, often qualitative, attributes considered important for decision-making. The same expert panel that was requested to pronounce itself on the maximum impact of the policy measures on the annual probability of diagnosis was consulted to determine these relative weights using the commercial ACA Sawtooth Software (Figure 4) [36].

It is important to note that the global policy impact defined for the LEHC project is solely a temporary solution based on an average value, as it is thought that each policy will have an inherent impact that may differ from those of the others. The found solution was based on a qualitative approach resulting from a consensus among hepatitis C experts to fill the gap of no quantitative studies being found on each of the 24 PHPs considered for the LEHC model. Considering this, further research is necessary to identify the impacts of each of the studied PHP, which requires various research lines encompassing elements such as different cultures and legislations in different countries. Nonetheless, the developed work in the LEHC project provides a basis for discussion toward future research, having defined a maximum policy impact of 30% in the model. Although defining the global impact of PHP is not within this study's scope, it is still important to identify it as a possible limitation.

Model Initialization

On the basis of the 2 main Markov model components of the LEHC health policy tool (CHC disease progression and CHC cure cascade), all individuals of a particular population subgroup (further stratified by age and gender) can be represented in a set of mutually exclusive states through which they move over time.

Starting from the current (ie, 2017) configuration of individuals over the different model states, the health policy tool aims to assess the viability of eliminating CHC infection by 2030, under different scenarios of policy measure implementation, in the different countries and population subgroups being assessed. Elimination is defined as a percentage reduction in CHC prevalence between 2015 and 2030 above a certain high threshold (eg, 90%).

Given the complexity of the model, considering simultaneously up to 9 progression health states, 8 cure cascade states, 7 age groups, and 2 genders, it is easily understood that the population is stratified over up to 1000 mutually exclusive model states at each point in time. Knowing that a large part of the population with CHC is suspected to be undiagnosed in many countries, it is highly unlikely to find any country or population subgroup

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where an exact or approximate distribution of all individuals over these many states might be available.

An informal back-calculation [37] approach was used to infer a plausible current configuration of individuals over the different model states. To this end, the best possible qualitative, quantitative, longitudinal, cross-sectional, and historical data available for each population subgroup were used. On the basis of these data, the informal back-calculation involved choosing parameter values (such as incidence and diagnosis rates), observing how closely the model simulations for the most recent years are aligned with the scarce data available, and adjusting accordingly.

Population Groups

The model integrates 5 different populations (Table 2) that are susceptible to HCV infection. These populations are dynamic inside each group but are considered mutually exclusive.

Table 2. Population groups included in the epidemiological model.

Group	Definition
Remaining population	This population includes the country's overall population, excluding all the individuals from the remaining population groups (people who inject drugs, prisoners, and people who use blood products).
People who inject drugs	This population represents the national population of injectable drug users. Note that this population does not include drug users who do not inject drugs. As there is a significant overlap between people who inject drugs and prisoners, as a great number of prisoners are also people who inject drugs, and as it has been assumed that the different groups in the model are mutually exclusive, it was defined that this population group only includes the people who inject drugs who are not incarcerated.
Prisoners	This population includes convicted prisoners with sentences >1 year. As the model was constructed on an annual basis, all the preventive prisoners and convicted prisoners with penalties <1 year were excluded.
People who receive blood products	This population includes individuals who have received blood transfusions or blood derivate products.
Individuals infected through vertical transmission	This population is included within the remaining population group. It represents all individuals who were infected through mother-to-child transmission during birth.
Total population	This population is composed of the whole country's population, meaning that it is the sum of all other population groups.

To simulate the epidemiological evolution of hepatitis C for the retrospective period between 1950 and 2016 (model initialization), a series of prespecified inputs must be collected from the available literature for each of the different population groups. Some of these inputs are also required prospectively for the period between 2017 and 2030. For all the missing information, a series of assumptions must be made. The methodology for data gathering, followed for data processing, is described below.

Demography

Demography refers to the population size over the years. For the remaining population, it consists of the resident population size of a country and the number of live births to estimate the changes in population size over time, every year between 1950 and 2018, stratified by gender and age classes.

The other population groups consist of the total number of individuals belonging to each one per year from 1950 to 2030 stratified by gender and age class.

Turnover

Turnover refers to the number of people who enter (turnover in) or exit (turnover out) the population group each year per age group between 1950 and 2030.

For the remaining population, turnover in consists only of live births. Turnover out should be equal to the number of people who enter other population groups.

For people who inject drugs, turnover in consists of people who start injecting drugs each year. By contrast, turnover out consists of all individuals who stop injecting drugs each year, thus leaving this population and becoming part of the remaining population.

For prisoners, turnover in consists of arrested and incarcerated people during that year, whereas turnover out consists of all individuals released from prison during that year, thus becoming part of the remaining population.

For patients receiving blood products, turnover in consists of people who enter the population each year. As people never stop being ex-transfused, it was assumed that there is no turnover out for this population other than mortality, which is a structural component of the model.

Background Mortality

Background mortality refers to the annual probability of death in each population group per year between 1950 and 2030 stratified by age group and gender.

Hepatitis C Incidence

Hepatitis C incidence refers to the number of new chronic HCV infections in each population group per year between 1950 and 2018 stratified by gender and age class. In the remaining population, all new infections occurring in the other population groups should be accounted for.

Hepatitis C Prevalence

Hepatitis C prevalence in the remaining population refers to the predicted prevalence of chronic HCV infections over the years, stratified by gender and age class. Only patients with CHC, who do not belong to any of the other population groups should be considered.

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Hepatitis C prevalence in the other population groups refers to the total number of chronic HCV infections in each population per year between 1950 and 2018 stratified by gender and age class.

Diagnosis

Diagnosis refers to the annual probability of an infected individual being diagnosed in each population group per year between 1950 and 2018 according to gender, age group, and disease stage.

Retain in Care

Retain in care refers to the annual probability of a diagnosed individual being retained in care in each population group per year between 1950 and 2018 according to gender, age class, and disease stage.

Treatment 1

Treatment 1 refers to the annual probability of an infected individual being treated for the first time against hepatitis C if already retained in care in each population group between 1950 and 2018 according to gender, age group, and disease stage.

Treatment 2

Treatment 2 represents the patients' second treatment against CHC and should only consider DAA class therapies. It refers to the annual probability of an infected individual being retreated if retained in care and previously treated in each population group according to age and disease stage for the years between 1950 and 2018.

SVR in Treatment 1

SVR in treatment 1 represents the probability of a patient achieving an SVR in the first treatment against HCV in each population group for the period between 1950 and 2030.

SVR in Treatment 2

SVR in treatment 2 represents the probability of a patient achieving an SVR with the retreatment with DAA therapy (treatment 2) in each population group for the period between 1950 and 2030.

Ethical Considerations

In compliance with Portuguese legislation, our study did not involve access to patients' clinical data, personal interactions with them, individual medical records, or consultations with hospital databases. Our research solely relied on elements published in peer-reviewed scientific literature or official state reports. As a result, ethical committee approval was not necessary.

Results

The construction of the LEHC model had to proceed with an adaptation to the practice, involving the construction of proxies in the modeling process. The LEHC model comprised an average production time of 3000 hours per country, considering all the interventions, from data collection to obtaining a fitting.

The model was applied to a set of countries; studies in 5 of these countries have already been completed or are currently under publication process [38-42], and those in the remaining countries are in different conclusion phases, with data being available on the LEHC website for the period between 2017 and 2019.

The double imputation model allowed the assessment of a set of indicators such as LT, incidence, and deaths year by year until 2030 in different risk groups.

Initial feedback from decision makers in pilot countries suggests that the modeling tool was helpful for the politicians. The tool allows people to simulate even seemingly strange or counterintuitive solutions with privacy simply to verify data movements' sensitivity. The simulation processes enabled the health decision makers and the politicians to provide answers about the tool's performance limits and illustrate with concrete, measurable, and externally verifiable facts [38-42].

Discussion

Principal Findings

It was possible to create a gamified system in which even people who are not experts in the field of hepatitis C can have an informed opinion and simulate different technical solutions for their country. This technological opacity solution allows people to use a modeling tool without the need for knowledge about medicine or mathematics. The gamification of the tool allows people to get an idea of which policies can be invoked and the corresponding degree of application by testing different scenarios. This process enables people to be knowledgeable about the impact of policies on different populations and the country as a whole.

The "democratization" provided by gamification puts citizens involved in patient advocacy on the same level as people linked to patient associations and other civil society members (patients, family members, and employers, among others). This is due to allowing the discussion with a technical basis regarding the impact of policies that can be implemented and the practical limitations in contexts with a strong will to eliminate hepatitis C by 2030.

Similarly, for politicians and health system decision makers, the gamification of scenarios allows an instantaneous simulation of each policy's impact on the main health indicators explained earlier.

Limitations

Several types of limitations were identified throughout LEHC, and some of them are highlighted subsequently.

Model Construction

In terms of model construction, there were many requests from politicians and health system decision makers to add a component of financial analysis to the routines and simulation algorithms, which is not very complex. However, it was not possible to take this step because of the lack of funding for this component. This would also further increase the number of statistical series to be collected and worked on, which would not be feasible with the available resources. Nevertheless, we consider that this new functionality would be very advantageous, as it would allow countries to simulate the policy itself and

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verify the financial impact that one option has in comparison with another, although it may only be in order of magnitude.

How countries collect and systematize their data varies enormously, complicating and sometimes even preventing direct comparability between identical statistical series. In addition, there is still a need to unify the systematics and ontologies related to hepatitis C (at least at the European level). Even at the country level, the existence of autonomous regions means that there are different health conditions, health legislations, and assistance rights of citizens existing in parallel, making it difficult to obtain a national framework. The solution we found was to work with only 1 region, for example, as was the case in the United Kingdom, where LEHC was applied to England (study on which is almost complete but not finalized), or to work in all autonomous regions, as was the case in Spain, by creating unification proxies, which required tremendous effort and caused great difficulty. In our reading, the only solution for the future will be to create an LEHC at 2 levels, national and regional, for countries that have autonomous health systems. If this option is to be chosen, the efforts made for a country should be multiplied by the number of autonomous regions in that country, provided that all the regions have detailed data for hepatitis C.

Model Application

It must be noted that no country managed to have all the necessary data for the LEHC model. When the series existed in >1 bibliographic source, they were almost always partial or contradictory. There was a need to produce hundreds of proxies with the support of local research teams and validate the data with the NABs based on international experts' experiences.

Even the statistical series available on hepatitis C and populations with risk behaviors for this disease have always been incomplete in terms of the model's requirements. Specific data often focused on specific populations. Even when considering a population with risk behaviors, data sometimes represented specific time periods, specific regions, or different data collection methodologies, which necessitated enormous efforts in finding common denominators.

Another limitation of the model was that the experts constituting the NABs often seemed to be comfortable assessing the impact of some of the modeled policies but not the others. An important predictor of this difficulty was the professional experience of NAB members with specific populations.

Comparison With Prior Work

This work differs from the existing models, as it targets the simulation of PHPs focused on hepatitis C in an innovative way by using gamification processes, allowing citizens to simulate PHP application in the disease, a possibility that until now has been reserved for specialists. The epidemiological modeling in LEHC was seamlessly integrated into decision-making processes through a unified solution.

As in previous works mentioned in the literature review [15,18-21,23], modeling allowed obtaining a set of indicators, as explained above. Similarly, as stated in the appointed application articles for this model [38-42], although there were differences in the year of elimination of hepatitis C (according to WHO criteria), these were not structural until the COVID-19 pandemic. It must be noted that COVID-19 represents a threat to allocated efforts to achieve the elimination of hepatitis C by 2030, with the disease elimination programs being highly impacted [43-45]. In addition, the results that were different were essentially because of distinct assumptions regarding the implementation intensity of PHPs, which points toward an interesting concurrent validity.

Conclusions

The LEHC model combines epidemiological mathematical modeling in its classic sense with the modeling of political decision-making in a single solution. It can simulate different policies with different implementation degrees, thus allowing the anticipation of results concerning different options, making it a potential tool for political decision-making on hepatitis C.

One of the main conclusions is that the tool is able to generate solutions that can be specific for each reality, in which each country ends up needing a set of specific PHPs to address the need to eliminate hepatitis C by 2030. This means that there is an enormous cultural component in the sense of diverse lifestyles, legislations, and social history in general, which the LEHC tool, with its adaptive flexibility, responds to.

This does not mean that the values provided by the LEHC tool should be understood as exact numbers from the past or the future. Like all models, LEHC depends heavily on the quality of the input data, and it was very clear to the authors that there is unlimited dominance in the data from all countries, namely for highly specific data, such as information about people who inject drugs. Therefore, this explains how even the largest organizations have made epidemiological corrections of 40% to 50% in recent years. In our reading, this limitation does not remove the merit and interest of the LEHC tool, and on the contrary, it encourages research and may also be a call for research.

The general meaning of PHP turns out to almost always be the intensity of its use and the potential consequences that can be gained by intensifying it. This is where LEHC provides invaluable help to decision makers and patient advocates, as per feedback that has been collected from these 2 social groups.

The integration of the tool into a gamification system allows anyone interested in hepatitis C to forecast both the current policies that appear as standard and those that are intended to be tested to seek alternative paths. Therefore, it is legitimate to point LEHC as a patient advocacy tool.

Hepatitis C is going through a very problematic phase, discovering millions of cases that still exist outside the health systems; those that were in the area of knowledge in general have already been integrated into the processes of diagnosis and treatment. Because those who remain outside the system are socially opaque, they cannot not be integrated into treatment using just the usual clinical and public health measures because if that were possible, after 8 years of efforts by the health systems, these people would already have been treated.

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We have to get out of the standard practices and find social forms based on social segmentation, with PHPs that cover beyond the usual spheres of health to capture the tens of millions of people who are outside. If such a strategy is not adopted, we will somehow be doomed to have viral reservoirs in uncertain parts of the social system, which will feed the reinfections of those who have already been treated as well as disseminators among those who are not yet sick.

LEHC being an integrated and articulated structure of PHPs can make a very positive contribution to join all the other structures that are currently being developed throughout the disease cure cascade.

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Authors' Contributions

RB-L, HL, BV, JF contributed to study concept and design. HL, BV, and JF were involved in data acquisition. BV, JF, HL, TC, and HB were involved in data analysis and study supervision. HL, HB, and DF drafted the manuscript and provided administrative support. RB-L and HL critically revised the manuscript for important intellectual content. All the authors approved the final version of the manuscript for publication.

Conflicts of Interest

None declared.

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Abbreviations

ACA: adaptive conjoint analysis
CHC: chronic hepatitis C
DAA: direct-acting antiviral
DC: decompensated cirrhosis
HCC: hepatocellular carcinoma
HCV: hepatitis C virus
LEHC: Let’s End HepC
LT: liver transplant
NAB: National Advisory Board
PHP: public health policy
PLT: post–liver transplant stage
SVR: sustained virologic response
WHO: World Health Organization

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Protocol

Development of the ehive Digital Health App: Protocol for a Centralized Research Platform

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Abstract

Background: The increasing use of smartphones, wearables, and connected devices has enabled the increasing application of digital technologies for research. Remote digital study platforms comprise a patient-interfacing digital application that enables multimodal data collection from a mobile app and connected sources. They offer an opportunity to recruit at scale, acquire data longitudinally at a high frequency, and engage study participants at any time of the day in any place. Few published descriptions of centralized digital research platforms provide a framework for their development.

Objective: This study aims to serve as a road map for those seeking to develop a centralized digital research platform. We describe the technical and functional aspects of the ehive app, the centralized digital research platform of the Hasso Plattner Institute for Digital Health at Mount Sinai Hospital, New York, New York. We then provide information about ongoing studies hosted on ehive, including usership statistics and data infrastructure. Finally, we discuss our experience with ehive in the broader context of the current landscape of digital health research platforms.

Methods: The ehive app is a multifaceted and patient-facing central digital research platform that permits the collection of e-consent for digital health studies. An overview of its development, its e-consent process, and the tools it uses for participant recruitment and retention are provided. Data integration with the platform and the infrastructure supporting its operations are discussed; furthermore, a description of its participant- and researcher-facing dashboard interfaces and the e-consent architecture is provided.

Results: The ehive platform was launched in 2020 and has successfully hosted 8 studies, namely 6 observational studies and 2 clinical trials. Approximately 1484 participants downloaded the app across 36 states in the United States. The use of recruitment methods such as bulk messaging through the EPIC electronic health records and standard email portals enables broad recruitment. Light-touch engagement methods, used in an automated fashion through the platform, maintain high degrees of engagement and retention. The ehive platform demonstrates the successful deployment of a central digital research platform that can be modified across study designs.

Conclusions: Centralized digital research platforms such as ehive provide a novel tool that allows investigators to expand their research beyond their institution, engage in large-scale longitudinal studies, and combine multimodal data streams. The ehive platform serves as a model for groups seeking to develop similar digital health research programs.

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KEYWORDS

digital health; wearable devices; research platform; eHive; smartphone; wearables; digital technologies; digital study; multimodal data collection; framework; development; centralized digital research platform; ehive app; mobile phone

Introduction

Background

The increasing use of smartphones has provided an opportunity for the growth of mobile health apps for studying health and disease. These apps enable engagement with participants throughout the day, remotely, and at a high frequency. They allow for the collection of patient-reported outcomes measures (PROMs) through surveys, the assessment of social media use, website tracking, and the examination of patterns of phone use [1]. Similarly, wearable and connected devices for ambient sensing are increasingly accepted and used in the United States [2]. Commercial and custom devices can collect physiological data from users continuously and without active input.

Digital technologies are increasingly used to help overcome the limitations of traditional research, such as limitations to recruiting sufficiently large and diverse cohorts and tracking day-to-day changes in participant conditions [3,4]. Remote digital study platforms represent a subset of digital platforms comprising a patient-interfacing digital application that enables multimodal data collection from a mobile app and connected sources. They offer an opportunity to recruit at scale, acquire data longitudinally at a high frequency, and engage study participants at any time of the day in any place [5,6]. These multimodal platforms collect PROMs, provide study content such as videos or other engagement tasks, and collect objective environmental and connected device data. They can enable the electronic onboarding of participants through an e-consent process and establish individual baselines that allow for the construction and forecasting of individual patient trajectories [7].

Many app-based studies and platforms often suffer from low rates of retention and adherence [8-11]. Factors such as perceived utility, value, convenience, and usability have been identified as barriers to use [12]. However, a centralized and agile digital research platform offers an opportunity to improve engagement and mitigate many factors that drive low adherence rates. Through the concerted development and expansion of a central modifiable research application, usability and engagement tools can be optimized across the platform. This mitigates the need to develop single-use applications, enabling the successful growth of digital research across disciplines. The ehive studies platform is the centralized digital research application of the Mount Sinai Health System (MSHS) in New York. It is a proof-of-concept platform that incorporates the elements and features most necessary across studies, uses recruitment and retention features, outlines data collection elements, and assures patient privacy and safety. It serves as a potential model for other health systems and organizations seeking to develop centralized digital research programs.

Overview

Here, we describe the ehive research platform and its features to provide a road map for the development of similar infrastructure. In the following sections, we first describe the technical aspects and functionalities of the ehive platform, including participant consenting procedures and privacy protection. Then, we provide information about ongoing studies hosted on ehive, including usership statistics and data infrastructure. Finally, we discuss our experience with ehive in the broader context of the current landscape of digital health research platforms.

Methods

Digital Platform Development

The MSHS (New York, New York) includes the Icahn School of Medicine at Mount Sinai and 8 hospitals in the New York metropolitan area. It comprises the largest health system in New York City, with one of the most diverse patient populations in the United States [13]. The Hasso Plattner Institute for Digital Health at Mount Sinai (HPI.MS) was founded in 2019 and represents an international academic collaboration between the Hasso Plattner Institute for Digital Engineering in Potsdam, Germany, and the MSHS in New York City, United States [14]. The COVID-19 pandemic highlighted the need for a digital alternative to the in-person studies conducted by the MSHS, which was seen as an imperative future direction. To meet this need, HPI.MS launched the ehive digital research platform in early 2020 with the initial goal of creating a platform to support multiple studies and study types. The initial design of ehive drew upon the prior experiences of the digital health and clinical research faculty, who were charged with its development. The ehive platform is overseen by a program within HPI.MS called the Digital Discovery Program (DDP [15]). The DDP is responsible for maintaining ehive and determining which studies will use the platform and how the platform will be modified and evolve over time. Although the DDP determines the short- and long-term goals of the app, input is solicited from researchers using the app and study participants. Study-specific modifications are undertaken during the planning and development phase of each study, which can be applied across the platform. Any unsolicited feedback from the participants using the app is evaluated by the DDP and incorporated into future modifications.

This multimodal digital platform can be used on both iOS (Apple Inc) and Android (Google LLC) mobile devices and is designed to support multiple independent research studies via the collection of remote consent and PROMs and integration of data from commercial and custom wearable devices, electronic health records (EHRs), and biobanks.

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Recruitment, Retention, and Monitoring

Research participant recruitment and retention is challenging and an important determinant of research success [16]. Digital tools such as email messages, SMS text messages, websites, and smartphone apps are increasingly used to assist with participant recruitment and retention and help eligible participants find potential studies [17]. The ehive platform was developed with unique capabilities to assist investigators with study recruitment, including bulk messaging through the EPIC EHR system and standard email portals. The lists of potential study participants meeting the specified inclusion criteria can be generated through a data warehouse system hosted by Mount Sinai. This system collates identified and deidentified data from the EHR, including email addresses. Using this infrastructure, investigators can run queries through the EPIC system to find participants who meet the study eligibility criteria. Through ehive, investigators can send automated recruitment messages to the EPIC MyChart messaging inbox of this cohort. Alternatively, ehive can send automated messages via email using prespecified email distribution lists collected from the data warehouse. These 2 approaches allow for broad engagement with potential participants, enhancing study visibility throughout the health system. This facilitates the recruitment of diverse participant populations, the lack of which is a significant limitation in many digital studies. The ability to engage with individuals across the health system ensures that a large population of patients can become aware of specific studies relevant to them, including patient populations that may be difficult to reach via traditional recruitment methods and across socioeconomic statuses.

Participant retention and engagement are key drivers of data quality and research study success. Over half of the participants in digital studies stop participating after the first week [18]. Frequent light-touch reminders for participants to engage in study activities are often used in digital studies to maintain compliance [12]. The ehive platform was developed with several light-touch features. Smartphone push notifications are generated at customizable frequencies, in customizable language, and at modifiable times of the day to remind participants to complete study tasks and use their connected devices. The app can send modifiable email messages to participants that welcome them to the study, thank them for participating, and remind them to maintain engagement. The ehive app is designed for automated compliance monitoring using customizable engagement thresholds for each study, which generate these customized push notifications or emails for participants or study staff. This permits the passive monitoring of a large number of study participants and initiates re-engagement if compliance drops below the specified thresholds. Depending on the specific study, the app allows participants to tailor their ehive experience based on their daily schedule, providing them the option to customize when they receive notifications and which notifications they receive.

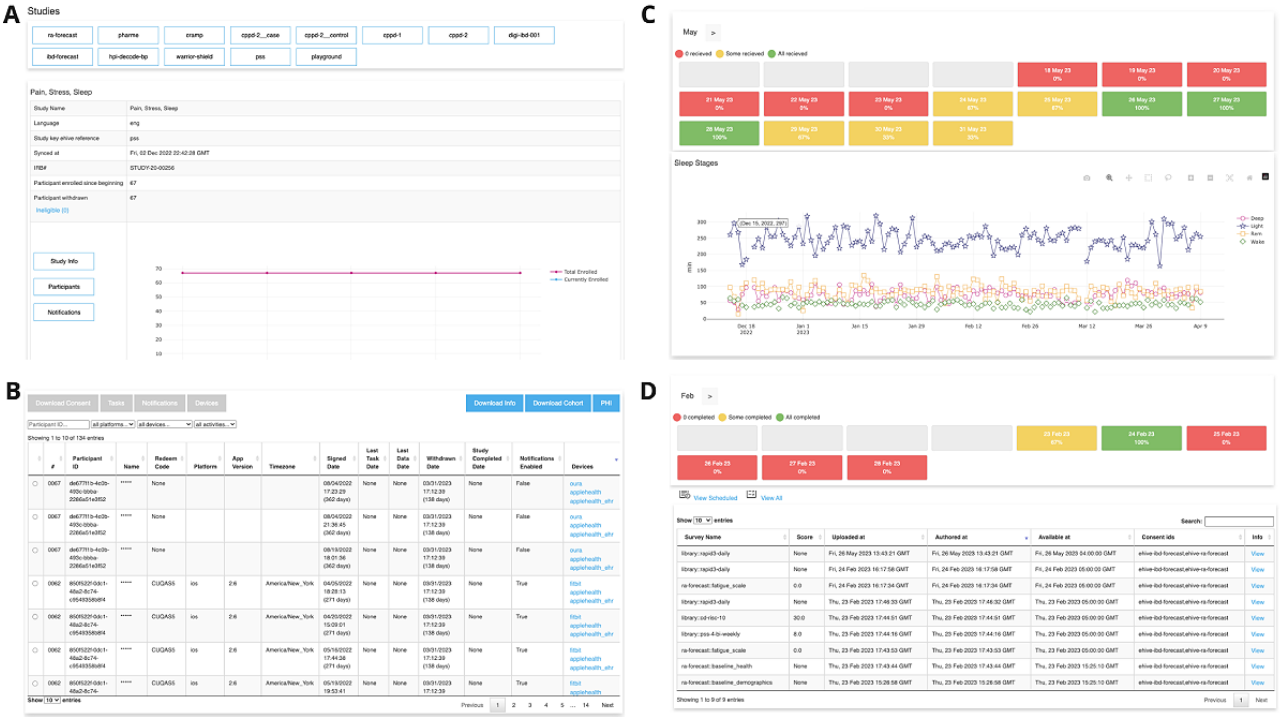
Research Dashboard

A central ehive dashboard is available to monitor participant engagement across studies (Figure 1). The dashboard allows the visualization of ongoing and completed studies and can be tailored to grant specific personnel access to specific studies. Access is granted via invitation, and the dashboard is accessible only through the MSHS virtual private network. The Azure Active Directory manages dashboard log-ins, and role access is managed by an honest broker who has administrative access to the dashboard. The dashboard has multiple features, including an interface for participant and study team communication, a data review feature, and a feature for visualizing data trends based on the information collected from wearable devices and PROMs. Access to each feature can be granted based on the role of the user in each study, as specified in the institutional review board (IRB) approval. This allows research coordinators to actively interact with study participants through custom push notification features or emails, which can be generated within the dashboard. In addition, this allows researchers to interact with the data in a deidentified or an identified fashion based on the study requirements.

Various customizable features allow the study team to change the consent language, task language, and task scheduling as well as to add and remove integrated wearable devices. Customization can be done seamlessly and does not require the release of an app update. This agile solution enhances user experience by allowing researchers to correct errors and provide real-time feature deployment without triggering app updates. Major app updates are available on digital stores (Apple App Store [Apple Inc] and Google Play [Google LLC]), and participants are automatically notified to manually update the app. The ehive team encourages a soft launch of each study to enable the identification and correction of any problems. After the enrollment of the first several participants, study compliance and data quality can be reviewed to enable early modifications of task language or schedules before full-scale enrollment is undertaken. Each data point collected through ehive is time-stamped. All changes to the consent procedure, tasks, or other study components are stored in a change log within GitHub. Using the time stamp associated with study data and the change log, data versions can be tracked and evaluated during the analysis phase.

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Figure 1. The ehive study dashboard for participant monitoring. (A) Individual studies can be selected to gather study details and visually track enrollment and compliance. (B) Participant information can be visualized for each study, which is provided as an interactive list with participant contact information, unique study IDs, date and time of enrollment, withdrawal date, copies of each signed consent form, and information on patient-reported outcomes measures (PROMs) and wearable data. (C) Wearable device data trends can be visualized for each participant, including sleep and heart rate variability data. (D) Survey data from each participant can be visualized.



Downloading ehive and Providing e-Consent

The ehive app can be downloaded free of charge from the Apple App Store and Google Play and is designed for users to remotely onboard themselves (Figure 2). The introduction screen allows individuals to view publicly available studies and publications generated from research conducted on the platform. This interface allows users to explore publicly available studies and join these studies if they meet the eligibility criteria. Non–publicly available studies are not visible in the ehive app unless potential participants are provided with a link and log-in credentials to reveal and unlock the study on their ehive dashboard.

The consent process is customizable for each study and can include a brief study introduction; an eligibility screener; and, subsequently, an e-consent review and signature process (Figure 3). The eligibility screener verifies that the participant meets the study criteria. This verification of inclusion and exclusion criteria matches user's answers to questions locally on the phone and does not store this information as study data, as this is done before the study consent process. The subsequent e-consent process incorporates visualizations on the interface to explain concepts, communicate the impacts of the study, and highlight the benefits and risks to participants. This process allows potential participants to read and learn about the study information at their own pace, with the option of contacting the study team with questions at any point. A review of the concepts of e-consent is followed by a series of comprehension questions that assess the participant's understanding of the key aspects of the study. The e-consent process allows participants to move back and review any material again, as needed. If potential participants fail the study concept quiz 3 times, they are deemed ineligible for the study, and the study is locked to future enrollment. This can be manually reset by the study team if required. Once the study concept quiz is completed by a potential participant, the IRB-approved consent form is available for review and electronic signature. A signed pdf version of the consent form is then generated and stored in the app for future reference. Depending on the study requirements, the e-consent process can be performed either solely by the participant or can involve a study coordinator (Figure 4).

After the e-consent form is signed, participants can review and select the data streams to be shared with the research team through a data control permission process (Figure 5). Data streams can range from wearable device data to other modalities such as EHR data. If a participant is enrolled in a second study, the app will notify them regarding the need to once again select the data streams to be shared. Permission for wearable data access is provided at the study level, which allows the participant to use the same or additional devices and decide which data to share for each study. This places data-sharing control in the hands of participants and allows them to customize their choice for each study. This permission is modifiable and can be edited or revoked by participants at any time.

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Figure 2. An overview of the major features of the ehive app. Participants can scroll through the available studies, provide consent for studies that interest them and whose eligibility criteria they meet, complete daily tailored study tasks, and share wearable and other health data. IBD: inflammatory bowel disease.

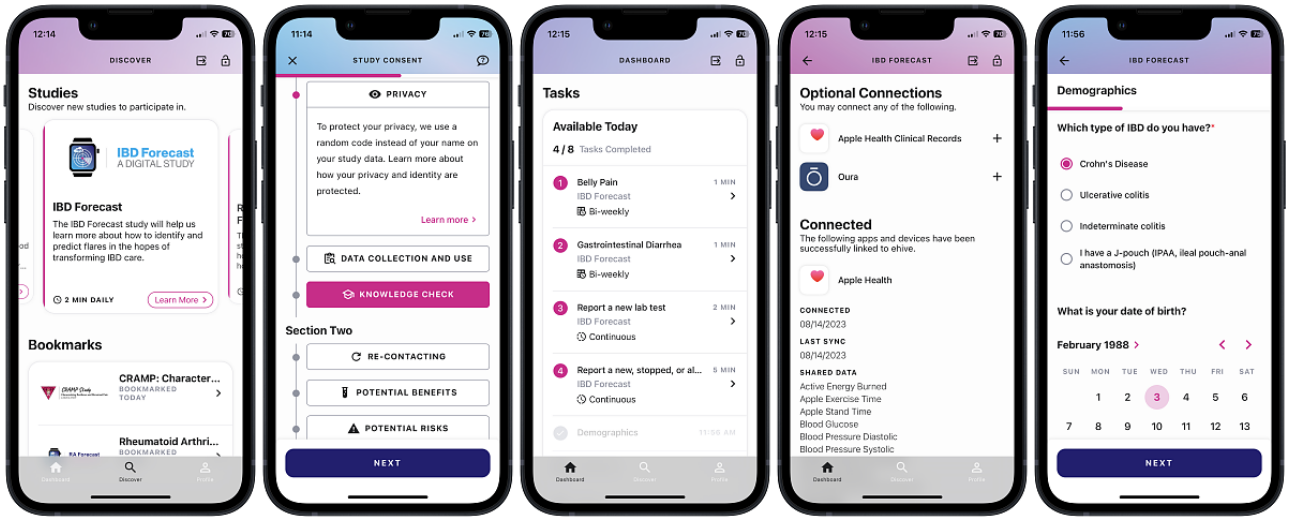
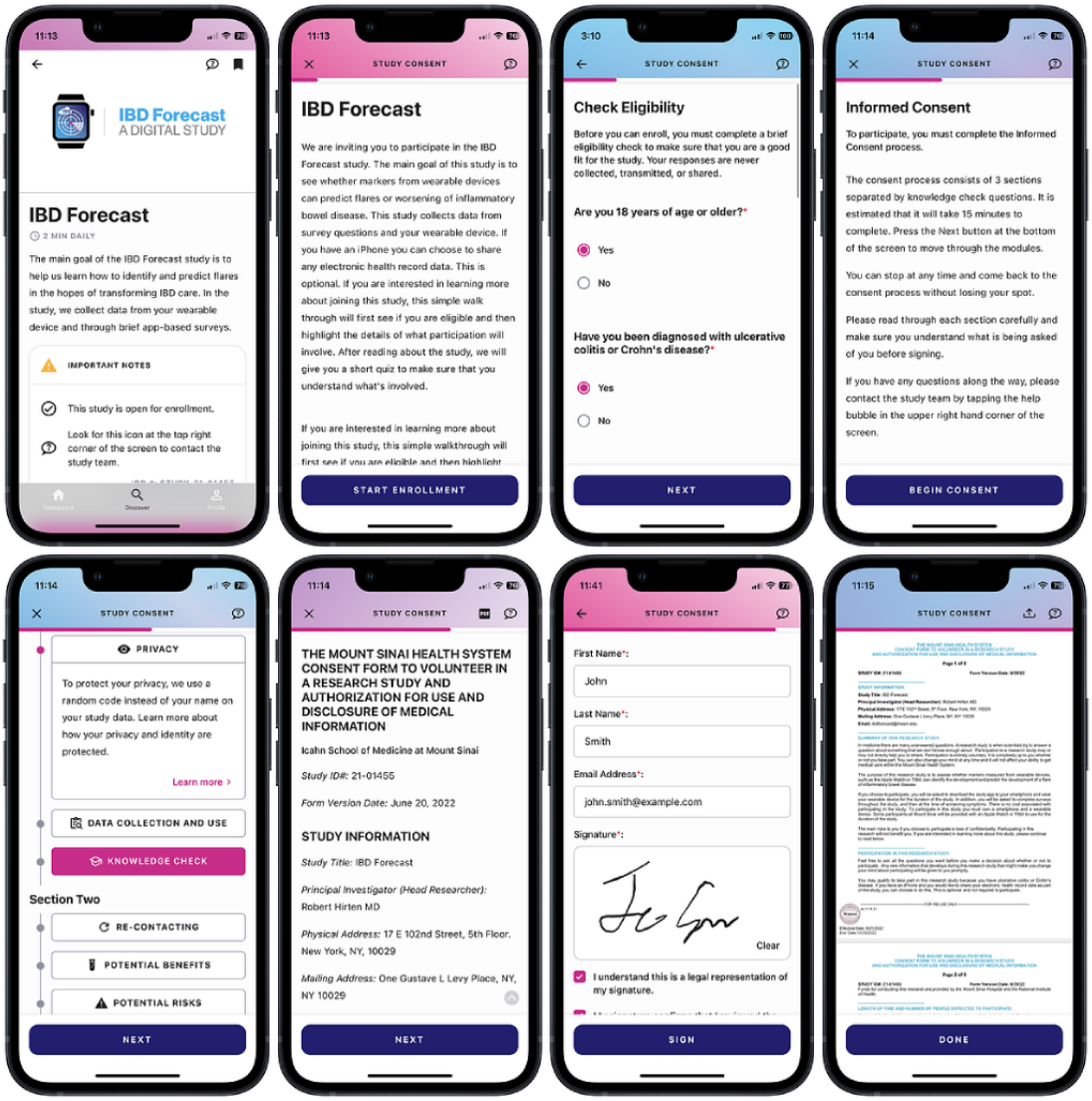


Figure 3. The sample e-consent process in ehive. A brief introduction to the study is provided, followed by participants checking whether they meet the eligibility criteria. If inclusion and exclusion criteria are met, participants are taken through the consent form and required to complete a study comprehension quiz. If this is successful, participants can read through the institutional review board–approved consent form and provide an electronic signature. A pdf version of the signed consent form is generated and available for review. IBD: inflammatory bowel disease.



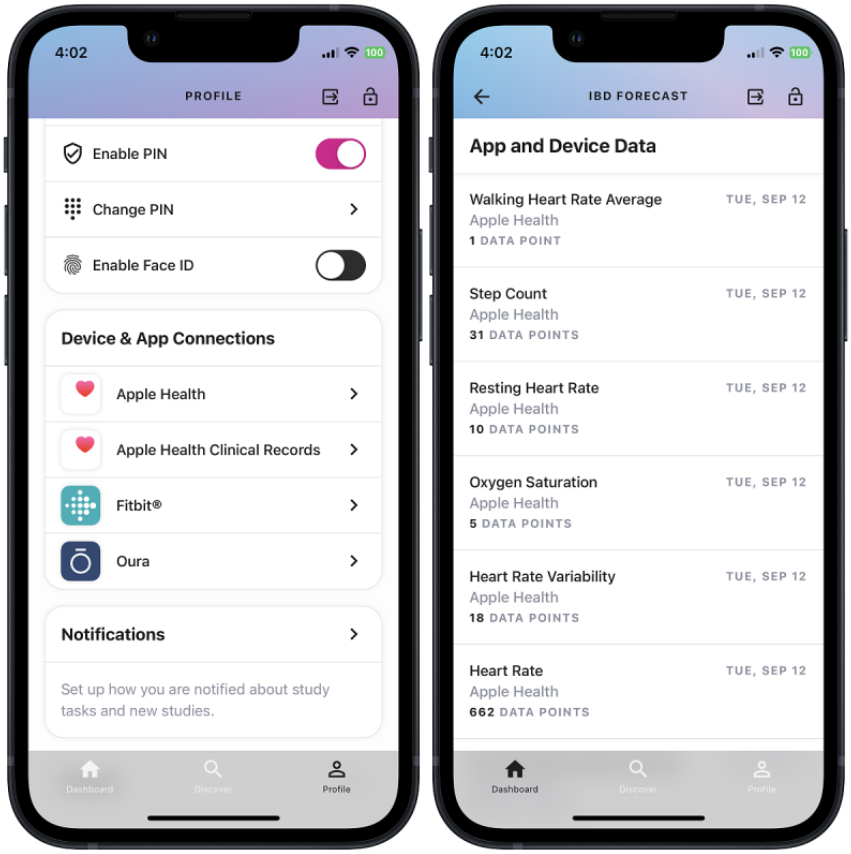
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Figure 4. The consent flow for prospective study participants. The consent flow consists of 6 main screen groupings: (A) selection of the study, (B) review of detailed study information, (C) eligibility screening, (D) walkthrough of consent details and knowledge checks, (E) consent document review and signature, and (F) enrolled patient-facing study dashboard. Studies that are fully remote and have no active research coordinator participation include consents using each of these groups. Consent flow is indicated by the solid line in the flow diagram. The consent process of studies using an active research coordinator may skip certain groups if desired by following the dashed line on the flow diagram. CRC: clinical research coordinator; IBD: inflammatory bowel disease.



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Figure 5. Study integration with external data sources, such as wearable devices. Participants can link connected devices to the ehive app and choose which device data to share with the study team. Participants can verify that app and device data have been shared with the study team. IBD: inflammatory bowel disease.



Ethical Considerations

All ehive studies that involve human participants require separate approval from relevant IRBs. Ongoing IRB approval is required for the study to remain active on the platform. Approval is needed for any secondary analyses of research data, for the sharing of data outside the study team, and during the data extraction and analysis period. Each study incorporates its own IRB-approved data-sharing and consent framework. Compensation is individualized for each study. The ehive platform is itself approved by the IRB at the Icahn School of Medicine (STUDY-21-01500) to assure compliance of its consent and data storage approaches with relevant institutional guidelines for the ethical conduct of research. All the data presented in the subsequent sections were approved by the Mount Sinai IRB.

Patient-Facing Dashboard and Tasks

Study participants can manage individual study activities on their smartphone via ehive's patient-facing dashboard. This user-friendly interface provides an overview of the study tasks and activities as well as a list of completed tasks and future tasks. Participants can also access a summary of the types of device data they are sharing with the study team. Additional features include detailed information about the study's IRB approval, contact information of the study team, and the signed consent form. Participants can withdraw from the study through the app.

Through the task list on the ehive dashboard, participants can complete custom or standardized surveys as well as view videos and educational content. Additional integration with the EHR is possible. Participants can grant permission for the EHR to be read via Apple's HealthKit. When connected, EHR data are pulled directly from the HealthKit database into the ehive platform via Fast Healthcare Interoperability Resources (FHIR). Currently, this interface allows participants to visualize the data collected from connected devices or scored survey results. However, in the future, it is planned to enable the visualization of wearable metrics by participants within the patient-facing dashboard. Depending on the specific study, this information can be masked to minimize bias.

The ehive app is designed to collect multimodal data, including PROMs. PROM questionnaires are delivered as study tasks, with participants' responses saved directly in the ehive database in the FHIR Questionnaire Response format. New questionnaires are created using a configuration file that is deployed to the ehive server and added to a study's task schedule. Questionnaires are created, scheduled, modified, and deployed without requiring an app update. The ehive app has built-in support for 23 question types (ie, multiple select, year, yes or no select, drag or drop reorder, text, etc) and branching logic to show or hide questions based on the participant's responses. The ehive backend is integrated with the REDCap (Research Electronic Data Capture; Vanderbilt University) platform, enabling it to write and read questionnaire responses with REDCap, if requested by the study team. Previously used

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surveys are stored in a data library to allow for ease of use in future studies.

Data Integration

The ehive platform is integrated with external data sources using two primary mechanisms: (1) via a web application programming interface (API) or (2) via a software development kit (SDK). For security purposes, ehive integrates only with web APIs that implement the Open Authorization 2.0 (OAuth 2.0) protocol. OAuth 2.0 is an authorization standard that enables a third party to request a service on behalf of the resource owner. Using the OAuth 2.0 protocol, the resource owner retains full control of an individual's log-in credentials and the shared data. When initiating a request to share data, ehive specifies exactly which scopes (data types) the study is interested in. The participant chooses which of these scopes he or she wishes to authorize, and then the external service releases a short-lived access token and a refresh token. The access token grants temporary access to the authorized data. After the access token expires, a new access token may be released using the provided refresh token. These tokens are stored in the database and used for server-to-server communication, allowing ehive to pull external data without continued interaction with the ehive mobile app. The study participant can revoke ehive's access at any time, whereupon the refresh token will be invalid, no new access tokens will be released, and no more data will be obtained from the participant.

OAuth 2.0-enabled web APIs are ubiquitous among commercial and research-grade wearable device companies. As the authorization logic is identical among external services and all API methods are simple http requests, little effort is required to integrate with a new data source. In addition, web APIs can be used to integrate data for any service that chooses to expose an API (eg, device data, genetic data, and social media data). SDKs are primarily used to integrate wearable devices. Unlike web APIs that permit server-to-server communication, SDKs require specific code to be bundled with the ehive mobile app to handle communication with the device. Using an SDK is significantly more complicated than using a web API. There are few similarities among SDKs, even among those from the same manufacturer (eg, HealthKit and SensorKit [Apple Inc]), making meaningful abstraction impossible. Furthermore, using SDKs can lead to imbalances between platforms because some SDKs are only available on iOS (eg, HealthKit), whereas others are only available on Android (eg, Samsung Health [Samsung Electronics]). Additionally, iOS and Android require the use of different programming languages and tools. Therefore, when an SDK is to be made available on iOS and Android devices, it must be implemented separately for each platform. These complexities prolong the time required to integrate a new SDK into platforms such as ehive. In addition to the primary integration mechanisms discussed earlier, ehive has access to unique data set integrations only available within the MSHS, such as genomic and proteomic biobanks. This data integration is automated and does not require any action on the part of participants.

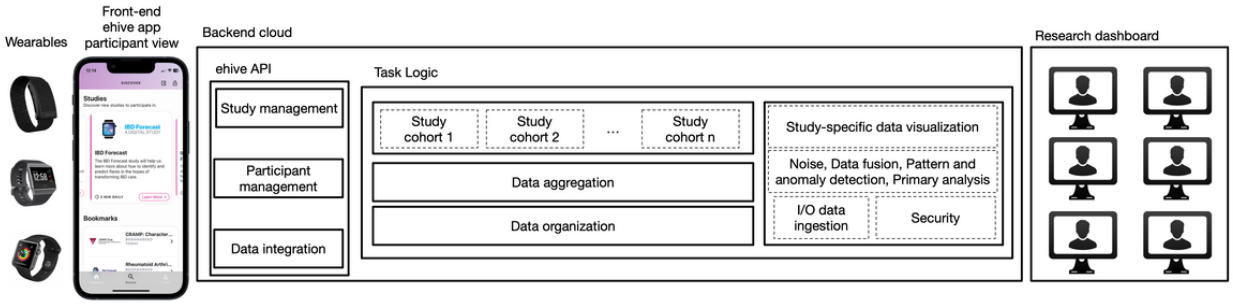
Multi–data sets such as pathology data, radiology images, EHR in Observational Medical Outcomes Partnership format, and genetics data are stored in a different environment within the MSHS called AIR.MS for efficiency and security purposes [19]. They can be accessed and integrated with ehive data with IRB approval and participant consent. The ehive platform collects information such as medical record numbers, name, sex, date of birth, and zip code. When the bootstrapping process is initiated in both environments, a lookup table with the hash value of the medical record number, the date of birth, and a random value is exchanged between the 2 domains using a public or private key exchange protocol. After the bootstrapping process, when a new patient is added to AIR.MS, a unique hash value is inserted into the AIR.MS lookup table. The same steps are performed on ehive when a new participant signs in to assess whether he or she is in MSHS. A new record is added to the ehive lookup table. If the security of the lookup table is compromised, a new public or private key is generated, and a random value is shared. Both AIR.MS and ehive must then recompute their lookup tables for future matching between the data sets. Principal investigators (PIs) interested in using multiple data sets from both environments must be granted access and have IRB approval. Once access is granted, a software agent returns the number of data points available for the time range requested by the PI. The PI can then verify the data quantities returned and decide whether they meet the criteria to build the cohort. If the cohort meets the PI criteria, an automatic process deploys a new virtual machine accessible to the researchers on the IRB who have valid Mount Sinai Azure Active Directory credentials. The virtual machine has automated access only to the data requested by the PI.

Data Infrastructure

The ehive backend runs on Health Insurance Portability and Accountability Act–compliant Azure cloud infrastructure (Figure 6). It uses Docker (Docker Inc) and a microservice architecture pattern to simplify the maintenance and deployment of new features. Each service has its database, which contains the data required to perform its duties. No sensitive information is stored within the microservices themselves. Database access keys and API keys are stored in Azure Key Vault, and all data are stored in an encrypted Postgres database. A flexible Postgres service that scales dynamically to meet the current workload is used to improve performance and availability. App-related data are stored primarily using relational database techniques. However, PROMs and data from external integrations are stored directly in JavaScript Object Notation format. Using JavaScript Object Notation, the ehive mobile app and backend can communicate using the FHIR standard. This design choice allows ehive data to be interpretable by other health organizations, a benefit of which is the possibility of generating interoperable data analyses and merging with EHR and other health data sources.

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Figure 6. The ehive platform encompasses a front-end patient-facing smartphone app, backend cloud, and research dashboard. External to the ehive digital ecosystem are third-party apps and wearable devices. Their integration to ehive is mainly through the REST application programming interface paradigm. When data integration through the REST application programming interface is unavailable, as with Apple Watch, ehive accesses the data through software development kits. The ehive data architecture is based on Azure cloud, managed by the Mount Sinai Health System. Investigators interact with the collected data, the study's status, and the study's configuration through the research portal that runs on the Azure cloud. IO: input-output.



Data shared with ehive are authorized on a per-study basis. If a participant is enrolled in multiple studies that request the same data integration, the participant will be asked to provide authorization for each study individually. This process provides transparency and control, allowing participants to decide which data are accessed by each study. Gaps in wearable device data can occur for several reasons. For example, this can occur (1) when the device runs out of battery and is unable to sync with the app's backend, (2) when the participant ceases wearing the device, or (3) when a data sync fails for unforeseen technical reasons. It is vital to the success of each study to minimize gaps in the collected data. Several services run on the backend of ehive to check whether new data are available and whether any gaps exist. In case of a sync failure, the backend will make ad hoc data requests to fill in any missing data. When the gaps cannot be filled via ad hoc requests, an automated message is delivered to participants, notifying them of the issues with their device use patterns.

Results

The ehive Platform

The ehive platform was launched in 2020 and has since hosted 8 ongoing or completed studies, with 7 additional studies planned for launch. This study composition is 6 observational cohort studies and 2 clinical trials. The observational studies encompass a range of disease and health states. These include studies recruiting healthy health care workers throughout the MSHS for the development of algorithms to predict COVID-19 infections, studies for understanding the psychological well-being of health care workers during the COVID-19 pandemic, and studies aimed at developing machine learning algorithms to predict psychological states from passively collected wearable data. Beyond the MSHS, the platform has hosted 2 national studies enrolling individuals with chronic diseases from across the United States aimed at predicting disease exacerbations using wearable device data [20,21]. The clinical trials hosted on ehive are fully digital. The Warrior Shield study was such a siteless trial, which enrolled 127 health care workers and aimed at building resilience using digital interventions that modified heart rate variability. The physiological effects of the intervention were monitored using wearable devices.

Participant Recruitment and Engagement

Through January 2023, a total of 1484 participants downloaded the ehive app, with 1044 (70.35%) of them meeting the inclusion criteria for study enrollment. Over 51 million wearable device–based data points have been collected and over 132,241 surveys have been conducted through the ehive app. This demonstrates ehive's ability to recruit across multiple studies and the digital ecosystem's ability to simultaneously run multiple individual cohort studies and clinical trials. Importantly, ehive-based studies have engaged with and recruited diverse populations. For example, the Warrior Watch study, which developed machine learning algorithms aimed at predicting COVID-19 infections, enrolled 297 participants across racial and ethnic groups (Table 1) [22]. Although most ehive study participants are centered around the New York City metropolitan area, individuals across 36 states within the United States have enrolled (Figure 7).

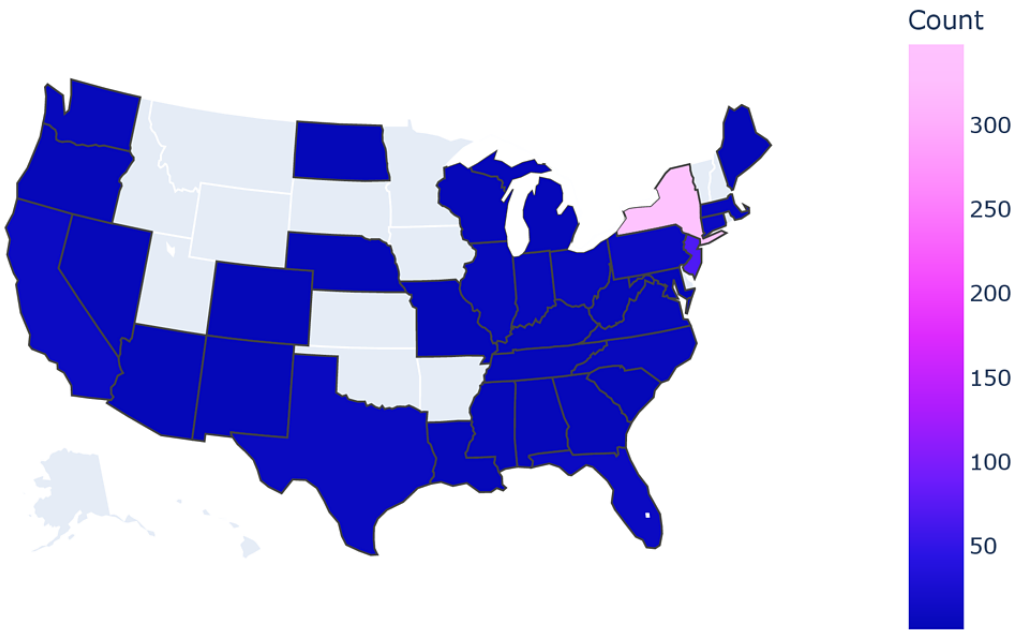
Participant engagement and the use of the ehive platform have steadily increased as the number of studies supported by the app have increased. In addition, modifications that enhance engagement and retention have been continually made and improved, as discussed earlier. The app has an average of 148 (SD 11.43) unique daily users over a 7-day period (April 2023; Figure 8). Highlighting the role that light-touch engagement measures play in the interaction with ehive, we found that measures such as push notifications result in a marked increase in user engagement shortly after being implemented (Figure 9). This highlights the ability of these light-touch measures to remind and engage participants in ongoing studies that require either daily or sporadic tasks within the app.

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Table 1. The ehive platform has enrolled diverse patient populations. The demographic profile of the participants enrolled in one ehive study, the Warrior Watch Study, is described to highlight participant diversity (n=297).

Characteristics	Value
Age (years), mean (SD)	36.3 (9.8)
Sex (female), n (%)	204 (68.7)
Race, n (%)	
Asian	73 (24.6)
Black	29 (9.8)
White	108 (36.4)
Other	43 (14.5)
Hispanic ethnicity, n (%)	44 (14.8)

Figure 7. The number of individuals participating in ehive-related studies in each state in the United States.



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Figure 8. A trend line of the total weekly number of ehive participants from April 2021 through January 2023, demonstrating high rates of use and engagement.

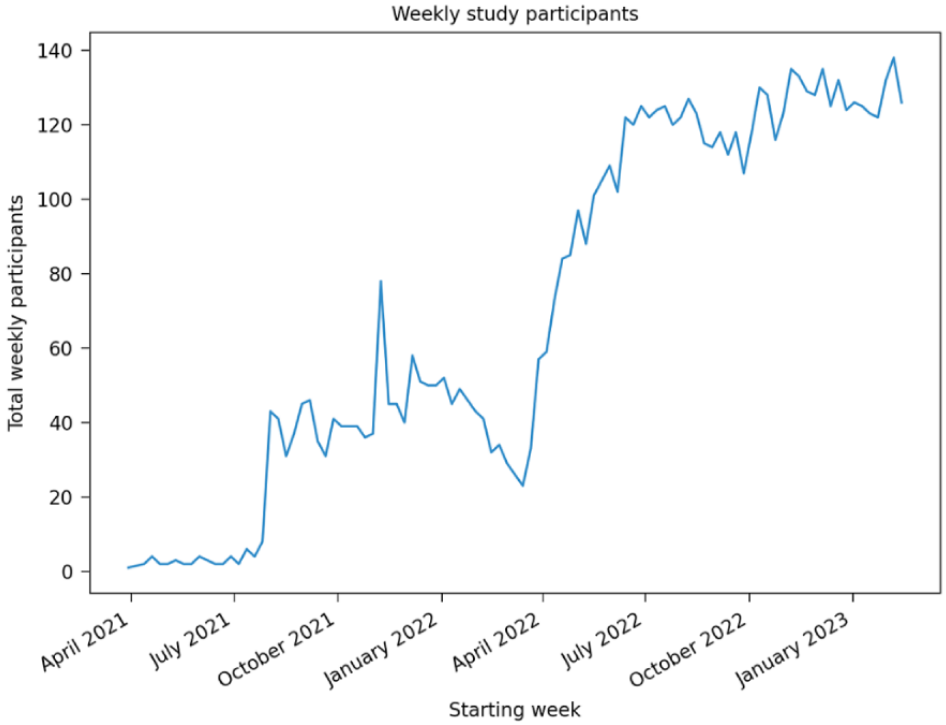
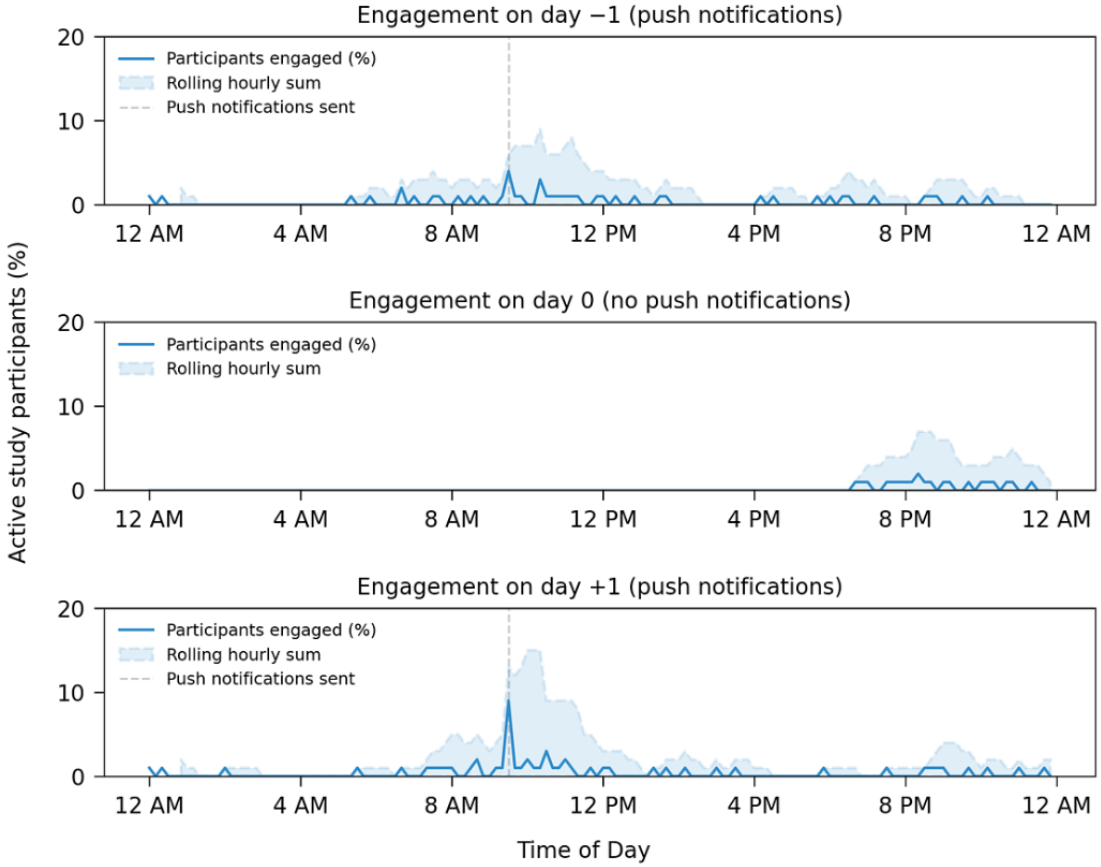


Figure 9. An example of engagement in the ehive app on 3 sequential days. Push notifications were delivered to study participants on day −1 and day +1 as a reminder to complete daily survey tasks. No notifications were delivered on day 0. The percentage of participants who engaged with ehive and the rolling hourly sum of participants using the app is visualized over each 24-hour period.



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Discussion

Principal Findings

There are limited descriptions of centralized digital research applications in the literature to help guide their development. The ehive app represents such a model that can be used to grow digital health research. Here, we provide an overview of the infrastructure and design of ehive, which was developed to help mitigate many of the limitations that have historically impacted digital studies. This platform has successfully hosted 8 observational studies and clinical trials that include over 1044 participants across 36 states. Such a centralized digital ecosystem fosters the opportunity for conducting digital health research at scale across multiple studies, participant populations, and data modalities.

The advent of the COVID-19 pandemic has highlighted the need to be able to perform research remotely and engage traditionally underrepresented patient populations. The ehive platform represents a model that academic and other institutions can use to meet these needs and grow research opportunities in an increasingly remote and digital world. The modifiability of platforms such as ehive enables multiple types of study that incorporate various data streams to be conducted. This includes opportunities for the digitization of clinical trials, which has been increasingly emphasized by industry and funding agencies, including the National Institute of Health [6,23]. Digital solutions present an opportunity to streamline clinical trial costs, improve efficiency through investigator support, provide novel physiological data streams, and offer new end points. In addition and as demonstrated, they enable expanded study recruitment, compliance monitoring, and enhanced automated retention modalities [24].

Such platforms enable the integration of multimodal data streams, including wearable outputs, biobank specimens (ie, genomic and proteomic biobanks), EHR outputs, and PROMs. The integration of multiple data streams allows data sources to complement each other, amplifying the derived information beyond each individual data stream [25]. The ability of centralized digital research platforms to add multiple data modalities that can evaluate information on different scales results in improved predictive ability and the potential for artificial intelligence and machine learning techniques to unlock novel capabilities. Although this is implemented at scale in large biobanks, such as the United Kingdom biobank or the National Institutes of Health All of Us initiative, centralized digital platforms, such as ehive, enable this performance on a modifiable and tailored basis [26,27]. An additional benefit of a central research app is that capital improvements in the app are translated across studies, thereby optimizing institutional or organizational investment in digital research infrastructure. This allows the entire digital ecosystem to benefit from system upgrades and modifications and avoids the duplication of effort and, thereby, costs that would occur if similar improvements were applied to single-use apps.

However, only limited descriptions of such platforms are available in the literature. Published descriptions of modifiable central digital research platforms focus on specific study types. For example, the StudyU platform is a customizable app that enables clinicians and researchers to design and implement N-of-1 trials. This unique platform is similar to ehive to the extent that it leverages its centralized features to host individual studies that capitalize on central app developments [28]. However, descriptions of fully modifiable centralized platforms that can support multiple studies and study types are lacking. In academics, such platforms include the myPHD app from Stanford University, whereas in industry, the evidations research app and Apple Research app (Apple Inc) have similar capabilities [11,29,30]. However, robust descriptions of their capabilities have not been published.

The modifiability of the ehive research ecosystem enables its evolution and expansion over time. Several future app developments are planned. Given the importance of participant compliance and engagement, ehive updates are focused on maximizing this aspect of the app. A micropayment system is planned, which will allow participants to easily track their study progress and acquire points or monetary compensation after hitting study milestones. This feature will enable the automatic payment of participants through ehive, mitigating the need for study coordinators to track and remit compensation. In addition, an expansion of the patient-facing dashboard is planned. This will enable participants to not only track their wearable data in aggregate but also download their granular wearable data during the study period. This will increase participant engagement with the app, enable participants to share their data with their doctors if needed, and convey the impression that the collected data are being engaged with and used by the researchers. Further scaling of the ehive platform through research collaborations with academic and industry partners as well as through the exploration of platform licensing options is also planned.

A strength of the ehive platform is the ability of individual studies to use existing features or develop new ones. However, this app has several important limitations. Although we have worked to develop light-touch measures to maintain engagement with the app, we still note that participant engagement decreases over time. Although this is a limitation in all studies, ongoing efforts are needed to continually improve how participants interact with the app. Our planned micropayment system and an improved patient-facing dashboard will hopefully further engage participants. Another limitation in studies hosted on ehive is restrictions on data access. Wearable device companies often have limitations on the type and granularity of data that can be accessed. In addition, there can be intellectual property limitations on the downstream uses of these data, which can impact the ownership of the study results and algorithms. This highlights the need for greater collaboration between device companies and health researchers as well as solutions in which raw data access can be obtained for reasonable compensation. An additional limitation is that if study participants do not have automatic updates turned on, the ehive team has to manually reach out to participants to have them update the app. Although this happens infrequently if there is a major app update that impacts a large number of participants, it can be a significant limitation. Finally, there are significant costs related to running and maintaining a centralized research platform that require upfront institutional investment. Although subsequent

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app-driven revenue streams can support ongoing operations, the initial development costs often require external support.

Conclusions

The ehive app is a promising proof-of-concept centralized research solution for complex health care systems that see value in building a secure mobile health research platform that can support multiple studies. It is a novel tool that offers investigators the capability to expand their research beyond their institution, engage in large-scale longitudinal studies, and combine multimodal data streams. It serves as a model for groups seeking to develop similar digital health research programs.

Data Availability

The data sets generated and analyzed during this study are not publicly available. This is because the data summaries presented represent the composites of individual datasets from multiple studies. Each study has its own restrictions on data access.

Authors' Contributions

RPH, MD, MZ, and EG developed the study concept. RPH, MD, KL, and MZ assisted with the drafting of the manuscript. RPH, MD, KL, MZ, EG, GO, JR, IE, EA, EB, GNN, TJF, and ZAF critically revised the manuscript for important intellectual content. RPH, MD, KL, MZ, EG, GO, JR, IE, EA, EB, GNN, TJF, and ZAF provided final approval for the version of the manuscript to be published and agree to be accountable for all aspects of the work. All authors approved the authorship list. All authors had full access to all the data in the manuscript and had final responsibility for the decision to submit it for publication. RPH, ZAF, KL, and MD have verified the presented data.

Conflicts of Interest

RPH has served on the advisory board of Bristol Meyers Squibb. EB reports consultancy agreements with Deloitte and Roland Berger; ownership interest in Digital Medicine E Böttinger GmbH, EBCW GmbH, and Ontomics, Inc; receives honoraria from Bayer, Bosch Health Campus, Sanofi, and Siemens; and serves as a scientific adviser or member of Bosch Health Campus and Seer Biosciences Inc. GNN reports employment with, consultancy agreements with, and ownership interest in Pensieve Health and Renalytix AI; receives consulting fees from AstraZeneca, BioVie, GLG Consulting, and Reata; and serves as a scientific adviser or member of Pensieve Health and Renalytix AI. ZAF discloses consulting fees from Alexion, GlaxoSmithKline, and Trained Therapeutix Discovery and research funding from Daiichi Sankyo, Amgen, Bristol Myers Squibb, and Siemens Healthineers. ZAF receives financial compensation as a board member of and an adviser to Trained Therapeutix Discovery and owns equity in Trained Therapeutix Discovery as a cofounder. All other authors declare no other conflicts of interest.

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Abbreviations

API: application programming interface
DDP: Digital Discovery Program
EHR: electronic health record
FHIR: Fast Healthcare Interoperability Resources
HPI.MS: Hasso Plattner Institute for Digital Health at Mount Sinai
IRB: institutional review board
MSHS: Mount Sinai Health System
PI: principal investigator
PROM: patient-reported outcomes measure

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REDCap: Research Electronic Data Capture
SDK: software development kit

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Protocol

Designing Mobile Phone Text Messages Using the Behavior Change Wheel Framework to Influence Food Literacy in Adults With Type 2 Diabetes in Kenya: Protocol for a Systematic Development Study

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Abstract

Background: The worldwide prevalence of type 2 diabetes (T2D) has increased in the past decade, and it is projected to increase by 126% by 2045 in Africa. At the same time, mobile phone use has increased in Africa, providing a potential for innovative mobile health interventions to support diabetes care.

Objective: This study aimed to apply the Behavior Change Wheel (BCW) framework to develop text messages to influence food literacy in adults with T2D in urban Kenya.

Methods: The 8 steps of the BCW framework guided the development of text messages: (1) Define the problem in behavioral terms; (2) select target behaviors; (3) specify the target behaviors based on who needs to perform the behaviors, what needs to change, and when, where, how often, and with whom; (4) identify what needs to change; (5) identify intervention functions; (6) select policy categories; (7) select behavior change techniques (BCTs); and (8) select the mode of delivery. Recent exploratory studies in Kenya and other low- and middle-income countries provided information that was used to contextualize the intervention.

Results: In step 1, the behavioral problem was defined as unhealthy dietary patterns among adults with T2D. In step 2, based on a qualitative study in the target population, the target behavior was selected to be evaluation of reliable sources of information, and selection and preparation of healthy food. In step 3, unhealthy dietary patterns were selected. In step 4, 10 domains of the Theoretical Domains Framework were identified, and in step 5, 5 intervention functions were linked to the domains and unhealthy dietary patterns were specified. In step 6, communication and regulations were identified as policy categories, while in step 7, 9 BCTs were selected from the Behavior Change Technique Taxonomy version 1. In step 8, the most suitable mode of delivery was determined to be mobile text messages. A total of 36 mobile text messages were developed based on the 9 BCTs.

Conclusions: This study shows the step-by-step application of the BCW framework to develop mobile text messages to influence food literacy in adults with T2D.

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KEYWORDS

behavior change techniques; Behavior Change Wheel; type 2 diabetes; low-income populations; mHealth; mobile health; glycemic control; adults; diabetes; Africa; mobile phone; support care; care; support; behavior; diabetes

Introduction

Worldwide, the prevalence of diabetes has been on the rise in the past decade, with more than half a billion people with diabetes in 2021, of which more than 90% had type 2 diabetes (T2D) [1]. Currently, in Africa, 24 million people have diabetes, and it is projected that this prevalence will rise by 126% to 55 million in 2045 [1]. This projected rise in the African region will be the highest compared to all other worldwide regions [1]. In Kenya, 3% of adults aged 20-79 years have diabetes, with a higher prevalence in urban (3.4%) compared to rural (1.9%) areas [2]. Further, in Kenya, older age (60-69 years) is associated with a higher incidence of diabetes [2]. In addition to the rising prevalence of T2D in Kenya, only 36.6% of patients achieve glycemic control [3]. Glycemic control in diabetes is defined as glycated hemoglobin (HbA_{1c}) levels of <7% (53 mmol/mol) [4]. Poor glycemic control increases the risk of the development and progression of micro- and macrovascular complications in people with diabetes [5]. As such, achieving glycemic control soon after diagnosis is an important goal in the management of diabetes. In addition to diabetes self-management medical actions, a recent prospective analysis showed that optimization of dietary patterns is an effective strategy to achieve glycemic control [6]. Poor dietary quality has been assumed to be associated with a lack of food-related knowledge and skills [7]. However, food literacy has been used to improve dietary behavior associated with healthy dietary patterns [8,9]. Food literacy enables the application of information about food choices and critical reflection on the effect of food choices and has the potential to prevent disease, promote optimal health, and sustain the environment [9,10].

As the prevalence of T2D is on the rise, mobile phone subscription in low- and middle-income countries (LMICs) has been on the rise in the past 2 decades. Recent data show that mobile cellular subscriptions per 100 people in LMICs and Kenya rose from nearly 0% in 2000 to 104% and 123%, respectively, in 2021 [11]. This increase in mobile phone subscriptions in LMICs has resulted in a commensurate rise in the use of mobile health (mHealth) in behavior change interventions [12,13]. Optimization of glycemic control in adults with T2D through a food literacy intervention requires behavior change. Therefore, a systematic approach to developing an intervention and its subsequent implementation and evaluation was used [14]. In this study, we used the Behavior Change Wheel (BCW) framework [15] to systematically develop intervention components. Given that the BCW framework has been used widely to design and evaluate several behavior change interventions [16-20], we used it to develop text messages. Specifically, the BCW framework helps in the systematic identification of target behaviors that need to be changed to improve health outcomes and to select appropriate intervention functions, policy categories, and behavior change techniques (BCTs) based on the analysis of the sources of behavior (capability, opportunity, and motivation) [14].

The BCW is a 3-stage comprehensive framework for designing complex interventions (Figure 1) that integrates behavior theory by using expert consensus and a validation process [14]. The BCW framework has been designed to help understand and select relevant mechanisms of action for an intervention [15]. The BCW framework uses the 3-layered capability, opportunity, motivation for behavior (COM-B) model (Figure 2) to analyze and diagnose behavior. The first, core layer of the COM-B model is further expanded to physical and psychological capability, social and physical opportunity, and automatic and reflective motivation. According to Michie et al [15], core domains are needed to increase the likelihood of performing the target behavior. COM-B is supported by the Theoretical Domains Framework (TDF), which describes 14 constructs from 33 behavior change theories [21]. The second layer of the BCW framework is composed of 9 intervention functions: education, persuasion, incentivization, coercion, training, enablement, modeling, environmental restructuring, and restrictions. These intervention functions indicate how an intervention changes behavior and are linked to a taxonomy of 93 replicable BCTs (Behavior Change Technique Taxonomy version 1 [BCTTv1]) [22]. The third, outermost layer of the BCW framework is composed of 7 policy categories that can be applied to support the delivery of the intervention functions. Although text messaging is increasingly used in health care and the demand for interventions based on theory, existing text messaging interventions often overlook the theoretical basis for their development [23,24]. This study therefore aimed to apply the BCW framework to develop text messages to influence food literacy in adults with T2D in urban Kenya. The specific objectives of this study were to (1) define the problem affecting adults with T2D in behavioral terms, (2) define the intervention and implementation options of the identified target behaviors, and (3) develop text messages to influence food literacy in adults with T2D in Kenya.

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Figure 1. Stages and steps in the BCW. Adapted from Michie et al [15]. BCW: Behavior Change Wheel.

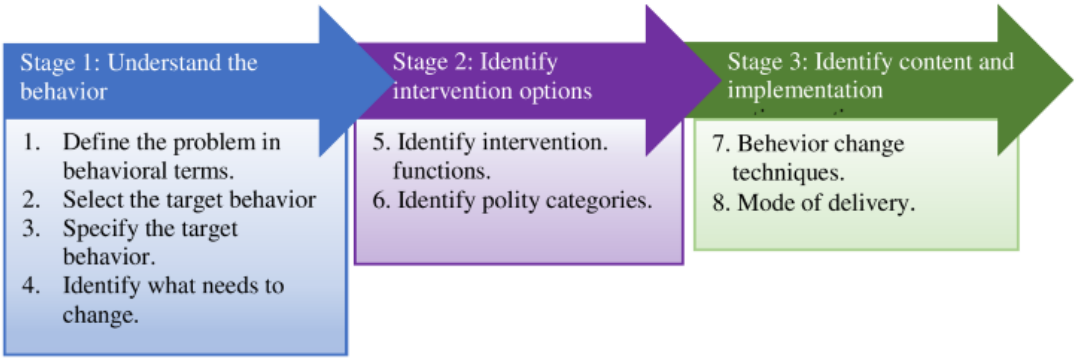


Figure 2. The COM-B model. Adapted from Michie et al [15]. COM-B: capability, opportunity, motivation for behavior.



Methods

Study Design

Developing this intervention involved 3 stages of the BCW framework: (1) understanding the behavior and user preferences, (2) identifying intervention options, and (3) identifying content and implementation options. These stages were further subdivided into 8 steps and are further explained in detail later (Figure 1). The process of intervention development was iterative and was conducted by the research team (authors MM, FK, PY, RV, TB, JLK and CM). The team consisted of dieticians, nutritionists, public health specialists, and an endocrinologist.

Stage 1: Understanding the Behavior and User Preferences

Step 1: Define the Problem in Behavioral Terms

Defining the problem in specific behavioral terms included an in-depth description of the target population and the specific behavior [15]. We used the recent and contextually relevant literature [25-27] to refine our understanding of the target population's dietary behavior to optimize glycemic control from health providers' and patients' viewpoints.

Step 2: Select Target Behaviors

Target behaviors were selected by applying a systems analysis approach, as recommended by Michie et al [15]. First, we used the list of facilitators of and barriers to healthy dietary behavior in adults with TDM from our previous phenomenological qualitative study conducted in Kenya [28]. In that study, 30 male and female respondents were interviewed through mobile telephones, revealing that facilitators of and barriers to healthy dietary behavior are related to food literacy. We ranked the various facilitators and barriers based on the number of thematic nodes (collection of references about a specific theme) generated by NVivo software (Lumivero). Table 1 shows the ranking of thematic nodes.

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Table 1. Ranking of thematic nodes.

Food literacy component	Number of nodes	Rank of priority
Plan	42	4
Prepare	60	3
Select	168	2
Eat	171	1

Second, we used the criteria recommended by BCW guidelines to prioritize the target behaviors. The criteria include the following considerations: (1) the relative impact of the behavior, (2) the likelihood of changing the behavior, (3) the potential for spilling over into other relevant dietary behaviors, and (4) the ease of measurement of the behavior. Finally, we categorized each selected behavior as very promising, promising, unpromising but worth considering, or unacceptable based on guidance by Michie et al [15]. These decisions were made by consensus by the expert panel and then tabulated for each selected behavior.

Step 3: Specify the Target Behavior

Step 3 involved specifying the context in which the target behavior will occur by asking specific questions: Who needs to perform the behavior? What needs to be done differently to achieve the change? Where and when do they need to perform the behavior? How often and with whom did they perform the behavior? To answer each of these questions, we used the findings from our qualitative study conducted on the target population [28].

Step 4: Identify What Needs to Change

Step 4 involved 2 substeps: (1) behavioral analysis using the COM-B model and (2) identification of what needs to change using the TDF.

In substep 1 of behavioral analysis, we mapped the specified target behavior from step 3 to the COM-B component and further explored what needed to happen for the target behavior to occur and whether there was a need for change to select and eat food known to contribute to glycemic control.

In substep 2, after determining what needs to change, we linked the behavior that needed to change based on BCW and TDF guidelines [15,29]. The TDF consists of 14 domains: knowledge; skills; memory, attention, and decision processes; behavioral regulation; social/professional role and identity; beliefs about capabilities; optimism; beliefs about consequences; intentions; goals; reinforcement; environment context and resources; social influences; and emotion. The domains identified in this step were tabulated and summarized to include the following aspects for the specified behavior: (1) COM-B component, (2) what needs to happen for the target behavior to occur, (3) whether there is a need for behavior change, (4) the domain linked to the COM-B component, and (5) relevance of the domain.

Stage 2: Identifying Intervention Options

Step 5: Identify Intervention Functions

Intervention functions were mapped onto each of the theoretical domains identified in step 4 [15]. The intervention functions that would most likely affect behavior change were selected based on the COM-B and TDF behavior analyses conducted in step 4. The relevant intervention functions were then assessed using APEASE (acceptability, practicability, effectiveness, affordability, side effects, and equity) criteria of the BCW framework [15]. The assessment included checking how the selected intervention functions meet the 5 components of the APEASE criteria.

Step 6: Select Policy Categories

The policy categories included communication/marketing, guidelines, fiscal measures, regulation, legislation, environmental/social planning, and service provision, which guide decisions made by authorities that help support and enact interventions [15]. We mapped the policy categories onto the intervention functions identified in step 5 using the APEASE criteria [15]. The selection of relevant policy categories was based on the matrix of links between intervention functions and policy categories described by Michie et al [15] and the APEASE criteria. The decisions on the APEASE criteria were informed by our understanding of the context, as revealed by our qualitative study [28].

Stage 3: Identifying Content and Implementation Options

Step 7: Identify BCTs

Based on the intervention functions identified in step 5, we selected BCTs from the BCTTv1 [22] and the APEASE criteria. The BCTTv1 is a standardized terminology used to specify the active ingredients of behavior change interventions and consists of 93 unique BCTs [22].

Step 8: Select the Mode of Delivery

The mode of delivery was guided by the taxonomy of the models of delivery for intervention functions that involved communication. Based on the taxonomy of the models of delivery, we selected the mode of delivery by using the findings from our qualitative study [15,30]. The taxonomy is structured into binary options, where we selected the most practical option using our understanding of the context and the target population [28].

Testing the Feasibility of the Intervention

The BCW guidelines recommend that developed behavior change interventions be tested for feasibility. As such, we were guided by the Medical Research Council (MRC) framework that illustrates the steps to be followed in the development and evaluation of behavior change interventions [31].

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Ethical Considerations

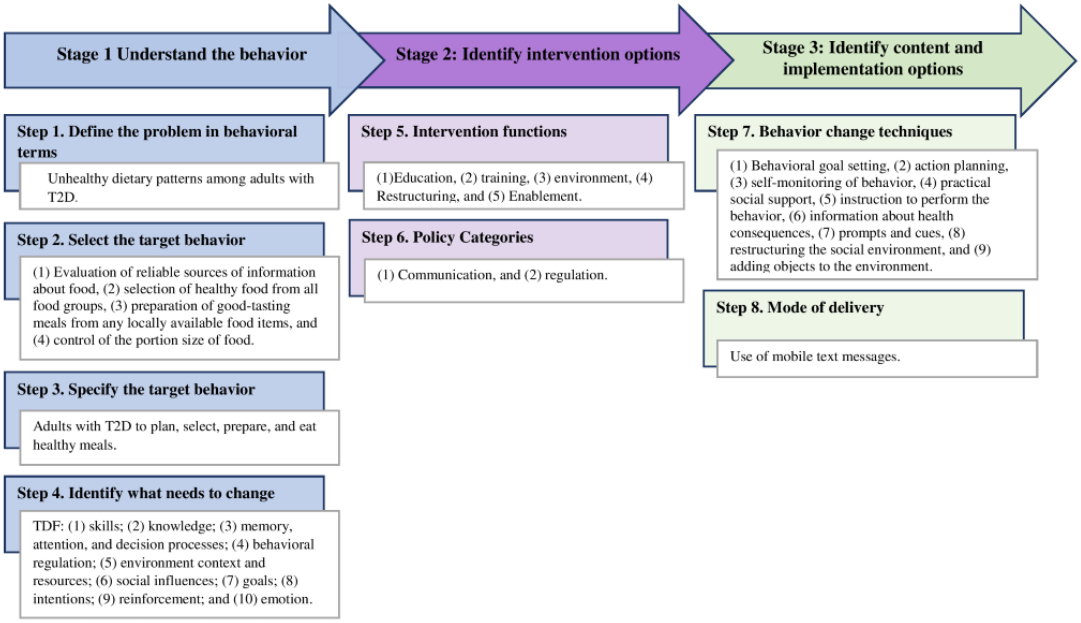
This being a study on the development of text messages to enhance food literacy in adults with T2D, human subjects were not directly involved. However, studies [25,27,28,30] that provided evidence in the development of this study sought ethical approval.

Results

Summary of Findings

Figure 3 summarizes findings from the 8 steps of the BCW framework.

Figure 3. Summary of findings from the steps in the Behavior Change Wheel.



Stage 1: Understanding the Behavior and User Preferences

Step 1: Define the Problem in Behavioral Terms

In defining the problem in behavioral terms, we considered findings from existing evidence in LMICs [25,27] and our previous studies [28,30]. The existing literature, however, is limited by the fact that it was conducted in different settings and that most of these studies lacked the rigor for replication in other settings [26]. Our qualitative study of facilitators of and barriers to healthy dietary behaviors among adults with T2D revealed the following facilitators: knowledge of healthy food choices, gardening, self-efficacy, food preparation skills and eating at home, education by health care workers, food availability, proximity to food-selling points, and family support. The barriers included tastes and preferences of food, health conditions barring the intake of certain foods, random eating of unhealthy food, socioeconomic status, seasonal unavailability of fruits, food safety concerns, and inaccurate beliefs and information about food and diet. In a systematic review of self-management of diabetes in sub-Saharan Africa, which included 43 studies, most of which were observational, there were misconceptions about and gaps of knowledge in what entails healthy food [27]. Further, the review found that interventions on dietary behavior led to relevant improvements in healthy eating habits. Another systematic review of adherence to diabetes self-care behaviors in LMICs found that adherence to dietary recommendations ranged from 29.9% to 91.7%, while consumption of fruits and vegetables averaged 3 times per week, although the portion sizes were not revealed [25]. In summary, the key gaps identified in these studies were related to our qualitative study [28], showing that dietary behavior is associated with food literacy. Food literacy is “the interrelated combination of knowledge, skills and self-efficacy on planning for meals, selecting foods, preparing food, eating and evaluating information about food with the ultimate goal of developing a lifelong healthy, sustainable and gastronomic relationship with food” [32]. Food literacy enables the application of information about food choices and critical reflection on the effect of food choices and has the potential to prevent disease, promote optimal health, and sustain the environment [9,10]. As such, the fundamental components of food literacy can be applied to positively influence behaviors required for healthy diet patterns. In practical terms, food literacy comprises planning, selection, preparation, and eating of food [33]. Based on these findings, we defined the problem in behavioral terms as unhealthy dietary patterns among adults with T2D.

Step 2: Select Target Behaviors

Based on a system analysis, we selected the following as target behaviors: evaluation of reliable sources of information about food, selection of healthy food from all food groups, preparation of good-tasting meals from any locally available food items, and control of the portion size of food (Table 2).

Based on the findings of our qualitative study on the same population [28], we prioritized the target behaviors in Table 3.

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Table 2. Identification of target behaviors.

Facilitator/barrier	Contextualized target behavior (components of food literacy) [33]
Access to reliable sources of information about food	Evaluation of information
Access to healthy food from all food groups	Selection of healthy food
Preparation of good-tasting meals from any locally available food items	Preparation of healthy meals
Control of the portion size of food	Eating a healthy diet

Table 3. Prioritization of the target behaviors.

Potential target behavior relevant to improving food literacy	Impact of behavior change[a]	Likelihood of changing behavior[b]	Spillover score[c]	Measurement score and means of measurement[d]
Evaluate reliable sources of information about food.	Very promising	Promising	Very promising	Promising (identify sources of reliable information)
Select healthy food from various sources to ensure varied consumption from all food groups.	Very promising	Promising	Very promising	Promising (proportion of healthy foods accessed)
Prepare healthy and good-tasting meals from locally available food and ingredients.	Promising	Unpromising but worth considering	Very promising	Promising (healthy and good-tasting meals prepared)
Consume a controlled portion size of food.	Promising	Promising	Promising	Promising (number of meals eaten that fit the plate model[e])

[a]Likely impact if the behavior were to be changed.

[b]Ease of likelihood to change dietary patterns.

[c]Likelihood of having an impact on other behaviors that may support a change in dietary patterns.

[d]Measurability either by routine data or through new data collection procedures.

[e]Plate model: a visual method for teaching meal planning, where the dinner plate serves as a pie chart to illustrate the proportions of the plate that should be covered by various food groups [34].

Step 3: Specify the Target Behavior

The target behavior was specified by answering the following questions, as illustrated in Table 4:

- Who? (Adults with T2D)
- Where? (At home or work)
- When? (When planning, selecting, eating, or preparing food)
- How often? (Every time or most of the time during consumption)
- With whom? (Either alone or with the family)

Table 4. Specification of the target behavior.

Specification	Description
Target behavior	Adults with T2D[a] to plan, select, prepare, and eat healthy meals
Who needs to perform the behavior?	Adults with T2D
What is to be done differently to achieve the desired change?	Plan, select, prepare, and eat healthy meals
When is it to be done?	Whenever eating
Where is it to be done?	At home, at work, or away from home
How often do they need to do it?	Every day
To whom do they need to do it?	Alone or with family or friends

[a]T2D: type 2 diabetes.

Step 4: Identify What Needs to Change

Identification of what needs to change was informed by findings drawn from the opinions in our qualitative study [28], in addition to recent and contextually relevant findings from Uganda [26]. Table 4 summarizes what needs to change based on the behavioral diagnosis using the COM-B model. A total of 10 TDF domains were identified: skills; knowledge; memory, attention, and decision processes; behavioral regulation; environmental context and resources; social influences; goals; intentions; reinforcement; and emotion. The behaviors diagnosed were further expanded to illustrate their relevance (Table 5).

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Table 5. Behavioral analysis and application of the TDF[a] in diagnosis.

COM-B[b] component and what needs to happen for the target behavior to occur	Is there a need for change?	TDF domain linked to the COM-B component	Relevance of the domain
Physical capability			
Search and access healthy food from all food groups.	Yes	Physical skills	Explain how to search for and access healthy food from all food groups.
Prepare healthy meals using locally available food ingredients.	Yes	Physical skills	Explain how to prepare healthy meals using locally available food ingredients.
Be able to serve controlled portion sizes using the plate model.	Yes	Physical skills	Explain how to serve controlled portion sizes using the plate model.
Psychological capability			
Know how to distinguish between reliable information and myths.	Yes	Knowledge	Create knowledge of various food groups and food sources.
Know where to search for reliable information.	Yes	Knowledge	Create knowledge on where to search for reliable information.
Know various food groups and locally available health food sources.	Yes	Knowledge	Create information on food groups and locally available food sources.
Advanced planning skills to ensure the availability of healthy food.	Yes	Memory, attention, and decision processes; behavioral regulation	Enable action-planning skills.
Know foods to avoid for optimal glycemic control.	Yes	Knowledge	Help in decision-making on the type and quality of healthy food.
Know the composition of the plate model.	Yes	Knowledge	Enable the serving of healthy portions of food.
Physical opportunity			
Be aware of where to get healthy foods (shops, markets, home garden), and establish or maintain kitchen gardens.	No: food is accessible in the target population.[c]	N/A[d]	N/A
Use the mobile phone or computer to search for information, where possible.	No: the proportion of the target population using smartphones or computers is low.[c]	N/A	N/A
Have the necessary cooking equipment.	No: patients commonly cook at home.[c]	N/A	N/A
Use smaller plates when serving food.	Yes	Environmental context and resources	Search and use a smaller plate to serve food.
Social opportunity			
Call health care workers when searching for information.	No: patients have access to health care workers during clinic visits.[c]	N/A	N/A
Challenge cultural beliefs regarding food choice.	Yes	Social influences	Understand that some cultural values are unhealthy.
Awareness to family members involved in meal preparation on the preparation of healthy meals.	Yes: some families provide support to adults with T2D.[a]	Social influences	Social support in the selection, preparation and eating of healthy food.
Change cultural habits regarding food portion size.	Yes	Social influences	Change perceptions on the amount of food to be eaten.
Reflective motivation			
Intend and prioritize seeking clarification of information when needed	Yes	Intentions	Encourage the intention to search for information through reliable sources.

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COM-B[b] component and what needs to happen for the target behavior to occur	Is there a need for change?	TDF domain linked to the COM-B component	Relevance of the domain
Establish routines and habits to eat healthy meals	Yes	Goals	Develop routines to eat healthy meals.
Intend to purchase and eat healthy food	Yes	Intentions	Encourage the intention to purchase and eat healthy food.
Plan to cook healthy meals	Yes: The target population cooks most meals at home.[c]	Goals	Plan to cook healthy meals.
Plan to serve healthy portion sizes	Yes	Goals (action planning)	Enable service of healthy portion sizes.
Automatic motivation			
Desire to look for information when in doubt	Yes	Reinforcement	Reinforce the habit of searching for reliable information.
Establish meal plans to ensure the intake of healthy meals	Yes	Emotion	Plan for healthy meals.
Establish routines and habits of serving healthy portions of food	Yes	Reinforcement	Have the desire to serve healthy portions of food.

[a]TDF: Theoretical Domains Framework.

[b]COM-B: capability, opportunity, motivation for behavior.

[c]Findings from our qualitative study [28].

[d]N/A: not applicable (because there is no need for change).

Stage 2: Identifying Intervention Options

Step 5: Identify Intervention Functions

Based on the APEASE criteria, a total of 4 intervention functions were mapped onto the 10 TDF domains identified in step 4. The identified intervention functions included education, training, environment restructuring, and enablement (Table 6).

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Table 6. Mapping intervention functions to corresponding COM-B[a] components and BCTs[b].

COM-B component and TDF[c] domain linked to it	Intervention function	Selected BCT
Physical capability		
Physical skills	Train how to search for and access healthy food from all food groups.	Instruction to perform the behavior
Physical skills	Train how to prepare healthy meals using locally available food ingredients.	Instruction to perform the behavior
Physical skills	Train how to serve controlled portion sizes using the plate model.	Instruction to perform the behavior
Psychological capability		
Knowledge	Educate where to search for reliable information.	Information about health consequences
Knowledge	Educate on various food groups.	Information about health consequences
Knowledge	Educate food local foods in various food groups.	Information about health consequences
Knowledge	Educate about food groups and locally available health food sources.	Information about health consequences
Knowledge	Educate foods to avoid for optimal glycemic control.	Information about health consequences
Knowledge	Train on the composition of the plate model.	Instruction to perform the behavior
Behavioral regulation	Train or enable planning for and accessing healthy food.	Instruction to perform the behavior
Memory, attention, and decision processes	Enable the distinction between reliable information and myths.	Information about health consequences
Memory, attention, and decision processes	Enable decision-making on the type and quality of healthy food.	Action planning
Physical opportunity		
Environmental context and resources	Enable environmental restructuring to use a smaller plate to serve meals.	Adding objects to the environment
Social opportunity		
Social influences	Enable environmental restructuring to modify cultural beliefs on food that affect the choice of food.	Restructuring the social environment
Social influences	Enable to challenge sociocultural habits regarding food portion sizes.	Practical social support
Social influences	Enable awareness creation among family members involved in meal preparation on how to prepare healthy meals.	Practical social support
Reflective motivation		
Intentions	Educate how to clarify information, when needed.	Prompts and cues
Goals	Enable establishment routines and habits to eat healthy meals.	Behavioral goal setting
Goals	Enable establishment routines and habits of observing optimal portion sizes when serving food.	Behavioral goal setting
Goals	Enable planning to serve correct portion sizes.	Behavioral goal setting
Goals	Enable planning to cook healthy meals.	Action planning
Intentions	Educate to prioritize the purchase and eating of healthy food.	Self-monitoring of behavior
Beliefs and consequences	Educate on foods to avoid for optimal glycemic control.	Information about health consequences
Automatic motivation		
Reinforcement	Persuade to look for information when in doubt.	Practical social support
Goals	Enable to establish meal plans to ensure the intake of healthy meals.	Practical social support

[a]COM-B: capability, opportunity, motivation for behavior.

[b]BCT: behavior change technique.

[c]TDF: Theoretical Domains Framework.

Step 6: Identify Policy Categories

Policy categories were selected based on our qualitative study after analysis using the APEASE criteria: (1) Most participants (90%) had an income of less than 400 euros (US $ 422.27) per month, and this had limited the control of fiscal decisions; (2) all participants owned a basic mobile phone; and (3) the process of developing guidelines by the Ministry of Health in Kenya is

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structured and involves multiple stakeholders, making it likely to be limited by time. Based on this, we identified communication and regulation as the most practical policy categories.

Stage 3: Identifying Content and Implementation Options

Step 7: Identify BCTs

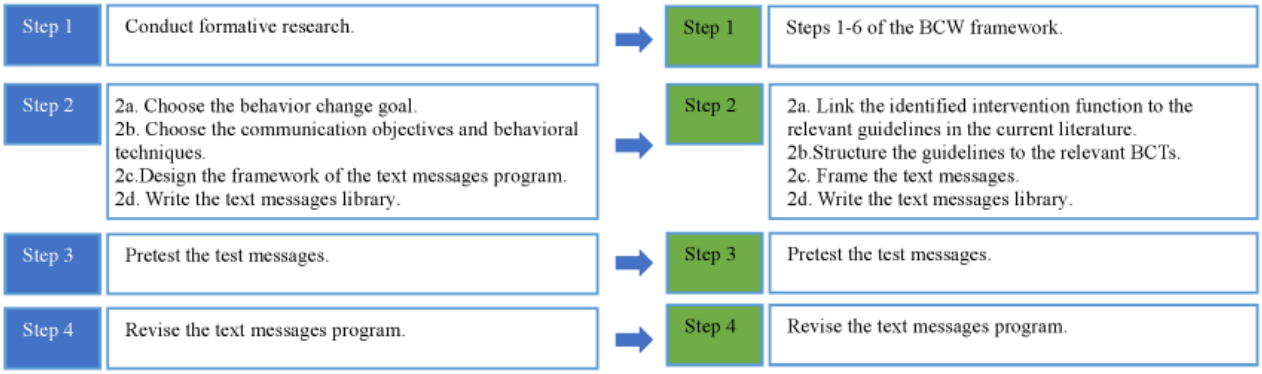
BCTs are the "irreducible, observable, and replicable components of an intervention designed to redirect behaviour" [35]. In this study, we selected 9 BCTs from the taxonomy of behavior change [36] to develop intervention content aimed at influencing dietary behavior (Table 5). These BCTs included behavioral goal setting, action planning, self-monitoring of behavior, practical social support, instruction to perform the behavior, information about health consequences, prompts and cues, restructuring the social environment, and adding objects to the environment.

Step 8: Select the Mode of Delivery

Based on findings from our qualitative study [28], most of the adults with T2D in the target population owned and used mobile phones. Additionally, our systematic review revealed that using text messages in LMICs is associated with a clinically significant effect on HbA_{1c} levels, in addition to being cheap and easy to use irrespective of socioeconomic status, and is not affected by racial disparities [30,37,38]. As such, we selected mobile text messages as the mode of delivery [28].

The text messages were developed based on Abroms et al's [39] 4 steps for developing a text messaging program: (1) formative research, (2) design, (3) pretest, and (4) revision. In this study, we modified steps 1 and 2, as shown in Figure 4. Specifically, we modified step 2 to include 3 substeps: (2a) linking the identified intervention function to relevant Kenyan and international guidelines and recommendations for a healthy diet [42-47], (2b) structuring guideline content to the relevant BCT, and (2c) gain- or loss-framing the text message. Gain-framed health promotion messages emphasize the benefits of engaging in a certain behavior, while a loss-framed message emphasizes the consequences of failing to participate in the behavior [46]. The messages were developed through a consultative process that included MM, CM, and FK. Table 7 illustrates a sample of the developed text messages.

Figure 4. Adaptation of the message development. Adapted from Abroms et al [39].



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Table 7. Sample text messages to be used in the mHealth[a] intervention.

COM-B[b] components and what needs to happen for the target behavior to occur	BCT[c]	Mobile text messages
Physical capability		
Be able to select healthy food	Instructions on how to perform the behavior	• To meet nutrient needs within calorie limits, choose a variety of nutrient-dense foods across and within all food groups in recommended amounts. Energy-dense foods include vegetables, fruits, whole grains, beans, nuts and seeds, and lean protein when prepared with little or no saturated fats, added sugars, and sodium. • There are 5 food groups: (1) vegetables and legumes or beans; (2) fruit; (3) lean meats and poultry, fish, eggs, nuts and seeds, and legumes or beans; (4) grain (cereal) foods, mostly whole-grain or high-cereal fiber varieties; and (5) milk, yoghurt, cheese, or alternatives, mostly reduced fat. • Most processed carbohydrate foods release glucose more quickly than whole-grain carbohydrates. Eat whole-grain carbohydrates, which produce a slower rise in blood glucose levels, which are called low-glycemic-index (GI) foods and result in better blood glucose control.
Psychological capability		
Know healthy food.	Information about health consequences	• The amount of carbohydrates in your meal has the greatest effect on blood glucose levels. Avoid big servings of carbohydrates in your meals and ensure most of your energy-giving foods are composed of whole meal or high fiber. Make vegetables and fruits take the larger portion of your plate. • There are 2 main types of fat: saturated and unsaturated. Excessive saturated fat in foods, such as fatty meat, sausages, and butter, can increase the amount of cholesterol in the blood, which increases your risk of developing heart disease.
Use advanced planning skills to ensure the selection of healthy food.	Information about health consequences	• Select whole or minimally processed foods, which help control your blood glucose. • Make an eating plan each week: this is the key to fast and easy meal preparation. This will also ensure that you plan for healthy diets and better-controlled blood glucose.
Know the composition of the plate model.	Information about health consequences	• Start with a 9-inch dinner plate. Fill half with nonstarchy vegetables, such as managu, Sukuma wiki, green beans, broccoli, cauliflower, cabbage, and carrots. Fill one-quarter with a lean protein, such as chicken, fish, legumes, beans, or eggs. Fill one quarter with whole-meal carbohydrate foods: grains, starchy vegetables (eg, potatoes and peas), rice, pasta, beans, fruit, and yoghurt. A cup of milk also counts as a carbohydrate food.
Social opportunity		
Change cultural habits on the portion size.	Restructuring the physical environment	• Controlled portion sizes of food are important to reduce calorific intake. To control your portion sizes, plan to use a smaller plate size when serving meals. • Your health is a personal responsibility. When eating, try to avoid places that may entice you to eat excessive food. Eat most of your meals at home for better control of healthy food and your blood sugar.
Reflective motivation		
Intend to select a healthy diet.	Information about health consequences, prompts/cues	• Make your shopping list ahead of time and do not go shopping while hungry. This helps you buy healthier items but also saves money and helps you select healthier foods. • Instead of purchasing processed grade 1 maize flour or Unga that is processed, use posho-milled Unga or whole-meal flour. Posho-milled flour contains fiber and other plant extracts that help in blood sugar control.
Intend to prioritize eating a healthy diet.	Information about health consequences, prompts/cues	• Small changes to more nutrient-dense, single food and beverage choices combine to make a nutrient-dense meal and can lead to a whole day of nutrient-dense meals and snacks, increasing your blood sugar control. • Place fresh and locally available low-carbohydrate fruits on the table or a place that is easy to reach to increase intake of fruits. This will enable you to eat healthy and avoid unhealthy snacking.
Automatic motivation		

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COM-B[b] components and what needs to happen for the target behavior to occur	BCT[c]	Mobile text messages
Establish routines and habits to select a healthy diet.	Instructions on how to perform a behavior	• Keep a food diary for a few days to evaluate what you eat every day. Note how you were feeling when you ate: hungry, not hungry, tired, or stressed? Create a list of cues by reviewing your food diary to become more aware of when you're triggered to eat for reasons other than hunger. Is there anything else you can do to avoid the cue or situation? If you cannot avoid it, do something different that would be healthier. Replace unhealthy habits with new, healthy ones.
Establish routines and habits to select a healthy diet.	Prompts/cues	• Replace white rice with whole-grain foods or brown rice. This ensures better blood sugar control.
Establish routines and habits to serve and eat a healthy diet.	Instructions on how to perform behavior	• Eat smaller meals more often. Eat at least 3 meals a day, with snacks in between. When you wait too long to eat, you are more likely to make unhealthy food choices.

[a]mHealth: mobile health.

[b]COM-B: capabilities, opportunities, and motivation for behavior.

[c]BCT: behavior change technique.

Testing the Feasibility of the Developed Intervention

According to the Medical Research Council (MRC) guidance on developing and evaluating complex interventions, the development of an intervention in this study is the first of 4 steps [31]. The other subsequent and iterative steps include feasibility, evaluation, and implementation. Based on this guidance, the intervention has been tested for feasibility through an exploratory trial in the target population, and the findings will be reported elsewhere.

Discussion

Principal Findings

This paper described the systematic development of an mHealth intervention using mobile text messages to optimize glycemic control in adults with T2D in Kenya following the BCW framework. Preparatory analysis preceding this study revealed that adults with T2D in Kenya have unhealthy dietary patterns and lack reliable sources of information to enhance food literacy [28]. The diagnosis also revealed that there are barriers to the target population's capability, opportunity, and motivation relating to food literacy. Based on the diagnosis, 4 intervention functions and 9 BCTs were selected to promote food literacy. Specific BCTs were selected to be integrated into this intervention: for example, adding objects to the environment (eg, using a smaller plate to serve food for portion control) and prompts or cues (eg, replacing white rice with whole-meal foods). The identified mHealth mode of delivery was mobile text messaging based on the practical applicability in the older population of adults with T2D.

When designing this study, we identified food literacy as a channel to address the problem of poor glycemic control. Food literacy has the potential to facilitate dietary behavior change through the connection of food and nutrition-related knowledge, and cooking skills [47]. Considering that food literacy explicitly focuses on health literacy skills in a food context [48], a positive correlation between health literacy and diabetes knowledge has been reported in patients with T2D [49]. Overall, the appropriate application of food literacy is associated with positive health outcomes in adults with T2D.

In this study, we used the BCW framework and contextual evidence to develop text messages for adults with T2D. The approach of basing the development on theory and the content of the text messages on the needs of the target population has been used variedly in recent studies [50-53]. In a recent 2-country African study [50], the BCW framework was used to develop text messages in 4 phases that included exploration of primary and secondary data and focus group discussions (FGDs), which were followed by pretesting through telephone interviews. Bartlett et al [51] developed text messages for patients with diabetes in the United Kingdom based on BCTs in a process that included health care specialist workshops, FGDs, and acceptability and fidelity surveys. MacPherson et al [53] developed text messages guided by BCTs, the motivational interviewing counselling style, and the Small Steps for Big Changes approach [54]. However, unlike our study in which we specifically developed text messages to facilitate food literacy, these studies [50,51,53] have focused on the wider multicomponent approach to diabetes management and prevention. The focused approach in our study was based on evidence showing that food literacy is an important problem in the target population [28], while a multicomponent approach to diabetes care is effective in optimizing glycemic control [55,56].

Strengths and Limitations

We acknowledge some strengths and weaknesses in using the BCW framework in this study. First, this study used contextual data to conduct behavioral diagnosis, which included our qualitative study of facilitators of and barriers to healthy dietary behavior in the target population, as recommended by Buchanan et al [57]. Second, the BCW framework provides a systematic method for designing a theory-based intervention, starting from a behavioral diagnosis of what needs to change, followed by linking the diagnosis to intervention functions, policy categories, and BCTs to change the target behavior. This approach enables the intervention to be contextualized to the needs of the target

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population, which increases its chances for success [58]. Third, the BCW framework uses a harmonized language of theoretical constructs and BCTs, which are important for the replication and synthesis of research and evidence [59,60].

However, this study was limited by the BCW framework's lack of a structured framework for operationalizing BCTs into mHealth methods of delivery [61], leaving it open to the creativity of the intervention developers and the context of the target population. However, to address this limitation, we modified previous guidance on the development of text messages [39] and developed messages based on target behaviors following guidelines on healthy diets that are linked to BCTs.

Conclusion

This study reported the systematic use of the BCW framework, the COM-B model, the TDF, and BCTs based on the contextual needs of the target population to develop text messages to influence food literacy in adults with T2D. The efficacy of the text messages will be evaluated through an exploratory trial in adults with T2D in the target population.

Acknowledgments

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Data Availability

The data generated during this study are available from the corresponding author upon reasonable request.

Authors' Contributions

MM and CM selected the approach and designed the intervention. MM, CM, FK, PY, and RV were part of the research team that contributed to the development of the intervention. MM wrote the first draft of the manuscript, while CM, FK, TB, PY, and RV reviewed, revised, and approved the final manuscript. Chatbots and generative artificial intelligence were not used in the conceptualization or any other part of this manuscript.

Conflicts of Interest

None declared.

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Abbreviations

APEASE: acceptability, practicability, effectiveness, affordability, side effects, and equity
BCT: behavior change technique
BCTTv1: Behavior Change Technique Taxonomy version 1
BCW: Behavior Change Wheel
COM-B: capability, opportunity, motivation for behavior
FGD: focus group discussion
HbA_{1c}: glycated hemoglobin
mHealth: mobile health
MRC: Medical Research Council
T2D: type 2 diabetes
TDF: Theoretical Domains Framework

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Protocol

Activating Relatives to Get Involved in Care After Surgery: Protocol for a Prospective Cohort Study

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Abstract

Background: Postoperative complications and readmissions to hospital are factors known to negatively influence the short- and long-term quality of life of patients with gastrointestinal cancer. Active family involvement in activities, such as fundamental care activities, has the potential to improve the quality of health care. However, there is a lack of evidence regarding the relationship between active family involvement and outcomes in patients with gastrointestinal cancer after surgery.

Objective: This protocol aims to evaluate the effect of a family involvement program (FIP) on unplanned readmissions of adult patients undergoing surgery for malignant gastrointestinal tumors. Furthermore, the study aims to evaluate the effect of the FIP on family caregiver (FC) burden and their well-being and the fidelity of the FIP.

Methods: This cohort study will be conducted in 2 academic hospitals in the Netherlands. The FIP will be offered to adult patients and their FCs. Patients are scheduled for oncological gastrointestinal surgery and have an expected hospital stay of at least 5 days after surgery. FCs must be willing to participate in fundamental care activities during hospitalization and after discharge. Consenting patients and their families will choose to either participate in the FIP or be included in the usual care group. According to the power calculation, we will recruit 150 patients and families in the FIP group and 150 in the usual care group. The intervention group will receive the FIP that consists of information, shared goal setting, task-oriented training, participation in fundamental care, presence of FCs during ward rounds, and rooming-in for at least 8 hours a day. Patients in the comparison group will receive usual postoperative care. The primary outcome measure is the number of unplanned readmissions up to 30 days after surgery. Several secondary outcomes will be collected, that is, total number of complications (sensitive to fundamental care activities) at 30 and 90 days after surgery, emergency department visits, intensive care unit admissions up to 30 and 90 days after surgery, hospital length of stay, patients' quality of life, and the amount of home care needed after discharge. FC outcomes are caregiver burden and well-being up to 90 days after participating in the FIP. To evaluate fidelity, we will check whether the FIP is executed as intended. Univariable regression and multivariable regression analyses will be conducted.

Results: The first participant was enrolled in April 2019. The follow-up period of the last participant ended in May 2022. The study was funded by an unrestricted grant of the University hospital in 2018. We aim to publish the results in 2023.

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Conclusions: This study will provide evidence on outcomes from a FIP and will provide health care professionals practical tools for family involvement in the oncological surgical care setting.

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KEYWORDS

family-centered care; postoperative; surgical oncology; cohort; prospective study

Introduction

Background

Postoperative complications and hospital readmissions are known to negatively influence the short- and long-term quality of life (QoL) of patients [1]. In addition, complications and readmissions also increase health care demands and costs [2,3]. Readmission rates after gastrointestinal surgery increase up to 30% [4] and are higher compared with general surgery in that these rates range from approximately 4% to 11% [5,6]. In addition, complication rates after gastrointestinal surgery are 34% [7], which is approximately 3 to 8 times higher compared with general surgery [8,9]. Frequent complications in this patient population include delirium, pneumonia, and wound infections [7]. Reducing these readmissions and postoperative complications in patients undergoing oncological gastrointestinal surgery is a priority.

Some postoperative complications are potentially preventable [10]. Several studies have shown that optimizing basic care by executing fundamental care activities prevents postoperative complications, such as pneumonia, urinary tract infections, and delirium [10-12]. Fundamental care activities include early mobilization, breathing exercises, dental hygiene, orientation in time and place, and eating together [13]. Although fundamental care seems simple, it is prone to be missed care [13,14].

The authors of a systematic review of 18 studies concluded that up to 75% of nurses omitted some kind of fundamental care tasks [15]. In a recently published meta-review of 7 systematic reviews, the following categories of missed nursing care were identified: (1) fundamental physical care; (2) communication and information sharing with patients and families; (3) self-management, autonomy, and education of patients and families, including care planning, discharge planning, and decisions; and (4) emotional and psychological care, including spiritual support [14]. Poorly executed or missing aspects of this care threaten patients' QoL and satisfaction, resulting in higher numbers of adverse outcomes and poor care experiences [13,14].

After hospital discharge, family caregivers often play an important role in the delivery of fundamental care activities to patients with cancer [16]. However, family caregivers often feel unprepared to deliver proper care of their loved ones after discharge, and they also feel that they lack the necessary skills and knowledge [17]. This might be because family caregivers are often considered visitors during patients' hospital stay and are sidetracked [18]. Thus, family caregivers are not normally actively involved in postoperative care during hospitalization.

Despite the uncertainty that family caregivers experience, in the past few decades, family-centered care (FCC) has been shown to potentially improve the quality of health care [13,19-21]. Family caregivers have become important care partners who are able to participate in all aspects of care delivery [22,23]. For instance, studies in which family caregivers were actively involved in performing fundamental care activities during hospital admission have shown a reduction in postoperative complications such as delirium and pneumonia [12,24]. The authors of a review of systematic reviews concluded that FCC could be an effective approach for improving the quality of health care, but there was a lack of high-quality studies investigating the effectiveness of FCC [25].

Family caregivers might be better prepared to deliver adequate care to their loved ones after discharge if they are involved in fundamental care during hospitalization, which could also lead to improved adherence to these care activities. Therefore, the incidence of complications and related readmissions might decrease. To promote active family involvement, we developed a multicomponent family involvement program (FIP) in which family caregivers could be actively involved in caring for their loved ones during hospitalization after oncological gastrointestinal surgery [26]. In a pilot study, our FIP was shown to be feasible for patients, family caregivers, and health care professionals [16,27]. In addition, family caregivers had a better understanding and knowledge of their loved one's recovery process [27].

Objectives

Although the results of our pilot study on the FIP were promising, the lack of evidence on the relationship between family involvement and outcomes in patients with gastrointestinal cancer after surgery points to the need for a prospective cohort study. Therefore, the main objective of this study is to evaluate whether FIP for adult patients undergoing oncological gastrointestinal surgery reduces the number of unplanned readmissions compared with usual care. The secondary aims are to evaluate the effect of the FIP on family caregivers by assessing caregiver burden and family caregivers' well-being and to assess the fidelity of the FIP. Here, we describe the study design and summarize the study protocol, which may also provide practical tools for health care professionals to adopt a more family-centered approach.

Methods

Study Design

This study is known by the acronym "ARTIS," which stands for Activating Relatives to Get Involved in Care After Surgery.

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The ARTIS study is a patient preference multicenter prospective cohort study. The study protocol described here is reported according to the applicable criteria of the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) [28] and the Template for Intervention Description and Replication (TIDieR) [29]. The results of this study will be reported according to the Strengthening the Reporting of Observational Studies (STROBE) [30].

Study Setting

The study will be conducted at 5 surgical wards that provide care to patients after oncological gastrointestinal surgery in two Dutch tertiary university hospitals in the Netherlands: (1) Amsterdam University Medical Center (UMC), location Academic Medical Center (AMC) and Vrije Universiteit Medical Center, Amsterdam, and (2) University Medical Center Groningen (UMCG), Groningen. The average number of patients undergoing oncological gastrointestinal surgery as treatment for malignant pancreatic, gastric, esophageal, liver, colorectal, or peritoneal tumors in Amsterdam UMC is 415 per year and in UMCG 330 per year. Each participating surgical ward has 25 to 30 beds with a nursing:patient ratio of either 1:4 or 1:5. The participating wards were chosen because health care professionals expressed a willingness to adopt a more family-centered approach to their care.

Eligibility Criteria

Patients

In this study, we will include adult patients (≥18 years) scheduled for gastrointestinal surgery as treatment for malignant pancreatic, stomach, esophageal, liver, colorectal, or peritoneal tumors. The expected hospital stay must be at least 5 days after the operation, which makes adequate training and coaching of family caregivers under the supervision of nurses possible. Furthermore, patients will have to be able to read and write the Dutch language and will be included after providing written consent. Patients will be excluded if they remain in the intensive care unit (ICU) for >72 hours directly after surgery, as family caregivers do not have the opportunity to be involved in care in the first 5 days after the operation. In addition, patients will be excluded if the tumor is considered unresectable during surgery, as these patients do not receive the intended surgery and are discharged after one day.

Family Caregivers

The eligibility criteria for adult family caregivers are that they are willing and able to deliver fundamental care during hospitalization (for a minimum of 8 hours per day) and after discharge (if needed). Furthermore, they should be nominated as the appointed family caregiver by the patient and should not require support from health care professionals to carry out their own self-care activities. Furthermore, family caregivers will have to be able to read and write the Dutch language and will be included after providing written consent. In this study, family caregivers could be relatives or close friends who know the patient and either live with or are involved in the care of the patient. They are individuals who provide support and with whom the patients have a significant relationship.

Intervention

Overview

The FIP is a multicomponent intervention developed using a multiphase quality improvement design [26]. The main components of the program are as follows: (1) active involvement of family caregivers and (2) training and coaching of health care professionals in the FCC. The development process and rationale of this program have been described in further detail by Eskes et al [26]. The FIP is performed in addition to the usual postoperative care.

Component 1: Active Involvement of Family Caregivers

For the first component, multiple tasks involving families in fundamental care activities are described.

Invite Family Caregivers to Participate in Fundamental Care Activities

To standardize FIP delivery, family caregivers will be asked to participate in evidence-based fundamental care activities (Textbox 1). In addition, family caregivers can participate in optional care activities (Textbox 2).

Textbox 1. Fundamental care activities executed by family caregivers.

- Three times a day
  - Mobilization defined as getting a patient out of bed (ie, sitting out of bed and ambulation) [12,31-33]
  - Encouraging oral intake and companionship during meals (ie, breakfast, lunch, and dinner) and ensuring that patients are seated at the table when meals are served [11,32]
  - Supporting patients in doing breathing exercises (ie, coughing and deep breathing) [12,34,35]
  - Supporting active orientation; specific time-, place-, and person-related information in the context of the present day; and daily discussions on actual items (eg, news) [31,32]
- Two times a day
  - Supporting in carrying out oral care (brushing teeth and using mouthwash) [12,34,35]

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Textbox 2. Optional care activities executed by family caregivers.

- General care
  - Washing and dressing of the patient
  - Assistance with the use of the toilet
- Wound-related care
  - Wound dressing
- Administering medication
  - Injecting anticoagulation
- Drain-related care
  - Taking care of abdominal drains
  - Taking care of nasogastric tubes

Information About Fundamental Care Activities

Family caregivers who participate in the FIP will gain access to a mobile app (so-called "Mantelzorgapp") before patients' hospital admission. The app has detailed descriptions of the following: (1) the rationale for performing the fundamental care activity, (2) preparation for the activity, (3) the needed material for the activity, (4) a step-by-step description on how to perform the activity, and (5) time and frequency of performing the activity. The app also includes a daily diary in which the family caregivers tick boxes if they have performed a fundamental care activity (yes or no) with writing space for comments. Furthermore, the app includes discharge information, such as whom to contact if they have concerns about patients' health condition. The app can be downloaded without any cost from the Apple Store (Apple Inc) and Google Play Store (Google LLC) and is suitable for several mobile devices (ie, phones and tablets). If family caregivers are unable to use the app, they will receive paper-based information.

Shared Goal Setting With the Patient, Family Caregiver, and Nurse

On the basis of mutual agreement among the patient, the family caregiver, and the nurse, a personalized plan for the patient and family caregiver will be made within 24 hours after the surgery. This plan includes the patient's care needs and personal goals of the family caregiver. This plan will be documented in the electronic patient record. Active participation will start on the first day after surgery in the ward (or within 72 hours in case of ICU admission) and will be continued for at least 5 days after surgery. After this period, the family caregivers choose whether or not to continue the program. We plan to work with the same family caregiver throughout the study period. However, if there are multiple family caregivers, we will recruit a maximum of 3 family caregivers who are available and interested. These family caregivers need to alternate during admission, and each family caregiver needs to be involved in the FIP for a minimum of one day.

Task-Oriented Training of Family Caregivers to Deliver Fundamental Care Activities

During the FIP, the family caregiver will receive training from a registered nurse. All the activities will be supervised by the nurse until the family caregiver is competent, as determined by the nurse, to carry out the activities on their own. To facilitate adequate care delivery, the objective of each activity, including instructions on how to deliver the activity, is described in full detail and accessible in the app. If the activity is carried out, the family caregiver registers it on the registration form in the app. Additional activities will also be recorded in the app.

Physical Proximity (Rooming-in)

Family caregivers are asked to stay with the patient for at least 8 hours per day during the first 5 postoperative days, which offers the opportunity to learn and become competent in new fundamental care activities under supervision. As most of these activities should be undertaken 3 times a day, presence of at least 8 hours provides them with the opportunity to complete these activities.

Presence of Family Caregivers During Medical Ward Rounds

Family caregivers are encouraged to be present and to be actively involved during medical rounds. Health care professionals (eg, doctors and nurses) will support the family caregivers throughout the hospital stay, answer questions related to the FIP, and identify unmet needs.

Component 2: Training and Coaching of Health Care Professionals

To support the delivery of the FIP, structured training sessions will be given to doctors and nurses. The training will mainly focus on the four core concepts of FCC: (1) dignity and respect, (2) information sharing, (3) participation, and (4) collaboration [26]. In the session, the rationale, goals, and benefits of the FIP and the concept of passive and active family involvement will also be explained. In addition, quality- and safety-related topics will be discussed. The training session will be delivered by one of the members of the research team.

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Usual Postoperative Care

Patients in the usual care group will receive care based on the Enhanced Recovery After Surgery principles, which include early mobilization, early postoperative feeding, goal-directed fluid therapy, and nonnarcotic analgesia [36]. In addition, patient engagement and a multidisciplinary team approach to the usual postoperative care will be used [36]. Patients will receive care pathways for their specific type of surgery in which day-to-day targets are provided, which promotes autonomy and cooperation from the patients. Patients are encouraged to actively mobilize from the day of surgery until hospital discharge (ie, stay out of bed for 2 hours on the day of surgery and at least 6 hours per day from the first postoperative day until hospital discharge). The patients will not receive detailed information about the content of the FIP. No rooming-in opportunities will be offered to the usual care group, except for family visits (ie, a maximum of 2 visitors at the patient's bedside between 11 AM and 8 PM will be permitted).

Outcomes

The primary patient outcome is the number of unplanned readmissions up to 30 days after surgery (Table 1). Secondary outcomes include the total number of complications at 30 and 90 days after surgery and the number of complications sensitive to fundamental care activities (eg, pneumonia, urinary tract infection, wound infection, deep vein thrombosis, malnutrition, and delirium) at 30 and 90 days after surgery. These data will be collected from patient records, and complications will be classified according to the revised version of the Clavien-Dindo classification system [37]. Secondary outcomes also include emergency department visits, ICU admissions up to 30 and 90 days after surgery, and hospital length of stay. Furthermore, patients' QoL will be measured using the EQ-5D-5L [38], and the level of anxiety and depression in patients will be measured using the Hospital Anxiety and Depression Scale (HADS; Table 1) [39,40]. Patient satisfaction with care and sleep quality will be measured using the numeric rating scale (NRS) ranging from 0 to 10, with higher scores indicating higher satisfaction or sleep quality (Table 1). Sleep quality will be assessed once a day, from the first day after surgery until 5 days after the operation. In addition, the amount of home care (in hours per week) after discharge will be measured (Table 1). The risk screening scores routinely measured during hospital admission will be collected, ie, the Short Nutritional Assessment Questionnaire score (SNAQ) [41], the Delirium Observation Scale score (DOS) [42], the Braden scale [43], the Amsterdam UMC Extension of the John Hopkins Highest Level of Mobility scale score (AMEXO) [44] and the John Hopkins Fall Risk Assessment (JHFRAT; Table 1) [45].

In addition to the effect of the FIP on patient outcomes, we measured the effect of the FIP on family caregiver outcomes, including caregiver burden and well-being up to 90 days after participating in the FIP (Table 1). The Valuation of Informal Care Questionnaire (iVICQ) measures objective burden using the following items: duration and intensity of informal care, patient health, need for permanent surveillance, patients' living situations, and use of professional care [46]. Subjective burden will be measured using the Caregiver Strain Index plus (CSI+) [47], self-rated burden scale [48], and perseverance time [49]. The well-being of family caregivers will be measured using the Care-related Quality of Life instrument (CarerQoL-7D) and Care-related Quality of Life–Visual Analog Scale (CarerQoL-VAS; Table 1) [50]. Finally, the costs of the FIP will also be measured using the iVICQ [46].

To measure adherence, which is considered a bottom-line measurement of intervention fidelity [51], we will record how many patients are offered the FIP and how many patients decline, including the reasons if they want to disclose. We will use the data recorded by family caregivers to assess the fidelity of the intervention. Up to 5 days after surgery, family caregivers will be asked to record the fundamental and optional care activities they have carried out in the app, and if not completed, to add a reason. The family caregiver registers the activity on the registration form of the app. If multiple family caregivers participate in the FIP, they will all be asked to record the executed activities. Rooming-in of the family caregivers during admission will be checked by ward nurses and researchers (SM, SK, and HWH).

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Table 1. Outcome variables for patients and their family caregivers.

	T0, baseline	T1, during 5 days after the operation	T2, at discharge	T3, discharge+30 days	T4, discharge+90 days
Patient					
Unplanned readmissions[a]				✓	✓
Complications (sensitive to fundamental care activities)[a,b,c]				✓	✓
First aid visit[a]				✓	✓
ICU[d] admission[a]				✓	✓
EQ-5D-5L	✓		✓	✓	✓
HADS[e]	✓		✓	✓	✓
NRS[f] patient satisfaction			✓		
NRS sleep quality		✓			
LOS[g]			✓		
Bodyweight (in kilogram)	✓		✓	✓	✓
Professional home care (indications)			✓	✓	✓
SNAQ[h]	✓			✓	✓
Braden scale	✓			✓	✓
DOS[i]	✓	✓		✓	✓
AMEXO[j]		✓		✓	✓
JHFRAT[k]	✓			✓	✓
Family caregiver					
Objective burden					
Duration of informal care	✓		✓	✓	✓
Intensity of informal care	✓		✓	✓	✓
Health of patient	✓		✓	✓	✓
Need for permanent surveillance	✓		✓	✓	✓
Patients' living situation	✓		✓	✓	✓
Use of professional care	✓		✓	✓	✓
Subjective burden					
CSI+[l]	✓		✓	✓	✓
Self-rated burden scale	✓		✓	✓	✓
Perseverance time			✓	✓	✓
Well-being					
CarerQoL-7D[m,n]	✓		✓	✓	✓

[a]Unplanned readmissions, complications, first aid visits, and ICU admissions will be measured 30 and 90 days after surgery.

[b]Complications will be classified according to the revised version of the Clavien-Dino classification system.

[c]Complications sensitive to fundamental care activities: pneumonia, urinary tract infection, wound infection, deep vein thrombosis, malnutrition, and delirium.

[d]ICU: intensive care unit.

[e]HADS: Hospital Anxiety and Depression Scale.

[f]NRS: numeric rating scale.

[g]LOS: length of stay.

[h]SNAQ: Short Nutritional Assessment Questionnaire score.

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[i]DOS: delirium observation scale.

[j]AMEXO: Amsterdam UMC Extension of the John Hopkins Highest Level of Mobility scale score.

[k]JHFRAT: John Hopkins Fall Risk Assessment.

[l]CSI+: Caregiver Strain Index plus.

[m]CarerQoL-7D: Care-related Quality of Life.

[n]CarerQoL-VAS: Care-related Quality of Life–Visual Analog Scale.

Study Procedure

During the preoperative outpatient clinic visit, the patients and their family caregivers will be screened for eligibility and informed about the study (Table 2). If they are interested, a researcher (SM, SK, or HWH) will contact the patients after the visit to determine their preference for the study arm. If patients prefer the intervention arm, at least 2 days before hospital admission, the researcher will confirm the patients' participation depending on the ward capacity. The FIP starts <72 hours after surgery when patients are transferred from the postanesthesia care unit to the participating surgical wards. Depending on the ward capacity and patient preferences, the program can be continued until discharge. During the follow-up period (ie, 30 and 90 days after surgery), the patient and family caregiver will be contacted by telephone by SM, SK, or HWH and asked to complete the questionnaires.

Table 2. Study procedure.

Timing	Activity
Prehospital admission[a]	
Outpatient clinic visit	• Recruitment of patients and family caregivers, screening for eligibility, and informed consent procedure • Group allocation based on patient and family preferences
1 week before hospital admission	• Patients and family caregivers from the intervention group will get access to the mobile app (so-called Mantelzorgapp)
2 days before admission	• The researcher will confirm the patients' participation in the intervention group depending on the ward capacity
Clinical phase[b]	
Within 24 hours after surgery	• Family caregivers will receive a personalized plan based on the identified patients' care needs, and the plan includes the personal goals of the family caregiver • Goals will be documented in the electronic patient record • Patients and family caregivers will complete questionnaires about their baseline characteristics
Day of surgery until 5 days after operation	• Family caregivers start by participating in the fundamental care activities (and optional care activities) • Family caregivers will register all activities in the app. • Depending on the ward's capacity and patients' preferences, the program could be continued until discharge
At discharge	• Patients and family caregivers will complete discharge questionnaires
After discharge	
Follow-up 30 days and 90 days after discharge	• The researcher will send questionnaires to patients and family caregivers for measuring outcomes • The researcher will contact the patient and family caregiver by telephone for outcome measures not mentioned in the questionnaires • The researcher will collect data on the number of readmissions and complications as registered in the electronic patient record

[a]Information about the FIP.

[b]The required clinical data regarding baseline characteristics and outcomes will be collected during hospitalization using standardized case report forms.

Allocation

Participation in the FIP is based on the preferences of patients and, if available, their family caregivers. This means that when the patients and their relatives want to participate in the program, they will be allocated to the intervention group and when the patients or their relatives do not want to participate in the program (but give consent for observation in the usual care group), they will be allocated to the usual care group. By using this patient preference study design, we might introduce

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contamination between the intervention and comparison groups, as patients in the comparison group might learn about fundamental care activities and adopt them themselves or receive informal care without the program. Nevertheless, this study design was selected deliberately because no clear signs of contamination were observed between the study groups in the pilot study [16]. To minimize the risk of between-group contamination, the information for patients and their families before inclusion will not include detailed information about the fundamental care activities that comprise the program.

Sample Size

The sample size is based on the primary objective of evaluating the effects of the FIP on unplanned readmissions. In our pilot study, we found an absolute reduction of unplanned readmission rates of 15% [16] and considered this 15% reduction of unplanned readmissions as clinically relevant, representing a readmission rate of 20% in the intervention group and 35% in the usual care group. To detect a 15% reduction in readmission rates at a 5% significance level (α) and a power of 80% ($1 - \beta$), a sample size of 136 patients per group is necessary, using a continuity-corrected chi-square test. We assume a 10% to 20% loss to follow-up (ie, not completing the questionnaires), and to compensate for this, the total sample size per group will be at least 150. Loss to follow-up is expected owing to the use of repeated questionnaires, which may burden patients. Recruitment ends as soon as both the groups have included 150 patients. To minimize attrition, we will collect detailed contact information and offer patients alternative data collection methods such as paper-based questionnaires if patients do not have an email address [52].

Data Collection Methods

Patients

At baseline, the following patient characteristics will be collected from the patient records: sex [53], age [53], length in cm, weight at admission in kg [54], BMI in kg/m^2 [54], WHO performance status [55], American Society of Anesthesiologists Physical Status Classification (ASA PS Classification) [55], use of ≥5 medicaments [56], preoperative diagnosis, tumor type, type of surgery (ie, open, minimally invasive, or robot-assisted), and type of resection. In addition, the risk screening scores (ie, SNAQ, DOS scale, Braden scale, AMEXO, and JHFRAT) will be collected on the day of hospital admission. The number of days spent in the postanesthesia care unit will be collected from the patient records.

Furthermore, socioeconomic data will be collected via a patient questionnaire on the day of admission, including the highest level of formal education, marital status, number of children (≤18 years), and number of live-in children, hours per week of unpaid work and paid work [53]. The degree of social isolation before admission could be a potential confounder, as it is known that socially isolated patients have worse outcomes [57] and will therefore be measured using the Friendship scale [58].

Family Caregivers

On the day of admission, baseline characteristics of the family caregivers will be collected using the iVICQ [46]. Background characteristics include sex, age, educational level, relationship between family caregiver and patient, household composition, unpaid and paid work, monthly net household income, and health status.

Data Management

Patient data will be entered into a web-based data management system (Castor Electronic Data Capture, version 2022.4.1.3), which complies with all applicable laws and regulations. Family caregivers' data will be entered into an online protected database connected to the app. If family caregivers are unable to enter their data into the app, we will provide written case report forms. Participants are assigned a study number but can be identified in the database by their ID number. The participation identification log will be kept separate from the patient data and will be safeguarded by the principal investigator. For the participating centers, a separate site-specific subject identification log will be kept at each study site.

The integrity of both patients' and family caregivers' data will be protected through a variety of mechanisms. Valid rules, range checks, and consistency checks against stored data will be supported. Access to the study data will be restricted, and a password will be used to control access. For the online database, 2-faced authentication is needed for access. Access to the app for family caregivers is password protected, which prevents the user data from being revealed if the device is stolen. Castor data will be stored on certified servers (ISO 27001, ISO 9001, and NEN 7510) as well as app data (ISO 27001 and NEN 7510). Data will also be stored locally in the department's computer system drive. All hard-copy original study forms will be stored in a secure and accessible place. Files will be stored for 15 years after completion of the study. This study will not be monitored because the potential risk to patients participating in the study is negligible.

Statistical Methods

Overview

Statistical analyses will be performed using the R statistical software package (version 3.6.2; R Foundation for Statistical Computing). Descriptive statistics will be used to summarize the baseline characteristics and process outcomes of the patients and family caregivers. Continuous variables will be presented as means and SDs or medians and IQRs according to the distribution of the variables. Categorical variables will be presented as counts and percentages (%), and numbers and frequencies will be presented for dichotomous data. The distribution of variables will be determined by inspecting histograms and box plots.

The patients' baseline characteristics of the study arms will be tested for statistically significant differences using the chi-square statistics, Mann-Whitney *U* test, independent samples 2-tailed *t* test, or Fisher exact test. If there are differences between the FIP and treatment groups, we will adjust for confounding variables using multivariate regression analyses.

Outcomes

Univariable regression and multivariable regression analyses will be conducted using stepwise backward selection. For the

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primary outcome (ie, unplanned readmissions up to 30 days after surgery), we will conduct logistic regression analyses. For continuous secondary outcomes, we will use linear regression analyses; for dichotomous outcomes, we will use logistic regression analysis. We will use a general linear mixed model to analyze differences in sleep quality, DOS scores, and AMEXO scores over 5 days after the operation (Table 1). If a difference is observed, a post hoc power analysis will be used to examine which time point differs significantly. A 2-sided *P* value ≤.05 will be considered statistically significant. A 95% CI for the beta coefficient (β) will be calculated.

Additional Analyses

In this study, some additional analyses will be performed. We will analyze whether performing one or more optional care activities (Textbox 2) and the involvement of multiple family caregivers per patient can modify patient outcomes. Furthermore, in a sensitivity analysis, we will compare outcomes from patients in the FIP study arm to those from the comparison group whose family caregivers decline to participate in the FIP. The analysis will be based on intention-to-treat principles, meaning that every patient and family caregiver will be analyzed in the group that they chose before surgery.

Handling of Missing Data

If >40% of the missing data in the data set occur, multiple imputation by the chained equations method in R will be used [59,60]. Overall, 5 independent copies of the data will be analyzed. The estimates of the variables will be pooled according to Rubin rules. The pooled analysis will be presented. A complete case analysis will be performed as sensitivity analyses [60]. If >40% of the data are missing, we will use the observed data and report the extent of the missing data [59].

Ethics Approval

The Medical Ethics Review Committee (METC) of the Amsterdam UMC (location AMC), Amsterdam, the Netherlands, approved the study. The METC reviewed the study protocol and concluded that the Medical Research Involving Human Subject Act did not apply to this study (reference number METC: W19_497#20.015). Written informed consent will be obtained from all the participants.

Results

The first participant in this study was enrolled in April 2019 at the Amsterdam UMC, AMC. The follow-up period of the last participant ended in May 2022. The study was funded by an unrestricted grant of the University hospital in 2018. We aim to publish the results at the end of 2023.

Discussion

Principal Findings

Currently, FCC is becoming more widespread in hospital environments [25]. However, there is still a lack of rigorous evidence regarding the effects of FCC interventions and programs [19]. This multicenter cohort study allows us to evaluate the effect and process of an evidence-based multicomponent FIP in comparison with the usual postoperative care in patients undergoing oncological gastrointestinal surgery. We hypothesize that the number of unplanned readmissions and complications could be reduced by the FIP without increasing caregiver burden.

Before we planned this substantial evaluation of the FIP, we followed a stepwise approach guided by the Medical Research Council framework, as the FIP can be considered a complex intervention [61]. The development phase of the FIP began in 2015. First, we developed an evidence-based and theoretically grounded program [26]. This phase was followed by testing program feasibility in a pilot study, which gave us input about the required sample size [16]. In addition, we evaluated the experiences of family caregivers who participated in the FIP in a qualitative study [27]. The results of the second phase were used to develop the intervention study in which we aimed to assess the effectiveness of the FIP. We initiated a randomized controlled trial (RCT; Dutch Trial Register: NL66712.018.18). However, after consenting, many patients and families mentioned a strong preference and withdrew from both groups directly after randomization, stating in their reasoning that they either be involved as participating family caregiver or not. Continuing the trial would have probably led to high dropout rates and, therefore, decreased the generalizability of results to clinical practice [62].

To deal with the strong preferences of patients and their families, we considered changing the design to a patient preference trial. These trials have been introduced to give patients the opportunity to participate in the study arm they prefer [63,64] and have the main advantage of a lower risk of bias, especially in subjective outcome measures, and a decrease in dropout rates [64]. A consequence of choosing this study design is that it requires a very large sample size when a considerable number of patients have a preference for one particular study arm [64] and that it still needs a group of patients (and families) without preferences who want to be randomized, which appeared not to be the case in our study. Therefore, the best available option was to change the design to a patient preference observational cohort study, which is considered a valuable alternative when an RCT does not meet patients' preferences [65].

Nevertheless, we realize that this patient preference study design still influences the external validity. Eligible patients without an available family caregiver cannot participate in the FIP, and most probably, a substantial number of patients need to decline this opportunity. On the basis of our previous work, we expect that this will be the case in approximately 20% of the patients and another 15% of the family caregivers are expected to decline participation [16]. Therefore, it is essential to compare as many prognostic variables as possible between the 2 groups to assess baseline comparability, including patients' perceived social isolation and living status [66].

Implementation of FIP

By conducting this study, we will gain a better understanding of the behaviors of patients, families, and health care professionals that need to be changed and which implementation strategies are valuable to achieve this change. This input is needed to implement the results after finishing our cohort study

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and to guide other organizations also in implementing the FIP. In the pilot study, we developed an implementation plan using Grol and Wensing model [67] that facilitates changes in health care using a stepwise approach. On the basis of the implementation recommendations derived from our pilot study, we implemented our FIP in this cohort study. A summary of our implementation recommendations and lessons learned were published in the article by Schreuder et al [16]. An understanding of how the FIP was implemented by assessing the adherence to the FIP, the bottom-line measurement of intervention fidelity [51], will provide valuable insights when interpreting the effects of the FIP [51].

A potential challenge for implementing the FIP is that it requires health care professionals to accept an FCC approach [21]. This is considered a challenge because some health care professionals may not yet regularly engage patients' family caregivers in their daily practice [21]. Therefore, training and coaching health care professionals in the FCC is an essential component of FIP. Based on our pilot study, acceptable levels of time investment by doctors and nurses were found, and for most nurses, the workload was reduced to some extent [16]. Furthermore, most doctors value the presence of family caregivers during medical ward rounds [16]. Because of the positive experiences of health care professionals during the pilot phase of the study, we did not investigate their experiences again in this study. Nevertheless, one should be aware that work role conflicts because of having family caregivers involved in care are associated with nurses' distress and impaired quality of care [68]. In addition, one should be aware that some patients and health care professionals might view the FIP as an economical solution, replacing nurses with family caregivers rather than trying to improve health care [69,70].

Conclusions

In conclusion, this study will provide health care professionals important information about the relationship between a multicomponent FIP and outcomes in a broad group of patients with cancer undergoing surgery and their family caregivers. The FIP, which consists of evidence-based fundamental care activities for family caregivers, will provide practical tools for health care professionals to adopt a more family-centered approach. Future research should focus on the implementation strategies of FCC, choosing study designs that deal with patient preferences in complex interventions and involving patients when designing studies.

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Data Availability

The data sets generated and analyzed during this study are not publicly available because they involve sensitive human research participant data but are available from the corresponding author upon reasonable request.

Conflicts of Interest

None declared.

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Abbreviations

AMC: Academic Medical Center
AMEXO: Amsterdam UMC Extension of the John Hopkins Highest Level of Mobility Scale
ARTIS: Activating Relatives to Get Involved in Care After Surgery
ASA PS Classification: American Society of Anesthesiologists Physical Status Classification
CarerQoL-7D: Care-related Quality of Life instrument
CarerQoL-VAS: Care-related Quality of Life–Visual Analog Scale
CSI+: Caregiver Strain Index plus
DOS: Delirium Observation Scale
FC: family caregiver
FCC: family-centered care
FIP: family involvement program
HADS: Hospital Anxiety and Depression Scale
ICU: intensive care unit
iVICQ: Valuation of Informal Care Questionnaire
JHFRAT: John Hopkins Fall Risk Assessment
NRS: numeric rating scale
QoL: quality of life
SNAQ: Short Nutritional Assessment Questionnaire score
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
STROBE: Strengthening the Reporting of Observational Studies
TIDieR: Template for Intervention Description and Replication
UMC: University Medical Center
UMCG: University Medical Center Groningen

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Protocol

The Predictive Value of A, B, and C-Type Natriuretic Peptides in People at Risk of Heart Disease: Protocol for a Longitudinal Observational Study

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Abstract

Background: Heart disease and stroke are major and often unheralded causes of serious morbidity and premature death in middle age. Early detection of those most at risk is an urgent unmet need for instituting preventative measures. In an earlier community study (Canterbury Health, Ageing and Life Course [CHALICE]) of healthy people aged 50 years, contrary to previous reports, low levels of the heart hormone B-type natriuretic peptide (BNP) were associated with reduced measures of heart function and higher markers of vascular risk. A specific gene variant (rs198358) was found to be an independent contributor to higher BNP levels. A closely related vascular hormone (C-type natriuretic peptide [CNP]) showed opposite associations—higher levels were correlated with higher vascular risk and reduced cardiac function. To determine whether these novel findings predict serious heart or vascular disease in later life, this proposal re-examines the same CHALICE participants 15 years later.

Objective: The primary objective is to determine the predictive value of (1) low plasma concentrations of the circulating cardiac hormones (atrial natriuretic peptide [ANP] and BNP) and (2) high levels of the vascular hormone CNP at age 50 years in detecting impaired cardiac and vascular function 15 years later. Secondary objectives are to determine specific associations of individual analytes (ANP, BNP, CNP, cyclic guanosine monophosphate [cGMP]) with echo-derived changes in cardiac performance at ages 50 years and 65 years.

Methods: All of the 348 participants (205/348, 58.9% female; 53/348, 15.2% Māori or Pacifica ethnicity) participating in the original CHALICE study—free of history of heart or renal disease at age 50 years and who consented to further study—will be contacted, recruited, and restudied as previously described. Data will include intervening health history, physical examination, heart function (speckle-tracking echocardiography), vascular status (carotid intimal thickness), and genetic status (genome-wide genotyping). Laboratory measures will include fasting blood sampling and routine biochemistry, ANP, BNP, CNP, their downstream effector (cGMP), and their bio-inactive products. Humoral metabolic-cardiovascular risk factors will be measured after an overnight fast. Primary outcomes will be analyzed using multiple linear regression.

Results: The study will commence in 2022 and be completed in 2024.

Conclusions: Proving our hypothesis—that low BNP and high CNP at any age in healthy people predict premature aging of heart and blood vessels, respectively—opens the way to early detection and improved outcomes for those most at risk. Confirmation of our hypotheses would improve current methods of screening and, in appropriate cases, enable interventions aimed at increasing natriuretic hormones and reducing risk of serious cardiovascular complications using drugs already available. Such advances in

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detection, and from interventional corrections, have the potential to not only improve health in the community but also reduce the high costs inevitably associated with heart failure.

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KEYWORDS

Cardiovascular risk; arterial and LV elastance; polygenic risk scores; cGMP; bioactive and amino-terminal natriuretic peptide; heart disease; cardiovascular; middle age; risk; prediction; biomarkers; detection

Introduction

Atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP) are cardiac peptides secreted by atrial and ventricular myocytes, respectively [1]. Both hormones circulate in plasma and, acting via a common guanylate receptor (NPR 1), serve to regulate the renal excretion of salt, lower systemic arterial pressure, and reduce intracardiac pressure [2]. A third member of the family (C-type natriuretic peptide [CNP]) acts in cardiac [3] and vascular intimal tissues [4] via a different guanylate cyclase receptor (NPR 2) to reduce inflammation and cell proliferation [4,5] and increase flow and pressure in the microcirculation [6]. In contrast to the endocrine and paracrine actions of ANP and BNP, actions of CNP are largely paracrine and, at levels found in healthy adults, are barely detectable in plasma. The bioactive forms (ANP, BNP, and CNP) of all 3 peptides have strong affinity for a third (non-guanylate cyclase) receptor (NPR 3) that internalizes and degrades these peptides. However, aminoterminal bio-inactive products of the prohormones synthetized in tissues (ie, aminoterminal ANP [NTproANP], aminoterminal BNP [NTproBNP], and aminoterminal CNP [NTproCNP]) are not NPR 3 ligands, have longer half lives in plasma, and serve as surrogates for the respective prohormone production in tissues [7-9]. Increase in intracardiac pressure is a strong stimulus to the secretion of the cardiac hormones, ANP and BNP, which are raised in patients with overt heart failure [2]. Factors regulating CNP are less clear but include cytokines [10] and shear stress [11] in vascular tissues. Numerous studies of community dwellers have shown that higher plasma concentrations of BNP products (BNP or NTproBNP) not only detect cardiac impairment but also predict adverse outcomes [12-14] in participants without evidence of heart disease. However, we found that, in participants without history of heart disease and with plasma concentrations of ANP and BNP within the normal range, higher values associate with lower markers of vascular and metabolic risk and with improved cardiac performance [15,16] (Figure 1). A specific gene variant (rs198358)—previously reported in a genome-wide association study (GWAS) to associate with lower blood pressure [17]—was found to be an independent contributor to BNP levels in 2 quite separate populations: one 28 years old [16] and another 50 years old [15]. Together with recent reports of other closely related gene variants in the community positively affecting BNP levels and reducing adverse cardiac outcome [18], we suggest that genetic factors drive the ANP and BNP links we identified with markers of cardiometabolic health. Acquired factors such as increased adiposity is associated with lower plasma concentrations of BNP [19]—possibly related to an effect of glycosylation on the assay of BNP in plasma [20]. Others have therefore suggested the recognized increase in adverse events such as the metabolic syndrome in obesity are consequent on a BNP-deficient state. Importantly, in our 2 previous community studies, lower BNP levels (which associate with markers of impaired metabolic health) were independent of adiposity.

Few, if any, studies have examined plasma concentrations of CNP products (CNP or NTproCNP) in this context. However, in both community studies [15,16], we found plasma CNP products—opposite to ANP and BNP—are higher in those with impaired cardiometabolic health. We suggest that these associations with CNP likely reflect an adaptive compensatory response to inflammation in vascular [21,22] and myocardial tissues [2,23,24]. Notably, in both age groups, plasma CNP was positively associated with markers of arterial and left ventricular stiffness in both sexes, whereas these associations with BNP were inverse except in older women (Figure 2).

The key question regarding the significance of these findings in predicting adverse cardiac or vascular outcome can only be answered by appropriate re-examination of the same participants at a later date.

Accordingly, here, we outline a proposal to comprehensively restudy participants aged 49 years to 51 years in the Canterbury Health, Ageing and Life Course study (CHALICE) study [15] undertaken 15 years previously. We postulate that (1) participants with lower levels of ANP or BNP at age 50 years will exhibit more advanced cardiac and metabolic impairment 15 years later and (2) higher levels of CNP products at age 50 years will associate with more advanced vascular and myocardial degenerative disease at age 65 years. Although protocols for the study of the predictive value of data on cardiovascular outcomes have been reported in specific disease states such as heart failure [25] or psoriasis [26], no previous study examining the predictive value of natriuretic peptides on cardiovascular outcomes in participants without evidence of heart disease has been reported to date.

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Figure 1. Beneficial and pathological circulating levels of aminoterminal B-type natriuretic peptide (NTproBNP) reflecting expression of the cardioprotective hormone BNP.

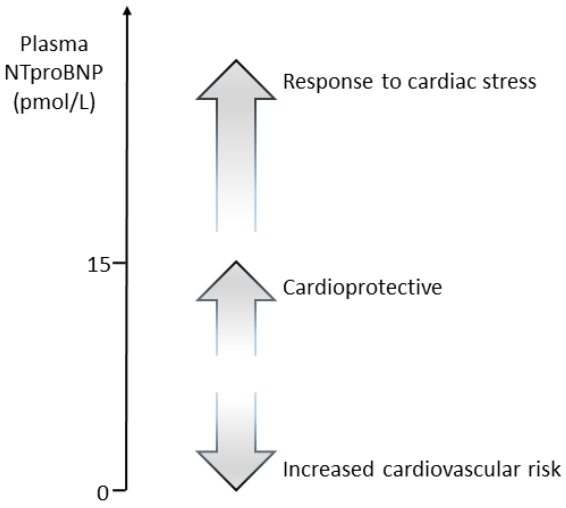
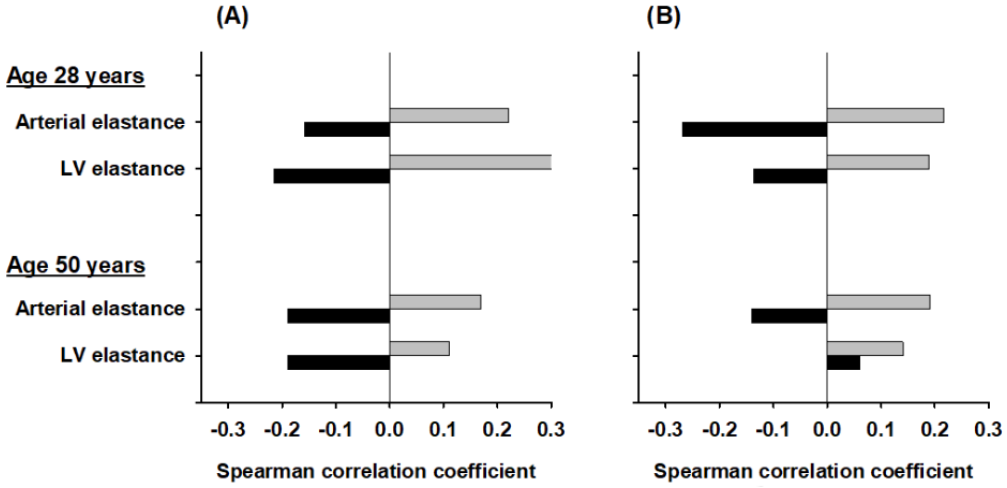


Figure 2. Comparison of Spearman correlation coefficients of aminoterminal B-type natriuretic peptide (NTproBNP; black bars) and aminoterminal C-type natriuretic peptide (NTproCNP; grey bars) with left ventricle (LV) and arterial elastance in healthy (A) men and (B) women aged 28 years and 50 years without a history of heart disease. Stiffer tissues equate with higher elastance. Coefficients >0.18 were significant.



Methods

Participants

All of the surviving 348 participants (205/348, 58.9% female; 53/348, 15.2% Māori or Pasifika ethnicity) participating in the CHALICE study [27] (free of history of heart or renal disease at age 50 years and who consented to further study) will be contacted, recruited, and restudied exactly as previously described [15]. Every effort will be made to re-establish contact with the CHALICE participants, including email, phone, surface mail, and cross checking with the electoral role, when necessary. Participants with cardiovascular events (ischemic heart disease, stroke, heart failure, atrial fibrillation) or renal disease developing since the previous study will be separately studied with respect to natriuretic peptide measurements at age 50 years but excluded in the main analysis of results at age 65 years. Records of hospital visits and admissions or death of participants since the previous review will be obtained from routine national data sets.

Ethics and Governance

All current participants gave written consent, and ethical approval was given by the Southern Health and Disability Ethics Committee (reference URA/10/03/021). Written informed consent will be sought from all participants agreeing to participate in further study. Relationships with Māori will be strengthened, and the studies' governance and policies will be updated to better align with Māori tikanga (customs) and to enhance Māori health outcomes [28].

Data Collection

After obtaining informed written consent, the following data will be obtained: health history (chronic morbidities and medications, tobacco consumption); physical examination (including blood pressure, height, weight, BMI); heart function as measured using echocardiography including speckle-tracking strain [29]; carotid artery intimal thickness as measured during echo examinations; laboratory measures (including fasting urine and blood sampling for routine biochemistry and plasma storage for measurements of natriuretic peptides, cyclic guanosine monophosphate [cGMP], and other analytes). Previously

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established metabolic-cardiovascular risk factors will be measured after an overnight fast [15]. Plasma ANP, BNP, CNP (measured after extraction by radioimmunoassay), NTproANP, NTproBNP, NTproCNP, and cGMP will be assayed as previously described [16,30,31]. Because of links between CNP and bone turnover markers [32], plasma type 1 collagen C-telopeptide (CTx) will be measured in these older participants.

In order to generate data for genetic studies, including calculation of polygenic risk scores, DNA extracted from peripheral blood of all consenting participants will be genotyped on an appropriate platform such as the Infinium Global Screening Array (Illumina, San Diego, CA), and imputation will be carried out using standard approaches [33]. Polygenic risk scores will be generated based on existing data for large GWAS of relevant cardiac phenotypes [34].

The predictive value of natriuretic peptides at age 50 years for impaired atrial and ventricular function and for carotid intimal thickness at age 65 years will be determined using multiple variable analysis. In participants excluded from the main analysis because of interval cardiac or vascular disorder after the original study, natriuretic peptides at baseline and at 65 years will be studied in relation to cardiac and metabolic indices documented in the unaffected population and to type of event.

Specific Objectives and Hypotheses Affecting ANP and BNP

Here, we hypothesize that (1) low BNP at 50 years old will be associated with impaired atrial and ventricular structure (volumes and mass) and function (atrial strain and ventricular ejection fraction) at 65 years compared with those with high BNP at baseline; (2) at age 65 years, the percentage increase of BNP in participants with low BNP at 50 years old will be significantly greater than in those with higher BNP at baseline; and (3) in women, for whom the inverse association of ANP/BNP with left ventricle (LV) elastance is lost at age 50 years (Figure 2), decline in cardiac performance at age 65 years will be greater than in men.

Objectives and Hypotheses Affecting CNP

For the first time in humans, CNP has been linked to measures of arterial and LV stiffening at both ages and in both sexes (Figure 2). Here, we hypothesize that (1) plasma NTproCNP at age 50 years will predict decline in atrial and ventricular function as measured by speckle echocardiography at age 65 years, (2) plasma CNP products at age 50 years will predict increased atrial and ventricular stiffness and carotid intimal thickening at age 65 years, and (3) change in plasma concentration of CNP products 15 years later will be linked to markers of impaired cardiac performance and metabolic health at 65 years of age. Again, the contribution of a longitudinal study, undertaken at a period of increasing incidence of heart disease, will be crucial to providing proof of the independent association of CNP's role in maintaining cardiovascular and metabolic health. Showing that CNP levels at 50 years of age heralds later risk of stroke or heart failure identifies likely preventive measures, including treatments augmenting CNP and BNP levels in blood.

Other Objectives

Associations of polygenic risk scores with phenotype (measures of cardiac, metabolic, and vascular status) and associations with plasma natriuretic peptides will be studied. On the basis of previous findings from a single variant, we hypothesize positive links will be strengthened using polygenic risk scores.

Relevance of cGMP in the assessment of cardiac and vascular risk is an important new objective considering its role in mediating actions of all 3 natriuretic peptides. Based on prior work [35-37], we postulate that ANP will be independently associated with cGMP at age 50 years and age 65 years. Increasing recognition of CNP's role in combatting myocardial stiffening and the higher sensitivity of the cGMP response to stimulation of the CNP receptor (natriuretic peptide receptor 2 [NPR2]) in cardiac tissues, compared with that of natriuretic peptide receptor 1 (NPR1), suggests that CNP will independently predict cGMP in women and strengthen further at 65 years of age.

Statistics

The primary outcomes (hypotheses 1, 2, and 3) will be analyzed using multiple linear regression. Allowing for 30% nonresponse (n=244) and 10 covariates, this will be able to detect an f^2 of 0.083 (small-to-medium Cohen effect size) with 80% power and α=.01, which includes a multiple testing correction equivalent to a Bonferroni correction for 5 independent predictors. Nonlinear relationships will be examined with generalized additive models, and all models will be graphically assessed for goodness of fit. Indices will be analyzed as continuous variables or categorized as appropriate. Additionally, mediation analysis [38] will be used to quantify the role of cGMP in the relationship between natriuretic peptides and cardiac structure and performance in the primary outcomes.

Results

In the 10-year follow-up period after the initial study visit, 6 participants have died (none from cardiovascular causes), and 36 (10% of the cohort) were hospitalized for cardiovascular events. Ischemic heart disease (10 participants) was the most common reason for cardiovascular admission. Baseline NTproBNP or NTproCNP concentrations for men or women subsequently hospitalized for cardiovascular events were not significantly different from values of study participants remaining free from cardiovascular events.

The project and protocol have been approved by the National Ethics Committee. Having received funding from the New Zealand Lottery Board (Health), re-enrolment of CHALICE participants commenced in October 2022. At the date of this manuscript submission, 21 participants had successfully completed the protocol without incident.

Discussion

Two separate community studies of participants free of heart disease showed that lower plasma concentrations of the cardiac hormones, ANP and BNP, are associated with increase in vascular stiffness and reduced metabolic health, whereas the

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opposite is true of CNP concentrations—lower levels associate with improved cardiometabolic health. These reproducible findings are independent of age and obesity. Restudy 15 years later of those aged 50 years will establish the value of natriuretic peptide levels in predicting adverse cardiac and vascular outcomes using clearly defined hypotheses based on data measured by the same laboratory using best practice quality control.

ANP and BNP as Paracrine and Endocrine Regulators of Cardiovascular Status

In light of strong evidence in experimental animals of protean beneficial actions of ANP/BNP across many tissues affecting the integrity of the cardiovascular system [2,39] and the deleterious impact of ablating ANP/BNP pathway activity [40,41], it is unsurprising that circulating concentrations of ANP/BNP products within the normal range have beneficial effects in maintaining cardiovascular and metabolic health in healthy people [42,43]. Whether these subtle differences in plasma concentrations predict subsequent cardiovascular health is the crucial question addressed in this prospective study. That genetic factors contribute is evident from several studies identifying a single [15,16,44] or more variants [39,45-47] in *NPPA* or *NPPB*. Plausibly, the accumulative impact of these explain, in part, the significant impact of subtle increases in circulating levels on "ideal cardiovascular health" [48] in either sex if maintained from early life. Obtaining array-based genotypes in CHALICE participants, as now proposed, will allow us to more closely examine impacts of additional natriuretic peptide and receptor genetic variants over and above that (rs198358) identified previously. The array data will also enable calculation of polygenic risk scores for various cardiac phenotypes and disease states and allow evaluation of the predictive or prognostic value of these in relation to existing clinical measures and risk factors. The value of this approach to identifying participants most at risk has been emphasized in a recent review of atherosclerosis [49]. Acquired factors such as obesity—lowering BNP [19]—also need consideration and will be assessed by changes in BMI. Although both ANP and BNP activate the same receptor (NPR1), their variable expression, location, and metabolism highlight the need to measure both bioactive forms in plasma [41] in associative studies linking levels with changing indicators of vascular, metabolic, and cardiac function in the 15 years after middle age when the incidence of heart disease increases greatly. No other study has examined these relationships in healthy participants. The conditions and blood sampling for measurements proposed in the re-examination will be undertaken exactly as they were previously (overnight morning fasting in the rested seated position) at one central location (University of Otago Nicholls Clinical Research Centre) utilizing standardized assays of natriuretic peptides developed by research staff of the Christchurch Heart Institute. Importantly, CNP concentrations in plasma will be measured using a validated and sensitive radioimmunoassay that, after extraction, has a plasma limit of detection of 0.2 pmol/L.

Strong evidence suggests that both ANP and BNP regulate energy balance by increasing mitochondrial efficiency and reducing lipogenesis in vitro and in experimental animals in vivo [2]. Our finding that both ANP and BNP in healthy participants at middle age are negatively related to lipid levels and other markers of the metabolic syndrome are consistent with these and other reports [50,51]. This inverse relationship is expected to strengthen over time. Conceivably, by reducing atherosclerotic changes and reducing arterial stiffness, these cardiac hormones ameliorate declines in LV strain and help to maintain high myocardial performance throughout life. Re-examination of cardiac performance after 15 years using speckle echocardiography is expected to reveal differential impacts of ANP and BNP on age-related changes in cardiac contractile function [29]. In this context, it needs to be emphasized that, in health, there is a progressive age-dependent decrease in LV stroke volume and LV volumes and an increase in LV mass along with an increase in LV and arterial elastance in both sexes [52,53]. Aligning with these age-related changes are increases in plasma ANP and BNP. Factors driving this progression are not known, but it is likely that increasing intramural pressure and myocardial inflammation and fibrosis play a major role (reviewed in Sayed et al [54]). Our findings of inverse associations of BNP with LV stiffening at age 28 years and at age 50 years in both sexes (except in older women) are consistent with these changes in chamber structure and function. Plausibly, waning estrogen production in older menopausal women may aggravate myocardial stress [55,56] and initiate an adaptive (compensatory) BNP response in those most at risk by lacking protective gene variants. Notably, a recent cross-sectional study using speckle-tracking echocardiography [29] found that left atrial dysfunction is the earliest sign of age-related cardiac pathology in a population of well people, mean age 65 (range 24-86) years, in which mean BNP level was 2-fold higher than we found in CHALICE. ANP values were not reported. These findings suggest that BNP increases as an adaptive compensatory response to atrial dysfunction [29]—analogous to the loss of the negative association of ANP/BNP with LV elastance we observed in older women (Figure 2). Understanding the impact of the much lower BNP values we identified at 50 years of age with adverse changes in cardiac function 15 years later therefore becomes a pressing need. Based on our findings at age 50 years, we anticipate that the increase in atrial strain will be greater in those with lower ANP and BNP and the percentage change in both peptides at age 65 years will be greater in those with lower levels at baseline (age 50 years). A similar pattern of change in the relationship of LV volumes with ANP and BNP is anticipated. However, it is interesting to note that, in a recent report [18] of the association of a gene variant—rs198389 (increasing BNP)—in preventing LV dysfunction [18] in participants known to be at high risk of developing heart disease, the percentage change in BNP was independent of levels at baseline. Clearly, further studies in healthy participants are needed, preferably when the strong impact of variable age is reduced. As mentioned earlier in this paragraph, a sex difference was noted for older women in whom the negative association of ANP and BNP with LV stiffening is lost. This will be an important finding to re-examine in postmenopausal years, particularly in light of the high incidence of diastolic dysfunction and emergence of heart failure with preserved ejection fraction (HFpEF) in older women [55]. The loss of arterial-LV coupling

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[57] implied by our findings at 50 years of age in older women—with an associated (adaptive) increase in BNP—suggests that this may portend more severe dysfunction in later years and can be expected to be clarified in this proposal.

Role of Paracrine CNP

The significance of circulating products of paracrine CNP for cardiometabolic health is less clear than for endocrine-paracrine/BNP [58] largely due to its unique specific (paracrine) actions, rapid degradation at source, and barely detectable levels of bioactive forms (CNP 22 and CNP 53) in adult plasma once growth plates have closed [7]. Nevertheless, there is evidence in experimental animals of important actions in maintaining flow and pressure in the microcirculation [6], counteracting myocardial inflammation and fibrosis [2,23,24], and preserving diastolic function [59,60]. Several studies have suggested these actions come into play after injury (that is, are adaptive) rather than conferring benefit pre-ictus [2,23]. It remains to be seen whether genetic variants increasing CNP/NPR2/cGMP signaling—including loss of function mutations in the natriuretic peptide clearance receptor gene [*NPR3*] [61]—could reduce the incidence of cardiometabolic disease. Other studies of genetic variants—reducing CNP/*NPR3*/Gi P/cAMP activity—reported increased incidence of circulatory disorders and high blood pressure [62]. Links of plasma CNP or NTproCNP with impaired cardiac function or with vascular degenerative disease have been reviewed previously [7] and support the view that the positive association is likely to reflect a compensatory response to loss of structural integrity. Very few, if any, other studies have examined the association of CNP products with measures of cardiac function in community dwellers. However, one large study of 1841 participants reported plasma CNP (using a direct less specific assay without extraction) identified a high-risk cardiovascular phenotype and future risk of myocardial infarction [63]. Consistent with adaptive and protective actions of CNP in humans are our previous findings in healthy volunteers without history of heart disease [64] in whom plasma values of the inactive product of proCNP 1-103 (NTproCNP) and bioactive CNP increased progressively at midlife in both sexes and showed univariate associations with renal function, high blood pressure, and markers of the metabolic syndrome. A key question arising is the likely source(s) of these products in view of the diverse range of tissues expressing *NPPC* [7]. In mature rodents, the vascular endothelium likely makes the major contribution (some 60%) to circulating levels of CNP [23,65]. Positive veno-arterial gradients of CNP across the heart in humans presenting with acute coronary syndrome [66] support contributions from the myocardial, endocardium, or coronary intimal tissues, as does the sustained increase in plasma CNP postictus in participants with acute coronary syndrome [67]. More focused associative studies have shown significant links of CNP products with recognized vascular and metabolic risk factors in both sexes in 2 separate community studies—one at age 28 years and the other at midlife (CHALICE) [15,16]. Importantly in both studies, significant positive associations of CNP products were found with higher arterial and higher LV elastance in both sexes and with lower LV stroke volume and lower LV end diastolic volumes. Likely sources of this increase in CNP are (1) increased vascular endothelial *NPPC* expression in response to shear stress [11] or inflammation [68] and (2) increased *NPPC* expression in LV myocardial tissue inflammation [3,24]. Increase in bioactive CNP rather than both products after cardiac injury [67] likely results from reduced clearance at the source [69,70]. Restudy of CHALICE participants 15 years later, we predict, will show more severe diastolic dysfunction in those with higher CNP levels at age 50 years—and will be greater in women 15 years after menopause [55]. Such findings could establish CNP as an endogenous marker for HFpEF, for which no suitable biomarker is currently available [56]. In this context, it is relevant to note that an increase in plasma NTproCNP was independently linked to adverse outcome in patients with HFpEF [71]. Aligning with CNP's adaptive role in combatting arteriosclerosis [21,22], we also anticipate carotid artery intimal thickening will correlate with CNP values at 50 years of age and with the proportional increase of CNP above values at baseline.

Taken together, this study has the potential to advance understanding of paracrine CNP's role in combatting not only disorders of cardiac function but also arterial degenerative changes not otherwise easily addressed in healthy aging humans. Supportive findings of CNP's independent association can be expected to identify therapeutic targets—for example, novel therapies using CNP agonists (now already approved for use in humans) or new drugs that increase CNP secretion [72] or raise natriuretic peptide levels by extending the half-life in tissues at risk [73].

Relevance of cGMP

An important additional analyte (cGMP)—not previously measured in CHALICE—could illuminate distinct tissue actions mediated by the membrane-bound guanylyl cyclase receptors NPR1 (activated by ANP and BNP) or NPR2 (activated by CNP). Both particulate receptors are widely expressed within the heart, vasculature, kidney, and brain [2], releasing cGMP into the cell and extracellular fluid after ligand binding [74]. We found that contrived increases in plasma ANP and BNP elicit consistent and proportionate changes in cGMP in plasma or urine, which, importantly, also link with respective changes in organ function [35]. ANP is 3-fold more effective in raising plasma cGMP when compared with BNP [75]. Previous studies have examined associations of plasma cGMP with vascular risk markers, plasma BNP, and cardiac function in community dwellers without heart disease [36,37] and concluded that the positive association of plasma BNP with plasma cGMP resulted from compensatory responses in cardiac secretion to increased myocardial wall stress. Importantly, ANP was not measured. To our knowledge, no study has examined links of each of the natriuretic peptides with cGMP and cardiac function in participants without a history of heart disease. Although contrived increases in circulating CNP levels are much less effective than ANP or BNP in increasing cGMP [75], the importance of cardiac *NPR2* signaling [76] and its diffuse distribution across cardiomyocytes, in contrast to the highly compartmentalized location of *NPR1* in tubular niches in myocardiocytes [59], may facilitate cGMP access to extracellular fluid and plasma. Further, in rodent adult cardiac fibroblasts, cGMP response to CNP far exceeds that from ANP

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or BNP [77]. Collectively, these findings indicate the need to study putative links of plasma CNP products and cGMP with changes in cardiac structure and function in the course of aging.

Strengths and Limitations

Compared with other community studies, the number of participants in CHALICE is small. However, the detailed and comprehensive assessment of genetic, metabolic, cardiac, and vascular status together with the complete suite of natriuretic peptide measurements—all undertaken at one site and using in-house validated assays—contribute to the unique features of this longitudinal study. The narrow age band (49 years to 51 years at baseline) eliminates variables related to age, which is a major confounder in most community studies. Although only a single sample for assay of natriuretic peptides is drawn at baseline and follow-up, we found excellent agreement between test and retest on different days in well participants when studied seated, after resting for 15 minutes. Whether associations reflect beneficial genetic effects versus organ adaptive compensatory responses can only be determined by longitudinal studies as planned here. The time span between data collection (around 15 years) encompasses the period after middle age when cardiovascular disorders become overt. For these reasons, our hypothesis—that higher concentrations of ANP/BNP at age 50 years reduces the incidence of impaired cardiovascular health—will be fully tested. Notwithstanding the importance if proven—enabling currently available clinical interventions—the opportunity to link change in function with *NPR1*/cGMP and *NPR2*/cGMP activity can be expected to clarify interactions of endocrine and paracrine components of these important hormones in maintaining cardiovascular health in humans for the first time.

Conclusions

In view of the high prevalence of cardiovascular disease and its high morbidity and mortality, there is an urgent unmet need for preventative measures including biomarkers of susceptibility that may allow early intervention in those most at risk. The discovery of the role of natriuretic peptides in maintaining a healthy circulation and metabolism opens up new ways of predicting those most at risk. Previous work in community participants free of heart disease showed that low plasma concentrations of ANP and BNP and higher levels of CNP at midlife associate with increases in pathological measures of cardiac and vascular stiffness and impaired metabolic health. This suggests that natriuretic peptide biomarkers will predict adverse outcomes in later years. Proving this, as described here, will lead to earlier detection of those most at risk and may enable novel preventive strategies augmenting natriuretic peptide levels or activity.

Acknowledgments

This study is supported by grants from the New Zealand Lottery Grants Board and National Heart Foundation of New Zealand.

Data Availability

The data sets generated after the completion of this study will be available from the corresponding author on reasonable request and dependent on study participant consent.

Conflicts of Interest

None declared.

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Abbreviations

ANP: atrial natriuretic peptide
BNP: B-type natriuretic peptide
cGMP: cyclic guanosine monophosphate
CHALICE: Canterbury Health, Ageing and Life Course
CNP: C-type natriuretic peptide
CTx: type 1 collagen C-telopeptide
GWAS: genome-wide association study
HFpEF: heart failure with preserved ejection fraction
LV: left ventricle
NPR1: natriuretic peptide receptor 1
NPR2: natriuretic peptide receptor 2
NPR3: natriuretic peptide clearance receptor
NTproANP: aminoterminal atrial natriuretic peptide
NTproBNP: aminoterminal B-type natriuretic peptide
NTproCNP: aminoterminal C-type natriuretic peptide

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Protocol

Measurement of Vital Signs by Lifelight Software in Comparison to Standard of Care Multisite Development (VISION-MD): Protocol for an Observational Study

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Abstract

Background: Measuring vital signs (VS) is an important aspect of clinical care but is time-consuming and requires multiple pieces of equipment and trained staff. Interest in the contactless measurement of VS has grown since the COVID-19 pandemic, including in nonclinical situations. Lifelight is an app being developed as a medical device for the contactless measurement of VS using remote photoplethysmography (rPPG) via the camera on smart devices. The VISION-D (Measurement of Vital Signs by Lifelight Software in Comparison to the Standard of Care—Development) and VISION-V (Validation) studies demonstrated the accuracy of Lifelight compared with standard-of-care measurement of blood pressure, pulse rate, and respiratory rate, supporting the certification of Lifelight as a class I Conformité Européenne (CE) medical device.

Objective: To support further development of the Lifelight app, the observational VISION Multisite Development (VISION-MD) study is collecting high-quality data from a broad range of patients, including those with VS measurements outside the normal healthy range and patients who are critically ill.

Methods: The study is recruiting adults (aged ≥16 years) who are inpatients (some critically ill), outpatients, and healthy volunteers, aiming to cover a broad range of normal and clinically relevant VS values; there are no exclusion criteria. High-resolution 60-second videos of the face are recorded by the Lifelight app while simultaneously measuring VS using standard-of-care methods (automated sphygmomanometer for blood pressure; finger clip sensor for pulse rate and oxygen saturation; manual counting of respiratory rate). Feedback from patients and nurses who use Lifelight is collected via a questionnaire. Data to estimate the cost-effectiveness of Lifelight compared with standard-of-care VS measurement are also being collected. A new method for rPPG signal processing is currently being developed, based on the identification of small areas of high-quality signals in each individual. Anticipated recruitment is 1950 participants, with the expectation that data from approximately 1700 will be used for software development. Data from 250 participants will be retained to test the performance of Lifelight against predefined performance targets.

Results: Recruitment began in May 2021 but was hindered by the restrictions instigated during the COVID-19 pandemic. The development of data processing methodology is in progress. The data for analysis will become available from September 2022,

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and the algorithms will be refined continuously to improve clinical accuracy. The performance of Lifelight compared with that of the standard-of-care measurement of VS will then be tested. Recruitment will resume if further data are required. The analyses are expected to be completed in early 2023.

Conclusions: This study will support the refinement of data collection and processing toward the development of a robust app that is suitable for routine clinical use.

Trial Registration: ClinicalTrials.gov NCT04763746; https://clinicaltrials.gov/ct2/show/NCT04763746

International Registered Report Identifier (IRRID): DERR1-10.2196/41533

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KEYWORDS

general practice; vital signs/methods; vital signs/standards; photoplethysmography; remote photoplethysmography; rPPG; Lifelight; contactless; software

Introduction

The measurement of vital signs (VS) provides important information about a patient's health and, importantly, a change in VS may herald a deterioration in health [1]. Despite the importance of VS to inform clinical decision-making, the accuracy and timeliness of measurement are in need of improvement [2-4]. However, the measurement of VS requires using multiple pieces of equipment that need to be calibrated regularly and is time-consuming. It may also be uncomfortable and stressful for patients, potentially compromising the utility of the information obtained. Standard-of-care medical equipment is not suitable for patients who require regular measurement of VS in the home or community setting to monitor long-term health conditions because of cost, the complexity of the measuring processes, and the need for calibration of equipment. A study of 725 patients reported that while 53% followed at least 10 of the recommended steps necessary for accurate blood pressure (BP) measurement at home, only 1% followed all 15 recommendations [5]. Thus, home measurement of VS is important—and respiratory rate and pulse rate in particular—but requires several pieces of equipment (BP monitor and pulse oximeter) and for patients to be educated in best practices. The COVID-19 pandemic highlighted the need for remote or contactless VS measurement to reduce the risk of infection, which can be operated by people without specific medical training. The shift away from face-to-face to digital consultations during the pandemic also points to the need for easy but accurate measurement of VS.

Photoplethysmography (PPG) is an optical technique based on the measurement of the light reflected from the skin surface, which changes due to volumetric changes in the facial blood vessels; small variations in perfusion provide valuable information about the cardiovascular system [6]. PPG has been used to measure pulse rate [7,8], oxygen saturation [9], BP [10,11], and respiratory rate [7,12] and to detect atrial fibrillation [13].

Lifelight (Xim Ltd) is an app being developed for the contactless measurement of VS using remote PPG (rPPG) via the camera on smart devices such as phones and tablets. The app captures the average color of the region of interest 30 times every second for 60 seconds and sends this as red, green, and blue values to the server for further processing. VS values are obtained from the green channel.

The VISION-D (Measurement of Vital Signs by Lifelight Software in Comparison to the Standard of Care-Development) study measured VS in 8585 patients and healthy volunteers simultaneously using Lifelight and standard-of-care methods. The data were used for machine learning to improve the accuracy of the Lifelight algorithms used to calculate VS. The smaller VISION-V (Measurement of Vital Signs by Lifelight Software in Comparison to the Standard of Care–Validation) study demonstrated the accuracy of the Lifelight app compared with standard-of-care methods for measuring pulse rate, respiratory rate, and diastolic BP [14], providing the basis for the current class I Conformité Européenne (CE) registration [15]. However, some of the methods used in the VISION-V study differed from the procedures described in the standard for BP measurement (ISO81060-2) because of the novel nature of the Lifelight technology. Furthermore, these early studies did not include participants with BP values across the full range likely to be encountered in clinical practice.

To further improve the accuracy of Lifelight, the Measurement of Vital Signs by Lifelight Software in Comparison to the Standard of Care–Multisite Development (VISION-MD) study is collecting data from a wide range of outpatients, inpatients, and patients who are critically ill, and across the full range of skin tones, for use in machine learning. In VISION-D and VISION-V, full-face videos were recorded, but a high proportion of data were not usable. Thus, high-resolution full-face videos are being recorded to maximize the opportunity for machine learning. These data will also be used to evaluate alternative methods of defining the region of interest, as the full face includes areas that are not relevant (eg, areas covered by facial hair and areas that illicit a poor signal).

Given that only a small proportion of the raw video signal is relevant for rPPG measurement of VS (1%-2%), we are developing ways to enhance data collection and signal processing. Video recordings will be of higher resolution than those in the VISION-V and VISION-D studies, and data processing is focusing on the midface region (cheeks, nose, and top of the lip), rather than the whole face; these areas are computationally efficient for rPPG because of their large area and good-quality signal [16] but are not likely to be affected by autoregulation of cerebral blood flow (which discounts the

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forehead) [17]. We are also developing a method to identify small regions of interest in the midface in each participant where signal quality is the highest. This approach is expected to overcome some of the challenges of rPPG for routine clinical use, such as positioning of the participant relative to the light source.

VISION-MD (Clinicaltrials.gov NCT04763746) aims to advance the development and accuracy of the Lifelight app as a noninvasive and easy-to-use device to measure VS in hospitals and the community. The study will collect data from a broad range of patients to further develop the accuracy of Lifelight to a level sufficient for clinical applications, including screening and monitoring of cardiovascular disease. The initial data collected are being used for machine learning; later data will be used to test the accuracy of Lifelight compared with standard-of-care measurement of VS.

Thus, the primary objective of VISION-MD is to further develop the Lifelight algorithms across extensive clinical ranges, including critically ill patients and in patients with different skin tones. Secondary objectives are: (1) to improve and test the efficacy of Lifelight estimates for BP, pulse rate, respiratory rate, and oxygen saturation in multiple clinical settings (eg, critical care, outpatient clinics, and general hospital wards); (2) to evaluate the impact of variables on the accuracy of Lifelight VS measurements (eg, age, sex, temperature, health condition, medication, skin tone, and ambient lighting); (3) to understand the health economic potential of Lifelight; and (4) to compare the patients' experience of current contact-based methods for measuring VS and Lifelight and to evaluate the patients' acceptance and appetite for Lifelight.

Methods

Ethics Approval

The VISION-MD protocol was approved by the South Berkshire Research Ethics Committee on November 24, 2020 (20/SC/0432). Before the study started, the initial study protocol was approved by Health Research Authority (HRA) Wales on January 18, 2021 (IRAS 289242). HRA Wales has also approved subsequent protocol amendments.

Participants and Recruitment

Participants are being recruited from multiple venues across Portsmouth Hospitals University NHS Trust, Barts Health NHS Trust, London, and from the community in London and Portsmouth (eg, religious places, community centers, offices, patient events, waiting areas in general practices, academic institutions, sports facilities, and care homes). The participants are inpatients, outpatients, friends and family of patients, visitors, hospital staff members, and the general public. The study staff approach inpatients during their hospital stay and outpatients while waiting for appointments. For adults lacking capacity (eg, critically ill patients), the next of kin are contacted by telephone. In addition, ethics-approved advertising materials are disseminated to Trust staff by email and in meetings, and posters are displayed in staff, patient, and public areas.

Inclusion criteria include individuals aged 16 years and older, sufficiently conversant in the English language, and able and willing to comply with all study requirements and to provide informed consent (either themselves or empowered by law to provide it). There are no exclusion criteria. Eligible potential participants are provided with an ethics-approved participant information sheet explaining the study aims, what is involved, and the requirements for participation; members of the team are available to discuss the study with interested individuals. Informed consent is obtained electronically using Research Electronic Data Capture (REDCap), a secure National Health Service (NHS)–compliant web-based platform for survey and database management (project-redcap-org). For adults lacking capacity, informed consent is obtained from a nominated consultee (next of kin or a doctor not involved in the study). Participation in the study is entirely voluntary, refusal to participate does not incur a penalty or loss of medical benefits, and participants may withdraw from the study at any time.

Recruitment started in May 2021 but was compromised by restrictions implemented during the COVID-19 pandemic to limit access to hospitals by the general public. Protocol amendments were made to increase community recruitment in light of these issues. Target recruitment is approximately 1950 participants to generate measurements for use in the initial training data set and for performance testing. However, the final sample size will depend on the incremental improvement in accuracy of the Lifelight algorithm and therefore cannot be predicted (see Sample Size section). The study will continue until the accuracy of Lifelight for measuring VS is sufficient for various clinical use cases.

Study Procedures

Premeasurement observations

A brief set of demographic and medical history questions are asked, limited to the presence or absence of conditions that might affect skin perfusion and pigmentation and cardiovascular processes and any prescription medicines for these conditions. The study staff record a set of premeasurement observations and the presence or absence of sweat on the participant's face; any facial hair on the cheeks; tattoos, jewelry, birthmarks, scars, or other features on the face; the use of foundation or concealer; and the position of the participant (seated, prone, supine, or lying on one side).

Subprotocol assignment

Patients with capacity are recruited into 1 of 3 subprotocols depending on premeasurement observations (Table 1). Participants may also be recruited to a subprotocol based on their skin tone (Fitzpatrick Skin Type scale [18]) to meet prespecified targets. Adults who lack capacity are recruited into subprotocol 4. Participants may be involved in up to 10 study sessions, allowing the collection of longitudinal data. The subprotocol approach allows the study personnel to focus on fewer tasks. It also enables high-quality data collection while avoiding the collection of data that would not be used to meet study objectives, consistent with the General Data Protection Regulation for data minimization.

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Table 1. Recruitment criteria and vital sign measurement in subprotocols 1-4.

Subprotocol	Recruitment criteria	Measurements				Measurements, n
		PR[a]	BP[b]	RR[c]	SpO_2[d]	
1	Abnormal BP[e]	✓	✓		✓	3
2	Any participant			✓	✓	2
3	Expected to have low SpO_2[f]				✓	2
4	Adults lacking capacity	✓	✓	✓	✓	3

[a]PR: pulse rate.

[b]BP: blood pressure.

[c]RR: respiratory rate.

[d]SpO_2: oxygen saturation.

[e]Abnormal defined as systolic blood pressure <100 mm Hg or >140 mm Hg.

[f]Low SpO_2 (anticipated to be ≤95%).

VS measurement

The study staff ensure that participants have been at rest for at least 10 minutes before VS measurement starts and that they have not consumed any food or drink in the previous 30 minutes (other than intravenous fluids or nasogastric feeding). In each study session, VS is measured as per the subprotocol using the standard-of-care equipment while simultaneously capturing a video of the participant's face using the Data Collect app running on a tablet (standard iPad 9.7, 2018) positioned approximately 1 m away and angled toward the participant's face. Controls and instructions on the device start and stop the 60-second video recording. Background luminosity is measured using a handheld lux meter. The study staff have been briefed on the optimum Lifelight measurement conditions. Recordings are repeated once or twice, as set out in Table 1. The app does not return any measurements to the user or participant.

VS measurements are taken and coordinated by 2 nurses, one of whom announces the start and finish of the recording period on the Data Collect app. BP is measured using a standard clinical automatic sphygmomanometer with an appropriately sized cuff (width at least two-thirds of upper arm length) on the participant's nondominant upper arm (unless contraindicated) or via an arterial line if fitted. BP is recorded at the start of the recording period. A standard clinical finger clip sensor for the measurement of oxygen saturation and pulse rate is placed on a finger on the opposite side of the body to the sphygmomanometer. Oxygen saturation and pulse rate are measured at 0, 30, and 60 seconds of the recording period and averaged. Respiratory rate is determined manually by counting chest rises throughout the 60-second period. The nurse may place their hand on the participant's chest to increase the accuracy of manual counting but being mindful not to obscure the camera's line of sight.

Each study session takes approximately 30 minutes. Once the measurements are completed, the study staff complete the postmeasurement observation questions relating to how much the participant moved, their position, whether they were wearing glasses, any hairstyle or other item (eg, face covering) that obscured any part of their face during the recording, and whether the software reported "face not found" at any point during the recording.

Patient Feedback

Equal proportions of participants in subprotocols 1-3 are being asked to complete a questionnaire related to VS measurement and their preferences. The data are fully anonymized and recorded without any identifiable information (including participant ID code).

Clinical Feedback

A questionnaire is available to garner feedback on the technology from the clinical user's point of view (ie, the nurses who take the VS measurements). Questionnaire and interview data are fully anonymized and recorded without any identifiable information.

Health Economics Data Collection

The study also includes activities to obtain information and data to assess the cost-saving potential of Lifelight in different clinical settings, including as a tool to detect undiagnosed cardiovascular disease and to monitor symptoms. The cost of BP monitoring equipment and its maintenance and calibration will also be determined.

Stopwatch observational studies are run to determine how long it takes to measure VS using standard-of-care equipment and Lifelight, starting from the time when the clinician decides to conduct a VS check and incorporating the time it takes to find the measuring equipment, roll up the patient's sleeve, put on the devices, wait for the result, and put the equipment away. This part of the study will involve approximately 20 participants.

Privacy and Data Collection

Each study participant is assigned a unique sequential ID; no identifiable data are stored. All documents are stored securely and are only accessible by the study staff and authorized personnel. The code linking the ID to the participant's personal information is kept within the hospital study site and can only be accessed by the research team.

Full-resolution video data are uploaded during the study. The consent form allows the participants to decide whether data can

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be shared as full-face video or with identifying features obscured.

Videos collected in the study constitute personal data, as it may be possible to identify participants, but are collected for research purposes only (not clinical care) and are processed within the legitimate interests of Xim Ltd. These data will be protected according to the General Data Protection Regulation.

Data Handling

For each reading, a high-quality video of the whole face is saved to the internal storage of the iPad in encrypted form. Anonymized rPPG data (the average color of areas of the face) are saved directly and immediately sent to an NHS-compliant cloud server.

Subsequent analysis will be performed using the encrypted files, which are downloaded to a processing site, decrypted, and processed automatically (ie, without any person viewing the videos). This procedure will result in anonymized aggregate data sets. Decrypted files will subsequently be deleted from the processing site.

All protocol-required information besides video data is collected in an electronic case report form. The REDCap electronic cloud is used to store and manage all consent and study data. All data collected about study participants are kept strictly confidential.

Performance Targets

The accuracy of Lifelight using the training data generated in VISION-D was sufficient to support the certification of Lifelight as a class I CE medical device [15]. However, the accuracy needs to be improved further for use in routine clinical practice. Table 2 lists the performance targets for Lifelight; training data collected during VISION-MD will support the progress toward these targets.

Table 2. Performance (accuracy) targets for Lifelight.

Vital signs	Accuracy target	Basis for target
Blood pressure	• SBP[a] can be measured with standard deviation ≤8 mm Hg • British Hypertension Society Grade C for SBP measurement	ISO81060-2[b] for blood pressure cuffs [19]
Pulse rate	• Root mean square error of ≤3 beats per minute	Most common accuracy of CE[c]-marked commercially available devices
Respiratory rate	• Maximum error tolerance of 5 breaths per minute	Accuracy of Philips Health watch, a CE-marked contact-based photoplethysmography device
Oxygen saturation	• Maximum error tolerance of 4%	ISO80601-2-61 standard for pulse oximeters [20]

[a]SBP: systolic blood pressure.

[b]ISO: International Organization for Standardization.

[c]CE: Conformité Européenne.

Sample Size

The sample size cannot be formally calculated because it depends on the incremental improvement in the accuracy of Lifelight achieved through machine learning using the training data generated in the study. However, indicative sample sizes for the 4 subprotocols have been calculated by assessing the optimal data requirements to enable algorithm training toward the standards defined in Table 3, balanced against the practicality of achieving the targets. The split between training and testing data will be determined during the study according to the quality of the data collected.

The initial protocol anticipated data collection from about 8400 participants for training and a further 1000 for independent testing of accuracy, but the recruitment has been compromised by restrictions implemented during the COVID-19 pandemic. However, the high-quality video recording (compared with VISION-D and VISION-V) supported a protocol amendment to reduce the recruitment to 1950 participants (see Results section), with the expectation that data from about 1700 will be used for training the algorithms and data from 250 used for testing. The study management team is monitoring the progress of data collection and accuracy, and updates the study teams monthly. The study will continue until the accuracy of Lifelight for measuring VS is sufficient for various clinical use cases.

As skin tone is expected to affect the accuracy of Lifelight, the aim is to recruit participants across the full Fitzpatrick skin tone scale (1-6). To allow the impact of skin tone measurement accuracy to be determined with statistical robustness, the full data set will be sampled to create a subset for skin tone analyses in which the prevalence of the usually less prevalent skin tones is amplified. This subset will contain 750-1000 measurements, with 15%-20% each from categories 1, 2 and 3, 4, and 5 and 6. These measurements should be spread across the subprotocols as indicated in Table 3.

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Table 3. Indicative sample size targets.

Subprotocol	Indicative sample size, n[a]	Characteristics	Participants with skin tone categories 1, 4, 5, and 6
1	1500	Roughly 100 participants will be recruited with SOC[b]-determined SBP[c] in each 10 mm Hg increment from <90 mm Hg to >200 mm Hg (ie, <90 mm Hg; 90-99 mm Hg; 100-109 mm Hg, etc)[d]	Ideally ≥4 in each SBP band
2	375	N/A[e]	Ideally ≥10 in each SBP band
3	35	Approximately 33% with SOC-measured oxygen saturation <88%, 88%-92%, and 93%-95%	Ideally, each band will include participants with each skin tone
4	No specific target; likely to be a small proportion	N/A	N/A

[a]Participants in subprotocol 4 (ie, those without the capacity to provide informed consent) are likely to have vital sign values outside of the normal range and will contribute to all subprotocol targets. Only the first study session per participant contributes to the sample size.

[b]SOC: standard of care.

[c]SBP: systolic blood pressure.

[d]Can include participants with SBP measured from an arterial line.

[e]N/A: not applicable.

Data Analysis

The training data will be used to further develop the signal extraction and processing methodology. The test data will subsequently be used to determine the performance of Lifelight against the targets set out in Table 2.

All statistical analyses will be performed using Microsoft Excel. All analyses will be completed per protocol since there is no intention to treat.

There will be no imputation of missing or implausible data, and any missing, implausible, or problematic readings will be excluded from the analysis. If the Lifelight software is unable to detect the participant's face during the measurement period, this will be recorded in the electronic case report form, and the measurements will be deleted from the data set.

Results

The prototype Lifelight technology has been in development since 2016. The recruitment of participants for VISION-MD started in May 2021 but was compromised by the restrictions implemented to manage the COVID-19 pandemic, including restricting hospital access to the general public. Protocol amendments were thus made to enhance community recruitment, including the use of incentives such as chocolates or gift cards. In addition, the higher-resolution video recording (compared with the earlier VISION studies) supported reduction of the recruitment target to 1950, which is expected to yield sufficient high-quality measurements for machine learning and subsequent testing (reflected in a further protocol amendment). An additional amendment allowed the measurement of BP and pulse rate using devices other than the standard-of-care Welch Allyn devices (and indicated in the electronic case report form), as not all participating centers had the originally specified equipment.

Data for analysis will become available from September 2022, and the algorithms will be continuously refined to improve clinical accuracy. We anticipate that the final analyses to determine the performance of Lifelight against the targets set out in Table 2 will be complete in early 2023.

Discussion

The VISION-MD study is expected to provide sufficient high-quality data from a wide range of healthy volunteers and patients (including critically ill patients) to further develop the accuracy of the software for estimating VS in clinical and community settings. While the VISION-V and -D studies demonstrated the potential value of Lifelight in the contactless measurement of VS and supported class I CE certification [15], further refinement of data collection and analysis methods is needed—particularly VS measurements outside the normal healthy range—to develop the algorithms for clinical use.

The high-quality videos collected in the VISION-MD studies will be instrumental in training the algorithms being developed for data processing. A proportion of the data collected will be retained for testing the performance of Lifelight in estimating VS compared with the standard of care.

The study findings will be published in high-impact peer-reviewed scientific journals and presented at international cardiology, respiratory, and medical device conferences.

Acknowledgments

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Data Availability

The data generated and analyzed during this study are commercially sensitive and are therefore not publicly available, as mandated by Xim's contractual obligations with its grant funders and investors. Furthermore, the informed consent provided by study participants only allows access to individual data, including in anonymized form, by authorized individuals of the research team based at the study sites, Xim, and Xim's authorized partners. Reasonable requests for access to the study data within these limitations will be considered by the corresponding author.

Conflicts of Interest

LP is the Founder of Xim Ltd and is a major shareholder in the company.

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Abbreviations

BP: blood pressure
CE: Conformité Européenne
HRA: Health Research Authority
NHS: National Health Service
PPG: photoplethysmography
REDCap: Research Electronic Data Capture
rPPG: remote photoplethysmography
VS: vital signs
VISION-D: Measurement of Vital Signs by Lifelight Software in Comparison to the Standard of Care–Development
VISION-V: Measurement of Vital Signs by Lifelight Software in Comparison to the Standard of Care–Validation
VISION-MD: Measurement of Vital Signs by Lifelight Software in Comparison to the Standard of Care–Multisite Development

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Protocol

A Stepped Health Services Intervention to Improve Care for Mental and Neurological Diseases: Protocol for a Prospective Cohort Trial

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Abstract

Background: Mental and neurological disorders cause a large proportion of morbidity burden and require adequate health care structures. However, deficits in the German health care system like long waiting times for access to specialized care and a lack of coordination between health care providers lead to suboptimal quality of care and elevated health care costs.

Objective: To overcome these deficits, we implement and evaluate a unique stepped and coordinated model of care (the Neurologisch-psychiatrische und psychotherapeutische Versorgung [NPPV] program) for patients with mental and neurological diseases.

Methods: Patients included in the program receive an appropriate treatment according to medical needs in a multiprofessional network of ambulatory health care providers. The therapy is coordinated by a managing physician and complemented by additional therapy modules, such as group therapy, internet-based cognitive behavioral therapy, and a case management. Statutory health insurance (SHI) routine data and data from a longitudinal patient survey will be used to compare the program with regular care and evaluate SHI expenditures and patient-related outcomes. A health care provider survey will evaluate the quality of structure and processes and provider satisfaction. Finally, an analysis of ambulatory claims data and drug prescription data will be used to evaluate if health care providers follow a needs-led approach in therapy. Ethics approval for this trial was obtained from the ethics committee of the chamber of physicians in North Rhine (September 13, 2017, reference No. 2017287).

Results: Patient enrollment of NPPV ended in September 2021. Data analysis has been completed in 2022. The results of this study will be disseminated through scientific publications, academic conferences, and a publicly available report to the German Federal Joint Committee, which is expected to be available in the first half of 2023.

Conclusions: The NPPV program is the first intervention to implement a stepped model of care for both mental and neurological diseases in Germany. The analysis of several data sources and a large sample size (more than 14,000 patients) enable a comprehensive evaluation of the NPPV program.

Trial Registration: German Clinical Trials Register DRKS00022754; https://tinyurl.com/3mx9pz5z.

International Registered Report Identifier (IRRID): DERR1-10.2196/37569

(JMIR Res Protoc 2023;12:e37569) doi:10.2196/37569

KEYWORDS

mental health; neurology; quality of care; organization of health services; primary care; mental disorder; intervention; neurological disease; healthcare system; accessibility; quality of care; therapy

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Introduction

Mental and neurological diseases continue to be a challenge for health systems worldwide. When measuring disability-adjusted life years, these diseases make up the largest share of all cause morbidity burden in the European Union [1]. Chronic mental and neurological diseases often lead to a loss of quality of life, disability, and even premature death and go along with significant direct and indirect costs of illness [2-4].

From 1990 to 2017, the 27 countries of the European Union and the United Kingdom showed an increase in prevalence of stroke (+25%), dementia (+62%), Parkinson disease (+72%), and multiple sclerosis (+41%), mainly due to demographic changes in an aging population [2]. According to the models by Brinks and Landwehr [5], the number of persons with dementia might increase 2-3 times by the year 2050. For Germany, Steffen et al [6] found an increase of 26% for depression between 2009 and 2017, especially for men and younger patients. Disease prevalence for depression with mild symptoms is on average higher in Germany as compared to other European countries [7].

The increasing burden of mental and neurological diseases will require robust health care structures in the near future to secure adequate treatment for these patients. However, several deficits in the German health care system prevent patients from getting the best possible care. First, timely access to specialized neuropsychiatric care is challenging for patients with mental and neurological diseases, mostly due to a lack of sufficient outpatient care facilities for neurology, psychiatry, and psychotherapy. Almost 3 quarters of patients with a mental disease in outpatient care are treated exclusively by their general practitioners and not by psychiatrists [8], and around 8.5% of patients fail to get an initial examination from a psychotherapist within 3 months [9]. Less than 55% of all patients with newly diagnosed multiple sclerosis receive specialized care by a neurologist within 6 weeks (dementia: less than 26%) [10]. Second, allocation of care occurs without adequate prioritization. According to Walendzik et al [11], half of the psychotherapists offer an appointment to the next inquiring patient without considering clinical needs. Third, treatments do not always follow medical guidelines. Even when excluding mild cases, about 50% of patients with depression do not receive the recommended standard of care at all or an adequate treatment with antidepressants or psychotherapy [12]. Fourth, the Advisory Council on the Assessment of Developments in the Health Care System in Germany criticized a lack of coordination and cooperation between health care sectors and professionals in the treatment of mental diseases and pointed out the need for a primary professional who coordinates the treatment of patients along clinical pathways [13].

To overcome these deficits and improve treatment of people with mental and neurological diseases, we developed a stepped and coordinated care program called “neurological-psychiatric and psychotherapeutic care” (Neurologisch-psychiatrische und psychotherapeutische Versorgung [NPPV]) for patients in the region of North Rhine, Germany. We hypothesize that our model of care will reduce direct and indirect costs of illness, improve quality of care and adherence with medical guidelines, enable a low-threshold access to care and increase health-related quality of life in patients as well as satisfaction with health care situation of patients and health care providers.

Methods

Intervention: The NPPV Program

The NPPV program is a stepped and coordinated model of care for mental and neurological diseases. The program aims at increasing efficiency of care, improve patients’ health outcomes, and reduce direct and indirect health costs. Each patient in the program receives an early evaluation of the patients’ needs for care followed by a timely and appropriate treatment in a multiprofessional network of outpatient health care providers. The network includes specialists from neurology and psychiatry as well as psychotherapists. To plan, coordinate, and ensure an individual treatment according to medical guidelines, every patient is assigned to a managing physician or therapist. These physicians/therapists are the primary contacts for the patients and guide the patient within the network and health care system in general. They also provide special consultation hours, cooperate with other health care professionals in the network and self-help organizations, and may choose from a wide range of additional therapy modules in the program. These modules include group therapy, internet-based cognitive behavioral therapy (ICBT), and an outpatient case management for patients carried out by the NPPV coordination office.

Group therapies are of particular importance for the treatment of mental and neurological diseases and are part of national medical guidelines for depression, posttraumatic stress disorder, or other severe mental diseases [14-16]. In the NPPV program, group therapies may be offered by all qualified health care providers in the network. Possible types of group therapy include (but are not limited to) psychoeducation, neuroeducation and training, strengthening of personal resources, and family counseling. These therapies are supported by the NPPV coordination office, for example, with regard to making appointments.

ICBT may be applied as an alternative or in addition to psychotherapeutic and psychiatric care. These therapies are low-threshold psychosocial interventions and are effective in reducing symptoms, especially for depression, anxiety disorders, panic disorders, and social phobia, and are highly accepted by patients [17-19]. In NPPV, we integrated the digital mental health program called Novego, which has been found to be effective in the reduction of anxiety and depressive symptoms in general and in patients with schizophrenia [20-22]. Novego offers 3 different courses with a focus on depression, burnout, or anxiety. The managing physician or psychotherapist can generate an access code to these courses for a patient. With these codes, patients are able to follow the courses on the internet in their own pace. The administrative tasks related to the courses are carried out by the NPPV coordination office.

Beside the central coordination office, health care providers in the NPPV network are supported by regional network managers. Tasks of the network managers are recruitment of new network

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members, implementation of trainings for the professionals, organization of regular quality circles, administrative support for professionals, and quality management. Additionally, physicians and psychotherapists are connected with a common web-based infrastructure ("IVPnet") for patient administration, treatment management, and communication.

The program is funded by the Innovation Fund ("Innovationsfonds"), which was established to support innovative health care projects in Germany in 2015, and financed by the statutory health insurance (SHI) system.

Study Design and Research Questions

The NPPV study is a prospective cohort study with a pragmatic design [23]. Beside the intervention group (participating patients), 2 control groups are drawn by matching techniques. Patients in the intervention group have immediate access to a stepped, coordinated, and comprehensive care program according to medical needs, whereas patients in the control groups receive regular care. In addition, health care providers are participating in a longitudinal survey.

We aim to answer the following research questions: first, does the intervention reduce SHI expenditures per patient? Second, are patients in the intervention group more satisfied with their treatment and do they show a higher quality of life than patients in the control group? Third, can the NPPV structures and processes be established as intended and do they lead to a higher satisfaction among health care providers? Fourth, can the NPPV program induce a more unmet-needs–based approach in the treatment of mental and neurological diseases (eg, do physicians and therapists focus on patient with a higher demand for care and do they follow medical guidelines more closely)?

Study Population and Recruitment

We plan to recruit up to 14,000 patients for the intervention group in the region of North Rhine, Germany. The enrollment period begins in December 2017 and ends in June 2021. Patients eligible for participation in the NPPV program will be identified by their regular outpatient or inpatient health care providers or by their nursing home. They will be referred to a physician or therapist within the NPPV network, who does an entry examination to check eligibility. Inclusion criteria are as follows: age≥18 years, insurance in one of the participating health insurance companies ("AOK Rheinland/Hamburg," "Continentale BKK," and "BKK Deutsche Bank"), and 1 or more medical condition of 7 indication groups as outlined in Table 1. Participation in the NPPV program is voluntary. All patients need to give written informed consent to participate in the program and accompanied study.

Table 1. Medical inclusion and exclusion criteria for indication groups.

Indication group	ICD-10-GM-Codes[a]	Additional criteria
Affective disorders (including anxiety and depression, excluding mania and bipolar disorder)	F30-F39, F41.2	Inclusion when more than 3 weeks unable to work OR at least 2 hospitalizations in 2 years OR minimum score in Mini-ICF Rating for mental disorders
Psychosis (including mania and bipolar disorder)	F20- F31	Inclusion of all patients
Posttraumatic stress or adjustment disorder	F43	Inclusion of all patients
Dementia	F00, F01, G30	Inclusion of all patients
Multiple sclerosis	G35	Inclusion of all patients
Parkinson disease	G20-G22	Inclusion of all patients except vascular parkinsonism (G21.4)
Stroke	I63-I64	Inclusion of all patients with dysfunctions or disabilities, for example, spasticity or cognitive impairment

[a]ICD-10-GM: International Statistical Classification of Diseases and Related Health Problems.

Study Outcomes and Data Sources

Overview

The primary study outcome is the overall SHI expenditures per patient in 12 months after inclusion. Secondary outcomes include SHI expenditures for psychiatric and neurological treatments, hospitalizations (frequency and length of stay), patient-related outcomes (ie, health-related quality of life, satisfaction with health care, and use of intervention modules), and provider-related outcomes (ie, satisfaction, structure and process quality, and needs-led approach).

Data to evaluate the outcomes stem from SHI routine data, outpatient claims data, drug prescription data, a patient survey, and a provider survey. All outcomes and the corresponding data sources are summarized in Table 2.

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Table 2. Study outcomes and data sources.

Outcomes	Data source
Primary outcome	
SHI[a] expenditures per patient over 12 months	SHI routine data
Secondary outcomes	
1. SHI expenditures for psychiatric and neurological treatments per patient over 12 months	SHI routine data
2. Frequency of hospitalizations and length of stay over 12 months	SHI routine data
3. Frequency of hospitalizations with ICD[b] codes from inclusion criteria and length of stay over 12 months	SHI routine data
4. Discontinuation of medical treatment over 12 months	SHI routine data
5. Number of days with incapacity for work over 12 months	SHI routine data
6. Health-related quality of life	Patient survey
7. Satisfaction with provided health care	Patient survey
8. Utilization of intervention modules	Patient survey
9. Health care provider satisfaction	Provider survey
10. Structure and process quality	Provider survey
11. Needs-led approach at health care provider level	Ambulatory claims data and drug prescription data

[a]SHI: statutory health insurance.

[b]ICD: International Statistical Classification of Diseases and Related Health Problems.

SHI Routine Data

The participating health insurance companies ("AOK Rheinland/Hamburg," "Continentale BKK," and "BKK Deutsche Bank") provide claims data on inpatient treatment, outpatient treatment, rehabilitation, drug prescriptions, and incapacity to work as well as basic personal information (eg, age, gender, and insurance periods) for participants as well as for 2 pools of control patients. Selection criteria for the first pool of control patients are ICD code of inclusion diagnosis (see Table 2; secured diagnosis of an outpatient health care provider that participates in the NPPV program), age≥18 years at time of diagnosis, and no participation in other special treatment contracts regarding the inclusion diagnoses (this is a pool to generate propensity scores for matching). The second pool consists of patients with the same selection criteria as the first pool, except that these patients should not be treated by a health care provider that is participating in the NPPV program (this is the pool to draw the control group via propensity score matching).

Data are provided at the end of the study and will include data from 4 quarters before inclusion date until March 2021 on each participant that started participation at least in March 2020 and control patients. Inclusion dates for potential control patients are determined by date of inclusion diagnosis. The permission to use the routine data of the participating insurance companies was granted by the State Ministry of Employment, Health and Social Affairs in North Rhine Westphalia.

Patient Survey

Patient-related outcomes are assessed in a longitudinal web-based patient survey. A control group is drawn by direct matching according to specific patient characteristics by the health insurance companies. Patients in the intervention group and the matched control group receive a link to a web-based survey from their respective health insurance company at 4 time points: immediately after inclusion in the intervention group (control group: after matching) and 3, 6, and 12 months after inclusion.

The questionnaire for the intervention and control group consists of several items on health care usage, satisfaction with health care (eg, waiting times and coordination of care), and health-related quality of life (see Multimedia Appendix 1). The latter is assessed using the WHOQOL BREF [24] in all indication groups complemented by indication-specific instruments on quality of life (Q-LES-Q 18 for affective disorders, psychosis and posttraumatic stress, or adjustment disorder [25]; DEMQoL for dementia [26]; MSIS for multiple sclerosis [27], PDQ-39 for Parkinson disease [28]; SA-SIP30 for stroke [29]). In addition, sociodemographic information (eg, age and gender) and data on general health status (eg, hospitalizations and comorbidities) are assessed.

Provider Survey

The quality of structure and processes and provider satisfaction is evaluated with a health care provider survey. All physicians, therapists, and case managers in the NPPV network are invited to participate in a survey carried out by the Central Research Institute of Ambulatory Health Care in Germany (Zi). The Zi developed a 2-part paper questionnaire (see Multimedia Appendix 2). Part A of the baseline survey contains 72 items and asks for an evaluation of structures and processes (eg, coordination and networking in NPPV and IT structures), provider satisfaction, and finally for an assessment of health care quality and workload. Part B of the baseline survey uses 10 questions to gather information about personal data such as

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age, gender, and details of health profession and health services. The anonymized questionnaire collects data every year to assess changes over time (4 times during the study period). In order to make comparisons, the structure of the surveys that followed the baseline survey remains the same. There were only additions that reflect current developments, for example, information on health care services during the COVID-19 pandemic.

Ambulatory Claims Data and Drug Prescription Data

An analysis of ambulatory claims data and drug prescription data from the Association of Statutory Health Insurance Physicians in North Rhine aims at evaluating if physicians and therapist focus on patients with high needs. As first source, the claims data contain, among others, outpatient diagnoses coded according to the German modification of the International Classification of Diseases (ICD-10-GM) from the first quarter of 2016 to the third quarter of 2020 for statutory healthinsured individuals in North Rhine. The second data source includes pharmacologic treatments information on the prescribed medication. The 2 data sources were linked together for the analysis. No data were available for residents with private health insurance.

Sample Size Calculation

We calculated minimum sample size for the primary outcome (overall SHI expenditures per patient in 12 months) for which we expect a reduction by 10% in the intervention group as compared to the control group (assuming a coefficient of variation of 0.96). To identify this effect with a statistical power of 80% (α=.05), a minimum sample size of 1456 patients is required in the intervention group and the control group, respectively.

For analyses of secondary outcomes, an effect size of Cohen *d*=0.3 is expected for patient's quality of life (mean difference of 5.38 points on the WHOQOL BREF scale between the intervention group and the control group with SD=17.92 [24]). The sample size required to identify this mean difference with a power of 80% (α=.05) is 175 patients per group.

Data Analyses

Overview

Patient data (SHI routine data and patient survey) are analyzed for the total sample and for different subgroups based on indication groups. There are 2 main subgroups: mental diseases (affective disorders, psychosis and posttraumatic stress, or adjustment disorder) and neurological diseases (dementia, multiple sclerosis, Parkinson disease, and stroke). If sample size is sufficient, single indications groups will be analyzed separately. There will be no linkage between the SHI routine data and patient survey. For all analyses, significance level is set to 5%.

Analyses in SHI Routine Data

SHI routine data are used to evaluate the primary outcome and the secondary outcomes 1-5 (see Table 2). For all outcomes, NPPV participants are compared to a control group that is matched by propensity score matching [30]. Propensity scores are calculated using the data of the first pool of control patients and the participants in a multiple regression model estimating probability of participation in the NPPV program by personal (eg, age and gender) and health characteristics in the 12 months before inclusion date (eg, hospitalizations and frequency of out-patient treatments). The control group consists of matched persons of the second pool of control patients using the estimated propensity scores. To evaluate the outcomes, multiple regression models are estimated, controlling for relevant confounders. If necessary (high intraclass correlation coefficient), multilevel models are used to account for the hierarchical data structure (patients nested in outpatient health care providers that participate in NPPV).

Patient Survey Data

For the analyses of the secondary outcomes 6-8, the data of the longitudinal survey of participants and a control group are used. The control group is drawn by direct matching with the following matching variables: inclusion diagnosis from a health care provider that is not participating in the NPPV program, 10 years age groups, gender, no resident in a care facility, no legal guardian, and grouped number of inhabitants of place of residence. To evaluate the outcomes, descriptive statistics and regression analyses are conducted using longitudinal multilevel modeling techniques.

Provider Survey Data

The evaluation of the developed structures and processes of the project and the health care provider's satisfaction (secondary outcomes 9 and 10 in Table 2) is based on provider survey data. These data were collected by interviewing all participants with a paper questionnaire. The aim is to evaluate if the processes and structures have been established as planned from the point of view of the participating providers. In this context, factors that promote or hinder the implementation of the project should be identified. All data will be collected completely anonymously, so that no conclusions can be drawn about the results of individual providers. Only an overall picture can be collected and compared. This analysis is part of the quality assurance and further development of the project.

Ambulatory Claims Data and Drug Prescription Data

To analyze secondary outcome 11, we use ambulatory claims data and drug prescription data. Ambulatory claims data are used to analyze the frequency of contact to ambulatory health providers. Therefore, the number of treatment cases will be compared to the need of a treatment. The question is if patients with more need of a treatment have higher numbers of treatment cases. A treatment case is defined as the sum of all medical services delivered by 1 physician during 1 quarter. Important diagnostic and therapeutic services for the NPPV patients will be defined and analyzed by checking if the patients receive these selected services and by computing the costs of ambulatory care. In addition, the analysis proves if the patients receive pharmacological care. It is analyzed whether they are under- or oversupplied. Within these analyses, patients who are part of the NPPV program are compared with patients who are not part of the NPPV program. The identification of patients who are part of the NPPV program is done by searching providers in the data who have billed NPPV services. When patients visit these providers, they are classified as an NPPV patient. The

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control group will be determined by using propensity score matching. The goal is to determine whether the treatment of the 2 patient groups differs and whether the program can improve the care of certain patient groups.

Ethics Approval

Ethics approval for this trial was obtained from the ethics committee of the chamber of physicians in North Rhine (September 13, 2017, reference No 2017287).

Results

Enrollment of physicians, therapists, and patients is completed. Data analysis was completed in the first half of 2022, and the results will be disseminated through scientific publications, academic conferences, and particularly a publicly available report to the German Federal Joint Committee. This report consists of a comprehensive summary over the study and a detailed description of all evaluation methods and corresponding results. The report is expected to be available after review by the German Federal Joint Committee in the first half of 2023 and can be found on the internet [31].

Discussion

Overview and Perspectives

This paper describes the protocol for a prospective cohort trial to evaluate the effects of the NPPV program. This program is unique and the first intervention to offer a low-threshold access for both mental and neurological diseases, implement a stepped model of care organized according to patients' medical needs, and it builds up on a strong network of multiprofessional health care providers in Germany. We expect that NPPV will in particular reduce costs of illness, improve quality of care, and increase patient and provider satisfaction.

The Act to strengthen care in SHI ("GKV-Versorgungsstärkungsgesetz") from 2015 included a structural reform of outpatient psychotherapy, which came into effect in 2017 [32]. While this reform improved the access to outpatient psychotherapeutic care [9], several evidence-practice gaps in the treatment of mental and neurological diseases prevail. We expect the consequences of the COVID-19 pandemic to further increase the medical and socioeconomic burden of both mental and neurological diseases and enhance the pressure on health care systems [33]. The NPPV program is designed to face these challenges and improve access to and quality of care. While there are several projects funded by Innovation Fund, which focus on mental or neurological diseases, most of them focus on selected settings, specific diseases, health care sectors, or treatment methods [13]. Section 92 of Book V of the German Code of Social Law (§92 SGB V) specifies that regulations on a multiprofessional, coordinated, and structured care for patients with severe mental diseases are to be established in order to advance the German health care system. Several elements of the NPPV program are part of this advancement.

Strengths and Limitations

Our study has some strengths. We include 14,000 patients over 7 indication groups and analyze several different data sources (both primary and routine data). We also consider perspectives of patients, providers, and SHI in our analysis. Taken together, this enables a comprehensive evaluation of the NPPV program for patients with a wide range of mental and neurological diseases. However, our study also has some limitations. First, although we use matched control groups for the patient survey and analysis of routine data, our evaluation has a nonrandomized design. Second, we cannot completely rule out differences in disease severity between intervention and control groups. While an acutely higher disease severity increases the likelihood of being included in the program, this characteristic is not reflected in routine data used for our matching procedure. Third, we may face a selection bias in the patient survey as patients who are younger, healthier, and more educated are more likely to be willing to participate in our study. Finally, long-term effects (>24 months) on costs and patient outcomes cannot be evaluated in our analyses.

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Data Availability

The data sets generated or analyzed during the current study are available from the corresponding author on reasonable request.

Conflicts of Interest

GN is board member of the Professional Association of Neurologists in Germany ("Berufsverband Deutscher Nervenärzte"). All other authors declare no conflict of interest.

Multimedia Appendix 1
Questionnaires patient survey.

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[PDF File (Adobe PDF File), 1140 KB - resprot_v12i1e37569_app1.pdf]

Multimedia Appendix 2
Questionnaires provider survey.
[PDF File (Adobe PDF File), 2118 KB - resprot_v12i1e37569_app2.pdf]

Multimedia Appendix 3
Confirmation government funding and assessment corresponding to a peer-review.
[PDF File (Adobe PDF File), 120 KB - resprot_v12i1e37569_app3.pdf]

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Abbreviations

GBA: German Federal Joint Committee
ICBT: internet-based cognitive behavioral therapy
ICD: International Statistical Classification of Diseases and Related Health Problems
NPPV: Neurologisch-psychiatrische und psychotherapeutische Versorgung
SHI: statutory health insurance

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Protocol

Physical and Mental Effects of Foot Baths Among Women in Labor: Protocol for a Pre-Post Test Experimental Design

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Abstract

Background: Foot baths are used in complementary and alternative therapy to improve the duration and quality of sleep and reduce tension, anxiety, fatigue, and confusion. They are also known to improve the frequency of labor contractions and to increase their duration in women; thus, they are commonly used by midwives in clinical settings in Japan. However, the physical and mental effects of foot baths during labor are unknown.

Objective: This study aims to assess the physical and mental effects of foot baths based on biomarker levels and self-administered questionnaires.

Methods: A single-arm pre-post test trial design is being used in this study, and the study is being conducted at a general hospital in Tochigi Prefecture, Japan. The target study population is women in the first stage of labor, the phase when the uterus starts to contract and when the cervix dilates to 10 cm, or those undergoing labor induction. Participants who meet the eligibility criteria are recruited, and written informed consent is obtained from them. They are asked to answer the questionnaire and to collect 1.5 mL of saliva in 2 microtubes each, before and after the intervention. The intervention is foot baths for 15-20 minutes using a foot bath device. Data on delivery, such as gestational age, gravidity, parity, diagnosis following the last vaginal examination, and presence or absence of membrane rupture, are retrieved from the medical records. The primary outcomes are salivary cortisol levels before and after the foot baths. The secondary outcomes are levels of relaxation and comfort, labor pain, body warmth, vital signs, and interval of labor pain before and after the foot baths, which are assessed using a numerical rating scale. A paired *t* test or Wilcoxon signed-rank test will be performed to compare the data for salivary cortisol levels and numerical rating scale scores.

Results: Data collection started on April 1, 2022. As of October 2022, we had enrolled 10 participants. Because of the COVID-19 pandemic in Japan, it is difficult for medical personnel to freely interact with women in labor until the results of the COVID-19 polymerase chain reaction test are available in the research facility, complicating the recruitment process.

Conclusions: This is the first prospective study to assess the effects of foot baths using a biomarker during the first stage of labor. The findings on the effects of foot baths on women in labor will provide novel insights that may improve the outcomes of delivery. A randomized controlled trial to investigate the effects of foot baths to obtain robust evidence should be conducted in the future.

Trial Registration: University Hospital Medical Information Network-Clinical Trial Registry UMIN000046539; https://tinyurl.com/2wwj7dns

International Registered Report Identifier (IRRID): DERR1-10.2196/39985

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KEYWORDS

foot bath; women in labor; salivary cortisol; pregnant; pregnancy; alternative medicine; complementary medicine

Introduction

Background

Foot baths are used for cleaning the feet and are useful in complementary and alternative therapy. Foot baths improve the duration and quality of sleep among postmenopausal and older adults [1-4], decrease low back pain in pregnant women [5], and have psychological effects, such as reduced tension, anxiety, fatigue, and confusion in women [6,7]. They are also known to be effective in decreasing edema of the lower limbs by improving blood circulation due to blood vessel dilation [8].

Studies evaluating the effect of foot baths in the first stage of labor reported that they improve the frequency of labor contractions in women with slow labor [9] and increase the duration of labor contractions in primiparous women [10]. Thus, foot baths may show effects on labor induction.

The epidural labor rate has been increasing in Japan (4.6% in 2014, 5.5% in 2015, and 6.1% in 2016) [11], although it remains lower than that in European or American countries [11-15]. One reason for the low rate of epidural labor in Japan is the low number of anesthetists and obstetricians in the country, affecting their availability for all cases. Therefore, several nonmedical methods are used for labor pain relief in clinical settings, including hot bath therapy, reflexology, aroma therapy, breathing, and massage [15-17]. Although previous studies have reported the psychological and labor-inducing effects of foot baths [6,7,9,10], the sample size of some of these studies was small, and others did not include women in labor. Furthermore, the physical and mental effects of foot baths during labor, such as the effects on relieving labor pain, improving relaxation, or decreasing stress, remain unknown, and no study has investigated the effect of foot baths on women in labor using biomarkers. Cortisol is a hormone secreted by the suprarenal cortex and is widely used as a biomarker to measure stress levels. If foot baths are shown to reduce stress in women in labor, they can be recommended for the nonmedical care of women in labor. Therefore, investigating the physical and mental effects of foot baths on women in labor, especially their pain-relieving effects, can facilitate mental relief and a satisfactory childbirth experience for women in labor. Foot baths are commonly used by midwives in clinical settings in Japan and are expected to have psychological and labor-inducing effects.

Study Aims

This study aims to investigate the physical and mental effects of foot baths using a biomarker and self-administered questionnaire.

Methods

Study Design

We are conducting a single-arm, pre-post test trial to evaluate the effectiveness of foot baths.

Study Setting and Population

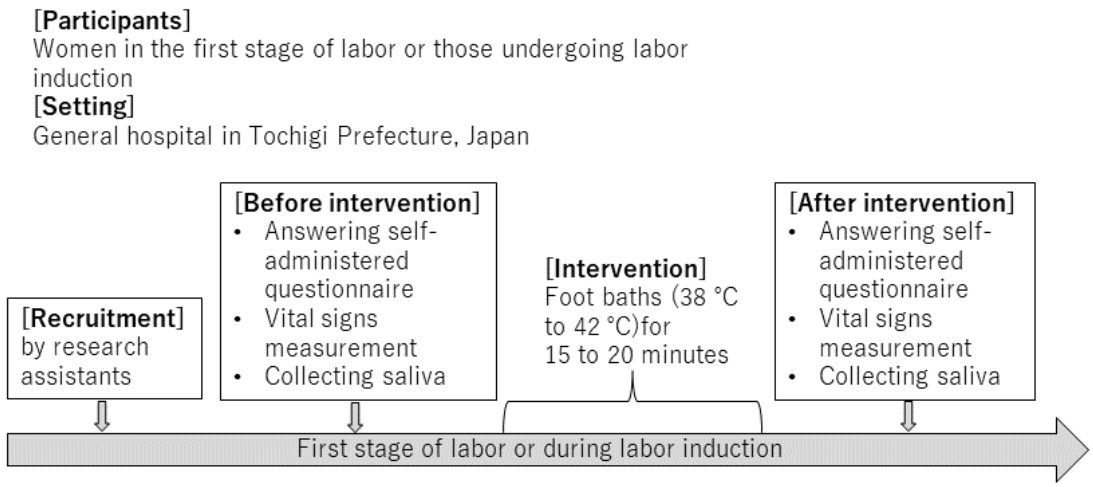
The study is being conducted at a general hospital in Tochigi Prefecture, Japan. The inclusion criteria are women in the first stage of labor or those undergoing labor induction. The first stage of labor is the phase when a pregnant woman's uterus starts to contract and they feel persistent contractions and relaxation, and the cervix dilates to 10 cm. Women who cannot complete the questionnaire or cannot participate in the study because of labor pain or those who are judged to have difficulty participating in the study by midwives because of low literacy of Japanese or due to mental illnesses are excluded from recruitment.

Intervention Description

This is a pre-post test trial; therefore, all participants are to receive the intervention. In this study, a foot bath is defined as the immersion of feet up to the ankle in hot water, set to a temperature that feels comfortable to the participants (38 °C to 42 °C) for 15-20 minutes (Figure 1). During the foot bath, other stimuli, such as pushing acupoints or massage, are avoided, because a meta-analysis has shown the effects of acupressure on labor duration [18]; this point was explained to all research assistants before starting this study. Participants receive the foot bath intervention only once, because midwives usually provide foot baths for women in labor only once in clinical settings; therefore, we aim to evaluate the effects of a single foot bath intervention. The intervention is discontinued if delivery progresses rapidly and if the midwives consider it difficult to continue.

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Figure 1. Protocol of the study.



Data Collection

Variables

Data collection is being undertaken by research assistants, who are midwives working in the hospital and on duty, as assigned by the midwife in charge.

Data are collected using a self-administered questionnaire, laboratory assay for the biomarker, anthropometric measurements, and medical records. The self-administered questionnaire was adapted from those developed in previous studies that assessed the effects of foot baths [7,19-23]. Participants are asked to answer a questionnaire evaluating sociodemographic data, such as age, marital status (married, single, divorced, or widowed), education level (junior high or high school; vocational school, junior college, or technical college; and university or graduate school), and occupation (employee, public servant, self-employed, part-time worker, unemployed or housewife, and others). Previous studies used a 10 cm ruler to assess the comfort or feeling of body warmth [19,24], with 0 cm meaning “not at all” and 10 cm meaning “extremely so”; thus, in this study, a numerical rating scale (NRS), ranging from 0 to 10, is being used to collect data on the levels of labor pain and comfort, relaxation, and degree of warmth of the legs and entire body. Participants are asked to provide 1.5 mL of saliva in 2 microtubes before and after the foot bath. Vital signs, such as blood pressure, body temperature, pulse rate, and respiratory rate, are measured by research assistants before and after the foot bath. Data on delivery (gestational age, gravidity, parity, diagnosis following the last vaginal examination [such as dilation, station, effacement, consistency, and position], presence or absence of membrane rupture, use of uterine contraction agents, and estimated fetal body weight) are retrieved from the medical records by the research assistants and entered in the questionnaire.

The primary outcome of this study is salivary cortisol levels before and after the foot bath. The secondary outcomes are levels of labor pain, comfort and relaxation, and leg and body warmth, assessed using NRS scores, vital signs, and intervals of labor pain before and after the foot bath.

Data Collection Methods

We asked some experienced midwives working at the hospital to assist in this study as research assistants. Before study initiation, instructions on data collection and intervention were provided and explained to the research assistants.

The research assistants recruit participants for the study and explain the purpose and contents of the study using an instruction sheet. After obtaining oral consent, written informed consent is obtained.

The research assistants provide the participants with the self-administered questionnaire along with a clipboard and pen. Participants are asked to complete the self-administered questionnaire. After completion, the midwives measure the participants’ vital signs (blood pressure, body temperature, pulse rate, and respiratory rate) and the interval and duration of labor pain.

They also request participants to provide 1.5 mL of saliva in 2 microtubes each. After saliva collection, the specimens are stored at −20 °C until analysis.

The research assistants provide foot baths to participants using a foot bath device (Hietori-kun Micon Premium, FB-C80, Koyo Co, Ltd, Gifu, Japan). The temperature of the water is set to 38 °C to 42 °C, as desired by the participants. AS mentioned, during the foot bath, the research assistants avoid applying pressure on acupoints. The participants are allowed to soak their feet in the bath quietly for 15-20 minutes.

After the foot bath, the research assistants provide the participants with a self-administered questionnaire with a clipboard and pen. After completing the questionnaire, they measure the vital signs (blood pressure, body temperature, pulse rate, and respiratory rate) and the interval and duration of labor pain.

After saliva collection, the specimens are stored at −20 °C until analysis. If the participants have difficulty providing saliva because of severe labor pain, only responding to the self-administered questionnaire and the measurement of the vital signs is allowed.

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After recruitment, all salivary cortisol level measurements are conducted at Yanaihara Institute Inc, Shizuoka, Japan.

We will continue to recruit participants until the target sample size is attained, and we may consider adding another hospital as a study setting in case the recruitment does not progress favorably because of the COVID-19 pandemic. It is difficult for medical personnel to freely interact with women in labor until the results of the COVID-19 polymerase chain reaction test are available, complicating the recruitment process.

Data are double-checked during entry, and the data ranges are checked to ensure data quality. The collected data and questionnaires are stored in a locked cupboard.

Sample Size Calculation

According to a previous study that investigated differences in salivary cortisol levels before and after foot baths [20], the sample size was calculated based on the following considerations: effect size (Cohen *d*)=0.4, α (2-tailed)=.05, and β=.80. We estimated the sample size using a two-tailed *t* test to be equal to 100.

Patient and Public Involvement

Neither patients nor the public are involved in the design, conduct, reporting, or dissemination of the study.

Data Analysis

Categorical variables, such as marital status, education level, and occupation, will be presented as n (%), and continuous variables (salivary cortisol levels; NRS scores for labor pain, comfort, and relaxation; and vital signs, such as blood pressure, body temperature, pulse rate, and respiratory rate) will be presented as mean (SD) if normally distributed or as medians and interquartile ranges if nonnormally distributed. We will perform paired *t* tests for continuous variables if the observations are normally distributed, and if they are not, we will perform the Wilcoxon signed-rank test to compare data before and after foot baths. Furthermore, we will divide the participants into 2 groups, nullipara and multipara, for sensitivity analysis. All missing pretest or posttest data for the main outcome will be excluded from the analysis.

All data will be analyzed using SPSS Statistics for Windows (version 28.0; IBM Corp). Two-tailed *P* values of <.05 will be considered statistically significant.

Harms

In this study, foot bath devices with a constant temperature of hot water are used. When preparing hot water, the midwives check the temperature using a thermometer; however, the possibility of burns to the feet cannot be ruled out. Moreover, water spills on the floor may cause falls. In case of accidents, the midwives report to the obstetrician of the maternity ward and arrange for a doctor's visit. The cost of medical treatment is to be covered by the participant's health insurance coverage.

Ethics Approval and Consent to Participate

This study was approved by the Research Ethics Committee of the School of Nursing, Dokkyo Medical University, Japan (No. Nursing 03019) and the Research Ethics Committee of Kamitsuga General Hospital (No. 2021-008). The research assistants explain the purpose and contents of the study using an instruction sheet. Participation is voluntary. The possibility of harm and financial burden in case of accidents is explained to the participants. Written informed consent is obtained from all participants. Participants' identifying information, such as their name, home address, and date of birth, is handled only by the hospital staff, and the information is never taken out of the research facility. All data will be analyzed anonymously, and participants' other identifying information will be removed before analysis. The results of this study will be disseminated to scientific meetings and journals.

Trial Registration

This study was registered in the University Hospital Medical Information Network-Clinical Trial Registry system (UMIN000046539) on January 17, 2022.

Results

Data collection started on April 1, 2022. As of October 2022, we had enrolled 10 participants. Because of the COVID-19 pandemic in Japan, it is difficult for medical personnel to freely interact with women in labor until the results of the COVID-19 polymerase chain reaction test are available in the research facility, complicating the recruitment process. Moreover, the number of medical personnel who can engage in the research decreased in the research facility because some staff were infected by COVID-19; thus, recruitment is currently not progressing.

Discussion

Principal Findings

This is the first prospective study that will assess the effects of foot baths using a biomarker (salivary cortisol) in the first stage of labor. Though foot baths are commonly used by midwives in clinical settings in Japan and are expected to have psychological and labor-inducing effects, psychological effects using biomarkers have not been shown. Participant recruitment started on April 2022, but because of the COVID-19 pandemic in Japan, recruitment is currently not progressing.

Though several studies have reported the physical and mental effects of foot baths, they did not include women in labor as participants [1-8]. Previous studies that targeted women in labor [9,10,25] had several limitations, which are as follows: had a small sample size [9], focused only on the progress of labor effects of foot baths [9,10], and used the visual analog scale to assess anxiety [25]. In clinical settings, midwives sometimes apply pressure to acupoints during foot baths, and they use aroma as part of a midwife's care during the first stage of labor. A meta-analysis has shown the effects of acupressure on labor duration [18], and aroma increased the effects of foot baths [25,26]. Therefore, in this study, we are implementing a simple foot bath without any acupressure or aroma, and the research assistants follow the study protocols because the effects of acupressure and aroma are widely known to midwives in Japan.

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In Japan, the rate of epidural labor has been increasing recently [11]. Midwives traditionally implement nonpharmacological care in Japan, and foot baths are a form of such care. However, the physical and mental effects of foot baths have not been fully investigated, especially using biomarkers. Therefore, the findings for the effects of foot baths on women in labor will provide a novel perspective that will be useful worldwide, especially in developing countries where pharmacological care is difficult to access.

The appropriateness of the methodology of this study should be discussed. In this study, the outcomes are measured using salivary cortisol and an NRS for the levels of labor pain and comfort, relaxation, and the degree of warmth of the legs and the entire body. Samples are collected during labor, and therefore, collecting saliva or answering the questionnaire may trigger pain or stress for some participants. However, scoring NRS is not time-consuming, and several studies have used visual analog scales to assess comfort or warmth [19,20,24]; thus, it may be better than using a mental scale. The information about the participants' characteristics, such as marital status, is obtained in this study because participants' characteristics may affect their mental condition under the stress of labor. Moreover, this study is conducted in only 1 prefecture in Japan; thus, participants' characteristics may be biased, and the results should be interpreted with caution.

Furthermore, we need to mention the potential physical harm from foot baths. Foot baths are one of the popular midwifery interventions in Japan due to their psychological and labor-inducing effects. Therefore, most midwives understand the necessary precautions, such as controlling the temperature of hot water and avoiding water spills on the floor. Nevertheless, in this study, we use foot bath devices to maintain the correct temperature of the hot water, although we cannot fully rule out the possibility of burns to the feet.

Moreover, this study uses a single-arm, pre-post test trial design; thus, the interpretation of the study findings requires some attention. With such a design, the results will only show within-individual differences. To obtain robust evidence on the effects of foot baths during labor, a randomized controlled trial should be conducted in the future.

Strengths and Limitations

The strength of this study is that this is the first study that assesses the effects of foot baths during the first stage of labor using a biomarker (salivary cortisol). Though several previous studies have reported the effects of foot baths, few have evaluated them using biomarkers; moreover, there are no studies using biomarkers among women in childbirth.

Nevertheless, this study has some limitations. First, the design of this study is a single-arm pre-post test trial; thus, it is difficult to judge the effects of foot baths. To obtain robust evidence of the effects of foot baths, randomized controlled trials should be conducted in the future. Second, because of the COVID-19 pandemic, participant recruitment has not progressed favorably. Therefore, adding another hospital as a study setting has to be considered.

Conclusion

This is the first prospective study that will assess the effects of foot baths using a biomarker (salivary cortisol) in the first stage of labor. Though participant recruitment has not progressed favorably because of the COVID-19 pandemic, if foot baths are shown to reduce stress in women in labor, they can be recommended for the nonmedical care of women in labor. A randomized controlled trial to investigate the effects of foot baths to obtain robust evidence should be conducted in the future.

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Availability of Data and Materials

Data sharing is not applicable to this article as no data sets have yet been generated or analyzed for the study.

Authors' Contributions

NH, RI, KM, and AI were involved in the conception, design, and drafting of this manuscript. NH was involved in the writing and revision of the manuscript. All authors have read and approved the final version of the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

NRS: numerical rating scale

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Protocol

A Prescription Digital Therapeutic to Support Unsupervised Buprenorphine Initiation for Patients With Opioid Use Disorder: Protocol for a Proof-of-Concept Study

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Abstract

Background: Home-based (unsupervised) buprenorphine initiation is considered safe and effective, yet many patients report barriers to successful treatment initiation. Prescription digital therapeutics (PDTs) are software-based disease treatments regulated by the US Food and Drug Administration (FDA). The reSET-O PDT was authorized by the FDA in 2018 and delivers behavioral treatment for individuals receiving buprenorphine for opioid use disorder (OUD). A prototype PDT (PEAR-002b) designed for use with reSET-O was developed to assist in unsupervised buprenorphine initiation.

Objective: The primary objective of this pilot study is to evaluate the acceptability of PEAR-002b in individuals with OUD who use it to support buprenorphine initiation, their unsupervised buprenorphine initiation success rate, and their medication adherence.

Methods: Ten adults with OUD will be recruited for acceptability and feasibility testing. Outcomes will be assessed using week-1 visit attendance, participant interviews and satisfaction surveys, and urine drug screening (UDS). Three tools will be used in the study: PEAR-002b, reSET-O, and EmbracePlus. PEAR-002b includes a new set of features designed for use with reSET-O. The mechanism of action for the combined PEAR-002b and reSET-O treatment is a program of medication dosing support during week 1 of the initiation phase, cognitive behavioral therapy, and contingency management. During the medication initiation phase, participants are guided through a process to support proper medication use. PEAR-002b advises them when to take their buprenorphine based on provider inputs (eg, starting dose), self-reported substance use, and self-reported withdrawal symptoms. This study also administers the EmbracePlus device, a medical-grade smartwatch, to pilot methods for collecting physiologic data (eg, heart rate and skin conductance) and evaluate the device's potential for use along with PDTs that are designed to improve OUD treatment initiation. Home buprenorphine initiation success will be summarized as the proportion of participants attending the post–buprenorphine initiation visit (week 1) and the proportion of participants who experience buprenorphine initiation–related adverse events (eg, precipitated withdrawal). Acceptability of PEAR-002b will be evaluated based on individual participants' ratings of ease of use, satisfaction, perceived helpfulness, and likelihood of recommending PEAR-002b. Medication adherence will be evaluated by participant self-report data and confirmed by UDS. UDS data will be summarized as the mean of individual participants' proportion of total urine samples testing positive for buprenorphine or norbuprenorphine over the 4-week study.

Results: This project was funded in September 2019. As of September 2022, participant enrollment is ongoing.

Conclusions: This is the first study to our knowledge to develop a PDT that assists with unsupervised buprenorphine initiation with the intent to better support patients and prescribers during this early phase of treatment. This pilot study will assess the acceptability and utility of a digital therapeutic to assist individuals with OUD with unsupervised buprenorphine initiation.

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International Registered Report Identifier (IRRID): PRR1-10.2196/43122

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KEYWORDS

buprenorphine; digital therapeutics; opioid use disorder; OUD; prescription digital therapeutic; PDT; reSET-O; unsupervised buprenorphine initiation; medication adherence; digital health intervention

Introduction

Unprecedented rates of opioid misuse and mortality have led to the current opioid epidemic in the United States [1], with approximately 2.5 million people in the United States meeting the criteria for opioid use disorder (OUD) in 2020 [2]. OUD is a chronic condition with numerous physical, psychological, and personal consequences, including a high risk of death, which has risen in recent years due to the increasing prevalence of potent synthetic opioids (predominantly fentanyl) [3]. According to the latest reports, 74,754 adults died from opioid-related overdoses in the 12 months ending September 2021, representing a daily average of 205 deaths [1], a 55% increase since September 2019 [4]. Opioid-related overdoses now account for 75% of fatal overdoses of all substances, up from 70.6% in 2019, with synthetic opioids accounting for 86.6% of opioid-related deaths [4].

Initiation of evidence-based medications for opioid use disorder (MOUD), such as buprenorphine, methadone, or naltrexone, remains limited; in 2020, only 11.2% of those with OUD received MOUD treatment [2]. One of the key barriers is limited access to MOUD treatment [2], which is amplified by health care provider reservations about prescribing buprenorphine for OUD. Key reasons for this hesitancy include logistical barriers, perceptions that people with addiction are difficult to treat, insufficient time and staff support, limited provider and staff knowledge and training, and lack of a support network of experienced prescribers [5-8]. Despite the recent removal of the "X waiver" training requirement, prescribers may still feel they are not adequately equipped to begin prescribing for the above reasons [9].

For individuals who do access MOUD, medication adherence is unsatisfactory, and medication discontinuation rates are high [10,11]. Buprenorphine discontinuation rates at 6 months range from 50% to 65%, with most discontinuations occurring within the first 3 months of treatment, particularly within the first 30 days, which is a crucial phase that includes initiation and titration of buprenorphine to achieve dose stabilization [10-14]. Evidence from different real-world settings suggests that MOUD discontinuation is estimated to increase the likelihood of relapse by roughly 10 times, with relapse being strongly associated with overdose and death [15-17].

The medication initiation phase for buprenorphine, in particular, is critical. Patients who have negative experiences initiating buprenorphine may not continue treatment beyond the first day of dosing [18]. Successful initiation of buprenorphine requires the patient to be in mild to moderate withdrawal before they begin the medication [19]. People's desire to avoid experiencing withdrawal symptoms is a primary reason they continue to use and can be a major barrier to beginning treatment [20]. Buprenorphine initiation is a high-touch process for clinicians that requires educating the patient on not only the risks and benefits of buprenorphine, but how the medication works, when to start treatment, and how to manage emotions like fear and anxiety that can complicate the process.

Providing an accessible tool that supports both the patient and clinician by offering education as well as motivational and skills-based support during this important phase of treatment could enhance the patient experience and help improve clinician willingness to prescribe. Unsupervised buprenorphine initiation, whether supported via telemedicine or traditional in-person provider interactions, is considered safe and effective and may be an equitable and accessible way to increase the rate of successful MOUD initiation [19]. One potential limitation of unsupervised MOUD initiation is the inability of physicians to monitor patient biometrics (eg, pulse, blood pressure, and oxygen saturation levels), which can inform treatment and dosing decisions. New devices exist to monitor biometrics, but whether unsupervised buprenorphine initiation protocols could benefit from data collected by passive biometric monitoring is unknown.

Another technology that may potentially be leveraged to improve the MOUD initiation process is prescription digital therapeutics (PDTs), which are software-based disease treatments evaluated for safety and effectiveness in randomized controlled trials and authorized by the US Food and Drug Administration (FDA). Prescribed by treating physicians and delivered on mobile devices, PDTs can expand access to evidence-based behavioral therapies across a variety of disease states, including OUD.

The reSET-O PDT was authorized by the FDA in 2018 for patients with OUD being treated with buprenorphine. The PDT delivers two evidence-based mechanisms of action: (1) an OUD-specific form of cognitive behavioral therapy (CBT) based on the community reinforcement approach, delivered as on-demand lessons and interactive text, video, and audio exercises and (2) reinforcement and motivation for lesson completion and abstinence via contingency management (CM), which involves eligibility for positive reinforcement messages or monetary digital gift cards. Moreover, there is currently no FDA-authorized PDT that provides assistance with home initiation of MOUD. Opportunities thus exist to better support patients with OUD in the medication initiation phase and to provide strategies to lower potential barriers to the implementation of buprenorphine MOUD treatment in clinical practice.

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Given the importance of buprenorphine adherence and the need to better support both patients and providers during the initiation process, we are conducting a pilot study to evaluate PEAR-002b, an investigational digital therapeutic intended to be used with reSET-O and designed to support patients during unsupervised initiation of buprenorphine. The study also includes a wearable device capable of capturing and transmitting biometric data to evaluate the feasibility of biomarker development.

Methods

Study Objectives

The objective of this pilot study is to evaluate device acceptability, home buprenorphine initiation success rate, and medication adherence rate among participants with OUD who use the PEAR-002b investigational tool.

Study Design

This will be a qualitative observational cohort study with a recruitment goal of 10 adults with OUD (inclusion and exclusion criteria are listed below).

Study Population and Sample Size

The trial will recruit 10 adults diagnosed with OUD. The investigator will ensure that participants being considered for the study meet all eligibility criteria (details are provided in the Study Procedures and Assessments section). No additional criteria will be applied by the investigator to ensure the study population will be representative of all eligible participants. Participants may undergo rescreening with approval of the medical monitor. Due to the exploratory nature of the study, no formal sample size calculations are required.

Inclusion Criteria

Study inclusion criteria are as follows: written informed consent provided prior to the performance of any study-specific assessments; age ≥18 years; English proficiency sufficient to meaningfully participate in the consent process, assessment, and intervention; a *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (*DSM-5*) diagnosis of OUD made by a treating clinician; desire to start buprenorphine treatment; capability of using common software applications on an internet-enabled mobile device (smartphone or tablet); interest in testing or using PEAR-002b; no prior history of reSET-O use; no participation in investigational drug trials within the past 30 days (or within 5 half-lives of any study drug, whichever is longer) of enrollment; and a judgment that the subject is appropriate for participation by the treating clinician.

Exclusion Criteria

Study exclusion criteria are as follows: currently on methadone or naltrexone pharmacotherapy; currently on buprenorphine MOUD treatment; planning to move out of the geographic area within 2 months; insufficient English fluency to participate in the consent process, intervention, or assessment; inability to comply with study procedures due to physical or mental condition; currently receiving inpatient treatment for OUD; and pregnancy.

Study Setting and Recruitment

The study will be conducted at a single site in the United States. Participants will be recruited verbally by participating clinicians and via community advertising.

Study Tools

Overview

Three tools will be used in the study: PEAR-002b, reSET-O, and EmbracePlus. PEAR-002b is a standalone software app that includes a new set of features designed for use with the reSET-O PDT. The mechanism of action for the combined PEAR-002b and reSET-O treatment is a program of medication dosing support during week 1 of the buprenorphine initiation phase, including psychoeducation, CBT, and CM. During the first week of treatment (ie, the buprenorphine initiation phase) participants are guided through the medication initiation process with psychoeducation to support proper medication use and a self-report withdrawal scale to advise the participant on when to take their buprenorphine. During the use of reSET-O, which occurs in weeks 2 to 4, participants are instructed to complete 4 lessons per week. The EmbracePlus device is a medical-grade smartwatch that will be used to collect physiologic data (eg, heart rate and skin conductance) from participants who agree to use the device.

The smartphones loaned to participants in this study include an installed security feature that blocks downloads of other apps, potentially limiting their market value and thus reducing the risk that the phones will not be returned at the conclusion of the study.

PEAR-002b Summary Description

PEAR-002b includes an algorithm designed to support buprenorphine dosing and provide associated therapeutic content related to medication and recovery. Medication dosing recommendations are based on provider input (eg, starting dose) and reported recent substance use. A withdrawal symptom scale based on the Subjective Opiate Withdrawal Scale helps participants identify when to take their medication and how to titrate their medication dose to manage withdrawal symptoms. Development of all features and content was informed by feedback generated through participant interviews and prototype testing sessions.

The PEAR-002b content was designed to maximize the efficacy of buprenorphine treatment by educating participants on the importance of proper buprenorphine use and adherence in recovery. Videos and text-based modules address the following topics: preparing for buprenorphine initiation; recognizing, coping with, and managing common opioid withdrawal symptoms prior to buprenorphine initiation; proper initiation of buprenorphine; techniques for sublingual or buccal dosing of buprenorphine to maximize absorption and therapeutic drug levels; how medication adherence supports treatment goals; misconceptions and stigma pertaining to buprenorphine treatment; proper storage and security of buprenorphine to minimize the risk of diversion; and the mechanism of action of buprenorphine treatment.

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reSET-O Summary Description

PEAR-002b is designed as an optional feature of the reSET-O PDT, which provides an 84-day course of behavioral treatment for OUD as an adjunct to standard buprenorphine MOUD treatment. The reSET-O PDT delivers behavioral therapy modeled on the Community Reinforcement Approach [21], which is a specific form of CBT designed for patients with OUD [22-24]. The PDT provides therapy through a series of 67 interactive lessons delivered via a patient-facing smartphone app. It also has a web-based dashboard for use by clinicians. A typical therapy lesson consists of a CBT component and skill-building exercises. Therapy lesson content is delivered primarily via written text but may also include videos, animations, and graphics. It also has an optional function that patients can use to set medication reminders. The first time a patient opens the app each day, they are asked to report whether they have taken their buprenorphine. Patients who report not taking it are asked to indicate the reasons for nonuse.

Therapy lessons are divided into "core" and "keep learning" lessons. Core lessons cover key CBT concepts, whereas "keep learning" lessons include more in-depth information on key CBT topics covered in the core lessons, as well as additional topics that may be of interest to patients. Once a core lesson is completed, patients can unlock the next lesson. "Keep learning" lessons can be completed in any order and are accessible once the core lessons are completed.

EmbracePlus Summary Description

EmbracePlus is a device worn on the wrist that collects, processes, stores, and wirelessly transmits physiologic parameters to a companion app and monitoring platform. The device consists of an electronic display, display case, wristband, and sensors. The device produces 2 types of data: raw data (high-frequency data recorded by EmbracePlus sensors) and digital biomarkers (computed from raw data using algorithms). Biomarkers aggregated by EmbracePlus (1 value per minute) include pulse rate, pulse rate variability, respiratory rate, blood oxygen saturation, sleep periods, movement, skin conductance, temperature, and wearing time. In addition to collecting physiologic data via its sensors, EmbracePlus enables the user to tag specific events by pressing a button on the side of the device. Data collected via EmbracePlus flow through the Empatica Care app (a participant-facing app that notifies the participant if action is required and provides a real-time display of digital biomarkers) to Empatica Cloud (for data storage) and the Empatica Care Portal (a web app to manage study participants and monitor digital biomarkers computed by EmbracePlus).

Ethical Considerations

Conduct of the Study

This study will be conducted in full accordance with all applicable policies and procedures and all applicable US federal and state laws and regulations, including the 45 Code of Federal Regulations 46, and the Health Insurance Portability and Accountability (HIPAA) Privacy Rule. Any episode of noncompliance will be documented. The investigator will perform the study in accordance with this protocol and will report unexpected problems in accordance with institutional review board (Advarra IRB Services; approval number Pro00037072) procedures and all federal requirements. Collection, recording, and reporting of data will be accurate and will ensure the privacy, health, and welfare of research participants during and after the study. All participants will be required to sign an informed consent document at the screening visit, prior to the start of any study-specific procedures. The informed consent document will include an overview of the study, including a clear description of all study procedures, potential risks and benefits of participating in the study, and alternatives to participating in the study. Participants have the right to withdraw from the study at any time and for any reason, and all participants are made aware that withdrawal will not affect their routine care.

Confidentiality

The anonymity of participants will be maintained. Participants will be identified by their initials and an assigned study number on electronic case report forms (e-CRFs) and other documents submitted to the study monitor. No protected health information will be stored outside of the study clinic, PEAR-002b system, reSET-O, or the encrypted HIPAA-compliant electronic data capture platform. Data collected by the PEAR-002b system will be securely transferred using industry standard encryption to the PEAR-002b backend services, which use a cloud-based infrastructure that serves and communicates with the patient-facing mobile app.

The backend services contain all data and analytics for reSET-O, PEAR-002b, and its clients (participants and clinicians). All data stored by the study devices are hosted and stored by Amazon Web Services (AWS). AWS follows a variety of internationally recognized security standards, such as the National Institute of Standards and Technology SP800-53 and HIPAA. All participant information is automatically encrypted by AWS when it is entered into the system, allowing for secure data transfer (from participant device to clinician device) and storage.

The EmbracePlus and Care apps are compliant with federal regulations, directives, and international standards for medical devices. Empatica Cloud is the infrastructure where the data recorded from EmbracePlus is collected and made accessible via web interfaces and data repositories. Empatica Cloud is HIPAA compliant. Participant data collected via EmbracePlus is securely stored and encrypted within the AWS cloud service.

Participants will be compensated for attending study visits and completing study assessments as follows (all values in US $): baseline clinic visit, $50; weekly study visit (n=4), $20; urine sample (n=5), $10; qualitative interview (n=2), $50; wearable use, $10 per study visit (n=4). Participants also have the chance to receive monetary rewards in the form of digital gift cards, ranging in value from $5 to $100, earned via the use of the CM functionality of the reSET-O study device.

Study Procedures and Assessments

Prospective participants referred to the study will be screened for eligibility criteria by a research assistant based on the study inclusion and exclusion criteria and clinical documentation of

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assessments as needed. Diagnoses of OUD will be made by treating clinicians following standard clinical protocols at the study site, based on *DSM-5* criteria. Recruited participants will be given standard screenings in accordance with the assessment schedule. For the convenience of participants, screening and baseline visits may be combined. All participants will be required to sign an informed consent form at the screening visit, prior to the start of any study procedures. Participants meeting eligibility criteria will be assigned a subject identification number during the baseline visit. Study participants will continue to receive standard treatment for OUD following prescriber-recommended instructions for medication formulation and starting dose, as well as clinic visits unrelated to the study (eg, for medication management or counseling). Standard treatment will be supplemented with the therapeutic tools (PEAR-002b and reSET-O).

Participants will be enrolled for 4 weeks to assess the acceptability and ease of use of the PDT. At baseline, if participants still meet all inclusion and exclusion criteria, study staff will provide them with a phone preloaded with the study apps. Participants will be asked if they also agree to wear the EmbracePlus smartwatch for the duration of the study, and those who agree will be provided the device. Study staff will train willing participants in use of the study apps and the EmbracePlus device. Additionally, a UDS will be performed, and the Clinical Opiate Withdrawal Scale (COWS) will be used. One week later, the participant will return to the clinic and complete a survey and an interview. Study staff will conduct another UDS, administer the COWS, and ask about any adverse events (AEs) or side effects. Following this visit, the participant will return weekly for a UDS and AE assessment. At week 4, the participant will return for a UDS and complete a final survey and exit interview. Primary, secondary, and exploratory objectives and end points are outlined in Textbox 1.

Textbox 1. Study objectives and end points.

Primary objectives

- To assess the effect of PEAR-002b on home buprenorphine initiation success rates (ie, the proportion of participants attending the post–buprenorphine initiation visit)
- To evaluate the acceptability of PEAR-002b
- To assess the effect of PEAR-002b on medication adherence rates

Primary end points

- Proportion of participants attending the post–buprenorphine initiation visit and the proportion of participants who experience buprenorphine initiation–related adverse events (eg, precipitated withdrawal)
- Participants' ratings of PEAR-002b for ease of use, satisfaction, perceived helpfulness, and the likelihood they would recommend it
- Participant self-report data and confirmation by urine drug screens

Secondary objectives

- To assess dosing and engagement of participants with PEAR-002b
- To evaluate the contingency management reward structure

Secondary end points

- Participants' use patterns of PEAR-002b, including lesson completion, self-report assessment completion, voluntary use of self-report features, and response to notifications
- Participant interviews and user satisfaction surveys

Exploratory objectives

- To evaluate the preliminary efficacy of PEAR-002b
- To evaluate compliance with wearing the EmbracePlus device
- To evaluate the feasibility of using digital biomarkers to predict withdrawal, craving, and opioid use

Exploratory end points

- Abstinence from illicit opioids and medication adherence, measured by urine drug screens, and retention in treatment, measured by time to dropout (if applicable)
- Device wearing time (eg, total hours worn and average percentage of time worn per day) measured by the device
- Prediction power based on physiologic data (eg, heart rate and skin conductance) collected via the device

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Demographics

Demographic information to be collected includes age at time of consent, sex, gender, race and predominant ethnicity, level of education, marital status, employment status, income, number of children, health insurance status, involvement in the criminal justice system, distance of residence from treatment site (in miles), and usual method of transportation.

Medical and Medication History

Relevant medical history and current medical conditions will be collected, including current or prior treatments received for mental health disorders, hepatitis C, HIV, and chronic pain syndromes. History of substance use will be collected for the following categories: opioids, cocaine, stimulants other than cocaine, alcohol, marijuana, benzodiazepines, and other substances. Data to be collected regarding each substance include onset of use, number of years used regularly, amount used, type used (eg, pill vs powder), route of use, history of overdose, and longest period of abstinence. History of substance use treatment will also be collected, including present and prior treatment, type of treatment facility, number of treatment episodes, and current recovery activities. Nicotine use history will also be collected, including type, route, quantity, duration of use, and prior use. Medication history will include the name, dose, frequency, start and stop dates of the medication, and the indication for use. Prior experience with medication for substance use disorder/OUD will also be recorded.

Evaluation of Phone Use

Study staff will evaluate participants' comfort level with using smartphones and navigating through common apps.

Interviews and Surveys

Interviews with participants will be conducted by study staff to evaluate their experiences with the PDT, particularly its ease of use and acceptability. Interviews may be performed in person or remotely via video or phone. These sessions may be recorded for transcript generation if informed consent is obtained from the participant, investigator, or both. Participant surveys will be completed by participants per the assessment schedule. Table 1 shows a schedule of study assessments.

Table 1. Schedule of study assessments.

Procedure/measure	Baseline	Post–buprenorphine initiation	Maintenance		End of study
Timepoint	Week 0 (day 0)	Week 1 (day 7, plus or minus 2 days)	Week 2 (day 14, plus or minus 2 days)	Week 3 (day 21, plus or minus 2 days)	Week 4 (day 28, plus or minus 7 days)
Informed consent	✓				
Inclusion/exclusion	✓				
Mobile use evaluation	✓				
Demographics	✓				
Medical history	✓				
Medication list/history	✓				
EmbracePlus monitor recording	✓	✓	✓	✓	✓
Urine drug screen	✓	✓	✓	✓	✓
Adverse events and side effects assessments		✓	✓	✓	✓
Clinical Opiate Withdrawal Scale	✓	✓			✓
Participant survey		✓			✓
Participant interview		✓			✓
Medication list changes		✓	✓	✓	✓
Timeline Followback Assessment	✓	✓	✓	✓	
Protocol deviations	✓	✓	✓	✓	✓

Data Management, Study Oversight, and Monitoring

Designated staff from the study sponsor (the study monitor) will review the e-CRFs entered by study staff for completeness and accuracy. Authorized study staff will respond to queries and make any necessary changes to the data. Oversight of data management, including data collection, storage, and export; security; tracking; data analysis; and quality assurance will be the responsibility of the sponsor. The study investigator will ensure the accuracy, completeness, and timeliness of the data reported to the sponsor and be responsible for ensuring that all study staff adhere to human subjects/IRB guidelines related to data management. Data files will be backed up at regular intervals and will be accessible only by trained study staff members.

The study monitor will ensure that the research is conducted and documented according to the protocol and in accordance with the guidelines for Good Clinical Practice. Virtual study monitoring visits will be conducted at appropriate times during the study per the monitoring plan.

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AE Reporting

The investigator or designee and research site staff are responsible for the detection, documentation, classification, reporting, and follow-up of events meeting the definition of an AE or serious AE (SAE). Spontaneously reported or observed AEs will be recorded throughout the study beginning at the time the participant gives informed consent. AEs will be elicited using a nonleading question at designated time points. Regardless of seriousness, intensity, or presumed relationship to PEAR-002b, all AEs will be recorded in the source documentation from the time of consent until the end of the last study visit. AEs that occur after screening and prior to implementation of PEAR-002b will be recorded in the source documentation under medical history. AEs occurring after baseline and until the last study visit, known as treatment-emergent adverse events (TEAEs), will be recorded in the AE page of the e-CRFs. All measures required for management of TEAEs will be recorded in the source documentation. The investigator will be responsible for informing the IRB and regulatory authorities of SAEs, as required by local and regional regulations.

Statistical Analysis Methods

This feasibility study is largely exploratory, with several end points focused on measuring participant satisfaction, attitudes, and use of the mobile app component of reSET-O and PEAR-002b. Therefore, many of the statistical analyses will be descriptive and will involve computing and reporting measures of central tendency (ie, mean and median) and variability (ie, variance and standard deviation) for the variables of interest. These statistics will highlight which aspects of the therapeutic and the experience are helpful and engaging to participants, and which aspects are less engaging.

Primary End Points

Home buprenorphine initiation success will be summarized as the proportion of participants attending the post–buprenorphine initiation visit (week 1) and the proportion of participants who experience buprenorphine initiation–related AEs (eg, precipitated withdrawal). Acceptability of PEAR-002b will be evaluated based on individual participants' ratings of ease of use, satisfaction, perceived helpfulness, and likelihood of recommending PEAR-002b. Descriptive statistics will be performed on Likert-scale and multiple-choice items that assess user satisfaction and attitudes about the app. Analyses will be conducted on data collected at each assessment point throughout the study, ratings over the course of the study, and for overall user satisfaction as measured at the end of the study. Medication adherence will be evaluated by participant self-report data and confirmed by UDS (ie, a positive result for buprenorphine and norbuprenorphine). UDS data will be summarized as means of individual participants' proportion of total urine samples testing positive for buprenorphine or norbuprenorphine over the 4-week study.

Secondary End Points

For dosing and engagement, descriptive statistics will be calculated for PEAR-002b module completion, assessment completion (both in the app and clinician delivered), voluntary use of in-app self-report features, and response to notifications. For CM rewards, descriptive statistics will be calculated on Likert-scale and multiple-choice items that assess participant satisfaction with and ease of use of the CM system and rewards. Descriptive analyses will examine the frequency of rewards earned throughout the study. Text analysis of qualitative responses and transcripts from interviews and focus groups will be used to identify themes in participant feedback.

Exploratory End Points

Abstinence will be defined by participant self-reports and confirmed by the absence of opioids (other than buprenorphine) in the UDS. UDS data will be summarized as means of individual participants' proportion of total urine samples testing negative for opioids other than buprenorphine over the 4-week study. Treatment retention will be measured as time to drop-out (defined as the last face-to-face contact with a participant) and analyzed using the Kaplan–Meier method.

Feasibility and acceptability of EmbracePlus will be assessed by measuring the total hours and percentage of weeks wearing the device. Week-by-week averages and the total number of hours across all weeks will be assessed. Acceptability will be evaluated based on participants' ratings of ease of use and satisfaction with EmbracePlus. Descriptive statistics will be calculated for Likert-scale and multiple-choice items that assess user satisfaction and attitudes about EmbracePlus. If physiologic data are sufficient, multiple statistical learning models will be used to evaluate if these models have sufficient power to predict withdrawal or opioid use events in advance, levels of cravings, or both.

Results

Recruitment for this study is currently open and will continue until the projected sample size is met. A sample size of 10 participants is standard for a feasibility study.

Discussion

PEAR-002b is being evaluated for its potential to support participants during unsupervised buprenorphine initiation. A comprehensive analysis of data collected in the first week will be used to evaluate feasibility and acceptability. Success will be demonstrated not only by attendance at the week-1 visit, but by evidence that participants engaged with PEAR-002b during the medication initiation process and found it acceptable (ie, helpful and easy to use). If the study is successful, future efforts may focus on refinement of PEAR-002b and its integration with reSET-O, in addition to the development of tools to support provider monitoring of the patient during home medication initiation. These future efforts may help mitigate inequities that impact how individuals access and engage with treatment. These tools may offer standardization and ease of implementation, ensuring proper clinical-care delivery while lightening the burden on health care workers. Future directions could also include providing patients preparing or planning unsupervised buprenorphine initiation with a list of provider-recommended over-the-counter medications to mitigate some of the withdrawal side effects, thereby encouraging patient buy-in and ownership

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of their health care during a process that is often perceived as uncontrollable.

Data acquired in this pilot study may also inform larger studies to evaluate the safety and effectiveness of PEAR-002b plus reSET-O. Together, PEAR-002b and reSET-O may improve the success rate of unsupervised buprenorphine initiation and medication adherence rates, which are crucial to an individual's success in OUD treatment.

The study may also guide efforts to refine the use of biometric outputs, such as heart rate and skin conductance, to monitor physiological symptoms of withdrawal and to provide objective data that could be incorporated into the dosing algorithm of the digital therapeutic to more accurately support dose titration. Biometric data could also be included in a dashboard, which would enable clinicians to better monitor their patients. Biometrics may help alert clinicians to patients at risk of precipitated withdrawal.

This is an early feasibility study, and as such, findings may not be generalizable due to the small sample size and the lack of a comparator arm; both of these limitations will be addressed in a full-scale study, should that be pursued. The simplicity of PEAR-002b is also a limitation of the study; for instance, it does not support all sublingual buprenorphine formulations (eg, Zubsolv), nor does it support all buprenorphine initiation protocols, as the current version of PEAR-002b is based on conventional buprenorphine initiation protocols. Due to the prevalence of potent synthetic opioids such as fentanyl in the illicit drug supply, conventional buprenorphine initiation protocols have become less predictable, with an increased risk of precipitated withdrawal, necessitating the development of alternative methods, such as low-dose buprenorphine initiation [25]. In order to create a more flexible and potentially scalable digital therapeutic, future development efforts may focus on incorporating a broader range of buprenorphine initiation protocols, including low-dose initiation, along with a dashboard that enables the prescriber to select the type of protocol, buprenorphine formulation, and starting dose.

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Data Availability

Requests for data required to support the protocol will be evaluated by the sponsor and provided if deemed appropriate. All study-related information will be regarded as confidential.

Authors' Contributions

HL and NE conceived the study concept and design. HL, NE, RG, SM, XX, CK, CC, YM, and JG contributed to the study design. RG and XX are the biostatisticians for the study. All authors reviewed drafts of the manuscript and contributed comments based on their review.

Conflicts of Interest

HL, RG, SM, XX, YM, and SB are consultants or employees of Pear Therapeutics (US), Inc. NE was an employee of Pear Therapeutics (US), Inc at the time this manuscript was written. Pear Therapeutics Inc provided digital therapeutic prescriptions at no cost to Kaiser Permanente Washington during a quality improvement pilot study that was led by JG. JG is a coinvestigator on a grant proposal awarded to Pear Therapeutics Inc by the National Institute on Drug Abuse, which evaluates potential improvements to reSET-O (R44DA042652). Pear Therapeutics does not provide funding to JG.

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Abbreviations

AE: adverse events
AWS: Amazon Web Services
CBT: cognitive behavioral therapy
CM: contingency management
COWS: Clinical Opiate Withdrawal Scale
DSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
e-CRF: electronic case report form
FDA: Food and Drug Administration
HIPAA: Health Insurance Portability and Accountability
IRB: institutional review board
MOUD: medication for opioid use disorder
OUD: opioid use disorder
PDT: prescription digital therapeutic
SAE: serious adverse event
TEAE: treatment-emergent adverse event
UDS: urine drug screen

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Protocol

The Effects of HIV Infection on the Immune Response to Malaria Among Pregnant Women in Kumba, Southwest Cameroon: Protocol for a Cross-sectional Study

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Abstract

Background: Malaria and HIV, 2 of the world's deadliest diseases, share a lot of territory in sub-Saharan Africa.

Objective: This study seeks to investigate the effect of HIV on the immune response to malaria infection among pregnant women in Kumba in the southwest region (SWR) of Cameroon. The study aims to determine the prevalence of malaria infection, assess the occurrence of Plasmodium falciparum genetic diversity, and evaluate the antibody (immunoglobulin [Ig]G and IgM: apical membrane antigen-1 [AMA1], merozoite surface protein [MSP]1, MSP2, MSP3, and erythrocyte-binding antigen [EBA]175) and cytokine (interleukin [IL]-10, tumor necrosis factor alpha [TNF-α], and interferon gamma [IFNγ]) response to malaria infection among pregnant women with and without HIV in Kumba.

Methods: The study will be a hospital-based cross-sectional design that will run from March 2022 to February 2023. It will recruit pregnant women with and without HIV who are in their third trimester of pregnancy. The study will be carried out in 5 health institutions in Kumba: General Hospital Kumba, Presbyterian Hospital Kumba, District Hospital Kumba-town, Kossala Integrated Health Center Kumba, and Catholic Hospital Kumba. About 3 mL of the mother's venous blood, placental blood, and baby cord blood will be collected from each pregnant women at the point of delivery. Microscopy, rapid diagnostic tests (RDTs), and nested polymerase chain reaction (PCR) will be performed to identify the malaria parasite in all the samples, and nested PCR targeting the different genetic diversity markers for *P. falciparum* will also be performed. Furthermore, sequencing will be performed to study the nucleotide sequence of different alleles, and the genetic diversity of the alleles responsible for malaria infection among pregnant women will be assessed. A multiplex assay will be conducted to analyze the peripheral blood plasma and cord blood plasma for the cytokine and total antibody response to malaria infection among pregnant women with and without HIV. The questionnaire for data collection will be pretested at the Kumba District Hospital, and ethical clearance will be obtained from the University of Buea and the Regional Delegation of Public Health for the SWR. Data will be analyzed using SPSS Statistics and STATA. All *P* values <.05 will be considered statistically significant. BioEdit 7.0.0 software will be used to align the nucleotide sequences of different genes after sequencing. Phylogenetic tree searching will be conducted using the maximum-likelihood (ML) method in MEGA V6.0.

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Results: The project started in March 2022 and will end in February 2023. Presently, three-fourth of the project funding has been disbursed to date. A total of 218 participants have been enrolled: 193 (88.5%) women without HIV and 25 (11.5%) women with HIV. Between February 2023 and March 2024, the following results will be ready for publication: maternal-neonatal malaria prevalence among pregnant women and babies in Kumba, the effect of HIV on (1) *P. falciparum* genetic diversity among pregnant women in Kumba, (2) the maternal and neonatal immune response to MSP1, MSP2, and EBA175 IgG antibody response to *P. falciparum*–caused malaria infection among pregnant women, and (3) the maternal and neonatal pro-inflammatory and anti-inflammatory cytokine response to malaria infection.

Conclusions: HIV infection increases the prevalence of malaria infection among pregnant women and also influences the genetic diversity of *P. falciparum*, with MSP1 alleles being the most prevalent. HIV infection also reduces the antibody response to malaria infection, as well as altering the level of pro-inflammatory and anti-inflammatory responses to malaria infection.

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KEYWORDS

malaria; HIV; co-infection; pregnancy; prevalence; allele; immunity; antibodies; cytokines; Cameroon

Introduction

Malaria and HIV, 2 of the world's deadliest diseases, share a lot of territory in sub-Saharan Africa. As a result, malaria and HIV coinfection is common in the region [1]. In 2019, malaria alone affected over 229 million people worldwide, with the majority (95%) of the cases occurring in 29 countries in sub-Saharan Africa: Nigeria (27%), Democratic Republic of Congo (12%), Uganda (5%), Mozambique (4%), and Niger (3%) [2]. Infection with malaria in humans is caused by 6 species, with *Plasmodium falciparum* being the most virulent of them all [3]. In Cameroon, malaria is a significant public health issue, with the whole nation in danger of transmission [4,5]. Despite considerable progress in recent years to reduce the burden of this infection due to the implementation of several malaria control strategic programs, the disease remains widely spread, with an estimated 3.3-3.7 million probable cases in health care facilities each year [4,6].

Infection with HIV or malaria during pregnancy is often harmful to both mother and child [7]. Coinfection raises the chances of adverse outcomes, which include maternal anemia, increased parasite sequestration at the placenta, low-birth-weight babies, and immune dysregulation to malaria [7]. The immunological reasons behind the increased malaria sensitivity of women with HIV, as well as the effect of coinfection on HIV transmission from mother to child, are major public health problems. Once again, these increased risks are greatest in multigravidae [8]. Epidemiological studies suggest that pregnant women with HIV have a considerable decrease in the acquired immunity to malaria, resulting in a diminished ability to limit *P. falciparum* infection. This finding is corroborated by the fact that sulfadoxine-pyrimethamine–intermittent preventive treatment's (SP-IPT) effectiveness in pregnant women with HIV reduces [7,8].

Prior studies have shown that HIV infection interferes with the breadth of the antibody response to merozoite surface protein (MSP) antigens. According to Daniel et al [9], the antibody response to MSP1, MSP2, and apical membrane antigen-1 (AMA1) reduced in children with HIV, and only AMA1 was statistically significant [9]. HIV was associated with a restricted spectrum of responses to certain merozoite antigens. HIV changed the pace of age-related antibody acquisition against schizont extract but not the rate of age-related response formation to particular merozoite antigens [9]. Another research in Kenya found that serum antibody levels to AMA1 and (MSP1 block 2, MSP2, and MSP3) are negatively associated with the likelihood of acquiring malaria, whereas levels of MSP1 and erythrocyte-binding antigen (EBA)175 are not [10]. Although the findings of this research are interesting, they are inconsistent. As a result, additional research is necessary.

Among pregnant women, studies have shown that HIV dysregulates the immune response to malaria infection, making them more vulnerable to malaria [11]. HIV decreases immunoglobulin (Ig)G levels to circumsporozoite protein (CSP) and terminal complement complex (TCC) in women with infection, while cord IgG to CSP, MSP1, and TCC is considerably lower in neonates delivered to mothers with HIV [12]. This study found that HIV infection is related to decreased levels of cord antibodies to malarial antigens and that hypergammaglobulinemia may contribute to impaired antibody transmission [12]. Another study found that interferon gamma (IFNγ) and tumor necrotic factor alpha (TNF-α) levels are lower in pregnant women who have both malaria and HIV infections. Nonetheless, pregnant women with coinfection had higher mean plasma TNF-α concentrations. It was also shown that interleukin-2 (IL-2) levels decreased in mothers with HIV and with coinfection before increasing in mothers with malaria. IL-10 levels among women with coinfection also decreased when compared to women without infection. There were strong significant associations between plasma IL-2 levels and infection status [13].

Djontu et al [14] revealed that placental malaria reduces maternal plasma levels of cytokines IL-17E, IL-27, and IL-28A, as well as neonatal plasma levels of cytokines IL-17E and IL-28A, which may aid in parasite clearance and enhance infant birth weight. IL-27 and IL-6 are 2 cytokines that can have both pro-inflammatory and anti-inflammatory actions. Indeed, IL-27 has been shown to activate the T-bet transcription factor, which promotes helper T (Th)1 cell differentiation [15,16]. Other investigations have shown that it suppresses the growth of IL-17–producing Th17 cells [17] and decreases the Th2 response

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[17]. IL-6 suppresses transforming growth factor (TGF)–induced IL-10–producing regulatory T-cell (Treg) development [18], but when combined with TGF-α, it preferentially promotes IL-17–producing Th17 cell differentiation [19]. Mucosal epithelial cells, as well as several immune cell types, such as mast cells, macrophages, eosinophils, Th2 cells, and NKT cells, can generate IL-17E (IL-25) [20,21]. It promotes Th2 cell responses, while suppressing Th17 cell responses [22]. Previous research identified IL-28A as a newly defined type III IFN, with antiviral properties [22,23] and generated primarily by antigen-presenting cells (APCs) [23]. This cytokine can enhance Th17-induced inflammation, offer Th1 polarization, and suppress Th2 responses [24]. As a result, IL-6, IL-27, IL-17E, and IL-28A are key cytokines that may be implicated in the control of human immunological disorders caused by Th1, Th2, Treg, and Th-17 response imbalance [25].

Cameroon approved the option B+ treatment strategy 2014 to prevent mother-to-child transmission (MTCT) of HIV in 2014 [24,26]. However, effevirenz has lately been replaced with dolutegravir. According to data of a trial study conducted in Cameroon, a dolutegravir-based regimen, which is a low-cost, generic, fixed-dose antiretroviral therapy (ART) combination containing tenofovir, lamivudine, and dolutegravir (TLD), is the preferred first-line treatment for patients with HIV-1 infection [25]. Nevertheless, there are concerns about the overall risks and benefits of use in women of childbearing potential [27]. That is why this study aims to determine the prevalence of malaria infection, assess the occurrence of *P. falciparum* genetic diversity, and evaluate the antibody (IgG and IgM: AMA1, MSP1, MSP2, MSP3, and EBA175) and cytokine (IL-10, TNF-α, and IFNγ) response to malaria infection among pregnant women with and without HIV in Kumba.

Methods

Study Design and Population

This will be a hospital-based cross-sectional study that will run from March 2022 to February 2023. It will enroll pregnant women with and without HIV who are in the third trimester of pregnancy (26-32 weeks) and have willingly accepted to participate in the study by signing a consent form. During delivery, samples will be collected and questionnaires will be appropriately filled.

Study Site

The study will be conducted in Kumba, which is a metropolitan city in Meme Division of the southwest region (SWR) of Western Cameroon. Meme Division is 1 of the 6 divisions of the SWR of Cameroon. It is made up of 5 subdivisions: Kumba I, II, and III (largely urban) and Mbonge and Konye (dominantly rural) [28].

Ethical Considerations

Ethical clearance for this study has been obtained from the Institute for Advanced Medical Research and Training (IAMRAT), College of Medicine, University of Ibadan, Nigeria (ID NHREC/05/01/2008a). However, ethical clearance from Cameroon has been obtained from the Institutional Review Board of the Faculty of Health Sciences at the University of Buea (ID 2022/1655-02/UB/SG/IRB/FHS). Administrative clearance has been obtained from the Ministry of Public Health, Regional Delegation of Public Health for the SWR (ID R11 /MINSANTE/SWR/RDPH/PS/276/281). Further authorization has been obtained from the Meme Health District Health service (ID 12/022/MINSANTE/RDPHSW/KHD/DMO/048). Directors of the health facilities involved have also provided an authorization letter for the study to take place in their various facilities. Participants who wish to participate in the study will first sign an informed consent form. For participants who are unable to read or write, the information will be read out and explained to them and their thumbprints will be taken. The study will consider pregnant women with and without HIV who are in the third trimester of pregnancy and are fully aware of their viral load counts.

Sample Size Determination

The estimated sample size for the study was calculated using the Cochrane formula [29]. The estimated prevalence of malaria among pregnant women with HIV is 81%, as obtained from a study looking at malaria prevalence in pregnant women with and without HIV in neighboring Nigeria [30]. The critical value and standard value for the corresponding level of confidence were 1.96, and the margin of error was 0.05. The estimated sample size is 236. The ratio of pregnant women with to those without HIV will be 1:1, which therefore implies that the total estimated sample size is 472. That is, 236 (50%) pregnant women with and 236 (50%) pregnant women without HIV will be enrolled in the study.

Inclusion and Exclusion Criteria

Inclusion Criteria

The study will enroll only pregnant women who are in their third trimester of pregnancy—that is, within 26-32 weeks of pregnancy—and who willingly provide their consent to participate in the study. The study will also consider only pregnant women who are aware of their HIV status as well as viral load. In addition, the study will accept only those attending antenatal care (ANC) visits at the selected health facilities and who are willing to deliver in the facility of enrolment.

Exclusion Criteria

The study will not consider pregnant women who are not in their third trimester of pregnancy and have not signed the informed consent form to participate in the study. All those who will be attending ANC visits at the selected health facilities but are not willing to deliver in those health facilities will not be considered.

Sampling Technique

A probability proportionate to size sampling will be used to determine the number of participants to be recruited in each health institution (Table 1). A simple random sampling method will be used each day to recruit participants as they come for their ANC visits to the selected health facilities.

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Table 1. Number of participants to be recruited in each of the selected health facilities (N=1180).

Sample	General Hospital Kumba			District Hospital Kumba-town			Presbyterian Hospital Kumba			Kossala Integrated Health Center Kumba			Catholic Hospital Kumba		
	2021 Stat[a], n (%)	*P* value	PSS[b], n (%)	2021 Stat, n (%)	*P* value	PSS, n (%)	2021 Stat, n (%)	*P* value	PSS, n (%)	2021 Stat, n (%)	*P* value	PSS, n (%)	2021 Stat, n (%)	*P* value	PSS, n (%)
Pregnant women with HIV	10/718 (1.4)	.014	3/27 (11.1)	10/280 (3.6)	0.036	8/27 (29.6)	20/800 (2.5)	.025	6/27 (22.2)	13/765 (1.7)	.016	4/27 (14.8)	17/685 (2.5)	.025	6/27 (22.2)
Pregnant women without HIV	708/718 (98.6)	.986	233/1153 (20.2)	270/280 (96.4)	0.964	228/1153 (19.8)	780 /800 (97.5)	.975	230/1153 (19.9)	752/765 (98.3)	.983	232/1153 (20.1)	668/685 (97.5)	.975	230/1153 (19.9)

[a]Stat: statistics.

[b]PSS: probability sample size.

Sociodemographic and Clinical Baseline of Study Participants

A well-structured semiquestionnaire will be used to collect demographic and clinical parameters from study participants. The questionnaire will be pretested at District Hospital Kumba-town before being issued to participants for data collection.

The result of the rapid diagnostic test and microscopy for each participant will be made available to them. This is to ensure that those positive for malaria should be placed immediately on treatment.

Sample Collection

Briefly, 3 mL of the mother's peripheral (venous) blood, placental blood, and baby cord blood will be collected into EDTA, heparinized, and sodium-citrated tubes, respectively. A capillary puncture will be made to collect the sample, and a thick-film smear will be prepared for microscopy. Smears will be allowed to air-dry and then carefully placed in well-cleaned slide boxes to be stored for further analysis.

Laboratory Analyses

Thick-Film Microscopy

The thick-film smears will be stained with 10% Giemsa for 15 minutes, and the slides will be rinsed and allowed to air-dry. After that, the smears will be examined for the presence of *P. falciparum* under the 100X oil emission objective of the microscope. The parasite density will be calculated using the formula [31]:

> Parasite density = (Number of parasites counted per 200 white blood cells [WBCs]/200) × 8000.

Rapid Diagnostic Test for Malaria

A drop of about 50 µL will be used to determine malaria infection in all the enrolled participants using an SD-Bioline RDT kit, which detects histidine-rich protein II and lactate dehydrogenase. After the application of the sample and buffer, the kit will be allowed to stand for 15 minutes according to the manufacturer's instructions, and results will be interpreted qualitatively and recorded.

DNA Extraction

Drops of venous, placental, and cord blood will be blotted on filter paper and allowed to air-dry. The blotted filter paper will be used to extract the DNA of malaria parasites using the hot chelex extraction method, as described by Musapa et al [32].

Nested Polymerase Chain Reaction

The DNA extract will be used to perform nested PCR using the mitochondria (cytochrome C oxidase 3 [Cox-3]) primers for the detection of *P. falciparum*, as described by Lloyd et al [33].

Genetic Diversity of MSP1, MSP2, and EBA175 Using Nested PCR

A portion of the DNA extract from placental and cord blood will be used to determine the genetic diversity for samples that test positive for *P. falciparum* at the level of placental and cord blood. The 3 polymorphism loci MSP1, MSP2, and EBA175 will be amplified using specific primers targeting the alleles of *P. falciparum* in nested PCR. Primary amplification followed by secondary PCR using specific primers for K1, Mad20, and RO33 (for *MSP1*) and 3D7 and FC27 (for *MSP2*) allelic families will be performed [34]. Primer sequences have been previously described [35]. For the EBA175 loci, specific primers targeting the F1 loop, F2 loop, and C loop will be used to determine the different alleles responsible for infection, as described previously [36].

Sequencing Analysis

A total of 10 samples positive for *MSP1*, *MSP2*, *MSP3*, and *EBA175* at the level of placental and cord blood will be randomly selected and sent for analysis to the Inqaba Biotechnical Industry in Nigeria for sequencing to identify and study the DNA sequences of the alleles responsible for placental and transplacental infection.

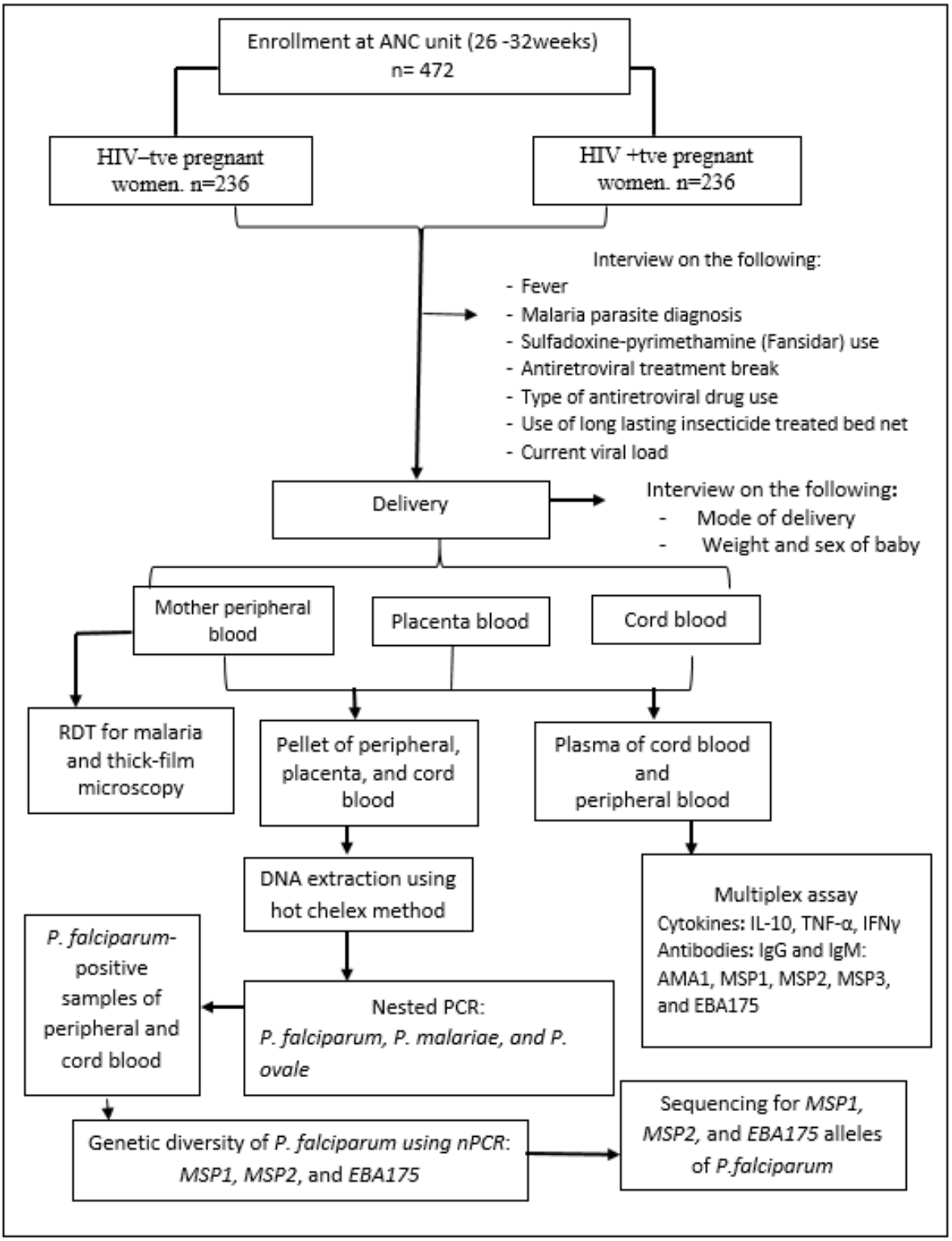
Cytokine and Antibody Analysis Using the Luminex Technique

The stored plasma will be used to determine levels of cytokines IL-10, TNF-α, and IFNγ using a magnetic multiplex screening assay (Luminex) with the help of a Human Multi-Analyte Premixed Kit (R&D Systems Inc, Minneapolis, MN, USA) [14]. A portion of the plasma will be used to evaluate the IgG

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antibody response level to MSP1, MSP2, and EBA175 using the multiplex assay, as described in previous studies for the detection of IgG antibodies to malaria [12,37]. A summary flowchart of the entire study can be seen in Figure 1.

Figure 1. Summary flowchart for the recruitment of participants into the study. AMA1: apical membrane antigen-1; ANC: antenatal care; EBA: erythrocyte-binding antigen; IFNγ: interferon gamma; IgG: immunoglobulin; IgM: apical membrane antigen-1; IL: interleukin; MSP: merozoite surface protein; nPCR: nested polymerase chain reaction; PCR: polymerase chain reaction; *P. falciparum*: *Plasmodium falciparum*; *P. malariae: Plasmodium malariae*; *P. ovale: Plasmodium ovale*; RDT: rapid diagnostic test; TNF-α: tumor necrosis factor alpha.



Data Management and Analyses

Data will be entered into Microsoft Excel, cleaned, and transformed for the different analyses to be performed. SPSS Statistics (IBM Corp) and STATA will be used for statistical analysis. A normality test will be performed to determine the different parametric and nonparametric tests to be used for the different analyses.

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Descriptive analysis of the general study population will be conducted, and both the mean and median of each parameter will be considered. The chi-square test will be performed to analyze categorical variables, and the Student *t*-test/Mann-Whitney *U* test will be performed to analyze continuous and categorical variables. The Kruskal-Wallis test/ANOVA will be conducted to analyze continuous and more than 2 categorical variables, while linear regression/Spearman correlation will be performed for multivariate analysis to determine the strength of association between different factors of the study and our dependent variables. All *P* values <.05 will be considered statistically significant. BioEdit 7.0.0 software will be used to align the nucleotide sequences of different genes after sequencing. Phylogenetic tree searching will be performed using the maximum-likelihood (ML) method in MEGA V6.0.

Results

The prevalence of malaria infection; the occurrence of *P. falciparum* genetic diversity of MSP1, MSP2, MSP3, and EBA175; and the total antibody (IgG and IgM: AMA1, MSP1, MSP2, MSP3, and EBA175) and cytokine (IL-10, TNF-α, and IFNγ) response to malaria among pregnant women with and without HIV will be evaluated.

The first part of the project funding was in December 2021, the second part was in May 2022, and the third part was in December 2022. Currently, three-fourth of the project funds have been released. Data and sample collection started in March 2022 and will end in February 2023. A total of 218 participants have been enrolled: 193 (88.5%) pregnant women without HIV and 25 (11.5%) pregnant women with HIV (see Table 2).

Table 2. Current level of enrollment of participants into the study (N=218).

Sample	General Hospital Kumba, n (%)	District Hospital Kumba-town, n (%)	Presbyterian Hospital Kumba, n (%)	Kossala Integrated Health Center Kumba, n (%)	Catholic Hospital Kumba, n (%)	Total, n (%)
Pregnant women with HIV (n=25)	7 (28)	6 (24)	6 (24)	0	6 (24)	25 (100)
Pregnant women without HIV (n=193)	25 (13.0)	40 (20.7)	10 (5.2)	33 (17.1)	85 (44.0)	193 (100)
Total	31 (14.2)	45 (20.6)	16 (7.3)	33 (15.1)	93 (42.6)	218 (100)

Discussion

Main Findings

Immune development during pregnancy is important as it determines the resistance of pregnant women to malaria transmission. Few studies have shown that women develop protective immunity against pregnancy-associated malaria (PAM), which is thought to be due to the acquisition of antibodies to the parasite variant surface antigen 2 chondroitin sulphate A (VAR2CSA) [38]. This immunity becomes stronger, especially in multigravidae [38]. However, this does not appear to be the case with pregnant women with HIV, as studies have shown that HIV alters the immunity against malaria, making both primigravidae and multigravidae vulnerable to PAM [11]. Although studies looking at malaria prevalence have been carried out in Kumba, studies evaluating the immune response of pregnant women with and without HIV to malaria have not been conducted. This study will attempt to determine the prevalence of malaria infection, assess the occurrence of *P. falciparum* genetic diversity, and evaluate the antibody (IgG and IgM: AMA1, MSP1, MSP2, MSP3, and EBA175) and cytokine (IL-10, TNF-α, and IFNγ) response to malaria infection among pregnant women with and without HIV in Kumba.

In Nigeria, the prevalence of malaria infection among pregnant mothers with HIV was 81% compared to 75% among pregnant women without HIV [30]. When compared to mothers without HIV, mothers with HIV have more moderate parasitemia [30]. This finding is in line with a similar study from Kumba, Cameroon, which reported a 61.5% prevalence of malaria among pregnant women with HIV [39]. Even though the prevalence of malaria in Kumba is high, it would have been much higher if more sensitive diagnostic techniques, such as PCR, had been used for diagnosis in this study rather than traditional microscopy, whose sensitivity is dependent on technician expertise [40], and RDTs, which lack specificity due to the high possibility of cross-reaction of antibodies [39]. Kenji et al [40] discovered that PCR could diagnose 64 misdiagnosed cases that were missed by RDTs and microscopy. In addition, in the Republic of Congo, it was discovered that the prevalence of malaria infection is high in pregnant women attending antenatal facilities or hospitalized and that it increases when HIV infection is present [41]. However, in Jos, Nigeria, the prevalence of malaria infection reduced from 34.1% to 7.2% among women administered cotrimoxazole and from 25% to 10% among women administered SP-IPT for malaria prophylaxis [42]. According to some studies, HIV and AIDS cause immunosuppression, which reduces the overall immune response to malaria parasitemia, increasing the frequency of clinical malaria attacks [43,44]. Effective implementation of IPT strategies among pregnant women reduces their likelihood of malaria infection [42]. Nevertheless, studies in Ghana have also shown that HIV infection increases the rate of vertical transmission of malaria to children born to a mother with HIV [45]. This study was able to show that HIV-malaria coinfection is a significant predictor of adverse perinatal outcomes and neonatal morbidity [45]. However, although national guidelines in Cameroon recommend the use of cotrimoxazole for pregnant women with HIV and SP for pregnant women without HIV at all ANC visits [46], most health facilities suffer from drug

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shortages, forcing women to attend some ANC visits without medication. The effect can be seen in a study carried out in Cameroon, where not taking Fansidar for IPT was found to be associated with the development of malaria among pregnant women [1].

Studies have shown that *P. falciparum*, the most virulent species, has a wide genetic variety at all degrees of endemicity, which is not surprising, given that genetic diversity has been shown to be a function of transmission in specific regions [47,48]. Oboh et al [49] discovered that the prevalence of the *FC27* allele type in pregnant women isolates is higher (33.3%) than that in nonpregnant women (29.2%) when looking at the genetic diversity of *P. falciparum* (*MSP1* and *MSP2*) infection among pregnant women in Lagos, Southwest Nigeria [49]. This finding is in line with a similar study carried out in Yaoundé, Cameroon [50]. Although no study has been conducted to assess the diversity of *P. falciparum* among pregnant women with and without HIV as 2 distinct entities, a couple of studies have evaluated the diversity of *P. falciparum* among individuals with HIV. In Mutengene, Cameroon, it was reported that the MSP1 allelic variants detected among patients with HIV were KI (65.22%), MAD20 (27.54%), and RO33 (27.54%), while the MSP2 allelic variants were FC27 (30.43%) and 3D7/IC (31.88%), which was high and associated with anemia [51]. A study in Senegal reported no difference in genetic diversity between *P. falciparum* isolates from patients with malaria and concurrent malaria-arbovirus in Kedougou [52]. However, the increased number of genotypes observed in the malaria group was attributed to the larger number of samples rather than the extensive genetic diversity of *P. falciparum* isolates from patients with malaria [52]. The frequency of all MSP1 allelic families (K1, MAD20, and RO33) and the IC/3D7 allelic family of MSP2 was high (>70%) and comparable between the 2 study groups in this study [52]. Nevertheless, clonal *P. falciparum* population dominance is expected to be observed in regions with declining endemicity as a result of genetic drift caused by scale-up interventions [53]. In other words, in parasite populations where control efforts have left behind lineages that create clusters of highly related parasites, the persistence of a specific haplotype throughout the year is expected [53,54]. As a result, unrelated parasites are unlikely to coexist in the same mosquito blood meal [53].

In addition, the protective role of antibodies to malaria cannot be overemphasized, as studies have shown that the antibody response plays a vital role in the protection of pregnant women against PAM infection [55,56]. A sero-surveillance study in Thai-Myanmar at the Shoklo Malaria Research Centre reported a significant variation in the antibody profiles of *Pf*AMA$_1$, *Pf*EBA175, *Pf*MSP$_2$, and *Pf*VAR$_2$CSA. Most controls' antibody profiles for *Pf*MSP$_3$ and *Pv*AMA$_1$ remained low throughout gestation regardless of malaria exposure, whereas the antibody response varied more among the cases and the control group of pregnant women with and without infection [57]. This study is in line with a study in Yaoundé that instead looked at the antibody response of malaria vaccine candidates among children [58]. This confirms that during a malaria infection, antibody levels should rise as an indication of immune protection. Alistair et al [59] even demonstrated that babies born to women with PAM with high levels of VAR2CSA antibodies are protected against the vertical transmission of malaria and have a higher mean birth weight than those with low VAR2CSA antibody levels [59].

In contrast, studies have shown that HIV infection amplifies the effect of malaria, especially among pregnant women [39,43,44]. One of these effects is the dysregulation of immunity to malaria in mothers and even their children exposed in utero [12,60]. In Yaoundé, it was reported that IgG levels to CSP and TCC were lower in mothers with HIV, as were cord IgG levels to CSP, MSP1, and TCC in neonates born to mothers with HIV [12]. This was in line with a study in Kenya that reported that HIV infection is associated with a decrease in the magnitude and breadth of IgG responses to merozoite antigens, as well as a delay in the age-related acquisition of the IgG antibody response to schizont extract [9]. The study also revealed that children with HIV are less likely to be high responders to AMA1 [9]. This effect can be seen in children, as studies have reported that children exposed to HIV are more susceptible to infections than children not exposed to HIV [60]. However, there is still a lack of understanding of why children born to these women are more susceptible to infections [60]. To better understand why children exposed to HIV are more susceptibility to infections, such as malaria, studies evaluating the effect of HIV infection on the vertical transfer of mononuclear WBCs, as well as a longitudinal study monitoring the immune response of these children exposed over time, are needed.

Cytokines and chemokines are elevated in peripheral blood during an acute malaria infection and contribute to parasite clearance, but they are also likely to be responsible for many of the symptoms and pathological changes seen during malaria [61,62]. The balance of pro- and anti-inflammatory signals appears to play a significant role in determining the outcome of an infection (ie, whether it leads to protection or immunopathology) [62]. Eduard et al [63] reported that an imbalanced pro-inflammatory cytokine response may exacerbate infection severity. Among pregnant women in Cameroon, it was realized that placental malaria reduces maternal plasma levels of IL-17E, IL-27, and IL-28A, as well as neonatal plasma levels of IL-17E and IL-28A, which may aid in parasite clearance and increase child birth weight [14]. This is in line with a similar study carried out by Megnekou et al [64]. Nonetheless, Djontu an coworkers [65] showed that IL-28A, IL-27, and IL-17E levels are higher in cord plasma than in maternal peripheral plasma and that they correlate positively with increasing baby birth weight. This positive relationship between birth weight and both Th1- and Th2-promoting cytokines (IL-27, IL-28A) is consistent with the findings of Chêne et al [65], who found a link between low birth weight and lower levels of IFNγ and IL-5 in intervellous plasma samples from Beninese women. A study carried out in Abia State, Nigeria, showed that cytokine levels in the same woman's peripheral and placental blood may differ [66]. It was realized that IFNγ is significantly higher in peripheral blood than in placental blood. IL-4 and IL-10 levels were significantly lower in peripheral blood than in placental blood [66].

Among pregnant women with HIV, it was discovered that cytokine activity during pregnancy, as measured by plasma

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cytokine concentrations, varies with antiretroviral therapy and *P. falciparum* coinfection [67]. In Mozambique, it was reported that among adults with HIV, IL-8 and IFNγ-induced protein 10 (IP-10) play a complex role in inflammation during *P. falciparum* infection and a potential pathogenic role [67]. Another study reported that patients with HIV and cerebral malaria have lower median plasma levels of TNF-α and IL-10 than patients without HIV [68]. This goes to confirm that HIV affects the cytokine response to malaria infection. Nevertheless, information about the cytokine response to malaria among pregnant women with HIV is scanty. However, studies comparing the levels of cytokine response in pregnant women with HIV and with and without malaria, as well as pregnant women without HIV and with and without malaria, are required to better understand the role of cytokines in the pathogenesis of malaria.

Future Directions

There is a need for research into the prevalence of malaria among pregnant women in Kumba, considering all trimesters. It is also necessary to conduct a study on *P. falciparum* resistance to SP-IPT as well as a longitudinal study on children born to mothers with HIV in order to understand why these children are more vulnerable to infections.

Conclusion

The results of previous studies depict that HIV affects the prevalence of malaria among pregnant women irrespective of gravidity; malaria prevalence turns out to be much higher among pregnant women with than pregnant women without HIV. It was also revealed that more *P. falciparum MSP1* alleles are associated with malaria infection among individuals with HIV and that genetic diversity is a function of malaria transmission in specific regions. In addition, HIV infection lowers the level of IgG response of antibodies to malaria infection for both mother and newborn babies. The likelihood of children with HIV to develop an immune response to AMA1 is low. HIV infection also alters the levels of the pro- and anti-inflammatory cytokine response, contributing to the lack of immune parasite clearance and parasite pathogenicity.

The findings of this work will be published in peer review journals and will be presented in seminars as well as conferences. Copies of the work will be submitted at the Pan-African University of Life and Earth Sciences Institute, University of Ibadan, Nigeria; the University of Buea; and the hospitals where the samples were collected. A copy will also be sent to the Union for African Population Studies.

Acknowledgments

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Data Availability

The terms and conditions established by the local ethical committee will govern whether the data sets generated/analyzed during this study will be made public. However, upon reasonable request, they will be made available to the corresponding authors.

Authors' Contributions

BNO conceived the project and designed the study protocol. JDB and DSN contributed ideas and supervised the project, while ZF and ELF contributed ideas and reviewed the protocol. AH and BNO in the laboratory team were in charge of sample analyses.

Conflicts of Interest

None declared.

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Abbreviations

AMA1: apical membrane antigen-1
ANC: antenatal care
CSP: circumsporozoite protein
EBA: erythrocyte-binding antigen
IFNγ: interferon gamma
Ig: immunoglobulin
IL: interleukin
IPT: intermittent preventive treatment
MSP: merozoite surface protein
PAM: pregnancy-associated malaria
PCR: polymerase chain reaction
***P. falciparum*:** *Plasmodium falciparum*
RDT: rapid diagnostic test
SP: sulfadoxine-pyrimethamine
SWR: southwest region
TCC: terminal complement complex
TGF: transforming growth factor
Th cell: helper T cell
TNF-α: tumor necrosis factor alpha
Treg: regulatory T-cell
WBC: white blood cell

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Protocol

An Intervention Program to Reduce Medication-Related Problems Among Polymedicated Home-Dwelling Older Adults (OptiMed): Protocol for a Pre-Post, Multisite, Pilot, and Feasibility Study

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Abstract

Background: Effective medication management is one of the essential preconditions for enabling polymedicated home-dwelling older adults with multiple chronic conditions to remain at home and preserve their quality of life and autonomy. Lack of effective medication management predisposes older adults to medication-related problems (MRPs) and adverse health outcomes, which can lead to the degradation of a patient's acute clinical condition, physical and cognitive decline, exacerbation of chronic medical conditions, and avoidable health care costs. Nonetheless, it has been shown that MRPs can be prevented or reduced by using well-coordinated, patient-centered, interprofessional primary care interventions.

Objective: This study aimed to explore the feasibility and acceptability of an evidence-based, multicomponent, interprofessional intervention program supported by informal caregivers to decrease MRPs among polymedicated home-dwelling older adults with multiple chronic conditions.

Methods: This quasi-experimental, pre-post, multisite pilot, and feasibility study will use an open-label design, with participants knowing the study's objectives and relevant information, and it will take place in primary health care settings in Portugal and Switzerland. The research population will comprise 30 polymedicated, home-dwelling adults, aged ≥65 years at risk of MRPs and receiving community-based health care, along with their informal caregivers and health care professionals.

Results: Before a projected full-scale study, this pilot and feasibility study will focus on recruiting and ensuring the active collaboration of its participants and on the feasibility of expanding this evidence-based, multicomponent, interprofessional intervention program throughout both study regions. This study will also be essential to projected follow-up research programs on informal caregivers' multiple roles, enhancing their coordination tasks and their own needs. Results are expected at the end of 2024.

Conclusions: Designing, establishing, and exploring the feasibility and acceptability of an intervention program to reduce the risks of MRPs among home-dwelling older adults is an underinvestigated issue. Doing so in collaboration with all the different actors involved in that population's medication management and recording the first effects of the intervention will make this pilot and feasibility study's findings very valuable as home care becomes an ever more common solution.

Trial Registration: Swiss National Clinical Trials Portal 000004654; https://tinyurl.com/mr3yz8t4

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KEYWORDS

protocol; pilot study; feasibility; medication safety; medication-related problems; medication management; home-dwelling older adults; informal caregivers; interprofessional collaboration; patient-centered care; quasi-experimental; pre-post study; polypharmacy

Introduction

Background

Older adults with multiple chronic health conditions—particularly those with cognitive impairment—frequently depend on complex medication regimens [1]. Although the use of ≥5 medications, known as polypharmacy [2], may be clinically appropriate in many cases, inappropriate prescriptions may put older adults at a greater risk of medication-related problems (MRPs) and adverse health outcomes [3,4]. MRPs can lead to degradation in a patient's acute clinical condition, physical and cognitive decline, an exacerbation of chronic medical conditions, and avoidable health care costs [5,6]. This public health issue has been highlighted in various European countries, including Portugal and Switzerland [7,8].

Nonetheless, MRPs have been demonstrated to be preventable or reducible using well-coordinated, patient-centered, interprofessional primary care [4,5,9]. Current evidence-based strategies for medication safety and the prevention of MRPs include medication reconciliation, systematic and comprehensive reviews of prescribed medications (including deprescribing), and electronic medication management systems [10,11]. Medication reconciliation is a well-documented evidence-based practice involving creating and updating a single list of an older adult's currently prescribed medications [12] and then systematically and comprehensively reviewing them. Prior research has shown that hospital discharge documents received by primary care professionals are frequently inaccurate and lack key information [13]. Regular medication reconciliation reduces medication errors owing to consistent communication during transitions of care, including changes in clinical settings, medical practitioners, or the level of care [14]. Regularly and systematically reviewing prescribed medications is a straightforward, effective means of reducing inappropriate prescribing and prescribing cascades and is, therefore, a preventive strategy for avoiding MRPs [15]. Inappropriate prescribing includes potentially inappropriate medications and potential prescribing omissions [15]. Existing assessment tools—such as the STOPP (Screening Tool of Older Persons' Prescriptions) and START (Screening Tool to Alert to Right Treatment) criteria—recognize the dual nature of inappropriate prescribing by including a list of potentially inappropriate medications (STOPP criteria) and potential prescribing omissions (START criteria) [16]. Complementary to this, the regularly updated American Geriatrics Society's Beers Criteria is a list of potentially inappropriate medications that older adults should avoid in most situations or in connection with particular health conditions [17]. By reducing inappropriate prescriptions, medication reviews also prevent prescribing cascades—a phenomenon in which an MRP is misinterpreted as a new medical condition, leading to the inadvertent prescription of a new, unnecessary medication to treat it [18].

Implementing effective primary care medication management for home-dwelling older adults with multiple chronic conditions should be a priority to address and prevent adverse health outcomes, avoid hospital admissions, promote and maintain autonomy in their daily lives, and, consequently, help them remain at home [19]. Primary care management requires interprofessional collaboration across different health care and social care providers, organizations, and departments [20]. Indeed, the complexity of dealing with home-dwelling older adults with multiple chronic conditions and needs leads them to be significant users of health services and consult different health care professionals [21]. Besides prescribers—usually general practitioners (GPs) and different specialist physicians—pharmacists, nurses, and other allied health professionals may also be involved in medication management [20]. Collaborative home medication reviews (ie, involving a GP and pharmacist) have demonstrated their effectiveness in preventing, detecting, and resolving MRPs among home-dwelling older adults [20]. Furthermore, adherence to prescribed medication can be improved by pharmacist- and nurse-led interventions [22-25]. However, the number of health care professionals consulted by home-dwelling older adults has been directly associated with fragmented and uncoordinated care [20]. Moreover, different health care professionals may have different treatment preferences, leading to differing prescriptions. Thus, home-dwelling older adults with multiple chronic conditions often receive inefficient and ineffective care [26] or uncoordinated care, even though they are more likely to benefit from it [27]. Failure to coordinate care contributes to MRPs [20]. Older adults who consult ≥3 health care professionals report receiving conflicting advice, making it difficult for them to know whose guidance they should follow. Inadequate explanations about medication result in omissions and incorrect dosages, but they can also lead to anxiety and confusion among older adults [28]. Older adults' safety could benefit from a more empowering approach, with health care providers sharing information on best practices in medication management and agreeing on responsibilities with older adults and their informal caregivers [29]. The World Health Organization defines empowerment as "a process in which patients understand their role, are given the knowledge and skills by their health care provider to perform a task in an environment that recognizes community and cultural differences and encourages patient participation" [30]. Four components have been reported as being fundamental to the process of patient empowerment: (1) they understand their own role, (2) they acquire sufficient knowledge to engage with their health care provider, (3) they develop skills, and (4) there is a facilitating environment [31]. To the best of our knowledge, these 4 components have never been explored for empowering older adults' and informal caregivers' medication management

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skills and promoting their active engagement in reducing the risk of MRPs.

In addition to health care professionals' contributions to effective medication management and identifying the risks of MRPs, informal caregivers could help ensure the safe and appropriate use of medication at home by older adults with multiple chronic conditions, notably among those who may also have a cognitive impairment or psychopathological disorder [32-34]. Informal caregivers are defined as any family member, neighbor, or friend who assists a dependent older adult. That assistance, help, care, or physical presence must be regular for ≥6 months, for at least 2 basic or instrumental activities of daily living, or to ensure patient safety [35]. Further interventional studies are required to explore how informal caregivers can be efficiently supported in their roles as medication managers, notably through the use of up-to-date, accurate, and easily understandable medication plans. Primary health care professionals should be assigned the task of cooperating with informal caregivers and integrating their shared decision-making experiences [32-34].

Previous research has shown the effectiveness of interprofessional intervention programs for reducing MRPs. These programs include risk assessments, health education for older adults and their informal caregivers, digital applications, and specialized counseling services or interventions provided by pharmacists and advanced practice nurses [32-34]. These elements should be tested in a standardized, evidence-based, multicomponent, interprofessional intervention program that embeds care in the context of where and how older adults live to prevent the onset or progression of MRPs.

Objectives

Before conducting a full-scale study with sufficient statistical power, a pilot and feasibility study is critical in the process of developing and testing the intervention. This is "a small-scale test of the methods and procedures to be used on a larger scale" [36]. Thus, our pilot and feasibility study's goal is not to test hypotheses about our intervention's impact but to assess the feasibility and acceptability of our approach [37].

Pilot Study Design

This quasi-experimental, pre-post, multisite pilot and feasibility study will focus on the feasibility components using an open-label design with participants knowing the study's objectives and relevant information. This will support the development of a standardized, evidence-based, multicomponent, interprofessional intervention program to reduce MRPs.

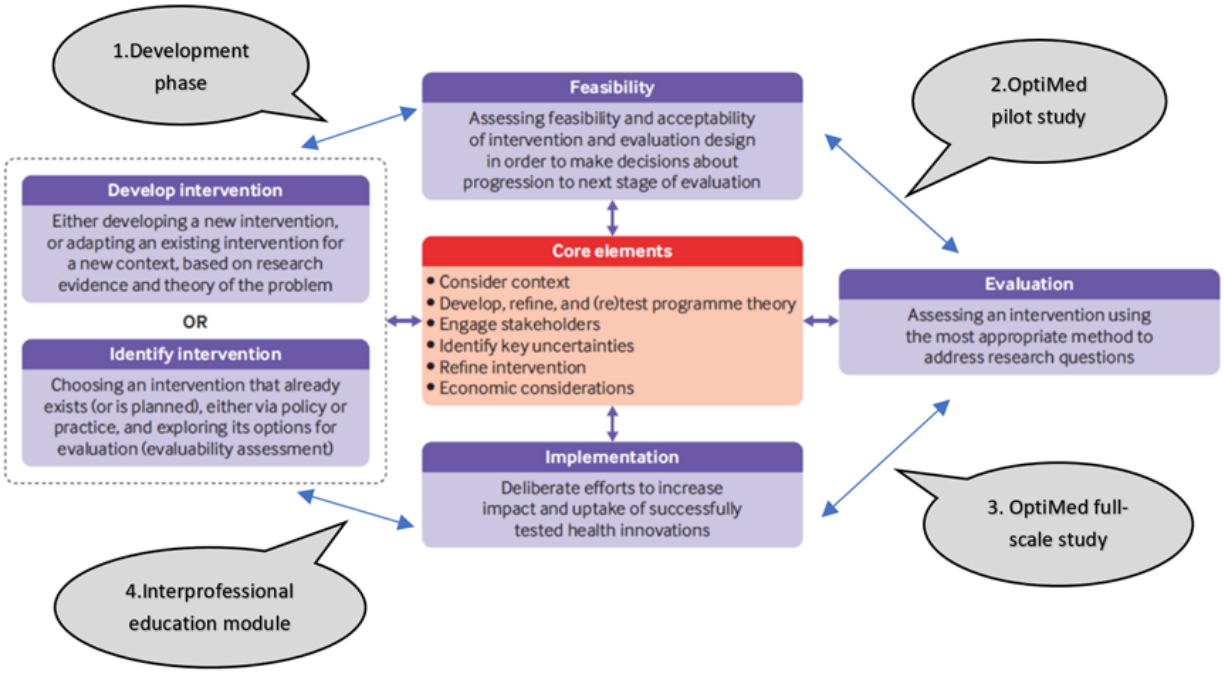
The OptiMed Pilot Study's Framework

Intervention studies in primary care are typically complex, multicomponent, interprofessional, and standardized, requiring considerable planning to be conducted successfully [38]. Thus, in accordance with the Medical Research Council's framework guidelines, we carefully planned the different steps required for the successful execution of this project with sufficient statistical power and the necessary number of participants in both countries (Figure 1) [39]. Designing the OptiMed pilot and feasibility study protocol is part of the development phase, which includes developing all the study's different components: identifying research gaps and the risks of MRPs, describing relevant concepts, and designing the intervention. Although the OptiMed pilot study (phase 2) will allow us to explore and test the feasibility of conducting the full-scale OptiMed study (phase 3), the latter will assess the effectiveness of the evidence-based, multicomponent, interprofessional medication management intervention program for polymedicated home-dwelling older adults. A comparative analysis of the resources used (costs) and outcomes obtained (effectiveness) will help estimate the health and non–health costs and benefits of this intervention program. As a secondary end point, we also expect to develop and implement a Swiss-Portuguese interprofessional training course about optimizing medication management among polymedicated home-dwelling older adults receiving community-based health care (phase 4).

Furthermore, the following 4 concurrently interacting components that improve the primary care of home-dwelling older adults with multiple chronic conditions—previously identified by Boult and Wieland [40]—will help to operationalize and implement the intervention program: (1) appropriate tools to comprehensively assess the risks associated with MRPs; (2) evidence-based, multicomponent, interprofessional care planning, interventions, and monitoring; (3) the promotion of active engagement in that care by patients and informal caregivers; and (4) coordination between professionals to ensure the best patient care. All 4 concurrent interacting components were tailored to meet the patient's goals and preferences. In this pilot study, these 4 components will be integrated into a medication management program focused on the context surrounding polypharmacy. Assigning roles and respecting the competencies of each member of the program's interprofessional team is key to ensuring optimal coordination and a systematic team approach.

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Figure 1. The 4 phases of the pre-post multisite OptiMed study and their relationships with the Medical Research Council's framework guidelines for complex interventions [38,39].



Methods

Participants, Interventions, and Outcomes

Study Setting

The OptiMed pilot study will be conducted in 2 primary health care centers (PHCs): the PHC "Unidade de Saúde Familiar Santiago–Marrazes" in Leiria, Portugal, and another in the French-speaking part of Switzerland.

Eligibility Criteria

The research population will include polymedicated home-dwelling adults aged ≥65 years, both men and women, at risk of MRPs and receiving community-based health care. Purposive sampling will recruit older adults taking ≥4 medicines per day and presenting with a risk of an MRP, as assessed using the doMESTIC risk tool, whose psychometric validation is ongoing. The criterion of ≥4 drugs is based on the Delphi study that developed this tool [41]. Older adult participants at risk of MRPs will be integrated into our investigation if their informal caregiver is involved in medication management and they provide informed written consent to participate. On the basis of our clinical experience, being a significant partner in an older adult's medication management involves at least one of the following activities: accompanying the patient to health consultations, assistance in obtaining medication, collecting or delivering medication, assistance with preparing or taking medication, monitoring effectiveness and side effects, assistance in maintaining the medication schedule, and organizing home care support.

Furthermore, throughout the investigation, each participant will be accompanied by the health care professionals designated as the professional most involved in their medication management. Table 1 presents the inclusion and exclusion criteria for each group of participants.

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Table 1. Inclusion and exclusion criteria for OptiMed pilot study participants.

Participants	Inclusion criteria	Exclusion criteria
Study participants		
Polymedicated home-dwelling older adults	• Aged ≥65 years for both men and women • People with multiple chronic conditions (≥2) • Managing at least 4 ore than 90 days [2] (explored during recruitment) • At risk of MRPs[a] identified using the doMESTIC RISK[b] tool • Living alone or with a partner in a rural or urban area • Supported by a primary health care center • An informal caregiver is involved in medication management • Given their written informed consent (Multimedia Appendix 1)	• Unable to speak and understand French (Swiss site) or Portuguese (Portuguese site) • Moderate or severe dementia criteria (≥10 on the 6-CIT[c]) • No risk of MRPs (doMESTIC RISK tool score <5[d]) • No informal caregiver
Collaborating participants		
Informal caregivers	• Designated by the older adult as the most significant informal caregiver involved in their medication management • Aged ≥18 years • Given their written informed consent (Multimedia Appendix 2)	• Unable to speak and understand French (Swiss site) or Portuguese (Portuguese site) • Moderate or severe dementia criteria (≥10 on the 6-CIT) • No risk of MRPs (doMESTIC RISK tool score <5[d]) • No informal caregiver
Nurse primary care manager	• Working for a primary health care center • Designated by the older adult as playing a key role in their medication management • Given their written informed consent (Multimedia Appendix 3)	• Student • Apprentice
Community pharmacist	• Working in a community pharmacy • Designated by the older adult as playing a key role in their medication management • Given their written informed consent (Multimedia Appendix 3)	• Student • Apprentice
Physician	• Older adult's general practitioner or specialist physician • Designated by the older adult as playing a key role in medication management • Given their written informed consent (Multimedia Appendix 3)	• Student • Apprentice

[a]MRP: medication-related problem.

[b]doMESTIC RISK: Medication Safety in Home Care.

[c]6-CIT: 6-item Cognitive Impairment Test.

[d]As assessed by the research team.

Primary and Secondary Feasibility and Acceptability Outcomes

The primary objective of this pilot study is to explore the feasibility and acceptability of an evidence-based, multicomponent, interprofessional intervention program with the support of informal caregivers to decrease MRPs among polymedicated home-dwelling older adults with multiple chronic conditions. As per Eldridge et al [42], a feasibility study "asks whether something can be done, should we proceed with it, and if so, how." Therefore, in line with the Medical Research Council's framework guidance [39], our study will gather information about the feasibility of recruitment, participant retention, intervention adherence (adherence to instructions by participants), intervention fidelity, and intervention dose [36,43] (Textbox 1 [44]). The quantitative cutoff point for our feasibility outcomes will be successful with at least 70% of participants [45]. Given the older adult participants' advanced age and chronic health conditions, the number of withdrawals for health reasons may be higher than in other studies. Acceptability will be assessed by measuring participants' satisfaction with each assessment instrument, home visits, and the targeted education plan. The secondary objective is to test the different data collection tools planned for use in the full study.

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Textbox 1. Outcomes and measurements of the OptiMed pilot study's feasibility and acceptability, based on the United States National Center for Complementary and Integrative Research recommendations [44].

- Measurements of feasibility
  - The target population is recruited: the number screened per month, the number enrolled per month, and the average time between screening and enrollment
  - Study participants are retained: treatment-specific retention rates for study measurements and reasons for dropouts
  - Study participants adhere to their instructions: treatment-specific rates of adherence to the study protocol (in-person session attendance, homework, home sessions, etc) and treatment-specific measurements of competencies
  - The medication review is successful: treatment-specific fidelity rates, time invested, number of discrepancies between professional sources, number of discrepancies between patient-reported medication use and professional sources, number of questions, number of items needing clarification, number of recommendations made by the pharmacist, and number of pharmacist's recommendations adopted by the physician
  - The credibility of each component of the interprofessional intervention program is assessed as positive: ratings for treatment-specific expectations of benefit
  - The relationship between the dose of nursing [46] and response to the program is measured: amount, frequency, intensity, and duration
  - Study displays clinical relevance: how participants perceive the intervention program, using patient-reported outcome measures [47]. Identify what is relevant for participants (such as quality of life or remaining at home). Enabling a choice of which outcomes from the pilot study will go into the intervention
- Measurements of acceptability
  - Participants are satisfied with each assessment instrument, home visits, and the targeted education plan: acceptability ratings are calculated using quantitative assessments, reasons for dropouts, and treatment-specific preference ratings (pre- and postintervention)
  - Assessments are not considered too burdensome: the proportion of planned assessments that are completed; duration of assessment visits; reasons for dropouts; ease of use of the doMESTIC RISK tool; ease of use of the structured medication review template

According to the Consensus-based Standards for the Selection of Health Measurement Instruments (COSMIN) recommendations [48], if the pilot study is conclusive, then the full-scale OptiMed study will adopt the standardized Core Outcome Set for its clinical trials of a medication review for multimorbid older adult patients with polypharmacy, as previously reported by Beuscart et al [49] in 2018 (Multimedia Appendix 4).

Study Intervention

Completing the intervention program with 1 participant requires 5 weeks. After the older adult participant has been recruited via their nurse primary care manager working for their PHC, the intervention's first component involves their baseline assessment at a meeting conducted by a research nurse (t0). The research is explained to the older participant in detail, both orally and in writing, and the consent form is signed (Multimedia Appendix 1). After this, the older participant is asked to answer some sociodemographic and health-related questions and provide a complete list of their current medication prescription. The research nurse completes a questionnaire on the risk of MRPs—doMESTIC risk questionnaire (Multimedia Appendix 5). A first meeting was also conducted individually with the informal caregiver (who will also answer some sociodemographic and health-related questions and describe their role in medication management; Multimedia Appendix 6). The older adult participant is asked to identify the health care professionals (GP or specialist, nurse primary care manager, or community pharmacist) most involved in their medication management.

The second component involves a review of the prescribed medications in week 1 (t1), including a medication reconciliation and a structured medication analysis by the study's partnering pharmacist to identify drugs with a high risk of MRPs among older adults. This will use the STOPP and START criteria, and undertreated indications or missed therapies will use the START criteria [16]. The older adult participant's physician will be invited to participate in the review of prescribed medications in collaboration with the study's partnering pharmacist. They will discuss validated, evidence-based, and internationally recognized guidelines to reconsider beneficial or nonbeneficial therapies or to simplify and focus on specific care goals and adjust medications to be consistent with the guidelines. If the older adult participant's physician adopts none of the proposed changes, despite the medication review (t1) highlighting their relevance, the research team will inform the older adult participant of their physician's decision and invite them to proceed with the study.

On the basis of the baseline assessment (t0), the research nurse will use a joint consultation in week 2 to explore the needs and care goals of the older adult participant and their informal caregiver to reduce the risk of MRPs (t2). In collaboration with the designated health care professionals, the research nurse will then design a targeted patient-centered education plan to empower older adult participants' medication management and reduce the risk of MRPs (t2). This is based on a four-step patient empowerment process: (1) the patient understands their role, (2) the patient acquires sufficient knowledge to engage with their health care professionals, (3) the patient improves their skills, and (4) there is a facilitating environment [31]. Each older adult participant's plan will be unique and consider their preferences, medication literacy, and treatment adherence.

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During weeks 3 and 4 (t3), the research nurse will help the older adult participant and their informal caregiver to implement their targeted education plan (t2) aimed at empowering their medication management and promoting their active engagement in reducing the risks of MRPs. Two joint consultations will be organized among the older adult participant, their informal caregiver, and the research nurse (once each week). During planned home visits, the nurse will periodically evaluate the older adult participant's medication status (primary and secondary outcomes) and promote communication between different professional and nonprofessional actors involved in medication management.

The research nurse will complete a final assessment (t4) of each older adult participant's risks of MRPs in week 5 (35-40 days after t0) in collaboration with the study's partnering pharmacist. The occurrence of MRPs and medication-related hospital admissions will be investigated. Finally, the health care professionals designated by the older adult participant will assess the acceptability of the interprofessional intervention program aimed at reducing MRPs by completing a final questionnaire (Multimedia Appendix 7). The pilot study will explore possible biases so that they can be correctly addressed in the full study (Multimedia Appendix 8) [36,38].

As already described, the medication management intervention program guiding OptiMed's pilot study comprises 4 components based on concurrently interacting processes previously identified by Boult et al [40] (Multimedia Appendix 9).

The schedule of enrollment, interventions, and assessments is presented in Table 2. The pilot study will be conducted over 12 months, including the recruitment phase (Multimedia Appendix 10).

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Table 2. OptiMed schedule of enrollment, interventions, and assessments based on Standard Protocol Items: Recommendations for Interventional Trials [50].

Time point	Study period					
	Enrollment	Allocation	Postallocation			Final end point
	$-t_1$	t0	t1	t2	t3 Wk3, Wk4, Wk5	t4
Enrollment						
Eligibility screening	✓					
Informed consent	✓					
Other procedures (to complete)						
Allocation	Not applicable in the pilot study	Not applicable in the pilot study	Not applicable in the pilot study	Not applicable in the pilot study	Not applicable in the pilot study	Not applicable in the pilot study
Interventions						
Medication review process examining the risks of MRPs[a]						
Targeted education plan to empower older adults' and informal caregivers' medication management to reduce the risks of MRPs						
Implementing the targeted plan to reduce the risks of MRPs						
Assessments		✓				
Baseline variables						
Older adult participants' sociodemographic data health status, and risks of MRPs						
Informal caregivers' sociodemographic data		✓				
Health care professionals' sociodemographic and professional data		✓				
Final assessment of older adult participants' risks of MRPs						✓
Medication reconciliation[b]						
Number of discrepancies			✓			
Number of clarifications needed			✓			
Medication analysis[b]						
Overuse			✓			✓
Underuse			✓			✓
Potentially inappropriate medications			✓			✓
Clinically significant drug-drug interactions			✓			✓
Monitoring requirements			✓			✓
Adverse events[a]						
Medication-related hospital admissions						✓
MRPs						✓

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Time point	Study period					
	Enrollment	Allocation	Postallocation			Final end point
	$-t_1$	t0	t1	t2	t3 Wk3, Wk4, Wk5	t4
Patient-reported outcomes[c] (will be defined by the pilot study)						✓
Feasibility outcomes						
Target population recruitment						✓
Retaining study participants						✓
Participants' adherence to what they are asked to do						✓
Medication reconciliation						✓
The burden of assessments						✓
Acceptability of each intervention						✓
The credibility of each intervention						✓
Relationship between the dose of nursing [46] and response to the program						✓

[a]MRP: medication-related problem.

[b]Primary outcomes.

[c]Secondary outcomes.

Sample Size and Recruitment

On the basis of the study by Hogget al [51], we planned to recruit 30 older adult participants (15 men and 15 women), 30 informal caregivers, and 30 health care professionals in collaboration with 2 PHCs: the Unidade de Saúde Familiar Santiago–Marrazes in Leiria, Portugal, and another in the French-speaking part of Switzerland. Nurse primary care managers partnering with the project will briefly explain the study to polymedicated home-dwelling older adults who meet the inclusion criteria. Eligible participants will be asked for permission to provide their names to the researchers, and a research team member will telephone them to ask for their agreement to participate in the study. If they agree, the first meeting with a research team member will be organized at the older adult participant's home or the PHC in the following few days. Given the 2 countries' different primary health care practices, eligible participants in Switzerland will be met at home, whereas participants in Portugal will be met at the PHC. Consenting older adult participants will be asked to designate the most significant informal caregiver, aged ≥18 years, involved in their medication management, and the research team will invite them to participate in the study. The older adult participants will be asked to designate the health care professionals (GPs or specialist physicians, nurse primary care managers, or community pharmacists) who are most prominently involved in their medication management. During the first meeting, the research nurse will explain the study's nature, purpose, and procedures to the older adult participant, along with its expected duration, potential risks and benefits, and any discomfort it may entail. Each older adult participant will be informed that participation in the study is voluntary, that they may withdraw from it at any time, and that the withdrawal will not affect their subsequent medical assistance and treatment.

Data Collection, Management, and Analysis

Data Collection Methods

Data on older adult participants' health status will be collected using the 6-item Cognitive Impairment Test (6-CIT), Tilburg Frailty Indicator (TFI), and the diagnosis list based on the 11th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-11). Current medication, previous MRPs, and the doMESTIC RISK tool will provide data on the risks of future MRPs and will be collected, when possible, from routinely collected PHC data or directly from older adult participants and their informal caregivers.

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Sociodemographic data and information about informal caregivers' contributions to their relatives' medication management will be collected. We will collect sociodemographic and professional data from health care professionals (GPs, nurse primary care managers, and community pharmacists), along with information about medication monitoring and follow-up, how they teach and train older adults and informal caregivers on medication management, how they assess their cognitive capacity to manage medication, stakeholder collaboration, and medication management.

The study will also collect participants' opinions on the acceptability of each intervention, reasons for dropout, and treatment-specific preference ratings (before and after the intervention).

Except for the doMESTIC risk tool, whose psychometric validation is ongoing, all other instruments in the study have demonstrated their reliability and validity in previous studies. Table 3 describes the measurements taken, the instruments used for data collection, and their respective purposes. To promote data quality, the nurses and pharmacists partnering with the study will undergo two 1-hour training sessions on assessment.

Table 3. Measurements and instruments used for data collection.

Participants	Measurements and instruments	Purpose
Study participants		
Home-dwelling older adults		
	Sociodemographic data (baseline assessment, t0; Multimedia Appendix 5)	Describe older adult participants' profiles (birthdate, gender household size, number of hospitalizations, and the date of the last hospitalization, etc)
	Six-item Cognitive Impairment Test (t0; Multimedia Appendix 5)	Perform brief cognitive screening recommended for use in primary care settings [52]
	TFI[a] (self-administered or at t0; Multimedia Appendix 5)	Assess multidimensional frailty among older adult participants via a self-administered questionnaire [53]
	11th revision of the ICD-11[b] diagnosis list (t0)	Describe older adult participants' morbidities based on the ICD-11 [54]. The list is useful when doing a medication analysis and evaluating prescription adequacy
	Current medication lists (t0)	Perform medication analysis (overuse, underuse, potentially inappropriate medications, and clinically significant drug-drug interactions) and medication reconciliation (number of discrepancies and clarifications needed)
	Previous MRPs[c] (t0)	Describe the history of past MRPs
	doMESTIC RISK Tool (t0 and final assessment, t4)	Identify older adult participants at a high risk of MRPs [41]
	Acceptability of the intervention [55] (t4; Multimedia Appendix 5)	Collect older adult participants' opinions on the acceptability of the medication management intervention program
Collaborating participants		
Informal caregivers		
	Sociodemographic data (t0; Multimedia Appendix 6)	Describe informal caregivers' profiles and their relationships with older adult participants
	Involvement in medication management (t0; Multimedia Appendix 6)	Describe types, frequencies, and intensities of informal caregivers' support activities
	Acceptability of the intervention [55] (t4; Multimedia Appendix 6)	Collect informal caregivers' opinions on the acceptability of the medication management intervention program
Health care professionals (nurse primary care manager, community pharmacist, and physician)		
	Sociodemographic and professional data (t0; Multimedia Appendix 7)	Describe professional caregivers' profiles and baseline involvement in medication management
	Acceptability of the intervention [55] (t4; Multimedia Appendix 7)	Collect professional caregivers' opinions on the acceptability of the medication management intervention program

[a]TFI: Tilburg Frailty Indicator.

[b]ICD: International Statistical Classification of Diseases and Related Health Problems.

[c]MRP: medication-related problem.

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Study Instruments

6-Item Cognitive Impairment Test

6-CIT was selected for the cognitive screening of older adult participants because it is brief, simple to apply, and requires no special training for administration. The 6-Item Orientation-Memory-Concentration Test was originally developed by Katzman et al [56] by shortening the Mental Status Test by Blessed et al [57]. The 6-CIT involves 3 temporal orientation tests (year, month, and time), 2 attention tests (counting backward from 20 to 1, reciting the months of the year in reverse), and 1 short-term memory test (a 5-item address) [52]. Scored out of 28, higher scores indicate greater impairment. The 6-CIT has been used in a broad range of settings, including screening for dementia in primary care, cognitive screening in acute care, large population-based studies, and Alzheimer disease studies [52]. In primary care, the English version's internal consistency (Cronbach α), stability over time (Pearson *r*), and agreement between successive tests (Cohen κ) reached values of .58, 0.62, and 0.45, respectively [58]. Sensitivity and specificity reached values of 0.49 and 0.92 at the 7/8 cutoff and 0.32 and 0.98 at the 10/11 cutoff, respectively [58]. The Portuguese version of the 6-CIT (6-CIT-P) presented a high test-retest reliability coefficient (r=0.95, P<.001; n=54), indicating good temporal stability [59]. 6-CIT-P has also shown strong internal consistency (Cronbach α=.88), and the corrected item-total correlations ranged between 0.32 and 0.90, representing a moderate-to-strong correlation between the items and total score. The 6-CIT-P and mini-mental state examination scores were strongly negatively correlated (r=−0.90) because of the polarity of the tests, indicating an acceptable convergent validity. The Global 6-CIT showed good sensitivity and specificity (82.78% and 84.84%, respectively) compared with the mini-mental state examination [59]. The French version is currently undergoing a validation study.

Tilburg Frailty Indicator

As polypharmacy has been associated with a higher incidence of frailty [60,61], the TFI will be used to assess multidimensional frailty among home-dwelling older adults [53]. Unlike other frailty assessment instruments, TFI does not focus exclusively on the physical dimension of frailty and does not include disability and diseases in its assessment. This contributes to a holistic perspective of human functioning in the community (including the physical, psychological, and social domains). The TFI consists of 2 parts: part A contains 10 questions on the determinants of frailty and multi-morbidity, whereas part B uses 15 questions to examine 3 domains of frailty (physical, psychological, and social) [53]. Each question is scored as 1 or 0. A total score of ≥5 suggests that a person is frail and the greater the score, the greater the degree of frailty is considered significant. The original English version's internal coherence demonstrated a satisfactory Cronbach α coefficient of .73 [62]. Construct validity between the different domains revealed significant Pearson correlation coefficients (P<.05): r=0.42 between the physical and psychological domains; r=0.19 between the physical and social domains; and r=0.18 between the psychological and social domains. Convergent and divergent validities were considered to be good. The TFI demonstrated good temporal-fidelity stability, with a frailty score of 0.90 after 2 weeks and 0.79 after 1 year [62]. The Portuguese version of the TFI showed good internal consistency (KR-20=0.78) and test-retest reliability (r=0.91), with Cohen κ coefficients showing substantial agreement for most items [63]. The French version is currently under validation.

doMESTIC RISK Tool

The doMESTIC RISK tool is used to identify patients at high risk of MRPs [41]. It is based on home-care–specific risk factors for medication safety as derived from the literature. Experts prioritized the tool's suggested items using a 2-round Delphi study. The final tool was statistically validated using a systematic medication review involving 150 home care patients. The tool's subsequent weighting improved the model's overall quality and resulted in a final doMESTIC RISK tool with 10 risk factors. The tool's strengths are its specific focus on the home care setting and the interprofessional input necessary for its completion [41]. French and Portuguese versions of the original tool will be used. The reliability, validity, and responsiveness of the doMESTIC RISK tool are being measured based on a quantitative analysis of field tests (factor analysis and item response theory) [48,64]. In this pilot study, an older adult's risk of MRPs and whether the medication management intervention program contributes to decreasing it will be assessed by 2 nurse research assistants in collaboration with 2 pharmacists using the doMESTIC RISK tool at the baseline assessment (t0) and the final assessment (t4).

Participant Retention and Completing Follow-up

On the basis of the best practice guidance [65], the following strategies will be used to promote the retention of older adult participants and informal caregivers and to complete follow-up:

- Involving informal caregivers.
- Allowing rest between measurements and interviews, as needed.
- Meeting older adult participants at home during visits by the PHC's home care services (Switzerland).
- Arranging transport to the meeting location or reimbursing transportation costs (Portugal).
- Keeping meetings short (<1 hour).
- Providing opportunities to build social support through organized educational sessions within the targeted plan.
- Keeping in touch by scheduling appointments in advance and sending reminders to both the older adult participant and informal caregiver.
- Providing regular feedback to study participants.

Participants will be able to withdraw their consent to participate in the study at any time, without having to justify themselves. Participants who discontinue, drop out, or deviate from the intervention program will be briefly interviewed to learn when and why they did so, and an intention-to-treat analysis will be conducted. In case of withdrawal from the study, the data collected will be anonymized using secuTrial search software and stored on secure servers at the School of Health Sciences, HES-SO Valais-Wallis, or at ciTechCare, Polytechnic of Leiria.

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Data Management

All data will be entered into the secuTrial electronic data capture system, either at the School of Health Sciences, HES-SO Valais-Wallis, or at ciTechCare, Polytechnic of Leiria. Original study forms will be scanned, stored electronically with limited access, and kept on file at the HES-SO and ciTechCare sites. Data entry screens will resemble the paper forms approved by the ethics committees. Data consistency will be ensured through various mechanisms, including referential data rules, valid values, range checks, and consistency checks against data already stored in the database (longitudinal checks). Checks will be applied when data are entered into a specific field and before they are committed permanently to the database. Modifications to the data in the database will be documented via an audit trail. Data in the secuTrial database will be retrievable through data entry applications. The types of activities that individual users may undertake will be regulated by the privileges associated with their user identification code and password.

The 2-country roll-out will allow greater standardization of the evidence-based, multicomponent intervention program for a future, full-scale, quasi-experimental, pre-post study. However, raw data will not be shared between countries, and the results obtained will be discussed only after being analyzed separately in each country. A joint publication is planned using aggregated data from the pilot study results.

Statistical Methods

The pilot study will compute descriptive statistics as distributions and central tendencies, as well as inferential statistics, to provide power analyses for the pilot study's proposed sample size. The pilot study's results will help provide a power analysis of the sample needed for a fully powered pre-post study. Analyses will be conducted in collaboration with a biostatistician using an up-to-date version of the SPSS software.

Handling Missing Data and Dropouts

We do not expect any missing data, as the protocol is limited and properly adapted to the potential participants' characteristics. The OptiMed pilot study will consider missing data and dropout rates as significant results for organizing recruitment, intervention adherence, acceptability, and subject retention in the full-scale study. Nevertheless, to fully evaluate the different components of the pilot study, we will replace dropouts with new participants until 30 of them have completed the study. Given the intervention program's 5-week duration and the older adult participants' multiple chronic health conditions (as they are all polymedicated), it is difficult to anticipate how many will complete the intervention and how many may interrupt it for health or availability reasons. This is also one of the rationales for conducting a pilot feasibility study before conducting a full-scale study.

Monitoring

Data Monitoring

secuTrial will help in monitoring both the pilot study and the full-scale study. Data monitoring will inform us of aspects of the study's conduct, such as ongoing recruitment, and help identify any need for adjustment.

Lausanne University Hospital's Clinical Trial Unit (CHUV-CTU) and Leiria's Regional Health Administration ("Administração Regional de Saúde" – ARS) will check the electronic case report forms (eCRFs) for consistency and completeness throughout the study. If an issue is detected, the monitor will open a query in the secuTrial software, and the investigator will be able to answer and correct the data in that software as needed. An overall data consistency check will be performed by the study monitor and the designated data manager. Any actions required to fix the data issues will be reported in the eCRFs. A final export of the data set will enable us to completely remove participants' identities, and the database will be locked.

Risk-Benefit Assessment

The research team will not add or change any medication. However, based on a medication review (made following validated, evidence-based, and internationally recognized guidelines), the study's partnering pharmacist may provide suggestions to older adult participants' GPs or specialist physicians. Thus, by participating in the project, older adult participants may be exposed to minor risks, such as a temporary alteration of their usual condition, if their physician modifies their treatment after discussion with the study's partnering pharmacist to avoid MRPs.

Medication management will be performed using validated, internationally recognized, and evidence-based guidelines for older adults. The medication management intervention program proposed to the older adult participants and their informal caregivers will be tailored (in intensity and duration) to each individual and will consider their health and medication literacy. This is important to avoid a lack of follow-up, particularly among those with a possible undiagnosed mild cognitive impairment. Older adult participants, informal caregivers, and prescribers should benefit from a more empowering approach to medication management.

Insurance

In case of any study-related damage or injury, the School of Health Sciences, HES-SO Valais-Wallis, and ciTechCare, Polytechnic of Leiria, may be liable for compensation, except for claims that arise from misconduct or gross negligence.

Auditing

Overview

CHUV-CTU and ARS will regularly monitor data quality and completeness. They will audit source documents in Switzerland and Portugal, respectively, with at least 1 research site monitoring visit every 6 months in each country throughout the study. The primary objectives of this study are education, support, and problem solving. The monitors will discuss the protocol in detail and identify and clarify any areas of weakness. The investigators will practice entering data so that the study monitors are assured of their proficiency in all aspects of data entry, query response, and communication with the CHUV-CTU and ARS. The monitors will audit the overall data quality and

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completeness, examine source documents and interview investigators, and confirm that the research site has complied with the protocol's requirements. The monitors will verify that all adverse events were correctly documented and consistent with the protocol's definition. They will review source documents (ICD-11 diagnosis list, current medication lists, and associated reports from PHCs) as needed to determine whether the data reported in secuTrial are complete and accurate. They will confirm that the regulatory binder is complete and that all associated documents are up to date. The regulatory binder should include the protocol, informed consent forms, ethics approval from both countries, and investigator agreements.

If a problem is identified during a visit (eg, poor communication with the CHUV-CTU and ARS, inadequate or insufficient staff to conduct the study, and missing study documents), the monitors will assist the research site in resolving its issues. Visits and electronic monitoring will focus on source document reviews and confirmation of adverse events. Monitors will verify the following variables for all study participants: date of birth, sex, signed informed consent, eligibility criteria, treatment assignment, adverse events, and end point. All parties involved will keep participants' data strictly confidential.

Ethics Approval

Ethics approval was obtained from the Human Research Ethics Committee of the Canton of Vaud (Commission cantonale d'éthique de la recherche sur l'être humain), Switzerland (2021-01843), and Leiria's ARS, Portugal (80-2021).

Protocol Amendments

Any substantial changes made to the study setup or organization, protocol, or relevant study documents will be submitted to the CER-VD and ARS for approval before implementation. In an emergency, deviations from the protocol may be made to protect human subjects' rights, safety, or well-being without the Ethics Committee's prior approval. Such deviations will be promptly documented and reported to the CER-VD and ARS.

Consent to Participate

All study participants will be provided with a participant information sheet and a consent form describing the study and providing sufficient information for them to make an informed decision about participation (Multimedia Appendices 4, 5, and 6). Participants will have up to 2 weeks to decide whether to participate in the study. Formal consent will be obtained using an approved consent form before the participant is sent for any study procedure. The investigator will sign and date the informed consent form simultaneously with the participant, 1 copy will be given to the study participant and the other will be retained in a secure location as part of the study records. Participants will also be requested to provide written informed consent for reusing the data in an encoded form.

Before the pilot study, the intervention program will be pretested on 3 to 4 study participants to evaluate how long, intense, and tiring it is. Participants' autonomy will be respected, and study participation will be voluntary. They will be able to refuse further participation or drop out of the study at any time. However, once collected, data will not be deleted. Throughout the process, the research team will tell the truth and ensure that it misleads neither its research partners nor the participants.

Older adult participants, their informal caregivers, and collaborating health care professionals will receive no compensation for their involvement in this research project. However, the study participants will benefit from the intervention program and provide superior support for medication management.

Confidentiality and Access to Data

Participant data will be handled with the utmost discretion and will only be accessible to authorized personnel who require that data to fulfill their duties within the scope of the study. In the eCRFs and other study-specific documents, participants will only be identified using their unique participant numbers. Study participants will be coded as follows: OPTIMED-01, OPTIMED-02, etc. Any links between that code and the participant's real identity will be protected by secuTrial, and only the research team will have access to the data collected. The types of activities that individual users may undertake will be regulated by the privileges associated with their user identification code and password. The original study forms will be scanned, stored electronically with limited access, and kept on a secure server at the School of Health Sciences, HES-SO Valais-Wallis, and at ciTechCare, Polytechnic of Leiria, for 20 years after the completion of the study.

Dissemination Policy

Knowledge transfer activities will promote this pilot study at professional and scientific conferences for primary health care professionals, within hospital care units, and to informal caregivers', patients', and older adults' associations. The findings of the pilot study will be submitted to a peer-reviewed journal.

Results

This paper describes the development of a pre-post, multisite pilot, and feasibility study to explore the feasibility and acceptability of an interprofessional intervention program to decrease MRPs among polymedicated, home-dwelling older adults with multiple chronic conditions. We expect our findings to provide sufficient methodological evidence regarding the rationale, design, and planning of the intervention to warrant a full-scale study. This methodological evidence will include approaches to recruitment and obtaining consent, ensuring adherence to each phase of the intervention program, and easing the burden of assessments. Although this pilot and feasibility study did not have sufficient statistical power to provide estimates of effect size, we expect that our findings will provide useful data to help define the final components of the full-scale study and research strategies.

Discussion

Designing, constructing, and exploring the effectiveness of an intervention program to reduce the risk of MRPs among home-dwelling older adults, in collaboration with all the different actors involved in their medication management, is an

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emerging but underinvestigated issue. Current knowledge in this area was developed in academic settings and acute and long-term care facilities; however, little is known about this topic in home care settings. Regarding the prevention of MRPs, research to date has been unable to simultaneously integrate the roles and perceptions of polymedicated home-dwelling older adults with multiple chronic conditions, their informal caregivers, and their health care professionals [66]. To close these gaps, our interprofessional intervention has been coconstructed with older adults and their informal caregivers and could contribute significantly to preventing hospital admissions, rehospitalizations, institutionalization in long-term care facilities, and early death. This could also limit the economic impact of MRPs on the already stretched health care systems [67]. The OptiMed study is a tailored intervention program based on a clear allocation of roles to reduce the risk of MRPs among home-dwelling older adults. This medication management program is underpinned by a complex intervention framework that includes development, implementation, and sustainability milestones [39]. It also considers the 4-fold aim of enhancing the patient's experience, improving population health, reducing costs, and improving health care professionals' working lives [68].

Acknowledgments

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Data Availability

The data sets used and analyzed during this study are available from the corresponding author upon reasonable request.

Authors' Contributions

FP and HV developed the original concepts. SGP, MdAD, CMM, and HV provided conceptual and methodological expertise in study design. CMM is the principal author of the doMESTIC risk tool. FP and HV were the major contributors to writing the manuscript. All authors have read, edited, and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Older adults' consent form (in French).
[DOCX File , 70 KB - resprot_v12i1e39130_app1.docx]

Multimedia Appendix 2
Informal caregivers' consent form (in French).
[DOCX File , 69 KB - resprot_v12i1e39130_app2.docx]

Multimedia Appendix 3
Health care professionals' consent form (in French).
[DOCX File , 68 KB - resprot_v12i1e39130_app3.docx]

Multimedia Appendix 4
Outcomes OptiMed full-scale study.
[DOCX File , 17 KB - resprot_v12i1e39130_app4.docx]

Multimedia Appendix 5
Older adults' questionnaire (in French).
[DOCX File , 87 KB - resprot_v12i1e39130_app5.docx]

Multimedia Appendix 6
Informal caregivers' questionnaire (in French).
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Multimedia Appendix 7
Health care professionals' questionnaire (in French).
[DOCX File , 52 KB - resprot_v12i1e39130_app7.docx]

Multimedia Appendix 8
Feasibility questionnaire.
[DOCX File , 59 KB - resprot_v12i1e39130_app8.docx]

Multimedia Appendix 9
Overview of the OptiMed pre-post and multisite pilot and feasibility study.
[DOCX File , 23 KB - resprot_v12i1e39130_app9.docx]

Multimedia Appendix 10
Timetable for the OptiMed pilot study.
[DOCX File , 14 KB - resprot_v12i1e39130_app10.docx]

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Abbreviations

6-CIT: 6-item Cognitive Impairment Test
ARS: Leiria's Regional Health Administration
CHUV-CTU: Lausanne University Hospital's Clinical Trial Unit
eCRF: electronic case report form
GP: general practitioner
MRP: medication-related problem
PHC: primary health care center
START: Screening Tool to Alert to Right Treatment
STOPP: Screening Tool of Older Persons' Prescriptions
TFI: Tilburg Frailty Indicator

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Protocol

An Exploratory Trial of EPI-589 in Amyotrophic Lateral Sclerosis (EPIC-ALS): Protocol for a Multicenter, Open-Labeled, 24-Week, Single-Group Study

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Abstract

Background: Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disorder, with its currently approved drugs, including riluzole and edaravone, showing limited therapeutic effects. Therefore, safe and effective drugs are urgently necessary. EPI-589 is an orally available, small-molecule, novel redox-active agent characterized by highly potent protective effects against oxidative stress with high blood-brain barrier permeability. Given the apparent oxidative stress and mitochondrial dysfunction involvement in the pathogenesis of ALS, EPI-589 may hold promise as a therapeutic agent.

Objective: This protocol aims to describe the design and rationale for the EPI-589 Early Phase 2 Investigator-Initiated Clinical Trial for ALS (EPIC-ALS).

Methods: EPIC-ALS is an explorative, open-labeled, single-arm trial that evaluates the safety and tolerability of EPI-589 in patients with ALS. This trial consists of 12-week run-in, 24-week treatment, and 4-week follow-up periods. Patients will receive 500 mg of EPI-589 3 times daily over the 24-week treatment period. Clinical assessments include the mean monthly change of Amyotrophic Lateral Sclerosis Functional Rating Scale–Revised total score. The biomarkers are selected to analyze the effect on oxidative stress and neuronal damage. The plasma biomarkers are 8-hydroxy-2′-deoxyguanosine (8-OHdG), 3-nitrotyrosine

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(3-NT), neurofilament light chain (NfL), phosphorylated neurofilament heavy chain (pNfH), homocysteine, and creatinine. The cerebrospinal fluid biomarkers are 8-OHdG, 3-NT, NfL, pNfH, and ornithine. The magnetic resonance biomarkers are fractional anisotropy in the corticospinal tract and N-acetylaspartate in the primary motor area.

Results: This trial began data collection in September 2021 and is expected to be completed in October 2023.

Conclusions: This study can provide useful data to understand the characteristics of EPI-589.

Trial Registration: Japan Primary Registries Network jRCT2061210031; tinyurl.com/2p84emu6

International Registered Report Identifier (IRRID): DERR1-10.2196/42032

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KEYWORDS

amyotrophic lateral sclerosis; biomarker; clinical trial; magnetic resonance imaging; oxidative stress

Introduction

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease that is characterized by progressive upper and lower motor neuronal dysfunction and loss [1]. The mean survival time is 3-5 years after the onset [2]. ALS is diagnosed in 1-2 individuals per 100,000 each year in most countries, whereas its prevalence is approximately 5 cases per 100,000 people, reflecting the rapid disease lethality [3]. The pathogenic processes underlying ALS are considered multifactorial, including complex interaction of genetic factors, oxidative stress, excitotoxicity, and protein aggregation, as well as impaired RNA processing, axonal transport, and mitochondrial function [4]. Thus far, only a few interventional drugs, including the antiglutamatergic small molecule riluzole [5] and the antioxidant edaravone [6], have been approved by the United States Food and Drug Administration for ALS. Riluzole prolongs survival by only 2-3 months [5]. Edaravone, a strong antioxidant and free radical scavenger [7], slows down the loss of motor function in patients with ALS by 33% compared with a placebo [6,8]. A retrospective study demonstrated that edaravone prolonged tracheostomy-free survival [9], and a 5‐year prospective observational study is ongoing to investigate the long-term safety and effects of edaravone on ALS [10,11]. In addition, a cohort study, using propensity score matching, found safety but not disease-modifying benefit of long-term intravenous edaravone for patients with ALS [12]. Considering these circumstances, new therapies for ALS are highly anticipated.

A redox homeostasis dysfunction that causes oxidative stress has been linked to ALS pathogenesis [13], and markers of oxidative stress, such as 3-nitrotyrosine (3-NT) [14,15] and 8-hydroxy-2′-deoxyguanosine (8-OHdG) [16], are reportedly upregulated in the tissue of patients with ALS [17]. As the disease progresses, nutritional deficiency, cachexia, psychological stress, and impending respiratory failure become evident in ALS, which may be associated with a further increased oxidative stress [18]. EPI-589, also known as (R)-troloxamide quinone, is an orally available, blood-brain barrier–penetrable small-molecule designed as a novel redox-active agent to facilitate catalytic activity on oxidative stress control and mitochondrial energy metabolism. EPI-589 was more potent than edaravone in protecting the cells in an oxidative stress and mitochondrial dysfunction model [19,20]. In wobbler mice experiments, EPI-589 revealed dose-dependent effects to slow motor function deterioration [20,21]. Moreover, nonclinical study results revealed that EPI-589 had effects on 8-OHdG and neurofilament [20]. Given the apparent oxidative stress and mitochondrial dysfunction involvement in ALS pathogenesis, EPI-589 may hold promise as a potential therapeutic agent. In a phase 1 study, EPI-589 at 1500 mg per day was well-tolerated [22]. An early phase 2 trial (ClinicalTrials.gov identifier NCT02460679) revealed that EPI-589 at 500 mg twice daily was safe and well-tolerated with effects on disease progression in patients with ALS. However, the modes of action of EPI-589 for ALS remain unclear, and thus, further analysis is needed to elucidate its effects. Herein, we planned an early phase 2, single-arm, open-labeled exploratory trial of EPI-589 (EPI-589 Early Phase 2 Investigator-Initiated Clinical Trial for ALS [EPIC-ALS]). The primary objective of EPIC-ALS is to evaluate the safety and tolerability of EPI-589 at 500 mg 3 times daily for patients with ALS. The exploratory objectives are to monitor clinical course when receiving EPI-589 and to explore plasma, cerebrospinal fluid (CSF), and magnetic resonance imaging (MRI) results for potential EPI-589 biomarkers. An important characteristic of EPIC-ALS is the evaluation of multiple biomarker measurements in parallel with clinical assessment before, during, and after the intervention in patients with ALS. Here we provide an outline of the clinical trial protocol of EPIC-ALS version 1.0, which was prepared on July 29, 2021.

Methods

Study Setting

This investigator-initiated, open-labeled, multicenter, single-arm, and early phase 2 exploratory trial is designed to assess the safety and tolerability. Preliminary efficacy including clinical assessments and biomarkers of EPI-589 will be evaluated in patients with sporadic ALS. Patients will be recruited from the following ALS centers in Japan: Tokushima University Hospital, Aichi Medical University Hospital, and Osaka University Hospital. The total trial duration for each patient is 40 weeks, composed of 12-week run-in, 24-week treatment, and 4-week follow-up periods.

Eligibility Criteria

Patients' inclusion and exclusion criteria are depicted in Textbox 1. Patients will be assessed for the inclusion criteria 1-9, 11, and 12 at screening, 10 and 11 at the run-in period enrollment,

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and 11 again at the treatment period enrollment. Patients will need to meet none of the exclusion criteria at screening, run-in, and treatment period enrollment.

Textbox 1. Inclusion/exclusion criteria.

Inclusion criteria

1. Patient providing written informed consent to participate in this trial. (If the patient is underage at the time of consent, written consent from the patient's legal representative is required in addition to the written consent from the patient.)
2. Patient between 18 and 79 years of age (inclusive) at the time of consent.
3. Patient diagnosed with clinically definite, probable, or probable laboratory-supported sporadic amyotrophic lateral sclerosis (ALS) by the revised El Escorial criteria.
4. Onset of ALS within 1.5 years at screening.
5. Patient with mean monthly progression rate (calculated as follows: mean progression rate = [score at screening − score at onset]/time from onset to screening [expressed as the number of months rounded to one decimal place]) faster than −0.3 calculated based on Amyotrophic Lateral Sclerosis Functional Rating Scale–Revised (ALSFRS-R) total scores during the period from onset to screening (score at onset 48).
6. Patient whose score for each of the first 9 questions of ALSFRS-R is ≥2 points at screening.
7. Patient whose score for each of the 3 respiration-related questions (dyspnea, orthopnea, and breathing insufficiency) of ALSFRS-R is 4 points at screening.
8. Patient whose score for the swallowing-related question of ALSFRS-R is ≥3 points at screening.
9. Patient whose % slow vital capacity is ≥80% at screening. (A predicted value for % slow vital capacity was calculated using the equation of Baldwin et al [23].)
10. Patient on riluzole must be on a stable dose and regimen for at least 30 days prior to enrollment in the run-in period.
11. Patient who is able to visit the trial site as an outpatient.
12. Patient who agrees to provide blood sample to be used for genetic analysis.

Exclusion criteria

1. Patient who has concurrent or a history of clinically significant severe disease besides ALS and who is considered by the principal investigator or subinvestigator ineligible for the trial.
2. Patient who has concurrent psychiatric disorder, cognitive disorder, or Parkinson disease.
3. Patient who has undergone tracheostomy.
4. Patient who has used a noninvasive respiratory support device.
5. Patient who has a history of or concurrent drug allergy or severe allergic disease (eg, anaphylactic shock).
6. Patient with concurrent or a history (≤5 years before informed consent) of malignant tumor.
7. Patient from whom cerebral spinal fluid cannot be collected.
8. Patient who is unable to undergo magnetic resonance imaging (including diffusion tensor imaging and magnetic resonance spectroscopy).
9. Patient whose aspartate aminotransferase and alanine aminotransferase levels at screening are ≥3 times higher than the upper limit of normal.
10. Patient whose creatinine kinase at screening is ≥2.5 times higher than the upper limit of normal.
11. Patient whose estimated glomerular filtration rate at screening is <45 mL/min/1.73 m^2.
12. Patient who is or who may be pregnant or who is breastfeeding.
13. Patient who or whose partner wishes to be pregnant or who does not agree to use adequate contraceptive methods during the period from informed consent to 30 days after the final dose of the investigational drug.
14. Patient who has used edaravone within 30 days before the enrollment in the run-in period.
15. Patient who has changed the dosing regimen of riluzole or who has discontinued the use of riluzole later than the date of informed consent.
16. Patient who has previously received EPI-589.
17. Patient who participated in another clinical trial before the provision of consent for this trial and received another investigational drug within 30 days before consent for this trial (or within 5 times the half-life of another investigational drug if 5 times the half-life of another investigational drug is longer than 30 days) or patient who is participating or scheduled to participate in another clinical trial at the time of consent for the present trial.
18. Patient who has received cell therapy or gene therapy before provision of informed consent.
19. Patient who is, in the opinion of the principal investigator or subinvestigator, unsuitable to participate in this trial.

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Interventions

Patients will be administered EPI-589 at 500 mg (2 tablets of 250 mg) 3 times daily at least 60 minutes before meals during the 24-week treatment period. Based on the previous phase 1 results [22], when administered under fed conditions, the C_{max} decreased to 62.6% of the C_{max} under fasting conditions. Area under the curve was comparable between the fasted and fed states. Therefore, the timing of administration was decided "before meals" to maximize the exposure. Sumitomo Pharma Co., Ltd. will provide EPI-589 free of charge. Eligible patients should be on a stable dose of riluzole. Patients will be prohibited from the concomitant use of drugs with antioxidant potential, including edaravone, coenzyme Q10, and minocycline, as well as other potentially effective ALS drugs and therapies to evaluate the effects of EPI-589 on oxidative stress (Multimedia Appendix 1).

Outcomes, Patient Timeline, and Data Management

Trial assessments and procedures per visit are presented in Multimedia Appendix 2. Genetic analysis, including C9orf72 repeat expansion and whole-exome sequence, will be performed to avoid confounding due to genetic effects. Genetic analysis for C9orf72 repeat expansion will be evaluated at Tokushima University, whereas the whole-exome sequencing will be conducted at TAKARA Bio Inc.

The clinical course will be assessed by the change in Amyotrophic Lateral Sclerosis Functional Rating Scale–Revised (ALSFRS-R) scores, as well as by the mean change rate of ALSFRS-R scores per month, time to death, tracheostomy, whole-day use of noninvasive positive pressure ventilation, and physical findings. Variations in ALSFRS-R scores between assessors may be minimized by having each assessor master the scale in advance through a training program. Physical findings include slow vital capacity, manual muscle test total score, grip strength, the modified Norris scale total score, and the Amyotrophic Lateral Sclerosis Assessment Questionnaire-40 (ALSAQ-40) total score.

The safety will be evaluated by adverse events, laboratory tests, vital signs, 12-lead electrocardiogram, and the Columbia-Suicide Severity Rating Scale. To rule out any contraindication for receiving EPI-589, laboratory tests will be performed by a local laboratory, along with urinalysis and urine pregnancy tests.

The biomarkers in plasma and CSF were set to analyze the effect on oxidative stress (8-OHdG and 3-NT), neuronal damage (neurofilament light chain [NfL] and phosphorylated neurofilament heavy chain [pNfH]), and others such as ornithine, creatinine, and homocysteine. Plasma biomarkers are 8-OHdG, 3-NT, NfL, pNfH, homocysteine, and creatinine. CSF biomarkers are 8-OHdG, 3-NT, NfL, pNfH, and ornithine. Plasma and CSF samples will be immediately centrifuged after collection at 3000 rpm (1750*g*) for 10 minutes at 4°C and stored at −80°C at each site. The samples will be gathered and analyzed at a laboratory center.

The MRI data will be obtained with a 3.0-Tesla scanner at each site (Tokushima University Hospital and Osaka University Hospital, GE Healthcare; Aichi Medical University Hospital, Siemens Healthineers). The sequences will consist of T2-weighted imaging, 3D T1-weighted imaging, diffusion tensor imaging (30 motion probing gradient directions, b=1000 s/mm^2), and magnetic resonance spectroscopy (MRS) obtained with point-resolved spectroscopy with short and long echo time (30 and 135 ms, respectively) in the bilateral primary motor area, with a total scan time of less than 30 minutes for each patient. Optional sequences will include synthetic MRI with magnetic resonance image compilation and chemical exchange saturation transfer echo-planar imaging in the primary motor area. The imaging acquisition parameters were standardized beforehand (Multimedia Appendix 3). Anonymized MRI data will be sent to the Imaging Review Committee at Tokushima University. MRI biomarkers are diffusion tensor imaging–derived fractional anisotropy and apparent diffusion coefficient in the corticospinal tract; cerebral cortex parameters derived from 3D T1-weighted imaging; and *N*-acetylaspartate adjusted by creatine, choline, or creatine + choline measured by MRS in the primary motor area [24]. MRI biomarker values will be harmonized across the 3 institutions using healthy control MRI data obtained in an ancillary multicenter study.

Data will be abstracted into standardized data collection forms at patient enrollment. The ALSFRS-R will be assessed every 4 weeks through this trial. Clinical parameter assessments, including the manual muscle test, grip strength, modified Norris scale, and ALSAQ-40, are set to be evaluated at visits 2, 3, 6, and 9, where plasma biomarkers at visits 2, 3, 6, 9, and 10; CSF and MRI biomarkers at visits 2, 3, and 9; and optional MRI biomarkers at visits 6 and 10 will be collected and evaluated. Data will be monitored and audited by an independent contract research organization (CMIC Co., Ltd.).

Severe adverse events (SAEs) will be reported by the investigator within 24 hours of awareness by telephone, fax, email, or written document. As the secondary reporting, "SAEs reporting" will be submitted within 7 days of the investigator's awareness if detailed information is not included in the primary reporting. However, in case of an adverse reaction that should be reported to the regulatory authority within 7 days, care should be taken to obtain information within the period for reporting to the regulatory authority. The Safety Monitoring Board will review data on SAEs. The Safety Monitoring Board is an organization independent of the trial representative, coordinating investigator, investigators, subinvestigators, or contract research organization, and has authority to recommend the discontinuation of the study if there is any safety concern. The investigator, after consultation with the coordinating investigator, will seek advice from the Safety Monitoring Board about the continuation or discontinuation of the study as needed and determine measures to be taken. If an SAE (eg, death or a life-threatening event) is observed, for which a causal relationship with the investigational drug cannot be ruled out, enrollment will be suspended and a review of the Safety Monitoring Board will be sought.

The coordinating investigator will terminate or interrupt the entire trial in the following cases: (1) death or a life-threatening SAE, for which a relationship with the investigational drug cannot be ruled out, occurs (patient enrollment should be suspended in this case); (2) following the Safety Monitoring

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Board's recommendation on the termination or interruption of the entire trial, the coordinating investigator judges that the entire trial should be terminated or interrupted; (3) the Institutional Review Board recommends that the entire trial should be terminated or interrupted; (4) a change is made to the development policy of the coordinating investigator; (5) the regulatory authority recommends the termination of the trial; (6) any other situations, where partial or complete termination or interruption of the trial is needed, occur.

Telephone Survey

Telephone-based assessment will be permitted for the evaluation of adherence, ALSFRS-R score, events, tracheostomy, concomitant medications and therapies, and adverse events at visits TEL1, TEL2, 5, 7, or 8 because the ALSFRS-R telephone-based assessment was shown as reliable as in-person visits [25,26]. However, the telephone-based assessment will be used only in a state of emergency, including the COVID-19 pandemic, other infection pandemics, natural disaster, and terrorism, to ensure patient safety. Consecutive telephone-based assessment is prohibited.

Sample Size and Recruitment

Based on the results of the previous early phase 2 trial (NCT02460679), and also in light of the feasibility of this study, 10 patients were selected as the target sample size. Information on this trial will be disseminated via press coverage and websites to achieve timely adequate patient enrollment.

Statistical Analysis

The primary analysis, based on intention-to-treat principles, includes the full analysis set (FAS) including patients who received at least one dose of the investigational product and had a baseline measurement and at least one postbaseline measurement of efficacy endpoints or biomarkers, regardless of any protocol deviation. The secondary analysis includes the per-protocol set excluding patients with medication compliance of less than 70%, patients whose dosing period was less than 8 weeks, and patients with an important protocol deviation from FAS. The analysis with the per-protocol set is performed as a sensitivity analysis that confirms the consistency of FAS results. All patients who received EPI-589 are included in the safety analysis.

Changes of 20%-25% or greater in the ALSFRS-R slope would be a clinically meaningful effect [27]. Based on the finding, responders are defined as patients with an improvement in the rate of declined ALSFRS-R total score by 30% compared with the rate in the run-in period. The detailed definition of responders is presented in the following section.

> [The mean change of ALSFRS-R total score per month in the treatment period (each visit) – The mean change of ALSFRS-R total score per month in the run-in period]/|The mean change per month of ALSFRS-R total score in the run-in period| × 100 ≥30%.

The proportion of responder and CI will be calculated for each visit. In addition, a Z-test will be performed for the binomial proportion assuming a 10% threshold for the proportion of responders. However, patients with no change or increase in the ALSFRS-R total score in the run-in period will be excluded from this analysis. A total of 10 patients with a 2-sided α of .1 will provide more than 80% power to reject the null hypothesis (the proportion of responders equals 10%) based on a previous clinical trial (NCT02460679).

The mean ALSFRS-R changes per month will be compared between the run-in and treatment periods using the paired *t* test. In addition, the mixed model will be used to compare the ALSFRS-R slope between the run-in and treatment periods. Some evidence suggested that functional decline may not be linear [28-30]; however, a previous open-label 24-week extension study revealed that ALSFRS-R scores changed almost linearly from baseline through 48 weeks in the edaravone treatment group [8]. The change from baseline and the change per month for all continuous efficacy endpoints will be descriptively summarized at each visit and compared between the run-in and treatment periods using the paired *t* test. The number and percentage of patients with each outcome will be summarized by visit for parameters with categorical outcomes. Time to event since the first dose of the study drug will be analyzed by the Kaplan-Meier method and plotted by the Kaplan-Meier curve. The statistical significance will be set at a 2-sided level of .1. All analysis will be conducted using SAS software (version 9.4 or higher; SAS Institute Inc.).

We will also provide a list of adverse events, the number of patients completing the study, the CONSORT (Consolidated Standards of Reporting Trials) flow diagram, and the mean changes from baseline in the biomarkers. Individual data trajectories in a panel plot will also be made.

Patient and Public Involvement

Patients or the public were not involved in the design, conduct, reporting, or dissemination plans of our research.

Ethics Approval and Dissemination

This trial was approved by the Institutional Review Board of Tokushima University Hospital in August 2021 (approval number 2125 [03-10]), Aichi Medical University Hospital in October 2021 (approval number 202115), and Osaka University Hospital in November 2021 (approval number 219005-A) based on the Declaration of Helsinki, Good Clinical Practice, and associated Japanese regulations. The protocol has been approved by the Japanese regulatory authority Pharmaceuticals and Medical Devices Agency before the commencement of the trial. This trial was registered at the Japan Registry of Clinical Trials (JRCT ID: jRCT2061210031; registered on August 27, 2021 and last modified on July 25, 2022). Substantial amendments of the protocol must be approved by each institutional review board. Written informed consent will be obtained from all potentially eligible patients after the investigators provide a detailed explanation. Personal information about potential and enrolled patients will be masked to protect confidentiality before, during, and after the trial. If health injury (eg, adverse drug reaction) occurs in the patient in association with this trial, the head of the trial site will follow necessary procedures including provision of adequate medical care to the patient. For death/physical impediment that is within the scope of

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compensation, compensation will be paid in accordance with the terms and conditions of a clinical trial insurance contract. Compensation will not be paid if the health injury is not related to the trial or is caused by the patient's intentional misconduct or gross negligence or the protocol treatment has no beneficial effects. This trial received funding from Sumitomo Pharma Co., Ltd.

Results

This trial began data collection in September 2021 and is expected to be completed in October 2023. The ancillary study to obtain healthy control MRI data has been approved by the Ethics Committee of Tokushima University Hospital (approved on May 31, 2021; No. 3997), the Aichi Medical University School of Medicine Ethical Review Board, and the Osaka University Research Ethics Committee. The principal and coordinating investigators (YI and KF) will have access to the final trial data set. The results will be disseminated by presentations at scientific meetings and published in a peer-reviewed scientific journal.

Discussion

The pathogenic processes that underlie ALS remain unclear; however, accumulating evidence suggests that oxidative stress and mitochondrial dysfunction may play a pivotal role [4]. Oxidative stress is typically defined as an imbalanced production of free oxygen radicals, reactive oxygen species (ROS), or reactive nitrogen species. The mitochondrial wall contains the respiratory chain, which consumes 85%-90% of the total oxygen that is consumed by the body, but also produces the highest ROS levels in the cell due to electrons that escape from the respiratory chain and oxygen molecules that are incompletely reduced in aerobic metabolism [1]. Neurons are particularly susceptible to damage from oxidative stress for the following reasons [31]. First, neurons are remarkably large cells with large metabolic and high oxygen demand causing increased ROS production [32-34]. Second, motor neurons express relatively low calcium-binding protein levels. Thus, excess calcium ions tend to enter the mitochondria, leading to increased ROS production [35,36]. Third, some protective antioxidant protein expression is lower in motor neurons than in other cell types [37,38]. Patients with familial and sporadic ALS have elevated oxidative damage biomarkers in the spinal cord and motor cortex, mostly in large ventral horn motor neurons [14,39-41].

Edaravone is an antioxidant drug that is approved for ALS, which improves motor functions or oxidative stress in mutant SOD1 transgenic mice and rats and patients with ALS [6,42-46]. Edaravone reacts with oxidative radicals by an electron transfer reaction that consumes edaravone anion, which is converted to edaravone radical. Edaravone radical is transformed into 4,5-dione via edaravone peroxyl radicals with molecular oxygen reaction, followed by hydrolysis, to afford 2-oxo-3-(phenylhydrazone)-butanoic acid [47]. Edaravone increases nuclear factor erythroid 2–related factor 2 (Nrf2) expression, an oxidative stress inhibitor [48]. The overexpression of Nrf2 in astrocytes significantly delayed the onset and extended the survival in the SOD1-G93A mouse model of ALS [49]. Nrf2 overexpression in astrocytes reversed SOD1-G93A toxicity and protected the motor neurons from neurodegeneration in the SOD1-G93A mouse model [49]. In humans, edaravone significantly reduced the oxidative stress biomarkers, including 3-NT, in CSF of patients with ALS at an early stage [46]. However, edaravone has a limited effect, thus more effective drugs are urgently needed.

EPI-589 offers an effective novel antioxidant for ALS with advantages in drug delivery because it is orally bioavailable and is a small-molecule catalyst with high blood-brain barrier permeability. Previous studies revealed antioxidant reactions of the reduced EPI-589 form in the cell-free system. Moreover, EPI-589 is expected to not be hydrolyzed when scavenging radicals and to preserve the repeated catalytic activity. *In vitro* studies have revealed EPI-589 as more protective of cell viability against oxidative stress than edaravone (approximately 1000 times more potent with a difference in half maximal effective concentration for fibroblast cells derived from patients with ALS with FUS c.1566G>A mutation and SOD1 E50K mutation) [19,20].

A phase 1 trial in healthy participants (jRCT2071210022) [22] revealed that EPI-589 was safe and well-tolerated as a single daily dose of up to 1000 mg. In addition, EPI-589 was safe and well-tolerated when participants received 750 mg 2 times daily (1500 mg per day) in the multiple-dose part. In a phase 2 open-label trial (NCT02460679), 19 patients with ALS received EPI-589 500 mg 2 times daily. As in the phase 1 studies, no EPI-589–related SAEs were observed and most adverse events were mild or moderate. In our trial, we set the dose of EPI-589 to 500 mg 3 times daily because 1500 mg per day is the maximum daily dose used in the previous phase 1 study. Although EPI-589 500 mg 2 times daily showed possible efficacy on ALS progression in a phase 2 open-label trial (NCT02460679), given that the terminal elimination half-life of EPI-589 is relatively short [22], dosing 3 times a day rather than 2 times a day is preferable to maximize the efficacy.

EPI-589 slowed the symptomatic and pathophysiological progression of the wobbler mouse motor neuron disease model, with a higher effect than edaravone or riluzole [20,21,50]. Moreover, the disease-modifying effect was higher in the concomitant use of EPI-589 and riluzole than a single use of EPI-589 [20,50]. Thus, patients with concomitant use of riluzole were considered eligible for this trial.

We planned to monitor potential biomarkers throughout the trial duration to gain insight into the modes of action of EPI-589 in human patients. EPI-589 acts as a redox-active protectant against oxidative stress under experimental conditions relevant to ALS. Therefore, we will analyze the oxidative stress biomarkers (8-OHdG and 3-NT) as well as neuronal damage biomarkers (NfL and pNfH) [51] in plasma and CSF to obtain robust data to support this concept. We will evaluate other relevant factors, including ornithine in CSF and creatinine and homocysteine in plasma. Of these, plasma 3-NT, which reflects peroxynitrite-mediated oxidative damage, has been studied in multiple sclerosis [52] and Parkinson disease [53] but not in ALS. Moreover, prior studies revealed that a wobbler mouse model had a significantly increased plasma pNfH and decreased

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N-acetylaspartate level on MRS in the spinal cord compared with the wild type; EPI-589 administration improved these biomarkers [20]. These results suggest the effect on motor neurodegeneration, thus we set to evaluate *N*-acetylaspartate in the primary motor area. In addition, previous reports showed longitudinal changes in fractional anisotropy in the corticospinal tract that correlated with the slope of ALSFRS-R [54,55]. Therefore, we will assess fractional anisotropy in the corticospinal tract.

This trial has a couple of limitations. First, the trial size is relatively small. Second, this is an open-labeled, single-arm trial. Instead of a placebo, the 12-week run-in period will be used as control. As the primary objective of this trial is to evaluate safety and tolerability, placebo-controlled trials will be needed to confirm the efficacy.

In summary, this trial will evaluate the safety and tolerability of EPI-589 in combination with longitudinal changes in clinical parameters and biomarker candidates of plasma, CSF, and MRI. Data of the multiple biomarkers will help assess the modes of action of EPI-589 on ALS. This pilot trial will provide insights into the variability of efficacy endpoints and the feasibility of the next large randomized controlled trial.

Acknowledgments

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Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed.

Authors' Contributions

YI and TH conceptualized and designed the work with other authors. SH drafted the work with KF, RO, TH, and YI. All authors critically revised the work for important intellectual content. KF is the coordinating investigator of the trial and the principal investigator of the ancillary MRI study. SH, KF, YK, YM, and MH are the members of the Imaging Review Committee, where YK is the chairperson. TK provided statistical expertise. YO, SN, and NA are the lead investigators at each site. YI is the principal investigator of the trial. All authors approved the final version.

Conflicts of Interest

TH is an employee of Sumitomo Pharma Co, Ltd.

Multimedia Appendix 1
List of prohibited drugs and therapies.
[PDF File (Adobe PDF File), 24 KB - resprot_v12i1e42032_app1.pdf]

Multimedia Appendix 2
Schedule of assessments.
[PDF File (Adobe PDF File), 220 KB - resprot_v12i1e42032_app2.pdf]

Multimedia Appendix 3
Protocols of magnetic resonance imaging and spectroscopy.
[PDF File (Adobe PDF File), 186 KB - resprot_v12i1e42032_app3.pdf]

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Abbreviations

3-NT: 3-nitrotyrosine
8-OHdG: 8-hydroxy-2′-deoxyguanosine
ALS: amyotrophic lateral sclerosis
ALSAQ-40: Amyotrophic Lateral Sclerosis Assessment Questionnaire-40
ALSFRS-R: Amyotrophic Lateral Sclerosis Functional Rating Scale–Revised
CONSORT: Consolidated Standards of Reporting Trials
CSF: cerebrospinal fluid
EPIC-ALS: EPI-589 Early Phase 2 Investigator-Initiated Clinical Trial for ALS
FAS: full analysis set
MRI: magnetic resonance imaging
MRS: magnetic resonance spectroscopy
NfL: neurofilament light chain
pNfH: phosphorylated neurofilament heavy chain
ROS: reactive oxygen species
SAE: severe adverse event

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Protocol

Estimating the Burden of Disability From Road Traffic Injuries in 5 Low- and Middle-Income Countries: Protocol for a Prospective Observational Study

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Abstract

Background: Road traffic injuries (RTIs) are a leading cause of death and unintentional injuries globally. They claim 1.35 million lives and produce up to 50 million injuries each year, causing a major drain on health systems. Despite this high burden, there is a lack of robust data on the long-term consequences of RTIs, specifically the level of disability experienced by many survivors and its impact on their everyday lives.

Objective: This study aims to characterize RTIs, disability level, and related consequences affecting adult road traffic crash survivors in 5 low- and middle-income countries (LMICs). In addition, this study estimates the role of demographic and crash- and treatment-related factors in predicting adverse outcomes and disability as well as examining the disability level among patients with RTIs, likelihood of return to normal life, and the environmental factors that may influence these outcomes after discharge from the hospital.

Methods: This prospective observational study was conducted at selected hospitals in Bangladesh, Cambodia, Ethiopia, Mexico, and Zambia. The study sample included all adult patients with RTIs admitted to the hospital for at least 24 hours. Consecutive sampling was performed until the minimum required sample size of 400 was reached for each participating country. Data were collected from patients or their caregivers using a hospital-based surveillance tool administered at the participating sites as well as a telephone-based follow-up instrument administered 1, 3, and 6 months after discharge. Descriptive analysis and multivariate models will be used to estimate the contribution of a range of factors in predicting adverse outcomes, disability, and return to normal life.

Results: Enrollment began in June 2021 and was completed in April 2022. Follow-up data collection ended in September 2022. Data analysis is currently underway, with results expected for publication in mid-2023. Expected results include estimates of disability among patients with RTIs as well as identifying the predictors of adverse outcomes, disability, and the likelihood of return to normal life.

Conclusions: Research findings will help better understand the long-term burden of disability from RTIs in the 5 LMICs and the challenges facing survivors of road traffic crashes. They will be used to inform interventions aimed at improving the health care, social, physical, and policy conditions in LMICs that can facilitate recovery and rehabilitation for patients with RTIs, reduce the burden of disability, and enhance their participation in society.

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KEYWORDS

road traffic injuries; road traffic crashes; trauma care; disabilities; rehabilitation environmental factors; low- and middle-income countries

Introduction

Background

Road traffic crashes are a leading cause of trauma admissions in hospitals worldwide [1-3]. They claim 1.35 million lives and cause up to 50 million injuries each year, causing a major burden on health systems and other services [4]. According to the Global Burden of Disease Study, between 1990 and 2019, road traffic injuries (RTIs) were among the top 10 contributors to the increase in global disability adjusted life years (DALYs) [5]. In 2019, RTIs ranked seventh among the leading causes of global DALYs for all age groups and first for people aged 10 to 49 years [5].

Despite some recent improvements in global road safety, there have been persistent disparities in the burden of RTIs across world regions [4,6]. In 2019, RTIs accounted for 3.8% of the total deaths in Africa, 3.0% in the Eastern Mediterranean, 2.4% in South-East Asia, 2.3% in the Western Pacific, 2.2% in the Americas, and 0.8% in Europe [6]. In addition, RTI-induced death and disability are disproportionately higher in low- and middle-income countries (LMICs) than in high-income countries [6]. As in many other aspects of health, disparities exist in the risks and consequences affecting people with RTIs. For example, RTIs are the leading cause of death among children and young adults aged between 5 and 29 years [7]. They disproportionately affect males aged <29 years, who are far more likely to be involved in road crashes compared with females, and people from lower socioeconomic backgrounds have a higher likelihood of RTI-induced death and injury [7]. Other risk factors include driving speed; vulnerability of road users (eg, pedestrians and motorcyclists); nonuse of safety equipment (ie, motorcyclist helmets, seatbelts, and child seats); distracted driving; driving under the influence of alcohol or drugs; unsafe road infrastructure; unsafe vehicles; inadequate enforcement of traffic laws; and inadequate postcrash care [7]. These risk factors not only increase the likelihood of a road traffic crash but are also linked to the characteristics and impact of RTIs themselves. This research landscape on road traffic crashes in LMICs demonstrates important associations between crash circumstances and the consequences of RTIs. Studies have shown that crash circumstances (eg, method of transportation to the hospital, type of road user, alcohol use, and type of vehicle) are associated with morbidity and mortality after an RTI [8-13].

Research findings on RTI-induced disabilities demonstrate a high prevalence of disability among patients with RTIs in LMICs and highlight marked disparities in the experiences of injury, disability, and socioeconomic impact linked to sociodemographic, crash, and injury characteristics of patients with RTIs [10,12,14-18]. Despite their burden, many LMICs lack reliable and high-quality surveillance data on RTIs [4,19]. Only 66% of middle-income countries and 74% of low-income countries have trauma registry systems [20]. Surveillance data on the rate and severity of RTI-induced disabilities are also lacking in LMICs [4]. In addition, differences in methodologies and approaches to disability measurement underscore the continued need for more data to understand the consequences of RTIs beyond initial clinical outcomes [10,12,21,22]. The World Health Organization International Classification of Functioning, Disability, and Health framework defines disability as the interaction between a health condition (ie, an injury, disease, or disorder) and contextual factors, which include both personal and environmental factors. According to the International Classification of Functioning, Disability, and Health, environmental factors have a direct effect on disability outcomes caused initially by health conditions [23]. However, little is known about the impact of environmental barriers on the functioning of patients with RTIs after the initial treatment. Thus, a thorough understanding of disability after receiving trauma care is necessary to understand the extent to which environmental factors, such as access to medical and rehabilitation services, social support, and the physical environment, contribute to the recovery of patients with RTIs and the severity of their disability.

Goal of This Study

The primary goal of this study is to develop a clear understanding of RTIs and their consequences in LMICs to inform advocacy actions and policies. The specific aims of this study are to describe the characteristics and initial treatment outcomes of RTIs; estimate the role of demographic, crash-related, and treatment-related factors in predicting injury severity and disability-related outcomes; and estimate the impact of environmental barriers on the level of disability experienced by patients with RTIs after hospital discharge. Our study focuses on measuring constructs within disability (activities and participation) as well as the environmental barriers that may affect them to generate the evidence needed to inform interventions and policies that address the specific needs of patients with RTIs after treatment.

Methods

Study Design and Settings

This prospective observational study was conducted at 9 selected hospitals in Bangladesh, Cambodia, Ethiopia, Mexico, and Zambia (Table 1). According to the Global Burden of Disease report, the 2019 death rate (per 100,000) due to RTIs was 5.41 in Bangladesh, 17.53 in Cambodia, 8.56 in Ethiopia, 16.89 in Mexico, and 12.53 in Zambia [24]. By contrast, the number of DALYs per 100,000 lost due to nonfatal injuries was 549.61 in Bangladesh, 1006.57 in Cambodia, 546.35 in Ethiopia, 945.19 in Mexico, and 768.33 in Zambia [24].

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Table 1. Selected countries and cities.

World Bank region, country, name of hospital	City	City population[a], n
East Asia and Pacific		
Cambodia		
Calmette Hospital; Preah Kossamak Hospital	Phnom Penh	1,952,000
Latin American and Caribbean		
Mexico		
General Hospital of Axochiapan "Dr. Ángel Ventura Neri"	Axochiapan, Morelos	39,174
General Hospital of Cuautla "Dr. Mauro Belaunzarán Tapia"	Cuautla, Morelos	187,118
General Hospital of Cuernavaca "José G. Parres"	Cuernavaca, Morelos	1,043,000
General Hospital of Temixco "Enf. María de la Luz Delgado Morales"	Temixco, Morelos	122,263
South Asia		
Bangladesh		
National Institute of Traumatology and Orthopedic Rehabilitation	Dhaka	19,578,000
Sub-Saharan Africa		
Ethiopia		
Addis Ababa Burn Emergency and Trauma Hospital	Addis Ababa	4,400,000
Zambia		
University Teaching Hospital	Lusaka	2,524,000

[a]On the basis of 2018 United Nations, Department of Economic and Social Affairs population estimates for metropolitan areas (Dhaka and Cuernavaca), urban agglomerations (Phnom Penh and Lusaka), and cities proper (Addis Ababa and Kyiv) [25]. Axochiapan, Cuautla, and Temixco (Mexico) populations are based on 2020 estimates from the National Institute of Statistics and Geography (INEGI) [26].

Countries were selected to include representation in each region of the world where the World Bank operates, although we were unable to include a site from the Middle East and North Africa. Ukraine was originally selected as the site for Europe and Central Asia; however, we could not include it in the study because of the current conflict affecting the country. Hospitals were identified and selected based on previous research collaborations between national research teams and the study authors. Where possible, hospitals that were designated as trauma centers or that were present in large urban centers were prioritized. Some countries have included >1 hospital to achieve the desired sample size.

Eligibility Criteria

The study population included adults (aged ≥18 years) of either sex admitted to the hospital because of a moderate to severe RTI, which is defined as the injury being severe enough to require hospitalization for at least 24 hours. Study participants included patients admitted to the emergency department as well as other relevant hospital departments or units (eg, neurosurgical or orthopedic surgery units). Participants were able to give consent or had a suitable proxy who gave consent on their behalf if they were unable to do so. Individuals were excluded from the study if they were aged <18 years, were discharged <24 hours after being admitted to the hospital, or were unable to communicate verbally and did not have a proxy.

Study Sample

For the hospital surveillance portion of the study, we estimated the proportion of moderate to severe injuries in the target population of patients with RTIs. The required sample size for each country was calculated using the following equation:

$$n = p \times (1 - p) \times (z / e)^2 \textbf{(1)}$$

where n is the sample size required for a large population, p is the proportion of the population sustaining severe injuries from a road traffic crash, z is the confidence level, and e is the margin of error. p is based on the estimate that 30% of the adult study population may sustain moderate to severe injuries from road traffic crashes according to studies in LMICs [10,12,21]. z is defined as 1.96 (for a 95% confidence level [α]) and e at 5%. With these considerations, the sample size is calculated to be 323, which indicates that this is an adequate sample size for estimating the proportion of moderate to severe injuries from the total population of patients with RTIs in participating hospitals. Given the sample size calculations and accounting for 20% of the combined refusal and attrition, a minimum target sample size of 400 was set for each participating country. Consecutive sampling was done such that every patient who met the inclusion criteria was selected until the required sample size was reached at the participating hospital or hospitals in each country.

For the disability portion of the study that follows the recruited patients with RTI at 3 time points within 6 months after discharge, the sample included those patients who were identified at the first follow-up. Using α value of 0.05, a sample of 320 (based on 20% loss to follow-up 6 months after discharge), and a 0.5 baseline measure adjustment (correlation of repeated measures), the study has 99% statistical power to

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detect a 0.3 SD difference in the mean disability score between patients without a supportive environment (ie, those who report facing environmental barriers) compared with those with a supportive environment.

Recruitment and Data Collection

Overview

Patients were screened for inclusion and exclusion criteria by the data collectors at each facility at the following two points: (1) upon arrival at the emergency department and (2) at discharge from any department of the hospital. This allowed us to capture patients who came directly to the hospital, as well as patients who were transferred from other facilities and bypassed the emergency department.

Two instruments that were used for data collection are a hospital-based RTI surveillance tool and a follow-up disability-related assessment questionnaire (Table 2). The hospital-based RTI surveillance tool includes the following: (1) general patient information, (2) prehospital care, (3) RTI details, (4) initial clinical assessment and care provided, (5) disposition, (6) payment information, and (7) disability history.

Table 2. Data collection instruments.

Instrument	Content	Data source	Data collection method	Data collection time points
Hospital-based RTI[a] surveillance tool	Sociodemographic characteristics, crash circumstances, prehospital care provided, clinical assessment, and disposition	Medical records	In-person	During hospital stay
Hospital-based RTI surveillance tool	Cost or payment information and history of disability	Patient or proxy interview	In-person	During hospital stay (day of discharge)
Disability assessment and environmental factors tool	Demographic characteristics, activity limitations, participation restrictions, use of or need for assistive devices, perceived return to preinjury activities, and environmental factors	Patient or proxy interview	Phone-based	1, 3, and 6 months after discharge

[a]RTI: road traffic injury.

The disability follow-up questionnaire consists of 3 modules. Module A includes selected questions from the short form of the World Health Organization Disability Assessment Survey 2.0 (WHODAS 2.0), which is a general disability instrument that measures limitations in performance in 6 life domains that are understanding and communicating, getting around, self-care, getting along with people, life activities, and participation in society [27]. Module B includes questions pertaining to returning to normal life and work and questions about assistive devices. Module C, which was administered only at 3- and 6-month follow-up time points, includes selected questions from the short form of the Craig Hospital Inventory of Environmental Factors (CHIEF) version 3 [28]. CHIEF measures perceived physical, social, and political barriers to societal participation for people with disabilities [28].

Informed consent was obtained from the patients (or proxy) in the hospital for enrollment in the study. Both study instruments were pretested with 5 to 7 patients in each participating country before the start of data collection.

Hospital-Based Data Collection

As part of RTI hospital surveillance, data was collected by obtaining information from the patient's medical record and by conducting interviews with the patient (or caregiver) directly. We aimed to extract the following information from the medical record, depending on the availability (Textbox 1): sociodemographic information (age, sex, education, employment status, current partnership status, total number of persons living in household, and annual household income); prehospital care (if care was provided, by whom, type of care provided, mode of arrival at hospital, and transport time to hospital); RTI details (type of road, type of vehicle, mobile use, counterpart, and safety equipment use); and initial clinical assessment and care provided (vital signs, initial Glasgow Coma Scale, suspected alcohol and drug use, treatment, region of injury, pathology, operation, and number of days in the intensive care unit). We collected the following information through patient (or proxy) interviews: payment information (if a fee was paid, amount paid, type of service paid for, hospitalization cost, means of payment, and annual household income) and disability history (if the patient had a disability before RTI, severity of the disability, and domains affected by the disability). We also attempted to gather data from the patient or proxy if it was missing in the medical records, as appropriate.

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Textbox 1. Variables from hospital-based surveillance tool.

Sociodemographic variables

- Age group in years (18-24, 25-44, 45-64, 65-74, and >75)
- Sex (male or female)
- Educational level (no formal education, primary, secondary, college or university, professional, graduate, vocational or technical, and other)
- Employment status (daily-wage laborer, salary worker, self-employed, military, homemaker, student, retired, beggar, unemployed, unable to work, and other)
- Partnership or marital status (currently married, cohabiting, separated, divorced, widowed, and never married)
- Number of persons in household
- Annual household income (local currency)

Prehospital care variables

- Care provided at scene (yes, no, or unknown)
- Who provided care (person involved, bystander, relative, friend, police, ambulance staff, emergency medical technician, unknown, and other)
- What care was provided (C-spine immobilization, fracture immobilization, control of bleeding, wound care, Cardiopulmonary Resuscitation, intravenous fluids, and other)
- Mode of arrival to hospital (walk-in, auto-rickshaw, car, ambulance, taxi, motorized 2-wheeler, and other)
- Transport time to hospital (0-30 min, 30 min-1 hour, 1-2 hours, 2-6 hours, 6-24 hours, and >24 hours)

Crash characteristics (road traffic injury [RTI] details)

- Time of injury (day, evening, and night)
- Type of road (highway, main road, side street, village road, and other)
- Type of road user (pedestrian, driver, passenger, and other)
- Type of vehicle (car, minibus or van, bus, bicycle, motorcycle, truck or lorry, auto-rickshaw, and other)
- Mechanism of injury of pedestrian (boarding or exiting bus, boarding or exiting other vehicle, standing or walking on side of road, and crossing the road)
- Counterpart (car, minibus or van, bus, animal, auto-rickshaw, motorcycle, bicycle, nonmotorized vehicle, truck or lorry, other, skid or rollover, fall form moving vehicle, stationary or fixed object, and other)
- Mobile phone use (yes or no)
- Safety equipment (helmet, seatbelt, and other) used (yes or no)
- Suspected alcohol use with 6 hours of RTI (yes or no)
- Suspected substance use within 6 hours of RTI (yes or no)

Hospital variables

- Physiological Assessment
  - Glasgow Coma Scale (mild 13-15, moderate 9-12, and severe 3-8)
  - Systolic blood pressure (mm Hg; <90, 90-120, and >120)
  - Diastolic blood pressure (mm Hg; <60, 60-80, and >80)
  - Pulse rate (<60, 60-90, and >90)
  - Respiratory rate (<12, 1-18, and >18)
  - Lost consciousness (yes or no)
- Patient care
  - Emergency room patient (yes or no)
  - Anatomy (anatomical region, site of most severe injury; head and neck, face; chest, abdomen, extremities, and external)
  - Number of severely injured sites (1-3)
  - Pathology (none, concussion, muscle injury, etc)
  - Treatment (none, operation, observation, antibiotics, etc)

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- Operation (internal-fixation, external-fixation, laparotomy, amputation, etc)
- Intensive care unit (ICU; yes or no)
- Number of days in ICU

- Disposition
  - Disposition (died in hospital, discharged to rehabilitation, discharged to home, transferred to another hospital, absconded or left against medical advice, other, and unknown)

- Cost or payment
  - Pay fee upon arrival (yes or no)
  - Amount paid (local currency)
  - Type of service paid for (registration, medicine, x-rays, laboratory tests, blood transfusion, and other)
  - Hospitalization cost (local currency)
  - Means of payment (had money of his or her own, borrowed from family or friends, took a loan, sold assets, and other)
  - Annual household income (local currency)

- Disability history
  - Preexisting disability (yes or no)
  - Severity of disability or impairment (none, mild, moderate, severe, and extreme)
  - Life domains affected (understanding and communicating, getting around, self-care, managing domestic life, getting along with people, engaging in major life areas, and participation in society)

Follow-up Data Collection

Using participant contact information provided at the hospital, data collectors called each study participant 1 month, 3 months, and 6 months after hospital discharge to conduct follow-up interviews. Data collectors asked questions about their level of functioning using the WHODAS 2.0 short form (module A). The WHODAS 2.0, a valid and reliable instrument for several patient populations, was developed to allow for comparison across cultures based on a study spanning 19 countries [27]. The instrument consists of 36 items that ask about difficulty in performing activities in the last 30 days, scored on a 5-point Likert scale, as follows: 0=No difficulty, 1=Mild difficulty, 2=Moderate difficulty, 3=Severe difficulty, and 4=Extreme difficulty or inability to do.

WHODAS 2.0's shortened form consists of 12 items. The short form has been found to be valid and reliable among populations with RTIs in LMICs [29,30]. Scores are calculated for each subscale by adding points from each response. The minimum and maximum total scores of WHODAS 2.0 are 0 to 48, with higher scores indicating higher levels of disability [27]. Three additional questions ask about the number of days participants experienced difficulties in the past 30 days (Table 3).

Module B contains 5 questions. Two questions ask about whether the participants have returned to their preinjury activity and if they have returned to work for those previously employed. Three questions ask about the current use of assistive devices or modifications to their home, the type of equipment or modifications used, and for those reporting not using any, whether they need such assistive devices or modifications. Module C uses 12 selected questions from the CHIEF instrument [28]. This instrument has been implemented and validated in several LMICs [31-36]. The first 3 questions ask whether the participants have the same opportunities as other people to participate and take advantage of the areas of education, employment, and leisure. Nine questions ask about the barriers to participation in activities since the injury. Participants report the frequency of experiencing these barriers (ie, daily, weekly, monthly, monthly, or never). If the item occurs, participants are asked to report the magnitude of this problem (ie, big problem or small problem). The CHIEF questions used in module C were slightly modified from their original form by asking the participants to think about barriers since the occurrence of the injury rather than in the past 12 months.

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Table 3. List of variables for the follow-up instrument.

Module and measures	Variables
A[a]	
Understanding and communicating (cognition)	• Difficulty in concentrating on doing something for 10 minutes • Difficulty in learning a new task
Getting around (mobility)	• Difficulty standing for long periods such as 30 min • Difficulty in walking a long distance such as a kilometer
Life activities	• Difficulty in taking care of household responsibilities • Difficulty in day-to-day work or school
Participation in society	• Difficulty in joining in community activities • How emotionally affected by health problems (response options for this item are 0=Not Affected, 1=Mildly Affected, 2=Moderately Affected, 3=Severely Affected, and 4=Extremely Affected)
Self-care	• Difficulty in washing whole body • Difficulty in getting dressed
Getting along with people	• Difficulty in dealing with people you do not know • Difficulty in maintaining a friendship
Number of days with difficulties	• Overall, in the past 30 days, how many days were these difficulties present? • In the past 30 days, for how many days were you totally unable to carry out your usual activities or work because of any health condition? • In the past 30 days, not counting the days that you were totally unable, for how many days did you cut back or reduce your usual activities or work because of any health condition?
B[b]	
Return to usual activity	• Return to normal life or usual activity (yes or no) • Return to work (yes or no)
Assistive devices	• Currently using personal equipment, special adapted devices, and or physical modifications to home (yes or no) • Type of equipment used (mobility aids, hearing aids, visual aids, communication aids, cognitive aids, physical modifications, devices for performing tasks, other) • Need for assistive devices (yes or no)
C[c]	
Having equal opportunities as other people	• Education (yes or no) • Employment (yes or no) • Recreation or leisure (yes or no)
Services and assistance barriers[d]	• Experience problem with availability of transportation • Experience problem with availability of information • Experience problem with availability of health care services • Need for help at home and not getting it easily
Attitudes or support barriers[d]	• Experience prejudice and discrimination
Work or school barriers[d]	• Experience problem with people's attitudes at school or work • Need help at school or work and did not get it easily
Policy barriers[d]	• Experience difficulty due to government programs and policies
Physical environment barriers[d]	• Experience difficulty with natural environment (temperature, terrain, climate, etc)

[a]Variables from World Health Organization Disability Assessment Survey 2.0 short form (module A). Response options: 0=No Difficulty, 1=Mild Difficulty, 2=Moderate Difficulty, 3=Severe Difficulty, 4=Extreme Difficulty or Cannot Do.

[b]Variables related to return to usual activities and assistive devices (module B).

[c]Variables from Craig Hospital Inventory of Environmental Factors (module C).

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[d]Response options: 4=Daily, 3=Weekly, 2=Monthly, 1=Less than Monthly, 0=Never, Not applicable.

Data Collection Training, Storage, and Management

Data collectors were trained on the study protocols, and each local team of data collectors and data managers will conduct regular reviews of the data to identify any issues in the data collection process or data quality. The Survey Solutions software developed by the World Bank was used for data collection [37]. Survey Solutions can operate in mixed mode, and data can be collected offline on tablets (computer-assisted personal interviewing), on the web using a web interface (computer-assisted web interviewing), or via phone interviews (computer-assisted web interviewing). Data from the hospital surveillance instrument will be linked to the follow-up data through a unique participant ID. Android-based devices are used to collect, store, and transfer hospital-based and follow-up data. The collected data are transmitted to the survey headquarters for real-time quality control and analysis. The software works offline in areas with limited internet access and later synchronizes data once the internet access is available.

Ethics Approval

Ethics approval was obtained from the ERES Converge institutional review board in Zambia (reference number 2021-Jan-003), National Ethics Committee for Health Research in Cambodia (reference number 018 NECHR), the institutional review board of the Ethiopian Public Health Association (reference number OG/039/21), the Centre for Injury Prevention and Research in Bangladesh Ethical Review Committee (reference number 2021/01), and the Instituto Nacional de Salud Pública in Mexico (reference number 1729), as well as the George Washington University's Office of Human Research.

Potential participants were informed of the aims and content of the study and were required to give written, informed consent before enrollment. The participants did not receive any compensation for their participation in the study. All data collected in the Survey Solutions software for this study was deidentified.

Statistical Analysis

Overview

Stata 14 (StataCorp) will be used for the data analysis [38]. First, descriptive statistics will be generated for several variables captured in the hospital-based tool to examine the demographic, clinical, and treatment characteristics of the initial study sample. Descriptive statistics of disability-related variables collected through the follow-up survey will also be generated at each follow-up measurement occasion. Comparing the descriptive statistics of the sample at each time point will help to identify selection bias because of loss to follow-up.

Analyses of the follow-up data will include cross-sectional and linear mixed models to assess the relationship between different predictors (eg, hospital variables) and the study's 2 key outcome variables (ie, disability score and perceived return to usual activities) at the 3 follow-up time points. The analyses will adjust for differences at baseline (eg, disability history) and confounding variables.

Cross-sectional Analysis

To identify significant predictors of disability, a bivariate analysis will be performed at each follow-up time point by regressing the overall disability score against each of the explanatory variables from the hospital-based tool (ie, sociodemographic, preexisting disability, crash circumstances, prehospital, and hospital variables); use of assistive devices from the follow-up tool; and environmental barriers and previous disability score (for the second and third follow-up). Given the large number of variables in the hospital-based tool, there are many potential covariates. A critical assessment will be done to identify the most important independent variables to include in a linear regression model. Variables that show a significant association with the outcome in the bivariate analysis as well as those with associations found in the literature will be retained in the regression model. In addition, testing for multicollinearity in each of the regression models will be performed by determining the variance inflation factor, in which values >10 will be investigated. Collinear variables will be dropped iteratively until the model no longer has variables with a variance inflation factor >10. These measures will ensure that the regression model estimates of the coefficients are stable. This analysis will be repeated using logistic regression and *return to preinjury activity* as the outcome variable.

Attrition Analysis

Because disability-related data will be collected longitudinally (repeated measures), it is expected that the sample size at the third follow-up will be smaller than that from the previous follow-ups. An attrition analysis will be performed to test for correlation between demographic and clinical variables and loss to follow-up at each measurement occasion. It is expected that loss to follow-up will be between 4% and 28% at the 6-month follow-up [22,39]. The relationship between nonparticipation in the follow-up and sociodemographic, crash, and clinical variables (collected at the hospital) will be examined to assess whether loss to follow-up from each measurement occasion is associated with the possible predictors of the study outcomes.

Longitudinal Analysis Using Mixed Effects Model

Using panel data, the change in the main outcomes of interest (disability score and perceived return to preinjury activity) across the 3 follow-up points will be examined (Table 4). First, attrition analysis will be performed with panel data (all rounds of data collection) to assess whether clinical characteristics such as injury severity and disability score predict loss to follow-up. The loss to follow-up variable will be coded according to the follow-up responses and regressed against injury and disability severity variables. Imputation techniques will also be considered to handle missing data and increase the sample size, depending on the results from the attrition analysis.

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Table 4. Key outcome variables from the follow-up instrument.

Indicator	Survey questions	Specifications
Disability score	WHODAS[a] 2.0's shortened form consists mainly of 12 questions capturing the following domains: understanding and communicating; getting around; self-care; getting along with people; life activities; and participation in society. Response options: 0=No Difficulty, 1=Mild Difficulty, 2=Moderate Difficulty, 3=Severe Difficulty, 4=Extreme Difficulty or Cannot Do.	Scores are calculated for each subscale by adding the points from each response. The minimum and maximum total scores are 0-48, where higher scores indicate higher levels of disability.
Perceived return to preinjury activity or "normal life"	As of today, do you consider yourself to have returned to your normal life or to doing your usual activities your injury? Response options: Yes; No.	This question is intended to capture whether the participant has returned to their usual activities as they see it. Participants may consider themselves to have returned to usual activities or normal life *because of or despite* using an assistive device, whereas other participants may consider themselves not back to "normal" life if they have to use a device or rely on a modification to their physical space. Because this tool is focused on activities and participation, we define "return to normal life" as being able to do the things one was able to do before their injury.

[a]WHODAS: World Health Organization Disability Assessment Survey.

Next, descriptive analysis will be conducted for the complete cases (participants in all 3 follow-up rounds), followed by longitudinal analysis, which will account for the correlation between repeated measures and heterogeneity of variance inherent to longitudinal data. A mixed effects model will be used for the analysis, which accounts for both fixed effects (population-averaged response) and random effects (subject-specific) [40]. This model allows for the comparison of changes in disability scores over time and can accommodate continuous covariates as well as incomplete data [40].

Finally, although we assume a linear relationship in the response over time, this may be relaxed to include a quadratic term for time in the model or a log transformation. *P* values will be considered significant at .1. The longitudinal analysis will be replicated for repeated binary measurements of the return to preinjury activities outcome variable, using logistic regression to model the binary outcome.

Results

Enrollment in the study began in June 2021 and was completed in April 2022. Follow-up data collection ended in September 2022. Data analysis is currently underway, with results expected for publication in mid-2023.

Discussion

Principal Findings

The proposed study will provide an estimate of the burden on patients due to RTI-induced disability in several LMICs. It will also provide a thorough understanding of the rate and severity of RTI-induced disability and its impact on road traffic crash survivors by examining disability scores and perceived return to preinjury activities. The data will identify disparities in recovery from RTIs and return to preinjury activity or "normal life" based on differences in environmental factors surrounding crash survivors after hospitalization. This will provide an opportunity to uncover barriers that impede recovery and return to usual activities, including service and assistance barriers as well as physical, social, and policy barriers.

Strengths

This study uses a prospective design to develop estimates of disability among patients with RTIs using a validated instrument 1 month, 3 months, and 6 months after injury from 9 hospitals in 5 LMICs. Implementing a multicountry design provides a large sample size that will strengthen the accuracy of our findings, reduce the margin of error, and increase the generalizability of the findings. This prospective design will allow for a better understanding of the predictors that influence the recovery process and provide more efficient estimates of the effects of time-varying covariates, such as injury severity or treatment.

Limitations

This study has a few limitations. The first limitation is related to sampling. With only a small number of hospitals in each country, our sample is not nationally representative. The study populations that were recruited at these hospitals are not necessarily representative of the injuries and treatment-related factors in each country because of differences in the regional and facility-specific characteristics of the participating hospitals and their patient populations. Thus, the study's findings will not be generalizable at the country level. In addition, our sample size calculation may not properly reflect the complexity of sample variations, meaning that a sample size of 400 is insufficient for estimating the national disability burden of road traffic crashes, especially for subgroups. Furthermore, because the sample only includes adults with moderate to severe injury, this study will not estimate the full extent of the burden of RTIs because it excludes injuries of children and minors. Second, the COVID-19 pandemic and related restrictions have caused some hospitals to make changes in their inpatient and outpatient case prioritization procedures that may have affected eligibility and recruitment. For example, patients with RTIs with moderate injury who may have normally been admitted to the inpatient ward may have been discharged within 24 hours and scheduled for outpatient procedures. This would render them ineligible

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for the study and could have created difficulties to achieve the desired sample size as well as potentially cause sampling bias. Even outside of COVID-19, some eligible cases in sampling may have been missed because of premature discharge or transfer of hospital. For example, it is possible that some patients were discharged within 24 hours of admission for unknown reasons despite having moderate to severe RTIs. Similarly, patients who bypassed the emergency department may have also been missed despite our best efforts to recruit eligible patients. Third, a significant portion of the study is longitudinal, which uses phone-based interviews to conduct follow-up data collection, so there is a threat of loss to follow-up. Potential loss to follow-up will reduce the sample size and potentially bias results if missingness is directly linked to health and demographic variables. Fourth, it is likely that the study will have missing data at the hospital level because much of the patient information will be extracted from medical records by nonclinical data collectors. A fifth limitation of this study is that we were not able to collect injury severity score, an important measure of severe injury, because physicians in the participating sites in this study do not routinely calculate this measure. However, other variables were collected, which can act as proxy measures to assess injury severity. Finally, we did not measure the quality of care provided or factors such as psychosocial stress and pain that may directly affect disability-related outcomes.

Conclusions

This research will be key to expanding the evidence base needed to develop strategies to improve the quality of life and lessen the social and economic burden on those with crash-induced disability. Thus, the findings of this study will help advocate not only for improved road safety but also for informed decision-making by the government to adopt and implement appropriate policies and interventions to address factors contributing to the severity of RTIs and associated disabilities and the contexts under which they occur.

Dissemination Plan

This research is intended for public health professionals, researchers, trauma care providers, rehabilitation providers, policy makers, and advocates interested in the link between RTIs and disability and rehabilitation. Findings from this study will be reported in peer-reviewed journal articles and conference presentations and shared with the study participants. Publications will be authored jointly by country teams.

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Data Availability

The data sets generated and analyzed during this study are available from the corresponding author upon reasonable request.

Authors' Contributions

SM, NP, and AAH conceptualized the study, and HER, KN, LWM, and MKK helped develop the protocol. MKK and HER drafted the manuscript, and all the other authors critically revised the manuscript for important intellectual content. All authors have approved the final version of the manuscript for publication.

Conflicts of Interest

SM, KN, and LM were employed by the donor agency. AAH, NP, HER, and MKK received funding from the World Bank to support this study.

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Abbreviations

CHIEF: Craig Hospital Inventory of Environmental Factors
DALY: disability adjusted life year
LMICs: low- and middle-income countries
RTI: road traffic injury
WHODAS 2.0: World Health Organization Disability Assessment Survey 2.0

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Protocol

The Health Care Trajectories of Older People in Foster Families: Protocol for an Observational Study

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Abstract

Background: With aging of the population, the search for alternative models of care adapted to older people with dependency is necessary. In this setting, foster families (1-3 older people per family) could be an alternative to nursing homes, residential care facilities, or community- and home-based care.

Objective: The KArukera Study of Ageing in Foster Families is a prospective cohort study designed to investigate the care pathways of older people with dependency in foster care over a year. The 1-year hospitalization rate (main objective), cost of hospitalization, incidence of mortality, prevalence of geriatric syndromes, and quality of life of residents will be assessed. Quality of life and burnout of their respective foster caregivers will also be studied.

Methods: This study cohort will include 250 older people living in foster families in Guadeloupe (French West Indies), as well as their respective foster caregivers. Both older people and caregivers will be interviewed concurrently on site at three time points: (1) at baseline, (2) at 6 months, and (3) at 12 months. For older people, we will collect anthropometric measures, cognitive impairment, depressive and anxiety symptoms, functional abilities, physical frailty, information on general health status, quality of life, and care pathways (hospitalization, mortality, and medical and paramedical consultations). We will also assess the quality of life and burnout symptoms of family caregivers at each follow-up. A phone update of vital status (alive or death) and care pathways of residents will be carried out at 3 and 9 months after the baseline examination.

Results: Recruitment opened in September 2020 and ended in May 2021, with 109 older people recruited and 56 respective foster caregivers. The 1-year follow-up was ended in June 2022. Data analyses are ongoing and the first results are expected to be published in May 2023.

Conclusions: Foster families are a potentially innovative way to accommodate dependent older people. This study could help define the clinical profile of older people adapted to foster families in the transition from frailty to dependency. The effectiveness of foster families, in terms of hospitalizations and mortality, will be compared with other models of care, particularly nursing homes. In this setting, a twin study carried out in nursing homes in Guadeloupe with similar aims and outcomes will be conducted. Beyond mortality and morbidity, the numerous outcomes will allow us to assess the evolution of geriatric syndromes over time.

Trial Registration: ClinicalTrials.gov NCT04545775; https://clinicaltrials.gov/ct2/show/NCT04545775

International Registered Report Identifier (IRRID): DERR1-10.2196/40604

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KEYWORDS

older people; foster family; hospitalization; geriatric syndromes; mortality; quality of life

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Introduction

The Caribbean region is a heterogeneous canvas of autonomous states and dependent territories of sovereign states. In this area, the French West Indies constitute a specific cultural topic. A total of 90% of its population is of African descent. Although the official language is French, the medical and cultural realities are quite different from mainland France. There is little epidemiological data on this population, despite strong specificities, in terms of prevalence of specific diseases (hypertension, diabetes, etc), specific genetic risk factors, and socioeconomic characteristics or access to health care [1].

On January 1, 2016, there were officially 394,110 inhabitants in Guadeloupe, a number that has been decreasing by 0.5% every year since 2011 [2]. This decrease is the result of both a slowdown in demographic growth and a constant negative net migration rate, due to high unemployment rates and lack of economic prospects. As a result, by 2030, people older than 65 could represent 28% of the population [2] and the number of dependent older people should double. This older population will have age-related medical problems, especially chronic (hypertension, diabetes, and cancer) or neuropsychiatric pathologies. An increase in dependency and its associated consequences, such as an increase in hospitalizations and nursing home admissions, is to be expected. Early detection is lacking, and general practitioners cannot compensate for the shortage of medical specialists. In the current context, the economic, medical, social, and human stakes are considerable and finding the appropriate care option for older people with dependency has become a critical issue.

Despite strong family support, living at home is sometimes difficult or impossible for seniors and their caregivers [3] (heavy dependency, exhaustion of caregivers, regular decompensation of chronic pathologies, etc). Moreover, social isolation, social vulnerability, and loneliness among older people living at home [4,5] increase the risk of adverse health events, notably mortality [6]. The most developed and successful model for dependent persons in high- and middle-income countries is the nursing homes. However, the transition from one's home to a nursing home usually disrupts residents' social life and lifestyle, and institutionalized older people experience a steeper cognitive decline than community-dwelling people [7], as well as a drop in quality of life [8] and an increase in psychotropic drug use [9]. For these reasons, we need to study alternative and transitional care models between home care and nursing home care, such as foster families. Because fostered older people (while still moving out of their own homes) are taken care of within a family context instead of a nursing home or other collective settings, foster care placement processes could be an alternative to institutionalization. This model has developed to a greater extent over the last few years in Guadeloupe. Nearly 200 foster families care for about 300 dependent older people, whereas there are 21 nursing homes for approximately 1500 residents. Foster caregivers, after getting official approval and attending a 20-hour training course, usually accommodate 1 to 3 people in exchange for a monthly fee. Their mission is to ensure the well-being of their residents and to enable them to maintain close social and family relationships. Other professionals may also provide additional nursing care if necessary. Little is known about the characteristics of foster caregivers and their residents. Two decades ago, a study from Cébula and Horel [10] showed that 61% of fostered older people were older than 80 years in France, and two-thirds were women. Every 6 of 10 older people lived at home or with their own family before entering foster care, and foster care was requested by the older person's household in 63% of cases. Most foster caregivers were women (96%). Two-thirds of the foster caregivers were between 40 and 60 years old, and 16% of them were older than 60 years. Every 8 of 10 foster caregivers were "partnered people," the majority of them being single-family home owners (95%). Nearly half of the foster caregivers were in a nonemployment situation (inactive, unemployed, integration, and training) before obtaining their foster caregiver license. The cost of foster family accommodation for seniors depends on the number of caregiving hours, because of the length and frequency of stay (in 94% of cases, it is a full time) and geographical location. The monthly fee includes rent, services rendered, a maintenance allowance, and a daily allowance. Monthly cost ranges from €1400 to €2100 (US $1521.98 to US $2282.97) per month [11].

Foster families have also been tried out in others countries (eg, United States, Belgium, Italy, Russia, and Finland), but few scientific studies have assessed its effectiveness and efficiency. A Cochrane meta-analysis published in 2015 compiled 10 studies comparing home care or foster care with nursing home care for 16,377 older participants [12]. Because of the methodological limitations of the studies included, the meta-analysis failed to determine whether or not this type of accommodation was the most efficient in terms of mortality reduction, physical function, quality of life, or hospitalization rates. Indeed, the available studies relied on small samples and had high risks of bias (design bias, evaluation bias), and the baseline characteristics of the participants were very heterogeneous. Three 30-year-old studies focusing on foster care in the United States were included [13-15]. Two of them are of interest [13,15]. Braun and Rose [13] compared 269 older participants: 100 lived in foster care, 101 in nursing homes, and 68 at home. After 3 months, Activities of Daily Living (ADL) scores only improved in the foster care group, and costs were lower than those for the other 2 groups (US $28 per day vs US $74 for nursing homes and US $45 for home). There was no difference in morbidity, defined as the number of infections, injuries, skin problems, and hospitalizations. In their randomized study on 112 participants in foster care or nursing homes, followed for 12 months, Oktay and Volland [15] found no difference in mortality rates between settings (32.0% vs 28.8%). Stabilization or improvement of ADL and cognitive status, as well as overall lower health care expenses (25% less), was in favor of foster care. Nevertheless, nursing home residents' level of satisfaction compared favorably with that of foster family residents. In any case, available data are scarce, assessed with short follow-ups, lack essential clinical outcomes, and definitely need to be updated.

To date, we do not know whether foster care is an alternative to nursing home care, as suggested by the limited existing literature, or a transitional care setting between home care and

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nursing home care. Epidemiological and medicoeconomic data on older people in foster families are essential to assess the relevance of this type of care, in particular, according to the severity of dementia or the degree of dependence in ADLs. Several issues need to be clarified: what is the residents' annual hospitalization rate and the associated costs? What is the health care pathway of residents in terms of consultations with general practitioners, specialists, and paramedics? What is the prevalence of geriatric syndromes in this population, and the incidence of mortality? What is the incidence of pneumonia, the leading cause of death and emergency hospitalization in older people? What is the quality of life of the residents and their foster caregivers? The Karukera Study of Ageing in Foster Families (KASAF) is a prospective cohort study, designed to investigate these questions. This longitudinal study will assess the health status and medical and economic data of 250 foster family residents and their foster caregivers over a year.

Methods

Overview

The KASAF is a prospective, longitudinal cohort carried out in Guadeloupe (French West Indies), France, among foster families for older adults. This study will collect the socio-medico-economic data of older residents of foster families over a year, with a focus on hospital admissions. We will collect data using face-to-face interviews with the participants and their foster caregivers at baseline and after 6 and 12 months, and using phone interviews with the foster caregivers after 3 and 9 months.

Objectives

This study is an epidemiological study that aims to explore the characteristics of foster family residents and caregivers. We have identified a number of outcomes that may provide insight on their profile. As hospitalization is the main expensive item in the health trajectories of older people [16], the primary objective of the KASAF is to study hospital admission rates of residents of foster families over a year.

Several secondary objectives are also targeted: length of hospital stays during the 12-month follow-up period; number of consultations with a general practitioner, a medical specialist, or a paramedical professional; global cost of hospital stays; prevalence of geriatric syndromes (frailty, undernutrition, depressive symptoms, incontinence and dependency, sensory impairments; falls; polypharmacy; bedsores; and cognitive impairment); incidence of lower respiratory tract infection; quality of life of foster care recipients and their foster caregivers; and burnout in foster caregivers.

Study Sample

A total of 250 residents will be recruited over 6 months among the 300 older residents currently in foster families. The primary end point will be the hospitalization rate at 12 months. A 30% hospital admission rate over a year has been reported in the Incidence of pNeumonia and related ConseqUences in nursing home Resident study in nursing home residents [16]. A change in the hospitalization rate from 30% to 15% would be considered as significant from a clinical and public health point of view. For an risk of 5% and 250 participants, the expected CI will be 4.4% for a hospitalization rate of 15% and 5.7% for a 30% rate.

Study Recruitment

Inclusion Criteria

To be eligible for the study, residents must be older than 60 years. They must live in a foster family in Guadeloupe and benefit from the French social security.

Exclusion Criteria

The only exclusion criterion is refusal from the resident or his or her legal guardian to participate in the study.

Preinclusion Visit

Before the start of inclusions, residents, their families, and the foster caregivers will be informed of the goals and methods of the KASAF via information meetings and emailing campaigns.

The on-site investigator will screen for eligible participants among the residents of the foster family he or she is responsible for and will visit every resident meeting the criteria. He or she will inform them of the aims of the study, the computerized processing of their personal data, the access to their data in the local PMSI (Program for Medicalization of Information Systems [Programme de médicalisation des systèmes d'information]) server, and their right to object to their participation at any given time. An information leaflet will be given to every participant and to the referring professional caregiver identified by the investigator to complete the interviews. Foster caregivers and residents have a right to oppose the collection of their personal data.

Data Collection

At inclusion, nurses, geriatricians, and psychologists will collect sociodemographic, health-related, and psychosocial information. The inclusion visit is the first on-site interview and will be followed by 4 visits: 2 on-site visits 6 and 12 months after the inclusion visit, and 2 phone interviews 3 and 9 months after the inclusion visit (Table 1).

The interviewers will be conducted by health care professionals: psychologists, interns, and nurses, trained by the INSERM Team SEPIA (UMR 1219) from the University of Bordeaux, a team having expertise in implementing cohort studies.

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Table 1. Expected timeline for the KASAF[a].

Time line	Goal
July-September 2020	• Ethics Committee approval • Registration on ClinicalTrials.gov
September 2020	• Training sessions for the interviewers
November 2020-May 2021	• Inclusion period
February 2021-February 2022	• 3-, 6-, and 9-month follow-up
February 2022-May 2022	• End of 12-month follow-up (end of data collection)
June 2022-March 2023	• Data analysis
From May 2023	• Scientific communications

[a]KASAF: Karukera Study of Ageing in Foster Families.

On-site Interviews

Participants will be interviewed at baseline, after 6 months, and after 12 months. At each visit, different function domains will be assessed to measure (1) the ability to perform ADLs (eg, personal care, eating, and mobility) and (2) the ability to perform instrumental ADLs (eg, using the telephone, shopping, and managing finances). In fact, the interview implies both a physical evaluation (grip strength, gait speed, and blood pressure) and a cognitive and a psychological assessment. The estimated time for completion is 30 minutes but may vary depending on the participant's physical and cognitive status. Each of the participants will remain in the study for further follow-up interviews even if he or she is unable to answer, and reasons for incomplete data will be documented by the interviewers. Interviewers may split the visit into 2 parts to respect the participant's rhythm and to avoid missing data.

During on-site visits, foster caregivers will provide their own sociodemographic data (as well as information on the caregiving burden borne) and those of the elders to be cared for. Thus, both the quality of life of foster caregivers and the main sociodemographic or health data of the participants (eg, medical history, medication, nutrition, and ADL/Instrumental Activities of Daily Living [IADL] performance) are the primary focus of the study.

Phone Interviews

Interviewers will phone the foster caregivers twice to collect data on participants 3 and 9 months after the first visit. This phone call will provide an update on the mortality status of foster elders and health care services (ie, types and frequency of use). In the event of the death of a participant, date and cause of death will be sought and documented whenever possible.

Outcomes

Information on health care pathway comprises hospitalizations and consultations with general practitioners, specialists, and paramedics.

Primary Outcome

The main outcome is the number of hospitalizations over a year. The French hospital discharge database (PMSI) will provide information on hospital admissions. This information will be retrieved with the approval of the participants or their legal representative. Information on hospital admissions will also be collected from the foster caregiver for confirmation.

Secondary Outcomes

The secondary outcomes are as follows:

1. Length of hospital stays during the 12-month follow-up period, in terms of days and nights, will be collected. The number of consultations with a general practitioner, a medical specialist, or paramedical professional will be reported on the case report forms (CRFs). This information will mainly be collected during interviews with the foster caregiver using the RUD-Lite scale (Resource Utilization in Dementia questionnaire) [17]. This scale assesses the use of health care resources by people with dementia. The foster caregiver will complete this questionnaire at baseline and at subsequent follow-up visits (T3, T6, T9, and T12).
2. Global cost of hospitalization will be retrieved from the local PMSI databases.
3. Vital status (alive or deceased) will be collected at T3, T6, T9, and T12.
4. For the diagnosis of lower respiratory tract infections, at least two of the following symptoms must be present and a doctor must confirm the clinical evidence: (1) cough (starting or worsening), which may produce phlegm; (2) specific clinical signs during auscultation; (3) fever (≥38 °C); (4) chest pain; (5) rapid, shallow breathing (≥25 per minute); and (6) confusion or increased dependency [16].
5. Geriatric syndromes [18] in participants will be assessed at T0, T6, and T12 as follows:
    - Frailty will be assessed using Fried's phenotype [19], that is, 5 predefined physical frailty criteria such as weight loss, slowness, low physical activity, weakness, and exhaustion. This will be analyzed as a dichotomous variable, that is, 1=frail and 0=not frail.

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- The level of cognitive deterioration of the participants will be assessed using the Mini-Mental State Examination (MMSE) [20,21]. This 30-item scale assesses the severity of cognitive deterioration through items such as orientation, learning, attention, arithmetic, memory, language, and constructive praxis. The scale is rated from 0 to 30, reflecting the level of cognitive impairment.
- Depression will be assessed using the Center for Epidemiologic Studies—Depression Scale (CES-D) [22] validated in French by Fuhrer and Rouillon [23]. This 20-item questionnaire assesses depressive symptomatology, including 4 positive polarity items (happiness, self-worth, confidence, and enjoyment). The frequency of symptom occurrence during the past week is assessed by the participant using a 4-point Likert scale (never, occasionally, quite often, and frequently). The score ranges from 0 to 60. The higher the score, the more significant the symptomatology. High depressive symptomatology corresponds to a score above 16. Data will be collected at baseline, T6, and T12. For statistical analyses, the variable will be dichotomized (1=presence of depression and 0=absence of depression).
- The total number of medications taken by participants will be collected directly from the RUD-Lite questionnaire, at T0, T3, T6, T9, and T12, to assess polypharmacy.
- The total number of falls since the last visit will be collected at each follow-up from the foster caregivers.
- The Short Physical Performance Battery [24,25] will help to assess sarcopenia. Three subtests measure lower-extremity functions: keeping balance (feet side-by-side, semitandem, tandem balance position, to be kept for 10 s each); walking 4 m at usual pace, yielding a gait speed ratio (meter per second); standing up and sitting down 5 times as quickly as possible with the arms folded. Each movement is scored 0-4 points out of a total score from 0 to 12, with higher scores showing better physical performance. If the total score is below 8, there is a risk of sarcopenia. For the analyses, the variable will be dichotomized accordingly (1=sarcopenia; 0=no sarcopenia).
- Undernutrition will be assessed with the short version of the Mini Nutritional Assessment [26]. This questionnaire assesses nutritional status. A score below 12 indicates probable undernutrition. For the analyses, the variable will be dichotomized accordingly (1=undernutrition; 0=no undernutrition).
- Sensory impairments (audition and vision) will be collected by directly asking the foster caregiver. Variables will be dichotomized accordingly (1=hearing/vision impairment; 0=hearing/vision impairment).
- The level of independence in ADL and incontinence will be assessed using the Katz scale [27], a 6-item scale assessing independence in 6 basic ADLs: bathing, toileting, transferring, eating, dressing, and incontinence. For each activity, a score of 1 indicates complete autonomy, a score of 0.5 indicates partial autonomy, and a score of 0 indicates complete dependency.
- The level of independence in IADL will be assessed using the Lawton IADL scale [28]. The Lawton IADL scale measures 8 items: using the telephone, shopping, preparing food, housekeeping, doing laundry, using transportation, handling medications, and handling finances. The score is from 0 to 8; a score of 8 indicates total autonomy, and 0 indicates total dependency. In France, the Autonomy, Gerontology Iso-Resources (AGGIR) questionnaire has been developed by public authorities to quickly assess the degree of dependency of elderly people and assign a dependency group, ranging from 0 (bedridden, completely dependent) to 6 (no help required, the person is autonomous in everyday activities).
- Psychological and behavioral symptoms in dementia will be assessed with the short version of the NeuroPsychiatric Inventory or NPI [29,30]. This scale assesses the psychological, behavioral manifestations (agitation, hallucinations, apathy, etc), neurovegetative symptoms (sleep and appetite), and the impact on the professional's workload.

6. Feeling of loneliness will be captured with the 14th item of the CES-D [22,23]: I felt lonely. The answer possibilities are never, occasionally, often, and frequently. The answer "often" or "frequently" indicates a feeling of loneliness.
7. Risk of developing pressure ulcers will be assessed with the Braden scale, and pressure ulcers will be classified according to the National Pressure Ulcer Advisory Panel, European Pressure Ulcer Advisory Panel, and Pan Pacific Pressure Injury Alliance [31].
8. Quality of life and adaptation will be assessed as follows:
    - Quality of life of the participant will be assessed at baseline, T6, and T12 using the Questionnaire Quality of Life—Alzheimer's Disease (QoL-AD) [32,33]. This 13-item questionnaire assesses the participant's physical condition, mood, relationships with friends and family, financial difficulties, and overall quality of life. The questionnaire is to be administered to both seniors and caregivers, and thus is based on both self-rated health problems and proxy ratings from foster families. The items are evaluated using a 4-point ordinal scale ranging from poor to excellent, with a total score ranging from 13 to 52. For the weighted score, the participant's score is multiplied by 2, the caregiver's score is added, and the total is divided by 3 to bring the score back to the initial scale. In the proxy version, the foster caregiver will be asked to try to give the answer they think the participant would give.
    - Health-related quality of life of the participant will be assessed with the EQ-5D questionnaire [34]. This questionnaire assesses health conditions. It is the most widely used questionnaire in medicoeconomic analyses. It allows health outcomes to be assessed in terms of quality-adjusted life-years (QALYs). This indicator summarizes the length and quality of life in a single figure. The result of a cost-utility analysis is expressed

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in terms of the cost of gaining one QALY (ie, 1 year lived in perfect health). To estimate QALY, health-related quality of life is designed on a continuum from 0 (death) to 1 (perfect health). Each health status is thus assigned a weight of 0 to 1; the higher the score, the higher the corresponding quality of life.

- On the first page, the participant has to indicate, for each of the 5 dimensions assessed (mobility, independence, routine activities, pain or discomfort, and anxiety or depression), the state in which he or she finds himself or herself, by choosing 1 of the 3 options with increasing severity: no problems, problems, and extreme problems. The answers can be combined to describe the residents' health status, using a 5-digit number corresponding to the 5 answers.
- On the second page, the participant assesses his or her overall health using a standard vertical 20 cm visual analog scale (EuroQol visual analog scale), graduated from 0 to 100, from "best imaginable state of health" to "worst imaginable state of health."
- The score will be collected at T0, T6, and T12. The interviewer will use both the participant version and the proxy version. In the proxy version, the foster caregiver will be asked to try to give the answer they think the participant would give.

- Adaptation to the nursing home setting will be assessed at baseline, T6, and T12 using the Castonguay and Ferron scale [35]. This is a 17-item scale designed to identify who do not experience a favorable adaptation to the living conditions in nursing homes. The participants answer yes or no to a series of statements about their daily life and habits in the residence. A score of 16 or 17 indicates a good general adaptation to life in the residence, whereas a score of 11 or less indicates significant difficulties.
- Foster caregivers' quality of life will be assessed with the Medical Outcomes Study Short-Form General Health Survey—36 items (SF-36) [36], a widely validated health-related quality of life questionnaire that uses questions on physical, social, and psychological domains.
- Symptoms of burnout will be assessed with the Professional Quality of Life (Pro-QoL) scale [37]. This 30-item questionnaire yields 3 domain-specific scores: compassion fatigue (ie, the pleasure of being able to do your job well), work satisfaction, and burnout in helping professionals.

Table 2 shows an overview of data collection at each follow-up.

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Table 2. Data collection over time in the KASAF[a].

	Baseline (T0)	Phone interview (T3 months)	Follow-up (T6 months)	Phone interview (T9 months)	Final visit (T12 months)
Older residents—self-rated questionnaires and anthropometric measures					
CES-D scale[b]	X[c]		X		X
QoL-AD scale[d]	X		X		X
EQ-5D-3L scale[e]	X		X		X
Adaptation to the institution scale	X		X		X
MMSE score[f]	X		X		X
SPPB scale[g]	X		X		X
CDR score[h]	X		X		X
Foster caregivers—proxy-rated questionnaires about the resident					
Medical characteristics	X		X		X
Prescribed drugs	X		X		X
NPUAP-EPUAP[i] score[i]	X		X		X
Braden scale	X		X		X
ADL[j] and IADL[k] scales	X		X		X
AGGIR score[l]	X		X		X
MNA-SF scale[m]	X		X		X
NPI-ES scale[n]	X		X		X
QoL-AD scale	X		X		X
EQ-5D-3L score	X		X		X
RUD-Lite scale[o]	X	X	X	X	X
Health events		X	X	X	X
Alive/dead status		X	X	X	X
Foster caregivers—self-rated questionnaires					
Sociodemographic characteristics	X		X		X
Pro-QoL scale[p]	X		X		X
SF-36 scale[q]	X		X		X

[a]KASAF: Karukera Study of Ageing in Foster Families.

[b]CES-D: Center for Epidemiologic Studies—Depression Scale.

[c]X: information that will be collected during the indicative period.

[d]QoL-AD: Questionnaire Quality of Life—Alzheimer's Disease.

[e]EQ-5D-3L: EQ-5D three-level version.

[f]MMSE: Mini-Mental State Examination.

[g]SPPB: Short Physical Performance Battery.

[h]CDR: Clinical Dementia Rating.

[i]NPUAP-EPUAP: National Pressure Ulcer Advisory Panel–European Pressure Ulcer Advisory Panel.

[j]ADL: Activities of Daily Living.

[k]IADL: Instrumental Activities of Daily Living.

[l]AGGIR: Autonomy, Gerontology Group Iso-Ressources.

[m]MNA-SF: Mini Nutritional Assessment Short-Form.

[n]NPI-ES, NeuroPsychiatric Inventory for Health Staff.

[o]RUD-Lite: Resource Utilization in Dementia—Lite Version.

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[p]Pro-QoL: Professional Quality of Life.

[q]SF-36: Short-Form General Health Survey—36 items.

Expected Timeline

The first participant was included on November 16, 2020. The 1-year follow-up was ended in June 2022 (Table 1).

Patient and Public Involvement

There was no patient or public involvement in the design and conduct of this study. Nevertheless, we have had discussions with associations of foster caregivers who would like to use our results to strengthen their professional training.

Data Analysis

First, the analysis will describe the number of included participants, the inclusion curve (evolution of the number of people included between the first and last inclusion), the number of theoretical visits, the number of visits actually made, and the ratio of both (number of visits made or number of theoretical visits).

A description of the rate and causes of death and study dropout will also be provided.

The following quantitative variables described in terms of number of staff, mean, and interindividual SD and 95% CI of the mean, median, range, and IQR values: number of hospitalizations, total length of hospitalization, total cost related to hospitalizations, total number of consultations with a general practitioner, total cost of low respiratory infections, total number of falls, MMSE score, total number of drugs, NPI score, QoL-AD score, SF-36 score, and Pro-QoL score.

Qualitative variables (ordinal: AGGIR grid, feeling of loneliness; dichotomous: vital status; presence or absence: frailty syndrome, depression, undernutrition, visual impairment, hearing impairment, incontinence, ADL dependency, IADL dependence) of participants at inclusion will be described in terms of frequency and number.

Comparisons between the 3 times (T0, T6, and T12) will be performed using repeated-measures ANOVA for quantitative variables and the Cochran-Armitage test for trend for qualitative variables.

Statistical analyses will be performed using the RStudio software (version 2.7; Posit Software).

Quality Control

During the study, quality control will be carried out by the project manager and the clinical research assistant. All interviewers will be required to attend training on data collection and data reporting. Under no circumstances should the names or addresses of the individuals concerned be made clear.

The electronic CRF will allow single data entry, which will be double checked by the investigators. Data management will be performed using the Capture System software (Clinsight). The Clinsight web-based module will allow remote access to the database, with a 128-bit SSL encryption. Each interviewer will have a personal and unique name and access code that will allow him or her to enter and correct data—everything is documented and saved every day on another server.

Ethics and Dissemination

The KASAF is an observational study involving human participants without any identified risk for the participants' safety. In accordance with this status, the need for a signed consent form has been waived off by the regulating bodies (law 2012-300). Residents will be provided with an information leaflet outlining the key points of the study. Participation is voluntary and residents can refuse to participate or discontinue participation at any time without prejudice. Considering the high proportion of family foster residents with cognitive impairment, the on-site investigator will ensure that the residents have understood the implications of their participation. If the resident is under guardianship and/or is unable to understand, nonopposition from the legal guardian or a documented contact person will be sought as well.

Nonopposition or opposition will be documented in the participant's medical file.

This study will be carried out in accordance with state laws regulating research involving human participants and with the Helsinki declaration.

The KASAF was registered under the RGB-ID number 2020-A00620-39 and was approved by the French Sud Méditerranée III Ethics Committee on July 1, 2020. Data analysis will be performed on-site (University Hospital, Guadeloupe). All documents related to this research will be archived for 15 years after completion of the study.

Results

Recruitment opened in September 2020 and ended in May 2021, with 109 older people recruited and 56 respective foster caregivers. The 1-year follow-up was ended in June 2022. Data analyses are ongoing, and the first results are expected to be published in May 2023.

Discussion

Foster families are a potentially innovative way to accommodate older people with dependency. Epidemiological data from the study will describe the clinical characteristics of older people in foster families. Beyond mortality and morbidity, the numerous outcomes will allow assessing the evolution of geriatric syndromes over time. In addition, this study will also look at the sociodemographic profile of foster family caregivers—who are not necessarily health professionals—in terms of age, life course, quality of life, or burnout. It may offer a basis for specific training courses and help the authorities to better characterize the requirements an applicant must meet to become a fully-fledged foster caregiver.

This descriptive study could help define the place of the foster family in the transition from frail elderly to dependent elderly status. Indeed, foster family could also be an intermediate stage

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between home care and nursing home care. The epidemiological data obtained will be compared with data from other management systems. In this perspective, we will conduct a twin study in nursing home, the KArukera Study of Aging in EHPAD (KASEHPAD) study, which will take place in 14 nursing homes in Guadeloupe. Both studies will have similar designs and objectives. The protocol for the KASEHPAD study has been registered on ClinicalTrials.gov (NCT04587466). If patient characteristics are similar, it will be possible to compare mortality, hospitalization rates, and all variables of interest, including cost of care, between these 2 care settings. Depending on the profile of the KASAF's participants, we could also compare foster care with home care or residential care facilities [38]. The collection of epidemiological data in foster family is therefore an essential step to carry out randomized studies between these different care pathways, with the aim of determining the most effective and efficient care.

Foster families have never been formally assessed, the most robust results dating back to 30 years. In theory, it is less expensive than nursing homes for the community, but in the absence of scientific studies on the associated health outcomes (number of hospitalizations, deaths, etc), this model has not been validated and remains rare in metropolitan France. Yet, foster caregivers could be valuable assets in health care, thanks to their intimate knowledge of older persons and their pathologies, compared with nursing home staff, which have a high turnover, thus reducing avoidable hospitalizations and medical consultations.

Moreover, in the event of a health crisis such as the one experienced with the COVID-19 pandemic, measures of isolation and social distancing are much easier to implement, as foster family residents live in small family units, usually have single rooms, with less comings and goings than in nursing homes. The collected data will be used for exploring the characteristics of the foster home residents with aims that might not be considered today (1) because they are out of topic and (2) because science evolves.

This study presents limitations. We will not have access to data from informal caregivers, who could provide different insights on the participant's state of mind or daily life. Also, cost analyses will focus only on hospitalization costs. This is why an ancillary study will be carried out after the end of the KASAF, using information from the national health insurance database. This study will accurately assess the cost of the entire health care pathway, including nursing, medical transportation, and other health care expenses. Finally, the KASAF does not include randomized interventions versus nursing home limiting causal interpretations of the results.

We hope that our results will help introduce more rationality into social and economic debates, sometimes led by accounts of personal experiences and extrapolated indicators, often for lack of robust data, and help ensure that public health policies are based on sound scientific evidence. Indeed, our data will be used to support the coordination of institutional funding bodies, especially resource allocation.

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Data Availability

The data sets generated during and analyzed in this study are available from the corresponding author on reasonable request.

Authors' Contributions

RV, DB-M, and MT-T wrote the initial protocol. DB-M and RV wrote the manuscript. MT-T, NS-T, JFD, and HA reviewed and updated the manuscript. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

ADL: Activities of Daily Living
AGGIR: Autonomy, Gerontology Group Iso-Ressources
CES-D: Center for Epidemiologic Studies—Depression Scale
CRF: case report form
IADL: Instrumental Activities of Daily Living
KASAF: KArukera Study of Ageing in Foster Families
KASEHPAD: KArukera Study of Aging in EHPAD
MMSE: Mini-Mental State Examination
NPI: NeuroPsychiatric Inventory
PMSI: Program for Medicalization of Information Systems
Pro-QoL: Professional Quality of Life
QALY: quality-adjusted life-year
QoL-AD: Questionnaire Quality of Life—Alzheimer’s Disease
RUD-Lite: RUD-Lite: Resource Utilization in Dementia—Lite Version
SF-36: Short-Form General Health Survey—36 items

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Protocol

An Adapted Cancer Screening Education Program for Native American Women With Intellectual and Developmental Disabilities and Their Caregivers: Protocol for Feasibility and Acceptability Testing

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Abstract

Background: Women with intellectual and developmental disabilities (IDD) do not undergo breast and cervical cancer screening at the same rate as women without IDD. IDDs are diagnosed in childhood, are lifelong, and involve difficulties in adaptive behaviors and intellectual functioning. Native American women also experience disparities in breast and cervical cancer screenings. Despite known disparities, women with IDD are often not included in health promotion programs, and there is a need for evidence-based programming for those with intersectional identities, such as Native American women with IDD.

Objective: This study aims to assess the feasibility and acceptability of My Health My Choice (MHMC), an adaptation of the Women Be Healthy 2 program. There are 2 parts to the study: adaptation of the Women Be Healthy 2 program and feasibility and acceptability testing of MHMC.

Methods: Individuals aged over 18 years who identify as Native American females with IDD and their caregivers (N=30 women-caregiver dyads) are eligible for the study. Participants, who are affiliated with 2 partnering sites in Arizona (1 rural and 1 urban), complete pre- and postsurveys assessing knowledge, self-efficacy, and screening expectations before and immediately after completing the program. In addition, all participants complete brief satisfaction surveys after each of the 6 educational sessions. A subsample of Native American women with an IDD (n=12), caregivers (n=12), and community health educators (n=2) who participate in the MHMC program will provide semistructured qualitative input regarding the content, delivery, and cultural relevance of the program.

Results: The adaptation of the culturally responsive MHMC program was completed in August 2021. In November 2021, the project team began recruitment for feasibility and acceptability studies. Feasibility will be examined using participation metrics, and acceptability will be measured using satisfaction measures. Pre- and postmeasures in cancer screening knowledge, self-efficacy, and screening expectations will examine improvements among participants.

Conclusions: The results of feasibility and acceptability testing of MHMC will guide future implementation studies of the program.

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KEYWORDS

community-engaged research; community-engaged; engagement; cancer; breast; cervical; screening; breast cancer screening; cervical cancer screening; intellectual; developmental; cognitive; disability; disabilities; Native American; indigenous; women's health; feasibility; acceptability; patient education; prevention; patient knowledge; health knowledge; health education

Introduction

Background

About 1 in 4 adults in the United States report living with a disability [1]. Among US adults with disabilities, the prevalence of disability is higher among Native American populations and among young adults (aged 18-44 years), cognitive disabilities (including intellectual and developmental disabilities [IDD]) are the most prevalent [1]. IDDs are disabilities diagnosed in childhood that involve difficulty with adaptive behaviors and can include limitations in intellectual functioning [2].

Cancer Screening in Women With Disabilities and Native American Women

Although screening rates for Native American women with IDD are not available, we do have data that indicate suboptimal screening in the intersectional population, especially regarding cervical cancer screening. Women with disabilities, particularly those with IDD, do not undergo cancer screening at the same rate as those without disabilities [3,4]. One reason that individuals with IDD do not receive cervical cancer screening may be that they have been perceived as asexual [5] and are thus less likely to receive comprehensive preventive sexual health care than women without IDD or other disabilities. For example, women with IDD are less likely to receive human papillomavirus screening compared with women without IDD [6]. While nearly 3 quarters of individuals with IDD (74%) reported having had a mammogram (vs 65.6% of women in the general population), only 57% of women with IDD reported cervical cancer screening in the past 3 years (vs 68.1% of women in the general population) [5-7]. Native American women are also less likely than the general population to undergo breast cancer screening (56.7% vs 71.5%, respectively) and cervical cancer screening (76.9% vs 83%, respectively) [8-10].

Factors Influencing Adherence to Cancer Screening

The complex interplay among disability, culture, and health system-level factors complicates adherence to cancer screening. Many Native American people in the United States live in rural areas that present unique challenges to participating in preventive health care and require persistence to complete screenings [11,12]. Individuals with disabilities face cultural biases that affect the way health care professionals perceive them and may influence their preventive health care, including cancer screening [13,14]. Women with IDD and Native American women are at an increased risk of interpersonal violence [15-19]. In addition, individuals with IDD have experienced ableism and trauma in broader society and health care interactions [17], and those who are also Native American experience historical trauma [18]. Historical trauma refers to the violence imposed on Native American communities over multiple generations and includes US policies of forced relocation, family separation, and the prohibition of spiritual activities [20]. While violence and trauma arise from different histories, these individual and collective experiences may result in hesitance to engage with health care institutions [18]. We discuss our approach to address these experiences in the *Theoretical Frameworks* section.

Furthermore, family and support networks may influence adherence. Culturally responsive health education programs for people with IDD [21] and Native American communities [22] often involve families or other supporters. Women with IDD who live at home with their families are less likely to receive preventive health care services compared with those living in residential facilities [23]. Individuals from racial and ethnic minority groups, including Native Americans, are more likely to live with family caregivers compared with residential facilities [24]. Specifically, in Arizona, where this research is being conducted, 78% of individuals with IDD live with family caregivers [25]. Research indicates that caregivers (including family, friends, or paid support professionals) may believe that cancer screenings are unnecessary or that they do not want to make decisions for a person who cannot communicate their consent. Caregivers believe that by avoiding screening, they protect a woman with IDD from discomfort during screening or a possible cancer diagnosis [26]. Adding to the complexity of women's self-advocacy, women with IDD living with family caregivers have less knowledge about breast and cervical cancer screenings compared with women with IDD living alone or with a spouse [27,28].

Efforts to develop educational resources specific for women with IDD to encourage breast and cervical cancer screening have demonstrated promising results [29-31]. *Women Be Healthy 2 (WBH2)* was developed to assist women with IDD who had expressed difficulties with or had never undergone breast or cervical cancer screening. After attending the *WBH2* program, participants showed improved knowledge about breast and cervical cancer screenings [31]. However, the *WBH2* curriculum was not implemented with Native American women; therefore, its relevance for this population is uncertain. In collaboration with community partners, this project aims to test the feasibility and acceptability of *My Health My Choice* (MHMC), an adaptation of the *WBH2* program for Native American women with IDD, to improve their cancer screening knowledge and self-efficacy.

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Original Intervention—WBH2

WBH2 was selected for adaptation and testing, as a previous implementation of the program led to knowledge gains regarding breast and cervical cancer screenings among women with IDD [31]. *WBH2* consisted of 11 twice-a-week 60-minute sessions focused on the education about breast and cervical cancer screening, self-advocacy skill development, and techniques for anxiety reduction in women with IDD. The classes contained information on mammography or Papanicolaou testing, preparation for mammography or Papanicolaou testing procedures, breast and pelvic anatomy, and tools and skills for cancer screening visits. The course content was taught in an interactive way. For example, instructors read scenarios and asked students to consider what they would do if they were confronted with the challenges in the scenarios. Field trips to health providers to touch and see the equipment used in cancer screenings were also part of *WBH2*. *WBH2* did not proactively include caregivers as colearners in the program. *WBH2* was implemented and tested in a population of White and African American–identifying women with IDD attending urban adult day programs in a southeastern state in the United States [31]. Adult day programs are professionally run programs that adults with IDD attend to receive community living and other health-related programming [32].

Theoretical Frameworks

Overview

This project is guided by the social model of disability [33] and socio-ecological model [34], which acknowledge the influence of political, social, and interpersonal structures on health. These frameworks allow the study team to complete a multilevel assessment of cancer screening disparities experienced by Native American women with IDD, which needs to be addressed in the content and structure of the education program. In the final refinement and testing of the culturally informed curriculum, we used the social cognitive theory (SCT) [35] in the design of our intervention, since it has been used previously by other researchers as a theory to affect cancer screening behavior change among Native American women [36]. SCT includes a construct, reciprocal determinism, which frames the interactions of women with IDD and influences their decisions to complete cancer screenings. This theory guides our data collection and analysis and is inclusive of other concepts, such as trauma-informed care and self-determination.

Trauma-Informed Approach and Self-determination

Within SCT, using a trauma-informed approach addresses internal and external reinforcements and their impact on health care decision-making. Trauma-informed approaches can also address the expectations construct in SCT, as women may have expectations about cancer screenings, based on previous trauma-inducing health care interactions. Trauma-informed approaches aim to prevent future retraumatization by providing a wide variety of delivery methods [37,38]. The program includes training for interventionists on trauma-informed methods and identifying potential behavioral triggers so that they are prepared to handle situations in which a program participant finds the course material emotionally difficult. The program also creates a safe space with ground rules for the discussion of topics.

Another important framing concept for this project is self-determination, which is central to both the Native American community and the IDD self-advocacy movement [39,40]. Self-determination among adults with IDD means making one's own decisions regarding one's needs and has been found to be a critical component for maintaining a good quality of life and for addressing population-level health disparities [41,42]. Among Native Americans, self-determination is necessary to reclaim ownership and control of community resources to meet the needs of the Native American population. Native American self-determination is needed for research on Native American populations [43]. This project promotes self-determination throughout the research process, as a community-engaged approach requires researchers and community members to work in equal partnerships through data collection, data analysis, and dissemination [44].

Objectives and Research Aims

The long-term goal of this community-engaged research project is to decrease breast and cervical cancer disparities among Native American women with IDD through culturally responsive and universally designed education in a southwestern US state. This paper provides a study protocol for an ongoing community-engaged research study focused on addressing breast and cervical cancer screening disparities among Native American women with IDD, via the delivery of a health education program titled MHMC. Here, we briefly describe how we used community-engaged methods to develop the MHMC program and then describe the feasibility and acceptability testing methods.

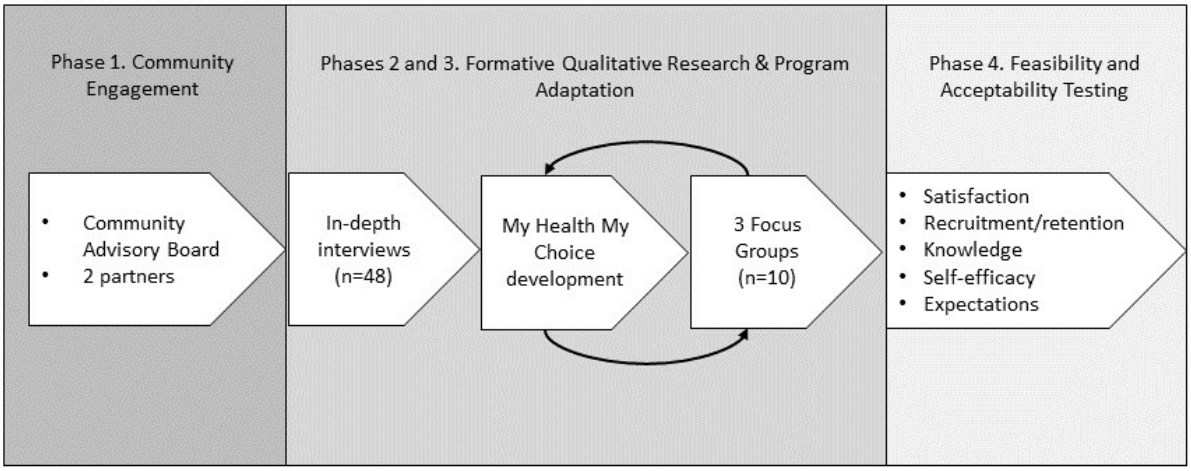
Methods

Project Timeline

This project was initiated in September 2017 with the establishment of an advisory board and relationship-building with community partners in the research project. Once urban and rural community partnerships were established, the project team began 2 steps of formative qualitative research to inform the adaptation of *WBH2 (September 2019-August 2021)*. The project team began feasibility and acceptability testing of MHMC in November 2021. Figure 1 illustrates the study flow, including the phases of development, implementation, and testing of MHMC described in further detail below.

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Figure 1. Study flow.



Ethics Approval

The study was approved by the Institutional Review Board of the University of Arizona (STUDY00000034, September 28, 2021, with original protocol number 1709856263, approved September 27, 2017), with a ceded review by the Northern Arizona University Institutional Review Board (protocol #1132744-7). The study was also approved by all required tribally affiliated entities.

Phase 1: Community Engagement

This study uses a community-engaged approach. Similar to Community-Based Participatory Research, community-engaged research is an equity-based approach that involves communities throughout the research process by considering important elements of the community (eg, resources and strengths that the community brings) [43,45,46]. This approach also consists of building trust with communities and involving community members throughout all phases of the project, including defining, implementing, and engaging in research. This project utilizes an advisory board design to serve as an element of community feedback and research oversight. This 11-person advisory board includes community members with familial ties to Native American women with IDD and representatives from cancer control programs, Native American health programs, and disability services. The advisory board has met quarterly for 1 to 2 hours since the inception of the project to provide ongoing supervision and feedback on the project, including ideas about how the program could be enhanced to meet community needs and suggestions for implementation. Early in the project, the advisory board was asked for input on initial revisions to *WBH2*, offering thoughts about the content and structure, including the need for cancer diagnosis information and for a reduction in the number of sessions [47]. A community-engaged approach was chosen for the project because of the growing recognition of the importance of including community members as partners in research efforts focused on addressing health [48,49].

Phase 2: Formative Qualitative Research

Cultural adaptation of the *WBH2* curriculum in partnership with a Native American urban health and social services provider and a Native American rural cancer screening and support provider was complete at the time of this writing. Cultural adaptation occurs in 2 steps. In step one, individual in-depth interviews with Native American women with IDD, caregivers, health care and disability providers, and community members were completed. The results of the interviews [50] were discussed with the advisory board and members suggested program activities to address these findings. The results of the interviews provided an initial framework for culturally adapting the program, now called MHMC. Formative research and advisory board feedback on the findings led to changes in the program's content and structure, including how and by whom it should be delivered. A total of 3 focus groups (n=10) were completed with both partner sites and throughout the state of Arizona to review and update the program. Preliminary program recommendations were reviewed via focus group discussions at each partner site with partner site program staff, caregivers, and Native American women with IDD to help the team refine the program.

Our community partners represent multiple tribal identities; one represents one tribe in the state, and the other is an urban Indian center that serves tribal members from all over the United States living in Southern Arizona. Acknowledging the diversity of tribal groups and the diversity among women with IDD allows the project to identify the diversity and commonality of experiences with breast and cervical cancer screening among Native American women with IDD.

Phase 3: Adapting the Program (MHMC)

Overview

The adapted program takes place in six 1-hour sessions provided weekly over the course of 6 weeks. The education program addresses the personal, interpersonal, and environmental barriers to cancer screening experienced by Native American women with IDD. The program's six learning objectives include (1) identify healthy lifestyle habits for women, (2) practice managing anxiety about cancer screenings, (3) identify what cancer is and the parts of the body being screened for cancer, (4) learn about breast cancer screening, (5) learn about cervical cancer screening, and (6) practice self-advocacy in health care. Figure 2 shows a screenshot of a program element. Key components include engaging Native American women with

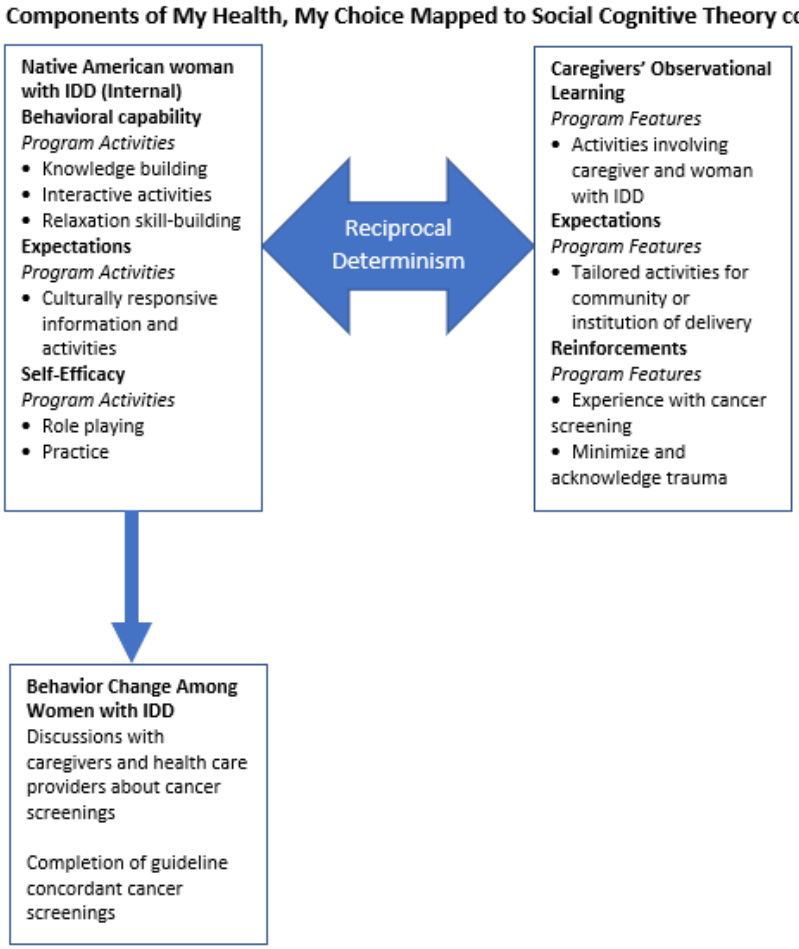
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IDD and their care providers in discussions regarding cancer screening decisions, bringing in culturally relevant ways to share knowledge, and providing resources for dealing with the next steps in the case of screening results that require diagnostic testing. Below, we discuss how each of these components aligns with the constructs of the SCT. Finally, we describe how the COVID-19 pandemic generated additional curriculum delivery decisions. Figure 3 provides a summary of the SCT constructs aligned with program features.

Figure 2. My Health My Choice (MHMC) program component.



Figure 3. Components of My Health My Choice mapped to the social cognitive theory constructs. IDD: intellectual and developmental disabilities.



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Caregiver Involvement

Involving caregivers in the MHMC intervention addresses the central concept of SCT, reciprocal determinism, as women will make individual decisions regarding cancer screenings (internal) in collaboration with their caregivers, who can reinforce the decision.

Native American Cultural Elements

Native American cultural elements were also included in the program. The content highlights self-advocacy, using peers from the same Native American community to deliver the intervention, and ensuring that indigenous female healers rather than male healers are included. Culturally relevant imagery and metaphors are used to share the concepts of health, cancer, and self-advocacy. Providing culturally relevant materials may help address SCT constructs of reinforcement and expectations. Reinforcements are responses to behavioral choices that may influence future behaviors. Providing culturally relevant concepts to explain the importance of cancer screening may reinforce or encourage the decision to undergo cancer screening. Expectations are expected consequences of completing an activity. Demonstrating that participating in cancer screening is something that is expected and culturally accepted through culturally relevant materials may encourage screening.

Hands-on Activities and Anxiety Management

The use of hands-on activities and anxiety reduction techniques is provided with the intent to build knowledge, skills, and confidence through observational and experiential learning about cancer screenings among women with IDD and their caregivers. Within SCT, one must have self-efficacy (or confidence) as well as behavioral capability (knowledge and skills) to initiate a behavior. Observational learning in SCT refers to behavior change that can be encouraged through observations of modeled behavior. The program provides opportunities for hands-on activities to improve knowledge and understanding about a healthy body and cancer screening. The program includes tactile craft activities that demonstrate what will happen to a breast during a mammogram (ie, pressing a stress ball between your hands) and teaching about parts of the body involved in cancer screening (ie, creating a uterus and cervix with a baby sock). The stress ball activity can also help with anxiety in women with IDD about breast cancer screening as it shows pain visually (eg, showing a stress ball being squeezed in the mammogram machine) but also communicates how pain and discomfort pass. Each session opens and closes with relaxation technique exercises for women to practice managing their anxiety around cancer screening. Finally, women with IDD and their caregivers in the program also write out their plans and action steps to participate in cancer screening.

COVID-19 Modifications to Delivery of the MHMC Program

The plans for implementing the MHMC program were modified because of the COVID-19 pandemic. The project team modified the program to be delivered remotely to dyads of Native American women with IDD and their caregivers. Each participant has a MHMC toolkit delivered to their home with printouts of educational resources and items needed for hands-on activities. For women residing in urban areas with adequate internet access, the program is delivered via Zoom by a health educator. For women residing in more rural areas with limited or inconsistent internet access, the program is delivered over the phone by a health educator. A project website was developed to distribute educational materials. Videos were produced at each partner site using imagery and voice overs (ie, social story format) to walk women through the process of getting a Papanicolaou test and a mammogram with a local provider.

Phase 4: Feasibility and Acceptability Testing

Overview

The study's second aim, which is currently being completed, tests the feasibility and acceptability of MHMC and explores knowledge, self-efficacy, and screening expectation outcomes among Native American women with IDD and their caregivers. The culturally adapted MHMC program is implemented by female community health educators affiliated with our 2 community partners. Native American women with IDD (and their caregivers; N=30 student-caregiver dyads and n=15 dyads per partner site) complete pre- and postsurveys assessing knowledge, self-efficacy, and screening expectations before and immediately after completing the program. In addition, all participants complete brief satisfaction surveys following each of the 6 educational sessions (Multimedia Appendix 1). A subsample of Native American women with IDD (n=12), caregivers (n=12), and community health educators (n=2) who participated in the *My Health, My Choice* program provide semistructured qualitative input regarding the content, delivery, and cultural relevance of the program. Finally, the team tracks recruitment, attendance, demographic information, completion rates, and fidelity data for each session throughout the program.

The inclusion criteria for our second study aim are as follows: women with IDD must self-identify as Native American women with IDD and report being born a girl and caregivers must self-identify as caregivers for Native American women with IDD. Both types of participants must reside in Arizona, be aged over 18 years, and speak English or the other Native American language spoken in rural areas. Participating Native American women with IDD may choose a caregiver to participate in the program with them. The caregiver could be a family member, friend, legal guardian, or a paid support professional. If the caregiver identifies as a male, the questions collected at baseline and follow-up do not include information about their receipt of or intention to get screened for breast or cervical cancer. The following sections and Table 1 describe the measures and timing of the data collection (ie, T_0 is time zero and T_1 is time 1) used to evaluate the feasibility and acceptability of MHMC.

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Table 1. Measures by participant type and intervention session time point.

All measures	Participant type	Time							
		T_0	T_1	T_2	T_3	T_4	T_5	T_6	T_7
Demographics	Woman with IDD[a], caregiver	✓	—[b]	—	—	—	—	—	—
Cancer screening knowledge	Woman with IDD, caregiver	✓	—	—	—	—	—	—	✓
Cancer screening self-efficacy	Woman with IDD, caregiver	✓	—	—	—	—	—	—	✓
Cancer screening history	Woman with IDD, caregiver (female only)	✓	—	—	—	—	—	—	—
Cancer screening expectations	Woman with IDD, caregiver (female only)	✓	—	—	—	—	—	—	✓
Program satisfaction	Woman with IDD, caregiver	—	✓	✓	✓	✓	✓	✓	—

[a]IDD: intellectual and developmental disabilities.

[b]Data not collected at the time point.

Demographics and Screening History

We collect demographic information for each Native American woman with IDD (program participants) and their caregivers. Demographic information includes age, gender identity, disability status, race, ethnicity, level of education, employment status, health insurance coverage, home residence (ie, in one's own home or group home), and guardianship status. In addition to demographic data, we collect information about the participant and female caregiver breast and cervical cancer screening history using questions from the PhenX toolkit [51]. Funded by the National Institutes of Health, the PhenX toolkit is a collection of standard data collection protocols for conducting biomedical research, thus allowing cross-study analysis [51].

Knowledge and Self-efficacy

We collect the following data from each MHMC participant at baseline and follow-up: (1) breast cancer screening knowledge, self-efficacy, and screening expectations (female participants only) and (2) cervical cancer screening knowledge, self-efficacy, and screening expectations (female participants only). Mammography knowledge is measured using the Mammography Preparedness Measure developed by Wang et al [52] to measure the understanding of mammography's purpose and the procedure itself among women with IDD. Verbally administered, the instrument asks the participant to role-play, providing advice to the interviewer, who will be getting a mammogram. Questions are asked using plain language about the body parts checked by a mammogram, why it is used, how it is done, and how often it should happen. Parallel questions to assess cervical cancer screening or Papanicolaou testing knowledge along with scripts for both knowledge assessments were created by the authors of this study and are presented in Tables 2 and 3. We further adapted this instrument by including images of a mammography machine and an exam table with stirrups, as visual supports can assist individuals with IDD in processing information [53,54].

Self-efficacy refers to an individual's perception of their capacity to perform certain tasks in their life [35]. To assess self-efficacy in breast and cervical cancer screening, we modified the colorectal cancer self-efficacy instrument [55] that has been used in a Native American population [56], as shown in Table 3. Participants view an image of a ladder and read a script that is loosely based on the self-anchoring striving scale by Cantril. [57]. The bottom of the ladder corresponds with a score of zero, or *not sure at all* and the top of the ladder corresponds with a score of 10 for *very sure*. Participants are asked the following question, "Imagine that this ladder is a way of picturing your confidence, or how sure you are that you can do something. The top of the ladder indicates that you are very sure, and the bottom indicates that you are not sure at all. For these next questions, what place on the ladder (or number between 0 and 10) matches how sure you feel?" Native American women with IDD and their female caregivers are then asked 4 questions regarding their ability to *decide* and to *get* a cancer screening (Tables 4 and 5). Both male and female caregivers are asked parallel self-efficacy questions regarding their confidence in *supporting* a woman with a disability that they care for through the cancer screening process.

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Table 2. Breast and cervical cancer screening knowledge assessments script.[a]

Knowledge of breast cancer	Knowledge of cervical cancer
Script: *"A mammogram is a machine that looks for cancer in your body. Here is a picture of a mammogram machine. Today I am pretending to go to the doctor's office and will be asked to get a mammogram."* (Show image)	Script: *"Here is a picture of an exam table I would lay down on to get a Pap test*[b]*. Today I am pretending to go to the doctor's office and will be asked to get a Pap test."* (Show image)
"Think back to a time that you went to the doctor's office. Now, I want you to pretend that you are at the doctor's office with me. I need your help in understanding what the doctor is asking me to do. Thank you for helping me."	*"Think back to a time that you went to the doctor's office. Now, I want you to pretend that you are at the doctor's office with me. I need your help in understanding what the doctor is asking me to do. Thank you for helping me."*
"Do your best. If you don't know the answer it is okay."	*"Do your best. If you don't know the answer it is okay."*
"Please make sure you help me on your own, do not have your family or others help you."	*"Please make sure you help me on your own, do not have your family or others help you."*

[a]Questions regarding knowledge of breast cancer were adapted from the Mammography Preparedness Measure [52], and cervical cancer knowledge questions were modeled on these questions.

[b]Pap test: Papanicolaou.

Table 3. Breast and cervical cancer screening knowledge assessments.

Breast cancer questions	Answers considered correct	Cervical cancer questions	Answers considered correct
What part of the body is the mammogram for?	Breast (or any reasonable slang term)	What body part is a Pap[a] test for?	Cervix, or inside the vagina, or private parts (or any reasonable slang term)
Why would I have a mammogram?	To check for cancer, must include cancer and screening (not curing, etc)	Why would I have a Pap test?	To check for cancer, must include cancer and screening (not curing, etc)
Would I have to take my clothes off for a mammogram?	Yes, top only, shirt and bra, etc	Would I have to take my clothes off for a Pap test?	Yes, bottom only, pants, underwear
When I have the mammogram how long will I be in the machine?	Any answer under 30 min	When I have my Pap test, how long will it take?	Any answer under 10 min.
How often am I supposed to have a mammogram?	Every year or every other year, annually, or based on when your doctor recommends	How often should I have a Pap test?	Every 5 years or based on when your doctor recommends

[a]Pap test: Papanicolaou test.

Table 4. Breast cancer and cervical cancer screening self-efficacy assessment script[a].

Script	Assessment
Script: imagine that this ladder is a way of picturing your confidence, or how sure you are that you can do something. The top of the ladder means that you are very sure, and the bottom means you are not sure at all. For these next questions, what place on the ladder (or number between 0 and 10) matches how sure you feel." [b]	

[a]Original instrument measuring self-efficacy in colorectal cancer screening was assessed using a four-point scale by McQueen et al [55] and further described in a Native American context by Frerichs et al [56].

[b]Adapted from self-anchoring striving scale by Cantril [57].

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Table 5. Breast cancer and cervical cancer screening self-efficacy assessments.

Original question[a]	Breast or cervical cancer screening questions[b]	Caregiver modification[c]
How sure are you that you can decide whether or not to get screened for colon cancer?	How sure are you that you can *decide whether or not to get a mammogram/Pap*[d]*test?*	...support the woman with a disability that you care for in deciding whether or not to get a mammogram/Pap test?
How sure are you that you can complete colon cancer screening?	How sure are you that you can *get a mammogram/Pap test?*	...support the woman with a disability that you care for to get a mammogram/Pap test?
How sure are you that you can complete colon cancer testing even if you are nervous about it?	How sure are you that you can *get a mammogram/Pap test, even if you are nervous about it?*	...support the woman with a disability that you care for to get a mammogram/Pap test, even if she is nervous about it?
How sure are you that you can do what is needed to prepare for colon cancer screening?	How sure are you that you can do what is needed to prepare for a mammogram/Pap test?	Not assessed

[a]The original survey had 8 questions, of which we use 4.

[b]Mammogram and Papanicolaou test asked as separate questions.

[c]Text in this column replaces underlined words from the previous column.

[d]Pap test: Papanicolaou.

Cancer Screening Expectations

Using the same ladder image described for self-efficacy questions, participants are asked to rank how they feel about planning to get a screening with zero, indicating that they are not planning to get a screening to 10 that they are definitely planning to participate in cancer screenings. Native American women with IDD and their female caregivers are asked 3 questions regarding their personal expectations to get cancer screening (Table 6). Both male and female caregivers are asked about their expectations in assisting the woman they care for to get their cancer screening (Table 6).

Table 6. Questions assessing participant and caregiver expectations for getting, or assisting with getting, a mammogram or Papanicolaou test[a].

Breast or cervical cancer expectation questions[b]	Caregiver modification[c]
I plan to get a mammogram or Pap test[d].	Assist the woman with a disability I care for in getting
I plan to discuss getting a mammogram or Pap test with my doctor.	Support the woman with a disability I care for to discuss
I plan to discuss getting a mammogram or Pap test with people who support me (for example: family member, friend, staff, helper, direct support professional).	Not assessed

[a]0 to 10 scale, shown via a ladder for self-efficacy questions in Table 4.

[b]Mammogram and Papanicolaou test asked as separate questions.

[c]Text in this column replaces underlined words from previous column.

[d]Pap test: Papanicolaou.

Acceptability

The acceptability of the program is captured by asking program participants to complete a brief satisfaction survey regarding the session's format and content immediately after each session. Program feasibility is assessed by tracking the attendance and completion rates of all participants across all 6 sessions. A subsample of Native American women with IDD (12/30, 40%), caregivers (12/30, 40%), and community health educators (2/4, 50%) who participated in the *My Health, My Choice* program complete semistructured qualitative interviews regarding the content, delivery, and cultural relevance of the program. Fidelity is measured using data collected from Community Health Educators after each session. Data points include session start or end time, delivery method, challenges in delivery, ratings of the session, and participant engagement.

Analyses

Preliminary analyses of quantitative and qualitative data will be shared with the advisory board to assist with interpretation. On the basis of the advisory board input, we will finalize the analyses and determine the next steps for the research.

Statistical Analysis

Our primary outcomes will be participation metrics (feasibility and acceptability) including the percentage of women who choose to participate, the percentage of enrolled participants at each session, and the percentage of enrolled participants retained through the last session. A sample size of 30 Native American women with IDD and their caregivers from rural (15/30, 50% woman-caregiver dyads) and urban (15/30, 50% woman-caregiver dyads) settings will allow us to estimate participation and retention rates within an SE of 9% overall or within an SE of 13% within each setting (rural vs urban). Our secondary quantitative outcomes will be pretest to posttest differences for each of the following measures: (1) cancer screening knowledge and expectancy among Native American women with IDD; (2) self-efficacy scale for Native American women with IDD; (3) cancer screening knowledge and expectancy among caregivers; and (4) self-efficacy scale for caregivers. Assuming an attrition rate of 20%, a study with a

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sample size of 24 will provide 90% power to detect a standardized effect size of 0.66, that is, approximately two-third of SD in pre- and posttest scores. The 90% power estimate is conservative because it assumes the independence of the observations. However, when assessing these outcomes in the final analysis, we will address within-site (rural vs urban) and within-workshop session (1-6) correlation using mixed effects models. The proposed effect size of 0.66 is realistic based on a similar pre-poststudy conducted by Swaine et al [31], for which the effect size for composite score improvement was 0.83. For all other proposed comparisons, we believe that two-thirds of effect size represents a substantive improvement. We have not controlled for multiple comparisons in these analyses, but we note that the main purpose of this study was to be descriptive in nature, providing mean and variance estimates to be used for powering a future randomized controlled trial. All calculations herein assumed 2-sided tests with an α of .05.

Additional exploratory analysis will be conducted to assess relationships with variables that the investigators and previous research studies have identified as potentially influential on outcomes, such as participant residence (eg, group home, living independently, living with family, and urban or rural), the type of care provider attending the workshop (eg, paid and family), receipt of services from the state (eg, Medicaid, Indian Health Services, and Division of Developmental Disabilities), and the level of support needed. Specifically, we will examine whether changes in knowledge, attitudes, beliefs, and self-efficacy vary according to each of these variables. On the basis of previous studies, we anticipate that women who live in a group home or with the family will show greater knowledge and self-efficacy gains [26] and that women with greater support needs may show lower gains in knowledge and self-efficacy [31]. Because of the exploratory nature of this assessment, no adjustments will be made for multiple testing, and *P* values near .05 will be interpreted cautiously.

Qualitative Analysis

In-depth interviews will be transcribed and coded. Using methods for ensuring reliability among coders, transcriptions will be coded individually by separate members of the research team, who will then meet to analyze for agreement and reproducibility [58]. Coding will be completed in an iterative fashion, with initial (a priori) codes being drawn from the literature and additional codes based on themes that emerge from the data [59]. This modified grounded theory approach has been used by other qualitative researchers and proposed as a "best practice" to ensure content validity [60].

Advisory Board Involvement

Our advisory board will work with us to interpret quantitative and qualitative findings. The study team will present the findings at a quarterly advisory board meeting, inviting members who are interested in engaging in one-on-one discussions about the data with the university-based study team. Discussions with the advisory board will focus on understanding the data in light of the following topics: meeting community needs, opportunities for additional collaboration, and plans for further implementation.

Results

This community-engaged research project began in September 2017. The study team developed a productive advisory board and established 2 community partnerships. Together, the university and community partners have completed a qualitative needs assessment to guide the development of a culturally responsive *My Health, My Choice* cancer screening education program for Native American women with IDD (September 2019–August 2021). The findings of in-depth semistructured interviews with Native American women with IDD (n=12), caregivers (n=11), disability and health care providers (n=20), and community members (n=2) in rural and urban contexts guided the adaptation of the program and have been reported in a separate manuscript [50]. Major adaptations to the content include information about integrating traditional and biomedical healing, and culturally relevant activities. Adaptations to the program structure include shortening its length and transforming it into remote delivery because of the COVID-19 pandemic. Importantly, female health educators are members of native communities. The MHMC program is provided by local community health educators using phone or video conferencing and web- or paper-based learning materials. The feasibility and acceptability testing of the MHMC educational program began in November 2021 with the goal of recruiting 30 dyads of Native American women with IDD and their respective caregivers. Measures were carefully selected based on their prior use and validation among Native Americans [55,56] or individuals with IDD [52].

Discussion

Overview

This paper describes a study protocol for a community-engaged and ongoing research project focused on addressing cancer screening disparities among Native American women with IDD. Given the paucity of research regarding health care decision-making among those living with intersectional identities (Native Americans with IDD) in the United States, a community-engaged approach is necessary. To date, the project team has built a community-relevant, trauma-informed, and universally designed cancer screening education program for Native American women with IDD. The significance of this study lies not only in its community-engaged approach, but also in its theoretical approach (SCT), which accounts for the multifactorial influences of trauma on screening behavior and incorporates them into the intervention.

Principal Findings

We anticipate that the MHMC program will prove acceptable as assessed by a brief satisfaction survey, and feasible, as assessed by tracking attendance and completion rates of participants across all 6 sessions. We also expect to see an increase in cancer screening knowledge and self-efficacy across all participants.

Strengths and Limitations

As noted in the introduction, the lack of screening adherence data for Native American women with IDD limits our ability

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to understand the broad significance of this study. However, throughout the project, the team presented at local community events and participated as educational vendors to stay connected with local community needs. As others have noted, community engagement can be helpful for establishing mutually productive and collaborative relationships with Native American communities [39]. Our approach to community engagement is a strength for understanding the health and health care experiences of a largely underrepresented group of individuals in health disparities research, Native American women with IDD. Given this study's partnerships with specific Native American communities, the results of this work may not be generalizable to other groups of women with IDD from other Native American communities. However, these findings can provide a model for supporting Native American women with IDD in planning for cancer screenings, while considering the personal resources available to them.

Dissemination Plans

In addition to the development and public availability of MHMC, the study team has published 3 manuscripts covering the state of research on cancer screening and treatment for individuals with IDD and the lessons learned from our community-engaged processes [45,61-62]. A fourth manuscript sharing detailed results of community-based qualitative formative research has been published [50], and the results of feasibility and acceptability testing will also be submitted for publication.

Acknowledgments

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Data Availability

These data are not publicly available. Separate approvals must be obtained from tribal and community partners.

Conflicts of Interest

None declared.

Multimedia Appendix 1
My Health My Choice Instruments.
[DOCX File , 98 KB - resprot_v12i1e37801_app1.docx]

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Abbreviations

IDD: intellectual and developmental disabilities
MHMC: My Health My Choice
SCT: social cognitive theory
WBH2: Women Be Healthy 2

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Protocol

Health Care Resource Utilization in Adults Living With Type 1 Diabetes Mellitus in the South African Public Health Sector: Protocol for a 1-Year Retrospective Analysis With a 5-, 10-, and 25-Year Projection

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Abstract

Background: Type 1 diabetes mellitus (T1DM) is less common than type 2 diabetes mellitus but is increasing in frequency in South Africa. It tends to affect younger individuals, and upon diagnosis, exogenous insulin is essential for survival. In South Africa, the health care system is divided into private and public health care systems. The private system is well resourced, whereas the public sector, which treats more than 80% of the population, has minimal resources. There are currently no studies in South Africa, and Africa at large, that have evaluated the immediate and long-term costs of managing people living with T1DM in the public sector.

Objective: The primary objective was to quantify the cost of health care resource utilization over a 12-month period in patients with controlled and uncontrolled T1DM in the public health care sector. In addition, we will project costs for 5, 10, and 25 years and determine if there are cost differences in managing subsets of patients who achieve glycemic control (hemoglobin A_{1c} [HbA_{1c}] <7%) and those who do not.

Methods: The study was performed in accordance with Good Epidemiological Practice. Ethical clearance and institutional permissions were acquired. Clinical data were collected from 2 tertiary hospitals in South Africa. Patients with T1DM, who provided written informed consent, and who satisfied the inclusion criteria were enrolled in the study. Data collection included demographic and clinical characteristics, acute and chronic complications, hospital admissions, and so on. We plan to perform a cost-effectiveness analysis to quantify the costs of health care utilization in the preceding 12 months. In addition, we will estimate projected costs over the next 10 years, assuming that study participants maintain their current HbA_{1c} level. The cost-effectiveness analysis will be modeled using the IQVIA CORE Diabetes Model. The primary outcome measures are incremental quality-adjusted life years, incremental costs, incremental cost-effectiveness ratios, and incremental life years.

Results: Ethical clearance and institutional approval were obtained (reference number 200407). Enrollment began on February 9, 2021, and was completed on August 24, 2021, with 224 participants. A database lock was performed on October 29, 2021. The statistical analysis and clinical study report were completed in January 2022.

Conclusions: At present, there are no data assessing the short- and long-term costs of managing patients with T1DM in the South African public sector. It is hoped that the findings of this study will help policy makers optimally use limited resources to reduce morbidity and mortality in people living with T1DM.

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KEYWORDS

type 1 diabetes mellitus; South African public health care system; health care resource utilization; pharmacoeconomics; diabetes; adults; insulin; essential; policy makers

Introduction

Background

Approximately 11.3% of the South African population is living with diabetes [1], and according to a Statistics South Africa report on mortality and causes of death released in 2020, diabetes is the second most common cause of death in the country [2]. Although type 2 diabetes mellitus (T2DM) is more prevalent than type 1 diabetes mellitus (T1DM), the incidence of T1DM is increasing annually at rates of 2% to 5% [1].

T1DM is an autoimmune disease typically occurring in childhood or early adulthood, resulting in the inability to produce enough insulin because of the destruction of insulin-producing islet cells in the pancreas [2]. It is a debilitating disease with life-threatening acute and chronic complications such as diabetic ketoacidosis, coronary heart disease, cerebrovascular disease, retinopathy, and nephropathy. The financial burden associated with the management of this disease is significant [3]. Early diagnosis and intervention can improve morbidity and mortality. Despite improving globally, diabetes management in developing countries is lagging, predisposing people living with diabetes to increased morbidity and mortality [4].

Health care in South Africa is characterized by 2 disparate systems: a well-resourced private sector that serves the minority and the poorly resourced public sector that serves approximately 83% (50 million) of the population [5]. Individuals using the private health care system are either funded via medical aids/insurance or self-funded. Some individuals use both the private and public health care systems, using the latter when their medical aid funds have depleted or when they are facing monetary constraints [6].

The public health sector in South Africa is challenged with a multitude of illnesses including the HIV and tuberculosis epidemic and diseases of lifestyle [7]. Noncommunicable diseases are, however, a leading cause of death among adults in sub-Saharan Africa, which have a disproportionate impact on the economically active population [7].

Economic data from the United States indicate that the future cost implications of T1DM and its related emergency and long-term complications may have an unsustainable impact on patients and health care systems [8].

Epidemiological data on T1DM highlight a marked disparity in remaining life expectancy of people living with diabetes by income group. Although multifactorial, this disparity reinforces the need to improve access to diabetes education, blood glucose monitoring, skilled health care, and insulin [9]. Given the limited resources of the public health care system in South Africa and the large patient numbers under care, rational decision-making is required to optimally use limited human and financial resources.

The rising prevalence of T1DM, paralleled with the high mortality and morbidity of people living with diabetes, presents a challenge to health care systems and policy makers, particularly in the developing world [10]. Considering this, more effort should be channeled into reducing the financial burden on health care systems and patients [11]. To appropriately address the financial implications of managing people living with diabetes, pharmacoeconomic data are required. Unfortunately, to the best of our knowledge, there remain no data on the immediate and long-term costs of managing people with T1DM in the public health care setting.

It is through assessing and quantifying the health care resource utilization of patients living with T1DM that effective management initiatives can be implemented. Furthermore, this knowledge may help develop policies to ensure the optimal use of scarce resources.

Rationale

The public health care sector has very limited data in general and specifically on people living with diabetes. Given that diabetes mellitus is one of the leading causes of death in South Africa, it is important to quantify and optimize resource utilization for patients with diabetes mellitus in the public health care sector. The resource utilization data generated from this study could assist with future policy development and optimization of care by considering the cost of illness, the cost of treatment, and optimal clinical outcomes.

Definitions

An uncontrolled hemoglobin A_{1c} (HbA_{1c}) reading will be defined as a reading ≥7%, and controlled T1DM will be defined as an HbA_{1c} reading <7% [12].

Study Objectives

Primary Objective

The primary objective was to quantify the cost of health care resource utilization over a 12-month period in patients with controlled and uncontrolled T1DM in the public health care sector.

Secondary Objective

The secondary objective was to quantify the cost of health care resource utilization in patients with T1DM with controlled (HbA_{1c} <7%) versus uncontrolled (HbA_{1c} ≥7%) blood glucose level over a 12-month period and to compare the cost over a modeled 5-, 10-, and 25-year time horizon.

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Methods

Study Design

This was a national, multicenter, and observational study where a representative sample of patients was observed. Data were collected retrospectively over a 12-month period preceding the date of informed consent from patient chart data in the South African public health care sector.

Duration of Study Participation

A single visit was planned during which a patient signed an informed consent form to be included in the retrospective chart review. Eligibility criteria were confirmed and verified during the visit.

Selection of Patients

Consecutive patients who fulfilled the eligibility criteria were enrolled at each site. Competitive recruitment was used for this study.

Withdrawal Criteria

Withdrawal of informed consent was possible at the request of the patient or investigator.

Sample Size

A sample population of 224 consenting patients with T1DM fulfilling the eligibility criteria was recruited to participate in the chart review. Patients were recruited from 2 sites.

Determination of Sample Size

The sample size was calculated using SAS (version 9.4; SAS Institute) based on the assumption that both sites have a total population of 1129 patients with T1DM. The recommended HbA_{1c} readings were also taken into consideration; it was recommended that adults maintain an HbA_{1c} reading that is less than 7% to be classified as controlled T1DM. It was further assumed that 20% of the sample will have HbA_{1c} readings that are less than 7%. The population was also assumed to be normally distributed, using a margin of error of 5% and a confidence level of 95%; the sample size was calculated using the following formula:



where n_r is the required sample size,  is the corresponding standard normal variate for 5% type 1 error, P is the proportion of the population whose HbA_{1c} readings are <7%, and d is the margin of error set to 0.05.

The result was further adjusted relative to the population size of 1129 patients:



where N is the population size and n_a is the adjusted sample size relative to the population size.

The total sample size was 224 patients, adjusted for a 10% rate of patient files that may not be evaluable because of missing or incomplete data.

The inclusion and exclusion criteria are given in Textbox 1.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Signed informed consent at enrollment in the study
- Adults aged ≥18 years
- Patients with type 1 diabetes mellitus whose diagnosis had been confirmed
- History of being on human insulin therapy treatment for 12 months preceding the date of informed consent
- At least 1 hemoglobin A_{1c} reading recorded in the patient chart in the 12 months preceding the date of informed consent

Exclusion criteria

- Patients with type 2 diabetes mellitus
- Patients with gestational diabetes
- Patients with chronic pancreatitis
- Patients with latent autoimmune diabetes in adulthood
- Patients with maturity-onset diabetes in their youth
- Patients on analog insulin therapy (rapid acting and long acting)

Modalities of Recruitment

Each investigator included consecutive subjects who met the eligibility criteria. This consecutive recruitment limited biases of subject selection. If the first patient did not fulfill the eligibility criteria or declined to participate, the investigator continued with the next patient until the enrollment target for the study was reached. A patient only signed the informed consent form once they were fully informed about the study and understood the information provided to them in the consent form. A patient-tracking log form was used to document

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enrollment and ensure anonymity. Travel reimbursement was allocated per patient in line with local regulations.

Selection of Investigators

The investigators were chosen based on the following criteria: tertiary hospitals in South Africa and institutions with available comprehensive patient charts and records.

Analysis Populations

The full analysis set consisted of all patients included in the study, meeting all inclusion criteria and not meeting any exclusion criteria or withdrawal criteria. The per-protocol set consisted of patients who met all inclusion criteria and had no major protocol violations.

Statistical Methods

The data management team developed a statistical analysis plan before the database lock, which detailed the statistical analysis to be performed as well as the populations for analysis. A population review meeting was held after all data had been collected and cleaned and before the final database lock to determine which patients were analyzed in preparation for this retrospective analysis study.

Statistical analysis was performed after the database lock once all study data had been collected and cleaned. The statistical analysis was performed using SAS (version 9.4; SAS Institute).

Analysis Variables

All the patients in the analysis population were included in the data set for analyses. The analysis of data collected in this study was mainly descriptive. All collected data and end point variables were summarized using descriptive statistics.

Descriptive Analyses Included

For continuous variables, descriptive statistics included the number of patients, mean, SD, median, minimum, and maximum. Frequencies and percentages were displayed for categorical data. Percentages by categories were based on the number of patients with no missing data. Analysis was calculated according to the diagnosis group (uncontrolled vs controlled T1DM), as appropriate.

Modeling

The IQVIA CORE Diabetes Model (CDM) will be used to evaluate the health care resource utilization over a 12-month period in patients with controlled and uncontrolled T1DM in the public health care sector. Furthermore, the model will be used to project 5-, 10-, and 25-year costs.

Ethical Principles

This study was conducted in accordance with the principles laid by the 18th World Medical Assembly and all subsequent amendments [13]. Institutional permissions were received before the initiation of the study. Observation of both global and local regulations, including local data protection regulations, was maintained. Only data captured in patient records in the 12 months preceding the provision of informed consent were included in the study data. Participants were informed that their study-related data would be used by the sponsor in accordance with the local data protection law.

Results

Ethics clearance (reference number 200407) and institutional permissions were acquired. Funding was awarded and enrollment began on February 9, 2021, and was completed on August 24, 2021, with 224 participants. A database lock was performed on October 29, 2021. The statistical analysis and clinical study report were completed in January 2022.

Discussion

It is known that uncontrolled diabetes is associated with diabetic ketoacidosis and microvascular and macrovascular complications, which have associated cost implications. T1DM is a leading cause of morbidity, mortality, and health care resource utilization globally. Because the onset of T1DM typically arises early, effective disease management is imperative to limit its health and economic impact [14]. Existing literature has highlighted the higher cost of treating T1DM compared with T2DM [15]. To understand the economic impact of T1DM, the IQVIA CDM is used to evaluate the health care resource utilization over a 12-month period in patients with controlled and uncontrolled T1DM in the public health care sector. In addition, 5-, 10-, and 25-year projected costs are intended to be modeled to understand how costs change with the duration of the disease, assuming that patients maintain their current HbA_{1c} level.

Our discussion will largely focus on explaining the IQVIA CDM model, as it is a key instrument used to determine health resource utilization in this study.

The IQVIA CDM is a computer simulation model developed to determine the long-term health outcomes and economic consequence of interventions in T1DM and T2DM. The model is accessible on a licensed basis over the internet [16]. This is a non–product-specific diabetes analysis tool that performs real-time simulations taking into account intensive or conventional insulin therapy, oral antidiabetic drugs, screening and treatment strategies for microvascular complications, treatment strategies for end-stage complications, and multifactorial interventions [17].

The model simulates disease progression in both T1DM and T2DM. The IQVIA CDM is designed to take surrogate end points and translate them into long-term health economic outcomes. For example, HbA_{1c} is a surrogate marker that is linked to life expectancy [18].

Within the CDM, disease progression is based on a series of interdependent Markov submodels that simulate the progression of disease-related complications (angina, myocardial infarction, congestive heart failure, stroke, peripheral vascular disease, diabetic retinopathy, macular edema, cataract, hypoglycemia, ketoacidosis, nephropathy, end-stage renal disease, neuropathy, foot ulcer, and amputation) and other-cause mortality. The model is a fixed-time increment (annual) stochastic simulation with each submodel using time, state, and diabetes-type dependent probabilities. Monte Carlo simulations are performed at the individual patient level using tracker variables to accommodate complex interactions between submodels. The

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progression of relevant physiological parameters (eg, HbA_{1c}, systolic blood pressure, lipids, and BMI) is simulated based on long-term epidemiological data, and event risk is constantly updated on the basis of these risk factors. The model facilitates interconnectivity and interaction between the modeled complications, representing the complex and varied sequelae of diabetes [19].

Analyses can be performed on patient cohorts, defined in terms of age, gender, baseline risk factors, and pre-existing complications. Economic and clinical data in the disease management module can be edited by the user, ensuring adaptability by allowing the inclusion of new data as they become available and facilitating the creation of country, health maintenance organization, or provider-specific versions of the model. In analyses, patients remain on initial treatment either for a set period of time or until a threshold of HbA_{1c} is reached; treatment duration and thresholds are set according to individual country practice [18].

A core outcome of the model is the estimate of the incremental cost per quality-adjusted life year gained. The model therefore requires the input of a comprehensive set of utility weightings for each model state. In version 9.0 of the CDM, default utilities are updated through the systematic review and subsequent assimilation of utility data into a utility data set consistent with the National Institute for Clinical Excellence reference case and applicable across multiple geographies [3]. Quality-of-life values are then calculated for every patient in each year of the simulation and used to estimate the average quality-adjusted life expectancy. Utilities are assessed on a scale from 0 to 1, where 0 represents death (no quality of life) and 1 indicates a healthy person without complications. In effect, for each acute event that occurs during 1 year of the simulation, a quality-of-life disutility value is used to adjust the overall quality-of-life utility value for the patient. Disutilities range from 1 to 0 and therefore cause the quality-of-life utility to either decrease or remain constant. After an event, patients change state, and the new state is associated with different state utilities. A minimum approach is applied to the estimation of utilities—in the case of multiple events, the lower utility is applied for that period. This is a simple and well-established approach to the application of utilities in the case of multiple interdependent health states [17,19].

Clinical and economic outcomes are calculated within the model using a nonparametric bootstrapping approach. This process simulates the lifetime progression of diabetes in a cohort of hypothetical patients repeating the process over numerous simulations. If 1000 patients are run through 1000 iterations, this produces 1000 mean values of clinical effectiveness and lifetime costs, which are then used to generate a scatter plot diagram and acceptability curves to express the likelihood of a treatment being cost-effective versus a comparator. In the base-case analyses, second-order uncertainty is not applied, and stability of outcomes is reached through a run of 1000 patients through 1000 iterations. There is an existing and emerging body of evidence looking to quantify health care resource utilization and appropriately describe economic considerations in the management of people living with T1DM [14,15]. There is, however, a lack of such data within developing nations that are required to facilitate policy discussions pertaining to the health and economic impact of T1DM in South Africa.

Limitations

The study limitations include the retrospective study design and selection of only 2 health care facilities. Data entries were reliant on a chart review and hence entries from the treating health care worker.

Conclusions

For chronic diseases such as T1DM, providing treatments and therapies that produce the best clinical outcomes while containing health care expenses is a matter of importance for providers, policy makers, and research at large. Quantifying the economic burden of T1DM is needed to effectively implement treatment strategies and policies that are cost-effective.

Data Availability

The data sets generated during this study are in various stages of manuscript publication and development, and thus are not currently available to the public.

Conflicts of Interest

KN, NR, and LS are employees of Sanofi, South Africa. Sanofi markets analog insulins within the diabetes therapeutic area. PN was a previous medical manager at Sanofi, South Africa.

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Abbreviations

CDM: CORE Diabetes Model
HbA_{1c}: hemoglobin A_{1c}
T1DM: type 1 diabetes mellitus
T2DM: type 2 diabetes mellitus

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Protocol

Jordan's Population-Based Food Consumption Survey: Protocol for Design and Development

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Abstract

Background: One of the factors influencing health and well-being is dietary patterns. Data on food consumption are necessary for evaluating and developing community nutrition policies. Few studies on Jordanians' food consumption and dietary habits at various ages have been conducted, despite the increased prevalence of overweight, obesity, and chronic diseases. This will be the first study focusing on Jordanians' food consumption patterns that includes children, adolescents, adults, and older adults.

Objective: This cross-sectional study aims to describe the design and methodology of the Jordan's Population-based Food Consumption Survey, 2021-2022, which was developed to collect data on food consumption, including energy, nutrients, and food group intake, from a representative sample of Jordanians and to determine the prevalence of overweight and obesity and their relationship to food consumption.

Methods: Participants were selected by stratified random sampling, using the *Estimated Population of the Kingdom by Governorate, Locality, Sex, and Households, 2020* as the sampling frame. The food consumption survey sample was at the population level, representing gender and age classes (8-85 years old). The data collection period was 6 months. Food consumption was assessed using 24-hour dietary recall (2 nonconsecutive days, 1 week apart) interviews representing weekdays and weekends. In addition to data on food consumption, information on the use of food supplements, sociodemographic and socioeconomic status, and health was gathered. Weight, height, and waist circumference were all measured.

Results: The survey included 632 households with 2145 participants, of which 243 (11.3%) were children, 374 (17.4%) were adolescents, 1428 (66.6%) were adults, and 99 (4.6%) were older adults. Three food consumption databases were used to stratify the mean 24-hour dietary recall food consumption into energy intake, carbohydrates, proteins, fats, fiber, vitamins and minerals, and food groups. BMI was calculated and classified as normal, overweight, or obese. Central obesity was classified as normal or abnormal based on the waist-to-height ratio. The survey results will be disseminated based on age, energy, nutrient, and food group consumption. The prevalence of overweight and obesity by age group will be presented, as well as a comparison to the situation in Eastern Mediterranean countries.

Conclusions: The survey data will be helpful in nutritional studies, assessing changes in dietary patterns, and developing and evaluating nutrition or health policies. It will be a solid base for developing a future national surveillance system on food consumption patterns with comprehensive food consumption, physical activity, biochemical, and blood pressure data.

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KEYWORDS

household; food consumption; 24-hour dietary recall; children; adolescents; adults; older adults; overweight; obesity

Introduction

The prevalence of noncommunicable diseases (NCDs) such as cardiovascular disease, high blood pressure, diabetes mellitus, and several forms of cancer has increased globally, as has obesity and overweight, and these trends have been linked to each other [1]. One of the major modifiable risk factors for obesity and NCDs is dietary patterns [2] and nutrient intake [3-6]. There has been a global movement in diet quality and nutrient intake toward a more Westernized pattern, which is characterized by a diet that is higher in added sugar, processed foods, fast food, and saturated fat while consuming fewer fruits, vegetables, dairy products, and fiber-rich foods [2,6,7]. This shift has been linked to the prevalence of obesity and NCDs being studied widely. To address these issues, various researchers have proposed studying general dietary patterns by looking at how foods and nutrients are consumed together as a solution. Numerous researchers have looked into the relationship between dietary habits and obesity. Thus, food consumption surveys are conducted worldwide [6,8].

In some countries, such as the United Kingdom [9] and the United States, continuous surveys are conducted over time [10]. At the same time, some surveys are conducted regularly (annually or biennial), such as in Germany [11], Italy [12], and Mexico [13]. Some surveys, on the other hand, are conducted irregularly, such as in France [14], Brazil [15], and Ireland [16]. Other surveys were carried out to assess dietary patterns, energy or nutrient intakes, or foods and beverages consumption in specific population subgroups or regions [17,18]. Food consumption surveys attempt to estimate the amount of food consumed by individuals. The outcomes vary from country to country and even within the same country due to differences in age, gender, and socioeconomic level.

The 24-hour dietary recall (24-h DR) is one of the most commonly used methods to assess food consumption. In some countries, all participants were subjected to multiple recalls [19,20]; however, in others, duplicate recalls were applied to a subsample of participants. The 24-h DR was carried out in a face-to-face or telephone interview using 24-h DR sheets or software to allow the structured and standardized collection of dietary intake data [21].

Other less common methods were used for estimating food consumption, including the food frequency questionnaire and dietary records [12,16].

Many countries use the results of dietary and nutrition surveys to monitor their population's nutritional status, reveal trends in their health and dietary practices, determine links between food and health, identify populations at nutritional risk, and develop and implement nutritional policies tailored to reflect changes in dietary consumption [22-24].

The novelty of this study arises from the fact that it is the first to investigate the food consumption of different age groups in the Jordanian community, as well as obesity indices. Furthermore, the food consumption data were collected following the COVID-19 pandemic and its effects on food intake, body weight, and physical activity, primarily during school and university closures due to lockdowns. Therefore, this study aims to describe the design and methodology of Jordan's Population-based Food Consumption Survey (JPFCS), 2021-2022, which was developed to collect dietary habits and nutritional status in a representative sample of the general Jordanian population.

The specific study objectives were as follows:

- To evaluate the energy and nutrient intake in the general Jordanian population, including children
- To examine the differences in food, energy, and nutrient intake among different subgroups of the population and to identify subgroups at risk for a deficient or excessive intake of specific foods or nutrients
- To determine the prevalence of overweight and obesity in the Jordanian population and the correlation with food and nutrient intakes

Methods

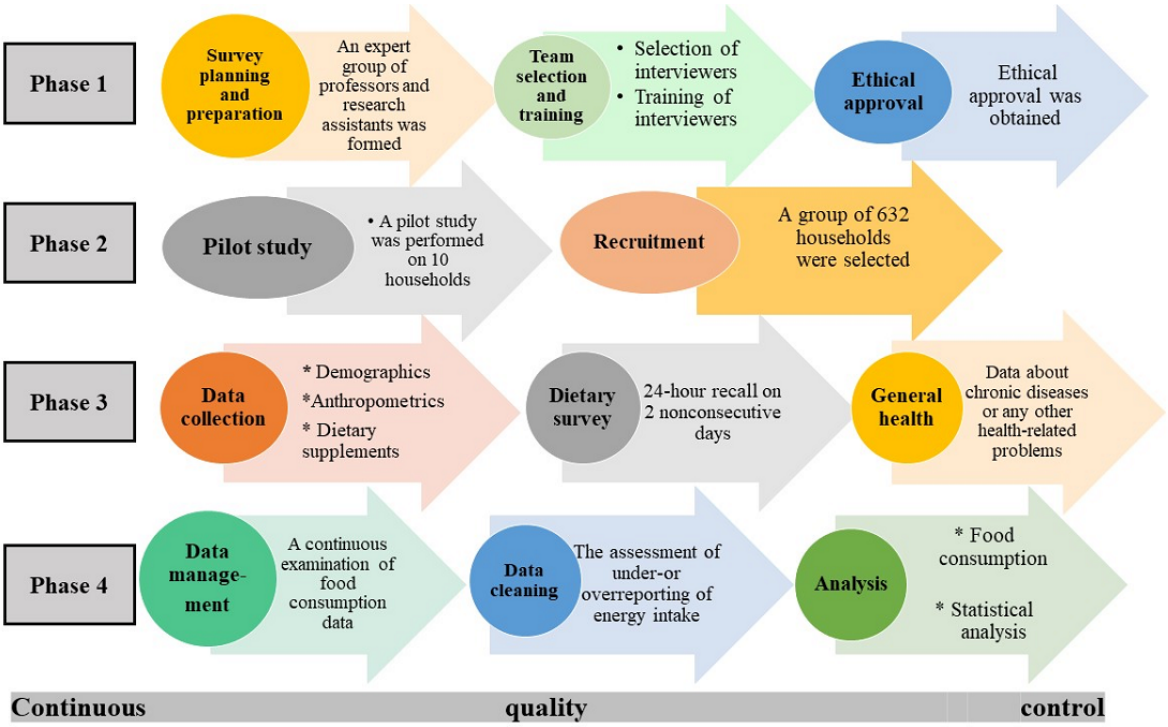
Design and Study Population

The JPFCS is a population-based cross-sectional study on household food consumption patterns that was conducted within all regions of the Hashemite Kingdom of Jordan between October 2021 and March 2022. Jordanians aged ≥8 years were defined as children, adolescents, adults, and older adults in the JPFCS study. Obtaining 24-h DR for children aged <8 years is difficult, especially out-of-home food intake (food eaten in schools, kindergarten, and daycare centers). Therefore, the data reliability is higher among children aged ≥8 years [22].

This study included 4 phases. The first phase included survey planning, questionnaire preparation, interviewer selection and training, and obtaining ethical approval. The second phase involved conducting a pilot study and selecting households. The third phase included data collection from eligible household members on demographics, health, anthropometrics, and food consumption. The final phase will involve data management and analysis. The study protocol flowchart is presented in Figure 1.

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Figure 1. Flowchart of the study protocol.



Sampling Frame

Jordan covers 89,342 km^2, with 10.8 million people in 2020 [25]. Geographically, the governorates of Jordan are located in 1 of 3 regions: the Central Region (Amman, Madaba, Balqa, and Zarqa), the Northern Region (Irbid, Mafraq, Ajloun, and Jarash), and the Southern Region (Aqaba, Karak, Ma'an, and Tafila). Each region has 4 governorates, including several districts and subdistricts, as shown in Figure 2. About 4.5 million people live in the Amman Governorate, almost half the country's population.

As a sampling frame, a sample of Jordanian households was selected using the *Estimated Population of the Kingdom by Governorate, Locality, Sex, and Households, 2020* [25]. The sample size was calculated using the following formula:

$$n=N*X / (X + N - 1)$$

where N is the population size and

$$X=Z_{\alpha/2}^2 \times p \times (1 - p) / MOE^2$$

where $Z_{\alpha/2}$ is the critical value of the normal distribution at $\alpha/2$ (eg, for a confidence level of 95%, α is .05, and the critical value is 1.96), *MOE* is the margin of error, *p* is the sample proportion.

A minimum sample size of 664 households was required. The number of governorate-selected households was calculated using the percentage of each region's households in the overall number of Jordanian households, as shown in Table 1.

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Figure 2. Map of regions and governorates in Jordan and the number of invited households.

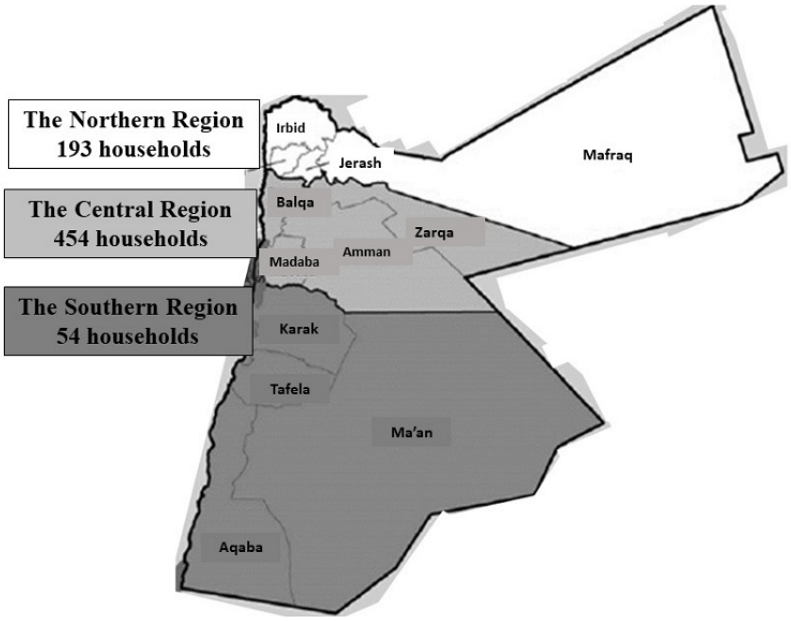


Table 1. Households distribution across regions.

Region	Households in each region (n=2,241,909), n (%)	Invited households, n (%)
Central	1,453,166 (64.8)	454 (64.8)
Northern	615,650 (27.5)	193 (27.5)
Southern	173,093 (7.7)	54 (7.7)
Total	2,241,909 (100)	701 (100)

Informed Consent

Individuals who agreed to participate in the survey received detailed information about the survey objectives and what was expected from them; a disclosure of the survey's requirements to preserve confidentiality, risks, and benefits; and a clear description of their decision to participate freely or not in the survey. After being presented with a detailed survey description, parents were asked for oral approval for their children to participate. No incentive money was offered for taking part in the survey. All data were recorded anonymously. Therefore, participants cannot be identified directly or through identifiers linked to the participants. At the start of the first home visit, participants or parents of children aged <12 years provided written informed consent.

Ethics Approval

The Institutional Board Review committee at The Hashemite University reviewed and approved the survey protocol (No.7/13/2020/2021).

Fieldwork Team: Management and Recruitment

During the project's development, an expert group of professors and research assistants was formed, which appointed a primary coordinator, 3 co-coordinators, and a data entry specialist. The group was responsible for planning this survey domain, determining and developing the instruments, conducting the training, monitoring data collection, and planning the cleaning and organization processing of the data.

In all, 14 interviewers with nutrition backgrounds joined the group because of the need for a thorough knowledge of the available foods on the market and the recipes usually prepared within the study population. The population density determined the number of interviewers assigned to each region: 9 were assigned to the Central Region, 3 to the Northern Region, and 2 to the Southern Region.

JPFCS Instruments

Structured Questionnaire and Data Management

A structured questionnaire was used to obtain information. The coding scheme of the participant's questionnaire consisted of a 5-digit number that includes the governorate number, subgovernorate number, interviewer number, household number, and participant number.

After signing the consent form, a face-to-face interview with the participant obtained sociodemographic information on age, gender, number of household members, and monthly household income. General health data and intake of dietary supplements of the participants were also obtained. Questions on the presence of chronic diseases or other health-related problems were included.

Anthropometrics, including weight, height, and waist circumference, were measured. Interviews were conducted at the participant's home at their convenience (usually outside working hours). Interviewers were encouraged to provide flexibility concerning appointment times. Additionally, the first

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24-h DR was collected during these face-to-face interviews, whereas the second 24-h DR was collected by telephone.

Dietary Survey Tools

Dietary assessment was performed by the 24-h DR method on 2 nonconsecutive days (weekday and weekend). After respondents completed the questionnaire, the interviewer asked the respondent to recall and state the foods, beverages, and dietary supplements consumed in the preceding day, including their quantity, most commonly from midnight to midnight in the previous day. The interviewer obtained the first recall in a face-to-face interview with the eligible household member. The 24-h DR was typically completed in 20-40 minutes for each household member. The second recall representing the weekend was obtained by phone and showed acceptable estimates of the means and distributions of nutrient intakes among groups of individuals [26].

Food Description

All foods, beverages, and dietary supplements were recorded per food consumption occasion (morning, midmorning, noon, afternoon, evening, and late evening). As this was the collection of the first recall during face-to-face interviews, the date and day of the recall were recorded. In addition, all consumed foods or beverages; estimated amounts; methods of preparation; and brand names, if available, were documented. Interviewers used the multiple-pass method recommended by the United States Department of Agriculture. A 5-step dietary interview included multiple passes through the 24-h DR of the previous day, during which participants received cues to help them remember and describe the foods they consumed [27].

Portion Size Determination

Estimating portion sizes is an integral part of the dietary assessment. Various portion estimating aids have been developed, such as household measurement items (eg, standard measuring glasses, cups, teaspoons, and tablespoons), food models, food portions (obtained from fact sheets and manufacturer's information presented on the product's containers), food pictures, and other visual aids that may be used to help the participants judge and report portion size.

Participants in this survey were assisted in describing the actual quantity of food or beverage consumed by giving them a well-known idea about the quantity by using a colored food atlas containing over 100 foods, and composite recipes comprising photos of various foods and meals regularly consumed in Jordanian diets were created. For each food item, at least four photographs showed portion sizes. However, to our knowledge, no comprehensive food atlas has been developed in Jordan.

The photographs were categorized into different groups: bread and grains, fruits and vegetables, milk and dairy products, meat and meat alternatives, sweets and desserts, fat, and composite dishes. In addition, photographs of standard measurement devices in the Jordanian diet, such as cups, teaspoons, and tablespoons, were included.

Dietary Supplements

This section highlights the usage of dietary supplements: the frequency and type of dietary supplements. Usually, the use of dietary supplements was recovered by 2 methods. The first method used the 24-h DR; dietary supplements were recorded per consumption occasion and quantified and described as consumed [28]. The second method asked the frequency of use, in the last 12 months, of a predefined list of different dietary supplement types (eg, supplements of vitamins, such as D and folate; supplements of minerals, such as calcium and iron; supplements of multivitamins; and supplements of fatty acids, herbs, plants, and probiotics) [28].

Dietary Database

The detailed food consumption data were entered into a food composition database. Three food composition databases were used: ESHA's Food Processor nutrition analysis software (version 11:0; ESHA Research); *Composition of Local Jordanian Food Dishes* [29]; and *Lebanon Food Composition Data: Traditional Dishes, Arabic Sweets, and Market Foods* [30]. The final dietary variables that will be generated will represent the average of 2 recalls and be used for further analyses. Data about the total daily energy intake, macronutrients, vitamins, and minerals will be evaluated for all age groups.

Training of Interviewers

Smaller-group interviewers received 1-day training from the subnational coordinators and Zoom training (Zoom Video Communications) upon need. The training content included general study information, study objectives, instructions on the interviewer's attitudes, coding scheme, procedures for completion of the 24-h DR, and the use of the colored photographic food atlas. Interviewers were provided with the protocol for home visits and telephone calls, the content of the questionnaires, and the anthropometric measurement procedure. New interviewers recruited during the fieldwork received the same training except individually. In total, the training was repeated at least five times.

Anthropometrics

Anthropometric measurements, including height (cm), weight (kg), and waist circumference (cm), were performed on children and adults according to standard procedures by a trained nutritionist. Height was measured to the nearest centimeter, with participants in a standing position with light clothing and barefoot, using a portable wall stadiometer. Body weight was measured in the same conditions to the nearest tenth of a kilogram using a digital scale (Microlife WS 50). Waist circumference was measured using an anthropometric tape at the narrowest point between the lower costal border and the iliac crest. BMI (kg/m^2) was calculated from the height and weight measurements according to the Quetelet formula [22]: $BMI = weight\ (kg) / height\ (m^2)$, and the waist-to-height ratio was calculated by dividing the participant's waist circumference by his or her height [22].

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Quality Controls

The following quality control steps were taken before, during, and after data collection:

1. A pilot study was performed for 10 households on the tools of the study to enhance the quality of the collected information.
2. Interviewers were chosen for their knowledge of 24-h DR interviews, market foods, traditional recipes, and anthropometric measurements. Furthermore, those having a solid background in the assessment of nutritional status, both theoretical and practical, and having received adequate training to conduct anthropometric measurements and assess food intake in various ways while studying at the university were chosen.
3. Training of the interviewers before data collection via face-to-face and Zoom meetings
4. A WhatsApp (Meta Platforms) group was formed to facilitate communication between the national coordinator, subnational coordinators, data entry specialists, and interviewers. It responds to and clarifies any study-related issue.
5. A continuous examination of food consumption data as they are entered into the nutrition analysis software
6. As an essential issue to consider, the assessment of under- or overreporting of energy intake was carried out using the cutoff points and method proposed by Goldberg et al [31] and Black [32].

Statistical Analysis

Data analysis was performed using SPSS software (version 22.0; IBM Corp). The normality of the distributions will be assessed through the Kolmogorov-Smirnov test and kurtosis and skewness values. Continuous variables will be presented as mean values and standard deviations, percentages for numerical variables, and frequencies (n and %) for categorical variables. This analysis will be stratified by sex and age.

Inferential statistics such as the Student *t* test (2-tailed), chi-square test, and independent samples *t* test (2-tailed) will be used based on the sample distribution and test statistics. Statistical significance will be accepted at $P<.05$, with a 95% confidence level.

Results

Sample Size

A representative sample of 701 households was randomly invited, and 632 households were included in the study, with a 90.2% response rate. A total of 2721 household members were approached, with a response rate of 78.8% (n=2145). Female subjects who were pregnant or lactating and children aged <8 years in the selected households were excluded from the study. The overall refusal rate of the included household members was 7.7% (210/2721). The hierarchical chart for household sampling, participant distribution, the number of excluded individuals, response rates, and refusals by region is shown in Figure 3.

The age groups for eligible male and female household members were as follows: 8-12, 13-19, 20-64, and ≥65 years. Table 2 summarizes the number of subjects interviewed for each sex of children, adolescents, adults, and older adults.

The 2145 subjects were divided into 4 age groups: 11.3% (n=243) were children (8-12 years), 17.4% (n=374) were adolescents (13-19 years), 66.6% (n=1428) were adults (20-64 years), and 4.6% (n=99) were older adults (≥65 years; Table 2).

The data collected included weight, height, and waist circumference measurements; the response rate for those measurements was high, with the lowest response rate (117/119, 98.3%) for waist circumference in girls aged 8-12 years. The collection of the second 24-h DR for dietary assessment revealed the lowest response rate (114/124, 91.9%) in boys aged 8-12 years (Table 3).

Before estimating nutrient and food group intakes, participants will be divided into 3 groups based on energy intake: underreporters, plausible reporters, and overreporters; plausible reporters will only be considered when estimating nutrient and food group intakes. The survey results will be disseminated in national and international scientific journals.

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Figure 3. Hierarchical chart for household sampling, participant distribution, the number of excluded individuals, response rates, and refusals by region.

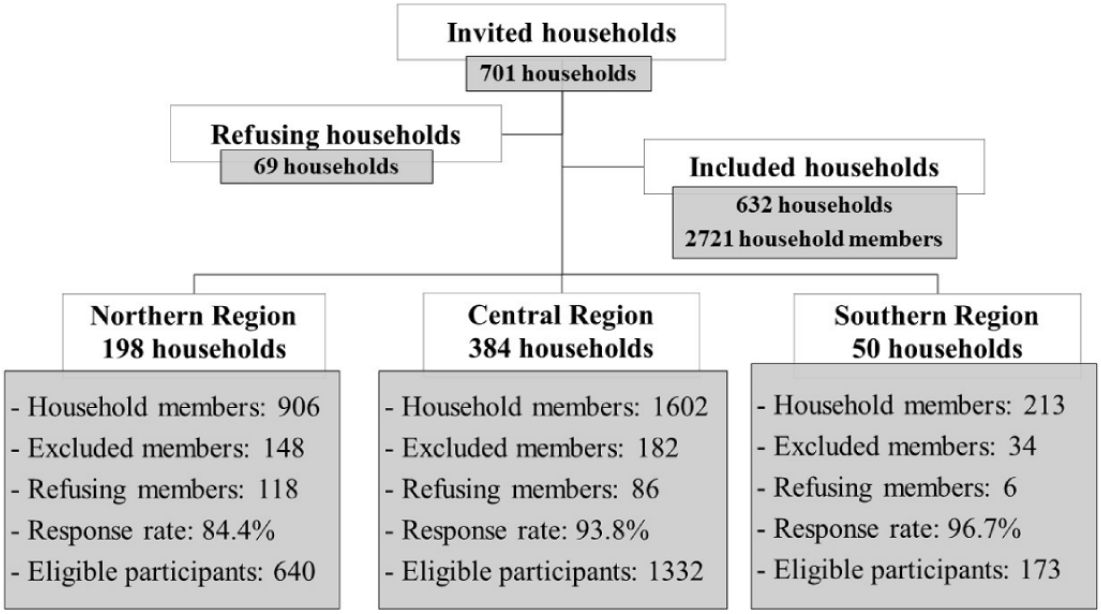


Table 2. Distribution of participants by sex and age group.

Age group	Total (n=2145), n (%)	Male (n=945, 44.1%), n (%)	Female (n=1200, 55.9%), n (%)
Children (8-12 years)	243 (11.3)	124 (13.1)	119 (9.9)
Adolescents (13-19 years)	374 (17.4)	163 (17.2)	211 (17.6)
Adults (20-64 years)	1428 (66.6)	608 (64.3)	820 (68.4)
Older adults (≥65years)	99 (4.6)	50 (5.3)	49 (4.1)

Table 3. Response rates of the collected data by gender and age group.

Collected data	Children		Adolescents		Adults		Older adults	
	Boys (n=124), n (%)	Girls (n=119), n (%)	Boys (n=163), n (%)	Girls (n=211), n (%)	Men (n=608), n (%)	Women (n=820), n (%)	Men (n=50), n (%)	Women (n=49), n (%)
Weight measurement	124 (100)	119 (100)	163 (100)	211 (100)	608 (100)	818 (99.8)	50 (100)	49 (100)
Height measurement	124 (100)	118 (99.2)	163 (100)	211 (100)	608 (100)	81 (99.8)	50 (100)	49 (100)
WC[a] measurement	124 (100)	117 (98.3)	163 (100)	211 (100)	608 (100)	817 (99.6)	50 100)	49 (100)
First 24-h DR[b]	123 (99.2)	119 (100)	163 (100)	210 (99.5)	608 (100)	818 (99.8)	50 (100)	49 (100)
Second 24-h DR	114 (91.9)	115 (96.6)	157 (96.3)	206 (97.6)	601 (98.8)	808 (98.5)	50 (100)	48 (98.0)
Both 24-h DRs combined	114 (91.9)	115 (96.6)	157 (96.3)	206 (97.6)	601 (98.8)	808 (98.5)	50 (100)	48 (98.0)

[a]WC: waist circumference.

[b]24-h DR: 24-hour dietary recall.

Discussion

Expected Findings

The study aimed to describe the design and methodology of a population-based food consumption survey to evaluate energy, nutrient, and food group intake in various age groups and the relationship with the prevalence of overweight and obesity.

Food consumption patterns in Jordan have not been studied at the population level. The published studies focused on specific age groups, such as food consumption among university students [33,34] and food and nutrient consumption in certain disease cases [35,36]. These studies used a food frequency questionnaire to focus on food group consumption, whereas 24-h DR was rarely used. Some of the studies mentioned above were pilot studies or had small sample sizes. Furthermore, food consumption data for various age groups and households are still scarce in many Middle Eastern countries.

The total number of respondents in this study was 2145, divided into 4 age groups: children, adolescents, adults, and older adults. The findings of this study will concentrate on food consumption

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patterns, food group consumption, macronutrient consumption, and some micronutrient consumption, as well as anthropometric indices of obesity such as BMI and weight-to-height ratio in the studied age groups. In line with this protocol, Bel and de Ridder [37] completed a national survey on the Belgian national food consumption data collection in 2200 individuals (aged 10-64 years). Food intake data were collected with 2 nonconsecutive 24-h DRs.

Data from national studies will assist governments and international organizations in supplying statistical elements that will eventually advise national social security and health policies [38]. Additionally, this population-based survey will shed light on the whole population's energy intake, risk assessment, and nutritional status studies, with essential suggestions for developing policies [37,38].

Strengths and Limitations

Among study limitations, the household sample size was smaller than recommended; biochemical data, blood pressure measurements, food safety, hygiene, and lifestyle pattern were not included. Moreover, it was challenging to collect data about food consumption for children aged <8 years. However, among the study's strengths is that the protocol was similar to other population-based dietary surveys. Participants in the survey were from both sexes and were distributed in all representative age groups in Jordan. Additionally, the distribution of interviews on weekdays and seasonality was confirmed. The core strength of this protocol is that the dietary assessment was completed following the standards of the Jordanian diet and Arabic regions that covers food and nutrient intake, nutritional status, and eating habits. Furthermore, precise and comprehensive food consumption data are crucial for the food consumption assessment based on the food atlas prepared and introduced by the team workers.

Future Perspectives

As the first population-based household survey, it will provide updated information about dietary habits and food consumption patterns for various age groups, especially because it was conducted following the COVID-19 pandemic. The findings serve as a descriptive baseline for future follow-up and a critical starting point for future food consumption pattern studies of some Jordanian age groups.

Conclusions

This population-based food consumption survey aims to collect data on the food consumption of a sample representing various age groups. It will provide the most comprehensive evaluation of food consumption, identify the components of consumed food and their nutrient contents, examine energy and nutrient intakes, and identify the prevalence of overweight and obesity in the Jordanian community. It will serve as a solid nutritional background for future studies, help assess dietary patterns changes, develop and evaluate nutrition policies, and serve as a solid foundation for developing a future national surveillance system on food consumption patterns.

Acknowledgments

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Authors' Contributions

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

JPFCS: Jordan's Population-based Food Consumption Survey
NCD: noncommunicable disease
24-h DR: 24-hour dietary recall

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Protocol

Diagnostic and Therapeutic Management of Urinary Tract Infections in Catalonia, Spain: Protocol for an Observational Cohort Study

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Abstract

Background: Antibiotic resistance is an individual and public health problem; multidrug-resistant infections could cause an estimated 10 million deaths worldwide by 2050. Unnecessary use of antimicrobials is the most important cause of resistance generation in the community, and an estimated 80% of antimicrobials are prescribed in primary health care, frequently for urinary tract infections (UTIs).

Objective: This paper presents the protocol for the first phase of the Urinary Tract Infections in Catalonia (Infeccions del tracte urinari a Catalunya) project. We aim to examine the epidemiology of the different types of UTIs in Catalonia (an autonomous community in Spain) and their diagnostic and therapeutic management by health professionals. Furthermore, we aim to evaluate the correlation between types and total consumption of antibiotics for recurrent UTIs in 2 cohorts of women with the presence and severity of infectious complications of urological origin, especially pyelonephritis and sepsis, and 2 potentially serious infections: pneumonia and COVID-19.

Methods: The study is a population-based observational cohort study including adults with a diagnosis of UTI registered in the Information System for the Development of Research in Primary Care (in Catalan: Sistema d'informació per al desenvolupament de la investigació en atenció primària), the Minimum Basic Data Sets of Hospital Discharges and Emergency Departments (in Catalan: Conjunt mínim bàsic de dades a l'hospitalització d'aguts i d'atenció urgent), and data from the Hospital Dispensing Medicines Register (in Catalan: Medicació hospitalària de dispensació ambulatòria) of Catalonia from the period between 2012 and 2021. We will evaluate the variables obtained from the databases to analyze the proportion of different types of UTIs, the percentage of adequate antibiotic treatments prescribed or received for recurrent UTIs according to the national guidelines, and the proportion of UTIs with complications.

Results: We expect to describe the epidemiology of UTIs in Catalonia from 2012 to 2021, as well as describe the diagnostic and therapeutic management of UTIs by health professionals.

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Conclusions: We expect to find a high percentage of UTI cases with inadequate management according to the national guidelines, considering that on many occasions UTIs are treated with second- or third-line antibiotic therapies with a preference for the longest regimens. Furthermore, the use of antibiotic suppressive therapies, or prophylaxis, in recurrent UTIs will likely be highly variable. Moreover, we aim to determine whether women with recurrent UTIs treated with antibiotic suppressive therapies have a higher incidence and severity of potentially serious future infections, with special attention to acute pyelonephritis, urosepsis, COVID-19, and pneumonia, compared to women who receive antibiotic treatment after they present with a UTI. This is an observational study of data from administrative databases that will not allow causality analysis. The limitations of the study will be handled according to the appropriate statistical methods.

Trial Registration: European Union Electronic Register of Post-Authorisation Studies EUPAS49724; https://www.encepp.eu/encepp/viewResource.htm?id=49725

International Registered Report Identifier (IRRID): DERR1-10.2196/44244

(JMIR Res Protoc 2023;12:e44244) doi:10.2196/44244

KEYWORDS

urinary tract infection; primary health care; anti-bacterial agents; diagnosis; drug resistance; electronic health records

Introduction

It is estimated that 10 million people could die worldwide by 2050 from infections caused by multidrug-resistant pathogens if urgent measures are not taken to combat the problem of antimicrobial resistance, mainly among gram-negative bacteria and especially enterobacteria [1]. Antibiotic resistance is an individual health and public health problem; increasing community resistance can prolong the infectious process, increase the risk of infecting other individuals, and in the long term, lead to increased costs. Inappropriate use of antibiotics increases the frequency of related and sometimes serious side effects and causes increased mortality [2,3]. Unnecessary use of antimicrobials is the most important cause of resistance generation in the community, and it is estimated that 80% of antimicrobials are prescribed in primary health care (PHC) [4].

Urinary tract infections (UTIs) are a common infection in PHC, and most patients are treated with antibiotics [5-7]. In Spain, UTIs represent the second most frequent cause of antibiotic prescriptions [8]. Almost 60% of women experience at least one episode during their lifetime [9,10]. Antibiotic treatment of uncomplicated UTIs is, in most cases, empirical, and the selection of the antimicrobial is made according to the most frequently involved pathogen and local resistance. Several studies have suggested that up to 50% of antibiotic prescriptions are inappropriate [11-13]. There is a tendency to use broad-spectrum antibiotics, which do not usually provide substantial improvements in efficacy over narrower-spectrum antibiotics and instead favor increased resistance [4].

Approximately 80% of cases of uncomplicated UTI are caused by *Escherichia coli*, so empirical treatment should cover this pathogen [14-16]. The resistance of uropathogens to classical antibiotics has increased significantly in recent years in Spain [17]. Various studies in Spain have described resistant *E coli* infections and shown that a high percentage are resistant to penicillins. A study published in 2017 that was conducted in our setting among patients with community-acquired pyelonephritis showed that 23% were resistant to ciprofloxacin, while 1% were resistant to fosfomycin [18]. In the program of surveillance of nosocomial infections in the hospitals of Catalonia (Vigilància de les infeccions nosocomials als hospitals de Catalunya [VINCat; all non-English abbreviations are in Catalan unless otherwise noted]), a local database from Catalonia (an autonomous community in Spain) that is part of the Antimicrobial Optimization Program (Programa d'optimització de l'ús d'antimicrobians [PROA]), it was shown that in 2020 *E coli* had a high sensitivity to fosfomycin (96.6%) and nitrofurantoin (98.5%); by contrast, its sensitivity to the amoxicillin/clavulanic acid combination, cotrimoxazole, and quinolones was much lower (75%, 74%, and 72%, respectively) [19]. Resistance of enterobacteria to third-generation cephalosporins, mediated by the production of extended-spectrum β-lactamases, is a growing problem in *E coli* and *Klebsiella pneumoniae* strains. Data from the VINCat PROA 2020 report show that the proportions of β-lactamase-producing *E coli* and *K pneumoniae* urinary tract infections in the community in Catalonia were 9% and 11%, respectively [19]. UTIs caused by resistant microorganisms are associated with longer symptom duration than infections caused by sensitive strains, and treatment is more likely to fail [20].

According to the recommendations of the Infectious Diseases Society of America, empirical antibiotherapy should not be used when resistance rates exceed 20% for all strains [21]. This means that the use of combined amoxicillin/clavulanic acid, as well as quinolones and cotrimoxazole, should no longer be recommended for empirical treatment of UTIs in our country. Current guidelines in PHC recommend prescribing a single dose of 3 grams of fosfomycin trometamol or nitrofurantoin for 5 to 7 days [22,23]. The rationale for this strategy is to specifically target the etiologic agents causing acute cystitis based on knowledge of the local resistance patterns to antimicrobials of the most frequent uropathogens [24]. In recent years, the use of fosfomycin as the therapy of choice for these infections has increased significantly in Spain. However, more than half of all physicians prefer the use of short-course therapies to single doses [25]. One of the reasons mentioned by professionals for not giving first-line treatments is to prevent complications, the most frequent being acute pyelonephritis; however, there is currently no predictive scale available to determine the risk that a UTI will worsen to pyelonephritis. Only 26% of antibiotic prescriptions for uncomplicated UTI were for fosfomycin

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trometamol (3-gram single dose) or nitrofurantoin in primary care management in Barcelona in the entire year 2020 (unpublished data).

Another dilemma faced by practitioners is the recommendation to give suppressive antibiotic treatment lasting more than 6 months to women who have repeated UTIs (defined as more than 2 UTIs in the last 6 months or more than 3 in the last year) [26]. However, this practice is not exempt from potential risks. In a recent article, a clear correlation was reported between a history of antibiotic use in the previous 2 years and the severity of COVID-19 (with severity defined as a variable combining death, hospitalization, and the presence of pneumonia), based on data from the Information System for the Development of Research in Primary Care (Sistema d'informació per al desenvolupament de la investigació en atenció primària [SIDIAP]) [27]. This correlation was very strong when antibiotics were taken in the previous 2 months, when there were more than 5 antibiotic regimens in the last 2 years, and when antibiotics were used that are critical and should be reserved for special cases, such as cephalosporins and quinolones. In addition, prudent use of antibiotics is necessary due to the increase in antibiotic resistance [3,28].

Urine culture requests are not always made according to guidelines. As early as 2000, it was documented that 44% of requests were made for cases of asymptomatic bacteriuria, a condition for which they should not be ordered and there should be no treatment [29]. In 2014, 92% of urine cultures that were ordered for a second time for patients with a UTI were not necessary [30]. In 2019, a range of 21% to 42% of requests for urine cultures were for uncomplicated UTIs in Barcelona city primary care management (in Spanish: gerencia *de atención primaria de Barcelona ciudad*), depending on the primary care center (unpublished data). The ordering of urine cultures for women with cystitis is only recommended in cases of (1) uncomplicated cystitis that, despite adequate antibiotic treatment, remains symptomatic (posttreatment urine cultures are used), (2) recurrent cystitis (pretreatment urine cultures are used), and (3) cystitis in pregnancy (both pretreatment and posttreatment urine cultures are used) [14]. The use of these tests when they are not necessary leads to antibiotic overprescription; moreover, since in many cases they are requested for cases of bacteriuria in elderly people who have been treated with antibiotics many times, the results of antibiograms recommend the prescription of second-line antibiotics for uropathogens that are often multidrug-resistant.

For all the above reasons, we propose the current protocol for the Urinary Tract Infections in Catalonia (Infeccions del tracte urinari a Catalunya [ITUCAT]) study, consisting of 4 work packages (WPs) that will be implemented successively in 3 phases, to evaluate different objectives related to UTIs in the adult population in Catalonia and investigate specific aspects of this condition in this population. The first phase of the project, which is presented in this paper, includes the first 2 WPs. WP 1 will evaluate the management of UTIs in Catalonia, and WP 2 aims to evaluate the correlation of antibiotic use for repeated UTIs with the presence of infectious complications in adult women. Subsequently, we will carry out the second phase with the data obtained from the first phase. At this stage, the aim is to create a scale to predict acute pyelonephritis in patients with UTI by evaluating clinical variables; this will be WP 3. Finally, in the third phase, we will perform WP 4, which aims to determine the degree of inadequacy in requests for urine cultures based on clinical practice guidelines and to establish the basis for a training intervention.

The study described in this paper corresponds to the first phase, which includes WP 1 and WP 2.

Methods

Study Design and Population

This is a population-based observational cohort study. The inclusion period was from January 1, 2012, to December 31, 2021. The study population was patients aged ≥18 years with a diagnosis of UTI registered in SIDIAP during the study period. UTI diagnoses included the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) codes (Table 1).

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Table 1. Health problems included in the study and their International Statistical Classification of Diseases and Related Health Problems, 10th Revision codes.

ICD-10 codes	Health problems
N10	Acute tubule-interstitial nephritis
N30	Cystitis
N30.0	Acute cystitis
N30.1	Interstitial cystitis (chronic)
N30.2	Other chronic cystitis
N30.3	Trigonitis
N30.8	Other cystitis
N30.9	Cystitis, unspecified
N34	Urethritis and urethral syndrome
N34.1	Nonspecific urethritis
N34.3	Urethral syndrome, unspecified
N39.0	Urinary tract infection, site not specified
N41	Inflammatory diseases of prostate
N41.0	Acute prostatitis
N41.1	Chronic prostatitis
N41.3	Prostatocystitis
N45	Orchitis and epididymitis
N45.0	Orchitis, epididymitis, and epididymo-orchitis with abscess
N45.9	Orchitis, epididymitis, and epididymo-orchitis without abscess

Data Collection and Data Sources

The data needed to carry out the project will be obtained from the SIDIAP database, the Minimum Basic Data Sets (Conjunt mínim bàsic de dades [CMBD]) of Hospital Discharges and Emergency Departments (Conjunt mínim bàsic de dades a d'hospitalització d'aguts [CMBD-HA] and Conjunt mínim bàsic de dades d'atenció urgent [CMBD-UR], respectively) registries, and data from the Hospital Dispensing Medicines Register (Medicació hospitalària de dispensació ambulatòria [MHDA]).

The SIDIAP contains pseudonymized clinical information from the Electronic Health Records in Primary Care (Estació clínica d'atenció primària) program [31], which is the electronic health records program for PHC of the Catalan Health Institute (Institut català de la salut [ICS]) in Catalonia. The ICS manages 279 PHC centers, covering a population of 5.8 million people (approximately 80% of the Catalan population). Among this adult population, information is available for more than 3384 PHC medical staff members.

The information recorded in SIDIAP contains sociodemographic data; health conditions, coded by ICD-10 [32]; clinical parameters; tobacco and alcohol use; diagnostic procedures; PHC laboratory test results; specialists' referrals; and prescriptions of PHC medical staff, with the corresponding pharmacy billing data, registered as anatomical, therapeutic, chemical (ATC) classification system codes [33]. Several reports have shown that SIDIAP data are useful for epidemiological research [34,35]. SIDIAP is listed under the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance resources database [36].

The CMBD is a population-based registry that collects information on pathologies treated in the health centers of Catalonia [37] and includes ICD-10 codes [32]. This registry contains information provided by all Catalan health care centers on health care activity and morbidity. The CMBD-HA contains information on acute hospitalizations, with reasons and dates for hospital admission. The CMBD-UR reports activity in emergency departments.

The MHDA is a registry containing information on specific drugs that are dispensed in hospitals and reimbursed by the Catalan health system [38,39].

Sample Size

A feasibility count was requested from the SIDIAP database for the years 2012 and 2021. It was estimated that approximately 2.5 million UTIs were registered in the Catalan population during the study period.

Variables

Variables included in WP 1 and WP 2 include sociodemographic information; clinical variables and health conditions, with ICD-10 codes; tobacco and alcohol use; PHC laboratory test results; vaccination status (for influenza, pneumococcus, and COVID-19); prescriptions, with their corresponding pharmacy invoice data registered as ATC codes [33] in addition to prescriptions for MHDA drugs [38,39]; dates of sickness leaves,

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visits, and referrals (to second- and third-level centers); sexual and reproductive health care; CMBD-HA hospital information; and CMBD-UR emergency department information (Multimedia Appendix 1).

Study End Points

Primary End Points

The primary end points of the first phase for WP 1 are the proportion of different types of UTI (uncomplicated UTIs, recurrent UTIs, and pyelonephritis), the percentage of first-line antibiotics used for different types of UTI according to the national guidelines [40,41], and the percentage of inappropriate prescriptions, with the type of antibiotic of these prescriptions. The primary end points for WP 2 are the percentage hospitalization rate and the proportion of UTIs with complications (ie, pyelonephritis, sepsis, pneumonia, and COVID-19). COVID-19 infection will be determined by ICD-10 codes, tests (ie, polymerase chain reaction tests, rapid antigen tests, and others), or both.

Secondary End Points

The secondary study endpoints are (1) types of UTI in women aged ≥18 years with the percentage of recurrent UTIs (defined as more than 2 UTIs in the last 6 months or more than 3 episodes in the last year); (2) types of UTI in men aged ≥18 years; (3) the percentage of urine cultures and laboratory tests ordered for the different types of UTI in both men and women; (4) the percentages of different types of antibiotics used in patients with UTIs, as well as dosage and duration of treatment; (5) the percentage of women with recurrent UTIs who were treated with suppressive therapy (ie, antibiotic treatment 3 times a week for 6 months or more) and the duration of the therapy; (6) the percentage of infectious complications, especially acute pyelonephritis and sepsis, in the 2 cohorts (ie, women with recurrent UTIs with suppressive therapy and women with recurrent UTIs without suppressive therapy but with UTIs treated punctually; (7) the percentage of pneumonia and COVID-19 infection in the 2 cohorts (ie, women with multiple antibiotic regimens for UTIs or suppressive therapy and women with UTIs treated punctually); and (8) the frequency of clinical variables of people affected by UTI who progress to acute pyelonephritis.

Statistical Analysis

Demographic and baseline characteristics of the participants will be reported as frequencies and percentages for categorical variables and means and standard deviation or median and interquartile range for continuous variables, as appropriate.

For WP 1, descriptive statistics will be reported for the results. For WP 2, a severity variable will be constructed that will include mortality and hospitalization, in addition to the presence of pneumonia in cases of COVID-19. Quantitative variables will be described as means and standard deviation, while categorical variables will be described as the proportion of exposed and unexposed individuals. Univariate tests will include the Student *t* test and the chi-square test, as appropriate. For the primary outcome, marginal structural models will be fitted to estimate causal effects by correcting for confounders. Inverse probability weights will be estimated as a function of propensity score using sociodemographic variables and clinical variables. The inverse probability weights will be used in the marginal structural model to estimate the risk ratio and confidence intervals for the prevalence of each outcome among individuals exposed to antibiotics versus those not exposed to antimicrobials. During the assessment of the correlation of prior antibiotic exposure with the different outcomes, patients will only be counted once and assigned to the worst outcome (with the severity of COVID-19 ranked in decreasing order as death, hospitalization, and pneumonia). The Wald test will be used to determine whether the adjusted risk ratios are significantly different from zero at a significance level of 5%.

Ethical Aspects and Data Confidentiality

The present study follows national and international regulations, including the Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects, Good Research Practice principles and guidelines, and the *Real Decreto 957/2020, de 3 de noviembre*, which regulates observational studies of medicines for human use. The study protocol was approved by the Institut Universitari d'Investigació en Atenció Primària Jordi Gol Clinical Research Ethics Committee, the reference institution for research in primary health care of the ICS, on September 27, 2022. In accord with Spanish legislation on confidentiality and data protection (*Ley Orgánica 3/2018, de 6 de diciembre de 2018, de Protección de Datos Personales y garantía de los derechos digitales*), data included in SIDIAP are always pseudoanonymized. Thus, it is not necessary to obtain informed consent from the participants.

Results

We expect to describe the epidemiology of UTIs in Catalonia during the period from 2012 to 2021, including the characteristics of the population, diagnoses of UTI, the use of urine cultures or laboratory tests, and different antibiotics prescribed according to treatment guidelines for dose and duration. Furthermore, we will report the degree of adequacy of the prescribed treatments and the clinical evolution of the patients (ie, the rates of clinical resolution, recurrence, hospitalization, and complications, such as acute pyelonephritis, urosepsis, pneumonia, COVID-19, and death).

The first phase of the ITUCAT project is expected to be completed during the second half of 2023. Phase 2 will start after the data from phase 1 are obtained and used to create the predictive scale for acute pyelonephritis in patients with UTI; phase 2 is expected to be completed in 2024. Phase 3 will be carried out during the second half of 2023 and during 2024 to evaluate the degree of inadequacy in requests for urine cultures according to the clinical practice guidelines and establish the basis for a training intervention.

The results obtained will be presented according to the Reporting of Studies Conducted Using Observational Routinely Collected Health Data Statement for Pharmacoepidemiology (RECORD-PE) recommendations [42].

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Discussion

We expect to find inadequate management in a high percentage of UTI cases, considering that on many occasions patients are treated with second- or third-line antibiotic therapies with a preference for the longest regimens. Likewise, the use of suppressive antibiotic therapy as a prophylaxis in cases of recurrent UTI is expected to vary in our study.

In addition, we aim to determine whether women with recurrent UTIs treated with antibiotic suppressive therapy have a higher incidence and severity of potentially serious future infections, with special attention to acute pyelonephritis, urosepsis, COVID-19, and pneumonia, in comparison to women who are treated with antibiotics only when they present with a UTI.

All the information obtained in this first phase will allow us to continue with the following WPs of the project. Furthermore, if we find the inappropriate use of antibiotics, we will work on the creation of proposals to promote the correct treatment of UTIs in our environment according to clinical guidelines [40,41]. In this way, we will promote responsible management of UTIs in PHC among health care personnel and patients. In addition, our study will provide valuable information for health care policy makers and national programs to optimize the use of antimicrobials.

Because this is an observational study based on data from administrative databases, it will not allow causality analysis. However, the results will be derived from health care carried out under conditions of routine clinical practice with data from electronic primary-care registries, including the SIDIAP, CMBD-HA, and CMBD-UR databases, which have proven to be valid and representative of the population in numerous previous studies [31,34,35]. Some limitations of these studies arose from underreporting of some variables and diagnoses that we will try to avoid with the use of the different databases. Another limitation of the databases is the lack of links between diagnoses and treatments. In order to deal with bias from this specific limitation, we plan to use proxy values available in the databases, such as dates of prescriptions and dates of diagnoses. An inherent limitation of observational studies is the presence of unmeasured confounding variables. A complete adjustment for all possible confounders would require detailed information on clinical parameters, lifestyles, socioeconomic conditions, use of over-the-counter medications, and personal circumstances, which is not routinely present in electronic health records, causing residual confounding bias. Nevertheless, this bias would affect all included populations equally. To minimize confounding, we will conduct sensitivity analyses and use external adjustments or specific statistical methods when appropriate [43]. We will also take this aspect into account in the scientific discussion of the results, as it is an inherent limitation of studies conducted with electronic health records.

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Data Availability

The data sets used and analyzed are available from the corresponding author on reasonable request.

Authors' Contributions

All authors designed the study and wrote the study protocol. SFG wrote the first version of the manuscript, which was reviewed and approved by all authors.

Conflicts of Interest

CL declares having received research grants from Abbott Diagnostics. The rest of authors have no conflicts of interest.

Multimedia Appendix 1
Description of the first phase variables.
[PDF File (Adobe PDF File), 127 KB - resprot_v12i1e44244_app1.pdf]

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Abbreviations

ATC: anatomical, therapeutic, chemical
CMBD: Conjunt mínim bàsic de dades (Minimum Basic Data Set)
CMBD-HA: Conjunt mínim bàsic de dades a d'hospitalització d'aguts (Minimum Data Set of Diagnoses at Hospital Discharge)
CMBD-UR: Conjunt mínim bàsic de dades d'atenció urgent (Minimum Data Set of Diagnoses at Emergency Departments)
ICD-10: International Classification of Diseases, 10th Revision
ICS: Institut català de la salut (Catalan Health Institute)
MHDA: Medicació hospitalària de dispensació ambulatòria (Hospital Dispensing Medicines Register)
SIDIAP: Sistema d'informació per al desenvolupament de la investigació en atenció primària (Information System for the Development of Research in Primary Care)
PHC: primary health care
UTI: urinary tract infection
WP: work package

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Protocol

The Vaping and Patterns of e-Cigarette Use Research Study: Protocol for a Web-Based Cohort Study

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Abstract

Background: In total, 3.2% of American adults report using e-cigarettes every day or some days. The Vaping and Patterns of E-cigarette Use Research (VAPER) Study is a web-based longitudinal survey designed to observe patterns in device and liquid use that suggest the benefits and unintended consequences of potential e-cigarette regulations. The heterogeneity of the e-cigarette devices and liquids on the market, the customizability of the devices and liquids, and the lack of standardized reporting requirements result in unique measurement challenges. Furthermore, bots and survey takers who submit falsified responses are threats to data integrity that require mitigation strategies.

Objective: This paper aims to describe the protocols for 3 waves of the VAPER Study and discuss recruitment and data processing experiences and lessons learned, including the benefits and limitations of bot- and fraudulent survey taker–related strategies.

Methods: American adults (aged ≥21 years) who use e-cigarettes ≥5 days per week are recruited from up to 404 Craigslist catchment areas covering all 50 states. The questionnaire measures and skip logic are designed to accommodate marketplace heterogeneity and user customization (eg, different skip logic pathways for different device types and customizations). To reduce reliance on self-report data, we also require participants to submit a photo of their device. All data are collected using REDCap (Research Electronic Data Capture; Vanderbilt University). Incentives are US $10 Amazon gift codes delivered by mail to new participants and electronically to returning participants. Those lost to follow-up are replaced. Several strategies are applied to maximize the odds that participants who receive incentives are not bots and are likely to possess an e-cigarette (eg, required identity check and photo of a device).

Results: In total, 3 waves of data were collected between 2020 and 2021 (wave 1: n=1209; wave 2: n=1218; wave 3: n=1254). Retention from waves 1 to 2 was 51.94% (628/1209), and 37.55% (454/1209) of the wave 1 sample completed all 3 waves. These data were mostly generalizable to daily e-cigarette users in the United States, and poststratification weights were generated for future analyses. Our data offer a detailed examination of users' device features and specifications, liquid characteristics, and key behaviors, which can provide more insights into the benefits and unintended consequences of potential regulations.

Conclusions: Relative to existing e-cigarette cohort studies, this study methodology has some advantages, including efficient recruitment of a lower-prevalence population and collection of detailed data relevant to tobacco regulatory science (eg, device wattage). The web-based nature of the study requires several bot- and fraudulent survey taker–related risk-mitigation strategies, which can be time-intensive. When these risks are addressed, web-based cohort studies can be successful. We will continue to explore methods for maximizing recruitment efficiency, data quality, and participant retention in subsequent waves.

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KEYWORDS

internet; web-based; cohort; survey; e-cigarettes; electronic nicotine delivery systems; ENDS; tobacco; recruitment; data collection; strategies; lessons learned; mobile phone

Introduction

Background

In the United States, 3.2% of adults, 7.6% of young adults [1], and 11.3% of high school students [2] use e-cigarettes (every day or some days for adults and use in the past 30 days for high school students), and the US Food and Drug Administration Center for Tobacco Products is interested in data-driven regulations that maximize public health benefits while minimizing unintended consequences [3].

Our team is conducting a web-based longitudinal survey to observe patterns that suggest the benefits and unintended consequences of three potential e-cigarette regulations: (1) limits on nicotine, (2) constraints on nicotine flux (ie, nicotine emitted over time) [4], and (3) reduction in flavor availability. Electronic nicotine delivery systems (ENDS) are e-cigarettes that heat a nicotine liquid into an aerosol that can be inhaled by a user, whereas electronic nonnicotine delivery systems (ENNDS) heat a nonnicotine-containing liquid (ENNDS are included in the study as ENDS users may become ENNDS users and vice versa). Both include a battery that powers a heating element, such as a metal coil, which is in contact with the liquid. Device size, shape, materials, features (eg, coil modifiability), and specifications (eg, battery voltage, coil resistance, and device wattage) vary considerably. The liquids are typically made of a propylene glycol and vegetable glycerin solution that contains flavorings and nicotine, a psychoactive and addictive drug [5].

Unlike cigarettes, which are all relatively similar in design, the heterogeneity of ENDS and ENNDS devices, settings, and liquid characteristics results in a highly customizable user experience. This heterogeneity and a lack of standardized reporting requirements for device specifications and liquid characteristics can lead to measurement challenges. For example, some manufacturers report liquid nicotine concentration as a percentage of the liquid solution, whereas others report it in milligrams per milliliter. These inconsistencies may partially explain why reporting liquid nicotine concentration accurately in surveys is challenging for some users [6,7]. In addition, liquid manufacturers sometimes inaccurately label nicotine concentration [8-10], and device manufacturers often do not publicize specifications such as device wattage, voltage, and resistance, thus creating additional challenges for researchers even after collecting the brand and model of a user's device. These data are critical for evaluating nicotine and toxicant emissions and delivery. For example, device wattage is a predictor of nicotine emissions and delivery to the blood [11,12].

Web-based survey methods also present challenges that must be addressed in both a preventive and ad hoc manner; such challenges include recruitment of lower-prevalence populations and navigating bots [13] and fraudulent survey takers [14], who primarily aim to deceive researchers for the purpose of receiving incentives. Nevertheless, web-based survey methods are an increasingly used avenue to recruit participants, collect data, and provide incentives across public health research domains, including ENDS and ENNDS research, and they may have several benefits over traditional methods, such as convenience for participants and researchers, scalability, reduced costs, and safety during extraordinary times such as the COVID-19 pandemic.

Studies that address these measurement and data integrity (eg, bots) challenges can offer a more detailed examination of frequent ENDS and ENNDS users' device features and specifications, liquid characteristics, and user behaviors while simultaneously benefiting from improved convenience, scalability, reduced costs, and safety. Moreover, through an improved understanding of the relationships among device type, features, specifications, liquid characteristics, and key user behaviors such as nicotine dependence, regulators may gain a more precise understanding of how regulating devices and liquids may positively or negatively affect users before implementing a regulation.

Objectives

Our aim is to describe the protocols for waves 1 to 3 of the Vaping and Patterns of E-cigarette Use Research (VAPER) Study, a web-based longitudinal cohort study of ENDS and ENNDS users (aged ≥21 years) who use devices ≥5 days per week and have a residential address in the United States. We also discuss our recruitment and data processing experiences and lessons learned, along with the benefits and limitations of implementing our strategies for mitigating measurement-, bot-, and fraudulent survey taker–related challenges.

Methods

Overview

The protocols for waves 1 to 3 are similar. Key differences will be addressed; where none are discussed, similar protocols were followed in all waves and will also be followed in future waves. Additional technical details can be found in Multimedia Appendix 1. All data are collected using REDCap (Research Electronic Data Capture; Vanderbilt University), a free, secure, and robust data collection platform.

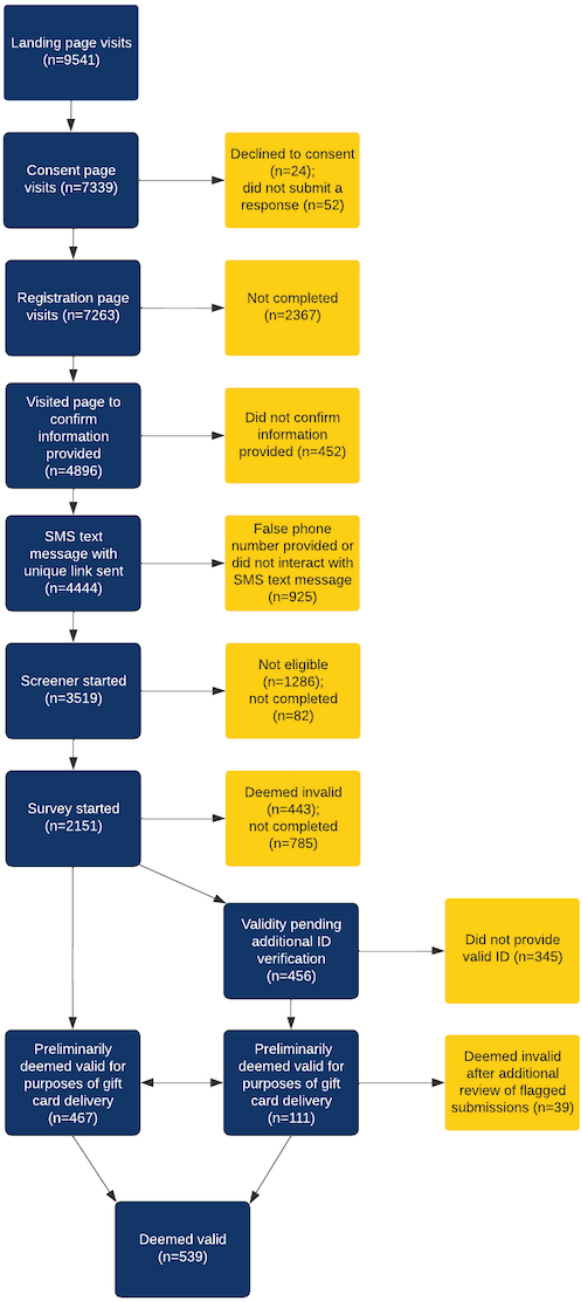
The VAPER Study is a cohort study conducted on the web, including participant recruitment, data collection, and incentive delivery to participants. A self-selection sampling method is used. Recruitment-related information for the baseline survey is posted on Craigslist Jobs and Gigs boards and directs potential participants to click a hyperlink to a study-specific landing page with a welcome message hosted on the Virginia Commonwealth University website (the web page is not accessible through other avenues unless the hyperlink is shared by participants). After

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providing informed consent, participants complete a registration form requesting the following information: name, email address, mobile phone number, residential address, and date of birth. Participants then review the information they provided and complete a phone number authentication that contains a unique link to the REDCap screener and survey. Before starting the survey, all participants are reminded of actions that can result in their disqualification (also present in the consent form). Upon survey completion, identity verification, and review of submitted data, participants are mailed a US $10 Amazon gift code (Figure 1).

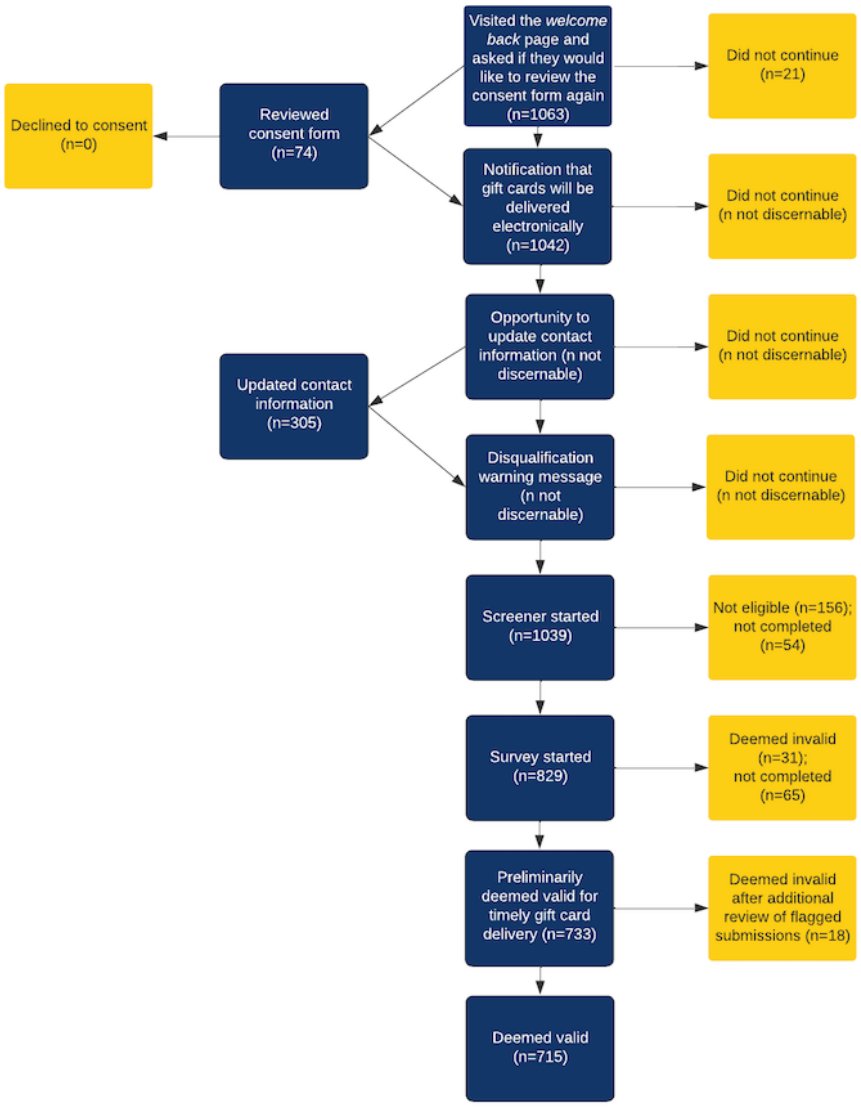
Participants who submit valid baseline surveys and indicate an interest in participating in additional surveys are invited to complete a follow-up survey in subsequent waves. Invitations are sent to their mobile phones and email addresses, and the links to the survey are tied to their previously established record ID number. Returning participants are greeted with a *welcome back* message and, before completing the screener, are provided with the opportunity to review the consent form again, are notified that they will receive their gift codes electronically, are asked to review and update their contact information (if necessary), and are again reminded of actions that can result in their disqualification (Figure 2).

Figure 1. Flow diagram of baseline survey participants from wave 3.



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Figure 2. Flow diagram of follow-up survey participants from wave 3.



To replace those lost to follow-up, new participants are recruited to complete the baseline survey, resulting in 2 concurrent REDCap surveys per wave: one for baseline participants and another for follow-up participants. Therefore, a new baseline cohort is created in each wave, with all previously established cohorts taking a concurrent and identical follow-up survey (Table 1). The measures in the questionnaire evolve as changes in the marketplace are recognized, as new information is learned about the quality of the questions and response options, and as the VAPER Study team fields requests from the funders and colleagues working on related laboratory-based projects. This evolution creates a layer of complexity when analyzing data longitudinally but will not affect cross-sectional analyses. For longitudinal data analyses, steps are taken to ensure that the underlying questions and response options are comparable. More specifically, a data workbook is used to track variable names for each wave and survey (ie, baseline and follow-up surveys); whether edits have been made to the question or response option text; and if "yes," what those edits were. Manuscript authors can then determine whether their measures can be used across waves in consultation with our statistician and wider team.

Table 1. Surveys taken in each wave, by cohort.

	Wave 1: May 2020-October 2020	Wave 2: December 2020-April 2021	Wave 3: September 2021-December 2021
Cohort 1	Baseline	Follow-up	Follow-up
Cohort 2	N/A[a]	Baseline	Follow-up
Cohort 3	N/A	N/A	Baseline

[a]N/A: not applicable.

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Sample

Participants are ENDS and ENNDS users who typically use e-cigarettes at least 5 days per week, are aged ≥21 years, and have a residential address in the United States. Adults are recruited for several reasons: (1) more adults (10.9 million) [15] than youth (2.2 million) [16] use ENDS and ENNDS; (2) school-based recruitment methodologies are slower, more expensive, and less scalable; and (3) most of our hypothesized relationships among devices, liquids, and user behaviors are expected to be present irrespective of age (eg, a negative correlation between device power and liquid nicotine concentration). The age of 21 years was chosen over 18 years because of institutional review board (IRB) guidance and state and federal legislation that raised the minimum age of purchase to 21 years. Users who use "At least five days per week" are recruited as we are primarily interested in within-person longitudinal data. Our rationale is that frequent ENDS and ENNDS users are more likely to continue using and remain in the sample compared with users using <5 days per week, thereby increasing the quality of the longitudinal data.

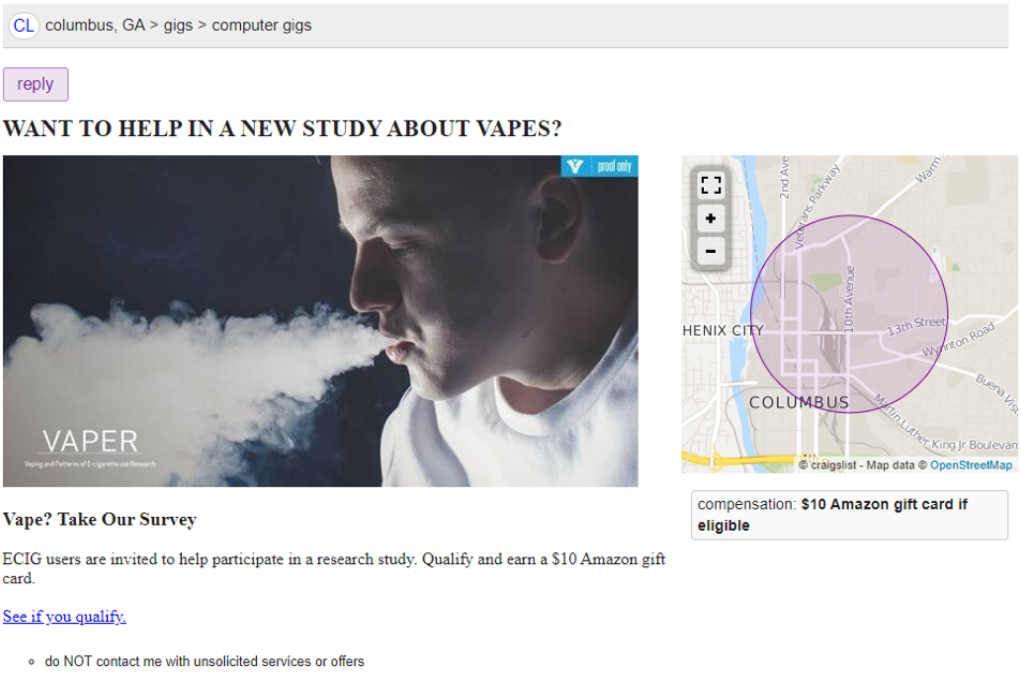
The intended sample size (N=900) was determined by assuming an effect size of 10% (for *t* tests to detect differences between 2 dependent means using a 2-tailed test), Cronbach α<.05, and power of 0.85. After adjusting for an anticipated loss to follow-up rate of 25%, we determined that a baseline sample of 1200 participants was required to ensure adequate power for the study duration.

Recruitment

Craigslist is used to recruit baseline survey participants. It has a high volume of website traffic, a user base interested in earning income, affordable rates for posting messages targeted to potential participants in the United States, and a track record of success in helping tobacco control [17] and other public health researchers [18] recruit participants. Craigslist postings include a photo and text indicating that we are recruiting ENDS and ENNDS users and will compensate participants with a US $10 Amazon gift code (Figure 3). Note that social media (ie, Facebook and Instagram) and vape shop customer recruitment were attempted early in wave 1 but, because of cost and efficiency reasons, were replaced by a Craigslist-focused strategy. Craigslist was used to recruit most of our wave 1 sample and to replace all participants lost to follow-up in waves 2 and 3.

The Craigslist postings are posted on the Jobs and Gigs boards in as many as 404 geographic locations per wave, including all 50 US states (Multimedia Appendix 1). Both boards were used in most geographic locations, but sometimes only 1 board was used. Geographic locations were selected based on population estimates of major US cities and states, with preference given to the most populous catchment areas (note that Craigslist regions can cover a single city, regions, or large geographic areas spanning entire states). To optimize recruitment efficiency, Craigslist postings are reposted at varying time intervals primarily based on the number of competing advertisers displacing our postings to a lower position on the page (eg, New York City boards need to be reposted 2 times per week, whereas others are reposted as infrequently as once per month). Other metrics are tracked and considered as well, including the fluctuating volume of clicks from different locations over the course of a survey wave (measured in real time using Google Analytics) and the number of participants completing the survey from each location (higher-yielding locations tend to be reposted more frequently).

Figure 3. An example Craigslist posting from wave 3.



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Communication Strategy for Maximal Retention

To invite participants who previously submitted valid surveys to complete additional survey waves, our team sends 2 pairs of emails and SMS text messages per week for 2 weeks at the start of each wave. Afterward, 1 pair of emails and SMS text messages is sent per week for 6 weeks to all participants who have not yet completed the survey. The subject lines and message content of the reminders vary from week to week to attempt to appeal to different audiences. Note that, at the start of wave 2, tests were conducted to select the most effective communication content (eg, varied email subject lines) and frequency of communications (ie, 1 vs 2 pairs of emails and SMS text messages sent per week for 2 weeks, with each pair sent simultaneously). The tests were conducted using a small subset of the wave 1 sample (n=148), and we found no statistically significant differences in valid survey completion rates or the rates of opting out of SMS text messages, and the absolute number of SMS text message opt-outs was minimal (n=5).

Engagement Strategy

Loss to follow-up is common in longitudinal studies. To increase engagement and minimize loss to follow-up, our participants are sent an annual postcard indicating that they are eligible for a raffle. The annual raffle has 4 winners, with each receiving a US $100 Amazon gift code. Completing 2 surveys will earn participants 10 chances to win the raffle, and completing 3 surveys will earn them 50 chances.

Measures

Measures in the questionnaire are from or derived from those found in the PhenX Toolkit (RTI International; a web-based catalog of high-priority measures), validated measures, or measures used in large national surveys whenever possible and appropriate. We developed measures in all other instances. Randomization of questions and response options is not used; however, adaptive questioning to reduce the number and complexity of the questions is used (eg, questions are tailored based on self-reported device features). The number of questions per page is limited to 1 whenever possible; however, it is necessary to have more than 1 question per page when participants are asked to further specify information or in instances where the questions are easier to respond to in sequence (eg, grid-style questions). The number of pages varies widely based on the devices and liquids used and related behaviors. To ensure completeness, all participants must provide a response to continue to the next page (an error message is received when participants attempt to continue without completing all the questions). To mitigate data integrity issues, a back button is not used.

The usability and technical functionality of the questionnaire are rigorously tested by the study team before fielding the questionnaire in each wave. All permutations of skip logic and response option constraints are tested, and before the first wave, mock participants not familiar with the study completed the questionnaire and provided feedback on wording of the prompts, questions, response options, functionality of specific features (eg, photo upload), and overall user experience. Although these actions greatly mitigate technical issues and improve user experience, participants who complete the study during each wave often provide comments and suggestions that are incorporated as well.

To discern the impacts of potential regulations, outcome measures include current ENDS and ENNDS use (≥5 days per week), current combustible cigarette use (past 30 days), product switching (eg, devices, device settings, and liquid nicotine concentration and flavor), do-it-yourself flavor mixing (ie, mixing their own flavored solution typically by mixing a combination of propylene glycol, vegetable glycerin, nicotine, and flavorings), ENDS dependence, and respiratory symptoms. Psychosocial mediators include quitting intentions, perceived risk and severity, and outcome expectancies related to use experience. Moderators include sociodemographic factors, tobacco cigarette history, ENDS and ENNDS history, and reasons for use. Full details for select measures are available in the following sections; the full questionnaire is available on our study website [19].

ENDS and ENNDS use was assessed using the following question: “How many days in a typical week do you use an e-cigarette or vaping device to vape e-liquids with or without nicotine?” Response options included “I do not use an e-cigarette or vaping device to vape e-liquids with or without nicotine in a typical week,” “1 day,” “2 days,” “3 days,” “4 days,” “5 days,” “6 days,” and “7 days.”

Dependence is measured using the E-cigarette Dependence Scale. Participants receive the following prompt: “The following questions are about your E-CIGARETTE use only. Please respond to each question or statement by marking the most appropriate response.” The statements include “I find myself reaching for my e-cigarette without thinking about it,” “I drop everything to go out and buy e-cigarettes or e-juice,” “I vape more before going into a situation where vaping is not allowed,” and “When I haven’t been able to vape for a few hours, the craving gets intolerable.” Response options include “Almost Always,” “Often,” “Sometimes,” “Rarely,” and “Never.”

Quitting intentions are assessed using the following questions: “Are you planning to quit vaping” and “Are you planning to quit smoking cigarettes.” Response options include “Within the next month,” “Between 1-6 months from now,” “Sometime in the future, beyond 6 months,” and “Not planning to quit.” For cigarettes, only those who indicate that they have smoked ≥100 cigarettes in their lifetime and a cigarette in the past 30 days are asked the question.

The questions and skip logic are designed to accommodate marketplace heterogeneity and user customization. For example, there are different skip logic pathways for participants with disposable devices; disposable pod– or cartridge-based devices; and refillable pod–, cartridge-, or tank-based devices. These pathways allow our team to tailor the questionnaire to each participant’s situation and experiences with the expectation of creating a better user experience for the participants, higher retention, and higher-quality data. Another byproduct of this approach is that it allows for inquiry about the devices, liquids, and related behaviors that do not apply to all participants, such as the addition of extra nicotine to one’s liquid (often called

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"nicotine boosters" or "nicotine shots"). Such behavior would only be applicable to participants who refill their device from a bottle of liquid. Please note that these device and liquid questions are not validated.

Device and Liquid Data Collection

Previous studies have suggested that self-report data alone may not be a viable strategy for capturing accurate device and liquid data [6,7]. To minimize reliance on these data, we require participants to submit valid photos of their most commonly used device, the current visual display screen (powered on) if available, and the most commonly used liquid for the device if available. Following a standard operating procedure, submitted photos are reviewed to identify the brand and model of the device. When the brand or model are not immediately apparent or found with the aid of a Google search, we use unique features, colors, and text on the device to conduct a Google image search. Upon identifying the brand and model, key variables are collected from manufacturer, academic, retailer, and review websites. YouTube product reviews are also helpful in understanding whether certain features are present when information is not readily available on the aforementioned websites (eg, adjustable airflow). To mitigate issues related to inconsistent reporting of device features and specifications and liquid characteristics across websites, data are collected preferentially from (1) manufacturer sites, (2) academic manuscripts, (3) retailer sites, (4) review sites, and (5) YouTube. Key variables collected for devices include wattage, voltage, resistance, coil modifiability, power modifiability, airflow adjustability, disposable versus reusable, and pod- or cartridge-based device versus tank-based device. Liquid variables include brand, flavor (primary and secondary), container size (mL), nicotine concentration (mg/mL), nicotine formulation (free base vs protonated), propylene glycol percentage, and vegetable glycerin percentage.

Missing Data

Missing data is a multifaceted issue. Participants may self-report not knowing the details of the products used and their related settings and specifications. Photos are also vulnerable to user error, with some participants not following instructions (eg, blurry images), resulting in unidentifiable device brands and models, visual display settings, and liquid characteristics. In addition, some web-based sources do not report all device features, specifications, and liquid characteristics.

We use several preventive strategies to mitigate these issues. First, by collecting device and liquid data via self-report and from photos and web-based sources and creating a combined variable that prioritizes photo and web-based data, we minimize missing data and reliance on participant expertise on the product details. Furthermore, participants are required to answer each question to advance and complete the questionnaire, resulting in minimal missing data for all questions without "Don't know" and "Prefer not to answer" response options (responses with identifying information were removed). Finally, for the collection of data from photo and web-based sources, participants are provided with instructions for submitting photos, and a comprehensive standard operating procedure is adhered to by the team to ensure that web-based data are reliably collected.

Despite these preventive efforts, missing data can still occur; therefore, we implement 3 additional post hoc strategies specific to device wattage, voltage, and coil resistance. The first strategy is to purchase the most prevalent devices in the sample with missing data for 2 or more of these device specifications, disassemble the devices, and directly measure the voltage and resistance using a multimeter when one or both values are missing. The second strategy is to use a power calculator (ie, a mathematical formula for calculating wattage, voltage, or resistance) when a single specification is missing. The third strategy is used when three conditions are met: (1) the device's range (eg, 0-80 W) is known, (2) the participant's current setting within the range is unknown (eg, the picture is blurry or there is no visual display), and (3) the setting is not self-reported by the participant. Under these conditions, we estimate the participant's setting by calculating the average midpoint for the device type (eg, the average refillable tank user used 35% of the allowable wattage range in wave 3). The average midpoint (eg, 35%) is then applied to the specific device's known range.

Data Integrity and Security

Rigorous measures are taken to prevent bots and fraudulent survey takers from subverting data integrity. All participants who register and complete the baseline survey provide identifying data and agree to participate in identity verification procedures. LexisNexis (RELX corporation), a third-party identity search engine, is used to verify identities before providing incentives. In instances where the LexisNexis database is not sufficient to identify participants, they are asked to provide a photo ID or utility bill that contains information confirming their identity.

Bot protections include a Completely Automated Public Turing test to tell Computers and Humans Apart (CAPTCHA), authentication of a mobile phone number, attention-checking questions, disabling the back button, and manual review of open-ended responses. The CAPTCHA is a well-known test that requests users to perform simple tasks that humans can accomplish easily but unsophisticated bots cannot. Authentication is used to confirm that phone numbers are real and to generate a new randomly generated survey link. By having 2 REDCap forms linked in this way, bots cannot easily generate new identities and immediately proceed to take the survey. Attention-checking questions not only help us identify participants quickly moving through the survey but also help identify unsophisticated bots who may be providing random answers to the questions. The back button is disabled to prevent participants who build bots from more easily learning the questionnaire and skip logic, thus making it more time-intensive to build a sophisticated bot capable of providing answers that closely mimic real users. The manual review of open-ended responses is particularly important as bots often use similar responses across multiple survey submissions. By screening the new survey submissions on a weekly basis for repeated phrases (particularly uncommon phrases), spelling, and formatting errors, we can more easily identify problematic cases and adjust the strategy as needed. However, the most sophisticated bots

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may be capable of circumventing these procedures and may be indistinguishable from real users. These strategies are meant to mitigate the chances of having bot-related issues.

Fraudulent survey takers are participants who are savvy enough to enroll in and complete surveys for which they are not qualified. Similar to bots, they may also attempt to take a survey multiple times. By using identity checks, the risk that participants will take the survey multiple times is lower (note that they can use another person's identity); however, they may not be truthful about their e-cigarette use behavior. To further mitigate the risk of enrolling fraudulent survey takers, we use clear warnings against misuse, require participants to submit a photo of their most used device from the past week, review each photo to verify that it is valid (ie, instructions were followed), and mail incentives. Our warning statement is placed in the consent form and at the start of the surveys: "As a reminder, any perceived attempt to speed through the survey, take the survey more than once, or provide false or misleading information will result in your disqualification from the survey and forfeiture of any promised incentives." This provides us with maximum flexibility for determining who should not receive an incentive and be included in our final sample. Requiring that participants submit a photo of their most used device from the past week is essential to ensuring that they are in possession of a device and, thus, more likely to be ENDS or ENNDS users. Photo submissions of their most commonly used devices from the past week are rigorously reviewed for the following evidence: the objects featured in the photo are not ENDS or ENNDS devices, the photos are downloaded from the internet, the photos are staged in a store, the photos are identical or nearly identical to submissions by other unique IDs, and the photo-coded brand and model do not match the self-reported brand and model for 3 devices that were provided as examples in the self-report brand and model question; that is, "What is the brand AND model of the device (e.g., JUUL, Vaporesso Luxe, Voopoo Drag 2, etc.)?"

Other rigorous data quality checks are also performed before participants receive their incentives. The checks include identifying the use of non-English or non-Spanish alphabet characters in open-ended responses; verifying that a proper mailing address has been provided; confirming that participants do not submit more than 1 survey within or across survey waves; and verifying that more than the minimal number of questions have been answered (skip logic is such that this is highly improbable), completion time is >5 minutes, and 2 attention-checking questions are answered appropriately (both require correct responses).

Data security is ensured through the use of REDCap and Twilio. REDCap is a secure web application that is used to build web-based surveys and databases. It collects any type of data and is geared toward supporting data capture on a server for category-1 data (ie, confidential data). Access to files with identifying information is restricted to approved research team members, all of whom are trained in standards of research privacy and confidentiality and who have secure passwords required to sign onto the data server. When off-campus, virtual private network services are used to access the server. Twilio is a web service used to send a private survey link to respondents. Participants' phone numbers do not remain in Twilio's logs but are removed shortly after being completed, which is done for security and privacy concerns.

Incentives

The incentive for completing the 15-minute survey is a US $10 Amazon gift code. Once submissions are determined to be preliminarily valid after the initial data quality review and participants' identities are confirmed, incentives are mailed to the physical address provided by baseline survey participants and emailed to follow-up survey participants. The data quality check and identity verification are typically completed within 3 days of submission, and incentives are mailed on a weekly basis. Baseline survey participants are mailed their incentives as a form of delayed gratification to deter them from attempting to take the survey multiple times. Post office box addresses and other nonresidential mailboxes are not accepted to prevent multiple submissions. Occasionally, incentives are returned to the sender, indicating that a false address was provided, the participant moved, or a typo was present in the provided address. These record IDs are reviewed more closely for other data quality issues (eg, responses indicating that they were likely not ENDS or ENNDS users). If other survey data are found to be of low quality, the corresponding participants are dropped from the data set and not invited to future waves but are still eligible to receive their incentive for the wave in question. To facilitate the emailing of gift codes to follow-up participants, Rybbon (BHN Rewards), a digital gift code delivery service, is used.

Final Data Quality Checks

Once data cleaning procedures are completed after each survey wave, additional data quality checks are completed when preliminarily valid records are flagged. These include instances of photos with multiple devices or liquids present, poor photo quality, photos or survey responses with non–propylene glycol and vegetable glycerin solutions (eg, tetrahydrocannabinol or cannabidiol), age of first use occurring before ENDS and ENNDS were commercially available in the United States (baseline only), select examples of REDCap skip logic not working as intended (investigated by REDCap; the software bug remains unknown), and incentives being returned to the sender (as previously described). When at least one flag is identified, all the survey responses are reviewed for additional evidence of poor data quality. For example, additional evidence may include the self-reported device brand and model not matching the photo brand and model or self-reported liquid flavors not matching their respective photos. A scoring system is used to determine whether the issues found warrant exclusion from the current and future waves of data collection. All excluded participants still receive their incentive for the survey wave in question.

Ethics Approval

The IRB at the Virginia Commonwealth University (HM20015004) approved the study protocol. The Johns Hopkins Bloomberg School of Public Health IRB (9277) approved reliance on the Virginia Commonwealth University IRB.

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Results

Recruitment and Retention

Funding for the VAPER Study began on September 1, 2018, and will conclude on August 31, 2023. Data collection for waves 1 to 3 was completed over 3 periods. Wave 1 was completed between May 18, 2020, and October 16, 2020 (n=1209); wave 2 was completed between December 10, 2020, and April 21, 2021 (n=1218); and wave 3 was completed between September 2, 2021, and November 18, 2021 (n=1254). Partially completed questionnaires are not analyzed.

Upon conclusion of wave 2, the retention rate of cohort 1 (baseline survey participants from wave 1; n=1209) was 51.94% (628/1209), and 5.29% (64/1209) of participants opted out of SMS text message reminders. For wave 3, a total of 37.55% (454/1209) of cohort 1 completed the survey, with 33.25% (402/1209) completing the wave 2 and 3 surveys (52/1209, 4.3% completed the survey for wave 3 but not for wave 2). A total of 7.03% (85/1209) of participants opted out of SMS text message reminders. Cohort 2 (baseline survey participants from wave 2; n=590) had a wave 3 retention rate of 44.2% (261/590), and 6.4% (38/590) of participants opted out of the SMS text message reminders.

Generalizability

For each wave, our wave 1 to 3 frequent users were largely generalizable to daily users of e-cigarettes in the United States (1185/1254, 94.5% of our wave 3 sample used ENDS or ENNDS 7 days per week; Table 2). There was no statistically significant difference between our wave 3 sample and the weighted 2019 Tobacco Use Supplement to the Current Population Survey data in terms of *age/gender/race* (P=.18) and *region* (P=.42). Compared with the Tobacco Use Supplement to the Current Population Survey, our wave 3 sample had a higher percentage of frequent ENDS or ENNDS users with an income of US <$60,000 (928/1225, 75.76% vs 804,024/1,537,547, 52.3%; P<.001). Applying poststratification weighting can help improve the representativeness of the data.

Table 2. A comparison of wave 3 and Tobacco Use Supplement to the Current Population Survey (TUS-CPS) 2019 frequencies for 3 weighting strategies.

	VAPER[a]—wave 3, n (%)	TUS-CPS 2019 (n=554)		
		Participants, n (%)	Weighted N (%)	SE of weighted frequency
Gender, age, and race (n=1233)[b]				
Men, <35 years, and non-White[c]	92 (7.5)	16 (2.9)	55,388 (3.6)	15,766
Men, <35 years, and White	216 (17.5)	139 (25.1)	370,806 (24.2)	33,224
Men, ≥35 years, and non-White	48 (3.9)	14 (2.5)	46,345 (3)	14,129
Men, ≥35 years, and White	183 (14.8)	159 (28.7)	414,366 (27)	32,117
Women, <35 years, and non-White	100 (8.1)	10 (1.8)	41,041 (2.7)	13,602
Women, <35 years, and White	250 (20.3)	85 (15.3)	243,554 (15.9)	28,760
Women, ≥35 years, and non-White	55 (4.5)	11 (2)	36,008 (2.4)	12,207
Women, ≥35 years, and White	289 (23.4)	120 (21.7)	327,967 (21.4)	29,119
Annual income (US $)[d] (n=1225)[e]				
<60,000	928 (75.8)	287 (51.8)	804,024 (52.3)	42,114
≥60,000	297 (24.2)	267 (48.2)	733,523 (47.7)	39,627
Region (n=1254)				
Northeast	172 (13.7)	89 (16.1)	258,265 (16.8)	28,287
Midwest	263 (21)	134 (24.2)	427,656 (27.8)	36,026
South	465 (37.1)	192 (34.7)	548,960 (35.7)	37,425
West	354 (28.2)	139 (25.1)	302,665 (19.7)	28,726

[a]VAPER: Vaping and Patterns of E-cigarette Use Research.

[b]Missing data: n=21.

[c]White includes single race White; non-White includes all other single races, including American Indian or Alaska Native, Asian or Asian American, Black or African American, Native Hawaiian or Pacific Islander, other, and multirace.

[d]Denotes a statistically significant difference between VAPER and TUS-CPS data at P<.001.

[e]Missing data: n=29.

Poststratification weighting normally requires the sample size of a subgroup to be >20. Thus, for the VAPER Study, creating 1 weight that covers all sociodemographic variables, including gender, age, race, income, and region, is not acceptable as the

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cell sizes would be under the minimum threshold. Therefore, 3 separate weights are available: a gender, age, and race weight; an income weight; and a geographic region weight. The variables for the gender, age, and race weight are dichotomized as men and women, <35 years and ≥35 years, and White and non-White populations. For the annual income weight, data are dichotomized as US <$60,000 and US ≥$60,000. Finally, for the geographic region weight, data are categorized into "Northeast," "Midwest," "South," and "West." The specific poststratification weight used in the dissemination of the survey findings will be hypothesis-driven and based on whether the characteristics incorporated into the weight are expected to be correlated highly with the primary outcome of interest.

Planned Analyses

Analyses will be designed to observe patterns that suggest the benefits and unintended consequences of potential regulations. Our data offer a detailed examination of frequent ENDS and ENNDS users' device features and specifications, liquid characteristics, and behaviors. A better understanding of how devices and liquids relate to one another and may be associated with key behaviors such as nicotine dependence can provide regulators with a more precise understanding of how regulating features, specifications, and characteristics may positively or negatively affect users before implementing a regulation. We intend to examine these relationships for three potential regulations: (1) limits on nicotine, (2) constraints on nicotine flux (ie, nicotine emitted over time), and (3) reduction in flavor availability (Textbox 1).

Textbox 1. Hypotheses regarding the 3 potential regulations for electronic nicotine delivery systems (ENDS).

- Limits on nicotine
  - As of May 2016, the European Union limits nicotine concentration in liquids; the US Food and Drug Administration (FDA) may consider a similar action. Hypotheses will be informed by the latest available data at the time of analysis, but a priori, we hypothesize that device wattage will be correlated inversely with nicotine concentration and directly with the amount of liquid consumed and that, across concentration, more dependent ENDS users are using higher-power devices. Over time, users who switch to lower-concentration liquids will begin using higher-power devices. This pattern would highlight how limiting liquid nicotine concentration to control nicotine delivery may fail when higher-wattage devices are available.
- Constraints on nicotine flux
  - Nicotine flux is a function of device specifications and liquid characteristics (ie, power and nicotine concentration) and helps determine user nicotine exposure; it can be predicted mathematically, suggesting that a flux-based product regulatory standard is possible. We will investigate flux standards by studying device wattage, nicotine concentration, and user dependence. Again, hypotheses will be informed by the latest available data at the time, but a priori, we hypothesize that higher flux conditions (eg, greater wattage and nicotine concentration) will be associated with greater dependence, lower flux conditions will be associated with less dependence, and transitions from lower to high flux conditions will be accompanied by higher flux. This pattern highlights nicotine flux as a potential regulatory target.
- Reduction in flavor availability
  - The FDA began prioritizing the enforcement of premarket of ENDS products in 2021 [20,21]. This action has likely decreased the variety of liquid flavors sold. A priori, we hypothesize that this decrease may lead users to change their preferred flavor for their most commonly used device, change their device specifications, or change their behavior to maintain their nicotine delivery. Transition patterns will highlight how reducing flavor availability may affect behavior.

Our primary aims are to evaluate the 3 potential regulations; however, the relative novelty of our methods for collecting detailed device features and specifications and liquid characteristics along with a new practice of analyzing device and liquid pairings rather than analyzing them separately warrants additional supportive and foundational analyses, respectively. As such, our team has identified additional priorities, including but not limited to examining the percentage of agreement between self-reported responses and photo data collection of devices and liquids, mitigating the impact of bots and fraudulent survey takers, and identifying common combinations of device specifications and liquid characteristics (and transitions).

There is no one primary analytic approach; statistical tests will vary based on the research question, measures used, and cross-sectional versus longitudinal nature of the analysis. In general, for longitudinal analyses, generalized estimating equations will be used to account for the variable times between survey waves.

Discussion

The VAPER Study uses a web-based longitudinal cohort design to observe patterns that suggest the benefits and unintended consequences of 3 potential Food and Drug Administration regulations. A priori, we hypothesize that we will identify relationships among device features and specifications, liquid characteristics, and user behavior. A better understanding of these relationships, particularly longitudinally, may allow regulators to better understand how regulations positively or negatively affect user health.

Most population surveys about ENDS and ENNDS are unable to describe device features and specifications, liquid characteristics, and user behavior in a detailed manner because of measurement-related challenges such as a highly customizable user experience [22] and a lack of standardized reporting requirements for device features and specifications and liquid characteristics [9]. Consequently, surveys often oversimplify use. For instance, surveys sometimes presume that a single

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device is used and request that participants indicate the device type, usually with predefined definitions that may not keep pace with market innovations (particularly salient for longitudinal surveys) [23,24] or terminology used by all participants [25]. Surveys that use such an approach also ignore the possibility that some users use multiple ENDS and ENNDS in varying amounts and that different device and liquid combinations (within and across device types) may affect nicotine and toxicant emissions and delivery [26]. Our study demonstrates potential solutions to these measurement challenges through survey questions that allow participants to describe their most commonly used device and most commonly used liquid for that device through the use of adaptive questions. In addition, we require valid photos of their most commonly used device and request photos of their most commonly used liquids for that device, thereby allowing our team to determine the device type, features, and specifications and liquid characteristics based on the photo and related website coded data independent of self-reported responses.

Web-based surveys have become increasingly common; however, reporting of contemporary methodologies to maximize data integrity and mitigate the impact of bots and fraudulent survey takers and best practices for de novo recruitment is lacking. Moreover, technology to evade basic survey protections has evolved since the Checklist for Reporting Results of Internet E-Surveys was developed in 2004, and the use of these technologies has become more common. For example, verifying that a sample does not contain duplicative IP addresses and use of "cookies" can be overcome through the use of virtual private network service providers that allow users easy access to hundreds of servers worldwide and the clearing of cookies (or use of another device), respectively. Our survey was able to address these challenges using a variety of strategies, such as identity verification.

Recruitment modalities beyond de novo recruitment were explored and given consideration for this study, including the use of existing panels. Although appropriate for other study designs and aims, existing panels were not considered a viable option for the VAPER Study. Existing panels at well-established research firms did not contain a sample large enough to recruit our population of interest (ie, ENDS and ENNDS users vaping ≥5 days per week). Mechanical Turk, a commonly used web-based panel, was considered as well but was also not large enough for our lower-prevalence population. Panels that aggregate participants from multiple panels are an option that might have yielded a large enough sample for wave 1; however, the recruitment methodologies are highly heterogeneous. In addition, they may not be large enough to replace those lost to follow-up in multiple waves. We were also advised by a company offering this aggregation service that high loss to follow-up rates should be expected; thus, panels that aggregate participants are not ideal for longitudinal studies.

Social media (eg, Facebook and Instagram) recruitment was attempted in consultation with a market research firm at the start of wave 1, but several challenges were encountered. Despite being an academic survey on ENDS and ENNDS use, our advertisements were repeatedly deleted by Facebook and Instagram for including images and text related to ENDS and ENNDS. Appealing these decisions became a regular and time-consuming phenomenon that was never resolved. Furthermore, the advertisements appeared to generate clicks, presumably by social media users interested in the survey; however, the number of advertisement clicks did not match the landing page traffic, and few valid surveys were submitted. Our approach to tracking landing page traffic was investigated for setup errors, and alternative back-end solutions were attempted, but no strategy improved our traffic. The high costs (US $280 per valid participant) combined with slow recruitment (approximately 5 valid participants per week) led us to switch to a Craigslist-focused recruitment strategy. Subsequently, wave 3 costs have decreased to US $10 per valid participant, and recruitment for the baseline survey has increased to approximately 53 valid participants per week.

Processing data and managing missing data are not without challenges. Coding photos and reviewing and abstracting manufacturer, retailer, and review site data are time-intensive and have practical limitations, including participants who do not follow photo submission instructions and inconsistent and incomplete device features and specifications available on the web. The resulting missing data present challenges, particularly given a lack of validated device and liquid questions and that some participants indicate that they do not know the details of their device features and specifications, settings, and liquid characteristics. Our solution is to implement comprehensive preventive and post hoc strategies that maximize the use of multiple data sources (ie, photos, self-report, and disassembled devices), tools (ie, multimeter), and formulas (ie, power calculator and an average midpoint calculation for each device type). The decisions were considered carefully based on the best available information; however, we cannot rule out the possibility that our underlying data sources, tools, or formulas are biased or inaccurate (eg, product packaging and labeling and manufacturer, academic, retailer, and review websites). Ultimately, we believe that the benefits of our approach outweigh the unknowns and are an opportunity to understand more deeply the interplay between devices, liquids, and user behavior as it pertains to regulations. Other strategies could be valuable, and our approach may change as better data sources emerge and more is learned about this topic.

The loss to follow-up rate is higher than initially presumed based on the expected loss to follow-up rates in more traditional cohort surveys. This presumption based on traditional cohort surveys was made after we were unable to find any web-based cohort surveys that reported their loss to follow-up rates during study design planning in 2019. The higher-than-expected rate is not readily explainable and is a matter of speculation. Our assumption is that it is owing to one or more of the following: (1) web-based cohort survey participants require larger incentives, (2) participants (and email providers) may believe that follow-up survey email and SMS text message invitations and reminders are spam, (3) participants may self-select out of the cohort survey if they no longer use e-cigarettes, and (4) participant commitment to web-based cohort surveys is lower given the lack of an in-person connection with the study team. We will attempt to lower the rate through several strategies. These include increasing the incentive to US $30 per participant,

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sending postcards to participants to remind them of their involvement with the study and our annual raffle, creating a password-protected study website for participants that contains announcements and descriptive data for participants to review, and allowing follow-up participants who no longer use the devices ≥5 days per week to complete the survey or a shorter survey if they have not used the devices in the past 30 days.

Furthermore, our team is committed to improving the survey with each successive data collection wave. We will continue to monitor and adjust the details of our Craigslist strategy, such as the number of cities and boards used, as we learn more about the recruitment and cost-efficiency of "jobs" versus "gigs" postings and specific locations. We are also considering alterations to the raffles based on the frequency of waves completed and participant follow-up rates and are exploring additional engagement strategies to increase retention rates. Other options include birthday and holiday messages, a website containing updates on findings and survey-related announcements, and alternative incentive structures for follow-up survey participants. Moreover, participants are encouraged to provide us with feedback at the end of the survey: "We would like to continually improve this survey. If you have any comments or suggestions about this survey, please provide them here." Feedback is reviewed during each wave for isolated issues (eg, survey response corrections) and at the end of the survey wave for consistent feedback that may warrant improvements to the survey. For example, participants noted that our survey responses did not include options for wrapping one's own device coils and adding extra nicotine drops to liquids. We subsequently edited the response options and added a question to account for these behaviors.

Another key lesson learned was the importance of bot and fraudulent survey taker mitigation strategies. These comprehensive steps were taken in consultation with experts after an initial attempt in 2019 to recruit participants using social media advertisements failed. At the time, the VAPER Study allowed for anonymous survey participants, had minimal review of data before incentive delivery by email, and used fraud detection software *intended* to prevent multiple completions by each participant. Initially, recruitment began slowly (as expected) but accelerated quickly, raising substantial concerns that led us to halt data collection. Survey submissions (n=1624) were investigated for evidence of bots and fraudulent survey takers, and only 22.35% (363/1624) of the survey completions were assessed to be likely valid. We subsequently restarted recruitment in May 2020 (wave 1) and implemented the aforementioned risk-mitigation strategy. As a result of these steps and the transition to a Craigslist posting strategy, the recruitment pace stabilized, and data quality has appeared adequate. The final wave 1 sample does not include those from our failed attempt at recruitment and data collection in 2019.

The VAPER Study has demonstrated that web-based recruitment and data collection for cohort studies is a promising approach that may offer benefits to researchers and participants, including convenience, scalability, reduced costs, and safety during extraordinary times such as the COVID-19 pandemic. More specifically, this study design has allowed us to recruit a generalizable and nationwide sample relatively quickly and cheaply, recruit a lower-prevalence population successfully, and disseminate high-level findings to regulators quickly. To the best of our knowledge, no other tobacco policy research team is collecting such detailed data on the scale at which we are operating, which differentiates the value of these data from those of other studies. These data better position us to address questions about the relationships among devices, liquids, and user behavior that relate to the benefits and unintended consequences of possible regulations. However, strong risk-mitigation strategies are essential to ensure data quality [13,14], and steps such as identity verification and manual review of photo data quality before sending the incentive are time-intensive and have required a team of individuals at 2 universities. Other limitations include a limited sample size for specific questions (because of skip logic and rare behaviors), missing data resulting from inconsistent and incomplete device and liquid data available on the web, website-reported data on devices and liquids that may or may not correlate with laboratory-measured device specifications (eg, coil resistance) or liquid characteristics (eg, nicotine concentration), and participants unable to recall or who may be misinformed about their device features and specifications or liquid characteristics. Future plans include further optimizing our recruitment and data processing procedures and conducting 2 waves of data collection over the next 12-month period.

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Data Availability

We intend to make deidentified data, codebooks, documentation, and research protocols available on a password-protected website by 2026 in accordance with the National Institutes of Health policy (notice: NOT-OD-03-032) released on February 26, 2003 [27], and IRB-approved protocols. Before or after the data are available on the aforementioned website, any investigator interested in collaboration or in using the data for their own work is invited to contact the corresponding author. They will be asked to submit a 1-page abstract of their proposed research, including purpose, analytical plan, and dissemination plans. An executive leadership committee will review these proposals and decide on each based on the individual merits (if a proposal is received after the end of the funding period, the principal investigator will review it). Review criteria and prioritization of projects include

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the potential of the proposed work to advance public health; qualifications of the applicant; potential for publication; potential for future funding; and enhancement of the scientific, geographic, and demographic diversity of the Vaping and Patterns of E-cigarette Use Research Study research portfolio.

Conflicts of Interest

TE is a paid consultant in litigation against the tobacco industry and also the electronic cigarette industry and is named on a patent for a device that measures the puffing behavior of electronic cigarette users, on another patent application for a smartphone app that determines electronic cigarette device and liquid characteristics, and on a third patent application for a smoking cessation intervention.

Multimedia Appendix 1
Craigslist posting locations and frequencies for waves 1 to 3.
[DOCX File , 98 KB - resprot_v12i1e38732_app1.docx]

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Abbreviations

CAPTCHA: Completely Automated Public Turing test to tell Computers and Humans Apart
ENDS: electronic nicotine delivery systems
ENNDS: electronic nonnicotine delivery systems
IRB: institutional review board
REDCap: Research Electronic Data Capture
VAPER: Vaping and Patterns of E-cigarette Use Research

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Protocol

Model for Achieving a Coordinated Access to Lung Cancer Care in Selected Public Health Facilities in KwaZulu-Natal, South Africa: Protocol for a Qualitative Study

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Abstract

Background: Timely delivery of high-quality cancer care to all patients is barely achieved in South Africa and many other low- and middle-income countries, mainly due to poor care coordination and access to care services. After health care visits, many patients leave facilities confused about their diagnosis, prognosis, options for treatment, and the next steps in their care continuum. They often find the health care system disempowering and inaccessible, thereby making access to health care services inequitable, with the resultant outcome of increased cancer mortality rates.

Objective: The aim of this study is to propose a model for cancer care coordination interventions that can be used to guide and achieve coordinated access to lung cancer care in the selected public health care facilities in KwaZulu-Natal.

Methods: This study will be conducted through a grounded theory design and an activity-based costing approach that will include health care providers, patients, and their caregivers. The study participants will be purposively selected, and a nonprobability sample will be selected based on characteristics, experiences of the health care providers, and the objectives of the study. With the study's objectives in mind, communities in Durban and Pietermaritzburg were selected as study sites, for the study along with the 3 public health facilities that provide cancer diagnosis, treatment, and care in the province. The study involves a range of data collection techniques, namely, in-depth interviews, evidence synthesis reviews, and focus group discussions. A thematic and cost-benefit analysis will be used.

Results: This study receives support from the Multinational Lung Cancer Control Program. The study obtained ethics approval and gatekeeper permission from the University's Ethics Committee and the KwaZulu-Natal Provincial Department of Health, as it is being conducted in health facilities in KwaZulu-Natal province. As of January 2023, we had enrolled 50 participants, both health care providers and patients. Dissemination activities will involve community and stakeholder dissemination meetings, publications in peer-reviewed journals, and presentations at regional and international conferences.

Conclusions: This study will provide comprehensive data to inform and empower patients, professionals, policy architects, and related decision makers to manage and improve cancer care coordination. This unique intervention or model will address the multifactorial problem of cancer health disparities. If successful, this study will affect the design and implementation of coordination programs to promote optimal cancer care for underserved patients.

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KEYWORDS

Africa; cancer care; cancer; coordination model; KwaZulu-Natal; lung cancer; lung; low income; middle income; LMIC; care access; care coordination; coordinated care; care model; cost; health care system; oncology

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Introduction

Background Information

Cancer is increasingly becoming one of the leading public health problems globally [1-4]. The World Health Organization's projections indicate that global annual estimates will increase to 29.5 million new cancer cases and 16.5 million cancer-related deaths by the year 2040 [2,3,5]. Of concern is the fact that the current evidence demonstrates that survival from all cancers, including preventable lung cancer, is poor [2-10], and this is partly reflective of the poor access to coordinated cancer care. The public health challenges of the escalating cancer burden are more pronounced in low- and middle-income countries (LMICs) [9]. Patients with cancer in these countries are often diagnosed late (at stage 3 and 4) and the pathways of care are not clearly defined, thus delaying treatment initiation and leading to disproportionately high mortality rates and reduced quality of life when compared to their higher-income counterparts [5,9,11-13].

Medical care is error-prone even when it is delivered by a single provider; the opportunities for serious issues or difficulties escalate when multiple providers are involved [14-21]. Inherent care complexities for patients with lung cancer make these patients likely candidates for shared care between primary care providers, oncologists, and other specialties. A study investigating barriers impeding quality care coordination for patients with lung cancer in South Africa, from the perspectives of the health care providers, identified these challenges as contributing to adverse outcomes in lung cancer care [14]. Issues relating to access, timely delivery, and coordination of care ranked the highest in the priority list shared by health care providers [22]. These issues appeared to facilitate the rising numbers of cancer fatalities in South Africa [14]. Evidence from South Africa is consistent with what has been found in other countries [13,23-25], asserting that when a diagnosis is accurate and timely, a patient has an increased opportunity for a positive health outcome [26-37].

Despite the potential benefits of patient access to coordinated cancer care services [26-37], most countries in LMICs, such as South Africa, do not have systems for achieving this coordination. Specifically, lung cancer diagnosis has far-reaching and life-changing consequences for patients [14,16,20,36,38-42], with the disease likely to be at an advanced stage at the time of detection [14,16,43]. In South Africa, the structural configuration of the health systems compounds the challenges relating to providing quality and coordinated cancer care [44]. These challenges include socioeconomic factors, the unavailability of technical support for diagnosis and disease staging, the initiation of and lack of resources for treatment, and the poor availability of palliative care and other support services [14,16,20,21,44-48]. The current referral pathways for patients with cancer between the health care team and cancer services are either not structured or are poorly documented [13,14,47]. Patients with cancer often have limited familiarity with the multidisciplinary team involved and therefore lack the specific knowledge and resources needed to navigate the specialists and services involved in their clinical care. In turn, each team brings varying perspectives to the care of the same patient, whose true value can be achieved through proper communication. The interface between primary and specialty care for patients struggling with cancer offers a valuable opportunity to appreciate the challenges of delivering well-coordinated care.

To be comprehensive, cancer care must be coordinated between primary care providers and oncology specialists; however, achieving this has proven to be considerably challenging [14-21]. Understanding the strategies that can be used to achieve this coordination is necessary for better cancer care. However, attempts to improve care coordination can only be achieved through a properly and intentionally designed care coordination intervention strategy [49]. The high inconsistency of practices, the diversity of definitions, and the underlying concepts [49-52] increase the current difficulty to standardize, replicate, transpose, and assess care coordination, especially within the South African health system context. As such, the aim of this study is to propose a model for cancer care coordination interventions that can be used to guide and achieve coordinated access to lung cancer care in the selected public health care facilities in KwaZulu-Natal, South Africa.

Study Aim and Objectives

This study aims to propose a model for cancer care coordination interventions that can be used to guide and achieve coordinated access to lung cancer care in the selected public health care facilities in KwaZulu-Natal. This will be carried out in 4 phases. The specific objectives are as follows:

Phase 1: Assess the factors that affect access or delivery of coordinated lung cancer care

- To identify health system barriers and key pillars affecting access to a coordinated lung cancer care continuum.
- To conduct a needs assessment to lung cancer care necessary for achieving coordinated care.

Phase 2: Identify a model relative to cancer care coordination interventions

- To understand the scope of cancer care coordination interventions and services employed in low-and middle-income countries, in order to synthesize the existing evidence and identify the key model and its elements used to manage and improve cancer care coordination in these settings.
- To systematically analyze the available evidence on the identified model's characteristics, outcomes, and effectiveness across the cancer care continuum in low-and middle-income countries.

Phase 3: Identify key elements of the proposed model

- To explore what the primary functions of proposed model will be.
- To identify the roles and skill sets needed for proposing the key personnel required to implement the proposed model.
- To explore how the proposed model can be better integrated into the clinical care program.

Phase 4: Costing of the proposed intervention model

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- To conduct a costing exercise in order to determine the feasibility of developing and implementing the proposed model.

Methods

Study Design

The study will use a mixture of the grounded theory (GT) approach and an activity-based costing (ABC) approach. The central principle of GT is that the researcher's theories about a topic are constructed based on their data [53]. It is appropriate when little is known about a phenomenon; the aim being to produce or construct an explanatory theory that uncovers a process inherent to the substantive area of inquiry [53-55]. GT sets out to discover or construct theory from data that has been systematically obtained and analyzed using comparative analysis. The study will predominantly be conducted through qualitative research methods, using participatory approaches. This is founded on the principles of active citizenry and constructivist theory, which views research participants as co-constructors of knowledge and not just passive subjects [56]. As a result, the study falls within the constructivism paradigm (interpretivist), as it aims to explore and understand the participants' experiences [57].

Described as "the most comprehensive qualitative research methodology available" [58], this approach is appropriate when research aims to explain a process where the concerns of those involved are central to its understanding and cannot be predetermined [55,58-60]. GT uses memoing or memos, which are ideas generated and documented through interacting with data to provide detailed records of the researchers' thoughts, feelings, and intuitive contemplations [54]. The theoretical sensitivity encompasses the entire research process; it is the ability to know when you identify a data segment that is important to your theory [54].

The ABC approach has 2 major elements: cost measures and performance measures. It is a methodology that measures the cost and performance of activities, resources, and cost objects [61]. Resources are assigned to activities, and then activities are assigned to cost objects based on their use. The basic concept of ABC is that activities consume resources to produce an output. It assists to identify activities in a project or organization and assigns the cost of each activity to all products and services according to the actual consumption by each [61]. This approach uses both financial and nonfinancial variables as bases for cost allocation. Today's health care system encompasses a wide variety of services. To manage them, it is important to determine the amount of resources that are consumed by each service. The complexity of widely varied service delivery systems can be readily managed with ABC, as its methodology is particularly suited to the complexities of health care service delivery [61].

Study Area

The study will be conducted in the province of KwaZulu-Natal. This province has the second-largest economy in the country [62]. The study will involve 2 cities, namely, Durban and Pietermaritzburg, which are within the KwaZulu-Natal province. KwaZulu-Natal has 1 metropolis and 10 districts. While Pietermaritzburg is the capital city of the province, Durban is the largest city in the province [63]. Durban and Pietermaritzburg have an estimated population of 3,120,282 and 750,845, respectively [64]. With the objectives of the study in mind, communities in Durban and Pietermaritzburg were selected as study sites, along with 3 health facilities that provide cancer diagnosis, treatment, and care in the province. In total, 3 of the communities are in Durban, and 2 are in Pietermaritzburg. These communities are Umlazi, Chatsworth, and South Durban Basin in Durban, and Imbali and Sobantu in Pietermaritzburg.

Study Settings

A geographical scoping and mapping of study clusters were done in each of the representative communities. In total, 40 out of 879 clusters were selected using probability proportional to population size sampling. Maps were used to identify the selected clusters along with their boundaries. This technical mapping exercise gave details of the location of the communities, population numbers, broad socioeconomic baseline characteristics of the communities, and resources available in the area, for example, clinics and hospitals, as well as other community social commons.

We selected both clinics and hospitals to ensure that the sampled data have implications for the full spectrum of cancer care providers. Furthermore, all public hospitals with oncology units in KwaZulu-Natal (Greys Hospital, Addington Hospital, and Inkosi Albert Luthuli Central Hospital) located in 2 cities will be recruited to participate in the study. These 3 participating health facilities were chosen on the basis that they are the only public hospitals offering oncology services in the province. Greys Hospital is located in Pietermaritzburg, whereas Inkosi Albert Luthuli Central Hospital and Addington Hospital are located in Durban.

Data Collection Process

Research staff will be concerned about participants' risks and also their risk of exposure during the collection of data. The study will be conducted in 4 phases.

Phase 1 will be through in-depth interviews (IDIs), determining the barriers and pillars affecting coordinated lung cancer care. Accomplishments and ongoing barriers to engagement in medical care identified in phase 1 will be prioritized and translated into service plans that will define the specific action steps in the proposed model. Throughout this phase, participants' demographic and clinical information will be collected.

Phase 2 will focus on identifying an intervention aimed at assisting patients in overcoming barriers to coordinated lung cancer care in KwaZulu-Natal. Based on phase 1 results, the models will be reviewed and modified to meet the needs identified in phase 1. The following will be key areas of focus for the strategy during the scale-up process. This phase will be conducted in two steps: (1) a scoping review to identify relevant models from the literature and all their components for coordinated care and (2) a systematic review of the identified or proposed care coordination model's effectiveness. The aim of this phase is to provide descriptions of a wide variety of care coordination interventions and thereafter propose an intervention

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or model. The search strategy will include PubMed, Scopus, Google Scholar, and Web science databases using keywords such as “cancer care coordination,” “coordination of care,” or “coordinated care.”

Phase 3 will be through focus group discussion (FGD). The approach will facilitate awareness, understanding, and commitment to the optimal proposed cancer care coordination model among stakeholders and facilities involved. The goal is to identify key elements of the proposed model and obtain stakeholder support for coordinated referrals and linkage pathways for patients with cancer. This is anticipated to inform the development and implementation of a coordination model to improve lung cancer care.

Lastly, in phase 4, a costing exercise will be conducted in order to determine the feasibility of the development and implementation of the proposed model; this may be useful in the move to certify and establish the intervention. This phase will be achieved through ABC.

Data Collection Tools

For this study, an IDI and FGD guide will be used to address the study objectives. These were developed for this study; however, the FGD guide will be informed by the IDIs’ and phase 2 responses. Both the IDIs and FGDs will be facilitated by the lead investigator, who is experienced in qualitative research. Lastly, the costing exercise will be informed by findings from the IDIs, FGDs, and reviews. Table 1 provides study data collection methodology by phases.

Table 1. Summary of data collection methodology.

Tools and data source	Variables	Analysis plan
Phase 1: assess factors that affect coordinated access to lung cancer care (interviews)		

Patients and caregivers	• Description of their care, barriers, and how it was managed
	  • When the diagnosis was made
	  • How the diagnosis was confirmed
	  • Treatment initiation
	  • Reasons for not initiating treatment
	  • Time of treatment initiation
	• Understanding of “care coordination”
	• Suggestions to improve care coordination
		GT[a] approach analysis

Health care providers	• Description of what “care coordination” services involve • Outline of their roles in a patient’s “care coordination” • Essentials of “care coordination” • Weaknesses in “care coordination” processes • Suggestions to improve care coordination	GT approach analysis
Phase 2: identify model relative to cancer care coordination interventions		
Scoping review		
Scopus, PubMed, and Google Scholar	• Relevant models and all its components relevant for coordinated care	PRISMA[b] guide
Systematic review		
Scopus, PubMed, and Google Scholar	• Informed by the scoping review	PRISMA guide
Phase 3: identify key elements of proposed model (focus group discussion)		
Identified stakeholders and health care professionals to be involved in the designing of the proposed model	• What will be the primary functions of the proposed model? What will they fulfill? • Outline of their roles in a patient’s “care coordination” • What additional roles and skills set needed • How model can be integrated into the current clinical cancer care	Thematic analysis
Phase 4: costing of proposed intervention model (ABC[c] approach)		
Variables included in phases 1, 2, and 3	• Human resource costs for recruitment and hiring • Operational costs • Capital equipment costs • Model specific training costs	Costing analysis

[a]GT: grounded theory.

[b]PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

[c]ABC: activity-based costing.

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Study Population

The study population will encompass patients, health care providers drawn from the participating health care facilities, including surgeons, radio-oncologists, medical oncologists, general practitioners, chemotherapy nurse practitioners, and social workers, all with a coordination activity for patients with cancer, and also the caregivers with whom they interact as part of their care activity. Caregivers will be proxies for patients who are unable or not in a condition to answer the questions and participate in the study. A proxy is a person authorized to act on behalf of someone else [65].

Inclusion and Exclusion Criteria

There are no exclusion criteria based on socioeconomic status, race, or sex, but patients with no lung cancer will be excluded. Textbox 1 summarizes inclusion and exclusion criteria for study participants by phases.

Textbox 1. Inclusion and exclusion criteria for study participants by phases.

Phase 1: patients with lung cancer (all stages), caregivers, and health professionals in lung cancer care

Inclusion criteria

- Patients diagnosed with lung cancer and are within the selected facilities
- Caregivers of patients who meet the inclusion criteria and are unable but willing to participate in the study
- Health professionals involved in the care and coordination of patients with cancer

Exclusion criteria

- Patients diagnosed with other diseases other than lung cancer
- Patients receiving care for lung cancer, but outside the selected facilities
- Caregivers of patients with lung cancer who do not meet the inclusion criteria
- Professionals who are not involved in the care of patients with cancer

Phase 2: systematic and scoping review

Inclusion criteria

- Studies presenting evidence published in low- and middle-income countries (LMICs)
- Studies presenting evidence on cancer care coordination
- Studies presenting evidence on coordination interventions or models
- Studies reported in English

Exclusion criteria

- Studies presenting evidence not published in LMICs
- Studies not presenting evidence on cancer care coordination
- Studies presenting evidence on coordination interventions or models
- Studies reported in English

Phase 3: identified stakeholders to be involved in the designing of the proposed model for coordination

Inclusion criteria

- Identified stakeholders to be involved in the designing of the proposed model for coordination
- Health professionals involved in the care activity of patients with cancer

Exclusion criteria

- Stakeholders with no coordination activity for patients with lung cancer
- Health professionals with no role in the care activity of patients with cancer

Phase 4: informed by phases 1, 2, and 3

Recruitment Procedure

Eligible patients will be identified during their visits or hospitalization in the participating facilities and will be informed about the study in a personal interview and with the help of written consent documents. A modified version of snowballing will be used to identify caregivers of patients not eligible to participate due to health conditions. Patients will be asked to invite their primary caregivers to participate in the study. Health care providers involved in cancer care (including surgeons,

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radio-oncologists, medical oncologists, general practitioners, chemotherapy nurse practitioners, and cancer nurse coordinators) will be approached directly by the research team to participate in a focus group or interview. Eligible potential participants will be invited by email or telephone to participate in the study. The invitation letter will include a general introduction to the research topic and the study's aim and rationale. They will also be presented with information about their involvement, such as the anticipated length of the interview and where it would be conducted. General information about measures taken to guarantee confidentiality and informed consent will also be given.

Sampling Strategy

In-depth Interviews

Purposive sampling will be used to identify the participants relevant to address the research objectives [53-55,60]. Participants will be selected based on their characteristics, experiences, and the objectives of the study [66]. Concurrent data generation and analysis are fundamental to GT research design [67]. Hence, data generation, data coding, and analyses will be done iteratively. Theoretical sampling will begin with the codes and categories developed from the first data set. Theoretical sampling is used to identify and follow clues from the analysis, fill gaps, clarify uncertainties, check hunches, and test interpretations as the study progresses [67]. The selection of the study sample will be done per study site and according to the study phases and objectives.

Focus Group Discussions

The sample for FGDs will be purposive and will include individuals with characteristics of the overall population. Purposive sampling is often used when a researcher wants information-rich participants [6], in the case of FGD, a sub-sample of insightful participants from the phase 1 interviews will be invited for discussion. Each focus group will have a professional or stakeholder representing all levels of the health care systems.

Sample Size

For the IDIs, sampling saturation will be achieved when the same stories, themes, or codes and issues are emerging from the interviewees, and then a sufficient sample size will have been reached (saturation). We will take note of the importance of availability (limited number of health providers working within the oncological units), willingness, and the ability to communicate experiences and opinions in an articulate, expressive, and reflective manner. It is anticipated that data saturation will be reached at 25 interviews for each category (patients and professionals) of participants. For FGDs, and with support from the literature, the sample size will be between 7 and 12 participants to be effective [68].

Data Quality Assurance

Internal Validity

Bias can arise from the approach or instrument adopted for collecting or measuring data in a study [69]. Information bias, otherwise known as misclassification, is one of the most common sources of bias affecting health research's validity [63]. This bias will be minimized through the extensive training of the research assistants. The questionnaires will be validated and standardized during the training. To ensure the quality of the translation, an experienced translator competent in both English and isiZulu will translate the questionnaires, and a different person will perform the back-translation. The principal investigator will compare the original copy with the back-translation, and where necessary, adjustments will be made.

Measuring the Trustworthiness of the Qualitative Data

Credibility is defined as the confidence that can be placed in the truth value of the research findings, which is essential in establishing whether or not the research findings represent plausible information drawn from the participants' original data and is a correct interpretation of the participants' original views [70]. In this study, credibility will be ensured through the search for alternative themes developing from the data and the use of verbatim quotes when reporting the findings. In certain circumstances, where the translation will diminish the original meaning, isiZulu quotes may be retained with explanatory text. The researchers who conduct the IDIs with the key informants will receive advanced training on interviews and other qualitative research processes in order to ensure the collection of high-quality data. Analyst triangulation will be performed, whereby the principal investigator and the supervisors will analyze the transcripts independently and later discuss the analysis. According to Bitsch [71], dependability refers to "the stability of findings over time." Dependability will be ensured through a clear exposition of data collection and analysis methods and also through data source triangulation (with various key informants).

The study results will be based on the data generated through the thick description (ie, a rich and extensive set of details) of the phenomenon in order to enhance the transferability of the findings. The thick description will also include the context in which the study was carried out. Transferability, a concept that is comparable to generalizability in quantitative research, refers to the degree to which the results of qualitative research can be transferred to other settings with comparable contexts [71]. Confirmability will be ensured by keeping an audit trail, carrying out source and data triangulation, and also carrying out peer review or debriefing. Confirmability refers to the degree to which the results of an inquiry could be confirmed or corroborated by other researchers [72].

Data Analysis

Data analysis will follow a GT approach, a constant comparative analysis [54,73]. In GT-based analysis, the researcher generally analyzes the data by (1) finding repeating themes by thoroughly reviewing the data, (2) coding the emergent themes with keywords and phrases, (3) grouping the codes into concepts hierarchically, and then (4) categorizing the concepts through relationship identification [73-76]. Finally, the categories created through this process, and the links found between them, are used as the basis for the development of a new theory [74]. These steps facilitate an analysis process that allows the researcher to construct new theories instead of simply collecting

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data to test how well an established theory applies to the social phenomena they are studying. Theoretical sampling joined with constant comparative analysis raises the conceptual levels of data analysis and directs ongoing data generation [54].

Results will be discussed until consensus between analysts is achieved. The construction process of these thematic categories and codes is both inductive and deductive because the development of themes and subthemes rests on both literature and emerging categories of empirical analysis [53-55,67,71,73,74,77,78]. Ongoing analysis and recruitment will be undertaken until saturation of themes is reached, which Hennink et al [79] refer to as code saturation. Interpretations of the findings will be supported by direct quotes from both FGDs and individual IDIs.

FGDs usually yield both qualitative and observational data where analyses can be demanding. For the discussion, thematic analysis, as the most common forms of analysis in qualitative research, will be used to analyze the data collected. It puts emphasis on, pinpoints, examines, and records patterns (or "themes") within the data [80]. Although the main source of data analysis is the recorded spoken language derived from the interview; nevertheless, reflection about the interview, the settings, and capturing the nonverbal communication expressed by the members of the groups would add a valuable dimension to the construction and analysis of data [81]. Prior to analysis, transcripts for each participant will be deidentified to ensure confidentiality and to limit analytical bias among researchers [82]. Qualitative data will be recorded, anonymously, integrally transcribed, and imported into the NVivo 12 software (QSR International), which will assist in the organization of the data during the analysis stage.

Ethics Approval

The study obtained ethics approval and gatekeeper permission from the University's Ethics Committee (Ref: BREC/00002153/2020) and the KwaZulu-Natal Provincial Department of Health (NHRD Ref: KZ_202010_030), as the study is to be conducted in health facilities in KwaZulu-Natal province. Written permission has been further sought from the concerned authorities and authorities from the different study sites to gain access to the facilities.

Risks

This study is anticipated to involve minimal risks. This means that the probability of harm or discomfort anticipated as a result of participation in the study is not greater than those ordinarily encountered in the daily lives of the participants. Adequate care will be taken to ensure the competence of the fieldworker for the study through continued educational sessions.

Potential Benefits

Participation in this research project will contribute to the improvement of collective medical, palliative, and public health knowledge that will enable the design of interventions to strengthen care coordination for patients with lung cancer while strengthening the cancer care program. The study will also provide strategic and scientific information on the implications of lung cancer during the access, diagnosis, referral, and treatment processes.

Informed Consent

Informed consent is sought in writing from every potential participant prior to participating in the study. Both the English and isiZulu versions of the participant information sheet will be appended to the protocol. The informed consent forms comprise 2 sections: the participant information sheet and the informed consent. These are shared with each potential participant a day or 2 before data collection to allow them time to read and process the documents. Measures are taken to ensure that the respect, dignity, and freedom of each participant are honored in the study. To guarantee the anonymity of each participant, the names of respondents, their addresses, or other identifying information will not be included in the transcripts, but a unique identification number will be used. Further, participants will be assured of the confidentiality of all their information. Their rights to refuse to participate and to opt out of the study at any time will be emphasized.

Results

This study receives support from the Multinational Lung Cancer Control Program, which is funded by Bristol-Myers Squibb Foundation. The support is granted for the lifespan of the study, from June 2020 to March 2023. The study obtained ethics approval and gatekeeper permission from the University's Ethics and KwaZulu-Natal Provincial Department of Health, as the study is being conducted in health facilities in KwaZulu-Natal province. As of January 2023, we enrolled 50 participants, both health care providers and patients. We started with data analysis of interviews with patients and their caregivers, saturation was reached at 21 interviews. We have concluded data collection and analysis of interviews with health care providers, and finalizing manuscript write-up. Once all the data are analyzed, the results will be consolidated into a coherent report for dissemination. In addition, manuscripts for all phases will be prepared for publication. A scoping review article emanating from results from phase 2 was published and is currently working on the next step which is a systematic review, assessing the effectiveness of the identified coordination model.

Discussion

Anticipated Findings

Cancer is a complex condition that often requires multiple interventions provided by a variety of health professionals within the health care continuum [14-21]. The identification of current obstacles has the potential to guide the development of a model to improve the quality of coordinated cancer health care. Care coordination strategies are of great interest as they have the potential to improve the quality of health care, effectiveness, and optimal patient health outcomes. Care coordination requires effective communication and consistent transfer of health information between the different levels of care [27,32,33,37,52,83-88]. There is adequate literature supporting the need for and benefit of care coordination for people affected by cancer [14,19,27,33,34,38,39,47,89-94]. Care coordination

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is a set of activities needed to minimize the dangers of fragmentation [95], including the sharing of important clinical information by all health care providers involved with clear, shared expectations about their roles in the patient care process [49,51,52,95]. They also include efforts to keep patients and families informed and engaged throughout the care process. People with cancer are particularly at risk of receiving poorly organized and fragmented care due to the complex nature of the disease and its management [1,10,14,19,50,96-105]. Consequently, there is an increasing body of evidence on the potential of the patient navigation approach as a coordinated cancer care model for the effective improvement of access to health care services, especially for the poor, the uninsured, and other medically underserved populations [29,32,96,104-112]. The inclusion of patient navigation services in high-income countries is associated with improvements in access to timely diagnosis, treatment, and follow-up, among other quality indicators [11,85,112-115], something that is lacking in the LMICs [12]. In addition, evidence from global cancer agencies shows that improving access to clinical preventive services like cancer screening, linkage activities, and coordinated care among multiple providers not only minimizes delays and confusion about conflicting care plans but can also potentially reduce and prevent the disease [116].

There is a need to continuously review multilevel barriers (primary, secondary, and tertiary care) that threaten cancer care coordination across different settings and levels of clinical care to identify potential solutions for improving care. This study carries the promise of generating pertinent information for both policy makers and health care professionals. Decision makers will be provided with important information, concerning the proposed model designed with a costing exercise to determine the implementation viability. Once all the study phases are complete, the results will be consolidated into a coherent report for dissemination to key stakeholders and will also be presented in conferences and seminars. A technical report or policy brief is also anticipated from this study. A meeting of the relevant stakeholders will be organized, where the results will be presented and discussed. The thesis will be one of the outputs of this study, and this will be available in the University of KwaZulu-Natal library. The findings of the study will also be published in Department of Higher Education and Training accredited peer-reviewed journals.

The results of this study may be biased toward those patients who proactively seek or positively respond to diagnostic and treatment referrals by the health care professionals at the lower levels of care. Since the participating hospitals and the community-level study sites are located within the 2 major cities in KwaZulu-Natal, the profiles of patients may not be fully reflective of the geographical spread of the province. In addition, the global pandemic has presented a variety of challenges, including physical, emotional, financial, and much more, the effects of which are only beginning to be felt [117]. In our roles as researchers, these circumstances require us to be alert, innovative, and flexible in our approaches to collecting and disseminating data. The COVID-19 pandemic has disrupted the way that research is conducted [117] to the point that alternative ways of conducting research have become necessary. We hope to be able to come together virtually, collect and analyze data, rapidly generate knowledge, and disseminate it widely to improve the care of patients with cancer. Fortunately, the increased engagement of users on the internet and social media during the pandemic brings opportunities to engage in research through novel strategies and methods [118]. The results will be written up for publication in open-access, peer-reviewed journals for access by the scientific community, and abstracts will be presented at different conferences locally and internationally to encourage dissemination of the results. Shared information will be anonymized to ensure confidentiality.

Conclusions

This study will provide comprehensive data to inform and empower patients, professionals, policy architects, and related decision makers to manage and improve cancer care coordination. This unique intervention will be designed to address the multifactorial problem of cancer health disparities. If successful, this study will help inform the design and implementation of coordination programs in LMICs to promote optimal cancer care for underserved patients.

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Authors' Contributions

BL, TG, and KH conceived the study protocol and its final design. BL drafted the manuscript, and all authors commented on and approved of the final version of the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

ABC: activity-based costing
FGD: focus group discussion
GT: grounded theory
IDI: in-depth interview
LMIC: low- and middle-income country

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Protocol

Estimating HIV Incident Diagnoses Among Men Who Have Sex With Men Eligible for Pre-exposure Prophylaxis but Not Taking It: Protocol and Feasibility Assessment of Data Sources and Methods

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Abstract

Background: HIV incidence estimates are published each year for all Ending the HIV Epidemic (EHE) counties, but they are not stratified by the demographic variables highly associated with risk of infection. Regularly updated estimates of HIV incident diagnoses available at local levels are required to monitor the epidemic in the United States over time and could contribute to background incidence rate estimates for alternative clinical trial designs for new HIV prevention products.

Objective: We describe methods using existing, robust data sources within areas in the United States to reliably estimate longitudinal HIV incident diagnoses stratified by race and age categories among men who have sex with other men (MSM) eligible for pre-exposure prophylaxis (PrEP) but not taking it.

Methods: This is a secondary analysis of existing data sources to develop new estimates of incident HIV diagnoses in MSM. We reviewed past methods used to estimate incident diagnoses and explored opportunities to improve these estimates. We will use existing surveillance data sources and population sizes of HIV PrEP-eligible MSM estimated from population-based data sources (eg, US Census data and pharmaceutical prescription databases) to develop metropolitan statistical area–level estimates of new HIV diagnoses among PrEP-eligible MSM. Required parameters are number of new diagnoses among MSM, estimates of MSM with an indication for PrEP, and prevalent PrEP use including median duration of use; these parameters will be stratified by jurisdiction and age group or race or ethnicity. Preliminary outputs will be available in 2023, and updated estimates will be produced annually thereafter.

Results: Data to parameterize new HIV diagnoses among PrEP-eligible MSM are available with varying levels of public availability and timeliness. In early 2023, the most recent available data on new HIV diagnoses were from the 2020 HIV surveillance report, which reports 30,689 new HIV infections in 2020, and 24,724 of them occurred in an MSA with a population of ≥500,000. Updated estimates for PrEP coverage based on commercial pharmacy claims data through February 2023 will be generated. The rate of new HIV diagnoses among MSM can be estimated from new diagnoses within each demographic group (numerator) and the total person-time at risk of diagnosis for each group (denominator) by metropolitan statistical area and year. To estimate time at risk, the person-time of individuals on PrEP or person-time after incident HIV infection but before diagnosis should be removed from stratified population size estimates of the total number of person-years with indications for PrEP.

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Conclusions: Reliable, serial, cross-sectional estimates for rates of new HIV diagnoses for MSM with PrEP indications can serve as benchmark community estimates of failures of HIV prevention and opportunities to improve services and will support public health epidemic monitoring and alternative clinical trial designs.

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KEYWORDS

HIV incidence estimates; pre-exposure prophylaxis; commercial pharmacy data; HIV; HIV epidemic; surveillance data; public health; men who have sex with men; health monitoring; clinical trial design

Introduction

There is an urgent need to develop additional options for HIV pre-exposure prophylaxis (PrEP) for men who have sex with men (MSM). MSM are disproportionately impacted by HIV in the United States and globally [1], and models in multiple countries have suggested that achieving high coverage of PrEP will be required to realize substantial reductions in HIV incidence [2-4]. The prevention value of PrEP has not been fully realized in the United States for several reasons [5]. First, levels of PrEP use in the United States are well below the levels of PrEP use that will be required to result in substantial reductions in HIV incidence [6]. Second, MSM are not monolithic, and future PrEP products should be developed to meet diverse prevention needs. For example, PrEP approaches that increase the flexibility of dosing regimens, minimize side effects, offer options for discretion, and offer multiple options that promote adherence and increase flexibility for men will help increase PrEP choices for diverse patient needs. Higher uptake, longer persistence, and higher adherence that can be realized through increased choices will increase the impact of PrEP on HIV incidence [2,7]. Third, although current levels of PrEP use are comparable in Black and White MSM [6], given the higher burden of new HIV infections that occur in Black MSM, equal use of PrEP is not equitable [8,9].

The US national Ending the HIV Epidemic (EHE) strategy is predicated on the need to concentrate resources for HIV prevention and treatment in a relatively small number of communities that are most highly affected by HIV. The plan identifies 57 priority jurisdictions that, together, account for 50% of new HIV infections in the United States [10]. Within these jurisdictions, there is considerable variability in HIV risk by behavioral risk, race or ethnicity, and age. Overall HIV risk varies across jurisdictions, but Black and Hispanic MSM have the highest HIV risk in nearly every geographic location [11]. To reach EHE goals for reductions in HIV incidence, effectiveness of prevention methods will need to be evaluated locally, and across key populations that vary by geography, age, and race or ethnicity. Currently, PrEP use relative to need is lower among Black versus white MSM, and this disparity may extend to, or even be exacerbated by, development of novel PrEP pharmaceutical products [6]. The availability of estimates of new HIV diagnoses over time—a proxy for HIV incidence—by geography, race, and age will help to monitor racial disparities in current and future PrEP use and demonstrate how improvements in adherence and the resulting effectiveness improve equity across populations.

We are now in a phase of increasing PrEP options beyond daily oral tablets and gluteal injections every 8 weeks [12-18]. Increased and equitable PrEP uptake will likely require the development of multiple formats for PrEP (eg, daily oral, event driven, monthly oral, and longer-acting injectable) that are congruent with users' lives, access to care, and preferences for prevention [19,20]. A more robust pipeline of PrEP products offers opportunities to reduce barriers for more people and increase effective PrEP use, as has been demonstrated in the contraceptive field [21]. However, there are clinical trial design challenges to sustaining the progress toward developing more modes for PrEP in populations with diverse needs and preferences.

Given the proven options for PrEP, the traditional trial design for new PrEP medications would be a noninferiority trial [22,23], such as the recently reported trials of combination emtricitabine and tenofovir alafenamide [15] and long-acting cabotegravir [24], designed to demonstrate that HIV incidence in those taking the experimental agent was not higher than incidence in those taking a proven PrEP option. These types of trial designs rely on enough incident infections within the trial population to demonstrate efficacy of the investigational agent. Demonstrating efficacy with these designs is becoming more challenging in the field of HIV prevention, where proven products are highly efficacious in clinical trial settings (with few incident infections), requiring impractically large sample sizes to achieve statistical power for noninferiority margins [25]. There is an argument that if multiple highly effective products are available such that traditional trials are not feasible, then there is no need for new products. However, this would ignore the ongoing HIV incidence outside of these highly controlled settings [26]. The significant ongoing unmet need for HIV prevention and the inequity it represents require us to develop methods that allow for rigorous efficacy and safety trial data for new HIV prevention methods.

Alternative trial designs for future HIV prevention products have been the topic of many recent meetings [27-29] and publications [25,30-33]. One of these alternative approaches is to compare the incidence in those receiving the investigational medication to the incidence in a counterfactual group (ie, a hypothetical contemporary group of persons with similar risk characteristics who would be eligible for the PrEP treatment, but who were not taking PrEP).

Ideally, a counterfactual group that would be used as a comparison group to evaluate the performance of a novel PrEP agent should reflect what the HIV incidence would have been

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in a comparable group of PrEP-eligible MSM (ie, men who would be eligible for PrEP by the Centers for Disease Control and Prevention [CDC] clinical criteria, but who were not enrolled in the trial and were not taking PrEP outside of the trial). MSM who live in the study community, who would meet study eligibility criteria, and who could enroll in the trial but do not enroll constitute a potentially appropriate control group. The development of such a counterfactual control group, however, has important challenges. First, there is no enumerated registry of MSM who would have indications for PrEP. Second, unlike in a trial, where participants are regularly screened for HIV infection as an outcome, not all community-acquired cases of HIV infection will be diagnosed and documented. Third, the characteristics of men who do not enroll in the trial of the novel agent might be different in important ways from men who choose to enroll (eg, for understandable reasons such as mistrust of health research [34], Black and Hispanic people were historically less likely to enroll in HIV vaccine trials [35]).

Here, we propose a protocol to estimate the incident HIV diagnoses as a proxy of HIV incidence of HIV among PrEP-eligible MSM at the level of metropolitan statistical area (MSA). These estimates could represent a valuable source of data as a counterfactual reference group to evaluate the efficacy of PrEP in future trials of novel PrEP agents and would have other benefits to community planning and prevention efforts. To increase the rigor of this approach, we propose incorporating multiple population-based data sources, building on previously published methods [36] and incorporating methodologic improvements, including multiple stratifications of men by age and race to reflect important heterogeneities in HIV risks.

Methods

Modeling Equation

This surveillance study will be conducted using structured secondary data and will build upon the methodology outlined by Mera et al [36]. To estimate the new HIV diagnosis rate among MSM with PrEP indications, we will estimate the number of new diagnoses among this group (numerator) and the total person-time at risk of diagnosis for this group (denominator) by MSA and year. The approach is summarized by Equation 1 and described in detail below.



where *i* is demographic strata, *j* is MSA,*k* stands for year, *N* is number of new HIV diagnoses, *n* is number of new HIV diagnoses that are not in the MSM transmission category, *prepI* is *number of MSM with indication for PrEP*, *prepN* is *number of MSM PrEP users*, and *prepPT* stands for *average amount of time on PrEP my MSM in year k.*

Numerator Data Sources

The numerator represents the annual number of new HIV diagnoses among MSM with an indication for PrEP, by MSA and demographic strata, and will use data from the annual CDC HIV surveillance reports [37,38]; these data are available through CDC AtlasPlus [39]. The surveillance data sets have been published using consistent methods since 2008 and are the largest and most representative data sources for HIV diagnoses in the United States. The HIV surveillance report includes the number of new HIV diagnoses reported per year to the National HIV Surveillance System stratified by transmission category (ie, MSM, people who inject drugs, and heterosexual), race or ethnicity (ie, American Indian or Alaska Native, Asian, Black or African American, Hispanic or Latino, Native Hawaiian or Other Pacific Islander, White, Multiple races), age (10-year increments), and residence. Additionally, the HIV surveillance report includes stratification by MSA, as defined by the Office of Management and Budget. As described by Mera et al [36], a cumulative total of all new HIV diagnoses can be adjusted by subtracting all new HIV diagnoses that are attributed to a transmission category that are not in the MSM transmission category.

Denominator Data Sources

The denominator represents the total time at risk among MSM at risk of HIV acquisition. To estimate this for each stratum of interest, we will start with estimates of the number of adults that would be expected to have indications for PrEP [40] and remove person-time during which persons were on PrEP or acquired an incident HIV infection. Previous analysis of surveillance data has resulted in cross-sectional estimates of the number of adults in each HIV transmission risk category at the state level, who are then presumed to have an indication for PrEP [40]. To estimate the proportion of adults with a PrEP indication in each MSA by year, we will need to assume the proportion of persons with a PrEP indication is consistent within a jurisdiction and over time.

Person-Time Calculations

The amount of person-time among PrEP users can be estimated with data on the total number of PrEP users within each jurisdiction and year and data on the average length of time that users were on PrEP during the calendar year. Large, national prescription data sets include information on the number of patients who received a prescription of emtricitabine/tenofovir disoproxil fumarate or emtricitabine/tenofovir alafenamide and corresponding diagnostic codes. Using a validated algorithm [41], we can exclude prescriptions that were made for other known indications, such as HIV treatment, postexposure prophylaxis, and chronic hepatitis B management. We will estimate the number of prevalent PrEP users by tabulating the number of persons that had at least one day of prescribed PrEP in the respective calendar year. AIDSVu.org [42] applies this algorithm to data from Symphony Health to report estimates of the total number of current PrEP users within each county [6]. The estimates from each central county within an MSA can be summed to calculate the number of current PrEP users within the MSA. Additionally, we will assume that the rate of new HIV diagnoses is constant throughout the calendar year. With this assumption, we expect, on average, that the amount of time at risk among persons who experienced a new HIV infection during the calendar year was 6 months (ie, half of a year).

Ethical Approval

The proposed analyses will use deidentified and aggregated data sets; data about individuals are not provided in the data

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sets. The Emory University IRB has determined that this project does not require institutional review board review because it is not research with "human subjects," nor is it a "clinical investigation" as defined in the federal regulations.

Results

In early 2023, the most recent available surveillance data on new HIV diagnoses were from the 2020 HIV surveillance report, which was published in May 2022 [11]. This report indicates there were 30,689 new HIV infections in 2020, and 24,724 of them occurred in an MSA with a population of ≥500,000. Additionally, this report presents the number of new reported HIV diagnoses by MSA. The number of new HIV diagnoses, stratified by transmission category, race or ethnicity, or age, is typically published in supplemental volumes to primary HIV surveillance report, and the most recent supplementary volume with these data reflects diagnoses that occurred in 2018 [11].

Smith et al [40] developed a methodology for estimating the number of adults with PrEP indications by race or ethnicity and transmission category within each state. The most recent application of this methodology yielded estimates that indicate 1.1 million adults (813,970 MSM, 258,080 heterosexually active adults, and 72,510 persons who inject drugs) had indications for PrEP use in 2015. The methodology and data sources for these estimates can be expanded and updated. Additionally, assuming the proportion of persons with a PrEP indication is consistent within a state allows for the calculation of the total number of persons within each MSA (by transmission category and race or ethnicity) that have a PrEP indication.

AIDSVu.org annually releases new estimates of the current number of PrEP users, stratified by US county [42]. The methods for the production of these data have been previously reported [43]. The most recent estimates reflect 2019 and are further stratified by age group. We will use the publicly available county-level estimates from AIDSVu, which are updated annually; we will also explore further analyses of commercial pharmacy claims data to further stratify PrEP users within counties by age and race or ethnicity. Race or ethnicity data will be obtained from the matching of commercial pharmacy claims data to commercial credit reporting data, as has been previously reported by the CDC [40]; these matches will be evaluated for completeness and for potential biases related to missing data. Additionally, line-listed data from commercial pharmacy claims will be used to calculate the average duration of use for each demographic group of interest, using methods previously reported using claims data from large national pharmacy claims [44]. Our previous methods were focused on daily oral PrEP dosing strategies; we will develop and validate algorithms for identifying injectable cabotegravir [24] from claims data, to include this new PrEP agent and delivery route, and will continue to address new PrEP agents or dosing schedules as new agents become available (eg, monthly oral PrEP) [16].

Discussion

Principal Findings

We present an analytic approach for estimating population-level HIV incident diagnoses among PrEP-eligible MSM by jurisdiction, age group, and race or ethnicity. The proposed methods rely entirely on existing data and largely on publicly available surveillance data. This method would, for the first time, facilitate counterfactual estimates for the evaluation of novel PrEP pharmaceutical products by important characteristics of person, time, and place. HIV infections among MSM are highly concentrated among groups characterized by geographic location, age, and race or ethnicity, making it critical to evaluate new prevention methods within risk strata. Ensuring access to effective HIV prevention among populations with the highest risks for infection will require a nuanced understanding of how effectiveness of novel methods may vary across the demographic characteristics that determine HIV risk.

Utility of New Data Produced

These estimates could be used in multiple ways to support alternative HIV prevention trial designs. They could serve as one estimate in building a background surrogate estimate for HIV incidence for an external control arm and could also be used in the context of noninferiority trials, the current standard for evaluating effectiveness of novel PrEP pharmaceutical products. These trials are costly and require large sample sizes to reach an adequate number of HIV infections among participants receiving prevention medications for comparison purposes. Dunn and Glidden [30] and Glidden et al [45] have proposed the ratio of averted infections in each trial arm as the summary measure for evaluating noninferiority of novel PrEP pharmaceutical products. This summary measure requires fewer assumptions about the noninferiority margin and a smaller sample size to evaluate noninferiority of the novel product than the commonly used ratio of HIV incidence in each trial arm. However, it requires an estimate of background HIV incidence for persons not taking either a proven PrEP product or the trial medication. Previously described approaches for estimating this counterfactual incidence parameter apply a Bayesian approach with estimates from historic research data on emtricitabine/tenofovir disoproxil fumarate effectiveness [32,45] or use the correlation between incidence of rectal gonorrhea and HIV to estimate the number of HIV infections that would have been observed in the absence of PrEP [46]. However, neither of these approaches makes use of population-based data, and they are therefore subject to bias to the extent that trial participants are dissimilar to persons among whom these assumptions are based.

The availability of estimates of PrEP incidence among PrEP-eligible MSM is also a critical building block to support the routine production of other data that will inform our understanding of the equitable use of PrEP and impact of PrEP. For example, we have described the PrEP-to-need ratio as an equity-based metric to depict the extent to which PrEP is used equitably by subpopulations (eg, Black and White MSM) [9]. These metrics have been calculated and reported at the state level [9], and the availability of data at the MSA level would

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allow the calculation of these metrics at levels relevant to local health jurisdictions. Our plan to produce stratified estimates by age will also allow the characterization and modeling of PrEP needs and exploration of PrEP prioritization strategies to maximize the impacts of PrEP in local communities.

Enhancements to Existing Methods

The approach outlined here is based on previously published work by Mera et al [36], in which HIV diagnosis rates among PrEP-eligible individuals are estimated from 2012 to 2017. However, we propose several utility-added enhancements. First, use of the most current surveillance data will facilitate updated estimates for background HIV risk among PrEP-eligible MSM. Second, in addition to using updated surveillance data, the proposed method uses surveillance data that are stratified by age and race or ethnicity within jurisdictions. Stratification of key parameters in the surveillance data facilitates estimates specific to jurisdiction, age, and race or ethnicity. Third, previous estimates represent all PrEP-eligible individuals and assume adherence and persistence are constant across risk groups (eg, people who inject drugs, high-risk heterosexuals, and MSM). In reality, there may be important differences by risk group or age, and ignoring this heterogeneity might result in biased estimates of PrEP impact [47,48]. By focusing on MSM, who have the highest burden of HIV infection of all risk groups and the most unmet need for PrEP [9], our method will produce estimates that are directly informative to a trial counterfactual for MSM and to evaluating prevention needs of this important population. Last, we propose this method at the MSA level, but due to transparency of parameters used, it could be used at any geographic level for which needed data are available.

Limitations

Despite these improvements, these methods have several continuing challenges. First, while we propose to use the most updated surveillance data for input parameters, surveillance data are typically published with a 1-2–year delay. If implemented for noninferiority trials, adjustments to HIV diagnoses based on historical reporting delays might be needed [49]. We acknowledge that this might be challenging in the coming 6-8 years because of disruptions in HIV diagnoses and reporting during the COVID-19 pandemic [50]. Moreover, modeled estimates needed for this work that rely on surveillance data inputs, such as the proportion of HIV-negative MSM with PrEP indications, require additional time to compute and publish after surveillance estimates are made publicly available. Population-based estimates of background HIV incidence will therefore not be perfectly contemporaneous to trial periods, due to reliance on publicly available data. Second, population-level HIV risk among PrEP-eligible MSM may be higher or lower than MSM enrolled in PrEP trials. To the extent that there is differential risk between trial participants and the background population, estimates of effectiveness of novel PrEP products may be subject to selection bias. However, the risk of selection bias is diminished substantially in the context of population-level estimation specific to jurisdiction, risk group, as well as age and race or ethnicity groups. Possibly the greatest limitation of population-based methods to estimate HIV incidence is that, currently, only HIV diagnosis data, rather than incidence estimates, are available within levels of needed stratifications. Therefore, the assumption must be made that diagnoses are roughly equal to incidence in a given year, and that this is constant across geography, age, and race or ethnicity. As HIV surveillance methods continue to improve, it is likely that incidence estimates will be available at finer levels of geography and demographic characteristics. Third, we recognize that the proportion of MSM with PrEP indications might not be stable over time. We will monitor the proportion of MSM with PrEP indications over time by using data from the American Men's Internet Survey [6] and will adjust this parameter if the proportion of MSM with indications changes substantially over time. We will also conduct sensitivity analyses to this parameter in the first implementation of the protocol.

There are additional limitations and related assumptions that need to be considered to produce these estimates. For example, prescription data do not represent a full census of PrEP prescriptions, so PrEP use is underestimated in all MSAs and could be differentially underestimated. We assume that the average duration of PrEP use is the same for people who are and are not matched to race data; there are few data on PrEP persistence from observational studies stratified by race to inform the reasonableness of this assumption. We also assume that the proportion of MSM eligible for PrEP but not taking it is constant in MSAs over time and is consistent with state-level data. Most PrEP users in pharmacy data are men, and we assume that men on PrEP in pharmacy data are mostly MSM [43]. Prescription databases document the location of the provider who prescribed the medication, and not the patient; however, data suggest that people in urban areas usually reside 2-3 miles from their health care provider [51].

Public Health Impact and Conclusions

Updates and improvements to some parameters outlined here would further increase the utility of these estimates. In particular, estimates for the population size of MSM in the United States and the proportion of HIV-negative MSM with PrEP indications should be updated with current data, and novel methods are needed to incorporate uncertainty around these estimates. Previous estimates of HIV incidence among PrEP-eligible individuals did not incorporate uncertainty from data sources derived from population samples [36]. Building uncertainty estimates into these 2 parameters would facilitate computation of standard errors around HIV incidence estimates that incorporate uncertainty across multiple data sources.

Population-based data on estimated incident HIV diagnoses among PrEP-eligible MSM at the MSA level are critical public health resources. Developing estimates of incident HIV diagnoses among PrEP-eligible MSM will provide an important data resource for use by local health departments to benchmark progress in HIV prevention programs. The use of local, meaningful indicators of HIV incidence and trends in incidence supports the essential functions of public health [52]. We plan to produce periodic updates to the estimates and make them publicly available to researchers and health departments through AIDSVu.org [42], as we have done with other data resources such as estimates of PrEP prescriptions among populations at

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the regional, state, and local geographic levels [9,43,53]. Estimates of incident HIV infections in PrEP-eligible MSM, in triangulation with other data sources, can inform assessments of local prevention coverage and opportunities.

Data Availability

Data used in the calculations will be available in aggregate form. Data on PrEP users is currently available through AIDSVu.org [54] for earlier years; updated public data sets will be posted as new data from this analysis are developed. Data on new HIV diagnoses will be taken from the CDC's AtlasPlus website [55]; these data are also publicly available.

Conflicts of Interest

TS is the Editor in Chief of JMIR Public Health and Surveillance. PSS and HB are editorial board members of JMIR Public Health and Surveillance.

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Abbreviations

CDC: Centers for Disease Control and Prevention
EHE: Ending the HIV Epidemic
MSA: metropolitan statistical area
MSM: men who have sex with other men
PrEP: pre-exposure prophylaxis

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Protocol

The Good Talk! A Serious Game to Boost People's Competence to Have Open Conversations About COVID-19: Protocol for a Randomized Controlled Trial

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Abstract

Background: Vaccine hesitancy is one of the many factors impeding efforts to control the COVID-19 pandemic. Exacerbated by the COVID-19 infodemic, misinformation has undermined public trust in vaccination, led to greater polarization, and resulted in a high social cost where close social relationships have experienced conflict or disagreements about the public health response.

Objective: The purpose of this paper is to describe the theory behind the development of a digital behavioral science intervention—*The Good Talk!*—designed to target vaccine-hesitant individuals through their close contacts (eg, family, friends, and colleagues) and to describe the methodology of a research study to evaluate its efficacy.

Methods: *The Good Talk!* uses an educational serious game approach to boost the skills and competences of vaccine advocates to have open conversations about COVID-19 with their close contacts who are vaccine hesitant. The game teaches vaccine advocates evidence-based open conversation skills to help them speak with individuals who have opposing points of view or who may ascribe to nonscientifically supported beliefs while retaining trust, identifying common ground, and fostering acceptance and respect of divergent views. The game is currently under development and will be available on the web, free to access for participants worldwide, and accompanied by a promotional campaign to recruit participants through social media channels. This protocol describes the methodology for a randomized controlled trial that will compare participants who play *The Good Talk!* game with a control group that plays the widely known noneducational game *Tetris*. The study will evaluate a participant's open conversation skills, self-efficacy, and behavioral intentions to have an open conversation with a vaccine-hesitant individual both before and after game play.

Results: Recruitment will commence in early 2023 and will cease once 450 participants complete the study (225 per group). The primary outcome is improvement in open conversation skills. Secondary outcomes are self-efficacy and behavioral intentions to have an open conversation with a vaccine-hesitant individual. Exploratory analyses will examine the effect of the game on implementation intentions as well as potential covariates or subgroup differences based on sociodemographic information or previous experiences with COVID-19 vaccination conversations.

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Conclusions: The outcome of the project is to promote more open conversations regarding COVID-19 vaccination. We hope that our approach will encourage more governments and public health experts to engage in their mission to reach their citizens directly with digital health solutions and to consider such interventions as an important tool in infodemic management.

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KEYWORDS

vaccine hesitancy; communication; serious game; conversation skills; self-efficacy; behavioral intentions; COVID-19

Introduction

Background

Vaccine hesitancy is one of the many factors impeding public health efforts to control the COVID-19 pandemic [1,2]. High vaccine uptake, especially in vulnerable and high-risk groups, is crucial to reduce severe disease hospitalization and death; however, vaccination rates differ markedly across countries (eg, 50% in Russia, 77% in Germany, and 91% in Singapore [3-5]). The World Health Organization (WHO) defines vaccine hesitancy as "a motivational state of being conflicted about, or opposed to, getting vaccinated; this includes intentions and willingness" [6], and it is a dynamic state that can evolve over the course of a pandemic. Reasons for vaccine hesitancy include a misunderstanding regarding COVID-19, a general mistrust of vaccination, safety and effectiveness concerns, concerns about the rapid development and testing of the vaccine, lack of awareness of the social benefits of vaccination, and logistical or opportunity-related factors [2,7-11]. These concerns have been exacerbated by the COVID-19 *infodemic*, in which "too much information including false or misleading information in digital and physical environments during a disease outbreak," can lead to confusion and loss of trust in health authorities and public health responses [12]. COVID-19 misinformation has not only undermined public trust in vaccination [13] but has also led to a high social cost where close social relationships have experienced conflict or disagreements about pandemic control efforts [14-16]. In response, the WHO and others have called for greater application of behavioral science interventions targeting behavioral change and to support individuals in dealing with the psychological burdens associated with pandemic prevention and response [17-19]. For instance, evidence-based interventions that can help strengthen the resilience of individuals and communities to misinformation and other factors affecting trust in information will be a valuable tool for infodemic management [20].

Objectives

The aim of this paper is to describe the theory behind the development of a new digital behavioral science intervention—*The Good Talk!*—designed to target vaccine-hesitant individuals through their close contacts (eg, family, friends, and colleagues) and to describe the methodology of a research study to evaluate its efficacy. *The Good Talk!* uses a serious game—a game that does not have "entertainment, enjoyment or fun as their primary purpose" [21]—to boost the competences of vaccine advocates to have open conversations regarding COVID-19 with their close contacts who are vaccine hesitant. Serious games have been used as educational tools to build skills, including teaching perspective taking to help students improve their open conversation skills [22] and inoculating people against misinformation (eg, the *Bad News* game [23]). Peer-led initiatives have been used to address mistrust in other domains, and communicating through relatable and trusted sources can lead to more acceptable and personal information exchanges, promoting prosocial behaviors when common identities are shared [1,19]. Furthermore, by focusing on boosting open conversation skills rather than addressing a specific cause of vaccine hesitancy, the approach has the potential to address a variety of reasons why an individual is vaccine hesitant [1,24] as well as build transferrable skills that can be applied across a variety of situations [25]. *The Good Talk!* is publicly available worldwide and will be evaluated in a preregistered randomized trial. Evaluating the impact of the intervention will be the subject of a future publication.

Vaccine Hesitancy, Polarization, and the Social Impacts of the COVID-19 Pandemic

In 2019, the WHO identified vaccine hesitancy as one of the 10 threats to public health [26]. Despite strong and sustained evidence of the efficacy of vaccinations, perceptions of the safety and effectiveness of some vaccines have varied over the past years [27,28], affecting vaccine uptake [29] and contributing to disease outbreaks [24]. The influence of vaccine hesitancy on public health efforts to manage disease outbreaks has been accentuated during the COVID-19 pandemic, in which vaccine uptake in some countries has been low or lagging despite high vaccine access [3,4,30,31]. Consequently, longer durations of public health and social measures to reduce COVID-19 transmission are required, resulting in a variety of economic, health, and social costs with substantial psychological burden on individuals and communities [19,32].

The social costs of vaccine hesitancy have also been fueled by the COVID-19 infodemic, in which an overabundance of information has made it more difficult for the public to differentiate between correct and misinformation. When the public's questions and concerns are left unanswered, information voids occur, which can lead to widespread false and misleading information. For instance, searches involving antivaccination rhetoric increased during the COVID-19 pandemic as people sought information about vaccine safety [33]. The infodemic has diluted trust in institutions, leading to confusion and disagreement about vaccination and safety measures [34,35], and has resulted in an increasingly polarized environment in which people avoid engaging with those who hold opposing or

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divergent views, negatively affecting interpersonal relationships [36].

For instance, 56% of participants in a nationwide UK-based study reported having arguments, feeling angry, or falling out with others because of discussions surrounding COVID-19 [16]. In addition, people report relationship strain, interpersonal conflict, and increased isolation associated with sharing differing opinions or information about COVID-19 with family members or friends or avoiding conversations altogether to prevent conflict [14,15]. Thus, interventions to help people develop skills to discuss potentially polarizing topics and maintain supportive relationships with those who hold different opinions are needed to reduce the negative social costs of the pandemic [15]. Furthermore, considering the evolving nature of COVID-19—both in terms of the emergence of new variants and cyclical gravity because of seasons—governments have imposed, lifted, and changed regulations frequently. As such, the topic of COVID-19 and vaccinations will hold relevance for many years to come [37].

Intervention Goal: Initiate One-on-One Open Conversations About COVID-19 Vaccination

We sought to develop an evidence-based behavioral science intervention that could address diverse drivers of vaccine hesitancy while also supporting individuals in managing the psychological burden of the COVID-19 pandemic. Vaccine hesitancy is context specific and falls along a dynamic continuum, with motivation toward vaccination existing on a spectrum of those who are fully, partially, or not yet vaccinated [6,38,39]. As such, one-size-fits-all public health communication strategies are unlikely to reach all such individuals and will require a tailored, targeted, and multifaceted approach [1,24].

Reviews of a broad range of intervention approaches for addressing vaccine hesitancy report a lack of evidence or mixed findings on the effectiveness of many interventions [6,40-42], with dialogue-based approaches being among the most effective strategies [40]. Dialogue-based approaches aim to facilitate and encourage open communication to understand a specific audience and their underlying concerns [40]. Open communication–based approaches have the potential to address the negative effects of the COVID-19 infodemic on polarization and interpersonal relationships. For instance, exposure to divergent views through interpersonal discussion can weaken the association between selective exposure—exposure to content and groups that reinforce one's opinions—and polarization [43]. Open communication is important for showing respect and empathy toward a communication partner, which can reduce defensiveness, increase receptiveness, and pave the way for open-minded conversations in which speakers are willing to share their views, consider new information, and potentially change their attitudes [44].

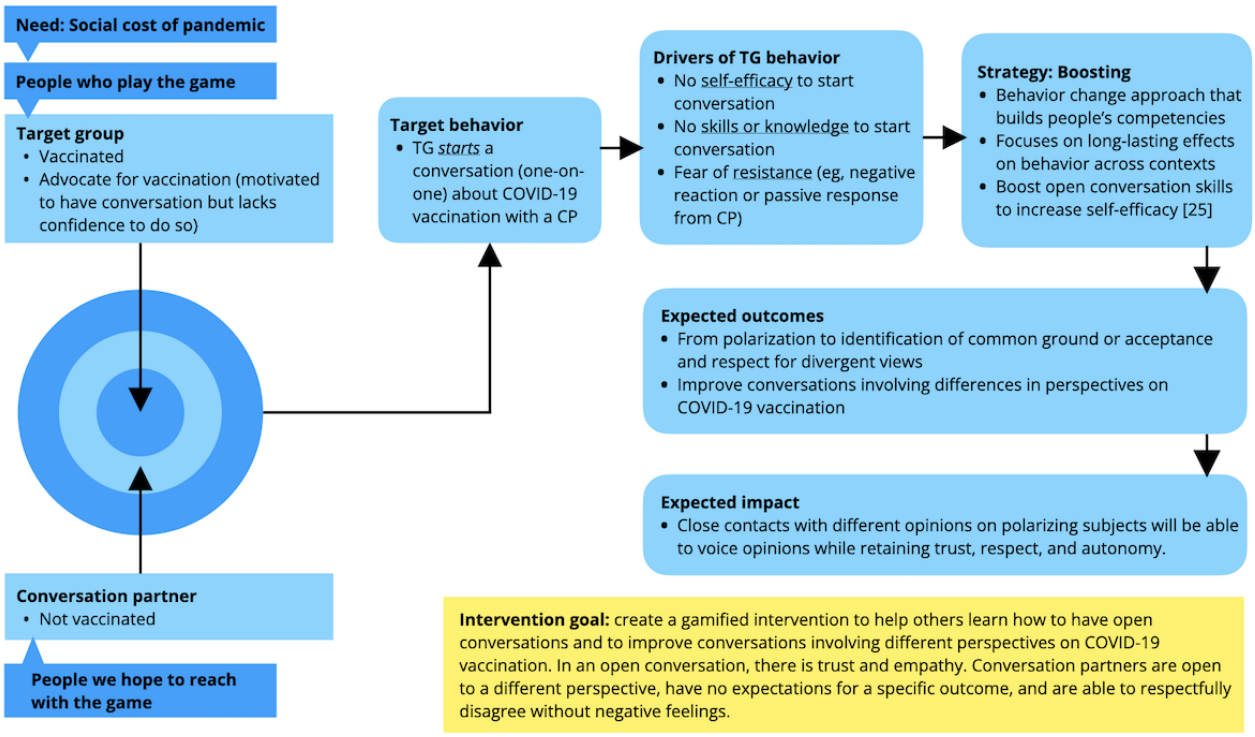
In addition, personalized communication can increase COVID-19 vaccine uptake, and these interventions are most effective when tailored to and delivered by a trusted peer or community member [6,42,45]. Advocating normative or prosocial behavior is more effective when a member of one's social network models the behavior and there is an expectation of social approval [19]. Social approval is important, as people have a strong need to belong [46] and people listen to others in their social environment [47]. Accordingly, vaccine-hesitant individuals may be more likely to listen to and trust their close ties, as public trust in health institutions among vaccine-hesitant individuals is exceedingly low [19,48], and peer-led initiatives have shown positive outcomes when addressing mistrust in other domains [1]. Peer-led initiatives capitalize on social networks to communicate and can influence social norms to promote behavior change [41]. Furthermore, communicating through trusted and relatable sources can facilitate more acceptable and personal information exchange [1].

Thus, the target group for the intervention is the close ties of vaccine-hesitant individuals who are vaccinated or are supportive of COVID-19 vaccination. For the purposes of this study, we refer to these individuals as *vaccine advocates*. As shown in the Theory of Change for the intervention (Figure 1), we aim to target vaccine advocates who are motivated to have a conversation about vaccination but lack the self-efficacy, skills, or knowledge to start a conversation or who fear resistance from their conversation partner. Motivation is an important driver of behavior change, and behavioral interventions are most effective when an individual is sufficiently motivated to learn new skills or competences [49,50]. In addition, targeting vaccine advocates increases the ecological validity and potential scope of the intervention, as they are likely to have more direct access and frequent encounters with vaccine hesitants and can reach broad and diverse audiences.

Accordingly, the goal of *The Good Talk!* intervention is to increase open conversations about COVID-19 vaccination by encouraging vaccine advocates to start a conversation with an individual they know or encounter who holds divergent or opposing views on vaccination or public health responses. We focus on *starting* an open conversation for several reasons. First, encouraging people to initiate a conversation is a first step to counter people's motivations to avoid conversations about difficult topics (eg, owing to conflict concerns) [51,52]. Second, starting an open conversation is a concrete behavior as opposed to the more ill-defined concept of *having* a conversation and does not focus on the outcome of the conversation as an indicator of success. Although open conversations are important for building trust over the longer term, they may not lead to immediate changes in vaccination behavior or in clearly identifiable positive or negative outcomes following each conversation instance [53]. Thus, the aim of the intervention is to develop a participant's competences, skills, and self-efficacy to approach rather than avoid conversations about COVID-19 vaccination. The intervention targets vaccine hesitancy indirectly by fostering more supportive interpersonal relationships between vaccine hesitants and vaccine advocates that encourage exposure to and consideration of divergent views. Ultimately, this should lead to continued exposure to divergent views between close ties and ongoing dialogue, which may eventually result in greater openness to the positions of others and remain open to evidence.

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Figure 1. Theory of change for The Good Talk! intervention. CP: conversation partner; TG: target group.



Applying Behavioral Science to Improve COVID-19 Vaccine Communication

We applied the theoretical framework of boosting to guide the development of our intervention. Boosting is an evidence-based behavioral science approach that focuses on building people's skills and competences rather than targeting a specific behavior [25,49]. The aim of boosting approaches is to foster people's existing skills and competences or to develop new ones, thus helping individuals build their skills, knowledge, and self-efficacy to shift their motivations and translate their intentions or preferences into behavior [25,49]. A core feature of boosts is that they preserve people's agency and enable them to exercise that agency to make their own choices [49]. Boosts are recommended for behavioral interventions where there is uncertainty or heterogeneity in people's goals, when generalizability and longevity of a behavior is desired, and boosts are most effective when people are motivated to acquire new skills or competences [49,54]. Accordingly, a boosting approach is well suited to the design of an intervention that seeks to develop open conversation skills that are generalizable and flexible to addressing diverse causes of vaccine hesitancy, and for interventions that enable individuals to make their own choices on how to apply the skills to achieve their interpersonal relationship goals.

The focus of boosting approaches on fostering competences aligns with the objectives and key drivers of the intervention target behavior. Competence in interpersonal communication skills is associated with positive conversational outcomes, such as personal conversational satisfaction and more positive evaluations from conversation partners [55,56]. Demonstrating open conversation skills also leads to reduced defensiveness, greater awareness of attitude contradictions, decreased attitude extremity, and more open mindedness in conversation partners [57-59]. Furthermore, interventions designed to teach open conversation skills (eg, high-quality listening) or simple receptive conversation strategies have been found to signal positive collaborative intentions and receptiveness to alternative views while reducing negative conversational outcomes, such as defensiveness or threat reactions [57,59].

Developing open conversation skills can also build confidence and self-efficacy in conversations [60,61], and perceptions of self-efficacy are associated with conversational satisfaction [55]. Boosts foster self-efficacy by helping people learn and apply skills and knowledge through the development of competencies, rather than by providing information per se [25]. For instance, rather than teaching universal skills (eg, declarative knowledge), boosts use techniques such as teaching procedural rules, simple heuristics, or trainings (eg, learning how to harness implementation intentions) that can be generalized across different contexts or environments. The approach is conceptually similar to the inoculation approach used in misinformation detection interventions (eg, the *Bad News* game [23]), in which participants are exposed to the *techniques* that underlie misinformation and encouraged to generate their own antibodies rather than learn passively through being shown examples of manipulative strategies [62]. Learning through feedback on the effectiveness of skills can help build self-efficacy and confidence in understanding where and when to apply the skills to achieve one's objectives [54].

Thus, our objective was to review the literature on open conversation skills to identify a set of simple strategies that could be integrated into a short behavioral intervention in the form of boosts. We aimed to design an intervention that would help individuals learn the effectiveness of these strategies on

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conversational outcomes through guidance and feedback, thus fostering participants' self-efficacy in applying these strategies to initiate open conversations. In the following section, we will provide an overview of the evidence basis for the open conversation skills. The *Methods* section describes how we designed the intervention to provide participants with the opportunity to apply the strategies through an engaging and motivational serious game: *The Good Talk!*

Open Conversation Skills

Overview

We conducted a narrative review of a broad range of literature on communication approaches to identify evidence-based open conversation skills that can be designed as boosts within the intervention. To align with the goals, we searched for communication literature that focused on developing or fostering supportive relationships, promoting self-efficacy and empowerment, or on psychological or therapeutic approaches developed to support behavior change. Specifically, we explored literature on the topics presented in Textbox 1.

Textbox 1. Communication literature reviewed to develop open conversation boosts.

- Communication theories or frameworks to support behavior change (eg, motivational interviewing [7,63-65] and Self-Determination Theory [66-69])
- Core communication skills for fostering ongoing, supportive relationships (eg, building trust, empathy, and autonomy) [70-73]
- Literature on specific topics related to persuasive communication and listening skills [56-58,72] as well as strategies to increase receptiveness of divergent views and reduce psychological reactance (eg, conversational receptiveness) [59,74,75]
- Psychological strategies on how to handle negative reactions or outcomes (eg, mindfulness and intellectual humility) [76-78]
- Conversation guidelines or recommendations for health risk communications (eg, crisis communication) or on how to communicate about vaccinations [1,32,45,79-81]

From this literature, we identified 8 general open conversation skills that we categorized into 4 main communication objectives: to build trust and respect, be supportive, be receptive and demonstrate empathy, and practice acceptance. These objectives can be represented as a mnemonic for *The Good Talk!* acronym: gain trust, offer support, open up, and don't be sad if it doesn't work out. We provide a brief overview of each of the objectives and skills in the subsequent sections. More detailed descriptions of the open conversation skills and summaries of the supporting literature can be found in Table S1 in Multimedia Appendix 1 [7,56,58,59,63,65,66,69,72-76,79,82-87].

Gain Trust

The first objective focuses on building trust and rapport with the conversation partner to develop or maintain a supportive relationship or establish a partnership. The first of the 3 open conversation skills, *find mutual value*, aims to find points of agreement or shared value between conversation partners to create a sense of partnership, shared identity, or establish a common fate that one can connect or appeal to [69,79]. Finding points of agreement also signals receptiveness and positive collaborative intentions [59]. The second conversation skill, *respect autonomy*, aims to foster empowerment and self-efficacy in the conversation partner by treating them as responsible agents who have autonomy over their choices. Autonomy is considered a primary psychological need in Self-Determination Theory [66]. Further, emphasizing that one has and is responsible for their own choices reduces psychological reactance [69,75,82] and lowers feelings of defiance [83]. Fostering autonomy is a key recommendation in health risk and vaccine communication guides [53,79]. The third conversation skill, *don't lecture or persuade (don't be an expert)*, focuses on using language or strategies that avoid perceptions of authoritarian, coercive, or persuasive intent, which can lead to greater reactance to change communication [66,69,75,79,84]. For instance, using hedging (eg, use of "might" or "somewhat") to soften factual claims has been found to signal collaborative intentions [59].

Offer Support

Offering support during a conversational exchange can facilitate relationship building and serves to foster self-efficacy in the conversation partner. The first conversation skill is to *ask for perspective* by showing interest in another's viewpoint and expressing genuine appreciation for their concerns, feelings, or perspectives. Feeling understood and cared for by others is a primary psychological need according to Self-Determination Theory [66,69], and showing interest in another's view leads to more positive evaluations of the conversation partner and greater receptiveness perceptions [56]. Affirmation of a conversation partner's concerns is a component of motivational interviewing to promote self-efficacy and boost their confidence in taking action to make behavioral changes [7,63]. The second skill is to *affirm feelings/perspectives and acknowledge past efforts and successes* and is also a core component of motivational interviewing to support self-efficacy. It focuses on emphasizing the strengths, past successes, and efforts of the conversation partner and encouraging them to highlight their own strengths [7,63]. Applications of Self-Determination Theory to COVID-19 communication suggest that providing constructive feedback on how successful people have been in adhering to measures fosters a sense of competence and motivation to continue engaging in them [69].

Open Up

Two open conversation skills relate to the objective to open up. First, *asking open questions* aims to encourage individuals to use open (as opposed to closed) questions to gain insights and understanding and to allow their conversation partner to discuss their story. Open-ended questions are 1 of the 4 core

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communication skills in motivational interviewing to help establish a mutually trusting and respectful relationship with a conversation partner [7,63] and a strategy to accommodate people's basic psychological need for relatedness in Self-Determination Theory [66,85]. Asking open questions is also an important active listening skill to enhance understanding and build relationships [73], and this communication skill is cited in numerous health risk communication guides [79,81]. Second, to *be resilient if the other* (conversation partner) *is right* promotes respect for divergent views (respectful disagreement) to foster open mindedness, shared identity, and more positive conversational exchanges [58,59,72]. At the same time, being willing to acknowledge and accept when a conversation partner is right or makes a valid argument demonstrates humility and openness to opposing views [76].

Don't Be Sad If It Doesn't Work Out

The final objective involves preparing the individual for a case in which their conversation will not necessarily lead to a positive outcome or observable behavior change [79]. The open conversation skill is to *accept negative outcomes* without judgment or negative evaluation of the situation or the conversation partner. Acceptance, nonjudgment, and nonreactivity are important for emotion regulation and for reducing strong negative emotions in mindfulness and acceptance and commitment therapy [70,78,86,88]. Accepting that the conversation may be one of several and leaving open the opportunity for future conversations can keep communication channels open and maintain ongoing relationships [79].

Intervention Delivery: Serious Game

We sought to deliver the intervention through a medium that had a strong evidence basis for promoting behavior change, was realistic and had strong ecological validity in terms of interpersonal communications during the COVID-19 pandemic, would motivate people to engage with the intervention, and could reach broad and diverse audiences. Gamified behavioral interventions have been found to promote positive behavior change across a variety of health-related areas, including asthma control, medication adherence, and diet [89], and were found to be more effective than inactive controls or nongamified interventions in improving physical activity behavior [90]. Games have also been used as educational tools across a variety of fields [91,92], such as teaching students role-playing and perspective taking to improve open conversation skills [22], and have been found to be effective at inoculating people against disinformation [93,94], specifically COVID-19 disinformation [95].

Serious games are games that do not have "entertainment, enjoyment or fun as their primary purpose" [21]. The learning benefits of serious games align with the goals of boosting interventions, in which the aim is to boost competences and in which motivation is key to intervention efficacy [49]. Serious games increase knowledge, build skills, and increase self-efficacy through design features within the game play that help players to select relevant information and integrate and organize the information with prior knowledge [96]. For instance, a first-person perspective can engage players in the learning experience, narrative and choice instill a sense of autonomy, interactions with game characters and personal reflection provoke empathy and relationship or community building, and mistakes and feedback processes can foster persistence [92,96]. Furthermore, serious games not only enhance motivation to learn but also have a strong motivational appeal [92,96].

Serious web-based games have the potential to reach a broad and diverse audience, can be accessed worldwide on mobile and desktop devices, and can be shared with others via web-based media. Edutainment mobile games aimed at educating remote or low-resource communities on issues such as agriculture and farming practices, health, livelihoods, and financial literacy have been disseminated in over 20 countries, with COVID-19–focused games reaching >2.7 million people across 11 countries in 2020 [97]. Furthermore, as social distancing and safety measures during COVID-19 have limited close interpersonal contact and people have increasingly turned to web-based communication to stay connected [98], mimicking widely used web-based communication applications (eg, using a messenger-type app) [99] has strong ecological validity [100]. Another goal of using this format was to facilitate adaptation, translation, and implementation into existing public health channels that may be fighting misinformation via chatbots (eg, WHO's Health Alert Services [101-103]), including in low-resource settings [104]. Therefore, we designed a serious game based on a messenger app to build self-efficacy and open conversation skills by mimicking real-world conversations between vaccine advocates and their close contacts. Further details on the specific design features of the serious game and how the open conversations skills were implemented are provided in the *Methods* section.

Overview of Intervention Hypotheses

In the previous sections, we have detailed the theoretical development of *The Good Talk!* intervention. Our next step is to conduct a research study to evaluate the efficacy of *The Good Talk!* serious game to improve people's skills and competences to have open conversations about COVID-19 with vaccine-hesitant individuals. In the following sections, we present a detailed research protocol describing the planned evaluation study to be conducted along with the implementation of the game. Once completed, the results of the evaluation study will be reported in a separate publication.

The efficacy of the intervention game will be evaluated in a preregistered randomized controlled trial. Specifically, we aim to answer the following research question: "How well does *The Good Talk!* game improve people's open conversation skills, perceptions of self-efficacy, and behavioral intentions to have open conversations with vaccine-hesitant individuals who are close contacts?" We will compare a group of participants who play the intervention game with a control group that will play the widely known noneducational game *Tetris*. *Tetris* was selected as the game for the control condition as it is in the public domain, and most people know how to play it without the need for practice or instruction. *Tetris* involves a similar amount of cognitive effort to play as the intervention game, it contains no content related to the study, and it has been used as

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a control game to validate other digital game-based learning interventions [62,94,105]. *Tetris* is an inactive control group (receiving no educational material), which is an appropriate design for assessing the absolute efficacy of the intervention [106].

Our primary hypothesis is as follows:

- *Hypothesis 1: Relative to the control group, The Good Talk! game will result in a greater increase (boost) in participant's skills to have an open conversation with a vaccine-hesitant individual.*

We also hypothesize the following:

- *Hypothesis 2: Relative to the control group, The Good Talk! game will result in a greater increase in individual's feelings of self-efficacy to have an open conversation with a vaccine-hesitant individual.*
- *Hypothesis 3: Relative to the control group, The Good Talk! game will result in a greater increase in intentions to have an open conversation with a vaccine-hesitant individual.*

Methods

Participants and Recruitment

Participants will be recruited to play the game via video or push notifications promoting *The Good Talk!* game on social media platforms (eg, WHO chatbot channels) and advertised via other WHO informational campaigns. Recruitment will be open to all interested individuals worldwide but will be limited to English language speakers. Participants will self-subscribe to the study by accessing the WHO game information web page via the public link or when shared by members in their social network. On the game information page, participants will be asked if, in addition to playing the game, they would like to participate in the research element (a similar approach was used to recruit participants to research elements in other serious web-based games [93,95]). Participants who are not interested in participating in the study will be sent directly to play *The Good Talk!* game; otherwise, they will be asked to opt-in to the study after giving informed consent. Participation in the research element of the game will be restricted to individuals aged ≥18 years. Participation in the study is voluntary, and no remuneration will be offered to complete the study.

Previous studies evaluating the effect of similar serious games on the development of competences report small-to-medium effect sizes averaging around f=0.18 [95,100,105]. A power calculation with a small effect size (f=0.18), power of 0.90, and α=.05 for an analysis of covariance on posttest open conversation skills suggests a total sample size of n=327. We will aim to collect 450 responses (225 per condition) to account for potential technical issues or possible poor-quality data. Data collection will continue until the prespecified sample size for each condition is reached. Preregistration of this study can be found on the Open Science Framework [107].

The Good Talk! Game

The intervention game was developed in collaboration with the game design company "Tiltstudio," that has experience designing serious games including "Bad News," "Go Viral," and "Harmony Square," targeting misinformation, COVID-19 misinformation, and political misinformation tactics, respectively. The game was designed to simulate messenger-type conversations between participants and close contacts in their social network. Messenger-type technologies are dyadic, informationally rich, synchronous, and mimic interpersonal communication and are therefore better suited for establishing a sense of connection and generating empathy [19]. At the same time, they represent a realistic communication platform familiar to many users worldwide [99], which increases the ecological validity of the intervention [100]. The game design implements instructional techniques found in a meta-analysis to be effective at improving learning and motivation in serious games, such as feedback (providing feedback or guidance on whether an answer is correct), reflection (participants are asked to reflect on their responses), level of realism (the game uses basic and cartoon-like representations), and narrative elements [96,108].

The game consists of 5 chapters in which the participants have conversations with characters representing their close contacts. In the first chapter, participants are introduced to the objective of the game, that is, to have as many people attend an event that they are organizing and to earn points for the good talk skills. The participant is asked to select an avatar to represent themselves and can choose between 1 of 4 social events they would like to organize (eg, birthday party, dinner, dance party, or housewarming).

The remaining 4 chapters see the participants encounter characters within their close ties who are motivated by reactance (negative affective reaction when one feels personal freedoms are being threatened), skepticism (doubting knowledge or claims), and inertia (opposing change or action) when discussing COVID-19 measures for the social event. As the conversation develops, the player must select from ≥2 conversational responses that affect the participant's pathway toward the game objective and the points they earn on a Good Talk Meter. The Good Talk Meter increases with response choices that represent good open conversation skills and decreases for those that represent bad open conversation skills. In each chapter, participants are guided by a *Good Talk Guide* who offers advice and reinforces or educates participants about the strategies based on their selections. A brief description of the objective of each chapter is provided in Table 1, and a screenshot of the game interface is shown in Figure 2.

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Table 1. Brief overview of the goal and open conversation skills for each chapter.

Chapter	Goal
Introduction	The participant is introduced to the objective of the game and asked to select an avatar and an event they would like to plan. An overview of *The Good Talk!* skills is provided to participants along with the definition of what it means to have an open conversation.
Gain trust	The participant converses with someone who is worried about their kids not being vaccinated and whose kids are skeptical about the government's use of COVID-19 antigen tests. The participant is encouraged to gain the trust of the conversation partner and, in turn, to encourage their partner to use open conversation skills to gain the trust of their children by expressing their concerns, finding mutual value, and supporting their kid's autonomy.
Offer support	In this chapter, the conversation partner mistrusts the seriousness of the pandemic, is skeptical about the evidence, and does not see a personal need to get vaccinated. The participant is encouraged to ask for the perspective of their conversation partner rather than argue, with the goal to understand their views and to continue the conversation. By acknowledging their partner's perspective and concerns, the participant is encouraged to find some common ground so that both feel comfortable attending the event.
Open up	The conversation partner is vaccinated but does not see a need to get the booster vaccination after reading some misinformation on the web and is reluctant to change their mind. The partner is overwhelmed by information and the impact of restrictions. By asking open questions, not being dismissive of their partner's feelings or concerns, and accepting their points while being respectful of divergent views, the goal is to help the partner overcome their inertia.
Don't be sad if it doesn't work out	In the final chapter, the participant encounters a conversation partner who is against vaccination, who mistrusts the government, and who continues to share fake news and misinformation rather than engage in an open conversation. Rather than argue, the participant is guided to not react negatively and to accept that the conversation will be unlikely to lead to a positive outcome.

Figure 2. Example of The Good Talk! game interface on a web browser.



Design

Participants who enter the game website and agree to participate in the research study will be randomized to the experimental or control group (between subjects) and complete both a pre- and postgame survey (within subjects). The experimental group will play *The Good Talk!* game, and the control group will play the noneducational game *Tetris*.

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Outcome Measures

Prior Experience With COVID-19 Vaccination

Participants will be asked whether they have had or are currently supportive of people getting the COVID-19 vaccination, whether they currently know someone who is hesitant toward getting the COVID-19 vaccination (and if so, their relationship with this individual), and whether they have previously tried to have a conversation about COVID-19 vaccination with a vaccine-hesitant individual.

Self-efficacy

Participants will rate how confident they are to be able to start a conversation about COVID-19 vaccination with a vaccine-hesitant individual on a 7-point scale ranging from "not at all confident" to "very confident." The self-efficacy item will be asked in the pre- and poststudy surveys.

Behavioral Intention

Participants will be asked to indicate how likely it is that they will start an open conversation about COVID-19 vaccination with a vaccine-hesitant individual in the next 4 weeks on a 7-point scale ranging from "I will definitely not start a conversation" to "I will definitely start a conversation." Consistent with recommendations for assessing intentions, the measure uses a likelihood scale and defines a timeframe for the behavior [109,110]. The behavioral intention item will be asked in the pre- and poststudy surveys.

Implementation Intention

Following the behavioral intention item in the poststudy survey, participants will be asked to plan their intention. Implementation intentions refer to intentions to enact a preplanned behavior and can mentally simulate the process of implementing a goal, aiding goal striving [110-112]. Participants will be asked to indicate which vaccine-hesitant individual they plan to have an open conversation about COVID-19 vaccination with (eg, a family member, friend, coworker, or someone else or indicate that they have no plan to have an open conversation with a vaccine-hesitant individual), when they plan to have the conversation (eg, in the next ___ hours/days/months), and to specify what their starting sentence will be.

Open Conversation Skills

Participants will be provided with conversation snippets presented as messenger app messages and asked to rate each statement according to how good or bad they think the response is when having an open conversation on a 5-point scale ranging from "very bad" to "very good." Participants will rate 8 conversation snippets in the prestudy survey and a different set of 8 conversation snippets in the poststudy survey. Using parallel versions of pre- and postintervention tests in the evaluation of serious games reduces practice effects [106,113]. In each survey, there will be 1 conversation snippet for each of the 8 open conversation skills (Table 2). For each open conversation skill, one item will represent a bad response example and the other will represent a good response example. Good and bad response examples for a single open conversation skill will not appear in the same survey. The open conversation skill snippets were reviewed by experts in behavioral science interventions.

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Table 2. Examples of good and bad open conversation skills included in the pre- and poststudy measure.

Objective and skill	Good response	Bad response
Build trust		
Find mutual value	• I am worried about the safety of the vaccine for my family. What if it made them sick?[a] • Response: I'm concerned about my family's health too and also feel responsible if something bad was to happen to them.	• Hey, so I'm unvaccinated but I'm still gonna go over to my friend's house who is really strict about people being vaccinated. • Response: Hmn, that's not something I would do. I would respect other's decisions.
Respect autonomy	• I can't believe the government is suggesting that everyone should get vaccinated. This is my health, my decision. • Response: The choice is yours and only you can make it. What would help you make your decision?	• These COVID regulations are ridiculous, next thing you know I'll have to wear a hazmat suit to go shopping.[a] • Response: You should respect other people's health and follow the regulations.
Don't lecture or persuade (don't be an expert)	• How can they even be sure the vaccine is safe if they made it so fast? It was rushed, who knows what steps they missed![a] • Response: I think it might have something to do with reducing all the red tape that helped speed things up but I'm not sure. Let's look into it together!	• I am concerned about the side-effects of the vaccine. I heard that they can get pretty bad. • Response: Have you looked at the data? I have, and the side-effects are minor. You should look into what can happen if you don't get the vaccine.
Offer support		
Ask for perspective	• My friend has a party but she says I need to be vaccinated to go, not sure how I feel about it? • Response: What makes you unsure?	• I don't believe getting a booster vaccine is really necessary.[a] • Response: It's interesting how you justify putting other people at risk.
Affirm feelings or perspective; acknowledge past efforts or successes	• I'm unsure about whether to take the vaccine, it seems dangerous.[a] • Response: It is good that you are critical and don't rush into things when you are unsure. Remember when you had to switch to that new medication and felt better when you looked into it more?	• Our neighbours were strict with the social distancing thing and one of them got it anyway. And they are both vaccinated! So I just don't see the point. • Response: That's not how to think about it. Just because they got it doesn't mean it's not worth you making any effort.
Open up		
Ask open questions	• For now, I don't want to get the vaccine. Just because everyone else has decided to get it, doesn't mean that I have to as well. • Response: If you were to consider getting the vaccine, what would change your mind?	• How would a mask even help against a virus?[a] • Response: Did you look at the evidence?
Be resilient if the other is right	• First we were told not to bother with masks, and then we were told to wear masks everywhere! These backflips don't help.[a] • Response: That's true, the changing recommendations about wearing masks did not help. It goes to show how uncertain things were at the beginning.	• I'm waiting, that's all. It takes time to make sure that the vaccine is safe for everyone. • Response: Yeah I've heard that point before but let's focus on why it is important that all healthy people should get vaccinated.
Don't be sad if it doesn't work out		
Accept negative outcomes (the conversation may not work out)	• It's clear that you and I are not on the same page about this. I have my reasons, you have yours. • Response: That's OK, thanks for helping me understand your reasons. It seems like it doesn't work out, so let's leave it there and maybe we can speak again next week?	• Look I just don't think we are ever going to agree on this.[a] • Response: You don't appreciate my views! But give me one more try and I bet I can change your mind on this one.

[a]Items included in the prestudy survey.

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Demographic Questions

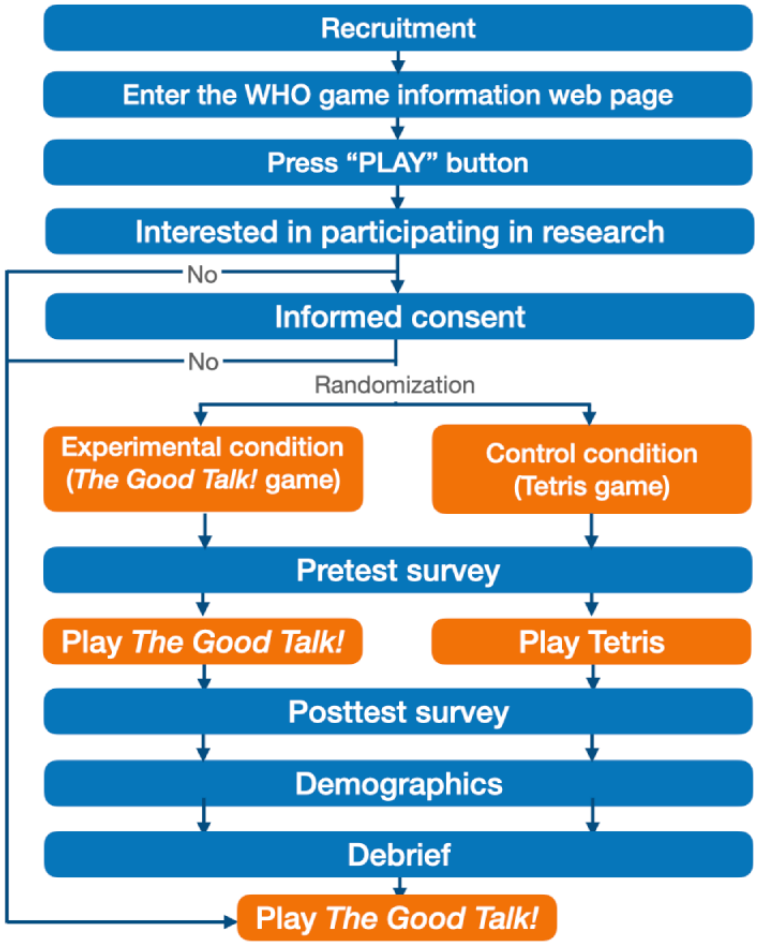
Participants will be asked to provide their age (in years) and indicate their gender, current level of English fluency, country of residence, and highest level of education obtained.

Procedure

Participants will first answer the questions regarding their support for COVID-19 vaccination and their past experience speaking with vaccine-hesitant individuals. Participants will then complete a pretest survey containing the 8 open communication skills items and the self-efficacy and behavioral intention items. The experimental group will then play *The Good Talk!* game, which will take approximately 10 minutes to complete. The control group will play *Tetris* for a similar amount of time.

Following the game, participants will respond to a posttest survey containing the open communication skills, self-efficacy, and behavioral intention questions. Participants will also complete the implementation intention questions and a short demographic survey. At completion of the study, participants will be thanked for their time and invited to share the study with their friends. Participants in the control group will be given the option to play *The Good Talk!*. Figure 3 presents the flowchart of the study design and procedure.

Figure 3. Flow diagram representing the study design and procedure. WHO: World Health Organization.



Ethics Approval

Ethics approval for the study has been submitted and is awaiting approval from the WHO Ethics Review Committee (application ID: CERC.0177).

Results

Recruitment and data collection are estimated to commence in early 2023. The efficacy of the study will be analyzed using an analysis of covariance with posttest open conversation skills as the dependent variable, controlling for pretest scores. Partially completed surveys will be included in statistical analysis whenever possible. As a sensitivity check, analyses will be repeated by excluding participants who complete the study less than 2 SDs below the median completion time as a data quality check.

The primary outcome is open conversation skills. The secondary outcomes are self-efficacy and behavioral intention items. Exploratory analyses will examine the effect of the game on implementation intentions as well as potential covariates or subgroup differences based on sociodemographic information or previous experiences with COVID-19 vaccination conversations.

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Discussion

Expected Outcomes

We hypothesize that *The Good Talk!* game will lead to a greater increase in open conversation skills, self-efficacy, and intentions to initiate conversations about vaccination between vaccine advocates and their vaccine-hesitant close ties relative to the control game. We hope that the game will help people to talk to one another so that supportive relationships can be maintained, and over time, opportunities to share with consideration of divergent views may help combat some of the negative social costs of the pandemic. Furthermore, we hope that this study will highlight how serious games can be a promising forum for delivering evidence-based health behavior interventions to the public.

Strengths and Limitations

The Good Talk! game represents an evidence-based behavioral science application based on the theoretical framework of boosting that aims to boost people's skills and competences rather than target a specific cause of vaccine hesitancy. As such, this approach has the potential to build transferrable skills that can be applied across a variety of situations. Delivering the intervention via a worldwide, publicly available serious game means that it has the potential to reach a broad and diverse audience while using an ecologically valid medium that mimics real-world web-based communications.

Nevertheless, there are potential limitations to the insights that can be drawn from this study. First, as participants will access the study via a public link that is associated with the promotion of the game, it is not possible to blind participants completely from their assigned experimental condition. Although participants will be blinded to their assigned conditions at the initial pretest survey stage, it is not possible to avoid dropouts or potential self-selection to their assigned condition. To limit this effect, all participants will be told that both games are very important for the research and that everyone will get the opportunity to play *The Good Talk!* game. We will also collect data on the number of dropouts and partially complete and completed surveys per condition to evaluate their impact on study completion. Second, the game may attract a diverse set of participants from various backgrounds worldwide, including different levels of English proficiency, experience with COVID-19 vaccination, and social and political contexts. However, as the intention for the game intervention is to reach a broad and diverse audience and be applicable to individuals from a wide range of cultural, economic, and educational backgrounds, the evaluation will also contribute data on the effectiveness of the intervention in a real-world context.

Future Directions

We envisage that the positive results of the study can lead to concrete practical applications, for instance, as a valuable resource for health care professionals whose patients request advice on how to have vaccination conversations with those close to them. Furthermore, health care systems can refer to *The Good Talk!* game to boost the competencies of their patients to have open conversations about other difficult topics with their close contacts. More broadly, we hope that this study can motivate health care policies to consider serious games such as ours as an additional and efficacious method for promoting behavior change in public health communications.

Conclusions

The Good Talk! intervention represents an application of boosting theory to the field of behavior change for public health purposes. By describing the methods through which the intervention was designed, we hope to enable others to replicate and innovate our findings. We hope our approach will encourage more health ministers to engage in their mission to reach their citizens directly with digital health solutions and to consider such interventions as an important tool in infodemic management.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Overview of open conversation boosts and supporting literature.
[DOCX File , 40 KB - resprot_v12i1e40753_app1.docx]

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Abbreviations

WHO: World Health Organization

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Protocol

Live and Recorded Music Interventions to Reduce Postoperative Pain: Protocol for a Nonrandomized Controlled Trial

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Abstract

Background: Postoperative patients who were previously engaged in the live musical intervention Meaningful Music in Healthcare reported significantly reduced perception of pain than patients without the intervention. This encouraging finding indicates a potential for postsurgical musical interventions to have a place in standard care as therapeutic pain relief. However, live music is logistically complex in hospital settings, and previous studies have reported the more cost-effective recorded music to serve as a similar pain-reducing function in postsurgical patients. Moreover, little is known about the potential underlying physiological mechanisms that may be responsible for the reduced pain perceived by patients after the live music intervention.

Objective: The primary objective is to see whether a live music intervention can significantly lower perceived postoperative pain compared to a recorded music intervention and do-nothing control. The secondary objective is to explore the neuroinflammatory underpinnings of postoperative pain and the potential role of a music intervention in mitigating neuroinflammation.

Methods: This intervention study will compare subjective postsurgical pain ratings among 3 groups: live music intervention, recorded music intervention, and standard care control. The design will take the form of an on-off nonrandomized controlled trial. Adult patients undergoing elective surgery will be invited to participate. The intervention is a daily music session of up to 30 minutes for a maximum of 5 days. The live music intervention group is visited by professional musicians once a day for 15 minutes and will be asked to interact. The recorded music active control intervention group receives 15 minutes of preselected music over headphones. The do-nothing group receives typical postsurgical care that does not include music.

Results: At study completion, we will have an empirical indication of whether live music or recorded music has a significant impact on postoperative perceived pain. We hypothesize that the live music intervention will have more impact than recorded music but that both will reduce the perceived pain more than care-as-usual. We will moreover have the preliminary evidence of the physiological underpinnings responsible for reducing the perceived pain during a music intervention, from which hypotheses for future research may be derived.

Conclusions: Live music can provide relief from pain experienced by patients recovering from surgery; however, it is not known to what degree live music improves the patients' pain experience than the logistically simpler alternative of recorded music. Upon completion, this study will be able to statistically compare live versus recorded music. This study will moreover be able to provide insight into the neurophysiological mechanisms involved in reduced pain perception as a result of postoperative music listening.

Trial Registration: The Netherlands Central Commission on Human Research NL76900.042.21; https://www.toetsingonline.nl/to/ccmo_search.nsf/fABRpop?readform&unids=F2CA4A88E6040A45C1258791001AEA44

International Registered Report Identifier (IRRID): PRR1-10.2196/40034

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KEYWORDS

live music intervention; recorded music intervention; pain VAS; postsurgical pain; neuroinflammation; pain management; intervention; music; postoperative; pain; perception; pain relief; live music; recorded music; music intervention; music; pain perception

Introduction

In recent research, postoperative patients exposed to a live musical intervention reported significantly reduced perception of pain than patients without the intervention [1]. This encouraging finding indicates a potential for postsurgical musical interventions to have a place in standard care as therapeutic pain relief. However, live music is logistically complex in hospital settings, and previous studies have reported the more cost-effective *recorded* music to serve as a similar pain-reducing function in postsurgical patients [2,3]. Therefore, this study primarily aims to compare the effectiveness of postoperative live versus recorded music interventions in reducing patients' perception of postsurgical pain. In order to potentially expand this finding from subjective to objective metrics, secondary outcomes will explore whether subjective pain perception is statistically related to more objective metrics such as pain medication dosage or respiration rate [4].

Although previous findings showed a convincing influence of music intervention on postsurgical pain perception [1-3,5-7], the physiological mechanisms that could make this possible are not yet understood [8]. It has been reported that music modulates psychoneuroimmunology [9,10] such as lowering stress-induced cortisol [11] and enhancing neurogenesis [12]. While chronic or long-term postsurgical pain has established links to neuroinflammation [13,14], the possibility exists that immediate postsurgical pain—before it reaches a chronic state—may have links to neuroinflammation as well [15]. Thus, one possibility is that music is mitigating postsurgical neuroinflammation, which could in turn be affecting the immediate postsurgical pain.

Therefore, further secondary outcomes will explore behavioral indicators (postoperative cognitive decline or POCD and delirium) and biological markers (interleukin-6 [IL6], C-reactive protein [CRP], neutrophil gelatinase–associated lipocalin [NGAL], and translocator protein [TPSO]) with established neuroinflammatory underpinnings [16-20] to see whether the primary pain outcome has a statistical relationship to these neuroinflammatory-related metrics. The exploratory electroencephalogram (EEG) analyses will also be conducted to see whether either entropy [21], alpha power [22], or delta/alpha power ratio [23,24] can provide neuroinflammatory markers, which could correlate with postoperative pain outcomes. Finally, we will explore whether these neuroinflammatory markers seem to be mitigated by either the live music or active control intervention to explain the reduced pain reported by postsurgical patients in music intervention studies [2,20].

The primary objective is to see whether a live music intervention reduces pain perception compared to both recorded music active control and standard care control groups. The secondary objective is to explore the role of music in mitigating the neuroinflammatory response to surgery, for future hypothesis-directed research.

Methods

Study Design

The study will take place at the University Medical Center Groningen (UMCG), which has already hosted the Meaningful Music in Healthcare (MiMiC) live intervention [25]. The intervention study follows an on-off nonrandomized controlled trial (NCT) design [26]. The NCT is necessary for this particular intervention in practice because the live music intervention cannot easily be randomized to skip patients in the same ward without them hearing the music or seeing the musicians as they play for other patients and nurses.

In this NCT design, treatments and data collection will be conducted in 15 blocks over the course of 4 years. According to the 29-day treatment block, the three 5-day treatments (live music intervention, recorded music active control intervention, and standard care control) will be offered with a 7-day washout between treatments. The washout will minimize the number of participants whose hospital stay overlaps with another treatment. Based on the previous research (UMCG research register 201600541), we expect approximately 8 full data sets per 5-day treatment block.

Note that while the intended outcome of the music intervention is therapeutic (eg, experiencing reduced pain), the music intervention is conducted by conservatory-trained music practitioners but not by music therapists. Music therapists are licensed therapists who have a degree in music therapy including clinical training. The music practitioners in this study are primarily professional musicians who have taken 1 music-conservatory course and several internships to train them for clinical settings but they are not therapists.

Design procedures are chronologically displayed in Figure 1. Preoperative questionnaires will be collected to assess cognitive function (6-item cognitive assessment [6CIT]) [27,28] and musical background (excerpt from the Dutch Musical Background Questionnaire [DMBQ]) [29,30]. Postoperative data collection procedures per day of treatment include pain visual analog scale (VAS) ratings, heart rate (HR), and blood pressure measuring 4 times a day (before, directly after, 3-hour, and 6-hour postintervention). EEG electrodes will be applied once in the morning and 4 EEG recordings will be collected with VAS ratings, HR, and blood pressure (before, during, 3-hour, and 6-hour postintervention). A blood sample will be collected once daily and integrated with standard care as far as possible (eg, if blood is drawn as part of standard care, the sample will be collected from the same needle). A schedule of assessments may be found in Table 1. Daily dosage of pain medication as well as any incidence of delirium (delirium

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observation screening scale [DOSS]) [31] or POCD will be collected.

Figure 1. Chronological walk-through of the design procedures. After entering the ward, subsequent steps repeat per each day of treatment. Blood sample, blood pressure, and heart rate are part of standard care measurements and will be incorporated with standard care whenever possible. 6CIT: 6-item cognitive assessment; DMBQ: Dutch Musical Background Questionnaire; fEEGrid: face electrode grid for electroencephalogram recordings; MiMiC: Meaningful Music in Healthcare; VAS: visual analog scale.

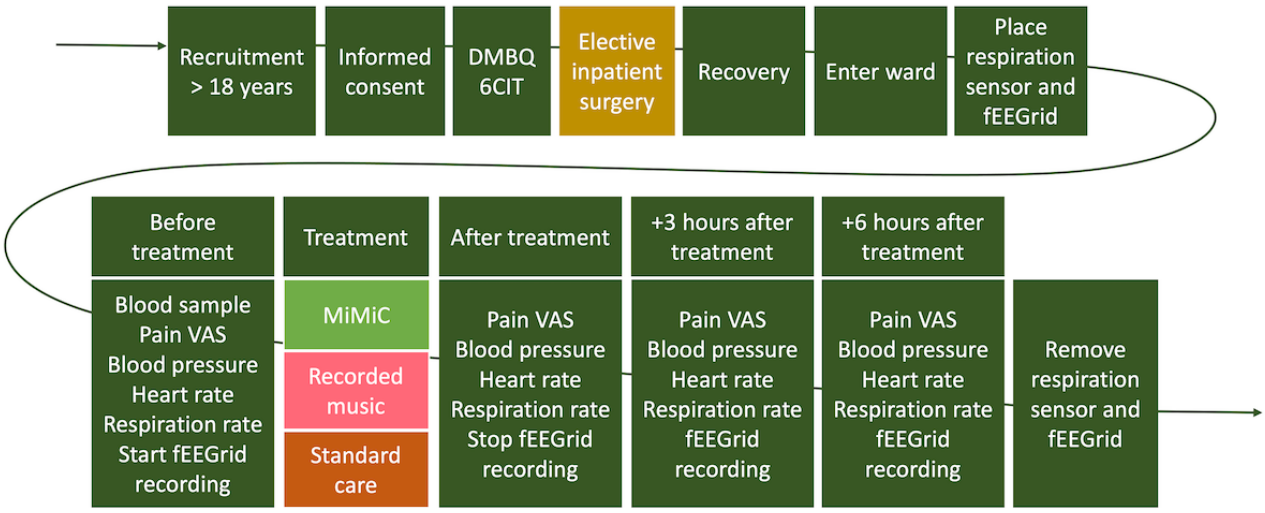


Table 1. Schedule of procedures.

Time	Procedures	Duration (minutes)
Preoperative	• Six-item cognitive assessment • Dutch Musical Background Questionnaire excerpt	7.5 and 4.5 (total 12)
Postoperative		
9 AM	• fEEGrid[a] preparation and placement • Respiration biosensor placement • Blood vial[b]	10
10:30 AM	• VAS[c] rating, HR[d], respiration rate, blood pressure, and start EEG[e] recording	5
10:40-11 AM	• MiMiC[f] or recorded music or no intervention • VAS rating, HR, respiration rate, blood pressure, and stop EEG recording	20
2 PM	• VAS rating, HR, respiration rate, blood pressure, and EEG recording	15
5 PM	• VAS rating, HR, respiration rate, blood pressure, and EEG recording	15
5:15 PM	• Remove fEEGrid and respiration biosensor	5
Total	• N/A[g]	70

[a]fEEGrid: face electrode grid for EEG recordings.

[b]The blood vial collection will be integrated into standard care as much as possible, thus, the time may not be 9 AM if other blood collection is at a different time.

[c]VAS: visual analog scale.

[d]HR: heart rate.

[e]EEG: electroencephalogram.

[f]MiMiC: Meaningful Music in Healthcare.

[g]N/A: not applicable.

Population (Base)

The study will include patients who have undergone elective surgery in the UMCG and are hospitalized for at least 1 day following surgery. All patients must be 18 years or older and able to make their own decisions. Patients must further be able to hear music with normal or corrected normal hearing (ie, a hearing aid).

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Inclusion Criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria: (1) 18 years or older, (2) postsurgery hospitalization (all surgery types), (3) elective surgery, (4) able to hear music, (5) able to give informed consent, and (6) able to communicate.

Recruitment

Patients will be informed as soon as the date of hospital admission is set in the weeks that the study is planned. The patient will receive an information letter and informed consent from the provider or it will be sent to them by email. A member of the research team will contact the patients after a minimum of 24 hours for participation and answer possible questions. Patients will have up to the time of their surgery to decide, allowing for time to fill out the preoperative questionnaires. Consent can be withdrawn at any time at which point all data collection and treatment will stop.

Ethics Approval

This protocol has been approved by the Central Medical Ethics Committee of the UMCG (METc2021.359) and is registered with the Netherlands central commission of human research (CCMO-register number NL76900.042.21). The informed consent letter is written in plain, nonacademic Dutch with no medical jargon. Only pseudoanonymized (deidentified) data will be published. Patients participating in the study will receive a small token gift (such as a hand lotion or lip balm).

Study Parameters and End Points

Main Study Parameter and End Point

Subjective pain ratings are determined with a VAS rating (0-10) [1].

Secondary Study Parameters and End Points

The secondary study parameters (Table 2) and end points are as follows: (1) objective pain metric (volume of administered pain medication); (2) respiratory rate and tidal volume; (3) HR; (4) blood pressure; (5) neuroinflammation blood markers (IL6, NGAL, CRP, and serum TPSO); (6) behavioral indicators of neuroinflammation (delirium [31] and POCD incidence); and (7) EEG markers of neuroinflammation (alpha power, delta/alpha power ratio, and entropy).

Table 2. Secondary study parameters.

Outcome	Metric	Statistics
Objective pain measure	Pain medication dosage (ccs)	Chi-square test
Neuroinflammation, blood markers	IL6[a], NGAL[b], CRP[c], and serum TPSO[d]	*F* test (RM[e] ANOVA, pre-post)
Neuroinflammation, behavioral indication	Incidence delirium and incidence POCD[f]	*F* test (one-way ANOVA)
Neuroinflammation, EEG[g] indication	Alpha power, alpha/delta power, and entropy	*F* test (RM ANOVA same as primary)
Neuroinflammation, physiological	HR[h], respiration rate, and blood pressure	*F* test (RM ANOVA same as primary)

[a]IL6: interleukin-6.

[b]NGAL: neutrophil gelatinase–associated lipocalin.

[c]CRP: C-reactive protein.

[d]TPSO: translocator protein.

[e]RM: repeated measures.

[f]POCD: postoperative cognitive decline.

[g]EEG: electroencephalogram.

[h]HR: heart rate.

Other Study Parameters

Other study parameters used in this study are as follows: (1) comorbidities (Charlson comorbidity index) [32]; (2) complications (Clavien Dindo [33] and nurse-sensitive outcomes [34]); (3) postoperative days (T0=surgery); (4) surgery characteristics (invasiveness, etc) [20]; (5) musical background (excerpt from DMBQ) [30]; (6) age; and (7) presurgery cognitive testing [22] (eg, 6-item cognitive impairment score) [28].

Treatment Allocation

This study will take the form of an on-off NCT [26]. An on-off NCT takes into account real-world setting limitations of certain intervention types and allocates participant inclusion by alternation. The main reason for this is that MiMiC is a well-researched intervention, whose practical implementation is not suited for randomly selected participants to not participate. On the one hand, musicians will visit the nurses' station and play music in various rooms around the ward; thus, it is not possible to prevent participants who may be allocated non-MiMiC treatment from hearing the live music. On the other hand, a central tenet of the MiMiC intervention is inclusion and participation, thus "rejecting" patients who would want to participate in music they hear on the ward, on the basis of trial group allocation, goes against the spirit of the intervention.

In contrast, the NCT relies on the randomness of who is scheduled for surgery during a given intervention week but does not exclude any patient from the activity being conducted (listening to live or recorded music). Therefore, the treatment schedule (live music intervention, recorded music active control, and standard care control) will be predetermined months in advance, and the patients included will be offered whichever

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treatment is occurring during their hospital stay. The patients will, however, be asked for their consent before they are informed which treatment will be offered during their surgery recovery. This will attempt to prevent patients who are initially biased for inclusion based on their affinity to music or not.

Study Procedures

After patients are recruited to the study, they will be allotted to the treatment occurring during the scheduled postoperative hospital stay. Noninvasive procedures include preoperative cognitive testing (6CIT), postoperative VAS pain ratings, HR, blood pressure, respiration rate, and EEG recording. Invasive procedures include obtaining blood samples, after which the serum will be analyzed in a laboratory for neuroinflammatory markers IL6, NGAL, CRP, and serum TPSO. An example schedule of procedures can be found in Table 1.

Primary End Point

The main end point, VAS pain ratings, requires patients to subjectively rate their pain on a plastic VAS where they move a tick mark to the desired location on a 0-10 scale [1].

Secondary End Points

The secondary end points, HR and blood pressure, will be collected from standard equipment on the ward at the time of obtaining VAS pain ratings.

Pulmonary Ventilation

Respiration rate and tidal volume have been linked to subjective pain experience in the literature [4]. Therefore, in order to see whether our pain findings extend from subjective to objective physiological measures, we will explore the association between these 2 objective metrics and subjective pain VAS ratings. A wearable biosensor that measures pulmonary ventilation metrics [35] will be placed on the chest of patients with an adhesive sticker and removed at the end of the day.

Blood Marker Analysis

One 10-ml vial of blood will be collected per day resulting in a maximum of 5 vials of blood over 5 days. The first sample must be taken before the first assigned intervention. Blood samples will be collected together with standard care insofar as possible. Serum extracted from blood samples will be processed by the Haemoscan lab and evaluated for the presence of 4 markers associated with neuroinflammation (IL6, NGAL, CRP, and serum TPSO; see “Introduction” section).

EEG Recordings

As opposed to typical electrode setup with, for example, a cap, the face electrode grids for EEG recording require minimal preparation of skin and are quickly applied. Each morning, the patient’s face will be cleaned and prepared with exfoliating gel, and electrodes will be applied with adhesive tape. The face electrode grid for EEG recordings will remain on the patient from morning until evening, spanning the first and last pain VAS ratings. Actual recordings will occur 4 times a day, in 15-minute increments, coinciding roughly with the times that pain VAS ratings are collected (before intervention, during intervention, 3-hour, and 6-hour postintervention). During the 15-minute EEG recording windows, the patients will be instructed to remain seated or lying doing a consistent activity of their choice, or otherwise as instructed during the assigned treatment.

Neuroinflammatory-Related Complications

After 30 days postsurgery, patient medical dossiers will be consulted, and any incidence of delirium and POCD will be recorded.

Other Parameters

A short, 6-item questionnaire [27,28] will be added to the standard preoperative intake in order to assess preoperative cognitive status, as well as a short questionnaire about the musical background (excerpt from the DMBQ) [29,30]. Both the cognitive status and the musical background will help to interpret the results. The preoperative cognitive status will serve as a baseline for postoperative cognitive status as well as alpha power in EEG recordings. The musical background will be assessed as a possible explanation for the success of the live or recorded music interventions. Other complications (classified according to Clavien-Dindo [33], nursing-sensitive outcomes such as dehydration and falling [34]) will be explored for changes in the music groups compared to care-as-usual to derive hypotheses for future studies.

Statistical Analysis

The primary outcomes of this study are VAS subject pain ratings. The *F* test is described immediately below. Statistics will be conducted with SPSS (IBM Corp) or equivalent software [36].

Primary Study Parameters

Pain ratings will be collected 4 times a day with a VAS. VAS mean and SD will be reported, and box plots, histograms as well as *P* values for Kolmogorov-Smirnov tests will be evaluated for normality of distribution. A univariate, one-way repeated measures (RM) ANOVA will be conducted with factors group (live music intervention, recorded music active control, and standard care control) by time points (1, 2, 3, 4). The α significance threshold will be .05. The result of interest is the significance of the training×time point interaction, that is, whether the course of the data across time points was altered by the training type. Data are planned with 4 time points; in case of up to 2 missing time points, data will be interpolated [37]. Cases with more than 2 missing time points will be excluded from the analysis. Alternatively, if the residuals of the ANOVA are not normally distributed, a similar Kruskal-Wallis one-way ANOVA will be conducted.

Secondary Study Parameters

For metrics that are collected on the same schedule as the VAS (EEG alpha power, delta/alpha power ratio, entropy metrics, HR, respiration rate, and blood pressure), the values per participant will be entered into the same *F* test described for the VAS ratings (as well as correlated with other baseline parameters as described in the “Other Parameters” section). For blood marker metrics that have 2 data collection points, a similar RM ANOVA will be conducted, but with 2 as opposed to 4 measures, and a significant interaction between treatment and time point would indicate whether treatment significantly

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impacted the amount of the neuroinflammatory blood marker. Categorical incidence metrics (delirium and POCD) will be evaluated with a one-way ANOVA to determine whether treatment impacted these neuroinflammatory-related complications. Delirium and signs of delirium will be perceived using the DOSS. The DOSS is a screening instrument for delirium, consisting of 13 items, and will be filled by a registered nurse during hospital admission until discharge. Nurses have frequent contact with the patients and are in a good position to observe behavior changes 24 hours a day when patients are admitted. The DOSS is already part of a routine in the surgical wards and all registered nurses are already trained. Likewise, scalar pain medication dosage will be averaged over 24-hour periods per patient and entered into a chi-square test to determine whether the dosage was significantly different across the 3 treatment groups. As this is exploratory and serves to inform future hypothesis-directed testing, we will not correct for multiple comparisons.

Other Study Parameters

Posthoc analyses will be conducted to inform recommendations for participant grouping in future studies. Continuous baseline parameters (eg, age; see "Other Parameters" section for a full list) will be treated as covariates in an ANOVA in order to see whether the addition of these elements improves the model for each outcome. Similarly, categorical baseline parameters (eg, type of surgery) will be coded and entered as an additional factor (two-way RM ANOVA: treatment×baseline×time point) to see whether the additional factor can explain more variance than in the primary analysis model.

Power

The sample size was calculated using G*Power 3.1 [38], an industry-standard software. Below, we explain the parameters for an RM between-subjects univariate ANOVA as well as the final sample size. The calculation was based on the desired ability to detect a within-between interaction (intervention group×time point), with recommended internal settings from [39], which would effectively indicate whether the live music intervention altered the slope of outcome measurements compared to the recorded music or do-nothing control groups.

The effect size (partial η^2=0.051, converted to f=0.2318206) was determined from a retrospective RM ANOVA with published data [1].

- Alpha: As we have a single quantitative outcome measure, alpha may remain at the conventional .05 significance threshold.
- Power: Following recent recommendations to set power above the typical 0.8 to 0.9 and higher [40], the threshold was set at 0.9.
- Number of groups or measurements: The design calls for 3 groups, with 4 RM (see "Study Design" section; before treatment, after treatment, 3-hour, and 6-hour follow-up) for each participant.
- Nonsphericity correction: As mentioned earlier, retrospective analyses were conducted with the data published in [1]. The ANOVA conducted with that data passed the assumption of sphericity (*P*=.07); therefore, no correction (1) was entered in the G*Power calculation.
- Sample size: The sample size (n=327, Table 3) outputted from G*Power represents the total number of participants in a 3-group design required to achieve 0.9 power with an effect size of ~0.232-109 per group. Padding for a 10% dropout rate raises the per group n to 120, for a total N of 360.

Table 3. G*Power sample size calculation.

Parameters	Value
Input parameters	
Effect size *f*(*V*)	0.2318206
α err prob	.05
Power (1−β err prob)	0.9
Number of groups	3
Number of measurements	4
Nonsphericity correction ε	1
Output parameters	
Noncentrality parameter λ	17.5732385
Critical *F*	2.1078920
Numerator df	6.0000000
Denominator df	972
Total sample size	327 (109 per group)
Actual power	0.9007901

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Results

The medical ethics committee of the UMCG approved the study in April 2022. This study began recruiting its participants in June 2022 and upon submission had recruited and collected data from 5 participants. Preliminary data analysis will commence once enough data have been collected to reach 0.8 power. Data collection is expected to be finished in 2026. The study results will be available within 1 year of completed data collection and shared in local, national, and international meetings within the medical, scientific, hospital administrative, and medical professional communities as well as the general public.

Discussion

Principal Findings

Previous studies have shown that postoperative pain management can be supplemented with music intervention. Yet, little is known about the benefits of live versus recorded music, or what physiological mechanisms may be mitigating pain perception as a response to listening to music. This NCT will compare the MiMiC live music intervention with listening to recorded music and care-as-usual. The primary objective is to see whether pain VAS ratings differ across the 3 conditions, and the secondary objective is to see whether postoperative neuroinflammation is reduced as a response to listening to music.

The strength of this study is the inclusion of preoperative assessments to establish some baseline characteristics of patients. First, the preoperative musical background questionnaire (selected items from [30]) assesses the estimated weekly hours of music listening as well as listening preferences for musical genre and whether or how the participant is musically trained. This provides us the opportunity to analyze how the extent of musical exposure may affect the primary outcome (pain VAS) of the intervention; depending on the strength of these findings, we may be able to even help inform future music interventions according to preoperative musical habits. Second, the preoperative cognitive assessment (6CIT) [28] serves as an important baseline for several secondary outcomes that may help to account for variability among the 3 intervention arms that otherwise might be attributed to the treatment. Specifically, the 6CIT will inform the interpretation of the postoperative cognitive status, and it may predict alpha power in EEG recording [22] that in turn may be linked to delirium [23,24]. If this proves to be the case, the preoperative cognitive status might be investigated in the future as a method to inform more at-risk patients who could especially benefit from supplementary nonpharmacological interventions [41] such as live or recorded music [42].

Limitations

While postoperative pain is common to most patients undergoing surgical intervention in hospital, other characteristics surrounding the surgery (eg, type of surgery, duration of surgery, and underlying medical need for surgery) are widely varied across patients. Thus, a limitation of the study is that we will have a heterogeneous patient group. Considering that reduced pain VAS among patients experiencing MiMiC live music intervention compared to care-as-usual was previously a robust finding in a heterogeneous patient group [1], we do not consider our primary outcome to be affected by this heterogeneity. However, secondary outcomes related to finding neurophysiological markers of inflammation, and whether they are influenced by a music intervention, might be greatly affected by this heterogeneity. Moreover, the short duration of the intervention may further limit proper interpretation of inflammatory biomarkers, since previous studies have found neuroinflammatory biomarkers readings to be informative to overall interpretation 5 to 14 days after a medical event [43,44]. We may therefore form posthoc groups with similar surgery types when evaluating secondary outcomes, which could inform future hypotheses for further, longer term clinical research on music interventions and postsurgical neuroinflammation.

Conclusions

Upon completing this study, we will contribute a systematic comparison of the effects of live versus recorded music on postoperative pain. This study can ultimately inform policy makers as to the benefits to patient pain outcomes when incorporating live versus recorded music in postoperative recovery settings.

Data Availability

When results from this trial are available, data sets will be deposited in a publicly available repository.

Conflicts of Interest

None declared.

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Abbreviations

6CIT: 6-item cognitive assessment
CRP: C-reactive protein
DMBQ: Dutch Musical Background Questionnaire
DOSS: delirium observation screening scale
EEG: electroencephalogram
HR: heart rate
IL6: interleukin-6
MiMiC: Meaningful Music in Healthcare
NCT: nonrandomized controlled trial
NGAL: neutrophil gelatinase–associated lipocalin
POCD: postoperative cognitive decline
RM: repeated measures
TPSO: translocator protein
UMCG: University Medical Center Groningen
VAS: visual analog scale

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Protocol

Violence Against Paramedics: Protocol for Evaluating 2 Years of Reports Through a Novel, Point-of-Event Reporting Process

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Abstract

Background: Violence against paramedics has been described as a serious public health problem with the potential for significant physical and psychological harm, but the organizational culture within the profession encourages paramedics to consider violence as just "part of the job." Therefore, most incidents of violence are never formally documented. This limits the ability of researchers and policy makers to develop strategies that mitigate the risk and enhance paramedic safety.

Objective: Following the development and implementation of a novel, point-of-event violence reporting process in February 2021, our objectives are to (1) estimate the prevalence of violence and generate a descriptive profile for incidents of reported violence; (2) identify potentially high-risk service calls based on characteristics of calls that are generally known to the responding paramedics at the point of dispatch; and (3) explore underpinning themes, including intolerance based on gender, race, and sexual orientation, that contribute to incidents of violence.

Methods: Our work is situated in a single paramedic service in Ontario, Canada. Using a convergent parallel mixed methods approach, we will retrospectively review 2 years of quantitative and qualitative data gathered from the External Violence Incident Report (EVIR) system from February 1 2021 through February 28, 2023. The EVIR is a point-of-event reporting mechanism embedded in the electronic patient care record (ePCR) developed through an extensive stakeholder engagement process. When completing an ePCR, paramedics are prompted to file an EVIR if they experienced violence on the call. Our methods include using descriptive statistics to estimate the prevalence of violence and describe the characteristics of reported incidents (Objective 1), logistic regression modeling to identify high-risk service calls (Objective 2), and qualitative content analysis of incident report narratives to identify underpinning themes that contribute to violence (Objective 3).

Results: As of January 1, 2023, 377 paramedics—approximately 1 in 5 active-duty paramedics in the service—have filed a total of 975 violence reports. Early analysis suggests 40% of reports involved a physical assault on the reporting paramedic. Our team is continuing to collect data with more fulsome analyses beginning in March 2023. Our findings will provide much-needed epidemiological data on the prevalence of violence against paramedics in a single paramedic service, its contributing themes, and potential risk factors.

Conclusions: Our findings will contribute to a growing body of literature demonstrating that violence against paramedics is a complex problem that requires a nuanced understanding of its scope, risk factors, and contributing circumstances. Collectively, our research will inform larger, multisite prospective studies already in the planning stage and inform organizational strategies to mitigate the risk of harm from violence.

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KEYWORDS

paramedic; emergency medical services; emergency; violence; harm; abuse; workplace violence; work; safety; occupational health; reporting; epidemiology; epidemiological; point-of-event: development; implementation; mixed methods

Introduction

Background

At the start of the COVID-19 pandemic, paramedics had some of the highest rates of posttraumatic stress injury (PTSI) among public safety personnel (PSP) in Canada. A recent cross-sectional survey of PSP in Canada found that 1 in 4 participating paramedics met the screening criteria for posttraumatic stress disorder (PTSD), 1 in 3 for major depressive disorder, and 1 in 3 for an anxiety disorder [1], with nearly half of the paramedics meeting the screening criteria for a current mental disorder [2]. Related research has also demonstrated high rates of exposure to trauma [3-5], disturbed sleep [6], adverse childhood experiences [7], chronic pain [2,8], and alarming rates of suicidality [9]—a situation that has since been described in research and policy as a "crisis in Canada" [10,11].

One dimension of the crisis that has received comparatively little attention is the exposure of paramedics to acts of intentional workplace violence. Although we know from previous research that situations involving threats to physical safety among PSP are associated with an increased risk of PTSI [3,5,12,13], the specific contribution of violence remains understudied. Part of the problem is that—in the absence of significant physical injuries—incidents of violence often go unreported. For example, in a 2014 survey of paramedics, over 75% disclosed having been subjected to workplace violence in the past calendar year. Despite these acts of violence negatively impacting their job satisfaction and home life, less than 20% of survey participants took any action to report the incidents to supervisors or the police [14]. This parallels a growing body of research internationally that indicates that violence against paramedics is a "serious public health problem" [15] that remains "vastly underreported" [16].

The organizational culture within the paramedic profession appears to contribute significantly to underreporting. In a qualitative study of paramedics in Ontario, Canada, we identified a complex interplay of organizational culture features in sustaining cultural norms that lead paramedics to downplay the significance of incidents and effectively position the ability for paramedics to "brush off" violent encounters as an expected professional competency [17]. Underreporting hinders the ability of researchers and policy makers alike to develop solutions to mitigate risk and enhance paramedic safety, as the scope of the problem, its contributing risk factors, and the potential harms remain poorly understood. Given the high rates of mental disorders among paramedics [1] and a growing hostility toward health care providers during the COVID-19 pandemic [18], the need for action has never been more apparent. Critical to intervening, however, is the need for robust epidemiological data to understand the problem more fully.

The EVIR Process

The External Violence Incident Report (EVIR) (Multimedia Appendix 1) is a novel, point-of-event reporting process embedded in the electronic patient care record (ePCR) in Peel Regional Paramedic Services (PRPS) in Ontario, Canada. Developed in 2020 through an extensive gap analysis, stakeholder consultation, and pilot testing process [19], the EVIR was launched in February 2021. When completing an ePCR after a 911 service call, paramedics in Peel Region are prompted to complete an EVIR if they experienced any form of verbal abuse, intimidating behavior, sexual harassment, or physical or sexual assault during the call. Using a series of drop-down menus and free-text narrative boxes, the EVIR gathers information about the type of violence, its source, and contributing circumstances in addition to administrative data (eg, time of day, call type, patient acuity, etc) that automatically populate from the corresponding ePCR. The goal of developing the EVIR was to produce a reporting process that minimized the administrative burden on the reporting paramedics by leveraging technological efficiencies (eg, by auto populating relevant fields) and minimize the amount of manual free-text entries or nonrelevant fields. The result is an accessible, user-friendly, and culturally accepted means of reporting violent incidents in real time.

Aim and Research Objectives

Following a year since the implementation of the EVIR, we aim to explore the prevalence of, risk factors for, and circumstances that contribute to incidents of reported violence against paramedics in Peel Region, Ontario, Canada. Using a convergent parallel mixed methods approach [20], our objectives are to (1) describe the prevalence and characteristics of violence against paramedics in the Peel Region; (2) explore features of 911 service calls associated with an increased risk of violence; and (3) qualitatively explore underpinning circumstances that contribute to incidents of violence, including harassment based on gender, race and related grounds, and sexual orientation.

Methods

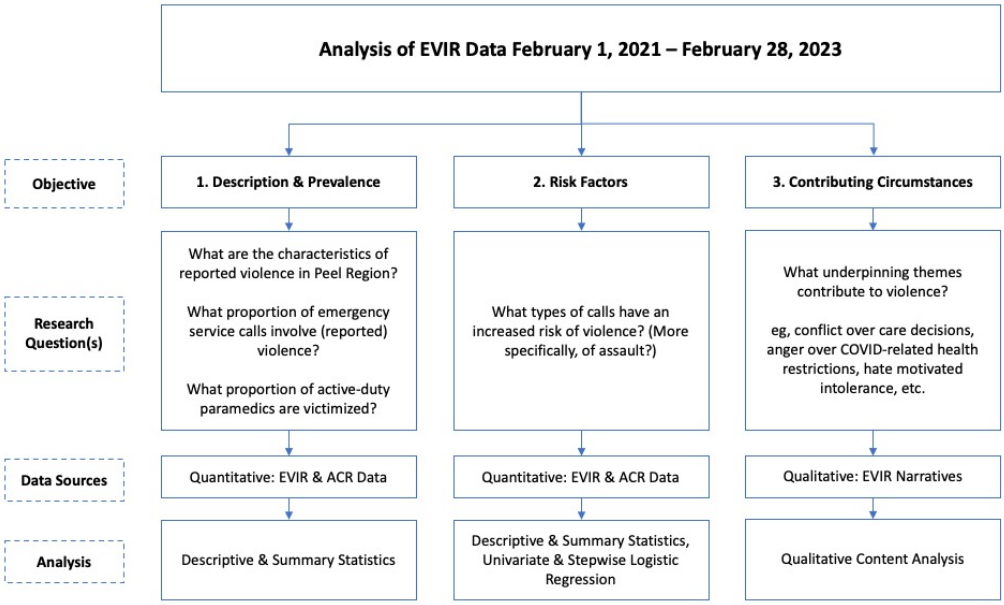
Overview

This program of research is situated within a realist ontology [21] and uses a convergent parallel mixed methods approach [20] to broadly explore the prevalence, risk factors, and circumstances that contribute to incidents of violence against paramedics. We provide an overview of our methods blueprinted for each research objective in Figure 1. In brief, our approach includes calculating descriptive and summary statistics to characterize the prevalence and features of reported violence (Objectives 1 and 3) and logistic regression modeling to explore risk factors (Objective 2). To address Objective 3, we will use qualitative content analysis [22] within an interpretivist epistemology [23] to identify and define themes that contribute to incidents of reported violence. Data for the research will be

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abstracted from completed EVIRs and other administrative data routinely gathered from ePCRs.

Figure 1. Overview of project objectives, research questions, data sources, and analysis plans. ACR: Ambulance Call Report; EVIR: External Violence Incident Report.



Ethical Considerations

Research ethics review for this program was submitted to the University of Toronto Research Ethics Board (REB protocol number 44162). All data used in the research will be scrubbed of direct identifiers (eg, patient or paramedic names, addresses of call locations, and call identification numbers). Anonymized alphanumeric participant identification codes will be substituted for paramedic names and the original linkages destroyed after deidentification. We will work to ensure that any potential combinations of indirect identifiers (particularly narrative descriptions of incidents) are presented in such a way as to reduce the risk of reidentification to the greatest degree reasonably possible.

There are 4 participant groups to whom consent requirements apply (Table 1). The EVIR has an embedded passive consent process wherein reporting paramedics (Group C) who do not want the information contained in the report used for research purposes can opt out by checking a box. During training on the EVIR, paramedics in the service were made aware that although the EVIR is not specifically intended as a research intervention per se, data from the EVIR may be subsequently used for research purposes in much the same way that health records are used retrospectively in medical research. Because of the sensitive nature of the data, we informed paramedics of the ability to indicate a preference (via the opt-out mechanism) for the future use of a specific report. This affords the paramedics the ability—at the time of reporting—to dissent to the future use of the report for subsequent research purposes.

Table 1. Participant groups included in the analysis.

Group	Violent incident	No violent incident
Patient	A	B
Paramedic	C	D

The Tri-Council Policy on the Ethical Conduct for Research Involving Human Participants [24] sets out specific criteria under which alterations to the consent process can be contemplated: (1) where the research involves no more than minimal risk to the participants, (2) the alteration to the consent requirements is unlikely to adversely affect the welfare of the participants, (3) it is impossible or impractical to conduct the research if prior consent of the participants is required, and (4) the precise nature and extent of the alteration to consent is defined. We will seek to waive the requirement for informed participant consent from patients (Groups A and B) on the grounds of minimal risk, necessity, and impracticality. Particularly for Group A, seeking prior consent from alleged perpetrators of violence would pose legitimate safety risks to the investigators. The information gathered from Group B is minimal and contains no direct or indirect risk of identification. Finally, no data are being collected directly from Group D, and we do not anticipate any risk of direct or indirect identification or harm to nonreporting paramedics.

Setting and Context

This research is situated in the Regional Municipality of Peel in Ontario, Canada. The PRPS is the publicly funded, sole provider of land ambulance paramedic services to this region, employing approximately 700 primary and advanced care paramedics (PCP/ACPs) [25]. Peel Region is divided geographically into 4 quadrants with 1 central paramedic headquarters facility per quadrant (called “divisions”).

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Paramedics report for work at 1 of the 4 divisions and are then deployed to several smaller community stations strategically located in a "hub and spoke" model. Crew configurations include PCP-PCP, ACP-PCP, and solo responder (of either classification) models on emergency response units. PRPS responds to over 130,000 emergency calls per year, making it the second-largest paramedic service organization in the province in terms of staffing and caseload. Documentation standards mandate the completion of an Ambulance Call Report (ACR) for any service call for which paramedics arrive on the scene. In 2019, the service launched the External Violence Against Paramedics working group with the 2-fold mandate of gathering data to develop evidence-informed strategies to mitigate the risk of violence and enhance paramedic safety.

In 2020, 1 year before the implementation of the EVIR, the service recorded a total of 60 documented incidents of injury resulting from workplace violence, with the type of violence and the requirement for injury reporting left to the discretion of the affected paramedic and their supervisor. Following the development of the EVIR, the service released a new policy for staff that outlines the roles and responsibilities of paramedics and service leadership in identifying, intervening in, and reporting incidents of violence. Importantly, the new policy specified the types of violence to be captured as part of the reporting process with definitions drawn from a review of the literature and relevant occupational health and safety legislation (Table 2).

Table 2. Definitions of incident types in the External Violence Incident Report (EVIR)[a].

Type of violence	Definition
Verbal abuse	Offensive or hateful language; yelling or screaming with the intent of frightening the paramedic
Intimidation	Purposely threatening, following, or using gestures to offend or frighten the paramedic
Assault	Physical attack or attempt to attack; punching or kicking or using a weapon with the intent of causing bodily harm
Sexual harassment	Sexual propositioning or unwelcome sexual attention from a perpetrator. Humiliation, remarks, or offensive jokes with sexual overtones, suggestive looks, or physical gestures
Sexual assault	Indecent assault. Brushing, touching, or grabbing of genitals or breast area

[a]Adapted from Bigham et al [14] with language from the Ontario Occupational Health and Safety Act.

Objective 1: Prevalence and Characteristics

Research Questions

Objective 1 is concerned with answering the following research questions: (1) What proportion of 911 service calls involve exposure to reported violence? (2) What proportion of active-duty paramedics report experiencing violence? (3) What are the characteristics (eg, type and source of violence, location, time of day, etc) of incidents of reported violence?

Data Sources

A detailed accounting of the variables included in this study is provided in Multimedia Appendix 2. We will abstract the following administrative data from all ACRs completed during the study period: paramedic station of origin (division), paramedic level of care (eg, PCP/ACP), date, call received time, pick-up location code, dispatch priority, dispatch problem code, primary problem code, and return priority.

Where an EVIR is completed for a particular service call, we will additionally abstract the following fields from the violence report: report creator, incident type, source of violence, location of the incident, contributing circumstances (eg, alcohol intoxication, drug use, cognitive impairment), police present (yes/no), police response helpful (yes/no; narrative), and address hazard flag (communicated, created/extended).

The data will be assembled in Microsoft Excel (Microsoft Corp). An anonymized alphanumeric participant code will be substituted for the report creator's name by the data custodian.

Analyses

We will use descriptive and summary statistics to characterize the data, including means and medians with measures of dispersion for continuous data and counts and percentages for categorical data. Continuous variables will be plotted and assessed for normality, both visually and with skewness and kurtosis tests. We will then calculate the proportion of paramedics reporting exposure to violence and the average number of reports per paramedic. We will assess for group differences in reporting using 1-way ANOVA for continuous variables or chi-square for proportions, with significance set at $P<.05$. All analyses will be carried out in SPSS (version 28; IBM Corp).

Objective 2: Risk Factors

Research Questions

Objective 2 is concerned with answering the following research questions: (1) What characteristics of emergency calls are associated with an increased risk of reported violence? (2) Relatedly, what characteristics of emergency calls are associated with an increased risk of a violent encounter resulting in any form of assault?

The goal here is to assess the degree to which characteristics of emergency calls that are typically known to the responding paramedics before arrival at the scene can be used to identify service calls that have a higher risk of violence. This information can be used to develop risk mitigation strategies, such as coordinated responses with paramedic supervisors, police, or mobile crisis intervention teams.

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Data Sources

Data for Objective 2 will be drawn from the ACR database and completed EVIRs with all the same data points listed in Objective 1.

Analyses

Our outcomes of interest are (1) whether an EVIR is filed for a particular service call ("EVIR"; yes/no) and (2) whether a service call results in a reported assault on a paramedic. Because paramedics can select multiple types of violence on the EVIR (eg, verbal abuse, assault, and intimidation), the assault outcome will require collapsing the incident type categories into a new output variable of ("Assault_Paramedic"; yes/no) that captures incidents that include combinations of violence that involve either physical or sexual assault.

Potential covariates in our analysis will include service call characteristics that are typically known to the responding paramedics at the point of dispatch. These include the day of the week, time of day, call/pick-up location (26 levels, eg, residence, street, restaurant/bar), dispatch problem code (55 levels, eg, unconscious, drug/alcohol overdose, dyspnea), patient sex (male/female/other), and patient age.

Paramedics in Peel Region normally work 12-hour day or night shifts with additional staff scheduled during "peak" demand periods (broadly, 10 AM to 10 PM). However, in our analysis, we will define 3 nonoverlapping 8-hour "buckets" adapted from paramedic shift scheduling: day (6 AM to 1:59 PM), afternoon (2 PM to 9:59 PM), and overnight (10 PM to 5:59 AM).

Given the large number of variables, our modeling approach involves several preliminary steps to whittle down the list of covariates to be included. We will first calculate frequencies by running cross tabulations for each variable with our outcomes of interest. Levels of variables (eg, pick-up location, dispatch problem code) with fewer than 10 observed events will be removed. Next, we will run univariate logistic regression analyses for each variable level in descending order of observed proportion. Variables that are significantly associated with each outcome at a threshold of $P<.10$ will be retained for the next stage of model construction.

Our interest in constructing multivariate logistic regression models is in the adjusted odds ratios (AORs) of the individual covariates rather than the predictive capacity of the model as a whole. We will construct our adjusted models using a forward step approach in declining order of significance (ie, starting with the smallest P values) with the condition that all included variables must retain a $P<.05$ with AORs whose confidence intervals do not include the null value. Finally, we will test for interactions between the pick-up location code and the dispatch problem code, constructing terms based on the significance of individual covariates in univariate modeling and introducing terms sequentially to the adjusted models for evaluation. Interaction terms that do not meet the significance threshold will be removed from the model.

The total number of included covariates will also necessarily be constrained by the observed event rate; consequently, we will not exceed an event-to-covariate ratio of less than 10:1.

Objective 3: Contributing Circumstances

Research Questions

Objective 3 is concerned with answering the following research questions: (1) What underpinning themes contribute to violence against paramedics? (2) Relatedly, what proportion of EVIRs involve harassment on grounds that are protected under the Ontario Human Rights Code (ie, gender, race/ethnicity, and sexual orientation)? (3) What is the potential contribution of conflict over COVID-19 health measures/restrictions to incidents of reported violence?

Data Sources

Each EVIR contains a space for the reporting paramedic to enter a narrative description in response to the "what happened?" prompt. During the rollout phase, paramedics were instructed to be detailed and specific in documenting the details of violent incidents and to include direct quotes where appropriate. We will abstract these free-text narratives for analysis.

Analyses

Approaching the data from an interpretivist epistemology [23,26], we will use qualitative content analysis [22,27] to answer each of our research questions. Qualitative content analysis is a technique for identifying themes in textual data using iterative, in vivo codes or the application of an a priori coding framework. As an analytical strategy, qualitative content analysis remains "close" to the surface of the data, avoiding the sort of deep inferences or abstractions that are germane to other qualitative methodologies (ie, grounded theory or ethnography). For Research Question 1, the incident narratives will be abstracted and imported into NVivo for Mac (QSR International) for analysis. We will inductively code the text using techniques described by Charmaz [28], with successive rounds of open [29] and then focused [30] coding to identify themes and then define categories based on conceptual similarity. This iterative approach will allow us to explore circumstances that underpin incidents of reported violence, such as conflict over patient care (eg, choice of hospital) that may escalate into violence.

For Research Question 2, we are guided by language in the Ontario Human Rights Code [31]. In brief, the law explains that all persons have the right to be free from discrimination and harassment based on 14 protected grounds. The code defines harassment as "engaging in a course of vexatious comment or conduct that is known or ought to be known to be unwelcome" [31]. The protected grounds include, among other things, age, disability, gender identity and expression, race and related grounds, and sexual orientation, with definitions for each derived from legislation and case law in Canada [31]. We are including 3 broad protected grounds in our analysis (Table 3), with the decision to exclude the remaining protected grounds because of the unreasonably high potential to identify study participants (eg, disability, age, citizenship, family status, marital status) or lack of plausibility (eg, record of criminal offenses, receipt of social assistance in housing).

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Table 3. Included grounds with defining language drawn from the Ontario Human Rights Code.

Ground	Defining language
Gender identity and gender expression	Gender identity is each person's internal and individual experience of gender. Gender expression is how a person publicly presents their gender.
Race and related grounds	Race is a social construct that includes geographic, historical, political, economic, social, and cultural factors, as well as physical traits. The code also includes ancestry, ethnicity, religion, and place of origin in this category.
Sexual orientation	Sexual orientation covers the range of human sexuality from lesbian and gay to bisexual and heterosexual.

With respect to potentially vexatious words, we will reference the definitions for each word (eg, fuck, bitch, cunt, fag, cock, etc) provided in the *Urban Dictionary* as a sensitizing concept to aid in the determination of the word's potential to offend. The *Urban Dictionary* is a Wikipedia-style website that allows users to populate definitions for specific words based on contemporary usage in society [32].

To prepare the data, we will abstract the free-text incident narratives into a Microsoft Excel (Microsoft Corp) file for analysis. Drawing on the definitions for harassment and protected grounds provided in the code, we will use independent raters to assess the proportion of EVIRs that involve harassment on 1 or more protected grounds of interest. Specifically, we will recruit 2 research assistants with knowledge of the paramedic context and legal experience (ie, through university training or labor relations involvement) for this task. Following a period of rater calibration [27] with the research team, each rater will then independently evaluate each incident narrative to answer the following question: "Does the narrative suggest harassment on the basis of gender identity or expression, race and related grounds, or sexual orientation?" (Multimedia Appendix 3). We will calculate Cohen Kappa as a measure of interrater agreement, with a member of the research team resolving any areas of disagreement on a specific incident narrative.

Finally, for Research Question 3, we will examine the EVIR incident narratives for comments that refer to anger over COVID-19 health measures (ie, vaccination, masking, social distancing) that contribute to violent encounters. This might include, for example, hostile reactions in response to paramedics' requests that patients or bystanders at scenes wear a mask. Again, we will abstract the EVIR incident narratives into a Microsoft Excel (Microsoft Corp) sheet and have 2 independent raters review each narrative to answer the following question: "Does the narrative suggest violence on the basis of conflict over COVID-19 health measures?" Using a similar approach to Research Question 2, we will engage in a period of rater calibration followed by independent coding and then use Cohen Kappa to measure interrater agreement.

All personnel recruited to analyze qualitative data will be required to undergo online research ethics training made available for free by the Government of Canada and be instructed to treat the data as strictly confidential. Because the incident narratives may include detailed descriptions of specific incidents that may later be identifiable to persons with knowledge of the events, we will not report direct quotes and will use general language in describing examples to support relevant themes during publication.

Results

Although we originally planned to study a 1-year period, we have expanded our study window to include all violence reports filed between February 1, 2021 and February 28, 2023. As of January 1, 2023, a total of 975 EVIRs have been filed. The research program remains internally funded by the Region of Peel's paramedic services division, and our analysis will begin when the data collection window closes on February 28, 2023. We anticipate the publication of several manuscripts blueprinted for each research objective in late 2023 through early 2024

We anticipate being able to deliver a detailed accounting of the prevalence of reported incidents of violence in the study site, as a proportion of both the total number of service calls and the number of active-duty paramedics in the service. Second, will compile a list of service call characteristics that suggest an increased risk of any form of violence and for violence resulting in an assault on a paramedic. Finally, we will generate a qualitative description of themes that underpin documented incidents of violence, including the potential contribution of violence based on gender, race and related grounds, sexual orientation, and conflict over COVID-19 public health measures.

Discussion

Overview and Strengths

Despite a growing recognition of the potential for significant physical and psychological harm [15,33-38], there is very little epidemiological data describing violence against paramedics [35,39]. Aside from some reviews of occupational injury statistics [34,37,40-43], much of the research on the topic has used cross-sectional survey approaches that ask paramedics about exposure to violence during the past 12 months or throughout their careers [14-16,33,35,39,44-49]. Although informative in drawing attention to the issue and demonstrating that a concerning majority of paramedics have been subjected to violence, the work leaves several important questions unanswered. Without robust, event-level reporting data, it is difficult to ascertain the scope of the problem and potentially modifiable risk factors—both of which are needed in developing organizational strategies to mitigate the risks and enhance paramedic safety.

The challenge in gathering robust data about violence is that the organizational culture within the profession has contributed to underreporting. When surveyed, many paramedics describe violence as just "part of the job" [14,15,17]. As a result, only a minority of incidents are reported to paramedic supervisors or the police. Our own work on the topic has demonstrated a cycle

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within which chronic exposure to violence, combined with its perceived inevitability and lack of consequences for perpetrators, serves to implicitly position the ability of paramedics to "brush off" violent encounters as an expected professional competency [17]. Breaking this cycle is an important step in understanding the scope of the problem. In that respect, our research has several strengths that will allow us to contribute meaningfully to this literature.

First, the reporting process was developed through an extensive stakeholder engagement and pilot testing process with the goal of promoting accessibility [19]. Embedding the EVIR within the patient care record gives us a streamlined, accessible, point-of-event reporting mechanism. This allows us to ask questions about the prevalence of violence as a proportion of both service calls and active-duty paramedics. We will also be able to generate a descriptive profile of the types of violence paramedics report, its sources, and contributing circumstances—an important first step to understanding the scope of the problem. Second, because the EVIRs are linked directly to ACRs, we will be able to evaluate the degree to which features of service calls that are generally known to the responding paramedics ahead of time (such as the nature of the problem) are associated with an increased risk of violence. This analysis can be used to develop strategies when responding to high-risk calls, such as coordinated response plans with police or mobile crisis teams. Third, qualitatively analyzing the free-text narratives potentially allows us to examine some of the root causes of violent encounters. It may be, for example, that violent encounters are precipitated by conflict over patient care, preferences, or psychosocial needs that can be better managed through improved policy or training. Relatedly, the degree to which paramedics are subjected to vitriol based on gender, race, or sexual orientation has not (to our knowledge) been previously studied and may be a novel contribution to the literature describing chronic stressors in paramedic work [50-52]. Examining the EVIR narratives for themes related to COVID-19 will generate modest empirical data in a local context on what media sources have been describing as a growing antipathy toward health care providers over public health measures, such as masking or vaccination mandates [18]. Finally, our analysis will enable refinements to the reporting mechanism itself. This can support both strengthened acceptance among the end users and scalability of the work to include other paramedic services in the province.

Limitations

We are placing some important boundaries on this research that need to be considered as limitations when interpreting our findings. First, we must acknowledge that all findings to be shared from this research are limited to reported incidents from a single study site. Although the development phase went to great lengths to address many of the organizational cultural barriers to reporting, we are mindful that the work is coming up against a very real and historically entrenched reluctance to report violent incidents. The degree of underreporting we will observe in our study is difficult to estimate. Both factors limit the generalizability of our findings. Second, we are gathering data about the incidents themselves but stopping short of evaluating the health consequences for the reporting paramedics in terms of physical injuries, lost time from work, or more nebulous psychosocial harms, such as burnout. Given the links between critical (or traumatic) stress and PTSI in the paramedic population, studying the impact on health and well-being will be an important next step in the research. Third, our statistical analyses will necessarily be constrained by the observed event rate, which is difficult to estimate ahead of time. Our evaluative time frame of 1 year following implementation is admittedly arbitrary, but it is reasonable from a feasibility perspective and aligns with the operational needs and priorities of the paramedic service.

Conclusion

Leveraging a novel, point-of-event reporting process, this study aims to describe the prevalence of violence against paramedics in the Peel Region, its risk factors, and underpinning themes. This research will broadly be used to develop evidence-informed risk mitigation strategies, support a wider-scale implementation of violence tracking, and contribute epidemiological data to what has been described as a "serious public health issue" [15].

Acknowledgments

This initiative is a collaboration between Peel Regional Paramedic Services (PRPS) and the University of Windsor, in Ontario, Canada. We wish to express our gratitude and appreciation to the members and leadership of PRPS, as well as the local executive committee of the Ontario Public Service Employees Union Local 277 for their support of this work.

Data Availability

Limited quantitative data from this study can be made available to interested parties upon request from the principal investigator. Note that this may require a formal data-sharing agreement.

Conflicts of Interest

JM is employed as an advanced care paramedic and researcher by the Peel Regional Paramedic Services.

Multimedia Appendix 1
External Violence Incident Report (EVIR).
[PNG File , 311 KB - resprot_v12i1e37636_app1.png]

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Multimedia Appendix 2
Data points to be analyzed as potential covariates from the ambulance call report.
[DOCX File , 19 KB - resprot_v12i1e37636_app2.docx]

Multimedia Appendix 3
Template for independent coding of incident report narratives for Objective 3, Research Question 2.
[DOCX File , 15 KB - resprot_v12i1e37636_app3.docx]

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Abbreviations

ACP: advanced care paramedic
ACR: Ambulance Call Report
AOR: adjusted odds ratio
ePCR: electronic patient care record
EVIR: External Violence Incident Report
PCP: primary care paramedic
PRPS: Peel Regional Paramedic Services
PSP: public safety personnel
PTSI: posttraumatic stress injury
PTSD: posttraumatic stress disorder

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Protocol

Patient Experiences With Prescription Cannabinoids in Germany: Protocol for a Mixed Methods, Exploratory, and Anonymous Web-Based Survey

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Abstract

Background: Medical cannabinoids are controversial. Their use is comparatively rare, but it is rising. Since 2017, cannabinoids can be prescribed in Germany for a broader range of indications. Patient surveys on these drugs are hampered by the stigmatization of cannabinoids and their (still) low prevalence in medical contexts. Against this background, patients' willingness to provide information is limited. Moreover, it is logistically challenging to reach them with a survey. A thorough knowledge of currently ongoing therapies and their effects and side effects, however, is important for a more appropriate and effective use of cannabinoids in the future.

Objective: This study is an exploratory data collection using a representative sample. The main goal is to provide a detailed picture of the current use of medical cannabinoids in Germany. It is intended to identify subgroups that may benefit particularly well or poorly.

Methods: We are conducting a representative, anonymous, cross-sectional, one-time, web-based survey based on mixed methods in 3 German federal states. Health conditions under cannabinoid therapy and before are documented with validated, symptom-specific questionnaires. This allows an estimation of the effect sizes of these therapies. The selection of parameters and questionnaires was based on the results of independent qualitative interviews in advance. Representative samples of the hard-to-reach study population are obtained by cluster sampling via contracted physicians of the statutory health insurance companies.

Results: Recruitment was ongoing until the end of June 2022, with 256 enrolled participants. Validated questionnaires on pain, spasticity, anorexia or wasting, multiple sclerosis, nausea or vomiting, depression, and attention deficit hyperactivity disorder (ADHD) were selected. Symptom scores are being assessed for both current conditions under cannabinoid therapy and conditions prior to this therapy (in retrospect). Validated questionnaires are also used for treatment satisfaction and general quality of life. These are supplemented by existing diagnoses, a detailed medication history, any previous experiences with cannabis or illegal substances, experiences with the prescription process, and sociodemographic data. Based on the results of the previous qualitative interviews, questions were added regarding prior experience with relaxation methods and psychotherapy, personal opinions about cannabinoids, pre-existing or symptom-related psychological trauma, and different experiences with different cannabis-based therapies.

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Conclusions: The exploratory mixed methods approach of this project is expected to provide valid and relevant data as a basis for future clinical research. The study design may be representative for a large proportion of outpatients treated with cannabinoids in the German federal states studied. It may have less bias toward social desirability and may provide valuable information in addition to existing studies. Due to the observational and cross-sectional nature of this study, various limitations apply. Causal relations cannot be drawn.

Trial Registration: German Clinical Trials Register DRKS00023344; https://drks.de/search/en/trial/DRKS00023344

International Registered Report Identifier (IRRID): DERR1-10.2196/38814

(JMIR Res Protoc 2023;12:e38814) doi:10.2196/38814

KEYWORDS

cannabis; cannabinoids; representative survey; pain; mixed methods

Introduction

Background

Cannabis plants contain a variety of active ingredients. More than 100 cannabinoid compounds have been identified [1]. The most relevant for medical applications are tetrahydrocannabinol and cannabidiol [2]. Many different pharmacologically active cannabis ingredients exist, especially terpenes and terpenoids, and the synergistic effects of different compounds are being discussed widely [2,3]. Nevertheless, pure tetrahydrocannabinol and cannabidiol drugs are also frequently used. After the discovery of the endocannabinoid system in the 1990s, interest in medical applications of cannabinoid drugs has been increasing [2,4]. At the same time, cannabinoids are still controversial in most countries, including Germany, despite changing legal frameworks in medicine and society [5].

Proponents of cannabinoid medications tout their benefits for a variety of conditions [2,6-8]. Cannabinoid drugs are already used in the fields of pain management for multiple sclerosis, chronic pain syndromes, and cancer-related pain. Currently, 73% of cannabinoid prescriptions in Germany are for pain [9]. Previous studies show a substantial improvement in 35.5% and a moderate improvement in 34.2% of patients treated [10]. Other common indications include spasticity in multiple sclerosis, nausea in patients with cancer, and specific mental health symptoms [11,12].

Feared side effects are psychosis, addiction, and physical intolerance reactions [13,14]. This includes dizziness, nausea, fatigue, euphoria, disorientation, confusion, loss of balance, and hallucinations [15]. The risk of side effects is higher for older adults due to their impaired metabolism and comorbidities, as well as their increased potential for drug-to-drug interactions [16]. Side effects also vary depending on the medication used.

Due to legislative changes in Germany in 2017, a wider range of cannabinoid medications can be prescribed medically [17]. By law, physicians who prescribe medical cannabinoids at the expense of statutory health insurance companies were required to participate in a mandatory monitoring study for each patient until 2022 [9]. Parameters included indication, effectiveness, drug, dosage, and quality of life. All were evaluated solely by the prescribing physicians. Patients with private health insurance and those who paid out of pocket were not monitored. Most of the scientific evidence on the current state of cannabinoid therapies in Germany stems from this source only. There is no representative data from direct patient surveys.

Considering the risks and benefits, as well as the ongoing social controversy, a more accurate mapping of the current use of medical cannabinoids in Germany is desirable. There is a need for precise differentiation according to the underlying illnesses, illness-related restrictions, and the resulting health and psychosocial consequences, involving patients and not only their physicians [18]. Such findings could be valuable for a more targeted use of medical cannabinoids and could help in the formulation of questions for future clinical research in this field.

Study Design and Goal

This is an anonymous, exploratory, cross-sectional, one-time, web-based survey using a mixed methods approach. All information is collected at the same point in time, past and current health status included. It aims to obtain representative, descriptive data on patients receiving outpatient treatment with medical cannabinoids in Germany and on their subjective treatment experiences. It is also intended to further explore the patient perspective of cannabis-based therapies and identify subgroups that may benefit particularly well or poorly.

Qualitative Preliminary Study

Between September 2020 and March 2021, after approval by the local ethics committee (8391_BO-K_2019), a qualitative survey was conducted at the Pain Clinic at Hanover Medical School, Germany. Upon written consent, 32 patients (15 women) with chronic pain who had taken cannabis-based medicines for at least 6 months were deliberately selected as a purposive sample, according to Moser and Korstjens [19]. Interviews took 16-88 minutes (on average, 35 minutes). These were semistructured interviews with no time limit. The interview guideline had been constructed according to Kallio et al [20]. It consisted of an introduction that explained the purpose of the interview as well as the process. This was intended to promote an open and trusting interview atmosphere. This was followed by open-ended questions about previous experiences with cannabis and the effects on different areas of life. The interviews were recorded and later transcribed. The data was analyzed according to Strauss et al (grounded theory) [21]. Data collection continued until qualitative saturation occurred, which means that no new knowledge could be generated by further collection of data [22].

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All participants were interviewed by the same researcher (FF), who also transcribed and analyzed the interviews. In addition, 3 selected interviews were independently analyzed by 3 other researchers (MK, MF, and FIK). Results were reviewed and discussed by the entire research team to achieve higher intercoder reliability.

The findings on the patient perspective of cannabinoid therapy were used as an additional basis for selecting outcome parameters and corresponding validated questionnaires. However, the detailed presentation of the analysis of these qualitative interviews is beyond the scope of this study and will be presented elsewhere.

The results led to questions about previous experiences with relaxation techniques or psychotherapy, as these methods are considered standard treatment for some of the reported symptoms [23-26]. The findings also resulted in the decision to inquire about the personal opinion about cannabinoids, preexisting or symptom-related psychological trauma, and about varying experiences with different cannabis-based medications.

Methods

Setting, Recruitment, and Sampling

We are surveying patients who receive prescription cannabinoids. The original target size is 300 participants. A representative sample for the German federal states of Berlin, Brandenburg, and Lower Saxony is drawn in a stratified procedure (see the *Data Collection, Management, and Analysis* section for details).

The web-based survey is conducted anonymously using mobile website technology. It starts with patient-adapted questions analogous to those in the mandatory monitoring survey. Based on this, further detailed information on the respective underlying disease is collected. The previous course of the disease and previous therapy attempts are asked in detail. In addition, information on cannabis use throughout the life course is requested, as well as on attitudes and opinions toward cannabinoids prior to the first prescription, where these stemmed from, and to what extent they have changed since the ongoing cannabinoid prescription.

Sample Size

A total of 300 patients currently receiving cannabinoid therapy were to be included in this study (see Textbox 1). Based on the mandatory survey data, approximately 210 patients (69%) will likely experience pain symptoms [9]. Based on this assumption, a power analysis for this exploratory study indicates that using the standard parameters of α=0.05 and β=0.20 (corresponding to a power of 80%), *t* tests used for the pre-post comparisons among the 210 patients with pain symptoms can detect all large, medium, and even smaller effects with effect sizes of Cohen $d \geq 0.20$

Textbox 1. Eligibility criteria.

Inclusion criteria

- Being 18 years or older
- Ongoing therapy with medically prescribed cannabinoids or therapy with medically prescribed cannabinoids in the 12 months prior to survey participation
- Stable internet access
- Have sufficient German language skills, as well as cognitive and physical abilities, to participate in a web-based survey in German, lasting approximately 30 minutes
- Active, written web-based consent (see Multimedia Appendix 1)

Exclusion criteria

- Lack of active, written web-based consent

Outcome Parameters

Overview

The most common reasons for prescribing cannabinoids in Germany are known from the abovementioned mandatory survey. They are chronic pain (73%), spasticity (10%), anorexia or wasting (6%), multiple sclerosis (6%), nausea or vomiting (5%), depression (3%), and attention deficit hyperactivity disorder (ADHD; 1%) [9]. Accordingly, validated questionnaires on these conditions were selected for this survey. Symptom scores are being assessed for both current conditions under cannabinoid therapy and conditions prior to the cannabinoid therapy (in retrospect). Validated questionnaires are also used for treatment satisfaction (current and in retrospect) and for general quality of life (current and in retrospect). These are supplemented by existing diagnoses, a detailed medication history, any previous experiences with cannabis or illegal substances, experiences with the prescription process, and sociodemographic data. Modifications and additions were made based on the results of the qualitative interviews (see the *Qualitative Preliminary Study* section).

Treatment Satisfaction Questionnaire for Medication Version II

The Treatment Satisfaction Questionnaire for Medication (TSQM) version II is a general measure of patients' satisfaction with their medication [27]. It is viewed as a reliable and valid instrument consisting of 4 scales: side effects, effectiveness, convenience, and global satisfaction [27-29].

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Patient-Reported Outcome Measurement Information Systems

The Patient-Reported Outcome Measurement Information Systems (PROMIS-29) represents an international standard for the evaluation of quality of life based on a patient report. This test consists of 29 questions about the domains of physical function, anxiety, depression, fatigue, sleep disturbance, the ability to participate in social roles and activities, pain interference, and pain intensity [30,31].

Face Pain Scale

The Face Pain Scale represents an intuitive and well-established way to assess pain. It has been validated for both children and adults in various contexts [32,33].

Multiple Sclerosis Spasticity Scale 88

Spasticity is assessed using the Multiple Sclerosis Spasticity Scale 88 [34]. Due to its considerable length, we decided to only include the 4 most clinically relevant subscales in the survey: muscle stiffness, muscle spasticity, walking, and physical movement.

Anorexia Nervosa Inventory for Self-Rating

For patients experiencing anorexia, we use the Anorexia Nervosa Inventory for Self-Rating which includes questions about figure consciousness, feeling of insufficiency, anancasm, adverse effect of meals, sexual anxieties, as well as bulimia [35].

Minimal Documentation System on Distressing Symptoms

The Minimal Documentation System on Distressing Symptoms (MIDOS^2) is a short questionnaire for non–anorexia-mediated weight loss and nausea or vomiting. This test inquires about a few symptoms associated with palliative care patients as well as their general condition and was validated for this patient group. Since the addressed items are not specific to palliative care, we expect MIDOS^2 to allow an adequate evaluation of the examined symptoms [36].

Hospital Anxiety and Depression Scale

For patients with depression, the Hospital Anxiety and Depression Scale is applied. This test, comprising 14 questions, is a very common, international instrument for quantifying anxiety or depression [37-39]. The Hospital Anxiety and Depression Scale can be used to track disease progression and response to psychotherapeutic and psychopharmacological interventions [40].

Adult ADHD Self-Report Scale

The Adult ADHD Self-Report Scale version 1.1 assesses ADHD and was originally developed in cooperation with the World Health Organization and the Workgroup on Adult ADHD. It consists of 2 parts, the first of which inquires about inattentiveness and the second of which evaluates hyperactivity and impulsivity [41,42].

Rights of Use of the Applied Questionnaires

The use of the validated questionnaires for academic purposes required the consent of the parties holding the copyright. For TSQM, PROMIS-29, and Multiple Sclerosis Spasticity Scale 88, licenses had to be obtained. The authors of the remaining questionnaires required proper referencing.

Data Collection, Management, and Analysis

A stratified random sample is collected via the prescribing contract physicians of the statutory health insurance companies. (88.1% of the German population has statutory health insurance [43]). All physicians with statutory health insurance contracts, medical specialist titles in anesthesiology, general medicine, neurology, and internal medicine, and who practice in the 3 federal states of Berlin, Brandenburg, and Lower Saxony are selected. According to the aforementioned mandatory monitoring survey, those 4 groups of specialists together account for 88% of prescriptions for cannabinoids in Germany [9].

Complete lists of these physicians are obtained by a formal request for academic research purposes from the corresponding medical councils at the federal state level. All physicians on those lists are contacted via email or, in the case of Lower Saxony, via fax (in Lower Saxony, email addresses could not be provided). In addition, physicians are contacted by telephone in random order and asked to invite their own patients who receive cannabinoid medication to partake in the survey, outpatient tertiary centers included. Randomization is done by random number values without duplicates using Microsoft Excel. In the event of unavailability, 3 attempts are made at different times. In the meantime, the next physicians on the list are called. This continues until the planned number of participants is reached.

Physicians who wish to forward study invitations to their patients send an email to the study secretariat requesting an appropriate number of anonymous study invitations. They can then forward the invitations either via email or as a printout to their patients. Each study invitation contains a unique participation code, which serves as the login code for the web-based survey. The study center never receives any personalized or pseudonymized patient data. In this way, a fully anonymous and representative survey is made possible. Both physicians and participants receive an incentive for participation. Physicians receive €50 (US $60) per patient of theirs who participates in the web-based survey as compensation for their time. Since it is known which physicians have received which codes to pass on to their patients, the compensation can be calculated. Information about which physician received which codes is strictly separated from the study data. The complete anonymity of the study participants is thus preserved. On the last page of the web-based survey, patients are shown an impersonalized voucher code worth €15 (US $18) for books from a German bookstore.

The web-based survey is conducted using LimeSurvey (version 5.1.10; Carsten Schmitz) running on a dedicated and secure local server at Charité—Universitätsmedizin Berlin. Entries made by the individual subjects are checked for plausibility and completeness, where possible. Possibly missing data will be imputed using the Multiple Imputation by Chained Equations algorithm [44]. Clearly implausible or very incomplete entries (>50% missing data) will be excluded from the analysis.

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Data from this exploratory cross-sectional study will be evaluated primarily using descriptive statistics. Parametrical figures will be provided, as well as risk and odds ratios for selected questions. Scores for all questionnaires are obtained twice from the participants in the same session. They are first instructed to answer the questionnaires based on their current state, and then on what they remember their state being like prior to the commencement of the cannabinoid therapy. Individual *t* tests will be applied to assess, on a strictly exploratory level, whether within-group changes constitute a substantial improvement. This assessment will rely on both significance levels and effect sizes (Cohen *d*). As there is no control group, findings will be interpreted with due precaution. Furthermore, as a sensitivity analysis, the results for the main tests for pain (numeric analog scale), treatment satisfaction (TSQM), and quality of life (World Health Organization-5 Well-Being Index) will be tested for confounders by extending the *t* test to ANOVA and analysis of covariance models. The authors are very aware of the limited informative value of a pre-post assessment as part of a one-time survey in an observational study design, especially with regard to causal attributions.

The data is stored at the Charité—Universitätsmedizin Berlin for 10 years before being deleted. Only the responsible staff of the study center has access. There is continuous monitoring of enrollment during the survey phase. This is necessary to reach the planned number of participants. If necessary, slow recruitment can be compensated for by contacting more physicians on the phone (this is in addition to contacting all physicians via email or fax). Phone calls are carried out by the responsible study physician, trained study nurses, and trained student assistants. Additional student assistants are available if speeding up recruitment is required. Monitoring of enrollment status is performed by the responsible study team. No data monitoring committee is required because this is a noninterventional observational study. No interim analysis of the data is planned.

Ethics Approval

The ethics committee of the Charité—Universitätsmedizin Berlin gave its approval to obtain, process, and analyze the data and to publish the results (German Clinical Trials Register DRKS00023344; ethics number EA1/327/20). All participants provided their informed written web-based consent to participate in the study. The study is conducted in accordance with the Declaration of Helsinki in its currently valid version, the guidelines of the International Conference on Harmonization of Good Clinical Practice, and the applicable German laws.

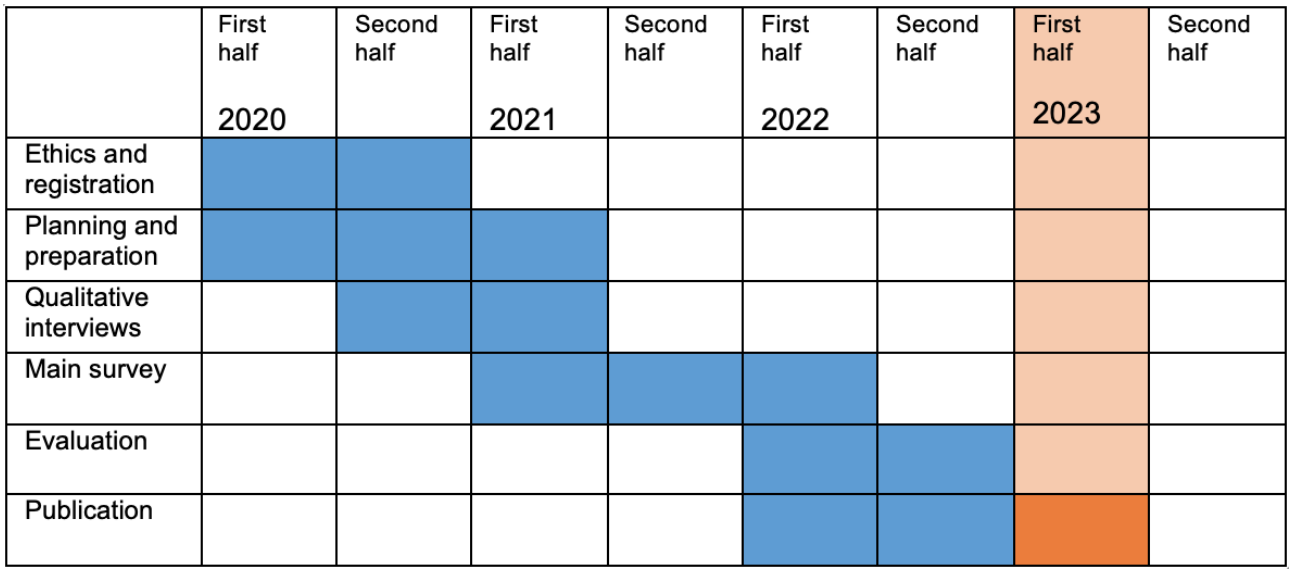
Patient and Public Involvement

Patients are not involved in the design, implementation, reporting, or dissemination plans of our research. Yet, they are a key element in the choice of parameters via qualitative interviews. All parameters in the survey are patient-reported parameters.

Timeline

The timeline of this study is presented in Figure 1.

Figure 1. Timeline.



Results

Recruitment was ongoing until the end of June 2022. A total of 11,744 physicians were contacted to invite their patients who receive cannabinoid medication to participate in the study (Berlin, n=1700; Brandenburg, n=2041; Lower Saxony, n=8003). At the time of submission, 256 participants had been enrolled. The COVID-19 pandemic markedly slowed down participant enrollment. Many physicians did not have the capacity to forward the study invitation to their patients as they had to cope with unusually high numbers of patients, sick leave among their own staff, and other extra duties. We were frequently told that while there was interest in principle in supporting the study, the pandemic conditions at the time did not allow for activities outside of regular patient care. Due to slow recruitment, the survey was later expanded to the federal state of Brandenburg (amendment approved by the ethics committee on January 20, 2022.) Here, all physicians were contacted once by email. Direct calling in random order could

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not be carried out in Brandenburg before the study was terminated. Recruitment was terminated as no further funding was available to extend the recruitment period. Results will be published in summer 2023.

Discussion

Principal Findings

We are conducting a one-time cross-sectional web-based survey of a cohort of patients receiving prescription cannabinoids in Germany. In addition, based on the results of a qualitative preliminary study, a clinically relevant selection of parameters was made for the study presented here. In addition to data on quality of life, psychological parameters (including anxiety and depression), and social participation over the course of cannabinoid treatment, we included questions on previous experiences with psychotherapy and relaxation procedures. We also included screening questions for trauma to detect differences in prevalence compared to the general population. While in the preceding qualitative interviews the effects of different cannabis-based preparations and doses were reported very differently (eg, from positive to negative by the same patient), we included questions on the cannabis-based preparations used and their respective perceived effects in their exact time course. This might help identify favorable dose ranges for different diagnoses and age groups based on patient experiences. The use of symptom-specific standardized questionnaires will also allow us to estimate effect sizes of cannabinoid therapies, while bearing in mind all present limitations within the scope of this study design. This survey collects detailed information on the patients' underlying diseases, previous treatment attempts, and individual attitudes toward cannabis.

A strength of this study is its sample of a rather hard-to-reach study population in Germany and Europe using a representative approach. Cannabis consumption is stigmatized in parts of German society [45]. The use of medical cannabinoids is also still rare in Germany (approximately 27,000 patients in a total population of 83.2 million) [9]. This study may represent up to 77.5% of total cannabinoid prescriptions in Germany. The proportion of the total population of outpatients who receive cannabinoid medications in Germany, which is depicted in this study, has been estimated as follows: proportion of all patients with statutory health insurance (who are accordingly treated by physicians licensed by the statutory health insurance) multiplied by the proportion of these patients who are treated by the specialist groups involved in this study, 88.1% (73.3 million/83.2 million) [43] × 88% (8809/10010) [9] = 77.5%. In comparison, the mandatory monitoring survey was able to generate 9000 complete records out of at least 27,000 reported prescriptions (33.3%) [9]. Our intention is to supplement the existing data with a sample that significantly adds to it by involving the patient perspective.

The study design also provides a substantial reduction in social desirability bias due to the full anonymity of participants. The existing mandatory monitoring survey is directed at prescribing physicians who may have an interest in justifying their own therapeutic approach. When patients are surveyed by their prescribing physicians, they too may be biased by social desirability.

In contrast, social desirability bias is potentially lower in this study since it is anonymous. It is also more independent from prescribing physicians, as they merely forward the invitation, and patients fill out the questionnaire without the doctor's presence at home. Lastly, the mixed method approach of this design is intended to provide especially valid and relevant data.

Nonetheless, there are several factors that may influence the answers in the questionnaires, like the doctor-patient relationship and the high patient compliance required for detailed data entry. The study's major limitations also include a risk of selection bias. The web-based survey will most likely underrepresent or not represent certain patient groups, such as patients who are very old or very sick and are not able to participate in a web-based survey. These represent a relevant proportion of the total prescriptions for cannabis-based medicines in Germany. Wasting (and anorexia) and nausea in patients with cancer are among the most common reasons for prescribing, at 6% (641/10.010) and 5% (511/10.010), respectively [9]. The results of this study will only be transferable to them to a limited extent.

There is a considerable risk of recall bias. We try to capture a large amount of information in a cross-sectional survey. Some pieces of information may relate to long-past events. Attempts are made to mitigate this by indicating in both the study invitation and the virtual login area that it may take up to an hour to complete the web-based survey. Participants are also asked to have all available medical records ready and to complete the questionnaire in a quiet place. Nevertheless, the validity of the results will, of course, not be comparable to those of a prospective study.

There is no absolute control over whether individuals completing the web-based survey are actually patients who receive cannabinoid medication. Invitations and login codes can theoretically be given to third parties to receive an incentive (a €15 (US $18) voucher code for books). We assume an extremely low rate of abusive participation but cannot completely exclude it, making it a minor limitation to the validity of this study.

Up until now, about half of the randomly selected doctors could be successfully called on the phone and were asked to invite patients to participate. All doctors did receive an invitation by either email (Berlin and Brandenburg) or fax (Lower Saxony). This creates a risk for systematic bias in the sample.

It is quite certain that the groups of specialists included in the study were affected by the COVID-19 pandemic to varying degrees. Thus, for example, a higher workload in general medicine could lead to an underrepresentation of patients treated there. Medical practices that were particularly affected by the pandemic were significantly less likely to invite patients to participate in the study, and vice versa. This is understandable, as they did not have time to attend to matters beyond regular patient care. For this reason, a risk of sample bias remains.

The qualitative interviews of the independently performed previous study were held, recorded, transcribed, and analyzed by a single researcher. Only 3 out of 32 interviews were interpreted independently by other researchers for intercoder

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reliability. The large number of interviews conducted until theoretical saturation was reached may reflect the individual diversity of cannabinoid therapies and how they are experienced. It could also be an indication of methodological uncertainties in conducting the qualitative interviews. However, coding and results were discussed among the entire research team, including 2 experienced qualitative researchers. There was unanimity regarding the data and its interpretation.

Finally, it must be said that all the usual restrictions apply with regard to the interpretability of data in the context of cross-sectional, observational studies. Accordingly, the results must then be discussed with all due restraint and contextualized in a reflective manner.

Conclusions

This study may contribute to a more comprehensive picture of experiences with medical cannabinoids from the perspective of patients with various diseases. Additional understanding of the risks and benefits of cannabinoid therapies may contribute to more appropriate use of these drugs and less societal stigma.

Acknowledgments

The study is funded by Vayamed GmbH, Jägerstr. 28-31, 10117 Berlin, Germany. Vayamed GmbH was not involved in the planning, design, conduct, analysis, and publication of this investigator-initiated study and will not have special or privileged access to study data at any stage. Special thanks to Nadine Sylvester, Miriam Rösner, Gunda Loibl, Daniel Itzlroither, Arnab Chakrabarty, and Carsten Schütz, without whom this study would not have been possible. We would also like to extend a heartfelt thank you to all participants and their supporting physicians.

Data Availability

In accordance with the granted ethics approval, the study data will not be made publicly available to protect participant data. The data sets can be requested from the corresponding author upon justified request.

Authors' Contributions

JMF, MK, and CSK conceived the study together. JMF, MK, and CSK developed the study design. JMF and F-IK analyzed the survey data. FF conducted and evaluated the qualitative interviews. JMF, F-IK, MK, and FF evaluated qualitative interviews for validation. JMF, MK, FF, and CSK conducted the survey. MK, AM, and CSK managed the resources. The curation of the data was done by JMF, F-IK, and LSZ. JMF and FF wrote the first draft of the manuscript. All authors participated actively in reviewing and editing the draft. JMF, MK, AM, and CSK supervised the project. JMF, MK, AM, and CSK were responsible for the project administration. CSK solicited funding for the project.

Conflicts of Interest

The study is funded by the pharmaceutical company Vayamed. Vayamed GmbH is not involved in the planning, design, conduct, analysis, and publication of this investigator-initiated study and will not have special or privileged access to study data at any stage. The study is entirely conducted by an established public research department at Charité—Universitätsmedizin Berlin. Financial dependencies with the funder do not exist. MK has received speaker honoraria from the Federal Association of Pharmaceutical Cannabinoid Companies Demecan, EVER Pharma, Grunenthal, Hormosan, IUVO Therapeutics, Lilly, the Medical Service of the Health Insurance Funds, Novartis, Stadapharm, Teva, and Tilray. He has received consultancy fees from Almirall. He has received expert opinion fees from several local and social courts. He is member of the ad hoc commission cannabis in medicine of the German Pain Society and the Science Network Cannabinoids in Medicine (Wissenschaftsnetzwerk Cannabinoide in der Medizin). CSK has received consultancy and speaker fees from Pedanios GmbH and Deutsches Institut für Medizinalcannabis more than 3 years ago. He is part of the Science Network Cannabinoids in Medicine (Wissenschaftsnetzwerk Cannabinoide in der Medizin). No further conflicts of interest related to this manuscript were declared.

Multimedia Appendix 1
Digital privacy and consent statement for participation in an anonymous survey as part of the EXCARP study
[DOCX File , 26 KB - resprot_v12i1e38814_app1.docx]

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Abbreviations

ADHD: attention-deficit/hyperactivity disorder
MIDOS: minimal documentation system on distressing symptoms
PROMIS: patient-reported outcome measurement information system
TSQM: Treatment Satisfaction Questionnaire for Medication

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Protocol

A Multicomponent Intervention to Train and Support Family Medicine Providers to Promote Pre-exposure Prophylaxis (PrEP) for Adolescent Girls and Young Women in the Deep South: Protocol for the PrEP-Pro Study

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Abstract

Background: Pre-exposure prophylaxis (PrEP) is a highly effective biomedical prevention intervention and a major strategy for reducing the HIV burden in the United States. However, PrEP provision and uptake remain lower than estimated needs, and in ways that may exacerbate HIV disparities among Black adolescent girls and young women in the southern United States. Data suggest that gaps in provider knowledge of HIV epidemiology and PrEP and skills assessing sexual health practices are important barriers to provision and uptake, with limited evidence-based interventions to address these gaps.

Objective: This paper describes the "PrEP-Pro" intervention, a multicomponent intervention to train and support family medicine (FM) trainees to promote PrEP for adolescent girls and young women in Alabama.

Methods: The PrEP-Pro intervention comprises 3 main components guided by the Capability-Opportunity-Motivation-Behavior (COM-B) model for behavioral change and the Consolidated Framework for Implementation Research (CFIR): (1) provider HIV epidemiology and PrEP education, (2) sexual history taking, and (3) PrEP Champions. In phase 1, we will work with community advisory boards (providers and clients) and then conduct focus groups with FM trainees to adapt content to train FM residents on HIV epidemiology and PrEP and develop implementation strategies, including provider-facing tools and client-facing educational materials. In phase 2, we will pretest and then pilot-test the initially adapted PrEP-Pro intervention with FM trainees. FM trainees will complete baseline, 3-, and 6-month questionnaires post PrEP-Pro intervention. We will also conduct in-depth interviews (IDIs) with FM pilot participants, adolescent girls and young women who accessed care after the PrEP-Pro pilot, and key

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stakeholders. The primary outcomes are PrEP-Pro acceptability and feasibility, which would be assessed using validated instruments at months 3 (among pretest participants) and 6 (among pilot participants). Secondary outcomes will also be assessed, including PrEP knowledge, sexual history-taking attitudes and practices, PrEP prescriptions among adolescent girls and young women encounters, and sexually transmitted infections (STIs) and HIV testing among adolescent girls and young women encounters in 6 months.

Results: Study results will be disseminated to practices, state health officials, and other key stakeholders to solicit feedback on implementation opportunities and challenges to inform a hybrid effectiveness implementation trial. Our results will also be presented at local and national conferences and submitted to peer-reviewed journals.

Conclusions: As PrEP grows, there is a pressing need to train FM providers and develop appropriate, contextually relevant tools to support PrEP implementation. The PrEP-Pro intervention is a multicomponent intervention to train FM residents across Alabama on sexual history-taking, PrEP provision for adolescent girls and young women, and supporting practice-based PrEP Champions. The PrEP-Pro intervention is anticipated to increase PrEP prescriptions for adolescent girls and young women and expand comprehensive sexual and reproductive health care for adolescent girls and young women in rural and urban Alabama.

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KEYWORDS

pre-exposure prophylaxis (PrEP); training; PrEP Pro intervention; family medicine trainees; adolescent girls and young women (AGYW); family medicine; teens; young women; prevention; HIV; community; sexual health; reproductive health

Introduction

In the United States, Black adolescent girls and young women are disproportionately affected by HIV compared to their White and Hispanic counterparts [1]. In 2019, Black adolescent girls and young women accounted for 54% of the approximately 36,801 new HIV diagnoses among women, despite representing just 13% of the female population [2]. Further estimates suggest that Black adolescent girls and young women are at disproportionately higher risk of HIV in the south than in other regions, where they account for 67% of new HIV diagnoses among women [3,4], with a growing number among those living in rural areas [4-6].

Pre-exposure prophylaxis (PrEP) is a highly effective biomedical prevention intervention and is an important strategy for ending the HIV epidemic in the United States. [7-9]. In 2012, the US Food and Drug Administration approved the first PrEP agent, a fixed oral combination of tenofovir disoproxil fumarate/emtricitabine for use in adults [10,11], and later broadened the approval to include adolescents in 2018 [12]. Most recently, in 2021, the Food and Drug Administration approved a long-acting injectable formulation, cabotegravir, as PrEP for adults and adolescents with vaginal or anal exposure to HIV [13].

Despite advances in biomedical PrEP therapeutics to reduce HIV incidence and increase patient autonomy, PrEP uptake remains low compared to estimated needs and in ways that may exacerbate disparities in HIV incidence [14,15]. In a cross-sectional study of 429 adolescents (aged 15-21 years) accessing preventive care in an urban adolescent primary care center in Alabama, almost half were PrEP-eligible, yet none were prescribed PrEP [16]. National data also suggest low PrEP prescription among adolescents and young women, as well as PrEP inequities by race and geographical location [14,17]. In 2019, only approximately 10% of women aged 16 years and older with indications for PrEP received a PrEP prescription [17]. Additionally, PrEP prescriptions among those with indications for PrEP were lowest among adolescents and young adults aged 16-24 years (16%) compared to adults aged 35-44 years (28%), and among Black individuals (8%) compared to White individuals (63%) [17]. Sullivan and colleagues [14] in a recent study using commercial pharmacy data to count PrEP users from 2012-2021 found the lowest PrEP use in the South compared to other US regions, and the lowest PrEP access in relation to the needs among the Black compared to the White individuals.

Multilevel barriers to PrEP provision and uptake include client-level barriers (such as low PrEP awareness, mistrust of the health care system, and PrEP-associated stigma) [18-21], health care system–level barriers (such as knowledge gaps and comfort among providers, unconscious bias, and racism) [22-24], and structural-level barriers (such as costs, reimbursement, and lack of health insurance) [24-26]. More specifically, in the South, PrEP provision and uptake have been limited by geographical factors—living in rural areas with limited access to PrEP providers [7], provider and health care system factors, including PrEP knowledge [27], provider sexual assessment skills [27], perceived provider racism [28], PrEP stigma [28,29], and health care capacity, among many other factors [7,30,31]. Thus, training providers in taking a sexual history and PrEP clinical care may be a successful strategy to increase PrEP use among Black adolescent girls and young women in the South [31-34].

Among health care providers (HCPs), family medicine (FM) practitioners have tremendous reach in rural communities and provide crucial preventive care for underserved populations [35]. They also provide transitional care as children advance into late adolescence, which often coincides with the onset of sexual activity [36-38]. In predominantly rural states like Alabama with high HIV incidence in rural communities, FM practitioners are a critical workforce to engage in HIV prevention methods like PrEP. Building the HIV workforce

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capacity is also responsive to the Ending the HIV Epidemic (EHE) national goals to improve our epidemic and decrease current inequities [39].

This paper outlines a protocol to develop and pilot a multicomponent intervention to train and support FM trainees to promote PrEP for adolescent girls and young women in Alabama. Our primary aims are to (1) adapt content to train FM trainees on HIV epidemiology and PrEP; (2) take a gender-neutral sexual history, and support "PrEP Champions," (ie, FM trainees committed to promoting PrEP within the clinic); (3) pretest and pilot test the initially adapted intervention; and (4) conduct a formative evaluation to explore determinants of implementation. This proposed intervention provides an opportunity to expand comprehensive sexual and reproductive health care for adolescent girls and young women and train providers in HIV prevention.

Methods

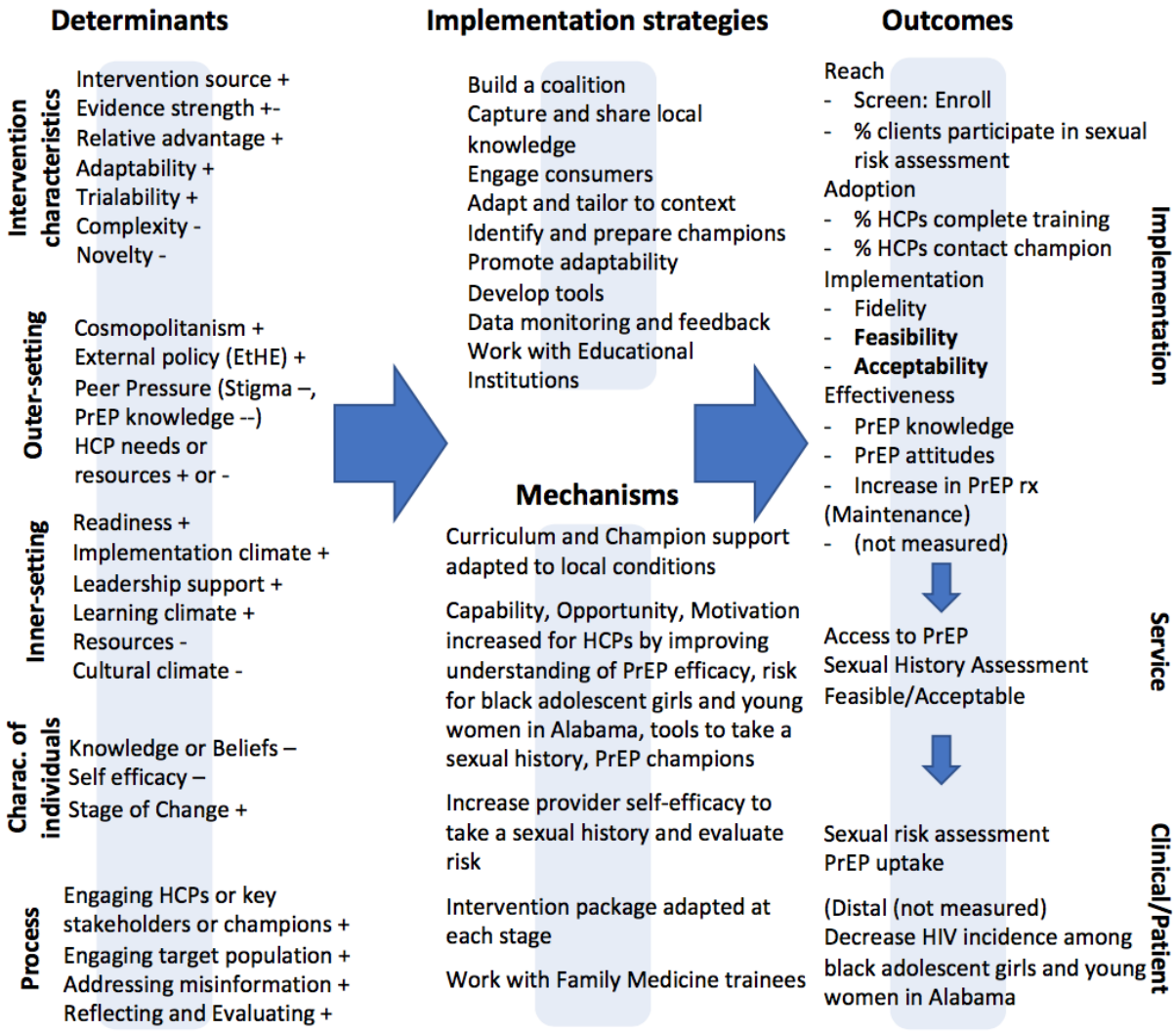
Study Design and Setting

We are conducting an implementation science mixed methods study to develop and pilot test a multicomponent intervention—PrEP-Pro—for FM trainees in urban and rural Alabama to promote PrEP education, counseling, and prescription to Black adolescent girls and young women in Alabama. We chose to work with FM practitioners who provide comprehensive health care services across the lifespan, including adolescent girls and young women, and dominate the rural workforce [35]. In addition, we opted to work with trainees as provider behavior change may be more effective when integrated into the formative stages of training [40,41]. The FM program partners include trainees and providers from 4 programs across the state of Alabama, including programs based in rural and urban areas.

The PrEP-Pro intervention is theoretically informed by the Capability-Opportunity-Motivation-Behavior (COM-B) model for behavioral change [42] and the Consolidated Framework for Implementation Research (CFIR) [43]. The COM-B model for behavioral change proposes 3 components to any behavior [42]. Capability (C) refers to how capable providers feel about performing a behavior. For example, FM residents must be able to efficiently take a sexual history from adolescents to assess risk. Opportunity (O) refers to the social and physical opportunity to engage in the behavior. FM residents need support (eg, PrEP Champions) to navigate health insurance, privacy issues, and community stigma to offer PrEP. Motivation (M) refers to the desire to carry out the behavior in the face of other competing interests and may be addressed by helping FM residents understand the effectiveness of PrEP or by engaging PrEP Champions to motivate FM residents to prescribe PrEP. Our PrEP-Pro intervention addresses each component of the COM-B model to facilitate the increase of PrEP prescriptions to Black adolescent girls and young women. We also apply CFIR to consider multiple determinants required to increase PrEP prescriptions to Black adolescent girls and young women. CFIR is an implementation science determinant framework widely used to guide the systematic assessment of multilevel contextual factors that affect implementation and includes 5 domains, 48 constructs, and 19 subconstructs [43,44]. The 5 domains are (1) intervention characteristics or innovation (ie, the product or the "thing" being implemented), (2) inner setting (ie, setting where the innovation is being carried out), (3) outer setting (ie, setting where the inner setting exists), (4) individuals (ie, roles and responsibilities of individuals), and (5) implementation process (ie, various activities carried out to implement the innovation) [44]. For example, the individual-level determinants at the provider level that may influence PrEP prescription include knowledge and beliefs around PrEP and conducting a sexual history or risk assessment, and self-efficacy as identified in our studies and also supported by prior literature [21,22,24,31,45]. The inner setting determinants include readiness for change, ease of access to knowledge and information about sexual history taking and PrEP, and leadership engagement within FM training programs to innovate and provide research opportunities for residents. The outer setting determinants include state-level EHE impetus and PrEP products in the pipeline. Therefore, guided by CFIR, we will draft and further explore and understand more granularly the implementation determinants of PrEP-Pro intervention to inform a future hybrid effectiveness/implementation trial (Figure 1).

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Figure 1. Implementation Research Logic Model (PrEP-Pro). The symbols "+" and "-" serve to indicate the "valence" of the determinants, or whether we anticipate the determinant will be a facilitator (+), a stronger facilitator (++), a barrier (-), a stronger barrier (—), or have a mixed impact *(+/-) on the implementation of the intervention. HCP: health care provider; PrEP: pre-exposure prophylaxis.



PrEP-Pro Multicomponent Intervention

The PrEP-Pro intervention consists of 3 main components. Tailored training in HIV epidemiology and PrEP basics, sexual history taking, and support practice–based PrEP Champions will be provided. We will first adapt and develop the PrEP-Pro intervention and then conduct a pilot test. To guide the systematic development of our intervention, implementation, and evaluation, we will use intervention mapping (IM) techniques [46,47].

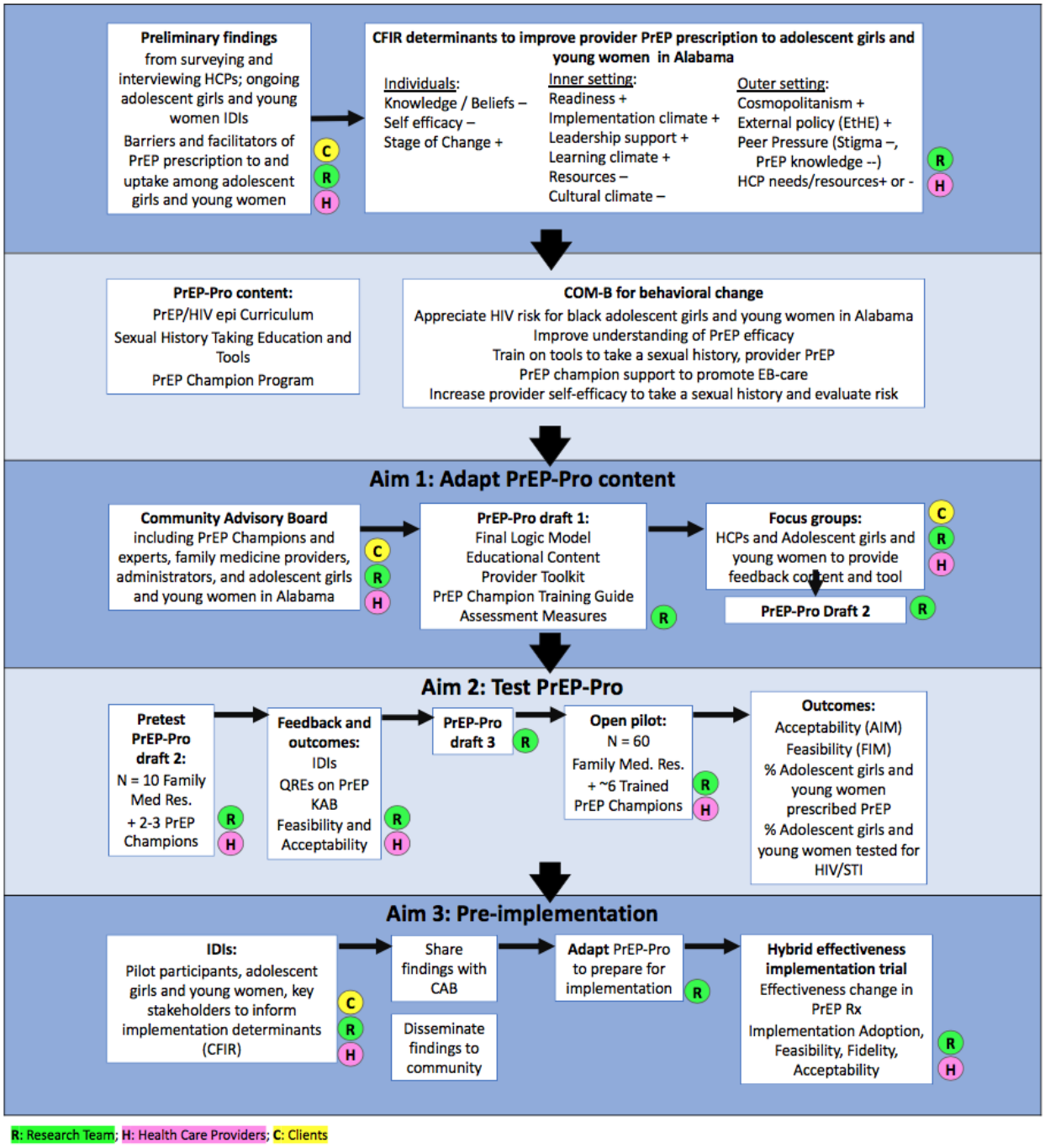
Phase 1: Development of the Multicomponent Intervention

Overview

In phase 1, we will develop a multicomponent intervention, PrEP-Pro intervention (Figure 2). This includes the adaptation of content to train on HIV epidemiology and PrEP and the development of implementation strategies including provider-facing tools and client-facing educational materials. We plan to make the content developed compatible with the Project Extension for Community Healthcare Outcomes to optimize dissemination opportunities [48]. Project Extension for Community Healthcare Outcomes is a disease management approach using case-based web-based learning to increase knowledge among providers and standardize best practices for the screening, care, and treatment of a disease [49,50].

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Figure 2. PrEP-Pro study flow and aims. AIM: Acceptability of Intervention Measure; CAB: community advisory board; CFIR: Consolidated Framework for Implementation Research; FIM: Feasibility of Intervention Measure; HCP: health care provider; IDI: in-depth interview; PrEP: pre-exposure prophylaxis; PrEP KAB: pre-exposure prophylaxis knowledge, attitudes, and behavior; QRE: questionnaire; STI: sexually transmitted infection.



Anticipated Adaptations

We plan to make adaptations or develop new content in the following areas: (1) epidemiology of HIV risk for Black adolescent girls and young women in Alabama; (2) PrEP indications for adolescent girls and young women; (3) PrEP knowledge, attitudes, and behavior (KAB) tool; (4) sexual history taking with focus on adolescent girls and young women needs and nuances in how to ask questions to this age group; (5) sexual history screening tool for adolescent girls and young women including strategies to optimize sexual behavior screening for adolescent girls and young women; and (6) PrEP champion toolkit.

Adaptation Process

Review of Existing Literature

To adapt content, the research team reviewed existing literature and web-based databases to identify relevant and more recent content on sexual history taking [51-54], HIV epidemiology [55-57], PrEP curriculum [58-61], local resources and tools for PrEP Champions, as well as relevant instruments to assess PrEP knowledge, attitudes, and beliefs [62,63]. The lead authors of publications were contacted through email to request additional materials discussed in their publications which are not accessible digitally.

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Review With the Scientific Advisory Board (SAB)

The research team worked with a broader scientific investigative team inclusive of expertise in adolescent health, medical education, FM training, and HIV prevention or PrEP care to solicit input and review materials and data gathered from the review of existing literature.

Community Engagement With the Community Advisory Board (CAB)

Drawing on the principles of cocreation [64,65], we developed 2 CABs, 1 group (N=7) comprising FM representatives from rural and urban settings, including FM trainees, administrators, and advocates, and a second group (N=4) comprising Black adolescent girls and young women. The CABs were convened separately due to the different roles, expertise, and comfort level in sharing. CAB members were identified and recruited based on recommendations from our scientific team and our collaborating FM programs. CAB members meet remotely for 1 hour every month to review and reach a consensus on the content of the curriculum and tools that address adolescent tenets, tools to measure PrEP knowledge, as well as provide input on optimal strategies to train FM residents and promote or offer PrEP. This process is ongoing, and details on the iterations made to the content of the curriculum and tools will be published in a subsequent paper. In addition to working with the CAB to adapt content, we also plan to work with the CAB throughout the study to help with the interpretation of results and dissemination of study findings.

Focus Group Discussions (FGDs) With FM Providers (Trainees)

Two FGDs comprising FM trainees will be conducted (December 2022-January 2023) to seek feedback on the draft PrEP-Pro content and a newly developed PrEP KAB tool. Provider participant eligibility criteria include (1) being a licensed HCP (MD, DO) trainee, (2) providing medical care to adolescent girls and young women in Alabama, (3) working in a clinic setting where at least 20% of the population is Black, and (4) being able or willing to provide informed consent. Participants will complete a brief questionnaire outlining sociodemographic and clinic practice characteristics. During the FGD, the facilitator will present the initial adapted PrEP-Pro intervention (including the initial draft of the PrEP-Pro content, badges, flow charts, and tools) iteratively to the 2 groups of 4-6 FM trainees. FGDs will be conducted virtually or in an enclosed private location and will last for approximately 60 to 90 minutes. Trained interviewers will facilitate all FGDs, including probing, asking open-ended questions, ensuring nonjudgmentalism, and using grounded theory. FGDs will be digitally recorded and transcribed. All FGD participants will be reimbursed US $50 for their time.

Phase 2: Testing the Initially Adapted PrEP-Pro Intervention

Overview

Using peer champions to improve provider knowledge and quality of care is an evidence-based implementation strategy [66]. Studies describe the presence of change champions within clinical practices as essential facilitators of quality improvement [67], and such champions can play an essential role in communication, marketing, education, skill-building, and assessment [68]. Provider champions are agents of change [69], empowering their peer providers within their practice to engage in innovations, practice new skills, and implement new care strategies with more ease and confidence.

The primary aim of phase 2 is to pretest and pilot-test the initially adapted PrEP-Pro intervention with FM trainees in Alabama (Figure 2). We will pretest the intervention by training 2 FM trainees as PrEP champions with the initially drafted curriculum, who will then deliver the draft curriculum and ongoing support to 8-12 FM trainees (from at least 1 urban and 1 rural setting). In addition to receiving additional training and support, PrEP champions will have access to PrEP consultants and experts.

The pretest phase will allow us to optimize the PrEP-Pro intervention (refine the number and length of sessions, educational material content, and other details that will be key to maximizing acceptability, feasibility, and impact). Thereafter, an open pilot trial of the PrEP-Pro intervention will be conducted by training an additional 6 FM trainees to serve as PrEP Champions and enrolling 60 unique FM trainees from rural and urban settings into the study.

Training PrEP Champions can thus support entire practices to sustain the provision of evidence-based care, navigate medical assistance programs and insurance coverage and troubleshoot new challenges [70].

PrEP-Pro Champion Training Workshop

PrEP Champions will complete an estimated 4 hours of training over 3 sessions using the PrEP Champion training tools. PrEP Champions will receive more comprehensive detailed training on HIV epidemiology and how to remain updated with the latest data, how to use the adapted sexual history-taking tool, PrEP efficacy, and indications. They will also be supported by an established PrEP Champion on our team to train on and role play, prescribing requirements, nuances to prescribing and fielding questions from adolescents, PrEP adherence support, medical assistance program navigation, and effective curriculum delivery to peers. An education expert member of the scientific team will coach PrEP Champions in effective curriculum delivery. PrEP Champions will also be trained to troubleshoot challenges that may arise and will be encouraged to set up a "community of practice" within their group for check-ins regarding challenges and solutions (eg, through a monthly call or WhatsApp or GroupMe chat). PrEP Champions will also log their time and provider contacts through a web-based app (eg, toggl.com, myhours.com, or text the project coordinator) over 3 months (pretest) and 6 months (pilot). To optimize PrEP-Pro intervention fidelity, PrEP Champions will complete standardized training and use structured protocols. Early training sessions will be monitored. Subsequently, a subset of sessions (at least one additional session per champion) will be audio-recorded and reviewed by the investigators, and a checklist will be developed for a protocol adherence. This will allow for real-time feedback and minimize drift in the approach [71]. After the initial training, PrEP Champions will complete

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an evaluation to assess HIV epidemiology, PrEP knowledge, and the acceptability and feasibility of training curricula.

Provider PrEP Education

Other FM trainees will receive 2 hours of case-based real-time sessions with a videoconference hosted by a local PrEP Champion including a 1-hour session on PrEP prescription and a 1-hour session on sexual history taking.

Participants and Eligibility Criteria

Participants will be identified and purposefully selected through FM partner program directors and faculty. The project coordinator will work with site leadership to generate a list and contact details for all practicing FM trainees at the study sites. A random-order list of eligible FM trainees stratified by gender, race, training site, year of training, and age quartiles will be generated. FM trainees will be approached by the project coordinator (via email, phone, or in person) and invited to participate in the pilot program. Reasons for declining will be recorded. Eligibility for PrEP Champions, pretest, and pilot participants will include (1) a licensed HCP (MD, DO) trainee, (2) providing medical care to adolescent girls and young women in Alabama, (3) working in a clinic where at least 20% of the population is Black, and (4) being able or willing to provide informed consent. The aim is to ensure that trainees feel free from coercion by including at least 1 trainee in our CAB. All language within the recruitment materials and consent forms will be explicit that participation in this study is not mandatory nor impacts trainee clinical obligations, clinical evaluations, or standing within the residency program. Participants will be reimbursed for their time.

Primary Outcomes

The primary outcomes to be assessed per our original protocol are PrEP-Pro acceptability and feasibility (Table 1). However, as we engage our CAB and SAB continually and iteratively, these outcomes are subject to evolve based on feedback.

Table 1. Primary and secondary outcomes.

Outcomes and measures	Source of data
Primary outcomes	
• Acceptability of Intervention Measure (AIM): 4 items, 5-point Likert scale • Intervention Appropriateness Measure (IAM): 4 items, 5-point Likert scale • Evidence-Based Practice Attitude Scale (EPAS-15): 15 items, 5-point Likert scale • Feasibility of Intervention Measure: 4 items, 5-point Likert scale • Number screened, eligible, and enrolled • Number or proportion who completes all planned training modules • Number or proportion who contact the PrEP[a] Champion at least once after training	Quantitative data (Survey/Process measures)
• PrEP-Pro Feasibility • PrEP-Pro Acceptability • Willingness to prescribe PrEP	Qualitative data (IDIs[b])
Secondary outcomes	
• PrEP knowledge • HIV epidemiology knowledge • Sexual history taking beliefs and attitudes • Willingness to prescribe PrEP	Quantitative data (Survey)
• Sexual history taking practices • HIV and STI[c] tests or adolescent girls and young women encounters • PrEP prescriptions or adolescent girls and young women encounters	Quantitative data (EMR[d])

[a]PrEP: pre-exposure prophylaxis.

[b]IDI: in-depth interview.

[c]STI: sexually transmitted infection.

[d]EMR: electronic medical record.

PrEP-Pro Acceptability

This will be assessed using three validated instruments: (1) Acceptability of Intervention Measure (AIM), a 4-item instrument with 5-point Likert scale response options [72], (2) Intervention Appropriateness Measure, a 4-item instrument with 5-point Likert scale response options [72], and (3) Evidence-Based Practice Attitude Scale, a 15-item instrument with 5-point Likert scale response options [73].

PrEP-Pro Feasibility

This will be assessed using the Feasibility of Intervention Measure, a 4-item instrument with 5-point Likert scale response options [72]. Additionally, to assess PrEP-Pro feasibility, the number of residents screened, eligible, and enrolled, the time to complete training, the number of participants who complete training, and the number of participants who contact PrEP champions at least once in the quarter after the training (as reported by each PrEP Champion via study logs) will also be described.

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To assess these outcomes, FM trainees will complete questionnaires at 0, 3, and 6 months post PrEP-Pro training. Enrolled FM trainees (PrEP Champions, providers who pretest PrEP-Pro, and pilot participants) will complete a baseline questionnaire to capture sociodemographic data (age, race, gender, years of practice, and client volume), PrEP KAB practices, and experiences with PrEP provision. PrEP Champions and providers that pretest PrEP-Pro will complete a posttraining or intervention questionnaire within 3 months of training or 6 months of training for pilot participants. Questionnaires will be completed in REDCap by the participants via a secure link sent to their computer, phone, or other electronic devices.

Secondary Outcomes

Other outcomes will also be assessed including PrEP knowledge, sexual history taking attitudes and practices [74], PrEP prescriptions at adolescent girls and young women encounters, and sexually transmitted infection (STI) and HIV testing at adolescent girls and young women encounters (Table 1). We aim to explore how to optimize PrEP-Pro to maximize acceptability, feasibility, and impact including barriers and facilitators to PrEP-Pro initially adapted intervention.

To assess these secondary outcomes, data will be extracted from electronic medical records at baseline, 3 months, and 6 months after enrollment to provide data on the number of PrEP prescriptions to adolescent girls and young women, HIV testing, and STI testing among adolescent girls and young women in the 6 months before or after PrEP-Pro training. Additionally, IDIs will be conducted with PrEP Champions and pretest participants within 3 months of scheduled training completion. Interview guides will be developed using our conceptual frameworks, a recent review of literature, and input from study team members and the CAB and will focus on challenges, successes, barriers, and facilitators to PrEP prescription to adolescent girls and young women and feasibility, acceptability, anticipated impacts of the draft PrEP-Pro intervention. To plan for the implementation of PrEP-Pro as an intervention strategy to promote PrEP prescription, IDIs will be conducted with 25 pilot participants, 25 adolescent girls and young women who accessed care after the PrEP-Pro pilot, and ~12 other key stakeholders (eg, administrators and support staff) to explore anticipated determinants of implementation based on CFIR [43,75]. PrEP Champions will inform process-level domains, PrEP-Pro pilot providers and adolescent girls and young women will inform individual-level domains, and key stakeholders will inform outer-setting domains. PrEP-Pro will be updated based on any interval innovations in PrEP implementation science and present the findings to the CAB and consultants to seek feedback on implementation determinants. Interviews will be conducted remotely or in an enclosed private location and will last for approximately 45 to 60 minutes. All interviews will be digitally recorded and transcribed.

Sample Size Justification

The plan to pretest PrEP-Pro with 12 providers is consistent with recommendations for pretesting from IM literature [76] and our pretesting sample in prior intervention development. For this pilot study, the importance of sample size lies in establishing acceptability and feasibility and the precision of estimated changes in PrEP prescriptions. There will be a recruitment of 60 FM trainees throughout Alabama. With our sample, we can estimate this measure with a 95% margin of error of 0.26 SD, where SD is the observed standard deviation of the Feasibility of Intervention Measure or AIM score. For example, if we observe an SD of 5, the 95% CI would be ±1.3. Similarly, the margin of error for the change in average PrEP prescriptions 6 months before to 6 months after the intervention is ±0.26 SD.

Ethical Considerations

Ethical approval for phase 1 of the study to assemble a CAB and conduct FGDs was approved by the Institutional Review Board (IRB) at the University of Alabama at Birmingham, Alabama (IRB-300008567). Written informed consent will be obtained from all FGD participants prior to their participation in the study. Both FGD participants and CAB members are compensated US $50 for their time (eg, an hour-long CAB meeting or an hour-long FGD). A separate ethics approval will be obtained from the institutional review board prior to commencing phase 2 of the study. All data will be kept confidential and stored in password-protected software with encryption. Only deidentified data will be reported.

Data Analysis

FGD Analysis

FGDs will be audio recorded, transcribed, and initially analyzed using a structured template and memo-based approach with subsequent transcription and coding [77]. This template approach will consist of team members reviewing the recordings of the FGD, making notes of important themes and responses, and then summarizing the interview content. Using this method, the research team will be able to quickly discuss and apply key data points to the implementation strategy design, and later, a more in-depth analysis of the transcribed discussions will be conducted using content analysis [78,79].

IDI Analysis

IDIs will be audio recorded, transcribed, and analyzed more in-depth using the content analysis approach [78,79].

Two investigators will independently review transcripts to generate an overarching thematic framework for data interpretation. Initial themes will be identified based on the initial readings of a subset of transcripts and guided by our theories or conceptual frameworks (COM-B and CFIR). Themes will be discussed among the scientific team, transcripts will be reread, and themes will be refined based on further review of the transcripts until saturation is achieved. Final themes including major themes and subthemes will be developed. A codebook will be developed with a detailed description of major themes and subthemes. The investigators will compare their thematic frameworks for consistency, and any discrepancies will be discussed until there is agreement on the thematic framework. Using multiple coders also enhances the validity of the analysis [80]. Kappa statistics will be computed to measure agreement between coders (interrater reliability test). Data will be reexamined, messages will be extracted and

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highlighted, and the ongoing discussion between coders will allow for further theorizing and interconnections between research questions, coding categories, and raw data (108). Emerging themes will be explored with the CAB and the SAB to enhance the validity of the findings. We will also compare data findings with results from our quantitative data and external review of the literature for consistency. NVivo (QSR International) software will be used to organize data and facilitate analyses.

Statistical Analysis

Descriptive statistics will be calculated to characterize acceptability and feasibility measures collected 3 months (PrEP champions and pretest participants) and 6 months (pilot participants) after enrollment. All scores will be summarized using appropriate descriptive statistics. The number of participants screened, eligible, and enrolled; the proportion of participants who complete all planned training modules; and the proportion of participants who contact the PrEP Champion at least once in the quarter after training will be described. We will also describe the data and compare pre- and post-PrEP prescription or tests per adolescent girls and young women visit with nonparametric measures. Agreement between pre– and post–PrEP-Pro tests for categorical measures will be assessed using the McNemar test bivariate and using multiple logistic regression of post–PrEP-Pro outcomes adjusting for pre–PrEP-Pro measures and covariates. Covariates in adjusted models will include individual providers (such as age and race) and selected setting variables (such as client demographics, number of clients seen per day, and environment toward PrEP). Poisson regressions will determine associations between post–PrEP-Pro count measures (such as the number of PrEP prescriptions) and pre–PrEP-Pro counts, both unadjusted and covariate-adjusted. Similarly, for continuous outcomes (such as percent of adolescent girls and young women with PrEP prescription), Wilcoxon signed rank tests and linear models of post–PrEP-Pro measures would be used. We will examine missing data, but as our primary outcomes are feasibility or acceptability in which missing data (no response) is informative, no adjustments will be made.

Results

Study results will be presented to the CAB members and disseminated to practices, state health officials, and other key stakeholders to solicit feedback on implementation opportunities and challenges to inform a hybrid effectiveness implementation trial. The results of this study will also be presented at local and national conference meetings and submitted to peer-reviewed journals for publication.

Discussion

Principal Findings

This protocol paper describes a research study to develop and pilot a theoretically driven multicomponent intervention, PrEP-Pro, to train and support FM trainees across Alabama on HIV epidemiology, sexual history taking, and PrEP provision for adolescent girls and young women. Although PrEP is a highly effective biomedical intervention that can reduce HIV incidence among adolescent girls and young women, uptake remains low among adolescent girls and young women populations due to several multilevel factors [8,14]. In Alabama, which has been identified in the EHE strategy for the United States as a geographic hot spot due to high rural incidence, almost half of new HIV infections occur in those aged 13-29 years [57]. As PrEP options expand, there is an urgent need for appropriate, contextually relevant training tools to support PrEP implementation. It is anticipated that the PrEP-Pro intervention will result in an increase in PrEP prescriptions for adolescent girls and young women and an expansion of comprehensive sexual and reproductive health care for adolescent girls and young women in rural and urban Alabama.

To our knowledge, this is the first provider intervention that seeks to promote PrEP prescription among adolescent girls and young women in the South. Working with FM trainees is an innovative approach to promoting PrEP provision among clinicians who work with adolescents in rural communities across the United States [35,81]. Adapting PrEP-Pro to trainees provides an opportunity to modify clinician behavior at an early stage of training and help seed the rural health workforce with effective HIV prevention advocates and providers. Combining education specialists in theory-based IM with community engagement allows us to adapt interventions with greater content retention and implementation.

Despite our proposed novel intervention, we acknowledge several limitations. Many PrEP uptake barriers in Alabama are structural, including structural racism, a lack of comprehensive education in school settings, costs to access repeated HIV or STI testing, transportation, and a lack of Medicaid expansion [7,25,26]. While our study aims to target provider-level barriers, delivering multilevel interventions to address client, provider, and structural-level barriers would be ideal. However, structural issues are addressed in other projects our group supports [82-84]. Another limitation is that our study focuses primarily on adolescent girls and young women, and our outcomes will assess PrEP prescriptions for adolescent girls and young women, such that our study findings may not be generalizable to all populations. However, we have developed our PrEP-Pro content and intervention so that FM trainees can support and prescribe PrEP to all populations. Additionally, our PrEP-Pro intervention provides content mainly on tenofovir disoproxil fumarate/emtricitabine PrEP agents, with some content on newer PrEP products (injectable PrEP). Further, there is the possibility of selection bias in those who choose to become PrEP Champions or engage in the pretest and pilot. Lastly, as this is a pilot study, there will be a lack of data to assess long-term changes in outcomes. Future prospective cohort studies with longer periods to assess implementation outcomes and effectiveness outcomes among adolescent girls and young women populations may be warranted.

Conclusions

In conclusion, this study applies implementation and health services research science to adapt strategies to increase provider PrEP prescribing to adolescent girls and young women in the southern United States. As PrEP options expand, there is a

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pressing need to train FM practitioners and develop appropriate, contextually relevant training tools to support PrEP implementation. Study findings on the acceptability and feasibility of our PrEP-Pro intervention will help to inform a future hybrid effectiveness-implementation trial.

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Data Availability

Deidentified quantitative data sets generated during the study will be uploaded into a data-sharing site to be determined by the research team when the data are cleaned and analyzed. Due to the small sample size and difficulties in redacting qualitative data collected from a small group (FM providers from select programs in a small state), qualitative data with providers will not be shared.

Authors' Contributions

LTM and LE are the principal investigators of the study. OOI drafted the protocol. SVH, BH, DK, DML, MEC, NVW, RGL, and TS contributed to the study design. SVH, MEC, NVM, LE, and LTM read and revised the draft. All authors are involved in the study implementation. All authors approved the final manuscript.

Conflicts of Interest

MEC has received research support (grants to the institution) from Gilead Sciences and Viiv Healthcare, has served on advisory boards for Roche Diagnostics Corporation and Viiv Healthcare, and has received personal fees for educational events from Vindico Medical Education, Practice Point Communications, and Prime Education. LTM has received research support (grants to the institution) from Gilead Sciences.

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Abbreviations

AIM: Acceptability of Intervention Measure
CAB: community advisory board
CFIR: Consolidated Framework for Implementation Research
COM-B: Capability-Opportunity-Motivation-Behavior
EHE: Ending the HIV Epidemic
FGD: focus group discussion
FM: family medicine
HCP: health care provider
IDI: in-depth interview
IM: intervention mapping
KAB: knowledge, attitudes, and behavior
PrEP: pre-exposure prophylaxis
SAB: scientific advisory board
STI: sexually transmitted infection

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Protocol

Digital Outcome Measurement to Improve Care for Patients With Immune-Mediated Inflammatory Diseases: Protocol for the IMID Registry

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Abstract

Background: Despite enormous clinical improvements, due to better management strategies and the availability of biologicals, immune-mediated inflammatory diseases (IMIDs) still have a significant impact on patients' lives. To further reduce disease burden, provider- as well as patient-reported outcomes (PROs) should be taken into account during treatment and follow-up. Web-based collection of these outcomes generates valuable repeated measurements, which could be used (1) in daily clinical practice for patient-centered care, including shared decision-making; (2) for research purposes; and (3) as an essential step toward the implementation of value-based health care (VBHC). Our ultimate goal is that our health care delivery system is completely aligned with the principles of VBHC. For aforementioned reasons, we implemented the IMID registry.

Objective: The IMID registry is a digital system for routine outcome measurement that mainly includes PROs to improve care for patients with IMIDs.

Methods: The IMID registry is a longitudinal observational prospective cohort study within the departments of rheumatology, gastroenterology, dermatology, immunology, clinical pharmacy, and outpatient pharmacy of the Erasmus MC, the Netherlands. Patients with the following diseases are eligible for inclusion: inflammatory arthritis, inflammatory bowel disease, atopic dermatitis, psoriasis, uveitis, Behçet disease, sarcoidosis, and systemic vasculitis. Generic and disease-specific (patient-reported) outcomes, including adherence to medication, side effects, quality of life, work productivity, disease damage, and activity, are collected from patients and providers at fixed intervals before and during outpatient clinic visits. Data are collected and visualized through a data capture system, which is linked directly to the patients' electronic health record, which not only facilitates a more holistic care approach, but also helps with shared decision-making.

Results: The IMID registry is an ongoing cohort with no end date. Inclusion started in April 2018. From start until September 2022, a total of 1417 patients have been included from the participating departments. The mean age at inclusion was 46 (SD 16) years, and 56% of the patient population is female. The average percentage of filled out questionnaires at baseline is 84%, which

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drops to 72% after 1 year of follow-up. This decline may be due to the fact that the outcomes are not always discussed during the outpatient clinic visit or because the questionnaires were sometimes forgotten to set out. The registry is also used for research purposes and 92% of the patients with IMIDs gave informed consent to use their data for that.

Conclusions: The IMID registry is a web-based digital system that collects provider- and PROs. The collected outcomes are used to improve care for the individual patient with an IMID and facilitate shared decision-making, and they are also used for research purposes. The measurement of these outcomes is an essential step toward the implementation of VBHC.

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KEYWORDS

immune-mediated inflammatory diseases; IMID; value-based health care; patient-reported outcomes; web-based; tool; disease; patient; inflammatory; medicine; dermatology; rheumatology; gastroenterology; immunology; quality of life; mHealth; web-based tool; digital system

Introduction

Background

Immune-mediated inflammatory diseases (IMIDs) represent a group of chronic conditions that share common pathophysiological pathways that cause acute or chronic inflammation [1,2]. Any organ system can be affected, resulting in a broad variety of conditions including inflammatory arthritis (IA), inflammatory bowel disease (IBD), cutaneous inflammatory conditions, and several immunologic disorders [1,2].

Many IMIDs are treated with immunosuppressive medication, such as biologicals and disease-modifying antirheumatic drugs [1-9]. Over the years, the innovation of management approaches and the development of new treatment options have led to significant improvement in clinical outcomes [1]. However, IMIDs still have a large impact on patients' lives, including lower quality of life, more disability, and productivity loss [10-12]. Moreover, treatment is also often associated with medication-related adverse events [1,13]. Therefore, we should not only focus on clinical outcomes, such as disease activity measures, but also on outcomes that are relevant for the individual patient.

These "patient-reported outcomes" (PROs) cover topics, such as fatigue, pain, treatment satisfaction, and quality of life, without interpretation by a health care provider [14]. They are measured with PRO measures that mostly consist of validated questionnaires. The measurement of PROs in daily practice has several potential benefits as they could (1) improve care for the individual patient, (2) provide real-world data for research purposes, and (3) serve as a valuable part in the shift toward value-based health care (VBHC).

As PROs provide insight in disease burden and its treatment from a patient's perspective, they could be complementary to conventional clinical measures that are normally used during outpatient clinic visits. The use of PROs in daily practice helps both the physician and patient in preparing the consultation, but also facilitates the prioritization of topics that need to be addressed, resulting in a more efficient and problem-focused consultation [15]. The health care provider may also have the opportunity to tailor the treatment to the patients' needs and recognize problems that might otherwise be overlooked [15]. Moreover, visualizing PROs over time makes it easier for both patient and physician to monitor progress or deterioration of outcomes [15]. Lastly, measuring and reviewing PROs together with the patients could contribute to shared decision-making [16,17]. All these advantages contribute to a more patient-centered care approach.

Data generated within registries can also be used for research purposes. These real-world data are very valuable because they, among others, show us the community effectiveness [18]. Community effectiveness studies often show less benefit than efficacy studies or randomized controlled trials. Community effectiveness is determined by the following variables: efficacy, access (coverage), diagnostic certainty, upholding management guidelines by the treating physician, and patient compliance [18]. Furthermore, the organization and delivery of care may differ between medical specialists who treat IMIDs. For example, current rheumatoid arthritis guidelines do not have a laboratory monitoring program for tumor necrosis factor inhibitors, but the European psoriasis vulgaris guideline has one [19-21]. Another example is the use of therapeutic drug monitoring for tumor necrosis factor inhibitors in daily practice, which is more common in IBDs compared to rheumatic diseases [22,23]. The ability to use these data gives us the opportunity to better understand not only the differences between the organization and delivery of care, but also the differences or similarities in clinical outcomes as well as PROs between IMIDs. These data might help us improve the care of the individual patient through direct implementation of our research findings.

Finally, routine outcome measurements could be the first step toward the implementation of VBHC. VBHC aims to improve care by focusing on value instead of volume [24]. Value is defined as gained health divided by resources spent [24]. Gained health includes clinical outcomes as well as PROs and is therefore broader than we are currently used to [25,26]. As IMIDs are chronic conditions with fluctuating disease activity, longitudinal measurement of outcomes is necessary to evaluate the sustainability of health, incidence of complications, and side effects [25].

Implementation of longitudinal outcome measurement is currently upcoming. This is challenging because both health care providers and patients may find it time-consuming or

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impractical [27]. Therefore, there should be a practical way for physicians and patients to report and access these data, which could be through a web-based system. Electronic distribution of surveys before and during outpatient clinic visits has several benefits [28]: (1) patients can fill them out at home, (2) it streamlines the data-entry process, and (3) it allows for computer adaptive testing to reduce user burden. It also allows for easy data visualization and linkage with the electronic health record (EHR) for easy access by the health care providers.

The IMID registry was developed to implement digital routine outcome measurements in daily practice (1) to improve individual patient care, including shared decision-making, (2) for research purposes, and (3) as a first step toward the implementation of VBHC in patients with an IMID.

Objectives of the IMID Registry

The objectives of the IMID registry include (1) improving patient care on an individual level through a patient-centered care approach, including shared decision-making; (2) collecting real-world data for research purposes, including evaluating community effectiveness; and (3) implementing VBHC for patients with IMIDs, for which—in our opinion—collection of patient- and provider-reported outcomes is a fundamental component.

Methods

Study Design

The IMID registry is a single-center prospective cohort within the Erasmus MC in Rotterdam, the Netherlands. Patients are recruited from the departments of rheumatology, immunology, gastroenterology, and dermatology. A steering committee was also formed and included representatives of all participating departments. All representatives were involved in the design of the registry and selection of outcome measures. The cohort combines provider-reported outcomes and PROs. On request, clinical and administrative data can be exported from the EHR and pharmacy database. These data may include disease activity measures, the number of outpatient clinic visits in a certain time period, laboratory results, and medication, including administration and dosage.

Patients

All adult patients diagnosed with one of the following conditions are eligible: IA (rheumatoid arthritis, psoriatic arthritis, juvenile idiopathic arthritis, and spondyloarthritis), atopic dermatitis, psoriasis, IBD (Crohn disease and ulcerative colitis), uveitis, Behçet disease, sarcoidosis, or systemic vasculitis. Patients are excluded if they have insufficient knowledge of the Dutch language or are unable to fill out web-based questionnaires. Health care providers of each department ask eligible patients for informed consent, after which patients are included in their specific trajectory of the registry, which is based on the diagnosis that is made by the treating physician.

Outcome Measures

For IBD and IA, the questionnaires were aligned with the corresponding International Consortium for Health Outcomes Measurement (ICHOM) outcome sets to make sure that all recommended questionnaires were included in the registry [29,30]. Generic and disease-specific outcomes that are used for each diagnosis include disease activity, disease damage as a result of active disease or complications (eg, changes in anatomy, physiology, pathology, or function), disease-specific and generic quality of life, treatment satisfaction, side effects, medication adherence, beliefs about medication, work productivity, disability, fatigue, and substance use. If available, validated questionnaires are used to measure these PROs. To reduce patient burden, the shortest versions of the questionnaires are used. See Table 1 for overarching outcomes and Table 2 for disease-specific outcomes. These outcomes can be linked to data from the EHR, such as medication, health care use, and disease duration.

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Table 1. Generic outcomes and questionnaires.

Outcome measure	Used questionnaire	Time point				
		Baseline	3 months	6 months	Yearly	Indicated time (minutes)
Treatment						
Side effects[a]		✓	✓	✓	✓	<0.5
Beliefs about medication	BMQ[b] necessity-concerns differential [31,32]	✓			✓	1.5
Medication adherence	MARS-5[c] [33]		✓	✓	✓	0.5
Treatment satisfaction	VAS[d] 0-100	✓	✓	✓	✓	0.5
Disease impact						
Quality of life	EQ-5D-5L[e] [34,35]	✓	✓		✓	1
Quality of life	PROMIS-10[f] [36,37]			✓	✓	1.5
Quality of life	SF-36[g,h] [38,39, 40]			✓	✓	4.5
Fatigue	NRS[i] 0-10	✓	✓	✓	✓	0.5
Work disability	WPAI[j] [41]	✓			✓	1
Physical activity	iPAQ[k] short form [42,43][h]	✓	✓		✓	3
Participation	Participation scale [44][h]	✓	✓		✓	3.5

[a]Questionnaire reported by patients and physician.

[b]BMQ: Beliefs About Medicine Questionnaire.

[c]MARS-5: 5-item Medication Adherence Report Scale.

[d]VAS: visual analog scale.

[e]EQ-5D-5L: 5-level EQ-5D.

[f]PROMIS-10: 10-item Patient-Reported Outcomes Measurement Information System.

[g]SF-36: RAND 36-item short form survey.

[h]These questionnaires were used earlier, but are not part of the questionnaire set anymore.

[i]NRS: numeric rating scale.

[j]WPAI: Work Productivity and Activity Impairment Questionnaire.

[k]iPAQ: International Physical Activity Questionnaire.

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Table 2. Disease-specific outcomes and questionnaires.

Disease group, disease, and questionnaires used	Outcome measure				
	Disease activity	Damage	Quality of life	Other[a]	Indicated time (minutes)
Inflammatory arthritis					
DAS[b]-28[c] [45]	✓				
Disease damage[c]		✓			<0.5
HAQ-DI[d] [46,47]				✓	2.5
DMARD[e] side effects[c]				✓	<0.5
BASDAI[c,f] (spondyloarthritis) [48,49]	✓				1
Inflammatory bowel disease					
IBD[g]-control-8 [50,51]	✓				1
iMTA[h] PCQ[i] [52]			✓		1
Manitoba IBD Index [53]	✓				0.5
Montreal classification[c,j] [54]			✓		0.5
Disease damage[j]		✓			<0.5
IBDQ[k] [55][j]			✓		5.5
Harvey Bradshaw Index (Crohn disease) [56][j]	✓				0.5
Immunology					
BDCAF[l,m] (Behçet disease) [57]	✓				2.5
Sarcoidosis disease activity[c] (sarcoidosis)	✓				0.5
VFQ[n]-25 (uveitis) [58]			✓		10
BVAS[c,o] (vasculitis) [59]	✓				0.5
VDI[c,p] (vasculitis) [60]		✓			0.5
Dermatology					
ADCT[q] [61]	✓				0.5
NRS[r] disease burden[c]		✓			0.5
DLQI[s] [62]		✓			1.5
PGA[t] or IGA[u] scale[c]	✓				<0.5
PASI[c,v] (psoriasis) [63]	✓				0.5
POEM[w] (atopic dermatitis) [64]	✓				1
EASI[x] (atopic dermatitis) [65]	✓				1

[a]Questionnaires involving side effects, physical functionality, and productivity loss.
[b]DAS: Disease Activity Score.
[c]Questionnaire reported by physician only.
[d]HAQ-DI: Health Assessment Questionnaire Disability Index.
[e]DMARD: disease-modifying antirheumatic drug.
[f]BASDAI: Bath Ankylosing Spondylitis Disease Activity Index.
[g]IBD: inflammatory bowel disease.
[h]iMTA: Institute for Medical Technology Assessment.
[i]PCQ: Productivity Cost Questionnaire.
[j]These questionnaires were asked earlier, but are not part of the questionnaire set anymore.

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[k]IBDQ: Inflammatory Bowel Disease Questionnaire.
[l]BDCAF: Behçet Disease Current Activity Form.
[m]Questionnaire reported by patients and physician.
[n]VFQ: Visual Function Questionnaire.
[o]BVAS: Birmingham Vasculitis Activity Score.
[p]VDI: Vasculitis Damage Index.
[q]ADCT: Atopic Dermatitis Control Tool.
[r]NRS: numeric rating scale.
[s]DLQI: Dermatology Life Quality Index.
[t]PGA: patient global assessment.
[u]IGA: Investigator's Global Assessment.
[v]PASI: Psoriasis Area and Severity Index.
[w]POEM: Patient-Oriented Eczema Measure.
[x]EASI: Eczema Area and Severity Index.

Generic Outcomes

Patient- and Physician-Reported Side Effects

Because health care providers might underreport side effects, both patients and physicians are asked about the occurrence of side effects [66]. If any side effects occur, respondents are asked to clarify the time of onset, severity, and if there are any persisting side effects after medication dosage was changed or stopped. The physician is asked to clarify if medication is switched or if additional medication (eg, antibiotics) is needed.

Beliefs About Medication

The Beliefs About Medicine Questionnaire has been validated for assessing medication beliefs in patients with somatic chronic illnesses and consists of a specific and general section [31,32]. For this cohort, we only use the "specific" section that measures patient beliefs about the necessity of prescribed medication to treat their disease and their concerns about potential adverse events of taking the medication. All questions are rated on a 5-point Likert scale. Higher scores indicate stronger beliefs about necessity of their medication or concerns.

Medication Adherence

The 5-item Medication Adherence Report Scale is used to assess nonadherence to medication using a 5-point Likert scale [33]. It addresses nonadherence in a nonjudgmental way, encourages patients to answer truthfully and avoid socially desirable answers. Higher scores indicate higher levels of self-reported adherence.

Treatment Satisfaction

Patients are asked to indicate their feeling of satisfaction with the effect of their current treatment on disease activity on a visual analog scale (VAS) from 0 to 100. Higher scores indicate higher treatment satisfaction.

Fatigue

This questionnaire asks patients to rate their fatigue level in the last 7 days using a numeric rating scale of 1 to 10. A higher score corresponds with more fatigue experienced.

(Health-Related) Quality of Life

(Health-related) quality of life is measured with 2 different questionnaires: the 5-level EQ-5D and the Patient-Reported Outcomes Measurement Information System (PROMIS-10) [34-37]. The 5-level EQ-5D is used to measure utility scores based on the Dutch reference values and consists of 5 questions representing 5 dimensions of health, namely, mobility, self-care, daily activities, pain and discomfort, and anxiety and depression [34,35,67]. Each dimension can be scored on a 5-point Likert scale. Higher scores indicate more reported problems in the stated health dimension. The sixth question consists of a VAS general health.

The PROMIS-10 measures general health-related quality of life using 10 questions on physical, mental, and social health, pain, fatigue, and overall perceived quality of life [36,37]. Answers are given using a 5-point Likert scale or a VAS from 0 to 10. Outcomes are summarized into a summary score for global physical health and global mental health with accompanying *t* scores that compare the patients' health to the general population.

Work Productivity

The Work Productivity and Activity Impairment questionnaire [41] measures sick leave or unemployment (absenteeism) and work impairment due to the disease (presenteeism) during the past 7 days. The questionnaire contains 6 questions regarding the effect of disease on work and productivity.

Other Questionnaires

Over the years, some of the used questionnaires have changed or have been adapted based on feedback from health care providers and patients. These questionnaires are shown in Tables 1 and 2.

Disease-Specific Outcome Measures

For each disease (group), disease-specific outcome measures were chosen. They cover outcomes about disease activity and damage, quality of life, functional ability, side effects, and productivity loss. These outcome measures along with their accompanying questionnaires are shown in Table 2.

Patient and Public Involvement

Patients were not involved in the design of the registry, but our patient participation panel and included IMID registry patients will be regularly asked to evaluate the questionnaire system,

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including the number and relevance of the questionnaires. The registry will be optimized based on their feedback.

Data Collection

To limit user burden, the questionnaires are divided over different time points. At baseline and 2 weeks before the outpatient clinic visits, an invitation to fill out new questionnaires is sent to the patient by email. The health care providers fill out the surveys during or right after the consultation. After 1 year, the questionnaires are filled out yearly. However, an exception is made for patients with IA, IBD, and atopic dermatitis, because they are asked to fill out questionnaires before each outpatient clinic visit or at fixed intervals, which were added on request of the participating departments. Surveys are filled out using a web-based questionnaire form (LimeSurvey) [68]. The questionnaires are managed by a data capture system (GemsTracker) [69], which is integrated in the EHR.

Data Visualization

Data are accessible through a web-based form, which is linked to the EHR. PRO scores are shown in the same manner as, for example, laboratory results and are also directly accessible through the EHR and visualized in graphs over time. For IA and atopic dermatitis, a dashboard has been developed, which allows visualization of several outcome measures over time in a comprehensive manner.

Training and Monitoring of the Implementation Process

Group trainings were given at the participating departments on the usage of the registry and how to access the data from the EHR. During the implementation phase, health care providers were supported during their consultations on the use of the data and how to discuss and interpret the PRO outcomes with the patients, including shared decision-making. Every 3 months, the IMID steering group comes together to discuss the progress of the registry, and every month multidisciplinary (scientific) meetings are held for all participating health care providers.

Ethics Approval

The IMID registry is a quality of care improvement initiative. Therefore, written informed consent is not mandatory for this purpose. Patients are asked by their health care provider to participate and give oral informed consent. In the web-based questionnaire form, they can opt-in for the use of their pseudonymized data for future scientific research. The Medical Ethics Committee of the Erasmus MC deemed the study to not be subject to Dutch law (WMO; Medical Research Involving Human Subjects Act) and provided a waiver (MEC-2018-1075).

Results

The IMID registry is an ongoing cohort with no end date. Inclusion started in April 2018. Until September 2022, a total of 1417 patients have been included in the registry. The included patients belong to the dermatology (n=477, 34%), immunology (n=153, 11%), gastroenterology (n=327, 23%), and rheumatology (n=460, 32%) departments.

The mean age at inclusion was 46 (SD 16) years, and 56% of the included patients are female. In Table 3, the demographics and baseline response rates are given, stratified for medical specialty. A total of 84% of patients filled out their questionnaires at baseline, which declined to 72% after 1 year of follow-up. In addition, a total of 92% of patients gave written informed consent for usage of their pseudonymized data for research purposes.

Table 3. Demographics and baseline response rate stratified for medical specialty.

Medical specialty	Response rate,[a] n (%)	Age (years), mean (95% CI)	Sex (female), %
Dermatology[b] (N=477)	378 (79)	41 (39-42)	43
Immunology[c] (N=153)	126 (82)	50 (47-52)	58
Gastroenterology[d] (N=327)	314 (96)	46 (44-47)	53
Rheumatology[e] (N=460)	415 (90)	49 (47-51)	68

[a]Percentage of patients who filled in the patient satisfaction questionnaire at baseline.

[b]Atopic dermatitis, psoriasis, and unclassified dermatologic diseases.

[c]Uveitis, Behçet disease, sarcoidosis, and systemic vasculitis.

[d]Crohn disease and ulcerative colitis.

[e]Rheumatoid arthritis, psoriatic arthritis, juvenile idiopathic arthritis, and spondyloarthritis.

Discussion

The IMID registry is a web-based system linked to the EHR that collects provider-reported outcomes and PROs. These outcomes are not only used to improve care for the individual patient with IMIDs including facilitation of shared decision-making, but they are also used for research purposes. Moreover, routine outcome measurements are an essential component in the implementation of VBHC. The registry has been used by the departments of rheumatology, gastroenterology, dermatology, and immunology, since 2018. Over the years, the outcome sets have been improved and adapted based on feedback from health care providers, patients, and current scientific insights. During the first 4 years, more than 1400 patients were included, which represents a broad uptake from all participating departments.

Previous publications have shown that patients with IMIDs may cope with lower quality of life, more disability, increased

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fatigue, pain, and productivity loss, but they also have more psychiatric comorbidity and medication-related adverse events [1,10-13,70]. The questionnaires were chosen to cover all aforementioned topics in a comprehensive manner to best reflect our overall health status of patients with IMIDs, but we also included the domains that matter most to our patients.

We chose to use generic questionnaires for several types of IMIDs, since these diseases may share common problems and patients may suffer from overlapping conditions within the IMID spectrum [1]. These diseases also share treatment strategies that may cause similar adverse events [1-9,13]. Generic questionnaires about these topics may lead to (1) evaluation of outcomes across patients with different conditions, (2) feedback from a larger patient-panel, and (3) improvements through the steering group's broad perspective.

Although the IMID registry has improved over the years, the cohort has some limitations. First, patients did not participate in the design of this registry. Currently, the IMID registry has been evaluated by 42% (n=467) of the patients that filled out a questionnaire in the past year. The survey included questions on the use of the system and length and content of the questionnaires. They also provided feedback on which topics they would like to discuss during consultations. The registry was adjusted based on their feedback. A couple of examples are rephrasing of some questions to make them more understandable, lowering the number of questionnaires before each visit, and changing the user interface to make them accessible for phone or tablet users. These evaluation rounds will be planned regularly.

The generalizability of the registry might be limited due to selection bias. Not all treating physicians use the registry during their outpatient clinic visits, and also not all patients are included or fill out their questionnaires. This could be due to the fact that patients cannot read or understand Dutch, have problems using a digital system, or the fact that the PROs are not discussed during consultation. Moreover, only patients who need specialized care are treated at the Erasmus MC. Finally, patients who tend to avoid care may cause nonresponse or selection bias. Although most of the included patients filled out their questionnaires at baseline, this percentage declines during follow-up. This is partly due to patients not filling out the questionnaires, but also on occasion, the questionnaire were not sent to the patient before the follow-up visit. In the near future, we hope to address these limitations by automatic inclusion of patients, giving them the opportunity to fill out questionnaires in the waiting room as well as by providing validated questionnaires in different languages. Providing more information about the use of the data, automatic distribution of questionnaires, as well as providing feedback about the filled out questionnaires during every consultation could also increase the response rate during follow-up.

We will also keep improving the IMID registry to optimize its relevance and feasibility. Currently, data are collected and visualized using a separate data collection tool, which is linked to the EHR. In the future, we will incorporate data collection directly into the EHR, as well as making it possible for the patient to visualize the data in a mobile app. Although routine outcome measurements are—in our opinion—a fundamental component in the implementation of VBHC, we hope to incorporate more VBHC principles in the future, as well as collaborating with other hospitals in the region, which has already been established for IBD and will soon be established for rheumatology [71].

In conclusion, the IMID registry provides a web-based outcome measurement system, which could facilitate the principles of VBHC, improve care on an individual patient level, and provide real-world data for research purposes.

Data Availability

Data are available from the corresponding author on reasonable request.

Authors' Contributions

All authors were involved in the writing or revision of the manuscript and approved the final version. JDB, JAMvL, DJH, PHPdJ, PHMvdK, and CJvdW were part of the IMID registry steering group and took part in the design or evaluation of the cohort.

Conflicts of Interest

CJvdW received grants and fee for advisory boards and presentations from Pfizer, Abbvie, Celltrion, Falk Benelux, Takeda, Janssen, and Ferring outside the submitted work. DJH is an investigator for AbbVie, Almirall, LEO Pharma, AstraZeneca, Novartis, and Sanofi and a consultant for Abbvie, Sanofi, LEO Pharma, AstraZeneca, Novartis, Janssen, Pfizer, and Lilly.

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Abbreviations

EHR: electronic health record
IA: inflammatory arthritis
IBD: inflammatory bowel disease
IMID: immune-mediated inflammatory disease
PRO: patient-reported outcome
PROMIS-10: Patient-Reported Outcomes Measurement Information System
VAS: visual analogue scale
VBHC: value-based health care

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Protocol

Evaluation of the Effectiveness of a Whole-System Intervention to Increase the Physical Activity of Children Aged 5 to 11 Years (Join Us: Move Play, JU:MP): Protocol for a Quasiexperimental Trial

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Abstract

Background: Daily physical activity is vital for the health and development of children. However, many children are inactive. Previous attempts to achieve sustained increases in daily physical activity in children have been ineffective. Join Us: Move Play (JU:MP) is a whole-system, complex, community-based intervention aiming to increase the physical activity levels of children aged 7 to 11 years who live in areas of Bradford, England, which are multicultural and have high levels of deprivation.

Objective: The purpose of this quasiexperimental controlled trial is to assess whether the JU:MP program increases primary school children's physical activity.

Methods: The study has a 2-arm, quasiexperimental, nonblinded, nonequivalent group design and will be conducted with primary school children aged 5 to 11 years at 3 timepoints, including baseline (before intervention), 24 months (during intervention), and 36 months (after intervention). Children attending primary schools within the intervention area will be invited to participate. Children attending similar schools within similar neighborhoods based on school and community census demographics (deprivation, free school meals, and ethnicity) outside of the JU:MP geographical area will be invited to participate in the control condition. At each timepoint, consenting participants will wear an accelerometer for 7 consecutive days (24 hours a day) to measure the primary outcome (average daily moderate-to-vigorous physical activity). Multivariable mixed effects linear regression will be applied to estimate differences in the primary outcome between the 2 arms at 24 months and 36 months on an intention-to-treat basis. The secondary outcome analysis will explore changes in socioemotional well-being (teacher reported), quality of life (parental/carer reported), and other contextual factors (parents/carer reported), as well as segments of the day activity, sleep, sedentary screen time, frequency of places to be active, parent practices (nondirective support and autonomy support), social cohesion, and neighborhood walking/exercise environment.

Results: Recruitment occurred from July 2021 to March 2022, and baseline data were collected from September 2021 to March 2022. As of March 2022 (end of baseline data collection), a total of 1454 children from 37 schools (17 intervention schools and 20 control schools) have been recruited. The first follow-up data collection will occur from September 2023 to March 2024, and the second and final follow-up data collection will occur from September 2024 to March 2025. Data analysis has not begun, and the final results will be published in December 2025.

Conclusions: This article describes the protocol for a quasiexperimental controlled trial examining a novel whole-system intervention.

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KEYWORDS

physical activity; accelerometry; complex intervention; whole system; children; quasiexperimental

Introduction

Background

Daily physical activity, particularly of moderate-to-vigorous intensity, is very beneficial for the physical, emotional, and social development of young people [1,2], and is preventive for the early onset of diseases and disorders [3-5]. This importance is enhanced when considering physical activity behaviors tracked through childhood into adulthood [6-9]. All 4 nations of the United Kingdom, along with the World Health Organization, recommend that children aged 5 to 18 years should engage in moderate-to-vigorous–intensity physical activity for an average of 60 minutes a day [10]. Since the publication of government guidance, evidence has shown that engaging in daily light-intensity physical activity [11] or increasing daily moderate-to-vigorous activity by an average of 10 minutes a day [12] can be beneficial for children and young people.

Worryingly, levels of inactivity are high across the globe [13,14]. Much effort has been made to combat levels of inactivity among young people [15,16], but previous interventions have been generally unsuccessful, especially in the medium to longer term [16,17]. The reasons for the lack of success so far include poor study design, poor methodology, and not considering the full complexity of physical activity, which is a behavior with much variance and heterogeneity across different groups and populations [16,17]. Previous interventions have only generally been discrete, simple, and 1-dimensional [16,17], although it has been over 3 decades since McLeroy et al [18] proposed that health promotion interventions and policies should consider every aspect of society from the social to physical environment, to individual personal traits. This socioecological perspective theorizes that change in such a complex behavior is not likely to occur just through individual motivation and desire alone, but instead through influencing every aspect of the socioecological model and wider system of society, to seek and promote more human movement. The challenge to decrease physical inactivity among all members of society, particularly children and young people, is only going to be addressed if future interventions and programs have a *systems thinking philosophy* and fully embrace the whole socioecological model within intervention and program planning and implementation [19]. The International Society of Physical Activity and Health supports this perspective with the publication of "Eight investments that work for physical activity," which advocates whole-system change across 8 domains, including schools, communities, travel, urban design, health care, workplaces, mass media, and sports and recreation [20].

In response to the growing realization of a need for whole-system approaches to physical activity, Sport England (a nondepartmental public body, which is the largest funder of physical activity and sport programs in England) funded 12 local delivery pilots over a 5-year period (2019-2024), to design and implement a whole-system place-based approach to reduce physical inactivity and health inequalities. All of the selected pilot areas are characterized by high levels of deprivation, but target different populations (eg, older people and whole communities), with the Join Us: Move Play (JU:MP) program being delivered in Northern areas of the City of Bradford, targeting children and young people aged 5 to 14 years. Bradford is the 7th largest metropolitan district in England and is home to more than half a million people. A quarter of Bradford's population is under the age of 16 years, making Bradford the "youngest" city in the United Kingdom [21,22]. Bradford is a culturally rich and ethnically diverse city with over 40% of children and young people being of South Asian heritage [23]. However, Bradford (city area) falls in the most deprived quintile of the index of multiple deprivation (IMD), with 60% of the population living in the poorest 20% of wards in England and with 24% of children living in poverty [21,22]. Given the high childhood population in Bradford and given that there is an inverse association between physical activity levels and age during childhood [24], successfully increasing physical activity for the child population in Bradford could have far reaching public health positives for the city in the future. For this reason, the JU:MP program is focused on increasing physical activity in the 27,000 children and young people aged 5 to 14 years and their families living in the area. This article details a protocol for the effectiveness evaluation of the JU:MP program and is part of a wider evaluation plan (including process evaluation – development, implementation, and evaluation), details of which have been described previously [25].

Aims and Objectives

The aim of this quasiexperimental trial is to explore whether JU:MP is effective at increasing physical activity among children aged 5 to 11 years. The specific research objectives are as follows:

1. Determine the effectiveness of JU:MP to increase device-measured (accelerometry) mean average daily moderate-to-vigorous physical activity among children aged 5 to 11 years 24 months and 36 months after the implementation of a whole-system community intervention.
2. Determine the effectiveness of JU:MP to improve secondary outcomes among children aged 5 to 11 years 24 months and 36 months after the implementation of a whole-system community intervention. The secondary outcomes are as follows: (1) mean average daily, weekday, and weekend day sedentary time (device measured [accelerometry]); (2) mean average daily, weekday, and weekend day light physical activity (device measured [accelerometry]); (3) weight status and body fat level (waist circumference and

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BMI); (4) socioemotional well-being, including prosocial behavior, emotional problems, behavioral problems, peer problems, and hyperactivity/inattention (teacher reported); and (5) children's quality of life (parental reported).

3. Undertake exploratory subgroup analysis (ie, neighborhood level and school level) investigating the change in the primary and secondary outcomes.
4. Investigate the potential meditating effects of changes in contextual factors (JU:MP is seeking to change; parental reported): (1) home physical activity, (2) school time physical activity, (3) children's sedentary screen time behaviors, (4) active travel and street physical activity, (5) parent practices (nondirective support and autonomy support), (6) neighborhood social cohesion, (7) neighborhood walking/exercise environment, (8) religious setting physical activity, (9) physical activity during sports and recreation, and (10) park/green space physical activity.

Methods

Intervention: JU:MP Program

A more comprehensive description of the JU:MP program can be found in the report by Hall et al [25]; a brief summary is contained herein.

The JU:MP program (Figure 1 outlines the SPIRIT [Standard Protocol Items: Recommendations for Interventional Trials] schedule [trial design and timescales]) is a whole-system, complex, community-based intervention that was originally developed in 2018 with underlying themes, a framework (settings, tools, and principles), and a theory of change being informed by community consultations, community priority setting workshops, data from the Born in Bradford research program [26-28], international peer-reviewed evidence [29,30], and the socioecological model [18,31]. After a period of development and piloting (2019-2020), the JU:MP program model was developed (Figure 2) [25]. The JU:MP program includes 15 interacting work streams, which include a focus on, for example, embedding physical activity in policy, parks and green spaces, communications and social marketing, and organizations including schools and faith settings. The program is being implemented within 8 distinct geographic "neighborhoods" within the Bradford local delivery pilot area (see Multimedia Appendix 1 for a map of the local delivery pilot neighborhoods). Neighborhood boundaries were based on having an area of green space with potential for development, at least 4 to 5 primary schools, and an active community organization. This hyper-local scale of whole-system delivery aims to foster genuine collaborative working and build strong sustainable relationships. Using an asset-based community development approach, JU:MP facilitates the development of an action group within each neighborhood, including key organizational partners, community members, and families. To allow the program to meet local needs and facilitate longer-term behavior change, the action group is responsible for designing and implementing change at the local level. Initially, the neighborhood approach was operationalized within 3 "pioneer neighborhoods" (2019-2021) to pilot and develop the program. Subsequently, the program will be delivered in the 5 remaining neighborhoods (2021-2024) to cover the whole local delivery pilot area. The remaining 5 neighborhoods are further broken down into those that are directly facilitated by the JU:MP team (n=3) and those whose delivery will be externally commissioned (n=2). Differences between implementation models are to permit examination of how JU:MP could be implemented differently in the future in different communities. The process evaluation outlined by Hall et al [25] will explore such differences; for the purposes of the trial described in this protocol, only effectiveness will be examined in the directly facilitated neighborhoods. The reason for this is a mixture of research capacity and a focus on the effectiveness of the fully developed JU:MP program.

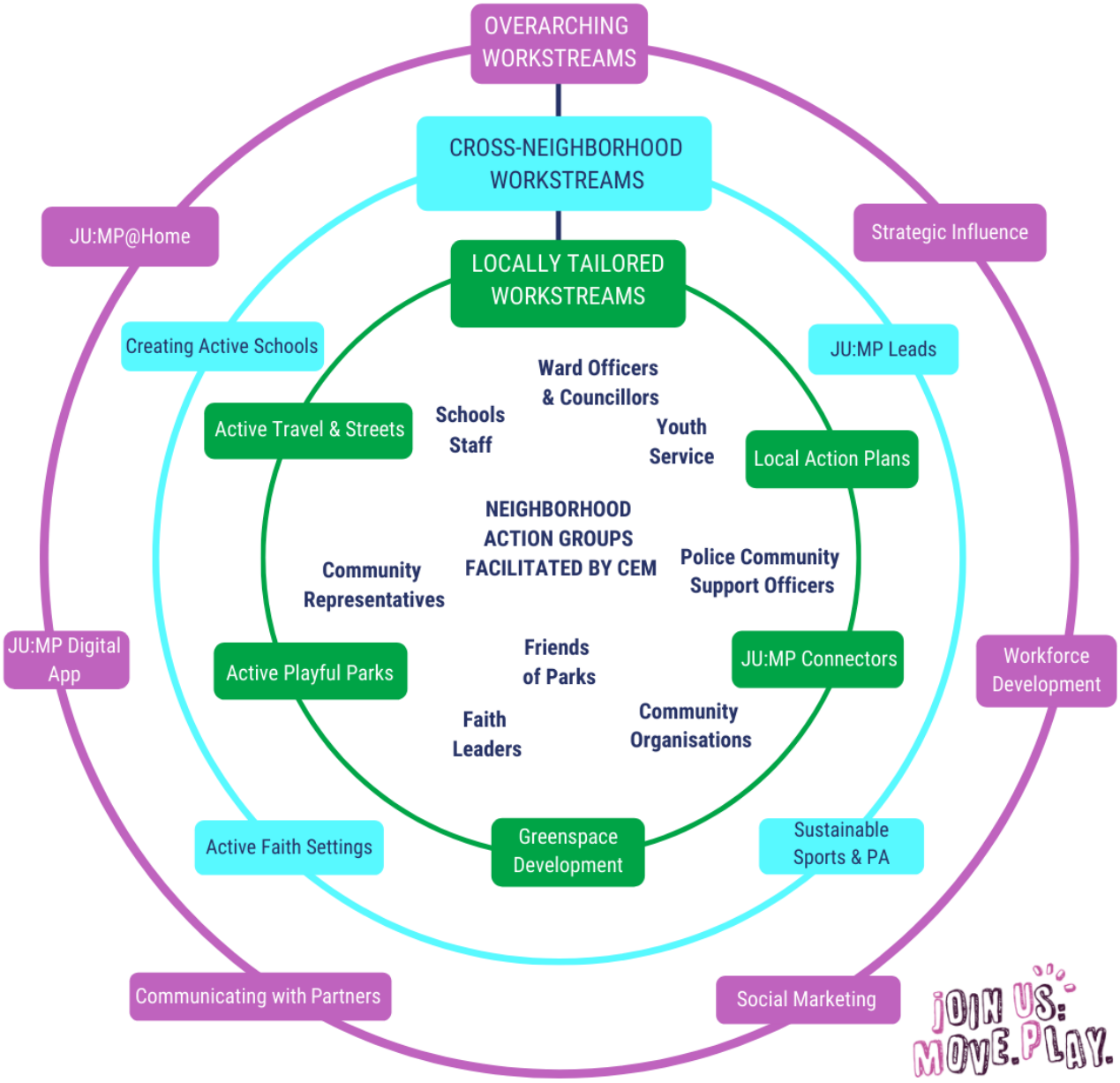
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Figure 1. SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) diagram illustrating the design and timescales of the JU:MP controlled trial. JU:MP: Join Us: Move Play.

	STUDY PERIOD						
	Enrollment	Baseline	Postallocation				Close-out
TIMEPOINT	$-t_1$	Month 0	*Start of intervention (Month 1)*	*12 months*	*24 months*	*End of intervention (36 months)*	*36 months*
ENROLLMENT:							
Eligibility screen	X						
School recruitment	X						
Informed consent - schools		X					
Informed parental consent - parents/careers		X					
Informed assent - child		X					
Identification of control neighborhoods		X					
Allocation	X						
INTERVENTIONS:							
JU:MP programme			←	—	—	→	
Control neighborhoods			←	—	—	→	
ASSESSMENTS:							
Child accelerometry		X			X		X
Child body mass index		X			X		X
Child waist circumference		X			X		X
Teacher-completed strengths and difficulties questionnaire		X			X		X
Parental/carer-completed child physical activities, child sedentary behaviors, child sleep time, places children are active, children's quality of life		X			X		X

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Figure 2. Join Us: Move Play (JU:MP) program model. CEM: community engagement manager; PA: physical activity.

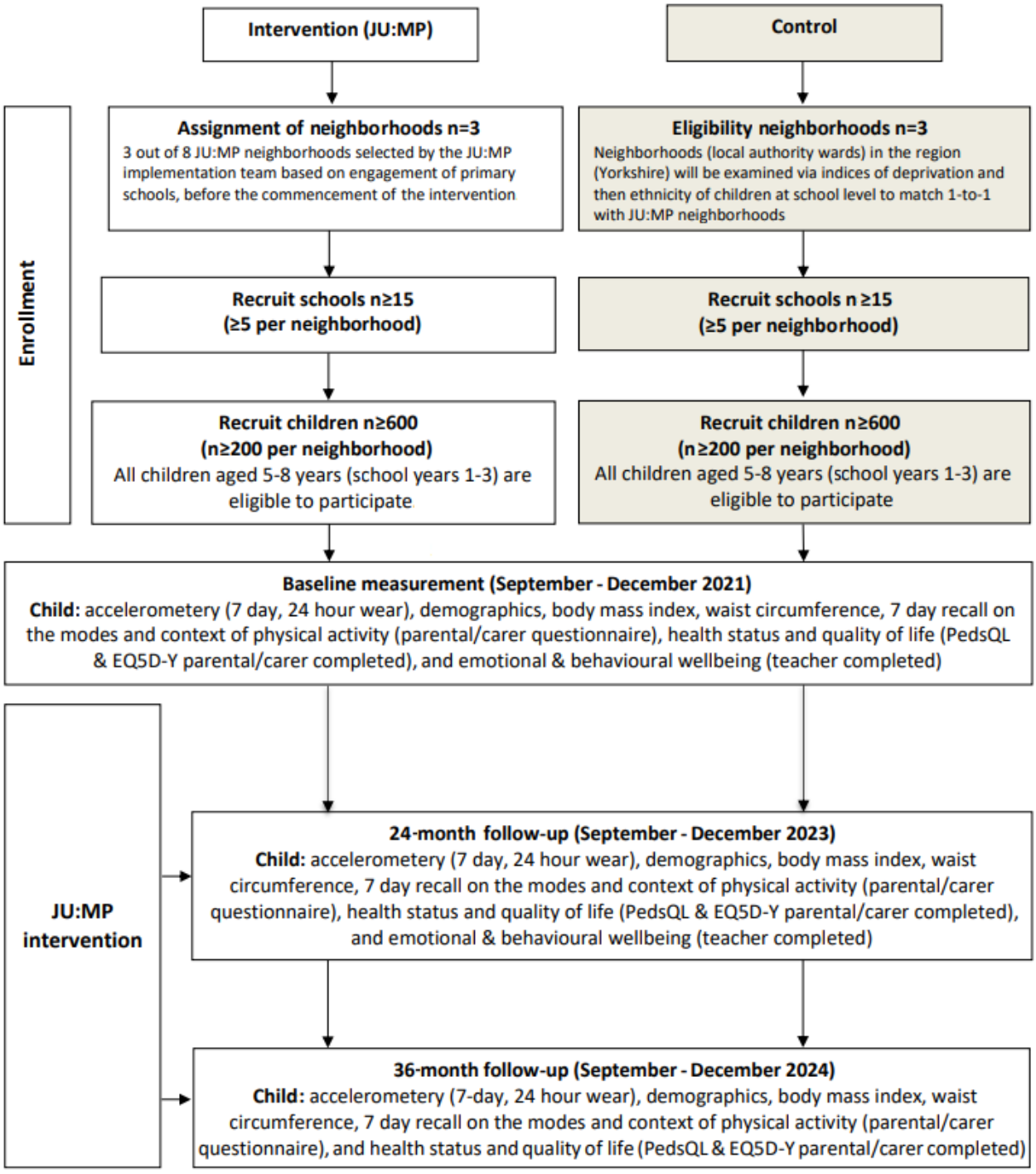


Design

The study has a 2-arm (intervention [JU:MP] and control), quasiexperimental, nonblinded, nonequivalent group design with 3 waves of data collection (baseline [before intervention], 24 months [during intervention], and 36 months [after intervention]). Figure 3 outlines the study flow diagram.

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Figure 3. Join Us: Move Play (JU:MP) program neighborhood, quasiexperimental, nonequivalent group trial. EQ-5D-Y: EuroQol 5-dimension youth version; PedsQL: Pediatric Quality of Life Inventory.



Setting

The research will be situated within primary schools located across the Northern English County of West Yorkshire. Recruitment and data collection are taking place through primary schools as they are located within JU:MP neighborhoods, and children tend to live in close proximity to the school they attend. Primary schools allow access to a large number of children as potential participants, and previous research has shown that it is feasible and acceptable to conduct physical activity trials through primary schools [32].

Identification of Neighborhoods

The JU:MP program is operating in 8 distinct neighborhoods. The 3 neighborhoods eligible for participation in this effectiveness trial are the 3 direct-delivery neighborhoods of JU:MP. Control neighborhoods will be based on local authority wards (local areas with elected officials representing the local area) and be in the county of West Yorkshire in order to ensure that neighborhoods would be politically and geographically similar to the JU:MP neighborhoods. Other neighborhoods/wards in Bradford have been excluded due to potential intervention contamination. Control neighborhoods

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must ideally have similar characteristics to the JU:MP neighborhoods to maximize internal validity. The process of identifying control neighborhoods will include pooling state-funded primary school census data [33], which are released from schools annually, for every ward in West Yorkshire and then calculating the median/mean of (1) the value of the school postcode-derived IMD (IMD 2019) [34]; (2) the proportion of children eligible for state-funded free school meals (school population measure of deprivation); and (3) the proportions of the 2 predominant ethnic groups in the 3 JU:MP areas (White British and South Asian heritage [combining Pakistani heritage, Bangladesh, Indian, and other South Asian ethnic groups]). Ward areas deemed to be suitable control areas must have no more than 1 IMD decile median difference than a JU:MP neighborhood and no more than 10% difference in the proportion of children eligible for free school meals, and the predominant ethnic group (majority or large minority) must be the same as that in a JU:MP neighborhood with ideally no more than 15% difference.

Recruitment of Schools

Once the neighborhoods are selected, government-funded primary schools located in the JU:MP and control neighborhoods will be invited to participate in the research. The number of control schools recruited will be dependent on the recruitment of intervention schools in the neighborhoods to the study. Private and designated special schools have been excluded from this study. Identified schools will be contacted via standardized emails and follow-up phone calls (48 hours later) to request and arrange an in-person/virtual meeting to discuss the study and school-level consent. The primary schools in the JU:MP neighborhoods will be part of the JU:MP program and will receive whatever benefits may be derived from participating in the program. The primary schools within the control areas will not be offered access to the JU:MP program and must agree in principle not to commit to any whole-system school physical activity research in the next 3 years. To incentivize such a commitment, each of the primary schools in the control areas will be offered a total of £600 (US $727), with the caveat that this should not be spent on physical activity provision (physical education, active travel, after school clubs, etc) for the duration of the 3-year study. The £600 (US $727) payment will be split into 3 instalments of £200 (US $242) to be paid after the competition of each of the 3 study data collections (baseline, 24-month follow-up, and 36-month follow-up). If the school agrees to participate in the study, arrangements will be made to begin recruiting children.

Recruitment of Children

All children in years 1, 2, and 3 (ages 5-8 years) at recruited schools will be invited to participate. Members of the research team will agree with school leadership on how best to speak and discuss about the study with all children in the school, but this will likely involve a researcher speaking to each class individually or the year groups collectively during a school assembly. Children will be provided with printed study information sheets and consent forms to take home for their parents/carers. The research team will ensure all forms are distributed to each class teacher and forms are sent home with children in book bags or school planners/diaries so that parents/carers can make an informed decision about whether their children can participate in the study. To ensure parents/carers have an opportunity to discuss the study with the research team, a time and day when they can attend a presentation and a question-and-answer session (within the school or virtually) will be arranged within a week of the information sheets and consent forms being issued. The research team will also seek to agree on times and days when researchers can be present in the school playground before and after school (pick up and drop off time). Short videos will also be produced, which will explain the study, and schools will be asked to distribute links of the videos (ie, YouTube) to parents. For children to participate, their parents/carers must provide informed consent. On the day of data collection, 2 members of the research team will discuss the study with each child and obtain verbal assent. For children with special educational needs/disabilities and those who do not have the capacity to provide assent, the research team will instead seek assent from a school staff member familiar to the child, with the child present. All children participating will receive a gift “goodie bag” worth an estimated £2 (US $2.42), which will include nonphysical activity–related items such as a book, stickers, and other similar items. The goodie bag will be given to each child at each data collection timepoint (baseline, 24 months, and 36 months).

Materials

Primary Outcome Assessment: Accelerometry

The primary outcome assessment of this study will involve waist-worn accelerometry. At each timepoint, researchers will support children to fit an accelerometer (ActiGraph) worn on a belt around the child’s waist, just above the right hip. Children will receive a demonstration by a member of the research team, showing them how to fit the accelerometer. Children will be asked to wear the accelerometer for 7 consecutive days (24 hours a day; only to be removed for showering, bathing, and swimming). Children will be told that if it is uncomfortable to sleep in, they can remove it for sleep and wear it when they wake-up. ActiGraph data will be analyzed using ActiLife v6 (ActiGraph) and downloaded in 60-second epoch files. Sleep will be removed using validated sleep period–detection algorithms [35,36] (requiring 60-second epochs for this process) to produce sleep start and sleep end times. To ensure consistency with the chosen calibration of cut points and therefore increase validity [37], data will be reprocessed using 15-second epoch data in order to correspond with Evenson cut points [38] to classify time spent being sedentary, in light physical activity, and in moderate-to-vigorous physical activity. Sleep time will be removed by treating the sleep start and end times as sleep diaries within ActiLife. Nonwear time will be defined as 20 minutes of consecutive zeros and will be removed from the data. A valid day for inclusion in the analysis will be a minimum of 600 minutes, and children with at least 3 days of wear time, including at least 1 weekend day of data, will be included in the analysis. This wear-time criterion has been calculated using local Bradford data and has an estimated intraclass correlation of 0.75 [26].

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Child Demographics and Anthropometric Data

After the receipt of parental/carer consent, researchers will request school-stored demographic data, such as date of birth, unique pupil number (linked to health records), biological sex, ethnicity, home postcode (for IMD calculation), child's disability or special educational needs, and receipt of government-funded free school meals, from participating schools. The immediate request is to ensure the research team can plan provisions for any children with any additional needs during testing. On the first day of data collection, the research team will ask schools to provide the most recent attendance records and educational attainment data, and a copy of the class timetable for 2 weeks starting from the date of data collection (for accelerometry data collection). Anthropometric measurements will include weight, height, BMI, and waist circumference; all will be measured by trained researchers within the school setting. Weight will be assessed barefoot and in light clothing using a digital scale (eg, Tanita body composition analyzer SC-240MA III). Height will be measured unshod, with the head placed in the correct position, on a Seca 213 stadiometer (graduation=1 mm). BMI will be calculated and converted to a BMI percentile and z-score based on UK reference data [39]. Waist circumference will be measured using a Seca 201 tape (graduation=1 mm).

Children's Socioemotional Well-being (Teacher Rated)

In order to measure children's socioemotional well-being, class teachers of the recruited children will be asked to complete an assessment of the child's behavior and socioemotional development using the strengths and difficulties questionnaire (SDQ) [40]. The SDQ is a short questionnaire (25 items) on positive attributes of the child as well as difficulties. The items are grouped into the following 5 subscales: "prosocial behavior" (ie, being helpful), "emotional problems" (ie, unhappiness), "behavioral problems" (ie, conduct problems), "peer problems" (ie, friendless), and "hyperactivity/inattention" (ie, restless). The SDQ teacher version has been found to have acceptable validity for evaluating psychosocial functioning in children [41].

Physical Activity, Sedentary Behavior, Sleep, and Quality of Life (Parent/Carer Rated)

On the day of data collection, children will be given a questionnaire to give to their parents/carers, which takes an estimated 20 minutes to complete. Parents/carers will complete this questionnaire at all 3 timepoints. Parents/carers will be asked to complete the questionnaire about their children's life, rather than asking the children themselves, due to the young age of the children at baseline (5-8 years), which limits questionnaire comprehension and increases the risk of social desirability bias. The purpose of collecting such questionnaire data is to attempt to understand potential mediating factors of children's accelerometer-measured physical activity. The content aligns with key components of JU:MP. This questionnaire has been piloted with groups of parents/carers living in West Yorkshire and has been deemed acceptable. The questionnaire comprises 6 sections. The first section relates to personal information of the children, including their name, school class, teacher's name, age, and relationship with the person completing the questionnaire. The second section is the youth activity profile (YAP) [42], which is a published child-answered questionnaire. However, for this trial, parents/carers will be required to complete the questionnaire (due to the young age of the children), which entails reporting the frequency and duration of physical activities engaged in through segments of a usual day (ie, before school, break time at school, lunch at school, and after school). The YAP is also used to estimate sedentary behaviors of the children while watching television, playing video games, using a mobile phone, and using a computer/tablet during the previous 7 days. The third section asks parents/carers to report the normal time their children go to bed and wake-up on weekdays and weekend days, in order to calculate average sleep time [43]. The fourth section asks questions about where the children are physically active and has 3 parts. In the first part, parents are asked to indicate places their children engage in physical activity for more than 10 minutes, and how many days their children have visited the place in the previous 7 days. The places are prespecified and include inside the home, garden/yard, street/streets around the home, organized sport or physical activity, swimming pool/leisure center, community center, religious setting (ie, madrassa, church, or temple), and any other places. The second part asks questions for those of the Muslim faith, and focuses on whether and how often their children have attended a mosque or madrassa in the last 7 days, what time they arrived and left, and whether they actively travelled to and from the mosque or madrassa. These questions were included because the neighborhoods of the JU:MP program have large proportions of Muslim families whose children may attend a mosque or madrassa weekly [27]. The third part includes questions regarding children's frequency of being active in parks and green spaces (ie, public gardens and playfields). The fifth section of the questionnaire comprises a series of questions asking parents/carers to consider their own parenting practices when it comes to physical activity (autonomy promotion and nondirective support), and how they themselves consider their own neighborhood (neighborhood social cohesion) and the walking/exercise environment characteristics of their neighborhood. These questions are taken from 2 validated questionnaires [44,45]. In the sixth section of the questionnaire, parents/carers will be asked to answer questions regarding their children's quality of life, which comes from the parent-reported version of the EQ-5D-Y (EuroQol 5-dimension youth version) [46-48] and PedsQL (Pediatric Quality of Life Inventory) [49].

Sample Size and Power Analysis

A sample size calculation was performed using Stata V.16 (StataCorp), with the function "power two means cluster," factored in 6 clusters (3 intervention neighborhoods and 3 control neighborhoods), and a 5% 2-sided alpha, as well as an assumed control average daily value of moderate-to-vigorous physical activity of 53.7 minutes, a SD of 19.7, and an intracluster correlation (ICC) value of 0.007, which was conservatively rounded up to 0.01. As the JU:MP project is a neighborhood/community-level intervention and no previous studies using accelerometry as an outcome assessment among children or young people could be identified, the values of average daily moderate-to-vigorous physical activity, SD, and ICC were derived from an unpublished pilot study (sample size n=564; 3 neighborhoods; 12 primary schools). The missingness

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of data was conservatively factored into the sample size calculation by assuming 30% accelerometer noncompliance at baseline, followed by further 50% loss of data (30% accelerometer noncompliance and 20% attrition) at both the 24-month and 36-month follow-ups. The parameters outlined led to a minimum recommended sample of 1200 children (600 per condition, 200 per neighborhood, and 32 per school) for adequate power (80%) to detect a change of at least 10 minutes in the primary outcome of average daily minutes of moderate-to-vigorous physical activity at both the 24-month and 36-month follow-ups.

Data Analysis

Data will be entered electronically with a double data entry protocol using REDCAP software. Data will be kept on a secure file storage system, which will also be password protected. Data will be anonymized by the assignment of a unique identification number (study ID) to each participant. The primary comparative analysis (objective 1) will be performed on an intention-to-treat basis, including all participants recruited and without imputation for missing data. Multivariable mixed effects linear regression will be used to estimate differences in the primary outcome (accelerometer-assessed mean daily minutes of moderate-to-vigorous physical activity) between the intervention and control groups. Demographic variables of gender and ethnicity will be treated as random effect variables, and baseline moderate-to-vigorous physical activity, age, accelerometer wear time, BMI z-score, school, neighborhood, and condition will be treated as fixed effect variables. Similar analyses will be repeated for secondary outcomes (objective 2). A sensitivity analysis, using a suitable imputation method, will be conducted to assess the effect of missing data. *P* values and 95% CIs will be calculated. A small number of prespecified subgroup analyses will be carried out to evaluate whether the intervention is differentially effective in different subgroups, such as by neighborhood and school (objective 3). The trial is not powered to detect effectiveness in subgroups, and this analysis will be treated as exploratory, presented using CIs, and interpreted with caution. Mediation analysis using structural equation modeling will be applied to look at whether any intervention effect is mediated by potential determinants (objective 4), including (1) home physical activity, (2) school physical activity, (3) children's sedentary screen time behaviors, (4) travel and street physical activity, (5) parent practices (nondirective support and autonomy support), (6) neighborhood social cohesion, (7) neighborhood walking/exercise environment, (8) religious setting physical activity, (9) physical activity during sports and recreation, and (10) park/green space physical activity, which the JU:MP program could have impacted based on the complexity of the program. Multimedia Appendix 2, Multimedia Appendix 3, and Multimedia Appendix 4 present 3 directed acyclic graphs that show the simple mediating pathways to be examined, the potential causal pathways between meditating variables, and the potential casual pathways between confounders (sex, ethnicity, age, socioeconomic status, and weight status), respectively.

Ethical Considerations

This study and all processes were given ethical approval by the University of Bradford Research Ethics Committee (Humanities, Social, and Health Sciences Research Ethics Panel; reference: E891). Informed consent will be sought from schools and parents. Children (participants) will also be asked to provide assent at every data collection timepoint. Schools in the control condition will be paid £600 (US $727) overall (£200 [US $242] for every data collection [baseline, 24-month follow-up, and 36-month follow-up]), and children will be given a "goodie bag" (includes books, stationery, and stickers) worth £2 (US $2.42) as a thank you each time they complete data collection. All data collected will be deidentified and anonymized by using ID numbers and storing all data on secure National Health Service servers, and only the principal investigator and senior researcher will have access to confidential information. All questionnaire data will be double data entered into secure databases created within RedCap.

Results

This study has been registered at ISRCTN (ISRCTN14332797). Recruitment occurred from July 2021 to March 2022, and baseline data collection occurred from September 2021 to March 2022. As of March 2022 (end of baseline data collection), a total of 1454 children from 37 schools (17 intervention schools and 20 control schools) have been recruited. The first follow-up data collection will occur from September 2023 to March 2024, and the second and final follow-up data collection will occur from September 2024 to March 2025. Data analysis has not begun, and the final results will be published in December 2025.

Discussion

This paper describes the protocol for a quasiexperimental, nonblinded, nonequivalent group design trial of the JU:MP program, a complex, community, whole-system children's physical activity intervention. The research outlined in this protocol seeks to explore whether the JU:MP program is effective at increasing the physical activity levels of children aged 5 to 11 years. The recruitment of this trial and baseline data collection have been completed, with 1454 children from 37 schools (17 intervention schools and 20 control schools) being recruited. This number indicates overrecruitment according to the power-calculated target of 600 children per condition (N=1200) and puts the future of this trial in good stead for follow-ups at 24 and 36 months.

Many children and young people do not engage in enough physical activity, with those from ethnic minority backgrounds and economically deprived backgrounds being at greater risk for inactivity and related ill-health. Previous attempts to change children's physical activity have largely been unsuccessful [15,16]. Moves to more complex interventions using the socioecological model and whole-system approach have increased public health, especially with regard to obesity and physical activity [19,25]. Effectiveness research of whole-system approaches for obesity has been mixed and unclear [50,51]; however, no known effectiveness evaluation has occurred for a whole-system children's physical activity intervention. The

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JU:MP program is a complex long-term whole-system intervention (≥2 years) in economically deprived neighborhoods with high proportions of people from ethnic minority groups. The planned and ongoing trial is one of the largest trials ever conducted with an accelerometry outcome measure, which if successful (recruitment and retention rates meet power calculations) will contribute to wider academic public health research by being able to assess the effectiveness of a whole-system approach, which is only currently theorized to be able to change the health of large populations. This effectiveness research is part of a wider body of research with complex process evaluations occurring simultaneously in order to fully examine the full complexity of a whole-system intervention and produce different types of knowledge about a phenomenon that can be combined to further advance knowledge [25,52]

As with all research, there are limitations with the proposed work detailed in this protocol. Namely, the quasiexperimental design of the work naturally has an increased risk of bias when compared with a randomized controlled trial, which is the gold standard way to detect the effects of programs and interventions [53]. However, a randomized controlled trial would not have been feasible for the JU:MP project due to the growing and developing nature of the program in preselected areas of Bradford [25]. Thus, we decided to seek to reduce the risk of bias with matching of neighborhoods based on key descriptive statistics. Another limitation of this work is the reliance on parental/carer and teacher proxy reports, which reduces the validation and reliability of the measures being taken. The reliance on proxy measures is due to the young age of the participants who will not have the capacity to accurately complete questionnaires on key health behaviors (screen time, modes of physical activity, and sleep) and secondary health outcomes such as quality of life and emotional well-being. However, the use of accelerometry as an outcome assessment overcomes the capacity issue of younger children and provides a more objective tool to measure the complex behavior of physical activity.

Many attempts have been made by researchers, practitioners, and policy makers to address children's physical inactivity. However, previous attempts have been unsuccessful in both intervention design and the application of complex evaluations. Lack of success leads to children's physical activity levels stagnating or worsening, increasing the risk of ill-health and negatively impacting the growth and development of young people. Sport England, the largest funder of sports and physical activity in England, has invested significant funds in 12 geographical areas in England to increase physical activity through a place-based whole-system approach. Methodologically rigorous and high-quality research is required to examine what works, why, for whom, and in what context, in order to understand the potential of whole-system approaches for increasing children's physical activity, and whether and how they can be replicated [25]. Research evaluating one of the geographical areas (the JU:MP project in the City of Bradford) seeks to achieve this endeavor. This protocol outlines the effectiveness part of the evaluation.

Acknowledgments

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Data Availability

This is not applicable at present as this is a protocol article. However, future and final data sets will be available from the corresponding author and a Born in Bradford (BiB) executive on reasonable request. Scientists are encouraged and able to use BiB data, which are available through a system of managed open access. The steps below describe how to apply for access to BiB data.

Before you contact BiB, please make sure you have read our guidance for collaborators. Our BiB executive reviews proposals on a monthly basis, and we will endeavor to respond to your request as soon as possible. You can find out about the different data sets available. If you are unsure if we have the data that you need, please contact a member of the BiB team. Once you have formulated your request, please complete the "Expression of Interest" form available and send it to borninbradford@bthft.nhs.uk. If your request is approved, we will ask you to sign a collaboration agreement, and if your request involves biological samples, we will ask you to complete a material transfer agreement.

Conflicts of Interest

None declared.

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Multimedia Appendix 1
Join Us: Move Play (JU:MP) neighborhood map. A geographical map of the JU:MP neighborhood boundaries within the local delivery pilot area. The depicted map is adapted from the QGIS Geographic Information System (2021) and Open Source Geospatial Foundation Project.
[PNG File , 1416 KB - resprot_v12i1e43619_app1.png]

Multimedia Appendix 2
Directed acyclic graph showing the potential casual pathways between mediators and the outcome. JU:MP: Join Us: Move Play; MVPA: moderate-to-vigorous physical activity; PA: physical activity.
[PNG File , 71 KB - resprot_v12i1e43619_app2.png]

Multimedia Appendix 3
Directed acyclic graph showing the potential casual pathways between mediators and the outcome, with interconnections between mediators. JU:MP: Join Us: Move Play; MVPA: moderate-to-vigorous physical activity; PA: physical activity.
[PNG File , 81 KB - resprot_v12i1e43619_app3.png]

Multimedia Appendix 4
Directed acyclic graph showing the potential casual pathways between mediators and the outcome, with possible casual pathways between confounders. JU:MP: Join Us: Move Play; MVPA: moderate-to-vigorous physical activity; PA: physical activity; SES: socioeconomic status.
[PNG File , 189 KB - resprot_v12i1e43619_app4.png]

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Abbreviations

ICC: intracluster correlation
IMD: index of multiple deprivation
JUMP: Join Us: Move Play
SDQ: strengths and difficulties questionnaire
YAP: youth activity profile

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Protocol

Assessment of Energy and Nutrient Intake and the Intestinal Microbiome (ErNst Study): Protocol and Methods of a Cross-sectional Human Observational Study

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Abstract

Background: On the national level, nutritional monitoring requires the assessment of reliable representative dietary intake data. To achieve this, standardized tools need to be developed, validated, and kept up-to-date with recent developments in food products and the nutritional behavior of the population. Recently, the human intestinal microbiome has been identified as an essential mediator between nutrition and host health. Despite growing interest in this connection, only a few associations between the microbiome, nutrition, and health have been clearly established. Available studies paint an inconsistent picture, partly due to a lack of standardization.

Objective: First, we aim to verify if food consumption, as well as energy and nutrient intake of the German population, can be recorded validly by means of the dietary recall software GloboDiet, which will be applied in the German National Nutrition Monitoring. Second, we aim to obtain high-quality data using standard methods on the microbiome, combined with dietary intake data and additional fecal sample material, and to also assess the functional activity of the microbiome by measuring microbial metabolites.

Methods: Healthy female and male participants aged between 18 and 79 years were recruited. Anthropometric measurements included body height and weight, BMI, and bioelectrical impedance analysis. For validation of the GloboDiet software, current food consumption was assessed with a 24-hour recall. Nitrogen and potassium concentrations were measured from 24-hour urine collections to enable comparison with the intake of protein and potassium estimated by the GloboDiet software. Physical activity was measured over at least 24 hours using a wearable accelerometer to validate the estimated energy intake. Stool samples were collected in duplicate for a single time point and used for DNA isolation and subsequent amplification and sequencing of the 16S rRNA gene to determine microbiome composition. For the identification of associations between nutrition and the microbiome, the habitual diet was determined using a food frequency questionnaire covering 30 days.

Results: In total, 117 participants met the inclusion criteria. The study population was equally distributed between the sexes and 3 age groups (18-39, 40-59, and 60-79 years). Stool samples accompanying habitual diet data (30-day food frequency questionnaire) are available for 106 participants. Current diet data and 24-hour urine samples for the validation of GloboDiet are available for 109 participants, of which 82 cases also include physical activity data.

Conclusions: We completed the recruitment and sample collection of the ErNst study with a high degree of standardization. Samples and data will be used to validate the GloboDiet software for the German National Nutrition Monitoring and to compare microbiome composition and nutritional patterns.

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Trial Registration: German Register of Clinical Studies DRKS00015216; https://drks.de/search/de/trial/DRKS00015216
International Registered Report Identifier (IRRID): DERR1-10.2196/42529

(JMIR Res Protoc 2023;12:e42529) doi:10.2196/42529

KEYWORDS

dietary assessment; human observational study; nutrient intake; human intestinal microbiome; biomarkers; 24-hour recall; validity; nutrition; diet; assessment; food; behavior

Introduction

Within the last decade, there has been a huge increase in research in the field of the human microbiome, leading to a new body of knowledge in this area. It is now well established that the human intestinal microbiome is an essential mediator in the interplay between diet and host physiology. Initiatives like the HDHL-INTIMIC Knowledge Platform on Food, Diet, Intestinal Microbiomics, and Human Health [1] were founded to collect and extend this knowledge by fostering multidisciplinary projects.

Many associations between diet and the microbiome have been described, for example, correlations of the long-term diet with differences in gut microbiota composition and functions [2-7]. However, until now, only a small part of gut microbiota variation has been attributed to nutrition [8]. The usual dietary pattern has a strong influence on microbiota composition, as has been shown for plant-rich diets such as the Mediterranean diet, vegetarian or vegan habits, and the abundance of *Prevotella* species [9-12]. It is important to understand how nutrition impacts microbiota, as a disturbance in the latter (dysbiosis) has been associated with many diseases, including diet-related diseases such as obesity and type 2 diabetes. Many studies have been performed on such specific topics, but the results are often inconsistent or even contradictory [13-15]. Such a variety of results can be partially explained by differences in the study population, but also by a lack of standardization of methods, including sample preparation, technology, and bioinformatic analysis [16-18].

Besides the importance of standard methods to determine the microbiome composition, the assessment of reliable representative dietary intake data also requires standardized and validated tools that are up-to-date with recent developments in food products and the nutritional behavior of the population. In Germany, the Max Rubner-Institut (MRI) is responsible for the national nutrition monitoring of the adult population and has so far conducted the second German National Nutrition Survey [19] and the longitudinal study NEMONIT [20]. National nutrition monitoring serves to assess food consumption, nutritional status, and nutritional behavior of the general population and specific population groups. In addition, trends in the nutritional behavior of the population can be monitored. The data are used to update national food-based dietary guidelines, to perform risk assessment by food consumption of the population toward chemical substances in food items, and to serve as decision support for national and European statutory rules. Sound and representative data on nutrition are, therefore, essential for policy-making, answering scientific questions, providing information on the population, and making national and international comparisons.

In this context, the European Food Safety Authority (EFSA) developed methodological guidelines for data assessment in national food consumption surveys [21,22]. Accordingly, 24-hour recalls should be applied to national nutrition monitoring as a dietary assessment method for the adult population. The software GloboDiet (previously EPIC-Soft; International Agency for Research on Cancer), developed as a software platform for a standardized, structured interview, fulfills the EFSA recommendations and thereby provides data with the required detail and quality for national nutrition monitoring [23,24]. In some countries across the European Union, GloboDiet is used for the assessment of representative detailed food consumption data [25,26]. GloboDiet was adapted for the German food market. For example, new foods available on the food market were added and obsolete foods were deleted. In addition, adjustments were made to the description and quantification of the foods in accordance with the abovementioned objectives of the German National Nutrition Monitoring. The standard units to assess the consumed quantity of different food items were updated, and the descriptions of the foods were adjusted to enable analyses of the consumption of ultraprocessed foods.

The ErNst (“Erfassung der Energie- und Nährstoffzufuhr”; English “assessment of energy- and nutrient intake”) study was conceived to address two independent objectives: (1) to verify whether food consumption, as well as energy and nutrient intake of the German population, can be recorded validly by means of the current version of the dietary recall software GloboDiet for the German National Nutrition Monitoring and (2) to obtain biosamples and high-quality data for an exploratory assessment of associations between dietary intake, microbiome composition, and microbial metabolites (as a proxy for functional activity of the microbiome). The purpose of this manuscript is to provide a comprehensive description of the study protocol and the methods used for the collection of biosamples and dietary intake data, combined with an overview of the number of samples and data points that will be available for further analysis.

Methods

Study Design and Setting

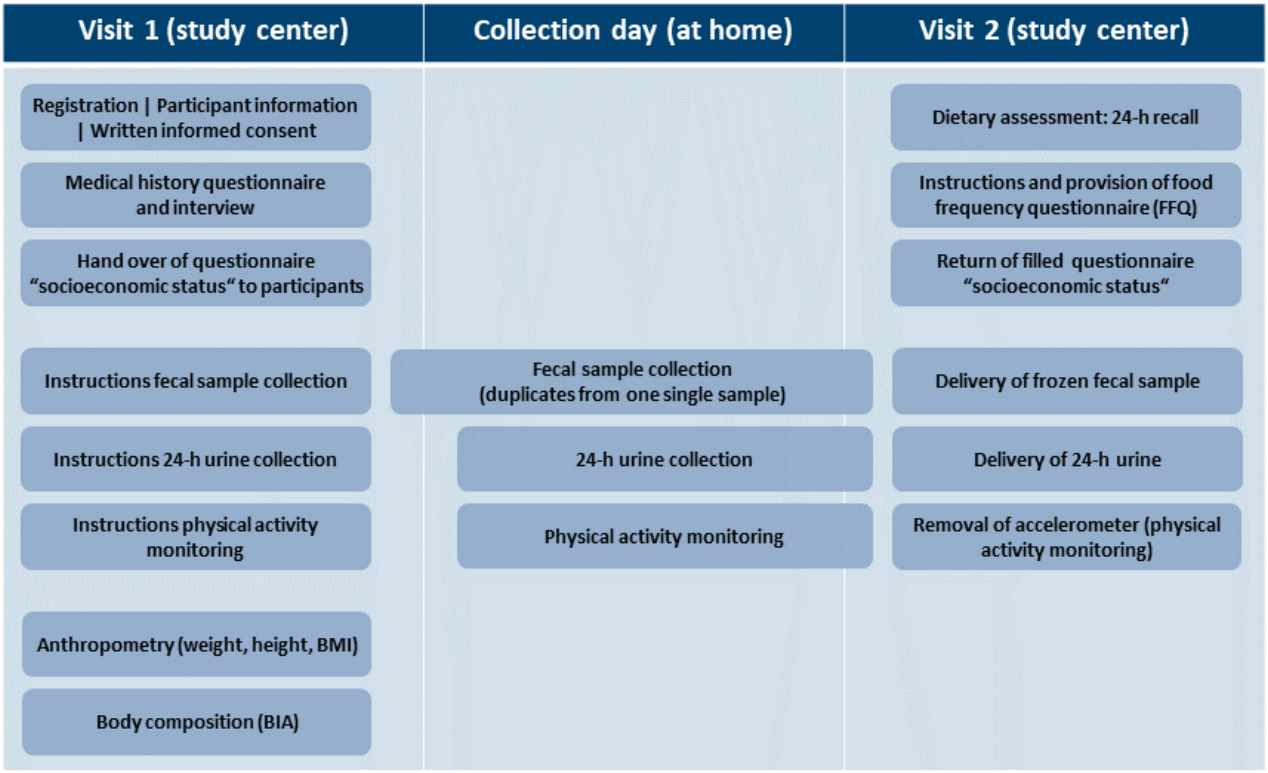
The ErNst study was designed as a cross-sectional observational study and performed at the Division of Human Studies of the Department of Physiology and Biochemistry of Nutrition at the MRI, Karlsruhe, Germany, between October and December 2018. On day 1, all volunteers visited the study center for registration, further instructions, application of the accelerometer

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device, and initial measurements (visit 1, Figure 1). Furthermore, participants were informed about the study procedures and gave their written consent (see also Ethics Approval). Either on the first or second day after the initial visit, participants collected stool and 24-hour urine samples at home (collection day) and brought them on the second visit to the study center the day after (visit 2). Questionnaires and interviews on nutritional intake were also completed on this day.

During visits 1 and 2, the participants underwent a series of standardized examinations described in detail below. For all interviews, examinations, measurements, sample collection, sample preparation, and storage, standard operating procedures were developed and tested for feasibility. Interviewers and examiners had been extensively trained and supervised during data collection.

Figure 1. Overview of the ErNst (Erfassung der Energie- und Nährstoffzufuhr) study days. Collection day was either on the first or second day after visit 1. Visit 2 followed immediately the day after collection day. BIA: bioelectrical impedance analysis.



Participants

Female and male volunteers aged 18-79 years without any known or apparent acute or chronic illnesses or diseases were eligible to participate. Detailed inclusion and exclusion criteria are listed in Textbox 1. Health status questionnaires were used to assess medical history, including potential confounding variables like the use of antibiotics within the last 12 months and smoking status.

Recruitment procedures included direct communication with previous study participants and MRI employees and their families, the use of flyers and other information materials provided to institutions in and around Karlsruhe, information about the study on MRI's homepage, and word of mouth. Initially, 230 interested persons contacted the study center (Figure 2). Those who passed an initial telephone interview (done with a checklist) were scheduled for their first study visit (n=133). Reasons for the exclusion of interested persons are also given in Figure 2. Participants included in the study were asked to complete a questionnaire regarding their marital status, partner relationship status, household size (the number of people living in the household, including children), net monthly household income, school education (highest school-leaving qualification), and occupational qualification.

Since the software GloboDiet shall be validated for the German National Nutrition Monitoring of the adult population, we recruited the participants of the ErNst study according to 3 preselected age groups (18-39, 40-59, and 60-79 years). The proportion of men and women in the respective age groups was equal, as was the total number of participants in each of the 3 groups.

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Textbox 1. Criteria for inclusion and exclusion.

Inclusion criteria

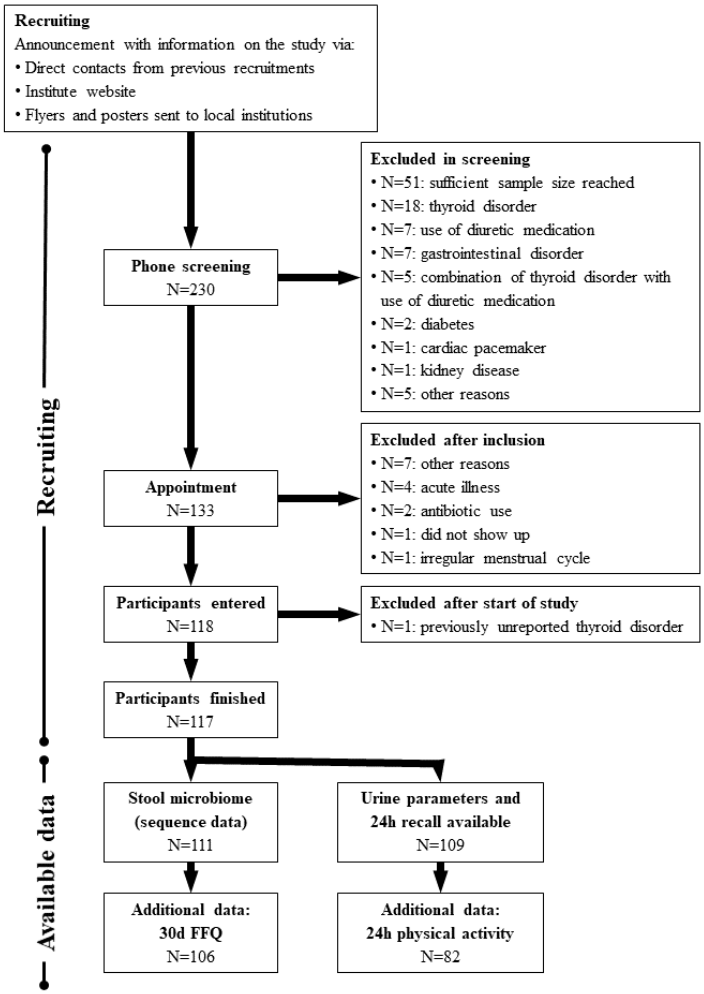
- Healthy female or male
- Able to complete all planned examinations, interviews, and questionnaires
- Written consent to participate voluntarily in the study
- Aged between 18 and 79 years

Exclusion criteria

- Pregnant or breastfeeding
- Diabetes mellitus
- Renal disease
- Use of diuretics
- Hyper- or hypothyreosis
- Currently on diet to reduce weight
- Technical implants (such as pacemaker)
- Amputation of arms or legs
- Diseases and treatments leading to malabsorption of energy and nutrients
- Blood donation within last 4 weeks
- Insufficient German language to complete interviews
- Use of antibiotics within last 12 months
- Tumors requiring therapy
- Acute or chronic infectious disease
- Abuse of drugs or alcohol
- Likely failure to comply with study conditions
- Persons who are kept in an institution by court or official order
- Failure or unwillingness to provide written consent of participation

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Figure 2. Flowchart describing the recruitment process and available data points of the ErNst (Erfassung der Energie- und Nährstoffzufuhr) study. The bifurcation of the available data separates long-term and short-term (current) data points. FFQ: food frequency questionnaire.



Anthropometric Measurements and Assessment of Body Composition

Anthropometric data were assessed using standard methods. Participants were asked not to eat or drink for 4-5 hours before the examination.

Body weight was measured to the nearest 0.05 kg in light clothing without shoes, and height was measured to the nearest 0.1 cm using the seca 285 measurement station (seca). Both parameters were used to calculate the respective BMI (kg/m²).

Bioelectrical impedance analysis (BIA) was used to assess body composition with the measurement device Nutriguard-MS (Data Input GmbH) using multifrequency technology (5.50-100 kHz; 0.8 mA). The analysis was conducted with NutriPlus software (version 5.3.0; Data Input GmbH).

Assessment of Physical Activity and Calculation of Total Energy Expenditure

The activity energy expenditure (AEE) was determined using accelerometers (ActiHeart from CamNtech) for at least 24 hours. Here, the heart rate was recorded together with the acceleration data, so that activities that took place in a sitting position and where the subject itself experienced little acceleration (eg, cycling) could also be adequately depicted. The software used for programming and reading out the acquired data was the ActiHeart software (version 4.0.131; CamNtech).

Resting metabolic rate (RMR) was calculated according to the formula of Müller et al [27] and considered fat-free mass as well as fat mass and the age of the participants.

Dietary-induced thermogenesis (DIT) accounts for about 10% of the energy content of the consumed food [28-30]. Total energy expenditure (TEE) was calculated using the following formula: TEE (kcal) = RMR (kcal) + AEE (kcal) + DIT (kcal)

Assessment of Current Food Consumption by Applying the Software GloboDiet (24-Hour Recall) and Calculation of Energy and Nutrient Intake

During the second visit to the study center, the food consumption of the participants was assessed face-to-face by trained interviewers using the software GloboDiet. The software was adapted to the current German food market and modified for use in the German National Nutrition Monitoring of the adult population. The structure and standardization procedures of GloboDiet have been described in detail elsewhere [24]. For the 24-hour recall, participants were asked in detail about their food and beverage consumption, as well as the use of dietary supplements on the previous day. Corresponding to a first so-called quick list of the consumed foods and beverages in

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chronological order of the meals, the reported food items were further described by facets and descriptors (eg, the applied preparation method, the preservation method, the flavor, and the fat content). Consumed quantities were assessed with a picture book, household measurements, as well as standard units. Interviews were conducted on Mondays, Wednesdays, and Thursdays, leading to results of food consumption on Sundays, Tuesdays, and Wednesdays, representing a balanced coverage of weekdays and weekends, which was intended regarding the validation of the GloboDiet software.

Based on the assessed food consumption, energy and nutrient intake were calculated using data from the German Nutrient Database version 3.02 [31].

Acquisition of Habitual Diet (30-Day Food Frequency Questionnaire)

The 48-item food frequency questionnaire (FFQ) that was used in this study is an adapted version of the validated 53-item FFQ applied in the German Health Examination Survey for Adults 2008-2011 [32]. The ErNst FFQ, therefore, includes questions on the frequency and amount of food groups consumed during the past 4 weeks. The questionnaire was given and explained to the participants on their second visit to the study center, with the request to complete it at home and return it. Frequencies for the consumption of food items were asked according to prespecified categories: never, once a month, 2-3 times a month, 1-2 times a week, 3-4 times a week, 5-6 times a week, 1 time per day, 2 times per day, 3 times per day, 4-5 times per day, and more than 5 times per day. Furthermore, participants had to report the portion sizes of the food items consumed in predefined answering categories. Portion sizes were based on common household measures such as a cup, a glass, a tablespoon, and so on, and, where applicable or necessary, supported by pictures to aid participants in estimating their usual intake. Habitual nutrient intake was calculated using the German Nutrient Database version 3.02 [31].

24-Hour Urine Collection

The 24-hour collection of urine by the study participants took place the day before the 24-hour dietary recall (visit 2). The study participants were provided with 2 urine collection containers (volume 2 liters, Sarstedt AG & Co) and were asked to store the urine at home in the refrigerator or in a cool bag with prechilled thermal packs to keep the collected urine permanently cool. This cool bag was also used to ensure the chilled transport of the urine collection until delivery to the study center. Urine collection was performed according to a standard protocol. On the first visit to the study center, participants were instructed by a study nurse and were given a protocol with written instructions and documentation. Subjects were interviewed about any difficulties during 24-hour urine collection on the second visit day (delivery of 24-hour urine). Urine samples were excluded from the analysis in case of collection errors, for example, if the collection time was interrupted, incomplete, or less than 20 hours, or if the first-morning urine was not discarded as described in the standard protocol.

Creatinine was analyzed as a reference value for potential urinary analytes using a method modified from Slot [33] and Heinegård and Tiderström [33,34] with the Urinary Creatinine Detection Kit from Arbor Assays (Ann Arbor) according to the manufacturer's protocol. The creatinine excretion in urine was also used to estimate the completeness of the urine collection. Creatinine is formed during the breakdown of creatine or creatine phosphate. This occurs almost exclusively in muscle tissue; therefore creatinine excretion in the urine is related to muscle mass or fat-free body mass. Since creatinine excretion in urine is subject to intraindividual fluctuations and depends on the creatine or creatinine content of food [35], it is only suitable for a rough estimate of the completeness of the 24-hour urine collection.

Stool Sampling and Storage

Study participants were provided with a prepacked stool collection kit ("Easy Sampler," GP Medical Devices A/S) and received precise oral instructions and a written manual for the sampling procedure. Each participant collected 2 independent, approximately nut-sized samples from the same stool. Samples were frozen at –20 °C immediately after collection, delivered frozen to the study center, and then stored at –80 °C until aliquoting. After all the samples were collected, multiple aliquots of 200 mg and 500 mg were kept at –80 °C until further analysis. One aliquot per sample was immediately transferred to and frozen in NucleoSpin Bead Tubes Type A (Macherey-Nagel GmbH & Co) for DNA extraction (see Microbiome Analysis).

Analysis of Biomarkers in Urine

Overview

The validation of the German GloboDiet version will use an approach with nitrogen and potassium urinary excretion as biochemical markers for protein, as well as potassium intake [36,37]. Nitrogen and potassium excretion were chosen because errors are likely to be independent between the measurements of biomarkers and dietary intake [38,39].

Nitrogen Content

Total urinary nitrogen was quantified by the Kjeldahl method using automated digestion and distillation units (Digestion Unit K-35, KjelFlex K360, Büchi). Concentrated sulfuric acid and Hg- and Se-free Kjeldahl catalyst tablets (Merck) were used for digestion. Titration was done with 0.05 M sulfuric acid. Individual urine volumes and an assumed specific gravity of urine of 1.020 g/mL were used to convert the nitrogen content into grams of nitrogen per 24 hours. The reference range for the specific gravity of urine is between 1.010 and 1.030 g/mL. The Karlsruhe Metabolomics and Nutrition (KarMeN) cohort [40] was used as the reference population.

Sodium and Potassium Content

Sodium and potassium measurements were performed in an accredited clinical laboratory (MVZ Labor PD Dr Volkmann and colleagues) using ion-sensitive electrodes.

In order to obtain the excreted urinary sodium and potassium amount per day, the respective concentrations (mmol/L) were

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converted into g/d while taking the volume of urine and the respective molar masses into account.

Osmolality

Osmolality in urine was measured using the freezing point osmometer, Advanced Osmometer Modell 2020 (Advanced Instruments LLC), and values were expressed in mOsm/kg. These values can be used as reference values for potential urinary analytes to be measured in the future.

Analysis of Stool Samples (Intestinal Microbiome)

Single aliquots of the 2 independent stool samples collected from each subject were used for DNA extraction using the NucleoSpin DNA Stool Kit (Macherey-Nagel). The 200 mg of stool, previously transferred to the bead tubes, were incubated with 850 µL lysis buffer at 70 °C for 5 minutes. A bead beating step was included using a FastPrep 24 machine (MP Biomedicals) at 6.0 m/s for 40 seconds, followed by washing and elution according to the kit's standard protocol. The purity and concentration of the extracted DNA were checked on a NanoDrop microvolume photometric device. The variable region V4 of the prokaryotic 16S rRNA gene was amplified in a single polymerase chain reaction (PCR) step with dual indexing primers as described by Kozich et al [41] with a modification to increase sensitivity toward Archaea [42] (Multimedia Appendix 1). Phusion Hot Start II DNA Polymerase (Thermo Fischer Scientific) was used in a 25 µL reaction mix with 1 ng template DNA, 0.5 µM of each PCR primer (forward and reverse), 0.2 mM dNTP mix, 0.25 µL enzyme, and 5 µL 5x HF buffer. The PCR program included initial denaturation for 2 minutes at 98 °C, 25 cycles of 30 seconds at 98 °C, 10 seconds at 55 °C, and 15 seconds at 72 °C, followed by terminal elongation for 5 minutes at 72 °C. PCR products were purified using magnetic beads (Mag-Bind RXNPure Plus, Omega) and their concentration was measured using a Quantus Fluorometer (Promega) with the QuantiFluor One dsDNA System (Promega), according to the manufacturer's recommendation. The PCR products were pooled at an equimolar concentration in 2 independent libraries that were subsequently sequenced on the Illumina MiSeq platform using a MiSeq Reaction Kit v3 with 2 × 301 cycles at a final concentration of 8 pM, adding 20 mol% of PhiX DNA.

Sample Size Calculation

The sample size was based on the validation of the 24-hour recalls using the difference between energy expenditure (EE) and energy intake (EI) as the end point. The statistical power for a paired *t* test of the hypotheses H_0: EI – EE = 0, H_1: EI – EE ≠ 0 was calculated by the Leibniz Institute for the Social Sciences (GESIS) in Mannheim, Germany. Statistical parameters were estimated using data from a study by Biltoft-Jensen et al [43], as this study used comparable methods for the estimation of EE and nutrient excretion. For an effect size d = (EE – EI)/SD (EE – EI), significance level α=.05, and group sizes of 50 female and 50 male participants, the statistical power was calculated to be >0.998. To prevent an age bias, the group sizes were distributed evenly to the 3 age groups, that is, recruiting at least 17 participants per sex and age group.

The second aim of the study, the analysis of microbiome composition and its association with nutrition, is exploratory and not hypothesis-driven. Therefore, no additional power or sample size calculations were required for this part of the study.

Ethics Approval

The study has been performed in accordance with the Declaration of Helsinki. It was approved by the Ethics Committee of the State Medical Chamber of Baden-Württemberg (EK LÄK BW; F-2018-055) in October 2018 and registered at the German Clinical Trials Register (DRKS00015216). All participants were informed in detail about the purpose of the study, examination procedures, measurements, and potential risks involved. Participants signed their consent to the procedures and the analysis of pseudonymized data, including their potential use for research related to nutrition and health. Privacy and confidentiality of personal data are guaranteed by following the regulations of the State Medical Chamber and the EU General Data Protection Regulation. Pseudonymization was achieved by assigning randomized subject identifiers. All participants received €50 (US $56.50) in compensation upon inclusion in the study.

Results

Recruitment of potential participants involved an initial telephone screening of 230 people who were interested in participating, of whom 133 were selected based on exclusion criteria (Figure 2). After their assignment to the study, 16 subjects had to be excluded for various reasons (Figure 2). Overall, a total of 117 participants completed the 2 visits to the study center (Table 1, Multimedia Appendix 2).

For 109 participants (57 women and 52 men), food consumption and nutrient intake data, assessed by a face-to-face 24-hour dietary recall, are available. The participants were equally distributed among the age groups (18-39 years of age: 36; 40-59 years of age: 35; 60-79 years of age: 38). Urine samples collected during a 24-hour period were provided and suited for analysis in 109 cases (nitrogen and osmolality measurements failed in 2 cases that could not be validly reproduced).

ActiHeart records were not complete in 27 cases, mostly because of the detachment of the device or similar technical problems that resulted in measurements shorter than the required 24 hours. Physical activity data were obtained for 82 of the 109 participants for which urine and current food consumption data were collected.

Nearly all participants provided the requested stool samples, but a few reported irregularities during sampling (eg, potential contamination with toilet water) that led to the exclusion of the samples from further analyses. A final available number of 111 stool samples, each consisting of 2 replicates, were attained.

FFQs were completed by 106 participants (53 women and 53 men) who also provided valid stool samples, equally distributed over the age groups (18-39 years of age: n=37; 40-59 years of age: n=31; and 60-79 years of age: n=38).

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Table 1. Study population characteristics (N=117).

Characteristics	Female participants, n (%)[a]	Male participants, n (%)[a]
Age group (years)		
18-39	21 (17.9)	18 (15.4)
40-59	19 (16.2)	19 (16.2)
60-79	21 (17.9)	19 (16.2)
Smoking		
Never	55 (47.0)	52 (44.4)
Occasionally	4 (3.4)	2 (1.7)
Daily	2 (1.7)	2 (1.7)
BMI		
<25.0	43 (36.8)	29 (24.8)
25.0-29.9	12 (10.3)	24 (20.5)
≥30.0	6 (5.1)	3 (2.6)
School education[b]		
≤9 years	5 (4.3)	4 (3.4)
10-11 years	13 (11.1)	7 (6.0)
≥12 years	43 (36.8)	45 (38.5)

[a]Of whole study population.

[b]Highest school-leaving qualification, recoded to years spent in school.

Discussion

Principal Findings

Within the study, 117 participants completed the recruitment. After the subtraction of some errors in sample collection and measurements, 106 stool samples are available with corresponding data on common nutrition (30-day FFQ). In addition, 109 face-to-face 24-hour recalls were conducted (data on current nutrition), with corresponding urine samples and measured urine parameters. For 82 of these data sets, additional data on physical activity have been collected.

The 2 main aims of the study were to collect samples and data for (1) validating the dietary recall software GloboDiet and (2) for studying the association between diet and the intestinal microbiome. The 117 participants who successfully completed the study were equally distributed with respect to sex and age groups. However, the fraction of participants with a BMI above 25 kg/m² was lower in the study (females: 18/61, 29.5%, males: 27/56, 48.2%) than observed in the official representative statistics of the German population in 2017 (females: 43.1%, males: 62.1%, data set 12211-9018 in the Genesis database [44]). In addition, the average level of education is high in the study population. Therefore, the study population could be somewhat biased toward a healthier lifestyle, including nutrition and activity, than would be expected in the general population.

For the validation of the updated GloboDiet version, protein and potassium intake determined with the software will be compared with the excretion of protein and potassium in the 24-hour urine collection. In addition, EI calculated from the 24-hour recall will be compared to TEE and RMR. To estimate the validity of the current GloboDiet version, different methods will be applied, like the Wilcoxon-signed rank test to test if the differences between nutrient excretion and nutrient intake, as well as TEE and EI, are different from zero, Spearman rank correlation coefficients to assess the strength of the correlations, as well as Bland-Altman plots [45,46]. Bland-Altman diagrams are suitable for visualizing measurement differences. In addition, participants will be grouped into tertiles to assess the agreement in ranking participants regarding nutrient intake and excretion, as well as EI and TEE. Furthermore, for EI, cutoff values according to Goldberg et al [47] and Black [48] will be calculated for group levels as well as for individuals.

With the samples collected in this study, we plan to further analyze the association between habitual diet and gut microbiota. The microbiota analysis will include single parameters (alpha-diversity and abundance of single taxa), which will be compared with specific food groups or nutrient intakes to identify biologically significant associations. More complex data, like beta diversity of the microbiome and dietary patterns, will be compared by means of ordinations or group categories like enterotype and dietary pattern (using both a priori and a posteriori approaches, such as principal component and principal coordinate analysis, reduced rank regression, or dietary indices). Thereby, we also aim at identifying which level of dietary data yields potential explanations for the observed microbiota variations (eg, dietary pattern, food group, or nutrient level). As a similar composition of the gut microbiota can lead to different activities and functions of this complex and versatile ecosystem within the host, it is important to look not only at the present bacteria but also at the metabolites they produce. Therefore, the fecal content of short-chain fatty acids and bile

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acids will also be determined. Correlation analyses between nutrition parameters and these functional indicators of microbial activity will further enhance the obtained information on associations between the microbiome and nutrition.

Besides the 2 primary aims of the study, the set of valuable samples and data offers opportunities for further analyses. The availability of 24-hour urine samples with corresponding information on nutrient intake, for example, enables the search for biomarkers associated with specific foods or food constituents. This data can be further enhanced or validated using data from the KarMeN study that was previously performed at the MRI [40].

Limitations

The study population was not recruited representatively. Therefore, the average BMI of study participants was lower than generally observed in the German population, indicating a potential bias toward healthier nutrition and lifestyles among the participants. With regard to recruitment, the focus was based on the sample size of the study population needed for the validation of the 24-hour recalls. A total of 50 women and 50 men provided sufficient statistical power for the planned analyses. However, the number of participants was comparatively low for the analysis of the microbiome, limiting the resolution to identify fewer common associations, for example, between nutrition and microbial features. Microbiome analysis based on 16S-rRNA genes is limited to identifying taxonomic composition, but available samples offer opportunities to measure metabolite concentrations or sequence the metagenomes to enable deeper insights.

A further limitation is that TEE was not measured using a doubly labeled water technique. This method has been shown to provide an accurate measure of the TEE [49-51]. At the time when the study was conducted, the use of doubly labeled water was not possible due to time and cost constraints.

Comparison With Prior Work

During the KarMeN study, the metabolomes of blood and urine samples from 301 participants were analyzed, enabling the identification of biomarkers for dietary intake [40]. In comparison, while lacking blood samples, ErNst includes urine samples that are available for metabolomics and adds the opportunity to measure the intestinal microbiome and metabolome using the collected stool samples.

Conclusions

We completed the recruitment and collection of samples and data for the ErNst study with a high degree of standardization. This enables the validation of the GloboDiet software, which will be used in the German National Nutrition Monitoring. In addition, microbiome composition and nutritional patterns will be compared to investigate functional associations and potential biomarkers.

Acknowledgments

We gratefully acknowledge the excellent assistance of Martina Broßart, Tanja Gadau, Eva Hoch, Susanne Jonatzke, Ulrike Rossi, and Ute Stadler-Prayle during recruiting, preparations, care of volunteers, sample management, and analyses. Selina Chabauty and Rebecca Seeger for microbial DNA isolation and amplification; Lilia Wiest, Melanie Huch, and Dominic Stoll for Illumina MiSeq sequencing; Iris Schwald for excellent assistance in planning and assessing the FFQs; Julia Geerlings, Anne Hirchenhein, Sigrun Pape, and Katrin Pfeiffer for participant interviews and 24-hour recalls; Diana Bunzel and Sepp Dieterich for nitrogen analytics; and Judith Lauvai for language editing.

Data Availability

In accordance with the informed consent of the ErNst (Erfassung der Energie- und Nährstoffzufuhr) participants, pseudonymized study data could be provided to external researchers upon request for cooperation or data-use purposes. In this case, a cooperation or data-use agreement must be concluded in advance. The use of ErNst study data is therefore possible with a detailed prior justification of its scientific purpose and after agreement with the MRI. However, informed consent would, in general, allow the publication of a publicly available data set of anonymized study data, which is also planned in the future.

Raw sequence data have already been deposited in the European Nucleotide Archive [52] under the accession number PRJEB51875. The study was included in the collection of human observational studies in the context of the INTIMIC Knowledge Platform [53], and study metadata were deposited on the project's metadata server, Mica [54]. Further data will be published later with the results of the ongoing analyses and could be shared earlier upon a reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
List of primers used for amplification and sequencing of the V4 region of the prokaryotic 16S-rRNA gene.
[XLSX File (Microsoft Excel File), 11 KB - resprot_v12i1e42529_app1.xlsx]

Multimedia Appendix 2

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Overview of availability of samples and data points per study participant.
[XLSX File (Microsoft Excel File), 18 KB - resprot_v12i1e42529_app2.xlsx]

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Abbreviations

AEE: activity energy expenditure
DIT: dietary induced thermogenesis
EE: energy expenditure
EFSA: European Food Safety Authority
EI: energy intake
ErNst: Erfassung der Energie- und Nährstoffzufuhr
FFQ: food frequency questionnaire
KarMeN: Karlsruhe Metabolomics and Nutrition
MRI: Max Rubner-Institut
PCR: polymerase chain reaction
RMR: resting metabolic rate
TEE: total energy expenditure

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Protocol

Utilization of Research in Clinical Nursing and Midwifery Practice in Ghana: Protocol for a Mixed Methods Study

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Abstract

Background: The International Council of Nurses' 2021 code of ethics mandates nurses to provide evidence-informed care to patients. Globally, using research evidence has led to improvement in nursing and midwifery practice, according to the World Health Organization. A study in Ghana found that 25.3% (n=40) of nurses and midwives use research in clinical care. Research utilization (RU) increases therapeutic effectiveness, improves health outcomes, and enhances the personal and professional development of clinicians. However, it is uncertain the extent to which nurses and midwives are prepared, skilled, and supported to utilize research in clinical care in Ghana.

Objective: This study aims to develop a conceptual framework that can facilitate RU among clinical nurses and midwives in Ghanaian health facilities.

Methods: This will be a cross-sectional study with a concurrent mixed methods approach. It will be conducted in 6 hospitals and 4 nursing educational institutions in Kumasi, Ghana. The study has 4 objectives which will be executed in 3 phases. Phase 1 follows a quantitative approach to describe the knowledge, attitudes, and practices of clinical nurses and midwives on the use of research in their practice. Using a web-based survey, 400 nurses and midwives working in 6 health facilities will be recruited. Data analysis will be conducted using SPSS, with statistical significance set at .05. Qualitative methodology, using focus group discussions with clinical nurses and midwives, will be conducted to identify the factors influencing their RU. In phase 2, focus group discussions will be used to examine and describe how nurse educators in 4 nursing and midwifery educational institutions prepare nurses and midwives for RU during their education. Views of nurse managers on the RU in Ghanaian health care facilities will be explored in the second section of this phase through one-on-one interviews. Inductive thematic analysis will be used to analyze the qualitative data, and Lincoln and Guba's principles of trustworthiness will be applied. In phase 3, the stages of model development proposed by Chinn and Kramer; and Walker and Avant will be used to triangulate findings from all objectives and formulate a conceptual framework.

Results: Data collection started in December 2022. Publication of the results will begin in April 2023.

Conclusions: RU in clinical practice has become an acceptable practice in nursing and midwifery. It is critical that nursing and midwifery professionals in sub-Saharan Africa shift their practice to embrace the global movement. This proposed conceptual framework will empower nurses and midwives to improve their practice of RU.

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KEYWORDS

clinical practice; educators; evidence-based practice; health facilities; managers; midwife; midwives; nurses; nursing practice; nursing; research utilization

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Introduction

The 2021 code of ethics of the International Council of Nurses mandates that nurses across the globe should provide evidence-informed health care to patients [1]. This requires the use of research in practice. Consequently, according to the World Health Organization, using research evidence has led to improvement in nursing and midwifery practice globally [2]. Using research evidence is a component of evidence-based practice (EBP), which is a great means for nurses and midwives to meet the changing health needs of the society [3,4]. EBP is a systematic approach to problem-solving for health care providers [5] which is characterized by using the best research evidence that is currently available, clinical expertise, and patient values for clinical decision-making to provide consistent and best possible care to patients [6,7]. The transition to EBP not only increases therapeutic effectiveness and improves health outcomes but also enhances the personal and professional development of clinicians [4]. Research utilization (RU) is vital to the successful implementation of EBP [4].

RU is defined as the process of analyzing, disseminating, and implementing research-produced knowledge to influence or improve current nursing practice [8,9]. This can be achieved through nurses' critical appraisal of research [10]. According to the World Health Organization, globally, nursing and midwifery services have been enhanced due to implementation of research evidence, which highlighted the significant role of nurses in patient care, especially for decision makers [2].

Globally, the use of research in nursing practice has been found to have enormous benefits for both providers and recipients of care [11]. The benefits extend to the public who receive care, the nurses and midwives who provide the care, and the health care system in which the health care is provided [12,13]. Nursing care that is based on the best available research evidence is vital to resolving problems in the clinical setting, improving patient outcomes, decreasing trial and error in nursing care, increasing nurses' confidence in decision-making, and supporting professional development [14-17]. RU contributes to the science of nursing through the introduction of innovation to practice [15]. RU is critical in evidence-based nursing practice because it can save time and money by improving the quality of patient care through cost reduction and effective treatment [18]. It provides a more solid foundation for health care investment decisions and collaboration for capacity development [4]. In the nursing profession, research has been a vital means of developing new knowledge [2]. The benefits of RU in clinical nursing and midwifery practice cannot be realized if it is not implemented.

In Ghana, most of the studies that have been conducted on nurses and research have focused on EBP [14,19-21] with only 1 study [22] focusing on RU. The latter looked at the barriers to RU, given the scarcity of data on the knowledge, attitudes, and practices of RU by nurses and midwives in Ghana. There is methodological limitation in most of the studies on EBP and the RU study in Ghana because they used 1 methodology (either quantitative or qualitative). In addition, the findings of the studies on EBP cannot be used as RU because they are not the same and there are variations in their meanings. This has led to limited published studies in the literature on RU in Ghana.

In addition, there is an urgent need for formal training of nurses and midwives on how to utilize research evidence in their practice. However, there have not been any studies focusing on how nurses are prepared to implement RU in Ghana. This has led to a dearth of information on how well RU is incorporated in both the undergraduate and postgraduate curriculum and the extent to which they are prepared to implement RU after their training. Moreover, leadership plays a key role in the implementation of programs that ensure improved clinical care, which includes RU [23]. Nurse managers have been found to be influential on their staff in translating research evidence into action [24]. This creates a need to identify the views of nurse managers in Ghana on RU and how they can or have been influencing its practice in their health facilities.

Globally, research evidence use in nursing practice has become imperative due to increasing knowledge and technology [25]. Using research evidence in clinical care has not been fully achieved in nursing practice due to the inability of nurses to translate research into practice [26]. This has been confirmed by studies in Singapore [27], Brazil [28], Malaysia [29], South Africa [30], Ethiopia [31], Kenya [11] and Ghana [22]. This inability of nurses to translate research into practice has reflected on their use of research, as studies show Nigeria uses 17% of research [32]. In Kenya, 20.6% of nurses have participated in work-related research and half of them (10.3%) have ever implemented research evidence in practice [11]. In Ethiopia, poor RU was also found [33] and in Ghana, 25.3% research use was found [22]. This shows that if nurses are provided with guidance, research use will be improved.

Further, due to the enormous benefits of RU and the interplay of factors that influence its implementation, evidence suggests that the recurring problem of implementing research in clinical nursing practice can be resolved by offering a framework to guide the implementation of evidence in practice [11,18,22,34,35]. This study aims to establish such a framework to guide RU in clinical nursing and midwifery practice. This study seeks to explore RU by Ghanaian clinical nurses and midwives in hospital settings to develop a conceptual framework to guide RU in clinical nursing and midwifery practice. This will be achieved through the following objectives: (1) describe the knowledge, attitudes, and practices of clinical nurses and midwives toward the use of research in clinical practice in Ghana; (2) identify the factors (barriers or facilitators) that influence the use of research by nurses and midwives in clinical practice; (3) explore the preparation of nurses and midwives to implement RU in Ghana by nurse educators in nursing institutions; (4) explore the views of nurse managers on the implementation of RU in their facilities; and (5) develop a conceptual framework to guide nurses and midwives to utilize research in Ghanaian health facilities to improve the implementation of EBP in Ghana.

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Methods

Study Design

The study will be cross-sectional, using a concurrent mixed method approach. The quantitative methodology will be used to identify the knowledge, attitudes, and practices of RU among the nurses. Concurrently, the researcher will collect qualitative data to explore the barriers to and facilitators of RU, the preparation of nurses and midwives, and the views of nurse managers on RU in health facilities. This will ensure synergy of the results to help in the development of a conceptual framework to facilitate RU in Ghanaian health facilities. This study will be implemented in 3 phases, chronologically. Quantitative data will be collected and analyzed independently, as well as the qualitative data. The results will then be interpreted and triangulated to inform the development of the conceptual framework of RU.

Study Setting

The study will be conducted in health care facilities and nursing and midwifery educational institutions within Kumasi city, in the Ashanti region of Ghana. The study sites are 6 health facilities and 4 nursing educational institutions, depending on the study phase and objective. Specifically, the health facilities are 1 teaching hospital, 1 quasi-health facility, and 4 Ghana Health Service facilities. The facilities were selected for the study because each represents an agency of the Ministry of Health in Ghana, which regulates their activities. The educational institutions are 2 degree-awarding universities and 2 diploma-awarding training colleges. The institutions were selected based on ownership, that is, private or public, and the level of education—diploma or bachelor's degree. This is to ascertain whether there are variations in the preparation of nurses and midwives based on the ownership and level of training.

Phase 1

This phase will be divided into 2 sections based on the specific objectives to be achieved. The study sites for this phase are 6 health facilities.

Phase 1: Objective 1

Overview

The goal of the first part is to describe the knowledge, attitudes, and practices of clinical nurses and midwives regarding the use of research in clinical practice in Ghana. The quantitative research methodology will be used to achieve this objective.

Population and Sampling

Nurses and midwives who work in the clinical units of the health facilities with a minimum educational qualification of a diploma in nursing or midwifery and who have worked for not less than 2 years post qualification will be included in the study. Nurses and midwives who will be on leave at the time of data collection or are working on a part-time basis will be excluded. A sample size of 400 was calculated using Taro Yamane's formula for calculating sample size and a 10% dropout rate. Multistage sampling, including proportionate and systematic sampling methods with a sampling interval of 9, will be used to achieve the target sample size in each health facility.

Data Collection

All the data for this PhD study will be collected by the primary investigator (LBO), who is also trained in qualitative and quantitative research methods. For this study phase, data will be collected using an adapted Evidence-Based Practice Questionnaire created by Upton and Upton [27], as permitted by the original authors. Knowledge or skills, attitudes, and practice are the 3 subscales of the tool, which are measured using a 5-point Likert scale, where 1=very poor, strongly disagree, or never, and 5=excellent, strongly agree, and always. In its original form, the overall Cronbach α is .87. Since this study focused only on RU, some questions were modified to focus on retrieving and implementing current research evidence in clinical practice. The modifications were based on RU literature and Rogers' theory of diffusion of innovation, which guides the overall study. The Cronbach α for the modified tool is .84. Data collection will be done using a web-based survey after obtaining the consent of participants.

Quantitative Data Analysis

Quantitative data will be analyzed using SPSS (version 25.0; IBM Corp) and Stata (version 16; StataCorp). Exploratory data analysis will be carried out for the sociodemographic characteristics of the respondents. Inferential statistics will be used to ascertain the association between demographics and knowledge, attitudes, and practice levels. The chi-square test for independence and its alternative the Fisher exact test will be used to examine the association between categorical variables, while the nonparametric signed rank test will be used to examine the difference in the participants' knowledge scores, and the Pearson and Spearman correlation coefficients will measure the degree of agreement between the scores. Structural equation model and factor analysis will be adopted to assess the effect of demographic characteristics (gender, educational level, age, and number of years of clinical practice) on RU in practice. Statistical significance will be established at *P* value of .05.

Validity and Reliability of Quantitative Data

To test the validity of the modified data collection tool, face validity was established by sending the questionnaire to 5 expert nurses and midwives who have a bachelor's degree and work in the clinical area. Their inputs were used to modify the questionnaire. Pretesting was then carried out with 40 nurses and midwives, representing 10% of the sample size, who work in 2 health facilities located within the study area but not included in the study, using a web-based survey. Results of the pretest and inputs from the study supervisors as well as consultant statistician were used to modify the questionnaire. Cronbach α was calculated for the tool after modification to ensure reliability thereof. The overall Cronbach α factor for the tool was .8438, which is acceptable.

Phase 1: Objective 2

The second objective of phase 1 will be to identify barriers and facilitators influencing RU by nurses and midwives in clinical practice. Qualitative methodology, specifically focus group discussions (FGDs) that will be held via Zoom for each facility, will be used to achieve this objective. The population will be

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the same as those who participated in objective 1 with 6-8 participants per group as suggested by Busetto et al [36] and Ochieng et al [37]. A note will be placed on the survey to request respondents who are interested in participating in the FGD to add their phone numbers. Those who provide their phone numbers will be contacted and asked to sign the consent form. An interview guide with 2 sections, exploring barriers to and the facilitators of RU will be used to direct and facilitate the discussions. Each FGD will last between 60 and 90 minutes as recommended [37-39] and based on the exhaustion of questions on guide and responses from participants. Data collection and analysis will be done simultaneously, and collection will be stopped when data saturation is achieved.

Phase 2

Overview

The study in this phase will be used to achieve objectives 3 and 4. It will take place in 2 settings with 2 populations as follows: nurse managers in the selected health facilities used in phase 1 and nurse educators in 4 nursing and midwifery educational institutions.

Phase 2: Objective 3

Overview

The objective here is to explore and describe nurse educators' preparation of nurses and midwives toward RU in nursing and midwifery educational institutions. The phase 2 study sites will be the 4 nursing educational institutions stated earlier.

Sampling and Data Collection

The study will purposively sample nurse educators who have not less than 2 years of teaching experience and teach core nursing courses like pediatric nursing, medical and surgical nursing, neonatal nursing, public health nursing, and puerperium in the selected institutions. FGDs via Zoom will be held under the direction of an interview guide. The guide has 3 broad, open-ended questions to lead the discussions, with an emphasis on how the nurse educators prepare the nursing and midwifery students for RU, the challenges students experience in RU after nursing education, and the strategies that nurse educators could use to enhance RU in clinical practice. The number of participants per group, the duration of discussions, and the number of discussion sessions will be same as phase 1, objective 2.

Phase 2: Objective 4

Overview

The second part of phase 2 is aimed at exploring the views of nurse managers on the RU in health facilities using qualitative methodology.

Sampling and Data Collection

Nurse managers in the 6 health facilities used in phase 1 will be engaged in a face-to-face key informant interview through purposive sampling. The interviews will be guided by a semistructured interview guide to solicit the nurse managers' views on RU in their various health facilities. Data collection and thematic analysis will be done simultaneously and terminated when data saturation is reached.

Qualitative Data Analysis

Data will be thematically analyzed using Braun and Clarke's thematic analysis process [28]. The recorded data will be transcribed. Codes will be generated in a systematic fashion across the entire data set and will be collated into themes and subthemes to generate a thematic "map" of the analysis.

Trustworthiness

A total of 2 researchers will analyze the data independently and hold coding meetings until they reach intercoder agreement. Themes which emerge will be discussed with a group of participants to achieve member checking, thereby ensuring credibility. Also, method triangulation where the use of FGDs and individual interviews for data collection will be done so that the limitations of each method is counterbalanced whiles their strengths are projected [40]. Again, data from multiple sources like nurse managers, nurse educators, and clinical nurses and midwives will be used to enhance the credibility of the study [40,41]. Transferability will be achieved by providing a thick description of the research context and clear methodology to enhance potential for replication of the study. Verbatim transcriptions and use of quotations from collected data in reporting the study will ensure confirmability [40].

Phase 3: Objective 5

This phase aims to develop a conceptual framework to facilitate RU by clinical nurses and midwives in Ghana. Findings from phases 1 and 2 will be triangulated and used to develop the conceptual framework. Data triangulation which uses data from multiple sources [41] will be performed in this study. This will be guided by Rogers' theory of diffusion of innovation and the 4 stages of model development proposed by Chinn and Kramer (2008) and Walker and Avant (2005), ie, concept development, statement development, model description, and model evaluation.

Ethical Approval

The study has been approved by the Health Research and Ethics Committee of North-West University in South Africa (NWU-00070-22-A1), the Ghana Health Service Ethics Review Committee (GHS-ERC 003/07/22), the Komfo Anokye Teaching Hospital Institutional Review Board in Kumasi (KATH IRB/AP/152/22), and the Committee on Human Research, Publication, and Ethics of the School of Medicine and Dentistry at the Kwame Nkrumah University of Science and Technology in Kumasi, Ghana (CHRPE/AP/762/22).

Results

Data collection started in December 2022. It is envisaged that the results from phase 1 will unveil the knowledge, attitudes, and practices of clinical nurses and midwives regarding the use of research as well as factors influencing research use by nurses and midwives in clinical practice in Ghana. Phase 2 will identify the views of nurse managers on RU in nursing practice in their facilities and how nurse educators prepared student nurses and midwives to utilize research. Once all the findings from different

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groups of participants have been analyzed, we expect that the conceptual framework will be developed.

Discussion

Overview

Globally, RU is of utmost importance in health care and therefore cannot be downplayed [10-12]. A systematic review identified that most studies conducted on RU in nursing practice used the quantitative method and were conducted in Sweden, the United States, and the United Kingdom [42] with a dearth of literature on RU in Ghana. This study will unveil the activities of nurses and midwives in implementing research in their clinical practice. Also, the factors influencing clinical nurses' and midwives' RU will be unearthed. This will lead to minimizing the barriers and enhancing the facilitators to promote RU. Moreover, assessing the nurse managers' views on RU will bring out how leadership in nursing influences RU in their various facilities. The study will identify how nurses are prepared for RU while they are in nursing school. This will guide the scope of the framework that will be developed. A systematic review of studies on barriers to RU in nursing practice from 2002 to 2021 by Jabonete and Roxas (2022) found that almost all studies on barriers to RU used the Barriers scale through a quantitative methodology. The review found that the Barriers scale is outmoded and therefore research on the barriers to RU requires a more robust approach to identify the challenges to nurses RU [42]. This study will use the qualitative methodology to identify the barriers to RU. The use of mixed methods will enable triangulation of findings, observation of the divergence and convergence of findings, and elimination of possible biases. This will also assist the researchers to examine the interplay of factors at the individual (clinical nurses and midwives), group (nurse educators), and organizational (nurse managers) levels [29]. Inclusion of nurse educators, managers, and clinical nurses and midwives as participants in the study contributes to the coproduction of knowledge and increases the chances of the acceptability and utilization of the framework. Nurses will use research if there is guidance on translating research into practice [31]. Consequently, several frameworks have been developed for RU [43]. However, few frameworks have been extensively used, in part because the dynamic processes and players involved are varied and context-specific but also because some frameworks offer little "how-to" guidance for implementation [44-46]. For an RU framework to be accepted for use, it must be contextually appropriate and suit the needs of countries with similar developmental classifications [45]. In the Ghanaian context, this is one of the first studies which focuses on RU. The conceptual framework that is developed will guide nurses and midwives on the implementation of RU in clinical care, guide the managers on how best they can support RU, and guide nurse educators on teaching of RU.

Expected Clinical Impacts

The outcome of this study will have clinical, scientific, and socioeconomic impacts as it aims to produce a conceptual framework that will guide nursing and midwifery practice. The use of this framework will enhance the scientific practice of nursing and midwifery by enhancing evidence-based nursing care through the introduction of innovation to practice. Clinically, the outcome of this study, which is the development of the RU framework, when implemented, will improve patient outcomes by implementing tried and tested treatment modalities that will guide nurses and midwives' decision-making and support their professional development. Socioeconomically, the implementation of the RU conceptual framework that will be developed at the end of this study will save time and money by improving the quality of patient care through cost reduction and effective treatment.

Limitations

The study should be considered with the limitation that the study will not validate the conceptual framework that will be developed since it is beyond the scope of this study. However, we believe that the strong theoretical underpinning, the methodology, and the population used in the study, as well as the triangulation of the results of the study that will be used to develop the conceptual framework, will make the framework a must-use approach in clinical practice to enhance nurses and midwives RU. We again believe that future studies will be conducted to validate and pilot the use of the conceptual framework.

Conclusions

RU in clinical practice has become an acceptable practice in nursing and midwifery. It is critical that nursing and midwifery professionals in sub-Saharan Africa shift their practice to embrace the global movement. This proposed conceptual framework will empower nurses and midwives to improve their practice of RU.

Acknowledgments

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Data Availability

Data sharing not applicable to this paper as no data sets were generated or analyzed during this study.

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Authors' Contributions

LBO conceptualized this study and wrote the initial draft of the manuscript. This is a proposed doctoral dissertation in fulfillment of the requirements for the award of a PhD in Nursing Science in the Quality Nursing and Midwifery (NuMIQ) Research Focus Area of the Faculty of Health Sciences of North-West University. NS and IST are supervisors of the doctoral research project of LBO; they helped in the conceptualization and design of the study, including reviewing and revising of the approved protocol and this manuscript.

Conflicts of Interest

None declared.

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Abbreviations

EBP: evidence-based practice
FGD: focus group discussion
RU: research utilization

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Protocol

The Evaluation of Health Care Services for Children and Adolescents With Post–COVID-19 Condition: Protocol for a Prospective Longitudinal Study

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Abstract

Background: Some children and adolescents suffer from late effects of a SARS-CoV-2 infection despite a frequently mild course of the disease. Nevertheless, extensive care for post–COVID-19 condition, also known as post–COVID-19 syndrome, in children and young people is not yet available. A comprehensive care network, Post-COVID Kids Bavaria (PoCo), for children and adolescents with post–COVID-19 condition has been set up as a model project in Bavaria, Germany.

Objective: The aim of this study is to evaluate the health care services provided within this network structure of care for children and adolescents with post–COVID-19 condition in a pre-post study design.

Methods: We have already recruited 117 children and adolescents aged up to 17 years with post–COVID-19 condition who were diagnosed and treated in 16 participating outpatient clinics. Health care use, treatment satisfaction, patient-reported outcomes related to health-related quality of life (the primary endpoint), fatigue, postexertional malaise, and mental health are being assessed at different time points (at baseline and after 4 weeks, 3 months, and 6 months) using routine data, interviews, and self-report questionnaires.

Results: The study recruitment process ran from April 2022 until December 2022. Interim analyses will be carried out. A full analysis of the data will be conducted after follow-up assessment is completed, and the results will be published.

Conclusions: The results will contribute to the evaluation of therapeutic services provided for post–COVID-19 condition in children and adolescents, and avenues for optimizing care may be identified.

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KEYWORDS

post-COVID; long COVID; post–COVID-19 condition; PCC; post–COVID-19 syndrome; PCS; CFS/ME; children and adolescents; health care services; EQ-5D; SDQ; PROMIS; DSQ-PEM; COVID-19; pediatrics; child; adolescent; service delivery; healthcare delivery; healthcare service; care network; healthcare; therapeutic service; healthcare utilization; patient reported outcome

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Introduction

Background

COVID-19, caused by the novel coronavirus SARS-CoV-2, is considered a multi-organ disease with varying symptom patterns [1]. Frequently occurring characteristics are fever, cough, headache, myalgia, or fatigue and in some cases, intestinal symptoms [2,3]. Research has focused on the treatment of acute COVID-19 cases, which mainly occur among elderly patients and people with preexisting comorbidities like diabetes or cardiovascular disease [4-6]. These persons belong to a risk group among whom a more severe form of the infection can also occur [7].

Children and adolescents are less affected by severe forms of the infection and usually have a mild course of disease [8,9]. Nonetheless, some of them still suffer from long-term consequences of the infection, referred to as "long COVID," post–COVID-19 syndrome (PCS) or post–COVID-19 condition (PCC) [10], which not only affect risk groups, but also people with a milder form of COVID-19 or even asymptomatic SARS-CoV-2 infection [11-13]. Those persistent clinical symptoms vary considerably but can be very restricting for the individual [10].

Currently, there is no clear and uniform definition of PCC [14]. According to the National Institute for Health and Care Excellence, 3 different phases of an infection with SARS-CoV-2 should be distinguished [10]. An acute COVID-19 infection is classified by signs and symptoms that can last up to 4 weeks. The next phase is between 4 and 12 weeks and is termed ongoing symptomatic COVID-19. If signs and symptoms last longer than 12 weeks, are consistent with SARS-CoV-2 infection, and cannot be explained by any other diagnosis, this is called PCC. The commonly used term "long COVID" includes ongoing symptomatic COVID-19 and PCC [10]. According to the World Health Organization (WHO), the following definition is used [15]:

> *Post COVID-19 condition occurs in individuals with a history of probable or confirmed SARS CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis.... Symptoms may be new onset following initial recovery from an acute COVID-19 episode or persist from the initial illness. Symptoms may also fluctuate or relapse over time. A separate definition may be applicable for children.*

Most recently, a modified Delphi consensus was used to suggest a first research definition of PCC in children and adolescents that complements the clinical case definition in adults proposed by the WHO [16]:

> *Post-COVID-19 condition occurs in young people with a history of confirmed SARS-CoV-2 infection, with at least one persisting physical symptom for a minimum duration of 12 weeks after initial testing that cannot be explained by an alternative diagnosis. The symptoms have an impact on everyday functioning, may continue or develop after COVID infection, and may fluctuate or relapse over time. The positive COVID-19 test referred to in this definition can be a lateral flow antigen test, a PCR test or an antibody test.*

Frequently reported long-term symptoms in children and adolescents after COVID-19 are fatigue, headache, sleep disturbance, concentration difficulties, abdominal pain, muscle and joint pain, cough, chest pain, loss of appetite or weight, disturbed smell or anosmia, and rash [11,12]. This symptom pattern appears similar to the one seen in adults [11,17]. Another symptom of PCC in children and adolescents is Kawasaki-like hyperinflammation, also known as multisystem inflammatory syndrome in children associated with COVID-2019 (MIS-C) or pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) [11,18]. Patients with this condition have persistent fever and high levels of inflammation in which several organs are affected [19,20]. In addition, acute SARS-CoV-2 infection can cause myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) [21,22]. The main symptoms of this complex, severe disease are fatigue and exercise intolerance with symptoms worsening after minimal exertion, which is referred to as postexertional malaise (PEM) [23,24]. In general, data on PCC in children and adolescents is still scarce [25,26].

The prevalence of PCC has been estimated at 0.8% to 13% in pediatric studies with uninfected controls [12,27,28]. The Follow CoKiBa study in Regensburg, Germany, found mild, long-lasting symptoms in 10% of children and adolescents aged up to 14 years who had a previous SARS-CoV-2 infection and severe, long-lasting symptoms in at least 3% of those who were affected with a mild, acute form of COVID-19 [29].

Due to the complexity of its symptoms, the diagnosis and treatment of PCC is time-consuming and often difficult [10]. In addition, children and adolescents can be affected by pandemic-related mental disorders [30,31], and differential diagnosis for these disorders and PCC is difficult [32]. Therapy should be carried out depending on a comprehensive differential diagnosis and the patient's symptoms. However, no data or recommendations on how to provide treatment are yet available [1,33].

There is an urgent need to create a comprehensive care network for children and adolescents with PCC. Models and structures of care are needed that enable interdisciplinary, somatic, and psychological diagnostics with subsequent comprehensive therapy. In Bavaria, Germany, such a network of physicians and specialized outpatient clinics, named Post-COVID Kids Bavaria (PoCo), has been established to provide specific care for young patients with PCC, including a specialized Post-COVID Fatigue Centre (PCFC). This should ensure that those who are affected receive appropriate care as close to home and with as little stress as possible. To the best of our knowledge, no other studies have been published that focus on the evaluation of health care services for children and adolescents with PCC.

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Aim of the Study and Hypotheses

The overarching aims of this study are to describe care pathways in the context of PCC in children and adolescents and to evaluate the effects of health care services from the perspective of affected children and adolescents within and outside the PoCo network.

We hypothesize that the health care being provided within the PoCo network is improving the subjective health status of young patients with PCC. Table 1 describes the specific objectives and hypotheses of the study.

Table 1. Objectives and hypotheses of the study.

Objectives	Hypotheses
Documentation of care pathways, including care structures used and therapeutic measures prescribed, with regard to post–COVID-19 condition.	Patients will have many contacts with the health care system within and outside the Post-COVID Kids Bavaria (PoCo) network.
Evaluation of the effects of therapeutic programs.	The patients' health status and quality of life will improve over time.
Evaluation of satisfaction with different care structures and therapeutic programs.	The patients will be mostly satisfied with care for post–COVID-19 condition and will use the different care structures.

Methods

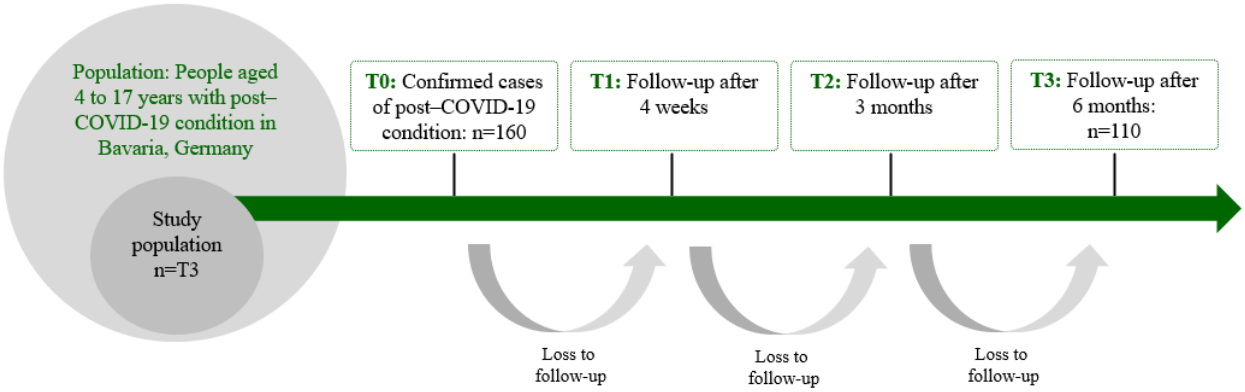
Study Design

This study is taking place within the PoCo network, which follows long-term conditions after COVID-19 in children and adolescents. The aim of the PoCo network is to provide optimal care for children and adolescents affected by PCC. This involves pediatricians and general practitioners (GPs) in private practice, as well as 16 specialized pediatric outpatient clinics all over Bavaria, including one with focus on the treatment of ME/CFS (PCFC). Thus, the network comprises ambulatory and stationary health care institutions throughout Bavaria. Statewide provision of care is ensured by trained, practicing physicians and supplemented by telemedical services.

Patients with severe forms of PCC are cared for in special outpatient clinics. If post-COVID ME/CFS is suspected, patients are treated in or together with the PCFC in Munich. Patients with severe limitations, such as pain, sleep disorders, cognitive problems, or orthostatic intolerance are cared for as inpatients in the pediatric rehabilitation center in Berchtesgaden or in the pediatric pain clinic in Garmisch-Partenkirchen. The latter has expertise in treating children with ME/CFS.

This study is dedicated to health-services research within the PoCo network. It has a longitudinal design (Figure 1). Patients were included in the study after the (suspected) diagnosis of PCC by participating special outpatient clinics. If patients had been treated before, a retrospective assessment of diagnoses and treatments was performed. Patients are assessed at baseline (ie, inclusion in the study; T0), after 4 weeks (T1), after 3 months (T2), and after 6 months (T3) using routine data, interviews, and questionnaires. The primary outcome is subjective health status after 6 months, measured by the visual analogue scale (VAS) of the EQ-5D [34].

Figure 1. Planned study sample and measurement points.



Sample and Recruitment

Study Sites

Pediatricians or GPs in private practice in the PoCo network all over Bavaria recruited patients and referred them to the participating outpatient clinics, where they were included in the study. Patients could also be included directly via the special outpatient clinic without having been referred by a pediatrician or GP.

Patients

Male and female patients aged 4 to 17 years were included in this study if they had a positive test for SARS-CoV-2 and showed clinically evident PCC symptoms or had a COVID-19 infection in the family environment in combination with PCC-typical symptoms. Textbox 1 shows the inclusion and exclusion criteria.

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Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Children and adolescents, male and female, aged 4 to 17 years
- Proficient German language skills
- Evident clinical abnormalities or symptoms of post–COVID-19 condition with one or both of the following (at least 4 weeks earlier):
  - A positive test for SARS-CoV-2, including any or all of the following: a polymerase chain reaction test, antigen test, and SARS-COV-2 antibodies
  - A verified SARS-CoV-2 infection in the family environment
- Current treatment at one of the participating outpatient clinics
- Written consent of the parents and the patient (depending on age)

Exclusion criteria

- Age <4 years or >17 years
- Nonproficient German language skills
- No positive test for SARS-CoV-2 or confirmed infection in the patient's family
- No current treatment at one of the outpatient clinics
- No written consent

Sample Size and Patient Flow

Based on the primary outcome (subjective health status, measured with the VAS), a sample size calculation was performed. Under the assumption of an effect size d=0.35, a significance level α=.05, and power β=.80, the calculated sample size was n=55. However, we assumed that there would be some patients who declined participation in the study, even after inclusion, or dropped out. Therefore, we planned to include 80 patients who were treated within the PoCo network. Patients included and cared for in the PCFC will be evaluated separately. The same assumptions for sample size and dropout were made for these patients, resulting in the inclusion of an additional 80 patients. Thus, the result of the sample size calculation was n=160.

Measurements

Table 2 provides an overview of the variables that are measured for answering the research questions.

A detailed list of all variables is presented in Multimedia Appendix 1 [10,16,34-38].

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Table 2. Overview of variables, constructs and scores, and measurement instruments.

Domains and variables/constructs	Scores, instruments, and data sources	Time point
Sociodemographic characteristics		T0
Patient's age, gender, current education/health care facility and health insurance status, family household size, other children living in the household, place of residence, parents' migration status, level of education and vocational education	Proxy questionnaire, hospital information system	
General medical characteristics		T0
Height, weight, current medication, chronic conditions and diseases	Hospital information system	
Medical characteristics relating to COVID-19 and its treatment		T0
History of SARS-CoV-2 infection, symptom patterns, use of ambulatory and stationary health care, comorbidities, treatment and medication of comorbidities, COVID-19 vaccination status	Hospital information system	
Characteristics of health care use		T1, T2, T3
Visits to physicians and therapists, recommended and used treatment, usefulness of treatment, recommended and used medication or supplements, visits to special outpatient clinic, length of stay and frequency of visits at special outpatient clinic, use of telemedicine, inpatient admission, days of absence from school or work due to illness, counselling on school attendance	Proxy questionnaire via telephone interview, hospital information system	
Patient-reported experience measures		T1, T2, T3
Treatment satisfaction	Proxy questionnaire via telephone interview	
Patient-reported outcome measures		T0, T1, T2, T3
Health-related quality of life	EQ-5D-Y [34], visual analogue scale [34]	
Fatigue	Patient-Reported Outcomes Measurement Information System (PROMIS) Pediatric Short Form version 2.0–Fatigue 10a [36]	
Postexertional malaise	DePaul Symptom Questionnaire Focusing on Post-exertional Malaise (DSQ-PEM) [37]	
Mental health	Strength and Difficulties Questionnaire (SDQ) [38], proxy questionnaire (age ≥12 years: self-reported questionnaire)	

Sociodemographic Characteristics

Sociodemographic information about the patients and their families characterizing the sample was obtained with a paper-based questionnaire (described in the Data Sources and Data Collection sections) handed out at baseline. These variables included patients' age, gender, level of education and health insurance, family household size, other children living in the household, place of residence, migration status, and parents' level of education and vocational education.

General Medical Characteristics

General medical information was also asked for at baseline, to obtain an overview of the patient's general state of health. Patients' height, weight, current medication used, and chronic conditions and diseases were assessed with routine data and questionnaires.

Medical Characteristics Relating to COVID-19 and Its Treatment

Different parameters relating to COVID-19 were recorded at baseline: history of SARS-CoV-2 infection, symptom patterns, use of ambulatory and stationary health care, comorbidities, treatment and medication against comorbidities, and COVID-19 vaccination. The information was obtained from routine data and questionnaires.

Characteristics of Health Care Use

To evaluate use of health care services within and outside the PoCo network, the following variables are recorded at T1, T2, and T3 by means of a telephone interview with the parents: visits to physicians and therapists, recommended and used treatment, usefulness of treatment, recommended and used medication or supplements, days of absence from school or work due to illness, visits to a special outpatient clinic, length of stay and frequency of visits at the special outpatient clinic, use of telemedicine, inpatient admission, and counselling on

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school attendance. Telemedicine includes structured correspondence of pediatricians and GPs with specialists via the post-COVID–specific PädExpert PraxisApp before admission to a hospital, as well as follow-up visits by phone, email, or video conference.

Patient-Reported Experience Measures

Information on patient experience is captured by the variable "treatment satisfaction." Data is collected via telephone interviews at the measurement timepoints T1, T2, and T3.

Patient-Reported Outcome Measures

The primary outcome is the VAS, scored on a scale from 0 to 100, of the EQ-5D-Y. Remaining questions of the EQ-5D-Y are answered on a 3-point Likert scale [34]. Secondary outcomes are fatigue and PEM. Fatigue is assessed with the PROMIS Pediatric Short Form version 2.0–Fatigue 10a questionnaire. The questionnaire comprises 10 items, which are answered on a 5-point Likert scale [36]. A total score is calculated by building the sum of the individual item scores, with higher scores indicating greater fatigue [39]. The DePaul Symptom Questionnaire Focusing on PEM (DSQ-PEM) provides information on the presence of PEM by asking about the frequency and severity of different symptoms [37]. Further, the emotional problems scale of the Strength and Difficulties Questionnaire (SDQ) is used to examine mental health. Items are answered on a 3-point Likert scale. By summing up the individual item scores, a total score is determined that indicates whether a patient shows abnormalities for mental problems, with higher scores implying higher risk for abnormalities [38]. Patient-reported outcome measures (PROMs) are assessed at all measurement points with proxy questionnaires for children aged 4 to 11 years and self-report questionnaires for adolescents aged 12 years and older. Only adolescents aged 12 years and older provide information about fatigue.

Data Sources and Data Collection

Data are derived from various sources. Characteristics relating to COVID-19 and its treatment, as well as general medical characteristics, were obtained from the hospital information system by health care providers and entered into an electronic database (DB), Qnome (Maganamed). Sociodemographic characteristics were assessed via paper questionnaires. These questionnaires were already filled out at baseline by the parents of the patients. Characteristics of health care use are measured via telephone interviews at different time points (Table 2). These questions are also answered by the parents. Some sociodemographic characteristics and characteristics of health care use were assessed via routine data from the hospital information system. PROMs are obtained via paper questionnaires at all time points from the participants themselves or from their parents if they are younger than 12 years. All questionnaires are sent to the study participants by mail. Completed paper questionnaires are manually entered into the electronic DB using the individual IDs of the participants.

Data Management and Quality Assurance

Qnome is used for electronic data collection and data management. The study participants were assigned to the Qnome DB after their parents (and, depending on age, the participants themselves) had confirmed their written consent to participate in the study. Within this overarching DB, however, separate DBs were set up for the individual data sources and types, which are stored separately from each other. A distinction is made between the DB of the trust center (TC) for personal data, the clinical DB for clinical data (including routine data) and the health-services research DB for health-services research data. The data of the study participants were pseudonymized and provided with different IDs: for the clinical data, the clinical data ID (C-ID) and for the health-services research data, the health-services research ID (H-ID). Each participant was assigned a randomly generated pseudonymized C-ID and H-ID. The C-ID was communicated to the attending physicians, who performed a structured clinical examination as part of patient care and documented and store all findings in the clinical DB with this C-ID. The H-ID is only used by the health services research team for their data. The TC is responsible for the provision of the different IDs and the linking to the personal data.

For the data collection for the health-services research (Figure 2), contact data are forwarded by the TC with the corresponding H-ID to the health-services research team. For this purpose, a list of persons to be contacted is compiled weekly and transmitted to the health services research team. The transmission of the personal data for contacting is carried out via Citrix ShareFile (Citrix), an internet-based platform for data transmission that is detached from the study DBs. The data are stored on the local server of the Barmherzige Brüder Hospital Regensburg for a short period of time. At the designated follow-up time points, the health-services research team contacts the person with custody to conduct the interview or to fill in the questionnaire. By means of the H-ID, the answers to the interview conducted by the health-services research team can be entered into the health-services research DB. After successful contact, the weekly list with the contact data and IDs will be destroyed.

When data assessment is complete, data sets will be prepared that do not contain the names or contact details of the study participants (Figure 3).

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Figure 2. Data collection and data storage. C-ID: clinical data ID; H-ID: health services research ID; DB: database; WECARE: Research and Development Campus Regensburg.

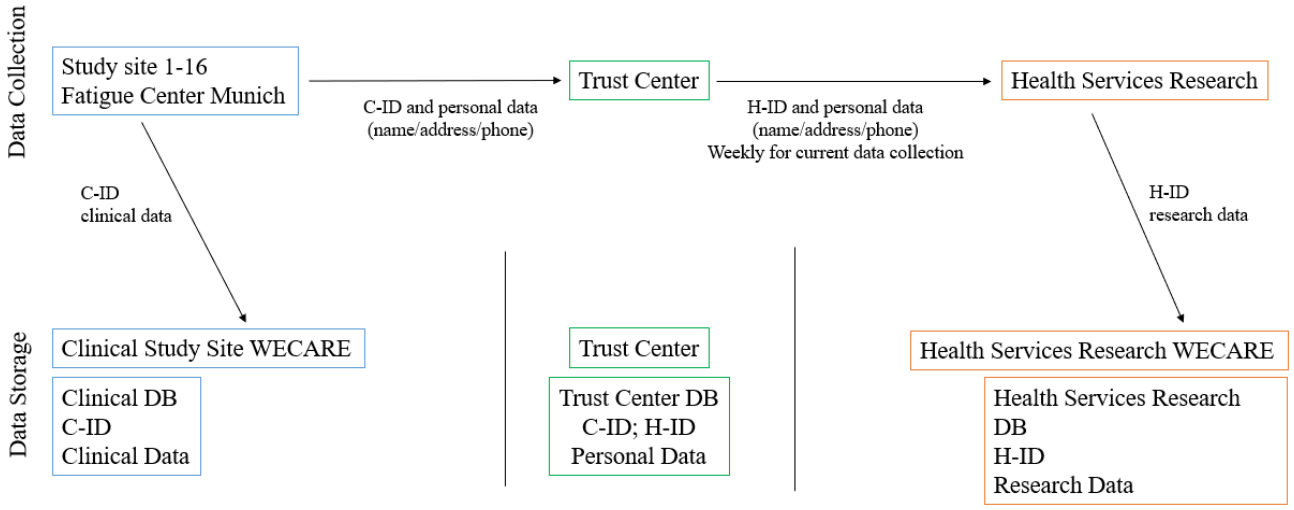
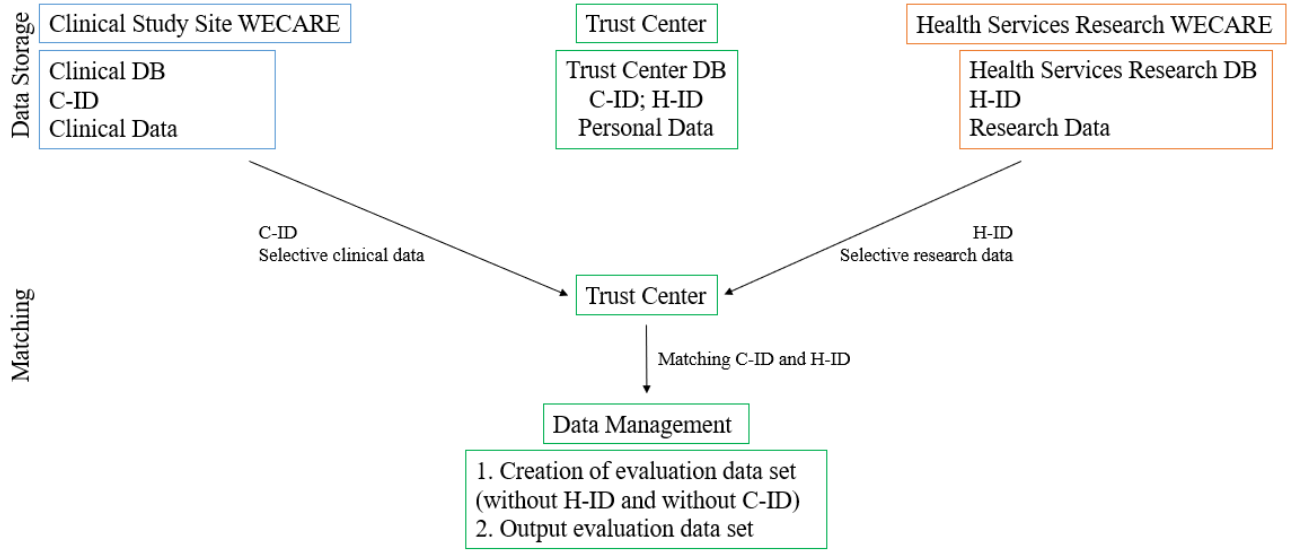


Figure 3. Data storage and matching (only for joint evaluation, if necessary). C-ID: clinical data ID; H-ID: health services research ID; DB: database; WECARE: Research and Development Campus Regensburg.



Statistical Analysis

Plausibility checks of the data are performed continuously during data collection and before data analysis. Patients who drop out during the course of the study will be compared to patients who stay in the study by comparing their general characteristics, such as age, education, and migration background, at baseline. When information is missing in the questionnaire, queries are sent to participants. Descriptive statistics will be used to analyze patient characteristics and to describe care pathways, diagnoses, and treatments. Parents' education will be transformed to categories according to the Comparative Analysis of Social Mobility in Industrial Nations (CASMIN) classification, and the children's BMI will be calculated using their height and weight [40]. Additionally, PROMs will be analyzed for each measurement point using descriptive statistics.

Therapeutic programs will be analyzed using a pre-post study design. The Wilcoxon signed-rank test for matched samples will be used, as outcome data (eg, VAS) are not assumed to be normally distributed. VAS scores at baseline and after 6 months will be compared in order to detect significant improvement after therapeutic interventions. A difference of 10 points on the scale indicates a clinically relevant change. Analyses of the minimal important difference (MID) for PCC in children and adolescents are not available. This assumption of 10 points was derived pragmatically. Half an SD is taken as the MID for quality-of-life measures [41]. A study on acutely ill children, chronically ill children, and children from the general population found a mean VAS score of 77.1 (SD 21.3) [42]. The value 10 is slightly less than half of 21.3. Studies in older people show lower SDs (eg, 18.5) [43]. Therefore, a minimal clinically important difference of 10 seems to be a pragmatic determination. All analyses will be carried out using SPSS (version 28; IBM Corp) and R (version 4.1.1; R Foundation for Statistical Computing).

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Ethics and Consent

The study received original approval on November 29, 2021, and approval of an amendment on March 10, 2022, from the ethics committee of the University of Regensburg (21-2691-101). The study received original approval on April 7, 2022, and approval of an amendment on April 26, 2022, from the ethics committee of the medical faculty of the Technical University Munich (2022-103 S-SR). All data collected will be pseudonymized. Written informed consent was obtained from all study participants at baseline, from their parents, and, depending on their age, from the participants themselves. Participation in the study is voluntary, and participants were reassured that they are free to withdraw from the study at any time without consequences.

Results

The recruitment process for the study ran from April 2022 to December 2022. Unfortunately, only 117 children and youth were included in the study. The planned sample size could not be reached within the period scheduled for recruitment. Interim analyses will be carried out and a full analysis of the data will be conducted after follow-up assessment is completed. The results will be published.

Discussion

The PoCo network aims to improve the care of young patients with PCC by providing comprehensive, multimodal, and intersectoral health services in Bavaria. The main focus is to ensure that comprehensive differential diagnosis is made and that subsequent patient-specific therapy is provided whenever indicated. The established network facilitates access to health services. Using a longitudinal study design, we will be able to evaluate the health care services provided within the PoCo network using outcomes assessed from the patient's perspective. To this end, we use extensively evaluated and widely used tools [37,44-46]. It is assumed that health-related quality of life, fatigue, PEM, and mental health will improve over time in children and adolescents participating in this study.

In addition, this study will improve our knowledge about medical characteristics relating to COVID-19 and its treatment as well as health services and treatments used by young patients with PCC. Risk groups can be identified that are particularly affected by the long-term effects of SARS-CoV-2, including patients with ME/CFS. The prospective evaluation of health care services for children and adolescents with PCC brings some challenges, including consideration of the heterogeneous symptoms of PCC and the complexity of therapeutic measures. In addition, the different age groups make it difficult to identify outcome measures suitable for all participants, and severely affected patients may have problems completing the self-reported instruments due to fatigue or exertion intolerance. Moreover, as in many longitudinal studies, patients might drop out of the study early on, due, for example, to the presumed improvement of symptoms through the care provided in the network. We acknowledge that the study is a single-group study and lacks a control group. We will therefore not be able to study the effects of the health services provided in the PoCo network in comparison to usual care or the improvement in health status caused by natural recovery over time. Also, we will not be able to investigate the effects of the different treatment strategies used in the PoCo network in a comparative manner. Nevertheless, this study will contribute to the evaluation of the health care services provided in the PoCo network in response to the needs of those children and adolescents who suffer from prolonged sequelae after COVID-19.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Detailed overview of variables.
[PDF File (Adobe PDF File), 160 KB - resprot_v12i1e41010_app1.pdf]

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Abbreviations

C-ID: clinical data ID
CASMIN: Comparative Analysis of Social Mobility in Industrial Nations
DB: database
DSQ-PEM: DePaul Symptom Questionnaire focusing on post-exertional malaise
GP: general practitioner
H-ID: health-services research ID
ME/CFS: Myalgic encephalomyelitis/chronic fatigue syndrome
MID: minimal important difference
MIS-C: Multisystem Inflammatory Syndrome in Children Associated with Coronavirus Disease 2019
PCC: post–COVID-19 condition
PCFC: Post-COVID Fatigue Centre
PCS: post–COVID-19 syndrome
PEM: postexertional malaise
PIMS-TS: pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2
PoCo: Post-COVID Kids Bavaria
PROM: patient-reported outcome measure
PROMIS: Patient-Reported Outcomes Measurement Information System
SDQ: Strength and Difficulties Questionnaire
TC: trust center
VAS: visual analogue scale
WHO: World Health Organization

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Protocol

Standardizing Cranioplasty Outcomes Following Stroke or Traumatic Brain Injury: Protocol for the Development of a Core Outcome Set

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Abstract

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Background: Core outcome sets (COSs) are important and necessary as they help standardize reporting in research studies. Cranioplasty following traumatic brain injury (TBI) or stroke is becoming increasingly common, leading to an ever-growing clinical and research interest, especially regarding the optimal material, cost-effectiveness, and timing of cranioplasty concerning neurological recovery and complications. Consequently, heterogeneous reporting of outcomes from such diverse studies has led to limited meta-analysis ability and an ongoing risk of outcome reporting bias. This study aims to define a standardized COS for reporting in all future TBI and stroke cranioplasty studies.

Objective: This study has four aims: (1) undertake a systematic review to collate the most current outcome measures used within the cranioplasty literature; (2) undertake a qualitative study to understand better the views of clinicians, patients' relatives, and allied health professionals regarding clinical outcomes following cranioplasty; (3) undertake a Delphi survey as part of the process of gaining consensus for the COS; and (4) finalize consensus through a consensus meeting resulting in the COS.

Methods: An international steering committee has been formed to guide the development of the COS. In addition, recommendations from other clinical initiatives such as COMET (Core Outcomes and Effectiveness Trials) and OMERACT (Outcome Measures in Rheumatology) have been adhered to. Phase 1 is data collection through a systematic review and qualitative study. Phase 2 is the COS development through a Delphi survey and consensus meetings with consensus definitions decided and agreed upon before the Delphi survey begins to avoid bias.

Results: Phase 1 started at the end of 2019, following ethical approval in December 2019, and the project completion date is planned for the end of 2022 or beginning of 2023.

Conclusions: This study should result in a consensus on a COS for cranioplasty, following TBI or stroke, to help standardize outcome reporting for future studies, which can be applied to future research and clinical services, help align future studies, build an increased understanding of cranioplasty and its impact on a patient’s function and recovery, and help standardize the evidence base.

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KEYWORDS

cranioplasty; TBI; stroke; core outcome set; domains; COMET; health Interventions; recovery; traumatic brain injury; neurological; neurology; reporting; outcome

Introduction

Background

Several randomized trials [1,2] have shown that decompressive craniectomy, which is a surgical procedure in which a large section of the skull is removed to accommodate brain swelling, can be helpful in the management of patients with substantial brain swelling and raised intracranial pressure after a traumatic brain injury (TBI) or stroke. Patients who survive usually have their skull reconstructed a few months later through an operation termed cranioplasty. Cranioplasty not only restores skull integrity, providing a degree of mechanical protection to the brain, but can also improve neurological function [3]. However, there are various interesting and unanswered clinical questions around cranioplasty, including complication rates, neurological recovery and outcomes, and the influence timing has on these [4], material choice, and overall cost-effectiveness. As a result, there are many studies published in the literature exploring these themes [3,5,6]. This has led to variability of the terminology used and heterogeneity of outcomes and outcome measures used. These aspects pose substantial barriers to establishing an evidence-based approach to clinical care and research for cranioplasty. Nevertheless, the development of common data elements (CDEs) and core outcome sets (COSs) is becoming increasingly common to overcome such obstacles.

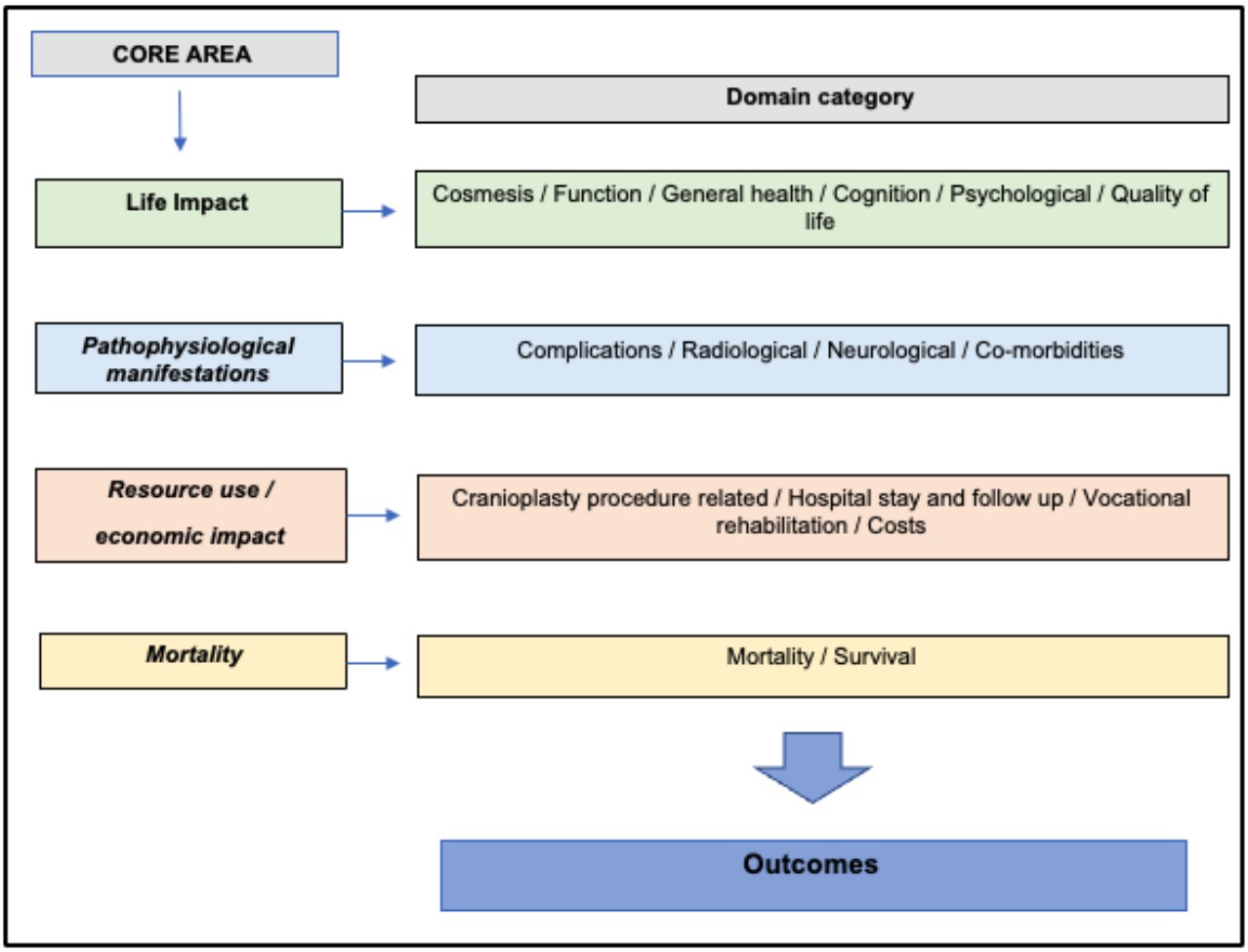
The importance of high-quality, evidence-based clinical practice is known to all, as without reliable, cost-effective interventions and treatments, clinicians' decision-making can become compromised. A core outcome set (COS) is defined as “an agreed standardized set of outcomes that should be measured and reported, as a minimum, in all clinical studies and trials in specific areas of health or health care” [7]. They are a strategy to help as they result in predefined, consensus-derived outcomes that should be reported on in any given condition. This can improve the quality of evidence by allowing studies to be combined for systematic reviews, meta-analyses, and clinical guidelines [8]. The concept was first developed in the early 1990s with the OMERACT (Outcome Measures in Rheumatology) group, which started by creating a COS for rheumatoid arthritis trials and now has a widely used methodological framework on which to identify and validate such sets [9]. Over the past 10 years, further initiatives, including the COMET (Core Outcome Measures in Effectiveness Trials) and the International Consortium for Health Outcomes Measurement, have also produced frameworks as a base for the development of a COS in a specified disease or health condition.

Conceptual models have been developed for studying health, diseases, and outcomes, but not all are appropriate for direct use in COS development [10]. The OMERACT initiative overcame this issue by broadening the scope of one of these frameworks, the International Classification of Functioning, Disability, and Health, by incorporating the Wilson and Cleary [11] model of health-related quality of life and thus developing what is now in its second iteration: the OMERACT Filter 2.0 [12], which is widely used as a framework primarily for COS development and has “4 core areas” broadly representing

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important categories of outcomes measurable in clinical trials (Figure 1). The core areas are "life impact," "resource use and economic impact," "pathophysiological manifestations," and "death." The core areas are defined, with domains of the specified health-related condition grouped within one of the core areas. For example, the life-impact core area can include domains from both the International Classification of Functioning, Disability, and Health and health-related quality-of-life frameworks. Resource use and economic impact should have domains describing the economic impact of the health condition for an individual and society and specific resource use. Finally, the pathological manifestation's core area is to assess whether the effect of the intervention targets the pathophysiology of the health condition explicitly. It is recommended that at least one domain from each core area is included in the COS [12].

Figure 1. Cranioplasty outcome domains and associated core area categorization using the OMERACT (Outcome Measures in Rheumatology) 2.0 filter.



Study Aims and Objectives

Aim

The aim is to develop a COS for cranioplasty research following TBI or stroke by defining a standardized and agreed set of outcomes that should be reported as a minimum [13] while adhering to the COS-STAD (Core Outcomes Set-Standards for Development) recommendations [14] for COS development (Textboxes 1 and 2).

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Textbox 1. Cranioplasty core outcome set scope.

Health condition

- Patients who have undergone a decompressive craniectomy secondary to a traumatic brain injury or stroke await a cranioplasty

Population

- Adult patients older than 16 years

Health intervention

- Cranioplasty

Context

- The core outcome set will be used in future cranioplasty clinical studies and clinical trials to inform clinical decision-making

Textbox 2. Study protocol definitions, adapted from the OMERACT (Outcome Measures in Rheumatology) filter 2.0.

Health

- A state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity.

Health condition

- A situation of impaired health.

Health intervention

- An activity performed by, for, with, or on behalf of a client(s) whose purpose is to improve individual or population health, alter or diagnose the course of a health condition, or improve functioning.

Core area

- An aspect of health or a health condition needs to be measured to assess a health intervention's effects appropriately.

Domain

- Component of core area: a concept to be measured, a further specification of an aspect of health, categorized within a core area.

Outcome

- Any identified result in a domain arising from exposure to a causal factor or a health intervention.

Measurement instrument

- A tool to measure the quality or quantity of a variable in a domain or a contextual factor. The tool can be a single question, a questionnaire, a score obtained through physical examination, a laboratory measurement, or a score obtained through observation of an image.

Outcome measurement instrument

- A measurement instrument was chosen to assess the outcome.

Core domain set

- For studies of health interventions, the minimum set of Domains and Subdomains is necessary to cover all Core Areas adequately, that is, sufficiently measure all relevant concepts of a specific health condition within a specified setting.

Core outcome measurement set

- The minimum set of outcome measurement instruments must be administered in each intervention study of a particular health condition within a specified setting to adequately cover a corresponding Core Domain Set.

Scope

- The set of factors describes the studies and circumstances to which the core outcome measurement set will apply.

Contextual factor

- A variable that is not an outcome of the study must be recognized (and measured) to understand the results.

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Objectives

This study has 4 objectives:

- Undertake a systematic review to collate the most current outcome measures used within the cranioplasty literature
- Undertake a qualitative study to understand better the views of clinicians, patients' relatives, and allied health professionals regarding clinical outcomes following cranioplasty
- Undertake a Delphi survey as part of the process of gaining consensus for the COS
- Finalize consensus through a consensus meeting resulting in the COS

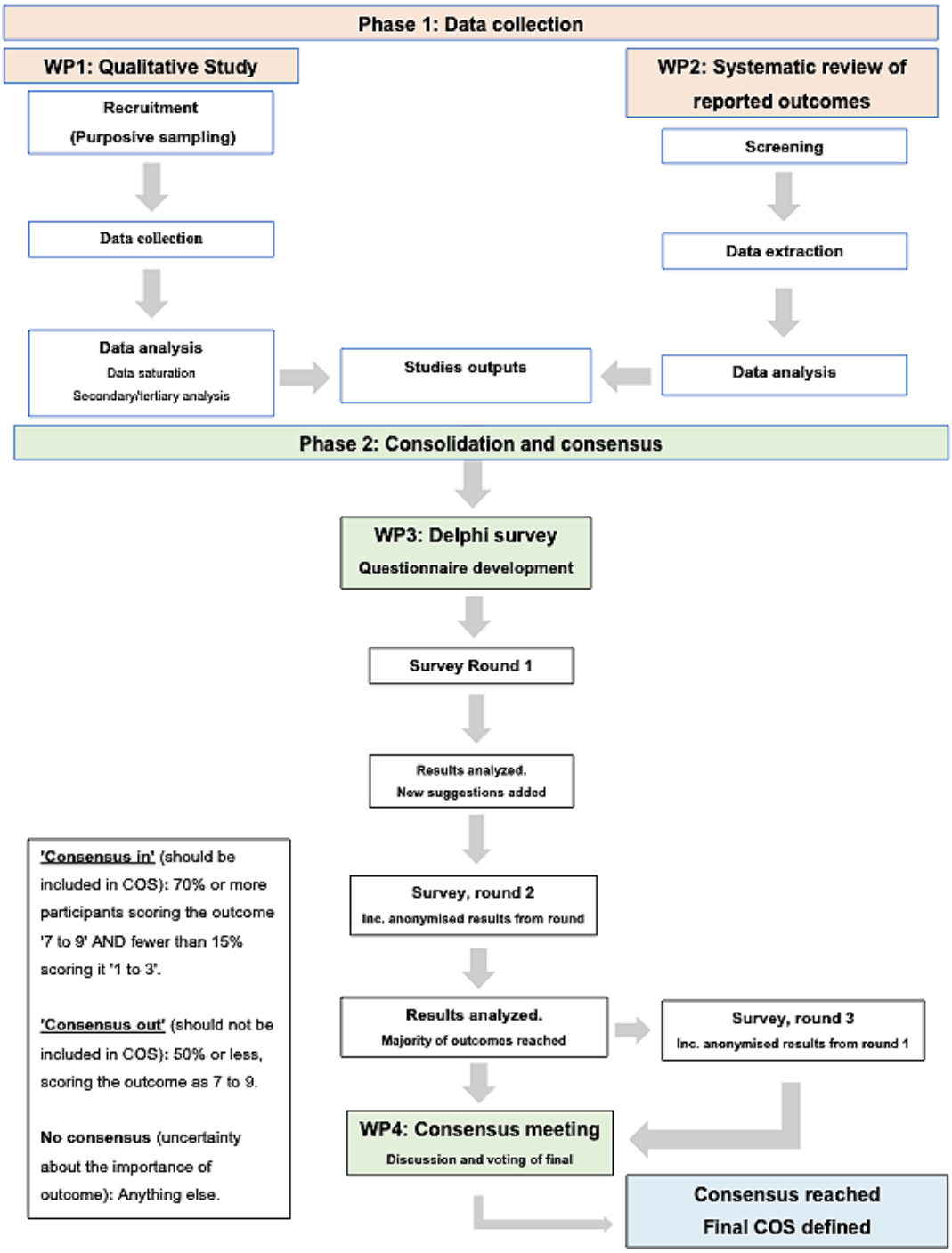
Study Design

This is a mixed methods study and will be divided into 2 main phases (Figure 2):

- Phase 1 (information gathering):
  - WP1: systematic review
  - WP2: a qualitative study producing a comprehensive list of outcome domains relating to the cranioplasty pathway
- Phase 2 (consolidation and consensus):
  - WP3: Delphi study
  - WP4: consensus meeting and finalization of COS

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Figure 2. Study Flowchart. COS: Core Outcome Set.



Stakeholder Involvement

Advocates from multiple stakeholder groups were a part of the COS development [13,15] by COS methodologists. Adhering to this, the COAST study has 4 stakeholder groups:

1. Patients and/or relatives: people who have had or are awaiting a cranioplasty or their relatives
2. Surgeons: experts who perform cranioplasty in their clinical practice
3. Physicians (nonsurgeons) and intensivists: physicians who care for and treat patients awaiting or having had a cranioplasty
4. Nurses, allied health professionals, and researchers: professionals who treat and help rehabilitate those patients who have had or are awaiting a cranioplasty or have a research interest

These 4 stakeholder groups represent the key personnel in the acute and long-term management and rehabilitation of patients who have undergone or will undergo a cranioplasty. The groups will provide a wealth of experience and views from all aspects of the patient's care pathway.

COS Development Team

An international steering committee has been formed to oversee the development of the COS. The committee represents a broad

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range of disciplines and regions of the world, all with clinical interest in and involvement with cranioplasty from a research perspective. A project team oversees the COS development process' day-to-day management, which includes 3 steering committee members and a coordinator. In addition, the project team will establish the methodology and address the key aspects of the project. Key definitions and concepts used to develop this COS have stemmed from the OMERACT initiative (Textbox 2).

Methods

Phase 1: Information Gathering

WP1: Systematic Review

Which outcome domains are used within the published literature for patients undergoing a cranioplasty following TBI or stroke and their recovery and rehabilitation?

Participants/population

Participants should be adult patients aged >16 years who have undergone a decompressive craniectomy.

Intervention

The intervention being studied will be cranioplasty.

Identification of Studies

A search of three databases (PubMed, Embase, and Web of Science) from 1990 to the present analysis will be undertaken to identify either prospective cohort studies with >10 cranioplasty patients or retrospective cohort studies with >20 cranioplasty patients, and two reviewers (AMCL and HM) will independently assess the abstracts of the studies resulting from the search.

Eligibility of Studies

Two reviewers (ACL and HM) will independently review the full texts of the screened abstracts, with any disagreements for inclusion being resolved through discussion. If required, a third reviewer (AK) will be consulted.

Data Extraction

Data will be extracted independently by two reviewers (AMCL and HM). The data will then be reviewed to ensure all outcomes have been identified and no unresolved issues arise. Any disagreements will be resolved through discussion with a third reviewer (AK) available for consultation if required.

Outcomes

The included studies' outcomes will be categorized into domains under one of the four core areas of the OMERACT 2.0 filter framework [12]. Outcomes will be classified as primary when explicitly identified by the study authors, and all other outcomes will be classified as secondary. Each core area and subsequent domain evaluation of the number and frequency of the different outcomes will be analyzed.

WP2: Stakeholder Consultation—A Qualitative Study

To ensure a comprehensive list of outcomes, a qualitative study involving participants in the 4 stakeholder groups will be run, exploring cranioplasty experiences and services and discussing which outcomes are essential to the individual or group. These will then be combined with the outcomes from WP1 to develop the Delphi survey questionnaire.

The qualitative study will include both interviews and focus groups. Participants will be sampled purposively, and the sample size will be guided by data saturation, with 25 and 40 participants across the stakeholder groups likely to be required to reach saturation. A thematic analysis [16] will be used using deductive and inductive coding to analyze known topics of interest and generate new information as the study proceeds. Disconfirming evidence and outlying data will be searched to enhance the reliability and rigor of the analysis process and findings [17]. Data will be compared across and within groups. Qualitative data analysis software (ATLAS.ti) [18] will facilitate data management and analysis.

Phase 2: Consolidation and Consensus

WP3: Delphi Survey

The survey will be online using the Delphi Manager software developed by COMET at the University of Liverpool. Participants will be asked to register and assign themselves to one of the four stakeholder groups. Registration will be implied consent.

Questionnaire Development

This will be drawn from outcomes collated in phase 1 (WP1 and 2) and reviewed and signed off by the steering committee before use.

Recruitment and Sample Size

This will involve centrally coordinating with phase 1 participants invited to participate in further recruitment by post, email, or in person. Participants will also be advised of the importance of completing the Delphi survey, and email reminders will be generated as required to help with compliance.

There are no specific guidelines for the optimal number of participants in a Delphi survey, with previous COS studies having reported 140-150 participants in total [19,20]. Therefore, a pragmatic approach will be taken with the number of participants recruited for each stakeholder group. No new recruitment will occur after the completion of round 1.

Rounds and Scoring

The survey is an iterative process, with a minimum of two rounds but occasionally requiring a third or fourth. All participants score all outcomes using a 9-point Likert scale [21] (Table 1). There will be an "unable to score" option, allowing participants to abstain from scoring a particular outcome if they feel they do not have the expertise to do so; this has been demonstrated to work well in previous COS development projects [22]. A comments box will accompany each outcome to allow feedback as required.

Between rounds, scores are analyzed, summarized, and fed back to all participants in a histogram displaying the distribution of the scores of each outcome, with their scores highlighted. In addition, if there are any descriptive comments for a particular outcome, these will be summarized and presented.

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Table 1. Likert scoring scale.

Likert scale	Outcome
1-3	Limited importance
4-6	Important but not critical
7-9	Critical
Unable to score	N/A[a]

[a]N/A: not applicable.

All outcomes from round 1 will be carried forward to round 2, with any additional recommended outcomes also included in round 2. Participants who completed round 1 in the time allocated will be asked to participate in round 2. Each participant will be shown all the outcomes and scores, the number of respondents, the distribution of respondents' scores, and their scores from round 1. The participant will then be asked to rescore each outcome measure with the feedback from round 1 but categorized by stakeholder group. Brookes et al [21] have shown that this feedback method may improve overall agreement in scoring because it enables reflection based on expert views in other groups. Following round 2, no new outcome measures will be considered, and the consensus definition (see WP4) will be applied.

The steering committee will be informed of scores and analysis between rounds, with any issues or conflicts being addressed.

WP4: Consensus Definition and Meeting

Consensus Definition

In line with a previously proposed definition by Williamson et al [13], our consensus definition has been discussed and agreed upon by the steering committee and will be applied in round 2 of the Delphi study.

- "Consensus in" (should be included in COS): 70% or more participants scoring the outcome "7 to 9" AND fewer than 15% scoring it "1 to 3"
- "Consensus out" (should not be included in COS): 50% or less, scoring the outcome as 7 to 9
- No consensus (uncertainty about the importance of outcome): Anything else

The consensus criterion needs to be met for each outcome across the 4 stakeholder groups separately for inclusion or exclusion in the final COS; otherwise, the outcome will be classed as "no consensus" and taken forward for discussion.

The results of the Delphi survey will be discussed at a "final consensus meeting" involving invited participants from the 4 stakeholder groups. Outcomes categorized as "consensus in" across the stakeholder groups during the Delphi will be included in the final COS, and those outcomes categorized as "consensus out" will be excluded. Other outcomes that either have no consensus or partial in or out consensus across the stakeholder groups will be discussed within the consensus meeting, including a round of voting on all debated outcomes. If a final COS cannot be decided by the end of this consensus meeting, further consensus meetings may need to be planned to reach the final consensus.

Ethics Approval

Ethical approval has been granted from the HRA Wales REC 7 committee for phase 1 and phase 2 of the COS study (19/WA/0314). Written consent is required for all face-to-face interviews or focus groups. Verbal recorded consent from health professionals being interviewed over the telephone is acceptable. Participants in the Delphi survey must register online, and implied consent would be assumed if this process is completed.

Safety Considerations

Due to the study type and voluntary nature of the survey, with the ability to withdraw participation at any time, there are no perceived risks to participants.

Follow-up

There is no follow-up as part of this study.

Data Management and Statistical Analysis

Descriptive statistics will display score distribution within stakeholder groups between Delphi rounds. In addition, an analysis of attrition bias will be undertaken.

Quality Assurance

All data will be stored securely, and all individuals accessing any of the data will comply with the requirements of the Data Protection Act 2018 and adhere to the General Data Protection Regulation (GDPR) and its statements regarding the collection, storage, processing, and disclosure of any personal information.

Expected Outcomes of the Study

This research will help standardize outcome definition, collection, measurement, analysis, and interpretation in subsequent studies for cranioplasty. In addition, the output will provide the platform for future patient-reported core outcome measures for use in cranioplasty clinical trials.

Project Management

There is an international steering committee overseeing the study and a working group meeting regularly and reporting to the steering committee.

Results

This study commenced in December 2019. Phase 1 has been completed, and phase 2 started in Spring 2022, with completion due at the end of 2022/beginning of 2023. The study length will be 3-4 years in total. In phase 2, each round of the Delphi will be 3-4 weeks in length, with a 3-week analysis period in-between rounds. The consensus meetings will then be held

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before a final consensus meeting with the key stakeholder groups to finalize the COS.

Discussion

This COS aims to standardize cranioplasty-specific outcomes that would then be recommended for future use across research and clinical practice. Categorizing outcomes into domains under one of the four core areas of the OMERACT 2.0 filter framework [12] will hopefully ensure a broad and patient-focused range of relevant outcomes. Cranioplasty needs to be viewed in context with the underlying brain injury. Therefore, the outcomes for this COS will be specific to the impact cranioplasty has on patients rather than an extension of outcomes of the underlying brain injury. There is overlap, but cranioplasty-specific outcomes will hopefully improve the understanding of the impact of cranioplasty on the trajectory of recovery for patients following brain injury.

We know of no published COS for cranioplasty following decompressive craniectomy for TBI or stroke. The COS is being developed with key stakeholder groups using a robust, standardized, and transparent methodology. This iterative process focuses on ensuring a clear, nonbias pathway for developing the cranioplasty COS, all detailed in this protocol. The continuing involvement of key stakeholder groups provides the relevance of this research to all groups involved and, hopefully, makes it accepted as helpful research in the future.

Acknowledgments

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Data Availability

Data sharing does not apply to this article as no data sets were generated or analyzed as this is a protocol.

Conflicts of Interest

The authors have no personal, financial, or institutional interest in any drugs, materials, or devices described in this article. PH is supported by the NIHR (Senior Investigator Award, Cambridge BRC) and the Royal College of Surgeons of England.

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Abbreviations

COMET: Core Outcome Measures in Effectiveness Trials
COS: core outcome set
OMERACT: Outcome Measures in Rheumatology
TBI: traumatic brain injury

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Protocol

Identification of Key Factors for Optimized Health Care Services: Protocol for a Multiphase Study of the Dubai Vaccination Campaign

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Abstract

Background: Mass vaccination of the global population against the novel COVID-19 outbreak posed multiple challenges, including effectively administering millions of doses in a short period of time while ensuring public safety and accessibility. The government of Dubai launched a mass campaign in December 2020 to vaccinate all its citizens and residents, targeting the population aged >18 years against COVID-19. The vaccination campaign involved a transformation of multiple commercial spaces into mass vaccination centers across the city of Dubai, the largest of which was the Dubai One Central (DOC) vaccination center. It was operational between January 17, 2021, and 27 January 27, 2022.

Objective: The multiphase research study aims to empirically explore the opinions of multiple health care stakeholders, elicit the key success factors that can influence the effective delivery of emergency health care services such as a COVID-19 mass vaccination center, and explore how these factors relate to one another.

Methods: To understand more about the operations of the DOC vaccination center, the study follows a multiphase design divided into 2 phases. The study is being conducted by the Institute for Excellence in Health Professions Education at Mohammed Bin Rashid University of Medicine and Health Sciences between December 2021 and January 2023. To elicit the key success factors that contributed to the vaccination campaign administered at DOC, the research team conducted 30 semistructured interviews (SSIs) with a sample of staff and volunteers who worked at the DOC vaccination center. Stratified random sampling was used to select the participants, and the interview cohort included representatives from the management team, team leaders, the administration and registration team, vaccinators, and volunteers. A total of 103 people were invited to take part in the research study, and 30 agreed to participate in the SSIs. To validate the participation of various stakeholders, phase 2 will analytically investigate one's subjectivity through Q-methodology and empirically investigate the opinions obtained from the research participants during phase 1.

Results: As of July 2022, 30 SSIs were conducted with the research participants.

Conclusions: The study will provide a comprehensive 2-phase approach to obtaining the key success factors that can influence the delivery of high-quality health care services such as emergency services launched during a global pandemic. The study's findings will be translated into key factors that could support designing future health care services utilizing evidence-based practice. In line with future plans, a study will use data, collected through the DOC vaccination center, to develop a simulation model outlining the process of the customer journey and center workflow.

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KEYWORDS

COVID-19; mass vaccination center; MVC; health care services; key success factors; critical success factors; CSFs; service-oriented architecture; SOA; campaign; vaccine; immunize; immunization; inoculation; health information system; HIS; information system; semistructured interviews; Q-methodology; vaccination; health promotion; vaccine campaign; health information; global health; health care service; simulation modeling

Introduction

Improving Health Care Services

Health care providers are continuously looking to innovate the design and delivery of health care services as it is essential to provide the highest level of patient and public health care [1]. In general, health care systems that can also include the design of health care services are deemed complicated since multiple parties are typically involved, such as health care experts, patients, indirect caregivers, governmental entities, political representatives, and the community [2]. The relationships between these diverse stakeholder groups may impact the planning and delivery of high-quality patient care [2]. Furthermore, Mosadeghrad [3] identified 5 specific features that are needed to provide high-quality health care, including environment, empathy, efficiency, effectiveness, and efficacy.

Gaining insight into the nature of the stakeholder's interactions and individual perspectives is valuable to consistently enhance the quality of care, ensuring that these 5 topics are also incorporated within health care design [2,3]. These insights can be integrated into a process known as design thinking, which is described as a systematic approach to executing progressive ideas through understanding the patients' and stakeholders' needs [1]. Studies have demonstrated the benefit of applying design thinking to the health care industry to meet patient needs and provide new services covering areas such as digital innovation, medical devices, new patient experiences, and upgraded hospital and clinic environments [1].

Critical Success Factors in Health Care

Another aspect of improving health care services is applying service-oriented architecture (SOA), which was found to reduce costs, improve patient care quality, and incorporate the organization's legacy system with updated IT infrastructure to be better aligned with the organization's principles and targets [4]. In addition, SOA encompasses the concept of reusability and focuses on streamlining processes within an integrated health care system [4].

Research surrounding the implementation of SOA in health care has identified critical success factors (CSFs) that can influence this process and are considered valuable for its success. Koumaditis et al [4] developed a proposed CSFs model comprising of 21 factors that can be used as a framework for the successful implementation of SOA in health care and the design of effective services. The factors were categorized into 5 groups consisting of managerial, operational, strategic, IT infrastructure, and organizational topics. The theory of proposing the CSFs model can support health care practitioners and researchers in classifying the importance of each CSF and its impact within each category. The significance of creating an integrated health information system is noted to reduce medical errors, improve medical data, and enhance governance and decision-making [4].

Health Care Services in Emergency Situations

During the COVID-19 pandemic, one of the health care services that needed to be immediately deployed was the creation of emergency vaccination centers to support the vaccination strategy [5,6]. When discussing the feasibility of introducing vaccine centers, multiple factors are considered, including the structure of the local health care system, infrastructural strength, and monitoring the success of the vaccination campaign [7]. Mass vaccination of the global population posed multiple challenges, including the effective administration of millions of doses in a short period of time while ensuring it can be safely and widely accessible to everyone [8].

The typical method to improve the effectiveness of mass vaccination during health emergencies or a global pandemic is the development of emergency points, also known as points of dispensing (PODs) [6]. PODs are physical locations that provide medical services such as vaccines to large populations in a short time frame. They differ from typical medical facilities as their primary purpose is to fairly provide medical supplies on a large scale [6]. Mass vaccination centers (MVCs) or PODs are commonly placed in nontraditional spaces or short-term sites such as converting parking lots or larger indoor areas due to the exceptional circumstances of the situation [8].

COVID-19 Management in Dubai

The novel COVID-19 outbreak was first declared a global pandemic by the World Health Organization on March 11, 2020 [9]. Due to the virus's fast-spreading nature, the pandemic began to globally disrupt daily life and compelled countries to announce extended periods of nationwide lockdowns and impose travel restrictions to curb the spread of the virus [10]. The United Arab Emirates (UAE) was no exception and began a partial lockdown campaign on March 22, 2020 [11]. Regaining any level of normalcy hinged on understanding a suitable way to manage symptoms from COVID-19 infection, the discovery of a possible treatment, and more importantly, the administration of effective vaccines [8,9]. The second half of 2020 carried promising news with the discovery and the initiation of mass production of several vaccines, initiated by the World Health Organization as part of their global effort to manage the pandemic [8,9]. Looking more closely at the UAE, the response protocols set by the National Emergency, Crisis, and Disaster Management Authority included large-scale testing, monitoring

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outbreak cases, creating emergency field hospitals, global cooperation, and the deployment of vaccination campaigns [12].

The government of Dubai, for example, launched a mass campaign to vaccinate all its citizens and residents who met the criteria in December 2020, also targeting the population aged >18 years. The collaborating authorities managing the launch of this campaign involved the Dubai Health Authority and Dubai's COVID-19 Command and Control Center. The expertise throughout the collective teams complemented each other; the Dubai Health Authority placed a medical guideline for the administration of the vaccines and shared updated protocols, whereas Dubai's COVID-19 Command and Control Center developed a strategy to open and manage multiple vaccination centers across the city. The implementation of this program stretched the resources of various governmental agencies to swiftly achieve and create accessible public vaccination PODs. It included transforming commercial spaces into dedicated vaccination centers, the largest of which was the Dubai One Central (DOC) vaccination center. This was the first vaccination center opened in Dubai and was operational between January 17, 2021, and January 27, 2022.

DOC Vaccination Center

The empty commercial spaces at DOC were swiftly transformed and equipped to become a fully functioning vaccination center in just 72 hours. Figure 1 shows one of the waiting halls in DOC. The transformation involved multiple streams of action, such as the placement of all necessary medical equipment, planning for the ultra-cold supply chain of vaccine vials and their storage, recruiting the required staff, as well as the mapping out of the customer journey and flow of people in and out of the center.

As a result, the team at the center administered 1,476,776 Pfizer-BioNTech vaccine doses (complete appointments) against the infection of COVID-19 in one year (367 operational days). They are considered as complete appointments once the customer completes the entire process of registering for and receiving a COVID-19 vaccine dose, whether it is the first, second, or third dose. The DOC vaccination center received between 147,836 and 211,859 customers per month during the peak operational times (May 2021 to September 2021), vaccinating between an average of 5280 and 7062 customers per day. Notably, the original capacity of the center was designed to hold a total of 4000 customers per day; however, through various operational improvements, the center was able to receive and vaccinate over 10,000 people per day.

Figure 1. Preregistration waiting area of the vaccination center in Dubai One Central.



Aim and Research Questions

Our review of the literature identified multiple studies that discussed the importance of exploring the patient's perspective when designing an optimized model to deliver a more efficient health care service [1,13,14]. To ensure that we are considering a more comprehensive perspective, our study aims to empirically explore the opinion of multiple health care stakeholders and elicit the key success factors influencing the delivery of quality care at the DOC vaccination center.

Through a comprehensive research design, the following 3 research questions will be addressed:

1. What key success factors can influence the delivery of a health care service during a public health emergency, such as a vaccination center?
2. How do these CSFs relate to one another?
3. To what extent do these CSFs impact the delivery of health care services?

Methods

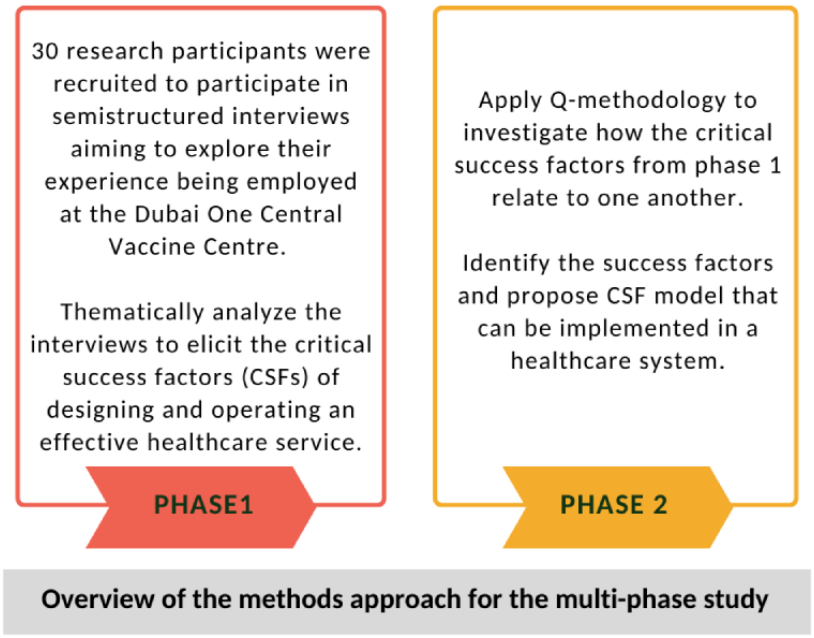
Study Design

The study is being conducted by the Institute for Excellence in Health Professions Education at Mohammed Bin Rashid University of Medicine and Health Sciences, located in Dubai,

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UAE, between December 2021 and January 2023. To better understand the CSFs of the DOC vaccination campaign, this study follows a multiphase design divided into 2 phases, as illustrated in Figure 2. This 2-step approach aims to investigate the key success factors that supported the design and delivery of a health care service implemented as part of nationwide efforts to combat a global pandemic. It further aims at documenting the efforts and exploring the operations of the first COVID-19 vaccination center opened in Dubai, the DOC vaccination center.

Figure 2. Overview of the methods approach for the multiphase study.



Phase 1: Conducting Semistructured Interviews

A qualitative design was applied to fulfill the study's aim and answer the first research question. Individual semistructured interviews (SSIs) were conducted via Microsoft Teams with a sample of staff and volunteers (n=30) working at the DOC vaccination center. The staff and volunteers of DOC were considered key contributors to the design and execution of the vaccination program. A total of 103 people were invited to participate in the research study, and 30 people agreed to participate in the SSIs.

Stratified random sampling was used to select the participants. The interview cohort included representatives from team leaders, the management team, the administration and registration team, vaccinators, and volunteers. The composition of the participants' roles is included in Multimedia Appendix 1. The inclusion criteria to participate in the study's interview phase included participants aged 18-70 years, who could fluently communicate in Arabic or English, and who worked for a minimum of 3 months at the DOC vaccination center. Based on previous research, a target of at least 30 participants is needed for the sample size to reach thematic saturation and were selected based on their experience at DOC and criteria eligibility [15].

The study's cohort was recruited via email or phone invitation. Before the start of any interview, the research participants were asked to sign a consent form that outlined their rights as a research participant and complete a questionnaire that collected general sociodemographic data before the start of the interview, which can be found in Multimedia Appendices 2 and 3. The approximate duration of the interviews was scheduled for 60 minutes.

The interview protocol was developed to capture the study's objectives and included 2 main elements: the opening statement by the interviewer and the interview script, including a set of questions acting as a guide during the discussion (Multimedia Appendix 4). The opening statement introduces the researcher, the interview's intention, how the interview result will be utilized, consent to the interview, confidentiality of the interviewee's identity, and options to withdraw at any stage of the process [16]. Before finalizing both versions of the interview guide, a pilot round of SSIs was performed with a sample participant group (n=8). It comprised experts who led the same roles as outlined in Multimedia Appendix 1. The process led to the interview protocol being revised twice after the pilot phase. In addition to testing the interview guide, if the opening statement and flow of questions were understood, the researcher practiced probing to extract key insights and expand on certain topics where needed. The interview guide was then translated to Arabic (Multimedia Appendix 5) to accommodate the language preferences of almost half (14/30, 47%) of the participants. The Arabic language SSI guide was revised by an independent reviewer and later back-translated by another translator to ensure it matched the copy of the English SSI guide.

Finally, the interviews were recorded through Microsoft Teams for documentation purposes, which later assisted with the transcription process. The SSIs conducted in English (n=16) were outsourced to be transcribed using the verbatim method and then revised by a researcher on the project. The Arabic interviews were also transcribed verbatim, translated to English,

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and then independently revised by a researcher. Finally, the content is currently in the process of being thematically analyzed using MAXQDA 2020 (VERBI Software) [17]. The thought process behind the thematic analysis is to use the topics outlined in the interview guide (Multimedia Appendix 4) as the main themes. During the coding process, subthemes are intended to emerge, which will shape the list of key success factors considered as the driving force behind operations of the vaccine center. Each of the themes and subthemes were assigned a number, and any mention of a specific theme (success factor) across all 30 interviews will be tabulated and categorized, as viewed by the research participants. The thematic analysis will be conducted by a researcher and reviewed by 2 independent reviewers. If discrepancies are found among the answers, they will be referred to the lead investigator for a final decision.

Phase 2: Applying Q-Methodology

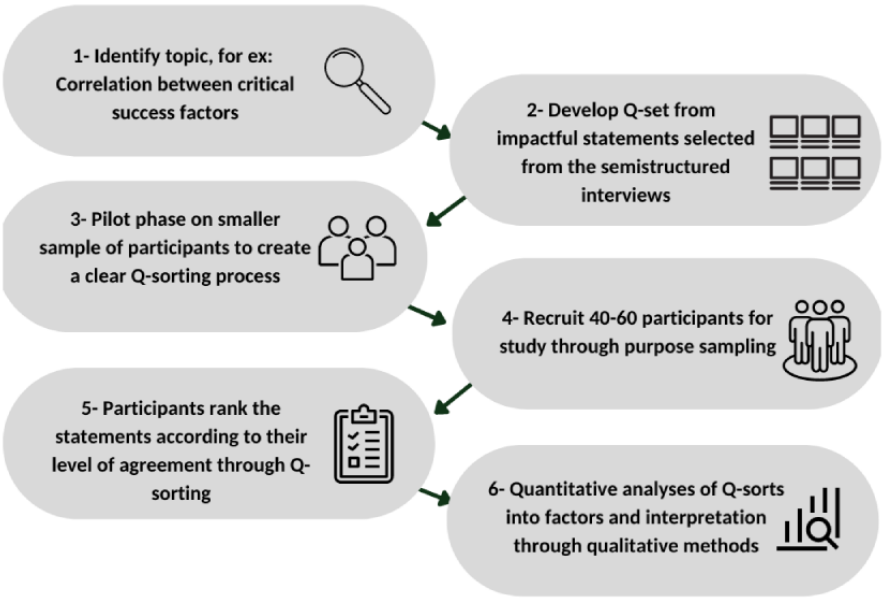
Combining qualitative and quantitative techniques, the Q-methodology aims to investigate one's subjectivity [1] analytically and will be applied to empirically investigate the opinions obtained from the research participants during phase 1. The entire process of the Q-methodology is illustrated in Figure 3 and is summarized across 6 stages. In addition, this technique has illustrated that it is suitable for use when various health care stakeholders are involved (Multimedia Appendix 1) [1].

To answer the second research question, a topic will be identified for the Q-methodology to examine how the identified success factors from phase 1 relate to one another. The "Q-set" will be developed based on the most common and impactful answers selected from the thematic analysis of the SSIs. This "Q-set" will be shared with a smaller sample group (n=10), and they will be asked to rank each of the statements based on purposefully defined criteria such as perceived importance [1]. After gathering feedback from the participants in the pilot phase, the content will be modified if needed and shared with a larger cohort (n=40 to 60) [1]. The inclusion criteria to participate in this phase of the study includes participants aged 18-70 years, who can fluently communicate in English or Arabic, and who worked for a minimum of 3 months at any of the vaccination centers in Dubai.

The next step is data collection and will include "Q-sorting," where each research participant ranks the statements in the "Q-set," following the same scale set in the pilot phase. After purpose sampling, a collection of the ranked statement by an individual, known as the "Q-sort," will be statistically analyzed using the inverted factor analysis methods [1]. During the "Q-sorting" stage, individuals will be asked postsorting questions about their experience participating in the research and their knowledge of the topic at hand, which could lead to additional qualitative insights [1].

Finally, the CSFs that may impact the delivery of health care services will be identified after discovering the relation between the factors. These CSFs will be mapped and categorized following the proposed model by Koumaditis et al [4].

Figure 3. Stages of the Q-Methodology to study the participants' perceptions collected from phase 1. Image inspired by the stages of Q-methodology from Churruca et al [2] which is published under Creative Commons Attribution 4.0 International License [18].



Ethics Approval

The Dubai Scientific Research Ethics Committee approved the study in November 2021 (DSREC-11/2021_04).

Informed Consent and Data Security

The research population included members directly involved in developing and implementing the COVID-19 vaccination campaign in Dubai and at the DOC vaccination center. All participants signed a consent form before the interview and were notified of the study's purpose in written and verbal communication. The identity of all participants will remain anonymous during the submission of the results for phases 1 and 2 of the study. All study data will be kept on a secure, password-protected computer accessible only to the research team (principal investigator and research assistant).

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Results

To fulfill the first research question, as of July 2022, 30 SSIs were conducted with the research participants outlined in Multimedia Appendix 1. On average, each interview lasted 45 minutes and ranged between 25 and 84 minutes.

Discussion

Expected Findings

The results from the project's first phase are expected to elicit the critical success factors, enablers, and barriers of the design and operation of the COVID-19 vaccination center at DOC.

Results from the project's second phase will highlight how the success factors identified in phase 1 will relate to each other, answering the study's second research question. Additionally, the expected results from the analysis will feature patterns of similarities and differences from the Q-sets. Finally, and to answer the third research question, we will identify the extent of these success factors' impact on the delivery of health care services.

Strengths of the Study

The SSIs were conducted to explore people's perceptions about the DOC vaccination center and elicit the key success factors surrounding its design and implementation. Another strength of the research study is the number and quality of interviews completed. The researchers organized 30 interviews—the recommended number of SSIs that need to be completed to provide meaningful results for a research study [15]. The group of interviewees included employees and volunteers from diverse professional backgrounds. The varying roles each of the interviewees held at the vaccination center (refer to Multimedia Appendix 1) provided the study with richer and diverse insights [19]. Furthermore, the open-ended question format of the SSIs allowed the participants to focus on each topic in detail and share varied responses based on their individual experiences [20]. This approach helps reduce the risk of bias relating to the researcher's preconceptions about the themes, as this style of data collection allows the use of follow-up probes throughout the discussion as directed by the participant [20].

In addition to completing the SSIs, the Q-methodology will focus on allowing participants to express their opinions about the subject while reducing former expectations and possible biases introduced by the researcher. It is also known as a people-centric approach that can provide a deeper view on the matter and is beneficial when studying complex health care topics [1]. This method is not commonly found in health care research and can potentially be a valuable tool [1].

The result of our research can help bridge a noted gap in the literature [4] as we explore each of the CSFs independently, their relation to each other and the health care service, as well as develop a CSFs model that can be applied to any level within a health care organization or service to improve the quality of patient care and organization of data [4]. Combined with the implementation of SOA, there is a real opportunity to achieve interoperability and flexibility to update medical processes in line with new regulations and improve decision-making [4]. According to research in this area, developing SOA culture and governance from the leadership are seen as a driving force for resisting change and successful execution [4].

It is noted that there is limited information in the medical literature on the systematic process of creating MVCs. Although mass vaccination campaigns have been mentioned as a general component for managing communicable diseases since the 1970s during the spread of H1N1 influenza, there is a lack of clear criteria to defining an MVC, such as pertaining to the number of doses and/or number of people served in a day [8]. For example, in the spring of 2021, Euro Disney Paris was transformed into an MVC with the capability of serving 1000 doses/day, whereas in Italian cities, they were able to vaccinate over 4000 people in one day [8]. Global health experts are executing their own strategies and procedures to administer the COVID-19 vaccines as the concept has more prominently emerged within the last 2 and a half years [8].

Comparison to Other Works

Studies surrounding the development of MVCs specific to the COVID-19 pandemic are still considerably low [8,21]. They are typically found to focus on documenting the MVC process, analyzing the vaccination system, and understanding people's perceptions about the COVID-19 vaccine [20,22]. However, the outcome from these studies is not usually connected to the enhancement of more general health care services and improving patient care. For example, Brambilla et al [21] studied the process surrounding mass vaccination. They outlined the method of developing a scalable and replicable MVC model in Lombardy, Italy, which can be adapted and created in non–health care locations, whereas Andrade et al [22] focused their research on investigating the UAE's population's motivation to receive the vaccine and its correlation to their level of understanding, acceptance, and conspiracy beliefs related to the vaccine. Another example of a recently published study illustrated the application of Lean tools to develop an MVC and investigated its effectiveness and whether this approach increases the efficiency of mass vaccination sites [23].

Since MVCs for COVID-19 are believed to be the first mass vaccination effort in the present era [8], it is considered integral to document the process of creating a high-volume MVC such as the DOC vaccination center and the collaborative efforts to safely administer over 1.4 million doses in the span of one year to everyone that required it. In addition to documenting these efforts, this study also aims to connect the results from understanding the key success factors of implementing an MVC to its potential impact on the delivery of health care services and improving patient care.

Knowledge generated from this study conducted in the Gulf Cooperation Council and the Middle East region will contribute to a more accurate global representation of the success factors, as we aim to empirically explore the opinion of multiple health care stakeholders and elicit the key success factors influencing the delivery of a health care service during a public health emergency, such as a vaccination center.

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Limitations of the Study

Due to restrictions imposed because of the COVID-19 pandemic, the SSIs were completed remotely, via the videoconferencing platform Microsoft Teams. This was often considered a challenge as there were technical difficulties while the interviews were taking place such as unreliable internet connection. Utilizing an online platform to collect data may have impacted the quality of recordings, which in turn may have affected the quality of the transcriptions. Additionally, attempting to schedule at least 30 interviews in a short time frame before the center's closure proved difficult to plan around the employee's schedules, and the interview schedule was continuously delayed. The SSIs were conducted with a sample of DOC vaccination center's staff and volunteers before the closure of the center by 2 months and were completed shortly afterward. Therefore, the time between data collection and the closure of the DOC vaccination center may have contributed to recall bias as the interviewees were asked to recollect events from the past. Finally, due to the workload of the front-line workers at the DOC vaccination center, pandemic fatigue may have also been a factor that could have influenced their responses in the interviews.

Future Work

Future research will leverage the data collected to contribute to the medical informatics field, specifically with the aims to explore approaches that can effectively analyze big data, include predictive analytics, and optimize decision-making [24]. In line with the future plans, a study will use data, collected through the DOC vaccination center, to develop a simulation model outlining the process of the customer journey and center workflow.

The simulation model will focus on capturing the data at 3 significant milestones, including when the center reached a daily capacity of administering 1000 doses, 4000 doses, and 10,000 doses to customers. This will showcase the center during various operational phases and the improvements that took place during each stage and identify areas that needed more enhancements to increase operational efficiency. Simulation modeling has been identified as a smart tool that offers the prospect of testing various scenarios using a cost-effective approach, obtaining solutions for obstacles during certain health care service phases, comprehensively visualizing the process [8].

This analytical phase of the study will focus on the operational aspect of designing a health care service and how it can assist with the decision-making process through an optimized health care service model [24]. In a way, the pandemic accelerated the growth of designing and delivering a high-capacity vaccination center. Therefore, it is recommended that the next phase of planning for health care services is to focus on operational efficiency, its link to patient satisfaction, high-quality care, and the need to apply a standard operating procedure across various processes and facilities [4].

Conclusion

The study provides a comprehensive 2-phase approach to eliciting the CSFs that can influence the delivery of high-quality health care services such as emergency services launched during a global pandemic. The findings from the study will be translated into key factors that could be optimized and applied when designing future health care services, utilizing evidence-based practice. Additionally, the results from the study conducted in the Middle East region will contribute to a more globally accurate representation of CSFs. Finally, the future work from this research study will explore methods to analyze data collected from the DOC vaccination center, include predictive analytics, and optimize decision-making.

Acknowledgments

This research was supported in part by the Al Jalila Foundation and is funded by a Pfizer Independent Medical Education Grant (number 69872363). However, the funding body was not involved in the study's design, data collection, or analysis.

Data Availability

The data sets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Table describing each of the research participants' roles at the Dubai One Central vaccination center and number of participants from each group.
[PDF File (Adobe PDF File), 91 KB - resprot_v12i1e42278_app1.pdf]

Multimedia Appendix 2
Consent form shared with all participants prior to the start of their semistructured interview.
[PDF File (Adobe PDF File), 87 KB - resprot_v12i1e42278_app2.pdf]

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Multimedia Appendix 3
Questionnaire which was used to collect sociodemographic information about each of the participants before their interview.
[PDF File (Adobe PDF File), 110 KB - resprot_v12i1e42278_app3.pdf]

Multimedia Appendix 4
Final version of the interview guide in English, developed for the semistructured interviews. The table outlines the themes of the groups of questions, their number, scheduled questions, and follow-up probes that could be used throughout the discussion.
[PDF File (Adobe PDF File), 140 KB - resprot_v12i1e42278_app4.pdf]

Multimedia Appendix 5
Final version of the translated interview guide in Arabic was developed for the semistructured interviews. The table outlines the themes of the groups of questions, their number, scheduled questions, and follow-up probes that could be used throughout the discussion.
[PDF File (Adobe PDF File), 205 KB - resprot_v12i1e42278_app5.pdf]

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Abbreviations

CSF: critical success factor
DOC: Dubai One Central
MVC: mass vaccination center
POD: point of dispensing
SOA: service-oriented architecture
SSI: semistructured interview
UAE: United Arab Emirates

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Protocol

The Development of a UK Culturally Adapted and Modified Version of the Person Attuned Musical Interactions Manual: Protocol for a 2-Phase Mixed Methods Study

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Abstract

Background: Previous research has suggested that care home interactions need significant improvements, especially those between staff and residents with dementia. Reasons for the lack of interactions are staff time pressures and residents' language impairments. Although residents may experience reduced language abilities, they can continue to communicate through other forms, including nonverbal communication and music. Person Attuned Musical Interactions (PAMI) is a staff training tool that provides staff with music therapy skill-sharing to promote high-quality interactions between staff and residents using nonverbal communication and music. The tool was originally developed in Denmark. To ensure that the tool is appropriate for UK care homes, a team of researchers in the United Kingdom have modified and culturally adapted the tool.

Objective: This study aims to investigate the appropriateness of the adapted and modified manual for UK care homes and to explore the impact of PAMI on residents with dementia and care staff.

Methods: The project consists of 2 phases, a qualitative field-testing study and a mixed methods evaluation study, which have been developed following the Medical Research Council's guidelines for complex interventions. Care staff and residents with dementia will be recruited from care homes in Lincolnshire, where the care staff will be trained in the PAMI intervention before implementing the intervention in their daily routines. Fortnightly reflective sessions will be provided throughout the phases to provide supervision and monitoring. The qualitative methods include interviews, reflective session transcripts, diary entries, and resident experience questionnaires. The quantitative outcome measures are residents' music engagement, staff's dementia competence, residents' quality of life, and staff burden. The resident's music engagement will be administered at 9 fortnightly time points. Staff's dementia competence, resident's quality of life, and staff burden will be administered at preintervention and postintervention time points.

Results: The study has been funded by The Music Therapy Charity as part of a PhD studentship. The study began recruiting in September 2021. The research team aims to publish the results of the first phase in July to September 2023 and those of the second phase in October to December 2023.

Conclusions: This study will be the first to investigate the modified version of PAMI. Therefore, it will provide feedback on the appropriateness of the manual for UK care homes. The PAMI intervention has the potential to offer high-quality music intervention training to a larger population of care homes who may currently be restricted by finances, the availability of time, and a lack of training opportunities.

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KEYWORDS

psychosocial intervention; music; dementia; interactions; care homes; care staff training tool; tool; research; impairment; training; communication; intervention; quality of life; care; development; language

Introduction

Care Homes and Residents With Dementia

People reside in care homes for several reasons, including old age, health conditions, and disability, but generally, care home residents require substantial help and support to complete activities of daily living, including personal care, and to access leisure activities. In the United Kingdom, between 408,371 and 490,326 individuals live in approximately 17,079 care homes [1,2]. Approximately 70% of the residents in care homes have a diagnosis of dementia [3]. Dementia is an umbrella term for a range of progressive conditions characterized by a slow deterioration in brain function, including memory, language, decision-making, and judgment [4-6]. Individuals with dementia can experience a range of symptoms because of the deterioration, including disorientation, anxiety, depression, apathy, agitation, restlessness, hallucinations, mobility issues, and personality changes, which can affect an individual's ability to complete daily tasks and live independently.

Care Home Communication

The care and assistance staff provide to residents compel the need for a strong relationship based on trust, respect, and understanding [7,8]. Care staff should aim to provide person-centered care and interactions to tailor care to the resident's needs, preferences, impairments, and abilities [9-11]. Staff should consider the individual as a whole person who is treated with respect and dignity. Person-centered care can be inconsistent among staff and care homes. During a 6-hour observation period, Willemse et al [12] reported, on average, 1.5 meaningful interactions, with one-third of participants experiencing zero meaningful interaction during the observation. Care home interactions are not only infrequent but can also be short, be fragmented, sometimes consist of "Elder speak," and be task orientated in nature [13,14]. "Elder speak" refers to interactions characterized by simplistic vocabulary and grammar, shortened sentences, slow speech, elevated pitch, and inappropriate use of endearments [14-16]. "Elder speak" has been compared with interaction techniques typically used with babies and leaves individuals feeling patronized. The frequency and quality of interactions generally correlate with the severity of the individual's dementia and impairments, including limited verbal language [14,17]. Understaffing and time pressures have been suggested to explain the limited interactions in some care homes and result in prioritizing physical care and safety over meaningful activities and interactions [18]. However, meaningful activities and interactions are equally essential to ensure that the resident's psychological, social, and emotional needs are met; the resident's identity remains; and dementia symptoms are managed. Therefore, interventions and staff training targeting interactions and meaningful activities in care homes without increasing staff time or burden are vital.

Music in Dementia Care

Although individuals can experience reduced verbal language, involvement in interactions can continue through nonverbal communication and other alternative communication styles [17,19,20]. However, as they are untraditional and less familiar to individuals, staff can miss or misinterpret more ambiguous and subtle communication cues [20].

Music, consisting of both verbal and nonverbal elements, has been highlighted as a potential alternative communication form accessible to individuals with dementia. Although language processing significantly deteriorates as dementia progress, music processing seems to remain intact, potentially owing to music processing requiring nearly all brain areas [21-23]. Music is an inclusive and adaptable tool not limited by age, culture, or health conditions and has been evidenced as a multibeneficial tool for various health conditions, including dementia [24,25]. Music in dementia care has the potential to improve well-being, alertness, anxiety, depression, agitation, and activity disturbance [26-28]. When care staff facilitate music activities, research has reported improvements in quality of life, job satisfaction, communication skills, stress, and burden [29]. Typically, music can be categorized into 2 intervention types: music therapy, facilitated by specialist music therapists [30]; and music activities, facilitated by care staff, family members, volunteers, and musicians. Both have highlighted the benefits of incorporating the intervention into dementia care. The most appropriate intervention depends on the aims of the intervention, symptoms, residents' preferences, and care home factors such as time and finances.

In the United Kingdom, music therapists are limited, with only 200 to 250 individuals working in the dementia field [30], resulting in the intervention being restricted to a limited number of individuals. In addition, care home finances can restrict care homes from employing music therapists. Research highlights that music therapy benefits generally only remain during and immediately after the session [31]. Therefore, to maintain the benefits, regular daily doses of music interventions should be provided in care homes, which may not be plausible with music therapy. Music activities have more flexibility and can be provided by anyone, making them a more viable option for long-term use in a larger proportion of care homes. When music activities are of high quality and implemented successfully, they can provide similar benefits to music therapy [32-36]. However, the implementation of care home music activities is currently minimal. In 2017, only 5% of care homes provided good quality arts and music interventions [37]. The lack of staff time knowledge, resources, and training may explain the lack of

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music interventions in UK care homes [38-40]. The lack of available time has been highlighted as a potential barrier to staff interactions and music interventions. However, a series of studies investigating music therapeutic care (MTC) demonstrated the plausibility of incorporating music into personal care tasks [32,41-45]. Because music was incorporated into other tasks, staff did not have to spend additional time or bear additional burden; instead, the intervention improved task efficiency. However, the issue remains that low-quality music activities implemented unsuccessfully can be ineffective and even harmful to residents with dementia [46].

Music Therapy Skill-Sharing

Music therapy skill-sharing provided by music therapists has been suggested as a solution to improve the implementation of high-quality music interventions facilitated by staff in care homes. Music therapists share their skills and knowledge of music therapy, allowing staff to incorporate indirect music therapy practices into their routines [46]. As previously highlighted, staff and family members may lack knowledge and experience in music interventions. Inappropriate or lack of space and support for staff to reflect on how to be with the individual and focus solely on the content can lead to a loss in benefits [40,46,47]. Currently, music therapy skill-sharing only occurs in care homes with employed music therapists. A structured manual developed from evidence-based practices that train staff in the type of music skills and how facilitators should deliver skills would enable music therapist knowledge to be shared with and accessible to a larger population of care homes.

Person Attuned Musical Interactions Manual

Person Attuned Musical Interactions (PAMI) is a structured staff training tool developed based on previous research that provides staff with music therapy skill-sharing training. The tool was initially created by a team of music therapist researchers at Aalborg University, Denmark [48], which aimed to promote 2-way attuned music interactions between care staff and residents with dementia. In the intervention, the PAMI research team train music therapists, who then go into care homes to train staff. The training provided to care staff consists of 3 elements: group theory and reflective training, group practical supervision, and individual practical supervision. In the group theory and reflective training, staff gain insight into the theory behind PAMI, complete reflective exercises, and learn about the PAMI skills. The group and individual supervision sessions involve the music therapists working with the care staff on the care home floor to assess and guide staff on the PAMI skills by observing them using the skills with residents. All the elements of the PAMI training are completed in person. On the basis of cultural adaptation intervention research [49,50]. A modified version of PAMI was developed by a team of researchers at the University of Nottingham to ensure that PAMI was culturally appropriate for UK care homes (Waters, B, Orrell, M, and McDermott, O, unpublished data, March 2023).

The researchers followed 2 cultural adaptation frameworks, the Barrera and Castro [51] framework and the Formative Method for Adapting Psychotherapy [52], to guide the development process. The first author's thesis reports the manual development process and the differences between the Danish and Modified version of PAMI (Waters, B, unpublished data, March 2023). Both frameworks advise that once adapted, the newly adapted intervention should be reviewed with stakeholders to test its appropriateness and obtain preliminary results.

Aims

The aims of this study are as follows:

1. To investigate the suitability, manual layout, and clinical relevance of the PAMI-Modified (PAMI-M) manual
2. To investigate the cultural adaptation appropriateness of the PAMI-M manual
3. To identify changes in staff's and residents' behavior and mood after using the PAMI-M manual
4. To identify staff's views on using the PAMI intervention within their care home
5. To investigate the factors influencing the implementation of PAMI in UK care homes

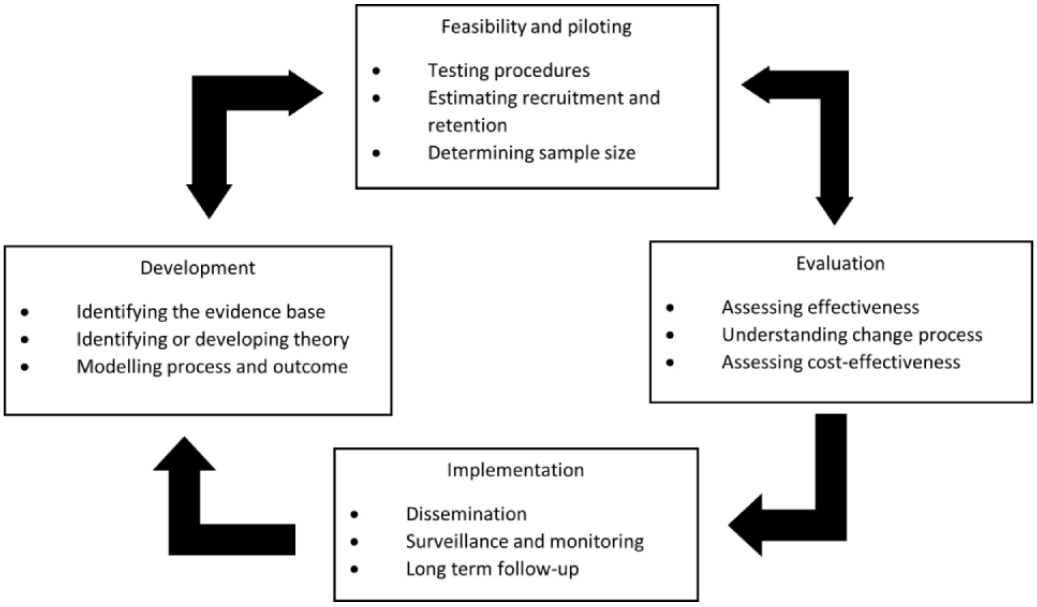
Methods

Medical Research Council Guidelines

The research team identified PAMI as a complex intervention; therefore, the Medical Research Council (MRC) guidelines have been followed for this study. Complex interventions refer to interventions consisting of several interacting components. Interventions may be complex for several reasons, including the number and difficulties of behaviors of those receiving the treatment, the requirements of the facilitator, the number and variability of outcomes, the degree of flexibility, tailoring of the intervention, and the number of groups targeted. The MRC created a framework for researching complex interventions to aid researchers in designing, running, and reporting complex interventions [53]. The framework consists of 4 phases (Figure 1): development, feasibility and piloting, evaluation, and implementation. This protocol focuses on the development phase and begins to explore the feasibility and piloting phase.

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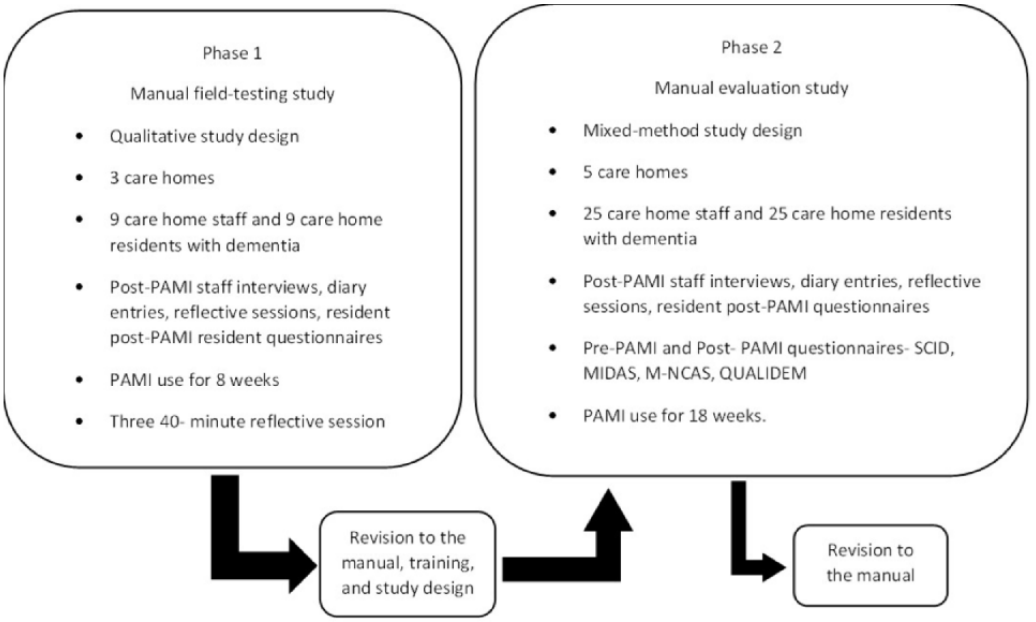
Figure 1. Medical Research Council complex intervention framework.



Study Overview

Two phases will be conducted to investigate the aims, which follow the stages of the MRC guidelines and cultural adaptation frameworks. A field-testing qualitative study will review the culturally adapted manual with its intended stakeholders to ensure appropriateness. Data will be collected on the factors influencing the implementation of the intervention and stakeholders' (care staff and residents) experience with PAMI, including changes in behavior and mood and care staff's views on using the intervention. The data collected in the first phase will aid adaptations to the manual in preparation for the second phase. The second phase is a mixed method study that will continue reviewing the culturally adapted manual with its intended stakeholders. In addition, the study will collect preliminary data on the impact of PAMI on staff and residents to begin investigating the feasibility and piloting stage of the MRC guidelines. The data collected in the second phase will aid final manual revisions and be used to develop future studies to continue exploring the feasibility and piloting stage of the MRC guidelines. Figure 2 displays the study overview.

Figure 2. Study overview consisting of 2 phases and 2 revisions stages. The study overview was developed based on the Medical Research Council guidelines for complex interventions and culturally adapting intervention frameworks. MIDAS: Music in Dementia Assessment Scale; M-NCAS: Modified Nursing Care Assessment Scale; PAMI-M: Person Attuned Musical Interactions-Modified; SCIDS: Staff Competence in Dementia scale.



Ethics Approval

The 2 phases received ethics approval from the London-Harrow Research Ethics Committee on June 29, 2021 (reference number 21/LO/0283). Amendments to the study were approved by the London-Harrow Research Ethics Committee on March 22, 2022.

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National Health Service Trust Partnership

A partnership with the Lincolnshire Partnership National Health Service (NHS) Foundation Trust was created early in the manual development process, which will assist with running the studies in care homes. As part of the partnership, PAMI will be advertised through the trust's Enabling Research in Care Homes (ENRICH) organization. ENRICH is a national organization developed by the National Institute for Health Research (NIHR) to support care home staff, care home residents, residents' families, and researchers to implement research into care homes more smoothly, accessibly, and effectively.

The Lincolnshire trust developed a pilot in-reach scheme in 2020 to improve the accessibility of care home research within Lincolnshire. The partnership between the research team and Lincolnshire NHS trust has led to an in-reach practitioner (RF) joining the team. The in-reach practitioner will liaise between the researchers and care homes with whom they already have a rapport. This rapport means that the in-reach practitioner is already aware of care homes potentially interested in the PAMI research, reducing the time needed for introductions, providing a recognizable face, and thus reducing anxiety among potential participants. The in-reach practitioner will support the researchers in setting up and running the study. The role involves introducing the study to care homes, recruiting participants, distributing documents, assessing capacity, obtaining consent, introducing the care homes to the research team, collecting documents, and being an in-person contact for the research team. When designing the study, the research team was uncertain about the possibility of the researchers attending the care homes owing to the COVID-19 pandemic; however, the in-reach practitioner is an NHS role, allowing them to continue attending care homes throughout the studies. The care homes involved in the in-reach pilot scheme belong to ENRICH and were invited to join the scheme.

Recruitment

Care homes will be recruited first through the in-reach scheme or advertisement through the Lincolnshire ENRICH. Once the care homes are recruited, 2 participant types will be recruited: care staff and residents with dementia. The researchers will contact care home managers and introduce the team to interested individuals. A management introductory letter will introduce the study and provide the potential benefits to the residents, care staff, and care home. The introductory letter will also inform managers of the required time commitment from themselves, the staff, and the residents to ensure that their care home can commit the required time. The welcome pack also contains introductory letters for the care staff, residents, and residents' families. The care home managers will be asked to distribute the welcome letters to the staff and residents. Care staff will be recruited first before residents to enable the staff to communicate the study to the residents. As the researchers cannot access residents' care plans, the researchers require care staff to distribute the information sheets to eligible individuals. Interested individuals can contact the researchers using the provided contact details or inform the in-reach practitioner when she attends the care home of their wish to participate. Information sheets and consent forms will be provided to interested individuals, with them given a week to consider their participation. The in-reach practitioner will organize visits with the care homes during recruitment to discuss the study and answer questions. Once care staff and residents are recruited, the residents will be paired with the participating care staff they have the most direct contact with daily.

Informed Consent

Written informed consent will be collected from all participants at the start. There are different information sheets for staff and residents. A dementia-friendly version of the resident information sheet is available for residents who may struggle to comprehend the formal participation sheet. If individuals wish to participate, a consent meeting is organized, where they can review the documents with the in-reach practitioner and sign the consent form. The consent meeting can be completed either in person at the participating care home or remotely via Microsoft Teams (Microsoft Corp). During the meeting, potential participants are given time to ask any questions or concerns. Once the consent forms are signed, 1 copy is given to the participant, and the research team keeps 1 copy. A third copy is kept in the resident's care file when resident participants consent. Consent is an ongoing process; therefore, the research team will continue checking participants' consent. Some resident participants may be unable to consent verbally; therefore, the researchers will work with the care home to determine the most appropriate form of communication for each resident.

Researching Adults Who Lack Capacity

The studies involve participants who may lack capacity owing to their dementia diagnosis. The Mental Capacity Act 2005 [54] will be followed to determine participants' capacity to consent. All research team members have previously worked in care homes, where their role required the understanding of the lack of capacity. All members have also completed training in informed consent with adults lacking capacity. With assistance from the care homes, the in-reach practitioner will assess the resident's capacity to consent during the consent meeting, which involves assessing whether the resident understands the study and what is required of them and ensuring that they understand the consent form and can follow the instructions to sign the form. A consultee, who is a family member, a friend, or an appointed power of attorney, will be appointed for residents who are deemed to lack capacity. Once a consultee is appointed, they will be provided with an invitation letter, a consultee information form, and a consultee declaration form, with time to consider their relative's (the term relative is used to also refers to those who's consultee is a friend or power of attorney) participation in the study before a consultee meeting is organized. The consultee meeting can take place in person or remotely via Microsoft Teams. During the consultee meeting, the consultee will be asked to sign the declaration form if they wish their relative to take part in the study. Staff and consultees can use the dementia-friendly information sheet to discuss with residents their participation in the study. For residents who are deemed to lack capacity to consent, on top of their consultee's declaration to participate, assent will be obtained to ensure that they agree to partake. Assent will be collected to allow residents to remain involved in the decision process when not legally able

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to consent. The most appropriate communication form for residents will be used to obtain assent. Researchers will ensure that residents continue to consent throughout the study, using their choose communication form. For residents unable to verbally assent, staff and researchers will assess residents' behavior for signs of wishing to withdraw or distress throughout the study.

Dementia is a progressive condition; therefore, some resident participants could lose capacity during the study. The researchers will review the resident's capacity throughout. If a resident is deemed to lose the capacity to consent during the study, a consultee will be appointed and asked to complete the consultee declaration form to allow the resident to continue the study.

Withdrawal

Care staff participants will be reminded at the start of each reflective session that their participation and their resident's participation are voluntary, and they can withdraw at any time without providing a reason. Participants will also be reminded that withdrawal from the study will not affect the care they receive as a resident or their employment as staff. During the reflective sessions, care staff will be asked to report any PAMI issues and whether residents have displayed signs of distress or wish to withdraw. In-between reflective sessions, participants can contact the researchers via email or telephone. All study activities will cease immediately if a participant withdraws, and no further data will be collected. However, the data that have already been collected will be used in the final analysis. As participants partake in the study as dyads, both participants will be withdrawn from the study. The only exception is if only the staff interview remains and the resident withdraws; in this case, the staff member can complete the interview but will only be able to report on their experience of the training. Withdrawn participants will not be replaced.

Setting

The 2 phases will be conducted in Lincolnshire care homes caring for individuals with dementia. The care homes can be private, voluntary, NHS or council owned and provide either residential, nursing, or both types of care. All care homes must meet the eligibility criteria.

The care home eligibility criteria are as follows: they should have received a score of "Needs improvements" or "good" on their most recent Care Quality Commission report and have adequate Wi-Fi for staff to be able to attend the PAMI training and reflective session.

The in-reach practitioner will review care homes' eligibility to determine to whom to introduce the study. The care homes in the in-reach pilot are all part of the ENRICH group, which promotes and supports care homes with research.

Remote Delivery

When designing the study, the UK COVID-19 guidelines restricted researchers from attending care homes. As a result, several study elements have been converted to take place remotely. The training, reflective sessions, and interviews will be completed remotely using a conference call platform. Microsoft Teams was selected because of its ease of use; it allows up to 250 individuals to join a call; it allows for screen sharing; it is not time limited; it can record sessions; and it is encrypted, making it safer. The NHS Transformation Directorate Department, formally known as NHS user experience, confirmed in 2020 that Microsoft Teams is safe to use in health care [55,56]. A Microsoft Teams channel will be created for each care home where the training session, reflective sessions, and interview meetings are scheduled. A Microsoft Teams information sheet has been created, providing information on joining Microsoft Teams channels and meetings. The information sheet will also be provided to consultees who complete their consultee advice meeting remotely. For ease and consistency, the research team decided to continue running the studies remotely when the UK COVID-19 guidelines were lifted.

Intervention

The PAMI intervention can be split into 3 elements: the paper copy of the PAMI manual, the initial training session, and fortnightly reflective sessions.

Manual

The PAMI manual consists of theory, reflective exercises, examples, and practical skills. The manual can be sectioned into 6 categories: interactions and music, the voice, framing, balancing, connecting, and practical tips and resources. Colored boxes have been used to separate the different elements to make it easier for staff to locate information. Staff are required to bring the paper manual to the initial PAMI training, as the reflective exercises in the manual are completed during the training.

The first section, interactions and music as communication, provides staff with theory on interacting with individuals with dementia. PAMI aims to be able to train all staff regardless their level of experience and training; therefore, this section provides the foundations of interactions in dementia care to ensure that everyone is at the same level before exploring the PAMI skills. This section also starts to explore using music therapeutically and the research highlighting the benefits of music for individuals with dementia. The second section begins to explore the voice as a musical element. The section reflects on when and how staff use their voice currently. The music parameters of the voice, including pitch, rhythm, tone, and volume, are explored in relation to the staff's roles. Framing explores adapting the care home environment to create security and predictability. This section introduces the skills of using music as a cue for tasks and sound environments. Balancing explores recognizing and adapting residents' arousal states using music, the voice, and the body when residents experience agitation or apathy. Staff also gain skills to recognize their arousal state and regulate it to ensure that their emotions are not impacting their interactions with residents. Connecting explores using meaningful music to connect and create relationships. Staff explore reminiscence and music therapy skills such as attunement, validation, and holding. The connecting section introduces the PAMI music care plan, providing residents with a tailored music plan that staff can use to implement music successfully. The final section provides practical tips to improve the implementation of the intervention.

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Training Session

The primary researcher (BW) will facilitate the training sessions with assistance from a music therapist (BS). BW is a nonmusic therapist with a background in psychology and has worked as a care home well-being therapist. BW was the researcher who developed the modified PAMI manual as part of her PhD. (Waters, B, unpublished data, March 2023). The PhD student was selected by the research team as the most suitable candidate for the role, and her experience complemented the rest of the team's expertise and knowledge. The primary researcher worked with the original Danish team and the principal investigator, who is also a music therapist, to ensure that the training covered all the appropriate areas of music therapy. Before the delivery of the training to any care homes, the primary facilitators ran the training with 2 music therapists, the principal investigator, and second PAMI facilitator, who provided feedback on the content and delivery of the training. The feedback was used to make final changes to intervention before its use in the study. A 3-hour group interactive webinar will be delivered via Microsoft Teams at the study's beginning. The training is organized at the convenience of the care homes and care staff. The training session follows the manual layout, with staff completing the reflective exercises in the manual during the session. Different learning elements have been used, including written text, pictures, talking, interactive activities, videos, and the music therapist experience, to make the training accessible to many learning styles. During the session, staff are provided with examples for implementing the skills and theories into practice. As PAMI's central ethos is person centered, what, when, and how frequent skills are used are at the staff's discretion. Staff are instructed to use PAMI in relation to their resident's needs, impairments, and preferences. However, they are advised to use PAMI regularly on every shift.

Reflective Sessions

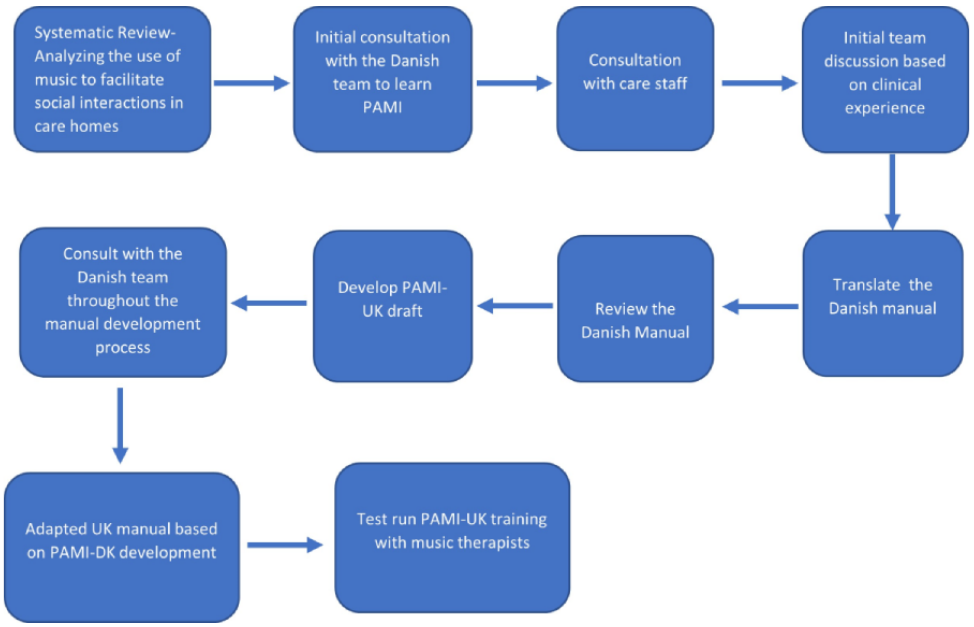
BS, a music therapist on the researcher team, will facilitate the reflective sessions with assistance from the primary researcher. The sessions will be conducted once a fortnight for 40 minutes via Microsoft Teams. The sessions hold two purposes: (1) to get staff to reflect on their practices and their experience implementing PAMI and (2) to collect data on using PAMI in care homes. Unlike the training, which has more structure, the reflective sessions are less formal, with sessions guided by the care staff. Three reflective sessions are more structured, each focusing on one of the specific PAMI elements to ensure that staff have understood each element and attempted to implement the skills in the care home. A reflective session outline has been developed by BS to guide the sessions and provides potential questions that the facilitator may wish to ask to prompt discussion.

Intervention Development

The research team completed a multistage process to culturally translate and adapt the Danish PAMI intervention for UK care homes (Figure 3). Throughout the process, the research team liaised with the Danish PAMI team to ensure that any adaptation and modification remained consistent with the PAMI ethos. The research team also incorporated public and patient involvement throughout the development stage to ensure that the intervention was appropriate and suitable for the intended setting and audience. A detailed manual development process is discussed in the primary author's thesis (Waters, B, Orrell, M, and McDermott, O, unpublished data, March 2023).

During the manual development process, several changes were highlighted to make the intervention more culturally appropriate for UK care homes Table 1.

Figure 3. The manual development process for culturally translating and modifying the Person Attuned Musical Interactions (PAMI) intervention for UK care homes. PAMI: Person Attuned Musical Interactions.



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Table 1. The changes between the Danish and Modified Person Attuned Musical Interactions (PAMI).

Element	PAMI[a]	PAMI-M[b]
Information booklets	• Theory book • Practical workbook for staff • Training book for music therapists • PowerPoint (Microsoft Corp) for workshop	• Training manual containing theory and practical exercises • PowerPoint for workshop
Facilitator	• PAMI team trains music therapists, who then train care staff in care homes	• PAMI team trains care staff in care homes
Training format	• In person	• Web based
PAMI elements	• Ramme (framing in Danish) • Regulering (regulation in Danish) • Relation (relation in Danish)	• Framing • Balancing • Connecting
Course layout	• 4 modules • Theory and exercise session • Practical hands-on training individually and in groups	• 4 modules • Interactive webinar consisting of theory and exercises • Reflective sessions

Training length	• 16 hours over 10 weeks:
	  • 8 hours of theory and exercises
	  • 4 hours of individual practical training
	  • 4 hours of group practical training
		• 3-hour interactive webinar
		• Fortnightly 40-minute reflective sessions

Wording	• Some of the wordings did not translate exactly or had different connotations in the United Kingdom:
	  • *Svag* (weak in Danish)
	  • *Spinkel* (flimsy in Danish)
		• Weak was changed to soft
		• Flimsy was changed to delicate

Song	• Uses Danish well-known songs and folk songs	• Uses English well-known songs

[a]PAMI: Person Attuned Musical Interactions.

[b]PAMI-M: Person Attuned Musical Interactions Modified.

Phase 1: Manual Field-testing Study

Overview

Phase 1 aims to review the culturally adapted manual with the intended stakeholders (care staff and residents with dementia). The study will explore the adapted manuals' suitability, layout, clinical relevance, and culturally adapted appropriateness. Data will also be collected on the factors influencing the implementation of PAMI to determine optimal use, use behavior, and the experience of staff and residents. The data collected in phase 1 will aid revisions to the manual and study design.

Phase 1 is a qualitative field-testing study consisting of interviews, reflective session transcripts, diary entries, and residents' postintervention questionnaires.

Participants

The study will recruit 9 care staff and 9 residents from 3 Lincolnshire care homes. Each staff member will be paired with a participating resident from their care home. Care staff and residents are required to meet the eligibility criteria.

The care staff inclusion criteria are as follows:

- Should be aged >18 years
- Should have the capacity to consent in accordance with the Mental Capacity Act 2005
- Should be permanently employed at the participating care home
- Should have been employed for at least 6 months with plans to remain working at the care home for the study duration (to ensure that staff are familiar with the residents)
- Should work a minimum of 2 shifts a week to ensure sufficient time to implement PAMI into routines
- Should have the ability to read, write, and communicate fluently in English
- Although any member of staff who has direct daily contact with residents can use PAMI, for this study, only staff who assist with activities of daily living or activity staff are eligible
- Should not be currently taking part in any other psychosocial interventions

The care staff exclusion criteria are as follows:

- Staff who are not an employee of the participating care home (eg, agency staff and external health care professionals)
- Members of staff who do not have sufficient direct contact with residents daily (eg, catering or housekeeping)

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The resident inclusion criteria are as follows:

- Should be aged >18 years (no upper age limit)
- Should have a diagnosis of dementia as described by the International Classification of Diseases, 11th Revision
- Should have the capacity to consent in accordance with the Mental Health Capacity Act 2005 or have a consultee who could advise on the individual's wishes if the individual is deemed to lack capacity
- Should have lived at the participating care home for at least 6 months with plans to remain residing at the care home for the duration of the study (to ensure that residents are settled and familiar with the staff)
- Should have sufficient hearing or use hearing aids
- Should have regular interactions with a participating staff member; this will be the staff member they are paired with
- Should not be currently taking part in any other psychosocial intervention research

The resident exclusion criterion is as follows: residents who are residing at the care home on respite or short-term stay.

Procedure

The study will run for approximately 10 weeks in each care home, with PAMI being implemented for 8 weeks. The in-reach practitioner will advertise the study to care homes in the in-reach scheme. The manager of eligible care homes will receive the PAMI welcome pack containing welcome letters for staff and residents, which they will be asked to distribute. Interested staff and residents can express their interest via email or to the in-reach practitioner when she attends the care home, after which they will be provided with a participant information sheet and consent form. A consultee will be appointed and provided with information sheets and declaration forms for residents deemed to lack capacity. Consent or consultee declaration forms will be signed for each participant before the start of the study. Once participants have been recruited, staff and residents will be paired into dyads.

At the beginning of the study, staff will receive a paper copy of the PAMI manual, staff and resident demographic questionnaires, a diary entry form, and the Dementia Severity Rating Scale (DSRS) and be asked to complete the questionnaires before the training. A dementia-friendly demographic questionnaire is also provided to assist residents who may struggle with the demographic questionnaire. Each care home is sent a care home demographic questionnaire to complete. The researchers will work with the care home and staff to organize a convenient time to complete the training. After the training, staff will implement PAMI in routines for 8 weeks. Staff are instructed to use the skills in relation to their resident's needs, impairments, and preferences; therefore, the skills used and frequency of use will vary among staff. However, staff are advised to use PAMI regularly on each shift. Staff are asked to complete the diary form each time they use PAMI with their resident. Once a fortnight, staff will attend a 40-minute reflective session via Microsoft Teams. The facilitators will monitor the study procedure during each reflective session to ensure that no issues or distress have occurred and that both staff and residents are happy to continue. Staff will complete a total of 3 reflective sessions. After the 8 weeks, staff will be invited to a semistructured interview to discuss their experience. The interview will be completed via Microsoft Teams and last approximately 30 minutes. A postintervention resident questionnaire will be sent to staff to complete with their resident if the resident has the ability to communicate their experience. Each care home will receive a participation certificate, and staff members will receive a certificate for completing the PAMI training. At the end of the study, the researcher team will meet to discuss the feedback from participants on the intervention and manual development. Once the team has decided on the required changes, the primary researcher will make revisions to the PAMI manual. The team will also discuss any changes needed to the study design for phase 2; after changes are made, the study will be resubmitted to the ethics committee for approval.

Phase 2: Manual Evaluation Study

Overview

The data collected in the manual evaluation study will aid final manual revisions and aid preparations for future studies. This phase aims to continue to review the culturally adapted manual with the intended stakeholders (care staff and residents with dementia). In addition, preliminary data will be collected on the impact of PAMI on residents and care staff. This phase will be the early stages of the feasibility and piloting stage of the MRC guidelines.

Phase 2 is a mixed methods exploratory study consisting of interviews, reflective session transcripts, diary entries, resident postintervention questionnaire, and pre-post outcome questionnaires.

Participants

The study will recruit 25 care staff and 25 residents from 5 Lincolnshire care homes. The care homes will be different from those recruited in the first phase. Each staff member will be paired with a participating resident from their care home. Care staff and residents will be required to meet the eligibility criteria. The same eligibility criteria as those used in phase 1 will be used.

Procedure

The study will run for approximately 20 weeks in each care home, with PAMI being implemented for 18 weeks. The recruitment procedure will remain the same as that in phase 1.

At the beginning of the study, staff will receive a paper copy of the PAMI manual, care staff and resident demographic questionnaires, a diary entry form, and the DSRS [57]. A dementia-friendly demographic questionnaire will also be provided to assist residents who may struggle with the demographic questionnaire. Staff will also receive the baseline questionnaires, including the Music in Dementia Assessment Scale (MIDAS) [58], Staff Competence in Dementia scale (SCIDS) [59], QUALIDEM [60], and Modified Nursing Care Assessment Scale (M-NCAS) [61]. Additionally, 8 MIDAS and 8 reflective session prompt sheets will be included in the pack, which staff will require for each reflective session. Staff will be asked to complete the questionnaires before training except for the MIDAS, which staff will be asked to bring to the training.

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Each care home will be sent a care home demographic questionnaire to complete.

The researchers will work with the care homes and staff to organize a convenient time to complete the training. At the end of the training, staff will be asked to complete the preintervention MIDAS form. The facilitators will then explain that staff should complete 1 reflective session prompt sheet each fortnight before attending the next session and bring the subsequent MIDAS to the session. After the training, staff will implement PAMI in routines for 18 weeks. Staff will be asked to complete the diary form each time they use PAMI with their resident. Once a fortnight, staff will attend a 40-minute reflective session via Microsoft Teams. The facilitators will monitor the study procedure during the session to ensure that there are no issues or distress and that both staff and residents are happy to continue. Staff will complete a total of 8 reflective sessions. During each session, the staff will be asked to complete 1 MIDAS and to use their reflective session prompt sheet to set a goal for the coming fortnight. After 18 weeks, the postintervention questionnaires, the SCIDS [59], M-NCAS [61], and QUALIDEM [60], will be sent to staff to be completed again. At the end of the study, staff will be invited to a semistructured interview to discuss their experience. The interview will be completed via Microsoft Teams and last approximately 30 minutes. A postintervention resident questionnaire will be sent to staff to complete with their resident if the resident has the ability to communicate their experience. Each care home will receive a participation certificate, and staff members will receive a certificate for completing the PAMI training.

Data Collection

Data is collected in several ways across the 2 phases. The qualitative data collection methods are the same in both phases. The preintervention and postintervention quantitative questionnaires will be collected only during the manual evaluation phase .

Demographic Questionnaires

Staff will be required to complete resident and staff demographic questionnaires. Staff should work with their resident to complete the resident version. Resident's involvement will be dependent on their impairments and communication abilities. A dementia-friendly questionnaire has been created to allow residents to have more involvement in the research without their impairments hindering participation. However, staff may need to complete the resident questionnaire. The staff questionnaire collects the following details: age, gender, nationality, length of time at the care home, length of time in dementia care, and views on music in dementia care. The residents' questionnaire collects the following details: age, gender, nationality, length of time at the care home, communication ability, and interest in music.

Participating care homes will complete a demographic questionnaire on the care home. The care home questionnaire collects the following details: care home type, resident type, number of residents in the care home, staff to resident ratio, the current availability of music and activities in the care home, and the availability of Wi-Fi and technology. The question about the availability of Wi-Fi and technology is to ensure that care homes have adequate accessibility for the staff to access the web-based training.

Staff members will complete the DSRS [57] for their residents to determine dementia severity. The DSRS is an informant-based multiple-choice assessment tool. The scale consists of 11 items covering a range of functions impacted by dementia. The areas covered in the DSRS are memory, language, recognition of family members, orientation to time, orientation to place, ability to make decisions, social and community activities, home activities and responsibilities, cleanliness, eating, control of urination and bowels, and ability to get from place to place. A score of 0 to 18 indicates normal to mild dementia, a score of 19 to 36 indicates moderate dementia, and a score of 37 to 54 indicates severe dementia. The DSRS has been calculated to have high internal consistency, high concurrent validity, and high test-retest and high interrater reliability, with carers rating similar to trained clinicians and nonmedical professionals [57]. The DSRS was selected because it is easy to use, can be completed without a researcher, and has high validity and reliability.

Diary Entries

Staff will keep a diary throughout the study to document their use of PAMI and thoughts. The primary researcher produced the diary forms. The paper and pencil method was selected over a more technology-based method to ensure that all staff could complete the diary entries during their shift, as the paper and pencil method does not rely upon regular access to a computer, a phone, or other devices. It is also suggested as one of the easiest diary methods; therefore, little instructions are required on it at the beginning of the study [62]. This study will use an event-contingent diary format where staff document every time PAMI interactions occur during the study. The use of diary entries in the PAMI studies allows the researchers to examine the regular use of PAMI in care homes. Data are collected on the time and date of interaction, interaction length time, which PAMI section the interaction corresponded to, what the interaction entailed, the resident's reaction, PAMI's impact on the interaction, and space for notes. The diary entry form has been kept simple and made such that it is quick to complete, with an entry taking participants only a few minutes, to improve the completion rate.

Reflective Sessions

Although the reflective sessions contribute to part of the PAMI training, they are also a form of data collection. The reflective sessions aim to collect qualitative data on the staff's experience implementing PAMI in care homes and the impact of PAMI on residents and staff. The reflective sessions are semistructured, with the staff's experience guiding sessions; therefore, there is no prior expectation of collecting specific information. However, in general, information on the staff's experience of using the skills, issues concerning the implementation of the intervention, the usability of the manual, and issues with specific skills and case anecdotes of specific interactions will be collected. At the beginning of each reflective session, staff will be asked for permission to audio record the session.

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Interviews

Staff will be invited to attend an interview at the end of the study to discuss their experience with PAMI. The interviews will follow a semistructured format with a topic guide, but interviewers will ask additional questions based on participants' responses. Either BW or BS will facilitate the interviews via Microsoft Teams. At the beginning, participants will be asked to provide permission to audio record the interview. Staff will be reminded to use participants' identity codes when discussing specific residents. However, any information identifying the care home, staff, or residents will be removed and anonymized at the transcribing level. Although face-to-face interviews are considered the gold standard of interview data collection methods [58], all interviews will be completed remotely owing to the uncertainty of COVID-19 restrictions when designing the study. Using a videoconference call to conduct the interviews was selected, as this allows for the closest simulation of an in-person interview [63]. It has also been suggested that when in-person interviews are unavailable, video interviews can create a closer bond between the interviewer and interviewee [63].

Quantitative Outcome Measures

A modified version of the MIDAS [58] was selected to measure residents' music engagement. Typically, the measure is proxy reported, completed by care staff and the music therapist before the beginning of music therapy and then again after the music therapy session to examine the change observed during the session. In the PAMI study, the MIDAS is still proxy reported. However, it will be completed only by care staff at 9 time points at fortnightly intervals, first in training and then at each reflective session. The measure uses a Visual Analogue Scale (VAS) without anchor points, with each VAS consisting of a 100-mm line. Staff will be asked to rate the individual based on their current stage of life; therefore, "highest" means the optimal level that the individual can achieve at that stage of their life. Each VAS has a maximum score of 100, and the MIDAS has an overall maximum score of 500. The MIDAS form consists of 5 VAS on interest, response, imitation, involvement, and enjoyment; a checklist question on major reactions; and any comments or questions. This measure was selected for the PAMI study, as it collects observational data on music engagement using proxy reporting methods, making it suitable for participants with moderate to advanced dementia. Studies investigating the psychometric properties of the MIDAS reported high internal consistency between the 5 VAS items, acceptable test-retest reliability, acceptable concurrent validity, and high construct validity.

The QUALIDEM [60] was selected to measure residents' quality of life. The QUALIDEM is a dementia-specific proxy rating scale for measuring the quality of life. The scale has been designed to be suitable for use in care homes. The QUALIDEM is completed before and after intervention, with 18 weeks between the 2 points. It is a 37-item multidimensional scale that consists of 9 homogeneous subscales. Each question has a 4-point scoring system ranging from 0 to 3. The scores on the subscales are calculated by adding up the item scores. The higher the score, the better the quality of life that the individual is expected to have for that quality of life domain. The QULIDEM was selected because it measures the emotional and social domains and investigates the care relationship and coping with the nursing home environment, a domain not investigated in other scales. The QUALIDEM has been reported to have moderate interrater reliability; moderate internal structure; and high convergent, discriminate, and concurrent validity [60].

The SCIDS [59] was selected to measure care staff's competence before and after PAMI. The scale can investigate the effects of training on staff and how these relate to care behavior and the residents' quality of life. The SCIDS is a professional caregiver's self-report measure comprising 17 items categorized into 4 subscales: professionalism, sustaining personhood, building relationships, and care challenges. Each question has a 4-point answer scale ranging from 1 to 4. Overall scores range from 17 to 68, with a higher score indicating a higher level of sense of competence. The SCIDS has been reported to have good internal consistency and substantial to moderate test-retest reliability.

The M-NCAS [61] was selected to measure staff burden before and after PAMI. The M-NCAS not only measures behavior but also addresses other aspects of nursing, including staff's perception of the meaningfulness of residents' lives and residents' gratefulness for care. The M-NCAS is a self-reporting staff measure consisting of 32 items. Each item has 2 domains: one explores the occurrence and intensity of the behavior, whereas the other explores the staff's rating of the difficulty of coping with the behavior. Each domain is scored on a 4-point scale. A lower score on both domains indicates a lower score of staff burden. The M-NCAS has been reported to have excellent to good internal consistency and reliability and moderate construct validity.

Analysis

Demographic Statistics

Data collected from the resident, staff, and care home demographic questionnaires and residents' DSRS scores will be entered into SPSS Statistics (IBM Corp). The mean and SD will be created for the demographic data.

Quantitative Outcome Measures

The data collected from the MIDAS, SCIDS, QUALIDEM, and M-NCAS will be imported into IBM SPSS Statistics. Two-tailed *t* tests will be conducted from the questionnaire data to determine a change before and after PAMI.

Qualitative Data

Transcribing

Before analyzing the reflective sessions and interviews, audio recordings will be transcribed. The University of Nottingham Automatic Transcribing Service will be used for the first transcribing stage. The service is secure, meets General Data Protection Regulation guidelines, and has an accuracy rate of 70% to 99% [64]. For recordings to be transcribed using the service, they needed to be in the format Mono MP3. The software Audacity (The Audacity Team) will be used to convert the recordings into the appropriate format [65]. Two reviewers will independently review the transcripts to determine accuracy.

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During transcribing, the names and personal information identifying the residents, staff, or care homes will be removed.

Thematic Analysis

NVivo (QSR International) will be used to analyze the transcripts [66]. Due to its flexibility, the researchers will use thematic analysis to analyze the qualitative data. Thematic analysis entails identifying, analyzing, and reporting themes within the chosen set of data [67]. A theoretical approach will be taken, where themes will be generated based on the research aims and questions set at the beginning of the study. Braun and Clark's [67] 6 steps for thematic analysis will be followed.

Braun and Clark's [67] 6 steps are as follows: familiarizing yourself with the data, generating initial codes, searching for themes, reviewing themes, defining and naming themes, and producing the report.

The 2 PAMI facilitators who conduct the interviews will also transcribe and conduct the thematic analysis, allowing the researchers to immerse themselves in the data from the beginning. The reviewers will independently generate codes before they are combined and analyzed for inter-reviewer reliability. The 2 reviewers will discuss the generated codes and resolve discrepancies. The reviewers will then independently cluster relatable codes to generate themes before they work together through discussions to develop one set of themes representing the data. Once the 2 reviewers agree, the set of themes will be shared with the research team for feedback.

The qualitative and quantitative data will not be combined in the analysis. The quantitative data are for exploring preliminary statistical findings and testing the appropriateness of the outcome measures for future studies, whereas the qualitative data are for exploring the participants' experience of using PAMI and reviewing the culturally adapted appropriateness of the manual.

Results

This project was funded by The Music Therapy Charity in October 2019 as part of a PhD studentship. The study's first phase began recruitment in September 2021 and continued until January 2022. A total of 8 care staff and 8 residents were recruited, with 5 dyads completing the study. The data have been analyzed that will be used in the primary researcher's thesis (Waters, B, Orrell, M, and McDermott, O, unpublished data, March 2023) and several papers in peer-reviewed journals. The research team aims to publish the results from the first phase in July to September 2023.

The second phase began recruitment in April 2022 and continued until December 2022. Overall, 20 care staff and 19 residents were recruited with 11 dyads completing the study. The researchers are currently in the stage of analyzing the data that will be used in the primary researcher's thesis (Waters, B, Orrell, M, and McDermott, O, unpublished data, March 2023) and published in peer-reviewed journals. The research team aims to publish the results from the second phase in October to December 2023.

Dissemination will also occur through conferences. Participating care homes will receive a summary of the results. A summary will be provided to the Lincolnshire NHS trust, which they can use to disseminate the results.

Discussion

Anticipated Findings

This study will be the first to investigate the modified PAMI-M. Therefore, the data collected in phases 1 and 2 will provide feedback on the appropriateness of the modified manual for care staff working in UK care homes. The data collected will aid final manual revisions. Due to COVID-19, the intervention was converted from an in-person training tool to an intervention delivered remotely. Therefore, this study will provide a greater understanding of the plausibility of providing PAMI remotely. The study investigates the implementation of PAMI in a real-life setting, highlighting potential barriers and allowing the researchers to adapt the intervention to accommodate.

Previous research has highlighted that implementing meaningful interactions and staff-led music interventions in care homes are challenging because of limited staff time, limited resources, and the lack of knowledge [68,69]. Music therapy skill-sharing can provide staff with music therapy skills to implement in routines without them having to spend additional time or bear additional burden [46,70]. Implementing music interventions in other care tasks can improve task efficiency and reduce staff time. Music therapy skill-sharing is only accessible to a few care homes owing to music therapists' availability and finances. A music therapy skills-sharing manual such as PAMI will make the intervention accessible to a larger population of care homes. Implementing PAMI in care homes in Denmark has begun and is displaying positive results [48]. This study will investigate whether the modified version of PAMI can benefit residents, care staff, and care homes in the United Kingdom.

Strength and Limitations

The main strength is the remote element. The remote-based conversion of PAMI has allowed the researchers to continue developing the intervention during the pandemic when there were uncertain COVID-19 regulations. Even as the regulations are dropped, care homes are still battling with care home lockdowns when outbreaks occur; and remote training will allow staff to continue training during these periods. Thinking long term, converting PAMI to remote training would make the intervention more accessible to a wider population of care homes, as the facilitators would not be limited by geographic distance or location. Although the remote element of PAMI is its main strength, it is also the main limitation. All study elements will occur via email and Microsoft Teams; therefore, data collection and implementation will rely on self-report. It will be challenging for the researchers to determine whether staff are using PAMI and are successfully implementing the skills.

Conclusions

The study will be the first to investigate the modified PAMI. The study will provide feedback on the appropriateness of the manual and explore participants' experience of using a modified

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version of PAMI. PAMI has the potential to offer music therapy skill-sharing training to a larger proportion of care homes, ensuring that high-quality appropriate music interventions are provided to residents in care homes where music therapy may be inaccessible. The intervention aims to promote 2-way attuned musical interactions between staff and residents with dementia through musical skills and nonverbal communication and has the potential to benefit residents, staff, and the overall care home.

Acknowledgments

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Data Availability

Data sharing is not applicable to this study as no data sets were generated or analyzed during the study.

Authors' Contributions

BW is an early career researcher under the supervision of OM and MO, who are both senior researchers. BW, OM, and MO are responsible for designing the study. BW took the lead in developing the study materials and intervention with support from OM. BW is responsible for promoting the study, recruiting the participants, running the intervention, and collecting data. OM and MO will provide guidance and support throughout the study.

Conflicts of Interest

None declared.

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Abbreviations

DSRS: Dementia Severity Rating Scale
ENRICH: Enabling Research in Care Homes
MIDAS: Music in Dementia Assessment Scale
M-NCAS: Modified Nursing Care Assessment Scale
MRC: Medical Research Council
MTC: music therapeutic care
NHS: National Health Service
NIHR: National Institute for Health Research
PAMI: Person Attuned Musical Interactions
PAMI-M: Person Attuned Musical Interactions–Modified
SCIDS: Staff Competence in Dementia scale
VAS: Visual Analogue Scale

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Protocol

Investigating the Comparative Effectiveness of Place-Based and Scatter-Site Permanent Supportive Housing for People Experiencing Homelessness During the COVID-19 Pandemic: Protocols for a Mixed Methods, Prospective Longitudinal Study

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Abstract

Background: Permanent supportive housing (PSH) is an evidence-based practice to address homelessness that is implemented using 2 distinct approaches. The first approach is place-based PSH (PB-PSH), or single-site housing placement, in which an entire building with on-site services is designated for people experiencing homelessness. The second approach is scatter-site PSH (SS-PSH), which uses apartments rented from a private landlord while providing mobile case management services.

Objective: This paper describes the protocols for a mixed methods comparative effectiveness study of 2 distinct approaches to implementing PSH and the patient-centered quality of life, health care use, and health behaviors that reduce COVID-19 risk.

Methods: People experiencing homelessness who are placed in either PB-PSH or SS-PSH completed 6 monthly surveys after move-in using smartphones provided by the study team. A subsample of participants completed 3 qualitative interviews at baseline, 3 months, and 6 months that included photo elicitation interviewing. Two stakeholder advisory groups, including one featuring people with lived experience of homelessness, helped guide study decisions and interpretations of findings.

Results: Study recruitment was supposed to occur over 6 months starting in January 2021 but was extended due to delays in recruitment. These delays included COVID-19 delays (eg, recruitment sites shut down due to outbreaks and study team members testing positive) and delays that may have been indirectly related to the COVID-19 pandemic, including high staff turnover or recruitment sites having competing priorities. In end-July 2022, in total, 641 people experiencing homelessness had been referred

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from 26 partnering recruitment sites, and 563 people experiencing homelessness had enrolled in the study and completed a baseline demographic survey. Of the 563 participants in the study, 452 had recently moved into the housing when they enrolled, with 272 placed in PB-PSH and 180 placed in SS-PSH. Another 111 participants were approved but are still waiting for housing placement. To date, 49 participants have been lost to follow-up, and 12% of phones (70 of the initial 563 distributed) were reported lost by participants.

Conclusions: Recruitment during the pandemic, while successful, was challenging given that in-person contact was not permitted at times either by program sites or the research institutions during COVID-19 surges and high community transmission, which particularly affected homelessness programs in Los Angeles County. To overcome recruitment challenges, flexible strategies were used, which included extending the recruitment period and the distribution of cell phones with paid data plans. Given current recruitment numbers and retention rates that are over 90%, the study will be able to address a gap in the literature by considering the comparative effectiveness of PB-PSH versus SS-PSH on patient-centered quality of life, health care use, and health behaviors that reduce COVID-19 risk, which can influence future public health approaches to homelessness and infectious diseases.

Trial Registration: ClinicalTrials.gov NCT04769349; https://clinicaltrials.gov/ct2/show/NCT04769349

International Registered Report Identifier (IRRID): DERR1-10.2196/46782

(JMIR Res Protoc 2023;12:e46782) doi:10.2196/46782

KEYWORDS

homelessness; housing first; permanent supportive housing; COVID-19; homeless; housing; health outcome; patient-centered; person-centered; photo-elicitation

Introduction

The COVID-19 pandemic has made housing and health care for people experiencing homelessness an important priority for the health care and public health systems in the United States. Due to this population's preexisting vulnerabilities [1-3] and difficulties in maintaining social distance and hygiene, researchers predicted at the outset of the COVID-19 pandemic that, without intervention, people experiencing homelessness would experience a 2-4 times higher risk of COVID-19 complications and fatality than the general population [4]. As a result of these concerns, more than US $2 billion from the US federal government's Coronavirus Aid, Relief, and Economic Security Act was aimed at protecting people experiencing homelessness by reducing shelter densities and placing people in more secure housing options.

Permanent supportive housing (PSH)—programs that provide immediate access to independent living situations coupled with support services—represent one of the most studied and effective approaches for serving highly vulnerable people experiencing homelessness [5]. Numerous studies have demonstrated PSH's effectiveness in improving housing retention, quality of life, and HIV outcomes. Nevertheless, a 2018 report by the National Academy of Medicine of the National Academies of Sciences noted the need for more research on PSH to establish what would constitute "housing-sensitive [health] conditions"—conditions whose transmissibility, course, and medical management are particularly influenced by homelessness and housing placement [5]. Two years after this report, COVID-19 and rapid policy decisions to address homelessness and expand housing during the pandemic offered a rare opportunity to address this gap in knowledge and advance research on housing as a social determinant of health.

This paper describes the protocols for the Person-Centered Housing Options, Outcomes, Services, and Environment (PCHOOSE) study, which examined the comparative effectiveness of 2 distinct approaches to implementing PSH. The first approach is place-based PSH (PB-PSH), or single-site housing placement, in which an entire building with on-site services is designated for people experiencing homelessness. The second approach is scatter-site PSH (SS-PSH), which uses apartments rented from a private landlord while providing mobile case management services. The limited research related to the comparative effectiveness of PB-PSH versus SS-PSH has been mixed. A meta-analysis of 8 studies with more than 3000 participants found 84% of people experiencing homelessness with mental disorders preferred SS-PSH [6], despite greater feelings of social isolation than those in PB-PSH. This is supported by qualitative research that has found people experiencing homelessness dislike the rules and limited privacy of PB-PSH [6-8]. Other studies have suggested PB-PSH may provide more supportive services [9] and may be more effective than SS-PSH in improving disability severity, community integration, and recovery [10]. Individuals with substance use disorders, those living with HIV, veterans, and women may also benefit more from PB-PSH programs than other populations because of the strong sense of community and mutual support they offer [11]. The PCHOOSE study intended to add to this literature by considering the comparative effectiveness of PB-PSH versus SS-PSH on patient-centered quality of life, health care use, and health behaviors that reduce COVID-19 risk.

Methods

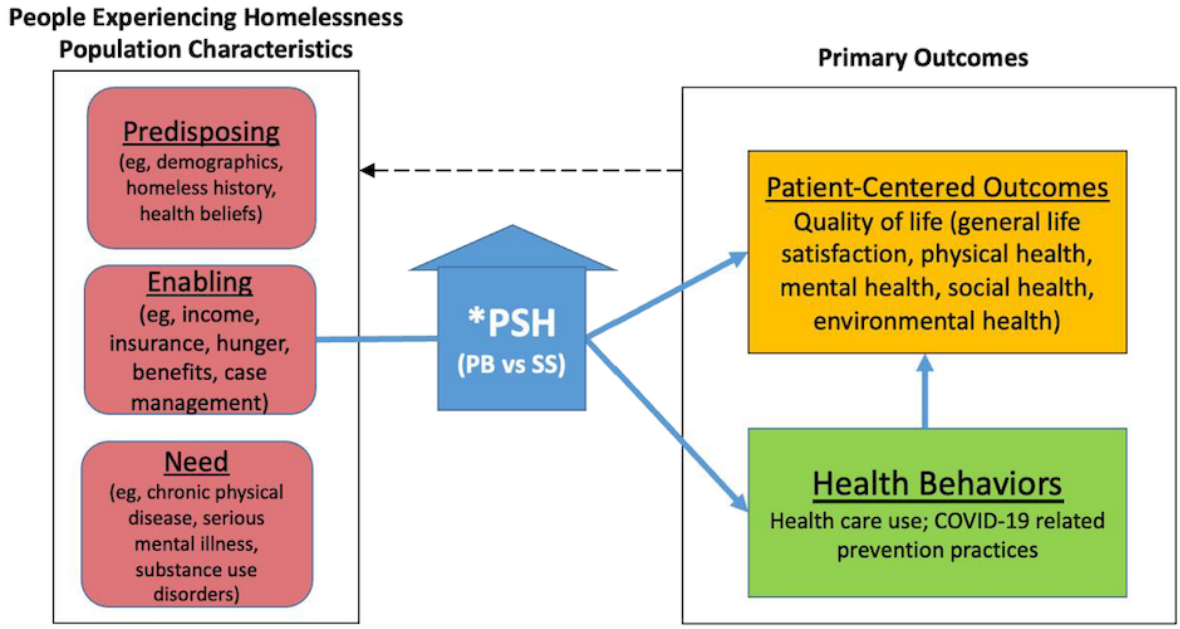
Setting and Conceptual Model

The PCHOOSE study is situated in Los Angeles County, California, which has the nation's largest unsheltered homeless population [12]. Los Angeles County also represents the country's largest natural experiment in housing interventions to protect people experiencing homelessness [13] due to a major taxpayer-funded US $1.2 billion homelessness initiative passed

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in 2016 that resulted in the opening of thousands of new PSH units in Los Angeles County during the pandemic [14]. The study followed a diverse sample of people experiencing homelessness placed in either PB-PSH or SS-PSH for 6 months; barriers and facilitators that may affect PSH implementation during the pandemic and its aftermath were also investigated. The study was guided by the Gelberg-Anderson behavioral model for vulnerable populations [15], which involves examining predisposing, enabling, and need factors that contribute to health behaviors and patient-centered outcomes (see Figure 1). PSH is positioned as a key enabling factor for people experiencing homelessness with the hypothesis that PSH type (ie, PB or SS) will affect THE quality of life (general life satisfaction; physical, mental, social, and environmental health, including housing and neighborhood characteristics) and health behaviors, including health care use (eg, receipt of health care, mental health care, and social supports) and COVID-19–related prevention practices. We also expected that changes to our primary outcomes would affect the predisposing, enabling, and need characteristics of the people experiencing homelessness population over time.

Figure 1. Gelberg-Anderson behavioral model for vulnerable populations (modified for PSH and COVID-19). PB: place-based; PSH: permanent supportive housing; SS: scatter-site.



In describing the protocols of the PCHOOSE study, this paper also highlights the challenges of conducting research with this vulnerable population in the United States during the highly dynamic COVID-19 pandemic. This includes steps taken to protect the research team, people experiencing homelessness participants, and PSH staff members, as well as the need to change survey instruments to reflect an evolving understanding of the COVID-19 virus, public health mitigation policies, and personal protective practices.

Design Overview

This study leveraged Los Angeles County's ongoing efforts to provide PSH to people experiencing homelessness during the COVID-19 pandemic using a mixed methods, prospective longitudinal design. We recruited people moving into PSH and provided them with smartphones with paid data plans to stay connected with the study for a 6-month period. All study participants were recruited through organizations that provide housing, supportive services, or both. Although PB-PSH is clearly defined in the homelessness services system, SS-PSH could have been officially categorized as a PSH program or a rapid rehousing program. Although rapid rehousing programs are typically short-term housing programs with time-limited and tailored assistance programs, during the pandemic, Los Angeles County expanded the use of rapid rehousing programs coupled with supportive services to quickly provide access to housing. Thus, for this study, we considered anyone receiving rapid rehousing assistance to be SS-PSH if they also received support services, and examined whether those receiving rapid rehousing differ in terms of demographics, health status, or homelessness histories.

For the study's quantitative arm, participants completed a baseline survey followed by 5 monthly follow-up surveys once in housing. For the qualitative arm, we recruited a purposive subsample of people experiencing homelessness from both PB-PSH and SS-PSH who participated in 3 semistructured interviews; the first was an in-depth interview when they initially moved into PSH, followed by 2 follow-up interviews conducted 3 and 6 months later. Focus groups with housing providers from the affiliated housing agencies were also conducted. Study protocols for each study component are described separately in more detail.

To ensure that the study addressed questions important to people experiencing homelessness, providers, and policy makers and that the data were correctly interpreted, we also established 2

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stakeholder advisory boards (SABs). The first advisory board is a lived experience group (LEG), which consists of 11 individuals who have personally experienced homelessness. The LEG meets quarterly and uses its lived experience, knowledge of what is important to people experiencing homelessness, and perspectives on how people experiencing homelessness may respond to study questions to inform recruitment strategies, interpretation of study findings, and dissemination efforts. The study's second advisory board is a SAB, which consists of 15 providers, administrators, policy makers, and researchers with expertise in homelessness and housing programs in Los Angeles County. Due to concerns about meeting in person during the pandemic, all LEG and SAB meetings have been conducted remotely via Zoom.

Ethics Approval

This human subjects' research has been performed in accordance with the Declaration of Helsinki and approved by the University of Southern California's Institutional Review Board (UP-20-01081) with a reliance agreement in place with the University of California, Los Angeles. All human subject participants provided informed consent via electronic signature. As described in more detail below, participants could receive up to US $105 in gift cards for participating in the quantitative survey component of the study and US $150 in gift cards for participating in the qualitative component of the study.

Recruitment of Study Participants

People experiencing homelessness were eligible to participate in the study if they were 18 years or older, had been approved for PSH, could be interviewed in English or Spanish, and were willing to provide informed consent. Enrollment included people experiencing homelessness who had been approved for PSH in Los Angeles County and had either been housed in the past 2 weeks or were expected to be placed in housing in 30 days. PSH placement is determined through a county-run coordinated entry system that identifies clients' needs and matches them with available housing options. Because the system typically assigns individuals approved for PSH to specific nonprofit, community-based agencies that are ultimately charged with securing housing and supportive services, recruitment was conducted through 26 agencies. The study began recruitment in January 2021 amid a significant surge in the COVID-19 pandemic in Los Angeles County. Therefore, in-person recruitment was not a viable option and instead depended on the case managers at each program, who were already interacting with people experiencing homelessness as part of the housing placement process. The study team relied on these agencies to inform anyone approved for PSH (or rapid rehousing who would be receiving supportive services) about the study. Study staff members then coordinated a meeting with the eligible people experiencing homelessness interested in the study via phone or Zoom to complete the enrollment process. Although this process remained largely intact throughout the recruitment period, in-person recruitment occasionally occurred when COVID-19 rates were low and visitors were allowed at program sites.

Recruitment for the qualitative portion of the study involved 2 sources. The qualitative people experiencing homelessness sample was selected from those who enrolled in the quantitative portion of the study. A subsample of study participants (N=40; 20 from each PSH model type) was selected for interviews using maximum variation sampling [16] based on demographic and health characteristics (ie, Black or African American people, women, individuals with chronic disease, individuals with serious mental illness, individuals with substance use disorders or individuals aged 60 years or older), and they separately consented to participate in qualitative interviews. The provider sample (N=48; 24 from each PSH model type) was selected from housing providers who worked at agencies that were study recruitment sites. Sites were asked to identify staff members who would be willing to participate in a focus group; staff members were asked to provide verbal consent at the outset of the focus group.

Enrollment and Quantitative Data Collection Procedures

To enroll, an agency staff member initiated the referral process for people experiencing homelessness by contacting the research recruitment team via phone, email, or text. A research recruitment team member then followed up to schedule an appointment with the potential participant to complete a screening to ensure eligibility, review the consent form, and answer any questions related to the study protocols. Case managers then distributed study phones that had been shipped to the recruitment site. Participants received a Samsung A01 Core smartphone with an unlimited data and calling plan, which allowed them to provide electronic informed consent and complete a self-administered questionnaire sent via text message. Participants were enrolled in the study once they provided informed consent by completing a web-based form that assessed study comprehension and documented their electronic signature.

Initially, participants completed a 20-minute survey upon enrollment in the study to capture basic demographic and historical information about their housing and health. Baseline outcome measures were then administered in a follow-up survey approximately 1 day later to help reduce the burden involved in completing a lengthy questionnaire at the time of enrollment. Participants received a US $15 electronic gift card incentive for completing the baseline outcome measure survey. Participants who enrolled in the study prior to moving into a housing unit were asked to complete a second baseline outcome measures survey once they moved in and received another US $15 electronic gift card incentive. After moving into PSH and completing the demographic and baseline surveys, participants received 5 monthly follow-up surveys and received a US $15 electronic gift card incentive for each completed survey. Participants could also complete surveys over the phone if they preferred to speak with a surveyor rather than self-administer the survey. Electronic gift cards were sent to an email address provided by the participant. The survey links were all sent via text message. The study team, in consultation with the LEG, opted to allow "prefer not to answer" as a response option for all historical and monthly survey questions to reduce any frustration among those who were not sure how to answer and minimize the possibility that some questions could be triggering given high rates of past trauma.

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Quantitative Measures

Patient-centered quality-of-life outcomes in this study were based on the World Health Organization's definition of health as "a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity" [17]. Table 1 describes the study's constructs and measures, with the exception of COVID-19–related outcomes, which are discussed in more detail subsequently.

Table 1. Study constructs and measures.

Construct	Variables and instruments
Patients experiencing homelessness population characteristics: covariates measured at baseline only [18]	
Predisposing	Demographics (ie, age, gender, marital status, and veteran status); health beliefs (ie, knowledge of disease and health services attitudes); social structure (ie, race and ethnicity, education, employment, religion, trauma, and homelessness history); systems involvement history (eg, foster care, criminal justice, and trauma); housing preference
Enabling	Income, insurance, benefits, case management, food insecurity, and social support
Need	Chronic physical disease, serious mental illness, and substance use disorder; baseline measures for physical and mental health status as noted in outcomes
Patient-centered outcomes: quality of life including physical, mental, social, and environment health, and measured monthly	
Life satisfaction	NIH[a] Toolbox Item Bank v2.0 General Life Satisfaction (10 items, self-rated life satisfaction) [19]
Physical health	PROMIS[b] Global Health Scale Version 1.2 (PROMIS; 2 items, self-rated physical health and activities) [19]
Mental health	PROMIS (2 items, self-rated mental health, frequency bothered by symptoms) [19]
Social health	PROMIS (1 item, self-rated satisfaction with social activities and relationships) [19]
Environmental health	Housing retention and Housing Environment Scale (4 items, residential satisfaction; 12 items, neighborhood quality and safety) [20]
Health behaviors: measured monthly	
Substance use	Collaborating Consortium of Cohorts Producing NIDA[c] Opportunities survey (12 items) [21]
Health care use	COVID-19– and non-COVID-19–related past-180-day use of physical, mental, substance use, social services, and PSH[d] support; medication adherence; ambulatory and emergency department visits and hospitalizations; barriers to care

[a]NIH: National Institutes of Health.

[b]PROMIS: Patient-Reported Outcomes Measurement Information System.

[c]NIDA: National Institute on Drug Abuse.

[d]PSH: permanent supportive housing.

COVID-19–Related Outcomes

Given that the study project period began in October 2020, with initial recruitment starting in January 2021, our initial survey questions focused on COVID-19–related protective health behaviors that were salient at the time—namely, social distancing and handwashing. As science and the pandemic evolved, questions about COVID-19 testing and vaccines were introduced as key protective health behaviors. For COVID-19 testing on the monthly surveys, we first asked whether participants had been tested in the past 30 days and, if so, the outcome of the test. For anyone who had not been tested in the past 30 days, we asked about barriers to testing (ie, "Did you want to get tested for coronavirus [COVID-19] in the past 30 days but were unable to?"). For those who replied affirmatively, possible reasons for not getting tested included: I didn't know how to make an appointment to be tested; I didn't know where to go; I don't think that I can afford the cost of the test; I didn't have time to get tested; I am unable to travel to a testing location; I am worried about bad things happening to me or my family if I get tested (including discrimination, government policies, or social stigma).

For vaccination status, questions evolved over time. When the study began and there was only 1 approved vaccine that was not readily available, participants were asked if they "have been offered the COVID-19 vaccine?" with branch logic based on whether they said they had received the vaccine or would receive it if offered. If participants responded "no" to having received the vaccine after being offered it or to a hypothetical offer, they were prompted about the reasons for not receiving the vaccine to better understand their hesitancy. Six months into data collection, when multiple approved vaccines were more readily available, the survey was revised to first ask if a participant had received the vaccine rather than if it had been offered. Questions about the type of vaccine (brand) and the number of doses received were also added to the monthly surveys. In June 2022, the survey was revised a final time to ask new questions about receipt of COVID-19 booster vaccines using the following three uniform questions: (1) "How many doses of the COVID-19 vaccine have you received (including booster shots)? Please indicate the brand of each dose you received and the month and date when you received it"; (2) "To the best of your knowledge, have you received all COVID-19 doses or boosters that you're eligible for?"; and (3) "In the future, how likely are you to receive another dose or booster of the COVID-19 vaccine if it's

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recommended?" Participants who had already completed the study and not been asked these questions were recontacted.

Qualitative Interview Procedures

Each member of the qualitative people experiencing homelessness sample was asked to complete 3 semistructured qualitative interviews. The first interview, conducted over the telephone and audio recorded, focused on questions concerning participants' (1) prehousing homelessness experiences; (2) experience obtaining PSH; (3) health, social services, and social experiences prior to and after obtaining PSH; and (4) management of COVID-19–related safety and concerns. These interviews lasted approximately 30-60 minutes each. The second and third interviews were conducted 3 and 6 months after the baseline interviews and used photo elicitation interviewing (PEI), a method that uses photographs taken by participants to guide interviews [22]. This method enhances the depth of each interview and increases the capacity to identify potential topics of interest that were not part of the study's original data collection plan. PEI is also an effective tool for building rapport, gaining access to participants' lived experiences, and relieving the strain of direct, extended verbal questioning, which can be particularly taxing for participants with cognitive or mental disabilities [23-25]. All client PEI interviews were conducted over the phone and lasted approximately 45 minutes. Each interview was recorded and transcribed for analysis, and participants received a US $50 gift card incentive of their choice (Visa, Amazon, or Target) after each interview.

PEI Methods

Participants were asked to use their study-issued cellphones to take photos that represent their daily lives and experiences in their housing placement for a 2-week period. There was no limit on the number of photos they could take, though they were asked to avoid taking any identifiable photos of any individuals to protect privacy. Participants were then asked to choose 5-10 of the photos that best captured their recent experiences and email or text them to the study coordinator, who then provided them to the interviewer. At the outset of each interview, interviewers asked participants to choose whichever photo they wanted to discuss first. For this photo and subsequent images, participants were asked first to describe each photo and then elaborate on how it reflects their recent experiences related to housing, health, service use, COVID-19 protection, safety, resources, relationships, personal growth, and daily functioning. Participants were also asked to come up with a title or theme that collectively described the photos they discussed, if there was anything they wanted to take a photo of but could or could not, and why, and any recommendations for improvements in services for others experiencing homelessness based on the photos. If any participant did not feel comfortable using the phone camera, they were offered the alternative of taking "mental snapshots," in which they made a list of 5-10 things they wished to discuss and shared this list with their interviewer. For the second PEI at the 6-month follow-up, participants were asked to go through the same procedures. However, during this PEI, participants were asked to focus on how things changed for them across the different domains and compare their photos from the 2 PEIs.

Focus Groups

Provider group interviews concentrated on learning provider perspectives on the difference between PB-PSH and SS-PSH, the strengths and weaknesses of each model in improving outcomes for people experiencing homelessness, and the impacts of the COVID-19 pandemic on PSH service delivery. Each focus group met for approximately 60 minutes and was conducted either in person or via Zoom, depending on the housing agency's preference. As with the client interviews, staff focus groups were recorded and transcribed for analysis, and participants received a US $50 gift card incentive of their choice (Visa, Amazon, or Target).

Quantitative Analysis

The statistical analysis will rely on bivariate and multivariate regression analysis to examine the relationship between PSH (SS-PSH vs PB-PSH) and quality of life and COVID-19–related health behaviors. For outcomes, we will use a pre-post design that treats Month 1 as the baseline and Month 6 as the endline and compares pre-post changes for SS-PSH and PB-PSH. For outcomes sensitive to monthly trajectory variation, we will use fixed-effects and random-effects models of monthly outcomes that test for interaction between the PSH model and months of exposure to each PSH type. These models will be informed by an analysis of baseline variation between SS-PSH and PB-PSH clients. We expect variations in the level of baseline morbidity. Thus, we will use both multivariate models that account for baseline differences and propensity score matching models that establish an area of common support for SS-PSH and PB-PSH comparisons. We will use calendar-month controls to account for historic changes in the ecology of health behavior, particularly in relation to rising and falling rates of COVID-19. We will also address the potential need for multilevel or mixed-effects models to account for potentially shared experiences by housing and service providers. Additional models will test for differences in housing outcomes by race, ethnicity, sex, and gender via interaction effects and stratified models. Further analysis will entail the use of a path modeling framework to understand the pathways leading from PSH types to outcomes of interest. Due to the decision to include "prefer not to answer" as an option for all questions, all analyses will account for the frequent use of this response option. In cases where "prefer not to answer" is a common or meaningful response option, such as regarding partisan political affiliation or experiences of trauma, we will include it as a response option. In cases where "prefer not to answer" appears to reflect a random nonresponse pattern, we will treat the value as missing, use multiple imputations to maintain sample size, and conduct robustness checks comparing the imputed and raw samples.

Qualitative Data Analysis and Integration

Client semistructured interview and focus group transcripts have been imported into Dedoose [26] for analysis. Analysis was conducted using template analysis, with thematic codes defined in relation to the study questions (eg, housing process and experiences, COVID-19 experiences, and posthousing experiences), and inductively through coding the transcripts [27]. Individual team members cocoded the transcripts and discussed the codes iteratively, including collapsing, expanding,

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and combining codes, until consensus was reached on the codebook. Any discrepancies in codes and excerpts were discussed in team meetings and resolved in discussion with the qualitative team leaders [27]. After initial cocoding, team members coded the remainder of the transcripts using Dedoose.

PEIs will be analyzed using 2 approaches—one for the interview text and one for the photographs. Interview text will be analyzed using template analysis as previously described. Photographs are analyzed through a process of initial categorization by theme, referencing interview texts to ensure proper interpretation, and group discussion to develop an initial visual code book. Members of the team will cocode photos from 5 interviews to test the codebook's utility and identify codes that needed further definition or clarity. Once the codebook is established, each photo will be coded independently by 2 researchers, who discussed discrepancies until they reached a consensus on all interpretations of images [22].

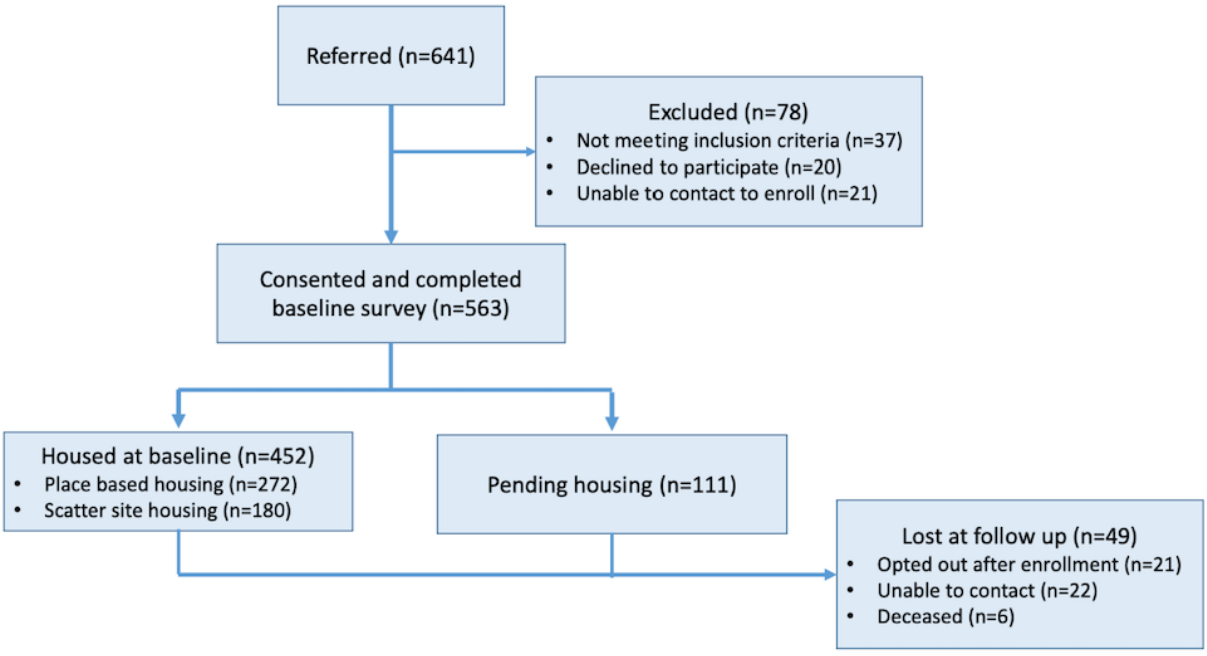
Mixed Methods Analysis

As appropriate, qualitative and quantitative data will be merged to achieve several functions. First, merged data will be used to identify convergences—areas where qualitative data confirm quantitative findings, and vice versa. Second, the research team will use qualitative data complementarily to provide depth and understanding to the findings that emerge from quantitative analyses. Third, qualitative data will be used to explain and expand on findings from quantitative data. The researchers will note areas where one data source generates insights but the other does not [28].

Results

Study recruitment was supposed to occur over 6 months starting in January 2021 but was extended due to delays in recruitment. These delays included COVID-19 delays (eg, recruitment sites shut down due to outbreaks and study team members testing positive) and delays that may have been indirectly related to the COVID-19 pandemic, including high staff turnover or recruitment sites having competing priorities. Given these delays, data collection and analysis are expected to be completed in 2023. As depicted in the consort diagram (see Figure 2), at the end of recruitment in July 2022, a total of 641 people experiencing homelessness had been referred from 26 partnering recruitment sites, and 563 people experiencing homelessness had enrolled in the study and completed a baseline demographic survey. Of the 641 referrals, 37 were not eligible to participate due to not meeting the criteria, 20 declined to participate, and our recruitment team could not reach 21 to complete enrollment. Of the 563 participants in the study, 452 had recently moved into the housing when they enrolled, with 272 placed in PB-PSH and 180 placed in SS-PSH. Another 111 participants were approved but are still waiting for housing placement. To date, 49 participants have been lost at follow-up, with 21 opting out of the study, 22 who could not be reached, and 6 participants who died.

Figure 2. Consort enrollment diagram. PSH: permanent supportive housing.



To date, 12% of phones (70 of the initial 563 distributed) have been reported lost by participants. Of those who reported losing their phone, we lost contact with 22 participants; 28 completed the study using a replacement phone provided by the study or an alternative phone number. Redemption of electronic gift card incentives has been high. To protect respondent privacy, gift card redemption data was not linked to respondents at the personal level, but we analyzed aggregate and monthly redemption rates for all completed surveys. Among all gift cards issued, 82% were redeemed. This figure likely reflects an underestimate of overall redemption rates because the denominator double-counts individuals who were reissued a second card after failing to redeem the first. Redemption rates improved during the study, from 75% in month 1 to 86% in

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month 5. Because redemption data were not linked at the person level, it was impossible to discern whether redemption affected retention or response rates.

Discussion

Principal Findings

This paper presents the protocols from the PCHOOSE study, a mixed methods prospective longitudinal study designed to examine the comparative effectiveness of PB-PSH and SS-PSH in promoting COVID-19 protective behaviors among people experiencing homelessness. To date, the study has successfully recruited 563 participants in the study, with 452 of those participants moving into housing (272 placed in PB-PSH and 180 in SS-PSH). Another 111 participants are still waiting for housing placement. As noted, however, recruitment during the pandemic was challenging given that in-person contact was not permitted at times either by program sites or the research institutions during COVID-19 surges and high community transmission, which particularly affected homelessness programs in Los Angeles County.

To overcome recruitment challenges, flexible strategies were used that included extending the recruitment period and the distribution of cell phones with paid data plans. Although this was a viable approach to recruitment and data collection, thus far, 12% of phones have been lost. It is not clear to what extent study recruitment rates would have been different without distributing phones given the high rates of phone ownership in this population, although maintaining consistent phone service is challenging [29]. Given current recruitment numbers and retention rates that are over 90% (only 49 have been lost to follow-up), the study will be able to address a gap in the literature by considering the comparative effectiveness of PB-PSH versus SS-PSH on patient-centered quality of life, health care use, and health behaviors that reduce COVID-19 risk.

Limitations

This study is unique in that it represents a large-scale study that started in the first year of the COVID-19 pandemic to better understand how housing programs serve as a social determinant of health for people experiencing homelessness [5]. Given this context, the study required ongoing changes to the survey instrument due to COVID-19–related outcomes, vaccine implementation, and community mitigation strategies that continued to change throughout the study period. Changing study instruments will pose challenges for analysis and also highlight the need to consider how period effects may drive changes in participant response as opposed to the time in housing that was originally planned. Other potential challenges may include discrepancies between qualitative and quantitative reporting, data richness due to qualitative phone interviews instead of in-person interviews, missing or inaccurate vaccine data, and participants failing to report on health risk behaviors such as drug use, receiving the vaccination, or other risky behaviors due to stigma. These issues will be examined and reported on after the study. We also note that this study represents a natural experiment and that people experiencing homelessness were not randomized to PSH type; further, participants were referred to the study through a case manager, which may introduce additional selection bias. Examining baseline characteristics will help determine whether there are selection differences between the 2 groups that will need to be adjusted during analyses.

Conclusions

The PCHOOSE study protocols demonstrate that recruitment of people experiencing homelessness is possible during a global pandemic but that significant flexibility is required to conduct research with an underresourced population during major historical events, such as the COVID-19 pandemic, which reflects a period where scientific knowledge and public policies evolved rapidly. At a minimum, information gained from this project can provide insights into how people experiencing homelessness navigated the pandemic, but we may also better understand the contextual factors that contribute to COVID-19 being a housing-sensitive condition. Given that few studies have compared PB-PSH and SS-PSH, let alone amid a global health concern such as COVID-19, this study will be able to address a gap in the literature regarding how different models of PSH can affect the patient-centered quality of life, health care use, and health behaviors that reduce COVID-19 risk, which can influence future public health approaches to homelessness and infectious diseases.

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Data Availability

All data from this research will be made available in a public data repository (TBD), as is contractually required by the funding organization.

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Authors' Contributions

BFH, RK, HP, and LG initially designed the study that secured funding. BFH, RK, HP, RI-M, GC, AL, JC, BTS, KDV, TH, MP, and WA all contributed to data collection and study implementation. BFH, HP, RI-M, GC, AL, and BTS initially drafted the manuscript, which all authors critically reviewed and revised. BFH and GC had full access to all recruitment data in the study and take responsibility for the integrity of the data and the accuracy of the data presentation.

Conflicts of Interest

None declared.

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Abbreviations

LEG: lived experience group
PB-PSH: place-based permanent supportive housing
PCHOOSE: Person-Centered Housing Options, Outcomes, Services, and Environment
PEI: photo elicitation interviewing
PSH: permanent supportive housing
SAB: stakeholder advisory board
SS-PSH: scatter-site permanent supportive housing

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Protocol

Impact of California's Senate Bill 27 on Antimicrobial-Resistant Escherichia coli Urinary Tract Infection in Humans: Protocol for a Study of Methods and Baseline Data

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Abstract

Background: Overuse of antibiotics contributes to antimicrobial resistance (AMR) and is a growing threat to human health worldwide. Previous work suggests a link between antimicrobial use in poultry and human AMR extraintestinal pathogenic *Escherichia coli* (E coli) urinary tract infections (UTIs). However, few US-based studies exist, and none have comprehensively assessed both foodborne and environmental pathways using advanced molecular and spatial epidemiologic methods in a quasi-experimental design. Recently, California enacted Senate Bill 27 (SB27), which changed previous policy to require a veterinarian's prescription for the use of antibiotic drugs, and which banned antibiotic use for disease prevention in livestock. This provided an opportunity to evaluate whether SB27 will result in a reduction in antimicrobial-resistant infections in humans.

Objective: We describe in detail the methods implemented to achieve the overarching objective of this study to evaluate the impact of SB27 on downstream antibiotic resistance rates in human UTIs.

Methods: A summary of the overall approach and the partnerships between Columbia University, George Washington University (GWU), Johns Hopkins Bloomberg School of Public Health, Kaiser Permanente Southern California (KPSC) Research and Evaluation, the Natural Resources Defense Council, Sanger Institute at Stanford University, Sutter Health Center for Health Systems Research, the University of Cambridge, and the University of Oxford is presented. The collection, quality control testing, and shipment of retail meat and clinical samples are described. Retail meat (chicken, beef, turkey, and pork) was purchased from stores throughout Southern California from 2017 to 2021. After processing at KPSC, it was shipped to GWU for testing. From 2016 to 2021, after clinical specimens were processed for routine clinical purposes and immediately before discarding, those with isolated colonies of *E coli*, *Campylobacter*, and *Salmonella* from KPSC members were collected and processed to be shipped for testing at GWU. Detailed methods of the isolation and testing as well as the whole-genome sequencing of the meat and clinical samples at GWU are described. KPSC electronic health record data were used to track UTI cases and AMR patterns among the

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cultured specimens. Similarly, Sutter Health electronic health record data were used to track UTI cases in its Northern California patient population.

Results: From 2017 to 2021, overall, 12,616 retail meat samples were purchased from 472 unique stores across Southern California. In addition, 31,643 positive clinical cultures were collected from KPSC members during the same study period.

Conclusions: Here, we presented data collection methods for the study, which was conducted to evaluate the impact of SB27 on downstream antibiotic resistance rates in human UTI. To date, it is one of the largest studies of its kind to be conducted. The data collected during this study will be used as the foundation for future analyses specific to the various objectives of this large body of work.

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KEYWORDS

AMR; antimicrobial resistance; E coli; Escherichia coli; urinary tract infection; UTI

Introduction

Worldwide, antibiotics are used to prevent and treat bacterial infections in both humans and animals. However, routine and inappropriate uses of antibiotics have contributed to antimicrobial resistance (AMR), which is a major challenge to human health worldwide [1]. In the United States, industrial food animal production drives antibiotic consumption through both therapeutic and prevention uses in animals [2]. The majority of medically important antibiotics are sold for use in livestock, with tetracyclines accounting for 66% of these antibiotics [3,4]. This livestock use may result in antimicrobial-resistant infections in humans. Prior work [5,6] has suggested a link between antibiotic use in poultry and antimicrobial-resistant extraintestinal pathogenic *Escherichia coli (E coli)* urinary tract infections (UTIs) in humans [7-11]. This suggests the potential for use of antibiotics in food-producing animals to be important to address to help curb AMR.

California has a large livestock industry and is one of the leading US producers of beef cattle, broiler chickens, and turkey [12,13]. It is also the most populous US state, with a human population larger than the Netherlands, Denmark, and Sweden combined (countries that lead the European Union science and policy on AMR in livestock [14,15]). In an effort to reduce AMR and related human infections, on January 1, 2018, California enacted Senate Bill 27 (SB27), which changed previous policy to require a veterinarian's prescription for the use of antibiotic drugs, and banned antibiotic uses for disease prevention in livestock [16]. A similar policy was enacted in the European Union in 2006, which led to reductions in antibiotic use and AMR [14,17-20]. SB27 was the first such legislation in the United States and provided a natural experiment with which to investigate whether a ban on antimicrobials used for disease prevention in livestock was associated with a decrease in antimicrobial-resistant *E coli* in retail meat and among UTI cases in humans.

Here, we describe the methods of a study that was a collaborative effort among Columbia University, George Washington University (GWU), Johns Hopkins Bloomberg School of Public Health (JHU), Kaiser Permanente Southern California (KPSC) Research and Evaluation, the Natural Resources Defense Council, Sanger Institute at Stanford University, Sutter Health Center for Health Systems Research, University of Cambridge, and the University of Oxford. Specifically, we describe the methods used to investigate whether the passage and implementation of SB27 were associated with a decrease in AMR among retail meat products in California and among *E coli* UTI at KPSC and Sutter. We simultaneously collected chicken, beef, turkey, and pork retail meat samples from across Southern California and clinical isolates from KPSC between 2017 and 2021. We also leveraged KPSC electronic health record (EHR) data to track UTI cases and AMR patterns among the cultured specimens. Similarly, Sutter Health EHR data were used to track UTI cases in its Northern California patient population. Whole-genome sequencing (WGS) was also performed by GWU on confirmed *E coli*, *Salmonella*, and *Campylobacter* isolates from retail meat and clinical samples.

Taken together, the aims of the study were to characterize and compare AMR phenotypes, genes, and *E coli* populations isolated from retail chicken and human clinical samples; to quantify changes in AMR phenotypes, genes, and *E coli* populations from retail chicken and human clinical samples before and after SB27 implementation; and to define the spatial relationship between livestock operations and patients with an antimicrobial-resistant *E coli* UTI. Under SB27, California was the first US state to ban nontherapeutic uses of antibiotics in livestock. At the time of this writing, this was the first population-based study in the United States to rigorously measure the association between AMR profiles of *E coli* isolated from chicken retail meat and human clinical samples during the implementation of a statewide policy meant to reduce antibiotic use. This descriptive assessment builds on a small number of early publications [16,21-24] to provide a common foundation for future analyses specific to the various objectives of this large body of work.

Methods

Partnerships and Summary of Approach

Meat and Human Clinical AMR Data

A prospective study design was used over the study period (2016-2021) to collect information on AMR in retail meat and human infections. Retail meat was purchased in Southern

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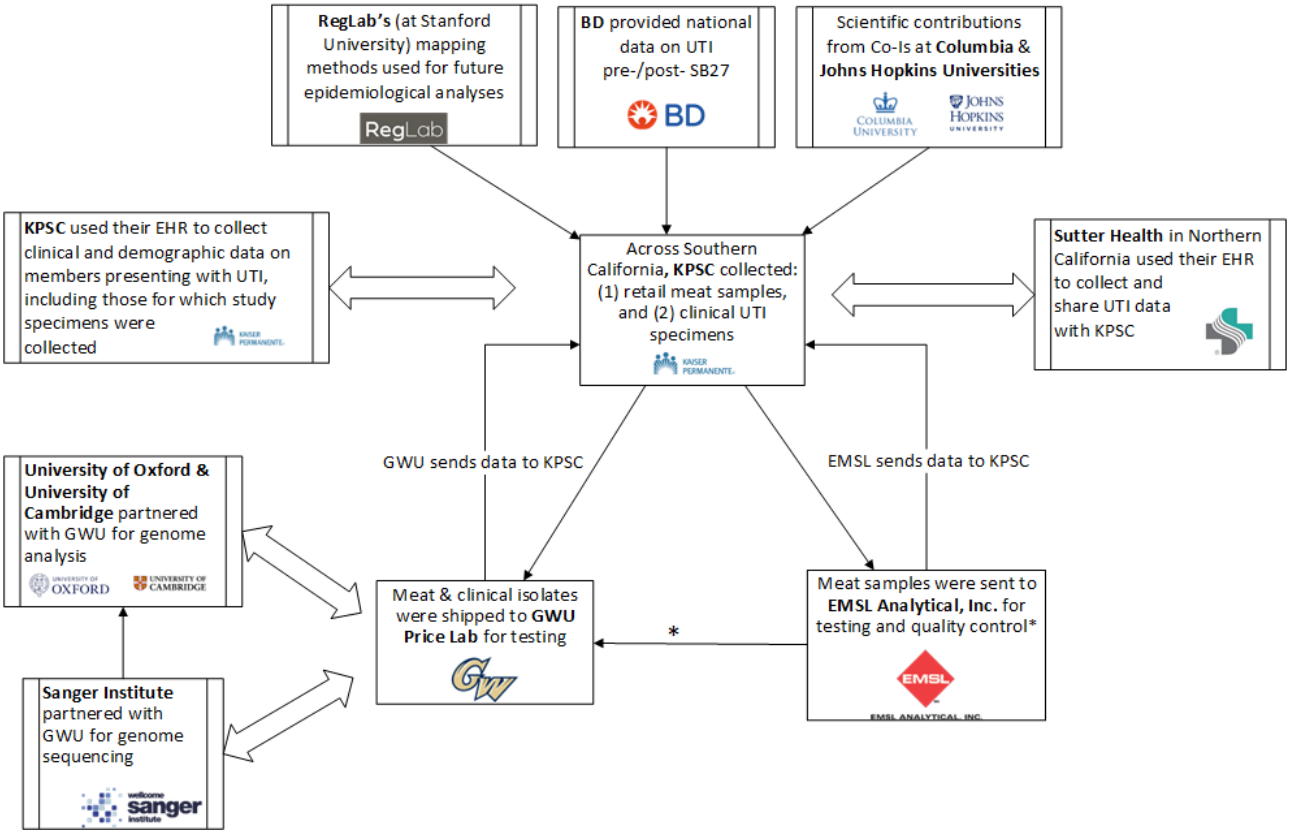
California and human infection data came from KPSC in Southern California and Sutter Health in Northern California. Each week, retail meat (chicken, turkey, beef, and pork) was purchased from stores across Southern California. Clinical and demographic data for members presenting with a UTI were extracted from the KPSC EHR along with ancillary information on *E coli* isolated from urine specimens. Study data were also obtained for KPSC members with *Salmonella* and *Campylobacter* isolated from stool samples. Each week all isolated *Salmonella* and *Campylobacter* and a subset of the isolated *E coli*, based on convenience sampling (samples processed across multiple shifts from Bacteriology), were collected from KPSC laboratories for additional analysis. Similarly, in Northern California, Sutter Health's EHR data were used to extract clinical and demographic data for patients who presented with a UTI; however, no clinical samples were collected from Sutter Health. The purchased meat and the subset of clinical isolates from KPSC were shipped to GWU (Price Laboratory). GWU isolated bacteria from the meat and conducted antimicrobial susceptibility testing of *E coli*, *Salmonella*, and *Campylobacter* from meat (Table S2 in Multimedia Appendix 1). Additionally, human isolates from KPSC were sent to GWU for further susceptibility testing to augment EHR resistance profiles with microbials that were not tested by the KPSC clinical laboratory.

Additional Partnerships

The study involved several additional key partnerships to conduct laboratory analyses, supply supplemental clinical data, identify livestock operation locations, and describe SB27 implementation. The Sanger Institute, the University of Oxford, and the University of Cambridge partnered with GWU on the WGS data management, genome assembly, quality control analysis, and sequence type assignment of select samples. The RegLab at Stanford University [25] developed a methodology to map animal production sites using satellite imagery and will be utilized in future spatial epidemiologic analyses to assess whether proximity to animal production sites increases the risk for AMR UTI; Beckton, Dickinson, and Company provided national data on UTI for a manuscript on UTI pre- and post-SB27; and KPSC used a local laboratory in Pasadena (EMSL Analytical, Inc [EMSL]) for quality control of meat testing. Finally, JHU partnered with the study team to (1) conduct parallel analyses of microbial recovery and AMR from the National AMR Monitoring System within and beyond California [26], and (2) undertake a qualitative study of food-animal producers and related agricultural stakeholders within and beyond California to describe attitudes, knowledge, beliefs, and practices around antimicrobial uses in food animal production, including in the context of SB27 [21].

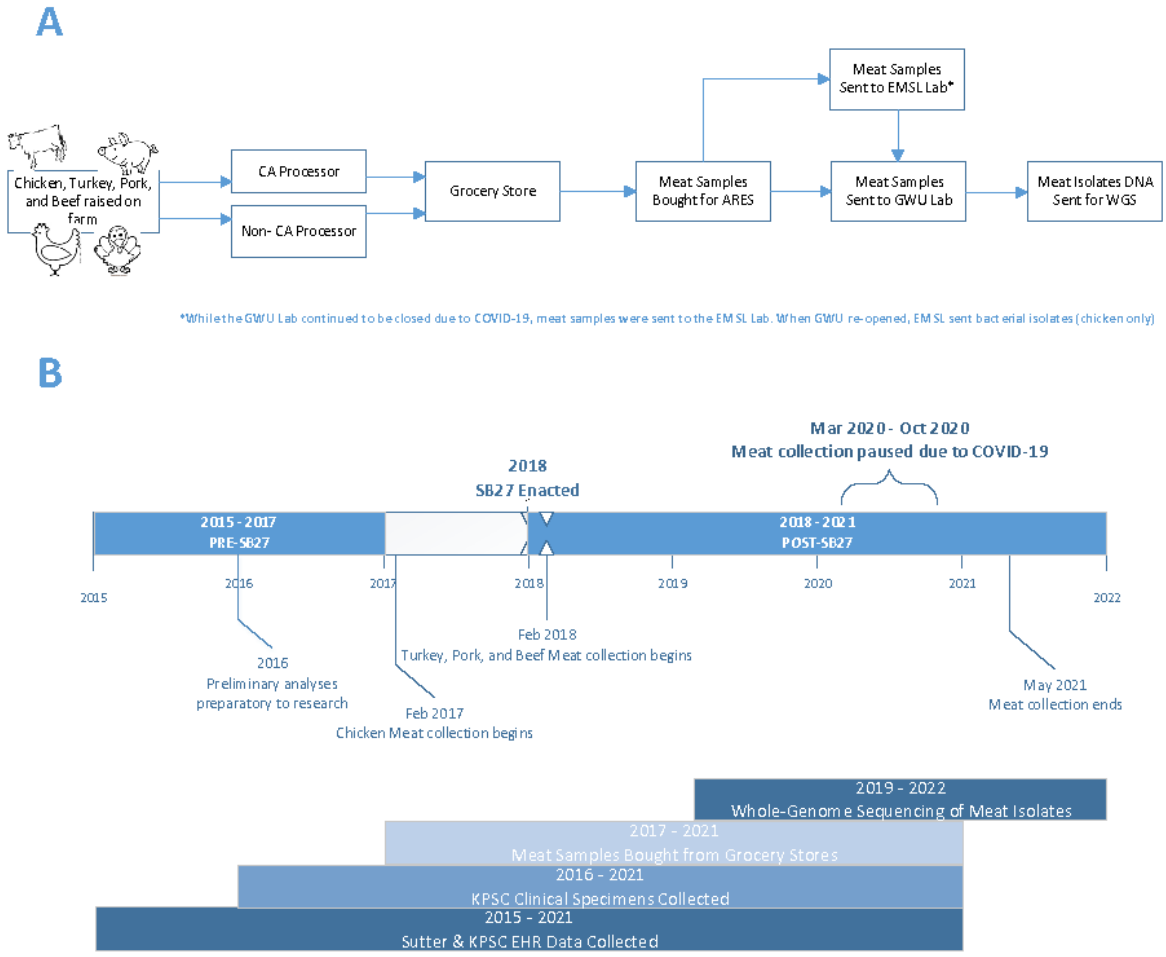
The partnerships are summarized in Figure 1. Timelines for EHR data, meat collection, and clinical sample collection activities are summarized in Figure 2.

Figure 1. Study partnerships flowchart. Meat collection paused due to the pandemic. Once we resumed meat collection during lockdown, samples were sent to EMSL only as GWU was closed. Once GWU re-opened, meat isolates were shipped from EMSL to GWU. BD: Beckton, Dickinson, and Company; EHR: electronic health record; GWU: George Washington University; KPSC: Kaiser Permanente Southern California; SB27: Senate Bill 27; UTI: urinary tract infection.



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Figure 2. Summarized study activities and timelines. (A) Flowchart of meat samples from farm to sequencing. (B) Timelines for all study components. ARES: Antimicrobial resistant Escherichia coli before and after California Senate Bill 27; CA: California; EHR: electronic health record; EMSL: EMSL Analytical, Inc.; GWU: George Washington University; KPSC: Kaiser Permanente Southern California; SB27: Senate Bill 27; WGS: whole-genome sequencing.



Retail Meat Samples

Collection and Shipment

Meat sample collection occurred from 2017 to 2021 (Figure 2B) in regions where KPSC facilities were located (from Bakersfield to San Diego). To ensure that the retail meat-sampling approach maximized the diversity of geography and meat processor facilities, from March through July 2017, we performed several inventory surveys of hundreds of stores to collect data on availability and attributes (eg, regulated label claims like United States Department of Agriculture [USDA]–certified organic or raised without antibiotics [if neither, then classified as "no restrictions"], and if processed in California or non-California) of meat. Research associates (RAs) surveyed stores across Southern California (Los Angeles, Inland Empire, and San Diego areas), taking photos of retail meat package labels and gathering all USDA Establishment (meat processor) code. Establishment codes are used to identify the facility in which the retail meats are processed [27]. These codes include p-codes used for poultry (chicken and turkey) and m-codes used for pork and beef. Surveys were repeated yearly to ensure ongoing representation of USDA establishment codes available for purchase in the retail establishments in our target region. The survey data informed the development of weekly shopping routes for retail meat collection, each of which included a list of designated stores and meat types to purchase. There were 53 different routes, each with assigned stores. The Los Angeles region was divided into 8 sections with 42 routes, the Inland Empire region had 6 routes, and the San Diego region had 5 routes. A Google Maps (Multimedia Appendix 2) account was used to document and save the routes.

The RAs followed prespecified criteria for retail meat purchasing. They were instructed to purchase smaller packages, valued under US $10 and weighing less than 2 lbs, when possible. Larger packages were permitted when no smaller packages existed for the brand or establishment code combination of interest. Only raw meat that had not undergone any secondary processing was purchased. Expiration or sell-by dates were to be at least 3 days after the date of purchase and the longest expiration period was to be purchased when possible. The RAs traveled with labels, cooler, ice packs, temperature gauge, assigned shopping list, Ziploc bags, paper towels, gloves, and insulated shopping bags. They also used a prepaid debit card to monitor the study budget.

After meat was purchased, a study ID was assigned. The shopping date was written on the ID label and placed close to the printed price label. Two pictures of the meat with the label (one of the whole package and the other, a close-up of the

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establishment code and label) were taken. A third photo was taken if the establishment code was not easily visible in the close-up photo. Sealed retail meat packages were then placed into a Ziploc bag with a paper towel. Retail meat packages were transported to the KPSC research facility, the same day of purchase, in a cooler, equipped with a thermometer, where the meat was kept cool, but never frozen; temperature logs were also kept.

Following transport to the research facility, retail meat packages were placed in a study refrigerator. Photos were uploaded by the RA into the secure study folder and saved per instructions in the standard operating procedures (SOPs). All meat-related data and photos were also entered into the study tracking database; a list of the variables in the tracking database is provided in Multimedia Appendix 3. This database was only accessible to approved study staff and saved in a secure KPSC network study folder. Tracking ensured the correct amounts of retail meat were purchased, shipments were sent on time every Tuesday to be received by GWU no later than Friday, and for other general tracking needs. The study tracking database was created using Microsoft Access and maintained by a data manager. The data manager was also responsible for all troubleshooting and for updating the database as needed. The database stored data on meat samples, tracked clinical samples, and shipping data.

Each meat sample was individually placed in a second Ziploc bag with a paper towel to prevent any leaks or cross-contamination. The paper towel was placed on the backside of the meat package to maintain the visibility of the ID labels. The individually packaged, double-bagged samples were placed into a study cooler. Ice packs wrapped in insulation were placed on the bottom of the cooler, followed by a double layer of meat samples. This was repeated until the cooler was full (approximately 3-4 rows of meat samples per cooler), and ice packs were added as the top layer. The temperature was monitored in all the study coolers.

Each cooler had a “Research Purposes Only” label attached on the outside, and a KPSC business card on the inside. The cooler was securely sealed before shipment through FedEx overnight “First Priority” to the GWU laboratory. If a FedEx pick-up could not be scheduled from the KPSC research facility, the designated RA would drop off the shipment at the nearest FedEx location. All shipment related details were tracked in the study tracking database.

During meat purchasing, transferring, and shipping, Occupational Safety and Health Administration (OSHA) standards and guidelines were followed by all study staff. All RAs were cross-trained in meat collection, tracking, safety, and shipping. RA meetings were used to help address or resolve study issues or concerns. Participants in these meetings included the study team, project coordinator or project manager (PM), and GWU (as needed).

Quality Control Testing

KPSC used EMSL, a laboratory located in Pasadena, which performs bacterial testing of meat, for quality control of the study retail meat samples. Each week, approximately 5-10 samples were randomly provided to EMSL for quality control. EMSL used their own SOPs adapted to align with SOPs developed by GWU.

The COVID-19 Pandemic

In March 2020, the study was paused through the middle of October 2020 due to the COVID-19 pandemic as staff was required to work from home. After the study resumed, EMSL became the primary laboratory as the GWU laboratory continued to be closed to in-person work. During April-May 2021, the GWU laboratory resumed on-site work and all retail meat isolates, including any samples tested by EMSL during the closure were sent to GWU for processing and testing.

Clinical Samples

Collection and Shipment

After clinical specimens were processed for routine clinical purposes and immediately before discarding, clinical specimens in the form of agar plates with isolation colonies of *E coli*, *Campylobacter,* and *Salmonella* from KPSC members were collected from Regional KPSC labs on a weekly basis from 2016 to 2021.

Under aseptic conditions, *E coli* was isolated by KPSC study laboratory technicians from 100 mm Blood Agar- Trypticase soy agar II MacConkey/ChomAGAR Biplates into Biobank tubes (Microbank tubes with beads, Pro-Lab Diagnostics) under a vented CLASS II hood. *Campylobacter* was isolated from *Campylobacter* blood agar plates and placed into Biobank tubes. *Salmonella* was isolated from Trypticase soy agar slants and placed into Biobank tubes. All Biobank tubes were labeled with custom −80 °C-resistant study labels and were stored frozen at −80 °C before shipping. All samples were maintained in the freezer and temperature logs were checked weekly to ensure no temperature deviations occurred. Samples were shipped through FedEx Priority Overnight First Delivery to GWU for testing. Before shipping samples to GWU, a GPS temperature monitoring probe was used to confirm the temperatures were acceptable for transport. In addition, through our study database, we were able to accurately track all samples and their location.

All clinical sample data were tracked in the study database that also maintained the retail meat sample data. Laboratory RAs entered the patient medical record number, sample type, accession number, study ID, and other variables outlined in Multimedia Appendix 4. Study IDs were used to maintain the privacy and security of the protected health information of the patient and their sample. This database was also used to generate on-demand reports of the number of samples collected and the demographic characteristics of the patients from whom the clinical samples were collected.

Testing of Meat and Clinical Samples at GWU

Isolation and Testing

To isolate bacterial species of interest from meat, 200±25 g of each retail meat specimen was aseptically transferred to a stomacher bag and 250±25 g of the appropriate enrichment broth was added. The bags were placed on a stomacher rack, briefly agitated on a benchtop shaker, then placed in an

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incubator. Species-specific selective and screening media were inoculated from the enrichment broth cultures, and several rounds of single-colony isolation were performed to obtain pure isolates of *E coli*, *Salmonella*, and *Campylobacter*. The species of each isolate was confirmed by quantitative polymerase chain reaction. *E coli* was isolated from all 4 meat types; *Salmonella* was isolated from chicken, turkey, and pork; and *Campylobacter* was isolated from chicken. Species-specific enrichment and isolation methods for each bacterial species are further detailed in Multimedia Appendix 1.

The "Antibiotic Susceptibility Testing" section in Multimedia Appendix 1 describes both types of tests conducted at GWU (Kirby-Bauer and Minimum Inhibitory Concentration [MIC]) to test *E coli*, *Salmonella* spp, and *Campylobacter* spp isolates for susceptibility to a panel of antibiotics. The Kirby-Bauer disc test was conducted on all meat isolates, as well as for the subset of human clinical isolates. MIC tests were conducted on a subset of both meat and human clinical isolates to augment K-B disc testing. Specifically, MIC testing by the broth microdilution method was conducted for antibiotics to which >5% of *E coli* or *Salmonella* isolates from any source were resistant.

Most of the susceptibility data for *E coli* from clinical isolates came from testing conducted as part of routine clinical microbiology protocols at KPSC; MIC data were obtained with the Beckton, Dickinson, and Company Phoenix method. During GWU's COVID-19 closure, when EMSL conducted testing of some meat samples, similar procedures and protocols were followed.

Preparation of Samples for WGS and Sequencing Procedures

DNA for genomic analysis was extracted from a subsample of the confirmed meat and clinical sample-derived *E coli*, *Salmonella* spp, and *Campylobacter* spp isolates using the PureLink Pro 96 Genomic DNA Purification Kit (Invitrogen). WGS was performed on the NovaSeq platform with a read length of 150 bp. Assemblies for downstream analyses were generated from raw sequencing data, and quality control of the sequencing run was performed by checking the quality of the trimmed sequencing reads. Multilocus sequence typing was performed for *E coli* using the Achtman scheme [28,29] and population structure was inferred using fastbaps. A midpoint-rooted species tree was built under a GTR+GAMMA substitution model. Additional detail on methods for WGS data processing and analysis is available in Multimedia Appendix 1.

EHR Data

KPSC and Sutter Health integrated health care systems have wide coverage areas, high completeness of data, racial, ethnic, and socioeconomic diversity among their members or patients, longitudinal health care usage information, and research infrastructure [30,31]. Both systems use Epic for their EHR data, allowing the synthesis of information across the 2 systems. Data were aggregated across both networks to identify UTI cases presenting for clinical care across California populations, thereby increasing the representation and generalizability of the results.

KPSC provides comprehensive care to more than 4.7 million members across 15 medical centers and 235 medical offices in Southern California. KPSC uses KP HealthConnect (an Epic system) as its EHR to capture all aspects of members' clinical care, encounters and communications, and administrative and demographic data. HealthConnect links all patient care information including primary and specialist care, outpatient surgery, laboratory services, radiology, pharmacy, patient-level demographic, and membership data and billing. The system links facilities across the region and provides members, physicians, and other authorized health care providers with online access to clinical information.

In Northern California, Sutter Health, a not-for-profit organization, provides care to more than 3 million patients across 22 counties, including rural, urban, and suburban communities. Like KPSC, Sutter Health uses a comprehensive Epic EHR system allowing researchers to access detailed clinical data, including physician orders and free text clinical notes, as well as the standard ambulatory, hospital, laboratory, and pharmacy data.

Researchers from KPSC and Sutter Health partnered to develop reproducible programing code to construct standardized data sets from the EHR representing episodes of UTI from 2015 to 2022. This collaboration included monthly meetings to discuss data extractions, share code, and monitor data quality. Early publications on trends in UTI and risk factors for UTI, including low socioeconomic status and ambient temperature, have been conducted on these data sets [22-24].

All analyses were conducted using SAS Enterprise Guide 8.2 (SAS Institute) at KPSC, and R at Sutter Health.

Training

All study staff were trained on study procedures by the PM. The PM had OSHA certification and trained staff on how to safely handle meat samples during the collection and shipment. SOPs were drafted to ensure consistency and accuracy in specimen collection, and a Project Management Plan was developed to ensure that all study milestones were met on time.

Ethics Approval

No patient recruitment or patient contact occurred as part of this study, and all study data will be limited [32]. Both health systems use an opt-out research participation system where members or patients can opt out of their health data being used for research. If they do not opt out, their data become available for research following institutional review board (IRB) approval and Health Insurance Portability and Accountability Act (HIPAA) compliance.

The study was approved by the Kaiser Permanente Southern California (KPSC) IRB (IRB #11284); GWU and JHU ceded review to the KPSC IRB. A waiver for the use of protected health information and of informed consent was approved for this study by the KPSC IRB. The study was also approved by the Sutter Health IRB (IRBNet #1063246) with a waiver of HIPAA authorization and informed consent. No IRB was required from the remaining collaborating sites as no data were collected at those sites.

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Results

Retail Meat Samples

Overall, retail meat samples were purchased from 472 unique stores. Between 2017 and 2021, chicken retail meat samples were purchased from 285 unique stores (Table 1). Starting in 2018, the study initiated the purchase of retail turkey, pork, and beef meat samples from 266, 267, and 253 stores, respectively (Table 1). Multimedia Appendix 2 shows the map of the stores throughout the Southern California region.

A total of 12,616 retail meat samples were collected from the 472 stores from 2017 to 2021 (Table 2). Of these, 6084 were chicken, 2701 were turkey, 2486 were beef, and 1345 were pork.

Table 1. Unique stores visited for retail chicken, turkey, pork, and beef meat purchases (2017-2021).

	Total number of unique stores visited, n					Total[a]
	2017	2018	2019	2020	2021	
Chicken	96	244	256	135	75	285
Turkey	N/A[b]	244	240	121	53	266
Pork	N/A	245	249	121	50	267
Beef	N/A	216	233	118	45	253

[a]Total of unique stores visited.

[b]N/A: not applicable.

Table 2. Meat samples (chicken, turkey, pork, and beef) collected (2017-2021; N=12,616).

Type of meat	Meat samples, n[a] (%)[b]					
	2017	2018	2019	2020	2021	Total
Chicken	1180 (19)	1964 (32)	2212 (36)	420 (7)	308 (5)	6084
Turkey	N/A[c]	979 (36)	1324 (49)	279 (10)	119 (4)	2701
Pork	N/A	442 (33)	719 (53)	133 (10)	51 (4)	1345
Beef	N/A	896 (36)	1259 (51)	233 (9)	98 (4)	2486

[a]n: sample size.

[b]Row percentages.

[c]N/A: not applicable.

Table 3 further details the retail chicken, turkey, pork, and beef samples collected from 2017 to 2021 by the state of processing (California and non-California) and by regulated label (USDA-certified organic, raised without antibiotics, and no restrictions). Among the retail chicken, pork, and beef samples bought, more came from a California processor than a non-California one. For the chicken, 1529 USDA-certified organic samples were identified. For the beef, 605 samples were identified as organic. Furthermore, for the pork, none of the samples were organic. Conversely, for turkey, non-California samples were more prevalent, with 441 being organic.

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Table 3. Meat samples (chicken, turkey, pork, and beef) collected by year, state of processing, and regulated label (2017-2021). All meat isolates were purchased in California.

	Meat samples, n[a]								
	Total[b]			Processed in California[b,c]			Processed outside of California[b,c]		
	Organic	RWA[d]	No restrictions	Organic	RWA[d]	No restrictions	Organic	RWA[d]	No restrictions
Chicken									
Total[e]	1529	3959	2041	1208	3113	1660	316	822	292
2017	247	584	530	209	490	468	37	91	45
2018	483	1319	639	381	1015	497	101	297	107
2019	599	1519	684	467	1188	541	129	319	115
2020	117	303	115	87	232	93	30	71	17
2021	83	234	73	64	188	61	19	44	8
Turkey									
Total[f]	441	927	1771	383	529	531	58	396	1238
2018	133	340	638	131	203	182	2	136	455
2019	235	452	871	197	252	263	38	199	607
2020	48	92	187	40	54	64	8	38	123
2021	25	43	75	15	20	22	10	23	53
Pork									
Total[g]	0	129	1216	0	106	366	0	8	142
2018	0	36	406	0	30	132	0	4	51
2019	0	68	651	0	56	184	0	4	75
2020	0	17	116	0	15	33	0	0	11
2021	0	8	43	0	5	17	0	0	5
Beef									
Total[h]	605	1236	1228	418	776	807	186	452	391
2018	200	433	456	124	249	264	75	177	170
2019	326	626	619	229	404	434	97	222	177
2020	54	119	113	43	80	80	11	39	33
2021	25	58	40	22	43	29	3	14	11

[a]n: sample size.

[b]Categories “Organic,” “RWA,” and “No Restrictions” are not mutually exclusive.

[c]Establishment codes were used to assign California versus non-California processing location; samples missing these codes were thus not assigned to either group.

[d]RWA: raised without antibiotics.

[e]Total: n=6084, processed in California: n=4847, and processed outside of California: n=1124 (for the latter 2, missing establishment codes (n): Chicken: 113).

[f]Total: n=2701, processed in California: n=1062, and processed outside of California: n=1635 (for the latter 2, missing establishment codes (n): Turkey: 4).

[g]Total: n=1345, processed in California: n=472, and processed outside of California: n=150 (for the latter 2, missing establishment codes (n): Pork: 723).

[h]Total: n=2486, processed in California: n=1589, and processed outside of California: n=859 (for the latter 2, missing establishment codes (n): Beef: 38).

Clinical Samples

A total of 31,643 positive clinical cultures were collected from KPSC members from 2017 through 2021 (Table 4). Of these, 28,647 tested positive for *E coli*, 1681 for *Campylobacter*, and 1315 for *Salmonella*.

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Overall, the mean age of KPSC members with a positive clinical specimen was 49.3 (SD 23.1) years (Table 5). This group was also primarily female (85.7%, 27,104/31,643) and Hispanic (44.1%, 13,945/31,643).

Table 4. Clinical specimens of Kaiser Permanente Southern California (KPSC) members collected (2017-2021; N=31,643).

Bacterium type	Clinical specimens, n[a] (%)[b]					
	2017	2018	2019	2020	2021	Total
Escherichia coli	4351 (15)	8285 (29)	8492 (30)	6269 (22)	1250 (4)	28,647
Campylobacter	254 (15)	479 (28)	623 (37)	271 (16)	54 (3)	1681
Salmonella	214 (16)	417 (32)	392 (30)	236 (18)	56 (4)	1315

[a]n: sample size.

[b]Row percentages.

Table 5. Demographic characteristics of Kaiser Permanente Southern California (KPSC) members with positive clinical specimens (2017-2021).

	Escherichia coli (N=28,647)	*Campylobacter* (N=1681)	*Salmonella* (N=1315)	Total (N=31,643)
Age (years), mean (SD)	50.9 (22.5)	36.4 (22.1)	31 (24.9)	49.3 (23.1)
Sex, n[a] (%)				
Female	25,632 (89.5)	785 (46.7)	687 (52.2)	27,104 (85.7)
Male	3015 (10.5)	896 (53.3)	628 (47.8)	4539 (14.3)
Race or ethnicity[b], n (%)				
Hispanic	12,391 (43.3)	870 (51.8)	684 (52)	13,945 (44.1)
White	10,864 (37.9)	503 (29.9)	412 (31.3)	11,779 (37.2)
Asian	2292 (8)	175 (10.4)	106 (8.1)	2573 (8.1)
Black	1894 (6.6)	40 (2.4)	54 (4.1)	1988 (6.3)
Pacific Islander	168 (0.6)	19 (1.1)	6 (0.5)	193 (0.6)
Native Am Alaskan	76 (0.3)	2 (0.1)	2 (0.2)	80 (0.3)
Am Indian or Alaska native	2 (0)	0 (0)	0 (0)	2 (0)
Other	344 (1.2)	25 (1.5)	19 (1.4)	388 (1.2)
Multiple	114 (0.4)	8 (0.5)	6 (0.5)	128 (0.4)
Unknown	488 (1.7)	36 (2.1)	26 (2)	550 (1.7)
Decline to state	13 (0)	3 (0.2)	0 (0)	16 (0.1)

[a]n: sample size.

[b]Missing: n=1 for *E coli*.

Discussion

We present data collection methods for the study which was conducted to help fill a gap in the literature by evaluating the impact of SB27 on downstream antibiotic resistance rates in human UTIs. To date, it is one of the largest studies of its kind to evaluate the relationship between antibiotic use in livestock production and AMR profiles in retail meat and humans before and after the implementation of a statewide policy meant to reduce antibiotic use in the livestock sector.

The study concurrently sampled retail meat (chicken, turkey, beef, and pork) and clinical specimens at regular time intervals. The study team cultured and isolated *E coli*, *Salmonella*, and *Campylobacter* from retail meat, and clinical specimens were processed by clinical laboratory staff at KPSC to isolate bacteria of interest. WGS was performed on a subset of *E coli* isolates, and all *Salmonella* and *Campylobacter* isolates. This study used expansive EHR data, before (2015-2017) and after (2018-2021) SB27 enactment, from KPSC and Sutter Health, 2 large and well-established health systems. Overall, 12,616 samples of meat were collected from more than 400 retail stores in Southern California. From 31,643 clinical specimens, 28,647 *E coli*, 1315 *Salmonella*, and 1681 *Campylobacter* isolates were collected. Our large study sample size thus allows us to support emerging evidence of the connection between AMR in livestock and human *E coli* UTI [33,34]. This study had complementary methodological components requiring different measurement techniques and areas of expertise, including laboratory-based methods, geospatial modeling, market-basket research design and techniques, incorporation of publicly available data sets, and use of secondary EHR data for population health research. Moving forward, the study data will be used for further analysis and manuscripts that address the project's various primary and

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secondary aims, as well as complementary work and secondary data analyses through various partnerships.

The study had strengths and limitations. It successfully collected retail meat, clinical microbiological specimens, and data over a 5-year period. Early in the study, there were no readily available data to help identify Concentrated Animal Feeding Operation locations. As a result, we sought out and partnered with Stanford University to classify Concentrated Animal Feeding Operation locations. To set up the study, huge, concerted logistical planning across various divisions had to be implemented. The coordination of laboratory leadership at KPSC to integrate research into the clinical flow had to occur, as well as hiring a large RA team to cover the large Southern California area needed to collect the meat samples. The RAs also had to ensure all the meat samples bought were kept at reasonable temperatures from purchase to delivery to GWU where they could properly be tested. The shipments themselves were an undertaking as they tended to be bulky and heavy, and they needed their temperatures constantly monitored. Additionally, we worked with the EMSL laboratory to mirror the main laboratory (GWU) procedures, to act as a quality control laboratory for the meat samples. Though the RA team covered many grocery stores throughout Southern California, we did not collect data on which products were more likely to be purchased by KPSC members. However, we strategically selected a representative sample of grocery stores to overlap with the geographic distribution of KPSC facilities and members. The study was also successful in gaining access to the clinical samples, and in being able to collect a large quantity for the study. A further limitation was the lack of routine testing for tetracycline for clinical UTI samples at KPSC. As a solution, we shipped all study samples to GWU for tetracycline susceptibility testing. Lastly, the COVID-19 pandemic impacted data collection, as testing laboratories were closed for several months, and meat purchasing was suspended for a short period due to safety concerns of field staff. However, data collection resumed in mid-October 2020 with additional pandemic procedures in place, such as the addition of personal protective equipment and other safety precautions.

This methods paper describes the processes of collecting, processing, and shipping meat and clinical samples, and can be used as a guide for any subsequent, similar research. The analyses implemented and subsequent results will provide the evidence necessary to evaluate the effectiveness of SB27 and will be detailed in forthcoming publications.

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Data Availability

Anonymized data that support the findings of this study may be made available from the investigative team in the following conditions: (1) agreement to collaborate with the study team on all publications, (2) provision of external funding for administrative

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and investigator time necessary for this collaboration, (3) demonstration that the external investigative team is qualified and has documented evidence of training for human subjects protections, and (4) agreement to abide by the terms outlined in data use agreements between institutions.

Authors' Contributions

JAC, KN, LBP, VQ, MFD, CML, AP, KJB, and SYT contributed to the concept and design. AF, MEP, HST, and SYT were responsible for drafting of the manuscript. JAC, KN, LBP, VQ, LDC, MFD, RW, VH, JHK, CML, AP, SR, KJB, and SBS were involved in critical revision of the manuscript. LDC, RW, VH, SR, and SBS were responsible for statistical and data support. All authors reviewed and approved the final draft.

Conflicts of Interest

AF received research support from Pfizer, Moderna, Gilead, and GlaxoSmithKline unrelated to this study. KJB received research support from Dynavax, GlaxoSmithKline, Moderna, and Pfizer unrelated to this study. SYT received funding from Pfizer paid directly to institution for work unrelated to this study.

Multimedia Appendix 1
GWU Isolation and Testing Methods.
[DOCX File , 27 KB - resprot_v12i1e45109_app1.docx]

Multimedia Appendix 2
Store distribution for collection of meat samples.
[DOCX File , 502 KB - resprot_v12i1e45109_app2.docx]

Multimedia Appendix 3
Data collected for each meat sample purchased.
[DOCX File , 14 KB - resprot_v12i1e45109_app3.docx]

Multimedia Appendix 4
Data collected for each clinical sample.
[DOCX File , 14 KB - resprot_v12i1e45109_app4.docx]

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Abbreviations

AMR: antimicrobial resistance
EHR: electronic health record
EMSL: EMSL Analytical, Inc
GWU: George Washington University
HIPAA: Health Insurance Portability and Accountability Act
IRB: institutional review board
JHU: Johns Hopkins Bloomberg School of Public Health
KPSC: Kaiser Permanente Southern California
MIC: minimum inhibitory concentration
OSHA: Occupational Safety and Health Administration
PM: project manager
RA: research associate
SB27: Senate Bill 27
SOP: standard operating procedure
USDA: United States Department of Agriculture
UTI: urinary tract infection
WGS: whole-genome sequencing

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Protocol

Traumatic Brain Injury Intensive Evaluation and Treatment Program: Protocol for a Partnered Evaluation Initiative Mixed Methods Study

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Abstract

Background: The traumatic brain injury (TBI) Intensive Evaluation and Treatment Program (IETP) is an innovative modality for delivering evidence-based treatments in a residential, inpatient format to special operational forces service members and veterans with mild TBI. IETPs provide bundled evidence-based assessment, treatment, referral, and case management in concordance with the existing guidelines for mild TBI and commonly co-occurring comorbidities. To date, there has been no formal characterization or evaluation of the IETP to understand the determinants of implementation across the system of care. The goal of our partnered evaluation initiative (PEI) with an operational partner, the Physical Medicine and Rehabilitation National Program Office, is to facilitate the full implementation of the IETP across all 5 Veterans Health Administration TBI–Centers of Excellence (TBI-COE) and to inform minimum standards while supporting the unique characteristics of each site.

Objective: This IETP partnered evaluation will describe each of the 5 TBI-COE IETP services and state of implementation to identify opportunities for adaptation and scale, characterize the relationship between patient characteristics and clinical services received, evaluate the outcomes for participants in the IETP, and inform ongoing implementation and knowledge translation efforts to support IETP expansion. In alignment with the goals of the protocol, ineffective treatment components will be targeted for deimplementation.

Methods: A 3-year concurrent mixed methods evaluation using a participatory approach in collaboration with the operational partner and TBI-COE site leadership will be conducted. Qualitative observations, semistructured focus groups, and interviewing methods will be used to describe IETP, stakeholder experiences and needs, and suggestions for IETP implementation. Quantitative methods will include primary data collection from patients in the IETP at each site to characterize long-term outcomes and patient satisfaction with treatment and secondary data collection to quantitatively characterize patient-level and care system–level data. Finally, data sets will be triangulated to share data findings with partners to inform ongoing implementation efforts.

Results: Data collection began in December 2021 and is currently ongoing. The results and deliverables will inform IETP characterization, evaluation, implementation, and knowledge translation.

Conclusions: The results of this evaluation seek to provide an understanding of the determinants affecting the implementation of IETPs. Service member, staff, and stakeholder insights will inform the state of implementation at each site, and quantitative measures will provide options for standardized outcome measures. This evaluation is expected to inform national Physical

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Medicine and Rehabilitation Office policies and processes and knowledge translation efforts to improve and expand the IETP. Future work may include cost evaluations and rigorous research, such as randomized controlled trials.

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KEYWORDS

service member; rehabilitation; traumatic brain injury; TBI; posttraumatic stress disorder; PTSD; pain; military; brain injury; trauma; traumatic; participatory; recovery; veteran; implementation; service delivery; protocol; treatment program; implementation; health care implementation; Consolidated Framework for Implementation Research; CFIR; cognitive; cognition; brain; script; Bayesian; network analysis; directed acyclic graph; effect size; missing data; inpatient; modality

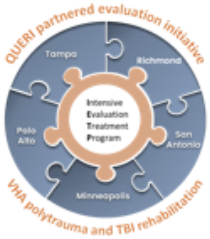
Introduction

Background

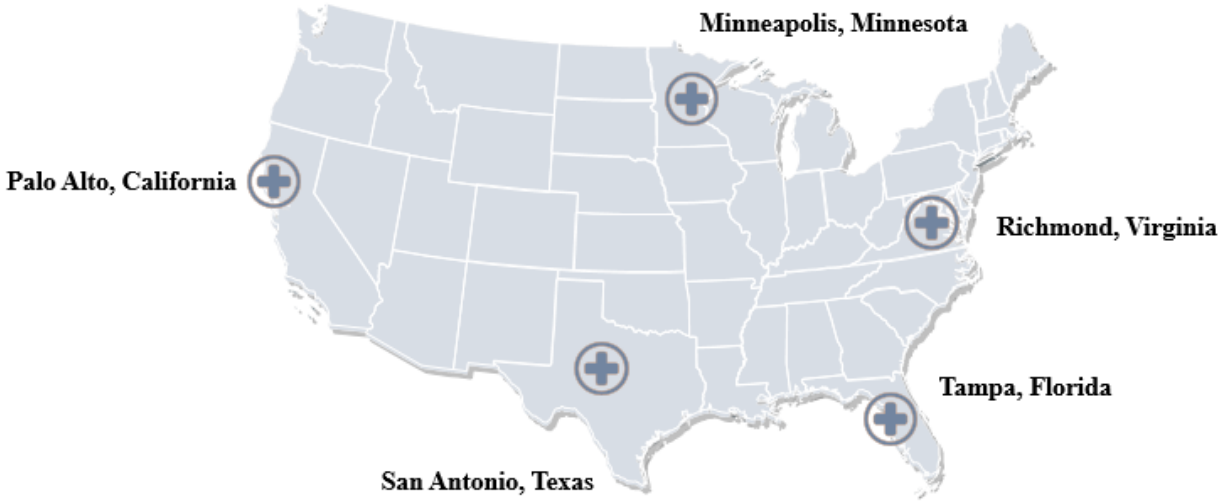
Record numbers of service members with traumatic brain injury (TBI) have flooded the Veterans Affairs (VA) and the Department of Defense (DoD) during the past 2 decades. Since 2000, a total of 430,720 service members have been diagnosed with TBI, and the majority (82.4%) have been diagnosed with mild TBI [1]. Service members consist of conventional forces and special operational forces (SOF). SOF service members undergo extensive training and experience increased risk exposure owing to deployment and job hazards [2]. Sequalae from mild TBI may co-occur with at least 1 of the following: posttraumatic stress disorder (PTSD), chronic pain, and visual and balance disturbances. In particular, the SOF population has a unique presentation of TBI sequala [3]. Interdisciplinary TBI rehabilitation, particularly for the SOF population, is intended to enhance functioning, reduce disability, and improve quality of life. To meet the demand for rehabilitation services required by SOF service members and veterans with TBI, the Veterans Health Administration (VHA) Physical Medicine and Rehabilitation (PM&R) National Program Office developed 5 specialty TBI–Centers of Excellence (TBI-COE) to provide a coordinated approach for comprehensive TBI rehabilitation (Figure 1). The TBI-COE sites are located at VA hospitals in Minneapolis, Minnesota; Palo Alto, California; Richmond, Virginia; San Antonio, Texas; and Tampa, Florida.

To date, there has been no formal characterization or evaluation of the TBI Intensive Evaluation and Treatment Program (IETP) to understand the implementation determinants or formalize core program components across the system of care. This limits the ability of VA to make evidence-based decisions for policy and planning to meet the long-term needs of this patient cohort. To expand the capacity for innovation in delivering guideline-concordant care, the PM&R National Program Office, our operational partner, is supporting a partnered evaluation to implement the effective components of this modality across VHA.

Figure 1. Five Intensive Evaluation and Treatment Program sites. QUERI: Quality Enhancement Research Initiative; TBI: traumatic brain injury; VHA: Veterans Health Administration.



- **Tampa, Florida**=Post-deployment rehabilitation and evaluation program **(PREP)**
- **Richmond, Virginia**=Service member transitional advanced rehabilitation **(STAR)** program
- **San Antonio, Texas**=Post-deployment accelerated comprehensive evaluation and rehabilitation **(PACER)** program
- **Minneapolis, Minnesota**=Rehabilitation evaluation and neurologic enhancement for warriors **(RENEW)** program
- **Palo Alto, California**=Polytrauma transitional rehabilitation program **(PTRP)**

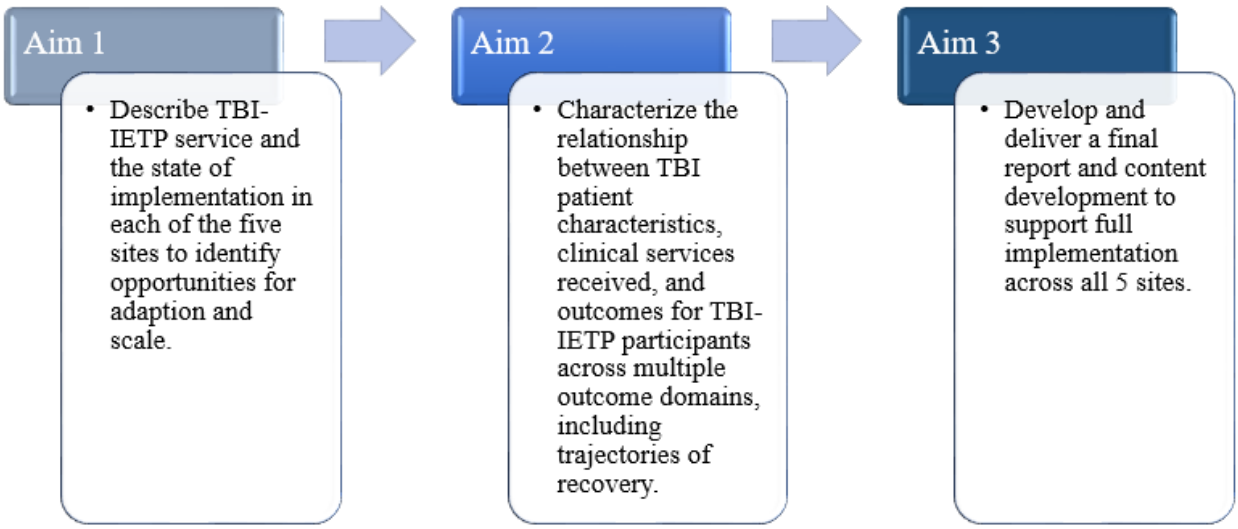


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IETP Partnered Evaluation Goal and Aims

The goal of our partnered evaluation initiative (PEI) is to facilitate the full implementation of the IETP across all 5 VHA TBI-COE sites and to inform minimum standards while supporting the unique characteristics of each site. The aims of this partnered evaluation are as follows: (1) describe IETP services and state of implementation of these services in each of the 5 sites to identify opportunities for adaptation and scale—the findings will identify IETP core aspects and determinants of implementation; (2) characterize the relationship between patient characteristics, clinical services received, and outcomes for participants in the IETP across multiple outcome domains, including trajectories of recovery; and (3) evaluate the clinical impact of IETP components and deliver a final report to include deliverables that support IETP implementation playbook content development (Figure 2). The completion of these aims will promote effective IETP practices across this polytrauma system of care. The development and dissemination of product deliverables from the evaluation will support IETP implementation and continued evaluation over time.

Figure 2. Intensive Evaluation and Treatment Program (IETP) partnered evaluation aims. TBI: traumatic brain injury.



TBI IETP—Innovative Modalities of Care

Innovative modalities of care improve access to evidence-based care for mild TBI. Innovative models of care have been developed within the polytrauma system of care, which includes 5 specialty TBI-COE that provide comprehensive rehabilitation services for veterans and service members with TBI. The TBI IETP is an innovation that has yielded high consumer demand across locations. The IETP delivers evidence-based care in a residential, inpatient format. The IETP provides bundled evidence-based assessment, treatment, referral, and case management in concordance with the existing guidelines for mild TBI and commonly co-occurring comorbidities (refer to the IETP characterization table in Multimedia Appendix 1 [4-23]). Indeed, the residential format has grown out of necessity to address the unique needs of the SOF population in a compressed, timely manner ideally suited for abbreviated inpatient treatment stays. A recent study by Dismuke-Greer et al [24] highlighted higher annual outpatient use and cost over protracted time intervals for veterans with mild TBI compared with non-TBI controls, highlighting extended intervals and delayed access to evidence-based care. Proponents of IETP emphasize its improved access to evidence-based care, including TBI-adapted treatment of mental health conditions previously published [25,26].

Responsiveness and Alignment With Goals: Quality Enhancement Research Initiative Implementation Roadmap

Overview

In response to this evaluation, engagement with partners and alignment with network director goals will guide implementation across the Quality Enhancement Research Initiative (QUERI) Implementation Roadmap. In response to the special solicitation for a PEI with VHA PM&R, the Characterization, Evaluation, and Implementation of Innovative TBI IETPs will evaluate the ongoing implementation of the IETP at all 5 TBI-COE sites to identify the effective and ineffective components. The project will align with the QUERI Implementation Roadmap, a functional framework for evaluating and contextualizing the implementation of IETP [27]. QUERI Implementation Roadmap elements provide a framework for planning, implementing, and sustaining programs—from reaching audiences to establishing effectiveness, promoting adoption and implementation, and ultimately sustaining maintenance over time. The partner priorities aligned with the roadmap of the framework are summarized in Table 1. Partner goals and challenges will be addressed across the study aims.

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Table 1. Integration of the Quality Enhancement Research Initiative Implementation Roadmap conceptual model with partner-identified goals, challenges, and partnered evaluation initiative (PEI) solutions.

Aims and partner goals	Partner-identified challenge	PEI solution
Pre-PEI		
Identify and align needs and goals	Work with a team that understands needs and goals from the TBI[a] and implementation perspective	Ongoing communication and meetings to understand needs and identify priorities
Engage stakeholders	Prior push to implement not successful	Site representatives recruited to facilitate a bottom-up pull and buy-in from local staff. Input on study design and findings were sought from a stakeholder panel including veterans, service members, VA[b] and DoD[c] administrators, and clinicians
Develop measures and data	Program evaluation data are not standardized and readily accessible	Site representatives recruited to facilitate engagement of stakeholders for data collection. Meetings with PM&R[d] partners and various stakeholders to identify and prioritize outcomes
Data to knowledge (preimplementation stage)		
Aim 1: characterize consumer demand	IETP[e] value from referrals within VA and DoD is unknown	Use of qualitative data collection with patients treated across fully and partially implemented sites
Aims 1-2: fully characterize the innovation (IETP)	IETP is a black box with poor characterization to duplicate and sustain across systems	Use of qualitative interview technique and quantitative analyses of administrative data sets to identify effective practice core elements and adaptation options
Aim 2: determine early and late outcomes from IETP	Outcome monitoring has not been the focus of the existing programs	Leverage existing data (eg, IETP data) and collect prospective outcome data to identify measures of success and establish baseline performance at the fully implemented site
Knowledge to implementation (implementation stage)		
Aim 1: characterize the degree of implementation	IETP innovations have occurred asynchronously with variation of implementation	Qualitative data collection with a purposive sample of clinicians at each site to understand the degree of implementation, inform selection, and tailor implementation to each site
Aim 3: disseminate and promote IETP implementation	Continued funding for TBI rehabilitation services in a competitive fiscal environment across the VA organizational hierarchy	Use participatory approach to (1) promote a bottom-up pull for "IETP evidence-based" practices, (2) disseminate implementation content, and (3) gather feedback for each site. Leverage existing reporting structures to summarize findings for reports to Congress including VA and DoD administrators, and clinicians for uptake and sustainment
Performance to data (sustainment; post-PEI)		
Implement IETP	Funding mechanism and timeline insufficient to achieve all partner goals	Will develop future proposals to evaluate the uptake of IETP, evaluate the ongoing implementation, and inform continuous learning

[a]TBI: traumatic brain injury.

[b]VA: Veterans Affairs.

[c]DoD: Department of Defense.

[d]PM&R: Physical Medicine and Rehabilitation.

[e]IETP: Intensive Evaluation and Treatment Program.

Preimplementation Stage: Data to Knowledge

Aim 1 qualitative methods will fully characterize the successful IETP model and the perceived value of IETP components. We will leverage existing data resources and prospective data collection to evaluate program outcomes prioritized by our operational partner and other stakeholders, including service members and veterans with mild TBI (aim 2). Findings from the first 2 study aims will be used to develop the foundation for the implementation of effective components and the deimplementation of ineffective components in aim 3.

Implementation Stage: Knowledge to Implementation

A participatory approach with IETP stakeholders will be used to develop implementation content that outlines "IETP evidence-based" practices. This effort will involve clinical and administrative IETP stakeholders across study sites as well as a formal stakeholder panel to inform and review a blueprint for implementation.

Sustainment: Performance to Data

Future work will address implementation, deimplementation, and their effects on the system and patient outcomes. Table 1 provides an overview of the timing and conduct of the 3 aims.

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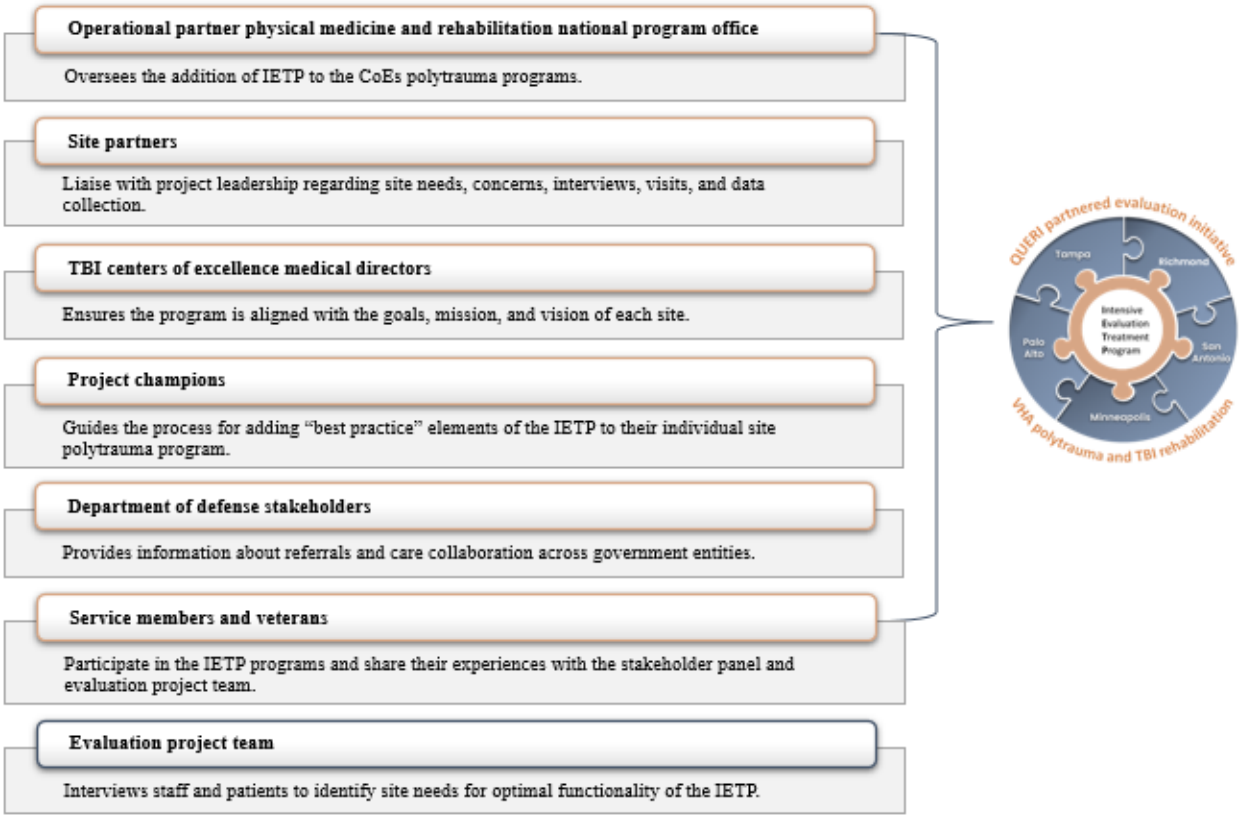
Methods

Partnerships, Research Team, and Relevant Experience

The multiple principal investigators (MPIs) have developed an interdisciplinary team to conduct this mixed methods partnered evaluation with PM&R leadership, informing the development of a stakeholder agenda that is reflected in the aims and deliverables.

The PEI engages a stakeholder panel representing multiple stakeholders in IETP from each study site as well as PM&R leadership (Figure 3). The primary goals of the stakeholder panel are to represent operational and clinical perspectives, collaborate on data collection tool development, facilitate site engagement, and identify preferred implementation strategies. Weekly meetings in years 1 through 3 will be held to gather stakeholder input on the study methodology, interpretation of findings, and deliverables.

Figure 3. Intensive Evaluation and Treatment Program (IETP) partnered evaluation collaborative roles. COE: Center of Excellence; QUERI: Quality Enhancement Research Initiative; TBI: traumatic brain injury; VHA: Veterans Health Administration.



Ethical Considerations

The project protocol was reviewed by James A. Haley Veterans' Hospital Research and Development Committee and deemed *nonresearch*, and no informed consent was necessary. Participants' identities are confidential, and deidentified data are stored behind VA firewalls. No compensation will be provided to the participants for this program evaluation project. All methods are performed in accordance with the relevant guidelines and regulations. All staff interviews were approved by the VA national union. Patients' interviews were reviewed by the QUERI administration and were exempt from Code of Federal Regulations Part 1320.3, as the project will evaluate the direct treatment currently provided.

Aim 1

Overview

We will use qualitative methods to describe and characterize IETP to support implementation efforts across all 5 TBI-COE. In alignment with the QUERI Implementation Roadmap, this project will coconstruct a meaningful theoretical context for identifying and describing the implementation of each IETP using the Consolidated Framework for Implementation Research (CFIR) [28,29]. In addition, project leadership will use an implementation evaluation process conducted in a *sister* project, Optimizing Rehabilitation Interventions (ORION) for Cognition Following Complex Traumatic Brain Injury funded by the DoD (W81XWH-19-1-0615), which will maximize the efficiency of this effort and promote interoperability and knowledge translation between VA and DoD. The PEI team will use this implementation evaluation process to present and review the content in initial development in Tampa. Subsequently, the materials will be used and further developed in an iterative fashion at the other IETP sites. The aim 1 deliverable is a characterization of the IETP, IETP Care Implementation Elements Inventory, and IETP Logic Model. The inventory and logic model will be iteratively developed and used to assess the implementation at TBI-COE sites.

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Sampling and Sample Size

We will collaborate with site partners to recruit a purposive sample of key informants and IETP team members, including a physician, nurse, and therapist, to attend focus groups at each of the 5 sites. As conceptual saturation is the goal, we will recruit the minimum sample necessary to represent the types of professional disciplines to compare experiences. We will also conduct interviews with a purposive sample of DoD IETP stakeholders involved in the referral and coordination of IETP, based on key informant referrals and feedback from our stakeholder panel. As part of a comprehensive evaluation, we will also conduct telephone interviews with service members and veterans from each site who previously participated in IETP, and contact information will be obtained from the data collected for aim 2. Participants will be purposively selected among those in the top and bottom quartiles of the Mayo-Portland Adaptability Inventory (MPAI; patient outcome across all 5 sites) at program discharge [30]. The MPAI reflects the outcomes prioritized by the operational partner. In qualitative projects, sample and size rely on the population characteristics and the quality and richness of information obtained [14,15]. Recruitment efforts will oversample women and minority individuals to ensure that their perspectives are represented in the data. Qualitative recruitment and sampling for aim 1 are presented in Table 2.

Table 2. Aim 1 qualitative recruitment.

Data collection activity	Participants	Site sample size:total sample size
Key informant interviews	Clinical team from IETP[a]	1:5
Focus groups	Physician, nurse, therapist, etc	15:75
Interviews	DoD[b] IETP stakeholders	15:75
Telephone interviews	Service members who previously received IETP	12:60
Demographic questionnaire	Physician, nurse, therapist, etc	15:75
Follow-up interviews	Subsample of key informant and focus group participants	15:75
Site visit observation	IETP representatives, leadership, and clinicians	N/A[c]

[a]IETP: Intensive Evaluation and Treatment Program.

[b]DoD: Department of Defense.

[c]N/A: not applicable.

Measures and Data Collection Procedures

We will use site visit observations, key informant interviews, focus group, and follow-up interviews to complete aim 1. We will also refine the fidelity checklist as part of aim 1 data collection (Multimedia Appendix 2). Data collection tools will include veteran and focus group demographic questionnaires (Multimedia Appendix 3), interview and focus group scripts, and a site observation guide and comparison checklist.

Initial Interviews

Qualitative researchers will conduct key informant initial interviews remotely with the program or medical director at each site. These participants will be purposively identified and confirmed by the operational partner. Informants will provide an overarching introduction to each site and the site's implementation efforts and then provide key referrals to recruit other team members for focus group interviews (Multimedia Appendix 4). Key informant interviews will be audio recorded and transcribed verbatim. Researchers will take field notes to capture nuances potentially missed by audio recordings and will facilitate preliminary data analyses when transcription is completed. All data will be stored on a secure VHA server with restricted access. The key informant will also facilitate the analysis of local program outcome data to help recruit local participants in the IETP eligible for telephone interviews.

Site Observation

A team of 2 qualitative researchers will travel to each site for site visits. Two-day site visits will comprise (1) a facility tour, (2) presentations from and discussions with program representatives, and (3) meetings with leadership and identified local stakeholders. The qualitative team will take field notes and photos with permission and collect site-specific artifacts. These items will be saved on a secure VHA server with restricted access and uploaded into ATLAS.ti 22 Windows software for organization, coding, and analysis. These partnering activities will be critical for developing relationships with site staff and setting the stage for subsequent aim 3 activities. Site observation guides will be used to assess sites qualitatively, and the checklist will be used in tandem to assess fidelity across sites (Multimedia Appendix 5).

Focus Groups

Focus groups, coordinated with the clinical partners to reduce interference with patient care, will be conducted using web conferencing technology to collect data from clinicians about their site's IETP. Participants will receive an email before the focus group, which will include interview questions. Each focus group will be facilitated by 1 qualitative researcher with a team of evaluation staff to take notes, manage any technological issues, and observe the chat box for any questions or comments. The focus groups will be audio recorded with permission. Information collected during focus groups will address IETP logic, program content, operationalization, and other relevant

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implementation factors (Multimedia Appendix 6) and will be stored on a secure VHA server with restricted access and uploaded to ATLAS.ti 22 Windows software for organization, coding, and analysis.

Follow-up Interviews

Follow-up interviews will be conducted by phone: (1) key informant follow-ups will be conducted to share data summaries, IETP checklists, and draft content and to assess validity and usefulness and (2) focus group member follow-up interviews will be conducted with a subsample of focus group participants to account for differences in knowledge and perspective by role, providing broad perspectives and accounting for potential power differentials. Individual interviews will ensure that team members have an opportunity to address personal perspectives, discuss issues that may not arise in focus groups, explore emergent themes, and review data summaries and content (Multimedia Appendix 7). Follow-up interviews will be conducted via web conferencing and will be audio recorded. Recordings will be transcribed verbatim. Researchers will take field notes to capture nuances potentially missed by audio recordings and facilitate preliminary data analyses when transcription is completed. All data will be stored on a secure VHA server with restricted access.

Veteran and Service Member Interviews

Interviews with service members and veterans who participated in IETP will be conducted at each site to describe patient experiences with IETP (Multimedia Appendix 8). These interviews will be audio recorded and transcribed verbatim. Researchers will take field notes to capture nuances potentially missed by audio recordings and facilitate preliminary data analyses when transcription is completed. All data will be stored on a secure VHA server with restricted access.

DoD IETP Stakeholder Perspectives

DoD IETP stakeholders will share their perspectives on IETP as consumers to assess the value of VA IETP services from a DoD perspective and obtain their perspectives of important outcomes and their perceptions of the projected trajectory for the continued patient need for IETP services (Multimedia Appendix 9). As with the other qualitative data collection methods, the interviews will be completed using web conferencing and will be audio recorded. Recordings will be transcribed verbatim. Researchers will take field notes to capture nuances potentially missed by audio recordings and facilitate preliminary data analyses when transcription is completed. All data will be stored on a secure VHA server with restricted access.

IETP Data Collection Content

In our project start-up, we are developing a preliminary IETP characterization table based on guidelines and subject matter expertise (refer to the preliminary summary in Multimedia Appendix 1). In tandem, using clinical team expertise and literature on evidence-based implementation strategies that are relevant to the IETP clinical components reviewed in the IETP characterization table, the process of implementation to date will be represented as a CFIR-based implementation research logic model (IRLM) [31]. The IRLM will use data on inputs, activities, and outcomes to specify the relationships among determinants of implementation, implementation strategies, and the mechanistic links between strategies and outcomes relevant to the following: (1) inputs—program referral patterns, characteristics of IETP patients, staffing and skills required to deliver the program, facilities, resources needed to deliver the program, and other program inputs evident in the literature review; (2) activities—set of therapeutic activities that comprise the program, characterized as core or peripheral and as individual or group interventions, along with the programmatic meetings and staff training that are necessary to deliver the program; and (3) outcomes—immediate and long-term outcomes that define program success [32]. The IRLM, contextualized by CFIR constructs, will be triangulated and analyzed as part of aim 1 and iteratively revised to reflect the clinical relevance for each site. The team will also refer to the validated inventory of implementation strategies in the development process by Powell et al [33]. The IRLM template is provided in Multimedia Appendix 10 [31].

Elicitation of IETP Contents and Operationalization

We will interview respondents to identify the inputs, activities, and outcomes that define the IETP. We will refer to the IETP characterization table to elicit inputs on convergence and divergence between their experience and the guidelines. The preliminary IETP characterization table will be used as a plausibility check for these initial interviews to evaluate, for instance, whether the elicited program inputs, activities, and outcomes are concordant with the published literature and whether the suggested links between program activities and outcomes are plausible. The analysis will be conducted within the context of CFIR to ensure strategic alignment with the implementation recommendations. The elicitation of program inputs, activities, and outcomes will be expedited by comparing similar products developed in the ORION project. ORION project library elements that correspond to IETP inputs, activities, and outcomes will be shared with the interviewees as examples. This process will support the iterative development of the IETP Care Implementation Elements Inventory. Multimedia Appendix 11 provides an example from the ORION project.

Data Analysis

Qualitative data collection and analysis will occur concurrently. Insights from the data analysis will be used to iteratively guide data collection. The evaluation team will work together to develop an a priori code book based on the 2009 CFIR constructs, as each interview guide is also based on the 2009 CFIR constructs. Transcripts, artifacts, and observation notes will be uploaded to ATLAS.ti 22 Windows software to organize and code data. Analysis methods will be used to identify domains related to data for specific data types, such as key informant interviews and focus groups [34]. Participant comments will be organized to develop codes and merged to develop categories. Categories will be compared, and relationships will be identified. Data samples will be extracted and coded by 2 project team members and evaluated for interrater reliability and credibility. The data sets for each site will be compared to determine the commonalities and

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differences between sites. The evaluation team will conduct a matrix analysis to analyze across-site domains and taxonomies [35]. Descriptive and comparative matrices will identify the patterns of regularities and inconsistencies and identify the relevant and representative components by site to support strategy development. Once cases and comparative matrices are developed, follow-up interviews will be reviewed by the stakeholder panel to verify the findings and provide additional input and clarification.

Aim 2

Aim 2 will use the existing data to identify IETP participants; types of care received; and long-term outcomes, including postdischarge needs and trajectories, of IETP. The models will be reviewed with clinical partners throughout, with the final analytic output delivered at the end of year 2.

Measures and Data Collection Procedures

Data from each IETP participant will be obtained from site leads beginning with Tampa (2015 to present; n=approximately 350). We will obtain identifiers that allow linkage to VA and DoD health system data and create a study crosswalk database behind the VA firewall that includes the encrypted identifier, a study ID, and contact information for interview and survey administration. We will obtain intake and discharge measures from each IETP site. We will assess IETP fidelity based on the IETP characterization table (Multimedia Appendix 1) using a checklist (Multimedia Appendix 2) and chart abstraction focusing on the admission note, admission IETP care plan, discharge TBI care plan, and discharge summary, which are highly accurate in describing the reasons for seeking treatment, baseline status, the type of treatment recommended, the type of treatment received, and outcomes on discharge (Multimedia Appendix 12).

We will also link these IETP data to VA and DoD health system data, as we have done previously [36], to obtain information on physical and mental health, medications, and military demographic data before and after IETP. As approximately 90% (225/250) of participants in the IETP are active duty at the time of treatment with the goal of returning to full duty and operational partner priority outcomes include return to duty or employment, the use of VHA data (eg, Patient Health Questionnaire-9 [PHQ-9] and PTSD checklist-5) is not a feasible approach to long-term outcomes. Therefore, we will conduct a survey using a VA-approved web-based survey software for participants of IETP (2015-2022; approximately 500) using a Modified Dillman Method, which we used in prior VA studies (Multimedia Appendix 13) [37-40]. We will begin a survey of earlier IETP graduates in the first year of the study and send surveys to new graduates 6-9 months post study completion. The final outcome measures included in the survey will be developed in collaboration with stakeholders. The current list of stakeholder-identified measures that are evaluated at intake and discharge include the PHQ-9, PTSD checklist-5, MPAI, and the Neurobehavioral Symptom Inventory.

We will also use VA and DoD health system data to describe health system outcomes such as use, new diagnoses, and adverse outcomes, which will, together with data baseline, discharge, fidelity, and discharge outcomes, be used to develop trajectories of recovery.

Characterize IETP Participants

We will begin characterization with the Tampa site (n=approximately 350) and Richmond site (n=approximately 150), followed by other sites. We will use VA and DoD health system data to characterize preadmission military and sociodemographic characteristics, TBI-related diagnoses (eg, PTSD, pain, and sleep), and medication use (eg, opioids, antidepressants, and sedative hypnotics). We will add data from TBI history and symptom inventories administered at IETP admission to develop mild TBI phenotypes [36,41,42]. This allows the characterization of participants in the IETP and the identification of groups that are likely to have similar courses of care.

Data Analysis

After calculating descriptive statistics (proportions and quantiles for discrete variables and means and SDs for continuous variables) of VHA and DoD intake measures before IETP admission, we will fit a latent variable mixture model, a multivariate statistical technique used to classify individuals into interpretable categories based on a set of measurements (described in the *Measures and Data Collection Procedures* section) [36,42-49]. Similar to cluster analyses, the latent variable mixture model is an exploratory technique to identify underlying constructs associated with multiple variables, in our case, the underlying comorbidity phenotypes. On the basis of prior work, we expect 2 to 3 groups each with n=approximately 100-200 participants [36]. Health system data identifying the treatment provided are not likely to have missing data owing to the professional responsibility to document. Each visit requires a primary diagnosis for care, which will lead to data available at each visit; therefore, we expect little to no missing data.

Identify Treatment Received During IETP

Consistent with prior studies [50-52], we will create an abstraction tool in collaboration with IETP clinicians and aim 1 data. Using the crosswalk database, we will conduct chart abstraction for IETP focusing on the initial assessment, TBI care plan, processes and amount of care received, discharge assessment, and TBI care plan. After finalizing the procedures and appropriate training, team members will independently review 10 charts and then meet to identify inconsistencies, errors, or disagreements and resolve any by consensus. This will continue until there is 90% agreement on all items abstracted, to ensure abstraction fidelity. The areas of uncertainty will be discussed with IETP clinicians. These data will be merged with IETP data, VA and DoD analytic file data, and survey data for the outcome analyses.

We will identify what happens during the IETP stay using descriptive statistics for the overall cohort, stratified by phenotypes from the measures listed in the *Measures and Data Collection Procedures* section. We expect that different types of care will be provided to individuals with different prior comorbidities and clinical presentations. We will apply Pearson chi-square test to assess the association between

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recommendations for admission TBI care plan and TBI phenotype.

Identify Components of IETP Associated With Sustainment and Improvement Trajectories

Outcomes currently identified by operational and clinical stakeholders that are collected at all sites (Tables 3 and 4) will be included in the survey to develop longitudinal outcome trajectories. On the basis of stakeholder feedback, we will also measure and describe community reintegration, employment, retention in the military where relevant, compliance to discharge from the TBI care plan, reasons for difficulty in care plan compliance, and unmet rehabilitation needs. Per operational partners' request, we will also use VHA and DoD data to identify use relevant to discharge (eg, TBI care plan within primary, mental health, specialty care, or emergency care).

We will use Bayesian network analysis to generate a directed acyclic graph, which probabilistically describes the trajectory of symptoms, care, and outcomes for IETP participants. This network will enable us to explore the contribution of the baseline phenotype to the decision to use a particular treatment course and the contribution of those treatments to the participants' resulting outcome measures [53]. Using a hill-climbing algorithm scored with the Bayesian information criterion, we will establish directional connections between nodes, called edges, and evaluate the robustness of the edges using bootstrapped samples of the data. We will a priori exclude any implausible directed edges (eg, IETP care cannot lead to precare symptoms). The resulting directed network will have edges between the levels: (1) phenotypes, (2) treatment, and (3) outcomes, while disallowing connections that go from levels 2 to 1 or 3 to 2 or 1. We can allow edges between nodes within the treatment level of the network to better understand the interactions between treatments and to assess how the treatments individually and in combination probabilistically affect patient outcomes. By fitting this model, we can isolate the most probable trajectories between TBI phenotypes and treatments and then determine which treatments have a higher probability of positive long-term outcomes. To gain an understanding of the treatment courses on outcomes, we will present a graphical display of the nodes and edges, the conditional probabilities calculated between nodes that estimate the probability of long-term outcomes given the participants' IETP components and comorbidity phenotypes, and the robustness measures from bootstrapping.

Table 3. Proposed measures for developing trajectory outcomes.

Measure	Baseline	Discharge	Survey	Construct
Mayo-Portland Adaptability Inventory	✓	✓	✓	Ability, adjustment, and participation
Patient Health Questionnaire-9	✓	✓	✓	Depression
PTSD[a] checklist-5	✓	✓	✓	PTSD
Neurobehavioral Symptom Inventory	✓	✓	✓	Postconcussion symptoms

[a]PTSD: posttraumatic stress disorder.

Table 4. Proposed measures for developing trajectory outcomes.

Health system data	Prebaseline	During IETP[a]	After IETP	Construct
Diagnoses	✓	✓	✓	History and emergence of physical or psychiatric comorbidity
Health care use	✓	✓	✓	Type of care received
Medications and procedures	✓	✓	✓	Type of pharmacological or nonpharmacological care

[a]IETP: Intensive Evaluation and Treatment Program.

Power and Missing Data

The analyses in this aim take an exploratory approach to establishing phenotypes with latent variable mixture models and isolating common trajectories based on Bayesian networks. As such, we do not have a targeted hypothesis with which to power this analysis for minimum detectable effect sizes but rather a model selection approach using the Bayesian information criterion. With 500 participants, we expect that our sample size will be well above the number of nodes in the Bayesian network, which will allow for an accurate estimation of the conditional probabilities in the network [54,55].

We will assess the risk of bias owing to missing data by looking at patterns of missing measurements at each phase of the patients' trajectories, although we expect most missingness to be postdischarge. Reasons for missing measurements will be tabulated with a focus on differentiating missed measurements for logistical reasons from dropouts or intermittent missingness potentially related to the condition of the patient. If >10% (25/250) of the patients have missing outcome measurements for any of the follow-up measures or if the comparisons of baseline characteristics between patients with missing and nonmissing measurements indicate considerable imbalances, rather than only looking at complete cases, we will apply the structural expectation-maximization algorithm, an imputation method that directly processes data with missing values while fitting the Bayesian network [56]. This method incorporates baseline and follow-up factors beyond the variable being analyzed to account for the dependence of missing data on other factors. TBI history is a primary piece of data required for admission to the program. It is unlikely that any data will be

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missing for TBI history. However, if >20% (>50/250) of the sample has missing data related to TBI history, the study should be stopped.

Aim 3

Overview

In aim 3, aim 1 and aim 2 data will be triangulated to develop a final report to support IETP full implementation at sites. The primary deliverable for aim 3 is a final report that will include the IETP characterization table, IETP Care Implementation Elements Inventory, IRLM, patient experience data summaries, implementation checklists, educational content, and templates. A concluding presentation will be delivered, and consultation on findings integration will be provided for each site. In year 3, we will conduct site visits and presentations with each program to present the developed content and consult with each site to individualize and prioritize how content can be tailored at each site to facilitate full IETP implementation, including the deimplementation of ineffective care.

Measures and Data Collection Procedures

For the purposes of this PEI, the final report will be delivered to operational partners as both (1) a tool that can be used at sites to strategize the implementation of effective IETP practices and deimplementation of low-value care and (2) a resource that will include education about research implementation to support knowledge translation.

The team will develop a product grid to propose and prioritize implementation content with the stakeholder panel. Prioritized products and content from the product grid will be developed and packaged into a comprehensive report. Although the team will leverage previous projects to expedite the PEI efforts, the products will be unique to this evaluation. The final report content will be developed iteratively, and components will be reviewed with participants throughout the PEI to ensure quality control and fidelity of the developed content. In addition, the team and stakeholder panel will attend a meeting in year 3 to review and validate the IETP content. The engagement of other key stakeholder groups will be determined based on data collected in aims 1 and 2. Potential groups include consultation specialists in sleep and pain, rehabilitation disciplines, and program administrators.

Characterizing the core components of IETP as a fully implemented program will inform subsequent staged implementation efforts across sites by establishing means for monitoring the fidelity, timing, and teaching of programs over time. Products will not be designed to clone IETP across sites but will rather support site-to-site harmonization and implementation, sustainment, or enhancement of key components. Although we have established a strategic plan for acquiring data to inform product development, to be stakeholder driven, we contend that to fully identify aim 3 activities before aim 1 and aim 2 data collection would be premature. Identifying implementation efforts, including best practices, facilitators, barriers, strengths, and challenges, will be a solid approach to developing tailored implementation content.

Results

Funding and start-up activities for the evaluation began in April 2021, and the evaluation officially began in October 2021. Data collection is underway at all 5 sites and is expected to continue through May of 2025. Key informant and staff focus groups have been completed at 4 of 5 sites; the fifth site was launched in April of 2023. DoD and patient interviews are underway at all 5 sites, with one site observation to be conducted. Data analyses are underway. The anticipated evaluation results will be disseminated by 2024 and thereafter.

Discussion

Principal Findings

The goal of this evaluation protocol is to facilitate the full implementation of IETP at all VA TBI-COE sites and to inform minimum standards while supporting the unique characteristics of each site. In alignment with the goals of the proposal, ineffective treatment components will be targeted for deimplementation. The findings of this mixed methods evaluation effort will allow the characterization, evaluation, and implementation of IETP across the VA polytrauma system to improve the standardization and fidelity of care for SOF service members and veterans with mild TBI and co-occurring conditions, while preserving the unique facets of the individual program sites.

Potential Limitations

The proposed PEI does not address implementation sustainment and cost. Implementation and cost evaluation elements are beyond the scope of this 3-year PEI; however, the proposed aims are foundational efforts that will facilitate a cost and sustainment evaluation after the proposed PEI. A “rigorous” design (eg, step wedge, randomized controlled trial) is not proposed. Our proposed mixed methods design is aligned with the preimplementation emphasis of operational requests and needs. There is a potential lack of clinician or administrator participation in aim 1. We partnered with coinvestigators at each study site to support recruitment. We will meet with them during “training time” or “clinical team meetings” to maximize their availability and convenience to participate. We will offer individual interviews (by phone or in person) to maximize participation for those unable to participate in the focus groups. We will conduct meetings in person or by phone to meet their preferences, particularly through individual interviews. All patients will be interviewed by phone. The time frame is compressed for study activities. For aim 1, we will conduct simultaneous site visits and rapid iterative analysis as data are collected and analyzed. Transcription turnaround time is minimized using an internal transcription service with an established protocol with the Tampa team. For aim 2, we will leverage existing data sets (i.e, IETP, TBI model systems, VA, and DoD data sets) and include site leads as experts in those data sets to facilitate timely analyses. A potential pitfall of aim 2 is the lack of participation in long-term outcome surveys; we will address this with an introductory letter from PM&R describing the importance of the study, as well as individualized follow-up strategies that have been effectively used by the team

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in previous projects. For aim 3, final report content development will begin at the onset of the PEI, supported throughout aims 1 and 2, relying on protocols and templates used in other projects. We will use an iterative design process that will support the development and validation of the content with the PEI stakeholder panel. There is no comparison group for this treatment modality. The operational partner did not want to prioritize this comparison and felt this would be better suited in subsequent proposals.

Management Plan and Timeline

This team initiated a comprehensive approach with operational partners to ensure timely deliverables. Operational partners have described their expectations and anticipated deliverables; as such, they informed and approved the proposed evaluation and activities. The proposed aims represent distinct deliverables as a result from each aim, which are to be delivered within the established project timeline (Multimedia Appendix 14). In addition to deliverables, the PEI team will provide operations with quarterly reports to include current tasks; progress; recruitment, data collection, and analysis benchmarks; PEI barriers and solutions; product development; and lessons learned.

Communication and Collaboration

This team has established effective communication and collaboration across sites to allow visual and audio access and secure shared folder and drive access. We will use 4 primary means of project management and communication to complete the study within the projected timeline. First, we conduct weekly meetings, attended via web-based platform by the team from the primary site, including MPIs, coinvestigators, and project managers, to address day-to-day activities. The MPIs also conduct weekly meetings with their operational partners. Second, at the onset of the study, the PEI team, site leads, and operational partners will attend a virtual kick-off meeting. At this kick-off, we will attend to start-up issues and collaborate with operational partners to confirm and refine needs and anticipated deliverables. As a result of this kick-off meeting, the team will initiate a Memorandum of Understanding outlining specific deliverables. The Memorandum of Understanding is a standard agreement between operational partners and research teams to establish expectations and performance outcomes relevant to project aims. Third, the team, including the stakeholder panel, will attend quarterly meetings with relevant agenda topics to address evaluation activities, benchmarks, project issues, and subsequent implementation efforts. We propose quarterly meetings with PEI team members and operations partners to facilitate ongoing data reports, operational updates, immediate reporting and resolution of any PEI barriers and concerns, and presentation of deliverables. This ongoing communication will facilitate any changes or operations-prompted amendments to the PEI, as warranted by operational partners. In this case, MPIs will consult with operations and reconceptualize project activities and deliverables as needed. As needed, updates will be made on the weekly meeting calls and email correspondence. Updates will be summarized in quarterly reports to the operational partners.

Conclusions

This PEI will examine the implementation of the IETP across 5 sites and characterize program participants, core components, and unique site adaptions. Components that are associated with improved participant outcome trajectories will be identified. This information will be the foundation for the future implementation of effective IETP components and deimplementation of ineffective components. Future work may include cost evaluations and rigorous research such as randomized controlled trials.

Acknowledgments

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Data Availability

The data for this project are available from the corresponding author upon reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Intensive Evaluation and Treatment Program characterization table.
[PDF File (Adobe PDF File), 175 KB - resprot_v12i1e44776_app1.pdf]

Multimedia Appendix 2
Intensive Evaluation and Treatment Program fidelity checklist.
[PDF File (Adobe PDF File), 194 KB - resprot_v12i1e44776_app2.pdf]

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Multimedia Appendix 3
Intensive Evaluation and Treatment Program demographic questionnaire.
[PDF File (Adobe PDF File), 131 KB - resprot_v12i1e44776_app3.pdf]

Multimedia Appendix 4
Intensive Evaluation and Treatment Program key informant interview script.
[PDF File (Adobe PDF File), 131 KB - resprot_v12i1e44776_app4.pdf]

Multimedia Appendix 5
Intensive Evaluation and Treatment Program site observations guide.
[PDF File (Adobe PDF File), 190 KB - resprot_v12i1e44776_app5.pdf]

Multimedia Appendix 6
Intensive Evaluation and Treatment Program focus group guide.
[PDF File (Adobe PDF File), 100 KB - resprot_v12i1e44776_app6.pdf]

Multimedia Appendix 7
Intensive Evaluation and Treatment Program follow-up interviews script.
[PDF File (Adobe PDF File), 125 KB - resprot_v12i1e44776_app7.pdf]

Multimedia Appendix 8
Intensive Evaluation and Treatment Program veteran and service member interview script.
[PDF File (Adobe PDF File), 117 KB - resprot_v12i1e44776_app8.pdf]

Multimedia Appendix 9
Intensive Evaluation and Treatment Program Department of Defense stakeholder interview script.
[PDF File (Adobe PDF File), 132 KB - resprot_v12i1e44776_app9.pdf]

Multimedia Appendix 10
Intensive Evaluation and Treatment Program implementation research logic model.
[PDF File (Adobe PDF File), 140 KB - resprot_v12i1e44776_app10.pdf]

Multimedia Appendix 11
Intensive Evaluation and Treatment Program implementation elements.
[PDF File (Adobe PDF File), 106 KB - resprot_v12i1e44776_app11.pdf]

Multimedia Appendix 12
Intensive Evaluation and Treatment Program chart abstraction.
[PDF File (Adobe PDF File), 400 KB - resprot_v12i1e44776_app12.pdf]

Multimedia Appendix 13
Intensive Evaluation and Treatment Program long-term outcomes.
[PDF File (Adobe PDF File), 435 KB - resprot_v12i1e44776_app13.pdf]

Multimedia Appendix 14
Gantt chart of project activities across the 3-year project.
[PDF File (Adobe PDF File), 106 KB - resprot_v12i1e44776_app14.pdf]

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Abbreviations

CFIR: Consolidated Framework for Implementation Research
DoD: Department of Defense
IETP: Intensive Evaluation and Treatment Program
IRLM: implementation research logic model
MPAI: Mayo-Portland Adaptability Inventory
MPI: multiple principal investigator
ORION: Optimizing Rehabilitation Interventions
PEI: partnered evaluation initiative
PHQ-9: Patient Health Questionnaire-9
PM&R: Physical Medicine and Rehabilitation
PTSD: posttraumatic stress disorder
QUERI: Quality Enhancement Research Initiative
SOF: special operational forces
TBI: traumatic brain injury

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TBI-COE: Traumatic Brain Injury–Centers of Excellence
VA: Veterans Affairs
VHA: Veterans Health Administration

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Protocol

Evaluating the Effect of Activity and Environment on Fall Risk in a Paradigm-Depending Laboratory Setting: Protocol for an Experimental Pilot Study

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Abstract

Background: Knowledge about the causal factors leading to falls is still limited, and fall prevention interventions urgently need to be more effective to limit the otherwise increasing burden caused by falls in older people. To identify individual fall risk, it is important to understand the complex interplay of fall-related factors. Although fall events are common, they are seldom observed, and fall reports are often biased. Due to the rapid development of wearable inertial sensors, an objective approach to capture fall events and the corresponding circumstances is provided.

Objective: The aim of this work is to operationalize a prototypical dynamic fall risk model regarding 4 ecologically valid real-world scenarios (opening a door, slipping, tripping, and usage of public transportation). We hypothesize that individual fall risk is associated with an interplay of intrinsic risk factors, activity, and environmental factors that can be estimated by using data measured within a laboratory simulation setting.

Methods: We will recruit 30 community-dwelling people aged 60 years or older. To identify several fall-related intrinsic fall risk factors, appropriate clinical assessments will be selected. The experimental setup is adaptable so that the level of fall risk for each activity and each environmental factor is adjustable. By different levels of difficulty, the effect on the risk of falling will be investigated. An 8-camera motion tracking system will be used to record absolute body motions and limits of stability. All laboratory experiments will also be recorded by inertial sensors (L5, dominant leg) and video camera. Logistic regression analyses will be used to model the association between risk factors and falls. Continuous fall risk will be modeled by generalized linear regression models using margin of stability as outcome parameter.

Results: The results of this project will prove the concept and establish methods to further use the dynamic fall risk model. Recruitment and measurement initially began in October 2020 but were halted because of the COVID-19 pandemic. Recruitment and measurements recommenced in October 2022, and by February 2023, a total of 25 of the planned 30 subjects have been measured.

Conclusions: In the field of fall prevention, a more precise fall risk model will have a significant impact on research leading to more effective prevention approaches. Given the described burden related to falls and the high prevalence, considerable improvements in fall prevention will have a significant impact on individual quality of life and also on society in general by reducing institutionalization and health care costs. The setup will enable the analysis of fall events and their circumstances

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ecologically valid in a laboratory setting and thereby will provide important information to estimate the individual instantaneous fall risk.

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KEYWORDS

fall risk; fall risk factor; fall-related activity; laboratory setting; study protocol; fall; fall risk model; older people; elderly; analysis of fall

Introduction

Falls are the most prominent cause of death due to injuries in older persons [1]. Falls are also a common event leading to serious physical consequences such as fractures as well as reduced quality of life, loss of independence, and institutionalization in nursing homes. In total, 1 in 3 community-dwelling people aged 65 years or older fall at least once a year, and half of them fall multiple times [2,3]. Falls are one of the leading health conditions associated with disability in populations aged 60 years and older [4]. Therefore, research on falls and fall-related aspects has been intensified in the past years.

The current Cochrane Review on fall prevention in community-dwelling older people lists several effective exercise programs [5]. However, there is limited impact at the population level with the risk of falls being reduced between 13% for balance and functional exercises and 22% for multiple types of exercises including resistance training. Tai Chi reduced the fall risk by 20%. Even less effective are interventions in residential aged care [6], where the effect of exercise on risk of falling makes little or even no difference. These numbers clearly show the need for further improvements in fall prevention programs. The limited effectiveness might be due to lacking task-specific exercises required to prevent falls. Perturbation training is a task-specific intervention with the aim to improve a person's reactive balance control under safe laboratory conditions [7]. Recent perturbation studies showed a significant reduction of falls among healthy older adults as well as patients with Parkinson disease and stroke [8]. Furthermore, clinically relevant reductions of fall incidence were shown in frail older adults. It appears that treadmill-based approaches, which enable multiple types and directions of perturbations, might be the most practical method and might be of the most benefit. Although recent studies showed the feasibility of perturbation-based training, conclusions related to the optimal perturbation number and type are difficult to make. Another promising task-specific approach is gait adaptability training [9]. During gait adaptability training, participants respond to environmental challenges by making quick and appropriate voluntary adjustments of gait patterns. A systematic review and meta-analysis by Nørgaard et al [9] showed a reduction of 42% in fall rate, and the proportion of fallers could be reduced by 43% in older adults. These results are in accordance with the results of perturbation-based interventions. It is likely that even more efficient strategies could be informed by a more comprehensive understanding of the causal pathways of falling and fall risk.

Analyses of fall risk factors suggest that we do not fully understand their complex interplay and factors triggering fall events. Meta-analyses identified about 30 fall risk factors for falls in community-dwelling older adults [10]. These include fall history, balance, and gait problems. The published fall risk models are unsatisfying considering the externally validated predictive accuracy. A systematic evaluation of 4 fall prediction tools in residential care showed that each model was unsuitable due to poor precision [11]. Sensitivity and specificity ranged from 0.50 to 0.80 and 0.32 to 0.80, respectively. The web-based FRAT-up (Fall Risk Assessment Tool) fall prediction tool, developed for community-dwelling older people, has an area under the curve of 0.65 and showed heterogeneity in results from different cohorts [12]. The performance of these fall risk models in individuals has been moderate at best and is therefore not sufficient to guide clinical practice and health policy.

With the rapid development of eHealth devices including body-worn sensor technology, small wearable and unobtrusive devices are now available; this can provide objective measures of physical activity, kinematics of human movement [13], and falls during everyday life [14]. Additionally, it is possible to examine environmental factors such as stairs, weather conditions, or indoor or outdoor environments using combinations of monitoring systems. Adding these measurements such as gait intensity and gait complexity to clinical risk factors improves the area under the curve for fall prediction from 0.68 to 0.82 [15]. However, the most important risk factor still remains the history of a prior fall. Other recent studies using information and computer technology to predict falls showed similar results. Internal and external validity is not yet firmly established as some models have been developed and validated on the same samples; thus, replication is required [16,17]. Furthermore, most of the above information and computer technology studies have limitations. They have used fall history, clinical fall risk assessment, or both to define fall risk, instead of the gold standard measure, which remains the prospective fall ascertainment [18].

Even if it is possible to replicate the results, there is still a large number of falls that are not predicted. Furthermore, a rarely discussed aspect in fall risk estimation is the time frame of prediction in which the event of interest occurs. A simple distinction between fallers and nonfallers is insufficient as most people will fall if the period of observation is long enough. The time window of prediction in most studies is 1 year based on the follow-up duration of the prospective fall recording. However, the question remains whether this follow-up period is sufficient or which period is necessary to cover a relevant fall risk. This question is also relevant in terms of feasibility for a

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clinical trial. Furthermore, the necessary duration may also depend on whether a fall is more likely due to a chronic disease or if a fall is merely due to random unpredictable circumstances. For effective and acceptable fall prevention measures on an individual level, much shorter prediction windows may be needed. In this context, an intervention that is able to directly test fall risk by exposing participant to hazardous ecologically valid situations would be conceivable.

Rubenstein and Josephson [19] drafted a conceptual model, which includes intrinsic risk factors, extrinsic risk factors, and precipitating causes. Klenk et al [20] further developed this concept by structuring the components and adding the dynamic nature of fall risk and thereby suggested a modified model, which includes intrinsic risk factors and the exposure. The model considers that fall risk factors may change over time due to individual and temporary exposure to hazardous situations, environmental factors, and unexpected events. Furthermore, different activities pose different levels of hazard, for example, it is riskier to run than to walk.

The complex interplay of different factors results in an individual instantaneous fall risk. If a person with impaired balance walks over slippery ground, the risk of falling is increased compared to a person with balance impairment who walks fast on dry ground.

The impact of one or more activities undertaken at the same time varies depending on cognitive capacity and environmental conditions. For instance, walking on an uneven surface while talking may result in a fall, whereas talking and walking on a smooth surface may not. Similarly, an unexpected event, such as a perturbation, or a visual startle may disrupt an otherwise simple maneuver. We posit that all mentioned components of risk do not simply sum linearly to a total, but the way they could be combined is likely to be complex. Components change over time, and the impact of the components could be additive, multiplicative, or weighted. A fall event occurs when the interplay of intrinsic risk factors and exposures reaches a threshold.

To operationalize the different components of the dynamic fall risk model, real-world fall events with detailed information about the fall events are necessary. Although falls are common, it is challenging to capture real-world fall signals due to the limited recording capacities of sensor devices. However, the Fall Repository for the Design of Smart and Self-adaptive Environments Prolonging Independent Living (FARSEEING) consortium, funded by the 7th EU Framework Program for Research, started to collect an ample data set of real-world falls by a preplanned collaboration of many research groups. Within the European FARSEEING project, a database of more than 200 validated real-world falls of older people measured by body-worn sensor technology was compiled [21]. First results in the field of fall detection show the potential to bridge existing knowledge gaps [22,23]. The fall events, collected in the FARSEEING database, provide the possibility to obtain knowledge concerning ecologically valid real-world fall scenarios, activities that were performed immediately before the fall as well as environmental factors.

However, most sensor devices are not able to provide information about context and environmental conditions as well as intrinsic fall risk factors triggering a fall event. The information available so far is not sufficient. A promising approach to add missing information is the re-enactment of known fall events. Connell and Wolf [24] previously proposed the method to validate subjective fall reports. Participants were interviewed and asked to re-enact in detail (if they felt comfortable) all activities, body movements, body part placements, and interactions with the environment at the location of the incident to obtain more precise information. Re-enactment is suitable in order to improve simulation protocols and produce more realistic fall simulations [25]. However, to further improve simulation settings and gain more knowledge, controllable and repeatable conditions are needed, which also realistically correspond to everyday situations. For certain everyday situations, these criteria can be met within a laboratory setting. This approach allows intrinsic risk factors as well as instantaneous dynamic risks (eg, activities and environmental conditions) and their complex interplay to be investigated in a controlled condition in realistically re-enacted everyday situations and thereby to provide a more comprehensive understanding of the causal mechanisms of falling and fall risk.

Therefore, we developed a setup to provide an experimental environment to simulate and measure selected paradigms under different conditions and adjustable factors in order to find individual fall thresholds. In this paper, we describe an experimental laboratory setting based on 4 ecologically valid real-world scenarios and the planned pilot study that will provide the data to operationalize a first simplified dynamic fall risk model.

Methods

Study Design

This study has an experimental design to analyze the interplay between intrinsic fall risk factors and exposure to hazardous environmental conditions and activity. All participants will obtain extensive clinical and quantitative assessment as well as perform the study protocol to evaluate the effect of different conditions on the individual fall risk in accordance with the study protocol at the Robert-Bosch-Hospital, Stuttgart.

Eligibility Criteria

German-speaking, community-dwelling, healthy as well as prefrail people aged 60 years or older will be recruited. Exclusion criteria are current diagnosis of a serious neurological or sensory disease; uncorrected visual difficulties; dizziness; uncontrolled or serious cardiovascular, metabolic, or psychiatric disorders; cognitive restriction and manifest daily relevant dementia; contraindications for perturbations, including osteoporosis, joint replacement, joint stiffening, severe spinal disease, or recent fracture as well as people who are unable to walk at least 5 minutes freely.

Recruitment

Participants (N=30) will be recruited from an existing pool of subjects who have already participated in studies and have given their written consent to participate in further studies. To obtain

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sufficiently meaningful results, see if the experimental setup needs adaption, and test the feasibility within this pilot study, sample size is sufficiently high and chosen pragmatically but not estimated [26]. Overall, 20 subjects will be used for the development of the prototypical fall risk model, and 10 subjects will be used for validation. Ideally, half of the subjects would be considered prefrail, but prefrail subjects may drop out during the experiment or will not participate at all. Participants will be contacted via telephone and informed about the study and the procedure if they are interested.

Clinical Assessments

To identify several fall-related intrinsic fall risk factors relevant to the model development and describe the cohort, appropriate clinical assessments were selected. The estimated total duration of clinical assessments and the trial protocol will be 120 minutes. Clinical assessments will be carried out for all participants before the experimental protocol. All assessments will be performed by trained assessors.

Clinical data like sex, age, body weight (BW), physical activity as well as medical history will be assessed. Furthermore, general state of health and comorbidity will be assessed using the Functional Comorbidity Index [27].

Occurrence of falls during the last 12 months will be inquired. For the assessment of fall-related self-efficacy, the Short Form of the Falls Efficacy Scale-International will be used. This scale has been shown to be highly related to previous and subsequent falling [28].

Physical performance will be assessed by the Short Physical Performance Battery [29] and the Timed Up-and-Go Test [30]. People who need >12 seconds for the Timed Up-and-Go test will be classified as individuals at a higher risk of falling [31]. Regarding the cutoff value of 12 seconds, we followed Jansen et al [31], who lowered the threshold of 13.5 seconds originally defined by Barry et al [32]. Additional gait analysis will be conducted for habitual and fast walking speed. Furthermore, gait analysis will be performed under dual-task conditions (fast gait speed and counting backward minus 7 beginning with 100). Cognitive condition will be examined using the Trail-Making-Test [33]. Assessment measurements are listed in Textbox 1.

Textbox 1. Listing of demographic and medical data as well as assessments.

Sociodemography

- Age and gender

Medical information

- Height, weight, BMI, comorbidities, occurrence of fatigue, and weight loss

Physical activity status

- Questionnaire: physical activity during the last 2 weeks
- Fall history and fall-related injuries in the past 12 months

Fear of falling

- Short Falls Efficacy Scale International [28]

Motor function

- Short Physical Performance Battery [29]
- Timed Up-and-Go [30]
- Gait performance (usual or fast pace, dual-task condition)

Cognitive status

- Trail-Making-Test [33]

Experimental Setup

Overview

All participants will perform the same protocol. The fall simulation experiments will collect the data needed to develop the simplified mathematical dynamic fall risk model. Ideally, the activities performed should not give the impression of a simulation for the subjects. They should behave as they would naturally, and our objective is to provoke a reaction that ideally cannot be consciously influenced by the individual. Due to safety reasons and to avoid injuries, participants will wear a safety harness that prevents any contact of the body with the ground except the feet. The safety system is adjusted accordingly. Also, the treadmill can be stopped immediately at any time by the trained study assistant who is always standing next to the treadmill at an emergency stop button during the measurements. The test protocol will comprise a series of the selected activities without and in combination with mediating environmental factors. The experimental setup has to be adaptable meaning that it is possible to adjust the level of fall risk for each activity and each environmental factor. The level of difficulty will be stepwise increased for each participant. The registration of more than 30% of the BW on a load cell attached

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to the safety harness will be used to define a fall event [34]. Several prototypical examples of everyday fall scenarios have been recorded in the FARSEEING database [21]. Based on this data, we will consider four prototypical scenarios, which are common and relevant from a public health perspective: (1) falling during walking backward while opening the door, (2) falling due to slippery surface, (3) falling due to a trip over an obstacle, and (4) falling in a bus while the bus is starting.

An experimental setup for each selected scenario will be established in the laboratory. The 4 selected fall scenarios and their implementation in the laboratory are shown in Figure 1.

Figure 1. Illustration of the 4 selected everyday fall-related scenarios and their implementation in the laboratory. (A) Opening a door, (B) slippery surface, (C) tripping over an obstacle, and (D) usage of public transportation.



Opening a Door

In front of the participant is a custom-built wooden door–like frame. Participants will be instructed to open the door. Following this baseline measurement, the participants will be repeatedly asked to open the door with additional activities and environmental factors: opening the door as fast as possible, carrying a laundry basket, balancing a ball on a scoop, and opening a rough-running door. The laundry basket will be represented by a wooden frame with handles to cause less occlusion (Figure 2). To simulate a rough running door, the door will be equipped with a neodymium magnet that increases the resistance when opening.

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Figure 2. Equipment for additional tasks: carrying a wooden frame that represents a laundry basket, carrying a backpack, balancing a ball on a scoop, and playing with a memory buzzer.



Slippery Surface

Within this scenario, participants will wear shoe covers while walking over an aluminum di-bond plate, so that there will be reduced ground friction. To make it harder to maintain balance, the following factors will be stepwise added and combined: walking as fast as possible, balancing a ball on a scoop, usage of a memory buzzer to increase cognitive load (Figure 2), walking up and down the inclined (5%) treadmill (h/p/cosmos venus; length 200 cm, width 75 cm, h/p/cosmos sports medical GmbH).

Tripping Over an Obstacle

Two retaining plates will be attached to the participants' heels with a custom-built fixation. At first, the participants will walk on the treadmill with self-selected gait speed in order to get used to the treadmill. After habituation, a neodymium magnet will be stuck to the retaining plate at the participants' heels (magnetic adhesive force=41 kg). The magnet will be connected to inelastic cords and will ensure that the blockage of the leg can be broken by detaching the magnet when swinging the affected leg forward. The 2 inelastic cords will be attached behind the treadmill, which will be shortened or lengthened with low resistance by a coil spring while the participant is walking. The continuous length variation of the cords can be interrupted at the push of a button. When pushing the button at the end of the stance phase, the subsequent swing phase is perturbed. In random time intervals, the participants' feet will be blocked for a very short moment until the button is released or the magnet is detached from the retaining plate in order to perturb the swing phase but enable continuous walking afterward without stopping or limping. The series of perturbations will be determined in advance and will be unknown to the participants. Additional factors will be carrying a laundry basket, playing with the memory buzzer, and increasing the self-selected gait speed by 33%.

Usage of Public Transportation

To simulate the starting of a bus, participants will stand on the resting treadmill, and suddenly the treadmill belt will be accelerated. By means of the coscom interface protocol coscom v4, acceleration values and duration as well as target speed can be accessed. A custom application is written in Python for this purpose. Each participant will start with several forward and medio-lateral right perturbations with lower intensity to become familiar with the perturbations and choose an individual standing position that is not allowed to be changed during the experiments. The selected position shall correspond to the position that the participants would also choose on a bus. Concerning forward perturbations, the treadmill will be accelerated for 1 second and thereby will reach a maximum acceleration of 1.61 m/s^2. Participants will stand against the running direction of the treadmill belt. Concerning sideward perturbations, the treadmill will accelerate for 0.75 seconds and will reach a maximum acceleration of 1.51 m/s^2. To realize sideward perturbations, the participants will stand crosswise to the running direction of the treadmill belt. In Stuttgart, Germany, Lindemann et al [35] measured the incident-type acceleration from standing extreme values of acceleration of 3.37 m/s^2 in buses. Therefore, the maximal possible acceleration values within this study will be lower compared to the real-life ones, but due to safety conditions and technical limitations, no higher acceleration will be realizable. Acceleration from resting state and stopping to standing of the treadmill belt depends on length of the treadmill. The entire acceleration and deceleration process has to result in a movement of the treadmill belt less than 2 m. By doing so, the subjects will not fall off the treadmill in case

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they would not do any recovery steps. After baseline measurement, which represents the participants' reaction to the perturbation without an additional factor, one or more additional factors will be combined. The additional factors for this fall scenario will be hearing bus-related noise, wearing a backpack, and playing with the memory buzzer. The backpack will be loaded with 10% of the subject's BW and will be carried symmetrically. Sahli et al [36] demonstrated that carrying a backpack loaded with 10% BW seems to alter balance of adolescents with mild idiopathic scoliosis.

Measurement Instruments

An 8-camera VICON T10 system (Vicon Motion Systems Ltd UK) will be used to record absolute body motions and limits of stability using the Plug-in-Gait full-body marker model. The VICON motion tracking system is able to measure a person's movement and duration very precisely.

To record further parameters, we will use 2 wearable sensors (Blue Trident inertial measurement unit, Vicon Motion Systems Ltd UK) with a combined triaxial accelerometer (sampling rate 1125 Hz; range ±16 g) and triaxial gyroscope (frequency 1125 Hz; range ±2000°/s). The sensors will be fixed with a custom-built elastic belt. Two synchronized Blue Trident inertial measurement units (Vicon Motion Systems Ltd UK) will be connected to the system. One will be attached to the lower back at L5 position, and the other one will be attached to the dominant leg at ankle height. To validate the results from the body-worn sensors, all laboratory experiments in this project will also be recorded by a video camera (Basler pilot piA640-210gc).

Participants' Safety and Adverse Events

All study participants will receive instructions for safe performance (shoes and safety harness) and will be asked to perform all paradigms as long as they feel comfortable. During the laboratory experiments, the participants will be protected from falling by a safety harness. Serious adverse events related or potentially related to the study participation will be reported to the responsible ethic review board.

Ethics Approval

The study will be conducted according to Good Clinical Practice and in accordance with the principles of the Declaration of Helsinki 1964 and all subsequent revisions. All procedures are approved by the local ethics committee (University of Tübingen, 245/2018BO2). All participants will have to give their written informed consent and will be insured. All project staff is bound by confidentiality. The results of the data collection in written form are subsequently digitized for evaluation. All data are pseudonymized. If a subject withdraws his or her consent, the corresponding data will be deleted immediately.

Outcome Measure and Data Analysis

Primary outcome will be the number of falls experienced by the participants during the experiment. Furthermore, the concept of margin of stability (MoS) will be used as a continuous measure to quantify the risk of falling [37]. MoS indicates the distance between the base of support of a person and the extrapolated center of mass in static and dynamic conditions.

As previously described, sociodemographic and medical information, physical activity status, fear of falling as well as motor function will be assessed and subsequently included as factors in the dynamic fall risk model.

The estimation of a person's individual fall risk will be based on the collected data. In the first step, logistic regression analyses will be used to model the association among activity characteristics, environmental fall risk factors, and falls. The optimal model for each scenario will be selected by receiver operating characteristic analyses. In the second step, continuous fall risk will be modeled by generalized linear regression models using MoS as outcome parameter. Nonlinear associations and interactions will be tested and modeled, if necessary.

Participants who will drop out or incomplete data will be included as long as the data set for at least 1 scenario is complete. It is planned to use the data sets of 20 subjects for model development, the other 10 data sets will be used for validation.

Results

This study was initially designed to begin recruitment in July 2020 after ethics approval has been received. First, measurements took place in October 2020, but not all subjects could be measured as planned because of the COVID-19 pandemic. Due to access restrictions in hospitals and difficulties in recruitment as a result of a lack of willingness in the target group to participate in the study, further measurements were not conducted until October 2022. In the meantime, the already recorded data were processed and prepared for subsequent analyses. Up to February 2023, a total of 25 of the planned 30 subjects have been measured. The submission of the manuscript including complete results is expected by August 2023.

Discussion

Principal Findings

Older people fall frequently with serious consequences, including injury and hospitalization. However, the knowledge about the causal factors leading to falls is still limited, and fall prevention interventions need to be more effective to limit the otherwise increasing burden caused by falls in older people. Therefore, the aim of this project is to operationalize a dynamic fall risk model by focusing on the time period close to the fall event where all domains of the dynamic fall risk model cumulate. This will help to further understand the complex interplay triggering a fall event.

To the best of our knowledge, this planned study is the first approach to assess the complex interplay of intrinsic risk factors and environment and activity exposure under controlled but realistic experimental conditions. We will consider 4 prototypical scenarios that are common and relevant from a public health perspective. The model-based assessment of fall risk under (simulated) real-life conditions in a safe environment will enable the systematic analysis of the complex relationship between fall risk factors. Based on the planned analysis of the MoS, even small perturbations that will not immediately lead to a fall show an effect on a person's dynamic stability. Such

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an in-laboratory fall simulation environment might also serve as an outcome parameter for intervention studies. A rarely discussed aspect in fall risk estimation is the required time window of prediction in which the fall event occurs. A simple distinction between fallers and nonfallers is not sufficient as most people will fall if the period of observation is long enough. The time frame of prediction in most studies is 1 year. However, the question remains whether this follow-up period is sufficient or which period is necessary to cover a relevant fall risk. For effective and acceptable fall prevention measures on an individual level, much shorter prediction windows may be needed. This would reduce costs and speed up the development of new fall prevention measures. In this context, an intervention that is able to directly test fall risk by exposing participant to hazardous ecologically valid situations would be conceivable.

Limitations

Nevertheless, this study has some limitations. First, the sample size will be relatively small. However, the subjects will be tested extensively with a standardized protocol. This setting will allow the extraction of relevant information and the development of the dynamic fall risk model. Although the laboratory setting will approach natural conditions, it will remain artificial insofar that subjects will partially walk on a treadmill in a sparse environment. Furthermore, the subjects will be aware of the objective of the study: reaching the fall threshold by creating a situation that becomes stepwise more challenging. In contrast, falls are a sudden and mostly unexpected event during everyday life, and normally, a person would not anticipate a falling situation. Another aspect is the acceleration of the treadmill belt. To simulate the starting of a bus, the treadmill will accelerate with a maximum of 1.61 m/s^2 due to safety reasons and technical limitation. Lindemann et al [35] measured extreme values of acceleration of 3.37 m/s^2 in buses. Therefore, the maximal possible acceleration is lower compared to the real-life ones. However, we believe that this setup will allow analysis of the association of environmental as well as intrinsic factors and activity exposure and thereby will lead to a better understanding of the complex interplay triggering fall events in individuals.

Conclusions

The results of the described study have the potential to expand knowledge regarding the complex interplay between environmental conditions, activities, and intrinsic fall risk factors triggering a fall event. The operationalization of the described prototypical dynamic fall risk model will enable the estimation of an individual fall risk and thereby improve several fields of fall prevention.

Acknowledgments

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Data Availability

Part of the data will be presented in the main manuscript. Raw data are not publicly available to preserve individuals' privacy under the European General Data Protection Regulation.

Conflicts of Interest

None declared.

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Abbreviations

BW: body weight
FARSEEING: Fall Repository for the Design of Smart and Self-adaptive Environments Prolonging Independent Living
FRAT: Fall Risk Assessment Tool
MoS: margin of stability

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Protocol

Promoting Evidence-Based Tobacco Cessation Treatment in Community Mental Health Clinics: Protocol for a Prepost Intervention Study

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Abstract

Background: Tobacco smoking is highly prevalent among persons with serious mental illness (SMI) and is the largest contributor to premature mortality in this population. Evidence-based smoking cessation therapy with medications and behavioral counseling is effective for persons with SMI, but few receive this treatment. Mental health providers have extensive experience working with clients with SMI and frequent treatment contacts, making them well positioned to deliver smoking cessation treatment. However, few mental health providers feel adequately trained to deliver this treatment, and many providers believe that smokers with SMI are not interested in quitting or have concerns about the safety of smoking cessation pharmacotherapy, despite substantial evidence to the contrary.

Objective: We present the protocol for the pilot "IMPACT" (Implementing Action for Tobacco Smoking Cessation Treatment) study, which aims to pilot test a multicomponent implementation intervention to increase the delivery of evidence-based tobacco smoking cessation treatment in community mental health clinics.

Methods: We are using a prepost observational design to examine the effects of an implementation intervention designed to improve mental health providers' delivery of the following four evidence-based practices related to smoking cessation treatment: (1) assessment of smoking status, (2) assessment of willingness to quit, (3) behavioral counseling, and (4) pharmacotherapy prescribing. To overcome key barriers related to providers' knowledge and self-efficacy of smoking cessation treatment, the study will leverage implementation strategies including (1) real-time and web-based training for mental health providers about evidence-based smoking cessation treatment and motivational interviewing, including an avatar practice module; (2) a tobacco smoking treatment protocol; (3) expert consultation; (4) coaching; and (5) organizational strategy meetings. We will use surveys and in-depth interviews to assess the implementation intervention's effects on providers' knowledge and self-efficacy, the mechanisms of change targeted by the intervention, as well as providers' perceptions of the acceptability, appropriateness, and feasibility of both the evidence-based practices and implementation strategies. We will use data on care delivery to assess providers' implementation of evidence-based smoking cessation practices.

Results: The IMPACT study is being conducted at 5 clinic sites. More than 50 providers have been enrolled, exceeding our recruitment target. The study is ongoing.

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Conclusions: In order for persons with SMI to realize the benefits of smoking cessation treatment, it is important for clinicians to implement evidence-based practices successfully. This pilot study will result in a set of training modules, implementation tools, and resources for clinicians working in community mental health clinics to address tobacco smoking with their clients. Trial Registration: ClinicalTrials.gov NCT04796961; https://clinicaltrials.gov/ct2/show/NCT04796961

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KEYWORDS

coaching; expert consultation; implementation; motivational interviewing; self-efficacy; serious mental illness; smoking cessation; system-level intervention; tobacco dependence

Introduction

Tobacco smoking is the largest contributor to premature mortality among persons with serious mental illness (SMI) [1-4]. An estimated 53% of US adults with SMI smoke tobacco [5], compared to 14% of US adults overall [6]. In general, US smoking rates have declined dramatically over the past 50 years, but smoking has persisted at consistently high rates among those with SMI [7,8], even though the majority of persons with SMI who smoke would like to quit [9]. Pharmacotherapy combined with behavioral counseling is effective and safe for people with SMI [10-13] and increases abstinence rates by up to 7 times over behavioral counseling alone [11,14].

The provision of effective, evidence-based smoking cessation treatment could substantially reduce the premature mortality experienced by people with SMI; however, few in this group receive evidence-based treatment [15-20]. In a large Maryland behavioral health system, less than 5% of persons with schizophrenia who smoke are prescribed evidence-based smoking cessation pharmacotherapy [8]. Limited available research shows similarly low rates of smoking cessation pharmacotherapy as well as behavioral smoking cessation counseling [21] delivery to the individuals with SMI who smoke in other states [15,18].

As many people with SMI receive the majority of their health care from the specialty mental health sector [22-24] and tobacco smoking is not typically a target behavior in mental health settings [21,22], it is critical to prepare mental health providers to deliver evidence-based smoking cessation treatment. Achieving this goal will require addressing knowledge and self-efficacy barriers among clinicians, including skepticism that people with SMI want to quit smoking, misperceptions about cessation treatment efficacy and safety for this group, and low self-efficacy to deliver evidence-based smoking cessation treatment for clients with SMI [15,25-28]. Mental health providers may also perceive smoking cessation treatment as outside their scope of practice [15,25-28]. Clinic-level barriers to treatment, such as lack of systems for assessing smoking status and interest in quitting among clients with SMI, may also need to be addressed [25,26]. Despite these known barriers, few published studies have evaluated implementation strategies to increase mental health providers' delivery of evidence-based smoking cessation pharmacotherapy and counseling for people with SMI [29].

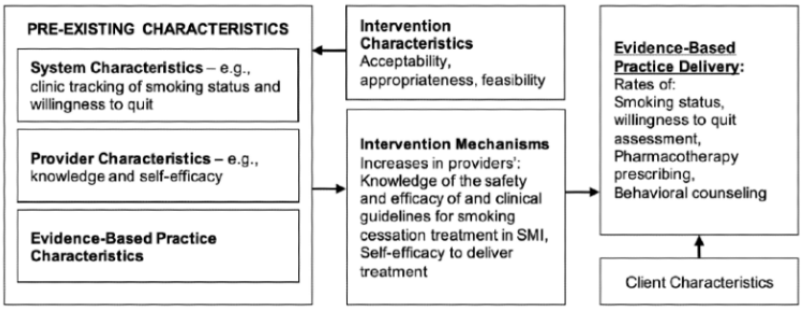
This protocol describes a pilot study of an implementation intervention of evidence-based smoking cessation treatment in community mental health clinics. We developed and are testing an implementation intervention designed to improve mental health providers' knowledge, self-efficacy, and delivery of evidence-based smoking cessation treatment. The shorthand name for the study is "IMPACT" (Implementing Action for Tobacco Smoking Cessation Treatment).

Methods

Conceptual Framework

Our study is grounded in Gurses et al's [30] model of interdisciplinary factors which promote clinicians' compliance with evidence-based guidelines. As shown in Figure 1, the model posits the importance of preexisting characteristics of the system (eg, tools and technologies and physical environment), providers (eg, knowledge and attitudes), and guideline characteristics (eg, relative advantage and complexity). These factors affect the implementation intervention characteristics (ie, how and when a practice is implemented) and mechanisms that, in turn, affect the delivery of evidence-based practices.

Figure 1. Gurses' interdisciplinary conceptual framework of clinician's compliance with evidence-based guidelines [30].



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Pilot Study Design

This is a prepost study examining the effects of a 12-month implementation intervention on providers' knowledge and self-efficacy and the mechanisms through which the implementation intervention is designed to improve the delivery of evidence-based smoking cessation treatment. We will also evaluate the effects of the implementation intervention on the delivery of evidence-based practices for smoking cessation. In addition, we will analyze measures of providers' perceptions of the acceptability, feasibility, and appropriateness of the implementation strategies and the IMPACT evidence-based practices.

Setting and Sample

The study is conducted in 5 community mental health clinics, all of which serve persons with SMI. Provider participants are employees of the community mental health organizations, including leaders and mental health clinicians (prescribers, including psychiatrists, nurse practitioners, and primary care physicians, therapists, and other clinicians, including licensed counselors, psychologists, social workers, and nurses). Data will also be analyzed from the clients served by the clinics around their receipt of the evidence-based practices. The research was approved by the Johns Hopkins University School of Medicine Institutional Review Board (IRB) (#IRB00231836).

Evidence-Based Practices

The intervention includes the following four evidence-based practices for smoking cessation that are based on consensus guidelines, recommendations for persons with SMI, and recent clinical trials [10,11,13,31-33]:

1. Assessment of smoking status involves asking adult clinic clients if they currently smoke tobacco and, if they respond yes, further assessing the severity of tobacco dependence [34].
2. Assessment of willingness to quit uses stage-of-change questions [34]. In this project, we classify those endorsing setting a quit date within 12 weeks as ready for active cessation treatment [35]. We targeted willingness to quit within 12 weeks rather than the standard 30 days in order to include motivational enhancement strategies for those not ready to commit to a quit date within 1 month and to give adequate time to complete behavioral counseling and achieve smoking cessation for those interested in quitting [36].
3. The focus of the behavioral counseling will vary depending on clients' willingness to quit. For clients who are not interested in quitting within 12 weeks, behavioral counseling entails an immediate, brief session (<10 minutes) using motivational interviewing techniques to explore the pros and cons of smoking, elicit client concerns about their smoking, and identify potential benefits of quitting [37]. The provider will also discuss the resources available to help the client if they decide to work toward quitting, including the benefits of using smoking cessation medications. Those clients who express a willingness to quit will be referred for ongoing smoking cessation behavioral counseling [36] and smoking cessation pharmacotherapy. The counseling sessions, which can occur remotely or in person, are cognitively tailored for those with SMI and address standard topics (eg, identifying personal reasons to quit, addressing smoking triggers, coping with nicotine withdrawal, and preparing for the quit date) [38]. Clients who do not quit are encouraged to continue counseling if they are interested in making a future quit attempt. When a client quits, counseling then focuses on relapse prevention, including refusal skills, responding to permission-giving beliefs, and developing personalized relapse prevention plans.
4. The fourth evidence-based practice is pharmacotherapy prescribing, in which a prescribing physician or nurse practitioner meets with clients undergoing smoking cessation behavioral counseling to encourage use of 1 of the following 3 Food and Drug Administration (FDA)–approved treatments: varenicline with or without nicotine replacement therapy (NRT), bupropion SR with or without NRT, or NRT alone [34]. When NRT is used, combination NRT (transdermal patch + lozenge or gum) is recommended. Medication choice is made by the prescriber in a collaborative discussion with the client, taking into account factors such as differential effectiveness, potential side effects, and clinical profile (eg, seizure history). Therapists and prescribers regularly share care of clients and will communicate about smoking cessation plans. Medication may continue for 1 year or longer as relapse rates are high without ongoing pharmacotherapy, particularly for those with SMI [10]. Those not willing to quit within 12 weeks will be offered, and if interested, referred for, a 1-month trial of varenicline to increase their readiness to quit [39]. The goal is that all clients who smoke should be offered treatment with a first-line smoking cessation pharmacotherapy, preferentially varenicline or combination NRT [40].

Implementation Strategies

Overview

To improve mental health providers' knowledge, self-efficacy, and delivery of evidence-based practices, the study will employ the following five implementation strategies: (1) training on evidence-based smoking cessation treatment, including an innovative web-based avatar module for motivational interviewing practice; (2) a tobacco smoking treatment protocol; (3) expert consultation for prescribers and therapists; (4) coaching; and (5) organizational strategy meetings (OSMs). A more detailed description of each component is outlined below.

Training

Trainings are conducted by study staff. All provider participants in the IMPACT project complete 1 hour of prerecorded web-based training modules. Then, therapists and prescribers use a video conferencing platform to participate in real-time training on delivering smoking cessation behavioral counseling, prescribing smoking cessation pharmacotherapy, and using motivational interviewing counseling skills when having conversations with clients about their smoking. Trainings are housed in a web-based management system that enables tracking

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of provider participation as well as continuing education credit. The training outline is shown in Textbox 1.

The real-time motivational interviewing training is supplemented with a web-based avatar practice module developed in partnership with Kognito [41,42]. The module includes a 15-minute didactic component during which clinicians are reminded about motivational interviewing techniques that can be used to guide clients with SMI toward health behavior changes and a 15-minute conversation simulation during which providers assume the role of a provider avatar and use motivational interviewing to discuss smoking cessation with a client avatar. A web-based avatar with simulated conversations enables the learner to use and receive immediate feedback about how different responses in a clinical encounter affect a conversation with a patient in which smoking cessation is discussed. The avatar is appealing and can be accessed at the convenience of the learner. Clinicians are encouraged to use the platform once per month throughout the intervention.

Textbox 1. Outline of provider training.

Prescribers (psychiatrists and nurse practitioners):

- Online training modules (1 hour)
  - Module 1: Why IMPACT (Implementing Action for Tobacco Smoking Cessation Treatment)?
  - Module 2: Evidence-based treatment for smoking cessation for persons with serious mental illness (SMI)
  - Module 3: Assessing smoking status willingness to quit
  - Module 4: Pharmacotherapy for smoking cessation
- Real-time trainings (in person or videoconferencing platform) (2 hours)
  - Training 1 (1 hour): Facilitating smoking cessation conversations
  - Training 2 (1 hour): Motivational interviewing approach to smoking cessation pharmacotherapy
- Online motivational interviewing avatar (recommended monthly 15-minute practice sessions)

Therapists (psychologists, social workers, counselors):

- Online training modules (1 hour)
  - Module 1: Why IMPACT?
  - Module 2: Evidence-based treatment for smoking cessation for persons with SMI
  - Module 3: Assessing smoking status willingness to quit
  - Module 4: Pharmacotherapy for smoking cessation
- Real-time trainings (in person or zoom) (4 hours)
  - Training 1 (2 hours): Facilitating smoking cessation conversations and an overview of behavioral counseling
  - Training 2 (2 hours): Motivational interviewing approach to smoking cessation behavioral counseling
- Online motivational interviewing avatar (recommended monthly 15-minute practice sessions)

Tobacco Smoking Treatment Protocol

The research team developed a tobacco smoking treatment protocol to assist clinicians in delivering evidence-based smoking cessation treatment. This protocol includes a resource guide that provides an overview of the IMPACT program and will help clinicians navigate their work on the project. Clients who report being current smokers (ie, have smoked a tobacco product in the past 7 days) are assessed for their willingness to quit. Based on client responses to the tobacco smoking status and willingness-to-quit assessment, instructions help clinicians facilitate brief smoking cessation conversations; all clients interested in quitting will be offered treatment. Clinicians are provided manuals for delivering smoking cessation behavioral counseling sessions and prescribing pharmacotherapy.

The smoking cessation behavioral counseling manual includes the outline for 13 session topics that can be delivered flexibly based on the client's current smoking status and the provider's judgment about what would be most helpful (see Table 1). A smoking cessation session may be "standalone" or part of a regularly scheduled therapy session and is designed to be 10-15 minutes in duration. Each session is expected to include an assessment of the client's past week's average cigarettes smoked per day, current smoking status and review of quit attempts since the previous visit, new session content, and collaborative identification of a smoking-related behavioral goal to focus on until the next therapy session.

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Table 1. Topics of behavioral counseling sessions.

Session	Topic[a]
1	Introduction: positives and negatives of smoking
2	Health effects of smoking and benefits of quitting
3	Smoking cessation pharmacotherapy to help you quit
4	Barriers to quitting and the 4 D's
5	Identifying triggers and high-risk situations
6	Smoking cessation medication adherence and coping with side effects
7	Planning for the quit day
8	Withdrawal symptoms and coping with withdrawal symptoms
9	Quit day follow-up
10	Developing a "Stay Quit" plan
11	Permission-giving beliefs and how to respond to them without smoking
12	Dealing with slips
13	Coping with symptoms of SMI[b] and staying strong

[a]Order and selection of topics to be made by therapists based on their clinical judgment and on the smoking status of the client.

[b]SMI: serious mental illness.

Expert Consultation

Expert consultation is available for prescribers and therapists to discuss issues and ask questions related to smoking cessation pharmacotherapy and behavioral counseling. Study team members who are experts in smoking cessation pharmacotherapy and behavioral counseling are available during the 12-month intervention to conduct as-needed phone or email consultation with clinicians.

Coaching

Coaching is available for therapists and prescribers to discuss specific client cases, develop smoking cessation behavioral counseling skills, and answer questions about prescribing smoking cessation pharmacotherapy. The coaching sessions, which will be offered monthly through a videoconferencing platform, will focus on skill development, overcoming barriers to providing evidence-based smoking cessation treatment, and additional training as requested. To increase participation, we aim to incorporate coaching sessions into regularly scheduled clinic meetings but will schedule individual coaching sessions as needed. The expectation is that providers attend at least one session per quarter.

Framework of OSMs

OSMs are designed to improve engagement in practice change. These meetings will occur monthly and consist of a 2-to-3–member clinic leadership team, including providers and staff leaders. OSMs will be a chance for the study team to work with the clinic to identify successful organizational-level processes, share implementation data, provide feedback, and problem-solve to overcome identified barriers to program delivery.

Data Collection

Data will be obtained from several sources, including provider surveys, provider interviews, web-based data collection regarding provider participation in training, and client data from the electronic medical record. Providers will be surveyed either by email with instructions and a link to the study assessments in the REDCap software or by paper-and-pencil, depending on-site preference; these assessments will be administered at baseline and at 12 months. Table 2 presents a summary of data collection and measures. Assessments will include measures of providers' knowledge about smoking cessation, self-efficacy about delivering smoking cessation treatment, motivation to deliver evidence-based practices, and beliefs about and confidence in using motivational interviewing. The surveys will also assess providers' views of the acceptability, appropriateness, and feasibility of the intervention and of the implementation strategies, implementation climate of the organization, and providers' social network ties within the organization. A convenience sample of providers and clinic leaders also will be interviewed at baseline and 12 months to elicit their perceptions of the intervention, implementation barriers and facilitators, and the implementation strategies used to overcome barriers.

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Table 2. Study data collection.

Measure	Description	Participants	Timing
Provider interviews	• Semistructured interviews using a standard protocol that will elicit providers' perceptions of barriers to smoking cessation treatment and implementation strategies to overcome barriers.	Selected providers, clinic director	Baseline, 12 months
Demographic characteristics	• Age, gender, race or ethnicity, length of time at program, role in program, years at clinic, work hours, previous motivational interviewing training	All providers, clinic leaders	Baseline
Knowledge of evidence-based smoking cessation treatment	• A 16-item scale developed by our team to assess knowledge	All providers	Baseline, 12 months
Self-efficacy	• To deliver evidence-based smoking cessation treatment, adapted version of Compeau and Higgins' task-focused self-efficacy scale [43]	All providers	Baseline, 12 months
Implementation climate	• A measure of the degree to which an organization supports evidence-based practice implementation [44]	All providers, selected clinic leaders	Baseline
Acceptability, appropriateness, and feasibility of the intervention implementation strategies	• Measured with a brief 4-item practice instrument (AIM[a], IAM[b], FIM[c]) [45]	All providers, selected clinic leaders	Baseline, 12 months
Acceptability, appropriateness, and feasibility of the evidence-based practice	• Measured with a brief 4-item practice instrument (AIM, IAM, FIM) [45]	All providers, selected clinic leaders	Baseline, 12 months
Clinic social network	• A 4-question survey used to collect data about social networks	All providers, selected clinic leaders	Baseline, 6, 12 months
Motivation measures	• Assessment of degree of agreement or disagreement with statements that deal with aspects of the intervention to improve use of evidence-based smoking cessation treatment	All providers	Baseline, 12 months
Beliefs about the Motivational Interviewing Questionnaire	• A 7-question survey assessing the extent to which each person agrees with statements about motivational interviewing.	All providers	Baseline, 12 months
Importance and confidence of using motivational interviewing	• A 6-question survey assessing the importance and confidence each person has to deliver motivational interviewing.	All providers	Baseline, 3, 6, 12 months
Avatar motivational interviewing performance measurements	• From use of motivational interviewing techniques in simulated web-based conversations	All providers	Baseline, 12 months
Motivational Interviewing Treatment Integrity Tool	• Validated tool used to measure fidelity to motivational interviewing from Standardized Actor Interviews	All providers	Baseline, 12 months
Fidelity to behavioral smoking cessation counseling	• Standardized Actor Interviews will be conducted to assess fidelity to smoking cessation behavioral counseling sessions	All providers	Baseline, 12 months
Guideline-concordant smoking cessation treatment	• Smoking status assessment rates • Willingness-to-quit assessment rates • Prescription of smoking cessation medication rates • Behavioral counseling rates	All clinic clients	Baseline through 12 months

[a]AIM: Acceptability of Intervention Measure.

[b]IAM: Intervention Appropriateness Measure.

[c]FIM: Feasibility of Intervention Measure.

Data on providers' competency using motivational interviewing skills will be obtained from scheduled avatar-simulated conversations and from standardized actor phone interviews, which will occur at baseline and 12 months at a minimum. Standardized client scenarios will be provided to actors that reflect the kind of situations community mental health clinicians would likely encounter with clients who smoke; this method has demonstrated predictive validity in terms of providers' performance with actual clients [46]. The research team will access data from the electronic medical record (EMR) system or site-specific documentation procedures to assess providers' uptake of the evidence-based practices (eg, percentage of clinic visits where a smoking assessment is documented) and

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client-level data (eg, demographics and primary mental health diagnosis).

Measures

The *primary outcomes* are changes in providers' knowledge about and self-efficacy to deliver evidence-based smoking cessation treatment from baseline to 12 months.

Secondary outcomes include change in the delivery of the recommended four evidence-based practices: (1) assessment of smoking status for all adult clinic clients (with quarterly follow-up assessments for smokers not yet willing to quit), (2) assessment of willingness to quit for smokers, (3) receipt of behavioral counseling for those willing to quit within 12 weeks, and (4) receipt of pharmacotherapy for those willing to quit within 12 weeks and referral for pharmacotherapy for those not willing to quit in this time frame. These outcomes will be measured by clinic documentation during client visits (in the EMR or site-specific documentation) and assessed at baseline and throughout the implementation period. When available, baseline documentation will include data from 3-6 months prior to project implementation. Additional secondary measures are changes in the acceptability, appropriateness, and feasibility of the intervention implementation strategies and of the evidence-based practices as assessed through the survey instrument.

To assess motivational interviewing skills, we will use the Motivational Interviewing Treatment Integrity coding system [47]. We will code random 20-minute segments of audio-recorded interactions with standardized client actors. The same interviews will be used to assess fidelity to the components of an IMPACT evidence-based smoking cessation counseling session.

Perceived barriers and facilitators on the part of clinic providers and leaders will be assessed based on qualitative interviews with individual providers before the start of the implementation intervention and at 12 months, and also with information obtained in monthly OSMs. We will also collect data about providers' and clients as shown in Table 2 including age, gender, race or ethnicity, and for providers, years worked at the clinic, and for clients, primary mental health diagnosis.

Data Analysis

We will conduct 2 main analyses. First, we will use survey data to assess the effects of the implementation intervention (baseline and 12 months) on providers' knowledge and self-efficacy, the mechanisms through which the implementation intervention is designed to improve the delivery of evidence-based smoking cessation treatment, using a generalized linear mixed effects modeling approach. The model will include a binary variable representing the prepost time points, fixed effects for the 5 study sites, and provider demographic characteristics. Second, we will evaluate the effects of the intervention (baseline and 12 months) on the implementation of evidence-based practices using a multilevel modeling approach. We will also assess the potential moderating effects of the implementation climate by adding appropriate interaction terms to the main models. We will use descriptive statistics to characterize staff perceptions of the acceptability, feasibility, and appropriateness of the implementation intervention strategies and the IMPACT evidence-based practices. Interview transcripts will be analyzed in MAXQDA (VERBI GmbH), using inductive coding to identify key themes. Survey analysis will be done using Stata 14 (StataCorp LLC) or SAS software (SAS Institute).

Ethical Considerations

The study was approved by the Johns Hopkins University School of Medicine IRB on January 14, 2021 (IRB number 00231836). Community mental health leaders and clinical staff will be appropriately recruited and informed of the study by the study team, with a waiver of documentation of informed consent. Patient data will be obtained per an approved waiver of consent. These waivers were approved by the IRB.

Each participant will be assigned a unique study ID number for data collection. Interview data will be audio recorded and transcribed by an approved vendor. Names will be removed from transcripts. Standardized actor interview will be stored on a secure network and participants identified by study number only. Study data will not be presented in such a way that identity can be inferred. Mental health leader and staff study participants will be paid US $50 for completing each interview and US $25 for each standardized actor interview as applicable. They will be paid up to a maximum total of US $60 for completing surveys at 4 time points.

Results

The study is underway at 5 clinic sites. More than 50 providers have been enrolled, exceeding our recruitment target. The study is ongoing. We anticipate that results will be reported in 2023 or 2024.

Discussion

Overview

Tobacco smoking is the leading cause of preventable mortality among persons with SMI and contributes to the reduced lifespan up to 25 years for persons in this population [1]. Evidence-based treatments for smoking cessation are available, safe, and efficacious for persons with SMI; however, few persons with SMI receive these treatments [38].

In order to realize the intended benefits of smoking cessation treatment for persons with SMI, it is important that mental health programs implement evidence-based practices. Current barriers faced by clinicians include not having the knowledge or confidence to deliver smoking cessation treatments, as well as misconceptions about the safety of smoking cessation medications and client interest in quitting [25-28]. There are also barriers at the organizational level; community mental health centers may not have standard systems for screening, monitoring, or treating tobacco smoking. In addition, the complexity of the evidence-based treatment, that is, the combination of behavioral counseling and pharmacotherapy, often delivered by different clinicians, contributes to the challenges of implementation [48]. In this pilot study, we will strive to address these barriers through the use of implementation strategies, including training about evidence-based smoking

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cessation treatment and motivational interviewing, a tobacco smoking treatment protocol, expert consultation, coaching, and OSMs.

Strengths and Limitations

While evidence-based smoking cessation treatments are not provided routinely in mental health clinics, where people with SMI receive the majority of their health care, these settings provide opportunities for the delivery of these recommended practices. We have specifically designed the training materials for providers in the community mental health center setting and have tailored the counseling manual for delivery to persons with SMI. We also worked with the sites' leadership to embed smoking cessation processes of care into the EMR and current workflow to increase clinician uptake. Using data from the EMR can provide an objective measure of smoking cessation evidence-based practices that are being implemented, enabling us to highlight areas of success and problem-solve barriers. At the completion of this study, we will have training modules, implementation tools, and resources for the delivery of smoking cessation treatment in community mental health centers. In order to address barriers to the implementation of these evidence-based practices, we are using a range of strategies, including asynchronous trainings and novel avatar simulations, to improve motivational interviewing counseling skills. We will collect data about the acceptability, appropriateness, and feasibility of both the evidence-based practices and implementation strategies that will inform future implementation efforts and planning for a randomized controlled trial.

In terms of limitations, our implementation intervention is effortful and multifaceted and may require additional supports to be carried out at other community mental health centers. The COVID-19 pandemic has created further challenges. As a result of pandemic-related restrictions, the study team had to adapt the implementation strategies to be delivered remotely rather than in-person, which, while being efficient to deliver, can make it more challenging to engage clinicians. Clinicians also had to adapt the counseling sessions to be delivered remotely if needed, which can be an added barrier for those less comfortable with technology. We also recognize that it may be difficult for providers to prioritize smoking cessation given other time-sensitive client concerns, such as those related to acute psychiatric symptoms and mental health crises [49]. Clinician challenges in delivering smoking cessation treatment may be exacerbated by staff shortages, which have occurred in many community mental health clinics during the pandemic and which have led to increased caseloads and other agency-related pressures. More generally, there are difficulties changing the culture in mental health organizations, many of which have been permissive about tobacco smoking in the past, in order to facilitate more active promotion and delivery of smoking cessation treatments [15]. Finally, our prepost design does not allow us to make causal inferences about the effects of our implementation strategies on outcomes.

Conclusion

The IMPACT study will provide evidence about the use of implementation strategies to increase providers' knowledge, self-efficacy, and delivery of the evidence-based practices for smoking cessation treatment for persons with SMI in community mental health center settings.

Acknowledgments

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Data Availability

The data sets generated and analyzed during this study will be available from the corresponding author on reasonable request with appropriate institutional review board approval and data use agreement.

Authors' Contributions

GLD, EMM, FD, AEE, and CC conceived the design of the study. NYW participated in the analytic and statistical analysis plans. AD, SG, and CTY contributed to the design of the intervention. BE, JVG, and EM directed data collection. FD, SG, EM, and CTY drafted the original version of the manuscript. All authors edited and approved the final manuscript.

Conflicts of Interest

CC and AEE received consulting from Charles River Analytics. The authors have no further interests to declare.

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Abbreviations

EMR: electronic medical record
IMPACT: Implementing Action for Tobacco Smoking Cessation Treatment
IRB: institutional review board
NRT: nicotine replacement therapy
OSM: organizational strategy meeting
SMI: serious mental illness

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Protocol

The Bunya Project: Protocol for a Mixed-Methods Approach to Developing a Culturally Informed Curriculum

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Abstract

Background: Indigenous peoples live across all continents, representing approximately 90 nations and cultures and 476 million people. There have long been clear statements about the rights of Indigenous peoples to self-determine services, policies, and resource allocations that affect our lives, particularly via the United Nations Declaration on the Rights of Indigenous Peoples. An area for urgent improvement is curricula that train the predominantly non-Indigenous health workforce about their responsibilities and that offer practical strategies to use when engaging with Indigenous peoples and issues.

Objective: The Bunya Project is designed to advance Indigenous community-led teaching and evaluation of the embeddedness of strategies to achieve an Indigenous Graduate Attribute in Australia. The project centers the relationships with Aboriginal community services to lead education design relating to Indigenous peoples. The project aims to articulate community recommendations for university education in allied health in the usable format of digital stories to create culturally informed andragogy, curriculum, and assessment measures for use in teaching. It also aims to understand the impact of this work on student attitudes and knowledge about Indigenous peoples' allied health needs.

Methods: Multilayered project governance was established, along with a 2-stage process using mixed methods participatory action research and critical reflection, using the reflective cycle by Gibbs. The first stage, *preparing the soil*, used community engagement, drew on lived experience, encouraged critical self-reflection, embodied reciprocity, and demanded working collectively. The second stage, *planting the seed*, requires more critical self-reflection, the development of community data through interviews and focus group discussions, the development of resources with an academic working group and community participants, the implementation of those resources with student feedback, the analysis of the feedback from students and community members, and reflection.

Results: The protocol for the first stage, *preparing the soil*, is complete. The results of the first stage are the relationships built and the trust earned and gained, and it has resulted in the development of the *planting the seed protocol*. As of February 2023, we have recruited 24 participants. We will analyze data shortly and expect to publish the results in 2024.

Conclusions: The readiness of non-Indigenous staff to engage with Indigenous communities has not been ascertained by Universities Australia, nor can it be assured. Staff preparation and skills to support the curriculum, create a safe learning environment, and develop teaching and learning strategies to guide academics to recognize that how students learn is as important as the content students learn. This learning has broad implications and benefits for staff and students within their professional practice and for lifelong learning.

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KEYWORDS

Indigenous; university; curriculum; leadership; cocreation; self-determination

Introduction

Overview

There are 476 million Indigenous peoples worldwide, who belong to the world's oldest continuing cultures and who have the right to self-determine health services to meet needs [1]. Health services are built upon and use the services of a predominantly tertiary-educated workforce. However, university health education contains little about Indigenous rights or knowledge [2]. Although immersion in cultural settings is recommended to stimulate transformation in knowledge and skills, current health curricula in Australia offer little toward this [3]. With few Indigenous staff at universities, responsibility lies with non-Indigenous staff, who are often underconfident in selecting and conveying information about Indigenous peoples [3]. Partnerships with Indigenous health organizations as experts in cultural models of care are essential; however, there are few examples in the literature to guide this [3]. An area for urgent improvement is curricula that train the predominantly non-Indigenous health workforce about their responsibilities and practical strategies they must use when engaging with Indigenous peoples and issues.

The Bunya Project is part of a participatory action research (PAR) project that aims to develop the skills and capabilities of academic staff to understand the principles and processes required to develop and embed Indigenous perspectives into the health care curriculum, ultimately influencing systemic change within the health care workforce.

This paper outlines a process for Indigenous community participation, showing how it is possible and important in developing culturally respectful engaging resources for students learning at university, across disciplines. The Bunya Project models processes and protocols for working with Indigenous peoples and community organizations that honor diverse Indigenous peoples' knowledge with authenticity, humility, and reciprocity, as per cultural and ethical protocols. This paper contributes to the narrative as to how and why universities should partner with Indigenous communities and organizations; the value of the Bunya Project lies not only in sharing important knowledge held by Indigenous community organizations and members but also in demonstrating how to bring community into university life. This Bunya Project protocol may be useful for Indigenous peoples around the world, to adapt to local circumstances in partnership with community organizations and local teaching institutions.

The Bunya Project protocol outlined in this paper provides the principles and strategic knowledge used by a university education health faculty in Australia, driven by the Indigenous health team. The early stages of the protocol describe what could be called the "pre-research" stage—much of this preliminary work is taken for granted by the authors as "proper ways" or a respectful process, knowledge of which is gained through lived experiences and social expectations in a community context. However, what is obvious to us may not be obvious to non-Indigenous academics. Therefore, this paper outlines the principles and processes required to implement this protocol, based on the authors' insider knowledge and lived experience as Indigenous peoples.

The Bunya Project is inspired by the tall Bunya tree of eastern Australia—*Araucaria bidwillii*—which grows slowly and, through its development, produces large pinecones that separate into edible nuts for current generations to be nourished by. It also spreads seeds for future generations to cultivate and grow. This Bunya Project provides a long-term, intergenerational, and unifying process for the voices of Indigenous peoples to be heard and shared in the allied health curriculum.

Background

Aboriginal and Torres Strait Islander peoples are the Indigenous populations of the continent referred to as Australia. Aboriginal peoples are heterogenous, with >250 different language groups [4], each with their own protocols and ceremonies. The Torres Strait Islands comprise 5 island clusters, consisting of 38 inhabited islands and 113 islands in total. The islands lie between the tip of Queensland on the Australian continent and Papua New Guinea. Acknowledging this diversity is foundational to understanding and approaching teaching and learning within Indigenous contexts.

Government Policy Context

In Australia, all national and state-based policies indicate that Aboriginal and Torres Strait Islander peoples have the right to cultures being at the center of decisions made, with full participation in decision-making [5,6] and its evaluation [7]. However, many of those currently in decision-making positions have had little education or support in understanding Australia's history, cultures, or rights [8]. There are limited representative mechanisms for Aboriginal and Torres Strait Islander peoples to formally be included in decision-making, as there is an inherent power imbalance [9,10]. Those agreements made between governments and peak Aboriginal and Torres Strait Islander organizational bodies often have little resourcing and no evaluation, which limits both their ability to act and accountability [11].

University Responsibilities and Realities

Current university education curricula produce graduates who often enter positions of power relevant to Indigenous peoples' realization of rights. However, their education is severely lacking and does not produce graduates who are sufficiently well developed to bring about the types of urgent health system or health workforce changes needed to influence the drastic improvements required [3,12]. This is a common issue for Indigenous peoples globally [13].

The embedding of Indigenous peoples' perspectives into mainstream university curriculum has been named for at least 2 decades in Australia [14,15] but only recently have structures been put in place by some universities [16,17] that help produce conditions for clear, evaluable actions. The peak body for

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Australian universities, Universities Australia, produced a strategy for 2017 to 2020 [18] and an Indigenous strategy for 2022 to 2025 [19], both of which make leadership statements but have not been wholly evaluated or updated for future developments.

Nonetheless, most Australian universities have committed to embedding Indigenous perspectives into their curriculum [20] and are seeking Indigenous peoples' leadership [21]. A specific strategy has been introduction of an "Indigenous Graduate Attribute" (IGA), a statement of attainment that is expected of all graduates in relation to Indigenous peoples [22]. In the health context, the IGA aims to improve graduates' knowledge about Indigenous peoples and issues and, where possible, provide experiences with Indigenous peoples, with the expectation that this will improve professional practice [23] and, ultimately, improve health outcomes for Indigenous peoples.

Unfortunately, there are few examples for universities about how to achieve the IGA. Universities have rarely met Indigenous staff targets [24], meaning that non-Indigenous people are largely responsible for developing and delivering curricula about Indigenous peoples and for driving the implementation and evaluation of the IGA. Perhaps in some recognition of this, Universities Australia recommends that tertiary institutions "build robust, respectful and collaborative partnerships between themselves and the Aboriginal and Torres Strait Islander communities that they serve" [14]. There are few practical strategies, scaffolding, or implementation guidance for university staff to create Indigenous community collaborations.

As an example of uninformed curriculum content, information about Indigenous peoples' health and well-being often begins with a focus on the most easily available information in the public domain—the Australian Government's Closing the Gap framework [25]. This framework has been designed to highlight inequity—the gap in processes and outcomes that Indigenous Australian peoples experience across many life domains compared with others in Australia [26]. In so doing, Closing the Gap powerfully reinforces negative stereotypes and assumptions about Indigenous Australian peoples, with no focus on strengths, local cultures, or worldviews about health. In the curriculum and in the classroom, this perpetuates stereotypes with a deficit lens [27] that is neither community driven nor reflective, entrenching in students' minds the notion that Indigenous peoples do not have the expertise to enhance mainstream learning or contribute to developing their professional practice in providing health care.

The holistic collectivist notion of Indigenous Australian peoples' health has much to offer to Western biomedicine in recognizing the whole person and their context: "Not just the physical wellbeing of an individual but refers to the social, emotional and cultural wellbeing of the whole community in which each individual is able to achieve their full potential as a human being, thereby bringing about the total wellbeing of their community. It is a whole-of-life view and includes the cyclical concept of life-death-life" [28].

To health educators who are versed in Western biomedicine, this holistic health concept seems complex and "too hard" [29]. Statistics used to measure and teach about health reinforce a power imbalance and dominance of the medical model [30]. With skilled, confident, and supported staff, more complex underlying contextual and environmental factors in health, including ongoing processes of colonization, systemic bias, and racism, are minimized [31]. Furthermore, the focus on Indigenous peoples' ill-health does nothing to challenge students to understand the influence of their own cultural lens [32] or the future risks of continuing to render invisible and devalue Indigenous models of health care.

Challenges in Allied Health Education

Allied health care professions are recognizably underdeveloped, particularly in relation to Indigenous peoples' ways of knowing, being, and doing in the curriculum and clinical practice [3]. Allied health education has a long history of excluding Indigenous knowledge [3,33]. The Indigenous allied health workforce and student cohorts are small; there is an assumption that more Indigenous allied health practitioners and students are required, but there is little critical thought in supporting Indigenous holistic health care and how that might shape the future health workforce [34]. There are clear gaps in research about allied health care needs of Indigenous peoples, and there is no attention to minority populations of Indigenous peoples such as those in prisons and those with disability or multiple, compounding issues. This limits the scope of exemplars available to inform curriculum. These gaps persist despite allied health professional education having specific accreditation requirements, often specific to the discipline and with mandatory renewal [35]. Furthermore, for example, the Australian Physiotherapy Council has strengthened its accreditation requirements to achieve more Indigenous student enrollments and include cultural safety in the curriculum [36], reinforced by changes to the National Safety and Quality Health Service Standards [37]. The Indigenous Allied Health Association provides some resources to guide health professionals and support students [38]; however, the implementation and use of available resources vary across institutions [39].

Expertise About Indigenous Health Does Not Lie in Universities

Statements implicating universities in perpetuating the disadvantage of Indigenous peoples' experience have recently been met with mixed responses in Australia, including denial and confusion [39,40]. The cultural load that Indigenous Australian staff experience in mainstream organizations—the additional expectations on Indigenous staff to fulfill tasks in accordance with position descriptions and educate others about Indigenous cultures [41]—is beginning to be aired. However, the experience of the relatively small number of Indigenous staff at universities is seldom acknowledged—having to both cope with stereotypes and exclusion of Indigenous knowledge and having to rectify the curriculum to meet accreditation while being understaffed [42]. University employment is not sustainable for Indigenous staff without the support of Indigenous community—personally or to help shape curriculum. Expertise about Indigenous health does not lie in universities. It is in the Indigenous community, which generally has few university graduates but has valuable expertise, cultural

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protocols, and appropriate positioning to identify and discuss key issues affecting their community and successful solutions.

Expertise of Indigenous Communities and Organizations

In contrast, mounting evidence exists for the success of Aboriginal community–controlled health organizations. The networked organizations (>140) across Australia have demonstrated leadership since the 1970s in effective and efficient holistic health care [43]. They address the social determinants of health [31] and recognize their successes emanating from continued cultural connections within Indigenous communities [44]. They carry across generations the Indigenous knowledge that has "multiple and interconnected discourses, social practices and knowledge technologies" [45] and they showcase Indigenous voices that carry within them the shared and lived experience of families and communities, beyond individuals [46]. Aboriginal community–controlled health organizations are now one of the largest workforces of Indigenous Australian peoples [47]; they demonstrate many strengths in models of care, staff, support, retention, and career progression [48] and are important leaders for any new curriculum development.

Project Context

Bunya has been designed as a central strategy for a university faculty (the University of Technology Sydney [UTS] Faculty of Health) and a graduate health school (the UTS Graduate School of Health) to support students to achieve IGA and to deliver curriculum for students embarking on a career in allied health care, specifically pharmacy, physiotherapy, clinical psychology, orthoptics, genetic counseling, and speech pathology. Bunya explores both how curriculum development processes can include Indigenous communities and Indigenous community members' experiences of allied health care.

The idea of seeking to connect a university health faculty with Indigenous communities to develop curriculum and to research the process and outcomes is very well supported by Australia's peak body for health and medical research, the National Health and Medical Research Council (NHMRC). The NHMRC guidelines, *Ethical conduct in research with Aboriginal and Torres Strait Islander Peoples and communities* and *Keeping research on track II*, were developed to promote health, prevent harm, and encourage best practice [49,50]. The NHMRC has also developed these specific guiding principles for conducting studies with Aboriginal and Torres Strait Islander peoples [49,50]. Historically, studies conducted in Aboriginal and Torres Strait Islander communities were extremely negative [50]. Previous studies conducted in Indigenous communities were, in some cases, physically barbaric [51]. Studies were designed to disempower, oppress, and silence Aboriginal and Torres Strait Islander peoples [52]. It is only in recent years that studies have been designed to be of benefit to Aboriginal and Torres Strait Islander peoples [53]. Aboriginal and Torres Strait Islander peoples are described as the most overresearched population in the world [54]. Processes have been put in place by governing research bodies such as the NHMRC and the Aboriginal Health and Medical Research Council of New South Wales. Both guidelines, *Ethical conduct in research with Aboriginal and Torres Strait Islander Peoples and communities* and *Keeping research on track II* [49,50], have been instrumental in the design and development of the Bunya Project and this protocol.

We have divided the Bunya Project into 2 stages—preparing the soil and planting the seed. Owing to the nature of PAR, it is impossible to separate protocols and learnings as clearly as in papers describing other forms of research, such as a clinical trial. The learnings from the *preparing the soil* stage influence the protocol developed in the *planting the seed* stage. As such, this paper will present some of the findings from the first stage, and a subsequent paper will elucidate them more clearly. The paper was written at the time of the transition from the first stage to the second stage.

Theoretical Frameworks

We have taken a PAR approach [55]. PAR is a qualitative research methodology that relies on the participation of the researcher and the participants to collaboratively gather and interpret data and findings throughout the project. The process of PAR is flexible and responsive to be able to adapt to the direction of the project, rather than being dictated or set from the beginning. PAR is a recognized Indigenous research methodology [56] designed to center and amplify Indigenous voices and self-determination [57], which is an underpinning value of the Bunya Project. PAR reduces power inequity and helps to ensure reciprocity.

PAR also reflects the authors' lived experiences of working with the community and as educators in the university context.

PAR prioritizes researchers and participants forming partnerships to identify issues of local importance and determine ways to understand the issues and strategies for action [58,59]. Furthermore, PAR methodology is used to understand complexities and influence change [55]. This resonates with the research team, given that Indigenous peoples have always implemented participatory principles within community governance through collective consultation and collective action [57]. PAR celebrates the complexity related to multiple contexts, including unique community settings and university education settings [60], with the ability to be agile to adapt to changing settings, participants, and ways of understanding [60].

In developing and articulating the preliminary process and protocol, the reflective cycle principles by Gibbs [61] were applied in a critical self-reflection context. The reflective framework principles by Gibbs also guided the authors to unpack informal conversations within the community engagement process, ensuring that the community remained central to the process and principles articulated [62]. Therefore, no data have been collected from student participants or will be reported here from external research associated with the Bunya Project. This paper presents critical reflection data from the research team to inform the project and its stakeholders. In evaluating Bunya, these are the foundational aspects required to build and replicate the project.

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Methods

Ethics Approval

The Bunya Project has been designed in accordance with NHMRC ethics guidelines regarding studies being conducted with Aboriginal and Torres Strait Islander peoples [49,50].

The Bunya Project has been approved by both the University of Technology Sydney Human Research Ethics Committee (ETH18-2618) and the Aboriginal Health and Medical Research Council of New South Wales Human Research Ethics Committee (1451/18).

Preparing the Soil

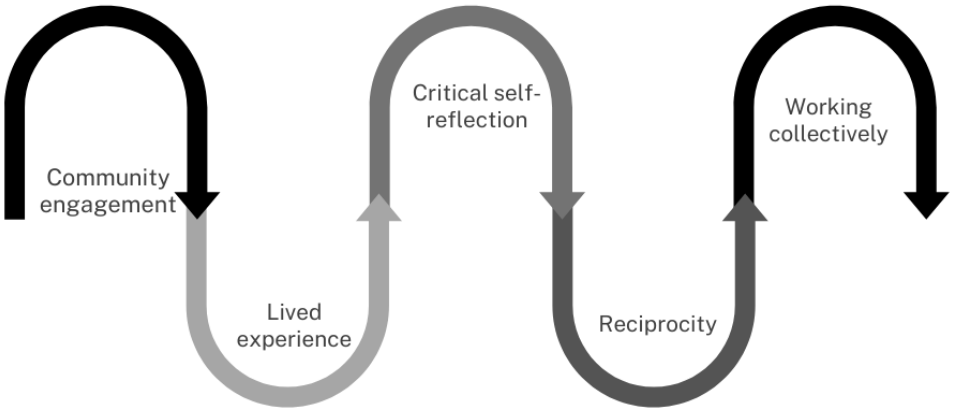
Overview

To develop the Bunya Project and method, the authors took into account cultural ways of working, along with community protocols and expectations. Overall, 5 steps were necessary to "prepare the soil" for the Bunya Project process. The five steps are as follows:

1. Community engagement—developing relationships to ensure that the project is of benefit to the community and responsive to the community objectives
2. Lived experience—humility in recognizing the influence of our own lived experience on our worldviews and interactions
3. Critical self-reflection—about our own perspectives and the influence these perspectives and experiences have on the formulation of ideas, conduct, and expectations
4. Reciprocity—which ensures that the benefit is mutual and the communities are meeting their objectives, not what the researcher thinks is of benefit to them
5. Working collectively—which creates the space for all participants to belong and feel empowered as an important part of the team, process, and outcomes achieved

Figure 1 shows these steps but note that they are fluid and may be repeated in part or whole throughout the process.

Figure 1. Preparing the soil in the Bunya Project.



Community Engagement

We identified four priority groups to engage with:

1. Indigenous community organizations
2. Indigenous community members and health care service users
3. University staff
4. University students

Invitations for group 1, Indigenous community organizations, to participate in the Bunya Project were circulated through networks and social media to encourage self-nomination. The research team visited community organizations and attended community events, circulating information and responding to queries. In total, 6 organizations signed up as Bunya Project collaborators. During the COVID-19 pandemic, this was reduced to 5 owing to travel distance restrictions and then to 4 because 1 organization ceased operating. A formal agreement was negotiated with each organization about their participation, including supporting curriculum development, assisting with the recruitment of Indigenous individuals who are willing to participate in data collection, and providing mentoring and peer support during the Bunya Project.

The Indigenous community organizations invited community members and health care service users (group-2 participants) to participate either directly or through social media. Information about the Bunya Project was circulated within each organization. Participants then self-nominated to participate. Participation includes interviews to collect data pertaining to insight into their own health care needs and strengths within their community influencing educational opportunities for allied health education. A total of 24 Indigenous community members and health care users were recruited to be interviewed.

Group-3 participants, university staff, were recruited through self-nomination.

University students (group-4 participants) will be invited to participate in the Bunya Project via the unit coordinator or class tutors. Participation is voluntary. Students who self-nominate will be required to complete premethod and postmethod surveys; we are aiming to survey most participants (n=169, 75.1%), with the total being 225 students.

The Bunya Project encourages connectedness wherever possible among project participant groups.

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Lived Experience

Lived experience recognizes the cultural, spiritual, physical, emotional, and mental experiences; circumstances; beliefs; and worldviews of a person, including the well-being of the individual, family, or community. A lived experience recognizes the ongoing impact of colonization experienced by Aboriginal and Torres Strait Islander individuals, families, and communities. Lived experience also recognizes specific events that have an impact on the social, emotional, and cultural well-being of Aboriginal and Torres Strait Islander peoples [63]. Lived experience as an Aboriginal person is complex, with many layers; is difficult to define but understood and recognized within the community and shared commonality; and does not need to be defined but is reflected through respecting protocols within the community [64]. Lived experience is an extremely valuable teaching tool, as students connect with shared lived experiences and the opportunity to learn from experiences that differ from their own. Lived experience also ensures that the teaching is authentic and relevant in a real-world context [65].

Critical Self-reflection

Critical self-reflection resulted in the identification of clear guiding principles for the conduct of the project. These guiding principles also reflect general cultural expectations when working with community and Indigenous knowledge. These principles are a guide for consideration in best practices for community engagement and leadership in teaching and learning and Indigenous research cultural protocols. As an Indigenous peoples–led research team, we cannot differentiate cultural protocols from research protocols; Indigenous culture informs knowledge production and the use of knowledge in research and practice.

Reciprocity

The research team actively participates in the Indigenous community organizations' business, supporting initiatives and events; contributing to committees; contributing skills, knowledge, and expertise; and providing access to university resources and networks.

The project continues to progress with mutual understanding of and agreement on key activities.

Working Collectively

Although the leadership of the Bunya Project rests with the Indigenous health academic unit within the faculty, the leadership has a clear desire to work collectively. The heads of each of the 6 postgraduate health disciplines were invited to nominate a staff member to join an academic working group fondly termed "the Bunya Nuts." These representatives provide discipline-specific expertise and guide curriculum development to ensure academic rigor and alignment with the curriculum that is already established.

The Bunya Nuts developed the terms of reference collectively; members are responsible for liaising within their discipline, inviting feedback, distributing community-developed video teaching resources, and facilitating student survey participation.

Objectives

The Bunya Nuts also selected the following objectives for its mixed methods PAR project:

1. Develop relationships with Aboriginal community services to support the project and understand community recommendations for university education in allied health
2. Conduct interviews and collect digital stories from Aboriginal and Torres Strait Islander peoples, to understand "what are their experiences, perspectives, knowledges and aspirations for their own health and wellbeing and in relation to allied healthcare?"
3. Create culturally informed andragogy, curriculum, and assessment measures for use among teaching staff and students
4. Implement an evaluation framework to understand the effects on student attitudes and knowledge about Indigenous peoples' allied health needs and aspirations and the authenticity, relevance, and accessibility of the curriculum for staff
5. Continue to develop culturally informed teaching and learning strategies

Results

Planting the Seed

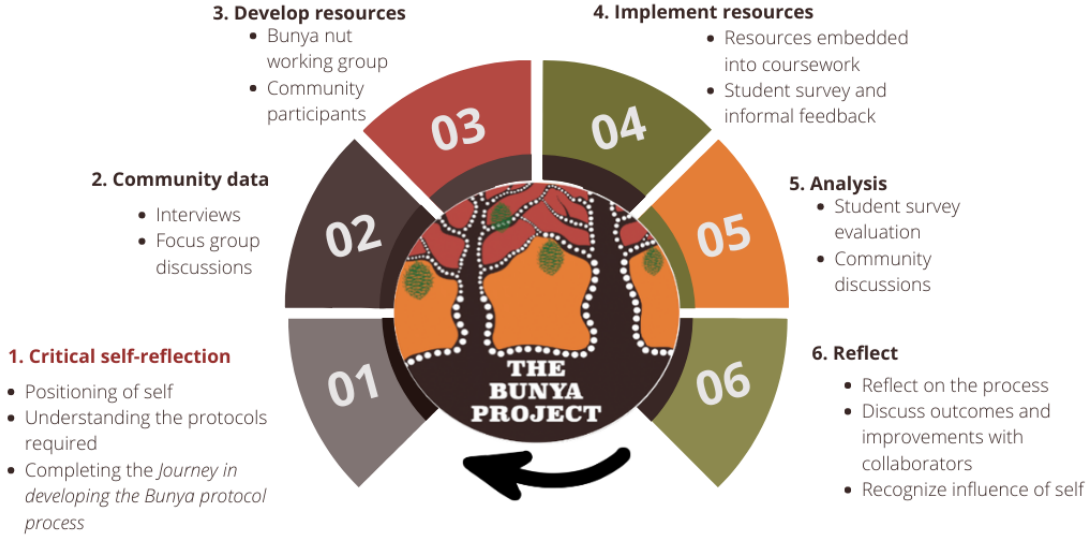
Overview

This section discusses the results of the "preparing the soil" process of the Bunya Project. The "preparing the soil" process resulted in key insights for the "planting the seed" stage including how future data are to be collected and the process and methodology for replication within the reader's own context.

As outlined in this paper, the Bunya Project uses PAR cycles to gather information, develop curriculum, use it, and evaluate it from multiple perspectives. As a PAR project, the "planting the seed" stage of Bunya itself has 6 stages, each stage influencing the next in a continuous cycle, as illustrated in Figure 2.

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Figure 2. Planting the seed—Bunya Project protocol phases.



The "planting the seed" process begins with critical self-reflection positioning by those guiding the project, their bias and influence, and ensuring that they have undertaken deliberate preparation to uphold the authenticity of the project. Phase 1 also incorporates the process in "preparing the soil" illustrated in Figure 1 previously. This involves recognizing their position, influence, and power and identifying the strategies and protocols required to privilege Indigenous voices and leadership and honor local protocols and expectations. Following this is community engagement and data collection; the data collected in each phase influence the following phases. Community data generate the content for the development and embedding of resources, and the resources activate thinking for the collaborative analysis of the survey and discussion. This is followed by a collaborative reflection about the process, improvements, and adjustments, and the cycle then commences again, with critical self-reflection of the person guiding the project.

As Figure 2 shows, Bunya is a PAR project because the overall community participation is central to all elements of the project. Phase 2 involves qualitative data collection, and phase 3 involves filming and editing the new teaching and learning resources and planning where in the curriculum they will be most effectively used, in collaboration with Bunya Nuts and community participants. Phase 4 involves using the resources and collecting a baseline survey from students and staff, and phase 5 involves the follow-up survey to help understand change and analysis of data. Phase 6 involves reflection with Bunya Nuts and community participants. PAR defines Bunya because it relies on community engagement throughout [55,58,61,66].

Critical Self-reflection

Critical self-reflection is again consciously used in the "planting the seed" stage of the Bunya Project, using the reflective cycle by Gibbs [61] to understand the experience, identify thoughts and feelings through the process, and recognize the importance of continuous improvement and the role of the researcher in modeling those processes as best practice. Undertaking this process at this point in the protocol provides the opportunity to highlight areas that may need to be revisited or unpacked further, in collaboration with the community involved.

Community Data

Focus Groups Discussions

In the future, focus group discussions will be conducted with Indigenous organization representatives. Focus group discussions encourage knowledge-producing dialogue in a group context. They allow the researcher to be part of the discussion [67]. This aligns with Indigenous ways of yarning and kapati, which encourages Indigenous peoples to talk freely about their experiences, thoughts, and ideas [68]. Furthermore, focus group discussions allow for broad discussion and framing and focusing questions and concepts to inform subsequent research phases, in this case, to inform semistructured interviews.

Focus group discussions will be semistructured, with guiding questions developed by the Bunya Nuts, and will be 30 to 60 minutes in duration.

The groups will have approximately 6 participants. Topics will range from health care knowledge and experiences to identifying needs and strengths within their community to influence the educational opportunities for tertiary education.

The focus group discussions will be audio recorded with written consent from all participants. Focus group participants will receive light refreshments in reciprocity of their time. All data collected during the focus groups will be deidentified.

Interviews

Interviews are designed to occur as a social interaction while sharing a cup of tea, known as kapati time, and create a safe space that facilitates yarning and storytelling [68]. Interviews stimulate knowledge sharing through storytelling and yarning [69]; storytelling is an important way of sharing information in Aboriginal and Torres Strait Islander cultures [67]. The interview structure will follow a line of questioning arising from the Bunya Nuts and the focus group discussions; however, this structure is intertwined with the informality of conversation and storytelling about experiences pertaining to the question.

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The interviews will be video recorded, with individual consent obtained from each participant before participation. Videos—digital stories—are a way of clearly displaying that the individual holds ownership over their knowledge, culture, and experiences and tells their story themselves, rather than having someone interpret their experience. Videos will then be edited for use, and written final approval will be obtained from the participant before the videos are implemented as internal teaching resources. Videos remain as the property of the participant and are not permitted to be changed or altered in any way unless additional consent is sought from the participant. The 24 interview participants will receive a gift card worth Aus $20 (US $13.23) as compensation for their participation.

Overall, 6 interviews will be conducted at each of the 4 locations.

Premethod and Postmethod Surveys for Staff and Students

The survey chosen to be used for the Bunya Project was designed as a university-wide instrument by the Centre for the Advancement of Indigenous Knowledges [8]. It measures students' attitudes, knowledge, and learning experiences pertaining to Indigenous ways of knowing, being, and doing. The premethod and postmethod survey measures whether the teaching and learning resources and strategies influenced change in staff and students' attitudes.

The survey assessment framework is based on 5 overarching themes that are aimed to critically engage with teaching and learning content related to the university's IGA. The overarching themes are as follows:

1. Knowledge
2. Critical reflectivity
3. Indigenous voice
4. Indigenous community engagement
5. Applied Indigenous knowledge [70]

The students will be provided with the survey through the survey platform. The Bunya Nuts representative for the discipline will upload the link to the learning management system for the subject. The link will be accompanied by an announcement to encourage student participation. The survey will remain open for at least 3 weeks, and students will be encouraged to complete it.

Develop Resources

The development of the resources begins with the Bunya Nuts working group to identify topics within the curriculum for each discipline. These topics will be discussed in focus group discussions with Aboriginal community–controlled health services, identifying the specific learning or information that the group determines as important for the students to know, understand, and apply within their professional practice. On the basis of the results of the discussions, one-on-one interviews will be conducted and video or audio recorded (according to participant preference). The interview questions and topics will be directly linked to the outcome of the focus group discussion, ensuring Indigenous self-determination throughout the process. The clips will be edited into short clips and reviewed by the participants to ensure that the message remained as intended.

Implement Resources

The resources developed will be made available to the school teaching staff within the various disciplines. The resources will be uploaded to the learning management system. Staff will be invited by the project team to access the resources. The project team will have control over who can access the resources and analytics to track where the resources are implemented within the learning management system, to ensure that the resources are only implemented in accordance with the ethical guidelines. The teaching staff will copy the resources into various points within their subjects to ensure that an Indigenous voice is present. The implementation of the resources will be accompanied by support processes outside this project, including teaching principles, an andragogy framework, and professional development opportunities for the staff. The project team recognizes the importance of not only what is taught (the content) but also how it is taught (the andragogy).

Analysis

The analysis of the data will be undertaken by the research team, in collaboration with the community partners and the Bunya Nuts. The andragogy framework guides the analysis, centering Indigenous knowledge and learning methodology within the context of adult education. Specific analysis will be conducted for each data set—the focus group discussions, interviews, and surveys.

Interviews will be transcribed and entered into NVivo (QSR International) [71] to be coded, with themes arising from the data. Codes will be compared, condensed, and organized into high-level themes to be communicated [72]. Focus group discussions will be managed similar to interviews, with the inclusion of group analysis [73]. Drafts and ideas about the data will be shared with the participating community organizations for their feedback. Furthermore, the qualitative interviews will be transformed and edited into digital stories, to be given to each participant and produce teaching resources for the disciplines. We will also draw on facilitator's written notes made during the focus group discussions.

The Centre for the Advancement of Indigenous Knowledges' processes for the analysis of data will be followed. The results of the validated survey will be analyzed to measure the impact of the authentic community-controlled teaching resources on the staff and students' attitudes, knowledge, and learning experiences in relation to Indigenous perspectives within their professional learnings. The quantitative data will be carefully cleaned, with frequencies identified using SPSS [74] to identify overall patterns, including across the 5 basic themes the instrument focuses on. Other basic statistical data analysis will occur including averages and partial correlation for associations with student outcomes.

Drafts and initial thoughts will again be shared with the community organizations to provide feedback regarding the progress and impact of the resources developed. The community guidance will influence modifications in the teaching resources for future implementation, beyond the scope of this project.

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Current Status

The protocol for the first stage, *preparing the soil*, is complete. The results of the first stage are the relationships built and the trust earned and gained, and it has resulted in the development of the *planting the seed protocol*. As of February 2023, we have recruited 24 participants. We will analyze data shortly and expect to publish the results in 2024.

Discussion

Summary

Through the "preparing the soil" stage of the PAR, the "planting the seed" Bunya Project protocol emerged, as depicted in Figure 2. This represents key findings, the importance of critical self-reflections in Indigenous health education and PAR, the importance of holding space in curriculum development and design to privilege Indigenous voices through the engagement of community data, collective development of resources, implementing resources in a culturally safe learning space, the analysis of the learning content and process, and reflection to ensure continuous improvement of the process and educators.

PAR is an empowering methodology that privileges local knowledge and lived experiences throughout every facet of the project [56,57]—the direction, implementation, analyses, and outcome. The Indigenous perspectives embedded within the curriculum are based on establishing relationships with the local community that are reciprocal and collaborative with Indigenous leadership and the university through the Bunya Nuts academic working group. The collaboration between the Bunya Nuts and the community is instrumental in the creation of new knowledge as this collaboration develops the capacity of both parties learning from each other through action [57,60,69]. The collective action involves creating videos and resources that honor and reflect the intended meaning and context from community to academia and from academia to community. This action extends to influence change in allied health care through educating and building a culturally responsive workforce. Bunya's andragogic framework is designed to reinforce the content, collaboration, and leadership of the community as the authoritative voice and knowledge holders [67].

This study encourages universities to develop partnerships with Indigenous community organizations in curriculum development. Establishing and maintaining authentic partnerships with Indigenous community organizations is important for the development of the future workforce and provides essential knowledge and skills for all graduates. Academic staff and institutions must move past an "othering" mindset, including the notion that developing relationships with Indigenous community organizations and including Indigenous perspectives in the curriculum is the sole responsibility of Indigenous academic staff. The reality is that Indigenous staff numbers in universities are low, globally. Embedding Indigenous perspectives into the curriculum is the responsibility and privilege of all the academic staff. It is not possible to create a checklist or a descriptive "how to" guide, as teaching and learning must be grounded and relevant to the local context. This paper outlines the guiding principles developed from the lived experience and reflectivity of the authors as community members and educators.

In Australia, government policy and legislative requirements have been introduced to ensure that curricula and workplaces implement training and professional development opportunities for students and staff, so that they can develop and apply knowledge and skills that create conditions for cultural safety and culturally responsive health care. Authentic partnerships with community organizations are an obvious place to start. Students can then commence their career with a strong foundation by understanding how to work authentically with Indigenous organizations and peoples. This paper outlines how to approach and achieve this outcome.

As this paper also shows, partnerships require reciprocal benefit and authenticity, creating the opportunity for universities to positively and authentically work with Indigenous community organizations to share knowledge skills and resources that will benefit not only the university and the students but also the community organizations and their staff and clients.

Comparisons With Previous Studies

The Bunya Project protocol unifies elements identified by past studies to form a comprehensive approach to embedding Indigenous perspectives within higher education with community engagement and leaders, andragogical framework, staff accountability, and student evaluation.

The growing momentum to include Indigenous perspectives into higher education and preparing graduates to work effectively with Indigenous populations is positive. However, current implementation processes in Australia lack accountability [63], evidence, and evaluation [8].

It has also been identified that Indigenous peoples cannot be solely responsible for all learning and teaching in academia. Indigenous and non-Indigenous academic staff must work together to implement the curriculum, using culturally safe [75] and relevant teaching and learning strategies [68,76,77]. This extends to the professional context whereby previous studies identified the importance of Aboriginal health workers and mainstream allied health workers working together within their professional context [75].

In accordance with United Nations Declaration on the Rights of Indigenous Peoples, Indigenous peoples have the right to self-determine health care and education [78]; therefore, they must be leaders in designing and informing curriculum, ensuring that learning is *with* Indigenous peoples and not *about* Indigenous peoples. This is demonstrated in various ways through previous studies, by applying and building on knowledge and experience with Indigenous peoples [79] to inform curriculum, through local Indigenous ways of knowing and learning in the classroom, and through community-engaged learning.

Previous studies in the area have identified the importance of the local context, of working with a single community—this does not reflect the diversity within Indigenous populations in Australia. The Bunya Project protocol extends this to include leadership from a diversity of communities.

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The Bunya Project protocol also challenges educators to push past the concept of pedagogy to ensure that teaching and learning are receptive to the adult learner [80].

Transformational learning is central to this space and was identified throughout previous studies [32]. The San'yas Indigenous Cultural Safety Training in Canada is implemented as an educational intervention to promote transformational change in health systems, policies, and practice [81]. The Bunya Project protocol incorporates and builds on the importance of transformational learning and recognizing the position of self by all involved, including community participants, academic staff, and students.

Limitations

COVID-19 affected the project, as lockdowns restrict interactions. Even during times of eased restrictions, communities were very cautious to engage owing to the risk posed by COVID-19 and have cancelled events or adapted to web-based events. However, the pandemic provided another opportunity to highlight Indigenous excellence as the overall response to the pandemic, including public health messaging and responses, and the rapid adaptability to web-based connectedness has been exemplary.

The Bunya Project was developed in 1 university and 6 communities, which does not reflect the diversity of Aboriginal peoples or Indigenous peoples globally.

Conclusions

This study reinforces the necessity for universities to be active in engaging with Indigenous communities to influence education content and, consequently, outcomes. It is not the responsibility of the few Indigenous staff to champion this; the implication is that the majority must authentically engage with the community and privilege their leadership and expertise within teaching and learning design, delivery, and evaluation.

The value and implication of the Bunya Project lies in its demonstration of how universities resource staff to engage with community organizations and members within the university setting. If working well with Indigenous peoples requires the readiness of non-Indigenous staff and students, universities need to provide staff with cultural capability training, facilitating opportunities to learn. This Bunya Project protocol and its "preparing the soil" and "planting the seeds" stages model a process for best practice and authentic engagement that creates space, respect, and recognition of the value and privilege to learn from Indigenous leadership and expertise.

PAR of the Bunya Project is working to evolve university education through the quality delivery of an IGA that prepares students to be informed professionals throughout their careers and to contribute to creating conditions for Indigenous peoples to experience cultural safety; this is a lifelong learning journey. The intended learnings from the Bunya Project are expected to extend beyond university through continuing personal and professional development and application throughout the individual's career.

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Data Availability

Data will be made available; however, they have not been collected yet.

Conflicts of Interest

None declared.

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Abbreviations

IGA: Indigenous Graduate Attribute
NHMRC: National Health and Medical Research Council
PAR: participatory action research
UTS: University of Technology Sydney

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Protocol

The Fatty Liver, Cirrhosis, and Liver Cancer Study (TENDENCY): Protocol for a Multicenter Case-Control Study

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Abstract

Background: Hepatocellular cancer (HCC) is associated with high mortality, and early diagnosis leads to better survival. Patients with cirrhosis, especially due to nonalcoholic fatty liver disease and viral hepatitis, are at higher risk of developing HCC and form the main screening group. The current screening methods for HCC (6-monthly screening with serum alpha fetoprotein and ultrasound liver) have low sensitivity; hence, there is a need for better screening markers for HCC.

Objective: Our study, TENDENCY, aims to validate the novel screening markers (methylated *septin 9*, urinary volatile organic compounds, and urinary peptides) for HCC diagnosis and study these noninvasive biomarkers in liver disease.

Methods: This is a multicenter, nested case-control study, which involves comparing the plasma levels of methylated *septin 9* between confirmed HCC cases and patients with cirrhosis (control group). It also includes the comparison of urine samples for the detection of HCC-specific volatile organic compounds and peptides. Based on the findings of a pilot study carried out at University Hospital Coventry & Warwickshire, we estimated our sample size to be 308 (n=88, 29% patients with HCC; n=220, 71% patients with cirrhosis). Urine and plasma samples will be collected from all participants and will be frozen at –80 °C until the end of recruitment. Gas chromatography–mass spectrometry will be used for urinary volatile organic compounds detection, and capillary electrophoresis–mass spectrometry will be used for urinary peptide identification. Real-time polymerase chain reaction will be used for the qualitative detection of plasma methylated *septin 9*. The study will be monitored by the Research and Development department at University Hospital Coventry & Warwickshire.

Results: The recruitment stage was completed in March 2023. The TENDENCY study is currently in the analysis stage, which is expected to finish by November 2023.

Conclusions: There is lack of effective screening tests for hepatocellular cancer despite higher mortality rates. The application of more sensitive plasma and urinary biomarkers for hepatocellular cancer screening in clinical practice will allow us to detect the disease at earlier stages and hence, overall, improve HCC outcomes.

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KEYWORDS

hepatocellular cancer; cirrhosis; methylated septin 9; urinary volatile organic compounds; urinary peptides; fatty liver; fatty liver disease; hepatitis; liver cancer

Introduction

Background

Hepatocellular cancer (HCC) has been the sixth most common cancer worldwide and the third most frequent cause of cancer-related deaths around the world in 2020 [1]. There has been a significant increase in the incidence of HCC in the United Kingdom and worldwide. Cirrhosis is the most potent risk factor for HCC and hence constitutes the major screening group for HCC globally. Cirrhosis can be caused by chronic viral hepatitis (B and C), chronic alcohol abuse, inherited metabolic diseases such as genetic haemochromatosis, or in some cases alpha-1-antitrypsin deficiency. The acquired metabolic disorder, nonalcoholic fatty liver disease (NAFLD), has also emerged as an important risk factor. NAFLD is a manifestation of the metabolic syndrome and is associated with type 2 diabetes mellitus and obesity. NAFLD affects around 20% to 30% of the adult population. Growing evidence suggests an increased HCC incidence in patients with NAFLD, and it will become the leading cause of HCC in the developed world [2,3].

The current screening strategy for HCC in the United Kingdom in established cirrhotic and high-risk groups is 6-month (twice a year) ultrasound surveillance scans and serum alpha fetoprotein (AFP) measurement. However, there are significant limitations associated with this approach. The sensitivity of AFP for HCC detection is only 60%, and the specificity is 87.7%. Previously, any attempts to increase the cutoff to increase the specificity had resulted in a lower sensitivity [4]. In fact, previous large-scale trials had shown that up to half of patients with primary liver cancer are AFP negative [5]. Hence, it is far from ideal as a screening test for HCC surveillance. Ultrasound liver is very much operator dependent, and again, the sensitivity remains modest around 63% for an early-stage HCC case [6].

There is always a significant risk of missing early-stage HCC or late diagnosis of HCC due to the poor sensitivity of the current screening modalities. Unfortunately, the late diagnosis of HCC is associated with overall poor outcomes, with a median survival of around 6 to 20 months post diagnosis [7]. Early diagnosis can be associated with curative options, including surgical resection, liver transplantation, and radiofrequency ablation. However, the chances of the earlier diagnosis rely mostly on better screening.

Current methods used to diagnose cirrhosis and NAFL have limitations. Transient elastography (TE) and enhanced liver fibrosis tests are used to check the presence of fibrosis, with TE also giving estimations of fatty changes in liver. However, they both have limitations, with enhanced liver fibrosis being a proprietary test [8] at a high cost (and with data coming from observational studies), and TE being operator dependent and nonconclusive in patients with a high BMI [9]. Hence, better noninvasive diagnostic tests are required for NAFLD and cirrhosis diagnosis and HCC screening.

Potential New Screening Markers for HCC and Liver Disease for Further Evaluation in TENDENCY

Methylated Septin 9

Studies on colorectal cancer have identified that methylation of the *septin 9* gene occurs during carcinogenesis and is released into the plasma, which leads to the development of blood-based *septin 9* gene methylation assays [10]. A study of 304 HCC tissue samples showed that methylated *septin 9(mSEPT9)* is a significant epi-driver gene in liver carcinogenesis [11]. He et al [12] conducted a case control study (64 patients with HCC, 44 patients with liver cirrhosis, and 298 healthy individuals) and demonstrated an overall plasma *mSEPT9* sensitivity of 76.7% for the detection of HCC. However, further work is required to validate these findings in screening a high-risk cohort [12].

Li et al [13] showed plasma *mSEPT9* to have a sensitivity of 82% and a specificity of 96% for HCC detection in a similar study carried out in Beijing (including 104 patients with HCC, 95 patients at risk of the disease, and 174 healthy controls).

A proof-of-concept study done as part of the TENDENCY study at University Hospital Coventry & Warwickshire (UHCW) with 141 participants (including 39 HCC cases) showed *mSEPT9* to have a sensitivity of 89% and a specificity of 81% (in comparison to an AFP sensitivity of 50% and a specificity of 97%) [14]. Thus, *mSEPT*9 has a far better sensitivity than AFP. However, in order to prove its applicability over the screening population, we require validation in a larger cohort of HCC cases against a control group of patients with cirrhosis (which is the major screening group in clinical practice).

Volatile Organic Compounds

Volatile organic compounds (VOCs) are endogenous and exogenous compounds with a lower boiling point and high vapor pressure. Endogenous VOCs are predominantly produced as a result of fermentation of nonstarchy polysaccharides and fibers in gut. These compounds then permeate the bowel wall and enter the portal circulation. Liver then plays further role in the metabolism of these compounds via various enzymes. The end products are subsequently excreted in various body secretions [15]. In addition, several volatile organic compounds are produced in liver as a result of complex metabolic processes (including lipid peroxidation, dextrose metabolism, and pathways involving cytochrome P450 enzymes). Any disruption in these metabolic pathways and possible oxidative stress can lead to fluctuations in the levels of relevant VOCs [16]. This fact has formed the basis for further studies involving the identification of various VOCs as possible biomarkers for liver diseases.

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The UHCW research group conducted a pilot study that provides proof of concept for further research into the role of VOCs in NAFLD. The aim of the study was to determine whether urinary VOCs could distinguish between various stages of fatty liver disease (NAFLD, nonalcoholic steatohepatitis [NASH], and NASH-C) and controls. The results suggested that urinary VOCs can help distinguish between NASH and NAFLD [17].

The analysis of urinary VOCs has a potential role in the screening of HCC. VOCs can be both released and metabolized by HCC cells. A pilot study at UHCW (as part of the TENDENCY project) has used gas chromatography–ion mobility spectrometry and gas chromatography–time-of-flight mass spectrometry to identify significant VOCs associated with HCC and liver fibrosis. The gas chromatography–Ion mass spectrometry data separated patients with HCC from the patients with fibrosis with an area under the receiver operating characteristic curve of 0.97. Seven compounds were identified to be provisionally associated with HCC from the gas chromatography–time-of-flight mass spectrometry data set. The compounds included 4-methyl-2,4-bis (p-hydroxyphenyl)pent-1-ene (2TMS derivative), 2-butanone, 2-hexanone, benzene, 1-ethyl-2-methyl-, 3-butene-1,2-diol, 1-(2-furanyl)-, bicyclo (4.1.0) heptane, 3,7,7-trimethyl-, [1S-(1a,3β,6a)]-, and sulpiride. However, the sample size was small, with 20 HCC and 38 non-HCC cases, and as a result, quantification was not possible [18] (Table 1).

Table 1. Volatile organic compound (VOCs) as potential hepatocellular cancer (HCC) biomarkers [18].

VOC identified during GC-TOF-MS[a]	Change in HCC
4-Methyl-2,4-bis(p-hydroxyphenyl)pent-1-ene,2TMS derivative	Lower
2-Butanone	Higher
2-Hexanone	Lower
Benzene, 1-ethyl-2-methyl-	Lower
3-Butene-1,2-diol, 1-(2-furanyl)-	Lower
Bicyclo[4.1.0]heptane, 3,7,7-trimethyl-, [1S-(1a,3ß,6a)]-	Lower
Sulpiride	Lower

[a]GC-TOF-MS: gas chromatography–time-of-flight mass spectrometry.

Urinary Peptides

Significant alterations in protein expression occur during carcinogenesis. These altered proteins then play an important role in tumor cells proliferation via the modification of signaling and other cellular metabolic pathways. Further characterization of protein alterations has shown a specific association for certain malignancies [19]. Hence, studies are being conducted to evaluate the role of these altered proteins as possible cancer biomarkers.

Several proteomics studies involving capillary electrophoresis coupled to mass-spectrometry (CE-MS) have demonstrated a good diagnostic potential of urinary peptide biomarkers [20]. A pilot study (joint collaboration of the United Kingdom and Germany) has shown that peptides specific to HCC can be identified by urinary CE-MS analysis. This study successfully identified a set of 31 urinary peptides showing an overall sensitivity of 79.5% for HCC. Further validation studies are required on a larger cohort of HCC urine samples [21].

Aims and Objectives

The aim of this study is to investigate the metabolic function in patients with liver disease and to identify the biomarkers in liver disease.

Primary Objectives

Our primary aim was to study the metabolome of patients with cirrhosis, NAFLD, and HCC to identify novel noninvasive diagnostic biomarkers.

Secondary Objectives

We also aimed to achieve the following:

1. Characterize the urinary VOC biological signatures to identify specific chemicals that can be used as biomarkers in HCC.
2. Identify a specific urinary protein biomarker in HCC via CE-MS.
3. Study blood for nuclear markers and compounds that can be used as diagnostic tests in HCC.

Methods

Overview

This is a multicenter case-control study comparing patients with HCC to patients with cirrhosis. Participants in the United Kingdom will be recruited from UHCW, Russells Hall Hospital, New Cross Hospital, and Royal Stoke University Hospital. These hospitals cover the majority of West Midlands and North Midlands in the United Kingdom, providing comprehensive liver services. In addition, participants will also be recruited from Pakistan Kidney and Liver Institute and Research Center.

The participants in this study will require one visit only. Following posting the participant information sheet and a phone call, the participant will be given an option of either attending a specified research clinic or meeting after a routine clinic appointment arranged for their care in UHCW. Urine and blood samples for the study will be collected during that appointment.

For recruitment, we will be identifying positive HCC cases through HCC multidisciplinary team meetings as per the

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international guidelines (inclusion criteria will include radiological or histological confirmation) [2,22]. We will recruit our control group of patients with cirrhosis (inclusion criteria comprises radiological or clinical confirmation) via our cirrhotic follow-up clinics.

Patients under the age of 18 years or pregnant or those unable to give consent will be excluded from the study.

Written informed consent will be taken by a member of the research team. Before taking consent, the patient will be given adequate time to read the participant information sheet and will be given the opportunity to ask any questions they may have. Baseline data (as mentioned in Table 2) will be collected upon the recruitment of the participants prior to the collection of samples. Participant flowsheet throughout the study can be seen in Textbox 1.

Table 2. Schedule of events.

Procedure	Screening	Appointment	Post appointment
Eligibility check	X		
Relevant participation information sheet and invitation letter posted to participant	X		
Participant contacted to confirm their interest in taking part	X		
Patient attends routine appointment or attends dedicated research clinic		X	
Informed consent		X	
Demographic data (eg, date of birth and sex)		X	
Medical history		X	
Current medications or treatment modalities planned or done		X	
Height and weight		X	
Taking blood sample		X	
Taking urine sample		X	X
Collecting relevant clinical data done as part of the standard clinical care		X	

Textbox 1. Participant flowsheet throughout the study.

- Patient screened
- Confirmed patient diagnosis and eligibility
- Postinvitation letter and relevant participant information sheet
- Phone call to confirm if interested in participating
- Patient attends routine appointment or attends dedicated research clinic
- Patient approached by member of research team on the day of recruitment
- Informed consent taken
- Blood and urine sample taken
- If patient was unable to provide urine sample on the day, an option to send it via post will be provided.

Sample Size Calculation

Definitive sample size calculations are difficult as the technologies used are novel with little available literature for comparison. However, we have estimated our sample size based on the preliminary findings of the TENDENCY pilot study conducted from 2019 to 2021.The pilot study conducted at UHCW (as part of TENDENCY) showed the sensitivity and specificity of *mSEPT9* as 89% and 81%, respectively, for detecting HCC in patients with cirrhosis [14]. Based on that, we have estimated our required total sample size using the method used by Buderer [23] to be N=308, with 88 (29%) patients with HCC and 220 (71%) patients with cirrhosis (considering a 10% dropout rate for HCC). The prevalence has been ascertained using cumulative 5-year incidence of HCC as 30% in certain groups of cirrhotic patients [24].

ME = half the 95% CI =0.05



Total sample size = n/prevalence

Storage and Analysis of Samples

After collection, urine specimens will be frozen at –80 °C in the tissue bank for later analysis. Prior to analysis, they will be left to thaw in a laboratory fridge overnight and aliquoted into appropriate sample bottles.

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Urinary Volatile Organic Compounds

The detection of the urinary VOCs will consist of sample concentration with a sample containment system, transfer of the VOCs from the air sample to the analytical device with an odor-sampling system, and detection and identification of each VOC with proprietary instrument for analysis. Gas chromatography–Ion mass spectrometry will identify different VOCs. The data generated will then be digitized and processed by computer software and subjected to principal-components analysis to ascertain whether there are differences between the different urine samples.

Urinary Proteomic Analysis

For the proteomic analysis, urine samples will be processed using the CE-MS to help identify proteins specifically linked to HCC. The principal stages involved in the process would include the removal of large molecular proteins, CE-MS analysis, CE-MS data processing, and support vector machine processing and classification.

Plasma Analysis for Methylated Septin 9

Blood samples will be centrifuged at 5000 revolutions per minute for 15 minutes, and at least 1 milliliter plasma will then be decanted in a separate aliquot. The plasma samples will then be frozen at –80 °C until the end of recruitment.

Plasma samples will then be analyzed using real-time polymerase chain reaction with a fluorescent hydrolysis probe for the methylation-specific detection of the *septin 9* DNA target (*mSEPT9*); this automated real-time polymerase chain reaction test is aimed at a qualitative detection.

Study Overview

UHCW is the sponsor for the study and provides indemnity for the study. An authorized representative of the sponsor has approved the final version of this protocol with respect to the study design, conduct, data analysis, interpretation, as well as plans for the publication and dissemination of the results.

Monitoring, Audit, and Inspection

The study will be monitored by the Research & Development department at UHCW as representatives of the sponsor to ensure that the study is being conducted as per protocol, adhering to Research Governance and Good Clinical Practice. The approach to and extent of monitoring will be specified in a study monitoring plan determined by the risk assessment undertaken prior to the start of the study.

Ethics Approval

TENDENCY has been approved by Northeast-York Ethics Committee (aproval number: 19/NE/0213). The Integrated Research Application System (IRAS) number for the study is 260179, and the National Institute for Health and Care Research (NIHR) portfolio ID is 42438. All the investigators will be granted authorship in the final study reports.

Data Protection and Patient Confidentiality

This study will comply with the current data protection regulations, and regular checks and monitoring will be undertaken by the UHCW Research & Development department, National Health Services to ensure compliance. Participants will be assigned a unique identifier upon enrollment into the study to allow link anonymization of patient-identifiable data. Access to patient-identifiable data will be restricted to members of the study coordination team, and electronic data will be stored on password-protected, encrypted drives.

Results

The recruitment stage was completed in March 2023. The TENDENCY study is currently in the analysis stage, which is expected to finish by November 2023. The results from TENDENCY will be published in medical journals and will be of specific interest to clinicians managing chronic liver disease. The results may form the basis for a possible change in the screening pathways for cirrhosis, NAFL disease, and hepatocellular cancer.

Discussion

The lack of more sensitive screening tests for HCC has prompted a search for the novel biomarkers. The noninvasive blood tests and urine tests can serve as an easier and more effective method of the close surveillance of patients at a high risk for liver disease. The findings of the TENDENCY study will provide a basis of formulating better pathways for HCC screening. This is the first large-scale UK multicenter study that incorporates both urinary and plasma biomarker testing for HCC screening. The findings from this study can provide a basis for the development of assays incorporating a combination of biomarkers for enhanced early-stage HCC detection.

Based on the findings of the study, the next step will be to study the plasma *mSEPT9* in posttreatment cohorts to study its prognostic value.

The application of more sensitive plasma and urinary biomarkers for hepatocellular screening in clinical practice could allow us to detect HCC at earlier stages and overall improve the outcomes.

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Data Availability

The data sets generated during this study are not publicly available as the study is still ongoing and sample analysis has not taken place.

Conflicts of Interest

None declared.

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Abbreviations

AFP: alpha fetoprotein
CE-MS: capillary electrophoresis coupled to mass spectrometry
HCC: hepatocellular cancer
***mSEPT9*:** methylated septin 9
NAFLD: nonalcoholic fatty liver disease
NASH: nonalcoholic steatohepatitis
TE: transient elastography
UHCW: University Hospital Coventry & Warwickshire
VOC: volatile organic compound

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Protocol

The Kinetics of Anti–SARS-CoV-2 Antibodies in Pediatric Patients and the Characterization of Post–COVID-19 Condition at 6 Months After Infection: Protocol for a Longitudinal Observational Study

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Abstract

Background: Data regarding the kinetics of anti–SARS-CoV-2 antibodies and information about post–COVID-19 condition (colloquially known as “long COVID”) in children are scarce, especially in low-income countries. Even though cases of COVID-19 in children are less prevalent than adults, post–COVID-19 condition cases in children are high and have a burden that may impact their growth and development. There are other features of antibody kinetics in connection with SARS-CoV-2 infection that are yet unknown as of this writing, especially in children following infection. Furthermore, the long-term results, risk factors, and underlying pathophysiology are still uncertain. To better understand post–COVID-19 condition in children, it is necessary to further investigate the impact of clinically significant factors such multisystem inflammatory syndrome and disease severity among hospitalized survivors through their SARS-CoV-2 antibody response.

Objective: We aim to analyze anti–receptor-binding domain SARS-CoV-2 immunoglobulin G antibodies over time and characterize the signs and symptoms of post–COVID-19 condition in pediatric patients at the time of diagnosis and at 2 weeks and 1, 3, and 6 months following infection.

Methods: This is a longitudinal observational study in Indonesia. Pediatric patients diagnosed with COVID-19 by positive molecular assay using nasopharyngeal swab will be tested for anti–SARS-CoV-2 antibodies using the Roche Elecsys Anti-SARS-CoV-2 S assay at the time of diagnosis and at 2 weeks and 1, 3, and 6 months following infection. Antibody titer data will be reported as means and SDs. The respondents’ signs and symptoms will be observed up to 6 months after the onset of infection, including the vaccination event, reinfection, rehospitalization, and mortality. The clinical features will be reported as frequencies and percentages.

Results: Participant enrollment began in February 2022. As of September 30, 2022, a total of 58 patients were enrolled. After data collection, results are expected to be analyzed in August 2023.

Conclusions: This study will allow us to know the kinetics of anti–receptor-binding domain SARS-CoV-2 immunoglobulin G antibodies and data regarding post–COVID-19 condition up to 6 months following infection in the Indonesian pediatric population. Furthermore, this study has the potential to serve as a foundation for government decisions about vaccination programs and prevention measures.

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KEYWORDS

kinetics; anti–SARS-CoV-2 antibodies; post–COVID-19 condition; long COVID; pediatric patient; antibodies; COVID-19

Introduction

COVID-19 is a pneumonia caused by the novel SARS-CoV-2 virus. It was first identified in Wuhan, China, in December 2019; it then spread rapidly across the globe and became an international public health emergency [1,2]. In March 2020, the World Health Organization (WHO) declared COVID-19 a pandemic [2]. SARS-CoV-2 is transmitted directly (droplet or person-to-person transmission through coughing, sneezing, or talking) and indirectly (contaminated objects and airborne) [1].

Data compiled by the WHO in 2021 showed that cases in children younger than 5 years from December 30, 2019, to September 13, 2021, were 1.8% of the world's cases [3]. Meanwhile, cases of COVID-19 at the age of 5-14 years were 6.3% of the world's cases. Older children (15-24 years) had more cases, which accounted for 14.5% of the world's total cases. The American Academy of Pediatrics in 2022 stated that the total number of cases in children were 18.5% of the total COVID-19 cases in the world [4]. In Indonesia, there were 77,254 children who were positive for COVID-19 until December 21, 2020, accounting for 11.5% of all positive cases in Indonesia [5].

To date, there are many aspects that remain unknown about the antibody kinetics related to SARS-CoV-2 infection, especially in children. Understanding the kinetics of humoral response in the pediatric population could help to develop more effective vaccination programs in children [6,7].

The spike protein of SARS-CoV-2 contains a receptor-binding domain (RBD) that mediates the entry into human cells by binding to the angiotensin-converting enzyme 2 (ACE-2) receptor [8]. A positive correlation between anti-RBD immunoglobulin G (IgG) antibody levels and neutralizing antibodies has been described [9]. However, data on children are still inconsistent. Some studies described a persistence in neutralizing antibodies over a period of up to 8 months and reported that younger children have a higher titer compared to older siblings or adults [10,11]. In contrast, another study described higher anti–spike protein IgG antibody levels at younger ages, without high levels of neutralizing activity [12].

Around 15% to 24% of children with COVID-19 are asymptomatic. The symptoms of COVID-19 that most often appear in children are fever and cough [13]. Some respiratory symptoms that rarely appear in children include nasal congestion, sore throat, and dyspnea [14]. Other symptoms, such as headache, fatigue or myalgia, diarrhea, and vomiting, only occur in less than 10% to 20% of children [13].

Generally, the symptoms appear for approximately 6 days in children aged 5-17 years. Some of these symptoms can appear longer, whereas 4.4% of symptoms persist up to 4 weeks and 1.8% of symptoms are still present up to 8 weeks [15]. "Long COVID," "post-COVID syndrome," or "post-acute sequel of SARS-CoV-2 (PASC)" are terms that are often used to describe symptoms that persist around 4-12 weeks after being infected [16]. Other literature defines post–COVID-19 condition as new symptoms that appear and persist about 8 weeks after being infected with SARS-CoV-2 [17]. The prevalence of post–COVID-19 condition in children is different in each study, ranging from 4% to 66% [18]. The most common symptoms of post–COVID-19 condition are cognitive difficulties, headache, fatigue, fever, myalgia, cough, dyspnea, abdominal pain, diarrhea, and anosmia or altered sense of smell [16]. Different symptoms and severity are associated with different immune responses. Many aspects of the immune response in children are still unclear due to limited research in this population [12]. Accordingly, in this study, we aim to examine anti-RBD IgG antibodies over time and characterize the signs and symptoms of post–COVID-19 condition in pediatric patients at the time of diagnosis and at 2 weeks and 1, 3, and 6 months following infection.

Methods

Study Design

This study is a single-center, longitudinal observational study. Pediatric patients diagnosed with COVID-19 confirmed by molecular assay using nasopharyngeal swab will be recruited. The patients will be tested at the time of diagnosis and at 2 weeks and 1, 3, and 6 months after diagnosis to observe the kinetics of anti–SARS-CoV-2 antibodies. The Roche Elecsys Anti-SARS-CoV-2 S assay will be used to quantify the immunoglobulin M (IgM)/IgG–spike protein–RBD titer. We will also observe the signs and symptoms of the patients up to 6 months after infection to identify the sequelae of the post–COVID-19 condition cases.

Study Setting

The study is being conducted in Dr Sardjito General Hospital, Sleman District, Yogyakarta Province, Indonesia. This is a tertiary referral hospital for Yogyakarta, Southern Central Java, and Eastern Indonesia regions.

Sample Size

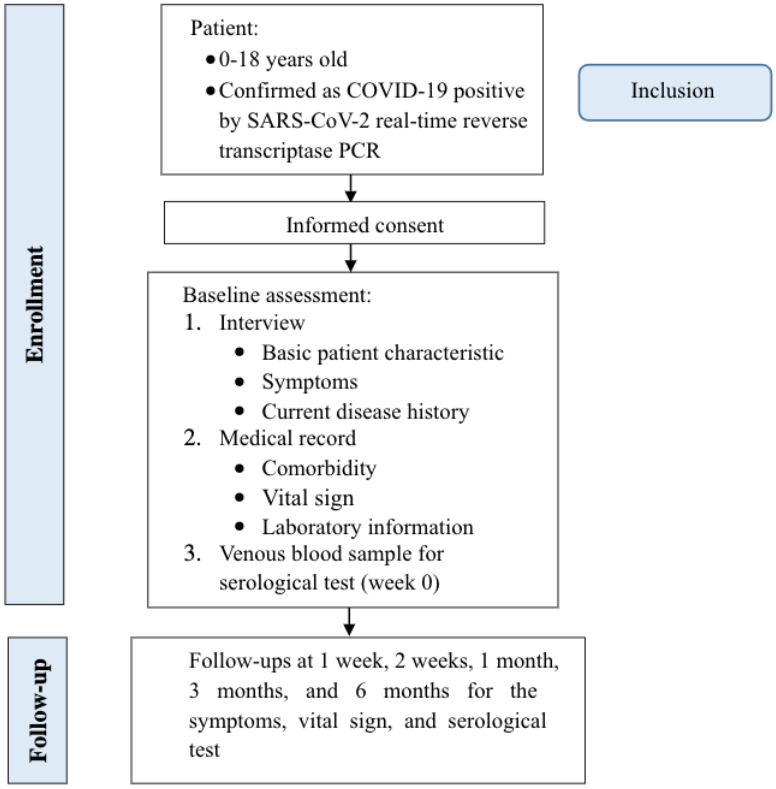
Samples were obtained by the total sampling method. We included all pediatric patients who met the inclusion criteria from February to April 2022.

Participants

Patients will be observed prospectively after a confirmed diagnosis of COVID-19 in isolation wards at Dr Sardjito General Hospital. The inclusion criteria for this study are all patients aged 0-18 years who are confirmed as COVID-19 positive by SARS-CoV-2 real-time reverse transcriptase polymerase chain reaction (RT-PCR) with their legal guardian's agreement to participate (Figure 1). There are no exclusion criteria for this study.

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Figure 1. Study flowchart of inclusion criteria and data collection. PCR: polymerase chain reaction.



Data Collection

Patient data will be retrieved from their medical records, which will include: (1) basic patient characteristic such as date of birth, sex, age, address, and referral case; (2) current disease history (symptoms, travel history, contact history in past 14 days, COVID-19 vaccination status, history of treatment in previous health facilities, and laboratory and imaging examination in previous health facilities); (3) comorbidity (diabetes; cancer; hypertension; obesity; heart disease; chronic obstructive pulmonary disease; chronic liver disease; chronic kidney disease; autoimmune disease; HIV; other infectious comorbidities such as hepatitis B and C, malaria, and dengue; and other immunodeficiencies such as long term steroid use and pelvic inflammatory disease); (4) vital signs and anthropometric parameters; (5) laboratory information (SARS-CoV-2 RT-PCR of the nasopharyngeal or oropharyngeal swab; complete blood count; electrolyte; blood glucose; ferritin; C-reactive protein; procalcitonin; lactate dehydrogenase; liver transaminases; serum blood urine nitrogen and creatinine; prothrombin time and activated partial thromboplastin time; D-dimer; lactate; blood gas analysis; cerebrospinal liquor examination; blood culture; broncho-alveolar liquid culture; and chest X-ray, computerized tomography scan, magnetic resonance imaging, or other imaging examination); and (6) clinical management data (drugs, intravenous fluid, supplements, oxygenation, blood transfusion, ventilator support, and other intensive care support).

Venous blood samples for serological tests will be drawn as a baseline when the diagnosis is made. Further serial blood samples will be collected at 2 weeks and 1, 3, and 6 months after the diagnosis (Figure 1). Samples will be collected in the clinical pathology laboratory. The data of any resolution or persistence of symptoms, such as fever, cough, runny nose, dyspnea, sore throat, seizure, cephalgia, malaise, nausea, vomitus, diarrhea, abdominal pain, myalgia, the loss of taste, the loss of smell, and dermatological disorder, in addition to patients' vital signs, travel history, contact history, compliance with health protocols, any possible COVID-19 reinfection, COVID-19 vaccination status, therapy, and blood test result, will be recorded in each subsequent monitoring time point. A flowchart of the inclusion criteria and data collection of this study is shown in Figure 1.

Blood Samples Collection and Storage

Samples will be collected in a vacutainer and sent to the pathology clinic laboratory for testing. The protocol is to proceed to centrifugation at 4000 rpm for 10 minutes. The samples will be uniquely coded and stored at –80 °C until use.

The Roche Elecsys Anti-SARS-CoV-2 S Assay

The Roche Elecsys Anti-SARS-CoV-2 S assay is an immunoassay for the in vitro quantitative determination of total antibodies to the SARS-CoV-2 spike protein RBD in human serum and plasma. The test is intended as an aid to assess the adaptive humoral immune response, including neutralizing antibodies to the SARS-CoV-2 spike protein after natural infection with SARS-CoV-2 or in vaccine recipients. The assay is run on a Cobas e 411 analyzer, which utilizes an electrochemiluminescence immunoassay with the double-antigen sandwich principle. Calibration and quality control will always be performed before running the samples. The values obtained should fall within the defined limits. The analyzer automatically calculates the analyte concentration of each sample in U/mL with value ≥0.80 U/mL as a cut-off for positive anti–SARS-CoV-2 spike protein [19].

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Data Management Plan

All data are collected in an application-based data collection tool. Data will be stored on self-managed servers and only can be accessed by authorized research personnel.

Data and Statistical Analyses

We will observe the kinetics of antibody response to the RBD of the spike protein of SARS-CoV-2 and the persistent signs and symptoms up to 6 months after the onset of infection.

Antibody titer data will be reported as means and SDs at baseline (when the diagnosis is made) and each monitoring time point (2 weeks and 1, 3, and 6 months after diagnosis).

The acute infection symptoms and post–COVID-19 follow-up clinical features will be reported in frequencies and percentages. The comparison of patient groups stratified by disease severity and RBD antibody will be analyzed and presented by graphs at the 1, 3, and 6-month follow-up time points.

Ethics Approval

This study was reviewed and approved by the Medical and Health Research Ethics Committee, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada (KE/FK/1288/EC/2021). The legal guardian of all participants will be provided with an information sheet detailing the aim and rationale for the research; inclusion and exclusion criteria; what will happen if they agree to take part; any risks of taking part in the study; the clarification of the process for ensuring anonymity and confidentiality, including any limits to confidentiality; what information will be held about them and who will have access to it; possible benefits; and plans for project report. All the legal guardians of the participants will then be required to sign the informed consent form before participating in the study. Additionally, all participants' identifiable data will first be anonymized. The identifiable and anonymized data will be stored in separate secure cloud-based databases before being transferred to the Research Data Store. Finally, each participant will be compensated Rp 50.000,00 (US $3.37) at each monitoring time point.

Results

Participant enrollment started in February and was extended to April 2022. The data collection was conducted up to 6 months following the last participant enrolled. As of September 30, 2022, a total of 58 patients were enrolled. After data collection, results are expected to be analyzed in August 2023.

Discussion

Expected Findings

This study aims to observe the kinetics of anti–SARS-CoV-2 antibodies and post–COVID-19 condition in children, up to 6 months after SARS-CoV-2 infection. SARS-CoV-2 consists of 4 main structural proteins, namely small envelope glycoprotein, membrane glycoprotein, nucleocapsid protein, and spike glycoprotein. The spike glycoprotein is divided into 2 subunits, S1 and S2. The S1 subunit includes RBDs that mediate viral binding to host cells via the ACE-2 receptor. Antibodies formed against the RBD on the S1 subunit have the potential to neutralize SARS-CoV-2 by preventing the binding of the virus' ACE-2 receptor and endocytosis [20].

It takes 18 days from RT-PCR positivity to seropositivity (ie, antibody detection) [21]. Antibodies are detectable by the end of the first week in most patients, but progression can take weeks in patients with subclinical or mild infections. SARS-CoV-2 antibodies can be used to detect the presence of COVID-19 infection 1-3 weeks after the disease onset. In the acute phase, IgM peaks around 2-5 weeks following disease onset and then declines in 3-5 weeks before being undetectable. The immunoglobulin A anti-S1 antibodies decreased 1 month after diagnosis and remained detectable thereafter. The IgG peaks later, around 3-7 weeks following disease onset, and then persists for at least 6-8 weeks. Survivors with more severe symptoms show a stronger antibody response than asymptomatic and symptomatic survivors, in which IgM, IgG, and immunoglobulin A were found at higher titers and last longer in the body [22].

Post–COVID-19 condition is a condition where the symptoms of COVID-19 persist for a few weeks or months after SARS-CoV-2 infection [23]. Symptom usually persist around 4-12 weeks after being infected with COVID-19 [16,24]. The common symptoms are fever, fatigue, dyspnea, and myalgia [25]. Other symptoms that are present include chest pain, paresthesia, headache, hair loss, anosmia-ageusia or parosmia/anosmia, gastrointestinal symptoms, dizziness, weight loss of more than 5% of body weight, arthralgia, tremor, cough, palpitations, tiredness, difficulty concentrating, and increased need for sleep [25,26].

Older age and the presence of allergies are associated with higher risk of persistent symptoms after being infected with COVID-19. Those aged 6-18 years have a 3 times higher risk of persistent symptoms compared to children aged <2 years [27]. Children with allergies have a 2-3 times higher risk of persistent symptoms [27,28]. Patients with preexisting neurological comorbidities are also associated with persistent symptoms and have a 4 times higher risk of persistent symptoms after COVID-19 infection [28].

Research related to SARS-CoV-2 antibody kinetics in children is limited, and studies concerning the post–COVID-19 condition cases are scarce. It is important to conduct more research to determine children's antibody response to SARS-CoV-2 infection and post–COVID-19 condition symptoms as the basis for patient management and forthcoming policy formulation.

This study will have recruitment and retention obstacles because it is difficult to get parental consent for serial blood sampling for children. This study will observe the development of post–COVID-19 condition symptoms and the kinetics of the COVID-19 antibodies for up to 6 months, making compliance from respondents and their families particularly important.

Conclusions

At the completion of this study, we will be able to learn more about the dynamics of anti-RBD SARS-CoV-2 IgG antibodies and gain valuable information concerning post–COVID-19 condition in children in Indonesia for up to 6 months following

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infection. Additionally, this research may serve as a foundation for government decisions about vaccination programs and prevention measures.

Acknowledgments

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Data Availability

The data sets generated during and/or analyzed during this study are available from the corresponding author on reasonable request to support scientific transparency.

Conflicts of Interest

None declared.

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Abbreviations

ACE-2: angiotensin-converting enzyme 2
IgG: immunoglobulin G
IgM: immunoglobulin M
RBD: receptor-binding domain
RT-PCR: real-time reverse transcriptase polymerase chain reaction
WHO: World Health Organization

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Protocol

Virtual Risk Management—Exploring Effects of Childhood Risk Experiences through Innovative Methods (ViRMa) for Primary School Children in Norway: Study Protocol for the ViRMa Project

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Abstract

Background: Research indicates that risky play benefits children's risk assessment and risk management skills and offers several positive health effects such as resilience, social skills, physical activity, well-being, and involvement. There are also indications that the lack of risky play and autonomy increases the likelihood of anxiety. Despite its well-documented importance, and the willingness of children to engage in risky play, this type of play is increasingly restricted. Assessing long-term effects of risky play has been problematic because of ethical issues with conducting studies designed to allow or encourage children to take physical risks with the potential of injury.

Objective: The Virtual Risk Management project aims to examine children's development of risk management skills through risky play. To accomplish this, the project aims to use and validate newly developed and ethically appropriate data collection tools such as virtual reality, eye tracking, and motion capturing, and to provide insight into how children assess and handle risk situations and how children's past risky play experiences are associated with their risk management.

Methods: We will recruit 500 children aged 7-10 years and their parents from primary schools in Norway. Children's risk management will be measured through data concerning their risk assessment, risk willingness, and risk handling when completing a number of tasks in 3 categories of virtual reality scenarios: street crossing, river crossing, and playing on playground equipment. The children will move around physically in a large space while conducting the tasks and wear 17 motion-capturing sensors that will measure their movements to analyze motor skills. We will also collect data on children's perceived motor competence and their sensation-seeking personality. To obtain data on children's risk experiences, parents will complete questionnaires on their parental style and risk tolerance, as well as information about the child's practical risk experience.

Results: Four schools have been recruited to participate in data collection. The recruitment of children and parents for this study started in December 2022, and as of April 2023, a total of 433 parents have consented for their children to participate.

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Conclusions: The Virtual Risk Management project will increase our understanding of how children's characteristics, upbringing, and previous experiences influence their learning and ability to handle challenges. Through development and use of cutting-edge technology and previously developed measures to describe aspects of the children's past experiences, this project addresses crucial topics related to children's health and development. Such knowledge may guide pedagogical questions and the development of educational, injury prevention, and other health-related interventions, and reveal essential areas for focus in future studies. It may also impact how risk is addressed in crucial societal institutions such as the family, early childhood education, and schools.

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KEYWORDS

anxiety; childhood education; childhood risk experiences; children; development; eye tracking; injury prevention; injury; motion capturing; physical activity; prevention; questionnaire; resilience; risk management; risky play; social skills; validation; virtual reality; VR; well-being; willingness; Xsens

Introduction

Background

How children learn to handle risk and avoid injuries is poorly understood by researchers. Injuries remain the leading cause of child death and a leading cause of hospitalization in high-income nations despite widespread prevention efforts. Among the leading mechanisms of injury are motor vehicle crashes (being a passenger in a car) [1] and falls (eg, from high playground equipment) [2]. Drowning, pedestrian, and cycling injuries also represent threats of serious injury and death [3]. Improved car safety has resulted in significant improvements in injury rates, but injury prevention efforts must be multifaceted, addressing the physical environment and individual risk factors [4]. One novel and promising approach to child injury prevention may be through improving children's own ability to assess risk. In this regard, *play* appears to be an ideal context for children's learning, as the pretend or nonliteral aspect allows the players to test out risky behavior, situations, or actions without the severe consequences of real life. *Risky play* has therefore emerged as a topic of interest for researchers, parents, teachers, policy makers, authorities, and others working with children over the last 20 years. A growing body of research investigates various aspects of risk-taking, including playful activities, and indicates that the concept reflects a basic aspect of human life.

The link between childhood risky play experiences and subsequent ability to cope with hazards of everyday life warrants investigation. A common definition of risky play is "thrilling and exciting forms of physical play that involve uncertainty and a risk of physical injury" [5]. Through observations and interviews with children and early childhood education and care (ECEC) staff, Kleppe et al [6] and Sandseter et al [7,8] identified eight categories of risky play: (1) play with great heights, (2) play with high speed, (3) play with dangerous tools, (4) play near dangerous elements, (5) rough-and-tumble play, (6) play where children go exploring alone, (7) play with impact, and (8) vicarious risk.

Qualitative studies suggest that children develop skills and learn to cope with risk through risky play that translates to real life and is retained for a lifetime [9-14]. Engagement in risk-taking activities leads to brain development, for example, and enhances the ability of 18- to 19-year-olds to predict outcomes, supporting the hypothesis that children and youth will learn risk assessment through risk experiences [15,16]. Moreover, there are indications that risky play in early childhood has a positive impact on the development of children's own risk management skills [11,17]. Researchers also suggest that the ability to handle risk is a favorable evolutionary trait [18] and that outdoor risky play offers several positive health effects for children such as resilience, social skills, physical activity, well-being, and involvement [19,20]. In addition, there are indications that the lack of risky play and autonomy increases the likelihood of anxiety, both in childhood [21-24] and subsequently in adolescence and adulthood [18,25-29].

Children's affective, cognitive, perceptual, and motor systems are all involved in children's behavior and activities in an integrated manner. Children's motor competence, including their capacity to execute fundamental motor skills as well as their perceived motor competence, therefore, impacts and is most likely reciprocally impacted by healthy risk-taking. Possessing high perceived or actual motor competence allows children to engage in different interactions with risky environments and tasks compared with children who possess lower perceived or actual motor competence because perception and action are intertwined processes occurring between the individual, the task, and the environment [30,31].

Despite its well-documented importance and the willingness of children to engage in risky play [5,6,32,33], there are indications that this type of play is increasingly restricted [34-37]. ECEC institutions restrict risky play because they fear being sued in case of child injury and they receive pressure from the insurance industry to avoid any injuries [32,35,36,38,39]. Moreover, parents restrict children from playing outdoors because they are concerned about traffic accidents [39-43], that children could be injured or kidnapped, or because they fear rainy or cold weather [39]. When children are prohibited from risky play through overprotection, there may be negative effects on their development.

The downward trend in children's opportunities for risk-taking in play [44,45] may also have wider negative consequences. First, an increased focus on safety has resulted not only in greater restrictions on children's movement but also less challenging and engaging play environments [35-37,46-50]. Second, there is concern that lack of play opportunities may

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result in negative long-term consequences such as reduced well-being and excessive or unhealthy risk-taking (eg, through risky substance use or sexual behavior).

As evidence accumulates concerning the benefits of risky play, both researchers and policy makers have begun to recognize the limitations of our current knowledge. Most existing data are based on descriptive studies and fail to offer rigorous data to address potential causal relationships between risky play and benefits to children's health, development, and learning. The field hypothesizes that engagement in risky play in childhood may reduce the likelihood of subsequent anxiety, faulty decision-making, and excessive risk-taking later in life. However, those hypotheses are generally based on data from small samples and frequently lack the rigor of longitudinal designs, randomization, and control groups.

One reason for the sparsity of rigorous data is that the hypotheses are difficult to test empirically. There are obvious ethical issues with conducting studies designed to allow or encourage children to take physical risks with the potential of injury. There are also ethical barriers to restricting children from playing freely or to randomly assigning some children to play freely and others not. Thus, assessing the long-term effects of play choices is problematic. Creative methodologies such as Kretch and Adolph's [51] and Adolph and Kretch's [52] experiments with the visual cliff (ie, allowing children to cross narrow bridges without the real possibility of falling) or Morgan et al's [53] laboratory-based activity room to assess behavior should be further developed, perhaps leveraging virtual reality (VR) technology [54,55] as a promising methodology. However, transferability of results from laboratory or other controlled environments to real-life contexts poses a potentially inappropriate leap [56]. There is a need to continue to develop VR, augmented reality, and other technologies to simulate real-life settings and strengthen ecological validity of research methods. Using VR or augmented reality enables researchers to test situations that would be too dangerous to investigate in real life. Adding measurements of bodily movement and eye-tracking equipment, mostly absent in the field, would contribute detailed data on children's reactions to stimuli in their environments. Understanding connections between risk experiences and risk management is central to understanding how risky play affects overall health and development.

In the Virtual Risk Management—Exploring Effects of Childhood Risk Experiences through Innovative Methods (ViRMa) project, risk is defined as future uncertainties that can entail negative or positive outcomes [44]. Further, risk is seen as both objective and subjective [57,58]. *Objective* risk refers to an estimation of the probability of an adverse event and of the expected harm or loss. The ways in which objective factors are experienced as risky depend on the individuals and are referred to as *subjective risk*. Both personality and temperament traits as well as cognition [59-62] and previous experience [57,63] affect an individual's subjective risk experiences and decisions. Risk decisions can be interpreted as representing a balance between an individual's propensity to take risks, the potential rewards of risk-taking, the perceived *danger* in the situation, and *previous experience* with injuries or losses [57].

In the ViRMa project, we aim to explore risks that are relevant to children's everyday life and that they can at least partly control themselves. These are risks where children's dynamic choices and actions matter. To capture this and to develop scientific measures, we have developed a conceptual framework (in process to be published in a theoretical paper) to describe the dynamic process through which children manage risks, a framework that captures how the child acts in an environment with potential for risk and where their risk willingness (ie, the emotional drive to seek and take risk, overlapping conceptually with sensation seeking and risk seeking), risk assessments (ie, the cognitive process of evaluating risk throughout a risk situation), and risk handling (the behavioral or motor process of managing a risk) can be observed through their actions and behaviors. Overall, children's dynamic risk management therefore represents the outcome of a defined task or the observable outcome of whether they fail or succeed in the risk situation.

Study Objectives

The aim of the overall ViRMa project is to develop, test, and validate ethically appropriate, technologically innovative, and easy-to-use methods to explore the relationship between children's risk experiences through play and daily activities and their risk management skills. We introduce methods that to our knowledge did not exist before ViRMa. Thus, the project focuses especially on method development and exploration concerning whether the methods are useful and valid to measure the relationships of interest.

This paper describes the protocol of the third stage in the ViRMa project. Stages 1 and 2 had the following aims: (1) develop VR, eye-tracking, and motion-capturing tools and software, plus psychometric scales and additional data collection methods to provide insight into how children assess and handle risk situations using ethical study designs; (2) conduct a small-scale pilot study to test the feasibility of the research methods, particularly the developed VR scenarios, the eye-tracking technology, and the motion capture system.

In the presently reported final stage, the tools and methods developed in stages 1 and 2 will be used for large-scale data collection. The aim of stage 3 is twofold: (1) establish measures for children's risk management, suggestively split into risk willingness, risk assessment, and risk handling through the VR, eye-tracking, and motion-capturing data, as well as validating the questionnaires to a Norwegian context, and (2) explore how children's past risk experiences through play and daily activities (collected through parent questionnaires) are associated with their risk management.

In this trial, we are measuring associations between behaviors in VR with demographics as a first step to validate the methods and explore relationships between children's risk experiences, their motor skills, and their risk management skills. If we succeed with the stage 3 ViRMa project, the long-term goal for the project group is to further develop a large-scale project with children and parents from different countries and cultural contexts, preferably with longitudinal data collection. This would enable both comparative analysis across cultures and longitudinal data on how children's motor skills and risk

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management skills develop over time in accordance with their opportunities for risk experiences.

Methods

Study Design

This study is a quantitative cross-sectional study of children's risk management in VR scenarios, measuring their risk willingness, risk assessment skills, and risk handling skills as well as their motor skills. Cross-sectional data on children's self-perceived motor skills and sensation seeking personality will also be collected. In addition, the study has a retrospective component that gathers extensive data from parents' questionnaires concerning the children's background experiences: parenting styles, parental risk tolerance, and children's practical risk experience from childhood. Analyses will explore associations between cross-sectional data and retrospective data.

Participants and Eligibility Criteria

We aim to recruit 500 children (50% girls and 50% boys) in second to fourth grade (7- to 10-year-old). This age group was chosen because we want to not only explore risk management skills among children as early in child development as possible but also consider practical matters such as the appropriate age to use current generations of VR goggles given their large size, weight, and functionality. VR technology develops rapidly, and studies involving even younger children would be an aim in the future. Further, children aged 7 to 10 years are likely familiar with navigating traffic and nature environments, while also remaining interested in exploring a playground, which reflects the tasks in the VR scenarios in this study. This is also an age group when children are more likely to behave independently and outside adult supervision, creating greater injury risk.

We aim to recruit children from both urban and rural primary schools in Norway because children in rural areas usually spend more time playing and being active in nature environments than children living in urban areas. The pilot study demonstrated that VR is a popular data collection method among children. To avoid excluding any children from a particular setting, we will select 4 primary schools from different parts of Norway and invite all children in the relevant age range at each school to participate. Inclusion criteria are as follows:

- Between the ages of 7 and 10 years (grades 2, 3, and 4 in Norwegian schools)
- Informed consent obtained from parents to participate
- Assent obtained from the child to participate.

We will contact selected schools through the principal and ask if they are willing to participate. If they agree, parents will then be contacted through the school's web-based information system, with information about the project and an electronic consent form provided. Children whose parents provide consent will then be placed on a participant list and names will be replaced with a random code. Children will also be asked for assent to participate, and if they decline, their name and code will be deleted.

Parents (both mothers and fathers) of children will be invited to complete the web-based survey.

Data Collection and Measures

VR

VR technology encompasses computer technology enabled by, in this case, head-mounted displays (goggles) in which one experiences and physically moves around in scenarios that closely represent real life. Participants will be fully immersed in the virtual environment, providing visual and auditory stimuli to create illusive feelings of physically existing in that environment [64]. VR technology is an innovative and successful strategy for training and research on health and safety behavior among both adults [64,65] and children, with a large body of child research focused on street-crossing [54,55,66,67] and bicycling tasks [68,69]. In this study, we use VR technology (HTC Vive Pro Eye VR headset), with 4 SteamVR 2.0 Base Stations defining a VR area of 6 × 7 m for free movement, to test how children manage different kinds of risk situations.

On the basis of research into common causes of injury among children [1-3], we developed three categories of VR risk scenarios: (1) street crossing, (2) crossing a river, and (3) Balancing on high playground equipment. All scenarios include various tasks with increasing levels of difficulty and risk.

The VR scenarios were developed through collaboration between the research group and a VR design company (Nordic Neurotech AS) from September 2021 to March 2022. The aim was to create fully immersive scenarios in a virtual world where children performed risky tasks and judged the experience to be as similar to reality as possible. The veracity of the VR scenarios is strengthened through realistic sounds integrated in the VR goggle headphones (eg, city sounds, car sounds, birdsongs, and sounds of running water). In all VR scenarios, children receive the same prerecorded messages before each task, telling them what to do (eg, "Cross the river without falling down").

The VR software provides data output in the form of a text file (.txt), with one line for each recorded hertz. Within each line, the position of the headset and the 5 Vive trackers are provided using the x, y, and z coordinates. Data on the headset and tracker's rotation are also available in the data set. Similarly, the position of every simulated moving object (cars and bicycles) is represented with coordinates. Quantitative data from this text file are obtained through MATLAB analysis.

Street Crossing

The street crossing scenario consists of 2 urban traffic environments. In both environments, children are exposed to 3 different tasks with varying levels of risk, with risk level varied by manipulating harm severity and probability of being hit [70,71]. The lowest risk scenario involves bicycles and the highest involves both cars and bicycles. Probability risk is adjusted through traffic density and speed and by including traffic from 1 direction versus 2 directions. The first environment represents a bicycle pathway and includes buildings, trees, and grass surfaces (Figure 1, left side). The second environment replicates a busy urban street with buildings, sidewalks, and parked cars (Figure 1, right side); it

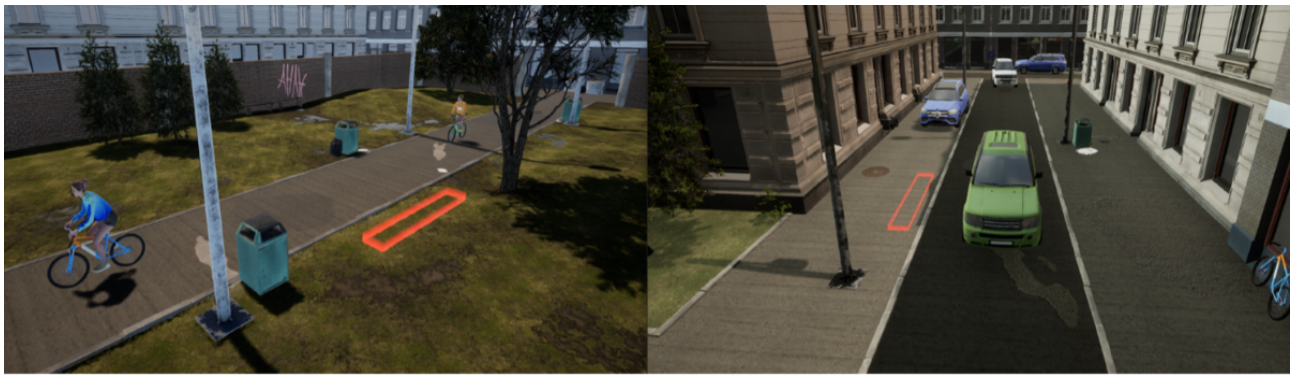
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includes a cars-only task as well as tasks with both cars and bicycles. In all cases, the child's goal is to cross the path or street without getting struck by a car or bicycle. All street-crossing scenarios incorporate realistic sounds from the urban environment (the sound of cars, bikes, people, etc).

If the child is hit by a bike or car, a new trial on that same task is provided. If the child is hit a second time, the VR continues to the next task. The time to complete tasks in the street-crossing scenario will vary across children because they will be free to take the time they need, both to assess the situation before acting and to perform the crossing. Pilot research found that children spent on average 3 minutes to complete the street-crossing tasks (Figure 1, left and right side).

Quantitative data points that will be obtained from the street-crossing tasks include measures related to the child's risk assessment (eg, time used to assess the environment before crossing the street and fixation on vehicles before crossing the street), risk willingness (eg, distance to vehicles when starting to cross the street), risk handling (eg, speed of crossing, running, acceleration, and deceleration), and risk management outcomes (eg, number of times the child was hit or almost hit by vehicles).

Figure 1. Screenshots of the virtual bicycle pathway environment and the virtual street environment. The red square represents the point where children are asked to move to.



River Crossing

The river-crossing scenario presents a rural environment with a flowing river. Children complete 7 tasks, each with the goal of crossing the river without falling into the water. Five of the tasks involve balancing on planks to cross the river, whereas in the other 2 tasks children must step or jump between elevated stones to cross. Similar to the street-crossing scenario, the 7 river-crossing tasks vary in risk, based on harm severity and probability of failure [70,71]. Harm severity risk levels are manipulated by the speed and depth of the river and the presence of rocks in the water. Probability risk is adjusted by the width (between 8 and 38 cm) of the balance planks and the placement of stepping stones (ie, how close or far they are from each other). In all river-crossing scenarios, children hear sounds from a rural nature environment (eg, the sound of running water, wind, and birds).

If the child falls into the water, a new trial on that same task is provided. If the child falls a second time, the VR continues to the next task. The time required to complete the river-crossing scenario tasks will vary between children because they are free to take the time they need, both to assess the situation before acting and to perform the crossing. Pilot research found that children spent on average 3 minutes to complete the river-crossing tasks (Figure 2).

Quantitative data points that will be obtained in the river-crossing tasks include measures related to the child's risk assessment (eg, time used to assess the environment before crossing the river), risk willingness (eg, opting out of the task, jumping between rocks, and choosing the narrow plank), risk handling (eg, speed of crossing, keeping both feet on the ground while balancing, acceleration, and deceleration), and risk management outcomes (eg, number of times the child falls into the river).

Figure 2. Screenshots of the river crossing scenario, one of the plank tasks and one of the stepping stones task.



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Playground

The playground scenario presents a balancing play structure in an urban playground environment. Unlike the first 2 scenarios, where children perceive a fixed and objective task to cross the street or river, in the playground scenario, children are free to move and play as they like, without fixed objectives or goals. The virtual balancing structure comprises a complex pattern of balance beams of varying widths, vertical pillars of varying diameters, and 4 different height zones above the ground surface. Similar to the first 2 scenarios, variation in harm severity and probability of failure occur within the playground scenario. Probability risk varies by the difficulty of the play areas (ie, a child could choose to balance on the narrowest beams or jump out to one of the pillars), whereas harm severity varies by the height zones children choose to explore. In the study, children are provided 3 minutes to explore the playground before the scenario automatically ends. If a child falls off the playground equipment, he or she will enter the starting point of the playground task and have the opportunity to further play and explore during the remaining time in the 3-minute period. The sounds of an urban environment (eg, cars, bikes, or people) are emitted through the headphones (Figure 3).

Figure 3. Screen shot of the playground scenario.



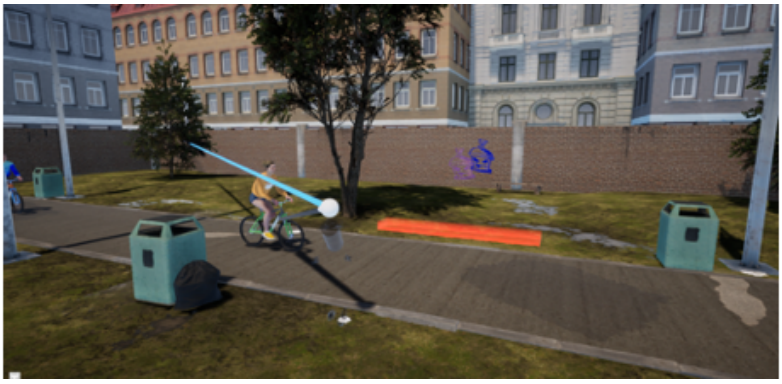
Quantitative data points that will be obtained during the playground task include measures related to the child's risk assessment (eg, time used before starting to balance on a beam), risk willingness (eg, stepping out on pillars, jumping over gaps, and time spent in high-risk zones), risk handling (eg, speed of balancing, keeping both feet on the ground while balancing, acceleration, or deceleration), and risk management outcomes (eg, number of times the child falls off the playground equipment).

Eye Tracking

Eye-tracking technology is used extensively in research to explore topics such as how humans learn [72] and how humans use their gaze when performing safety practices [73], as well as for medical training (eg, in laparoscopic surgery or when detecting anatomical injuries) [74]. The technology is also used to measure how children's eye movements are related to their performance, risk, and safety behavior when cycling [69]. In street-crossing VR tasks, eye-tracking data from one study demonstrated that children's ability to focus on factors most salient for a safe crossing is compromised when the environment is more visually loaded, possibly causing them to miss critical information [75]. However, knowledge about the relationships between children's eye movements and their risk management is limited.

In this study, we will use eye-tracking technology (Tobii Pro) integrated in the VR goggles to explore how children use their gaze and eye movements to identify risk factors that guide their navigation, bodily movement, and risk decisions in the VR scenario environments. Eye-tracking data will be logged in 90 Hz and provide data on the eye-tracking target (x, y, and z coordinates), including what object the child looks at. Because this information is provided continuously with a refresh rate of 90 Hz, it can be transformed into variables describing the length of time children look at various objects or parts of the environment, direction, and shifts of the child's focus and information about how children follow moving objects such as vehicles with their eyes (Figure 4).

Figure 4. Screen shot from the bicycle path scenario, showing eye-tracking as a blue line.



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The eye-tracking data from all VR tasks will be processed in MATLAB to generate quantitative measures related to the child's risk assessment (eg, fixation on vehicles before crossing the street, looking at oncoming or departing bicycles and cars before crossing, looking both ways before crossing the street, looking at planks and balance beams before and while crossing, looking at water and rocks, and looking at the ground below the playground equipment) and risk handling (eg, looking at oncoming bicycles and cars while crossing).

Motion Capturing and Analysis

Part of the innovative approach of this project is assessing children's motor competence when they navigate and explore VR scenarios. We will accomplish this through whole-body motion capture, which offers a comprehensive understanding of the individual's qualitative and quantitative signatures of movement. This methodology represents a novel approach toward the assessment and understanding of motor competence in children, extending current and predominant approaches that focus on tasks with down-scaled complexity, detailed instructions, and highly specific assessment criteria. Existing approaches have been critiqued for their lack of developmental and ecological validity [76].

The Xsens MTw Awinda system of motion-capturing technology is an innovative and user-friendly method to track human motion in real time. The portable system provides accurate time-synchronized data with accurate measures of whole-body movements. It has been used widely in research to capture human motion in sport, physical activity, and rehabilitation [77-80]. In this project, MTw Awinda is used to track and capture children's motion and bodily movements when handling risk in VR scenarios.

The Xsens MTw Awinda system consists of 17 wireless inertial measurement units, each of which consists of a gyroscope, an accelerometer, and a magnetometer. MTw Awinda samples data at 60 Hz through a proprietary radio protocol at 2.4 GHz, which provides accurate time synchronization across the wireless network within 10 µs. Physically, the inertial measurement units are 47 × 30 × 13 mm, weigh 16 g, and are attached to the children with Velcro straps on the following anatomical locations: forehead, sternum, palmar side of the hand (right or left), lateral side of the upper arm (right or left), wrist (right or left), lateral side of the lower leg (right or left), lateral thigh (right or left), foot (right or left), upper part of the scapula (right or left), and lower back (L5, height of the iliac spine). The system provides 3D kinematical data (position, velocity, acceleration, and orientation) on the movement of 23 different segments (eg, head, upper hand, or foot) as well as angular movements of 22 different joints. The dynamic accuracy is 0.75° root-mean-square (RMS) and 1.5° RMS for roll or pitch and heading, respectively. In the ViRMa project, children will wear the Xsens MTw Awinda sensors while completing all VR tasks.

The raw Xsens data will be exported and further processed in MATLAB R2022a (MathWorks Inc) by algorithms developed by the research group. After inspection of the frequency spectrum content of the raw data with the periodogram method, low-pass (zero-phase) Butterworth filtering procedures will be applied to remove unwarranted noise. To obtain numeric measures related to children's motor competence and risk handling strategies (ie, bodily movement strategies), 2 main approaches to movement analysis will be applied. First, analysis of children's overall locomotory strategies, defined as the movement (transport) of the entire body as children navigate the VR scenarios, will be conducted by examining the 3D kinematic variability of the pelvis segment (ie, the location of the body center of mass). This analysis generates variables on various motoric risk handling strategies, such as velocity and acceleration profiles (ie, speeding up or slowing down), angle of projection when moving across the road, and degree or pattern of postural movements to maintain balance and stability. In the second approach, the kinematic variability of the major joints from the whole body (ie, neck, shoulders, elbow, hip, knee, and ankle) will be analyzed. Here, numeric measures closely associated with motor competence, such as degree of repetitiveness and variation in joint movements (entropy), association between upper body versus lower body movements, and interjoint coordination patterns, will be examined.

Child Questionnaires

Children's Sensation Seeking

Sensation-seeking personality, defined as an innate willingness to take risks and the extent to which children seek risk in their everyday life, will be assessed using the Sensation Seeking Scale for Young Children (SSSYC) [81]. A 27-item instrument, the SSSYC was developed to assess sensation seeking among children aged 7-12 years. Each item presents 2 statements of preferences that child respondents choose between. As an example, children are presented the following options: (1) *I am the sort of person who would like to sled fast down a steep hill* compared with (2) *sledding fast down a steep hill sounds scary to me*. The SSSYC includes three subscales, each with strong evidence for internal reliability: (1) thrill seeking (α=.85), (2) behavioral inhibition (α=.83), and (3) behavioral intensity (α=.83) [81]. Selecting the statement indicating higher levels of the measured subscale earns 1 point on the overall subscale score. In the above example, selecting the first option earns 1 point on the thrill-seeking scale, whereas choosing statement 2 earns 0 points.

For this study, the SSSYC was first translated from English to Norwegian by author OJS. Then all primary researchers in the project group discussed the translation to revise unclear wordings and adapt words and phrases to fit the Norwegian context. Next, the Norwegian version of the scale was back-translated to English by a professional translator, and then the 3 versions (original English, translated Norwegian, and back-translated English) were discussed among the project group to ensure that the original meaning of the statements was reflected in addition to being relevant and understandable for Norwegian children. In the ViRMa project, we will administer the SSSYC orally, with a researcher recording the child's responses on the web.

Children's Perceived Motor Competence

The Pictorial Scale of Perceived Movement Skill Competence [82] will assess children's perception of their own motor competence. In this 18-item measure, children view 2 drawings

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of various movements or activities (eg, climbing up a rope or riding a kick scooter) in each item. In one drawing, the child manages the task well, and in the other, the child does not manage the task well. Children are asked which picture most resembles themselves and their skills and also to indicate their perceived competence in that skill as (1) really good, (2) pretty good, (3) sort of good, or (4) not too good. The scale has separate boys' and girls' versions, with three reliable subscales resulting (1) Active Play (α=.78), (2) Object Control—Hand Skills (α=.76), and (3) Fundamental Movement Skills with Leg Action (α=.84) [82].

For this study, the Pictorial Scale of Perceived Movement Skill Competence was translated from English to Norwegian by the author HL. Then, all primary researchers in the project group discussed the translation to revise unclear wordings and adapt words and phrases to fit the Norwegian context. Because this scale is primarily based on drawings and not words, it was not back-translated. In the ViRMa project, the Pictorial Scale of Perceived Movement Skill Competence will be conducted orally, with the drawings shown to the child on a tablet.

Parents Questionnaires

Parents' Tolerance of Risk in Children's Play

The Tolerance of Risk in Play Scale (TRiPS) [83] will be used to gather data on parents' tolerances of risk during their children's play. The TRiPS is a 31-item scale focusing on parents' willingness to let children take risks in play. Parents select "yes" or "no" for questions such as "Would you let your child jump down from a height of 3-4 meters (10-13 feet)," or "Would you allow your child to play on equipment if you thought there was the potential s/he may break a bone?" The original English version of the TRiPS was validated using Rasch analysis and found that all items had mean square values within an acceptable range for internal (construct) validity and that internal reliability statistics were excellent (showed a high person reliability index of 0.87) [83].

For this study, the TRiPS was first translated from English to Norwegian by the author EBHS. Then, all researchers in the project group discussed the translation to revise unclear wordings and adapt words and phrases to fit the Norwegian context. Next, the Norwegian version of the scale was back-translated to English by a professional translator, and the 3 versions (original English, translated Norwegian, and back-translated English) were discussed in the project group to ensure that the original meaning of the statements was retained in addition to being relevant and understandable for Norwegian children. In ViRMa, the TRiPS will be administered to all participating children's parents, both mothers and fathers, via a web-based platform using the survey tool SurveyXact [84].

Parenting Style

The Challenging Parenting Behavior Questionnaire (CPBQ) [85] will be used to assess the extent to which parents provide physical and verbal messages that encourage children to push their physical and mental limits. Parents are presented with 33 statements, such as "I play boisterously with my child" and "I encourage my child to do exciting things, such as jumping off high objects or climbing higher than he/she dares," which are answered on a scale from 1 (not applicable) to 5 (completely applicable). The instrument includes six subscales: (1) Teasing, (2) Rough-and-tumble play, (3) Encouragement of risk-taking, (4) Social daring, (5) Competition, and (6) Modeling. Internal reliability of the full scale ranges from α=.90 to α=.92 in samples of Dutch and Australian mothers and fathers, and the subscale reliabilities range between α=.63 and α=.84 in the same samples [85].

The original CPBQ was written in Dutch and translated to English using standard rigorous translation methods. For this study, the CPBQ was first translated from English to Norwegian by the author RK. Then, all primary researchers in the project group discussed the translation to revise unclear wordings and adapt words and phrases to fit the Norwegian context. Next, the Norwegian version of the scale was back-translated to English by a professional translator. The back translation to English was then discussed with Mirjana Majdandžić, who developed the original Dutch version, to ensure that the Norwegian version covered the meaning content of the original scale while still being relevant and understandable for Norwegian children. The project team also reviewed the back translation version in comparison with the original English version. In ViRMa, the CPBQ will be administered to all participating children's parents, both mothers and fathers, via a web-based platform using the survey tool SurveyXact [84].

Background and Demographic Information

To gather background and demographic information, children's parents, both mothers and fathers, will respond to items about children's age, ethnicity, past injury history, living conditions (urban vs rural), access and use of nature, modes of traveling to school, participation in extracurricular physical activity (eg, sports), ECEC experience, family socioeconomic background, and other relevant information. The survey will be administered along with the TRiPS and CPBQ via a web-based platform using the survey tool SurveyXact [84].

During the study, children will respond to questions to capture their experiences and feelings while participating in the VR scenarios. For example, they will be asked, "Did you feel it was for real?" and "Have you ever tried VR before?"

Data Collection Procedure

We will collect data in each school over the course of 2 to 3 weeks. We will install the VR equipment in a dedicated large room at each school, with enough space for a 7 × 6 m test area, with 4 SteamVR 2.0 Base Stations placed in each corner and room for children's free movement within the space. The test area, with all 4 base stations as well as the VR goggles, will be calibrated with the normal calibrating procedures in SteamVR 2.0. We will identify participating children individually in their classrooms and escort them to the test area. Sensors (17 Xsens sensors) and trackers (5 Vive trackers, version 3) will be placed on the child's body using Velcro bands. Next, we will introduce the child to the VR goggles and ensure that goggles are placed correctly on the head. VR goggles placement and eye-tracking measure sensitivity will then be calibrated through procedures in SteamVR 2.0. The child will enter a warm-up scenario in the virtual environment where they can explore a city park and

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familiarize themselves with being within, and moving around, the virtual world. During the warm-up, we will calibrate the Vive trackers to enable children to see their feet and also calibrate the Xsens sensors to ensure that motion-capturing measurements are correct. The last part of the warm-up scenario instructs the child about safety routines, as follows:

> *You will now be taken to three different scenarios where you should perform different tasks. The first scenario shows several traffic situations, including cars and bikes, where your task is to cross the street without being hit. The second scenario is a river in the forest where your task is to cross the river without falling into the water. Some tasks include balancing on a beam and some include stepping on stones to cross the river. The last scenario is an urban playground where you are allowed to do whatever you want and to play and explore the playground equipment as you like, for three minutes. I will be here walking next to you to make sure you don't trip on the cable (attached to the goggles). If you ever want to quit the trial or skip to the next task, you can just let me know and I will help you.*

When the child indicates that they are ready to start the test, we will initiate the surround-sound headset for further verbal instructions, and the child will enter the first and simplest street-crossing scenario task (ie, bicycle pathway). The verbal instructions built into the headset when entering each task are simple.

- Street crossing: "Cross the road without getting run over."
- River crossing: "Cross the river without falling down."
- Playground: "Here you can move around on the playground, explore if you want, and try not to fall down."

Risk levels increase with each scenario as described previously. Children will complete all tasks in each scenario in the following order: street crossing, river crossing, and playground. The pilot (stage 2 of the overall project) found that completing the warm-up or calibration and all tasks in all scenarios took approximately 15 minutes for each child.

After the child has completed all VR scenarios, we will remove test equipment from their body and ask them to join a researcher for a short interview. During the interview, which will last approximately 15 minutes, the researcher will use a tablet to complete the child scales and background questions orally with the child. Parents will receive the survey via email with a web-based link that includes a code that matches their child's code to enable matching the dyad's data.

Three researchers will conduct the data collection procedures in each school. The group of data collectors consists of 5 researchers (EBHS, OJS, HL, RK, and LS) who are well trained, have developed all the primary and secondary outcome measures in this study, and designed and prepared (including piloting the implementation of all test procedures) the study protocol.

Ethics Approval

The Norwegian Social Science Data Services approved the ViRMa project (project 324155). We treat all data and information related to the project in accordance with the ethical guidelines of Norwegian Social Science Data Services. Child-friendly methods of seeking informed assent from children will be used, and informed consent will be obtained from the children's parents or guardians. We will take careful measures to avoid placing research participants at risk by being sensitive to the specific challenges that arise in connection with involving children in research, as well as securing their right to withdraw from the research at any point. In the ViRMa project, we emphasize ethical responsibility in the presentation of all research results involving research participants in the project.

One possible undesirable effect of carrying out the data collection with VR scenarios is that children may become frightened of the simulated situations they encounter. A second risk is that children are overconfident, overestimate their risk management skills, and experience virtual falls in the VR scenarios that they find traumatic. Our pilot research suggested that these outcomes are both unlikely, but to address them, we will debrief all participating children, discuss their experiences, and remind them that their performance in VR tasks does not reflect reality.

Analysis

The measures obtained from the VR, eye-tracking, and Xsens data include quantitative variables related to the child's risk assessment, risk willingness, risk handling, and risk management. This study's explorative and groundbreaking nature implies that an essential part of the analysis is to develop and validate new measures based on VR, eye tracking, and motion capturing. Consequently, the plan for data analysis is relatively general. The study therefore sets a conservative significance level ($P<.01$) to reduce the risk of type 1 error.

Cluster analyses will be applied to group children's movement profiles based on the Xsens data divided into potential distinct groups by comparison of hierarchical agglomerative clustering methods: the Ward method and the between-groups average linkage method. For both methods, the squared Euclidean distance will be used as the measure of proximity. The final number of clusters will be determined by examining the agglomeration schedules and dendrograms generated for both techniques. Visual inspection of each cluster's membership will be conducted to assess the utility of each potential cluster solution. Once the most statistically robust and theoretical relevant cluster solution is identified, a K-means iterative partitioning method will be applied to fine-tune the clusters [86,87].

Global measures on the child's risk assessment, risk willingness, risk handling, and management will be established using exploratory factor analysis [88] drawing on data from VR, eye tracking, and motion capturing from the VR street crossing, river crossing, and playground tasks. RMS error of approximation (RMSEA), standardized root-mean-square residuals (SRMR), comparative fit index (CFI), and Tucker-Lewis index (TLI) will be used to evaluate and refine the established measurement models. Acceptable model fit is defined as RMSEA <0.1, SRMR <0.1, CFI >0.9, and TLI >0.9 [89]. Chi-square and chi-square difference tests will be conducted between the fitted and saturated models. However,

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no absolute thresholds for chi-square are set, following the sensitivity to sample sizes and the possibility that this measure may yield less precise estimates of the parameters [88,90]. Factor loadings will be investigated with the use of R^2 estimates (item >0.25) and standardized factor loadings (item >0.40) [88]. To validate the psychometric scales in the Norwegian context, factor analysis will be used. The scales with predefined subscales (SSSYC, Perceived Movement Skill, and CPBQ) will be validated using confirmatory factor analysis, and the TRiPS will be evaluated using exploratory factor analysis [88]. Acceptable model fit is defined as RMSEA <0.1, SRMR <0.1, CFI >0.9, and TLI >0.9. Factor loadings will be investigated with the use of R^2 estimates (item >0.25) and standardized factor loadings (item >0.40) [88].

Because the participating children are nested within schools, generalized structural equation modeling and multilevel regression analysis will be used in the primary outcome analysis to explore how children's past risk experiences through play and daily activities are associated with their risk management. Children's past risk experiences through play and daily activities will be measured primarily through the CPBQ and TRiPS, whereas measures related to the child's risk management will be obtained from global measures related to risk management from the VR simulation. The child's age, sex, and other relevant background and demographic information, as well as their sensation-seeking personality (measured through the SSSYC), will be included in the models.

Results

Funding to conduct the ViRMa project was confirmed in June 2021. From August 2021 to February 2022, the project group developed the VR scenarios, including eye-tracking technology and motion capturing, translated the scales, and developed the questionnaires. We will conduct the data collection from January 2023 to May 2023.

Four schools were recruited as data collection sites, with a total of approximately 660 students in second to fourth grade (7-10 years old). We aim to enroll 500 children and their parents for participation. The recruitment of children and parents for this study started in December 2022, and as of April 2023, a total of 433 parents consented for their children to participate.

Discussion

Principal Findings

This study will increase our understanding of child development. An essential goal of many educational, developmental, and pediatric health research studies is to understand how children's characteristics, upbringing, and previous experiences influence their learning and ability to handle challenges. This study focuses on children's abilities to manage risky scenarios and ties this to previous experiences. Using cutting-edge technology and previously developed measures to describe aspects of the child's past experiences, this project addresses crucial topics related to children's health and development. Such knowledge may guide pedagogical questions and development of educational and health-related interventions and reveal essential areas for focus in future studies.

One novelty of this study is related to technological and methodological advancements that may lead to new knowledge and discovery. The development and use of VR tools to explore how children handle real-life scenarios opens numerous avenues of research in different scientific fields. The integration of VR, eye-tracking, and motion-capturing technology has not been presented in published research to date and addresses many present scientific challenges. Moreover, the research represents methodological development in how VR technology may be paired with various measures in real time. Through life-like VR scenarios, it is possible to investigate children's risk-taking in a controlled and safe environment, which may lead to substantial theoretical and empirical progress. A key ambition of the study is to develop and use technology and methods in a way that enables large-scale, replicable, international studies in other cultural contexts. Thus, the tools and technology developed must be standardized and easy to use.

From the perspective of contributions to developmental science, the project can lead to further scientific understanding of children's motor competence and how it can be assessed. The combination of whole-body motion capture and VR embedded with tasks in which children can move around to explore and complete tasks represents a completely new research approach. With these features, children's motor competence can be examined through the lens of movement behaviors emerging when individual, task, and environmental components interact. This strategy circumvents shortcomings identified within existing motor competence assessments and has broad implications for further work in designing and evaluating interventions and programs, as well as for research into underlying developmental processes and the role of influencing factors in the adaptive change within individuals as they work toward motor competence throughout childhood and adolescence.

The ViRMa project results will also benefit societal goals related to health promotion, education, parenting, and city and regional planning. A cross-cutting trend today is related to risk aversion resulting from the fear of injuries to children. Compelling theoretical perspectives suggest that reducing children's possibilities to engage in risky situations may be counterproductive in terms of preventing injuries because children's opportunities to learn to estimate and manage risk are diminished. If this study establishes empirical support for this hypothesis, it may impact how risk is addressed in crucial societal institutions like the family, early childhood education, and schools. Specifically, the ViRMa project aims to develop knowledge that may lead to healthier lives and fewer injuries through new knowledge about how children best learn to judge and manage risky situations in playful contexts. Through the acquisition of knowledge about children's risk management in play, this study may benefit societal challenges related to children's health and development and reduce economic burden to society stemming from the cost of unintentional injury treatment among children and young people [91].

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Strengths and Limitations

The use of VR tools along with integrated eye-tracking and motion-capture technology to explore in real time how children handle real-life scenarios in a safe context opens numerous possibilities to address scientific challenges and answer critical gaps in both the scientific literature and application of science for societal needs. However, our ambition to develop and use scientific methods that can be used in various contexts with portable data collection equipment comes with limitations. The test setup might be incrementally more accurate and valid in a controlled laboratory setting where the equipment could be mounted permanently, and the surrounding environment is ideal for the Vive equipment. In a standardized laboratory setting, the simulated planks we use might be replicated with actual wooden planks on the floor that are positioned accurately to match the VR simulation using trackers. Such measures would improve the realism of the balancing tasks but were not possible given this study's mobile and cost-efficient methodology.

The VR tasks we use in this project are newly developed and have not been validated against children's behavior in real life. Such a study would shed light on a critical question: to what degree does children's behavior in risky VR tasks replicate their behavior in similar real-life tasks? Previous work studying children's pedestrian behavior suggests that behavior in VR can replicate real-world behavior [67], and we dedicated extensive work to ensure and validate that the VR tasks were as realistic as possible; thus, we suspect this limitation is minimal.

Although one of our fundamental interests in this study is to explore how past childhood experiences influence children's risk management, the study design is cross-sectional. Using only retrospective data to assess children's past experiences with risky play and risk-taking activities could constitute a risk to reliability and validity of the data as recall and response bias could influence responses. This strategy only establishes association, rather than causation, in any statistical analysis. Nevertheless, this study's solid theoretical foundation and rich methodology ensures the potential to generate casual hypotheses that will advance our understanding of how children develop risk management skills and can be tested in future controlled, randomized, or longitudinal studies.

Other limitations are related to sample recruitment strategies. Participating children are all Norwegian children, and they are enrolled based on their schools' and parents' willingness to participate. The sample is not recruited randomly. Norwegian children are believed to engage in more risky play behaviors than children in many other cultural contexts [12,14], which may influence the results. We have chosen recruitment through schools to get a high response rate among the selected age groups and to carry out effective data collection generating an adequate number of participants for sufficient statistical power. Nonetheless, the recruitment strategy has consequences for generalizability of the sample, and the background of the participating children and the lack of randomization in sampling must be considered when generalizing findings to other contexts.

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Data Availability

The data sets generated or analyzed from this study are available from the corresponding author on reasonable request.

Authors' Contributions

EBHS and MB conceived the study. EBHS led the development of the study design, with contribution from OJS, RK, HL, and MB. EBHS, OJS, RK, HL, and LS developed the data collection tools and conducted the pilot data collection. EBHS wrote the first draft of this manuscript and finalized the manuscript with input from all authors. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

CFI: comparative fit index
CPBQ: Challenging Parenting Behavior Questionnaire
ECEC: early childhood education and care
RMSEA: root-mean-square error of approximation
SRMR: standardized root-mean-square residuals
SSSYC: Sensation Seeking Scale for Young Children
TLI: Tucker-Lewis index
TRiPS: Tolerance of Risk in Play Scale
ViRMa: Virtual Risk Management—Exploring Effects of Childhood Risk Experiences through Innovative Methods
VR: virtual reality

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Protocol

Peer-to–Patient-Aligned Care Team (Peer-to-PACT; P2P), a Peer-Led Home Visit Intervention Program for Targeting and Improving Long-term Care Services and Support for Veterans With High Needs and High Risk: Protocol for a Mixed Methods Feasibility Study

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Abstract

Background: Keeping older veterans with high needs and high risk (HNHR) who are at risk of long-term institutional care safely in their homes for as long as possible is a Department of Veterans Affairs priority. Older veterans with HNHR face disproportionate barriers and disparities to engaging in their care, including accessing care and services. Veterans with HNHR often have poor ability to maintain health owing to complicated unmet health and social needs. The use of peer support specialists (peers) is a promising approach to improving patient engagement and addressing unmet needs. The Peer-to–Patient-Aligned Care Team (Peer-to-PACT; P2P) intervention is a multicomponential home visit intervention designed to support older veterans with HNHR to age in place. Participants receive a peer-led home visit to identify unmet needs and home safety risks aligned with the age-friendly health system model; care coordination, health care system navigation, and linking to needed services and resources in collaboration with their PACT; and patient empowerment and coaching using Department of Veterans Affairs whole health principles.

Objective: The primary aim of this study is to evaluate the preliminary effect of the P2P intervention on patient health care engagement. The second aim is to identify the number and types of needs and unmet needs as well as needs addressed using the P2P needs identification tool. The third aim is to evaluate the feasibility and acceptability of the P2P intervention delivered over 6 months.

Methods: We will use a quantitative-qualitative convergent mixed methods approach to evaluate the P2P intervention outcomes. For our primary outcome, we will conduct an independent, 2-tailed, 2-sample *t* test to compare the means of the 6-month pre-post

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differences in the number of outpatient PACT encounters between the intervention and matched comparison groups. Qualitative data analysis will follow a structured rapid approach using deductive coding as well as the Consolidated Framework for Implementation Research.

Results: Study enrollment began in July 2020 and was completed in March 2022. Our sample size consists of 114 veterans: 38 (33.3%) P2P intervention participants and 76 (66.7%) matched comparison group participants. Study findings are expected to be published in late 2023.

Conclusions: Peers may help bridge the gap between PACT providers and veterans with HNHR by evaluating veterans' needs outside of the clinic, summarizing identified unmet needs, and developing team-based solutions in partnership with the PACT. The home visit component of the intervention provides *eyes in the home* and may be a promising and innovative tool to improve patient engagement.

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KEYWORDS

older veterans with high needs and high risk; peer support specialists; unmet needs; home visit; patient engagement; home services; care coordination

Introduction

Background

Keeping older veterans with high needs and high risk (HNHR) who are at risk of long-term institutional care (LTIC) safely in their homes for as long as possible is a Department of Veterans Affairs (VA) priority [1,2]. The VA Geriatric and Extended Care Data Analysis Center (GECDAC) uses predictive modeling to identify veterans with HNHR at the highest risk of LTIC, hospitalization, or death [3]. The VA Geriatric and Extended Care (GEC) office recommends that veterans with HNHR be enrolled in long-term services and supports programs, including home- and community-based services, for best outcomes. Veterans with HNHR have complex needs that include not only physical but also mental, functional, and social needs, specifically frailty, social isolation, mobility challenges, and self-care deficits [4-8].

Older veterans with HNHR face disproportionate disparities and barriers to engaging in their care, which includes accessing care and services. Veterans with HNHR who are sicker and frailer often miss appointments and fail to visit the clinic for their care [9]. Their ability to maintain health is further complicated by complex unmet medical and social needs. When these needs go unmet, patients are at higher risk of adverse outcomes such as hospitalization, LTIC, and death [10-16]. Other adverse events include falls, inadequate nutrition, depression, incontinence, discomfort, and decreased quality of life [17,18]. Attending to the unmet health needs of older veterans with HNHR and planning services and solutions centered around what older people need based on *what matters most* to them is becoming an urgent public health priority [19,20]. Innovative interventions are needed to identify unmet needs and bridge the gap between needs and services in partnership with patients and family caregivers [1].

A promising approach to address these gaps at the VA concerns the use of peer support specialists (peers) [21-24]. Peers are veterans hired by the VA to help other veterans, usually those with serious mental illnesses, to engage them in their treatment successfully [25]. Peers are required to be veterans and must complete peer certification training. Peer certification training is conducted by a single contractor hired by the VA mental health services office. The training is at no cost to peers. Expected competencies include recovery principles, peer support practices, cultural competence, whole health approach to services, and advocacy. Continued education is required of all peers, including a minimum of 15 hours of competency-related training every year [25]. Peers promote recovery by using their common bond of being veterans and sharing their own recovery stories, providing encouragement, instilling a sense of hope, and teaching coping, empowerment, and social skills to veterans [25]. Peers understand the social and historical experiences shaping the veterans and connect with veterans in a different manner than the rest of their health care team. Being veterans themselves, peers are in a unique position to connect with veterans and assist with navigating the VA. Patient-aligned care teams (PACTs) at the VA are comprehensive medical homes that use a multidisciplinary team-based approach to effectively provide primary care and manage chronic conditions [26,27]. Preliminary studies suggest that embedded peers in mental health and primary care PACTs encourage veterans to be more active in managing their health [21-24,28-30]. Peers serve as role models, community connectors, and health care navigators. The preliminary success of the original peer support programs in specialty mental health led to congressional support for the creation of a peers-in-the-PACT program as part of the Maintaining Internal Systems and Strengthening Integrated Outside Networks (MISSION) Act of 2018 (section 506) with the implementation of peers at 30 VA sites [31]. Peers are relatively new members of the VA primary care PACT teams, and sites are working out the roles for peers in primary care.

Building upon the expansion of peers into VA primary care, we developed an innovative model for a peer-led home visit intervention to identify unmet needs in older veterans with HNHR as a home extension and *eyes in the home* for primary care PACTs called *Peer-to-PACT* (P2P). The peers work with the PACT to link veterans with HNHR to needed services and resources to address identified unmet needs. This paper describes the study protocol for a feasibility study to assess the preliminary

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effect of the P2P intervention on patient engagement and the factors that could affect its implementation in the VA setting.

Study Goals

This study has three aims: (1) test the preliminary effect of the P2P intervention on patient engagement in care, measured by PACT outpatient health care use; (2) describe the number and types of needs and unmet needs identified, as well as needs addressed, among P2P participants; and (3) evaluate the feasibility and acceptability of the P2P intervention. The goal of the P2P intervention is to improve access to geriatric care and home- and community-based support services for older veterans with HNHR by providing patient-driven, proactive, personalized, and team-based care to link veterans and their caregivers to needed services and supports. We hypothesize that the P2P intervention will result in improvements in patient engagement by identifying unmet needs and addressing them.

Methods

Conceptual Design

The theoretical foundation of the P2P integrated intervention is grounded in the Andersen Healthcare Utilization Framework [32]. The Anderson model illustrates 3 main factors that influence the use of health care services: *predisposing*, *enabling*, and *need factors*. It incorporates the concept of mutability of factors, meaning that a factor with a high degree of mutability can be changed. Factors with a high degree of mutability, such as enabling resources, may thus justify deployment of resources. Therefore, the focus of our design emphasizes a peer-based approach to screening and identifying unmet needs in the context of the VA age-friendly health system (AFHS) mobility, mind, medications, and matters most (4Ms) framework as well as the fifth geriatric M, multicomplexity (mobility, mind, medications, matters most, and multicomplexity are together referred to as the 5Ms of geriatrics) [20,33], and then providing care coordination to link veterans with HNHR with services and resources to address their unmet health and social needs.

During the protocol development phase, we conducted a literature review of peer support and community health worker interventions, as well as assessments of the needs and unmet needs of older adults to draft the initial P2P intervention protocol. The final protocol and its component implementation materials were developed after iterative adaptations incorporating feedback from peers, PACT providers, veterans, advisory panel members, and various stakeholders.

P2P Interventionists

Two certified VA peer support specialists were hired and paid through the VA mental health services office through usual VA hiring practices. Hired peers completed the P2P training program in addition to the training required for peer certification [25]. The P2P training program consists of 16 hours of didactic sessions covering topics such as veterans with HNHR, social determinants of health, activities of daily living, and VA and community resources, as well as 24 hours of hands-on training covering practice home visits, use of P2P data collection tools, and computerized patient record system (CPRS) documentation (discussed in further detail in the P2P Implementation Materials section).

Advisory Panel

We established a national project advisory panel to guide intervention design, implementation, and dissemination activities. This panel includes key stakeholders from the VA offices of GEC as well as Mental Health and Suicide Prevention, the GECDAC, and the national VA peers in the PACT implementation team from the VA Center for Integrated Healthcare. The panel also includes subject matter experts in peer work at the VA, veterans with HNHR, home-based primary care, mental health, cultural competence, and non-VA community health worker programs, as well as Miami VA Healthcare System primary care PACT members. A biannual panel meeting was held to provide updates, solicit feedback, and consult one-on-one for specific matters.

Study Setting

This P2P intervention feasibility study was conducted at the Miami VA Medical Center in Miami, Florida, United States.

Study Design and Sample Size

This study uses a mixed methods (qualitative-quantitative convergent) design involving a nonrandomized 2-arm trial comparing the 6-month P2P intervention group with a 1:2 matched comparison group.

As this study is a pilot intervention, sample sizes were determined by what was deemed feasible within the available time frame and resources rather than power calculations. We aimed to recruit 35 veterans with HNHR or referred veterans for participation in the P2P intervention.

Eligibility Criteria

To be eligible for the P2P intervention, veterans had to be aged ≥60 years, receiving care at the Miami VA Healthcare System, living within a 50-mile radius of the Miami VA facility, and not be planning to relocate in the next year. Veterans were excluded if they were enrolled in the VA home-based primary care program or residing in a hospice or nursing home. We also enrolled veterans who were referred by Miami VA Healthcare System PACT providers and met the eligibility criteria but were not on the HNHR list.

Recruitment and Enrollment

Participant recruitment for this study is complete. Participants were enrolled into the P2P intervention at the Miami VA Healthcare System by peers. The peers recruited participants using three strategies: (1) calling eligible veterans identified from the quarterly GECDAC HNHR list; (2) mailing opt-in recruitment letters to veterans on the HNHR list; and (3) referrals made by PACT primary care clinicians, nurses, or social workers. In recruitment calls with eligible veterans, the peers described the P2P intervention to the veterans and how they might help the veterans manage their health conditions. If the veterans were interested, the peers obtained verbal consent to participate.

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Matched Comparison Group

Veterans in the matched comparison group were identified from the HNHR list, similar to the method used to enroll veterans into the P2P intervention. Comparison group veterans did not receive any peer services before or during the study period as evidenced by CPRS chart reviews and use data provided by the GECDAC. Comparison group participants were matched with P2P intervention participants on age, care assessment need score [34], JEN Frailty Index [35], and Nosos score [36,37] from the HNHR list for the period during which the P2P participant was recruited. Veterans in the comparison group received care as usual.

P2P Intervention Overview

General Schedule

The P2P intervention is multicomponential and designed to support older veterans with HNHR to age in place. Peers provide usual peer support services (eg, facilitate peer support groups, advocate for veterans, and act as role models for recovery) in addition to the P2P intervention. The P2P intervention focuses on the home visit as an innovative tool to identify the unmet health and social needs of veterans with HNHR and linking them to solutions using an integrated P2P model. A general schedule of the intervention is presented in Table 1.

The intervention includes three main components detailed in the following sections: (1) needs identification via a peer-led home visit; (2) care coordination, health care system navigation, and linking to resources in collaboration with the PACT; and (3) patient empowerment and coaching using VA whole health principles.

Table 1. Peer-to–Patient-Aligned Care Team (P2P) intervention schedule.

When and what	How
Rolling recruitment and enrollment	
Patient identification	HNHR[a] list and PACT[b] referrals
Eligibility screening	Filtering of HNHR list for age, distance from Miami VA[c] Healthcare System, enrollment in HBPC[d], and hospice or nursing home residence
Recruitment	Telephone calls, letters, or referrals
Week 1: scheduling home visit	Peers schedule a home visit with veterans enrolled in the P2P intervention via telephone calls or remote video visits
Week 2: preparing for the home visit	Peers complete a chart review of problem list, consults, medication list, and past notes in the last 30 days
Week 3: home visit	Peers identify needs via home visits using the P2P needs identification tool; when a home visit is not possible, needs are identified via a remote video visit
Week 4: P2P care coordination	Care coordination to address unmet needs is discussed between the peers and PACT during team huddles, via telephone calls or Microsoft Teams messaging, or in person
Months 2-5	
Patient education	Peers and veterans meet once every 2 weeks via telephone calls, remote video visits, or in person to review relevant topics of the Passport-2-Wellness, an educational book encompassing 8 health-related topics; the educational component is flexible in terms of the needs of the veterans, and peers have flexibility on deciding when to cover topics during the follow-up months
Follow-up on care coordination	Peers follow up on the status of identified unmet needs (eg, resolved or not resolved) with both the veteran and PACT and assist with unmet needs; peers follow up on referrals and consults and complete follow-up notes in the CPRS[e]
Month 6	
Discharge	Peers assess whether further follow-up is needed to continue advocating for the veteran; peers complete a P2P discharge summary indicating reason for discharge (eg, veteran does not require any additional peer support, or veteran has stopped communication with peer, or voluntarily withdrawn) and summary of participation in the program

[a]HNHR: high needs and high risk.

[b]PACT: patient-aligned care team.

[c]VA: Department of Veterans Affairs.

[d]HBPC: home-based primary care.

[e]CPRS: computerized patient record system.

Needs Identification via a Peer-Led Home Visit

In preparation for the home visit, peers first ask pre–home visit safety questions, complete an initial contact note, and schedule a home visit. Before the home visit, peers review the patient's VA CPRS chart to ascertain medical problems, existing and previous VA services, recent VA visits, hospitalizations, emergency use, no-shows and appointment cancellations, mental

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health history, cognition problems, medication list, social concerns, upcoming appointments, pending or cancelled consults and orders, and telehealth use.

During the home visit, peers provide additional information about the P2P intervention and verbally administer the needs identification tool, which is a health and social needs questionnaire (described in full detail in the P2P Implementation Materials section). Through conversations with, and observation of, the veteran and caregiver or caregivers, if available, as well as inspection of their home environment, the peers help the veteran to identify the key unmet needs that affect their overall health and well-being. During the visit, peers ask the veteran for permission to see different parts of their house. Specifically, peers ask to see bathrooms, living rooms, kitchens, floors, and entry ways. Peers use a home safety checklist within the needs identification tool to look for potential fall hazards (eg, loose cords, clutter, and carpets) and potential home safety equipment needs (eg, bath rails and entry ramp). The home visit takes approximately 2 hours. During the home visit, peers also provide the veteran with the Passport-2-Wellness, an educational book encompassing 8 health-related topics, and give them an overview of its contents (described in full detail in the P2P Implementation Materials section).

Care Coordination, Health Care System Navigation, and Linking to Resources in Collaboration With the PACT

The peers document the identified needs and a narrative of their observations in a templated CPRS note and add primary care PACT team members as cosigners. Peers collaborate with the appropriate PACT team member (primary care physician, nurse case manager, social worker, or pharmacist) to coordinate the ordering of needed consults and services. Care coordination to address unmet needs is discussed during team huddles (limited during the COVID-19 pandemic), via telephone calls or Microsoft Teams messaging, or in person.

Examples of unmet needs and linking to resources in collaboration with the PACT may include reaching out to the social work department for transportation concerns, linkage to food banks and meals on wheels for food insecurity concerns, or homemaker and home health aide for self-care concerns; reaching out to pharmacy for medication concerns; or working with the PACT nurse case manager or physician to refer veterans with falls or safety concerns to the falls clinic or order physical therapy, home safety assessment, or prosthetics for needed home safety durable medical equipment.

Peers may increase veteran health care engagement by bridging veterans back to their primary care team. Peers help veterans to navigate the health care system (eg, schedule appointments, send reminders, and provide guidance through the health care system bureaucracy) and provide emotional and social support (eg, identify VA and local social resources programs such as food banks and tenant advocacy). They continue to communicate with the veterans on the progress of their care plan and follow up on the status of the identified unmet needs (eg, resolved or not resolved) and assist with unresolved unmet needs by following up on referrals, consults, and orders.

Patient Empowerment and Coaching Using VA Whole Health Principles

During the initial visit and follow-up phase, the peers provide health and behavior coaching to the veterans. They review relevant sections of the Passport-2-Wellness with veterans as they deem fit and provide needed counseling in the context of the 5Ms of geriatrics [20]. They use VA whole health principles to teach veterans to "take charge of my life and health," self-manage their chronic conditions, and take part in problem-solving. Peers also help the veterans to complete a VA whole health personal health inventory to assist them with setting goals, describing *what matters most* to them about their health, and identifying methods for filling unmet needs in alignment with their needs and preferences. Through continued contact via telephone, in person, or via videoconferencing, peers empower patients with problem-solving skills to manage their health, including self-care, medication adherence, nutrition, physical activity, and emotional well-being, and cover the relevant materials in the Passport-2-Wellness. Contacts last approximately 30 minutes and are tailored to meet patient goals and needs, access to services, and care coordination.

Peer Assessment

Peers work with the veterans to ensure that they receive the needed services to enable them to remain in the community and address care fragmentation across providers and services. The P2P intervention is designed to be 6 months in duration, including 1 home visit during month 1 and contacts once every 2 weeks thereafter. The peers assess whether further follow-up is needed, past the 6 months, to continue advocating for the veteran or whether the veteran could be discharged from the P2P intervention. Peers complete a P2P discharge summary indicating the reason for the discharge (eg, veteran does not require any additional peer support, or veteran has stopped communication with peer, or voluntarily withdrawn) and a summary of participation in the program.

Remote Care

In keeping with VA's preference for remote care to enhance access and efficiency—and safety during the COVID-19 pandemic—we, too, implemented remote video visits by peers. Veterans are asked about interest in, and willingness to receive, a remote video visit, access to needed technology (internet and camera phone or computer), and help with technology access or use as required. For remote home visits, peers use the same in-person home visit template to identify unmet needs. During the remote home visit, peers ask veterans, whenever possible and safe to do so, to walk them through different parts of their house. Communication with the PACT follows the same process as outlined previously. Peers are provided tablet devices to be able to *telepresent* the veteran to a PACT provider at the VA site as needed and when possible. Peers may also work with social workers to provide veterans with tablet devices for remote visits if they qualify.

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P2P Implementation Materials

Overview

The protocol development phase focused on planning the P2P intervention protocol and its component implementation materials, including (1) a needs identification tool and a CPRS template for documentation, (2) the Passport-2-Wellness education and resource book, and (3) a peer training curriculum. These have all been implemented and refined using an iterative series of modifications with feedback from the peers, PACT providers, and local and national stakeholders. Two certified peer support specialists were actively engaged partners in the design and trial phases, and the process was modified to stay within their scope of peer work (eg, advocate for veterans, act as liaison between staff and veterans, provide outreach and education and work with clinical teams [23]).

Needs Identification Tool

To effectively address the needs of veterans with HNHR, we developed a needs identification tool to identify and understand the needs and unmet needs of older adults and improve patient engagement through a peer-led home visit. Peers initially conducted home visits using a longer questionnaire of validated questions to identify needs. The needs identification tool was modified to reflect the peers' personalized holistic style using conversational language. The peers gather baseline information and identify unmet needs through a series of questions, conversations, and observations in the following domains: mobility, mind, medications, matters most, multicomplexity, and social determinants (Textbox 1). These needs domains were selected based on the 5Ms of geriatrics and previous studies showing that common barriers to patient engagement in outpatient programs include physical symptoms and limitations, mental illness, care fragmentation, isolation and lack of social support, financial insecurity, and poor social and neighborhood conditions [38-41]. These needs were then documented in a study-specific CPRS templated note to harmonize data collection and inform and coordinate care with the PACT regarding the veterans' needs.

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Textbox 1. Needs domains.

Mobility and function

- Mobility, past falls, frailty, gait, and balance
- Activities of daily living and instrumental activities of daily living
- Homebound status
- Current use of support services

Mind

- Memory
- Mood (depression and anxiety)
- Substance use

Medications

- Medication insecurity, refills, questions
- Medication adherence concerns

Matters most

- Meaningful health goals

Multicomplexity

- Chronic medical conditions
- Chronic disease–related health care needs
- Hearing or vision problems
- Health care use

Social determinants

- Social support
- Transportation
- Food insecurity
- Financial stability
- Housing insecurity, housing density, neighborhood safety
- Legal concerns
- Technology access and ability to use technology

Home safety concerns and needs

- Outdoor grab bar
- Walker
- Assistive devices
- Bathroom assistive devices
- Smoke detector
- Presence of clutter, rugs, cords

The Passport-2-Wellness

We designed the Passport-2-Wellness educational book with 8 topics that were identified as being most common for, and most relevant to, older veterans with HNHR in the context of the 5Ms of geriatrics (Textbox 2). This Passport-2-Wellness book, which also contains a *Telehealth Visits* section and a section entitled *Healthcare Tools and Notes*, is provided to enrolled veterans as a resource and used by the peers as an educational tool. Peers, in collaboration with the veteran, select relevant topics to review during the intervention.

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Textbox 2. Passport-2-Wellness educational topics.

Mobility and Safety

- Barriers to Healthcare
- Independent Living
- Home Safety Checklist
- Falls Prevention

Caregiver Support

- Caregiver Support Tips
- Caregiver Resources
- Disaster Planning

Whole Health

- Introduction to Whole Health
- Your Personal Health Inventory
- Self-care and Mind-Body Techniques

Age-Friendly Health System 4Ms

- What Is Most Important to You?
- Memory Tips
- Mood Tips
- Medication Tips

Multicomplexity

- Common Chronic Conditions: Diabetes and Hypertension
- What is Diabetes?
- What Are the Symptoms of Diabetes?
- How Can You Manage Your Diabetes?
- Monitoring and Testing Your Blood Sugar
- Managing your Blood Sugar
- What My HbA1c Means
- How to Use a Glucometer
- What is Hypertension

Nutrition and Physical Activity

- Food as Medicine
- What Foods to Eat
- What Foods to Avoid
- Benefits of Physical Activity
- Tips to Increase Physical Activity
- Where Should You Start?
- Chair Yoga
- Community Fitness Zones

Health Communication

- Doctor Visit Tips and Shared Decision-Making
- Advance Directives

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Care Plan and SMART Goals

- Care Plan Worksheet
- SMART Goals and Progress Worksheets

Extra Information

- Problem-Solving
- VA Claims, Disability and Pension
- Women Veterans Health Care
- Veteran Decision Aid for Care at Home or in the Community
- Community Dental Clinics
- Types of Vascular Disease
- Understanding Cholesterol
- Chronic Kidney Disease
- Congestive Heart Failure
- How You Can Reduce Heart Disease Risk
- Chronic Obstructive Pulmonary Disease (COPD)
- Understanding Insomnia

Peer Training Curriculum

Two hired peers were already certified peer support specialists [25]. There is onboarding training required for national peers in the PACT implementation team at all VA sites for usual peer activities. National peer training incudes competencies in recovery principles, peer support practices, cultural competence, communication, recovery and personal wellness goals, and whole health approaches to services. A complete list of expected knowledge and skill areas can be found in the *Peer Support Specialists Training Manual* [25]. To supplement this training, we developed an educational curriculum for the peers specific to the P2P intervention. This curriculum was developed integrating feedback from PACT providers, peers, key stakeholders, and the home-based primary care team. Overall, the duration of P2P intervention training is 40 hours: 16 hours for educational components and 24 hours for P2P hands-on training. Peer training was provided by multidisciplinary PACT and home-based primary care team members, including geriatricians, social workers, and nurses. Peers also received hands-on training in the use of VA CPRS, conducting chart review, and conducting a remote video visit. Peers made 3 home visits with the home-based primary care team to learn the process for conducting safe home visits, using personal protective equipment (because this intervention started during the COVID-19 pandemic) and checking for home safety and unmet needs. Some of the training was via *Talent Management System*, the VA's enterprise-wide education, leadership development, learning, and employee development system. Training components are shown in Table 2.

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Table 2. Peer support specialist Peer-to–Patient-Aligned Care Team (P2P) training curriculum.

Component	Required training	Duration (hours)	Modality
P2P didactic training			
Veterans with high needs and high risk			
	Identifying the needs and unmet needs of veterans with high needs and high risk	1	Remote presentation
	Social determinants of health	2	TMS[a] course
Safety	Personal protective equipment training	1	In-person meeting with local occupational health
Mobility and functional limitations	Falls, assistive devices, ADLs[b], and IADLs[c]	1	Remote presentation
Mental health	Managing depression, SUD[d], and stress	2	In-person meeting with local recovery coordinator and mental health peers for information on VA[e] resources and hospital tour
VA vehicle			
	Courses for driving a government vehicle	1	TMS course
	Defensive driving, driving fundamentals, credit card, and so on (varies by facility)	1	TMS course
Motivational interviewing	Understanding good communication practices	1	TMS course
Social work	Social work services: transportation and long-term support services, VA and community resources, and caregiver resources	2	In-person meeting with local social worker
Telehealth	Remote care technology and tablet device use, digital divide consult, and mock remote video visit	2	TMS course
Research	VA required training in human participant research and HIPAA[f]	2	TMS course
P2P hands-on training			
Home visit	HBPC[g] training and shadowing on home visit safety	12 (3 home visits)	In-person home visits with HBPC team
P2P tools	Use of the Passport-2-Wellness, needs data–gathering tools, and mock telephone calls	8	P2P team in person and remotely
VA records	Use of CPRS[h] and chart review training	4	In person with program coordinator
Recommended training			
Whole health			
	Introduction to whole health, health coaching, and goal setting: SMART[i] goals	2	TMS course
	"Taking charge of my life and health" facilitator training	25 (5 days)	Remote learning (Zoom; Zoom Video Communications, Inc) and class discussion, partner activities, and small groups
Diabetes mellitus overview	About type 2 diabetes, hyperglycemia, hypoglycemia, and complications	2	In-person meeting with local diabetes nurse practitioner
Nutrition	Healthy eating, portion sizes, if you drink alcohol, and food shopping tour	4	In-person meeting with local dietician and nurse practitioner

[a]TMS: Talent Management System.

[b]ADL: activity of daily living.

[c]IADL: instrumental activity of daily living.

[d]SUD: substance use disorder.

[e]VA: Department of Veterans Affairs.

[f]HIPAA: Health Insurance Portability and Accountability Act.

[g]HBPC: home-based primary care.

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[h]CPRS: computerized patient record system.

[i]SMART: strategic, measurable, attainable, results-oriented, and time-bound.

Data Collection

Demographic and Clinical Measures

The study team collected demographic, clinical, and use data from the CPRS and GECDAC on age, sex, race and ethnicity, marital status, care assessment need score [34], JEN Frailty Index [35], Nosos score [36,37], service-connected eligibility, 2-year emergency room visits, urgent care visits and primary care visits, and diagnosed conditions and services used among both intervention and comparison group participants (Table 3).

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Table 3. Data collection.

Outcome measures	Description of measures	Data source	Schedule	
			Baseline	6 months
Demographic and clinical data				
Demographics[a]	Age, sex, race, ethnicity, marital status, and rurality	CPRS[b] chart review and GECDAC[c] data pull	✓	N/A[d]
Clinical characteristics[a]	Dementia, comorbidities, Nosos, CAN[e], and JFI[f], service-connected eligibility, and 2-year emergency room and urgent care	GECDAC data pull	✓	N/A
Frailty	Fatigue, resistance, ambulation, illness, and loss of weight	Morley 5-item FRAIL[g] scale [42]	✓	N/A
Homebound status	Difficulty leaving the house and frequency of veteran leaving the house	NHATS[h] homebound status questionnaire [38]	✓	N/A
Aim 1: to test the preliminary effect of the intervention on patient engagement through PACT[i] health care use				
Patient engagement: Health care use and support services use[a]	Primary care PACT encounters, consults, and support services (eg, homemaker and home health aide)	CPRS chart review and GECDAC data pull	✓	✓
Aim 2: to identify the number and types of needs and unmet needs as well as needs addressed using the P2P[j] needs identification tool				
Needs identification				
Health needs	ADLs[k], IADLs[l], and help needed; mobility needs; hearing, vision, and memory problems; and medication refills and adherence	Katz ADL Index [43], Lawton IADL Scale [44], and study-specific questions	✓	N/A
Social needs	Food insecurity, housing insecurity, transportation, social isolation and loneliness, legal concerns, and technology needs	Two-item food insecurity screen [45], VA homeless screener [46], PRAPARE[m] survey [47], UCLA[n] Loneliness Scale [48], P2P legal concerns project-specific 1-item question, and VA digital divide consult	✓	N/A
Home safety needs	Home safety devices need (eg, grab bars and bathroom assistive devices) and safety concerns (eg, unsafe steps and dark or poor lighting)	P2P project-specific checklist	✓	N/A
Aim 3: to evaluate the feasibility and acceptability of the P2P intervention				
Process evaluation				
Feasibility and acceptability	Quantitative: number of unique veterans referred and enrolled, average number of visits per veteran, average total number of consults placed per veteran, and average total number of GEC[o] services received	CPRS chart review and GECDAC data pull	✓	✓
Facilitators, barriers, improvements, and satisfaction	Qualitative: study-specific questions and semistructured interviews of veterans, PACT providers, peers, and leaders	P2P study-specific questionnaires, semistructured interviews, and periodic reflections	✓	✓

[a]Data collected for both intervention and comparison groups.

[b]CPRS: computerized patient record system.

[c]GECDAC: Geriatric and Extended Care Data Analysis Center.

[d]N/A: not applicable.

[e]CAN: care assessment need.

[f]JFI: JEN Frailty Index.

[g]FRAIL: fatigue, resistance, ambulation, illnesses, and loss of weight.

[h]NHATS: National Health and Aging Trends Study.

[i]PACT: patient-aligned care team.

[j]P2P: peer-to–patient-aligned care team.

[k]ADL: activity of daily living.

[l]IADL: instrumental activity of daily living.

[m]PRAPARE: Protocol for Responding to & Assessing Patients' Assets, Risks & Experiences.

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[n]UCLA: University of California Los Angeles.

[o]GEC: Geriatric and Extended Care.

Primary and Secondary Outcome Measures

Our primary outcome was patient engagement, defined as the number of outpatient PACT encounters. We obtained these data from the GECDAC and from CPRS chart reviews for both intervention and comparison groups. Patient engagement is a broad concept that combines positive patient behavior, such as obtaining preventive care, with patient activation [49]. In this study, we measured veteran engagement with the VA health care system by measuring participation in outpatient care and services. Peers collected data on frailty [42], homebound status [38], health needs, needs related to social determinants of health, and home safety needs. Secondary descriptive outcomes among intervention participants included prevalence and types of needs and unmet needs, actions taken to assist with meeting needs, and use of health care services, specifically services in the home (Table 3).

Implementation Measures

Quantitative process measures included number of unique veterans referred and enrolled, number of visits per veteran, total number of consults placed per veteran, and total number of GEC services received. We also conducted semistructured interviews at baseline and ongoing throughout the intervention period with key stakeholders (VA facility PACT providers and leadership, GEC leadership, GECDAC directors and staff, experts on VA peer support specialists, and national peers in the PACT implementation team). Detailed notes were taken on the interviews, and some of the interviews were audio recorded. The research team held ongoing periodic reflections [50] with the peers and study team to explore challenges and successful and unsuccessful strategies, as well as the peers' perspective on their role as part of the clinical team [50]. In addition, study-specific questionnaires were used to collect data on satisfaction with the intervention as well as its feasibility and acceptability (Table 3).

Data Analysis

We will use a quantitative-qualitative convergent mixed methods approach to evaluate P2P intervention outcomes. Specifically, we will use the reach, effectiveness, adoption, implementation, and maintenance (RE-AIM) framework to guide a formative process evaluation and assess the 5 key RE-AIM outcomes [51].

Quantitative Analysis

For our primary outcome, we will first calculate the difference in the number of primary care PACT outpatient encounters 6 months before and after enrollment for each participant in both intervention and comparison groups. An independent, 2-tailed, 2-sample *t* test will then be used to compare the means of the pre-post differences in the number of outpatient PACT encounters between intervention and comparison groups. The mean pre-post difference will be reported for each group with the corresponding SDs and 95% CIs. The folded F statistics will be evaluated to report either the pooled or Satterthwaite *P* value. We will calculate group-specific means and proportions for sociodemographic and clinical factors. At baseline, categorical variables will be compared between groups with the Pearson chi-square test or with the Fisher exact test for rare outcomes. The *t* test will be used to compare means across groups. *P* values will be reported, with lower values interpreted as more stable and less likely to be sporadic. All quantitative analyses will be performed using SAS 9.4 (SAS Institute Inc).

Qualitative Analysis

Qualitative data analysis will follow a structured rapid approach using deductive coding as well as the Consolidated Framework for Implementation Research (CFIR) [52]. A mixture of detailed note-taking and audio-recorded semistructured interviews will be used. Interviews will be transcribed and deidentified. Researchers will enter transcripts into NVivo 12 (QSR International), a software program used for qualitative and mixed methods research, and begin by reading each transcript repeatedly from beginning to end. To facilitate qualitative data coding and organization, we will use an NVivo project template, prepopulated with CFIR construct codes. Codes selected a priori include constructs within the following domains: outer setting, inner setting, and implementation process. Although constructs are selected a priori, we will allow for the expansion of codes and emergent themes as necessary.

To enhance validity and reliability of the qualitative data analysis, we will conduct exercise debriefings within the study team to evaluate potential differences in coding across analysts and resolve coding differences as needed. Running documents of all coding decisions, processes, and analyses will be kept, ensuring proper data management and coding practices.

Ethics Approval, Participation, and Privacy Considerations

This study was approved by the Miami VA Healthcare System institutional review board (#1592752). No compensation was provided to veterans for participation. A waiver of Health Insurance Portability and Accountability Act (HIPAA) authorization was granted based on the determination that the risk to the privacy of individuals is minimal. To ensure privacy, efforts were taken to protect the identity of participants and ensure that data were kept confidential. Names, addresses, and social security numbers were replaced with a unique code and will only be maintained on a VA server; documentation of the procedure used to code the data will remain within the VA. All identifiers collected as part of this research project will be destroyed as per the records control schedule (RCS 10-1) of the Veterans Health Administration (VHA). Electronic files will be stored in folders with restricted access on a protected computer shared drive behind the VA firewall in a secure server. Nonelectronic records will be maintained in locked cabinets and behind locked doors. Information will be located in an area with limited public access. Data will not be transmitted as an attachment to unprotected email messages. The data will be accessible only to personnel involved in the study. All staff will be trained to avoid breach of confidentiality issues.

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Results

The P2P project was funded in October 2019. Study enrollment began in July 2020 and was completed in March 2022. Our sample size consists of 114 veterans: 38 (33.3%) P2P intervention participants and 76 (66.7%) matched comparison group participants. Data analysis is underway, and study findings are expected to be published in late 2023.

Discussion

Overview

Peers are increasingly being deployed in a variety of health care settings to provide patient-centered care. At the VA, efforts are underway to integrate peers in primary care settings. The role of peers is expanding and evolving, and peers are currently being proposed to be added in primary care PACTS at all VA facilities [53]. The use of peers in primary care settings at the VA is still relatively new, and innovative models for the use of peers are being developed at several VA sites based on local needs.

The P2P intervention aims to address unmet needs of older veterans with HNHR who are frail by addressing individual health and social needs as well as the home environment. Although peers are not medical providers, they are well suited to assess and understand patients' perspectives and needs and are empowered to recommend patient-centric strategies to address them. This intervention aims to improve patient health care engagement through the timely use of needed services and supports. The protocol presented has undergone multiple modifications using feedback from peers, the PACT, stakeholders, and veterans. This study originally aimed to test the integrated P2P intervention using a structured 6-month experimental design. However, veterans with HNHR are a population with complex needs and with multimorbidities and poor health care engagement. They are challenging to treat because they often have more immediate health and living concerns that make participating in long interventions a last priority. Taking these challenges into consideration, a more flexible intervention schedule was developed in response to feedback from veterans with HNHR regarding their concerns with the intervention duration and time commitment required. In practice, the educational components are not constrained to specific weeks within the 6 months; instead, peers have flexibility on deciding when to cover topics within the allotted time frame. This flexibility takes into consideration the heterogeneity and complex needs of this population.

During the design phase, we used several strategies to improve recruitment: reducing the number of data collection instruments to reduce respondent burden, allowing peers to use their peer style to gather data while maintaining trust with the veteran, increasing provider knowledge of referrals to the P2P intervention, accepting patients referred by PACT providers, mailing recruitment letters, and giving peers flexibility to adapt the intervention to make it more veteran-centric as needed.

Peers are currently delivering the P2P intervention, conducting home visits, and identifying unmet needs as part of their routine clinical duties at the Miami VA Healthcare System. Because of the limitations with enrolling participants owing to COVID-19–related delays and the complexity of veterans with HNHR, we obtained permission to use clinical data from all veterans who participated in the P2P intervention. Our ability to track health care use and collect demographic and clinical data from electronic medical records presents us with the opportunity to assess the efficacy of the P2P intervention with data that are not easily collected via questionnaires. The results from this study will aid our understanding of the acceptability and feasibility of the P2P intervention and its effect on health-related outcomes.

Strengths

The P2P intervention has several strengths. First, its novel approach of using peers in the PACT beyond the VA and into the home allows peers to serve as *eyes in the home* and identify needs that otherwise may continue to go unmet without proper care coordination. Second, using the AFHS and a whole health approach allows the peers and veterans to develop a personalized health plan based on individual values, needs, and goals. Third and last, prior VA research notes the need for functional and cognitive status as well as data related to social determinants of health to be a part of the routine electronic health record [54]. The needs identification tool we developed for this intervention was converted into a CPRS template with the goal of harmonizing data and coordinating care with the PACT on veterans' unmet health and social needs.

Limitations

As this is a nonrandomized study, the greatest challenge is the identification of an appropriate comparison group. We selected a matched comparison group from the same HNHR list from which the intervention participants were recruited to reduce selection bias. By selecting a matched comparison group that is similar according to a set of matching variables, we help to ensure that any observed differences in outcomes between the intervention and comparison groups can be more confidently attributed to the treatment itself, rather than other factors that may differ between the groups. The final sample size included 114 veterans: 38 (33.3%) P2P intervention participants and 76 (66.7%) matched comparison group participants. We made efforts to mitigate sample size limitations by including a 1:2 ratio of comparison group participants. In addition, the inclusion of referred patients may be deemed a deviation from the original protocol. However, the referred veterans will be assessed for comparable characteristics with veterans recruited from the HNHR list. Recent VA data demonstrate that using a combination of administrative data such as the HNHR list and clinician judgment is best suited for identifying patients for intensive care management interventions [54].

Safety precautions during the COVID-19 pandemic and home visits presented a potential risk for the intervention in terms of protection of the peers and the protection of older veterans with HNHR who are frail. The peers were trained by the home-based primary care team to make home visits and were trained on proper personal protective equipment use. Furthermore, peer use of remote care was limited by the access to, and willingness and ability to use, technology of the veteran with HNHR [55].

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Peers used remote care where suitable. This aligns well with national VA priorities and stakeholder feedback.

Conclusions

Peers may help bridge the gap between PACT providers and veterans with HNHR by evaluating veterans' needs outside of the clinic, summarizing identified problems, and developing team-based solutions in partnership with the PACT. The home visit component of the intervention provides *eyes in the home* and may be a promising and innovative tool to identify unmet needs and home safety risks. The focus of our design emphasizes a community-based approach to successfully identify unmet needs and link individuals with HNHR with needed and effective health care services.

This project is timely because the *Veteran Peer Specialist Act of 2021* (Bill HR 4575) was recently approved by Congress to expand the peers-in-the-PACT program to all VA sites. The P2P intervention offers a protocol for integrating peers into the PACT that enhances and adds to the services provided by peers at the VA. The P2P intervention is being tested under real-world conditions using certified VA peer support specialists selected through usual VA hiring practices and assigned to the VA primary care service. The results collected from this study will provide important information on the effectiveness of a peer-led home visit intervention for veterans with HNHR who are considered vulnerable as an innovative strategy to identify need gaps using the AFHS 4Ms framework and coordinate care to increase timely access to needed services. Our findings will further gauge the feasibility of this framework in the existing health care system using peers. This intervention may highlight the innovative role that peers in the PACT may play to extend the reach of the PACT into the veterans' homes to implement evidence-based long-term services and supports proactively and more equitably. Timely access to needed long-term care services and supports as a *preventive* measure may help meet veterans' preference to age in place.

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Data Availability

The data sets generated and analyzed during this study are not publicly available owing to Department of Veterans Affairs and ethical redactions as well as redaction of ethically sensitive information; however, instructions on obtaining the data are available upon request.

Authors' Contributions

All authors contributed to the concept, preparation, and revision of the manuscript and approved its final version. The investigators retained full independence in the conduct of this research. The views expressed in this paper are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs or the United States government. The authors assume full responsibility for the ideas presented.

This article was prepared while LSP was employed at the South Texas Veterans Health Care System. The opinions expressed in this article are the author's own and do not reflect the view of the National Institutes of Health, the Department of Health and Human Services, or the United States government.

Conflicts of Interest

None declared.

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Abbreviations

4Ms: mobility, mind, medications, and matters most
5Ms: mobility, mind, medications, matters most, and multicomplexity
AFHS: age-friendly health system
CFIR: Consolidated Framework for Implementation Research
CPRS: computerized patient record system
GEC: Geriatric and Extended Care
GECDAC: Geriatric and Extended Care Data Analysis Center
HIPAA: Health Insurance Portability and Accountability Act
HNHR: high needs and high risk
LTIC: long-term institutional care
MISSION: Maintaining Internal Systems and Strengthening Integrated Outside Networks
P2P: peer-to–patient-aligned care team
PACT: patient-aligned care team
RE-AIM: reach, effectiveness, adoption, implementation, and maintenance
VA: Department of Veterans Affairs
VHA: Veterans Health Administration

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Protocol

Evaluation of a Community Suicide Prevention Project (Roots of Hope): Protocol for an Implementation Science Study

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Abstract

Background: Roots of Hope (RoH) is a multisite Canadian community-based suicide prevention initiative developed by the Mental Health Commission of Canada (MHCC), which is based on evidence for intervention effectiveness and World Health Organization recommendations. Seven communities developed local activities in the following 5 pillars: specialized supports, training and networks, public awareness, means safety, and evaluation research.

Objective: We aim to use an implementation research approach to understand the RoH model for reducing suicidal behaviors and their impacts in communities, and the lessons learned for the equitable development and implementation of RoH in different contexts. Moreover, we want to understand how the program is implemented in relation to the context, the causal pathways, and the factors influencing successful implementation. The evaluation includes assessments of short-term and intermediate effects at each site and overall.

Methods: The principal investigator (PI) developed a consensus among local research coordinators on common approaches and indicators through ongoing participation in an online community of practice, and regular virtual and in-person meetings. At the completion of the pilot phase, the PI will summarize evaluation results across sites and conduct pooled analyses. The RoH theory of change and evaluation model shows how evaluation activities from the planning phase through the implementation of activities in each of the pillars can help clarify the viability of the RoH model and identify factors that facilitate and inhibit effective and equitable implementation in different contexts. Beginning with a situational analysis to identify resources in each community and local specificities, we will examine the implementation characteristics of conformity, dosage, coverage, quality, utility, equity, appreciation, facilitators, and impediments. Evaluation of short-term effects will focus on changes in knowledge, attitudes, behaviors, help-seeking, service use, stigma, media reports, empowerment, and care experiences. Intermediate effects, long-term effects, and impact will include assessments of the changes in suicides, suicide attempt rates, and suicide risk indicators. A variety of data sources, both quantitative and qualitative, will be used.

Results: The quantitative and qualitative data from all sites will be summarized by the PI in March 2023 to draw conclusions to help the MHCC in its improvements to the RoH model, and to inform communities about how to better implement RoH. Since

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the COVID-19 pandemic occurred at the beginning of program implementation, its impact and influence will be documented. The validity of RoH in contributing to the prevention of suicides and suicidal behaviors will be clarified in a variety of contexts. The final evaluation report will be available in September 2023.

Conclusions: The evaluation results, including the identification of factors that facilitate and inhibit the implementation of RoH and the adaptations to challenges, will be useful to the MHCC, current RoH communities, and those considering adopting the RoH model.

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KEYWORDS

suicide; prevention; community; evaluation; implementation science; implementation research; impact; mental health; psychological health; public health; community health

Introduction

Background

Roots of Hope (RoH) is a multisite national suicide prevention project initiated by the Mental Health Commission of Canada (MHCC) [1]. Its goal is to develop an evidence base, including best practices and suicide prevention guidelines and tools, to support the scaling up and implementation of a "made-in-Canada" community suicide prevention model across the country.

RoH was developed by the MHCC, based upon a systematic review the Commission conducted on the effectiveness of various suicide prevention programs and activities, as well as their review of evidence-based recommendations for community suicide prevention activities by the World Health Organization (WHO) [2,3]. The WHO proposes that key risk factors for suicide be aligned with relevant interventions at the societal, community, relationship, and individual levels. One of their key messages is that "Communities play a critical role in suicide prevention" [4]. This approach, which promotes community actions in suicide prevention, is mirrored in the comprehensive national Canadian Suicide Prevention Framework [5]. RoH provides structures around which communities can tailor their suicide prevention efforts to meet their unique needs. Each community develops strategies and activities in each of 5 "pillars" identified by the Mental Health Commission, which are evidence-based areas of prevention activities that can be found in all national suicide prevention programs that follow the WHO recommendations. The pillars are as follows:

1. Specialized supports: Prevention, crisis, and postcrisis services, such as peer support, support groups (including self-help), workplace interventions, and coordinated planning and access to services.
2. Training and networks: Training and learning opportunities for health care providers, such as physicians and nurse practitioners, mental health workers, as well as community gatekeepers, such as first responders, human resource staff, and teachers.
3. Public awareness campaigns: Locally driven campaigns to promote mental health awareness (posters, brochures, social media, etc) and collaboration with the media, with the goal of creating an effective suicide prevention awareness campaign and having safer conversations about suicide, including on social media.
4. Means safety: Identification of the methods or places where a high number of suicides occur and implementation of measures to ensure safe access to them. For example, building barriers on bridges or railway crossings, protocol for medication access, etc. These include helping to reduce suicides by creating a safer home.
5. Evaluation research: Setting research priorities, conducting surveillance, and monitoring and evaluating the implementation (using an implementation science approach) and effects of the project at each site and overall.

Evaluation Objectives

The overall objective of the evaluation is to understand RoH as a comprehensive model to reduce suicidal behaviors and their impacts in communities. Specific aspirational questions concerning this understanding that were formulated by the MHCC at the start of the project are included in Multimedia Appendix 1. An addition to these questions was made because of the timing of the implementation of the programs (an assessment of the impact of COVID-19 on the implementation and potential effects of the programs and their activities). The evaluation involves obtaining qualitative and quantitative data, including perspectives on the implementation and effects from members of the community, caregivers, and various stakeholders. The final report on the evaluation will identify lessons learned that could be useful for other communities implementing the model, and issues of equity and factors affecting the implementation will be discussed. In addition, actual and perceived impacts of the implementation of RoH will be assessed. We plan to analyze across sites the overall implementation and effects of common activities within each of the pillars, in order to better understand what appears to be effective and which factors influence the implementation of activities in different contexts. In addition to common quantitative metrics, a qualitative assessment will be carried out through semistructured interviews and focus groups. Analyses will include the assessment of possible unintended outcomes. In the RoH model, all of the areas of action have empirical evidence supporting the effectiveness of many activities. Most of the research has occurred in other cultures and in populations that may differ in terms of age, socioeconomic status, and local practices.

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Roles of the Principal Investigator and Local Research Teams, and Development of the Evaluation Plan

In May 2018, Professor Brian L Mishara, Director of the Centre for Research and Intervention on Suicide, Ethical Issues and End-of-Life Practices (CRISE) and Psychology Professor at the Université du Québec à Montréal was appointed by the MHCC as principal investigator (PI) for the evaluation research of the RoH project. The PI (BLM) received funding for administrative support from the MHCC, which was used to hire an assistant to serve as research coordinator (ATT). The role of the PI is to develop a consensus on research methodologies and, to the extent possible, ensure that local research teams use the same common indicators in their evaluations. The consensus, which is reflected in this evaluation research plan, was developed over the course of 2 years through regular in-person and online meetings, and participation in a community of practice for only the research coordinators and a combined community of practice with the researchers and the implementation coordinators for each site. They also used a RoH research community of practice website to share information among local coordinators. Information about how to conduct the evaluation was discussed, modified, and approved by the lead researchers in each of the provinces and then by all the provincial intervention coordinators and the MHCC. Some of the tools and indicators that were adopted had been developed or used already in one or more communities as part of their ongoing evaluation activities. Some were created or adapted by the PI and, after consultations and modifications, were accepted by the local teams. In addition, the PI is available to consult with the teams, respond to local issues and questions, collaborate with the MHCC, and help to ensure conformity of evaluation measures across sites through participation in an ongoing community of practice involving all the research coordinators. Besides group consultations during research community of practice meetings, one-on-one consultations are available by email, telephone, and video conferencing whenever requested by researchers from local sites.

Since it is important to also obtain qualitative data from interviews and focus groups involving the people in charge of the implementation and the evaluation, the role of doing this was delegated to the PI, with MHCC providing some additional necessary resources made available to local researchers (software licenses and transcription services). This is because it could be difficult for employees working for a research or implementation coordinator to conduct a completely nonbiased interview with one of their supervisors or employers. In addition to locally obtained data, the PI team will obtain some pertinent centralized national data to support and share with local research teams.

The local research teams, hired by the local organization responsible for the implementation, are responsible for data collection and analyses in their communities, and they provide local reports and summaries that are requested or needed by those involved in the local implementation. They have a mandate to collaborate with the PI to determine the research methods, as summarized in this document, and participate in a community of practice with the PI and other RoH community researcher coordinators. A data sharing agreement has been developed to specify ethical and practical aspects of sharing and use of data by local researchers, the PI, and the MHCC.

The PI also has the roles, mandated by the MHCC and agreed to by all the local research coordinators, of summarizing the data from each of the local research teams, pooling data when possible, conducting analyses on pooled data, drawing overall conclusions concerning the RoH model and specific activities that exist at multiple sites, discussing site-specific aspects of the implementation and effects, and presenting potential implications of the evaluation results for scaling-up and implementation in different sites and contexts.

Methods

Ethics Approval

This evaluation protocol has been approved by the Ethics Committee for Research with Human Subjects (“Comité institutionnel d’éthique de la recherche avec des êtres humaines”) of the Université du Québec à Montréal (dossier number 2758).

Participating Communities

The initial sites of the implementation of RoH were Newfoundland and Labrador, New Brunswick, Saskatchewan (3 sites), Alberta, Ontario, and Nunavut. The first province to become part of the RoH project was Newfoundland and Labrador, which partnered with the Mental Health Commission in January 2018. This collaboration was developed by Eastern Health and a community coalition on the Burin Peninsula. The province of Newfoundland and Labrador was joined by New Brunswick, which launched a community suicide prevention project in Northwestern New Brunswick in the County of Madawaska-Victoria, which includes Kedgwick, Edmundston, and Grand Falls. Three additional provinces (Sakatchewan, Alberta, and Ontaria) also joined RoH. In Saskatchewan, with partnerships between local community coalitions and the Saskatchewan Health Department, the project was implemented in the Northern communities of La Ronge and Meadow Lake. The community of Buffalo Narrows, Saskatchewan joined in 2020. In Alberta, RoH was implemented in Edmonton as part of the Living Hope community suicide prevention of that city, in collaboration with local organizations and a partnership with the Canadian Mental Health Association. The Waterloo-Wellington, Ontario community signed on to RoH in August 2019, with the Waterloo Region Suicide Prevention Council leading this initiative and partnering with Here4Hope, the Wellington Suicide Prevention Initiative involving the Canadian Mental Health Association Waterloo-Wellington and Wellington County. The city of Iqaluit in the Canadian Teritory of Nunavut joined RoH in 2021 as part of the Department of Health of the Government of Nunavut’s Inuusivut Anninaqtua Action Plan for suicide prevention. At the time this evaluation plan was submitted, Iqaluit had not yet completed its planning phase and had not yet started implementation and evaluation activities, partly due to the COVID-19 pandemic.

Theory of Change and Evaluation Model

A theory of change is intended to generate “a description of a sequence of events that is expected to lead to a particular desired

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outcome" [6]. Figure 1 presents a diagram with the theory of change and evaluation model for the implementation and evaluation of the RoH project. A theory of change, as represented in a diagram and narrative, aims to provide a guiding framework for the project team and stakeholders. The theory of change presented in Figure 1 is the result of a dynamic iterative process, based upon the study of documents provided by the MHCC and the PI, and discussions with the persons conducting the RoH program in each of the provinces and the provincial research coordinators, as well as the consideration of provincial evaluation proposals and local resources. The model in Figure 1 follows a logical sequential order, from the top to the bottom, with parallel evaluation activities being conducted at each step.

The evaluation model begins with an assessment of the planning, which occurred before implementation of the RoH activities and continues to be adjusted throughout the implementation of the activities. Changing realities oblige everyone involved in planning, implementation, and evaluation to constantly adapt what they are doing, based upon how they conceive of changing needs, priorities, and responses to their actions in the flux of change in complex real-life situations. For this reason, a theory of change has been described as both a process and a product that continually evolves over time [6].

The planning is based upon the community resources, strengths, and challenges, and the sociocultural community context. Furthermore, what constitutes evidence-based practices in suicide prevention is an important resource input to help guide planning of activities. In an ideal situation, before planning starts, one should begin with a needs assessment to understand the magnitude, nature, and characteristics of the target population, their needs, the community needs, and available resources. Although each of the RoH communities discussed and considered needs and resources in the development of their specific RoH activities before the evaluation team was put in place, this was not always complete, and certain aspects of needs were assessed differently at each site. Therefore, the evaluation of RoH includes a standardized systematic situational analysis in each of the communities in order to better understand the local contexts in which the RoH activities were developed. This situational analysis, conducted at each of the sites using available and reliable data sources, identifies the nature of the psychosocial context in the communities, the community resources and capacities, and the challenges within the community at the general level and for specific cultural and local subgroups, including particular populations at increased risk of suicidal behaviors.

Multimedia Appendix 2 lists the information gathered as part of the situational analysis. Besides describing the communities for use in local planning, the PI team summarized this information across communities in order to provide a portrait of similarities and differences. This comparative portrait can help in the interpretation of evaluation results by identifying common issues, strengths, and resources, as well as the specificities associated with each of the sites.

Planning in each site also involved consultations with stakeholders, structuring of roles, and concrete assessments of needs and resources. All this was considered in the context of the RoH model that was developed by the MHCC, which constitutes the basic framework according to which each community is expected to develop their local plan of activities.

The planning process in each community involves mobilization of stakeholders, service providers, and members of the community to become involved in both the planning and implementation activities of RoH. In each of the communities, collaborations need to be established. This was generally concretized in the form of local coordinating and planning committees, as well as community consultations to not only provide information about what to do and how to do it, but also develop active engagement by individuals, organizations, and community agencies for realizing the RoH project.

The planning phase, whose documentation is part of the RoH implementation evaluation, is translated in each site into specific implementation activities organized into the 5 "pillars" of RoH (Multimedia Appendix 2) as specified by the RoH model developed by the MHCC. For each activity, the nature and extent of resources allocated for each of the target populations, as well as the nature of the activities, need to be determined in relation to the community resources. Then, the delivery of services can begin. Characteristics of these services should be understood as part of the evaluation process in terms of their availability, accessibility, acceptability, and quality. In an ideal world, this results in the target populations receiving the activities as planned and intended. However, in reality, not everything can be implemented as planned, and multiple adjustments and adaptations need to be made throughout the implementation phase.

During this implementation phase, we assess important characteristics of the implementation of RoH activities in each of the pillars as follows: *conformity* in providing activities as planned; *dosage* (extent to which enough of the service or activity was effectively delivered); *coverage* (proportion of the general population and targeted populations reached); *quality* (degree to which activities and services were of high quality); *equity* (extent to which coverage was biased due to some systemic characteristics such as location and accessibility issues); *appreciation* (how services and activities were perceived and received by stakeholders and end users); and *conformity* to best practices in suicide prevention and to the RoH model (evidence based).

In addition, we focus on identifying facilitators that help with "successful" implementation and help the persons involved in the implementation address challenges and difficulties throughout the implementation process.

Although much of the RoH evaluation focuses on implementation, to the extent possible, the evaluation model includes assessments of short-term outcomes, and mid-term impacts and effects. As shown in Figure 1, the RoH evaluation focuses on the following 7 primary areas of short-term outcomes: (1) reductions in treatment gaps and inequities, (2) increases in skills, (3) community empowerment, (4) increases in capacity to deliver activities, (5) increases in knowledge, (6) improvements in attitudes, and (7) positive changes in behaviors

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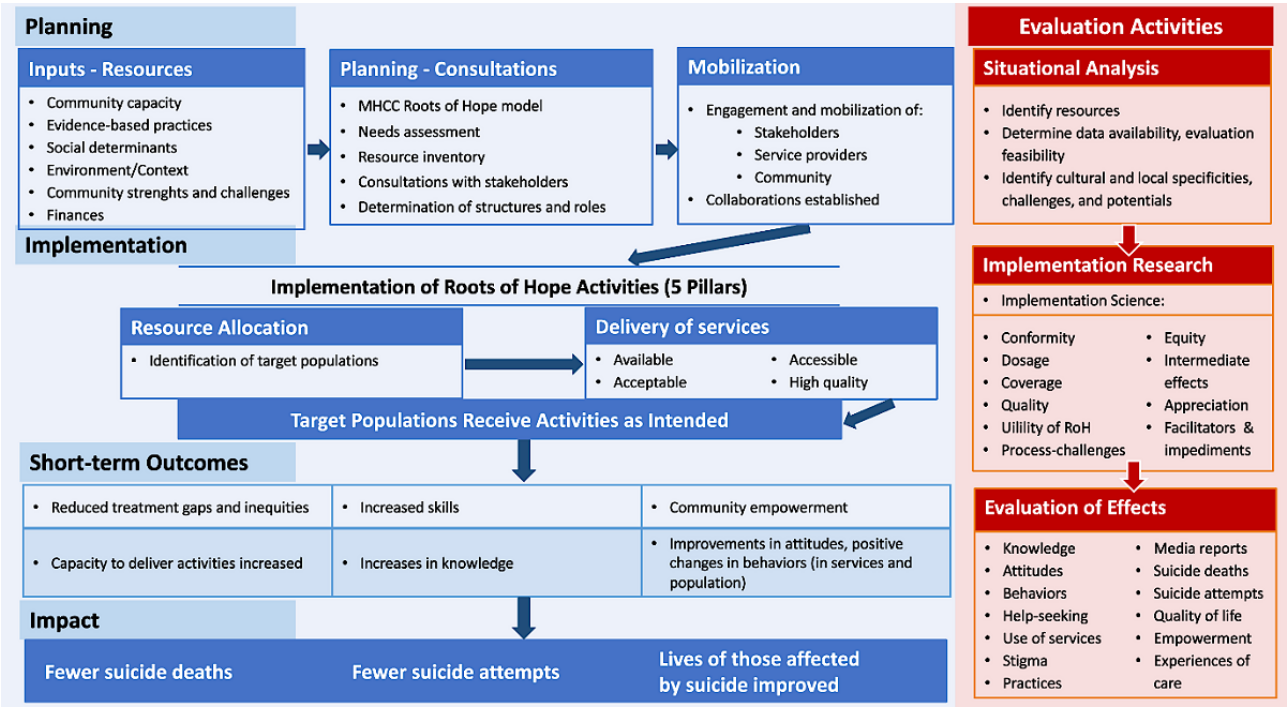
in providing services and the behaviors of members of the population.

The evaluation of effects is both specific to different RoH activities and general, in the sense that it also concerns the synergistic effects of the combination of all RoH activities in each community. Figure 1 lists the 12 main areas of the evaluation of effects. Most of these areas can be assessed in the short term regarding specific activities and more generally in the mid-term regarding the impact on the community. For example, evaluation of knowledge after participating in a training session can be assessed among participants in the session. However, a combination of multiple training and educational activities within the community could result in less stigma and negative attitudes about help-seeking. This, in turn, could facilitate increased use of mental health and suicide prevention services, and could have an impact on the prevention of suicidal behaviors.

Because of the low incidence of suicide deaths and the fact that suicide rates can have large fluctuations in relatively small communities, one cannot expect to observe significant decreases in suicide deaths over a short period (implementation period of approximately 2 years) and to reliably associate those changes with RoH. However, it is possible that pooling data across all RoH communities could indicate trends in suicide rates a few years after the implementation of RoH. Since there are far more suicide attempts than suicide deaths, if data are available, one may be able to document changes in suicide attempts in a shorter period of time. To the extent possible, RoH will examine existing data on attempted suicide. However, systematic suicide attempt data are not compiled in an exhaustive or accurate manner across Canada. Hospital records and visits to private physicians are rarely complete. Furthermore, a complete portrait of the incidence of suicide attempts in a community must include information from all individuals and institutions who have contacts with persons who have attempted suicide, which is often difficult and impractical. Again, we will analyze what data are available to determine if there is sufficient information to indicate changing trends in the rates of attempted suicide.

One can also assess the extent to which the lives of those affected by suicide may be improved as a result of RoH activities. Persons affected by suicide include those who are feeling suicidal and are in need of help; those at high risk of suicide who may or may not proceed with a suicide attempt; those who have attempted suicide and are at greater risk of attempting again; and the family, friends, and co-workers of persons who are thinking of suicide, who have attempted suicide, or who have died by suicide.

Figure 1. Roots of Hope (RoH) theory of change and evaluation model. MHCC: Mental Health Commission of Canada.



Methodologies and Measures

The methodologies and measures used to answer the major evaluation questions are listed in Multimedia Appendices 3-11. It is to be noted that all common measures proposed and listed are the result of a lengthy process of consultation and collaboration between the PI team and local researchers. They are to be understood as constituting a minimum set of information and data to be obtained in order to inform the implementation process of RoH as a whole. However, as explained below, this has proven to be particularly difficult in light of changing local contexts and resource limitations. Therefore, individual teams are encouraged throughout the process to make decisions on the most pertinent measures to retain in accordance with their local focus and the realities of local capacity. Nonetheless, all decisions concerning local measurements should be systematically documented and explained.

Although it seems desirable to determine which methodologies and instruments to use in advance and then simply proceed to

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gather the information, an implementation science approach obliges researchers to be constantly aware of the practicalities involved. They should consider the extent to which the instruments and methodologies they planned to use actually provide accurate and useful information that they require within the constraints of local contexts (research acceptability, availability of reliable data, resources, and capacity). Therefore, successful evaluations are iterative processes involving continued mindfulness of how well the evaluation is going at every step, and an openness to making changes and improvements throughout the process. The preceding statement proved particularly pertinent to the evaluation of RoH in the context of the COVID-19 pandemic. The COVID-19 pandemic occurred just as implementation of RoH was beginning in most communities. Not only were many activities and evaluation components put on hold during the COVID-19 pandemic, but also creative adaptations and changes were often made to continue some activities in other formats and adjust priorities in the identification of vulnerable populations. During this period, information about the changes associated with the COVID-19 pandemic and their impacts was systematically gathered as part of this evaluation. Multimedia Appendix 3 shows the information gathered and methodologies to determine what factors could affect the planning components of the RoH model in different contexts as well as overall. Data on planning are obtained from documents and the situational analysis (Multimedia Appendix 2 and the discussion in the following section). However, the evaluation of the planning components is complemented by qualitative data from interviews with each of the community coordinators and coordination groups, stakeholder focus groups, interviews with key RoH personnel, persons with lived experiences, and other available local data.

One of the key issues involves the extent to which the implementation of activities and services is both adequate and equitable. This involves not only an assessment of the extent to which each component is implemented, but also an understanding of key target populations in each community and the extent to which RoH activities provide interventions to various subgroups in a manner that meets their needs. Some of the measures concern the nature of the implementation process (conformity, dosage, quality, and coverage). However, a true understanding of adequate and equitable implementation involves including an assessment of the adequacy of the activities in meeting the needs of different target populations, and their real and perceived impacts (Multimedia Appendix 4).

Each of the RoH communities provide multiple training activities to care providers. Care providers include not only professionals, such as general practice physicians and workers at crisis centers, but also members of the community, such as those receiving peer-support training in a workplace. Multimedia Appendix 5 lists the data sources for evaluating training activities. These include descriptions of the nature and extent of training activities, participants, quality assessments of sessions and activities, and indications of the impact of specific training activities in increasing knowledge, improving attitudes, and increasing positive helpful behaviors.

The nature of awareness activities in this RoH awareness pillar varies greatly among communities, because of different target populations, community resources, and needs. Besides assessing activities to increase awareness and knowledge in the general population, several communities are also conducting general surveys to assess changes in stigma associated with suicide and mental health, attitudes, knowledge, and openness to seeking help (Multimedia Appendix 6).

The specialized support pillar of RoH includes a wide variety of specific services provided, expanded, or improved as part of RoH. The evaluation of these specialized support activities varies according to which activities are initiated in each community. For example, when decreasing wait times to obtain mental health services is a specific focus, the extent that wait times decrease needs to be assessed. When specific activities and programs are provided to help people bereaved by suicide, specific assessments need to be made to evaluate their impact on program participants. As seen in Multimedia Appendix 7, quantitative data using questionnaires and survey instruments are complemented by qualitative data from interviews and focus groups with key informants, clients, and service providers.

Reducing access to potential means for suicide is a RoH component whose activities depend upon which suicide methods are used or increasing in each community. Although it is possible to assess the roll out of these activities, and their nature and quality, most prior evaluations of promoting means safety have involved assessing decreases in deaths by suicide and suicide attempts. It is not realistic to expect that we would have sufficient data on suicide deaths to link those data to the targeted means safety activities in RoH communities. However, as indicated in Multimedia Appendix 8, we can assess the availability, acceptability, accessibility, and quality of the means safety activities and their coverage of target populations.

When we look at potential effects, the RoH evaluation model includes “classic” measures of suicidal behaviors (deaths, attempts, and possibly some information on the experiences of people with lived experience). However, as already discussed, the low incidence of suicide in general, lack of sufficient valid data on suicide attempts, relatively small population base in RoH communities, and limited time frame of the evaluation make it difficult to evaluation the impact of RoH on suicidal behaviors. Still, we will examine changes in the available data. However, we will also examine changes in other outcome measures that have been associated with decreases in suicidal behaviors in past research (Multimedia Appendix 9). These include improvements in services and changes in community perceptions and beliefs. Multimedia Appendix 10 provides several data sources for obtaining information on suicidal behaviors, as well as improvements that may be associated with fewer suicides and suicide attempts (community focus groups and surveys; administrative information and media reports; improvements in delivery capacity; identification of treatment gaps and inadequacies; and improvements in the skills, knowledge, and behaviors of service providers).

Because of the nature of community involvement throughout the process of planning, implementing, and evaluating RoH, we could expect increased community empowerment and quality of life, as well as improvements in perceptions of services and a diminution of barriers to accessing help. Decreasing stigma

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is one of the goals in each of the RoH communities that will be assessed. Increasing help-seeking behaviors, improving attitudes toward help-seeking, and increasing knowledge of services are the focuses of many of the RoH community interventions (Multimedia Appendix 10).

Data Analyses and Synthesis

The local evaluation research coordinators at each site will be responsible for conducting analyses of their quantitative and qualitative data and producing synthesis reports for local use and reports to the MHCC (Multimedia Appendix 11). The PI will be available to consult and assist local coordinators with their analyses and interpretation of results. The PI team will also propose guidelines for common coding and analysis to ensure consistency across sites. All results of the measures indicated in this plan, as well as additional measures used as part of the RoH evaluation, will be shared with the PI, including the necessary information needed to summarize results across sites. The PI will conduct additional analyses combining information from sites, synthesize and interpret the overall results, and provide reports in collaboration with all contributing local researchers. After consultations, reports combining and comparing information for the sites will be included in reports by the PI. All data sharing will observe the norms and procedures outlined in the Data Sharing Agreement signed by the provincial partners, the PI and his university, and the MHCC. All publications will follow the Publication and Dissemination Guidelines for RoH developed by the MHCC in consultation with the PI, provincial partners, and research coordinators.

Local research teams that could benefit from support and consultation in their analyses of qualitative data can call upon the PI and his team to help and support them with these analyses and their interpretation. The data gathered from the interviews and focus groups conducted by the PI's team at local sites will be analyzed by the PI team, and the results will be sent to the provincial research coordinators for use in their reports. The results combined across sites may be used in overall RoH reports and presentations produced by the PI and his team, in accordance with the Data Sharing Agreement and the Publication and Dissemination Guidelines, approved by the MHCC, the PI, and all local research coordinators.

Results

The evaluation research plan for RoH is a major initiative involving diverse sites across Canada, each implementing a variety of multifaceted suicide prevention–related activities to meet the local needs of various target populations. The RoH model, developed by the MHCC, includes "state-of-the-art" best practices that have been validated in prior research and are recommended by the WHO to be incorporated in national suicide prevention strategies. This model provides a general orientation to focus on 5 "pillars" of action, leaving it up to each site to engage in consultation, planning, and evaluation processes that take into account local problems, resources, and cultures, and the specific needs of priority target populations that are identified. In this context, one would expect that evaluations of the implementation and effects would need to be tailored to the local needs and resources, and the nature of the specific activities selected to be implemented as part of RoH at each site. Therefore, the evaluation model must carefully balance the need for standardization and the advantages of using common approaches and methodologies, against the necessity to tailor the evaluation activities at each site to the unique characteristics of the RoH activities that have been chosen. In this context, the extent to which the evaluation results across the diverse communities will be able to identify valid general conclusions that are applicable to current and future RoH sites will not be determined until the evaluation is completed.

The evaluation model presented in this document demonstrates the fruits of over 2 years of interactions between the PI team and local research and implementation coordinators, with input from the MHCC. Hopefully, this plan attains a balance between standardization and flexibility that will provide the necessary information to meet local needs at each site and also provide a comprehensive overall assessment of the RoH model across sites. However, differences in the nature and extent of funding at each site and differences in the availability of data in existing community organizations and records may compromise the ability of the evaluation to obtain enough of the essential information necessary to attain the evaluation goals.

We realize that real-world constraints and changes during the course of the RoH project will continually pose challenges to all those involved in the evaluation process. The COVID-19 pandemic is a powerful example of how radical changes in the planned roll out of the programs and evaluation activities had to be made, including refocusing and developing new activities to respond to suicide and mental health challenges associated with the pandemic, and changing data collection methods for the evaluation. These changes primarily concerned the need to cancel many in-person activities and replace them with online programs, services, and assessments. The advent of COVID-19 during the implementation phase resulted in the need to innovate and adapt, and caused delays in the implementation and evaluation processes. However, this also provided an opportunity to understand the process of adapting to the challenges of having COVID-19 present in communities, where new methods were developed to deliver services and to obtain data for the evaluation.

The quantitative and qualitative data from all sites will be summarized by the PI in March 2023 to draw conclusions to help the MHCC in its improvements to the RoH model, and to inform communities about how to better implement the RoH approach in an efficacious and equitable manner. Since the COVID-19 pandemic occurred at the beginning of program implementation, its impact on the implementation and evaluation activities and its influence on the RoH project will be documented. Overall, we aim to clarify the validity of RoH in contributing to the prevention of suicides and suicidal behaviors in a variety of contexts. The final evaluation report will be available in September 2023.

Discussion

Our aspiration for the evaluation is to be able to better understand the validity, feasibility, and evaluability of the RoH model for community suicide prevention. We also aspire to

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identify the processes in planning, implementation, and evaluation that facilitate its usefulness for communities and their members. We hope to clarify its validity in contributing to the prevention of suicides and suicidal behaviors in a variety of contexts. We also hope that it may help others who are interested in developing suicide prevention strategies and activities, including those who are considering adopting the RoH model. In addition, the evaluation results may provide useful information to the MHCC on how RoH could be modified and improved to be more effective in the future.

Besides reaching general conclusions about the practicality and usefulness of the RoH model for communities, we hope to be able to identify factors that facilitate its implementation, factors that inhibit its implementation, and different adaptations and innovations that can be used to deal with challenges occurring during its implementation. We aim to identify the extent to which the implementation is successful and equitable, and explain why problems may have arisen, what facilitates success, and how the Mental Health Commission may be able to modify the RoH model to facilitate the implementation, equity, and positive effects of the program.

Although the evaluation is not complete, challenges in coordinating locally funded evaluation programs in multiple sites are evident. A better future approach could be to obtain sufficient central funding for the entire implementation and evaluation. This would better ensure that all sites have the necessary resources to complete all the essential evaluation activities and would minimize discrepancies between sites in which activities are implemented completely as planned. In a provincial context, such as Canada, where health and mental health services are planned, funded, and delivered by provinces, it may not be feasible to ensure uniform funding for the implementation of community programs for sites in different provinces. However, since there are national research funding organizations, there is hope that multisite evaluations of the implementation and short-term effects could be funded.

Acknowledgments

We thank the personnel at the Mental Health Commission of Canada, particularly Karla Thorpe and Nitika Rewari, for their help and support.

Data Availability

Raw data gathered by the principal investigator that are not reported in the final report of the evaluation research may be obtained (anonymized) by contacting the principal investigator once the report and articles reporting the findings have been published. Data gathered locally at each of the sites, which will be synthetized or interpreted by the principal investigator in the final report, will be made available according to the policies of each of the local research coordinators who obtained the data.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Mental Health Commission of Canada aspirational questions.
[DOCX File , 16 KB - resprot_v12i1e39978_app1.docx]

Multimedia Appendix 2
Situational analysis.
[DOCX File , 316 KB - resprot_v12i1e39978_app2.docx]

Multimedia Appendix 3
Assessing planning: factors affecting planning components, methodologies, and sources of data.
[DOCX File , 15 KB - resprot_v12i1e39978_app3.docx]

Multimedia Appendix 4
Assessing implementation: adequacy of services and activities to target populations and equity issues, methodologies, and sources of data.
[DOCX File , 15 KB - resprot_v12i1e39978_app4.docx]

Multimedia Appendix 5
Training pillar: implementation common metrics, methodologies, and sources of data.
[DOCX File , 15 KB - resprot_v12i1e39978_app5.docx]

Multimedia Appendix 6

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Awareness pillar: implementation common metrics, methodologies, and sources of data.
[DOCX File , 15 KB - resprot_v12i1e39978_app6.docx]

Multimedia Appendix 7
Specialized support pillar: implementation common metrics, methodologies, and sources of data.
[DOCX File , 15 KB - resprot_v12i1e39978_app7.docx]

Multimedia Appendix 8
Means restriction pillar: implementation common metrics, methodologies, and sources of data.
[DOCX File , 15 KB - resprot_v12i1e39978_app8.docx]

Multimedia Appendix 9
Short-term outcomes, methodologies, and sources of data.
[DOCX File , 16 KB - resprot_v12i1e39978_app9.docx]

Multimedia Appendix 10
Impact on suicidal behaviors, quality of life, community empowerment, experience of care, and effects on practices.
[DOCX File , 16 KB - resprot_v12i1e39978_app10.docx]

Multimedia Appendix 11
Summary of common measures and assessments for quantitative and qualitative data.
[DOCX File , 17 KB - resprot_v12i1e39978_app11.docx]

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Abbreviations

MHCC: Mental Health Commission of Canada
PI: principal investigator
RoH: Roots of Hope
WHO: World Health Organization

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Protocol

Building Culturally Centered System Dynamics Logic Models for the Brown Buttabean Motivation Organization: Protocol for a Systems Science Approach

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Abstract

Background: Brown Buttabean Motivation (BBM) is an organization providing support for Pacific people and Indigenous Māori to manage their weight, mainly through community-based exercise sessions and social support. It was started by DL, a man of Samoan and Māori descent, following his personal weight loss journey from a peak weight of 210 kg to less than half that amount. DL is a charismatic leader with a high media profile who is successful in soliciting donations from corporations in money and kindness. Over time, BBM's activities have evolved to include healthy eating, food parcel provision, and other components of healthy living. A co-design team of university researchers and BBM staff are evaluating various components of the program and organization.

Objective: The purpose of this study is to build culturally centered system dynamics logic models to serve as the agreed theories of change for BBM and provide a basis for its ongoing effectiveness, sustainability, and continuous quality improvements.

Methods: A systems science approach will clarify the purpose of BBM and identify the systemic processes needed to effectively and sustainably achieve the study's purpose. Cognitive mapping interviews with key stakeholders will produce maps of their conceptions of BBM's goals and related cause-and-effect processes. The themes arising from the analysis of these maps will provide the initial indicators of change to inform the questions for 2 series of group model building workshops. In these workshops, 2 groups (BBM staff and BBM members) will build qualitative systems models (casual loop diagrams), identifying feedback loops in the structures and processes of the BBM system that will enhance the program's effectiveness, sustainability, and quality improvement. The Pacific and Māori team members will ensure that workshop content, processes, and outputs are grounded in cultural approaches appropriate for the BBM community, with several Pacific and Māori frameworks informing the methods. These include the Samoan *fa'afaletui* research framework, which requires different perspectives to be woven together to create new knowledge, and *kaupapa Māori*–aligned research approaches, which create a culturally safe space to conduct research by, with, and for Māori. The Pacific *fonofale* and Māori *te whare tapa whā* holistic frameworks for interpreting people's dimensions of health and well-being will also inform this study.

Results: Systems logic models will inform BBM's future developments as a sustainable organization and support its growth and development beyond its high dependence on DL's charismatic leadership.

Conclusions: This study will adopt a novel and innovative approach to co-designing culturally centered system dynamics logic models for BBM by using systems science methods embedded within Pacific and Māori worldviews and weaving together a number of frameworks and methodologies. These will form the theories of change to enhance BBM's effectiveness, sustainability, and continuous improvement.

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International Registered Report Identifier (IRRID): PRR1-10.2196/44229

(JMIR Res Protoc 2023;12:e44229) doi:10.2196/44229

KEYWORDS

systems logic model; cognitive mapping interview; group model building; community network; healthy lifestyle; weight reduction programs

Introduction

Background to Brown Buttabean Motivation

In 2014, DL, a man of Samoan and Māori descent, set up an organization called Brown Buttabean Motivation (BBM) in south Auckland, Aotearoa New Zealand. DL had a personal weight loss journey from a peak weight of 210 kg to less than half that amount [1]. BBM provides support for Pacific people and Indigenous Māori to manage their weight, mainly through community-based exercise sessions and social support. Pacific and Māori people have much higher rates of obesity- and weight-related diseases than non-Pacific and non-Māori people.

While exercise boot camps were the entry point for community engagement, over time BBM's activities have evolved to include healthy eating and other components of healthy living, which are woven into a collective journey toward health and well-being [2]. DL is the high-profile leader of BBM, which is now a limited liability company. BBM's operations staff includes both paid employees and volunteers. Its funding comes from a variety of sources, including philanthropy, the Ministry of Health, and donations through its Just Move Charitable Health Trust funding arm. Its members, largely but not exclusively of Māori and Pacific ethnicities, are now located not only in south Auckland but also in the west of the city and other parts of Aotearoa New Zealand.

Researchers at the University of Auckland were asked by BBM to co-design an evaluation of the various components of the program and the organization. A qualitative study has been conducted to understand how participants experience and engage with BBM as a grassroots, Pacific-, and Māori-led holistic health program [2]. Most interventions to address obesity do not result in sustained weight loss over time, and a review of the literature recommended "Māori and Pacific-led, culturally tailored weight loss programs that promote holistic, small, and sustainable lifestyle changes delivered in socially appropriate contexts" [3]. A pre-post longitudinal quantitative cohort study is underway to evaluate the effectiveness of BBM for sustained health and well-being outcomes, especially weight loss [4]. A further study is underway to conduct a mixed methods process evaluation of BBM's community engagement through in-person, social, and news media outreach activities with respect to the health and well-being of the Māori and Pacific communities over time [5].

Systems Science

Overview

A system is an interconnected set of elements coherently organized in a way that achieves something [6]. The structure of a system is therefore comprised of a complex interplay of 3 types of things: elements, connections, and a function or purpose. The meanings that people attribute to these elements may or may not be universally shared. Understanding these components is required to accurately model the system. People may have different mental models of the same events and data, and visual mapping and modeling tools can help reveal these different interpretations and combine them into an overarching perspective. Once the structure is identified, it can be altered in order to make changes to the system.

Logic Models of Change

A logic model is a theory of change. It demonstrates the inputs (what goes in), outputs (what comes out), outcomes (what results from this), and the relationships between them. Often, logic models are linear in nature (eg, inputs leading to processes, leading to outputs, leading to immediate impacts, and leading to long-term outcomes), showing the intentions, assumptions, and rationale of an intervention and how it can influence a system to achieve an outcome. A dynamic model identifies and uses feedback loops and can show what things may lead to another and different factors that might lead to change, both those that can be controlled and others unrelated to the program and hence out of the organization's control [6]. A systems approach that can incorporate feedback loops will create sustainability in a rapidly evolving, responsive program.

Logic models are graphic depictions of the relationships between resources, activities, outcomes, and impacts of a program or a system. They have been used in a variety of settings, for example, to inform the development of interventions such as a rehabilitation service for youth with concussion [7,8], mobile health support for physical activity in people with spinal cord injuries [9], and digital self-management in inflammatory bowel disease [10]. They have been used to understand how digital health interventions for self-management might be used to facilitate effective behavior change [11], how to design a plan to transform a health care system [12], and to capture complexities in systematic and scoping reviews [13]. Tools to create dynamic logic models include cognitive mapping interview (CMI), sometimes referred to as causal mapping and group model building (GMB). To appropriately represent the theory of change within a complex adaptive system, like BBM, system dynamics logic models need to account for the feedback loops intrinsic to the system.

Cognitive Mapping Interviewing

CMI is a visual technique that captures a stakeholder's perspective on a problem or issue and how they or their organization relate to the issue. This tool is used in systems

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research to view issues (for example, low fruit and vegetable consumption in children [14]) as emerging from complex and adaptive systems. A set process is followed during a semistructured interview to order and reflect the interviewee's view of the social system. The process of creating the CMI map aids participants' reflection and sense-making. The map produced during each interview consists of a network of nodes and arrows as links that are usually linear in structure. The themes that emerge from the analysis of the individual maps can then be combined to form a composite map, presenting the subjective data in a diagrammatic form that gives a holistic and systemic view of an issue. CMI has most often been applied to complex management problems and operational or action research. CMI was used in a health services project to develop a theoretical framework for implementing innovative practices in primary health care management in Aotearoa New Zealand [15], and other studies internationally have used similar system dynamics methods [16].

Group Model Building

GMB is a qualitative method that aims to engage stakeholders to collectively consider the dynamics of complex problems [17]. It involves a facilitation or modeling team and a group of stakeholders who cobuild a model to solve specific problems within a complex system [18,19]. GMB, as a participatory method, extracts the knowledge and understandings of a problem from people who engage with it by using a series of facilitated, structured discussions. GMB has applications ranging from problem definition to simulation system dynamics modeling [20]. In other words, in GMB sessions, people provide their individual perspectives on the problem, its structure, the resulting dynamic model, as well as its impacts and solutions. These views are improved by knowledge sharing among people, discussions, and group analysis. When a consensus model is achieved, the group then identifies leverage points within the system and the actions needed to reorient the system to resolve the problem. This approach ensures that people's perspectives and understandings are included, thereby increasing their commitment to execute their action tasks [21]. The GMB process enables the creation of visual system maps that identify the feedback loops that are holding a problem in place or that can be reoriented to reduce the problem.

Cultural Approaches and Frameworks

Overview

There are several Māori and Pacific frameworks and models that are appropriate to use in Aotearoa New Zealand to inform systems science approaches. The core personal and social values of Māori and Pacific people are love, humility, respect, and relationship. Connectedness and collectivity are key.

Kaupapa Māori

kaupapa Māori aligned research ensures that the experiences and outcomes of research are positive for Māori communities [22]. kaupapa Māori research prioritizes Māori knowledge, language, and customs research practice [23]. There are 5 key principles: tino rangatiratanga (self-determination), taonga tuku iho (cultural aspirations), ako Māori (Māori worldview), whānau (family), and kia piki ake i nga raruraru o te kainga (socioeconomic mediation) [24,25]. These key principles will guide the CMIs and GMB workshops to ensure that the researchers and the research process provide a culturally safe environment for our participants and that the outcomes of the study have a positive impact on Māori communities [25,26].

Fa'afaletui

The Samoan *fa'afaletui* research framework also informs our study design. *Fa'afaletui* requires different perspectives woven together to create new knowledge (from "ways of" [*fa'a*] "weaving together" [*tui*] deliberations of different groups or "houses"[*fale*]) and is derived from the Pacific philosophy of connectedness and a collective holistic approach [27,28]. This fits well with the use of a mixed methods approach with a range of different types and sources of data. This research framework is also reflected in our team, which includes researchers with expertise in obesity reduction, co-design, and systems science, as well as the Māori and Pacific investigators outlined below. In line with the *fa'afaletui* framework, the collective approach of our study places greater value on the research because of the shared vision and support of all members (researchers, BBM workers, and community members), which intertwines the skills and perspectives within the research team to work toward a shared goal [26]. The bodies of knowledge that each person brings are woven together to conduct this *mahi* (work). Different systems science methodologies will also be interwoven to create our system model of change.

Fonofale and Te Whare Tapa Whā

Fonofale (Pacific) [29] and *te whare tapa whā* (Māori) [30] models of inquiry are holistic frameworks for interpreting people's dimensions of health and well-being. These frameworks use the metaphor of a Samoan or Māori meetinghouse. In the fonofale model, the floor is the extended family and community; the 4 house pillars, or pou, represent physical, mental, spiritual, and sociodemographic components of health and well-being; and the cultural practices, beliefs, and values that shelter people are the roof. The fonofale is surrounded by the physical environment and the sociopolitical context and is set at a point in time. Similarly, the Māori te whare tapa whā model has the foundation of the house (whare) as the land and place of belonging (taha whenua), and the 4 posts are physical (taha tinana), mental (taha hinengaro), spiritual (taha wairua), and family (taha whānau) well-being. Good health requires that these 4 posts be balanced and in harmony with each other [31].

Why BBM May Have System Issues That It Would be Helpful to Address

BBM has a core vision to provide, in DL's own words, "a health hand-up" for Māori and Pacific people. This is a broad vision that, at its core, has the goal of improving the health of *whānau* (family). Consequently, BBM engages with the community to enhance physical, spiritual, mental, and social health. Specific examples of activities include addressing food insecurity, providing a hub for exercise, encouraging vaccination, and meeting the needs of those displaced by recent flooding in Auckland and Hawkes Bay. BBM changes its focus in direct response to perceived community needs. There is a risk that BBM will overextend and not be sustainable. The development

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of a dynamic logic model of change can help identify organizational aspects that are functioning well independently and those that rely on DL's input. This knowledge may help BBM adapt and remain an effective and sustainable entity in his absence.

Aim

We aim to build a culturally centered system dynamics logic model to serve as the agreed theories of change for BBM and provide a basis for its ongoing effectiveness, sustainability, and continuous quality improvements. To achieve this, we are combining systems science approaches with several Pacific and Māori frameworks for health and processes for research.

Methods

Overview

This research will be *kaupapa Māori*–aligned. The principal investigator is of Samoan and Māori descent; our team also includes a Māori researcher to guide the team on *kaupapa Māori* research methodologies; and BBM staff, including DL, who identifies as Samoan and Māori, are coresearchers. The principal investigator and Māori researcher have been involved in all aspects of study conceptualization, design, and processes and will oversee data analysis and interpretation to ensure that the research is mana-honoring and safe for Māori. In alignment with *kaupapa Māori*, this research has been co-designed with BBM staff to ensure that the needs of the organization and the community are of the utmost importance. This is an example of the key principle of *whānau* . In this research, *whānau* refers both to people in a family (immediate and extended) and also to how Māori practice *whanaungatanga* (the way family members interact with each other) [25,30]. Everyone involved in the study is part of the research *whānau* , and the knowledge that each person brings to this research *whānau* is shared and valued.

The Pacific (*fonofale*) [28] and Māori (*te whare tapa whā*) [29] holistic frameworks for health will inform our research. Although its initial focus was on weight loss, particularly for the Pacific and Māori communities, BBM has evolved to provide social support for the overall health and well-being of its community, in line with the *fonofale* and *te whare tapa whā* frameworks.

There are 3 phases to our research. In phase 1, key stakeholders will be interviewed to produce cognitive maps of BBM's goals and cause-and-effect processes.

These maps will inform the main themes for exploration and questions in phase 2, which involves 2 series of GMB workshops, one with BBM staff and another with BBM members. During these workshops, participants will build visual system models. The process will identify feedback loops between the elements, structures, and processes of the BBM system, providing the theories of change for BBM to drive its effectiveness, sustainability, and continuous quality improvement. The goal of the staff workshop is to map the dynamics of the key parts of the BBM program itself that relate to its quality and sustainability, such as the continuous development of staff, program content, and funding. The members' workshop will focus on how to maintain and enhance participant engagement with BBM because program engagement is the best determinant of successful long-term weight loss. In the final phase, these visual maps will be used to create an integrated system dynamics model of change and the associated action plans needed to reorient BBM systems so that they can deliver optimum benefits for the BBM community.

Phase 1: Cognitive Mapping Interviews

Overview

The CMIs for this research will be used to identify a shared understanding of the purposes and goals of BBM. They will also identify the components and cause-and-effect processes of success and sustainability for BBM to deliver its purposes and goals. These concepts will initially become the indicators of change to inform the questions for further exploration in the GMB workshops.

CMI Recruitment

Between 5 and 10 key informants will be recruited as CMI participants. Participants will include 2 to 3 key people from the following groups: BBM staff members, long-term community members (including volunteers) who are focused on sustained engagement with BBM, and relevant funding representatives to BBM who are interested in the program meeting its purpose and remaining sustainable. Inclusion criteria for BBM staff are the founder and chief of operations; for male and female participants, they are adult (≥18 years) community members who have engaged with BBM for at least three years; and for funding representatives, the criteria are known funders of BBM projects or have an interest in potentially funding BBM projects. Participants will all give informed consent. Given the small number of participants required for the study's recruitment, they will be individually approached by our lead researcher, who has strong connections within the BBM community.

While standard qualitative approaches using thematic analysis require continuing recruitment until data saturation is reached, in this study the data are the complex maps created during the interviews. The purpose of the CMIs is not to get definitive maps but to better understand how to frame and define the central "problem" being placed on the table as the purpose of the GMB workshops.

The interviews will generally be 30 to 60 minutes long with a researcher hand-drawing the maps. Seeking clarification that the relationships and directions of influence are being accurately represented will help keep the interviewees engaged.

Developing the CMI Questionnaire

An open-ended questionnaire will be co-designed in consultation with all of the investigators and our BBM partners. This will ensure that the questions are inclusive of the frameworks and approaches guiding this study. For instance, prompts will support participants to think holistically, upholding Pacific and Māori cultural values housed within the respective models described above. The questionnaire will be piloted prior to the CMIs and assessed for cultural relevance. We will use the "purpose of BBM" for the lead staff and the funders to identify

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common understandings of the BBM purpose and what drivers help if fulfill that purpose and what the consequences would be from achieving that purpose. For the participants, the central issue will be engagement with BBM—the antecedents that drive participation and the consequences of high participation.

CMI Processes

The purpose of the CMIs is to seek the views of these key stakeholders as to the purpose of BBM, what would ensure its success and sustainability in achieving that purpose, and what the outcomes for the community would be if BBM achieved that purpose. The interviews will be conducted by the lead researcher (FS), who is of Māori and Samoan descent, and an associate researcher (TH), who is of Māori descent. The mapping will be conducted by BS, who is experienced in CMI research. FS and TL have undergone training in CMI and GMB from Synergia, an analytical company with considerable experience and expertise in designing and developing health networks. Their combined knowledge and expertise will ensure appropriate cultural formalities to allow participants to feel comfortable and culturally safe during the interview process. Interviews can be conducted in English, Samoan, or Te Reo (Māori) if desired by the participants. To align with *kaupapa Māori* methodology, the interview will begin with the lead researcher offering a *karakia* (prayer) to appropriately open and guide the interview process. A closing prayer will be shared to bring the interview to an end for everyone involved. Interviews will be audiotaped to allow the researchers to refer back to their maps for review.

Consistent with Māori and Pacific preferences for engagement, we prefer that interviews occur face-to-face either at a BBM gym (for BBM staff) or at a location suitable to the participant. For external collaborators (eg, funding representatives), the researchers will offer a university campus meeting room (south or central Auckland), or participants may choose their place of employment. If face-to-face is not suitable, a virtual meeting platform (eg, Zoom) will be used, in which case only sound will be recorded. During the interview, one researcher will lead the interview guided by the questionnaire, and the other will construct a hand-drawn cognitive map. The interviewee will review the interviewer's interpretation of comments, illustrated in the map, throughout the session. The interview transcript, map, and consent form will be linked by participant number rather than name to maintain confidentiality. Participants will be given a small *koha* (gift) at the conclusion of the interview to thank them for their involvement and acknowledge their contribution to the study. Following the interview, the hand-drawn maps will be refined and drawn digitally. Participants will be emailed the transcript and the digital version of the cognitive map constructed during their interview, and they will be called to verify them and take any suggestions they offer.

The results from the interviews will form the basis of the GMB workshops. The purpose of using CMI is to generate an informed base of knowledge about what team members, community members, and funders believe are the strengths and challenges of delivering a holistic, effective, and sustained service for the community. In particular, the themes that emerge will provide the key indicators for the expected changes over time. These will form the "reference behaviors" for the GMB workshops. A reference behavior is a key indicator within the system that has a changing pattern over time and, looking into the future, has a more or less desirable trajectory. For example, participant engagement with the BBM sessions typically starts high with enrollment but then wanes over time. The less desired trajectory is a greater disengagement profile, in the future and the more desired trajectory is greater engagement because this is known to be a strong predictor of long-term weight loss maintenance. For sustainability, increasing funding will be needed over time, with declines in funding being the less desirable trajectory.

Phase 2: Group Model Building

GMB problems can be defined in terms of solutions; for example, how BBM may increase the degree and length of engagement of participants with BBM.

Developing the GMB Scripts

The structured scripts to use in the GMB workshops will be co-designed with the BBM coresearchers involved in this research project to align the research processes with the community's needs. Scriptapedia is a repository of short, facilitated activities (scripts). It is an evolving, open-source handbook of contributed scripts that can be considered best practices, promising, or under development [31]. These scripts can be easily edited to suit the local environment, cultures, and the problem or issue being investigated.

We will weave relevant scripts together to create the facilitated, structured discussions for our GMB workshops. This will help to ensure that the workshops achieve the desired outcomes of creating systems maps and action priorities, as well as upskill the participants in their systems thinking so that they can better understand the nature of the issue being mapped and the ways to orient the BBM systems for improved outcomes. The interactions within a group during a GMB workshop need to make the best use of their time and ensure that the overall process moves forward in an organized fashion, ultimately providing insights for the research team and stakeholders [20].

GMB Workshop Recruitment

Participants will be recruited for 2 series of workshops, with 15-20 participants per series. One series will be with BBM employees and volunteers (staff), and the other with active BBM community members, including volunteers, who engage with the organization on a regular basis (members). Each series will consist of 3 workshops with about 2 weeks between them. All workshops will be held at one of the BBM gyms in either south or west Auckland or the University of Auckland's south Auckland campus. Recruitment for both series will be a collaborative process between researchers and BBM staff to negotiate recruitment at a time and place suitable to participants and BBM. For BBM community members to be invited, they will need to have been active members for at least 6 months prior to the planned workshops and plan to continue to engage on a regular basis. BBM holds attendance records and member details, so the research team will work with BBM staff to purposively invite a representative balance of male and female adult (aged ≥18 years) members to participate. There will be

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no ethnic exclusions, but the aim is to have predominantly Pacific and Māori participants. People who have previously participated in the CMIs and those who are not fluent in English, Māori, or Samoan will be excluded. All participants will give informed consent and will be offered *koha* (reimbursement) for their time, in line with our ethics approval.

GMB Processes

The GMB workshops will be co-designed by the research team and the coresearchers from BBM (DL and FL) to ensure that the questions asked, processes put in place, and language used are appropriate for the participants. Prior to the first series of workshops, the researchers will carry out training with a single series of mock workshops with a small number of Māori and Pacific staff and students as test participants to trial the structured scripts and activities for flow, cultural appropriateness, and timing.

Each workshop will follow a defined structure and process. In alignment with *kaupapa Māori*, a *karakia* (prayer) will be used to open and close the workshops. *Kai* (food) and *koha* (a small gift) for participants will be included. *Kai* is a sign of hospitality, an example of showing *manaakitanga* (kindness) and willingness to create an inviting environment. *Koha* is a sign of reciprocity. The participants will be sharing their knowledge and perspectives; therefore, we must acknowledge their valuable contribution and the time they have taken to take part in our research project.

The aim is to keep each workshop to less than 3 hours and to allow for appropriate *whakawhanaungatanga* (introductions and group activities) and breaks, as well as covering the necessary content.

Previous co-design research combining Indigenous and Pacific knowledge and systems thinking will help shape our processes. The goal of workshop 1 will be to orientate the groups and develop a shared understanding of the key issues through a series of constructed activities through the scripts, designed and edited from Scriptapedia. The first will be “hopes and fears” [32], which will assist with the *whakawhanaungatanga* (getting to know each other) process. This will be followed by another script called “reference behaviors over time” to help participants start thinking dynamically by looking at the key indicators (reference behaviors) identified from the CMIs. This is followed by a third script, “connection circles,” using software called STICKE (systems thinking in community knowledge exchange), which has been developed in collaboration with Victorian communities through research undertaken by Deakin University. The process helps participants start thinking about the components of an issue and their relationships, or cause and effect (eg, increasing stories and photos through the BBM Facebook page and media increases the sense of engagement with BBM among participants).

In workshop 2, participants will start to construct a visual map of the BBM organization through a series of “feedback” loops, also known as causal loop diagrams (CLDs), which demonstrate sustainable cause and effect loops; a classic example is the chicken and egg loop. The CLDs are also developed in STICKE and are a continuation of the connection circles activity.

In the third workshop, the participants will review and explore further these CLDs to ensure they fully represent their perspectives and visual maps, make any further additions or adjustments, and identify future actions using the identified system levers. Action ideas would be assessed based on practicality, whether they are achievable, and the size of the effect.

Quality criteria for phase 2 are the use of *kaupapa Māori* principles to ensure that participants feel culturally safe and are treated with respect; the researcher training sessions of mock workshops; the use of standardized scripts; support in the development of CLDs; and a final reflective session to make additions and adjustments and make sure their action ideas are practical, feasible, and achievable. Additionally, *kaupapa Māori* allows for flexibility; while each workshop has a defined structure and process, researchers are willing to adjust those processes if they are not helpful for the participants or make anyone feel uncomfortable. Finally, the lead facilitators of these workshops will remove any jargon or intimidating terms that may discourage participants from engaging in the workshops. It is important to note that it is the researcher’s responsibility to ensure that the way the content is communicated is just as important as the content itself. The lead Māori and Pacific researchers will be constantly checking in with participants to encourage feedback, increase engagement, and establish trust with them.

Phase 3: The System Dynamics Logic Model and Action Plan

In phase 3, the outputs of the CMI will inform the development of 2 system dynamic logic models, one from BBM staff and one from BBM members. In alignment with our methodologies for this study, creating a dynamic model allows for more community input and engagement. Māori and Pacific communities are unique population groups that require a system that is tailored to their sociocultural values and beliefs.

By focusing on creating systems models with feedback loops rather than linear models, this study aims to incorporate and highlight the actions and factors that specifically relate to Māori and Pacific communities. This is done by the research team and members of the BBM team using the visual systems maps created during the GMB workshops to build a system model of change that benefits the BBM community. BBM senior staff members, including DL, and the research team will collectively develop an action plan based on the learnings from these models.

Quality criteria for phase 3 include the final 2 system dynamics logic models, one from BBM staff and one from BBM members, informed by the robust processes conducted in phases 1 and 2. Adherence to Māori and Pacific cultural values and principles means that the models and subsequent action plans incorporate and highlight the actions and factors that specifically relate to these communities.

Ethics Approval

Ethical approval for the evaluation study was given by the Health and Disability Ethics Committee New Zealand for 3 years on June 30, 2021 (21/STH/122), with an amendment for

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the cognitive mapping component of the project approved on November 9, 2022.

Participants in the CMI and GMB will be provided with participant information sheets and will give informed consent. All participants will be anonymous. Participants will receive NZD $50 (US $31) supermarket vouchers per session as compensation for their time.

Results

The 2 logic models will inform BBM's future developments as a sustainable organization. The end result of this study will be an action plan based on the logic model and system levers for how BBM can optimize its effectiveness, sustainability, and quality improvement.

BBM was developed by DL, who is a charismatic leader and continues to actively drive the organization in new directions to meet arising community needs. The action plan will include consideration of how and whether BBM can continue to grow and expand independently of DL's charismatic leadership.

Discussion

Summary of Findings

This study aims to build culturally centered system dynamics logic models to serve as the agreed theories of change for BBM and provide a basis for its ongoing effectiveness, sustainability, and continuous quality improvements. To achieve this, we will adopt a novel and innovative approach, using systems science along with collaborative co-design embedded within Pacific and Māori world views and weaving together a number of frameworks and methodologies to create a system dynamics logic model for BBM. These are highly compatible approaches with strong potential synergies.

The final result will be an action plan for BBM to hone the underlying system features identified in the 2 logic models.

A logic model that takes the dynamics of the system into account with feedback loops that improve effectiveness, sustainability, and quality can be explicitly considered in action plans for the ongoing success of BBM. The use of STICKE makes the process of creating the systems maps more accessible and available in real time.

The culturally centered design is to ensure relevance and connection to the cultures and world views of the participants, the BBM team, and their communities, and the innovations and learnings that could come from joining up these approaches will guide the further development of BBM.

How These Findings May Relate to the Literature

Having developed the models and the plan, we will determine how this compares with other published studies, and how it fits into the existing literature with respect to its interpretations and implications.

Limitations

The maps developed in the CMI phase will reflect the perceptions of the organizational structure of the key people selected to interview. There is a subjective component to generating these data. While 2 to 3 people selected for each of the 3 categories (staff, members, and funders) will be those seen as key personnel, it is possible that if a larger sample was used, there might be more variability in the information used to inform the GMB. However, we are not aiming to develop definitive themes from the CMIs. Instead, CLDs from these will provide a guiding example for the GMB participants who will go on to identify other major causal drivers to be considered thoroughly by the wider group.

Similarly, an increased number of participants in the GMI workshops might result in more divergency in the created maps.

Conclusions

This study will adopt a novel and innovative approach to co-designing culturally centered system dynamics logic models for BBM by using systems science methods embedded within Pacific and Māori world views and weaving together a number of frameworks and methodologies. These will form the theories of change to enhance BBM's effectiveness, sustainability, and continuous improvement.

Programs aiming to change people's health behaviors and reduce health inequities can be complex and fail to deliver because they do not overcome the barriers to the system and individual change that they encounter. This includes the application of Western principles to ethnic minorities. Beyond the goal of informing BBM on how it may introduce quality improvements and address identified system issues, we hope that our study will provide a framework for other organizations and networks to assess system factors that might be beneficial to address in a culturally centered and safe manner.

Acknowledgments

FS and TH drafted the preliminary protocol. FGS drafted the initial paper for publication. FS, FGS, WB, BS, DL, TH, and FL contributed to the design of the study. TH provided *kaupapa Māori* oversight. All authors contributed to the writing of the paper, and all have read and approved the final manuscript. This study is funded by the Health Research Council of New Zealand, (21-280) and University of Auckland (3722251). The funding body plays no role in the design of the study, the collection, analysis, and interpretation of data, or the writing of the manuscript.

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Data Availability

Data sharing is not applicable to this article as no data sets per se were generated during this study. The data generated during the study consisted of field notes and visual maps hand-drawn and then computerized from the interviews and group map-building workshops.

Conflicts of Interest

DL is the founder and FL is the chief operating officer of Brown Buttabean Motivation (BBM), and they are integral members of the research team. WB's wife is a Pilates instructor at BBM. No other authors have any conflicts of interest to declare.

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Abbreviations

BBM: Brown Buttabean Motivation
CLD: closed loop diagram
CMI: cognitive mapping interview
GMB: group model building
STICKE: systems thinking in community knowledge exchange

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Protocol

Recovery of Breakthrough Asthma Attacks Treated With Oral Steroids While on Monoclonal Antibody Therapy: Protocol for a Prospective Observational Study (BOOST)

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Abstract

Background: Asthma attacks are a common and important problem. Someone experiences an asthma attack in the United Kingdom every 10 seconds. Asthma attacks cause coughing, wheezing, breathlessness, and chest tightness and are highly stressful for patients. They result in reduced quality of life, with days lost from work or school. Asthma attacks are treated with oral corticosteroids (OCSs), but these have many short- and long-term side effects. Asthma monoclonal antibodies (mAbs) have revolutionized the treatment of severe asthma by reducing asthma attacks and OCS burden by over 50%, but some people still experience attacks while on mAbs. The MEX study showed that residual asthma attacks are broadly eosinophilic (high fractional exhaled nitric oxide [FeNO]) or noneosinophilic (low FeNO), but it did not measure response to OCS treatment. There is an evidence gap in understanding the clinical and inflammatory responses that occur when using OCSs to treat residual asthma attacks in patients taking asthma mAbs.

Objective: The primary objective is to compare the clinical recovery between high-FeNO and low-FeNO attacks after acute treatment with oral prednisolone among people established on long-term asthma mAb treatment. The exploratory objective is to compare the inflammatory response to acute treatment with oral prednisolone between high-FeNO and low-FeNO attacks.

Methods: BOOST (Breakthrough Asthma Attacks Treated With Oral Steroids) is a single-center, prospective observational study of 60 adults established on long-term asthma mAb treatment who receive acute treatment with oral prednisolone (usual care) for an asthma attack. The primary outcome will be the proportion of treatment failure (the need to start oral prednisolone or antibiotics or an unscheduled health care visit for asthma, following an attack) at day 28. The secondary outcomes will be the change in forced expiratory volume in 1 second and the change in visual analogue scale symptom score between the stable state, attack, day 7, and day 28 visits. The exploratory outcomes include the changes in sputum, nasal, and blood inflammometry between the stable state, attack, day 7, and day 28 visits.

Results: The last asthma attack visit is anticipated to occur in December 2023. Data analysis and publication will take place in 2024.

Conclusions: We will test the hypothesis that there is a difference in the rate of recovery of clinical and inflammatory measures between high-FeNO and low-FeNO asthma attacks that occur in patients on mAb therapy. The study data will help power a future randomized placebo-controlled trial of prednisolone treatment for nonsevere attacks in patients treated with asthma mAbs and will provide important information on whether corticosteroid treatment should be FeNO-directed.

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KEYWORDS

asthma; monoclonal antibodies; steroids; monoclonal antibody; oral steroid; asthma attack; quality of life; adult; inflammatory response; prednisolone treatment; treatment

Introduction

Asthma is a common and important problem. Clinically, asthma is characterized by variable symptoms of breathlessness, coughing, chest tightness, and wheezing. Asthma attacks are acute deteriorations in asthma symptoms and affect a person's physical activity, work, personal life, and mental health [1]. The presence of raised type 2 airway inflammation increases the risk of asthma attacks and lung function decline. Blood eosinophils and fractional exhaled nitric oxide (FeNO) have emerged as key biomarkers of type 2 inflammation [2].

The cornerstone of asthma treatment is inhaled corticosteroids (ICSs), which reduce type 2 inflammation. However, 10% of adults experience severe asthma with frequent asthma attacks, despite ICS treatment [3]. These attacks are treated with 5- to 7-day bursts of high-dose oral corticosteroids (OCSs), based on trial data showing a 50% lower risk of relapse at 21 days in comparison to a placebo [4]. However, all of the randomized placebo-controlled trials of OCSs for asthma attacks were conducted in an era before the widespread use of ICSs, implying that the efficacy of OCSs in mild to moderate attacks may be overstated. Moreover, OCSs have a significant acute side effect burden, and their cumulative toxicity is serious [5].

Asthma monoclonal antibody (mAb) therapies have revolutionized the treatment of severe asthma. They target specific parts of the type 2 inflammatory pathway and have fewer side effects than OCSs. The key classes of mAbs are anti-immunoglobulin E (omalizumab), anti–interleukin (IL) 5 and anti-IL5R (mepolizumab, reslizumab, and benralizumab), anti-IL4Rα (dupilumab), and anti–thymic stromal lymphopoietin (tezepelumab) [6]. The randomized trials of these drugs versus a placebo demonstrated an over 50% reduction in asthma attacks requiring OCSs [7]. On average, people continue to experience 1 asthma attack per year. The current practice is for these asthma attacks to be treated with OCSs.

Patients effectively treated with asthma biologics generally exhibit reduced type 2 inflammation. Consequently, they are ideal patients for testing the hypothesis that OCSs are only useful in treating attacks with evidence of type 2 inflammation. This has already been explored in patients with chronic obstructive pulmonary disease (COPD) but not asthma. Two randomized controlled trials undertaken in patients with COPD showed that among the patients with low blood eosinophil levels at the time of a COPD attack, OCS treatment did not improve outcomes, when compared with a placebo, in terms of treatment failure [8,9].

The MEX study was the first prospective, multicenter, observational study to characterize asthma attacks in patients on mepolizumab [10]. It found that attacks were often clinically mild and heterogeneous in nature. Attacks were broadly defined as eosinophilic (high FeNO) or noneosinophilic (low FeNO). BenRex is a similar ongoing study characterizing attacks in patients treated with benralizumab [11]. Neither study was designed to examine recovery from an attack after treatment with OCSs.

The findings from the MEX study point to a possible biomarker-directed option for treating asthma attacks based on FeNO. Attacks among people on anti-IL5 treatment with raised FeNO may imply ongoing IL-4, IL-13, or alarmin activity, which may be OCS-responsive [12]. The noneosinophilic attacks were frequently positive for viruses or bacteria and had a higher C-reactive protein level, indicating that they were probably pathogen-driven. This process would not be expected to respond to OCSs.

There is a large evidence gap in understanding the clinical and inflammatory responses that occur when using OCSs to treat asthma attacks in patients treated with asthma mAbs. Our prospective observational study will examine these responses to help inform whether a future randomized placebo-controlled trial of prednisolone treatment for nonsevere attacks in patients treated with asthma mAbs should be FeNO-directed.

Methods

Hypothesis

In people established on anti-IL5, anti-IL5Rα, and anti-IL4Rα mAb treatment for asthma, high-FeNO asthma attacks will show more clinical and inflammatory responses to acute oral prednisolone treatment than low-FeNO asthma attacks.

Objectives

The primary objective is to compare the clinical recovery between high-FeNO and low-FeNO attacks after acute treatment with oral prednisolone among people established on anti-IL5, anti-IL5Rα, and anti-IL4Rα treatment for asthma. The exploratory objective is to compare the inflammatory response to acute treatment with oral prednisolone between high-FeNO and low-FeNO attacks among people established on anti-IL5, anti-IL5Rα, and anti-IL4Rα treatment for asthma.

Study Design

BOOST (Breakthrough Asthma Attacks Treated With Oral Steroids) is a single-center, prospective observational study of 60 adults established on long-term asthma mAb treatment who receive acute treatment with oral prednisolone (usual care) for an asthma attack.

Participant Recruitment

All participants will be recruited from the Oxford Special Airways Clinic, which is based at the Oxford Centre for Respiratory Medicine at the John Radcliffe Hospital. This service provides specialist assessments for patients with complex airway diseases and has a large cohort of patients on asthma

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mAb treatment under regular review. The service also provides a rapid assessment clinic for the clinical review of patients who experience an asthma attack while on mAb treatment.

There are 2 routes for a participant to enroll into the study. Participants can be enrolled into a study pool at stable state. If they exacerbate, they can contact the department to initiate an attack visit to the rapid assessment clinic. Alternatively, participants may directly enter the study at the time of an attack if they have contacted the rapid assessment clinic for review but are not in the study pool. These participants will have a stable state visit at least 2 months after the attack date.

If a participant in the study pool has not experienced an asthma attack when the study's attack recruitment target has been met, they will be invited for an optional additional visit at stable state to form a stable control group.

Ethical Considerations

BOOST is a substudy of the Oxford Airways Study (Integrated Research Application System Project number: 234581; Oxfordshire Research Ethics Committee B reference number: 18/SC/0361). The Oxford Airways Study is an observational study that will measure clinical measures, biomarkers, inflammation, and mediators among participants with airway diseases at stable state and during an acute attack.

Participants will be consented to the Oxford Airways Study at their first study visit.

Inclusion Criteria

The inclusion criteria are as follows: (1) people treated with an anti-IL5, anti-IL5Rα, and anti-IL4Rα mAb for asthma (mepolizumab, benralizumab, reslizumab, or dupilumab) under the Oxford Special Airways Clinic; (2) patients established on the same mAb treatment for at least 2 months; (3) male or female patients aged 18 years or older; and (4) patients who experience at least 1 asthma attack requiring oral prednisolone treatment since starting mAb treatment.

Exclusion Criteria

The general exclusion criteria are as follows: (1) maintenance OCS treatment for asthma or any other condition, (2) people who are unwilling or unable to attend follow-up visits, (3) people who are pregnant or are planning pregnancy at the time of study entry, and (4) people on long-term systemic immunosuppressive treatment for a condition other than asthma.

At asthma attack visit, the following exclusion criteria will be assessed: (1) pneumonia on a chest radiograph at the time of an attack, (2) any treatment with OCSs in the preceding 1 month, and (3) the trial physician's opinion that a person needs hospitalization at the time of assessment.

Intervention at Asthma Attack Visit

A consultation will be arranged at the rapid assessment clinic if a participant feels that their asthma symptoms have deteriorated and they need treatment. The participant will be assessed by the study physician via medical history taking, clinical examination, and chest radiograph examination. This is in line with our usual practice. If a diagnosis of an asthma attack is made and the participant is eligible, they will start the study-specific measurements (Table 1).

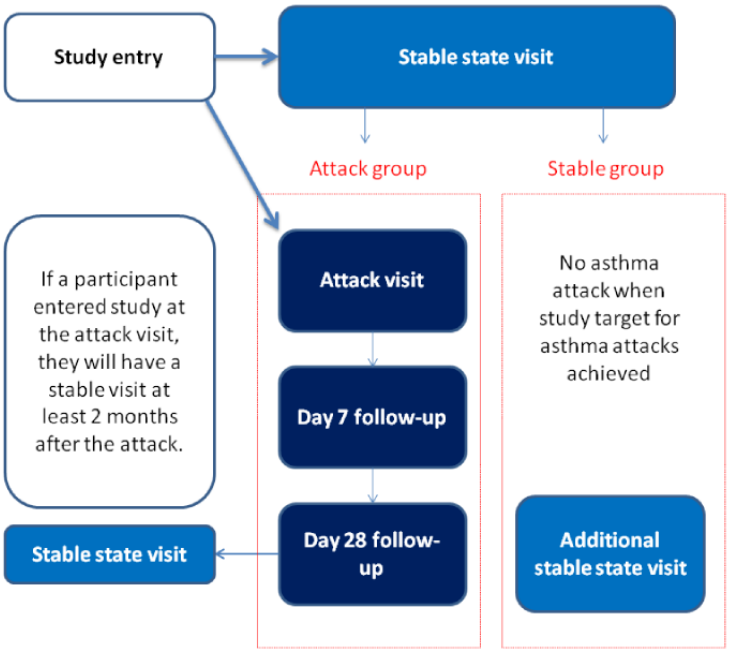
Each participant will be treated with 40 mg of oral prednisolone once per day for 7 days as part of usual care for an asthma attack, as per British Thoracic Society guidelines. Antibiotic treatment will not be routinely prescribed at the asthma attack visit. If a participant is already on antibiotic therapy prior to the attack visit (eg, prescribed in general practice), this will be continued until the prescribed course is complete, as per usual care (Figure 1).

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Table 1. Study measurements.

Measurements	Stable state visit	Asthma attack visit	Day 7 follow-up	Day 28 follow-up	Additional stable state visit
Informed consent	✓	✓			
Eligibility check	✓	✓			
Demographics	✓	✓			
Medical and asthma biologic history	✓	✓			
Medication check	✓	✓	✓	✓	✓
Physical examination	✓	✓	✓	✓	✓
Vital signs	✓	✓	✓	✓	✓
Spirometry	✓	✓	✓	✓	✓
Fractional exhaled nitric oxide	✓	✓	✓	✓	✓
Blood sampling	✓	✓	✓	✓	✓
Induced sputum sampling	✓	✓	✓	✓	✓
Nasosorption sampling	✓	✓	✓	✓	✓
Visual analogue scale symptoms	✓	✓	✓	✓	✓
Asthma Control Questionnaire and Asthma Control Test	✓	✓	✓	✓	✓
Medical notes review	✓	✓	✓	✓	✓
Chest x-ray		✓			
Nasal viral polymerase chain reaction test		✓			
Assessment for treatment failure			✓	✓	
Adverse event assessments			✓	✓	

Figure 1. Summary of planned study visits.



Unplanned Study Visits

If a participant feels that their asthma symptoms have deteriorated or that they need more treatment, between the attack visit and day 28 visit, they will be encouraged to contact the study team. As per usual care, the participant will be assessed by the study team, by the participant's general practitioner, or in an urgent care setting. If the participant is assessed by the study team, routine clinical measurements will be taken at the discretion of the study physician, but no research samples will be taken. If a participant is assessed by their general practitioner or in an urgent care setting, the study team will ask the

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participant what medical treatment they received and whether they needed a hospital visit. Where possible, this information will be corroborated with health records.

Outcomes

The primary outcome is the comparison of the proportion of treatment failure at day 28 between high-FeNO and low-FeNO attacks.

The secondary outcomes are as follows: (1) comparison of the change in forced expiratory volume in 1 second (FEV_1) from stable state to day 0, day 7, and day 28 between high-FeNO and low-FeNO attacks; (2) comparison of the change in visual analogue scale (VAS) symptom score from stable state to day 0, as well as daily VAS symptom score changes from day 0 to day 28, between high-FeNO and low-FeNO attacks; and (3) comparison of the change in Asthma Control Questionnaire and Asthma Control Test symptom scores from stable state to day 0, day 7, and day 28 between high-FeNO and low-FeNO attacks.

The exploratory outcomes are as follows: (1) comparison of the changes in sputum, blood, and nasal lining fluid inflammometry; (2) comparison of the changes in sputum and blood transcriptomics; (3) comparison of microbiology statuses at asthma attack; (4) comparison of neutrophil elastase detection findings at asthma attack; (5) comparison of genomic data; (6) determination of the predictors of clinical and inflammatory responses to prednisolone treatment; and (7) inhaler adherence data, which will be obtained from prescription refill records at asthma attack visit.

Sample Size Requirements

The clinical and inflammatory effects of prednisolone for asthma attacks in patients treated with asthma mAbs are unknown. Therefore, an important aim of this observational study is to understand the proportions and SDs of key measurements related to these effects. These will help determine if a future randomized placebo-controlled study of prednisolone treatment for attacks in people treated with asthma mAb therapy should be FeNO-directed.

Because there are no published data on treatment response to prednisolone for asthma attacks in this population, we based our hypothesis and sample size estimates on our clinical experiences with attacks that we assessed and treated locally over recent years. We estimated the proportion of treatment failure at 28 days to be 0.05 in the high-FeNO group and 0.35 in the low-FeNO group. Further, based on the MEX study, in which roughly half of the asthma attacks among patients on mAbs were high-FeNO attacks and the other half were low-FeNO attacks, we estimated an average treatment failure proportion of 0.2 for our sample. This proportion is consistent with published systematic review data on the treatment failure at 28 days after an asthma attack (ie, among patients not on mAb therapy) [13].

Using a 2-sided α of .05, a β of .8, an equal high-FeNO and low-FeNO group ratio, and a 10% dropout rate, the total sample size required to detect the estimated proportions of treatment failure described above was calculated to be 60 asthma attacks. Additionally, 60 asthma attacks are also adequate for detecting a clinically meaningful difference in the change in FEV_1 from day 0 to day 7 between the high-FeNO and low-FeNO groups (mean 0.4 vs mean 0, SD 0.5 L). Further, 60 attacks can be used detect a clinically meaningful difference in the change in VAS symptom score from day 0 to day 7 between the high-FeNO and low-FeNO groups (mean 15 vs mean 0, SD 17 mm).

Statistical Analysis Plan

Overview

Descriptive statistics will be used to describe variables. For continuous variables, the differences in the means and the corresponding 95% CIs will be reported between the high-FeNO and low-FeNO groups and for the overall sample. For categorical variables, chi-square tests will be used for comparing treatment groups if the variables are normally distributed. If a variable is not normally distributed, a nonparametric test will be used for the analysis.

Primary Analysis

In our study, treatment failure will be defined as a need to start oral prednisolone or antibiotics or an unscheduled health care visit for asthma.

The comparison of proportions of treatment failure at day 28 between the high-FeNO and low-FeNO groups will be conducted with a Fisher exact test. The comparison of the time to treatment failure between the high-FeNO and low-FeNO groups will be presented with a Kaplan-Meier analysis. Additionally, we will construct a Cox proportional-hazards model to compare the time to treatment failure between high-FeNO and low-FeNO groups based on the following two interactions: (1) specific mAb treatment and (2) the use of antibiotics within the 2 weeks preceding the attack visit (inclusive of the attack visit day). We will construct a forest plot to assess potential predictors of treatment failure among the high-FeNO and low-FeNO groups.

There is no consensus for a low-FeNO versus high-FeNO attack threshold regarding response to prednisolone. For the purposes of the primary statistical analysis, we prespecified 25 parts per billion (ppb) as the main threshold to define low-FeNO and high-FeNO attacks. This threshold is based on sputum eosinophil data from the MEX study [10].

Any missing treatment failure outcome data will be dealt with via nonresponder imputation.

Secondary Analysis

We will analyze treatment failure by using a threshold of 50 ppb to define low-FeNO and high-FeNO attacks. This is based on data showing that an FeNO level of ≥50 ppb (high FeNO) is associated with a high risk of future asthma attacks for any patient with asthma [14].

We will use linear mixed-effects models to compare continuous data from the three secondary outcomes, across different time points, between high-FeNO and low-FeNO attacks. The random effect will be the participants. The fixed effects will be (1) specific mAb treatment, (2) the use of antibiotics within the 2 weeks preceding the attack visit (inclusive of the attack visit day), (3) the number of asthma attacks in the 12 months prior

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to the attack visit, and (4) percent predicted FEV_1 at the attack visit.

Any missing secondary outcome data will be dealt with in the linear mixed-effects model by using the missing at random assumption.

The prediction of clinical responses to prednisolone will be performed via the generation of receiver operator characteristic curves and correlation coefficients, cluster analysis, and regression models.

Exploratory Analysis

We will run paired statistical tests and regression models to analyze the exploratory outcomes.

Results

Recruitment started in September 2022. The target number of asthma attacks is expected to be reached by December 2023. Data analysis and publication will take place in 2024. Results will be published in peer-reviewed journals.

Discussion

Our observational study aims to explore whether the presence of type 2 inflammation, as measured based on FeNO, predicts response to oral prednisolone for an asthma attack in an mAb-treated person. The study is novel because this response has not yet been assessed in a structured way before and after prednisolone treatment. We will measure response by using treatment failure, as this is a clinically important outcome for both people with asthma and health care professionals. It represents disruption to a person's life, as well as health care utilization. Additionally, it is equivalent to the relapse outcome measured in the randomized placebo-controlled trials of OCSs in the 1980s and 1990s [4]. Other important outcomes will include symptom recovery, which is important to patients, and lung function, which captures a physiological change. Exploratory outcomes will include nasal, sputum, and blood inflammatory markers, which will be measured by using immunoassays and transcriptomics to assess whether high-FeNO attacks display evidence of ongoing pathways of inflammation not targeted by the mAb treatment.

There are several goals in our observational study. First, we expect to see a better clinical response in high-FeNO asthma attacks than in low-FeNO asthma attacks among people on mAb therapy. This is based on evidence from COPD exacerbations, wherein biomarker evidence of inflammation predicts response to OCSs—an anti-inflammatory treatment [8]. These data will help inform whether a future randomized controlled trial of prednisolone treatment for nonsevere attacks in patients treated with asthma mAbs should be FeNO-directed. This future trial is important because OCSs have significant side effects; therefore, a precision medicine approach is preferable to the existing one-size-fits-all approach. Second, we will start to explore the question about whether high-FeNO attacks have different underlying pathophysiological processes that are still steroid-responsive. This will provide novel data to the field, and such data are important, as they will help with the development of biomarkers that can predict whether certain people will respond better to a particular mAb therapy.

The main limitation of the study is that it is observational in nature, with no randomization, blinding, or placebo control. It is therefore subject to selection, reporting, and experimenter biases. We have tried to minimize these with our inclusion and exclusion criteria and by controlling for confounders in the statistical analyses. Ultimately, our study is hypothesis-generating research and is pilot work on which a larger, definitive trial will be based.

With our study, we hope to continue precision medicine research in asthma and begin to challenge the dogma that OCSs are effective in all asthma attacks.

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The views expressed are those of the authors and not those of the National Health Service or NIHR.

Conflicts of Interest

SR received research funding from the National Institute for Health Research and the Australian Government Research Training Program. SR's institution (University of Oxford) received unrestricted grant funding from AstraZeneca which was used to fund a different research project. SR received personal speaker fees and conference travel support from AstraZeneca. IH received conference travel support from GSK. In the last 5 years IDP has received speaker's honoraria for speaking at sponsored meetings from Astra Zeneca, Boehringer Inglehiem, Aerocrine, Almirall, Novartis, Teva, Chiesi, Sanofi/Regeneron, Menarini and GSK and payments for organizing educational events from AZ, GSK, Sanofi/Regeneron and Teva. He has received honoraria for attending advisory panels with Genentech, Sanofi/Regeneron, Astra Zeneca, Boehringer Ingelheim, GSK, Novartis, Teva, Merck, Circassia, Chiesi and Knopp and payments to support FDA approval meetings from GSK. IDP has received sponsorship to attend international scientific meetings from Boehringer Ingelheim, GSK, Astra Zeneca, Teva and Chiesi. He has received a grant from Chiesi to support a phase 2 clinical trial in Oxford. MB reports grants from AstraZeneca and personal fees from AstraZeneca, Chiesi, GSK, Albus Health, and ProAxsis.

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Abbreviations

BOOST: Breakthrough Asthma Attacks Treated With Oral Steroids
COPD: chronic obstructive pulmonary disease
FeNO: fractional exhaled nitric oxide
FEV_1: forced expiratory volume in 1 second
ICS: inhaled corticosteroid
IL: interleukin
mAb: monoclonal antibody
OCS: oral corticosteroid
ppb: parts per billion
VAS: visual analogue scale

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Protocol

Design and Implementation of a Digitally Enabled Care Pathway to Improve Management of Depression in a Large Health Care System: Protocol for the Implementation of a Patient Care Platform

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Abstract

Background: Major depressive disorder (MDD) is a serious public health concern worldwide. A treatment approach that incorporates measurement-based care (MBC) and shared decision-making between patients with MDD and their providers may foster patient engagement and improve clinical outcomes. While digital tools such as mobile apps show promise for expanding health interventions, these apps are rarely integrated into clinical practice.

Objective: The primary objective of this ongoing study is to determine whether implementation of a digital tool—the *Pathway Platform*—in primary care improves adherence to MBC practices; here, we present the study methods.

Methods: This large-scale, real-world implementation study is based on a pilot study of an earlier iteration of a mobile app (the *Pathway app*) that confirmed the feasibility of using the app in patients with MDD and showed a positive trend in patient engagement in the app arm. In addition, a user-centered design approach that included qualitative assessments from patients and providers was used to improve understanding of the patient journey and care team workflows. User feedback highlighted the need for enhanced features, education modules, and real-time data sharing via integration with the electronic health record. The current iteration of the *Platform* includes the newest version of the *Pathway app*, education modules for both patients and providers, and real-time patient-level data sharing with the electronic health record. The study takes place in primary care sites within the Advocate Aurora Health system in Illinois and includes adult patients with MDD who were recently prescribed monotherapy antidepressant medication (defined as a new start, medication switch, or dose change in the past 3 months). Clinical performance and selected patient outcomes will be compared before and after the implementation of the *Platform*.

Results: Patient recruitment was completed in July 2022, with initial results expected in mid-2023.

Conclusions: This study will provide useful insights into real-world integration of a digital platform within a large health system. The methods presented here highlight the unique user-centric development of the *Pathway Platform*, which has resulted in an enhanced digital tool with the potential to foster MBC and shared decision-making, improve patient-provider communication, and ultimately lead to optimized treatment outcomes for patients with MDD.

Trial Registration: ClinicalTrials.gov NCT04891224; https://clinicaltrials.gov/ct2/show/NCT04891224

International Registered Report Identifier (IRRID): DERR1-10.2196/43788

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(JMIR Res Protoc 2023;12:e43788) doi:10.2196/43788

KEYWORDS

mental health; depression; depressive; major depressive disorder; depression management; primary care; patient engagement; measurement-based care; shared decision-making; user-centered design; mobile app; digital platform; mobile phone; mobile health; adherence

Introduction

Background

Major depressive disorder (MDD) is a common recurring mental health disorder and a serious public health concern worldwide [1,2]. In 2019, an estimated 19.4 million adults in the United States had at least 1 major depressive episode, which represents 7.8% of the adult US population [3]. The economic burden of MDD for 2020 in the United States was estimated at US $326.2 billion, with approximately 73.2% of the cost attributed to impairment in role function [4,5]. Many factors complicate the treatment of MDD, including multiple antidepressant therapy options, the importance of adherence and adequate duration of therapy to optimize response, and the variation commonly seen in time to response and medication tolerability among patients. American Psychiatric Association MDD treatment guidelines recommend considering many factors during initial treatment selection, such as patient symptoms and comorbidities, medication side effect profiles, and patient preference [6]. These guidelines suggest close monitoring of therapeutic benefit and tolerability during the first 4-6 weeks and then throughout treatment, incorporating structured measures of symptom severity, side effects, treatment adherence, and functional status to help assess response to treatment [6,7]. Systematic assessments and a strong therapeutic alliance between provider and patient remain key for tailoring a treatment plan to match the unique needs of each patient, highlighting the importance of measurement-based care (MBC) and shared decision-making (SDM).

Measurement-Based Care and Shared Decision-Making

MBC includes treatment adjustment evaluation using quantitative measures of symptoms, level of functioning, and quality of life while treating patients with MDD [7]. American Psychiatric Association clinical guidelines recommend MBC during initial screening as well as for monitoring depression throughout treatment [6]. By quantifying clinical outcomes, MBC provides guidance for timely treatment reassessment and modifications tailored to the individual needs of the patient and has been shown to improve outcomes and quality of care [8]. This systematic approach to treatment may have positive effects on the patient-provider relationship and enhance SDM. MDD often requires long-term antidepressant treatment; however, this is challenging for many patients because of barriers such as short consultation times with their care teams and limited involvement in the treatment decision-making process. An increased focus on MDD-relevant patient education, including clarification of the benefits of a specific treatment plan and alignment of such a plan with the patient's values, can help overcome treatment barriers. Primary care providers can incorporate MBC and play a major role by involving patients with MDD in the SDM process. In addition, SDM can foster patient-provider engagement and increase patient satisfaction [9].

Digital Tools in MDD

Overview

Many mobile apps have recently been developed and are available for the management of depression. Patients with MDD and their treatment providers may benefit from the use of these apps to assist in disease management. However, the majority of these apps have been assessed only in the research setting and have not been integrated into the clinical workflow. Most apps do not undergo a rigorous evaluation of interventions and instead rely on evidence-based theory for design; this may result in limited evidence of efficacy, leading to potential patient misinformation. Attrition is another major challenge for many depression management apps because of poor personalization to improve user-based engagement [10]. In addition, many mobile apps are only patient-facing and have not incorporated a care team interface, and the use of tracked content including symptoms and engagement with interventions in a single app is rare [10]. Creation of user-friendly mobile apps that incorporate user-centered design with input from patients with MDD and health care providers (HCPs) [11] can improve the development process, iteration speed, and implementation success, with the potential to improve patient outcomes in MDD [12-14].

Pathway App and Pathway Platform for Patients With MDD

Takeda Pharmaceuticals U.S.A., Inc., Lundbeck LLC, and Advocate Aurora Health (AAH) have partnered to cocreate a digitally enabled care experience with users (patients and care teams) and software developers, as well as health-tech product development specialists (Ctrl Group / Fora Health) to improve patient-provider engagement in the management and treatment of MDD. A digital mobile patient interface—the *Pathway app*—was designed with a conversational texting interface to allow patients to record daily mood symptoms, function, medication adherence, and side effects [11]. The *Pathway app* captures changes in a patient's response to antidepressant pharmacotherapy and includes standard outcome measures, such as the 9-item Patient Health Questionnaire (PHQ-9) for depression [11]. Patient interaction with the *Pathway app* allows for increased patient awareness of symptoms and overall functioning [11]. Through the *Pathway app*, up-to-date information can be shared with the patient's HCP to guide clinical discussions and enhance SDM between patients and their clinicians at routine visits as well as between visits, with the aim of optimizing individualized treatment plans and improving overall outcomes [11].

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Testing of Pathway App in a Pilot Feasibility Study

The *Pathway app* was tested within a real-world pilot feasibility study (ClinicalTrials.gov NCT03242213) in patients with MDD who had recently started or undergone a switch to antidepressant monotherapy [15]. Patients were randomized 1:1 to the control arm (standard of care; n=20) or the app arm (standard of care plus the *Pathway app*; n=20) [15]. The first iteration of the *Pathway app* included patient-reported outcomes (PROs) related to depression, well-being, cognitive symptom tracking, medication adherence, and side effects. The *Pathway app* enabled patients to track their symptoms, monitor their treatment progress, and manually share the data collected with their care team. Results from the pilot study confirmed the effectiveness and feasibility of using the *Pathway app* in patients with MDD and showed a trend toward improved patient engagement in the app arm, albeit in a small sample size [15].

Pathway App Follow-up Interviews (Round 1) With Patients and HCPs

After the pilot study, 2 rounds of semistructured qualitative research interviews were conducted by a study team with expertise in qualitative research and user-centered design methods; results were determined using thematic analysis based on a structural coding framework. Round 1 interviews were performed to obtain feedback from patients and HCPs to understand their experience and perceptions of current and new *Pathway app* features to help ensure creation of a more user-centered design [15]. The user-centric approach created an opportunity for continued reassessment based on user feedback, faster iterations, optimized system performance, and sustainability. It also helped enhance the usability of the system, with the ultimate goal of improving treatment outcomes by supporting an expanded understanding of MDD treatment, assisting care team workflows, and providing people living with depression additional support throughout their treatment journey [11]. New features were included in the *Pathway app* that were not part of the pilot feasibility study, such as HCP visit preparation, patient education, and goal setting.

Patients reported that the ability to prepare for HCP visits using the *Pathway app* helped reduce their anxiety, improved the ease of communication with their HCPs, and enhanced the efficiency and effectiveness of appointments. Patients also found that the goal-setting feature of the *Pathway app* helped them focus on their goals and find a constructive purpose. Among the feedback from HCPs on the patient education feature of the *Pathway app*, many commented that it reduced their burden and was visually appealing and engaging.

Development of the Pathway Platform

Data from the round 1 qualitative interviews gathered from the *Pathway app* pilot feasibility study pointed to the need for enhanced rapid communication of real-time data shared with the care team, integration of the app into the MDD care pathway within the electronic health record (EHR), and education of the care team about usage of these data [11,13]. Building on these results, the *Pathway Platform* was created, which includes a newer iteration of the *Pathway app*, real-time integration of patient data with the Epic EHR (Epic Systems Corporation), as well as an app-based education program for patients and a web-based educational training program for the care team (Figure 1).

Figure 1. Design of the Pathway Platform. EHR: electronic health record.



Pathway Platform Follow-up Interviews (Round 2) With HCPs

Round 2 of qualitative research interviews was conducted with HCPs to understand workflow, usability, and clinical use of the *Pathway Platform*. An ongoing partnership with care teams provided an opportunity for continuous reassessment of the *Pathway Platform* based on user feedback. Key insights included the importance of clinical visit preparation and data visualization for SDM, collaborative goal setting and tracking for patient engagement, and optimization of the educational support tools for both patients and care teams [15]. This feedback was used to add value to the *Pathway Platform* for all users and optimize features prior to the clinical integration study presented here.

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Rationale and Aim of the Study

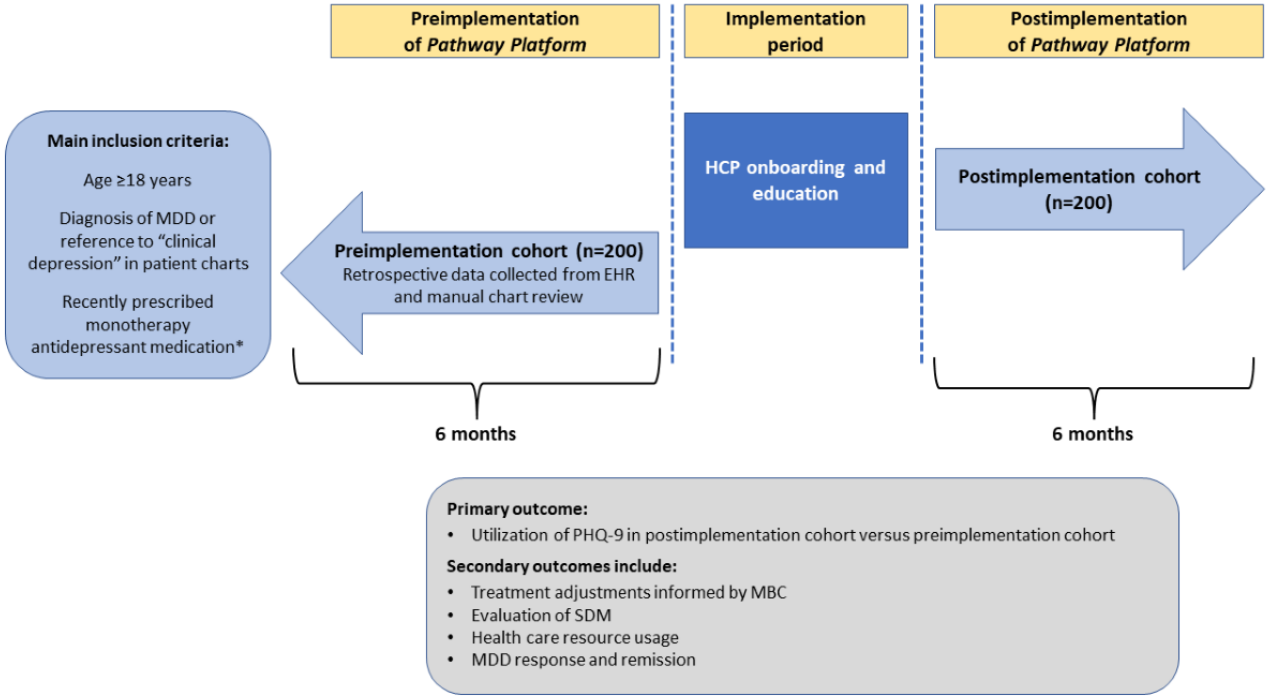
In this ongoing, large-scale, real-world implementation study, it is our aim to test the scaling and integration of the digitally enabled *Pathway Platform* along with educational interventions at multiple primary care sites within the AAH system [11] and assess its impact on MBC and other evidence-based processes (ClinicalTrials.gov NCT04891224). The primary objective of this study is to determine whether implementing the *Pathway Platform* in the primary care setting improves adherence to MBC through PHQ-9 usage. Secondary objectives are to determine improvement in the additional clinical process measures as well as MDD remission and response outcomes in patients using the *Pathway Platform*.

Methods

Study Design

This real-world interventional study uses a pre- and poststudy design to assess the impact of implementing the *Pathway Platform* in the primary care setting (Figure 2) [11]. Regarding implementation of the *Pathway Platform*, the study design is divided into 3 periods: preimplementation, implementation, and postimplementation.

Figure 2. Schematic representation of the real-world implementation study. EHR: electronic health record; HCP: health care provider; MBC: measurement-based care; MDD: major depressive disorder; PHQ-9: 9-item Patient Health Questionnaire; SDM: shared decision-making. *New start, medication switch, or dose change in the past 3 months.



Preimplementation

The preimplementation cohort consists of patients who meet the inclusion criteria for enrollment in the study and have visited one of the participating clinics at least 6 months prior to implementation of the *Pathway Platform*. Study outcomes will be assessed using retrospective data collection, including chart reviews and electronic data pulls 6 months prior to implementation of the *Pathway Platform*.

Implementation

The implementation period will entail educating care team members before the enrollment visit and onboarding. To confirm eligibility, patient history will be evaluated for 3 months prior to enrollment. During the implementation period, the care team members involved in MDD management will receive education on evidence-based clinical practices for depression care, such as MBC and SDM. Training will be provided for patient onboarding to the *Pathway Platform* and usage of the EHR to view data collected in the platform.

Postimplementation

The postimplementation cohort consists of up to 200 patients from the same participating clinics who meet the eligibility criteria and provide written informed consent to download the *Pathway app*. In this cohort, data on patient outcomes will be collected prospectively over 6 months with the option to continue using the app at the 6-month mark until a common study end date (data collected beyond 6 months will be used for exploratory analysis). At the end of 6 months, retrospective EHR and manual chart reviews will be conducted, and performance related to MBC and SDM will be assessed. Clinical performance and selected patient outcomes will be compared before and after implementation of the *Pathway Platform*. Additional patient outcomes will be assessed after implementation among patients with MDD using the *Pathway Platform*.

Study Sites and Centers

This study is being performed within up to 20 primary care clinics in the AAH care system and will include up to 400

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patients with MDD. Advocate is the largest HCP organization in Illinois, with 12 hospitals, 20 health centers, and more than 250 care sites. It is one of the largest accountable care organizations in the United States, caring for more than 2 million patients annually. General practitioners at AAH provide diagnoses, treatment, and clinical care for adults aged ≥18 years experiencing chronic diseases, with MDD often being included among those. Sites representing different geographic locations, patient populations, and care models for depression management, including behavioral health integration models, will be identified to participate in the study.

Ethical Considerations

This study will be conducted in accordance with legal and regulatory requirements, and the protocol was reviewed by the AAH institutional review board prior to patient recruitment or data collection (approval number AHC-6680-75000249). Because this is designed as a real-world evidence study, investigators and study team members will not be physically located at the sites routinely, so all patients will provide consent through an e-consent process.

Study Population

All trained care team members who manage patients with MDD within the participating AAH clinics will be invited to participate in this implementation study and will have access to a web-based educational resource center and an app-based educational program for patients.

Inclusion and Exclusion Criteria

Eligible patients aged ≥18 years, diagnosed with MDD based on *International Classification of Diseases, Tenth Revision*, codes or who have a reference to "clinical depression" in their patient charts, and have recently (past 3 months) been prescribed monotherapy antidepressant medication or had a recent switch (past 3 months) in medication or medication dose, will be included in this study. Patients should be able to use the *Pathway Platform* based on clinician's judgment (eg, own an Apple iPhone version 5 or later version or a smartphone with an Android operating system and have an active data plan or regular Wi-Fi access).

To be eligible, patients should have tolerability concerns or an inadequate response determined by a PHQ-2 (includes the first 2 questions of the PHQ-9, which cover the degree to which a patient has experienced depressed mood and anhedonia within the past 2 weeks) score ≥3, or a PHQ-2 score <3 with a PHQ-9 score of ≥5 recorded in medical records in the past 6 weeks or during screening [16]. Patients with a missing PHQ-2 score in the past 6 weeks or who are unable to perform PHQ-2 during the enrollment visit; who have been diagnosed with bipolar depression, schizophrenia, or schizoaffective disorder; or who are no longer under primary care for depression (have transitioned to a psychiatric care team) will be excluded from this study.

Study Procedures and Measurements

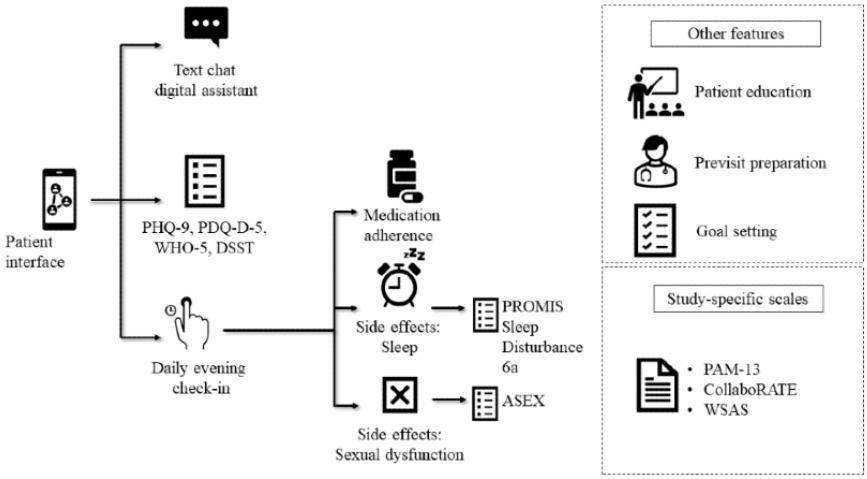
The *Pathway Platform* consists of 3 components: the latest iteration of the *Pathway app*, EHR integration, and educational scaffolding.

Pathway App

This study will deploy the most recent iteration of the *Pathway app*, which prompts patients to complete the following 4 scales every 2 weeks: PHQ-9 and 5-item Perceived Deficits Questionnaire–Depression (PDQ-D-5) to assess depression status, 5-item World Health Organization Well-being Index (WHO-5) to assess quality of life, and Cognition Kit Digit Symbol Substitution Test to assess cognition [17-20]. The *Pathway app* also includes a daily evening check-in to collect information on medication adherence and side effects; patients reporting side effects related to sleep will be prompted to complete the Patient-Reported Outcomes Measurement Information System (PROMIS) Sleep Disturbance item 6a, and patients reporting side effects related to sexual dysfunction will be prompted to complete the Arizona Sexual Experience Scale (ASEX). There will be an optional function to set and track goals using the goal attainment scale adapted for depression during clinical visits with an HCP [21]. Patients are also provided with a feature they can use to prepare for an upcoming visit with their care team, along with other features (Figure 3).

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Figure 3. Features of the *Pathway app*. ASEX: Arizona Sexual Experience Scale; DSST: Digit Symbol Substitution Test; PAM-13: 13-item Patient Activation Measure; PDQ-D-5: 5-item Perceived Deficits Questionnaire–Depression; PHQ-9: 9-item Patient Health Questionnaire; PROMIS: Patient-Reported Outcomes Measurement Information System; WHO-5: 5-item World Health Organization Well-being Index; WSAS: Work and Social Adjustment Scale.



For purposes of evaluating this implementation study, 3 additional scales assessing patient-provider engagement and functional improvement will be deployed at baseline and at the end of the study (13-item Patient Activation Measure [PAM-13], CollaboRATE [also included as a 3-month postenrollment assessment], and Work and Social Adjustment Scale [WSAS]) [22-24]. During the study, if a patient's response to item 9 of the PHQ-9 indicates a change in their suicidal ideation, they will receive a pop-up notification to contact their HCP or emergency services immediately. A similar instruction is also given in routine clinical practice. Patients will also be informed during the consent process that the information provided to the *Pathway Platform* is not directly or continuously monitored in real time by care teams.

EHR Integration

Data collected by the *Pathway app* will be electronically transmitted and stored in the patient's EHR. The data will be accessible to the care team and provide a longitudinal summary that may assist in SDM and depression management. Providers can view the data either before or during the patient visit and use it to discuss future depression management.

Educational Scaffolding

A web-based educational training program for primary care team members was developed using evidence-based medicine, building on the concepts of MBC and SDM as they relate to depression management. This education resource center houses a series of videos where key leaders in depression treatment and management from psychiatry and primary care speak about the strategies to optimize patient outcomes and suggest practical applications of the *Pathway Platform* in primary care along with supporting evidence from the pilot study. Care team members are asked to review the videos before the first patient is enrolled, which will be tracked to evaluate the proportion of providers who completed the education. Additionally, a guide for the care team is available. The training program includes a care provider audit and feedback where provider performance related to PHQ-9 use will be presented during the study period. An app-based education program along with a training manual was developed for patients, which describes the functionality of the *Pathway Platform* and how to use and interpret the data collected.

Study Outcomes

Evaluation of the success of the *Pathway Platform* implementation will be performed by comparing study outcomes among both cohorts (pre- and postimplementation). The primary outcome will be usage of PHQ-9 in the postimplementation cohort versus the preimplementation cohort over a 6-month period. The primary end point will be the change in the proportion of patients with at least 2 PHQ-9 scores before and after implementation. Secondary outcomes will include treatment adjustments informed by MBC, evaluation of SDM, MDD remission and response, and health care resource usage, including referrals to behavioral health and primary care follow-up after hospitalizations. Results from PRO scales, such as PAM-13, CollaboRATE, and WSAS will be assessed to compare baseline and 6-month follow-up data among patients using the *Pathway Platform*.

Exploratory outcomes, including medication adherence, goal attainment, and PHQ-9, PDQ-D5, and WHO-5 scores, will be evaluated among patients who use the *Pathway Platform*. Safety assessments will include adverse events related to the *Pathway Platform*. No adverse events are expected in this minimal-risk study; however, all serious adverse events that are spontaneously reported during the study period will be collected. Causality with study procedures will be determined for all serious adverse events and deemed "related" or "not related" to the intervention.

Statistical Analysis Plan

The following hypotheses will be examined: (1) PHQ-9 use will be greater after implementation compared with before implementation of the *Pathway Platform* and (2) provider processes and patient depression-related outcomes will have greater improvements after implementation of the *Pathway Platform* compared with previous practice patterns. For primary and secondary hypothesis testing, process measures, patient clinical outcomes, and health care resource usage will be compared before and after implementation of the *Pathway*

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Platform. Additional PROs will be evaluated after implementation only, which will be from patients using the *Pathway Platform* at baseline and at the end of the study.

For preimplementation, outcomes will be assessed among patients who visited one of the study clinics at least once over the preimplementation study period and were eligible to use the *Pathway Platform* if it had been available. For the postimplementation period, the *Pathway Platform* will be the data source for paired *t* test analysis, assessing change in continuous variables, including PHQ-9 scores. Categorical outcomes will be presented as proportions and compared using the Pearson chi-square test. Continuous outcomes will be assessed for normality and presented as means and SD or medians and IQRs; continuous outcomes will be compared using the Student *t* test for independent groups. Two-tailed tests using a significance threshold of P=.05 will be used for all tests.

Data Collection and Management

The schedule of evaluations is given in Table 1. Data from the EHR and manual chart reviews will be collected from two cohorts: (1) patients attending clinics after implementation (postimplementation cohort) and (2) patients attending clinics before implementation (preimplementation cohort). For each cohort, data will be collected over a 6-month period. Data on patient outcomes and *Pathway Platform* usage will be collected throughout the study starting on day 1 through month 6 for each patient using the platform. Similarly, data on report usage by the care team will be collected throughout the study. In addition, the number of times the care team educational resource material is viewed will be recorded between day 1 and month 6.

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Table 1. Schedule of postimplementation evaluations.

Study day	Baseline assessment (day 1)		Final assessment (month 6)	
	EHR[a]	*Pathway Platform*	*Pathway Platform*	EHR
Demographic characteristics	✓	—[b]	—	—
Number of PHQ-9[c] scores documented	✓	—	✓	✓
Treatment adjustments	✓	—	✓	✓
Referral to behavioral health	✓	—	—	✓
PHQ-9 scores	✓	—	✓	—
ED[d] visits	✓	—	—	✓
ED visits due to mental illness	✓	—	—	✓
Hospital admissions	✓	—	—	✓
Follow-up after ED and hospital visits	✓	—	—	✓
Hospital admissions due to mental illness	✓	—	—	✓
Outpatient visits, including phone calls	✓	—	—	✓
Outpatient visits, including phone calls due to mental illness	✓	—	—	✓
Remission and response (using PHQ-9 data)	✓	—	✓	—
PAM-13[e]	—	✓	✓	—
CollaboRATE	—	✓	✓	—
WSAS[f]	—	✓	✓	—
PHQ-9	—	✓	✓	—
WHO-5[g]	—	✓	✓	—
PDQ-D-5[h]	—	✓	✓	—
DSST[i]	—	✓	✓	—
Medication adherence	—	✓	✓	—
Side effects	—	✓	✓	—
PSD-6[j] (only if reporting side effects of sleep problems)	—	✓	✓	—
ASEX[k] (only if reporting side effects of sexual problems)	—	✓	✓	—
Goal setting	—	✓	—	—
Goal attainment	—	—	✓	—
App analytics	—	✓	✓	—
Report analytics	—	✓	✓	—
Educational material analytics	—	✓	✓	—
AEs[l] or SAEs[m,n]	✓	✓	✓	✓

[a]EHR: electronic health record.

[b]—: Not available.

[c]PHQ-9: 9-item Patient Health Questionnaire.

[d]ED: emergency department.

[e]PAM-13: 13-item Patient Activation Measure.

[f]WSAS: Work and Social Adjustment Scale.

[g]WHO-5: 5-item World Health Organization Well-being Index.

[h]PDQ-D-5: 5-item Perceived Deficits Questionnaire–Depression.

[i]DSST: Digit Symbol Substitution Test.

[j]PSD-6: Patient-Reported Outcomes Measurement Information System (PROMIS) Sleep Disturbance 6a.

[k]ASEX: Arizona Sexual Experience Scale.

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[l]AE: adverse event.

[m]SAE: serious adverse event.

[n]During the conduct of the study, adverse events or serious adverse events will be reported. As such, reports will be spontaneously notified, and causality of any AEs will be assumed unless there is evidence to the contrary.

Results

Patient recruitment was completed in July 2022, with initial results expected in mid-2023. Findings are expected to provide insights into the improvements that can be made in clinical workflows to enhance collaborative care, depression management, clinician and patient experience, adherence to medication, patient-provider engagement, and depression outcomes in the primary care setting for patients with MDD [11]. EHR integration and efficiencies with current AAH information technology platforms will also be assessed [11].

Discussion

Primary care centers are significant providers of mental health services for patients with MDD. Among US adults with MDD, 33% reported receiving mental health treatment within primary care during the previous 12 months compared with 21% who received treatment from a psychiatrist [25]. MBC in patients with MDD allows the primary care provider to accurately identify whether a patient is making enough progress toward their treatment goals. Treatment decisions based on MBC give patients a better understanding of the disease, including how adherence impacts their symptoms [8].

A common barrier to adherence is when an HCP's choice of treatment plan is not agreed upon by the patient. SDM is a systematic approach that improves patient education and helps primary care physicians provide treatment in conformity with evidence-based guidelines [26,27]. SDM can help increase adherence to drug treatment in the primary care setting and results in improved social functioning compared with usual care when used as part of a multifaceted relapse prevention program [9,28]. Involvement in SDM is associated with a higher probability of receiving quality care and improvement in symptoms [29].

Digital technology platforms, such as mobile apps, can offer low-cost interventions to monitor and improve services for certain patient populations that are difficult to retain in treatment and may also promote better health [30]. The *Pathway Platform* is a digital platform designed to improve patient outcomes by supporting an expanded understanding of MDD treatment, assisting care team workflows, and providing additional support to patients with depression throughout their treatment journey [11,15]. The patient-facing interface includes a digital assistant that allows those with MDD to interact with the *Pathway Platform* in a chat-based conversational text interface. The information collected from a patient using the *Pathway Platform* is intended to assist the care team in managing the patient's depression through improving MBC and SDM, thereby enhancing patient-provider engagement and ultimately patient outcomes.

The uniqueness and strengths of this study design are the real-world implementation of a digitally enabled care pathway with EHR integration in real time for patients with MDD and a continuous educational program for both patients and care teams in the primary care setting. In addition, the care team interface and patient-provider engagement help incorporate the use of PROs and emphasize the importance of SDM. Integrating the *Pathway Platform* to support MBC and SDM will improve the clinical workflow, depression management, adherence to medication, patient-provider engagement, as well as depression outcomes and care.

SDM and the involvement of both patients and physicians promote healthy relationships, with the benefit of helping patients with MDD feel greater support throughout their treatment, including web-based connections and care when needed, and can help ensure the safety of everyone involved in the process. By cocreating the *Pathway Platform* with users, including user-centered design methods, extensive preimplementation feedback and optimization, incorporation of the care team workflow, and patient preferences, the chances for successful implementation are greater. From a digital perspective, the *Pathway Platform* has the potential for eventual scalability and sustainability outside a research setting. Clear documentation of the study design and implementation methods will allow for replication at other health care institutions.

Limitations include a smaller sample size and geographically limited study centers, which prevent broader generalizability. Additionally, the use of a pre- and postevaluation design and lack of randomization can be seen as sources of accidental bias.

Data obtained from this real-world implementation study will allow for functional assessment of the *Pathway Platform* within the AAH care system and will determine its effects at a primary care level in patients with MDD. The *Pathway Platform* has the potential to improve patient-provider engagement for patients diagnosed with MDD and will address whether engaging these patients on an ongoing basis using digital tools can lead to better health outcomes. Overall, the study is planned to demonstrate the value of an appropriate MDD clinical care pathway by providing useful insights into a high-impact health care system.

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Data Availability

This study is ongoing. Further information regarding the study design is available from the corresponding author upon reasonable request.

Authors' Contributions

RK, M McCue, CB, JF, BF, JK, SS, LC, M Martin, CK, and DEK contributed to conceptualization of the study. RK, M McCue, CB, BF, JK, LC, M Martin, CK, and DEK supported the development of the study methodology. CB, BF, JK, and CK supported the software components of the study. RK performed the validation and formal data analysis, and RK and LC contributed to data visualization. CB, JF, BF, JK, CK, and DEK contributed to data collection and provision of study resources. RK, CB, BF, JK, LC, CK, and DEK provided oversight for research planning and execution. RK, CB, AR, BF, JK, and DEK provided management, coordination, and execution of research activity. M McCue, CB, AR, and SS acquired the financial support for the project. All authors contributed to draft review and critical revision of the manuscript and gave final approval of the version to be published.

Conflicts of Interest

RK, CK, JF, and DEK are employees of Advocate Aurora Health. DEK has received remuneration from Takeda for activities unrelated to the conduct of the study. M McCue, CB, SS, and M Martin are employees of Takeda Pharmaceuticals U.S.A., Inc. M McCue and SS received annual stock options from Takeda. LC and AR were employees of Takeda Pharmaceuticals U.S.A., Inc., at the time of study. BF and JK are Directors of Ctrl Group / Fora Health. BF is also a director of Cognition Kit.

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Abbreviations

AAH: Advocate Aurora Health
ASEX: Arizona Sexual Experience Scale
EHR: electronic health record
HCP: health care provider
MBC: measurement-based care
MDD: major depressive disorder
PAM-13: 13-item Patient Activation Measure
PDQ-D-5: 5-item Perceived Deficits Questionnaire–Depression
PHQ-9: 9-item Patient Health Questionnaire
PRO: patient-reported outcome

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PROMIS: Patient-Reported Outcomes Measurement Information System
SDM: shared decision-making
WHO-5: 5-item World Health Organization Well-being Index
WSAS: Work and Social Adjustment Scale

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Protocol

Capability, Opportunity, and Motivation Model for Behavior Change in People With Asthma: Protocol for a Cross-Sectional Study

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Abstract

Background: Asthma is a common lung condition that cannot be cured, but it can usually be effectively managed using available treatments. Despite this, it is widely acknowledged that 70% of patients do not adhere to their asthma treatment. Personalizing treatment by providing the most appropriate interventions based on the patient's psychological or behavioral needs produces successful behavior change. However, health care providers have limited available resources to deliver a patient-centered approach for their psychological or behavioral needs, resulting in a current one-size-fits-all strategy due to the nonfeasible nature of existing surveys. The solution would be to provide health care professionals with a clinically feasible questionnaire that identifies the patient's personal psychological and behavioral factors related to adherence.

Objective: We aim to apply the capability, opportunity, and motivation model of behavior change (COM-B) questionnaire to detect a patient's perceived psychological and behavioral barriers to adherence. Additionally, we aim to explore the key psychological and behavioral barriers indicated by the COM-B questionnaire and adherence to treatment in patients with confirmed asthma with heterogeneous severity. Exploratory objectives will include a focus on the associations between the COM-B questionnaire responses and asthma phenotype, including clinical, biological, psychosocial, and behavioral components.

Methods: In a single visit, participants visiting Portsmouth Hospital's asthma clinic with a diagnosis of asthma will be asked to complete a 20-minute questionnaire on an iPad about their psychological and behavioral barriers following the theoretical domains framework and capability, opportunity, and motivation model. Participants' data are routinely collected, including demographics, asthma characteristics, asthma control, asthma quality of life, and medication regime, which will be recorded on an electronic data capture form.

Results: The study is already underway, and it is anticipated that the results will be available by early 2023.

Conclusions: The COM-B asthma study will investigate an easily accessible theory-based tool (a questionnaire) for identifying psychological and behavioral barriers in patients with asthma who are not adhering to their treatment. This will provide useful information on the behavioral barriers to asthma adherence and whether or not a questionnaire can be used to identify these needs. The highlighted barriers will improve health care professionals' knowledge of this important subject, and participants will benefit from the study by removing their barriers. Overall, this will enable health care professionals to use effective individualized interventions to support improved medication adherence while also recognizing and meeting the psychological needs of patients with asthma.

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International Registered Report Identifier (IRRID): DERR1-10.2196/44710

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KEYWORDS

adherence; asthma; behavioral barriers; psychological barriers; capability, opportunity, and motivation model of behavior change; COM-B; medication; theoretical domains framework

Introduction

Background

Asthma is a common lung condition affecting over 5.4 million people in the United Kingdom. For some people, it can affect daily activities and lead to life-threatening consequences [1]. Asthma cannot be cured, but it can usually be effectively controlled with available treatments, provided they are taken as recommended [1]; however, it is well recognized that up to 70% of patients do not take their asthma treatments as recommended (ie, they are nonadherent) [2]. This is perhaps not unexpected in the context of a chronic condition requiring daily treatments, which must be taken even when the person feels well [3]. People may also have concerns about using long-term medicines (including steroid inhalers), or there may be other psychological or behavioral barriers to adherence [4]. Nonadherence to asthma treatments results in poor asthma control with persistent asthma symptoms, more frequent asthma attacks, and greater impairment in quality of life [5]. There are also significant economic implications associated with "wasted" medications and additional health care requirements, such as doctors' appointments and visits to the accident and emergency department, which contribute to the overall cost of asthma care in the United Kingdom, exceeding £1 billion (1£=US $1.103) per year [6].

Health care professionals play an important role in engaging and educating patients about the importance of their asthma treatments, monitoring asthma control, and identifying whether a patient is adherent or not [7]. Adherence is a complex process for the patient, who must be able to start prescribed medications, take the medications as prescribed (correct dose, inhalation technique, and frequency), and be persistent (obtaining refills to maintain adherence over time) [8]. There are limited resources available in a busy health care setting to ensure a complete understanding of each individual's psychological and behavioral barriers, with a one-size-fits-all approach obtaining limited success [9]. As such, there is a persistent unmet need for a tool that can effectively identify these barriers to adherence in a clinical setting, allowing health care professionals to provide effective personalized treatments for nonadherence in patients with asthma.

Asthma adherence research has been able to identify population-specific psychological or behavioral needs, including (1) partnership between patient and health care professional [8], (2) issues around medication, (3) education about asthma and its management, (4) health beliefs, (5) self-management interventions, (6) comorbidities, (7) mood disorders and anxiety, (8) social support, (9) nonpharmacological methods, (10) access to health care, and (11) professional factors. However, in the clinical field, such knowledge is relatively limited, with findings only showing that people with asthma are vulnerable to adherence problems and that targeted adherence interventions to facilitate population-specific barriers are not always effective. Thus, beyond identifying the vulnerability to nonadherence and targeting known barriers, a patient's personal psychological needs must be understood with in-depth and detailed insight. In addition, there is a need to establish which techniques, tools, or services are likely to successfully promote individualized ways to encourage behavioral change and adherence optimization.

In a clinical setting, health care professionals only have the resources to identify whether a patient is adherent or nonadherent to treatment; as a result, they are responsible for engaging and educating patients about the importance of their asthma treatments and monitoring asthma control. This assessment does not consider the individual barriers to each patient's adherence, and the one-size-fits-all strategy is not optimum. However, because the patient's complete picture is not presented (due to lack of feasibility, such as health care professionals' time), health care professionals lack the resources to empower the patient to address their psychological needs. Therefore, a practical resource is needed for the health care provider to receive a 360-degree picture to help personalize each patient's treatment effectively.

The Theory

It is important that the psychological needs of patients can be easily assessed to allow for the patient's personal needs to be understood, promoted, improved, and supported [10]. When focusing on adherence behavior, the currently available tools are questionnaires, but these are long and complex to complete. The capability, opportunity, and motivation model of behavior change (COM-B) model is a new questionnaire that is shorter and easier for patients to complete [11]. It involves 3 key components: capability, opportunity, and motivation [12]. This theoretical approach has not been used extensively for people with asthma. However, COM-B is meant to be comprehensive, concise, and applicable to all behaviors. The COM-B is designed to serve as a starting point for selecting interventions that are most likely to be beneficial, and particular interventions to address each component have been identified [13].

The model suggests that at any time, a particular behavior will occur when the person concerned has the capability and opportunity to engage in the behavior and is more motivated to enact the behavior over other competing behaviors. Having high COM would lead to the successful performance of behavior (see Figure 1 for a visual representation of the COM-B for adherence [14]). COM-B is designed to provide an overarching model that captures all the factors known to influence behavior change: physical capability, psychological capability, physical opportunity, social opportunity, reflective motivation, and automatic motivation [15]. Its origin can be found in the 14 domains of the theoretical domains framework (TDF: see Table 1). The TDF is an overall theoretical framework consisting of

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14 domains that integrate components from numerous health behavior change theories; hence, these 14 domains are regarded as essential aspects of behavior change in health psychology. The TDF can be used to help discover the elements influencing a certain behavior without overlooking key factors. As a result, the COM-B model comprises components that are hypothesized to drive behavior. Additionally, the COM-B can be placed at the heart of the behavioral change wheel (see Figure 2); thus, this framework can be used as a mapping system [16].

Despite the COM-B model being widespread, there is only one generic self-evaluation questionnaire to assess people's perceptions of capabilities, opportunities, and motivations intended for use in multiple behaviors and a range of diverse populations [13]. Although there was evidence of this questionnaire's acceptance, validity, and reliability, this questionnaire has not been used with patients in a medical setting. As a result, this study will be able to further demonstrate the questionnaire's usefulness and reliability.

Figure 1. Application of the capability, opportunity, and motivation model of behavior change to adherence [16].

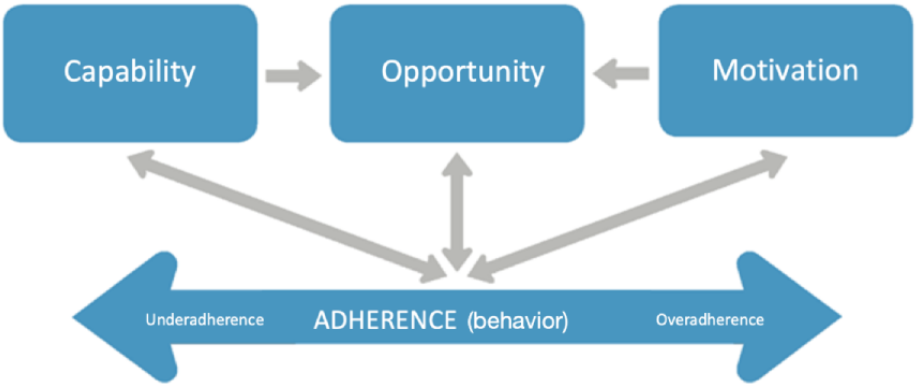
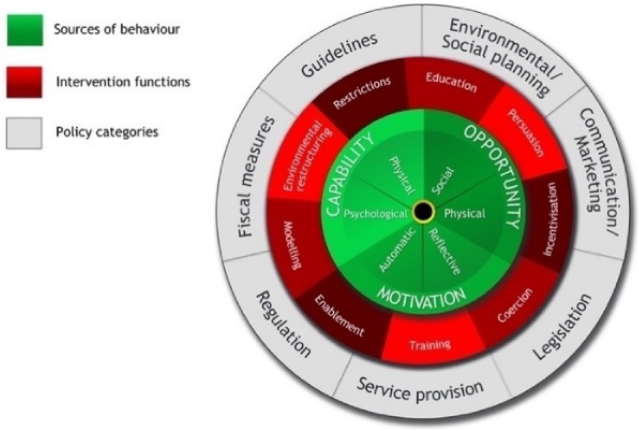


Table 1. Capability, opportunity, and motivation model of behavior change and the 11 domains of the theoretical domains framework mapped out [10].

Components of the capability, opportunity, and motivation model of behavior change	Domains in the theoretical domains framework
Capability	
Psychological	• Knowledge • Skills • Memory, attention, and decision processes • Behavioral regulation
Physical	• Skills
Opportunity	
Social	• Social influences
Physical	• Environmental context and resources
Motivation	
Reflective	• Social or professional role and identity • Beliefs about capabilities • Optimism • Beliefs about consequences • Intentions • Goals
Automatic	• Social or professional role and identity • Optimism • Reinforcement • Emotion

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Figure 2. The behavioral change wheel, capability, opportunity, and motivation model of behavior change at the center [15].



Overview

This study will assess whether the brief COM-B questionnaire can identify the same psychological and behavioral barriers as the current longer questionnaires (barriers to medication adherence questionnaire) and therefore assess the COM-B questionnaire's ability to identify any important factors that may need to be addressed to support patients to take their asthma treatments as recommended.

We will also see whether there are any links between the type and severity of asthma that someone has, their other medical problems, how much treatment they have to take each day, and the COM-B questionnaire responses. This may help us better identify people who may struggle to take their medications properly and why. Again, we will use information routinely collected in the clinic, including lung function test results and medication prescription reviews, to do this.

Methods

Overview

This study will employ a cross-sectional survey design focusing on adherence to asthma treatment. It will be delivered through REDCap, a web-based platform. Participants will be recruited when attending their routine clinical review with the asthma service or while an inpatient at Queen Alexandra Hospital in Portsmouth, United Kingdom. Routinely collected patient data, including demographics, asthma characteristics, asthma control, and medication regime that is already collected as part of their clinical review, will be recorded on an electronic data capture form (e-CRF) through the REDCap platform. They will then be asked to complete the series of questionnaires, all completed on the web. Patients will also be provided with a paper copy of each questionnaire. When the questionnaire is completed, the user will be provided with debriefing information.

Participants will be asked to complete a set of questionnaires that will assess the following:

1. Psychological and behavioral barriers that may affect the participant being able to take their asthma treatments as recommended: the brief COM-B questionnaire (which is being validated as part of this study) and the 61-item Theoretical Domain Framework Questionnaire.
2. Their asthma symptoms and how well controlled their asthma is (Asthma Control Questionnaire [ACQ-6]), the impact their asthma has on their quality of life (Mini Asthma Quality of Life Questionnaire), and the level of anxiety or depression they may be experiencing (Hospital Anxiety and Depression Scale). All of these questionnaires are used routinely at clinic reviews.
3. Their use of technology at home and any challenges they face with this: Digital Readiness Questionnaire.

The COVID-19 pandemic has changed the way people with asthma access their care with a move to remote consultations and questionnaire completion. The COM-B questionnaire may well be suitable for this approach. However, it is essential to assess digital readiness in this population to understand whether this is feasible and inform the design of future studies if the COM-B questionnaire proves to be successful.

It should not take more than 20 minutes to complete. The questionnaires are all validated and approval has been granted for their use in this study.

Eligibility Criteria

Participants will be drawn from a range of adults with asthma who take regular medication for their condition. The inclusion and exclusion criteria are presented in Textbox 1.

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Textbox 1. Inclusion and exclusion criteria of the study participants.

Inclusion criteria

- Aged 18 years or above
- Willing and able to give informed consent for participation in the study
- Diagnosing of asthma confirmed by a health care professional and requiring maintenance asthma treatment, including an inhaled corticosteroid.

Exclusion criteria

- Unable to comprehend the study and provide informed consent, for example, insufficient command of English in the absence of someone who can adequately interpret.

Sampling and Sample Size

A power calculation was conducted to determine the sample size, using the 6 components of the COM-B model that are hypothesized to drive behavior, namely physical capability, psychological capability, physical opportunity, social opportunity, reflective motivation, and automatic motivation. Using the G-power analysis for 6 predictors, a minimum of 146 participants are needed. The G-power analysis was run using SPSS to offer a sensitivity power analysis of the effect size that this sample size was sensitive to detect.

As a result, to detect a standardized effect size of Cohen *d*=0.43 with 80% power (α =.05, 2-tailed), G*Power suggests we would need 146 participants in independent tests. A paired sample *t* test with 30 participants would be sensitive to the effects of Cohen *d*=0.53 with 80% power (α=.05, 2-tailed). This means the study would not reliably detect effects smaller than Cohen *d*=0.53. To detect a Pearson correlation coefficient of ρ=.21 with 80% power (α=.05, 2-tailed), G*Power suggests we would need 146 participants.

Recruitment

All people with asthma who are under the care of the asthma service at Portsmouth Hospitals University National Health Service (NHS) Trust will be invited to participate in this study. This will include recruitment from primary care sites. In addition, both outpatients and inpatients will be approached and invited to participate.

Study Assessment

This section describes the information that will be recorded in the participant's RedCap report, which will be anonymized using the participant's unique study number.

Participant Clinical Characteristics

The following information is routinely collected and used as part of standard care and following consent and recruitment to the study will be transcribed from a participant's clinical care records and will be recorded on the e-CRF.

Patient Details and Demographics

1. Age, gender, ethnicity, school or work status, educational level
2. Smoking status and pack-year smoking history
3. Asthma severity is defined using British Thoracic Society stages
4. New or established patients to the asthma service
5. Medical comorbidities

Asthma Characteristics

1. Age when asthma diagnosis was made
2. Spirometry—this will either be captured as part of their routine clinic visit or can be historic (within the last 12 months)
3. Type 2 (T2) biomarkers: peripheral blood eosinophil count and fractional exhaled nitric oxide (FeNO)—this will either be captured as part of their routine clinic visit or can be historic (within the last 12 months)
4. Number of exacerbations in the preceding 12 months (number of courses of steroids, number of emergency department attendances or hospital admissions)
5. Current asthma treatments

Adherence Assessment

1. Medicines possession ratio (MPR)—this measurement will consider the past 12 months of the participant's adherence. Adherence will be defined as an MPR ≥80%
2. Advanced measures of adherence (such as FeNO suppression) where available

Complexity of Medication Regime

1. Total number of medications taken each day
2. Number of doses of inhaled medications per day

Questionnaires Collected

The asthma COM-B questionnaire [13] measure will be responsible for identifying one's capabilities, opportunities, and motivations regarding asthma medication adherence. In the questionnaire, these measures will be presented as individual questions, forming 6 matrix tables.

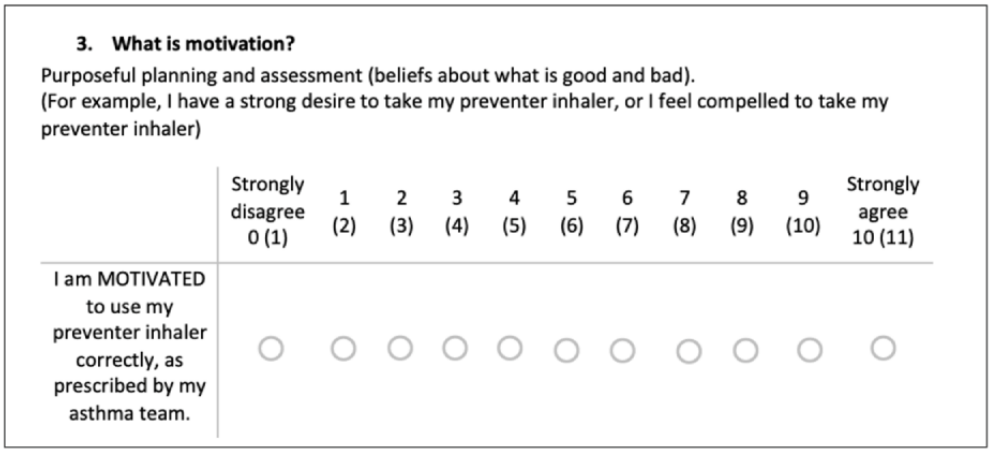
This questionnaire will be brief, with 6 items asking them to rate their understanding of their psychological and physical capacities, opportunities, and motivations for adhering to asthma treatment on a Likert scale (see Figure 3, for example items from the questionnaire adapted from Keyworth et al's [17] COM-B measure). This tool would follow the structure, formatting, and length of other questionnaires given to patients during their initial assessments. As a result, it will be easily integrated into the health care system, providing health care providers with immediate responses to patients' psychological needs and potentially getting a better understanding when meeting with the patient.

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The ACQ [15,18] consists of 6 items covering day and nighttime symptoms, activity limitations, and rescue bronchodilator use. A score of ≥1.5 reflects poor asthma control.

The Mini Asthma Quality Of Life Questionnaire standardized version [16,19] measures four domains: symptoms, activity limitation, emotional function, and environmental stimuli.

Figure 3. Items 1 of 6 from the adapted capability, opportunity, and motivation model of behavior change questionnaire to target known drivers of adherence in people with asthma. This figure was adapted from Keyworth C et al [17] which is published under Creative Commons Attribution 4.0 International License [20].



Adherence Measures

The 61-item Theoretical Domain Framework Questionnaire [21,22] will determine the individual's behavior in terms of the theoretical domains framework (see Table 1).

The Test Of Adherence To Inhalers [23,24] is a 12-item questionnaire designed to assess adherence to inhalers in patients with asthma.

Digital Readiness Measure

The Digital Readiness Scale [17] was followed to investigate the effectiveness of using technology tools for medical practices in the NHS. This scale will be adapted to 6 items assessing participants' use of digital tools, interest in digital tools, and challenges faced by participants while using digital tools [25].

Statistical Analysis

Data Exclusion

Participants are free to withdraw from the study, and this will not affect their treatment. Participants will consent at the start of the survey to allow their anonymized study data to be retained and analyzed by the study team if they withdraw from the study. Withdrawn participants will not be replaced.

Data will be analyzed once 146 participants have completed the questionnaire. All data will be handled within the general data protection regulations conditions, which came into force in May 2018.

Once a survey is completed, it is locked, and time-stamped so the survey responses cannot be edited further. Required fields are specified on the survey form, and partial or incomplete responses will not limit the survey response. Once the survey response limit is reached, the public URL will redirect to a message notifying that the survey is closed.

Data Management

All data collection will be completed on the web. The research team will use the Redcap electronic cloud solution to store and manage all consent and study data. The cloud services are NHS compliant and approved for use in surveys.

Data will be stored on a secure password-protected electronic research database hosted on a secure NHS server with appropriate backup systems, antivirus software and security protocols compliant with NHS information governance standards. Data entered into the electronic database will be accessible only by a restricted number of research personnel listed in the delegation log of the survey master file.

There will be a survey master file with a delegation log of approved users in the file. Before anyone can use the database, they will have to be included in this list, with the approval of the chief investigator. The chief investigator and survey coordinator will have access to all research data collected in this study to perform the data analyses required.

A data manager will perform regular data quality control checks, and reporting and statistics will be performed using tools built into the survey distribution platform. A comprehensive audit log will be maintained throughout the study and exported and stored in the survey master file on study closer.

Overview

Patient scores for the behavioral components of physical capability, psychological capability, social and physical opportunity, and reflective and automatic motivation will be tabulated, so that adherence and asthma characteristics can be recorded for each behavioral source against predefined behavioral change techniques based on the behavioral change wheel [12].

Summary Statistics

Demographics or baseline characteristics of each participant will be produced, as well as summaries for all participants

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combined. Normally distributed continuous variables will be summarized by the mean to characterize the population. Nonnormally distributed variables will be summarized by the median to characterize the population.

Primary Analysis

The primary analysis will comprise the correlation of outcomes from the brief COM-B questionnaire and the TDF questionnaire, as well as the Spearman rank correlation coefficients (ρ; strength of the relationship) and a hierarchical multiple regression analysis. For example, the capability result of the questionnaire will be compared to knowledge, skills, memory attention and decision processes, behavioral regulation, and skills. In addition, some exploratory analysis between the variables will be conducted—this will be used to derive the content validity of the brief COM-B questionnaire.

Secondary Analysis

Descriptive statistics will be used to illustrate levels of asthma control, medication adherence, and perceptions of capabilities, opportunities, and motivations. One-sample *t* tests, within participants' ANOVA and deviation contrasts will be used to explore differences between levels of capabilities, opportunities, and motivations regarding adhering to their asthma medication programs.

For each capability, opportunity, and motivation variable, separate cluster analysis models will be used to examine associations between the COM-B with levels of adherence measured by MPR and FeNO suppression to explore the key psychological and behavioral barriers indicated by the COM-B questionnaire and methods of determining adherence in a clinical setting.

Multiple regressions will be conducted to test the levels of adherence. In addition, other variables such as demographics and asthma characteristics will be taken into consideration.

Exploratory Analysis

Network analysis between variables including (but not limited to):

1. Type of asthma (T2 or non-T2 defined by the presence of a T2 inflammatory signal assessed using FeNO and peripheral blood eosinophil count)
2. Asthma severity using British Thoracic Society or Scottish Intercollegiate Guidelines Network (SIGN) stage
3. Level of asthma control assessed using the ACQ6 questionnaire (a score of ≥1.5 reflects poor asthma control)
4. Quality of life measured using the mini-asthma quality-of-life questionnaire score
5. Number of comorbidities
6. Complexity of treatment (number of inhaled doses per day, total number of medications taken each day)
7. Informative analysis of digital readiness will be performed by summarizing all participants combined responses, reported in percentages

Procedure for Missing, Unused, or Spurious Data

There are no plans for multiple imputations or other corrections for missing data.

Ethical Considerations

Statement of Compliance

All staff working on this study will hold evidence of good clinical practice training before undertaking any responsibilities, and all staff working within the research study team are also part of the respiratory clinical care team and are involved in PhD supervision. Written informed consent will be obtained from all participants after an adequate explanation of the aims, methods, and anticipated benefit of the study using the participant information sheet. A signed copy of the consent form will be given to the participant, and copies will be filed in the study master file and the participants' medical notes.

Participants' anonymity will be maintained throughout by identification on a password-protected electronic database and e-CRFs only by initials and participant ID number. All documents will be stored securely and only accessible by study staff and authorized personnel; the study will comply with the Data Protection Act.

Potential Benefits or Risks of Study Participation

This study is a low-risk questionnaire study; however, any risks to the participants have been carefully considered—any participants who were observed struggling with the psychological aspect of the questionnaire or the questionnaire raised further issues patients will have these errors highlighted and will be informed with the correct health care professional to look after their care. This is a beneficial outcome for participants' self-care and management and ensures that they obtain the correct level of care.

This study analyzes a wide variety of behavioral barriers and will help provide a clear picture of the psychological needs that are associated with asthma adherence. Understanding this information is important in the context of managing lung conditions, from treating patients in primary care through to feeding this information back to intervention designers.

Other Ethical Considerations

The study will not be initiated before the protocol, and the survey's material such as the consent forms, survey answers, and participant information sheets have received favorable opinions from the health research authority and the respective NHS research and development (R&D) departments. Should an amendment be made that requires Research Ethics Committee (REC) approval, as defined by REC as a substantial amendment, the changes will not be instituted until the amendment has been reviewed and received approval or favorable opinion from the REC and R&D departments. However, a protocol amendment intended to eliminate an apparent immediate hazard to participants may be implemented immediately, providing that the REC is notified as soon as possible, and approval is requested. Other amendments will be implemented under the direction of the REC.

All participants will have adequate time to consider participation in the study, as per good clinical practice guidelines.

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Participants who are already enrolled in other research surveys will be invited and allowed to participate in the study if they so wish.

Patient Public Involvement Process

Patients having first-hand knowledge of coping with chronic respiratory disease were sought out for patient involvement in this study. We have spoken with our respiratory patient representatives in person, over the phone, and via email. These individuals have participated in earlier research projects and have lived with respiratory problems. To ensure that we address the issues that are pertinent to persons with airway disorders, they helped define the main questions and establish our study objectives. To reduce waiting times for patients who decided to participate in the study, assistance was also sought with the design of participant recruitment and the implementation of the study within a typical clinical visit. Additionally, they contributed to creating the participation information sheet and cowrote the lay summary.

Results

The study is already underway, and it is anticipated that the results will be available by early 2023.

Discussion

The COM-B asthma study will investigate an easily accessible theory-based tool (a questionnaire) for identifying psychological and behavioral barriers in patients with asthma who are not adhering to their treatment. This will provide useful information on the behavioral barriers to asthma adherence and whether or not a questionnaire can be used to identify these needs. The highlighted barriers will increase health care professionals' knowledge of this important subject, allowing for practice change and better information for interventions to remove those barriers. Overall, this will enable health care professionals to use effective individualized interventions to support improved medication adherence while also recognizing and meeting the psychological needs of patients with asthma.

Acknowledgments

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Data Availability

The data sets generated or analyzed during the current study are available from the corresponding author on reasonable request.

Conflicts of Interest

TB reports personal grants and personal fees from AstraZeneca, grants, personal fees, and nonfinancial support from GlaxoSmithKline; personal fees and nonfinancial support from Teva; nonfinancial support from Napp Pharmaceuticals; and personal fees and nonfinancial support from Novartis. All these grants and personal fees are outside of the submitted work. AJC reports honoraria and lecture fees from TEVA, AstraZeneca, and Sanofi; and research grants from Airsonett, Novartis, and GlaxoSmithKline. All these grants and personal fees are outside of the submitted work.

AJC reports honoraria and lecture fees from TEVA, AstraZeneca, and Sanofi; and research grants from Airsonett, Novartis, and GlaxoSmithKline. All these grants and personal fees are outside of the submitted work.

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Abbreviations

ACQ: asthma control questionnaire
COM-B: capability, opportunity, and motivation model of behavior change
e-CRF: electronic data capture form
FeNO: fractional exhaled nitric oxide
MPR: medicines possession ratio
NHS: National Health Service
R&D: research and development

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REC: Research Ethics Committee
SIGN: Scottish Intercollegiate Guidelines Network
T2: type 2
TDF: theoretical domains framework

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Protocol

Frequency of Prenatal Care Visits: Protocol to Develop a Core Outcome Set for Prenatal Care Schedules

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Abstract

Background: Prenatal care, one of the most common preventive care services in the United States, endeavors to improve pregnancy outcomes through evidence-based screenings and interventions. Despite the prevalence of prenatal care and its importance to maternal and infant health, there are several debates about the best methods of prenatal care delivery, including the most appropriate schedule frequency and content of prenatal visits. Current US national guidelines recommend that low-risk individuals receive a standard schedule of 12 to 14 in-office visits, a care delivery model that has remained unchanged for almost a century.

Objective: In early 2020, to mitigate individuals' exposure to the SARS-CoV-2 virus, prenatal care providers implemented new paradigms that altered the schedule frequency, interval, and modality (eg, telemedicine) of how prenatal care services were offered. In this paper, we describe the development of a core outcome set (COS) that can be used to evaluate the effect of the frequency of prenatal care schedules on maternal and infant outcomes.

Methods: We will systematically review the literature to identify previously reported outcomes important to individuals who receive prenatal care and the people who care for them. Stakeholders with expertise in prenatal care delivery (ie, patients or family members, health care providers, and public health professionals and policy makers) will rate the importance of identified outcomes in a web-based survey using a 3-round Delphi process. A digital consensus meeting will be held for a group of stakeholder representatives to discuss and vote on the outcomes to include in the final COS.

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Results: The Delphi survey was initiated in July 2022 with invited 71 stakeholders. A digital consensus conference was conducted on October 11, 2022. Data are currently under analysis with plans to submit them in a subsequent manuscript.

Conclusions: More research about the optimal schedule frequency and modality for prenatal care delivery is needed. Standardizing outcomes that are measured and reported in evaluations of the recommended prenatal care schedules will assist evidence synthesis and results reported in systematic reviews and meta-analyses. Overall, this COS will expand the consistency and patient-centeredness of reported outcomes for various prenatal care delivery schedules and modalities, hopefully improving the overall efficacy of recommended care delivery for pregnant people and their families.

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KEYWORDS

core outcome set; Delphi; prenatal care schedules; telemedicine; prenatal; pediatric; maternal; obstetric; core outcome; pregnant; pregnancy; care delivery; care schedule; infant; review method; systematic review

Introduction

Prenatal care, one of the most common preventive care services in the United States, endeavors to improve pregnancy outcomes through evidence-based screenings and interventions [1]. Despite the prevalence of prenatal care and its importance to maternal and infant health, there are several debates about the best methods of prenatal care delivery, including the most appropriate schedule frequency and content of prenatal visits [2]. For patients, adaptable scheduling and assimilation of telemedicine into prenatal care visit schedules provide convenience, save time, and reduce resource outlays for patients. For prenatal care providers and clinics, it allows enhanced operation of facility space by permitting flexibility in scheduling and prioritizing in-person access for pregnant individuals with acute needs. With many regions facing limited access to timely obstetrical care across the United States, whether due to the clinic's capacity or geographic limitations (eg, travel time), innovative application of new approaches to prenatal care will become essential. Current US national guidelines recommend that low-risk individuals receive a standard 12 to 14 in-office visit schedule—a care delivery model that has remained unchanged for almost a century. Other guidelines from peer countries (eg, Canada, Europe, and Australia), as well as national consensus panels, have recommended a reduced visit schedule based on recommended prenatal care services for average-risk people, typically 7 to 11 visits [3-6].

In early 2020, to mitigate individuals' exposure to the SARS-CoV-2 virus, prenatal care providers implemented new paradigms that altered the schedule frequency, interval, and modality (eg, telemedicine) of how prenatal care services were offered. COVID-19 pandemic–related changes to how prenatal care was provided accelerated existing plans of the American College of Obstetricians and Gynecologists (ACOG) to redesign prenatal care for low-risk pregnant people. ACOG urgently convened a multidisciplinary panel to review how prenatal care was administered to the average-risk individual [5]. The panel provided recommendations for (1) prenatal visit schedules (care initiation, visit timing, and frequency); (2) integration of telemedicine (web-based visits and home devices); and (3) care individualization. However, it was recognized that there were significant gaps in evidence needed to guide national policy change on prenatal visit schedules, including visit frequency and modality. Meta-analyses of studies that addressed the prenatal care visit schedules and the effects on maternal or infant outcomes have noted inconsistencies in which outcomes are routinely collected and reported [7-10]. There is a need for consistent reporting of maternal and infant outcomes in future clinical trials that compare the traditional 12 to 14 in-office visit approach with new models of prenatal care schedules that incorporate different frequencies of visits and use of telemedicine.

Core outcome sets (COSs) are key tools for ensuring consistent, homogenous reporting of outcomes across studies. The use of COS can result in improved clinical practice via standardization of outcomes across studies, thereby making it easier to compare outcomes. Furthermore, the use of COS can reduce the risk of outcome-reporting preference, ensuring that all trials contribute functional information [11]. The objective of this study is to develop a COS to standardize outcome selection, collection, and reporting for future studies that compare prenatal care schedules with different frequencies of prenatal visits delivered across any modality (eg, in-office care, group prenatal care, or telemedicine).

Methods

Steering Committee

This study has been prospectively registered with the Core Outcome Measures in Effectiveness Trials initiative website (registration number 2021). We will follow reporting guidelines for developing COS, as outlined by the Core Outcome Set-Standards for Development and follow the Core Outcome Set-Standardised Protocol Items statement [12,13]. A steering group including prenatal care providers, clinical researchers, and obstetric health care policy makers has been formed to guide the development of this COS. Members of the steering group were selected to represent various disciplines, geographical areas, and expertise. Within the steering committee, a study advisory board has been established, which consists of a study coordinator (BN) and 2 members of the steering committee (MT and AP) who will conduct the day-to-day management of the study.

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Definitions

The steering committee recommended that the COS should apply to clinical studies evaluating the frequency of prenatal care schedules for average-risk individuals receiving prenatal care when compared to current US national guideline recommendations of a 12 to 14 in-office visit schedule. Average risk was defined broadly using a prior consensus committee definition and includes all pregnant individuals seen by maternity care providers (eg, obstetrician gynecologists, family medicine physicians, nurse practitioners, and certified nurse-midwives), without significant comorbidities requiring exclusive care by a maternal-fetal medicine physician [5]. The potential interventions covered by the COS could include the recommended frequency of prenatal care visits in several modalities: (1) traditional 12 to 14 in-office appointments versus reduced number of in-office visits; (2) method of delivery of the frequency of various types of prenatal care visit recommendations (traditional 12 to 14 in-office visits versus a reduced number of visits provided by a hybrid of in-office combined with telemedicine modalities); and potentially (3) other innovative models of prenatal care schedule recommendations (traditional 12 to 14 in-office visits compared to a reduced number of scheduled visits using care delivery models such as group prenatal care or pregnancy medical homes that incorporate either in-office only or a hybrid of in-office and telemedicine).

Study Overview

Overview

This study will be divided into three separate phases: (1) ascertaining potential core outcomes, (2) defining core outcomes for inclusion, and (3) consensus meeting.

Phase 1: Developing a Preliminary Core Measurement Outcome Set

Two systematic reviews were recently commissioned for evaluating the effect of varying the frequency of prenatal care visit schedule recommendations on maternal and infant outcomes [5,10]. To identify any additional outcome measures published in the literature, we will supplement these systematic reviews with an electronic investigation with no date or language boundary using the databases of MEDLINE via the PubMed interface, Web of Science, Embase, and CENTRAL to identify outcome measures in systematic reviews that reported on the effect of different frequency of prenatal visit recommendations on maternal and infant outcomes. We will evaluate unpublished collected works (ie, "gray literature") by searching Google Scholar and screening the first 100 results as is commonly done, based on the assumption that the most applicable results would emerge first [14].

We will also identify potentially relevant outcome measures from the medical literature to inform the consensus process. Data sources that may be considered as systematic reviews of published studies and reviews of published qualitative work that have evaluated the effect of the recommended frequency of scheduled prenatal visits on maternal and infant outcomes. A list of outcomes from published studies will be supplemented by a review of qualitative research studies investigating patients' opinions regarding the frequency of prenatal care visits.

Steering group members will be provided with a preliminary outcome list, as well as a summary of the systematic reviews and the strength of evidence for each outcome (based on either the Cochrane Handbook for Systematic Reviews of Interventions [15] or the Grading of Recommendations Assessment, Development and Evaluation [16]). The list of core outcomes will be piloted and adjusted by the steering group, incorporating both professional expertise and public member perspectives, before finalizing. The steering group members will be asked to "From the following list choose the 'minimum standard outcomes' that you think are important when developing a COS for the frequency of prenatal care visits (FORCAST) recommended schedule." Every respondent will be given the option to include, exclude, or combine each outcome with other outcomes that have similar clinical definitions (eg, combining gestational age at birth and preterm birth into a single outcome) to limit the number of COS outcomes and increase the likelihood that the COS is applied in future research. Steering group members will also be given the opportunity to add outcomes they believe are critical for the COS. Steering group members will be encouraged to base their COS decisions on the strength of evidence reported in the medical and public health literature. Steering group member responses will be tabulated into an outcome inventory spreadsheet. Responses to the survey will be reviewed independently by the advisory board members, duplicate suggestions will be removed, and the remaining responses will be grouped into domains of maternal or infant outcomes. Additional outcomes proposed by the steering committee will be added to the COS if at least 2 members write in the outcome, per specifications of the Core Outcome Measures in Effectiveness Trials handbook [11]. The steering committee will then review the domains and finalize a comprehensive list of outcomes. Following the steering group's consensus, the list of outcomes will then be prepared for the Delphi survey [11]. All language for the COS will be developed using definitions from professional organizations and patient-facing resources tested across diverse populations where possible. Definitions will be piloted with 3 public members to confirm readability and comprehension.

Phase 2: Conducting a Delphi Survey to Gain Consensus Opinion on Items to Include in a Standardized COS

Overview

We will conduct a Delphi panel to develop the stakeholder-informed COS [11]. In a COS structure, this method is used for attaining convergence of opinion from stakeholders on the importance of different outcomes in sequential questionnaires sent electronically. We will use sequential web-based questionnaires with participant feedback between rounds to incorporate the perspectives of diverse stakeholders who contribute to and receive prenatal care, including (1) public members: persons who are currently using prenatal care, have used prenatal care in the past year, or provide nonmedical support to pregnant and postpartum people (eg, pregnant and postpartum people, family members); (2) prenatal care providers and researchers: health care providers who administer prenatal

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care (eg, obstetrician or gynecologists, family medicine physicians, neonatologists, advanced practice practitioners, and nurses) with representation from both academic and community health settings and investigators involved in perinatal research (eg, clinical researchers and health services researchers); (3) public policy members: individuals involved in development of guidelines, regulation, and payment for pregnancy and postpartum care (eg, clinical guideline developers, public health representatives, and medical insurance payer representatives).

Recruitment

We aim to recruit a minimum of 20 public members, 20 providers and researchers (including a mixture of academic and community providers), and 20 public health and public policy members, with balanced representation across identities, including race and US geographic regions. Potential participants will be invited to participate in the Delphi survey with a personalized email describing the project. Public participants, including patients who have experienced prenatal care and their support people, will be recruited through patient organizations and community members affiliated with the ACOG and other national maternity care organizations. Patient advocacy groups that serve historically marginalized populations (eg, pregnant people of color) will be specifically contacted through professional networks of the steering committee and professional organizations to ensure the representation of diverse perspectives. Following these initial contacts, we plan to use snowball sampling, a research technique in which recruited individuals help to identify other potential participants, with a focus on expanding the diversity of geography and lived experiences of included perspectives. Prenatal providers and researchers will be recruited through professional maternity care organizations (eg, the ACOG, Society of Maternal Fetal Medicine, American Academy of Family Physicians, and American College of Nurse Midwives). Additional leaders in prenatal care practice and research will be identified by the steering committee and invited to participate. Public policy members will be recruited from leading organizations supporting prenatal care policy and payment such as the ACOG, Centers for Disease Control and Prevention, and medical insurance payers. Participants must be able to speak and read English fluently, but no other exclusion criteria will be applied. Baseline demographic information (age, gender, race, and ethnicity) and practice information (if a prenatal care provider) will be obtained for each participant at the beginning of the survey. Participants will be asked to complete the survey in 7 days, with a reminder email sent at the end of 14 days to prompt completion. Participation will be optional and consent to participate will be implied if a contributor responds to the survey.

Delphi Procedures

Before starting the survey, participants will be assigned a unique identifier to anonymize their responses and allow identification and linkage of individual responses in rounds of the Delphi exercise and feedback. Participants will be invited to provide their name and consent to be acknowledged as a member of the Delphi panel in the publication arising from this research. We anticipate a 3-round survey; however, the round 2 results will be reviewed by the steering committee to consider the need for a further Delphi survey round. All participants who complete the first round of the Delphi exercise will be invited to participate in the second. All participants who complete the second round will be invited to participate in the third. The first-round survey will include scoring of core outcome measurement items informed by the preliminary list from phase 1. Outcomes will be ranked on a 1-9 Likert scale, ranging from least important to critical importance (1-3 is of limited importance, 4-6 is important but not critical, and 7-9 is critical) [16]. In round 1, participants can suggest new items to be included in the second round. If 2 or more participants suggest an additional core outcome measure, it will be reviewed by the steering group and unique outcomes will be entered into round 2. All core outcome measures from round 1 will be carried forward to round 2. Participants will also be given the opportunity to share explanations for their ratings through web-based message boards.

Following round 1, the study advisory board will calculate the median and range of scores for each round 1 outcome by the stakeholder group, as well as the pooled median and range for all participants. Explanations shared through message boards will also be collated and shared with scoring summaries. For each round, the number of participants who were invited but do not participate (ie, attrition rate) will be calculated and shown in the final publication of the COS. Prior to completing round 2, each participant will receive their own score on each potential core outcome measure, as well as the scores by stakeholder group and overall. Participants will be asked to reflect on their own scores and on the scores of other participants before rescoring each individual outcome. After the round 2 survey has closed, the percentage of participants scoring each outcome will be calculated and tabulated for each individual, the stakeholder groups, and the overall pooled group. If 70% of the core outcomes have reached a consensus to be either included or excluded (as defined below) after round 2 of the Delphi survey, the third round of the Delphi will be omitted, and the group will proceed to the consensus meeting. If participants have not come to a consensus at the conclusion of round 2, similar procedures will be repeated for round 3.

Consensus for inclusion will be defined as when ≥70% of participants scored the outcome “critical” for decision-making (a score of 7-9) and <15% of participants in the stakeholder group scored the outcome of “limited importance for decision-making” (a score of 1-3). Consensus for an outcome to be excluded from the COS will be defined when ≥70% of participants in the stakeholder group scored the outcome of “limited importance for decision-making” (a score of 1-3) and <15% of participants in the stakeholder group scored the outcome as “critical for decision-making” (a score of 7-9) [11]. Although there is no consensus regarding the ideal number of outcomes to include in a COS, based on existing literature and expert opinion, the steering committee has established a preset goal of 10 outcomes for the COS to enable the implementation and use of the COS [17]. Items that reach consensus to be included (as defined above) for all 3 stakeholder groups will be automatically included in the final set of FORCAST COS recommendations, even if there are more than 10 core outcomes. Items that reach consensus to be excluded (as defined above) by all 3 stakeholder groups will be removed. If after the final

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round of the Delphi survey no core outcome measures are excluded, the steering committee will determine outcomes to be brought forward to the consensus meeting using at least one of the following three criteria: (1) the mean outcome measure is scored as critical (a score of 7-9) by ≥70% of all participants included in the Delphi survey; (2) the top 10 outcome measures from the 3 different stakeholder groups (public members, prenatal care providers and researchers, and public policy members); or (3) outcome measures considered critically important by ≥70% of 1 or more of the different stakeholder groups [17].

Phase 3: Holding a Consensus Meeting to Identify the Main Items to be Included in the COS

A web-based consensus meeting will be held to review outcomes without consensus, resolve remaining discrepancies, and approve a final COS for the frequency of scheduled prenatal care visits. The consensus meeting will include at least 7 of the 9 steering committee members and 3 representatives from each of the 3 stakeholder groups (9 members), selected to maximize diversity, as voting members. Additionally, any participant who completed all 3 rounds of the Delphi survey will be invited to observe and provide their perspective in discussions. The meeting will begin with an initial briefing on the purpose and scope of the meeting, including a summary of the results from the initial rounds of the Delphi, outcomes with consensus for inclusion and exclusion, and outcomes where consensus has yet to be reached. The panel will begin with outcomes that reached consensus from all stakeholder groups for inclusion or exclusion to approve those results. The panel will next consider items that did not reach a consensus. These items will be the focus of the meeting. All consensus meeting participants will be given an opportunity to discuss each item and share their perspectives on why it should or should not be included in the final COS. Members of the steering group and the 3 representatives from each stakeholder group will receive a summary of the results and be asked to independently consider items remaining that did not reach consensus to be either automatically included or excluded. The steering committee and stakeholder representatives will then take a majority vote on whether the core outcome measure should be included in the final COS. While the preset goal of the consensus meeting is to encompass no more than 10 outcomes, if it is determined that more than 10 outcomes are necessary, these additional outcomes will be included. A summary of this process and the voting results will be published with the final report. Those outcomes excluded will be listed in the final publication. The final COS will be sent to all participants who participated in the 3 Delphi rounds in order to give them the opportunity to comment on the final results. The steering committee will draft the FORCAST COS guideline for publication and dissemination.

Ethical Considerations

The study was determined exempt by the University of Michigan institutional review board, as it was deemed nonhuman subject research (HUM00217486).

Results

The Delphi survey was initiated in July 2022 with 71 invited stakeholders. A web-based consensus conference was conducted on October 11, 2022. Data are currently under analysis with plans to submit them in a subsequent manuscript.

Discussion

Applying a COS for the frequency of recommended scheduled prenatal care visits and mode of visit interaction is needed to assist forthcoming clinical studies, systematic reviews, and evidence-based clinical guidelines to decide which prenatal care approach has the strongest efficacy and clinical usage, and for whom. Many prenatal care interventions, including laboratory tests, vaccinations, and routine screenings, are supported by robust randomized controlled trial evidence with consistent outcomes demonstrated through meta-analyses. However, schedules and methods of prenatal care delivery recommendations overall have not yet been subjected to these rigorous standards of assessment.

Maternity care stakeholders, including health care providers, health systems leaders, and payers, have numerous methods of prenatal care delivery to choose from, including the traditional visit schedule (visits every 4 weeks until 28 weeks, every 2 weeks until 36 weeks, and weekly until delivery); reduced visit schedules (8-9 visits based on necessary prenatal services); telemedicine; group prenatal care; and others. Establishing this COS may potentially generate a set of measures for assessing the relationship, effect, and magnitude of prenatal care visit schedules on maternal and infant health outcomes and help stakeholders to determine the comparative value of recommended prenatal care visit schedules. Establishing a COS is paramount to ensure pregnant individuals have access to the most effective prenatal care recommendations, delivered through the most efficient care delivery model.

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We wish to thank Lamiya Ahmed and Megan McReynolds from the American College of Obstetricians and Gynecologists for the organizational support of this project and providing layperson feedback for core outcome set definitions as well as editing the manuscript as public member representatives. We also wish to thank Sarah Block for her assistance with the preparation of this manuscript.

BC was affiliated with the Department of Medical Education at the University of Tennessee College of Medicine, UT Health Sciences Center at the time of the trial and is currently affiliated with the Baptist University College of Osteopathic Medicine, Baptist Health Sciences University, Memphis, TN.

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Data Availability

All data sets used and analyzed during the FORCAST study will be held by the FORCAST team at alexfrie@med.umich.edu

Authors' Contributions

MT and AFP are the chief investigators; they conceived the study and led the proposal and protocol development. All authors made substantial contributions to the conception and design of the core outcome set study. B-HN was the lead trial methodologist. MT and AFP drafted the manuscript. All authors commented on revisions to draft versions of the manuscript, read, commented on, and approved the final manuscript. All authors are members of the overall FORCAST study team.

Conflicts of Interest

AFP is a consultant for Maven. TAMS is a consultant to MCPAP for Moms as obstetric engagement liaison, which is supported via Beacon Health Options via the Massachusetts Department of Mental Health and Medical Director of Lifeline for Moms through UMass Chan Medical School; both focus on perinatal mental health. TAMS has received a speaker honorarium from Miller Medical Communications. The remaining authors declare that they have no competing interests.

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Abbreviations

ACOG: American College of Obstetricians and Gynecologists
COS: core outcome set
FORCAST: frequency of prenatal care visits

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Protocol

Duration of Protection From Pneumonia After Pneumococcal Vaccination in Hemodialysis Patients (DOPPIO): Protocol for a Prospective Multicenter Study

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Abstract

Background: Pneumonia is a leading cause of death in patients with end-stage chronic kidney disease treated with dialysis. Current vaccination schedules recommend pneumococcal vaccination. However, this schedule disregards findings of rapid titer decline in adult hemodialysis patients after 12 months.

Objective: The primary objective is to compare pneumonia rates between recently vaccinated patients and patients vaccinated more than 2 years ago. As an exploratory objective, antipneumococcal antibody titers in hemodialysis patients will be determined as a function. Factors influencing antibody kinetics will be identified.

Methods: Within this prospective multicenter study, we aim to compare 2 strata of vaccinated patients: those recently vaccinated and those vaccinated more than 2 years ago. A total of 792 patients will be enrolled. Twelve partner sites (within the German Centre for Infection Research [DZIF]) with allocated dialysis practices participate in this study. All dialysis patients who are vaccinated against pneumococcal infection in accordance with Robert Koch Institute guidelines prior to enrollment will be eligible. Data on baseline demographics, vaccination history, and underlying disease will be assessed. Pneumococcal antibody titers will be determined at baseline and every 3 months for 2 years. DZIF clinical trial units coordinate titer assessment schedules and actively follow-up on study patients for 2-5 years after enrollment, including validation of end points of hospitalization, pneumonia, and death.

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Results: The study has enrolled 792 patients and the last follow-up has been completed. Currently, the statistical and laboratory analyses are ongoing.

Conclusions: Results will increase physician adherence to current recommendations. Establishing a framework for the efficient evaluation of guideline recommendations through a combination of routine and study data will inform the evidence base for future guidelines.

Trial Registration: ClinicalTrials.gov NCT03350425; https://clinicaltrials.gov/ct2/show/NCT03350425

International Registered Report Identifier (IRRID): DERR1-10.2196/45712

(JMIR Res Protoc 2023;12:e45712) doi:10.2196/45712

KEYWORDS

Streptococcus pneumoniae; pneumococcal; vaccination; hemodialysis; clinical trial; vaccine; pulmonary; pneumonia; infectious disease; communicable disease; dialysis; kidney

Introduction

Background

The global burden of disease continues to shift from acute communicable to chronic noncommunicable diseases and from years of life lost to years lived with disability [1]. Advanced chronic kidney disease (CKD; stages 3, 4, and 5 out of 5) is among the most common chronic health conditions in Germany [2]. Among CKD 5D (chronic kidney disease stage 5 with an indication for dialysis) patients, acute infections remain a leading cause of morbidity, mortality, and costs [3]. The most common infectious disease in CKD 5D patients is vaccine-preventable pneumonia. Recommendations in current vaccination guidelines acknowledge this substantial risk [4,5].

Observational studies suggest that pneumococcal vaccines lower mortality and morbidity in CKD 5D patients [6,7]. While a recent meta-analysis demonstrated the efficacy of pneumococcal vaccination in reducing pneumonia in the overall adult target population [8], randomized or well-designed prospective studies in a hemodialysis population are still lacking. Prior immunological studies in hemodialysis patients have been limited by low patient numbers and mixed populations (CKD 1-4, hemodialysis, and renal transplant recipients) [9]. While these studies suggest good immunogenicity of the vaccines, no attempts were made to verify the relevance of titers toward clinical end points in this population.

Current vaccination schedules recommend pneumococcal vaccination for patients older than 60 years or at increased risk for invasive pneumococcal disease every 6 years [4,5]. However, this schedule ignores preliminary findings of rapid titer decline in hemodialysis patients. Specifically, titers seem to decline substantially after 6 to 12 months in adult dialysis patients [10]. A limited number of studies with a longer follow-up period suggest a possible benefit of revaccination after 2 years [11,12].

Scientific Rationale

Pneumonia is a leading cause of death in patients with end-stage chronic kidney disease (stage 5) treated with dialysis (CKD 5D). Acknowledging that many infectious complications are vaccine-preventable, specific recommendations have been issued for patients at risk.

In CKD 5D patients, these recommendations are based on weak evidence, namely immunologic studies [9] demonstrating the induction of antibody production and retrospective cohorts compare vaccinated to unvaccinated patients. Until today, not a single prospective study demonstrating a clinical benefit of pneumococcal vaccination in hemodialysis patients has been published. Furthermore, the aforementioned immunological studies suggest a rapid decline of protective antibodies in such patients, calling the current Robert Koch Institute (RKI) recommendation of vaccinating every 6 years into question.

While further research into the efficacy of pneumococcal vaccinations in hemodialysis patients is required, withholding vaccines would be unethical. However, comparing vaccinated patients to patients unwilling or unable to be vaccinated is likely to be a biased approach. We will thus compare 2 strata of vaccinated patients—those recently vaccinated and those vaccinated more than 2 years ago—concerning their protective antibody titers and their rates of pneumonia. We hypothesize that patients vaccinated more than 2 years ago, while in line with the current recommendation, no longer possess sufficient antibody response (<0.35 µg/mL serotype-specific IgG as defined in the World Health Organization [WHO] recommendation [13]) and thus have a risk of pneumonia comparable to an unvaccinated patient. Simultaneously, we will analyze titers of protective antibodies over time and identify factors predicting a more rapid decline.

Objectives

Primary Objective

The primary objective is to compare pneumonia rates between newly vaccinated hemodialysis patients and those vaccinated against pneumococcal infection more than 2 years ago.

Explorative Objectives

The explorative objectives are as follows:

- To describe the pneumococcal antibody titers in hemodialysis patients as a function of time since vaccination
- To determine factors influencing antibody kinetics (eg, age, prior or ongoing immunosuppression, medication, and prior vaccination history)
- To explore the relationship between antipneumococcal antibody titers and the incidence of pneumonia in

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hemodialysis patients and to extrapolate a possible cutoff for protection from pneumonia
- To evaluate the role of patients' history (eg, underlying kidney disease) and clinical course (eg, prior hospitalizations) on pneumonia and vaccine response

Methods

Study Design

This is a prospective, multicenter, noninterventional study of vaccine efficacy in hemodialysis patients. All dialysis patients who are vaccinated against pneumococcal infection in accordance with RKI guidelines before enrollment will be eligible. Eligibility depends on the agreement of signing an informed consent allowing for data entry into the study electronic case report form (eCRF) and participation in the electronic quality registry, thus enabling data transfer from the patient's Kuratorium für Dialyse und Nierentransplantation e.V. (KfH) electronic health record into the eCRF, titer assessments, and active follow-up observation. A minimum of 792 patients will be enrolled.

Participating sites will screen all hemodialysis patients at their outpatient dialysis clinic for eligibility. Eligible patients will be approached and informed by their physicians. If a patient agrees to participate in the study and signs an informed consent form (ICF), basic data regarding vaccination history, underlying disease, and so on will be entered or imported electronically into the study eCRF. Pneumococcal antibody titers will be drawn at baseline and every 3 months. For newly vaccinated patients, baseline titers will be drawn 4 weeks after vaccination. Deutsches Zentrum für Infektionsforschung (DZIF; English: German Center for Infection Research) clinical trial units (CTUs) will coordinate titer assessment schedules and inform the participating physicians of upcoming blood samplings. The samples will be taken on dialysis days from an already inserted-intravascular catheter. DZIF CTUs will actively follow up on study patients for 2-5 years after enrollment. This follow-up will include validation of all hospitalizations and deaths documented in the electronic registry to assess whether the primary end point (all-cause pneumonia) occurred. During months 25-30, only the primary end point will be recorded (ie, no blood samples will be taken). Additionally, dialysis units will be contacted every 6 months to assess if pneumonia occurred that did not require hospitalization. Blood samples will be stored frozen at DZIF CTUs, and titers will be analyzed at the end of this study. All therapies and diagnostics, including vaccinations, will be administered solely as part of the clinical routine and as recommended by appropriate guidelines (eg, RKI Ständige Impfkommission [STIKO] recommendations). Thus, Arzneimittelgesetz (AMG) does not apply to this study, and participating physicians do not require Good Clinical Practice (GCP) certification.

Data Collection

Study nurses will enter data into the eCRF either directly or by transfer of an extract from the patient's electronic registry file (Qualität in der Nephrologie [QiN]; English: Quality in Nephrology database). The registry will also alert the study nurse to events during follow-up such as hospitalization, death, and transfer out of the dialysis unit, which are reliably captured because they are needed for billing purposes.

The central data repository will be the eCRF. Source documents will be stored in each patient's study file.

Study Procedure

In principle, all KfH dialysis practices will be eligible to participate in this study. KfH practices can be considered representative of the German dialysis population since they are widely distributed throughout Germany and about 20%-25% of all hemodialysis patients are treated there. Site selection will depend on the willingness of the attending physicians to participate and key characteristics of the practice (eg, site location and number of patients). Criteria for site selection will be developed by QiN-group and DZIF-Köln. A number of suitable KfH dialysis practices will be allocated to each of the 12 DZIF CTU sites: Universitätsklinikum Bonn, Medizinische Klinik Borstel, Universitätsklinikum Eppendorf, Universitätsklinikum Gießen und Marburg, Standort Gießen, Medizinische Hochschule Hannover, Universitätsklinikum Heidelberg, Universitätsklinikum Köln (AöR), Universitätsklinikum Schleswig-Holstein/Campus Lübeck, Universitätsklinikum Gießen und Marburg, Standort Marburg, Klinikum der Universität München, Technische Universität München, and Universitätsklinikum Tübingen.

QiN-group will assist DZIF CTU personnel with site selection and internal KfH study participation formalities. DZIF CTU personnel will cooperate with the KfH physicians to assist in setting up subject prescreening and informed consent procedures. Informed consent will be obtained by treating physicians.

The sample size has been calculated to demonstrate a significantly lower all-cause community-acquired pneumonia (CAP) rate in newly vaccinated patients compared to patients vaccinated more than 2 years before enrollment.

The incidence of pneumonia in hemodialysis patients was reported as 29.0/100 patient-years (py) [14]. Data on the efficacy of pneumococcal vaccines for preventing pneumonia in hemodialysis patients is lacking. However, a recent meta-analysis demonstrated pneumococcal vaccination to result in a relative risk for pneumonia of 0.72 (95% CI 0.69-0.94) in an immunocompetent target population (ie, adults at risk or >65 years) [8].

In general, immunological studies in hemodialysis patients have been carried out with limited patient numbers and in mixed populations (CKD, hemodialysis, and renal transplant recipients) [9]. Most studies suggest good initial immunogenicity, but titers seem to significantly decline after 6 to 12 months in adult dialysis patients [10]. The limited number of studies with longer follow-up periods suggests a possible benefit of revaccination after 2 years [11,12].

For the purpose of this calculation, we assume protection from pneumonia in the first 2 years to be equal to the protection recently demonstrated in an adult immunocompetent target population (relative risk 0.72) and afterward return to baseline. Thus, expected rates of pneumonia are 29.0/100 py in patients

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vaccinated >2 years ago and 20.88/100 py in patients vaccinated <2 years ago, respectively. To demonstrate the superiority of a more recent vaccination in preventing pneumonia with α=.05 and (1–β)=0.80, we would thus require 2 groups of 442 patients each (884 patients overall). Furthermore, the rate of pneumonia is also likely to be greater in an underprotected population than seen in the overall hemodialysis population, which includes a relevant number of freshly vaccinated patients. Additionally, the possibility of an unbalanced distribution of recently vaccinated patients (in a ratio of up to 1:7) was considered. A first statistical analysis will be discussed in an interim study report after 18 months.

Amendment After Interim Study Report

After an enrollment period of 18 months, which had been extended twice, 710 patients had been included in the study and had a fully documented vaccination status, 174 less than planned. 596 had been vaccinated less than 2 years ago, and 114 had been vaccinated 2 or more years before enrollment, respectively. This represents a ratio of 1:5, which was well within the range of an unbalanced patient distribution, which had been explored in the sample size calculation. Assuming that further recruitment would continue at this ratio and that risk reduction remained at 0.72, 792 patients were then considered sufficient if the observation period was extended to 2.5 years. These assumptions yielded a power (1–β) of 0.81 while keeping the type-I error at α=.05.

Eligibility Criteria

Inclusion Criteria

The inclusion criteria included:

1. Patients who signed ICF, including enrollment in the registry database (QiN-registry)
2. Patients with stage 5 CKD treated with chronic hemodialysis
3. Patients who are vaccinated against pneumococcal infection in accordance with current STIKO recommendations
4. Patients who were 18 years or older

Exclusion Criteria

The exclusion criteria included patients unwilling or ineligible for vaccination against pneumococcal infection under current STIKO recommendations.

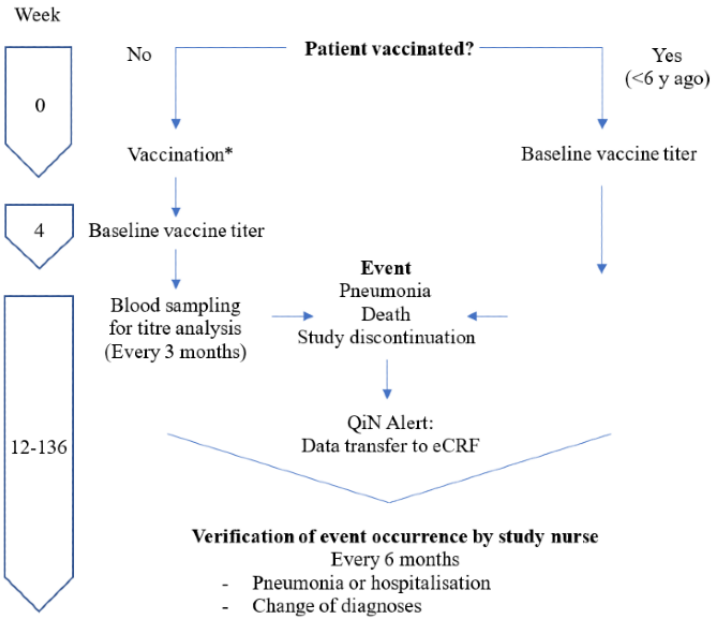
A subject may withdraw from the clinical trial at any time for any reason without consequences. Discontinuation from the study will have no influence on the availability of vaccination for that patient. In case of premature discontinuation, the reason for discontinuation should be collected, but it is not obligatory. In the event of withdrawal, all blood samples will be destroyed according to data protection requirements. Data cannot be removed from already-completed studies or scientific analyses. A subject who discontinues the trial will not be replaced.

Enrollment of Study Subjects

Eligible study subjects will be identified by their dialysis physician. If the subject does satisfy eligibility criteria and signs the ICF, he or she will be enrolled into the Duration of Protection From Pneumonia After Pneumococcal Vaccination in Hemodialysis Patients (DOPPIO) study by entering their data into the enrollment log and registering the subject in the eCRF. Basic data regarding vaccination history, underlying disorders, and so on will be captured directly in the study eCRF or transferred into the eCRF from the QiN database. The study's conduct is illustrated in Figure 1.

Blood samples for pneumococcal antibody titer analysis will be drawn at baseline and every 3 months (with a range of 6 days). For newly vaccinated patients, baseline titers will be drawn 4 weeks after vaccination (Figure 1). A total of 6750 blood samples from 789 study subjects will be collected and analyzed.

Figure 1. Schedule of vaccine titer assessments in the course of the Duration of Protection From Pneumonia After Pneumococcal Vaccination in Hemodialysis Patients (DOPPIO) study. *Decision for or against vaccination will be based upon the advice of the treating physician previously (along STIKO [Ständige Impfkommission]–criteria) and is not related to DOPPIO. eCRF: electronic case report form; QiN: quality in nephrology.



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DZIF CTU study nurses will coordinate titer assessment schedules and inform participating physicians of upcoming blood samplings. Samples will be drawn over an existing venous or arteriovenous access before dialysis and thus constitute only a minimal additional burden for both patients and physicians. All titers will be analyzed at the end of the study. An enzyme immunoassay will be performed to detect the presence of pneumococcal antibodies.

Management of Samples

For all subjects, 9 mL of blood will be collected in a 9-mL tube provided by the sponsor. Samples will be taken every 3 months after the baseline sample. For newly vaccinated patients, baseline samples will be taken 4 weeks after vaccination.

Immediately prior to the blood draw, the staff member performing the procedure will verify the subject's identity. A label will be attached to the tube. The tube will be centrifuged within 3 hours after sampling. The tube will be shipped to the allocated DZIF site and frozen within 24 hours. Subject number, date of sampling, number of aliquots, date and time of preparation, and the subject's consent are documented in a sample identification list at the KfH dialysis practices and recorded as source data. Samples will be stored at DZIF CTUs and sent frozen in 1 batch to the laboratory at the end of the study. Results will be transferred electronically to the study nurses at the end of the study for recording into the eCRF.

Data Management Plan

The data will be recorded securely and electronically. The data are the sole property of the sponsor and must not be made available in any form to third parties, except for authorized sponsor's representatives or appropriate regulatory authorities, without written permission from the sponsor. Data obtained from KfH via QiN becomes the property of the sponsor, as specified in the agreement between KfH and DZIF. Only data from enrolled patients will be transferred. The investigator will ensure that all data are entered legibly, completely, accurately, and conform to source documents.

The investigator will review and approve data, with the investigator's validation serving as attestation of the investigator's responsibility for ensuring that all data are complete, accurate, and authentic.

All information obtained during the study will be recorded digitally in conformity with the applicable laws and regulations.

Ethics Approval

Overview

The study was approved by the lead Ethics Committee of the Medical Faculty of the University of Cologne (Cologne, Germany; No. 17-274) and subsequently received secondary approval by the 11 Ethics Committees of the respective DZIF CTU sites (ref. DZIF CTU site list, section study procedure).

The study was further approved by the Paul-Ehrlich-Institut (PEI), Federal Institute for Vaccines and Biomedicines, as a noninterventional study (NIS401) and registered at ClinicalTrials.gov with the identifier NCT03350425.

The study will be performed in accordance with all applicable laws and regulations, including the International Conference on Harmonization Guideline for Good Clinical Practice (GCP), the ethical principles that have their origins in the Declaration of Helsinki (current official version: World Medical Association [15]), and applicable privacy laws such as national laws and the General Data Protection Regulation, which has been in effect since May 25, 2018. The minimum required deidentified personal data will be captured in an electronic database, and any publication of study results will be anonymized, only containing summarized statistical analyses.

Subject-Informed Consent

KfH physicians will assist in setting up subject prescreening and informed consent procedures. Informed consent will be obtained by the treating physicians. The ICF will be signed prior to any study activities by the subject and treating physician conducting the informed consent process. No compensation is foreseen for study participants.

Study Conduct and Statistical Analyses

The primary objective of this study is to compare pneumonia rates and outcomes between both groups. To achieve this, the raw number of events and raw rates of events per 100 patient years will be computed. For each group, the mean, median, SD, IQR, and minimum and maximum of demographical variables like age and sex will be computed. These observed variables will be used to build a Cox proportional hazard model. If applicable, this model will incorporate time-varying covariates and consider recurring events. To quantify the expected protective effect of a high titer level, multiple functional relationships will be explored, including but not limited to linear, quadratic, and step functions. Step functions will be created by dividing the titer levels into 10 mutually exclusive strata and estimating each risk individually. If possible, the largest difference between 2 neighboring strata will be identified as a threshold for an adequate titer level.

The secondary objectives of this study are to describe antibody titers as a function of time and factors influencing antibody kinetics. Descriptive statistics for titer levels at all intervals will be computed for absolute values as well as relative values (relative to the first observed or personal maximum). Levels for patients grouped by age, sex, and other variables of interest will be calculated. To allow a comparison, the mean, median, SD, IQR, and minimum and maximum titer levels will be calculated.

To identify which factors influence the absolute antibody titer level, multiple multivariate models will be built. In patients with available titers, risk factors for insufficient protection will be determined by multiple regression analyses of data including vaccination history and timing, medication exposure since last vaccination, history of underlying kidney disorder, dialysis, and demographic factors.

The titer levels will be assessed graphically by comparing boxplots of the titer levels at different time intervals. Concurrent titer levels will be tested for statistically significant differences by using a *t* test or a Mann-Whitney U test, whichever is applicable.

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Differences in hospitalization as well as vaccination rates between KfH centers will be studied. QQ plots and tests for normal distribution will be performed on the observed hospitalization rates. Vaccination rates will be studied for outliers. For all factors used in model building, a region of common support will be established.

Results

The study has enrolled 792 patients and the last follow-up has been completed. Currently, the statistical and laboratory analyses are ongoing.

Discussion

Overview

Patients on dialysis are among the best documented for any chronic condition in outpatient medicine. This prospective study is among the first to capitalize on that and to demonstrate the integration of routine data and study data into a single data set. This framework for the efficient evaluation of guideline recommendations will form the evidence base for future guidelines and will increase physician adherence to current recommendations.

Principal Results

Data on baseline demographics, vaccination history, and underlying disease will be assessed. Pneumococcal antibody titers will be determined at baseline and every 3 months for 2 years. DZIF CTUs coordinate titer assessment schedules and actively follow up on study patients for 2 years after enrollment, including validation of hospitalization, pneumonia, and death. We will analyze antibody titers over time and identify factors influencing antibody kinetics. In addition, the relationship between antibody titers and the incidence of pneumonia in hemodialysis patients will be investigated, and a possible cutoff for protection from pneumonia will be extrapolated.

Limitations

Our study has several limitations. The study is conducted during the SARS-CoV-2 pandemic, which leads to interruptions in observation (especially serologically) and a novel cause of pneumonia. In addition, the study does not investigate the causative pathogen of pneumonia. However, *Streptococcus pneumoniae* has historically been the most common cause of pneumonia, by far [16], and remains the most common bacterial cause of CAP, leading to the hospitalization of adults today. In the United States, 5 to 15 percent of CAP cases have been attributed to *S pneumoniae* [17-19]. More recent comprehensive molecular testing of lower respiratory tract specimens indicates that this is an underestimate and suggests more than 35% of cases may be due to *S pneumoniae* [20]. This percentage has been proven to be even higher in Europe [21,22]. Finally, the study was performed in a single country with a homogeneous population of participants, which limits generalizability to other populations.

Nonetheless, we believe that the study is suited to answer the clinically important question of the duration of antipneumococcal vaccination.

Conclusions

Current vaccination schedules recommend pneumococcal vaccination for CKD-5D patients every 6 years. However, this timing disregards findings of rapid titer decline in adult hemodialysis patients after 6 to 12 months. By comparing pneumonia rates between recently vaccinated patients and those who were vaccinated more than 2 years ago, we may estimate the duration of protection by antipneumococcal vaccination. In addition, antipneumococcal antibody titers in hemodialysis patients will be determined as a function of time since vaccination and provide further conclusions.

Through its conduct, this prospective study will increase physician adherence to current recommendations. Establishing a framework for the efficient evaluation of guideline recommendations through a combination of routine and study data will inform the evidence base for future guidelines.

Data Availability

Data will be available as publication after finalization of the study.

Conflicts of Interest

SM reports grants from the University of Cologne (KoelnFortune), grants from the Dr Manfred Plempel Stipend, grants from German Centre for Infection Research (DZIF) Clinical Leave, and personal fees from Octapharma outside the submitted work. JJV has personal fees from Merck/MSD, Gilead, Pfizer, Astellas Pharma, Basilea, DZIF, University Hospital Freiburg/Congress and Communication, Academy for Infectious Medicine, University Manchester, German Society for Infectious Diseases (DGI), Ärztekammer Nordrhein, University Hospital Aachen, Back Bay Strategies, German Society for Internal Medicine (DGIM), Shionogi, Molecular Health, Netzwerk Universitätsmedizin, Janssen, and NordForsk, and grants from Merck/MSD, Gilead, Pfizer, Astellas Pharma, Basilea, DZIF, German Federal Ministry of Education and Research (BMBF), University of Bristol, and Rigshospitalet Copenhagen. OAC reports grants or contracts from Amplyx, Basilea, BMBF, Cidara, DZIF, Directorate-General for Research and Innovation (EU-DG RTD, 101037867), F2G, Gilead, Matinas, MedPace, MSD, Mundipharma, Octapharma, Pfizer, and Scynexis; consulting fees from Abbvie, Amplyx, Biocon, Biosys, Cidara, Da Volterra, Gilead, IQVIA, Janssen, Matinas, MedPace, Menarini, Molecular Partners, Mycosis Study Group Education & Research (MSG-ERC), Noxxon, Octapharma, Pardes, Pfizer, PSI, Scynexis, and Seres; honoraria for lectures from Abbott, Abbvie, Al-Jazeera Pharmaceuticals, Astellas, Gilead, Grupo Biotoscana/United Medical/Knight, Hikma, MedScape, MedUpdate, Merck/MSD, Mylan, Noscendo, Pfizer, and

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Shionogi; payment for expert testimony from Cidara; participation on a data safety monitoring board or advisory board from Actelion, Allecra, Cidara, Entasis, IQVIA, Janssen, MedPace, Paratek, PSI, Pulmocide, Shionogi, and The Prime Meridian Group; a patent at the German Patent and Trade Mark Office (DE 10 2021 113 007.7); stocks from CoRe Consulting; and other interests from DGHO, DGI, ECMM, ISHAM, MSG-ERC, and Wiley outside the submitted work. BJL reports grants from Pfizer during the conduct of the study. The remaining authors have nothing to disclose.

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Abbreviations

CAP: community-acquired pneumonia
CKD: chronic kidney disease
CTU: clinical trial unit
DOPPIO: Duration of Protection From Pneumonia After Pneumococcal Vaccination in Hemodialysis Patients
DZIF: Deutsches Zentrum für Infektionsforschung (German Center for Infection Research)
eCRF: electronic case report form
ICF: informed consent form
KfH: Kuratorium für Dialyse und Nierentransplantation e.V.
QiN: Qualität in der Nephrologie (Quality in Nephrology)
RKI: Robert Koch Institute
STIKO: Ständige Impfkommission

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Protocol

Understanding Resilience and Mental Well-Being in Southwest Indigenous Nations and the Impact of COVID-19: Protocol for a Multimethods Study

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Abstract

Background: Despite experiencing many adversities, American Indian and Alaska Native populations have demonstrated tremendous resilience during the COVID-19 pandemic, drawing upon Indigenous determinants of health (IDOH) and Indigenous Nation Building.

Objective: Our multidisciplinary team undertook this study to achieve two aims: (1) to determine the role of IDOH in tribal government policy and action that supports Indigenous mental health and well-being and, in turn, resilience during the COVID-19 crisis and (2) to document the impact of IDOH on Indigenous mental health, well-being, and resilience of 4 community groups, specifically first responders, educators, traditional knowledge holders and practitioners, and members of the substance use recovery community, working in or near 3 Native nations in Arizona.

Methods: To guide this study, we developed a conceptual framework based on IDOH, Indigenous Nation Building, and concepts of Indigenous mental well-being and resilience. The research process was guided by the Collective benefit, Authority to control, Responsibility, Ethics (CARE) principles for Indigenous Data Governance to honor tribal and data sovereignty. Data were collected through a multimethods research design, including interviews, talking circles, asset mapping, and coding of executive orders. Special attention was placed on the assets and culturally, socially, and geographically distinct features of each Native nation and the communities within them. Our study was unique in that our research team consisted predominantly of Indigenous scholars and community researchers representing at least 8 tribal communities and nations in the United States. The members of the team, regardless of whether they identified themselves as Indigenous or non-Indigenous, have many collective years of experience working with Indigenous Peoples, which ensures that the approach is culturally respectful and appropriate.

Results: The number of participants enrolled in this study was 105 adults, with 92 individuals interviewed and 13 individuals engaged in 4 talking circles. Because of time constraints, the team elected to host talking circles with only 1 nation, with participants ranging from 2 to 6 in each group. Currently, we are in the process of conducting a qualitative analysis of the transcribed narratives from interviews, talking circles, and executive orders. These processes and outcomes will be described in future studies.

Conclusions: This community-engaged study lays the groundwork for future studies addressing Indigenous mental health, well-being, and resilience. Findings from this study will be shared through presentations and publications with larger Indigenous and non-Indigenous audiences, including local recovery groups, treatment centers, and individuals in recovery; K-12 and higher education educators and administrators; directors of first responder agencies; traditional medicine practitioners; and elected community leaders. The findings will also be used to produce well-being and resilience education materials, in-service training sessions, and future recommendations for stakeholder organizations.

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KEYWORDS

community-engaged research; Indigenous; Native nations; COVID-19; resilience; well-being

Introduction

Background

The widespread COVID-19 pandemic has tested the limits of medical resources and public health, moved society toward a more isolated lifestyle, and challenged the lives of many, including several heavily impacted populations [1]. At the time this project started (2020), some of the populations most affected by COVID-19 in the United States were living in the 22 sovereign Native nations in Arizona. More than 103,000 cases of COVID-19 were diagnosed in the citizens of Native nations in Arizona, accounting for 50% of the cases in some counties [2]. Compared with other races and ethnicities in the United States before the COVID-19 pandemic, American Indian and Alaska Native populations (note that we use the terms American Indian and Alaska Native, Native American, Indigenous, and Native for this paper interchangeably to refer to Indigenous Peoples of the United States) were disproportionally affected by illnesses and chronic diseases and had an overall lower life expectancy [3]. Despite experiencing many adversities, American Indian and Alaska Native populations have demonstrated tremendous resilience during the COVID-19 pandemic, drawing upon Indigenous determinants of health (IDOH) and Indigenous Nation Building [4].

Purpose

Our multidisciplinary team of scholars sought to implement the study described in this paper to achieve two aims: (1) to determine the role of IDOH in tribal government policies and actions that support Indigenous mental health and well-being and, in turn, resilience during the COVID-19 crisis; and (2) to document the impact of IDOH on Indigenous mental health, well-being, and resilience of 4 specific community groups—first responders, educators, traditional knowledge holders and practitioners, and the substance use recovery community living or working (or both) in or near 3 Native nations in Arizona. The overarching research question for the study was as follows: What are the IDOH in Native nations and communities that shape mental health and well-being and, in turn, resilience during the COVID-19 pandemic? We posited that the use of IDOH, an Indigenous Nation-Building framework [5,6], and complementary data collection methods would be useful for understanding the mental health needs, assets, and resources of Native nations during the COVID-19 crisis to best formulate future research, practices, and policy initiatives [6]. Native nations have maintained a sense of autonomy as sovereign entities and have responded to the pandemic by leveraging community assets informed by language, land, history, and ceremony [7]. This research was designed to guide tribal programs to improve the mental health and well-being of Indigenous Peoples in Arizona, especially during tumultuous times such as a pandemic.

Conceptual Framework

To guide this study, we developed a conceptual framework (Figure 1) based on the IDOH, Indigenous Nation Building, and concepts of Indigenous mental well-being and resilience. Social determinants of health (SDOH) refer to conditions in the environments where people are born, live, learn, work, play, worship, and age that affect a wide range of health, functioning, and quality-of-life outcomes and risks [8]. Indigenous Peoples have unique historical, political, and social contexts that also affect health and differ from the traditional definitions of the SDOH. IDOH includes a wide variety of physical, social, and cultural conditions that can affect the health status of Indigenous Peoples [4,9]. Poverty, racism, geographic location, and education systems are examples of social impacts on the health and life expectancy of American Indian and Alaska Native populations that can put them at an increased risk for COVID-19 [9-12].

Indigenous Nation Building refers to “the political, legal, spiritual, educational, and economic processes through which Indigenous Peoples engage in order to build local capacity to address their educational, health, legal, economic, nutritional, relational, and spatial needs” [13-15]. These processes are an assertion of the federally recognized sovereignty of the Native nations. Sovereignty, applied to federally recognized Indigenous nations in the United States, means that such nations are distinct political entities with the right of self-government. Recognized through treaties, acts of congress, and presidential executive orders, Indigenous nations have a government-to-government relationship with the federal government [16,17]. During the pandemic, Native nations took the steps necessary to ensure the protection of their citizens from the threats of COVID-19 with the implementation of stay-at-home orders; weekend lockdowns (restricting citizens from leaving their communities); and the closure of businesses, establishing vaccination centers, mask mandates, and other preventive recommendations. The assertion of sovereignty serves as an important means of managing the risks to citizens’ health, a mechanism for maintaining adequate sociocultural strength, health, and well-being in Indigenous populations [18].

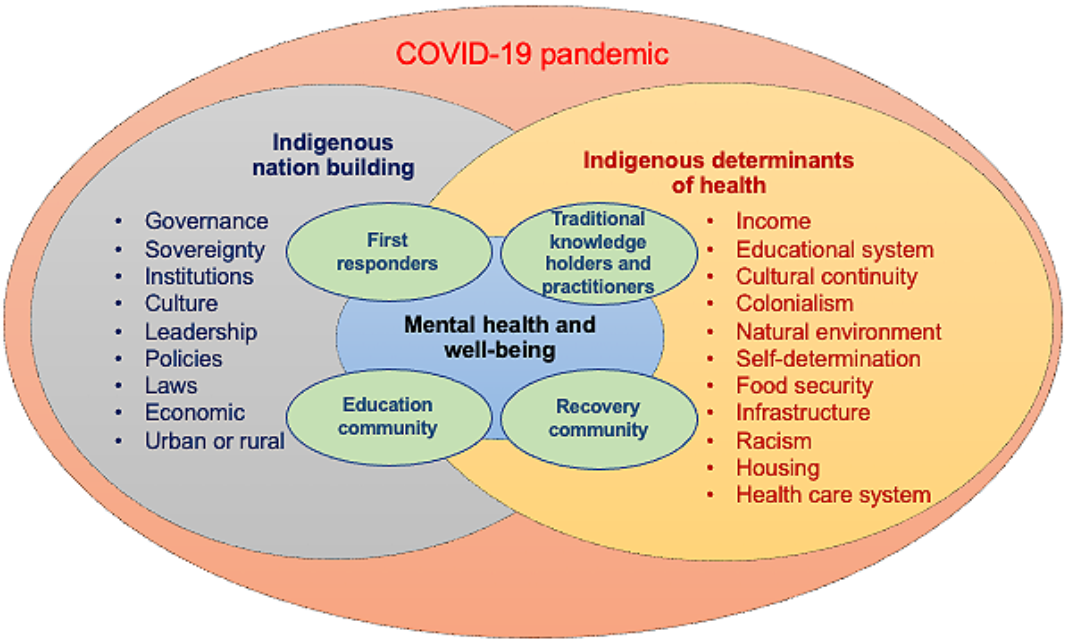
The concept of Indigenous mental health and well-being is receiving increased attention in the literature as scholars uncover the unique stressors that Indigenous Peoples face as well as the culturally distinct approaches that Indigenous nations and communities use to support resilience [19-21]. A key component of Indigenous mental health and well-being is the recognition of the impact of historical trauma. Historical trauma is a cumulative, multigenerational experience of trauma that impacts emotional and psychological well-being from one generation to the next and can disrupt the strength of the community in Native nations [22,23]. The impact of historical trauma is reflected in American Indian and Alaska Native populations

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using drugs and alcohol at younger ages and at higher rates than other populations [24-27], reporting serious psychological distress at higher rates [28], and committing suicide at younger ages than non–American Indian and Alaska Native populations [29]. Historical trauma affects Indigenous populations and manifests in many ways, including by impacting Indigenous mental health and well-being outcomes. Even with historical trauma, American Indian and Alaska Native populations have maintained their resilience through the continuation of ceremonial practices, speaking heritage languages, passing on oral histories, and implementing local strategies to reinforce social support systems and cultural capital [30].

In the United States, approximately 4.2 million Americans identify as American Indian and Alaska Native [31]. The living conditions for American Indian and Alaska Native populations vary greatly, with 78% living off reservations and 22% living on reservation lands [32]. Regardless of residence, the cultures of American Indian and Alaska Native populations generally emphasize connections to others, the past, the natural world, and traditional homelands [21,33]. This worldview is demonstrated by strong family bonds, respect for the wisdom of elders, and the maintenance of cultural traditions. These practices preserve, maintain, protect, and serve as solutions against threats to mental health and well-being in Indigenous communities [21,34].

Figure 1. Conceptual framework.



Methods

Overview

This study merged the IDOH and Indigenous Nation-Building frameworks to establish an understanding of the interrelationship of sovereignty, land jurisdiction, cultural identity, continuing effects of colonialism, and resilience that impact mental health and well-being. The research design focused on 4 groups in 3 Native nations and an urban Indigenous health center near one of these nations that have served their communities while remaining exposed to the effects of the COVID-19 pandemic or were heavily impacted by physical distancing restrictions. These groups included first responders, educators, traditional knowledge holders and practitioners, and members of the substance use recovery community.

In the analysis, mental health and well-being were not addressed from a psychological or individual clinical orientation but through a contextual and external environmental lens, otherwise understood as a systems orientation [35]. A systems orientation has been used in understanding perspectives within human service program systems and the relationship of organisms in their natural habitat, but to our knowledge, it has never been used to investigate mental health and well-being in Native communities [36].

Indigenous Guided Research

The research process was guided by the Collective benefit, Authority to control, Responsibility, Ethics (CARE) principles for Indigenous Data Governance to honor tribal and data sovereignty [37-39]. The CARE principles ensure that, when working with external research partners, Native nations receive the following: (1) collective benefit of research findings, (2) authority to control data, (3) responsible research partners who support self-determination, and (4) ethical research partners who honor the rights and well-being of sovereign nations and their community members. Individuals from 3 Native nations and an urban Indigenous health center in Arizona participated in this study with approval from their institutional review board (IRB), Tribal Council, or Cultural Preservation Office. The research approval process spanned 7 months (June 2020 to January 2021) and was preceded by multiple years of relationship building through research and service between members of the research team and each of the 3 nations. Our study was unique in that our research team consisted predominantly of Indigenous scholars representing at least 8

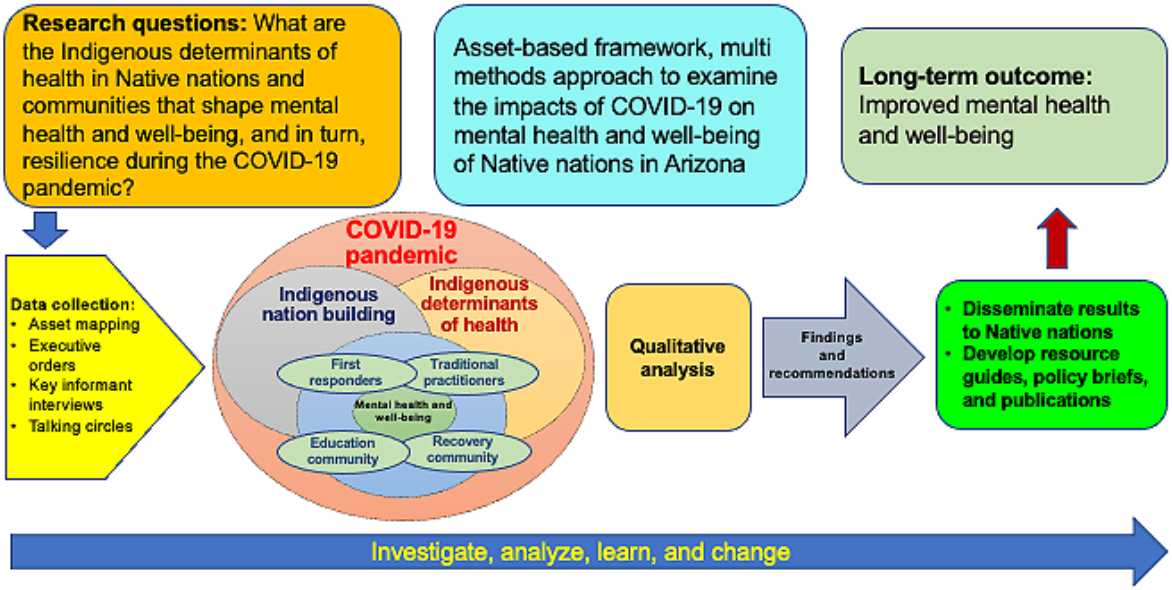
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tribal communities and nations in the United States. The members of the team, regardless of whether they identified themselves as Indigenous or non-Indigenous, have many collective years of experience working with Indigenous Peoples and are committed to the health and well-being of tribal communities. A community researcher from each Native nation was hired as a vital member of our research team to aid in recruiting participants, scheduling interviews and talking circles, translating interviews from the Native language into English, and providing overall expertise to ensure that methodologies and approaches were culturally congruent and respectful.

Research Design

The team investigated the resilience and contextual factors that either facilitated or hindered these efforts. The goal of understanding resilience was informed by the Indigenous Nation-Building framework [14,40]. As depicted in Figure 2, data were collected through a multimethods research design that documented the contextual factors that contribute to mental health and well-being among the people of the Native nations. Contextual factors included educational systems, socioeconomic status, access to food and health care, and systemic oppression. Special attention was placed on the assets and culturally, socially, and geographically distinct features of each Native nation and the communities within them. Indigenous Peoples and nations demonstrated resilience in many ways during this difficult period. American Indian and Alaska Native populations have experienced substantial and unique challenges during the pandemic, including increased levels of anxiety, stress, and depression. The team explored these emotions and resilience strategies through interviews and talking circles. Figure 2 provides an overview of the research questions, data collection methods, and the expected outcomes. This paper presents our methodological protocol for each aim.

Figure 2. Research methodology.



Aim 1: Determine the Role of IDOH in Tribal Government Policy and Action That Support Indigenous Mental Health, Well-Being, and, In Turn, Resilience During the COVID-19 Crisis

Asset Mapping

Community asset–based mapping is a process that actively seeks the best use of community resources and creates a profile of existing buildings, programs, and services in the community [41,42]. Our team began the study by searching Google Maps, publicly available reports, and other relevant community resources. A spreadsheet of electronically available assets was compiled, including the title or name of the asset, contact information, and type or category of the asset. Categories of assets included mental health; general health; education; cultural resources including traditional knowledge holders, economic, recreation, and government and social services; and other resources including religious and spiritual resources. The team consulted with community researchers and a select group of community members from each Native nation to confirm the accuracy and completeness of the lists. Next, the team worked with colleagues at our university's Geographic Information System laboratory to create resource maps. The maps were created for each of the 3 Native nations, including separate maps according to the asset type or category for each nation. The research team then reviewed the full list and maps and coded each asset using a codebook developed from key terms in the conceptual framework. At least 2 researchers independently coded each nation's asset list; any discrepancies were discussed, and a final coding was determined by the team. Finally, the team created a community resource guide for each of the 3 nations; these guides were organized by category and included both the lists and the maps of the assets identified through this phase of the study.

Executive Orders Coding

Executive orders, executive directives, and public health emergency orders were collected for each of the 3 participating nations from March 1, 2020, to June 15, 2022. Each executive order or directive (1 nation uses the term directives rather than executive orders) was scanned for content, and a team of 6

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researchers, working in pairs, developed a codebook based on the content of all the orders. The orders were coded according to the issuing authority (ie, top-ranking executive leaders or public health authority), the topics, and any requirements of the order. For example, an executive order issued by the Native nation's president or chairperson requiring employee vaccinations was coded by the nation, the issuing office or authority, and the code "vaccination requirement." Each order or directive was coded by an independent researcher and verified by a second researcher. Any discrepancies as well as the need to establish new parent or child codes were discussed by the entire coding team; final decisions were reached through consensus of the team.

Federal executive orders or directives, such as a federal mask mandate, and guidance from the Centers for Disease Control and Prevention (CDC) may have informed the executive orders, directives, or public health emergency orders of the participating Native nations. For example, the CDC issued the guidance for safety measures such as social distancing, hand washing, and mask wearing, which, in turn, was followed by governments across the country. Native nations also instituted CDC-recommended safety measures and encouraged their citizens to follow them, as evidenced in the executive orders, executive directives, and public health emergency orders examined in this study. However, as federally recognized Native nations are sovereignty entities and have a legal status higher than the states [43], the state executive orders of states adjacent to or surrounding the lands and jurisdictions of the participating Native nations are not included in the coding or analysis.

Upon the completion of the coding, the analysis will begin. Using content analysis, researchers will examine the orders to determine what actions governments took or policies were developed to support the resilience and mental well-being of their citizens.

Aim 2: Document the Impact of IDOH on Indigenous Mental Health, Well-Being, and Resilience of 4 Specific Community Groups

Recruitment

Recruitment parameters for participants were that they must be aged 18 years; identify as someone who works in or is a citizen of 1 of the 3 participating Native nations; and identify as a member of one of the four informant groups: (1) first responder—identify as a first responder (ie, they are associated with law enforcement, fire department, or emergency management training or work as emergency room doctors or nurses); (2) educator—identify as an educator or teacher; (3) traditional knowledge holder or practitioner—identify as a traditional medicine person or as being a part of a medical people association and have the knowledge and experience in maintaining, participating in, and practicing traditional Native ways of life; and (4) substance use recovery member—identify as a substance use recovery provider or an individual in substance use recovery who uses recovery services. Exclusion criteria were being incarcerated, incapacitated, or unwilling to provide informed consent to participate in the study activities or currently participating in a substance use recovery program (recovery group only). We prioritized recruiting individuals who identified as American Indian and Alaska Native. However, for some subgroups, providers and personnel included non-Indigenous individuals who worked within or for the participating communities. These individuals represented 13% (12/92) of all the interviewees. For the recovery community, the team also recruited from an urban Indigenous health center, Native Americans for Community Action, based in Flagstaff, Arizona.

Participants were recruited through email, in-person presentations to related entities and individuals within specified subgroups and communities, and face-to-face interactions. The research team used snowball sampling and social networks guided by community researchers' and investigators' community contacts.

Informed consent was obtained using multiple methods in an effort to provide flexibility as the COVID-19 situation evolved. These methods primarily included a signed informed consent form mailed to the participants, the review of an oral or web-based script via phone, and verbal consent given by the participants. If participants provided oral consent, the researchers documented the participant's name, date of consent, and specified the conditions of consent. In some cases, oral consent was provided in the participants' respective Indigenous language.

All subgroups (first responders, educators, traditional knowledge holders and practitioners, and members of the substance use recovery community) from each partnering community participated in key informant interviews. Only 1 Native nation and 3 subgroups (educators, members of substance recovery community, and traditional knowledge holders and practitioners) participated in talking circles. In an effort to follow the CDC guidelines for safety during the pandemic, interviews and talking circles were conducted via a password-secured Zoom link or by telephone. Talking circles were conducted after the interviews were completed.

Key Informant Interviews

Each participant completed an individual 1- to 2-hour interview intended to identify SDOH and the conditions that may have contributed to mental health stressors or sources of strength during the COVID-19 pandemic and IDOH contributing to stress or strength. The interviewees were given a US $25 gift card for their time. Guided by the need to obtain a representative sample, the team attempted to conduct at least 4 interviews with a goal of 10 with each subgroup from each participating nation. The protocol for the key informant interviews for all 4 subgroups was similar but had some nuances by subgroup, as described in subsequent sections for each community group. The interview questions were developed and edited by the whole team for a period of 2 to 3 months. The research team aimed to create "core" questions that could be used to analyze themes across groups and group-specific questions that allowed for the identification of group-specific challenges and solutions. Each group was asked 5 core questions, with additional questions relevant to the specific group. The 5 core questions were as follows:

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1. Please talk about your tribal government's response during the COVID-19 pandemic?
2. What does the term "mental well-being" mean to you?
3. Has your (insert Indigenous community) cultural identity affected your mental well-being during the COVID-19 pandemic? If so, how?
4. What does the term "resilience" mean to you?
5. Has your (insert Indigenous community) cultural identity affected your resilience during the COVID-19 pandemic? If so, how?

The first responder research group was interested in learning how the pandemic may have changed the workload for first responders and how changes owing to the pandemic affected them on a personal level (eg, physical, emotional, spiritual, cultural, mental, and financial levels and on the basis of family or home and food security). We were also interested in learning about the resources that were available to them and what resources they needed during the pandemic to stay healthy. Examples of group-specific questions for the first responders group were as follows:

1. Have there been any effects of COVID-19 on you personally, and if so, how? (prompts: physically, emotionally, spiritually, culturally, mentally, family, finances, and food security)
2. Has COVID-19 affected your job? If yes, how?
3. Is there anything else that could be done by people at your work to help you? (prompts: check on you, talk with you, use humor, do things different, and if so, like what?)
4. What, if any, resources are available to you to help you stay healthy? (prompts: agencies, people, and places)

The education research group was interested in understanding how educators responded to the transition from face-to-face learning to web-based learning and sometimes having to switch between the 2 modalities after in-person COVID-19 exposure. Because of the circumstances experienced by the teachers, it was particularly important for the educator research group to learn about and understand their experiences of resilience and mental well-being. Specifically, it was important to give educators time to speak about the impact of COVID-19 on them individually and on their respective professional roles in education, as well as what resources and support they accessed during that time. Another area of focus was to learn more about how the range of decision-making entities (ie, school boards, tribal governments, and federal governments) impacted their role as educators. Finally, we asked questions related to personal and classroom resources that were helpful or would have been helpful during the pandemic. The questions for this group included the following:

1. What has been the impact of COVID-19 on you? (prompts: physically, emotionally, spiritually/culturally, mentally, family, finances, and food security)
2. How has COVID-19 impacted doing your work as an educator?
   - What has helped you as an educator adapt to changes caused by COVID-19?
   - How have you responded to the ways in which COVID-19 has affected your families and students?
   - How has your broader community/school responded to COVID-19?
3. What resources have you used during this pandemic to help you stay healthy?
   - What resources have you used to support students and families?
   - What resources do you wish were available to support your health and the health of students and families?
4. Tell me about the various levels of leadership that you believe impact your role as an educator.
   - How have these levels responded?
   - How has school/district leadership responded and how has it impacted you in your professional role?

In times of uncertainty, many Indigenous Peoples went to traditional knowledge holders and practitioners for assistance in resolving health issues, and the pandemic was no exception. Given that there were no Western medicines available to combat COVID-19 at the time, traditional knowledge holders and practitioners became especially important. The questions focused on how the patients of traditional knowledge holders and practitioners were affected by the pandemic and how they were coping. Furthermore, understanding how the pandemic might have impacted the tasks and duties of traditional knowledge holders and practitioners was critical to highlighting the role of cultural capital in resilience. We asked the following questions about how traditional knowledge holders and practitioners viewed the meaning of resilience and mental well-being:

1. Have the people you serve maintained resilience during the pandemic?
   - If so, how? If not, why not?
2. Has your cultural practice been impacted by COVID-19? (prompts: physically, emotionally, spiritually/culturally, mentally, financially, and adaptations)
   - If so, how? If not, why not?
3. What do you think about the changes you made?

The members of the substance use recovery research group were particularly interested in how restrictions imposed on social gatherings affected the practice of recovery for American Indian and Alaska Native populations. Although programs exist that are specifically constructed for Native American recovery (ie, The Red Road to Wellbriety and Healing of the Canoe) [44,45] and place Native American culture as central to treatment, most recovery programs that are altered to serve American Indian and Alaska Native populations use traditional practice as an added element to mainstream programs such as Alcoholics Anonymous or Narcotics Anonymous [46]. The group process, intended to remove stigma and promote social support, is an important evidence-based practice in almost every recovery program. Most American Indian and Alaska Native cultures emphasize connectedness to tribes, clans, and families. Therefore, the recovery group asked nonleading questions such as the following to understand the impact of social restrictions on recovery:

1. Please describe to me how your work has changed because of the COVID-19 pandemic.

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2. Please describe to me any special qualities or circumstances that have allowed Native Americans in recovery to adapt positively to the new circumstances presented by the presence of the virus.
3. Please describe to me any special qualities or circumstances that have affected Native Americans in recovery to negatively respond to the new circumstances presented by the presence of the virus.

Talking Circles

The talking circle is a common and respectful way of sharing, listening, and learning among North American Indigenous Peoples [47,48]. Talking circles are also referred to as "sharing circles" by some Indigenous Peoples [47,49]. Facilitators of talking circles used open-ended questions designed to assess specific direct and indirect impacts of the pandemic and ways of adapting and responding to those impacts (resilience). Talking circles for this study lasted for 1 to 3 hours and included 2 to 6 individuals. The research team conducted 1 talking circle session with educators, 2 with substance use recovery community members, and 1 with traditional knowledge holders and practitioners, each of which consisted of members from a single participating nation. Talking circle participants were recruited through community partner agencies and by the community researchers. Each participant was given a gift card worth US $50 for their time. Each talking circle included variations in the key informant interview questions. The talking circle questions are presented in Textbox 1.

Textbox 1. Talking circle questions.

Educators

- To the extent you feel comfortable, share the impact of COVID-19 on you.
- How has COVID-19 impacted your work as an educator (principal, counselor, teacher, etc)?
- What resources have you used during this pandemic to help you stay "healthy"?
- Tell me about the various levels of leadership that you believe impact your role as an educator.

Substance use recovery community

- To the extent that you feel comfortable sharing, how have you been impacted by COVID-19?
- How has your recovery been impacted by COVID-19?
- How did you adapt to and respond to the impact on your recovery? Can you identify the methods, strategies, or specific programs that supported your recovery?
- What do the terms "mental well-being" and "resilience" mean to you?

Traditional knowledge holders

- To the extent that you feel comfortable sharing how has your cultural practice been impacted by COVID-19?
- How have you adapted and responded to those impacts?
- What methods or strategies have you used during this pandemic in your role as a practitioner/knowledge holder to support people?

Coding and Analysis

With participant permission, interviews and talking circles were audio recorded and transcribed verbatim for analysis. One subgroup transcribed the audio recordings from Native language to English for analysis. For Zoom sessions, participants had a choice to turn their video on or off during the interviews and talking circles. If a participant did not want their name to be displayed on the video screen, the community researcher helped the participant change their name to an alias name on the screen. If the participants chose to keep their video on, they were reminded that all video and audio sessions would be recorded. Once the audio segments from all sessions were saved, the video portions were deleted. If a participant did not wish to be audio recorded, then a researcher (not the facilitator) took thorough notes for further analysis. The research team deidentified all data, including any tribal affiliations or agency names before further analysis because participating Native nations requested that data should not be identified by the tribal communities. Participants were assigned a unique ID code to remove any connections to their personal identifying information. No identifying information was included in the descriptive or analytical result tables or reports.

Once interviews and talking circles were completed, the research team conducted quality checks of the audio recordings to ensure that the transcriptions were accurate and to eliminate any identifying information before analysis. A secondary codebook (similar to the asset mapping codebook) was created based on the conceptual framework presented in the *Introduction* section. Members of the research team, including researchers from American Indian and Alaska Native nations, regularly met to discuss the definitions and applications of the codes. After developing the initial draft of the codebook, all members of the coding team coded the same transcript to compare coding and address any issues with the codebook. The codebook was refined when new themes emerged. The codebook consisted of 30 codes and child nodes that were entered into the NVivo software (NVivo 12 Pro; Lumivero). One team member was appointed to create and manage the NVivo master project that was used to house the master codebook. The NVivo software was used

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to categorize quotes with codes to perform qualitative analyses of the topics discussed in both the interviews and talking circles.

Because of the large number of transcripts, each transcript was coded by 1 coder, and interrater reliability was not calculated. Regular coder debriefing sessions, a highly structured codebook, and the purposeful discourse and integration of Indigenous and non-Indigenous interpretations of narratives ensured the reliability of the coding process [50,51]. All the coders were involved in codebook development, which included biweekly meetings for the duration of the coding process. Biweekly coding meetings allowed coders to ask for clarification on the application of the codes in the context of the interviews they were coding. This ongoing communication supported and built a consensus on the application of the codes and child nodes. In addition, as alternate interpretations of a code were discussed, analysis was guided in the codebook by the addition of inclusionary and exclusionary examples extracted from the narratives to yield agreement in the coding process [50].

This triangulation of methods (interviews, talking circles, asset mapping, and coding of executive orders) and data (eg, narratives, maps, and categories of orders) informed our understanding of the context and strategies of American Indian and Alaska Native populations and Native nations and overall research credibility. Triangulation was further strengthened through coders working in teams and through the biweekly meetings of the entire coding team.

Ethics Approval

The study was reviewed and approved by IRBs and entities that provide research oversight for the university and each of the participating Native nations (Northern Arizona University approval 1693297). Informed consent was obtained from the participants for both the interviews and talking circles that were conducted. This process has been described in the Indigenous Guided Research section. The study data were anonymized or deidentified. Individuals participating in the interviews received US $25 gift cards and those participating in the talking circles received US $50 gift cards.

Results

The number of participants enrolled in this study was 105 adults, with 92 individuals interviewed and 13 individuals engaged in 4 talking circles (Table 1). Although the goal was to interview 10 individuals from each subgroup (ie, first responders, educators, traditional knowledge holders and practitioners, and members of substance use recovery community) from each of the 3 nations, this number was not consistently achieved.

The number of interview participants in each subgroup and each community ranged from 4 to 10. Because of time constraints and challenges bringing people together during the pandemic, both via web-based platforms and in person, the team elected to host talking circles with only 1 nation, with participants ranging from 2 to 6 people. Because of the limited availability of participants, a talking circle was not conducted with the first responder subgroup.

The participant demographics are presented in Table 2. In total, 63% (58/92) of the participants identified as female and 87% (80/92) identified as Indigenous. Participant age was evenly distributed among 3 age ranges: 35 to 44 years (25/92, 27%), 45 to 54 years (25/92, 27%), and 55 to 64 years (20/92, 22%). In total, 9% (8/92) of participants were in the age range of 25 to 34 years, and 15% (14/92) of participants were aged 65 years or older.

Currently, we are in the process of conducting a qualitative analysis of the transcribed narratives from interviews, talking circles, and executive orders. These processes and outcomes will be described in future studies.

Table 1. Number of participants in interviews and talking circles.

Community	Nation A	Nation B	Nation C	Urban[a]	Total
Key informant interviews (number of participants interviewed/goal), n/N					
First responders	10/10	8/10	7/10	—[b]	25/30
Educators	10/10	9/10	7/10	—	26/30
Traditional knowledge holders and practitioners	10/10	6/10	6/10	—	22/30
Members of substance use recovery	1/10	4/10	8/10	6/10	19/40
Subtotals by community	31/40	27/40	28/40	6/10	92/130
Talking circles (participants), n (n)					
First responders	0 (0)	—	—	—	0 (0)
Educators	1 (2)	—	—	—	1 (2)
Traditional knowledge holders and practitioners	1 (6)	—	—	—	1 (6)
Members of substance use recovery	2 (5)	—	—	—	2 (5)
Subtotals by community	4 (13)	—	—	—	4 (13)

[a]Participants recruited from an urban Indigenous health center in Arizona.

[b]Data not available.

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Table 2. Demographics of key informants by nation (N=92).

Community	Nation A (n=31), n	Nation B (n=27), n	Nation C (n=28), n	Urban[a] (n=6), n	Total, n (%)
Gender					
Female	16	19	18	5	58 (63)
Male	15	7	10	1	33 (36)
No response	0	1	0	0	1 (1)
Ethnicity					
Indigenous	30	26	19	5	80 (87)
Non-Indigenous	1	1	9	1	12 (13)
Age range (years)					
25-34	4	1	2	1	8 (9)
35-44	5	10	9	1	25 (27)
45-54	7	6	9	3	25 (27)
55-64	4	7	8	1	20 (22)
65 or older	11	3	0	0	14 (15)

[a]Participants recruited from an urban Indigenous health center in Arizona.

Discussion

Principal Findings

This study embraced community-engaged research approaches to determine the role of IDOH and Indigenous Nation Building in supporting American Indian and Alaska Native mental health and well-being and, in turn, resilience during the COVID-19 crisis. The study documented the impact of COVID-19 and the resilience of 4 specific community groups of 3 Native nations and an urban Indigenous health center near one of these nations, including first responders, educators, traditional knowledge holders and practitioners, and members of the substance use recovery community. The IDOH and Indigenous Nation-Building frameworks allowed the study team to acknowledge the COVID-19 protocols implemented by sovereign nations and governing leaders to use resources and take actions needed to mitigate the impact of the pandemic. The collection and analysis of tribal policy documents, communications, actions, and available assets allowed our team to understand the communities' networks, infrastructures, and perspectives.

Engagement with members of each nation's subgroups was key to understanding the Indigenous concepts of well-being linked to collective mental health and resilience. The communication between researchers and citizens of the collaborating nations was culturally adapted to create a trusted relationship between the research team and the sovereign nations [52]. Indigenous communities have been harmed by unethical research practices in the past [52]. Developing culturally respectful research protocols renews confidence in future ethical research and aids in the protection of the sovereign nations [52]. Other practices included ensuring confidentiality of information, receiving explicit consent for participation and recording interviews, encouraging individuals to communicate their answers in their Native language, and providing mental health resource lists for each participating community. The team conducted talking circles rather than focus groups, as they were deemed more culturally congruent than focus groups in this population. For many Native communities, talking circles provide a sacred environment for mutual respect in the sharing of personal observations, often pertaining to health disparities and actions that affect them within their tribal community [47-49]. In this study, talking circles were used to observe the communication of community members in discussing the impact of COVID-19 on their mental well-being and subsequent resilience.

By working alongside our university IRB, tribal IRBs, tribal councils, Cultural Preservation Offices, and tribal leaders, the team was able to ensure cultural sensitivity throughout the multimethods design and analyses of data. As sovereign nations, all research taking place within a Native nation must be approved by a tribal research review board, a tribal council, or a cultural review board. The research guidelines include ensuring benefits to the nation and its citizens and the nation's ownership of the data gathered. Regular communication and engagement with each nation—including, but not solely, the community researcher of each nation—ensured respectful interaction with tribal members and established their values and rights as citizens of sovereign nations in our research.

Our study was unique in that our research team consisted of predominantly Indigenous scholars representing at least 8 tribal communities and nations in the United States and other non-Indigenous colleagues, collectively with many years of experience working with Indigenous Peoples. The development of this team was not happenstance but intentionally crafted because the team members understood the importance of bringing together people with the right expertise, identity, and relationship. The team included 1 community researcher from each of the 3 nations; these individuals lived and worked within the communities and had multiple relationships with the community members. Although other members of the research team also had long-established relationships with the Native nations, the inclusion of individuals who lived, worked, and

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interacted with the immediate local community was a critical component of the research design. These individuals not only played important roles in the recruitment of study participants but also provided key insights into the data analysis and interpretation of findings. Overall, our team's background and experience were vital to the development of socially conscious decisions in the methods used throughout the study.

Findings from this study will be shared through presentations, papers, and publications with larger Indigenous and non-Indigenous audiences, including collaborating and stakeholder organizations; local recovery groups, treatment centers, and individuals in recovery; K-12 and higher education educators and administrators; directors of first responder agencies; traditional medicine people; and elected community leaders. Data and results will be used to produce resource maps to promote service availability; advocate for research and resource expansion in the region; and be disseminated at local, regional, and national conferences and advocacy events as well as peer-reviewed journals. The findings will be used to produce well-being and resilience education materials, such as print and digital toolkits, in-service training sessions, educational materials specific to Indigenous audiences, and future recommendations for stakeholder organizations. The pending articles will consist of data analysis and results pertaining to asset mapping analysis, executive orders, and the development of a codebook. In addition, each of the 4 subgroup interviews and talking circles will be analyzed for existing patterns to address present community needs and potentially new needs that have emerged from the COVID-19 pandemic.

Limitations of the Study

This study included a small subset of 3 nations from 570 federally recognized tribal nations. Furthermore, the study was limited to Native nations within 1 geographic region of the US Southwest. In addition, among the 4 identified subgroups of the participating tribal nations, the number of interview respondents and talking circle participants was low. Finally, not all study participants were American Indian and Alaska Native. These limitations may have implications for the results. For example, very remotely located tribal communities in other areas of the country or tribal nations with differently organized leadership may have experienced COVID-19 dissimilarly than the individuals from Native nations participating in this study; therefore, a similar study conducted in a different area of the country might yield very different results than this study.

This study examined questions through a framework of Indigenous Nation Building and IDOH, which the research team determined to be the most appropriate framework for examining the issue. Other studies using a less Indigenous-centered approach could yield somewhat different findings.

Conclusions

In conclusion, this community-engaged study lays the groundwork for future studies addressing Indigenous mental health, well-being, and resilience in other communities during global crises. Asset mapping resource guides can create more opportunities for resource expansion in each participating community. Geographic Information System mapping can be further used for spatial analysis and to understand the distribution and availability of key resources in Native lands. Future intervention-based studies can also address mental well-being to enhance community resilience. The intentionality of linking Indigenous researchers with Indigenous communities to address pressing matters related to IDOH exemplifies the value and importance of the practice to build trust and mutual respect among communities, Native nations, and the academic community; it also reflects the 4 R's (respect, relationship, reciprocity, and responsibility) approach described by Brayboy et al [14], which is crucial to Indigenous research methodologies. Furthermore, Indigenous Nation Building is centered in our multifaceted and interdisciplinary approach to learn from each stakeholder group toward informing tribal sovereignty and responding to a pandemic crisis through the lens of the Indigenous community. This commitment was clearly demonstrated in 1 meeting with Indigenous elders, where the elders explicitly communicated in the Native language their appreciation for this research that included a researcher who knows the language and knows the people.

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Data Availability

The data sets generated and analyzed during this study are not publicly available because they include data from participants of sovereign Native nations, and these data cannot be released without explicit permission from each nation. Please feel free to contact the principal investigator, Dr Julie Baldwin, if you have questions.

Conflicts of Interest

None declared.

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Abbreviations

CARE: Collective benefits, Authority to control, Responsibility, Ethics
CDC: Centers for Disease Control and Prevention
IDOH: Indigenous determinants of health
IRB: institutional review board
SDOH: social determinants of health

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Protocol

A "Bundle of Care" to Improve Anticoagulation Control in Patients Receiving Warfarin in Uganda and South Africa: Protocol for an Implementation Study

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Abstract

Background: The quality of warfarin anticoagulation among Sub-Saharan African patients is suboptimal. This is due to several factors, including a lack of standardized dosing algorithms, difficulty in providing timely international normalized ratio (INR) results, a lack of patient feedback on their experiences with treatment, a lack of education on adherence, and inadequate knowledge and training of health care workers. Low quality of warfarin anticoagulation, expressed as time in therapeutic range (TTR), is associated with higher adverse event rates, including bleeding and thrombosis, and ultimately, increased morbidity and mortality. Processes and interventions that improve this situation are urgently needed.

Objective: This study aims to evaluate the implementation of the "warfarin bundle," a package of interventions to improve the quality of anticoagulation and thereby clinical outcomes. The primary outcome for this study is TTR over the initial 3 months of warfarin therapy.

Methods: Patients aged 18 years or older who are newly initiated on warfarin for venous thromboembolism, atrial fibrillation, or valvular heart disease will be enrolled and followed up for 3 months at clinics in Cape Town, South Africa, and Kampala, Uganda, where the warfarin bundle is implemented. A retrospective review of the clinical records of patients on warfarin treatment before implementation (controls) will be used for comparison. This study uses a mixed methods approach of the implementation of patient- and process-centered activities to improve the quality of anticoagulation. Patient-centered activities include the use of clinical dosing algorithms, adherence support, and root cause analysis, whereas process-centered activities include point-of-care INR testing, staff training, and patient education and training. We will assess the impact of these interventions by comparing the TTR and safety outcomes across the 2 groups, as well as the cost-effectiveness and acceptability of the package.

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Results: We started recruitment in June 2021 and stopped in August 2022, having recruited 167 participants. We obtained ethics approval from the University of Cape Town Faculty of Health Sciences Human Research Ethics Committee, the Provincial Health Research Committees in South Africa, the Joint Clinical Research Centre Institutional Review Board, Kampala, and the University of Liverpool Research Ethics Committee. As of February 2023, data cleaning and formal analysis are underway. We expect to publish the full results by December 2023.

Conclusions: We anticipate that the "bundle of care," which includes a clinical algorithm to guide individualized dosing of warfarin, will improve INR control and TTR of patients in Uganda and South Africa. We will use these findings to design a larger, multisite clinical trial across several Sub-Saharan African countries.

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KEYWORDS

drug monitoring; international normalized ratio; Sub-Saharan Africa; warfarin bundle; warfarin; anticoagulation control

Introduction

Background

Oral anticoagulation is vital for several diseases that are prevalent and increasing in Sub-Saharan Africa (SSA). Warfarin remains one of the most frequently used oral anticoagulants, particularly in lower-resource settings, such as SSA [1], but is difficult to use because of its narrow therapeutic index, wide variability in individual daily dose requirements required to achieve the desired effect and need for frequent monitoring. Achievement of the target international normalized ratio (INR) is critical to prevent the recurrence of thrombosis and bleeding. Several studies have described low time in therapeutic range (TTR) [2]. In our previous study, our own cohorts in Uganda and South Africa demonstrated a TTR of 41% [3] compared to TTRs of up to 70% in high-income settings [4].

We identified several reasons that contributed to this low quality of anticoagulation, including a lack of standardized dosing algorithms with different practices in different clinics, difficulty in providing INR results at the time patients attend clinic, a lack of patient feedback on their experiences while on treatment and education on adherence, inadequate knowledge and training of health care workers, a lack of standardization of quality improvement procedures, and the lack of availability of different dosage strengths of warfarin tablets.

A simulation study [5] in the United States suggested that improving TTR by 5% resulted in a 7.2% reduction in all adverse events in a population of 67,070 patients anticoagulated for atrial fibrillation over a 2-year period. This included 183 ischemic strokes, 269 major hemorrhages, and 662 deaths. Increasing TTR by 5% saved US $15.9 million and gained 863 quality-adjusted life years (QALYs) during this period [5]. In our population, with a median TTR of 41% [3], an improvement in TTR would be expected to have a greater impact since the relationship between TTR and mortality is nonlinear.

We aim to introduce a package of measures using a mixed methods approach, which we have termed the "warfarin bundle," in anticoagulation clinics in 2 cities (Cape Town, South Africa, and Kampala, Uganda), to improve the quality of anticoagulation. The bundle includes patient-centered and process-centered activities, namely (1) implementing a clinical warfarin dosing algorithm, (2) providing adherence support, (3) conducting root-cause analysis of warfarin-related adverse events, (4) implementing point-of-care INR testing, and (5) providing staff training. We anticipate that this warfarin bundle will be a cost-effective approach for better INR control compared to the current standard of care.

Hypothesis

Our underlying hypothesis is that implementing a bundle of measures, including a clinical algorithm to guide individualized dosing of warfarin, will improve INR control and TTR in patients in Uganda and South Africa.

Objectives

The primary objective of this study is to evaluate whether implementation of the warfarin bundle improves TTR. Secondary objectives include evaluating whether implementation of the warfarin bundle improves time to achieving a therapeutic INR or reduces the occurrence of adverse effects, assessing the acceptability of the bundle, exploring patients' experiences, and estimating cost-effectiveness.

Methods

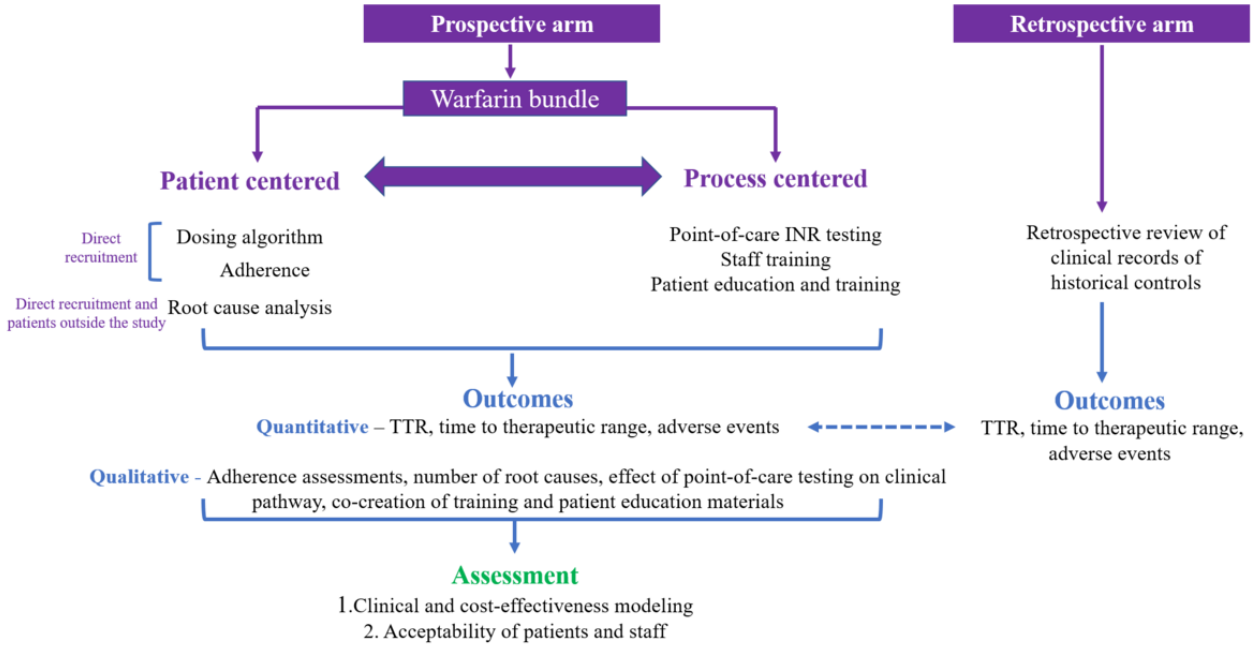
Study Design and Setting

This is a mixed methods implementation study of patient- and process-centered activities to improve the quality of anticoagulation in Sub-Saharan African patients involving 3 hospitals in Kampala, Uganda (Mulago National Referral Hospital, Uganda Heart Institute, and Kiruddu National Referral Hospital) and 2 hospitals in Cape Town, South Africa (Groote Schuur Hospital and Tygerberg Hospital).

The general study design is described in Figure 1.

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Figure 1. Study design highlighting prospective and retrospective components and outcomes. INR: international normalized ratio; TTR: time in therapeutic range.



Patient Centered Components of the Warfarin Bundle

Implementing the Use of Dosing Algorithms

Participants of Black African ancestry will be dosed according to the warfarin dose initiation algorithm developed in our preceding study in Black African patients in Uganda and South Africa, which takes account of patient age, weight, target INR, and HIV status [6] (Multimedia Appendix 1). In South Africa, patients of other ethnicities will be initiated on warfarin using warfarin dosing algorithms which have already been published [7,8] (Multimedia Appendix 2). We will collaborate with their treating clinicians and calculate a warfarin initiation dose using the relevant algorithm.

Day 0 is considered the first day that warfarin is taken. We recruited participant up to 7 days before and no more than 1 day after warfarin was initiated, meaning some individuals may have taken a single warfarin dose. We will use a paper-based dosing table, using dose formulations currently available, which has been developed for implementation (Multimedia Appendix 1).

Adherence Support

The package of adherence support offered will include data-driven counseling and interactive weekly text messaging. We will assess adherence by means of a composite of INR values above and below the therapeutic range, TTR, and self-report.

Root Cause Analysis

Root cause analysis (RCA) will be undertaken in all patients on warfarin at the INR clinic or hospital who are seen with serious thrombotic or hemorrhagic events. An RCA committee at each clinic, comprising a multidisciplinary team of 4-6 individuals, will review each case using the 9-step process of RCA described by Charles et al [9]. Root causes and corrective actions developed will be categorized on a standardized RCA data collection form to ease analysis [10]. The results of each RCA (root causes, contributing factors, and corrective actions) will be shared with staff at the clinic. Findings of RCA will be discussed at monthly study meetings to inform the overall warfarin bundle implementation (in areas such as adherence, monitoring, and education).

Process-Centered Components of Warfarin Bundle

Point-of-Care Testing

We will make point-of-care INR testing a central part of improving the clinical pathway. Currently, some patients must wait at least a day to receive their INR result and subsequent dosing guidance.

Staff Training

We will include co-design workshops discussing the rationale for the bundle and likely implementation issues with a team of clinicians involved in the provision of anticoagulation services. Training will be personalized based on local requirements, depending on the site and staff involved.

Cocreation of Patient Education and Training

Co-design workshops for the development of training material to be used in patient education will bring together patient or community representatives, health care staff, the research team, and a representative from policy makers. Different methods will be discussed and explored by the cocreation team in collaboration with representatives from the community and health care workers to ensure they are applicable to the local setting.

Participant Eligibility Criteria

Participants will be included in the study if they are adults aged 18 years or older; newly initiated on warfarin anticoagulation for the first time for venous thromboembolism, atrial fibrillation,

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or valvular heart disease; provide informed consent; and are willing to comply with study procedures. We will exclude participants who are on treatment for tuberculosis, pregnant women, and patients who have had more than one dose of warfarin. For the retrospective study, we will include adults newly initiated on warfarin for more than 3 months before we implement the trial.

Sample Size and Power Calculations

To calculate our sample size, we assumed TTR in current practice to be 0.41 (based on average TTR from our audit) and the SD of TTR to be 0.25 on the basis that anticoagulation control before implementing the bundle is better than that found during the audit (0.33), due to the introduction of the clinical algorithm in a preceding pilot implementation study. We also assumed a Type I error rate of 0.05, power of 80%, and that the retrospective and prospective ratio would be 2:1. To achieve a minimum clinically important difference of 0.07 (ie, improvement from 43% to 50% TTR), we calculated that we would need at least 304 retrospective and 152 prospective participants (including a 10% contingency for losses to follow-up). This is in total across both Uganda and South Africa.

Participant Recruitment

Prospective Study

We will recruit participants for whom a decision has already been made to initiate warfarin by the managing clinician (Figure 2). Decisions regarding whether or not patients require inpatient management for the initiation of warfarin are also made by the managing clinician. Participants who meet the inclusion criteria will be consecutively screened and enrolled in the study. In cases where participants are discharged from the hospital and referred for follow-up in a clinic close to their home or in the outpatient clinic of the hospital, the clinical records used at the recruitment site and those at the referral clinic will be reviewed.

The participant's first 3 days of dosing will be driven by our new algorithm (Multimedia Appendix 1). Thereafter, dose revisions will be made according to current guidance outlined in the "Standard Treatment Guidelines and Essential Medicines List for South Africa" [11]. We will repeat the INR of participants every 2-4 days until stability is reached (2 consecutive INRs are in the target range). We will ensure close monitoring during the first 14 days of treatment. If stability is reached before the 14th day, we will continue to closely monitor the patient for the first 14 days. If the participant has not reached stability at 14 days, we will continue to monitor the participant with INRs every 2-4 days and adjust the warfarin dose until stability is reached. As we measure participants' INR every 2-4 days over this period of close follow-up, we will propose dose adjustments to the clinical team based on INR results. The clinical team will still be free to override proposed adjustments based on their clinical expertise. Once stability is reached, we will perform one more INR 1 week later, after which the participants' care will be fully handed back to the clinical team, and participants will continue to follow-up according to the local standard of care. We will continue to monitor and record all consecutive INR results for 3 months through direct contact with the participant at outpatient clinic, home visits, or electronic or paper record review.

We will collect the following data: age, sex, weight, height, indication for anticoagulation, target INR range, HIV status, recruitment center, all INR measurements during the first 3 months and the first INR after completion of the first 3 months, any dose changes, and any hospitalizations or adverse events (Table 1). We will also complete the EQ-5D-3L questionnaire and a patient-cost questionnaire to enable us to measure changes in quality of life and out-of-pocket expenditures, respectively.

We will test all patients for genetic variants that are determinants of warfarin dose and elucidate whether any patients who were poorly controlled on warfarin had a genetic profile which may have adversely affected their INR control. The genetic testing will be done at the end of the study and will also help with our future plans to validate a genetic dosing algorithm derived from our previous study's analysis of genome-wide data. (South Africa HREC: 672/2017, Uganda: JC3017). We will also obtain consent to undertake genome-wide analysis in this patient group, which will help in future meta-analyses with our previous studies' data to identify other genetic loci.

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Figure 2. Flow diagram of prospective recruitment and follow-up. INR: international normalized ratio. War-PATH: Warfarin Anticoagulation in Patients in Sub-Saharan Africa.

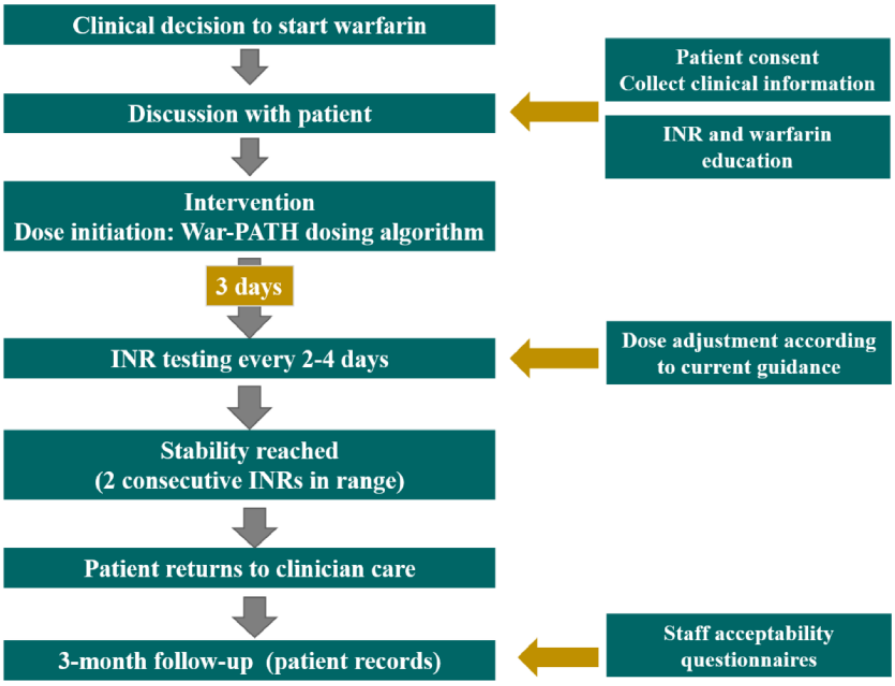


Table 1. Participant groups.

	Prospective	Retrospective
Population	Participants starting warfarin and consenting to implementation bundle	Historical controls started on warfarin at anticoagulation clinics where warfarin bundle is implemented
Sample size	152	330
Inclusion criteria	• New initiators on warfarin • Indication for warfarin is VTE[a], AF[b], or VHD[c] • Adults (ie, 18 years or older) • Participant is resident in and willing to be followed up at a health facility where follow-up is feasible	• New initiators on warfarin • Indication for warfarin is VTE, AF, or VHD • Adults (ie, 18 years or older)
Exclusion criteria	• Pregnancy • Received more than one dose of warfarin prior to recruitment • Diagnosed with and currently on treatment for Tuberculosis	• Pregnancy • Diagnosed with and treated for Tuberculosis at time of warfarin initiation
Self-reported ethnicity	Yes	No
EQ-5D-3L questionnaire	Yes	No
Participant expenses tool	Yes	No
Baseline INR[d]	Yes	Yes
INRs during the first 3 months of treatment	Yes	Yes
All adverse events	Yes	Yes
Hospital admissions	Yes	Yes

[a]VTE: venous thromboembolism.

[b]AF: atrial fibrillation.

[c]VHD: valvular heart disease.

[d]INR: international normalized ratio.

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Retrospective Review of Patients' Clinical Records

The following data will be collected from clinical records: age, sex, weight, indication for anticoagulation, target INR range, HIV status, recruitment center, all INR measurements during the first 3 months, any dose changes, and any hospitalizations or adverse events. If participants in the retrospective review were initially hospitalized and then discharged, the recruitment hospital site clinical records as well as the clinical records at the referral clinic will be reviewed.

Withdrawal Criteria

A participant can withdraw from the study at any time if it is his or her wish or if it is medically necessary, as judged by the Investigator. A participant will be withdrawn if any of the following applies:

1. Voluntary discontinuation by the participant, who is at any time free to discontinue their participation in the study without prejudice to further treatment.
2. Incorrect enrollment of the participant (ie, the participant does not meet the required inclusion and exclusion criteria).
3. Participant fails to comply with the protocol requirements or fails to cooperate with the investigator.
4. Participants experiencing severe adverse events who return to standard care.

Sample Collection

Two tubes of blood (10 or 12 ml total) will be collected in ethylenediaminetetraacetic acid (EDTA) tubes and used for DNA extraction. The EDTA blood sample will be stored at either –20 C or –80 C. One tube will be shipped to the United Kingdom, and 1 kept in Cape Town or Kampala. DNA will be extracted from the EDTA sample at the Wolfson Centre for Personalised Medicine in Liverpool. We will seek ethical approval from the University of Cape Town HREC/Joint Clinical Research Centre Institutional Review Board Office, Kampala, for any future use.

Adverse Events

The decision to start warfarin will already have been made by participants' clinical teams before enrollment. We will capture warfarin-related adverse events as part of the secondary outcome measures. A blood test to obtain DNA may sometimes lead to bruising at the site of venepuncture, but all blood will be taken by trained and experienced staff. All adverse events will be recorded and appropriately reported. Investigators will assess whether adverse events were related to warfarin using the Liverpool Adverse Drug Reaction Causality Assessment Tool [12].

Cost-Effectiveness

We will perform a cost-effectiveness analysis to judge whether the warfarin bundle represents good value for money. These will be based on estimated costs associated with warfarin treatment and health outcomes expressed as QALYs and disability-adjusted life years (DALYs). Resource use will include hospital admissions, outpatient clinic visits, phlebotomy, Point-of-Care and laboratory INR tests, additional blood tests, and prescribed warfarin. External data (which may require extrapolation from other studies or countries) may be required to estimate the costs of managing rare adverse events, including strokes and major bleeds. Unit costs will be identified from a number of sources, including the Western Cape Department of Health (eg, Uniform Patient Fee Schedule), the Ugandan Joint Medical Stores catalog, and the World Health Organization "Choosing Interventions that are Cost-Effective" (WHO-CHOICE) model for estimating unit costs for hospitalizations [13]. Patients will be asked to complete the EQ-5D-3L to estimate health utilities at the initial visit and 1 follow-up visit and to complete a questionnaire to record out-of-pocket costs by telephone. The economic analysis will estimate the incremental costs per QALY gained and DALY averted and inform policy.

Study Outcomes

The primary outcome for this study is TTR over the initial 3 months of warfarin therapy, which we will measure using the Rosendaal linear interpolation method [14]. We will compare time in the therapeutic INR range between the prospectively followed participants who receive the warfarin bundle and a retrospectively reviewed patient group. This will yield an estimate of the impact of the warfarin care bundle as a whole. It will not be possible to distinguish the effect of the individual components of the warfarin bundle on TTR.

The secondary outcomes include time to achieve therapeutic INR and number of adverse events (death, bleeding, or thrombosis), which will be compared between the prospectively followed-up participants and the retrospectively reviewed patient group. We will also explore staff and patient experiences and acceptability of the warfarin bundle using in-depth interviews or focus group discussions and conduct an economic analysis of the cost-effectiveness of the warfarin bundle. In addition, we will perform a qualitative assessment of useful lessons from the RCA.

Patient and Public Involvement

Patients or the public will not be involved in the design, conduct, or reporting of this study. However, where possible, study findings will be disseminated through public and patient engagement activities.

Data Analysis Plan

For the prospective and retrospective studies, all statistical analyses will be undertaken in R. For determining percentage time in target range for each participant, all INR measurements during the first 12 weeks as well as the first INR measurement after the 12-week time point will be used, and the method of Rosendaal et al [14] will be applied. Percentage TTR will be compared between the prospective implementation group and the retrospective standard of care group using the Student *t* test. Time to achieving target INR (defined as the first of at least two INR measurements in range at the same dose) will be compared between the prospective and retrospective groups using the log-rank test (to compare the survival distributions of the 2 groups, and these will be calculated using the Kaplan-Meier estimator). Adverse events will be compared between the 2 groups using a chi-square test. A significance threshold of $P<.05$ will be applied.

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The primary analysis will include all participants who remain in the project for at least 2 weeks (14 days). Our primary analysis will include only patients who have at least two weeks' follow-up, since it is unlikely that those with less than 2 weeks' follow-up will have sufficient information on INR measurements for TTR to be reliably estimated. A sensitivity analysis will be undertaken, including only participants who have completed 12 weeks (84 days) of follow-up.

We will also conduct both an intention-to-treat analysis (including all recruited patients) and a per-protocol analysis (excluding patients where health care provider decided to reject the dose recommended by the dosing algorithm). The project will follow national guidelines for best practice and be guided by local policy. Relevant data will be made openly available to other researchers in a timely way (after primary outputs are published) with as few restrictions as possible unless we are protecting intellectual property, respecting confidentiality, or honoring third-party agreements. The program management board will review access to data and will provide a governance mechanism.

We will perform a secondary analysis comparing the primary and secondary outcomes between retrospective controls from the pre–COVID-19 and COVID-19 periods to measure the impact of the pandemic on anticoagulation control.

Total direct costs will be calculated for each patient over the course of the 12 weeks. Utilities will be estimated from the administration of the EQ-5D-3L questionnaire (available in 8 languages spoken in South Africa and 2 in Uganda) and valued using the Zimbabwean value set, as none exist for these countries [15]. Regression analyses using transformed utility (or cost) as the dependent variable and controlling for clinical and demographic factors will be used to estimate the association between health utility (or cost) and TTR. These will be incorporated in a decision analytic model, also populated with data from evidence on the relationship between TTR and health outcomes (strokes, hemorrhagic events, etc), to estimate overall costs and QALYs.

In accordance with World Health Organization recommendations, the number of DALYs, expressed as the collective number of years lost due to ill health, disability, or early death, will be calculated by adding the adjusted number of years lived with disability and the number of years of life lost due to premature mortality. The years lived with disability component represents a duration that is scaled by disability severity weights that range from 0 (no adverse impact on quality of life) to 1 (burden equivalent in preference to being dead). Weightings will be applied to time with disability based on disease areas [16] and DALYs for individuals will be calculated and used as an alternative metric of cost-effectiveness (cost per DALY averted).

Ethical Considerations

The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki, 1964, and revisions up to and including Fortaleza [17]. We obtained approval from the University of Liverpool Research Ethics Committee (reference number: 9963), the University of Cape Town Faculty of Health Sciences Human Research Ethics Committee (reference number: 710/2020), the Provincial Health Research Committees in South Africa, and the Joint Clinical Research Centre Institutional Review Board, Kampala (reference number: JC2120), before the study commenced.

Each participant in the prospective arm was required to provide written informed consent to enter the study only after a full explanation had been given and an information leaflet had been offered. Signed participant consent was obtained. For participants that were unable to read and write, an impartial witness was present during the informed consent process to witness thumbprint consent. The right of the participant to refuse to participate without giving reasons was respected. All participants were free to withdraw at any time. We did not seek patient consent for the retrospective record review; a waiver of consent was sought from the corresponding ethics committees.

All study data will be deidentified. All documents and logs containing identifiable private information about participants will be kept securely and only accessible by study staff and investigators.

Results

We started recruitment in June 2021 and stopped in August 2022, having recruited 167 participants. As of February 2023, data cleaning and formal analysis are underway. We expect to publish the full results by December 2023.

Discussion

Overview

This protocol will evaluate the implementation of the "warfarin bundle," a group of interventions aiming to improve the quality of warfarin anticoagulation in SSA. Given the complex and multifaceted challenges contributing to suboptimal anticoagulation in these populations, a mixed methods protocol, including both patient-centered and process-centered activities, was designed.

The study design has several limitations, primarily relating to the complexity of the population, the challenges of investigating anticoagulation in this particular setting, and the selection of a bundle of interventions, including patient and provider education, rather than a single intervention.

In Uganda, anticoagulation services are centralized in Kampala, and there are no control clinics that could be run concurrently in a cluster randomized trial design; within South Africa, selection of appropriate control clinics would necessitate involving another city in addition to Cape Town, thereby bringing unfeasible logistic challenges and cost. Therefore, a before-and-after design was considered most appropriate. We have shown in the preceding Audit study that we can get high-quality data from the case notes [3].

An eligibility criterion for participants in the prospective evaluation is their willingness and ability to comply with study procedures. In practical terms, this excludes individuals who travel long distances from peripheral regions of Uganda to the

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tertiary facilities where anticoagulation is accessed; this may mean that the participants in the retrospective and prospective arms are not perfectly matched in terms of socioeconomic status. However, the recruitment sites are in the area of highest population density, and the majority of individuals in both the retrospective and prospective arms are anticipated to reside within Kampala and the surrounding Wakiso district.

Through the selection of a bundle of interventions, it will not be possible to attribute improvement to a single element of this. However, this is a complex patient group requiring holistic care, and several important areas have been identified for improvement. The health, economic, and qualitative aspects of the protocol are designed to evaluate the benefits of the bundle as a whole.

Conclusions

We anticipate that the "bundle of care," which includes a clinical algorithm to guide individualized dosing of warfarin, will improve INR control and TTR in patients in Uganda and South Africa. This has the potential to reduce the substantial morbidity and mortality seen among individuals requiring oral anticoagulation in these settings. We will use these findings to design a larger, multisite clinical trial in other Sub-Saharan African countries.

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We would like to thank all staff at the outpatient and anticoagulation clinics of Mulago National Referral Hospital, Uganda Heart Institute, Kiruddu National Referral Hospital, Groote Schuur Hospital, and Tygerberg Hospital for their input during the planning and implementation of this study. This study is funded by the National Institute for Health Research (NIHR; project ref. 16/137/101) using UK aid from the UK Government to support global health. The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.

Data Availability

Relevant data will be made openly available to other researchers in a timely way (after primary outputs are published), with as few restrictions as possible unless we are protecting intellectual property, respecting confidentiality, or honoring third-party agreements. Data sharing is not applicable to this article as no data sets have yet been generated or analyzed.

Authors' Contributions

The study concept and design were conceived by ALJ, CO, CW, CHT, CSW, DAH, EA, EO, GT, JPM, KC, MB, ML, and MP. MP led the funding acquisition for this study. Analyses will be conducted by ALJ, DAH, GC, and IGA. JRS prepared the first draft of the manuscript. All authors critically revised the manuscript and approved the submitted version.

Conflicts of Interest

MP has received partnership funding for MRC Clinical Pharmacology Training Scheme (cofunded by MRC and Roche, UCB, Eli Lilly, and Novartis). MP also has unrestricted educational grant support for the UK Pharmacogenetics and Stratified Medicine Network from Bristol-Myers Squibb. He has developed an HLA (human leukocyte antigen) genotyping panel with MC Diagnostics but does not benefit financially from this. He is part of the IMI Consortium ARDAT. CW is supported by the Wellcome Clinical Research Career Development Fellowship 222075_Z_20_Z.

Multimedia Appendix 1
Warfarin clinical dosing algorithm for participants of Black African ancestry.
[DOCX File , 32 KB - resprot_v12i1e46710_app1.docx]

Multimedia Appendix 2
Warfarin dosing algorithms for other ethnicities.
[DOCX File , 28 KB - resprot_v12i1e46710_app2.docx]

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Abbreviations

DALY: disability-adjusted life year
EDTA: ethylenediaminetetraacetic acid
INR: international normalized ratio
QALY: quality-adjusted life year
RCA: root cause analysis
SSA: Sub-Saharan Africa
TTR: time in therapeutic range

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Protocol

Performance and Safety of a New Medical Device (Polybactum) for Reducing the Recurrence Rate of Bacterial Vaginosis: Protocol for a Multicenter, Open-Label, Noncontrolled International Clinical Trial (POLARIS Study)

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Abstract

Background: The medical literature has reported that recurrent bacterial vaginosis (RBV) has a relapse rate of 35% within 3 months and 60% within 12 months after antibiotic administration. Products that are able to provide a barrier effect against the biofilm produced by *Gardnerella vaginalis* could play a role in improving the results of bacterial vaginosis (BV) treatment.

Objective: This study aims to assess the performance and safety of a medical device (Polybactum) containing polycarbophil, lauryl glucoside, and glycerides (PLGG) for reducing the rate of recurrence of BV.

Methods: The study includes women who are aged above 18 years, are willing to provide signed informed consent, have a diagnosis of BV according to the Amsel criteria, and have been affected by at least 2 episodes of RBV in the last 12 months. The trial includes 2 phases. In the first phase (according to an open-label noncontrolled design), the treatment involving PLGG is administered for 3 cycles and is followed by a 1-month period of follow-up without treatment. In the second phase, a 9-month follow-up period is envisaged. Thus, for each patient, a 10-month follow-up period without treatment is planned. The study involves 5 centers (2 in Italy and 3 in Romania). We calculated a sample size of 44 pairs to achieve a power of 80% and a 1-sided significance of 5% for detecting a difference of 0.25 between marginal proportions, in comparison with the mean recurrence rate of BV reported in the medical literature. We estimated a potential dropout rate of 20%, and thus, we decided to enroll 55 patients (1-group chi-square test).

Results: The study received ethics approval in 2016 in Romania and 1 year later in Italy. Recruitment started in September 2016. An interim analysis was performed in 2019, and full study analysis results are expected in July 2023.

Conclusions: The tested medical device involving PLGG could modify the mechanisms involved in the pathogenesis of BV and could improve microbiological parameters owing to the acidifying effect on vaginal pH. We believe that the findings of our

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study could be useful for other investigators who want to test different products against RBV using a standardized protocol and standardized procedures.

Trial Registration: ClinicalTrials.gov NCT02863536; https://clinicaltrials.gov/ct2/show/NCT02863536

International Registered Report Identifier (IRRID): RR1-10.2196/42787

(JMIR Res Protoc 2023;12:e42787) doi:10.2196/42787

KEYWORDS

bacterial vaginosis; recurrent bacterial vaginosis; biofilm; polycarbophil

Introduction

Overview

The vaginal cavity is colonized in its natural state by Doderleïn bacilli, which include different species of lactobacilli. They form a biofilm over the mucous membrane and hinder the growth, adhesion, and expansion of other potentially pathogenic microorganisms.

These lactobacilli inhibit the growth of pathogens by different means involving several agents [1]. First, lactic acid, produced by the hydrolysis of glycogen contained in vaginal cells, keeps the vaginal pH at a level between 3.8 and 4.5, and thus has a bacteriostatic effect on most vaginal pathogens (excluding *Candida albicans*). Second, hydrogen peroxide, an oxidizing agent secreted by certain lactobacilli (especially *Lactobacillus crispatus* and *Lactobacillus jensenii*) present in 96% of normal vaginal microbiota, hinders the proliferation of anaerobic bacteria [2]. Third, bacteriocins, antimicrobial protein derivatives with a restricted spectrum, act by binding to a specific receptor in the target cell and destabilizing the cytoplasmic membrane through the formation of pores.

Moreover, these lactobacilli produce a barrier against the adhesion of pathogens by means of biosurfactants, which act on surface tension and inhibit the expansion of pathogens through their co-aggregation properties. Bacterial aggregation is a mechanism that leads to the formation of biofilms. Some lactobacilli not only autoaggregate, but can also co-aggregate with pathogenic microorganisms, thus creating a particular microenvironment around the pathogen with significant levels of inhibitors. *Lactobacillus acidophilus*, *Lactobacillus gasseri*, and *Lactobacillus jensenii* co-aggregate with *Candida albicans*, *Escherichia coli*, and *Gardnerella vaginalis*, preventing these pathogenic strains from expanding and adhering to the epithelium [3]. Bacterial vaginosis (BV) is a polymicrobial disease that generally occurs when the protective antibacterial activity of vaginal lactobacilli is impaired, permitting an overgrowth of anaerobes and other pathogens, such as *Gardnerella vaginalis* and *Mycoplasma hominis* [4]. BV occurs in 20% to 25% of the general female population and is the most frequent cause of vaginal discharge [5].

Because of the several risk factors associated with BV, the etiology and pathogenesis of this disease are not completely understood, and the treatment adopted is not always effective, resulting in high recurrence rates [6].

Rationale

Recurrent bacterial vaginosis (RBV) is defined by 2 to 3 episodes of BV per year [7,8]. The recurrence rates are up to 35% within 3 months [9], 43% to 61% within 6 months, and 49% to 66% within 12 months [10]. It was proven that the tendency to relapse is essentially linked to the capacity of *Gardnerella vaginalis*, and to a lesser extent of *Atopobium vaginae* (recently reclassified as *Fannyhessea vaginae*), to adhere to the mucous membrane, producing a thick biofilm that adheres strongly to the surface of the vaginal mucous membrane [11]. This biofilm is generated within 2 days after the end of standard antibiotic treatment [6]. Thus, several medical reports suggest the use (no later than 24 hours after the discontinuation of antibiotic treatment) of products able to provide a barrier effect against the production of the biofilm by *Gardnerella vaginalis*. Starting from this rationale, it was necessary to find a novel, safe, and effective product able to hinder the formation of this vaginal biofilm, without damaging the fragile equilibrium of the vaginal microbiota.

Objectives

The primary objective of the study is to evaluate the performance and safety of a 3-cycle treatment of the test product (Polybactum) for reducing the rate of recurrence of BV, considering a 10-month follow-up (ie, without treatment), and compare the obtained results to those reported by appropriately selected international literature.

The secondary objectives are to evaluate the rate of return to normality of the vaginal microflora (defined as vaginal microflora with numerous pleiomorphic lactobacilli, and no other bacteria, clue cells, or hyphae) [12] after the study therapy and to evaluate the safety of the test product.

Methods

Overview

The author FM (Milan, Italy) conceptualized the study (ClinicalTrials.gov registration: NCT02863536) and created a team involving a network of gynecologists coordinated by the University of Medicine and Pharmacy “Victor Babe ” (Timisoara, România). The team conducted a systematic review on products already on the market known to be able to provide a barrier effect against biofilm production, assuming that these products, if administered immediately after standard antibiotic therapy, could play a role in improving the results of BV treatment. The literature review established that no gold standard therapy was recommended and that the available treatments were not always effective, resulting in high recurrence rates [4].

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In addition, it evidenced, on the one hand, the proven protective activity of these products, and on the other, the low number of clinical trials performed (insufficient to statistically confirm a decrease in the recurrence rate).

In the initial step, the team was involved in building the outline of the protocol and clarifying the yet pending or not identified clinical issues (ie, the product to test and the antibiotic to use). A modified Delphi method [13] was used as a reliable approach to build and create consensus among team attendees. The procedure was defined as follows:

- Polycarbophil would be tested in the planned clinical trial. The characteristic of this well-known product is the formation of a film, which acts as a mechanical barrier able to reduce specific pathogen colonization. The product is already on the market, and the related instruction for use specifies its posology.
- Metronidazole would be the antibiotic therapy to administer following the indication reported in the international guidelines [6]. This drug is the standard treatment for BV at the sites of the involved investigators.
- BV diagnosis would be performed using the Amsel criteria [14], and the Nugent test would be considered as an optional evaluation.
- Patients would be monitored during a 10-month follow-up period (ie, after the end of therapy) to verify the recurrence rate.

The concept synopsis of the planned trial was presented to Effik Italia SpA (Italfarmaco Group, Cinisello Balsamo, Italy) (Multimedia Appendix 1). The company manufactures Polybactum, a medical device containing polycarbophil, lauryl glucoside, and glycerides (PLGG), and it offered the investigator team the medical device and a partial grant to perform the trial on RBV. The agreement between the parties specified that the funder would not have any role in the design and planning of the study, or in the collection, analysis, and interpretation of the data of the future manuscript disclosing the results.

Finally, the team chose the logo (Multimedia Appendix 2), the study name POLARIS (Polybactum to Assess Recurrent Bacterial Vaginosis), and the contract research organization (Opera CRO, a Tigermed Group company, Romania) that would be in charge of the logistics and the management of the trial (protocol submission, project management, site monitoring, data management, and statistical analysis). The coordination of the scientific activity (training of investigators at satellite sites, checking the application of ethics requirements, and circulating scientific information to the study team) would be managed by the Department of Clinical Trials of the University of Medicine and Pharmacy “Victor Babe ” (Timi oara, Romania). By applying this clear division of roles [15], there would be no influence or potential persuasion by the sponsor in the study design, data collection, interpretation, or publication.

Ethics Approval

The study involved 2 centers in Italy and 3 in Romania. The National Agency for Medicines and Medical Devices of România (*Agentia Nationala a Medicamentului si a Dispozitivelor Medicale*) has approved the study, and the Italian Ministry of Health has received the notification before the start of the trial. The local ethics committees (ECs) in Romania approved the protocol on July 29, 2016 (*EC Clinica Medicală Dr Cri an*; investigator Dr Cri an), October 24, 2016 (*EC Clinica Medicală Dr Cri an*; investigator Dr Biris), and August 22, 2016 (*EC Clinica Medicală Dr Sîrbu*; investigator Dr Sîrbu), and all are located in Timisoara. The formal approvals by Italian ECs were received some months later on December 14, 2016 (#8643/2017; *EC Area 1* in Milan; investigator Dr Murina) and February 15, 2017 (#566/2017; *EC Lazio 1* in Rome; investigator Dr Inghirami) (Multimedia Appendix 3). On March 14, 2018, the study protocol was amended to extend the follow-up period, to allow the calculation (not mandatory) of the Nugent score at baseline and the final visit, and to perform an interim analysis 6 months after the inclusion of the first patient. The results of the interim analysis have been recently published [16].

Study Design

The trial includes 2 phases. In the first phase (according to an open-label noncontrolled design), the treatment involving PLGG is administered for 3 cycles, and the treatment is followed by a 1-month follow-up. In the second phase, a 9-month follow-up period is envisaged. This entails that for each patient, a 10-month follow-up is planned as follows: 1 month (from the end of the 3rd cycle of PLGG to day 78 [±6 days as the window range]) plus an additional period of 9 months (±2 months as the window range) without treatment from that date to the final visit.

Study Setting and Patient Recruitment

The 5 centers involved in the study have been selected for their previous large experience in treating BV and for their wide catchment area for patients affected by this infection. The coordinator center is located in Milano (Italy), and the remaining 4 sites are satellite centers (Table 1). In each center, a principal investigator is appointed to be responsible for identification, recruitment, data and sample collection, completion of case report forms, and checking patient adherence to the protocol during the study period.

In addition, each principal investigator is responsible for the transportation of the collected samples to the local laboratory. Indeed, a close relationship between the clinical centers and the laboratories is mandatory to assure optimal performance of the study and to maintain the planned rate of enrollment. Local laboratories analyze each patient’s vaginal smear by phase-contrast optical microscopy. The characteristics of the selected laboratories are reported in Table 2.

Any patient visiting the involved clinical centers during the study period could be enrolled. No flyers, social media, or other advertising methods are used to invite patients to participate in the study.

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Table 1. Centers involved in the study.

Center type and investigator	Hospital	Town and country
Coordinator center		
Dr Murina	Ospedale Vittore Buzzi	Milano, Italy
Satellite center		
Dr Inghirami	AIED, Via Gorizia	Roma, Italy
Dr Cri an	Clinica Medicală Dr Cri an Ciprian	Timisoara, Romania
Dr Biris	Clinica Medicală Dr Cri an Ciprian	Timisoara, Romania
Dr Sîrbu	Clinica Medicală Dr Sîrbu Daniela	Timisoara, Romania

Table 2. Laboratories involved in the study.

Center type and investigator	Hospital	Town and country	Laboratory details
Coordinator center			
Dr Murina	Ospedale Vittore Buzzi	Milano, Italy	The laboratory is inside the center, and the phase-contrast optical microscope is in the same room used for visits.
Satellite center			
Dr Inghirami	AIED, Via Gorizia	Roma, Italy	The laboratory is a private laboratory with extensive experience of collaboration with the lead investigator of the site.
Dr Cri an	Clinica Medicală Dr Cri an Ciprian	Timisoara, Romania	The center is required to send the samples to a unique specialized laboratory (Bioclinica SA).
Dr Biris	Clinica Medicală Dr Cri an Ciprian	Timisoara, Romania	The center is required to send the samples to a unique specialized laboratory (Bioclinica SA).
Dr Sîrbu	Clinica Medicală Dr Sîrbu Daniela	Timisoara, Romania	The center is required to send the samples to a unique specialized laboratory (Bioclinica SA).

Inclusion Criteria

Patients could enter the study if they fulfilled all of the following criteria: (1) presence of RBV, that is, at least 2 episodes in the last 12 months, including the episode treated before the baseline visit of this study; (2) age above 18 years; (3) BV diagnosis by the Amsel criteria in the 6 to 9 days before the study and cure with metronidazole vaginal formulation (gel for 5 days or ovules for 7 days); (4) no lactation, or lactation and no amenorrhea; and (5) willingness and ability to provide signed informed consent.

Exclusion Criteria

Patients fulfilling one or more of the following exclusion criteria would be excluded from the study: (1) menstruation at the screening or baseline visit, menopausal transition, or postmenopausal period (2001 STRAW criteria); (2) pregnancy; (3) known allergy to metronidazole or to the tested PLGG ingredients; (4) mixed vaginitis or candidiasis; (5) HIV or other immunodeficiency; (6) sex worker; (7) concomitant enrollment in other interventional clinical trials; (8) unwillingness to provide informed consent; and (9) time between the last day of the last menses and the baseline visit of >16 days or ≤5 days (this criterion was necessary to avoid bias in case of menstrual bleeding occurring during the first PLGG cycle and the consequent need to interrupt the tested product administration).

Intervention

Overview

As specifically requested by ISO 14.155 and MEDDEV 2.12/1 for postmarketing clinical follow-up (PMCF) studies, all the treatments are performed as indicated in the instruction for use for each product.

Tested Product

The tested product involving PLGG is a class IIa medical device already on the market as CE QPZ-1805-15 (issue date: March 30, 2015) presented as vaginal ovules. Its components are polycarbophil (Noveon AA1), a barrier-forming agent well known for its lack of toxicity; lauryl glucoside, a nonionic surfactant that enhances barrier properties by reducing surface tension; and Witepsol W35, an administration vehicle. It is a hard, fat suppository base delaying the sedimentation of solid components and promoting the wetting of mucous membranes.

The reasons to choose PLGG for testing in the study are as follows [17]:

- PLGG does not have any effect in terms of general tolerance, because it does not cross the epithelium. Locally, even after prolonged exposure, it does not cause any irritation to the vaginal wall, has no toxic effect on epithelial cells, and does not trigger any sensitivity reaction.

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- PLGG has a specific bacteriostatic action that inhibits *Gardnerella vaginalis* growth. In fact, it has been proven that the growth of *Gardnerella vaginalis* was reduced for 48 hours on contact with PLGG (shown already at 24 hours). The inhibitory activity of PLGG has also been demonstrated against *Streptococcus agalactiae* and *Neisseria gonorrhoeae*.
- PLGG has a mucoadhesive property impairing the formation of the biofilm produced by *Gardnerella vaginalis* and allowing the product to stay on the vaginal mucosa for at least 72 hours.
- PLGG has an acidifying effect on vaginal pH, which favors the growth of lactobacillus microbiota and, at the same time, maintains a hostile environment for the recolonization of the vagina by the polymicrobial flora involved in BV.

The mass of the ovule (2.05 g each) ensures coverage of the whole vaginal cavity (about 40 cm^2).

PLGG vaginal ovule administration is started between 12 and 24 hours after the end of metronidazole vaginal treatment. Each cycle of PLGG has a duration of 1 week as follows: 1 ovule is inserted in the vagina on day 1, 1 ovule is inserted on day 4, and 1 ovule is inserted on day 7. Three cycles of treatment (minimum 72 and maximum 84 days) are required for each patient. At the baseline visit, each patient receives a total of 9 ovules for the whole study duration (3 ovules for 3 cycles). The patient is informed by the investigator to lay in the supine position for some time after ovule insertion.

The baseline visit and the first cycle of PLGG vaginal ovule administration is between 6 and 16 days after menstrual bleeding and after the end of metronidazole treatment. The following warnings are considered:

- If the baseline visit is performed in the morning (and the metronidazole treatment is terminated the previous day), the investigator would give PLGG to the patient to allow PLGG self-administration in the evening.
- If the baseline visit is performed in the evening (and the metronidazole treatment is terminated the previous day), the investigator would deliver PLGG to the patient, permitting PLGG administration directly in the medical office or self-administration at home, in the evening of the same day.
- If the baseline visit is performed in the morning of the same day when the metronidazole treatment is terminated, the investigator would give PLGG to the patient and prescribe PLGG self-administration in the evening with an interval of 12 hours from metronidazole treatment.

In the second and third cycles, PLGG vaginal ovules are administered immediately after the end of the previous menstrual bleeding. For safety reasons, the investigator could stop the administration of PLGG at any time and could prescribe different therapies necessary for the patient's health.

Antibiotic Treatment

Metronidazole (vaginal administration) is the chosen antibiotic therapy (5 g of 0.75% gel once daily for 5 days or 500 mg ovules once daily for 7 days). This drug is largely indicated by the literature as one of the best antibiotic treatments for BV, even if its extensive use and frequent patient nonadherence limit its efficacy in avoiding recurrences [18].

Interventions Not Allowed

The following concomitant medications and interventions are not allowed during the study period: oral or vaginal probiotics (eg, vaginal lactobacilli), vaginal tampons, an etonogestrel/ethinyl estradiol vaginal ring (Nuvaring) or intrauterine device, vaginal or oral antibiotic therapy or other vaginal therapies (like spermicide and douching), and other products to treat BV.

Statistical Methods

Power

Data from the medical literature evidenced that the mean recurrence rate of BV after the first episode was from 30% to 50% within 3 months after the appropriate antibiotic therapy [19]. The patients enrolled in our study, after metronidazole treatment, are not allowed to use any vaginal or oral antibiotic therapy. Thus, in this study, it would be realistic to have a mean recurrence rate of 40% after 3 months. Data collected on the recurrence rate after treatment with PLGG vaginal ovules (Effik Italia SpA, unpublished data) showed a 2% correlation between paired observations. We applied a continuity correction, and we obtained a sample size of 44 pairs to achieve a power of 80% and a 1-sided significance of 5% for detecting a difference of 0.25 between marginal proportions. We considered a potential dropout rate of 20%, and thus, we decided to include 55 patients (1-group chi-square test). At 95% CI, a P value <.05 is considered statistically significant.

Statistical Analysis

The values between visits for the primary objective are analyzed using a *t* test or chi-square test for quantitative variables. In case of binary variables and qualitative variables, a McNemar test and a symmetry test, respectively, are applied. The time to event for BV recurrence is analyzed using Kaplan-Meier curves.

The statistical tests for secondary objectives are chi-square and McNemar tests for categorical data. Moreover, a nonlinear mixed effects model analysis is applied.

All tests are 2-sided, with a nominal level of α=5%. In the primary outcome analysis, P values are not adjusted for multiplicity. Statistical analyses are carried out using SAS 9.2 (SAS Institute Inc).

Evaluation Outcomes

Primary Outcome

RBV identified by the Amsel criteria [14] is the primary outcome. The diagnosis requires that 3 of the following 4 criteria are met: (1) vaginal secretion pH greater than pH 4.5; (2) proportion of clue cells ≥20% of total epithelial cells on microscopic examination of the vaginal saline wet mount; (3) off-white and thin vaginal discharge with minimal or absent pruritus and inflammation of the vulva and vagina; and (4) fishy odor on a whiff test.

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The Amsel test is considered negative (no diagnosis of BV) when no or only one criterion is met. If 2 criteria are met at baseline, the test is considered unclear, and adopting a conservative approach, the patient is not included. When 2 criteria are met in the final visit, treatment failure is declared.

The Amsel criteria are analyzed by investigators according to the following parameter characteristics:

- Color (off-white, white-grey, or milky) and type (thin and homogeneous) of the vaginal discharge: The investigator performs a direct evaluation of the vaginal secretion.
- Vaginal pH: It is evaluated by investigators using pH paper (Merck) with a range of 4.0 to 7.0. The paper is placed on the lateral vaginal wall to avoid contact with the alkaline secretion of the cervix. Alternatively, pH is evaluated by putting the paper on a swab.
- Whiff test: A sample of the vaginal discharge is placed on a glass slide or in a test tube, and a drop of 10% potassium hydroxide (10% KOH) is added to evaluate the presence of a fishy odor caused by the release of amine.
- Clue cells: Clue cells are checked in local laboratories. A vaginal smear of each patient is collected at the clinical center and sent to the local laboratory. Two drops of vaginal discharge are covered with a coverslip and examined using a phase-contrast optical microscopy technique. Clue cells are identified as vaginal epithelial cells with such a heavy coating of bacteria that the peripheral borders are obscured. The test is positive if microscopic examination of the vaginal saline wet mount shows the presence of clue cells and if the proportion is greater than 20%.

The primary outcome is measured at baseline (day 0), 30 days after discontinuation of PLGG treatment (day 78 [±6 days]), and at the end of follow-up (month 10 [±2 months]). Additional measurements for the primary outcome are performed at unscheduled visits. This is carried out whenever patients report symptoms of RBV to the investigator. The percentage (%) of RBV is calculated considering both the primary outcome results (recurrence of BV identified by means of the Amsel criteria) and the treatment failures reported in the unscheduled visits.

Secondary Outcomes

The secondary outcomes are listed and detailed in Table 3.

The secondary outcomes also include the patient global evaluation of performance using a 4-point scale as follows: 1=very good improvement; 2=good improvement; 3=moderate improvement; and 4=negligible improvement.

Safety is evaluated by collecting and analyzing the data on adverse device effects/serious adverse device effects/unanticipated serious adverse device effects and adverse events/serious adverse events during the study period and by globally assessing the safety according to the investigator, using an analogic 4-point scale as follows: 1=excellent; 2=good; 3=fair; and 4=poor.

All secondary endpoints are measured at baseline (day 0) and 30 days after discontinuation of PLGG treatment (day 78 [±6 days]). Only vaginal lactobacilli microbiota is also assessed at the end of follow-up (month 10 [±2 months]).

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Table 3. Secondary outcome details.

Outcome and score	Evaluation
Vaginal lactobacilli microbiota	
+1 or +2 (normal)	Numerous pleomorphic lactobacilli, and no other bacteria, clue cells, or hyphae. Lactobacillary grade I or IIa.
+3 (partially impaired)	Population of lactobacilli is severely decreased. Lactobacillary grade IIb.
+4 (pathological)	Lactobacilli are severely depressed or absent because of overgrowth of other bacteria, clue cells (>20%), or hyphae. Lactobacillary grade III.
Vaginal discharge (over the last 24 hours)	
0	Not present or physiological with regard to quantity, color, and type (white, thin, and flocculent)
1	Mild abnormal (abnormal quantity with normal color and type)
2	Abnormal quantity, color, and type (white curdy, or thin, greyish, white homogeneous)
Burning (over the last 24 hours)	
0	Not present
1	Mild
2	Moderate
3	Severe
4	Unbearable
Erythema	
0	No symptoms
1	Slight
2	Moderate
3	Marked
4	Very marked
Dyspareunia	
0	Absent
1	Present

Study Procedures and Visits

Prior to any procedure of the trial, each patient is informed about the purpose and nature of the study, the potential risks, and the benefits, and is requested to provide consent by signing an informed consent form. Before starting the follow-up period, the patient is required to sign an additional informed consent form detailing the second part of the study.

The visits planned during the study period (Figure 1) are as follows: visit at day 0 (baseline), visit at day 78 (±6 days; 30 days after discontinuation of PLGG treatment), and visit at month 10 (±2 months; end of the follow-up period).

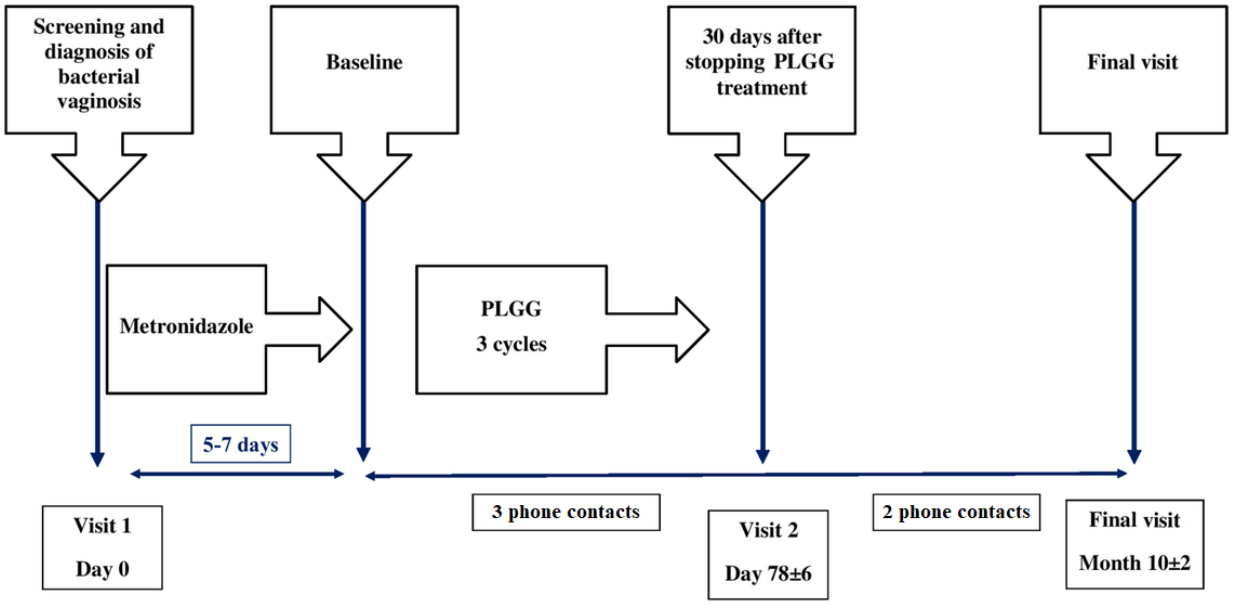
Phone calls with the patient are also planned as follows: first phone contact at 28 (±1) days after the last day of the last menses, second phone contact at 28 (±1) days after the first phone contact, third phone contact at 28 (±1) days after the second phone contact, fourth phone contact at the fourth month of follow-up, and fifth phone contact at the seventh month of follow-up.

During any phone contact, the investigator checks if the patient has BV symptoms, and if present, an unplanned visit is scheduled to confirm the diagnosis of BV based on the Amsel criteria.

The study timeline is presented in Table 4.

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Figure 1. Visits and phone calls planned during the study period. PLGG: polycarbophil, lauryl glucoside, and glycerides.



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Table 4. Study timeline.

	Study period							
	Visit 1 (baseline)	Cycle			Visit 2	Month assessment		Final visit
Timepoint	Enrollment (day 0)	1st cycle	2nd cycle	3rd cycle	Day 78±6[a]	Month 4	Month 7	Month 10±2[a]
Eligibility screening	✓							
Medical history	✓							
Informed consent	✓							
Vaginal swab for lactobacilli determination	✓				✓			
Amsel criteria								
Vaginal pH	✓				✓			✓
Whiff test	✓				✓			✓
Vaginal discharge	✓				✓			✓
Clue cells	✓				✓			✓
Signs and symptoms of BV[b]								
Vaginal discharge	✓				✓			
Burning	✓				✓			
Erythema	✓				✓			
Dyspareunia	✓				✓			
Patient global evaluation of performance	✓				✓			
PLGG[c,d] administration		Within the 6th and 16th day after menstrual bleeding	Immediately after the end of the previous menstrual bleeding	Immediately after the end of the previous menstrual bleeding				
Phone contact		28±1[a] days after the last day of the last menses	28±1[a] days after the 1st phone contact	28±1[a] days after the 2nd phone contact		✓	✓	
Physical examination	✓				✓			
Concomitant medication recording	✓	✓	✓	✓	✓	✓	✓	✓
Check for adverse events	✓	✓	✓	✓	✓	✓	✓	✓
Unused PLGG returned to the investigator					✓			
Diary card delivery	✓				✓			
Diary card collection					✓			✓

[a]Visit window range.

[b]BV: bacterial vaginosis.

[c]PLGG: polycarbophil, lauryl glucoside, and glycerides.

[d]Each cycle of PLGG has a duration of 1 week as follows: 1 ovule is inserted in the vagina on day 1, 1 ovule is inserted on day 4, and 1 ovule is inserted on day 7.

Results

The recruitment of patients started on September 8, 2016 (first patient and first visit). An interim analysis was conducted in 2019, which has already been published [16], and the results of the full study analysis should be available in July 2023.

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Discussion

Gardnerella vaginalis is able to adhere to and displace precoated protective lactobacilli from vaginal epithelial cells, while other BV-associated anaerobes, such as *Fannyhessea vaginae* and *Prevotella*, are less active [20]. Consequently, the current paradigm is that the establishment of the biofilm of *Gardnerella vaginalis* is a required event for the initiation and progression of BV. Since the bacteria within biofilms are not effectively eliminated by the immune system or fully destroyed by antibiotics, biofilm-related infections tend to persist, and thus, not surprisingly, BV tends to have a high rate of relapse and recurrence [5]. PLGG has a specific bacteriostatic action, which inhibits *Gardnerella vaginalis* growth, and its mucoadhesive property could impair the formation of the biofilm produced by these bacteria. The PLGG constituents have important effects on the mechanism involved in the pathogenesis of BV.

In addition, the acidifying effect of PLGG on vaginal pH (favoring the growth of lactobacillus microbiota and maintaining a hostile environment for vagina recolonization by BV polymicrobial flora) could play a key role in improving the microbiological parameters over a long period.

We believe that the findings of our study could be useful for other investigators who want to test different products against RBV using a standardized protocol and standardized procedures. Regarding this, it would be interesting to collaborate with other investigators to test, using the methodology applied in this study, antibiotic therapies indicated in international guidelines [6,21] that are different from metronidazole, as well as other products to replace PLGG. Finally, it could be extremely challenging to conduct our study in geographical regions other than Europe (such as Asia or Africa) or in climatic situations radically different from the continental climate of Romania. In fact, seasonal patterns of abnormal vaginal microbiota have been recently reported in the Burkina Faso population [22], and treatment with oral metronidazole is often ineffective in African women [23].

The absence of an untreated control group represents the main limitation and weakness of the study, but we believe that it is unethical to choose patients experiencing two or more episodes of RBV as an untreated control group. In the near future, when the results of this study are analyzed, we will individuate the proper power of PLGG, and using this information, we will calculate the sample size for a comparative study involving PLGG versus a comparator (ie, a different treatment able to prevent RBV).

The Amsel criteria as originally reported [14] state the presence of clue cells on wet mount microscopy as 1 of the 4 criteria for the diagnosis of BV. The FDA guidelines [24] require not only that clue cells be present, but also that their proportion be greater than 20% of total epithelial cells. This is the clinical practice of the 5 centers involved in the study and is therefore reported in the study protocol, even though it may underestimate RBV cases.

Acknowledgments

Effik SpA (Italfarmaco group), the study sponsor, offered the tested medical device and partial grant support. The funder had no role in the design of the study; in the collection, analysis, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results. We thank Adrian Bratu for support in data management and Marius Ardelean for assistance in statistical analysis.

Data Availability

The full protocol of the study has been deposited at protocols.io [25]. In addition, the data sets analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

Conceptualization, FM; methodology, FM and DFB; formal analysis, FM and SR; investigation, FM, PI, MB, DS, and CDC; writing-original draft preparation, FM, FS, SR, and DFB; writing-review and editing, FM and DFB; visualization, SR; supervision, FM; project administration, DFB, MM, LIA, and EC. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

FM, PI, MB, DS, SR, and CDC declare no conflicts of interest. DFB and FS are employed at Opera Contract Research Organization, the Contract Research Organization that managed the study; EC is a medical consultant for Italfarmaco SpA; and LIA and MM are employed at Italfarmaco SpA.

Multimedia Appendix 1
Visual abstract of the POLARIS (Polybactum to Assess Recurrent Bacterial Vaginosis) protocol.
[PDF File (Adobe PDF File), 518 KB - resprot_v12i1e42787_app1.pdf]

Multimedia Appendix 2
POLARIS logo.

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[PNG File , 166 KB - resprot_v12i1e42787_app2.png]

Multimedia Appendix 3
Ethics committee approvals.
[PDF File (Adobe PDF File), 508 KB - resprot_v12i1e42787_app3.pdf]

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Abbreviations

BV: bacterial vaginosis
EC: ethics committee
PLGG: polycarbophil, lauryl glucoside, and glycerides
RBV: recurrent bacterial vaginosis

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Protocol

Sexual Health and Drug Use Prevention for Black Girls (The Dreamer Girls Project): Protocol for an Intervention Development

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Abstract

Background: Substance use among adolescent girls is associated with numerous risk characteristics, including engaging in sexual risk behaviors, which can lead to HIV and sexually transmitted infection (STI) diagnoses. This is an important phenomenon to target as there is a significant race-gendered paradox that occurs when Black girls use and misuse drugs. When misuse occurs among this group, they are more likely to face harsher consequences and worse health outcomes than boys and other ethnic-minority girls. Therefore, there is a need to understand the risk and protective factors of drug use and sexual risk behaviors among Black girls and develop a robust intervention that can cater for this group.

Objective: We propose the development of a strengths-based prevention education intervention for Black girls between the ages of 13 and 18 years to promote protective factors.

Methods: A sequential, mixed methods study will be conducted, and we will use the first 3 steps of the ADAPT-ITT (assessment, decision, adaptation, production, topical experts, integration, training, testing) framework to begin the development of the intervention. Three aims will be described in this protocol. First, aim 1 is to explore sociocultural risk and protective factors among Black girls between the ages 13 and 18 years in drug use and HIV/STI prevention using focus group methodology and surveys. We will conduct at least 10 focus groups to include up to 75 Black girls or until we reach saturation. Our target sample size for the quantitative portion of the study will be 200 participants. Aim 2 will focus on deciding upon an intervention based on findings from aim 1 and forming a youth advisory board to guide intervention development. Aim 3 will be to conduct a pretest of the intervention with the youth advisory board to determine if the intervention is feasible and will be accepted by Black girls.

Results: The study is part of a 2-year research pilot study award from the National Institutes of Mental Health. Data collection for this study began in October 2021. For aim 1, data collection is 95% complete. We expect to complete all data collection for aim 1 on or before May 30, 2023. Study activities for aim 2 are occurring simultaneously as data are being collected and analyzed and will be completed in the summer of 2023. Study activities for aim 3 will begin in the fall of 2023.

Conclusions: This study will be one of the few interventions that address both sexual health and drug use together and cater to Black girls. We anticipate that the intervention will be beneficial for Black girls across the nation to work on building culturally appropriate prevention education and building peer social supports, resulting in reduction or delayed substance use and improved sexual health.

Trial Registration: ClinicalTrials.gov NCT05014074; https://clinicaltrials.gov/ct2/show/NCT05014074

International Registered Report Identifier (IRRID): DERR1-10.2196/45007

(JMIR Res Protoc 2023;12:e45007) doi:10.2196/45007

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KEYWORDS

HIV prevention; drug use prevention; Black girls; youth; formative; Black; girl; adolescent; drug abuse; substance abuse; HIV; prevention; patient education; education intervention; sexual transmission; sexually transmitted; sexually transmitted disease; STD; sexually transmitted infection; STI; sexual health; health promotion; ethnic; minority

Introduction

Despite substantive literature on the relationship between adolescent drug use and sexual risk behavior, gaps in prevention research may continue to place Black girls between the ages of 13 and 18 years in the United States at risk. Historically, girls of all racial and ethnic groups in the United States have had lower drug use rates than boys [1]. However, over the past decade, the prevalence of smoking cigarettes, drinking alcohol, and using illicit drugs such as marijuana has increased among adolescent girls, and specifically increased as they get older [2,3]. In the past decade, Black girls have begun to engage in substance use more frequently and at rates similar to their male counterparts [2]. This is concerning because drug use among adolescent girls is linked to a variety of risk factors, including engaging in sexual risk behaviors [4,5]. According to the 2019 Centers for Disease Control and Prevention Youth Risk Behavior Survey, while cigarette use is almost nonexistent for this group, 38.6% of Black girls admitted to using electronic vapor products, with 17% of them using within the past 30 days. Similarly, 37% of Black girls in the study used marijuana, with 24.8% using marijuana within the past 30 days [2]. The rates of marijuana among Black girls have also increased significantly from early to late adolescence [6,7]. Black girls may face a significant "gender paradox" where although they are less likely to use substances than boys and other ethnic-minority girls, they tend to face more negative health consequences from use [8].

Black girls are more at risk of being persuaded to engage in sexual risk behavior such as drinking alcohol or using drugs before having sex, having sex without a condom, and having multiple sexual partners than their White counterparts [9]. These behaviors may be the direct consequence of belonging to multiple marginalized groups (eg, race, ethnicity, class, and gender), resulting in intersecting multiple levels of oppression [10]. Such behaviors may arise from the historical and contextual factors of trauma, gendered racism, and sexual exploitation that are pervasive in the lives of Black girls [11-13]. Lack of discussion and knowledge of HIV/AIDS prevention strategies, limited or nonexistent community-based preventive resources, and gender- and racial-specific behavioral interventions in urban, underresourced communities can significantly contribute to increases in sexual risk behaviors [14,15]. Sexual health disparities and drug misuse that affect Black girls not only produce poor health outcomes but can also contribute to educational inequities [16], increases in school suspension rates [17], criminal involvement [18], income inequality [19], and sexual victimization [20].

The multiple marginalized identities of Black girls place them at increased risk of early sexual debut (ie, having sex at or before the age of 14 years), making them more susceptible to condomless sex and having partners that encourage sexual risk behaviors and making them more likely to be sexually abused, which increase their risk for HIV and sexually transmitted infections (STIs) [14,21]. In one study, the authors found that among sexually active Black girls between the ages of 14 and 19 years, 48% were diagnosed with at least 1 sexually transmitted infection [22]. Being diagnosed with an STI places individuals at an increased risk of contracting HIV [23]. In addition, adults living with HIV/AIDS are more likely to engage in risky sexual behavior during adolescence [24]. As Black women currently represent 61% of women living with HIV/AIDS [25], it is crucial to intervene with Black girls in order to provide them with prevention strategies that can be used as they transition into adulthood.

Although HIV and drug abuse prevention initiatives for adolescents exist, many are homogeneous, aim to be generalizable in nature, and do not consider unique racial and gender differences in risk and protective factors [26]. Furthermore, there are very few integrated HIV and drug abuse prevention interventions for Black girls [27]. As age can limit mobility geographically, which may then contribute to the further marginalization of Black girls due to limited power and dependency on others [28]. Multiple contextual factors that are present in the lives of Black girls are often ignored, thus leaving many strategies that are embedded in prevention interventions, such as educational components that do not center the lived experiences of Black girls, not helpful for this group [27]. Researchers have called for HIV and drug use prevention research that uses an intersectional framework to examine how multiple identities interact to have an impact on attitudes and behaviors [29,30].

This study protocol is describing the formation of a mixed methods study called "The Dreamer Girls Project," which will first understand the challenges and protective factors present in the lives of Black girls related to substance use and sexual health and then use the findings to develop a strengths-based prevention intervention. The study team will work collaboratively with a youth advisory board and use formative data collection to inform the development of the intervention. The study aims are shown in Textbox 1.

This study has the potential to provide new information about risk and protective factors for Black girls and strengths-based strategies that can be infused in HIV, STI, and drug use prevention for Black adolescents between the ages of 13 and 18 years.

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Textbox 1. Study aims.

- Aim 1: Understand sociocultural risk and protective factors among Black girls between the ages 13 and 18 years in drug use and HIV/STI prevention using focus group methodology and surveys.
  - Aim 1a: Quantify the prevalence rates of drug use and behaviors associated with HIV risk among Black girls aged 13-18 years.
- Aim 2: Decide upon an intervention based on findings from aim 1 and form a youth advisory board to guide intervention development.
- Aim 3: Assess the feasibility of the intervention through theater testing.

Methods

Conceptual Framework

The study will use intersectionality theory as a theoretical framework to guide the formative phase and overall development of the intervention [31-33]. Our usage of intersectionality theory will incorporate a culturally relevant perspective that includes the voices of Black girls, allowing them to redefine themselves, include discussions around protective factors that they themselves perceive as beneficial in their lives, and celebrate supportive structures that nurture their ability to be resilient. An intersectional perspective, therefore, provides a unified lens through which to view health disparities and develop interventions that are more responsive to race, ethnicity, gender, age, and class [28]. Intersectionality functions as a framework in this study to understand the experiences of Black girls, who possess a different social location than Black women based on their age and cognitive and psychological development. In addition, because an intersectional perspective can be strengths based, it moves the blame away from individual behaviors to systemic and contextual factors that have historically placed Black girls at risk. The framework considers the cultural and historical context of Black girls that influences their susceptibility and exposure to drug use and sexual risk behaviors, as well as highlights the significance of systemic racism, classism, and misogyny within the United States as contributing factors to their exposure. Such a framework has been useful not only in designing and guiding social programs but also in developing ethnic, racial, gender, and class-responsive research for girls. It is to be acknowledged that Black girls are not a homogenous group, which means that significant within-group differences will exist. Therefore, the use of intersectionality theory as a framework allows for our study team to account for those differences in order to make interventions more appropriate to the experiences of Black girls [31].

Study Design

We will conduct an exploratory, sequential mixed methods study. The protocol is registered on ClinicalTrials.gov (NCT05014074) and was approved by Yale University Institutional Review Board.

Eligibility

Adolescent girls who identify as (1) Black, (2) identify as female, (3) are between the ages of 13 and 18 years, (4) can speak and understand English, and (5) live in the United States will be allowed to participate in this study.

Ethics Approval

All procedures performed in studies involving human participants are in accordance with the ethical standards of the institutional and national research committee, the 1964 Helsinki Declaration and its later amendments, or comparable ethical standards. The study was funded by the National Institute of Mental Health (R25MH087217) and approved by the Yale University Institutional Review Board in 2020 (IRB-2000026660). Due to the sensitivity of the research questions, we requested that written parental consent be waived for the young participants. All youth who participate in the study (including focus groups and completing surveys) will receive a youth information sheet and parents and guardians will receive a parent information sheet. Youth must give verbal consent in order to participate in the study. We will obtain informed consent from all girls who meet the eligibility criteria and want to participate before they are enrolled in study activities.

Recruitment

Purposive sampling for focus group recruitment will be used to ensure a representation of different subgroups of Black girls. The research team has relationships with community-based organizations in New Jersey and organizations that serve Black girls across the nation. Flyers will be given to program administrators at these organizations to disseminate to interested participants. Flyers for the recruitment of focus groups will also be posted on social media sites such as Facebook, Instagram, and Twitter. All girls who are interested in being a part of the focus groups will have to complete an eligibility form on Qualtrics (Qualtrics International Inc), which will ask for demographic information and contact information. Only girls who identify as Black and female, are between the ages of 13 and 18 years, and live in the United States will be allowed to participate. Research staff will contact eligible participants and will inform them of the purpose of the study and will screen them to confirm that they are eligible to participate based on inclusion criteria. Potential participants will be told that all data will be kept anonymous and confidential and that a monetary incentive of US $30 will be provided for participants who complete the focus group. Potential participants for the qualitative component of this study will also be informed that their responses to questions will be recorded. Upon confirmation of their desire to participate, they will be given a date, time, and Zoom (Zoom Corp) link if web-based or a physical location if appearing in person. The institutional review board has approved this study and agreed to waive parental consent due to the sensitivity of the topic. Youth assent will be obtained verbally. All youth and parents and guardians will be provided an information sheet regarding their daughter's participation in the

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study. All participants and parents and guardians of participants younger than 18 years will be told that they can opt out at any time during the study. Community organizations who are able to provide us with space for in-person focus groups will receive honorariums. Recruitment for survey data collection will involve sharing the survey link on various social media platforms and community organizations that serve Black girls. Only girls who identify as Black and female, are between the ages of 13 and 18 years, and live in the United States will be allowed to complete the survey. All participants who completed the survey were compensated with a US $10 gift card.

Procedures

A semistructured interview guide using intersectionality theory will be developed to explore drivers of substance use, social supports necessary to promote the prevention of substance use and supports necessary to reduce HIV risk behaviors. The study principal investigator (PI) and first author of the protocol (IO) is an expert in using intersectionality theory as a framework for studies involving Black girls. More specifically, the study PI has published studies that used intersectionality theory as a framework in analyzing quantitative and qualitative data [10,34,35] and teaching courses using an intersectionality framework [36]. After the interview guide was developed, another expert who serves as a coauthor of this protocol (KB) will review and revise the guide to ensure that questions use an intersectionality framework. KB is an expert on intersectionality theory and qualitative methodology with Black cisgender and transgender girls and women. Collectively, the study team including the study PI, who has several years of experience in designing studies for Black girls, will develop questions to ensure that girls across the development age span of 13 to 18 years would be able to understand the questions.

Data collection will involve in-depth focus groups to be conducted in a group setting at a community partner's location sites (mainly in New Jersey due to the study team's relationships with New Jersey–based community organizations) and web-based groups will be conducted on Zoom. Research in web-based settings has been increasing due to the COVID-19 pandemic and may continue to be a major platform to connect with participants. Research conducted in web-based settings has been established as effective venue for research on multiple content areas [37]. Efforts will be made to place participants into groups that are separated by demographic variables such as age or religion (ie, aged 13-15 and 16-18 years) as it is recommended to group individuals with similar life experiences for optimal focus group dynamics. Each focus group will be audio recorded, transcribed by trained research assistants, and entered into NVivo 11 (QSR International), a qualitative data analysis software package. Focus groups will aim to uncover how Black girls view substance use and sexual risk behavior in their community. Questions that will be discussed in the focus groups are (1) How do race, gender, and class impact views on drug use and sexual risk behavior among Black girls? (2) How do Black girls view their identity and expectations that they perceive from society? (3) What are the risk factors of engaging in drug use and sexual risk behavior that are specific to Black girls? (4) What are protective factors and what do they look like? and (5) What would a successful prevention intervention look like for Black girls in various communities? While 3 or 4 focus groups are recommended for saturation [38], we aim to conduct at least 10 focus groups or until no new data emerge from focus group discussions.

Training of Interviewers

Interviewers will be research staff who identify as Black women, trained by a qualitative methodology expert (KB) on how to engage and conduct focus group interviews with Black girls. The training will involve discussions around being aware of power dynamics that may emerge during the interview in order to facilitate the focus groups effectively. In addition, interviewers will be challenged on assumptions and biases that they may have of Black girls in order to assure that data collection is conducted in an objective and respectful manner that honors Black girls. All facilitators and cofacilitators must identify as Black women, as there is evidence of the importance of racial and gender matching when conducting research with vulnerable and marginalized groups such as Black girls [39].

Data Analysis

Aim 1: Understand What Environmental and Sociocultural Factors Influence Drug Use and Sexual Risk Behavior Among Black Girls

Aim 1a. Determine Prevalence Rates of Substance Use and Sexual Risk Behaviors Among a Sample of Black Girls

Within this aim, we will use a sequential exploratory study design [40] to understand risk and protective factors that are specifically mentioned by Black girls through engaging in mixed methodologies. Sequential exploratory design is used when a study team wants to follow-up or explains qualitative findings with quantitative analysis. This 2-phase approach is particularly useful for our study as we are interested in understanding the unique perspective of Black girls and want to develop an intervention catered for this population.

First, we will use focus group methodology, which will allow the study team to receive insight from Black girls themselves about what they perceive as the challenges but also strengths that may be present in their environments, families, and communities involving drug use and sexual health. Focus group methodology is useful in this phase as it not only provides a rich source of data but also allows the researcher to examine the interaction among participants [41]. We will aim to conduct at least 10 focus groups, with a goal to obtain a sample size of 75 Black girls or until data saturation is reached. We acknowledge that this is a large sample size. However, since we will be interviewing Black girls from across the nation, we believe that having a large sample size will give us richness in the data and allow us to explore differences and similarities across the groups.

After focus groups are conducted and before the analysis begins, facilitators of the focus groups will participate in debriefing meetings. These meetings will provide a space for facilitators to process each focus group and discuss possible issues of countertransference that may have occurred. This is necessary as we want to minimize any potential to influence the results of the study. In addition, the debriefing meetings provide

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facilitators the space to discuss their feelings and emotions that arose during the groups. The data analysis team will include at least 3 research assistants and the study PI who has experience in analyzing qualitative analysis and leading qualitative studies. To establish confirmability the research team will code all of the transcripts. Data will be coded using NVivo version 11. Data from the interviews will be first analyzed by interviewers using open coding, whereby concepts were identified and labeled as they emerged from the data and across the focus groups. Each member of the research team will read and reread all the transcripts and develop initial codes in isolation. During weekly research meetings, the initial codes will be reviewed and discussed. Using multiple coders provides insight into finding consistency and minimizing researcher bias [42]. The team will triangulate codes, notes, and memoranda of analyses until >95% substantive agreement is achieved. Prevalent codes (based on the frequency in which a code is used by participants across and within groups) will be grouped by similarity and relevance into themes and subthemes. To increase the rigor of the study, the researchers intend to use prolonged engagement, regular team debriefings, and member checking with participants [43]. Participants of the focus groups will be asked if they are interested in being a part of the youth advisory board. The youth advisory board will be developed for the sole purpose of confirming the findings and developing the intervention. We will aim to recruit 8-10 youth upon completion of the qualitative portion of the study.

Aim 1b: Quantitative Data Collection

Based on the findings from the qualitative focus groups and the use of a sequential exploratory study design, data will be analyzed rapidly [44] and inform the development of the survey that will be administered to Black girls. In order to accurately perform rigorous statistical analysis tests such as structural equation modeling, we proposed a sample size of 200 girls as performing structural equation modeling on data requires a sample size of at least 150 [45]. We anticipate including standardized measures such as 30-day drug use and sexual risk behavior measures, adapted by the Centers for Disease Control and Prevention Youth Risk Behavior Survey [2]. In addition, we will include measures pertaining to ethnic identity, sexual orientation racial discrimination, and gender identity.

Aim 2: Decide Upon an Intervention Based on the Findings From Aim 1 and Form a Youth Advisory Board to Guide Intervention Development

Because the goal of this study is to obtain information from Black girls in order to develop an intervention for them, we will use an implementation science framework that centers the voices of participants. We will use ADAPT-ITT (assessment, decision, adaptation, production, topical experts, integration, training, testing) [46], an implementation framework that has been commonly used to adapt HIV interventions. The ADAPT-ITT model involves eight steps: (1) assessment of priorities, (2) decisions on adapting, (3) administration of intervention, (4) production of adapted version, (5) topical experts, (6) integration of feedback from topical experts, (7) training staff to implement, and (8) testing the adapted intervention. Because of the nature and funding restrictions of this pilot study, we will only complete the first 3 steps.

For aim 1, the assessment step requires researchers to obtain a comprehensive understanding of the target population. Next, for aim 2, a youth advisory board of 8-10 Black girls will be formed and will select the interventions that they will decide to adopt or adapt. The decision phase will be guided by themes that arose from the focus group and quantitative findings, in order to assure we will be choosing interventions that best meet the needs of Black girls. Our youth advisory board will first be presented with common HIV prevention interventions catered toward Black girls and women such as SiHLE (Sistering, Informing, Healing, Living, and Empowering) [47] and will be asked to vote on each of their strengths and weaknesses. We will then work with our study team, guided by the youth advisory board to either modify components of a particular intervention or create our own intervention. The study team has conducted a systematic review of the most commonly used HIV and drug use interventions that include large samples of Black girls and has expertise in the various components of interventions for this group [27].

Aim 3: Assess the Feasibility of the Intervention Through Theater Testing

Using the ADAPT-ITT framework, we will enter into step 3, which is the adaptation phase. This phase involves using an innovative pretesting methodology known as theater testing to adapt the evidence-based intervention that the study team and youth advisory board decide upon. Theater testing is a type of pretesting methodology that is commonly used to test products, such as television advertisements, videos, print advertisements, and public service announcements [48]. Using this methodology, participants, which will be the youth advisory board, will be invited to laboratory or community site to respond to a demonstration of a product (ie, of the adapted intervention). At the end of the demonstration, participants will receive a questionnaire and answer questions designed to gauge their reaction to the product. An important strength of this methodology is the opportunity to obtain reactions to messages, concepts, and visual materials in a relatively short period. Furthermore, this methodology closely resembles what is experienced by the target population; thus, an accurate assessment of their reactions to the product can be obtained.

Results

The study is part of a 2-year research pilot study award that received funding from the National Institutes of Mental Health. Data collection for this study began in October 2021. The remaining year will focus on completing data collection, analysis, and dissemination and developing the intervention components. We have published 1 manuscript based on the formative work for the development of this intervention, which was a systematic review of sexual health and drug use prevention interventions for Black girls [27]. Moreover, data collection for aim 1 is 95% complete. We expect to complete all data collection for aim 1 on or before May 30, 2023. Recruitment for aim 2 will begin in the summer of 2023.

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Discussion

Anticipated Findings

The goal of this study is to understand the lived experiences of Black girls and obtain information that can be used to develop and pilot a race-specific intervention for this group. We anticipate that having Black girls co-design this intervention with the research team will have great potential to facilitate healthy behaviors and challenge negative stereotypes that impact Black girls' decision-making over the course of the study and thereafter. This study has the potential to transform the way researchers work with Black girls and cocreate in order to develop sustainable solutions toward ending the HIV epidemic and addiction. The development of racial- and gender-specific intervention specifically for Black girls is essential, and developing interventions specific to a certain demographic has proven to produce successful results in health-promoting behaviors. For instance, one HIV prevention intervention tailored to the experiences and needs of Black women in Atlanta, Georgia was assessed for efficacy at improving condom use after 1 session. The authors found that at the 6-month follow-up women who participated in the session reported more frequent condom use and recent HIV screening [49]. Gender- and racial-specific interventions often move beyond individual risk behaviors and focus on social, environmental, and political influences on the well-being of women and girls. Specific focus on racial and gender pride, healthy relationships and healthy sexuality, reproductive justice, sexual communication, and empowerment around sexual refusal are just a few key aspects of effective interventions for Black women that may be tailored to Black girls [50]. The findings of this study will assist with identifying the elements of HIV prevention interventions specific to Black girls that can be applied broadly in the area to improve sexual health and HIV and STI prevention broadly. Given the current climate, interventions that address key factors such as racism, ethnic identity, and gendered racism must be integrated with intervention efforts for adolescent girls.

Limitations

This is a formative sequential exploratory study design using mixed methods (qualitative data, cross-sectional survey data). A limitation of this study is that data will be collected via self-report and subject to response bias.

Conclusions

The Dreamer Girls Project lessons learned will aim to provide real-world contributions to implementation science regarding the uptake of a combination of evidence-based prevention interventions guided by Black girls. The evidence from this study will be used for the preparation of a feasibility trial and a more robust and larger HIV, STI, and drug use prevention clinical trial specifically for Black girls.

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Data Availability

The data sets generated during and analyzed during this study are not publicly available due to confidentiality reasons but are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

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Abbreviations

ADAPT-ITT: assessment, decision, adaptation, production, topical experts, integration, training, testing
PI: principal investigator
SiHLE: Sistering, Informing, Healing, Living, and Empowering
STI: sexually transmitted infection

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Protocol

Enhancing the Introduction and Scale Up of Self-Administered Injectable Contraception (DMPA-SC) in Health Systems (the EASIER Project): Protocol for Embedded Implementation Research

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Abstract

Background: The introduction of self-administered injectable contraception presents an opportunity to address the unmet need for family planning. As ministries of health scale up self-administered injectable contraception, there is a scarcity of knowledge on the implementation practices and contextual conditions that help and hinder these efforts. The World Health Organization has launched the “enhancing self-administered family planning through embedded research project” (EASIER) to address this challenge.

Objective: EASIER’s objectives are to: (1) assess the coverage of self-injectable contraception, and the readiness of health systems to integrate it into the contraceptive method mix; (2) document strategies used to introduce and scale up self-injectable contraception and understand practices that have led to success and challenges; (3) identify the contextual factors that affect the adoption and implementation of self-injectable contraception throughout health systems; (4) understand whether implementation addresses users’ preferences and needs; (5) strengthen collaboration between decision makers, researchers, and implementers; support and build capacity to use evidence.

Methods: EASIER developed a global protocol that implementation research (IR) teams in Burkina Faso, Ghana, and Kenya adapted into country-level embedded IR projects. In all countries (1) at the national level, IR teams evaluate the policy environment for scaling up by conducting a desk review and in-depth interviews; (2) at the local level, IR teams implement quantitative questionnaires on structural and organizational readiness to integrate self-injection into the method mix; (3) in “case study” localities, IR teams conduct in-depth interviews and focus group discussions with implementers, method users, and community members; and (4) IR teams use participatory action research to elicit stakeholder participation and translate findings into programmatic decisions.

Results: EASIER has been launched in all 3 countries. Preliminary findings are available from Burkina Faso and Kenya. In Burkina Faso, IR teams identified the need to strengthen health worker training approaches to ensure that family planning providers at primary health care facilities are adequately oriented to depo-medroxyprogesterone acetate subcutaneous (DMPA-SC) and self-injection and capacitated to initiate women to the method. In addition, they report the need for service communication strategies that reach potential users of the method with knowledge about self-injection and how to initiate the practice. In Kenya, the findings illuminate the need for practice guidelines that county health teams can use to coordinate the rollout of self-administered DMPA-SC. In addition, Kenya’s findings underscore the importance of addressing logistical bottlenecks to help avoid stock-outs.

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Conclusions: EASIER presents a strategy to embed IR in contraceptive method introduction and scale-up, address local knowledge needs, devise ways to maximize the impact of new technologies in health systems, and build capacity for using evidence in programmatic decisions. Adaptation and implementation of country-level IR studies will advance the use of IR to strengthen family planning programs.

Trial Registration: Australia New Zealand Clinical Trials Registry ACTRN12622001228774; https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=384534&isReview=true

International Registered Report Identifier (IRRID): DERR1-10.2196/44222

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KEYWORDS

contraception; depo-medroxyprogesterone acetate subcutaneous; DMPA-SC; family planning; implementation research; scale up; self-care

Introduction

Overview

In recent years, self-care interventions have received attention in the global health community because of their unique potential to alleviate constraints on individuals' access to services and the pressure of increased service use on health systems [1]. Self-care encompasses manifold strategies that emphasize the needs and abilities of individuals, families, and communities to promote health, prevent and control disease, facilitate self-medication, provide care to dependent persons, rationalize the use of formal health care services, and facilitate rehabilitation [2,3]. In doing so, self-care can empower vulnerable communities to go beyond conventional health system responses and meet their needs despite health care worker shortages, humanitarian conflict, disease outbreaks, geographic barriers, and rising out-of-pocket health expenditures [4].

Unintended pregnancy, resulting from the unmet need for contraception, threatens the lives and well-being of girls and women globally. An estimated 214 million women in low- and middle-income countries (LMICs) have an unmet need for a modern method of contraception, and over half of these women live in sub-Saharan Africa and South Asia. According to the Guttmacher Institute, if all such women's demand for contraception were satisfied, there would be a 75% decline in unintended pregnancies and 76,000 fewer maternal deaths per year [5]. Since 2013, evidence on the potential of self-care approaches in family planning (FP) has emerged. It builds on the accumulation of lessons from studies that demonstrated the safety, effectiveness, and acceptability of a woman-centered intervention for increasing access to the most popular contraceptive method in sub-Saharan Africa, depo-medroxyprogesterone acetate (DMPA) [6]. DMPA subcutaneous (DMPA-SC) can be administered by trained persons, including users themselves [7]. In 2019, the World Health Organization (WHO) issued global guidelines for sexual and reproductive health self-care interventions, which encouraged member states to introduce self-injectable DMPA into the method mix and scale up access to the method throughout health systems [1].

Ministries of health (MOHs) in LMIC and FP stakeholders require knowledge on ways to harness the potential of self-care to improve the effective coverage, acceptability, and use of national FP programs and strategies to maximize the impact of self-injection for women. Guidance on scaling up access to new contraceptive methods has emphasized the need to embed research in introduction processes and support implementers to learn, adapt, and use new knowledge to improve how health systems incorporate new technologies and reach users with them as part of a broader method mix [8-10]. Facilitating these opportunities in health systems can help ensure that FP managers and practitioners have the knowledge, tools, and support necessary to promote self-care, integrate self-injection into the method mix, and assure its availability to populations consistently and in a manner that meets clients' needs. Implementation research (IR)—the systematic, scientific approach to determine how to get evidence-based interventions (EBI) to people who need it with greater speed, fidelity, efficiency, quality, sustainability, and relevant coverage—can help address this gap [11]. IR emphasizes collaboration between policy makers, decision makers, implementation teams, and local scientists who cocreate studies that are embedded in the reality of implementing organizations and address challenges to the optimal reach, delivery, and sustainment of EBI. Additional defining characteristics of IR are responsiveness to local demand for information and the positioning of research within planning and decision frameworks that use findings to improve services and systems [12].

In 2020, the WHO Department of Sexual and Reproductive Health and Research started the "enhancing self-administered family planning through embedded research" project (EASIER). EASIER is a global project which draws upon IR as a tool to help MOHs and their partners identify and evaluate programming strategies to best integrate self-injectable contraception into the method mix and support the spread of the method throughout health systems. The EASIER concept originated at the WHO based on requests from member states for support with monitoring and evaluating method introduction and scale-up. In 2021, EASIER launched an IR collaboration with partners in Burkina Faso and Kenya, and in 2022, it did so in Ghana. Although the EASIER approach emphasizes contextualization of IR studies to local conditions, across its applications, EASIER also emphasizes (1) partnerships between MOHs, local implementation teams, and local research institutions focused on identifying implementation challenges and positioning research within program processes; (2) building

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capacity for data use and knowledge translation so that IR partners cocreate solutions to implementation challenges based on evidence; and (3) the dissemination of lessons learned within and across countries to help improve self-injection program implementation at scale.

To launch EASIER, the WHO developed a global protocol. The global protocol provides IR teams in different countries with common research questions, methodological guidance, and data collection instruments that they can adapt and use to facilitate systematic learning about introducing self-administered DMPA-SC and scaling up. The protocol adopts a focus on clarifying the programmatic strategies countries have used, the contextual factors that helped or hindered implementation, and the implementation challenges and outcomes that have arisen as a result. In addition, it includes guidance on how IR teams can parlay evidence generation into the design of strategies to address implementation challenges. To date, the protocol has been adapted by IR teams in Burkina Faso, Ghana, and Kenya to develop site-specific IR projects. The purpose of this paper is to describe the global protocol and, in doing so, promote opportunities for global FP stakeholders to embed IR into the rollout of new contraceptive methods, or other EBI, in health systems. In addition, the paper provides readers with access to EASIER's data collection instruments.

EASIER Global Protocol: Objectives, Theoretical Influences, and Teams

The global protocol lays out the following objectives for country-level IR teams to adapt in site-specific IR protocols:

1. Understand the coverage of self-administered DMPA-SC and the readiness of national and local health systems to integrate it into the contraceptive method mix.
2. Document strategies used to integrate self-administered DMPA-SC into the method mix, identify practices that have led to success and challenges, and obtain insight on why these did or did not work
3. Identify the contextual factors that affect the adoption and implementation of self-administered DMPA-SC throughout the health system, including service provision and user settings where the method is practiced.
4. Understand user perspectives on their demand for the method and the degree to which their preferences and needs are addressed through implementation.
5. Strengthen collaboration between decision makers, researchers, and implementers; support and build capacity to use evidence to plan and improve implementation.

To develop these objectives, the WHO synthesized elements from multiple theories and frameworks, notably Social Ecological Theory and the Consolidated Framework for Implementation Research (CFIR) [13,14]. The former, which has been applied in public health to understand health behavior change, purports that health behaviors take shape and change as the product of numerous factors that emanate from multiple levels of context and affect individuals independently and synergistically. To adapt this perspective to the study of health care systems, we blend it with the CFIR, a determinants framework that guides the study of evidence-based interventions in complex systems and why they succeed or fail. Combining these frameworks was appropriate for the EASIER global protocol, given that its goal is to understand how implementation outcomes related to introducing DMPA-SC self-administration in systems were shaped as a product of strategic implementation by actors from multiple levels of health systems (eg, community, facility, district management, and national policy) and its interaction with contextual factors which also play out at multiple levels of context. The global protocol also reflects insights from the Promoting Action on Research Implementation in Health Services framework to develop guidance on research use approaches related to objective 5 [15] (Figure 1).

The EASIER global protocol objectives reflect the need to integrate knowledge on the performance of EBI in health systems from multiple domains of program implementation, which, in the case of self-administered DMPA-SC, includes users themselves and the communities in which they are nested, as well as the need to support structures for collaborative learning, adaptation, and evidence use. Figure 2 illustrates how IR will guide efforts to integrate and support the spread of self-injectable contraception in health systems.

The research methods and procedures described in this paper are adapted into country-specific protocols in Burkina Faso, Ghana, and Kenya. To catalyze this process, staff from WHO global headquarters and country offices engage MOHs in selecting decision makers from national and local levels of health systems to serve as principal investigators (PI) of country-level IR. The role of the PI is to position the IR within policy and program implementation cycles, ensuring that research is integrated with processes used by ministries, local health management teams, and implementation partners to introduce self-injection into the method mix and scale it up. PIs have a prominent role throughout the research process, establishing partnerships with local research institutions with whom they work to identify specific implementation issues to address, select and adapt methodologies, oversee data collection, interpret results, and stimulate the use of findings in programmatic decisions. In other words, decision makers in the EASIER project are both "knowledge producers" and "knowledge consumers." In all countries, WHO country offices play a central role in helping to facilitate interactions between members of collaborative research partnerships and ensure that technical assistance is available to them when needed. See Table S1 in Multimedia Appendix 1, which describes the technical assistance that the WHO provides to in-country IR teams.

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Figure 1. EASIER (enhancing self-administered family planning through embedded research project) global protocol objectives and instruments. DMPA-SC: depo-medroxyprogesterone acetate subcutaneous.

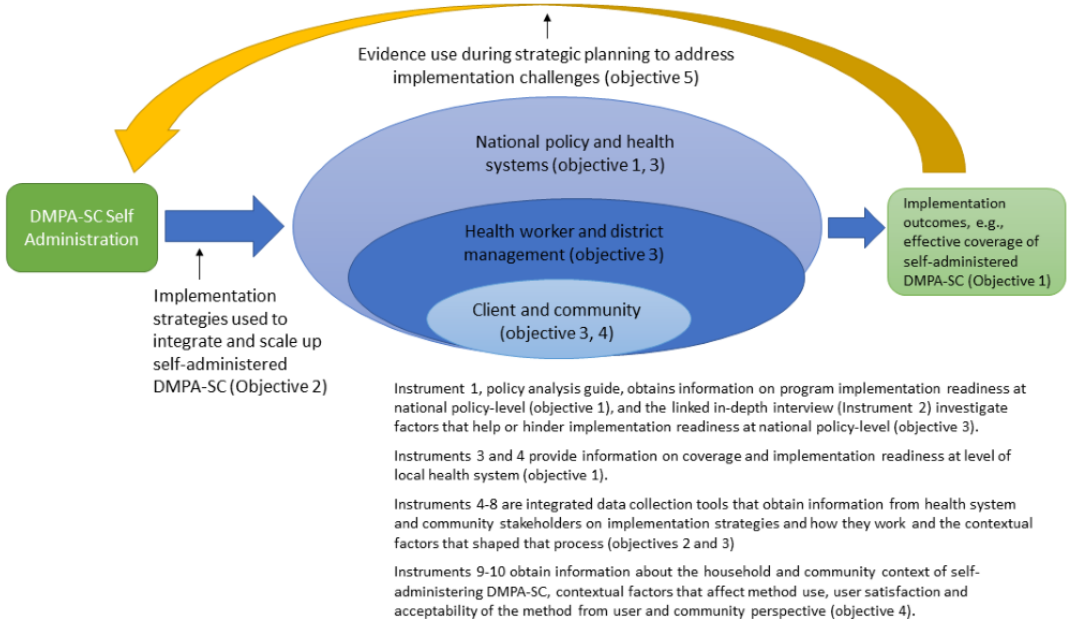
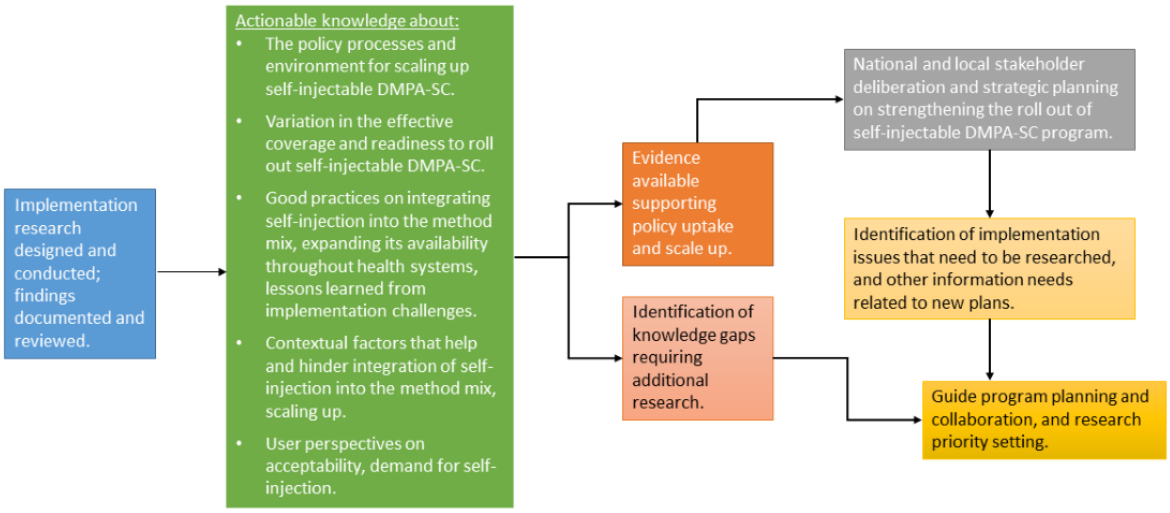


Figure 2. Role of implementation research in EASIER (enhancing self-administered family planning through embedded research project). DMPA-SC: depo-medroxyprogesterone acetate subcutaneous.



Methods

Study Environments and Design

The sections that follow describe the study design and data collection methods and procedures that are described in the EASIER global protocol. It calls for data collection to be carried out: (1) at the national level, where IR teams will evaluate the policy environment, assets, constraints, and processes for introducing and supporting the scale-up of DMPA-SC for self-administration; (2) at the local government level (eg, district, county, and provincial) in which MOHs have introduced DMPA-SC self-administration, where IR teams will assess implementation strength, service availability, and readiness to integrate the new method; and (3) in up to 6 “case study” districts (or counties and provinces) where IR teams will conduct in-depth qualitative research. The global protocol advises local IR teams on using maximum variation sampling techniques to select a geographically representative sample of districts for the qualitative case studies. Within each level of organization (national, case study county, and community), the research will sample individuals to participate in the study. The research will adopt a mixed methods design, including (1) qualitative methods at the national level and within case study countries to address objectives 1-4, that is, desk reviews of policy-related materials, in-depth interviews (IDIs) and focus group discussions (FGDs); (2) quantitative methods at the local government level in areas where governments’ have introduced self-injection to appraise implementation strength and readiness to integrate self-injection into the FP method mix (also objective 1); and (3) participatory action research (PAR) at the national level and within the case study counties to enable evidence use in programmatic decisions (objective 5).

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Sampling and Procedures

Objective 1

Lessons learned from previous WHO guideline introduction activities in countries revealed that the absence of policy implementation guidance represents a chief barrier to the incorporation of WHO FP guidelines in member states' policy processes [16]. Other studies of evidence use in policy environments illuminate how this challenge plays out at the upstream stages of policy making and further downstream, where local health teams (eg, district health management teams) implement health policy [17]. To address these challenges, the EASIER global protocol describes methods IR teams can use to (1) understand the national-level policy environment for scaling up self-administered DMPA-SC at scale in countries and (2) gauge self-injection policy implementation at subnational (eg, district- and provincial-level) levels within countries. Regarding the policy environment, the study will use a policy analysis guide and IDI guide (see Instruments 1 and 2 in Multimedia Appendix 2). IR teams will use the former to review policies, guidelines, and other strategic documents relevant to the national policy and programmatic changes that were required to introduce self-injection into health systems. They will conduct IDI to understand more about the processes, arrangements, capacities, and resource considerations in relation to policy implementation generally and with respect to DMPA-SC self-administration, as well as participants understandings of the factors that have helped and hindered national-level efforts to introduce self-injection into the method mix. Researchers will first conduct the desk review and use the findings from it to customize lines of inquiry for the subsequent IDI. Purposive and snowball sampling approaches will be used to select the stakeholders for IDI. Before the interviews, stakeholders will be asked to supply IR teams with any documents relevant to the desk review that the latter were unable to obtain independently or through their professional networks. IDI participants will include MOH officials, FP experts, donor representatives, representatives from private sector nongovernmental implementing partners, private for-profit and private not-for-profit sector organizations, and health care professional organizations. For the IDIs, the sample size may vary across countries; however, the EASIER global protocol suggests that IR teams select 3 respondents from each of the 8 categories listed above (n=24). To be selected for IDIs, key informants will have to be involved with the DMPA-SC program and belong to any of the groups identified above. IR teams, in consultation with the MOH and WHO county offices, will draw a list of potential key informants from these groups. IDI informants will include those with knowledge of the reviewed documents and be available to clarify gaps in aspects of policies and pertinent issues that were not clear in the document review.

To help IR teams measure and compare across districts the degree to which local authorities have adopted and delivered self-administered DMPA-SC and the status of implementation, the EASIER global protocol has developed 2 instruments for local adaptation and use. The first is a coverage and structural readiness assessment (see Instrument 3 in Multimedia Appendix 3). In the districts (or counties) in which the government has authorized the rollout of self-administered DMPA-SC, IR teams will request leaders of local health management teams to complete this assessment, which asks for information on the availability of equipment, supplies, commodities, and infrastructure, human resources, health management information systems, supervision capacity, task shifting, community outreach, planning processes and support, financial resources, orientation to DMPA-SC guidelines, training capacity, etc. The second instrument is an organizational readiness for implementing change assessment (see Instrument 4 in Multimedia Appendix 4). For this, IR teams will enroll an additional 20 participants per implementing district (or county) to complete a questionnaire that elicits participants' perceptions of DMPA-SC self-administration, organizational culture, the existing evidence base on the EBI, the capacity of their organization to adopt self-injection as a part of the method mix and implement it, the commitment of the organization to implement it, leadership, management, and teamwork issues. Participants in this questionnaire may include district directors of health services, district reproductive health focal persons, officers responsible for supply chain, health information systems, and community health services, and private sector (ie, nongovernmental organization and private pharmacy) representatives involved in DMPA-SC.

Objectives 2 and 3

Despite their differences, all programs to introduce self-injection in primary health care settings have employed good practices and experienced challenges from which valuable learning can arise. Further, they are all subject to contextual influences that have helped or hindered programs' ability to effectively integrate and expand coverage of the new method. Understanding how these factors affect implementation effectiveness is needed to guide programmatic decisions to strengthen the scale-up of DMPA-SC self-administration in health systems. To address this information need, the EASIER global protocol provides IDI and FGD guides for IR teams to include in their qualitative case studies. These are integrated data collection tools that elicit data on the innovation characteristics and implementation strategies, whether they are effective or not, and why (objective 2), and explore how contextual factors at the district and community levels influence the DMPA-SC self-administration interventions (objective 3; see Instruments 5-8 in Multimedia Appendices 5-8). Participant selection will ensure representation of stakeholders from local health management teams, health facilities, other sectors, and communities whose insights will generate strategically relevant information on best practices, barriers and facilitators to effective implementation, and needs for adapting and enhancing interventions used to introduce and scale up the method. IR teams will purposively select district-level IDI participants, including district medical officers, reproductive health focal persons, district-level staff responsible for method procurement and supply chain logistics, health information, and community health services; representatives of nongovernmental organization involved with DMPA-SC; private sector clinicians and pharmacy workers that deliver the method; public sector health workers; and facility in-charges. At the community level, within each case study, the following groups of people will be purposively selected for the IDIs: community leaders, community health volunteers, influential men and

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women from communities where self-injection has been introduced, and persons that volunteer for health activities in the community. To obtain insights on collective attitudes and beliefs about themes that emerged in IDI, IR teams will enroll groups of people from each category of participants that had participated in objective 2 and 3 IDIs at the county and community levels in FGDs. These will include public health care workers, staff from private sector venues, community leaders, and members. Among health care professionals, FGD will be segmented according to sector (public and private) and rank. At the community level, FGD will be segmented by sex. In each case study locale, IR teams are advised to conduct 20 IDIs and 3 FGDs. Each FGD should include no more than 8 participants.

Objective 4

Strategies to integrate new interventions into health systems are prone to failure if they are not optimized to address user attitudes and characteristics. Similarly, interventions that are not attuned to the realities of the wider social and cultural environment may not reach target populations effectively or change behaviors. Accordingly, the EASIER global protocol incorporates "demand-side" research. This component of the study aims at understanding the household, community, and sociocultural context of introducing self-injectable contraception, how these factors affect demand for the new method, and ways in which implementation can be optimized to address women's preferences and perceived needs. To obtain information from self-injection clients, the EASIER global protocol recommends that IR teams enroll 6 women per case study district in IDI that takes place 3 months after they initiated DMPA-SC self-administration (see Instrument 9 in Multimedia Appendix 9). The selection criteria for recruitment in these IDIs are that, upon their first interview, women were doing self-injection for the first time. IR teams should segment enrollment in these IDIs by age to ascertain a sample of an equal number of women younger than 25 years, 25-34 years, and 35 years or older, and complete interviews in private settings near participants' homes or the closest health care facility. Interviewers will ask participants to discuss their demand for contraception and the factors that condition it, the acceptability and accessibility of DMPA-SC self-administration services, their perceived needs from a FP program, whether their expectations and needs have been met, their satisfaction and experience with the method, and reasons for continuation, or discontinuation or method switching. The success of implementation also depends on the extent to which programs are attuned to the norms and realities of the communities targeted by interventions. Accordingly, the EASIER global protocol recommends IR teams to carry out FGD in case study locations with community members, such as opinion leaders, DMPA-SC users, spouses of DMPA-SC users, and religious leaders (see Instrument 10 in Multimedia Appendix 10). FGD will elicit from community members their perception regarding the compatibility between interventions used to introduce DMPA-SC self-administration and communities' shared beliefs, practices, and attitudes with respect to, for example, gender, religion, social relations, sexual and reproductive health, and the need for FP services. In addition, FGD will ask participants to reflect on the ways in which implementation can be adapted according to such factors, including influential social and communication networks that may influence the nature of demand for self-injection and FP services in general. The global protocol recommends that IR teams enroll 8 respondents per FGD in 3 FGDs per case study county.

Objective 5

The global protocol calls on IR teams to conduct PAR with study participants following the completion of Objectives 1-4 research and the analysis of preliminary findings. The purpose of PAR in EASIER is to engage participants in using evidence and translating findings into programmatic decisions toward improving the coverage, implementation, and sustainability of self-administered DMPA-SC services. The global protocol suggests that IR teams convene PAR at the national and case study levels and limit participation to individuals that were enrolled in IDI. IR teams are advised to conduct 2 PAR sessions at the national level: the first is a dissemination meeting of national stakeholders, which will involve those who participated in the national-level formative research (n=24) and up to 26 other relevant stakeholders from policy, programming, and donor circles (n=50); the second is a smaller meeting that will comprise of key national stakeholders (n=15) who will deliberate on findings and agree on implementation strategies to prioritize in the future. During PAR sessions at the national (session 1) and case study levels, IR teams will embed facilitators and rapporteurs in the large group of participants and break participants into small groups in which facilitators will guide discussions on the evidence, encouraging participants to brainstorm root causes of problems identified and understandings of why good practices were effective, rank and prioritize implementation issues that need to be addressed, discuss solutions, and recommend next steps for strengthening the introduction and scale up of DMPA-SC self-administration. Crucially, the case study-level PAR sessions will include community members and method users that participated in Objective 4 research. Their participation will be crucial to ensure that next steps reflect the perspectives of current and potential clients and the need for person-centered implementation strategies. Rapporteurs will document these discussions, recording data in a manner that does not include identifiable or personal information about PAR participants. Data collected during PAR will comprise of rapporteur reports and notes from small group activities and plenary discussions. The same data collection will be carried out in the first of the national- and case-study-level PARs. For the second national-level meeting, the research team will take notes and disseminate a meeting report.

Analytical Approaches

Objective 1

The EASIER global protocol advises IR teams on ways to triangulate qualitative analysis methodologies, including content analysis of documents analyzed from the desk review and framework analysis of IDI, to depict the policy-making and implementation characteristics, capacities, and processes in relation to the public sector rollout of DMPA-SC self-administration at the national level [18,19]. Data from the

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structural and organizational readiness questionnaires will be analyzed through univariate and bivariate statistical procedures. IR teams will generate descriptive analyses to capture variation across districts in terms of levels of adoption of the new method, structural readiness, and organizational readiness to scale it up. They will draw on these data to formulate dependent variables and carry out exploratory analysis to identify factors that are associated with that outcome. This will include correlation analyses between independent variables identified from these data sets to assess potential collinearity between measures. This will inform the basis for potential multivariate analysis that brings in adjustment terms and provide a richer understanding of factors in our data that are associated with readiness for implementation and implementation strength.

Objectives 2-4

The global protocol outlines procedures for analyzing the qualitative data collected in each case study location. These data will be analyzed independently to obtain a rich picture within each case study, respectively, of the implementation process–related and contextual factors that influence the adoption and delivery of DMPA-SC self-administration and the outcomes that emerge as a product of context-process interactions. This analysis will reflect the theoretical influence of contextual analysis, a concept from "realistic evaluation" that is based on the principle of "generative causation" [20]. Contextual analysis holds that what works and for whom is contingent upon the circumstances in which initiatives are implemented. The global protocol suggests that IR teams blend framework analysis and steps adapted from grounded theory analysis to, first, identify segments of the qualitative data that reflect the context of self-injection implementation, implementation processes and characteristics, and implementation outcomes [18,21]. IR teams should then draw on methods such as "constant comparison" to compare data from alternative transcripts within each case study to generate preliminary causal pathway models (CPM) that connect implementation strategies, preconditions, implementation mechanisms, and processes with proximal and, if possible, distal outcomes [22,23]. Based on this, IR teams will generate a codebook with codes to represent each of the components of the CPM for each case study and use these to analyze the qualitative data. IR teams will formulate "context-mechanism-outcome" (CMO) configurations based on the coded data for each case study [20]. They will compare each CMO configuration against each preliminary CPM to assess the strength of the explanatory framework they have posited for each case study and the need for modifications and refinements. Depending on their conclusions, they may revert to the data analysis to carry out additional phases of coding to integrate concepts included in the initial codebooks for refined analyses (ie, axial coding), and, after this, research team members will review reports from the second rounds of coding, formulate CMO configurations, and re-examine their CPM [21]. This cycle will continue until IR teams reach consensus on their satisfaction with CPMs that are finalized based on CMO analyses. With this, IR teams will generate explanations for how contextual factors and implementation mechanisms shape the outcomes of self-injection implementation in case study locations. The research team will compare the CMO analyses and final CPM of each case study to obtain a nuanced understanding of the determinants, processes, and outcomes of DMPA-SC self-administration introduction in each country.

Objective 5

Each PAR meeting will be led by an experienced moderator and small group discussion facilitators. IR teams will present salient findings from the research and then divide the plenary group of each dissemination into small groups for discussion. Data collectors will be embedded in each discussion to take detailed notes and facilitate group discussions using flipcharts, markers, and other materials as necessary. The underlying purpose of PAR activities described above, such as reflection on root causes of problems or drivers of implementation success, is to engender among participants the capacity and impetus for "systems thinking" (ie, seeing wholes, perceiving structures that underlie dynamically complex systems, and identifying high leverage opportunities), and the elaboration of "mental models" (ie, reflection, inquiry, testing, and improving of assumptions about how things work within organizations) [24]. Using these tools, facilitators will guide small groups in discussion. During discussion, these groups will prioritize implementation issues to address in the future and suggest actions that should be taken to do so. Large group discussions will proceed, facilitated by the moderator, during which small groups will present and debate their priorities. This will continue until the large group achieves consensus on a limited set of future activities associated with the next stages of the DMPA-SC self-administration scale-up. A multistep ranking process will ensue whereby each participant ranks, individually and confidentially, each of the selected activities. The moderator and data collection team will review the activity rankings submitted by each participant and calculate for each activity the number of submissions that ranked it number 1, number 2, number 3, etc until all activities have been prioritized. The intention of this activity is to establish a shared vision for future scale-up within each case study and at the national level. This will continue until each activity is ranked in an action plan or discarded. Altogether, each PAR session should take 1 full working day.

Ethics Approval

This research protocol has been reviewed by the research project review panel (RP2), an external scientific review body that is assembled by the Department of Sexual and Reproductive Health and Research of WHO to review the department's research protocols, as well as the WHO Ethical Review Committee (protocol number WHO ERC A66003) and the adapted country protocols registered in the respective country's local institutional review boards.

Results

As of October 2020, EASIER started data collection in Kenya and Burkina Faso and started the process of protocol adaptation in Ghana. In preliminary analysis of the data from Kenya, a key emerging theme is the challenges that arise at the local management and service delivery levels owing to the absence of practice guidelines. Although policies and training curricula

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are in place, implementation teams report that they lack a clear strategy on how to operationalize this policy decision. To address this, teams ask that practice guidelines provide operational detail on how county health teams should roll out the new method. Specifically, participants ask for guidance on how county health teams should adapt training, counseling, routine supervision, quality assurance, health information, and community outreach procedures to optimize the introduction of the new method and best leverage existing community-based and private sector delivery channels. A second key theme from Kenya concerns lapses in the availability of DMPA-SC commodities, which arise from bottlenecks in the procurement and distribution of the method at the national and local levels. Preliminary findings have been shared with the MOH and remedial actions are underway to address challenges.

In Burkina Faso, preliminary findings suggest that the effort to scale up self-administered DMPA-SC has achieved a relatively large scale in the country. However, health workers based at the lowest levels of care were not adequately trained to initiate women's self-injection. Although investment has been made in expanding coverage of the method, the voices of stakeholders indicate that the MOH and implementation partners should consider reforming scale-up processes to ensure that staff at primary health care facilities, which are usually closest to communities, are reached with the training they require to become able to initiate and support clients on self-injection. A second emergent theme that has arisen from preliminary analysis of the Burkina Faso IR data relates to women's awareness of the opportunity to practice self-injection. Despite efforts to make the method available, most women in the sample indicated that they had not been informed of the opportunity to self-inject DMPA-SC. The findings further imply that devising strategies to leverage community-based structures and other service communication channels to spread understanding of self-administered DMPA-SC and its availability will be crucial to strengthening the scale-up of the method. Preliminary evidence from the IR project in Ghana will become available in January 2023.

Discussion

Overview

We expect that both the quantitative and qualitative pieces of these studies will be robust. Specifically, we anticipate that the former will generate important information on the variation of coverage and implementation strength of efforts to expand the method mix through self-administration of DMPA-SC and decisions on where future interventions are required in order to address disparities and gaps. In addition, we expect that qualitative data will inform the design of implementation strategies that FP programs in the 3 countries will use to enhance method introduction and scale-up processes. By engaging stakeholders from multiple levels of the countries' health systems in PAR, we expect subsequent steps that aim at strengthening and accelerating scale-up efforts to be led by policy makers and decision makers and integrated into the implementation processes and cycles of local health care delivery teams. To facilitate this process, EASIER IR teams in each country receive support from the WHO to work with MOH counterparts and, as a group, reflect on Objectives 1-5 research findings to refine an implementation strategy that addresses priorities and challenges that were identified during PAR sessions. Based on this, IR partners in each country will develop an IR protocol to evaluate that strategy in a subsequent phase of the EASIER project. During this process, WHO will provide technical assistance to IR partners in each country, orienting them to evidence-based strategies that have been proven to address the specific issues that IR partners address in their implementation strategies, including the use of technology to enhance future implementation efforts (eg, training videos, user-clinic apps, SMS message reminder systems, etc). In addition, the WHO will support IR partners in adapting their chosen evidence-based approaches to their context and incorporating them into their plans.

Strengths and Limitations

A strength of EASIER is that it leverages a variety of implementation science frameworks and approaches to understand outcomes that have emerged from early efforts to scale up self-administered DMPA-SC in countries as well as the generative process that explains differences in these outcomes across diverse geographies within countries. The use of a global protocol will help ensure that findings across countries are comparable and that collectively they can help advance the global evidence base on the barriers, facilitators, and good practices associated with implementation success and challenges with respect to the scale-up of DMPA-SC self-administration. Further, the WHO approach to using multidisciplinary teams that place decision makers and implementers at the helm of the IR and its use of PAR integrate IR and FP program processes and create opportunities for evidence use as part of scaling up. The EASIER protocol has limitations as well. The use of a global protocol implies a rigorous adaptation process at the country level to ensure that it addresses local knowledge needs and implementation challenges and maximally benefits local actors involved in scaling up. It is primarily focused on obtaining a thorough understanding of method introduction, scale-up progress, processes, and problems in order to pinpoint challenges and prescribe solutions based on evidence. It does not evaluate specific strategies aimed at accelerating scale-up or strengthening systems, even though EASIER's findings can establish a strong foundation for doing so.

Conclusions

The emergence of DMPA-SC for self-administration has the potential to transform access to the contraceptive method considered most popular in settings where better variety and access to FP are critical for achieving global health goals. Global organizations have recognized self-administered DMPA-SC as an EBI and recommended its inclusion in countries' FP programs; however, countries lack contextually appropriate strategies for integrating it and supporting its introduction and scale-up in health systems. IR offers ways to address this gap by bringing into focus underlying implementation issues and challenges related to the introduction of new methods and explaining the implementation process–related and contextual

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factors that shape whether the introductory and scale-up efforts are effective. IR also supports knowledge translation frameworks through which stakeholders use evidence to make programmatic decisions on how to address challenges. The EASIER project demonstrates ways to embed IR within the health system and employ it to help guide scaling up access to self-injectable DMPA as part of contraceptive method choice. If successful, the protocol described in these pages will propagate additional cycles of learning, adaptation, implementation, and research, with the goal of supporting the spread of this promising contraceptive method based on local evidence in Burkina Faso, Ghana, Kenya, and additional countries that join the EASIER project. Altogether, this will create new and meaningful opportunities to advance the use of IR to strengthen FP programs.

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Disclaimer

The authors alone are responsible for the views expressed in this article and they do not necessarily represent the views, decisions or policies of the institutions with which they are affiliated.

Data Availability

The sharing of data used and analyzed during this study must adhere to the WHO data sharing policy [25]. Deidentified data used and analyzed during this study can be requested from the corresponding author. Data will be shared contingent on approval by the WHO Ethical Review Committee and local ethical review committees in the study countries.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Table 1: Technical Assistance offered by WHO (headquarters and country offices).
[DOCX File , 14 KB - resprot_v12i1e44222_app1.docx]

Multimedia Appendix 2
Instrument 1 and 2: Self-Administered DMPA-SC Policy Assessment Tool and National Level In-depth Interview Guide.
[DOCX File , 45 KB - resprot_v12i1e44222_app2.docx]

Multimedia Appendix 3
Self-Administered DMPA-SC Coverage and Structural Readiness Assessment.
[DOC File , 242 KB - resprot_v12i1e44222_app3.doc]

Multimedia Appendix 4
Self-Administered DMPA-SC Program: Organizational Readiness for Change Assessment.
[DOC File , 463 KB - resprot_v12i1e44222_app4.doc]

Multimedia Appendix 5
Subnational (eg, district-level) In-depth Interview Guide with local health system staff.
[DOCX File , 35 KB - resprot_v12i1e44222_app5.docx]

Multimedia Appendix 6
Subnational (eg, district-level) In-depth Interview Guide with members of communities and community organizations.
[DOCX File , 35 KB - resprot_v12i1e44222_app6.docx]

Multimedia Appendix 7
Subnational (eg, district-level) focus group discussion guide for local health system staff.
[DOCX File , 37 KB - resprot_v12i1e44222_app7.docx]

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Multimedia Appendix 8
Subnational (eg, district-level) focus group discussion guide for community members and members of community organizations.
[DOCX File , 36 KB - resprot_v12i1e44222_app8.docx]

Multimedia Appendix 9
Self-Administered DMPA-SC Client In-depth Interview Guide.
[DOCX File , 33 KB - resprot_v12i1e44222_app9.docx]

Multimedia Appendix 10
Self-Administered DMPA-SC Community-level Focus Group Discussion Guide.
[DOCX File , 33 KB - resprot_v12i1e44222_app10.docx]

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Abbreviations

CFIR: Consolidated Framework for Implementation Research
CMO: context-mechanism-outcome
CPM: causal pathway model
DMPA: depo-medroxyprogesterone acetate
DMPA-SC: depo-medroxyprogesterone acetate subcutaneous
EASIER: enhancing self-administered family planning through embedded research project
EBI: evidence-based intervention
FGD: focus group discussion
FP: family planning
IDI: in-depth interview
IR: implementation research
LMIC: low- and middle-income countries
MOH: Ministry of Health
PAR: participatory action research
PI: principal investigator
RP2: research project review panel
WHO: World Health Organization

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Protocol

Efficacy and Safety of the Smallpox Vaccine for Postexposure Prophylaxis in Monkeypox: Protocol for an Open-Labeled, Single-Armed Study

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Abstract

Background: In May 2022, a case of monkeypox (currently known as “mpox”) with no history of overseas travel was reported in the United Kingdom, followed by reports of infections reported in Europe, the United States, and other countries worldwide. Due to the significant overlap in immune responses among viruses of the genus *Orthopoxvirus* (including smallpox virus, mpox virus, and vaccinia virus), it is believed that cross-immunity can be achieved by administering the smallpox virus vaccine. In Japan, a smallpox vaccine (LC16m8 strain vaccine) has been approved; however, there was no regulatory approval for the mpox vaccine during the design of this study. Although it is believed that individuals exposed to the mpox virus may receive smallpox vaccination as mpox prophylaxis, the existing evidence is not clear.

Objective: The primary objective was to evaluate the efficacy of the LC16m8 strain vaccine, approved for smallpox in Japan, for postexposure prophylaxis against mpox when administered to close contacts of individuals with mpox. The secondary objective was to investigate the safety of the vaccine for postexposure prophylaxis against mpox.

Methods: The study aimed to enroll 100 vaccinated participants who had been identified as close contacts of individuals with mpox. Consent was obtained, and the participants are inoculated with the vaccine. Daily recordings of symptoms (body temperature, headache, rash, and side effects) were made until day 21 and then again on day 28. Furthermore, additional evaluations of adverse events were performed by the investigators on days 7, 14, 21, and 28. Considering that the maximum incubation period for mpox is 21 days, the primary end point is the presence or absence of the disease 21 days after close contact. The primary analysis focused on cases within 4 days of intense contact as it has been reported that vaccination within this timeframe can reduce the incidence of the disease.

Results: The first trial participant was enrolled on July 28, 2022, and the research period concluded in March 2023. The study results will be published in a peer-reviewed scientific journal.

Conclusions: This study allowed us to investigate the efficacy and safety of the LC16m8 strain vaccine in postexposure prophylaxis against mpox.

Trial Registration: Japan Registry of Clinical Trials jRCTs031220137; https://jrct.niph.go.jp/en-latest-detail/jRCTs031220137

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KEYWORDS

monkeypox; post-exposure prophylaxis; smallpox vaccine; vaccinia virus; LC16; poxvirus; smallpox; vaccination; smallpox virus; orthopoxvirus; immunity; epidemiology; zoonosis; virus; vaccine; Disease Control and Prevention; inoculation; injection site; body temperature; headache; rash; lymphadenopathy; infectious disease; endpoint analysis

Introduction

Monkeypox is a zoonotic pathogenic virus belonging to the genus *Orthopoxvirus* of the family Poxviridae. It was initially isolated from a cynomolgus monkey in 1958 and was named monkeypox [1]. However, in November 2022, the World Health Organization (WHO) changed the name to “mpox” as its natural host is considered to be a rodent [2]. Mpox circulates within a transmission cycle involving rodents and monkeys in tropical rainforests spanning from Central Africa to West Africa [3]. Since the first confirmed human infection in the Democratic Republic of the Congo in 1970 [4-6], human infections have been reported following bites from virus-infected monkeys and rodents, as well as, through the ingestion of undercooked meat. Human-to-human transmission via droplets and direct contact has also been documented [3,7,8]. While outbreaks have primarily occurred in central to western Africa, sporadic outbreaks have been reported in other regions as a result of travel to endemic areas in Africa. In 2003, an outbreak was reported in Texas, United States, likely caused by the importation of an infected rodent [1,9].

Mpox usually develops after a latency period of 6-13 days (maximum 5-21 days) following viral exposure [10]. After the latent period, symptoms such as fever, headache, lymphadenopathy, and myalgia persist for approximately 1 to 5 days, followed by the development of a rash. The eruptions often appear on the face and extremities and gradually elevate, forming bullae, pustules, crusting, and eventually heal 2 to 4 weeks after onset. The fatality rate is reported to be 0%-11% and tends to be higher in children; however, no deaths have been reported in the developed nations [11,12].

Currently, tecovirimat is approved by the Food and Drug Administration for the treatment of mpox [13,14], but there is no approved medication for mpox in Japan. As a preprophylaxis measure, vaccination using the smallpox vaccine has been reported to be beneficial due to the significant overlap in immune response among viruses of the *Orthopoxvirus* genus (including smallpox virus, mpox, and vaccinia virus). Furthermore, based on the genomic analyses of mpox strains isolated in Europe, the mpox strains circulating since May 2022 more likely originate from the West African clade and exhibit a higher homology to smallpox virus strains [15]. An analysis of epidemiological data on mpox in the Republic of Zaire during the 5-year period from 1980 to 1984 suggests that smallpox vaccination prevents approximately 85% of mpox cases [16]. For postexposure prophylaxis, the Centers for Disease Control and Prevention recommends administration of the mpox vaccine for prophylaxis, ideally within 4 days of exposure, with vaccination within 14 days also being considered; however, the efficacy may be inferior after 4 days [17].

The smallpox vaccine has been classified into 3 generations by the WHO [18]. The first generation includes the Lister strain vaccine and Wyeth's Dryvax (NYCBH strain), which were manufactured and used during the smallpox eradication program by the WHO, contributing to smallpox eradication [19]. The second-generation smallpox vaccine uses the same smallpox vaccine strain as the first-generation vaccine and clonal viral variants purified from conventional vaccine strains, including ACAM2000 [20,21]. The third-generation smallpox vaccine is an attenuated vaccine strain specifically developed as a safer vaccine at the end of the eradication phase by cell culture and animal passage with LC16m8 strain vaccine and Bavarian Nordic's MVA-BN (JYNNEOS/Imvanex/IMVAMUNE) [22-24]. Among these, the third-generation LC16 is currently approved in Japan, although it is not widely distributed and cannot be used in general practice.

In this study, the close contacts of patients with mpox were vaccinated with the LC16, which is the approved smallpox vaccine in Japan, to determine the efficacy and safety of LC16 for postexposure prophylaxis against mpox.

Methods

Overview

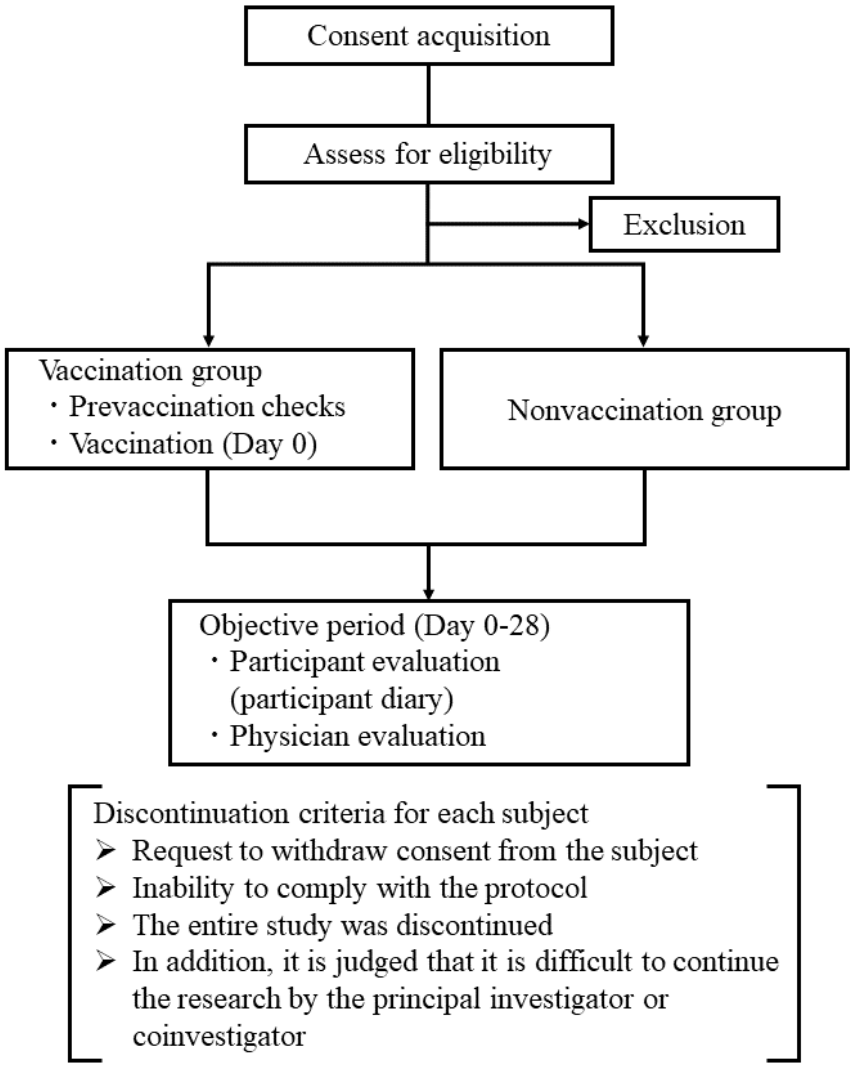
This is a prospective, interventional, single-arm study aimed at evaluating the efficacy and safety of the LC16 smallpox vaccine for individuals who have had close contact with patients diagnosed with mpox.

The study was conducted according to the schedule described in Figure 1 and Table 1. Informed consent was obtained from the participants within 14 days after mpox exposure, which is defined as day 0. Only participants who provided consent to be vaccinated received the vaccine. Close contacts who did not wish to be vaccinated were included in the study for reference purposes and were observed for follow-up if they had consent to participate. Participants self-recorded their body temperature, presence of headache, rash, and lymphadenopathy daily for 21 days after vaccination (or vaccine refusal), as well as on day 28. On days 7, 14, 21, and 28 after vaccination (or vaccine refusal), the investigators or clinical research coordinator contacted the participants to inquire about any reported adverse events. The investigators also evaluated the onset of mpox 21 days after close contact (day 7 to 21). The definition of mpox onset is based on the notification of the Infectious Disease Law. In the cases of nonreserved visits or cancellations, the investigators confirmed the presence or absence of onset and any side effects. The primary end point includes the presence or absence of mpox 21 days after close contact. Secondary end points include postvaccination adverse reactions, the rate of severe disease, death, presence of symptoms (fever, headache, and lymphadenopathy), and complications (secondary skin infections, bronchopneumonia, sepsis, encephalitis, and keratitis).

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The investigators decided whether to administer other live vaccines within 27 days. The investigators also explained to the participants that after inoculation with a vaccine, the participant may not be inoculated with other vaccines for a stipulated time period.

Figure 1. Overview of the study process.



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Table 1. Study time line.

Category	Time period (day)								
	–14 to –1	0	1 to 6	7 (allowable by ±2)	8 to 13	14 (allowable by ±2)	15 to 20	21 (allowable by ±2)	28 (allowable by ±2)
Prevaccination checks									
Criteria	✓	—[a]	—	—	—	—	—	—	—
Obtaining consent	✓	—	—	—	—	—	—	—	—
Registration	✓	—	—	—	—	—	—	—	—
Background	✓	—	—	—	—	—	—	—	—
Concomitant medications	✓	—	—	—	—	—	—	—	—
Vaccination	—	✓[b]	—	—	—	—	—	—	—
Primary end point[c]	—	—	—	✓[d]	✓[d]	✓[d]	✓[d]	✓[d]	—
Participant evaluation (participant diary)									
Body temperature	—	✓	✓	✓	✓	✓	✓	—	✓
Headache	—	✓	✓	✓	✓	✓	✓	—	✓
Rash	—	✓	✓	✓	✓	✓	✓	—	✓
Lymphadenopathy	—	✓	—	—	—	—	—	—	—
Physician evaluation									
Complication	—	—	—	✓	—	✓	—	✓	✓
Any injection-site reaction (“take”)[e]	—	—	—	—	✓	✓	—	—	—

[a]Not applicable.

[b]Only participant to consent for vaccination.

[c]The primary end point is assessed through participant evaluation of symptoms (body temperature, headache, rash, and lymphadenopathy), as well as physician evaluation of complications and any local reactions at the injection site.

[d]Investigators evaluate the onset of mpox 21 days after close contact.

[e]Investigators evaluate any injection-site reaction (“take”) by examination or by reviewing a picture of the inoculation site.

Study Setting

This study was conducted solely at the Center Hospital of the National Center for Global Health and Medicine (NCGM), Tokyo, Japan. NCGM is a 749-bed general hospital with close relationships to the Ministry of Health, Labour and Welfare (MHLW) and is a center for infectious disease treatment in Japan. In cases where a close contact is identified in an area far from Tokyo, a researcher from NCGM personally delivered the smallpox vaccine to the contact, obtained their consent for the study, and administered the vaccine if consent was granted. The MHLW has issued a notice on this policy and informed health centers throughout Japan. Close contacts cannot be vaccinated without participating in this study, indicating that although this is a single-center study, it encompasses the entire country of Japan.

Eligibility Criteria

The eligibility criteria for this study are shown in Textbox 1.

The primary inclusion criteria are as follows: age of 1 year or older at the time of consent, participation within 14 days of close contact with an individual diagnosed with mpox, and no clear indication of mpox.

The main exclusion criteria are as follows: evident immunopathy, use of adrenocorticosteroids or immunosuppressants, history of anaphylactic shock caused by ingredients of the smallpox vaccine, and the presence of prevalent skin disease and potential disability by vaccination.

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Textbox 1. Eligibility criteria.

Inclusion criteria

- Provided written consent from the principal or proxy for participation
- Age of 1 year or older at the time of consent
- Participation within 14 days of close contact with an individual diagnosed with mpox. The definition of "close contact" refers to an individual who is determined to be a contact in an active epidemiological study conducted by the health center of the patient's address based on the criteria of an active epidemiological study issued by the Ministry of Health, Labour and Welfare
- No clear indication of mpox

Exclusion criteria

- Evident immunopathy
- Use of adrenocorticosteroids or immunosuppressants (such as cyclosporine, tacrolimus, and azathioprine)
- History of anaphylactic shock caused by ingredients of the smallpox vaccine
- Fever
- Presence of a serious acute disease
- Pregnancy
- Prevalent skin disease and potential disability by vaccination
- Not appropriate for vaccination
- Considered to be unfit to participate in this study by the principal investigators

Informed Consent

Before obtaining informed consent, the investigators ensured that the participants were given sufficient time and opportunity to gather information about the study's details and make an informed decision regarding their participation. Participation in the study was voluntary, and participants could refuse to participate or withdraw from the trial at any time without penalty or loss of benefits to which the participant is otherwise entitled. The written informed consent was signed and dated by the participant and investigators. The explanatory and consent documents were approved by the authorizing clinical study examination committee and the MHLW.

Interventions

The vaccine used in this study is a freeze-dried cell culture of smallpox vaccine LC16 (LC16m8 strain vaccine), manufactured by KM Biologics, Japan. It is a third-generation smallpox vaccine manufactured by cell culture of the attenuated virus strain [25]. The vaccine is dissolved in 0.5 mL of the attached solvent (20 vol% glycerylated water for injection) and inoculated into the skin with a bifurcated needle. The number of compressions at the site of vaccination is, as a guide, 5 for first-time inoculations and 10 for others.

Criteria for the Discontinuation of Treatment or Intervention

The investigators review the continuation of the study when the following events occur: participant requests withdrawal of consent, inability to comply with the research protocol, discontinuation of the entire study, and decision of the investigator to conclude the study due to challenges in its continuation.

Statistical Analysis

The study population (Full Analysis Set) excludes ineligible participants and those with missing data on efficacy end points among the enrolled participants. The study population for safety end point analysis is defined as the enrolled participants excluding nonvaccinated participants.

According to a systematic review on the epidemiology of mpox [26], 4 studies reported the incidence of mpox in nonvaccinated close contacts. Among individuals who were not vaccinated, 7.4% of close contacts developed mpox (92 cases out of 1238 close contacts). Therefore, for this study, we set the threshold for the incidence of mpox among nonvaccinated individuals at 7.4%. An older study also reported an incidence rate of 3 of 40 (7.5%) among family members who have been in close contact with the disease [27]. The incidence of mpox among vaccinated participants is calculated, and Bayes' theorem is used to determine the probability of the incidence being lower than 7.4% (posterior probability). Additionally, for the prior distribution of the vaccinated participants, we assume an uninformative distribution and determine that if the estimated posterior probability exceeds 90%, the vaccine has a certain effectiveness. In case no incidences of mpox occur, 33 cases within 4 days of close contact are required to obtain a 90% posterior probability.

Primary end point analysis will be performed among Full Analysis Set who had contact with an infected person within 4 days. The incidence rate and its 90% and 95% CI are calculated, as well as the posterior probability of the incidence rate less than 7.4%. For the secondary end points analysis, the severity rate, death rate, and their 95% CI for vaccinated cases are calculated. For the safety end points analysis, the number of adverse events and the incidence rate are calculated for each event using the safety population.

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Ethical Approval

This study was conducted in compliance with the ethical principles stipulated in the Declaration of Helsinki, the Clinical Research Act, relevant notices, and this research protocol. Ethical approval of the research protocol and the consent document have been obtained from the Certified Review Board of the National Center for Global Health and Medicine (NCGM-C-004504-02), and the study is registered in the Japan Registry of Clinical Trials (jRCTs031220137).

Results

The first participant was enrolled on July 28, 2022. Recruitment and registration ended on December 16, 2022. Date fixation was completed in December 2022, and and the study was concluded in March 2023.

Discussion

This is a study protocol to evaluate the efficacy and safety of the smallpox vaccine, LC16m8 strain vaccine, as a postexposure prophylaxis measure in individuals who have had close contact with patients with mpox.

Owing to changes in vaccine guidelines during the study, the number of compressions at the site of vaccination is, as a guide, considered as 15 [28]. The anticipated result of this study is to demonstrate the effectiveness of postexposure vaccination as a prophylaxis measure against mpox onset and severe disease. Specifically, the absence of symptoms (fever, headache, rash, and lymphadenopathy) listed in the diary recorded by the participant during the observation period after vaccination, and the presence of antibodies at the injection site (“take”) determined by the doctor's evaluation. These findings could provide new evidence for mpox treatment with postexposure vaccination recommended by the Centers for Disease Control and Prevention.

There are some limitations to this study. First, this study had to be conducted in a short period of time owing to the rapid spread of the epidemic, and we could not afford to design a multicenter study. However, because the researchers visited participants residing in distant areas, the study can be considered to cover the whole of Japan, thus ensuring its validity. In addition, this study is open-labeled as there was insufficient time to establish a blinding system and prepare a placebo. While it is impossible to completely eliminate bias in the evaluations conducted by investigators and participants, there are objective criteria for the diagnosis of mpox; therefore, bias in the primary end point can be eliminated. Additionally, although 2 groups (vaccinated and nonvaccinated) have been formed, they were not randomized, rather participants decided whether to be vaccinated or not based on their personal preferences. Comparison between the 2 groups is challenging since this is a nonrandomized study. However, the efficacy is evaluated based on the reported incidence of mpox.

In conclusion, this is an ongoing, open-label trial, and observing the incidence of mpox in the vaccine group will provide the most definitive efficacy comparison data and other important clinical outcome data to date. If the incidence of mpox is below 7.4% in the vaccination group and the hypothesis that the LC16m8 strain vaccine is safe is valid, the LC16m8 strain vaccine would be an important treatment option for individuals in close contact with patients diagnosed with mpox. This outcome could lead to the swift integration of the LC16m8 strain vaccine into clinical practice.

Acknowledgments

The research funds used in this study and the test drug, LC16, were provided by the Ministry of Health, Labour and Welfare.

Data Availability

There are no plans to share data. As the possibility of secondary data use is explained in the consent document, secondary use of data is possible as long as a new research protocol is prepared, reviewed, and approved by the appropriate review committee.

Conflicts of Interest

None declared.

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Abbreviations

MHLW: Ministry of Health, Labour and Welfare
NCGM: Center Hospital of the National Center for Global Health and Medicine
WHO: World Health Organization

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Protocol

Evaluating Allied Health Clinical Placement Performance: Protocol for a Modified Delphi Study

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Abstract

Background: University-affiliated student-led health care services have emerged in response to the challenges faced by universities in securing quality clinical placements for health care students. Evidence of the health care benefits and challenges of student-led health care services is growing, while evidence of clinical placement performance remains variable and not generalizable. Though there have been previous attempts to develop a framework for evaluation of clinical placement performance, concerns have been raised about the applicability of these frameworks across the various placement settings. Additionally, the perspectives of all key stakeholders on the critical areas of clinical placement performance have yet to be considered.

Objective: This study's objective is to gather information on areas of measurement related to student learning outcomes, experience of placement, and costs of placement and then develop consensus on which of those areas need to be included in a framework for evaluation of clinical placement performance within the context of student-led health care services. The aim of this paper is to outline a protocol for a modified Delphi study designed to gain consensus on what is important to measure when evaluating an allied health clinical placement.

Methods: We will recruit up to 30 experts to a heterogeneous expert panel in a modified Delphi study. Experts will consist of those with firsthand experience either coordinating, supervising, or undertaking clinical placement. Purposive sampling will be used to ensure maximum variation in expert panel member characteristics. Experts' opinions will be sought on measuring student learning outcomes, student experience, and cost of clinical placement, and other areas of clinical placement performance that are considered important. Three rounds will be conducted to establish consensus on what is important to measure when evaluating clinical placement. Each round is anticipated to yield both quantitative data (eg, percentage of agreement) and qualitative data (eg, free-text responses). In each round, quantitative data will be analyzed descriptively and used to determine consensus, which will be defined as ≥70% agreement. Qualitative responses will be analyzed thematically and used to inform the subsequent round. Findings of each round will be presented, both consensus data and qualitative responses in each subsequent round, to inform expert panel members and to elicit further rankings on areas of measurement yet to achieve consensus.

Results: Data analysis is currently underway, with a planned publication in 2024.

Conclusions: The modified Delphi approach, supported by existing research and its ability to gain consensus through multiround expert engagement, provides an appropriate methodology to inform the development of a framework for the evaluation of clinical placement performance in allied health service.

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KEYWORDS

clinical placement; cost of placement; learning outcomes; student experience; student-led health care services

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Introduction

Universities face many challenges in sourcing and securing clinical placements for health students [1]. For regional universities, there is the added pressure of limited health care services from which to secure sufficient clinical placements [2]. The cost associated with paid placements is also a major concern, as paid placements can potentially create issues around placement outcomes and add to the financial burden on universities [3,4]. For example, the question for universities securing paid placements is whether the student learning outcomes or the student experiences achieved in these placements are equivalent to the amount paid. Conversely, the question may be whether an equivalent or greater outcome could be achieved through an alternate clinical placement. Placement providers also report increased costs associated with supervising students on clinical placement, including loss of productivity when working with inexperienced students, increased recruitment requirements to manage the additional workload, supervision of students on top of clinical workloads, and procuring and maintaining state-of-the-art equipment for teaching [5]. Cost of clinical placement to the clinical placement provider has been estimated to be an average of Aus $34,326 (US $22,531.3) per year for 1 student [5], influencing a health care provider's ability to offer placements without compensation [4]. As a result, university-affiliated student-led health care services have emerged to address the many challenges faced by universities in securing quality clinical placements for health care students [6].

Student-led health care services are often seen as innovative health care models providing much-needed services to disadvantaged or underserviced populations [7]. There is mounting evidence supporting the benefits of student-led health care services as both adequate providers of care and attractive educational opportunities [8]. In a recent study, allied health students co-designed and implemented a health service in a remote Aboriginal community in northern Australia, where students learned how to adapt their skills and approaches to the cultural needs of the Aboriginal community [9]. However recent reviews of the outcomes of student-led health care services more broadly, indicate the need for more rigorous reporting [10], with more specific attention to students' skill development, knowledge, and behavior required [11]. If students are not adequately prepared to operate in a fashion similar to that of qualified health care professionals, then it is possible that undertaking placement in a student-led health care service may be detrimental to their learning outcomes and overall experience of placement. Conversely, providing students with the ability to operate in authentic clinical environments where they can collaborate and regulate their own learning needs may improve overall student experience. Current findings from evaluations of student-led health care services as providers of clinical placement lack generalizability [11,12] and there is little consensus on the most critical educational outcomes that need to be measured when students are on placement within these settings [12]. Therefore, further research is needed to establish a consensus on how to evaluate student-led health care services as clinical placement providers.

Clinical placement evaluation has typically been specific to a single element of student experience, for example student confidence [13] or student satisfaction [14], or alternatively, a specific learning outcome related to a single health profession, such as clinical competency of physiotherapy students [15]. To effectively evaluate the performance of student-led health care services as providers of clinical placement, all elements of the experience that are deemed to be important must be considered together. Furthermore, an evaluation framework that can be applied to student-led health care services, which includes elements of placement performance specific to the needs and expectations of the student, the placement supervisor, the placement coordinator and to the profession is required.

Applying an evaluation framework across various health professions and health care services is not without its challenges. Previous national stakeholder consultation on use of a universal framework indicated that disciplinary and contextual differences in supervision would impact on the effectiveness of such a framework [16]. Therefore, any framework used to evaluate the quality of clinical placement needs to be consultative, collaborative, and comprehensive, so that it can accurately assess clinical placement performance across different health care settings. In addition, the framework needs to be all-encompassing and flexible so that it can be applied across different clinical placement models and different health professions [16]. A framework that can be used to effectively evaluate all clinical placement will offer the opportunity for standardization and comparability, but more importantly measure the quality of placement experience, enable quality improvement, and enhance educational opportunities [17,18].

Previous studies that have used a Delphi approach to evaluate clinical placement, or to identify factors influencing clinical placement quality, predominately exist within the medical, nursing, and allied health literature. For example, the Delphi approach has been used to engage clinical placement key stakeholders to revise clinical placement evaluation tools in physiotherapy [19], as well as to generate expert consensus between nurse clinical educators to identify important factors influencing student learning during clinical placement [20]. Additionally, a modified Delphi approach was adopted to identify key features within a quality measures framework to guide clinical placement in allied health, dentistry, medicine, and pharmacy [18]. These studies support previous notions that current tools and approaches to evaluating clinical placement quality and performance are limited in their generalizability and that key factors influencing quality in clinical placement need to be considered, that is, student learning outcomes, experience of placement, and cost of placement.

The aim of this paper, therefore, is to outline a protocol for a modified Delphi study designed to gain consensus on what is important to measure when evaluating an allied health clinical placement. This study's objective is to gather information on areas of measurement related to student learning outcomes, experience of placement and cost of placement and then reach consensus on which of those areas need to be included in a framework for evaluation of clinical placement performance within the context of student-led health care services.

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Methods

The Delphi Approach

A 3-round modified Delphi study design will be conducted to establish consensus on what is important to measure when evaluating clinical placement, from the perspective of students, placement supervisors, and coordinators, as experts with firsthand experiences of clinical placement.

The Delphi is a mixed methods approach to systematically collect judgments and opinions on a topic, through sequential questionnaires to gain respondents feedback on responses from earlier rounds of questioning [21]. The primary aim of the Delphi technique is to obtain consensus among a selected panel of experts. The Delphi approach will allow for drilling down into common areas of clinical placement through multiple rounds of questioning, as well as analysis of conflicting and common viewpoints through statistical methods [22]. The Delphi technique has been used extensively in higher education, health, and social sciences to inform the development of criteria, forecasting, issue prioritization, policy formation, and framework development [23,24].

Approaches to using the Delphi technique have evolved over time, which has led to some criticism on the validity of this approach. At the heart of the Delphi technique is the ability to form consensus between experts within a particular field. However, there is currently no set level for consensus [24] with consensus previously set anywhere from 51% to 100% [25]. Additionally, previous studies indicate that panel size and the area of investigation influences consensus [26] and consideration needs to be given to achieving an expert panel of an appropriate size and make up [27].

Anonymity, iteration, controlled feedback, and statistical stability of consensus are essential components of the Delphi approach [28]. However, the time it takes to complete these types of studies is often underpredicted [24] and has been found to influence low response rates in later rounds [24,25,27]. The several adaptations of the Delphi technique have also received criticism, as many Delphi studies lack detailed methodologies, influencing their reproducibility [24,28]. Additionally, the relevance of using experts to inform research has been questioned [25-27], as expert opinion is considered inferior to more highly regarded evidence-based methods [28,29]. The term *expert* has also broadened over time and is now not only used to refer to an individual's scientific or professional expertise but can include patients or users of an intervention to create diversity within the expert panel [30]. It is not clear what the effects of a heterogeneous expert panel has on consensus building [30], however, this has become a defining feature within the Delphi technique [31].

Currently, no proven quality indicators for Delphi studies exist [30]. However, the Delphi technique does provide an opportunity to draw on the experiences and expertise of a range of key stakeholders with a diverse set of perspectives in an iterative process where complex ideas can be examined and built on to form consensus. Therefore, considering the limitations of this approach, it is crucial to plan and set standards before commencing the process to improve the robustness of the Delphi technique [28].

Expert Panel Members

Overview

A minimum of 18 and maximum of 30 experts will be recruited to the expert panel, with a minimum of 6 members (hereafter referred to as *experts*) for each identified group (ie, recent allied health graduates, placement supervisors, and placement coordinators). This panel size is viewed as manageable, where available resources can be applied to vigorously promote high response rates within rounds [32]. To achieve heterogeneity within the panel, purposive sampling to ensure maximum variation in expert characteristics will be undertaken. Experts will consist of those with firsthand experience either coordinating placement, supervising placement, or undertaking clinical placement. All experts will be aged 18 years or older, be an Australian resident, and be English speaking. Additionally, clinical placement coordinators will be required to be employed in an Australian university allied health program, with involvement in coordinating or undertaking assessment of clinical placement within the past 2 years; clinical placement supervisors will be required to be located within Australia, and have had supervised allied health students from Australia-based universities within the past 2 years; and graduates will be required to have completed their allied health program within the past 12 months from an Australian university, successfully completing a clinical placement subject of an applied or immersive nature (eg, not solely an observational placement).

Consistent with the Delphi technique, the aforementioned approach to sampling will elicit expert opinion on the topic in question, and the disciplinary areas of expertise required [33]. Suitability of panel membership has been generally based on a background or experience concerning the target issue and an ability to contribute helpful inputs to the questions being asked [33]. The heterogeneity of the expert panel, as a critical feature within the Delphi technique [33], is required to maintain quality in research design and uncover the entire spectrum of opinion on the topic [27].

Expert Panel Member Recruitment

Potential experts will be identified, and if interested, will be invited to register through an electronic short survey sent through email. In the survey, they will be asked to confirm their interest in taking part in the study or to forward it to other potential experts meeting the target group criteria. The eligibility of potential experts who have registered will be assessed and if deemed to meet the target group criteria, will be invited to participate in the study.

Placement supervisors will be identified based on their previous or current involvement in hosting allied health students on clinical placement. Placement supervisor information from across Australia will be identified through the James Cook University placement software database (InPlace) and by snowball sampling. InPlace is a web-based software application developed by QuantumIT Pty Ltd to enable universities to identify supervisors for a given site, coordinate and manage

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clinical placements, and store data on placement contact information.

Placement coordinators will be identified by their previous or current involvement in coordinating clinical placement within Australian universities. Placement coordinator information will be identified through academic role descriptions on Australian university websites and membership details within discipline specific clinical placement committees.

Recent graduates will be identified by their past enrollment in a placement subject within an Australian university allied health program. This information will be identified through James Cook University alumni networks and snowball sampling whereby contact will be made with key people within clinical placement partnerships and those who hold key positions within Australian universities to identify members of the target groups who meet the inclusion criteria. Key people within clinical partnerships will include national clinical placement committed groups within professional registration bodies (eg, Exercise and Sport Science Australia, Australian Health Practitioner Regulation Agency, Occupational Therapy Australia, and Speech Pathology Australia) and existing placement arrangements with external clinical placement sites.

Panel Characteristics

Purposive sampling of experts to ensure equal representation across placement coordinators, placement supervisors, and recent graduates and to achieve maximum variation in expert characteristics, will be conducted using a matrix method to gain representation based on geographical location, experience, and exposure to clinical placement, as well as the allied health profession they represent. Textbox 1 outlines the expert panel selection criteria and the specific factors of variation intended to be achieved through purposive sampling techniques.

Textbox 1. Selection criteria and considerations for variation in expert panel members.

Placement coordinators:

- Duration in the role of placement coordinator
- Geographical locations of placements coordinated, that is, rural or remote, regional, or metropolitan areas
- Types of clinical placement coordinated, for example, student-led, role-emerging, traditional, and interdisciplinary
- Allied health discipline for which they coordinate placement

Placement supervisors:

- Level of experience supervising students on clinical placement
- Geographical locations of previous and current employment, that is, rural or remote, regional, or metropolitan areas
- Types of clinical placement supervised, for example, student-led, role-emerging, traditional, and interdisciplinary
- Allied health discipline for which they currently supervise

Recent graduates:

- Level of exposure to areas of practice while on placement
- Geographical locations of placements completed, that is, rural or remote, regional, or metropolitan areas
- Types of clinical placement completed, for example, student-led, role-emerging, traditional, and interdisciplinary
- Allied health discipline from which they graduated

Survey Design and Facilitation Within Delphi Rounds

The Delphi technique uses several rounds, whereby a series of questionnaires are provided to experts until consensus is reached [27]. Following each round, a summary of results from the previous round is provided to the experts to either gain consensus or elicit further discussion [27]. In this study, 3 or more consensus rounds will be conducted with survey questionnaires sent to each expert electronically.

Like that of a classical Delphi, the survey design will use open-ended questions, aimed at facilitating idea generation and eliciting opinion [27]. Three overarching themes, predetermined through a review of the literature, will be used to identify common areas of measurement when evaluating student-led health care services and clinical placement. These overarching themes include “learning outcomes,” “student experience,” and “cost of placement.”

A pilot questionnaire for round 1 will be tested with a small sample of people including 1 allied health placement supervisor, 1 recent graduate, and 1 allied health academic to ensure clarity of each question [34]. Textbox 2 outlines open-ended questions 1 to 5 that will be included in the round 1 questionnaire.

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Textbox 2. Proposed round 1 survey questions.

Question 1: Reflecting on previous experience, what is important to measure when evaluating clinical placement?
Question 2: When evaluating learning outcomes of clinical placement, please describe what variables to measure. (Provide an example where necessary)
Question 3: When evaluating student experiences of clinical placement, please describe what variables are essential to measure. (Provide an example where necessary)
Question 4: When evaluating costs associated with clinical placement, please describe what variables are essential to measure. (Provide an example where necessary)
Question 5: Is there any additional information that you would like to provide in relation to what is important to measure when evaluating clinical placement?

Question 1 is designed to set the scene and encourage the experts to respond to the question more broadly, without leading their responses. Questions 2-4 are designed to solicit information around specific areas of clinical placement related to the predetermined themes and to direct experts to consider what specific areas of clinical placement, that is, subthemes of measurement, exist when evaluating clinical placement. The final question in the survey will allow experts to discuss other areas of clinical placement evaluation, not yet covered.

Round 2 will include a structured questionnaire that will focus on areas of measurement identified in round 1 and relate to the overarching themes of learning outcomes, student experience, and cost of placement. Experts will rank the level of importance for each area of measurement using a 4-point Likert-type scale ranging from 1=not very important to 4=very important [34]. Experts will be given the opportunity to provide suggestions on any current methods of measurement for each of the proposed areas of measurement, which then will be analyzed and presented in subsequent rounds [35].

In round 3, a list of prioritized areas of measurement from the previous round will be presented. Experts will be asked to rank their level of agreement on the areas of measurement required, using 2 options: agree or disagree. Additionally, any specific methods of measurement identified in round 2 will be ranked using a 5-point Likert-type scale ranging from 1=least effective to 5=most effective [34]. Once again, experts will be invited to provide free-text comments to further explain their position.

Data Collection

All responses will be captured using the Qualtrics web-based survey platform (version 2009; Qualtrics). For each round, each expert will be sent a unique web link to access the surveys. Expert panel members will be provided with a minimum of 4 weeks to complete all surveys within each round, with only those who participated in previous rounds being invited to participate in subsequent rounds. Weekly reminder emails will be sent to each expert until each round is completed. Once the final deadline is reached, surveys will be closed to all experts and responses will be analyzed before commencing the next round. Each survey will take no more than 40 minutes to complete and all responses will be deidentified and coded to maintain anonymity between experts.

Data Analysis

Round 1 responses will be analyzed using thematic analysis to generate themes related to “learning outcomes,” “experience of placement,” and “cost of placement,” as well as any additional themes identified through the process. The thematic analysis will follow Braun and Clark’s [36] 6-phase framework for analyzing qualitative data [36]. These steps include becoming familiar with the data, generating initial codes, searching for themes, reviewing, and defining themes, as well as the final write-up [37]. Qualitative data analysis software, NVivo (version 12; NVivo Inc), will be used to code and group data. Additionally, triangulation will occur between the main research team (LS, FB, and RB) and an independent researcher with experience in thematic analysis to ensure validity of our assumptions through the convergence of themes from different sources [38].

Round 2 and 3 quantitative data will be analyzed using percentage of agreement to confirm whether consensus had been achieved. As identified in other Delphi protocols within health and education fields, combined scores of importance and agreement must equal ≥75% to achieve consensus [39]. In accordance with round 1, qualitative data from rounds 2 and 3 will be analyzed thematically, where common themes will be identified and presented as statements in subsequent rounds.

Ethical Considerations

Informed consent will be obtained before participating in the research project through a unique electronic link, which will form the first page of the questionnaire in round 1. Expert anonymity will be maintained through coding of participant responses and any identifying information will not be linked with any research materials or questionnaires developed through the modified Delphi process or in the outputs that result from this research. Additionally, no compensation will be offered to selected experts for their participation in this study.

Ethical approval has been obtained through the James Cook Human Research Ethics Committee (H7541).

Results

Data analysis is underway, with the results of the modified Delphi study expected to be submitted for publication in 2024.

Discussion

Overview

The aim of this modified Delphi study is to obtain consensus from a panel of experts on how to measure the salient areas of student learning outcomes, student experience, and cost of clinical placement, and to gain valuable insight into the important areas of clinical placement measurement. The

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outcomes of this project are intended to inform the development of a framework for evaluation of clinical placement performance.

The strength of using a modified Delphi study design for this proposed study is that it will allow for multiple perspectives from the range of stakeholders whose experiences are influenced by clinical placement performance. As a result, experts will be drawn from a variety of backgrounds to produce heterogeneity and will ensure investigation of the full scope of opinions associated with the topic [27]. The Delphi principle of anonymity also provides strength to this study's design, as it offers an equal chance for each expert to respond in a fashion that is unbiased by the identities of the other panel members [40]. By maintaining communication through electronic means and providing deidentified results in each subsequent round, this study will ensure each expert has the opportunity to react independently, eliminating subject bias and avoiding the potential of power influenced dynamics between experts [41].

Within the Delphi approach, the notion exists that members of the panel are experts in the area of interest, where the term *expert* has been defined as "an informed individual," a specialist in their field, or someone who is knowledgeable in a specific subject [27]. Within this study, the definition of *expert* is based on key stakeholders of clinical placement, which is commonly identified as students, universities, placement supervisors, and the organizations in which placement takes place [4,42], all of which, significantly influence clinical placement quality and performance. Incorporating the knowledge, views, and experiences of key stakeholders is critical to determining a best practice approach to the evaluation of clinical placement performance. Criticism of the expert opinion sought within the Delphi approach applies to the terminology used, determining who is an expert and what degree of expertise is required to offer opinion [27]. Expert opinion has also been criticized as a poor basis for making judgments on a topic and that researchers should consider whether the research question could be better answered through a systematic review [31,43]. However, current systematic reviews on clinical placement performance in student-led health care services identified limitations in the overall quality and generalizability of the research [10-12]. Therefore, this study will inform the critical appraisal of studies that intend to evaluate student-led health care services as providers of clinical placement and whether this is aligned to key stakeholder perspectives.

Consensus will be determined in this study using percentage of agreement, where scores of importance, effectiveness, and agreement must equal ≥75% to be deemed consensus. As seen in similarly designed studies [32,39], this approach favors the majority, but also allows for the anticipated variability in opinion from a heterogeneous expert panel. As a group of experts are unlikely to demonstrate 100% agreement, consensus forming is the essence of the Delphi technique, wherein an appropriate level of consensus needs to be determined to avoid bias [31,43]. Determining consensus remains a contentious issue with critics of the Delphi approach [27,32], however most Delphi researchers agree that the approach needs to be determined in advance and that resistance to consensus needs to be considered carefully, as this will yield new perspectives on the topic in question and will require further investigation [32,44].

Conclusion

This protocol paper describes a modified Delphi study design, to explore key stakeholder perspectives on important areas of clinical placement performance measurement, related to learning outcomes, student experience, and cost of placement. Despite the limitations of the Delphi approach, existing research, and its ability to gain consensus through multiround expert engagement supports this methodology as appropriate to inform the development of a framework for the evaluation of clinical placement performance. As such, the outcomes of this study are intended to form part of a framework for the evaluation of allied health student-led health care services.

Data Availability

The data sets generated and analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

All authors contributed to the design of the research, selection of expert panel members, and writing of the manuscript.

Conflicts of Interest

None declared.

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Protocol

Graphical User Interface Development for a Hospital-Based Predictive Risk Tool: Protocol for a Co-Design Study

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Abstract

Background: This co-design research method details the iterative process developed to identify health professional recommendations for the graphical user interface (GUI) of an artificial intelligence (AI)–enabled risk prediction tool. Driving the decision to include a co-design process is the belief that choices regarding the aesthetic and functionality of an intervention are best made by its intended users and that engaging these users in its design will promote the tool's adoption and use.

Objective: The aim of this research is to identify health professional design and uptake recommendations for the GUI of an AI-enabled predictive risk tool.

Methods: We will hold 3 research phases, each consisting of 2 workshops with health professionals, between mid-2023 and mid-2024. A total of 6 health professionals will be sought per workshop, resulting in a total enrollment of 36 health professionals at the conclusion of the research. A total of 7 workshop activities have been scheduled across the 3 workshops; these include context of use, notifiers, format, AI survey–Likert, prototype, AI survey–written, and testing. The first 6 of these activities will be repeated in each workshop to enable the iterative development and refinement of GUI. The last activity (testing) will be performed in the final workshop to examine health professionals' thoughts on the final GUI iteration. Qualitative and quantitative results data will be produced from tasks in each research activity. Qualitative data will be examined through inductive thematic analysis or deductive thematic analysis in accordance with the Nonadoption, Abandonment, and Challenges to the Scale-up, Spread, and Sustainability (NASSS) framework; visual data will be examined in accordance with "framework of interactivity;" and quantitative data will be examined using descriptive statistics.

Results: Project registration with the Australia and New Zealand Clinical Trial Registry has been requested (#384098). Finalized design recommendations are expected in early to mid-2024, with a results manuscript to be submitted in mid-2024. This research method has human research ethics approval from the South Australian Department of Health and Wellbeing (#2022/HRE00131) as well as from the Human Research Ethics Committee of the University of South Australia (application ID#204143).

Conclusions: Understanding whether an intervention is needed in a particular situation is just the start; designing an intervention so that it is used within that situation is paramount. This co-design process engages end users to create a GUI that includes the aesthetic and functional details they need in a manner that aligns with their existing work practices. Indeed, interventions that fail to do this may be disliked, and at worst, they may be dangerous.

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KEYWORDS

co-design; health information technology; health professional; user-centered design; user interface

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Introduction

Dashboards summarize information in a meaningful manner to ensure users can make informed decisions in accordance with organizational objectives [1]. They can take many forms, such as electronic medical records (EMRs) or electronic health records (EHRs), as well as computerized provider order entry (CPOE), to name but a few. Each is advocated as a tool that increases productivity and efficiency, improves patient health care outcomes [2], and assists health professionals to avoid errors and drive down health care costs [3]. Yet despite their advocated benefits, health professionals encounter barriers to their use and sustainability [4].

In many instances, barriers result from dashboards' imposition on the way health professionals deliver care or the way in which they are required to interact with the platform in their professional practice. A thematic analysis of physician interviews identified that using the platform not only disrupted their patient consultation but also resulted in an additional time burden due to the need to record diagnostic codes [5]. Confidence in the quality of information within these records is of concern for health professionals, with "prescriber" views reporting that patient files included "untrustworthy" information and produced "irrelevant" alerts [6]. Distrust as to the true intent of health information technology (HIT) has also been identified, with some health professionals reporting feeling that their CPOE systems are a mechanism for oversight and performance monitoring [7]. How health professionals interact with dashboards can also create issues, with research identifying pharmacist views that CPOE use can be time consuming [8] and a struggle due to functional and navigational issues [9].

Workplace practice and navigational issues, among others, can accumulate and result in a negative experience for health professionals. Of the interviewed physicians, 64.2% reported "agreeing" or "strongly agreeing" that EMRs added to the "frustration of their day." Furthermore, these physicians also had significantly higher odds of burnout [10].

The introduction of artificial intelligence (AI)–enabled technologies in health care has been reported to raise several concerns for health professionals, specifically ethicality, data management, and its influence on health care delivery [11]. Alternatively, research on AI adoption reports that as health professionals' exposure to AI increases, their positive feelings toward it also increase, as do their satisfaction and use intentions [12]. It is critical, therefore, that health professionals' engagement with AI occurs in a positive manner to encourage adoption and repeated use.

Positive interaction with AI can be achieved through end-user engagement in graphical user interface (GUI) design. Indeed, the GUI is the most prominent, and perhaps the only, element of AI-enabled software with which the user will interact. Its appropriate design is therefore paramount. Co-design as a participatory process enables meaningful engagement with relevant users [13]. It is a process where the contributions of different users are synthesized [14], and it collaboratively integrates design thinking, stakeholder knowledge, scientific evidence, and the bottom-up approach of participatory action research to produce solutions to identify and address what is important within the local context [4]. Co-design will be used by this research to develop the notifiers (eg, graphs, dials, and icons) and layouts required because it places the user at the center of the research and development process with the goal of creating the version of the GUI that best represents their design needs.

The research method detailed herein will be performed as part of a PhD project and forms part of the larger Predictive Harm Response Management (PreHaRM) Algorithmic Tool to Reduce Adverse Events in Health Care Settings project. The purpose of the larger project is to develop and test an AI-enabled predictive risk algorithm and interface for use within the hospital setting (the PreHaRM tool). The PreHaRM tool will focus on the prediction of 3 adverse events: patient falls, medication errors, and occupational violence (patient or caregiver toward staff). The larger project, including this co-design project, is supported by Digital Health Cooperative Research Centre (DHCRC) Limited. DHCRC Limited is funded under the Australian Commonwealth Government's Cooperative Research Centers Program (Project #DHCRC-0156). The co-design workshops will develop health professionals informed recommendations for the visualization of the DHCRC PreHaRM tool.

Methods

Objective

The aim of this research is to identify health professional design and uptake recommendations for the GUI of an AI-enabled predictive risk tool. The primary and secondary objectives are described in the following sections.

Primary Objective

Objective 1: Identify health professionals design preferences for GUI aesthetics and function.

Secondary Objectives

Objective 2: Identify health professional usability levels for professional practice and PreHaRM GUIs.

Objective 3: Identify health professional acceptability levels for professional practice and PreHaRM GUIs.

Objective 4: Identify health professionals' perceptions of AI in health care in relation to its implementation and adoption.

Outcome Measures

Outcome measures developed in accordance with objective 1 are as follows:

- Participant for GUI aesthetic and function preferences tabulated and narratively synthesized according to the framework of interactivity.
- Participant visual design preferences tabulated and narratively synthesized according to the elements and principles of visual design.

Outcome measures developed in accordance with objective 2 are as follows:

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- Participant System Usability Scale (SUS) scores for professional and PreHaRM GUIs.

Outcome measures developed in accordance with objective 3 are as follows:

- Barriers and enablers for professional and PreHaRM GUIs tabulated and narratively synthesized according to the theoretical framework of acceptability.

Outcome measures developed in accordance with objective 4 are as follows:

- Participant "AI potential impact" scores measured by the 10-question Shinners Artificial Intelligence Perception tool.
- Participant "AI readiness" scores measured using the 10-question Shinners Artificial Intelligence Perception tool.
- Barriers and enablers to AI adoption in health care tabulated and narratively synthesized according to the Nonadoption, Abandonment, and Challenges to the Scale-up, Spread, and Sustainability (NASSS) framework.

Study Design

A total of three 2-month research phases have been scheduled from mid-2023 to mid-2024, with 2 co-design workshops scheduled per phase, one in Adelaide (University of South Australia city west campus), the other in Tonsley (Tonsley Innovation District) for Central Adelaide and Southern Adelaide Local Health Network staff, respectively. If required, participants may attend using teleconferencing software (eg, Zoom) and collaborative software (eg, Miro). Each workshop will be led by an experienced facilitator and run for approximately 2 and a half hours. A total of 2 support staff will also be in attendance: one will observe and note proceedings while a second will provide operational support to the facilitator (eg, information technology troubleshooting, handing out and collecting activity sheets).

Members of the PreHaRM clinical implementation team (CIT) will be asked to promote each workshop by circulating an invitation to colleagues within their peer network. Individuals who confirm their interest in the workshop will be emailed workshop details (ie, session date, time, and location). A total of 6 participants will be enrolled in each workshop, resulting in a total of 12 participants per research phase, for a maximum total of 36 participants (Table 1). The total number of individuals may be less than 36, as participants will be allowed to attend more than one workshop should they choose to; however, this repeat attendance is not a requirement and will be made at their discretion.

Table 1. Research phase and co-design workshop schedule.

Phase and location	Participants, n	Date[a]
Research phase 1		
CALHN[b] workshop 1	6	September
SALHN[c] workshop 1	6	September
Research phase 2		
CALHN workshop 2	6	November or December
SALHN workshop 2	6	November or December
Research phase 3		
CALHN workshop 3	6	January or February
SALHN workshop 3	6	January or February

[a]Proposed 2023 time period.

[b]CALHN: Central Adelaide Local Health Network.

[c]SALHN: Southern Adelaide Local Health Network.

Inclusion and Exclusion Criteria

Nurses have been identified as the target user of the GUI, and as such, the inclusion and exclusion criteria below reflect the need to attract a diverse range of participants from this professional group; for example, nurses of all levels (including enrolled, registered, and nursing unit managers) will be sought so the diversity of their experience can benefit the design. Criteria for enrollment are listed in Textbox 1 below.

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Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Enrolled nurses
- Registered nurses
- Nursing unit managers
- Nurses in noncare roles
- Use health information technology in professional role
- Able to provide informed consent

Exclusion criteria

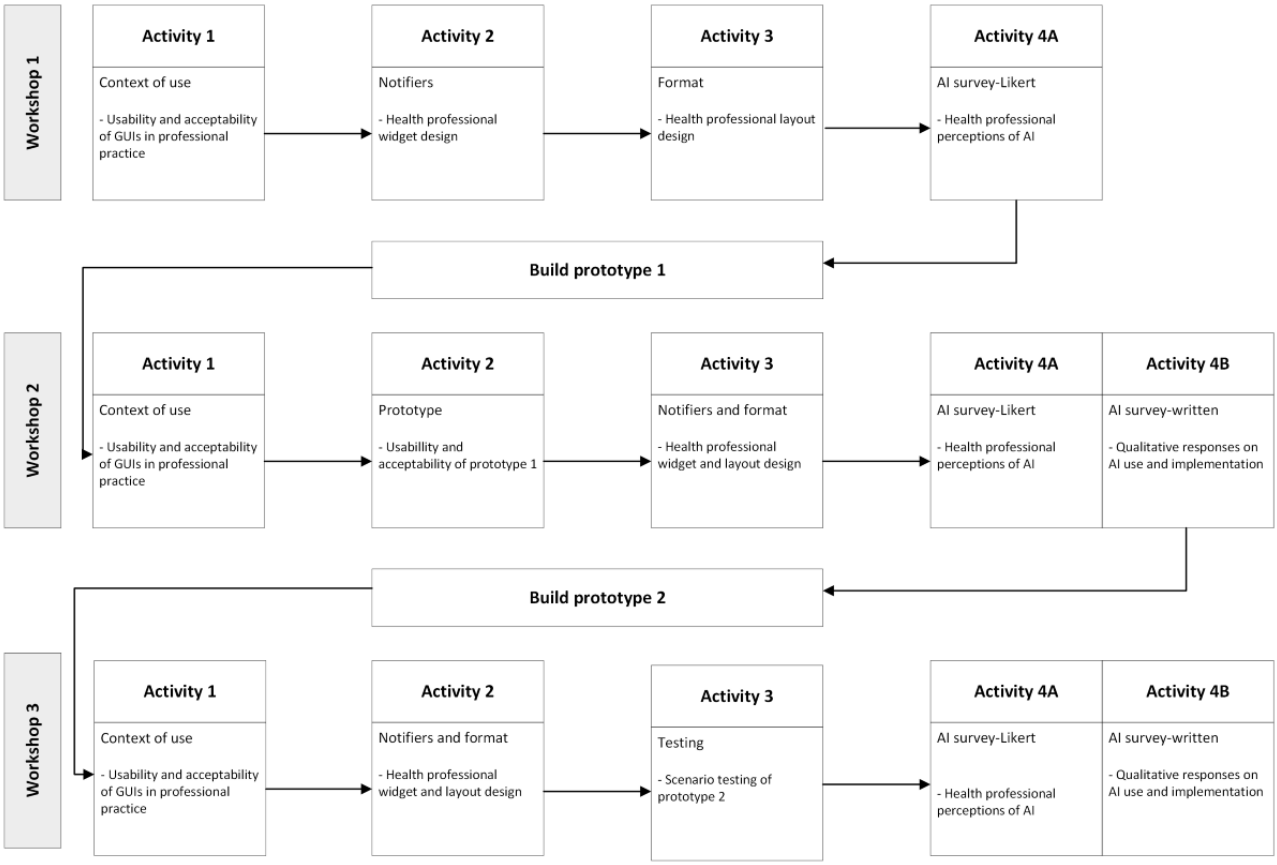
- Not employed by SA Health
- Unable to provide informed consent

Iterative Workshops

An iterative co-design process will run across each of the workshops. Each workshop includes predesign and generative activities, noting that these activities will culminate in the testing activity held in the third workshop. Figure 1 illustrates the focus and relationship of each workshop, as well as the overall iterative co-design process.

A description of each workshop activity is provided in Table 2 below.

Figure 1. Iterative co-design process. AI: artificial intelligence; GUI: graphical user interface.



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Table 2. Workshop activity matrix.

Activity	Description	Tools
Context of use	Participants will be asked about their use of GUIs[a] at work.	• Web-based survey • Moderator guide
Notifiers	Participants will be asked to design notifiers (eg, graphs, dials, or icons) that they would like to see on the PreHaRM[b] GUI.	• Generative toolkits
Format	Participants will be asked to arrange their chosen visualizations on a mock GUI.	• Generative toolkits
AI survey–Likert	Likert scale questions will investigate participant feelings toward AI[c] enabled software in health care.	• Web-based survey
Prototype	Participants will be asked to provide feedback in relation to the potential usability of the PreHaRM prototype 1.	• Web-based survey • Moderator guide
AI survey–written	Participants will be given results from previously completed surveys and asked to contextualize the results from their point of view.	• Web-based survey
Testing	Participants will be asked provide feedback on their use of prototype 2 in relation to a mock workplace scenario.	• Scenario testing • Web-based survey

[a]GUI: graphical user interface.

[b]PreHaRM: Predictive Harm Response Management.

[c]AI: artificial intelligence.

Workshop Tools

Workshop tools and the method for analyzing their respective results data are described in the follows sections.

Surveys

A background survey will be used to obtain basic participant demographic information (workshops 1-3). The SUS will be used to examine participants views on the usability and acceptability of GUIs currently used in their professional practice (“context” activity, workshops 1-3) [15]; a sample survey has been included for reference (Multimedia Appendix 1). The SUS activity survey will also be used to understand participant views on the PreHaRM prototypes 1 and 2 (“prototype” activity, workshop 2, and “testing” activity, workshop 3). The Shinners Artificial Intelligence Perception (SHAIP) framework will be used to identify health professionals’ perceptions of AI in health [11] (AI survey–Likert, workshops 1-3). The third survey will present results from the AI survey–Likert alongside written questions asking participants to interpret and report what these results mean (AI survey–written, workshops 2-3). All surveys will be delivered using a web-based platform (eg, Microsoft Forms). All data will be downloaded from the web-based survey platform for analysis. Quantitative data collected from the background, SUS, and SHAIP surveys will be examined using descriptive statistics calculated in R (version 4.2.0; R Core Team). Qualitative data collected from the AI Survey–written will be coded against the 22 themes within the NASSS framework in NVivo (version 14; QSR International) [16]. Coding will be performed by NM with checking by a second researcher; any disagreements will be reviewed by KCC.

Moderator Guide

Health professionals’ acceptance of professional practice GUIs as well as the PreHaRM prototype GUI will be examined through questions contained in a semistructured moderator guide. Their responses will be audio recorded and transcribed, and the coding of responses will then be performed against the 8 domains of the theoretical framework of analysis (TFA) [17]. Coding will be performed by NM and checked by a second researcher, with any disagreements reviewed by KCC.

Generative Toolkits

For notifier development, participants will be given example cut-outs and asked to amend them to represent how they’d prefer it to look. Blank paper, colored markers, and other materials will be provided for participants should they prefer to draw their own notifiers. For layout development, participants will be given GUI screen templates (and blank pieces of paper) onto which they can arrange their chosen notifiers to design their preferred GUI (“notifiers” and “format” activities, workshops 1-3).

Notifiers and layouts will be produced using generative toolkits. Both artifact types will be assessed to identify their aesthetic and functional characteristics. Aesthetic characteristics will be examined in relation to the visual elements that comprise each artifact (ie, line, shape, color palette, texture, typography, and form) as well as the use of visual design principles (ie, unity, gestalt, space, hierarchy, balance, contrast, scale, dominance, and similarity) [18]. Functional (or interactive) characteristics will be examined using the framework of interactivity [19]; this will be used to categorize each artifact in regard to its ideational, interpersonal, and textual intent. All artifacts will be examined by NM, with results recorded on an Excel spreadsheet developed a priori. These will be checked by a second researcher, with KCC adjudicating any disagreements. Review of the content

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and frequency of these results will inform the PreHaRM design recommendations.

Scenario Testing

A mock scenario to test PreHaRM prototype 2 will be developed using CIT, the technical advisory group (TAG), and research staff input. Participants in workshop 3 will be offered 1 opportunity to attempt the tasks within the scenario ("testing" activity, workshop 3). All attempts will be video recorded, either through screen capture software or a separate video camera. Participant attempts will be examined using "navigation testing," where participants' time taken as well as navigation hits and misses will be recorded. Exploration results will be examined using descriptive statistics calculated in R. Following their completion of the scenario, they will be asked to complete the SUS questionnaire, and the resultant data will be examined as per the process described above.

Unstructured Interviews

Following the completion of each workshop, attendees will be offered the opportunity to participate in voluntary, one-on-one, unstructured interviews with NM. The purpose of the interview is to enable participants to provide further information about their workshop feedback or to provide new feedback if they feel uncomfortable raising it in a group context. Interviews will be offered through teleconferences only (Zoom; version 5.12.8; Zoom Video Communications Inc). These interviews will be offered as an opt-in opportunity, and it will be explained that participation in any workshop is not contingent on their participation in the interviews.

In unstructured interviews, it is unclear what participants may choose to discuss; consequently, inductive thematic analysis will be used to examine participant interview transcripts. This will be performed using NVivo. Participant perspectives will be coded by NM and examined by KCC.

Data Management

All workshops and follow-up interviews will be audio recorded using a digital recording device; scenario testing activities will be recorded using video cameras; hardcopy artifacts (ie, visualizations and dashboards) will be collected by PreHaRM researchers; and participant surveys will be collated using web-based software. Audio recordings will be transcribed using voice recognition Rev (Rev.com, Inc); video recordings will be reviewed using Adobe Premiere Pro (version 23.0.0; Adobe Inc); Microsoft Forms will host each survey and automatically collate responses. Once the survey period has ended, collated responses will be downloaded. All electronic data will be stored in password-protected folders at the University of South Australia, Australia. All artifacts will be stored in facilities at the University of South Australia, Australia. All data will be retained for a minimum of five years after project completion in accordance with Australian State and Commonwealth guidelines.

Peer-reviewed manuscripts, posters, and oral presentations detailing the co-design process and results will be produced; information used in these research outputs will be deidentified. If video recordings are used, then participant likenesses (audio and visual) will be obscured. Data sets generated and analyzed during this research are not publicly available due to dissemination restrictions resulting from the ethics approval process.

Ethical Considerations

A participant information sheet and consent form will be emailed to all participants before each workshop. Hardcopies will be available at the start of each session, and all individuals must read the information sheet and sign the consent form before participating. This research method has human research ethics approval from the South Australian Department of Health and Wellbeing (#2022/HRE00131) as well as from the Human Research Ethics Committee of the University of South Australia (application ID#204143). No research activity will commence until approvals from both committees have been received. All research data will be deidentified by researchers. Participants will be offered an AU $50 (US $32.82) gift card for their attendance.

Results

Recruitment for this project will commence in mid-2023, with data collection scheduled to commence in mid- to late 2023 and end in mid-2024. Co-design and review will occur throughout the data collection period.

Discussion

Strengths

The key strength of this research and the broader PreHaRM project is the purposeful engagement of end users in each research activity; this is research with health professionals for health professionals. Preliminary engagement with the state government and local health networks has been achieved through engagement with the CIT. Comprised of senior hospital staff and government health care data professionals (managers and stewards), this group provides strategic information on data collection and use within the local health care system. This insight provides PreHaRM researchers with a deeper understanding of the administrative and technical context in which health professionals work. Similarly, the PreHaRM TAG includes leaders in AI software development and interface design. This group guides researchers' thinking on the capacity of the PreHaRM algorithm. Both the CIT and the TAG have already been central to the predesign phase [20] and will continue to remain involved in the upcoming stages of the design process. Health professionals drive the generative phase of the PreHaRM tool primarily through their efforts in the "notifiers" and "format" activities, but also through their descriptions of software use and their feelings toward AI within health care. The evaluative activities of researchers and the presentation of these results back to health professionals further involve them in the iterative and generative process at the crux of this research. The broad contextualization of the health care system and guidance of AI development from the CIT and TAG, respectively, are operationalized through the generative activities of health professionals at the "coal face."

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Limitations

As primary end users, nurses are the target cohort for each workshop, and their input in these sessions will inform the PreHaRM GUI. Within the hospital context, however, it is possible that other health professionals may also use the PreHaRM GUI. Callen et al [21] identified that differences in organizational culture along professional lines represent differences in attitudes toward HITs. Therefore, the focused recruitment of one health professional group is a potential limitation; future research should broaden recruitment to capture the design requirements of additional health professional cultures. Additional in situ research should be conducted with health professionals to confirm the issues they noted in the sessions are as consequential as they are real and to seek further refinements that improve the adoption of the PreHaRM tool.

Practical Significance

This project will engage health professionals in an iterative co-design process across 3 workshops. This process of repeat engagement will enable researchers to refine recommendations for the aesthetics and functionalities of the PreHaRM GUI. It is anticipated that by adopting their recommendations, health professionals will be more likely to accept and use this tool and to prevent forecast events from occurring. The target audience of this protocol is other health researchers, health professionals interested in research, and user interface and user experience design researchers.

Conclusions

The PreHaRM tool will combine an AI-enabled predictive risk algorithm with a co-designed GUI. The purpose of this algorithm is to identify the potential occurrence of adverse events, whereas the purpose of the GUI is to convey these potential events to health professionals in a meaningful manner. Indeed, the presentation of the algorithm results is paramount if the warning it displays is to be acknowledged and actioned. Co-design will be used in this research to identify end user aesthetic and functionality design recommendations to help ensure the appropriateness of the final product and its incorporation with existing work practices. This research takes as a basic assumption that the PreHaRM GUI, designed with input from health professionals, will be used by professionals to the benefit of patients and their families.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Professional practice dashboard use web-based survey.
[PDF File (Adobe PDF File), 30 KB - resprot_v12i1e47717_app1.pdf]

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Abbreviations

AI: artificial intelligence
CALHN: Central Adelaide Local Health Network
CIT: clinical implementation team
CPOE: computerized provider order entry
DHCRC: Digital Health Cooperative Research Centre
EHR: electronic health record
EMR: electronic medical record
GUI: graphical user interface
HIT: health information technology
NASSS: Nonadoption, Abandonment and Challenges to the Scale-up, Spread and Sustainability
PreHaRM: Predictive Harm Response Management
SALHN: Southern Adelaide Local Health Network
SHAIP: Shinners Artificial Intelligence Perception
SUS: System Usability Scale
TAG: technical advisory group
TFA: theoretical framework of analysis

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Protocol

Multidimensional Analysis of a Cell-Free DNA Whole Methylome Sequencing Assay for Early Detection of Gastric Cancer: Protocol for an Observational Case-Control Study

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Abstract

Background: Commonly used noninvasive serological indicators serve as a step before endoscope diagnosis and help identify the high-risk gastric cancer (GC) population. However, they are associated with high false positives and high false negatives. Alternative noninvasive approaches, such as cancer-related features in cell-free DNA (cfDNA) fragments, have been gradually identified and play essential roles in early cancer detection. The integrated analysis of multiple cfDNA features has enhanced detection sensitivity compared to individual features.

Objective: This study aimed to develop and validate an assay based on assessing genomic-scale methylation and fragmentation profiles of plasma cfDNA for early cancer detection, thereby facilitating the early diagnosis of GC. The primary objective is to evaluate the overall specificity and sensitivity of the assay in predicting GC within the entire cohort, and subsequently within each clinical stage of GC. The secondary objective involved investigating the specificity and sensitivity of the assay in combination with possible serological indicators.

Methods: This is an observational case-control study. Blood samples will be prospectively collected before gastroscopy from 180 patients with GC and 180 nonmalignant control subjects (healthy or with benign gastric diseases). Cases and controls will be randomly divided into a training and a testing data set at a ratio of 2:1. Plasma cfDNA will be isolated and extracted, followed by bisulfite-free low-depth whole methylome sequencing. A multidimensional model named Thorough Epigenetic Marker Integration Solution (THEMIS) will be constructed in the training data set. The model includes features such as the methylated fragment ratio, chromosomal aneuploidy of featured fragments, fragment size index, and fragment end motif. The performance of the model in distinguishing between patients with cancer and noncancer controls will then be evaluated in the testing data set. Furthermore, GC-related biomarkers, such as pepsinogen, gastrin-17, and *Helicobacter pylori*, will be measured for each patient, and their predictive accuracy will be assessed both independently and in combination with the THEMIS model

Results: Recruitment began in November 2022 and will be ended in April 2024. As of August 2022,250 patients have been enrolled. The final data analysis is anticipated to be completed by September 2024.

Conclusions: This is the first registered case-control study designed to investigate a stacked ensemble model integrating several cfDNA features generated from a bisulfite-free whole methylome sequencing assay. These features include methylation patterns, fragmentation profiles, and chromosomal copy number changes, with the aim of identifying the GC population. This study will determine whether multidimensional analysis of cfDNA will prove to be an effective strategy for distinguishing patients with

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GC from nonmalignant individuals within the Chinese population. We anticipate the THEMIS model will complement the standard-of-care screening and aid in identifying high-risk patients for further diagnosis.

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International Registered Report Identifier (IRRID): DERR1-10.2196/48247

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KEYWORDS

gastric cancer; circulating cell-free DNA; early detection; methylation; fragmentation; chromosomal instability; whole methylome sequencing; multidimensional model

Introduction

Gastric cancer (GC) is one of the most commonly diagnosed digestive tract tumors, accounting for approximately 1.08 million new cases and an estimated 769,000 deaths in 2020 worldwide (7.7% of total cancer-related deaths), ranking fifth for age-standardized incidence and fourth for cancer-related mortality worldwide [1]. China is among the countries with the highest incidence rate of GC, although a gradual decline has been observed in recent years [2,3]. Early GC detection and its prompt treatment are strongly associated with improved prognoses for patients with GC. In Japan and South Korea, population-wide screening has been extensively implemented, resulting in effective diagnosis of tumors at early stages and improved survival rates [4]. Unfortunately, in China, most patients are diagnosed with advanced GC, probably owing to the large population and lack of standardized screening programs. While gastroscopy (upper gastrointestinal endoscope) and biopsy procedures conducted during gastroscopy remain the gold standard methods for GC diagnosis, gastroscopy is an invasive operation often met with poor compliance. Moreover, insufficient endoscopy physicians and endoscopic equipment, as well as the lack of a standardized endoscopic examination in China, present challenges for endoscopy to be used as a population-wide screening method [5].

Currently available noninvasive blood biomarker–based approaches could serve as a step before endoscope diagnosis and aid in identifying the high-risk GC population. However, these methods are associated with high false positives and high false negatives, which can potentially lead to overdiagnosis or underdiagnosis. Serological indicators such as *Helicobacter pylori* antibodies lack specificity for GC detection due to their strong association with atrophic gastritis and gastric ulcers [5]. Other indicators, including serum pepsinogen (PG), serum gastrin-17 (G-17), and MG7-Ag, are not recommended for standalone use due to their poor sensitivity and specificity [6]. A new GC score system based on age, sex, PG, G-17, and *H pylori* antibodies was introduced in China's early GC screening process expert consensus [5]. While this new GC score system might exhibit improved prediction performance [7], the cost-benefit of its clinical application needs to be analyzed. Plasma tumor markers, such as carcinoembryonic antigen, cancer antigen (CA) 19-9, CA 72-4, CA 125, and CA 242, are linked to patient prognosis but are not suitable for early cancer detection [8]. Furthermore, circulating molecules such as miRNAs have garnered attention; however, their sensitivity and specificity are limited [9,10].

Rapid advancements in technology and analysis have identified cell-free DNA (cfDNA) as a new, simple, and noninvasive method for early cancer detection, offering enhanced specificity and sensitivity. The cancer-related features of cfDNA have been exploited in several aspects to distinguish cancer samples from healthy cases: (1) genetic alterations [11-13], (2) microsatellite instability [14], (3) hypermethylation or hypomethylation of certain genes [15,16] or across the genome [17-19], (4) chromosomal alterations [20], and (5) unique fragmentation patterns [21,22]. Among these aspects, identifying cfDNA genetic alterations poses a challenge due to the low fraction of mutation-bearing circulating tumor DNA (ctDNA) fragments in early-stage diseases or certain tumor types [23,24]. The combination of multiple features has enhanced detection sensitivity in comparison to relying on a single feature, as studied in kidney cancer [25], hepatocellular cancer, and pancreatic ductal cancer [26].

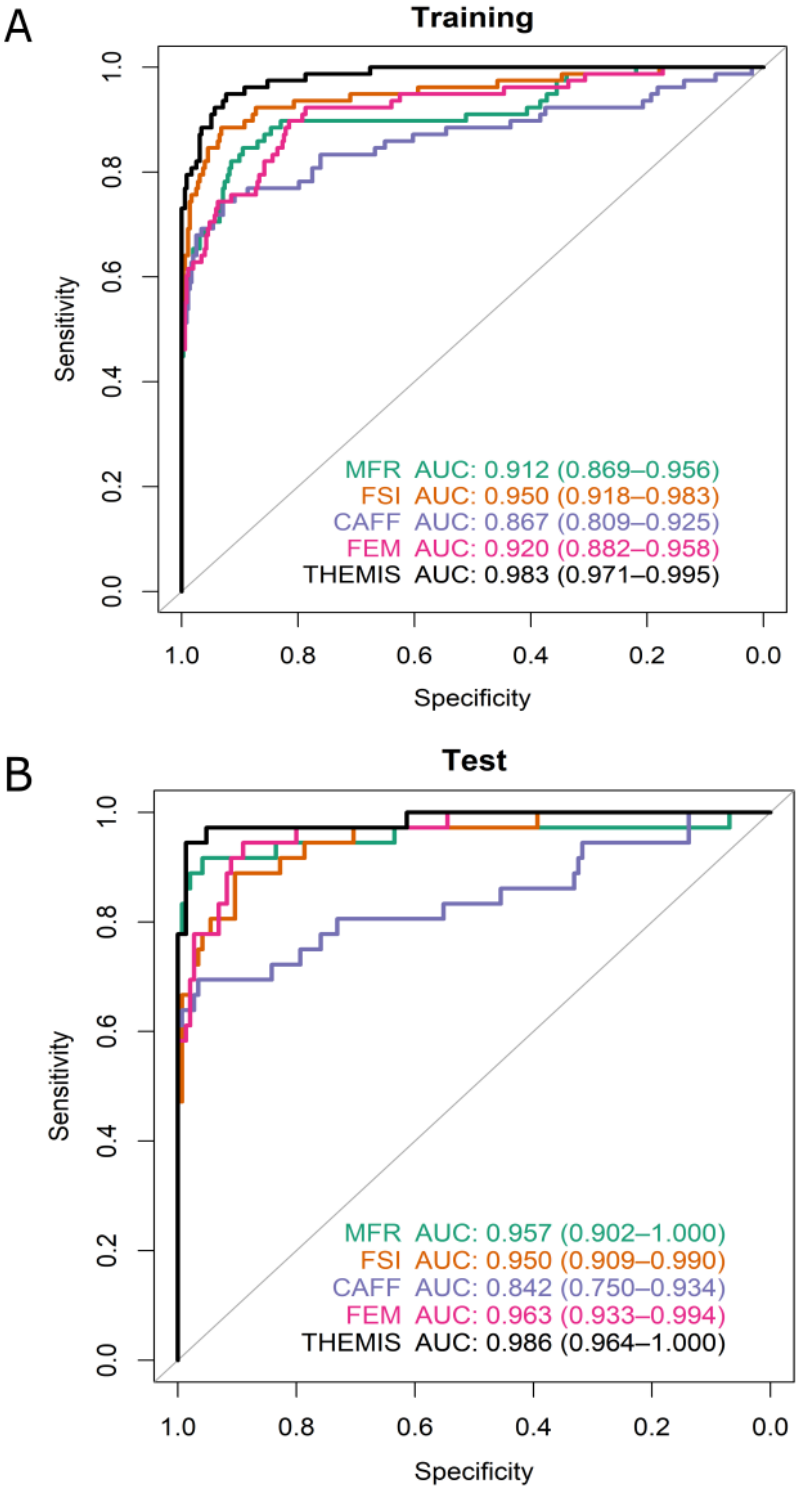
We have also previously developed a multidimensional ensemble model named Thorough Epigenetic Marker Integration Solution (THEMIS). This model integrates various cfDNA features, including methylated fragment ratio (MFR), chromosomal aneuploidy of featured fragments (CAFF), fragment size index (FSI), and fragment end motif (FEM), enabling highly sensitive early detection across a pan-cancer cohort [27]. In a subgroup comprising 114 patients with GC and 497 healthy controls, the THEMIS model showed an estimated area under the curve of 0.983 for the training data set (Figure 1A) and 0.986 for the test data set (Figure 1B). However, the fact that the model was trained on a pan-cancer cohort and the control group did not contain individuals with benign gastric diseases limits its predictive reliability for GC.

This study aimed to develop a highly sensitive GC-specific THEMIS model for the early detection of GC. This study's design is illustrated in Figure 2. Patients with GC will be enrolled in the malignant group, while the control group will comprise not only healthy individuals but also participants with benign gastric diseases, such as gastritis, gastric ulcers, and gastric polyps. Consequently, a novel model will be developed to differentiate malignant cancer from nonmalignant gastric status. A nonbisulfite enzymatic whole methylome sequencing (WMS) assay [28] will be applied to ensure the preservation of methylation signals from the cfDNA alongside the molecular fragmentation profile. The sequencing data generated from cfDNA will then be analyzed across the abovementioned multiple dimensions, encompassing methylation patterns, chromosomal copy number alterations, and fragmentation profiles. In addition, GC-related biomarkers, such as PG, G-17,

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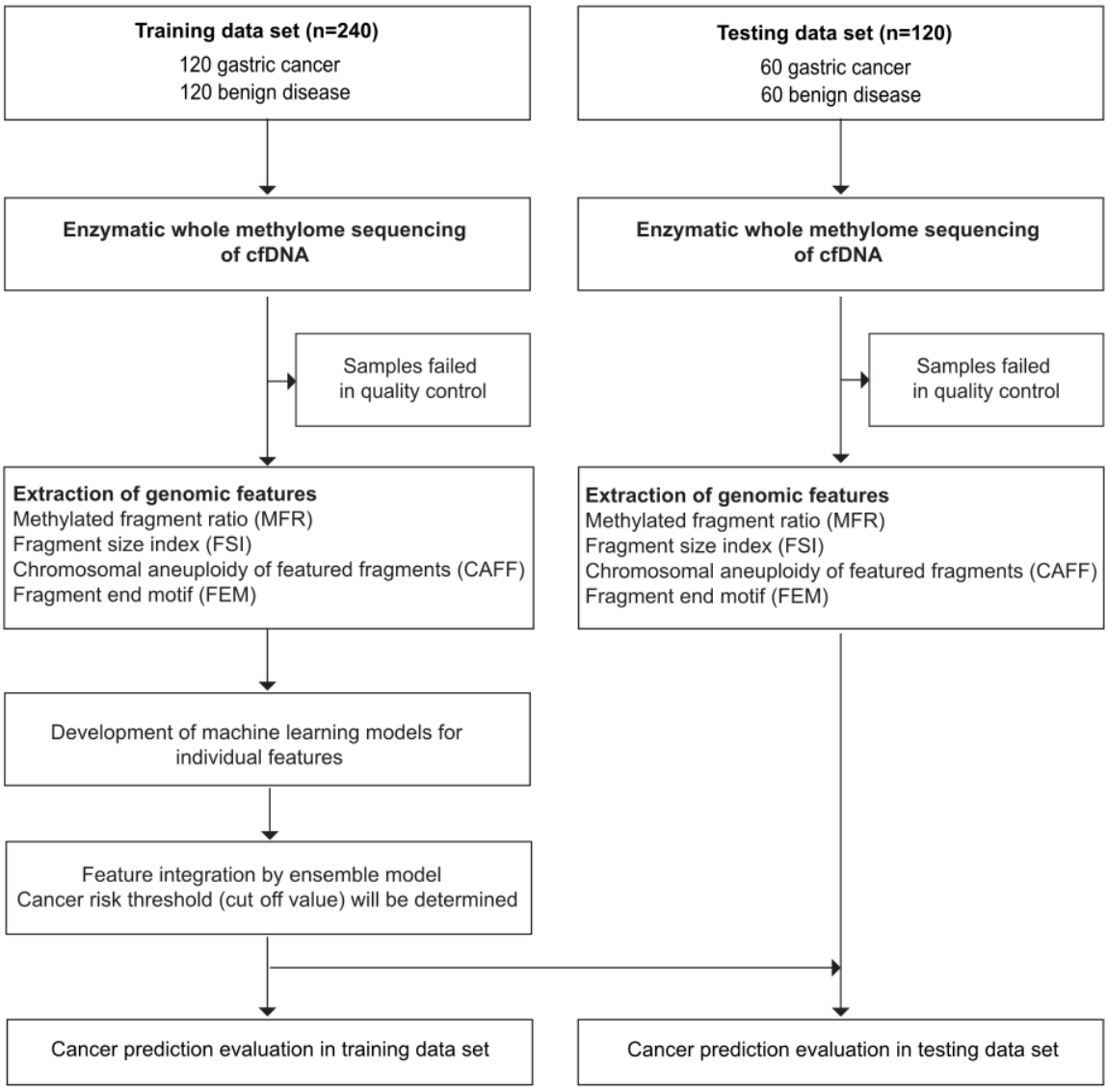
and *H pylori*, will be evaluated either independently or in combination with cfDNA features during model training to enhance the detection sensitivity. The overall clinical performance of the model, as well as its performance in each clinical stage, will be evaluated.

Figure 1. Receiver operating characteristic curve analysis showing the cancer prediction performance of the THEMIS model in the GC subgroup: (A) training data set; (B) test data set. The AUC together with the 95% CI is shown. AUC: area under the curve; CAFF: chromosomal aneuploidy of featured fragments; FEM: fragment end motif; FSI: fragment size index; MFR: methylated fragment ratio; THEMIS: Thorough Epigenetic Marker Integration Solution.



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Figure 2. Flowchart of patient recruitment, sample collection, and statistical analysis strategy. cfDNA: cell-free DNA.



Methods

Study Objectives

This study aims to develop and validate a novel blood-based WMS method followed by the development of a multidimensional model for the analysis of various features of cfDNA specifically for early GC detection. We expect that this noninvasive liquid biopsy assay will be instrumental in distinguishing individuals with a high probability of GC. Individuals who receive a positive test result will subsequently obtain a confirmed diagnosis by gastroscopy. Conversely, individuals who receive a negative test result will considered as having a low probability of GC. For this group of patients, they would be recommended to undergo a deferred gastroscope, and possibly a repeated test annually.

The primary objective is to validate the overall diagnostic specificity and sensitivity of the model and additionally assess its performance in each clinical stage of GC. The secondary objective is to investigate the specificity and sensitivity of the model when combined with potential biomarkers such as PG, G-17, or *H pylori* levels, aimed at enhancing early GC detection.

Study Population

This study will enroll individuals who receive gastroscopy at Xijing Hospital of Air Force Military Medical University, Xi'an, China. Further, 2 groups will be formed based on the outcomes of gastroscopy: a malignant group and a nonmalignant group. The malignant group will include patients diagnosed with high-grade intraepithelial neoplasia or GC (more than 90 patients corresponding to >50% of patients in stages I and II), while the nonmalignant group will include both healthy individuals and patients with gastritis, gastric ulcers, gastric polyps, or other benign gastric diseases.

Clinical parameters, such as personal history, family history of digestive tract cancer, gastroscopic findings, and GC staging, will be systematically collected for each subject. Blood samples will be collected for WMS analysis, the results of which will be used to establish a GC diagnostic model.

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Inclusion Criteria

Subjects will be enrolled after understanding and signing the informed consent form, ensuring their eligibility based on the provided inclusion or exclusion criteria.

Inclusion criteria must be fulfilled: (1) age 18 years or older, male or female; (2) availability of complete clinical information; and (3) agreement of the patient to join this study with signed consent and good compliance.

An additional specific inclusion criterion for subjects to be included in the malignant group must be fulfilled: confirmation of gastric adenocarcinoma through histopathology in accordance with the American Joint Committee on Cancer's 8th Edition Cancer Staging Manual, with a pathological stage ranging from stage I to IV. This includes patients with esophageal gastric junction adenocarcinoma, regardless of histology types.

Exclusion Criteria

Subjects will be considered ineligible if any of the following exclusion criteria are met: (1) they have previously been diagnosed with any kind of malignant tumor, (2) they have received total or partial gastrectomy, (3) they have received bone marrow or organ or stem cell transplantation, (4) they have received blood transfusion within the past 6 months, (5) they have previously received any form of local or systematic antitumor treatment, (6) they had ongoing fever or received anti-inflammation therapy within 14 days prior to blood draw for this study, (7) if female, they were pregnant or lactating, and (8) clinical information was incomplete or the subject was unqualified to participate in this study.

Discontinuing Study Interventions and Patient Withdrawal

If the ongoing study is later considered to be infeasible, the principal investigator shall submit a termination application to the institutional review committee (IRC). The decision for the termination will be made by the IRC. Following the decision, the principal investigator shall provide a clinical trial termination report to the IRC.

Subjects may be withdrawn from this study for the following reasons: (1) subjects request to exit the trial and withdraw informed consent, (2) subjects refuse to have blood samples collected, even after providing informed consent, (3) sufficient blood sample collection is difficult for the subjects, and (4) subjects enrolled by mistake and are later assessed to be unsuitable for this study.

Sample Collection

In total, 20 ml of peripheral blood will be collected from each subject and stored in a Cell-Free DNA Storage Tube (Cwbiotech). Each subject's information, such as index, name, sample type, and collection time, will be marked clearly. Blood samples shall be delivered to the laboratory within 72 hours at 15 °C-35 °C to proceed with plasma extraction. In situations where timely delivery to the laboratory is not feasible, the blood samples shall be centrifuged at 4000 × g for 15 min at 4 °C and the upper layer containing plasma will be transferred to a new tube. Approximately 4 ml of plasma will be obtained and stored at −80 °C until use. Alternatively, for a period of no more than 1 month before transportation, the plasma can be stored at –20 °C.

cfDNA Extraction

The plasma samples that were prepared in the previous step will be processed for cfDNA extraction by using the MagMAX Cell-Free DNA Isolation Kit (Thermo Fisher Scientific) per the manufacturer's instructions. The quantity and quality of extracted cfDNA will be assessed with a Bioanalyzer 2100 (Agilent).

WMS Library Construction

The entire amount of extracted plasma cfDNA (capped at 15 ng if exceeding what is needed) for each sample will be used to generate WMS libraries with the NEBNext Enzymatic Methyl-seq Kit (New England Biolabs) according to manufacturer instructions, with 1 modification: 100 ng of carrier RNA (TIANGEN) will be added before denaturation by sodium hydroxide. The generated libraries will be amplified with 9 polymerase chain reaction cycles, followed by quantification using the Qubit dsDNA HS Assay Kit (Thermo Fisher Scientific). After that, the constructed libraries will be subjected to sequencing on a NovaSeq 6000 system (Illumina) with a paired-end read length of 100 bp.

Model Establishment

The estimation data set will be used to establish a machine learning model aimed at predicting cancer probability. Various features associated with plasma cfDNA fragments, such as their methylation status, will be subjected to data preprocessing, feature filtering, and model selection. This will lead to creation of respective classifier models. In a prior context, we defined these features as MFR, CAFF, FSI, and FEM.

MFR Feature

Genomic methylation status undergoes substantial alterations even in the early cancer development stage. The release of ctDNA by cancer cells can lead to changes in the methylation levels of cfDNA present in the plasma. To quantify these changes, the whole genome will be tiled into nonoverlapping 1 Mb windows. The methylation levels within each window will be quantified by the fraction of fragments featuring fully methylated CpGs, thereby resulting in the computation of MFR.

CAFF Feature

Cancer cells often exhibit chromosomal instability, with instances of partial or complete amplification or loss of chromosomal arms [29,30]. To account for this, a previously described plasma aneuploidy score will be calculated for each sample. This calculation will rely on the levels of copy number alterations in 5 specific chromosome arms, which exhibited the most significant copy number alterations when compared to baseline samples [20].

FSI Feature

The size frequency of ctDNA fragments released from cancer cells differs from that of cfDNA [31]. By tiling the whole genome into nonoverlapping 1 Mb windows, the read ratio between short fragments (100-166 bp) to long fragments (169-240 bp) will be computed, resulting in the determination

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of the FSI. Subsequently, the FSI of each sample will be contrasted with the healthy population baseline, and the cancer risk for each subject will be estimated.

FEM Feature

The preferred FEMs of ctDNA differ from those of cfDNA due to DNA nuclease downregulation in the cfDNA fragmentation process [31]. The frequency of a total of 256 4-nucleotide (ie, 4-mer) fragment 5' end motifs will be analyzed, with the following modifications: (1) only fragments shorter than 171 bp will be selected for analysis, and (2) only reads mapped to the Crick strand will be used for calculation.

An ensemble classifier named THEMIS has been developed based on a generalized linear model incorporating elastic-net penalization. THEMIS is established by integration of the 4 abovementioned features, which includes the predicted cancer probability scores by MFR, FSI, and FEM along with the plasma aneuploidy scores of CAFF. R packages such as *CARET* under 20-fold cross validation will be used.

Sample Size Estimate and Statistical Analysis

The sample size was estimated using the strategy mentioned by Negida et al [32]. Based on the abovementioned pilot study, the ensemble THEMIS model reached a sensitivity of 0.94 with 0.95 specificity (Figure 1). We expect that the new model integrating similar features as THEMIS will attain a sensitivity of at least 0.9. If we consider the 95% CI width of 0.08 (2-sided test α=.05), then at least 54 cancer cases will be required. If we also expect a certain amount of dropout, such as 10%, a minimum of 60 cases will be needed. The same number of patients will be enrolled in the nonmalignant control group for this case-control study. The plan is to allocate both groups of subjects by the same 2:1 ratio into training and testing data sets. Ensuring at least 60 cases and 60 controls within the testing data set, a total of 360 subjects (180 cancer cases and 180 controls) will be enrolled. This ensures that each group is composed of no fewer than 180 subjects. The malignant group and the control group will be matched by age and sex to minimize possible confounding factors (Figure 2).

The area under the curve, constructed with a receiver operator characteristic analysis calculated by the *pROC* package, will be used to evaluate individual classifier models as well as the ensemble model's performance in distinguishing between cancer and noncancer conditions. Clinical diagnosis results, including but not limited to gastroscopy or pathological determinations, are considered the "gold standard." The cancer risk threshold (cutoff value) will be determined based on the training data set. After that, the prediction performance of the established model will be evaluated in the testing data set in several aspects, including sensitivity, specificity, positive prediction value, and negative prediction value. These variables, as well as 95% CI, will be calculated using the *epiR* package. The Cohen κ score will be calculated with the *vcd* R package to demonstrate the concordance of the predicted results versus the pathological diagnostic results. A single-blind analysis will be applied, which means that the bioinformatics analysts will be blinded to whether the subjects have GC or not. The results are considered significant if the *P* value is <.05. All statistical analyses will be performed in R (version 3.6.3; R Core Team).

Patient and Public Involvement Statement

Patients, healthy subjects, and the public will not be involved in our studies for reporting, designing, or implementation. We have no intention of sharing this study's results with the participants, unless they proactively request to receive this information.

Ethics Approval

The design and implementation of this study strictly followed the Declaration of Helsinki and Chinese medical research norms and regulations. This protocol was approved by the Medical Ethics Committee of the First Affiliated Hospital of the Air Force Medical University (Xi'an, China; approval No. KY20222222-F-1). This study was also registered at ClinicalTrial.gov (NCT05668910).

All enrolled subjects signed informed consent forms for blood sample retention, and they were fully informed that their blood samples would be used for scientific experimental research. A primary principle of this study is to protect the rights and interests of the subjects while ensuring the scientific nature of this study and the authenticity of the data. The subjects shall be volunteering to participate in this study, and their privacy will be fully respected. Throughout this study, all the data will be anonymized and maintained with confidentiality.

Results

Recruitment began in November 2022 and as of August 2023, we enrolled 250 patients. The last recruitment is expected to finish by April 2024. As for data analysis, it is anticipated to be finalized by September 2024.

Discussion

The primary aim of this study was to evaluate the effectiveness of using combined cfDNA features, determined through WMS analysis, for early cancer detection. If our model is incorporated into current clinical practices, an individual with a positive result would subsequently undergo either a gastroscopy, a biopsy, or both to ascertain the presence of GC. Conversely, a negative result would indicate a low likelihood of GC and prompt recommendations for a deferred gastroscopy, along with the possibility of an annual repeated test.

The major strength of this study is that this is the first registered observational study, to our knowledge, designed to evaluate the integrated analysis of methylation patterns, fragmentation profiles, and chromosomal copy number changes in cfDNA for early GC detection. Additionally, cfDNA studies designed for the Chinese GC population are limited. Our study will reveal whether multidimensional analysis of cfDNA is an effective strategy for differentiating patients with GC from nonmalignant individuals in the Chinese population.

This study has several potential limitations. Foremost among these is the fact that it is a case-controlled study with a relatively modest cohort size. We acknowledge that case-control studies,

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especially those performed at a single site, are susceptible to selection bias. Individuals enrolled from a single hospital may not be fully representative of the diversity of a general screening population. Given these limitations, a comprehensive and sizable prospective validation within a screening population will be pursued prior to considering clinical implementation. Another limitation would be that it is impossible to include all the possible benign gastric disease types in the control group; therefore, the constructed model might have limited ability to differentiate GC from other types of benign diseases beyond this study. In addition, although the individuals will be prospectively enrolled in this study, the analysis will be carried out retrospectively. However, it is notable that the bioinformatics analysts will remain blinded to the true pathological outcomes during the validation of the model in the testing cohort, thereby mitigating the potential analysis bias.

Should the results of this research align with our expectations, they will furnish support for the use of ctDNA in early detection of patients with GC. The THEMIS model could significantly contribute by complementing the standard-of-care screening and aiding in the differentiation of high-risk patients warranting further diagnostic evaluation. The findings of this study, looking ahead, could substantially enhance early screening and early diagnosis practices, potentially resulting in a shift toward earlier-stage diagnoses and consequently elevating the 5-year survival rate for patients with GC.

Acknowledgments

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Data Availability

All data generated or analyzed throughout the course of this study, if not already included within this paper or its Multimedia Appendix files, can be obtained from the corresponding author upon submitting a reasonable request for research purposes.

Authors' Contributions

YH and XL originated this study’s concept and formulated the initial idea. XL is the principal investigator and is responsible for protocol review and approval. JW, WW, and RG were involved in the submission and obtaining of ethical approval. NS, XS, YN, and WC were involved in development of the protocol. LDX and YL were involved in this paper’s drafting. All coauthors have reviewed and approved the final version.

Conflicts of Interest

NS, XS, YN, YL, LDX, and WC are employed by Genecast Biotechnology Co, Ltd. Other authors have declared no conflicts of interest.

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Abbreviations

CA: cancer antigen
CAFF: chromosomal aneuploidy of featured fragments
cfDNA: cell-free DNA
ctDNA: circulating tumor DNA
FEM: fragment end motif
FSI: fragment size index
G-17: gastrin-17
GC: gastric cancer
IRC: institutional review committee
MFR: methylated fragment ratio
PG: pepsinogen
THEMIS: Thorough Epigenetic Marker Integration Solution
WMS: whole methylome sequencing

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Protocol

Health Care Provider Stigma Toward Patients With Substance Use Disorders: Protocol for a Nationally Representative Survey

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Abstract

Background: The US overdose epidemic is an escalating public health emergency, accounting for over 100,000 deaths annually. Despite the availability of medications for opioid use disorders, provider-level barriers, such as negative attitudes, exacerbate the treatment gap in clinical care settings. Assessing the prevalence and intensity of provider stigma, defined as the negative perceptions and behaviors that providers embody and enact toward patients with substance use disorders, across providers with different specialties, is critical to expanding the delivery of substance use treatment.

Objective: To thoroughly understand provider stigma toward patients with substance use disorders, we conducted a nationwide survey of emergency medicine and primary care physicians and dentists using a questionnaire designed to reveal how widely and intensely provider attitudes and stigma can impact these providers' clinical practices in caring for their patients. The survey also queried providers' stigma and clinical practices toward other chronic conditions, which can then be compared with their stigma and practices related to substance use disorders.

Methods: Our cross-sectional survey was mailed to a nationally representative sample of primary care physicians, emergency medicine physicians, and dentists (N=3011), obtained by American Medical Association and American Dental Association licensees based on specified selection criteria. We oversampled nonmetropolitan practice areas, given the potential differences in provider stigma and available resources in these regions compared with metropolitan areas. Data collection followed a recommended series of contacts with participants per the Dillman Total Design Method, with mixed-modality options offered (email, mail, fax, and phone). A gradually increasing compensation scale (maximum US$250) was implemented to recruit chronic nonresponders and assess the association between requiring higher incentives to participate and providers stigma. The primary outcome, provider stigma, was measured using the Medical Condition Regard Scale, which inquired about participants' views

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on substance use and other chronic conditions. Additional survey measures included familiarity and social engagement with people with substance use disorders; clinical practices (screening, treating, and referring for a range of chronic conditions); subjective norms and social desirability; knowledge and prior education; and descriptions of their patient populations.

Results: Data collection was facilitated through collaboration with the National Opinion Research Center between October 2020 and October 2022. The overall Council of American Survey Research Organizations completion rate was 53.62% (1240/2312.7; physicians overall: 855/1681.9, 50.83% [primary care physicians: 506/1081.3, 46.79%; emergency medicine physicians: 349/599.8, 58.2%]; dentists: 385/627.1, 61.4%). The ineligibility rate among those screened is applied to those not screened, causing denominators to include fractional numbers.

Conclusions: Using systematically quantified data on the prevalence and intensity of provider stigma toward substance use disorders in health care, we can provide evidence-based improvement strategies and policies to inform the development and implementation of stigma-reduction interventions for providers to address their perceptions and treatment of substance use.

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KEYWORDS

substance use disorders; provider stigma; cross-sectional survey study; provider attitudes; survey methodology

Introduction

Background

The US overdose epidemic is a public health emergency that continues to escalate, accounting for over 100,000 deaths annually [1]. Fueled largely by the use of prescription opioids, heroin, and synthetic opioids other than methadone (primarily fentanyl) [2-4], which contributed to 75% of overdose deaths in 2021, the epidemic has been further intensified by rises in stimulant-related overdose deaths, particularly those linked with cocaine and psychostimulants [5]. Rising cocaine and psychostimulant-related overdose deaths also often involve opioid use [6-8], and polysubstance use involving both stimulants and opioids is a growing pattern that warrants focused interventions [9]. In addition, the accidental overdose epidemic has been attributed to "multiple distinctive sub-epidemics of different drugs" that have treatments that are different, such as the availability of medications for opioid use disorder (MOUD) versus the range of behavioral health services to treat stimulant use [7,10].

National attention to this overdose epidemic highlights the need for resources for health care providers to enhance the prevention and treatment efforts toward substance use disorders [7], including provider training and integration of substance use treatment within current health care systems. Barriers may arise from providers' negative attitudes toward persons with substance use disorders [9,10], including provider stigma, defined as the negative attitudes, perceptions, and behaviors that providers embody and enact toward their patients either subtly or involuntarily [11,12]. Provider stigma is increasingly recognized as an important and understudied barrier to the effective treatment and prevention of substance use [13-15], as well as one that is notably complex. Given that it encompasses stigma professionally and personally (eg, applying labeling, stereotypes, discrimination, and social marginalization) [16], provider stigma is one of the more substantive forms of stigma that people with substance use disorders may experience, even compared with friends, family, and coworkers, and often manifests as facing scrutiny and skepticism, treatment refusal, and delayed or substandard treatment [17-19]. There are also many causes of provider stigma, including negative perceptions and attitudes (eg, viewing the "illness ahead of the person"), compassion fatigue and professional burnout, biases (both conscious and unconscious), therapeutic pessimism and helplessness (eg, negative outlook on the likely benefits of treatment), and inadequate training and skills [20-26]. As such, research efforts that focus on quantifying and addressing the scope of provider stigma toward persons who use drugs is a critical first step in enhancing the health care response to expanding the delivery of substance use treatment [27-29].

Key Scientific Objectives of Clinical Trials Network 0104

Providers are increasingly called upon to identify patients with substance use disorders and refer patients to MOUD and other treatment resources [16,30]. Thus, understanding provider stigma and attitudes toward patient substance use is especially important in developing interventions to expand access to substance use treatment. The specific aims of this study are as follows:

1. Define the scope of provider stigma toward substance use by substance type and compare this stigma to provider stigmas directed at other medical conditions.
2. Compare providers' screening, treatment, and referral practices for substance use with their screening, treatment, and referral practices for other medical conditions.
3. Identify factors related to the delivery of substance use treatment in US-based primary care and emergency medicine settings to inform educational and intervention strategies addressing provider stigma.

Methods

Study Overview and Design

This study examines provider stigma by conducting a cross-sectional national provider survey of general practice, emergency medicine, and the dental workforces (October 2020 to October 2022). A representative sample of physicians and dentists was surveyed to better understand their attitudes and

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stigma toward patients with substance use disorders, and the role that these attitudes and stigma play in shaping providers' screening, treatment, and referral practices concerning the provision of substance use treatment.

Ethics Approval

The study was reviewed and approved by the single Institutional Review Board (IRB) at the University of Miami (UM; IRB# IRB00010711) that provided regulatory oversight over all the participating sites. Consent forms were not used because of the nature of the study, which involved minimal participant risks. Instead, we received a waiver of informed consent from the UM IRB, whereby the cover letter provided the required consent information needed to help inform the participant's decision to participate. Consent was, therefore, not documented in writing, but rather implied through survey completion. Opt-out, passive consent methods have been shown to be more cost-efficient and feasible, without violating participants' autonomy or essential interests [31-33]. Confidentiality was maintained using unique participant ID numbers. The master list linking participant ID numbers to participant contact information was maintained at a secure location by the designated staff for recruitment purposes. At the end of data collection, only deidentified study data were made available to the study investigators. Compensation for participation was issued, as described in further detail in the section on incentives.

Participants

Overview

The study population consisted of primary care physicians, emergency medicine physicians, and dentists. Given their regular contact with patients with substance use disorders, these providers are well positioned to either refer for or deliver substance use treatment within their routine clinical care practices [34]. We now detail the rationale for including each provider group.

Primary Care Physicians

Efforts to expand substance use treatment have largely turned to primary care settings, especially to reach patient populations that heavily rely on public health care systems (eg, those who are homeless and have low income) and that present with multiple comorbidities (eg, those with substance use and HIV) [35-37]. Recent stigma studies among primary care physicians have largely focused on opioids, particularly their attitudes toward patient opioid use and their clinical practices related to prescribing MOUD. These studies have documented negative attitudes toward persons with opioid use disorders (OUD) as well as associations between higher provider stigma and minimal offering of OUD treatment practices and referrals for the treatment of OUD in these settings [13,38-40].

Although the practice of primary care is described as the services provided from a patient's first point of "entry" on through their continued comprehensive care, primary care also routinely involves collaborating with other health care providers, including consultations and referrals [41]. Therefore, we sought to survey all primary care specialties as defined by the American Medical Association (AMA), including family medicine, general practice, internal medicine, obstetrics/gynecology (OB/GYN), and pediatrics [42]. With regard to the field of OB/GYN medicine, preventive gynecologic appointments (eg, Papanicolaou smears) often represent women's only contact with a medical care provider and thus are the only opportunity for these women to be screened and treated for other medical conditions [43-45]. A 2017 study found that around half of women either identify their OB/GYN as their primary care provider or do not have a primary care provider [46]. In addition, in the field of pediatrics, substance use is increasingly prevalent among youth and young adults; opioid misuse is being initiated at a young age, increasing the risks for future substance use disorders [47-52], whereas stimulant use (eg, methamphetamine and inhalants) is also increasing at striking rates, with about half of graduating high school students reporting the use of a stimulant at least once [53,54]. In response, the American Academy of Pediatrics has advocated the expanded use of substance use treatment for youth and adolescents and called upon pediatricians to intervene early and help prevent potential substance use among their patients [55].

Finally, as specialists in internal medicine, infectious disease physicians were specifically included in our sample, as they also often provide primary care treatment for patients with HIV, especially as HIV treatment has evolved from a fatal disease to a manageable chronic condition that warrants screening for other major medical comorbidities [56-58]. A 2018 study showed that three-fourths of infectious disease physicians also act as the primary care physicians for patients with HIV [59]. Studies suggest that the increasing rates of infectious diseases such as HIV/AIDS are driven by the opioid crisis and that integrated substance use disorder and infectious disease treatment can reduce substance misuse and infectious disease transmission, respectively [60]. The National Institute of Allergy and Infectious Diseases and the Institute of Human Virology have underscored the significant role of infectious disease providers in addressing substance use among patients in their practices [61].

Emergency Medicine Physicians

Emergency medicine physicians were included in the study population, given that they frequently encounter patients with substance use disorders, especially those at high risk for overdose, trauma, or suicide [62-64]. These patients often do not regularly seek primary care and instead use and rely on emergency departments for medical treatment [65,66]. Prior studies assessing emergency medicine physicians' regard for patients with substance use disorders have featured small sample sizes, and their findings were often limited in generalizability [17,62]. Overall, these studies documented low regard for patients with substance use disorders by emergency medicine physicians compared with patients with other medical conditions [17]. Studies have suggested that such negative attitudes can be mitigated by providing physicians with evidence-based trainings [62].

Dentists

The professional role of dentists has evolved into one that is more medically focused and encompasses limited preventive primary care, including medical chairside screenings [67]. As

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health care providers who regularly manage and treat patients with dental pain, dentists encounter challenges analogous to those of other health care practitioners who encounter and treat patients who live with substance use disorders [68-70]. Dentists have reported concerns that patients are using substances, yet they often do not routinely query patients about it [71-74]. Dentists are responsible to treat many oral implications of substance use, such as rampant caries, xerostomia, tooth loss, and the pathognomonic and overt dental disease known as "meth mouth" [75,76]. However, dentists across the United States have reported minimal, if any, prior training and knowledge in the area of patient substance use [73]. As such, the American Dental Association (ADA) has called for dentists to obtain continuing education in opioid-related practices and use brief interventions to encourage and refer patients for opioid use treatment [77]. However, there are limited data regarding dentists' stigma and attitudes toward addressing substance use in their clinical practices.

Eligibility Criteria

Study participants were required to (1) currently be in clinical practice (and planning to remain so for the next year) as a primary care or emergency medicine physician (Doctor of Medicine or Doctor of Osteopathic Medicine) or a dentist (Doctor of Dental Medicine or Doctor of Dental Surgery), (2) have a current US medical or dental license (ie, not revoked or expired), and (3) agree to complete and return the survey after reading the elements of informed consent in the cover letter.

Recruitment

We purchased our sample from a licensee of the AMA and ADA who provided a systematic random sample of providers based on our selection criteria. The national sampling frame of practicing primary care and emergency medicine physicians provided by the licensee was obtained from the AMA Masterfile, the most commonly used and comprehensive sampling source for surveys of physicians in the United States [78-81]. Similarly, the sampling frame of dentists provided by the licensee came from the ADA, which maintains a list of active dentists in the United States. Our purchased sample frame from the licensee included provider name; type of degree; and any available contact information (postal address, telephone number, and email address).

We defined 6 different strata for our sample: AMA primary care physicians, AMA emergency medicine physicians, and dentists, with the members of each category identified by metropolitan and nonmetropolitan practice locations. Metropolitan and nonmetropolitan areas were defined using Metropolitan Statistical Areas, as defined by the Office of Management and Budget and used by the census. We specifically oversampled nonmetropolitan practice areas, given that there may be differences in provider stigma and attitudes, along with available treatment and referral resources, in nonmetropolitan regions compared with metropolitan ones [82] (see the section *Data Analysis Sample Size*). Systematic random samples were drawn from each stratum; every nth record was included in the sample based on the quantity requested versus the quantity available according to our specified criteria of provider characteristics. To assist our efforts to create sample weights for data analysis, the licensee provided the current population numbers for each stratum that we planned to sample.

To ensure that we only captured physicians and dentists currently in practice, we added a survey question on the cover page to assess whether the respondent was currently engaged in direct patient care. Although the AMA and ADA do track this information, we wanted to ensure that we omitted recent retirees or nonpractitioners. Within this survey question, we also asked whether the respondent planned to be in clinical practice for the next year. We chose to exclude those who planned to retire within the year, as their willingness to perform certain behaviors in the future (eg, receive future training programs and offer screening or treatment practices) may not be reflective of the current practicing workforce.

Incentives

Providers were compensated for their time dedicated to completing the survey. In line with the Dillman [83] Total Design Method (TDM), each survey included an initial payment (US $10), regardless of survey participation, with the prenotification letter. Respondents who completed the survey then received additional compensation upon completion, which was gradually increased throughout the study. This methodology of a gradually increasing compensation was used in our prior national survey of dentists and helped substantially increase our response rate [73,84-86]. Furthermore, the amount of incentive that prompted a dentist to respond proved to be a significant covariate in that study's primary outcome paper: dentists requiring enhanced incentives were significantly less likely to view expanded HIV screening (and other preventive health screenings) favorably as part of their professional role [86].

Participants were given options when selecting their method of compensation: an electronic gift card to 3 predetermined companies (Target, Walmart, and Amazon), a Visa debit card, or a mailed check. The participants also had the option of not receiving the compensation. The compensation scale upon completion of the survey (separate from the US $10 incentive in the first mailing) started with an initial payment of US $50. When the follow-up telephone prompting was initiated to recruit chronic nonresponders (ie, participants who had not responded to the initial recruitment attempts), we implemented an experimental design whereby the sample eligible for telephone prompting was randomized to receive an offer of either US $100 or US $150 upon completion (Table 1). After the US $100 and US $150 incentives were offered through the experimental design, we then offered chronic nonresponders an incentive of US $250 to complete the survey. This became necessary due to COVID-19–related challenges to the health care community, which caused staff shortages, large patient demand, and overburdened offices and hospitals; as such, increasing the incentive to US $250 helped compensate overly taxed providers who were experiencing significant clinical work burdens and time constraints during the pandemic. Notably, the availability of gradually increasing compensation time points (US $50, US $100, US $150, and US $250) will serve as important covariates in future study analyses.

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Table 1. Design of the experiment.

Factor A: incentive offers in prompting	Factor B: prompter placing follow-up telephone calls	
	B1: NORC[a] telephone prompter (control)	B2: study investigator (treatment)
A1: US $100 offer upon completion (control)	A1B1	A1B2
A2: US $150 offer upon completion (treatment)	A2B1	A2B2

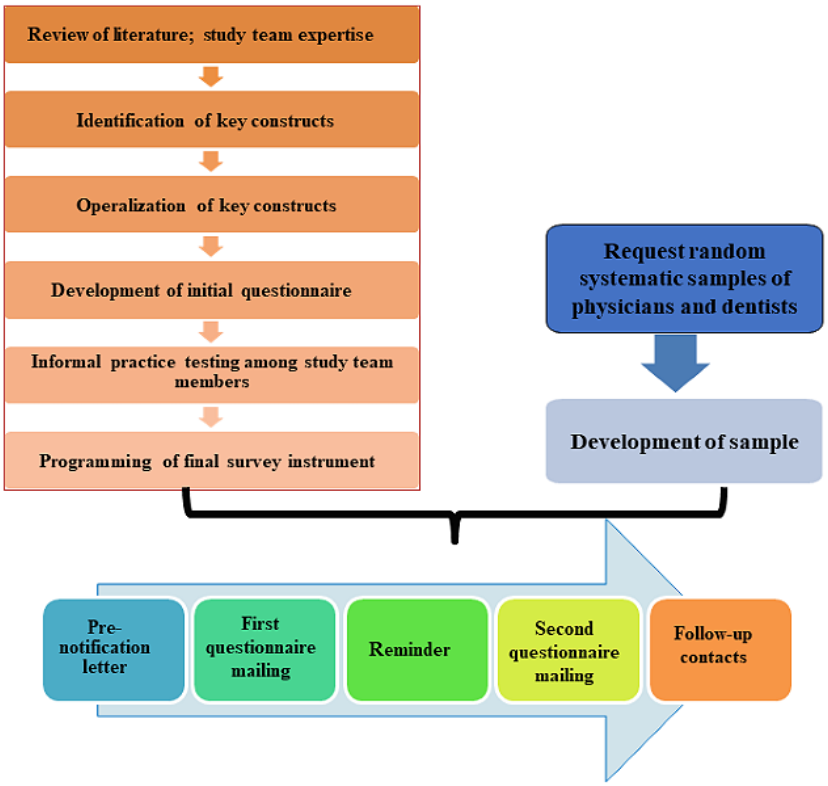
[a]NORC: National Opinion Research Center.

Study Procedures

Study procedures were implemented as a collaborative effort between the study investigators and the National Opinion Research Center (NORC). The NORC has administered leading social science surveys and has extensive experience in sampling design, survey data collection, recruitment of nonresponders, nonresponse bias analysis, and weight creation.

The overall methodology behind our study procedures was guided by the TDM, which implements strategies to help achieve a high response rate for survey studies (Figure 1) [83]. We followed the TDM-recommended series of contacts with participants in the following order: prenotification inquiry, initial questionnaire mailing (which included a link to a secure internet survey site), thank-you or reminder contact, replacement questionnaire, and follow-up telephone calls. Follow-up telephone calls to nonresponding providers were made with the goal of establishing personal contact, verifying the receipt of study materials, answering questions, and prompting for questionnaire return. In addition to the alternative options, respondents were given the option to complete the survey via telephone. These telephone calls were a collaborative effort between NORC staff (telephone interviewers) and the study investigators. Prior studies have shown some significant increases in response rates when physicians conduct follow-up prompting to other physicians [87-89]. Therefore, the telephone prompting phase was designed so that the sample eligible for telephone prompting was randomized to receive an initial follow-up prompting phone call from either an experienced NORC telephone interviewer or a study investigator (one with Doctor of Philosophy credentials and the other with Doctor of Dental Medicine and Doctor of Philosophy credentials). Similar to the case of our gradually increasing compensation, our future study analyses will have the option to include telephone prompting personnel (experienced NORC telephone interviewer vs study investigator) as a covariate (Table 1).

Figure 1. Study schema.



The initial study procedure protocols included offering the option of in-person completion, whereby NORC field managers would perform in-person visits to provider offices to prompt providers to complete and return the survey and offer providers the option to complete the survey in person with the field manager. However, due to the COVID-19 pandemic, we were not able to implement in-person study visits, given the restrictions implemented at hospitals and health care offices limiting visitors and guests, in addition to the travel-related transmission concerns that NORC staff would have encountered.

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Participants were given multiple options to complete the survey. Internet- and mail-delivered surveys are strategies that have proven to be more cost-effective than traditional telephone surveys and are more compatible with health care providers' constrained schedules [90]. Because the evidence comparing the effectiveness of mail- versus internet-based surveys is not conclusive, mixed-mode approaches that offer both methods of completion are generally common [91,92]. Mixed-mode approaches allow health care professionals to choose their preferred mode of response, which may be influenced by factors such as provider age, comfort with technology, personal contact, and security or privacy concerns [92,93]. As a result, the NORC continues to conduct many of their national survey studies using mixed-mode methods [94-99]. In addition, the task force of the American Association for Public Opinion Research recommends using a mail modality if using a single mode or a mixed-mode design that first uses mail contact and subsequently includes an internet-based response option [100].

We used other strategies endorsed by the TDM and supported by other studies to increase response rates, including prepaid incentives, personalized cover letters, and prepaid postage [101-103]. The survey's self-completion methodology, use of a participant identification number, and specification (in the cover letter) that survey completion implies informed consent (in lieu of a signed consent) were additional methods used to minimize time constraints and maximize completion flexibility [104].

Description of Study Assessments

Overview

The study assessment consisted of a 1-time cross-sectional survey instrument that, based on pilot-testing, required approximately 20 to 30 minutes to complete. Because research has shown that lengthier surveys result in lower response rates, especially among busy health care providers, brevity and reduced respondent burdens were both priorities in developing the survey instrument [101,105]. To ensure succinctness and respondent acceptability of our proposed survey instrument, we conducted informal practice testing among the key study team members and affiliates. The goal of this informal practice testing was to identify (1) the time required to complete the survey; (2) any questions that were confusing, difficult to interpret, inadequately written, or nonapplicable (logistical issues); and (3) any questions that were perceived as not important or too invasive (personal concerns). The feedback provided through this informal testing provided valuable input, suggestions, and edits that were reviewed by the study team for application to the final survey instrument.

The survey instrument administered to physicians differed slightly from that administered to dentists, reflecting the different scopes of practice for physicians versus dentists, along with differences in their expected training and backgrounds [106,107]. For example, survey questions querying about offering certain medical treatment practices (eg, prescribing MOUD and initiating antiretroviral therapy) were not included in the instrument disseminated to dentists. Notably, however, most measures were identical, including those assessing provider stigma.

The survey instrument included items related to providers' attitudes and stigma. The Medical Condition Regard Scale (MCRS) [108] queried participants about their views on 3 categories of substance use (opioids, stimulants, and alcohol) as well as other medical conditions (type II diabetes, depressive disorder, and HIV) selected by the study team to assess the primary outcome. Specifically, these questions asked whether a provider views a given condition as enjoyable, treatable, and worthy of resources by asking them to report their agreement with a series of statements concerning a specified medical condition (eg, "Insurance plans should cover patients like this to the same degree that they cover patients with other conditions," "Patients like this irritate me," "I wouldn't mind getting up on call nights to care for patients like this," and "Patients like this are particularly difficult for me to work with").

In addition to our primary assessment of stigma using the MCRS, we included additional measures of stigma in the attitude-assessing section, such as the Drug and Drug Problems Perception Questionnaire [109], which focuses on provider stigma in the form of provider "motivation" to treat patients with substance use disorders. We adapted other prior scales for appropriateness, such as the Link [110] study that assessed stigma in the form of general social distance and perceived dangerousness toward people with mental health disorders; in our survey, we instead assessed perceived dangerousness and social distance or isolation toward people with substance use disorders [110]. Other provider stigma measures related to persons with substance use disorders included general attitudes, attitudes toward providing medical or dental care, stereotypes, and familiarity. We also queried the providers' personal history of substance use and treatment [109-120].

The instrument included many questions assessing providers' clinical practices. To understand provider practices related to substance use treatment within the context of their overall practices, we asked participants how, if it all, they are addressing a myriad of different health care conditions that generally fall under the scope of primary care (and, in the case of dentists, general dental care): (1) type II diabetes, (2) depressive disorder, (3) HIV, (4) substance use, (5) alcohol use, and (6) tobacco or nicotine use. Of note, 5 of these conditions were queried in the MCRS section to assess providers' attitudes toward these medical conditions. However, we collapsed opioid and stimulant use into 1 condition ("drug use") and added tobacco or nicotine use to this section, as it is imperative to understand participants' clinical practices related to forms of legal substance use (tobacco or nicotine), which can then be compared with their practices related to substance use. For each health condition, physicians were asked about their screening, treatment, and referral practices related to this condition; dentists were asked a similar set of questions but were not asked about providing treatment, given their differing scope of practice under their professional license.

Additional measures included social determinants of health (ie, whether providers are addressing patients' social needs, such as homelessness, transportation, and interpersonal violence [121]); risk behaviors (in their personal lives and professional roles) [122]; subjective norms and social desirability (ie, their colleagues' and patients' perceptions of their professional role

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in substance use treatment); clinical knowledge (ie, prior education or training and future training needs in addressing substance use); clinical practice (ie, year of graduation, type of clinical setting, clinical discipline or specialty, patient insurance information, and patient population); and sociodemographics (ie, age, race, ethnicity, and gender).

Data Analysis Sample Size

The data analysis plan was developed to identify significant differences among the 3 subgroups of clinicians (primary care physicians, emergency medicine physicians, and dentists). In addition, we wanted to ensure that there was significant power to find clinically meaningful relationships in our planned secondary analyses. Primary care physicians were the largest planned subgroup within our study sample due to their diverse training backgrounds (n=1411), while emergency medicine physicians (n=800) and dentists (n=800) were also included as subsets of the population of health care providers in the general care workforce. The final target population was 3011, which was the target sample from which invitations to participate were sent. Allowing for a 70% response rate would provide an expected sample of 2108. The sample size needed to be further refined to account for the planned oversampling of nonmetropolitan clinicians. Oversampling resulted in slightly different design effects (Deff) within each of the other strata (primary care physicians: Deff=1.076, effective n=918; dentists: Deff=1.067, effective n=525; emergency department physicians: Deff=1.062, effective n=527). Applying the design effect induced by the oversampling of nonmetropolitan clinicians provides an expected effective sample of 1970 (primary care physicians: n=918, 46.6%; emergency medicine physicians: n=527, 26.8%; dentists: n=525, 26.6%). Power was calculated using PASS 2020 [123] with the expected effective sample sizes and a type II error rate of 20% (for 80% statistical power). We also report the power for a 50% response rate.

With our expected effective sample size, there is 80% power to construct CIs of the mean score on the MCRS with width of 0.088 SD of the MCRS. The CI width is 0.172 SD for dentists or emergency medicine physicians and 0.13 SD for primary care physicians. The intervals widen with a 50% response rate, ranging from 0.104 SD to 0.202 SD. When comparing MCRS scores between 2 different medical conditions, there is 80% power to uncover a difference when that difference is truly at least 0.06 of the SD for the full sample. This required true difference is 0.12 SD for dentists and emergency medicine physicians and 0.08 SD for primary care physicians. For a lower response rate of 50%, the required true differences to achieve 80% power move to 0.07 SD, 0.11 SD, and 0.14 SD for the full sample, primary care physicians, and emergency medicine physicians or dentists, respectively. When comparing MCRS scores between the different clinician types, there is 80% power to uncover a true difference that is 0.20 SD between dentists and emergency medicine physicians and when the true difference is 0.18 SD between either dentists or emergency medicine physicians and primary care physicians. The corresponding required effect sizes increase to 0.24 SD and 0.20 SD if the response rate is 50% rather than the targeted 70%. These effects are all considered small effect sizes.

Furthermore, the survey was designed to have sufficient power for secondary outcomes. To illustrate this, we used a binary secondary outcome (yes or no): “addressing substance use treatment (including providing substance use treatment/prescribing medications for OUD by physicians and screening and referral by dentists) = yes” versus “not addressing substance use treatment (not providing substance use treatment/not prescribing medications for OUD by physicians and screening and referral by dentists)= no.” Calculations were again made using PASS 2020 [123] with a 2-tailed test, α=.05, β=.2 (80% power). We assumed moderately conservative values of baseline probability (P_0=.10 to .20) and R^2 of 0.2 to 0.3 for other variables in the model and examined the impact of a 1 SD change in a continuous variable (such as the MCRS score) in predicting the binary outcome. With a 70% response rate, we have >80% power to uncover a significant effect if the true associated odds ratio is in the range of 1.19 to 1.29 for the full sample (1.23-1.35 if there is a 50% response rate). This range is 1.32 to 1.45 (1.36-1.55 for a 50% response rate) for primary care physicians and 1.41 to 1.63 (1.50-1.78 for a 50% response rate) for dentists or emergency medicine physicians. These effect sizes are in the small to moderate range.

Outcomes

Our primary outcome is providers’ “regard” for patients with substance use disorders, as measured by the MCRS [108], which will be assessed by 3 separate classes of substance use: (1) opioid use (including heroin, fentanyl, and nonmedical pain medication use); (2) stimulant use (including methamphetamine, cocaine, and crack use); and (3) alcohol use. These classes of substance use will be compared with providers’ “regard” toward the other assessed medical conditions. This MCRS measure is based on an 11-item scale that is scored as a continuous indicator, ranging from 11 to 66. Lower scores indicate “low regard” (ie, high stigma), while higher scores indicate “high regard” (ie, low stigma) for the given medical condition. This measure will be assessed for both physicians and dentists.

The secondary outcomes are specific to the provider type. For physicians, the secondary outcome will assess whether US primary care providers are currently offering on-site treatment for substance use (collapsed into 1 condition, “drug use”) in their clinical practice. For dentists, the secondary outcome will assess whether US dentists are referring patients for substance use treatment in their clinical practice. We are particularly interested in exploring the relationship between provider stigma toward persons with substance use disorders and practices related to addressing substance use in their clinical settings. The analyses of the outcomes related to physicians and dentists will be addressed separately.

Statistical Analysis

Overview

In general, statistical tests are determined by the distributional properties of dependent or outcome variables. The binary secondary outcomes will be tested using chi-square tests of independence for comparisons between groups and logistic regression for the multivariable case. For binary outcomes that are not rare, we will use Poisson regression with robust SEs to

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directly estimate the risk ratio (rather than the odds ratio, which diverges from the risk ratio when an outcome is not rare). According to the literature [62,108,124-126], we anticipate that "regard" will behave as a normally distributed continuous variable though the exact method of analysis will depend on the realized distribution of "regard" in the final survey data.

Our statistical approach will include descriptive statistics (mean, SD, and 95% CI) as well as mixed models and ANOVA to compare the regard for different medical conditions and across different practice settings, respectively. We will also model all outcomes as a function of a set of covariates and develop parsimonious models to identify provider characteristics associated with each outcome using the appropriate modeling procedure based on the outcome's distribution (logistic regression for binary outcomes and linear regression for "regard"). All statistical analyses will use an α level of .05.

Item and Survey Nonresponse

Our first set of analyses will explore the potential biases that might arise if nonresponders differ significantly from responders along such dimensions as urbanicity. We may then explore the patterns of missing data. We would first derive binary measures that indicate whether the value of each variable for a respondent is missing. We would then relate these new measures to "key attributes" and consider statistically significant relationships as an indication of possible bias. Key attributes would be selected on the basis of (1) likely limited degrees of missing data and (2) substantive imports. If we find nonrandom patterns of item nonresponses, we will use multiple imputation methods [127] to minimize potential resulting biases. In addition, we will examine variables such as race, gender, and region in our nonresponse analysis to assess representativeness. If necessary, we would consider using nonresponse weighting to ensure that the results reflect the population.

Data Management

Data collection activities were overseen by the NORC. All the invited providers were assigned a unique study ID number in their personalized cover letters; to ensure confidentiality, the cover letter emphasized the confidentiality of their survey participation, and their responses would not be linked to their identification. Any documentation linking provider information with the assigned unique ID was stored securely, with the access limited to specified NORC study personnel.

The NORC information technology team oversaw the data entry technology involved in electronic submissions, while production clerks were responsible for questionnaire receipt and library filing for those participants who completed the survey using paper (ie, self-administered paper questionnaire or fax. Once a completed self-administered paper questionnaire was returned to the NORC, it was sent to NORC's Computer-Assisted Data Entry vendor for data entry and subsequent posting on a secure File Transfer Protocol site.

Study Leadership and Investigator Procedures

This study was a collaborative effort among the lead Clinical Trials Network (CTN) study team, NORC, and National Institute on Drug Abuse (NIDA). The lead study team is a varied group of investigators with depth and breadth of experience in substance use disorders or treatment, internal medicine, infectious diseases, dentistry, epidemiology, public policy, social sciences, study training and supervision, provider surveys, and quality assurance monitoring. The NORC, founded in 1941, is one of the nation's well-respected survey organizations. Their widespread staff members have extensive experience in achieving a high response rate in surveys, especially those of health care professionals, as well as in sampling design, recruitment of hard-to-reach participants, nonresponse bias analysis, and weight creation, which helped ensure that the best data were obtained for our national survey. Regular biweekly conference calls were conducted via videoconferencing between the study teams and the NIDA Scientific Officer throughout the study period to discuss survey activities, recruitment, and progress.

Results

The study protocol was approved by the CTN Protocol Review Board in April 2020 and the UM IRB in August 2020. The survey instrument was officially mailed to the study sample in October 2020. Although we originally anticipated a 1-year follow-up period for data collection, our timeline was ultimately extended to 2 years due to unexpected disruptions caused by the COVID-19 pandemic. As such, data collection officially ended in October 2022, with an overall Council of American Survey Research Organizations rate of 53.62% (1240/2312.7; physicians overall: 855/1681.9, 50.83% [primary care physicians: 506/1081.3, 46.79%; emergency medicine physicians: 349/599.8, 58.2%]; dentists: 385/627.1, 61.4%). Note that the ineligibility rate among those screened is applied to those not screened, causing denominators to include fractional numbers. These rates resulted in a sample of 506 primary care physicians, 349 emergency medicine physicians, and 385 dentists.

Data analysis for the primary outcome paper, along with multiple planned secondary analyses, is currently underway, with plans to disseminate study findings in subsequent manuscripts in peer-reviewed journals. Findings from the analyses will be disseminated to CTN investigators, community partners, and representatives of the National Institutes of Health/NIDA. The planning, preparation, and submission of publications will follow the policies of the CTN Publications Committee. In addition, we plan to share our findings with a broad scientific audience through presentations at local and national conferences.

Discussion

Summary

Health care providers who practice primary care, emergency medicine, and dentistry are increasingly being called upon to help meet the growing demand for substance use treatment that surpass the availability of services [16,30]. Given their regular contact with patients with substance use disorders, these providers are well positioned to deliver and expand substance use treatment within their clinical settings [34]. However, before we can bridge this gap, we must first systematically and comprehensively understand the role of stigma in US health

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care providers' treatment and clinical management of patients with substance use disorders.

Within this context, our survey findings assessed a wide range of attitudes, practices, and backgrounds of providers practicing throughout the nation. Our sampling methodology and high response rate have produced a particularly robust data set that will allow us to identify the factors, such as clinical setting and description of patient populations, related to provider stigma and the current state of substance use treatment delivery, as stated in our specific aims. In addition, our use of the MCRS will allow us to understand the magnitude and extent of provider stigma by the type of substance (opioids, stimulants, and alcohol). These 3 classes were specifically selected for not only being the most frequent types of substance use but also for being detrimental to individual and population health through overdoses, substance-related violence, and substance-related motor vehicle crashes [128-130]. Moreover, the availability of treatment modalities for these 3 classes differs; there are treatments for both OUD and alcohol use disorders [131], but recent research findings offer promise for stimulant use disorder treatment [132]. Assessing these 3 types of substance use will significantly contribute to the body of literature that assess provider stigma against substance use by substance class and how substance-specific stigma is associated with their respective screening and treatment clinical practices.

Furthermore, our study findings allow us to define provider stigma toward substance use in the context of other commonly stigmatized health conditions. The range of other conditions that we queried included different somatic, mental, and behavioral conditions (type II diabetes, depressive disorder, and HIV). Different chronic conditions can solicit different stigmas based on their visibility and perceived individual responsibility in causing the condition [133,134]; thus, it is important to select a range of chronic conditions that represent these differing manifestations and associations. In the case of HIV, provider stigma not only encompasses attributes such as prejudicial attitudes and discriminatory actions but also mortality-related judgment (due to values related to sexual practices and risk behaviors associated with HIV transmission) and fear of physical contagion from occupational exposure [135,136]. By contrast, provider stigma studies focusing on obesity and type II diabetes have shown provider stigma to be related to negative perceptions of patient behavioral factors (eg, laziness, lack of self-control, and dishonesty) [137,138]. In the context of mental health disorders, other constructs related to provider stigma include social distance (ie, self-reported willingness to engage and socialize with someone who has a mental health disorder) and perceived dangerousness (ie, the perception that people with mental health disorders are violent and should be feared) [25,139-141]. In the case of both HIV and mental health disorders, providers who elect to treat patients with these conditions have been shown to be particularly susceptible to "courtesy stigma" (ie, the subjective norms of other professionals), as colleagues and social relations question their willingness to treat patients perceived as socially or morally objectionable, which can impact providers' social and professional reputation and also contribute to provider stigma [135,142-146]. Allowing for comparisons to be made between these chronic conditions, alone and in comparison with the substance use classes, is especially critical for comprehensively capturing the lens through which health care providers view and relate to the very patients they are being called upon to treat.

The limitations of our study include the cross-sectional nature of our methodology, which limits our ability to make causal inferences or assess temporal relationships. In addition, as the survey queried provider attitudes toward conditions that are commonly stigmatized as well as potentially sensitive topics (eg, prior substance use history of family, friends, colleagues, and self), there is potential for information bias in our study findings in the form of social desirability. However, our use of a participant ID and our security of a waiver eliminating the need for a signed informed consent form was specifically implemented for confidentiality purposes, which may have mitigated any reluctance to respond to the survey truthfully.

Conclusions

Our survey was designed to identify barriers to addressing the overdose epidemic as faced by primary care physicians, emergency medicine physicians, and dentists who workforces called upon to change the way substance use treatments are delivered nationally and across patient populations. Our results can be used to inform future public health campaigns and provider-based interventions that provide new models of care, demonstrating the efficacy of initiating medication-assisted treatment in these settings [147,148]. By understanding providers' subjective norms, the ways in which they view and address substance use, and their attitudes toward patients with substance use disorders, we plan to inform the development and implementation of stigma-reduction interventions that address providers' perceptions and treatment of substance use. Although some effective interventions reduce stigma overall [149], the development of interventions specific to primary care and emergency medicine physicians and dentists requires a more granular understanding of substance-related stigma across the primary health care spectrum, particularly in settings that frequently encounter patients with substance use disorders.

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Data Availability

This study complies with the National Institute of Health Data Sharing Policy and Implementation Guidance [150]. Deidentified study data will be available to the public at the National Institute on Drug Abuse data repository, per the National Institute on Drug Abuse Clinical Trials Network policy. Details of data sharing can be found on the website [151].

Conflicts of Interest

This paper was prepared while PJ was employed at the National Institute on Drug Abuse.

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Abbreviations

ADA: American Dental Association
AMA: American Medical Association
CTN: Clinical Trials Network
Deff: different design effects
IRB: Institutional Review Board
MCRS: Medical Condition Regard Scale
MOUD: medications for opioid use disorder
NIDA: National Institute on Drug Abuse
NORC: National Opinion Research Center

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OB/GYN: obstetrics/gynecology
OUD: opioid use disorder
TDM: Total Design Method
UM: University of Miami

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Protocol

Enhancing Transsectoral Interdisciplinary Patient-Centered Care for Patients With Rare Cancers: Protocol for a Mixed Methods Process Evaluation

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Abstract

Background: Rare cancers account for approximately 24% of all new cancers. The category of rare tumor diseases includes almost 200 different entities. In particular, the treatment of patients with extensive care needs requires cooperation between service providers, both between sectors (outpatient and inpatient) and within sectors (eg, between different medical disciplines). The treatment pathway is associated with a high need for coordination and information sharing between providers. When crossing sectoral boundaries in the German health care system, interface problems between the outpatient and inpatient sectors can lead to gaps in care delivery. The multicomponent program *Trans-sectoral Personalised Care Concept for Patients with Rare Cancers* aims to optimize transsectoral cooperation and coordination of care to enhance patient involvement and the medical care coordination of patients with rare cancers.

Objective: This process evaluation will contribute to answering questions about intervention fidelity and the implementation of transsectoral communication, identifying and describing the intended and nonintended effects of the intervention, and exploring the barriers to and facilitators of the implementation.

Methods: We will include patients who participate in the intervention phase; all persons and staff involved in the development and implementation of the intervention (Onco Coach, psychologists, physicians on the contact platform, IT staff, and staff of the Bavarian Association of Statutory Health Insurance Physicians); physicians from the Ludwig-Maximilians-University Hospital Munich and the hospital of the Technical University Munich who are involved in the treatment of patients during the course of the project; and participating office–based hematologists and oncologists. Data collection will be conducted at the beginning, during, and at the end of the intervention using mixed methods. Data will be collected from questionnaires, document analyses, semistructured interviews, and structured observations and will cover different aspects of process evaluation. These include examining the context to explore existing patterns, changes in patterns, attitudes, and interactions; analyzing the implementation of intervention elements; and exploring the complex causal pathways and mediators of the intervention. Qualitative data will be analyzed using thematic analysis. The data will then be combined using between-methods triangulation.

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Results: This project received funding on March 1, 2022. The intervention phase and recruitment for the process evaluation began on March 1, 2023, and the recruitment is expected to end on September 30, 2025. At the time of protocol submission in June 2023, a total of 8 doctors from hematology and oncology practices were enrolled. Data collection began on March 14, 2023.

Conclusions: The *Trans-sectoral Personalised Care Concept for Patients with Rare Cancers* project is a complex intervention that is to be implemented in an equally complex health care context. The process evaluation will help understand the influence of contextual factors and assess the mechanisms of change.

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KEYWORDS

process evaluation; study protocol; logic model; complex intervention; coordination of care; rare cancer; mobile phone

Introduction

Background

Approximately 24% of all emerging cancers are rare cancers, making them cancers with an incidence of <6 in 100,000 people per year. The *rare tumor diseases* category includes almost 200 different entities. Compared with patients with common tumor diseases, patients with rare tumor diseases develop the disease at a younger age, and the overall survival is significantly poorer [1].

Patients in the German health care system can be treated as both inpatients and outpatients in office-based settings. In particular, patients with rare, chronic, or complex diseases often cross the sector boundaries because of their complex treatment plans and the various professions involved. In the German health care system, interface problems between the office-based and inpatient sectors may cause gaps in the delivery of care [2]. Therefore, it is important to improve the design of interfaces and, thus, the coordination and integration of inpatient and office-based health care. It is the physicians' task to ensure continuous medical treatment during the transition from the inpatient sector to the continuing care sector. In particular, the treatment of patients with extensive care needs requires cooperation between service providers, both in the intersectoral area (office-based and inpatient) and intrasectoral area (eg, between different medical disciplines). The treatment path is associated with a high level of coordination and information needs between colleagues providing cotreatment or further treatment [3] (eg, information about supportive treatment, potential side effects, or complications during hospitalization). Digitalization is essential for the development of transsectoral and cross-disciplinary supply structures. Digital technologies can help improve documentation, communication, and networking in medical care [4].

Patients with cancer have to face complex considerations when making decisions about their own treatment [5] in a challenging life situation. They show a strong preference for shared decision-making (47.1%). Slightly more than one-third (36.3%) of German patients with cancer want to decide alone, and 15.9% want the physician to decide [6]. Despite the benefits of shared decision-making (eg, greater satisfaction with the treatment decision and improvement in adherence to cancer treatment), its implementation in clinical practice has hardly improved over the years [5]. Therefore, it is important to address this issue.

Trans-Sectoral Personalised Care Concept for Patients With Rare Cancers

The Trans-sectoral Personalised Care Concept for Patients with Rare Cancers (TARGET) project includes targeted digital interventions to optimize transsectoral cooperation and coordination of care to improve patient involvement (including shared decision-making) and the medical care of patients with rare cancers. The intervention will be implemented in the model region of Southern Bavaria (Swabia, Upper Bavaria, and Lower Bavaria), Germany, with a maximum of 45 hematologic and oncologic participating practices and the Comprehensive Cancer Center (CCC) Munich. For the evaluation and implementation of TARGET, the Bavarian Association of Statutory Health Insurance Physicians (KVB) and the Professional Association of Resident Haematologists and Oncologists in Bavaria will invite all office-based oncology and hematology specialists to take part. Only patients who are legally insured by AOK Bavaria, the largest statutory health insurance provider in Bavaria, will be recruited.

Deviating from the registration of the main trial [7], the summative evaluation of TARGET will adopt a prospective parallel group design with patients clustered in practices, comparing the control group (practices in Northern Bavaria) with the intervention group (practices in Southern Bavaria). The protocol of the summative evaluation will be published separately. The primary end point is the coordination of care from the patient's perspective, which will be measured using the validated German version of the Care Coordination Instrument [8]. The secondary end points include progression-free survival, overall survival, course of therapy, time up to diagnosis, and patient-reported outcomes (health-related quality of life, condition, symptoms, and health literacy). An economic evaluation using retrospective data provided by AOK Bavaria will also be conducted. This protocol describes the process evaluation that will occur alongside the main trial.

Objective

TARGET consists of a variety of components that aim at different target groups, are offered by different groups of professionals, and concern different aspects of patient care.

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Therefore, a comprehensive process evaluation following the Medical Research Council guidance for process evaluation of complex interventions [9] is planned (1) to analyze contextual factors and their interactions with the intervention components; (2) to describe the intervention, its causal assumptions, and the implementation process; and (3) to assess the mechanisms of change such as participant responses and mediators. The aims are to assess intervention fidelity and the implementation of transsectoral communication, identify and describe the intended and nonintended effects of the intervention, and explore the barriers to and facilitators of implementation [9].

Methods

The reporting of this protocol follows the criteria of the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) [10] (Multimedia Appendix 1) and the UK *MRC framework for the development and evaluation of complex interventions* [11]. Mixed methods will be applied to assess processes and mechanisms at different levels.

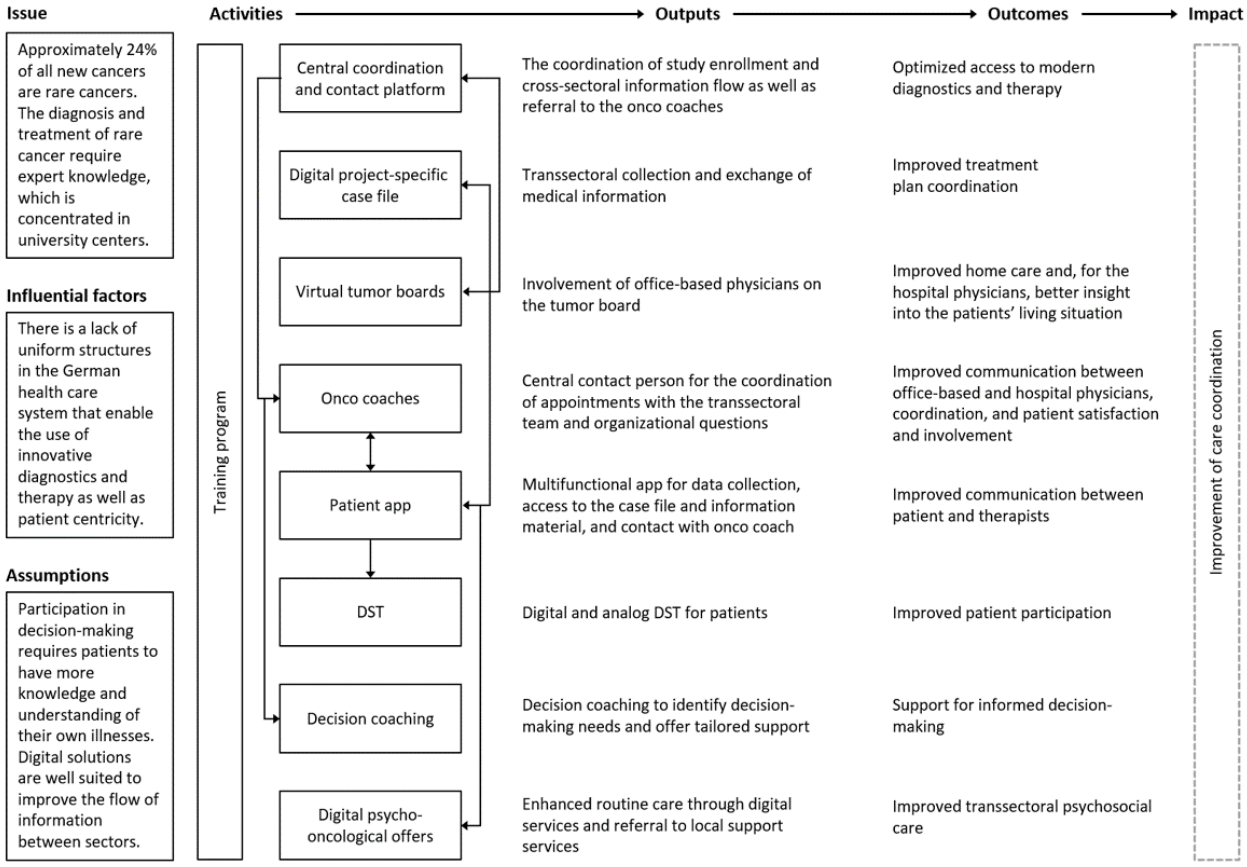
Ethical Considerations

Ethics approval was obtained from the ethics committee of the Martin Luther University Halle-Wittenberg (MLU; 2023-032). The ethics committee will be informed of any changes in the procedure. All the participants will provide written informed consent. They will be informed of their possibility to terminate their participation at any time. The personal data collected are subject to the obligation of confidentiality and provisions of the General Data Protection Regulation. Participating practices will be reimbursed via the selective contract with AOK Bavaria for the time and effort required to participate in the training sessions, interviews, and virtual tumor boards as well as for patient inclusion and data documentation. The total compensation amount is based on the services actually provided. Patients will not receive any compensation.

Logic Model

A logic model was developed for TARGET, along with those responsible for developing the intervention components. This will guide data collection and analysis and is intended to help clarify causal assumptions. The logic model describes the intervention, its components, and its implementation. It also identifies the target group of an intervention component and how it interacts with other components and describes the current context (Figure 1).

Figure 1. Logic model of the Trans-sectoral Personalised Care Concept for Patients with Rare Cancers (TARGET) intervention. DST: digital support tool.



TARGET Intervention and Implementation

TARGET is a complex intervention comprising different components designed to promote cross-sectoral exchange and patient-centered care. The components of the intervention are as follows.

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Central Coordination and Contact Platform

The participating hematologic and oncologic practices have the opportunity to quickly contact the team at the CCC Munich through phone or email via the central coordination and contact platform. The contact details can be found on the CCC Munich website. The platform will be staffed by a physician throughout the duration of the TARGET project to coordinate the enrollment of patients into the study and guarantee an optimal exchange of information between the different sectors to optimize joint patient care. The data of the patients enrolled in the study will be sent to Onco Coach for appointment scheduling to enable rapid referral to the respective expert team at the CCC Munich. The overall goal of the central coordination and contact platform is to bring the patient to the right expert as quickly as possible (eg, to optimize access to modern [molecular] diagnostics and therapy). It also serves as an interface for office-based hematologists and oncologists.

Onco Coach

All enrolled patients are assigned an Onco Coach as a central contact person for health care coordination issues. The Onco Coach play an important role in coordinating appointments with patients within the transsectoral team and mediate participation in training and supportive measures. In addition, the Onco Coach has limited access to the patient app and will reach out to all the patients via the chat function to establish contact with the treatment team. Patients can chat with the Onco Coach regarding organizational questions and problems. As a result, there is a continuous exchange between the Onco Coach and the treatment team.

Decision Coaching

Patients experiencing a decisional conflict will be offered decision coaching delivered by a trained Onco Coach or a physician in the hospital. According to the Ottawa Decision Support Framework [12], the decision coach will identify decisional needs, such as inadequate knowledge, unrealistic expectations, or unclear values, and offer tailored support to address these needs (eg, providing information, verifying understanding, or clarifying personal values).

Digital Project-Specific Case File

The digital project-specific case file is used for the transsectoral collection and exchange of medical information by establishing a link between the participating hematologic and oncologic practices and the CCC Munich and thus connects all relevant actors. The aim is to enhance coordination regarding the treatment plan. Interoperability is an essential aspect of the case file. The IT project was registered in vesta, the interoperability directory of the German health care system [13]. Availability is ensured using a platform-independent web application. The case file is a CentraXX-associated module from Kairos GmbH, which was expanded to include an oncological module for TARGET. CentraXX is a research portal focusing on the structured recording of content using biobanking and study management modules. An electronic patient record is the central storage unit in CentraXX [14]. It is technically operated by the Ludwig-Maximilians-University (LMU) Hospital Munich and professionally supervised by the CCC Munich. Plausibility checks ensure improved data quality. The web application will be set up in the hematologic and oncologic practices by the IT department of the CCC Munich. In addition, the practices will receive an on-site briefing and a manual on how to use the case file.

Patient App

The patient app is a smartphone app that is used for data collection as well as part of the intervention. It is compatible with and based on the project-specific case file with the following three basic functionalities: (1) documentation and use of various integrated forms, (2) customizable view of the coordinated case file, and (3) provision of information and training materials (eg, information on nutrition and exercise for cancer and fatigue, a decision support tool [DST], and other sources of information and support).

The assessment questionnaires can be accessed and completed via the app interface. Patients can also access a summary of the quality of life, functional, and symptom questionnaires, which can be used as personal documentation and for medical consultations. These documents are also made available to the transsectoral treatment team through the project-specific case file. The results of the questionnaires assessing care coordination and health literacy are not visible to the treatment team. This will be communicated to the patients in the study documents and within the questionnaires to avoid social desirability bias. In addition to data collection, the National Comprehensive Cancer Network (NCCN) distress thermometer [15] serves as a screening tool for the provision of psycho-oncology services (see the *Digital Psycho-Oncological Offers* section).

The patient app also allows the Onco Coach to contact the patient. All data are transmitted to the CentraXX department of the LMU Hospital. This integration makes it possible to combine all the recorded parameters and scientifically evaluate the collected data. The app is available for iOS (Apple Inc) and Android (Google LLC) and can be downloaded by patients via a QR code. Patients will receive instructions from their attending physician when they are enrolled in the study.

DST for Informed Decision-Making

To prepare for medical consultations, patients will have access to a generic DST [16] that aims at supporting informed decision-making. It is based on the Ottawa Personal Decision Guide and has been complemented with decision-related questions from question prompt lists for patients in oncology [17]. The DST will enable patients to ask for important information about their options regarding treatment or diagnostic procedures and to weigh their preferences for these options. It also includes guidance on how to deal with decisional needs, such as missing information, decisional uncertainty, and a lack of support. The tool will be available as a PDF version and in a web-based format via LimeSurvey (LimeSurvey GmbH). The links to the PDF version and LimeSurvey will be made available via the patient app and a flyer.

Virtual Tumor Boards

TARGET involves the establishment of internet-based transsectoral tumor boards, which enable joint decision-making and transsectoral information flow. Internet-based tumor boards

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have already been established at the CCC Munich and will be made available to office-based hematologists and oncologists as a component of TARGET. Within the tumor boards, office-based hematologists and oncologists and the physicians of the CCC Munich discuss and jointly determine therapeutic paths. Especially in the field of precision oncology, the participating office–based hematologists and oncologists will benefit from the expertise at the CCC Munich, as a molecular tumor board has already been established there. The transsectoral tumor board allows for the sharing of this knowledge across sectors. Thus, close-to-home care can be improved, and the CCC Munich physicians can gain deeper insights into the patient's living situation. Furthermore, central tumor boards provide optimized access to clinical studies.

Digital Psycho-Oncological Offers

Psycho-oncology is standard care in certified centers such as the CCC Munich but not nationwide in outpatient settings. The aim of this intervention component is to improve cross-sectoral psychosocial care delivery and thus overcome urban-rural and outpatient-inpatient differences by ensuring the availability of timely psycho-oncological support.

For patients participating in this study, intensive multiprofessional collaboration, the rapid availability of services, and specific expertise and background knowledge in the psycho-oncological counseling context are required. To initiate psycho-oncological counseling, the NCCN distress thermometer [15] will be provided at the initial visit and every 4 weeks via the patient app. If the score is ≥5 or if the patient requests psycho-oncological support, the patient will be contacted by a psycho-oncologist within the first 24 to 48 hours after distress screening. The patient will also receive contact details. The consultation can take place via telephone, in person at the CCC Munich, or digitally via RED Connect (RED Digital Cinema, LLC) [18] and will last approximately 50 minutes. All existing psycho-oncological support opportunities will be offered to the patients (one-on-one counseling, couple or family consultations, open consultation hours, and group offers for patients and their relatives or caregivers). In addition, patients will receive information about different support offers as well as patient events, and patient chats via the patient app.

Provision of information about and potential referral to local support services will be facilitated through an intensive exchange with the existing networks called Network Psychosocial Oncology Munich, the KVB, the Bavarian Chamber of Psychotherapists, and the Bavarian Cancer Society.

Training Program

For the successful implementation of the new care concept, a modular training concept was developed, which will be implemented via the KVB's e-learning platform, CuraCampus. The training concept includes (1) training on the overall project, (2) training in shared decision-making, and (3) web-based learning after 1 year of the project.

First, the training on the overall project is mandatory for physicians from hematologic and oncologic practices. The asynchronous web-based course will last a maximum of 45 minutes.

Second, the 45-minute asynchronous web-based training on shared decision-making aims to introduce the concept of informed shared decision-making and the use of the DST in consultations. For physicians from hematologic and oncologic practices, this course is also offered on CuraCampus and advertised in mandatory training. Physicians at the hospital will also have the opportunity to take part in the course via a cloud-based platform of the University of Bremen. The offer is advertised via flyers. Teaching methods include a screencast lecture and a best practice video of a simulated physician-patient consultation in which a decision is made about palliative treatment options for pancreatic cancer. In addition, barriers and facilitators for implementing the concept of informed shared decision-making will be discussed. A voluntary multiple-choice knowledge test at the end of the course allows participants to earn continuing medical education credits. Physicians are also invited to participate in a voluntary 2-hour web-based communication training to achieve shared decision-making skills through simulated patient discussions.

Third, after 1 year of the project, another training will be offered as a refresher and update to discuss previous barriers and process adjustments and changes.

In addition, office-based hematologists and oncologists will be trained on how to use the digital case file by the IT team.

The Onco Coach will have the opportunity to participate in a 1-day decision coaching training in a blended learning format. A preexisting training program for decision coaches in oncology [19] was adapted to the special needs of the target group and to decision-making in the field of rare cancer diseases. It focuses on skills in decision coaching, shared decision-making, evidence-based health information, and (risk) communication. Decision coaching skills are trained through simulated conversations based on case vignettes.

Participants and Recruitment

We will include the following people in this evaluation.

1. We will include patients who participate in the intervention phase. Using theoretical sampling, we will take into account factors such as gender, age, diagnosis, time up to diagnosis, and course of therapy. These patient characteristics and clinical data will be extracted from medical records. The willingness to participate in an interview is requested via the central coordination and contact platform. Over the entire intervention period, a total of approximately 40 interviews are planned. Theoretical data saturation will be the decisive criterion for the number of interviews.
2. We will include all persons and staff involved in the development and implementation of the intervention (Onco Coach, psychologists, physicians on the contact platform, IT staff, and KVB staff)
3. We will include physicians from the LMU Hospital and the hospital of the Technical University Munich (TUM) who are involved in the treatment of patients during the course of the project. Owing to the number of departments in the clinics, we will use a theoretical sample based on the extent of patient contact or contact with the intervention components. At the physician level, a snowball sampling

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will be used. Recruitment will be done by approaching supervisors via either email or telephone. We estimate the number of interviews over the course of the project to be 10 to 15, taking theoretical data saturation into consideration.

4. We will include participating physicians from the hematologic and oncologic practices. In the preliminary phase, the first interview is conducted with physicians from all the partaking practices. The second interview will take place at different times during the intervention phase. The sampling will be based on the characteristics of the practices and physicians (eg, the size of the practices or experience of the physicians), recruitment rate, and contact with the intervention components (eg, participation in the virtual tumor board). The aim is to map as many different contextual conditions and factors of the intervention as possible. Recruitment will be done via telephone or email.

Data Collection

Overview

Data will be collected using a mixed methods approach at the beginning, during, and at the end of the intervention. Data will be collected through questionnaires, document analyses, semistructured interviews, and structured observations and will cover different aspects of process evaluation.

The personal data collected are subject to the obligation of confidentiality and the provisions of data protection law. The data will be used exclusively for the purpose specified in the consent form. Initially, the data will be pseudonymized, and then they will be anonymized during the later course of the study. After completion of the study, the transcribed audio files will be deleted.

If available, the pseudonyms assigned in the main trial will be used. Patients will be referred for the process evaluation through the established central coordination and contact platform. The key list remains at the LMU. By agreeing to participate in an interview as part of the process evaluation, the patients explicitly consent to being contacted by the staff of the MLU.

All data collected are processed on access-protected computers and then stored safely and securely for 10 years at the Institute of Health and Nursing Science at the MLU. The pseudonymized data will not be passed on to third parties. The publication of the data takes place exclusively in an anonymized form.

All participants will receive information about the study, and informed consent will be obtained (Multimedia Appendix 2). Informed consent will be obtained by a member of the MLU evaluation team, except for patients whose consent will be obtained through the central coordination and contact platform. Interested persons will receive written information about the study project, with the opportunity to ask questions via a conversation. They will then be provided with a consent form to sign. Before data collection begins, there will be another opportunity to ask questions and confirm consent.

After the inclusion of the physicians from the hematologic and oncologic practices, the baseline characteristics are recorded using the web-based survey application LimeSurvey. The link to the survey and an individual access code will be sent to the practices via email. If necessary, an email reminder will also be sent.

Several interviews will be conducted in person, through video conference via Cisco Webex [20], or through telephone. Interview guides were developed for each target group and topic of interest, which will be piloted in the first 3 to 5 interviews and adapted, if necessary. The audio-recorded interviews will be transcribed. There is no plan to send the interview transcripts to the participants. Structured observations will be conducted using a protocol with guiding themes. The protocols will also be piloted during the first structured observations. The objectives of the data collection are described in subsequent sections and summarized in Tables 1 to 3.

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Table 1. Data collection on the context of the intervention.

Intervention components and participants	Method	Assessments
Central platform for coordination and contact		
Physicians from the coordination platform and office-based hematologists and oncologists	Semistructured interviews	Experiences and facilitating and hindering factors regarding the contact platform
Onco Coach		
Onco Coach	Semistructured interviews	Baseline data (eg, vocational education and training and professional experience) and understanding of one's role and expectations
Patients, hospital physicians, office-based hematologists and oncologists, and project participants of other intervention components	Semistructured interviews	Experiences and facilitating and hindering factors regarding cooperation
Digital project-specific case file		
Users (hospital physicians, office-based hematologists and oncologists, and project participants of other intervention components)	Semistructured interviews	Experiences and facilitating and hindering factors regarding the use of the case file
Office-based hematologists and oncologists	Questionnaire	Baseline data on the practice and person (location, area covered, connections to clinics or centers, composition and characteristics of the practice team, and IT equipment)
Patient app		
Patients and users of other intervention components (Onco Coach and psycho-oncologists)	Semistructured interviews	Experiences and facilitating and hindering factors regarding the use of the app
Virtual tumor board		
Hospital physicians and office-based hematologists and oncologists	Semistructured interviews and structured observation	Existing structures, experiences, and facilitating and hindering factors with regard to participation in and cooperation on the tumor board
Decision support tool		
Patients, office-based hematologists and oncologists, and hospital physicians	Semistructured interviews	Experiences and facilitating and hindering factors regarding the application
Decision coaching		
Patients and Onco Coach	Semistructured interviews	Experiences and facilitating and hindering factors regarding the decision coaching
Digital psycho-oncological offers		
Patients and psycho-oncologists	Semistructured interviews	Existing structures, experiences, and facilitating and hindering factors regarding the services offered
Training program		
Hospital physicians, office-based hematologists and oncologists, and Onco Coach	Semistructured interviews	Experiences and facilitating and hindering factors regarding the training program

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Table 2. Data collection on the implementation process.

Intervention components and participants	Method	Assessments
Central platform for coordination and contact		
Documentation of the central platform for coordination and contact	Document analysis	Number of contacts (medium and topic) and recruitment rate
Hospital physicians, Onco Coach, office-based hematologists and oncologists, and physicians from the contact platform	Semistructured interviews	Experiences regarding accessibility, cooperation, and consequences of the contact and changes during the process
Onco Coach		
Onco coach documentation	Document analysis	Number of contacts with patients, hospital physicians, and office-based hematologists and oncologists and medium and topic of the contact
Patients, Onco Coach, and hospital physicians	Semistructured interviews	Experiences regarding accessibility, cooperation, and consequences of the contact and changes during the process
Digital project-specific case file		
Users	Semistructured interviews	Application of the digital case file and exchange among participants with the help of the case file
IT department	Document analysis and semistructured interviews	Support requests and solutions and changes during the process
Patient app		
Patients and users of other intervention components (Onco Coach and psycho-oncologists)	Semistructured interviews	Use of the app and changes during the process
IT department	Document analysis and semistructured interviews	Support requests and solutions and changes during the process
Virtual tumor board		
Hospital physicians and office-based hematologists and oncologists	Semistructured interviews and structured observation	Tumor board procedure and cooperation between hospital physicians and office-based physicians and participation of office-based hematologists and oncologists
Decision support tool		
Patients, office-based hematologists and oncologists, and hospital physicians	Semistructured interviews	Use of the decision support tool
Decision support tool	Document analysis	Number of times the decision support tool was used and frequency of the topics for which the tool was used
Decision coaching		
Patients and Onco Coach	Semistructured interviews	Services offered and procedure of the decision coaching
Decision coaching documentation	Document analysis	Number of times decision coaching was carried out
Digital psycho-oncological offers		
Patients and psycho-oncologists	Semistructured interviews	Experiences and facilitating and hindering factors regarding the services offered
Documentation of the digital psycho-oncological offers	Document analysis	Cooperation with external psycho-oncologists
Training program		
Hospital physicians, office-based hematologists and oncologists, and Onco Coach	Semistructured interviews	Satisfaction and practical applicability of the contents
Training program documentation	Document analysis	Number of users and evaluation of test results

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Table 3. Data collection on the mechanisms of impact.

Intervention components and participants	Method	Assessments
Central platform for coordination and contact		
Physicians from the coordination platform and office-based hematologists and oncologists	Semistructured interviews	Experiences and attitudes regarding the contact platform in terms of care coordination
Onco Coach		
Patients, hospital physicians, office-based hematologists and oncologists, and project participants of other intervention components	Semistructured interviews	Experiences and attitudes regarding the services supplied by the Onco Coach in terms of care coordination
Digital project-specific case file		
Users (hospital physicians, office-based hematologists and oncologists, and project participants of other intervention components)	Semistructured interviews	Experiences and attitudes regarding the case file in terms of care
Patient app		
Patients and users of other intervention components (Onco Coach and psycho-oncologists)	Semistructured interviews	Experiences and attitudes regarding the app in terms of care
Virtual tumor board		
Hospital physicians and office-based hematologists and oncologists	Semistructured interviews	Experiences and attitudes regarding the tumor board in terms of care
Decision support tool		
Patients, office-based hematologists and oncologists, and hospital physicians	Semistructured interviews	Experiences and attitudes regarding the decision guide in terms of care
Decision coaching		
Patients and Onco Coach	Semistructured interviews	Experiences and attitudes regarding the decision coaching in terms of care
Digital psycho-oncological offers		
Patients and psycho-oncologists	Semistructured interviews	Experiences and attitudes regarding the services offered in terms of care
Training program		
Hospital physicians, office-based hematologists and oncologists, and Onco Coach	Semistructured interviews	Experiences and attitudes regarding the contents in terms of care

Context of the Intervention

To better understand the mechanisms of change and identify barriers and facilitating factors for implementation, contextual factors will be examined. For this purpose, we will conduct semistructured interviews with responsible persons of the CCC Munich at different points during the intervention phase to explore existing structures, changes in structures, attitudes, and mutual influences. In addition, we will conduct semistructured interviews with the responsible persons, staff, and stakeholders of the intervention components and collect descriptive data on the existing resources. To better understand and describe the context in which hematologic and oncologic practices are embedded, we will also conduct semistructured interviews during the intervention phase. Baseline characteristics such as the location of the practice, practice structures, connections or cooperation with a clinic or center, and IT equipment will be assessed.

Implementation Process

We will document the implementation process of the intervention, success and failure of recruitment, and participation rates. To answer the question of how the intervention components were implemented, we will conduct semistructured interviews with all persons involved in the intervention (patients, physicians in hematologic and oncologic practices, and staff of the CCC Munich). Furthermore, we will address the question of whether individual intervention components were implemented as intended. This includes the fidelity of the intervention, the degree of implementation, conscious and unconscious adjustments, and the extent to which the respective components reached the target group. For this purpose, we will conduct quantitative and qualitative document analyses on different issues (eg, the number of participants in the training courses, the frequency of psycho-oncological consultations, the completeness of documentation, the use of the DST, and IT support). We will also use structured observations for individual intervention components (eg, the tumor board).

Mechanisms of Impact

To understand the impact of the intervention components on care coordination, we will conduct semistructured interviews with patients in the intervention group, physicians in hematology and oncology practices, persons and staff responsible for the

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intervention components, and physicians in the LMU and TUM. The aim is to understand the complex causal pathways and mediators of the intervention. The theoretical concept of care coordination will be the basis for the exploration. In particular, the focus is on the domains of communication and information (including all processes, communication, and information within the attending practice) and needs-based navigation (need-assessment and needs-based navigation outside the caregiver's institution, including all stakeholders in the health care process). Furthermore, spontaneously reported unintended effects of both the intervention components and the process evaluation itself will be collected. Significant influences will be discussed with the project team.

Data Analysis

Analyses of the baseline characteristics will be descriptive. The quantitative data will be evaluated through descriptive analysis. Qualitative data will be collected and analyzed in an iterative process until data saturation is reached through thematic analysis, according to Braun and Clarke [21]. Data analysis will be carried out by 2 people independently. In case of disagreement, consensus will be reached through discussion with a third person. Finally, the data will be combined using between-methods triangulation [22], the individual components of the process evaluation will be brought together, and configurations that have led to a high degree of cross-sectoral coordinated care will be identified at the practice level. The results of the triangulation will be analyzed in reflection talks after the completion of the study. The reflection talks serve to ensure sustainability, exchange experiences, and jointly evaluate the results. The processes of data collection and analysis are iterative until data saturation is assumed. The results of the interviews will be sent to all the participants via email.

Results

The project received funding on March 1, 2022. The intervention phase and recruitment for the process evaluation began on March 1, 2023, and the recruitment is expected to end on September 30, 2025. At the time of protocol submission in June 2023, a total of 8 doctors from hematology and oncology practices were enrolled. Data collection began on March 14, 2023.

Discussion

Overview

The TARGET project is a complex intervention that is to be implemented in an equally complex health care context. Whether the implementation is successful and the intervention achieves its desired effect depends on various factors and their interactions, for example, the contextual factors in the outpatient and clinical settings, the behavior and attitudes of the different stakeholders involved, and the intervention components in relation to routine care. A comprehensive analysis of processes and an assessment of diverse perspectives have been planned alongside a logic model. The logic model will guide data collection and analyses and is intended to help clarify causal assumptions. The findings of the primary outcome *coordination of care* from the patient's perspective, measured using the validated German version of the Care Coordination Instrument [8], will be accompanied by in-depth interviews with patients and perspectives of physicians. The results will finally be reported according to the Template for Intervention Description and Replication (TIDieR) checklist [23].

The summative evaluation study will follow a parallel group design, and eligible patients will be a heterogeneous group in terms of diagnosis, stage of disease, and course of treatment. Therefore, a comprehensive process evaluation is all the more important to understand the influence of contextual factors, assess the mechanisms of change, identify intended and nonintended effects, and explore the barriers to and facilitators of implementation.

As the evaluators who conduct the process evaluation are an external team from the MLU, it is important to establish a good working relationship with all the stakeholders involved in the intervention development and implementation to ensure a close observation of the intervention. Maintaining sufficient independence while observing the work of the different stakeholders is crucial. Another challenging question is whether the emerging findings should be communicated to the stakeholders. The evaluators can either act as passive observers reporting the results at the end of the project or help correct implementation problems while they occur [9]. We will not engage in continuous quality improvement activities because this might compromise the external validity of the evaluation [9], although serious observations will be discussed with the project team.

Limitations

This process evaluation also has limitations. Even after intensive exchange with the developers of the intervention, some ambiguity over the content of the intervention, its components, and how it is intended to work remains. Owing to the high complexity, it is hardly possible to record all processes and data, so some uncertainties will remain. For example, no observation or analysis of consultations is planned. Furthermore, it will be difficult to find out the reasons for nonparticipation, both for physicians and patients, because there will be no direct access to the group. However, it is better to answer the most important core questions well than to try to answer too many questions [9]. Therefore, we started to list causal assumptions within a logic model. Moreover, additional questions may arise during the course of the process evaluation [9]. Overall, it should be considered that access to the participants and data depends on the readiness and feasibility for it in an overburdened health care system.

Conclusions

The results and detailed descriptions of the process evaluation will help interpret the results of the TARGET intervention and put them into the correct context. In addition, the results may inform future projects that adapt TARGET or its individual components to different fields of cancer care or beyond. The results may also raise needs regarding the enhancement of the skills of the involved professions.

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Data Availability

The data sets generated and analyzed during this study are available upon request from AS.

Authors' Contributions

JH and SZ wrote the first draft of the paper with significant input from JL. JL, BB-H, KB-T, VK, and AS reviewed and edited the manuscript. All the authors read and approved the final version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist.
[PDF File (Adobe PDF File), 599 KB - resprot_v12i1e49731_app1.pdf]

Multimedia Appendix 2
Model informed consent form.
[PDF File (Adobe PDF File), 157 KB - resprot_v12i1e49731_app2.pdf]

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Abbreviations

CCC: Comprehensive Cancer Center
DST: decision support tool
KVB: Bavarian Association of Statutory Health Insurance Physicians
LMU: Ludwig-Maximilians-University
MLU: Martin Luther University Halle-Wittenberg
NCCN: National Comprehensive Cancer Network
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
TARGET: Trans-sectoral Personalised Care Concept for Patients with Rare Cancers
TIDieR: Template for Intervention Description and Replication
TUM: Technical University Munich

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Protocol

Prehabilitation in an Integrative Medicine Day Clinic for Patients Undergoing Neoadjuvant Treatment: Single-Center Feasibility Pilot Study

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Abstract

Background: Patients with cancer receiving neoadjuvant treatment prior to surgery are in a very stressful situation. Chemotherapy and radiation therapy put a strain on the quality of life and the pending surgery poses a relevant burden for many patients. Preparation of these patients for the intervention in terms of prehabilitation has great potential to reduce the burden of postoperative complications and may improve the clinical outcome. A prehabilitation approach also yields the possibility to address unmet patients' needs and to help them modify their lifestyle in a maintainable way. Therefore, a multimodal approach is mandatory during this critical period.

Objective: The aim of this study is to assess the feasibility of prehabilitation in an integrative medicine day clinic (PRIME-DC) prior to cancer surgery at a major university clinic. PRIME-DC is considered feasible if 80% of enrolled patients are willing and able to complete at least 6 out of the 8 weekly meetings, each lasting 6.5 hours, at such a clinic. Secondary end points aim to evaluate this multimodal program.

Methods: The PRIME-DC intervention combines mind-body medicine, exercise therapy, nutrition therapy, naturopathic counseling, and the application of a yarrow liver compress. Adult patients with cancer, with a primary tumor in the abdomen (including intraperitoneal cancer, stomach cancer, and extraperitoneal cancers such as pancreatic, bladder, rectal, esophageal, endometrial, ovarian, and cervical cancer) or the breast requiring a neoadjuvant oncological treatment setting are eligible to participate. The addressed cancer entities imply either an extensive surgical intervention with an expected need for prehabilitation (eg, abdominal surgery) or a neoadjuvant treatment of several months with a high burden of treatment-associated side effects (breast cancer). Adherence to the day clinic program is the primary end point being defined as presence during the day clinic session. Secondary end points are physical assessment and quality of life, together with a structured assessment of neoadjuvant treatment-associated side effects. Furthermore, to collect qualitative data voluntary participants of the day clinic will be interviewed in a semistructured way after completion of the day clinic program on each component of the study (mind-body intervention, exercise, nutrition, naturopathic counseling, and a yarrow liver compress).

Results: The procedures used in this study adhere to the tenets of the Declaration of Helsinki. As of February 2023, we enrolled 23 patients; the dominant cancer entity is breast cancer (18 enrolled patients).

Conclusions: The presented protocol combines prehabilitation, lifestyle modification, naturopathic counseling, dietary assistance, and naturopathic treatment in an innovative and integrative way.

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Trial Registration: Deutsches Register Klinischer Studien German Clinical Trials Register DRKS00028126; https://drks.de/search/de/trial/DRKS00028126

International Registered Report Identifier (IRRID): DERR1-10.2196/46765

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KEYWORDS

supportive care; prehabilitation; neoadjuvant treatment; integrative medicine; multimodal prehabilitation; cancer; oncology; surgery; preoperative; feasibility; integrative; naturopathy; naturopathic; diet; nutrition

Introduction

Surgical interventions are burdensome for patients with cancer. Especially the period between diagnosis and surgery is a major challenge for the patient in many ways. Besides the psychological strain of the upcoming intervention, the physiological burden of an extensive surgery, for example, an abdominal operation can be compared with running a marathon [1]. The more extensive the surgery, the higher the rate of relevant postoperative complications, particularly in patients who are frail and those with an extensive medical history.

Conventional treatment plans include rehabilitation after medical or surgical treatment. Innovative concepts developed in the mid-1990s use the preoperative phase for various measures to improve patients' postoperative results with fewer and less severe complications. Analysis of these concepts of "prehabilitation" indicated efficacy [2,3]. The initial results were positive even in rather short (2-4 weeks) interventions comprising several sessions.

However, there is growing evidence that these early prehabilitation concepts lacked fundamental aspects of preparation [4]. First, they did not address anxiety, patients' empowerment, or strengthening of self-efficacy, which is well known to have a beneficial effect on cancer care [5]. Moreover, the idea arose that preparation for extended surgery represents a "teachable moment," a point in the life of a patient where long-lasting lifestyle modification is possible [6].

To date, no such program has been installed at the University Hospital Ulm. Nonetheless, the period of neoadjuvant chemotherapy, extending over a number of months provides time for a concise, integrative prehabilitation program addressing more than just the physical aspect of prehabilitation.

A promising integrative therapy for lifestyle modification, stress relief, and reduction of anxiety is mind-body medicine (MBM). The National Cancer Institute defines mind-body practice as "a health practice that combines mental focus, controlled breathing, and body movements to help relax the body and mind. It may be useful to control pain, stress, anxiety, and depression, and for overall health" [7]. The combination of mind-body practice, which includes a variety of mindfulness-based interventions, with aspects of cognitive behavioral therapy to enhance stress-coping mechanisms, is called MBM. This integrative treatment modality was established and adapted for a day clinic setting by Paul et al [8] and Dobos and Paul [9]. The concept of MBM within a day-hospital setting is traditionally applied to groups of 8-12 patients and is believed to be most effective in this group size with respect to lifestyle modification and stress management.

MBM shows positive effects in the treatment of fatigue [10] in patients with cancer while reducing anxiety about cancer recurrence [11]. Assuming the existence of a rationale for applying MBM in advance of surgery, it is noteworthy that postoperative pain and use of opioids are reduced even with a short MBM intervention, as shown by Pester et al [12] and Hanley et al [13]. The group setting is a hallmark of MBM therapy and enables the patients to learn from one another.

Another approach to enhance patients' self-efficacy and address an unmet need in the treatment of patients with cancer may be the integration of naturopathic therapy in an evidence-based manner. There is evidence that naturopathic counseling enhances quality of Life (QoL) of patients with cancer [14]. Many patients use naturopathic methods as an additional complementary therapy, commonly without informing their oncologists [15] and without being aware of the risks of interactions between naturopathic medication and their chemotherapy. In order to save patients from falling for false claims or risking adverse effects, the Association of the Scientific Medical Societies in Germany has issued a medical guideline for the complementary treatment of patients with cancer [16]. The evidence-based foundation of this guideline enables empowering counseling of patients with cancer about how to deal with cancer- or treatment-related side effects. Work on the establishment of a structured counseling program based on this guideline is in progress [17].

The yarrow liver compress is included in the day clinic setting as it has been shown to be effective against treatment-associated fatigue [18] and to increase sympathetic modulation assessed by heart-rate variability [19]. The main topic of this session is to give the patients an experience of a specific naturopathic treatment that is recommendable for fatigue and yields a very low risk of adverse effects.

The combination of harmonizing supportive therapies might meet the needs of highly vulnerable patients during neoadjuvant treatment facing surgery. None of the named interventions has been used to support prehabilitation at University Hospital Ulm so far.

Preoperative multimodal interventions such as exercise, nutrition, and mindfulness-based treatments are thought to improve patients' physical, nutritional, and mental status. Furthermore, cancer prehabilitation may improve patients' participation in rehabilitation after cancer treatment and maintain their ability to engage in salutogenic activities. Such an

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integrative approach should include exercise for physical prehabilitation, mindfulness-based interventions to improve patients' ability to cope with stress and anxiety prior to surgery, cognitive behavioral aspects to change high-risk lifestyles for the better, and last but not least, empowerment of patients to apply naturopathic therapies independently in an evidence-based manner. This combination of measures represents a promising portfolio and may show strong synergistic effects.

Methods

Overview

This study is a single-center, single-arm interventional study evaluating the feasibility of an 8-week prehabilitation program before, during, or after neoadjuvant treatment before surgery at University Hospital Ulm.

Recruitment

During the recruitment period, all patients who are being treated for abdominal or breast cancer at the University Hospital Ulm on the Comprehensive Cancer Center Ulm and for whom neoadjuvant treatment is planned or performed with curative intent are screened for eligibility. Ineligible patients are listed, and in the case of refusal to participate, the reason, if communicated, is documented. Up to 15 patients who have given informed consent are enrolled in each cycle of the study (see sample size calculation). The addressed cancer entities imply either an extensive surgical intervention with an expected need for prehabilitation (eg, abdominal surgery) or a neoadjuvant treatment of several months with a high burden of treatment-associated side effects (breast cancer).

Patients may participate in the pilot study if they meet all of the following criteria: (1) diagnosis with intracavity cancer (including stomach cancer and extraperitoneal tumors such as prostate, bladder, rectal, esophageal, endometrial, and cervical cancer) or breast cancer; (2) planned or ongoing neoadjuvant treatment prior to planned curative resection; (3) aged 18 years or older; and (4) ability to understand the nature and individual consequences of the clinical trial. Patients are excluded from participation if their American Society of Anesthesiologists physical status classification system grade is >3, if they are immobile or unable to walk unassisted, or if they are already enrolled in a study that would interfere with the intervention and outcome of this trial.

Intervention

Overview

The intervention consists of a standardized MBM program (a group-based semi-individual approach to address lifestyle medicine and to enhance mindfulness) and naturopathic counseling, which is both led by a trained doctor and mind-body therapist, application of a yarrow liver compress which is applied by specially trained nurses, physical training therapy which is led by a sports therapist, a 1-day intervention in a teaching kitchen, and an organic lunch provided by a local caterer comprising a salad, a vegetarian protein-rich meal, and a dessert. The day clinic is scheduled once weekly, each session lasting 6.5 hours. This duration is common among other day clinics in the same setting [8]. The approach is group-based to enhance social support during the process. A detailed plan of the sessions and the scheduled topics is presented in Table 1.

Apart from allergic reactions to yarrow, no specific adverse effects are expected. A casualty insurance is contracted.

The study protocol has been presented to and discussed with patient representatives, the heads of the department of gynecology, urology, gastro-oncology, and radiation therapy, and the director of Comprehensive Cancer Center Ulm. This steering committee is informed intermittently about the status of the study.

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Table 1. The weekly schedule of day clinic activities.

Week	Activity (duration)
1	• Questionnaire (15 min) • Get together or group forming (75 min) • Exercise therapy (60 min) • Lunch (45 min) • Yarrow liver compress (60 min) • Introduction to mind-body-medicine (105 min) • Meditation (30 min)
2	• Questionnaire (15 min) • Week review (30 min) • Naturopathic consult (45 min) • Exercise therapy (60 min) • Lunch (45 min) • Yarrow liver compress (60 min) • Stress enhancing thought (105 min) • Meditation (30 min)
3	• Questionnaire (15 min) • Week review (30 min) • Naturopathic consult (45 min) • Exercise therapy (60 min) • Lunch (45 min) • Yarrow liver compress (60 min) • Reflection about personal stress response (105 min) • Meditation (30 min)
4	• Questionnaire (15 min) • Group cooking (255 min) • Yarrow liver compress (60 min) • Week review and naturopathic consult (30 min) • Meditation (30 min)
5	• Questionnaire (15 min) • Week review (30 min) • Naturopathic consult (45 min) • Exercise therapy (60 min) • Lunch (45 min) • Yarrow liver compress (60 min) • Stress and communicating with oneself (105 min) • Meditation (30 min)
6	• Questionnaire (15 min) • Week review (30 min) • Naturopathic consult (45 min) • Exercise therapy (60 min) • Lunch (45 min) • Yarrow liver compress (60 min) • Changing habits (105 min) • Meditation (30 min)
7	• Questionnaire (15 min) • Week review (30 min) • Naturopathic consult (45 min) • Exercise therapy (60 min) • Lunch (45 min) • Yarrow liver compress (60 min) • Mindfulness retreat (105 min) • Meditation (30 min)

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Week	Activity (duration)
8	• Questionnaire (15 min) • Week review (30 min) • Naturopathic consult (45 min) • Exercise therapy (60 min) • Lunch (45 min) • Yarrow liver compress (60 min) • Review of day clinic and future plans (105 min) • Meditation (30 min)

Mind-Body Intervention

We use a modified version of the standardized MBM approach established by Dobos and Paul [9]. The mind-body intervention combines aspects of the MBSR program developed by Kabat-Zinn and elements of the MBM cancer program established by Henry Benson at Harvard Medical School [20]. It combines relaxation techniques and group-based cognitive therapy to address lifestyle modification. Patients have access to digital copies of verbal instructions (script and audio files) and are encouraged to practice mindfulness techniques at home. The therapist in charge of the mind-body intervention is a board-certified internist and attended an advanced training as a mind-body-medicine therapist described in Mind-Body Medicine in Integrative and Complementary Medicine [9].

Naturopathic Counseling

Naturopathic counseling is known to enhance the QoL of patients with cancer [14] and a high percentage of patients use naturopathic methods sometimes without informing their oncologists [15]. Therefore, everyday clinic session includes naturopathic counseling based on the current guideline for complementary medicine in oncology. The counseling aims to enhance patients' self-efficacy and enables them to address neoadjuvant treatment-associated side effects at home. The counseling embraces topics such as teas, compresses, the importance of sleep and sleep-enhancing rituals, as well as aspects of aromatherapy. Patients are free to utter their personal complaints during the last days or questions about possible side effects of the neoadjuvant treatment and are given advice based on the current guidelines for complementary medicine in oncology.

Exercise Therapy Interventions

Prehabilitation exercise therapy includes a combination of strength, cardiovascular or aerobic training, yoga, qigong, and stretching exercises. The program focuses on the educational aspect, giving advice on additional home-based exercises. The duration of the supervised intervention is 1 hour a week and the intended intensity is moderate.

Liver Compress

A yarrow liver compress is applied after the patient has eaten lunch at the day clinic. The liver compresses are prepared and applied by trained nurses. We infuse 1 tablespoon of yarrow tea with cut blossoms, stems, and leaves of common yarrow (*Achillea millefolium*) with 250 mL boiling water, letting it infuse until the tea takes on a yellow color (approximately 7 min) for each patient. We soak a cotton cloth in the infusion and then wring it out. The cloth is then fanned and gently draped over the patient's right upper abdomen. A towel is wrapped around the patient's abdomen and a hot-water bottle is placed over the compress. We cover the patient with a blanket followed by a rest for 30 minutes. The cotton cloth is then removed and the patient rests for another 30 minutes.

Nutrition and Teaching Kitchen

Nutrition is addressed during each day's clinic session. It may be a topic during naturopathic counseling depending on the individual needs of the participants. Each day clinic session includes an organic lunch provided by a local caterer. The participants eat together, which enhances group cohesion. One visit to the day clinic is dedicated to a session in a teaching kitchen. Participants prepare a meal under the guidance of a trained nutritionist. Apart from the group-forming aspect of preparing and eating a meal together, this session includes counseling about nutrition during cancer and cancer therapy focusing on the individual needs of the participants. In order to support the muscle status of the participants, they are counseled to adhere to a protein-rich (1-1.5 g/kg/day) diet without specific restrictions concentrating on maintaining the pretreatment weight with respect to the individual needs of each participant.

Outcomes

Each patient's adherence to the day clinic program is the primary end point measured via the noted presence during the day clinic sessions. The secondary end points are patient-reported outcomes assessed by means of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30) [21], the Common Terminology Criteria for Adverse Events (PRO-CTCAE) [22], the Quality of Recovery-15 score (QoR-15) [23], the 4-item patient health questionnaire for anxiety and depression (PHQ-4) [24], the Pittsburgh Sleep Quality Index (PSQI) [25], the Five-Facet Mindfulness Questionnaire (FFMQ-D) [26], and fatigue (using a numeric rating scale) and clinician-reported outcome measures such as postoperative complications ≥3 according to Dindo and Clavien [27] within 30 days after the index operation, duration of postoperative hospital stay, readmission after initial discharge from the index operation within 30 days, 6-minute walking distance (6-MWD), hand grip strength (HGS), the result of the 1-minute sit-to-stand test (1-MSTS), the intensity of analgesic treatment according to the WHO pain ladder, and adherence to neoadjuvant treatment during the day clinic program. The physical assessment is conducted by study personal. The times of assessment of the end points are shown in Table 2.

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Table 2. The visit and corresponding time of data collection.

Visit	1	2-9	10[a]	10[b]	11	12	13
Time	Screening	Weeks 1-8 of prehabilitation	Post prehabilitation	1-10 days before surgery[c]	POD[d] 4	Day of discharge	POD[d] 30
Inclusion							
Informed consent	✓	N/A[e]	N/A	N/A	N/A	N/A	N/A
Eligibility criteria	✓	N/A	N/A	N/A	N/A	N/A	N/A
Assessments							
Demographics and baseline clinical data	✓	N/A	N/A	N/A	N/A	N/A	N/A
BMI	✓	N/A	✓	N/A	N/A	N/A	✓
Questionnaires							
EORTC QLQ-C30[f]	✓	N/A	✓	✓	✓	N/A	✓
PRO-CTCAE[g]	✓	✓	N/A	N/A	N/A	N/A	N/A
Fatigue scale	✓	✓	✓	✓	✓	✓	✓
QoR-15 GE[h]	✓	N/A	N/A	N/A	✓	N/A	N/A
PHQ-4[i]	✓	N/A	✓	✓	N/A	N/A	✓
Pittsburgh Sleep quality Index	✓	✓[j]	✓	✓	N/A	N/A	✓
Five-Facet Mindfulness Questionnaire	✓	N/A	✓	✓	N/A	N/A	✓
Physical examination							
6-minute walking test	✓	N/A	✓	N/A	N/A	N/A	N/A
Hand grip strength using a dynamometer	✓	N/A	✓	N/A	N/A	N/A	N/A
1-minute sit to stand test	✓	N/A	✓	N/A	N/A	N/A	N/A
Assessment of postoperative complications	N/A	N/A	N/A	N/A	✓	✓	✓
Intensity of analgesic treatment	✓	N/A	N/A	N/A	✓	✓	✓
Readmission to hospital	N/A	N/A	N/A	N/A	N/A	N/A	✓
Reoperation	N/A	N/A	N/A	N/A	N/A	N/A	✓
Time of stay on intensive care unit	N/A	N/A	N/A	N/A	N/A	N/A	✓
Adherence to neoadjuvant treatment	N/A	✓	N/A	N/A	N/A	N/A	N/A
Evaluation day clinic satisfaction	N/A	N/A	N/A	N/A	N/A	N/A	✓

[a]Only if time between end of prehabilitation and surgery >14 days.

[b]Every 4 weeks during prehabilitation.

[c]Only if time between end of prehabilitation and surgery >14 days.

[d]POD: postoperative day.

[e]N/A: not applicable.

[f]EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30.

[g]PRO-CTCAE: Common Terminology Criteria for Adverse Events.

[h]QoR-15: Quality of Recovery-15 score.

[i]PHQ-4: 4-item patient health questionnaire for anxiety and depression.

[j]Every 4 weeks during prehabilitation.

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Statistical Analysis

Sample Size Calculation

Prehabilitation in an integrative medicine day clinic (PRIME-DC) is a pilot study with an explorative approach and will be held in 3 cycles. Thus, no formal sample size calculation is needed. A group size of 6-12 patients per cycle was considered reasonable for evaluation of feasibility and acceptance of the prehabilitation day clinic setting. Patients who withdraw are not replaced, which is inherent for a closed group. Therefore, a sample of 18-45 patients is to be recruited. As the patients follow a group-based MBM program, the sample size has to fit the range appropriate for an MBM therapy group, that is, 6-15 patients.

Data Analysis Plan

The data analysis will give a comprehensive picture of the data through descriptive statistics and assess the precision and certainty of estimates using different CI widths.

First, descriptive statistics are used to summarize and describe the main features of the data set. This includes measures such as mean, median, SD, minimum, maximum, and percentiles. These statistics provide a clear and concise summary of the data's central tendencies and dispersion.

Further, the impact of different CI widths on the results and conclusions is of interest. CIs with 3 different widths, namely 75%, 85%, and 95%, are planned to be calculated and compared. The estimate becomes more precise as the CI narrows, albeit with reduced certainty regarding the capture of the true parameter [28].

Once the CIs are calculated, they will be interpreted in the context of the minimal clinically meaningful difference. This refers to the smallest change in the observed variable that is considered clinically relevant or significant. If the CI includes values within the range of minimal clinically meaningful difference, it may suggest that the observed effect is practically significant.

It is a robust approach to draw meaningful insights from the collected data while considering the practical implications of the findings [28].

Ethical Considerations

The study has been approved by the University Ethic Committee of Ulm University (77/22). Before study entry, all potential participants are comprehensively informed about the project and a written declaration of consent for participation is obtained. Access to the trial is open to all patients, regardless of their statutory health insurance provider. There are no additional costs or disadvantages for the participating patients. Patients' participation is voluntary. Participants will be informed verbally and in writing about the nature and scope of the planned procedure before the start of the study. Patients can withdraw their informed consent, including the processing of their data, at any time and without giving reasons. Disclosure takes place in pseudonymized form for the analysis. The names of the participating patients and all other confidential information are subject to medical confidentiality and the provisions of the European General Data Protection Regulation of May 25, 2018. After completion of the analyses, the data are made available on reasonable request in anonymized form in accordance with the institutional regulations and the General Data Protection Regulation. The study results are presented to academic audiences through publication in peer-reviewed journals and presentations at national and international conferences. The results are disseminated in the wider community. If shown to be feasible, the concept will be assessed with regard to its efficacy in reducing postoperative complications.

Results

This trial started on June 13, 2022, and the first 2 groups of patients have already completed their day clinic sessions. The current day clinic cycle takes place from January to March 2023. Data collection is to be completed by June 2023. As of February 2023, we enrolled 23 participants, 18 of whom were diagnosed with breast cancer, 2 with rectum carcinoma, 1 with esophageal cancer, 1 with stomach cancer, and 1 with pancreatic cancer. We expect the final results to be published by December 2023.

Discussion

Overview

This study is meant to prepare patients for surgery taking into consideration physical, nutritional, and psychological aspects. Neoadjuvant treatment is a very sensitive phase in cancer treatment and many patients search for assistance. Up to now this demand often remains unheard. We want to support patients with this comprehensive program, empower them to take control of some of the treatment-associated side effects, and help them prepare for the surgery. Establishing the feasibility of such program is the first step to show the efficacy of comprehensive integrative prehabilitation.

Principal Results

The main outcome is the adherence to the day clinic program measured via physical attendance at the weekly meetings.

Limitations

It will not be possible to establish significant data about the efficacy of such an approach as this study is meant to be a feasibility trial. The protocol does not include randomization; hence this is a feasibility study. The importance of the group-based setting may impede recruitment. The restricted cancer types included in the study might hamper the possibility of generalizing the results.

Conclusions

A PRIME-DC is a promising concept to address many unmet needs of patients undergoing neoadjuvant treatment combining aspects of movement therapy, naturopathic treatment, naturopathic counseling, dietary advice, and other lifestyle modifications like stress management.

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Acknowledgments

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Data Availability

The data sets generated and analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

All authors contributed to the conceptualization. CDH, CR, JT, and SO contributed to the investigation. CDH, KK, ALM, CR, JT, and SO contributed to the methodology. CDH, CR, JT, and SO contributed to the formal analysis and investigation. CDH, CR, JT, and SO contributed to writing—original draft preparation. CDH, KK, ALM, CR, JT, and SO contributed to writing—reviewing and editing.

Conflicts of Interest

None declared.

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Abbreviations

1-MSTS: 1-minute sit-to-stand test
6-MWD: 6-minute walking distance
EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30
FFMQ-D: Five-Facet Mindfulness Questionnaire
HGS: Hand grip strength
MBM: mind-body medicine
PHQ-4: 4-item patient health questionnaire for anxiety and depression
PRIME-DC: prehabilitative in an integrative medicine day clinic
PRO-CTCAE: Common Terminology Criteria for Adverse Events
PSQI: Pittsburgh Sleep Quality Index
QoL: Quality of life
QoR-15: Quality of Recovery-15 score

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Protocol

Hepatitis A Vaccination Coverage Among People With Chronic Liver Disease in England (HEALD): Protocol for a Retrospective Cohort Study

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Abstract

Background: Hepatitis A outbreaks in the United Kingdom are uncommon. Most people develop mild to moderate symptoms that resolve, without sequelae, within months. However, in high-risk groups, including those with underlying chronic liver disease (CLD), hepatitis A infection can be severe, with a higher risk of mortality and morbidity. The Health Security Agency and the National Institute of Health and Care Excellence recommend preexposure hepatitis A vaccination given in 2 doses to people with CLD, regardless of its cause. There are currently no published reports of vaccination coverage for people with CLD in England or internationally.

Objective: This study aims to describe hepatitis A vaccination coverage in adults with CLD in a UK primary care setting and compare liver disease etiology, sociodemographic characteristics, and comorbidities in people who are and are not exposed to the hepatitis A vaccine.

Methods: We will conduct a retrospective cohort study with data from the Primary Care Sentinel Cohort of the Oxford-Royal College of General Practitioners Clinical Informatics Digital Hub database, which is nationally representative of the English population. We will include people aged 18 years and older who have been registered in general practices in the Research and Surveillance Centre network and have a record of CLD between January 1, 2012, and December 31, 2022, including those with alcohol-related liver disease, chronic hepatitis B, chronic hepatitis C, nonalcohol fatty liver disease, Wilson disease, hemochromatosis, and autoimmune hepatitis. We will carefully curate variables using the Systematized Nomenclature of Medicine Clinical Terms. We will report the sociodemographic characteristics of those who are vaccinated. These include age, gender, ethnicity, population density, region, socioeconomic status (measured using the index of multiple deprivation), obesity, alcohol consumption, and smoking. Hepatitis A vaccination coverage for 1 and 2 doses will be calculated using an estimate of the CLD population as the denominator. We will analyze the baseline characteristics using descriptive statistics, including measures of dispersion. Pairwise comparisons of case-mix characteristics, comorbidities, and complications will be reported according to vaccination status. A multistate survival model will be fitted to estimate the transition probabilities among four states: (1) diagnosed with CLD, (2) first dose of hepatitis A vaccination, (3) second dose of hepatitis A vaccination, and (4) death. This will identify any potential disparities in how people with CLD get vaccinated.

Results: The Research and Surveillance Centre population comprises over 8 million people. The reported incidence of CLD is 20.7 cases per 100,000. International estimates of hepatitis A vaccine coverage vary between 10% and 50% in this group.

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Conclusions: This study will describe the uptake of the hepatitis A vaccine in people with CLD and report any disparities or differences in the characteristics of the vaccinated population.

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KEYWORDS

chronic liver disease; computerized; data accuracy; data extract; ethnicity; fatty liver disease; general practitioner; hepatitis A vaccination; hepatitis; liver disease; medical record systems; primary care; routine data sets; Systematized Nomenclature of Medicine; vaccination monitoring and surveillance; vaccination

Introduction

Overview

Hepatitis A (Hep A) is a viral infection of the liver caused by the hepatitis A virus (HAV). HAV is transmitted through the fecal-oral route, mainly by exposure to contaminated water sources. Hep A outbreaks are uncommon in the United Kingdom, and most people manifest mild to moderate symptoms that tend to resolve, without sequelae, within several months. In high-risk groups, however, such as people with an underlying chronic liver disease (CLD), a superimposed acute infection with HAV can be severe, potentially requiring hospitalization and carrying a higher risk of death. According to the World Health Organization, approximately 100 million Hep A infections occur globally per year, resulting in 15,000 to 30,000 deaths per year [1]. Of these, the number of people with a preexisting CLD diagnosis remains unclear.

CLD largely results from the progressive destruction and regeneration of hepatocytes, leading to fibrosis and cirrhosis, and has a range of etiologies. The most common causes of CLD include alcohol-related liver disease (ALD), chronic hepatitis B (CH-B) infection, chronic hepatitis C (CH-C) infection, and nonalcoholic fatty liver disease (NAFLD), the latter being associated with metabolic syndrome and obesity [2,3]. Deaths in the United Kingdom from CLD have increased annually for the past decade, peaking at 20.6 per 100,000 population in 2020 [4,5], and are expected to surpass the numbers of premature deaths from coronary heart disease [3], CLD-related hospitalizations in the United Kingdom have increased by half, contributing to the £2.1 (US $2.62) billion per year currently spent on treating liver disease [4,6].

The UK's public health body, the Health Security Agency, and the national guideline body, the National Institute for Health and Care Excellence, recommend preexposure Hep A vaccination to all people with CLD, regardless of the cause [7,8]. The Hep A vaccine series consists of 2 doses, with the second dose at least 6 months after the first.

The data from the United States have shown that less than one-third of at-risk adults receive any vaccination for Hep A, and only one-fifth receive both doses [2,9-12]. Adherence to the vaccination schedule was worse at the extremes of adult age, in ethnic minorities, and in those of low socioeconomic status [10]. The same is true in the United Kingdom; under 35% of eligible people receive the complete Hep A vaccination course, though these data are presented for all eligible patients, regardless of CLD status [13].

Hence, there are no published reports of Hep A vaccination coverage in people with CLD. The purpose of this study is to report Hep A vaccine coverage in people with CLD in UK primary care, with a focus on whether there are disparities as to which people with CLD receive Hep A vaccination.

Aims

The aim of this study is to report Hep A vaccination coverage in people with CLD in English primary care and the predictors of receiving a single dose or full vaccination course.

Objectives

The objectives of this study are as follows:

1. To report yearly Hep A vaccination coverage in people with CLD by:
   - sociodemographic characteristics (eg, age, sex, ethnicity, deprivation, BMI category, smoking status, and alcohol consumption)
   - etiology of CLD (eg, ALD, CH-B, CH-C, and NAFLD).
   - CLD complications (eg, renal disease, ascites, liver failure and transplant, and other cardiometabolic diseases, including diabetes and heart disease)
   - comorbidities and exposures (eg, Cambridge Multimorbidity Score [CMMS], bile duct and colon cancers, at least three doses of COVID-19 vaccine, and flu vaccination).
2. To report the predictors of 1 and 2 doses of Hep A vaccination in people with CLD.

Methods

Study Design

This is a retrospective cohort study using data from the nationally representative Primary Care Sentinel Cohort (PCSC) of the Oxford-Royal College of General Practitioners (RCGP) Research and Surveillance Centre (RSC) [14]. The RSC is one of Europe's oldest sentinel systems, and hepatitis is one of its 32 monitored conditions [15]. The database has previously been used for liver disease and hepatitis research [3,16].

We will use electronic health record data for the period between January 1, 2012, and December 31, 2022. Data will be extracted retrospectively at the time of the beginning of the study.

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Setting

Data Source

Data will be extracted from the PCSC of the RSC. The PCSC consists of a nationally representative sample of 7.4 million patients registered in primary care practices in England [17,18]. Pseudonymized data will be extracted from the secure environment of the Oxford-RCGP Clinical Informatics Digital Hub (ORCHID) [19].

CLD Ontology and Curated Variables

Key population characteristics, index conditions, and outcomes will be identified using the Systematized Nomenclature of Medicine Clinical Terms (SNOMED CT), in accordance with NHS Digital [20]. To identify these, we will curate data to ensure its use in future studies, supporting the findable, accessible, interoperable, and reusable open science principles [21].

The preliminary SNOMED CT codes to be used to identify CLD as an index condition are summarized in Multimedia Appendix 1. A conceptual model and suitable ontology are developed before carrying out the data extraction [22,23]. The identification of CLD-related concepts will be based on the clinical diagnoses as recorded in primary care; the researchers will not develop ad hoc diagnostic criteria. Clinical codes for CLD will be grouped by their main etiology; a hierarchical ontological approach using the conceptual model will be followed if overlapping concepts are encountered.

Data Quality

The RSC has over 55 years of experience in infectious disease surveillance, including vaccination coverage and effectiveness studies [18,24,25]. Viral hepatitis is one of the RSC's monitored conditions.

Study Population

We will include adults registered in general practices within the RSC network with a diagnosis of CLD, as defined by our ontology, within the period between January 1, 2012, and December 31, 2022. The following inclusion criteria will be applied: (1) people registered in the RSC general practices, aged 18 years and older, with a diagnosis of CLD; and (2) the ontology for CLD includes ALD, CH-B, CH-C, NAFLD, Wilson Disease, hemochromatosis, autoimmune hepatitis, primary sclerosing cholangitis, and primary biliary cholangitis [2-4].

The following exclusion criteria are applied: (1) patients with recorded contraindications to the Hep A vaccine (confirmed anaphylactic reaction to a previous dose of Hep A containing vaccine or to any of its components); and (2) records of administration of postinfection or risk-of-infection immunoglobulins.

Variables

Overview

The study population is those with CLD as an index condition, as defined in the inclusion criteria. The variables will be curated for the identification of CLD-related codes in the computerized medical records of adults registered in the RSC network (Multimedia Appendix 1).

Comparisons will be conducted between population subgroups with different CLD etiologies, sociodemographic characteristics, complications, and comorbidity profiles.

The outcome of the first objective will be the coverage rates of Hep A vaccination among those with CLD.

For the second objective, we will explore significant independent predictors of the following outcomes among those with CLD: (1) one dose of Hep A vaccination and (2) two doses of Hep A vaccination.

Hep A vaccination, as defined by the UK vaccination scheme, includes an initial 0.5 mL for 1 dose, followed by a booster dose of 0.5 mL after 6-12 months. The booster dose may be delayed by up to 3 years if not given after the recommended interval following the primary dose [8]. For this study, we will report boosters administered within 12 months of the first dose for the base case analysis and 3 years from the first dose for a sensitivity analysis. Hep A vaccination in the United Kingdom is available as a monovalent vaccine, as a combined Hep A and hepatitis B vaccine, and as a Hep A and typhoid vaccine [7]. We will consider any Hep A vaccination type as an outcome.

Covariates

Sociodemographic characteristics will be reported closest to the earliest date of CLD diagnosis as baseline, within a 10-year range for time-sensitive variables. These include age, gender, ethnicity (categorized into White, Black, Asian, multiracial, and other), rurality (measure of population density), region, socioeconomic status (measured using the index of multiple deprivation), obesity, alcohol consumption, and smoking. A history of comorbid conditions and complications will be extracted from 10 years of computerized medical records, including osteoporosis, bile duct and colon cancers, renal disease (including calculi), ascites, liver failure and transplant, and cardiometabolic disease. The CMMS will be used to report on comorbidity profiles [26,27].

Study Size

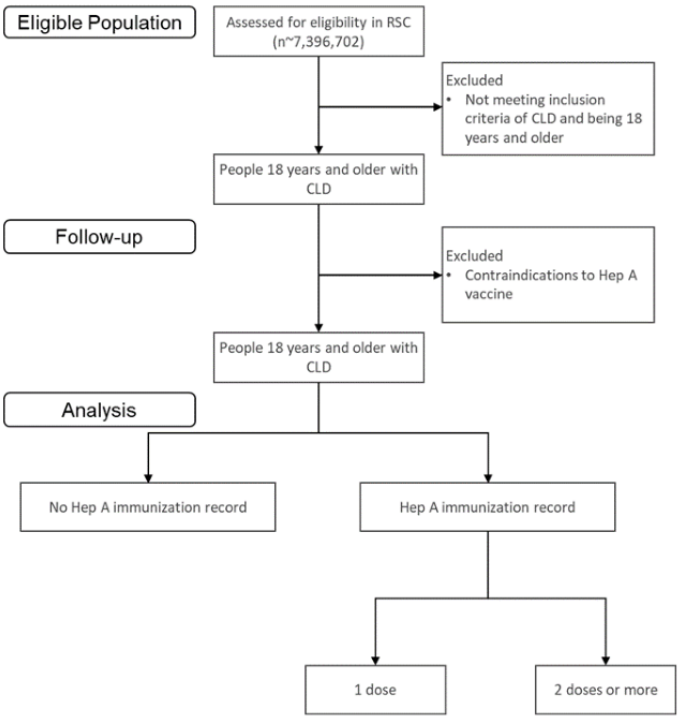
Age-standardized incidence rates for CLD worldwide are reported as 20.7/100,000 [28]. The RSC network comprises a nationally representative sample of 7.4 million registered patients. This brings an estimate of up to 1656 potential patients with CLD per year of study to be included in our final study population. This is consistent with previous reports on the CLD population in the RSC network [29].

In the United States, Hep A vaccination coverage is reported to range between 10% and 50% [2,9]. Therefore, we expect between 165 and 828 individuals to be found to have both the index condition and outcome of interest per year for a 10-year study period.

The study population will be categorized and stratified for analysis following the CONSORT (Consolidated Standards of Reporting Trials) diagram (Figure 1).

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Figure 1. Consolidated Standards of Reporting Trials diagram for eligible individuals in the Research and Surveillance Centre (RSC) network for a retrospective cohort analysis of adults with chronic liver disease (CLD) in England between January 1, 2012, and December 31, 2022, evaluating hepatitis A vaccination with 1 and 2 doses as outcomes.



Statistical Analysis

Reporting Hep A Vaccination Coverage in People With CLD

Hep A vaccination rates will be calculated using the number of vaccinated people with CLD as the numerator and estimates of the CLD population in the ORCHID data set as the denominator. Baseline characteristics of each study group (eg, age and gender) will be summarized using descriptive statistics, including measures of dispersion (eg, SDs and IQRs).

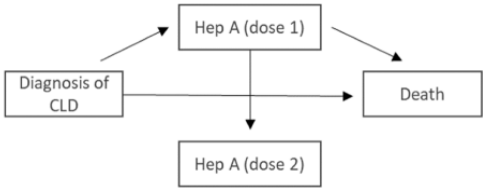
To compare individual characteristics by vaccination status (eg, CLD disease type, sociodemographic characteristics, complications, and comorbidities), we will use descriptive statistics, with pairwise comparisons using the chi-square or Fisher exact tests for categorical variables and the *t* test or Wilcoxon test for continuous variables. If stratification involves more than 2 groups, differences across groups will be tested using the Kruskal-Wallis test for continuous variables and the Pearson chi-square test for categorical variables, followed by pairwise comparisons as above described. All statistical tests will be 2-sided with $P<.05$ considered statistically significant.

Reporting Predictors of 1 and 2 Doses of Hep A Vaccination in People With CLD

Overview

A multistate model will be used on a retrospective cohort of individuals identified in the ORCHID diagnosed with CLD. People enter the study on the first diagnosis of CLD, and we will model the transition probabilities between the identified states: diagnosed with CLD, first dose of Hep A vaccination, second dose of Hep A vaccination, and death (Figure 2).

Figure 2. State transition diagram for competing risks multistate model for a retrospective cohort of adults with chronic liver disease (CLD) in England between January 1, 2012, and December 31, 2022, evaluating hepatitis A (Hep A) vaccination with 1 and 2 doses as outcomes and death as a competing risk represented as an absorbing state.



A multistate survival model will be fitted to estimate the transition probabilities between the 4 identified study states (Figure 2). The states are (1) diagnosis of CLD, (2) first dose of Hep A vaccination, (3) death, and (4) second dose of Hep A vaccination. The outcome of interest is the Hep A vaccination. Therefore, the state of a second dose of Hep A vaccination is a censored state, with no further transitions to death; the moment a patient receives 2 doses of Hep A vaccination, the follow-up ends. Death is an absorbing state, with no further transitions allowed. Death is included as a competing risk for vaccination, not as an outcome. This means that when calculating the transition probabilities to vaccination, we adjust for when a person is not vaccinated because of death before vaccination rather than for any other predictors of nonvaccination.

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Patients lost to follow-up will be right censored and evaluated accordingly as per the likelihood function of the "msm" R package [30].

Multistate probabilities are based on the same assumptions as a Markov process:

1. The health states considered in the model are thorough and mutually exclusive.
2. The probability to move from one health state to following states only depends on (is conditioned on) the health state of the individual at transition time (memoryless process).
3. Transition probabilities are steady over time.

The state transition probabilities will be estimated conditional on the study risk factors. Study risk factors include (1) etiology of CLD (eg, ALD, CH-B, CH-C, and NAFLD); (2) sociodemographic characteristics (eg, age, sex, ethnicity, deprivation, obesity, smoking, and alcohol consumption); (3) CLD complications (eg, bile duct and colon cancers, renal disease, ascites, liver failure and transplant, and cardiometabolic disease); and (4) comorbidities (eg, CMMS, bile duct and colon cancers, at least 3 doses of COVID-19 vaccine, and flu vaccination).

The multistate model will be estimated using the "msm" (version 1.6.9) package in R [31].

Missing Data

Descriptive analyses will be conducted on the overall study population and applicable subgroups. Data that are not documented in our database will be reported as missing.

Missing data will be presented as a separate category in univariate statistics and compared to the reference category through univariate odds ratios. Missing data categories will be imputed to the reference category if no significant differences are found in the reference category. Missing data categories will be otherwise included in the analysis as an independent category if evidence suggests they are not missing at random; for example, significant differences to the reference category exist.

Sensitivity Analysis

We will estimate 2 multistate models by varying the definition of Hep A dose 2. In the first model, the second dose must be administered within 1 year of the first dose; in the second model, dose 2 may occur within 3 years of the first administered dose. A 3-year time window between vaccinations is likely to exclude those who have been recently vaccinated. Hence the need for such a sensitivity analysis. A complete-case analysis to assess any differences due to missing data can be conducted after assessing the missingness of the descriptive data.

Spurious Data

Data quality (eg, consistency and accuracy) will be assessed at the point of data extraction through an outlier analysis comparing the covariate's values to plausible biological measures. Spurious values will be categorized as missing values and handled according to the methodology layout.

Ethical Considerations

Anonymized electronic health record data were accessible for research purposes following ethical approval from the Central University Research Ethics Committee at the University of Oxford (under reference R80951/RE001) for human participant research. Anonymized patient data were retrieved from electronic health record providers from those users who had consented for their data to be used for secondary research purposes. No form of compensation was provided to participants. Generative artificial intelligence was not used in any portion of the manuscript.

Results

The primary care cohort comprised 1704 practices and 7,396,702 registered patients between the January 1, 2012, and December 31, 2022 (Figure 1). We have created an initial clinical code ontology using existing SNOMED CT–curated variables for our sociodemographic variables, hepatitis, and CLD by etiology (Multimedia Appendix 1). The ontology will be expanded to include paraclinical indicators of CLD to identify cases where an explicit diagnosis or specific etiology has not been recorded. Other relevant covariates will be created as required for the study.

The phases of this study will include curating the required variables, conducting our data extraction, statistical analysis, and reporting of the findings through scientific publications.

Discussion

Overview

This study will inform on the state of preventive Hep A vaccination for people with CLD in a representative primary care sentinel network in England. From a total of 7.4 million patients in the RSC network, we will report on the sociodemographic and clinical characteristics of people with CLD with and without Hep A vaccination, for 1 and 2 doses.

The multistate model, adjusted for study risk factors, will identify those associated with having the vaccination. This will inform on the individual characteristics that are associated with an immunization, informing on the subgroups that could benefit from higher engagement with preventive primary care. Any disparities identified could be used to target clinical and public health interventions to improve vaccination coverage in this at-risk group.

Comparisons With Previous Work

The results will be compared to previous reports on preexposure Hep A vaccination coverage rates of 10%-50% in the United States [2,9,10,12]. For the United Kingdom, there are no published reports on vaccination coverage in this subpopulation, to the best of our knowledge.

Limitations

Selection and misclassification biases can be associated with the retrospective study design. However, this can be mitigated by the availability of reliable records in the database. Similarly, the retrospective study design has a limitation to establishing

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causal relationships due to the temporality and lack of randomization. However, retrospective associations can be a timely source of epidemiological data to guide further research.

There exists potential confounding due to case-mix characteristics, which will be mitigated through multivariate time-to-event modeling in the multistate model.

Large general practice databases are susceptible to coding errors or inaccuracies that may be associated with ascertainment and misclassification biases. This is mitigated by the large representative sample of UK practices within the RSC network, which controls for random error and variation on these parameters [18].

Conclusions

This descriptive epidemiological study will fill an important gap in our knowledge about Hep A vaccination in people with CLD in the United Kingdom by describing the uptake of Hep A vaccine in people with CLD and reporting any disparities or differences in characteristics of the vaccinated population.

Data Handling and Record Keeping

Data are held on dedicated, secure servers at the RCGP data and analytics hub in the Clinical Informatics and Health Outcomes Research Group, based at the Nuffield Department of Primary Care Health Sciences, University of Oxford. The research group's secure network is sited behind a firewall within the university's network; all inbound connections are blocked, but outbound connections are allowed. Only staff members or associated members of the research group approved by the head of department can access the data from a virtual desktop (on the ORCHID secure server) using a University of Oxford computer and their unique access credentials. The use of personal equipment is not permitted and cannot be connected to a secure network. Pseudonymized study data will be archived for at least 5 years.

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Data Availability

Apart from necessary access by the research team, direct access may be granted to authorized representatives from the sponsor or host institutions for monitoring or audit of the study to ensure compliance with regulations.

Researchers will maintain a log of data gathering using study IDs rather than personal identifying information.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Preliminary list of SNOMED CT codes used to identify individuals with chronic liver disease registered in the RSC network in England between the 1st January 2012 and the 31st December 2022.
[PDF File (Adobe PDF File), 406 KB - resprot_v12i1e51861_app1.pdf]

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Abbreviations

ALD: alcohol-related liver disease
CH-B: Chronic hepatitis B
CH-C: Chronic hepatitis C
CLD: chronic liver disease
CMMS: Cambridge Multimorbidity Score
CONSORT: Consolidated Standards of Reporting Trials
HAV: hepatitis A virus
Hep A: hepatitis A
NAFLD: nonalcoholic fatty liver disease
ORCHID: Oxford-RCGP Clinical Informatics Digital Hub
PCSC: Primary Care Sentinel Cohort
RCGP: Royal College of General Practitioners
RSC: Research and Surveillance Centre
SNOMED CT: Systematized Nomenclature of Medicine Clinical Terms

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Protocol

Human Papillomavirus (HPV) Infections Among Participants Undergoing Chlamydia trachomatis Testing in Reunion Island (RUN-SurV-HPV Study): Protocol for a Prevalence Study

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Abstract

Background: Infection by human papillomavirus (HPV) induces various cancers, mainly cervical cancer but also anal and pharyngeal cancers. Reunion Island is a French department in the Indian Ocean. Due to the history of its settlement, the island's population has a wide variety of origins, and the population's sociodemographic characteristics differ from those of the French mainland. These characteristics make the island's population an original French population in its own right, particularly in terms of health. Cervical cancer incidence and mortality in Reunion Island are 10.4 per 100,000 and 4.4 per 100,000, respectively, both of which are much higher than those in mainland France. There is also a disparity in the prevalence of different HPV types, with types 33 and 52 being overrepresented and type 18 being underrepresented. However, vaccination and screening coverage in Reunion Island is low. It is important to understand the burden of infection and its risk factors in members of the young Reunionese population at risk of HPV infection to promote and evaluate the implementation of future vaccination and screening programs on a larger scale.

Objective: The RUN-SurV-HPV study will have the following four objectives: (1) to describe the prevalence of HPV genotypes in a population at risk of sexually transmitted infections in Reunion Island; (2) to describe the prevalence of HPV genotypes by anatomical site, gender, and sexuality; (3) to describe the correlates and risk factors for HPV detection; and (4) to examine HPV genotypes between different anatomical sites.

Methods: Cross-sectional analyses of 1200 routine vaginal, anal, pharyngeal, and urinary samples collected between October 2020 to December 2022 from female and male patients aged 16 to 30 years undergoing *Chlamydia trachomatis* testing at a sexually transmitted infection (STI) testing center at Reunion Island will be performed. The population included 333 women who all had vaginal and pharyngeal swabs, with 80 of them also having had an anal swab. There are 167 men who have sex with men who have had anal and pharyngeal swabs, and 120 men who have sex with women who have had a urine swab only. Results will be correlated with sociodemographic and clinical data collected routinely during the consultations. HPV detection and genotyping will be performed using the Anyplex II HPV28 detection assay (Seegene).

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Results: The first polymerase chain reactions should begin in November 2023. The first results should be submitted for publication in 2024.

Conclusions: The study will determine HPV prevalence by age, sex, male sexual preference, human immunodeficiency virus status, and STI co-infection. Collecting data from young patients not usually routinely screened for HPV infection will be a simple and reproducible way of better understanding local specificities, encouraging vaccination campaigns in the short-term, and evaluating their effectiveness in the future.

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KEYWORDS

human papillomavirus; HPV; Reunion Island; epidemiological study; vaccination; vaccine; sexual health; sexual transmission; sexually transmitted infection; STI; epidemiological; epidemiology; cross-sectional; genotyping

Introduction

Human papillomavirus (HPV) is the most common sexually transmitted infection (STI) in the world. There are more than 100 types of HPV, with 13 classified as oncogenic. Of these, HPV types 16 and 18 are the cause of 70%-80% of invasive cervical cancers [1-3], which comprise the fourth most common cancer worldwide [4]. HPV infections also cause cancers of the vulva, vagina, penis, anal canal, and oropharynx; therefore, they affect both women and men.

Reunion Island is a French overseas department located in the Indian Ocean that is populated by more than 850,000 inhabitants. Due to the history of its settlement, the population of the island has very varied origins (ie, East Africa, the Comoros Islands, Madagascar, India, China, and Europe) that differ from mainland France. The geographical distance and its sociodemographic characteristics make it an original French population in its own right. In Reunion Island, cervical cancer is the fourth most common type of cancer in women. From 2013 to 2015, cervical cancer incidence and mortality were 10.4 per 100,000 and 4.4 per 100,000, respectively, making it the eighth deadliest cancer, 2 times higher than in mainland France [5]. These disparities can be explained partly by a low cervical cancer screening rate in the 1990s and 2000s [6] compared to the French national average, but the trend now seems to be reversing. Cervical cancer screening is a secondary prevention approach that is universally considered to be effective in reducing the incidence and mortality of this cancer in the general population. It is recommended in most developed countries. Furthermore, several studies have shown that risk factors for infection (eg, early sexual activity, high parity, precariousness) by the various STIs do not totally overlap with those in mainland France, and are, in fact, overrepresented in Reunion Island [7,8]. However, the only study to examine the link between this overrepresentation of risk factors and the incidence of cervical cancer in Reunion Island did not explain this difference in cancer incidence rates [9].

The first HPV vaccine was marketed worldwide in 2006. Initially, the first 2 vaccines protected against 2 genotypes (16 and 18) or 4 genotypes (6, 11, 16, and 18). Currently, the latest vaccine protects against 9 genotypes (6, 11, 16, 18, 31, 33, 45, 52, and 58). In 2007, the French High Authority for Health (HAS: Haute Autorite de la Sante) first implemented a community-based vaccination program that recommended HPV vaccination for girls aged 11 to 14 years with the possibility of catching up until 19 years of age. In 2019, the program was extended to include boys in the same age groups [10]. This officially came into effect in January 2021 [11]. In 2021, vaccination coverage was only 37.4% in mainland France [12]; it thus remains one of the lowest in Europe [13]. In Reunion Island, coverage was only 12.2% in 2021 based on the results of one available local research study [12]. Coverage is far short of the 90% elimination target [4]. This low vaccination rate in Reunion Island has in large part been driven by a lack of information and mistrust of vaccination from parents and caregivers [14].

The peculiarity of this population regarding its low vaccination coverage, high cancer rate compared to the national average, diverse ethnic origins, and risk factors encourages local exploration and monitoring of HPV genotype specificity. Furthermore, a previous study in women with atypical squamous cells of undetermined significance (ASCUS) Papanicolaou test results (age: mean 35.4, SD 12.3 years) and cervical biopsies of high-grade histological lesions or cancer (age: mean 48.6, SD 17.1 years) identified that the distributions of different types of HPV in Reunion Island were not similar to those observed in mainland France (eg, underrepresentation of HPV 18, overrepresentation of HPV 52, high proportion of co-infections) [15]. Moreover, there are no data on the prevalence of oncogenic HPV in Reunion Island in women younger than 30 years (for the cervical, pharyngeal, and anal areas), men who have sex with women (MSW), or men who have sex with men (MSM).

In the RUN-SurV-HPV study, we want to analyze the distribution of different oncogenic HPV types (16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 69, 73, and 82) in a population of women and men at risk of STIs attending an STI testing center for *Chlamydia trachomatis* (CT). The inclusion of young patients at risk of STIs, and therefore at risk of HPV infection, including both women and men, will enable us to study a population in which the incidence of HPV infection will likely be high. The inclusion of men, whether MSM or MSW, is in line with the recent extension of vaccination to French men and women, regardless of their sexuality [10]. Indeed, MSM have a higher risk of anal cancer [16], and MSW, even if in a smaller proportion, are still affected by HPV-induced cancers and can be vectors of infection for women. By including men, this study will improve our understanding of HPV infection

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in men and provide arguments to encourage them to be vaccinated. This type of study will allow us to obtain a more precise mapping of different oncogenic HPV genotypes in this population and evaluate an early surveillance system for changes in HPV distribution following vaccination campaigns.

The main objective is to describe the prevalence of infection by at least 1 of the 7 high-risk oncogenic HPV genotypes contained in the GARDASIL 9 HPV vaccine (16, 18, 31, 33, 45, 52 and 58) in women younger than 30 years who have had a vaginal swab and MSM who have had an anal swab for CT infection in the Reunion Island population.

The secondary objectives are as follows:

1. To describe the prevalence of infections by different high-risk (16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 69, 73, and 82) and low-risk (6, 11, 40, 42, 43, 44, 54, 61, and 70) HPV genotypes in samples from routine vaginal, anal, or pharyngeal CT testing from women younger than 30 years; urine samples from MSW younger than 30 years; and anal samples associated with pharyngeal CT testing from MSM.
2. To investigate HPV distribution in the same patient (women and MSM) according to the swabbed location.
3. To describe the correlates and risk factors for HPV infection, including age, CT status, status of other STI infections, socioeconomic status, sexuality, reasons for consultation, HPV vaccination status, and human immunodeficiency virus (HIV) status, by patient and type of specimen.

Methods

Study Design

This protocol is for a single-center, descriptive, cross-sectional study of all samples collected from male and female patients undergoing routine CT testing at the STI testing center of University Hospital (UH) in south Reunion Island between October 2020 and December 2022.

Setting

The national recommendation for CT screening in France suggests screening all woman from 15 to 25 years of age (pregnant women included) as well as those older than 25 years with risk factors and all men (all ages). In this study, samples were obtained from patients who went to an STI testing center mainly because of a recent sexual risk or symptomatic genital affection or to be able to remove the condom in a stable relationship.

Study Population

Inclusion Criteria

The following patients were included in the study:

1. Those who consulted the STI testing center of the UH site in south Reunion Island between October 1, 2020, and December 31, 2022;
2. Female patients younger than 30 years because the national recommendation for HPV screening is from 30 years of age and following a younger population would provide insight about the first impact of the national vaccination program;
3. MSM (all ages) because they have a higher risk of anal cancer;
4. MSW younger than 30 years because they are also affected by HPV-induced cancers, are included in the new French vaccination recommendations, and comprise a specific population that is able to infect women;
5. Those who were tested for CT infection on at least 2 different anatomical sites (vaginal, pharyngeal, and anal) for women, first pass urine for MSW, and at least 2 different sites (anal and pharyngeal) for MSM;
6. Those whose residual samples were available at the microbiology laboratory of the UH of Reunion Island.

Exclusion Criteria

The following patients were excluded from the study:

1. Those who were outside the study age range,
2. Those who did not consent to the use of their data for research,
3. MSW with no sites collected and women and MSM with less than 2 sites collected,
4. Those for whom there was insufficient biological material.

Data Collection

Social and demographic data were extracted from routine clinical records. These data were collected for each person presenting for screening via a self-administered questionnaire that was routinely administered and completed during the consultation (Multimedia Appendix 1). This questionnaire met the annual variables requested by France Public Health (Sante Publique France) from STI testing centers. It included age, gender, sample type, CT test result, HPV vaccination status (self-reported), male sexual preference, and social and demographic data. The collected information was anonymous in this testing center, but patients had a choice to link their clinical data with an anonymity number or their name for each sample. For this research, data will be entered into a secure anonymous database according to current national guidelines.

Data Extraction

Data Processing by the Laboratory

Sample collection at the laboratory, the supply of sampling equipment, and the transport of the samples was carried out in compliance with the NF EN ISO 15189 standard, thus guaranteeing the integrity of the samples and their traceability.

Samples were transported to the laboratory at 4 °C in eSwab transport media (COPAN Diagnostics) for swabs (vaginal, oral, and anal) and in sterile preservative-free flasks for urine. After the CT polymerase chain reactions (PCRs) were performed, residual samples were frozen at –80 °C to perform this study.

Enclosures equipped with range temperature sensors (SpyRF) are metrologically monitored using a monitoring web platform software (JRI-MySirius), allowing the exploitation of alarms and data. An Ethernet modem is installed in each lab, thus ensuring radio frequency communication with the SpyRF.

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HPV Detection and Genotyping

Samples will be tested with the Anyplex TM II HP28 Detection kit (Seegene), a semi-qualitative test for the detection of DNA and genotyping of HPV types. DNA extraction will be performed using the STARMag Universal extraction kit (Eurobio Scientific) on the STARlet (Seegene) automated system. After extraction, genotyping will be done by amplification on a CFX96 TM thermocycler (BioRad). This kit uses the human housekeeping gene, beta globin, as an endogenous internal control to verify the DNA extraction, PCR reaction, and presence of cells in each sample. This real-time multiplex assay allows simultaneous amplification, detection, and differentiation of target nucleic acids of 28 HPV types (6, 11, 16, 18, 26, 31, 33, 35, 39, 40, 42, 43, 44, 45, 51, 52, 53, 54, 56, 58, 59, 61, 66, 68, 69, 70, 73, and 82).

Processing of Medical Records, Questionnaires, and Patients' Results

Using standard software extraction tools, throughout the study, researchers will generate a list of all the information included in patients' records and self-administered questionnaires issued and completed on the day of collection. This anonymous information will then be extracted into a secure Excel spreadsheet (Microsoft Corp). HPV genotyping results will also be extracted into a secure Excel spreadsheet.

Statistical Considerations

Sample Size

Sample collection started in October 2020 and ended in December 2022. For women, 1436 swabs were collected from 665 women. A vaginal and pharyngeal swab was collected on the same day from 333 women younger than 30 years, 80 of whom also had an anal swab. For MSM, 738 samples were collected from 258 MSM. An anal and pharyngeal swab was collected on the same day from 167 MSM. Finally, 661 MSW provided a urine sample and 324 were younger than 30 years. Between 120-180 urine samples from MSW will be randomly selected for inclusion in the study, depending on the availability of stored samples from women and MSM. A total of 1200 samples will be tested (Table 1). Due to the absence of data with this type of methodology in Reunion Island, an estimated 95% CI for different prevalence levels was calculated using STATA 17.0 software (StataCorp) from vaginal swabs from women and anal swabs from MSM to address our primary objective (Table 2). This ranking was from 1% to 50% prevalence of HPV infection corresponding to 1 of the 7 potential oncogenic HPV genotypes contained in GARDASIL 9 in our previous study on ASCUS Papanicolaou tests and cervical biopsies (conservative assumption) [15].

Table 1. Description of the number of samples by gender, sexuality, and anatomical site of collection obtained between October 2020 and December 2022 from patients of all ages undergoing *Chlamydia trachomatis* testing at a sexually transmitted infection testing center in Reunion Island as part of the RUN-SurV-HPV study.

Anatomical site (n=1200)	Women (n=333), n	MSM[a] (n=167), n	MSW[b] (n=120), n
Pharyngeal	333	167	N/A[c]
Vaginal	333	N/A	N/A
Anal	80	167	N/A
Urine	N/A	N/A	120

[a]MSM: men who have sex with men.

[b]MSW: men who have sex with women.

[c]N/A: not applicable.

Table 2. Estimation of the 95% CI for human papillomavirus prevalence among women and men who have sex with men (MSM) who visited a sexually transmitted infection testing center from October 2020 to December 2022 in Reunion Island as part of the RUN-SurV-HPV study.

Prevalence (%)	Women (n=333), 95% CI	MSM (n=167), 95% CI
1	0.30-3.30	0.10-4.25
5	3.00-8.00	2.09-9.22
10	6.90-13.60	6.04-15.79
20	15.90-24.80	14.00-26.61
30	25.15-35.26	23.10-37.49
40	34.63-45.42	32.62-47.97
50	44.35-55.35	41.88-57.52

Analysis Plan

Patient characteristics will be described in terms of numbers and percentages for qualitative variables and in terms of mean and SD, median and IQR, and range for quantitative variables. The prevalence of HPV infections will be expressed as percentages. The exact binomial method will be used to calculate 95% CIs. Analysis of primary assessment criteria will be performed per patient considering only vaginal samples for women and anal samples for MSM. For analysis of factors

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associated with HPV infections, associations with factors of interest will be carried out for qualitative variables by chi-square test or Fisher exact test (depending on the conditions of validity); comparisons concerning continuous variables will be carried out by Student *t* test or Wilcoxon test depending on the conditions of validity. To account for confounding effects and to identify factors independently associated with HPV infections, a multivariate analysis by logistic regression will be performed. The dependent variable will be HPV infection (yes or no). The independent variables will come from the self-administered questionnaire and laboratory results and will include sex, age, CT status, status of other STIs, socioeconomic status, sexuality, reasons for consultation, HPV vaccination status, and HIV status. The independent variables entered in the model will be variables for which the significance level will be $P<.2$ in the bivariate analysis; variables will be selected using backward stepwise regression with a significance level for removal from the model of $P\geq.1$. To investigate whether factors associated with HPV infection differ according to sex and type of specimen, subgroup analyses will be performed by swab site and sex. McNemar tests will be used to assess differences between matched samples. Cohen κ will be calculated to check the concordance of HPV infections between matched samples from the same patient. To assess this concordance for women and MSM, individuals with samples from 3 sites will be preferred over those with samples from only 2 sites. A random selection will be made to select individuals with only 2 samples in order to meet the allowable sample size.

The significance threshold for the tests will be 5% ($P<.05$). CIs will be calculated at 95%. The statistics will be calculated with the STATA 17.0 software.

Ethical Considerations

The expected benefits outweigh the potential risks to patients.

National cervical cancer screening with HPV PCR is recommended by the HAS for individuals 30 years and older. In our study population, and in accordance with national recommendations, there is no obligation to follow up or to carry out additional examinations in the event of a positive result for HPV at the cervix-vaginal level, particularly if it is one of the oncogenic or probably oncogenic HPV types. The natural history of HPV infections is specific to the population younger than 30 years. The incidence and prevalence of HPV infections are at their highest levels due to the presence of major risk factors, such as number and frequency of new sexual partners. These infections are responsible for minor cytological lesions that evolve spontaneously and favorably in the majority of cases. Indeed, in this population, viral clearance is earlier and more marked than in older women, with 50% clearance of the infection within the first 6 months and 90% clearance within 2 years. In France, to date, there is no recommendation for HPV screening, nor is there a recommendation for treatment in the event of the discovery of an oncogenic HPV infection, whether it be anal, pharyngeal, or urinary, in women, MSM, or MSW.

An information note will be given at the time of the consultation setting out the objectives of the research organized based on data collected during care.

In compliance with national legislation, ethics approval has been obtained from the ethics evaluation committee of INSERM (French National Institute of Health and Medical Research; Opinion number 22-953) and all procedures were performed in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975.

Results

Patient recruitment began in October 2022 and ended in December 2022. Approximately 1200 samples were collected from 333 women, 167 MSM, and 120 MSW. Funding was obtained thanks to the support of the University Hospital of La Reunion. The first PCRs are scheduled for November 2023. We expect to submit the first results in 2024.

Discussion

Expected Outcomes

The results of this study, carried out in a largely unvaccinated population, will enable us to give more details on the distribution of HPV infections in the Reunion Island population before vaccination. Currently, in France, but also locally in Reunion Island, there is a desire to promote a community-based vaccination program with GARDASIL 9 to achieve a national coverage target of 80% among those aged 11 to 19 by 2030 [17,18]. The identification of the transmission of genotypes that are mostly covered by the 9-valence vaccination of patients in Reunion Island will help to reassure the general population and the doctors about the necessity of this vaccination. For MSM, it will be the first study to assess the prevalence of HPV in anal samples.

Vaccination has already been shown in several studies to be effective in reducing HPV infections [19] and precancerous lesions [20]. The Swedish study by Lei et al [21] followed a cohort of more than 1.6 million patients aged 10 to 30 years between 2006 and 2017 before, during, and after large-scale vaccination was introduced in Sweden. It showed a significant reduction in cervical cancer in vaccinated populations, with a favorable incidence rate ratio of 0.37 (95% CI 0.21-0.57) after covariate adjustment.

The Swedish team of Söderlund-Strand et al [22] has already used residual CT screening samples to carry out a prevalence study of HPV infections in a defined Swedish region and population of women and men in 2008. From 2012 to 2013, the team carried out the same study on the same population and in the same region of Sweden to identify changes in the prevalence of HPV infections. It is interesting to note that the first state-funded subsidies for HPV vaccination in Sweden were introduced in 2006 and the state vaccination campaigns began in 2012. In both cases, these vaccination recommendations were aimed solely at girls. Vaccination coverage was measured using various national registers. In 2008, when the first study was carried out, vaccination coverage among women in the population studied was 1.2%. Between 2012 and 2013, vaccination coverage among women was between 6.6%-7.5%. Coverage was highest among women and girls younger than

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23 years, with a maximum of 77.8% coverage among 14-year-olds. In this study, the majority of samples were genital and came from women aged 18 to 23 years. This study identified a significant drop in the prevalence of HPV genotypes 6, 11, 16, 18, 52, and 56 in women of all ages between 2008 and 2012-2013. These results are difficult to interpret given that detection of HPV by PCR in urine is known to be low. There was variability in the prevalence of HPV genotypes not covered by the vaccine, with an increase in HPV genotypes 52 and 56 but a decrease in genotype 31. The fact that the prevalence of HPV genotypes covered by the vaccine decreased mainly in the age groups of the most highly vaccinated populations is a strong argument for vaccine efficacy and is consistent with studies carried out in other countries. On the other hand, the decrease in the prevalence of HPV infections by covered genotypes in the population studied and the fact that certain noncovered genotypes tended to increase is not consistent with the data on cross-protection by the vaccine. It would therefore be interesting to monitor locally for the possible emergence of these HPV genotypes [22]. Other teams have carried out repeated cross-sectional surveys to measure vaccine pressure on HPV infections; for example, Markowitz et al [19] carried out 2 studies in the prevaccination era (2003-2006) and vaccination era (2007-2010) among more than 4000 patients recruited through national public health surveys, which included cervico-vaginal HPV tests in women aged 14 to 59 years. This study showed a significant drop in the prevalence of HPV 6, 11, 16, and 18 vaccines in women aged 14 to 19.

These different studies, each with their own specific design, demonstrate the value of carrying out this type of cross-sectional study repeatedly over time. With regard to Reunion Island and the prospect of repeating the RUN-SurV-HPV study in several years' time, it will be important to monitor changes in vaccination coverage locally. The next study should be carried out sufficiently far in advance of the current one so that vaccination has had time to become more widespread in Reunion's population. We can then hope to demonstrate the effect of vaccination with GARDASIL 9 by identifying a significant reduction in HPV infections and monitor the appearance of other genotypes in our population of women and MSM younger than 30 years.

Comparison With Previous Work

In this study, we expect to have different results from the studies already conducted in Reunion Island. The last genotyping study of HPV infections in Reunion Island was conducted from 401 ASCUS Papanicolaou tests and 94 cervical biopsies with histopathological diagnosis of high-grade lesions or cancer performed between 2008 and 2012 [15]. After analysis, 162 (40.4%) Papanicolaou tests and 63 (67%) biopsies were HPV DNA positive. Of the 162 Papanicolaou tests, HPV genotyping was possible for 100 samples. Co-infection was found in 60% of the Papanicolaou tests. The most common HPV genotypes in the Papanicolaou tests were 51 (12.3%), 31 (10.3%), and 16 (8.4%). Of the 63 HPV DNA positive biopsies, the most frequent HPV genotypes detected were 16HR (41.3%), 52HR (16.3%), and 33HR (11.5%). Co-infections were detected in 50.7% of these biopsies [15]. It will therefore be interesting to compare our results with those of this study, which is already more than 10 years old, taking into account that the type of sampling and the characteristics of the patients will not be superposable. In addition, in our work, the number of samples taken will be twice as high and will likely have different HPV positivity rates because the samples will be taken in a population largely free of any induced HPV lesions but at risk of STIs. The samples will be more recent in healthy participants for whom social and demographic data will be available. Moreover, the evolution of HPV infection from asymptomatic to precancerous or even cancerous is slow and takes several years, reinforcing the idea that the previous study may no longer reflect the seroprevalence of HPV types in the Reunion Island population. Because of the size of our sample, our data will be more robust than the previous study, but also more up to date. Our results will not be representative of the general population of Reunion but will represent the populations most concerned by vaccination and the prevention of induced HPV lesions.

Identifying the prevalence of HPV genotypes by analyzing samples collected for CT testing has been done in several countries to map HPV infections and assess the impact of their vaccination programs [23,24]. In a pilot Australian study by Shilling et al [23], 362 residual genital CT samples were matched to vaccination status and analyzed for HPV using the Anyplex II HPV 28 detection assay. All samples were from young women aged 16 to 24 years, the majority of which were of cervical origin. In the samples analyzed, 7.8% were positive for CT. HPV genotypes 16 or 18 were detected in 3% of the women, while HPV genotypes 31, 33, 45, 52, or 58 were detected in 19% [23]. The Swedish study by Söderlund-Strand et al [24] analyzed more than 44,000 residual CT specimens, mostly from women. In women, HPV test positivity was 37.8%, of which 10% were positive for HPV 16 and 6% for HPV 51. In men, 11.2% of the samples collected were positive for HPV, primarily HPV 16 (2.1%) and HPV 6 or 51 (1.7%) [24]. In these two studies, the high prevalence of HPV infection in populations consulting for CT testing provides a suitable sample for surveillance surveys of HPV vaccination programs. These previous studies from different countries reinforce the feasibility and relevance of our study.

The concordance of HPV genotypes in the same individual at different anatomical sites remains controversial in the literature. Müller et al [25] identified a much higher prevalence of anal HPV than pharyngeal and urinary HPV in 200 MSM but found concordance for HPV 16. The work of Nugent et al [26] identified good concordance between HPV-specific anal swabbing and residual swab analysis but the latter was a combination of pharyngeal, urinary, and anal swab residue. Nakashima et al [27], on the other hand, identified good concordance between HPV in the pharyngeal and urinary tracts. The British study by King et al [28] did not identify a concordance between HPV detected at the anal and pharyngeal levels in HIV-negative MSM. Finally, the Vietnamese team of Le et al [29] identified a weak concordance of HPV infections detected at the pharyngeal and genital levels in men co-infected with other STIs. Indeed, out of 198 patients analyzed, HPV was detected at both sites with only 1 genotype match in 1 patient. All these very discordant data from the literature lead us to explore the specificities of the Reunion Island territory locally

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to better understand the modalities of HPV infection of different anatomical sites in the same person.

Strengths of the Study

The strengths of this study lie in the originality of its design, with a data collection method (anonymous and tube-based analyses) that is not restrictive for the participants and investigators. This method makes it possible to include a large number of participants for more representative results. It is also easily reproducible over time, which will make it possible to repeat this type of study to monitor the evolution of HPV infections in the Reunion Island population.

The characteristics of the study population are also interesting. First, it is composed of both women and men, which coincides with the recent extension of French vaccination recommendations against HPV to adolescents of both sexes [10]. To our knowledge, there has been no previous study carried out in Reunion Island on the prevalence of HPV in men and in the pharyngeal or anal region in women. The young age of the participants matches the period of life when the prevalence and incidence of HPV infection is highest. Patients consulting STI testing centers are often in a precarious situation with risk behaviors that favor co-infections with another sexually transmitted disease, such as risk factors for HPV infections. These characteristics will therefore give us a better idea of the current mapping of HPV infections in Reunion Island. All these social and demographic data will be easily accessible to us thanks to the self-administered questionnaires systematically filled in during each consultation. These data will allow us, through subgroup analyses, to identify in our population the patients most at risk of being infected by an oncogenic HPV genotype, and thus to better target them for future preventative actions. Finally, comparison of the results from different sites in the same patient correlated with sociodemographic data will provide us with additional information on the modes of transmission and infection of HPV and will also allow us to better delimit the complementarity or similarity of screening for this infection to continue or stop it. These results will also provide information on potential targets for HPV vaccination depending on the infected site.

Limitations of the Study

This study has several limitations. The main limitation is the selection bias of our population. The population consulting STI testing centers is a specific population that cannot be extrapolated to the general population of Reunion Island. This population has an increased risk of HPV infection, and our results may be affected by this. The fact that the patients were recruited via a free screening center where they could consult spontaneously and anonymously reduced the risk of selection bias in our population. In our study, the proportion of under-age patients is likely to be low, even though this population is the main target for vaccination. Unfortunately, despite our efforts, it is difficult to have them consulted spontaneously and to include them while respecting both the anonymity of the consultation and the legislative framework for protecting the data of minors. Finally, this study was only carried out in one screening center, which could affect the results. The results may also be affected by the way the test is performed and its performance, even though it has already been validated in several studies [30,31]. The Anyplex II HPV28 detection assay is also one of the tests that will be evaluated by the VALGENT4 study with the aim of obtaining international clinical validation for uterine cervix cancer screening [32]. Although we have taken all possible precautions to avoid technical errors, results may also be influenced by the quantity and quality of viral material available in the samples collected, which is dependent on how the samples are collected, transported, and stored.

Conclusion

This original epidemiological study, which has already proved its worth in other countries, will have rapid implications by promoting vaccination campaigns and identifying the populations most at risk of being infected by an oncogenic HPV genotype. By comparing the prevalence of HPV infection in the same person and at different anatomical sites, this study will also provide a better understanding of its pathogenicity and mode of transmission and better delineate the complementarity of certain screenings. In the long term, these studies will allow for monitoring of the evolution of HPV infections and the impact of HPV vaccination campaigns in the Reunion Island population.

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Data Availability

The data sets generated and analyzed during the current study are not publicly available due to privacy issues of the participants. Data are available from the corresponding author request.

Conflicts of Interest

None declared.

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Multimedia Appendix 1
Santé Publique France data collection questionnaire. Identifying data, such as full date of birth (only year of birth and age will be extracted) and transgender sex (only original sex will be extracted), will not be extracted.
[DOCX File , 19 KB - resprot_v12i1e47379_app1.docx]

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Abbreviations

ASCUS: atypical squamous cells of undetermined significance
CT: Chlamydia trachomatis
HAS: Haute Autorite de la Sante (High Authority of Health)
HIV: human immunodeficiency virus
HPV: human papillomavirus
MSW: men who have sex with women
MSM: men who have sex with men
PCR: polymerase chain reaction
STI: sexually transmitted infection
UH: University Hospital

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Protocol

Investigating Attraction and Retention of Staff Within Public Mental Health Services in Victoria, Australia: Protocol for a Mixed Methods Study

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Abstract

Background: A large proportion of Australians are affected by mental illness each year, and treatment gaps are well known. To meet current and future demands and enable access to treatment that is safe, effective, and acceptable, a robust and sustainable mental health workforce is required. Factors reported to attract people to work within the mental health sector include aspiring to help others, having an interest in mental health and human behavior, the desire to make a difference and do something worthwhile, personal lived experience, recognition, and value of discipline-specific roles. However, despite the various reasons people enter the public mental health workforce, recruitment and retention continue to be ongoing challenges. To date, there has been limited investigation into understanding which factors are most relevant to the current Victorian workforce. Furthermore, a comparison to health care workers outside of mental health is also needed to better understand the specific needs of staff within the mental health sector.

Objective: This study aims to explore factors related to attraction, recruitment, and retention of the public mental health workforce in Victoria, Australia.

Methods: The study is a multisite, mixed methods cross-sectional study to be conducted at 4 public hospital services within Victoria, Australia: 2 in metropolitan and 2 in regional or rural locations. Current, previous, and nonmental health workers will be asked to complete a 20-25–minute web-based survey, which is developed based on previous research and offered participation

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in an optional 30-60–minute semistructured interview to examine personal experiences and perceptions. Both aspects of the project will examine factors related to attraction, recruitment, and retention in the public mental health workforce. Differences between groups (ie, current, past, and nonmental health workers), as well as location, discipline, and health setting will be examined. Regression analyses will be performed to determine the factors most strongly associated with retention (ie, job satisfaction) and turnover intention. Qualitative data will be transcribed verbatim and thematically analyzed to identify common themes.

Results: As of May 2023, we enrolled 539 participants in the web-based survey and 27 participants in the qualitative interview.

Conclusions: This project seeks to build on current knowledge from within Australia and internationally to understand role and service/system-related issues of attraction, recruitment, and retention specifically within Victoria, Australia. Seeking up-to-date information from across the health workforce may provide factors specific to mental health by illuminating any differences between mental health workers and health care workers outside of mental health. Furthermore, exploring motivators across health care disciplines and locations to enter, stay in, or leave a role in public mental health settings will provide valuable information to support how the sector plans and develops strategies that are fit for purpose.

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KEYWORDS

mental health personnel; career choice; recruitment; retention, turnover intention; public mental health; mental health; workforce; challenges; attraction; retention of staff; staff retention; human resources; human resourcing; HR; hire; hiring; new hire; onboarding; orientation; workforce

Introduction

Background

One-fifth of Australians experience mental illness each year, and treatment gaps both in type and quality are well known [1,2]. Within Australia, there was a reported treatment gap of 45% for people with major depression, while the average duration of untreated psychosis was reported to be 6 months [3]. Moreover, among adolescents who perceived the need for mental health (MH) treatment, only 53% received it [4]. To enable access to treatment and care that is safe, effective, and acceptable to patients and their families, a robust and sustainable MH workforce is required. The Royal Commission into Victoria's Mental Health System described historical underinvestment and increasing demand, alongside updated models of care driven by the promotion of well-being rather than an illness focus, resulting in an outdated and crisis-driven service that is ill-equipped to respond adequately to people living with mental illness, their families, and caregivers [5]. A critical issue is attracting and retaining staff in the MH workforce [6]. Evidence suggests that compared to other departments (eg, general medical and surgical), the MH workforce experiences higher rates of staff turnover and lower retention, although there is a paucity of exact statistics [7]. In order to understand the factors related to the recruitment and retention of MH workers, it is important to appreciate what attracts individuals to the MH workforce, what factors impact retention, and why people leave their role in public MH.

Past research has identified barriers to people choosing to enter the public MH workforce, including the stigma of working in MH, lack of opportunity for advancement, and disparity of remuneration between the public and private sector [8,9]. However, there are also several factors that attract people to work within the MH sector including aspiring to help others, having an interest in MH or behavior, the desire to make a difference and do something worthwhile, personal lived experience, recognition and value of discipline-specific roles, and being able to use skills and knowledge within their professional framework [5,10-14]. Despite the unique reasons that motivate people to work in MH, recruitment and retention of an adequate number of trained and experienced MH staff is an ongoing concern.

In Australia, as in other jurisdictions, the demand for public health services is growing, and there is a critical shortage of experienced MH professionals, particularly within the public MH sector [5]. This problem is further exacerbated in rural and remote areas, whereby there is significant maldistribution of the MH workforce [15]. During the COVID-19 pandemic, this problem became more pronounced as staff members were seconded to help with the response to COVID-19 (eg, to work in vaccination clinics), with not all returning to their previous role as vaccination clinics wound down. Compounding this issue, international border closures prevented overseas professionals from being granted entry into Australia, which has long been a pipeline for recruitment into the MH workforce.

In summary, there are significant factors that may contribute to low recruitment and retention within the public MH workforce; yet, there has been limited investigation into understanding which of these factors are most relevant in Victoria, Australia, and where differences may be in comparison to health care workers outside of MH. This lack of data and broad consultation across the workforce may result in initiatives being misplaced or failing to address problematic areas despite best efforts. Understanding the differences between MH workers and health care workers outside of MH will reveal the most pertinent factors that may be specific to MH. Furthermore, exploring what motivates people across health care disciplines to work or not work in public MH settings or decide to leave a job in public MH across both metropolitan and regional or rural workplaces

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can inform how the sector plans and develops strategies that are fit for purpose.

Study Aims

This study aims to explore factors related to the attraction, recruitment, and retention of the public MH workforce in Victoria, Australia. Specifically, the study aims to identify (1) the reasons for entering the MH workforce, (2) the reasons for staying in the MH workforce, (3) the reasons for leaving the MH workforce, and (4) reasons for not entering the MH workforce.

This information will then be used to generate and provide specific strategies that will address the challenges identified in the evaluation.

Methods

Study Design and Setting

The study is a multisite, mixed methods cross-sectional study to be conducted at 4 public hospital sites in Victoria, Australia (2 in metropolitan and 2 in rural locations). A steering committee consisting of all investigators across the 4 sites will meet regularly to oversee all operational, procedural, and policy aspects of the project's conduct.

All employees working within the MH department at each of the participating sites will be asked by email to complete a web-based survey. Staff from the wider hospital (ie, past MH workers or non-MH workers) at each site will also be invited to participate via a service-wide broadcast email. Past MH workers from each participating site who are no longer employed within the service will also be invited to participate by current employees forwarding information. Employees across all sites will also be invited to participate in a qualitative interview. Table 1 outlines the research framework.

Table 1. Research framework.

Dimensions	Attractiveness and recruitment	Retention	Method
Indicators	Reasons for joining or not entering the MH workforce	Reasons for staying in or leaving the MH workforce	N/A[a]
Phase 1	Current methods of assessment of reasons for joining or not entering the MH workforce	Current methods of assessment of reasons for remaining in or leaving the MH workforce	Preliminary interviews with managers of MH workforce
Phase 2a	Quantitative survey collection of reasons for joining or not entering the MH workforce	Quantitative survey collection of reasons for remaining in or leaving the MH workforce	Anonymous survey distribution across four sites
Phase 2b	Qualitative interview collection of reasons for joining or not entering the MH workforce	Qualitative interview collection of reasons for remaining in or leaving the MH workforce	Interviews with staff working in MH and in other departments across four sites
Phase 3	Compile a strategy for improving the attractiveness of working in public MH services	Compile a strategy for improving retention of staff working in public MH services	Propose methods to improve the attractiveness and retention of staff in MH services through data collected in Phase 2.

[a]N/A: not applicable.

Participants

Inclusion Criteria

Participants who satisfy the criteria for any of the following groups will be eligible to participate in the quantitative survey and the qualitative interview or focus group: (1) staff who are currently employed within the MH department at each of the 4 study sites, (2) staff who were previously employed within the MH department at each of the 4 study sites, and (3) staff who are currently employed outside the MH department at each of the 4 study sites and have never worked within the MH department.

Exclusion Criteria

Other than sufficient English language ability to respond to the questionnaires and interview questions in a meaningful manner, there will be no specific exclusion criteria for this study to ensure representativeness and generalizability.

Sample Size Estimation and Justification

Based on the current employment records, this study aims to collect questionnaire feedback from all employees working within the MH department of each health service; however, previous such studies have shown an approximate 30% response rate, with calculations as follows: (1) metropolitan site 1 (n=135 people), (2) metropolitan site 2 (n=150 people); (3) rural site 1 (n=111 people), and (4) rural site 2 (n=65 people).

Across the 4 sites, the aim is to collect information from 461 current MH workers. In addition, the study aims to collect feedback from 461 past MH workers and 461 non-MH workers. The overall projected sample size is 1383 participants.

Study Procedures

Consent and Recruitment

Informed consent will be obtained from all participants prior to the completion of the survey or interview. Advertising of the project will be conducted with authorization by the principal

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investigator and Human Research Ethics Committee at each of the 4 sites for a period of 4 months. The study will be advertised through the distribution of emails to staff and posting information through staff intranet portals as well as by strategically placed physical posters. An email will be circulated via a broadcast that will include a link to the questionnaire, at which point they will be asked to provide informed consent to take part in the study. Current MH workers at each site will also be asked to forward the invitation to past MH colleagues who have left the public MH workforce. Participation in a qualitative interview will be offered through an indication of willingness to participate as indicated at the end of the web-based survey (see Multimedia Appendix 1) through expressions of interest in response to the flyers and through emails circulated via hospital broadcasts. There will be no costs associated with participating in this research project nor will participants be paid.

Survey Data Collection

The anonymous web-based survey was developed in conjunction with the steering committee and based on themes identified in the literature and preliminary interviews with senior hospital staff. In instances where there were no available validated measures, the research team created questionnaires for the purpose of this study based on the information available in the current literature and preliminary interviews. The survey will assess reasons for entering, staying in, or leaving public MH services, or reasons for having chosen not to work in the public MH sector. The survey will take approximately 20-25 minutes to complete. Participants will be asked to indicate their age, gender, ethnicity, highest level of education, current position, previous position (for past MH workers), discipline, hospital site, health service setting, current employment status, working hours preference, whether they are employed on a contract or an ongoing basis, duration in current position and duration working in MH (current and previous MH workers). The measures included in the web-based survey are detailed in Table 2. See Multimedia Appendix 2 for the full data collection instrument.

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Table 2. Quantitative assessments in the survey.

Variable	Measure	Participants
Reasons for entering the public MH[a] workforce	Eight key factors were identified in the literature plus an option to specify others. Participants will be asked to select all the responses that apply to their circumstances.	Current and previous MH workers
Attraction to the current organization	Sixteen key factors were identified in the literature plus an option to specify others. Participants will be asked to select all that apply to their circumstances.	All
Expectations and reality of working in public MH	The reality of working in public MH compared to expectations based on prior understanding of what a career in public MH looked like will be measured on a scale from 1 to 5, where a higher score is indicative of greater consistency between reality and expectations. This was developed for this study a review of the literature and themes identified in preliminary interviews with senior hospital staff. An additional open-ended question will assess reasons why expectations were or were not met.	Current and previous MH workers
Importance of MH care	Perceptions of the importance of MH care in comparison to other health care disciplines will be assessed by 2 statements that participants will be asked to respond to on a 5-point Likert scale (1=strongly disagree to 5=strongly agree). The statements were developed for this study based on a review of the literature and themes identified in preliminary interviews with senior hospital staff. These statements assess personal opinions and general health care worker beliefs.	All
Job readiness and career development	Job readiness (ie, sufficient training) and level of career development opportunities will be assessed by 6 statements that participants will be asked to respond to on a 5-point Likert scale (1=strongly disagree to 5=strongly agree). The statements were developed for this study based on a review of the literature and themes identified in preliminary interviews with senior hospital staff.	All
Workplace flexibility	Participants will be asked to rate the perceived level of their organization's workplace flexibility on a 10-point Likert scale, with 1 being not flexible at all and 10 being very flexible.	All
Resilience	The 9-item Employee Resilience Scale [16]. Responses will be measured on a 5-point Likert scale (1=strongly disagree to 5=strongly agree). Scores will be summed to produce a total score (range=9-45), whereby higher scores are indicative of greater levels of resilience in the workplace.	All
Burnout	Measured using the Oldenburg Burnout Inventory [17] which measures 2 dimensions of burnout: disengagement and exhaustion. Disengagement refers to distancing oneself from one’s work and having negative feelings towards one’s work or service recipients, while exhaustion refers to the depletion of physical and emotional energy.	All
Turnover intention	Measured by 3 statements: “I am actively looking for another job,” “As soon as I find another job, I will quit,” and “I often think about quitting my job” [18]. Each statement has three response options: (1) no, (2) unsure, and (3) yes. Overall turnover intention will be the average of the 3 responses, with higher scores indicating higher levels of turnover intention.	All
Current employment intention	Six statements developed through a review of the literature and anecdotal evidence will assess current employment intention. Participants will be asked to select all that apply to their circumstances.	All
Team leadership	Staff perceptions of team leadership and management qualities will be assessed by 5 statements measured on a 5-point Likert scale (1=strongly disagree to 5=strongly agree). These statements were developed for this study based on a review of the literature and themes identified in preliminary interviews with senior hospital staff. A total score was produced by summing all items (range=5-25), whereby higher scores were indicative of greater perceived leadership.	All that reported being in a nonleadership role
Understaffing	A 6-item measure of understaffing [19]. Participants are asked to respond to statements on a 5-point Likert scale (1=strongly disagree to 5=strongly agree). The measure provides subscale scores for manpower understaffing and expertise understaffing (range=3-15), whereby higher scores are indicative of greater understaffing. An additional question was developed for this study specifically related to staff shortages as a result of the COVID-19 pandemic, “COVID-19 has created additional staff shortages within our department/team.”	All
Job satisfaction	The 15-item Job Satisfaction Scale [20] with slight variations in wording to suit health care workers. Participants will be asked to respond on a 5-point Likert scale (1=very dissatisfied to 5=very satisfied). This measure provides 2 subscales of job satisfaction (extrinsic and intrinsic), as well as an overall score of job satisfaction (range=15-75), whereby higher scores are indicative of greater overall job satisfaction.	All

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Variable	Measure	Participants
Workplace or occupational violence	A modified 9-item version of the World Health Organization Joint Program on Workplace Violence in the Health Sector questionnaire [21] will be used to assess workplace violence.	All
Moral injury	A modified 8-item version of the validated 10-item Moral Injury Symptom Scale-Health Professionals [22]. Each item is scored on a 5-point scale (1=strongly disagree to 5=strongly agree). Items are summed to create a total score (range=8-40), whereby higher scores are indicative of higher severity of moral injury. An additional item will also be used to assess the level of distress or impairment the moral injury has caused on their lives rated on a 5-point Likert scale (1=not at all to 5=extremely).	All
Reasons for leaving public MH workforce	Seven key factors were identified in the literature and preliminary interviews with senior hospital staff, plus an option to specify others. Participants will be asked to select all that apply to their circumstances.	Past MH workers
Reasons for not entering the MH workforce	Seven key factors were identified in the literature and preliminary interviews with senior hospital staff, plus an option to specify others. Participants will be asked to select all that apply to their circumstances.	Non-MH workers

[a]MH: mental health.

Qualitative Data Collection

A semistructured interview will be offered to those interested in providing more detailed information and recommendations for change within the field. This will enable a nuanced exploration of the most pertinent, empirically relevant themes associated with attraction, retention, and reasons for leaving or not entering the MH workforce. Interviews will be approximately 30-60 minutes in duration and conducted one-on-one with the research clinician either face-to-face or via a video call (ie, Teams, Microsoft Corp or Zoom, Zoom Technologies, Inc), depending on the participants' preference. The qualitative component will cover the four areas: (1) participant demographics including age and gender; (2) questions regarding current employment information (eg, discipline and location, ie, rural or metro); (3) questions regarding the positive and negative aspects of working in the MH field, specifically related to attraction, recruitment, retention, or not entering the MH field (see Multimedia Appendix 2). Additionally, the themes identified in the literature (eg, burnout, understaffing, and moral injury) will be targeted through questioning to explore their relevance; and (4) any other factors perceived by the participant as relevant or important to attraction, recruitment, or retention.

Participant Withdrawal

Participants will be free to withdraw from the study without reason or explanation. Data collected will be retained unless otherwise specified by the participant. However, as the web-based survey is anonymous, it will not be possible for participants to withdraw their survey data.

Statistical Analysis

Quantitative Data Analysis

Quantitative data analyses will be performed using SPSS (version 27; IBM Corp). Descriptive data will be presented using means, IQR, and percentages. Descriptive statistics that will be reported include discipline, employment status, hospital site location (ie, rural and metropolitan), health care setting (ie, inpatient and outpatient), duration of current position, and duration of working in health care. Groups will be categorized according to the variables listed as follows: (1) current MH worker, previous MH worker, and non-MH worker; (2) discipline (ie, nursing, medicine, allied health, and lived experience); (3) hospital site location (ie, regional or rural, metropolitan, using pooled rural and metropolitan data); and (4) health setting (ie, inpatient, community, and nonpatient facing).

Differences between groups on outcome measures will be compared using appropriate inferential tests. Regression analyses will also be conducted to determine predictors of retention (ie, job satisfaction) and turnover intention among the metropolitan workforce, and the regional or rural workforce.

Qualitative Data Analysis

Interviews will be recorded (with informed consent), transcribed verbatim, coded, and thematically analyzed to identify common emerging themes [23-25]. Transcripts will be continuously revisited, and the accuracy verified by listening to recordings and comparing them with the transcripts. Coding of data will be conducted using Excel (Microsoft Corp).

Data Management

All electronic data will be stored securely via password protection within the primary hospital IT system in accordance with appropriate data management policies, with access available only to the research team. This includes electronic consent forms, interview transcripts, interview recordings, and survey data. All other investigators will be given access to the deidentified and pooled group data if required. Physical forms (ie, participant information and consent forms) collected during the interview or focus group process (if conducted face-to-face) will be stored in a secure, locked, cabinet at the primary hospital site and handling of the forms will be in accordance with hospital data management policies. Upon receiving informed consent to participate in the interview, the research clinician will assign participant IDs. All collected data will be stored in a deidentified manner using participant codes. The data will be reidentifiable using the code key, which will be stored separately from the data files. Only researchers employed on the project at the primary hospital site will have access to the code key.

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Information that is collected for this project will be stored for 7 years and then securely disposed of.

Ethical Considerations

This study has been approved by the primary hospital Human Research Ethics Committee (HREC #008/22), and subsequently, governance approval was provided by the human research ethics committees at the other 3 sites. The findings from this project will be published and presented in a variety of forums, including peer-reviewed scientific journals and academic conferences. In all instances, information will be presented in a way that individuals and services cannot be identified achieved through presenting pooled group data only.

Results

The project received funding in May 2021, and data collection commenced in July 2022. As of May 2023, we enrolled 539 participants in the web-based survey and 27 participants in the qualitative interview. Data analysis has commenced, with results expected to be published by December 2023.

Discussion

Summary

This project seeks to evaluate factors that influence attraction, recruitment, and retention within the public MH workforce in Victoria, Australia. The design of the project, based on previous research that illustrated both role and service/system-related difficulties, sought to build on current knowledge from within the Australian context and abroad. For instance, in its investigation of Victoria's Mental Health System, the Royal Commission discovered numerous obstacles that MH workers face, which may contribute to issues of retention. These included occupational burnout, violence and aggressive behavior from patients, frequent staff turnover, insufficient staffing levels, and, in some cases, a lack of management support [5]. Similarly, MH workers in Ghana cited job-related challenges such as lack of resources and workplace violence (eg, patient aggression and physical violence), as well as service- or system-based problems including rigid hierarchical organizational structure, limited opportunity for advancement, unclear pathways for progression, and lack of feedback or recognition regarding work performance, as significant issues related to retention [11]. These challenges and barriers in retention are potentially compounded by difficulties in attracting people to specific roles, and the MH sector more broadly. This may be reflected in the reported shortage of supply in appropriately qualified people applying for advertised positions and an inability to backfill roles where someone has been promoted [19,26].

Beyond aspects of the role that may contribute to problems with retention, previous studies have also demonstrated that due to the environment (ie, design not conducive to promoting safe practices for staff and patients and burdensome procedures), MH workers are at an increased risk of experiencing job-related stressors [27,28]. These stressors warrant further attention as they have been reported to contribute to decreased staff well-being and increased rates of attrition. For example, occupational burnout and workplace violence (both physical and psychological) have been reported among MH workers and are associated with reduced job satisfaction [27,28]. Job satisfaction has been reported to be lower in health care workers compared with workers in other professions [29]. Given the high-risk environment of MH, job satisfaction may be especially low in MH settings, although to date, this has not been investigated. Furthermore, job satisfaction has been linked to higher turnover intention (ie, the desire to leave one's job) [27], which in turn may exacerbate staff shortages [29]. By exploring the relationships between these factors using both quantitative and qualitative methods, our study seeks to provide greater clarity relating to environmental aspects.

Although this study is somewhat limited by the participation of only a portion of the full workforce, one particular strength is the inclusion of both metropolitan and regional or rural services. This will allow investigation of similarities and differences and exploration of some of the unique challenges that may need to be considered in each setting. Furthermore, our study will build on others that have been conducted in regional and rural areas of Australia. Among these previous studies, factors specifically affecting attraction and retention have been explored in regional and rural areas of Queensland and New South Wales. Results indicate there are some unique differences when compared to metropolitan areas. For example, the distance and long travel times between towns that may not be adequately factored into workload expectations, limited transport options, reduced availability of services and amenities for workers and their families, less anonymity, perceptions of reduced opportunities for career advancement due to working in much smaller teams, and increased workload due to the expectation of having to educate other staff have all been reported as factors that influence staff turnover in regional and rural areas [30-32]. On the other hand, there may be particular strengths, and investigating the experiences of staff across both metropolitan and regional or rural settings will allow an examination of specific needs, and also how strengths may be leveraged.

To plan for the future and ensure that strategic initiatives are fit for purpose and aligned across employment settings, it is essential that a comprehensive evaluation of the life cycle of employment in MH settings be undertaken. Two factors should be considered. First, understanding what motivates people to work in public MH and second, how people subsequently perceive and experience their jobs, specifically what motivates them to stay or leave. Overall, this information will provide support for critical workforce planning to target the most pertinent factors identified by the current workforce, which will assist in ensuring the alignment of job supply with the demand required by the MH system, in order to create a sustainable MH workforce.

Limitations

A limiting factor of this study is the potential for participant responses to inaccurately depict those of the population, a common issue within opt-in survey designs [33]. Moreover, the location may be considered a limitation given participants were only recruited from 4 health care services within Victoria, Australia. To address this, services were selected by the Victorian Department of Health, with the goal of capturing the

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most variety across the locations as possible. This study aimed to elucidate the challenges experienced by multidisciplinary teams specifically within Victorian public MH services. This means that generalizability beyond MH and Victoria may be hindered, and a potential future direction could be to replicate and extend this research more broadly for comparison and to increase the breadth of knowledge. The use of self-report measures is another limitation worth noting; and in an attempt to address this, this study selected to primarily use validated measures.

Conclusions

With this study, we aim to broaden current knowledge regarding the recruitment and retention of multidisciplinary public MH care teams, specifically within Victoria, Australia. The findings of the study will be analyzed and used to inform necessary workforce planning, which supports the alignment of job supply with the demand required by the MH system into the future.

Acknowledgments

This work is supported by the Victorian Government.

Data Availability

The data that support this study will be available upon reasonable request from the corresponding author.

Authors' Contributions

KC, IG, and ZMJ developed the protocol. KC drafted the manuscript. IG, ZMJ, DH, RB, IB, ARNL, RB, and DJC reviewed and edited the manuscript. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Interview expression of interest form.
[DOCX File , 14 KB - resprot_v12i1e48855_app1.docx]

Multimedia Appendix 2
Data collection instruments.
[DOCX File , 70 KB - resprot_v12i1e48855_app2.docx]

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Abbreviations

MH: mental health

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Protocol

Twice-Weekly Outpatient Rehabilitation Intervention for Young Children With Spinal Muscular Atrophy Treated With Genetic-Based Therapies: Protocol for a Feasibility Study

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Abstract

Background: Spinal muscular atrophy (SMA) is a progressive neuromuscular disorder that causes muscle weakness and is the leading genetic cause of infant mortality worldwide. While no definitive cure exists, the approval of 3 genetic-based therapies in Canada since 2018 has led to significant improvements in muscle function for children with SMA. With that, there are no evidence-based rehabilitation interventions and minimal evidence on the combined effects of genetic-based therapies and rehabilitation.

Objective: This protocol describes the methodology to assess the feasibility of a twice-weekly outpatient rehabilitation intervention focusing on gross and fine motor function to inform the methodology and sample size of a definitive clinical trial.

Methods: We will conduct a single-center nonrandomized pilot and feasibility trial to explore an outpatient rehabilitation intervention for children aged 6 months to 3 years with SMA treated with genetic-based therapies. Participation in the study will occur over a 25-week period, with a baseline assessment visit followed by a 12-week intervention period and a 12-week nonintervention period. The rehabilitation intervention comprises weekly physical and occupational therapy for 11 weeks. Assessments will occur at baseline (week 0), end of intervention or early withdrawal (week 12), and follow-up (week 24). Predetermined feasibility indicators will evaluate study feasibility across process (recruitment rates, eligibility criteria, adherence rates, retention rates, questionnaire suitability, and acceptability), resource (time, implementation, and execution), management (materials and data), and scientific (safety, tolerability, and preliminary efficacy) domains.

Results: This project was funded in March 2022, and data will be collected between March 2023 and December 2023. Data analysis will occur between January 2024 and March 2024, with publication expected in the fall of 2024. The protocol for the feasibility trial will be considered successful if it meets the success criteria set out for the feasibility indicators. Indicators of specific interest include all process indicators, as well as time. Exploratory indicators will be reported. Pragmatically, the results of the feasibility trial will inform changes to the protocol and the start-up of a definitive multisite trial.

Conclusions: This novel twice-weekly outpatient rehabilitation intervention will be the first step toward filling the need for an evidence-based rehabilitation intervention for children with SMA treated with genetic-based therapies. It is expected that consistent and intensive rehabilitation therapy will augment functional gains being observed in this population. In the future, a definitive trial will measure the efficacy of the intervention.

Trial Registration: ClinicalTrials.gov NCT05638750; https://clinicaltrials.gov/study/NCT05638750

International Registered Report Identifier (IRRID): DERR1-10.2196/46363

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KEYWORDS

active rehabilitation; atrophy; child; feasibility trial; feasibility; genetic-based; genetic-based therapy; infant; occupation therapy; pediatric; physical therapy; physiotherapy; pilot trial; rehabilitation; spinal muscular atrophy

Introduction

Spinal muscular atrophy (SMA) is a progressive neuromuscular disorder in which there is a gradual degeneration of motor neurons due to a loss-of-function mutation in the survival of motor neuron 1 (SMN1) gene, which enables proper functioning of motor neurons and therefore muscle function [1-3]. There are 3 pediatric subtypes (types I, II, and III) of SMA based on the age of onset of muscle weakness and motor milestones achieved [3]. All SMA subtypes demonstrate a decline in function over time. SMA type I presents the most rapid onset and severe decline [1,4,5]. SMA types II and III have a later onset and more gradual decline [5,6]. SMA affects 1 in 6000 to 10,000 births worldwide [7-10]. As of 2020 in Canada, there are an estimated 700 to 2140 cases of SMA [11,12] with approximately 35 new cases per year [10]. SMA is one of the most common genetic causes of mortality in infants [3,13]; however, there is optimism that this will change due to the availability of new treatments.

Health Canada has approved 3 genetic-based therapies for individuals with SMA: nusinersen (brand name Spinraza, 2018), onasemnogene abeparvovec (brand name Zolgensma, 2020), and risdiplam (brand name Evrysdi, 2021). These genetic-based therapies aim to increase the production of the SMN protein and improve muscle function [14]. As a result of these new treatments, Ontario, Canada, has included SMA in newborn screening programs since 2020, enabling treatment shortly after birth [15]. Implementation of these genetic-based therapies has demonstrated significant and clinically meaningful gains in physical function in clinical trials in both individuals receiving a genetic-based therapy presymptomatically as well as after the onset of clinical symptoms, which was previously unheard of in the SMA population [16-24]. For example, presymptomatic infants who received nusinersen within 6 weeks of birth gained the ability to sit without support (100%), walk with assistance (92%), and walk independently (88%) [18]. Additionally, 57% of children with later-onset SMA treated with nusinersen saw increases in motor function compared to 26% of children in the placebo control group [22].

The most recent standards of care for SMA were published in 2018, before the widespread approval of genetic-based treatments internationally [14,22,25]. Additionally, there is minimal evidence-based guidance in the literature regarding rehabilitation interventions to proactively optimize function for children with SMA treated with genetic-based therapies [3]. With that, there is a paucity of published long-term evidence regarding rehabilitation programs and their impact on physical function in individuals with SMA treated with genetic-based therapies to guide program development and funding of rehabilitation programs. Few studies have explored the combined effects of genetic-based therapy and rehabilitation therapy for children with SMA; however, preliminary research indicates promising synergies [26]. For example, a retrospective study reported that individuals treated with nusinersen who attended physiotherapy (PT) 5 days per week experienced a 12.7% (P<.001) improvement in gross motor gains compared to a 5.4% increase in those who only received nusinersen and less than 1 PT session per week at 1 year after starting nusinersen [26].

Due to the progression of SMA, PT and occupational therapy (OT) historically focused on the provision of equipment, compensatory strategies, and reducing the risk of secondary complications, such as joint contractures [3]. With new disease-modifying treatments, families of young children with SMA are seeking proactive rehabilitation to enhance and optimize physical function [27,28]. The intervention presented in this protocol proposes rehabilitation therapy that draws upon models of service delivery used in pediatric populations at the delivering institution. Goal-directed therapy will be implemented, which has been shown to be the most effective type of therapy for commonly studied pediatric neurological conditions such as cerebral palsy [29-31]. Additionally, based on previous SMA exercise therapy intervention studies that were tolerable and safe [32], a 12-week therapy block duration has been proposed. Drawing from the aforementioned proposal, further evaluation of the effects of therapy and the efficacy of this rehabilitation program is crucial to improving the quality of care for this population and the optimization of their function [26].

The objective of the study is to assess the feasibility of a twice-weekly outpatient rehabilitation intervention focused on gross motor and manual function to inform the methodology and sample size of a definitive clinical trial according to specific feasibility indicators (process, resources, management, and scientific) [33]. This protocol will describe the pilot and feasibility trial for this evidence-informed outpatient rehabilitation intervention for children with SMA treated with genetic-based therapies. The Standard Protocol Items–Recommendations for Interventional Trials (SPIRIT) guidelines, the Consolidated Standards of Reporting Trials (CONSORT) extension for feasibility and pilot trials, and the Template for Intervention Description and Replication (TIDieR) checklist for intervention description and replication guided the reporting of this protocol.

Methods

Design

The study is a single-center nonrandomized pilot and feasibility trial to explore the feasibility of an outpatient rehabilitation intervention for children 6 months to 3 years of age with SMA treated with genetic-based therapies. Participation in the study will occur over a 25-week period, with a baseline assessment visit followed by a 12-week intervention period and a 12-week nonintervention period. The trial site will be a pediatric rehabilitation hospital in Toronto, Canada.

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Participants

A convenience sample of 5-10 participants (children and parent or guardian dyads) will be enrolled. Current standards of practice deem formal sample size calculations unnecessary for feasibility trials since findings obtained from the small sample size in this study will allow for generalization to a larger definitive trial. Thus, a pragmatic approach will be undertaken, justifying the sample size used in this study [34]. This also supports the practicality of this study design, as the participant pool does not need to be exhausted to deliver the intervention.

Eligibility Criteria

The inclusion criteria are as follows: (1) SMA (type I, II, or III) diagnosis; (2) received or receiving a genetic-based therapy; (3) age 6 months to 3 years; (4) able to participate in twice-weekly therapy at the study site; (5) able to bring appropriate respiratory equipment to weekly therapy sessions, if required; (6) parent or guardian must be able to speak and read English; (7) child participant must be able to understand and follow directions in English, as age appropriate; and (8) parent or guardian must consent to participate on behalf of their child.

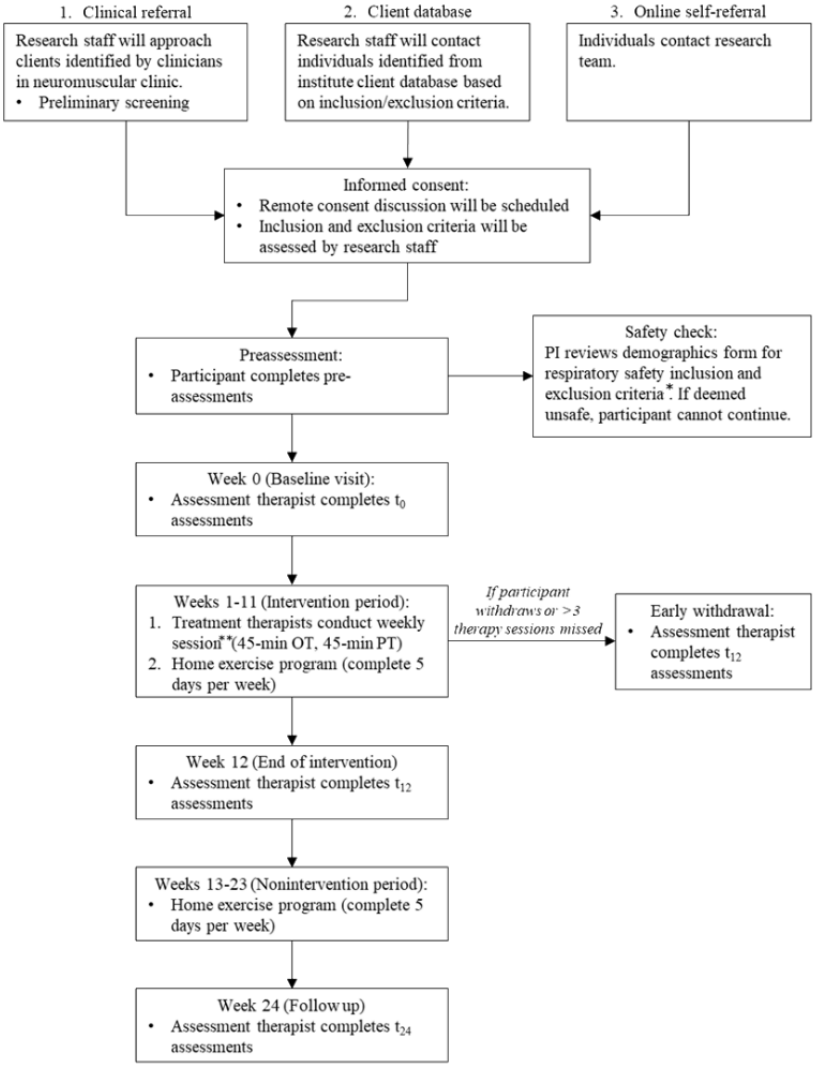
The exclusion criteria are as follows: (1) live outside of Ontario, and (2) tracheostomy or use of daytime ventilation (excluding ventilation used during naps).

Inclusion and exclusion criteria will be assessed during the recruitment process. Respiratory safety screening will be conducted by the principal investigator if the use of respiratory equipment is identified.

Recruitment

Participants will be recruited from across Ontario, Canada. A multipronged recruitment strategy will be implemented using active (clinical referrals and an institutional research client database) and passive (self-referral through web posts) approaches. Posts include institutional internet posts (social media and the institution's website) as well as social media sharing on websites commonly accessed by families with children with SMA. Figure 1 describes potential recruitment pathways and participant flow.

Figure 1. Recruitment path and participant flow for the twice-weekly outpatient intensive rehabilitation intervention for young children with spinal muscular atrophy treated with genetic-based therapies. *The respiratory safety inclusion and exclusion criteria include 5 inclusion criteria and 2 exclusion criteria. **Up to 3 weeks of therapy sessions can be missed or held on the internet (ie, 3 OT and 3 PT sessions may be missed or held virtually). OT: occupational therapy; PI: principal investigator; PT: physiotherapy.



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Intervention

Parents will consent on behalf of their child before study visits are conducted by trained research staff. The intervention comprises a 12-week intervention period (OT and PT sessions plus a home exercise program) followed by a 12-week nonintervention period (home exercise program only). The 12-week intervention period was based on previous exercise therapy studies on pediatric neurological conditions such as cerebral palsy [29-31], and a small number of SMA exercise studies [23,32,35,36]. The on-off block structure is what is typically offered at the institution.

Participants will not be required to stop any additional private therapies during the study. However, participants will be asked not to start any new treatments or therapy during the study. All additional activities should be recorded in the home exercise diary.

In week 0, therapy goals will be set using the Canadian Occupational Performance Measure (COPM) and Goal Attainment Scaling (GAS) goals created with the participant's parents, and baseline functional assessments will be completed. OT and PT goals will be individual to each participant. With that, the therapy sessions are created and personalized to the participant and their goals.

During the intervention period, active therapy will be delivered in person through weeks 1-11. A total of 2 therapy sessions (one 45-minute PT and one 45-minute OT session) per week in addition to a home exercise program will be completed. It will be recommended that participants complete the home exercise program 5 days per week in addition to the 2 therapy sessions (OT and PT). During the nonintervention period, the home exercise program will be continued. Functional assessments will be reevaluated at week 12 and then again at week 24 to determine whether functional gains were maintained. See Figure 1 for a detailed participant flow. A total of 3 weeks of sessions will be permitted to be missed or conducted through video conferencing software over the intervention period.

During the nonintervention period, the participant will receive an updated home exercise program to be completed 5 days per week. A research team member will contact the participant every 2 weeks to review the home exercise diary and other activities in which the participant is participating and to reiterate the importance of the home exercise program.

All on-site therapy and assessment sessions will be completed in a private therapy room; however, sessions could occur in a group therapy room if needed.

Assessment

Assessments will be administered at prescribed time points, as described in Table 1.

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Table 1. Intervention and assessment time points for the twice-weekly outpatient rehabilitation intervention for young children with spinal muscular atrophy treated with genetic-based therapies. The intervention period occurs between t_1 and t_{11}, and the nonintervention period occurs between t_{13} and t_{23}.

Measure	Assessment			
	Preassessment	t_0 (baseline)	t_{12} and t_{10} (EOI[a] and EW[b])	t_{24} (follow-up)
Demographics survey[c]	✓			
ITQOL[c,d]		✓	✓	✓
COPM[e,f]		✓		
GAS[e,g]		✓		
CHOP-INTEND[h] or HFMSE[e,i,j]		✓	✓	✓
Bayley (All)[e]		✓		
Bayley (motor domain only)[e]			✓	✓
Evaluate COPM and GAS goals[e]			✓	✓
AIM[k], IAM[l], FIM[c,m]			✓	

[a]EOI: end of intervention.

[b]EW: early withdrawal.

[c]Completed by participant parent or guardian.

[d]ITQOL: Infant Toddler Quality of Life Questionnaire.

[e]Conducted by assessment therapist.

[f]COPM: Canadian Occupational Performance Measure.

[g]GAS: Goal Attainment Scaling.

[h]CHOP-INTEND: Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders.

[i]CHOP-INTEND used with nonindependent sitters and HFMSE used with independent sitters.

[j]HFMSE: Hammersmith Functional Motor Scale-Expanded.

[k]AIM: Acceptability of Intervention Measure.

[l]IAM: Intervention Appropriateness Measure.

[m]FIM: Feasibility of Intervention Measure.

Intervention Providers

The intervention uses 2 types of providers: assessment therapists and treatment therapists. Assessment therapists will complete the listed outcome measures at week 0, end of intervention or early withdrawal (week 12), and follow-up (week 24). Treatment therapists will plan and conduct the therapy sessions based on the COPM and GAS goals created by the assessment therapists. For a participant, the assessment and treatment therapists will be different to avoid bias.

The assessment and treatment therapists will be OTs and PTs with previous experience and training working with young children with SMA. Assessment therapists will complete the standardized training for the respective assessments. Assessment OTs will complete the Bayley Scale (all sections except the gross motor function), COPM, and GAS. Assessment PTs will complete the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) or Hammersmith Functional Motor Scale-Expanded (HFMSE), gross motor section of the Bayley Scale, COPM, and GAS.

Outcome Measures

Demographics Survey

This 15-item purposefully developed survey will capture participant characteristics (eg, age at intervention commencement [year and month], sex, parent report of genetic condition, therapies received, and timing or frequency).

Infant Toddler Quality of Life Questionnaire

The ITQOL (Infant Toddler Quality of Life Questionnaire) [37] comprises 103 items on 12 scales pertaining to the past 4 weeks, covering physical and psychosocial domains and the impact of child health on parents. Scales include physical functioning, growth and development, bodily pain, temperament or moods, general behavior, getting along, general health perception, parental-emotional, parental time, family activities, family cohesion, and change in health. Multi-item scales showed adequate internal consistency (Cronbach α=.81). Overall, 4 scales showed adequate (intraclass correlation; ICC ≥0.70; P<.01), 6 scales showed moderate (ICC=0.50-0.70; P<.01), and 1 scale had poor test-retest reliability [37].

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COPM Measure

The COPM [38,39] measures an individual's self-perception of occupational performance on self-care, productivity, and leisure and is used by OTs in initial assessments to set goals and plan treatment focusing on activities that an individual needs, wants, or is expected to do. The importance of activities is rated on a 10-point scale (1=not important at all to 10=extremely important). The individual selects the 5 most important activities, which are rated on a 10-point performance scale (1=not at all able to 10=able to perform extremely well) and for satisfaction (1=not at all satisfied to 10=extremely satisfied).

GAS Measure

GAS [40,41] will evaluate an individual's progress toward participant and family goals. Each scale is developed based on assessment and collaboration between the therapist and the participant and family. A 5-point scale, ranging from –2 to +2, is used. A numeric value is assigned to each level of performance. On the scale, 0 is used to represent the expected level of outcome, with +1 and +2 indicating greater than expected progress and –1 and –2 indicating less than expected progress.

CHOP-INTEND Measure

The CHOP-INTEND [42] evaluates the motor skills of individuals with SMA type I aged 3 months to 4 years or older over 16 items. Items are scored on a 4-point scale (0=no response, 1=partial level of response, 3=nearly full level of response, 4=complete level of response). The assessment has good internal consistency (Cronbach α>.70) and strong intrarater reliability (ICC=0.96). CHOP-INTEND will be used with participants who do not sit independently.

HFMSE Measure

The 33-item HFMSE [43] assesses the functional motor ability of individuals with SMA who are able to sit and walk using a 3-point scoring system (0=unable to perform, 1=performs with modification, adaptation, and compensation, 2=performs without modification, adaptation, and compensation). The HFMSE will be used with participants who are able to sit independently.

Bayley Scales of Infant and Toddler Development, 4th Edition

The Bayley Scale is a developmental assessment tool for diagnosing developmental delays in early childhood (16 days to 42 months) across 5 domains: cognitive, language, motor, social-emotional, and adaptive behavior. The entire Bayley Scale can take 30-70 minutes to administer, depending on the participant's age. The entire Bayley Scale will be completed at week 0, and only the motor scales will be completed at weeks 12 and 24.

Acceptability of Intervention Measure, Intervention Appropriateness Measure, Feasibility of Intervention Measure

The Acceptability of Intervention Measure (AIM), Intervention Appropriateness Measure (IAM), and Feasibility of Intervention Measure (FIM) [44] are each 4-item surveys to evaluate the acceptability, appropriateness, and feasibility of the intervention from a personal perspective using a 5-point Likert scale (1=completely disagree to 5=completely agree). Internal consistency (α) of the 3 measures ranged from .87 to .89, and they take less than 5 minutes each to complete.

Home Exercise Diary

This purposefully developed form will be completed by the participant's parent or guardian each time the home exercise program is completed. During the intervention period, the diary will be reviewed by the therapists weekly, and during the nonintervention period, a research team member will call the participant every 2 weeks to review the diary. For each time the home exercise program is completed, the participant will complete the intervention week, the day of the week (eg, Monday), OT and PT exercises completed, and any comments (ie, about the participant's mood, adverse events, and duration of the exercises). Additionally, the parent or guardian will indicate if any additional activities were completed.

Data Management

All assessment measures except the participant-facing measures (ie, demographics survey, ITQOL, AIM, IAM, and FIM) will be completed in hard copy. A trained research team member will input the data into Research Electronic Data Capture (REDCap) [45,46] forms for secure retention and ease of exportation and analysis. Participant-facing measures will be completed by parents or guardians electronically on REDCap.

Feasibility Indicators and Data Analysis

The trial's feasibility will be evaluated using process, resource, management, and scientific domains [33]. Specific feasibility indicators within the domains, their data management plan, and success criteria are described in Table 2.

Process indicators will examine key items to ensure the success of the trial. Recruitment rate, eligibility criteria, adherence rate, and retention rate data will be collected from recruitment logs. Results for these indicators will be reported as ratios, means, and frequencies. Questionnaire completion times and completion correctness will be reported as means and frequencies. Item scores for acceptability measures (AIM, FIM, and IAM) will be summed by each participant and reported as averages for each measure. Resource indicators will assess time and resource issues that could occur when running a definitive trial. Therapists will record session and documentation durations for all visits. These results will be presented as a ratio and compared to the success criteria. With the same data, session and documentation times will be compared to similar values in the literature as well as clinician reports. Last, protocol deviations will be reviewed by deductive content analysis to determine if protocol revisions are required. Management indicators will assess potential human and data management issues when running the trial and will be evaluated through deductive content analysis of completed measures and data analysis notes. Adverse events will be analyzed by deductive content analysis. Feasibility indicators will be compared to the success criteria, as appropriate.

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From a scientific standpoint, a preliminary examination of the intervention's effectiveness will be assessed through safety and efficacy. Participant demographics and medical history collected from the demographics survey will be summarized descriptively. Preliminary efficacy will be evaluated through descriptive statistics and within-subject change scores of intervention assessment measures (ie, ITQOL, CHOP-INTEND or HFMSE, Bayley, COPM, and GAS goals). No between-subject analysis will be completed due to the small sample size. Change scores will measure functional gains and losses during the intervention period (t_{12}-t_0), nonintervention period (t_{24}-t_{12}), and the entire trial (t_{24}-t_0) for each participant separately.

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Table 2. Feasibility indicators to measure the success of the twice-weekly outpatient intensive rehabilitation intervention for young children with spinal muscular atrophy treated with genetic-based therapies with data management (data collection methods and analysis) and a priori success criteria.

Feasibility indicator	Data management	Success criteria
Process		
Recruitment rates	• Ratio of enrolled participants vs approached potential participants; number screened and enrolled per month; and time from screening to enrollment to baseline visit	• ≥10% response rate from eligible participants [47]
Eligibility criteria	• Ratio of eligible vs screened participants	• >70% meet eligibility criteria
Adherence rates	• Therapist documentation (attendance at study visits) • Home exercise diary during intervention and nonintervention (weekly average completion rate of prescribed home exercise program)	• ≥75% attendance to therapy sessions[a] • At least three days per week
Retention rates	• Ratio of participants who successfully complete the study (including outcome measures) vs enrolled participants	• ≥70% retention of participants [48]
Questionnaires	• Participant-reported outcome measures (time to complete forms and correctly completed forms)	• Exploratory
Acceptability	• AIM[b], IAM[c], and FIM[d]	• ≥90% on the AIM, IAM, and FIM [49]
Resources		
Time	• Therapist documentation (ratio of actual vs estimated durations)	• Assessment: meets time prescribed in protocol (±5 min) • Documentation: ≤15 min
Implementation	• Therapist documentation (cost analysis of therapist time compared to standard care)	• Exploratory
Execution	• Protocol deviations (amount, frequency, and type)	• Exploratory
Management		
Materials	• Patient-facing materials and outcome measures (evaluate whether revisions are required)	• Exploratory
Data	• Data analysis notes (evaluate if additional data are required for efficacy analysis in a definitive trial)	• Exploratory
Scientific		
Safety and tolerability	• AE[e] and SAE[f] documentation (type and cause)	• Exploratory
Preliminary efficacy	• Efficacy (functional assessment change scores between t_0, t_{12}, and t_{24} time points for within-subject changes) • Sample size calculations for a larger definitive trial	• N/A[g]

[a]A total of 3 weeks of sessions will be permitted to be missed or conducted through video conferencing software over the course of the 12-week intervention period.

[b]AIM: Acceptability of Intervention Measure.

[c]IAM: Intervention Appropriateness Measure.

[d]FIM: Feasibility of Intervention Measure.

[e]AE: adverse event.

[f]SAE: serious adverse event.

[g]N/A: not applicable.

The sample size for a larger equivalence trial will be calculated [50]. Specifically, the trial will test whether the intervention (genetic-based therapy and the intervention) and standard treatment (genetic-based therapy only) are equally effective. With that, there are 2 null hypotheses:  and , where T=intervention, S=standard treatment, and δ=clinically admissible margin of equivalence. Using the information gained from the completed outcome measures, a primary end point will

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be confirmed. Calculations for continuous outcome measures by Zhong will be used:



Where N=size per group; z_x=standard normal deviation for 1- or 2-sided  and ; δ_0=clinically acceptable margin; and s^2=polled SD of both comparison groups. As per convention, α will be set at .05 and β will be set at .80. δ_0 will be calculated as the difference between the mean changes in the chosen primary end point for the current intervention (taken from this feasibility study) and typical change scores for the age-matched populations from the literature minus one.

Monitoring

A data safety monitoring board (DSMB) will be established to review and evaluate the accumulated study data for participant safety. The DSMB will function independently from the study investigators and have no direct involvement with study conduct. Any recommendations regarding the continuation, modification, or termination of the trial will be made to the study investigators based on the received reviews. A DSMB term of reference was prepared and is available upon request.

Adverse events or serious adverse events will be collected and reported by therapists and research personnel. The study doctors will assess the seriousness of adverse events or other unintended effects and will propose a management plan as required. Serious adverse events will be reported to the DSMB.

Ethical Considerations

This study has been approved by the Research Ethics Board at Holland Bloorview Kids Rehabilitation Hospital in Toronto, Canada (REB#0550). All participants, through a substitute decision-maker, will partake in an informed consent discussion and sign an informed consent form before being enrolled in this study.

Results

This project was funded in March 2022, and data will be collected between March 2023 and December 2023. Data analysis will occur between January 2024 and March 2024, with publication expected in the fall of 2024.

This feasibility trial will be considered successful if it meets the success criteria set for the feasibility indicators. Indicators of specific interest include all process indicators as well as time. Exploratory indicators will be reported. Pragmatically, the results of the feasibility trial will inform updates to the design of the intervention and the protocol, as well as the start-up of a definitive multisite trial.

Discussion

This nonrandomized pilot and feasibility trial aims to assess the feasibility of the twice-weekly outpatient rehabilitation intervention for young children with SMA treated with genetic-based therapies. The description of this protocol and the future results are poised to make several valuable contributions to the functional and motor capabilities of children with SMA.

First, this innovative study is one of the first of its kind and will provide insight into the therapy potential for young children with SMA treated with genetic-based therapies. With the approval of genetic-based therapies to treat individuals with SMA as well as the introduction of newborn screening across Canada within the past 5 years, children are being diagnosed and treated earlier in the disease course [15]. With these previously unheard-of functional opportunities and the lack of knowledge of the long-term efficacy and tolerability of genetic-based therapies, it is important for children with SMA treated with genetic-based therapies to receive appropriate rehabilitation therapy. The current SMA standards of care include recommendations for exercise therapy as well as PT and OT involvement in bracing, positioning, and equipment [3,25]. However, these recommendations were published before the widespread approval of genetic-based therapies, and therefore the efficacy of PT and OT treatment blocks in this population has yet to be explored. This protocol will be a first step toward establishing an evidence-based rehabilitation intervention therapy program for children with SMA treated with genetic-based therapies.

Additionally, previous studies and therapy recommendations for children with SMA identify therapies to maintain function [23,32,35,36,51]. However, the proposed outpatient rehabilitation intervention is hypothesized to increase function in participants in combination with genetic-based therapies.

While there are several promising outcomes to the proposed pilot and feasibility trial, it does have its limitations. For instance, the implementation of the nonrandomized study design will not yield definitive efficacy data at this time. Additionally, the nonrandomized study design will not enable the measurement of subgroup differences. With that, nonrandomized pilot studies are still an effective method to evaluate a novel intervention, such as the trial outlined in this protocol [52]. It is expected that this pilot and feasibility trial will provide important insight into both the feasibility of the intervention itself and a future definitive trial.

Challenges to the implementation and feasibility of the intervention are foreseen. Recruitment will be a challenge due to the rarity of the disease and the large recruitment area (ie, anywhere in the province of Ontario, Canada). However, it is expected that families will travel far distances to receive therapy sessions at no cost with therapists with expertise working with young children with SMA. Additionally, the long potential travel distances may impact retention, adherence, and protocol deviations. However, the protocol includes that 3 OT and PT sessions can be held on video conferencing software or be missed. This allows families and therapists to be flexible in the delivery of the sessions without encountering large amounts of protocol deviation. Last, adherence to the home exercise program, particularly during the nonintervention period, may be a challenge. In past clinical experiences, the clinical team has seen functional gains lost when home exercises were not completed after a therapy block. Therefore, a research team member will contact the family every 2 weeks during the

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nonintervention period to remind them of the importance of completing the home exercise program.

Overall, it is expected that when coupled with available genetic-based therapies, the consistent PT and OT provided as part of the proposed rehabilitation intervention will augment the functional gains being observed in this treated population. We aim for this feasibility trial to reflect the realities of participants and their families, as well as therapists and institutions that may deliver this intervention. In sharing this protocol, we hope to achieve widespread awareness of this new potential rehabilitation intervention with the future goal of making direct clinical impacts in the SMA community.

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Data Availability

The data sets generated during and/or analyzed during this study are available from the corresponding author on reasonable request. Further details can be provided by the authors to interested parties when the request is made.

Conflicts of Interest

None declared.

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Abbreviations

AIM: Acceptability of Intervention Measure
CHOP-INTEND: Children’s Hospital of Philadelphia Infant Test of Neuromuscular Disorders
CONSORT: Consolidated Standards of Reporting Trials
COPM: Canadian Occupational Performance Measure
DSMB: data safety monitoring board
FIM: Feasibility of Intervention Measure

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GAS: Goal Attainment Scaling
HFMSE: Hammersmith Functional Motor Scale-Expanded
IAM: Intervention Appropriateness Measure
ICC: intraclass correlation
ITQOL: Infant Toddler Quality of Life Questionnaire
OT: occupational therapy
PT: physiotherapy
REDCap: Research Electronic Data Capture
SMA: spinal muscular atrophy
SMN1: survival of motor neuron 1
SPIRIT: Standard Protocol Items—Recommendations for Interventional Trials
TIDieR: Template for Intervention Description and Replication

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Protocol

Moral Distress, Mental Health, and Risk and Resilience Factors Among Military Personnel Deployed to Long-Term Care Facilities During the COVID-19 Pandemic: Research Protocol and Participation Metrics

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Abstract

Background: The earliest days of the COVID-19 pandemic in Canada were marked by a significant surge in COVID-19 cases and COVID-19–related deaths among residents of long-term care facilities (LTCFs). As part of Canada's response to the COVID-19 pandemic, Canadian Armed Forces (CAF) personnel were mobilized for an initial emergency domestic deployment to the hardest-hit LTCFs (Operation LASER LTCF) to support the remaining civilian staff in ensuring the continued delivery of care to residents. Akin to what was observed following past CAF international humanitarian missions, there was an expected increased risk of exposure to multiple stressors that may be psychologically traumatic and potentially morally injurious in nature (ie, related to core values, eg, witnessing human suffering). Emerging data from health care workers exposed to the unprecedented medical challenges and dilemmas of the early pandemic stages also indicated that such experiences were associated with increased risk of adverse mental health outcomes.

Objective: This study aims to identify and quantify the individual-, group-, and organizational-level risk and resilience factors associated with moral distress, moral injury, and traditional mental health and well-being outcomes of Operation LASER LTCF CAF personnel. This paper aimed to document the methodology, implementation procedures, and participation metrics.

Methods: A multimethod research initiative was conducted consisting of 2 primary data collection studies (a quantitative survey and qualitative interviews). The quantitative arm was a complete enumeration survey with web-based, self-report questionnaires administered at 3 time points (3, 6, and 12 mo after deployment). The qualitative arm consisted of individual, web-based interviews with a focus on understanding the nuanced lived experiences of individuals participating in the Operation LASER LTCF deployment.

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Results: CAF personnel deployed to Operation LASER LTCF (N=2595) were invited to participate in the study. Data collection is now complete. Overall, of the 2595 deployed personnel, 1088 (41.93%), 582 (22.43%), and 497 (19.15%) responded to the survey at time point 1 (3 mo), time point 2 (6 mo), and time point 3 (12 mo) after deployment, respectively. The target sample size for the qualitative interviews was set at approximately 50 considering resourcing and data saturation. Interest in participating in qualitative interviews surpassed expectations, with >200 individuals expressing interest; this allowed for purposive sampling across key characteristics, including gender, rank, Operation LASER LTCF role, and province. In total, 53 interviews were conducted.

Conclusions: The data generated through this research have the potential to inform and promote better understanding of the well-being and mental health of Operation LASER LTCF personnel over time; identify general and Operation LASER LTCF–specific risk and protective factors; provide necessary support to the military personnel who served in this mission; and inform preparation and interventions for future missions, especially those more domestic and humanitarian in nature.

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KEYWORDS

mental health; military; Canadian Armed Forces; operational organization; logistics support; health care; moral distress; moral injury; deployment; risk factors; COVID-19; quarantine; readiness; well-being; resilience; long-term care facility; centre de soins de longue durée; survey; older adult; qualitative interviews; quantitative

Introduction

Background

As part of Canada's response to the COVID-19 pandemic, Canadian Armed Forces (CAF) personnel were deployed on Operation LASER to support various aspects of the civilian health care sector in addressing and mitigating the impact of the COVID-19 pandemic across Canada. The scope of the mission expanded as the pandemic progressed, with activities that included contact tracing, CAF personnel vaccinations, COVID-19 testing at land ports of entry, and the subsequent deployment of intensive care unit nurses in several Canadian provinces.

The earliest days of the pandemic were marked by a significant surge in COVID-19 cases and COVID-19–related deaths among long-term care facility (LTCF) residents. In Canada, 3% of COVID-19 cases and 43% of COVID-19–related deaths occurred in LTCF residents, primarily in the provinces of Ontario and Québec [1]. The civilian staff were also falling ill with COVID-19 in high numbers and were unable to adequately mitigate the unprecedented challenges brought upon by the pandemic. Hence, on April 15, 2020, the CAF received a request for assistance to support the provision of care to residents of select LTCFs (also known as *centres d'hébergement et de soins de longue durée*) in the provinces of Québec and Ontario [2].

As part of this initial Operation LASER response, which occurred between April 2020 and July 2020, involved CAF personnel (ie, medical and support personnel, as well as command teams) were deployed to support the hardest-hit LTCFs: 47 *centres d'hébergement et de soins de longue durée* in Québec and 7 LTCFs in Ontario (all located in the Greater Toronto Area). The goal of this initial emergency deployment, hereafter referred to as *Operation LASER LTCF*, was to support the existing civilian staff in ensuring the safety of residents, maintain adequate staffing, and assist with infection control. The dire circumstances experienced in certain LTCFs were reported by the media and in CAF reports [3,4]. Similarly, anecdotal information was provided to our research team by CAF leadership.

These various reports highlighted that personnel deployed in support of the LTCFs may be exposed to multiple stressors that may be psychologically traumatic and potentially morally injurious (ie, related to important values) in nature (eg, witnessing human suffering); this is akin to what was observed in past CAF international humanitarian missions and recent experiences of health care workers (ie, medical challenges and dilemmas) during the early stages of the pandemic. More uniquely to Operation LASER, especially in the earliest days of the crisis, the COVID-19 pandemic posed a serious health and economic threat to people in Canada, not to people in a far-off land. As such, it held greater implications for the loved ones of Operation LASER personnel than perhaps any other domestic mission to date. Moreover, understanding concerning the lethality and transmissibility of the virus was unfolding and being updated on an almost daily basis at that time. Finally, the deployment was focused on assisting the most sick and vulnerable Canadian older adult patients and residents of LTCFs, a population that even seasoned CAF medical personnel were largely unfamiliar with. This combination of traditional and new stressors meant that the initial Operation LASER deployment was unique in many ways. Drawing on previous literature, such psychologically traumatic and morally injurious stressors may increase individuals' risk of adverse mental health outcomes such as posttraumatic stress disorder (PTSD), depression, and moral injury [5-9].

Previous deployments where CAF personnel were exposed to such psychological stressors were typically international, which came with inherent logistical challenges related to implementing timely, comprehensive, and secure research data collection [10]. These are typically overcome by a rigorous chain of command that allows for direct and efficient communication between researchers and the military chain of command. Although Operation LASER was a domestic deployment, the same challenges were encountered and mitigated by the CAF Surgeon General, Canadian Joint Operations Command (CJOC) chain

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of command, and the Department of National Defence (DND). Understanding the challenges facing personnel in this deployment, the Surgeon General and Chief of Military Personnel, with the approval and facilitation of CJOC, requested research investigating the individual-, group-, and organizational-level risks, resilience factors, and mental health outcomes of Operation LASER LTCF personnel. In response, a multiorganizational collaborative Operation LASER research team was established to comprehensively capture and better understand the impact of this deployment on the well-being of Operation LASER LTCF personnel.

The Structure of the Initial Operation LASER LTCF Deployment

Operation LASER LTCF personnel were typically divided into teams comprising 1 senior medical authority and a number of medical workers and support personnel. They answered to various command teams from CJOC and Canadian Forces Health Services Group (CF H Svcs Gp), as well as Land Force Command. The total number of serving military personnel ranged from 14 to 60 per facility, and they liaised with and supported the civilian medical and administrative staff on-site. In accordance with provincial health care regulations, their responsibilities included accompanying and assisting residents with daily tasks (eg, building and personal hygiene and feeding), preparing and distributing medical products, preparing meals, and maintaining medical and nonmedical equipment. To limit the potential spread of COVID-19 to their social networks, most Operation LASER LTCF personnel stayed in hotels for the duration of their deployment. Through initial discussions with CJOC, CF H Svcs Gp, and Land Force Command, the research team identified 4 overarching duty types: group 1 (Operation LASER 1) comprised medical and health care personnel who worked inside the LTCFs, group 2 (Operation LASER 2) comprised nonclinical personnel who worked inside the LTCFs (ie, provided support to clinical personnel inside the LTCFs), group 3 (Operation LASER 3) comprised nonclinical personnel who did not enter LTCFs (eg, outside general duties), and group 4 (Operation LASER 4) comprised personnel who provided support roles involved in Operation LASER (eg, Headquarters or Command, support, resupply, Company Quarters, Military Police, and clinical leadership not embedded inside the LTCFs). Before deploying to the LTCFs, Operation LASER LTCF personnel received medical briefings and were trained to use appropriate personal protective equipment (PPE) according to the level of protection required for the tasks performed or depending on the availability of the material, keeping in mind the quickness of the CAF response to the pandemic. They also received training on the physical needs and psychological and spiritual reactions that might be experienced by personnel in the context of their Operation LASER LTCF work and ways to maintain resilience and well-being.

Most of the Operation LASER LTCF deployment occurred between April 20, 2020, and June 26, 2020, for Québec and between April 27, 2020, and July 3, 2020, for Ontario [2], although many military personnel saw their engagement continue until August 31, 2020. However, germane to the study and this paper, at the time of the study protocol development (between April 2020 and May 2020), the situation was still unfolding, and certain aspects of Operation LASER LTCF were still unknown or in flux. This presented the research team with particular challenges in identifying the optimal study design for this initiative, all under tight time frames (ie, because of incomplete awareness of Operation LASER LTCF details and changes to Operation LASER LTCF parameters that were assumed to be static; for more information on specific challenges and lessons learned, refer to the study by Fikretoglu et al [11]). For instance, the deployment start date and end date were not identical for all personnel; start and end dates depended on LTCF location, and staffing requirements may have fluctuated across time (requiring reallocation of personnel to more than one Operation LASER role). Following deployment, Operation LASER LTCF personnel should have participated in a 3-day decompression session, which included additional resilience training; they then should have undergone a 14-day isolation period. However, reports from CJOC and CF H Svcs Gp indicated that the redeployment processes were not consistent across Operation LASER LTCF personnel in different roles and LTCFs. These nuances required careful data collection, protocol adjustments from the first to the third iteration of the web-based survey, and analytical considerations throughout to allow for the most accurate characterization of the sample.

Risk and Resilience Factors and Mental Health Outcomes in Military Personnel

There is extensive research enumerating the factors that may affect short- and long-term psychological well-being and mental health outcomes following exposure to psychological trauma [12,13]. We approached the research questions by applying and testing key constructs from previous literature to the Operation LASER LTCF context and integrating them with the emerging literature on moral distress and injury. For instance, certain personal background characteristics, health status variables, and occupational roles may place military personnel at greater risk of experiencing negative reactions following Operation LASER LTCF [7,14,15]—those with prior trauma or preexisting physical or mental health conditions, those who become infected and enter extended self-isolation and quarantine, those with lower income, visible minority groups, and women may be at greater risk of adverse mental health outcomes [13]. In addition, individual-level factors such as exposure to stressful deployment experiences and maladaptive coping styles may also be associated with poorer outcomes [7,16].

Regarding stressful deployment experiences, we expected that, although some of these would be organizationally related and be commonly experienced in any deployment regardless of its nature (eg, logistical issues), other Operation LASER LTCF–specific experiences would be linked to fundamental values that an individual holds dear (eg, the need to provide care to the sick and vulnerable). Thus, we anticipated that at least some Operation LASER LTCF personnel would encounter morally laden experiences that could engender significant amounts of what is termed moral distress. Such moral distress can lead to moral injury (ie, profound and lingering psychological distress that is particularly associated with intense value conflicts [17]) and has been demonstrated to be a risk factor for depression and PTSD in CAF personnel [7,18]. Recent research with health care workers exposed to morally distressing

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experiences during the COVID-19 pandemic highlights the strong association between moral distress and adverse mental health outcomes, including depressive symptoms and burnout [19]. The increased recognition of moral injury as a clinically important construct [20] and the challenges it poses during help seeking and treatment [21] further underscore the necessity to understand this issue and identify opportunities for early intervention, prevention, and support.

Other research suggests that many psychosocial dimensions at the social, unit, leader, and organizational levels may also influence the effect of stressful experiences on the well-being of military personnel. Specifically, findings sourced from previous DND Human Dimensions of Operations surveys have demonstrated that poor social support, as well as less trust in units and leaders and lower feelings of relatedness to others on the mission, are more likely to be associated with poorer psychological well-being and mental health outcomes (Michaud K, unpublished data, December 2021). Past research with CAF personnel has documented gaps in mental health service use [22,23] and several unique barriers to help seeking among CAF members [24]. Moreover, the literature also demonstrates that military personnel with prior experience, training, and preparation (both for crisis work and psychological reactions) and adequate social support from personal and organizational sources (during and after deployment) fare better after stressful experiences [12,25]. Finally, those who are able to derive a sense of meaning and accomplishment as a result of the mission may be better protected from negative reactions and more likely to experience positive outcomes such as posttraumatic growth [12,25].

Given the many stressors that appear inherent to the Operation LASER LTCF deployment, lessons concerning risk and protective factors and effective preparation to promote psychological well-being following crisis work needed to be captured.

Research Objectives

The research objectives were as follows:

- Identify and quantify the individual-, group-, and organizational-level risk and resilience factors associated with moral distress, moral injury, and traditional mental health and well-being outcomes of Operation LASER LTCF CAF personnel and, to the extent possible, determine any changes that may occur over time.
- Gain a lived experience perspective through in-depth discussions with Operation LASER LTCF participants to develop a deeper understanding of their deployment experiences. Primary areas of exploration included views regarding particular risk (eg, Operation LASER LTCF COVID-19–specific stressors) and resilience (eg, predeployment Operation LASER LTCF training, prior CAF resilience training, and adaptive coping strategies) factors and the effects of these on mental health, well-being, and recovery.
- Identify lessons that can be used to inform the decisions of senior commanders in the event of similar future deployments.

In this paper, we document the protocol for this multimethod initiative (ie, composed of quantitative surveys and qualitative interviews) [26]. Specifically, we report on the study design, sampling details, measures used, sampling weight creation, and study implementation procedures. Considering that the data collection is complete, we also report on participation profiles and metrics, which provide insights into the nature of the sample and may be useful in guiding the protocol development of future research in this field and population.

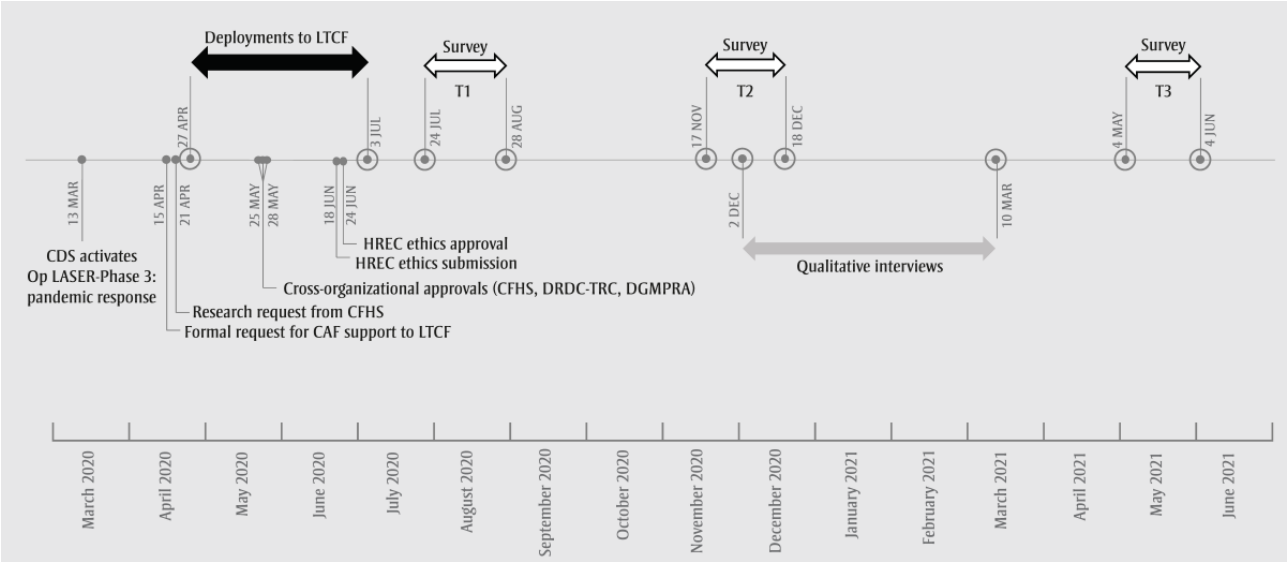
Methods

Study Design

This multimethod research initiative comprised 2 interrelated arms: a quantitative arm (ie, survey) and a qualitative arm (ie, interviews). The quantitative arm was a complete enumeration (ie, census) survey (ie, email invitations to participate were sent to all Operation LASER LTCF personnel) with self-report questionnaires administered remotely at 3 time points (referred to as *Survey*), allowing for cross-sectional and, for a subset of respondents, longitudinal analyses. The qualitative arm was a collection of in-depth, individual interviews with a focus on understanding the nuanced lived experiences of individuals taking part in the Operation LASER LTCF deployment (referred to as *Interviews*). Figure 1 shows the deployment, administrative approval, and data collection timelines (adapted with permission from the study by Fikretoglu et al [11]). No remuneration was provided for research participation.

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Figure 1. Timeline of Operation LASER long-term care facility (LTCF) deployment, approvals, and data collection. CAF: Canadian Armed Forces; CDS: Chief of Defence Staff; CFHS: Canadian Forces Health Services; DGMPRA: Director General Military Personnel Research and Analysis; DRDC-TRC: Defence Research and Development Canada–Toronto Research Centre; HREC: Human Research Ethics Committee; T1: time point 1; T2: time point 2; T3: time point 3.



Survey

Participants

The target population for this survey was the entire cohort of CAF personnel deployed to Ontario and Québec LTCFs as part of Operation LASER LTCF. A list of the names and email addresses of 2595 CAF personnel, representing the deployed cohort at the time (June 26, 2020), was provided to the research team; military personnel on this list were eligible for participation in the study. There were no exclusion criteria.

Recruitment

An administrative manifest of all Operation LASER LTCF personnel deployed to Ontario and Québec as of June 26, 2020 (provided by CJOC), was used to establish the sample frame and disseminate survey invitations. The administrative list contained names, contact email addresses, military rank, and deployment location (ie, Québec or Ontario) for all CAF personnel deployed to Operation LASER LTCF. Considering that many Operation LASER LTCF personnel were reservists (who may not always have immediate access to internal Defence Wide Area Network [DWAN] email accounts), the list contained a mix of personal or DWAN addresses. As the survey invitation was sent to all individuals intended to be deployed to Operation LASER LTCF, survey sampling (eg, stratified random sampling) was not required or implemented. All personnel with valid contact information received an invitation email written in English and French at each data collection time point sent from the dedicated positional Operation LASER LTCF research project DWAN email address. Emails were individually and personally addressed (ie, rank and name) and briefly outlined the research objectives, methods, participant rights, risks, risk mitigation measures, benefits of the study, and relevant contact information. If individuals wished to participate, they were able to access the web-based questionnaire via individualized hyperlinks (directed to either the French or English version of the survey), which were accessible through the personal or DWAN email account. At each time point, reminder emails were sent to all participants who had not yet completed the survey for that specific time point. Each individual received a maximum of 2 email reminders per time point, spaced approximately 2 weeks apart.

Survey Administration Time Points

Survey invitations were sent on July 24, 2020; November 17, 2020; and May 4, 2021, for time point 1 (T1; 3 mo), time point 2 (T2; 6 mo), and time point 3 (T3; 12 mo), respectively. The respective data collection windows for the survey were July 24, 2020, to August 28, 2020; November 17, 2020, to December 18, 2020; and May 4, 2021, to June 4, 2021.

Measures

Overview

An overview of the measures included in the survey is presented in Table 1. To reduce respondent burden, branching logic was implemented where appropriate (ie, displaying relevant and hiding irrelevant sections of the survey based on previous responses). Similarly, not all sections were necessary to repeat at follow-up sessions (ie, demographic information and predeployment training). Most of the included measures had been validated in both French and English. Scales were adapted only in cases in which the item wording was not appropriate for the CAF or Operation LASER LTCF context (see the following sections).

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Table 1. Operation LASER quantitative measure overview.

Assessment	Domain	Items, n	Baseline	Follow-up
Sociodemographic and military characteristics	Sociodemographics	7	✓	✓ (reduced)
Deployment characteristics[a]	Deployment characteristics	5	✓	✓
Predeployment training satisfaction[a]	Training	16	✓	—[b]
Prior CAF[c] mental health or resilience training[a]	Training	8	✓	—
Personal protective equipment use[a]	Training	17	✓	—
Postdeployment satisfaction[a]	—	5	✓	—
C-PIQ[d]	COVID-19 impact	16	✓	—
Stressful experiences				
Deployment stressors[a]	Stressful experiences	9	✓	✓ (reduced)
MMD-LASER[a,e]	Moral distress	18	✓	✓ (expanded for T2 and T3)
Mental health				
PHQ-9[f]	Depression symptoms	9	✓	✓
GAD-7[g]	Anxiety symptoms	7	✓	✓
PCL-5[h]	PTSD[i] symptoms	21	✓	✓
K-10[j]	General psychological distress	10	✓	✓
MIOS[k]	Moral injury expression	40	✓	✓ (reduced to 14 items)
Positive moral emotion outcomes[a]	Positive moral emotions	7	✓	✓
Mental health service use	Mental health service use	3	—	✓
Barriers to mental health service use	Barriers to mental health service use	23	—	✓ (expanded)
Coping and social support				
COPE[l] Inventory (brief version)	Coping styles	12	✓	✓
Social support sources[a]	—	7	✓	✓
Human Dimensions o f Operations				
Meaning scale[m]	Meaningfulness of work	3	✓	—
Morale[m]	Motivation and enthusiasm	6	✓	—
Relatedness[m]	Peer relatedness	7	✓	—
Trust in teams[m]	Trust	9	✓	—
Trust in leadership[m]	Trust	9	✓	—

[a]Scale or items created specifically for Operation LASER.
[b]Not collected.
[c]CAF: Canadian Armed Forces.
[d]C-PIQ: Complementary and Integrative Research Pandemic Impact Questionnaire.
[e]MMD-LASER: Measure of Moral Distress for Healthcare Professionals adapted to Operation LASER.
[f]PHQ-9: Patient Health Questionnaire–9.
[g]GAD-7: Generalized Anxiety Disorder Scale.
[h]PCL-5: Posttraumatic Stress Disorder Checklist for the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.
[i]PTSD: posttraumatic stress disorder.
[j]K-10: Kessler Psychological Distress Scale.
[k]MIOS: Moral Injury Outcome Scale.
[l]COPE: Coping Orientation to Problems Experienced.

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[m]Self-report assessment is a component of the Director General Military Personnel Research and Analysis (DGMPRA) Human Dimensions of Operations (HDO) data collection battery. Assessments were validated by the DGMPRA and designed specifically for administration to CAF personnel in HDO research.

Sociodemographic and Military Background

Information on age, gender, educational background, family status (ie, marital status, living arrangements, and dependents), military rank, length of military service, and component (ie, regular or reserve) was collected. These variables were selected based on previous research identifying them as potential predictors of psychological outcomes.

Operation LASER LTCF Roles and Duties

Participants were asked about the start and end dates of their Operation LASER LTCF deployment, military occupation (included only at T3), and the closest researcher-derived operational group they belonged to (Operation LASER 1, 2, 3, or 4; *other*; or *no role assigned*; the *no role assigned* option was available only at T3).

Predeployment Training and Postdeployment Decompression Satisfaction

Satisfaction with various aspects of predeployment training (ie, both for deployment duties and deployment psychological reactions) was assessed using 16 items that asked participants about their agreement with the following statement—*I am satisfied with my training for:*—for each of the 16 training components on a 7-point scale (ie, 1=*Strongly disagree*; 7=*Strongly agree*). A similar set of 5 questions assessed satisfaction with postdeployment training using an identical response format.

Prior CAF Mental Health or Resilience Training Questions

Exposure to and perceived utility of prior resilience training was assessed using items adapted from the 2013 Canadian Forces Mental Health Survey (CFMHS), a cross-sectional epidemiological survey conducted by Statistics Canada on behalf of the DND [27]. Items assessing the perceived utility of the training were adapted to be anchored to the Operation LASER LTCF context.

Coping

Various adaptive coping strategies were assessed using 16 items carefully selected from the well-established Brief Coping Orientation to Problems Experienced [28] based on the maximum relevance for Operation LASER LTCF as determined a priori by subject matter experts (SMEs). The selected items assess active coping, positive reframing, acceptance, use of emotional support, use of instrumental support, denial, substance use, and self-blame coping strategies. The following subscales were excluded: humor, venting, behavioral distraction, religion, behavioral disengagement, and self-distraction.

Social Support

Social support from various sources, including family, friends, employers, medical staff, religious or spiritual advisors, strangers, and online support groups, was assessed using a matrix of 7 items adapted from multiple sources, including the 2013 CFMHS [27]. Participants indicated their agreement with the following statement—*I received support from:*—on a 7-point scale (ie, 1=*Strongly disagree*; 7=*Strongly agree*).

Exposure to General Deployment Stressors

Exposure and perceived stress in response to general deployment stressors were captured using 9 items drawn from prior Human Dimensions of Operations surveys and from recent CAF Operation LASER LTCF reports [3,4] (Multimedia Appendix 1). Respondents indicated how stressed they felt in response to each of the situations (at the time of exposure) based on a 5-point scale (0=*No stress*; 4=*Extreme stress*, in addition to *N/A*=no exposure). The items were related to logistic support, accommodations, problems with infection control, lack of equipment and medication problems (eg, PPE), lack of civilian personnel, communication problems, absenteeism by civilian employees, and leadership or management issues. Participants were directed to indicate their degree of stress when the stressor was present (ie, at the time of deployment). Following T1 and T2 data collection, 3 items were excluded at T3 (ie, *problems with infection control*, *lack of equipment and medication problems (eg, PPE)*, and *civilian employee's absenteeism problem*) because of redundancy and overlap with moral distress items (see the following section).

Exposure to Morally Distressing Experiences in Operation LASER LTCF

To assess the potential for moral challenges and distress in Operation LASER LTCF, we adapted the Measure of Moral Distress for Healthcare Professionals (MMD-HP [29]) for the context of Operation LASER LTCF (the adapted version was named MMD-HP adapted to Operation LASER [MMD-LASER]; Multimedia Appendix 2). Accordingly, participants were asked to rate how distressed they currently felt according to a 4-point scale in response to 20 moral situations adapted from the MMD-HP and via input from Operation LASER LTCF SMEs (eg, leadership, chaplains, and reports from deployed personnel). Scale modifications included reducing the number of items to display only those situations that may be encountered during Operation LASER LTCF and only measuring the degree of distress to reduce respondent burden (the original MMD-HP scale captured both frequency and distress). Participants were instructed to rate their degree of moral distress on a 4-point scale (ie, 1=*No moral distress*; 4=*Extreme moral distress*, in addition to *N/A=I have not experienced this situation*) for each of the potentially morally distressing experiences. The English-language MMD-LASER and the translated French version were not psychometrically tested at the time of survey administration. However, considering the formative model of measurement for this type of scale, ensuring that the scale contains a breadth of relevant exposures through rigorous consultation with Operation LASER LTCF SMEs may be a better indicator of scale quality than common quantitative psychometrics (eg, factor analysis and indexes of model fit), which are more appropriate for reflective measurement models [30].

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Meaning

Grounded in theoretical understanding of psychological empowerment in the workplace [31], participants rated the perceived meaning of their duties during the operation using 3 statements on a 5-point scale (ie, 1=*Strongly disagree*; 5=*Strongly agree*, eg, *the work I do is very important to me*).

Relatedness

Relatedness refers to the sense of belonging a person experiences with others in the workplace [32]. Such attachments lead to a sense of being supported and can reduce the adverse effects of workplace stressors on mental health. Participants were asked to assess the extent to which they felt connected to the people they worked with by rating their level of agreement with 7 statements pertaining to perceived social support using a 5-point scale (ie, 1=*Totally disagree*; 5=*Totally agree*, eg, *at work, I can talk with people about things that really matter to me*).

Trust in Teams and Trust in Leadership

Participants were asked to rate their trust in their peers or team (eg, *My teammates were capable of doing their job*) and immediate leaders (eg, *My leader performed his/her job well*) [33] each using 9 items rated on a 5-point scale (ie, 1=*Completely disagree*; 5=*Completely agree*).

Morale

Participants were asked to rate their level of agreement with 6 statements pertaining to their morale and enthusiasm for accomplishing the objectives of Operation LASER LTCF using a 5-point scale (ie, 1=*Very low*; 5=*Very high*, eg, [Please rate] *your level of motivation*) [34].

Psychological Distress

Psychological distress was assessed using a self-report measure, the Kessler Psychological Distress Scale (K-10) [35]. The K-10 is a 10-item questionnaire assessing nervousness, agitation, fatigue, and negative affect. Good internal consistency (Cronbach α=.89-.92) and construct validity of the K-10 have been established in general population and military samples [35,36]. The French version of the K-10 has also shown good reliability (Cronbach α=.84) and validity [37].

Anxiety

The Generalized Anxiety Disorder Scale (GAD-7) [38] was used as a measure of anxiety. The GAD-7 is a 1-factor, 7-item self-report questionnaire that has demonstrated good internal consistency (Cronbach α=.89) and validity in both general population and primary care samples [39-41]. The French version of the GAD-7 has demonstrated good reliability (Cronbach α=.86) in a general population sample of French Canadians [42].

Depression

Severity of current depressive symptoms (ie, past 2 wk) was assessed using the Patient Health Questionnaire–9 (PHQ-9) [38]. The PHQ-9 is a validated and widely used brief, single-factor, 9-item self-report questionnaire with well-established reliability, validity, and sensitivity [43-45]. The French version of the PHQ-9 has demonstrated good internal consistency (Cronbach α=.83) [42] that is comparable with that of the original instrument.

Posttraumatic Stress Symptoms

Posttraumatic stress symptoms were assessed using the most commonly used self-report instrument for research purposes, the 20-item PTSD Checklist [46], which is based on the most recent conceptualization included in the Diagnostic and Statistical Manual of Mental Disorders [47]. A French-Canadian version has also undergone validation [48]. A new item was added at the end to determine whether the reported symptoms were related to or exacerbated by Operation LASER LTCF.

Moral Injury

Moral injury expression was assessed using the 14-item Moral Injury Outcome Scale (MIOS) self-report questionnaire [49]. To date, assessing moral injury has been a significant challenge because of the lack of well-conceptualized measures [50,51]. To address this gap, the MIOS was developed by an international consortium of leading experts in moral injury (across the United States, United Kingdom, Israel, Canada, and Australia). On the basis of the most distressing, potentially morally injurious event, participants were asked to indicate whether they would agree or disagree with statements that capture 6 domains: alterations in self-perception (eg, *my actions don't fit with who I thought I was*), alterations in moral thinking (eg, *I have trouble seeing goodness in others*), social impacts (eg, *I feel rejected by people*), self-harming and self-sabotaging behaviors (eg, *I keep myself from having success*), emotional aftermath (eg, *I feel guilty*), and beliefs about life meaning and purpose (eg, *I lost a sense of meaning in life*). The MIOS has additional questions that further characterize the morally injurious event that the responses were based on. The version of the MIOS that was included in this study was a nonreduced 34-item version of the scale; scale validation on veteran samples has indicated a 14-item, 2-factor structure that will be used for scoring [49]. The French version of the MIOS has not yet been cross-validated.

Positive Reactions to Morally Challenging Situations

Haidt [52] has also suggested that, in addition to negative reactions such as moral injury, a number of positive reactions regarding oneself or others can result following the encounter of moral situations. As no validated measure exists for this construct, we created 7 items based on the description by Haidt [52], for instance, feeling pride in oneself or having faith in the goodness of humanity. Respondents were asked to indicate their agreement on a 5-point scale (ie, 0=*Strongly disagree*; 4=*Strongly agree*, eg, *I feel a sense of honour*) as to whether each of the statements characterized their reaction in the past month to their Operation LASER LTCF experience. This measure is currently not validated in English or French.

Posttraumatic Growth

Posttraumatic growth was assessed using 5 items drawn from the Posttraumatic Growth Inventory [53]. These items were selected to reflect the 5 factors assessed by the Posttraumatic Growth Inventory: stronger relationships, new possibilities, identification of personal strengths, spiritual change, and increased appreciation of life.

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Perceived Need for Care

Participants were asked to indicate their subjective need for mental health care using a single, dichotomous self-report item adapted from the Canadian Community Health Survey [54] and the 2013 CFMHS [27] by Statistics Canada, which asked whether help for mental health problems (including emotions, mental health, or use of alcohol or drugs) was needed at any point since the start of Operation LASER LTCF.

Mental Health Service Use

A total of 3 items were taken from the 2013 CFMHS [27] to assess mental health service use at T2 and T3. The first item assessed access to formal and informal mental health support, and 2 follow-up items asked specifically about the Canadian Forces Member Assistance Program and web-based resources.

Barriers to Mental Health Service Use

Individuals may fail to seek care because of a denial of the need for treatment or because of perceived barriers to care [55]. Barriers to mental health care were measured using an 8-factor, self-report questionnaire developed by the Director General Military Personnel Research and Analysis (DGMPRA) in both French and English for a prior research project (Born, J, unpublished data, October 2021). Barriers to mental health care were explored using 29 items from the Operation LASER LTCF survey. A subset of 21 items was derived from the original 8-factor Barriers to Access to Care Evaluation, a 52-item scale that has demonstrated good internal consistency (Cronbach α=.86-.97) and validity (all factors predicted intention to seek care, and items are loaded in a theoretically logical manner) in a sample of CF H Svcs Gp personnel [24]. The abbreviated scale included 2 to 3 items per factor (8 factors in total: knowledge and ability to access care, organizational and social support, staffing and workload resources, concerns about privacy, alternative treatment options [eg, intention to self-treat], health care provider identity, conflict with career goals, and discomfort accessing care at work) selected from the larger Barriers to Access to Care Evaluation scale based on item factor loading scores, correlation of new factors with the original scale factor (r>0.90), and completeness of the factor's content while maximizing both internal consistency and validity within the original sample of CF H Svcs Gp personnel. In addition, 3 new items were included in the survey to explore concerns about moral discomfort (eg, *Not comfortable discussing experiences where I felt I/others could/should have done more/acted differently*), 3 new items were added to explore revisiting trauma (eg, *I did not want to revisit stressful or traumatic experiences that would make me feel distressed*), 1 new item was added to explore quality of care (eg, *I did not have access to quality care*), and 1 item was added to explore past experiences (eg, *I have had a negative experience getting help in the past*) as barriers to mental health service use. Barriers to mental health service use were assessed at T2 and T3 using a 7-point scale rating agreement (ie, −3=*Strongly disagree* to +3=*Strongly agree*). The text of the chosen items was modified to distinguish between barriers experienced in the Operation LASER LTCF context for those with a perceived need for care and hypothetical barriers for those without a perceived need. At this point, neither the French nor the English version of the scale have been fully validated; nevertheless, it represents the only applicable measure currently available.

Survey Programing and Presentation

The survey was programmed in Snap Surveys (Snap Surveys Ltd [56]), a web-based survey platform that adheres to the Government of Canada's quantitative research security policy. Individualized survey hyperlinks were given to each participant and were uniquely linked to each respondent's email address; the web-based survey platform linked and stored contact information and a survey ID number separately from survey research data. This procedure preserved the deidentification of respondents while allowing for the linkage of their data across questionnaire administrations (ie, across different time points).

The survey began with a question that asked participants to select their preferred language (materials were available in both official languages of Canada [ie, English and French]). Once their preferred language was selected, an information page was displayed that reviewed the instructions, aims of the study, participant rights, and confidentiality. This was followed by questions that assessed demographics, prior training (Operation LASER LTCF–specific training for deployment duties and for psychological reactions, as well as prior resilience training), exposure to stressful experiences, moral injury, risk and resilience, and psychological health outcomes. The last section of the survey thanked respondents for their participation, informed them of the opportunity to volunteer for interviews (ie, interview study), and provided a list of available CAF mental health resources (from the CAF Directorate of Mental Health).

Review of survey content for relevance and order of presentation of various measures, dry-run completion for timings (to estimate respondent burden), and proofreading were conducted by internal research team members, CAF members either deployed to or familiar with Operation LASER LTCF, and carefully selected DND SMEs.

Data Analysis Plan

Survey Weight Generation

Depending on the patterns of nonresponse, certain demographic or military characteristics could be under- or overrepresented in the final sample. Estimates produced using the final sample without any weight adjustment would be representative of the sample itself but not necessarily of the source population. To reduce nonresponse bias and improve the representativeness of the study findings to the source population, we generated survey weights based on available sociodemographic and military characteristics of the source population (see the *Data Linkage* section). A total of 5 characteristics were available for the source population: age, gender, force type, rank, and province deployed. Given our limited sample size, we could not conduct poststratification using all 5 weighting factors. To maximize the effect of using weights to adjust for nonresponse bias, we combined poststratification and propensity score inverse weighting in generating our survey weights [57]. We first used propensity score inverse weighting with all 5 weighting factors included in a binary logistic regression model predicting response at each time point. Given the sample size, the interaction terms of the weighting factors were not included.

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For each respondent, a weight was created as the inverse of the propensity score of responding with the sum of the weights equal to the sample size of the source population. The second step was to poststratify weights from the first step based on age and gender information. A total of 4 cells were created, and weight adjustment was used for each participant according to which cell the participant fell into. For each cell, the weight adjustment factor was calculated as the ratio of the sum of the weights from the first step to the sample size of the source population in that cell. This step ensured that the weighted sample had the same distribution in terms of age and gender as the source population. The third step was to apply a weight adjustment to reflect the original sample size at each time point. This step served to avoid artificially inflating the sample size while preserving the representativeness of the source population. The last step was to give participants with missing information in the 5 weighting factors a weight of 1 (2.7% of the source population). This step allowed for keeping these participants in the data analysis in the absence of information by adjusting for their response bias. Analyses with the application of the generated survey weights are expected to provide estimates that are statistically adjusted to reflect key source population parameters, making the results generalizable to the source population. Using the same process, an alternative set of survey weights was generated based on a sample (981/1088, 90.17% at T1; 445/582, 76.5% at T2; and 403/497, 81.1% at T3) where the definition of a partial responder had a higher threshold for completion (ie, at least 1 section answered that related to a study outcome, defined as any of the assessments following Operation LASER LTCF Roles and Duties [see the *Measures* section for survey order]). This approach treated early *break-off* participants as unit nonresponders, similar to previously published guidelines [58]. A sensitivity analysis will be conducted to assess the effect of using different samples for weight generation on the study findings.

Data Linkage

To compute sample weights for source population representativeness, additional demographic variables (ie, date of birth, gender, force type, years of service, Operation LASER LTCF role, time in mission, occupation, unit name, deployment start date, and deployment end date) were required. In early March 2021, a Military ad hoc request was submitted to the office of the Assistant Deputy Minister (Information Management) to provide these additional variables, as well as variables for data linkage (ie, service number [SN], first name and last name), for all CAF personnel who were deployed on Operation LASER LTCF between April 1, 2020, and August 30, 2020. Typically, a unique identifier variable (ie, SN) would be used to link datasets; however, although SNs were provided in the ad hoc administrative file for all members, SNs were missing for 32% of members from the original administrative list. To confidently match as many members from the administrative list as possible, a sequence of automated and manual matching iterations was completed on the available identifiers, resulting in a total of 2536 (97.77% of the sample linked to administrative data) confirmed matches of 2595 possible matches. This allowed for a fairly accurate computation of sample weights for further weighted analyses.

Careless Responses

Checks for careless responders at each time point were conducted using a combination of post hoc methods following recommendations by Meade and Craig [59]. The *careless* R package (R Foundation for Statistical Computing) [60] was used to assist in computing carelessness indexes. Specifically, indexes included longest identical sequence, average identical sequence, intraindividual response variability split across 5 equal sections of the survey (starting with MMD-LASER, see the following rationale), psychometric synonym index, and Mahalanobis distance (for more information, see the study by Meade and Craig [59]). We avoided calculating carelessness indexes in sections where conditional question presentation (ie, display logic) was common (eg, training satisfaction and deployment details); as such, all scales including and following the MMD-LASER were used in the calculation of the indexes. These indexes were mapped to response times to identify individuals with unusual response patterns (ie, very short completion times in combination with significant outlier values [–2.5-+2.5 SD] on 1 or more of the carelessness indexes). The responses of these individuals were then manually checked by a research team member to confirm their response patterns and identify substantive evidence for careless responses. A conservative approach of not excluding any participants was taken in light of the nature of the sample (ie, largely psychologically healthy) and the measures (ie, largely clinical) that were included in calculating the indexes; a floor effect on these scales may create false positives for certain indexes, such as the longest and average identical sequence.

Statistical Analysis

Depending on the analytical objectives, the data will be analyzed cross-sectionally or longitudinally. Population-averaged approaches, such as generalized estimation equations, will be chosen for objectives that aim to assess population means. For objectives that aim to identify risk factors at the individual level, individual-specific approaches such as hierarchy regressions will be chosen. Sample weights will be used in all analyses to improve the representativeness of the study estimates for the source population. Considering the response rate and uncertainty of the reason for nonresponse, both weighted and unweighted estimates will be presented, and their discrepancies will be discussed. In addition, weights will be applied to all longitudinal analyses to account for bias owing to potential differential attrition. A 95% CI for estimates will be provided wherever possible.

No individual-level data or tables (eg, cross-tabulations) that may identify individuals will be produced. Cell sizes of <5 will not be reported. Descriptive statistics (eg, mean, SD, and frequencies) summarized at the group level will be used to capture key outcomes cross-sectionally (ie, at each of the 3 time points). Inferential statistics (eg, ANOVA, regression, and correlation) using T1 data will be conducted to examine the relationships between the risk and resilience factors and the key outcomes, as well as the differences that may exist between subgroups of the cohort (eg, differences in trust or relatedness between ranks).

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Path analysis and structural equation modeling using T1 data will be used to analyze potential conceptual models. Predictive models (eg, linear and binary logistic regressions) using T1 data to capture changes over time will be used to assess associations between risk and resilience factors and the key outcomes. SPSS Statistics (version 23; IBM Corp), R (version 4.0.5), RStudio (version 1.4; Posit, PBC), and SAS (version 9.4; SAS Institute) will be used for all data management and analyses.

Interviews

Participants and Recruitment

The target population for the interview component of the project was the entire cohort of CAF personnel deployed to Ontario and Québec LTCFs as part of Operation LASER LTCF. Considerations regarding project resourcing and data saturation limited the maximum sample size of the qualitative interviews to approximately 50. Interviews were conducted in the participants' choice of French or English. There were no exclusion criteria.

On December 2, 2020, an email call for participants (written in English and French) was sent from the dedicated positional Operation LASER LTCF research project DWAN email address to the entire cohort of CAF personnel deployed to LTCFs (N=2595) to invite them to participate in a confidential interview with the research team. Similar to the survey study, emails were individually and personally addressed (ie, rank and name) and briefly outlined the study objectives, methods, participant rights, risks, risk mitigation measures, benefits of the study, and relevant contact information. Interested personnel were instructed to reply to the email to contact a member of the research team to obtain more information about the study or schedule an interview. The Operation LASER LTCF study email address was monitored by 2 members of the research team. Responses to prospective participants were provided in the same language as that used in their email inquiries.

In an effort to select a representative sample, from the pool of personnel who expressed interest in taking part in the interview study, participants were selected based on their Operation LASER LTCF role, rank, gender, component, province of deployment, and marital status. At the time of recruitment for the interview study, the research team did not have access to the ad hoc report, which provided demographic information for the entire population of Operation LASER LTCF personnel. As a result, participants were selected to ensure that the overall demographic breakdown of the interview study sample reflected that reported by respondents in the T1 survey. This sampling method yielded relatively representative proportions of the overall population (Table S1 in Multimedia Appendix 3) and ensured relative representation from subpopulations with a range of responsibilities and experiences. A member of the research team emailed the selected participants to schedule a 1-hour interview based on participants' availability and language of choice. A study information sheet was attached to the scheduling email to provide further details.

Interview Process

The interviews were conducted using Teams (Microsoft Corp), a DND-approved communication platform that allows for web-based synchronic audio and video discussions. Participants had the choice to join the web-based discussion, with their video turned on or off, or to dial in by telephone. At the outset of each scheduled interview, the research goals, as well as participant rights and protections stated in the information sheet, were outlined. Verbal consent to participate in the interview and to have their interview audio recorded (to assist the researchers with note taking) was obtained from each participant. Each interview was conducted in the official language of the respondents' choice. For consistency, one interviewer conducted most of the interviews while a second interviewer took notes, managed the audio recorder, and asked follow-up questions when applicable. Each interview was scheduled for 1 hour; however, an additional 30 minutes was scheduled between interview sessions in the event that a participant desired more time to share the details of their unique experiences. The duration of the interview was ultimately up to the participant. A semistructured interview approach was used, in which participants were guided by specific questions that aimed to explore their pre-, peri-, and postdeployment experiences. All interviews were conducted between December 2, 2020, and March 30, 2021.

Interview Content

The discussion domains are summarized in Multimedia Appendix 4 and fall under the general categories of (1) demographic and background variables, (2) predeployment experiences, (3) perideployment experiences, and (4) postdeployment experiences. These areas allowed for a nuanced view of demographic and background factors that may affect the Operation LASER LTCF experience [7,13,14]; Operation LASER LTCF–specific risk and protective factors, such as individual exposure and psychological reactions to stressful Operation LASER LTCF events; coping styles; and experiences related to moral challenges, moral emotions, moral distress [61], and potential moral injury [12,17,25,52,62]. Participants were also asked about group cohesion and leadership factors that may have affected their experience as past research has demonstrated that social-, unit-, leader-, and organizational-level factors may also affect team dynamics (Michaud K, unpublished data, December 2021). Participants were also asked about mental health service use and barriers to help seeking among CAF members [22-24]. Finally, participants were queried on any lessons learned that could be shared with military leadership to inform preparation and support for future missions of the same nature. Although these predefined topics guided the discussions, participants were free to raise additional issues to discuss in the interviews.

Analytical Approach to Qualitative Data

The audio recording of each discussion conducted in either French or English was transcribed verbatim into a text file. French transcriptions were translated into English for data analysis purposes, and the English transcriptions were uploaded to the NVivo qualitative analysis software (QSR International). Each discussion was first analyzed by the research team (who were also the interviewers) to identify the main topics addressed (called nodes) throughout the data. Once this coding scheme was complete, NVivo was used to generate a word search to

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discover trends throughout the discussions. For example, the program identified how often certain words were used, especially with regard to military training, military experience, and postdeployment particularities. By choosing keywords or nodes, the software presented each of the references related to a specific node, which allowed for the comparison of the results across different keywords or nodes and the detection of trends throughout the discussions.

Each interview transcript was manually coded according to the following contexts: before deployment (eg, the military role in Operation LASER LTCF, the predeployment training according to that role, and the domestic operation dimension and expectations), during deployment (eg, location, duration, role, experience, competence, chain of command, communication with civilian staff and with other military personnel, and sanitary measures), and after deployment (eg, quarantine, postdeployment training, return home and family, and willingness to deploy to another similar domestic or overseas operation). Further details on the qualitative methodology will be reported in follow-up manuscripts specific to each analysis and research question.

Ethical Considerations

The CAF Surgeon General and Chief of Military Personnel were the sponsors of this research, and CJOC approved access to Operation LASER LTCF personnel. This survey was conducted jointly by Defence Research and Development Canada, DGMPRA, CF H Svcs Gp, and the Royal Military College of Canada. It was reviewed and approved by the Defence Research and Development Canada Human Research Ethics Committee (approval HREC 2020-026 and 2020-040) and coordinated by the DGMPRA Social Science Research Review Board in accordance with Defence Administrative Orders and Directives 5062-0 and 5062-1 (coordination 1897/20N). The questions asked in this research fell under the current Treasury Board of Canada Secretariat definition of public opinion research. Thus, public opinion research approval from the Deputy Minister was obtained before the survey launch (ie, July 21, 2020). Although CJOC approved and facilitated this study by coordinating the provision of contact information of potential participants, neither the research sponsors nor CJOC were directly involved in participant recruitment for any phase or aspect of the study, nor did they know the identities of the individuals who elected to participate. An unsigned consent procedure was used, consistent with the methodology used in previous surveys administered by DGMPRA. All data used for analysis were deidentified. No participant remuneration was provided.

Results

Survey

Cohort and Survey Frame Size

A total of 47, 12, and 13 invitations were not delivered because of automated email bounce messages for T1, T2, and T3, respectively (representing 13/2595, 0.5% to 47/2595, 1.81% of all eligible personnel). Both the Ontario and Québec points of contact were asked for updated email addresses for members whose email addresses were invalid. An updated Québec list was received soon after the initial T1 invitation email was distributed; thus, members with an updated email address were sent the initial T1 survey invitation and all subsequent reminders. For Ontario members, an updated list was received before the distribution of the initial T2 survey invitation, which accounts for the decrease in undeliverable emails between T1 and T2. Although most invalid email addresses were personal, a few emails to DWAN accounts also bounced; the reason for this issue was unknown. A total of 0.31% (8/2595) of the personnel asked to be removed from the distribution list after either the T2 or interview study emails were sent out; an additional member asked to be removed after the initial T3 email was sent. Ultimately, survey invitations were sent to 2595 members at T1 and T2 and 2587 individuals at T3.

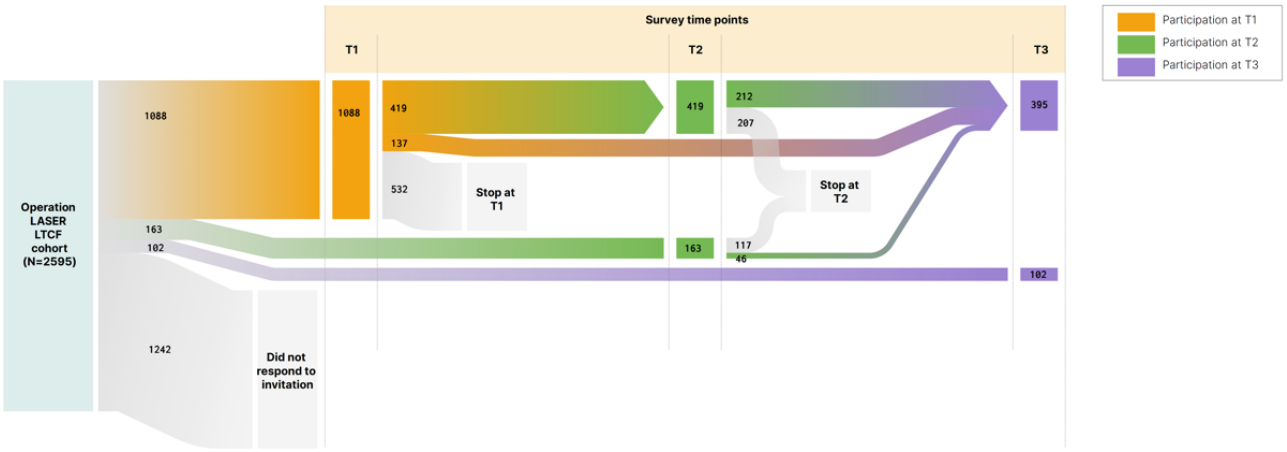
Participation Metrics and Sample Characteristics

Participation Across Time Points

The participation flow across the 3 data collection time points is shown in Figure 2. Overall, 1088, 582, and 497 individuals responded in T1, T2, and T3, respectively (see Tables 2-4 for unweighted and weighted sample characteristics). An individual was classified as a responder if they completed at least one question in the first section of the survey (ie, demographics and Operation LASER LTCF role). Relative to the total cohort eligible for participation (N=2595), this represented a participation rate of 41.93% (1088/2595), 22.43% (582/2595), and 19.15% (497/2595) for T1, T2, and T3, respectively. Close to half (532/1088, 48.9%) of the T1 participants did not return for follow-up at T2 and T3. Of those 1088 who participated in T1, a total of 419 (38.5%) had data at T2, a total of 212 (19.5%) had data for all 3 time points, and 137 (12.6%) had data only for T1 and T3. Not all individuals who participated in the follow-up time points (ie, T2 and T3) participated in T1. At T2, a total of 28% (163/582) of all participants took part for the first time. More than a quarter of these T2 first-time participants (46/163, 28.2%) continued to T3. T3 had 20.5% (102/497) of first-time participants.

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Figure 2. Survey participation flow across data collection time points. LTCF: long-term care facility; T1: time point 1; T2: time point 2; T3: time point 3.



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Table 2. Unweighted and weighted frequencies and percentages of sample characteristics at time 1.

Characteristics	Unweighted results (n=1088), n (%)[a]	Weighted results (n=1088.02), n (%; 95% CI)[a]
Demographics		
Age group (y)		
17-29	558 (56.08)	650.57 (65.29; 62.40-68.17)
30-39	295 (29.65)	234.64 (23.55; 21.05-26.04)
40-58	142 (14.27)	111.24 (11.16; 9.37-12.95)
Gender		
Female	280 (26.02)	205.55 (19.11; 16.97-21.25)
Male	796 (73.98)	869.85 (80.89; 78.75-83.03)
Marital status		
Single	610 (56.12)	672.14 (61.81; 58.90-64.72)
Separated, divorced, or widowed	46 (42.3)	38.18 (3.51; 2.48-4.54)
Married or common-law partnership	431 (39.65)	377.1 (34.68; 31.84-37.51)
Home situation		
Dependents	307 (28.37)	260 (24.03; 21.55-26.51)
No dependents	775 (71.63)	822 (75.97; 73.49-78.45)
Military factors		
Force type		
Regular force	511 (47.67)	452.51 (42.24; 39.23-45.25)
Reserve force	561 (52.33)	618.68 (57.76; 54.75-60.77)
Rank		
NCM[b]	862 (79.45)	909.71 (83.81; 81.77-85.86)
Officer	223 (20.55)	175.69 (16.19; 14.14-18.23)
Operation LASER		
Province		
Ontario	338 (31.98)	351.25 (33.31; 30.34-36.28)
Québec	698 (66.04)	683.99 (64.87; 61.87-67.87)
Both	16 (1.51)	14.77 (1.4; 0.70-2.11)
Other	2 (0.19)	2.03 (0.19; 0-0.47)
Other but could be both	3 (0.28)	2.32 (0.22; 0-0.47)
Role		
Operation LASER 1	382 (35.87)	351.03 (33.08; 30.21-35.95)
Operation LASER 2	210 (19.72)	241.55 (22.76; 20.05-25.48)
Operation LASER 3	71 (6.67)	78.46 (7.39; 5.70-9.09)
Support roles	344 (32.3)	328.76 (30.98; 28.14-33.82)
Other	45 (4.23[c])	47.82 (4.51; 3.18-5.83)
None	13 (1.22)	13.54 (1.28; 0.56-1.99)

[a]Raw n may not always be equal to the total sample size due to data missingness. Percentages are based only on data that is present.

[b]NCM: noncommissioned member.

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Table 3. Unweighted and weighted frequencies and percentages of sample characteristics at time 2.

Characteristics	Unweighted results (n=582), n (%)[a]	Weighted results (n=582.01), n (%;95% CI)[a]
Demographics		
Age group (y)		
17-29	263 (50.87)	327.51 (63.62; 59.53-67.71)
30-39	161 (31.14)	120.38 (23.38; 19.93-26.84)
40-58	93 (17.99)	66.92 (13; 10.39-15.61)
Gender		
Female	142 (25.54)	107.69 (19.47; 16.35-22.59)
Male	414 (74.46)	445.47 (80.53; 77.41-83.65)
Marital status		
Single	292 (52.05)	336.64 (60.21; 56.06-64.35)
Separated, divorced, or widowed	28 (4.99)	24.66 (4.41; 2.73-6.09)
Married or common-law partnership	241 (42.96)	197.85 (35.38; 31.39-39.38)
Home situation		
Dependents	182 (32.62)	148.00 (26.6; 22.98-30.22)
No dependents	376 (67.38)	408.00 (73.4; 69.78-77.02)
Military factors		
Force type		
Regular force	273 (49.28)	235.65 (42.8; 38.53-47.07)
Reserve force	281 (50.72)	314.96 (57.2; 52.93-61.48)
Rank		
NCM[b]	424 (75.58)	464.03 (82.99; 80.19-85.79)
Officer	137 (24.42)	95.11 (17.01; 14.21-19.81)
Ope ration LAS ER		
Province		
Ontario	176 (31.43)	182.24 (32.67; 28.53-36.80)
Québec	367 (65.54)	360.16 (64.56; 60.36-68.77)
Both	13 (2.32)	11.78 (2.11; 0.91-3.31)
Other	1 (0.18)	1.46 (0.26; 0-0.78)
Other but could be both	3 (0.54)	2.22 (0.4; 0-0.86)
Role		
Operation LASER 1	206 (36.79)	192.42 (34.49; 30.40-38.59)
Operation LASER 2	110 (19.64)	132.41 (23.74; 19.83-27.64)
Operation LASER 3	35 (6.25)	40.27 (7.22; 4.83-9.61)
Support roles	183 (32.68)	164.20 (29.43; 25.57-33.30)
Other	15 (2.68)	17.16 (3.08; 1.48-4.67)
None	11 (1.96)	11.39 (2.04; 0.77-3.31)

[a]Raw n may not always be equal to the total sample size due to data missingness. Percentages are based only on data that is present.

[b]NCM: noncommissioned member.

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Table 4. Unweighted and weighted frequencies and percentages of sample characteristics at time 3.

Characteristics	Unweighted results (n=497), n (%)[a]	Weighted results (n=497.00), n (%;95% CI)[a]
Demographics		
Age group (y)		
17-29	208 (46.12)	282.60 (63.08; 58.67-67.48)
30-39	149 (33.04)	101.76 (22.71; 19.14-26.28)
40-58	94 (20.84)	63.66 (14.21; 11.35-17.06)
Gender		
Female	116 (23.82)	89.94 (18.54; 15.17-21.91)
Male	371 (76.18)	395.19 (81.46; 78.09-84.83)
Marital status		
Single	229 (46.83)	274.53 (56.42; 51.79-61.04)
Separated, divorced, or widowed	26 (5.32)	20.25 (4.16; 2.44-5.89)
Married or common-law partnership	234 (47.85)	191.83 (39.42; 34.92-43.93)
Home situation		
Dependents	173 (35.45)	136.00 (27.88; 23.92-31.84)
No dependents	315 (64.55)	351.00 (72.12; 68.16-76.08)
Military factors		
Force type		
Regular force	251 (51.54)	213.61 (44.06; 39.39-48.73)
Reserve force	236 (48.46)	271.18 (55.94; 51.27-60.61)
Rank		
NCM[b]	376 (76.89)	404.08 (83.01; 79.86-86.15)
Officer	113 (23.11)	82.73 (16.99; 13.85-20.14)
Operation LASER		
Province		
Ontario	171 (35.19)	163.01 (33.64; 29.18-38.11)
Québec	301 (61.93)	310.13 (64; 59.47-68.54)
Both	12 (2.47)	10.20 (2.1; 0.84-3.37)
Other	0 (0)	0 (0; 0)
Other but could be both	2 (0.41)	1.23 (0.25; 0-0.60)
Role		
Operation LASER 1	178 (36.85)	159.74 (33.35; 28.93-37.77)
Operation LASER 2	92 (19.05)	116.18 (24.26; 19.86-28.65)
Operation LASER 3	22 (4.55)	27.08 (5.65; 3.29-8.02)
Support roles	165 (34.16)	149.78 (31.27; 26.92-35.62)
Other	7 (1.45)	6.21 (1.3; 0.26-2.33)
None	19 (3.93)	19.99 (4.17; 2.24-6.11)

[a]Raw n may not always be equal to the total sample size due to data missingness. Percentages are based only on data that is present.

[b]NCM: noncommissioned member.

Completion Time

Multimedia Appendix 5 describes the quantiles of completion time for individuals who completed the survey (ie, reached and submitted the final page). Survey duration for partial completers (ie, completed at least one question in the first section of the survey and left the survey before reaching the final page) was not available because of the manner in which time stamps were established by the survey platform (ie, only recorded at the start

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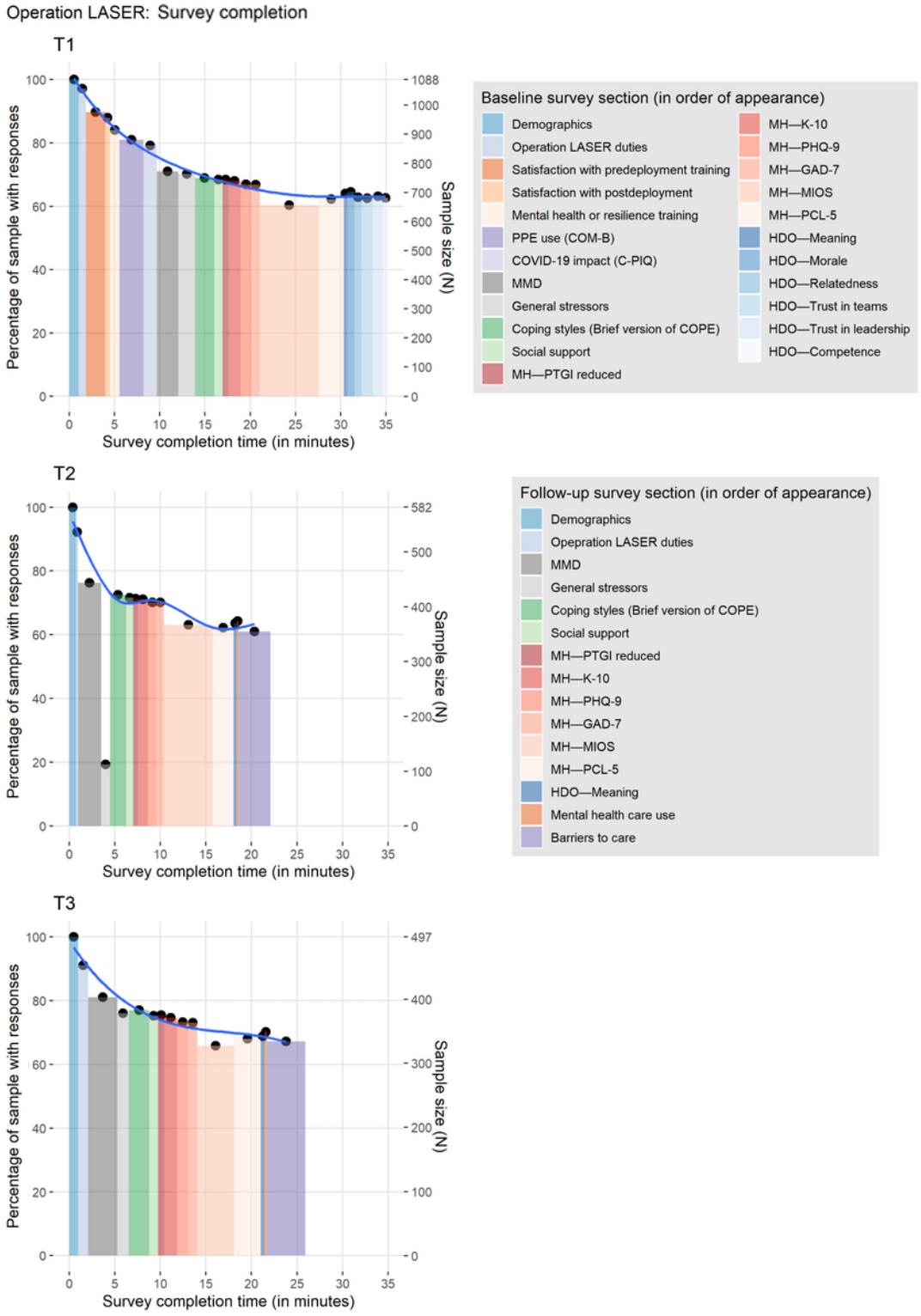
of the survey and once participants submitted the final page). After the removal of unreasonably long durations (ie, >500 min, likely because of participants completing the survey in multiple sittings), the median completion time for T1, T2, and T3 was 35.2 (IQR 26.3) minutes, 22.1 (IQR 16.0) minutes, and 25.9 (IQR 19.6) minutes, respectively. As expected, T1 had the longest completion duration because of the number of scales and items in the survey. Although T2 and T3 were very similar in content, additional questions were included in T3 that were not present in T2 (eg, additional items in the MMD-LASER). In reviewing the completion dates of the unusually long survey durations, it was evident that respondents returned to the survey on a different day to complete it as it aligned with the dates when reminder emails were sent. This pattern indicated that reminder emails were effective in encouraging a portion of partial completers to complete the survey at a later date (representing approximately 5%-10% of respondents at each time point).

Attrition Across Survey Sections

Common to many web-based surveys, not all participants in our study who started the survey completed it (see Figure 3 for attrition across survey sections). Survey completion at each time point was approximately 60% to 65% (relative to the number of individuals who completed the first section of the survey at each time point). Attrition across survey sections was largely a function of time spent in the survey, where approximately 80% of participants were retained at the 5-minute mark and 70% of participants were retained at the 10-minute mark.

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Figure 3. Participant attrition across survey sections. C-PIQ: Complementary and Integrative Research Pandemic Impact Questionnaire; COM-B: Capability, Opportunity, and Motivation–Behavior; COPE: Coping Orientation to Problems Experienced; GAD-7: Generalized Anxiety Disorder Scale; HDO: Human Dimensions of Operations; K-10: Kessler Psychological Distress Scale; MH: mental health; MIOS: Moral Injury Outcome Scale; MMD: Measure of Moral Distress; PCL-5: Posttraumatic Stress Disorder Checklist for the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; PHQ-9: Patient Health Questionnaire–9; PPE: personal protective equipment; PTGI: Posttraumatic Growth Inventory; T1: time point 1; T2: time point 2; T3: time point 3.



Interview

A total of 208 members responded to our request for participants for the interview study, representing approximately 8.02% (208/2595) of the eligible cohort. Of the 208 participants who responded, 185 (88.9%) expressed interest in participating, 14 (6.7%) requested more information, and 9 (4.3%) declined the invitation to participate or requested to have their name removed from the distribution list for future Operation LASER LTCF research invitations. In total, 53 interviews were conducted

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(n=23, 43% in French, n=27, 51% in English, and n=3, 6% in both languages). Multimedia Appendix 4 shows the characteristics of the interview participants.

All participants except 1 (52/53, 98%) consented to having their discussion audio recorded. In the case of the individual who declined audio recording, the investigator leading the discussion took detailed notes. The interviews ranged in duration from 34 to 98 minutes, lasting approximately 70 minutes on average. All discussions were transcribed verbatim (with the exception of the one interview in which the participant did not consent to audio recording). The number of words per transcript ranged from 3114 to 19,340, with a mean of 9779 words. Most of the personnel who participated in the interview study also completed the survey (51/53, 96%).

Discussion

This paper documents the methodology and implementation of a longitudinal study that aims to explore the psychological impact and mental health outcomes of CAF personnel deployed domestically to support civilian health care in LTCFs during the COVID-19 pandemic (as part of Operation LASER). Owing to the moral nature of the stressors encountered by personnel deployed to LTCFs and the insufficiently researched link between morally injurious experiences and mental health outcomes, it was important to understand their impact on mental health and well-being. The research objectives included identifying and quantifying individual, group, and organizational risk and resilience factors associated with these mental health outcomes; gaining an in-depth understanding of the personnel's lived experiences during deployment; and extracting lessons to inform decisions for similar future deployments.

Overall, the study rollout and data collection were successfully executed despite the complexity of the study design. The participant response rates, ranging from 19.15% (497/2595) to 41.93% (1088/2595) depending on the time point, are typical and consistent with those of other studies [63], including those in military populations [64-66]. Of those who started the survey, most completed it in its entirety. The likelihood of survey dropout was a function of survey length, with the largest dropout (approximately 20%) occurring within the first 5 minutes. This attrition across survey sections is comparable with that of other web-based surveys, suggesting that, as the time requirement for a survey increases, the completion rate decreases [67,68].

Among the several objectives of this study, a critical gap that this research intended to address lay in the area of moral injury. Military personnel often face situations that may be perceived to transgress deeply held moral beliefs and values; this includes through acts of commission of, omission of, learning about, or being a victim of betrayal [69,70]. Such experiences can lead to moral injury, causing intense feelings of guilt, shame, spiritual conflict, social alterations, and changes in moral thinking, which are distinct from PTSD but can coexist with it [71,72]. Understanding the nuances of moral injury (ie, its risk factors and mechanism of development) can help further differentiate it from PTSD and develop more tailored mental health interventions. These interventions can range from predeployment training programs that prepare military personnel for the moral complexities of operations to therapeutic approaches that can assist in the healing process for those experiencing moral injury. Finally, the identification and recognition of the scope and impact of moral injury can help foster a military culture that is more aware of and responsive to the moral and ethical challenges of military service, particularly when emerging research highlights the protective role of organizational support and sound leadership against the development of distress in the aftermath of exposure to potentially morally injurious events [19,73]. Addressing these gaps is not only a priority for military personnel [50,74] but also relevant to other high-stress occupational settings where individuals may be presented with moral conflicts in high-stakes environments (ie, first responders, health care workers, and the legal system) [75-77].

Despite the longitudinal and mixed methods nature of the study, the substantial effort made to optimize the study design mitigates bias (eg, attrition and nonresponse bias and careless responding). This study is not without limitations. Specifically, the lack of a time point preceding deployment limits the ability to draw strong causal inferences linked to the experiences during deployment. Data for this study were collected using web-based self-reports, which may carry the inherent bias associated with most self-reports, including measurement error, human error, response bias (eg, social desirability), memory recall bias, interpretation challenges, and lack of verifiability. Inherent to longitudinal surveys, attrition bias and panel conditioning may have been a factor. Finally, the 3–time point longitudinal design, although superior to trend study designs, has limited time resolution and restrains the granularity of temporal changes in the key outcomes captured in this survey.

The quantitative and qualitative data generated through this research provide an opportunity to characterize the well-being and mental health of Operation LASER LTCF personnel over the year after this deployment, identify general and Operation LASER LTCF–specific risk and protective factors, and inform preparation and interventions for future missions.

Acknowledgments

Funding for this work was provided by the Department of National Defence.

Data Availability

The data sets generated and analyzed during this study are not publicly available. Access to research data is restricted and governed by Department of National Defence and Director General Military Personnel Research and Analysis policies.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
General deployment stressor items.
[DOCX File , 17 KB - resprot_v12i1e44299_app1.docx]

Multimedia Appendix 2
Items on the Measure of Moral Distress for Healthcare Professionals adapted to Operation LASER.
[DOCX File , 15 KB - resprot_v12i1e44299_app2.docx]

Multimedia Appendix 3
Interview study discussion domains.
[DOCX File , 19 KB - resprot_v12i1e44299_app3.docx]

Multimedia Appendix 4
Characteristics of the interview study sample.
[DOCX File , 18 KB - resprot_v12i1e44299_app4.docx]

Multimedia Appendix 5
Distribution of completion times for time points 1, 2, and 3.
[DOCX File , 15 KB - resprot_v12i1e44299_app5.docx]

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Abbreviations

CAF: Canadian Armed Forces
CF H Svcs Gp: Canadian Forces Health Services Group
CFMHS: Canadian Forces Mental Health Survey
CJOC: Canadian Joint Operations Command
DGMPRA: Director General Military Personnel Research and Analysis

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DND: Department of National Defence
DWAN: Defence Wide Area Network
GAD-7: Generalized Anxiety Disorder Scale
K-10: Kessler Psychological Distress Scale
LTCF: long-term care facility
MIOS: Moral Injury Outcome Scale
MMD-HP: Measure of Moral Distress for Healthcare Professionals
MMD-LASER: Measure of Moral Distress for Healthcare Professionals adapted to Operation LASER
PHQ-9: Patient Health Questionnaire–9
PPE: personal protective equipment
PTSD: posttraumatic stress disorder
SME: subject matter expert
SN: service number
T1: time point 1
T2: time point 2
T3: time point 3

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Protocol

Clinical Utility Assessment of a Nursing Checklist Identifying Complex Care Needs Due to Inequities Among Ambulatory Patients With Cancer: Protocol for a Mixed Methods Study

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Abstract

Background: Disparities in cancer incidence, complex care needs, and poor health outcomes are largely driven by structural inequities stemming from social determinants of health. To date, no evidence-based clinical tool has been developed to identify newly diagnosed patients at risk of poorer outcomes. Specialist cancer nurses are well-positioned to ameliorate inequity of opportunity for optimal care, treatment, and outcomes through timely screening, assessment, and intervention. We designed a nursing complexity checklist (the "Checklist") to support these activities, with the ultimate goal of improving equitable experiences and outcomes of care. This study aims to generate evidence regarding the clinical utility of the Checklist.

Objective: The primary objectives of this study are to provide qualitative evidence regarding key aspects of the Checklist's clinical utility (appropriateness, acceptability, and practicability), informed by Smart's multidimensional model of clinical utility. Secondary objectives explore the predictive value of the Checklist and concordance between specific checklist items and patient-reported outcome measures.

Methods: This prospective mixed methods case series study will recruit up to 60 newly diagnosed patients with cancer and 10 specialist nurses from a specialist cancer center. Nurses will complete the Checklist with patient participants. Within 2 weeks of Checklist completion, patients will complete 5 patient-reported outcome measures with established psychometric properties that correspond to specific checklist items and an individual semistructured interview to explore Checklist clinical utility. Interviews with nurses will occur 12 and 24 weeks after they first complete a checklist, exploring perceptions of the Checklist's clinical utility including barriers and facilitators to implementation. Data describing planned and unplanned patient service use will be collected from patient follow-up interviews at 12 weeks and the electronic medical record at 24 weeks after Checklist completion. Descriptive statistics will summarize operational, checklist, and electronic medical record data. The predictive value of the Checklist and the relationship between specific checklist items and relevant patient-reported outcome measures will be examined using descriptive statistics, contingency tables, measures of association, and plots as appropriate. Qualitative data will be analyzed using a content analysis approach.

Results: This study was approved by the institution's ethics committee. The enrollment period commenced in May 2022 and ended in November 2022. In total, 37 patients with cancer and 7 specialist cancer nurses were recruited at this time. Data collection is scheduled for completion at the end of May 2023.

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Conclusions: This study will evaluate key clinical utility dimensions of a nursing complexity checklist. It will also provide preliminary evidence on its predictive value and information to support its seamless implementation into everyday practice including, but not limited to, possible revisions to the Checklist, instructions, and training for relevant personnel. Future implementation of this Checklist may improve equity of opportunity of access to care for patients with cancer.

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KEYWORDS

cancer; oncology; cancer nursing; clinical utility; nursing checklist; social determinants of health; equity; cancer care; disparity; barrier; checklist; nursing; nurse; caregiver; specialist nurse; patient outcome

Introduction

The past decade saw remarkable advances in cancer care, treatment, and outcomes, but these benefits were not equitably realized. Concerningly, cancer disparities between populations of high and low socioeconomic status continue to widen, and those disadvantaged by social determinants of health experience a disproportionate burden of poorer cancer outcomes [1]. Social determinants of health, such as income and social protection, education, food security, and social inclusion and nondiscrimination, have major impacts on health and health outcomes of populations [2,3]. This is especially true for people affected by cancer, whereby those disadvantaged due to the impact of social determinants experience significantly more disease burden and are more likely to die from their cancer than others [2,4].

A significant proportion of this burden is due to systemic barriers influencing access to diagnosis, treatment, and care. For example, distance from treatment centers, out-of-pocket costs associated with accessing treatment and care, and overly complex health care systems that are difficult to navigate without adequate information and support [5,6]. In countries like Australia, health services inadequately address the requirements of the communities they serve; for example, insufficient provision of information in languages other than English, and institutional racism that particularly affects experiences and outcomes for Aboriginal and Torres Strait Islander patients [7]. The evolution of the concept of the "complex patient" acknowledges that individual patients are not inherently complex, but rather face a complex intersection of interrelating factors on multiple levels: biomedical (diagnoses and comorbidities), individual (language, literacy, and cultural), social (support, inclusion, and discrimination), and environmental (access to food, housing, and transportation) [8]. If unaddressed, these factors may manifest in a higher risk of morbidity, challenges to accessing appropriate health care, receipt of worse care, and consequently worse health outcomes. Although these findings are well recognized, few attempts exist to systematically integrate point-of-care interventions to rapidly identify people requiring early support or increased follow-up to address or mediate access barriers and systemic inequities that maximize health outcomes.

Evidence demonstrates that cancer nurses address critical gaps in care coordination for patients with cancer resulting in improved health outcomes and overall survival [9]. Cancer nurses are therefore ideally placed to identify and address these consequences flowing from structural inequities that impact equitable access to diagnosis, treatment, and care. However, there are considerable and increasing discrepancies between the available cancer nursing workforce and the demand for services, with a recent report published by the World Health Organization estimating a global shortage of 5.7 million nurses by 2030 [10]. There are also policy and funding barriers to innovations in care, such as nurse-led services.

Concurrently, there is a projected 47% increase in cancer burden expected from 2020 to 2040 across all settings globally, though particularly affecting low-resource settings [11]. With growing numbers of patients with cancer without a corresponding increase in specialist nurses, the ability to quickly identify and target those most in need of timely support is critical. Resourcing cancer nurses with validated tools to efficiently and systematically identify people with or at risk of complex care needs presents an overlooked opportunity to redress inequities in cancer care. For the purpose of this study, "complex care needs" are defined as the presence of access barriers to care and increased needs individuals newly diagnosed with cancer face due to the presence of social determinants of health and associated systemic barriers. The Complexity Checklist (the "Checklist") is a novel cancer nursing checklist developed to facilitate early identification of newly diagnosed patients with cancer at risk of poor experiences and outcomes due to complex care needs. In a review of internationally published papers, no similar checklist exists for oncology settings.

To generate evidence regarding the potential benefit of the Checklist, this study will undertake a comprehensive assessment of the Checklist's clinical utility. Clinical utility refers to the practical usefulness of an intervention to improve health outcomes. This study is informed by Smart's multidimensional model of clinical utility, which describes 4 dimensions that impact on an intervention's clinical utility: appropriateness, accessibility, acceptability, and practicability (Table 1) [12]. "Accessibility" will not be examined as it pertains to economic considerations of an intervention, which is out of the scope of this study. "Appropriateness" explores the evidence of the effectiveness and relevance of an intervention to clinical decision-making, and disruptions to current work and care [12]. Acceptability explores whether the intervention is acceptable to service users, providers, and broader society [12]. "Practicability" examines suitability, whether the intervention performs in real-world settings; functionality, whether the intervention, training, and instructions are complete and in

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working order; as well as current and future training and knowledge requirements [12].

Table 1. Study objectives, type of data, and data source for a mixed methods case series study investigating the clinical utility of a nursing checklist for newly diagnosed patients with cancer in a specialist cancer hospital. Data collection activities occur over a 6-month period.

Study objective	Type of data	Data source
To determine patient and specialist nurse perspectives regarding the relevance or importance of the Checklist for decision-making, and disruptions to current work and care.	• Perspectives of patients and CNCs[a] of ease of use of Checklist and meaning and relevance of information obtained. • Time taken to complete the Checklist and make referrals.	• Interviews with patients (T1) and CNCs (T2 and T3). • CNC postchecklist survey, patient and CNC interviews.
To determine whether the Checklist is acceptable to patients newly diagnosed with cancer and specialist nurses delivering care.	• Perspectives of patients and CNCs. • Number of patients approached and recruited for the study. • Number of Checklists completed at T1.	• Interviews with patients and CNCs. • Checklist, operational, and EMR[b] data.
To determine whether the Checklist, training, and instructions are complete and in working order.	• Perspectives of patients and CNCs regarding whether the Checklist addresses all issues of importance/relevance to participants.	• Interviews with patients and CNCs.
To determine the perspectives of specialist nurses regarding the adequacy of training and current staff knowledge to use the Checklist and future needs.	• Perspectives of CNCs on the adequacy of training delivered to use the Checklist in practice and perceptions of future needs.	• Interviews with CNCs.
To explore the predictive value of the Checklist.	• CNC classification at enrollment and at 24-week follow-up.	• Checklist, operational and EMR data (internal and external referrals and internal uptake), and patient interview data (external uptake).
To explore concordance between specific checklist items and PROMs[c].	• Responses to prespecified Checklist items and relevant PROMs scores.	• Checklist, PROMs data.

[a]CNC: clinical nurse consultant.

[b]EMR: electronic medical record.

[c]PROMs: patient-reported outcome measures.

This study aims to provide an assessment of the clinical utility of the Checklist. Perspectives of newly diagnosed patients with cancer and specialist nurses will be used to explore the following 4 primary objectives:

- To determine patient and specialist nurse perspectives regarding the relevance or importance of the Checklist for decision-making, and disruptions to current work and care.
- To determine whether the Checklist is acceptable to patients newly diagnosed with cancer and specialist nurses delivering care.
- To determine whether the Checklist, training, and instructions are complete and in working order.
- To determine qualitative perspectives of specialist nurses regarding the adequacy of training and current staff knowledge to use the Checklist and future needs.

In addition, 2 secondary objectives have also been identified:

- To explore the predictive value of the Checklist.
- To explore concordance between specific checklist items and patient-reported outcome measures (PROMs).

Methods

Study Design and Setting

This prospective mixed methods case series study was designed to investigate the clinical utility of a nursing complexity checklist. The study will be conducted in accordance with the Joanna Briggs Checklist for Case Series [13]. Specialist nurses will complete the Checklist with consecutive patients newly diagnosed with cancer; then quantitative and qualitative data will be collected multiple times following completion of the Checklist at enrollment up to 24 weeks post Checklist completion. The study will be conducted at a specialist cancer center in Victoria, Australia. Ethical approval was granted by the institutional ethics committee (HREC/84219/PMCC).

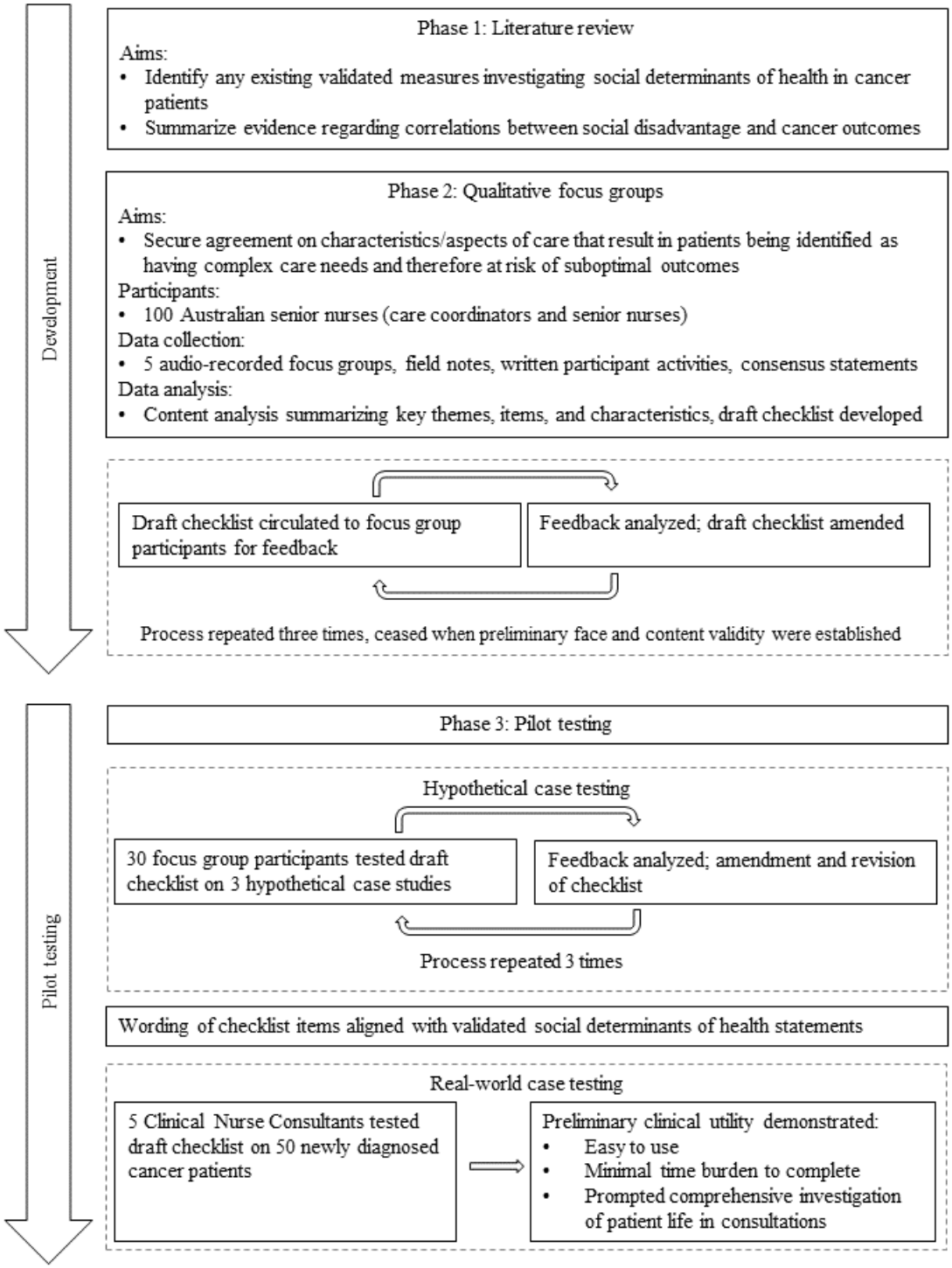
Development

The Checklist was developed between 2016 and 2019 by members of our team (MK, DM, AH, and KG; Figure 1). A comprehensive review of published literature was undertaken to identify existing measures investigating social determinants of health in patients with cancer and to summarize evidence on associations between social disadvantage and cancer outcomes. Next, 100 Australian cancer nurses from Victoria, New South Wales, Queensland, South Australia, and Western Australia participated in 5 qualitative focus group consultations conducted face-to-face and digitally. Focus groups aimed to secure

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agreement on characteristics or aspects of care that result in a patient having complex care coordination needs likely to increase their risk of suboptimal outcomes. Audio-recorded and written qualitative data were analyzed using content analysis. The first iteration of the Checklist was developed and circulated to nurse participants for feedback. This process occurred 3 times until no new characteristics or aspects of care were proposed for inclusion (preliminary content validity) and participants felt items included were easily understood (preliminary face validity).

Figure 1. Development of a nursing checklist to assess patients with cancer for risk of complex care needs with senior cancer nurses in Australia, 2016-2019.



The Checklist was then pilot-tested through hypothetical and real-world case testing. In total, 30 nurses (drawn from focus group participants) tested the Checklist with 3 hypothetical case studies to provide data on ease of use, and interpretation of the items when applied to a patient case. Feedback guided amendment and revision of the number of items included in the

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Checklist (for example, items were collapsed or excluded as repetitive) over 3 iterative cycles until no further modifications were required. Following the establishment of Checklist constructs, a series of study team workshops were undertaken to operationalize constructs identified in the nurse workshops into quantitively measurable index items. Items were aligned items with existing psychometric and clinical assessments, as well as standardized definitions to enhance face and construct validity. The revised Checklist was then tested by 5 Clinical Nurse Consultants (CNCs) at a specialist cancer hospital in Australia who each used the Checklist in real-world consultations with 10 newly referred patients with cancer. Pilot-testing found the Checklist to be easy to use, took minimal time to complete, and prompted CNCs to ask their patients questions they may not otherwise have done.

Description

The Checklist comprises 15 items mapping to 4 domains: demographic, disease, health status, and symptomatology (Figure 2). Items are answered using a yes/no response format. The Checklist has been designed as a tool to prompt systematic assessment of newly diagnosed patients with cancer during consultations. This is achieved by guiding nurses through a comprehensive clinical consultation, to elicit all relevant information on factors that may add to a person's experiences of complexity. Data generated by the Checklist will be used by the CNCs to initiate referrals and with other members of the treating team; for example, through the electronic medical record or multidisciplinary team meetings.

Figure 2. The Complexity Checklist, a novel nursing checklist to identify patients with cancer at risk of complex care needs developed in Australia 2016-2019.

Demographic		
Social Support	Does the patient have adequate care support from family or friends?	Yes/No
Living arrangements	Do you consider the patient's current living arrangements or discharge destination suitable and able to meet their care needs?	Yes/No
Distance from Treatment	Is distance likely to impact on safety and accessibility of care?	Yes/No
Financial Toxicity	Does the patient have financial concerns which will require referral?	Yes/No
Indigenous or Torres Strait Islander	Does the patient identify as Aboriginal and/or Torres Strait Islander?	Yes/No
CALD	Does the patient require an interpreter?	Yes/No
Caregiver Anxiety	Nurse Assessment: Are close family or primary caregiver highly anxious or distressed by the cancer diagnosis?	Yes/No
Patient Capacity	Does the patient have family and/or work commitments which will be significantly impacted by their diagnosis and require extra intervention?	Yes/No
Disease Status		
Advanced Disease	Does the patient have advanced disease?	Yes/No
Diagnosis	Despite investigations, is the patient's diagnosis unknown?	Yes/No
Health Status		
Functional Capacity	Does the patient have a functional impairment (cognitive or physical) likely to complicate their care?	Yes/No
Psycho-pathology	Does the patient have a psychological illness which requires intervention or support?	Yes/No
Health/Lifestyle	Does the patient have health lifestyle factors likely to complicate their care including (tick which): Obesity Substance use/abuse (specify_____) Sedentary Lifestyle	Yes/No
Comorbidities	Does the patient have one or more comorbidities likely to complicate their cancer care? Specify:_____	Yes/No
Symptomology		
Uncontrolled symptoms	Does the patient have poorly or uncontrolled physical symptoms which require prompt intervention?	Yes/No

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CNC Training

Nurses will participate in a training session on the use of the Checklist to optimize generalizability across observers (or raters). The session will provide guidance for specific items such as recommended daily exercise and guidelines regarding safe alcohol intake [14,15].

Patient and Public Involvement

This study builds upon preliminary clinical utility data from 5 CNCs who used the Checklist with 50 newly diagnosed patients with cancer. In addition, 2 consumer representatives were appointed to the study's steering committee following protocol development and have assisted with guiding the study amendments and direction.

Participants

A consecutive sample of newly diagnosed patients with cancer from 4 cancer streams (gynecological, urological, head and neck, and lung cancers) will be recruited. In accordance with the equity focus of the Checklist, support to enable participation of non-English speaking patients is provided. As this study investigates care delivery, the study targets people with a new diagnosis of cancer or where a previous diagnosis was managed with a simple excision. Patients attending the health service solely for the provision of clinical trial access are also excluded as trial care is not standard of care. Potential patient participants will be identified by participating CNCs from clinic and referral triage lists. A project officer (PO) will screen identified patients according to the following eligibility criteria:

- are 18 years or older
- have a histologically confirmed cancer diagnosis
- are expected to survive at least 24 weeks from the time of recruitment, as determined by tumor stream CNC
- are referred to the head and neck, gynecological, urological, or lung treating teams at the hospital for major surgery, more than a single fraction of radiotherapy or systemic therapy.
- are approached to participate within a 4-week window of their first appointment at the hospital or are approached within 4 weeks following a confirmed cancer diagnosis (for patients referred for diagnostic workup)
- are able to complete Checklist-related questions and take part in an audio-recorded semistructured interview either independently or with support (such as a caregiver, family member, or interpreter) as per usual clinical care
- are able to give informed consent
- have no previous cancer diagnosis (except basal cell carcinoma and squamous cell carcinoma type skin cancers and in situ carcinomas)
- have not been referred to Peter Mac solely to access treatment through a clinical trial

Eligible patients will be approached via telephone to introduce the study and invite participation via telephone. Interested eligible participants will be requested to provide written informed consent. CNCs from each participating cancer stream will be eligible to participate in the study. A maximum of 5 CNCs from each cancer stream will be recruited, to ensure all CNCs gain familiarity with delivering the tool.

Ethical Considerations

This study protocol has been approved by the relevant institution's Human Research Ethics Committee (22/39L). Written informed consent will be requested from all participants prior to study enrollment. Verbal reconfirmation of consent is audio-recorded at the beginning of semistructured interviews with all CNC and patient participants. Participants will not receive compensation for their involvement in this study. Participant data will be stored in accordance with National Health and Medical Research Council guidelines and deidentified where possible (refer to data management below for further detail).

Study Size

The study will aim to recruit 15 patients from each participating cancer stream (60 patient participants in total), and a minimum of 1 to a maximum of 5 CNCs working in each of the 4 participating cancer streams. The sample size is pragmatic based on study timeframes, clinical throughput and funds available These sample sizes will provide adequate information to achieve the primary study objectives, explored through qualitative interviews with patients and CNCs [16].

Data Sources and Measurement

Data collection activities will occur at 4 timepoints (Figure 3). Study enrollment of patient participants is confirmed once the intervention (the Checklist) is completed with their CNC (T0). Study enrollment for CNC participants is similarly confirmed the first time they complete a Checklist with a patient participant. Patients will complete 5 PROMs and an audio-recorded semistructured interview within 2 weeks of completing the checklist (T1), and a follow-up interview at 12 weeks post completion (T2). CNCs will complete 2 qualitative semistructured interviews at 12 weeks (T2) and 24 weeks (T3) after completing their first checklist. Medical record data to describe each patient's care events across the 24-week data collection period will be collected at T3. Qualitative and quantitative data collected will be used to evaluate multiple aspects of the clinical utility of the Checklist (Table 2).

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Figure 3. Study schema for a mixed methods case-series study investigating the clinical utility of a nursing checklist for newly diagnosed patients with cancer in a specialist cancer hospital. Data collection activities occur over a 6-month period. CNC: clinical nurse consultant; PROM: patient-reported outcome measure.

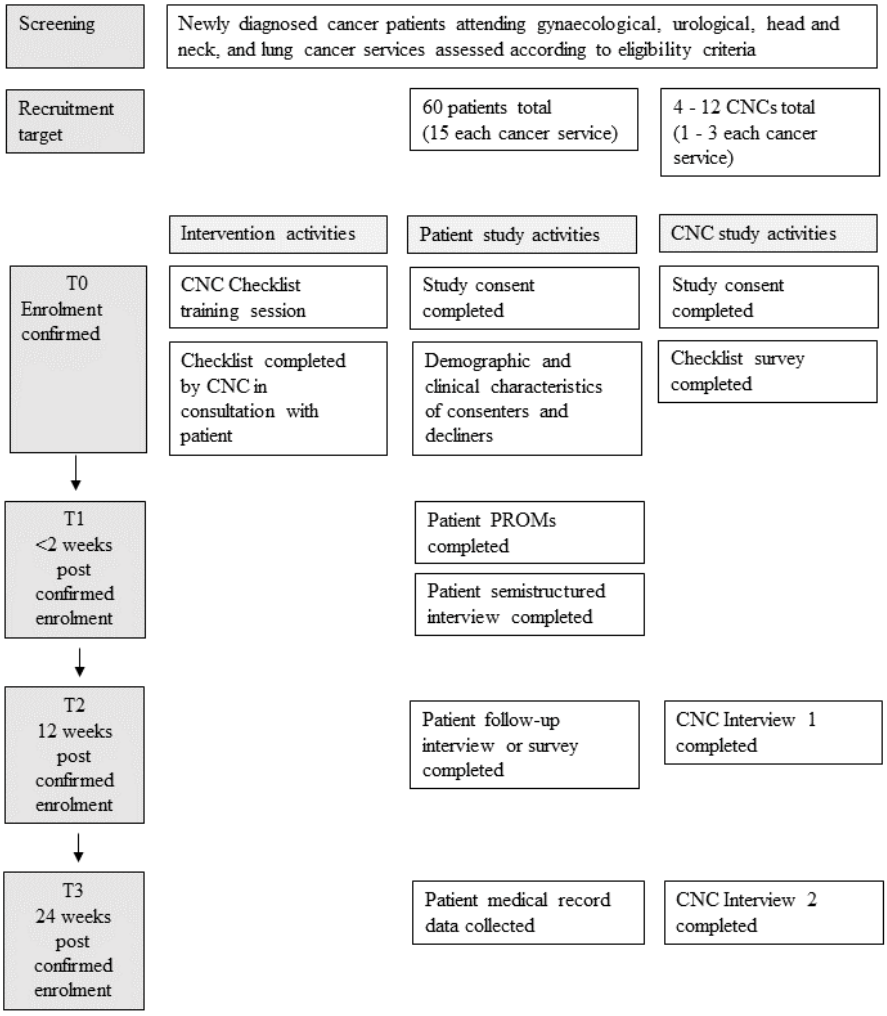


Table 2. Checklist items and corresponding PROMs[a] used to investigate concordance in a mixed methods case series study at a specialist cancer hospital.

Complexity Checklist item	Corresponding PROM
1) Social support	PROMIS[b] Instrumental Support SF[c] [17]
4) Financial toxicity	COST-FACIT [18]
8) Patient capacity	PROMIS ability to participate in social roles and activities—SF [17]
11) Functional capacity	PROMIS physical function SF [17]
15) Uncontrolled symptoms	PROMIS self-efficacy for managing symptoms SF [17]

[a]PROM: patient-reported outcome measure.

[b]PROMIS: patient-reported outcomes measurement information system.

[c]SF: short form.

T0 Data Collection Activities and Procedures

Operational Data

Details of patients screened, approached, consented, and declined will be entered into a password-protected Excel (Microsoft Corp) spreadsheet, hosted on a secure hospital server.

Patient Information

Demographic, disease, and treatment-related data will be extracted from the electronic medical record (EMR) by members of the project team (HC and EC) for all patient participants (consenters). Data will include sex, age, marital status, country of birth, primary language spoken, postcode, living situation, disease type and stage, comorbidities, treatment plan, and treatment intent and entered into Research Electronic Data

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Capture (REDCap; Vanderbilt University)—a web-based electronic data capture tool hosted by the hospital [19,20]. Demographic and disease data will also be extracted from the EMR for all eligible participants who decline to participate (decliners) and entered into a separate REDCap database.

CNC Postchecklist Survey

CNCs will complete a paper-based or electronic checklist with patient participants. After completing each checklist, CNCs will also complete a study-specific survey to record: whether the checklist was completed face-to-face or digitally (telephone or telehealth); whether and from who the patient received assistance answering checklist items; and whether the CNC deemed the patient as having complex care needs based on Checklist items (response options: complex, not complex, and unsure). Checklist and CNC survey data will be entered into a web-based REDCap database by a study PO.

T1 Data Collection Activities

Initial Patient Interview

Patient participants will take part in an audio-recorded semistructured interview investigating patients' experiences and views regarding the acceptability, appropriateness, and practicability of the Checklist. Interviews will be conducted by a study PO face-to-face, by telephone, or via videoconferencing as per participant preference, and will take approximately 20-30 minutes to complete.

PROMs

Patient participants will complete 5 PROMs at the beginning of their semistructured interview (listed in Table 2). PROM data will be entered into a web-based REDCap database by a study PO. Four PROMS are drawn from the Patient-Reported Outcomes Measurement Information System, a system of widely used, highly reliable, and precise measures of patient-reported health status for physical, mental, and social well-being [17]. The fifth measure is the COST-FACIT scale, an 11-item measure of the impacts of chronic illness and its treatment on financial status [18].

T2 Data Collection Activities

Patient Follow-Up Interview

Approximately 12 weeks after administration of the Checklist, patient participants will be invited to complete a short follow-up interview. The purpose of this is to understand each patient's pattern of service use regarding uptake of internal and external referrals made at and following T1, and unplanned service use, particularly external care not captured by the hospital EMR.

Initial CNC Interview

CNCs will participate in an audio-recorded semistructured interview 12 weeks after they first administered a Checklist. This interview will explore the CNCs' perspectives on the appropriateness, acceptability, practicability, and clinical application of the Checklist. Demographic data will be collected at the start of interviews and comprise role title and discipline, years working at Peter Mac, and cancer stream affiliation. Interviews will be conducted face-to-face or by videoconferences as per participant preference and will take approximately 45-60 minutes to complete.

T3 Data Collection Activities

CNC Follow-Up Interview

Approximately 24 weeks after the first Checklist administration, CNCs will participate in a second audio-recorded semistructured interview. The purpose of this interview is to explore CNC perceptions of the discriminatory capacity of the Checklist, as well as its clinical utility and application. Additionally, checklist, operational and EMR data combined with CNC judgment will be used to determine complex care needs "caseness" at 24 weeks after enrollment. Interviews will be conducted as per participant preference and take approximately 20-30 minutes to complete.

Patient EMR Data

POs will complete a review of the patient's EMR to record treatment-related outcomes 24 weeks after patient participants complete the Checklist. These data include whether treatment was completed, amended, or the patient has withdrawn from treatment, transitioned to a clinical trial, or transitioned to palliative care. Referral data will also be collected, to add to and cross-check patient T2 follow-up. Data will capture types and dates of internal and external referrals, unplanned contacts with nurses and other health care professionals, and information regarding the uptake of internal referrals.

Data Analysis Plan

Qualitative Data

Audio-recorded interviews will be translated (as required), transcribed verbatim, and deidentified. NVivo 12 (QSR International) will be used to assist with data management. Three distinct tranches of semistructured interview data (patient T1, CNC T2, and CNC T3) will be analyzed separately using deductive and inductive content analysis. Content analysis allows for systematic and objective descriptions of phenomena such as views and perceptions of participants and is well-suited to informing clinical improvements [21].

An initial deductive approach will operationalize the prespecified study objectives (Table 1) to construct an initial, unconstrained, coding frame for each tranche of interviews. The coding frames will be tested and inductively revised to classify data into relevant codes and categories under clinical utility themes. In addition, 2 POs (HC and EC) trained in qualitative research will independently code 10% of each interview tranche to test and revise the coding frames. Iterations of the coding frames will be discussed, and discrepancies within coding frames will be resolved by consensus. The project principal investigator (MK) will be assigned a "third reviewer" role if HC and EC are unable to resolve discrepancies. Upon conclusion of the qualitative analysis, findings (codebooks and summaries) will be presented and discussed with members of the study team. Any divergence or disagreement with interpretation will be resolved by consensus. Following the completion of coding frames, qualitative data will be synthesized to explore similarities and disagreements between participant cohort perspectives regarding the clinical utility of the Checklist.

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Quantitative Data

Data will be exported from REDCap, and then imported into R for scoring and analysis (reference index version 4.2.3 or higher). PROMs will be scored according to author guidelines and standard recodes applied as required [22-27]. T0 "caseness" classifications will be recoded to a discrete variable comprising 2 categories: case or noncase (noncase and unsure).

Counts and percentages will be used to summarize missing operational, participant characteristics (patient and CNC), checklist, EMR, and PROMs data. Missing data will not be imputed. Descriptive statistics (counts and percentages, means and SDs, medians and IQRs, and ranges, as appropriate) will be used to summarize the characteristics of patient consenters and decliners for the full sample and by cancer service, as well as the demographic and professional characteristics of CNC participants. Counts and percentages will be used to summarize "caseness" data (complex, not complex, unsure) from the CNC survey completed at enrollment. Contingency tables and conditional probabilities will be used to explore the predictive value of the Checklist by assessing agreement between T0 and T3 "caseness" variables. Descriptive statistics, measures of association, and graphical displays will be used to examine the concordance between prespecified checklist items and PROMs scores [28].

Data Management

Data Storage and Access

Demographic, Checklist, and PROMs data will be recorded onto hard-copy paper forms and entered into a study database developed and stored on the hospital REDCap platform. All study data (such as REDCap exports, qualitative data files, and analysis files) will be stored securely in password-protected electronic folders, housed on a secure hospital server. Quality checks will be undertaken at regular intervals by POs during data collection to ensure completeness, precision, and timeliness of data. Access to all hard-copy and electronic data will be restricted to the project principal investigator and POs directly involved in data collection and analysis.

Privacy

Study identification codes will be assigned to each participant and decliner and used to label data collected to protect privacy. Separate master lists, linking study identification codes to identifiable information (such as demographic and contact data) will be constructed for participants and decliners. Separate REDCap databases will be developed to store the participant master list, decliner master list, and Complexity study data. As above, only key project staff will be given access to these databases.

Data Retention and Disposal

At study closure, REDCap databases will be archived from the platform. Password-protected exports of all databases will be saved onto the secure hospital server, and hard-copy data placed into secure storage. All study data will be stored in accordance with National Health and Medical Research Council guidelines for the conduct of research for the duration of the study and 5 years post publication, in accordance with best practice research guidelines [29].

Results

This study received a grant from Perpetual's IMPACT Philanthropy Application Program in 2021 and was approved by the Peter MacCallum Cancer Centre Human Research Ethics Council in May 2022 (HREC/84219/PMCC). In total, 37 patient participants and 7 CNC participants were recruited across gynecological, head and neck, lung, and urological cancer streams from May 10, 2022, to October 19, 2022. Data collection, cleaning, and analysis activities are ongoing, and data collection will be concluded in April 2023. Study results are expected to be disseminated by the end of 2023.

Discussion

Principal Findings

This study will provide a comprehensive assessment of the Complexity Checklist's acceptability, appropriateness, and practicability (as defined by Smarts' multidimensional model of clinical utility) [12]. These data will provide understanding regarding patient and CNC perspectives on the Checklist's clinical utility and inform recommendations for changes to the Checklist (addition, removal, and modifications of items), and changes to training and instructions provided to clinicians delivering the Checklist. Findings from exploratory objectives will give early evidence of the Checklist's predictive capability and concordance with evidence-based measures. These findings will guide Checklist refinement, as well as justification and development of future studies assessing the Checklist's predictive capability and potential to impact clinical outcomes

Recent literature promotes the importance of understanding the impacts of social determinants of health (SDoH) on clinical care, though the definition and inclusion of SDoH in previous clinical checklists are varied [1,30]. The Complexity Checklist comprises structural (gender, education, and socioeconomic position) and intermediary determinants (psychosocial, behavioral, and biological factors), as well as individual medical factors that senior cancer nurses identified as contributing to worse patient experiences and outcomes [3]. This checklist has the potential to serve dual purposes: informing care for individual patients, while also gathering structured data that will enrich health service understanding of the distribution and impact of SDoH within their patient population to inform system and service level change.

Limitations

This mixed methods study is not sufficiently powered to establish statistical evidence for the Checklist, though the target sample size is suitable to inform qualitative findings. The case-series approach, with no control group, aims to describe the characteristics and outcomes of patient participants rather than investigate the effectiveness of the intervention. These limitations will be addressed in a future large-scale trial if this study supports justification for further investigation. Recruitment will occur at a specialist metropolitan cancer hospital in Victoria, and a lack of diversity in patient participants may result.

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However, inclusion criteria have been developed to enable participation from non-English speaking persons. Future studies will specifically explore the clinical utility of the Checklist in culturally diverse cancer populations, acknowledging the importance of constructing cross-culturally valid measures [31].

Dissemination

Following data analysis, findings will be presented to the study funder as required by the funding agreement. Findings will be disseminated through standard scientific channels including peer-reviewed publications, conference presentations, and communities of practice, as well as to a broader audience including media, government, service users, and clinicians. The study investigators have a strong interest in promoting awareness of how social disadvantage affects cancer experiences and outcomes, and how inequities in cancer care can be addressed.

Conclusions

Structural and intermediatory determinants of health can result in access barriers to health care, posing a significant risk to achieving equity in cancer care. The Checklist aims to assist nurses to quickly and in a standardized manner, identify people disadvantaged due to social determinants of health at risk of complex care needs, so necessary supports can be provided. Pilot-testing had shown early evidence of potential. The study outlined above will assess the acceptability, appropriateness, and practicability of the measure, from the perspectives of newly diagnosed patients with cancer and specialist nurses involved in their care. Findings will inform further development and future studies to assess the Checklist. Integration of the Checklist into routine care offers the opportunity to improve patient care and outcomes, as well as create data sets with information regarding the SDoH to inform health service reform.

Acknowledgments

The authors acknowledge and thank all previous project team members and nurse participants who contributed to the development of the Checklist. We would also like to thank all nurse and patient participants for their willingness to take part and give their time to this study. This study has been funded by the Perpetual Foundations' IMPACT Philanthropy Application Program.

Data Availability

Data generated by this study will be available from the corresponding author upon reasonable request.

Authors' Contributions

MK, DM, AH, KG, and SA conceptualized the study. MK, KG, and SA designed the methodology. HC and EC are currently undertaking study activities outlined in this paper. All authors contributed to the preparation, reviewing, or editing of this paper.

Conflicts of Interest

None declared.

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Abbreviations

CNC: clinical nurse consultant
EMR: electronic medical record
PO: project officer
PROM: patient-reported outcome measure

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REDCap: Research Electronic Data Capture
SDoH: social determinants of health

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Protocol

Drug Repurposing for Cancers With Limited Survival: Protocol for a Retrospective Cohort Study

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Abstract

Background: Only 5% of the molecules tested in oncology phase 1 trials reach the market after an average of 7.5 years of waiting and at a cost of tens of millions of dollars. To reduce the cost and shorten the time of discovery of new treatments, "drug repurposing" (research with molecules already approved for another indication) and the use of secondary data (not collected for the purpose of research) have been proposed. Due to advances in informatics in clinical care, secondary data can, in some cases, be of equal quality to primary data generated through prospective studies.

Objective: The objective of this study is to identify drugs currently marketed for other indications that may have an effect on the prognosis of patients with cancer.

Methods: We plan to monitor a cohort of patients with high-lethality cancers treated in the public health system of Catalonia between 2006 and 2012, retrospectively, for survival for 5 years after diagnosis or until death. A control cohort, comprising people without cancer, will also be retrospectively monitored for 5 years. The following study variables will be extracted from different population databases: type of cancer (patients with cancer cohort), date and cause of death, pharmacological treatment, sex, age, and place of residence. During the first stage of statistical analysis of the patients with cancer cohort, the drugs consumed by the long-term survivors (alive at 5 years) will be compared with those consumed by nonsurvivors. In the second stage, the survival associated with the consumption of each relevant drug will be analyzed. For the analyses, groups will be matched for potentially confounding variables, and multivariate analyses will be performed to adjust for residual confounding variables if necessary. The control cohort will be used to verify whether the associations found are exclusive to patients with cancer or whether they also occur in patients without cancer.

Results: We anticipate discovering multiple significant associations between commonly used drugs and the survival outcomes of patients with cancer. We expect to publish the initial results in the first half of 2024.

Conclusions: This retrospective study may identify several commonly used drugs as candidates for repurposing in the treatment of various cancers. All analyses are considered exploratory; therefore, the results will have to be confirmed in subsequent clinical trials. However, the results of this study may accelerate drug discovery in oncology.

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KEYWORDS

cancer; death; drug repurposing; epidemiology; mortality; oncology; pharmacoepidemiology; pharmacology; side effects; survival; survivors

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Introduction

The usefulness of new cancer treatments is traditionally analyzed in clinical trials, which are considered the most rigorous design to study the effects of a treatment on a disease. Despite their strengths, clinical trials have significant limitations, such as cost and time. In a typical clinical trial, one or very few treatments are tested over a course of 7.5 years, and in oncology, the costs range from US $4.5 million (phase I) to US $22.1 million (phase III) [1-4]. Despite this, the clinical trials database ClinicalTrials.gov registers more than 22,000 trials each year, accounting for billions spent annually on clinical trials [5].

In oncology, the results of this substantial financial investment are modest, at best. As an example, only 5% of the molecules tested in phase 1 trials are marketed, and even if they are, they rarely generate a substantial change in the prognosis of patients [6,7]. In addition, the issue seems to be getting worse because the number of approved molecules has not increased in recent decades, but investment by the pharmaceutical industry has increased significantly [8].

Various strategies have been used to try to improve the efficiency of clinical trials. One of the most interesting is drug reuse (drug repurposing), with the aim of finding new uses for existing drugs approved for another therapeutic indication. This approach can, in most cases, allow research to begin with phase 2 trials because preclinical, pharmacokinetic, pharmacodynamic, and toxicity data are usually already known [7]. Looking for new treatments among already known molecules does not seem unreasonable, because in Spain alone, there are more than 2600 active ingredients approved and in use; it makes sense to think that some of them may have unknown effects on cancer. This approach, however, faces significant challenges since the complex and heterogeneous nature of cancer means that drugs with an effect on one type of cancer may not exhibit similar efficacy in several subtypes of cancer. Additionally, issues related to intellectual property, regulatory pathways, and the need for robust clinical evidence contribute to the complexity of drug repurposing efforts in oncology [9,10].

Another approach that substantially lowers the cost of pharmacological discoveries is the use of secondary data for research. Secondary data, which are used in some epidemiological designs, are those that are not collected for the purpose of the investigation but for another purpose, generally before the start of the study. Traditionally, data of this type are of poor quality because they are collected for other purposes, without the rigor of prospective studies. The number of variables may be incomplete because the data collection was not designed to address the research question. However, the technological revolution in recent decades has led to a paradigm shift, leading to reconsiderations of the classic axiom that secondary data are of low quality. New technologies and social networks produce a substantial amount of population data, which are not always of poor quality. The application of these technologies to medicine has led to the implementation of electronic health records and electronic prescription. Although the data in these 2 registries are not research data, they are of high quality, as they are used in clinical practice to manage people's health. Electronic prescription in Catalonia, for example, is how treatments are prescribed to users of the National Health System; therefore, it contains the drugs, doses, and guidelines actually prescribed to millions of people by their doctors. In addition, these doctors do not type the active ingredients in the prescription, which could lead to errors, but rather select them from lists in drop-down windows; therefore, the database is completely encrypted and does not contain transcription errors, in addition to being continuously updated. Other current databases, such as the mortality registry of the National Institute of Statistics (INE) or the Minimum Basic Data Set (CMBD) registry, where the diagnoses and procedures performed on hospitalized patients in Spain are recorded, can offer sufficient quality, in combination with electronic prescription, to draw conclusions about some of the effects of commercialized drugs [11,12].

Thus, combining the 2 strategies discussed above, we have designed a drug epidemiological study using population databases to identify drugs whose consumption is associated with changes in the survival of patients with cancer. For this, the pharmacological agents consumed by long-term survivors of incurable cancer will be compared with the drugs consumed by patients with shorter survival. We hope that this will allow, with a minimum investment of time and money, the identification of hitherto unknown effects of the molecules marketed in Spain on various oncological diseases.

This paper presents the general protocol for the study; the primary objective is to identify drugs whose consumption influences the survival of patients with high-lethality cancer (defined as those with a 5-year average survival of less than 20%, according to the statistics available at the time of database creation), and the secondary objective is to study the relationship between nonneoplastic diseases of patients with cancer and their survival. Given the diversity of the expected results with respect to different drugs and cancer diseases, we plan to publish the most relevant results in independent papers, in which the methodological details of each substudy will be described, as well as the specific interpretation of the results and their implications, depending on the nature of the findings and the associated cancer.

Methods

Design

This will be a retrospective cohort study in which a cohort of patients with high-lethality cancer (cohort 1) and another control cohort composed of people without cancer (cohort 2) will be studied.

Participants and Settings

The study population will be patients with the following cancers whose estimated survival at 5 years is less than 20%: lung, pancreas, esophagus, gastric carcinomas, hepatocarcinoma, and metastatic cancers.

Cohort 1 will include all patients registered in the databases of the public health system in Catalonia (Spain) who were diagnosed with any of the diseases under study between 2006 and 2012 (Textbox 1 contains the list of International

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Classification of Diseases, Tenth Revision [ICD-10] codes) and who have complete data regarding the study variables (see "Outcome Measurements and Variables" section).

Textbox 1. Diagnostic codes (International Classification of Diseases, Tenth Revision [ICD-10]) for the pathologies under study.

Neoplasm lung

- C34.0, C34.00, C34.01, C34.02, C34.1, C34.10, C34.11, C34.12, C34.2, C34.3, C34.30, C34.31, C34.32, C34.8, C34.80, C34.81, C34.82, C 34.9, C34.90, C34.91, and C34.92

Neoplasm pancreas

- C25, C25.0, C25.1, C25.2, C25.3, C25.7, and C25.9

Neoplasm hepatic

- C22, C22.0, C22.1, C22.2, C22.3, C22.4, C22.7, C22.8, and C22.9

Neoplasm gastric

- C16, C16.0, C16.4, C16.3, C16.1, C16.2, C16.5, C16.6, C16.8, and C16.9

Neoplasm esophagus

- C15, C15.3, C15.4, C15.5, C15.8, and C15.9

Metastasis

- C78.0, C78.00, C78.01, C78.02, C78.1, C78.2, C78.3, C78.30, C78.39, C78.4, C78.5, C78.6, C78.7, C78.8, C78.80, C78.89, C79.0, C79.00, C79.01, C79.02, C79.1, C79.10, C79.11, C79.19, C79.2, C79.3, C79.31, C79.32, C79.4, C79.40, C79.49, C79.5, C79.51, C79.52, C79.6, C79.60, C79.61, C79.62, C79.7, C79.70, C79.71, C79.72, C79.8, C79.81, C79.82, C79.89, C79.9, and C80.0

In cohort 2, a total of 4 control participants will be included for each patient with cancer included in cohort 1. Control participants will be selected from those registered in the databases of the public health system in Catalonia whose diagnostic codes do not include neoplasm diseases (ICD-10 codes C00 to D49). The 4 control participants will be matched with the cases in cohort 1 by place of residence and date of birth, of which 2 controls will have been born in the same year and the other 2 controls will have been born 10 years earlier, with the aim of generating an older subcohort with, therefore, higher expected mortality.

Participants who, due to their unique health characteristics, including rare diseases or peculiar sociodemographic data such as extreme ages or residing in sparsely populated areas, were at risk of being identified were excluded from the sample.

Duration

The patients in cohort 1 will have been diagnosed with the cancer under study between 2006 and 2012, both inclusive, and their survival will be retrospectively monitored for 5 years after diagnosis or until death if it occurs earlier. Cohort 2 will include patients without cancer who have had any type of contact with the health care system between 2006 and 2012, and these individuals will be followed up retrospectively for 5 years or until death if it occurs earlier.

Data Sources

The study will be carried out using secondary data previously collected from various health databases at the population level. The researchers accessed the data set through the PADRIS program (Programa públic d'analítica de dades per a la recerca i la innovació en salut a Catalunya) of AQuAS (L'Agència de Qualitat i Avaluació Sanitàries de Catalunya) [13]. This program is designed to facilitate research by reusing data from the Catalan Public Utilization System (Sistema Sanitari Integral d'Utilització Pública de Catalunya [SISCAT]) with maximum ethical and data protection guarantees. The data will be pseudonymized and subjected to a study of the risk of reidentification of individuals from the data set, thus minimizing this risk before being used by the researchers.

The general characteristics of the original databases from which the study data will be obtained are summarized below:

- Hospital CMBD is a database in which diagnoses and procedures performed on hospitalized patients are recorded throughout the Spanish territory; all public hospitals and the majority of private hospitals (>95% hospital coverage) are included [14].
- Estació Clínica d'Atenció Primària (ECAP) is an electronic medical history program launched in 2001 and used by family doctors, pediatricians, and nurses from the Catalan Institute of Health (Institut Català de la Salut [ICS]) primary care centers when they visit patients; it includes all previous illnesses known to the primary care physician and records of the health care process in the outpatient setting, including assessments by health care personnel, diagnostic tests, and treatment, among others. The PADRIS program has only provided data since 2006, after which data are considered to be of good quality.
- The registry of causes of death is prepared by the INE using data from the Medical Certificate of Death or Statistical Bulletin of Death, Statistical Bulletin of Judicial Death, and Statistical Bulletin of Childbirth. It is prepared following the criteria established by the WHO (World Health

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Organization) in the International Classification of Diseases (ICD), which includes more than 12,000 diseases.
- Electronic prescription has been implemented in Catalonia progressively since 2010 and is currently deployed in 100% of primary care centers, pharmacies, and public hospitals in Catalonia. Prescribing and dispensing data will be obtained from the Comprehensive Health Information System of the Catalan Health Service (Servei Català de la Salut [CatSalut]), which is a computerized system used by the doctors of the national health system in Catalonia to prescribe financed pharmacological treatments to their patients and the pharmacies to dispense them; it contains information on the date of the prescription, the active ingredient, and dose, among other variables. Unfunded treatments can be prescribed using this tool but are often prescribed by other means (paper prescriptions).

Outcome Variables and Measurements

The primary end point is survival, calculated from the date of entry in the database until death or until 5 years of follow-up are reached. For patients in cohort 1, the earliest date of cancer diagnosis for which they have been selected to be part of the cohort will be considered the date of entry into the study (inclusion criterion).

As study variables, the following data will be collected from all patients:

- List of diagnosed diseases (data source: CMBD and ICS ECAP diagnostic registry)
- Date of death (data source: INE cause of death registry)
- Cause of death (data source: INE cause of death registry)
- Pharmacological treatment (data source: Catalan electronic prescription), including all prescribed active ingredients, drug withdrawal dates from pharmacies, consumed doses, and prescribed regimen, during the entire follow-up period
- Sex (data source: Sistema Integral d'Informació de Salut)
- Date of birth (data source: Sistema Integral d'Informació de Salut)
- Basic health area (data source: Sistema Integral d'Informació de Salut)

For the patients included in the study with one of the cancers under study (cohort 1), the following variables will also be collected:

- Type of cancer and presence of metastases (data source: CMBD and ICS ECAP diagnostic registry)
- Date of diagnosis for which the patient is included in the cohort (data source: CMBD and ICS ECAP diagnosis registry)
- Surgical treatment of the cancer (data source: CMBD)
- Date of surgical treatment (data source: CMBD)

Data Curation

The data used in this study will be obtained from different databases, which must be merged for the analysis. None of the databases will be sorted by patient but by other types of entries (drugs, diagnoses, procedures performed, etc); therefore, the same patient could appear multiple times in each of them. Thus, first, a date will be associated with each event, and the information in the databases will be sorted by patient, with each patient as an entry that appears only once.

The coding of diseases and therapeutic procedures has undergone changes during the years of collection in the cohort, transitioning from using International Classification of Diseases, Ninth Revision (ICD-9) coding to ICD-10 coding. Consequently, all the data with ICD-9 coding will have to be converted to ICD-10 using the conversion tables provided by the Government of Catalonia (Generalitat de Catalunya) on their website [15].

In the pharmacological dispensing database, the active principles will be collected through the Anatomical Therapeutic Chemical (ATC) Classification System, and the amount dispensed monthly will be determined using the number of defined daily doses (DDDs) [16]. DDDs change over the years and are not uniform for different active ingredients or for drugs that form different groups as defined by the ATC4 codes. Thus, when necessary, DDDs will be transformed into units of mass for each of the drugs using the tables provided by the WHO with the evolution of DDDs over time [17].

One of the databases managed includes patients with metastases of any origin. For these patients, their previous diagnoses will be traced, and all the codes for both the CMBD and the ECAP will be analyzed to search for cancer diagnoses before metastasis to determine the origin of the cancer.

Finally, a patient rejection process will be applied based on the consistency of dates between the different databases. Following this principle, all those patients who, having been included in the database, do not have electronic prescription records will be rejected. In addition, all patients without registration or enumeration in the death databases will be excluded. Finally, patients with inconsistent dates will be excluded, for example, with postdeath records in the CMBD, ECAP, or electronic prescription.

Machine Learning

Machine learning techniques can reveal associations between variables, which are difficult to discover through statistical analyses [18]. Given the large volume of active ingredients to be analyzed and the high number of cases included in the database, in this study, as an additional step to the statistical analyses described below, machine learning techniques will be used to identify associations between the consumption of drugs and survival. The associations identified by machine learning techniques will later be confirmed by the classical statistical analyses described below.

Association rule mining (ARM), widely used for medical data analysis, will be used [19-21]. Through this method, association rules (ARs) are constructed that represent possible relationships between different elements within large data sets, identifying the most relevant ones. ARs consist of an antecedent (left hand side), which can be made up of several elements (drugs, age, etc), and a consequent (right hand side), which is made up of a single element, in the case of this study, survival at 5 years. In this study, a total of 2 sets of different ARs will be built using two approaches: (1) based on the amount of drug consumed, and (2) based on the time of drug consumption.

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All variables will be previously categorized for use by the ARM technique. The survival variable will be treated dichotomously, depending on whether the patient has survived for at least 5 years. To obtain the set of rules based on the time of consumption of the drugs (active principles [ATC4] and families [ATC5]), the information will be categorically organized by quarters: whether the drug has been consumed during the quarter or not. To construct the set of rules related to the doses of drug consumed, the average DDD, discretized in 3 quantiles, will be used during the survival time of the patient.

Among all the rules generated by this methodology, the relevant ones will be selected. For this, an a priori algorithm [22] will be used to extract element frequencies, as it has been shown to be effective and is widely used in the literature [23].

Of all the rules produced using this methodology, only those that are met in at least 5 patients will be taken into consideration, and the most relevant will be selected using the following set of metrics:

- Support is a measure that indicates the frequency of the combination of the antecedent and consequent in the data set.
- Confidence is a measure that indicates the probability of obtaining a consequent given an antecedent.
- Lift is a measure that indicates how much more the combination of the antecedent and consequent occurs compared with what would be expected if they were statistically independent.
- Conviction is a measure that evaluates the relationship between the antecedent and the consequent of a rule [24]. This measure takes into account the occurrence of both independently. It is defined as the ratio of the expected frequency of incorrect predictions made by the rule to the actual frequency of incorrect predictions made by the rule. As a general rule, those values that are further from 1 usually indicate the most interesting rules.

First, the data are preprocessed to obtain a column for each active substance in each patient and, depending on the desired screening, the amount of the active substance taken in the different quarters. Other relevant data, such as age and sex, are also added.

Subsequently, AR search algorithms are run on the processed data, with a support threshold set to avoid generating nonrelevant rules, for example, less than 5 patients. However, this support can be filtered again later. Obtaining ARs that indicate static relationships between the different attributes, filtering now those that present survival.

Finally, the filtered rules are sorted by the desired metric (eg, lift). This metric was chosen especially for its ability to find active ingredients with a higher-than-expected survival rate. In the example shown in Table 1, active substance 3 in a medium dose leads to 6 times longer survival than expected in these patients.

Table 1. Example of the use of the association rule mining method for the analysis of survival associated with different active ingredients and combinations of active ingredients.

Antecedent	Quantity	Consequents	Support	n	Confidence	Lift	Conviction
Single active ingredient							
active-3	Medium	Survival	0.0079	30	0.5000	6.4054	1.8438
active-5	Low	Survival	0.0081	31	0.4366	5.5934	1.6364
active-1	Low	Survival	0.0013	5	0.4166	5.3378	1.5804
active-4	High	Survival	0.0013	5	0.4166	5.3378	1.5804
active-2	Low	Survival	0.0021	7	0.4000	5.1243	1.5365
Combination of active ingredients							
active-3 and active-2	Medium, low	Survival	0.0021	7	0.8888	11.3873	8.2974
active-5 and active-1	Low, low	Survival	0.0015	6	0.7500	9.6081	3.6877
active-4 and active-2	High, low	Survival	0.0013	5	0.7142	9.1505	3.2267

In addition, it is possible to filter by age, gender, or patient group, as well as search for relationships between them and their survival. Similarly, combinations of active ingredients can be sought that lead to increased survival (Table 1).

Statistical Analysis

To achieve the primary objective, several exploratory analyses will be performed. These will look for an association between the use of the different drugs available in the database (the exposure variable) and patient survival (the outcome variable). The exposure variable will be treated both dichotomously (exposed or not exposed) and quantitatively. The time exposed to the drug, the average monthly dose, the maximum dose, or the cumulative dose per unit of time will be considered. Specific analyses will be carried out on the effect of 2 or more drugs that have been shown to influence survival when they have been consumed, either simultaneously or sequentially, within the time unit being analyzed. The outcome variable is survival during the observation period. Patients who are censored, for whom no death is recorded during the follow-up time, are considered alive at the end of the period.

In addition to the machine-learning techniques described above, the association between exposure and outcome will be investigated using 2 different approaches. The exposure odds

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for each drug will be calculated, and this exposure will be compared between patients considered alive at 5 years and those who have died using odds ratios (exposure odds ratio). The group of nonsurvivors will be selected with different time criteria in a sensitivity analysis: deceased in the 1st, 2nd, or 3rd year after diagnosis. Second, the survival time of participants exposed and unexposed to each drug available in the database (individual agents, ATC5 codes) or to each family of agents (ATC4 codes) will be compared.

To avoid bias due to a lack of randomization, in both approaches, matching will be carried out between the groups with respect to confounding variables. In addition, if residual confounding is suspected or an imbalance between groups remains after matching, adjustments for age, sex, and diagnostic groups will be performed. A Cox regression model will be constructed to estimate the effect of the evaluated drug. The hazard ratio (HR) and its 95% CI will be reported. Hazard proportionality will be assessed graphically by Schoenfeld residuals.

As a secondary objective, we plan to analyze the relationship between the presence of various nonneoplastic diseases and the survival of patients with cancer. To do this, we will compare the survival of patients with a specific disease to those who do not have it, adjusting multivariate models for age, gender, other conditions that may impact survival, and medications that have previously been shown to modify survival in previous analyses.

All analyses conducted in the cohort of patients with cancer will be replicated in a control patient group matched by age to the patients with cancer (with expected lower mortality) and in another group of older patients, where each control will be 10 years older than their cancer counterpart (with expected higher mortality). The findings that are reproduced in these groups of the control cohort will be discarded, as they are considered the result of uncontrolled biases or general effects on survival, not related to the cancers under study.

To consider a result statistically significant, the P value will be set at P=.05. All analyses are considered exploratory and hence subject to confirmation in new studies; therefore, no correction techniques will be applied to the P values obtained. All statistical analyses will be performed using R statistical software (version 4.1.0 or higher; R Core Team).

Methods to Address Potential Sources of Bias

This study, given its retrospective nature, is potentially affected by a series of biases, whose prevention or compensation will be attempted through various techniques. The 3 most important biases are discussed below:

- Reverse causality bias: drugs that are prescribed to patients near death to control their symptoms will appear associated with an increased risk of death in the analyses, with the prescription of these drugs not being the cause of death but a consequence of proximity to death. This bias will be alleviated by eliminating the drugs prescribed 3 months before death from the analysis.
- "Immortal patient" bias: the longer a patient survives, the more likely he or she is to be diagnosed with pathologies and to consume drugs. This can give the false appearance that the drugs consumed throughout life are the cause of prolonged survival. To control this effect, the analyses only considered the drugs consumed up to a certain date in the group of patients who survived until that same date. For example, in the group of patients who have survived at least 3 months after the diagnosis of their cancer, only drugs consumed at any time up to month 3 after the cancer diagnosis will be considered. Thus, the consumption of the drug will not be explained by longer survival because the entire group will have survived until the moment when the drugs under study are consumed. Patients who consume the study drugs after the established time cutoff point will be eliminated from the analysis. As a comparison group, only patients who have not consumed the drug at any point in their disease evolution will be taken into account.
- Diagnostic anticipation or "medical surveillance" bias: this bias occurs when patients are included in studies who are in a screening program for cancer because, in such programs, the cancer is diagnosed earlier, which causes the erroneous impression that the individuals live longer. In our database, patients with certain diseases may have undergone frequent diagnostic tests, thus triggering early cancer detection. For example, patients with chronic obstructive pulmonary disease (COPD) may have undergone periodic radiographs, in which lung cancer has been detected early. This may give the impression that COPD, or the drugs used by patients with COPD, are associated with increased survival from lung cancer. To control this bias, patients with a previous pathology that produces greater medical surveillance of the organ where the cancer developed will be eliminated from the analysis.

Sample Size Considerations

Based on a maximum 5-year survival probability of 20% (P=.2, *Q*=.8) and with a significance level of 5% (95% CI) and a power of 80%, it will be possible to detect a difference of 10% between 2 groups with 294 individuals per group. Table 2 shows an initial estimate of the number of survivors at 5 years available during the study period. According to preliminary data not shown, the database available for the study includes a total of 102,860 patients diagnosed with the cancers under study.

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Table 2. Incidence and estimated survival for the main pathologies under study.

Cancer	New cases each year, n	Estimated 5-year survival, n (%)	Cumulative survivors throughout the study, n
Lung	4079	738 (18.1)	3691
Metastatic colon	6128	852 (13.9)	4259
Metastatic bladder	2444	122 (5)	611
Metastatic kidney	1094	131 (12)	656
Metastatic melanoma	860	171 (19.9)	856
Pancreas	1168	96 (8.2)	479
Esophagus	616	116 (18.8)	579
Metastatic stomach	1089	57 (5.2)	283
Liver	670	118 (17.6)	590

Ethical Considerations

Data handling will comply with Spanish Organic Law 03/2018 for data protection, the General Data Protection Regulation 2016/679, and local data protection regulations. Fundació Unio Catalana Hospitals' ethics committee reviewed the study (CEI 18/37) and waived patient consent due to anonymized retrospective data review.

Results

The study is currently in progress, with access to various databases. The data have undergone harmonization and curation, and they are now ready for analysis. We have initiated statistical and machine learning analyses. We anticipate discovering multiple significant associations between commonly used drugs and the survival outcomes of patients with cancer (the primary objective). Additionally, we aim to identify relevant associations between the presence of certain chronic diseases and survival outcomes in different cancer types (the secondary objective). There will be specific effects for particular cancers and general effects that impact the survival of a broad range of cancers. The initial publications containing the first relevant results are expected to be released in the first half of 2024.

Discussion

The aim of this study is to identify drugs for commercial use for pathologies with an effect on the survival of patients with cancer. For the study, diseases that have high lethality (survival rate <20% at 5 years) will be selected because they are a priority in terms of the search for new therapies and because for these diseases, conventional treatment has had little impact on survival, which facilitates the observation of additional survival effects from other drugs. The diseases have also been selected for their high frequency, so that, despite the high lethality, the group of survivors at 5 years will be large enough to allow comparisons with the deceased group with sufficient statistical power.

Despite the good quality of the data used, this study is based on analyses of secondary data and, therefore, has certain limitations that, although hypotheses can be established, make it necessary for these hypotheses to be tested through trials that generate primary data.

First, we do not have all the variables that can act as confounding factors in patient survival. For example, we do not have data on the histology of the various tumors, which can impact survival. Especially important is also the absence of data on hospital treatment for cancer, which does not appear in any of the available databases. Due to this limitation, the study has been designed to investigate "long survivors" (5 or more years) because, for the diseases studied, there are no treatments that have been shown to extend survival to the fifth year. For this reason, it is not probable that hospital treatments act as a confounding factor (because they have no known association with the outcome studied: survival after 5 years).

Second, patient registration in the databases does not coincide exactly with disease onset, resulting in a shortened estimated time to death. This limitation is greater in the CMBD than in the ECAP databases; therefore, one database will be complemented with the other to alleviate this limitation. However, this temporal bias has an established direction: registration in the databases always occurs after the diagnosis. This allows all cases to be classified correctly in the group of patients identified as long survivors because patients who lived 5 years since their inclusion in the database will have lived at least 5 years from disease diagnosis. However, there will be a classification error whereby some long survivors, for whom their data were entered late in the databases used, will fall within the comparison group (classified as "nonlong survivors"). This error will affect at most 20% of the comparison group because that is the maximum survival at 5 years estimated for the diseases under study. Therefore, the specificity of the classification will be at least 80%, and for some cancers, it will reach 95% (such as metastatic bladder cancer or metastatic stomach cancer). This classification error will bias the results toward the null hypothesis, not invalidating the differences ultimately found between groups, although it does detract from the power of the study. Given that the magnitude of the effect sought is very large, we do not believe that the decline in power due to classification bias prevents the observation of these differences.

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Third, despite the shortening of the time frame of the data analysis for each patient to control for reverse causality and "immortal patient" biases, there may be a residual effect derived from these biases within the time frame not eliminated from the analysis; however, we expect this effect to be much smaller. In addition to the aforementioned biases, there may be information biases, mainly due to pathologies not registered in the database. We do not expect that these biases will significantly affect the main variables because cancer diagnoses are usually registered in the databases used as soon as they are known, the pharmacological registry includes drugs dispensed in pharmacies (not only prescribed), and registry mortality is very reliable.

Finally, such a broad exploration of variables and results will lead to the discovery of many random results due to biological variability that may not be able to be replicated in future research. The researchers will consider the implementation of adjustments such as the "false discovery rate." Notably, the study is exploratory, and the results must be confirmed in subsequent studies designed to test each hypothesis derived from this study.

In conclusion, this will be a pharmaco-epidemiological study with great potential to discover new drugs that influence cancer, but that, by design, will serve only as a preliminary step, guiding subsequent research aimed at the repurposing of active molecules for the treatment of cancer.

Acknowledgments

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The authors declare that no artificial intelligence has been used to prepare any section of the text of this manuscript.

Data Availability

The databases used in this study are managed by the PADRIS program (Programa públic d'analítica de dades per a la recerca i la innovació en salut a Catalunya) of AQuAS (L'Agència de Qualitat i Avaluació Sanitàries de Catalunya). The authors cannot give access to the aforementioned databases. Any researcher interested in using data from the Catalan Public Utilization System (Sistema Sanitari Integral d'Utilització Pública de Catalunya [SISCAT]) must contact directly the PADRIS program [25].

Conflicts of Interest

None declared.

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Abbreviations

AQuAS: L'Agència de Qualitat i Avaluació Sanitàries de Catalunya
AR: association rule
ARM: association rule mining
ATC: Anatomical Therapeutic Chemical
CatSalut: Servei Català de la Salut
CMBD: Minimum Basic Data Set
COPD: chronic obstructive pulmonary disease
DDD: defined daily dose
ECAP: Estació Clínica d'Atenció Primària
HR: hazard ratio
ICD: International Classification of Diseases
ICD-10: International Classification of Diseases, Tenth Revision
ICD-9: International Classification of Diseases, Ninth Revision
ICS: Institut Català de la Salut
INE: National Institute of Statistics
PADRIS: Programa públic d'analítica de dades per a la recerca i la innovació en salut a Catalunya
SISCAT: Sistema Sanitari Integral d'Utilització Pública de Catalunya
WHO: World Health Organization

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Protocol

Efficacy and Safety of Pre-Exposure Prophylaxis to Control HIV and Sexually Transmitted Infection Among Men Who Have Sex With Men: Protocol for a Single-Arm Interventional Study

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Abstract

Background: Pre-exposure prophylaxis (PrEP) against HIV infection is a new approach that involves the prophylactic use of the anti-HIV drug Truvada (tenofovir disoproxil fumarate [TDF] and emtricitabine [FTC]) by people not infected with HIV.

Objective: The objective of this investigator-initiated clinical study of PrEP was to evaluate the incidence of HIV and sexually transmitted infection (STI), safety and efficacy of PrEP in PrEP users, and their compliance with PrEP medication. The social, medical, and economic benefits of PrEP in Japan was assessed.

Methods: This single-center feasibility study of PrEP was conducted at the National Center for Global Health and Medicine, Tokyo, Japan, where a cohort of men who have sex with men without HIV was established in January 2017. This single-arm interventional study compared the efficacy and safety of PrEP in a single group of men who have sex with men who participated in PrEP cohort studies. For reference, the cohort study participants who did not participate in the PrEP study were included for comparison. Blood samples were collected for storage at baseline and clinic visits at 1, 3, and 6 months after starting PrEP and every 3 months thereafter. The participants were administered with 1 tablet of Truvada once daily as PrEP. They underwent blood and anal swab tests 1 and 3 months after starting PrEP and then HIV and STI infection assessments at 3-month intervals. Blood samples were centrifuged at the AIDS Clinical Center Laboratory. PrEP safety was evaluated by monitoring serum creatinine levels for symptoms of renal function disorders. The primary end point was the incidence of HIV in PrEP users (100 person-years). The secondary end points were the incidence of STI in PrEP users (100 person-years), incidence of adverse events caused by Truvada, frequency of high-risk sexual activity, and adherence to periodic visits and medication.

Results: The study protocol was reviewed and approved by the certified review board of the National Center for Global Health and Medicine (NCGM-C-003129-03) on April 20, 2020. Changes to the study plan were submitted for review by the certified review board and approved before implementation. Recruitment was completed on March 28, 2019, and the study was completed (last adult participant and last time point) on March 31, 2021. The data were analyzed, and the main results of the study have been published in a peer-reviewed journal.

Conclusions: The findings indicated that PrEP is a highly effective and feasible strategy against HIV infection in terms of prophylactic response, retention, and compliance.

Trial Registration: UMIN Clinical Trials Registry UMIN000031040; https://tinyurl.com/3msdkeb8 and Japan Registry of Clinical Trials jRCTs031180134; https://tinyurl.com/2p88mhyr

International Registered Report Identifier (IRRID): RR1-10.2196/50919

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KEYWORDS

pre-exposure prophylaxis; human immunodeficiency virus infection; Truvada; men who have sex with men cohort; Japan

Introduction

The government of Japan formulated the "Tourism Vision for Graphics" in March 2016, in which a target of 40 million foreign visitors to Japan in 2020 and 60 million in 2030 was set to stimulate the travel economy; it is expected to result in a large number of foreigners entering Japan and increased cases of HIV and sexually transmitted infections (STIs). Our hospital is situated in Tokyo, the capital of Japan, and is one of the world's leading entertainment centers, attracting men who have sex with men (MSM). Given the importance of the MSM community to HIV transmission, there is an urgent need to address this issue in Tokyo [1]. Unfortunately, Japan's ongoing measures against HIV transmission have been inadequate, with approximately 1500 new HIV infections diagnosed each year. Lifetime medical expenses per case of HIV infection are approximately ¥100 million (approximately US $660,641.69 as of November 1, 2023) in Japan, making the introduction of effective measures against infection an urgent issue.

Pre-exposure prophylaxis (PrEP) against HIV infection is a new approach that is gaining popularity in many countries worldwide [2-4]. PrEP involves preventing HIV infection through the prophylactic use of the anti-HIV drug, Truvada (tenofovir disoproxil fumarate [TDF] and emtricitabine [FTC]), by people not infected with HIV and is expected to reduce HIV infections by approximately 90% [5-7]. It is recommended as an effective preventive strategy in the United States and by the World Health Organization, whereas Europe, Canada, Australia, Thailand, South Korea, Taiwan, and other Asian countries have started to introduce PrEP [8-10]. However, Truvada is not indicated or approved for PrEP use in Japan, and this strategy remains unexplored.

PrEP is aimed at populations at high risk of HIV infection, defined by the International AIDS Society as those with a new HIV infection rate of 2.0/100 person-years or higher and by the World Health Organization as with a new HIV infection rate of 3.0/100 person-years or higher [2,11]. The MSM population accounts for 2.9% to 4.6% of the male population in Japan. However, it accounted for 71% (670/940) of new HIV cases, and 54.4% (205/377) of new AIDS cases in 2018. These percentages are much higher than those in other Asian countries [12]. Thus, MSM may be considered a population at high risk of infection. By 2016, we had performed 1402 mail-based surveys among MSM in Tokyo. The results showed an HIV prevalence of 3% (13/429) among MSM in the study area (unpublished data). HIV incidence in a hospital sexual health (SH) outpatient target group has been reported to be 3.8/100 person-years of HIV incidence.[13]; however, given the increase in foreign visitors to Japan, MSM in Tokyo seems to be a sufficiently valid population for PrEP.

In PrEP, anti-HIV drugs are administered to healthy people not infected with HIV in an ongoing basis to prevent HIV infection; hence, people receiving PrEP must periodically visit a hospital to be tested for HIV and other STIs and check for adverse reactions to anti-HIV drugs. Healthy individuals receiving PrEP should be sufficiently prepared and knowledgeable to complete periodic hospital visits. Although success rates for PrEP vary greatly outside Japan, success or failure depends not only on PrEP providers but also on the degree of awareness and readiness of PrEP recipients [14]. Therefore, to ensure the effective implementation of PrEP, our hospital has been building an MSM cohort since the establishment of an SH outpatient clinic in January 2017 to facilitate the implementation of PrEP as a package that includes provider-side testing systems and education to build awareness among PrEP recipients. This investigator-initiated clinical study delivered PrEP as a strategic package to patients in a registered MSM cohort who wished to undergo PrEP. If the PrEP package is effective, it may lead to the regulatory approval for the PrEP use of Truvada, eventual establishment of PrEP in Japan, and decreased number of new HIV infections.

There is abundant evidence supporting the efficacy of PrEP, and PrEP has already been described in clinical guidelines [2]; therefore, a randomized controlled trial that compares PrEP with a placebo would be unethical. Our MSM cohort was scheduled to visit the SH outpatient clinic once every 3 months for a year as part of a phase of understanding and preparing for PrEP. Patients who were successfully checked for STIs and HIV during this period were deemed eligible for the study. Patients with a history of STIs were considered the preferred study candidates, although STI infection during the observation period had no bearing on study inclusion. The objectives of this investigator-initiated clinical study of PrEP were to evaluate HIV and STI incidence, safety, and efficacy of PrEP in PrEP users and compliance with PrEP medication. This study assessed the social, medical, and economic benefits of PrEP in Japan.

Regarding the effective implementation of PrEP, the hospital opened an SH-based outpatient clinic in January 2017. The MSM cohort study that preceded this study (establishment of the MSM cohort in Tokyo for the 2020 Tokyo Olympics and preparation for PrEP implementation and expansion; Human Research Ethics Committee of National Center for Global Health and Medicine [NCGM] [NCGM-G-002333-00]) was conducted. MSM cohort participants from the previous study who participated in this study received 1 Truvada tablet daily as PrEP and a single-arm intervention study to assess HIV and STI incidence before and after PrEP initiation. The patient population in the previous MSM cohort study enabled the development of a protocol for a clinical trial designed to assess the efficacy and safety of PrEP, even in a single-arm study.

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Methods

Ethical Considerations

The study protocol was reviewed and approved by the certified review board of NCGM (NCGM-C-003129-03). Changes to the study plan were submitted for review to a certified review board and approved before implementation. This study was registered with Japan Registry of Clinical Trials (jRCTs031180134).

This study followed the principles of the Declaration of Helsinki and was conducted in accordance with the "Ethical Guidelines for Medical and Health Research Involving Human Subjects" and "Clinical Trials Act." All the researchers involved in this study adhered to the above ethical standards.

The SH outpatient intern who attended to the participants and a nurse clinical research coordinator obtained informed consent from the participants. In accordance with the "Clinical Trials Act," written materials were used to explain the study to the participants, and after confirming that the study candidates understood the details of the study, voluntary informed consent was obtained in writing. Study candidates were made fully aware that their decision to participate in the study was voluntary; that once consent was provided, it could be withdrawn at any time with no special disadvantage to the participant; and that results already presented at academic meetings or published in research papers prior to the withdrawal of consent would not be removed. The original copy of the consent form was kept by the study organizer, and a copy of the consent form was handed to each consenting participant. The participants did not receive compensation for the study.

Stored specimens were used in subsequent evaluations, provided more detailed information, was required only for this study, and were not allowed to be used for any other purpose. The use of stored specimens for any new study warranted additional written informed consent. The model consent form is written in Japanese and can be provided upon request.

Study Design and Setting

This single-center feasibility study of PrEP was conducted at the NCGM, Tokyo, Japan, where a cohort of MSM without HIV was established in January 2017. This single-arm interventional study compared the efficacy and safety of PrEP in a single group of MSM who participated in PrEP cohort studies. For reference, the cohort study participants who did not participate in the PrEP study were compared.

In a previous MSM cohort study (establishment of MSM cohort in Tokyo toward the 2020 Tokyo Olympics in preparation for PrEP implementation and expansion—approved by the Human Research Ethics Committee of the NCGM; NCGM-G-002333-00; unpublished), HIV-negative MSM attending the SH outpatient clinic at NCGM were tested every 3 months for HIV and STIs (syphilis, pharyngeal, rectal *Chlamydia trachomatis*, and gonorrhea) and received guidance on safer sex. Participants who wished to undergo PrEP were included in this study. Interns specializing in HIV treatment attended patients at the SH outpatient clinic. The schedule of enrollment, interventions, and assessments are shown in Table 1.

The participants were administered 1 tablet of Truvada once daily as a PrEP. The participants underwent blood tests and anal swab tests 1 and 3 months after starting PrEP and then at 3-month intervals were assessed for HIV and STI infection. Blood samples were centrifuged at the AIDS Clinical Center Laboratory. In total, 5 mL of blood serum was frozen and stored at –80 °C in a deep freezer. The specimens were managed based on study IDs. The safety of PrEP was evaluated by monitoring serum creatinine levels for symptoms of renal function disorder, which is a known adverse reaction to Truvada. Truvada was discontinued in subjects with an estimated glomerular filtration rate (eGFR) below 60 mL/min/1.73 m^2.

The feasibility of PrEP implementation in Japan was examined through a cohort analysis of patient behavior based on medication adherence and hospital visits. Sexual behavior was assessed every 3 months in MSM cohort participants using a questionnaire (Multimedia Appendices 1 and 2) to determine whether PrEP increases high-risk sexual activity.

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Table 1. Participant timeline for the schedule of enrollment, interventions, and assessments.

Schedule	Time point[a]						
	Enrollment	Postenrollment					Close-out
	$-t_0$	Day 0	1 month	Every 3 months	Every year	When necessary	t_x
Enrollment							
Eligibility screen	✓						
Informed consent	✓						
List other procedures	✓						
Interventions							
Truvada combination tablet, 1 tablet, once a day	✓	✓	✓	✓	✓	✓	
Assessments							
Patient information	✓	✓	✓	✓	✓	✓	✓
Outcome (HIV testing [generation IV])	✓	✓	✓	✓	✓	✓	✓
STI[b] check (TPHA[c] quantification, RPR[d] quantification, pharyngeal and anal Chlamydia trachomatis or gonorrhea [genetic diagnostic method: TMA[e]])	✓	✓		✓	✓	✓	✓
Safety check (HBs[f] antigen or antibody, HBc[g] antibody, HCV[h] antibody, and amoebic antibody)	✓	✓			✓	✓	✓
Laboratory data (serum creatinine, eGFR[i], and liver function tests)	✓	✓	✓	✓	✓	✓	✓
HIV RNA testing and blood tenofovir levels						✓	

[a]Time points: patients were enrolled at premedication screening. The date of medication initiation will be day 0, with blood tests to confirm safety at the first month after medication initiation and every 3 months after that and at each yearly milestone to confirm infection. If necessary, HIV infection activity will be confirmed, and all tests will be confirmed at the end of the study. HIV RNA testing and blood tenofovir levels are performed when necessary.

[b]STI: sexually transmitted infection.

[c]TPHA: *Treponema pallidum* hemagglutination test.

[d]RPR: rapid plasma reagin.

[e]TMA: transcription-mediated amplification.

[f]HBs: hepatitis B surface antigen.

[g]HBc: hepatitis B core antigen.

[h]HCV: hepatitis C virus.

[i]eGFR: estimated glomerular filtration rate.

Study Participants

Sample Size Determination

Considering the HIV incidence of 7% without prophylactic drugs over the study period and possible decrease to approximately 0.7% by prophylactic treatment (90% effective), a minimum of 88 participants were needed for a binomial evaluation with a 1-tailed 5% level of significance and statistical power of 90%. A sample size of 120 was chosen to account for study dropouts and other factors.

Inclusion and Exclusion Criteria

The incidences of HIV and STI were analyzed in a sample of 120 participants using data collected for over 2 years. A previous MSM cohort study (NCGM-G-002333-00) had recruited approximately 500 participants. From this cohort, 120 participants were chosen for this study based on the statistical rationale described in the previous section.

Among the participants of a previous study performed at our hospital, those who adhered to regular hospital visits for 1 year and wished to receive PrEP were included in this study. Participants who met the inclusion criteria and none of the exclusion criteria (Textbox 1) were enrolled in this study. Enrollment took place between the approval of the ethics review committee and March 2019. Patients with suspected acute HIV infection were rescreened for study participation after a 1-month interval and could participate in the study if confirmed to be HIV-negative.

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Textbox 1. Study participation criteria.

Inclusion criteria

- HIV-negative men who have sex with men who practices anal intercourse
- 20 years or older
- At high risk of HIV infection (any of the following apply):
  - Contracted a sexually transmitted infection within the past year
  - Practiced anal intercourse without a condom within the past 6 months (insertive or receptive)
  - Has an HIV-positive sex partner
  - Used stimulants within the past 6 months
- Lives in Japan and understands Japanese
- Is a participant in the men who have sex with men cohort study, has completed 1-year of periodic hospital visits, and understands the significance and importance of HIV prevention by pre-exposure prophylaxis
- Has read the patient information and consent form carefully and indicated their willingness to participate in the study by signing the consent form

Exclusion criteria

- Suspected symptoms of acute HIV infection
- Serious liver damage or renal dysfunction (estimated glomerular filtration rate <60 mL/min/1.73 m^2)
- Taking a nephrotoxic drug (high doses of nonsteroidal anti-inflammatory drugs)
- Allergic to tenofovir disoproxil fumarate or emtricitabine
- Taking a drug that includes tenofovir disoproxil fumarate or emtricitabine
- May not be unable to take Truvada throughout the study period
- Otherwise deemed unsuitable for pre-exposure prophylaxis

Before enrollment, it was confirmed that the study participants met all the inclusion criteria and none of the exclusion criteria, and all necessary information was entered into a case enrollment form (CRF-1) that was submitted to the data center. The data center used the CRF-1 to check for eligibility and enroll subjects. The data center assigned an enrollment number and issued an "Outpatient Visit Schedule." The patients were observed for a minimum of 2 years and a maximum of 3 years. The study duration ranged from the day of the ethics committee approval to March 2022.

Interventions

The PrEP used in this study was FTC-TDF combination tablets. The product name and distributor was Truvada Combination Tab, Torii Pharmaceutical Co, Ltd. Each blue film-coated tablet contained 200 mg FTC and 300 mg TDF. The drug identification code of the drug was GILEAD-701. The tablets were stored at room temperature in an airtight container containing a desiccant. Once opened, they were stored away from moisture. As this was a single-arm interventional study, the choice of comparator was not applicable. In this open-label study, allocation sequence generation, adoption of a concealment mechanism, or blinding were not required.

Considering the range of enrollment periods and different durations of treatment for each participant, and assuming treatment for 100 study participants for 3 years, 100 (participants) × 12 (months) × 3 (years) = 3600 bottles of the study drug were procured for the 120 participants. Each patient was administered with 1 tablet daily. Treatment was initiated from the point of enrollment until March 2021. The study drug could only be prescribed by physician collaborators and dispensed by pharmacists. Drug information was excerpted from the January 2016 revision of the drug package insert, and only the latest version of the drug package insert was used.

The study drugs were stored, managed, and tracked for records of the supply, dispensing, retrieval, disposal, and return of drugs by the Department of Pharmacy of the NCGM. All surplus drug bottles were retrieved.

Data Collection and Assessment

Patient information included age, sex, ethnicity, HIV status (infected or not infected), current and past history of STIs (yes or no), sexual behavior (anal intercourse, number of sex partners, condom use, drug use, frequency of injected drug use [yes or no], and HIV and STI status of partner), timing of the most recent HIV and STI tests, medical history, complications, concomitant medications, and study drug adherence.

Blood specimens were collected and stored for periodic investigation before starting PrEP, 1 and 3 months after starting PrEP, and every 3 months thereafter. These periodic investigations included HIV testing (fourth generation), *Treponema pallidum* hemagglutination test quantification, rapid plasma reagin quantification, pharyngeal or anal *C trachomatis*, gonococcal testing (genetic method of diagnosis: transcription-mediated amplification), serum creatinine, eGFR, hepatic function testing, and testing to confirm a positive HIV

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test. HIV RNA testing, blood tenofovir levels, and other investigations should be performed when required. In addition to the above periodic investigations, hepatitis B surface antigen antibodies, hepatitis B core antigen antibodies, hepatitis C virus antibodies, and amoebic antibodies were assayed. Information on self-reported adherence rates and pill counts by pharmacists between visit intervals was collected every 3 months.

Outcomes

The primary and secondary end points that were assessed to evaluate HIV and STI incidence and the safety and efficacy of PrEP in Japanese PrEP users are listed in Textbox 2.

Textbox 2. End points of the study.

Primary end point

- HIV incidence in PrEP users (/100 person-years)

Secondary end points

- STI incidence in PrEP users (/100 person-years)
- Incidence of adverse events caused by Truvada
- Frequency of high-risk sexual activity
- Adherence to periodic visits and medication

Criteria for Discontinuing or Modifying Allocated Interventions

Participation was considered discontinued when a participant refused the use of their personal information and data, any deviation from an inclusion criterion or an applicable exclusion criterion was noticed, or when continuation of the study was otherwise deemed difficult by a supervising physician or the principal researcher. The entire study was subject to discontinuation on the order of the head of the study site or when the principal researcher deemed continuation of the study difficult.

Study drug treatment was scheduled for discontinuation or temporary suspension in cases of HIV infection. If the HIV test was positive, the patient was to be transferred to the AIDS Clinical Center for medical care. The initial examination at the AIDS Clinical Center included testing for anti-HIV drug resistance as part of the routine medical care to confirm whether the patient had acquired resistance to TDF or FTC. The drug resistance test results were to be collected as relevant information for this study. Other criteria for discontinuing the treatment were decrease in eGFR below 60 mL/min/1.73 m^2, report of adverse events related to the drug, and when the use of a prohibited concomitant drug was deemed essential. As the patient recovered from the adverse event or stopped requiring the prohibited concomitant drug, the prescription of the study drug could be restarted after rescreening the patient for eligibility and a negative HIV test result.

Relevant Concomitant Care Permitted or Prohibited During the Trial

Drugs that were prohibited from concomitant use included nephrotoxic drugs and drugs containing FTC or TDF, lamivudine, and adefovir. Drugs that could be used concomitantly were the ones that were excreted by active tubular transport, such as acyclovir, valacyclovir, ganciclovir, and valganciclovir. However, these drugs may compete with Truvada for the excretion pathway, thereby increasing the risk of adverse events. Therefore, the concomitant use of these drugs was permitted only temporarily. There is a risk that patients with chronic hepatitis B would experience reactivation upon discontinuing Truvada. Therefore, extreme caution was exercised when suspending treatment with this drug.

The blood concentrations of FTC and tenofovir can be elevated in patients with renal disorders. Patients with a past history, presence of, or risk of developing renal disorders with this drug were monitored carefully during treatment for changes in blood creatinine and blood phosphate, and appropriate measures were taken. A study on tenofovir preparations reported a loss of bone density in the lumbar spine and femoral neck after 144 weeks of treatment [15]. Although the clinical significance of this finding remains unclear, patients with a history of pathological fractures or other chronic bone diseases were carefully observed and appropriate measures, such as discontinuing treatment, were to be taken in case of any abnormalities.

Clinical indemnity and liability insurance were obtained prior to the start of the study. Insurance payments were made according to the insurance policy for nonfault deaths or disabilities resulting from participation in this study. However, medical expenses were not covered by the insurance and were borne by the patient. In the event of a study-related injury, there was provision for appropriate and immediate action to be taken within the scope of insured medical care. The duration of insurance coverage was until the end of the study in March 2021. Participants who wished to receive PrEP after the end of the study could purchase Truvada at their own expense and receive medical follow-up at the AIDS Clinical Center while continuing to take the drug. However, medical fees associated with this were not covered by insurance.

Safety Assurance and Reporting of Adverse Events

Although Japan has not approved Truvada for PrEP use, it is frequently used in the routine medical care of patients with HIV. Evidence has also demonstrated that Truvada for PrEP use is safe, though prompt medical care was to be provided in case of any adverse events.

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In this study, adverse events that were grade 3 or more severe (grade determined using a grade table) or lead to suspension of treatment will be immediately reported to the principal researcher. An adverse event report form (CRF-4) was also to be completed and information was to be shared with the study group. Incidences of serious adverse events were reported by the principal researcher to the Clinical Study Quality Management Office; the ethics committee; and the Minister of Health, Labor and Welfare when necessary.

Serious adverse events were defined as those that resulted in death, were life-threatening, required hospitalization or prolongation of existing hospitalization for treatment, resulted in persistent or significant disability or incapacity, caused a genetic abnormality in children, or were otherwise judged serious based on the reports of the principal researcher.

Caution was exercised in patients with a history of renal function disorders and those taking nephrotoxic drugs. Since severe renal function disorders such as renal insufficiency, renal failure, acute renal failure, proximal renal tubular dysfunction, Fanconi syndrome, acute tubular necrosis, nephrogenic diabetes, and nephritis may occur, participants were observed carefully with periodic testing. If laboratory abnormalities were observed, appropriate measures were taken, such as discontinuing treatment.

Statistical Methods

The main analysis included the estimation of the rate of new HIV infections during the study, either by dividing the number of infections by the number of subjects or by using a Kaplan-Meier estimate, estimating the 90% CI, and deciding whether PrEP was effective if the upper bound of the CI did not exceed 7%. However, given the expected increase in high-risk sexual behaviors, a log-linear model was used to assess whether the ratio of HIV to STI incidence at the end of the study differed between the participant cohort who did not wish to receive PrEP and the PrEP cohort. Behavioral evaluation included a quantitative assessment of risky sexual behavior (HIV Incidence Risk Index for MSM) score and a Wilcoxon signed rank test to determine whether there was a significant difference in sexual behavior before and after PrEP. A sensitivity analysis was performed using the least-squares method with a linear model or mixed-effects models for repeated measures (MMRM).

Oversight and Monitoring

The study was approved by the certified review board of NCGM. The certification review board was established by the President of NCGM and Director of the Centre Hospital of the NCGM, and the members met once a month.

To confirm whether the study was conducted safely and according to the protocol as a general rule, all participants underwent individual monitoring 1 month after enrollment. Subsequently, 10% of enrolled participants underwent annual monitoring. The monitoring included the matters listed in Textbox 3. Monitoring was performed via direct verification of source materials. The principal researcher designated a monitor among the study collaborators. After monitoring, the monitor promptly prepared a report and submitted it to the principal researcher. Monitoring reports were stored in the study office. In the event of a serious violation or deviation, the principal investigator reports the violation to the President through the Office of Clinical Research Quality Management. No audits were conducted during the study.

As a general rule, periodic centralized monitoring was performed twice a year to confirm that the study was being conducted safely and according to the protocol. Centralized monitoring was performed using the data entered into the records (CRF) collected by the data center. A periodic monitoring report prepared by the data center was submitted to the principal researcher and the study office. The matters subjected to centralized monitoring are listed in Textbox 4.

Textbox 3. Matters subject to monitoring.

- Consent obtained in writing and retention of the patient information or consent form
- Eligibility of subject inclusion criteria
- Referencing of data entered into case report forms against medical records (direct verification of source materials)
- Occurrence and reporting of adverse events
- Occurrence of protocol deviations
- Circumstances of stored specimen management
- Circumstances of study-related stored documents and case files
- Any other problems related to study progress and safety

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Textbox 4. Matters subject to centralized monitoring.

- Number of enrollees
- Subjects receiving protocol treatment, discontinued subjects, and reasons for discontinuation
- Serious adverse events
- Adverse events and adverse reactions
- Protocol deviations
- Other problems related to study progress and safety

Data and Information Confidentiality

The following steps were followed to ensure confidentiality:

- Personal information and data collected during this study were handled only by the researchers involved, and the information was meant to be used for any purpose other than this study. Researchers exercised due care in handling personal information and data, and the principal researcher took necessary measures to ensure the proper handling of personal information and data.
- Data were anonymized before being added to the database. The study database and all temporary digital files contained no personal identifying information other than study IDs.
- The study database was stored on a hard disk on a password-protected computer located in a lockable room. The keys and passwords were managed appropriately by the study groups. Other printed matter and materials generated during study-related tasks were also managed appropriately, such as being viewed in locations that were not accessible to third parties and stored in a lockable cabinet. Portable electronic media were avoided whenever possible; however, when the use of portable electronic media was unavoidable, it was reported to the principal researcher and handled with the utmost care.
- The principal investigator was responsible for managing the master key and supervising its use. After the data in the study database were locked, the master key was submitted to the director of the planning and strategy of the AIDS Clinical Center and was not retained by the study group.
- Personal information and data are planned to be retained up to the day when 5 years have elapsed from the day when the end of the study was reported to the director, or up to the day when 3 years have elapsed from the day when the final publication of study results is reported to the director, whichever occurs later. Any printed materials, and electronic media will be disposed of after the content is rendered physically unreadable. Rewritable electronic media can be reused after rendering the study data entirely unrecoverable by overwriting them multiple times using dummy data.
- Care was taken when publishing the study results to ensure that individuals could not be identified.
- No specific limit was placed on the retention duration of the stored specimens owing to the importance of the samples.

Reporting of Protocol Modification, Deviations, and Violations

Any amendments to the protocol, violations of the above ethical standards, or deviations from the protocol was to be promptly reported to the ethics committee, including details, reasons, and responses to the violation or deviation.

In principle, a “violation” was defined as any deviation from the protocol rules that fell under more than 1 of the following categories: influence the evaluation of study end points, intentional or systematic, the degree of risk or deviation is significant, and clinically inappropriate.

Permissible deviation was to be considered if any of the following occurred: deviation did not affect the evaluation of a study end point, deviation was unintentional, and the severity of danger or extent of deviation was not significant. Deviations were incidents of nonadherence that did not fall under violations or permissible deviations. Consent procedures for study participation, eligibility determinations, drug treatment, laboratory tests, adverse event reporting, and other matters not performed in accordance with the provisions of the protocol were considered protocol deviations.

In principle, the monitoring process included the need to describe instances of suspected violations and deviations in a monitoring report and published paper of the study. However, there were no incidences of protocol modifications, violations, or deviations.

Frequency and Plans for Auditing Trial Conduct

The following matters were reported to the director in a preestablished format: (1) a report on the state of the progress of the study was made once a year; (2) study discontinuation or temporary suspension, restarting the temporary suspension, and ending the study; (3) occurrence of serious adverse events; (4) annual report on the state of the study progress; and (5) publication of study results.

Under the Clinical Trial Act in Japan, auditing the trial proceedings is not required in the absence of any conflicts of interest. No audits were conducted in this study.

Dissemination Plans

The results of this study belong to the NCGM. The first author, coauthors, and order of the papers that published the findings from this study were decided by the study manager. The main published papers was submitted to an English-language journal upon the completion of the primary end point analysis. If multiple papers were to be published, the themes and authors

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of the papers will be coordinated by the principal researcher. The materials and results to appear in the papers will also be agreed upon by the study group before submission. The main analysis paper of this study was published in a peer-reviewed journal [16].

Results

The study protocol was reviewed and approved by the certified review board of the NCGM (NCGM-C-003129-03) on April 20, 2020. Changes to the study plan were submitted for review by the certified review board and approved before implementation. Recruitment was completed on March 28, 2019, and the study was completed on (last adult participant and last time point) March 31, 2021. The data were analyzed and the main results of the study have already been published in a peer-reviewed journal [16]. The findings indicated that PrEP is a highly effective and feasible strategy against HIV infection in terms of prophylactic response, retention, and compliance.

Discussion

This protocol of an investigator-initiated clinical study was designed to evaluate the safety and efficacy of PrEP in PrEP users as well as the compliance with PrEP medication among the users. It also aimed to assess the social, medical, and economic benefits of PrEP in Japan.

In Japan, MSM population covers less than 5% of male population. However, in 2018, the MSM population disproportionately accounted for 75.4% of HIV cases and 58.1% of AIDS cases in men and 66% of new HIV reports [12]. Despite having an established and equitable health coverage system, funding for treatment and preventive initiatives against HIV in Japan is limited. The national health insurance system of the country does not subsidize PrEP and access and uptake of PrEP are scarce [17]. An ethnographic study has shown that awareness and the observable presence of PrEP in conservative Japanese community is sparse [17]. Furthermore, the country lacks publicly funded health services focused on MSM resulting in insufficient and uncoordinated preventive activities against HIV. These gaps reflect the vulnerability of Japanese population to HIV [17,18]. Therefore, conducting PrEP trials among MSM population are the need of the hour to nudge the Japanese policy makers to steer in the direction of a more comprehensive HIV response and management plan. Our planned trial design was an invasive interventional study that administered the anti-HIV drug Truvada to prevent HIV infection and evaluated HIV and STI tests.

The results of the feasibility study conducted on the basis of this protocol showed that among 309 MSM registered in the cohort, 124 were included in the study on the basis of defined inclusion criteria. However, the rest of the patients were continuously monitored. We found that the incidents of HIV infection reduced significantly among PrEP users (0 infections, 235.5 person-years) compared to non-PrEP users (11 infections [3.4%/y], 318.9 person-years; P=.01) [16].

The government of Japan is implementing rapid measures to increase the number of foreign visitors to Japan to stimulate the travel economy. To ensure public health and reduce the spread of HIV and other STIs, it is necessary to assess the social, medical, and economic effects of PrEP as an effective counter measure of these diseases. An analysis of an economic model developed with epidemiological estimates for each of the 47 prefectures in Japan showed that over a 30-year time horizon, once daily use of PrEP among MSM resulted in 48% to 69% reduction of HIV infections and AIDS cases across all prefectures in Japan in comparison to no PrEP. Daily use of PrEP was cost-effective, owing to lower monitoring costs and general medical costs across Japan, especially in the prefectures with higher incidence of HIV [19]. PrEP adherence differs considerably among by countries and regions [20]. Nevertheless, the study conducted based on this protocol showed that the adherence to PrEP was as high as 95% and the retention rate at 2 years was approximately 80%, probably due to increased awareness [16].

The major strength of this protocol was the provision of capturing detailed information regarding risk behavior and STI incidence not only from MSM before and after PrEP but also from non-PrEP users that acted as a reference group. The use of PrEP to counter HIV infection is often considered to be associated with reduced condom use and increase in number of sexual partners, eventually leading to higher risk of developing STIs [21,22]. The design of the trial helped to shed light on the sexual behavior of PrEP users. The study based on this trial revealed a decrease in condom use and an increase in the incidence of STIs, including syphilis, chlamydia, and gonorrhea infection after PrEP initiation.

While this protocol led to a successful clinical study that provided important insights, a few limitations were perceived. First, this single-center trial involved a relatively small sample size. Second, the single-arm study design made the comparison of effectiveness of PrEP in HIV prevention with other randomized control trials difficult. Nevertheless, we succeeded in recruiting high-risk participants as no other organizations in Japan offered SH services to HIV-free MSM population. In addition, although the preventive effects of PrEP against HIV were already demonstrated in a number of RCTs, and the local HIV incidence (3.8%/y) reflected a risk considerably high enough for PrEP indication [13].

Although the safety of Truvada has been demonstrated in HIV treatment as well as for prophylactic use in PrEP, adverse events caused by Truvada may be considered a disadvantage of study participation because there is no history of Truvada use for PrEP in Japan. Another disadvantage of participation is the minor invasiveness of blood collection and the need for an additional 7 mL of blood for storage.

Conversely, the participants were expected to obtain a potent prophylactic effect against HIV infection, which can be considered a major benefit of participation in this study. Regarding the burden of cost for the participants, the Truvada drug used for PrEP and some HIV and STI tests were free for the participants.

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After completion of the study based on this protocol, 78% participants continued receiving PrEP by buying tenofovir or FTC themselves, reflecting a strong demand for PrEP in this population [16].

Overall, the outcomes of the study based on this protocol strongly supported the implementation of PrEP in Japan in addition to promoting the use of condoms and safe sexual behaviors. The results of this study may lead to the approval of Truvada for PrEP use in Japan, a development that promises to help stop the spread of HIV.

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Data Availability

The data sets generated and analyzed during this study are available from the corresponding author on reasonable request.

Conflicts of Interest

Torii Pharmaceutical provided the study drug but was not involved in any way during the planning, analysis, and publication of the study. Conflicts of interest with companies providing the study drug were reviewed and managed appropriately by the National Center for Global Health and Medicine Conflict of Interest Management Committee. SO received research grants from ViiV Healthcare and Gilead Sciences, and honorariums for lectures from ViiV Healthcare and Gilead Sciences.

Multimedia Appendix 1
Questionnaire (English).
[DOCX File , 54 KB - resprot_v12i1e50919_app1.docx]

Multimedia Appendix 2
Questionnaire (Japanese).
[DOCX File , 57 KB - resprot_v12i1e50919_app2.docx]

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Abbreviations

CRF: case enrollment form
eGFR: estimated glomerular filtration rate
FTC: emtricitabine
HBc: hepatitis B core antigen
HBs: hepatitis B surface antigen
MSM: men who have sex with men
NCGM: National Center for Global Health and Medicine
PreP: pre-exposure prophylaxis
SH: sexual health

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STI: sexually transmitted infection
TDF: tenofovir disoproxil fumarate

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Protocol

Guideline-Adherent Physiotherapy for Patients With Hip and Knee Osteoarthritis in Germany: Protocol for an Implementation Research Project Using the Theoretical Domains Framework and the Behavior Change Wheel

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Abstract

Background: Hip and knee osteoarthritis is common and leads to pain, stiffness, and disability. Clinical practice guidelines provide recommendations based on the best available evidence to assist health care professionals and patients in clinical decision-making. However, several studies have reported a gap between guideline recommendations and clinical practice in physiotherapy. Improved implementation strategies and the removal of existing barriers may facilitate the transfer of evidence into clinical practice and contribute to optimized quality of care.

Objective: This paper presents the protocol for a study that aims to describe the current physiotherapy practice in patients with hip and knee osteoarthritis and to investigate physiotherapists' adherence to clinical practice guidelines, to identify and specify barriers to and facilitators of guideline use and implementation, and to develop and pilot test a theory-based tailored implementation intervention aiming to increase guideline use in osteoarthritis care.

Methods: The research project is divided into 4 parts. During the first part, we will conduct a nationwide web-based survey among German physiotherapists to evaluate the current management of hip and knee osteoarthritis and to evaluate whether treatment aligns with guideline recommendations. Subsequently, semistructured interviews will be conducted to specify barriers to and facilitators of guideline use and implementation among physiotherapists (part 2). On the basis of these findings, in part 3, we will develop a theory-driven implementation intervention based on the Theoretical Domains Framework and the Behavior Change Wheel, which will be evaluated in a controlled pilot study in terms of effectiveness, feasibility, and acceptability (part 4).

Results: Data collection of the web-based survey among German physiotherapists (part 1) was completed in December 2021. The semistructured interviews (part 2) were conducted between January and September 2023. Recruitment of physiotherapy practices to participate in the development of the implementation intervention is expected to start in January 2024.

Conclusions: This research project aims to develop a theory-driven implementation intervention to facilitate the transfer of evidence from hip and knee osteoarthritis guidelines in physiotherapy practice. We hypothesize that successful implementation will lead to increased guideline adherence in physiotherapists, which in turn will improve the quality of care. The results from our project will provide valuable knowledge concerning the development process and effectiveness of tailored implementation interventions.

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KEYWORDS

osteoarthritis; physiotherapy; guideline; implementation; clinical practice

Introduction

Osteoarthritis is the most common chronic joint disease and is mainly present in the lower extremity joints such as hips and knees [1]. In Germany, the prevalence of outpatient diagnosed hip and knee osteoarthritis in older patients is 21.8%, whereas osteoarthritis is more common in women than in men and its prevalence increases with age [2]. Osteoarthritis is characterized by inflammation and degenerative changes in the joints, causing pain, stiffness, functional disability, and reduced quality of life [3]. In addition to its effects on individuals, osteoarthritis is associated with an enormous burden on the health care system. The average annual costs per patient living with osteoarthritis in the lower extremities worldwide were estimated to be €11,100 (US $11,722) [4]. In Germany, the direct costs for osteoarthritis (*International Classification of Diseases, 10th Revision*: M15-M19) amounted to €7.62 (US $8.05) billion in 2008. Data on indirect costs are not available, but with 114,975 cases of work incapacity owing to knee osteoarthritis and 44,637 cases owing to hip osteoarthritis (2011), an enormous burden on the national economy can be assumed [5].

There are numerous treatment options available including conservative (eg, physiotherapy) and operative methods to manage hip and knee osteoarthritis, which vary with respect to efficacy and costs. To facilitate the implementation of research findings in clinical practice, clinical practice guidelines (CPGs) summarizing study results have been developed. CPGs are described as "statements that include recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options" [6].

In recent CPGs [7-9], conservative nonpharmacological methods, particularly education and therapeutic exercise (and weight loss if overweight or obese), are widely recommended and are seen as first-line treatment for patients with hip and knee osteoarthritis. Other interventions (eg, pain medication or gait aids) can be used to relieve pain and to support first-line treatment. Joint replacement surgery is usually considered when osteoarthritis symptoms become intolerable and significantly affect quality of life, and other nonsurgical therapies have been ineffective or unsuitable [9].

Physiotherapeutic interventions play a key role in the conservative management of hip and knee osteoarthritis and have been shown to be effective in improving pain, quality of life, and physical function [10]. On the basis of the German health insurance data, Postler et al [2] identified that approximately 63.4% of patients (aged ≥60 y) diagnosed with hip or knee osteoarthritis receive pain medication (44.1% of which are nonsteroidal anti-inflammatory drugs), whereas physiotherapy is prescribed only to 43.1% of the patients, with decreasing numbers with increasing age.

However, deficits in osteoarthritis management are not only evident in physicians' prescribing behavior. Recent studies involving physiotherapists from Italy [11] and Belgium [12] indicated a gap between clinical practice and research findings, as treatment of hip and knee osteoarthritis often is not in line with current guideline recommendations. Instead of providing first-line treatments, many physiotherapists include interventions that do not contribute to high-quality care. This is consistent with findings from a systematic review in which Zadro et al [13] found that the median percentage of physiotherapists who chose treatments recommended in CPGs (eg, advice to stay active, aerobic, and strengthening exercises) was 58%, whereas 98% of the physiotherapists provided treatments with low or conflicting evidence in the management of knee osteoarthritis (eg, exercise that is neither aerobic nor strengthening). With regard to the nonpharmacological treatment of people with osteoarthritis, Hagen et al [14] noted that there is substantial room for improvement in the care of individual patients.

The limited use of evidence in clinical practice is a well-known problem, and the reasons for not using CPGs are manifold. Important barriers to the implementation of CPGs in physiotherapy mentioned in the literature are, for example, lack of time, lack of generalizability of research findings to individual patients, conflicting patient preferences, and lack of support in the workplace [15-19]. In addition, physiotherapists are often unaware of current CPGs [20,21]. Owing to the characteristics of the German health care system and the education of most physiotherapists in Germany at vocational schools instead of at institutions of higher education, it can be assumed that there are further barriers specific to the German context.

Publication and dissemination of guidelines alone is not sufficient to change clinical practice. It requires organizational change and behavioral change in individual health care professionals toward their use of guideline recommendations. Therefore, CPGs need to be accompanied by evidence-based implementation strategies [17]. There is evidence that tailored implementation programs targeting specific barriers and facilitators are more likely to improve professional practice than nontailored interventions or passive guideline dissemination [22,23]. It is recommended to use theories and frameworks to guide the implementation process and facilitate the identification of determining factors in health care professionals' behavior [24]. Moreover, using theories allows for a better understanding of the generalizability and replicability of implementation interventions [25].

A promising approach to developing a tailored, theory-driven implementation intervention might be the involvement of the Theoretical Domains Framework (TDF) and the Behavior Change Wheel (BCW). As one of the most commonly used theories in health care settings [26], the TDF synthesizes different theories of behavior change into one framework and is commonly used to explore factors that influence clinical behavior and guideline adherence. The 14 domains of the TDF include knowledge; skills; social or professional role and identity; beliefs about capabilities; optimism; beliefs about consequences; reinforcement; intentions; goals; memory, attention, and decision processes; environmental context and

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resources; social influences; emotion; and behavioral regulation [27]. The BCW is a synthesis of 19 theoretical frameworks of behavior change and provides a systematic approach to developing a tailored guideline implementation intervention. The barriers and facilitators identified through the TDF can be used to expand the Capability, Opportunity, Motivation–Behavior components (COM-B), the core of the BCW, which indicates that behavior change occurs when there is a change in an individual's capability, opportunity, and motivation [28].

To date, little is known regarding the current physiotherapy practice for hip and knee osteoarthritis in Germany and whether its management is in line with guideline recommendations. We hypothesize that guideline adherence among physiotherapists is low, as in Germany, an academic level of physiotherapy education is not mandatory and only about 3% of the physiotherapists have graduated from higher educational institutions [29]. Most physiotherapists in Germany are trained at vocational schools where skills and knowledge regarding the implementation of guidelines and evidence-based practice are not an integral part of the curriculum. Given the burden of the disease and the high costs associated with osteoarthritis, as well as the importance of physiotherapy interventions in the treatment of hip and knee osteoarthritis, it is important to address this lack of research. Developing a tailored implementation intervention can increase evidence uptake in clinical practice and thus, improve quality of health care.

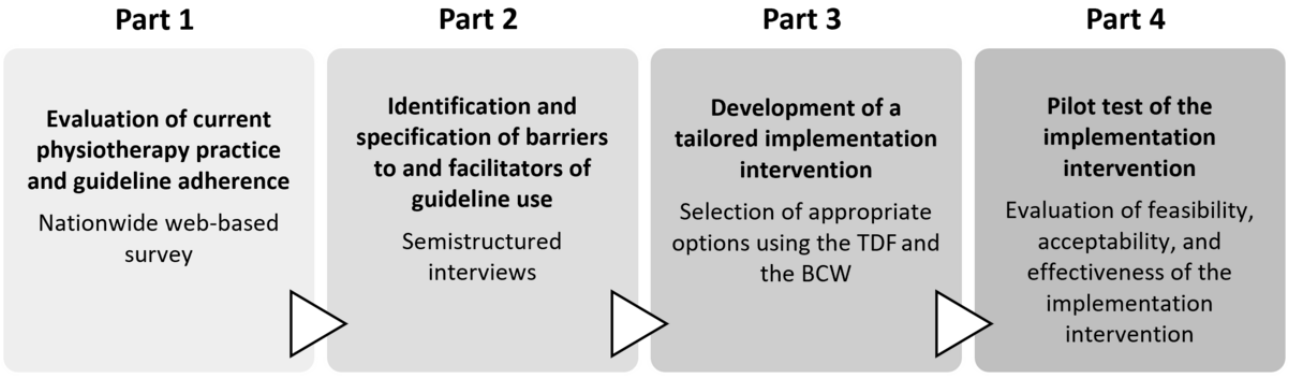
The objectives of the research project are (1) to describe the current physiotherapy practice in patients with hip and knee osteoarthritis in Germany and to investigate physiotherapists' adherence to CPG recommendations; (2) to identify and specify barriers to and facilitators of guideline use and implementation; and (3) to develop and (4) pilot test a theory-based tailored implementation intervention that aims to increase guideline use in the physiotherapy care of patients with hip and knee osteoarthritis in the German context.

Methods

Overview

The study was divided into 4 parts (Figure 1). In the first part, we will evaluate the current physiotherapy practice regarding the management of patients with hip and knee osteoarthritis. Subsequently, we will identify and specify barriers to and facilitators of guideline use among physiotherapists using a qualitative approach. On the basis of these findings, in part 3, we will develop a tailored implementation intervention to increase guideline use in clinical practice, which will be evaluated in a pilot study in part 4.

Figure 1. Flowchart of study parts. BCW: Behavior Change Wheel; TDF: Theoretical Domains Framework.



The evaluation and implementation of guideline-adherent care will be based on the German guidelines for hip and knee osteoarthritis [30,31]. These guidelines are aimed specifically at physicians working in musculoskeletal care and serve as information for general practitioners, physiotherapists, and occupational therapists, for example.

Part 1: Evaluation of Current Physiotherapy Practice and Guideline Adherence

A nationwide web-based survey among physiotherapists will be conducted to evaluate the current management of patients with hip and knee osteoarthritis and to explore adherence from physiotherapists to guideline recommendations. The reporting of the study will follow the Strengthening the Reporting of Observational Studies in Epidemiology statement [32] and the Consensus-Based Checklist for Reporting of Survey Studies [33].

A self-administered questionnaire will be developed based on the recommendations regarding conservative nonpharmacological management listed in the German CPGs for hip and knee osteoarthritis [30,31]. The questionnaire will be divided into three sections to assess (1) the demographic and working characteristics of the participants, (2) the current physiotherapy practice in patients with hip and knee osteoarthritis, and (3) perceived barriers to the implementation and clinical use of guidelines. We will use a mix of multiple choice questions and yes or no questions. To evaluate the current clinical practice, study participants will be asked to rate different treatment modalities for osteoarthritis on a 4-point Likert-type scale (1=never, 2=sometimes, 3=mostly, and 4=always). Specific barriers and facilitators regarding the German guidelines for hip and knee osteoarthritis will be assessed using the translated and cultural adapted version of "The Barriers and Facilitators Assessment Instrument" [34]. For participants who reject using CPGs in clinical practice, reasons against guideline use will be

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explored based on barriers identified from literature. Adaptive questioning will be used to minimize the response burden and to reduce complexity of the questions. The web-based survey will be conducted using LimeSurvey, a free and open source web-based tool for research projects. The survey will be accessible without restrictions (password or registration) via an internet link to the LimeSurvey platform with no incentives offered. Before initiating the survey, the study participants have to read and accept written informed consent and are required to verify self-reported eligibility criteria. Participation will be voluntary and anonymous. To improve the quality and understanding of the questionnaire, a pretest of the web-based survey with 10 physiotherapists representative of the physiotherapists targeted with the survey will be conducted.

We will include physiotherapists mainly working in Germany who treat patients with hip or knee osteoarthritis in clinical practice and who are able to read and speak the German language. Only physiotherapists with a professional degree will be eligible; therefore, students will be excluded. The recruitment of participants will be initiated through announcements and calls on different physiotherapeutic networks, social media, and personal contacts of the study team. According to the snowball sampling approach, study participants will be invited to further distribute the participation invitation. As this study has an explorative character, no sample size calculation will be performed. There are approximately 203,000 physiotherapists working in Germany [29], but the number of physiotherapists involved in osteoarthritis care is unclear. We will target a total sample size of 1000 participants to allow regression analyses with subgroups of sufficient sample size. As survey participation is anonymous and different recruitment strategies will be used to maximize the response rate, there is a risk of duplicate responses. Therefore, we will systematically review all the responses to identify any surveys with matching demographics and answers.

Data analysis will be performed using the R software (version 4.0.3; R Foundation for Statistical Computing). Participants' characteristics and current clinical practice will be analyzed using descriptive statistics. Guideline adherence will be defined as accordance between recommendations retrieved from the German guidelines for knee and hip osteoarthritis [30,31] and the therapists' treatment choices. As there is no standardized method to evaluate guideline adherence, we will use 2 different approaches that have been recently used in previous studies. In the first approach, guideline adherence will be determined using a points system. The participant's treatment choices will be compared with the current guideline recommendations, and in case of adherent behavior, each will be scored with one point. The benchmarks for good adherence will be set at ≥80% of the maximally achievable points [20]. Assessing guideline adherence on the basis of the methods of Battista et al [11], participants will be considered as *delivering*, *partially delivering*, and *nondelivering* depending on their chosen treatment. For example, a participant will be classified *delivering* if all recommended interventions have been chosen without considering nonrecommended treatments. To assess possible determinants of guideline adherence, regression analyses will be conducted. The potential determinants will be selected based on the literature. The level of statistical significance will be set at $P<.05$.

Part 2: Identification and Specification of Barriers to and Facilitators of Guideline Use

A qualitative approach including semistructured interviews will be used to identify and specify barriers and facilitators to guideline use in the management of hip and knee osteoarthritis specifically for the German context. The reporting of this study will be in accordance with the Consolidated Criteria for Reporting Qualitative Research [35].

Purposive sampling will be used to gain a wide range of information. We aim to recruit a diverse sample of physiotherapists based on age, gender, work experience, and professional education level. Only physiotherapists mainly working in Germany who treat patients with hip or knee osteoarthritis in clinical practice and who are able to read and speak the German language will be included. The invitation to participate in one-to-one semistructured interviews will be distributed through announcements and calls on different physiotherapeutic networks, social media, and personal contacts of the study team. Recruitment will continue until data saturation has been reached (a minimum of 10 participants). Data saturation will be defined as the point when 3 consecutive interviews had been conducted with no additional information on barriers and facilitators emerging [36].

An interview guide will be developed based on the TDF [27]. Questions will be informed by key findings from the previous survey and information on barriers and facilitators to guideline use identified through literature. The guide will explore the domains of the TDF to understand the factors that influence guideline use in clinical practice in the management of hip or knee osteoarthritis. The interview guide will be pilot tested with 2 physiotherapists before use. Feedback on comprehension and content will subsequently be incorporated into the interview guide after discussion with the study team.

The interviews are anticipated to last approximately 45 to 60 minutes and will be conducted via telephone or video call. Before entering the study, the participants will receive a written informed consent. Interviews will be audio-recorded and transcribed verbatim. Data collection and storage will be done pseudonymously. To give participants the opportunity to review the transcript and to make any modifications, the transcripts will be sent to the participants for member checking.

Thematic analysis following the 6 stages from Braun and Clarke [37] will be used to analyze the interviews. The first transcript from the semistructured interview will be pilot coded independently by 2 researchers to develop a coding strategy. The remaining interviews will be analyzed iteratively by the first author who will discuss any difficulties with a second researcher. Finally, the barriers and facilitators will be mapped onto relevant domains from the TDF. Data will be analyzed using MAXQDA (version 22; VERBI GmbH) software.

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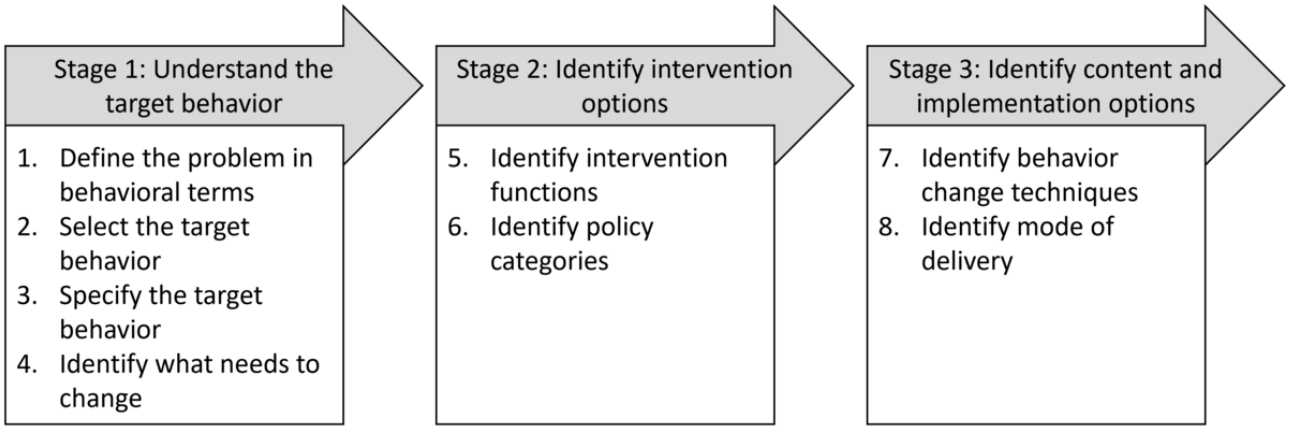
Part 3: Development of a Tailored Implementation Intervention

Overview

In this step, 6 outpatient physiotherapy practices will be recruited, 3 of which will be randomly selected to participate in the development process of the tailored intervention. In these physiotherapy practices, the intervention will be implemented (study part 4), whereas the remaining practices will serve as a control group. We will include physiotherapy practices in the region of Brandenburg and Saxony (Germany) with >5 physiotherapists who treat patients with hip or knee osteoarthritis in clinical practice.

The development of the implementation intervention will be guided by the BCW and follows 3 stages, as outlined by Michie et al [28]: understand the target behavior, identify intervention options, and identify content and implementation options. These can be further divided into key substeps as illustrated in Figure 2 [28].

Figure 2. Stages and steps involved in the development of an intervention using the Behavior Change Wheel.



Stage 1: Understand the Target Behavior

The key barriers identified from the semistructured interviews (part 2) will be used to define the problem in behavioral terms and to specify the behavior and target population (step 1). From a list of all potential candidate behaviors, the study team will choose 1 or 2 core behaviors that appear to be promising in increasing guideline adherence in physiotherapists (step 2). The target behavior will be selected considering each potential impact, likelihood of change, spillover effect, and ease of measurement. After specifying the target behavior in detail and its context (who, what, when, where, how often, and with whom; step 3), focus groups will be conducted to identify what needs to change in the individual or the environment to achieve the desired behavior change (step 4).

The reporting of the focus groups will be guided by the Consolidated Criteria for Reporting Qualitative Research checklist [35]. One to 2 focus groups will be conducted at each participating physiotherapy practice. The focus groups will take place at the participants' worksite and will be moderated by 2 members of the research team. Mixed groups of 6 to 10 participants recruited from each physiotherapy practice representing different stakeholders (eg, physiotherapists, patients, management, administration, and other health professionals) will be invited to participate to promote diversity and to encourage a wide range of information on what needs to change regarding the target behavior. All participants will receive and approve a written informed consent before initiating the study. The topic guide will be developed using the TDF. The standardized guide will be used across all focus groups with some flexibility through open questions to allow further discussion between participants. Before the focus groups, basic demographics (eg, age, gender, job type, and working hours) will be collected from each participant. The focus group discussions will be audio-recorded while simultaneously handwritten field notes capturing relevant nonverbal responses or dynamics of the group will be documented. Data from the focus groups will be transcribed verbatim and will be analyzed following the same process used for the semistructured interviews described in the *Part 2: Identification and Specification of Barriers to and Facilitators of Guideline Use* section.

Stage 2: Identify Intervention Options

On the basis of the findings from the focus groups, relevant intervention functions will be identified using a matrix that systematically maps TDF domains to intervention functions (eg, education, training, persuasion; step 5). As changes at the policy level will be beyond the scope and time constraints of our project, and intervention programs targeting individual level and local barriers have been shown to be effective [38], policy categories (eg, regulation, communication or marketing, and service provision) provided by the BCW guidance will not be considered in this study (step 6). To select the most appropriate and effective intervention functions for our implementation intervention, the affordability, practicability, effectiveness and cost effectiveness, acceptability, side effects or safety, and equity criteria will be used [28].

Stage 3: Identify Content and Implementation Options

On the basis of the intervention functions selected in step 5, behavior change techniques (BCTs) will be identified (step 7). We will use BCT taxonomy (version 1; BCTTV1) [39] to generate a list of BCTs mapped to our intervention functions. Regarding the affordability, practicability, effectiveness and cost effectiveness, acceptability, side effects or safety, and equity criteria, the research team will work in close collaboration with

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the stakeholders from the participating physiotherapy practices and discuss the included BCTs as well as possible modes of delivery for the intervention (step 8). Those that are likely to be the most effective and feasible to increase guideline adherence will be selected. Reporting of the intervention developed will be consistent with the recommendations for specifying and reporting implementation strategies in research studies proposed by Proctor et al [40] and the Template for Intervention Description and Replication checklist [41].

Part 4: Pilot Test of the Implementation Intervention

A controlled pilot study will be conducted to evaluate the effectiveness, feasibility, and acceptability of the tailored intervention implementation. The pilot study will simultaneously test a clinical intervention and an implementation intervention or strategy and thus will be a hybrid study [42]. The Standards for Reporting Implementation Studies statement [43] and the CONSORT (Consolidated Standards of Reporting Trials) statement [44] for pilot and feasibility trials will be used to guide the reporting of study methods and results.

The previously designed intervention will be implemented and evaluated at the 3 physiotherapy practices recruited in part 3 that participated in the development process, whereas the other 3 recruited practices will serve as the control group.

All physiotherapists involved in osteoarthritis management will be invited to participate. Patients will be eligible if they (1) are aged ≥18 years, (2) are primarily diagnosed with hip or knee osteoarthritis, and (3) have no restraint to receive physiotherapy. Participation will be voluntary, and informed consent will be obtained before the recruitment of any participant into the study.

To explore effectiveness at the patient level, the assessment of primary patient-relevant outcomes will follow the Outcome Measures in Rheumatology-Osteoarthritis Research Society International core domain set for clinical trials in hip and knee osteoarthritis and will include 5 domains: pain, physical function, quality of life, patient's global assessment of the target joint, and adverse events [45]. Patient outcomes will be assessed at baseline, at the end of physiotherapy treatment, and after 6 months. Physiotherapists' adherence to the osteoarthritis guidelines will be evaluated using a documentation questionnaire after each physiotherapy session. The implementation process will be evaluated using the Acceptability of Intervention Measure, Intervention Appropriateness Measure, and the Feasibility of Intervention Measure [46,47]. Additional outcomes will be the recruitment and retention rate [48]. Results from the pilot study will be used to inform sample size calculation for a subsequent study.

Patient and Public Involvement Statement

Patients and the public were not directly involved in the design or conduct, reporting, or dissemination plans of this research.

Ethical Considerations

Ethics approval for each part of the study will be sought from the ethics committee of the Brandenburg University of Technology Cottbus-Senftenberg, Germany. Permission for the nationwide web-based survey (study part 1) and the semistructured interviews (study part 2) has already been obtained from the ethics committee of the Brandenburg University of Technology Cottbus-Senftenberg, Germany (EK2021-10, EK2022-15). Throughout the research project, the principles established in the Declaration of Helsinki [49] will be strictly followed. Participants who are eligible for any part of the study will be informed about the respective objectives, content, and procedures of the study. Written informed consent will be obtained from all patients before enrollment. Participation will be voluntary, and participants are free to withdraw from the study at any moment.

The findings from this research project will be disseminated through open-access publications in international peer-reviewed journals and presentations at national and international scientific meetings. In addition, we will use social media (eg, X, formerly known as Twitter) to spread our findings to the public.

Results

In December 2021, the survey among German physiotherapists was completed, and results on the management of patients with hip and knee osteoarthritis and guideline adherence were published [50] (part 1 of the research project). Ethics approval for the second part of the research project was obtained in August 2022, and the semistructured interviews were conducted between January and September 2023. Recruitment of physiotherapy practices to participate in the development of the implementation intervention is expected to start in January 2024.

Discussion

Overview

The described research project aims to evaluate and improve the implementation of hip and knee osteoarthritis guidelines in physiotherapy in Germany, which to our knowledge has not been performed to date. Considering the burden of disease and the importance of physiotherapy interventions in the management of osteoarthritis, as well as findings from other countries indicating gaps between clinical practice and research findings [11,12], it seems important to address this lack of research.

The implementation of research findings into clinical practice is considered relevant for improving quality of care but is often hindered by various barriers [51]. Although guidelines are considered helpful in translating research findings into clinical practice by providing recommendations that can be used by health care professionals, patients, policy makers, and other stakeholders, many guidelines include no or a variety of guideline implementation tools for different stakeholders [52]. There are few studies on how to choose implementation strategies that address guideline-specific barriers, but education for clinicians or patients and printed materials were the most commonly used strategies for translating guidelines into practice [53]. Holm et al [54] reported that the limited use of CPGs may be because of insufficient knowledge of current evidence or that clinicians and patients may find it difficult to break old habits and abandon existing low-value treatment and also because the increasing number of frameworks and checklists

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for guideline implementation makes implementation strategies too comprehensive and complicated.

For the management of people with osteoarthritis, pragmatic approaches to implementing osteoarthritis guidelines exist. For example, Good Life with osteoArthritis in Denmark (GLA:D) or Active with osteoArthritis (ActiveA) have been implemented in several countries [54]. GLA:D, which is currently being implemented in Germany, and ActiveA are both effective in reducing pain intensity and increasing quality of life, physical activity, or physical function [10,55-58]. Østerås et al [59] showed that a structured implementation of ActiveA in primary care resulted in a higher quality of osteoarthritis care as compared with usual care. However, it is unclear if such approaches can be implemented as standard care in the German health care system, as GLA:D does not fit into the German catalog of remedies, which defines the number and type of physiotherapeutic treatments, and is therefore only available based on special contracts with health insurance companies or must be paid for privately by patients. Furthermore, not all patients can (eg, owing to limited access to physiotherapy practices) or want to (eg, because they do not want to train in a group) participate in GLA:D. Therefore, it is necessary to evaluate how to increase guideline use in osteoarthritis care and thus improve the quality of care in addition to the ongoing implementation of GLA:D in Germany. With regard to physiotherapists in Germany, it was recently shown that the implementation of evidence-based practice in clinical practice is insufficient [60]. In a recent nationwide survey on physiotherapy management of low back pain, less than one-third of the participating physiotherapists reported being aware of the National Disease Management Guideline for “non-specific low back pain” or have dealt with its recommendations [20]. Similar results were shown by another survey, in which only 47% of the responding physiotherapists reported being aware of the German guidelines on stroke rehabilitation [61]. One reason for the low awareness of CPGs could be that the entry level for German physiotherapists is vocational school education. Furthermore, physiotherapists report limited access to guidelines [19] and often do not know where to find them [20]. We hypothesize that the physiotherapy management of persons with hip or knee osteoarthritis will most likely not be guideline adherent and therefore needs to be improved, which is the aim of this study.

There are numerous frameworks, models, and theories that provide guidance in developing strategies to facilitate guideline implementation [62]. However, many guideline implementation studies do not report explicit theory use or theory is not used consistently and transparently [26,63]. Choosing the most appropriate theory-driven approach is challenging as such models can be complex, that is, difficult for both researchers and health care practitioners to understand and operationalize, or lack comprehensiveness [64]. Although the TDF and BCW are comparatively new implementation frameworks, they have already been used in several studies to understand and promote the uptake of evidence in clinical practice [65-67], including in the field of physiotherapy [68]. For this research project, we decided to use the TDF as it has proven to be a comprehensive and accessible way to understand the barriers and facilitators to best practice in primary and secondary care in Western countries [64]. There is evidence that TDF-based interview schedules achieve a broader range of responses than when using a nontheoretical approach [69]. Therefore, the TDF is described as an “inclusive” rather than a “selective” approach [70]. The TDF works within the BCW framework as it provides a more detailed understanding of the behavior components of capability, opportunity, and motivation. The BCW provides a systematic and pragmatic approach to developing implementation interventions. It encourages intervention designers to comprehensively consider the full range of options and select those that are most promising for the context. In addition, it allows for a detailed specification of the content using agreed labels and definitions [28].

Conclusions

The results from our project will provide valuable knowledge concerning the development process and effectiveness of an intervention to implement hip or knee osteoarthritis guidelines in physiotherapy practice. We aim to develop an implementation intervention that can also be transferred to other health conditions, with modifications, if necessary. We hypothesize that successful implementation will lead to increased guideline adherence in physiotherapists, which in turn will improve the quality of care.

Acknowledgments

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Data Availability

The data sets generated during the research project will be available on the Open Science Framework: 10.17605/OSF.IO/A7P3W.

Authors' Contributions

CB, BS, and CK conceptualized the design of the research project and drafted the manuscript. All authors contributed to the development of this manuscript and have read and approved the final version for publication.

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Conflicts of Interest

None declared.

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Abbreviations

ActiveA: Active with osteoArthritis
BCT: behavior change technique
BCW: Behavior Change Wheel
CONSORT: Consolidated Standards of Reporting Trials
CPG: clinical practice guideline
GLA:D: Good Life with osteoArthritis in Denmark
TDF: Theoretical Domains Framework

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Protocol

Characteristics of Interstitial Pneumonia With Autoimmune Features (IPAF): Protocol for a Multicenter Prospective Study

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Abstract

Background: “Interstitial lung disease” (ILD) is a broad term encompassing diseases of different backgrounds. “Interstitial pneumonia with autoimmune features” (IPAF) is a recent term that implies the presence of autoimmunity.

Objective: This study aims to determine the characteristics of Polish patients with IPAF, compare them with patients with other interstitial pneumonias, and search for the prognostic and diagnostic biomarkers of IPAF in serum and bronchoalveolar lavage fluid (BALF).

Methods: This multicenter prospective study plans to recruit 240 participants divided into 1 study group and 2 control groups. Biological fluid samples will be collected according to Polish Respiratory Society management guidelines and stored at –80°C for further tests. Prospective 5-year observations of 60 newly diagnosed individuals are planned. The study will be divided into subsections. First, we plan to characterize Polish patients with IPAF (study group) against their peers with other ILDs (2 control groups). Control group 1 will comprise patients with idiopathic ILDs, including mainly idiopathic pulmonary fibrosis and nonspecific interstitial pneumonia. Control group 2 will comprise patients with connective tissue disease–associated interstitial lung diseases, such as rheumatoid arthritis, systemic sclerosis, polymyositis, dermatomyositis, Sjögren’s syndrome, mixed connective tissue disease, and systemic lupus erythematosus. Radiological and functional parameters will be analyzed. Patients will be compared in terms of high-resolution computed tomography results, the 6-minute walking test performance, and pulmonary function test parameters. The diagnosis of IPAF will be reassessed on a regular basis through multidisciplinary discussion in order to determine its clinical stability. In the laboratory arm, inflammation and fibrosis pathways will be assessed. Cytokine levels (interleukin 8, transforming growth factor beta 1, chemokine C-C motif ligand [CXCL]18, CXCL1, surfactant protein [SP]-A, SP-D, Krebs von den Lungen-6 protein, and chitinase 1) will be measured in serum and BALF. A comparative analysis of serum and BALF cytokine levels will be performed in order to establish potential differences between systemic and local inflammatory pathways. In the quality of life (QoL) arm of the study, dyspnea and cough and their impact on various aspects of the QoL will be assessed. Depression and anxiety will be measured with the Hospital Anxiety and Depression Modified Scale and the 9-item Patient Health Questionnaire, and potential correlations with symptom prevalence will be assessed.

Results: This study will start recruiting patients to phase 1 in October 2023. The final results will be available in 2028. We plan to publish preliminary results after 2-3 years from the start of phase 1.

Conclusions: This study will be a step toward a better understanding of IPAF etiopathogenesis and outcomes.

International Registered Report Identifier (IRRID): PRR1-10.2196/44802

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KEYWORDS

IPAF; interstitial pneumonia with autoimmune features; CTD; connective tissue disease; interstitial lung disease; idiopathic interstitial pneumonia; lung disease; pneumonia; respiratory; radiology

Introduction

Background

Interstitial pneumonia with autoimmune features (IPAF) was defined in 2015 by the Working Group of the European Respiratory Society (ERS) and the American Thoracic Society (ATS) as interstitial pneumonia with some clinical or serological or both types of features suggesting the presence of an underlying autoimmune disorder. However, no diagnostic criteria for any autoimmune disease are met in these patients during thorough rheumatological workup [1].

"Interstitial lung disease" (ILD) is a broad term encompassing a varied group of disorders. This includes idiopathic interstitial pneumonias (IIPs) and ILDs stemming from environmental exposure or occurring during the course of systemic diseases [2,3].

Data regarding the etiopathogenesis and natural course of IPAF are still lacking. As this is a diagnosis at the crossroads of pulmonology and rheumatology, retrospective and optimally prospective observational studies may cast more light on this subject. Retrospective studies suggest that survival in IPAF does not substantially differ from that in connective tissue disease–associated interstitial lung disease (CTD-ILD) or idiopathic pulmonary fibrosis (IPF), and prospectively, merely 10% of patients with IPAF are reclassified as having CTD-ILD, mostly on the myositis spectrum [4].

Another clinical challenge is in establishing a subset of clinical traits associated with the development of progressive interstitial fibrosis and the loss of lung function. Another retrospective study [5] on individuals with IPAF and CTD-ILD revealed that yearly decline in the forced vital capacity (FVC) is significantly more pronounced in IPAF than in CTD-ILD. Progression is influenced by the presence of anti–Sjögren's syndrome–related antigen A (anti-SSA) antibodies and postexercise pulse increase in the 6-minute walking test (6MWT) [5].

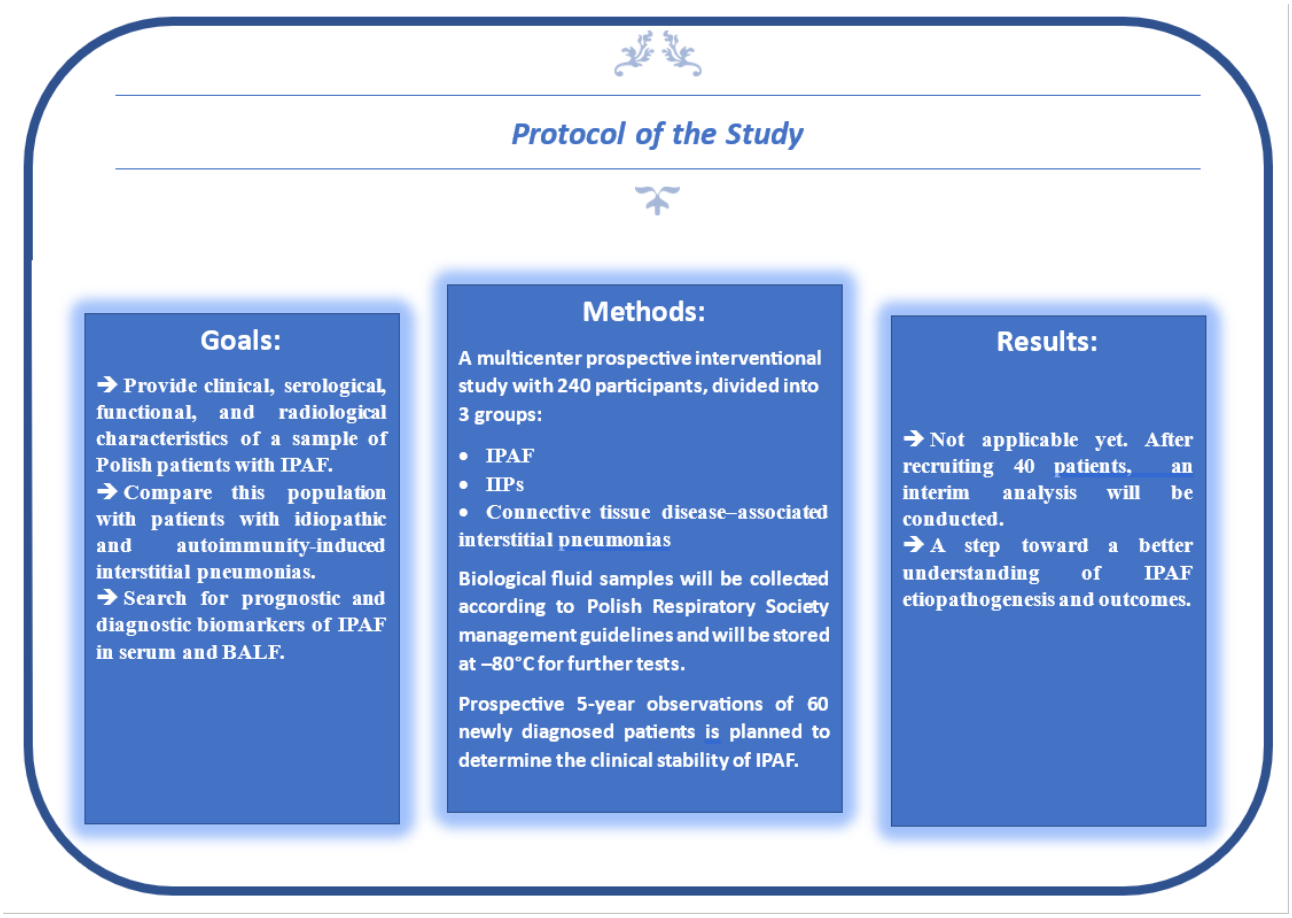
Most available analyses of the ILD-related quality of life (QoL) and the influence of respiratory and psychological symptoms focus on the most prevalent entities (eg, IPF or sarcoidosis). Research on QoL evaluation in IPAF and its comparison with other ILDs is still scarce. Individuals with chronic disease often present with multiple symptoms, which results in decreased functioning and high medical and societal costs [6]. Depression and anxiety also contribute to the burden of chronic disease.

Objectives

The primary purpose of this study is to determine the incidence of IPAF in comparison with IIPs and ILDs occurring during the course of autoimmune diseases in 6 Polish pulmonological centers. Further objectives of this study include determination of the clinical, serological, functional, radiological, and histopathological characteristics of patients with IPAF; analysis of diagnostic strategies for specific IPAF subgroups; determination of the potential diagnostic, predictive, and prognostic features of IPAF; and prospective 5-year assessment of patients with IPAF in order to determine the stability of the diagnosis and potential progression to other diseases (eg, CTDs). Please see Figure 1 for the study protocol. To the best of our knowledge, this is the first prospective study focused on patients with IPAF, CTD-ILD, and IIP in Eastern Europe.

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Figure 1. Study protocol. BALF: bronchoalveolar lavage fluid; IIP: idiopathic interstitial pneumonia; IPAF: interstitial pneumonia with autoimmune features.



Methods

Study Population

Inclusion criteria are as follows: individuals with ILDs, aged ≥18 years, and able to provide informed consent.

The study group will comprise patients with IPAF defined according to the criteria established by the Working Group of the ERS and the ATS [1]. Control group 1 will comprise patients with the following CTD-ILDs: rheumatoid arthritis (RA), systemic sclerosis (SSc), polymyositis (PM), dermatomyositis (DM), Sjögren's syndrome (SS), mixed connective tissue disease (MCTD), and systemic lupus erythematosus (SLE) diagnosed according to the diagnostic criteria issued by the European League Against Rheumatism (EULAR) or the American College of Rheumatology (ACR). Control group 2 will comprise patients with the following IIPs: IPF, nonspecific interstitial pneumonia (NSIP), cryptogenic organizing pneumonia (COP), acute interstitial pneumonia (AIP), respiratory bronchiolitis–associated interstitial lung disease (RB-ILD), desquamative interstitial pneumonia (DIP), and lymphocytic interstitial pneumonia (LIP). Previously untreated patients with a new diagnosis of ILD were recruited for a pilot study (a separate population of patients) [7].

Exclusion criteria include age<18 years; respiratory tract infection, including minor upper respiratory tract infections (eg, the common cold) 4 weeks prior to the diagnostic process; asthma; tuberculosis; asbestosis; chronic hypersensitivity pneumonia; Hermansky-Pudlak syndrome; and other causes of genetic ILDs (eg, lymphangioleiomyomatosis, tuberous sclerosis complex [TSC], Birt-Hogg-Dubé syndrome, dyskeratosis congenita, familial forms of ILD, immunodeficiency syndromes); a history of therapy for ILD, including systemic glucocorticosteroids (GCs; both pulsed and long-term low-dose therapy); pregnancy and nursing; malignancy; HIV seropositivity; and a lack of ability to provide informed consent. For the QoL arm of the study, we will also exclude participants unable to communicate verbally.

Ethical Considerations

The study will be carried out according to the Code of Ethics of the World Medical Association (Declaration of Helsinki). This protocol was reviewed and approved by the Ethical Board Committee of the Medical University of Silesia (decision no. KNW/0022/KB1/130/18/19). The trial is registered with reference number NCT03870828. All participants will sign the informed consent form prior to recruitment and will be informed of their right to waive consent at any time without a negative effect on their care. The informed consent form was reviewed and accepted by the Ethical Board Committee in terms of informativeness and understandability. The form allows for clinical data collection and secondary analysis. A copy of the form will be provided to each participant.

The study team will explain data analysis, the study duration, and objectives to the participants. We find it worth mentioning

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that in addition to drawing larger volumes of blood, storing biological fluids, and completing the questionnaires, no procedures beyond standard care will be performed. Therefore, participants will not be burdened with additional risks or prolongation of hospitalization/outpatient clinic visits. Study data will be deidentified to protect the privacy of participants. Data confidentiality will be maintained. No monetary compensation will be given to the participants. Voluntary participation and the time of the participants will be respected.

Study Design

Phase 1

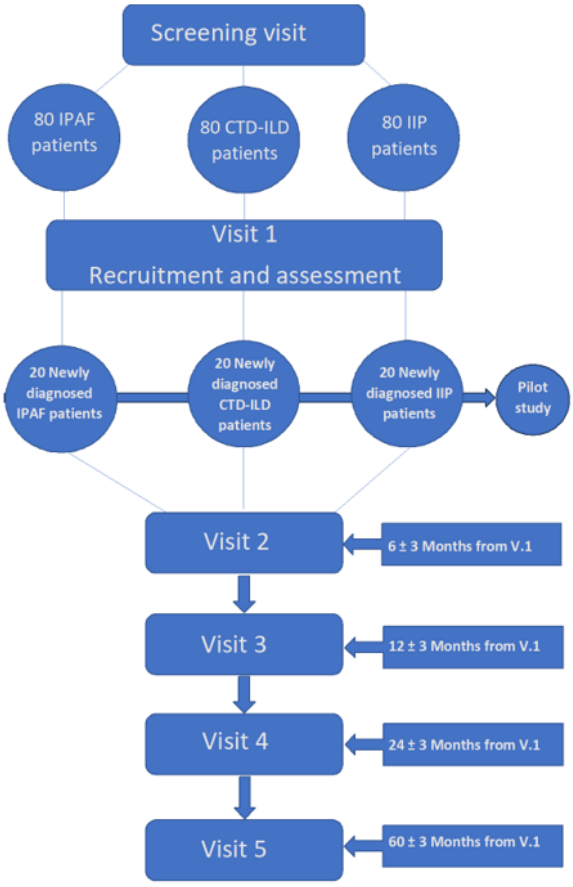
All patients meeting the inclusion criteria and not meeting the exclusion criteria regardless of prior treatment history will be recruited to phase 1 of the study. The recruitment process duration is estimated at 12 months. The previous recruitment of 40 patients led to a pilot study [7], which impacted further study design. The maximum number of patients included in this phase will be 80 (33.3%) in the IPAF group, 80 (33.3%) in the CTD-ILD group, and 80 (33.3%) in the IIP group.

Phase 2

Only patients with newly diagnosed disease (eg, no prior diagnosis of ILD and, hence, no prior treatment) will be recruited. The estimated recruitment duration is 36 months. The number of patients to be included in this phase will be 20 (33.3%) in the IPAF group, 20 (33.3%) in the CTD-ILD group (only those with RA, SSc, PM/DM), and 20 (33.3%) in the IIP group (only those with IPF, NSIP, COP, LIP; optimally 10, 50%, patients in the IPF subgroup and 10, 50%, in the non-IPF subgroup). Patients who were previously recruited to phase 1 of the study and meet the inclusion criteria of phase 2 may also be included.

Please see Figure 2 for a flowchart of the study design.

Figure 2. Flowchart of the study design. CTD-ILD: connective tissue disease–associated interstitial lung disease; IIP: idiopathic interstitial pneumonia; IPAF: interstitial pneumonia with autoimmune features; V: visit.



Visit 1

A thorough medical history will be obtained using the Visit 1 questionnaire. During the first hospitalization, the following procedures will be performed:

- Pulmonary function tests (PFTs)
- Depression and anxiety assessment
- Blood analysis
- Fiberoptic bronchoscopy (FOB) with bronchoalveolar lavage (BAL) and bronchial mucosa sampling
- The 6MWT
- Computed tomography (CT)
- Transthoracic echocardiography (TTE)

Visit 2

Only patients who qualify for phase 2 of the study will have further visits (60 newly diagnosed patients). The following

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procedures will be performed after an average of 6 (SD 3) months from visit 1:

- The Visit 2 questionnaire
- Cough assessment
- Dyspnea assessment
- Depression and anxiety assessment
- PFTs, the 6MWT, and oxygen saturation (SpO2) measurement
- Arterial blood gas (ABG) analysis (if indicated)

Visit 3

The following procedures will be performed after an average of 12 (SD 3) months from visit 1:

- The Visit 2 questionnaire
- Cough assessment
- Dyspnea assessment
- Depression and anxiety assessment
- PFTs and the 6MWT
- High-resolution computed tomography (HRCT)
- Blood sampling (including testing for autoantibodies and potential biomarkers)
- FOB with BAL (optionally, if clinically indicated)
- Capillary blood gas (CBG) analysis
- TTE
- Rheumatological consultation

Visit 4

The following procedures will be performed after an average of 24 (SD 3) months from visit 1:

- The Visit 2 questionnaire
- Cough assessment
- Dyspnea assessment
- Depression and anxiety assessment
- PFTs and the 6MWT
- HRCT (if clinically indicated)
- Blood sampling (including testing for autoantibodies and potential biomarkers)
- FOB with BAL (if clinically indicated)
- CBG analysis

Visit 5

The following procedures will be performed after an average of 60 (SD 3) months from visit 1:

- The Visit 2 questionnaire
- Cough assessment
- Dyspnea assessment
- Depression and anxiety assessment
- PFTs and the 6MWT
- HRCT (if clinically indicated)
- Blood sampling (including testing for autoantibodies and potential biomarkers)
- FOB with BAL (if clinically indicated)
- CBG analysis
- Rheumatological consultation

Diagnostic Procedures

Pulmonary Function Tests

PFTs will include spirometry with a reversibility test (in the case of obstruction), body plethysmography, and diffusion capacity for carbon monoxide (DLCO). Both absolute and predicted values will be recorded: forced expiratory volume in 1 second (FEV_1), FVC, vital capacity (VC), FEV_1/VC ratio, total lung capacity (TLC), diffusing capacity for carbon monoxide measured by the single-breath method (DLCO SB), inspiratory thoracic gas volume (ITGV), and residual volume/total lung capacity (RV/TLC) ratio. Cough assessment will be conducted using the Leicester Cough Questionnaire and numeric scale. Dyspnea assessment will be performed using the Likert scale and the Modified Borg Scale.

Depression and Anxiety

Depression and anxiety assessment will be conducted using the Hospital Anxiety and Depression Modified Scale (HADS-M) and the 9-item Patient Health Questionnaire (PHQ-9).

Blood Analysis

Briefly, a vein will be punctured in order to take a blood sample, and 30 mL of blood will be drawn. Next, 15 mL of plasma and 15 mL of full blood will be stored separately at –80°C. The following will be analyzed: N-terminal prohormone of brain natriuretic peptide (NT-proBNP) biomarkers routinely used during rheumatological workup and potential IPAF biomarkers. For this, 15 mL of venous blood will be drawn and divided into 2 parts (10 mL and 5 mL), and no anticoagulant will be added to the samples.

The first sample (10 mL) will be sent to the local laboratory for routine analysis of NT-proBNP and rheumatological factor (RF) and for anti–cyclic citrullinated peptide (anti-CCP) and antinuclear antibody (ANA) screening tests. In the case of the confirmed presence of ANAs and the determination of a fluorescence pattern (eg, homogenous, speckled, peripheral, nucleolar), further tests will be ordered: anti–double-stranded DNA (anti-dsDNA), anti-Smith (anti-SM), anti-SSA/Ro, anti-SSB/La, anti–topoisomerase I (anti-Scl70), and antiribonucleoprotein (anti-RNP) antibodies and myositis-specific autoantibodies, such as anti–histidyl-tRNA synthetase (anti-Jo1), anti–threonyl-tRNA synthetase (anti-PL7), anti–alanyl-tRNA synthetase (anti-PL12), anti–Mi2 antigen (anti-Mi2), anti–human exosome complex (anti-PmScl), and anti–melanoma differentiation–associated 5 (anti-MDA5) antibodies.

From the second sample of 5 mL, after clot formation, approximately 2.5 mL of serum will be separated and then divided into 5 portions of 0.5 mL each and placed in Eppendorf tubes. The samples will be marked according to a system allowing for patient anonymization: medical center symbol (sample number - type of biological material - date of sample collection, eg, A12-S_10/04/18). The samples will be stored at –70°C. They will be then used for IPAF biomarkers' identification. This includes testing for chemokine C-C motif ligand 18 (CXCL18), surfactant protein (SP)-A, SP-D, Krebs von den Lungen-6 protein (KL-6), and chitinase 1 (CHIT1).

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For genetic testing, 15 mL of full blood will be collected and divided into 10 Eppendorf tubes containing 1.5 mL of blood each. Samples will be marked according to the aforementioned organizational pattern and stored at –80°C.

Fiberoptic Bronchoscopy With Bronchoalveolar Lavage and Bronchial Mucosa Sampling

Before FOB, local anesthesia with lidocaine and conscious sedation with midazolam and optionally fentanyl will be performed according to detailed anesthesia protocols used in the endoscopy units of the respective medical centers taking part in the study. An intravenous cannula will be inserted prior to the procedure. During the endoscopy, the patient will be monitored according to safety protocols effective in the respective endoscopy units.

Bronchoalveolar lavage fluid (BALF) will be obtained from areas characterized by the greatest interstitial fibrosis involvement on HRCT. If such an area cannot be distinguished, BALF will be obtained from the middle lobe bronchus or the lingula on the side (B4, B5). Localization will be chosen based on HRCT results and will be recorded in the patients' medical files. Next, 200 mL of sterile 0.9% saline solution, previously warmed to body temperature, will be inserted in parts through a 25 mL syringe to perform BAL. For the test to be deemed diagnostic, the protocol will target BALF salvage of at least 60%.

BAL will be performed according to the guidelines of the ERS [8] and the practical guidelines of the Polish Respiratory Society [9]. A differential cell count will be performed in every sample. BALF samples will be processed by an experienced laboratory technician based on Polish Respiratory Society guidelines [9].

Microscopic slide preparation, determination of cell viability, and determination of the dominant population will be performed according to standard laboratory procedures in the Polish Respiratory Society guidelines. The whole-cell count and cell viability will be measured in a sample derived from fluid that has undergone filtration or the first centrifugation. Samples will be prepared with the cytospin method (routinely 1200-2000 rpm for 10 minutes), and cellular smears will be assessed in cytospin samples stained according to the May-Grünwald-Giemsa method.

BALF samples will be secured for further tests, including testing for potential IPAF biomarkers. Briefly, 15 mL of BALF will be divided into 10 Eppendorf tubes containing 1.5 mL of BALF each and stored at –70°C. Low-speed centrifugal supernatants of BALF will be obtained from each sample. We will measure the concentration of potential biomarkers in each sample using the sandwich enzyme-linked immunosorbent assay (ELISA) technique.

Next, 5 mucosa samples will be obtained from the middle lobe bronchus for histopathological assessment later. Directly after sample collection, they will be put into dry Eppendorf tubes and frozen at –80°C. In addition, transbronchial lung cryobiopsy may be used to obtain material for histopathological assessment.

The 6-Minute Walking Test

The submaximal exercise 6MWT, which entails the measurement of the distance walked over a span of 6 minutes, will be performed according to the detailed protocol used in the respective medical centers. The blood pressure (BP), heart rate (HR), and SpO_2 will be measured directly before and after the test. The following will be recorded: whether the patient completed the test, the distance walked (m), SpO_2, the SpO_2 nadir, and dyspnea sensation measured with the Modified Borg Scale and the Visual Analogue Scale (VAS). If the test is stopped or paused before 6 minutes, the reason (eg, dyspnea, high BP, cardiac arrythmia, limb pain, angina, or other) will be recorded.

The 6MWT will be performed according to Polish Respiratory Society guidelines [10]. Participants will be informed at 30-second intervals about the amount of time remaining. The predicted distance will be calculated based on the equation published in Polish Respiratory Society guidelines for the interpretation of the 6MWT as the most accurate for participants' characteristics [10].

Pulse oximetry will be performed for all patients. If $SpO_2<92\%$ or there are clinical indications for oxygen therapy, ABG analysis will be performed. For ABG analysis, an artery (radial or femoral) is punctured in order to take a sample of arterial blood. The artery is then compressed in order to prevent bleeding/hematoma. The procedure is performed according to ERS guidelines [11].

Computed Tomography

HRCT of the lung will be performed during hospitalization. If the patient provides a CT scan from up to 6 months prior to recruitment (eg, from the outpatient clinic), we will analyze both scans and the radiological descriptions. To ensure the patient's anonymity, a CD containing the patient's scans will be marked by the technician according to the aforementioned pattern. Radiological analysis will be performed using the OsiriXLite DICOM Viewer. The following densitometric values will be measured: mean lung attenuation (MLA), kurtosis, skewness, and deviation of lung radiodensity (SD_{IR}). Statistical analysis of the data will be performed using Statistica software. Data will be presented as the median value and IQRs. Differences between quantitative data will be analyzed using the Kruskal-Wallis test and the post hoc Dunn test.

Transthoracic Echocardiography

TTE with a thorough right heart description will be performed. The following parameters will be noted in the patient's medical file: main pulmonary artery diameter; acceleration time; pulmonary valve peak velocity, tricuspid annular peak systolic velocity (TAPSV), tricuspid annular plate systolic excursion (TAPSE), and tricuspid valve peak regurgitation velocity; right ventricular basal and right ventricular midcavity diameters; right ventricular outflow tract and proximal and distal right ventricular outflow; right atrial short- and long-axis, inferior vena cava, and superior vena cava diameters; and right ventricular wall thickness.

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Rheumatological consultation will be provided to patients with IPAF and CTD-ILD to verify the diagnosis.

Choice of Candidate IPAF Biomarkers

KL-6 (mucin 1) is a glycoprotein encoded by the *MUC1* gene and is expressed on the outer surface of type II alveolar epithelial cells and the airway epithelium. It has been proposed as a biomarker of IPF [12]. KL-6 probably promotes fibroblasts' migration, proliferation, and survival in the respiratory system [12]. High serum KL-6 levels have been found in patients with IPF, NSIP, and other ILDs [13-15], which is associated with an aggressive clinical course and could also serve as a predictor of acute exacerbation [16]. High KL-6 levels have also been found in the BALF of individuals with various ILDs, including IPF [17].

Another proposed ILD activity biomarker is CC-chemokine ligand (CCL)18. In a population of patients with idiopathic ILD and SSc, it was revealed that the BALF CCL18 level was negatively correlated with the TLC and the DLCO and positively correlated with BALF neutrophil and eosinophil cell counts. During the follow-up period of ≥6 months, a negative correlation was observed between the decrease in the predicted TLC and the increase in serum CCL18 levels [18]. We hypothesize that such correlation also exists in IPAF, and we will test the theory that patients with IPAF with autoantibodies associated with SSc (anti-PmScl) have higher serum or BALF CCL18 levels than those who test negative for these autoantibodies.

Surfactant proteins SP-A and SP-D are large hydrophilic molecules produced by Clara cells and type II alveolar epithelial cells. SP-A and SP-D play an important role in innate immunity and modulate the excessive inflammatory response on the alveolar surface [19-21]. SP-A and SP-D levels are higher in patients with IPAF than in healthy individuals, patients with infectious pneumonia, or patients with nonfibrotic lung diseases [22-24]. Moreover, serum SP-D levels are lower in the IIP non-IPF group than in the IPAF group [22]. SP-A levels cannot be used to differentiate between patients with IPAF and CTD-ILD [24].

According to Xue et al [22], a negative correlation of serum SP-A levels and the DLCO was revealed in the IIP group (which included 27/69 patients with IPAF, although this subgroup was not separately analyzed). A negative correlation was also revealed with FEV_1 and the FVC [22]. This conclusion was partially confirmed by Wang et al [23], who revealed a negative correlation between serum SP-A levels and changes in the DLCO, FEV_1, and FVC values after treatment. Additionally, Wang et al [23] suggested a prognostic role of SP-A: the pretreatment levels were found to be significantly lower than the posttreatment ones in individuals with progressive fibrosis during the course of IPAF. Moreover, a positive correlation was found between shifts in KL-6 and SP-A levels [23]. In a prospective study, Xue et al [24] observed a significant difference in serum SP-A levels measured at baseline and after 1-year follow-up. In individuals whose condition had exacerbated, SP-A levels were correlated with lung involvement scores on HRCT [24].

These findings need to be validated in European populations. There is a need to determine whether there is a correlation between lung involvement and a decrease in pulmonary function and SP-A/SP-D levels in the bodily fluids of patients with IPAF.

CHIT1 is a member of the glycosyl hydrolase family 18. It is expressed predominantly in polarized and differentiated macrophages and acts as an innate immune mediator digesting cell walls of pathogens that contain chitin (eg, fungi). CHIT1, due to its dysregulated activity, is a proposed marker in granulomatous and fibrotic ILDs associated with interstitial inflammation and lung tissue remodeling.

A study by Bargagli et al [25] revealed elevated CHIT1 activity in the BALF of individuals with IPF in comparison with the healthy control group; however, no significant differences in the serum levels were noted. This suggests the role of CHIT1 expression in interstitial macrophages in tissue injury and remodeling. We hypothesize that CHIT1 may play an important role in the pathogenesis of other ILDs, including IPAF, especially with a progressive fibrosing phenotype.

Lee et al [26] revealed that in 2 different cohorts of individuals with SSc, CHIT1 activity and concentrations increased in the serum and BALF compared to demographically matched healthy controls. Individuals with SSc-ILD, in comparison with patients without lung involvement, were characterized by higher CHIT1 serum activity, which was also correlated with disease severity. The authors revealed that CHIT1 upregulates transforming growth factor beta 1 (TGF-β1) receptor expression and its signaling in fibroblasts, which makes CHIT1 a modulator of progressive interstitial lung fibrosis [27].

These findings raise the question whether CHIT1 or TGF-β1 and their interaction could be a potential target for SSc pharmacological therapy. As the etiopathogenesis of IPAF is still obscure, we plan to analyze both circulatory and lung activities of the enzyme to establish its potential role in the disease pathogenesis.

S100A9, also referred to as myeloid-related protein 14 or calgranulin B, is a member of the calcium-binding protein S100 family and is mostly expressed in neutrophils but also on vascular endothelial cells and mature macrophages. S1009A expression is enhanced by some chronic inflammatory factors [28]. It acts as an immunomodulatory, proinflammatory, and profibrotic agent [29]. It is mostly secreted in inflammatory lesions [30], and it has been suggested as a potential target for IPF treatment [31] and as a candidate biomarker to differentiate between IPF and other fibrotic ILDs [32]. However, convincing evidence from contemporary trials is yet scarce.

Elevated serum S100A9 levels have been reported in samples obtained from patients with RA, SLE, SSc, vasculitis, lung cancer, and various other diseases associated with chronic inflammation [33-35]. It has also been demonstrated that S1009A may promote atherosclerosis [36]. In an observational study by Lin et al [37], it was revealed that S100A9 levels were significantly elevated in BALF samples obtained from patients with severe IPF. It has also been demonstrated that S100A9 levels in the BALF of patients with IPF are positively correlated with the percentage of BALF neutrophils. This suggests a

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relationship between S1009A levels and disease activity. Some studies have reported that BALF S100A9 levels are significantly elevated in individuals with pulmonary involvement during the course of SSc [38,39].

CCL2 is a protein that attracts T lymphocytes, natural killer lymphocytes, and fibrocytes [40]. It is associated with inflammatory processes, cell migration and activation, fibrosis, and angiogenesis [41] through its 7-transmembrane-spanning G-protein-coupled CC-chemokine receptor 2 [42]. CCL2 plays a significant role in the pathogenesis of various diseases, such as tuberculosis [43], asthma [44], and RA [45].

A connection was established between CCL2 polymorphism and the occurrence of autoimmune disorders. The *CCL2* gene (–2518G/A) single-nucleotide polymorphism has been shown to be associated with sarcoidosis [46]. Increased CCL2 levels have been found in the serum and BALF of patients with IPF [47]. In vitro and in vivo studies have revealed that CCL2 is associated with fibrosis by supporting monocyte-/macrophage-mediated inflammation, angiogenesis, collagen synthesis, myofibroblast cell differentiation, and fibroblast activation [48].

It remains unclear whether the chemokine profile of serum and BALF of individuals with IPAF, especially patients with progressive fibrosis, resembles that of patients with IPF.

Data Collection

Data will be collected via questionnaires: the Leicester Cough Questionnaire, St. George's Respiratory Questionnaire, the Fatigue Assessment Score and 36-item Short Form (SF-36) v.2 Quality of Life Questionnaire, the HADS-M, and the PHQ-9. To help unify data and due to copyright reasons, surveys for physicians will be set up on servers of the Medical University of Silesia. All the aforementioned documents will be provided to the patients in their native tongue and have been validated in the Polish population.

Statistical Analysis

Statistical tests will be chosen due to variable distribution. To verify the normality of variable distribution, the Shapiro-Wilk test will be performed. To compare parameters between the 1 study and 2 control groups, ANOVA or the Kruskal-Wallis test will be performed (for normal or nonnormal variable distribution, respectively). To correlate the variables, Pearson or Spearman correlation tests will be performed (for normal or nonnormal variable distribution, respectively). To determine the relationship between variables, the linear regression test will be performed.

Results

Although the study was designed and Ethical Board Committee approval granted in the past, we have experienced difficulties in the phase of patient recruitment due to the outbreak of the novel coronavirus.

It is worth noting that the majority of tests are routinely performed in the diagnostic workup of patients with ILDs; therefore, patients will not be subjected to additional risks. Discomfort may be caused by the drawing of more blood samples than usual; however, this will be reduced by the use of vacuum blood collection systems.

This study will start recruiting patients to phase 1 in October 2023. The final results will be available in 2028. We plan to publish preliminary results after 2-3 years from the start of phase 1.

Discussion

Summary

As IPAF is an exclusion diagnosis, we believe that in the era of genetic testing advancements, genetic disorders manifesting as ILDs should be considered as alternative etiologies. In our study, the local bioethics committee granted permission to perform genetic testing, and we plan to bank full blood, with the intention to perform such procedures.

There have been clinical reports of individuals with signal transducer and activator of transcription 3 (STAT3) gain-of-function syndrome [49] or cytotoxic T cell antigen 4 (CTL-A4) checkpoint haploinsufficiency [50], which could fulfill the 2015 criteria. Moreover, a newly discovered coatomer protein complex subunit alpha (COPA) syndrome causes progressive ILD [51]. The impaired COPA protein may contribute to endoplasmic reticulum stress and therefore trigger interferon signaling pathways and T cell–mediated inflammation [51].

Newton et al [52] revealed that the leukocyte telomere length is longer in individuals with IPAF and CTD-ILD than in those with IPF. The telomere length correlates with lung function and lung transplant outcomes in IPAF. Moreover, mucin 5B (MUC5B) and Toll-interacting protein (TOLLIP) polymorphisms are associated with both IPAF and IPF, which suggests that these 2 clinical entities have similar genetic backgrounds. Various polymorphisms are found in CTDs, such as RA, SS, and SSc, but to date, there are no data on whether the presence of these polymorphisms is associated with the development of IPAF. Hopefully, an in-depth understanding of molecular pathways could lead to the development of targeted therapies.

A practical question we are going to face stems from the fact that instructions for most ELISA kits that are available for research use in our area only contain suggestions/guidelines for serum dilution. Therefore, we will need to either predict the levels of the aforementioned proteins in BALF or experiment with dilution. As we are unsure how much time it will take to recruit the adequate number of individuals, we plan to perform a miniexperiment beforehand: First, we will test the serum according to the manufacturer's guidelines. If the standard 1:40 dilution does not lead to the detection of predicted concentrations, we will check the 1:20 dilution, 1:5 dilution, and undiluted samples. The next step will be testing BAL samples. We will test 1:20 dilution samples, and again, if this does not result in the detection of protein concentrations within the range provided in the kit instruction, we will test the 1:5 dilution and undiluted specimens.

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The clinical stability of IPAF is an important subject, as the development of mild extrapulmonary symptoms may be overlooked. In our opinion, this specific population requires above-average clinical vigilance due to the fact that reclassification as definite CTD-ILD prompts a change in the therapeutic approach based on ACR/EULAR guidelines. This is why we plan to cooperate closely with rheumatologists regarding assessment of the extrapulmonary manifestations of autoimmunity. However, there is also a possibility that an entity that had been initially classified as idiopathic ILD may later be reclassified as IPAF. To test this hypothesis, we plan periodic rheumatological revaluations of this subgroup, together with retesting for ANAs (serological domain of IPAF).

Data on the progression of IPAF to CTDs are scarce and conflicting. Scirè et al [53] reported that 42% of patients with IPAF with antisynthetase antibody positivity were ultimately reclassified as RA-ILD, PM/DM-ILD, or myositis-RA overlap syndrome. Ito et al [54] also reported that 12.2% of individuals meeting IPAF serological and morphological criteria were diagnosed with CTD during a median follow-up period of 54 months. However, Chartrand et al [55] found that none of the 56 individuals with IPAF was rediagnosed over a follow-up period of 48 months.

Another question is when to initiate treatment during the course of IPAF. Before IPAF was defined, ILD with symptoms of underlying autoimmune disorder but without extrapulmonary manifestation could have been classified as IIP and therefore have delayed treatment initiation. In our prospective observational study, we will surely face a challenge in identifying patients with IPAF who require early clinical intervention. We hope that during the 60-month observation period, we will be able to identify molecular, radiological, and functional prognostic factors, which, in the future, will help lay the foundation for IPAF therapy guidelines.

In a study on 412 patients with CTD-ILD or IPAF, Li et al [56] analyzed the relationship between these 2 entities in order to identify which individuals with IPAF should commence treatment early. They concluded that based on similar yet milder symptoms and ANA positivity, IPAF is in fact an early stage of CTD-ILD and therefore treatment should commence early. After immunosuppressive treatment, they reported an increase in the FVC and DLCO in this population. The choice of adequate pharmacotherapy is another clinical question that we will face during prospective observation.

D'Silva et al [57] presented a case series of 50 patients from 2 centers who were treated with rituximab (RTX). The majority experienced either clinical improvement or stability understood as global assessment of performance in terms of oxygen requirement, unplanned hospitalization due to respiratory reasons, and 1-year survival, despite baseline differences regarding age, comorbidities, and prior treatment history.

Although we do not plan a randomized controlled trial, in prospective observation, we will face clinical decisions regarding treatment implementation. We hypothesize that some patients will have a history of treatment with systemic GCs or cyclophosphamide (CYC), and we wonder whether the results of studies on CTD-ILDs can be extrapolated to the IPAF population. The use of CYC is associated with an increased risk of malignancy, infections, and bone marrow suppression [58].

Some patients in this study had previously used mycophenolate mofetil (MMF) or tacrolimus, which may have impacted their performance on RTX. The implementation of RTX therapy, especially in patients with refractory ILD, should be considered due to its favorable safety profile [59]. We also hypothesize that a usual interstitial pneumonia (UIP) radiological pattern, which is associated with higher mortality in patients with IPAF [60], may impact treatment efficacy.

We wonder whether studies on patients with RA-ILD who generally have a UIP pattern may be extrapolated to this specific IPAF population, and in prospective observation, we plan to exteriorize 2 subpopulations (UIP-RA and UIP-IPAF) and compare patients' outcomes in terms of oxygen requirement, PFT results, 6MWT performance, and 1-, 3-, and 5-year survival.

We are looking forward to cooperating with rheumatologists for multidisciplinary discussion.

Impact of Pilot Study Results on the Protocol

In our pilot study [7], we revealed a greater prevalence of gastrointestinal reflux disease (GERD) in the CTD-ILD group than in the IPAF and IIP groups. Data on the impact of GERD on fibrosis pathogenesis are conflicting. There are data suggesting that exposure of the interstitial tissue to a low pH results in repeated lesions and, consequently, progressive fibrosis. However, there are also data supporting a hypothesis that GERD actually results from progressive fibrosis and a shift in intrathoracic pressure due to altered anatomy. Therefore, we decided to launch a substudy on patients with progressive fibrosing ILD (PF-ILD), focusing on the impact of GERD on the disease course. We will monitor 24-hour impedance-pH to objectify GERD episodes and correlate them with symptoms.

In the pilot study [7], it was also revealed that BALF levels of interleukin 8 (IL-8), CXCL1, and TGF-β1 were significantly higher in the CTD-ILD group than in the IPAF and IIP groups. We hope that the analysis of 240 subjects in this full-size study will reveal more defined differences between study groups. We plan to analyze subgroups (eg, RA-ILD or SSc-ILD) and compare them with their IPAF counterparts (based on the presence of clinical symptoms and specific autoantibodies). We also plan to distinguish an IPAF subgroup associated with the presence of antisynthetase autoantibodies and compare it with the PM/DM-ILD subgroup in terms of clinical stability and outcomes.

Our pilot study [7] also revealed that the BALF IL-8 concentration is associated with the presence of skin teleangiectasias. IL-8 is a known proangiogenic factor. In this full-size study, we plan to perform videocapillaroscopy to stratify participants according to the Cutolo nailfold capillaroscopy classification and measure the concentration of proangiogenic cytokines in both serum and BALF. We will be able to compare corresponding Cutolo subgroups of SSc-ILD and IPAF and determine the impact of proangiogenic factors on pathological angiogenesis.

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We also hypothesize that there will be significant intergroup differences between the reported severity of cough and dyspnea as well as psychological symptoms and their impact on various aspects of the QoL.

Conclusion

This study will be a step toward a better understanding of IPAF etiopathogenesis and outcomes.

Acknowledgments

This study will not receive any external funding.

Data Availability

Due to privacy reasons, anonymized data will be available upon request from the corresponding author.

Conflicts of Interest

None declared.

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Abbreviations

6MWT: 6-minute walking test
ABG: arterial blood gas
ACR: American College of Rheumatology
ANA: antinuclear antibody
anti-SSA: anti–Sjögren's syndrome–related antigen A
ATS: American Thoracic Society
BAL: bronchoalveolar lavage
BALF: bronchoalveolar lavage fluid
CBG: capillary blood gas
CCL: CC-chemokine ligand
COP: cryptogenic organizing pneumonia
COPA: coatomer protein complex subunit alpha
CT: computed tomography
CTD-ILD: connective tissue disease–associated interstitial lung disease
DLCO: diffusion capacity for carbon monoxide
DM: dermatomyositis
ERS: European Respiratory Society
ELISA: enzyme-linked immunosorbent assay
EULAR: European League Against Rheumatism
FEV1: forced expiratory volume in 1 second
FOB: fiberoptic bronchoscopy
FVC: forced vital capacity
GERD: gastrointestinal reflux disease
HADS-M: Hospital Anxiety and Depression Modified Scale
HRCT: high-resolution computed tomography
IIP: idiopathic interstitial pneumonia
ILD: interstitial lung disease
IPAF: interstitial pneumonia with autoimmune features
IPF: idiopathic pulmonary fibrosis
LIP: lymphocytic interstitial pneumonia
MCTD: mixed connective tissue disease
NSIP: nonspecific interstitial pneumonia
PFT: pulmonary function test
PHQ-9: 9-item Patient Health Questionnaire
PM: polymyositis

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QoL: quality of life
RA: rheumatoid arthritis
RB-ILD: respiratory bronchiolitis–associated interstitial lung disease
RTX: rituximab
SpO_2: oxygen saturation
SS: Sjögren's syndrome
SLE: systemic lupus erythematosus
SSc: systemic sclerosis
TGF-β1: transforming growth factor beta 1
TLC: total lung capacity
TTE: transthoracic echocardiography
VC: vital capacity

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Protocol

Deciphering the Role of Insulin-Like Growth Factor 1 in Endometrial Cancer in Patients With Polycystic Ovary Syndrome: Protocol for a Methodological Approach Using Cell Culture Experiments

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Abstract

Background: Endometrial cancer (EC) is the most common gynecological cancer in women globally. It is linked to increasing obesity rates and longer life spans. The molecular mechanisms leading to EC are unclear; however, women with polycystic ovary syndrome (PCOS) have a 3- to 5-fold increased EC risk. According to a pilot study conducted in the United Kingdom, insulin-like growth factor-1 (IGF-1) gene and protein were raised in the endometrium and blood of women with EC and PCOS, compared with those without PCOS (controls). Therefore, raised serum IGF-1 levels may contribute to an increased EC risk in women with PCOS, but it is necessary to test this hypothesis since not all studies have demonstrated this association.

Objective: This study aims to investigate the role of IGF-1 in mediating EC risk in PCOS. This will be achieved by evaluating the proliferative effects of PCOS serum, IGF-1, and IGF-1 antagonist on human endometrial cancer 1-A and 1-B cell lines, with a comparison to controls (using serum from women without PCOS and cell culture media). The study will also identify differentially expressed genes and pathways activated by various treatments.

Methods: We intend to recruit 20 women with PCOS and 20 women without PCOS for this cross-sectional study. All experiments will be carried out 4 times to ensure consistency. We will perform transcriptomic and phosphoproteomic profiling to identify differentially expressed genes and phosphoproteins between different treatments using RNA sequencing and phosphoproteomics. We will also perform bioinformatics pathway analysis to identify whether any unique collection of genes or phosphoproteins explains increased EC risk in PCOS. The primary outcome measure will be the cell proliferation (growth) difference measured by cell index values. Our protocol stands out due to its unique approach; no previous study has used this approach to investigate the oncogenic effect of serum from women with PCOS. Additionally, no previous study has considered the differential mutations of genes related to the insulin signaling pathway across various types of human EC cell lines and the potential impact of these variations on their experimental findings.

Results: Participants are currently being recruited. It is expected that preliminary findings suitable for analysis and publication will be available by the summer of 2024.

Conclusions: Although we currently do not have any results to report, sharing our protocol at this stage will aid in research collaboration, provide an opportunity for early feedback, and help reduce duplication of effort by other research groups. The findings of our study will have broader implications. A deeper understanding of the mechanisms underlying the regulation of the IGF system in PCOS and EC will improve our ability to develop effective treatment modalities for EC and will be a vital step toward reducing EC in women globally.

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KEYWORDS

endometrial cancer; polycystic ovary syndrome; insulin-like growth factor-1; IGF-1; cell culture; United Arab Emirates; PCOS; polycystic ovary syndrome; women's health; gynecology; oncology; cancer; endocrinology; serum; endometrium; endometrial; cell; biology; gene; genetic; genetics; genes

Introduction

Overview

Endometrial cancer (EC) was the sixth most diagnosed cancer in women globally, in 2020 [1], with 417,000 new cases and 97,000 deaths. The incidence is also increasing rapidly with rising rates of obesity [2] and longer life expectancy. It is estimated that the incidence will increase by more than 50% worldwide by the year 2040 [1]. EC was also the most common gynecological cancer in the United Arab Emirates in 2020, with a 5-year prevalence of 491 per 100,000 individuals [3]. The most common type of EC is type 1 (endometrioid), which is present in 80% of tumors. Treatment often involves hysterectomy—a major surgical operation with serious implications, such as infertility, for younger women [4], which is of growing concern in the United Arab Emirates [5]. There is, therefore, an urgent need for research to prevent and improve the management of EC in the United Arab Emirates and globally. However, uncertainty persists about the precise molecular mechanisms leading to EC, which hinders facilitating EC prevention and treatment.

Some of the known risk factors for EC include polycystic ovary syndrome (PCOS), diabetes, obesity, inflammation, insulin resistance, high estrogen concentrations, and possibly, high circulating insulin-like growth factor 1 (IGF-1) levels [6]. PCOS is, however, the most common female endocrinopathy [7] in women of reproductive age, and potentially, it could account for many cases of EC. PCOS is associated with obesity, infrequent menstrual periods, infertility, hirsutism, enlarged ovaries with many small follicles on ultrasound imaging, increased risks of type-2 diabetes in later life, and a 3- to 5-fold increased risk of EC [8,9], with higher risks in premenopausal women. Mechanisms thought to increase EC risk in PCOS include raised estrogen levels, obesity, anovulatory menstrual cycles, and unopposed (from progesterone) estrogen stimulation of the endometrium; however, the degree to which these mechanisms increase EC risk or interact with each other to underpin EC risk in PCOS is uncertain [10]. Genomic and proteomic approaches [11] have also identified potential new genes and proteins that might explain the link between PCOS and EC and could upregulate genes associated with the insulin signaling pathway in PCOS.

Over the past few years, research studies have investigated the potential role of insulin resistance and IGF-1 in the association between PCOS and EC [12,13]. The possible role of insulin resistance and IGF-1 in the association between PCOS and EC is supported by observations that endometrial dysfunction, causing miscarriages in PCOS, has been linked to insulin resistance and the associated elevation in serum IGF-1 levels in individuals with PCOS [14]. Epidermal growth factor, IGF-1, and IGF-2 were also found to stimulate a time-dependent mitogenic response in human EC cell lines [15]. The most frequently altered mutation in type 1 EC is the phosphoinositide 3-kinase (PI3K) pathway [16]. Elevated IGF-1 and insulin levels have been shown to directly stimulate cell proliferation by activating the phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha pathway [17]. However, the precise association between serum IGF-1 and EC is still uncertain, and results from case-control studies are conflicting [18]. Multiple other molecular pathways also contribute to EC progression. Dysfunction in the TP53 pathway is common in type 2 EC, resulting in the loss of crucial p53 functions. Additionally, the overactivation of the mitogen-activated protein or extracellular signal-regulated kinase (ERK) pathway promotes EC cell proliferation and migration. These pathways, however, interact with IGF-1 signaling, and IGF-1 gene promoter polymorphisms are associated with EC [18].

The importance of investigating the IGF-1 pathway in the association between EC and PCOS is justified. This is because EC is a disease mainly driven by phosphoinositide 3-kinase (PI3K), as the PI3K pathway is aberrant in more than 90% of ECs. PI3K signaling is the main pathway cascade of insulin or IGF-1 signaling [19].

Prior Work

In a pilot study in which 102 women were recruited, the investigators found for the first time that IGF-1 gene and protein levels were raised in the endometrium and serum of women with PCOS and EC, compared with controls. These two groups exhibited similar levels of obesity [13]. Raised serum IGF-1 levels may, therefore, contribute to an increased risk of EC in women with PCOS; however, there is a need to test this hypothesis since not all studies have demonstrated an association between serum IGF-1, IGF-binding protein 1, IGF-binding protein 3, and insulin levels with EC [20]. A recently published systematic review [21] found that IGF-1 levels in women with PCOS were elevated compared with controls, as found in our pilot study. A total of 20 studies were included in the meta-analysis [21] involving 657 individuals: 362 patients with PCOS and 295 normal controls. The results of the meta-analysis showed that serum IGF-1 levels were significantly higher in patients with PCOS compared to controls (standard mean difference 0.89). Subgroup analysis based on BMI showed that elevated IGF-1 levels were associated with normal-weight and overweight patients in the PCOS group. Further clarification is required about the interplay between PCOS, IGF-1, and the endometrium as well as the impact they have on EC.

Aims

The aim of this study is to further investigate the possible role of IGF-1 in mediating the risk of EC in women with PCOS.

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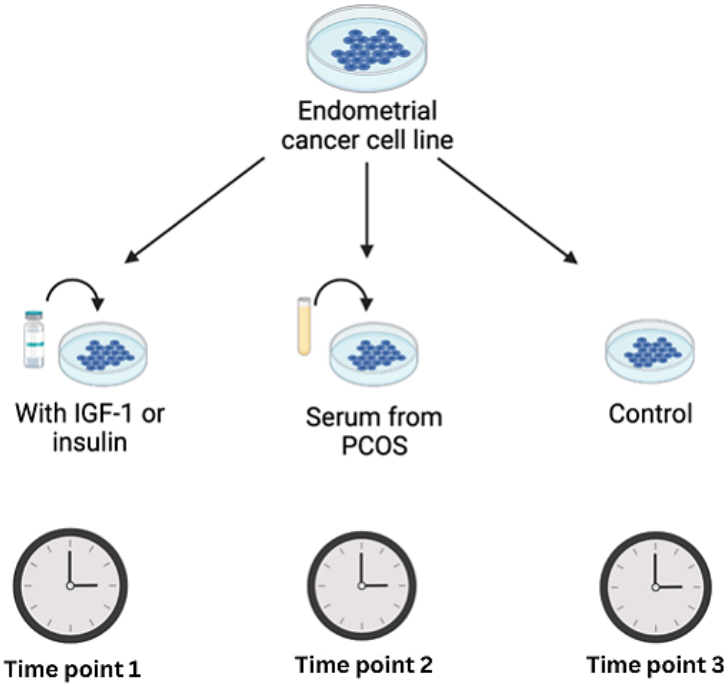
Objectives

The objectives of the study are as follows:

- To compare the oncogenic effect of PCOS serum, IGF-1, and IGF-1 antagonist on EC cell lines in women with PCOS and controls (using serum from women without PCOS and cell culture media)
- To identify differentially expressed genes and pathways activated by different treatments used in the previous objective
- Perform a bioinformatics pathway analysis to identify whether any unique genes or nodes can explain the increased EC risk in PCOS

Although using cell culture experiments, as described in this paper, is not a novel approach for studying molecular mechanisms to help the prevention and treatment of diseases [22], the unique aspects of our protocol lie in the fact that no previous study has used this approach to investigate the oncogenic effect of serum from women with PCOS. More importantly, no previous study has considered the differential mutations of genes related to the insulin signaling pathway in human endometrial cell lines, as identified in the Cancer Dependency Map Portal [23], and what impact this may have on their experimental findings (Figure 1).

Figure 1. Comparing the oncogenic effect of polycystic ovary syndrome (PCOS) serum on endometrial cancer cell lines with the effect of serum from women without PCOS (controls) and insulin-like growth factor 1 (IGF-1).



Methods

Ethics Approval

Ethics approval for this study has been obtained from the research ethics committees of Mohammed Bin Rashid University of Medicine and Health Sciences (MBRU IRB-2022-149) and Kings College London in Dubai (October 12, 2022). Approvals from other hospital sites (Latifa Women and Children's Hospital and Mediclinic Hospitals in Dubai) will be sought, as appropriate, based on participant recruitment rates.

Recruitment

The study will aim to recruit 20 women with PCOS and 20 women without PCOS aged between 18 and 45 years. We will recruit women with PCOS and controls into the study if they have a BMI below 30 and are not on any medications. This is to mitigate the possible confounding effect of obesity on EC risk. Inclusion criteria for women with PCOS will involve a diagnosis using the Rotterdam Criteria [24], which encompasses the presence of 2 or more of the following conditions: clinical or biochemical evidence of hyperandrogenism, chronic oligo-ovulation or anovulation, and the observation of polycystic ovaries on ultrasound, with the exclusion of other causes of chronic oligo-ovulation or anovulation (eg, hyperprolactinemia and hyperthyroidism). Controls will be women with regular menstrual cycles identified from a gynecology or other appropriate outpatient setting at Kings College Hospital, Latifa Women and Children's Hospital, or Mediclinic Hospital in Dubai, without a diagnosis of polycystic ovaries on ultrasound scan. Male patients will be excluded from this study, as they do not develop EC.

Women identified as having PCOS or controls will be identified by gynecologists in participating hospitals and provided a patient information sheet. If the patient agrees to participate, written consent will be obtained. One of the study investigators will then be informed by the clinician or gynecologist who recruited the patient into the study. The investigator will then contact the participant to arrange a mutually convenient time for sample collection. For women with and without PCOS recruited into the study, participation will not involve any extra visits to the hospital in addition to visits required as part of their clinical care. Fasting blood samples will be obtained following the

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exclusion of a possible pregnancy. With the permission of the participants, we will review their electronic medical records to obtain details on their medical and gynecological history, including the reason for clinical presentation, menstrual history, date of last menstrual period before sample collection, past medical or surgical history, medication, allergies, and smoking history. The most recent height, weight, and blood pressure measurements in the electronic medical record will be recorded. The details of their last pelvic ultrasound scan will also be recorded to confirm if their ovaries did or did not look polycystic.

Participants can withdraw from the study at any stage without their clinical care being affected. We do not anticipate any issues with adverse effects; however, the research team aims to meet fortnightly as a research group during the study, with steering committee meetings arranged as indicated. The principal investigator will report any relevant data safety issues reported during these meetings or from any other sources to the Mohammed Bin Rashid University's Institutional Review Board (IRB).

Blood Tests

Following informed consent, 1 extra sample of blood (in addition to the other blood tests required as part of their clinical care) will be obtained from the participant's arm and collected into 1 vacutainer for the study. Whole blood collected from patients with PCOS and controls will be stored for a maximum of 24 hours before the serum is separated. Samples will be transported from the gynecology clinic to the laboratory at Mohammed Bin Rashid University, ideally within 6 hours of whole blood collection, in dry ice between 2˚C and 8˚C, with the tubes stored in specimen bags.

We anticipate no major problems with side effects; nonetheless, following the blood tests, the participants may experience minor bruising in the area from which blood was obtained. However, all the blood tests will be taken by an experienced staff member, which should help minimize this risk. Participants will be informed that during the cell culture studies, we may identify incidental factors that might be associated with an increased risk of EC. Should this occur, the results will be made available to participants and their general practitioners or family medicine doctors if they so wish, and they will be offered appropriate counseling. They will also be informed that we may not find any significant differences between blood samples taken from women with PCOS and controls and that there will be a need for further studies on more women to confirm any of our findings. The experiments will not involve any techniques that will put staff at risk or produce environmental contaminants. Participants will also be informed that the potential benefits are that this study might identify new genetic or chemical factors that may prove significant in future studies for the prevention and treatment of EC and that this will be a vital step in reducing the incidence of EC in women living in the United Arab Emirates.

Processing and Storage of Blood Samples

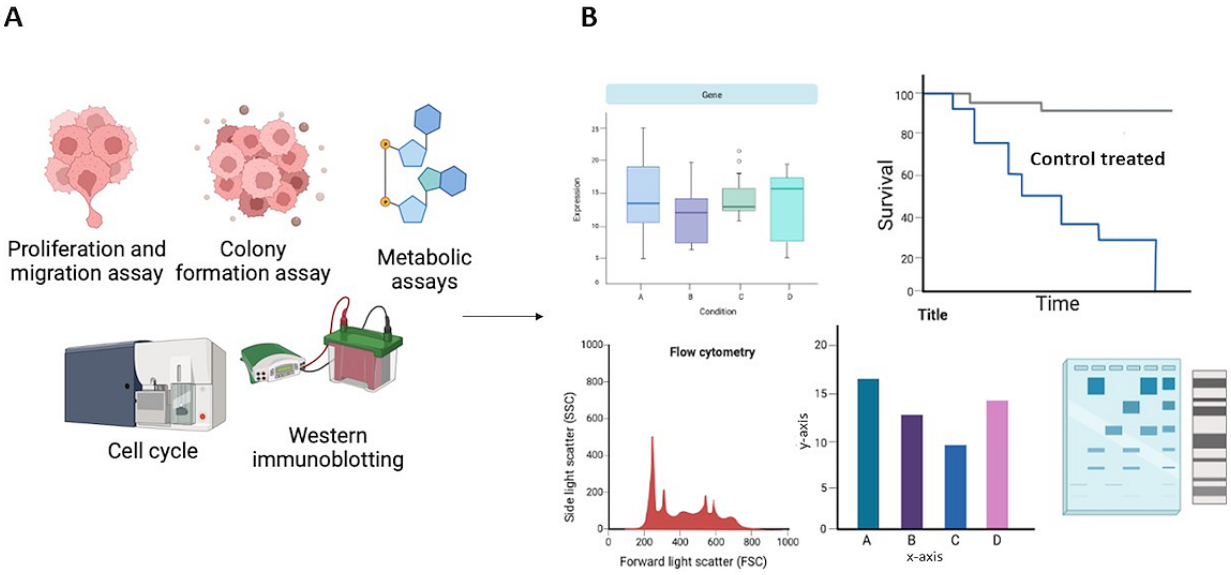
Whole blood will be allowed to clot for 15-30 minutes at room temperature or left at 4˚C until the reaction is complete. We will aim not to exceed 24 hours and isolate serum within 1 or 2 hours of blood collection. Once the blood has been clotted, it will be centrifuged at 1000 x gravitational units (g) for 10 minutes in a refrigerated centrifuge (at 4˚C) to facilitate the separation of the serum. A barrier will form between the serum and the cells; if no barrier is formed, the sample will be respun for 5 minutes. The serum will be carefully extracted using a fine-bore pipette to prevent the inclusion of red blood cells and will be aseptically transferred to a sterile vial. The samples will be kept at temperatures ranging from 2°C to 8°C during handling. The serum will then be stored without delay at –80˚C in 0.5 mL aliquots to prevent the disintegration of serum proteins. Upon completion of the initial studies with the blood tests obtained from the participants, with their consent, we will retain some of the remaining serum samples for long-term storage to allow further studies if newer technology for carrying out these studies becomes available. However, if participants do not wish to have their serum samples retained for this part of the study, the sample will be discarded in accordance with the established laboratory protocols immediately after the cell culture study. Permission will be sought from the research and ethics committee prior to conducting any further studies using the stored blood samples.

Objective 1: Comparing the Oncogenic Effect of PCOS Serum on EC Cell Lines With the Effect of Serum From Women Without PCOS (Controls) and IGF-1

To further investigate the possible role of IGF-1 in mediating the risk of EC in women with PCOS we will evaluate the proliferative effects of PCOS serum, IGF-1, and IGF-1 antagonists on human endometrial cancer 1-A and 1-B cell lines, through a comparison with controls (using serum from women without PCOS and cell culture media; Figure 2).

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Figure 2. Comparing the oncogenic effect of polycystic ovary syndrome (PCOS) serum on endometrial cancer cell lines with the effect of with the effect of serum from women without PCOS (controls) and insulin-like growth factor 1 (IGF-1). (A) various assays. (B) measures to compare oncogenic effect.



Endometrial Carcinoma Cell Lines

Human endometrial cancer (HEC)-1-B and HEC-1-A cell lines will be used in this study. Cells will be treated with the study groups outlined below:

- PCOS serum alone
- PCOS serum and IGF-1
- PCOS serum with IGF-1 antagonist applied
- PCOS serum and IGF-1 with IGF antagonist applied
- Control serum alone
- Control serum and IGF-1
- Control serum with IGF-1 antagonist applied
- Control serum and IGF-1 with IGF antagonist applied
- Cell culture media alone
- Cell culture media and IGF-1
- Cell culture media with IGF-1 antagonist applied
- Cell culture media and IGF-1 with IGF antagonist applied

The treatment will be administered in different time periods, and all experiments will be carried out in quadruplicates. We will examine the effect of cell treatment on cell lines using proliferation, migration, cell cycle analysis, soft agar colony formation assays, and IGF cell signaling. Cell proliferation will be measured using xCELLigence real-time cell proliferation experiment; migration will be measured using xCELLigence real-time cell migration experiment and wound-healing assays; cell cycle analysis will be done using propidium iodide, flow cytometry, and IGF cell signaling, as previously described [25]. Activation of IGF or IGF receptor pathway will be assessed by western blots using the following: antibodies against phospho-IGF-1 receptor, IGF-1 receptor beta-subunit, insulin receptor, protein kinase B (AKT; a serine or threonine protein kinase encoded by the oncogene in the transforming retrovirus isolated from the thymoma cell line AKT-8, derived from the Stock A Strain k AKR mouse originally inbred in the laboratory of Doctor CP Rhoads by KB Rhoads at the Rockefeller Institute), phospho-AKT, phosphor–extracellular signal-regulated kinases (ERKs) 1/2, poly adenosine diphosphate ribose polymerase caspase 3, phosphor–adenosine monophosphate-activated protein kinase, adenosine monophosphate-activated protein kinase, mammalian target of rapamycin and phosphor–mammalian target of rapamycin, as well as PI3K, protein 85 (protein 85 refers to the regulatory subunit of phosphoinositide 3-kinase), ERK1, protein 21, B-cell lymphoma 2, tumor protein 53, phosphatase and tensin homolog, cyclin D1, and caspase 9.

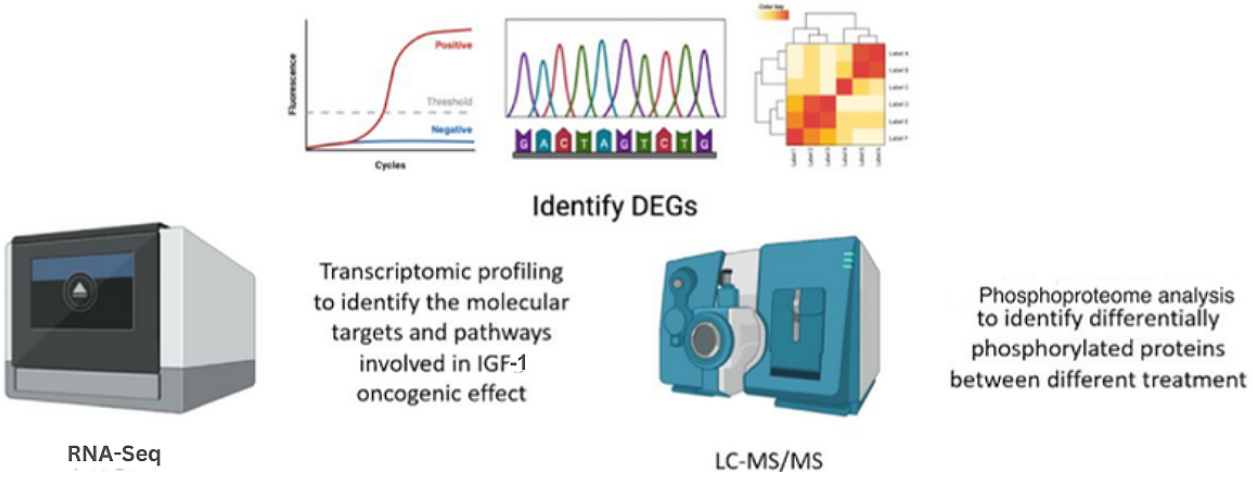
The primary outcome measure will be the difference in cell proliferation measured by cell index values during the xCELLigence real-time cell proliferation experiment. Comparison of cell index values from cells treated in different groups will be performed by the Kruskal-Wallis test followed by multiple comparison tests.

Objective 2: Identifying Differentially Expressed Genes and Pathways Activated by the Treatment of Endometrial Cell Lines of the Different Study Groups Listed in Objective 1

We will perform transcriptomic profiling of endometrial cell lines to identify differentially expressed genes in response to different study conditions outlined previously, using RNA Sequencing (RNA-Seq) to identify the molecular targets and pathways involved in the oncogenic effects (Figure 3).

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Figure 3. Identifying differentially expressed genes (DEGs) and pathways activated by the treatment in objective 1 of the study protocol. IGF-1: insulin-like growth factor 1. LC-MS/MS: Liquid chromatography with tandem mass spectrometry; RNA-Seq: RNA sequencing.



The steps for the RNA-Seq include the following:

- Total RNA will be extracted using a RNeasy extraction kit, with on-column DNase digestion.
- RNA quality will be assessed using an Agilent bioanalyzer.
- Samples will be analyzed on an Illumina HiSeq platform using standard protocols.
- For quantitative reverse transcriptase PCR validation of RNA-Seq results, a subset of the groups described in objective 1 will be used.
- The expression of identified differentially expressed genes will be compared in the publicly available RNA sequencing databases.

At the same time, we will use phosphoproteome analysis to identify differentially phosphorylated proteins between different study conditions using liquid chromatography with tandem mass spectrometry measurement.

The steps involved in the phosphoproteomics will be as outlined below:

- Cell lysis, protein digestion, and labelling
- Peptide enrichment, immunoprecipitation, and offline fractionation
- Mass spectrometry data acquisition
- Peptide and protein database searching
- Proteomics data analysis
- Phosphoproteomics and acetyl-immunoprecipitation data analysis

Objective 3: Bioinformatics

We will perform bioinformatics pathway analysis to identify any key genes and proteins involved in the association between PCOS and EC, after transcriptomic and phosphoproteomics profiling, as identified in objective 2 (Figure 4). The results from the same HEC-1-B and HEC-1-A cell lines and treatment groups, as outlined in objectives 1 and 2, will be used.

The methodology for the RNA-Seq data analysis will be as previously published [26], paired end raw reads (FASTQ format) will be quality- and adapter-filtered using Trim Galore wrapper for FastQC and Cutadapt [27]. The retained paired reads will be aligned to the Ensembl-annotated HG19 human Illumina iGenome build using Tophat2. Subsequently, differential gene expression will be calculated for the different cell culture study groups in comparison to the control specimen, using Cuffdiff, based on fold changes >1.5 and a *P* value <.05. Statistically significantly enriched gene ontologies and pathways for differentially expressed genes will be obtained using WebGestalt and the Cytoscape GeneMANIA plug-in. Next-generation RNA-Seq and associated clinical information will be obtained from publicly available data sets.

The methodology for the phosphoproteomics data analysis will also be as previously published data analysis for the phosphoproteomics data; label-free quantitative data will be filtered with a cutoff of ≥2 observations in the 4 repeats of at least 1 time point. Log transformation will be performed before any missing data points are imputed using random values generated from a normal distribution centered at the 1% quantile and the median SD. The abundance of phosphopeptides will be normalized to the abundance of corresponding parental proteins. The Limma package will be used in the R environment to identify differential proteins or phosphorylation with a false discovery rate–corrected ANOVA *P* value of .05. The k-means clustering approach will be used to analyze the patterns of the differential proteins and phosphorylation events. For functional annotation and network analysis, the differentially regulated proteins will be searched against the String database, and the networks will be visualized by using Cytoscape.

Although the study will aim to recruit 20 women with PCOS and 20 women without PCOS aged between 18 and 45 years, we will begin with a pilot study of samples from 3 women with PCOS and 2 controls and perform validation studies in the larger cohort of 20 women with PCOS and 20 women. The experimental plate design for the cell-culture studies in this feasibility study is illustrated in Table 1.

It will be 1 plate per cell line for each time point (24 h and 48 h). All experiments will be conducted in quadruplicates. We recognize that opinions differ about the ideal sample size for cell-culture experiments [28]; however, we believe our proposed experiments are stringent enough to make the results believable.

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Figure 4. Bioinformatics pathway analysis to identify any key genes and proteins involved in the association between polycystic ovary syndrome (PCOS) and endometrial cancer (EC).

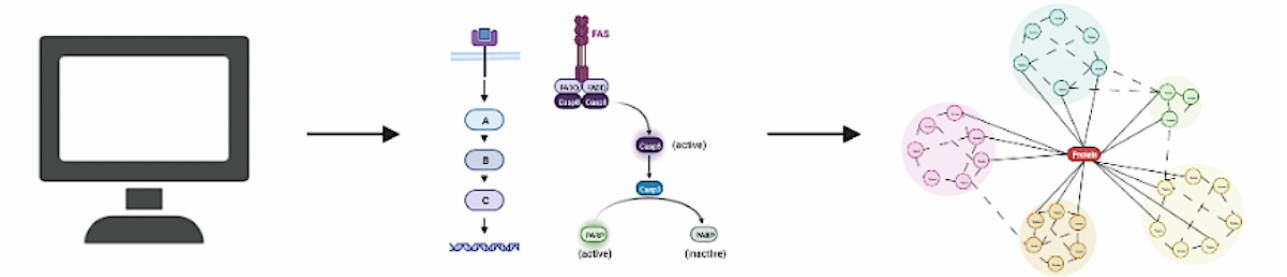


Table 1. Experimental plate design for cell culture studies.

Plates											
1	2	3	4	5	6	7	8	9	10	11	12
PCOS[a] 1	PCOS 1 + IGF[b]	PCOS 1 + Inhibitor	PCOS 1 + IGF + Inhibitor	PCOS 2	PCOS 2 + IGF	PCOS 2 + Inhibitor	PCOS 2 + IGF + Inhibitor	PCOS 3	PCOS 3 + IGF	PCOS 3 + Inhibitor	PCOS 3 + IGF + Inhibitor
PCOS 1	PCOS 1 + IGF	PCOS 1 + Inhibitor	PCOS 1 + IGF + Inhibitor	PCOS 2	PCOS 2 + IGF	PCOS 2 + Inhibitor	PCOS 2 + IGF + Inhibitor	PCOS 3	PCOS 3 + IGF	PCOS 3 + Inhibitor	PCOS 3 + IGF + Inhibitor
PCOS 1	PCOS 1 + IGF	PCOS 1 + Inhibitor	PCOS 1 + IGF + Inhibitor	PCOS 2	PCOS 2 + IGF	PCOS 2 + Inhibitor	PCOS 2 + IGF + Inhibitor	PCOS 3	PCOS 3 + IGF	PCOS 3 + Inhibitor	PCOS 3 + IGF + Inhibitor
PCOS 1	PCOS 1 + IGF	PCOS 1 + Inhibitor	PCOS 1 + IGF + Inhibitor	PCOS 2	PCOS 2 + IGF	PCOS 2 + Inhibitor	PCOS 2 + IGF + Inhibitor	PCOS 3	PCOS 3 + IGF	PCOS 3 + Inhibitor	PCOS 3 + IGF + Inhibitor
Control 1	Control 1 + IGF	Control 1 + Inhibitor	Control 1 + IGF + Inhibitor	Control 2	Control 2 + IGF	Control 2 + Inhibitor	Control 2 + IGF + Inhibitor	Media (FBS[c])	Media (FBS) + IGF	Media (FBS) + Inhibitor	Media (FBS) + IGF + Inhibitor
Control 1	Control 1 + IGF	Control 1 + Inhibitor	Control 1 + IGF + Inhibitor	Control 2	Control 2 + IGF	Control 2 + Inhibitor	Control 2 + IGF + Inhibitor	Media (FBS)	Media (FBS) + IGF	Media (FBS) + Inhibitor	Media (FBS) + IGF + Inhibitor
Control 1	Control 1 + IGF	Control 1 + Inhibitor	Control 1 + IGF + Inhibitor	Control 2	Control 2 + IGF	Control 2 + Inhibitor	Control 2 + IGF + Inhibitor	Media (FBS)	Media (FBS) + IGF	Media (FBS) + Inhibitor	Media (FBS) + IGF + Inhibitor
Control 1	Control 1 + IGF	Control 1 + Inhibitor	Control 1 + IGF + Inhibitor	Control 2	Control 2 + IGF	Control 2 + Inhibitor	Control 2 + IGF + Inhibitor	Media (FBS)	Media (FBS) + IGF	Media (FBS) + Inhibitor	Media (FBS) + IGF + Inhibitor

[a]PCOS: polycystic ovary syndrome.

[b]IGF: insulin-like growth.

[c]FBS: fetal bovine serum.

Results

In this study, we have described the protocol for an ongoing study to investigate the role of IGF-1 in mediating the risk of EC in women with PCOS. The study will aim to recruit 20 women with PCOS and 20 controls and measure the effect of serum from these women on cell proliferation and molecular pathways in human EC cell lines, compared with IGF-1 and IGF-1 antagonists. Recruitment for the study is currently ongoing. The project was funded in June 2022 and approved by the Mohammed Bin Rashid University of Medicine and Health Sciences' IRB in October 2022; funds were released in January 2023, and data collection began on 16 March 2023 and is ongoing. Three women with PCOS and 2 controls have been recruited as the date of this submission from 1 hospital site and IRB permission for further participant recruitment at a second hospital site was granted in October 2023. Data analysis has not yet commenced. We anticipate that initial results for analysis and publication will be available by the summer of 2024.

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Discussion

Expected Outcomes

Although the protocol (using cell culture) described in this paper is not novel for studying molecular mechanisms to help in the prevention and treatment of diseases, the unique aspect of it is that no previous study has used this approach to investigate the oncogenic effect of serum from women with PCOS. More importantly, no previous study has considered the differential mutations of genes related to the insulin signaling pathway in human endometrial cell lines and the potential impact this may have on their experimental findings.

A possible limitation of our protocol includes the risk that the IGF-1 present in the serum of women with PCOS may become diluted in the cell culture media to an extent where the in vitro effects do not represent the in vivo activity. We will, however, aim to mitigate this risk by using Sep-Pak C18 for the extraction, concentration, and fractionation of peptides from PCOS and control serums [29]. We will also begin with a pilot study of samples from 3 women with PCOS and 2 controls to identify any other potential methodological problems before performing validation studies in the larger cohort of 20 women with PCOS and 20 women without PCOS. Another limitation of our protocol is that the use of these cell lines may limit the generalizability of the findings from our study. However, our results may inform future studies by independent research groups using primary cell lines or patient tumor samples.

We are aware of only 1 study [30] in which serum from women with PCOS has been used in experiments on EC cell lines. The study, however, was not designed to answer our research question, as it investigated the potential stimulatory effects of serum exosomes isolated from patients with PCOS on EC cell lines and explored the underlying mechanism. The study [30] found that EC cell lines exposed to exosomes derived from the serum of patients with PCOS exhibited an enhanced migration and invasion phenotype. The study also found that levels of 55 mature micro RNAs significantly differed in serum exosomes from patients with PCOS compared to those from normal controls and that MiR-27a-5p was the most significantly elevated in the serum exosomes of patients with PCOS. Furthermore, in vitro experiment results confirmed that MiR-27a-5p prohibited migration and invasion via Suppressor of Mothers Against Decapentaplegic-4 downregulation, suggesting that serum exosomal MiR-27a-5p may play a role in EC development in patients with PCOS. The implications of these findings for our study are that we may also find enhanced migration and invasion in our PCOS group compared to controls, independent of whether IGF-1 antagonist is present, which would imply that pathways other than IGF-1 may also be at play in the association between PCOS and EC. However, the planned transcriptomic profiling in our study will offer the opportunity to identify any interactions between messenger RNAs and IGF-1 in the possible association between PCOS and EC.

Conclusions

In conclusion, this study describes a protocol for an ongoing study to investigate the role of IGF-1 in mediating the risk of EC in women with PCOS, by investigating the effect of serum from women with PCOS and controls on cell proliferation and molecular pathways in human EC cell lines. Although we currently do not have any results to report, reporting our protocol should aid research collaboration and early feedback; it could also reduce duplication of effort by other research groups. The broader implications of the findings of our study, when available, are that a deeper understanding of the mechanisms underlying the regulation of the IGF system in PCOS and EC will improve our ability to develop effective treatment modalities for EC. Specifically, investigating how IGF-1 in PCOS participates in the development of EC may identify novel genetic associations between EC and PCOS. This will also facilitate future systems biology–based pathway analysis to explore further molecular mechanisms leading to EC and will be a vital step in reducing EC in women globally.

Data Availability

Data sharing is not applicable to this study, as no new data were created or analyzed.

Authors' Contributions

WA, MH, and FA conceptualized the study. WA, MH, and FA designed the methodology. WA prepared and wrote the original draft. WA, MH, FA, and SA contributed to the writing; they also reviewed and edited the manuscript. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

AKT: protein kinase B
EC: endometrial cancer
ERK: extracellular signal-regulated kinase
HEC: human endometrial cancer
IGF-1: insulin-like growth factor 1
IRB: Institutional Review Board
PCOS: polycystic ovary syndrome
PI3K: phosphoinositide 3-kinase
RNA-Seq: RNA sequencing

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Protocol

The Effects of Quality Assurance System Implementation on Work Well-Being and Patient Safety: Protocol for a Mixed Methods Study

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Abstract

Background: Systematic monitoring of work atmosphere and patient safety incidents is a necessary part of a quality assurance system, particularly an accredited system like the Joint Commission International (JCI). How the implementation of quality assurance systems affects well-being at work and patient safety is unclear. Evidence shows that accreditation improves workplace atmosphere and well-being. Thus, the assumption that an increase in employees' well-being at work improves patient safety is reasonable.

Objective: This study aims to describe the protocol for monitoring the effects of implementing the quality assurance system of JCI at Orton Orthopedic Hospital on employees' well-being (primary outcome) and patient safety (secondary outcome).

Methods: Quantitative (questionnaires and register data) and qualitative (semistructured interviews) methods will be used. In addition, quantitative data will be collected from register data. Both quantitative and register data will be analyzed. Register data analysis will be performed using generalized linear models with an appropriate distribution and link function. The study timeline covers the time before, during, and after the start of the accreditation process. The collected data will be used to compare job satisfaction, as a part of the well-being questionnaire, and the development of patient safety during the accreditation process.

Results: The results of the quality assurance system implementation illuminate its possible effects on the patient's safety and job satisfaction. The repeatability and internal consistency reliability of the well-being questionnaire will be reported. Data collection will begin in May, 2024. It will be followed by data analysis and the results are expected to be published by 2025.

Conclusions: The planned study will contribute to the evaluation of the effects of JCI accreditation in terms of well-being at work and patient safety.

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KEYWORDS

Joint Commission International; health and safety; JCI; human resource management; organizational development; quality in health care

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Introduction

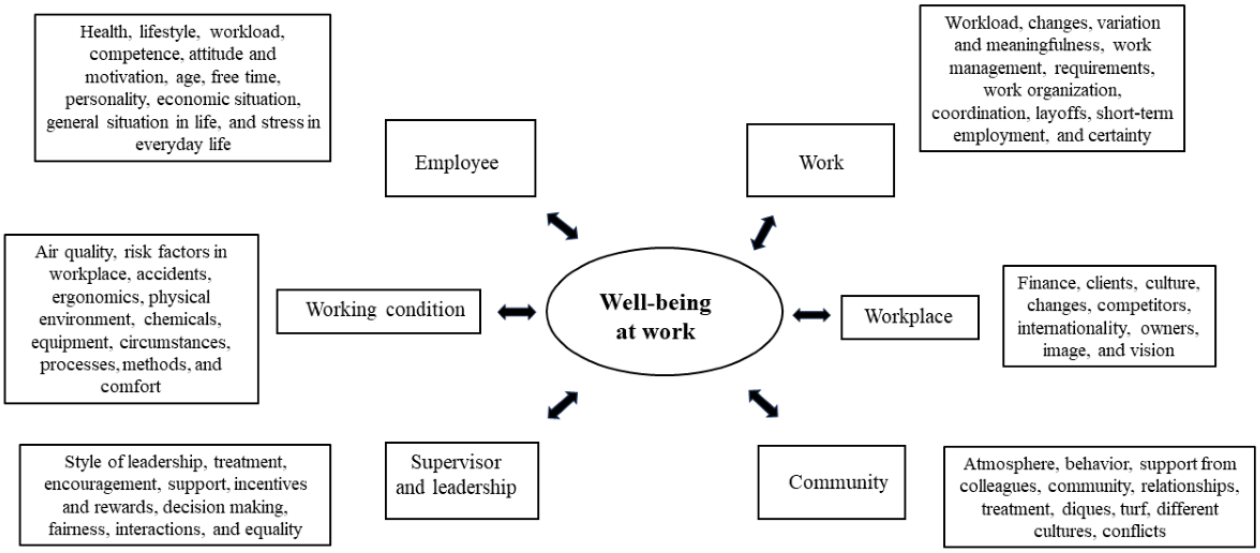
Overview

Systematic monitoring of work atmosphere and patient safety incidents is a necessary part of a hospital's quality assurance systems, particularly an accredited system like the Joint Commission International (JCI) [1,2]. Accreditation and related education have been shown to increase motivation and improve work atmosphere and awareness of patient safety. Statistically significant improvements have been noted in defect management (particularly in the context of instrument cleaning and disinfection effectiveness) in a randomized controlled trial evaluating the impact of JCI accreditation [3]. Physician-nurse relations as well as management-line staff relations have been reported to improve along accreditation [4].

Accreditation is a costly and time-consuming process [5], causing a legitimacy problem for a hospital's management [6]. This situation raises a fundamental question: Is accreditation worth pursuing considering the time and effort it requires? Thus, further research is needed from a different view. How the implementation of quality assurance systems affects well-being at work and patient safety is not studied extensively [7]. The effects of quality assurance systems on work atmosphere and patient safety are challenging to determine due to numerous potentially confounding factors [8,9]. However, assuming that well-being at work and work satisfaction are strongly correlated with good outcomes in health care service delivery, including patient safety, is reasonable. This assumption is supported by Schwarz et al [10], who found that work-life integration among health care workers is associated with improvements in teamwork and safety across various safety culture domains [10]. In a study by Lopes et al [11], job satisfaction and safety culture were directly proportional. Better working conditions can provide a virtuous cycle of patient safety and occupational health [11].

The Finnish Institute of Occupational Health defines well-being at work as safe, healthy, and productive work, which is carried out by competent employees and work communities in a well-managed organization. Employees and work communities experience their work as meaningful and rewarding, and they consider work to support their life management [12]. The importance of well-being at work is highlighted in health care services, as labor input is directed toward patients. Well-being improves work performance, further promoting good workplace outcomes. For instance, well-being at work reduces the risks of exhaustion, workplace accidents, illnesses, and the loss of tacit knowledge regarding drug abuse [13]. The well-being of the working community is comprised of the performances of its members and linked to factors beyond each employee's performance and influence. In this study, the operationalization of well-being is based on a model that considers worker health, subjective well-being, capabilities, motivation, the organizational management model, management workload, company values, and the overall atmosphere as well as the conditions of the work environment, such as work content and instruments with which the work is executed (Figure 1) [14].

Figure 1. Domains well-being at work by Naumanen (2018) [14].



Aim and Objectives

This protocol will describe the procedure and methods for monitoring the effects of implementing the quality assurance system of JCI at Orton Orthopedic Hospital on employees' well-being (primary outcome) and patient safety (secondary outcome). The system implementation effects will be evaluated through work-related well-being surveys using direct and indirect evaluations, and patient safety will be evaluated using register data.

Methods

Overview

The study sample will include about 200 employees working in a hospital. The hospital is a private orthopedic hospital focused on joint replacements and back surgery and has a rehabilitation center. This hospital is owned by a large public health care hospital, which also performs JCI implementation. Table 1 illustrates the accreditation process and its monitoring. Textbox 1 [15] presents the registry data collection system. The

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implementation will begin following a JCI orientation training organized by JCI. The company must organize their employees during the process. The JCI procedure is designed to be ready in 4 years. Baseline surveys (questionnaires and interviews) will be conducted, and all surveys will be repeated when the implementation is 50% complete.

Table 1. Methods and data collection system during the accreditation process.

Baseline surveys[a]	Data collection system
Questionnaires	• A total of 35 questions; registering and monitoring the well-being of the employees of the Orton Orthopedic Hospital • Repeatability test of the questionnaires
Register data	• HaiPro[b] • Absence due to illness • Employee turnover • Injuries of the employees • Cost of occupational health case • Patient insurance cases • Rate of wound infections • Revisions • Time of surgery
Qualitative method (semistructured interviews)	• A total of 4 groups (doctors, nurses, therapists and administration, and support staff)

[a]Surveys, including questionnaires and register data, as well as qualitative methods (semistructured interviews) will be repeated after half of the implementation and after finishing accreditation.

[b]HaiPro is a web-based tool for reporting patient safety incidents. Anonymous and voluntary input ensures confidential reporting and processing of the safety incidents. The HaiPro method does not seek to blame [15].

Textbox 1. Register data collection 2 years prior to implementation, when the implementation process is 50% complete, and when the facility is ready for accreditation. A web-based tool (HaiPro) will be used for reporting patient safety incidents and risk events, which are divided into near-miss and injurious events.

Register data collection

- HaiPro—near-misses and misses (n)
- Absence due to illness (days)
- Employee turnover (n)
- Employee injuries (n)
- Cost of occupational health care (€/year)
- Patient insurance cases (n)
- Rate of wound infections (n)
- Time per surgery (h/min)
- Revision surgery (%)

Quantitative Studies

Questionnaires

This study applies a mixed methods approach, including quantitative (questionnaires and register data) and qualitative (semistructured interviews) methods [16]. The study uses a convergent design, where both qualitative and quantitative data are collected as well as analyzed and results are reported at the same time [17]. The occupational well-being questionnaire in this hospital was developed before the planned study to facilitate good personnel management. In the questionnaire, job requirements and job resources have formed the theoretical framework of the survey [18-20]. It also included 4 questions designed to capture the participants' views on leadership, values, expertise, and work atmosphere, based on Otala and Ahonen [21].

The questions are divided into 3 sections: questions 1-6 ask for the participants' background information, questions 7-31 focus on physical and psychological well-being and connect to functional capacity, and questions 32-35 concern work satisfaction (Multimedia Appendix 1). The first section ascertains the employees' health and well-being regarding work burden and the effects of illnesses and strains on functional capability. The questions will be evaluated on a 10-point Numeric Rating Scale (1=no work-related problems; 10=completely unable to work). Questions 7-21 evaluate perceived health and mood, distress, anxiety, and the ability to take care of oneself on a 3-point Likert scale (1=no problems;

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3=completely unable). These questions are evaluated on a 5-point Likert scale (1=completely agree; 5=completely disagree).

In the third section, question 32 describes management from the viewpoint of an immediate superior. Question 33 explores the know-how viewpoint, aiming at charting the perspective to improve one's competence and knowledge. Question 34 focuses on company values and acting upon them. Question 35 concerns team spirit, which is one of the company's most important values. Questions 32-35 are evaluated on a 5-point Likert scale (1=completely agree; 5=completely disagree).

Register Data

Register data, including the employees' sick leave and work accidents, will be collected from 2 years prior to implementation to 2 years after implementation. We will also use a web-based tool (HaiPro) for reporting patient safety incidents, which are all treatment events that either harmed or could have harmed them [15]. HaiPro is a web-based tool for reporting patient safety incidents. Anonymous and voluntary input ensures confidential reporting and processing of safety incidents and risk events. These events are called risk events and are divided into near-miss and injurious events [15]. In addition, the number of reoperations, the rate of wound infections, surgery times, and notices of injuries reported to the Finnish Patient Insurance Center will be collected. Textbox 1 shows the register data collection during the accreditation process.

Statistical Analysis

Primary and secondary end point analysis will be performed on all participants receiving 1 or more administrations of study treatment (the intent-to-treat population). However, no sample size calculation will be performed in advance due to the unavailability of accurate and reliable data for making such estimates. We will include all individuals who will respond to the questionnaire in this study. The descriptive statistics are presented as means (SDs), medians (IQRs), or counts with percentages. The groups will be compared using the *t* test, permutation test, and ANOVA for continuous variables and the Pearson chi - square test or Fisher exact test for categorical variables. Register data analysis will be performed using mixed-effect linear models with an appropriate distribution and link function; models do not require complete data and can be fit even when individuals or data do not have observations at all time points (missing data will be handled by using available-data analysis) [22]. Confounding factors will be adjusted. Models include age, sex, working time, education years, and employment status. In case there are violations of the assumptions or theoretical distribution of the test statistics (eg, nonnormality, skewness, kurtosis, or a small number of observations), a bootstrap- or permutation-type analysis will be used.

Traditional test theory analyses will be used to verify the reliability and validity of the questionnaire. These analyses include internal consistency using Cronbach α, inter-item correlations, and exploratory factor analysis (using the iterated principal-factor method for factoring and oblique promax-rotated factor loadings on polychoric correlation matrix). The test-retest reproducibility will be evaluated by intraclass correlation coefficients using the 1-way random effects model. Coefficients of reproducibility and their 95% CIs will be also calculated. Correlation coefficients will be calculated by the Pearson or Spearman method. Normal distributions will be evaluated graphically and with the Shapiro-Wilk W-test. Stata 17.0 (StataCorp LP) will be used for the analysis.

Qualitative Studies

Participants in the focus group interviews include working community members. The groups consist of multiprofessional individuals, and the interviews last about an hour. These qualitative interviews aim to broaden the baseline views, conceptions, and expectations of the personnel regarding quality assurance and their well-being before implementing the JCI quality assurance system. The semistructured interviews will be conducted by an external interviewer with knowledge of different quality assurance systems and conducting qualitative research.

Qualitative data are collected in 3 thematic group interviews that feature 12 participants. To create the groups for the interviews, a list of the hospital's employees will be collected and grouped into 4 categories: physicians; nurses; therapists, other medical staff, and the administration; as well as support staff and secretaries. The personnel will be listed in each category in alphabetical order. Consequently, random selections will be made from the staff at the hospital, stratified by occupation, for all groups. After the draw, each employee can opt out of their assigned group. In such cases, the group is supplemented with the next person on the list. The researchers conducting this study are exempted from the lists. After 3 semistructured focus group interviews, the main themes will presumably recur, and the point of saturation will be reached [23].

The interviews will be recorded with the participant's permission, and the tapes will be transcribed subsequently. The interviews will be analyzed using qualitative content analysis, a conventional content analysis [24]. The analysis aims to gain an understanding of how individuals in the small groups perceive the quality assurance system, assess its usefulness, and recognize the need for its development, all from the perspectives of different employees. The semistructured interviews ask participants about their expectations of the quality system, their involvement in the JCI orientation, as well as the perceived benefits and drawbacks of the quality system. In addition, the focus group interviews will ask about staff experiences in relation to safety, well-being, and motivation at work as well as the prospects of the hospital. The interviews will conclude with questions on quality factors related to surgery (eg, surgery times), patient safety, and experiences of patient care. Textbox 2 includes the semistructured interview questions.

The content of the open-ended questions will be coded according to the themes emerging from the data. The most prevalent themes will be selected and reported in the study. These themes will help explain and deepen the understanding of the responses to the quantitative approach of the study in describing the perceived conceptions of the quality system and its relationship to occupational safety, patient safety, and surgery.

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The interviews will be renewed after half of the implementation is completed. The same groups will be requested to participate in the interviews; however, certain community members may change their working place or may not participate in the renewed test. Those members will be replaced by other members of the working community. If the point of saturation is not reached in the midterm interviews after 3 interviews, 4 or more interviews will be conducted [23].

Textbox 2. Semistructured interview questions.

Expectations from the quality assurance system, participation in orientation, perceived benefits of the quality assurance system, results, and their quality

- How have you participated in the quality assurance work?
- How have you experienced the training related to the quality assurance system and other orientations?
- What expectations do you have for the quality assurance system (ie, Joint Commission International)?
- What kind of benefits can the quality assurance system have? Do you think it might have some disadvantages as well?
- What kind of results can the quality assurance system have?
- How does it affect the quality of activities in the hospital?
- What kind of changes does the quality assurance system bring to your everyday work?
- In what state do you think the quality assurance system is right now?

Occupational safety of personnel, work motivation, and prospects of the hospital

- How does the quality system affect occupational safety?
- What about work motivation?

Occupational well-being

- What do you perceive as factors related to well-being at work?
- What are the driving forces of occupational well-being in our hospital?
- What kind of effects the quality assurance system can have on well-being at work?
- Which aspects of occupational well-being are affected by the quality assurance system?

Factors related to surgery (eg, surgery times), patient safety, and patient care

- What kind of effects does the quality assurance system have on factors related to surgeries?
- What kind of effects does the quality assurance system have on surgery times?
- What about patient safety?
- What other effects does the quality system have in relation to patient care?
- How do you think the quality assurance system will affect the future of the hospital?
- What else would you like to say about the quality assurance system or occupational well-being?

Ethical Considerations

The study was submitted to the University of Oulu Human Sciences Ethics Committee. An ethical review was not required based on their criteria. Participants will provide their written consent for the interviews.

Results

The results of the quality assurance implementation will illuminate the possible effects on patient safety and job satisfaction. The repeatability and internal consistency of the well-being questionnaire will be reported. The qualitative research results describe the employees' experiences with the quality implementation process. Data collection will begin in May, 2024. It will be followed by data analysis and the results are expected to be published by 2025.

Discussion

Expected Outcomes

The Finnish Institute of Occupational Health defines well-being at work in 3 different ways: the first one is based on doing in the sense of accomplishing, the second emphasizes experience, and the third provides a description of the experience [25]. Well-being results from the fulfilment of the important needs of individuals and the realization of goals and plans set for one's life. Goal-oriented activity and commitment to tasks lead to well-being. However, the history of well-being at work is short. The concept of quality and productivity in working life has only recently evolved and includes aspects such as learning and social activities [25]. Well-being at work is also subject to various perspectives in different countries and cultures and even in different workplaces within the same country. That is why we

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believe it is crucial that in the planned study, we use a customized questionnaire for well-being at work; this questionnaire will encompass generic items from the Finnish working life context and will be supplemented with specific questions that are important for Orton Orthopedic Hospital.

The need for quality assurance systems in health care is widely accepted. However, the added value of an accredited quality assurance system has not been widely studied. When undertaking such a large task, the effects of pursuing an accredited quality assurance system should be evaluated. The analysis will be challenging in a comparative study design due to practical and ethical reasons, although a randomized controlled trial published recently offers some insight [3]. Therefore, in this study protocol, a quasi-experimental study design will be followed [26], with a focus on employee well-being and patient safety, under the assumption that they are interlinked. Therefore, procedures and practices will be clarified for workers to diminish errors and increase patient safety. The added value of branding and marketing will be ignored, but accredited quality influences these issues as well.

In this protocol, the primary and secondary outcomes are well-being at work and patient safety, respectively. Patient safety has 4 main items: all the HaiPro notices [15], the number of wound infections, the number of patient insurance cases, and the number of revision surgeries. Certain overlaps exist between these items and must be considered in the analysis. Worker well-being register data will also be collected, including information on illness-related absences, employee turnover, employee injuries, and the costs of occupational health care.

A staff survey is an efficient way to learn the views of all personnel. Surveys also help employees evaluate their efforts and input [27]. Our study will use various evaluations. The most important variable is employee well-being, which is evaluated through the questionnaire. This questionnaire is specifically developed for the study and complemented with the register data follow-up regarding sick leave, employee turnover, and costs of occupational health care.

We acknowledge the problem of presenteeism, which involves the act or culture of employees continuing to work as a performative measure, despite negative consequences); this is a rising issue in the workplace. If left unrecognized and unresolved, presenteeism can lead to poor well-being, low morale, burnout, and increased employee turnover. It also poses a huge threat to productivity because employees who show up to work when they are not feeling mentally or physically well cannot provide their best performance [28]. Indirectly, the effects of presenteeism can be evaluated in this study using specific questionnaire items and register data. However, due to the absence of readily available indicators to apply here, a more comprehensive examination of the issue may be reserved for future studies.

We are aware that some parts of the accreditation are demanding and require going over the allotted work-hour resources. The hospital may have to spend additional time in ensuring the smooth operation of new formats. There might be a need for extra personnel for accreditation-related work. We have the approval from the hospital management and the commitment of the staff to this endeavor.

Numerous confounding factors exist. Health care is greatly influenced by cultural norms and is strictly regulated by legislation. The strength of qualitative studies is to raise points of view that are formulated through study questions. The qualitative approach in research is exploratory and helps develop hypotheses for future studies. To the best of the authors' knowledge, the combination of the qualitative and quantitative approaches (ie, mixed methods) has not been used in research on hospital accreditation.

Limitations

This protocol has certain limitations. The study will be a monocentric study; thus, comparative data from other hospitals are not collected. The lack of a comparative design is a limiting factor in the study protocol. However, comparing 2 hospitals, one with quality assurance implementation and the other without, presents challenges. These 2 hospitals have different personnel, patient profiles, and managerial routines as well as different practices and philosophies in quality assurance work. Probably all the confounding factors cannot be considered in this planned comparison. To overcome the lack of a comparative design, we are planning to apply a mixed methods approach that includes quantitative (questionnaires and register data) and qualitative (semistructured interviews) methods. The study also uses a convergent design [17], where both qualitative and quantitative data are collected as well as analyzed and results are reported at the same time.

The application of a locally developed questionnaire can be considered a limitation of the study. We argue, however, that it is well reasoned to apply this occupational well-being questionnaire in the planned study. The results would facilitate the development of Orton Orthopedic Hospital presumably more accurately than using a generic questionnaire. The whole concept of occupational well-being is novel and strongly influenced by cultural factors, supporting the use of local applications [25]. It is also worth noticing that when we compared the Parker and Hyett [29] questionnaire with ours, there were multiple similarities. Personnel turnover is also a limiting factor to be considered in the analyses.

Acknowledgments

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Data Availability

The data sets generated and analyzed in this study are not publicly available due to data access but are available from the corresponding author upon reasonable request.

Authors' Contributions

AV, HH, LR, and MH wrote the manuscript. AV, HH, LR, PH, and MH designed the protocol. AV, MH, PH, and LR were responsible for recruiting participants for the interview. HK and MH performed statistical and thematic analyses. All authors reviewed and edited the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Occupational well-being questionnaire.
[PDF File (Adobe PDF File), 194 KB - resprot_v12i1e45200_app1.pdf]

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Abbreviations

JCI: Joint Commission International

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Protocol

Facility-Based Audit System With Integrated Community Engagement to Improve Maternal and Perinatal Health Outcomes in Rural Pakistan: Protocol for a Mixed Methods Implementation Study

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Abstract

Background: Maternal and newborn mortality in Pakistan remains as a major public health challenge. Pakistan faces significant infrastructure challenges and inadequate access to quality health care, exacerbated by sociocultural factors. Facility-based audit systems coupled with community engagement are key elements in achieving improved health system performance. We describe an implementation approach adapted from the World Health Organization audit cycle in real-world settings, with a plan to scale-up through mixed methods evaluation plan.

Objective: This study aims to implement a locally acceptable and relevant audit system and evaluate its feasibility within the rural health system of Pakistan for scale-up.

Methods: The implementation of the audit system comprises six phases: (1) identify facility and community leadership through consultative meetings with government district health offices, (2) establish the audit committee under the supervision of district health officer, (3) initiate audit with ongoing community engagement, (4) train the audit committee members, (5) launch the World Health Organization audit cycle (monthly meetings), and (6) quarterly review and refresher training. Data from all deliveries, live births, maternal deaths, maternal near misses, stillbirths, and neonatal deaths will be identified and recorded from four sources: (1) secondary-level care rural health facilities, (2) lady health workers' registers, (3) community representatives, and (4) project routine survey team. Concurrent quantitative and qualitative data will be drawn from case assessments, process analysis, and recommendations as components of iterative improvement cycles during the project. Outcomes will be the geographic distribution of mortality to measure the reach, proportion of facilities initiated to implement an audit system for measuring the adoption, proportion of audit committees with community representation, and proportion of audit committee members' sharing feedback regularly to measure acceptability and feasibility. In addition, outcomes of effectiveness will be measured based on data recording and reporting trends, identified modifiable factors for mortality and morbidity as underpinned by the Three Delays framework. Qualitative data will be analyzed based on perceived facilitators, barriers, and lessons learned for policy implications. Results will be summarized in frequencies and percentages and triangulated by the project team. Data will be analyzed using Stata (version 16; StataCorp) and NVivo (Lumivero) software.

Results: The study will be implemented for 20 months, followed by an additional 4-month period for follow-up. Initial results will be presented to the district health office and the District Health Program Management Team Meeting in the districts.

Conclusions: This study will generate evidence about the feasibility and potential scale-up of a facility-based mortality audit system with integrated community engagement in rural Pakistan. Audit committees will complete the feedback loop linking

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health care providers, community representatives, and district health officials (policy makers). This implementation approach will serve decision makers in improving maternal and perinatal health outcomes.

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KEYWORDS

audit system; perinatal outcome; neonatal mortality; stillbirth; maternal; mortality; implementation research; death audit

Introduction

Background

Pakistan is a low-income country with significant infrastructure challenges, poor allocation of government funding for health, poor access to essential health care services, low-quality health care services [1], sociocultural constraints, and a feudal system that affects all aspects of province life [2]. One of the main impacts of these governance and funding challenges relates to the health of mothers and their newborn children—2 cohorts that are already categorized as populations at high risk. The manifestations of this burden include a persistently high neonatal mortality rate, accounting for 57% of child deaths across the nation [3], with 41 out of every 1000 born babies dying before the end of their first month [4] and a maternal mortality ratio of 186 per 100,000 live births [5]. Pakistan's perinatal, neonatal, infant, under 5 years, and maternal mortality rates remain unacceptably high, with estimates of >399,429 children dying per year [6]. Although efforts to improve the quality and timeliness of care in district and regional facilities are being made, progress has been painfully slow [7].

Audits and review systems, especially those with community engagement, are 2 key elements that have been shown to improve the health system's performance and maternal and perinatal health outcomes for at-risk populations [8]. Audits provide a documented history of the events leading up to the death and highlight process failures amenable to process redesign and teachable moments to prevent similar untoward events. Introducing audits and reviews can reduce inpatient maternal mortality (adjusted odds ratio 0.85, 95% CI 0.73-0.98; 191,167 deliveries; moderate certainty evidence) and likely inpatient neonatal mortality (adjusted odds ratio 0.74, 95% CI 0.61-0.90; moderate certainty evidence) [9]. Findings from a meta-analysis of 7 pre-post studies of facility-based perinatal mortality audits in low- and middle-income countries indicated a reduction in perinatal mortality of 30% (95% CI 21%-38%) after introduction of perinatal audits [10].

The District Health Information System (DHIS) seldom records and reports mortality (eg, maternal mortality and neonatal mortality) and severe morbidity indicators consistently and reliably (eg, birth asphyxia and preeclampsia), leading to challenges in data completeness in capturing vital statistics through routine health and administrative data. Audit systems at the facility levels can provide for sustained improvements in the quality of provision and delivery of services. Community linkages and engagement ensure proactive and detailed discussion of the causes and modifiable factors leading to the deaths, essential for improved working relationships between community members, health providers, and policy makers [11]. Audits of stillbirths and neonates also contribute to achieving Every Newborn Action Plan goal for reducing stillbirths and neonatal deaths to <12 newborn deaths per 1000 live births [12].

The Three Delays Framework for Maternal and Perinatal Mortality

Pregnancy-related maternal, neonatal, and infant mortality is attributed to delays in using the Three Delays framework [13] with time-related consequences—the "first delay" around the decision to seek medical care, "second delay" attributed to the time to reach the health facility, and "third delay" caused by receiving inappropriate care after reaching the medical facility [14-16]. In Pakistan, the "first delay" has been further divided into two subgroups: (1) delay in recognition of the severity of illness and danger signs contributed to 18% of all delays and (2) delays in decision-making by virtue of limited action of women to make decisions regarding their transfer to facilities contributed 34% [7].

The impacts of delays in care can be seen in the recent Verbal Autopsy and Social Autopsy mortality survey in Table 1. More than half of the deaths (26%-55%) occurred at the community level (the first delay), 4% to 13% of deaths occurred in route to the facility (the second delay), and the remaining occurred within health care systems (the third delay).

Table 1. Locations of neonatal, child, and maternal deaths according to the unpublished Verbal Autopsy and Social Autopsy results (2019).

Indicators	Hospital, %	Other health provider or facility, %	In route to health provider or facility, %	Home, %	Others, %
Location of neonatal deaths	55.3	2.3	4.1	38.2	0
Location of child deaths	35	0.9	7.1	54.7	2.2
Location of maternal deaths	56.8	11.4	12.5	26.4	3

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History of Perinatal Audit Systems in Pakistan

Previous efforts to introduce facility audit systems by the Pakistan Ministry of National Health Services, Regulations, and Coordination have used the phased implementation of the Maternal and Perinatal Death Surveillance and Response to enhance reporting, recording, tracking, and auditing of deaths [17]. The World Health Organization (WHO) is currently assisting Khyber Pakhtunkhwa and Baluchistan provinces, and United Nations International Children's Emergency Fund (UNICEF) is helping the Sindh province in implementing audit mechanisms, but results have not been made public. The United Nations brief on COVID-19 [18] and the Pakistan Health Report 2020 [19] have stated that the Maternal and Perinatal Death Surveillance and Response has great potential for success.

We hypothesize that a WHO audit cycle that is locally acceptable in close consultation with local community representatives and health care providers is feasible for implementing a robust audit system in rural settings. Specifically, we asked the following questions:

1. Is the implementation of facility-based maternal and perinatal mortality audits in combination with targeted community engagement feasible in rural Pakistan?
2. Will the maternal and perinatal audits improve the reporting of deaths and maternal near misses at the DHIS health facilities?
3. Will the audit systems help better identify medical and nonmedical factors of deaths and near misses, and how doable recommendations are implemented through integration of feedback loops within the health facilities and communities?
4. Will the community-facility audit interaction improve the early referral proportions?

Primary Objectives

The primary objectives include the following:

1. Identify and establish audit committees at health facility levels with integrated community engagement, and
2. Determine the feasibility of implementing an acceptable audit system with community representation in existing secondary health facilities and serving catchment populations.

Secondary Objectives

The secondary objectives include the following:

1. Identification of "first delay" (care-seeking decision), "second delay" (identification and reaching the health facility), and "third delay" (receiving adequate care and treatment at facilities) among mortality and morbidity cases, and
2. Propose solutions and record actions taken to improve the access to quality of care through integrated feedback loops within health facilities and communities.

Primary Outcomes

The primary outcomes include the following:

1. Proportion of facilities initiated to implement an audit system for measuring the adoption of audit system,
2. Proportion of audit committees with community representation and proportion of committee audit members sharing feedback regularly to measure the feasibility of the audit system, and
3. Qualitative narrative approach for acceptability and exploring the facilitators of and challenges in implementing audit systems.

Secondary Outcomes

The secondary outcomes include the following:

1. Geographic distribution of mortality to measure the percentage coverage or reach in the implementation district,
2. Change in trends in data recording and reporting to measure effectiveness,
3. Categorization of mortality and maternal near-miss cases among Three Delays framework,
4. Number of awareness sessions covering the proportion of the catchment population,
5. Number of referrals in and out of the health facility,
6. Number of transport mechanisms linked to health facilities by audit committee members, and
7. Proportion of health facilities implementing actionable recommended actions at the facility level.

Methods

Overview

We will conduct a mixed methods study that integrates formative research and evaluative components into iterative improvement cycles. The planned interventions will examine the feasibility and document the process and challenges of implementing an audit system at scale. The study was also registered on ClinicalTrials.gov (NCT05640050).

Study Setting

The study will be conducted in 1 district—Matiari (Sindh) with a population of 770,040 (Pakistan Bureau of Statistics–2017). The district selection was based on the operational ease with past positive experiences in efficient rollout of health services. Moreover, the district health office (DHO) of Matiari is actively involved in DHIS feedback meetings to improve the data quality.

Study Population

The eligible population includes all women who had deliveries at community and health facilities that result in a maternal death or maternal "near miss," stillbirths, or neonatal death (perinatal death).

Inclusion Criteria

Women aged between 15 and 49 years who reside in the selected district are eligible to participate. Secondary-level public health facilities that offer obstetric and postnatal care and respective catchment areas supported by lady health workers (LHWs) are included in the study. Data for all maternal mortality, maternal "near misses," and perinatal and neonatal mortality recorded for all women and newborns delivered at home (through LHW monthly reports) and who contact the health facility within 42 days after delivery, regardless of whether they delivered at the health facility, will be collected.

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Exclusion Criteria

Women who are nonresidents of the study district and who do not provide consent are not eligible to participate.

Operational Definitions

The outcomes are defined in Textbox 1, using the International Classification of Disease–10 classification system by WHO [20].

Textbox 1. Operational definitions—International Classification of Diseases–10.

Stillbirth

- Stillbirth is the delivery of baby with no signs of life after ≥22 weeks of gestation.

Neonatal mortality

- Neonatal mortality is the death of a newborn within the first 28 days of life.

Perinatal mortality or death

- Perinatal mortality or death is a death that occurs around the time of birth. It can involve a still birth or be an early neonatal death that occurs up to 7 days after birth.

Maternal *near miss*

- Maternal *near miss* is a situation in which a pregnant woman nearly dies but survives a complication that occurred during pregnancy, during childbirth, or within 42 days of the termination of pregnancy. It can involve severe pregnancy-related complications (severe postpartum hemorrhage, severe pre-eclampsia, eclampsia, sepsis, and ruptured uterus) or critical interventions (blood transfusion, laparotomy, admission to an intensive care unit, hysterectomy, and other emergency surgical interventions in the abdominal cavity).

Maternal mortality or death

- Maternal mortality or death is the death of a woman during pregnancy or within 42 days of delivery or the termination of pregnancy, irrespective of the duration or site of the pregnancy, from any cause related to or aggravated by the pregnancy or its management, but not from accidental or incidental causes.

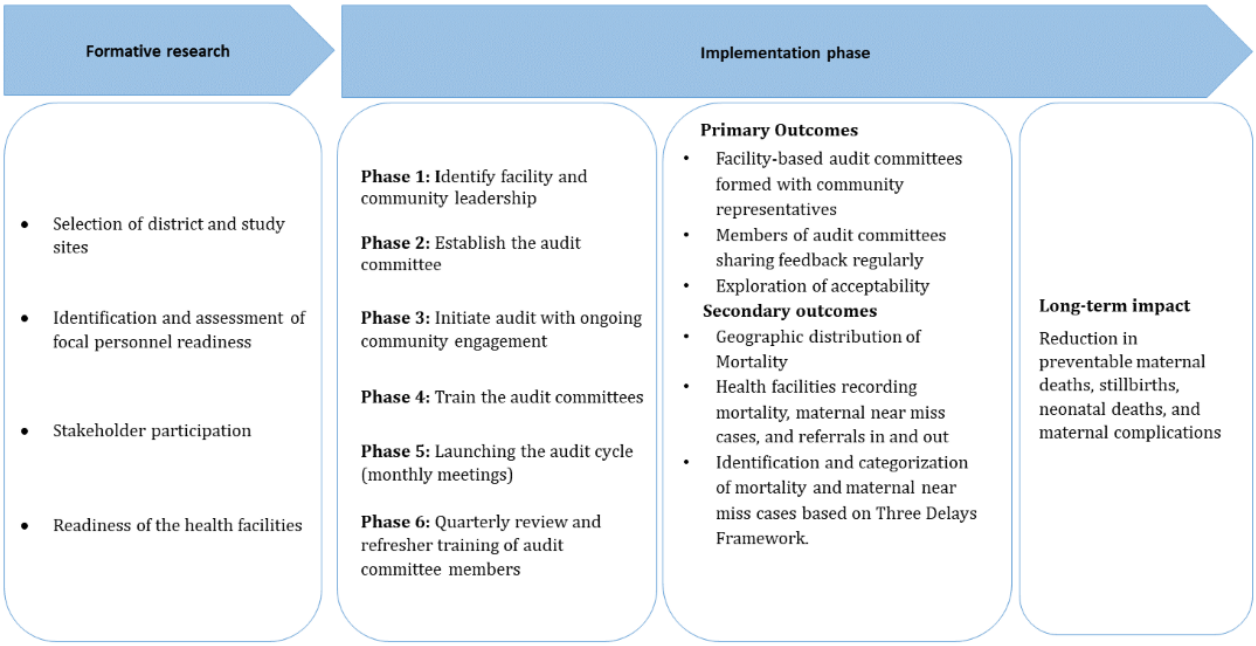
Sample Size

Population size is a challenge in the rural setting, however this study intend to cover all records of stillbirths, neonatal deaths, maternal deaths, and maternal "near misses" from four sources: (1) secondary health facilities, (2) LHW registers, (3) audit committee's community representatives, and (4) project routine survey team.

Study Timeline

The implementation of the audit system intervention is planned for 20-month period. To account for the effects of maturation (ie, 28 days after delivery for neonatal outcomes and 42 days after pregnancy for maternal near-miss outcomes), an additional 4 months will be added to the end of the intervention. Figure 1 Illustrates the implementation framework.

Figure 1. Implementation framework.



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Audit System Implementation Phases (6 Phases)

The project development is based on formative studies that identified the importance of health care providers' readiness, stakeholder and community participation, and health facilities' readiness. The process will include consultative meetings with project's core committee members, program advisory committee members, Director General of Health, and DHO staff.

Phase 1: Identify Facility and Community Leadership

The project's core team and district manager identify facilities and community representatives who will coordinate and liaise with other district stakeholders to implement the community audit interventions.

Phase 2: Establish the Audit Committee

The person in charge of the health facility will establish an audit committee using existing health committees at the Tehsil Head Quarters, quality control committees, medical inspection committees, health welfare committees, and joint health inspection committees in health facilities at Matiari. Audit committees will be led by the medical superintendent of the hospital, with a member from administration, 3 to 4 consultants or medical officers from various departments (gynecologist; pediatrician; ear, nose, and throat [ENT] specialist; pathologist; head of the emergency department; and head nurse), district magistrate, or focal person from DHOs. The community engagement and audit system for project audit committee will be established at each facility; preferably, members will be at least 2 obstetricians, 2 pediatricians, 1 administrator, project focal person, and community representatives as community audit representative. Responsibilities and audit committee structure will be described. Members of the audit committee will update their credentials every month, and trickle-down training will be conducted by audit committee members.

Phase 3: Initiate Audit With Ongoing Community Engagement

Community representatives (1-3 individuals) will be identified as community audit representatives. They will be invited to attend the monthly audit meetings with facility-based audit committee members to discuss the community perspectives (delays 1 and 2) and other issues pertaining to the negative maternal and perinatal outcomes. LHWs, lady health visitors, community midwives (CMWs), male community mobilizer (village or otaq leader or any other active member of village), or any other influential women in the village will be engaged for audit committee decisions. They will provide timely oversight, monitor, and respond to adverse events and later confer in the audit meetings.

Phase 4: Train the Audit Committees

Training for audit representatives and members of the audit committee, will be conducted using 3-day training workshop, which includes the following:

- Day 1: Maternal death, near misses, and perinatal death (stillbirth and neonatal deaths),
- Day 2: The Three Delays framework and identifying modifiable factors, and
- Day 3: Mentoring regarding the identification of the audit committees and initiating the audit implementation committee.

The audit committee will be trained to follow ethical guidelines in maintaining an empathetic gesture while recalling the adverse patient events by the respondents. Training will also include standardized case studies and completion of audit meeting minutes and action item tools.

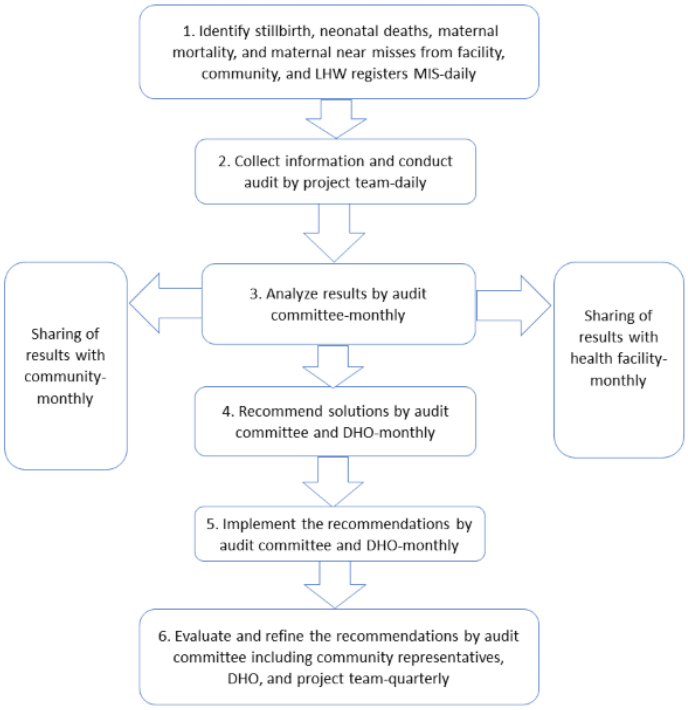
Phase 5: Launch the Audit Cycle (Monthly Meetings)

Overview

The WHO audit system [20] will be adapted to assess maternal, perinatal, and neonatal deaths with 6 steps. Audit process in health facilities and communities is illustrated in Figure 2. Following are the steps and their processes involved in audit cycle.

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Figure 2. World Health Organization audit cycle. DHO: district health officer; LHW: lady health worker; MIS: management information system.



Step 1: Identifying Cases for Review

The district supervisors will record all maternal deaths, maternal near misses, deliveries, births, stillbirths, and neonatal deaths that occur in the delivery ward, neonatal unit, and postnatal ward, ensuring the capture of the minimum set of perinatal indicators in a source register. Efforts to collect and record data on maternal deaths, near misses, and perinatal and neonatal deaths that occur in the community will be made through monthly reporting from LHWs or CMWs to their associated health facility or by women who contact the health facility after delivery. Specific strategies will be put in place to ensure that all deaths are captured and filtered to the mortality audit committee, so that cases can be selected for review and discussion at the mortality audit meetings.

Step 2: Collecting Information

The aim is to empower designated staff to collect a standardized set of information from the patient file or register as soon as possible after the death. For every death, decisions will be taken regarding what information is recorded, where the information is recorded, who records it, and who collates it on a periodic basis both for the death review process and for reporting to other levels within the health system. It should be noted that if the use for the data cannot be identified, the data will not be collected. Before collecting the information, the audit committee will have a clear understanding of the data analysis plan to help identify the data to collect. Data abstraction or collection forms will be either electronic or paper-based, depending on the infrastructure and capacity of the health facility. Clear directions about the exact data and qualitative information that should be collected will be included.

All data collected will be stored on password-protected laptops or tablets or locked cabinets in locked offices within the health facility. Before implementation, data collection forms will be piloted and revised as needed. The minimum data collected will include the following: information about the mother's condition, baby's condition on admission and at the onset of labor (for antepartum and intrapartum deaths), baby's condition at birth (stillbirth or live birth), baby's condition on discharge from the health facility (alive, transferred to another facility, or dead], and date and time of birth and death (so that the age at death can be calculated in hours rather than days).

As part of the intervention, each facility audit system is planned to be comprehensive to ensure that it captures data on each death and includes the relevant cause of death; link to maternal condition; demographic data; and a list of contributing, modifiable factors corresponding to codes for analysis and linked to recommendations. To ensure that phase-1 and phase-2 delays are captured, all efforts to link deaths that occur in the community to the facility audit system will be conducted by the trained LHWs, CMWs, and project team. The audit committee will hold follow-up monthly meetings with designated community engagement members to initiate the chain of notifications within the audit cycle as it relates to the implementation of recommendations and solutions.

Step 3: Analyzing the Information

The aim is to identify problems in the system that may have contributed to maternal death, stillbirths, and neonatal deaths, especially those that could have been averted. Data analysis will include quantitative components, such as identification of trends in rates and causes of death and geographic location. Qualitative analysis will provide additional insight into the problems that caused the deaths of individual cases and more general information about groups of deaths caused by similar contributing factors. The use of both types of data together will

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provide a more robust analysis of the problems and aid the audit committee to identify priorities for action.

Step 4: Recommending Solutions

The aim of this critical step is to find ways to move from problems to action by identifying specific, measurable, attainable, relevant, and time-bound solutions. A formal platform will be created to present the findings of the audit process. The moderator will guide the discussion and present aggregated data and trends in addition to selected individual cases presented anonymously without bias. It is recommended that no more than 2 cases per 2-hour session shall be reviewed per month. After the presentation of the case summary, the main facts are analyzed by the audit members. Discussion will follow the presentation, reflecting on the modifiable factors of specific cases and any changes in trends from meeting to meeting.

A systematic and exhaustive analysis of the case should be conducted to effectively understand the chain of events related to the case. After identifying the main problems at the various steps described previously, the audit committee is invited to discuss and make the case for why a procedure or an act should be considered adequate or inadequate, by referring to the established standards of practice. Dysfunctions and their causes should be prioritized, and energy should be devoted to solving the most significant problems and those for which the implementation of a solution is feasible. Then, the committee will investigate what its causes and related factors may be, and these can be related to (1) personnel: qualification, skills, availability, attitude, and so on; (2) drugs, supplies, and equipment: availability, accessibility, and so on; (3) protocols: availability, knowledge, understanding, use, and so on; (4) management or care organization: coordination, communication, and so on; and (5) patient and his family: financial accessibility, misunderstanding, willingness, and so on. Final step will be the identification of cause of morbidity or death by (1) reviewing the medical cause of severe morbidity or death and identifying the various factors or events that may have contributed to the outcome, (2) comparing the cause of the morbidity or death documented in the patient's record with the audit committee findings, and (3) determining whether the death was preventable.

Following the abovementioned steps in analyzing the case, the moderator leads the discussion to select the problems to be solved in order of priority. Problems must be prioritized based on the significance of their effect on prognosis and the feasibility of the actions necessary to solve them. Through the moderator, the audit committee will then reach a consensus on appropriate, evidence-based strategies to address the main gaps at the health facility level (phase-3 delay). The solutions will balance the priorities based on burden and feasibility and may be related to ongoing or one-off activities.

In addition to possible solutions at the health care facility level, the audit committee in the community will identify cases that are closely linked to the community and agree on select cases to present during the postaudit community feedback meeting. Community-level solutions will be directly related to phase-1 and phase-2 delays. The audit committee will ensure that findings are shared in the appropriate forum and work with the community to develop solutions that are clear, attainable, and straightforward about the potential for improving care, without placing blame.

Recommending realistic solutions to reduce the factors associated with maternal, perinatal, and neonatal morbidity and mortality in the community can be challenging. Careful considerations regarding the capacity of the community to implement the recommendation and the method of communication will be prioritized. The 2016 WHO guidelines for audit and review of stillbirths and neonatal deaths advises formulating a recommendation in collaboration with community leaders empowered to make the recommended change to ensure it is effective. To alleviate the risk of developing distrust between the community and the health system, recommendations will not be "handed down" from the health facility audit committee but rather discussed as a partnership with the community. In addition, effective communication, relayed consistently and sensitively, will be developed through the early selection of appropriate community representatives to participate in the audit meetings. Through the deliberate selection of key community representatives, efforts will be made to encourage an open, synergetic, and nonjudgmental forum between the community and health facility to ensure that the chosen recommendation is attainable and will ultimately strengthen the community voice.

Our data suggest that the process of fostering active partnerships between health care providers and community members through dialogue, planning, and collective action by learning from what went wrong and emerging lessons can improve community trust and quality of care [21].

Step 5: Implementing Changes

The aim is to take immediate, medium-term, or long-term actions to prevent maternal deaths, stillbirths, and neonatal deaths, using successes to advocate for and spur further action. Implementing changes is the primary objective of the audit cycle. To be more effective, the audit committees will focus on the modifiable factors that are within the control of health workers and the community.

The findings of the audits will be shared with the concerned authorities in health facilities, program managers, and community representatives to spur policy and practice related change. DHO will be onboard to ensure that the decisions agreed upon are implemented at the facility and community levels. The decisions proposed by the audit committee and endorsed by DHO will be implemented to address the bottlenecks at the demand side (delay in care and financial and mobility challenges) and the supply side (lack of hospital supplies, staff, and resources).

Step 6: Monitoring and Evaluation

In addition to the monthly audits, the project committee will also collect administrative and survey data to capture the process and outcome indicators. From independent, third-party surveys and data sources such as DHIS, facility registers, and LHW management information system, the impact of the intervention will be evaluated based on the maternal perinatal and neonatal mortality and morbidity outcomes and rated for all pregnant women, mothers, and newborns.

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The model will contain audit guidelines, protocols, and training materials and tools for effective monitoring at the facility level in the targeted districts with their respective catchment populations. A monthly monitoring cycle will be set up within the implementing facilities to ensure effective implementation of the audit systems.

Phase 6: Quarterly Review and Refresher Training of Audit Committee Members

For a sustainable audit system, recognition and reinforcement is inevitable. Refresher training and recertification will be conducted quarterly.

Data Management and Analysis

The data collection tool will be developed in English and then translated into the local language to be administered to the local community visiting the health facilities. Data will be collected manually and entered through a specifically designed application. The application will be installed on laptop or desktop at each health facility under the supervision of project leadership. The Aga Khan University Data Management Unit will develop an electronic database that includes the filters and data quality check indicators. Data will be entered at the end of every week and uploaded onto the Aga Khan University Data Management Unit server. All data files will be stored for 5 to 7 years and then deleted according to organizational procedures for the permanent destruction of electronic and paper data.

Descriptive statistics will be used to estimate maternal, neonatal, and other key quantitative variables. The Three Delays framework will be used to categorize the identified modifiable factors. Action reports will be submitted based on the recommendations proposed by the audit committee. The data will be analyzed using Stata (version 16; StataCorp) and NVivo (Lumivero) software and password-protected Excel (Microsoft Corp) files. A unique code identifier will be assigned for the cases to be selected for discussion in audit meetings. The village name and health facility name will be kept confidential in audit meetings and, instead, codes will be used. In addition, regular meetings, planned dissemination of study findings including manuscript publication, stakeholder knowledge sharing workshop including community participation, and conference presentations will be conducted.

Ethical Considerations

The study was approved by the ethical review committee of Aga Khan University (ethical review committee number 2021-6426-19638). The project committee will be trained in conducting human subject research keeping in mind the ethics guidelines and respecting the autonomy of the participants. Using a noncoercive attitude, informed consent and maintenance of privacy will be assured while collecting data. Respondents will be asked to participate voluntarily after giving written informed consent. Respondents will be free to ask any questions or may ask to skip any question or may withdraw from interview at any moment without incurring any penalties.

Results

The study implementation will be for 20 months, followed by an additional 4-month period for follow-up. Initial results will be presented to DHO and the District Health Program Management Team Meeting in the districts.

Discussion

Expected Outcomes

The study introduced a research protocol that outlines an intent to establish a systematic audit system for recording, assessing, and evaluating maternal deaths, near misses, stillbirths, and neonatal deaths in rural Pakistan. Previous endeavors of similar nature have been conducted in high-income countries and various low- and middle-income countries [22]. These initiatives underscore the significance of executing a thorough audit cycle, involving effective leadership, engaging relevant health care practitioners, and using participatory methods within communities. Targeting all cases through mortality audits to enhance the standard of care for mothers and newborns. Hence, this subject holds considerable importance for Pakistan's health care system, particularly for this type of project, which has not been pursued previously to enhance feasibility, continuity, and sustainability.

Risk Management

There are minimal risks associated with this study. Community members and health care providers may experience some psychological and social risks associated with recalling the consequences surrounding a death. In the event a woman becomes emotionally distressed during the survey, participants will be provided the opportunity to stop and take a break or discontinue the interview completely. Similarly, through the identification and discussion of causes resulting in specific deaths, there is the risk of blaming and shaming of potential health facility staff or community members. All efforts to allay these risks and the repercussions will be made by ensuring that all names of the health care staff who provided care and patients remain anonymous.

The goal of the audit approach is to identify why a death or severe outcome occurred, so that changes can be made to prevent similar events in the future. The purpose is not to cast blame or punish individuals, groups, or institutions. Audit committee members will be encouraged to develop a code of practice to foster an environment of collaboration rather than blame. Accountability for adverse actions will be encouraged through approaches that seek to improve care by educating both the health care provider and community. There is the potential risk that given the size of a catchment area, community representatives may have immediate knowledge about the case under discussion. To create an environment for change in the community, in addition to anonymizing all providers and patients, community representatives will be strategically selected to ensure that they are well respected and have strong, effective communication skills. As the primary factors related to patient-level, family-level, or community-level delays 1 and 2 are associated with knowledge about danger signs and plans for

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delivery, such as transportation, there is minimal risk associated with individual blaming or shaming. Approaches for implementing the recommendations will be enhanced through the form of media favored by the community, such as radio, television, theater, and murals, in addition to written materials. No unexpected or adverse events are anticipated as a result of the audit reviews.

Policy and Practice Change Implications of the Audit System

Initially, based on the advice of the district health officer, the meetings will be conducted monthly. Later, dissemination of the implementation study findings will be shared quarterly at the District Health Program Management Team Meeting. This meeting comprises key stakeholders including those in charge of health facilities, DHIS focal person, LHW program focal individuals, and other members involved in and contributing to the design, implementation, and rollout of the audit system delivery model. Consistent liaison with these provincial-level stakeholders will allow for the integration of infrastructural changes and practice changes at the facility level, conducive to the effective implementation of the audit system. Conducting audits focused on maternal and perinatal mortality presents an opportunity to implement effective actionable actions for improving the well-being of mothers and children in limited-resource communities. The implementation approach will be used for integration of decision makers, health care providers, and community members, as they are vital components of the comprehensive audit cycle proposal.

Limitations

Our project is unique with its focus on community engagement and representation integrated into the facility-based audit system. As such, it has strong implications for scale-up and uptake across Pakistan's regional districts. Nevertheless, the primary limitation of this study is the recording of neonatal and maternal deaths and their complete medical history from health facilities. To overcome this challenge, there will be planned quarterly refresher training for the facility staff regarding source register apprising and DHIS. Moreover, in monthly audit cycles, the cases will be presented by audit committee members including community representatives. This will help support local ownership for facilitating and using existing resources. DHOs will ensure the presence, retention, and participating attitude of audit committee members. The implementation design includes quantitative and qualitative approaches, which can provide strong evidence for the impact generated by the audit system implementation.

Patient and Public Involvement

The public was not involved in the development of the study design, but they are an integral part of the implementation of this study, and their perspectives and engagement are key components of the study. The key findings will be regularly shared with the public sector authorities.

Conclusions

The study will generate evidence about the feasibility and potential scale-up of a facility-based mortality audit system with integrated community engagement in rural Pakistan. Audit committees will complete the feedback loop linking health care providers, community representatives, and district health officials (policy makers). Analyzing the burden of deaths in the area and delving into individual cases aid in identifying the causes and modifiable factors to prevent future adverse events. This implementation approach also serves the purpose of establishing a regular dissemination platform for decision makers to prioritize the actionable recommendations for improving maternal and perinatal health outcomes.

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Data Availability

The data set will be available upon request. The data will be restored under Aga Khan University data security and retention policy.

Authors' Contributions

ZAB led the funding acquisition for this implementation study under the large grant of Umeed e Nau (New Hope) project. ZM conceptualized this study with guidance from PB and ZAB. WA, SM, SS, and AR provided theoretical and technical support in the development of this protocol. SC provided the input for drafting the phases of the study. ZM drafted the first version of the manuscript and incorporated feedback from all coauthors. ZM, WA, SM, SS, SC, AR, PB, and ZAB reviewed the subsequent drafts of the manuscript. The final manuscript has been reviewed and approved by all the authors.

Conflicts of Interest

None declared.

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Abbreviations

CMW: community midwife
DHIS: District Health Information System
DHO: district health office
ENT: ear, nose, and throat
LHW: lady health worker
UNICEF: United Nations International Children's Emergency Fund
WHO: World Health Organization

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Protocol

Phenotypic Environmental Sensitivity and Mental Health During Pregnancy and Post Partum: Protocol for the Experiences of Pregnancy Longitudinal Cohort Study

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Abstract

Background: Mental health problems during pregnancy and post partum are common and associated with negative short- and long-term impacts on pregnant individuals, obstetric outcomes, and child socioemotional development. Socio-environmental factors are important predictors of perinatal mental health, but the effects of the environment on mental health are heterogeneous. The differential susceptibility theory and the environmental sensitivity framework suggest that individuals differ in their degree of sensitivity to positive and negative environments, which can be captured by individual phenotypes such as temperament and personality. While there is strong evidence for these models in childhood, few studies examined them in adults, and they were not examined in pregnancy.

Objective: The primary objective of the Experiences of Pregnancy study is to explore whether childhood and current environments are associated with mental health and well-being in pregnancy and whether these effects depend on individual sensitivity phenotypes (personality). This study also aims to gather important psychosocial and health data for potential secondary data analyses and integrative data analyses.

Methods: We will conduct a longitudinal cohort study. The study was not registered elsewhere, other than this protocol. Participants will be recruited through social media advertisements linking to the study website, followed by an eligibility call on Zoom (Zoom Video Communications). Participants must be aged 18 years or older, currently residing in the United States as citizens or permanent residents, and currently planning to continue the pregnancy. A minimum of 512 participants will be recruited based on power analyses for the main objectives. Since the data will also be a resource for secondary analyses, up to 1000 participants will be recruited based on the available budget. Participants will be in their first trimester of pregnancy, and they will be followed at each trimester and once post partum. Data will be obtained through self-reported questionnaires assessing demographic factors; pregnancy-related factors; delivery, labor, and birth outcomes; early infant feeding; individual personality factors; childhood and current environments; mental health and well-being; attachment; and infant temperament. A series of measures were taken to safeguard the study from web robots and fraudulent participants, as well as to reduce legal and social risks for participants following *Dobbs v. Jackson*.

Results: The study received ethics approval in April 2023 from the University of Oklahoma-Norman Campus Institutional Review Board. Recruitment occurred from May to August 2023, with 3 follow-ups occurring over 10 months.

Conclusions: The Experiences of Pregnancy study will extend theories of environmental sensitivity, mainly applied in children to the perinatal period. This will help better understand individual sensitivity factors associated with risk, resilience, plasticity, and receptivity to negative and positive environmental influences during pregnancy for pregnant individuals.

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KEYWORDS

anxiety; biological sensitivity to context; depression; diathesis-stress; highly sensitive person; moderation; resilience; sensory processing reactivity; substance use; vantage sensitivity

Introduction

Background

Pregnancy is a period of increased risk for mental health problems, which are one of the leading preventable causes of morbidity and mortality during the perinatal period in high-income nations [1-3]. Among people who are pregnant, approximately 20% to 30% experience elevated symptoms of anxiety or depression [4-6]. In turn, these symptoms are associated with short- and long-term parental and child health and well-being. Elevated and sustained prenatal psychological distress can often lead to long-term disturbing emotional experiences such as anger, anxiety, and depression in the postpartum period and beyond [7-9]. Prenatal stress and distress may impair bonding with the fetus and child [10,11] and may lead to strained familial and social relationships. In infants, exposure to prenatal stress and mental health problems has been found to be associated with a more difficult temperament and impaired cognitive and motor development [12]. Impacts on children may be long-term, with prenatal stress and distress being associated with disorganized attachment, poorer socioemotional development, learning deficits, and mental health problems across the internalizing and externalizing spectrums in children and adolescents, including attention-deficit/hyperactivity disorder, anxiety, depression, and behavioral problems [12-15]. Finally, prenatal stress and distress are also associated with obstetric and birth outcomes, with research showing links with early gestational age, low weight at birth, preeclampsia, hypertension, and reduced lactation [8,12,16-19].

Considering these broad negative impacts, understanding the risk and protective factors for mental health problems during pregnancy, as well as factors associated with well-being, is essential to promoting parental and child health. Environmental factors, both in early life and during pregnancy, have been found to be associated with perinatal mental health. For example, a meta-analysis found that adverse childhood experiences are a risk factor for prenatal and postpartum depression and anxiety, with the number of adverse childhood experiences being positively associated with symptom severity [20]. Sociodemographic factors are also important, with a meta-analysis showing that lower educational level and poor economic status are risk factors for perinatal depression [21]. Finally, research on current social environment factors shows that low social support from family members, friends, or community members [22], as well as poor romantic relationship satisfaction [23,24], are risk factors for perinatal depression, anxiety, and self-harm. The effects of the environment on mental health are, however, heterogeneous.

A proper understanding of the associations between environmental factors and mental health requires studying for whom the environment is influential. In turn, this can inform better targeted prevention efforts when psychosocial resources are limited. A frequently used theoretical model in psychiatry is the diathesis-stress model of vulnerability and resilience [25,26]. According to this model, some pregnant individuals would be vulnerable to adverse environments, leading to higher levels of psychological distress, while others would be resilient to such environments, leading to low levels of psychological distress despite negative environmental conditions. An alternative model, the differential susceptibility model [27,28], suggests that pregnant individuals who are sensitive to their environment would have higher levels of psychological distress than their peers in adverse environments but also lower levels of psychological distress and higher levels of well-being than their peers in positive environments. Thus, rather than being only vulnerable to adverse environments, individuals could be sensitive to both positive and negative environments, “for better or for worse” [29]. Individuals could also, however, be sensitive only to positive environmental influences, which was proposed in the vantage sensitivity model [30].

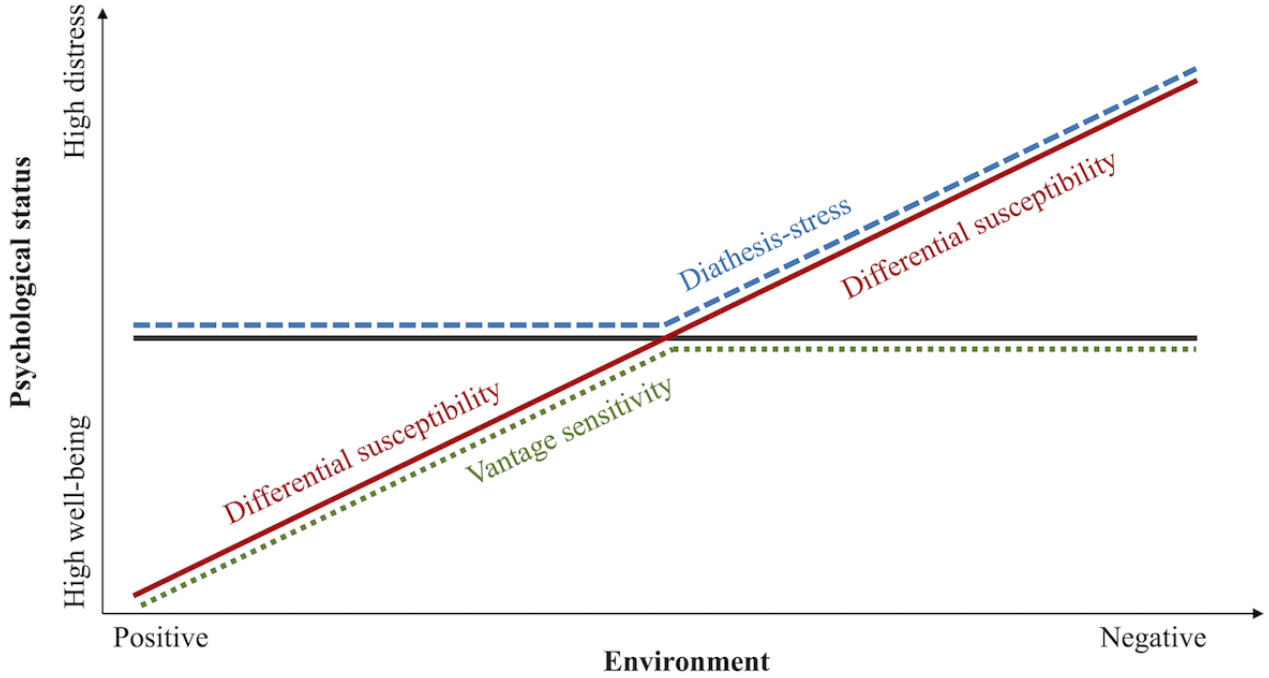
The environmental sensitivity framework [31] (Figure 1 [32]) comprehensively integrates these theoretical models of psychosocial person-environment interactions. According to this model, individuals differ in their degree of sensitivity to the environment. Based on an individual sensitivity factor, individuals may differ in their sensitivity to adverse or negative environments only (diathesis-stress), to enriched or positive environments only (vantage sensitivity), or to both (differential susceptibility) [31]. Furthermore, some evidence suggests that this sensitivity may be domain specific rather than domain general, meaning different individual characteristics may capture sensitivity to different environments [33]. It is thus important to further elucidate for whom, when, and under which environmental conditions diathesis-stress, vantage sensitivity, and differential susceptibility apply. This is important because individuals’ differences in their receptivity to environmental inputs can influence their response to treatment interventions [34]. A better understanding of environmental sensitivity can thus help determine the best intervention and treatment on an individual basis, as well as inform targeted prevention efforts and psychoeducation [34,35].

The differential susceptibility and environmental sensitivity models were proposed by developmental psychologists and have been thoroughly studied in children, with several reviews showing that individual-level factors originally thought to be vulnerability factors to adverse environments supported differential susceptibility, reflecting sensitivity to certain positive and negative environments [27,28,36]. We still know very little,

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however, about how these models apply to adults. Theory suggests that some adults are sensitive to positive and negative environmental conditions in the prediction of mental health, but very few empirical studies have examined the patterns of interaction of the environmental sensitivity framework based on phenotype in adults [37-39]. Thus, research is needed to elucidate environmental sensitivity factors in adulthood, including during pregnancy, a key period of heightened risk for psychological distress [1,5,40].

Figure 1. Integrated model of environmental sensitivity. The diathesis-stress model captures individual sensitivity to negative environments only. The vantage sensitivity model captures individual sensitivity to positive environments only. The differential susceptibility captures sensitivity to both negative and positive environments within the same individuals (adapted from Belsky et al [32], which is published under Creative Commons Attribution 4.0 International License [41]).



Objectives

The primary objective of the Experiences of Pregnancy study is to explore whether childhood and current environments are associated with mental health and well-being in pregnancy and whether these effects depend on individual sensitivity phenotypes (personality) through a longitudinal cohort study design. Considering there are few empirical studies on this topic in adulthood in general and no data to our knowledge in pregnancy, the study aims to document a variety of individual, environmental, and mental health factors to clarify models of sensitivity in adults and pregnant people. Following epidemiological cohort principles, this study also aims to gather important psychosocial and health data for potential secondary data analyses [42] and integrative data analyses [43].

Methods

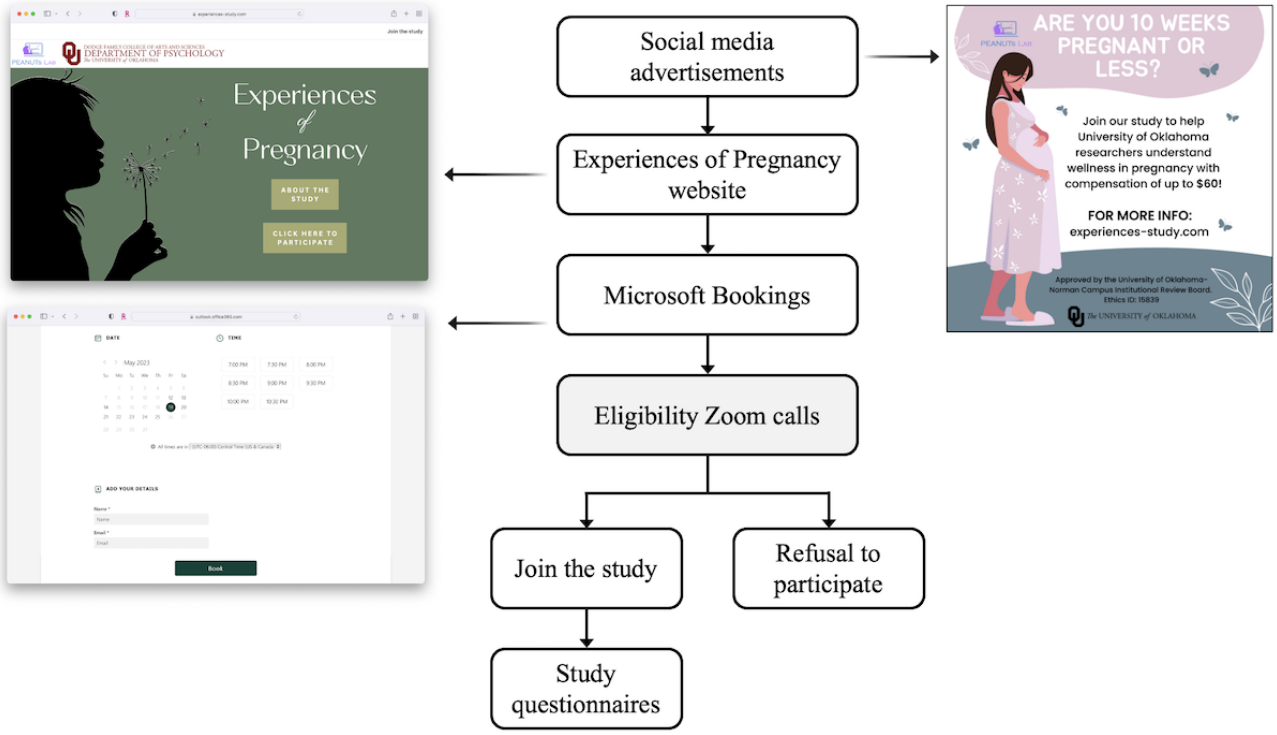
Participants and Recruitment

Figure 2 shows the recruitment process to occur from May to August 2023. Participants will be recruited on the web through advertisements (Figure 2) on Facebook, Instagram, Twitter (subsequently rebranded X), and Reddit, as well as posts on the Reddit forums “r/Maternity” and “r/lgbtstudies.” Participants will be directed to the study website [44], where they will find general information about the study, eligibility criteria, and a link to join the study. Through this link, interested participants will be directed to a REDCap (Research Electronic Data Capture; Vanderbilt University) [45,46] survey protected by a reCAPTCHA Inc (Google) verification and redirecting to a Microsoft Bookings (Microsoft Corporation) page to schedule their call, with availabilities open for the next 14 days. Zoom (Zoom Video Communications) calls with undergraduate and graduate research assistants (RAs) will confirm their eligibility and go over the study process. Eligible and interested participants will receive their personal survey link through email after their call.

Participants are eligible to enroll if they are aged 18 years or older, currently live in the United States, are citizens or permanent residents of the United States, and can read and write in English. Pregnant people of all gender identities are eligible to enroll in the study [47]. Furthermore, participants have to be currently planning to continue the pregnancy (see the *Ethical Considerations* section) and be in their first pregnancy trimester to join the study. Eligibility is to be 10 weeks pregnant or less when they signal their interest in the study (make their appointment through Microsoft Bookings) to allow time for their Zoom call confirming eligibility and for filling out the first survey. They remain eligible if they are 12 weeks pregnant or less by the time of their Zoom call. Overall, this allows for 2 weeks to schedule the Zoom call and gives them at least 1 week to fill out the first survey.

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Figure 2. Flowchart of the study procedure for participant enrollment for the Experiences of Pregnancy longitudinal cohort study, United States, planned for 2023-2024.



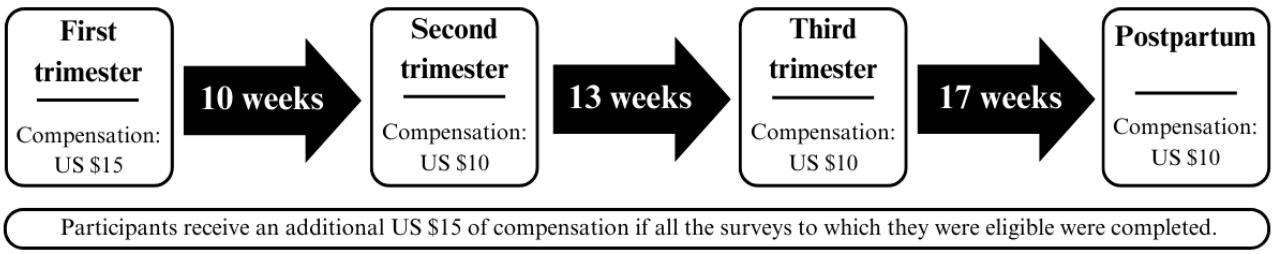
Follow-Ups and Study Design

Participants will fill out 4 questionnaires: 1 questionnaire per trimester of pregnancy (3 first questionnaires) and 1 after birth (Figure 3). This follow-up schedule will allow collection of data during each key developmental period (trimester) of pregnancy. For this study, this follow-up schedule was also based on research showing individual differences in how mental health changes across each trimester [48-51] and highlighting the importance of repeated measurements at each pregnancy trimester in assessing prenatal mental health.

At each follow-up survey, participants will first be asked if they are still pregnant. In the event that a participant experiences pregnancy loss or premature birth, they will remain eligible to fill out the current survey as their last assessment (ie, 1 survey after loss or after birth). Depending on group sample sizes, this may allow for the examination of mental health and resilience factors after a pregnancy loss. At the end of each survey, the "submit" button redirects participants to resources on the study website, with resource lists for pregnancy, pregnancy loss, and post partum that include crisis lines, mental health services, information, and networks.

Based on an estimate of 4 to 7 items per minute for participants who do not regularly participate in survey studies [52], the first survey is expected to take between 50 and 70 minutes. The following 3 questionnaires are expected to take between 40 and 60 minutes; participants will be informed of these time estimates during their Zoom call. Based on the upper range of US minimum wages, participants will be compensated for their time, receiving US $15 of compensation for the first questionnaire (longer questionnaire) and US $10 for each subsequent questionnaire. As an incentive to complete the study and to reduce attrition, participants who complete all 4 questionnaires (or all questionnaires for which they are eligible in the event of a pregnancy loss or premature birth) will receive an additional US $15. Compensation will be in the form of Amazon or Giftogram e-gift cards sent by email within 2 weeks of each questionnaire's completion. To receive compensation, participants must submit the survey but are free not to answer questions they are uncomfortable with or do not wish to answer.

Figure 3. The timeline of completion of the study questionnaires for the Experiences of Pregnancy longitudinal cohort study, United States, planned for 2023-2024.



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Study Measures

All study data will be obtained through self-reported questionnaires. Table 1 summarizes study measures across assessments. All personality measures will be collected at survey 1 only as potential moderators. Childhood environments will be retrospectively self-reported once as potential predictors. Adverse and benevolent childhood experiences will be assessed at survey 1, but parental bonding (a retrospective measure of the parenting styles of participants' parents in their childhood) will be assessed at survey 2 to reduce the burden of the longer first questionnaire. Current environments will be measured repeatedly at each assessment and include recent stressful experiences, everyday discrimination, social support, couple satisfaction, romantic intimate bonding, and social and digital media use. Mental health and well-being measures will be measured repeatedly at each assessment and include depressive symptoms, anxiety symptoms, anger, well-being, life satisfaction, sleep, disturbed dreaming, substance use (alcohol, tobacco, cannabis, and other drugs), and mental health service use. The initial (survey 1) substance use questionnaires will also assess substance use in the year before pregnancy as well as the age of onset for each substance. Attachment (prenatal or postnatal) will also be measured at all assessments. Finally, infant temperament will be measured after birth. Both postnatal attachment and infant temperament will be measured only for singleton pregnancies, as these questionnaires are specific to 1 baby, and the surveys would be much longer if asked for multiple babies.

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Table 1. Study measures at each assessment for the Experiences of Pregnancy longitudinal cohort study, United States, planned for 2023-2024.

Study measures	Survey 1 First trimester	Survey 2 Second trimester	Survey 3 Third trimester	Survey 4 Post partum
Demographic, pregnancy, and delivery information				
Demographic information	All[a]			
Relationship status	All	All	All	All
Daily activities and responsibilities	All	All	All	All
Pregnancy status		All	All	All
Previous pregnancies and due date	All			
Pregnancy intendedness [53]	All			
Health conditions before pregnancy	All			
Health conditions during pregnancy	All	P[b] and LD[c]	P and LD	LD
Height	All			
Weight	All	P and LD	P and LD	
Prenatal care	All	P and LD	P and LD	
Delivery and birth outcomes		LD	LD	LD
Early breastfeeding and formula feeding		LD	LD	LD
Labor and Delivery Index [54]		LD	LD	LD
Individual and personality factors				
10-item Big Five Inventory [55]	All			
Highly Sensitive Person 12-item Scale [56]	All			
Substance Use Risk Profile Scale [57]	All			
Environmental factors				
Expanded Adverse Childhood Experiences Scale [58]	All			
Benevolent Childhood Experiences Scale [59]	All			
Parental Bonding Instrument [60]		All		
Recent Stressful Experiences Checklist [61]	All	All	All	All
Everyday Discrimination Scale [62]	All	All	All	All
Multidimensional Scale of Perceived Social Support [63]	All	All	All	All
Couple Satisfaction Index [64]	All	All	All	All
Intimate Bond Measure [65]	All	All	All	All
Social and digital media use	All	All	All	All
Mental health and well-being measures				
PROMIS[d] Anger [66]	All	All	All	All
Generalized Anxiety Disorder 7-item scale (GAD-7) [67]	All	All	All	All
Depression: Patient Health Questionnaire (PHQ-9) [68]	All	All	All	All
Substance use	All	All	All	All
Psychological Well-Being Scale [69]	All	All	All	All
PROMIS General Life Satisfaction [70]	All	All	All	All
Sleep duration	All	All	All	All
PROMIS Sleep Disturbance [71]	All	All	All	All
PROMIS Sleep-Related Impairment [71]	All	All	All	All
Disturbing Dreams and Nightmare Severity Index [72]	All	All	All	All

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Study measures	Survey 1 First trimester	Survey 2 Second trimester	Survey 3 Third trimester	Survey 4 Post partum
Mental Health Service Use Questionnaire [73]	All	All	All	All
Attachment				
Maternal Antenatal Attachment Scale [74]	All	P	P	
Maternal Postnatal Attachment Scale [75]		LD	LD	LD
Infant temperament				
Early Infancy Temperament Questionnaire [76][e]		LD	LD	LD
Other				
Intention to participate in follow-up surveys[f]	All	P		

[a]All: study measure is included in regular follow-ups and shown to all participants regardless of pregnancy status.

[b]P: pregnant; this indicates study measure is included for participants who are still pregnant at the time of that questionnaire.

[c]LD: live delivery; this indicates study measure is included for participants who experienced a (term or preterm) live delivery at the time of that questionnaire. Participants who experience a pregnancy loss or neonatal death are only shown instruments labeled "All" and are not shown instruments related to pregnancy, labor, delivery, or the child.

[d]PROMIS: Patient-Reported Outcomes Measurement Information System.

[e]Only the subscales "Rhythmicity," "Intensity," and "Threshold" are included.

[f]See the *Missing Data Mitigation* section for details.

Sample Size Considerations

We aim to recruit between 512 and 1000 participants. This study's main objective is to explore person-environment interactions in the prediction of perinatal mental health and well-being. We examined power for the simplest model to meet these objectives (1 interaction effect in a multiple regression model). Power analyses were run using the *InteractionPoweR* Shiny app [77], with moderate main effect sizes and small interaction effect sizes based on our previous differential susceptibility research [78-80]. Measurement reliability was integrated into the power analyses, with good (environmental and personality variables) and excellent (mental health) reliabilities [23,56,80,81]. This analysis indicated that the minimum sample size to detect the interaction effects with 80% power is 341. Simulation studies suggest that for tests of differential susceptibility, 50% more cases are required to achieve 80% power compared with power for the interaction effect [82], yielding a minimum sample size of 512. This study is also designed to serve as a secondary data analyses related to mental health and well-being during pregnancy and post partum. To maximize possibilities for longitudinal modeling, we will be recruiting up to 1000 participants, with the maximum being based on budgetary considerations.

Web-Based Data Integrity

Measures were used to safeguard the study against web robots (bots). To prevent enrollment from bots and fraudulent participants, participants will be individually screened through Zoom calls. Individually screening participants has been deemed one of the most reliable methods to protect web-based data collections [83,84]. Considering recent advances in artificial intelligence (AI) language, calls were deemed more secure than emails for participant screening. Zoom calls were easier to implement administratively than phone calls, as there were already organizational accounts set up for Zoom, but phone accounts had to be purchased. Finally, appointments were expected to be more efficient than trying to reach participants through phone calls after they provided their information without a set time.

To safeguard the Zoom call bookings from being targeted by bots, which could prevent genuine participants from enrolling due to appointments being unavailable, a total of 4 measures recommended to deter bots from studies were used. First, because bots are particularly interested in studies with financial incentives [83], monetary compensation was included in the images of the social media advertisements but will not be mentioned in any of the text accompanying the advertisements. Second, a total of 2 links will have to be accessed to get to the call bookings (the social media advertisement link and the link to join the study on the website). Direct links to Microsoft Bookings will not be posted on social media [83,85]. Third, a reCAPTCHA verification will protect the REDCap survey leading to the bookings page [83,85]. Finally, Microsoft Bookings settings will include 1-time passwords, where a numeric code will be sent to each participant's email address to complete the booking.

RAs conducting Zoom calls will complete 2 trainings. The first training (in person) will go over the study protocol, the steps for confirming calls with participants through email, conducting the call, and sending surveys, including how to use Microsoft Bookings, the study email account, and REDCap. Each RA will have a printed copy of a manual covering all these steps, along with access to a digital version of the manual. RAs will also practice all steps, including the calls, during the first training. The second training will be on Zoom, where RAs will practice calls further in a more similar setting to calls with participants. The principal investigator (CR) will have weekly scheduled meetings with RAs to discuss progress, questions, and any perceived issues during the calls, including potential fraud. RAs will also be able to share any perceived issues with a call in a

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rapid manner through the laboratory's communication platform, Slack (Slack Technologies). This will allow the identification of any unforeseen issues during recruitment and the adaptation of call protocols if needed.

Missing Data Mitigation

To reduce attrition rates, an incentive of US $15 is offered for completing all 4 surveys (or all surveys a participant is eligible to in the event of a pregnancy loss or premature birth; see the *Follow-Ups and Study Design* section). Because participants are actively recruited and join the study through a Zoom call instead of only filling out the survey on the web, we expect more participant investment in the study than traditional web-based questionnaires.

In analyses with missing data rates up to 10%, deletion techniques may be used as they are not associated with increased bias [86]. In analyses above this missing data rate (which can be expected for longitudinal analyses), recommended missing data treatments, including full information maximum likelihood (FIML) and multiple imputation, will be used [87]. These missing data treatments are most effective at preventing biased results when predictors of missing data (ie, predictors of the missing at random [MAR] mechanism) are included as auxiliary variables [87]. At the first 2 assessments, we provided a study timeline of the next surveys and their associated compensation and included 1 question asking participants "Currently, how likely do you think you are to complete the follow-up surveys?" with answers ranging from "very unlikely" (score 1) to "very likely" (score 4), presented in Table 1. This question was included to serve as a potential predictor of the MAR mechanism (ie, potential auxiliary variable) in addition to the main survey questions.

Data Management

All data will be collected and managed using REDCap tools hosted at the University of Oklahoma Health Sciences Center [45,46]. REDCap is a secure, web-based software platform designed to support data capture for research studies, providing (1) an intuitive interface for validated data capture, (2) audit trails for tracking data manipulation and export procedures, (3) automated export procedures for seamless data downloads to common statistical packages, and (4) procedures for data integration and interoperability with external sources. Metadata will be submitted to the Maelstrom Catalogue [88] to support harmonization initiatives among epidemiological cohorts. The research team welcomes collaboration on the study; access to the data dictionary and data request form will be available upon reasonable request made to the corresponding author.

Data Analyses

Analyses for the primary aim will follow recommendations for testing person-environment interactions based on the environmental sensitivity framework and differential susceptibility. Linear moderated regressions will be conducted. To test for diathesis-stress, vantage sensitivity, and differential susceptibility, the nature of significant interactions will be further examined using regions of significance analyses, the proportion of interaction (PoI) index, and the proportion affected (PA) index [89]. The best-practice recommendations are to use a combination of these indices to confirm support for one of the environmental sensitivity models [82,89].

Regions of significance analyses use the Johnson-Neyman technique to identify at what levels of the environmental variable individuals differ in their mental health based on their phenotype [89]. The PoI index will quantify the "proportion of the total area of the interaction" that is attributable to the positive environment. Prototypical models would have a PoI of 0.5 for differential susceptibility, 0.0 for diathesis-stress, and 1.0 for vantage sensitivity. Proposed criteria are that a PoI of 0.2-0.8 supports differential susceptibility [82], with a PoI <0.2 supporting diathesis-stress and a PoI >0.8 supporting vantage sensitivity. The PA index will quantify the "proportion of participants" who benefit from the positive environment. Similar to the PoI index, prototypical models would have a PA of 0.5 for differential susceptibility, 0.0 for diathesis-stress, and 1.0 for vantage sensitivity. Proposed criteria are that a PA value <0.16 is considered as indicative of diathesis–stress [89], making a PA value >0.84 indicative of vantage sensitivity.

Ethical Considerations

The study received ethics approval from the University of Oklahoma-Norman Campus Institutional Review Board (IRB #15839). All participants will sign an electronic informed consent form once during the study through the REDCap eConsent framework [90] before completing the first questionnaire.

Special considerations were taken to reduce the legal and social risks and protect participants from their data being used in legal proceedings related to abortion. First, a National Institutes of Health Certificate of Confidentiality was obtained. Second, inclusion criteria explicitly include the intention to keep the pregnancy, so that pregnancy losses recorded in the study would not be assumed to be from intentional abortion. Third, while our pregnancy-information questionnaire would have typically included the following questions—(1) How many total times have you been pregnant? (2) Have you ever had a miscarriage? and (3) How many children do you currently have at home?—in order to avoid combined answers to these questions being used to deduce the possibility of a past abortion, questions 2 and 3 were removed, and question 1 was changed to "Is this your first pregnancy?" Fourth, while we initially planned an open-ended question following pregnancy losses where participants could tell us about their experience, we opted to remove that open-text field to avoid inadvertently recording liable information.

Results

The study received ethics approval in April 2023. Recruitment occurred from May to August 2023. After the first survey, participant follow-ups will occur over 10 months.

Discussion

The Experiences of Pregnancy study will assess individual personality factors, social environmental factors, and psychological distress and well-being factors throughout pregnancy and post partum. The Experiences of Pregnancy study will allow extending theories of environmental sensitivity

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mainly applied in children to the perinatal period. This will help better understand individual characteristics associated with risk, resilience, plasticity, and receptivity to negative and positive environmental influences during pregnancy. In turn, this could help inform intervention and prevention efforts tailored to peoples' individual sensitivity to their environment [34,35]. While measures on individual phenotypes, social environments, and mental health outcomes were prioritized, the principal investigator's (CR) expertise in longitudinal study designs, population studies, and advanced quantitative analyses allowed the integration of a broader set of measures that will allow secondary data analyses and could contribute to data harmonization efforts addressing related developmental and epidemiological questions.

Recruitment for Experiences of Pregnancy is occurring nationwide, is completely web based, and will be carefully tracked. The infiltration of web-based data by bots and fraudulent participants has been a major concern in recent years [91,92]. In this study, we implemented many steps to ensure data integrity and protect the study from bots and fraudulent participants while ensuring feasibility, including not linking surveys directly on social media, reCAPTCHA verification, email verification, and a Zoom call. The study has the potential to contribute to the design of future studies looking to conduct reliable and safe web-based data collection. This could help future epidemiological and medical research since web-based data collection can have advantages in collecting data from minority populations and from hard-to-reach populations [93-96]. This is not limited to self-report surveys such as ours since many aspects of data collection, including, for example, some biological assays [97-100], neurobehavioral and cognitive assessments [101-103], stress tests [104,105], and parent-child observations [106], have been successfully adapted to be conducted remotely. Finally, our data on social media advertisement costs and success will also be documented and could help inform recruitment budgets for future web-based studies on pregnant populations.

The main weakness of the Experiences of Pregnancy study at the design stage is that all data will be self-reported. However, initial insights into environmental sensitivity and differential susceptibility in pregnancy stemming from this study could inform future investments in research integrating other measurement methods, such as examining genotypic and endophenotypic sensitivity factors [28,107]; recruiting participants' social network (eg, parents, siblings, friends, and romantic partners) to measure their social environment through multiple informants [108]; integrating objective stress measures; or accessing medical record information for participants' health, mental health, and birth outcomes. The generalizability of the results stemming from this study will also be limited to English-speaking US residents and citizens.

Overall, the Experiences of Pregnancy study will help improve our understanding of risk and protection factors for perinatal distress, as well as how different factors interact with each other to predict mental health and well-being. In turn, this can help inform efforts aiming to reduce the high prevalence rates of mental health problems during the perinatal period.

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Data Availability

The data sets generated during this study are not publicly available as this study is not completed. Data will be available from the corresponding author on reasonable request upon conclusion of the study.

Authors' Contributions

CR conceptualized the study. All authors contributed to the design of the study. CR, DCF, and PNH programmed the study questionnaires. CR, DCF, JLL, MEA, KKL, and MTD are contributing to the investigation process through participant recruitment. CR, PNH, and NTM prepared visualizations and figures for the study and this paper. CR wrote the initial draft. All authors reviewed and edited the paper. CR provided resources, supervised the research team, and coordinated the project.

Conflicts of Interest

None declared.

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Abbreviations

AI: artificial intelligence
FIML: full information maximum likelihood
MAR: missing at random
PA: proportion affected
PoI: proportion of interaction
RA: research assistant
REDCap: Research Electronic Data Capture

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Protocol

Investigating the Culture Around Sexual Harassment in First-Generation Universities in Southwestern Nigeria: Protocol for a Mixed Methods Study

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Abstract

Background: The phenomenon of sexual harassment (SH) is a complex issue with multiple prongs that concerns all members of academia and raises serious challenges, particularly regarding prevention and response. SH in tertiary institutions remains a huge problem worldwide, leading to severe emotional, academic, and career difficulties, as well as undue suffering. Institutions have responded in various ways to alleviate the burden of SH with little success, especially in Nigeria. The prevalence is high but reportage is low because of the culture of silence around SH in most educational institutions. This study aims to identify factors associated with SH in tertiary institutions in Nigeria and explore factors surrounding reportage or nonreportage following the experience of SH, the institutional mechanisms to prevent and respond to SH, and the lived experience of survivors of SH.

Objective: The objective of this study was to present a study protocol that is designed to identify factors associated with the experience of SH in tertiary institutions in Nigeria, the institutional mechanisms to prevent and respond to SH, and the lived experience of survivors of SH.

Methods: A mixed (quantitative and qualitative) methods approach is used consisting of a policy review of existing antisexual harassment policies in the selected universities, a quantitative survey to determine the correlates of SH, focus group discussions to explore the perspectives of the university community concerning SH, in-depth interviews to explore the lived experiences of survivors of SH, and key informant interviews to understand the perspectives of people who provide interventions to survivors.

Results: This study was funded in July 2022 by the Consortium for Advanced Research Training in Africa, and data collection started in November 2022. The SH policies were comprehensive, with clear policy statements and definitions, and recognized a wide range of survivors and perpetrators. However, there was no clear mention of prevention and response to same-sex SH. Lived experiences showed negative psychological and social sequelae and little institutional support.

Conclusions: This is the first study that has a component investigating same-sex SH in tertiary institutions in Nigeria. This is also one of the first studies to explore the lived experiences of survivors of SH in Nigerian universities. The findings from this study suggest that periodic evaluation of SH policy implementation will improve institutional support, thus creating safe spaces for survivors and will thereby encourage reportage and support; prevention and response strategies need to be more inclusive; and more interventions should focus on strengthening prosocial skills and healthy, equitable relationships.

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KEYWORDS

protocol; sexual harassment; SH; universities; support; institutions; Nigeria

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Introduction

Background

Sexual harassment (SH) in educational institutions remains a pervasive problem, and the institutional climate is still the best predictor of the occurrence of SH [1]. SH is not easy to define, partly because it does not involve a homogenous set of behaviors [2]. However, it includes requests for sexual favors and verbal or physical sexual activities in exchange for using or awarding academic marks [3]. When the advances are rejected, a hostile learning environment is created.

There are 2 main types of SH that are recognized in the literature. These include quid pro quo harassment, which is typically exchanging sex for benefits (usually performance or academic favors) or to avoid some detriment (demotion at work or academic failure), and a hostile environment (when speech or conduct creates an intimidating or humiliating environment that negatively affects an individual's academic or job performance) [4]. Till [5] categorized SH as gender harassment when general sexist or offensive remarks and jokes were made, seductive behavior when inappropriate flirting and sexual advances were made without threat of sanctions, sexual bribery when there was a reward for sexual activity, sexual coercion when the conditions of education were contingent upon sexual cooperation, and sexual imposition also known as sexual assault. Although it is usually easy to identify less ambiguous forms of SH (sexual bribery, sexual coercion, and sexual imposition), it is more difficult to define the more ambiguous forms of SH (gender harassment and seductive behavior), especially gender harassment, which is by far the most prevalent type of SH [1].

The global prevalence of SH in tertiary institutions is high. More than a third of university women in the United Kingdom reported having experienced unwelcome sexual advances (touching, including inappropriate groping) [6]. Nearly 18% of 221 Lebanese women in educational institutions reported being harassed by their professors [7]. In Canada, >80% of the female students surveyed had been sexually harassed in a school setting [8].

In Nigeria, SH came into the limelight through the Cookey Commission panel that was established to address allegations of female students failing examinations for reasons not based on their scholastic abilities [9]. The prevalence of SH in tertiary institutions is higher in Nigeria, ranging from 68% to 80% among female participants [10-12]. The wide range of prevalence rates may reflect the use of diverse instruments to measure SH.

Survivors and perpetrators of SH can be lecturers, students, administrative staff, and any gender [13], although more women than men experience SH and more men than women are likely to be perpetrators [1,8,14]. There are also cases of same-sex SH in tertiary institutions [15], although this experience is less explored. It must be noted that more studies have focused on female students as survivors and men as perpetrators [16,17].

Macrolevel factors for SH range from weak educational systems; low levels of institutional accountability; high population levels of poverty; gender inequality; and poorly trained, underpaid, and understaffed educators [18]. Factors that have been linked to SH in Nigerian universities include contextual societal factors such as gender stereotypes, oppression of women, the patriarchal construct of manhood, the patriarchal configuration of many African societies, communal pressure to secrecy, and the lack of specific policies that address the problem of SH [11,19].

Indecent dressing has been cited in the Nigerian literature as a factor in whether an individual will experience SH or not. This often leads to "victim-blaming." A common recommendation in the literature is the propriety of dressing for females as a means to prevent SH [12,20-25]. However, confounding factors such as a high sex drive of individual perpetrators have not been fully investigated in this setting [26].

SH in tertiary institutions is a huge concern because of its associated adverse effects [1] such as suboptimal academic fulfillment and withdrawal from academic activities [27,28]; psychological distress with symptoms of depression, stress and anxiety, self-blame, lowered self-esteem, and generally impaired psychological well-being [29-32]; and physical health issues such as headaches, exhaustion, sleep problems, gastric problems, nausea, respiratory complaints, musculoskeletal pain, and weight loss or gain [33,34].

It is known that because of the complexity of SH, the timing, duration, and severity of these effects will vary depending on the individuals affected. Adverse effects are found with gender harassment (the most common) as well as unwanted sexual attention and sexual coercion [35]. These adverse effects seem to be worse when SH is committed by a superior than when committed by peers [36], but it is established that individual reactions vary greatly [37].

SH in colleges and universities is grossly underreported [2]. Survivors rarely report their SH experiences. This is often because of unequal power relations; the fear of loss of status, marks, or job as retaliation; and the associated stigma that it brings [38,39]. Survivors cope with SH in many ways, including by ignoring or appeasing the harasser or seeking social support [1].

The prevalence and associated factors of SH in Nigeria have been investigated [6,7,10,11] but few studies have explored the reasons why SH is underreported and what can be done to improve reporting. In addition, there are no methodical studies on the assertion that indecent dressing is a risk factor for SH [12,20-22], and most studies on SH in Nigeria have focused almost exclusively on heterosexual SH, despite the possible risk of same-sex SH. This study will investigate the culture associated with SH in universities in Nigeria.

This study is based on the integrated conceptualization of SH, founded on the synthesis of the work by Hofstede [40] and Schwartz [41], which explored behaviors directed toward women in different countries and cultures. Luthar and Luthar [42] proposed that the likelihood of experiencing SH perpetrated by men, as well as the tolerance of SH by women, vary between different countries because of the fundamental differences in cultures and values. This study seeks to explore how culture may influence the perception and response to SH experiences in tertiary institutions in Nigeria. However, the study will expand

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its inquiry to explore how the sociocultural context of same-sex relationships may affect the perception and response of people in same-sex relationships who experience SH in tertiary institutions in Nigeria.

This Study

This study aimed to identify factors associated with the experience of SH in tertiary institutions in Nigeria, the institutional mechanisms to prevent and respond to SH, and the lived experiences of survivors of SH; explore how the experiences of SH survivors differ between men and women in heterosexual and same-sex relationships; and interrogate how sociocultural contexts and perceptions about dressing, including institutional practices, may influence the experience and responses of survivors to SH perpetrated in tertiary institutions in Nigeria.

Methods

Research Design

This study used a concurrent mixed methods design that consisted of a policy review, a quantitative survey, focus group discussions (FGDs), in-depth interviews (IDIs), and key informant interviews (KIIs).

Study Sites

The study focused on the experiences of staff and students at tertiary educational institutions in Nigeria. There are >170 universities in Nigeria, of which 79 are privately owned and 43 are funded by the federal government [43]. The study recruited participants from 3 public universities owned by the Federal Government of Nigeria, located in southwest Nigeria. The study focused on public tertiary institutions that have existed for >60 years and have a large student and staff population.

The study was also limited to southwest Nigeria because of the homogeneity in the cultural norms and practices of this region. The 3 institutions selected for this study are in the Yoruba-speaking area of southwest Nigeria. Common ties in the language and practices of the community in which the 3 institutions are located may enhance the use of a sociocultural lens to explore the findings of this study.

Study Population

The target population for this study comprised staff and students of the selected institutions. Study participants were staff or students of the 3 selected universities who were aged >18 years and who gave consent to participate in the study. Staff or students who were severely physically or mentally ill and who lacked the capacity to participate in the study were excluded.

Quantitative Study

Sample Size Determination

The sample size for the survey was computed based on a sample size formula using a margin of error of 2.5%, a confidence level of 95%, and a population estimate of 120,000. The minimum sample per institution was 506 participants and 1518 participants for the study. This was increased to 550 participants per institution to adjust for possible incomplete responses to the questionnaire and to increase the power for subanalyses such as for sex differences. Thus, 1650 participants were surveyed from the 3 institutions using a proportionate sampling technique.

Data Collection Procedures

Overview

The quantitative survey was developed to explore the perceptions of university community members about SH. The survey focused on the experience of and risk indicators for SH (including mental health determinants) and the reporting of cases within the university community. The survey also explored perceptions of the link between dressing and SH. The questionnaire consisted of questions from validated instruments that measure the phenomena of interest. These were (1) the Sexual Experiences Questionnaire (SEQ) to measure the experience of SH, (2) the Administrator - Researcher Campus Climate Collaborative tool to measure the campus climate, (3) the Campus Conduct Survey on Sexual Assault and Sexual Misconduct tool to measure the institutional response, (4) pictures and questionnaire items to assess the tendency to perceive a link between provocative dressing and SH, (5) the Changes in Sexual Functioning Questionnaire to measure sexual desire, (6) the Patient Health Questionnaire-4 (PHQ-4) to measure anxiety and depression, and (7) the Suicidal Behavior Questionnaire-Revised (SBQ-R) to measure suicidal behavior.

SEQ Measure

The SEQ is the most widely used and validated measure of SH to date [44]. It was developed and validated by Fitzgerald et al [45]. The SEQ has been used in different settings and with different population groups over time. It has been noted that the factor structure of the SEQ (gender harassment, unwanted sexual attention, and sexual coercion) has remained stable across time, culture, and the occupational sector, even when there were variations in the specific items assessing each construct with good psychometric properties [46].

Administrator - Researcher Campus Climate Collaborative Tool

The Administrator - Researcher Campus Climate Collaborative tool is the result of collaborative efforts by students, legal affairs professionals, campus advocates, campus law enforcement, and sexual assault and harassment researchers [47]. The tool is organized into different modules that allow researchers to determine the length and content of their surveys. They include modules on possible outcomes (which encompasses a standardized 4-item measure of depression and anxiety [PHQ-4]), demographics, campus safety, SH by students and staff (which used questions from the SEQ), and institutional response [46]. All the measures mentioned above were used in this study.

Campus Conduct Survey on Sexual Assault and Sexual Misconduct

The Campus Conduct Survey on Sexual Assault and Sexual Misconduct is a survey questionnaire developed by the Association of American Universities [48]. This questionnaire assessed students' perceptions of experiencing sexual assault

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or sexual misconduct and their perceptions of institutional response to reporting.

The Provocativeness of Dressing

The sexual provocativeness of dressing was assessed by presenting the research participants with 4 pictures, comprising 2 each of a male and a female dressed provocatively and nonprovocatively. Each respondent was shown each of the 4 pictures separately and asked a series of questions concerning them. A total of 2 pictures were shown, each for males and females, respectively. There was 1 picture per sex that depicted a nonprovocative dressing and a sexually provocative dressing. The pictures were taken by a professional photographer using the same background and similar postures as the models. The faces of the models were pixelated to ensure anonymity. The participants were asked to rate the 4 pictures for sexual provocativeness of dressing on a 7-point Likert scale ranging from 1 (not provocative at all) to 7 (extremely provocative) [49,50]. The participants were further asked to indicate the extent to which they expected the individual in the picture to experience SH. This was assessed with the single-item question scored on a Likert scale, such as "How likely is the person in the photograph to be sexually harassed?" (7=likely and 1=not likely).

A pilot study was conducted among 70 students of the Obafemi Awolowo University who were not included in the main study to select the pictures to be used for assessing the sexual provocativeness of dressing. These were selected as follows: 6 pictures each of male and female models in different forms of dressing were taken by a professional photographer with a similar background. The faces of the models were pixelated to ensure anonymity. Each picture was graded based on the level of sexual provocativeness of the dressing on a Likert scale ranging from 1 (not provocative at all) to 7 (extremely provocative). A total of 4 pictures labeled the most provocative and least provocative, 2 each for both males and females were then used in the main study.

Using questions adapted from Moor [51], participants' perceptions about the motivation of people for wearing provocative clothing as well as their reaction to people wearing such clothing items, were assessed. Participants were instructed to rate motivations for wearing provocative clothes by indicating how much they agreed with 10 statements such as "they wish to feel attractive" or "they intend to convey an interest in sex," on a 5-point Likert scale from 1 (strongly disagree) to 5 (strongly agree). Participants were also asked about their own customary style of dress and their own motivations for that style. Participants were instructed to respond to 7 questions on a 3-point scale (1 indicating "no," 2 "sometimes," and 3 "yes"), such as "Do you dress provocatively in order to feel attractive?" or "Do you dress provocatively to be seductive?"

Furthermore, they were asked about their responses to people who wear what they perceive to be provocative clothing. Items included such questions as "Do you feel that provocatively dressed people are attempting to tempt you?" or "Are you aroused by provocatively dressed people?"

Sexual Desire

Sexual desire was assessed using 6 questions from the Changes in Sexual Functioning Questionnaire [52], which assessed sexual desire and ease of arousal. Each item was rated on a 5-point Likert scale ranging from 1 (never) to 5 (always). Higher scores indicated higher sexual motivation and attribution for personal or others' dressing.

PHQ-4 Questionnaire

The PHQ-4 to measure anxiety and depression [53] is a 4-item self-screening measure that combines the items of the Patient Health Questionnaire-2 and Generalized Anxiety Disorder Scale-2, which both contain the 2 core items of depressive and generalized anxiety disorder symptoms. It is used to assess anxiety and depression. It is scored on a 4-point Likert scale, with responses ranging from 0 ("not at all") to 1 ("several days"), 2 ("more than half of the days"), or 3 ("nearly every day"), with a maximum possible score of 12.

The PHQ-4 compares favorably to the Medical Outcomes Study Short-Form Health Survey subscales in that increasing PHQ-4 scores correlate significantly with declining functional status [53]. It has a high internal consistency, with a Cronbach α of >.80 among the patient population in the United States [53], which compares to a study in Tanzania by Materu et al [54], who reported a Cronbach α of .81. It has good construct validity and has been validated in Germany [55], the United States [56], and Africa [54].

SBQ-R Questionnaire

The SBQ-R is a 4-item self-administered questionnaire designed to assess the lifetime and 1-year history, frequency, and severity of suicidal behaviors [57]. Each item in the SBQ-R scale measures a different dimension of suicidal behavior, and it has been found to be straightforward, brief, and easy for participants to complete [58]. The total score on the SBQ-R ranges from 3 to 18, with higher scores reflecting a greater risk of suicidal behavior. The questionnaire exhibited a sensitivity of 80% and a specificity of 91% at a cutoff point of 8 in a sample of adult American psychiatric inpatients [58]. In Nigeria, the questionnaire has been shown to be a valid and reliable suicide risk assessment tool among adolescents and young adults, with a cutoff point of 8 [59].

The data were collected using a secured web-based platform—Google Docs platform. Study participants who were recruited had the option of self-administering the questionnaire using a shared link or using a tablet operated by research assistants (RAs). Students and staff in each institution were categorized by faculties into 3 clusters: Science, Social science, and Arts. In total, 5 Departments were randomly selected from the faculties in each faculty cluster using a ballot. The RAs attended the lecture halls of the selected departments and approached the students. The RAs ensured that all the levels in any chosen department were represented. In addition, links were shared when more than 1 participant was eligible to fill out the questionnaire at the same time. Informed consent was obtained verbally before sending links to the participants, which was also the first question on the web-based questionnaire page.

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Data Analyses

All quantitative data were coded and entered into SPSS (version 20; IBM Corp) for descriptive analyses. All continuous variables were expressed as means (SD), and categorical variables were summarized using frequencies and percentages. Bivariate and multivariate regression analyses with SH as the outcome variable were used to investigate the relationships between the predictors and SH, as stated in the objectives of the study. Bivariate and multivariate regression analyses with the likelihood of SH as the outcome variable and sociodemographic characteristics, dressing perception, and sex drive as the predictors were performed. For all quantitative analyses, we repeated the analyses with male and female participants to test for sex differences. Differences in sex and sexual orientation were investigated at all levels of the analyses. A P value of <.05 was considered statistically significant.

Qualitative Study

Sample Size and Technique

This had two levels:

1. Desk review: a purposive sampling approach was adopted to identify, screen, and select policy documents on SH across the 3 institutions. All the documents were analyzed based on their contents.
2. IDIs, KIIs, and FGDs: participants were recruited for the interviews and the FGDs. Purposive sampling was adopted to identify and recruit key informants from the Directorate of Student Affairs and from members of the antisexual harassment and disciplinary committees in each of the 3 universities. A total of 5 KIIs were conducted in each institution. Both students and staff who had survived SH were targeted for the IDIs. Recruitment was conducted through interactions with the core units of each university, such as the Directorate of Student Affairs, the security unit, the personnel unit, and nongovernmental organizations that have had interactions with SH survivors across the 3 universities. The recruitment and interview processes ensured privacy, confidentiality, and the freedom to share experiences without reservation. In total, 4 IDIs were conducted in each institution. The medium for conducting the interviews (face-to-face, through telephone, or through video calls) was chosen by the study participants.

The FGD participants were randomly selected through multiple calls on identified portals for students and staff at the targeted universities to join a FGD on SH. Participants were chosen based on their consent to participate. Equal gender representation was prioritized. The sample size for the FGDs ranged from 6 to 10 participants per session. A total of 2 student and 1 staff FGD session were held per university.

Data Collection Procedures

IDIs, KIIs, and FGDs: The IDIs focused on the experience of SH from the perspective of the survivor, the consequences, whether it was reported, the outcomes, and how the survivor felt about the outcome. The KIIs focused on the perceptions of counselors, SH committee members, and student and faculty on disciplinary committees on SH, institutional response, their experiences, and issues around vicarious trauma. The FGDs were conducted to explore the university community's perception of SH, its determinants, and how it can be prevented. The focus was also on how dressing is related to SH and the perceptions around same-sex SH.

Data Analysis

Desk review consisted of a content analysis of existing SH policies in the 3 selected universities, conducted between September 2022 and February 2023. Common themes and areas of divergence will be highlighted. In addition, the analysis attempted to determine how well the policies aligned with global best practices in the SH field. This was performed by the principal investigator (PI) and coinvestigators.

Analysis of the IDIs, the KIIs, and the FGDs commenced with verbatim transcription of the audio recordings to a Word (Microsoft Corporation) document to avoid misrepresentation and minimize bias. The accuracy, integrity, and completeness of all transcriptions were verified by the PI and coinvestigators by passing them through a 2-level proofreading. At each level, the recordings were listened to and read along with the typed transcripts, ensuring that all discrepancies were corrected. Then, a thematic analysis was conducted, all transcripts were coded by 3 experts, areas of divergence were resolved, and the analysis was managed using NVivo 12 Pro (QSR International). The interviews and the FGDs were synthesized and presented under subheadings to answer the research questions.

Data Management and Storage

The data collected using web-based surveys was stored on a secure, password-protected laptop. The audio recordings were destroyed immediately after transcription, and deidentified transcripts were saved on a password-protected computer that only the PI, coinvestigator, and statistician had access to. An external hard drive was used as the backup and was stored using a password. The transcripts were shared only with the other members of the research team.

Ethical Considerations

The research protocol was submitted for ethical review, and approval was received from the Institute of Public Health Research Ethics Committee (IPH/OAU/12/2028), Obafemi Awolowo University, the University of Ibadan Health Research Ethics Committee (UI/EC/22/0313), and the University of Lagos Health Research Ethics Committee (CMUL/HREC/08/22/1082). Written consent was obtained from the participants. Ethics approval at all 3 institutions was obtained between August and September 2022. Preliminary meetings with stakeholders across the 3 universities took place between September and October 2022. Training for the RAs took place in September 2022. Confidentiality was ensured and psychological first aid was offered to interview participants. Furthermore, referrals for therapy were offered to participants who exhibited or reported distress, although none of them took up the offer.

Knowledge Dissemination

The findings of the project will be summarized and disseminated through the development of institution-specific policy briefs detailing SH issues revealed during the study, which will be

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given to each institution during a dissemination meeting with recommendations on how to improve prevention and response to SH. In addition, findings from the study will be shared with the scientific community through the presentation of papers at regional or international conference(s) and the publication of scientific papers in peer-reviewed journals. The findings will also be shared with the general public on the project website.

Results

This study was funded in July 2022 by the Consortium for Advanced Research Training in Africa, and data collection started in November 2022. Ethical approval at all 3 institutions was obtained between August and September 2022. Preliminary meetings with stakeholders across the 3 universities took place between September and October 2022. Training for the RAs took place in September 2022. Content analysis of the antisexual harassment policies of the 3 selected universities took place between September 2022 and February 2023. Recruitment and data collection for both the quantitative survey and the qualitative study took place concurrently between November 2022 and February 2023.

The data from the IDIs has been developed into a manuscript titled "Stifled screams: experiences of survivors of SH in first-generation southwestern Nigerian universities," which has been published in the *Social Sciences* (Multidisciplinary Digital Publishing Institute).

The SH policies were comprehensive with clear policy statements and definitions, and recognized a wide range of survivors and perpetrators. However, there was no clear mention of the prevention and response to same-sex SH. The forms of SH experienced ranged from physical touch to assault, attempted rape, and rape. The locations of the incidents included the perpetrator's abode, office, lecture theater, library, and a party. Survivors used several coping mechanisms, including talking with peers, joining social clubs, and heavy drinking. Consequences included not trusting others, blaming themselves, and feeling sad, suicidal, angry, and guilty.

The data analysis for the quantitative survey is ongoing. Dissemination meetings for the selected universities, presentations at scientific conferences, and subsequent publications in peer-reviewed journals are expected to be completed before the end of 2023.

Discussion

Principal Findings

To our knowledge, this is the first study that has a component investigating same-sex SH in tertiary institutions in Nigeria. It is also one of the first studies to explore the lived experiences of survivors of SH in Nigerian universities. This study hypothesizes that there will be a high prevalence of SH in the selected institutions; however, there will be underreportage of SH, and many students will find the institutional measures inadequate to curb SH. Globally, most studies have shown mixed results on the prevalence of SH in tertiary institutions [10,60-65]. Numerous studies have shown that both males and females are survivors of SH, although females are more affected [66,67]. Factors that influence nonreportage among students include shame, fear of retribution by the lecturer, and godfatherism, among others [38,39,68]. There has been extensive research regarding dressing and SH [12,20-25,51], with mixed results; some studies found that provocative dressing increased the likelihood of an individual being sexually harassed [69,70].

Although the 3 universities have antisexual harassment policies, reports of SH still appear in the news from these universities [60-62] signifying that the existence of SH policies is not enough to curb SH. It is hoped that the dissemination of content analysis will emphasize the need to supervise the implementation of institutional SH policies to improve prevention and response. In addition, the reports from lived experiences highlighted survivors' experiences of SH, the mental health consequences, how they have coped, the responses from their institutions, and barriers to reporting both to the institutions and law enforcement agencies. It has been shown that the lived experiences of survivors can be a powerful tool for advocacy and action in the response to SH [66]. The survey focused on the prevalence and correlates of SH, focusing on gender differences and differentiating between same-sex and heterosexual SH. It also examined the campus climate and how it influenced the experience of SH for the campus community.

Limitations

One of the limitations of this study is that the quantitative aspect is cross-sectional and cannot be used to determine causality. The qualitative aspect of the study regarding the lived experiences of survivors is retrospective in nature and may be subject to recall bias.

Conclusions

It is hoped that the findings from this study will improve our understanding of the factors that drive SH among staff and students in tertiary education institutions in Nigeria and the risks susceptible populations face. This information will help with the design and implementation of policies and programs that can reduce the risk of susceptible populations to SH, in view of the long-term and or lifetime mental health consequences and social effects of SH on survivors and improve reportage among survivors. Future research needs to focus on contextualized interventions for the prevention and response to SH in tertiary institutions.

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Data Availability

The data sets generated during this study are available from the corresponding author upon reasonable request.

Authors' Contributions

BM, IO, and OO contributed to the conceptualization, literature review, and design of the study, as well as discussions and drafting of the manuscript. BM, IO, and OO assisted with the revision and drafting of the manuscript. AH provided further revision and supervision of the project. BM received funding for the article processing charges. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

FGD: focus group discussion
IDI: in-depth interview
KII: key informant interview
PHQ-4: Patient Health Questionnaire-4
PI: principal investigator
RA: research assistant
SBQ-R: Suicidal Behavior Questionnaire-Revised
SEQ: Sexual Experiences Questionnaire
SH: sexual harassment

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Protocol

Effects of Episodic Food Insecurity on Psychological and Physiological Responses in African American Women With Obesity (RESPONSES): Protocol for a Longitudinal Observational Cohort Study

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Abstract

Background: Food insecurity is a risk factor for multiple chronic diseases, including obesity. Importantly, both food insecurity and obesity are more prevalent in African American women than in other groups. Furthermore, food insecurity is considered a *cyclic phenomenon*, with episodes of food adequacy (ie, enough food to eat) and food shortage (ie, not enough food to eat). More research is needed to better understand why food insecurity is linked to obesity, including acknowledging the episodic nature of food insecurity as a stressor and identifying underlying mechanisms.

Objective: The objective of this study is to investigate the episodic nature of food insecurity as a stressor via responses in body weight and psychological and physiological parameters longitudinally and do so in a health-disparate population—African American women.

Methods: We enrolled 60 African American women (food-insecure cohort: n=30, 50%; food-secure cohort: n=30, 50%) aged 18-65 years with obesity (BMI 30-50 kg/m^2) to measure (1) daily body weight remotely over 22 weeks and (2) psychological and physiological parameters via clinic assessments at the beginning and end of the 22-week study. Furthermore, we are assessing episodes of food insecurity, stress, hedonic eating, and appetite on a weekly basis. We hypothesize that food-insecure African American women with obesity will demonstrate increased body weight and changes in psychological and physiological end points, whereas food-secure African American women with obesity will not. We are also examining associations between changes in psychological and physiological parameters and changes in body weight and performing a mediation analysis on the psychological parameters assessed at the study midpoint. Psychological questionnaires are used to assess stress; executive function, decision-making, and motivation; and affect and nonhomeostatic eating. Physiological measurements are used to evaluate the levels of cortisol, dehydroepiandrosterone-sulfate (DHEA-S), C-reactive protein, thyroid hormones, blood glucose, glycated hemoglobin, and insulin, as well as allostatic load.

Results: This study has completed participant recruitment (n=60). At the time of study enrollment, the mean age of the participants was almost 47 (SD 10.8) years, and they had a mean BMI of 39.6 (SD 5.31) kg/m^2. All data are anticipated to be collected by the end of 2023.

Conclusions: We believe that this is the first study to examine changes in body weight and psychological and physiological factors in food-insecure African American women with obesity. This study has significant public health implications because it addresses the cyclic nature of food insecurity to identify underlying mechanisms that can be targeted to mitigate the adverse relationship between food insecurity and obesity and reduce health disparities in minority populations.

Trial Registration: ClinicalTrials.gov NCT05076487; https://clinicaltrials.gov/study/NCT05076487

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International Registered Report Identifier (IRRID): DERR1-10.2196/52193

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KEYWORDS

food security; body weight; racially minoritized group; low income; stress; cortisol; allostatic load

Introduction

Background

Food insecurity, or the lack of sufficient food in both quality and quantity for an active and healthy life, is a prevalent public health concern in the United States, with >10% of households reporting food insecurity in 2021 [1,2]. Experiencing food insecurity can lead to adverse chronic health effects, including an increased risk of cardiovascular disease [3-7], type 2 diabetes [7-9], and mortality [10-12]. These associations are important considering chronic disease prevalence among American adults, including >9% with diabetes [13], approximately 33% with hypertension, and another 33% with prehypertension [14]. Because of this, health care spending in the United States is greater in food-insecure adults than in those who are food secure [15].

Food insecurity is linked to poor diet quality [16-19], maladaptive eating behaviors [20-22], and weight gain [23]. Importantly, food insecurity is linked to greater body weight and adiposity among American adults [24-27], with this relationship being the most unequivocal in women [27,28]. The burden of obesity is disparate across population subgroups. By 2030, severe obesity will become the most common BMI category among women, non-Hispanic African American adults, and adults with low income in the United States [29]. Both food insecurity and obesity are more prevalent in African American women than in other racial and ethnic and biological sex groups [30,31]. The prevalence of obesity has been shown to be almost 50% greater in African American women with food insecurity (52.1%) than in White women with food insecurity (26.5%) [32]. These data highlight African American women as a health-disparate population when considering the food insecurity–obesity linkage.

Research on the episodic nature of food insecurity, which is largely understudied in the literature (yet broadly hypothesized), may help elucidate its association with greater body weight (ie, obesity). Most studies that associate food insecurity and obesity are cross-sectional studies [24-28], which is a major limitation, given that food insecurity is considered a *cyclic phenomenon*, with episodes of food adequacy and food shortage [24,33,34]. Those who are food insecure may experience periods when food is more readily available and overconsume during this time, as well as periods of food scarcity that cause restricted food consumption [33,35,36]; for example, the largest federal nutrition assistance program, Supplemental Nutrition Assistance Program (SNAP), provides monthly benefits that are typically dispensed within the first 2 weeks of a month. Given this, food-insecure households may experience food availability in the first weeks of a month and overeat during this time, followed by food scarcity in the latter weeks of the month and constrained food consumption until the beginning of a new month [24,34,35]. Further evidence shows that soup kitchens see an increase in meals served toward the end of the month [37]. This highlights the need for longitudinal studies examining the episodic nature of food insecurity. Furthermore, alternating episodes of food adequacy and food shortage potentially shape body weight response in food-insecure individuals by increasing stress, which has both psychological and physiological manifestations [38].

Stress is a central component in the pathway leading from food insecurity to chronic disease [33,39]. Specifically, "weight gain in food-insecure environments may actually represent a complex network of stress-related reactions" [40]. Experiencing food insecurity can elicit a stress response that leads to the activation of the hypothalamus-pituitary-adrenal (HPA) axis and the release of cortisol [34,41]. Allostasis is the ability to adaptively react to perceived challenges by activating these stress-response processes [42]. Chronic stress and repeated activation of these processes, as brought upon by cycles of food insecurity, can result in maladaptive response, including elevated cortisol levels and higher allostatic load [43]. This has both psychological and physiological costs, leading to increased disease risk [44-46]. Physiological parameters that play a mechanistic role in body weight accretion, such as metabolic and endocrine processes and allostatic load, have not been well assessed in relation to food insecurity. Furthermore, although researchers have found cross-sectional associations between food insecurity and psychological factors, such as poorer cognitive-based decision-making [47,48] and disordered eating [21,22], these associations were not triangulated with body weight. Psychological pathologies and physiological processes may hold insight for elucidating the food insecurity–obesity linkage.

Objectives

The primary objective of the RESPONSES (Effects of Episodic Food Insecurity on Psychological and Physiological *Responses* in African American Women With Obesity) study is to investigate the association between food insecurity as a stressor and obesity in African American women by assessing longitudinal responses in body weight and psychological and physiological parameters.

Methods

Overview of Study Design

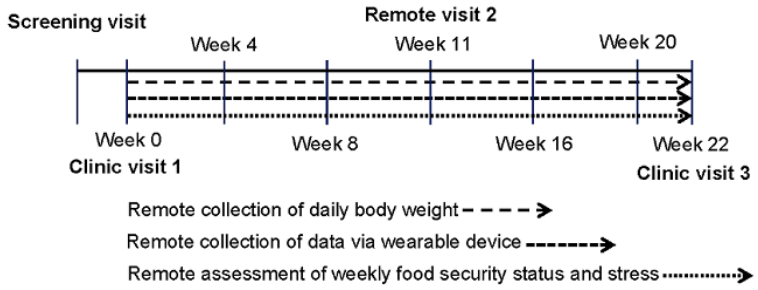
This study is a 22-week longitudinal observation cohort study conducted at Pennington Biomedical Research Center in Baton Rouge, Louisiana. A total of 60 African American women with obesity—30 (50%) who report being food insecure and 30 (50%) who report being food secure at baseline—have been enrolled in the study. Daily body weights are remotely obtained from participants. Wearable devices are also given to participants to wear throughout the duration of the study to collect additional

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data. Weekly food security status and stress assessments are remotely conducted to ascertain episodes of food insecurity and self-reported stress. Psychological and physiological parameters are measured at the beginning (week 0 at clinic visit 1) and conclusion (week 22 at clinic visit 3) of the study. There is also a midpoint remote assessment of selected psychological parameters (week 11 at remote visit 2). Figure 1 presents the RESPONSES study design and timeline.

The study was registered at ClinicalTrials.gov (NCT05076487) on September 30, 2021.

Figure 1. RESPONSES (Effects of Episodic Food Insecurity on Psychological and Physiological Responses in African American Women With Obesity) study design and timeline.



Aims

The RESPONSES study will address the following aims.

- Aim 1: the study will longitudinally assess body weight in addition to psychological and physiological parameters in food-insecure and food-secure African American women with obesity. Body weight is collected to assess the change from week 0 to week 22. Psychological parameters (stress; executive function, decision-making, and motivation; and affect and nonhomeostatic eating) are measured via validated questionnaires. Physiological parameters are measured via 24-hour urine (cortisol) and blood (dehydroepiandrosterone-sulfate [DHEA-S], C-reactive protein [CRP], thyroid hormones, blood glucose, glycated hemoglobin, and insulin) samples as well as an allostatic load total score. These parameters are measured at week 0 and week 22 to examine changes in psychological and physiological mechanisms. We hypothesize that food-insecure African American women with obesity will demonstrate increased body weight and changes in psychological and physiological parameters consistent with elevated stress over 22 weeks compared with food-secure African American women with obesity.
- Aim 2: the study will examine associations between changes in body weight and psychological and physiological parameters in food-insecure and food-secure African American women with obesity. We are examining associations between (1) change in body weight collected over 22 weeks and change in psychological and physiological parameters collected 22 weeks apart and (2) changes in psychological and physiological parameters.
- Exploratory aim: the study will longitudinally examine cyclic patterns in body weight, food insecurity, and stress in food-insecure and food-secure African American women with obesity. Body weight is collected daily to assess average weekly change. Food insecurity and stress are assessed weekly via questionnaires. We are examining weekly patterns of body weight, food insecurity, and stress to determine how changes in body weight are related to episodes of food insecurity and stress. Finally, we are assessing mediation analysis of the psychological questionnaires.

Recruitment and Screening

The target sample is 60 food-secure and food-insecure African American women with obesity; participants are enrolled 1 (food-insecure cohort: n=30, 50%) to 1 (food-secure cohort: n=30, 50%) for an equal number of food-insecure and food-secure participants (1:1) with reported income ≤250% of the federal poverty level. Participants are being recruited from the Greater Baton Rouge, Louisiana, area in designated community locations by trained study staff who assess each prospective participant's potential eligibility and interest in participating in the study. Community-based recruitment allows for engagement with potential participants in a setting that is familiar and comfortable. Recruitment sites include partnering food pantries, local YMCAs, and other community centers. Community recruitment efforts include, but are not limited to, flyers, presentations, health fairs, and attendance at site-specific community events. Additional recruitment efforts include email blasts, social media posts, and newsletters.

For prescreening, investigators at Pennington Biomedical Research Center use a telephone screener and/or an initial web screener to determine whether potential participants meet basic eligibility criteria. Study staff follow up with potential participants via telephone call to schedule a screening visit to determine eligibility. Ridesharing (eg, Uber and Lyft) is offered to all participants to travel to and from all clinic visits. During the screening visit, potential participants provide written informed consent before the collection of measurements.

Eligibility is assessed using the criteria presented in Textbox 1 (if eligible, participants are enrolled into the study).

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Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Willing to provide written informed consent
- Female
- Self-reported race of African American or >1 race in which African American is identified
- Aged 18 to 65 y
- BMI 30 to 50 kg/m^2 (inclusive)
- Reported income ≤250% of the federal poverty level
- Ability to complete questionnaires in English
- Willing to archive blood and urine samples
- Willing to fast for a minimum of 8 to 10 h before clinic visits

Exclusion criteria

- Male
- Self-reported race other than African American or >1 race in which African American is not identified
- Reported income >250% of the federal poverty level
- Given birth within the past 6 mo, currently pregnant, or plans to become pregnant within 6 mo
- Currently breastfeeding
- Currently participating in a weight loss program
- Current use of prescription or over-the-counter medication specifically for weight loss
- Recent weight loss (+5% to −5% weight change in last 6 mo by self-report; if participant is on a prescription medication that impacts weight but meets weight stability criteria [+5% to −5% weight change in last 6 mo by self-report], participant will be deemed eligible)
- Past bariatric surgery or plans for bariatric surgery within 3 mo
- Active cancer or cancer treatment
- Serious digestive disorders that significantly alter metabolism and weight (such as uncontrolled inflammatory bowel disease)
- Current diagnosis of, and active treatment for, alcoholism or other illicit drugs of abuse
- Uncontrolled significant thyroid disorder
- Uncontrolled significant diabetes (fasting blood glucose level >250 mg/dL) or hypertension (blood pressure >180/100 mm Hg)
- Current diagnosis of, or treatment for, heart failure
- Serious psychiatric illness, including bipolar disorder and schizophrenia
- Current or recent diagnosis (within last 5 y) of an eating disorder
- Persons who weigh >380 pounds (172 kg; due to scale requirements)
- Not willing to be recontacted
- Are unable to use devices and applications as required for study participation
- Have another member of the household (same address) who is a participant in the study
- Other conditions that affect metabolism or body weight as determined by the principal investigators and medical investigator
- Presence of any cognitive, psychiatric, behavioral, or medical disorder that, in the opinion of the principal investigators or medical investigator may interfere with study participation

Outcome Measures and Study Procedures

Overview

The primary outcome of the RESPONSES study is the change in *body weight*. The secondary outcomes include *psychological parameters* (stress; executive function, decision-making, and motivation; and affect and nonhomeostatic eating measured via psychological questionnaires) and *physiological parameters* (cortisol, DHEA-S, CRP, thyroid hormones [thyroid-stimulating hormone, free tri-iodothyronine, and free thyroxine], blood glucose, glycated hemoglobin, and insulin levels measured via blood and urine samples, as well as an allostatic load total score). Table 1 summarizes the data collection schedule of study procedures.

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Table 1. Schedule of RESPONSES (Effects of Episodic Food Insecurity on Psychological and Physiological Responses in African American Women With Obesity) study procedures.

Study procedure	Screening visit	Clinic visit 1 (week 0)	Remote visit 2 (week 11)	Clinic visit 3 (week 22)
Informed consent and HIPAA[a] authorization	✓			
Health questionnaire and medical history	✓			
Medication inventory	✓			
Anthropometrics				
Height	✓			
Weight	✓	✓		✓
Waist and hip circumference	✓	✓		✓
Bioelectrical impedance analysis	✓	✓		✓
Blood pressure	✓	✓		✓
Pulse	✓	✓		✓
Metabolic or endocrine markers				
Fasting blood sample	✓	✓		✓
24-h urine collection		✓		✓
Questionnaires				
Health literacy	✓			
Food security status	✓	✓	✓	✓
Food assistance	✓	✓	✓	✓
Sociodemographics	✓	✓	✓	✓
Dietary quality		✓		✓
Psychological questionnaires[b]		✓	✓[c]	✓

[a]HIPAA: Health Insurance Portability and Accountability Act.

[b]A complete list of psychological and physiological parameters and corresponding questionnaires and measures is presented in Textbox 2.

[c]Excluding International Physical Activity Questionnaire–Long Form, Pittsburgh Sleep Quality Index, and Food Craving Inventory.

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Textbox 2. Psychological and physiological parameters assessed in the RESPONSES (Effects of Episodic Food Insecurity on Psychological and Physiological Responses in African American Women With Obesity) study.

Psychological parameters and questionnaires

- Stress
  - Perceived Stress Scale (PSS): PSS-10 (clinic visits) and PSS-4 (weekly remote assessment)
- Subjective social status
  - MacArthur Scale of Subjective Social Status
- Executive function
  - Delay discounting: Kirby 27-item Monetary Choice Questionnaire
- Decision-making
  - Grit: 8-item Short Grit Scale
  - Future time orientation: Zimbardo Time Perspective Inventory, Consideration of Future Consequences Scale-14
  - Financial planning
  - Longevity
- Motivation
  - Retrospective Visual Analog Scale
- Affect
  - Positive and Negative Affect Schedule
- Psychological distress
  - 6-item Kessler Psychological Distress Scale
- Nonhomeostatic eating
  - Food craving: Food Craving Inventory (trait) and Food Craving Questionnaire-State
  - Eating disorder: Eating Disorder Diagnostic Scale
  - Food addiction: Yale Food Addiction Scale
  - Restraint, disinhibition, and hunger: Eating Inventory and Power of Food Scale
- Well-being
  - Patient-Reported Outcomes Measurement Information System-43
- Physical activity
  - International Physical Activity Questionnaire–Long Form
- Sleep
  - Pittsburgh Sleep Quality Index

Physiological parameters and measures and assessments

- Stress
  - Cortisol: 24-h urine collection
  - Dehydroepiandrosterone-sulfate (DHEA-S): fasting blood sample
- Metabolic or endocrine marker
  - C-reactive protein, thyroid-stimulating hormone, free tri-iodothyronine, free thyroxine, blood glucose, glycated hemoglobin, and insulin levels: fasting blood sample
- Allostatic load total score

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- Cardiovascular health: systolic blood pressure, diastolic blood pressure, pulse, high-density lipoprotein, and total cholesterol levels
- Metabolic markers: albumin levels, waist to hip ratio, and glycated hemoglobin levels
- Immune markers: C-reactive protein levels

Screening Visit

All participants undergo a screening visit to determine eligibility. At the screening visit, medical history information is collected, and medications are assessed. Anthropometrics, including height, weight, waist and hip circumference, and blood pressure, are obtained. Height is measured with a standard stadiometer. Measurements are taken without shoes and recorded to the nearest 0.1 cm. For screening purposes, a fasting blood sample was obtained to measure blood glucose, triglycerides, and total cholesterol levels, as well as standard clinical indicators of liver and kidney function.

Remote Daily Assessments

Body Weight

Body weight is obtained remotely via scales given to participants to take home and weigh themselves at approximately the same time each day. The scales transmit each participant's body weight data to a secure website to which study staff have access. Participants are given instructions on how to weigh themselves on the scale (eg, flat surface) to obtain accurate data. Ideally, weights are collected in a fasted state. Study staff inspect scale data and contact participants when necessary to ensure compliance with daily weighing.

Wearable Device

A wearable device (Fitbit Sense) is provided to each participant at clinic visit 1 to be worn throughout the duration of the study to collect physical activity, sleep, and other device-specific accessible data. The wearable device is used as a monitoring tool, and data are automatically and wirelessly sent to the Fitbit device database. Participants are trained in how to use the device, including how to sync it and charge it regularly.

Remote Weekly Assessments

Food Security Status

This is assessed via a 2-item food insecurity screener [49,50], which references the previous week, to measure episodes of food insecurity. Weekly food assistance use (eg, SNAP and Special Supplemental Nutrition Program for Women, Infants, and Children benefits, as well as visits to food banks, food pantries, or soup kitchens) and receipt of income from any source (eg, traditional employment and federal financial assistance [Supplemental Security Income, Temporary Assistance for Needy Families, and unemployment benefits]) are also assessed to further augment the assessment of episodic food insecurity.

Self-Reported Stress

This is measured using the Perceived Stress Scale-4 (PSS-4).

Nonhomeostatic Eating

We also assess nonhomeostatic eating in tandem with weekly assessments of food security status and stress by measuring appetitive drive to consume palatable foods in the absence of hunger via the Power of Food Scale (PFS) [51].

Hunger and Fullness

Last, we examine hunger and fullness with 2 questions from the Retrospective Visual Analog Scale [52,53]. These assessments are conducted remotely (eg, via telephone, text, email, or video) on anchor days (eg, Wednesday) for each participant.

Clinic Visits 1 and 3

Anthropometrics

Fasting *weight* is measured using a standard digital scale. Measurements are taken without shoes and recorded to the nearest 0.1 kg. Measures are taken twice and if not within 0.5 kg are taken a third time. BMI is calculated. *Waist* and *hip circumference* are measured using standardized procedures. Waist circumference is taken from the natural waist. This area is midway between the inferior border of the rib cage and the superior aspect of the iliac crest. The hip circumference is measured at the level of the trochanters, which is usually the maximal extension of the buttocks. Both measures are taken twice and if not within 0.5 cm are taken a third time. Average values are calculated for weight, waist circumference, and hip circumference measurements. Body fat and lean mass are assessed using a body composition analyzer and bioelectrical impedance analysis, which is accurate to within 5% of body fat estimation by dual energy x-ray absorptiometry with a reliability of <1% in variation within itself [54]. *Blood pressure* and *pulse* are taken.

Blood Collection

Fasting blood draws are collected. From a chemistry 15 panel, blood glucose, albumin, triglycerides, and cholesterol (total, low-density lipoprotein, and high-density lipoprotein) levels are measured. In addition, DHEA-S, CRP, thyroid-stimulating hormone, free tri-iodothyronine, free thyroxine, and insulin levels are measured.

Urinary Cortisol

Urinary cortisol level is obtained from 24-hour urine collections. Participants are provided instructions, a urine hat, and a urine jug. Participants perform the first 24-hour urine collection within 3 days (ideally within 24-48 h) before clinic visit 1. An immunoassay with chemiluminescent detection is used to determine cortisol concentration from urine.

Allostatic Load

An *allostatic load total score* is calculated from selected clinic assessments described previously [55].

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Textbox 2 presents each psychological and physiological parameter assessed in the RESPONSES study, as well as the relevant questionnaire or metabolic or endocrine assessment used to measure each parameter.

Questionnaires

Health Literacy

The Rapid Estimate of Adult Literacy in Medicine–Short Form (REALM-SF) is used to measure health literacy in participants. This assessment is a standardized series of 7 words. The score (0-7) provides an assessment of how well a participant will be able to understand the additional questionnaires. Participants scoring 0 to 3 on the REALM-SF are aided by study staff in completing the other questionnaires. Patients scoring 4 to 7 on the REALM-SF complete the other questionnaires on their own but are offered assistance as needed.

Food Security Status

This is measured using a modified version of the 6-item Food Security Scale [56,57]. This scale is a well-validated measure of food security developed by researchers at the National Center for Health Statistics. Two or more affirmative answers indicate food insecurity.

Food Assistance

Participants will be asked about their use of federal food assistance (eg, SNAP [food stamps] and Special Supplemental Nutrition Program for Women, Infants, and Children) and other forms of nonfederal food assistance (eg, visits to food pantries and soup kitchens).

Sociodemographics

Participants complete a questionnaire that assesses age (date of birth), race, ethnicity, sex, marital status, the highest level of education completed, annual household income, the number of people in the household, occupation, employment status, home street address (including city and zip code), sources of financial support, dependent status, insurance and health care coverage, and smoking status.

Dietary Quality

A screener that assesses dietary fat, fruit, vegetable, and alcohol intake is completed by participants. The screener contains scales from several sources. The National Cancer Institute fat screener estimates the percentage of energy from fat by asking participants to report the frequency of consuming specific foods over the past 12 months [58,59]. A standard 7-item fruit and vegetable screener developed by the National Cancer Institute and the National 5 a Day Program asks how often fruit and vegetables were consumed in the past month [60,61]. Three questions related to the frequency of alcohol (beer, wine, and hard liquor) intake were adapted from the Brief Questionnaire to Assess Habitual Beverage Intake [62].

Psychological Questionnaires

Participants also complete multiple self-report questionnaires to measure psychological constructs related to stress; executive function, decision-making, and motivation; and affect and nonhomeostatic eating, as well as overall well-being, physical activity, and sleep. All questionnaires are reliable and valid as described in the following subsections.

Perceived Stress Scale

The Perceived Stress Scale-10 (PSS-10) is the most widely used psychological instrument to measure the perception of stress [63]. This questionnaire includes 10 items that measure the degree to which situations in one's life are appraised as stressful. The PSS-4 is a shortened version of the PSS-10 designed for telephone interviews. Items are designed to tap how unpredictable, uncontrollable, and overloaded respondents find their lives. Higher scores on the PSS-10 and PSS-4 indicate greater stress.

Subjective Social Status

This construct indicates one's self-perceived social position in American society and will be measured using the MacArthur Scale of Subjective Social Status [64]. This scale presents a *ladder* and asks participants to select a rung on which they feel they stand compared with other people in the United States. Scores range from 1 to 10, with higher scores representing higher subjective social status.

Kirby 27-Item Monetary Choice Questionnaire

Delay discounting is a bias toward smaller immediate rewards versus larger delayed rewards [65] and will be assessed via the Kirby 27-item Monetary Choice Questionnaire [66]. This questionnaire presents participants with a set of choices between smaller immediate monetary rewards and larger delayed monetary rewards. Participants who discount the value of the delayed rewards more steeply are considered to be more impulsive [66].

8-Item Short Grit Scale

Grit is a measure of trait-level perseverance and passion for long-term goals and will be assessed using the 8-item Short Grit Scale [67]. Scores range from 1 (not at all gritty) to 5 (extremely gritty).

Zimbardo Time Perspective Inventory–Future Scale

Future time perspective is a comprehensive assessment of one's orientation toward the future [47,68]. The *future* scale of the Zimbardo Time Perspective Inventory measures psychological orientation toward the future [69]. This scale comprises 13 statements with Likert-type responses. Higher scores indicate greater future time perspective.

Consideration of Future Consequences Scale

This scale is a valid and reliable 14-item measure of the extent to which a participant considers future outcomes in relation to current behaviors. The measure assesses two subscales—(1) consideration of immediate consequences and (2) consideration of future consequences—to assess the extent to which a participant feels that they may be influenced by an abstract consequence. The participant indicates how much they agree with the statement on a scale from 1 (not at all like you) to 7 (very much like you) [70-72]. Higher scores indicate greater consideration of future consequences.

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Financial Planning

Participants will be asked a single question to assess the time period considered for financial planning: "In planning your, or your family's, saving and spending, which of the following time periods is more important to you and your partner, if you have one?" with the following response options: no planning, day to day, the next few weeks, the next few months, the next year, the next few years, the next 5 to 10 years, longer than 10 years [73,74]. Higher values indicate greater future time perspective.

Longevity

Participants' subjective appraisal of longevity will also be assessed via a single question: "What do you think are the chances you will live to age 75 or more (where 0 means there is not a chance you will live to 75 or more, and 100 means you will definitely live to 75 or more)?" [73,74]. Higher values indicate greater future time perspective.

Retrospective Visual Analog Scale

This scale contains 9 items to measure the average ratings of appetitive sensations that participants experienced over the past week. This method of collecting visual analog scale data has been found to be consistent with daily assessments of satiety [52], and support has been found for the reliability and validity of the visual analog scale for measuring subjective states related to energy intake [53].

Positive and Negative Affect Schedule

This is a self-report measure that is made up of 2 mood scales, 1 measuring positive affect and 1 measuring negative affect [75]. It has 10 items measuring positive affect and 10 items measuring negative affect on a 5-point Likert scale ranging from 1 (very slightly or not at all) to 5 (extremely). Scores can range from 10 to 50 on each scale, with higher scores representing higher levels of positive affect and lower scores representing lower levels of negative affect.

Psychological Distress

The Kessler Psychological Distress Scale (short version) is a 6-item self-report measure of psychological distress [76]. Respondents indicate how often they have had 6 different feelings or experiences during the past 30 days using a 5-point Likert scale: 4 (all of the time), 3 (most of the time), 2 (some of the time), 1 (a little of the time), and 0 (none of the time). The feelings and experiences are the following: *nervous*, *hopeless*, *restless or fidgety*, *so depressed that nothing could cheer you up*, *that everything was an effort*, and *worthless*. The score ranges from 0 to 24, with higher scores indicating greater psychological distress.

Food Craving Inventory

This is a 33-item measure of food craving [77,78] and assesses the frequency with which an individual experiences a craving for a particular food. The measure consists of 5 empirically derived factors: high fats, sweets, carbohydrates and starches, fruits and vegetables, and fast-food fats.

Food Craving Questionnaire-State

This questionnaire was developed to measure state (at the moment) craving for food using 15 items [79]. The reliability and validity of the state version of the Food Craving Questionnaire have been established.

Eating Disorder Diagnostic Scale

This brief scale contains 18 self-report items to assess eating disorder pathology and has been shown to be reliable and valid [80]. This measure can diagnose anorexia nervosa, bulimia nervosa, and binge eating disorder.

Yale Food Addiction Scale

This is a 27-item self-report questionnaire [81] used to identify individuals showing tendencies for addictive-like behaviors toward certain types of foods, such as those high in fat or sugar. The measure also allows participants to subjectively identify specific problem foods.

Eating Inventory

The Three-Factor Eating Inventory is designed to measure different dimensions of eating behavior. Three factor-analyzed subscales (cognitive restraint, disinhibition, and hunger) are derived from the questionnaire [82]. The 51-item questionnaire is divided into 2 parts: part I is composed of 36 true-false items, and part II is composed of 15 rating scale items.

Power of Food Survey

The PFS measures loss-of-control, or nonhomeostatic, eating. The PFS comprises 15 items that use a 5-point Likert scale to assess the intensity of desire to consume delicious food when not hungry [51]. Higher scores indicate greater hedonic hunger.

Patient-Reported Outcomes Measurement Information System-43

The Patient-Reported Outcomes Measurement Information System (PROMIS) is a system of highly reliable and precise measures of patient-reported health status for physical, mental, and social well-being [83,84]. The PROMIS-43 is a 43-item health-related quality-of-life questionnaire that includes questions covering the health-related domains of physical function, anxiety, depression, fatigue, sleep disturbance, ability to participate in social roles and activities, pain interference, and pain intensity.

International Physical Activity Questionnaire–Long Form

This is a 7-day recall of the intensity of physical activity and has acceptable reliability [85]. The results are reported as a continuous measure in median metabolic equivalent of task minutes per week.

Pittsburgh Sleep Quality Index

This is a self-rated questionnaire to assess sleep quality and disturbance over a 1-month time interval [86]. A total of 19 individual items generate 7 *component* scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, the use of sleeping medication, and daytime dysfunction. The sum of the scores for these 7 components yields 1 global score. Acceptable measures of internal homogeneity, consistency (test-retest reliability), and validity have been obtained [86].

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Resource Packet

Given the focus on women who experience food insecurity, a resource packet was developed for the RESPONSES study that identifies community resources and services available to participants who may face resource deficits that compromise their overall health. Importantly, participants may identify multiple resource deficits beyond food insecurity during their participation in the study. The resource packet includes relevant community resources and services that address a range of health-related issues and concerns, including food insecurity, medical and dental care, mental health, substance abuse, and domestic violence. The resource packet is given to all participants regardless of study completion or food security status.

Management of Study Data

Portions of RESPONSES study data are collected and managed using Research Electronic Data Capture (REDCap; Vanderbilt University) hosted at Pennington Biomedical Research Center. REDCap is a secure Health Insurance Portability and Accountability Act–compliant web-based application designed to support data capture for research studies, providing (1) an intuitive interface for validated data entry, (2) audit trails for tracking data manipulation and export procedures, (3) automated export procedures for seamless data downloads to common statistical packages, and (4) procedures for importing data from external sources [87].

Sample Size and Statistical Power

Change in body weight was used to compute a minimum sample size for at least 80% power to examine response to episodic food insecurity longitudinally in African American women with obesity. Specifically, the power analysis is based on a study by Wilde and Peterman [23], which used nationally representative data to examine change in body weight over a 1-year period by food security status in women and men. We chose these data on body weight because we expect this measure to be responsive to episodic food insecurity. Wilde and Peterman [23] found that food-secure women had a 10.4% chance of gaining between 2.27 kg and 4.54 kg and a 20.7% chance of gaining >4.54 kg during a 1-year period. Food-insecure women had a 13% chance and a 31.7% chance of gaining between 2.27 kg and 4.54 kg and >4.54 kg, respectively. Using these estimates, an expected change over 22 weeks in the food-secure group is 0.54 kg, and an expected change in the food-insecure group is 0.80 kg. An SD of 22-week change in body weight, 0.24 kg [88], was increased to 0.30 kg to account for higher variability and ensure that the proposed study is well powered. Thus, with 60 participants, the study is well powered (>80%) to detect differences in body weight changes for aim 1. Furthermore, this study is also powered to detect a correlation as small as 0.40 for aim 2.

Planned Statistical Analysis

All available daily body weights will be used for analyses. For aim 1, body weight and psychological and physiological parameters will be analyzed using a mixed effects model with time, food security status, baseline BMI, and age. Models will be checked for both normality and heterogeneity of variance in potential subgroups (eg, age and BMI category). Least squares means and tests for differences by food security group will be the primary results. The analysis of aim 2 will focus on correlations among the outcomes from aim 1. Both Spearman and Pearson correlation coefficients will be used to determine the pairwise relationships among outcomes. Depending on the collinearity among outcomes, factor analysis will also be used to explore these relationships. Analysis of the exploratory aim will determine whether the weekly patterns of change in body weight, food security status, and perceived stress are different by food security group and how well these measures are associated with each other over time.

For aim 1, mixed effects models will be used to model psychological and physiological parameters. Furthermore, a linear mixed effects model will be used to model the daily weight over time. In addition to overall changes in body weight between the groups adjusted for BMI, age, and other baseline covariates, smaller temporal changes (ie, weekly) will also be a focus. Modeling these smaller changes should account for the increased fluctuations in the weight of the food-insecure women.

For aim 2, mixed effects models will assess how daily weight change is associated with changes in psychological and physiological parameters. Initial weight, overall weight change, and weekly weight change will all be considered as predictors in addition to more exploratory weight variables, such as the number of days significantly above or below starting weight or average absolute daily weight changes. These variables will be interacted with food security status (group) to determine whether the weight changes have greater effect on food-insecure women.

Analysis of the exploratory aim will determine whether the weekly patterns of change in body weight, food security status, and perceived stress are different by food security group and how well these measures are associated with each other over time. The first part of this analysis will use a mixed effects model, testing food security group differences at each week, whereas the second part will test correlations. Mediation analyses will be applied using both structural mean models and principal stratification [89]. Weekly food assistance use may be used for subgroup analyses to explore how food assistance use influences body weight.

Ethical Considerations

The Pennington Biomedical Research Center Institutional Review Board approved the study protocol (2021-022-PBRC), and all patients provided written informed consent. All attempts are made to maintain participant privacy and confidentiality. Safeguards such as password-protected computers and networks are in place to limit access to participant data. Study data are labeled with a unique series of letters and numbers. Pennington Biomedical Research Center stores data with this unique identifier. Participants receive up to US $300 for completed participation in the study. This includes compensation of US $50 for completion of visit 1, US $50 for completion of visit 2, and US $125 for completion of visit 3. Participants also receive the wearable device upon completion of the study.

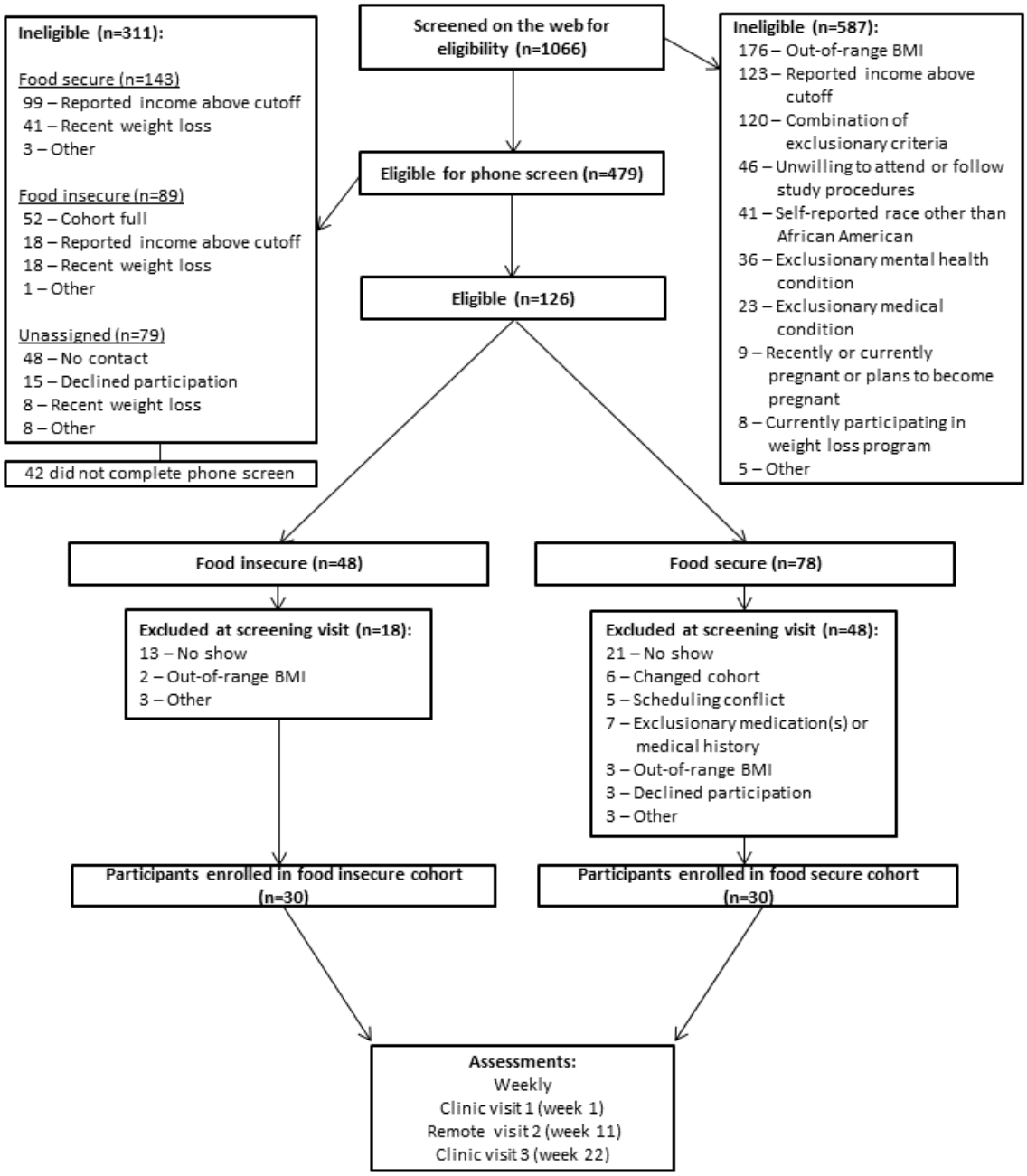
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Results

Overview

The RESPONSES study has completed participant recruitment (n=60). The flow of participants from screening to enrollment is shown in Figure 2. A total of 1066 potential participants were screened via a web screener for enrollment, and 587 (55.07%) were ineligible for study participation; the most common exclusionary criteria were out-of-range BMI (n=176, 30%) and having a reported income above the cutoff (n=123, 21%). Of the 479 potential participants who were screened via a telephone call, 311 (64.9%) were ineligible owing to exclusionary criteria. Of the 126 potential participants who were eligible after the telephone screener, 48 (38.1%) were food insecure, and 78 (61.9%) were food secure. At screening visits, of the 126 potential participants, a combined 66 (52.4%) were excluded from study participation to reach the target sample size of 60 (47.6%; food-insecure cohort: n=30, 50%; food-secure cohort: n=30, 50%). All data are anticipated to be collected by the end of 2023.

Figure 2. RESPONSES (Effects of Episodic Food Insecurity on Psychological and Physiological Responses in African American Women With Obesity) participant flow diagram.



Participant Characteristics

Table 2 presents the baseline characteristics of the participants enrolled in the RESPONSES study. On average, participants were aged almost 47 (SD 10.8) years with a mean BMI of 39.6 (SD 5.31) kg/m^2 at the time of study enrollment. Regarding marital status, 76% (45/59) of the participants were divorced, separated, widowed, or never married. In terms of education level, 58% (35/60) of the participants had a high school diploma,

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General Educational Development Test certificate, or 1 to 3 years of college. Regarding income, 31% (17/55) of the participants reported an annual income of <US $30,000, and 24% (13/55) reported an annual income of >US $50,000. In terms of employment status, 58% (33/57) of the participants reported being employed full time. The mean poverty-to-income ratio (PIR) among all participants was 1.96 (SD 0.83), whereas the food-insecure cohort reported an average PIR of 2.03 (SD 0.79), and the food-secure cohort reported an average PIR of 1.88 (SD 0.89).

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Table 2. Baseline characteristics of participants enrolled in the RESPONSES (Effects of Episodic Food Insecurity on Psychological and Physiological Responses in African American Women With Obesity) study.

Characteristics	Food-insecure cohort	Food-secure cohort	Overall
Age (y)			
Participants, n	30	30	60
Value, mean (SD)	46.93 (10.45)	46.47 (11.32)	46.7 (10.8)
Weight (kg)			
Participants, n	30	30	60
Value, mean (SD)	106.42 (17.13)	105.82 (14.94)	106.12 (15.94)
BMI (kg/m^2)			
Participants, n	30	30	60
Value, mean (SD)	39.31 (5.4)	39.95 (5.29)	39.63 (5.31)
Waist circumference (cm)			
Participants, n	29	30	59
Value, mean (SD)	114.49 (11.33)	112.9 (10.46)	113.68 (10.83)
Hip circumference (cm)			
Participants, n	29	29	58
Value, mean (SD)	126.69 (13.87)	126.98 (10.7)	126.84 (12.28)
Waist to hip ratio			
Participants, n	29	29	58
Value, mean (SD)	0.91 (0.07)	0.89 (0.08)	0.9 (0.07)
Pulse			
Participants, n	29	30	59
Value, mean (SD)	66.55 (9.65)	67.33 (9.39)	66.95 (9.44)
Marital status, n/N (%)			
Married	5/30 (17)	9/29 (31)	14/59 (24)
Divorced, separated, widowed, or never married	25/30 (83)	20 (69)	45/59 (76)
Education, n/N (%)			
High school diploma, GED[a] certificate, or 1-3 y college	20/30 (67)	15/30 (50)	35/60 (58)
Bachelor's degree or postgraduate degree	10/30 (33)	15/30 (50)	25/60 (42)
Annual income (US $), n/N (%)			
<30,000	8/29 (28)	9/26 (35)	17/55 (31)
30,000-39,000	8/29 (28)	5/26 (19)	13/55 (24)
40,000-49,999	9/29 (31)	3/26 (12)	12/55 (22)
>50,000	4/29 (14)	9/26 (35)	13/55 (27)
Household size			
Participants, n	29	29	58
Value, mean (SD)	2.48 (1.48)	3 (1.54)	2.74 (1.52)
Employment status, n/N (%)			
Employed full time (40 h/wk)	16/28 (57)	17/29 (59)	33/57 (58)
Employed part time	3/28 (11)	3/29 (10)	6/57 (11)
Unemployed	2/28 (7)	1/29 (3)	3/57 (5)
Retired	0/28 (0)	4/29 (14)	4/57 (7)
Medical disability	2/28 (7)	1/29 (3)	3/57 (5)

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Characteristics	Food-insecure cohort	Food-secure cohort	Overall
Student	0/28 (0)	2/29 (7)	2/57 (4)
Self-employed, homemaker, or other	3/28 (11)	1/29 (3)	4/57 (7)
Other	2/28 (7)	0/29 (0)	2/57 (4)
Financial support, n/N (%)			
Family	2/16 (13)	2/10 (20)	4/26 (15)
Employment	8/16 (50)	5/10 (50)	13/26 (50)
Government	2/16 (13)	1/10 (10)	3/26 (12)
Scholarships	2/16 (13)	1/10 (10)	3/26 (12)
Loans	0/16 (0)	0/10 (0)	0/26 (0)
Other	2/16 (13)	1/10 (10)	3/26 (12)
Dependent, n/N (%)			
Yes	2/30 (7)	0/30 (0)	2/60 (3)
No	28/30 (93)	30/30 (100)	58/60 (97)
Insurance, n/N (%)			
None	1/30 (3)	0/30 (0)	1/60 (2)
Private	16/30 (53)	17/30 (57)	33/60 (55)
Medicare	4/30 (13)	5/30 (17)	9/60 (15)
Medicaid	9/30 (30)	8/30 (27)	17/60 (28)
Use parents' or legal guardians' insurance coverage	0/30 (0)	0/30 (0)	0/60 (0)
Poverty-to-income ratio			
Participants, n	28	26	54
Value, mean (SD)	2.03 (0.79)	1.88 (0.89)	1.96 (0.83)
Creatinine, n (mean, SD)			
Participants, n	30	30	60
Value, mean (SD)	0.82 (0.21)	0.86 (0.18)	0.84 (0.19)
Potassium			
Participants, n	30	30	60
Value, mean (SD)	4.23 (0.39)	4.24 (0.37)	4.24 (0.37)
Uric acid			
Participants, n	30	30	60
Value, mean (SD)	5.49 (1.03)	5.51 (1.06)	5.5 (1.04)
Calcium			
Participants, n	30	30	60
Value, mean (SD)	9.4 (0.36)	9.39 (0.36)	9.4 (0.36)
Magnesium			
Participants, n	30	30	60
Value, mean (SD)	2.01 (0.16)	2 (0.21)	2.01 (0.19)
CPK[b]			
Participants, n	30	30	60
Value, mean (SD)	134.6 (110.47)	148.3 (97.23)	141.45 (103.41)
ALT[c]			
Participants, n	30	30	60

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Characteristics	Food-insecure cohort	Food-secure cohort	Overall
Value, mean (SD)	19.33 (6.87)	17.33 (0.87)	18.33 (6.42)
ALK[d]			
Participants, n	30	30	60
Value, mean (SD)	77.93 (27.01)	69.13 (19.78)	73.53 (23.89)
Iron			
Participants, n	30	30	60
Value, mean (SD)	66.13 (23.08)	62.5 (24.41)	64.32 (23.62)
Type 1 diabetes, n/N (%)			
Yes	2/30 (7)	1/30 (3)	3/30 (5)
No	28/30 (93)	29/30 (97)	57/30 (95)
Type 2 diabetes, n/N (%)			
Yes	4/30 (13)	8/30 (27)	12/60 (20)
No	26/30 (87)	22/30 (73)	48/60 (80)
High blood pressure, n/N (%)			
Yes	13/27 (48)	12/28 (43)	25/55 (45)
No	14/27 (52)	16/28 (57)	30/55 (55)
High cholesterol level, n/N (%)			
Yes	9/26 (35)	4/28 (14)	13/54 (24)
No	17/26 (65)	24/28 (86)	41/54 (76)

[a]GED: General Educational Development Test.

[b]CPK: creatine phosphokinase.

[c]ALT: alanine transaminase.

[d]ALK: alkaline phosphatase.

Discussion

Summary

The RESPONSES study is investigating the association between food insecurity and obesity in African American women by measuring the episodic nature of food insecurity, related stress, and the role of psychological and physiological mechanisms. We have completed participant enrollment with 60 African American women (food-insecure cohort: n=30, 50%; food-secure cohort: n=30, 50%). The mean age of participants at enrollment was almost 47 (SD 10.8) years, and they had a mean BMI of 39.6 (SD 5.31) kg/m^2. Once data collection is complete by the end of 2023, we will fulfill the study aims to (1) longitudinally assess body weight in addition to psychological and physiological parameters in food-insecure and food-secure African American women with obesity, to test our hypothesis that food-insecure African American women with obesity will demonstrate increased body weight and changes in psychological and physiological parameters consistent with elevated stress compared with food-secure African American women with obesity; (2) examine associations between changes in body weight and psychological and physiological parameters in food-insecure and food-secure African American women with obesity; and (3) longitudinally examine cyclic patterns in body weight, food insecurity, and stress in food-insecure and food-secure African American women with obesity and carry out a mediation analysis using the results from the psychological questionnaires.

The significance of the RESPONSES study is evidenced by a number of factors, including (1) an explicit focus on health disparities driven by both sex and race or ethnicity as evidenced in African American women, who experience a greater prevalence of both food insecurity and obesity; (2) the assessment of episodic food insecurity via longitudinal observational data collection; and (3) the triangulation of body weight and psychological and physiological parameters in the context of episodic food insecurity as a stressor. These points of significance directly relate to the *Strategic Plan for NIH Nutrition Research* by addressing the multiple recommendations highlighted in the position paper on food insecurity and obesity by Brown et al [90]. This study explicitly acknowledges the *episodic nature* of food insecurity by using a longitudinal study design to examine how the cyclic nature of food insecurity relates to body weight. Furthermore, this study will investigate the mechanisms underlying the linkage between food insecurity and obesity by focusing on a range of relevant psychological and physiological factors. Examining the interplay between psychological and physiological factors may be important to understanding the disparate rates of obesity-related comorbidities (eg, diabetes and hypertension) in African American women. Finally, the results from the RESPONSES study will hold important considerations for the assessment of

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body weight and psychological and physiological parameters in studies, wherein the assessment of these markers might need to consider corresponding episodes of food insecurity.

The RESPONSES study uses a longitudinal observational cohort design. Given the study objective, it is important not to intervene; thus, this study would not be possible with a randomized controlled trial design. Interventions should occur after a thorough understanding of the episodic nature of food insecurity and its impact on body weight and psychological and physiological processes. We recognize that only screening for dietary quality and not obtaining food intake data are study limitations, but this aspect of food insecurity (ie, energy-dense and nutrient-poor diet) is very well established in the literature, and body weight can serve as a proxy for food intake [19,20,91]. We are also measuring more tertiary constructs (eg, physical activity) that could be measured via more rigorous methods in future studies, such as energy intake via dietary recall or food pictures and energy expenditure via metabolic chamber or other methodology (eg, doubly labeled water and metabolic cart) to better assess energy metabolism.

Conclusions

To our knowledge, the RESPONSES study will be the first to examine changes in body weight and psychological and physiological factors in food-insecure African American women with obesity during episodes of food insecurity. The findings from this study will provide a range of novel data with significant public health implications by addressing the cyclic nature of food insecurity to identify underlying mechanisms that can be targeted to mitigate the adverse relationship between food insecurity and obesity and reduce health disparities in racially minoritized populations.

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Data Availability

RESPONSES (Effects of Episodic Food Insecurity on Psychological and Physiological Responses in African American Women With Obesity) study data will be a deidentified participant-level data set that will include all data points necessary to validate the anticipated research findings. A cleaned, deidentified data set will be encrypted and stored on a secure server at Pennington Biomedical Research Center. At study completion, data will be made available to users via request from the Pennington Nutrition Obesity Data Repository. The mission of the Pennington Nutrition Obesity Research Centers Biorepository is to advance the knowledge of obesity, nutrition, and human health through the sharing of deidentified data and biospecimens collected from human participant research at Pennington Biomedical Research Center.

Conflicts of Interest

None declared.

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Abbreviations

CRP: C-reactive protein
DHEA-S: dehydroepiandrosterone-sulfate
HPA: hypothalamus-pituitary-adrenal
PFS: Power of Food Scale
PIR: poverty-to-income ratio
PROMIS: Patient-Reported Outcomes Measurement Information System
PSS-10: Perceived Stress Scale-10
PSS-4: Perceived Stress Scale-4
REALM-SF: Rapid Estimate of Adult Literacy in Medicine–Short Form
REDCap: Research Electronic Data Capture
RESPONSES: Effects of Episodic Food Insecurity on Psychological and Physiological Responses in African American Women With Obesity
SNAP: Supplemental Nutrition Assistance Program

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Protocol

Dazhu Hongjingtian Injection for Ischemic Stroke: Protocol for a Prospective, Multicenter Observational Study

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Abstract

Background: Although results from in vitro studies and small randomized controlled trials have shown positive effects of Dazhu hongjingtian injection (DZHJTI) on acute ischemic stroke (AIS), their generalizability to routine clinical practice remains to be established.

Objective: The primary aim of this study is to evaluate the effectiveness of DZHJTI treatment for AIS with regard to changes in the stroke-related neurological deficit from baseline to outpatient follow-up, mortality, subsequent vascular events, disability, and traditional Chinese medicine syndrome in real-world clinical settings. By monitoring for adverse events or significant changes in vital signs and laboratory parameters, we also aim to assess the safety of DZHJTI.

Methods: This prospective, multicenter cohort study plans to enroll 2000 patients with AIS within 14 days of symptom onset from 30 hospitals across China. Eligible patients will be followed up for 6 months after initiating medication treatments. The primary outcome will be the change in the National Institute of Health Stroke Scale score from baseline to outpatient follow-up. The secondary outcomes include overall mortality, stroke recurrence, new-onset major vascular events, global disability, and improvement of traditional Chinese medicine syndrome in 6 months. Adverse events or clinically significant changes in vital signs and laboratory parameters, regardless of the severity, will be recorded during the trial to assess the safety of DZHJTI. An augmented inverse propensity weighted estimator will be used to reduce variability and improve accuracy in average treatment effects estimation.

Results: The clinical trial registration was approved in October 2022, and the recruitment and enrollment of participants started in November 2022. The study's outcomes are expected to be published in 2025 in reputable, peer-reviewed health-related research journals.

Conclusions: This real-world cohort study is the first to assess the effectiveness and safety of DZHJTI in treating AIS. It may provide additional clinical evidence, including the duration of response, long-term drug effectiveness, and subgroup efficacy data. The study results will be valuable for clinicians and patients seeking optimal treatment for AIS and could lead to better use of DZHJTI and improved patient outcomes.

Trial Registration: ITMCTR ITMCTR2022000005; http://tinyurl.com/554ns8m5

International Registered Report Identifier (IRRID): DERR1-10.2196/52447

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KEYWORDS

ischemic stroke; study protocol; complementary and alternative therapies; prospective study; stroke; observational study; effectiveness; treatment; optimal treatment; medication; DZHJTI treatment; clinical setting; therapy; cohort study; androgen

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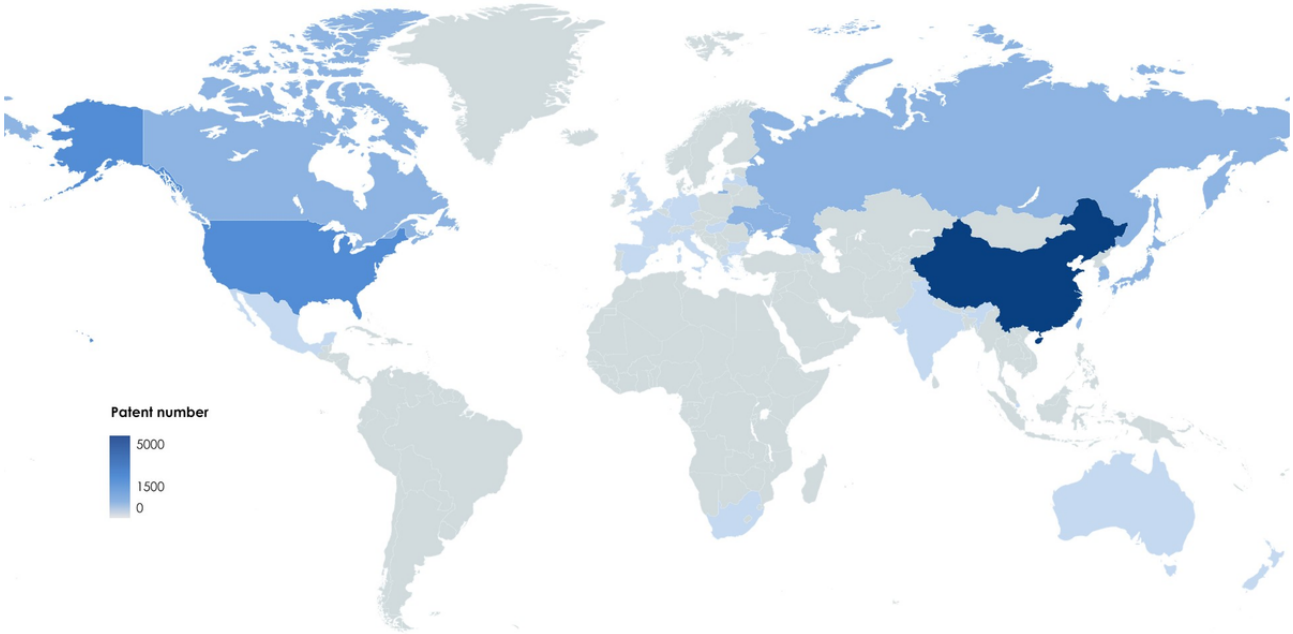
syndrome; patients with AIS; patient with AIS; China; stroke recurrence; traditional medicine; laboratory parameters; health; tissue plasminogen activator (tPA); tPA; stroke treatment; plasminogen

Introduction

The high morbidity, mortality, and disability rates associated with stroke impose a significant health and economic burden not only in China but globally [1]. The annual stroke mortality rate in China is approximately 153.9 per 100,000 people, which is 4 times that of American and European countries [1-3]. As the most common subtype of stroke, ischemic strokes accounted for 82.6% (2,818,875/3,411,168) of stroke cases in China admitted in 2019 [4]. Despite receiving guideline-recommended care, including intravenous thrombolysis and endovascular therapy, many patients with stroke continue to experience nerve dysfunction. Recent research conducted in 30 provinces of China revealed that up to 78.7% of first-ever stroke survivors developed poststroke cognitive impairment within 3-6 months following the initial stroke event [5]. This highlights the urgent need to identify a medication with proven efficiency and safety in improving neurofunctional recovery, thereby alleviating the substantial burden on patients and the health care system.

Dazhu hongjingtian (DZHJT) or *Rhodiola wallichiana* var *cholaensis* (Praeger) SH Fu belongs to the family Crassulaceae in the genus *Rhodiola*. Plants of this genus have a long history of traditional use and are included in the official pharmacopeia of Asia, Europe, North America, Latin America, Oceania, and Africa, which is attributed to their proven efficacy in stimulating the nervous system, alleviating fatigue, and preventing high altitude sickness [6,7] (Figure 1). Rhodiola dietary supplements have been recognized by the European Food Safety Authority for their contribution to optimal mental and cognitive activity [8]. DZHJT injection (DZHJTI) is produced from dried roots and stems of DZHJT using processes approved by the Food and Drug Administration of China. Extensive research on the chemical constituents of DZHJTI has identified a total of 49 compounds using ultra-high–performance liquid chromatography coupled with quadrupole time-of-flight mass spectrometry analysis, and a fingerprint has been established by high performance liquid chromatography [9,10]. The primary active constituent of DZHJT, salidroside, has demonstrated various biological activities in both in vitro and in vivo studies, including effects on the central nervous system, cardiac vessel dilation, antihypoxia, and anti-inflammatory properties, among others [11-13].

Figure 1. Worldwide patent application for Rhodiola. Data collected from the Lens (searching term: Rhodiola) as of July 20, 2023.



Several clinical studies have investigated the effects of DZHJTI on acute ischemic stroke (AIS). A pooled analysis of 18 trials involving 1713 participants demonstrated that DZHJTI combined with guideline-recommended therapy was superior to the control group in decreasing the National Institute of Health Stroke Scale (NIHSS; standardized mean difference –0.77, 95% CI –1.52 to –0.02). Moreover, when combined with basic therapy, DZHJTI can also significantly improve the whole blood viscosity, plasma viscosity, and level of fibrinogen, as well as decrease fasting blood glucose and levels of total cholesterol [14]. However, the relatively insufficient sample sizes and ambiguous study designs of previous studies urge high-quality real-world evidence from a rigorous research process.

To enhance the quality of clinical evidence and promote standardized development in clinical research related to traditional medicine on a global scale, we have established the International Traditional Medicine Clinical Trial Registry (ITMCTR), the world's first international clinical trial registration platform for traditional medicine. This accomplishment has earned ITMCTR the distinction of being

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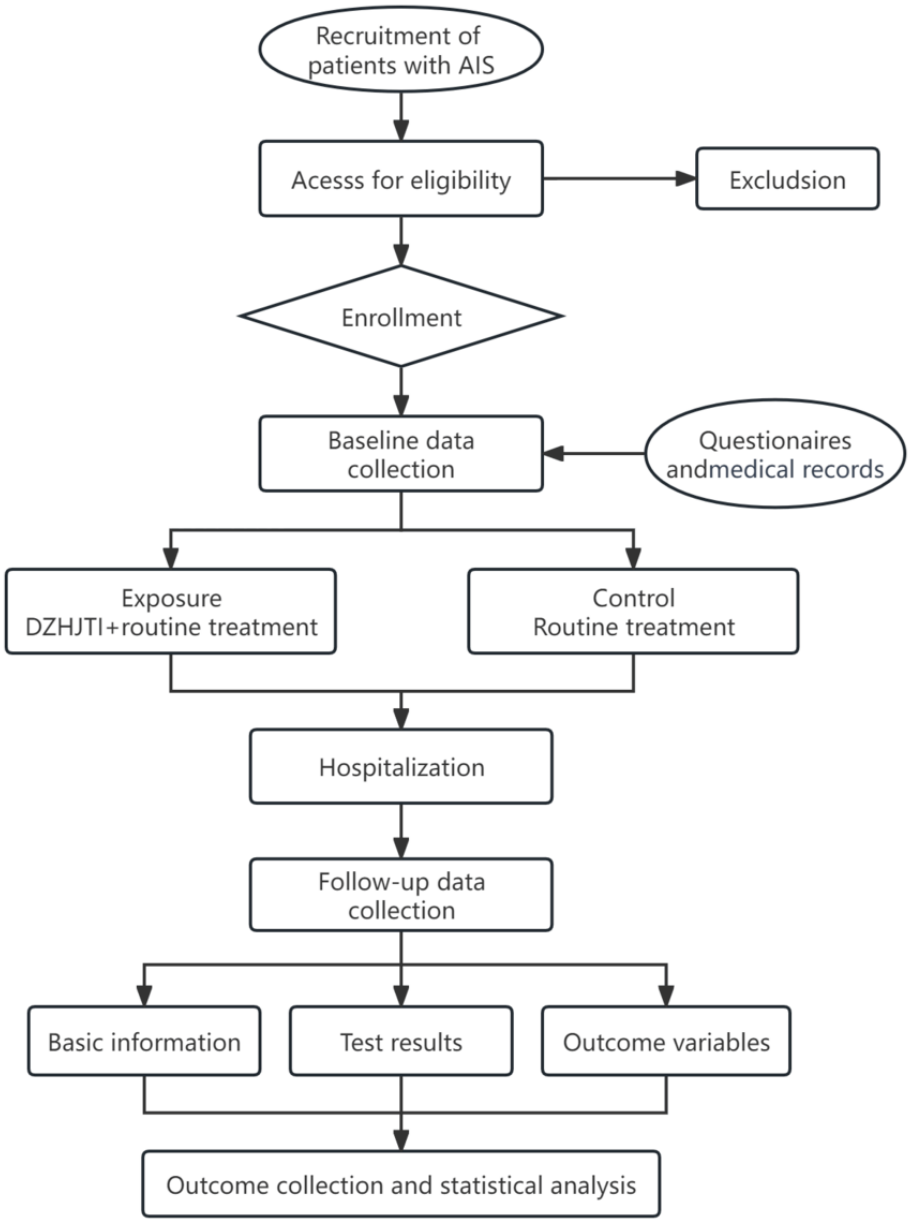
approved as a level 1 World Health Organization international clinical trial registration institution. ITMCTR became a member of the Primary Registry Network of the International Clinical Trials Registry Platform and the trials registered with ITMCTR have been added to the International Clinical Trials Registry Platform database. Building upon the foundation of this endeavor, we conducted a multicenter, prospective cohort study to assess the effectiveness and safety of DZHJTI as adjuvant therapy for patients with AIS in a real-world setting. With a complete and accurate study design and prospective registration, this study will provide qualified evidence for DZHJTI.

Methods

Study Design

Our study is a prospective, multicenter cohort study conducted in a real-world setting. An overview of the study flowchart is presented in Figure 2. It is planned to enroll 2000 patients with AIS, as defined in the *Chinese Guidelines for Diagnosis and Treatment of Acute Ischemic Stroke 2018* [15] and *Stroke Diagnosis and Effectiveness Evaluation Standards* [16]. A total of 3 visits will be carried out within a 6-month follow-up period. Baseline demographic data, therapeutic effects, adverse events, and complications associated with DZHJTI will be analyzed.

Figure 2. Flowchart of the study design. AIS: acute ischemic stroke; DZHJTI: Dazhu hongjingtian injection.



Participants

To collect a representative sample, the nephrology departments of 30 secondary or tertiary hospitals in multiple regions of China will continuously recruit and enroll patients. Recruitment began in November 2022 and will continue until at least 2000 participants are recruited. Potential patients will undergo eligibility screening based on the inclusion and exclusion criteria. Eligible patients or their legally authorized representatives will provide written informed consent before undergoing any study-specific procedures. Textbox 1 provides detailed information on the inclusion and exclusion criteria.

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Textbox 1. Inclusion and exclusion criteria of the cohort study.

Inclusion criteria

- Female or male patients aged ≥18 years
- Meeting the acute ischemic stroke diagnostic criteria
- Time from symptom onset to the hospital admission ≤14 days
- Willingly participates in the clinical study and signs the informed consent

Exclusion criteria

- Clinically silent acute ischemic stroke
- Minor stroke or minor neurological deficit (National Institute of Health Stroke Scale score of 0-5), nondisabling or rapidly improving transient cerebral ischemia
- Severe hypertension or diabetes that is still unable to control the disease after treatment
- Other conditions that cause motor dysfunction (claudication, severe osteoarthrosis, rheumatoid arthritis, gouty arthritis, etc)
- Unable to complete daily activities independently due to various diseases and physical weakness before this disease, which seriously affects the effectiveness evaluation
- Known complications affecting drug evaluation, including severe cardiac insufficiency, renal insufficiency, severe mental illness, depression after stroke, dementia, cerebral hemorrhage after cerebral infarction, and so forth
- Known contraindications of Dazhu hongjingtian injection: pregnancy, allergic constitution, multiple drug allergies, allergy to ingredients in Dazhu hongjingtian injection, known adverse reactions to any component of the Dazhu hongjingtian injection
- Controls who used other dosage forms of Dazhu hongjingtian injection (tablets, capsules, etc)
- Unsuitability for participation as judged by the investigators

Treatment Regimens

All patients will receive current guideline-recommended treatments according to *Chinese Guidelines for the Diagnosis and Treatment of Acute Ischemic Stroke 2018* [15]. The most commonly used medications and treatments include intravenous thrombolysis drugs, antiplatelets, anticoagulants, drugs for volume expansion, neuroprotectants, medicines for improving cerebral blood flow, and traditional Chinese medicine. Cases will be recruited from patients who receive DZHJTI according to the physician's order. The DZHJTI will be manufactured and supplied by Tonghua Yusheng Pharmaceutical Co, Ltd (approvals Z20060361 and Z20060362), with identical appearance, color, and flavor. The fingerprint-based quality control and ingredient identification met the Chinese pharmacopeia's reference requirements (detailed information is provided in Multimedia Appendix 1). The administration and dosage of DZHJTI will be determined by the attending physicians based on the patients' medical history and clinical manifestations.

Data Collection and Monitoring

Trained research personnel at each participating site will collect baseline data during patient admission, including prehospital care and treatment, prestroke symptoms, and the NIHSS. They will also conduct assessments using the prestroke modified Rankin Scale scores and Barthel Index. Patient information, including demographics, medical and family history, physical examination, auxiliary examination, risk factor assessment, and clinical diagnosis, will be obtained from medical records. The classification of stroke etiology, related complications, and new cerebrovascular events will be documented, and the etiology of AIS will be determined according to the Trial of Org 10172 in Acute Stroke Treatment criteria [17]. Besides standard therapies, the administration of DJHJTI during hospitalization will be documented by the research team.

The collection and reporting of data will use a secure electronic data capture (EDC) system that follows the current clinical protocol and provides each patient with a unique ID. Authorized research personnel can access the EDC system both on personal computers and smartphones, enabling them to complete data collection during daily ward rounds. An overview of the measurement data collection schedule is shown in Table 1. In the EDC system, personal identifiers such as names, ID numbers, and contact information are removed or replaced with unique codes to ensure participant anonymity.

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Table 1. Schedule of assessments in the cohort study.

Participant assessment	Time point and form				
	Baseline (acute phase)		Follow-up 1	Follow-up 2	Follow-up 3
	Admission	Discharge	1 month	3 months	6 months
	Visit	Visit	Visit or telephone interview	Visit or telephone interview	Visit or telephone interview
Eligibility screen	✓[a]				
Informed consent	✓				
Demographic and anthropometric data	✓				
TCM[b] questionnaire	✓				
NIHSS[c]	✓	✓			
mRS[d]	✓	✓	✓	✓	✓
BI[e]			✓	✓	✓
Laboratory examination	✓	✓	+[f]	+	+
Imaging examination	✓	✓	+	+	+
Admission status		✓			
Discharge status		✓			
Follow-up interview			✓	✓	✓
AE[g]		+	+	+	+
Outcomes		+	+	+	+

[a]Required data.

[b]TCM: traditional Chinese medicine.

[c]NIHSS: National Institutes of Health Stroke Scale.

[d]mRS: modified Rankin Scale.

[e]BI: Barthel Index.

[f]Optional data to be collected based on the actual occurrence of related events in patients.

[g]AE: adverse events.

Follow-Up Procedures

All patients will be identified and followed up using individual identity cards, which are mandatory for all Chinese citizens, enabling unambiguous linkages. Research personnel will conduct regular face-to-face or telephone follow-up at 1, 3, and 6 months after stroke onset. Information on patient outcomes, including mortality, functional status, activities of daily living, cognitive function, and cardiovascular or cerebrovascular events, will be obtained during follow-up. Mortality will be confirmed through a death certificate issued by the local civil registry or the attending hospital. New cardiovascular or cerebrovascular events requiring rehospitalization will be verified by the discharge diagnosis. In the absence of hospitalization, a committee responsible for determining end points will evaluate suspected recurrent cardiovascular or cerebrovascular events [18].

Outcomes

In this study, the primary outcome will be the distribution of scores on the NIHSS before and after treatment among patients. Secondary outcomes will be assessed at different follow-up visits and will include death, a composite of new clinical vascular events, neurological function, and improvement of traditional Chinese medicine syndrome. Safety assessment will be performed by monitoring adverse events. The complete study outcomes are illustrated in Table 2.

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Table 2. Outcome variables and definitions.

Outcome variables	Definitions
Primary outcome	
Improvement degree of clinical NIHSS[a] scores	• Basic recovery (NIHSS score decreased by more than 90%) • Significant improvement (NIHSS score decreased by 46%-89%) • Improvement (NIHSS score decreased by 18%-45%) • No change (NIHSS score decreased 0%-18% or increased<18%) • Deterioration (NIHSS score increased more than 18%) • The basic recovery, significant improvement, and improvement were regarded as effective. The no change, deterioration, and death were regarded as inefficient [19]
Secondary outcomes	
Overall mortality	—[b]
Stroke recurrence	—
New-onset major vascular events	• Major adverse vascular events include ischemic stroke, hemorrhagic stroke, transient ischemic attack, myocardial infarction, and vascular-related death
Global disability	• Measured by BI[c] and mRS[d] scale
improvement of TCM[e] syndrome	• Measured by TCM questionnaire
Adverse events	• Undesirable experiences occurring to participants during the trial are considered to be related to the DJHJTIf

[a]NIHSS: National Institute of Health Stroke Scale.

[b]Not available.

[c]BI: Barthel Index.

[d]mRS: modified Rankin Scale.

[e]TCM: traditional Chinese medicine.

[f]DZHJTI: Dazhu hongjingtian injection.

Study Sites and Data Source

The cohort study's steering committee will conduct a rigorous screening process of hospitals nationwide, aiming to represent the population from each region in mainland China. Only hospitals admitting over 100 patients with stroke annually, experienced in multicenter studies, and equipped with magnetic resonance imaging or computed tomography machines will be considered. After a thorough evaluation, 30 participating sites with proven research capabilities and a demonstrated commitment to the study will be selected.

Quality Control and Management

Before the study begins, the steering committee will create training materials outlining the study protocol and standard operating procedures for patient screening, recruitment, informed consent, and data collection. Research personnel must complete the training videos and pass an examination to obtain a study permit. The end-point judgment committee will establish standard operating procedures for the proper use of scales, outcome assessment, and reporting procedures. An independent data safety and monitoring board will oversee data monitoring to guarantee adherence to the study documentation, reporting procedures, and the study protocol. This board will be responsible for ensuring that the study is conducted in accordance with good clinical practice guidelines.

Sample Size

According to the previous studies, the ineffective rate assessed by NIHSS score (percentage of patients experiencing no change and deterioration) in controls was 8.75% (7/80), and the ratio of cases to controls was 0.31 [14]. To test the hypothesis that adjuvant treatment with DZHJTI significantly reduces the ineffective rate with a 2-sided α of .05, power of 0.80, and a 20% (n=248) dropout rate, a sample size of 619 cases in each group is required. Nevertheless, a sufficiently large sample size is also necessary to reduce the bias in real-world studies. Therefore, a total of 1000 case participants per group will be included.

Statistical Analysis

A statistical analysis plan was developed prior to initiating the cohort study. Continuous data will be summarized using mean, median, standard deviation, or IQR, while categorical data will be presented as counts and percentages. Between-group comparisons will be conducted using appropriate parametric tests (such as the 2-tailed Student *t* test) or nonparametric tests (such as the chi-square test, Fisher exact test, or Mann-Whitney *U* test). Time-to-event analysis will involve censoring patients at their last follow-up assessment when experiencing a clinical event, at the end of the study, or at the time of withdrawal from the study. Cumulative clinical events will be reported as Kaplan-Meier estimates. Hazard ratios will be calculated at 95% CIs using Cox proportional hazard regression methods.

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During data analysis, both confounding factors and missing values will be taken into account. The augmented inverse propensity weighted (AIPW) estimator will be used to obtain a marginal estimate of the treatment effect rather than a conditional estimate. AIPW analysis creates a pseudopopulation in which the relationship between the confounders and the exposure is blocked. Multiple imputation will be used to handle missing values of covariates, and both complete case and imputed data sets will be analyzed. For each imputed data set, the AIPW estimator will be used to estimate the treatment effect, and Rubin rules will be used to combine these estimates and obtain an overall estimate [20]. Sensitivity analyses for unmeasured confounding in observational studies will be performed using the methodology proposed by VanderWeele and Ding [21]. All statistical tests will be 2-sided with statistical significance set at $P<.05$. Statistical analyses will be conducted using SAS software (version 9.4; SAS Institute Inc).

Ethical Considerations

This clinical trial will be conducted in accordance with the principles outlined in the Declaration of Helsinki. Prior to enrollment, all participants or their authorized representatives will be provided with a written informed consent form and will be required to provide their consent. The ethics committee of the Institute of Basic Clinical Research, China Academy of Chinese Medical Sciences (P22004/PJ04) granted approval for the trial on July 18, 2022. The authors declare that the results will be submitted to an international peer-reviewed journal for their prompt dissemination.

Results

The clinical trial registration for this study was approved in October 2022, and recruitment and enrollment of participants commenced in November 2022. We anticipate that the future outcomes of this study will be published in reputable, peer-reviewed health-related research journals around 2025.

Discussion

We present the rationale and design of a prospective, multicenter observational study that aims to evaluate the clinical effectiveness and safety of DZHJTI in the treatment of AIS in real-world settings. Rhodiola has long been used in Eurasian traditional medicine as a natural tonic, but DZHJTI's efficiency in treating AIS is not well known because previous studies had limited external validity [22,23]. Thus, it is necessary to collect large longitudinal data to confirm the practical benefits and disadvantages of DZHJTI treatment in patients with stroke. These data can then be used to develop initiatives to improve evidence-based care and patient outcomes.

Adjuvant treatment with DZHJTI has been shown to have an additional positive effect on improving clinical symptoms and hemodynamic indexes in patients with AIS [14,24]. This beneficial effect may be attributed to the ability of its ingredients, including salidroside, tyrosol, and *Rhodiola* polysaccharide, and the fact that it contains flavonoids, phenolic compounds, trace elements, and amino acids. This has been demonstrated to activate antioxidant enzymes' activity in brain tissue, reduce the oxidative damage of free radicals to cells, and improve glucose and lipid metabolism [25,26]. However, the evidence for the effectiveness of DZHJTI is still limited due to a lack of large controlled studies, and the strict treatment regimes in randomized controlled trials may be not applicable in clinical practice [14]. Therefore, well-designed prospective real-world studies with large sample sizes are necessary to evaluate the evidence.

Our study uses an observational design, and the treatments will not be specified by the study protocol. This approach has the advantage of reflecting real-world clinical practice, including therapy switches and concomitant medications, which can provide valuable insights into treatment effectiveness in diverse patient populations. Additionally, studying how DZHJTI is prescribed by health care providers and used in everyday environments can offer valuable information about the people and settings that are often underrepresented in randomized controlled trials, potentially leading to improvements in the way medicines are prescribed and used among these patient populations.

However, it is important to note that biases are common in real-world studies. Participants from different study sites may differ in characteristics, and combined treatments can vary widely. Additionally, incomplete data can be a significant issue with real-world data sources. Therefore, we plan to use the AIPW estimator, which involves a doubly robust procedure to minimize bias if either the treatment or outcome model is correctly specified [27]. The accuracy of the AIPW estimator for the average treatment effect has been demonstrated under different scenarios of misspecification [27]. To perform propensity score analysis when data are missing, we will conduct the analysis in each imputed data set and then combine the estimates of the treatment effect to obtain an overall estimate. This method has been demonstrated to be unbiased under a missing at random mechanism, and Rubin rules have been shown to provide reliable variance estimates and show good balancing properties [20].

Another key consideration in this trial is selecting an appropriate primary outcome, which depends largely on the disease and should reflect the treatment effect and expected mechanism. NIHSS is a tool used to objectively quantify neurological impairment after stroke [28], while the modified Rankin Scale and modified Barthel Index are commonly used scales to measure disability or dependence in daily activities in patients with stroke or other neurological dysfunction [29]. Previous studies on herbal injection often have limited follow-up periods of up to 3 months due to drug metabolism. However, since AIS neurological function recovery is a slow process, with the main recovery period occurring within 2 to 6 months after onset [30], we evaluated the effects of DZHJTI on neurological recovery for a period of 6 months after discharge from the hospital.

To our knowledge, this is the first and largest prospective cohort study in China that evaluates the real-world effectiveness and safety of DZHJTI in the treatment of AIS. It may provide additional clinical evidence, including the duration of response, long-term drug effectiveness, and subgroup efficacy data of DZHJTI treatment for patients with AIS under the influence of

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other confounding factors. Ultimately, the results of this study will help optimize individualized interventions with DZHJTI for the treatment of AIS in China, leading to better patient outcomes and more standardized treatment practices.

Acknowledgments

The study received grants from the China Academy of Chinese Medical Sciences Innovation Fund (CI2021A00702-3), the National Key Research and Development Project of China (2022YFC3501104), the National Natural Science Foundation of China (82174532), and the 2022 Qi Huang Young Scholar program of the National Administration of Traditional Chinese Medicine (Z0841). The support of this work is gratefully acknowledged by all the hospitals and individuals who will participate in the study. We used the generative artificial intelligence tool ChatGPT by OpenAI [31] to polish the drafted manuscript, which was further reviewed and revised by the study group.

Data Availability

The data sets generated and analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

All authors participated in the design of the study and will perform the trial. QZC, TS, and NL contributed equally to the drafting of the manuscript and were listed as cofirst authors. YPW and NNS proposed and coordinated the clinical trial. ZC helped to modify this prospective trial. JG performed the statistical analysis and estimated the sample size. XYL provided assistance with data administration and collection. LY was in charge of the trial's quality assurance. YJ kept track of the trial's progress. All coauthors have read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Fingerprint chromatogram.
[DOCX File , 316 KB - resprot_v12i1e52447_app1.docx]

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Abbreviations

AIPW: augmented inverse propensity weighted
AIS: acute ischemic stroke
DZHJT: Dazhu hongjingtian
DZHJTI: Dazhu hongjingtian injection
EDC: electronic data capture
ITMCTR: International Traditional Medicine Clinical Trial Registry
NIHSS: National Institute of Health Stroke Scale

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Protocol

Enhancing Veteran Community Reintegration Research (ENCORE): Protocol for a Mixed Methods and Stakeholder Engagement Project

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Abstract

Background: Veteran community reintegration (CR) has been defined as participation in community life, including employment or other productive activities, independent living, and social relationships. Veteran CR is a Veterans Health Administration priority, as a substantial proportion of veterans report difficulties with veteran CR following discharge from military service.

Objective: Enhancing Veteran Community Reintegration Research (ENCORE) is a project funded by Veterans Health Administration's Health Service Research and Development Service. The goal of ENCORE is to maximize veteran and family reintegration by promoting innovative research and knowledge translation (KT) that informs and improves equitable Department of Veterans Affairs (VA) policies, programs, and services. Overall, 2 strategic objectives guide ENCORE activities: mobilize veteran CR research and promote innovation, relevance, and acceleration of veteran CR research and KT.

Methods: ENCORE uses a mixed methods and stakeholder-engaged approach to achieve objectives and to ensure that the KT products generated are inclusive, innovative, and meaningful to stakeholders. Project activities will occur over 5 years (2019-2024) in 5 phases: plan, engage, mobilize, promote, and evaluate. All activities will be conducted remotely owing to the ongoing COVID-19 pandemic. Methods used will include reviewing research funding and literature examining the gaps in veteran CR research, conducting expert informant interviews with VA program office representatives, and assembling and working with a Multistakeholder Partnership (MSP). MSP meetings will use external facilitation services, group facilitation techniques adapted for virtual settings, and a 6-step group facilitation process to ensure successful execution of meetings and accomplishment of goals.

Results: As of December 2022, data collection for ENCORE is ongoing, with the team completing interviews with 20 stakeholders from 16 VA program offices providing veteran CR–related services. ENCORE developed and assembled the MSP, reviewed the VA funding portfolio and veteran CR research literature, and conducted a scientific gap analysis. The MSP developed a veteran CR research agenda in 2021 and continues to work with the ENCORE team to prepare materials for dissemination.

Conclusions: The goal of this program is to improve the impact of veteran CR research on policies and programs. Using a stakeholder-engaged process, insights from key stakeholder groups are being incorporated to set a research agenda that is more likely to result in a relevant and responsive veteran CR research program. Future products will include the development of an effective and relevant dissemination plan and the generation of innovative and relevant dissemination products designed for rapid KT.

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KEYWORDS

veteran; community; community reintegration; stakeholder engagement; veterans community integration; veteran health administration; knowledge translation; research promotion; veterans association policy; policy

Introduction

Overview

Enhancing Veteran Community Reintegration Research (ENCORE) is a 5-year project funded by Veterans Health Administration (VHA) in July 2019. The goal of ENCORE is to improve the Department of Veterans Affairs (VA) policies, programs, and services related to veteran community reintegration (CR), which is a VHA priority [1]. Veteran CR has often been defined as participation in community life, including employment or other productive activities, independent living, and social relationships [2]. ENCORE will achieve its goal by (1) mobilizing veteran CR research and (2) promoting innovation, relevance, and acceleration of veteran CR research and knowledge translation (KT). The ENCORE team developed a road map establishing how these 2 strategic objectives will guide activities to meet the project's impact goal. This protocol paper outlines this road map, including the methods that will be used to determine the current state of veteran CR research, engage stakeholders in shared decision-making using a Multistakeholder Partnership (MSP), and communicate with diverse audiences about veteran CR research needs and priorities. This protocol paper is intended to inform researchers and other professionals on underused methods to engage multiple stakeholders while prioritizing research, program, and policy needs of specific populations.

Veteran CR is a key determinant of veteran health, functioning, and quality of life [3]. A substantial proportion of veterans report difficulties with veteran CR following discharge from military service including poor social and family relationships, unemployment, financial strain, homelessness, and decreased physical and mental health [4,5]. These difficulties are further compounded for veterans with disabilities including the approximately 4.9 million veterans having a service-connected disability [6,7]. Successful veteran CR for all populations emphasizes engagement with community, peers, and family. VHA strategic initiatives outline the importance of establishing and enhancing community relationships that affect and promote veteran CR health [4,5].

ENCORE focuses on two critical domains of veteran CR: (1) work and other productive activities and (2) social relationships and activities (eg, interaction with family members and friends, parental or marital relationships, and marital issues). Employment or other meaningful and productive activity is directly related to income stability, independence, health, and a sense of meaning and purpose in life [8-10]. Evidence demonstrates that the strength and quality of one's social relationships and perceived social support also play key roles in health and well-being [8,11].

Background

KT Strategies

KT, defined "as a dynamic and iterative process that includes the synthesis, dissemination, exchange and ethically sound application of knowledge to improve health, provide more effective health services and products, and strengthen the health care system" [12], is a key component that underpins ENCORE's strategic objectives. Knowledge creation, distillation, and dissemination alone are not sufficient to ensure evidence-informed decision-making [12]. KT is widely used to ensure that decision makers at all levels of the health system (eg, consumers, patients, practitioners, managers, and policy makers) are aware of and can access and use research evidence to inform health-related decision-making [13-16]. Critical considerations suggest that KT should include all stakeholder groups (eg, patients, health care providers, and policy makers) in the actual process of using knowledge to facilitate decision-making [17,18]. Strategies for KT must vary according to the target audience (eg, researchers, clinicians, policy makers, and public) and the type of knowledge being translated (ie, clinical, biomedical, and policy-related) [18-20].

Stakeholder Engagement

Stakeholder engagement in KT is increasingly recognized as important [21,22]. Stakeholders are defined as "individuals, organizations or communities that have a direct interest in the process and outcomes of a project, research or policy endeavor" [23]. The Institute of Medicine, Agency for Healthcare Research and Quality, James Lind Alliance, and Patient Centered Outcomes Research Institute have all developed frameworks for systematically including patients in research, from topic generation to dissemination of results [24-28]. The involvement of relevant stakeholders in all phases of research has been called authentic stakeholder engagement [29].

Authentic engagement includes stakeholders as full partners in setting research priorities; forming research questions; and shaping the design, funding, conduct, and dissemination of studies. Authentic stakeholder engagement must be built on a foundation of trust between researchers and stakeholders [29,30]. In their review of the literature in 2018, Boaz et al [21] described 3 broad categories of important requirements for building this trust and authentically engaging stakeholders: organizational, value, and practice requirements. At the organizational level, researchers should begin by embedding stakeholder engagement into the frameworks of their projects and then allocating resources to support not only the engagement activities but also the evaluation of engagement and rewarding successes [21]. Next, researchers should foster shared values among researchers and stakeholders, including understanding roles, expectations, and activities and encouraging commitment to sustained and continuous engagement [21]. Finally, Boaz et al [21] identified 5 practices focused on ensuring that stakeholder engagement

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activities are flexible and systematically enacted and that stakeholder feedback is collected and applied to improvement efforts.

Within VHA, the use of stakeholder engagement methods has steadily increased in the past 2 decades [22]. Methods including the use of advisory councils, veteran engagement groups (VEGs), community-based participatory research, action research, patient-centered research, and human-centered design have become popular within VHA [22]. There is still a need to identify ways to measure and evaluate the quality of stakeholder engagement and its outcomes [31-33]. However, the impacts of stakeholder engagement on research have been documented in the literature both within the VHA [22] and within the broader scientific community [21]. Partnerships among those who produce research and those who use it are likely to enhance the relevance of research and facilitate its use [30]. An engaged stakeholder-driven process to generate and prioritize a research agenda increases the relevance and utility of sustainable interventions and services [34].

The Need to Assess Gaps in Current CR Research

In 2010, a Rehabilitation Research and Development (RR&D) state-of-the-art (SOTA) conference was convened on *issues in defining and measuring veteran CR* [9]. At the SOTA conference, researchers discussed ways to improve the measurement of outcomes for veteran CR, including outlining goals to accomplish this, based on current gaps in the literature.

Since the SOTA conference, the bulk of veteran CR research has focused on assessing CR among individuals with mental health conditions, including projects focusing specifically on posttraumatic stress disorder (PTSD), traumatic brain injury (TBI), and polytrauma [11,35-51]. Some of the SOTA goals have received limited attention, such as the need for more comprehensive measurement approaches for veteran CR. Although new measurements were in development at the time of the SOTA conference (eg, Military to Civilian Questionnaire [M2CQ], [52]; Community Reintegration of Injured Service Members [CRIS], [9]; and Community Reintegration of Injured Service Members Computer Adaptive Test [CRIS-CAT], [9]), other measures are yet to be developed and validated within the VA [52-55]. Moreover, little research has been conducted to complete head-to-head comparisons of CR measurements and instruments [55,56].

Another goal that has received limited attention is the need to measure veteran CR across the life span. Given that veteran CR is often a cyclical process that occurs throughout the lifetime of a veteran, this is an aspect of veteran CR research that requires more attention in coming years [51,57]. Similarly, the effect of veteran CR on society also needs to be studied more, as the CR struggles of veterans may have ripple effects within their communities [58-60].

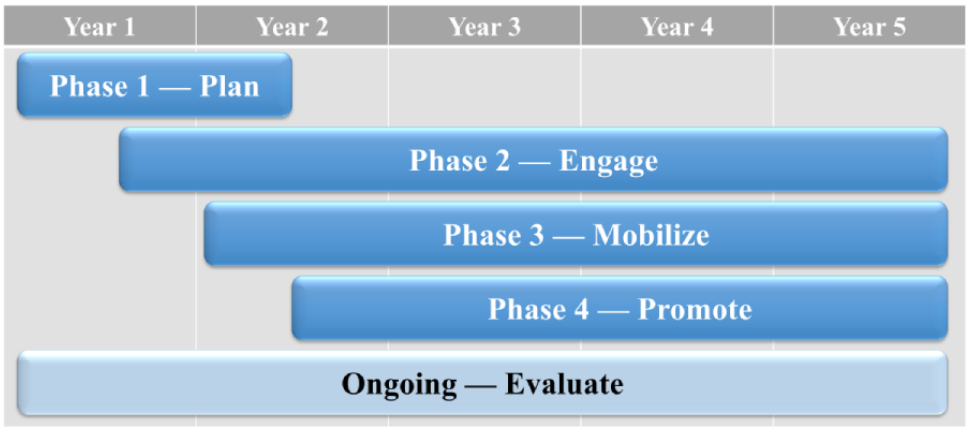
Since Resnik et al [9] published the SOTA proceedings in 2012, it has become a seminal reference in veteran CR research, particularly for VA-funded research. In support of the goal of this project to enhance the impact of VA research for improving veteran CR, the SOTA conference became a natural point of reference. It became a starting point for the need to assess where the current gaps in the science of veteran CR research remain.

Methods

Design and Overview

The ENCORE project's 5-year road map contains five phases of activities designed to accomplish project objectives (Figure 1): (1) plan, (2) engage, (3) mobilize, (4) promote, and (5) evaluate. This project uses primary and secondary data and stakeholder engagement activities. The methods used during these phases will be described in detail in the following sections.

Figure 1. Timeline for the Enhancing Veteran Community Reintegration Research project's 5-year road map.



Phase 1 (Plan): Review of Research and Assemble the MSP

Review of Research

The findings of the 2010 RR&D SOTA conference on *issues in defining and measuring veteran CR* will be used as a starting point for the review of veteran CR research [9]. At the SOTA conference, researchers discussed ways to improve the measurement of outcomes for veteran CR, including discussions of how veteran CR should be measured, challenges that arise when measuring veteran CR, and recommendations for improving veteran CR measurement. In addition, recommendations were made for future research and policies on veteran CR.

For VA-funded veteran CR grants, the review will focus on grants funded by the VA's Office of Research and Development

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and specifically through the following service lines: Health Services Research and Development, RR&D, and Clinical Science Research and Development. For non–VA-funded veteran CR grants, the review will identify grants sponsored by the National Institutes of Health, Department of Defense, and private foundations (eg, Robert Wood Johnson Foundation). Searches will be conducted within VA research databases (including Office of Research and Development) and the National Institutes of Health Reporter and PubMed databases. Research that examined veteran CR issues will be inputted into a Microsoft Excel (Microsoft Corp) tracking sheet. Additional searches for veteran CR research projects will be conducted within Google Scholar for investigators who were known to be linked to VA veteran CR research (VA principal investigators) to identify any missing studies. As the identified literature is reviewed, the reference lists will also be reviewed for relevant publications that did not appear in the literature searches.

The VA Evidence Synthesis Program (ESP) is a resource program that provides timely and accurate syntheses of targeted health care topics of importance to clinicians, managers, and policy makers, as they work to improve the health and health care of veterans [61]. The project team will collaborate with the VA ESP to conduct a search for published literature on veteran CR research focusing on the following question: What studies have examined interventions for promoting veteran CR (eg, reintegration into work, school, or other productive activities or reintegration into social relationships) among Operation Enduring Freedom, Operation Iraqi Freedom, and Operation New Dawn veterans with PTSD, TBI, spinal cord injury (SCI), or polytrauma? This ESP review focused on this selected group of veterans for both pragmatic and scientific reasons. Most of the studies reviewed for the SOTA conference consisted of studies conducted in rehabilitation populations, which include veterans with diagnoses such as PTSD, TBI, SCI, and polytrauma. The ESP review will enable a targeted review of interventions for these populations that have been published since the SOTA conference was conducted. In addition, focusing the ESP review on these populations will enable the team to conduct a more comprehensive review of the veteran CR literature, which includes work involving the military to civilian transition and other CR-related topics. Finally, the general review of the veteran CR literature will focus on the following questions: (1) What are the gaps in evidence that could be informed by future research? and (2) What are the recommendations for future research? This review will include search results from PubMed, VA research databases, Google, and Google Scholar and will focus on published peer-reviewed journals and the *gray literature* (eg, congressional reports and technical reports).

Assemble the MSP

The MSP was strategically assembled to set a veteran CR research agenda for the VA. An MSP is a collaboration across multiple sectors with vested interests in an issue [22,34,62].

Sampling

Overview

Members of the MSP will have experience in veteran CR and a vested interest in advancing impactful research in this field. The MSP will comprise (1) VA CR program leaders; (2) representatives from community-based veteran service organizations (VSOs); (3) veterans, their families, and caregivers; and (4) researchers with expertise in veteran CR. ENCORE can provide stipends to 16 non-VA employee members of the MSP. Microsoft Excel will be used to build a database of potential MSP members. The database will be organized according to member type. A nonexhaustive list of potential MSP members will be added to the database using a set of inclusion criteria (Textbox 1).

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Textbox 1. Inclusion criteria for the Multistakeholder Partnership member groups.

Inclusion criteria for Department of Veterans Affairs community reintegration (CR) program leaders

- Program office goals and services align with at least one of the primary veteran CR domains of focus: (1) work and other productive activities and (2) social relationships and activities
- Program office supports either one of the following:
  - Priority populations that are at great risk for veteran CR challenges
  - Priority populations that are underrepresented in veteran CR research
  - Services that address specific diagnoses that place veterans at great risk for veteran CR challenges
  - Nominated by operational partner during expert interview

Inclusion criteria for community-based veteran service organizations

- Organization passes Department of Veterans Affairs due diligence criteria
- Organization has specific veteran-focused programming that addresses primary veteran CR domains of focus: (1) work and other productive activities or (2) social relationships and activities
- Organization supports priority populations that are at great risk for veteran CR challenges or those that are underrepresented in veteran CR research
- Organization is not engaged in lobbying, for-profit activities, or sponsoring research
- Organization has transparent financial and affiliate information

Inclusion criteria for veterans, their families, and caregivers

- Expressed interest in veteran CR
- Commitment to collaborate with Multistakeholder Partnership by sharing CR experiences and abiding by rules of group engagement
- Willing to participate in the Multistakeholder Partnership for 1-2 years

Inclusion criteria for CR researchers

- Demonstrated expertise in veteran CR that resulted in the development of a model, instrument, policy, collaboration, and so on, related to veteran CR
- Demonstrates a broad and historical view of veteran CR
- Work aligns with at least one of the primary veteran CR domains of focus: (1) work and other productive activities and (2) social relationships and activities
- Does not have another role in the Enhancing Veteran Community Reintegration Research project
- Willing to participate for 1-2 years

VA CR Program Office Leaders

Expert informant interviews with this group will be used to recruit VA veteran CR program office leaders into the MSP. Interviewees will be asked to participate in the MSP or nominate someone to represent the program office on their behalf.

Representatives From Community-Based VSOs

As the scope of ENCORE was on veteran CR research agenda to target future research and increase the impact of existing research, recruitment focused on national organizations and programs that still have critical contact with veterans who are not enrolled in or using VA services. To build the list of potential non-VA community veteran CR program leaders, members of the research team will search for VSOs using the following resources:

1. The national directory of VSOs assembled by the VA
2. The VA's congressionally chartered National Advisory Committee list of VSOs
3. The VA Office of Community Engagement's current list of VA-partnered community organizations
4. Internet search engines, using combinations of the following terms: "Veteran," "community," "reintegration," "integration," "inclusion," "return," "nonprofit," and "service"

In addition, the ENCORE team will ask for VSO nominations from the James A Haley Research Service VEG.

To refine the database, ENCORE will assess the appropriateness of partnering with each organization with the VA's internal *Non-Profit Organization Due Diligence Worksheet* [63] to ensure that the nonprofit organization serves veterans with transparency and integrity (ie, clear mission, goals, and history; available list of board and staff members; available list of services, products, and clientele; verified in nonprofit integrity databases; and not associated with controversy or lawsuits). Organizations that pass the due diligence assessment will be scored against additional inclusion criteria (Textbox 1).

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Veterans, Their Families, and Caregivers

We will use snowball sampling to identify potential veteran and family member participants. We will ask our network of veteran contacts (eg, the James A Haley Research Service VEG) to provide us with the names of other veterans and family members who may be interested in the MSP, using our inclusion criteria as a guide. We conducted outreach with potential veteran candidates through personal conversations with the veteran or family member to ensure a shared understanding of responsibilities, interests, and goals. Veterans and family members can decide on their own whether to participate in the MSP. The goal of recruiting veterans and family members is to establish collaborative relationships through the MSP, whereby veterans are viewed as equal partners to achieve shared goals [30].

Veteran CR Researchers

The ENCORE team will develop a list of researchers who have demonstrated publishing and research record focused on veteran CR. Specifically, we will identify researchers whose work has resulted in the development of CR models, policy, CR measurements, and innovations that align with the goals of ENCORE. CR researchers will be identified through a review of the veteran CR literature, and a database will be created based on the stated inclusion criteria and will include researchers who work in the VA and those from outside the VA.

Recruitment

ENCORE team members will recruit MSP members via email. Invitations will include the targeted language for each of the MSP stakeholder groups. Potential participants will receive a 2-week response deadline within which to respond. Up to 3 reminders will be sent within the 2-week response time frame, and the last reminder will include discrete response options: (1) yes and (2) no, not at this time.

Phase 2 (Engage): Conduct Expert Interviews and Engage the MSP

Expert Informant Interviews

Sampling

Expert informant interviews will be conducted with representatives from VA program offices to learn about the VA's efforts to address and provide services related to veteran CR. The goals of the interviews will be to learn how VA program offices define veteran CR, what direct or indirect services they provide to veterans, how they set priorities around veteran CR, how their VA program aligns with other VA program offices to address veteran CR, and what studies are needed to improve veteran CR services at the VA (Multimedia Appendix 1). The same inclusion criteria described in Textbox 1 for the MSP members will be used to determine which VA program offices should be contacted for interviews. For VA program offices that meet the inclusion criteria, participants for expert informant interviews will be identified by reviewing public-facing program office websites and VA intranet sites. This activity is focused on the breadth of services and programs used by the VA to support veteran CR and how research can support organizational and program priorities for great impact.

Recruitment

Potential expert informant interview participants will be emailed directly with an invitation to participate in a 30-minute virtual interview. Up to 3 recruitment emails will be sent. The email invitation will include the request for the person to designate another appropriate contact in their office or program if they are unable to participate.

Data Collection Procedures

All expert informant interviews will be conducted virtually using Microsoft Teams. Each participant will receive a short demographic questionnaire to complete and an audiovisual consent form, giving permission for the interview to be recorded. Interviews will be led by 2 experienced qualitative researchers, with one person conducting the interview using a semistructured interview guide (Multimedia Appendix 1) and the other person taking notes using a structured note-taking template. In addition, each expert informant interview participant will be asked for referrals to other VA program personnel who would have expertise relevant to the project.

Data Analysis

A rapid assessment process and qualitative matrix [64] will be used to analyze key informant interviews with VA program office staff. The rapid assessment process is an iterative team-based technique in which data management and analysis can occur concurrently [65]. Transcript notes will be created, which will represent the interview discussion. As a first level of analysis, notetakers will summarize these interview notes by question.

Next, a qualitative matrix will be developed using Microsoft Excel spreadsheet to organize and visualize the interview data. Transcript note summaries will be entered into the matrix according to case (rows) and questions and quotes (columns), so that in each cell, the source information is summarized as it relates to each case and question. Overall, 2 experienced qualitative team members will code the transcript note summaries using Microsoft Excel columns. Codes are words or short phrases that describe the essential meaning of textual data [66]. Qualitative consensus on the transcript note summaries and thematic descriptions will be achieved through several team meetings.

Engage the MSP

Meeting Facilitation

MSP meetings will be conducted using group facilitation techniques commonly used in organizational development and qualitative research to help groups make decisions or guide them to reach consensus [67,68]. Such techniques offer structure and leadership in group meetings without assuming authority over or responsibility for group outcomes [67,69]. Techniques include flip-charting [67,69,70], asking open-ended and probing questions, and checking in with the group to ensure that everyone is comfortable with group dynamics and processes [69]. ENCORE will collaborate with a facilitator from the Veterans Integrated Service Network 8 Organizational Development Team who is external to the project team. This facilitator will help the MSP to determine and enforce ground

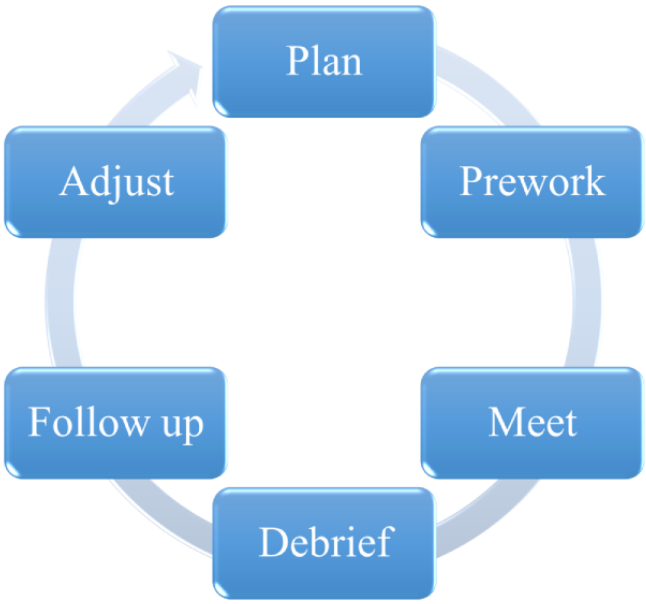
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rules and achieve their overall and individual meeting goals and objectives.

Owing to the ongoing COVID-19 pandemic, meetings will be conducted virtually, and facilitation techniques will be modified for the virtual environment. Best practices for conducting virtual group facilitation will be identified by reviewing the literature on virtual qualitative data collection methods. Qualitative researchers have long described this approach, and increasingly, since the beginning of the COVID-19 pandemic, this approach has become more common [71-75].

ENCORE will develop and use a 6-step process for conducting virtual meetings (Figure 2). This process will be developed in conjunction with a VA facilitation expert external to the team. *Step 1* is to plan. The goal of this step is to set tangible outcomes for the meeting. Here, the ENCORE team will set meeting objectives, develop an agenda, determine staff and technology needs for the meeting, identify the meeting structure (eg, Will all work be accomplished as a single large group, or will small breakout groups be required to facilitate discussion?), and gather any materials that the MSP will need to review ahead of the meeting.

Figure 2. The 6-step Enhancing Veteran Community Reintegration Research Multistakeholder Partnership group facilitation process.



Step 2 is prework. The goal of this step will be to ensure that everyone comes to the meeting with the baseline knowledge or information that they need to accomplish the meeting goals. In this step, the ENCORE team will develop and send materials to the MSP for review; gather baseline information from the MSP by sending opinion polls and surveys to the group, if applicable; develop any presentation and breakout group materials for the meeting; and assign staff roles for the meeting. Roles will include the following: (1) facilitator, in charge of leading the meeting; (2) producer, responsible for ensuring the smooth flow of the meeting from activity to activity and troubleshooting any technology issues; (3) notetaker, in charge of observing and documenting group processes and discussions; (4) chat monitor, responsible for monitoring the chat feature of the virtual platform, responding to chats, and bringing important points to the attention of the group verbally; and (5) breakout group facilitators, in charge of facilitating small group sessions.

Step 3 is to meet. ENCORE team members will convene half an hour before each scheduled meeting to check whether their audiovisual technology works and troubleshoot any issues. Next, a technology check will be conducted for MSP members, so that they can verify their audiovisual connections for the meeting. The group facilitator will present the goals and objectives of the meeting, review the group's ground rules, and ensure that the group is on track to meet their goals. In some sessions, breakout groups (small groups of 4-6 MSP members and an ENCORE group facilitator and notetaker) will be needed to encourage rich discussion of a topic. After the large group reconvenes, MSP members from breakout groups will report the results of their discussion.

Step 4 is to debrief. This critical step will directly follow the meeting during which the ENCORE team and the external facilitator will discuss what worked, what did not work, and what needs to change before the next meeting. After debriefing, *step 5* is to follow-up. During this step, the MSP will receive an *engagement and satisfaction survey* (Multimedia Appendix 2); notes from the meeting; and occasionally, a request for feedback and approval of a product developed during the meeting. This will provide the ENCORE team with an opportunity to extend engagement with the MSP. Finally, *step 6* is to adjust. The adjustment step will allow the team to synthesize information from the MSP meetings (step 3), impressions from the team debriefing (step 4), and results from the *engagement and satisfaction survey* (step 5; follow-up) to determine if and how the approach or processes need to be modified.

Surveys

Qualtrics [76], a web-based survey platform, will be used to survey MSP members throughout the project. Before their first meeting, MSP members will receive a *welcome survey* (Multimedia Appendix 2), which asks how they or their organization defines veteran CR, what is needed to improve

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veteran CR research, and demographic information. Refer to phase 5 for further information about evaluation activities.

Meeting Notes and Breakout Activities

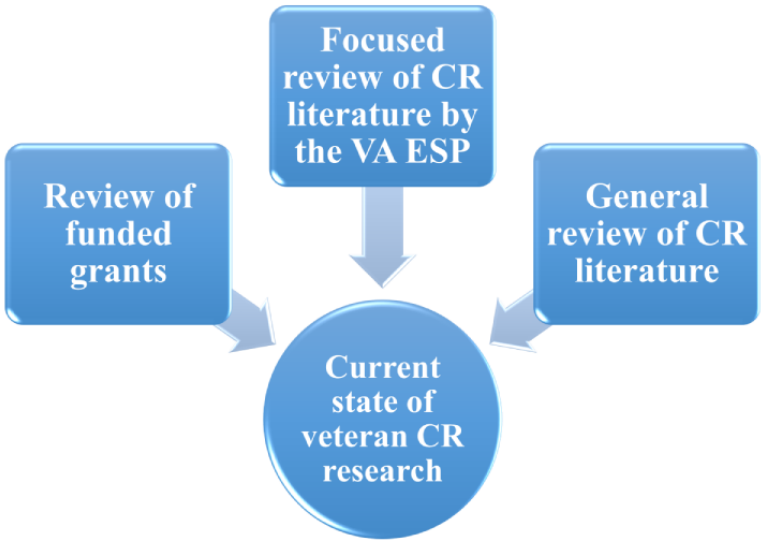
A dedicated notetaker will monitor and record group processes, discussion topics, consensus, and outcomes during each meeting. Notes will be reviewed by the ENCORE team members directly following each meeting and amended, if necessary. Chat box conversations will also be included in these notes and contextualized to document every form of participation that occurs. Notes will be shared with the MSP and analyzed using rapid content analysis [77-79] to refine products, determine areas for improvement in meeting processes, and earmark items for follow-up.

Phase 3 (Mobilize): Gap Analysis and Technical Assistance for Researchers

Gap analysis is a tool or process used to identify and define current issues within a department or field of study. Gap analysis of the relevant literature and funded veteran CR–related studies that have been published over the past 10 years will be conducted to gain a more comprehensive understanding of the state of veteran CR research. Furthermore, the areas of research on veteran CR that have received the most and least attention will be identified to highlight areas of focus that may require additional research in the future.

Gap analysis of the state of veteran CR research will be framed by ENCORE's two key veteran CR domains of focus and will use a three-step process (Figure 3): (1) review veteran CR research that was funded by VA and non-VA grants in the past 10 years; (2) collaborate with the VA ESP to compile an evidence compendium of veteran CR research focusing on interventions that promoted veteran CR among veterans with PTSD, TBI, SCI, or polytrauma; and finally, (3) review the veteran CR literature not included in the other 2 searches. Findings from research portfolio reviews, ESP requests, and literature reviews will be aligned with the 2010 RR&D SOTA goals to evaluate progress and critical gaps. This activity will form the evidence base for the research agenda–setting activities.

Figure 3. Sources contributing to the Enhancing Veteran Community Reintegration Research gap analysis. CR: community reintegration; ESP: Evidence Synthesis Program; VA: Department of Veterans Affairs.



In years 4 and 5, ENCORE will also offer technical assistance services to researchers, VA program offices, and community organizations seeking to conduct research that is related to veteran CR. Activities and services will focus on (1) consultations that provide insight and assistance on leveraging the elements of the ENCORE veteran CR research agenda, (2) providing feedback about grant solicitations and grant proposals through the MSP meetings, and (3) connecting with experts in the field for additional support.

Phase 4 (Promote): Communication Plan

In the *promote* phase, the ENCORE team will connect with the VA Health Services Research and Development Center for Information Dissemination and Education and consult with experts in dissemination and implementation (D&I) and KT. The primary target audiences for D&I and KT activities will be veteran CR researchers both within and outside VHA. The goal of this phase will be to communicate veteran CR research needs for great impact of research on policies and services. Through continued MSP engagement in the format of regular meetings and email communications (as described previously), a stakeholder-driven and prioritized D&I plan will be developed for ENCORE project deliverables and ENCORE-informed research, policies, and practices. Secondary audiences (eg, policy makers, service providers, and VA patients) will be targeted based on stakeholder input. In partnership with MSP stakeholders, public-facing dissemination products and resources will be developed and refined with the help of an ENCORE VEG to ensure that the products are meaningful to and tailored to meet the needs of multiple audiences. In addition, a public-facing website that contains links to selected products will be created and hosted through the Center for Information Dissemination and Education. Dissemination activities beginning in this phase, including the development of publications, are estimated to continue for at least 1 year after completing the project.

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Phase 5 (Evaluate): MSP Surveys

Following each MSP meeting, participants will receive a *meeting satisfaction and feedback survey* (Multimedia Appendix 2), asking for comments on their experiences and seeking feedback about ways to improve. Occasionally, surveys will be sent to MSP members, asking them to finalize products, make decisions, and prioritize the next steps for upcoming meetings and products. Close-ended survey items will be analyzed using descriptive statistics. Open-ended survey responses will be analyzed using a matrix analysis process [64,80]. Given the iterative nature of the project, ENCORE will review the evaluation needs regularly.

Ethical Considerations

The local VA Research and Development Committee at the James A Haley Veterans' Hospital has determined this evaluation to be a quality improvement project with nonresearch status. Therefore, it is not subject to human participants research ethical reviews, and written informed consent will not be required before data collection [81]. However, owing to local facility policies, written consent for audio-recording the interviews will be required for data collection.

Privacy and Security

Interviews will be recorded using Microsoft Teams, and audio files and notes will be saved in a secured network folder. The secured folder is accessible to the members of the evaluation team. When reporting the results of the interviews, all efforts to preserve confidentiality will be made, and data will be reported in the aggregate when appropriate.

Ensuring Inclusion and Accessibility

All recruitment and data collection materials will be drafted between eighth and tenth grade level using *plain language* principles for clear communication [82]. Technology checks and one-on-one technical assistance will be offered to ensure that all participants can fully participate in virtual meetings regardless of visual, hearing, or cognitive impairments.

Results

As of December 2022, data collection for ENCORE is ongoing. So far, 20 representatives from 16 VA program offices providing veteran CR–related services participated in a 30-minute telephone interview. Notably, through these interviews, veteran CR was understood to occur at any time after separation, not just immediately after military separation or retirement. Furthermore, veteran CR is cyclical and extends across the veteran's lifetime as opposed to a single point in time. ENCORE developed and assembled the MSP, reviewed the VA funding portfolio and veteran CR research literature, and conducted a scientific gap analysis. The MSP comprises VA program directors (10/25, 40%), veterans and caregivers (5/25, 20%), established veteran CR researchers (5/25, 20%), and representatives of community-based VSOs (5/25, 20%). The MSP developed a veteran CR research agenda that included 3 research priorities [22]. In addition, the MSP is currently working with the ENCORE team to prepare materials for dissemination. The ENCORE project is funded till June 2024.

Discussion

Significance

ENCORE's 5-year road map contains 5 phases of activities that are essential to achieve the overall impact goal of ENCORE, which is to improve VA policies, programs, and services related to veteran CR. The ENCORE protocol engages the MSP as full partners throughout the process, including in the formation of research questions and in shaping the design, funding, conduct, and dissemination of studies [29]. Therefore, the ENCORE protocol is uniquely situated to not only identify gaps in the veteran CR research literature but also to determine a ranking of the priority of those gaps. An engaged stakeholder-driven process to generate and prioritize a research agenda is known to increase the relevance and utility of sustainable interventions and services [29,34]. Owing to the stakeholder engagement activities that ground this project and the overlapping timelines for all phases, detailed planning of each activity is critical to avoid delays and ensure that all stakeholder activities run smoothly.

Engagement is becoming understood to be central to the development, implementation, and dissemination of research activities [83]. The use of an MSP for engaging stakeholders to identify research priorities and develop a research agenda is a novel approach for mobilizing veteran CR research [84]. It differs from traditional methods for reaching consensus across sectors as a means of engagement. For example, the more traditionally used Delphi method aims to reach consensus through indirect methods such as questionnaires and typically relies on experts instead of those directly affected [85,86]. In contrast, ENCORE uses an MSP to engage stakeholders, allowing for their direct input. The MSP's feedback will help to ensure that veteran CR research will have a lasting impact by addressing research questions identified as relevant by the veteran community [83].

Strengths and Limitations

Strengths of this project include stakeholder engagement activities that were deliberately and thoughtfully planned to achieve project goals. A rigorous process is being used to select candidates for the MSP, and additional efforts are being made, such as using an external facilitator for well-planned and executed meetings. Given the diversity of perspectives, MSP products are more likely to be relevant and responsive. Limitations include the resources (eg, staff and time) available, which affected the project's scope and narrowed the focus to veterans (not active duty service members); VA programs; and other governmental and nongovernmental organizations discussed by VA stakeholders, which did not include the Department of Defense. Similarly, limited resources also affected the team's ability to plan and conduct projects that prioritize stakeholder engagement. The veteran and family member group did not constitute a representative sample of veteran viewpoints but rather a collaborative partnership where their shared voices and experiences were valued in the process of shared decision-making. In addition, owing to COVID-19, some MSP members had additional responsibilities that precluded them from attending all meetings.

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Conclusions and Implications

The goal of ENCORE is to improve the impact of veteran CR research on policies and programs. This protocol describes methods that can be used by researchers and other professionals for engaging multiple stakeholders to prioritize research, program, and policy needs of specific populations. By grounding activities in authentic stakeholder engagement to accomplish project objectives, ENCORE can work toward achieving its goal. Using a stakeholder-engaged process is more likely to result in a relevant and responsive veteran CR research program.

Acknowledgments

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Data Availability

The data sets generated and analyzed during this study are not publicly available owing to the Department of Veterans Affairs record and access policies but are available from the corresponding author upon reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Enhancing Veteran Community Reintegration Research expert informant interview guide.
[DOCX File , 18 KB - resprot_v12i1e42029_app1.docx]

Multimedia Appendix 2
Multistakeholder Partnership questionnaires—welcome survey and engagement and satisfaction survey.
[DOCX File , 20 KB - resprot_v12i1e42029_app2.docx]

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Abbreviations

CR: community reintegration
CRIS: Community Reintegration of Injured Service Members
CRIS-CAT: Community Reintegration of Injured Service Members Computer Adaptive Test
D&I: dissemination and implementation
ENCORE: Enhancing Veteran Community Reintegration Research
ESP: Evidence Synthesis Program
KT: knowledge translation
M2CQ: Military to Civilian Questionnaire
MSP: Multistakeholder Partnership
PTSD: posttraumatic stress disorder
RR&D: Rehabilitation Research and Development
SCI: spinal cord injury
SOTA: state-of-the-art
TBI: traumatic brain injury
VA: Department of Veterans Affairs
VEG: veteran engagement group
VHA: Veterans Health Administration
VSO: veteran service organization

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Protocol

Evaluation of the Care Pathway in the Context of the Dispensing of Emicizumab (Hemlibra) in Community Pharmacies in France: Protocol for a Cross-sectional Study Based on the Kirkpatrick Model

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Abstract

Background: Commercialized since 2019, emicizumab (Hemlibra) was available only in French hospital pharmacies for prophylaxis of hemophilia A with or without inhibitors. Since June 15, 2021, patients can choose between a hospital and community pharmacy. These changes in the care pathway have important organizational consequences for patients, their relatives, and health professionals. Two training programs are available for community pharmacists: the "HEMOPHAR" training program proposed by the national reference center for hemophilia and the Roche training program proposed by the laboratory that markets the product.

Objective: The PASODOBLEDEMI study aims to evaluate the direct impact of the training programs provided to community pharmacists in the context of the dispensing of emicizumab, and to evaluate patients' satisfaction with their treatment whether they choose dispensation from a community pharmacy or retained dispensation from the hospital pharmacy.

Methods: We designed a cross-sectional study based on the 4-level Kirkpatrick evaluation model: the immediate reaction of community pharmacists following training (*Reaction*), the knowledge acquired during the training (*Learning*), the professional practice of community pharmacists during dispensing of the product (*Behavior*), and patients' satisfaction related to the treatment whether it is dispensed from a hospital or from a community pharmacy (*Results*).

Results: Considering that single outcome measures cannot adequately reflect the complexity of this new organization, the Kirkpatrick evaluation model provides 4 distinct outcomes: the immediate reaction after the HEMOPHAR training program, the level of knowledge acquired after the HEMOPHAR training program, the impact of training on professional practice, and patient satisfaction with access to emicizumab. We developed specialized questionnaires for each of the 4 levels of the Kirkpatrick evaluation model. All community pharmacists involved in dispensing emicizumab, whether they have followed the HEMOPHAR or the Roche training program or neither, were eligible for inclusion. All patients with severe hemophilia A were eligible, irrespective of inhibitor use, age, treatment with emicizumab, and whether they chose dispensation from a community pharmacy or retained dispensation from a hospital pharmacy.

Conclusions: The new organization for dispensing emicizumab to patients with hemophilia A in French community pharmacies must be accompanied by optimal safety and quality conditions due to the risk of serious and urgent bleeding situations in the

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management of rare bleeding diseases. The elaboration of the PASODOBLEDEMI protocol has already a positive impact with the commitment of all health professionals, physicians, hospital and community pharmacists, and the patient community. The results will be disseminated among the French authorities and will enable, if necessary, proposing this access model to other rare diseases.

Trial Registration: ClinicalTrials.gov NCT05449197, https://clinicaltrials.gov/ct2/show/NCT05449197?term=NCT05449197; ClinicalTrials.gov NCT05450640, https://clinicaltrials.gov/ct2/show/NCT05450640?term=NCT05450640

International Registered Report Identifier (IRRID): DERR1-10.2196/43091

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KEYWORDS

hemophilia; care pathway; healthcare management; emicizumab; Kirkpatrick model; Kirkpatrick; emicizumab; dispense; pharmacy; pharmacist; pharmaceutic; dispensing; dispensary; dispensation; patient satisfaction; pharma; community pharma; community health; hospital pharma; prophylaxis; hemophilia; knowledge acquisition; learning; cross-sectional; e learn; e-learning; questionnaire; survey

Introduction

Background

Severe hemophilia A is an inherited bleeding disorder due to the deficiency of clotting factor VIII (FVIII), which causes bleeds occurring internally into joints and muscles, or external bleeding from minor cuts, surgical procedures, or injuries. The frequency and intensity of bleeding depends on the level of FVIII deficiency. In high-income countries, the life expectancy of patients with severe hemophilia A is decreased by 37%, the prevalence is estimated to be approximately 6 per 100,000 males, and prevalence at birth is to be approximately 9.5 cases per 100,000 males [1]. In France, the prevalence of severe hemophilia A has been estimated to be approximately 2095 patients in September 2022 [2]. Conventional management consists of FVIII replacement therapy. To maintain a sufficient level of clotting factor in the bloodstream to prevent bleeds, patients with severe hemophilia A are typically prescribed prophylactic treatment that consists of regular administration of FVIII, for example, every day, week, or month, according to how long the factor lasts in the body. Although effective, this treatment can only be administered intravenously, and in France, as well as in other countries [3-6], dispensation FVIII is only available from hospital pharmacies; they both contribute to organizational and geographical constraints [7] as well as a significant mental burden for patients and their caregivers, particularly for the parents of children with hemophilia [8].

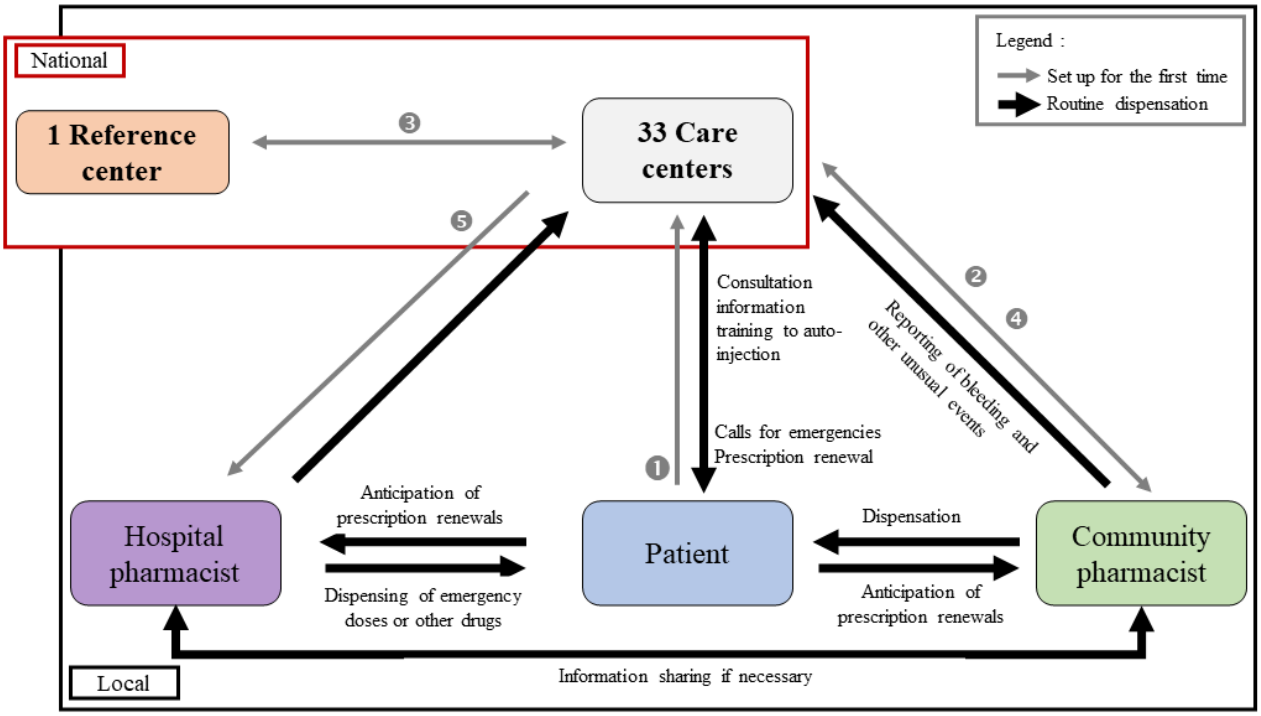
Dispensing Circuit of Emicizumab in France

Emicizumab (Hemlibra) is a laboratory-engineered protein that works by performing a key function in the clotting cascade that is normally carried out by the FVIII protein [9-12]. It can be prescribed for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults and children of all ages, newborn and older, with hemophilia A, with or without treatment with an FVIII inhibitor [13-15].

In 2019, emicizumab received marketing authorization for severe hemophilia A with or without an inhibitor in Europe [16]. This drug was initially available only from French hospital pharmacies, but from June 15, 2021, it has also been available in community pharmacies. The availability of emicizumab in community pharmacies was accompanied by the implementation of a rigorous new organization of the care pathway (Figure 1), ensuring that all professionals involved in the management of patients were identified by community pharmacists for an optimized exchange of information with the hospital pharmacy and the national reference center for hemophilia. Community pharmacists have the possibility to follow the training program by making a request to the reference center for hemophilia. The e-learning course called “HEMOPHAR” is based on the disease and its issues, and was designed by a multidisciplinary team of health care professionals from the reference center for hemophilia, as well as the platform for exchange and research on blood-derived medicines and their recombinant analogues (Plateforme d'Echange et de Recherche sur les Médicaments DErivés du Sang et leurs analogues recombinants) of the French society of clinical pharmacy (Société Française de Pharmacie Clinique). Also, a short training session organized by Roche, which that markets the drug, validated by the French medicines agency (Agence nationale de sécurité du médicament et des produits de santé) is proposed to pharmacists who order the drug; this is dispensed by telephone and aims to review the key points on the proper use of this medicinal product (including storage methods and ordering).

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Figure 1. New organization of the dispensation circuit of emicizumab since June 15, 2021, in France. The black arrows indicate the routine dispensing organization, including emergency management of bleeding episodes. The gray arrows represent the setting up of the organization for the first time initiated by the patient, whose steps are numbered in the order of implementation. The patient indicates his/her chosen community pharmacy to one of the 33 care centers. The care center requests the connexion codes for the e-learning course "HEMOPHAR" from the reference center for hemophilia, and the community pharmacist is invited to follow the training. To facilitate the relationships between hospital and community pharmacists, practical information sheets are shared, including a contact sheet, checklist for dispensing emicizumab, and liaison sheet between the community pharmacist and the care center. The hospital pharmacy is informed by the care center about the transition of dispensing emicizumab in community pharmacy.



Objectives of the PASODOBLEDEMI Study

These changes in the dispensing circuit have important organizational consequences for community pharmacists, becoming both new stakeholders and contacts in the patient care pathway [17]. The effectiveness of this new organization, and in particular the training, therefore needs to be evaluated. To address this, we designed a national study that aims to evaluate the direct impact of the training programs provided to community pharmacists in the context of the dispensing of emicizumab, and to evaluate patient satisfaction with their treatment whether they choose dispensation from a community pharmacy or retained dispensation from the hospital pharmacy.

Methods

Evaluation Strategy: the Kirkpatrick Model

Overview

The Kirkpatrick model (KM) represents a reference for the evaluation of training programs. Studies of various designs and purposes were addressed using the KM; for example, to evaluate a nutritional education program provided by health care professionals [18], to evaluate a train-the-trainer program for health care providers [19], to assess the training of cardiopulmonary resuscitation for nurses [20], to evaluate educational programs for undergraduate dental students regarding appropriate prescribing behavior during their early educational years [21], or to determine the effectiveness of a course for community health workers [22].

The popularity of the KM can be traced to several factors [23]. First, it addressed the need for training professionals to understand training evaluation in a systematic way by providing a straightforward language for communicating about training outcomes. Second, the KM provides trainers with a way to measure the results of what they do in terms of economic impacts and outcomes, which also measures the success of the organization. In addition, to simplify the complex process of training evaluation, a guide to the type of questions and the criteria that may be appropriate to focus on at different temporalities and information levels is provided.

Level 1: Reaction

The first level of evaluation consists of collecting immediate feedback from participants after completing the training. This information can be used to determine which elements of the training are working well or appreciated, and which ones need to be improved. Indicators such as participation rate, completion rate, or time spent on training are typically collected to supplement participant feedback.

Level 2: Learning

The second level is to accurately measure what participants did or did not learn during the training. Usually, the KM suggests a pre- and posttraining evaluation to quantify progress, for example, through knowledge tests or competency interviews. In contrast to immediate reactions to training, this level allows

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for the measurement of specific outcomes by identifying *Learning* objectives or targeting expected effects of training. When pretraining data are missing, the knowledge acquired post training is evaluated in accordance with the expected knowledge.

Level 3: Behavior

The third level is to determine if the training had a direct impact on the participants' behaviors. This level of evaluation is the most time-consuming because it takes several weeks or months for participants to build confidence and apply their knowledge in their professional practice. To measure *Behavior*, data collection and feedback experience are needed to give participants the opportunity to apply the skills they learned during training; for example, by exposing them to a simulated situation. It is important to mention that a lack of behavioral change does not necessarily mean that the training was ineffective.

Level 4: Results

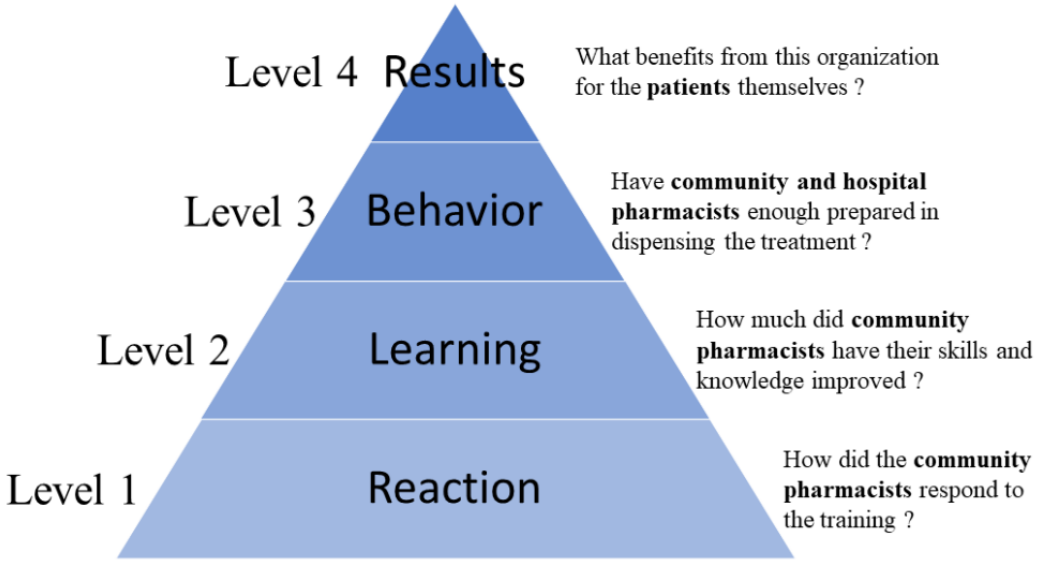
The fourth level consists of assessing the impact of behavioral changes of the participants on the systemic organization, and in determining if the training reached the expected impact or improved the organization.

Methodology

Study Design

We designed a cross-sectional study based on the KM. The first 3 levels are based on the data directly collected from the pharmacists. Level 1 refers to the evaluation of the immediate reaction of community pharmacists who followed the HEMOPHAR e-learning program and level 2 to their knowledge acquisition. Level 3 consists of evaluating the professional practice of both hospital and community pharmacists in the dispensation of emicizumab. The fourth level of the KM refers to the patients' satisfaction related to treatment, whether dispensed from a hospital or a community pharmacy (Figure 2).

Figure 2. The Kirkpatrick model adapted to the PASODOBLEDEMI study.



Study Populations

The Community Pharmacists Dispensing Emicizumab

Community pharmacists who received personalized login codes for the HEMOPHAR e-learning program from the national reference center for hemophilia were eligible for inclusion in this study for the evaluation of *Reaction* and *Learning*. All community pharmacists involved in the dispensing of emicizumab since June 15, 2021, whether they have followed the HEMOPHAR training program or the Roche training program or neither, were eligible for the evaluation of *Behavior*. Retired community pharmacists are excluded, as are those who have changed practice locations and are no longer practicing in a community pharmacy dispensing emicizumab.

Patients With Severe Hemophilia A With or Without an Inhibitor

All patients with severe hemophilia A, with or without an inhibitor, regardless of age, treatment with emicizumab, and whether they chose dispensation from a community pharmacy or retained dispensation from a hospital pharmacy, were eligible for the evaluation of the results. For those younger than 18 years, a legal representative fills out the questionnaire, and for those aged 18 years or older who need assistance in completing the questionnaire, this may be provided by caregivers or relatives.

Time Frames

A clinical research associate (CRA) is specifically dedicated to contact community pharmacists, informing them of the study modalities and outcomes, and inviting them to complete the e-questionnaires at the appropriate time (Table 1). Immediately after training is completed, the community pharmacists are invited to complete a questionnaire; this will be used to evaluate *Reaction*. The CRA is also able to incite community pharmacists—who have received their connexion codes but who have not yet started the HEMOPHAR learning program—to finalize the HEMOPHAR training program. During the HEMOPHAR training program, community pharmacists also

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complete 4 quizzes related to the following sections: presentation of the disease, therapeutic management, organization of care, and practice in the community pharmacy. The responses to the quizzes will be used to evaluate *Learning*. All community pharmacists are invited to complete the e-questionnaire related to *Behavior* at least 3 months after the implementation of the organization. Patients treated with emicizumab are invited to complete the appropriate questionnaire related to *Results*, an e-questionnaire specific to dispensation from hospital pharmacies, and a second e-questionnaire specific to dispensation from community pharmacies.

Table 1. Objectives, the eligible population, time frames, and measurement tool per levels of evaluation.

Levels	Objectives	Eligible population	Time frame	Measurement tool
Level 1: Reaction	To evaluate immediate reactions after the HEMOPHAR training program	Community pharmacists who followed the HEMOPHAR training program	Immediately after the HEMOPHAR training program	Short e-questionnaire and invitations sent by email
Level 2: Learning	To evaluate the level of knowledge acquired after the HEMOPHAR training program	Community pharmacists who followed the HEMOPHAR training program	During the HEMOPHAR training program	Responses to quizzes
Level 3: Behavior	To evaluate the impact of training on professional practice	All community pharmacists	At least 3 months after the implementation of the organization	e-Questionnaire and invitations sent by email
Level 4: Results	To evaluate the patients' satisfaction regarding access to emicizumab	All patients treated with emicizumab	At least 3 months after the implementation of the organization	e-Questionnaire available with a QR code or specific URL

Development of the Questionnaires

The e-questionnaire related to *Reaction* was intentionally short and composed of 8 questions, including 5 questions based on the 4-item Likert-scale (not at all satisfied, not very satisfied, somewhat satisfied, and very satisfied) and 3 closed-ended questions (yes/no; Multimedia Appendix 1). The estimated time to complete this e-questionnaire is estimated to be approximately 1 minute.

The e-questionnaire related to *Behavior* was composed of 13 multiple-choice questions (Multimedia Appendix 2). The estimated time to complete this questionnaire is estimated to be approximately 8 minutes.

The e-questionnaires related to *Results* were adapted to the dispensing choice of the patient (Multimedia Appendices 3 and 4). They were composed of 33 questions. The estimated time to complete this questionnaire is estimated to be approximately 6 minutes.

The content of the questionnaires was initially defined by a multidisciplinary team composed of hospital and community pharmacists and research scientists specialized in methodology and care accessibility. A scientific committee was specifically constituted for the PASODOBLEDEMI study in order to challenge and validate the purposes, methodology, questionnaires, and expected outcomes. This committee was coordinated by the reference center for hemophilia and composed of hospital and community pharmacists, physicians, and the French association of patients with hemophilia (Association Française des Hémophiles). Following the recommendations of the scientific committee, the content of the e-questionnaires has evolved by integrating operational and organizational aspects and optimizing literacy. The e-questionnaires were finally tested in real-life conditions on a sample of eligible populations. The content of the questionnaires was finally validated by the scientific committee in July 2022.

Ethical Considerations

The study complies with the reference methodology for studies and evaluations in the health field [24]; therefore, it did not require written consent to participate. The ethics committee of the Hospices Civils de Lyon approved the study (n°2022-06-01 obtained on June 14, 2022). The PASODOBLEDEMI study was registered in ClinicalTrials.gov (NCT05449197 related to the evaluation of *Reaction*, *Learning*, and *Behavior*, and NCT05450640 related to the evaluation of *Results*).

Results

Administration

All e-questionnaires may be filled out using a PC or mobile device. The hospital and community pharmacists are invited by email to complete the e-questionnaires accessible using a login and password sent by the CRA for the evaluation of *Reaction* and *Behavior*; this also allowed the linking of data between evaluation levels. The e-questionnaire related to *Results* is accessible to eligible patients via a QR code or a specific URL presented on a paper information note, hand-delivered by the community pharmacist or hospital pharmacist when the patient comes for treatment or consultation.

Data Collection

Data collection for the first 3 levels started on July 1, 2022, and for the fourth level, the questionnaires for patients were available since September 12, 2022. The study ended on December 31, 2022.

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Discussion

Anticipated Findings

The availability of emicizumab in community pharmacies represents a significant advancement of the care pathway for patients with hemophilia A. The direct expected benefit concerns the improvement of the patients' satisfaction by reducing the mental burden due to the geographical and organizational constraints to hospital pharmacies [8]. As observed in the management of other diseases, distance to the pharmacy may play a role in pharmaceutical management, leading, for example, to inappropriate and inadequate medication and management of asthma for patients living further from their preferred pharmacy [25]. Also, the dispensing by community pharmacies may provide better access and satisfaction to the patients [26]. For example, it is reported that the dispensing in community pharmacies of medicines previously only available from hospital pharmacies during the first wave of the COVID-19 pandemic in Portugal led to a significant increase in satisfaction levels in all evaluated domains: pharmacist's availability, opening hours, waiting time, privacy conditions, and overall experience [27]. In the United States, satisfaction of patients with schizophrenia was improved by dispensing a long-acting injectable medication in community pharmacies during the COVID-19 pandemic [28]. In addition, a collaboration between opioid treatment programs and community pharmacists supported the feasibility and acceptability of physician prescribing and community pharmacy for access to methadone [29].

The new organization for dispensing emicizumab to patients with hemophilia A in French community pharmacies must be accompanied by optimal safety and quality conditions due to the risk of serious and urgent bleeding situations in the management of rare bleeding diseases. Based on the KM, the PASODOBLEDEMI study focuses on the evaluation of the training program and patient satisfaction 1 year after the implementation of the community-based dispensing of emicizumab. Widely used in the literature [30], the KM presents advantages, including ease of implementation and provision of evaluation of the systemic impacts on the organization. Considering that single outcome measures cannot adequately reflect the complexity of the organization, the KM provides 4 distinct outcomes.

The KM presents limitations [23] because the 4-level implementation can be time-consuming and requires an expensive investment to collect data and analyze learning outcomes. It is also difficult to establish a direct link between outcomes and training.

Other methodologies have been developed and used for evaluation of training programs, but which were not adapted to the PASODOBLEDEMI study. For instance, the Context-Inputs-Process-Product model (or the Stufflebeam model) [31,32] is based on the comparison of pre- and posttraining program evaluation to assess the gain in knowledge and confidence of participants; the Levels of Learning model (or the Kaufman model) is based on the use of specific evaluation scales (Kaufman Test of Educational Achievement) as an individually administered battery that provides in-depth assessment and evaluation of skills [33], but the design of this model is too rigid for the objectives of this study; and the Success Case Method (or the Brinkerhoff model) that is closer to an economically oriented performance scale with a study design based on a survey and semistructured interviews [34].

Conclusions

The elaboration of the PASODOBLEDEMI protocol has already had a positive impact with the commitment of all health professionals, physicians, hospital and community pharmacists, as well as the patient community. The results will be disseminated to the French authorities and will enable, if necessary, proposing this access model to other rare diseases.

Acknowledgments

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Data Availability

The data sets generated during and/or analyzed during the current study are not publicly available due to their confidentiality but aggregated results are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1

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Questionnaire for the evaluation of Reaction.
[DOCX File , 20 KB - resprot_v12i1e43091_app1.docx]

Multimedia Appendix 2
Questionnaire for the evaluation of Behavior.
[DOCX File , 24 KB - resprot_v12i1e43091_app2.docx]

Multimedia Appendix 3
Questionnaire for the evaluation of Results (To patients or legal representatives or caregivers who have chosen community pharmacy dispensing).
[DOCX File , 20 KB - resprot_v12i1e43091_app3.docx]

Multimedia Appendix 4
Questionnaire for the evaluation of Results (To patients or legal representatives or caregivers who have retained hospital pharmacy dispensing).
[DOCX File , 20 KB - resprot_v12i1e43091_app4.docx]

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Abbreviations

CRA: clinical research associate
FVIII: clotting factor VIII
KM: Kirkpatrick model

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Protocol

Web-Based Patient Recommender Systems for Preventive Care: Protocol for Empirical Research Propositions

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Abstract

Background: Preventive care helps patients identify and address medical issues early when they are easy to treat. The internet offers vast information about preventive measures, but the sheer volume of data can be overwhelming for individuals to process. To help individuals navigate this information, recommender systems filter and recommend relevant information to specific users. Despite their popularity in other fields, such as e-commerce, recommender systems have yet to be extensively studied as tools to support the implementation of prevention strategies in health care. This underexplored area presents an opportunity for recommender systems to serve as a complementary tool for medical professionals to enhance patient-centered decision-making and for patients to access health information. Thus, these systems can potentially improve the delivery of preventive care.

Objective: This study proposes practical, evidence-based propositions. It aims to identify the key factors influencing patients' use of recommender systems and outlines a study design, methods for creating a survey, and techniques for conducting an analysis.

Methods: This study proposes a 6-stage approach to examine user perceptions of the factors that may influence the use of recommender systems for preventive care. First, we formulate 6 research propositions that can be developed later into hypotheses for empirical testing. Second, we will create a survey instrument by collecting items from extant literature and then verify their relevance using expert analysis. This stage will continue with content and face validity testing to ensure the robustness of the selected items. Using Qualtrics (Qualtrics), the survey can be customized and prepared for deployment on Amazon Mechanical Turk. Third, we will obtain institutional review board approval because this is a human subject study. In the fourth stage, we propose using the survey to collect data from approximately 600 participants on Amazon Mechanical Turk and then using R to analyze the research model. This platform will serve as a recruitment tool and the method of obtaining informed consent. In our fifth stage, we will perform principal component analysis, Harman Single Factor test, exploratory factor analysis, and correlational analysis; examine the reliability and convergent validity of individual items; test if multicollinearity exists; and complete a confirmatory factor analysis.

Results: Data collection and analysis will begin after institutional review board approval is obtained.

Conclusions: In pursuit of better health outcomes, low costs, and improved patient and provider experiences, the integration of recommender systems with health care services can extend the reach and scale of preventive care. Examining recommender systems for preventive care can be vital in achieving the quadruple aims by advancing the steps toward precision medicine and applying best practices.

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KEYWORDS

recommender systems; preventive care; health information systems; eHealth; clinical quality measures

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Introduction

Current State of Recommender Systems in Health Care

The integration of recommender systems into eHealth or e-medicine is an underexplored area in research [1]. With the abundance of medical information available on the web, expertise and context-specific knowledge are needed to analyze it effectively [2]. Implementing technology such as recommender systems in health care services can bring about several benefits. First, it can enable aging population groups such as baby boomers, Generation X, and millennials to effectively process and filter the information they find on the web or receive from medical professionals [3]. Second, it can assist insurers and health care providers to shift toward a merit-based payment system, in which providers are compensated based on their patients' outcomes and the ability to lower costs while keeping patients healthy [4]. To facilitate this transition, recommender systems will act as part of the patient-centered team-based workflow, by supporting patient compliance with the treatment protocol. This shift can encourage providers to adopt a preventive approach, rather than just treating secondary and tertiary medical conditions.

Objectives

This study examines the extant literature and formulates quantitative propositions to explore the factors influencing patient use of recommender systems for preventive health decision-making. A proposition is a statement formulated for empirical testing that may be true or false based on some observable phenomena. It also proposes a study design and methods for developing a survey and conducting an analysis. Preventive care helps patients to identify diseases that can cause medical problems before they become serious. Many Americans are unaware of simple tests that could save their lives or prevent years of costly treatment [5,6]. For example, the US Preventive Services Task Force recommends initiating low-dose aspirin use for the primary prevention of cardiovascular disease. In 2019, the Centers for Disease Control and Prevention reported that stroke (cerebrovascular disease) was the fifth leading cause of death in the United States. Patient use of recommender systems can predict and enhance the treatment protocol for diseases such as stroke [7] and could reduce the number of deaths.

The existing literature lacks information about the factors motivating patients to use recommender systems for preventive care. The propositions developed in the study are intended to assist patients in deciding whether to use the available recommender systems for preventive care. We also aim to provide a starting point for future researchers interested in using recommender systems for preventive care. We begin this inquiry into the eHealth recommender system by describing the types of recommender systems. We develop practice-based empirical propositions and further the applied research angle by identifying salient issues with recommender systems. Finally, we discuss general issues with recommender systems and provide strategies to address them to improve the use of recommender systems.

Recommender System Types and Applications

Overview

Traditional recommender systems can be classified as collaborative, content based, and hybrid [8]. Recommender systems also use the following algorithmic approaches to recommend items: group and knowledge-based recommendations [9] and demographic filtering [10]. Finally, there is a context-aware filtering classification.

Collaborative Filtering

Collaborative filtering is the most used type of recommender system built on a collaborative algorithm that uses 1 user's choice to predict subsequent user preferences [11]. Correlation among users plays an essential role in this type of recommender system. Collaborative filtering applications are heavily used in e-tourism, where the preferences of previous visitors are used to predict activities that new travelers may engage in [10]. In addition to traditional collaborative filtering methods, *matrix factorization* improves the algorithm by using a baseline [12]. Other proposed enhancements to the collaborative filtering method include using trust as a replacement for the evaluation performed by a user. Results from studies indicate that using trust as a filler for rating preserves the accuracy and coverage of the predictions provided by the recommender systems [13]. To improve customer resource management, researchers modified the collaborative filtering method to include a multifactor for a bipartite network—that is, an affiliation network. The proposed model improved the recommendations' accuracy and diversity [14].

Researchers have proposed a hybrid method to address the limitations of the traditional collaborative filtering approach. By incorporating the Big 5 personality dimensions, the collaborative filtering algorithm's active learning capabilities are enhanced, allowing for the use of personality type to overcome the problem of sparsity, resulting in improved accuracy and a great number of recommendations [15]. Other modifications include developing new systems that can learn and adapt to user feedback to elicit changes in health behaviors. For example, researchers have proposed a collaborative filtering-based computer-tailored health communications system that delivers personalized messages to individual patients based on explicit feedback (ratings) about past messages. These studies suggest that most users have positive opinions about smoking cessation support messages recommended based on their past ratings [16]. Another example of adapting to user feedback is creating an algorithm to recommend treatment based on patients' pretreatment preferences and posttreatment satisfaction. This study demonstrates the feasibility of using a collaborative filtering recommender system to provide accurate recommendations and guide shared decision-making [17].

Furthermore, collaborative filtering and clustering can be used to develop a drug recommendation system that suggests medications for patients with diabetes by comparing a specific patient profile with those of patients with similar characteristics [18]. Similarly, collaborative filtering and clustering can be used to develop a recommender system for patients with cardiovascular diseases [19]. Although the number of studies

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on collaborative filtering systems is increasing, their application in the health care domain remains limited. The use of this type of recommender system for computer-tailored interventions and health recommendations is still in its early stages. However, there is potential for these systems to determine appropriate drugs and treatments for patients and deliver personalized messages that motivate behavior change.

Content-Based Filtering

Content-based recommender systems (CBRSs) rely primarily on item descriptions [20]. They evaluate options and recommend a product, person, or service based on a user's previous acquisitions or suggested preferences [21]. The process of a CBRS is divided into 3 steps. First, the content is represented in a processable format. Then, the algorithm learns about the user. Finally, a recommendation is made for that specific user. The advantage of a content-based system is that it offers personalized recommendations and does not require a rating or previous documentation of an item, thus making the recommendation process more efficient [22]. However, the complexity of the current e-service and e-product landscape requires CBRS users to integrate it with other recommender algorithms.

CBRSs have a range of applications in health care, such as promoting data set reusability, refining the research process, and recommending health education. They accomplish this by streamlining the process of identifying relevant data sets. For example, by deducing researchers' academic interests from their list of publications, the system can make data set recommendations that users may find useful or interesting [23]. In addition, the process of conducting clinical research studies is refined by calculating the similarity between annotated publications and the research query and recommending the most relevant literature. This enhanced recommender system can be integrated into research platforms to support future medical studies by helping researchers refine their research questions [24]. Furthermore, CBRS can be used to develop a content-based system that recommends health educational websites to users based on the metadata of the videos they have watched. The system suggests relevant websites for a given health video and facilitates the search for additional related content [25]. Although existing studies propose novel approaches, they have yet to be implemented in the broader health care context, and their limitations warrant further exploration. However, as the volume of health-related information increases, solutions that assist users in selecting relevant information become increasingly important. This recommender system can support health information retrieval by reducing the burden of searching for relevant information.

Hybrid Filtering

The hybrid filtering recommender system aims to compensate for the shortcomings of a classification model or enhance others with the advantages of an algorithm [21]. Hybrid recommender systems are a special type that combines ≥2 recommendation strategies. For example, researchers combine collaborative and knowledge-based filtering systems to create hybrids in the restaurant industry. When using hybrid systems, rich data, such as how a particular food helped reduce weight [26], can act as a filtering mechanism for group members. Results show that semantic knowledge-based ratings improve the collaborative filtering model [27]. Subsequent studies build upon previous findings by including an additional contextual modification that improves the performance of the recommender system [27]. Traditional methods of accessing videos, audio, and television have changed; a technological development is IP television, which streams content over proprietary IP-based networks. The recommender systems proposed by researchers suggest videos to users, which they would not have selected otherwise. Results show that recommender systems provide valuable recommendations despite high demand [28]. Most models today are developed as hybrids because they are more robust.

An example of hybrid collaborative filtering is a system that recommends search terms for a given patient to clinicians. The proposed hybrid model outperforms top-N recommendations by improving the efficiency and effectiveness of retrieving relevant patient information [29]. Another example is a Drug Development Recommendation model that supports pharmaceutical companies in determining which drug groups to develop. The Drug Development Recommendation model supports decision-making before companies initiate new drug development and improves the success rate by making recommendations tailored to a specific company and its unique business conditions. Another hybrid recommender system was developed to generate peer and content recommendations for patients with diabetes based on their profile, health status, and ratings of personalized content. This development offers a glimpse into the potential of recommender systems to promote a positive, healthy lifestyle via the implementation of a personalized, mobile peer support system [30]. The applications of hybrid recommender systems in health care are emerging; however, they are not used extensively in the health domain. The number of published studies on the use of hybrid models in health care is minimal so far. However, the limitations of content-based and collaborative recommender systems suggest that new studies will likely explore applications of the hybrid approach further.

Group Recommendation

Group recommendations are based on the collaboration of an entire group [9,31]. Alternatively, some refer to this recommendation type as community based [32]. An individual's community may include colleagues, friends, and family; members typically have a common outlook. Expansions in this area include travel and location-based services, where the trust walker algorithm enhances users' perception of the reliability of location recommendations given [32]. Another study concentrated on folk recommendations with a tripartite composition, suggesting that this type of filtering connects users with the same interests via social tagging; a well-known example of this recommender system is Flickr [33]. The group recommender system matrix is sparse, and users' preferences are unknown. Sparsity is a problem in a group recommender system matrix, and researchers developed a memory-based technique to resolve the sparsity issue. The results indicated that the proposed method performs better than existing approaches in generating group recommendations [34].

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Group recommender systems support decision-making by integrating the preferences or attributes of members. There is an increase in the number of studies that evaluate group recommender systems; however, their exploration remains low in the eHealth and e-medicine categories. Previous studies have assessed the composition of a group and ways to optimize the accuracy of recommendations. A study found that personality could improve the accuracy of predictions [35]. Another network-based recommender algorithm in an Italian health care organization computed similarities among patients. It generated a ranked list of physicians and hospitals suitable for a given patient profile using health data shared by the community [36]. It will be challenging to generate a real group consensus in the health care domain; however, studies show that there are ways for group recommender systems to achieve a high level of agreement among their members [37].

Context-Aware Recommender Systems

The context-aware recommendation system (CARS) category is relatively new; it modifies the content-based or collaborative filtering classes. This category is noteworthy owing to its potential for expanding research on recommender systems. Certain factors define CARSs, some of which include purchase purpose, location, and time. The e–health care, e-music, and e-travel domains successfully use the CARS algorithm. Change over time is an assessment of contextual factors that points to change over time to determine static or dynamic elements. Factors are assessed based on what is known about the facet and whether it is unobservable, partially observable, or fully observable. There are 3 forms of context-aware recommendations (prefiltering, postfiltering, and context modeling), which include the context as part of the rating process [38]. Adding context and trust enhances the collaborative filtering algorithm to combat the sparsity problem. The results from studies including these modifications indicate better recommendations [39]. A prefilling contextual technique referred to as item splitting is used to separate the characteristics of an item into a minimum of 2 distinct contextual factors; this is another method of improving the sparsity problem [40]. Hybreed is a tool developed to integrate context in the recommender system design [41]. Using accuracy and diversity as performance measures, a comparison of the 3 forms of contextual recommendation models indicates that the task affected both performance measures. Therefore, further studies in this area are needed, as no attempts have been made to reproduce the 3780 experiments conducted in this study [42].

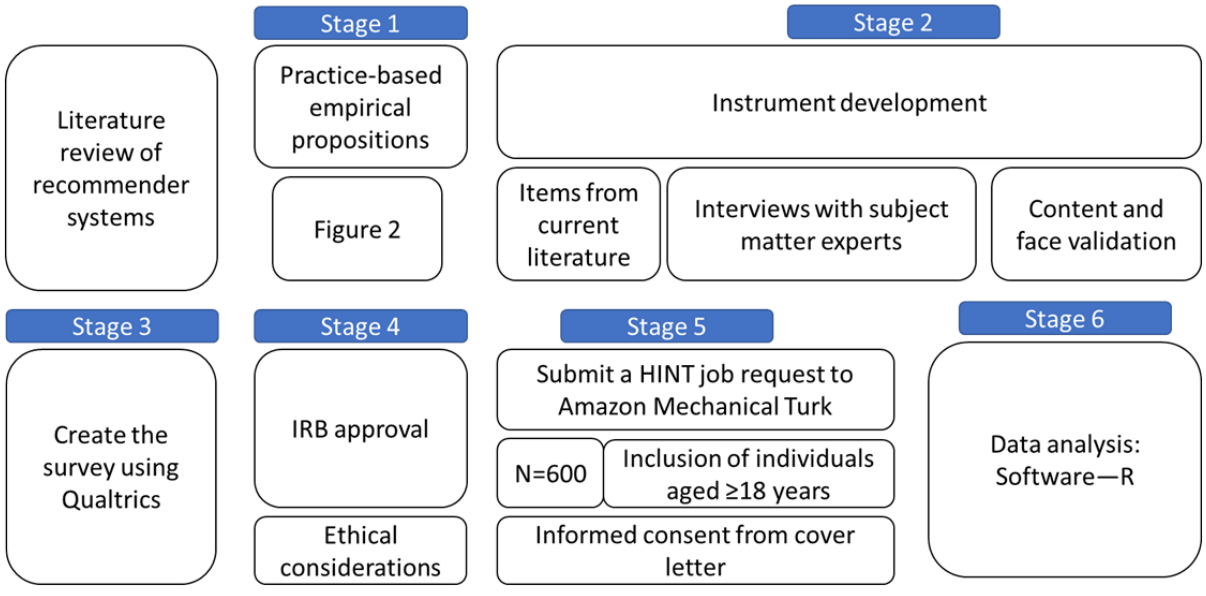
A detailed review of context awareness and health awareness in eHealth revealed that both factors are essential for developing user-personalized recommender systems [43]. Considerable amounts of data have accumulated in clinical databases. Recommender systems can supply patients with basic descriptions of information in health records to facilitate the comprehension of their health status. A study hypothesized whether the retrieval precision of an advanced health recommender system was higher than that of a naive system. The results indicated that advanced health recommender systems enhanced patient understanding of health records more than a naive system [44]. Researchers from a separate study proposed a cloud-based hybrid predictive model for a personalized health information service. Experiment results discovered that participants have a positive response toward usability measurement dimensions [45-47] of the system, such as perceived usefulness, expectation confirmation, perceived value, satisfaction, and perceived trust [48].

Methods

Overview and Workflow

This study will use a multistage qualitative methodology to explore patient perceptions about using recommender systems for preventive care decisions. Stage 1 of the framework focuses on developing practice-based empirical propositions. Stage 2 includes the development of survey instrument. Then, we will obtain institutional review board (IRB) approval for the study in stage 3, before data collection and analysis can be conducted in stages 4 and 5, respectively (Figure 1).

Figure 1. Study design and workflow. IRB: institutional review board; HINT: Human Intelligence Tasks.



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Stage 1—Practice-Based Empirical Propositions

Overview

Although recommender systems are seen as valuable in health care, no studies synthesize the factors leading patients to use this technology. The following sections present the propositions developed from constructs in previous studies that may influence patient recommender systems. Examining factors influencing the use of this technology is vital because it will support achieving the quadruple health aims—improving the patient population, reducing the cost of care, enhancing the patient experience, and improving provider satisfaction [49].

Privacy

Privacy is an issue within the literature on recommender systems [50]. Privacy concerns stem from the need for users to disseminate personalized information to allow for the best recommendation [51]. Researchers have developed methods to combat privacy challenges; however, this factor may still affect the patient's perception of usability. Strategies to protect privacy include the secure processing architecture and the anonymous contributions architecture [52]. Another attempt to reduce privacy concerns in recommender systems is justification messages to improve the experience with a recommender system [53]. A recommender system can also assist individuals in making decisions regarding their privacy by providing them recommendations and warnings based on their privacy preferences [54].

Privacy concerns present unique challenges when adopting technology in health care. For example, users of wearable medical devices are vulnerable to data security and privacy protection issues [55]. Wearable technology data security can be classified into technical security, data management, or laws and regulations. Privacy concerns challenge mental health care providers with each advancement in technology used to deliver psychotherapy services [56]. Although using email, SMS text messaging, telehealth, electronic medical records, and mobile apps aid mental health providers, such technologies simultaneously increase the risks of unintended breaches of confidentiality. As privacy and confidentiality are regarded as essential considerations in mental health care, telepsychology is limited by concerns around privacy. To address these concerns, several researchers develop a risk assessment tool to assess whether health ITs (HITs) comply with privacy policy standards [57]. They find that users of HITs emphasize the need for transparency and policies that define the type of data collected and used. Thus, as privacy risks emerge as a common concern for health care professionals and patients, privacy issues undermine users' confidence and willingness to use HITs. Privacy concerns affect the adoption of technology in health care. Therefore, maintaining the security and privacy of protected health information will be crucial for the future of health care.

Proposition 1—Privacy concerns may negatively affect the use of health care recommender systems for preventive care.

Trust

A social network of interlinked nodes connected by their confidence relations is a trust network [58,59]. Trust-based models help resolve sparsity problems [60]. Modifying existing recommender system classifications with trust improves ratings' accuracy [61]. An early study on peer production services revealed that trust-based recommender systems can substantially enhance services and overcome the issue of information overload [62]. Trust can be aggregated into ontology and used to update user profiles to improve the recommendation process [63]. In scenarios where patients or individuals face conflicting recommendations, trust can help the user to make a better choice regarding the accuracy of the results [64]. Trust represents a vital antecedent of the acceptance and use of technology in health care. A recent study identifies perceived usefulness, usability, training, and technical support as trust facilitators. In contrast, the lack of privacy, perceived risks, and cost and security issues represent the main barriers [49]. Similarly, another study analyzes the enablers and impediments of trust in digital health. These trust factors indicate whether to place trust in digital health technologies [65]. Asan et al [66] focus on clinicians as primary users of artificial intelligence (AI) systems and how trust shapes their use and adoption of AI. In this context, trust refers to applying AI-based systems to support clinical decision-making. The lack of trust in AI deters users' adoption of this technology in health care. As trust is the most notable factor influencing the adoption of wearable health devices [67], understanding how users define trust in the health care technology context provides insight into the use of technologies.

Proposition 2—Trust may positively affect the use of health care recommender systems for preventive care.

Effectiveness

An effective recommendation will help a customer make a better choice or choose a product that they would otherwise not have selected. Studies have shown that a combination of rating and content can increase effectiveness [68]. Systems can provide less effective measures by overestimating or underestimating a recommendation for a particular patient [69]. Variations in predictions should be carefully considered during the development of a health system. For preventive care measures, overestimation may cause the most ripple effects. For example, a test ordered very frequently could increase costs, or inaccurate preventive measures could have considerable medical consequences. The lack of effectiveness is an issue when adopting technology in health care. For example, technological tools, including telehealth, mobile app, and SMS text messaging, can address the mental health crisis during the pandemic. Each tool helps provide the needed psychological support; for instance, the effectiveness of telehealth is comparable with that of in-person counseling services [70]. A similar study assesses the effectiveness of mobile health (mHealth) technology in suicide prevention. The results suggest that these mHealth technology tools effectively reduce suicide-specific outcomes [71]. In addition, digital health technology effectively monitors and treats asthma [72]. Ineffectiveness is a considerable adoption

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barrier because it indicates the future utility of a given technology in health care.

Proposition 3—Effective recommendations positively affect the use of health care recommender systems for preventive care.

Accuracy

Accuracy is one of the most frequently used measures for evaluating a recommender system; however, these often include complex calculations that average customers are not privileged to access. The patient's perception of whether the system is making correct predictions may influence use [69]. Service providers use accuracy measures to help customers make better product and service selections. Will the patient's perception that the recommendations are correct affect their opinion and usability of preventive health recommendations? Accuracy is also an issue when adopting technology in health care because the low accuracy of these technologies raises concerns regarding the threat posed to patient safety [73]. The adoption of these technologies should be carefully considered, especially if their performance is inferior to that of current practices. A recent study examines the quality of information provided by web-based symptom checkers, where physicians outperform symptom checkers regarding the accuracy of diagnostic data [73]. This accuracy concern highlights the need for further studies on symptom checkers. Users cannot solely depend on the technology; for example, the Apple Watch overestimates the value for energy expenditure of patients with cardiovascular disease but accurately measures their heart rate [74]. These accuracy issues imply that it is premature to use the Apple Watch for cardiac rehabilitation. Therefore, caution should be exercised when adopting technology with accuracy issues in health care.

Proposition 4—Perceived accuracy positively affects the use of health care recommender systems for preventive care.

User Satisfaction

User satisfaction refers to the perception of the system services after personally experiencing the system [75]. The level of satisfaction that patients receive from using community-based health care recommender systems may vary across individuals. If customers are more satisfied, they tend to implement the recommendations; the opposite is true if they are dissatisfied [48]. HIT literature reports high user satisfaction leading to increased adoption of technology in health care in various health care settings. For example, patients' acceptance of the health technology program increased with high patient satisfaction with the digital tools incorporated into the program [76]. Patient satisfaction with telemedicine determines its long-term viability beyond the pandemic [77]. Patients experienced higher satisfaction with web-based visits than with in-person visits, which is not surprising considering that health care professionals can still address patients' questions and concerns without compromising quality. High user satisfaction leads to great acceptability for lifestyle apps in mHealth [78]. User satisfaction indicates that a specific technology sufficiently satisfies patients; however, low satisfaction rates suggest that the barrier to adopting that technology in health care is important.

Proposition 5—User satisfaction positively affects the use of health care recommender systems for preventive care.

Efficiency

A fundamental business system requirement is efficiency. For example, one of the largest recommender systems, Google, searches in seconds. Similarly, more specialized recommender systems are expected to perform tasks quickly or reduce the time it takes to make choices [79]. Efficiency is the user's perception that the recommendation improved decision-making [47]. When adopting HIT such as recommender systems, efficiency is important. HIT refers to technology that assists in preventing, diagnosing, and treating diseases. HITs, such as electronic health records and health information exchanges (HIEs), facilitate care coordination by making information available and providing real-time decision support to physicians [80]. HIEs enable the sharing of patient health information electronically among providers, patients, and payers across different health care settings [81,82]. Researchers have assessed the impact of HIT's efficiency. The findings demonstrated that HIT improves efficiency by decreasing use rates [83]. A similar study found that adopting HIT enhances hospital efficiency. However, adopting HIT and increasing the employment of physicians nullifies the positive impact on hospital efficiency [84]. Finally, another study aimed to determine whether participating in HIE networks improves hospital efficiency. The author concludes that participating in HIEs improves hospital efficiency but calls for more research [85]. Similar to the implementation of other large-scale HIT, recommender systems may affect patient efficiency.

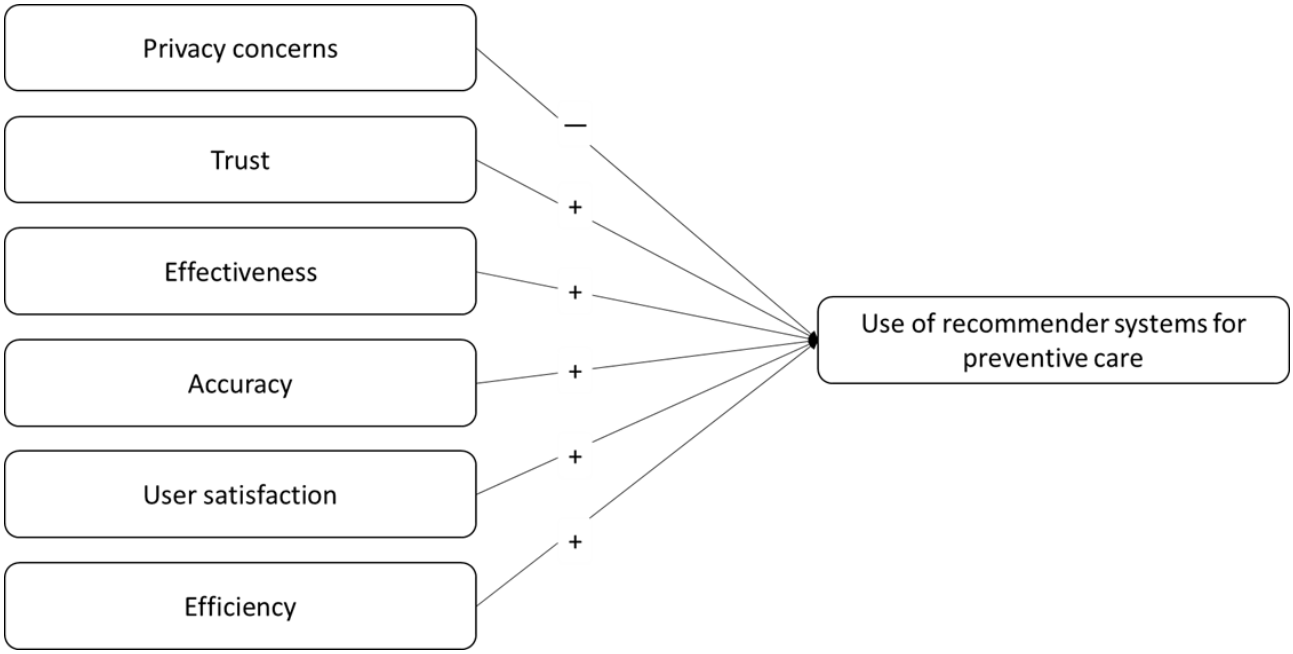
Proposition 6—Perceived efficiency positively affects the use of health care recommender systems for preventive care.

Stages 2 and 3—Instrument Development and Operationalization of Variables

Researchers can develop an instrument after literature reviews and interviews with subject matter experts, including information systems professionals, physicians, and patients. An expert in survey design will be consulted to ensure that the questions are phrased appropriately to elicit proper responses for the measured factors. The review team can consist of 3 to 5 individuals to represent the abovementioned expertise, including the principal investigator. Before the final items are selected for the survey, we will assess content and face validity using a short questionnaire that includes the items and construct definitions [86,87]. IRB approval may not be required for this process; 25 to 30 professionals or students can be used to elicit the validation results. Items will be rated on a 7-point scale from 1 (not at all) to 7 (completely), aligned with the construct's definition. Items that do not match precisely with the construct definitions—responses below the mean—should be refined or removed from the final instrument. Discarded questions can be replaced with new ones, and the validation process can be repeated. Figure 2 depicts the plausible measurement model for the likelihood of using recommender systems for preventive care with several reflective indicators. Table 1 presents the constructs and references.

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Figure 2. Research model—propositions for evaluating a recommender system for preventive care.



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Table 1. Recommender system constructs and references.

Constructs and items	Studies
Privacy concerns	Xu et al [88,89]
I am concerned that the recommender system will collect large amount of personal information from me.	—[a]
I am concerned that the recommender system will use my personal information for unauthorized purposes.	—
I am concerned that unauthorized people will have access to my personal information.	—
Trust	Liu and Tao [90] and Kim et al [91]
The recommender system is trustworthy.	—
The content of the recommender system is reliable.	—
Overall, I trust the recommender system.	—
Competency-related trust	Esmaeilzadeh [92], Mpinganjira [93], and McKnight et al [94]
The recommender system is competent.	—
The recommender system performs its role very well.	—
Effectiveness	Liu and Tao [90]
The recommender system provides personalized recommendations that are based on my information.	—
The recommender system personalizes my health care experience by acquiring my personal preferences.	—
The recommender system delivers personalized health care services.	—
Accuracy	Yang et al [95]
The recommender system offers consistent results over time.	—
I feel confident that the recommender system offers error-free results.	—
User satisfaction	Park et al [96]
Overall, I am satisfied with the recommender system.	—
The recommender system meets my expectations.	—
I recommend the recommender system to others in health care.	—
Efficiency	Garg et al [97]
The recommender system will help in providing health care services.	—
The recommender system will increase the speed of services.	—
The recommender system will increase efficiency.	—

[a]Not applicable.

The dependent variable—the use of recommender systems—can be modeled based on the theory of planned behavior using a binary item [98-100]. This theory contends that behavioral, normative, and control beliefs affect a person's intentions to perform a particular behavior; the strength of these intentions influences an individual's actual behavior [101,102]. This proposed study design adopts the theory of planned behavior as a fundamental behavior theory to represent patient behavior, especially in terms of their use of recommender systems. Researchers can examine patients' adoption of recommender systems by extending the theory of planned behavior to the health care context. Individual attitudes, subjective norms, and perceived control influence patients' intention to use recommender systems. Therefore, individual perception and social influences are antecedents of their intention to use recommender systems; the greater this intention, the more likely that the adoption behavior will be realized. The use variable can be dichotomous (yes or no).

Privacy concerns can include 3 items [88,89]. When formulating trust items, researchers can combine two trust constructs: (1) general trust [90,91] and (2) competency-related trust [92-94]. The effectiveness construct can use 3 reflective items [90]. The accuracy construct can be measured using 2 items [95]. Short-form measures have limitations; however, they are as effective at capturing a construct as extended scales when adequately designed [103]. Possible robustness checks are discussed in the *Stage 6—Data Analysis* section. Overall, 3 reflective items can be used to measure user satisfaction [96] and efficiency [97]. Scale scores can be computed as the averages of individual items and anchored to strongly agree,

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agree, somewhat agree, strongly disagree, disagree, and somewhat disagree.

Stage 4—Ethics Approval

This study has been submitted for ethics approval to the California State University Institutional Review Board (reference number: 2038900-1) through a secure web portal. Approval may take 4 to 6 weeks, depending on whether revisions are required and the frequency with which the board meets. It will be approved if the board finds that this study involves minimal risk to the participants. Participants are informed that they can skip questions they do not feel comfortable answering or choose not to participate. The survey is anonymous, and participants cannot be identified.

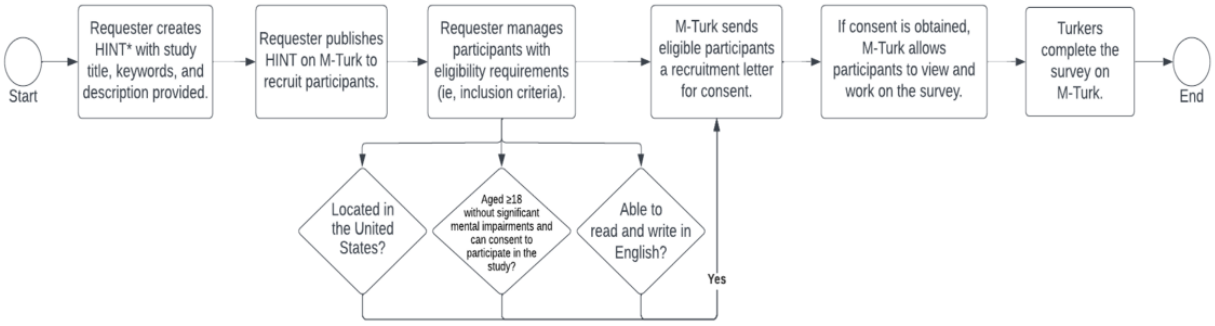
Stage 5—Initial Data Collection: Amazon Mechanical Turk

Overview

This study will be conducted via the web; this aligns with the study's aims to examine the perceptions of adults in need of preventive care. Data will be collected using Qualtrics (Qualtrics) via an anonymous survey link. Qualtrics is a web-based data collection tool; its functionality allows users to create a customized survey.

Amazon Mechanical Turk is a hosted platform that allows researchers access to a wide range of participants [104]. Participants are called *turkers* or *crowdworkers*. They browse their profile for Human Intelligence Tasks (HINT), which includes a brief description of the responsibilities. Posting the survey on the HINT list will initiate participant recruitment for the study. Amazon Mechanical Turk allows requesters to select worker requirements to enforce the inclusion and exclusion criteria. To be included, participants should be aged ≥18 years without serious mental impairments and consent to participate in the study. Participants must be in the United States and be able to read and write in English. The procedure for recruiting individuals and how participants access and complete the survey is depicted in Figure 3.

Figure 3. Amazon Mechanical Turk (M-Turk) workflow. HINT: Human Intelligence Tasks.



The survey cover page will be used to distribute the recruitment letter and obtain informed consent. The letter will also provide an overview of the study, participation criteria, and any benefits or risks to the participant. Completed survey data are automatically stored if Qualtrics is used. It is reasonable to assume that the time needed to complete the survey will be approximately 10 to 15 minutes. Before beginning the survey, all participants will receive a vignette [105] describing what a recommender system is and an example of how it will be used in their care.

Sample Vignette

Recommender systems are the systems that are designed to suggest things to the user based on many different factors. They are used by companies such as Google, Instagram, Spotify, Amazon, Reddit, and Netflix, to entice users with relevant content. A health recommender system may propose preventive measures to patients based on their clinical history and demographic characteristics. For example, based on available data, it may recommend talking to a primary care provider about the decision to initiate low-dose aspirin use for the primary prevention of cardiovascular disease.

Participants will answer 19 to 20 reflective questions to measure each construct, as outlined in Table 1. They will answer demographic questions on ethnicity, race, sex, income, education, employment, and the number of chronic conditions. No compensation will be provided for participating in the study. A sample size of approximately 600 participants may result in a medium effect size where the *r* value varies from 0.3 to 0.4. Effect size is a quantitative measure of the magnitude of the experimental effect [106].

Stage 6—Data Analysis

Researchers can use R to analyze the research model; it is stage 5 of the proposed study design. The following robustness check can be used to evaluate the measurement instrument. Principal component analysis will be performed; only factors with eigenvalues >1 will be selected; and then, a visual assessment will be conducted using a scree plot. A parallel analysis will be completed to review the eigenvalues for the 6 factors in the conceptual model. A Harman Single Factor test can be performed to test the effect of common bias to ensure that a single factor does not emerge. To assess discriminant validity, exploratory factor analysis will be performed. Then, any factor loading <0.70 will be examined; a loading value of 0.55 is considered as good and 0.45 is considered as fair [107]. Reliability and validity will be examined using Cronbach α; a value >0.7 is satisfactory. Multicollinearity should be examined as part of the analysis; correlation should fall below the conventional threshold value of 0.6 [108,109].

To establish the reliability and convergent validity of individual items, the average variance extracted for each construct will be

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calculated. Composite reliability measures the overall reliability of a collection of heterogeneous but similar items. Composite reliability >0.70 threshold and extracted variance >0.50 threshold are recommended [110]. The analysis of *variance inflation factors* will determine whether multicollinearity exists among the tested variables. Variance inflation factors are a scaled version of the multiple correlation coefficients between 1 variable and the remaining independent variables. Variance inflation factors below the cutoff value of 10 indicate that multicollinearity among the variables is not supported [111]. Researchers should perform confirmatory factor analysis. The goodness-of-fit indices [112-114], adjusted goodness of fit, comparative fit index, Normed Fit Index by Bentler and Bonett [115], root mean square error approximation, and root mean square residual will be examined.

Results

Data collection and analysis will begin after institutional review board approval is obtained.

Discussion

This study proposes practice-based empirical propositions for developing recommender systems in health care, focusing on identifying the factors influencing patients' use of these systems. We also provide a study design and methods for creating a survey and conducting an analysis. Our study highlights the potential of recommender systems to improve population health by educating patients about disease prevention and motivating them to use preventive services. This study aims to guide future research in the health care domain by exploring the application of recommender systems in preventive care.

Clinical quality measures such as preventive metrics are essential for monitoring health care quality. Often, patients are unaware of the many preventive quality metrics that can help improve their health care outcomes. Improved patient awareness of preventive measures helps not only them but also physicians and insurers to meet the metrics of clinical quality initiatives from advanced payment models such as primary care first, accountable care organization, merit-based incentive payment system, and Healthcare Effectiveness Data and Information Set. Hybrid recommender systems can help patients filter and use data about preventive quality metrics, making the information more accessible. Using the propositions mentioned in this paper, health care professionals and researchers can examine the factors that will lead patients to use recommender systems for preventive care.

There are advantages to implementing recommender systems and general issues that may influence patient use of the systems. As discussed in the propositions, patient privacy concerns may affect patients' likelihood of using recommender systems. Issues stemming from privacy concerns may lead patients to not share their medical records, resulting in the cold start problem. The cold start problem affects recommender systems because new users do not have a profile, thereby limiting the ability of the recommendation systems to provide meaningful information. Another privacy concern is the intrusive nature of recommender systems [69]. Algorithms require direct feedback that is linkable to a particular user; this may engender privacy concerns. Patients may be less likely to seek recommendations if their searches or history can be linked to them by administrators.

To improve patient use of recommender systems, developers must be able to improve the trust in the systems they use or the administrators governing the data collection, processing, and dissemination processes. An issue with recommender systems is overspecification, which could result in duplicate preventive testing. Patients who receive duplicated recommendations may reduce their trust in the system's capabilities. Duplicate testing may result in 2 issues: patient fatigue may reduce trust or overuse may increase costs. To reduce the influence of overspecification on preventive recommendations, developers may consider integrating current structured data from the patient's medical records to train and test recommender systems.

Perceptions about the effectiveness and accuracy of recommender systems also reduce the likelihood of patients using them. A factor that could cause efficiency or accuracy issues with algorithms is the sparsity problem, in which some services have many ratings and others do not. Data accumulation is a method to rectify the sparsity problem to facilitate accurate predictions [8]. Efforts to address this data sparsity issue should include developers working closely with insurers, providers, and patients to limit the factors affecting their likelihood of sharing data. Data blocking on the physician's side may also lead to sparsity; in response, the Cures Act should limit this practice by 2023. Furthermore, a patient may choose to share the data; however, it may not be exportable or interoperable with data from the internet or other sources. Unfortunately, data from multiple inoperable sources can lead to low efficiency. Health care organization professionals can tackle this challenge by implementing systematic data standards such as Systematized Nomenclature of Medicine, Logical Observation Identifiers Names and Codes, Current Procedural Terminology, and International Classification of Diseases and the fast health care interoperable resource standards.

This study does not address all the psychological aspects of recommender systems. Further studies are needed to better understand the physiological effects of these systems on users [69]. The trust construct developed in this study does not relate to the patient-physician trust. However, when addressing concerns about privacy and sensitive patient data, it is crucial to consider the patient-physician relationship in the design of web-based recommender systems. Developers should include features for effective communication and collaboration between patients and qualified health professionals.

Providing access to IT support services and mobile options for accessing preventive recommendations can improve patient satisfaction. Efficiency and scalability also play key roles in determining the success of recommender systems. As the amount of data available on the web continues to grow, algorithms must be able to handle the increased computational demands. Studies have shown that accuracy does not necessarily increase with large amounts of data, but computation time may [116]. Health care professionals may consider partnering with large IT companies that offer cloud computing resources to address

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scalability issues. Federal insurers such as Medicaid may also consider using a portion of cost savings from tracking preventive care to fund cloud computing hubs.

Additional studies are necessary on the physiological aspects of recommender systems [69]. In doing so, developers may improve user satisfaction and, therefore, the likelihood of use. Health care records can contain some of the most sensitive data about a person's life. Addressing the intrusive nature of recommender systems and the sensitivity of patient data leveraging the patient-physician relationship is paramount. Developers of web-based recommender systems should include features for effective communication and collaboration between patients and qualified health professionals. It may not be feasible to grant patients access to their private physicians; however, allowing access to a professional may improve patient satisfaction. Recommender systems should provide, at minimum, some IT support services and offer a mobile way to access preventive recommendations [117]. Many large IT companies such as Amazon, Microsoft, and IBM have entered the health care arena; it may be opportunistic for health care professionals to partner with them to access cloud computing resources.

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Data Availability

The data sets generated during and analyzed in this study will be available from the corresponding author upon reasonable request after completion of the study.

Conflicts of Interest

None declared.

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Abbreviations

AI: artificial intelligence
CARS: context-aware recommendation system
CBRS: content-based recommender system
HIE: health information exchange
HINT: Human Intelligence Tasks
HIT: health IT
IRB: institutional review board
mHealth: mobile health

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Protocol

Value of Including the Children's Experience for Improving Their Rights During Hospitalization: Protocol for the VoiCEs Project

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Abstract

Background: Users' feedback is a key asset for organizations that want to improve their services. Studying how organizations are enabling their users to participate in evaluation activities is particularly important, especially when there are vulnerable or disadvantaged people, and the services to be evaluated can be life-changing. This is the case in the coassessment by pediatric patients experiencing hospital stay. The international literature reports a few attempts and several challenges in systematically collecting and using the pediatric patient experience with respect to hospitalization, to undertake quality improvement actions.

Objective: This paper describes the research protocol of a European project intended to develop and implement a systematic pediatric patient-reported experience measures (PREMs) observatory that will be shared by 4 European children's hospitals in Finland, Italy, Latvia, and the Netherlands.

Methods: The VoiCEs (Value of including the Children's Experience for improving their rightS during hospitalization) project uses a participatory action research approach, based on a mixture of qualitative and quantitative methods. It consists of 6 different phases, including a literature review, an analysis of the previous experiences of pediatric PREMs reported by project partners, a Delphi process, a cycle of focus groups or in-depth interviews with children and their caregivers, a series of workshops with interactive working groups, and a cross-sectional observational survey. The project guarantees the direct participation of children and adolescents in the development and implementation phases of the project.

Results: The expected results are (1) a deeper knowledge of published methodologies and tools on collecting and reporting pediatric patients' voice; (2) lessons learnt from the analysis of previous experiences of pediatric PREMs; a consensus reached through a participatory process (3) among experts, (4) pediatric patients and caregivers about a standard set of measures for the evaluation of hospitalization by patients; (5) the implementation of a European observatory on pediatric PREMs; and (6) the collection and comparative reporting of the pediatric patients' voice. In addition, the project is aimed at studying and proposing innovative methodologies and tools for capturing the pediatric patients' feedback directly, avoiding the intermediation of parents/guardians.

Conclusions: Over the last decade, the collection and use of PREMs have gained importance as a research field. Children and adolescents' perspectives have also been increasingly taken into consideration. However, to date, there are limited experiences regarding the continuous and systematic collection and use of pediatric PREMs data for implementing timely improvement actions. In this perspective, the VoiCEs project provides room for innovation, by contributing to the creation of an international,

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continuous, and systematic pediatric PREMs observatory that can be joined by other children's hospitals or hospitals with pediatric patients, and foresees the return of usable and actionable data in benchmarking.

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KEYWORDS

patient experience; patient-reported experience; PREM; pediatric patients; children; adolescents; coproduction; coassessment; health care services; hospitalization

Introduction

Context

Children are one of the most fragile segments of the population and they might be disadvantaged in expressing their opinions, experiences, or preferences. As stated by the Manual for Human Rights Education with Young People, "the child has the right to express freely views on all matters affecting him/her, and the child's views should be given due weight." Great efforts have been made in Europe to strengthen "the right of the child to be heard" [1]. Recently, the European Union (EU) and the UNICEF (United Nations International Children's Emergency Fund/United Nations Children's Fund) promoted #TheRealChallenge campaign to raise attention on this right and make children express their views [2]. The European Youth and Information Counselling Agency (ERYICA) aims to uphold the right of young people to be empowered, make informed choices, and be active in society [3]. The project GIOCONDA financed under the LIFE+ program involves young people as protagonists of an action of participative democracy, with special attention to environment and health policies [4]. The Council of Europe "Guidelines on Child-Friendly Health Care" has promoted the design of health care services centered on children's rights and needs, considering their opinion and easing their participation. The World Health Organization (WHO) has also promoted a tool to assess the quality of hospital care provided to children in a systematic and participatory way, as well as children's rights in a hospital [5,6].

Literature and practice are demonstrating the centrality of listening to children and young people's voices on health care, both to increase the awareness of how this vulnerable population experiences care and to improve health care policy and practice [7]. Coproduction is among the most promising forms of participation with young people [8].

Current Knowledge and Previous Experiences

Evaluation of health care services is a coassessment process including comonitoring and coevaluating activities of lay people [9]. The most used definition of coproduction in the public sector defines coassessment as being focused "on monitoring and evaluating public services where state and lay actors work together to assess service quality, problems, and/or areas for improvement" [10, p. 772]. Consequently, coassessment usually happens retrospectively, when the service has been already experienced, but with the possibility of prospectively affecting the future design or delivery of the services [10]. The use of coassessment results can inform co-design and coinnovation processes aimed at improving or innovating services [11].

The participation of lay actors in coassessment processes remains rare in several sectors [12-14]. Strokosch and Osborne [12] described the negative experiences of assessment processes involving people with disability in the United Kingdom, by either public social and health care organizations or for-profit organizations. Loeffler and Timm-Arnold [13] reported a low or bad level of public involvement in coassessment initiatives concerning public safety and social services not only for young people, but also for elderly people, both using digital channels and traditional methods. Indeed, the level of participation depends also on the successful design and implementation of these coassessment initiatives. Among the most important antecedents of public participation in the evaluation of services, the so-called opportunities are those more closely linked to the service organization's activities. Organizations create opportunity of public participation by facilitating the citizens' engagement in the processes; by increasing the people's ability to effectively coproduce; by reducing the difficulties of participation [15,16]; or by setting motivational incentives, nudges, and other levers of participation [17,18]. Pestoff [19] referred to the "ease of involvement," which encompasses the cost of the involvement, the professional support including capacity building and direct mobilization of coproducers, and the definition of motivational incentives and nudges. Working on people's ability encompasses investigating these factors, which include human capital and socioeconomic conditions [20], individual characteristics (ie, age, sex, educational level), and being a user of the service to be evaluated as a factor affecting the internal efficacy of people, namely, how much they feel able to participate in certain activities, as well as their engagement [21].

From this perspective, studying how health care organizations can facilitate public participation in coassessment of services is extremely relevant. This is particularly important when the application of such research activities concerns the participation of vulnerable or disadvantaged people, and the services to be evaluated can be life changing. This is the case of the coassessment by pediatric patients experiencing hospitalization. As hospitalization represents a very delicate moment, it is especially important to focus on health-related vulnerable children and adolescents. This research project focuses on raising children's and adolescents' voices on their experience with hospital care, by studying and implementing opportunities for them to coassess and, consequently, contribute to the improvement of hospitalization services.

There are several experimental or cross-sectional studies aimed at investigating children's perceptions during hospitalization [22-25]. Using the Hospital Consumer Assessment of Healthcare

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Providers and Systems Survey (HCAHPS) [26] and the Picker Institute [27] questionnaires, health care organizations or systems periodically collect measures of experience with services, as perceived by samples of patients. At the EU level, only sporadic international attempts were found in the literature on children's experience of hospitalization, which aimed at detecting their voices on a census-like, continuous, and systematic basis [28,29]. Nevertheless, previous experiences were mainly time-constrained and did not include systematic data collection. Moreover, they were mainly sample based, not involving potentially all children, without a systematized cross-border perspective and impact.

Although children are one of the most fragile segments of the population and the hospitalization experience can per se make them more vulnerable, usually hospitalized children do not have a chance to express an opinion about the care they received. Conversely, practitioners should make decisions considering children's preferences and opinions. To this end, it is necessary to develop a tool able to give pediatric patients the opportunity to make their voices heard about such delicate moments. Developing a common and scalable observatory that continuously collects data on children's and parent's experiences with hospital care across the EU is an ambitious goal that allows the children's right of expression to be guaranteed. To the best of our knowledge, there is no European standard on patient-reported experience measures (PREMs) for children, nor an example of pediatric PREMs observatory that can be joined by European and non-European countries in the future, for collecting and benchmarking the pediatric patient voice.

This protocol presents the VoiCEs (Value of including the Children's Experience for improving their rightS during hospitalization) project, which represents a fundamental step toward the improvement of children's rights of coassessing and coinnovating health care services, as well as of practitioners' attention on their young patients' rights. This paper presents the (1) settings, (2) aims, (3) methods and analysis, and (4) ethical aspects of the VoiCEs project.

Setting

The project will be conducted by a public university in Italy, which is the principal investigator (PI) and works with a dedicated research team.

A total of 4 children's clinical university hospitals from different European countries will be directly involved as project partners:

- Meyer Children's University Hospital, Florence, Italy (AOU Meyer)
- Children's Clinical University Hospital, Riga, Latvia (CCUH)
- HUS New Children's Hospital, Helsinki, Finland (HUS)
- Erasmus University Medical Center, Sophia Children's Hospital, Rotterdam, The Netherlands (EMC)

The 4 countries cover the European south-north-east-west areas, which will ease the development of a scalable model at the European level. The 4 hospitals involved have already worked on the collection of hospitalized children's voices. In the Finnish project LAPSUS, digital methods have been piloted to capture experiences from children and teenagers [30]. The children's hospitals in Florence (Italy) and Riga (Latvia), and several university children's hospitals in the Netherlands as well, adopted PREMs for children's hospital care [28,29,31,32], reporting results on web platforms to support children-driven improvements [28,29,33,34]. These valuable experiences achieved good results in terms of child participation, and they will be the starting point to design a new European tool.

To this end, the participation within the consortium of the UNICEF, with its international and local experience on the promotion of children's rights, will ensure the focus on the priority, synergies with other European projects concerning children's rights, and a wider impact of the project.

This positive impact at the European level will be also enhanced by the support to the project from other organizations, such as:

- The European Children's Hospitals Organisation (ECHO), which supports cross-border collaborative actions and learning processes for promoting children's rights in European hospitals and improving health and care for pediatric patients;
- The Italian Association of Children's Hospitals (AOPI), which will help further promote the results among the children's hospitals in Italy;
- The Picker Institute, whose competence and interest on patient experience will contribute to increase the strength of the scientific approach adopted in the project and support a wider dissemination of its results.

Aims

The aim of the VoiCEs project is to design and implement a system ensuring that hospitalized children can continuously be involved and heard. This would help identify which aspects of care in pediatric hospitals should be improved from their point of view. The long-term objective is to make inpatient care more child-friendly in children's hospitals.

The specific objectives to be reached within the duration of the project are as follows:

- To develop a common list of measures and questions to collect the experience of pediatric patients and their parents, by directly involving experts among researchers, hospital staff and stakeholders, and children from the 4 European countries of the participating children's hospitals;
- To implement and to provide hospitalized children a mechanism to express their feelings and perceptions about their hospitalization experience in a continuous way;
- To enhance the attention of children's hospital professionals on the relevance of hearing and taking into consideration the voices of their pediatric patients in evaluating and improving services;
- To provide hospital professionals with guidelines for defining information material and organizing training programs, with the aim of promoting children's rights to make their voices heard on the experience of hospitalization; and using children's feedback for supporting improvement actions.

The project will contribute to enhancing children's participation in the evaluation and improvement of health care services during

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hospitalization. This will be done with the implementation of a common PREMs tool and benchmarking system in the 4 children's hospitals and with the planning of quality improvement activities. At the local level, one of the expected results is the increased awareness among hospital staff, as well as external stakeholders, of the relevance of listening to the voices of children as patients. This makes it possible to ensure high-quality health care services and a better experience during hospitalization. Another important outcome that can be expanded to a national level will be the benefits of child-friendly care developed using the results of the PREMs observatory. The middle-term impact will be the improvement of children's rights in the setting of the 4 children's hospitals involved in the project. At the European level, the project will make a common tool available to collect the children's experience of hospitalization, such as the validated PREMs questionnaire, and technical protocols to implement the systematic data collection. These tools will be available for other children's hospitals at the European level within the ECHO network and beyond, who can easily join the children PREMs observatory in the future.

Methods

Overview

The project will use an integrated mix of qualitative and quantitative methods that "seeks convergence, corroboration, correspondence of results from the different methods" [35, p. 259]. It provides a more complete picture, seen from different perspectives, so supporting a more in-depth understanding of the phenomenon. Within a mixed methods strategy, the adoption of different methods of data collection will be used as a means of advancing the analysis, with the results of one method at an earlier stage of research being used to inform the following one, introduced sequentially [35]. Indeed, for each phase of the project, a specific approach, as described below, will be used for producing evidence to be used in the following phases: (1) literature review; (2) analysis of the previous experiences of pediatric PREMs; (3) Delphi process; (4) focus groups (FGs) or in-depth interviews (IDIs) with children and their parents; (5) workshops with interactive working groups; and (6) cross-sectional observational survey.

The project will be based on the participatory action research approach [36,37]. Practitioners and scholars will promote the direct patient participation in research activities [38]. The children's involvement in all project steps, from the definition of the tool to collect their experience to the definition of information materials and training programs, will allow them to express their views.

The collaboration between university and children's hospitals will ensure the integration of the scientific approach and interest in new knowledge with the push toward action and engagement to improve the real life of children during their experience of hospitalization. The partnership of the consortium members with key research players, such as the Picker Institute, will support the rigor of the adopted methods. Researchers, hospital managers, and professionals with clinical competences will work together to understand general and context-specific opportunities and challenges, and to support the organizations to make changes in their services to improve the children's experience. In addition, the direct target of the project, such as children and adolescents, will be engaged directly thanks to the involvement activities carried out by the children's hospitals.

The project will be inspired by the human rights–based approach to health care [6], aiming to ensure availability, accessibility, acceptability, and quality of health services, specifically hospitalization services for pediatric patients. The principles the project will refer to are nondiscrimination, accountability for health services, as well as enhancing patient-centered health care addressing inequalities. Accordingly, the project will focus not only on outcomes, but also on processes, in particular, assessment and analysis, priority setting, program planning and design, implementation, and monitoring, facilitated by the support of the PREMs that will be implemented. In this way, the project will strengthen the capacities, on the one hand, of the pediatric patients as rights holders to make their claims and, on the other one, of the children's hospitals as duty bearers to meet their obligations and ensure health care of good quality, using the domains of patient-centered care as a basis [39] and catering for the specific needs of children.

The 2 aforementioned approaches will pervade the methods used in each project phase to achieve their objectives, as will be described in the following sections.

Literature Review

A systematic scoping review, based on peer-reviewed articles, gray literature, and project reports, will be conducted with the aim of drawing from the literature evidence on the collection of children's and adolescents' reported experience of hospitalization. Inclusion criteria, guiding the definition of the search algorithm, will be (1) as specific setting, the hospital stay; (2) as specific target, children and adolescents; (3) PREMs, thus excluding satisfaction and patient-reported outcome measures; (4) tools to collect data on children's experience, by identifying mechanisms that are aimed at giving children the right to express their voices; (5) use of children's feedback for quality improvement, in particular at a micro level within a health care organization, namely, PREMs data reporting at the ward level. The results of the literature review will inform the following collaborative process, including the Delphi process, as well as the FGs and IDIs.

Analysis of the Previous PREMs Experiences in Children's Hospitals

The project encompasses the analysis of the previous experiences of children PREMs implementation and data collection in the children's hospitals where a children's involvement initiative has been already implemented. This activity will aim at identifying and sharing lessons learnt by the children's hospitals, by analyzing their current or previous experiences in terms of pros and cons, strengths, and weaknesses, as well as good practices concerning PREMs implementation. The experiences will be described by each hospital using a common grid of analysis and shared during a workshop for comparing findings. Field notes will be taken by the participants and used together with the analytical documents

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on the previous PREMs experiences as complementary data to be analyzed. The analysis will be performed starting from an exchange of knowledge and practices among the children's hospitals, particularly on tools and mechanisms they used/are using for listening to children's voices, and on how to include children's voices in the hospital's processes of decision making (ie, health care quality improvement actions, hospitalization services' co-design processes). Also in this case, the results of the previous PREMs experiences' analysis will inform the collaborative process, namely, the Delphi process, and the FGs and IDIs.

The Delphi Process

A collaborative, consensus-building process involving children and their families as well as experts and professionals will ensure the development of the PREMs questionnaire as a common tool among the children's hospitals. This collaborative process based on a Delphi methodology will be implemented for achieving a multidisciplinary consensus on target populations, experience domains and subdomains, specific questions, and administration tools for gathering children's voices during their hospital stay. The members of the panel will express their opinions on techniques, mechanisms, and tool for engaging with children and adolescents in a systematic, continuous, and structured way, bringing the perspective of their domain of expertise.

The panel will include at least fifty participants, with different professional backgrounds and profiles, such as researchers, hospital staff, and stakeholders, from the various countries and the supporting bodies involved.

Panel members will be contacted and enrolled by the research team, the 4 children's hospitals, and other supporting institutions, also involving experts from organizations not directly involved in the project, to ensure a wide participation.

Upon acceptance, the members of the panel will receive a detailed informative pack, based on the results of the literature review, on the analysis of the previous PREM experiences and attend a preparatory event. After the latter phase, the panel members will be emailed an invitation to participate in a survey consisting of structured questions for evaluating the PREMs questionnaire for pediatric patients. Two or three rounds are expected, to define a questionnaire for collecting the pediatric patients' experience. The Delphi process will also include topics for defining the most appropriate tool to directly engage children and adolescents. A final consensus conference will be organized to finalize the process and release the questionnaire as the key final output.

The output of the Delphi process will represent the baseline of the following action research phases.

FGs and IDIs

For directly involving pediatric patients and their caregivers, each children's hospital will organize and conduct at least one FG or IDI with children and parents' representatives. Because of the COVID-19 pandemic, some partners could not adopt this in-dept methodology or will conduct only IDIs. IDIs provide rich qualitative information, although interactions among children or parents cannot be monitored directly.

The objectives of FGs and IDIs will be (1) to explore dimensions and subdimensions of experience with hospitalization that are relevant from the point of view of pediatric patients and parents; (2) to discuss the most appropriate way to involve children and adolescents in providing direct feedback on their experience of hospitalization; and (3) to validate the questions that will be used for PREMs data collection.

Detailed guidelines will be defined by the PI, to guide the hospital partners in the enrollment of pediatric patients and their caregivers, conducting FGs or IDIs or both, and in the data collection and analysis phases. The target population will be:

- Pediatric patients (4-17 years); younger children can be involved for testing dimensions and questions, according to the guidelines.
- Their parents or caregivers (≥18 years).

The enrollment technique and procedure will consider the complexity and specificity of each hospital population, practices, and context. Each hospital will enroll convenience samples, determined by the availability of patients and caregivers, as allowed by the COVID-19 pandemic.

IDI transcripts, field notes, and documents will be kept in text files.

Workshops With Interactive Group Activities

The project's most important tool for meeting the objective of the PREMs observatory implementation will be based on the organization of well-prepared workshops. The workshops will focus progressively on the operative design and implementation of PREMs data collection and sharing, the promotion of the awareness among pediatric patients and their caregivers/guardians as well as among professionals about the relevance of PREMs data collection, the mechanisms for benchmarking the PREMs data and their visualization, and, finally, the strategies for using PREMs results for the children's hospital quality improvement.

Professionals in different areas (ie, technical, communication, data protection, and management) from each partner of the project will work together under the supervision of the Steering Committee and of the Board responsible for the action to produce practical protocols or guidelines that will guide the activities of the projects. Each partner will identify professionals with expertise in the area that is the object of the action to work together: at least one expert for each partner will be selected because of their professional proficiency on the topic.

The Technical and Data Protection Committee of the project will hold a series of videoconferences and workshops. For each topic, a draft protocol will be prepared and discussed during the workshops, with the aim of incorporating the amendments into the documents and distributing them among partners and projects' boards. This process will allow the committees to define common protocols to design a web system to collect and report survey data. Moreover, collaborative webinars and workshops will be used to define models and guidelines of information materials and training programs for improvement

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actions based on the PREMs results. Field notes will be taken during the workshops.

The PREMs Observatory

The outcome of all the previous research activities will be the implementation of a system for digitally and continuously collecting, reporting, and benchmarking data on pediatric experience with hospitalization. Moreover, the project will contribute to identifying and experimenting an innovative tool for the direct involvement of children and adolescents in the PREMs data collection.

It is expected to collect data on children and their caregivers' experience during a hospital stay in a systematic way and involve all patients and caregivers like a census [28,29,34,40]. Each hospital will systematically engage pediatric patients (0-17 years old) to request their participation in the PREMs data collection.

During the implementation phase of the survey, for administering and collecting the PREMs questionnaire, the hospitals will be free to adopt the organizational and operational processes they prefer to enroll and engage children in participating in the survey. In any case, each hospital will adhere to all the requirements established and agreed to in the previous phases of the project, to perform the PREMs collection on a continuous basis, that is, the participating hospitals will use a minimum standard set of common questions defined throughout the Delphi process and FGs or IDIs, and the same output in terms of data collection, registration, and management. The shared questionnaire might be integrated with other questions relevant for each children's hospital context. Data will feed a common data reporting web platform for benchmarking children patient–reported experience indicators among hospitals.

It is expected to accompany the survey implementation process with information and communication activities, to make both children and adults aware of the possibility to report about their experience in the hospital. Health care professionals will be also engaged in the training processes. To this end, the project partners will collaboratively design and produce information and communication materials to inform children and caregivers of the PREMs existence. All materials will be designed to be child friendly. While the design will be collaborative, the executive elaboration will be done directly by each hospital, by translating materials and adapting them to the specific context, also deciding what kind of materials to produce.

The PREMs observatory will also allow the design and test of an innovative tool addressing children and adolescents, appropriate for different age groups and enabling them to participate actively in providing their evaluation of the hospitalization experience.

Ethical Considerations

As the project will directly or indirectly encompass the interaction with humans, specifically with minors, the ethical aspect will be carefully considered. As mentioned in the "Ethical Approval" section, the general protocol of the VoiCEs project has been submitted to an ethics committee by the PI. In addition, all participating hospitals, which will have direct contact with pediatric patients and caregivers and manage individual-level data, will submit the protocol to their Ethics Committee for the research activities directly involving them. This activity will imply ethics review, exemptions, and approvals, with the definition by each hospital of the informed consent process and documents, and of data confidentiality, ownership, use and purposes, treatments, security measures, and appointments for external privacy officers. One of the outputs of the research is a unique data protection and sharing protocol focused on ethics and privacy issues, based on the EU and national laws, including privacy laws, General Data Protection Regulation (GDPR), and the Convention of the Rights of the Child. This document will be used by each hospital for internally defining the detailed and context-specific ethical aspects of the VoiCEs project.

Ethical Approval

The protocol of the VoiCEs project has been submitted to the approval of the Ethics Committee of the Sant'Anna School of Advanced Studies and Scuola Normale Superiore of Pisa. The approval was obtained on March 25, 2022 (protocol number 07/2022). All participating hospitals submitted the protocol to their Ethics Committee for the research activities involving them directly.

Data Management and Oversight

Data collection, processing, and sharing processes will be different for each research activity.

The literature review will encompass the search of evidence using literature databases and sources. Data obtained from the search and the consequent analysis will use digital documents and tables with cells organized into rows and columns, such as Excel (Microsoft Inc), Stata (StataCorp), or SAS files (SAS Institute).

For FGs and IDIs, data will be collected through observations, notes, recordings, transcripts, and reports that the hospitals responsible for the activity will prepare. Data will be collected and elaborated by the PI in a final report that will be provided to Delphi panelists, shared with other partners, and submitted to a qualitative comparative analysis.

The Delphi process will encompass an online form to collect the point of view of the panelists. The panelists will give their point of view by accessing a platform using personal identification credentials that will be provided to them via email. Data from each round will be assembled and sent back anonymously to all panel members. Additional rounds will be organized, as the first one, until consensus is reached.

During the workshops, data will be collected through notes, reports, and minutes. Data will be elaborated in a final document (either a protocol or a set of guidelines).

The PREMs survey will gather data with an online questionnaire, or with specific innovative tools or both, according to the outputs of the previous research activities of VoiCEs. The details concerning the content and the process of administration as well as those on data processing and management procedures will be established using the technical and data-sharing protocols that will be developed collectively

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by the partner under the supervision of the Technical Board and the Data Protection Board:

- A data-sharing protocol focused on privacy issues, setting out the basis on which patient experience data will be collected and used for subsequent actions. The partners will consider the EU and national laws, including privacy laws, GDPR, and the Convention of the Rights of the Child, to ensure the experience data of children are reported in a legal and ethical manner. This protocol will ensure ownership and buy-in of data collection and sharing processes, and will describe all potential and permitted uses of collected patient data for subsequent actions (eg, performance measurement and evaluation, research activity).
- A technical protocol allowing for the creation of a solid web platform to share data. The technical creation of the web platform will be entrusted to a company under the supervision of the Technical Board. It will be a tool to visualize the data.

The main features of the data reporting platform will be the presentation and visualization of quantitative and, if possible, qualitative data collected using tables and graphics, besides assuring the benchmarking activity between hospitals (or single wards) using specific indicators based on the data collected from each hospital.

After sufficient data have been collected, they will be made available to each hospital, and to each ward of the hospitals, whenever data are enough to guarantee the anonymity of respondents. The web platform functionalities will be shared and approved during a specific web workshop.

The data will be conserved for the duration of the project and for the time necessary to complete the reports and the scientific publications envisaged in the project.

Data from the children PREMs observatory will be conserved permanently, and will be stored on servers located in Europe.

The collection and storage systems (eg, web, platforms, servers) will follow the information and communication technology policies of the PI, and additional details and conditions will be established on the data protection protocol that will be collectively elaborated under the supervision of the Data Protection Board.

Results

Literature Review

The main objective of the literature review is to map existing evidence on measuring children's and adolescents' experience of hospitalization. The research group has analyzed and organized the results by identifying themes and patterns emerging from existing research. The analysis of peer-reviewed papers, reports, and gray literature has explored the following aspects: type of dimensions and subdimensions of children patients' experience of hospitalization; list of sources (question banks) and previously used questionnaires; type of methodology of the paper; administration and data collection methods; type of population targets to be engaged, such as children of different age groups or with specific health conditions and needs; countries and languages of the study; and use of data for quality improvement actions.

Analysis of the Previous PREMs Experiences of Children's Hospitals

The analysis of the previous experiences in PREMs data collection of the children's hospitals involved in the project will allow to identify the key aspects of these experiences (ie, start date, duration, method of implementation) and the list of questions already used. A comparison of the dimensions and subdimensions covered by these questionnaires will be made, to identify the diverse questions used to investigate the same area. A SWOT analysis will be finally conducted to synthetize the strengths, weaknesses, opportunities, and threats of the process implementation of the PREMs data collection within the children's hospitals. Results will be checked with data from other sources of information on the topic (ie, websites, reports, articles) to corroborate the findings [35]. Computer software, possibly SAS or Stata, will be used for qualitative data analysis that will follow the approaches suggested by Bailey [41] and Gioia [42].

Delphi Process

The feedback and evaluations provided by panelists in each round of the Delphi process through closed- and open-ended questions about the content and form will be analyzed by the research team in a descriptive statistical process with measures of central tendency and variability, and qualitatively to synthesize the key emerging themes. The report of each round will be sent back anonymously to all panel members to share answers and discussions, thereby enabling the participants to reflect on different views and modify their own, until the consensus is reached.

Variables of analysis are expected to be related to the relevance of the following areas, disaggregated for characteristics of panelists:

- target groups' populations in terms of type, age, disease, access to care;
- phases of the hospitalization journey to be investigated;
- type of data collection tool to be administered;
- time of data collection tool administration;
- dimensions and subdimensions of children patients' experience of hospitalization;
- preferences in terms of the most appropriate way (ie, an eventual innovative tool) to directly engage children and adolescents in collecting their voices.

The results of the Delphi process will be analyzed by performing descriptive statistics, using software such as Stata. If possible, statistical tests will be performed to provide an estimate of the probability that any association among variables is genuine. For instance, additional t tests or χ^2 tests could be performed for investigating any differences in the preferences and opinions of different groups of panelists (ie, different stakeholders, different ages, different countries).

The output of the Delphi process, and of the FGs and IDIs, will inform the following phase with the interactive working group realized during online and in-person workshops.

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FGs and IDIs

The results of the FGs and IDIs will be analyzed and presented by focusing on the following contents: type and relevance of dimensions and subdimensions of pediatric patients' experience of hospitalization; type of data collection tools more appropriate to engage an active participation of children and adolescents (ie, an innovative tool); and validity of questions in cognitive, psychometric, cultural, and linguistic terms. The primary data will be collected directly by the children's hospitals realizing the FGs or IDIs. Qualitative data will be analyzed using computer software packages by a group of at least two individuals for each hospital. Before the analysis, the research group will define the relevant categories of analysis and the key issues and concerns, also in the form of keywords associated with the themes [35]. In a first phase, the analysis of the qualitative data will be aimed at identifying key aspects for each aforementioned category by target population. Extracts from IDIs and FGs will also be reported in each hospital reports. Each hospital will be responsible for this first analysis of the results and for sharing them with the other partners in a brief report in English. In a second phase, researchers will look for relationships and connections in data from different hospitals, trying also to report the results in diagrams showing the link between concepts and adding some transparency to the process of qualitative data analysis [35]. Finally, the results of the FGs or IDIs will be merged with those of the Delphi process, to ensure the centrality of the children's and adolescents' perspectives in the consensus building process on the identification of PREMs data collection tools. This second phase will involve the PI who will conduct a comparative analysis among the results of the 4 hospitals to value the contribution of children's and caregivers' involvement.

Workshops With the Interactive Working Groups

The process of action research implemented during the workshops is based on discussion, comparison, evaluation, and critical analysis of practices by experts to produce an improvement in the field of experience. Before each workshop, the researchers will define the most important contents to be registered and eventually coded (ie, the type of event, participants, shades of opinion, use of a particular word or expression, references provided by participants) [35]. The analysis of these qualitative data could also be conducted using software such as NVivo (QSR International) for facilitating both organization, storage, coding, and analysis of data. The results of this research work will allow the definition of shared documents containing an analysis and interpretation of the contents shared during the workshop, which will act as a base for shared protocols and structured rules of the project.

In addition, quantitative variables will be used to measure the results of the interactive group activities, which will allow to compute process indicators related to (1) the number of people involved and variability of their profile, (2) time spent versus time expected for producing the outputs, and (3) the number of protocols and guidelines finalized.

The PREMs Observatory

The PREMs observatory will include a questionnaire measuring the experience. This latter questionnaire will be designed according to what emerged during the collaborative process. Each children's hospital is responsible for the data collection and will send aggregated data to the PI, who will realize comparative analyses and benchmarking on secondary data.

The variables used will measure both process and outcomes [43]. The results of the activity in terms of process will be measured by considering the hospitalization rates and the expected response percentage in each of the children's hospitals involved in the project. The outcome will be measured in terms of PREMs, distribution among hospitals, and their trend over time in accordance with the improvement actions that will be implemented in each hospital.

The innovative tool will be considered as an additional result, and the feedback from children and adolescents during its experimental use will be analyzed.

Discussion

Expected Findings

The VoiCEs project will provide room for innovation, by contributing to the creation of an international and systematic, pediatric PREMs observatory that can be joined by other children's hospitals or hospitals with pediatric patients, foreseeing the return of usable and actionable data in benchmarking.

Among the expected results, the project will allow:

- the implementation of a European observatory on pediatric PREMs;
- the collection and benchmarking of the pediatric patients' voices;
- the design and test of innovative methodologies and tools for capturing the pediatric patients' feedback directly, avoiding caregivers' intermediation; and
- for a more children- and adolescent-driven health care services' design.

The VoiCEs project will contribute to enhancing direct participation of children and adolescents in the evaluation and improvement of health care services during hospitalization, considering the scarcity of systematic processes of coassessment [12,13,44]. The project will directly involve young individuals, in addition to adults with various expertise, knowledge, and skills, in a circular process of coassessment for co-design and coinnovation. Indeed, coproduction processes have the most potential in terms of meaningful, effective, and sustainable participation of young people [8]. The final aim is to put in place a system for improving service quality, improving the experience of young people with services, and enhancing the adherence to the principles of public governance with young populations, for which feasibility is not easily or always possible [45].

This project is contributed by the study of the most effective methodologies for collecting the perspectives of children and adolescents, with caution exercised for the customization of

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tools, techniques, and processes considering their abilities and preferences. Studies have shown that the ability to participate and the opportunity for participation are key antecedents that organizations should consider when designing these processes of direct engagement [15-18]. Moreover, a recent review of the literature showed that the lack of time availability seems to constrain coproduction [44]. Thus, directly involving children and adolescents, who usually have lower limitations in time availability, could be an opportunity to increase the participation of individuals in assessing and designing services better.

The first evidence collected on this topic shows that previous experiences are experimental or single shot [22-25], or struggled in really involving children and adolescents, mainly engaging with parents, particularly mothers [28]. This project will reach its goals by also developing a common standard to be adopted by pediatric hospitals, or hospitals with pediatric patients, for collecting comparable data and activating learning processes among providers.

This use of the results of pediatric patients' and caregivers' coassessment can activate a positive circle, by comparatively emphasizing problems or areas for improvement and good practices to learn [10, p. 772]. This implies a prospective use of these data for the future co-design, coinnovation, or codelivery of services [11,12,46]. Benchmarking of these data provides suitable feedback for professionals to enable improvement and reputational mechanisms [47,48], as well as identifying the good performers and the good practices to be disseminated [49].

Another key additional step will be sharing the impact that these data had on the practice. While there is conflicting evidence on the effect of public disclosure on citizen behavior [50]; thus, future research should study people's preferences with and reaction to the exposure to different forms of information based on patient data.

From this perspective, providing organizations with evidence on how to really ensure participation of young people in coassessment of services is extremely relevant for allowing a concrete engagement of the most fragile segments of the population who might be disadvantaged in expressing their opinions, experiences, or preferences. In this sense, this project will contribute to strengthening "the right of the child to be heard" [1].

Limitations

The project encompasses a coordinated and integrated use of different research methodologies. Their coordination over time is a critical aspect. The research group and the partners from each hospital will identify and minimize issues related to each research approach and methodology.

For the FGs, IDIs, and Delphi process, a principal bias that can be anticipated using relatively small explorative samples is the lack of compliance with the selection criteria, due to the availability of different profiles and the critical circumstances resulting from the pandemic. Concerning the FGs and IDIs, the heterogeneity of feedback, preferences, and needs can be achieved by ensuring the presence of subgroups among the participants, based on relevant characteristics such as age, sex, citizenship, socioeconomic level, and health problems.

In the case of Delphi panelists, special attention will be focused on the representation of different countries, at least on those from which the participating institutions originated (ie, Italy, Latvia, Finland, and the Netherlands); further, owing to the participation of the ECHO network, we will be able to focus on other European countries. Moreover, we will consider different professions and profiles to ensure heterogeneity of opinions and a variety of perspectives. An oversampling of panelists will be performed for minimizing the eventuality of a low response rate.

The PREMs observatory implementation will have to face the obstacles and constraints resulting from the specific contexts and practices already in use, as well as from different policies of data protection and sharing.

Conclusions

Coassessment may contribute to cocreating public value at different levels [51]. However, it is essential to put in place adequate opportunities to assure people the rights of participating in evaluation initiatives. This is particularly important for vulnerable people in delicate moments. This protocol presents the VoiCEs project, its methodology, and expected results. It aims at studying, identifying, and sharing cocreated methodologies and tools for facilitating the participation of young people in the evaluation and improvement of health care services.

The VoiCEs project will lead to the development of a European observatory on children's and adolescents' voices, especially regarding their experience of hospitalization, which would represent a fundamental step in facilitating pediatric patients' and their caregivers' participation in coassessment and, lastly, coinnovation processes in health care.

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Data Availability

Data generated or analyzed during this study will be included in future published articles. Moreover, data collected and compared among providers will be published on a public section of the project website [52] as an output of the project itself.

Authors' Contributions

MB contributed to methodology, supervision, validation, formal analysis, writing—reviewing and editing, project administration, and funding acquisition. EC contributed to project administration. IC was responsible for formal analysis, methodology, writing—reviewing and editing, data curation, visualization, and investigation. SDR took care of methodology, supervision, validation, formal analysis, writing—original draft preparation, writing—reviewing and editing, project administration, and funding acquisition. VS performed formal analysis, methodology, data curation, visualization, and investigation. MV was responsible for conceptualization, supervision, writing-reviewing, and editing. All authors reviewed, edited, and approved the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

AOPI: Italian Association of Children's Hospitals
AOU Meyer: Meyer Children's University Hospital
CCUH: Children's Clinical University Hospital
ECHO: European Children's Hospitals Organisation
EMC: Erasmus University Medical Center
ERYICA: European Youth and Information Counselling Agency
EU: European Union
FG: focus group
GDPR: General Data Protection Regulation
HCAHPS: Hospital Consumer Assessment of Healthcare Providers and Systems Survey
HUS: HUS New Children's Hospital
IDI: in-depth interview
PI: principal investigator
PREM: patient-reported experience measure
UNICEF: United Nations International Children's Emergency Fund/United Nations Children's Fund
VoiCEs: Value of including the Children Experience for improving their rightS during hospitalization
WHO: World Health Organization

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Protocol

Variation in Experiences and Attainment in Surgery Between Ethnicities of UK Medical Students and Doctors (ATTAIN): Protocol for a Cross-Sectional Study

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Abstract

Background: The unequal distribution of academic and professional outcomes between different minority groups is a pervasive issue in many fields, including surgery. The implications of differential attainment remain significant, not only for the individuals affected but also for the wider health care system. An inclusive health care system is crucial in meeting the needs of an increasingly diverse patient population, thereby leading to better outcomes. One barrier to diversifying the workforce is the differential attainment in educational outcomes between Black and Minority Ethnic (BME) and White medical students and doctors in the United Kingdom. BME trainees are known to have lower performance rates in medical examinations, including undergraduate and postgraduate exams, Annual Review of Competence Progression, as well as training and consultant job applications. Studies

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have shown that BME candidates have a higher likelihood of failing both parts of the Membership of the Royal Colleges of Surgeons exams and are 10% less likely to be considered suitable for core surgical training. Several contributing factors have been identified; however, there has been limited evidence investigating surgical training experiences and their relationship to differential attainment. To understand the nature of differential attainment in surgery and to develop effective strategies to address it, it is essential to examine the underlying causes and contributing factors. The Variation in Experiences and Attainment in Surgery Between Ethnicities of UK Medical Students and Doctors (ATTAIN) study aims to describe and compare the factors and outcomes of attainment between different ethnicities of doctors and medical students.

Objective: The primary aim will be to compare the effect of experiences and perceptions of surgical education of students and doctors of different ethnicities.

Methods: This protocol describes a nationwide cross-sectional study of medical students and nonconsultant grade doctors in the United Kingdom. Participants will complete a web-based questionnaire collecting data on experiences and perceptions of surgical placements as well as self-reported academic attainment data. A comprehensive data collection strategy will be used to collect a representative sample of the population. A set of surrogate markers relevant to surgical training will be used to establish a primary outcome to determine variations in attainment. Regression analyses will be used to identify potential causes for the variation in attainment.

Results: Data collected between February 2022 and September 2022 yielded 1603 respondents. Data analysis is yet to be competed. The protocol was approved by the University College London Research Ethics Committee on September 16, 2021 (ethics approval reference 19071/004). The findings will be disseminated through peer-reviewed publications and conference presentations.

Conclusions: Drawing upon the conclusions of this study, we aim to make recommendations on educational policy reforms. Additionally, the creation of a large, comprehensive data set can be used for further research.

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KEYWORDS

diversity in surgery; Black and Minority Ethnic; BME in surgery; differential attainment; diversity; surgery; health care system; surgical training; disparity; ethnic disparity; ethnicity; medical student; doctor; training experience; surgical placements; physician; health care provider; experience; perception; cross-sectional; doctor in training; resident; fellow; fellowship; questionnaire; survey; Everyday Discrimination Scale; Maslach Burnout Inventory; Higher Education; ethnicities

Introduction

Overview

Diversity and inclusion in the health care workforce is fundamentally important to the delivery of health care. There is strong evidence to suggest that an inclusive workforce is able to better meet the needs of a diverse patient population and leads to better patient outcomes [1,2]. According to the latest available data from National Health Service Digital, as of September 2021, the share of Black and Minority Ethnic (BME) staff in the National Health Service workforce in England was 24.2%, which is higher than the proportion of BME people in the general population (18%) [3].

One of the current barriers to a diverse workforce is differential attainment. This is defined as “an unexplained variation in results in assessment, training, and recruitment outcomes seen in candidates based on factors other than academic ability when compared to their peers” [4] and is presently observed across several important demographic characteristics, including gender, age, socioeconomic status, and ethnicity. It is well recognized that Asian and BME trainees are more likely to perform poorly in undergraduate and postgraduate medical examinations [5,6], Annual Review of Competence Progression, and applications for training and consultant posts [7,8]. A BME candidate is independently more likely to fail both part A and Part B of the Membership of the Royal Colleges of Surgeons (MRCS) examinations and 10% less likely to be deemed appointable for core surgical training [9,10]. Additionally, only 20% of leadership roles across the surgical colleges are held by BME surgeons [11] despite BME staff making up 46% of the medical workforce [12]. Furthermore, BME surgeons are disproportionately more likely to be referred to the General Medical Council (22% BME vs 17% White) [10].

The current understanding of causes of differential attainment is derived from thematic analyses on the barriers and issues facing BME doctors. There are several recognized factors, including curriculum and examination biases; relationships between BME trainees and trainers; a lack of support and mentorship; differences in social and cultural capital; and feelings of workplace exclusion due to microaggressions, harassment, and discrimination [13-17]. The Royal College of Surgeons of England’s Kennedy Report specifically attributes these factors as potential barriers to the progression of equality and diversity in surgery [10]. This is significant as surgical training has a unique reliance on the “apprenticeship” between the trainee and the trainer, leading to potentially unique differences in the relative effect of the aforementioned factors associated with differential attainment in surgery.

Rationale for This Study

The evidence base for determining differential attainment is generated by smaller scale, qualitative studies, which have demonstrated that the experience of BME students and trainees

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is a factor contributing to differential attainment. However, smaller-scale studies may only capture a limited insight of the experiences of BME trainees and provide limited appreciation of the heterogeneous mix of different trainees of different ethnicities with a variety of experiences under the BME umbrella. Additionally, there is little published evidence that focuses on assessing the unique elements of the "surgical" experiences of surgical trainees, junior doctors, and medical students. This observational, multicenter study aims to compare both the experiences of surgical training between different ethnicities and the level of attainment reached. This study will ultimately aim to evaluate the relationship between educational and training experiences in surgery and attainment and analyze the role of ethnicity in this relationship.

Aims and Objectives

The ATTAIN (Variation in Experiences and Attainment in Surgery Between Ethnicities of UK Medical Students and Doctors) study aims to answer the following questions:

- Are the experiences and perceptions of surgical education different between BME and non-BME medical students and junior doctors? If so, how and where are these differences seen?
- In what ways are measures of attainment in surgery linked to experiences and perceptions of surgical education?

Primary Objective

The primary objective of this study is as follows:

- To compare the effect of experiences and perceptions of surgical education of students and doctors of different ethnicities.

Secondary Objectives

The secondary objectives of this study are the following:

- To measure potential differences in both the experiences and perceptions of surgical education of students and doctors of different ethnicities on attainment.
- To identify potential factors associated with potential differences in educational experience and attainment between the aforementioned cohorts as areas of further study.

Methods

This study will consist of a 15-minute questionnaire (Multimedia Appendix 1), which will be administered over a 28- to 32-week period. This will be distributed to every medical school and Higher Education England region.

Our population of interest consists of all medical students and nonconsultant grade doctors, including doctors in training and nontraining roles in foundation year, core or specialty trainee, as well as fellowship or staff and associate specialist (SAS) grade equivalents, with any experience of surgical training in the United Kingdom. This will be defined as any substantial period of time (being more than a total of 4 weeks) when the primary place of work or learning was (or is) in a surgical department or specialty, including but not limited to medical school rotations, assistantships, and clinical roles.

Inclusion Criteria

The following will be included in the study:

- Medical students at UK medical schools, identified by the Medical Schools Council, who have self-identified as having experience of surgical training as defined above.
- Anyone who has worked as a nonconsultant grade doctor (including doctors in training and nontraining roles in foundation year, core or specialty trainee, as well as fellowship or staff and SAS grade equivalents) in the United Kingdom, regardless of the country of graduation with experience of surgical training as defined above, either during medical school (if graduated in the United Kingdom) or when working as a doctor in the United Kingdom.

Exclusion Criteria

The following are excluded from the study:

- Doctors or medical students who have not had either a surgical placement during medical school or experience of surgical training in the United Kingdom as defined above.
- Doctors or medical students who have not either attended medical school in the United Kingdom or worked in the United Kingdom in a clinical role as a doctor.
- Consultant doctors who have completed their surgical training, attained their certificate of completion of training, and are employed as a temporary or permanent consultant.

Survey Development

The survey was developed using the guidance set out in "Developing questionnaires for educational research: AMEE Guide No. 87" [18]. An initial literature review was conducted based on the General Medical Council's "Evaluating the impact of interventions aimed at addressing variation in progression associated with protected characteristics known as Differential Attainment" [19]. Expert opinion was sought from academic surgeons and medical educationalists (Katherine Woolf, PAB, SF, EI, and SV) to increase content validity. Questions were integrated from previously validated questionnaires, such as the Everyday Discrimination Scale [20] and Maslach Burnout Inventory [21], to increase the construct validity of our survey. A further focus group was conducted to ensure the conceptualization of our constructs matched how respondents thought of them, to increase the face validity of our questionnaire. A pilot questionnaire (N=78) was conducted to ensure reliability and to determine construct validity. This is a first of its kind cross-sectional survey; therefore, we will be using the preliminary survey with results as a comparator to assess reliability of the study. In addition, questions were based on literature and evidence-based theories that underwent peer review from established experts in this field. Our questionnaire will collect demographic data, including questions on protected characteristics such as self-defined ethnicity, socioeconomic status, gender, and grade. Data on academic attainment will consist of questions detailing a participant's achievements, including medical school decile, prizes, publications, Annual Review of Competence Progression outcomes, MRCS examination results, and specialty training application outcomes. Surgical experiences will consist of questions around the working relationships participants have with colleagues,

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experiences of discrimination due to ethnicity, and feelings of burnout.

Patient and Public Involvement Statement

This study will involve input of medical students and doctors of different grades. An initial survey was distributed at a national medical conference, which yielded information on topics of interest. The preliminary questionnaire was piloted among medical students and junior doctors, who gave qualitative feedback on the design of the study. The finalized questionnaire was distributed to collaborators who gave additional feedback.

Data Collection

Eligible participants will be invited to participate via web-based and in-person recruitment, including but not limited to medical school societies, medical school mailing lists, organizations focused on medical education, social media, surgical colleges, Higher Education England deaneries, and independent professional surgical bodies.

Additionally, snowball sampling will be incorporated, as eligible participants will be invited to collaborate as regional leads prior to the study period, with one collaborator per medical school or deanery. The collaborators will ensure that their medical school or training deanery is engaged with the study; they will be responsible for dissemination of the questionnaire and are recruited specifically to ensure participants are representative of their local population to prevent bias. Eligible regional leads will be acknowledged as collaborative authors under the "ATTAIN Study Group" in future publications. Participants will also be asked to share the questionnaire with other eligible colleagues.

Data Protection, Consent, and Confidentiality

The questionnaire will be hosted and stored in Jisc [22], which is compliant with regulations including General Data Protection Regulation and good clinical practice guidelines (ICH E6). The research team will have access to data determined by the study lead. Audit logs are also available to provide an overview of data access and modifications. Participants will receive a participant information sheet before starting the questionnaire. Participants will give consent for publication on completion of the questionnaire; consent can be rescinded up until completion of the questionnaire for any or no reason. On completion and submission of the questionnaire, consent cannot be withdrawn, as no identifiable data are collected. If the questionnaire is not completed, data will not be collected or stored. The only personal data collected from participants is ethnicity, participants' names or email addresses will not be collected. Any data collected will only be accessed by the members of the research team at any time. Upon the completion of each questionnaire, all documentation will be stored on a secure server that will be only accessible to the chief investigator, study leads, and statistics team.

Data Analysis

Statistical Analysis

The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) [23] guidelines for cross sectional studies will be followed. Participants will be stratified by level of training prior to analysis, and results will be presented separately. Methods of data imputation will not be used. Descriptive statistics will be presented by ethnicity. Demographic characteristics and questionnaire responses will be described by the following statistics: mean (SD), median (IQR), and frequency with proportion. All hypotheses will be tested at a 5% significance level. Differences in participant characteristics and questionnaire responses between ethnicities will be assessed using parametric and nonparametric tests, including chi-square tests, ANOVA, and Kruskal-Wallis H tests, which will be followed by multiple appropriate post hoc pairwise comparisons with Bonferroni correction. An explanatory model will be created by hierarchical multiple linear regression, with the dependent variable attainment and the following covariates: ethnicity, perceptions of surgical training, surgical experience, sex, socioeconomic status, and age. A correlation matrix will test for the presence of multicollinearity. Another possible confounding variable will be geographical location; the data will be stratified by region and examined for such an effect for those regions with a sufficient number of respondents. SPSS (version 28; IBM Corp) [24] will be used for analysis. Post hoc analyses may be undertaken in the future as part of follow-up studies.

Sample Size Calculation

A priori sample size calculation was performed for a 2-tailed test of 2 independent proportions using G*Power (version 3.1.9.7; Heinrich-Heine-Universität Düsseldorf) [25], based on a comparison of MRCS A pass rates between White and BME candidates. Our predicted effect size was estimated based on historical data sourced by Scrimgeour et al [9] from the Intercollegiate MRCS database held by the Royal College of Surgeons of England. With α and β error probability set to .05 and .2 respectively, a minimum of 318 participants per group will be required. Broadly stratifying by level of training (eg, medical student, foundation or core trainee, and registrar or SAS grade) and dividing into BME versus non-BME, this means that 1908 participants will be required ($318 \times 6 = 1908$).

Ethics Approval

The protocol was approved by the University College London Research Ethics Committee on September 16, 2021 (19071/004). Participants gave informed consent for their anonymized responses to be used for research purposes, including for analysis, presentation, and publication of data. There will be no compensation type for participation in the study.

Results

Data collected between February 2022 and September 2022 yielded 1603 respondents. Data analysis is yet to be competed. The findings will be disseminated through peer-reviewed publications and conference presentations.

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Discussion

Overview

Impact

Understanding the combined effect of individual experiences of surgical training is important in breaking barriers and promoting change within the medical workforce, leading to a more diverse and inclusive profession. To our knowledge, this is the first study to evaluate the relationship between educational and training experiences in surgery and attainment and analyze the role of ethnicity in this relationship. Although both the presence of [7-17] and possible causative factors for differential attainment based on gender, ethnicity, and socioeconomic status have been demonstrated [26-28], a comprehensive, high-powered data set linking experience and attainment is not currently present.

Expected Impact

The ATTAIN study's findings will add value to the current body of work in differential attainment by providing further insight and context to the interaction between different causative factors. We also hope to highlight areas of excellence and areas of improvement in surgical education, directing suggestions for evidence-based changes to undergraduate and postgraduate surgical education. Our findings offer policy makers evidence-informed recommendations to improve undergraduate and postgraduate surgical education, which will guide the creation and expansion of resources that can efficiently mitigate differential attainment. As society moves to tackle systemic inequalities, we hope our study will demonstrate a commitment to achieve this within medicine and surgery.

We also hope to remind the workforce of the principles of respect that are pivotal to our duties as health care professionals. Mental well-being and burnout are key performance indicators and should be protected to drive excellence in an individual's career progression.

Limitations

One of the potential limitations of this study is the lack of prior validated questionnaires on differential attainment. It could be argued that the topic of "differential attainment" is so large that a single questionnaire would not be an appropriate method able to collect valid or reliable data. We have tried to improve the quality and rigor of our questionnaire by using a well-established methodology for questionnaire construction and incorporating elements from previously validated questionnaires that are valid for our research question. However, bias cannot be eliminated from the study. Sampling bias may occur if recruitment is limited to streams disproportionately used by one group (eg, overusing social media may attract more medical students and junior trainees). This will be minimized by using multiple communication channels, including professional bodies and trainee-led organizations. Additionally, recall bias is unavoidable in sections of the questionnaire where past achievements are recounted.

We also recognize that our research question is heavily focused on ethnicity; however, there are several different factors that are known to be independently associated with differential attainment, including gender and socioeconomic status.

Although these factors may be controlled for in the study, it may be difficult to completely account for nonlinear intersectional relationships between factors. Future research should be considered to explore the relationships between these different factors in more detail.

Conclusions

We envisage that the results of the study will provide us with an advancement in knowledge on factors that correlate to attainment and provide us with greater depth in understanding the link between attainment in surgery and experiences of surgical training. Following the results, we aim to create national guidance for independent surgical bodies to incorporate into the current strategies used to tackle the inequalities and injustices in health care.

Acknowledgments

We would like to thank and acknowledge Professor Katherine Woolf for her input into the design of the questionnaire.

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Data Availability

The data sets generated during and analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

IO and SB conceived the study and have contributed equally as first authors. All authors have made significant contributions to the design of the questionnaire and the protocol paper and fulfill the ICMJE (Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals) criteria for authorship.

Conflicts of Interest

None declared.

Multimedia Appendix 1

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The ATTAIN (Variation in Experiences and Attainment in Surgery Between Ethnicities of UK Medical Students and Doctors" study survey.
[PDF File (Adobe PDF File), 376 KB - resprot_v12i1e40545_app1.pdf]

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Abbreviations

BME: Black and Minority Ethnic
MRCS: Membership of the Royal Colleges of Surgeons
SAS: staff and associate specialist
STROBE: Strengthening the Reporting of Observational Studies in Epidemiology

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Protocol

The Impact of Counseling on the Dignity of Older People: Protocol for a Mixed Methods Study

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Abstract

Background: Psychological counseling is perceived as a treatment that could significantly improve older individuals' psychological and behavioral functioning. There is a dearth of information on the impact of psychological counseling on preserving dignity and facilitating good aging among older people in Singapore.

Objective: The objectives of this study are as follows: (1) to assess advance care planning among older people and their perception of life and health, end of life, and end-of-life care; (2) to explore older people's accessibility and receptiveness toward counseling; (3) elucidate older people's perspectives on counseling and its impact on emotional management and decision-making; (4) to assess older people's competencies in emotional management; and (5) to propose an intervention model for enhancing older people's well-being and dignity through psychological counseling in Singapore.

Methods: A mixed method study design involving quantitative and qualitative methods will be used. Older individuals receiving some form of preventive, primary, or long-term care in the community through voluntary welfare organizations from the senior activity centers located in eastern Singapore participated in the qualitative phase. Six older individuals from each senior activity center have been enrolled for the interview phase to explore 6 components: the Advanced Care Planning (ACP) booklet, Trait Meta Mood Scale (TMMS), accessibility and receptiveness toward counseling, and emotional management and decision-making. The ACP, an instrument designed to assess advanced care planning among older individuals, and the TMMS, an instrument developed to measure meta-mood experience and emotional management, were used in the quantitative phase among 100 participants. The data will be analyzed thematically using NVivo version 12, whereas descriptive statistics and a 2-tailed, 1-sample *t* test will be conducted in SPSS (version 25; IBM Corp) for empirical data analyses.

Results: The qualitative phase, which involves a semistructured interview, has been completed among 20 older individuals aged 66-86 years. Thematic analysis of the data is still ongoing. Meanwhile, the quantitative phase commenced on March 22, 2022, with 100 participants providing signed informed consent to participate in the study. The study is expected to be completed by March 2023.

Conclusions: The mixed methods study will document the current awareness of ACP, accessibility and receptiveness toward counseling, and the potential use of psychological counseling in enhancing well-being and dignity among older people in Singapore. The research findings will benefit policy makers in their decision-making when attempting to mitigate the potential barriers to seeking counseling assistance among older people.

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KEYWORDS

counseling; dignity; elderly; emotional management; psychological; Singapore

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Introduction

Overview

The current rising older population in Singapore reflects that one-fourth and half of the population will be older than 65 years by 2030 and 2050, respectively [1]. Previous studies have demonstrated that older people experience diverse aging-related complexities that require counseling intervention: depression, anxiety, grieving, loss of functional health abilities, financial dependence following retirement, social isolation, intergenerational and marital conflicts, and mental and emotional challenges [2,3]. These issues have been increasingly reported among older parents filing for financial maintenance with the tribunal court [4]. Hence, the prevalence of depressed older adults is expected to rise from 19,000 to 50,000 by 2020 [3].

Depression among older people is one of the main causes of suicide in comparison to other age groups globally. Despite implementing relevant policies and high awareness of mental health issues in Singapore to reduce recent suicide rates, the numbers among older adults remain relatively high [5]. For instance, individuals aged 60 years and older accounted for 25%-30% of suicide cases reported in Singapore in 2016, rising to 35.7% in 2017 [5]. Chan [6] also reported that older individuals with extensive depressive symptoms are among the main focus of the Singaporean government.

Recent studies have disclosed the need to accommodate the impacts of demographic shifts on Singapore's health care eldercare initiatives [7]. The Singapore Ministry of Health provides intermediate and long-term services to address these concerns about the country's aging population. These policies come in the form of community and residential health care services. While community clinics include hospitals for the chronically ill and nursing homes that are responsible for the provision of residential health care services, center-based health care services are provided by rehabilitation, day care, and psychiatric centers [8].

The Singaporean government has taken diverse approaches to provide better care for older people. For instance, the government is on the verge of increasing the number of nursing home beds to 14,000, accounting for a 50% increase from the report in 2010 [9]. These measures were based on the expected increase in demand for beds as the aging population continues a rising trend [6]. The Ministry of Health has also used smart technologies to facilitate cost-effective eldercare services [10]. Kong and Woods [10] recommended collaborative and contextually sensitive strategies to design and develop smart solutions for older people. Likewise, Ansah et al [11] suggested that resource planners and policy makers proactively review health needs and improve the dignity of the aging population in Singapore.

Despite the availability of previous treatment plans for psychiatric care, counseling is a current treatment approach, especially in recent cases of depression among older people [12]. Psychological counseling is presently perceived as a treatment that could significantly optimize individuals' psychological and behavioral functioning [12,13]. As most older people spend the remainder of their lives within the community, insights into how residents uphold their sense of dignity within the community are valuable to managing aging stressors. An aging population creates both opportunities and pressures for Singapore's welfare and health sectors. More importantly, the risk of dignity loss is high among older people during acute hospital care [14].

Dignity is vital to older individuals and their caregivers. However, it remains unclear how older people define dignity or dignified care and how it is influenced by psychological counseling [15]. Past research investigated how older people's dignity could be safeguarded or enhanced by facilitating individual autonomy [16], providing personalized care, reinstating control, portraying respect, and conducting advocacy and sensitive listening [13]. Identifying older people as individuals and the aspects and values important to them are also fundamentals of care that could potentially conserve their dignity before death [13].

Why Is It Important to Conduct This Study?

Approximately 30% of the 400 suicide cases reported in Singapore in 2019 involved individuals aged 60 years or older [7]. The number of Singaporeans older than 65 years who lived alone increased from 47,000 (9.7%) in 2016 to 67,600 (11.6%) in 2019 [7]. Previous studies also revealed that older adults with ailments and disabilities are exposed to cumulative suicide risks [17] and depression symptoms [3]. As the implications of aging reflect mental health complexities, aging is affected by several losses that require constant adjustments. Aging-oriented losses involve potential stress factors, specifically for older adults with compromised health conditions. Past studies have also highlighted how ailments and disabilities pose risks to older people and how mitigating factors could substantially reduce diseases and mortality rates among older adults [18].

Given the rising aging population, Singapore's government health care is unable to accommodate all older people in hospitals and nursing homes. Hence, the Ministry for Social and Family Development developed a policy for older adults to "age in place," in which they could independently live in their homes and communities. The policy encourages good health by increasing preventive, primary, and long-term care [19]. Additionally, these various types of care offer health and social care needs to support the families of older adults and can be successfully implemented with effective psychological counseling. As physical and cognitive activities represent essential and modifiable protective factors for cognitive decline and dementia, counseling interventions could assist in preventing these issues in older people [3,11].

There is a dearth of information on the effectiveness of counseling older adults in the Singaporean context. However, certain issues have been reported in the literature to impact accessibility and receptivity toward counseling services among the aging population. For instance, the cultural stigmatization associated with psychological counseling services specifically among older people [20,21] makes individuals believe seeking professional counseling is socially unacceptable [22].

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Thus, older adults are less inclined and receptive to counselling, even when such assistance is necessary, based on their low awareness of the benefits. Likewise, older adults tend to be deterred by health and disability issues during counseling sessions due to accessibility and receptiveness. These concerns could adversely affect older individuals' daily functioning and dignity preservation levels.

Counseling could be advantageous for older adults with emotional and psychological issues as a form of antidepressant and for ameliorating various mental disorders for behavioral shifts [23]. Counseling can also assist older adults' emotional management and decision-making processes by addressing psychological issues. Hence, counseling in emotional management and decision-making processes would enhance the individuals' sense of dignity in life and aging-oriented transitions. Apart from establishing government-funded counseling services under the family service centers [20], Singapore has also developed social welfare agencies, religious institutions, educational schools, and other governmental institutions that offer counseling services to the general public. Counseling services are also provided by multiple social service agencies and public and private hospitals [21].

Nevertheless, these various counseling services have not been elucidated in the context of Singapore as the impact of psychological counseling in preserving dignity and facilitating good aging among older people remains unknown. In other words, the experience and benefits of the counseling services provided to older citizens are underreported. To fill this research gap, this study aims to propose an intervention model for enhancing older people's well-being through counseling.

Research Objectives

The objectives of this study are as follows: (1) to explore older people's accessibility and receptiveness toward counselling; (2) to assess the improvement of older people's dignity in emotional management and decision-making processes following psychological counseling; and (3) to propose an intervention model for enhancing older people's well-being through psychological counseling.

Research Questions

Due to the paucity of data regarding the impact of counseling services on older adults' dignity and the aging process, this study aims to answer the following questions:

- Do older people in Singapore have counseling access and receptiveness?
- Do counseling services improve emotional management among older people?
- Do counseling services improve dignity among older people?
- Do counseling services affect decision-making processes among older people in Singapore?

Methods

Study Design and Study Area

This study uses a mixed method research design by combining quantitative and qualitative approaches to explore the life experiences of Singaporeans older than 60 years and interpret their lived experiences, such as interactions with qualified counselors accredited by the Singapore Association of Counseling and Singapore Association of Social Workers or social workers. Data are gathered using an exploratory sequential mixed methods design, thereby broadening the scope and dimension of the study. Both qualitative and quantitative approaches offer exceptional strengths that will facilitate robust findings in this study [24-26].

The 5 Singaporean estates with a high number of individuals aged 60 years and older [27] were identified. Bedok and Tampines in the eastern part of Singapore have the largest older populations, with 62,750 and 43,700 people, respectively, followed by Hougang in the northeastern part of Singapore with 41,920 older residents and Ang Mo Kio in the northern part of Singapore with 41,390 older residents. Given the high population of older individuals in Bedok and Tampines, older individuals receiving some form of preventive, primary, or long-term care in the community through voluntary welfare organizations (VWOs) have been recruited for this study. Furthermore, a total of 78 senior activity centers (SAC) in Singapore (a VWO with 10 SACs is located in eastern Singapore) were selected for this study.

Study Population

The study population comprises individuals aged 65 years and older from various parts of Singapore.

Inclusion and Exclusion Criteria

Textbox 1 shows the inclusion and exclusion criteria for selecting the study participants.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Participants must be 65 years of age or older on the first day of selection.
- Participants must be living in the community.
- Participants must be interested in the study and receive some form of preventive, primary, or long-term care services.
- Participants must be willing to attend counseling sessions in emotional management and decision-making processes.

Exclusion criteria

- Older individuals who are currently admitted to a nursing home.
- Older individuals who are mentally incapacitated based on a history of confirmed mental disorder or unable to understand the research protocol when briefed by the researcher.

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Sample Size Calculation and Sampling Technique

The sample size for the quantitative phase was estimated based on the total population of older people in the study locations, the 95% CI, a precision error of 5%, and estimates from previous related studies on the proportions of participants with satisfactory accessibility and receptiveness levels toward counseling [28]. Specifically, the sample size was estimated by using the formula for analytical and cohort studies presented below:



Where

n = sample size

$z_{1-\alpha/2}$ = z statistic for 95% CI = 1.96

$z_{1-\beta}$ = z statistic for 90% power = 1.28

P_1 = Proportion of participants with satisfactory accessibility and receptiveness levels toward counseling in 1 group and

P_2 = Proportion of participants with satisfactory accessibility and receptiveness levels toward counseling in 1 group

P_1 and P_2 were obtained from previous studies reporting the proportions of participants with satisfactory accessibility and receptiveness levels toward counseling [15,28]. The obtained values were substituted into the equation to calculate the required sample size (n). The computed sample size was adjusted for eligibility by assuming that approximately 30% of the participants have access to and are receptive to counseling. Furthermore, a nonresponse rate of 20% was also considered before deciding on the final sample size.

The probability proportionate to size method was used to allocate sample size for each region and part of Singapore to facilitate proportionate distribution of older individuals receiving some form of preventive, primary, or long-term care in the community through VWOs. Thereafter, a simple random sampling technique was used to obtain the required number of participants from each region. Meanwhile, purposive sampling was used in selecting the SACs.

Qualitative Phase: Study Instrument and Interview Session

A small sample of participants was invited to participate in the qualitative phase, with an equal number of samples from each SAC. As described by previous scholars, 10% of the computed sample size for the quantitative phase was recruited for the interview session. However, an equal number of older individuals were selected from each SAC in various parts of Singapore to participate in the study. The interview session was performed using a semistructured questionnaire. The instrument enables participants to share their views and experiences of counseling services, while some of the responses can be measured numerically.

Six components were explored during the interview session, including the use of the Advanced Care Planning (ACP) booklet among older people, the Trait Meta Mood Scale (TMMS), older people's accessibility and receptiveness toward counseling, and the improvement of older people's dignity in emotional management and decision-making. The interview guide was reviewed in subsequent sessions to explore any new emerging themes.

Quantitative Phase: Instrument Development and Administration

This study uses the ACP and the TMMS instruments. The ACP is a booklet that was designed by the Agency for Integrated Care for recording and planning health and personal care. It comprises 5 main sections that focus on important lifestyle activities, concerns about current health status, views toward life and health, end of life, and preferred end-of-life care. The items are presented as either multichoice options or on a 5-point Likert scale ranging from 1 to 5, depending on the section. For the section on lifestyle activities (4 items), 1="there is little point in being alive without the quality of life," while 5="I would like to be able to live for as long as possible." For the section on participants' views toward end of life (4 items), 1="strongly disagree" and 5="strongly agree." On the other hand, the section on preferred end-of-life care is presented as multichoice options with 9 items.

Meanwhile, the TMMS is a 24-item instrument that was developed to measure meta-mood experience [29]. The TMMS is considered suitable for this study as it is the most used self-administered measurement for individuals' emotional management [29]. The instrument comprises 3 subscales (Attention to Feelings, Clarity of Feelings, and Mood Repair) with 8 items each that evaluate the 3 meta-mood experience components with a 5-point Likert scale ranging from 1="strongly disagree" to 5="strongly agree." The Attention to Feelings Subscale measures attention to personal and external moods and emotions; the Clarity of Feelings Subscale assesses personal abilities to discriminate feelings among one another; and the Mood Repair Subscale evaluates older individuals' ability to perform self and external regulations [30].

A structured questionnaire was also developed to assess participants' views regarding counseling and its impact on their dignity and decision-making process. This was based on the themes identified in the qualitative study and an in-depth review of several studies in the literature. Operational definitions were also developed based on the themes obtained. Three experts assessed the questionnaire for content validity. Thereafter, the instrument was distributed to 10 social workers or counselors for face validity assessment. The comments received were reviewed and necessary modifications were made. The final questionnaire was presented in English, and no translation into local languages was conducted. Pretesting was performed on 20 older individuals from selected SACs for internal consistency and reliability. Findings from the experts' opinions and pilot testing were used to prevent potential ceiling and floor effects from the questionnaire items that may affect accurate data interpretation. The developed questionnaire was distributed to randomly selected older individuals at all selected SACs. The data obtained from the quantitative and qualitative approaches were combined to provide a more robust assessment of the study. Table 1 depicts the research matrix.

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Table 1. Research matrix.

Research objectives	Quantitative	Qualitative
To assess advance care planning among older people and their perception of life and health, end of life, and end-of-life care	✓	✓
To explore older people's accessibility and receptiveness toward counseling		✓
To elucidate older people's perspectives on counseling and its impact on emotional management and decision-making		✓
To assess older people's competencies in emotional management	✓	
To propose an intervention model for enhancing older people's well-being and dignity through psychological counseling	✓	✓

Ethical Considerations

Ethical considerations in this study entail 2 key ethical principles: honesty and respect for human rights [27,31-33]. Certain ethical questions need to be addressed, since older individuals are research participants. The privacy, safety, and confidentiality of participants' data are guaranteed. Hence, both informed and signed consent were obtained before the interview and questionnaire administration. A cover letter with vital information on the research objectives was attached to the questionnaire and interview guide. This study protocol has been approved by the Universiti Sains Malaysia Human Research Ethics Committee (USM/JEPeM/21110760).

Management

Participants' anonymity will be protected in this study [34-36]. Data will be kept confidential to ensure that the identities of older individuals are protected [37-39]. Research instruments and clinical records containing participants' data will be represented in a coding system. Thus, participants' private information will not be revealed when submitting the data and findings to regulatory institutions or sponsors [40,41]. Only the researchers will be able to access the participants' records and the coding system. Two copies of consent forms were provided to be signed by the researcher and each participant. All the files will be stored in a single folder in a secured location.

This research poses no risk to the participants. No personal expenses will be incurred by the participants during the study. Furthermore, no incentives or financial compensation will be given for participation. The research budget will be used for any further expenses. This study is based on voluntary participation and has no implications for the participants' counseling if they decide not to participate. Older individuals can decide to withdraw from the research regardless of time, if desired, without any consequences to their counseling or care at the SACs. The expected research findings might be published in a journal article or presented at conferences or meetings; however, participants' identities will remain confidential.

Quality Control Measures

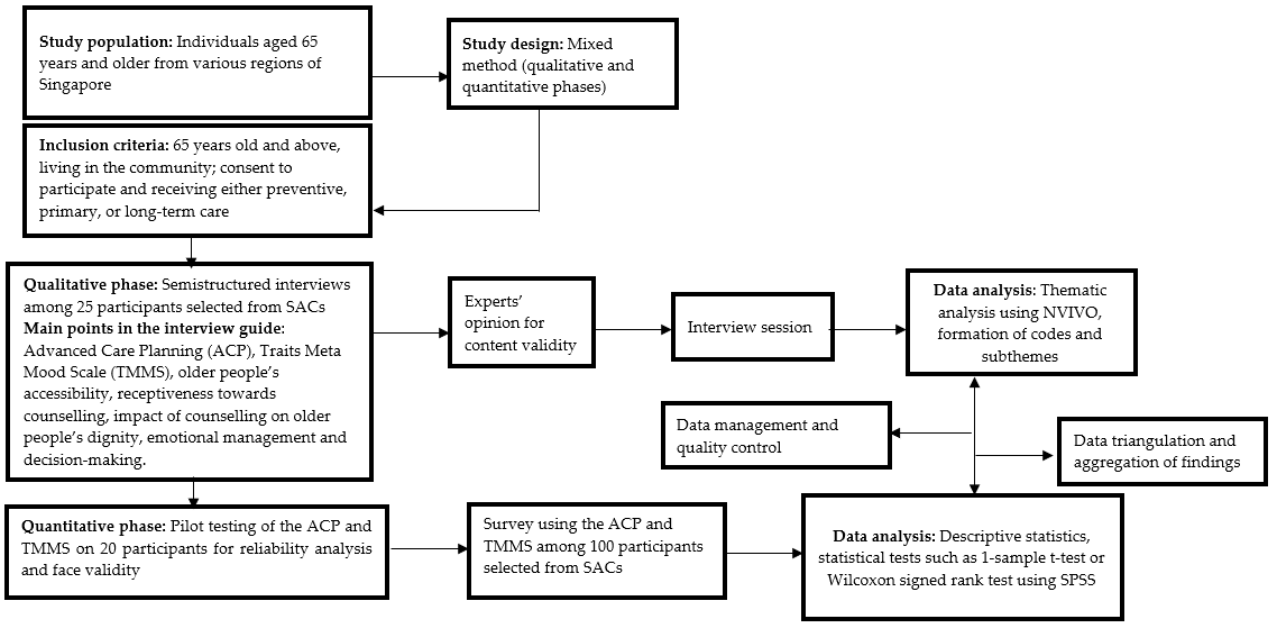
A number of methodological resources, such as mixed method study design, inclusion criteria, and random sampling, were used in this study to minimize bias and ensure quality data collection. The interview session was performed by the principal researcher, while trained enumerators assisted in the quantitative phase of data collection. The enumerators were trained during the pilot test to familiarize them with the research instrument. To further ensure quality control, the principal researcher assessed the enumerators periodically to see if they were following the survey protocol. If necessary, the enumerators also assisted the participants while they completed the questionnaire to minimize missing data. Quality control was assessed in the retrieved questionnaires based on the quality and completeness of the data.

Data Analysis

Findings from the qualitative study will be transcribed and coded. Interview transcripts will be analyzed using NVivo (version 12; QSR International). The identification, coding, and categorization of meaningful patterns into themes and subthemes will be performed to facilitate the construction of a structured questionnaire for the quantitative study. For the quantitative phase, the internal consistency of the questionnaire items will be evaluated using a reliability test based on Cronbach α values. Items will be considered acceptable and reliable if the Cronbach α value is equal to or greater than .7. Participants' background information and other sections in the questionnaire will be analyzed using descriptive statistics. Continuous variables will be subjected to normality tests using the Smirnov-Kolmogorov test and presented as means (SD) or medians (IQR) accordingly. Statistical tests such as a 2-tailed, 1-sample *t* test or Wilcoxon signed rank test will be applied. A *P* value of .05 will be considered statistically significant, and all empirical analyses will be performed using SPSS (version 25; IBM Corp). The flow of the research process, including the vital concepts, is presented in Figure 1.

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Figure 1. Sequential explanatory approach of the research. ACP: Advanced Care Planning; SAC: senior activity center; TMMS: Trait Meta Mood Scale.



Timeline

Older individuals for the quantitative study have been recruited, and the phase was completed in February 2022. Participant recruitment for the quantitative phase commenced immediately upon executing the qualitative phase. The quantitative phase began on March 22, 2022, and was completed in May 2022. Data analysis was performed in September 2022, and the research was completed in March 2023.

Results

We have obtained ethical approval to conduct this study from the Universiti Sains Malaysia Human Research Ethics Committee (USM/JEPeM/21110760). The qualitative phase, which involved a semistructured interview, was conducted from January 14, 2022, to February 16, 2022, among 25 individuals aged 66-86 years. Thematic analysis of the data is still ongoing. Meanwhile, the quantitative phase commenced on March 22, 2022, with 100 participants providing signed and informed consent to participate in the study. The face-to-face administration of the ACP and TMMS instruments and data collection closed on May 10, 2022. Data analysis and manuscript writing was performed in March 2023.

Discussion

Expected Findings

Old age comes with various losses of functions and roles, thereby leading to an increased reliance or dependency on others. Thus, the first objective of this study is to use mixed methodology in assessing older people's perspectives on ACP, life and health, end of life, and end-of-life care. The ACP instrument is a booklet designed by the Agency for Integrated Care for recording and planning health and personal care, and the main sections comprise important lifestyle activities, concerns about current health status, views toward life and health, end of life, and preferred end-of-life care. Findings from this study will elucidate participants' views of these pertinent aspects of ACP.

Policymakers in Singapore have recently highlighted the need to provide a conducive environment for older people to age effectively and to be independent for as long as possible [20]. For instance, it is estimated that by 2030, due to the nation's ultralow fertility rate, those older than 65 years will be supported by only 2.1 million Singaporeans of working age [27]. Hence, the results will assist to understand if participants' views align with the government's position to ensure improved independence among the nation's aging population.

In addition, information about perceived social support, the connection between health and exercise, and current health status or comorbidity will be gleaned from the ACP instrument. Perceived social support is an important predictor of quality of life and satisfaction with life among adults aged 65 years and older [42]. Understanding how older people define physical activity has also been associated with the perceived benefits of healthy aging [43,44]. In terms of health status, a recent study on the epidemiologic characteristics of multimorbidity in Singapore's aging population found that hypertension and lipid disorders were among the most prevalent disease combinations [45]. Singapore was also reported to have a higher prevalence of multimorbidity compared to several countries worldwide [46], with more than 19% of the population having multimorbidity. Thus, participants' concerns regarding their health status and present comorbidity will add to the current knowledge pool.

The second objective focuses on qualitative analyses of participants' perspectives on counseling, awareness and receptiveness toward counseling services, and potential barriers to seeking counseling assistance. Counseling and psychotherapy are confidential conversations between a counselor and a client that are performed to provide solutions to problems [47,48].

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Factors such as perception and attitude toward counseling, affordability, financial status, and accessibility are some of the consistent factors influencing receptiveness toward counseling among older individuals [49-51]. Given the limited information on the aforementioned aspects in the Singaporean context, findings from this study will provide opportunities for relevant bodies to ascertain the factors to focus on in enhancing the receptiveness toward counseling among older people.

Our third objective was to understand older people's perspectives on dignity and how their emotional management and decision-making are influenced by counseling. End-of-life patients' dignity is a vital theme in the context of palliative care, and health care professionals are expected to address complicated decisions on specific aspects of patients with terminal illnesses [52,53]. Given that older people tend to be more vulnerable to loss of dignity following advanced age and deteriorating health, dignified care is a significant health care goal that ought to be preserved during counseling interventions, especially for older people [54]. Previous studies conducted elsewhere found that terms such as *self-worth*, *self-recognition*, and *self-expression* were used by older participants in describing dignity [55,56]. We expect the participants in this study to use similar terms but tailored to the nation's context given the different cultural backgrounds compared to Western perspectives.

In terms of the impact of counseling on emotional management and decision-making, diverse views ranging from positive to negative effects may be conveyed by participants since they might have faced challenges in seeking counseling assistance. For instance, a previous study conducted in Tehran, Iran, found that psychological counseling on mental well-being had a positive impact on emotion and self-management ability among older women [57]. Dai et al [58] also performed a meta-analysis of studies conducted among Chinese populations and found that psychologically based therapies were effective in ameliorating depression symptoms among older people. The contents of the ACP instrument used in this study entailed pertinent topics on mental health, the selection of treatment goals (comfort-focused vs full treatment), available care options in the community, and available care options during end of life, which might have a positive effect on emotional management and decision-making. However, difficulties in assessing counseling services or challenges are faced during the counseling process.

The fourth objective of this study emphasized participants' competencies in emotional management after counseling assistance. This objective will entail both a semistructured interview and a quantitative analysis by using the TMMS, which focuses on participants' attention (perceived attention paid to personal emotional conditions), clarity (perceived understanding of personal emotional conditions), and repair (perceived ability to regulate personal emotional conditions). The TMMS is one of the most commonly used self-administered measurements for perceived emotional competence in older people [29]. It provides the opportunity to bridge current empirical gaps on emotions and to elucidate developmental trajectories throughout a person's life span. Based on the alignment between the ACP contents and items in the TMMS, as well as findings from previous local studies on the impact of counseling [20], we expect older people's competencies in emotional management and decision-making to improve after seeking counseling assistance. Results from this study may assist policymakers in deploying strategies to promote mood repair and emotional management in the Singaporean aging population to improve their receptiveness toward counseling interventions.

Overall, this study takes a holistic look into novel approaches to developing an effective counseling intervention for older people in Singapore. By considering older people's perspectives on pertinent issues regarding dignified care, life and health, end-of-life care, and the impacts of counseling, the challenges and prospects of available counseling services offered at various centers in Singapore can be elucidated. Moreover, patients, health care professionals, and social workers play pivotal roles in decision-making processes and ensuring optimum care during routine hospitalization of older patients' at their end of life. We anticipate that the data gleaned from this study will provide important insights regarding the approaches to developing a feasible and acceptable counseling intervention for older individuals in Singapore, as well as incorporating the intervention into routine care and accentuating potential barriers to seeking counseling assistance among this older population.

Implications

The findings in this study, particularly older people's perspectives on ACP, dignity, life and health, end of life, accessibility and receptiveness toward counseling, and competencies in emotional management and decision-making, should be beneficial to relevant policymakers in Singapore. Counseling is still an emerging field in Singapore, and there is a lack of mandatory counseling service regulations in Singapore. Given the various counseling services provided by professional organizations and private individuals, policymakers may consider the findings in standardizing the service training and counseling content for the increasing older population in Singapore.

This research is also promising in enhancing the target group's health, cognitive, and social functioning aspects. Given the current aim of the Singaporean government to tailor counseling for older people toward their cultural backgrounds [20] and coupled with the fact that older Singaporeans have less access to Western perspectives [59], the findings may assist in incorporating their perspectives into developing effective counseling interventions. Diverse perspectives have been reported to affect older individuals' receptiveness to counseling interventions [55,57].

Another important implication of this study is for the social workers, counselors, and health care professionals who are expected to deliver effective services to older individuals. The findings on older people's perspectives on ACP, dignity, life and health, and end-of-life care could be used to bridge the gap between the various players toward holistic patient-centered care. Moreover, counselors are expected to upgrade their professional knowledge and skills to ensure that older people live with dignity and access essential health and social services for optimal autonomy and independence. Thus, counselors in Singapore may find this study an opportunity to equip themselves with clinical skills to counsel older people.

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Strengths and Limitations

Given the paucity of research on counseling as an intervention to enhance older people's dignity within the community, this study has attempted to fill in the research gap between counseling and Singaporean government policy on aging in place, thus adding to the current body of knowledge and literature in the research area both at local and global levels. The variables and specific events investigated in this study, such as receptiveness and accessibility to counseling centers, improved emotional management and decision-making, and quantitative assessment of perceived attention, clarity, and mood repair among older individuals, represent the novelty of this research. To date, only a few studies have considered the lived experiences and interactions of older adults with counselors or social workers. This study represents the first attempt to use mixed research methods to bridge the research gap. This combined approach will facilitate the collection of vital data through in-depth interviews and survey methods to elucidate older individuals' lived experiences and interactions with qualified and Singapore Association of Counseling and Singapore Association of Social Workers–accredited counselors or social workers.

However, the study design enabled the recruitment of participants with similar characteristics, and the inclusion and exclusion criteria used in selecting the study participants might have excluded older individuals with pertinent information on the research topics. Furthermore, the use of semistructured interview sessions also has its limitations, as respondents might be unwilling to provide in-depth information to the questions being asked. Moreover, the ACP instrument used in the qualitative phase has some closed-ended questions in which participants were not free to express their opinions. This might contribute to a degree of response bias. Last, this study has a cross-sectional design, and the findings will only reveal the association between the studied variables, such as accessibility and receptiveness toward counseling, perspectives on dignity and barriers to counseling assistance, and the related impact on emotional management and decision-making. In other words, no causal relationships can be inferred. Longitudinal, prospective, and randomized control study designs are more likely to generate the required data to infer causal effects and relationships between the studied concepts.

Conclusion

Accumulated evidence reflects the paucity of data on the impact of counseling on older people's dignity and emotional management in Singapore. Moreover, their accessibility and receptiveness toward counseling remain underreported. With the rising older population and the need for better care and effective aging, this research will be pertinent in elucidating the role of counseling in addressing the aforementioned issues. Policymakers and relevant bodies can use the findings to implement a model that will enhance older people's receptiveness toward counseling and derive vital benefits from such an intervention.

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Data Availability

All data generated or analyzed during this study will be included in the published article and its supplementary information files.

Conflicts of Interest

None declared.

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Abbreviations

ACP: Advanced Care Planning
SAC: senior activity centers
TMMS: Trait Meta Mood Scale
VWO: voluntary welfare organization

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Original Paper

Digital Health Dashboards for Decision-Making to Enable Rapid Responses During Public Health Crises: Replicable and Scalable Methodology

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Abstract

Background: The COVID-19 pandemic has reiterated the need for cohesive, collective, and deliberate societal efforts to address inherent inefficiencies in our health systems and overcome decision-making gaps using real-time data analytics. To achieve this, decision makers need independent and secure digital health platforms that engage citizens ethically to obtain big data, analyze and convert big data into real-time evidence, and finally, visualize this evidence to inform rapid decision-making.

Objective: The objective of this study is to develop replicable and scalable jurisdiction-specific digital health dashboards for rapid decision-making to ethically monitor, mitigate, and manage public health crises via systems integration beyond health care.

Methods: The primary approach in the development of the digital health dashboard was the use of global digital citizen science to tackle pandemics like COVID-19. The first step in the development process was to establish an 8-member Citizen Scientist Advisory Council via Digital Epidemiology and Population Health Laboratory's community partnerships. Based on the consultation with the council, three critical needs of citizens were prioritized: (1) management of household risk of COVID-19, (2) facilitation of food security, and (3) understanding citizen accessibility of public services. Thereafter, a progressive web application (PWA) was developed to provide daily services that address these needs. The big data generated from citizen access to these PWA services are set up to be anonymized, aggregated, and linked to the digital health dashboard for decision-making, that is, the dashboard displays anonymized and aggregated data obtained from citizen devices via the PWA. The digital health dashboard and the PWA are hosted on the Amazon Elastic Compute Cloud server. The digital health dashboard's interactive statistical navigation was designed using the Microsoft Power Business Intelligence tool, which creates a secure connection with the Amazon Relational Database server to regularly update the visualization of jurisdiction-specific, anonymized, and aggregated data.

Results: The development process resulted in a replicable and scalable digital health dashboard for decision-making. The big data relayed to the dashboard in real time reflect usage of the PWA that provides households the ability to manage their risk of COVID-19, request food when in need, and report difficulties and issues in accessing public services. The dashboard also provides (1) delegated community alert system to manage risks in real time, (2) bidirectional engagement system that allows decision makers to respond to citizen queries, and (3) delegated access that provides enhanced dashboard security.

Conclusions: Digital health dashboards for decision-making can transform public health policy by prioritizing the needs of citizens as well as decision makers to enable rapid decision-making. Digital health dashboards provide decision makers the ability to directly communicate with citizens to mitigate and manage existing and emerging public health crises, a paradigm-changing approach, that is, inverting innovation by prioritizing community needs, and advancing digital health for equity.

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KEYWORDS

big data; COVID-19; digital citizen science; digital dashboards; digital epidemiology; digital health; digital health platforms; eHealth; health equity; mHealth; pandemics; public health surveillance; virtual health care; mobile phone

Introduction

In this digital age, human engagement with and through internet-connected devices generates a substantial amount of big data [1]. The ever-increasing usage of information technology in all spheres of human life has contributed to this phenomenon [2]. The use of these big data, which traditionally exist outside health care systems, has significant implications for the prediction and prevention of population health crises [3]. However, the exponential growth of big data creates challenges to meaningfully extract useful and timely information to inform public health policies [2,4].

Decision-making processes, particularly from the health systems perspective are complex. This complexity is compounded during population health crises, as evidenced by the difficulty that governments and health systems faced during the COVID-19 pandemic [5]. The challenges that the COVID-19 pandemic continues to pose reiterate the need for timely, appropriate, and precise evidence to inform decision-making during the evolving nature of public health crises [6].

The COVID-19 pandemic has revealed the gaps in governmental and health system decision-making while clarifying the need for a transformative change in the way public health crises need to be managed in the future [7]. The challenge in monitoring, managing, and mitigating public health crises, particularly rapidly spreading and evolving communicable disease epidemics and pandemics, is the need to coordinate decision-making processes across local, provincial, national, and international jurisdictions [8].

The COVID-19 pandemic particularly demonstrated the challenges faced by local jurisdictions in implementing federal or state or provincial mandates [9] due to the lack of timely access to jurisdiction-specific evidence [9]. The COVID-19 pandemic has also reiterated the need for cohesive, collective, and deliberate societal efforts to address inherent inefficiencies in our health systems and overcome decision-making gaps using real-time data analytics [10]. Nonetheless, the pandemic has also provided opportunities to decentralize and democratize technology that can support local decision makers with real-time access to big data for timely decision-making [11,12].

However, ethically obtaining, processing, and visualizing big data from citizens is critical to transforming local jurisdictional decision-making processes that impact public health [3,13]. To achieve this, decision makers need independent and secure digital health platforms that engage citizens ethically to obtain big data, analyze and convert big data into real-time evidence, and finally, visualize this evidence to inform rapid decision-making [3,14].

This visualization of data can be realized by the development and implementation of digital health dashboards [15], which are powerful tools to facilitate rapid decision-making [7]. This study enumerates the development of replicable and scalable jurisdiction-specific digital health dashboards for rapid decision-making to ethically monitor, mitigate, and manage public health crises via systems integration, that is, going beyond health systems.

Methods

Dashboard Development Process

The development of the digital health dashboard was in response to transform rapid responses to pandemics such as COVID-19 as well as to decentralize technology that can be sustainable, and scalable across jurisdictions. The primary approach in the development of the dashboard was the use of global digital citizen science to tackle pandemics like COVID-19 [3], which identifies the development of decision-making dashboards as a critical advancement in addressing public health crises via real-time data analytics using citizen-driven big data.

The methodology intersects digital citizen science and mHealth to conceptualize and develop digital health platforms that enable ethical surveillance, integrated knowledge translation, and real-time interventions [12]. Such development requires robust theoretical underpinnings such as the Smart Framework [12], which integrates citizen science, community-based participatory research, and systems science through ubiquitous tools to conduct population health interventions in the digital age. Smart Framework operationalizes the repurposing of citizen-owned ubiquitous communication devices (ie, smartphones), an approach that was incorporated into the development of this digital health dashboard. However, beyond the ability to ethically generate big data for rapid responses, this methodology also operationalizes the capacity of smartphones to enable health equity by empowering disenfranchised citizens to inform jurisdictional policies, that is, digital health for equity.

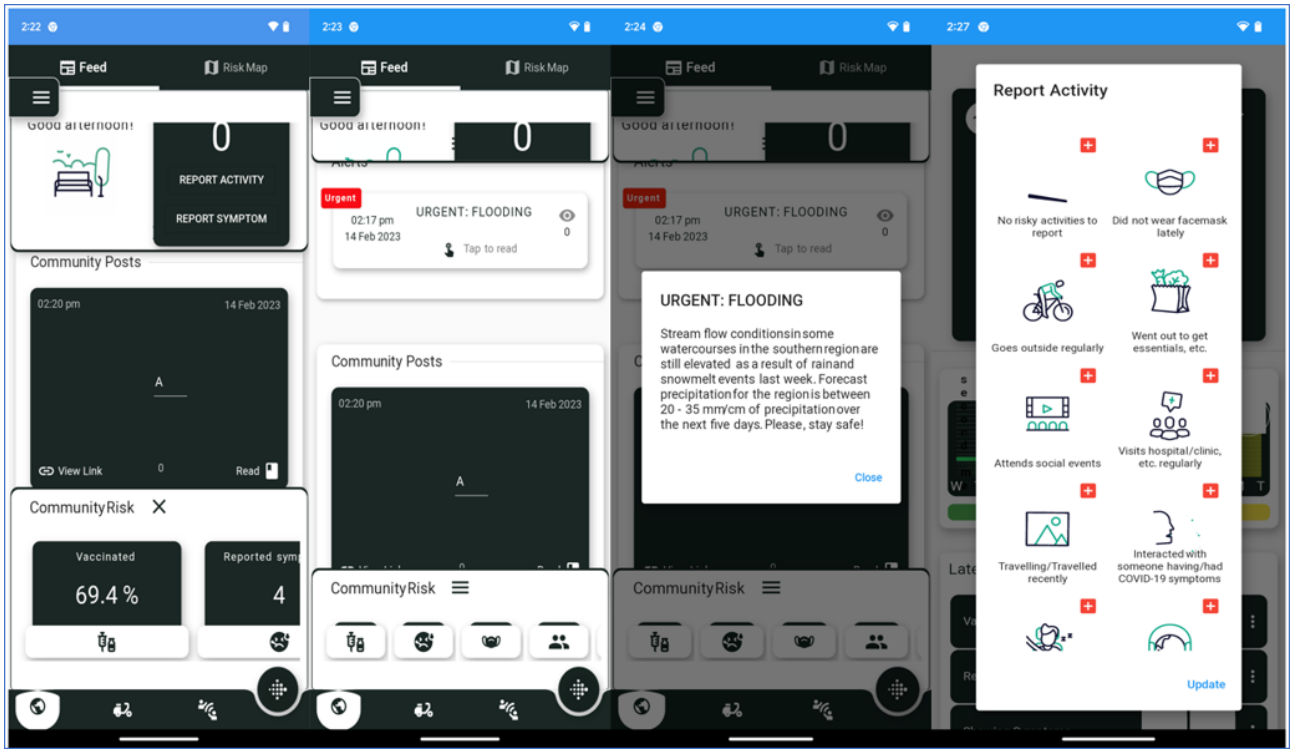
The first step in the development process was to establish a Citizen Scientist Advisory Council using Digital Epidemiology and Population Health Laboratory's (DEPtH Lab) community partnerships [16]. The diverse and inclusive 8-member council had representation from across varied groups that included gender, ethnicity, and socioeconomic diversity. More importantly, the council consisted of both community members and decision makers, a key component in the development of jurisdictional-specific digital health dashboards for decision-making.

Based on the consultation with the council, three critical needs of citizens were prioritized: (1) management of household risk of COVID-19, (2) facilitation of food security, and (3) understanding citizen accessibility of public services. Thereafter, a progressive web application (PWA) was developed to provide daily services that address these citizen needs (Figure 1). The big data generated from citizen access to these PWA services

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are set up to be anonymized, aggregated, and linked to the digital health dashboard for decision-making, that is, the dashboard displays anonymized and aggregated data obtained from citizen devices via the PWA.

Figure 1. Screenshots of progressive web application.



The dashboard was developed to achieve the following objectives identified by the global digital citizen science policy [3]: (1) implementation of ethical real-time surveillance to assess community health risks, (2) implementation of near real-time integrated knowledge translation based on the data provided by citizen usage of PWA, (3) implementation of evidence-based real-time public health communication, (4) evidence-based decision-making using real-time data analytics to mitigate health risks, and (5) addressing existing and evolving public health crises by developing adaptable, scalable, and replicable digital infrastructure.

The PWA (Figure 1) serves as a public health advising platform for citizens within a jurisdiction, where community members can manage their household risk of COVID-19 based on an evidence-based algorithm that takes into consideration not only the number of members in a household but also individual and collective household behaviors and symptoms. Using the PWA, citizens are also able to interact with jurisdictional decision makers, request food when in need, and report issues with access to public services within their jurisdiction. The PWA also has the capacity to directly receive alerts from decision makers via the digital health dashboard.

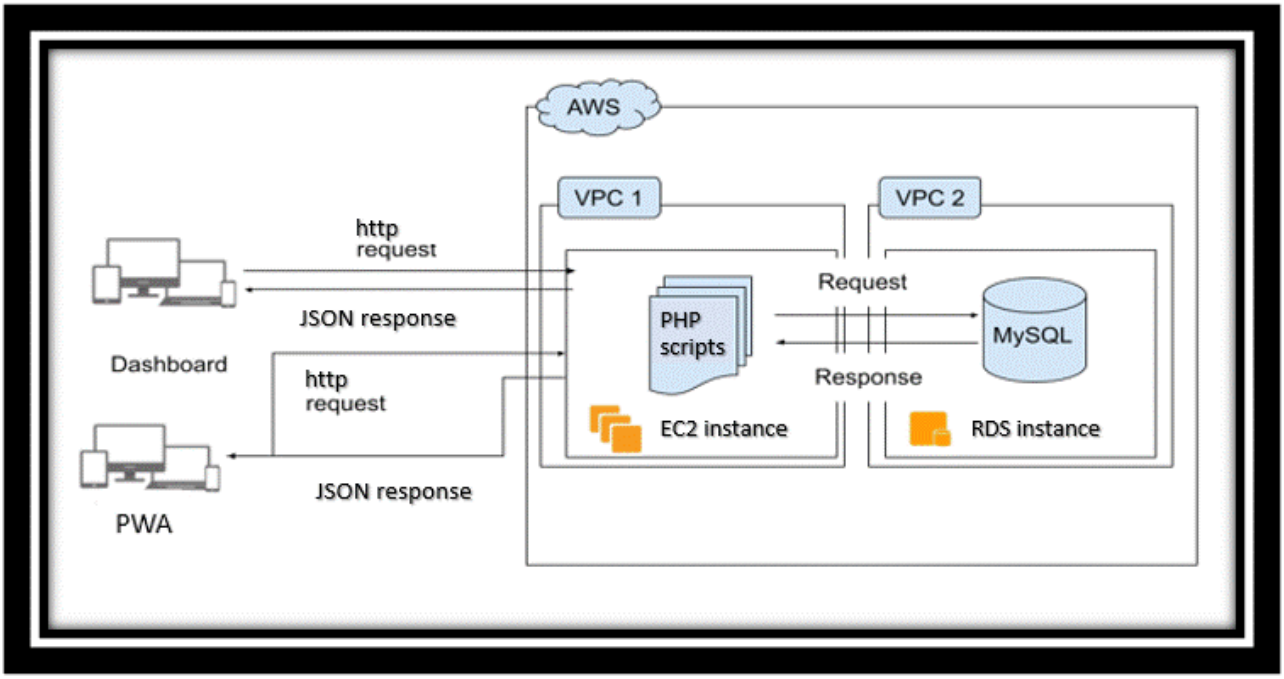
The PWA was designed using gamification features derived from Animaker [17], a software developed by RS Raghavan and coded using Flutter Framework. Flutter is an open-source user interface development kit developed and launched by Google Inc (Mountain View, California) and can be used to develop cross-platform applications for Android, iOS, Linux, macOS, Windows, Google Fuschia, and the web using a single codebase [18,19]. Flutter applications are written in Dart programming language [20].

The PWA is linked to the digital health dashboard through the "hypertext transfer protocol" (http) request and "hypertext preprocessor" (PHP) coding, an open-source server-side scripting programming language, which executes programming instructions at runtime [21]. http and custom-written PHP scripts act as a bridge that relays data from one end to another—PWA to database to Digital Health Dashboard [22]. All functionalities of the PWA are directly linked to the connection made with the backend database, via http request and PHP scripts.

Two virtual private cloud environments, which are hosted on Amazon Web Services (AWS), securely store and communicate data between the database, PWA, and the digital health dashboard (Figure 2) [23]. A virtual private cloud is a private cloud computing environment on shared public cloud infrastructure, which allows for secure computing, networking, and storage of information [24]. Within the virtual private cloud environment, both the Amazon Elastic Compute Cloud servers and the Amazon Relational Database servers are located. Amazon Elastic Compute Cloud servers provide secure and reliable server infrastructure with the flexibility to scale-up or -down server needs [25].

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Figure 2. Digital health dashboard data flow processes showing linkage between PWA, dashboard, and cloud storage. AWS: Amazon Web Services; EC2: elastic compute cloud; MySQL: structural query language; PHP: hypertext preprocessor; PWA: progressive web application; RDS: relational database service; VPC: virtual private cloud.



Amazon Elastic Compute Cloud servers host the digital health dashboard through a PHP script run from within the server. Amazon Relational Database Server is a database service provided by AWS that stores, organizes, and makes data available through cloud infrastructure [26]. All data that are being generated through the interaction of citizens with PWA are stored and organized in the Amazon Relational Database using MySQL, an open-source relational database management system [26].

The PHP scripts communicate with the Amazon Elastic Compute servers, and MySQL is used to communicate with the Amazon Relational Database servers to organize incoming data in the database. The activities of the Amazon Elastic Compute Cloud servers and the Amazon Relational Database servers are communicated to both the PWA and digital health dashboard via http [27].

The digital health dashboard is coded and developed in PHP, which allows for the creation of dynamic content on websites to interact with databases [28]. Within the digital health dashboard, there is an interactive community statistical navigation system that was designed and developed using the Microsoft Power Business Intelligence tool [29,30]. Microsoft Power Business Intelligence is a tool that connects data from different sources to provide advanced and interactive data analytics via an automatic data feed to the dashboard. This data gateway ensures near real-time visualization of big data on the dashboard, which can be updated from intervals of 5 to 30 minutes. To ensure the availability of a consistent data feed to the digital health dashboard, the MySQL relational database management system is used to query, access, prepare, and integrate the most recent data points [24].

The dashboard system is set up to anonymously assign QR codes to households within a jurisdiction, which allows the PWA to be used only when QR codes are scanned. Figure 2 presents the complete data flow between the PWA, the Amazon Relational Database, the Amazon Elastic Compute Cloud, and the digital health dashboard. Data at rest are encrypted using randomized keys generated by AWS key management service that gives centralized control over the cryptographic keys used to protect data. All users' passwords are hashed and stored using Secure Hashing Algorithms [31], which shorten passwords into smaller forms that cannot be understood using bitwise operation, modular additions, or compression functions.

Data in transit are protected by Cloudflare. All media data are stored in Amazon Simple Storage Service [32], which is an object storage service that offers scalability, security, and performance [32]. Media files are moved through AWS CloudFront, a process that prevents users from directly accessing or manipulating Amazon Simple Storage Service [33,34]. Cloud database access is controlled by AWS Identity and Access Management service [35], which helps to securely control access to AWS resources. Finally, all database access processes are audited through AWS CloudTrail [36], which tracks actions taken on AWS accounts [36], an additional security protocol to monitor and prevent data breaches.

Ethical Considerations

This development process is exempt from ethics review, as study participants were not included in this endeavor. When the digital dashboard will be launched, informed consent will be obtained via the PWA before any data are collected. The information in the informed consent will include the project title, purpose and objectives of the digital health dashboard and PWA, potential benefits and risks, data collection and storage procedures, right to withdraw or drop out and delete the PWA, and contact information for questions, queries, and concerns. Citizens will have to provide informed consent before signing

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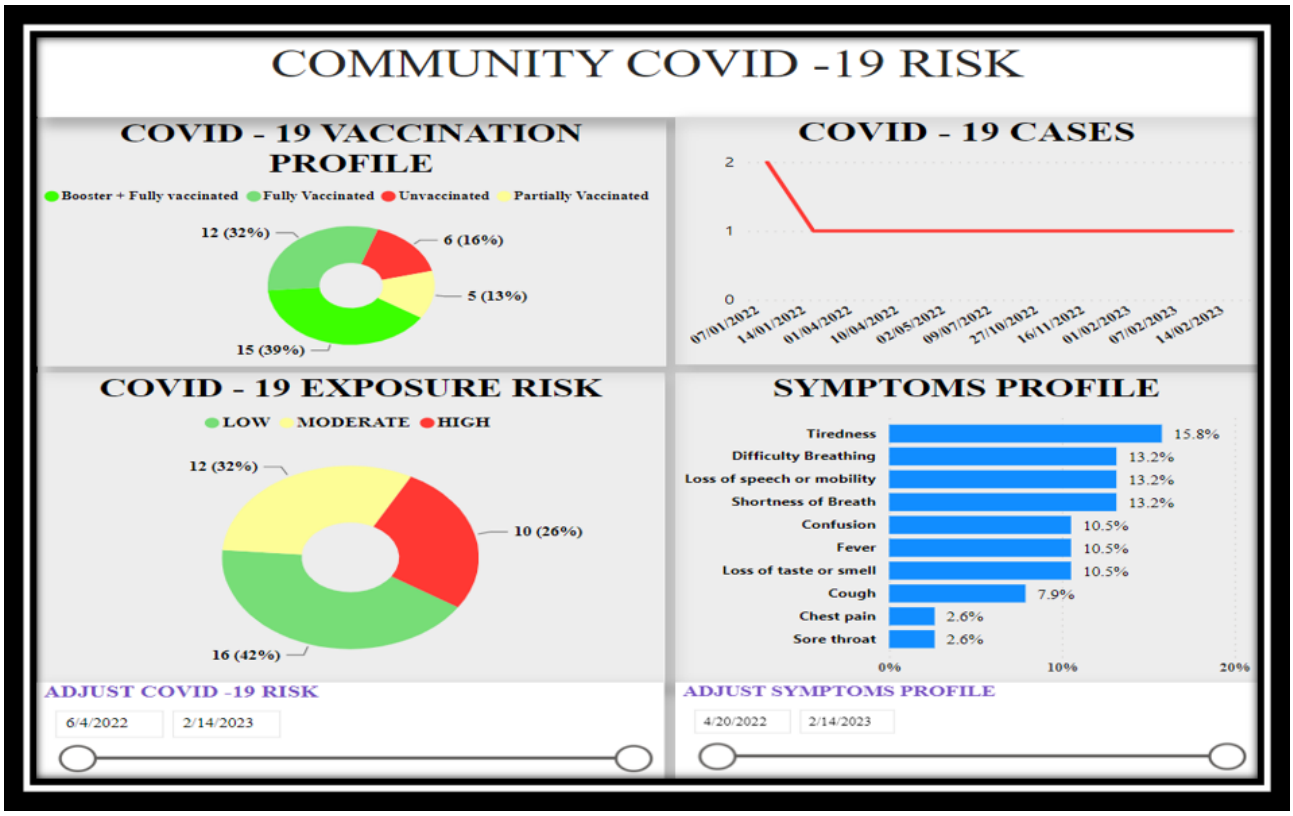
up to use the PWA. All data from citizens will be anonymized and aggregated before data visualization, analyses, and dissemination.

Results

Overview of the Developed Dashboard

The development process resulted in a replicable and scalable jurisdiction-specific digital dashboard for decision-making that was tested within the DEPtH Lab to confirm not only the real-time linkage between the PWA and the digital health dashboard but also the functionality of all the resultant features. The big data that are relayed to the dashboard in real time reflect usage of the PWA that provides households the ability to manage their risk of COVID-19, request food when in need, and report difficulties and issues in accessing public services. The main components of the dashboard are (1) community COVID-19 risk profile (Figure 3), (2) food security status (Figure 4), and (3) citizen reporter statistics (Figure 5). However, beyond these core components, there are three additional features of the dashboard: (1) delegated community alert system that enables direct communication with community members (Figure 6), (2) direct bidirectional engagement system (Q & A) that allows decision makers to directly respond to citizen queries (Figure 7), and (3) delegated dashboard access (Figure 8) that provides key decision makers to control and specify staff access to individual components of the dashboard, such as the food security status.

Figure 3. Dashboard of home page displaying community COVID-19 risk profile.



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Figure 4. Dashboard of food security status, which allows decision makers to manage food requests. FS: food security.

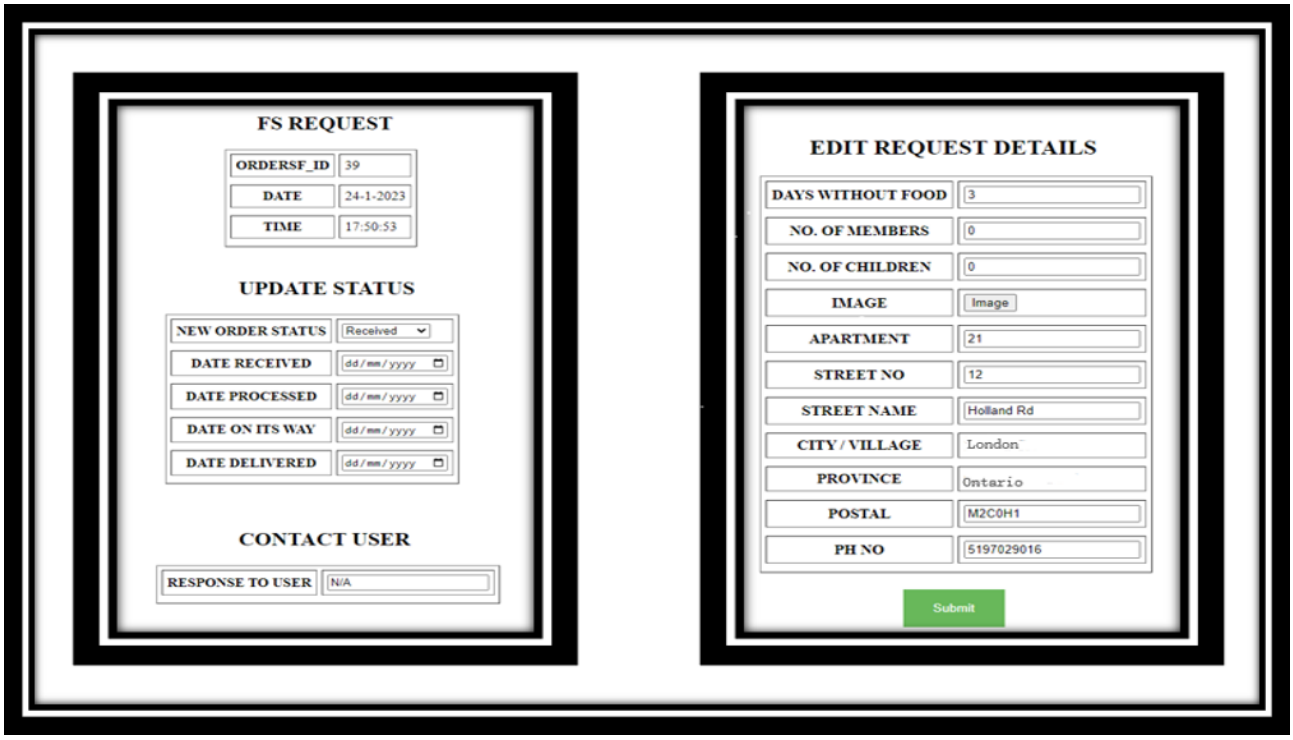
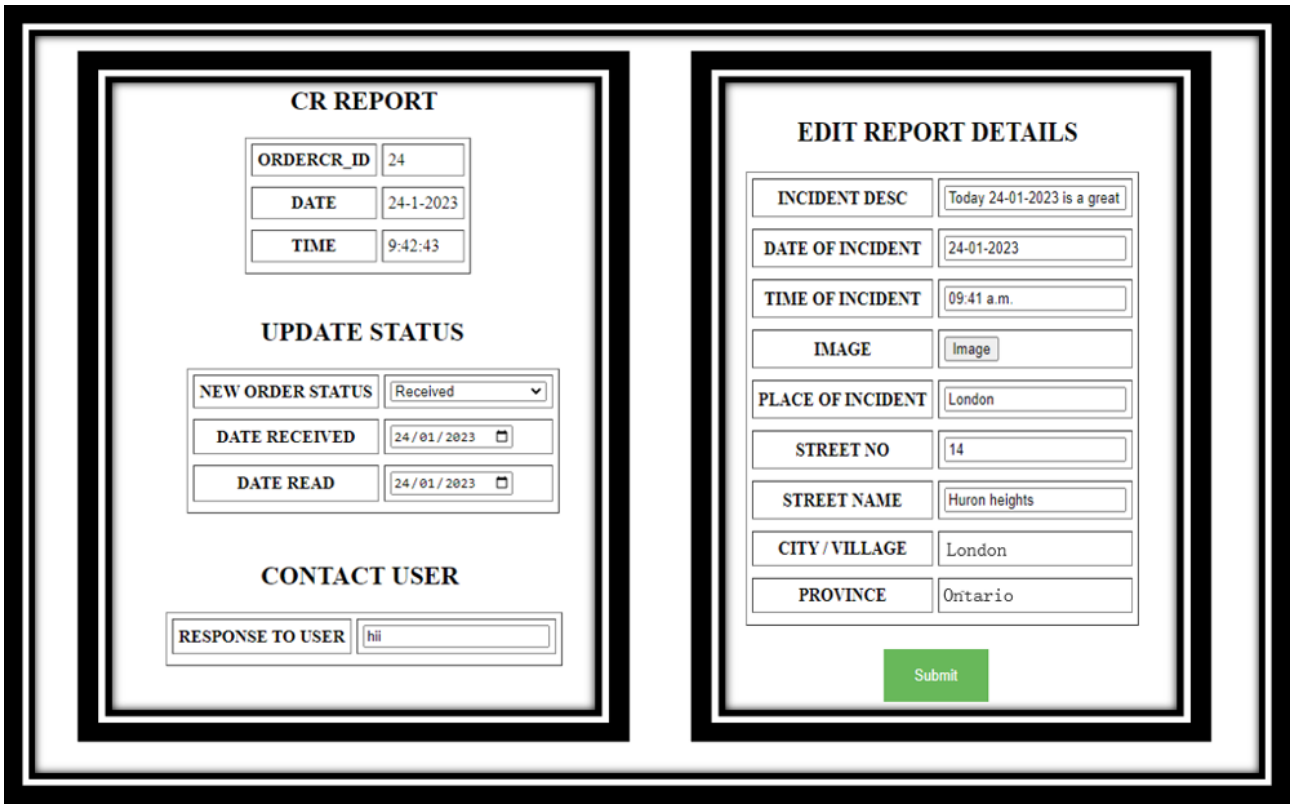


Figure 5. Citizens reporter page, which allows decision makers to view citizen issues in real time. CR: citizen reporter.



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Figure 6. Delegated community alert system, which enables decision makers to send alerts via the direct bidirectional engagement system (Q & A).

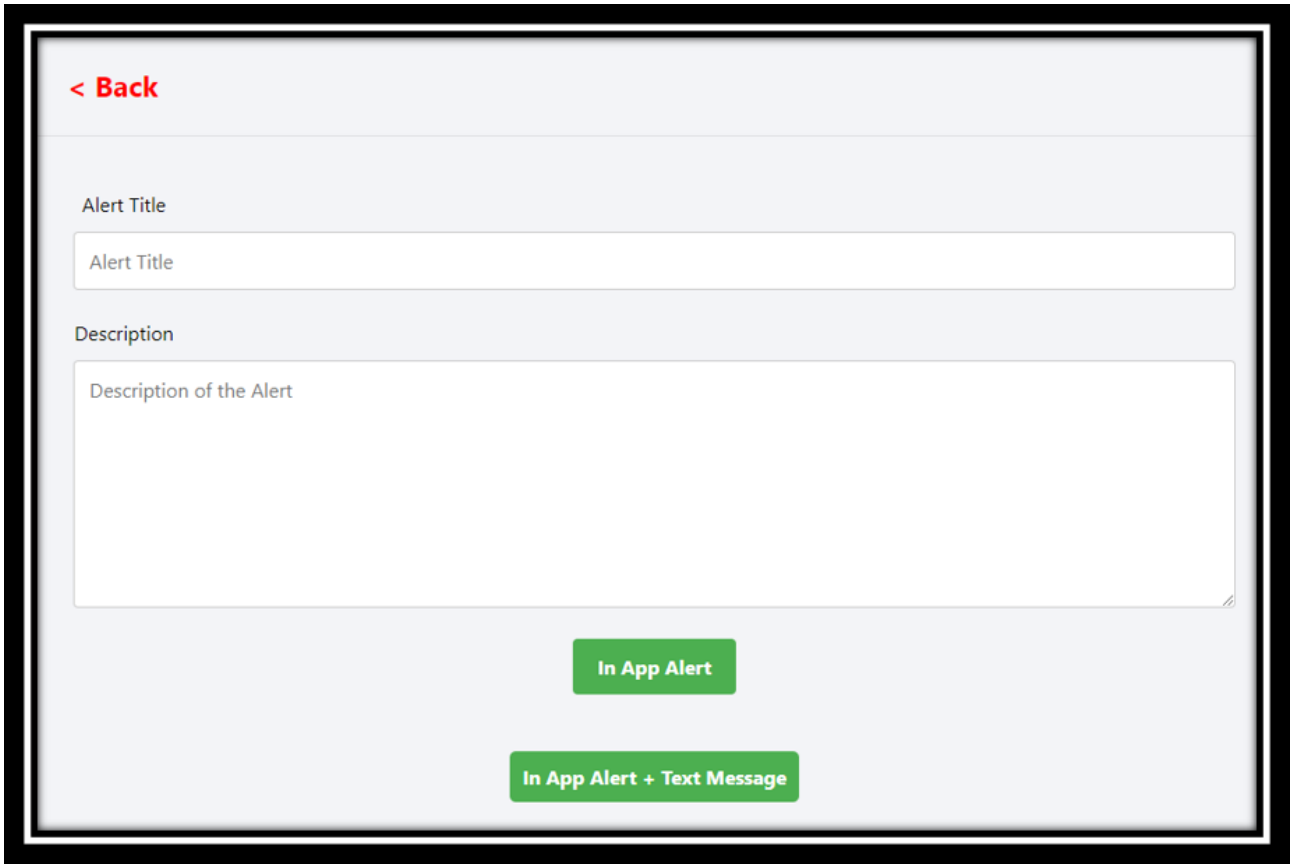
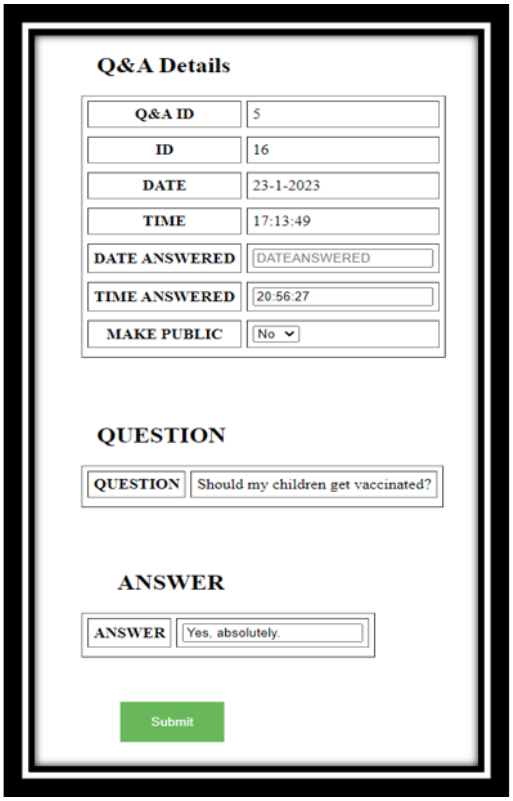
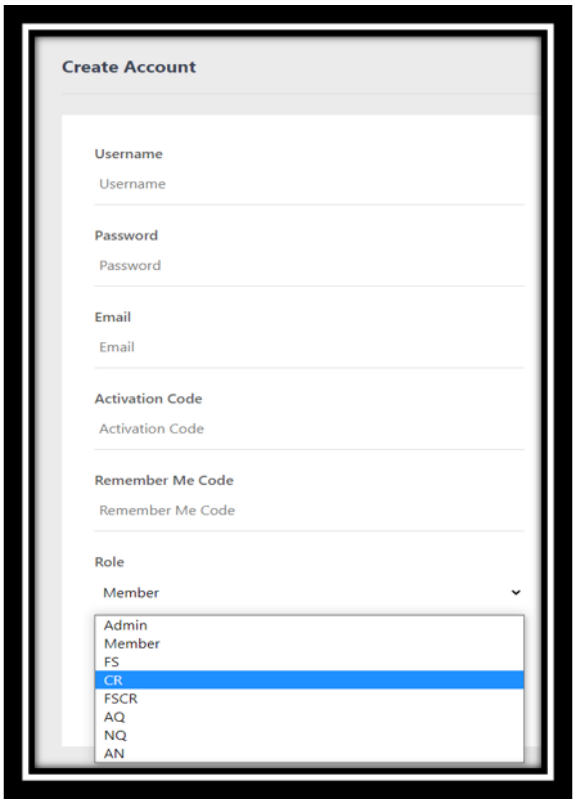


Figure 7. Direct bidirectional engagement system depicting decision makers' response to anonymous queries.



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Figure 8. Delegated dashboard access showing categories that can be assigned by the super administrator. AN: alert and community alert; AQ: alert and question and answer; CR: citizen reporter; FS: food security; FSCR: food security and citizen reporter; NQ: community alert and questions and answer.



Community COVID-19 Risk Profile

It depicts the trend lines of COVID-19 cases in a jurisdiction, the COVID-19 vaccination status of the community, which includes the number and proportion of fully (in this case, 2 doses of Health Canada–approved vaccines) and partially vaccinated community members as well as community members who have obtained booster doses. The vaccination profile also depicts the number and proportion of unvaccinated individuals in the community. In addition to this, based on the algorithm developed by the DEPtH Lab, the daily household COVID-19 risk that PWA users obtain at the frontend is anonymized and aggregated before being reflected on the dashboard within the community COVID-19 risk profile. This feature of the dashboard also shows the evolving picture of community symptoms and behavior profile.

Food Security Status

The food security status feature is a comprehensive decision-making system that enables decision makers to respond to and manage the needs of households in near real time. With a delegated access option, which can be linked with local food banks, the food security status feature provides time-stamped management, displaying the status of the request at various stages: received, processed, dispatched, and delivered. This change of status is reflected in near real time on the PWA, which allows citizens to monitor the progress of their request.

Citizen Reporter Statistics

This feature reflects time-stamped, and detailed statistics of public services access issues reported by citizens within the jurisdiction, including the description of the issue as detailed by the citizens. The dashboard is set up to respond to the citizens' report to ensure that there is clear communication between the decision makers and the citizens. For instance, the citizen reporter statistics are further categorized based on the selected time period to show various aspects of the reports, including the number and proportion of acknowledged reports, and the number and proportion of reports yet to be acknowledged. In addition, there are 2 data visualization layers that display the number of reports awaiting a response and number of reports that received a reply.

Delegated Community Alert System

The decision-making dashboard has a delegated alert system (Figure 6) to send alerts to citizens in the jurisdiction in real time to manage risks, communicate directly, and update citizens of events in the jurisdiction. The delegated level of alerts provides the flexibility to the decision makers to prioritize alerts into urgent and nonurgent alerts. The decision makers have the flexibility to use the alerts from disaster preparation and management to communication of policies.

Direct Bidirectional Engagement System (Q & A)

To enable anonymized engagement with citizens, a bidirectional engagement system (Figure 7) provides decision makers the ability to address citizen queries and inquiries related to jurisdictional policies and procedures. To provide clarity of communication, the citizens are able to visualize the status of their queries and inquiries at various stages, from "received" and "acknowledged" to "processing" and "responded." More

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importantly, the decision makers are able to delegate the queries to ensure that the responses are provided in a timely manner.

Delegated Dashboard Access

The dashboard is set up to delegate tasks across decision makers, minimize risk of inappropriate access to data, and manage the needs of jurisdictions efficiently by spreading the load of work across several levels of decision makers (Figure 8). For instance, there is a primary "super administrator" who has access to all aspects of the dashboard and has the capacity to delegate access across 7 different categories, which would delineate access to manage specific systems of the dashboard such as "food security" or "citizen reporter."

Data Visualization

Finally, data that flow from the AWS Relational Database cloud server are processed and converted into meaningful statistics—a key component that enables all dashboard functions. Through data layering, each visual on the interactive and dynamic dashboard can be explored to ascertain specific and more detailed information about the aggregated visualization. The visualization flexibility allows decision makers to understand patterns that are important for rapid decision-making. For instance, a decision maker might be interested in knowing the demographic distribution of fully vaccinated citizens, which can be visualized by selecting the dropdown options within the dashboard.

Discussion

Implications of the Developed Dashboard

During the COVID-19 pandemic, jurisdictions across the world and particularly communities in rural and remote regions faced the need to overcome the decision-making gap that was created due to the lack of timely access to jurisdictional specific information [37]. The pandemic highlighted the inequities between communities, where risk and spread of illness varied due to unequal distribution of adequate health facilities, health care workforce, and health literacy, among other factors [37,38]. The urgency created by the pandemic clarified the need for jurisdiction-specific decision-making technology to address public health crises that prioritizes citizen needs [3]

The pandemic also reiterated the need to decentralize and democratize public health decision-making processes, which would enable rapid responses to public health crises [11,12]. The primary goal of this study was the development of replicable and scalable jurisdiction-specific digital health dashboards for rapid decision-making to ethically monitor, mitigate, and manage public health crises via systems integration, that is, going beyond health systems. The developed dashboard achieves the 5 objectives articulated by the global digital citizen science policy [3].

The community COVID-19 risk profile (Figure 3) feature achieves objective 1 of the dashboard development in implementation of ethical real-time surveillance to assess community health risks [39]. The citizen reporter feature (Figure 5) adds another dimension in achieving objective 1 of dashboard development in obtaining personalized and qualitative perception of citizens in understanding access to public services. Food security feature (Figure 4) achieves objective 2 of the dashboard development in implementation of near real-time integrated knowledge translation based on the information provided by citizens. In visualizing the food security status within the dashboard, decision makers not only understand the aggregated needs of households in the community but also respond to the specific needs of each household requesting food [40].

The delegated alert system (Figure 6) addresses objectives 3 and 4 of the dashboard development: implementation of evidence-based real-time public health communication and evidence-based decision-making using real-time data analytics to mitigate health risks. Bidirectional engagement system (Figure 7) adds personalization in achieving objective 3 of the dashboard development: real-time public health communication [41]. The digital health dashboard in general addresses objective 5 of the dashboard development, that is, development of adaptable, scalable, and replicable digital infrastructure to address existing and evolving public health crises. For instance, using the developed digital health infrastructure, changes can be made to the features of the dashboard to suit jurisdictional, citizen, or crisis-specific needs [40].

More importantly, the digital health dashboard that was developed operationalizes four key processes that have important implications in transforming public health policy in the digital age: (1) evidence-based decision-making, (2) digital citizen science for health equity, (3) rapid responses to public health crises, and (4) social innovation: decentralization of technology, and data sovereignty and security.

Evidence-Based Decision-Making

Decision-making from the perspective of managing public health crises goes beyond health systems to include key aspects for survival and societal functioning, such as food security [42,43], maintenance of law and order [44,45], and social support to vulnerable groups [46], that is, systems integration for cohesive decision-making. However, making informed decisions in public health crises can be extremely challenging without accurate data and evidence, particularly in situations like pandemics, where disjointed and disparate information from multiple sources can result in poor decision-making [7,47]. This challenge was particularly pronounced in terms of ineffective information sharing across different levels of governments, with municipal governments having to take decisions at the local level, without concrete evidence [48,49].

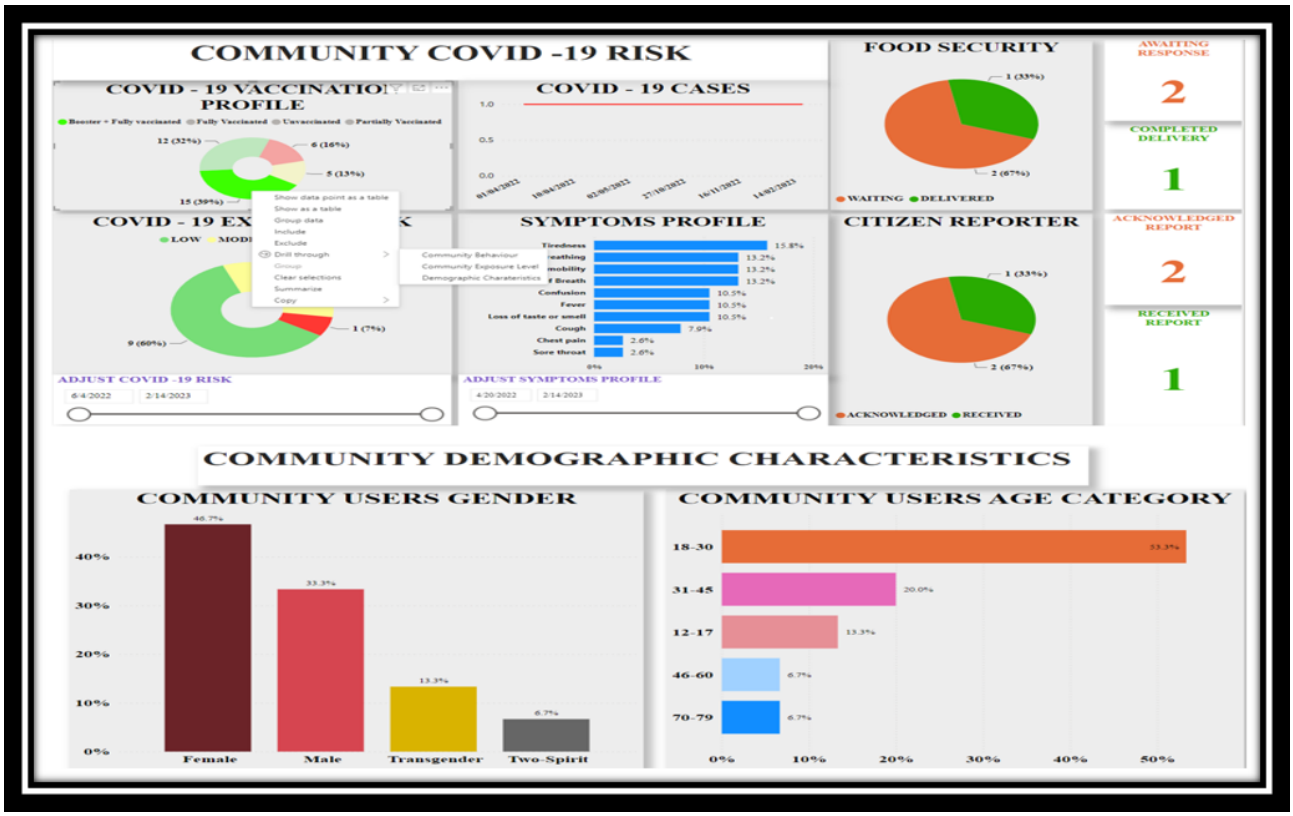
To overcome these challenges to timely evidence-based decision-making, citizen-driven big data, which is not only timely but also relevant to specific jurisdictions, can transform local jurisdictional decision-making [3,7,49]. The digital health dashboard for decision-making that we conceptualized and developed, at its core, addresses these challenges by providing municipal decision makers access to ethically obtained big data from their own citizens to enable evidence-based decision-making. The decision-making dashboard can not only provide time-stamped big data about a specific public health crisis (ie, COVID-19) but also enables the management of citizen-reported issues that can range from food insecurity to

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access to public services—a functionality that can ethically monitor the status of community health [50].

There is growing evidence that COVID-19–specific dashboards have played a significant role in pandemic management, particularly with regards to vaccine uptake to promote health equity [37]. The decision-making dashboard we developed provides detailed and anonymized aggregation symptoms, behaviors, and vaccine uptake status, which enabled decision makers to develop targeted public health communication in near real time to manage community risks. The data visualization of evolving and time-stamped statistics driven by real-time big data from the citizens of the community (Figure 9) provides a detailed picture of the changing nature of potential public health crises. For instance, it would be possible to understand the variation of prevalence and incidence of symptoms across specific time periods using dashboard functionality. This can be transformative not only for public policy but also for epidemiology in the digital age, where risks can be monitored in real time [51,52].

Figure 9. Data visualization depicting demographic characteristics along with community risks.



In enhancing the operational capacity of digital dashboards, particularly from the perspective of improving jurisdictional capacity, it is important to create delegated access to the dashboard. For instance, our digital dashboard has 7 different categories of access that enable the delegation of day-to-day tasks to ensure evidence-based decision-making across the jurisdictional operations. Moreover, the delegation of decision-making can even be outsourced to different operational sections within a municipal government or even outside the government. For instance, the food security feature could be delegated to a local food bank to ensure timely access to food. Perhaps more importantly, such delegated access enhances data security by providing permission-based restricted access to the dashboard.

In developing digital health dashboards for nonacademic users, particularly decision makers, it is important to prioritize intuitive visualization that does not require basic training in statistics or epidemiology. The data visualization within the dashboard is designed to be dynamic to make complex data sets easy to understand and explore by nonacademic audiences (ie, decision makers and public health practitioners), to extract information quickly, and enhance real-time rapid responses, particularly in the event of a public health crises. To ensure ease of uptake and use of the dashboard, we designed it to be interactive with the layering of data visualization, which allows decision makers to use intuitive tabs or dropdown menus to delve deeper to obtain the information they seek for evidence-based decision-making. For instance, if decision makers seek to obtain more information about community risk of COVID-19, such as distribution of vaccination status across age cohorts, or gender, they are able do this by selecting the available dashboard visualization options. Another key feature of the dashboard is depicting the temporality of data using data slicers, which allow decision makers to streamline evidence by specific time periods. For instance, data for a specific category of information (eg, COVID-19 vaccination) can be displayed over a specific time period, and compared with another category of information (eg, community symptoms) to understand how community behaviors correlate with general health of the community.

In terms of evidence-based decision-making in a world where there are new strains of COVID-19 as well as other evolving epidemics [53], the scalability and adaptability of the dashboard

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infrastructure are key to the sustainability of this innovation. Although this digital health dashboard was designed in response to the COVID-19 pandemic, this platform can be easily scaled up and adapted to monitor other epidemics and pandemics by using the developed digital infrastructure. The scalability is not limited to other epidemics or pandemics, but also across different levels of jurisdictions to ensure ethical monitoring, management, and mitigation of existing and emerging public health crises.

Digital Citizen Science for Health Equity

Although citizen science is primarily considered a research approach that is participatory in nature and can range from contribution and collaboration with citizens to cocreation of knowledge [3], it is rarely used in the development of digital health platforms. However, the application of citizen science to public health decision-making processes has gained considerable momentum recently [54-58]. This potential and promise of citizen science informed our methodology for the development of our digital health dashboard. In developing this dashboard, we drew from the principles of the SMART Framework [12] that integrates citizen science, community-based participatory research, and systems science as well as the approaches of the global digital citizen science policy to tackle pandemics [3].

The DEPtH Lab's Citizen Scientist Advisory Council enabled us to shape the dashboard to the needs of both the citizens and the decision makers [59]. The ability to balance both citizen and decision maker needs is critical to the success of digital health dashboards in providing a value perspective to both citizens at the frontend (PWA) and to the decision makers at the backend (digital health dashboard). The value perspective to the citizens is their ability to manage their household risks as well as understand community risks, which is inextricably linked to the functioning of the dashboard, which uses anonymized data derived from the PWA to understand and manage community risks along with the ability to respond to citizen needs in near real time.

Although the application of citizen science to public health is not new [60], this approach of citizen science for the development of digital health dashboards enables new opportunities to address public health crises from a systems perspective. For instance, the development of features to address food security and access to public services was based on the need identified by citizens, an approach that integrates health, food, and social service systems. The development of digital health dashboards using citizen science can potentially improve uptake from citizens as well as enhance scalability and adaptability across jurisdictions, that is, dashboards that are developed to address needs identified by citizens, an approach that will in turn meet decision maker goals in addressing citizen needs [59]. Thus, digital dashboards developed using citizen science can potentially transform public policy in multiple jurisdictions [61]. However, the biggest impact of these dashboards will be in promoting health equity by prioritizing and addressing the needs of citizens in near real time by developing equitable evidence-based policies using big data generated by the citizens themselves [12].

Rapid Responses in Real Time

The real-time notifications feature of the digital health dashboard enables decision makers to engage with their community members effectively and directly to not only inform them about existing and emerging community risks but also to provide evidence-based public health communication. The big data received by the dashboard can be updated at intervals of 5 to 30 minutes to provide decision makers with recent and accurate community health information that can be used for rapid responses. From a public health management perspective, for instance, decision makers can inform community members of evidence of an increase in certain symptoms so that community members are aware of the changing dynamics of the health risks in their community.

However, the digital infrastructure of the dashboard can be repurposed based on the needs of jurisdictions, decision makers, or their citizens. Digital health dashboards can be paradigm changing in the age of climate emergency [62], where disaster management is directly linked with public health. For instance, currently, the digital dashboard is set up to send urgent alerts both with PWA and text alerts to inform citizens of all emergencies. This direct and rapid communication is critical for managing evolving risks that can range from pandemics and floods to forest fires and earthquakes [63,64].

Digital health dashboards can also be used to provide evidence-based public health information as well as policy and program information on a continuous basis. This feature can play an important role in minimizing misinformation and disinformation that is pervasive in this digital age [65]. The misinformation and disinformation related to public health [65], particularly in terms of pandemics, where false narratives about the disease and vaccines can cause considerable public health risks [66], can be minimized using digital health dashboards. The validity of the information can be cited or sourced using trusted external agencies such as the World Health Organization [67]. Nevertheless, it is difficult to address citizen mistrust in institutions, and the digital dashboards that are built using citizen science [3], and that operate using anonymized citizen data to generate evidence, can make incremental changes in citizen perception. Finally, the dashboard also provides a direct, bidirectional, and anonymized engagement with citizens that the citizens can initiate using the "Q & A" feature, which further enhances real-time engagement to build trust.

Social Innovation: Decentralization of Technology and Data Sovereignty and Security

Digital health dashboards for decision-making that are developed for jurisdictions, at their very core, are operationalizing decentralizing of technology and democratization of data using digital citizen science [3,10]. This approach in essence is social innovation that ethically leverages the power of digital technology for decentralization and democratization to enable data sovereignty of individuals and jurisdictions. The decentralization is two-fold: (1) the development of a PWA that takes the platform ecosystem away from the monopolization of big technology launch platforms, that is, Google Play Store and Apple Store, and (2) the dashboard is set up to decentralize access to information, hence enhancing self-determination of

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individual jurisdictions. This decentralizing paves the way for the democratization of data, which are owned by citizens at the individual level and, by the jurisdictions, at the aggregated level [68].

This approach facilitates the data sovereignty of both citizens and jurisdictions, which is another important byproduct of the decentralization of technology. The decentralization of technology, democratization of data, and data sovereignty at both individual and jurisdictional levels provide the foundation for robust data security protocols. The design, implementation, and optimal functioning of digital health dashboards are dependent upon data privacy, and security. Apart from the standard measures of user authentication at both frontend (PWA) and backend (digital health dashboard) using multifactor authentication, data security protocols are enabled for both data at rest and data in transit in multiple layers. For data at rest, the first layer of security ensures restricted access to AWS account through identity and access management roles with multifactor authentication.

The second layer ensures that all data at rest are server encrypted using keys generated by AWS Key Management Service. The third layer ensures that all user database passwords are hashed and stored using Secure Hash Algorithm (SHA)-256 and SHA-512. For data in transit, to prevent distributed denial-of-service attacks, we use the Cloudflare-distributed denial-of-service mitigation service to ensure masking of website internet protocol address [69,70]. A distributed denial-of-service attack is a deliberate attempt to stymie a server, service, or network's regular activity by saturating the target or its surrounding infrastructure with a deluge of internet traffic. To further ensure privacy and security of data in transit, Cloudflare server is used for key exchange and establishing the identity of a server by providing forward secrecy, and Advanced Encryption Server 128- Galois counter mode is used to encrypt the Hypertext Transfer Protocol Secure request. All responses are encrypted in the Transport Layered Security connection data and personally identifiable data are stored within user or citizen devices.

Strengths and Limitations

A major strength of jurisdictional-specific digital health dashboards for decision-making is their potential to invert innovation [71]. Inverting innovation is defined as innovation that addresses a critical societal problem by satisfying 3 key criteria: transforming weaknesses into strengths, prioritizing citizen needs over corporate profits, and providing a pathway for rapid scale-up. Our digital health dashboard can respond rapidly to public health crises, by prioritizing both citizen and decision maker needs, and the digital infrastructure can be scaled-up based on evolving needs.

This inverting innovation potential of the digital health dashboard is driven by the digital citizen science approach [3], which is another major strength that ensures that the development process takes into consideration citizen needs. This focus on citizen needs also influenced our decision to prioritize decentralization of technology, democratization of data, and data sovereignty at both individual and jurisdictional levels—all aspects, which are significant strengths of the digital health dashboards. Finally, the primary purpose of development of jurisdictional-specific digital health dashboards is rapid responses using ethically obtained big data to monitor, mitigate, and manage population health crises, which is the most significant strength.

Even though rigorous data protection and security processes are layered into the dashboard development, risks to data security always exist, which need to be assessed on a consistent basis and addressed. Redundancies built into AWS databases allow us to protect the dashboard from ransomware attacks [72], and encryption and anonymization of data secure data privacy. Nevertheless, data privacy protocols need to be addressed on an ongoing basis to ensure that the dashboards comply with laws and regulations that govern jurisdictions [73]. Finally, citizen-driven digital health dashboards are limited by the uptake from citizens within jurisdictions, and the uptake is in turn influenced by internet equity [3] as well as digital divides within and across jurisdictions [74]. Although there is growing evidence of the potential of digital health dashboards to transform health care systems [15], the digital health dashboard that we developed needs to be tested in real-world settings. While the strengths and limitations of this study are specific to the development methodology and approaches, digital health dashboards powered by citizen-driven big data need to be tested in real-world settings to generate empirical evidence that can confirm not only the validity and veracity of citizen-driven big data but also the compliance of citizens and decision makers in using such dashboards for rapid decision-making.

Conclusions

Digital health dashboards for decision-making can transform public health policy by prioritizing the needs of citizens as well as decision makers to enable rapid responses to public health crises. Digital health dashboards also provide decision makers the ability to directly communicate with community members to mitigate and manage emerging population health risks, a paradigm-changing approach to tackle future epidemics and pandemics, that is, inverting innovation by prioritizing community needs with digital technology. Finally, digital health dashboards that are built by using digital citizen science approaches can catalyze systems integration and pave the pathway for rapid scalability to ensure digital health for equity.

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Data Availability

The data generated by the progressive web application that are visualized in the digital health dashboard can be shared upon request.

Conflicts of Interest

None declared.

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Abbreviations

AWS: Amazon Web Services
DEPtH Lab: Digital Epidemiology and Population Health Laboratory
PHP: hypertext preprocessor
PWA: progressive web application
SHA: Secure Hash Algorithm

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Protocol

Patient and Public Acceptance of Digital Technologies in Health Care: Protocol for a Discrete Choice Experiment

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Abstract

Background: Strokes pose a particular challenge to the health care system. Although stroke-related mortality has declined in recent decades, the absolute number of new strokes (incidence), stroke deaths, and survivors of stroke has increased. With the increasing need of neurorehabilitation and the decreasing number of professionals, innovations are needed to ensure adequate care. Digital technologies are increasingly used to meet patients' unfilled needs during their patient journey. Patients must adhere to unfamiliar digital technologies to engage in health interventions. Therefore, the acceptance of the benefits and burdens of digital technologies in health interventions is a key factor in implementing these innovations.

Objective: This study aims to describe the development of a discrete choice experiment (DCE) to weigh criteria that impact patient and public acceptance. Secondary study objectives are a benefit-burden assessment (estimation of the maximum acceptable burden of technical features and therapy-related characteristics for the patient or individual, eg, no human contact), overall comparison (assessment of the relative importance of attributes for comparing digital technologies), and adherence (identification of key attributes that influence patient adherence). The exploratory objectives include heterogeneity assessment and subgroup analysis. The methodological aims are to investigate the use of DCE.

Methods: To obtain information on the criteria impacting acceptance, a DCE will be conducted including 7 attributes based on formative qualitative research. Patients with stroke (experimental group) and the general population (control group) are surveyed. The final instrument includes 6 best-best choice tasks in partial design. The experimental design is a fractional-factorial efficient Bayesian design (D-error). A conditional logit regression model and mixed logistic regression models will be used for analysis. To consider the heterogeneity of subgroups, a latent class analysis and an analysis of heteroscedasticity will be performed.

Results: The literature review, qualitative preliminary study, survey development, and pretesting were completed. Data collection and analysis will be completed in the last quarter of 2023.

Conclusions: Our results will inform decision makers about patients' and publics' acceptance of digital technologies used in innovative interventions. The patient preference information will improve decisions regarding the development, adoption, and pricing of innovative interventions. The behavioral changes in the choice of digital intervention alternatives are observable and can therefore be statistically analyzed. They can be translated into preferences, which define the value. This study will investigate the influences on the acceptance of digital interventions and thus support decisions and future research.

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KEYWORDS

health preference research; stated preference survey; discrete choice experiment; study protocol; digital transformation; digital technologies; digital interventions; health care; rehabilitation; stroke; mobile phone

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Introduction

Background

Strokes pose a particular challenge to the health care system. Although stroke-related mortality has declined in recent decades, the absolute number of new strokes (incidence), stroke deaths, and survivors of stroke has increased [1]. Approximately 40% of patients with stroke present with persistent cognitive, perceptual, and participative disabilities [2,3]. Stroke is the second leading cause of acquired disability [4]. Neurorehabilitation reduces disability and improves functional outcomes [5]. Stroke-related limitations are treated in neurorehabilitation. Most recovery of functions is achieved in the subacute phase (3-6 months after the stroke event) [6]. Neurorehabilitation is a combination of various disciplines [7]. Because of the need for a comprehensive therapy approach, strokes are one of the most cost-intensive diseases in the German health care system, with current treatment costs of approximately €43,000 (US $48,040.40) per patient [8].

Objectives

With the increasing need of neurorehabilitation and the decreasing number of professionals, innovations are needed to ensure adequate care [9]. Digital transformation has opened avenues for improving services, products, and interventions through the increased use of digital technologies [10,11]. In the project *evidence-based robotic assistance in neurorehabilitation* (E-BRAiN), a robot was developed to support daily therapy practice [12]. Researchers investigated the use of the humanoid robot "Pepper" by SoftBank Robotics owing to interaction [13], motivation, software and hardware capabilities, and acceptance. To decide on implementing innovative therapies, decision makers should consider the trade-offs that patients are willing to accept [14]. Discrete choice experiments (DCEs) are a way to identify trade-offs by analyzing preferences [15]. The acceptance of new therapies is a key success factor and is determined by the fulfillment of needs [16-18]. When acceptance information is considered in decision-making, the utility of care decisions can be maximized in the short term [19,20], can strengthen patient orientation and adherence in the intermediate term, and can improve clinical effects in the long term. Financially, the health care system can benefit from faster and more efficient therapeutic outcomes [21,22].

Methods

Ethics Approval

The preference survey instruments, informed consent form, and study design were reviewed and approved by the ethics committee of Hochschule Neubrandenburg (HSNB/177/21). The study considers the Declaration of Helsinki, the Deutsches Bundesdatenschutzgesetz (the German Data Protection Act), the European privacy policy, and Guideline on Good Clinical Practice (CPM/ICH/135/95) regarding the obligation to report serious adverse events.

Informed Consent, Participation, and Dissemination

Participant confidentiality was ensured by pseudonymization of the qualitative interview recordings and will be ensured by anonymizing the data from the quantitative survey (DCE). All participants have provided informed consent in the completed qualitative interviews. Informed consent is also obtained in the quantitative survey. Participants have the right to withdraw from the study at any time and without giving reasons and to request the deletion of the collected data at any time during the survey. All participants will be informed on the opening page of the web-based questionnaire that participation is voluntary. All identifiable details will be removed during future dissemination of findings and in presentations and publications. Researchers' contact information is provided on the last page in case the participants have questions. The participants can contact the researchers directly by phone or via a contact email address. The results of this study will be presented at national and international conferences and published in peer-reviewed journals.

Research Questions and Study Aim

This ongoing study will address the following question: Which criteria of digital technologies impact patient and public acceptance? The aim is to investigate patient and public preferences to generate information on acceptance and analyze the value of digital interventions. Preference evidence is a series of observable human behaviors that can be analyzed by the choices individuals make between alternative health states, health services, or health interventions. Choices define the value of attributes and alternatives in health care.

Acceptance is a requirement for active patient engagement and thus for efficiency (the greatest possible result with the least possible effort) and effectiveness (ability of the intervention to positively improve patients' state of health in a targeted manner). To obtain information on acceptance, it is necessary to understand the trade-offs that patients make by weighing the advantages and disadvantages of therapy options using digital technologies. We also ask whether patients would accept a humanoid robot in neurorehabilitation. Our primary objective is to weight the criteria that impact patient and public acceptance. Secondary objectives include (1) a benefit-burden assessment (estimation of the maximum acceptable burden of technical features and therapy-related characteristics for the patient or individual, eg, no human contact), (2) overall comparison (assessment of the relative importance of attributes for comparing digital technologies), and (3) adherence (identification of key attributes that influence patient adherence). Our exploratory objectives include (1) heterogeneity assessment (how preferences differed based on participant characteristics) and (2) subgroup analysis (to explore and explain heterogeneity based on the correlation between therapy preferences and participants' sociodemographic information, experience-based treatment history, and attitudes). Our methodological aims are to investigate the use of DCE and the impact on data quality, preferences, and choice consistency.

The following assumptions and hypotheses will be examined:

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1. Patients engage in a health care process to meet their needs. Health-related needs include therapy outcomes. Therapy outcomes can be measured by goal achievement. Therapy outcomes influence the choice of intervention.
   - H1: The higher the expected success rate, the higher the probability of choosing an alternative.
   - H0: The success rate of an intervention has no influence on the probability of choosing an alternative.
2. Needs involve technical aspects of digital technologies. Undesirable features will have a negative impact on the decisions.
   - H1: The more burdensome or worse a technical aspect is rated, the lower the probability of choosing an alternative.
   - H0: The rating of a technical aspect has no influence on the probability of choosing an alternative.
3. The complete absence of human contact has a negative effect on the decision.
   - H1: The fewer the opportunities for human contact, the lower the probability of choosing an alternative.
   - H0: The opportunity for human contact has no influence on the probability of choosing an alternative.
4. Digital technologies should have certain characteristics according to the goals of a digital transformation (eg, flexibility, adaptability, participation, and empowerment). Characteristics that do not condition flexibility, adaptability, participation, or empowerment negatively impact patients' therapy decisions.
   - H1: The fewer the goals of the digital transformation that can be achieved by the digital technology, the lower the probability of choosing an alternative.
   - H0: Flexibility, adaptability, participation, and empowerment have no influence on the probability of choosing an alternative.
5. Interventions should be individualized for patients in a patient-centered health care system. Patients' preferences differ with respect to their characteristics (sociodemographic characteristics, clinical and digital experiences, attitudes, expectations, norms, behaviors, and abilities).
   - H1: The less patient centered an intervention is, the lower the probability of choosing an alternative.
   - H0: The characteristics of different patients have no influence on the probability of choosing an alternative.

Target Population

We include two study populations: (1) an experimental group (patients with stroke) and (2) a control group (the general population). Only individuals diagnosed with a stroke will be included in the experimental group. For both groups, only individuals aged ≥18 years, who reside in Germany, and who can read and understand German will be included. Limitations in recruitment were expected because of the COVID-19 pandemic at the beginning of the study and during the development of the experiment. Therefore, we decided to include a control group.

Overall Project Design

Both qualitative and quantitative methods are used in this health preference research (HPR) study. A completed qualitative prestudy was used to identify which decision criteria patients consider when choosing innovative therapy options using digital technologies. Furthermore, the impact of these attributes will be determined in a quantitative survey using a DCE. DCE is a stated preference method for economic evaluation [23,24]. This DCE will be used to analyze how patients define the "value" of a digital technology. The analysis is performed using repeated choices between hypothetical therapy alternatives with different attribute levels [25]. The choices can identify which attributes and levels are preferred. Patient benefit derives from preferences, and thus, the benefit can also be defined as value [26]. DCE is a preference elicitation method [27-29]. The use of such choice experiments is also presentive in medicine [30,31]. There are many guidelines and recommendations for the DCE [32,33]. The increasing popularity of DCE reinforces the intention in this study. This paper describes the protocol of the DCE to investigate patient and public acceptance of digital technologies in health care. This paper also describes the methodology used in our ongoing work.

Relevance of the DCE

A targeted literature research on acceptance models was conducted to analyze acceptance dimensions and criteria that impact individual's acceptance. Criteria from different perspectives, such as those of the patients, system, and provider, were analyzed to investigate the concept of acceptance with respect to the value of digital interventions. Acceptance refers to the willingness of individuals to engage in a health intervention or health service [34]. Technology acceptance models provide information on variables that influence acceptance, such as perceived usefulness, perceived ease of use, subjective norms, or user experience [35-37]. Extensions of the models explain the interrelationships between the beneficial influencing factors and the burdensome influencing factors as a balancing process [38]. However, the models are limited in evidence regarding specific attributes that represent a benefit or a cost or burden to individuals or, specifically, patients. No information is provided on how impactful individual aspects of digital information are. HPR studies were conducted to generate evidence regarding the weighting of attributes. Thus, the presented DCE was developed.

The aspects of digital technologies (eg, data processing) have already been examined in various studies. There are studies that focus on digital apps on mobile devices [39,40]. Among these studies, attention is partly focused on data processing only [41,42]. Other studies examine factors of communication (eg, information giving, information transfer, and contact) [41-43]. Most of the studies do not include health-related goal variables [39,44]. Thus, there is a gap in holistic evidence on preference research on digital interventions. This study aims to generate evidence for all possible digital technologies (not only digital apps).

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Development of Attributes and Levels

Different digital technologies have been investigated in different studies in the context of therapies and were therefore considered in the prestudy (robots, voice assistants, digital health apps, digital health devices, etc). As digital technologies have an unlimited set of attributes, limitations arise from the fact that decision makers cannot consider all possible attributes in their evaluation [18]. In a DCE, alternatives are described by decision-relevant criteria that are identified from the set of possible attributes [18].

A targeted literature search was conducted to identify the characteristics of health-related interventions in the context of the digital transformation associated with the use of digital technologies. First, digital transformation in health care was considered. Digital transformation became essential due to the rapidly changing and increasing needs and expectations in health care [45-47]. Digital technologies are innovations to achieve certain goals of digital transformation: flexibility of place and time, flexibility of the range of care, expansion of access for patients considering gains and pains, improvement of health literacy, participation and personal responsibility of patients, and improvement of information structures [11,48]. Certain characteristics (attributes) of digital technologies are necessary to achieve these goals. In total, 17 attributes were identified in the literature: communication, emergency communication, contact with professionals, distance to technology, emotions, speech, participation, recognition, feedback, data security, pick-up and drop-off function, entertainment, usefulness, place, location dependency, duration, and frequency.

Formative qualitative research is foundational to the development process of HPR studies [49]. Therefore, we conducted semistructured pilot interviews with patients with stroke (n=14) and experts in neurorehabilitation (n=5) to identify and cluster the decision-relevant criteria from the subset of 17 attributes. Patients were asked to describe their physical and daily living limitations owing to the diagnosis and their experiences with neurorehabilitation. The patients were also asked about their attitude, opinions, and expectations regarding digital technologies. After the humanoid assistance robot "Pepper" was presented, the participants were asked about their attitude toward the robot. Attributes defined from the literature were presented with descriptions on cards. The patients were asked to rank the attributes according to their relevance. Furthermore, the patients described what they thought a future therapy might look like by using a different card of attributes. An interview guide was used for this process. We used semistructured interviews, which allow an open discussion style and an interview to be individualized, allow spontaneous in-depth discussion of interesting statements, and allow a return to relevant key questions [50]. Experts estimated the patients' point of view regarding the questions asked according to their experience. A list of seven decision-relevant criteria was developed: (1) explanation and presentation of exercises, (2) information from digital technologies, (3) contact with professionals, (4) patients' choice in the therapy process, (5) data processing, (6) copayment per month, and (7) therapy success within 6 months. Thus, the list included 5 attributes that are technical aspects (attributes 1-5). In addition, copayment per month and therapy success within 6 months complete the decision context. Therapy success refers to an individual's goal attainment. Goal attainment is determined by the improvement in body function, which in turn leads to a resumption of activities of daily living. The full list was concretized through discussion rounds, such as focus groups and workshops with experts in health care. The final list was transformed into a decision model.

Descriptive Framework

Preference evidence can be identified by observing human behaviors using elicitation tasks. In a preference elicitation task, participants evaluate assigned alternatives or objects according to their preferences. In this study, we determined that the preference elicitation task would lead to the goal of determining a patient's willingness to accept the trade-offs between the characteristics of therapy using digital technologies. The descriptive framework was created to contain all decision-relevant attributes, levels, and descriptions of the decision context that will be used to communicate the content of the elicitation tasks (Table 1).

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Table 1. Descriptive framework.

Attributes	Description	Level 1	Level 2	Level 3	Level 4	Level 5
Explanation and presentation of therapy exercises	Patients receive information, instructions, and assistance on how to perform the exercises, with an explanation and presentation of therapy exercises.	Sounds and speech	Descriptive texts	Images	Videos	Spatial movement
Information in therapy	Patients receive information from the digital support system in digital therapies, but there are also digital therapies where patients do not get any information.	No information	Therapy and rehabilitation process	Diagnosed disease	Patient's current health status	Change in health status owing to therapy
Contact with health care professionals	Patients have contact with health care professionals in a digital therapy, but there are also digital therapies in which patients have no contact with professionals.	No contact	Contact is indirect (messages)	Contact is direct (telephone or video)	—[a]	—
Patients' choice in the therapy process	Patients have certain choices in a digital therapy. Therefore, patients have an influence on the design of therapy processes, but there are also therapies where patients have no influence.	No influence	Selection of therapy exercise with a certain degree of severity	Pace of therapy exercise	Time of therapy (frequency, duration, and start)	Place of therapy (eg, home, clinic, or practice)
Data processing	There is data processing in digital therapies. Data about patients are collected and forwarded, but there are also digital therapies where no data are processed.	No data processing	Processing of data about the person	Processing of data about the diagnosis	Processing of data about the progress of the therapy	—
Copayment per month	Patients in digital therapies contribute to the cost of the therapy with a copayment per month. There are also digital therapies where patients have no copayment.	€80 per month	€60 per month	€40 per month	€20 per month	No copayment
Therapy success within 6 months	Patients have success in a digital therapy by achieving their therapy goals. Therapy goals are set at the beginning of a therapy, but not all patients achieve their goals within 6 months.	60 out of 100 patients	70 out of 100 patients	80 out of 100 patients	90 out of 100 patients	100 out of 100 patients

[a]The number of levels of each attribute is not necessarily equal, so the number varies between 3 and 5 levels. Therefore, for the attributes contact with health care professionals, no data are available for levels 4 and 5, and for the attribute data processing, no data are available for level 5. Furthermore, the respondents in the study were recruited in Germany. Accordingly, the data on the copayment per month were given in euros (€) and not in US $ (€0.92=US $1). For visual representations of each level, see Multimedia Appendix 1.

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Choice Context

In choice experiments, participants are asked to assume that their therapy decision is made in the context of a specific or their current health condition. Our study sample included both therapy-experienced and therapy-inexperienced participants. Therefore, the participants are asked to assume a health condition that requires rehabilitative therapy.

Elicitation Tasks

The challenge in a DCE is to dissolve the response uncertainty and to trace the preference information back to the individual attributes through repeated choice tasks, with participants "forced" to make a decision between digital therapies. For the professional group, there was no choice available within the choice task. The underlying choice task is a ranking task, which follows a fixed procedure. The choice starts with the selection of the best alternative among 3 choices. The choice is iterated with the remaining 2 so that a complete ranking is achieved. Thus, the DCE uses a best-best choice format [51].

Participants' willingness to choose the digital therapy was determined by the following follow-up question: "Would you really choose the previously selected digital therapy in real life to improve your health?" Recently, the dual response "none" has been established as a variant in choice experiments [52,53]. A dual response of "none" asks for 2 responses for each task: one choice between the available product alternatives and one between the "none" concept and the previous alternatives. Essentially, it is a choice between the most preferred alternative and none. If participants would actually buy or take the alternative, they would not prefer none, but if they would not buy or take the alternative, they would prefer none to the given alternative [54]. The dual response "none" design takes more time to answer and is an increase in analysis effort owing to a complex design. However, more information is generated, which makes the design more efficient and powerful. Estimation errors are reduced, and the underlying model estimate is not significantly changed [52]. This design provides a higher resolution for individual-level preferences. As there is less "missing" information when participants select "none" as their preferred alternative, more information is available for individual-level modeling [54]. The final survey instrument comprised 6 choice tasks. The number of choice tasks was determined by the underlying experimental design, possible number of participants, and information received per task. No names, brands, or companies were named in the presentation of the choice tasks; therefore, the tasks were unlabeled. In addition, unlabeled alternatives were preferred because the study objectives were to estimate the marginal rates of substitution and value equivalents for therapy attributes [18].

Elicitation Format

Participants will be familiarized with the attributes and expressions through descriptions and explanations before the first task. In addition, participants will see a tutorial and exercises to answer the choice tasks. Participants will answer a choice task with a clearly dominant alternative (copayment=none; treatment success=100%) so that an understanding of how to answer the DCE is tested.

Experimental Design

Proper design and implementation of the DCE requires the consideration of the choice context, composition of choice sets, and framing of choice questions and instructions [55]. The results of the preliminary study indicated lower attention and concentration abilities in the experimental group. This finding, along with the evaluation of participants, led to the decision to use a partial design (choice tasks include 4 of the 7 attributes) [18,56]. Experimental design software was used in this study (Sawtooth Software Inc; ChoiceMetrics).

The underlying experimental design is a fractional-factorial efficient Bayesian design (D-error) to maximize the ability to identify participant preferences and variability in preferences across participants [56].

The experimental design was based on the following assumptions: minimal overlap, level balance and orthogonality. *Minimal overlap* means that each level is shown as few times as possible in a task. If the number of levels of an attribute is equal to the number of concepts in a task, each level is shown exactly once. Assumptions also were *level balance* which means that each level of an attribute is shown approximately the same number of times. *Orthogonality* means that levels are chosen independent of other levels so that the benefit of each level can be measured independent of all other effects).

Owing to the complexity of the experimental design in terms of the size of the decision model (7 attributes and 3-5 levels), the experiment was blocked. Combinations of alternatives are drawn from the total selection in 20 blocks in such a way that each level is combined as often and as evenly as possible. The study will analyze both the main and interaction effects. By combining all possible levels with each other (2-way frequency), sufficient information is generated to be able to measure the interaction effects. The allocation of the blockers is randomized. When a survey is stopped and choice tasks are not completed, they are made available to other participants so that all choice tasks are provided.

Survey Instrument Design

Designing an effective survey instrument requires numerous connected decisions that are built on the decision context, attribute selection, and experimental design. The DCE requires a survey instrument that (1) explains to participants the various aspects of digital technologies that may differ across therapy options and (2) asks participants to indicate their preference for therapy options as aspects change. The final instrument is web based and self-completed by the participants.

The information presented to participants was developed by preparing descriptions for each attribute and level. Patients with stroke often experience cognitive impairment. Therefore, special attention must be paid to the layout of the survey. The design of the survey and the potential layout of the choice task should include the appropriate use of text and icons. An appropriate and well-designed layout can minimize the cognitive efforts required to compare alternatives and evaluate trade-offs. Because of the visual perceptual deficits in patients with stroke, icons should have good color contrast, clearly delineated lines, and a monochromatic design. We assessed the clarity and

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completeness of the DCE survey instrument and tested different choice formats (selection from 2 or 3 alternatives, best vs best-worst selection, and full vs partial design).

We limited the time required to complete the survey to a maximum of 30 minutes to minimize dropouts and to reduce data quality toward the end of the survey. First, we administered the quantitative survey with the final survey design in the control group. A pilot test was conducted, and the data collection was stopped after 150 completed questionnaires in the control group. Preference data were tested using a conditional logistic regression model to check for appearance validity, assumed signs and coefficients, and estimation problems.

We planned 3 sections for the web-based questionnaire: a study description and introduction to the attributes, the DCE, and the question section on sociodemographic and therapy and technology experience. The content of the survey will be clarified through an introductory description of the DCE survey technique at the beginning of the questionnaire. Here, participants will learn that they will be presented with hypothetical therapy alternatives in various combinations and that each alternative is described by 7 attributes. The questionnaire is expanded with questions on sociodemographic factors (including for inclusion and exclusion), sociocultural background, therapy-related and technology-related experiences, and health and quality-of-life assessment [57]. The questionnaire also includes a questionnaire assessment and questions on digital health literacy [58]. Different questions are designed to analyze the cognitive and perceptual limitations of the experimental group (Textbox 1). Metadata (or paradata) will provide information about the content of the health preference data. These data include the time taken to complete the survey and each question as well as information on dropout rates. The coding software used was Survey Engine GmbH. Textbox 1 presents the structure and content of the survey questionnaire.

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Textbox 1. Structure and content of the survey questionnaire.

Introduction to the survey: data protection and technical instructions

- Information on data protection regulations
- Information on responding via tablet and computer or laptop (exclusion: smartphone or iPhone)
- Information sheet for participants (PDF download)
- Declaration of consent for participants (as PDF download)
- Obtaining consent
- Instructions on how to respond to the survey, introduction to question formats, and options for saving an intermediate response status

Testing of cognitive abilities and perception

- A total of 5 picture and text questions (picture recognition, object naming or assignment, temporal or spatial orientation, and memory)
- Identification of cognitive and perceptual limitations with possible influence on the questionnaire response
- Basis: standardized assessments for identification of aphasia, apraxia, visual or perceptual deficits, and cognitive deficits

Introduction to the survey: background of the digital stroke rehabilitation

- Information about the diagnosis of stroke (incidence and shortage of specialists)
- Information about digital technologies (ie, digital support systems) in therapies
- Introduction of terms (digital support systems and digital therapies)
- Information about patient and public preferences, survey content (preference information, experiences, expectations, attitudes, and sociodemographic data), and survey process and structure

Inclusion and representativeness of the study population

- Inclusion: age <17 years, German language skills=intermediate to very good, and, only for experimental group, diagnosis of stroke=is present
- Representativeness in control group based on quota in age, sex, education, and state (for state, not present as quota in sampling)

Diagnosis-related questions

- Objective: to separate the study populations into patients with stroke and the general population
- Diagnosis of stroke; time of diagnosis; consequences of stroke related to physical functions, daily life, and support needs; and current treatment needs

Introduction to the preference survey

- Description of the scenario: rehabilitative therapy using digital technology
- Description and explanation of digital therapies (wording: digital support systems)
- General definition and delimitation of the terms attributes and attribute level
- Description and illustration of all 7 attributes and attribute expressions
- Example or tutorial for answering a choice set

Preference elicitation or discrete choice experiment

- Dominance test: selection from a choice set with an openly dominant alternative (no copayment and 100% treatment success) to test the understanding of choice tasks and quality (validity)
- 6 Choice tasks: choice best, choice second best, and dual response

Additional questions

- Evaluation of therapy goals as activities in daily life via a 5-point Likert scale
- Assessment of digital transformation goals in terms of flexibility of place, time, performance, and adaptability via ranking
- Sociodemographic questions (expanded) on marital status, household or residential situation, and occupational status
- Health status and quality of life
- Rehabilitative therapy experiences
- Experiences with and attitudes toward digital technologies for one's own health

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- Questionnaire assessment to evaluate the quality of the survey
- Questions on digital health literacy

Completion of the survey

- Acknowledgment
- Information on how to contact the study team and collaborators

Statistical Analyses

Discrete choice models differ from regular logistic regression because the data are grouped. These models consider the structure of the DCE data, with the same participant providing multiple results for a sequence of different election scenarios [59].

We analyzed the results using conditional logistic and mixed logistic models and performed a latent class analysis to identify heterogeneous preferences [60]. We used the conditional logistic model to calculate the coefficients whose signs indicated a preference direction. Positive coefficients indicated a positive influence of a trait expression, and negative coefficients indicated a negative influence. The larger the coefficient, the greater the influence on the choice decision. The distances between 2 property expressions indicated the magnitude of the influence. The assumption of normal distribution in the conditional logistic model limited the informative value of the calculated coefficients. We used mixed logistic models to analyze preference differences as a function of each individual by calculating SDs and SEs. We tested assumptions to determine whether the preferences of specific groups differed from each other in terms of characteristics, experiences, and cultural background. Latent class analysis was used to generate information on the heterogeneous groups. We used StataCorp LLC to conduct our statistical analyses.

For our analysis, the results from both groups were compared. We did not directly compare the coefficients because of scale effects [61]. The comparison was made by considering the influence of the covariate general population.

Study Sample

We include study participants depending on the target population, sample selection, and the qualitative or quantitative study part of the survey. The quantitative pilot interviews were conducted between March and September 2020. The qualitative pretest interviews were conducted between October and December 2021. The quantitative survey was started by pilot testing (n=150) in January 2022. After pilot testing, participants of the general population will be recruited via a panel provider and patients with stroke will be recruited via a panel provider, E-BRAiN clinical study and Stiftung Deutsche Schlaganfall-Hilfe, and from social networks. The study sample is based on a nonprobability ad hoc sample selection as a self-selection sample depending on availability and on a nonprobability ad hoc sample selection as a quota sample [62,63]. Regarding the full E-BRAiN project, recruitment and in-person participation of patients with stroke were planned within the clinical project. The DCE project was planned in relation to the clinical recruitment and was adjusted according to the pandemic-related constraints and financial resources. Therefore, panel recruitment was expanded to include patients with stroke in the DCE project.

Data Collection

Calculating the sample size for the choice experiments is complex [64]. The question format, complexity of the choice task, desired precision of the results, and need for subgroup analysis are criteria that could modify the sample size [29,65].

For a robust quantitative evaluation of the main effects of a DCE in a simple logistic regression model (eg, mixed logit regression model or conditional logistic model), we calculated the sample size using the following formula: $(n \times t \times a) / c \geq 1000$; $n = (1000 \times c) / t \times a$, where n=number of participants, t=number of choices (choice sets), a=number of choice alternatives per choice set, and c=number of levels (for main effects, c=number of levels of the attribute with the highest number of levels and for interaction effects, c=the largest product of the levels of the 2 attributes with the highest number of levels).

Given 6 choice tasks and 3 alternatives described by attributes with a maximum of 5 levels, a minimum number of 300 participants ($n = [1000 \times 5] / [6 \times 3]$) is needed to represent at least the main effects approximately 1000 times. This resulted in a target sample size of 300. When considering the interaction effects (c=15 in the formula), the resulting n is at least 1000 ($n = [1000 \times 15] / [6 \times 3]$). To adequately account for interaction effects, a sample size of at least 1000 is required to ensure sufficient representation. The final target sample size is approximately 1000 participants.

Data Quality

Our data quality criteria are as follows. First, we require data security. The web-based survey is developed and scripted by the research team. Quality assurances are also conducted. The quality tests follow a predefined test grid. Second, we ensure data integrity by conducting several quality assurance steps, including extensive end-to-end testing, data export and tabulation of test data before the live sample will be launched, validation of the experimental design scripts, and validation of the data analysis scripts. Third, our data require validity and reliability. The following indicators of validity and reliability are collected: completion of the entire web survey in a short period, selection of the predominant alternative in the fixed-choice question, selection of a different alternative in the repeat question, selection of “best” and “second-best” levels always based on a single attribute, straightlining (ie, always the

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same answer choice in each choice set), and additional questions to verify DCE data and class determination.

Results

The literature review, qualitative preliminary study, survey development, and pretesting were completed. Recruitment of the experimental group and the control group started in January 2022. Recruitment of the experimental group (patients with stroke) will be conducted in conjunction with the clinical trial of the collaborative project E-BRAiN. All patients in the clinical trial will be surveyed. Data collection and analysis will be completed in the last quarter of 2023.

Discussion

Principal Findings

Acceptance is a multidimensional construct. The requirements for digital technologies include various dimensions [66]. Digital technologies in postacute rehabilitative therapies are increasingly used for patients classified as cognitively, perceptually, and participatively impaired. [67]. These technologies are still largely unknown to users. Successful implementation depends on the acceptance of the patients [18]. In addition to expected clinical success, technical features also affect consumer acceptance.

This paper describes the development of a HPR study. Patient preference information will be provided by analyzing 7 attributes in a DCE. With respect to the mantra of HPR that "choice defines value," the study objective is to weight criteria that impact patient acceptance. Furthermore, a benefit-burden assessment, an overall comparison of different alternative digital interventions, interpretation of adherence, analysis of heterogeneity, and subgroup analysis are aimed at improving decision-making for innovative interventions, such as adopting new digital technologies such as artificial intelligence (AI). This study includes several aspects that further test the hypotheses related to needs, outcomes, technical aspects, human contact, goals of digital transformation, and personal information about patients.

To achieve the objectives, formative preliminary studies were conducted. A list of 17 attributes was tested. The final list of attributes represents the decision context of digital transformation in health care: explanation and presentation of therapy exercises, information in therapy, contact with health professionals, and data processing. To complete the decision context, copayment per month and therapy success within 6 months were added.

To develop the final survey instruments, attributes were described and visualizations for each level were added in a descriptive framework. The developed fractional-factorial efficient Bayesian (D-error) experimental design includes a best-best ranking task in a partial profile. A web-based questionnaire was developed by integrating additional questions on patients' characteristics, experiences, and cultural background. Pretest interviews and pilot testing have led to the holistic adaptation of the survey instrument in terms of descriptions, visualizations, and questions to enhance patient understanding as well as the testing of the experimental design. The analysis, with the help of a conditional logit model, proved the assignment of substantially results and unambiguous β coefficients to the attributes and levels, thereby demonstrating the effectiveness of the experimental design. The further study will use mixed logit models and heterogeneity analysis to evaluate the final study results.

This study demonstrates the importance of investigating patient acceptance and the technical aspects of digital technologies such as AI. Dai and Tayur [68] highlighted in their research that the uniqueness bias is a barrier to patient acceptance, as patients attribute more individuality to a human-guided therapy than to an AI-based solution. To solve this bias, a study of patient perceptions and preferences is recommended [68]. Furthermore, research on rhetoric to improve the adoption of digital technologies such as AI shows the importance of communicative strategies [69]. Another aspect that influences patient acceptance is data privacy and security and the associated risk [70].

To the best of our knowledge, this HPR study conducted a DCE. We attempt to develop a generic model that generates preference information to provide information on patient acceptance of digital technologies.

Limitations

Further investigation must consider the following limitations and challenges:

- Digital transformation in health care is characterized by a large number of attributes to achieve goals (eg, flexibility). The development of the underlying descriptive framework was difficult. Therefore, we consider the goal of digital transformation.
- The characteristics of the experimental group lead to different challenges. Patients with stroke often have limitations related to their cognition, perception, and movement (motor function). This leads, on the one hand, to recruitment challenges owing to lower participation possibilities and lower response rate and, on the other hand, to challenges in the design, layout, and formulation of the questionnaire. Furthermore, pandemic-related inaccessibility was expected.
- Limited financial resources limit the additional number of patients with stroke that can be enrolled via a panel.
- Owing to the recruitment challenges, we decided to include a control group (the general population). Because of the scale effects, the coefficients will not be compared directly. The comparison will be made by considering the influence of the covariate general population.
- Analysis of preference differences between the experimental and control groups will be limited because financial resources do not allow adequate number of patients with stroke to be available via a panel survey.

Another limitation relates to the interpretation of the concept of "value." The term "value" is a broad term used in different contexts. In general, "value" refers to the worth, importance, or usefulness assigned to something based on individual perceptions. However, "value" can be determined by a wide range of terms, such as personal beliefs, societal norms,

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economic considerations, and preferences. The economic perspective considers the exchangeable value of goods or services. In contrast, “value” can also compass moral, ethical, or philosophical principles that guide individuals’ behavior. Therefore, it is crucial to emphasize at this point that there is a potential limitation in this paper where the term “value” may be subject to misunderstanding. In this study, the concept of “value” is distinguished from “value judgments”. The term “value judgments” describes the context of ethical, moral, or philosophical aspects [71]. In the context of HPR, “value refers to the subjective assessment of the importance, desirability, or utility individuals assign to specific health-related outcomes or interventions.” It involves understanding and measuring the preferences of individuals when making decisions related to their health and health care. In contrast to judgments, preferences relate to individual choices that are based on subjective likes or dislikes. This is unclear as is. Do you mean “The guiding principle of HPR is encapsulated in the mantra “choice defines value.” This concept highlights the importance of gaining a deeper understanding of patients' preferences, enabling health care providers, regulators, and policy makers to better address the needs of patients? Please revise as applicable [72,73]. As preferences can be influenced by judgments, social determinants, environmental factors, or experiences, we included several questions in the final survey instrument that could be mapped to these influencing factors (eg, cultural background, experiences in therapy, experiences with digital health, and attitudes toward digitization). These questions can be consulted when analyzing the differences between patient groups.

Conclusions

This HPR study provides information on preferences to analyze the criteria that impact acceptance and the value of innovative interventions using digital technologies. Developers, health care providers, and policy makers often make difficult decisions about development, reimbursement, and the choice of the benefit-maximizing intervention for each patient (group). These decisions require information on the value of clinical and nonclinical criteria derived from patient preference information. As patients are the ones who ultimately experience the positive and negative outcomes of treatment, decisions related to health care intervention options should be patient centered and reflect patient values. This is where HPR comes in, providing information about patient values relevant to decision-making [16,17]. This study will inform decision makers about the factors impacting patient and public acceptance. Understanding acceptance will improve decisions and investigations of the development, adoption, and pricing of innovative digital interventions. Furthermore, the aim of reporting the development of this DCE is to represent the standards of DCE development, provide reproducibility to verify the results, ensure transparency and ethical considerations, and improve the efficiency of the research. This protocol offers a transparent, practical, and scientific approach for eliciting patient preferences.

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Data Availability

The data sets generated and analyzed during this study are available from the corresponding author upon reasonable request.

Authors' Contributions

AF was responsible for data curation. ACM obtained the funding. AF and ACM jointly conducted the research, methodology, and project administration. AF was responsible for software use. ACM was responsible for the supervision of the project. AF completed the visualization and the preparation of an original draft. ACM did the review and editing of the draft. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Visual representations of the levels of each attribute.
[DOCX File , 94 KB - resprot_v12i1e46056_app1.docx]

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Abbreviations

AI: artificial intelligence
DCE: discrete choice experiment
E-BRAiN: evidence-based robotic assistance in neurorehabilitation
HPR: health preference research

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Protocol

Validation of a Geriatric Bedside Swallowing Screen (GEBS): Protocol of a Prospective Cohort Study

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Abstract

Background: Demographic changes will raise the need for specialized care of older patients. Oropharyngeal dysphagia has recently been declared a geriatric syndrome reflecting its multifactorial background. Alongside multimorbidity, sarcopenia, frailty, and disability, swallowing disorders increase with advancing age, with prevalence rates reported to be as high as 44% in acute geriatric hospital settings and 80% in long-term care facilities. Hence, systematic screening of older patients to diagnose dysphagia and initiate treatment is of paramount importance to prevent bolus death, aspiration pneumonia, and malnutrition and improve quality of life. Several screening tools have been evaluated in emergency and stroke units. However, no published dysphagia screening tool has been validated in the hospitalized, older adult population using a gold standard in dysphagia diagnostics as a reference test. The validation of the proposed test is a first step.

Objective: The Geriatric Bedside Swallowing Screen (GEBS) study aims to validate a new screening tool developed specifically for older inpatients against an instrumental swallowing evaluation, the flexible endoscopic evaluation of swallowing (FEES), which is considered a gold standard. Primary outcomes to be evaluated are sensitivity and specificity for the GEBS in the detection of dysphagia in a mixed older adult population. The presence of dysphagia will be defined by an instrumental swallowing evaluation (FEES), analyzed by the standardized penetration-aspiration scale.

Methods: To validate the GEBS, a prospective cohort study will be carried out. Two institutions, an acute geriatric department and a long-term care facility, will aim to recruit a total of 100 patients aged ≥75 years. After giving their informed consent, patients will undergo the full screening protocol described in the GEBS as well as an evaluation of swallowing function using the FEES. Investigators will be blinded to the results of the respective other testing. The analysis of pseudonymized data sets will be done by a third investigator. Outcomes to be considered are sensitivity, specificity, diagnostic odds ratio, positive and negative likelihood quotient, and the reliability of the proposed dysphagia screening tool using the κ coefficient.

Results: Recruitment started in October 2022 and will end in April 2024. Data publication is planned for early 2025.

Conclusions: If proven to be a valid screening tool for the early detection of dysphagia, further studies including different older adult populations as well as studies to determine the impact of systematic dysphagia screening on parameters, such as rates of aspiration pneumonia or nutritional status, should be planned. Effective screening of dysphagia will lead to earlier detection of patients with impaired swallowing. Those who fail the screening will be referred to speech language pathology for further diagnosis, thus optimizing care while streamlining personnel resources.

Trial Registration: ISCRTN Registry ISRCTN11581931; https://www.isrctn.com/ISRCTN11581931

International Registered Report Identifier (IRRID): DERR1-10.2196/46252

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KEYWORDS

dysphagia; geriatrics; swallowing disorder; assessment; screening; cohort study; multimorbidity; hospital setting

Introduction

Background

Due to demographic changes, by 2100, about a third of the population in the European Union will be aged 65 years and older [1]. Medical professions will need to be specialized in the treatment of older patients. This includes the development of efficient diagnostic pathways to ensure optimal care while not overburdening health care systems. Thus, efficient prevention, early detection, and treatment are becoming more important. One important discipline in the care for older patients is *speech language pathology* (SLP), which contributes to the prevention, diagnosis, and treatment of hearing disorders; voice impairments; difficulties with language production; active communication; and swallowing disorders, also known as *dysphagia*.

Dysphagia has been declared a geriatric syndrome by the European Society for Swallowing Disorders, thus highlighting its importance for medical personnel working with older patients. Common causes for dysphagia are stroke, traumatic brain injury, neurodegenerative diseases, as well as surgeries—most commonly following cancer treatment of the mouth and neck. It is important to note that changes to the swallowing process due to aging, which is known as *presbyphagia*, are not considered pathological. If presbyphagia does not cause nutritional decline or the development of aspiration pneumonia, presbyphagia is considered healthy, older-age swallowing [2,3]. If the aging process, specifically the loss of muscle mass within the swallowing muscles, leads to functional deficits and disordered swallowing with pathological consequences without a known neurological or structural cause, it is defined as *sarcopenic dysphagia* [4]. To distinguish between presbyphagia and dysphagia, regardless of etiology, sound knowledge of a healthy, older-age swallowing process is necessary. The loss of muscle mass associated with normal aging, that is, *sarcopenia*, causes *dynapenia*, which is a loss of function and strength within the skeletal muscles [5]. Continual sarcopenia leading to functional decline contributes to the geriatric syndrome known as *frailty*, which is linked to a higher prevalence and worse prognosis for dysphagia [6]. Dysphagia of all different etiologies affects up to 40% of patients in acute hospital settings as well as up to 80% in long-term care facilities [7-9]. The prevalence of sarcopenic dysphagia in older patients admitted to acute hospitals has been determined to be around 30% [10]. As oropharyngeal dysphagia is closely associated with central nervous system diseases, the prevalence for dysphagia in patients with central nervous system diseases is higher as the diseases progress, with estimates of around 85% in older patients [9].

The diagnosis of dysphagia is typically a 2-step process with a clinical swallowing examination by an SLP, who might refer to an instrumental swallowing examination. There are 2 objective instrumental diagnostic tools. The *flexible endoscopic evaluation of swallowing* (FEES) consists of a protocol to evaluate different consistencies of bolus under visual observation of the pharynx and upper laryngeal structures through a transnasal endoscope [11]. The second possibility is a *videofluoroscopic swallowing study*, where a high-resolution x-ray of the mouth and throat produces a video of the whole swallowing process [12]. Since the FEES system is portable, it can be carried out in a bedside setting and does not require as much compliance as the videofluoroscopic swallowing study. The FEES is considered the gold standard in the dysphagia diagnostics of older patients [13].

Study Goal

As previously described, the identification of patients with impaired swallowing function is of high priority to prevent the occurrence of malnutrition and aspiration pneumonia, as well as bolus death. Considering the demographic changes, routine referral of all newly admitted older patients to an SLP examination will not be feasible. Screening for dysphagia risk has proven to significantly lower pneumonia rates in emergency and stroke units [14-17]. There are several validated screening tools for those populations, for example, the *Gugging Swallowing Screen* [18] or the *Toronto Bedside Swallowing Screening Test* [17], which have excellent sensitivity and specificity for their intended use. Older patients, however, are faced with the challenge of drastically increased time frames for the oral phase of swallowing. This would be a predicator for dysphagia in healthy, younger adults but does not have the same implication in older adults [19].

To search for a screening tool that is validated for an older adult population aged ≥75 years against a gold standard, a systematic review of published screening tools was carried out by the first author, which yielded no results [20]. Of the 40 screening tools that were found (as shown in Table 1), none could be included for further assessment, with the main exclusion criteria being a noninstrumental reference test and a studied population aged <75 years. Some of the studies proposed a new protocol of instrumental swallowing assessments or a clinical bedside swallowing evaluation by an SLP under the term “screening”; those studies were also excluded.

These findings have been replicated by a recent review by Estupiñán Artiles et al [21], as well as the *Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften* (Association of the Scientific Medical Societies in Germany) guidelines for geriatric assessment [22].

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Table 1. Review of published screening tools.

Exclusion criteria	Screening tools (n=40), n (%)
Reference test	1 (2.5)
Population	8 (20)
Reference test + population	26 (65)
Reference test + population + screening tool	2 (5)
Screening tool + population	3 (7.5)

In accordance with diagnostic study guidelines such as STARD (Standards for Reporting Diagnostic Accuracy) and QUADAS (Quality Assessment of Diagnostic Accuracy Studies), new tests should be validated against a robust reference test, usually the gold standard [23,24]. Following these outcomes, this study aims to fill the gap by validating a specific screening tool—the *Geriatric Bedside Swallowing Screen* (GEBS)—to detect dysphagia in a mixed older adult population aged ≥75 years. The aim is to validate the GEBS using the primary outcome measures of sensitivity and specificity concerning the detection of dysphagia when compared to an instrumental swallowing evaluation.

Methods

Test Construction

The starting point for the GEBS was a screening tool already in use at the Department of Geriatric Medicine, Christian Doppler University Hospital, in Salzburg, Austria. It has been demonstrated to be a convenient tool in clinical practice but has never been formally validated. Combined with the results of a thorough review of published evidence on possible reliable predictors for dysphagia, it was developed into a 3-step screening tool. In the first step, 6 risk factors are assessed by observation, patient reports, and chart review (Textbox 1).

Following the assessment of present risk factors and the assurance of patient vigilance, a water swallow test is administered. This consists of swallowing 10 teaspoons of clear water with breaks for voice production and 1 self-administered sip out of a cup. The test is stopped if clinical signs of aspiration such as coughing or wet voice are noted, as well as after the occurrence of one of the following items is noted: breathing difficulties, as a result of the lack of maintaining alertness, head position, or saliva control.

If the water test shows signs of dysphagia and more than one risk factor is present, the third step will be administered, which consists of swallowing a pureed bolus with a consistency of level 4 in the *International Dysphagia Diet Standardisation Initiative* (IDDSI) framework [25]. After making sure that the patient is able to stay awake and upright for 15 minutes; has control over saliva, for example, shows no sign of drooling; and is able to produce voice, several teaspoons of puree are administered with breaks for voice production. The screening must be stopped for decreased vigilance, clinical signs of aspiration, and severe drooling without compensation. Coughing, wet voice, and oral residues are considered indicators for dysphagia.

A point score will be calculated, where a score of 5 points would allow for oral nutrition and medication with pureed food of IDDSI level 4 and thickened liquids of IDDSI level 2 until further examination by an SLP; a score of <5 points would result in the instruction of *nil by mouth* until further examination with a high risk for dysphagia.

This 3-step process of determining risk factors; applying a water-swallow test; and if necessary, administrating a pureed bolus test ensures patient safety while aiming for a high specificity and sensitivity [21,26].

Textbox 1. Risk factors for dysphagia.

1. Neurological or neuropsychiatric disease
2. Pneumonia within the last 12 months
3. Sarcopenia
4. Unintentional weight loss
5. Symptoms of dysphagia (drooling, wet voice, and coughing)
6. Impaired oral health

Recruitment

Two Austrian institutions will recruit a total of 100 patients with and without known or suspected dysphagia. One study center is an acute geriatric department, whereas the other is a long-term-care facility. Patients' inclusion criteria are an age of 75 years or older and the ability to give informed consent. Exclusion criteria are a history of severe brain stroke with a cut-off of 20 points on the *National Institutes of Health Stroke Scale* [27]; a diagnosis of moderate to advanced stages of cognitive diseases defined by 20 points or lower on the *Mini Mental State Examination* [28]; as well as the presence of a tracheostoma with or without dependence on ventilation [29]. Independently of age, these 3 factors are associated with a high prevalence of dysphagia and would be considered too high for risk of bias for the first validation on a mixed older adult

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population. All patients admitted to the acute geriatric department after the start of recruitment fulfilling the inclusion criteria will be considered and asked to participate in the study. In the long-term-care facility, staff will screen patient data and nominate possible participants, who will then be approached for their consent to participate. Recruitment started in October 2022 with a planned time frame of 18 months.

Application of the Index Test GEBS

Patients who have agreed to participate in the study will be screened with the full GEBS even if they do not show a risk of dysphagia after the first 2 steps. If any occurrence during the screening indicates dysphagia and requires the screening to be stopped and the patient to be referred to further assessment, the test result can be included in the study as "fail." To ensure broad validation of the GEBS, the screening can be carried out by nurses, physicians, or SLPs. Investigators will be educated on the correct process and scoring of the GEBS prior to the study. To ensure intrarater reliability, 15 patients will be screened twice with the GEBS by the same investigator with a minimum of 4 hours between both events. To calculate the interrater reliability, another 15 patients will be screened twice by 2 independent investigators blinded to the respective other result of the GEBS.

Application of the Reference Test FEES

Within 7 days of the first assessment using the GEBS, the reference test FEES will be carried out to verify the results. This time frame limits possible changes in the patients' medical status between the 2 investigations of their swallowing function. The FEES is considered the gold standard, objective diagnostic tool for dysphagia in older patients and is considered particularly safe and only mildly uncomfortable for the majority of patients. Reported adverse events are epistaxis, bradycardia or tachycardia, lowering of blood pressure, and changes in heart rate, all of which are rare with a reported occurrence of less than 4%. None of these reported events that were directly caused by undergoing the FEES have ever been reported as leading to permanent damage; all are self-limited and of a very short duration [30,31]. The results of the FEES will be reported using the *penetration-aspiration scale* developed by Rosenbek et al [32] in 1996; it is an internationally established 8-point scale to rate the severity of dysphagia. To limit uncomfortable sensation for the patients while the endoscope is passed through the nasal cavities, a local anesthetic can be used, which does not affect the swallowing function if used correctly [33,34]. The FEES investigators will be blinded to the results of the GEBS.

Statistical Analysis

Outcomes

The 2 main outcomes to be analyzed are sensitivity and specificity to detect dysphagia. These will be calculated using a 2 × 2 matrix. Further, positive and negative likelihood quotient and diagnostic odds ratio will be calculated. To assess intra- and interrater reliability, the κ coefficient will be evaluated. Additional cross-analysis with acquired data such as age; gender; medical diagnosis, including severity if assessed (National Institutes of Health Stroke Scale and Mini Mental State Examination); current diet; and dependency on activities of daily living will be considered as secondary outcomes. Calculations will be carried out using Excel (Microsoft) and SPSS (IBM Corp).

Data Management

Acquired data for the study will be managed and pseudonymized with the keys being stored at the recruiting institution and not available to the study coordinator. Data will be stored using Excel (Microsoft) following the legal requirements of the Austrian government.

Ethics Approval

Ethics approval has been obtained for both study centers. First, the ethics committee of the City of Vienna approved the study (EK 21-212-1021) in March 2022. The ethics committee of the Province of Salzburg gave approval (EK-Nr. 1040/2022) in June 2022. Required changes were the complete exclusion of patients who are not able to give their informed consent due to cognitive diseases as well as minor clarifications in the patients' information document. The study was registered with the ISCRTN registry (11581931) in March 2021.

Results

Recruitment started in October 2022 and will end in April 2024. A planned total of 100 participants will be aimed for. Since there have not been prior studies using the GEBS, no expected effect can be used to calculate a power analysis. Regarding previously published, internationally established screening tools, a case number of 100 patients was decided on. However, if, by the end of the study period, fewer results have been obtained, recruitment will not be extended further. Data publication is planned for early 2025, following the end of the collection period.

Discussion

Expected Findings

The GEBS is, to our best knowledge, the first screening tool for the assessment of dysphagia in older patients to be validated against an instrumental swallowing assessment in accordance with guidelines, such as STARD and QUADAS, while taking into consideration individual predisposing factors. This is highly relevant considering the growing demand for personalized medicine in this age group. Similar to children not being small adults in regard to medication, older patients with frailty are to be considered differently for their changed muscle function, metabolism, and physical activity.

This study aims to provide geriatric facilities in the acute setting as well as in long-term care with a reliable, useful tool to screen patients for dysphagia. If the GEBS shows sufficient results to be recommended for broader use in different geriatric settings, further studies in different geriatric settings are advisable. The impact of systematic dysphagia screening with the GEBS should be evaluated by using end points such as rates of aspiration pneumonia, nutritional status, occurrence of bolus death, as well as the patient's quality of life. Other populations such as patients with moderate to severe cognitive decline or tracheotomy tubes

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should also be included in further studies, to determine the validity of the GEBS in different patient groups.

Several studies have shown significant changes in the parameters mentioned above, namely pneumonia rates, nutritional status, bolus death, and quality of life, upon systematic screening for dysphagia in emergency departments or stroke units, so there is reason to expect similar effects in geriatric facilities when using a specialized geriatric dysphagia screening tool [14,16].

The screen will be used as a 2-step process in clinical use after having been validated, so the third part will only be administered if no SLP is available. If patients show a risk for dysphagia during the water swallow test and an SLP is available, the screen will be discontinued, and the patient will be referred to an SLP evaluation straight away. Especially in long-term care facilities in Austria, the presence of an SLP is not always the case. Thus, it is necessary for nursing and medical staff to be able to determine the safest method of oral intake until the swallowing function can be assessed by a specialist.

To spare patients unnecessary diagnostic processes and restrictions in their oral intake, specific diagnostic pathways and case-specific treatment need to be administered. A fast and safe way to ensure oral intake and medication in older patients can assist doctors and nursing staff upon the admission of new patients and streamlines SLP personnel resources.

Limitations

A limiting factor is the exclusion of patients with moderate to severe cognitive diseases. This is a growing population that is highly susceptible to developing dysphagia. This might be a future project after a first successful validation of the GEBS.

Conclusions

With this study, we hope to fill the gap in the health care of the older adult population by minimizing risk factors for patients and workload for caregivers at the same time. Optimized protocols and diagnostic pathways can be developed by implementing systematic, low-level screening protocols. If the results are positive in terms of high sensitivity and specificity, the GEBS will be published internationally, which might have a positive impact on workplaces and the health care of older patients.

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This study is part of SMJ's dissertation project with BI being the primary supervisor.

Authors' Contributions

RR was involved with planning the study. BI and RR functioned as the primary investigators. SMJ wrote the manuscript, and BI and RR were involved with revision and editing. All authors agreed to the final version.

Conflicts of Interest

None declared.

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Abbreviations

FEES: fiberoptic endoscopic evaluation of swallowing
GEBS: geriatric bedside swallowing screen
IDDSI: International Dysphagia Diet Standardisation Initiative
SLP: speech language pathology (or pathologist)
STARD: Standards for Reporting Diagnostic Accuracy
QUADAS: Quality Assessment of Diagnostic Accuracy Studies

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Protocol

Toward Shared Decision-Making in Degenerative Cervical Myelopathy: Protocol for a Mixed Methods Study

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Abstract

Background: Health care decisions are a critical determinant in the evolution of chronic illness. In shared decision-making (SDM), patients and clinicians work collaboratively to reach evidence-based health decisions that align with individual circumstances, values, and preferences. This personalized approach to clinical care likely has substantial benefits in the oversight of degenerative cervical myelopathy (DCM), a type of nontraumatic spinal cord injury. Its chronicity, heterogeneous clinical presentation, complex management, and variable disease course engenders an imperative for a patient-centric approach that accounts for each patient's unique needs and priorities. Inadequate patient knowledge about the condition and an incomplete understanding of the critical decision points that arise during the course of care currently hinder the fruitful participation of health care providers and patients in SDM. This study protocol presents the rationale for deploying SDM for DCM and delineates the groundwork required to achieve this.

Objective: The study's primary outcome is the development of a comprehensive checklist to be implemented upon diagnosis that provides patients with essential information necessary to support their informed decision-making. This is known as a core information set (CIS). The secondary outcome is the creation of a detailed process map that provides a diagrammatic representation of the global care workflows and cognitive processes involved in DCM care. Characterizing the critical decision points along a patient's journey will allow for an effective exploration of SDM tools for routine clinical practice to enhance patient-centered care and improve clinical outcomes.

Methods: Both CISs and process maps are coproduced iteratively through a collaborative process involving the input and consensus of key stakeholders. This will be facilitated by Myelopathy.org, a global DCM charity, through its Research Objectives and Common Data Elements for Degenerative Cervical Myelopathy community. To develop the CIS, a 3-round, web-based Delphi process will be used, starting with a baseline list of information items derived from a recent scoping review of educational materials in DCM, patient interviews, and a qualitative survey of professionals. A priori criteria for achieving consensus are specified. The process map will be developed iteratively using semistructured interviews with patients and professionals and validated by key stakeholders.

Results: Recruitment for the Delphi consensus study began in April 2023. The pilot-testing of process map interview participants started simultaneously, with the formulation of an initial baseline map underway.

Conclusions: This protocol marks the first attempt to provide a starting point for investigating SDM in DCM. The primary work centers on developing an educational tool for use in diagnosis to enable enhanced onward decision-making. The wider objective is to aid stakeholders in developing SDM tools by identifying critical decision junctures in DCM care. Through these approaches, we aim to provide an exhaustive launchpad for formulating SDM tools in the wider DCM community.

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KEYWORDS

degenerative cervical myelopathy; spine; spinal cord; chronic; aging; geriatric; patient engagement; shared decision-making; process mapping; core information set; decision-making; patient education; common data element; Research Objectives and Common Data Elements for Degenerative Cervical Myelopathy; RECODE-DCM

Introduction

Background

Degenerative cervical myelopathy (DCM) [1,2] arises when age-related changes progressively narrow the cervical spinal cord canal, resulting in neurological dysfunction secondary to cord compression [3]. Its exact epidemiology is poorly understood, likely owing to widespread underdiagnosis [4,5]. However, estimates based on imaging studies suggest that DCM could affect as many as 1 in 50 adults [2]. Although surgical decompression can halt disease progression and afford varying levels of recovery in functional status, pain, and quality of life [6-8], most people with DCM [9] will experience lifelong residual disability despite treatment [8,10]. This is often associated with a poor quality of life [11,12], high unemployment rates [8,13], and mental health difficulties [10]. From a socioeconomic point of view, DCM places a substantial financial burden on society [14,15]. In England, United Kingdom, alone, the cumulative costs associated with disability payments, lost productivity, and hospital admission are conservatively estimated at £0.7 billion (US $0.9 billion) per annum [15]. Moreover, DCM affects not only people with DCM but also their families and caregivers, who experience a low quality of life owing to caregiving strain [16]. As the incidence of DCM is expected to increase with aging populations [17], interventions that target the human and economic cost of illness associated with this condition represent an immediate priority for global health care systems and the wider community [18]. Shared decision-making (SDM) represents one such potential cost containment and patient outcome improvement strategy that could be implemented.

A Role for SDM in DCM

Involving patients in collaborative deliberations about their care can foster improved clinical outcomes [19,20] and curtail the needless use of health care resources [21,22]. The epitome of this patient-centric paradigm is SDM, an approach to clinical care wherein clinicians and patients work together to reach evidence-based solutions that prioritize patients' values and preferences [23,24].

Over several decades of scholarship since its emergence in the early 1980s [25], SDM has risen to prominence as a hallmark of quality clinical practice, notably in the realm of unresolved, chronic illnesses [26]. Given the evolving and cyclic nature of many chronic conditions, continual reevaluation and adjustment of initial health management judgments are often required as patients progress through the trajectory of their illness [27-29]. Furthermore, the complexity of chronic illnesses tends to expand over time, presenting patients and health care providers with multiple options, each with its own set of benefits and drawbacks [30]. By engaging patients in the decision-making process and considering the unique circumstances and preferences of each patient along with the potential trade-offs of each option [31], SDM can facilitate the selection of the most appropriate course of action, ultimately leading to improved health outcomes [32]. Indeed, the health management decisions of people with chronic illnesses are optimal when founded on consideration of their preferences, values, and circumstances [33-36].

Therefore, the application of SDM in DCM is likely highly pertinent. People with DCM encounter care decisions that are contingent upon personal, contextual, and technical factors on a fairly recurrent basis [13,37,38]. For example, the clinical manifestation of DCM has a diverse spectrum, with symptomatology that varies from person to person [39]. In the views of people with DCM, seemingly unrelated ailments such as loss of bowel or bladder control can be traced back to the spinal cord [2]. This is important as efficient monitoring of neurological deterioration and understanding when to report novel or developing symptoms is critical [40]. The decision to undergo surgery is a significant consideration, as evidenced by the frequent queries of people with DCM about the suitability of surgery and the best type of surgery for their circumstances [13,37]. For those treated surgically, a range of surgical approaches can address the degenerative changes in the cervical spine [41]. Nonetheless, the decision to offer surgery and its timing is nuanced owing to its risks and the potential for DCM to remain mild [42]. Furthermore, surgery seldom leads to a full recovery; instead, a heterogeneous and lifelong disability is generally expected [8,10-13]. The implications of this can involve multiple distinct complex care pathways, necessitating collaboration across an array of health care disciplines less familiar with DCM [43]. Therefore, it is essential that people with DCM are well prepared to navigate a host of complex decisions. Finally, although treatment decisions are often the focus of SDM tools [44], they represent one of many care decisions that patients encounter [45]. Our experience at Myelopathy.org, a DCM scientific and clinical charity, is that patient health care inquiries encompass a broad spectrum, ranging from "should I modify my day-to-day activities?" to "should I undergo a dynamic MRI?" This variability underscores the diverse range of decisions that people with DCM confront, necessitating decisional support. It is also our experience that these inquiries are often hindered by patients' inadequate knowledge and perhaps misconceptions of DCM [45]. In this regard, people with DCM are poorly supported by a lack of comprehensive, patient-centric, and up-to-date educational resources [45].

The aforementioned considerations, coupled with the inherent recurrent nature of decision-making in DCM, underscore the pressing need for people with DCM to engage in meaningful dialogue with health care professionals (HCPs) and have access to high-quality decisional support. In line with other chronic illness research, we hypothesize that a structured and well-orchestrated communication framework, as formulated within SDM tools, is ideally placed to successfully guide people with DCM through their health journey. Thus, investigating this

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area is warranted. In addition, the strategic incorporation of SDM has the potential to aptly support knowledge translation endeavors by identifying critical knowledge gaps and providing a framework for the assimilation of new knowledge into clinical practice [45-47]. This is currently a major challenge in DCM, where awareness of the condition continues to be suboptimal in the medical profession [48]. This is even conspicuous among spinal surgeons, who are considered authorities in the field of DCM [49,50]. To illustrate, a retrospective analysis of surgical decision-making in the United Kingdom found that only the amount of cord compression (as opposed to the guideline recommendations of disease severity) predicted the likelihood of a patient being offered surgery [49,51-53]. As the patient is perhaps the most motivated stakeholder and, importantly, a more recent student of DCM, addressing SDM may also support more consistent and immediate evidence-based care [54-57].

The Rationale for Developing a Core Information Set and Process Mapping Patients' Health Care Journeys

Patients' understanding of their baseline circumstances represents a fundamental starting point for SDM [58]. This is crucial for patients to aptly recognize care options and articulate their preferences [59]. Core information sets (CISs) were pioneered as a means to support informed consent before surgery [60-62] and comprise a distilled list of information items akin to a checklist. Their purpose is to guide an educational conversation between HCPs and their patients by ensuring that critical information about a topic is shared and considered. CISs can help reduce variation in the practice of providing information to patients [63]. Their structured and condensed nature can also circumvent the potential for information overload [64]. Therefore, a DCM CIS centered on delivering information material to the diagnosis stage could assist the efficiency of clinical interactions and quality of onward health decisions by improving patients' knowledge of the condition and their circumstances. As CISs are coproduced using multistakeholder input, their consensus-derived nature would also ensure that the information considered is of agreed importance to both professionals and patients.

Beyond diagnosis, the successful development of SDM tools depends on characterizing the critical decision points along patients' care pathways [65]. A key aspect of quality improvement interventions is identifying whether and when a decision is required [66,67]. Process mapping, the diagrammatic representation of workflows, is frequently used in health settings to understand care processes [68]. By capturing all relevant steps in a sequence of actions, a process map can provide a comprehensive overview of an activity and its potential strengths, vulnerabilities, and limitations. As with CISs, process maps are coproduced via the input of key stakeholders who describe the workflows and cognitive decisions associated with a process [69,70]. Therefore, process mapping the key decisions of people with DCM is instrumental in paving the way for the development of SDM tools, ensuring their foundation in clearly delineated needs.

This research protocol describes the preliminary groundwork required to enable the exploration of SDM tools for DCM. First, we outline the development of a DCM CIS tailored to guide a material discussion between professionals and their patients at diagnosis. Second, we detail the procedure for formulating a global DCM process map that comprehensively captures common critical decisions in the patient journey.

Methods

Overview and Scope

Myelopathy.org and the Research Objectives and Common Data Elements for Degenerative Cervical Myelopathy Community

Myelopathy.org is the first and currently only scientific and clinical charity dedicated to improving the outcomes of people with DCM [71]. The charity has a global professional and lay audience, making it well suited for spearheading the initiative described in this protocol, which forms part of a larger enterprise aimed at promoting SDM in DCM. This will occur through the Research Objectives and Common Data Elements for Degenerative Cervical Myelopathy (RECODE-DCM) platform, an international community of professionals with diverse expertise in spinal care, and people with DCM registered with the charity working together to accelerate knowledge discovery in DCM.

The community was formed in collaboration with AO Spine (a nonprofit organization supporting education and research for spinal surgeons) to develop a research toolkit aimed at accelerating knowledge discovery in DCM [1,4,18,72]. Recognizing the broader opportunities for this community to address knowledge gaps in DCM and support their implementation led to its recognition as a distinct entity [73-75]. The network is now maintained by Myelopathy.org under its advisory board.

The research team formulated 2 objectives for this study, as outlined in the following sections.

Objective 1: To Enhance Knowledge of the Condition Among People With DCM

This will be achieved by developing the first DCM diagnosis CIS using an international multistakeholder (Delphi) consensus process.

Objective 2: To Identify Critical Decision Points in the Medical Care Product Life Cycle That May Benefit From SDM Tools

This will be achieved through a process map exercise involving an international multidisciplinary team of key stakeholders, including patient representatives.

Information on the status of each phase is shown in Table 1.

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Table 1. Research study stages, findings summary, and status.

Description	Findings summary	Status
Core information set		
Scoping literature review of educational resources in DCM[a]	>80% of resources geared toward professionals	Completed
Semistructured patient interviews	Varied information needs throughout the patient journey	Completed
Survey of professionals	Survey of professionals to collect their views on the information that people with DCM need	Completed
Delphi consensus survey of professionals and patients	Pending	In preparation
Process mapping		
Preparation, planning, and process identification	Pending	Completed
Data gathering	Pending	In planning
Process map generation	Pending	In planning
Analysis	Pending	In planning
Taking it forward	Pending	In planning

[a]DCM: degenerative cervical myelopathy.

Study Design

Enacting SDM requires insight into decisional dynamics. At its core, this entails discerning the critical timing of decisions and navigating factors related to decisional conflict—a state of uncertainty over a course of action when multiple options are present, each requiring careful evaluation of risks, benefits, and alignment with personal values. Key among the latter is an understanding of the informational demands associated with each decision-making juncture. To meet these requirements, our protocol proposes a mixed methods design that combines the structured, quantitative Delphi consensus procedure with the qualitative, visual approach of process mapping. By leveraging both methods, our study aims to translate evidence-based knowledge and stakeholder experiences into clinically actionable tools for enhancing the health outcomes of people with DCM [76]. The following sections elaborate on our application of the Delphi procedure in constructing the first DCM CIS and process mapping to highlight patients' key decision points.

Objective 1: To Enhance People With DCM's Knowledge of the Condition—Developing the First CIS for Use in DCM at Diagnosis

Delphi Consensus Process Overview

The Delphi technique is a well-established method for achieving consensus among experts on a given topic [77]. It is particularly suited to contexts in which knowledge is ambiguous, empirical evidence is scarce, or priority setting is required [78]. In this procedure, a panel of preselected experts are engaged in a series of structured surveys. Each round incorporates controlled feedback, usually a blend of quantitative and qualitative data, the purpose of which is to foster insights from previous rounds, prompting reflection and the potential revision of viewpoints [79]. Designed to incrementally foster a convergence of opinions, the procedure is usually conducted anonymously, allowing participants to freely articulate their perspectives [80]. The number of rounds, execution of question delivery and response acquisition, and standards of achieving of "consensus" can vary within this general framework. Figure 1 provides a schematic overview of our approach, comprising 2 anonymized web-based surveys followed by a consensus meeting hosted over the internet. Consensus meetings offer a platform for real-time dialogue [81]. This face-to-face component has been observed to play a role in refining and enhancing the group's collective understanding, paving the way for a more sophisticated consensus [82].

The Delphi method has been widely used in health sciences [83] to generate clinical recommendations [84] and standards and guidelines for theoretical or methodological issues [83,85,86] for a range of chronic illnesses such as diabetes [87,88], cancer [89,90], asthma [91], rheumatoid arthritis [92], and spinal cord injury [93,94]. Our objective using a Delphi procedure is to develop a CIS that facilitates optimal communication of information to people with DCM about the condition at the point of diagnosis. Figure 2 shows an overview of the phases involved in developing the CIS.

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Figure 1. Overview of the Delphi rounds and consensus meeting.

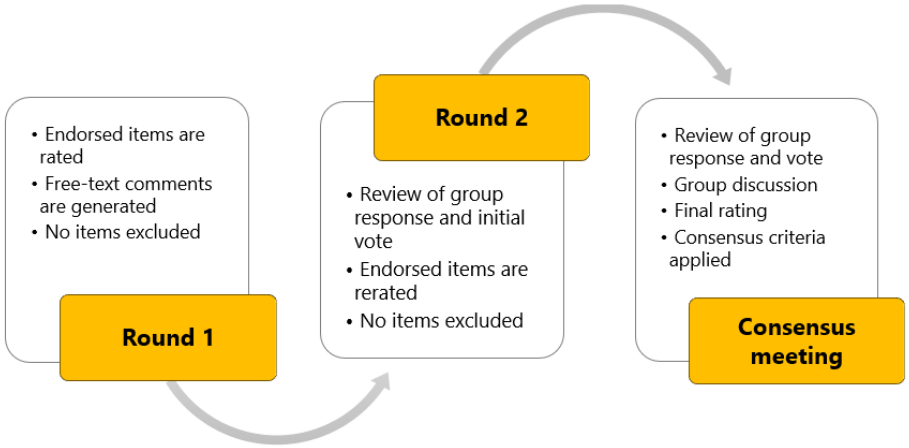
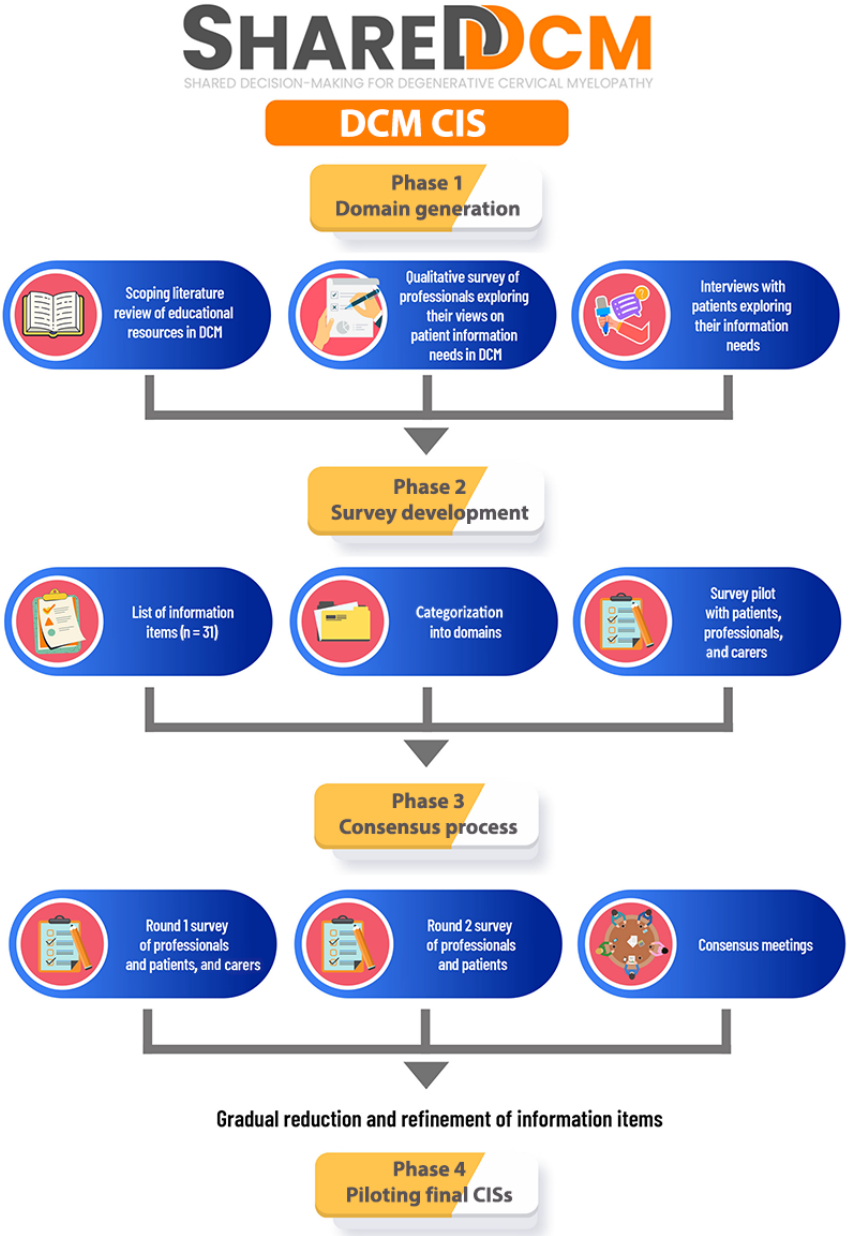


Figure 2. Overview of the phases involved in the development of the degenerative cervical myelopathy (DCM) diagnosis core information set (CIS).



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Sample Size

The optimal participant head count for a Delphi study remains a subject of ongoing discussion [82], as exemplified by the historical variance in sample sizes [95]. However, representativeness is not shaped by conventional sampling strategies [96,97] but rather through the expertise of the panel members [98]. Guidelines suggest a minimum of 7 to 15 panelists for optimal reliability [78]. Some believe that exceeding 30 participants adds little value [99-101]. To develop a relevant CIS, our study aims to target the 2 primary DCM stakeholders: people with DCM and HCPs managing DCM. We propose enlisting at least 15 experts from each category, with no upper limit [78,95,102]. We address potential carer involvement in the following section.

Expert Selection

The sample composition significantly determines the validity of the study results [103,104]; therefore, an element of careful judgment is warranted to ensure a "balanced" panel [104-106]. To ensure a judicious selection of experts, this study will use a purposive sampling approach, drawing surgeons, other HCPs, and people with DCM as participants from the specialized RECODE-DCM community. People with DCM will be considered if they (1) have been formally diagnosed with DCM and are at least 6 months after surgical decompressive treatment, the time point at which neurological recovery is considered to halt for most [107], or (2) have undergone at least 6 months of nonoperative management [49]. Professional stakeholders will be invited to participate if they (1) are experienced in managing DCM for at least 5 years; (2) belong to key clinical disciplines, including spinal surgery, neurology, combined physical and psychological rehabilitation medicine, physiotherapy, pain management, and primary care [4,108]; and (3) have no conflict of interest in developing a CIS. All participants will be English-speaking adults (aged ≥18 years).

A diverse and geographically representative panel will be sought, in keeping with the aim of developing an internationally suitable CIS. Adequate patient involvement is vital to this endeavor to help foster evidence-based decision-making [109]. Recognizing the importance of patient perspectives, we propose aiming for a stakeholder target ratio of 1:1:2 (surgeons:other HCPs:people with DCM). The increased representation of people with DCM addresses their typically minor role in such studies and considers recent findings indicating a divergence in clinician- and patient-prioritized outcomes [4] and information needs [45]. This ratio also aligns with the status of people with DCM as the principal beneficiaries of the CIS and enhances its applicability from a patient and public perspective.

For balanced geographical stakeholder representation, a 1:1:1 target ratio is proposed, spanning North America and Australasia; Europe and the United Kingdom; and "elsewhere," comprising Africa and Asia. Including stakeholders from these regions will help ensure that the CIS considers a wide range of health care systems, cultural practices, and resource availability. However, it is worth noting that engaging participants from the "elsewhere" category may prove difficult. These regions, which are often underrepresented in the research community owing to fewer research resources and infrastructure [110], are similarly underrepresented in our specialized RECODE-DCM community. Recognizing this potential recruitment challenge upfront, we will aim to achieve equal regional representation during the final consensus meeting, with no items removed before this stage.

Carers (informal and formal) of people with DCM will also be invited to participate in the Delphi process as they offer significant practical and emotional support to people with DCM [16] and likely hold unique perspectives with regard to their information needs at the time of diagnosis. Consultation with informal carers, often subject to significant caregiving strain [16], may indirectly contribute to their welfare by promoting improved standards of care. However, we acknowledge that the recruitment of carers may be challenging as they are less likely to self-identify, as documented in related research domains [111]. In addition, the number of carers involved in the RECODE-DCM community is currently limited. For these reasons, no stakeholder or geographical target ratios will be specified for this group. Their involvement will be encouraged by existing HCPs and people with DCM in the community.

Participants will be invited to complete round 2 of the Delphi survey only if they have responded to round 1. A dropout rate of approximately 20% is expected from previous Delphi exercises [95,112]. Respondents who complete the Delphi process will be acknowledged in published material. No monetary incentives will be offered.

Generating Information Items

The first step in the Delphi process involves generating a list of information items for the voting consensus process. The procedure comprises 3 steps, described in the following sections.

Scoping Literature Review and Patient Interviews

In structuring the Delphi procedure, we sought to cover the wide spectrum of DCM-related information with the potential to foster patient understanding of the condition, facilitate informed decision-making, and promote efficient self-management. Clinically pertinent items were derived from scientific publications, patient leaflets, health websites, and videos identified in a scoping review of DCM education resources [38]. In total, 150 information resources were reviewed, spanning 115 (76.7%) scientific publications, 28 (18.7%) videos, and 7 (4.7%) health organization resources and health education websites. Items sourced in this manner characterized the disease etiology, pathophysiology, epidemiology, management, and outcome prediction. Additional multidimensionality was added via items sourced from qualitative research involving patient focus groups [10,113] and semistructured interviews [45]. These provided valuable additions focused on the impact of DCM on employment, mental health, and quality of life. The process of deriving the information items was iterative. Each new unique piece of information was noted as an item, and multiple returns to the data were made to ensure the avoidance of duplicates and omissions. This process continued until a preliminary list of information items (n=95) was collated and no new items could be identified.

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Professionals' Perspectives

Professionals' views on the information items to be included in the diagnosis CIS were identified using an open-ended qualitative questionnaire (SurveyMonkey; Momentive Inc). Respondents were provided with relevant information via a web hyperlink to the Participant Information Sheet. The sheet included a summary of the research project, its objectives, the inclusion and exclusion criteria, anonymity and confidentiality, and the anticipated time commitment required to complete the survey. To stimulate participant engagement, a short educational video explaining the purpose of the procedure was presented [114]. Biographical information, including training specialty (surgery or other HCP), was collected from consenting participants. Respondents were subsequently directed to a page containing the following open-ended question: "What information do you think people with DCM need to be told at the point of diagnosis about their condition?" It is acknowledged that free-text questions do not generate rich qualitative data [115]. However, our objective was not to elicit robust qualitative insights but rather to generate a list of information items from the professionals' perspectives. To mitigate this limitation, participants were asked to provide a short rationale for each recommended information item. This approach can act as a proxy for qualitative interviews administered to convenience samples [116] and allowed the study team to improve evaluative rigor by understanding the rationale behind the recommendations received. There was no limit on the number of information items that the HCPs could submit.

To facilitate reflective consideration from respondents, participants were presented with a word cloud upon submitting their initial recommendations (Multimedia Appendix 1). Word clouds are a graphic representation of textual data that use frequency counts to display effective summaries of common themes within a given text [117] and have been successfully used previously in DCM consensus work [118,119]. The word cloud generated for this study was produced using qualitative codes derived from the thematic analysis of interviews with people with DCM on the topic of their information needs [45]. This approach was selected to mitigate issues related to language variability that can arise from using direct quotes from the participants, which may be influenced by individual differences in language proficiency, education, and cultural background, and to improve the comprehensibility of the word cloud. Similar adjusted approaches have been used by others [117]. Participants were asked to reconsider their recommendations after viewing the word cloud. As word clouds have been found to promote critical thinking and reflection [120], we hypothesized that this approach would help stimulate professional stakeholders to generate insightful recommendations that are better aligned with patients' needs. The open-ended questionnaire was not issued to people with DCM as their perspectives have already been collected [45].

The Questionnaire

A total of 46 respondents, predominantly spinal surgeons (n=33, 72%), suggested information items (n=312) for inclusion in the Delphi survey. Contributors also included physiotherapists (8/46, 17%) and other HCPs, including neurologists, family physicians, allied health professionals, and researchers (5/46, 11%). The items received were carefully scrutinized for redundancy. On inspection, suggestions paralleled our existing list, demonstrating a broad alignment across all information sources, including the expert clinician group. A multidisciplinary study committee comprising 3 people with DCM, 3 neurosurgeons, a neurologist, 2 consultant physiotherapists, a lay representative, and the study coresearcher condensed the list to 31 information items and classified them into 8 distinct categories deemed to accurately represent their content. For the purposes of developing a CIS, the term "information item" was conceptualized as overarching categories or topics that house more specific, detailed information. For example, the item "lifestyle factors" was an inclusive banner for detailed subjects such as the effects of smoking and occupational trauma on DCM. This approach was chosen to ensure the appraisal of *meaningful* concepts or core educational aspects. The detailed content within each item, although not voted upon, will be accessible for participants' reference throughout the Delphi study. Categorizing information items in Delphi studies is crucial in reducing redundancy and ensuring that all relevant concepts are captured as well as promoting consensus building among expert panelists by clarifying the meaning of each item [79,80]. This also facilitates a systematic and standardized approach to synthesizing diverse perspectives, thereby generating informed recommendations [79,121]. In preparation for pilot-testing, the research team created a draft survey based on the final list and evaluated the software settings, automation, flow, ease of navigation, and completion time. For ease of navigation, only 1 information item was presented per page [122].

Pilot Survey

Pilot-testing was conducted with the study committee. Feedback concerning the language, structure, readability, comprehension of statements, and formatting of the questionnaire was collected through open- and closed-ended questions.

Delphi Survey

An email campaign will be created in Gmail (Google) using a newsletter layout template and sent to HCPs, people with DCM, and carers in the contact directory of the RECODE-DCM network using the multisend function. The multisend option is a built-in mass-email feature that allows emails to be sent in bulk to distinct recipients, thus preserving their anonymity, which is a key feature of the Delphi method [98]. Participants will have the option to opt out of the process at any point through a unique "unsubscribe" link automatically added to each email. Recipients who unsubscribe will be removed from future email campaigns. The email will provide prospective Delphi panelists with a brief overview of the study. Potential panelists will be directed to Delphi round 1 via a SurveyMonkey web link embedded in a participation button at the bottom of the email. The survey will open to a short explanatory video and a web link to the Participant Information Sheet, which will provide a summary of the research project, aims, the inclusion and exclusion criteria, anonymity and confidentiality, and anticipated time commitment. The following biographical data will be collected for people with DCM: age, year of diagnosis, history of surgery or nonoperative management, and employment status. For HCPs, information about their

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profession, specialty, job title, and experience in managing DCM will be captured.

Panelists will be asked to independently rate the importance of information items using a 4-point Likert scale ("essential," "very important," "unimportant," and "not at all important"). This range of response categories is more likely to produce stable findings in Delphi studies [95]. Respondents will also be asked to provide a brief rationale for their responses and whether the information items presented could be modified to improve their relevance using a comment box. It is common practice to include in questionnaires that respondents themselves complete an invitation to add issues not covered in the main part of the questionnaire or to expand on terms [123]. The presentation of information items will be randomized using a pseudorandom number generator throughout both rounds [124]. No more than 3 rounds will take place to ensure that the process does not become too repetitive and time-consuming to maintain an adequate response rate [80]. After each round, participants will be asked to read the feedback before responding again to statements.

Data Analysis

Overview

Qualitative and quantitative summaries will be used to understand areas of agreement or disagreement between panelists, generate feedback, and stimulate participants' reflections. All forthcoming data analyses will be carried out by a postgraduate research assistant. Both quantitative and qualitative methods will be used to analyze interround feedback, and the findings will be reported to the panelists and the core research team after each round. The provision of both types of data is essential to enhance rating accuracy [125].

Qualitative Analysis

Free-text comments will be analyzed using inductive content analysis [126], a procedure commonly used with text-based data. Its pragmatic emphasis on theoretical constructs makes this approach particularly suited to practically oriented research where the goal is to describe a phenomenon of interest [127] and generate answers for the application of findings [128]. A summary of the remarks made by other panelists will be displayed anonymously to participants after each round.

Descriptive Statistics

Following each round, panelists will receive aggregate-level summary statistics for each item in the form of frequency percentages, medians, ranges, and IQRs [129]. Participation and attrition rates will be summarized as frequencies and percentages after round 2. Participants will be asked to read the summarized feedback before responding to round 2 statements.

Interrater Stability

Descriptive statistics reflect the level of overall consensus in a given sample but may not account for random change agreement and, therefore, may fail to accurately depict "true" consensus [130]. The κ statistic measures agreement beyond that expected by chance [130]. A weighted κ coefficient will be calculated after round 2 for the between-participant agreement on each information item. This variant is preferred compared with its unweighted equivalent as it is more suited to ordinal data given its ability to account for the magnitude of differences between the agreement levels [131]. The κ statistic will be particularly helpful for guiding the direction of conversations during the consensus meeting, ensuring that discussions are rooted in objective findings. κ calculations will be provided for each information item along with the reference value description of the agreement level in accordance with the study by McHugh [132] (Table 2).

No information items will be removed during these rounds. Data analyses will be conducted using SPSS (version 26; IBM Corp), and graphs will be produced using Microsoft Excel (Microsoft Corp).

Table 2. Level of agreement represented by κ values[a].

κ value	Agreement level
0.0-0.2	None
0.21-0.39	Minimal
0.40-0.59	Weak
0.60-0.79	Moderate
0.80-0.90	Strong
≥0.90	Almost perfect

[a]Adapted from the study by McHugh [132].

Consensus Criteria

Delphi studies lack consensus on the specific threshold for agreement. Significantly, Linstone and Turoff [133] posit that an agreement of >80% is neither the central objective of the Delphi process nor always practically possible. In this study, items rated as "essential" or "very important" by ≥75% will qualify for inclusion, whereas those judged as "unimportant" or "not at all important" by ≥75% will qualify for exclusion. Items not fulfilling these criteria will be defined as not having reached a consensus. This threshold value [134,135] is situated between the 50% consensus supported by some [136,137] and the 100% cutoff point suggested by others [138]. Consensus criteria will be applied after the consensus meeting.

To gain additional insights into the perspectives of the 3 stakeholder groups, comparative statistics will be calculated after each round for review by the core study team. The

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parametric 1-way ANOVA will be used to investigate differences in stakeholder responses during each round if the assumptions of normal distribution and homoscedasticity are met [139]. These will be inspected using histograms and the Shapiro-Wilk test and the Levene test for equality of variances, respectively. Statistically significant results will be investigated using post hoc analyses to be chosen in accordance with whether homoscedasticity is met [140]. In the event of violations of the assumptions of normality, the Kruskal-Wallis *H* test, a nonparametric alternative, will be used as it is predicated on rank-based assessment and does not presuppose normality or homogeneity of variance [141]. Moreover, in the event that we are unable to identify sufficient carers to complete the Delphi survey, we will use the independent-sample 2-tailed *t* test to investigate statistically significant differences between HCPs and people with DCM. If the assumptions for the test are not met, we will use its nonparametric equivalent, the Mann-Whitney *U* test. Significance will be assumed at $P<.05$.

Consensus Meeting

The consensus meeting via Google Meet (Google LLC) will be attended by a maximum of 20 randomly selected HCPs, people with DCM, and carers who have completed both rounds of the Delphi survey, preserving the key stakeholder and geographical representation previously described. Participants will be presented with round 2 voting results, as previously described, and asked to anonymously rate the importance of each item for a final time using the polling tool. Frequency percentages will be generated in real time and presented to the voters on-screen to facilitate discussion. The facilitator will guide further discussion regarding any items garnering equal consensus (50%) between the agreement ("essential" and "very important") and disagreement ("unimportant" and "not at all important") before asking participants to vote again. In all other cases, items failing to meet the predetermined ≥75% consensus score will be eliminated.

Reporting the Survey Results

To ensure a thorough description of the Delphi process, survey results will be reported following the Checklist for Reporting Results of Internet E-Surveys [142].

Objective 2: To Identify Critical Decision Points in the Care of People With DCM—Process Mapping the Patient Journey

Overview

Critical decision points in the trajectory of patients will be identified using process mapping, a technique that can aptly describe the workflow and cognitive procedures associated with an activity at the desired level of granularity [143]. We define a critical decision point as a distinct juncture in the care pathway when a professional-patient discussion leads to a care decision. These are essential "go-or-no-go" decisions [59]. Our process map protocol follows the quality criteria framework set out by Antonacci et al [69] to ensure compliance with best practice recommendations. Our approach to each phase is described in the following sections.

Preparation, Planning, and Process Identification

The process map exercise described in this protocol is guided by the need to characterize common critical decision points that adequately represent the global DCM health care pathway. To obtain broad insights, we define the starting point as the time when a person with DCM is diagnosed with DCM and the end point as the time when a person with DCM engages in posttreatment management of the condition. We will define the patient group under investigation as people with moderate or severe DCM treated surgically and people with mild DCM treated nonoperatively [2]. This approach will ensure an all-encompassing investigation of the care route for people with DCM.

Steering Group

It is good practice for process map exercises to be led by a steering group comprising at least one member with lived experience of the condition under investigation and a member with previous process map experience [144]. Following these recommendations, our process map activities will be supervised by the same multidisciplinary study committee overseeing the Delphi consensus process. At a minimum, the committee is envisaged to meet at the beginning and end of project activities, with further meetings as required. Decisions made at meetings will be binding when the meetings are quorate, that is, attended by at least one member of the core research team, one patient representative, and one member with process map experience. Project-relevant communications may also take place via email correspondence as necessary.

Recruitment Strategy and Skills Training

Key informants—English-speaking adults (aged ≥18 years)—will be drawn from the specialized RECODE-DCM community using a convenience sampling approach. Professionals will be approached for participation if they belong to key clinical disciplines, including spinal surgery, neurology, combined physical and psychological rehabilitation medicine, physiotherapy, pain management, and primary care [4,108], and have at least 5 years of experience in managing DCM. People with DCM will be eligible if they have undergone surgical decompressive treatment at least 6 months before, the time point at which neurological recovery is considered to halt [107], and if they have experienced the common care pathway for spinal disorders from primary care to rehabilitative services [145]. This criterion will ensure that participants with DCM are familiar with a wide range of interventions and services along the global spinal care pathway and, therefore, can provide an informed view of its workflow and cognitive decision points. To ensure a global representation of the spinal care workflows and cognitive decisions, both professionals and participants with DCM will be sought at the previously described geographical target ratio. In addition, a 1:1 ratio corresponding to HCPs to people with DCM will be sought in the development of the baseline process map.

An electronic study pack will be provided to those interested in participating, comprising a written study summary, this study protocol, and a Participant Information Sheet containing the study investigators' contact details. To equip respondents with

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the necessary process map skills, all consenting participants will be issued a short explanatory document outlining relevant process map symbols alongside an example of a finalized map from a different health care process. Participants will be given the opportunity to contact the study team should they have any questions or require further clarification before commencing study activities.

Data Gathering

To enhance accessibility and foster participant engagement [146], data will be collected using one-to-one semistructured interviews, estimated at approximately 60 minutes and conducted via Google Meet. The interview schedules will be grounded in the literature, aiming to capture information on each step of routine clinical care under investigation [144,145]. To enhance comprehensiveness and incorporate expert input, the topic guide will undergo review and approval by the aforementioned steering group. In total, 2 distinct interview guides will be developed to interview clinicians and people with DCM. For clinicians, we propose a tailored approach in recognition of the specialization inherent in each HCP's role. For example, primary care physicians are instrumental in recognizing the condition and its associated clinical examinations for referral to a spinal surgeon [42]. Specialist surgeons, under the remit of neurosurgery or orthopedics, play a pivotal role in steering the course of management [147]. Specialist practitioners such as physiotherapists play a vital role in assisting in the management of DCM via preoperative physiotherapy and neurorehabilitation programs, primarily used in the context of DCM to manage disability postoperatively [40,148]. Therefore, our interview guide will account for differences in specialists' knowledge of care for DCM by asking HCPs an open question regarding how they manage people with DCM in their role specifically. From there, prompts relevant to each clinician's profession and based on the information they provide will be used to guide the interview. By grounding the topic schedule in the particularities of each professional's role, our approach can help ensure a thorough exploration of clinicians' perspectives, accounting for the nuanced differences across specialties and individual clinical roles within the DCM care pathway. We also recognize that the care pathways of people with DCM differ owing to variations in patients' DCM, flow times between different regions in the world, and guidelines of care [149]. Therefore, patients will be encouraged to share their experiences navigating the care system, focusing particularly on key decision-making points. Prompts will be used to elicit detailed accounts of their journey, the information sources they relied on, their understanding of their condition at each stage, and their level of satisfaction with the decision-making process. Interviews will be conducted until data saturation is reached, that is, until no new information is identified with respect to the research question [150]. At a minimum, it is envisaged that this will involve 20 interviews with HCPs and people with DCM. To allow for the incorporation of new insights generated during the data collection process, the interview guide may be adapted as necessary [151].

A baseline map will be developed by interviewing 3 surgeons and 3 people with DCM from each of the geographical target areas. This approach seeks to ensure that international perspectives are adequately represented from the onset. As surgical intervention is the cornerstone treatment for DCM and surgeons preponderate the research community [50], professional transcripts derived from surgeons specifically (rather than other HCPs) will inform the preliminary map. As women remain underrepresented in clinical surgical practice [152], we will seek to recruit the views of at least one female spinal or orthopedic surgeon in the development of the baseline map. This preliminary map will be developed iteratively through a series of additional interviews with surgeons, other HCPs, and people with DCM while ensuring geographical representation. Interviews will be audio recorded and written informed consent will be sought from all participants. Following their interview, each participant will be provided with a copy of their transcript, a process map created from their interview data, and the evolving baseline map. Participants will be asked to reflect on their interviews and consider whether they wish to supplement the process map. This approach will be used as a means of ensuring data validation and quality and promoting further unbiased contributions to the data [153,154].

Upon reaching data saturation, a selection of interviews will be chosen based on their richness, and the final process maps will be refined by referring to them. Data richness will be defined as "thick" data that best capture the multifaceted complexities of the process under investigation [155]. Participants will be assigned unique study numbers to anonymize their identities in the transcripts.

Map Generation

The baseline map will be developed and schematically represented using Lucidchart (Lucid Software Inc), a web-based diagramming application, and developed iteratively based on information obtained during subsequent interviews. A level of complexity associated with ad hoc variation in the international processes and cognitive decision points is anticipated. To accurately depict this, several process maps may need to be generated. For example, a separate process map may need to be created for preoperative, operative, and postoperative processes. Where possible, relevant clinical pathway documents provided by participants will be used in the development of the process map.

Data Analysis

Interviews will be transcribed verbatim and analyzed using inductive thematic analysis according to Braun and Clarke [156]. This will involve a coding process whereby segments of text are systematically organized according to common concepts and broader themes developed to encapsulate the main topics present in the interview data. The synthesis of these themes will be used to develop a visual representation of the interview data within the process map. The map will be developed iteratively, ensuring the inclusion of emerging themes. The final stage will involve validation to ensure the accuracy and reliability of the process map. This can be achieved through methods such as member checking, peer debriefing, or triangulation, ensuring the credibility and dependability of the findings [157]. The final process maps will be shared with the key participating stakeholders for comments and validation over email. Participant demographic characteristics will be collected during the

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interviews and presented in tabular form using frequencies, means, and SDs as appropriate. For HCPs, demographic data will include age, gender, job title, a brief description of their duties, and number of years managing DCM. For people with DCM, this will include age, gender, occupation, year of diagnosis, and treatment (where applicable).

Future Steps

Process maps should be used to guide process improvement initiatives [158]. The process maps generated following this study protocol will inform future efforts by Myelopathy.org to develop SDM tools that will help people with DCM participate in making specific and deliberate choices regarding their health. In particular, at the time of writing this protocol, it is considered that identifying critical decision-making points will allow for the development of widely used evidence-based SDM tools such as patient decision aids [159-162] or patient road maps [28].

Ethics Approval

The University of Cambridge Human Biology Research Ethics Committee has approved the study (approval HBREC.2023.04).

Informed Consent, Data Protection, and Dissemination Strategies

Written informed consent will be sought from participants for both study objectives, that is, in the development of the CIS and process map exercise. All data will be handled under UK data protection regulations. Dissemination strategies for this project will include scientific publication and communication of findings via the Myelopathy.org website and Myelopathy Matters podcast.

Results

Recruitment for the Delphi consensus study began in April 2023. The pilot-testing of process map interview participants started simultaneously, with the formulation of an initial baseline map developed at the end of June 2023.

Discussion

The proposed study protocol outlines a Delphi consensus process that draws on the expertise of clinicians experienced in managing DCM and of people with DCM to formulate a diagnosis-specific CIS. It provides the rationale for undertaking an international process map exercise to characterize the common decision points in the health journey of people with DCM and outlines a strategy for generating outputs that aptly fit the needs of the global DCM community via broad stakeholder consultation.

Significance of the Study

To the best of our knowledge, this is the first initiative that aims to engage people with DCM in the management of their care. Given the high global incidence of DCM [2,163], the outputs of this preliminary study are relevant to a substantial cohort of people with DCM, clinicians, and policy makers worldwide. Most importantly, the CIS aims to address the significant educational deficit identified in DCM [38,45]. Drawing on the tangible impact of structured patient education [164-169], we anticipate that the CIS has the potential to reduce knowledge discrepancies and advance equitable opportunities for quality health management decisions. In particular, as CISs are developed using key stakeholder input, they are ideally placed to facilitate a well-orchestrated communication that mitigates the biases or inadequacies associated with purely professional-led communication [60,63]. Furthermore, educating patients on the condition is one facet of improving their openness to and, arguably, time to surgery [45], potentially driving improvements in health care outcomes [170,171]. This is important as many people with DCM misunderstand the necessity and immediacy of surgery [45]. An appraisal of the CIS will be undertaken following its implementation to assess its efficacy in clinical practice.

In addition, we anticipate that the benefits of the process map in the international DCM care pathways may extend beyond SDM, for example, to addressing timely treatment and improving knowledge exchange [69]. Characterizing the key decision points and matching them to the current evidence base may expose critical knowledge gaps that must be served with targeted research. This means that, as the evidence is updated, so can be the SDM tool, helping accelerate the adoption of evidence into practice. In addition, providing a tangible visual tool to convey the patient experience across different health care settings and among various stakeholders may enhance communication among multidisciplinary teams [69], a recognized objective in DCM [172]. In the long run, the process map can serve as a valuable tool for patient advocacy, spotlighting areas of the care process that are particularly challenging [45], allowing policy makers and care providers to be better informed about the realities of living with DCM. This takes on added significance in low- and middle-income countries [173], where the burden of DCM is high yet access to care remains substandard [149]. Finally, developing a globally shared understanding of DCM care, with its similarities and differences, may facilitate opportunities for local redesign, development, or evaluation [69], leading to improvements in access to treatment [13].

Strengths and Limitations

The proposed study has several methodological strengths and limitations. First, the Delphi method offers an unbiased manner of soliciting consensus when this is lacking [174]. The guarantee of anonymity reduces expert-layperson power asymmetries between clinicians and patients, which are inherent in typical health care interactions [175]. This provision is particularly important to people with DCM, the beneficiaries of the CIS, to assert their viewpoints without reservation. Furthermore, the provision of systematic and controlled feedback fosters transparency, dialogue, learning, and sometimes novel insights that might not have been apparent in isolation [78]. Through its systematic progression, the Delphi method allows for gradual refinement of ideas [176]. Information items put forward for consensus in this manner are likely to become more patient-centric, relevant, and clear, ultimately resulting in the production of a more pertinent CIS. In addition, conducting the survey over the internet broadens the inclusion of people with

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DCM, including presurgical DCM, which is poorly represented in the conventional literature [50,177].

This approach also has a number of limitations. Despite comprehensive efforts to source a broad range of expert participants, the conclusions of the study may suffer from limitations associated with the panel's composition. This is the case with any Delphi study [178]. In this regard, our purposive sampling approach may lead to outputs that may not fully reflect all health care contexts and stakeholders' perspectives. Pilot-testing the survey with a smaller representative sample can help ensure its comprehensiveness [179]. Expert judgment may also be influenced by cognitive biases, which is a well-recognized limitation of Delphi studies [79]. To mitigate this, we are curating an expert panel diverse in both roles and geographic locations to promote a more balanced collective judgment [180]. Other efforts to minimize bias throughout the Delphi process include the randomization of survey statements to eliminate primacy effects, requests to participants to include a rationale for their choices, and providing feedback in the form of median rather than mean values [116,124,125]. Compared with evidence-based approaches, expert surveys do not capture cause-effect relationships and are, therefore, definitive [181]. That is, our experts' agreement on the final CIS does not assure the tool's efficacy. To address this concern, the CIS will be evaluated, the specifics of which will be laid out in a separate study protocol.

Finally, inductive thematic analysis provides an adaptable methodology for developing the process map. Its flexibility allows for the generation of unanticipated themes and patterns [156]. Coding and organizing the data around common concepts aids in translating potentially complex data into a digestible visual representation [182]. The iterative nature of this method allows for continuous refinement of the process map, thereby increasing the reliability of the results [183], whereas validation strategies such as member checking and peer debriefing ensure the accuracy, credibility, and dependability of the findings [157].

Conclusions

This is the first study to establish an international-led collaborative framework aimed at enabling SDM in the management of a chronic illness. To the best of our knowledge, this approach has not been used before. The projected benefits of this initiative are poised to improve people with DCM's knowledge about their condition. In the long term, this study is intended to drive the development and deployment of SDM tools in DCM care.

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Data Availability

The data sets being generated and analyzed in this ongoing study are not publicly available at this time because of the need to preserve the integrity of the ongoing Delphi consensus process but will be shared in subsequent publications after the study concludes.

Authors' Contributions

BMD contributed to conceptualization, funding acquisition, supervision, original draft preparation, and review and editing. BG contributed to conceptualization, methodology, and funding acquisition. IS contributed to conceptualization, methodology, original draft preparation, and review and editing. GA contributed to conceptualization, methodology, draft preparation, and review and editing. AM contributed to methodology, draft preparation, and review and editing. The other authors contributed to review and editing.

Conflicts of Interest

MRNK is a trustee of the Myelopathy.org charity.

Multimedia Appendix 1
Word cloud of qualitative codes generated from the thematic analysis of interviews with people with degenerative cervical myelopathy.
[PNG File , 279 KB - resprot_v12i1e46809_app1.png]

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Abbreviations

CIS: core information set
DCM: degenerative cervical myelopathy
HCP: health care professional
RECODE-DCM: Research Objectives and Common Data Elements for Degenerative Cervical Myelopathy
SDM: shared decision-making

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Protocol

Development of an Information Guideline for Kidney Transplant Recipients in a Clinical Trial: Protocol for a Modified Delphi Method

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Abstract

Background: Renal transplantation is the treatment of choice for most cases of end-stage renal disease. Recipients need to lead a healthy lifestyle to minimize the potential side effects of immunosuppressive drugs and improve transplant outcomes. There is not much evidence about the best way to increase adherence to healthy lifestyles in kidney transplant recipients, so one of the objectives set by the nursing team is to train people to acquire the necessary skills and tools to be able to take care of themselves. In this sense, the consensual development of appropriate materials may be useful and of interest.

Objective: The aim of this study was to develop an information guide for adults with kidney transplants to be assessed in a subsequent clinical trial as an intervention to increase adherence to healthy habits.

Methods: We used a 3-step, methodological, sequential approach: (1) training from a group of experts and item consensus; (2) review of the medical literature available; and (3) use of the Delphi technique with on-site meetings. A total of 5 nurses from the Community of Madrid Kidney Transplantation Unit in Spain were asked to participate. The patients' lifestyle factors that, according to the medical literature available and experts' opinions, have the greatest impact on the survival of the transplanted organ and the recipients themselves were all described.

Results: After using the modified Delphi method to reach a consensus on the items to be included and the information needed in each, an information guide for adult kidney transplant patients was developed. This guide facilitates the structuring of health care, information, and recommendations necessary for effective self-care for each person. The result is considered to be an easy-to-understand tool, useful for transplant doctors and nurses, in simple language, with information based on the latest scientific-medical evidence published to date, aspects of which will be evaluated in a clinical trial designed for this purpose.

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Conclusions: Currently, this guide is the main intervention variable of a clinical trial (registered on ClinicalTrials.gov; NCT05715580) aimed at improving compliance with healthy habits in kidney transplant recipients in the Community of Madrid, Spain. The method used in its development has been useful and agile, and the result is a guide that can be easily updated periodically following the same procedure.

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KEYWORDS

compliance; Delphi method; guideline; kidney transplantation; patient adherence; patients

Introduction

Overview

Kidney transplantation is the treatment of choice for most cases of end-stage renal disease because this therapy brings better quality of life and prolonged survival. Also, in the long run, it is less expensive compared to dialysis [1-3].

In Spain, the number of kidney transplants has gone up over the past few years, from 52 transplants per million inhabitants back in 2011 to 62.3 transplants per million inhabitants in 2021 [4].

Importance of Adherence to Healthy Habits and Medication

When someone undergoes a kidney transplantation, they need to change a few habits [5]. This, added to compliance with the drug therapy prescribed, is the key to a successful transplantation procedure [6,7]. Also, to prevent possible side effects associated with immunosuppressant medication and improve the results of transplantation, the patient needs to develop healthy habits [8-14].

According to the kidney transplantation protocol, health care providers should have the necessary tools to provide scientific evidence–based, updated, and quality information to implement measures to help patients with kidney transplantation improve their health-promoting lifestyles after the transplant [15]. This should result in longer survival rates for the organ, fewer complications, and lower health costs.

Promoting healthy habits should be encouraged by health professionals involved in patient care on a routine, daily basis since they can have an impact on the patients' decision-making process in this setting [16,17].

Relevance of Evidence and Consensus in Clinical Practice

The aim of developing this information guide for adult kidney transplant recipients is to increase compliance with healthy habits by harmonizing best practices, which are associated with better outcomes for both the organ and the recipient [18]. This guideline will provide the necessary information regarding self-care. Therefore, patients will be able to manage their own health-disease process and reduce the level of concern as they acquire knowledge on the entire transplantation process.

Also, this information guideline for adults with kidney transplantation will unify criteria regarding the scientific evidence–based information that should be given. Therefore, nurses from the kidney transplantation unit will be able to use this guideline to manage the information that should eventually be given to adult patients with kidney transplants by standardizing practice by espousing structured care and doing so in plain language.

Contribution

The aim of this study was to develop a consensus document providing information for adults with kidney transplants, and this paper aims to present the elaboration process, which we believe has been appropriate and yielded robust results. The secondary objectives were (1) to describe the habits that have an impact on the proper functioning of the transplanted kidney and, therefore, on the survival of the latter, and (2) to identify the most relevant evidence regarding self-care for patients with kidney transplantation. The effect of the developed guideline is being evaluated in a large clinical trial (registered on ClinicalTrials.gov; NCT05715580) titled "Impact of Nursing Intervention on Adherence in Kidney Transplant Recipients."

Methods

Overview

We used a 3-step sequential methodologic approach, as explained in this paper. It is worth mentioning that the development of this guide is part of a much broader research project whose objective is to evaluate the educational process using the information guide as the main tool. This is a clinical trial intended to increase the compliance of the adult population with kidney transplantation with drugs and healthy habits through an informative intervention implemented by the nursing team from the Community of Madrid Kidney Transplantation Unit in Spain. It is expected that by increasing compliance, clinical parameters indicative of poor renal function will improve as well.

First Step: Training From a Group of Experts—Consensus and Item Decision-Making

In the first place, to develop the information provided by the guideline, a group of experts were asked to provide the topics they thought should be included to give adequate and complete information to adults with kidney transplantation.

To select the group of experts, the lead investigator contacted the nurses from 5 different specific kidney transplantation units that are currently operative in the public hospital system of the Community of Madrid, Spain.

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During this first contact, nurses were asked to give their consent to receive information on the project, giving them the possibility to participate in such a project.

After obtaining their permission, they were sent an email including an invitation explaining how to participate in the project, information on its objectives, different phases, what their contribution would be, and the informed consent form to participate in it. To select the items that should be included in the guideline, a web-based open first round of questions was sent through email to all participants with all the items they thought should be included in the guideline.

Afterwards, a web-based survey was created that was later developed by the research team from January to April 2022, including two parts: (1) questions on the social and demographic data of the participants; and (2) questions on the content of the guideline; these questions were answered in step 3 of the process, once the bibliographical review that was the basis of the guide had been made.

Second Step: Bibliographic Search

A review of the available medical literature was conducted to define the items that should be included in the information guideline for adults with kidney transplants. Through this review, the most relevant elements that should be taken into consideration regarding proper self-care practices in adults with kidney transplants were identified. Also, the most influential elements affecting the survival of the organ were identified. In addition, the compliance of patients with healthy habits was also assessed, as were the elements that might affect it.

The search was conducted in 3 different electronic databases: Medline/PubMed, Web of Science, and CUIDEN, from January 1, 2012, to December 31, 2022.

Search algorithms were based on the Population, Intervention, Comparator, Outcomes (PICO) strategy (population: adults with kidney transplants; intervention: any intervention aimed at promoting compliance with healthy lifestyles; comparator: no intervention or a different intervention; and outcomes: change in compliance with healthy lifestyles) [19] by selecting keywords using medical subject headings (MeSH) terminology [20]. The key terms used were “kidney transplant* / renal transplant*” and “lifestyle” plus “intervention” and “compliance.” Search strategies were adapted to databases by using different Boolean operators. Search was restricted to reports and manuscripts published over the past 10 years in such a way that all relevant studies that were not obsolete could be retrieved. The eligibility criteria were primary research studies written in any language and describing nonpharmacological interventions to improve compliance in adults with kidney transplants, and the lifestyles proposed by the medical literature. Only clinical trials were considered since only the effects of interventions were sought. No restrictions were put on the study duration or size of the sample. Reference lists of the included publications were also screened to identify additional articles. Reading and data mining were both conducted by 2 independent authors. Dissenting opinions were resolved through consensus.

Afterwards, based on the information provided by the group of experts and the information found in the bibliographic search, the information guideline for adults with kidney transplantation draft version 1 was created. Then, it was emailed to the panel of experts with a web-based survey.

Third Step: Delphi Process With On-Site Phase

In the third step, a consensus group was created using the Delphi technique, followed by an on-site phase. The Delphi technique was based on the following 4 fundamental pillars [21]:

- An iterative process in which experts gave their opinion more than once was created. This gave them the opportunity to reflect on the opinions given based on the proposals made by others.
- Controlled feedback was given after each round, which allowed the free circulation of information inside the group, thus establishing a common language.
- Anonymity was kept during the first round and across the web-based survey, in the sense that none of the group members knew who had given a particular answer. However, and this is why the Delphi modified technique was used [22], this was not possible during the on-site discussion that, nonetheless, brought agility to the consensus process. We consider that this option, the face-to-face discussion, which represents a modification of the Delphi technique, has contributed to fostering the discussion and refining the subtleties of the responses. Textbox 1 depicts the characteristics involved in this modified Delphi technique.
- Finally, a globally calculated answer of the group was given, in which the individual results were included.

Textbox 1. Characteristics of the modified Delphi technique. Modified from Humphrey-Murto et al [22].

1. Email questionnaires
2. Collect decisions anonymously
3. Obtain formal feedback as group ratings
4. Carry out face-to-face interactions
5. Carry out structured interactions

Therefore, to proceed with the modified Delphi technique, the items of the questionnaire—which was web-based—were elaborated to later move on to an on-site discussion.

The following questions were asked across the survey to assess each section of the guideline:

- Do you think that the topics of discussion in this section are appropriate? With a dichotomous response of yes or no,

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if the answer is negative, a box opens immediately with the following question: What would you add or suppress?
- Do you think that the message transmitted with the content of this section is appropriate? With a dichotomous response of yes or no, if the answer is negative, a box opens immediately with the following question: What would you change?
- Do you think it is long enough? With three response options: (1) yes; (2) no, it is too short; and (3) no, it is too long. If the answer is negative, a box opens immediately with the following question: What would you add or suppress?
- Do you think that the information provided is appropriate? With three different response options: (1) yes; (2) no, I think some information is missing; and (3) no, I think there is too much information. If the answer is negative, a box opens immediately with the following question: What would you change in the information provided?
- Do you think that the information provided is up-to-date? With a dichotomous response of yes or no, if the answer is negative, a box opens immediately with the following question: What part would you say is outdated? Please, if possible, provide current references.
- Rank from 0 to 4 the relevance of the information provided, with 0 being irrelevant and 4 being positively relevant.

The survey included a total of 105 questions. Given the limited number of participant experts, consensus was only achieved on items on which 4 of 5 respondents (80%) agreed, with mean scores >3.5 out of 4 possible points regarding the relevance of the information provided in each section.

In a third communication with respondents, the information guideline on adults with kidney transplantation draft version 1 was submitted, including a link to a web-based survey.

Finally, after the review that followed the web-based survey, the information guideline draft version 2 was created, followed by an on-site meeting with the group of experts.

On-Site Discussion

Participants were summoned to an on-site meeting that was held at Hospital Clínico San Carlos de Madrid, Madrid, Spain, in October 2022. A total of 5 experts attended the meeting.

A semistructured interview was held at that meeting, where the lead investigator acted as the moderator to discuss topics on which no agreement had been reached. At the end, some time was given to express all comments, suggestions, and doubts deemed necessary by the experts.

After all these steps and their corresponding changes to the information provided, the guideline was edited by inserting images to make it more pleasing and enjoyable for the reader.

The final draft of the guideline was submitted, seeking the approval of the Madrid Health Authority Technical Coordination Commission. A positive report on the guideline was given by this commission.

Ethical Considerations

Study participation was voluntary, and participants were given the option to withdraw their consent and walk away from the study at any time without any repercussions.

The project was conducted in full compliance with the latest iteration of the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice Guideline (ICH GCP).

All personal data were tagged with a single code. Only the investigator was authorized to associate data with each participant. The lead investigator is responsible for guarding this information in a confidential way as long as legally required and in full compliance with the Spanish legislation: Organic Law 3/2018, of December 5, Protection of Personal Data and Guarantee of Digital Rights (LOPDGDD), and European legislation regarding data protection: Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation).

This project was submitted to the Hospital Clínico San Carlos Research Ethics Committee as part of the clinical trial project to assess the impact of a nursing intervention on compliance with medication and healthy habits in adult patients with kidney transplantation (22/325-EC_X).

Results

The mean age of the 5 participant nurses was 52.2 (SD 9.7) years, and 80% (4/5) were women with a median of time working as a nurse, at the nephrology unit, and at the kidney transplantation unit of 27 (IQR 19.5-30) years, 21 (IQR 7-24) years, and 3 (IQR 2.5-7.5) years, respectively.

Regarding training, 60% (3/5) were graduates or undergraduates, while 20% (2/5) were holders of a master's degree in nephrology. They all had previously received specific training on kidney transplantation through continuing medical education courses.

In the first round, when an email was sent with an open question to elicit topics of interest that should be included in the information guideline on adults with kidney transplantation, 3 of the 5 nurses involved sent the information they were giving adults with kidney transplantation from their offices, while the remaining 2 responded to the open question with topics of discussion interesting to them and consistent with the information provided by the rest of the group.

After grouping the information provided by the group of experts and the information found in the medical literature available, the information guideline on adults with kidney transplantation draft version 1 was created, including 10 different sections or topics of discussion (Textbox 2).

Through the web-based survey, consensus data shown in Table 1 with all the questions from each section were obtained.

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Textbox 2. Information guideline for adults with kidney transplantation draft version 1.

Table of contents

1. Introduction: What does a kidney transplantation actually mean?
2. Drug therapy. Immunosuppressant drugs.
3. Recommendations and care
    - Hygiene and skin care
    - Food and diet
    - Active way of life and exercise
    - Transplant-related safety
        - Home
        - Pets
        - Gardening
4. Emotional status
5. Sexuality
6. Travels
7. Frequently asked question
8. In conclusion: recommendation and overall pieces of advice
9. Emergency. Reason for going to the hospital.
10. References

Table 1. Consensus measures reached after completing the web-based survey for each of the sections included in the information guideline for adults with kidney transplants (N=5).

Section	Distribution of scores for relevance of the information[a]						Consensus reached, %	Draft version 2 was changed
	0, %	1, %	2, %	3, %	4, %	Mean (SD)		
Title	N/A[b]	N/A	N/A	N/A	N/A	N/A	100	No
Introduction	0	0	0	20	80	3.8 (0.4)	80	No
Drug therapy	0	0	0	20	80	3.8 (0.4)	60	Yes, with sections pending the on-site meeting
Recommendations and care: hygiene and skin care	20	0	0	0	80	3.4 (1.34)	80	Yes, with sections pending the on-site meeting
Recommendations and care: Food and diet	0	0	20	0	80	3.6 (0.9)	60	Yes
Recommendations and care: Active way of life and exercise	0	0	20	20	60	3.4 (0.9)	80	Yes, with sections pending the on-site meeting
Recommendations and care: Transplant-related safety	0	0	20	0	80	3.6 (0.9)	80	No
Emotional status	0	0	0	20	80	3.8 (0.4)	100	No
Sexuality	0	20	0	20	60	3.2 (1.3)	80	Yes
Travels	0	0	20	0	80	3.6 (0.9)	80	No
Frequently asked questions	0	0	20	0	80	3.6 (0.9)	80	No
In conclusion	0	0	20	20	60	3.4 (0.9)	80	No
Emergency	0	0	20	20	60	3.4 (0.9)	60	Yes, with sections pending the on-site meeting
References	N/A	N/A	N/A	N/A	N/A	N/A	60	Yes, with sections pending the on-site meeting

[a]Assessed using a Likert scale, with 0=not relevant at all and 4=completely relevant.

[b]N/A: not applicable.

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After reviewing the feedback received from the participants through the web-based survey, the contents of the sections on which consensus was reached regarding modifications were eventually updated. The format of the table of contents proposed in draft version 1 was kept and gave way to the information guideline for adults with kidney transplantation draft version 2. Sections on which experts did not agree with the information provided and no consensus was reached on what should be changed were proposed as topics of discussion during the on-site meeting and left for future change (Table 1).

Draft version 2 was discussed in the on-site meeting. After this meeting, the contents were updated once again. Draft version 3 is still pending. However, it will include the index that has not been modified and that coincides with Textbox 1 and all the content approved by consensus from the panel of experts.

After all these steps, it was decided to edit the guideline. Also, to achieve a more visually appealing guideline for the reader, original images created for this purpose were added by the author, who provided them for free.

Discussion

Overview

Health training and education are 2 of the nursing competencies most present in the entire health care process, as are prevention and the promotion of self-care at the base of these processes [23].

The beginning and development of this project took place for 2 main reasons. On the one hand, it was a response to the doubts and questions posed by health care personnel regarding compliance with healthy habits in adult patients with kidney transplants. On the other hand, it was born as a response to a growing demand for information from users who, thanks to patient-centered care and individual empowerment to improve one's own health, have become more self-aware of the entire health-disease process.

As a reflection, this methodology for the creation of an effective guideline—agreed and based on the best evidence available—has been agile, useful, and allowed periodic updates with limited effort.

The usefulness of this guide will be evaluated in the clinical trial (ClinicalTrial.gov; NCT05715580), whose goal is to analyze the impact of an informative nursing intervention on adherence to drug treatment and a healthy lifestyle in patients with kidney transplants and the effect of poor adherence on clinical predictors of poor kidney function.

It seems evident that, beyond the imprint left by each health professional in his or her respective office or unit, having common tools and resources available promotes the development of similar health care strategies within a standardized system of health care provision.

Limitations

One of the limitations in this study was the small group of experts that, although it included all nurses from the kidney transplantation units of the public network of the Community of Madrid, did not take into consideration other professional profiles. Also, given the method used to collect the experts, it was impossible to maintain the anonymity of the group.

On the other hand, a small group was good for obtaining the involvement and cooperation of participants during the entire process—something that was confirmed by the lack of withdrawals—which is typical of this kind of methodology.

Additionally, it is possible that the participants, as experts, only confirmed the relevance of the topics instead of considering all possible issues to address. This could potentially lead to confirmation bias, which could have been mitigated by involving patients or patient associations in the guide development process.

Finally, in the case of the responses requested from the group of experts in the survey, they may be biased by the "framing effect," whereby the formulation, structure, and presentation of the questions could lead to changes in opinion or bias the response. This is a factor that needs to be taken into consideration [24].

Conclusions

Thanks to the methodology used in this research, we managed to describe the habits that, based on the medical literature available and the opinion of experts, have played a key role in the good functioning of transplanted kidneys, thus impacting the survival of both the organ and the recipient.

Therefore, in the information guideline for adults with kidney transplants created as a result of this project, self-care practices identified as necessary and relevant to guarantee the success of transplantation were included.

Although other informative documents already existed for adults with kidney transplantation, the creation of this guideline allowed us to structure the necessary health care, thus generating a single document with all the necessary information and recommendations for patients to implement self-care measures effectively.

Therefore, a useful, easy-to-understand tool for health professionals in the field of kidney transplantation was created using simple language and with the latest scientific evidence available to date.

We hope this new tool will make the work of health professionals involved in kidney transplantations easier. At the same time, we hope it improves the quality of life of adult patients with kidney transplants as well as the quality of care they perceive.

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Data Availability

The data sets generated during and/or analyzed during this work are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

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Abbreviations

ICH GCP: International Conference on Harmonization Good Clinical Practice
LOPDGDD: Organic Law on Protection of Personal Data and Guarantee of Digital Rights
MeSH: medical subject heading
PICO: Population, Intervention, Comparator, Outcomes

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Protocol

Understanding Whether and How a Digital Health Intervention Improves Transition Care for Emerging Adults Living With Type 1 Diabetes: Protocol for a Mixed Methods Realist Evaluation

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Abstract

Background: Emerging adults living with type 1 diabetes (T1D) face a series of challenges with self-management and decreased health system engagement, leading to an increased risk of acute complications and hospital admissions. Effective and scalable strategies are needed to support this population to transfer seamlessly from pediatric to adult care with sufficient self-management capability. While digital health interventions for T1D self-management are a promising strategy, it remains unclear which elements work, how, and for which groups of individuals.

Objective: This study aims to evaluate the design and implementation of a multicomponent SMS text message–based digital health intervention to support emerging adults living with T1D in real-world settings. The objectives are to identify the intervention components and associated mechanisms that support user engagement and T1D health care transition experiences and determine the individual characteristics that influence the implementation process.

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Methods: We used a realist evaluation embedded alongside a randomized controlled trial, which uses a sequential mixed methods design to analyze data from multiple sources, including intervention usage data, patient-reported outcomes, and realist interviews. In step 1, we conducted a document analysis to develop a program theory that outlines the hypothesized relationships among "individual-level contextual factors, intervention components and features, mechanisms, and outcomes," with special attention paid to user engagement. Among them, intervention components and features depict 10 core characteristics such as transition support information, problem-solving information, and real-time interactivity. The proximal outcomes of interest include user engagement, self-efficacy, and negative emotions, whereas the distal outcomes of interest include transition readiness, self-blood glucose monitoring behaviors, and blood glucose. In step 2, we plan to conduct semistructured realist interviews with the randomized controlled trial's intervention-arm participants to test the hypothesized "context-intervention-mechanism-outcome" configurations. In step 3, we plan to triangulate all sources of data using a coincidence analysis to identify the necessary combinations of factors that determine whether and how the desired outcomes are achieved and use these insights to consolidate the program theory.

Results: For step 1 analysis, we have developed the initial program theory and the corresponding data collection plan. For step 2 analysis, participant enrollment for the randomized controlled trial started in January 2023. Participant enrollment for this realist evaluation was anticipated to start in July 2023 and continue until we reached thematic saturation or achieved informational power.

Conclusions: Beyond contributing to knowledge on the multiple pathways that lead to successful engagement with a digital health intervention as well as target outcomes in T1D care transitions, embedding the realist evaluation alongside the trial may inform real-time intervention refinement to improve user engagement and transition experiences. The knowledge gained from this study may inform the design, implementation, and evaluation of future digital health interventions that aim to improve transition experiences.

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KEYWORDS

digital health; emerging adults; realist evaluation; self-management; transition to adult care; type 1 diabetes

Introduction

Type 1 diabetes (T1D) is a common chronic condition that affects 9 million people globally [1], including over 650,000 children (aged 0-14 years) and 560,000 teenagers (aged 15-19 years) [2]. T1D management requires knowledge, skills, and motivation to perform daily self-management as well as routine health care management and monitoring throughout the lifespan [3-5]. A total of 42% of individuals with T1D onset during childhood often experience deterioration in glycemic management, which confers an increased risk of chronic complications and acute diabetes complications such as life-threatening ketoacidosis during adolescence and early adulthood [1,6]. Effective health care management and a smooth transition from pediatric to adult care can help mitigate this risk [5,7,8]. Unfortunately, the transition period is fraught with challenges in part because it coincides with emerging adulthood, when individuals are facing a series of changes in their independence and responsibilities for disease management [9]. Current estimates suggest that over 20% of emerging adults experience a gap of over 6 months between pediatric and adult care medical visits during transition [10,11]. Effective transition support must attend to medical, psychological, educational, and vocational needs in order to support sufficient self-management skills [12-14]. Failure to address these needs may lead to adverse health outcomes [14], decreased health system engagement [10], and increased hospital admissions [15].

Strategies to improve the transition process have been implemented at the patient, provider, and service levels [16,17], but are often institution-specific or resource-intensive, thereby limiting their accessibility, scalability, and generalizability [18-20]. Digital health interventions are increasingly used to address these limitations while also leveraging the high prevalence of smartphone use among youth [21]. The hypothesized benefits are also compelling, including the flexibility to access and exchange information instantly, irrespective of geographic constraints, at low cost, and the potential to provide more personalized support [22]. Digital health T1D management interventions, through mobile apps [23-25], websites [26], and text messages, emails, or telephone calls [25,27-29], have become increasingly common [23-29] and acceptable [23,26,27] to young adults, with demonstrated impacts on clinic attendance [28] and glycemic control [29]. A recent paper by Cafazzo et al [23] piloting a T1D management mobile app in adolescents found 88% of participants were satisfied with the app. Moreover, they found a significant increase in the frequency of blood glucose measurement among their participant sample. In a pragmatic clinical trial, Butalia et al [28] observed significantly greater outpatient appointment attendance in transitioning youth living with T1D who received a communication technology-based (SMS text message, email, or telephone) transition coordinator intervention as compared to those who received care as usual. Also, through a crossover trial with adolescents, Rami et al [29] found SMS text messaging-based telemedical support feasible and helpful in improving hemoglobin A_{1c} (HbA_{1c}).

However, potential impact can be undermined by the often-reported rapid drop in intervention engagement, which occurs sometime between 2 weeks and 6 months after initial use [30,31]. Among adolescents living with T1D exposed to a

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mobile self-management tool, 1 study reported that only 35% of participants were either moderately or highly engaged over the 12-month intervention [24]. Despite this well-known risk, comparatively little is known about how to overcome this common challenge. Relatedly, many multicomponent digital health interventions report aggregate effects [27-29], limiting our ability to understand which elements contribute to achieving the distinct but related goals of ensuring sustained intervention engagement while also effectively addressing the known barriers to desired outcomes.

Realist evaluation, a theory-driven evaluation framework [32], seeks to unpack the black box of interventions by establishing the causal links between intervention resources and associated outcomes while identifying the circumstances needed to facilitate the change in a Context-Mechanism-Outcome (CMO) framework [33-36]. Given the complex and context-specific nature of health interventions [37], they have been increasingly adopted in the health field [34,38-40] to solve the question of what works, for whom, and in what circumstances [41-43].

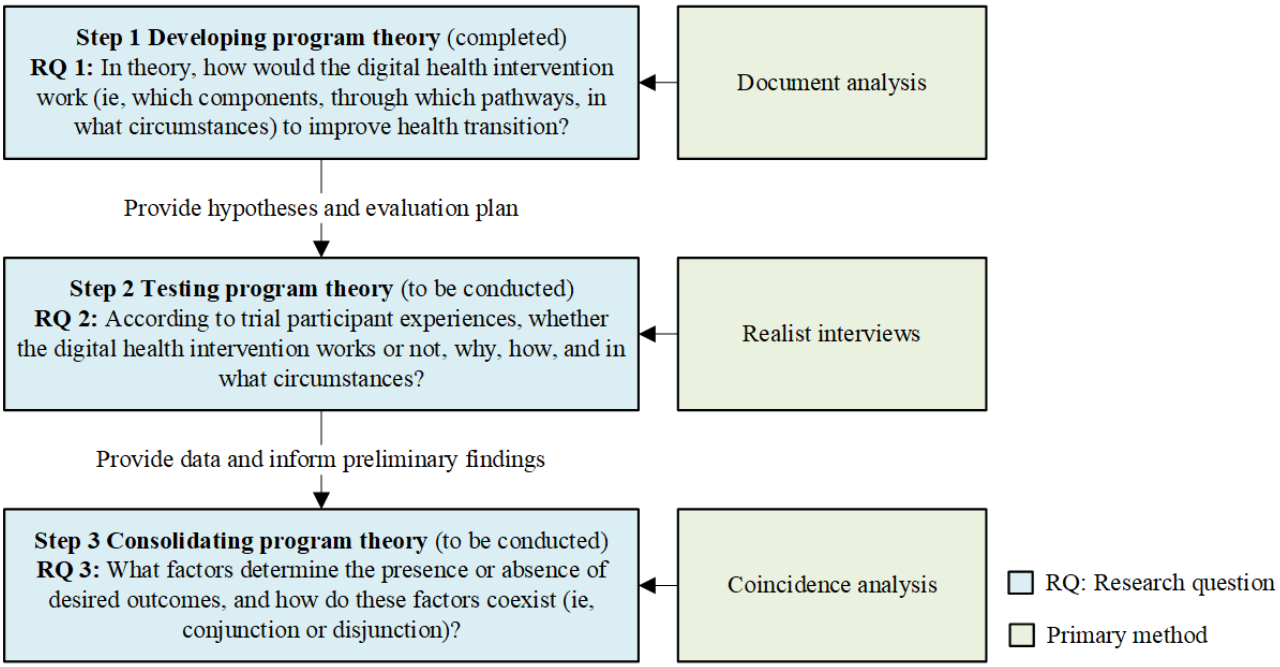
By acknowledging the potential of realist evaluation in addressing the abovementioned knowledge gaps, we have developed a protocol for a sequential mixed methods realist evaluation embedded alongside a randomized controlled trial (RCT) evaluating the effect of a digital health intervention on the transition experiences of emerging adults living with T1D. Using a realist evaluation framework, the specific objectives of the embedded realist evaluation will be to (1) develop and test the intervention program theory that identifies what elements of the intervention contribute to successful engagement and improve transition experiences, how they do it, and for which groups of individuals; and (2) consolidate the intervention program theory by identifying the crucial combinations of factors that are minimally sufficient for an effective implementation of the digital health intervention and their coexistent causal pathways.

Methods

Study Design

Following Mirzoev et al [40], we plan to conduct this embedded realist evaluation in 3 steps (Figure 1), which include developing (step 1; completed), testing (step 2; to be conducted), and consolidating the program theory (step 3; to be conducted).

Figure 1. Study design and methods.



As a theory-based evaluation and in line with best practices [32,44], this study is guided by a program theory outlining the hypothesized mechanisms through which the digital health intervention is expected to work and the corresponding context, with specific attention paid to user engagement (step 1). We have added an explanatory factor "intervention" (I) to the conventional "context-mechanism-outcome" (CMO) framework [45] following Breton et al [46] and Shams et al [47] to disaggregate the 2 major components of mechanisms (M) in the conventional CMO framework (ie, intervention resources and recipients' reasoning) [36]. This will enable us to specify which elements of this multicomponent intervention contribute to the desired outcomes and how they are influenced by context [44]. Specifically, we have developed the initial program theory in the framework of "context-intervention-mechanism-outcome" (CIMO) to understand for individuals with which contextual characteristics (C), which intervention components and features (I), trigger what mechanisms (M), and therefore yield what target outcomes (O). This initial program theory informs the following data collection and analysis [39].

Since realist evaluation is method neutral [48], this study uses mixed methods and integrates multisource data to test and consolidate the program theory. In step 2, we plan to conduct semistructured realist interviews with participants in the RCT intervention arm in a "teacher-learner cycle" [49]. The interviews will aim to test each of the hypothesized CIMO

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configurations by exploring individual perspectives and experiences using "Keeping in Touch" (KiT), including how participants interact with KiT and under what circumstances it facilitates (or fails to facilitate) mechanisms that lead to engagement and improved transition experiences.

Multicomponent interventions often achieve desired outcomes through distinct combinations of factors that interact to produce the outcome, as well as through multiple mechanisms [38]. For instance, the combination of a high level of positive outcome expectancies (ie, belief about the consequence of performing a specific behavior) and a high level of self-efficacy (ie, confidence about the ability to perform a specific behavior) may lead to improved diabetes self-care [50,51], whereas the combination of a high level of outcome expectancies and a low level of self-efficacy may lead to poorer diabetes self-care [51]. This highlights the need to identify difference-making factors as well as the settings in which they make a difference. Coincidence analysis (CNA) is a novel configurational approach underpinned by Boolean algebra to identify the crucial difference-making conditions, which include combinations of factors (including contextual factors and intervention components) necessary to achieve target outcomes and the causal pathways (mechanisms) that lead to positive effects [52]. Therefore, in step 3, we will leverage intervention usage data, patient-reported outcomes, and interview data and perform CNA to gain such an in-depth understanding, according to which we will consolidate the program theory.

Step 1: Developing Program Theory

Document Analysis

We conducted a document analysis to develop the program theory using 2 data sources. First, we reviewed the program documentation, including the intervention design documents, RCT protocol, and data collection materials, to identify its intervention components, extract the corresponding features, understand the assumptions of the designers on how this multicomponent digital health intervention would lead to desired outcomes, and select the corresponding outcome indicators. Second, we reviewed published research articles on behavioral science theories, with special attention paid to digital behavior change interventions (DBCIs) and chronic disease self-management. The objective for reviewing pre-existing theories was twofold: (1) to inform the coding of intervention features, determine the key mechanisms, and identify the individual characteristics that may influence the implementation process; and (2) to select appropriate preexisting conceptual frameworks to inform the development of CIMO configurations, that is, build causal relationships among the constructs [53]. We focused on microlevel theories according to the study objective, that is, to understand the implementation process of a digital health intervention among individuals.

Intervention Components and Features

The KiT intervention [20] was developed using a user-centered design approach that engaged adolescents and emerging adults living with T1D as well as adult and pediatric diabetes providers. Specific intervention content was informed by clinician consultation and an environmental scan of diabetes transition resources mapped to domains of the "readiness of emerging adults with diabetes diagnosed in youth" (READDY) tool with the aim of improving the transition experiences among emerging adults living with T1D (Textbox 1). In addition to providing care coordination support (eg, appointment note-keeping and reminders), KiT is designed to provide personalized T1D informational support (eg, educational content and a question and answer feature) based on an individual's interests and self-reported confidence about their diabetes knowledge and skills using a set of "if-then" rules (Multimedia Appendix 1).

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Textbox 1. Brief description of the digital intervention.

Intervention name: Keeping in Touch (KiT)

Delivery method: SMS chatbot

Study population: Emerging adults living with type 1 diabetes (T1D) residing in Ontario or Quebec who are within 4 months of their planned transfer to adult care

Intervention length: 12 months

Intervention development methods: Based on user-centered design approaches (detailed information can be found [54])

Intervention components:

- Informational content (one topic per month):
  - Topics received by all users: 4 topics provided to all participants at months 1, 4, 7, and 10 respectively. Topics include coping with T1D, care navigation, sick day and ketone management, medical insurance and financial support.
  - Topics based on user needs and interests: 8 topics from a pool of 10 candidate topics provided at the rest of 8 months. Topics are determined by the participant's baseline transition readiness status (self-reported confidence about diabetes knowledge and skills measured by the "readiness of emerging adults with diabetes diagnosed in youth" READDY tool) and their interests. Topics include hypoglycemia, pumps and pump programming, insulin adjustments, drugs and alcohol, travel, driving, school and work accommodations, exercise, nutrition and carbohydrates, and sexual health.
- **Question and Answer**: KiT recognizes key words in participants' T1D-related questions and automatically pulls resources from the KiT database to answer their question. Interaction with participants by periodically asking for feedback 5 minutes after providing question and answer responses.
- **Transition care coordination:**
  - Reminder: KiT sends reminders for participants to book appointments and requests them to input their appointment information in the chatbot. KiT then sends appointment and bloodwork or urine test reminders at the participant's preferred times.
  - Note-keeping: KiT allows participants to save a list of items to discuss in their appointments, which is sent back to them 1 hour before their scheduled appointments.
  - Care coordination support: KiT sends prompts to help participants prepare for appointments and reflect on their care experiences.
  - Clinic information: KiT sends information on the adult clinic that the participant will be attending, for clinics included within the chatbot database.

We have identified intervention components and features (Table 1). By performing deductive coding according to existing literature, we extracted several common components and features of DBCIs, including personalization [55,56], problem-solving support [57-59], reminders [55], real-time interactivity [55,60], credible sources [57], user-friendly SMS text message tone [55], and diverse forms of information (enhanced media) [56]. We classified the remaining KiT components (eg, coping with T1D and care navigation) through inductive coding.

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Table 1. Keeping in Touch (KiT) intervention components and features.

Intervention strategy and content	Timeline (month)	Component or feature
Informational content		
Topics received by all users		
Coping with T1D	1	• Stress management strategies[a]
Care navigation	4	• Transition support information[a]
Sick day and ketone management	7	• T1D self-management information and suggestions[a]
Medical insurance and financial support	10	• T1D self-management information and suggestions[a]
Topics based on user needs and interests (selected by baseline readiness status and personal preferences [once every 3 months])		
Hypoglycemia	2, 3, 5, 6, 8, 9, 11, 12	• T1D self-management information and suggestions[a] • Personalization[b] [55,56]
Pumps and pump programming	2, 3, 5, 6, 8, 9, 11, 12	• T1D self-management information and suggestions[a]
Insulin adjustments	2, 3, 5, 6, 8, 9, 11, 12	• Personalization[b] [55,56]
Drugs and alcohol	2, 3, 5, 6, 8, 9, 11, 12	• T1D self-management information and suggestions[a]
Travel	2, 3, 5, 6, 8, 9, 11, 12	• Personalization[b] [55,56]
Driving	2, 3, 5, 6, 8, 9, 11, 12	• T1D self-management information and suggestions[a]
School and work accommodations	2, 3, 5, 6, 8, 9, 11, 12	• Personalizationb [55,56]
Exercise	2, 3, 5, 6, 8, 9, 11, 12	• T1D self-management information and suggestions[a]
Nutrition and carbohydrates	2, 3, 5, 6, 8, 9, 11, 12	• Personalization[b] [55,56]
Sexual health	2, 3, 5, 6, 8, 9, 11, 12	• T1D self-management information and suggestions[a]
Question and answer		
T1D self-management knowledge chatbot	1-12	• T1D self-management information and suggestions[a] • Problem-solving support[a] [57-59] • Real-time interactivity[b] [55,60]
Transition care coordination		
Reminders	1-12	• Transition reminders[a] [55]
Note-keeping	1-12	
Care coordination support	1-12	• Transition support informationa • Personalization[b] [55,56]

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Intervention strategy and content	Timeline (month)	Component or feature
Clinic information	1-12	• Transition support information[a] • Personalization[b] [55,56]
Message content		
Information topics and resources were selected based on credibility	—[c]	• Credible sources[b] [57]
Young-adult friendly educational text messages	—	• User-friendly message tone[b] [55]
Message format		
Educational information in forms including but not limited to text, graphics, images, and videos	—	• Diverse forms of information (enhanced media)[b] [56]
Settings		
Frequency of receiving education content	—	• Personalization[b] [55,56]
Time of receiving messages	—	• Personalization[b] [55,56]
Times of receiving appointment reminders	—	• Personalization[b] [55,56]
Option to take a break from educational messages for 2 weeks (maximum 2 times throughout the intervention)	—	• Personalization[a] [55,56]

[a]Intervention component.

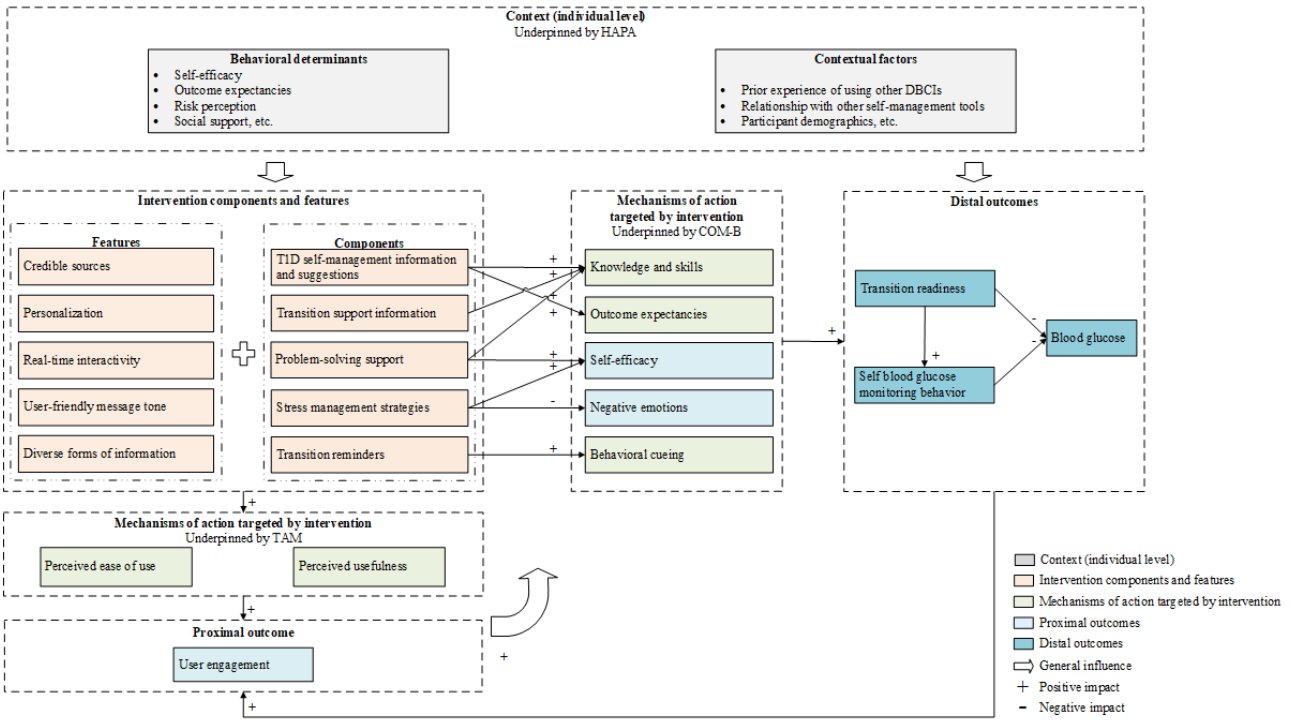
[b]Intervention feature.

[c]Not available.

Initial Program Theory

We have developed the initial program theory (Figure 2) by integrating 3 empirically validated individual-level behavioral change theories, including "capability, opportunity, motivation, and behavior" (COM-B) [61], "health action process approach" (HAPA) [62], and "technology acceptance model" (TAM) [63].

Figure 2. Initial program theory of the Keeping in Touch (KiT) intervention. COM-B: capability, opportunity, motivation, and behavior; DBCI: digital behavior change interventions; HAPA: health action process approach; T1D: type 1 diabetes; TAM: technology acceptance model.



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Informed by COM-B [61], we hypothesize that KiT may improve participants' transition outcomes (ie, transition readiness, self-management behavior, and health outcomes) by triggering changes in individual motivation (ie, self-efficacy, negative emotions, outcome expectancies, behavioral cueing) and capability (ie, knowledge, skills). T1D self-management information and suggestions, transition support information, and problem-solving support may increase participants' T1D and transition-related knowledge and skills [64], and therefore, capability [61]. T1D self-management information and suggestions [65] and problem-solving support [59] may improve one's outcome expectancies and self-efficacy, respectively, which are the key motivational factors of an individual's behavioral change [66]. One's self-efficacy may also be improved by receiving stress management strategies [67]. Meanwhile, stress management strategies may lead to reduced negative emotions [58,67], which have been recognized as one of the most prominent motivational challenges to a successful T1D health care transition [14,68]. Transition reminders may function as behavior cueing to plan for and attend clinic appointments [69]. Well-designed intervention functions, such as personalization, credible sources, and diverse forms of information, may amplify the impact of KiT's intervention content.

The extent to which KiT can trigger changes in health care transition capability and motivation is hypothesized to be dependent on the level of user engagement [38,55,70,71]. Positive intervention outcomes (eg, improved transition readiness) may in turn incentivize increased user engagement [55], suggesting a positive feedback loop. According to TAM [63], user engagement is influenced by 2 core factors, that is, perceived usefulness and perceived ease of use [72], which may be influenced by intervention content and technological functions [73].

Intervention effectiveness depends heavily on the interaction of the intervention with users and their context [55], yet there is a paucity of contextual insights in the DBCI literature, creating a gap in our understanding of which contextual factors influence the efficacy of intervention mechanisms in T1D and how [74]. According to the HAPA framework [62], behavioral determinants, such as self-efficacy [75], outcome expectancies [66,75], risk perception [65,76], and social support [66,77], impact both outcome and the intervention implementation process itself. Contextual factors, such as the complementary or substitute relationships between KiT and other conventional self-management tools (eg, handwritten methods) [38], may also predict user engagement alongside more traditional variables (ie, participant demographics [55,70]).

Step 2: Testing Program Theory

Participants

Eligible participants will include English- or French-speaking emerging adults living with T1D enrolled in the RCT intervention arm who provided informed consent to be contacted for the embedded process evaluation at the time of enrollment in the RCT. We are targeting a conservative sample size of 25-30 participants for the interviews based on previous realist interviews and CNA studies [38,42,78,79].

To increase the representativeness of the interview sample, we will purposively select participants with desired and undesired proximal outcomes of user engagement. This will be achieved by identifying "high-engagers" and "low- to medium-engagers" according to the intervention usage data at month 3 of the RCT. As there is no standard classification or threshold of DBCI engagement, we have used early KiT intervention usage data to identify a feasible definition of engagement. Considering the data availability, we conservatively define "high-engagers" as those with a 100% response rate to question prompts, with all other participants classified as "low- to medium-engagers." All low- to medium-engagers will be invited for an interview. Should resource constraints not allow us to interview all high engagers, we will purposively sample to balance representation by gender and site of recruitment. The iterative sampling will continue until we reach thematic saturation (ie, no new themes are identified in the multisource data analysis), or all interested participants have been interviewed.

Data Collection

To test the initial program theory developed in step 1, we will perform semistructured realist interviews in a "teacher-learner cycle" [49]. The interviews will start with some general questions about the participants' experiences managing T1D and engaging with KiT [80,81]. Based on their level of engagement and responses, the interviewer will act as a teacher to introduce the candidate CIMO configurations to the participant for their comments. After learning about the CIMO configurations, the participant will then act as teacher to confirm, extend, or refute the hypothesized pathways with their own examples of how they reacted to specific intervention components or features, what they saw as influencing their decision-making, and how this was perceived to affect their outcomes [80,82]. For low- to medium-engagers, the interview topics will focus on CIMO configurations regarding user engagement. For high engagers, the interview topics will focus on CIMO configurations regarding user engagement as well as distal outcomes (ie, transition readiness, self-blood glucose monitoring, and blood glucose). The interview guides (Multimedia Appendix 2) will first be piloted to ensure a comprehensive assessment of all relevant CIMO constructs. Interviews will be conducted by PhD-trained research coordinators with qualitative interview training, previous experience conducting semistructured interviews, and in-depth knowledge of the initial program theory. They will also receive study-specific training from the senior study lead, who is an experienced qualitative researcher. Research coordinators will have no previous relationship with study participants or the T1D community. Interviews will be transcribed verbatim by an independent third party.

Data Analysis

Transcripts will be coded using MAXQDA, a software for interview data analysis, and analyzed using the principles of thematic analysis strategies [82,83]. Data will be deductively coded and mapped to the predefined CIMO constructs to reflect triads (eg, context + intervention outcome, intervention mechanism outcome) and tetrads (context + intervention mechanism outcome) that would confirm, extend, or refute the

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current CIMO configurations [84]. Open coding will be applied when themes are identified that do not fit within the definitions of predefined CIMO constructs. The findings will be compared against the hypotheses developed in step 1, with a label of "supported," "refined," or "rejected" given to each hypothesized pathway based on the evidence.

Several strategies will ensure the fidelity and credibility of the interview data, such as using multiple sources of data; creating a chain of evidence that documents all elements of the study database; having both broader research team members and interview participants participate in the triangulation analysis and the return of findings (construct and external validity); examining points of convergence and divergence within and among the data set (internal validity through cross-comparative analyses); and having a stepped analysis process with an initial independent review of the data by 2 reviewers who then meet to reach consensus around the common themes.

Step 3: Consolidating Program Theory

Data Integration and Factor Calibration

We plan to triangulate information from realist interviews, intervention usage data, patient-reported outcomes, and a demographic survey as outlined in Table 2. Patient reported outcome and demographic information will be collected through RCT baseline and follow-up surveys. Intervention usage data will be collected by our third-party collaborator, Memotext, which delivers and manages the RCT intervention. Memotext's system logs all incoming and outgoing messages, and they will be sharing them with the research team periodically.

We will create a data set in which each interview participant is treated as a unique case and each CIMO element is included as a variable (as defined in the initial program theory outlined in Figure 2). Where variables are continuous (eg, self-efficacy, negative emotions, transition readiness, and blood glucose), we will include them directly. Where variables are qualitative (eg, knowledge and skills, outcome expectancies, behavioral cueing), we will convert them to data-driven categorical variables that will be defined by the research team and reported in the final manuscript.

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Table 2. Data collection plan for the realist evaluation (new variables may derive from the realist interviews).

Categories and construct	Data source	Measure	Time of measurement (months)
Context (individual level)			
Behavior determinants and contextual factors except demographics	Interview	Self-reported influences on behavior and engagement	Time of interview
Demographics	Demographic questionnaire	Gender, ethnicity, insurance type, etc.	0
Intervention components	Intervention usage data and interview	Number of messages sent by KiT chatbot and how the participant perceives each component	
T1D[a] self-management information and suggestions			2, 3, 5, 6
Stress management strategies			1
Transition support information			4
Problem-solving support			1, 2, 3, 4, 5, 6
Transition reminders			1, 2, 3, 4, 5, 6
Intervention features	Interview	How the participant perceives each feature	Time of interview
Credible sources			
Personalization			
Real-time interactivity			
User-friendly message tone			
Diverse forms of information			
Mechanisms of action targeted by intervention	Interview	Self-reported behavior changes and perceived impact on targeted mechanisms of action	Time of interview
Knowledge and skills			
Outcome expectancies			
Behavioral cueing			
Perceived ease of use			
Perceived usefulness			
Proximal outcomes			
User engagement[b]	Intervention usage data	Response rate to question prompts	1, 2, 3, 4, 5, 6
Self-efficacy[b] and negative emotions[b]	Patient-reported outcomes	SEDM[c] and BDA Stigma Subscale[d]	0, 6
Distal outcomes	Patient-reported outcomes		0, 6
Transition readiness		READDY[e]	
Blood glucose		Self-reported HbA_{1c}[f]	
Self-blood glucose monitoring		Sensor use and additional measures of glycemia for glucose sensor user: whether the participant has been using a sensor for over 70% of the time during the past 14 days at the time of the survey.	

[a]T1D: type 1 diabetes.

[b]Factors will be cross validated using interview data.

[c]Stanford Self-Efficacy for Diabetes Management.

[d]Barriers to Diabetes Adherence in Adolescence Questionnaire Stigma Subscale.

[e]Readiness of Emerging Adults With Diabetes Diagnosed in Youth.

[f]HbA_{1c}: hemoglobin A_{1c}.

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Data Analysis

We will conduct CNA using the R package "cna" to consolidate the initial program theory using a bottom-up, data-driven approach [85]. In order to identify the crucial difference-makers of outcomes from a large number of candidate-influencing factors (ie, context, intervention, and mechanism), we will screen the exogenous factors of each outcome before developing CNA models to demonstrate the causal relationships among them.

To achieve factor reduction, we will begin with exploratory data analysis using a routine that operates within the same regularity framework as CNA. Specifically, we will apply the "minimally sufficient condition" (msc) function in the "cna" package to search across the entire data set (ie, all variables and all cases) at once to identify factors with the strongest connections to target outcomes, following the process outlined in Miech et al [86]. We will perform separate analyses in order to identify the minimally sufficient conditions for the presence of desired outcomes (ie, engagement and transition readiness) and those for the absence of desired outcomes, respectively [52,78,79]. For each outcome condition, we will run the "msc" routine 5 times at consistency thresholds of 0.95, 0.90, 0.85, 0.80, and 0.75, examining all 1-, 2-, and 3-condition configurations that meet consistency requirements; have the highest coverage score for their complexity level; and align with theory, background knowledge, case familiarity, and logic [78,87]. Through this process, we will identify a subset of factors to use in the subsequent modeling phase.

In the modeling phase, we will iteratively develop preliminary and final models based on the following criteria: overall model consistency of 0.80 or greater; overall model coverage of 0.80 or greater; and aligns with theory, experience, background knowledge, and logic. Since CNA analyzes data in a bottom-up manner, such analysis will provide empirical findings that can be used to consolidate the initial program theory.

Ethics Approval

Ethics approval for this study was obtained from the Trillium Health Partners Research Ethics Board (ID: 1086). Ethics for the RCT were obtained from Clinical Trials Ontario through the Hospital for Sick Children Research Ethics Board (Project ID: 3986). The registration number for the larger RCT is NCT05434754.

The participants for this realist evaluation will provide their written informed consent at the time of RCT enrollment. The realist evaluation research team will reach out to consenting RCT participants with a web-based survey link and letter of information with the intention of recruiting and scheduling an interview.

This letter informs participants of their privacy and confidentiality protections, specifically that transcripts will be anonymized and that direct quotes used in reports or publications will not contain any information that could be used to identify them. A deidentified file with the study ID and associated participant information (ie, demographic information, transcript number, intervention usage data, and RCT patient reported outcome data) will be used to organize participant information and will only be accessible by the study coordinator. Only deidentified data will be used for subsequent analyses.

Participants will receive a CAD $25 (US $18.50) electronic gift card for completing the interview.

Results

The KiT RCT commenced in January 2023. As of May 17, 2023, a total of 36 participants had been enrolled in the RCT. Of the 15 participants who have been assigned to the intervention arm, 13 consented to realist evaluation. Participant enrollment for this realist evaluation was anticipated to start in July 2023 and continue until we reach thematic saturation, or all interested participants have been interviewed. The study findings are planned to be disseminated through peer-reviewed publications and conference presentations in 2024.

Discussion

Project Findings and Significance

It is widely agreed that digital health technologies have considerable potential to facilitate diabetes self-management and that user engagement is central to whether or not there is an impact [56]. This study will address several gaps in existing literature, including the identification of which specific features of a digital health intervention facilitate sustained engagement, which threshold level of user engagement leads to desired outcomes, and what individual-level contextual factors facilitate or hinder the implementation process [56,88]. This is a novel application of a realist evaluation to explore nuanced relationships in the context of digital health interventions and T1D health care transitions. It may contribute to knowledge from practical and methodological perspectives, respectively.

While implementation strategies are increasingly informed by implementation science, evidence-based selection of combinations of strategies is often lacking [89]. This realist evaluation is conducted in parallel alongside the RCT implementation, which will enable us to inform real-time refinement of KiT by identifying the features that contribute to desired outcomes and demonstrating the mechanisms of action in real-world settings. Further, this contextualized understanding of whether and how KiT leads to change prioritizes the usefulness of information for decision-making by identifying enablers of and constraints on its delivery across a range of settings [37]. The findings may also shed light on the design, implementation, and evaluation of future digital health interventions that aim to improve transition experiences.

This study will synthesize multiple data sources (ie, qualitative interviews, patient-reported outcomes, and intervention usage data) to enable rich complementary insights [90]. Moreover, this study uses CNA, a novel analytical approach underpinned by Boolean algebra. This approach systematically identifies a "minimal theory," that is, the crucial combinations of factors linked to target outcomes [89]. By incorporating CNA, we will be able to evaluate empirically the theory-driven configurational models and refine the initial program theory as needed.

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Limitations

First, we are not able to quantify user's engagement relating to informational content (eg, active days of engagement for a specific module [30]) due to intervention constraints, limiting our ability to understand the value of specific educational elements. Moreover, due to the limited number of interactive SMS text messages, we are not able to measure the change in user engagement frequency using indicators such as the daily SMS text message response rate [91]. As an exploratory mitigation, we will use self-report data gathered by semistructured interviews. We will also use the available intervention usage data to create a composite variable (ie, response rate at 3 months) as a proxy to measure the general level of user engagement. Future studies may benefit from collecting user engagement data at the level of each intervention component and increasing the number of web-based texts to facilitate a more accurate measurement of user engagement. Second, we only consider individual-level contextual factors due to the study objective (ie, identifying target populations for the digital health intervention) and data availability. The omission of setting-level factors (eg, access to health care system, social norms) may limit our ability to comprehensively understand the complex conditions that influence emerging adults' sustained engagement and health care transition experiences and therefore limit the transferability of our findings under some circumstances [55]. Third, data collection and analysis will occur in parallel alongside the RCT implementation in order to inform real-time intervention refinement. However, timing the study ahead of RCT end point outcome analysis will limit our ability to understand the impact on end point trial outcomes [90]. This was a conscious decision, as many RCTs show suboptimal results [71,92,93], suggesting a need to focus on upstream outcomes such as engagement as a first step.

Conclusions

Digital health interventions have emerged as a promising resource to support diabetes self-management capacity among emerging adults living with T1D. However, little is known about what components of these interventions are effective, how they are effective, and for whom they are most effective. Taking KiT as an example, our embedded realist evaluation will address this knowledge gap by using a mixed methods design and focusing on an important but often overlooked upstream outcome—user engagement. Besides informing real-time intervention refinements, the knowledge gained from this study may shed light on the design, implementation, and evaluation of future digital health interventions that aim to improve transition experiences.

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Data Availability

The data set of this study will be available from the corresponding author on reasonable request.

Authors' Contributions

LD and RS originated the idea for the project. LD and RW were primary drafters and editors of the manuscript. GR, GLB, A-SB, NE-D, MT, JAC, MG, MN, and RS contributed to manuscript revision. All authors have read and approved the final version of this manuscript.

Conflicts of Interest

RS has received speakers and advisory board fees from Dexcom. A-SB has received speaker fees from Dexcom. A-SB is a Fonds de recherche du Québec en Santé (FRQS) research scholar. MN is supported by an FRQS Senior Salary Award. The other authors declare that they have no competing interests.

Multimedia Appendix 1
KiT if-then logic.
[DOCX File , 40 KB - resprot_v12i1e46115_app1.docx]

Multimedia Appendix 2
Interview guides.
[DOCX File , 27 KB - resprot_v12i1e46115_app2.docx]

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Abbreviations

CIMO: context-intervention-mechanism-outcome
CMO: context-mechanism-outcome
CNA: coincidence analysis
COM-B: capability, opportunity, motivation, and behavior
DBCI: digital behavioral changing intervention
HAPA: health action process approach
HbA_{1c}: hemoglobin A_{1c}
KiT: Keeping in Touch
msc: minimally sufficient condition
RCT: randomized controlled trial
READDY: Readiness of Emerging Adults With Diabetes Diagnosed in Youth
T1D: type 1 diabetes
TAM: technology acceptance model

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Protocol

Technology-Enabled Collaborative Care for Concurrent Diabetes and Distress Management During the COVID-19 Pandemic: Protocol for a Mixed Methods Feasibility Study

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Abstract

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Background: The COVID-19 pandemic disrupted the delivery of diabetes care and worsened mental health among many patients with type 2 diabetes (T2D). This disruption puts patients with T2D at risk for poor diabetes outcomes, especially those who experience social disadvantage due to socioeconomic class, rurality, or ethnicity. The appropriate use of communication technology could reduce these gaps in diabetes care created by the pandemic and also provide support for psychological distress.

Objective: The purpose of this study is to test the feasibility of an innovative co-designed Technology-Enabled Collaborative Care (TECC) model for diabetes management and mental health support among adults with T2D.

Methods: We will recruit 30 adults with T2D residing in Ontario, Canada, to participate in our sequential explanatory mixed methods study. They will participate in 8 weekly web-based health coaching sessions with a registered nurse, who is a certified diabetes educator, who will be supported by a digital care team (ie, a peer mentor, an addictions specialist, a dietitian, a psychiatrist, and a psychotherapist). Assessments will be completed at baseline, 4 weeks, and 8 weeks, with a 12-week follow-up. Our primary outcome is the feasibility and acceptability of the intervention, as evident by the participant recruitment and retention rates. Key secondary outcomes include assessment completion and delivery of the intervention. Exploratory outcomes consist of changes in mental health, substance use, and physical health behaviors. Stakeholder experience and satisfaction will be explored through a qualitative descriptive study using one-on-one interviews.

Results: This paper describes the protocol of the study. The recruitment commenced in June 2021. This study was registered on October 29, 2020, on ClinicalTrials.gov (Registry ID: NCT04607915). As of June 2022, all participants have been recruited. It is anticipated that data analysis will be complete by the end of 2022, with study findings available by the end of 2023.

Conclusions: The development of an innovative, technology-enabled model will provide necessary support for individuals living with T2D and mental health challenges. This TECC program will determine the feasibility of TECC for patients with T2D and mental health issues.

Trial Registration: ClinicalTrials.gov NCT04607915; https://clinicaltrials.gov/ct2/show/NCT04607915

International Registered Report Identifier (IRRID): DERR1-10.2196/39724

(JMIR Res Protoc 2023;12:e39724) doi:10.2196/39724

KEYWORDS

collaborative care; type 2 diabetes mellitus; technology; mental health; diabetes; diabetic; feasibility; coaching; patient education; satisfaction; qualitative; nursing; nurse; virtual care; eHealth; digital health; health outcome; substance use

Introduction

In Canada, type 2 diabetes (T2D) affects more than 1 in 10 adults. It is the single most common cause of adult-onset blindness, amputations, and kidney failure and a risk factor for cardiovascular disease, strokes, cancer, mental health disorders, and poor outcomes for all other chronic conditions [1,2]. In addition to the physical challenges, adults living with T2D are at greater risk for mental health issues than the general population. The prevalence of clinically depressive symptoms among people with diabetes is about 30%, which is 2-fold greater than that among individuals without T2D [3]. As such, a comprehensive approach to diabetes management would provide services for both physical and mental health concerns in a personalized and accessible manner [4-7].

Additionally, the negative impacts of COVID-19 on mental health and well-being among adults living with T2D are a growing concern, as this population is at greater risk for diabetes-related distress and depression [8,9]. COVID-19 has accelerated the emergence of web-based care in primary and specialist care in Canada and has resulted in the virtualization of diabetes care and support (physical and mental health) [10,11]. The rapid virtualization of diabetes care has highlighted disparities in the availability and application of digital technologies at the patient and provider level, such as having necessary resources (eg, devices, data sharing, and internet availability) and implementing telehealth effectively [12,13]. The net result is an inconsistent taxonomy and understanding of what constitutes web-based diabetes care and how to provide patient-centered care.

Currently, there is inconsistent or limited access to interprofessional diabetes education, care, and follow-up, and comorbidities such as depression, hypertension, and smoking cessation are often neglected [5,8,14-17]. Few studies have examined a web-based collaborative care model, and none, to our knowledge, have examined web-based care models addressing both mental health symptoms and physical health and diabetes management [18-22]. Overall, these programs consist of technology-mediated communications between patients and various health provider teams. However, not all interventions included a care manager or comprehensive health support (ie, psychosocial, substance use, mental and physical health, and contact with primary care or community providers). Given the greater risk that individuals with T2D will develop physical challenges and mental health issues, it is essential to build on these technological innovations and expand them to provide more comprehensive and collaborative care.

Our innovative solution will leverage a novel approach to web-based care, the Technology-Enabled Collaborative Care (TECC) model [23]. This program will provide a comprehensive approach, including a registered nurse who is a certified diabetes educator (CDE), who will support the management of individuals with T2D and mental health symptoms alongside a multidisciplinary health care team to offer health coaching for behavior change and to provide peer support. The intervention will also support people with their mental health symptoms

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(anxiety or depression) that may arise as a result of their diabetes diagnosis, treatment (eg, safe and effective insulin dosing schedules), or worry about access to care during the COVID-19 pandemic through one-on-one health coaching. The goal of this study is to examine the feasibility and acceptability of the TECC model designed to support patients with T2D (or the "TECC-D program") and mental health concerns during the COVID-19 pandemic.

Methods

The research team used the expertise of the investigative team, the CDE, research coordinators, and patient partners to co-design the format of the research study. Guiding principles include the use of existing and available technology for patients, providers, and health systems; structured and measurement-based care; collaboration across institutions and settings; integration of physical and mental health expertise; and client-centered care.

Study Design and Workflow

This is an 8-week feasibility study. Thirty participants who meet the eligibility criteria will participate in the TECC-D program.

Study Setting

Overview

This study is conducted on the internet, using readily available technologies, including REDCap (Research Electronic Data Capture; Vanderbilt University) [24] and Cisco Webex (or "Webex"). REDCap is a secure data-capturing application used to create and manage web-based surveys. Webex, a secure videoconferencing service, is used to communicate directly with participants and to support communication within the study team and the virtual care team (VCT). Participants are also given the option of using a telephone. Email is used to send participants appointment reminders and educational materials. Participants are not required to attend in-person visits, and the existing relationships with their health care providers remain unaffected. Participants are in the study for 8 weeks and followed up at 12 weeks. Participants are not reimbursed for taking part in the study.

Co-design With Providers

The provider-facing side of REDCap is co-designed by our CDE and principal investigators, who specialize in the clinical treatment of individuals with T2D, mental health conditions, or addiction issues. Such co-design efforts include creating a secure documenting section for post–health coaching session calls and a summary page of participant assessment data.

Co-design With Patient Partners

Three patient partners, who are individuals diagnosed with T2D, are involved in the research and VCT aspects of the study. On the research end, the patient partners will review research ethics board submissions, study-specific processes, phone scripts with participants, study assessment types, REDCap presentations of study assessments, and manuscript writing. Specific to the VCT, the patient partners will engage in weekly VCT rounds to discuss participant cases and provide feedback from a patient-partner perspective.

Inclusion and Exclusion Criteria

To enhance generalizability, we use minimum exclusionary criteria. Inclusion criteria were as follows: (1) being an Ontario resident; (2) being 18 years or older; (3) having a clinical diagnosis of T2D for at least 1 year; (4) having access to diabetes education or management in the past; (5) having access to the telephone or internet through computer or mobile; (6) self-reporting experiencing some distress related to COVID-19; (7) being able to provide informed consent; and (8) being able to understand, write, and read English. Exclusion criteria included participants who are pregnant or planning to get pregnant during the course of the study (ie, in the following 12 weeks). Of note, lack of access to digital communication technology is not an exclusion criterion.

Sample Size

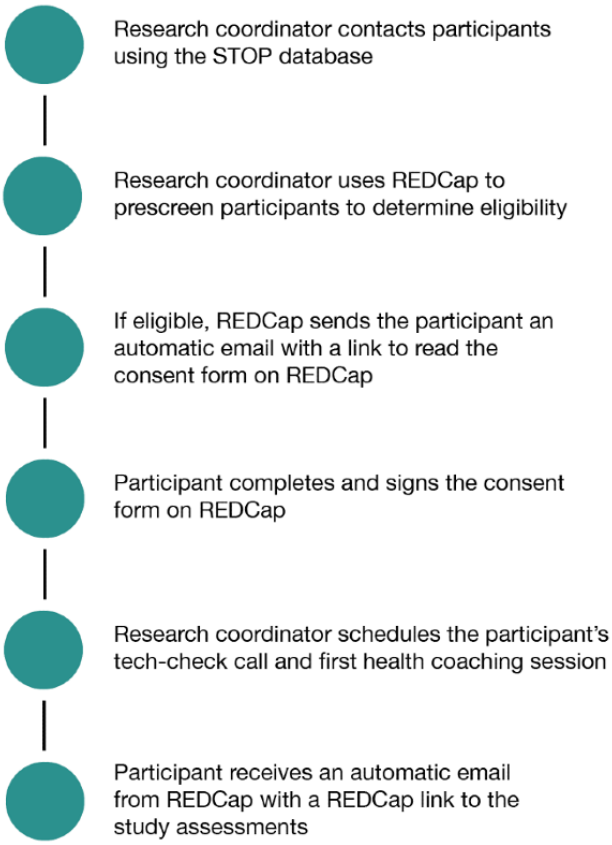
This is a single-group feasibility study that aims to gather preliminary data on retention, baseline means, and variances, and examine the degree of and variability in change over time. To meet these goals, we have set the sample size at 30. Given the expected diversity of clinical presentations, patient behaviors, and comorbid mental health conditions, we believe that a moderate number of patients are necessary to allow common challenges in implementation to be identified. This sample size will also enable reasonably good characterizations of variable distributions (eg, for a variable with a mean of 50 and an SD of 10, a 95% CI for n=30 would be 46.3 to 53.7) with descriptive statistics.

Recruitment, Consent, and Enrollment

Individuals will be primarily recruited by a research coordinator via the STOP (Smoking Treatment for Ontario Patients) Program database at the Centre for Addiction and Mental Health (CAMH) in Toronto, Ontario, Canada. The STOP program delivers smoking cessation treatment to people across Ontario through various sectors, including family health teams, community health agencies, aboriginal health access centers, and addiction or mental health agencies. We will contact participants, via e-mail or telephone, who have agreed to be contacted for future research studies and who have a self-reported diagnosis of diabetes, to explore their interest in participating in this study. As most participants will likely come from the STOP Program database, our study population will include individuals who were or are daily smokers. Eligible participants will receive an automatic email to read and complete the electronic consent form via REDCap. An informational video that summarizes the consent form is provided alongside the document. Participants receive a second automatic e-mail with a link to their study assessments and 2 online follow-up appointments: (1) a technology check with a research coordinator to ensure that they are able to access REDCap and download the Webex program and (2) their first session with the CDE. Please see Figure 1 for details.

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Figure 1. Recruitment, enrollment, and consent process via REDCap. REDCap: Research Electronic Data Capture; STOP: Smoking Treatment for Ontario Patients.



For participants who do not have access to the internet, the research team will use a verbal consent process, following the organization's research ethics guidelines. First, the study team will send the prospective participant a hard copy of the consent form via mail. Once received, 2 research coordinators will be present during the phone call, where verbal consent will be obtained from the participant. Second, the research coordinators will complete the consent form documentation after obtaining consent and provide a hard copy to the newly enrolled participant via mail. For participants who do not have access to the internet, the study's research coordinator will assist the participants in completing the survey and other study-related steps via telephone.

Intervention—TECC-D Program

After providing consent, all participants will participate in the TECC-D program during their participation in the study. In this 8-week web-based collaborative care model, participants are paired with a CDE with expertise in health coaching, cognitive behavioral therapy, and motivational interviewing. Participants are asked to complete their first set of assessments before their first session. The first session (week 1) is approximately 45-60 minutes, and subsequent sessions (weeks 2-8) are 15-20 minutes. Additional 2 weeks are provided (ie, weeks 9 and 10) as an opportunity to make up for missed earlier appointments (ie, weeks 1-8). In each session, the CDE may address diabetes self-management, mental health concerns, or broader health behaviors (including diet, physical activity, smoking, alcohol use, sleep, and stress) using a client-centered approach. The role of the CDE in the participants' care includes weekly web-based check-ins, weekly VCT rounds for individual case reviews, developing individual treatment plans, communicating with the participants' care team (only if consent is received and as needed), and providing community resources. The CDE will help participants create goals, provide educational materials, and explore other health areas. Additionally, the CDE helps facilitate collaborative communication with the participants' existing primary care team and may refer participants to other specialized health services. All sessions are offered via Webex or telephone.

On a weekly basis (or as needed), the CDE connects with the VCT via Webex to review the participants' concerns and goals. The team will comprise a psychiatrist, a psychotherapist, an addictions specialist, a dietitian, and a patient partner. Other specialists (eg, an endocrinologist) will be included as needed. To facilitate asynchronous communication, the CDE uses Webex's chat feature to send the VCT members a REDCap link to the participants' profile and treatment summary. Here, the VCT can provide recommendations in the participants' treatment plan synchronously during a VCT meeting or asynchronously by securely providing their recommendations in the Webex chat. Afterward, the CDE discusses the recommendations from the VCT with the participants to determine how best to implement these recommendations into their treatment plan. Participants are encouraged to communicate these recommendations to their local care providers. The intervention is articulated in Multimedia Appendix 1 [23,25,26], using the Template for Intervention Description and Replication checklist [25].

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For participants who do not have access to a computer or smart device (smartphone or tablet), the research team will contact them over the telephone (landline or cell phone). As such, appointments with the CDE will be held via telephone, and if they do not have an email address, then reminder phone calls can be scheduled between the research team and the participant if needed. Any study-related material (consent forms and education materials) is sent via mail using the organization's research ethics guidelines. For participants who have limited knowledge of technological and smart device use, the research team will provide technical support (eg, downloading applications, accessing appointments, and study documents) whenever needed.

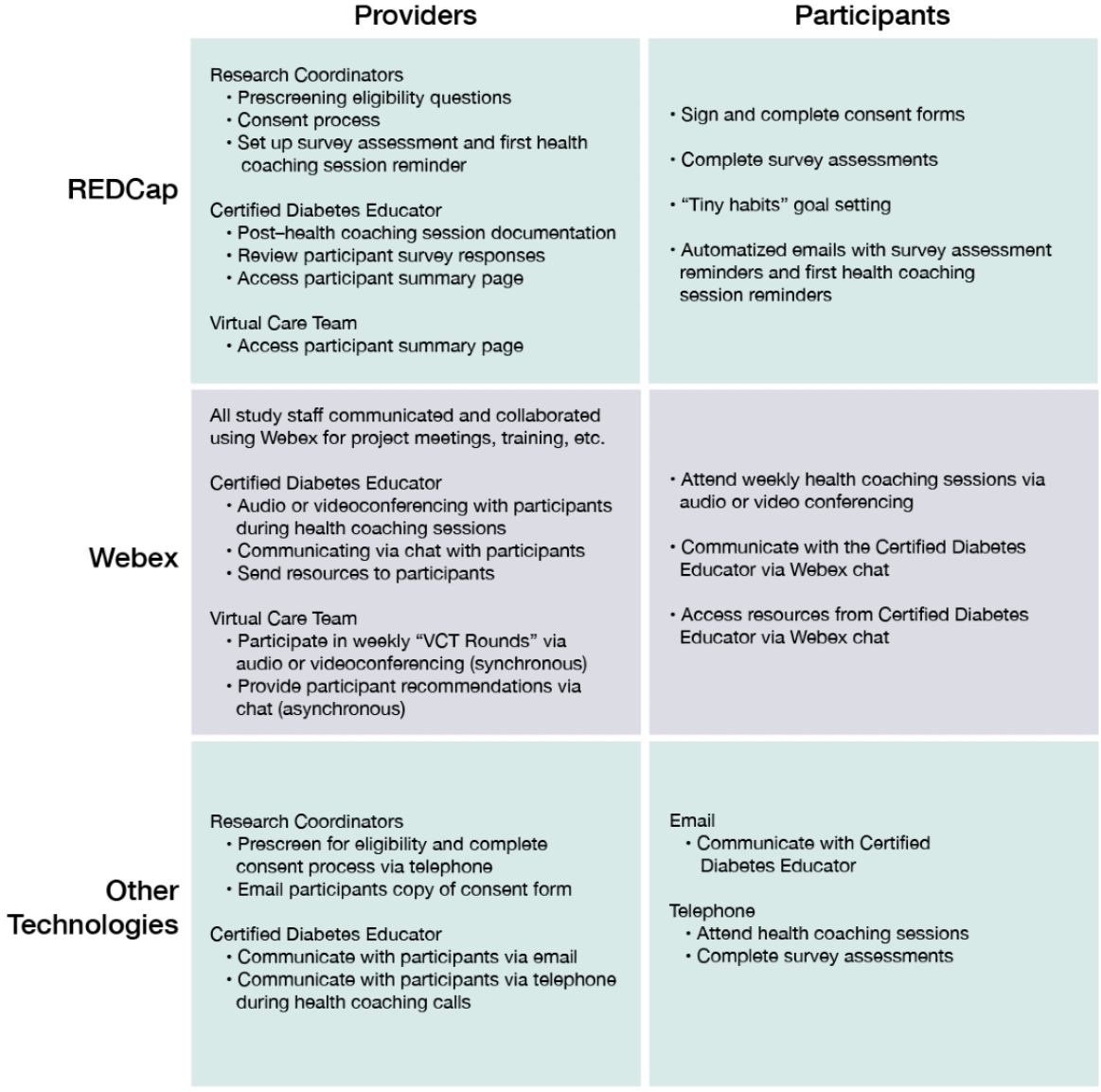
Institutional Collaboration

This study includes institutional collaboration between Principal Investigators and research team members from McMaster University and the CAMH, an academic specialty hospital affiliated with the University of Toronto. Essential considerations required for this study, given the institutional collaboration, include the secure transfer of data and information, privacy matters, data and study material access, abiding by the best practices and guidelines from both institutions (eg, research ethics), and finances for study-related costs.

Program Architecture

With the use of REDCap and Webex, the study team is able to build a technology-based collaborative care program to enhance the experience for both participants and the study team. In summary, Figure 2 presents the use of both programs at the participant and provider levels.

Figure 2. Program architecture using REDCap, Webex, and other technologies among providers and participants. REDCap: Research Electronic Data Capture; VCT: virtual care team.



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Ethics Approval

Our research is conducted in compliance with the Declaration of Helsinki [27]. This trial was approved by the CAMH in Toronto on January 18, 2021 (REB: 104-2020).

Safety Assessment

Any adverse events will be reported and documented throughout the study period. Research staff are trained to assess for suicide risk and provide crisis interventions to participants who become distressed or endanger themselves or others. To mitigate risk, regular clinical supervision by a registered psychotherapist and a medical doctor and regular meetings with the VCT will be provided in addition to the existing care provided by the participant. Lastly, to monitor the participants' mood, they will complete a depression scale [28] at several points throughout the study, which assesses low mood and suicidality.

Primary Outcomes

As this is a feasibility study, we used a convenience sampling approach to assess the primary outcomes of feasibility (ie, if our intervention can be used successfully in our setting) and acceptability (ie, if our treatment is satisfactory) [29-31]. These include assessing participant recruitment (the recruitment rate [60%] is the number of participants enrolled in the study divided by the total number of eligible participants) and retention rates (the number of participants that completed the program). Key secondary outcomes include the number of participants enrolled, the number of sessions attended, and assessment completion [30-32]. Additionally, this includes how many participants chose to fill out stage 2 ("optional") surveys, to further inform co-design with our participants for future studies. Lastly, the delivery of the intervention will be assessed, including the planned intervention sessions, the duration that the CDE was in each session, the mode of interaction (ie, whether the participant completed their visits via telephone, web-conferencing, or a combination of both), and strategies used by the CDE during health coaching sessions (eg, frequencies and examples of strategies and recommendations posed during visits), using a reporting template used in previous coaching trials [33,34].

Exploratory Outcomes

The exploratory outcomes include clinical health outcomes related to T2D, mental health, substance use, and general health measures using valid and reliable self-reported tools. Please see Multimedia Appendix 1 for details on the rationale, procedures, and methods relating to measuring health outcomes.

Stakeholder Experience and Satisfaction

Stakeholders, including study participants and CDE and VCT members, will have the opportunity to share their experience and satisfaction through interviews in a qualitative descriptive study. Participants will participate after the intervention, following study completion. Brief interviews will be completed one-on-one over the phone or using web conferencing technology. Each interview will be audio recorded, transcribed verbatim, and analyzed using thematic analysis. Research study members, including members of the VCT, will participate when the study is completed.

Data Analysis

In the quantitative analysis, descriptive statistics will characterize the study sample and describe the study assessment data. This will include means, medians, ranges, and distribution.

In the qualitative analysis, a qualitative descriptive design will be used. This includes a close, comprehensive summary of experience and satisfaction using the language of the participants. All interview data will be recorded and transcribed, with close coding used to identify themes through inductive thematic analysis. One study team member will lead the analysis using Atlas.ti (version 22), with other team members contributing to organization and interpretation of identified themes.

Following the analysis of the quantitative and qualitative data, where appropriate, a mixed methods joint display will be created. This joint display will integrate the quantitative and qualitative data and help to explain the study findings more fully.

Assessments

All participants are encouraged to complete the mandatory baseline study survey (stage 1); they have the option to complete an optional set of measures to provide more details about their health (Stage 2). This technique was used to reduce the burden of the survey on participants, as suggested by our patient partners. The first subset of assessments (stage 1) includes demographic and physical health (eg, weight and height, medications, COVID-19–related stress) questionnaires. The Diabetes Self-Management Questionnaire [35] assesses diabetes self-care activities associated with glycemic control. The Diabetes Distress Scale captures 4 critical dimensions of distress: emotional burden, regimen distress, interpersonal distress, and physician-related distress among patients with diabetes [36]. Quality of life is measured using the EuroQol-5 Dimension [37]. Tobacco use is measured using the History of Smoking Index [38]. Psychological and behavioral problems will be measured using the Global Appraisal of Individual Needs Short Screener [39].

The second subset of assessments (Stage 2) includes a visual analog scale (available in Multimedia Appendix 2) to assess the self-perceived benefit and the readiness ruler to assess the motivation and confidence of changing physical activity, nutrition, smoking, alcohol, stress, sleep, and other self-reported behaviors. Alcohol use is measured with the Alcohol Use Disorders Identification Test [40]. The Mediterranean Diet Adherence Screener is used to measure adherence to the Mediterranean diet [41]. Physical activity is measured with the International Physical Activity Questionnaire—Short Form. The Brief Pain Inventory measures pain symptoms [42]. Mental health symptoms will be measured using the Generalized Anxiety Disorder scale for anxiety symptoms [43], the Patient Health Questionnaire for depressive symptoms [28], and the Perceived Stress Scale for stress symptoms [44]. Assessment scales and tools used in this study are consistent with those employed in a previous iteration of the TECC model and supported by the study team.

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Results

At the time of submission, recruitment for this feasibility study is complete, and the remaining study participants are finishing the intervention. Data analysis is projected to commence in the fall of 2022, with the results of this study anticipated to be published by September 2023.

Discussion

This is the first study to include a TECC program for adults with T2D (ie, the TECC-D program), including the aforementioned features, where access to digital technology by the patient is not an exclusion criterion.

The primary aim of the study is feasibility and acceptability. All participants receive the TECC-D intervention, which includes weekly health coaching calls with a CDE and personalized recommendations from a VCT. The researchers anticipate that the main finding of the study will be the feasibility of technological and collaborative health program providing diabetes- and mental health–related services to adults with T2D.

As previous studies on technology-based interventions for adults with T2D generally focused on symptom improvement and medication adherence, the goal of this study was to address other characteristics of behavioral change, including physical activity, diet, and smoking.

Additionally, previous studies have seldom engaged the individuals' existing primary and community care teams in their collaborative care treatment.

As such, our TECC-D program puts forward a novel approach to address gaps in both research and health care among individuals with T2D. By using the existing technology in the health care system, implementing co-design of study features with practitioners and patients, and engaging patient partners with T2D, the TECC-D program illustrates a more integrated approach to collaborative care. This program aims to reduce access-related barriers to care to ensure that adults with T2D can receive the personalized, holistic care and the psychoeducation that they require.

Acknowledgments

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Data Availability

This article reports the protocol of our study. No data are currently available.

Authors' Contributions

This study was conceptualized and designed by DS, RD, FN, SMA, OCM, AC, PG, MH, SK, BM, ES, FT, SR, GL, SS, and PS with study funding acquired by DS, MH, SK, BM, and PS. LV, DS, RD, IA, CW, JM, and PS contributed to project administration with data curated by LV, IA, and LTG, and study resources and software maintained by LV, IA, OCM, and CW. All authors contributed to the writing, review, and editing of this manuscript. CW, LTG, and JM will lead the formal analysis of data supervised by DS, RD, SV, SH, and PS.

Conflicts of Interest

LV, DS, RD, IA, SV, FN, SMA, AC, SH, SK, ES, LT-G, CW, JM, FT, SR, SS, and GL have none declared. OCM reports receiving grant and salary support from the CAMH and AMS Healthcare. PG reports receiving research support from the Canadian Institute of Health Research (CIHR), the Ontario Ministry of Health and Long-Term Care, the Ontario Mental Health Foundation (OMHF), the CAMH, the CAMH Foundation, and an Academic Scholars Award from the Department of Psychiatry, University of Toronto. MH reports receiving consulting fees from Alkermes. BM reports receiving support from the Labatt Family Chair in the Biology of Depression in Late-Life Adults at the University of Toronto. BM currently receives or has received over the past 3 years research support from Brain Canada, the Canadian Institutes of Health Research, the CAMH Foundation, the Patient-Centered Outcomes Research Institute (PCORI), the US National Institute of Health (NIH), Capital Solution Design LLC (software used in a study founded by the CAMH Foundation), and HAPPYneuron (software used in a study founded by Brain Canada). Within the past 3 years, BM has also been an unpaid consultant to Myriad Neuroscience. PS reports receiving grants, salary, and research support from the CAMH, Health Canada, the Ontario Ministry of Health, the Canadian Institutes of Health Research (CIHR), the Canadian Centre on Substance Use and Addiction, the Public Health Agency of Canada (PHAC), the Medical Psychiatry Alliance, the Canadian Cancer Society Research Institute (CCSRI), Cancer Care Ontario, and the National Institutes of Health (NIH). PS also reports receiving funding and honoraria from the following commercial organizations: Pfizer Canada Inc. and Patient-Centered Outcomes Research Institute. Through an open tender process, Johnson & Johnson, Novartis, and Pfizer Inc. are the vendors of record for providing smoking cessation pharmacotherapy, free or discounted, for research studies in which PS is the principal investigator or co-investigator.

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Multimedia Appendix 1
TIDieR checklist.
[DOCX File , 30 KB - resprot_v12i1e39724_app1.docx]

Multimedia Appendix 2
Visual analogue scale for perceived benefit.
[DOCX File , 126 KB - resprot_v12i1e39724_app2.docx]

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Abbreviations

CAMH: Centre for Addiction and Mental Health
CDE: certified diabetes educator
REDCap: Research Electronic Data Capture
STOP: Smoking Treatment for Ontario Patients
T2D: type 2 diabetes
TECC: Technology-Enabled Collaborative Care
TECC-D: Technology-Enabled Collaborative Care for Diabetes
VCT: virtual care team

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Protocol

Design and Implementation of the Surveys of Women: Protocol for an Address-Based Sampling Multimodal Study

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Abstract

Background: Studies conducted in the United States such as the National Survey of Family Growth (NSFG) and the Pregnancy Risk Assessment Monitoring System (PRAMS) collect data on pregnancy intentions to aid in improving health education, services, and programs. PRAMS collects data from specific sites, and NSFG is a national household-based survey. Like NSFG, the Surveys of Women was designed to survey participants residing in households using an address-based sample and a multimode data collection approach. The Surveys of Women collects data from eligible participants in 9 states within the United States on contraception use, reproductive health, and pregnancy intentions. In this paper, we focus on the baseline data collection protocol, including sample design, data collection procedures, and data processing. We also include a brief discussion on the follow-up and endline survey methodologies. Our goal is to inform other researchers on methods to consider when fielding a household-level reproductive health survey.

Objective: The Surveys of Women was developed to support state-specific research and evaluation projects, with an overall goal of understanding contraceptive health practices among women aged 18-44 years. The project collects data from respondents in 9 different states (Arizona, Alabama, Delaware, Iowa, Maryland, New Jersey, Ohio, South Carolina, and Wisconsin) over multiple rounds.

Methods: Households were selected at random using address-based sampling methods. This project includes a cross-sectional baseline survey, 2 or 3 follow-up surveys with an opt-in panel of respondents, and a cross-sectional endline survey. Each round of data collection uses a multimode design through the use of a programmed web survey and a formatted hard copy questionnaire. Participants from the randomly selected households access their personalized surveys through a web survey or mail in a hard copy questionnaire. To maximize responses, these surveys follow a rigorous schedule of various prompts bolstering the survey implementation design, and the participants received a modest monetary incentive.

Results: This is an ongoing project with results published separately by the evaluation teams involved with data analysis.

Conclusions: The methods used in the first baseline survey informed modifications to the methods used in subsequent statewide surveys. Data collected from this project will provide insight into women's reproductive health, contraceptive use, and abortion attitudes in the 9 selected states. The long-term goal of the project is to use a data collection methodology that collects data from a representative sample of participants to assess changes in reproductive health behaviors over time.

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KEYWORDS

multimode; web survey; cross-sectional; women's health; reproductive health; methods; data collection; implementation; survey; contraceptive health; contraception; survey methods; data collection; data processing

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Introduction

National studies, such as the National Survey of Family Growth (NSFG) and the Pregnancy Risk Assessment Monitoring System (PRAMS), collect data on pregnancy intentions among women of childbearing age to aid in improving health education, services, and programs. Unintended pregnancies, in particular, can have negative health, economic, and psychological impacts on individuals and families. While the rates of unintended pregnancy have declined nationally in the United States since 2008, data indicate that 45% of pregnancies in 2011 were unintended [1,2]. At the state level, the rates of unintended pregnancy among women aged 15-44 years vary from 32 per 1000 women to 62 per 1000 women, with Delaware reporting the highest rate [3].

To support state-specific research and evaluation projects, the Surveys of Women was developed to assess changes in pregnancy intentions and attitudes toward contraception. Initially conceptualized as 2 cross-sectional surveys (a baseline survey followed by an endline survey approximately 5 years later), the project evolved to include follow-up surveys with an opt-in panel to meet the needs of the evaluation team. The Surveys of Women was first launched in the states of Delaware and Maryland with the administration of the baseline survey in 2016.

Data collection for this study used an address-based sampling (ABS) multimode approach. ABS methodological approaches have become the preferred method for respondent selection, compared with random digit dialing designs that rely on telephone interviews. Randomly selecting addresses from a list of known households in an area allows researchers to maximize coverage and improve response rates [4]. Further, the data collection methodology used a series of mailings and nonresponse follow-up activities as recommended by Dillman et al [5,6]. The Dillman method is a well-established method that recommends using distinct contacting strategies to encourage response.

The project increased in scope to support additional research, which included the incorporation of additional evaluation teams as the project expanded into new states and the addition of a follow-up component between the baseline and endline surveys. In addition to Delaware and Maryland, the project has conducted surveys in Arizona, Alabama, Iowa, New Jersey, Ohio, South Carolina, and Wisconsin.

The following report summarizes the study methodology used for the baseline surveys in each state, with a section on the planned differences for the follow-up survey administration.

Methods

Study Overview

The Surveys of Women are multimode, multistate studies with the overarching aim of measuring contraceptive use and understanding reproductive health practices among women aged 18-44 years in 9 states. Data are collected over multiple rounds—a baseline cross-sectional survey, 2 to 3 follow-up surveys, and an endline cross-sectional survey. During the baseline survey, households were selected at random using ABS methods, with any 18- to 44-year-old woman in the household eligible to participate. Women from the baseline could opt-in to participate in additional follow-up surveys. The final stage is a second cross-sectional endline survey. For the purpose of this paper, we will address the methodology for the baseline surveys followed by a brief discussion of the follow-up survey methodology. We also briefly discuss the endline survey, which will follow the same methodology as the baseline administration.

Ethical Considerations

All questionnaires and data collection methods were reviewed and approved by the NORC (National Opinion Research Center at the University of Chicago) institutional review board (IRB). NORC's IRB has obtained a Federal Wide Assurance and is registered with the US Federal Office for Human Research Protections (FWA #00000142). The IRB protocol submitted included sufficient detail on the methodology to ensure that subjects' privacy is protected, and data confidentiality is maintained. Materials reviewed for the Surveys of Women included a description of the study's sample, the methodology used including recruitment methods and incentives, the informed consent language, and the survey questionnaire. All survey administrations (baseline, follow-ups, and endline) included informed consent information for participants on the login page for the web survey and the first page of the formatted hard copy. The consent information included standard provisions related to the voluntary nature of the survey, the right to refuse to answer any question, the confidential nature of responses, the incentives provided, and the contact number for the IRB representative in the event of questions about their rights as a study participant. A specific project toll-free number and email address were provided to respondents as well as for questions and concerns.

Sample Design

Overview

The target number of completed surveys for each baseline was 2000 per state; therefore, the sampling plan for each baseline survey was designed to meet these targets. The sample frame for the cross-sectional baseline surveys was the United States Postal Service computerized delivery sequence (CDS) file enhanced with age-targeted lists [7,8]. The CDS was licensed from an independent vendor and is also referred to as the DSF (delivery sequence file). We geocoded the CDS and, using the geocodes, appended the file with area-level demographic information from the American Community Survey for purposes of stratification. To maintain the coverage of the CDS and allow for oversampling of women with a particular characteristic, the updated CDS frame was deduplicated against a list procured from a vendor—a sample of addresses likely to contain a woman in the target age range of 18-44 years.

Stratification

In all states, the sample was stratified into "high" and "low" density areas for specified variables of interest, such as minority status, rurality, or poverty level. The variables of interest and geographic unit varied depending on the state as shown in Table 1. We adjusted the degree of stratification between the baseline in the original sites (Delaware, Maryland, South Carolina, and

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Alabama) and subsequent sites that targeted minorities in order to increase the share of non-White, non-Hispanic respondents. This approach resulted in 4 strata per state: CDS-only low density, CDS-only high density, list low density, and list high density, where list refers to those likely to contain women in the target age range. The CDS-only high-density and list high-density strata were oversampled relative to the respective low strata in each baseline data collection.

Table 1. Baseline sample size and variables of interest.

State	Variables of interest	Unit of stratification	Overall addresses released, n	CDS[a]-only low density, n	CDS-only high density, n	List low density, n	List high density, n
Delaware	Non-White, non-Hispanic population; poverty status	Census tract	14,375	3229	5417	1875	3854
Maryland	Non-White, non-Hispanic population; poverty status	Census tract	13,875	2817	5425	1982	3651
South Carolina	Rural populations (in low-density counties)	County	18,400	6600	4000	4900	2900
Alabama	Rural populations (in low-density counties)	County	18,400	5200	4800	4200	4200
Iowa	Non-White, non-Hispanic population; poverty status	Census tract	14,700	5400	3200	4300	1800
Ohio	Rural Appalachia	County	20,100	9300	2700	6400	1700
Arizona	Non-White, non-Hispanic population; poverty status	Census tract	18,138	7885	1559	6505	2189
New Jersey	Non-White, non-Hispanic population; poverty status	Census tract	24,499	9531	3767	8518	2683
Wisconsin	Non-White, non-Hispanic population; poverty status	Census tract	12,481	4886	1679	4264	1652

[a]CDS: computerized delivery sequence.

Questionnaire

Overview

The goal of each questionnaire was to capture data on respondents' contraceptive use, pregnancy history, health status, and opinions on abortion. Variations among individual state questionnaires existed, including items tailored to their respective state, such as insurance plans or state-specific clinics. All questionnaires were offered in English and Spanish languages.

Questionnaire Development

The initial questionnaire (developed for the Delaware and Maryland baseline survey) consisted of items drawn from existing sources, such as the American Community Survey, the Behavioral Risk Factor Surveillance System, the NSFG, the PRAMS, and the Delaware Household Survey. A copy of the questionnaire can be found in Multimedia Appendix 1.

Subsequent baseline state questionnaires were created using the original questionnaire developed for Delaware and Maryland. Prior to the start of each baseline survey, the respective evaluation teams had the option to propose new questions relevant to their goals or propose modifications to existing items.

All questionnaire items were formatted to be self-administered and were formatted with the goal of visual consistency and presentation among self-administered modes (ie, web and paper self-administered questionnaire [SAQ]). For example, questions that were programmed as grids on the web were formatted as such on the paper version. Similarly, items where a follow-up question was embedded into the stem question were indented with arrows directing the respondent to the correct follow-up item on the paper version. A computer-assisted telephone interview (CATI) was programmed and administered during the Delaware, Maryland, South Carolina, and Alabama baseline surveys. Due to low productivity rates with the CATI survey (ie, only 9 completed CATI interviews), the telephone survey was abandoned after the South Carolina and Alabama baseline surveys.

Cognitive Interviews

A total of 11 cognitive interviews (8 with English speakers and 3 with Spanish speakers) were conducted prior to the start of data collection in Delaware and Maryland. Cognitive interviews allow researchers to identify any potential issues within the questionnaire, such as question comprehension, illogical flow, and appropriateness of response options. As a result of cognitive interviews, duplicative questions were identified and removed, double-barreled questions were corrected, response options were modified, and images for birth control methods (eg, intrauterine device, implant, and birth control pills) were added to clarify for respondents what each type of birth control was.

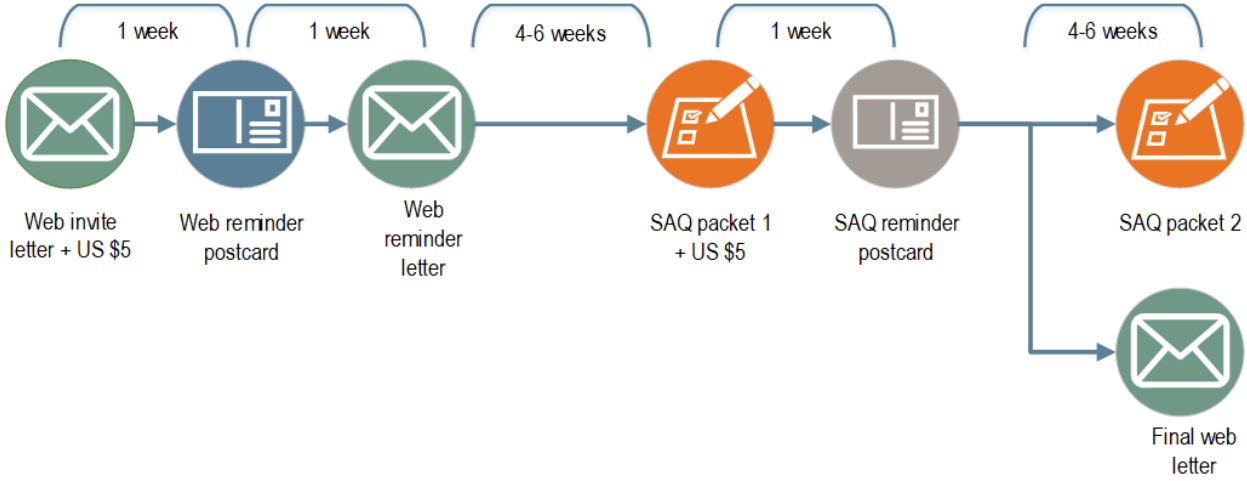
In addition, cognitive interviews were conducted with 10 South Carolina residents and 10 Alabama residents prior to the data collection launch. Cognitive interviews were not conducted prior to the launch of data collection in Iowa, Ohio, Arizona, New Jersey, or Wisconsin as these surveys used established items that did not require additional review.

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Survey Design

All Surveys of Women data collections follow a similar methodology, with a series of prompts to encourage response as shown in Figure 1. Respondents were offered the option to complete the web survey first; those who do not complete via the web survey were sent a paper SAQ. A vendor-supplied flag appended to the sample file indicated which addresses may have a Spanish speaker and would benefit from bilingual materials.

Figure 1. Baseline survey case flow. SAQ: self-administered questionnaire.



Data Collection Methods

Respondent Mailings or Prompts

A Surveys of Women study logo was developed and displayed on all printed materials and within the header of the web survey. Four images that represented each state were selected and displayed as an image carousel on the state's web survey login page as well as static images on the front cover of the state's paper questionnaire. All respondent materials contained a project-specific email address and toll-free telephone number should respondents have a question about the study or their participation.

The baseline surveys in each state followed a similar protocol when mailing printed copies of materials. The baseline surveys for Delaware, Maryland, South Carolina, and Alabama offered CATI as a third mode of data collection. A subset of nonrespondents whose addresses could be matched to a telephone number were contacted by trained telephone interviewers to complete the survey over the telephone. Due to low overall response in these 4 states, it was deemed that CATI was not a viable option for attaining completion for this population and was dropped from subsequent survey administrations.

Each mailing was sent to the sampled address and addressed to "[STATE] Resident." The types of respondent contacts are described below.

Web Mailings

First Web Invitation Letter

The first point of contact was an invitation letter, which described the purpose of the study and provided the survey link and the respondents' unique personal identification number. Included with the letter were a noncontingent cash incentive (a US $2 bill for Delaware and Maryland residents and a US $5 bill for all other survey administrations) and a web instructional insert, which showed how to access the survey.

Web Reminder Postcard

Approximately 1 week after the web invitation letter, a reminder postcard was sent to all sampled households reminding them to participate.

Second Web Letter

Sampled addresses that had not responded to the first 2 mailings were sent a second letter requesting participation via the web survey instrument.

Last Chance Letter

A final letter was sent to those who had not yet responded during the final weeks of data collection. The purpose of the letter was to encourage participation before data collection closed.

SAQ Mailings

SAQ Packet 1

Paper questionnaires were sent to sampled addresses who had not responded to the web survey invitation. The packets contained a cover letter, a copy of the questionnaire, an additional noncontingent cash incentive (a US $1 bill for Delaware and Maryland and a US $5 bill for other states), and a postage-paid envelope to return the completed questionnaire.

SAQ Reminder Postcard

Approximately 1 week after sending the initial paper questionnaire packet, a reminder postcard was sent to sampled addresses to remind them to complete and return their paper questionnaire.

SAQ Packet 2

A second and final paper questionnaire was sent to sampled addresses who had not completed the web survey or returned a paper version of the questionnaire. The second packet contained

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a cover letter, paper questionnaire, and postage-paid return envelope.

Household Rostering

With almost 10% of households estimated to contain more than 1 eligible respondent, it was important to collect data from additional eligible women in the household, particularly as their reproductive health choices may be different. Therefore, during the baseline surveys, respondents had the option to provide the name and email address of up to 2 additional women, aged 18-44 years, who were living in the household. If additional women were rostered through the web survey, we automatically sent them an invitation letter and unique personal identification number at the email address specified. Women who were rostered via the paper questionnaire were sent an email invitation once the data from the questionnaire had been entered, and the name and email address were made available to project staff.

Incentives

Noncontingent Cash Incentives

All web invitation letters and initial paper questionnaire packets included a noncontingent cash incentive. In the Delaware and Maryland baseline survey, the noncontingent cash incentive was a US $2 bill for the web letter and a US $1 bill for the first paper questionnaire mailing. Due to a lower-than-anticipated response for that baseline study, all future baseline studies increased the preincentive amount to US $5 for both the web invitation letter and the initial paper questionnaire packet mailing.

Postsurvey Completion Incentives

Respondents who completed the baseline survey received a US $10 postincentive in the form of an electronic gift code. Initially, the postincentive offered was in the form of an Amazon gift code. Participants in Arizona, New Jersey, and Wisconsin baseline surveys were offered their choice of an Amazon, Target, or Walmart electronic gift code at the completion of the baseline survey.

Data Processing

Eligibility

At the start of the baseline surveys, two screening questions were asked of household members: (1) “What year were you born?” and (2) “What is your gender?” For those who refused to provide their year of birth, a follow-up question was asked with a list of age categories from which the respondent could select the appropriate age range. To note, Delaware and Maryland used a variation of the age screener item at baseline, originally asking “What is your age (in years)?” These screening questions served to confirm eligibility—a woman aged 18-44 years at the sampled address. Those individuals who did not meet the screening criteria were screened out of the survey, and no further data were collected. Those who were eligible continued into the main questionnaire.

Throughout data collection, cases were reviewed for eligibility. The web was programmed with automated screen-out language, and the paper questionnaire was printed with instructions for the respondent to stop responding and return the questionnaire if either screening question made them ineligible. During postprocessing, ineligible respondents who disregarded these instructions and completed the questionnaire were identified. The main questionnaire data for these respondents were not included in the final data set, and the overall case status was changed to an ineligibility status.

Weighting

Overview

Weights were applied to all data sets and underwent the same set of steps: (1) base sampling weight (W_1); (2) adjustment for unknown eligibility (W_2); (3) adjustment for nonresponse to the questionnaire (W_3); (4) adjustment for household size (W_{4a}); and (5) poststratification (W_4).

Step 1: Base Sampling Weight

All sample lines received a base weight, which reflects the probability of a household being selected and is equal to the inverse of the probability of selection. Each stratum had a different base weight, with the base weight for the list sample being equal to the inverse of the sum of the list probability and the DSF probability.

Examples of the list strata versus DSF strata base weight calculations are:

Stratum 1 (Delaware low-density DSF)



Stratum 2 (Delaware low-density list)



Step 2: Adjustment for Unknown Eligibility

This adjustment to the weights accounted for those who were unable to be contacted and whose eligibility status was unknown. This adjustment used the Census’ Public Use Microdata Sample (PUMS) data to estimate household eligibility for each stratum within a state. Completed cases had no adjustment, while incomplete cases received this calculated rate.

Step 3: Adjustment for Interview Nonresponse

This weight adjustment compensated for differences in response across eligible survey subgroups. Adjustment cells for the interview nonresponse rate are usually defined by state and high or low density.

Step 4: Adjustment for Household Size

The final weight adjustment accounted for within-household eligibility. PUMS data were used to estimate within-household eligibility using race or ethnicity as a comparison point. That is, it was assumed that households with 1 respondent would have the same number of eligible women as average PUMS household data with more than 1 eligible women in the same state and race or ethnic group. The same was true for households with 2 or 3 eligible respondents.

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Step 5: Poststratification

This step was a 2-part process—imputation first and then raking. Hot-deck imputation was used to impute missing values for the variables used during the raking process. Across the baseline studies, the missing values imputed for the raking variables ranged from approximately 0.6% to approximately 18%.

Once the values had been imputed, raking was performed across 8 variables—age, nativity, employment, marital status, race or ethnicity, housing tenure, children younger than 18 years in the household, and education crossed with income. The purpose of raking was to reduce bias in survey estimates and achieve representativeness of the target population across those variables of interest. The 8 variables selected represent optimal design based on criteria, such as design effect, weight distribution, and the impact of raking on select outcome variables.

Follow-up Survey Methods

Overview

As mentioned previously, the project includes a set of follow-up surveys that occur in the years between the baseline and the endline surveys. The motivation for the follow-up surveys is to continue to assess contraceptive use and changes in attitudes among participants. The sample for each state's follow-up surveys consists of baseline survey participants who agreed to be recontacted for future studies. Table 2 shows the number of initial respondents who opted into each state's follow-up survey.

Participants can request to be removed from future contact at any point but remain in the panel. In addition, participants are removed from the study panel if the study team learns that the participant was not actually eligible to complete the baseline survey (eg, older than 44 years or younger than 18 years at the time they completed the baseline survey).

Table 2. Panel size by state.

State	Initial panel size, n
Delaware	983
Maryland	957
Alabama	1675
South Carolina	1658
Iowa	1946
Ohio	2066
Arizona	1588
New Jersey	1600
Wisconsin	1577

Methodology

Overview

All follow-up studies follow a similar data collection methodology when mailing printed copies of materials as described earlier for the baseline survey. However, there are a few deviations from the baseline survey protocol, which include (1) locating current contact information, (2) incorporating email and SMS text message prompts, and (3) offering incentive amounts. These differences are described below.

Locating

As the follow-up surveys follow a panel of respondents over a period of up to 3 years, using updated and adequate contact information for the panel is key. Follow-up surveys will be conducted 3 times for participants in South Carolina, Alabama, Iowa, and Ohio, while participants in Delaware, Maryland, Arizona, New Jersey, and Wisconsin will only be contacted for 2 follow-up surveys. Prior to the start of a follow-up survey, the project team sends an email to all panel members who provided an email address with a request to confirm or update their existing contact information.

Throughout data collection, the project team may also conduct individual searches via Accurint, a commercially available locating tool developed by LexisNexis, to locate updated address information for those individuals who have not responded to the mailings or provided the project team with an updated mailing address.

Email Prompts

During each baseline survey, participants were asked to provide their name and contact information (address, telephone number, and email address) to facilitate contacting them for future studies. Email addresses are used to send email prompts and serve as another manner of respondent contact. For participants who had an email but not a name, their initial invitation to participate in the follow-up is sent via email.

The number of prompts and timing of these reminders are at the discretion of the data collector, though all follow-up studies conclude data collection with 1 final email prompt to any sample member who has not yet responded.

SMS Text Message Prompts

Women who participated in the first follow-up surveys for Iowa and Ohio and the baseline surveys for Arizona, New Jersey, and Wisconsin could consent to future contact via SMS text message. Therefore, SMS text message reminders are used for participants in these states. The SMS text messages are sent with an embedded link to the state's web survey log-in page and provide respondents with another way to access the survey.

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SMS text messages were only sent to participants who consented to receive these messages and provided a valid telephone number.

Incentives

For those who participate in the follow-up studies, their postincentives are still in the form of electronic gift codes though in increasing amounts. The postincentive for the first follow-up is US $20; it is US $30 for the second follow-up and US $40 for the third follow-up.

Eligibility

Eligible respondents who completed the baseline survey and agreed to future contacts constituted the panel of respondents who would be contacted for the state's follow-up studies. As with all follow-up surveys, it is important that the same respondent participates in each round. As a measure of confirming the individual who responded to a follow-up survey was the same as the original baseline respondent, select demographic variables (age, education, and race) are used as confirmation variables.

During the first follow-up surveys for Delaware, Maryland, South Carolina, and Alabama, these demographic variables were prefilled with the baseline response (if known) into the web survey. The respondents would see the response prefilled and were asked to confirm or update their response.

Regular data reviews, including a review of the demographic variables, are completed during the follow-ups. The study team follows these general steps when reviewing completed cases: (1) Names are compared; if the names match, no further action is taken. (2) If the name does not match, email addresses are reviewed. If email addresses match, no further action is taken. (3) If both the name and email address do not match, responses to age, education, and race are reviewed. If these variables are consistent or there is only 1 variable flagged as a discrepancy, the case is considered a match and no further action is taken. (4) If more than 1 demographic variable is flagged and there is no reasonable explanation for the change (eg, age discrepancy due to change in how the question was asked, increase in education), the case is considered a nonmatch and flagged as the incorrect respondent.

The process to confirm eligibility was refined prior to the start of the first follow-up survey in Iowa and Ohio so that the check on the selected demographic variables was performed systematically. The 5 demographic questions—items about age, gender, ethnicity, race, and education—were moved to the beginning of the survey. Respondents did not see their responses from a prior round; however, the survey was programmed to compare responses to age, education, and race against preloaded values for the case.

With this process, flags are assigned if a response differed from the one previously provided. Respondents continue into the survey if 1 or no flags are triggered. Cases with 2 or more flags indicate discrepant responses; these respondents are taken to a new screen that informs them there is an error with the survey and requests they contact us. Respondents who reach this screen are unable to log back into the survey and are shown this screen until they contact the project team to verify they are the eligible person.

Weighting

The follow-up surveys follow the same weighting methodology as described earlier for the baseline surveys.

Endline Survey Methods

The endline surveys for all states will follow the same sampling approach, data collection methodology, and weighting plan as used for the baseline surveys described earlier. The first endline survey was fielded in 2020-2021 in Delaware and Maryland; at the time of this writing, data processing was underway. Endline survey data collection for the remaining states will continue through August 2023.

Results

This is an ongoing research project and results from data collected from this study will be published independently by separate research and evaluation teams.

Discussion

Conclusions

In summary, the Surveys of Women project follows a standard approach to multimode data collection, which uses a series of prompts to encourage response to the survey. This data collection approach is informed by Dillman et al [5,6] research on multimode surveys and is widely documented in the extant survey methods literature. Additionally, using an address-based sample for the baseline allows the survey to maintain adequate coverage within a state, with the sample stratified into areas in an effort to reach target populations. This project provides an opportunity to use a well-established survey methodology to capture data from a target population on potentially sensitive topics. We will also learn which overall methodology works best for initial participation and subsequent participation in the opt-in panel for follow-up studies, which will be useful for any subsequent, similar projects.

Limitations

As in any household-based web or mailed questionnaire study, there is no accurate or cost-effective way to confirm that all participants met eligibility criteria definitively. Respondent verification was included in the opt-in follow-up surveys to confirm whether the same individual was participating across rounds, but respondent verification is not feasible for the cross-sectional baseline and endline surveys.

Additionally, as noted in "Data Collection Methods" section, we increased our preincentive amounts and modified our follow-up language after baseline participation, and follow-up panel opt-ins were less than expected in Delaware and Maryland. The changes in approach were applied to the subsequent state surveys and allowed for a more robust sample in those states comparatively.

Another limitation to the survey is that it was offered only in English and Spanish languages. Additionally, as a

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self-administered survey, it relied on respondent literacy for questionnaire completion and comprehension.

Acknowledgments

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Data Availability

The data sets generated and analyzed during the Surveys of Women study are not publicly available at this time due to the exclusive data usage rights of the funded research and evaluation teams. Data may be made available from the corresponding author upon reasonable request. Data may also become available as restricted use or public use data sets at some point in the future.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Draft copy of the questionnaire items used in the Delaware and Maryland baseline survey.
[DOCX File , 130 KB - resprot_v12i1e40675_app1.docx]

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Abbreviations

ABS: address-based sampling
CATI: computer-assisted telephone interview
CDS: computerized delivery sequence
DSF: delivery sequence file
IRB: institutional review board
NSFG: National Survey of Family Growth
PRAMS: Pregnancy Risk Assessment Monitoring System
PUMS: Public Use Microdata Sample
SAQ: self-administered questionnaire

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Protocol

German Health Update Fokus (GEDA Fokus) among Residents with Croatian, Italian, Polish, Syrian, or Turkish Citizenship in Germany: Protocol for a Multilingual Mixed-Mode Interview Survey

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Abstract

Background: Germany has a long history of migration. In 2020, more than 1 person in every 4 people had a statistically defined, so-called migration background in Germany, meaning that the person or at least one of their parents was born with a citizenship other than German citizenship. People with a history of migration are not represented proportionately to the population within public health monitoring at the Robert Koch Institute, thus impeding differentiated analyses of migration and health. To develop strategies for improving the inclusion of people with a history of migration in health surveys, we conducted a feasibility study in 2018. The lessons learned were implemented in the health interview survey German Health Update (Gesundheit in Deutschland aktuell [GEDA]) Fokus, which was conducted among people with selected citizenships representing the major migrant groups in Germany.

Objective: GEDA Fokus aimed to collect comprehensive data on the health status and social, migration-related, and structural factors among people with selected citizenships to enable differentiated explanations of the associations between migration-related aspects and their impact on migrant health.

Methods: GEDA Fokus is an interview survey among people with Croatian, Italian, Polish, Syrian, or Turkish citizenship living in Germany aged 18-79 years, with a targeted sample size of 1200 participants per group. The gross sample of 33,436 people was drawn from the residents' registration offices of 99 German municipalities based on citizenship. Sequentially, multiple modes of administration were offered. The questionnaire was available for self-administration (web-based and paper-based); in larger municipalities, personal or phone interviews were possible later on. Study documents and the questionnaire were bilingual—in German and the respective translation language depending on the citizenship. Data were collected from November 2021 to May 2022.

Results: Overall, 6038 respondents participated in the survey, of whom 2983 (49.4%) were female. The median age was 39 years; the median duration of residence in Germany was 10 years, with 19.69% (1189/6038) of the sample being born in Germany. The overall response rate was 18.4% (American Association for Public Opinion Research [AAPOR] response rate 1) and was 6.8% higher in the municipalities where personal interviews were offered (19.3% vs 12.5%). Overall, 78.12% (4717/6038) of the participants self-administered the questionnaire, whereas 21.88% (1321/6038) took part in personal interviews. In total, 41.85% (2527/6038) of the participants answered the questionnaire in the German language only, 16.69% (1008/6038) exclusively used the translation.

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Conclusions: Offering different modes of administration, as well as multiple study languages, enabled us to recruit a heterogeneous sample of people with a history of migration. The data collected will allow differentiated analyses of the role and interplay of migration-related and social determinants of health and their impact on the health status of people with selected citizenships.

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(JMIR Res Protoc 2023;12:e43503) doi:10.2196/43503

KEYWORDS

migration; interview survey; hard-to-survey; health inequalities; mixed-mode; multilingual

Introduction

Migration in Germany

Germany is a country of immigration and was the second top destination country worldwide after the United States in 2019 [1]. In 2020, 27% of the population had a so-called migration background, which is defined by the Federal Office for Statistics as the person themselves or at least 1 of their parents were born with a citizenship other than German [2]. In Germany, 17% of the population had their own history of migration [2]. One of the relevant events in the recent history of immigration to Germany was the signing of multiple so-called guest workers recruitment contracts with countries in Southern Europe such as Turkey and Italy and countries in North Africa from the 1950s onward, followed by many returns but also by the immigration of some of the workers' families. Since the 1950s, the immigration of the so-called (late) repatriates from countries of the former Soviet Union began, with most people immigrating during the 1980s and 1990s. During the 1990s, people from the former Yugoslavia fled the wars, and since the 2000s, people from Eastern European countries, for example, Poland, Romania, and Bulgaria, immigrated to Germany or commuted between Germany and their countries of origin in accordance with the European Union Freedom of Movement Act. In particular, during the 2010s, refugees came to Germany from countries such as Iraq, Afghanistan, or Syria. All of these different and heterogeneous groups of migrants and their descendants are subsumed under the statistical category of people with a migration background—except for the so-called (late) repatriates—although their duration of residence, reasons for migration, experiences during the migration process, residence status, and living situations differ. Hence, to identify health resources and health risks in epidemiological research on migration and health, multiple determinants that go beyond the category of migration background need to be considered.

Migration and Health

Previous research showed specific differences in health outcomes between the general population and people with a history of migration in Germany. For example, higher rates of chronic preconditions or diseases, such as vascular and heart disease, obesity, and diabetes, are observed in people with a history of migration [3]; the prevalence of diabetes (mellitus and gestational) is found to be higher in first-generation migrants from Turkey [4]. Furthermore, the prevalence of specific infectious diseases, such as tuberculosis, is higher in migrant groups from endemic areas (eg, several Eastern European and Central Asian countries) [5,6]. Lower outcomes regarding psychological well-being were reported for asylum seekers and refugees than for the general population [7]. In addition, differences were observed in the utilization of health care services, for example, in terms of specialist health care, medication use, or therapist consultation, which are utilized less often by people with a migration background than by those without a migration background [8]. Moreover, the rates of utilization of preventive services, such as cancer screening or health checkups [9], as well as rehabilitative care services [10], are lower among people with a migration background.

The mechanisms underlying these differences in health outcomes cannot be explained by solely focusing on the category of migration background. Social determinants of health—as in the general population as well—need to be considered, for example, living situation; income; the risk of poverty; working conditions [10]; the impact of perceived discrimination [11,12]; or structural barriers in accessing health care services, which are especially prevalent among asylum seekers and refugees [13-15]. To facilitate such analyses, it is essential to include people with a history of migration into national public health monitoring, namely (1) equivalent to their proportion of the population and (2) considering their heterogeneity, for example, by offering different modes of survey administration or questionnaire languages to satisfy different needs.

Participation of People With a History of Migration in Interview Surveys

During recent years, the participation of people with a history of migration was low in the "German Health Update" (Gesundheit in Deutschland aktuell [GEDA]), which is 1 of 3 parts of the national public health monitoring in Germany conducted by the Robert Koch Institute (RKI). For example, in GEDA 2019/2020, overall, 9% of the participants reported a country of birth other than Germany compared with 18.4% of the adult population whose country of birth is not Germany according to population statistics, and 3.9% reported a citizenship other than German compared to the 12.5% of adults living in Germany who have a citizenship other than German [16]. Thus, analyses of differences in health outcomes are difficult, as a selection bias among people with different countries of birth or citizenship might be assumed. Other studies focused on specific migrant groups, for example, those of Turkish origin [4,17,18], so-called (late) repatriates [19,20], or refugees [13,15,21]. Migration-related factors influencing health status can be analyzed within these groups; however, analyses across these groups are mostly not possible, as sampling procedures, methods of data collection, and survey indicators

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might differ. Moreover, comparability with the data from population-based public health monitoring is limited.

To overcome these issues, the project "Improving Health Monitoring in Migrant Populations" (IMIRA) was initiated at the RKI in 2016 [22]. One of its aims was to develop strategies for improving the inclusion of people with a history of migration in interview surveys. Therefore, a multilingual mixed-mode feasibility study was conducted among people with Croatian, Polish, Romanian, Syrian, or Turkish citizenship in 2 German federal states, namely Berlin and Brandenburg [23,24]. The findings and lessons learned from this feasibility study were subsequently implemented in the interview survey GEDA Fokus.

Objectives of GEDA Fokus

As described, people with a history of migration are often underrepresented in the RKI health interview surveys (GEDA). Therefore, with GEDA Fokus, we aimed to conduct an interview survey among people with selected citizenships to provide comprehensive data on specific migrant groups to facilitate the analyses of relevant factors impacting their health status. The objectives of GEDA Fokus were as follows:

1. Description of the health status of the participants stratified by migration-related factors: the health status of the participants will be described based on a set of core indicators [25], considering migration-related factors with assumed impact on their health, such as duration of residence, residence status, motives of migration, German language proficiency, or perceived discrimination.
2. Methodological analyses to improve the response rate of people with a history of migration in future public health monitoring: the heterogeneity within people with a history of migration in terms of their level of education or income, German language proficiency, or trust in institutions makes differentiated approaches necessary for enabling the accessibility of (interview) surveys for different groups of people. Detailed analyses of recruitment strategies and the use of modes of administration can contribute to a better understanding of how specific subgroups can be reached in future interview surveys.

Methods

Study Design

The interview survey GEDA Fokus was a multilingual survey (Arabic, Croatian, Italian, German, Polish, and Turkish) applying a sequential mixed-mode design, offering a self-administered questionnaire on the web and, in the case of initial nonresponse, on paper. In larger municipalities, personal interviews by (partly) multilingual interviewers to be held either in the study persons' homes or by telephone were also offered. The study persons were randomly selected from residents' registration offices.

Selection of the Study Population

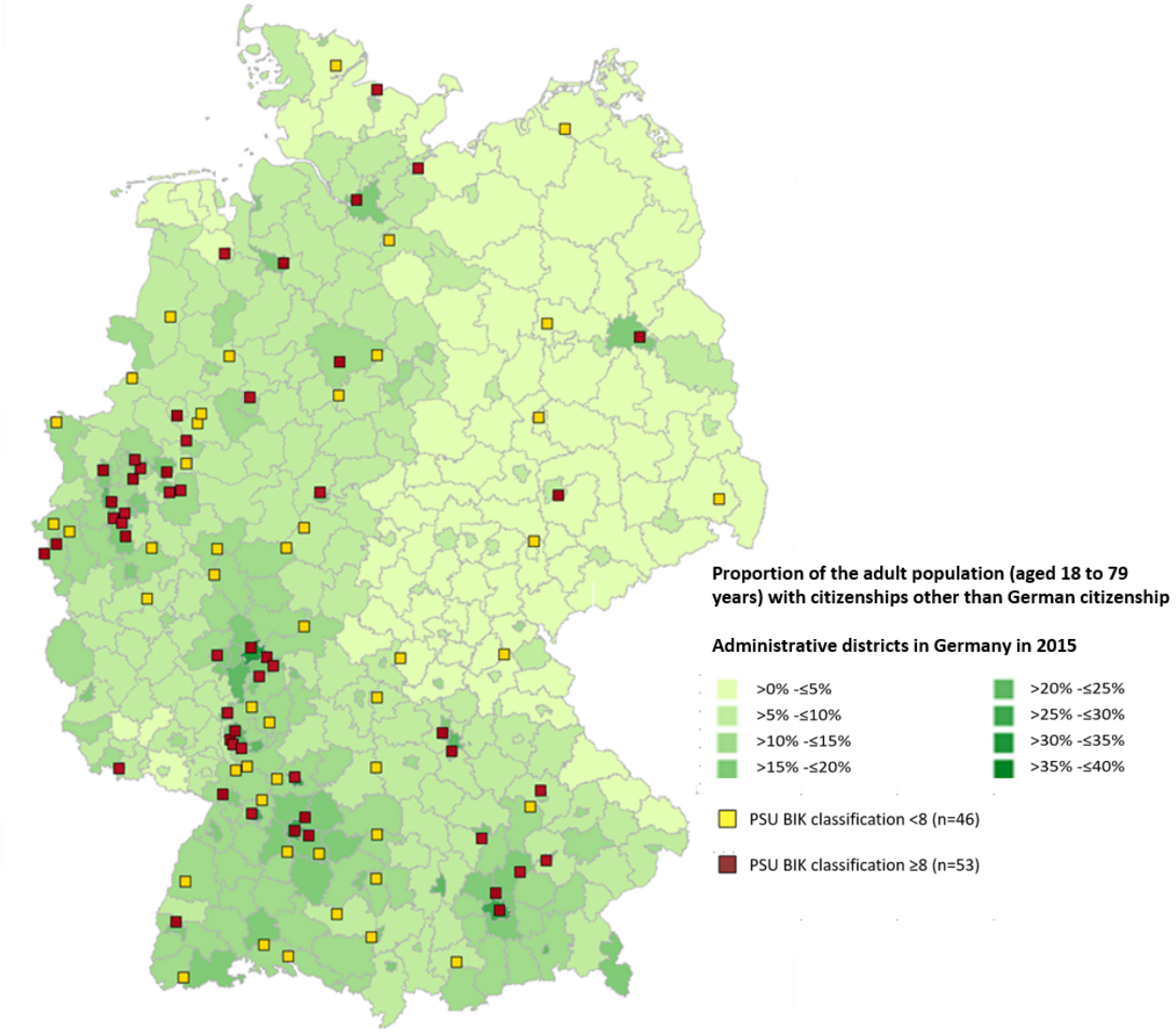
Registries of residents' registration offices were used for sampling, which provides a solid sampling frame for population surveys. Citizenship is the only characteristic captured here that can approximate migration history. By selecting people in this manner, naturalized persons or those of the second migrant generation with only German citizenship cannot be identified. To determine which citizenships to include in the survey (by citizenship), we used data from the Central Register of Foreigners from 2015 to 2017. We conducted model calculations using the Foreigners' Statistic, which is based on the Central Register of Foreigners, considering the current stock, as well as the dynamics (inward and outward migration) of the top 10 citizenships according to the Foreigners' Statistic in 2017. The most common citizenships identified over time in this manner were Italian, Polish, Romanian, Syrian, and Turkish; however, our feasibility study [23,24] showed that sampling from residents' registration offices did not seem effective enough to reach people with Romanian citizenship because of high rates of ineligible addresses. Therefore, it was decided in accordance with the views of the members of the projects' advisory board that Croatian citizenship be included instead of Romanian citizenship, as it was the next most relevant citizenship according to the model calculations. Thus, our study population included people with a registered Croatian, Italian, Polish, Syrian, or Turkish citizenship. Within residents' registration offices, up to 3 citizenships of residents are captured, and all were considered.

Selection of the Primary Sampling Units

Primary sampling units (PSUs) were selected by colleagues at the GESIS Leibniz Institute for the Social Sciences using a Cox algorithm. This selection was based on the following stratification: the classification of federal states into regions (north, south, east, and west), the number of districts and urban municipalities per federal state, and the average proportion of the population without German citizenship within the districts and urban municipalities per federal state. Overall, 120 PSUs were selected (crude number of PSUs=99, as bigger cities such as Berlin were selected more than once): 74 with a Beratung Information Kommunikation (BIK) classification of ≥8 (urban PSUs; crude n=53) and 46 PSUs with a BIK classification of <8 (merely rural areas and smaller cities). The BIK classification systematically structures areas by describing relations between cities and surrounding areas in Germany [26]. A BIK classification of 8 is ascribed to the core areas of cities with 100,000 to 500,000 inhabitants, and classifications of 9 and 10 are ascribed to the core and surrounding areas of cities with ≥500,000 inhabitants [26]. The PSUs selected for GEDA Fokus are displayed in Figure 1.

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Figure 1. Primary sampling units (PSUs) of the interview survey German Health Update Fokus (GEDA Fokus). BIK: Beratung Information Kommunikation.



Participants and Inclusion Criteria

People were included in GEDA Fokus if they:

- had a Croatian, Italian, Polish, Syrian, or Turkish citizenship (first, second, or third citizenship according to residents' registration office),
- were aged between 18 and 79 years,
- had their principal residence in one of the selected PSUs, and
- were able to give written informed consent for survey participation.

People were excluded from the survey if:

- their language proficiency in German or one of the offered translation languages was insufficient to answer the questionnaire or interview or
- they were not able to give written informed consent for survey participation.

Sampling Procedures

Sampling was carried out at the RKI in 2 tranches; data were cleaned upon reception from the residents' registration offices and forwarded via a secured data link to the external service provider "Kantar GmbH," who conducted the data collection on behalf of the RKI. Kantar GmbH is a market research company that conducts social science and health research surveys. Tranche 1 included 15 PSUs with a BIK classification of <8 and 30 PSUs with a BIK classification of ≥8 (crude n=17). Tranche 2 included 31 PSUs with a BIK classification of <8 and 44 PSUs with a BIK classification of ≥8 (crude n=36). The gross sample comprised 39.53% (13,216/33,436) of study persons in tranche 1 and 60.47% (20,220/33,436) of study persons in tranche 2.

Recruitment of the Participants

In the first study phase, all the selected study persons (N=33,436) received an invitation to participate by postal mail, including a link and log-in information to the web-based questionnaire. The invitation letter and the study information leaflet were bilingual, with a German version on one side and the respective translated version on the other. In the web-based survey, the participants were able to select the German language–only or a bilingual version (eg, German-Italian) of the questionnaire. To ask questions regarding the survey itself

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or to refuse participation, the study persons were offered contact options (hotline or email address). In addition, frequently asked questions were posted on a multilingual website.

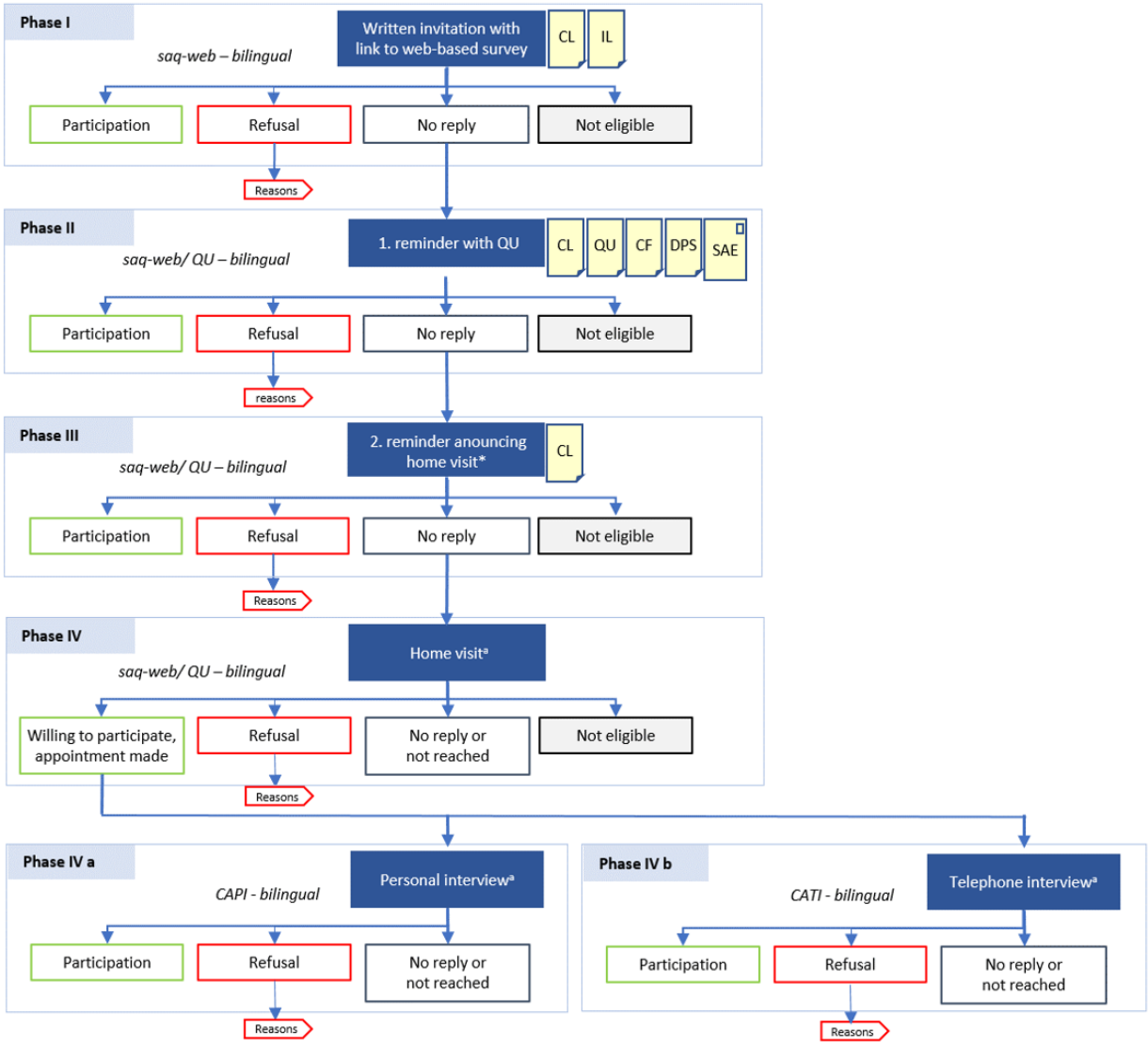
In the second study phase, all the study persons who neither took part nor refused participation received postal mail with a bilingual reminder including the web link and log-in information for the web-based survey, a study information leaflet, a data privacy statement, and a bilingual paper-based questionnaire. The paper-based questionnaire featured a line-by-line translation (eg, German-Italian). At the end of the paper-based questionnaire, a bilingual consent form was attached that the study persons needed to sign and send back.

The third study phase varied between PSUs with a BIK classification of <8 and those with a BIK classification of ≥8. Study persons in the smaller PSUs only received a second bilingual reminder letter in the form of an enveloped postcard including the web link and log-in information for the web-based questionnaire. In the PSUs with a BIK classification of ≥8, a home visit was announced with the purpose of conducting a personal interview.

In the last study phase, the interviewers (partly bilingual) visited the study persons who had not taken part or refused participation at their homes to either conduct a personal interview or, depending on the preference of the study persons, obtain their telephone number and conduct a telephone interview afterward. The latter option was particularly offered to account for the SARS-CoV-2 pandemic.

If study persons refused participation, the reasons for nonparticipation were collected either on the telephone (hotline) or during personal contact at their home. The study flow is displayed in Figure 2. Data were collected from November 2021 to May 2022.

Figure 2. Study flow of the interview survey German Health Update Fokus (GEDA Fokus). CAPI: computer-assisted personal interview; CATI: computer-assisted telephone interview; CF: consent form; CL: cover letter; DPS: data privacy statement; IL: information leaflet; QU: paper-based questionnaire; SAE: self-addressed envelope.



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Sample Size and Anticipated Response Rates

The calculated sample size was 1000 to 1200 participants per citizenship to enable stratified analyses by gender and 3 age groups for an expected prevalence of 5%. The anticipated response rate was 15% on average based on the experience of the feasibility study [23,24], resulting in a gross sample of 33,500 people.

Anticipated response rates were calculated per citizenship based on the response rates observed in the feasibility study (for web-based and personal interviews) and experiences from the GEDA survey 2014/2015 to account for the effect of the paper-based questionnaire on the response rate. The response rate of people with Italian citizenship was estimated as the mean of the response rates of the other citizenships. The response rate of people with Turkish citizenship was comparatively low in the feasibility study and was, therefore, corrected by calculating the mean of the response rate of the group with Turkish citizenship from the feasibility study and the estimated response rate of the group with Italian citizenship for GEDA Fokus. As phase IV in the feasibility study only took place among the groups with Syrian and Turkish citizenship, we estimated the effect of this study phase as the mean of both groups for the groups with Croatian, Italian, or Polish citizenship. We assumed a proportion of quality neutral losses of 10% in the PSUs with a BIK classification of <8 (n=46) and a proportion of 15% for the PSUs with a BIK classification of ≥8 (n=53). Table 1 summarizes the results of these calculations.

Table 1. Anticipated response rates and number of cases of the interview survey German Health Update Fokus (GEDA Fokus), stratified by Beratung Information Kommunikation (BIK) classification and study phases.

Citizenship	Anticipated response rates, %		Gross sample (unadjusted[a]), n		Gross sample (adjusted[b]), n		Participants (net sample), n			
	Phases I-III	Phase IV	BIK<8	BIK≥8	BIK<8	BIK≥8	Phases I-III		Phase IV	Total
							BIK<8	BIK≥8	BIK≥8	
Italian	15.23	5.85	867	5893	788	5125	120	780	300	1200
Croatian	14.3	5.85	923	6164	839	5360	120	766	314	1200
Polish	19	5.85	695	4998	632	4346	120	826	254	1200
Syrian	20.6	7.4	641	4436	583	3857	120	795	285	1200
Turkish	11.11	5.08	1188	7673	1080	6672	120	741	339	1200

[a]Includes the assumed proportion of quality neutral losses.

[b]Excludes the assumed proportion of quality neutral losses.

Measurements

Key aspects of the survey are the core indicators for describing the health status of people with a migration background that were developed within the IMIRA project [25]. We added several social determinants of health, additional aspects of the utilization of health care, indicators for describing the impact of the COVID-19 pandemic, and the utilization of testing and vaccination. The approximated time for completing the questionnaire was 30 to 45 minutes. Textbox 1 lists the topics covered in the questionnaire.

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Textbox 1. Topics covered within the German Health Update Fokus (GEDA Fokus) questionnaire.

Personal information

- Age
- Sex and gender

Overall health status

- General health status
- Impairments in daily life
- Chronic diseases

Diseases

- Myocardial infarction
- Cardiac insufficiency
- Hypertension
- Asthma
- Tuberculosis
- Autoimmune disease
- Chronic kidney disease
- Rheumatoid arthritis
- Lipometabolic disorder
- Depression
- Anxiety disorder
- Coronary heart disease
- Stroke
- Diabetes
- Obesity
- Chronic bronchitis, chronic obstructive pulmonary disease, and emphysema
- Allergies
- Chronic liver disease
- Arthrosis or degenerative joint disease
- Chronic back pain
- Cancer

SARS-CoV-2 or COVID-19

- Laboratory test
- Hospitalization
- Effects of infection control measures
- Diagnosis
- Vaccination

Health care

- Hospitalization
- Utilization of therapy
- Need for health care services
- Vaccinations and utilization of medical services
- Utilization of general and specialist medical care

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- Health insurance status
- Incapacity to work due to illness
- Care

Living conditions

- Social support and contacts
- Self-efficacy
- Subjective social status and life satisfaction
- Sense of belonging
- Self-perceived discrimination
- Religion and faith

Health behavior

- Physical activity
- Alcohol consumption
- Body weight and height
- Smoking
- Dietary intake
- Health information

Migration status

- Country of birth
- Reasons for migration
- Residence status
- Year of immigration
- Citizenship or citizenships
- Language proficiency (German and native language if other than German)

Household and housing situation

- Marital status
- Number of household members
- Type of building
- Size of living space

Employment situation

- Formal and vocational education
- Workplace exposure, shift work, and temporary employment
- Employment and occupational status
- Unemployment
- Income

Weighting Procedures

A total of 2 weighting factors were calculated: one of them allows overall analyses across all 5 citizenship groups, and the other considers the marginal distributions within each citizenship group. On the one hand, the weighting factors control for the sampling of the PSUs, and on the other hand, they fit the sample to the marginal distribution of the population. When fitting the sample to the marginal distribution of the population, the weighting factors consider the distribution of region, gender, age, education (International Standard Classification of Education 2011), and the duration of residence of the 5 citizenship groups. Marginal distributions were taken from the Mikrocensus 2018 [27] after restricting the data to the 5 citizenship groups (including dual citizens).

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Quality Assurance

The translation of the questionnaire was done by 2 independent translators per language and was followed by a 2-stage editing process. In the first stage, an editor with a medical science background chose the better translations point by point. In the second stage, an editor without a medical scientific background proofread for general comprehensiveness. After typesetting (web-based and paper-based questionnaires), native speakers confirmed the correct translations as well as typesetting.

The data collection process was regularly monitored based on predefined indicators. The interviewers received training on the study aims and study design as well as on data protection and ethical aspects. Regular meetings for process evaluation took place, enabling the exchange of recruitment strategies between the interviewers and addressing the questions they raised.

Ethics Approval

Ethics approval was received on December 22, 2021, from the ethics committee at the Medical University of Charité, Berlin (EA1/250/21). The study was approved by the Commissioner for Data Protection of the RKI without concern as of October 26, 2021. Written informed consent was obtained from all the study participants who completed a paper-based questionnaire or had a face-to-face interview. Oral consent was obtained from the study participants who had a telephone interview. Those who participated on the web consented by clicking on a respective button. The consent form was available in all 6 study languages. The interview data were anonymized and are stored at the RKI. After participation, all the study participants received an incentive in the form of a voucher worth €10 (US $11.4 as of January 3, 2022).

Results

Overall¸ 6038 study participants took part in the survey, of whom 2983 (49.4%) were female. The median age was 39 years, and the median duration of residence in Germany was 10 years, with 19.69% (1189/6038) of the sample being born in Germany (unweighted). The characteristics of the study population stratified by citizenship group are displayed in Table 2. The overall response rate according to the American Association for Public Opinion Research (AAPOR; response rate 1) [28] was 18.4%, ranging from 13.8% in the group with Turkish citizenship to 23.9% in the group with Syrian citizenship. Furthermore, the response rates differed between the smaller municipalities where personal interviews were not offered (12.5%) and bigger cities where personal interviews were offered (19.3%). The self-administered web-based questionnaire (3028/6038, 50.15%) was the most opted mode of administration, followed by the paper-based version (1689/6038, 27.97%). Personal interviews in the study participants' homes were conducted with 17.12% (1034/6038) of the participants, and telephone interviews were conducted with 4.75% (287/6038) of the participants. Of the 6038 participants, 2527 (41.85%) indicated that they had answered the questionnaire in German only, 1008 (16.69%) exclusively used the translation, and 2503 (41.45%) used both languages in the bilingual version of the questionnaire. More detailed results will be published soon.

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Table 2. Description of the study population of the interview survey German Health Update Fokus (GEDA Fokus) (n=6038).

	Croatian (n=1223)		Italian (n=1205)		Polish (n=1193)		Syrian (n=1209)		Turkish (n=1208)	
	n (%)[a]	Weighted % (95% CI)	n (%)[a]	Weighted % (95% CI)	n (%)[a]	Weighted % (95% CI)	n (%)[a]	Weighted % (95% CI)	n (%)[a]	Weighted % (95% CI)
Region										
North	176 (14.39)	6.6 (2.4-16.7)	193 (16.02)	6.6 (2.9-14.4)	161 (13.5)	20.4 (9.5-38.6)	157 (12.99)	19.4 (9.8-34.7)	154 (12.75)	13.5 (6.0-27.5)
East	157 (12.84)	5.3 (1.5-16.8)	209 (17.34)	5.9 (1.9-17.1)	189 (15.84)	14.0 (4.1-38.3)	169 (13.98)	20.8 (7.4-46.1)	199 (16.47)	6.4 (1.6-21.9)
South	380 (31.07)	63.3 (50.1-74.9)	382 (31.7)	53.0 (40.1-65.5)	366 (30.68)	28.5 (18.6-41.0)	420 (34.74)	27.5 (17.4-40.6)	396 (32.78)	36.7 (25.3-49.8)
West	510 (41.7)	24.8 (15.7-37.0)	421 (34.94)	34.5 (23.7-47.2)	477 (39.98)	37.1 (24.8-51.3)	463 (38.3)	32.4 (21.2-46.1)	459 (38)	43.5 (30.7-57.2)
BIK[b] classification										
<8	125 (10.22)	29.7 (19.7-42.0)	148 (12.28)	36.2 (25.0-49.0)	134 (11.23)	26.0 (16.8-38.0)	148 (12.24)	35.9 (23.3-50.8)	152 (12.58)	19.3 (12.5-28.4)
≥8	1098 (89.78)	70.3 (58.0-80.3)	1057 (87.72)	63.8 (51.0-75.0)	1059 (88.77)	74.0 (62.0-83.3)	1061 (87.76)	64.1 (49.2-76.7)	1056 (87.42)	80.8 (71.6-87.5)
Sex										
Female	663 (54.21)	47.7 (42.6-52.8)	581 (48.22)	40.5 (35.1-46.1)	685 (57.42)	51.4 (46.4-56.4)	759 (62.78)	64.6 (59.9-69.1)	604 (50)	49.0 (44.8-53.2)
Male	560 (45.79)	52.3 (47.2-57.4)	624 (51.78)	59.5 (53.9-64.9)	508 (42.58)	48.6 (43.6-53.7)	450 (37.22)	35.4 (30.9-40.1)	604 (50)	51.0 (46.8-55.2)
Age (years)										
Median (range)[a]	42 (18-79)	N/A[c]	39 (18-79)	N/A	44 (18-79)	N/A	34 (18-79)	N/A	41 (18-79)	N/A
18-29	259 (21.18)	17.3 (13.3-22.2)	286 (23.73)	19.9 (16.0-24.4)	204 (17.1)	20.2 (15.9-25.2)	399 (33)	46.1 (40.1-52.3)	356 (29.47)	20.9 (17.6-24.6)
30-39	297 (24.28)	20.9 (16.8-25.6)	324 (26.89)	20.4 (15.4-26.4)	283 (23.72)	27.3 (23.4-31.5)	399 (33)	30.6 (26.5-35.0)	217 (17.96)	19.9 (16.0-24.4)
40-49	279 (22.81)	22.0 (17.9-26.7)	226 (18.76)	16.7 (12.7-21.7)	250 (20.96)	22.9 (19.3-27.0)	219 (18.11)	14.4 (11.1-18.5)	256 (21.19)	24.1 (20.6-28.0)
50-59	189 (15.45)	15.1 (11.0-20.4)	182 (15.1)	20.5 (15.8-26.1)	220 (18.44)	17.4 (13.8-21.8)	118 (9.76)	6.0 (4.5-7.9)	217 (17.96)	18.7 (16.0-21.8)
60-69	97 (7.93)	9.8 (7.0-13.7)	121 (10.04)	16.1 (12.0-21.2)	163 (13.66)	10.4 (7.7-13.9)	56 (4.63)	2.1 (1.4-3.2)	80 (6.62)	7.6 (5.5-10.5)
70-79	102 (8.34)	14.8 (10.3-20.9)	66 (5.48)	6.4 (4.4-9.4)	73 (6.12)	1.8 (1.3-2.5)	18 (1.49)	0.8 (0.4-1.6)	82 (6.79)	8.7 (6.1-12.4)
Education (ISCED[d] 2011)										
Low	255 (20.85)	29.8 (23.6-36.9)	252 (20.91)	44.7 (39.4-50.1)	239 (20.03)	19.8 (15.7-24.6)	452 (37.39)	54.2 (47.0-61.3)	506 (41.89)	62.9 (58.1-67.5)
Middle	592 (48.41)	56.4 (50.0-62.6)	413 (34.27)	39.2 (34.7-43.8)	500 (41.91)	55.7 (50.2-61.1)	385 (31.84)	28.6 (23.8-34.0)	370 (30.63)	30.6 (26.4-35.2)
High	373 (30.5)	13.8 (10.6-17.8)	536 (44.48)	16.2 (12.6-20.6)	447 (37.47)	24.5 (21.1-28.3)	364 (30.12)	17.2 (13.7-21.3)	322 (26.66)	6.5 (5.0-8.4)
Missing	3 (0.24)	N/A	4 (0.33)	N/A	7 (0.59)	N/A	8 (0.66)	N/A	10 (0.83)	N/A
Duration of residence (years)										
Median (range)[a,e]	8 (1-79)	N/A	11 (1-68)	N/A	22 (1-67)	N/A	7 (1-64)	N/A	26 (1-74)	N/A
≤5	284 (23.22)	15.3 (11.4-20.2)	177 (14.69)	6.9 (4.5-10.5)	121 (10.14)	12.2 (9.2-16.0)	232 (19.19)	21.6 (16.8-27.2)	165 (13.66)	3.1 (1.9-5.0)

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	Croatian (n=1223)		Italian (n=1205)		Polish (n=1193)		Syrian (n=1209)		Turkish (n=1208)	
	n (%)[a]	Weighted % (95% CI)	n (%)[a]	Weighted % (95% CI)	n (%)[a]	Weighted % (95% CI)	n (%)[a]	Weighted % (95% CI)	n (%)[a]	Weighted % (95% CI)
6-10	232 (18.97)	13.1 (9.8-17.4)	213 (17.68)	8.7 (6.0-12.5)	168 (14.08)	22.6 (17.3-28.8)	822 (67.99)	72.2 (66.2-77.4)	60 (4.97)	2.4 (1.4-4.1)
11-20	57 (4.66)	6.7 (4.1-10.7)	101 (8.38)	6.4 (4.1-10.0)	198 (16.6)	24.7 (19.8-30.2)	48 (3.97)	3.2 (1.8-5.9)	86 (7.12)	8.4 (5.8-12.0)
≥21	386 (31.56)	47.2 (39.9-54.6)	324 (26.89)	46.4 (40.8-52.0)	549 (46.02)	36.4 (30.4-42.8)	64 (5.29)	2.2 (1.2-4.2)	475 (39.32)	54.7 (50.1-59.3)
Since birth	251 (20.52)	17.7 (13.5-23.0)	381 (31.62)	31.6 (26.5-37.2)	125 (10.48)	4.2 (3.1-5.8)	36 (2.98)	0.8 (0.4-1.8)	396 (32.78)	31.4 (27.0-36.1)
Missing	13 (1.06)	N/A	9 (0.75)	N/A	32 (2.68)	N/A	7 (0.58)	N/A	26 (2.15)	N/A

[a]Crude.

[b]BIK: Beratung Information Kommunikation.

[c]N/A: not applicable.

[d]ISCED: International Standard Classification of Education.

[e]Without the category “since birth.”

Discussion

Principal Findings and Outlook

We recruited the first nationwide sample of people with selected citizenships in Germany, representing the major groups with citizenships other than German. The sequential mixed-mode design and provision of multilingual study materials facilitated the participation of different groups of people in the study, for example, participants with lower proficiency in German or less preference for web-based participation. The data from this study will allow us to expand public health reporting on people with a history of migration in Germany, considering the core indicators developed within the scope of the IMIRA project [25]. Furthermore, we will be able to expand the knowledge on the impact of the COVID-19 pandemic on people with a history of migration. In addition, this sample will allow us to analyze factors associated with the health of people with a history of migration in a more differentiated manner, considering different migration-related and social determinants of health such as duration of residence, residence status, or living and working conditions.

Limitations

First, sampling was only possible based on citizenship, as no other migration-related indicator is reliably captured within the residents’ registration offices. Therefore, not all groups of people with a history of migration are included, for example, naturalized people with only German citizenship or people with citizenships other than those that were selected. Therefore, conclusions cannot be drawn for all people with a history of migration living in Germany and can be drawn only for those with the 5 selected citizenships.

Sampling of the PSUs has some limitations, as we do not know the exact number of people with selected citizenships living within the municipalities and cities in Germany; this is especially the case for people with dual or multiple citizenships, as they are not captured within the Foreigners’ Statistics. Therefore, sampling was based on the overall proportion of people without German citizenship within the rural and urban districts. It was not always possible to sample the required number of people per citizenship (gross sample) within the smaller municipalities; this is especially true for people with Italian or Croatian citizenship in the northern and eastern parts of Germany. We filled these gaps by oversampling within the PSUs with a BIK classification of ≥8. Furthermore, the original selection of PSUs was based on the presumption that one-third of the net sample could be recruited in the PSUs with a BIK classification of <8. Once we encountered the problem of drawing enough people for the gross sample within the smaller PSUs, we adjusted this goal to recruit 10% of the net sample within the PSUs with a BIK classification of <8. This might result in cluster effects toward larger cities, which might limit comparisons between the rural and urban areas. Furthermore, this leads to a higher variance of the weighting factors for the participants in the PSUs with a BIK classification of <8. A higher variance of the weighting factors is associated with a lower precision of the estimates.

Furthermore, we offered only 6 languages, whereas other languages might have been required for respondents, for example, Kurdish, which might have been preferable for some people with Turkish or Syrian citizenship. In addition, we originally planned to apply a team translation approach, where 2 independent translators would translate the questionnaire, which would be followed by a moderated process with an editor to find the most accurate translation. Instead, translations underwent a 2-stage editing process; however, it was not possible to manage the moderated adjudication process of the team translation approach under the COVID-19 pandemic circumstances and time constraints.

The COVID-19 pandemic might have impacted the willingness to participate in the survey, as the public opinion on this topic, on the RKI as a national public health institute, and on the measures taken to slow down the spread of the virus were quite controversial during the period of data collection. This might have deterred some study persons from taking part in the survey; others might not have participated because of the fear of

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infection during the personal interviews. We attempted to address this issue by offering telephone interviews; however, the pandemic situation might have caused selection bias.

Strengths

Besides these limitations, we want to highlight some strengths of the interview survey GEDA Fokus. First, it resulted in the largest sample of people with their own or a familial history of migration in Germany up to now. Although the indicator "citizenship" has its limitations, as mentioned earlier, we have certain marginal distributions according to Mikrocensus for the people with the selected citizenships, which allow us to weight data to yield generalizable results for this defined group.

The multimodal survey design resulted in accessibility for different groups of people, for example, for older people preferring paper-based questionnaires. In addition, the home visits with personal interviews as the gold standard [29-34] increased participation as personal contact builds trust, and concerns could be addressed directly. Offering multilingual questionnaires facilitated participation for study persons with lower German language proficiency because of, for example, a shorter duration of residence [23,24], as was the case among the participants with Syrian citizenship. Further methodological analyses will contribute to the understanding of how certain hard-to-survey subgroups among people with a history of migration can be reached and will be published soon.

The most newly developed survey instruments underwent cognitive pretesting [35,36] in the 5 translation languages before their application in GEDA Fokus to ensure a common understanding and comprehension of the questions [16,37]. Migration-related concepts, as well as indicators on discrimination, feelings of belonging, and self-efficacy, in connection with other social determinants of health, for example, housing, living, and socioeconomic aspects, will provide important insights into the complex interdependencies between social determinants and migrant health. Reporting the core indicators on the health of people with a migration background [25] will deliver important data to inform public health intervention planning. The indicators used in GEDA Fokus were also used in the European Health Interview Survey (EHIS), which will enable comparisons of the health status with the general population in Germany.

Conclusions

We recruited approximately 6000 participants with Croatian, Italian, Polish, Syrian, or Turkish citizenship (1200 per group) living all over Germany. Multimodal survey administration, including the provision of personal interviews and bilingual study materials, facilitated the participation of different subgroups of people in the survey, resulting in a heterogeneous sample of people with their own or a familial history of migration with selected citizenships. Future data analyses will provide insights into the complex interplay between migration and health, considering different migration-related, social, and structural determinants of health.

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Data Availability

The data sets generated during this study are not publicly available because of data protection reasons but are available from the corresponding author upon reasonable request.

Conflicts of Interest

None declared.

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Abbreviations

AAPOR: American Association for Public Opinion Research
BIK: Beratung Information Kommunikation
EHIS: European Health Interview Survey
GEDA: German Health Update (Gesundheit in Deutschland aktuell)
IMIRA: Improving Health Monitoring in Migrant Populations
PSU: primary sampling unit
RKI: Robert Koch Institute

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Protocol

Examining Visual Attention to Tobacco Marketing Materials Among Young Adult Smokers: Protocol for a Remote Webcam-Based Eye-Tracking Experiment

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Abstract

Background: Eye tracking provides an objective way to measure attention, which can advance researchers' and policy makers' understanding of tobacco marketing influences. The development of remote webcam-based eye-tracking technology, integrated with web-based crowdsourcing studies, may be a cost-effective and time-efficient alternative to laboratory-based eye-tracking methods. However, research is needed to evaluate the utility of remote eye-tracking methods.

Objective: This study aimed to detail the process of designing a remote webcam-based eye-tracking experiment and provide data on associations between participant characteristics and the outcomes of experiment completion.

Methods: A total of 2023 young adult (aged 18-34 years) cigarette smokers in the United States were recruited to complete a web-based survey that included a 90-second remote eye-tracking experiment that examined attention to e-cigarette marketing materials. Primary outcome measures assessed the completion of the remote eye-tracking experiment—specifically, experiment initiated versus not initiated, experiment completed versus not completed, and usable versus nonusable eye-tracking data generated. Multivariable logistic regressions examined the associations between outcome measures and participants' sociodemographic backgrounds, tobacco use history, and electronic devices (mobile vs desktop) used during the experiment.

Results: Study recruitment began on April 14, 2022, and ended on May 3, 2022. Of the 2023 survey participants, 1887 (93.28%) initiated the experiment, and 777 (38.41%) completed the experiment. Of the 777 participants who completed the experiment, 381 (49%) generated usable data. Results from the full regression models show that non-Hispanic Black participants (adjusted odds ratio [AOR] 0.64, 95% CI 0.45-0.91) were less likely to complete the eye-tracking experiment than non-Hispanic White participants. In addition, female (vs male) participants (AOR 1.46, 95% CI 1.01-2.11), those currently using (vs not using) e-cigarettes (AOR 2.08, 95% CI 1.13-3.82), and those who used mobile (vs desktop) devices (AOR 5.10, 95% CI 3.05-8.52) were more likely to generate usable eye-tracking data.

Conclusions: Young adult participants were willing to try remote eye-tracking technology, and nearly half of those who completed the experiment generated usable eye-tracking data (381/777, 49%). Thus, we believe that the use of remote eye-tracking tools, integrated with crowdsourcing recruitment, can be a useful approach for the tobacco regulatory science research community to collect high-quality, large-scale eye-tracking data in a timely fashion and thereby address research questions related to the ever-evolving tobacco marketing landscape. It would be useful to investigate techniques to enhance completion rates and data usability.

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KEYWORDS

eye tracking; remote eye tracking; e-cigarette marketing; young adults; mobile phone

Introduction

Traditional Eye-Tracking Tools and Emergent Challenges

Eye tracking has become an increasingly popular method of assessing visual engagement with marketing and communication materials in tobacco control research and tobacco regulatory science [1,2]. In particular, eye tracking has been used to gain insight into how people pay attention to pro- or antitobacco communication efforts, such as industry marketing tactics [3,4], warning labels [5-10], and other tobacco-related health messages [11-13]. Unlike self-reported surveys or qualitative assessments that could introduce recall and response biases, eye tracking provides objective measures of visual attention to tobacco marketing stimuli that are predictive of information recall and processing [1,14], which can lead to changes in perceptions about tobacco products. Studies using eye tracking can help inform researchers and policy makers about the influence of tobacco marketing exposure among various populations.

Eye tracking is typically conducted in an in-person research setting, with participants entering a computer laboratory equipped with specialized, infrared eye-tracking equipment, operated by at least 1 research staff member. Challenges associated with traditional eye-tracking studies include the costly and tedious process of study implementation [15], which requires bringing people into a laboratory where they can be tracked individually, as well as geographic restrictions regarding the sample because most study recruitment takes place locally. Such challenges have been exacerbated by the recent COVID-19 pandemic, further highlighting the need for remote, web-based alternatives.

Advantages of Remote Webcam-Based Eye Tracking

Recent developments in web-based remote eye tracking, which accesses users' webcams to capture video images of the face to predict gaze location on the screen, as opposed to the traditional corneal and pupil reflection used in most laboratory eye trackers, make this approach an attractive, available alternative when laboratory studies are not possible. This approach may largely remove the restrictions of conducting traditional eye-tracking studies [16]. There are several benefits of using remote eye-tracking studies. Mainly, these studies can support large-scale, crowdsourced web-based research without geographic restrictions or restrictions pertaining to equipment or staff availability; researchers are also able to immediately and simultaneously obtain eye-tracking data from a large sample of participants. In addition, participants can perform tasks whenever and wherever they choose, as long as they have a computer or smartphone or tablet device equipped with a camera and an internet connection. The ability to conduct an eye-tracking study on participants' own devices in their natural environment makes it ideal for studies that examine participants' attention to commercial marketing materials seen in real life rather than within a controlled laboratory environment.

Remote eye tracking may be especially useful for conducting tobacco marketing research. First, compared with a laboratory setting, performing eye-tracking tasks on personal electronic devices in participants' natural environment may more realistically mimic the context of tobacco marketing exposure, particularly when the marketing stimuli consist of materials publicized on websites and social media platforms. As social media and web-based content become an increasingly common channel of tobacco marketing exposure for young people [17-20], the ability to perform eye-tracking tasks on personal electronic devices becomes especially important. In addition, the capability of remote eye-tracking technology to be compatibly used with large-sample crowdsourced data will facilitate researchers' and regulators' understanding of the influence of tobacco marketing materials at the population level and among subgroups (eg, tobacco users, former users, and never users). Finally, studies examining ever-changing tobacco marketing practices require designs that reflect the most recent marketing tactics and policy changes. Research that integrates remote eye-tracking technology with crowdsourcing data collection can provide rapid responses to surveillance needs and regulatory challenges requiring immediate attention.

Recent research studying the efficacy of remote eye-tracking technology shows that this new technology produces satisfactory accuracy (defined as the capacity to truthfully describe the location of a person's gaze on a screen) compared with the data gathered from a traditional infrared-based eye tracker used in a controlled laboratory setting [16,21-24]; for example, researchers were able to obtain comparable results from a remote versus laboratory-based eye-tracking experiment in 3 tasks commonly used for eye tracking (fixation, pursuit, and free viewing) and found that webcam-based eye tracking is generally suitable for all 3 tasks and holds promise in cognitive science–based research [21]. Together with the potential aforementioned benefits, remote eye tracking may be a potentially viable alternative for researchers that substantially reduces the time and costs associated with conducting a laboratory-based eye-tracking study.

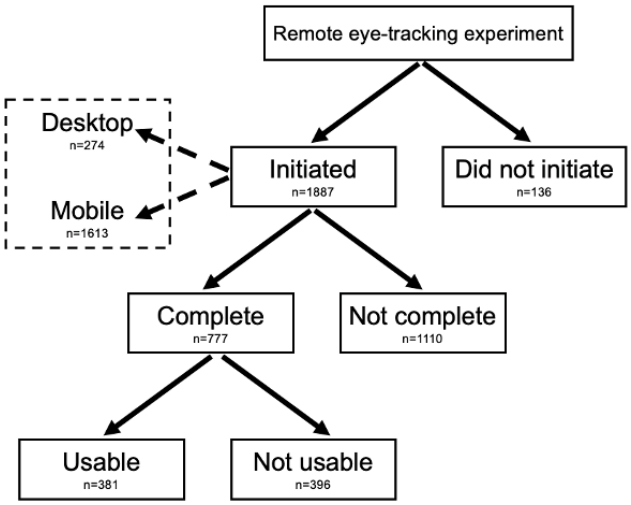
Research Questions and Study Objectives

Because of the novel nature of remote eye-tracking platforms, relatively few publications describe the process of configuring such experiments and integrating them with large-scale crowdsourcing survey platforms. In particular, there are questions of how this innovative method can be used to examine the influence of tobacco marketing materials among a large sample of tobacco users and which subpopulations (characterized by age, biological sex, race and ethnicity, and

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other factors) may be more likely to participate in remote eye-tracking studies. Using a large sample of young adult cigarette smokers who participated in a web-based survey through crowdsourcing, this study had two goals: (1) to provide a detailed description of our approach to configuring a remote eye-tracking experiment embedded in Qualtrics (Qualtrics International Inc), a research company used for conducting behavioral science research, including tobacco research and (2) to document associations with demographic, smoking history, and other characteristics of study participants who completed various stages of the remote eye-tracking experiment (Figure 1). Given the potential utility of remote eye-tracking tools for academic researchers, this paper further describes key features of the platform and integrated survey system for remote eye-tracking studies, details potential challenges that may occur before and during data collection, and recommends solutions to streamline the use of the tool and improve data collection quality.

Figure 1. Remote eye-tracking experiment flowchart and distribution of experiment completion. Definition of initiating the experiment: participants who chose to proceed to the eye-tracking experiment using either desktop or mobile devices. Definition of complete: participants who completed the entire experiment (participants who started the experiment but did not meet technical requirements or closed the browser or had timed out before reaching the end were considered "not complete"). Definition of usable: participants whose gaze and emotion were trackable during their session, that is, had proper lighting and did not move.



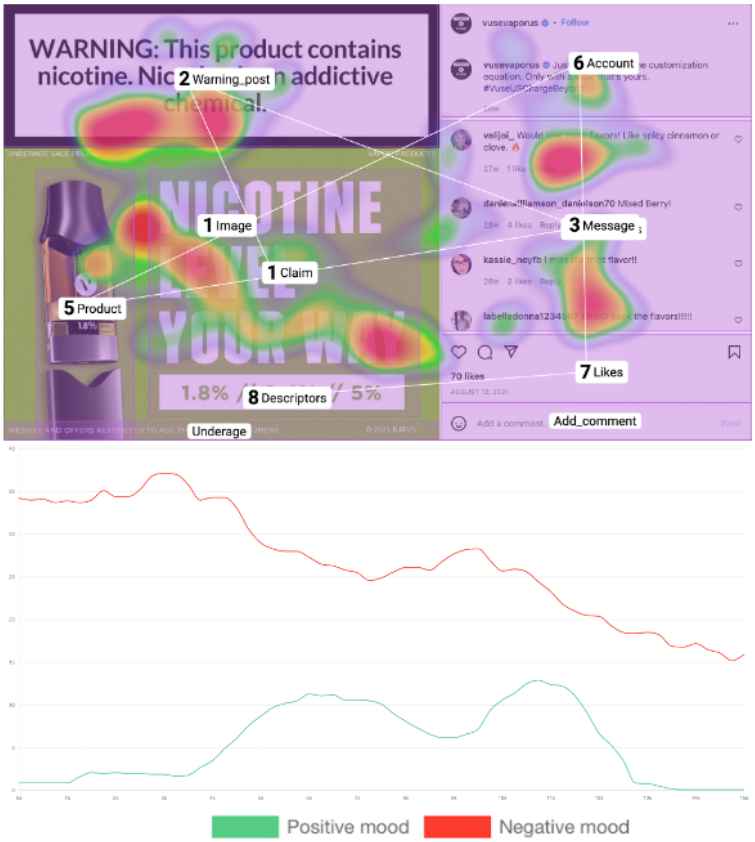
Methods

Remote Eye-Tracking System

This research used Sticky by Tobii (Tobii AB), a remote webcam-based eye-tracking tool that provides a cloud-based eye-tracking measurement of attention and emotional responses. This tool combines survey questions with remote webcam eye-tracking technology that can be used with cameras for tablet devices and mobile phones as well as webcams for laptop and desktop computers. It can be integrated with a web-based survey tool such as Qualtrics, which can help expand the research team's access to a larger study sample while providing various options for survey formatting. Through designating certain areas of interest (AOIs) on the experimental stimuli, researchers can identify participants' attention and emotional responses to different areas of the stimuli. Data generated from the experiment are automatically streamed to the cloud as they are recorded. On the basis of the analysis of participants' webcam video recordings, the cloud-based eye-tracking software platform generates attention data (measured by gaze patterns via webcam-based eye tracking) and emotion metrics (measured by various emotional expressions via webcam-based facial coding) within hours of data collection (refer to Figure 2 for examples of gaze patterns and emotion metrics). The software also generates heat maps of static gaze visualizations at individual and group levels, which serve as a graphical representation of fixation counts and duration. In addition, researchers can insert questionnaires before or after the stimuli presentation. Data collected from the remote eye-tracking tool and the integrated web-based survey platform can be downloaded from the relevant platform and merged using unique participant IDs.

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Figure 2. Example of gaze metrics generated by remote eye tracking.



Study Participants and Procedures

Between April 14, 2022, and May 3, 2022, we recruited a web-based convenience sample (N=2023) of young adult cigarette smokers (aged 18-34 years) via Qualtrics. Qualtrics recruits participants through their web-based study panels by sending email invitations to potentially eligible participants. Participants interested in the study first completed a screening survey to confirm their eligibility, for which the criteria were as follows: (1) aged between 18 and 34 years, (2) smoked at least 1 cigarette in the past 30 days, and (3) smoked ≥100 cigarettes over their lifetime. Eligible participants were then shown an informed consent page that described the purpose of the study (to examine the influence of e-cigarette marketing features) and provided details about the survey and the embedded remote eye-tracking experiment. They were instructed that they would need to turn on their cameras to complete the eye-tracking experiment. Participants were also told that their faces would be recorded by video during the remote eye-tracking task; however, they were assured that the researchers would not have access to any recordings of their faces or surroundings. In addition, participants were told that they would receive a complete code for full survey compensation even if they decided to skip the remote eye-tracking section of the study.

Participants who agreed with the informed consent proceeded to the web-based survey, where they answered a series of questions about their sociodemographic background (eg, biological sex, race and ethnicity, and subjective financial status) and tobacco use history (eg, current cigarette smoking and e-cigarette use frequency). Next, participants proceeded to the introduction of the remote eye-tracking experiment, which stated, "Now, we will ask you to look at a few e-cigarette images through a remote eye-tracking experiment. Your participation in this experiment is very important as your response will help us understand the impactful features of e-cigarette advertisements. We greatly appreciate your time and efforts in completing this experiment." Subsequently, participants were asked to indicate the device they were using or opt to skip the eye-tracking section: "If you wish to proceed, please select the type of device you are currently using for completing the survey," with the response options "I do not wish to proceed," "Desktop or laptop screen," "Mobile, tablet," and "Mobile, phone." Those who chose the first option were directed to the end of the survey, where they viewed health education messages about the harms of tobacco use and methods of quitting tobacco before they exited the survey.

As the software requires different experiment setups for mobile (tablet and phone) and desktop (desktop and laptop) devices, participants who wished to initiate the experiment were directed to the corresponding mobile- or desktop-based experiment in accordance with the device they chose. The total time participants engaged with the entire course of the experiment was approximately 5 minutes, which included reading the instructions, processing calibrations, viewing the experimental stimuli, and completing the survey items. Participants who completed the experiment were then directed to view the health education messages on Qualtrics before exiting the survey. In the following sections, we describe the process of configuring the remote eye-tracking experiment and embedding it within the Qualtrics web-based survey platform.

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Remote Eye-Tracking Experiment Setup

Experiment Setup and Calibration

After choosing to initiate the remote eye-tracking experiment, participants were shown instructions related to the use of the software (Figure 3). After they completed reading through a brief consent message, they were told that their cameras needed to be activated to detect and properly position their gaze before they viewed the experiment's stimuli. After the default setup for calibration had been set up, 2 calibration points were used in our experiment. The first calibration point was set up before participants saw the instructions to properly view the stimuli, and the second calibration point was set up after participants had viewed the stimuli. During calibration, participants were told to attentively follow a moving icon on the screen.

After completing the first calibration, participants were presented with instructions specific to the experiment, which differed slightly for mobile- and desktop-based experiments. For the mobile-based experiment, the instructions read, "Now you will see a social media post about e-cigarettes. Please view the following image by tapping on your screen. When you are finished viewing (scrolling is enabled), tap your screen again to answer the question. Please stay as still as possible during the experiment." The instructions for the desktop-based experiment differed slightly in that scrolling was disabled, and participants could click the mouse or press the spacebar to proceed. We set a duration (ie, 20 seconds) for presenting the instructions, enabling the software to proceed automatically if a participant did not advance manually.

Figure 3. Remote eye-tracking platform use instructions (screenshots).



Designing Stimuli for the Eye-Tracking Experiment

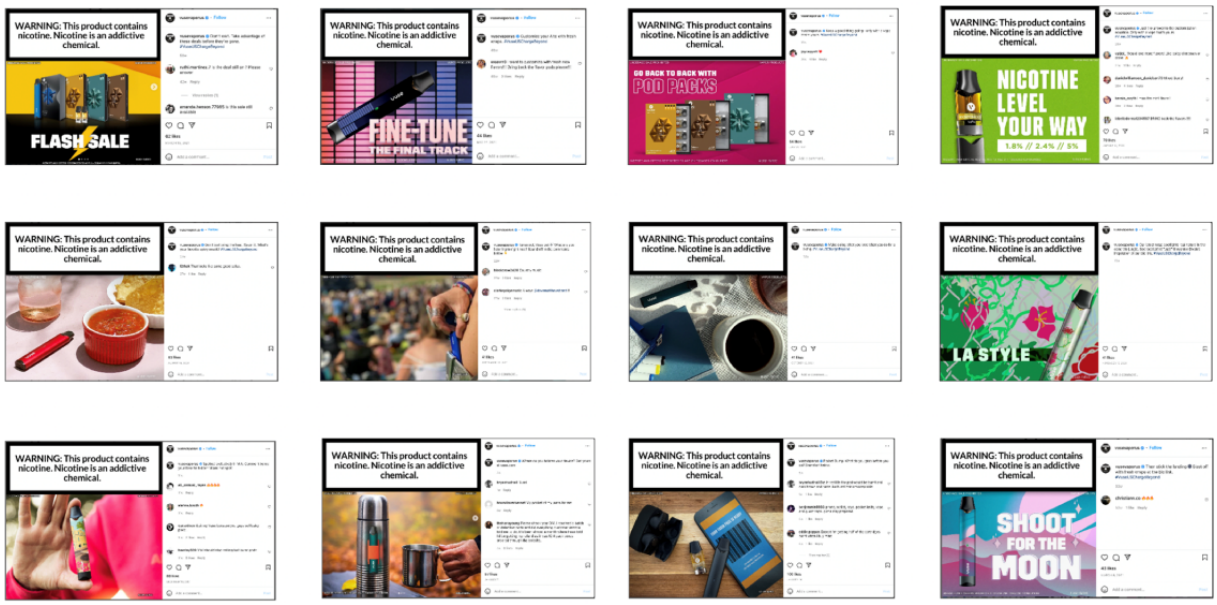
After advancing, participants viewed the experiment's stimuli that consisted of static images of 12 e-cigarette social media posts obtained directly from the official Instagram account of Vuse, a commonly used e-cigarette brand (Figure 4). To fit the stimuli for each experiment on the screen, the posts used in the mobile-based experiment were directly obtained from

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Instagram's mobile app, whereas the same posts used in the desktop-based experiment were obtained from Instagram's website. For both experiments, we randomly assigned 1 of the 12 images to be presented to the participants by selecting the option "randomly displaying 1 out of 12 media" within the experiment setup page. We set each stimulus to *fit to screen* for the desktop-based experiment and be *scrollable* for the mobile-based experiment. Participants using desktop devices were allowed to proceed through all stimuli *on mouse click* or *by pressing the spacebar*, and those using mobile devices were allowed to proceed by tapping the screen. We also set a *maximum duration* (ie, 15 seconds) for presenting each stimulus, in the event that a study participant did not advance manually.

While preparing for the experiment, the research team created AOIs within each stimulus. The AOIs were based on systematic coding of the stimuli before designing the remote eye-tracking experiment. Two coders carefully viewed each stimulus and marked visible features (including the image portion and the comment section of the social media posts). To obtain a final set of codes for each stimulus, agreement on the coding was decided after discussion with a third coder. The research team set up the AOIs by creating either rectangular or free-form shapes around the features. We named each AOI according to its content (eg, warning label, package, and marketing claim), which was directly informed by the coding results. Participants were not able to view the boundaries or names of the AOIs.

Figure 4. Vuse social media posts used in the experiment (screenshots).



Setting Up the Survey Question

Immediately after the e-cigarette stimuli presentation, participants were asked about their willingness to use e-cigarettes. After completing this survey question, participants were told that they had successfully completed the remote eye-tracking experiment and were automatically returned to the Qualtrics survey.

Integration of the Remote Eye-Tracking Experiment With the Qualtrics Survey Platform

Setting Up the Audience

The audience portion included selecting the participant source, setting the panel size, and configuring participant settings. In selecting the participant source, we were given the option of sourcing our own participants or having Tobii recruit and field participants based on our eligibility criteria. Our research team chose the former option, and we recruited participants through Qualtrics' web-based study panel.

Embedding the Remote Eye-Tracking Experiment With Qualtrics

As described previously, the Qualtrics survey for this study was configured to redirect users to the remote eye-tracking experiment depending on the device being used by the participant. Consequently, we were required to create 2 remote eye-tracking experiment blocks within our Qualtrics survey: one for desktop users and another for mobile users. We then used display logic on Qualtrics to route people to the relevant eye-tracking experiment. Configuring participant settings gave us the option to create a redirect link and a JavaScript link through which participants could access the eye-tracking experiment. Therefore, we configured participant settings using the Qualtrics survey platform by including the remote eye-tracking experiment *in an external survey platform with JavaScript*. Upon selecting Qualtrics as the survey provider, we were prompted to read a series of instructions on how to properly embed the remote eye-tracking experiment into the Qualtrics survey.

Verification, Review, and Launch

After setting up the audience and embedding eye-tracking experiments within the Qualtrics survey, we proceeded to the

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verification page to assess the functionality of our experiments before officially launching them. We ran multiple test sessions for both the mobile- and desktop-based experiments before the official launch. The experiment took <90 seconds to complete. After making a few changes, we launched the experiment, at which point adjustments could no longer be made. The crowdsourcing data collection through Qualtrics' web-based panel took 20 days, and data were obtained from young adult cigarette smokers (N=2023) who completed the survey and passed Qualtrics' data quality checks.

Assessing the Characteristics of the Participants Who Completed the Remote Eye-Tracking Experiment and Generated Usable Data

Survey Measures

A series of survey measures programmed in the Qualtrics survey platform assessed participants' characteristics and tobacco use history. These measures were used to assess which subgroups of young adult cigarette smokers would be more likely to initiate and complete the remote eye-tracking experiment. Specifically, sociodemographic characteristics included biological sex, age, race and ethnicity, sexual orientation, marital status, highest education level, current employment status, current school enrollment, and subjective financial status (Table 1). Tobacco use statuses included cigarette smoking frequency (daily vs nondaily) and current e-cigarette use status (current use vs nonuse). Finally, devices (mobile vs desktop) used for completing the survey and remote eye-tracking experiment were also included in the analysis.

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Table 1. Characteristics of participants (web-based sample of young adult cigarette smokers) and remote eye-tracking experiment completion on a Qualtrics survey.

	Full sample (N=2023), n (%)	Remote eye-tracking experiment completion				*P* value
		Did not initiate the experiment (n=136), n (%)[a]	Initiated but did not complete the experiment (n=1110), n (%)[a]	Completed the experiment but generated nonusable data (n=396), n (%)[a]	Completed the experiment and generated usable data (n=381), n (%)[a]	
Biological sex[b]						.02
Female	1017 (50.3)	65 (6.4)	624 (61.4)	120 (11.8)	208 (20.5)	
Male	1006 (49.7)	71 (7.1)	599 (59.6)	162 (16.1)	174 (17.2)	
Age range (years)						.14
18-21	182 (9)	16 (8.8)	103 (56.6)	17 (9.3)	46 (25.3)	
22-25	475 (23.5)	38 (8)	289 (60.8)	65 (13.6)	83 (17.6)	
26-29	682 (33.7)	36 (5.3)	415 (60.9)	97 (14.2)	134 (19.5)	
30-34	684 (33.8)	46 (6.7)	418 (61.1)	102 (14.9)	118 (17.3)	
Race and ethnicity						.07
Non-Hispanic White	1284 (63.5)	78 (6.2)	770 (60)	188 (14.7)	248 (19.4)	
Non-Hispanic Black	208 (10.3)	12 (5.7)	145 (69.9)	15 (7.2)	36 (17.2)	
Hispanic	366 (18.1)	28 (7.6)	216 (59.1)	57 (15.5)	65 (17.7)	
Non-Hispanic other[c]	165 (8.2)	16 (9.8)	97 (58.9)	20 (12.3)	32 (19)	
Sexual orientation						.86
Heterosexual	1491 (73.7)	97 (6.5)	908 (60.9)	209 (14)	277 (18.6)	
Other orientations[d]	532 (26.3)	39 (7.3)	317 (59.6)	72 (13.5)	104 (19.6)	
Marital status						.003
Married	431 (21.3)	36 (8.4)	269 (62.4)	69 (16.1)	57 (13.3)	
Living with partner	490 (24.2)	27 (5.5)	268 (54.7)	74 (15.1)	121 (24.7)	
Single, never married	1001 (49.5)	67 (6.7)	629 (62.8)	126 (12.6)	179 (17.9)	
Other[e]	101 (5)	6 (5.9)	59 (58.8)	12 (11.8)	24 (23.5)	
Highest education level						.15
Less than high school	139 (6.9)	10 (7.5)	82 (59)	18 (13)	29 (21.6)	
High school	791 (39.1)	47 (6)	483 (61)	111 (14.1)	150 (19)	
Less than college degree	724 (35.8)	50 (6.9)	448 (61.9)	84 (11.6)	142 (19.6)	
College degree or higher	368 (18.2)	31 (8.1)	222 (57.6)	71 (18.4)	62 (16)	
Current employment status						.12
Work full time	1131 (55.9)	86 (7.6)	694 (61.4)	161 (14.2)	190 (16.9)	
Work part time	299 (14.8)	14 (4.7)	189 (63.2)	38 (12.7)	58 (19.4)	
Unemployed	375 (18.5)	24 (6.4)	217 (57.9)	57 (15.2)	77 (20.5)	
Other[f]	218 (10.8)	12 (5.5)	125 (57.3)	26 (11.9)	55 (25.2)	
Currently in school						.99
No	1541 (76.2)	103(6.7)	934(60.6)	214(13.9)	290(18.8)	
Yes	482 (23.8)	33(6.9)	291(60.5)	66(13.7)	92(18.9)	
Subjective financial status						.67
Comfortable	563 (27.8)	37 (6.6)	353 (62.7)	76 (13.5)	97 (17.2)	
Meet needs	544 (26.9)	45 (8.1)	318 (58.3)	72 (13.1)	109 (20)	

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	Full sample (N=2023), n (%)	Remote eye-tracking experiment completion				*P* value
		Did not initiate the experiment (n=136), n (%)[a]	Initiated but did not complete the experiment (n=1110), n (%)[a]	Completed the experiment but generated nonusable data (n=396), n (%)[a]	Completed the experiment and generated usable data (n=381), n (%)[a]	
Just meet needs	611 (30.2)	36 (5.9)	363 (59.5)	87 (14.3)	125 (20.3)	
Do not meet needs	305 (15.1)	19 (6.2)	188 (61.7)	47 (15.4)	51 (16.7)	
Smoked cigarettes						.18
Daily	744 (36.8)	43 (5.8)	455 (61.2)	106 (14.2)	140 (18.9)	
Nondaily	1279 (63.2)	106 (8.3)	761 (59.5)	172 (13.4)	240 (18.8)	
Frequency of using e-cigarettes						.26
Noncurrent	202 (10)	13 (6.4)	129 (63.9)	32 (15.8)	28 (13.9)	
Current	1821 (90)	125 (6.8)	1096 (60.2)	249 (13.7)	353 (19.4)	
Device used for completing the experiment[g]						<.001
Mobile	1730 (85.5)	N/A[h]	1135 (65.6)	217 (12.5)	378 (21.8)	
Desktop	293 (14.5)	N/A	177 (60.6)	84 (28.5)	32 (10.6)	

[a]The denominators for the percentages in these column are the n values from the "Full sample" column in the same row.

[b]Participants who responded "Other" or "Prefer not to say" to the biological sex question were excluded because of the small sample size (n=7).

[c]"Non-Hispanic other" includes non-Hispanic Asian, American Indian or Alaska Native, Native Hawaiian or Pacific Islander, multiracial, and other races.

[d]"Other orientations" status includes asexual, bisexual, gay, lesbian, pansexual, queer; questioning or unsure; another identity not listed; and prefer not to disclose.

[e]"Other" marital status includes widowed, separated, divorced, and other not specified in the available categories.

[f]"Other" employment status includes in military service, retired or disabled, and homemaker.

[g]Data for devices used to complete the experiment relate to those who decided to proceed to the Sticky experiment (n=1887).

[h]N/A: not applicable.

Eye-Tracking Data Processing and Completion Metrics

After reaching the recruitment goal, we used the software to generate various eye-tracking metrics (eg, fixations and dwell time), which took approximately 12 hours. Attention data were automatically streamed to the cloud as they were recorded, then processed for completeness while eye-tracking calibration quality was validated. The validation process measures eye-tracking data accuracy by how much the ground truth validation points differ from gaze predictions [25]. The validation results determine the usability of the data for each individual participant: a difference lower than a threshold value of 0.18 is considered usable [25].

Once the eye-tracking data were processed and validated, the software presented several experiment completion metrics that we used as the outcome of our study (Figure 1). Specifically, for data analysis, we generated a variable, *experiment completion*, to capture participants' status of completing the experiment with four mutually exclusive outcomes: (1) did not initiate the experiment (ie, selected "I do not wish to proceed" just before the experimental portion), (2) initiated the experiment but did not complete it, (3) completed the experiment but did not generate usable data, and (4) completed the experiment and generated usable data. Completing the study and generating usable data were determined by the direct output from remote eye-tracking software. Experiment completion data were then merged with the Qualtrics survey data using unique participant IDs.

Statistical Analysis

To understand which subgroups of young adult cigarette smokers were more likely to complete the remote eye-tracking study, we first assessed the sociodemographic backgrounds and tobacco use history of study participants as well as the outcomes from those completing the remote eye-tracking experiment. Next, we used Pearson chi-square tests to examine the bivariate associations between participant characteristics and the experiment completion variable. Post hoc analyses using the Fisher exact test [26] were further conducted to examine the subgroup differences, given the statistically significant chi-square test results. In addition, we ran separate logistic regression models to examine the associations between participant characteristics and experiment completion using models with various outcomes (initiated the experiment vs did not initiate the experiment, completed the experiment vs did not complete the experiment, and generated usable data vs generated nonusable data). After implementing the multivariable regression models to examine the associations between sociodemographic characteristics and experiment completion, we further controlled for participants' tobacco use history, including frequency of cigarette smoking and current e-cigarette use. Finally, we controlled for the device (desktop vs mobile)

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used to complete the remote eye-tracking experiment. We analyzed the data using Stata (version 16.0; StataCorp LLC) and set the statistical significance to .05 (2-tailed).

Ethics Approval, Participation, and Informed Consent

This study was approved by the institutional review board at Rutgers University (Pro2022000190). Participants who completed the survey (whether or not they completed the remote eye-tracking experiment) were compensated according to Qualtrics' compensation policy. All participants viewed the informed consent page (including the details of the remote eye-tracking experiment) and agreed to participate in the survey study before they started the survey items.

Results

Table 1 presents the distributions of sociodemographic backgrounds, tobacco use history, and experiment completion of the sample (N=2023). Approximately half of the participants (1018/2023, 50.3%) were female, and more than half (1284/2023, 63.47%) were non-Hispanic White. More than half of the participants (1279/2023, 63.22%) smoked cigarettes on a nondaily basis, and most of the participants (1821/2023, 90.01%) had used e-cigarettes at least once in the past 30 days. Of the 2023 participants, 1887 (93.28%) initiated the experiment, and 777 (38.41%) completed the experiment. Of the 777 participants who completed the experiment, 381 (49%) generated usable data. When considering only mutually exclusive categories, 6.72% (136/2023) of the participants did not initiate the experiment, 54.87% (1110/2023) initiated but did not complete the experiment, 19.57% (396/2023) completed the experiment but did not generate usable data, and 18.83% (381/2023) completed the experiment and generated usable data.

Table 1 shows that biological sex (P=.02), marital status (P=.003), and the electronic device used for completing the experiment (P<.001) were all significantly associated with remote eye-tracking experiment completion. Post hoc analyses show that female participants were more likely than male participants to generate usable data compared with generating nonusable data (P=.01). Among those who completed the experiment, participants who reported having a partner, being single, or having *other* marriage status were more likely to generate usable data (P=.002) compared with those who were married. In addition, participants who used mobile devices were more likely than those who used desktop devices to generate usable data compared with generating nonusable data (P<.001).

Multivariable logistic regressions (Multimedia Appendix 1) show that no participant characteristic was associated with initiating the experiment. In the multivariable regression model that controlled for all covariates, including electronic devices used for the eye-tracking experiment, the results show that non-Hispanic Black participants (adjusted odds ratio [AOR] 0.64, 95% CI 0.45-0.91) were less likely to complete the eye-tracking experiment than those who were non-Hispanic White and that those who lived with a partner (AOR 1.69, 95% CI 1.25-2.28) were more likely to complete the experiment than those who were married. In addition, female participants (AOR 1.46, 95% CI 1.01-2.11), those who currently used e-cigarettes (AOR 2.08, 95% CI 1.13- 3.82), and those who used mobile devices (AOR 5.10, 95% CI 3.05-8.52) were more likely to generate usable data than male participants, those who did not use e-cigarettes, and those who used desktop devices, respectively.

Discussion

Principal Findings

This is one of the first studies to provide a detailed description of the use of remote webcam-based eye-tracking technology to examine attention to tobacco marketing materials, particularly in the context of a web-based sample of participants recruited from a large-scale crowdsourcing effort. This is also one of the first studies to delineate the participant characteristics associated with completing remote eye-tracking experiments and generating usable data. Overall, 49% (381/777) of the young adult smoker participants who completed the remote eye-tracking experiment generated usable data within a 20-day data collection period. This equates to generating usable eye-tracking data from approximately 19 participants per day, potentially signifying a higher efficiency than traditional eye-tracking studies conducted in a laboratory setting. Although the total participation duration for the remote eye-tracking experiment was approximately 5 minutes, approximately 90 seconds of this time was devoted to eye-tracking data collection.

Our results show that several participant characteristics were associated with the completion of the eye-tracking experiment (eg, race and ethnicity) and with the generation of usable (vs nonusable) eye-tracking data (eg, biological sex, current e-cigarette use, and device type). The information gleaned from this study can be used to guide future remote eye-tracking research efforts to investigate attention to tobacco marketing stimuli among various populations.

Remote Eye-Tracking Experiment Completion and Data Usability

Our study shows that of the 2023 participants who provided initial informed consent and started the web-based survey, very few participants (n=136, 6.72%) chose to opt out of the remote eye-tracking experiment even when all participants were informed that they needed to turn on their camera during the experiment and could still receive full compensation if they opted not to initiate the experiment. This finding suggests that, in general, our participants were open to participating in a remote eye-tracking task embedded in the web-based survey. In addition, according to our results, young adult cigarette smokers with various sociodemographic and tobacco use characteristics chose to initiate the experiment in a similar pattern, suggesting that receptivity may be high across various groups.

However, our results also show that more than half of the participants (1110/1887, 58.82%) initiated the remote eye-tracking experiment but did not complete it. There are several reasons why participants might not complete the experiment. Participants might have started the experiment but did not meet the technical requirements—such as having a

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camera installed on their electronic device—or they may have been unwilling or unable to turn on the camera at this point once it became mandatory. In the case of those who turned on their camera, they might have had issues related to low internet speed or a webcam with a low sample rate that generated unsatisfying video resolution. In addition, some of these participants may have intentionally closed the browser or timed out before reaching the end of the experiment. This could be due to concerns about personal privacy or because the participants' environment prevented them from engaging in a webcam-based experiment at that time.

Furthermore, our results show that a portion of study participants (396/777, 51%) completed the experiment but did not generate usable eye-tracking data. This might be because of the lighting setup in the participants' environment (background light that was too dark or too strong) or large head or body movements during the experiment. Other possible reasons for generating nonusable data include participants not paying attention to the stimuli during the experiment and not following the calibration dots. It has been shown that eye-tracking data accuracy is directly determined by whether participants can focus on the stimuli with their full attention [27]. In addition, reflections from the participants' glasses may have interfered with the ability to collect eye-tracking gaze data.

Characteristics of Participants by Experiment Completion and Data Usability

Our results further suggest that the majority of our participants (1613/1887, 85.48%) who initiated the eye-tracking experiment used mobile devices rather than desktop devices. This distribution may reflect the overall electronic device preferences of the crowdsourced participants recruited from the web-based study panels. Importantly, our analysis shows that although participants who used mobile devices and those who used desktop devices did not differ in their completion of the experiment, those who used mobile devices were approximately 5 times as likely to generate usable data compared with those who completed the experiment on their computers. We suspect that this may be because of the fewer technical requirements needed to achieve high-quality data collection through mobile devices compared with desktop devices. Alternatively, mobile device users may have different user preferences and backgrounds that contribute to this outcome; for example, mobile device users may be more attentive to the social media marketing stimuli used in our experiment, and therefore they generate more usable data. Future research is needed to explore different contributing factors that lead to generating usable (vs nonusable) eye-tracking data between mobile and desktop users (and the potential implications of this) to inform researchers of best practices for performing such experiments on both devices.

We also found that current e-cigarette users were more likely than nonusers to generate usable data. It is possible that current e-cigarette users were more likely to be interested in e-cigarette–related marketing materials and therefore paid more attention to the stimuli, which resulted in their generating more usable data than non–e-cigarette users. Further analysis based on the eye-tracking data collected from this study will be used to investigate the differences in the eye-tracking metrics (eg, fixations and dwell time) related to viewing the e-cigarette marketing stimuli between e-cigarette users and nonusers. In addition, we observed that female participants were more likely to generate usable data than male participants, even after controlling for all other potential contributing factors. As this is one of the first studies to explore the sociodemographic differences in participants' completion of a remote eye-tracking experiment, little evidence is available to explain this difference among the sexes. In the same vein, little evidence is available to explain the demographic differences (race and ethnicity and marital status) that we observed in completion (vs noncompletion) of the remote eye-tracking experiment; for example, we observed that non-Hispanic Black participants were less likely to complete the experiment than non-Hispanic White participants. We suspect that participants' real-time environment (eg, at work or home, in public or private spaces, with or without others in the background) and engagement in other activities (eg, childcare and performing chores) when completing the experiment may be relevant to study participants' demographic characteristics. These factors may also lead to differential experiment completion outcomes because they may directly affect participants' willingness to turn on their cameras or affect their ability to follow instructions or fully engage with the experiment.

More studies are needed to look into potential explanations of these findings and take into consideration the implications of the differential completion outcomes from participants with various demographic characteristics. If future remote eye-tracking studies continue to show variance in completing the experiment among participants of different sexes and races and ethnicities, it may be necessary for researchers to oversample certain subgroups in remote eye-tracking studies to achieve a balanced data set. This may be particularly true for race and ethnicity and reaching Black and other underrepresented participants, given that one of the potential benefits of remote eye-tracking methodology is the ability to reach and include a more diverse sample, which is important in nicotine and tobacco research for addressing known health disparities.

Recommendations for Improving Experiment Completion and Data Usability

On the basis of our experience in implementing this study, we recommend several strategies to increase data completion and data usability rates for future remote eye-tracking studies. First, researchers can include certain technical requirements for participant eligibility, such as using high-speed internet and using a computer equipped with a high-speed camera. Second, researchers can add certain constraints regarding study completion in the informed consent form—such as participants needing to complete the remote webcam-based eye-tracking experiment, which requires turning on the camera—to receive the full compensation. This may discourage participants who do not wish to turn on their cameras from initiating the experiment and reduce the possibility of participants exiting the experiment before finishing. Third and last, researchers can show participants the instructions before or during the eye-tracking experiment, including reminding them to keep their heads still, avoid sitting near windows, and keep light

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sources above or in front of them rather than behind them. Useful instructions for study participants to follow are presented in Textbox 1.

Textbox 1. Tips to be included in remote eye-tracking study instructions to improve data usability.

Before we begin, here are a few tips to help you to better self-calibrate:

- You must sit still and centered for the entire session.
- You must have a strong internet connection.
- Make sure you are in a well-lit room with no light or window behind you.
- Your computer should be placed on a steady table or desk.
- Make sure you are in a comfortable seated position.
- Make sure your sound is turned on.
- Please remove your glasses if you do not need them to see the screen clearly.
- If you need your glasses, ensure that you are in a well-lit room with no light source directly in front that can cause a glare.
- Before you start the session, ensure that you will have at least 5 minutes uninterrupted.

Potential Challenges of Conducting Remote Eye-Tracking Experiments

Given the promising utility of the remote eye-tracking experiment, it is important to note the potential challenges that may arise before and during such an experiment within academic settings. First, although our overall data usability rate was low, almost half (381/777, 49%) of those who completed the experiment generated usable data. Future studies may need to factor in potential data loss when planning participant recruitment and adopt strategies introduced in this paper to improve data usability rates. Future studies may also consider how remote and in-person laboratory studies may be used in tandem; for example, research might incorporate a remote eye-tracking study into a survey with a large participant sample to explore general viewing patterns of stimuli of interest, which may then stimulate research questions and hypotheses that are examined in a more controlled in-person laboratory study. Second, there are limited opportunities for researchers to obtain raw eye-tracking data through using the software. Only some categories of eye-tracking metrics were provided by the software (eg, fixation and dwell time), limiting researchers' ability to gain a more comprehensive understanding of the data generated from the experiments. Third, there may be challenges related to protecting participant privacy because remote eye-tracking data collection requires recording a video of the participant's face. It is recommended that researchers review and evaluate the privacy policies of the eye-tracking software, including limitations on transferring participant data (eg, personal identifiers or video recordings) to researchers or third parties and permanently deleting the data after certain periods of time. It is recommended that researchers include these policies during their submission of the study protocol to an institutional review board. Fourth and last, according to our findings, certain characteristics of study participants who generated usable eye-tracking data may be different from those of study participants who did not generate usable data or did not complete the experiment. Therefore, the results generated from remote eye-tracking experiments may need to be interpreted with caution to avoid population bias.

Study Limitations

The generalizability of our remote eye-tracking study may be limited because of the following reasons. First, the completion rates of the eye-tracking experiment among our participants—young adult cigarette smokers—may be different from those of similar studies among participants with different sociodemographic characteristics or tobacco use history. Specifically, young adults may be more skilled in successfully navigating the technical requirements (eg, turning on the camera) of remote eye-tracking software and less worried about web-based privacy issues than older adults. By contrast, older current cigarette smokers may be less likely to perform attention-intensive tasks such as repeatedly following the movements of dots and carefully viewing the assigned stimuli when they experience nicotine withdrawal symptoms [28]. This may be especially true when the eye-tracking experiment is embedded at the end of a survey after participants have already responded to a series of survey questions and when no additional compensation is provided to encourage the specific completion of the experiment. Second, it is possible that study participants who did not wish to take part in the remote eye-tracking experiment may not have agreed with the study consent to start with. Therefore, we were not able to assess the backgrounds and characteristics of this particular group. Third, the rates of completing the experiment and generating usable data may be different when the remote eye-tracking experiment is designed differently; for example, our experiment involves participants completing 2 calibration points and responding to a survey question at the end, which may be more complicated than other experiments that include 1 or no calibration points or no survey questions. Adding calibration points may improve the accuracy and usability of the data generated by the eye-tracking software but may also potentially extend the length of the experiment and reduce the experiment completion rate. Fourth and last, this study only introduced the process of designing 1 particular remote eye-tracking experiment using 1 particular software platform (ie, Sticky by Tobii). Experiments using other remote eye-tracking tools (eg, Webgazer.js) or with different study designs or experiment setups may involve unique challenges and generate different experiment completion outcomes [29].

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Conclusions

Eye-tracking methodology can greatly advance researchers' and policy makers' understanding of individuals' visual engagement with marketing and communication materials in tobacco control research and tobacco regulatory science. Although in-person laboratory methods are considered the gold standard for collecting these types of data, recently developed remote webcam-based eye-tracking technology integrated with large-scale crowdsourcing efforts may be a particularly time-efficient and resource-effective tool for addressing limitations posed by in-person research. This paper describes the process of designing a remote eye-tracking study to explore young adults' attention to e-cigarette social media marketing materials. The experiment completion outcome data from this study are promising because the study generates usable eye-tracking data from approximately 19 participants per day during a 20-day data collection period. The study also provides information on the characteristics of study participants who might be more likely to complete the remote eye-tracking experiment and generate usable eye-tracking data. We believe that remote eye-tracking experiments, integrated with large-scale crowdsourcing efforts, will be a useful tool for the tobacco regulatory science research community to expand the collection of eye-tracking data on a variety of tasks relevant to the impact of tobacco marketing.

Acknowledgments

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Data Availability

Survey data may be available upon request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Characteristics of participants (web-based sample of young adult cigarette smokers) and devices used for completing the remote eye-tracking experiment on a Qualtrics survey.
[DOCX File , 24 KB - resprot_v12i1e43512_app1.docx]

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Abbreviations

AOI: area of interest
AOR: adjusted odds ratio

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Protocol

Internet of Things and New Technologies for Tracking Perioperative Patients With an Innovative Model for Operating Room Scheduling: Protocol for a Development and Feasibility Study

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Abstract

Background: Management of operating rooms is a critical point in health care organizations because surgical departments represent a significant cost in hospital budgets. Therefore, it is increasingly important that there is effective planning of elective, emergency, and day surgery and optimization of both the human and physical resources available, always maintaining a high level of care and health treatment. This would lead to a reduction in patient waiting lists and better performance not only of surgical departments but also of the entire hospital.

Objective: This study aims to automatically collect data from a real surgical scenario to develop an integrated technological-organizational model that optimizes operating block resources.

Methods: Each patient is tracked and located in real time by wearing a bracelet sensor with a unique identifier. Exploiting the indoor location, the software architecture is able to collect the time spent for every step inside the surgical block. This method does not in any way affect the level of assistance that the patient receives and always protects their privacy; in fact, after expressing informed consent, each patient will be associated with an anonymous identification number.

Results: The preliminary results are promising, making the study feasible and functional. Times automatically recorded are much more precise than those collected by humans and reported in the organization's information system. In addition, machine learning can exploit the historical data collection to predict the surgery time required for each patient according to the patient's specific profile. Simulation can also be applied to reproduce the system's functioning, evaluate current performance, and identify strategies to improve the efficiency of the operating block.

Conclusions: This functional approach improves short- and long-term surgical planning, facilitating interaction between the various professionals involved in the operating block, optimizing the management of available resources, and guaranteeing a high level of patient care in an increasingly efficient health care system.

Trial Registration: ClinicalTrials.gov NCT05106621; https://clinicaltrials.gov/ct2/show/NCT05106621

International Registered Report Identifier (IRRID): DERR1-10.2196/45477

(JMIR Res Protoc 2023;12:e45477) doi:10.2196/45477

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KEYWORDS

internet of things; artificial intelligence; machine learning; perioperative organization; operating rooms

Introduction

Operating rooms (ORs) are responsible for a large amount of profit and cost [1]. About 60% of all hospitalized patients are treated in the OR [2]. Surgical scheduling is a key process in perioperative organization; it begins by analyzing a list of daily cases and their expected duration. If cases consistently run longer, OR overuse will result in costly overtime pay and staff dissatisfaction. On the other hand, if actual case times are shorter than expected, OR underuse will lead to staff idle time, which is associated with up to 60% higher costs [3-5]. Also, decisions about the number of surgeries to perform during a typical day or week of activity in the OR have a considerable impact on downstream resources and on the efficient flow of patients in the system. Combining higher-level decisions, optimization logic, and management policies with an analysis of the consequences of these decisions that is enabled by simulation tools is an effective approach in health care [6-8]. Also, simulation is useful for testing the expected performance of a process, as well as its performance when it has been revised, modified, or optimized, before implementing it in practice and can also evaluate unexpected scenarios. Case duration prediction is usually demanded by the surgeon who reserves the time slot. With this method, it has been proven that surgeons underestimate case duration up to 42% of the time and overestimate it 32% of the time [9]. Another common approach is to use the electronic health record (EHR) to calculate case duration based on historical data for a given procedure. Decisions based on EHRs have a higher accuracy [10], but available EHRs only generate case durations for the average patient and do not take into account the patient's specific profile (eg, their age, sex, BMI, allergies, or comorbidities). The rise of big data offers novel possibilities for patient-targeted predictions by exploiting machine learning (ML) and deep learning (DL) techniques. In particular, supervised learning techniques are able to identify latent patterns among large quantities of data by training the model to minimize a loss function between the actual output and the desired (ie, supervised) one. The model is afterward able to generalize on unseen cases that belong to the same data distribution. For this reason, ML is also gathering attention in the medical field for both clinical and organizational purposes. Notwithstanding this, we are still in the early phase, and there are several challenges to deal with [11-14] .The main issue to exploit ML is providing accurate and noise-absent samples to the model, which is critical when historical data are collected by human processes. In light of this, the aim of our research project is to develop an integrated technological-organizational model capable of exploiting data derived from ORs to optimize the management and organization of the whole operating block. To achieve such a result, we have first developed an internet of things (IoT) architecture that is able to collect real data to minimize the presence of errors or noise in data and maximize ML performance. Next, we will proceed to develop an optimal scheduler for surgical procedures supported by simulation and able to integrate clinical and anamnestic information with data derived from an analysis of surgical timing and time spent in the recovery room (RR) so as to optimize the system's organization [15].

Methods

Overview

Our research work is a prospective, single-center, interventional study. Patients are included if they are older that the age of majority (18 years in the country where the protocol was drafted); provide signed informed consent; and are undergoing elective abdominal, thoracic, vascular, gynecological, or plastic surgery. If the patient agrees to participate in the study, data will be collected on the expected and actual time from the patient's entry to the operating compartment to their exit. In particular, time spent in the operating room, surgical time, and length of stay in the operating room will be recorded. This information will be integrated with anamnestic data and data relating to hospital stay [16-18]. The goal is to create a technological-organizational programming model able to optimize operating block management. In this work, we identified 50 simple variables for each patient. These features will form a single data set instance. We decided to focus our attention on ML methods instead of traditional methods, as the latter may not be sufficient for this task, often requiring assumptions about data distribution, and may not be able to handle the complexity and volume of the data that we want to use to make predictions. On the other hand, ML methodologies can capture nonlinear relationships between variables, which can be important for predicting times accurately. Moreover, ML algorithms can benefit from large amounts of data to identify patterns, and EHR data contains a large number of variables, including patient anamnestic data, medical records, and surgical details. ML algorithms can extract knowledge from this data and use it for making a much better and more accurate prediction. Finally, ML methods can handle outliers, which can be common in EHR data, and ML methods can generalize well to new data. This is important because we can make predictions for surgery time for patients who are not in the original data set. In this study, we will collect data from 1200 patients. Bearing in mind that this data set will have to provide data to both create the model and validate it, the data set will be divided into 3 parts: a training set (60%), a validation set (20%), and a test set (20%). The project is divided into three phases: (1) using the IoT for data collection and patient enrollment, (2) machine learning for time prediction, and (3) optimization with discrete-events simulation.

In the first phase, which forms the focus of this paper, we developed an IoT architecture to perform indoor localization of patients in ORs and in RRs. Patients who decide to participate in the study are asked to give informed consent. If they agree, they are provided with a personal Bluetooth Low Energy (BLE) beacon tag when entering the operating block or in the ward. The tags are detected by detectors (Raspberry Pi devices; Raspberry Pi Ltd) that are located in the environment of interest. The detectors communicate with a private local area network

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(LAN) to manage data flow and to provide additional security levels. Moreover, the LAN does not have any internet access, so the network is not vulnerable to any external attacks. The access to the server, to the sensor configuration module, and to the association interface is password protected and all communication to the server is encrypted. In this section, we describe the components and our solution for monitoring patients' movements inside the surgical block. We realized a client-server architecture that provides communication between the sensor modules and the server in our system. The whole IoT system has several parts, which are listed below.

BLE Beacons

BLE is a wireless communication technology designed for low-power devices that require short-range connectivity and is widely used in IoT environments [19]. BLE technology operates on 2 main channels: advertising and data. For our purposes, we decided to use only the advertising channel in order to detect beacons when they are near to our sensors. For this reason, we adopted the iBeacon protocol (Apple Inc). The iBeacon protocol identifies beacons with a triplet of universally unique identifiers (UUIDs). For this prototype we used the BlueUp (BlueUp Srl) beacon, which has 800 milliseconds of advertisement time. Each patient will be associated with a beacon connected to a numerical, progressive, and anonymous ID to respect patient privacy. The beacon is assigned to each patient and is worn as a bracelet with a wrist band. Being affixed to the patient's wrist is the best compromise between comfort and signal efficiency.

Sensor Modules

As a sensor module, we used a Raspberry Pi 4 device running the 64-bit Raspian OS. The sensor module continually scans for BLE advertisements, checking them against a list of preregistered beacons provided by the central server. Using a list allows us to ignore nonregistered beacons, saving bandwidth and processing resources. The sensors autoconfigure themselves. They can be rebooted or shut down at any time. When the sensors receive a beacon advertisement, they append the package received and its timestamp into a JSON file and forward the information to the central server over a transmission control protocol.

We estimate the patient's presence inside a specific room in the operating block using the residence time within the range of action of the sensor. Every sensor has its own residence time and a tunable threshold of signal sensitivity. This last parameter can increase or decrease the sensor's range of action. If the beacon remains for a certain amount of time in the action range of a sensor, the beacon is marked as entered into the room.

Central Server

The central server indexes and collects the data coming from the sensor modules. It has the following duties: (1) storing records coming from each detector in a MongoDB database (MongoDB Inc); (2) coordinating distributed solution and message exchange using a publish-subscribe mechanism based on message queue telemetry transport (MQTT), and finally, (3) exposing a web server that is used as a unique interface between the software architecture and the hospital medical staff. The central server hosts the eclipse Mosquitto-based MQTT broker (Eclipse Foundation Inc). When it receives the packets from the sensors, it determines whether the beacon is in the room where the sensor is located. Our implementation of the beacon server used a Python-based service and exploited the MongoDB database to store the various events. The data format is shown in Table 1. The central server also has the duty to send information to the edge modules regarding the list of preregistered beacons, the identity of the sensor itself, and a time-synchronization message.

Table 1. Data stored by the server for each sensor when an entry is recorded in the database.

Fields	Description
uuid	Universally unique identifier for the beacon
minor	Contains the unique beacon ID
macAddress	Beacon MAC address
timestamp	First detection timestamp
last_detection	Last detection timestamp (continuously updated)
flag	Boolean value that if true specifies that the patient is currently in that specific room
Patient ID	Unique number assigned to a specific patient

Client Interface

The client interface, hosted by the central server, offers several functionalities. The first is enrollment. Patient enrollment is done by a member of the medical staff when the patient enters the operating block to undergo surgery. The enrollment is performed using a tablet device that communicates with the web application and by providing the necessary information. The system also provides a graphical interface able to monitor in real time the various movements of patients (Figures 1 and 2).

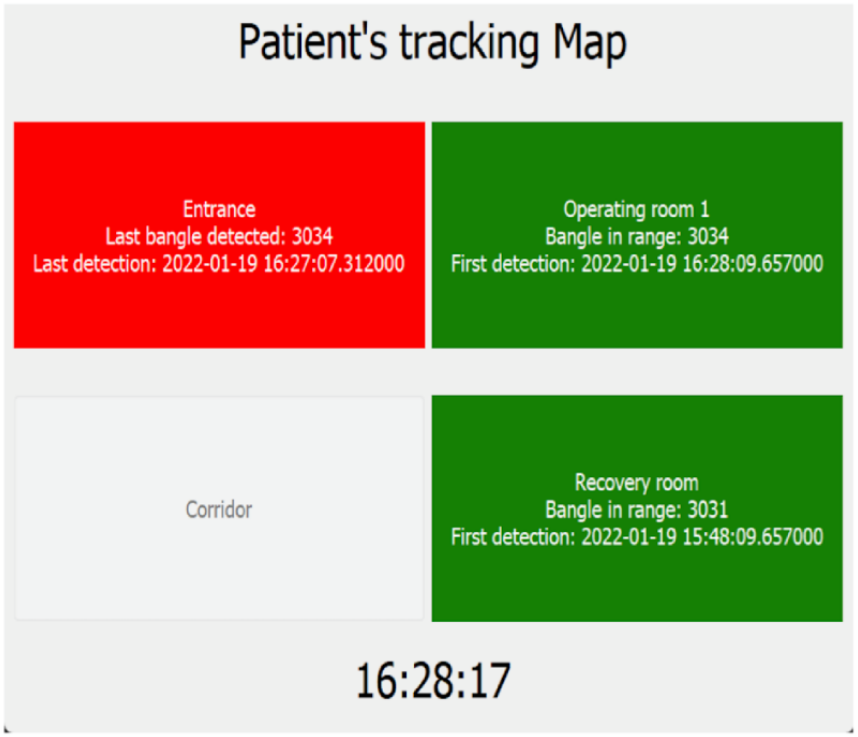
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Figure 1. Screenshot of the home page of the web application responsible for the beacon-patient association. (In the web application, the term “bangle” is used to describe the beacon.).



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Figure 2. Screenshot of the graphical interface for monitoring patient movements inside the operating block. Green cells indicate that the patient is near the sensor that is associated with that specific room or place. Red cells indicate that no tracking device has been detected for some time. Finally, gray cells indicate that there is no tracking data for that place.



Ethics Approval

The study was approved by the Comitato Etico Unico per l'Area Vasta Emilia Nord, a local ethics committee (1284/2020/OSS/AOUPR), and was registered on ClinicalTrials.gov on January 11, 2021 (NCT05106621). Written informed consent was obtained for all study participants. The participation of individuals of legal age capable of giving informed consent as subjects in medical research must be voluntary (World Medical Association Helsinki Declaration). The data are collected anonymously and with respect for the privacy of patients.

Results

This research was financially supported by the FIL-Quota Incentivante program of the University of Parma and cosponsored by Fondazione Cariparma with approval in the second half of 2019. As of February 2023, approximately 1000 patients have been enrolled, with an enrollment target of not less than 1200 to 1300.

We schematized a generic path a patient could follow inside the operating block (Figures 3-6).

In addition, if a patient agrees to participate in the study, we collect the following: data about the surgical procedure, personal and anamnestic data, data from the RR, and data on the hospital stay, such as whether the patient was admitted to the intensive care unit.

The prototype of the IoT architecture described and illustrated above was installed successfully in the surgical block and is still functional. We collected data from more than 100 patients. It is possible to see in the final output illustration (Table 2) that combining the data from various sensors allowed us to reconstruct the patient's path.

The second step will involve the application of ML and DL algorithms to study the feasibility of predicting surgical procedure time by providing features of the patient and of the surgery as input. Because of the lack of public data sets or similar approaches in the scientific literature, we are currently performing a feature selection task among more than 50 variables to identify which features can maximize prediction accuracy in terms of the root mean squared error of surgery time. Several ML approaches are possible since the task of intraoperative time prediction can be modeled in different ways. Since the total time in the operating block is the sum of the time spent in the OR and in the RR, this prediction task can be modeled using 2 different ML models or a unique one that tries to directly estimate the total time. Moreover, depending on the data set size, tree-based ensemble models (eg, gradient boosting or extreme gradient boosting; XGBoost) could better suit the task. On the other hand, the complexity of the task and the nonlinear dependency of several features within the target variable of "time required" may require the use of deep neural networks. DL requires larger data collection, but at the same time, it would be possible to exploit its ability to perform representation learning of the input, requiring less feature engineering.

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Figure 3. Generic patient path illustration within the operating block. The patient accesses the operating block at tracking point 1. Then, the patient's stretcher is swapped at point 2, and a member of medical staff assigns them a beacon and sets up the associated ID. Next, the patient goes to the assigned operating room (point 3). Once the surgical procedure ends, the patient is transferred to the recovery room (point 5), where they are monitored after the procedure. The patient can then either exit the operating block from point 6 or can return to the operating room if there are acute surgical complications. Moreover, during these activities, the patient can remain idle at an unspecified point in the corridor, represented by point 4. Personal data are extracted from the information systems of the Ospedale Maggiore of Parma using pseudoanonymization techniques.

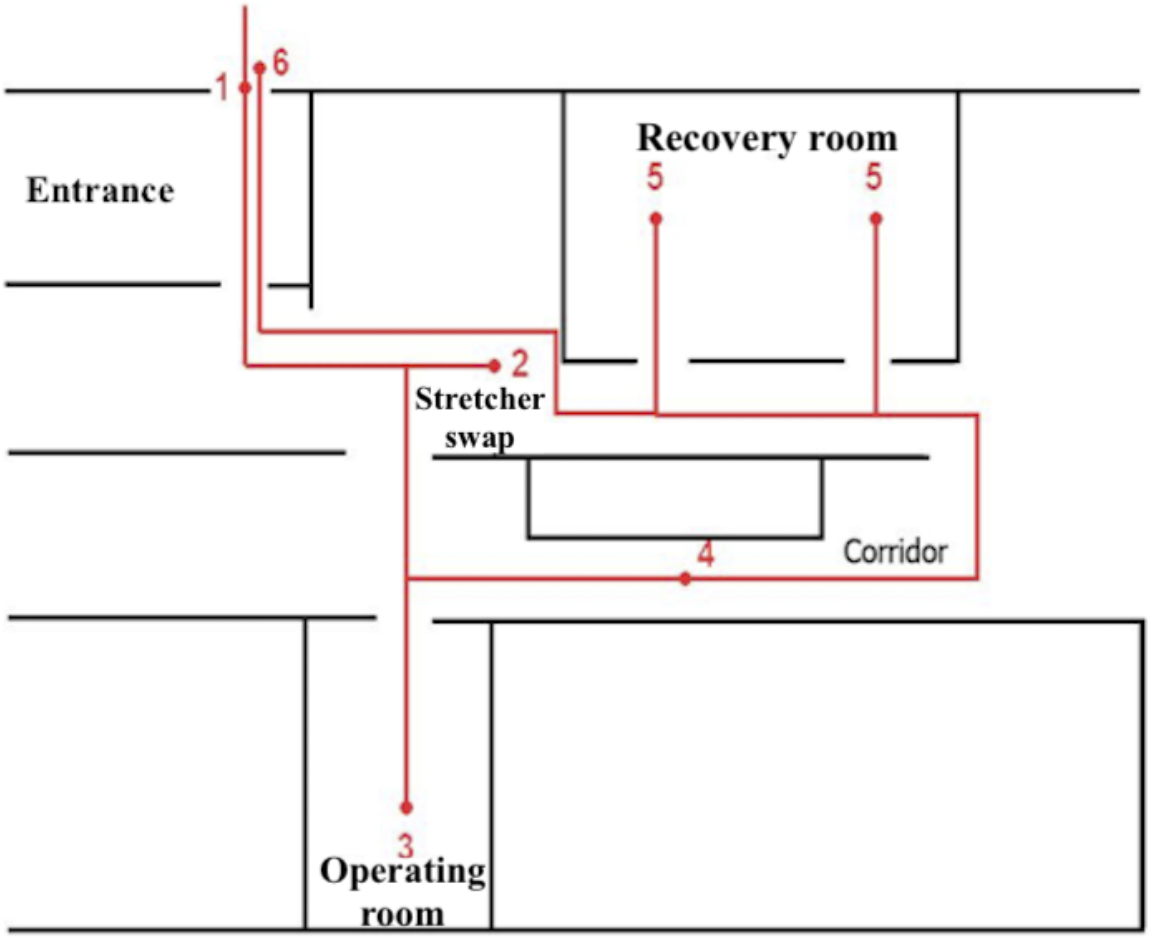
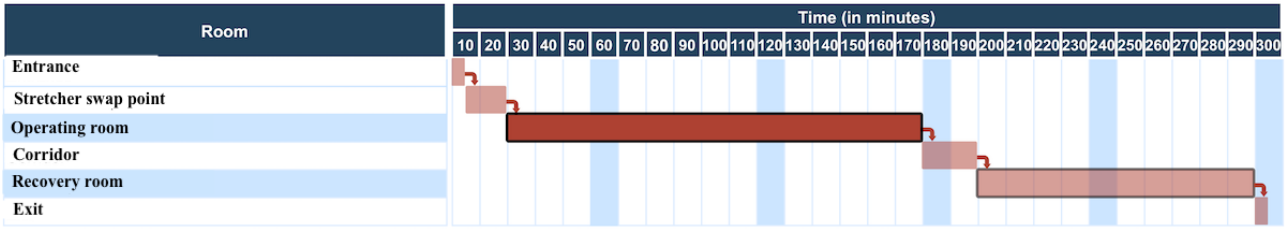


Figure 4. Visualizing patient flow with a Gantt chart showing average time spent by patients in each room over time.



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Figure 5. Easy identification of the patient in the operating block through the association with a tag and a code.

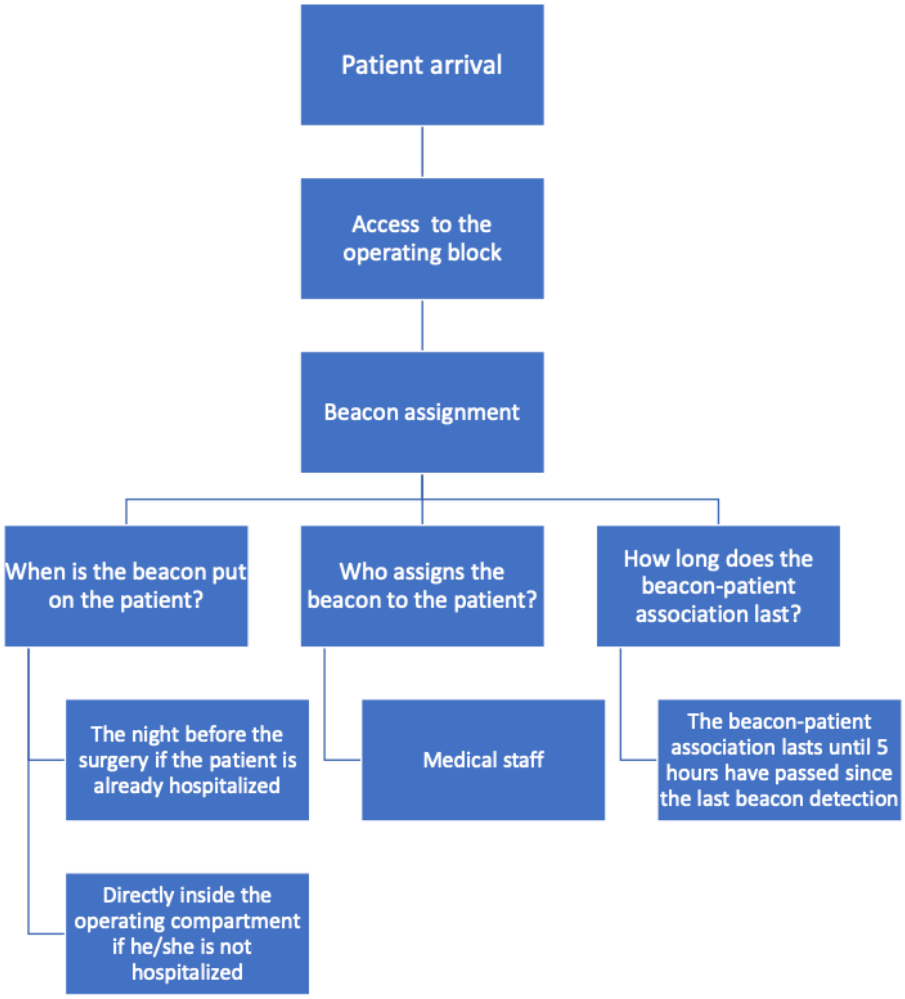
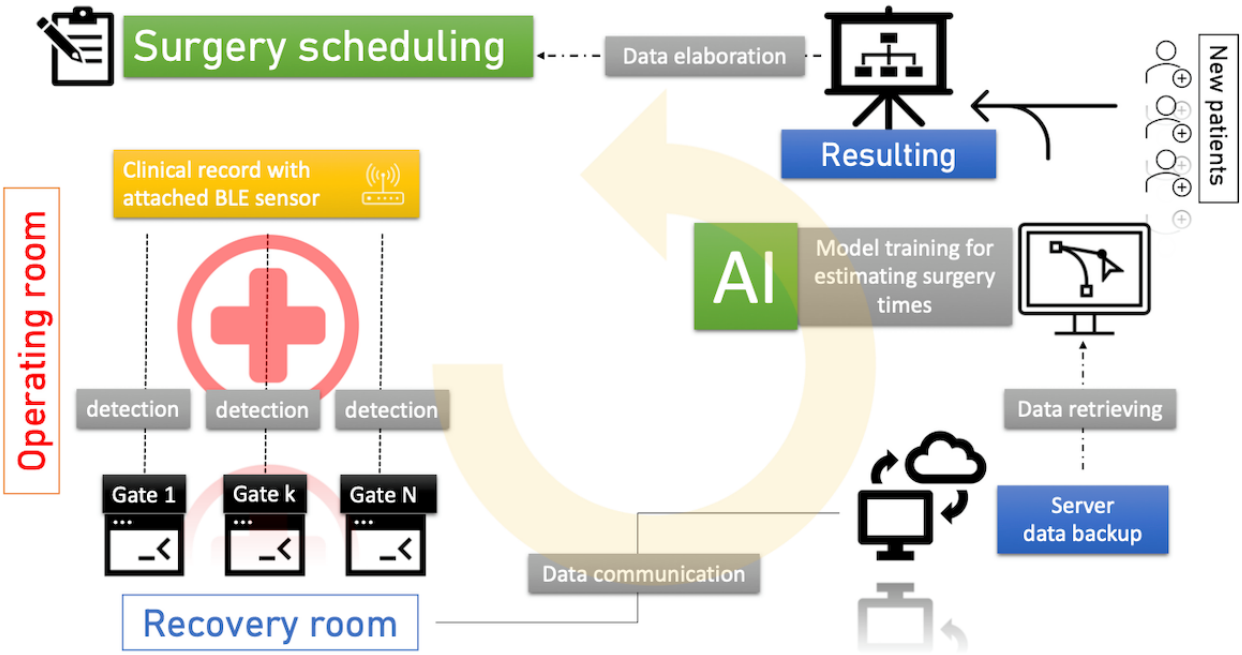


Figure 6. Logical schema of the indoor patient tracking system, data storage, and data set analysis using machine learning models. Data security is ensured by different levels of protection at different steps. AI: artificial intelligence; BLE: Bluetooth Low Energy.



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Table 2. The patient's path within the operating block with the relative timestamps and time spent in every room.

Beacon ID	Patient ID	Room sensor	First timestamp	Last timestamp	Total time
3287	PR-0170	Entrance	2022-05-24 07:47:31.988000	2022-05-24 07:51:18.086000	00:03:46.098000
3287	PR-0170	Corridor	2022-05-24 07:51:50.639000	2022-05-24 07:53:03.557329	00:01:12.918329
3287	PR-0170	Operating room	2022-05-24 07:54:52.586975	2022-05-24 10:59:05.650000	03:04:13.063025
3287	PR-0170	Recovery room	2022-05-24 11:00:08.795296	2022-05-24 12:54:34.885000	01:54:26.089704
3287	PR-0170	Entrance	2022-05-24 12:54:44.533703	2022-05-24 12:57:04.107000	00:02:19.573297

Once ML is trained to predict the surgery time, we will proceed to step 3, which is the use of simulation models of discrete events. In these models, an "event" is an instantaneous occurrence that involves a change in the value of at least one of the system variables; for instance, it could be the entrance of a new patient, the exit of a patient from the system, or the transition of the patient from one room to another. The goal of the simulation model is to reproduce the patients' path within the operating block (including the preoperative, operative, and postoperative phases) to optimize their flow in the system. To this end, some selected key performance indexes will be embodied in the simulation model; examples of these indexes are the number of patients treated daily, use of the OR, and the need for extra time working in the OR. Simulation will be first used to evaluate these indexes in the current scenario ("as is" analysis) then to reproduce new logic for scheduling surgical interventions ("to be" re-engineering) based on multiple prioritization logics or multi-objective optimization. The improvement achieved in the performance indexes will also be evaluated [20].

Discussion

Principal Findings

The use of artificial intelligence (AI), and in particular ML, is expanding in every area, including health care. Many results are now available on the excellent predictive capabilities of these new tools in medicine. Thanks to their use, intelligent tools useful to support health care professionals in daily practice will be increasingly available. Their possible exploitation in the health organization is no exception. Liu et al [21] showed that ML is superior to logistic regression for risk estimation in the context of hospital performance assessment. Furthermore, similar applications can be found in the context of forecasting health care costs, risk of readmission, and hospitalization [21-24].

The study by Luo et al [24] is also very interesting; ML models were applied with the intent of estimating the risk of cancellation of an operating session with the negative impact that this entails both in terms of costs and on waiting lists; therefore, cancellation also translates into delayed access of the patient to surgery. Moreover, a novel approach has been presented by Abbou et al [25]. The authors gathered EHR data from December 2009 to May 2020 for a total of 297,480 interventions at 2 public hospitals in Israel. They predicted the duration of the surgery based on preoperative data, including patient clinical data, the experience of the surgeons, patient nationality, and results of analyses carried out before the operation. They compared the predictions between a naive model and an ML model (XGBoost) with various metrics and found that the use of big data was useful for predicting the duration of interventions in the operating room and that the ML model performed better than their naive model.

However, to apply these models, it is essential to obtain data with quality and precision. Currently, recording times and patient movements within the surgical block is often done manually by the various medical staff involved and subsequently reported in computer systems. However, this detection method is often partial and usually not done in real time. The possibility of enabling direct recording with minimum human interference could increase the quality of the data set and let us obtain more precise results [26-28]. Furthermore, having a system equipped with the ability to independently record the patient's movements, besides reducing the error rate, could allow for lightening the workload of the medical staff themselves and indirectly reducing the changeover time between different patients [24,28-32]. Nevertheless, building a tracking system inside a hospital is not a simple task. Not all hospitals are equipped with the highest technology available. Some hospitals are small and do not have sufficient resources available to install high-technology organizational systems. Others, despite being larger in size, have old structures in which it is not always easy to implement new technologies. Therefore, we decided to look for a solution that suits our needs and is economical, does not require an expensive infrastructure, and is achievable in most situations.

To understand which technologies were the best for our use case, we decided to analyze several options and constraints. The main constraints encountered were ease of installation, the tracking device's battery life, and the tracking device's reuse and cleaning.

Considering these major constraints, we analyzed and considered several technologies. The first was radio frequency identification (RFID); unfortunately, this technology had a cumbersome structure for tracking and the range of action was limited, which could have brought discomfort to the members of the medical staff. Moreover, the RFID device's battery life was not sufficient for our case study. Next, we analyzed ultrawideband (UWB),

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which was discarded as well due to the low autonomy of the devices. Finally, we decided to use a BLE tracking device.

BLE fitted our use case because the detectors are small and easy to install, the device's range of action is very wide, and the tracking device's battery life can last several months. Furthermore, our use case does not involve tracking health care personnel, only patients.

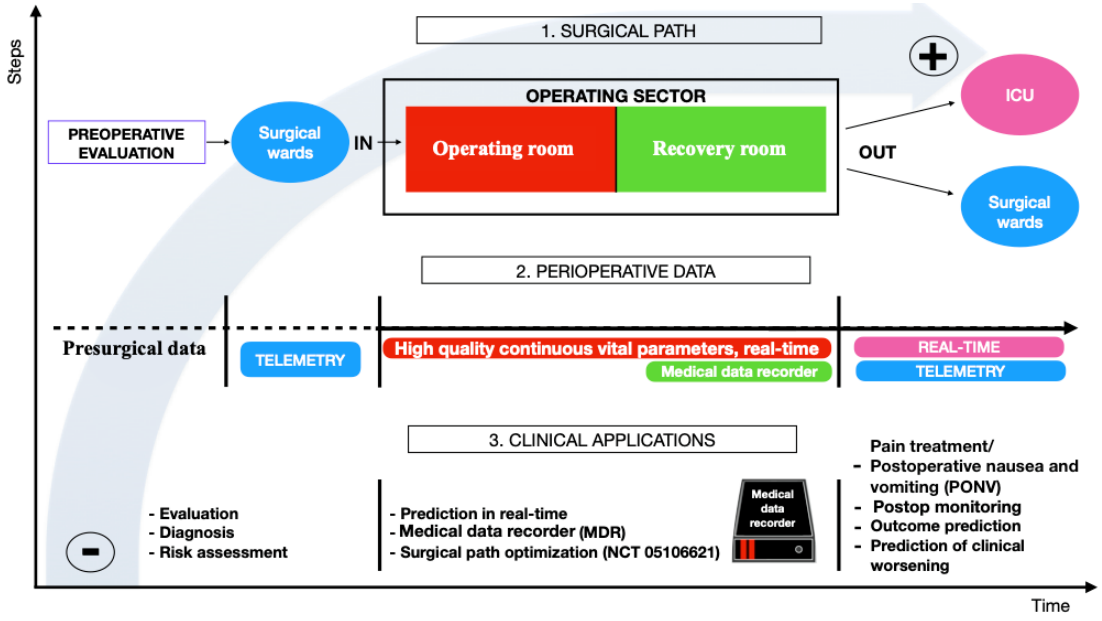
Building a tracking system using BLE also has economic advantages; it does not burden the hospital budget and is cost-effective. The system presented above can trace the movements of patients within the OR. The data obtained will form a data set that can be used to perform ML tasks. By combining the tracking data with clinical assessment data, it will be possible to create an algorithm capable of predicting the duration of a specific surgical intervention.

The IoT architecture developed in this study will be useful to collect real data about patient flow in the surgical department. Nonetheless, having solid data and predictions about OR occupancy is still not enough. It is also necessary to create organizational systems capable of using that information. In fact, not being able to transform these results into intelligent tools that can be used in daily practice has been recognized as one of the major limitations that currently hinder the use of these technologies in medicine [33]. To overcome these limits, a simulation model will be developed for reproducing patient flow in the operating block. This model, fed with high quality data, will be used to determine the best scheduling logic in order to optimize the use of resources in the OR. Preliminary testing of the model was performed using randomly generated patient data in an attempt to check its effectiveness in reproducing the system, as well as to embody alternative scheduling logics and return the performance indexes as outcomes. Results, both in terms of the model capability to reproduce the current system and in evaluating its performance, are promising and at the same time highlight the potential for improvement in the efficiency of the surgery department, which is the ultimate aim of the project. In a more advanced phase of the research, the simulation and scheduling logics will be enhanced and further improved by the availability of accurate predictions enabled by an ML model. In general terms, it is expected that an accurate evaluation of patient flow (based on real data) and a reliable prediction of surgery cases (based on the ML model) will make it possible to optimize planning of surgical procedures, consequently decreasing unused OR time and hopefully increasing the number of surgical interventions in a day. This is an innovative aspect of the whole project; indeed, although ML, simulation, and scheduling have been applied in health care environments, their combined use opens new ways for process improvement. This approach, thanks to its consistent predictive performance over various forecast intervals, can positively influence the choices of health care personnel for short-term and long-term strategic planning [34-36].

Conclusions

Surgery has a great impact on the health economy; thus, optimal management of resources destined for the OR becomes crucial. Considering the literature and our preliminary results, it therefore seems possible to assume that the application of AI models in the context of OR organization, associated with an indoor patient traceability system, is not only feasible but could also lead to more targeted organization (Figure 7) [37,38].

Figure 7. Use of artificial intelligence in the operating sector for a more targeted organization of resources. ICU: intensive care unit.



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Acknowledgments

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Data Availability

The data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' Contributions

All authors contributed to the study conception and design. E Bottani, VB, MM, MC, and E Bignami contributed to the acquisition and analysis of the data and prepared the figures. E Bottani, VB, MP, MM, GL, and BF contributed to the elaboration of the data and prepared the tables. All authors contributed to writing and manuscript review.

Conflicts of Interest

None declared.

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Abbreviations

AI: artificial intelligence
BLE: Bluetooth Low Energy
DL: deep learning
EHR: electronic health record
IoT: internet of things
LAN: local area network
ML: machine learning
MQTT: message queue telemetry transport
OR: operating room
RFID: radio frequency identification
RR: recovery room
UUID: universally unique identifier
UWB: ultrawideband
XGBoost: extreme gradient boosting

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Protocol

Ultrasound-Assisted Continence Care Support in an Inpatient Care Setting: Protocol for a Pilot Implementation Study

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Abstract

Background: This nonrandomized exploratory intervention and feasibility study examines how digital assistive technology (DAT), comprising a DFree ultrasound sensor, affects nursing care for continence support and evaluates nurses' willingness to incorporate DAT into the planning and practical implementation of care processes.

Objective: The relief provided by DFree in the clinical care setting and the extent to which it supports nursing care for activities of daily living pertaining to "micturition" is unclear. DAT DFree is expected to reduce nurses' workload in clinical continence-care settings and was designed as a human-technology interaction that ensures a high level of usability for the subjects (ie, the nurses) and increases user acceptance by at least one level (eg, from average to slightly above average) during the study.

Methods: Approximately 45 nurses from neurology, neurosurgery, and geriatric medicine clinics and polyclinics at the University Medicine Halle will be included in the 90-day (3-month) intervention on-site in the respective wards. After the wards are equipped with digital technologies, the participating nurses will be trained to use DFree and will be able to select DFree as a possible patient-care resource if the anamnesis includes bladder dysfunction among only patients who are willing to participate. The willingness of nurse participants to use DFree in planning their care process will be assessed using the Technology Usage Inventory at 3 measurement points. The primary target values include the results of the multidimensional Technology Usage Inventory assessment that will be processed using descriptive statistics. Ten participating nurses will be invited to conduct extensive guided interviews that are intended to provide information about the device's usefulness and feasibility in the specific field of continence care and possible improvements.

Results: It is expected that the intention to use will be confirmed by nurses, and the number of nursing problems, such as bladder dysfunction-induced bedwetting, will be reduced with a high rating of DAT usability.

Conclusions: First, this study aims to produce multilevel innovative impacts, including practical, scientific, and societal effects. The results will provide practical solutions for workload reduction in the field of nursing support for continence care, where digital assistive technologies are becoming increasingly important. The DFree ultrasonic sensor is a new technical tool for the treatment of bladder dysfunction. Generating feedback to improve technical applications can increase the user-friendliness and usefulness of the device.

Trial Registration: Deutsches Register Klinischer Studien DRKS00031483; https://drks.de/search/en/trial/DRKS00031483

International Registered Report Identifier (IRRID): PRR1-10.2196/47025

(JMIR Res Protoc 2023;12:e47025) doi:10.2196/47025

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KEYWORDS

bladder control; bladder dysfunction; continence care; digitization; incontinence; nursing; selfmanagement; ultrasound; urology; user requirements

Introduction

Bladder dysfunction is a health problem that affects approximately 50 million people worldwide [1]. Urinary diseases are diverse and range from simple cystitis to acute postrenal kidney failure [2]. Physical limitations caused by bladder dysfunction can lead to other problems, such as general insecurity, iatrogenic damage, shame, skin damage, irritability and cognition or instability, and the risk of falls [3]. Bladder dysfunction increases the workload of nurses and the costs of care facilities [4-7]. In a rapidly aging society, the number of people with bladder dysfunction will continue to increase [8,9]. "Excretion support," as part of planned, professional nursing care processes pertaining to the activities of daily living [10,11], benefits from digitization when it improves structure, process, and outcome quality in continence care [7]. New digital assistive technologies (DAT) [12,13] possess great potential for meeting both current and future challenges in continence nursing care [14] as DAT promote independence and participative opportunities for individuals with urological conditions [15,16] and support the care of people with bladder dysfunction [17-20]. As the ability to control bladder muscles represents a milestone in achieving independence in early childhood, the loss of bladder control is psychologically stressful. People affected by bladder disorders often isolate themselves and subsequently experience dramatic reductions in their quality of life [4,21-23]. Besides societal problems such as social isolation, exclusion, and loneliness, bladder dysfunction represents a significant risk factor for more frequent hospitalization and nursing home admissions [24]. For example, an increased risk of hip and thigh fractures was associated with urinary incontinence and nocturia [23]. Despite the availability of an increasing number of DAT to support continence care [6,20], the health systems mostly use wearable absorbent products or absorbent pads to report urine leakage and alarms that are evinced with audible, visual, or graphic signals [4-6]. DFree enables incontinence relief by predicting micturition needs and helping people regain control of micturition [25,26]. However, the relief DFree provides and the willingness of nurses to use DFree remain unclear. Despite the high degree of user acceptance demonstrated within a group of patients in preliminary studies [14,19], the questions of workload reduction in continence care for nurses and cost reduction for continence care materials remain unanswered. To bridge this research gap, this study investigates the use of DFree Professional in an inpatient care setting to extend the results of the previous groundwork. This study examines how the DFree Professional facilitates continence care in the inpatient setting and how health and nursing care professionals assess the "usability" of this DAT. Usability refers to the quality of technology use through human-technology interaction, specifically in relation to nursing professionals and their adoption of DAT in their nursing process planning, and this encompasses several aspects, including significance, transparency, and physical access to sociotechnical components, as well as meaningfulness and effectiveness, all of which should be easily accessible to users [27,28]. Usability in this sense depends "on the significance, transparency, and physical access to sociotechnical constellations" [28] as meaningfulness and effectiveness must be particularly accessible to the users [27,28]. Therefore, the following specific research objectives will be evaluated:

1. As a primary objective, it is assessed how DFree supports and facilitates free professional continence care by nurses in inpatient care settings?
2. Identify and describe changes and barriers in the intention to use (ITU) DFree.
3. As a secondary objective, nurses' reception of integrating sensors and the associated software into the operational organization of inpatient care processes, as well as cocreative designing of a process that has a high level of acceptance, get surveyed.

Methods

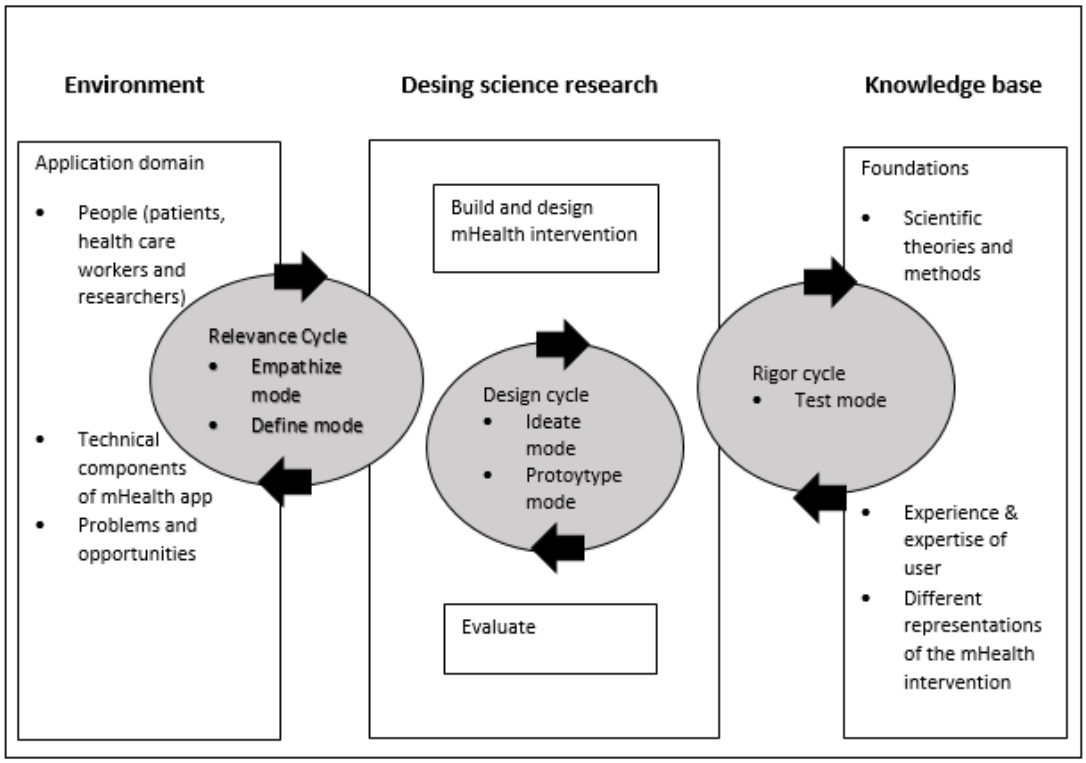
Design and Conceptual Framework

To ensure that the DFree achieves high usability and acceptance, this study uses a mixed methods design and follows the methodological specifications of a cocreative user-centered design (UCD) that was previously described by Farao et al [29]. UCD is used to determine the context of mobile health apps and the consequences of their implementation from the design stage [29,30]. The implementation of mobile health apps without end-user involvement compromises desired outcomes and leads to unmet health goals and adverse outcomes [29,31]. UCD is an evidence-based approach that involves end users in the development and implementation of technologies and prioritizes their needs [29,32]. The 2 proven UCD approaches comprise the information systems research framework (ISR) and design thinking (DT). The ISR comprises 3 cycles that integrate the everyday realities of end users (relevance cycle) and the scientific and economic knowledge base (precision and rigor cycles) into the development of technical products (design cycle) [31,33-35]. Furthermore, DT uses different modes that occur in iterative processes; the empathize mode determines the end user's initial understanding, which is further analyzed in the defined mode to identify specific needs. Subsequently, the development of a technical product undergoes several rounds of ideation (idea mode, ie, generating multiple ideas), prototyping (prototyping mode, ie, translating ideas into physical representations), and testing (testing mode, ie, refining and improving the prototypes and simulating their use in context). In a further step (implementation mode), a medium- to long-term result evaluation is undertaken that possibly leads to the first step for determining need [36]. Despite these advantages, both approaches have disadvantages. The role of stakeholders in ISR is unclear, particularly in the relevance cycle. This means that scientists are primarily responsible for laboratory and field tests and that stakeholders only participate to a small extent in the planning and implementation stages. In the design cycle, the

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technical requirements are disconnected from feasibility, whereas in the precision cycle, economic interests dominate the users' points of actual applicability [37]. In DT, the components that improve usability and effectiveness are unclear, and there is no evidence of the generalizability of the identified key needs to a broader group [36]. UCD combines these 2 user-centric approaches and thereby balances the disadvantages of 1 model with the advantages of the other (Figure 1) by combining empathy and the definition mode of DT and integrating the relevance cycle of ISR [29]. Both approaches show positive effects for improving the identified outcomes, higher usability, and user acceptance of technical products [36,37]. Additionally, the combination pursues the purpose of specifying technology requirements with regard to needs assessment as well as improving cooperation between scientists and end users. Thus, intervening in the precision cycle (ISR) with the test mode (DR) connects the knowledge base of the precision cycle with end-user cooperation for product evaluation, as relying only on the test mode is inadequate to enable further technical product development. Instead, the abovementioned combination makes it possible to include health goal attainment as an evaluation factor of product function and success. In particular, with regard to the design cycle mode, the preliminary work of the research group helped to modify the tasks of this project [14]. The design cycle of the ISR is linked to the idea and prototype modes of the DT. With this combination, end users participate in technical (further) development. An advantage of ISR is that the necessary knowledge for further technical development emerges from empirical results, whereas in DT, the knowledge emerges from end users and developers. Thus, the combination of both approaches was suitable for implementation in this study because of the possibility of comparative analysis to improve DFree by factoring in the interests of users and developers, besides increasing usability. Peters and colleagues [38] showed that usability alone does not enable statements on the actual ITU by potential users, as the satisfaction of basic human needs is a decisive factor in "usability" [28,38-41]. In Basic Psychological Need Theory, the more interaction with a system that satisfies basic psychological needs, the greater the technological engagement of end users [41]. Three basic psychological needs describe more proactive, committed, passive, and demotivated human characteristics: competence (ie, feeling capable), connectedness (ie, feeling connected to others), and autonomy (ie, feeling self-determined) [39-41]. Accordingly, the technological influence on end-user well-being can be better understood and evaluated if the abovementioned 3 basic needs are considered in the developmental process [38], as the needs function as mediating variables between a technical product and the end users' ITU. This means that an increase in autonomy leads to higher engagement. Motivation to use increases with higher competence, whereas increased connectedness increases well-being and ITU. The model assumes that psychological needs consider 5 different levels of analysis: starting with the introduction of technology (adaptation), through interface interaction (interface), dealing with technology-specific tasks (task), technology-supporting behavior (behavior) for the entire life of the end user (life), and the societal level (society). In the METUX model, the basic psychological needs for autonomy, competence, and connectedness positively mediate the design and outcomes of the end-user experience, such as motivation, engagement, and well-being. These variables represent specific, measurable parameters that developers can use to support the fulfillment of basic needs.

Figure 1. Combination information system research and design thinking (adapted/reproduced from Farao et al [29], which is published under Creative Commons Attribution 4.0 International License [42]). mHealth: mobile health.



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This monocentric, exploratory, mixed methods study was planned with multiple measurement times that correspond to the "Evaluation" phase in the Medical Research Council framework [43]. Therefore, a concurrent mixed methods design was used to facilitate the concurrent collection of different forms of data, separate analysis of the data, and final merging of the findings [44,45]. By combining qualitative descriptions of nurses' experiences with quantitative ratings of nurses' ITU, we developed more comprehensive knowledge of the influence of DAT DFree in reducing nurse workload in continence care. This study is the first to test and evaluate a DFree ultrasonic sensor in an inpatient care setting with patients and various health care providers (nurses and physicians). In a (cocreative) process for the integration of DFree into the operational organization of the ward's everyday routine, concrete scenarios are outlined to make DFree usable for practical implementation. Finally, we will collect data on user acceptance while testing the DAT under real-world, everyday ward conditions.

Technical Description

The DFree Ultrasound Sensor (Triple W Japan KK) is a DAT that comprises 2 parts: a controller and an ultrasound probe that has the potential to predict the need for voiding (Figure 2).

DFree is a supportive tool for patients with bladder dysfunction. The basic principle of the sensor is based on measuring the degree of bladder expansion during filling by using ultrasound measurements, which then notifies nursing professionals through a signal emitted through an iOS operating system app. For this research project, it was necessary to connect the "Wi-Fi Base Station" to the network of the hospital, which comprises internet access (Figure 3). Owing to the strict security measures of university data centers, this interface issue is a specific challenge in the implementation of projects and introducing data analysis technology into health care provisions in general.

DFree uses ultrasound waves at 10-second intervals to measure the degree of change in the urinary bladder during urine filling. A dedicated notebook app provided information on the expected timing of the next visit to the toilet. The display of bladder filling on the screen can be scaled to 10 levels, triggering an alarm when an individually set threshold is reached. The digitally captured degree of bladder expansion was converted into a numerical value and displayed on a mobile phone or notebook app. Thus, DFree represents a potential supportive therapy option for bladder dysfunction that could help nurses reduce their workload.

Figure 2. DFree ultrasound sensor.



Figure 3. DFree data transfer.



Quantitative Evaluation

Figure 4 shows technology-specific (orange) and psychological (blue) factors of the Technology Usage Inventory (TUI).

As shown in Figure 4, the 8 TUI scales are divided into technology-specific (orange) and psychological (blue) factors and grouped around the ninth scale, ITU. The wording of the individual items, with the exception of the scales "anxiety in technology" (Technologieängstlichkeit = ANG) and "interest" (Interesse = INT), is related to a specific technology. Each scale comprises 3 to 4 items, each of which is to be rated on a 7-point Likert scale. The INT scale uses 3 items on a visual analog scale to record the ITU's specific technology. Overall, the TUI consists of 33 items and encapsulates a modular design whereby individual scales are excluded and item formulations must be adapted to the circumstances (eg, specific naming of technology). The internal consistencies of the scales can be rated as good overall (Cronbach α=.70 to α=.89). Furthermore, the TUI scales (with the exception of ZUG) based on heart rate and heart-rate variability have been positively validated as indicators of stress and were positively validated as indicators of stress and relaxation [46]. Except for the immersion (IMM) scale, all the scales offered by the TUI were used in the DFree study. Immersion refers to the evaluation of the intensity of sensory impressions when using a specific virtual reality app, and this scale is excluded because it was not part of the research question (Table 1).

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Figure 4. Technology Usage Inventory assessment (adapted from Kothgassner et al [46], with permission from Oswald Kothgassner).

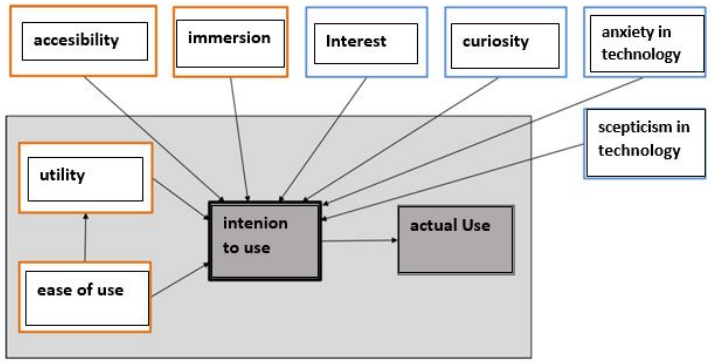


Table 1. Description of the Technology Usage Inventory Scales.

Scale	Description
Curiosity (NEU)	Curiosity and inquisitiveness of a person regarding a specific technology
Fear of using a technology (ANG)	Regardless of specific technology. Overwhelm, fear of using technology
Interest (INT)	Regardless of specific technology. Interest in technology and willingness to obtain information independently
User friendliness (BEN)	Perceived user-friendliness (in the sense TAM[a]) of a specific technology
Usefulness (NÜT)	Perceived usefulness (in the sense of TAM) of a specific technology. Refers to support in everyday life.
Skepticism (SKE)	A person's skepticism and distrust about the use of a specific technology. Assessment of risk, danger, disadvantages
Accessibility (ZUG)	Perceived accessibility (in the sense of availability, buying process) of a specific technology
Immersion (IMM)	Refers to virtual reality apps and is therefore not used here.
Intention to use (ITU)	intention to actually use a specific technology.

[a]TAM: Technology Acceptance Model.

In this study, 3 measurement times (T1, T2, and T3) have been defined (Table 2), and the questionnaire is used at each time point. Before the commencement of the application test (adaptation in the relevance and design cycle), the TUI I Original questionnaire pre-post version—TUI Prä—is used to collect data on a general tendency about technology (fear and curiosity) in the group of nurses before the prototype is introduced. At T2, the prototype is presented for the first time and is thus introduced (design cycle of the interface analysis level). Therefore, the TUI II parallel questionnaire (complete version) will be surveyed in its entirety, and the scales INT, BEN, NÜT, SKE, ZUG, and ITU will be introduced to the nursing staff. At T3 (DT prototyping: testing and implementation mode), measurement will be undertaken, and the group of nursing professionals will test DFree wherein the full version of the TUI II parallel questionnaire (complete version) is represented. The measurement allows statements about changes in the ITU.

For the evaluation, a cumulative value was formed for each scale wherein the ticked answers were added, whereby some items had to be reversed beforehand. The cumulative value starts with 1 as the lowest level of the construct and, depending on the number of items, ranges from 21 (3 items) to 28 (4 items; the highest level). The ITU Scale is an exception because, to evaluate this scale, we measure the distance from the right end point (full rejection) to the answer at the intersection of the line. The distance in millimeters was determined and added to all 3 items (A, B, and C). The maximum scale value achievable is 300. Total scale values are converted into standard values (stanins and percentage rankings) using a standard table (Table 3). Thus, a statement of the relative proportion of participants who achieved the same or lower values is feasible. Therefore, a percentage ranking between 40 and 60 represents the absolute average [46].

The System Usability Scale (SUS) assesses the usability of a system that is subjectively perceived by the user and is demonstrably technology-independent, that is, SUS can be used for a wide range of systems and technologies [47,48]. The 10 items of the SUS are divided into 5 positive and 5 negative statements, each of which is represented on a Likert scale from 0 to 5. The responses are used to derive the SUS item score, which is then converted into the overall SUS score (from 0 to 100). To calculate the overall SUS score, the raw value minus 1 was calculated for all odd items in the first step, whereas the raw value of 5 was subtracted from the even items. For example, if item 1 had a raw score of 4, the score would be 3 (obtained as 4 − 1). For item 2, if the raw score was 2, then the score was 3 (derived as 5 − 2). Next, the newly calculated scores were summed and multiplied by 2.5 to obtain the overall SUS score [49]. Systems are considered fit if they achieve a benchmark of 68 [48,49]. The score is not to be understood as a linear percentage but moves on a percentile and requires a corresponding interpretation [48-50]. In a preliminary study, an adjective scale was developed for a more comprehensive classification of the SUS scores [50] (Table 4).

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Table 2. Measurement times Technology Usage Inventory (TUI).

Measure times	TUI version[a]	Scale
T1: Adoption—before the technology was introduced	TUI original questionnaire (pre-post version)	NEU[b] and ANG[c]
T2: Task—testing the technology	TUI II parallel questionnaire (complete version)	NEU, ANG, INT[d], BEN[e], NÜT[f], SKE[g], ZUG[h], and ITU[i]
T3: Behavior—end of technology testing	TUI II parallel questionnaire (complete version)	NEU, ANG, INT, BEN, NÜT, SKE, ZUG, and ITU

[a]Designation according to the official TUI manual (Kothgassner et al [45]).
[b]NEU: curiosity.
[c]ANG: fear of using a technology.
[d]INT: interest.
[e]BEN: user friendliness.
[f]NÜT: usefulness.
[g]SKE: skepticism.
[h]ZUG: accessibility.
[i]ITU: intention to use.

Table 3. Percentage ranks and stanins.

Percentile rank	Stanine	Percentage (%)
0-4[a]	1	4
>4-11[a]	2	7
>11-23[b]	3	12
>23-40[b]	4	17
>40-60[c]	5	20
>60-77[d]	6	17
>77-89[d]	7	12
>89-96[e]	8	7
>96-100[e]	9	4

[a]Strongly below average.
[b]Slightly below average.
[c]Average.
[d]Slightly above average.
[e]Strongly above average.

The measurement time T1 of the SUS was parallel to the measurement time T3 of the TUI at the end of the trial.

Statistical advice for study planning was obtained from the Institute for Medical Epidemiology, Biometry and Computer Science. As this involved an explorative approach, calculation of the number of cases was unnecessary and was therefore derived from investigations by Faulkner [51], who examined the number of problem identifications in relation to their dependence on the number of subjects. With a sample size of 5 subjects, an average of 85% and at least 55% of 100 problems could be identified, with a very high SD of 9.3. Faulkner [51] indicates that at least 50 subjects are needed to identify an average of 100% of the 100 given problems. As the study duration and the intensity of data acquisition are limited by the human resources available for the project and the project duration, this study used a sample size of up to 45 nurses, which means that 15 nurses are evaluated per ward and per clinical unit.

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Table 4. Adjective scale of the System Usability Scale (SUS) score (Bangor et al [50]).

Acceptance range and SUS score	Adjective scale
Acceptable	
90-100	Outstanding: best imaginable
80-89	Excellent
68-79	Good
Marginal	
50-67	So-so
Not acceptable	
35-49	Mad
0-34	Very bad: not imaginable

Qualitative Evaluation

The number of nursing staff members who participate in the expert interviews [52] is limited to 6 to 10 nurses. The selection follows the principles of theoretical sampling, and the aim of the surveys is not to achieve statistical representativeness [53]. Using guided interviews, the survey will be conducted with the clear aim of obtaining specific knowledge that is necessary to answer the precise (and theoretically embedded) research question. The interviews conducted after the completion of the empirical research program on the DFree Professional are useful for obtaining either supply-relevant and "practical" background knowledge or information on the practical implementation of the ultrasonic sensor [52]. The methodological preparation was based on the mechanism-exploring research paradigm of qualitative content analysis that was described by Gläser and Laudel [54], who suggested a 5-step approach commencing with the development of the interview guide and ending by logging the respective surveys [52,54]. Herein, individual steps may be simultaneously taken in parallel to optimize the overall processing time for data collection. The sets of questions fixed in the guidelines were based on preliminary considerations and were developed into a complete guide after the interviews in the first submission (Multimedia Appendix 1).

The methodological recourse to guided interviews for data collection originated from the fact that conducting expert interviews requires good knowledge of the field of investigation [14]. However, challenging hurdles to field access exist within the framework of the DFree study and include the implementation of the DAT and its components in the ecosystem of a clinical ward during normal operational business hours. For example, Adner and Kapoor [55,56] argue that the impact of external challenges through innovation depends not only on their magnitude but also on their position in the respective ecosystem. This implies that the physical functionality of the technology during regular operations in the clinical ward ecosystem is of fundamental importance for assessing the technology itself. Overcoming these hurdles ensures that the surveys of nursing staff on their experiences using DFree Professional within the framework of the nursing process are actually theory-based and methodologically reflected. In the expert interviews, narrative elements relate to the perception of free fitting to problems in continence care from the perspective of nurses are a key focus area [57,58]. The interview guidelines have been developed iteratively using SPSS Statistics 25 [59]. At the end of the 3-month trial period, face-to-face interviews will be conducted using the Phillips Voice Tracer device. All interviews will be transcribed and analyzed based on the content analysis method [54] supported by Microsoft Excel 2016 (Microsoft Corporation) to process data.

All nursing professionals in this study will be recruited through contact with the University Clinic Halle (Saale) and will include those who are employed in clinics for neurology, neurosurgery, and geriatrics. The staff council was informed in advance, and approval of the project was requested.

Ethics Approval

All procedures involving human participants or human tissue will be performed in accordance with the institutional and national research committee ethical standards and tenets of the 1975 Declaration of Helsinki and its later amendments or comparable ethical standards. Informed consent will be obtained from all the participants. This study was approved by the Ethics Committee of the Faculty of Medicine, Martin-Luther-University Halle-Wittenberg (approval no. 2023–031, dated May 9, 2023). The study was registered in the German Register of Clinical Studies (registration no. DRKS00031483), and the protocol has not been published previously.

Results

Data collection would begin in the summer of 2023, and the initial results are expected in the winter of 2023. This study will evaluate the implementation of DFree to support nurses in reducing their workload pertaining to continence care. A change in ITU (TUI Scale) is expected. To investigate the possible causes for the measured change, 7 additional characteristics—curiosity (NEU), anxiety about technology, interest (INT), usability (BEN), usefulness (NÜT), skepticism (SKE), and accessibility (ZUG)—will be evaluated 3 times. Furthermore, this study will generate structured feedback that can support developers in further improving DAT DFree. Consequently, a reduction in the number of unsuccessful toilet visits or uncontrolled micturition events while wearing DFree will be recorded and documented by nurses through numerical counting. This will show whether the use of DFree is a practical

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and advantageous measure for mitigating the nurses' workload in the context of continence care. As nurses are often poorly equipped to respond to such DAT implementation, the results should serve as a guideline for further improvement of DFree. The combination of qualitative and quantitative instruments addresses the additional aspects that nursing staff would have in mind but will not be assessed using only a quantitative instrument (TUI). Additionally, a change in the perceived usability of the DFree app among nurses is expected.

Discussion

This pilot study will implement DFree in continence care, give nurses an opportunity to try DFree in real-world practice, and enable the possibility of further cocreative development. The study design enables a novel practical testing of a DAT together with an opportunity for cocreative improvement through direct user feedback. This was the first pilot study to evaluate the use of the DFree ultrasound sensor in an inpatient care setting. This study is the first of its kind and is highly relevant, especially in the context of the barriers to the practical implementation of measures for the digital transformation of health care. The results and experiences from this study facilitate an effect assessment for subsequent studies and serve as a basis for methodological and organizational modifications. Therefore, it is important to evaluate quantitative data in terms of technically meaningful measures. Nonetheless, the study has some limitations, such as the small sample size, diversity of bladder dysfunctions (urinary incontinence and urinary retention), and the impossibility of extrapolating quantitative results to other populations. Additionally, no control group has been included in this study. Nevertheless, this pilot study provides the first assessment of nurses' ITU a DAT, the DFree ultrasound sensor, and provides initial data for further controlled clinical studies. The strengths of this study include the triangulation of quantitative and qualitative data. With regard to the first question on increasing usability, an increase in the SUS score could be considered a technically meaningful measure. Furthermore, changes in the TUI-ITU scale reflect changes in intended use, which is a logical preliminary stage for actual use of the intervention. Finally, at the societal level, the study's results will help explain the influence of DFree on reducing the workload of nurses and encourage nurses to use the DAT in nursing care as an additional resource for better outcomes in bladder dysfunction interventions.

In conclusion, this research protocol has been designed to develop a reflective implementation strategy for DAT with a focus on the provision of support in continence care based on scientific and experiential knowledge. The possible use of the intervention is initiated by a change in the ITU as a logical preliminary stage pertaining to actual use. The possibility of practical testing influences the intended use, which, in the next step, affects the actual use in everyday work. The results of this study will encapsulate practical, scientific, and societal implications and would likely pave the way for further studies and interventions to reduce nurses' workload.

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Data Availability

The data sets generated and analyzed in this study are available from the corresponding author upon reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Interview guideline Dfree Trial.
[PNG File , 31 KB - resprot_v12i1e47025_app1.png]

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Abbreviations

ANG: fear of using a technology
BEN: user friendliness
DAT: digital assistive technologies
DT: design thinking
IMM: Immersion
INT: interest
ISR: information systems research framework
ITU: intention to use
NEU: curiosity
NÜT: usefulness
SKE: skepticism
SUS: System Usability Scale
TUI: Technology Usage Inventory
UCD: user-centered design
ZUG: accessibility

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Protocol

Referring Adolescent Primary Care Patients to Single-Session Interventions for Anxiety and Depression: Protocol for a Feasibility Study

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Abstract

Background: Despite the growing prevalence of depression and anxiety among adolescents, fewer than half access appropriate mental health care. Single-session interventions (SSIs) for depression and anxiety offered in primary care are a promising approach to bridging the treatment gap.

Objective: We aimed to implement a clinical workflow for primary care and behavioral health providers to refer patients aged 13 to 17 years with mild to moderate depression and anxiety symptoms to Project YES (Youth Empowerment and Support), an open-access SSI platform, in a large group medical practice with an integrated behavioral health department.

Methods: Pediatric primary care and integrated behavioral health providers will be educated on the benefits of Project YES for adolescent anxiety and depression and trained in a workflow integrated within the electronic health record system, Epic, to refer patients during well-child visits and pediatric behavioral health visits. Patients with mild to moderate internalizing symptoms based on the 17-item Pediatric Symptom Checklist or youth Pediatric Symptom Checklist will be invited to try an SSI through Project YES. We will examine provider uptake and perceptions of acceptability, feasibility, and appropriateness over time.

Results: The rollout will take place between November 2022 and May 2023, when outcomes will be evaluated. Data analysis and manuscript writing are anticipated to be completed during the summer of 2023.

Conclusions: SSIs such as those available through Project YES have the potential to provide low-cost, evidence-based mental health treatment to adolescents with mild to moderate depression and anxiety. If deemed feasible and acceptable, providing SSIs in primary care settings could significantly improve access to mental health care without taxing pediatric primary care and behavioral health providers.

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KEYWORDS

adolescents; behavioral health care; mental health; primary care; single-session interventions

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Introduction

Overview

Among adolescents, the incidence of depression and anxiety has increased significantly over the past decade. In 2019, 37% of adolescents (in the United States) experienced symptoms of sadness or hopelessness, while 21% received a diagnosis of major depressive disorder and 9% were diagnosed with an anxiety disorder [1]. Exacerbating the crisis in youth mental health, the COVID-19 pandemic led to unparalleled disruption in the day-to-day lives of youth and adolescents. School and social events were put on hold, and they observed the consequences of COVID-19 in their families and communities, resulting in a 2-fold increase in depression and anxiety [2].

Despite the rising prevalence of mental health concerns among adolescents, 75% of adolescents with mental health conditions do not receive appropriate care [2] due to a lack of access and acute shortages of qualified pediatric mental health clinicians [2]. Primary care providers are increasingly called upon to identify and intervene with mental health concerns [3], and it is therefore critical for pediatric primary care providers to have effective tools to offer to patients and their families to help manage symptoms. However, such resources are often not available to primary care providers, and patients often wait months before receiving care from licensed mental health professionals following a referral from primary care. Self-guided and web-based single-session interventions (SSIs) are an effective treatment for adolescents with mild to moderate mental health concerns [4] and may provide a stopgap for patients in need of more intensive care who are waiting to receive services. This paper presents the protocol for a novel clinical process for pediatric and integrated behavioral health care providers to refer adolescent patients to use the SSI platform Project YES (Youth Empowerment and Support) at a large group medical practice with an integrated behavioral health department.

Access to Mental Health Care Among Adolescents

In 2021, the surgeon general declared a mental health emergency, prompting responses from multiple sectors to allocate resources to pediatric mental health care [5]. Yet, despite such calls, the population-level mental health of adolescents has worsened throughout the pandemic as growing patient needs are compounded by acute shortages of qualified providers [2,6]. While more than half of all adolescents with mental health concerns do not receive any treatment, even among those who are treated, most do not complete a full course of evidence-based treatment and rarely attend more than 3 to 4 sessions [7]. Beyond the issue of supply and demand, barriers to accessing and completing a clinically appropriate course of treatment for mental health concerns are many. Among adolescents, stigma, shame, and beliefs about who seeks mental health care may inhibit adolescents from accessing necessary interventions [8]. Confidentiality from parents is another important barrier and the Adolescent Health Care Barrier Survey revealed that nearly 40% of adolescents reported forgoing mental health services because they did not want their parents to know [9]. These barriers highlight the need for evidence-based tools which are both acceptable and directly accessible to youth presenting with mood- and anxiety-based symptoms.

SSIs are designed to be intentionally brief, flexible, and potent. Digital SSIs, which can be web-based and self-guided, are a sustainable and low-cost means of disseminating evidence-based treatments at scale [4,10]. SSIs do not rely on patient-provider ratios and can be offered to many patients by just a few providers in under 5 minutes. Their broad accessibility can reduce stigma around mental health concerns and help to normalize the use of appropriate care, whether a patient is going through a challenging time or working through a persistent mental health condition. Furthermore, SSIs can be disseminated in a variety of settings, such as schools and through social media [10,11], and adolescents can use SSIs with confidentiality from their parents. Despite the demonstrated efficacy of SSIs disseminated through social media, they are seldom made available in pediatric health care settings. As digital technologies are increasingly leveraged to close the gap in mental health care, SSIs may provide an additional resource for providers to deploy to adolescent patients.

Evidence for SSIs

Given their demonstrated effectiveness and flexible nature, web-based SSIs allow youth to access mental health support when and where they need it. A growing body of evidence suggests that SSIs hold the potential to reduce a variety of mental health problems. In a meta-analysis of 50 randomized controlled trials targeting youth mental health issues, SSIs were effective (Hedges g=0.32) in improving several clinically relevant outcomes [12]. Notably, SSI effectiveness did not significantly differ between therapist-administered and self-administered interventions. In addition, shorter (<60-minute) interventions were found to be as effective as longer SSIs [12].

In a randomized controlled trial, a virtual, self-administered growth mindset intervention reduced depression symptoms in high-symptom youth 9 months after completion [13]. Other trials of digital SSIs teaching growth mindsets similarly demonstrated their potential to reduce depression symptoms [14-16]. In a diverse group of adolescents recruited from all 50 US states, 2 SSIs improved youth agency immediately postintervention and decreased anxiety, depression, hopelessness, and restrictive eating behaviors 3 months later [17]. Importantly, these SSIs appear to be similarly effective for youth of diverse racial-ethnic identities, gender identities, subjective family social status, and sexual orientations [18].

Web-based SSIs have been evaluated in a more naturalistic setting through an open-access web-based platform called Project YES [19]. Project YES allows adolescents (aged 11 to 17 years) to choose from 3 web-based interventions, each of which spans approximately 30 minutes and includes a core element of evidence-based treatment [10]. Youth may choose from Project Personality (which teaches that personality traits can change), Project CARE (which centers on the benefits of self-compassion), or the Action Brings Change (ABC) project (which encourages youth to engage in activities to improve their mood). Youth can complete as many interventions as they would like, as often as they choose to, and entirely free of charge. In a pilot trial, adolescents who completed an intervention through

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the Project YES platform experienced immediate improvements in hopelessness, self-hatred, perceived control, and agency. In addition, youth rated the interventions as acceptable, and 34.32% of youth who started an intervention completed it [10]. This surpassed completion rates for other digital interventions in naturalistic settings (1%-28%) [20].

Project YES has also been culturally adapted and translated into Spanish for youth living in San Antonio, Texas. Through a series of semistructured focus groups, San Antonio youth stakeholders shared their lived mental health experiences and co-designed the adapted interventions [21]. San Antonio youth who completed an intervention in English experienced immediate improvements in hopelessness, self-hatred, and perceived agency. Similarly, youth who completed a culturally adapted and translated intervention experienced immediate improvements in self-hatred [21]. The completion rate was 49.6%, and the interventions were rated as acceptable by youth [21].

Each SSI in Project YES includes shared core elements thought to underlie its effectiveness. Namely, the interventions (1) present youth with brain science to validate the concepts introduced in the activity, (2) empower youth by placing them in an "expert" role, (3) promote retention of the material with "saying is believing" exercises, and (4) include vignettes from peers and valued others [19]. Conceptually, the SSIs operate by shifting proximal beliefs or behaviors (eg, hopelessness, agency, expectancy that change is possible), which are thought to spark behavior change underlying a longer-term reduction of internalized symptoms [17,22]. SSIs are designed with a few key assumptions: (1) something good can come in 1 session, and 1 session may be the last; (2) change can, and is expected to, occur in the moment; (3) and individuals already have the inner capacity to alter their thoughts, emotions, and behaviors to create meaningful change [23]. Altogether, web-based SSIs, such as those in Project YES, are promising options for delivering brief, evidence-based mental health support with the potential to fill need-to-access gaps [24] for youth experiencing mental health problems.

Although SSIs disseminated through social media have been explored in other contexts, less is understood about how to optimize their implementation in primary care settings and integrate them into existing clinical workflows. Identifying best practices for integrating SSIs into current pediatric provider workflows may give providers an additional resource to recommend to their patients experiencing symptoms of anxiety or depression. To this end, the primary objective of this quality improvement pilot is to establish the feasibility and acceptability of delivering a SSI to adolescents with mild to moderate depression and anxiety in pediatric primary care and behavioral health.

Methods

Setting

Reliant Medical Group (RMG) is a multispecialty group medical practice in Massachusetts. With 19 clinics, RMG provides services to 240,000 patients per year, including 64,000 pediatric patients, 29% of whom have been diagnosed with a mental health condition. RMG has an integrated behavioral health department in which patients are triaged by a licensed mental health care provider from primary care to integrated behavioral health services within RMG or in the community. The pediatric behavioral health team has 13 providers, including psychologists, master's level clinicians, nurse practitioners, and psychiatrists who handle prescribing needs. However, the integrated model only serves one-third of the patient population. In 2021, a total of 1910 pediatric patients who were not appropriate matches for the integrated care model were referred outside of RMG to receive services in the greater community. RMG also has a practice research network that includes a team of research scientists and coordination staff to oversee research studies and evaluate quality improvement initiatives. This protocol was developed by a multidisciplinary team including a research scientist, pediatrician, pediatric psychologist, and pediatric psychiatrist in collaboration with the Lab for Scalable Mental Health at Stony Brook University.

Study Design

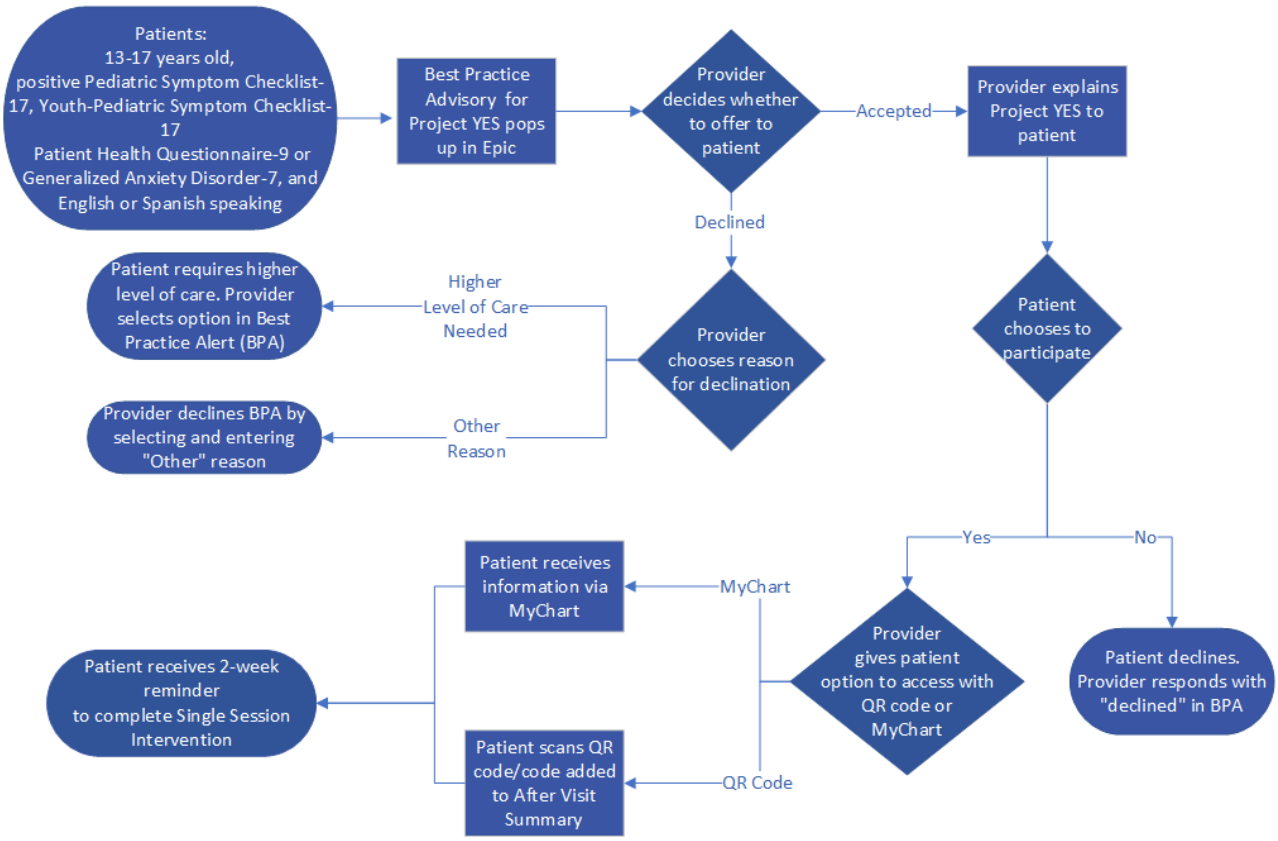
This paper describes a quality improvement pilot designed to evaluate the feasibility and acceptability of disseminating Project YES in primary and behavioral health care, as well as evaluate short-term changes in mental health outcomes among participants.

Patient Screening

Figure 1 displays the clinical workflow for screening and referring patients to Project YES. First, as part of routine mental health screening during well-child visits, pediatric primary care and behavioral health providers or their medical assistants administer either the 17-item Pediatric Symptom Checklist (PSC-17) [25] or the Youth PSC-17 (Y-PSC-17) [25] to all patients aged between 13 and 17 years. When the total internalizing symptom score is elevated on either of these scales, follow-up screeners such as the Patient Health Questionnaire-9 (PHQ-9) [26] and the General Anxiety Disorder-7 (GAD-7) [27] are administered. Information from these screeners is used to determine whether patients meet criteria for a clinical diagnosis on the spectrum of depression or anxiety and whether routine follow-up is necessary. The PHQ-9 and GAD-7 screeners are also routinely administered as independent screening tools by behavioral health providers as part of the behavioral health visit. Providers will have the opportunity to refer patients to Project YES when the following criteria in Textbox 1 are met:

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Figure 1. Clinical workflow for referring patients to Project YES.



Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Patient is aged between 13 and 17 years.
- Patient meets at least one of the following criteria at the visit or in the preceding 3 months: (1) Patient Health Questionnaire-9 (PHQ-9) score >5; (2) Y-PSC-17 or PSC-17 internalizing score ≥5; (3) total Youth 17-item Pediatric Symptom Checklist (Y-PSC-17) or 17-item Pediatric Symptom Checklist (PSC-17) score ≥15; and (4) General Anxiety Disorder-7 (GAD-7) score ≥5.
- Comfortable speaking and reading in either English or Spanish.

Exclusion criteria

- Active suicidal ideation (score ≥1 on question 9 of the PHQ-9, if completed).

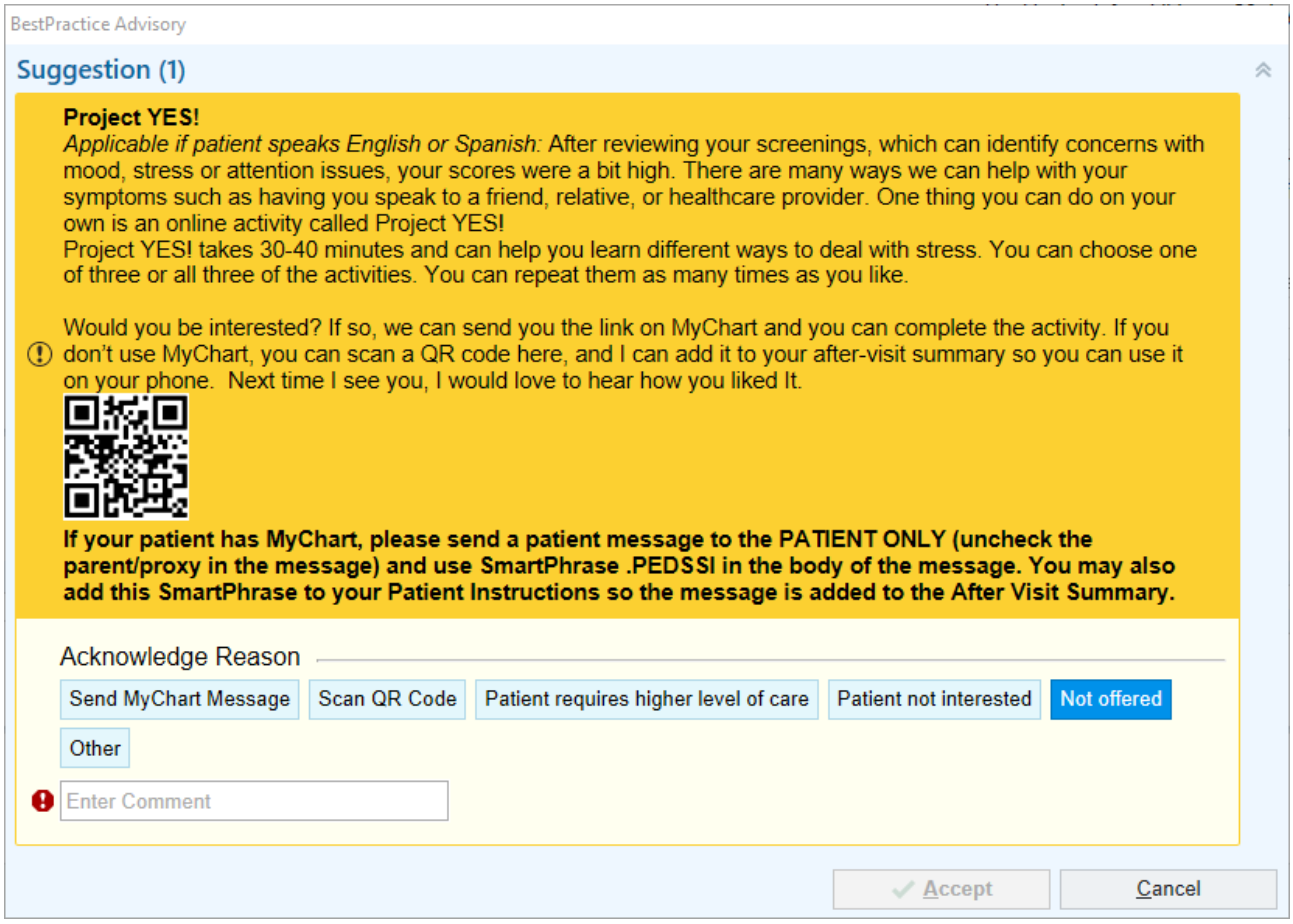
Best Practice Alert

When a patient meets the eligibility criteria, a best practice alert (BPA), displayed in Figure 2, will be triggered in Epic, RMG's electronic health records (EHR) system. The BPA pop-up screen provides instructions for referring a patient to Project YES, including a brief overview of Project YES, its potential benefits, and how to access it. If the patient indicates that they are interested, the provider can offer SSI in 1 of 2 ways:

1. Send the patient a QR code or a link to participate in the SSI through MyChart (the patient front-end of Epic). The MyChart message will include a link to Project YES at the Lab for Scalable Mental Health website and instructions for participating.
2. Provide the patient with a QR code displayed in the BPA that patients may scan using their mobile device, allowing for the retrieval of Project YES for later use. The QR code is also included in the after-visit summary for later use. The QR code will direct patients to Project YES at the Lab for Scalable Mental Health website.

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Figure 2. Best practice alert screen.



Educating Providers on Project YES

First, to ensure representation from participating departments, the implementation team included a pediatrician from the pediatrics department and a pediatric clinical psychologist and pediatric psychiatrist from the behavioral health department. Initial permission and buy-in were sought from the key leadership, including the chief of pediatrics and chief of behavioral health, before designing the workflow. The SSI workflow is targeted toward pediatric and behavioral health providers, including pediatricians, nurse practitioners, clinical psychologists, and master's-level mental health clinicians. All pediatric medical providers and integrated behavioral health providers will be given a brief presentation by members of the implementation team at monthly department meetings, 4 weeks before launching the workflow, and again the week before launch. The introductory presentation covers the gap in care that SSIs can fill, the core elements of Project YES and its 3 interventions, an example of 1 of the SSIs, the evidence base for Project YES, and instructions for referring patients to Project YES during care. Monthly check-ins at department meetings will be held to review processes, answer questions, and gather assessments as well as informal feedback. The monthly check-ins are led by the pediatric behavioral health lead, who is available to answer any questions and address and track comments or concerns. Her contact information is also provided on all materials in the event a provider has questions in real-time.

Each unique clinic also holds individual site meetings where the behavioral health lead will reiterate the core components of Project YES to the staff and providers at each individual clinic. This will also provide the lead an opportunity to introduce new clinical team members to the intervention and referral processes during their orientation. To allow for broader dissemination of information, a monthly behavioral health newsletter sent to all staff in behavioral health and pediatrics will also contain information about the intervention. Lastly, additional materials, such as the PowerPoint slides and other informational materials, will be posted to department shared drives for on-demand review.

Patient Participation

Patients will receive an invitation to participate with a link to the SSI and instructions for participating through MyChart (Multimedia Appendix 1). The patient will click on the link in their MyChart messages that will take them to the Lab for Scalable Mental Health's website. They will be asked to select the module they want to participate in and indicate that they are aged between 13 and 17 years and a patient at RMG in Massachusetts before beginning. The patient will not enter any potentially identifying information. By entering that they are an RMG patient, the Lab for Scalable Mental Health will be able to filter RMG's data for the program evaluation. Before and after completing the module, the patient will be invited to complete a series of anonymous, optional questionnaires within Project YES' Qualtrics interface. In the event a participant in Project YES experiences distress, the Project YES platform

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provides a "Need help now?" button on the main website and on each page of the platform that leads to [28]. The linked page provides immediately accessible crisis resources such as the Crisis Text Line, the National Suicide Prevention Lifeline, and a Hotline for LGBTQ+ Youth.

Data Collection

Provider referral records will be collected through RMG's EHR, and anonymous patient engagement and outcomes data will be collected within Project YES' Qualtrics interface by the Lab for Scalable Mental Health and sent to RMG for analysis. Table 1 describes the specific data to be collected and the corresponding methods of analysis.

Table 1. Overview of data collected and analytic methods.

Data	Items	Analytic methods
Behavioral health and primary care providers: EHR[a] data	• Number of eligible patients seen. • Number of referrals made. • Reasons indicated for not providing SSI[b] (patient inappropriate, not interested, or other). • Number of patients selecting QR code versus MyChart message access.	• Descriptive statistics: proportion of providers in each department offering SSI.
Patients: engagement metrics and feedback	• Number of RMG[c] patients who entered the site. • Total number of patients who completed the SSI. • Program Feedback Scale	• Descriptive statistics.
Providers: data collected at monthly behavioral health and pediatric department meetings	• Acceptability of Implementation Measure (AIM). • Feasibility of Implementation Measure (FIM). • Intervention Appropriateness Measure (IAM).	• Descriptive statistics. • Repeated measures ANOVA.

[a]EHR: electronic health record.

[b]SSI: single-session intervention.

[c]RMG: Reliant Medical Group.

Provider Measures

A total of 3 implementation outcome measures will be collected from providers to evaluate the implementation of Project YES. Each outcome measure consists of 4 items rated on a 5-point Likert scale ranging from "completely disagree" to "completely agree." The scales demonstrate high reliability, with Cronbach α reported between .85 and .91, structural validity indicated by factor loadings between 0.75 and 0.89, and test-retest reliability coefficients between 0.73 and 0.88 [29].

Acceptability of Intervention Measure

The Acceptability of Intervention Measure (AIM) measures the appeal of an intervention to target providers (eg, Project YES meets my approval) [29].

Intervention Appropriateness Measure

The Intervention Appropriateness Measure (IAM) measures whether an intervention is fitting and relevant to the target participants within a given setting (eg, Project YES seems applicable) [29].

Feasibility of Implementation Measure

The Feasibility of Intervention Measure (FIM) measures whether implementing a given intervention is achievable within the setting given the time and resources required to carry it out successfully (eg, Project YES seems doable) [29].

Participant Measures

The following measures are the same as those described in previous reports on Project YES; however, in the context of this data collection, we include both the English and Spanish versions. Additionally, this study implemented a single-item question in both English and Spanish surveys, asking whether the participant was a patient with RMG. Only data from participants who select yes to confirm patient status with RMG and report being between the ages of 13 and 17 years will be included in the final analysis.

Demographics

Participants will identify their age range (provided in ranges to maintain anonymity: 10 years or younger, 11-12 years, 13-15 years, 16-17 years, 18 years or older), sex assigned at birth, gender identity, sexual orientation, race or ethnicity, how they learned about Project YES, and whether they are patients at RMG in Massachusetts.

Program Feedback Scale

The Program Feedback Scale (PFS) [30], which is routinely used to evaluate acceptability and user perceptions of SSIs [4,21,23,31] asks participants to rate agreement with 7 statements indicating perceived acceptability and feasibility of their selected SSI (eg, "I enjoyed the program") on a 5-point Likert scale (1="really disagree;" 5="totally agree"). The scale was adapted from existing, validated acceptability assessments of digital interventions; adaptations from existing scales were necessary to exclude items that are inapplicable to web-based SSIs (eg, items referencing frequency of use or interest in continuing to revisit the program). The PFS will also assess participants' open-response feedback. PFS item scores may be evaluated individually or through a mean score across items. Mean responses to each PFS item will be evaluated separately

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to gain insight on the acceptability in specific domains (eg, ease of use and understanding, enjoyability).

Ethical Considerations

This quality improvement project was exempted from review by the Optum Office of Human Subjects Research Institutional Review Board (IORG0010356) as it was deemed not human subjects research.

Results

The program was initiated in November 2022 at 1 site to ensure Epic components functioned as intended and then expanded across all sites in December 2022. The program will continue for 6 months before the program evaluation will commence; however, referral, implementation assessment, and patient engagement data will be reviewed iteratively to identify any adaptations that need to be made. Data analysis and manuscript writing are expected in the summer of 2023.

Discussion

Overview

Closing the gap in pediatric mental health care requires rethinking how care is delivered and innovative models to overcome the common barriers of face-to-face therapy while delivering effective, evidence-based treatments. Calls for innovation in mental health care have been made [32,33] and COVID-19 has catalyzed the development of digital technology for mental health [34,35]. Such technology is not often available in primary care settings. Single-session treatments, which provide a single session of face-to-face psychotherapy to patients, have been explored in mental health care settings, reporting medium to large effect sizes [36-38], although they are not as commonly deployed in primary care settings. Importantly, compared to single-session treatments, SSIs may be self-guided and rapidly disseminated among patients by providers without special training. Given that the modal number of psychotherapy sessions patients attend is 1 [7], while a minimum of 12-20 sessions may be required for symptom resolution, SSIs developed with the explicit intention of resolving symptoms in just 1 session are not only more accessible but may also be a more appropriate approach to improving treatment for adolescent mental health conditions. In addition to being a front-line intervention for primary care providers, SSIs may also be leveraged by behavioral health providers and offered as adjunctive or follow-up care for traditional face-to-face therapy.

Strengths and Limitations

Offering patients SSIs in primary care and behavioral health settings is an efficient and cost-effective approach to narrowing the treatment-to-service gap in adolescent mental health care. Approaching this as an implementation project will allow us to understand the feasibility, acceptability, and appropriateness of SSI delivery in a pediatric primary care and integrated behavioral health setting and thus identify potential barriers and facilitators providers may face when offering Project YES to their patients. This information may be used to iteratively adapt the clinical workflow described to streamline the process for providers and patients alike, thus improving uptake. This protocol was developed in close collaboration with a pediatric clinical team and feedback from leadership to ensure that it is relevant, efficient, and can be easily grasped and deployed by providers. Further, making the SSIs accessible to patients with a wide range of symptoms may help reduce stigma around mental health care. Finally, adolescents who may otherwise forgo behavioral health services due to concerns about their confidentiality from their parents can use the SSIs privately without their parents being notified.

Nonetheless, there are several limitations to the study design. Participation is contingent on elevated scores on the screener questionnaires. However, patients who may not meet clinical criteria may also benefit from the SSIs, which can be effective for subclinical internalizing symptoms. To address this, future iterations of this project may explore expanding referrals to all adolescent patients, regardless of meeting screening criteria, or advertising the program on waiting room monitors and in other patient-facing materials. Additionally, this work is only being piloted at a single-group medical practice in Massachusetts and may not be generalizable to other populations. Furthermore, RMG has a predominantly White, English-speaking patient population. Although the intervention is available to Spanish-speaking patients, more work may be needed to understand its feasibility and acceptability in other clinical contexts and among diverse patient populations. Finally, without the use of a placebo-control group to control for potential effects of participating in an SSI in and of itself, the effectiveness data from this study may overestimate potential improvements in symptoms.

Conclusion

While this work explores the dissemination of SSIs in primary care and pediatric behavioral health, SSIs have great potential as a proactive approach to the prevention of mental health concerns. Future work could explore the provision of SSIs to a wider range of adolescents in primary care to examine their potential upstream preventive effects. Furthermore, previous research indicates that parents of adolescents may also benefit from SSIs that are as brief as 15 minutes [4]. While the present workflow was designed to be accessed confidentially by adolescents, SSIs may be effectively disseminated to adolescent parents in primary care settings to raise their expectations for treatment, thus improving patient engagement [4].

SSIs are highly accessible and potent interventions that effectively help to fill the adolescent mental health treatment gap at low costs and require minimal provider time and resources. We anticipate that referring patients to Project YES will be both feasible and acceptable for primary care providers, and its use will be acceptable and effective for patients.

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Acknowledgments

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Conflicts of Interest

JS receives consulting fees from Kooth, LLC and Woebot Health; is Co-Founder and Co-Director of Single Session Support Solutions; and receives book royalties from New Harbinger, Oxford University Press, and Little Brown Book Group.

Multimedia Appendix 1
MyChart message to patients who elect to participate.
[DOCX File , 15 KB - resprot_v12i1e45666_app1.docx]

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Abbreviations

ABC: Action Brings Change
AIM: Acceptability of Intervention Measure
BPA: best practice alert
EHR: electronic health record
FIM: Feasibility of Intervention Measure
GAD-7: General Anxiety Disorder-7
IAM: Intervention Appropriateness Measure
PFS: Program Feedback Scale
PHQ-9: Patient Health Questionnaire-9
PSC-17: 17-item Pediatric Symptom Checklist
RMG: Reliant Medical Group
SSI: single-session intervention
YES: Youth Empowerment and Support
Y-PSC-17: Youth 17-item Pediatric Symptom Checklist

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Protocol

A Clinical Model for the Differentiation of Suicidality: Protocol for a Usability Study of the Proposed Model

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Abstract

Background: Even though various types of suicidality are observed in clinical practice, suicidality is still considered a uniform concept. To distinguish different types of suicidality and consequently improve detection and management of suicidality, we developed a clinical differentiation model for suicidality. We believe that the model allows for a more targeted assessment of suicidal conditions and improves the use of evidence-based treatment strategies. The differentiation model is based on the experience with suicidality that we have encountered in clinical practice. This model distinguishes 4 subtypes of entrapment leading to suicidality. The earliest description of this model and a proposal for usability research has been previously presented in a book chapter.

Objective: In this study, we present the most recent version of the 4-type differentiation model of suicidality and a protocol for a study into the usability of the proposed model.

Methods: The 4-type differentiation model of suicidality distinguishes the following subtypes: (1) perceptual disintegration, (2) primary depressive cognition, (3) psychosocial turmoil, and (4) inadequate coping or communication. We plan to test the usability of the 4 subtypes in a pilot study of 25 cases, and subsequently, we will include 75 cases in a follow-up study. We looked at the case notes of 100 anonymized patients with suicidality who presented to mental health care emergency service in The Hague International Center. The summary and conclusions of the letters sent to the patients' general practitioners after suicide risk assessment will be independently rated by 3 psychiatrists and 3 nurse-scientists for absolute and dimensional scores. The Suicidality Differentiation version 2 (SUICIDI-II) instrument, developed for this study, is used for rating all the cases. Intraclass correlation coefficients for absolute and dimensional scores will be calculated to examine type agreement between raters to examine the usability of the model and the feasibility of the SUICIDI-II instrument.

Results: We consider the model tentatively valid if the intraclass correlation coefficients are ≥0.70. Subsequently, if the model turns out to be valid, we plan to rate 75 other cases in a follow-up study, according to a similar or adjusted procedure. Study results are expected to be published by the end of 2023.

Conclusions: The theoretical roots of the differentiation model stem from classic and contemporary theoretical models of suicidality and from our clinical practice experiences with suicidal behaviors. We believe that this model can be used to adjust

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the diagnosis, management, treatment, and research of suicidality, in addition to distinguishing different dynamics between practitioners and patients with suicidality and their families.

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(JMIR Res Protoc 2023;12:e45438) doi:10.2196/45438

KEYWORDS

differentiation; suicidality; suicidal behavior; subtype; subcategory; category; categories; categorize; subcategories; validation study; mental health; suicide; suicidal; differentiation; classification; psychiatry; classify; psychiatric; suicide prevention; suicidal ideation; mental illness; suicidal thought; dying; perceptual disintegration; PD; primary depressive cognition; PDC; psychosocial turmoil; inadequate communication; intraclass correlation coefficients; ICC

Introduction

Thoughts of death or suicide, planning or preparing suicide, attempting suicide, and completing suicide are defined as suicidality [1]. Although suicidal thoughts, plans, and attempts are common, completed suicide is rare. Suicidality is a symptom often found in patients experiencing mental disorder [2]. Except in case of a diagnosis of major depressive disorder or borderline personality disorder [3], suicidality is not a symptom required to meet the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, criteria for any other psychiatric diagnosis.

Suicidality is still defined as a uniform concept [3-5], even though it is complex and multilayered and there are multiple risk and protective factors, including mental disorder, personality traits, biological factors, and psychosocial factors (to name a few) playing a role in the onset and duration of suicidality [6,7]. Scientific knowledge, such as theoretical concepts derived from neuroimaging and research into genetic vulnerability for suicide, will be difficult to apply in clinical practice [8,9], as science has not been able to distinguish different kinds of suicidality or pinpoint drivers or etiology.

It is widely accepted and acknowledged that clinical differentiation of somatic disorders has resulted in improved diagnosis and treatment strategies, for example, for breast cancer [10], diabetes [11], and dementia [12]; yet, no lucid clinical differentiation model for suicidality is available for mental health care [13], and as a consequence, general texts, suicide prevention, treatment guidelines, and scientific research hardly differentiate between various types of suicidal behaviors [14-16].

Mental health professionals confronted with suicidality are not just expected to adequately assess the suicide risk but also to manage the risk and all complexities around those risks [3]. Even when risk and protective factors are identified, the assessment of suicide risks remains complex and completed suicide is unpredictable. Professionals' responsibility and liability are difficult to put into operation when it comes to suicide prevention, and another layer to the complexity of suicide risk assessment is added [17].

The pathway of referral to services partially defines the responsibilities of professionals involved at any point of the pathway. They do not just need to share the responsibilities for prevention of suicide with other professionals and referrers but also share this responsibility in a rational and reasonable manner with the patient or the relatives [18-20]. Everyone involved needs to be aware that not all patients with suicidality can be safeguarded by admission. Admission may protect (temporarily) against suicide but can engender an iatrogenic effect, resulting in maintaining the suicidal state rather than reducing it, which is unwanted [21,22]. This is why the emphasis of the management of patients with suicidality is often focused on safety planning and, if applicable, the treatment of underlying mental health disorders.

The complex dynamics around the risks resulting from suicidality and the focus on safety may lead to formalized and restrictive defensive practice. This is why we believe that it will be helpful to discern different types of suicidality and consider to what extent the patient with suicidality is able to take responsibility for their own safety during recovery from a suicidal condition. Differentiation may also help to determine which treatment conditions could be more tailor-made to diagnosis and treatment in mental health. The differentiation of suicidality may encourage practitioners from various networks to apply clear unambiguous language about suicidality.

The result of the scientific quest for suicidal typologies for clinical practice in mental health care was the development of several theoretical models [23-30]. Those models offered improved insight into the complex processes leading to suicide [29-31]. Classical, contemporary, and empirical typologies of suicide have been established [13] and were important for the development of the model under investigation. For instance, the Integrated Motivational-Volitional Model of Suicidality [31] distinguishes between the onset of suicidal thoughts and the dynamic process of engaging into suicidal acts. However, existing theoretical and empirical typologies of suicidality have limited use [3] in clinical practice for various reasons as follows:

1. The application of suicide typology, which is based on variables not related to entrapment, may result in unreliable suicide risk estimates.
2. The context in which suicidality appears—next to theoretical and empirical typologies—determines whether specific, individual factors increase or mitigate the suicide risk [32]. For example, unemployment, a risk factor for suicide, may result in sudden and quick increase in suicide risk when a breadwinner of the family is laid off, whereas someone with long-term unemployment may experience chronic suicidality due to longstanding exposure to stress, substance abuse, and depression. For people who find it hard to maintain themselves in a work environment,

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unemployment can be a blessing in disguise and as such may become a protective factor for suicidality.

The experience of entrapment seems to play a crucial role in the etiology of suicidality as also described in the integrated model of stress vulnerability [33,34] and entrapment [35], which has been developed for the Dutch suicide prevention guideline [16]. The principles of the entrapment theory [23] of suicidality were integrated in the current differentiation model. Entrapment is a mental state in which a person is trapped in the perception that escape is possible by ending their life. We hypothesize that there are 4 ways in which someone might become entrapped. We hypothesize there may be overlap between those paths. We developed a clinical differentiation model for suicidality: the (hypothetic) 4-type model of entrapment of suicidality (h4ME; Figure 1). This model describes 4 subtypes of entrapment of patients with suicidality, with or without mental disorder. Many scientists and practitioners were involved in the development of the h4ME model [3]. The model was revised in 2 Delphi rounds with psychiatrists, psychologists, and mental health nurses who were not involved in the proposed study. The first meeting was in March 2017 with a selection of psychiatrists, people with lived experience with suicidality, peer supporters, nurses, and psychologists employed by Parnassia Mental Health Institute. Feedback from participants of the meetings was provided by email. The second meeting was held during the Dutch Annual Conference of Psychiatrists in 2018 and was attended by psychiatrists only [36]. Feedback from attendees was provided by email.

Another contributor to the development and evolution of the h4ME model was the Dutch Multi-Disciplinary Guideline for the Assessment and Treatment of Suicidality [16] and the Professionals In Training to STOP suicide study [37] examining the effect of an e-learning “train the trainer model on education” and training of mental health care professionals in the application of the guideline principles [38]. Mental health care professionals are trained to assess suicidality in accordance with the Clinical Assessment of Suicidal Episodes [39] to assess to what extent the patient feels trapped (entrapment); the stronger the feeling of being trapped, the higher is the suicide risk [35]. This inspired us to differentiate between etiologies of entrapment (Textbox 1). We hypothesize that all kinds of suicidality encountered in clinical practice (as well as cases of completed suicide) can be assigned to one of the following 4 types [40]:

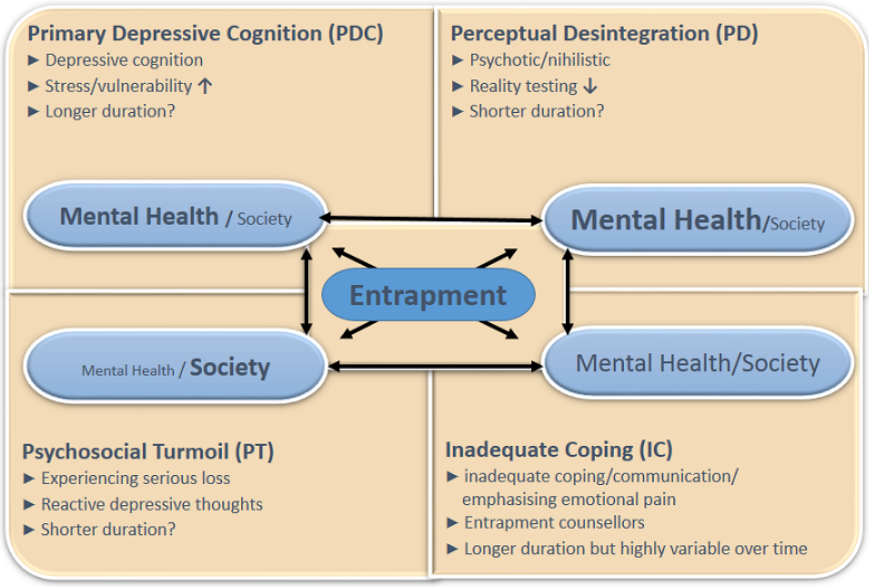
1. Perceptual disintegration (PD): entrapment originating in the context of disturbed perceptions or (affective) psychotic behaviors
2. Primary depressive cognition (PDC): entrapment in the context of (a) depressive cognition(s)
3. Psychosocial turmoil (PT): entrapment in the context of acute reactivity to a (perceived or actual) loss, offence, adversity, or doom
4. Inadequate coping or communication (IC): entrapment in the context of communicating intense distress or emphasizing emotional pain

It is not known whether this model will encompass the full range of suicidal behaviors occurring in mental health care services though. To optimize the assessment of suicide risks and the care of patients with suicidality, it is necessary to test the usability of this model before it is applied in clinical and research practice (Textbox 2). The objectives of our intended study are as follows:

1. Investigate the usability of the h4ME model—examine whether the h4ME model accurately describes the complete spectrum of suicidality as encountered in specialist mental health care services.
2. Examine whether the Suicidality Differentiation version 2 (SUICIDI-II) instrument allows clinicians to assign cases of suicidality to subtypes as described in the h4ME model.
3. Investigate whether the h4ME model and the SUICIDI-II should be adjusted if it appears that subtypes of entrapment overlap.

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Figure 1. The 4 subtypes of entrapment of suicidality and theoretical aspects.



Textbox 1. Descriptions of the 4 subtypes of suicidality (use of narcotics or other substances or somatic symptoms can be viewed as adjustors of which the effect depends on the differentiation of suicidality).

Primary depressive cognition

Suicidality stems primarily from a depressive thought process and there are no psychotic features (yet). The depressive state can be present for a while (eg, weeks or months). Thoughts of suicide, which are part of the cognition and present on a daily basis, are characteristic. There is clear evidence of distress, which can be noticed by the examiner because of the depressive thought process. A classic example would be a depressive disorder, but primary depressive cognition may also be part of an anxiety disorder, autism, etc. The features of a personality disorder may be mixed with the depressive state, or the depressive state may be caused by a personality disorder and become part of a returning thought pattern in which negative cognitions and Beck cognitive triad can be present (negative views about oneself, negative views about the world, and negative views about the future).

Perceptual disintegration (psychotic disturbed perception or behavior)

Suicidality originates from psychosis, which can often be accompanied by affective (depressive) dysregulation or can be affected by it. Usually, the psychotic state has only been present for probably a short time (rather days or weeks than months) and is noticed (or becomes apparent) because of its severity. Suicidality may originate from depressogenic cognition; however, in that case, the severity has developed to such a level that it can be seen as a mood-congruent or mood-incongruent psychotic state. The distress can be understood, but the severity cannot be perceived as comprehensible anymore by the examiner. A classic state is a depression with mood-congruent psychotic features. However, it can also appear among people who, while in a psychotic state, are ordered by their delusions to hurt themselves.

Psychosocial turmoil

Suicidality stems primarily from a severe loss or blow to the ego, leading to a complete upheaval of someone's life. The person experiences enormous guilt, severe shame, or does not dare to look another in the eye anymore or experiences a downfall without being in a psychotic state. There is an unbearable anguish, which leads to a need for release from that pain or the need not to exist anymore, to not be able to feel or escape the awful misery or pending dread. Usually, someone has been in this state for a short time (hours, days, or weeks). Drug use can be extra provoking. The stress is perceivable for the examiner from the perspective of loss or a blow to the ego and there may be slight psychotic features, but one can follow the narrative. Underlying dysregulation of the impulsivity can worsen the state and increase the risk of a lethal outcome.

Inadequate coping or communication

Suicidality stems from a severe feeling of distress and not being able to communicate this properly. There is difficulty with formulating an adequate request for help and one seems to be hoping for a solution by demonstrating suicidality. This behavior usually exists for a longer period (months) and fluctuates severely. This type of a more chronic suicidality is often seen as part of a personality disorder such as a borderline personality disorder. Also, drug use can be an important provoking factor. Suicidality is perceived by others as "externalizing" and fake and can result in aid workers feeling "trapped" in the dynamics. The behavior can coincide with experiences of loss with which the powerlessness is externalized and not internalized. Often, the support system is exhausted and professionals are viewed as failing. The major risk is for professionals to feel manipulated and for the person who is assessed to feel misunderstood and not taken seriously, which leads to an amplification of the behavior, accompanied by an increased risk of suicide. Contrary to how it is perceived by others, the person is genuinely distress. Suicide can be used as the ultimate way to communicate about the distress caused by the perceived unfair or rejection judgment of the person (especially recognizing and exploring the countertransference and offering help to the underlying motivators of suicidality are essential with this type).

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Textbox 2. Examples of conclusions and vignettes of entrapment of suicidality typology.

Vignette 1: Perceptual disintegration

This case concerns a mental health act assessment of a 25–29-year-old woman with no history of mental illness, except for a previous one-off assessment. She has 2 (biological) children younger than 4 years of age. She came to the notice of the police when she—in company of the children—started to ring the bells at the houses of total strangers after a 1-sided car accident (total loss) and expressed suicidal and homicidal thoughts, leaving the children behind in a confused state. People involved in the incident were shocked by the bizarre presentation. At the time of the mental health act assessment, we saw a very tense woman who was clearly trying to keep up a facade and could not reason or answer questions adequately. The presentation was suspect of a paranoid state, which possibly already existed for some time. During the police investigation, her statements were bizarre, for example, mentioning that she was murdered. There was some suspicion of substance abuse. The assessment could not confirm direct symptoms of acute suicidality; however, taking into consideration the events, earlier statements, and the ensuing silence, suicide risk was assessed as acutely increased. Because she showed no insight and refused voluntary admission, an involuntary admission was arranged and agreed. The children were placed with foster parents by social services and child and family services.

Vignette 2: Primary depressive cognition

This case concerns a 50–54-year-old man who was referred by the mental health nurse working in the general practitioner practice. He was referred for an emergency assessment within the community team because of low mood and suicidal ideation. He had consistent ideas of different ways to kill himself, though he considered himself a coward. During the assessment, we saw a depressed man with low self-esteem who normally pushes away emotions. After a small incident at work, he completely broke down and has been on sick leave for the last 4 weeks with low mood, anhedonia, ruminations, and sleep problems. Fifteen years ago, he experienced a similar episode and at that time, he did a suicide attempt with medication and alcohol after the death of his father. At the time, he was referred and treated by the community team. Six years ago, he had a myocardial infarction. He was diagnosed with depression. It was possible to agree to a safety plan, and the suicide risk was considered not to be acutely increased. The patient was referred to the community team—with a safety plan in place—for the treatment of depression.

Vignette 3: Psychosocial turmoil

This case concerns a home assessment of the suicide risk of a 20–24-year-old woman with no previous psychiatric history. The general practitioner asked for an assessment after she made suicidal statements following several serious and negative life events over the last few weeks (relationship breakup, termination of pregnancy, debts, death of grandfather, suicide of friend, loss of accommodation). During the assessment, we saw a tense, desperate woman with insufficient coping strategies to manage the situation, becoming overwhelmed as a result. She was unable to pull herself out of the situation and feels so miserable that she does not have any hope of a good outcome. She expressed suicidal ideas and her support system was unable to support her. Her limited coping skills were possibly due to a disturbed personality development and below average intelligence. A respite admission (time out admission) was indicated to stabilize this patient and work toward follow-up treatment in the community. It was not possible to arrange admission or involve intensive home treatment because of limited capacity within those services, though it was possible to set up a safety plan until the next morning and arrange for alternative follow-up care in the community.

Vignette 4: Inadequate coping or communication

This concerned a suicide-risk assessment at “services for acutely disturbed people” of a 45–49-year-old female who wanted to be addressed as male, without a gender reassignment or transformation having taken place yet. They are known with posttraumatic stress disorder, personality problems, autism spectrum disorder, gender dysphoria, and dissociative episodes. In the past, they attempted suicide on several occasions and autoamputated fingers and toes. Patient was discharged from the admission wards 7 days ago or 7 days before the current assessment. Specialized in-patient treatment for this patient with severely disturbed behavior was terminated because adequate treatment was not possible due to splitting, dismissing, and devaluating the treatment plan, projection, and denial demonstrated by the patient. Patient now comes to the attention of community mental health services, referred by the police, after they made serious suicidal statements and threw the phone down when called by the crisis services. The crisis team contacted the police, who found the patient near a canal, in possession of a knife. During the assessment, the patient displayed complex, claiming behavior possibly because she was unable to acquire Dormicum from the assessing team. Prescription of Dormicum was denied because of the inappropriateness of the request. Patient stated they cannot agree to a safety plan a long as they are not provided with Dormicum. Admission was not considered to be suitable because of the recent discharge and the lack of cooperation with the proposed treatment plan in the patient ward. The outcome of the assessment was to send the patient home and contact the responsible professional of the community team. When the outcome was communicated with the patient, they decided to agree with some form of a safety plan.

Methods

Design: Explorative Qualitative Study

Sampling

In a previous study conducted at The Hague Emergency Service, one-third of the assessed patients exhibited suicidality [41,42]. In this study, 100 cases of patients with suicidality were included in the order of entry. For the pilot study, 25 cases will be included. Subsequently, feedback from raters is collected and procedures may be adjusted. Then, 75 other cases (numbered 26-100) will be rated. The identity of the referrer, the patient, the (nurse) practitioner, and the general practitioner cannot be deduced from the results and conclusions.

Raters

Raters (n=6) will be recruited from RFPdW’s professional network (3 psychiatrists and 3 registered nurses); all are employed at psychiatric emergency services. They all have extensive knowledge and experience in assessing suicidality due to clinical or scientific positions outside The Hague Emergency Service. The raters are not involved in any of the cases included in this study. RFPdW will not be a rater. Raters will be asked to independently assign cases to entrapment types by using the SUICIDI-II, an instrument especially developed for this study to investigate to what extent raters agree on the entrapment type that should be assigned to each case (further indicated: type agreement [TA]). Before scoring, raters will be trained in the h4ME model and in using the SUICIDI-II.

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The SUICIDI-II: An Instrument for Assigning Cases to Entrapment Types

To determine TA, the SUICIDI-II was designed for this study. The SUICIDI-II should be considered a preliminary systematic description of the 4 entrapment types. From 2018 onward, the SUICIDI-II and previous versions and the h4ME model were presented and discussed during conferences in the context of suicide prevention in the Netherlands and abroad [19,36]. The feedback of the attendees was collected during the meetings. The feedback was processed by RFPdW and MHdG and led to adjustments of subsequent versions of the SUICIDI. The SUICIDI-II describes each entrapment type by 3 propositions. The propositions are hierarchically formulated to indicate whether a type is applicable or not. Scores are rated as 0=type is not applicable, 1=type leaves room for other entrapment types, and 2=matches type and excludes other types. See the following link [43] for the SUICIDI-II questionnaire.

Outcome Measures

TA will be investigated in two ways: (1) by calculating an absolute TA (aTA) score and (2) by two different dimensional agreement scores (d1TA and d2TA). The dimensional scores were introduced because we expect that cases might be assigned to more than 1 subtype. aTA will be examined by asking raters to allocate each case to only 1 entrapment type (type PD, PDC, PT, or IC). This will result in an aTA score. Dimensional TA is scored as follows:

1. d1TA: raters are asked to allocate a total of 4 points to one or more subtypes (minimum 0 to maximum 4 for a subtype); the higher the allocated score, the more a subtype applies.
2. d2TA: raters indicate which proposition (1 or 2) most likely applies to the types they scored for the d1TA as proposed in the SUICIDI-II instrument. Subtypes that were not chosen automatically scored 0 (=not applicable).

Data Analysis

Intraclass correlation coefficients (ICCs) will be calculated to quantify the degree of agreement between the raters on the assigned subtypes: aTA, d1TA, and d2TA. Differences between measurements can be due to real differences (between persons or within persons on repeated measurements) or from noise (differences due to imperfections in the description of the types). This is why we will also calculate an ICC for the extent to which raters agree on which statement (1 or 2) best describes the chosen type (d2TA). In SPSS (version 23.0; IBM Corp), the analyses will be performed with a 2-way mixed-effects model, aTA, according to the guidelines of selecting and reporting ICC [44]. ICCs are numbers between 0.0 and 1.0 with a 95% CI. In a perfect model, when ICC=1, all differences are completely real. In a completely invalid model, all differences are noise and ICC=0. In other words, the higher the ICC, the more the raters agree. An ICC<0.50 is indicated as poor, 0.50-0.75 is indicated as moderate, 0.75-0.90 is good, and >0.90 is excellent [44]. The model is considered valid if the ICC for aTA and the 2D TAs (d1TA and d2TA) are ≥0.70. The model will be adjusted if the ICC or the aTA or d1TA are ≤0.70. The propositions in the SUICIDI-II are considered valid usable if the ICC of d2TA is >0.70 and will be adjusted if the ICC is ≤0.70.

Schedule

The first step is to carry out a pilot study in which we examine the usability of the h4ME model of suicidality. We aim to answer the following questions:

1. Is a selection of mental health care workers capable of dealing with the h4ME model and the SUICIDI-II instrument?
2. Can conclusions from patient records of high-risk patients with suicidality assessed by the outreach psychiatric emergency services be used for rating absolute and dimensional TA?
3. Are the proposed subtypes (PD, PDC, PT, and IC) validly definable when various clinicians independently allocate cases to subtypes? How are subtypes distributed?
4. Are these subtypes dimensionally delineated by using 2 different modes of scoring, and is there consensus when different clinicians independently score them? What is the reliability of the different modes of scoring?
5. Which form of dimensional scoring is preferred?
6. If applicable, how can we improve the SUICIDI-II instrument?
7. What feedback can we provide to raters when there is any indication that raters scored incorrectly?

Step 2 is a follow-up study of 75 cases according to the same (or eventually adjusted) procedure. Further, overlap between subtypes will be investigated.

Ethical Considerations

The Medical Research Ethics Committee Leiden the Hague Delft involving the Human Subjects Act (*Wet medisch-wetenschappelijk onderzoek met mensen*) was consulted prior to the start of this study. The committee decided in 2020 that no approval was needed (G21.021/PV/pv). The medical directorates and privacy officers of the Mental Health Institute Rivierduinen and Parnassia Mental Health Institute approved the study, and both institutes financed the study [3].

Results

Between January 2018 and January 2020, a total of 503 cases of patients with suicidality were examined and assessed by the outreach psychiatric emergency service of The Hague in the Netherlands [42]. Of the 503 cases, 100 were included in this study in the order of entry. RFPdW was medically responsible for the cases. Cases were anonymized, and summarized conclusions were taken from the general practitioners' discharge letters, which were sent after the patients' assessment. Patients gave consent to be included in this study. The letters to the patient's general practitioners are saved in the electronic patient record and were cosigned by RFPdW. The summarized conclusions were copied from the electronic patient record and pasted into a Microsoft Word file. These were distributed among raters. We have elaborated previously on risk management and treatment algorithms (including pharmacological and psychological interventions) across the 4 types (see Table 1), as described before in a book chapter of de Winter et al [3], and revised it.

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The results of our study are expected to be published by the end of 2023. Findings of this study will be published in peer-reviewed journals and presented at regional, national, and international professional conferences and meetings.

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Table 1. Hypothetical risk management and treatment algorithm

	Perceptual disintegration	Primary depressive cognition	Psychosocial turmoil	Inadequate coping or communication
Severity of the suicide risk	++++[a]	++	+++	+
Duration	Days or weeks	Weeks or months	Days	Days or hours; often exacerbation of chronic suicidality
Influence culture	+	++	++++	+++
Religion	+	++	++++	+++
Spiritual affiliation	+	++	++++	+++
Economic conjuncture	+	++	++++	+++
Social disorder (war, pandemic, etc)	+	++	++++	+++
Live events or loss experiences	++	++	++++	+++
Genetic biochemical factors	Yes	Yes	Maybe	Probably
Influence personality	+	++	+++	++++
Major life events	Yes	Yes	Yes	Yes
True mental disorder	Yes	Yes	Maybe	Mostly
Expected course	Reduction after treatment of psychosis	Reduction after biological and psychological treatment	Reduction when tunnel vision decreases, reduces when peak of mourning has passed	Nonspecific reduction within hours or days or when behavior has been exposed or when underlying problems have come to the surface, risk of acute shift from chronic risk and shift to another type
Recurrence	New psychotic episode, triggering of trauma	Recurrent affective disorder	Recurrent episode of psychosocial stress or continuation of severe stress, received narcissistic affront	Interpersonal stress and perceived powerlessness, lack of external recognition of underlying distress
Reassessment of suicide risk	Several times a day, continuous during treatment, after recovery, with the recurrence of a new episode as precaution during trauma therapy	Several times a day, regularly during treatment, after recovery, new episode when the mood deteriorates	Several times a day, ranging from a few times a day to often, in the aftermath of an acute suicidal episode, during a new episode of severe psychosocial stress or new setback	After the suicidal episode, when continued or renewed lack of recognition of underlying distress, during interpersonal stress and perceived powerlessness
Pharmacotherapy	Antipsychotics (clozapine) or mood stabilizer (lithium), possibly additional benzodiazepines in the event of major anxiety	Antidepressant or mood stabilizer (lithium), restrained use of benzodiazepines when increased risk of impulsivity, short-term benzodiazepines for sleep deprivation	Restrained use of medication, possibly symptom relief for sleep deprivation or great anxiety	Hold back medication when possible (changes in or addition to) pharmacological treatment
Actions during crisis	Admission (if needed), intensive home treatment if risk is acceptable	Emergency care, intensive home treatment	Organize mourning, support from family and relatives, brief admission	(F)ACT, crisis plan, maintain autonomy
Relatives	Involving relatives for discussing acute risk, safety, and treatment	Involving relatives for safety and treatment	Involving relatives for direct support and interaction	Involving relatives more for exploring dynamic interactions

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	Perceptual disintegration	Primary depressive cognition	Psychosocial turmoil	Inadequate coping or communication
Follow-up	Outpatient treatment of psychotic symptoms, trauma treatment	Outpatient treatment of depressive symptoms with cognitive behavioral therapy, Collaborative Assessment and Management of Suicidality, Eye movement desensitization and reprocessing	General practitioner	(F)ACT[b], additionally, DBT[c] or Collaborative Assessment and Management of Suicidality or collaborative care; eye movement desensitization and reprocessing; vigilant for change of symptoms
Responsibility of the patient	Increasing when disintegration reduces	Increasing when depressive symptoms reduce	Increasing when "tunnel vision" fades	Retain as much responsibility as possible but be careful by disstress
Responsibility of the caregiver	Decreasing when disintegration reduces	Decreasing when depressive symptoms reduce	Decreasing when "tunnel vision" fades	Holding back of taking over control; offer maximum support; recognize emotional distress

[a]More + symbols indicate greater influence or risk.

[b]ACT: Assertive Community Treatment.

[c]DBT: Dialectical behaviour therapy.

Discussion

Principal Results

The h4ME model, whose usability will be examined in this study, has been designed on the basis of clinical experience with suicidal behavior. Rather than taking the usual route of applying theoretical knowledge to practice, we took the reverse route by proposing a theoretical model based on practical experience [3]. We differentiated appearances of suicidal behavior into types of entrapment—the mental state in the way someone feels trapped in their belief that dying is the only way to escape from distress. In this model, we identified and described 4 different pathways to entrapment. We hypothesize that it depends on the entrapment mode whether the patient is able to take responsibility. We believe that the management of suicidality in accordance with the h4ME model may improve suicide risk assessment; enhance the application of evidence-based treatment strategies; and will be supportive in research of suicide prevention strategies whether it is biological, psychotherapeutic, or social research [2,45-49] or research of effective implementation of suicide prevention tools in clinical practice.

For professionals, the practical management of acute suicide risks is a priority rather than appraising theoretical or scientific concepts about the etiology of suicidal behavior. They may benefit from a theory-based but accessible framework similar to the h4ME model, which is eclectic and based on a fusion of well-known and generally accepted theoretical concepts of suicidality. The main inspiration for the model includes concepts of "dimensions of psychopathology" and the "temperament and character inventory." This model incorporates 2 subtypes of the psychopathology dimension: PD and affective dysregulation (PDC) [50]. The remaining subtypes PT and IC are derived from the "Temperament and Character Inventory" [51], stating that there may be a relationship between personality dimensions, including 2 out of 3 dimensions of character (self-directedness and cooperativeness) and 3 out of 4 dimensions of temperament (harm-avoidance, novelty seeking, reward dependence). Differentiation may provide better insight into etiological relationships between underlying psychological or biological dysregulation processes. We estimate that in the future, the model can be used to determine which available evidence-based treatment strategies are most promising for the various subtypes. For instance, we suggest that the patients with suicidality of subtypes PD and PDC may recover with the treatment of the underlying mental disorders, whereas patients with subtype PT or IC may take advantage of treatment focusing on strengthening coping skills.

We assume that practitioners using the model will find it less complicated to consider suicidality and to put the risks of suicidality in context, and patients with suicidality may feel more comfortable when practitioners better understand patients' motives to contemplate suicide. Additionally, the model can be used to determine the best fitting of a suitable treatment strategy. Finally, application of the model for scientific research may lead to the discovery of novel and more effective treatment strategies and ultimately to more effective suicide prevention. We do not rule out that the 4 proposed types, especially in the context of effective treatment, might be more defined and specified. Additionally, we do not rule out that more subtypes can be identified in clinical and nonclinical populations.

Limitations

The development of the h4ME model is a venture into unknown territory. Little is known of the nature and origin of suicidality, so the model does not provide explanations or answers to the many questions about the onset of suicidality. A limitation of this study is that cases who will be included were willing to seek help. We are convinced that this population does not represent all kinds of people with suicidality, especially those who refuse help or hide suicidal ideation. This may affect the outcomes. In addition, we identified 4 subtypes, automatically excluding possible other types. For instance, people experiencing declining somatic health, loneliness, and existential questions around the end of life are not represented in the model and consequently cannot be rated. This may also affect the outcomes, as raters are forced to indicate a limited spectrum of suicidality,

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and this may increase the chance that a high level of TA will be achieved. The anonymized cases and summarized conclusions taken from general practitioners' discharge letters used for this study may be biased because they contain subjective information, written by a clinically experienced nurse and a junior doctor. There may be distortion of the real suicidal symptoms due to a variety of factors such as countertransference, a diversity of professional backgrounds, or the lack of clinical experience.

Suggestions for Further Research

The majority of suicide cases occur outside the reach of mental health care services. Research among these groups is likely difficult because of privacy and ethical issues. Psychological autopsy studies of cases of suicide who are not accessed by mental health care may be useful for further development or fine-tuning of the model. It may reveal a different distribution of types, additional types, and specific information about entrapment pathways, for instance, whether certain types are preceded by other types in the model or whether certain types are the superlative of another type. In future studies also, Likert-scale items reflecting psychopathological symptoms, behaviors, thoughts, emotions, duration, temperament, and character may be used for the eventual differentiation of subtypes. It is important to include other mental health care workers—other than psychiatrists and nurses—in future validity research. It would also be useful to include multidisciplinary teams (including psychiatrists, nurses, nurse practitioners, psychologists, general practitioners, and social workers) as clusters of raters; these teams all may contribute to adjustment and usability of the model and the feasibility of the SUICIDI-II instrument. The usability strategy may be adjusted in future studies. Finally, correlations between subtypes and demographic, context, and (mental) health variables might be investigated.

Conclusions

One of the most poignant results of this model is that the differentiation of professional responsibilities has emerged. Improved clarity about those professional and personal responsibilities allows a more evidence-based discussion, for instance, about working as team, about sharing responsibilities, or supporting others when needed. Ultimately, this is what makes the model truly stand out and gives it added value. The model and the research proposal are in its infancy. So far, the model has been considered useful by clinicians who have rated it or worked with it. It is found to be practical and easy to apply. We welcome feedback, critical considerations, discussions, and suggestions from clinicians, scientists, researchers, and policy makers.

Acknowledgments

We would like to thank the health care workers of the psychiatric outreach emergency service of The Hague and Melissa Hoek-Hus for help in the preparation of the manuscript.

Data Availability

The data sets generated during this study are publicly available as an SPSS file [52]; all parameters (for some that are traceable to an individual) have been coded. The keys for the coded parameters are available from the corresponding author on reasonable request.

Authors' Contributions

All authors made substantial contributions in drafting and critically revising the manuscript. RFPdW, MHdG, DPdB, and MCH contributed to conceptualizing and designing the study and to data acquisition, analysis, and interpretation. DS contributed as an experience expert and peer supporter and to conceptualizing the study. GEvS assisted in outcome interpretation. CMM, ATvdB, JHE, NKG, MvG, and MG contributed as evaluators and raters in the study. All authors approved the final draft and agreed to be accountable for all aspects of the work.

Conflicts of Interest

None declared.

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Abbreviations

aTA: absolute type agreement
h4ME: (hypothetic) 4-type model of entrapment of suicidality
IC: inadequate coping or communication
ICC: intraclass correlation coefficient
PD: perceptual disintegration
PDC: primary depressive cognition
PT: psychosocial turmoil
SUICIDI-II: Suicidality Differentiation version 2
TA: type agreement

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Protocol

Supervised Home-Based Exercise Prehabilitation in Unfit Patients Scheduled for Pancreatic Surgery: Protocol for a Multicenter Feasibility Study

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Abstract

Background: Morbidity rates in pancreatic surgery are high, and frail patients with low aerobic capacity are especially at risk of complications and require prophylactic interventions. Previous studies of small patient cohorts receiving intra-abdominal surgery have shown that an exercise prehabilitation program increases aerobic capacity, leading to better treatment outcomes.

Objective: In this study, we aim to assess the feasibility of a home-based exercise prehabilitation program in unfit patients scheduled for pancreatic surgery on a larger scale.

Methods: In this multicenter study, adult patients scheduled for elective pancreatic surgery with a preoperative oxygen uptake (VO_2) at the ventilatory anaerobic threshold ≤13 mL/kg/min or a VO_2 at peak exercise ≤18 mL/kg/min will be recruited. A total of 30 patients will be included in the 4-week, home-based, partly supervised exercise prehabilitation program. The program comprises 25-minute high-intensity interval training on an advanced cycle ergometer 3 times a week. Training intensity will be based on steep ramp test performance (ie, a short-term maximal exercise test on a cycle ergometer), aiming to improve aerobic capacity. Twice a week, patients will perform functional task exercises to improve muscle function and functional mobility. A steep ramp test will be repeated weekly, and training intensity will be adjusted accordingly. Next to assessing the feasibility (participation rate, reasons for nonparticipation, adherence, dropout rate, reasons for dropout, adverse events, and patient and therapist appreciation) of this program, individual patients' responses to prehabilitation on aerobic capacity, functional mobility, body composition, quality of life, and immune system factors will be evaluated.

Results: Recruitment for this study began in January 2022 and is expected to be completed in the summer of 2023.

Conclusions: Results of this study will provide important clinical and scientific knowledge on the feasibility of a partly supervised home-based exercise prehabilitation program in a vulnerable patient population. This might ease the path to implementing prehabilitation programs in unfit patients undergoing complex abdominal surgery, such as pancreatic surgery.

Trial Registration: ClinicalTrials.gov NCT05496777; https://classic.clinicaltrials.gov/ct2/show/NCT05496777

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KEYWORDS

preoperative care; prehabilitation; preoperative training; high-intensity interval training; pancreatic resection; cardiorespiratory fitness

Introduction

The incidence of pancreatic malignancies is predicted to rise as the aging population grows [1]. The only curative treatment option remains pancreatic surgery, which is highly complex and known for its high postoperative morbidity [2]. Within this already vulnerable patient group, there are unfit patients with low aerobic fitness, translating into a limited reserve to withstand stress during surgery [3,4]. As a consequence, these patients are more prone to postoperative morbidity after pancreatic surgery [5,6]. To effectively identify unfit patients who are in need of preoperative intervention to reduce their perioperative risks, specific preoperative risk assessment is required. In the search for valid preoperative risk assessment diagnostics, preoperative aerobic fitness has been found to have a persistent relationship with postoperative outcomes in major elective intra-abdominal surgeries [5,7,8]. A cardiopulmonary exercise test (CPET), which determines 2 meaningful risk indicators, that is, the oxygen uptake (VO_2) at the ventilatory anaerobic threshold (VAT) and VO_2 at peak exercise (VO_{2peak}), can be used to acquire an objective representation of a patient's aerobic capacity [9].

Physical exercise training before surgery has been reported to effectively increase the aerobic capacity of patients scheduled for major abdominal surgery [10-17]. In the trial of Barberan-Garcia et al [18], high-risk patients scheduled for major abdominal surgery were subjected to a multimodal prehabilitation program consisting of (1) motivational interviewing, (2) a personalized program to promote daily physical activity, and (3) a supervised high-intensity endurance exercise training program. The mean duration of their program was 6 weeks, and it not only improved preoperative aerobic capacity, but also resulted in a 51% reduction in postoperative complications [18]. Regarding prehabilitation programs in pancreatic surgery, Ausania et al [14] subjected patients with a pancreatic or peripancreatic malignancy, regardless of their physical fitness, to a multimodal prehabilitation program consisting of 5 daily sessions of supervised high-intensity endurance training in the outpatient clinic. Furthermore, patients were trained to perform unsupervised home-based functional and breathing exercises, and nutritional support, as well as pancreatic exocrine insufficiency, was addressed [14]. Although the authors reported an improvement in physical fitness as determined by the 10-meter walk test, no differences in postoperative outcomes were observed [14]. However, since high-risk patients are hypothesized to benefit the most from exercise prehabilitation, adequate patient selection seems essential and greatly influences the effect of an exercise prehabilitation program on improving a patient's aerobic capacity [11,12]. Another important factor influencing the feasibility and effect of a prehabilitation exercise program is the setting in which it takes place. Most reported prehabilitation programs have been carried out in an outpatient clinic. However, as pointed out by Ferreira et al [19], patients prefer a home-based prehabilitation program for reasons such as traveling issues or because a hospital- or community-based exercise program is regarded as too time-consuming. These perceived barriers will negatively influence a patient's adherence to a physical exercise training program, likely resulting in a suboptimal training effect [19]. On the other hand, a possible disadvantage of unsupervised home-based exercise training could be a lack of adherence of the patient, lack of appropriate exercise intensity, and therefore lack of benefit [4]. It is therefore important to provide adequate supervision, preferably by an experienced physical therapist.

In exercise prehabilitation programs within a limited preoperative time window of 4 to 6 weeks, the most efficient training modality to increase aerobic capacity seems to be high-intensity interval training (HIIT) [17,20]. In a study by van Wijk et al [17], high-risk patients scheduled for liver or pancreatic surgery participated in a partly supervised home-based bimodal prehabilitation program consisting of HIIT and high-intensity endurance training combined with nutritional support. Their 4-week prehabilitation program was shown to be feasible and improved aerobic capacity by 17% as determined by performing a CPET pre- and postintervention.

Although several studies investigated the effect of exercise prehabilitation in major abdominal surgery, there is a large heterogeneity in patient selection and prehabilitation program setting, which notably influences its effectiveness and adequate interpretation of results. Therefore, the primary aim of this study is to determine the feasibility of a 4-week, home-based, partly supervised exercise prehabilitation program in unfit patients scheduled for pancreatic surgery. Secondary aims of the study are to evaluate the individual responses to the program on aerobic capacity, functional mobility, muscle strength, body composition, level of perceived fatigue, quality of life, and immune system factors.

Methods

Study Design

The described study is a multicenter feasibility study, and the study will have a pretest-posttest design. The latest version of the study protocol (version 7; May 2022) is presented in this manuscript. Protocol amendments will have to be approved by the Medical Research Ethics Committee of the Maastricht University Medical Center+ and Maastricht University (METC azM/UM).

Eligibility Criteria

In order to be eligible to participate in this study, patients must meet all of the following criteria: (1) age 18 years or older, (2) planned for elective pancreatic surgery at Maastricht University Medical Center+ or at the University Medical Center Groningen, and (3) providing informed consent to participate. Patients are considered eligible (4) if they have a VO_2 at the VAT ≤13 mL/kg/min or a VO_{2peak} ≤18 mL/kg/min. A patient who meets

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any of the following criteria will be excluded from participation in this study: (1) they require acute surgery, (2) they undergo surgery in another hospital, (3) they are not able to cycle on a cycle ergometer, (4) contraindications are identified for them to physical exercise training (eg, heart rhythm disturbances, ischemia of the heart muscle), (5) they are unable to cooperate during the testing procedures (eg, insufficient understanding of the Dutch language), and (6) no certified physical therapist is available in their living area.

Recruitment

All patients eligible for pancreatic surgery will be identified at the multidisciplinary team meetings and evaluated by the surgeon at the outpatient clinic. During the outpatient clinic visit, patients will be given full details of the study, and after a few days, patients from the Maastricht University Medical Center+ will be contacted by telephone by a designated investigator to provide extensive information about the study. If patients are interested in participating in the study, a CPET will be performed to check whether the patient fulfills the inclusion criteria, after which an appointment will be planned to perform baseline assessments and to retrieve written informed consent. At the University Medical Center Groningen, all patients scheduled for pancreatic surgery perform a CPET as part of usual care. Based on the CPET results, patients will be asked to participate in this study and an appointment will be planned to perform the remaining baseline assessments and receive written informed consent.

Interventions

Preoperative Home-Based Physical Exercise Training Program

Participating patients will engage in a home-based, partly supervised exercise prehabilitation program before elective pancreatic surgery. The physical exercise training program will consist of HIIT on an advanced cycle ergometer that is placed at the patient's home (Lode Corival Home+, Lode BV; see Figure 1), with the goal to improve the patient's preoperative aerobic fitness. A certified community physical therapist in the living area of the patient will be asked to partly supervise the physical exercise training program. The community physical therapist will receive verbal and written instructions on the use of the cycle ergometer and the goals and content of the program. The duration of the exercise program is 4 weeks, and the training frequency will be 3 sessions per week. The supervising community physical therapist will visit the patient 3 times during the first week, and once in the weeks thereafter to monitor training progression and provide additional instructions if needed. Patients are encouraged to find a training buddy (eg, their partner or a close relative) to help and to motivate them for the unsupervised training sessions. Patients may choose the day and time point of their unsupervised training themselves, with the recommendation to leave at least one day between training sessions for recovery. This approach was chosen in order to promote adherence to the program. Each first training session of the week will be preceded by a modified steep ramp test (SRT) [21] executed under the supervision of the community physical therapist. The SRT, a short-time maximal exercise test on a cycle ergometer, has been proven to be a valid tool to estimate aerobic capacity and allows for individual optimization and progress monitoring of the HIIT program [21-23]. The training program on the cycle ergometer will be personalized weekly to each participant based on their performance during the SRT. Based on SRT performance, the consecutive training sessions comprise HIIT, consisting of a 3-minute warm-up at 20 watts, 14 high-intensity intervals of 30 seconds at 60% of the peak work rate (WR) achieved at the SRT interspersed with 14 low-intensity intervals of 60 seconds at 20 watts and a cooldown of at least 1 minute, thereby taking at least 25 minutes to execute (Table 1). Directly after each completed HIIT session of 20 minutes, the patient is asked by the program installed on the cycle ergometer to fill out the 6-20 Borg scale for rating of perceived exertion. Data about the duration, intensity (WR), heart rate, pedaling frequency, and rating of perceived exertion of each SRT and HIIT session at the cycle ergometer will be automatically recorded by the cycle ergometer at the end of each SRT and HIIT session and uploaded to a web-based platform (Figure 2). As such, community physical therapists and local investigators are able to remotely supervise and monitor training progression and adherence. Once a week, during the supervised SRT and HIIT session, the physical therapist will discuss these findings with the patient. In case of unexpected problems, the community physical therapist can consult the local investigator of the study.

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Figure 1. The Lode Corival Home+ cycle ergometer used in this study.



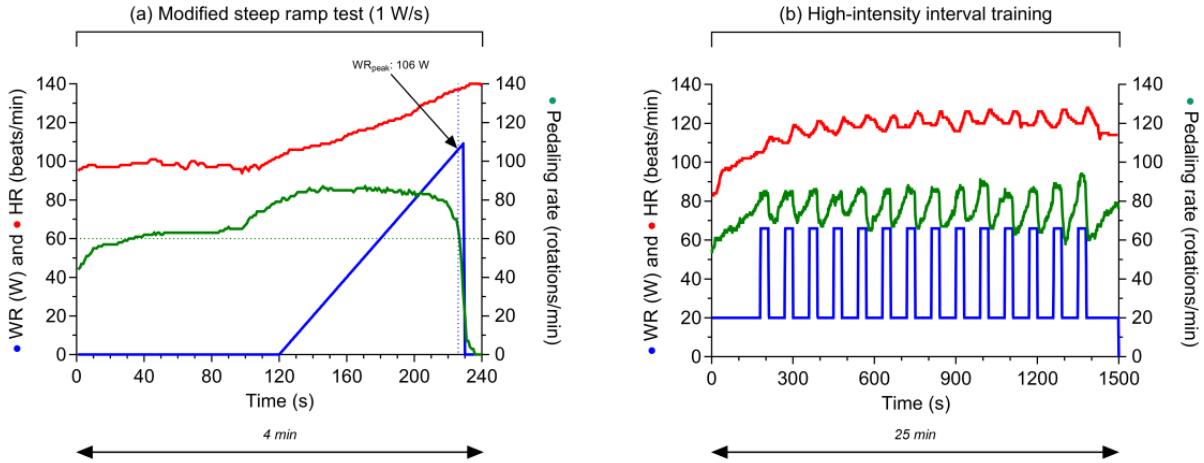
Table 1. High-intensity interval training structure.

Exercise phase	Exercise intensity	Pedaling frequency (rotations/min)
Warm-up (3 min)	20 W	40-80
Interval training (21 min)		
Work interval intensity (14 repetitions)	30 sec at 60% of WR_{peak}[a] of the steep ramp test	60-100
Rest interval intensity (14 repetitions)	60 sec at 20 W	40-60
Cooldown (1 min[b])	20 W	40-80

[a]WR_{peak}: work rate at peak exercise.

[b]Duration of cooldown can be extended when preferred.

Figure 2. (a) Example of modified steep ramp test performance. (b) Results of a consecutive high-intensity interval training session at 60% of steep ramp test WR_{peak}. HR: heart rate; WR: work rate; WR_{peak}: work rate at peak exercise.



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Functional Task Exercises

Next to HIIT on the cycle ergometer, patients will be instructed to carry out functional task exercises 2 times a week on training days at which the HIIT session is not preceded by an SRT, thereby practicing activities relevant to the patient (eg, elastic band exercises, stair-climbing, brisk walking) [24]. An overview of the structure of the overall training program can be found in Table 2. The patient will be instructed to perform at least 3 repetitions of about 30 seconds of different functional task exercises with 30 seconds of rest in between. The functional task exercises will be chosen individually, consisting of activities relevant to the patient, and the intensity and complexity of exercises will be individually reviewed weekly by the physical therapist. Patients will be instructed to perform as many repetitions as intensely as possible, but at least three per functional task exercises. Next to an increasing exercise intensity or frequency, functional task exercises can also progress in difficulty in terms of making exercises more complex and by adding variation.

Table 2. Overall training program structure (weeks 1-4).

Training session 1 (Monday or Tuesday)		Training session 2 (Wednesday or Thursday)		Training session 3 (Friday or Saturday)	
Workout	Duration	Workout	Duration	Workout	Duration
SRT[a]	4-7 minutes	HIIT[b]	25 minutes	HIIT	25 minutes
HIIT	25 minutes	Functional task exercises	15 minutes	Functional task exercises	15 minutes

[a]SRT: steep ramp test.

[b]HIIT: high-intensity interval training.

Usual Care

As part of usual care, all patients are screened at baseline for risk factors associated with postoperative complications and are treated accordingly. This includes screening for nutritional deficits, mental resilience, anemia, iron deficiency, hyperglycemia, and substance abuse (eg, smoking, alcohol consumption). In both participating centers, patients are screened by a trained dietitian as part of usual care. Patients at risk of malnutrition will receive additional nutritional support. When patients are in need of additional support in any of the other areas, such as psychological support or intervention for smoking cessation, this will also be implemented as a standard of care in both centers.

Measurements

Before, during, and after the preoperative home-based physical exercise training program, several outcome measurements will be obtained (Table 3).

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Table 3. Schedule of enrollment, intervention, and assessments.

	Preintervention	Home-based exercise prehabilitation				Postintervention	Follow-up (30 days postoperatively)
		Week 1	Week 2	Week 3	Week 4		
Enrollment							
Eligibility screening	✓						
Informed consent	✓						
Intervention							
Home-based exercise prehabilitation		✓	✓	✓	✓		
Assessments							
Baseline characteristics	✓						
Feasibility	✓	✓	✓	✓	✓	✓	
Aerobic capacity							
CPET[a]	✓					✓	
SRT[b]		✓	✓	✓	✓		
Muscle strength							
Handgrip strength	✓					✓	
Body composition							
Anthropometry	✓	✓	✓	✓	✓	✓	
L3[c] index	✓					✓	
Functional mobility							
30-second chair-stand test	✓	✓	✓	✓	✓	✓	
2-minute walk test	✓					✓	
Immunological phenotyping	✓					✓	
Questionnaires							
MFI[d]	✓					✓	
EORTC QLQ-C30[e]	✓					✓	
SARC-F[f]	✓					✓	
Program appreciation[g]						✓	
Postoperative outcomes							
Surgical complications							✓
Length of hospital stay							✓
30-day readmission							✓

[a]CPET: cardiopulmonary exercise test.

[b]SRT: steep ramp test.

[c]L3: third lumbar vertebra.

[d]MFI: Multidimensional Fatigue Index.

[e]EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality-of-life Questionnaire Core 30.

[f]SARC-F: strength, assistance with walking, rising from a chair, climbing stairs, and falls.

[g]Patient and community physical therapist appreciation.

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Program Feasibility

Feasibility will be determined by (1) monitoring the participation rate of this study as well as reasons for nonparticipation. Reasons for nonparticipation will be asked for during a short interview with the coordinating investigator or treating surgeon. Furthermore, feasibility will be determined by (2) evaluating adherence and fidelity of patients to the physical exercise training program as objectively recorded by the cycle ergometer, which provides insight into training session content (eg, frequency, intensity, duration, premature termination of a training session), (3) dropout rate and reasons for dropout, (4) number and severity of adverse events, and (5) patient and therapist appreciation after completing the program by filling out a short questionnaire based on a previous study [25]. If a patient drops out before the end of the training program, the reasons will be investigated through a short interview with the coordinating investigator.

Aerobic Capacity CPET

For all patients, a preintervention CPET will be performed by a clinical exercise physiologist (Maastricht University Medical Center) or sports physician (University Medical Center Groningen) to assess baseline aerobic capacity, which will be used to make a selection of eligible unfit patients and thereupon invite them to participate in the study (VO_2 at the VAT ≤13 mL/kg/min or VO_{2peak} ≤18 mL/kg/min). After completion of the program, a postintervention CPET will be performed. The outcome thereof will be used to assess the effectiveness of the home-based physical exercise training program to improve aerobic capacity.

The CPET will be executed under controlled conditions using a calibrated electronically braked cycle ergometer in an upright position; the Lode Corival CPET (Lode BV) will be used at Maastricht University Medical Center and the Lode Excalibur Sport (Lode BV) will be used at the University Medical Center Groningen. Patients will be fitted with a 12-lead electrocardiogram to rule out strain-related cardiac ischemia, arrhythmias, and other contraindications for intense physical exercise training during the consecutive exercise program. During the test, patients will breathe through a face mask connected to a metabolic cart; the Vyntus CPX (Vyaire Medical) will be used at the Maastricht University Medical Center and the Quark CPET (Cosmed) will be used at the University Medical Center Groningen for measurements of breath-by-breath VO_2, minute ventilation, and carbon dioxide production throughout the CPET. Finally, heart rate and blood pressure will be monitored, and peripheral oxygen saturation will be measured at the index finger. After 2 minutes of rest measurements, the patient is asked to start cycling. The first 2 minutes consist of unloaded cycling. Thereafter, the WR will be linearly incremented with a 5, 10, 15, or 20 W/min ramp protocol (depending on the patient's self-reported physical fitness) to ensure a test duration between 8 and 12 minutes. Patients will be instructed to maintain a pedaling frequency of around 80 revolutions/min. The test effort will be considered maximal when the patient shows objective signs (ie, heart rate at peak exercise >95% of predicted or a respiratory exchange ratio at peak exercise >1.10) or subjective signs (eg, unsteady biking, sweating, clear unwillingness to continue exercising despite strong encouragement) of maximal effort. CPET interpretation will be performed according to international guidelines by an experienced sports physician or medical physiologist [26]. The last 30 seconds before termination of the test will be used to calculate absolute values at peak exercise. Peak heart rate is the highest heart rate achieved throughout the test. The VAT is described as the point at which the partial end-tidal oxygen tension and the ventilatory equivalent for oxygen reached a minimum and thereafter began to rise in a consistent manner, corresponding with an unchanged ventilatory equivalent for partial end-tidal carbon dioxide tension and carbon dioxide [26]. If this method provides unreliable results, the V-slope method will be applied instead [27].

Aerobic Capacity—Modified SRT

During the physical exercise training program at the patient's home, the physical therapist will assess and monitor aerobic fitness by performing a modified SRT [21] on a weekly basis on the advanced cycle ergometer (Lode Corival Home+; Lode BV) in an upright position. Training intensity will be adjusted based on SRT performance, which is expected to maintain a sufficient training stimulus. A heart rate belt will be fitted around the patient's chest (Xand Cycling) during the test. The SRT starts with 2 minutes of unloaded cycling. Next, the WR will be increased in a ramp-like manner by a constant increment of 10 W/10 s (1 W/s). The total test duration is estimated to be 4 to 7 minutes. The patient is instructed to keep the pedaling frequency constant between 60 and 80 revolutions/minute. The main outcome of the SRT is the work rate at peak exercise (WR_{peak}), defined as the point at which there is a sustained drop in pedaling frequency from 60 revolutions/min despite strong verbal encouragement. After attaining their WR_{peak}, patients will be asked their level of perceived exertion by filling out the 6-20 Borg scale for rating of perceived exertion. They will conclude the SRT with a 2-minute cooldown phase consisting of unloaded cycling at a pedaling frequency of about 40 revolutions/min.

Muscle Strength

To assess the effect of the exercise prehabilitation program on muscle strength, handgrip strength (in kilograms) will be measured at baseline and postintervention using the Jamar dynamometer (Sammons Preston; Rolyon) [28]. Muscle strength, as measured by handgrip dynamometry, is considered to be an indicator of frailty and an independent predictor of complications after surgery [29,30]. Patients will be asked to sit in an upright position with the elbows stretched in a straight line downwards. Patients will be asked to squeeze the handle as forcefully as possible for about 2 seconds, starting with the dominant hand. A total of 3 grip measurements per hand will be performed, with a 15- to 20-second pause between each measurement.

Body Composition

The patient's body height (determined to the nearest 0.5 cm) and body mass (determined to the nearest 0.1 kg) will be measured with a metric measuring tape with a wall stop and an electronic scale (Seca 803; Seca), respectively, at baseline and

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postintervention. During the prehabilitation program, the community physical therapist will measure the patient's body mass weekly.

Myosteatosis (ie, skeletal muscle fat infiltration) is a biomarker for cancer cachexia (ie, a multifactorial wasting syndrome leading to loss of skeletal muscle mass with or without loss of fat mass, subsequently inducing progressive functional impairment) and sarcopenia (ie, loss of skeletal muscle tissue). Myosteatosis alone, as well as cancer cachexia and sarcopenia, are associated with increased morbidity and mortality [31,32]. Meanwhile, it has been suggested that physical exercise training improves muscle quality [33]. Therefore, we will evaluate skeletal muscle quantity and quality at baseline and after prehabilitation by analyzing a single slice of a computerized tomography (CT) scan at the midlevel of the third lumbar vertebra (L3), which is where both transverse processes are visible. Body composition analysis will be performed using an automated segmentation system (Mosamatic) developed and validated at Maastricht University [34,35]. Visceral adipose tissue, subcutaneous adipose tissue, and skeletal muscle tissue will be normalized for the patient's body height to calculate the L3 index in cm^2/m^2. Radiation attenuation will be determined by calculating the average Hounsfield unit value of the areas. Low skeletal muscle radiation attenuation is associated with increased myosteatosis [36]. For this study, the CT scans that are part of the standardized diagnostic work-up of patients will be analyzed. Since CT imaging prior to oncologic surgery should not be older than 6 weeks, preoperative CT scans are performed on a regular basis in patients.

Functional Mobility

Functional mobility will be assessed using the 2-minute walk test and 30-second chair-stand test at baseline and postintervention at the hospital, as well as weekly at the patient's home. The 30-second chair-stand test evaluates a combination of lower leg muscle strength, balance, and functional mobility by testing the number of repetitions standing up from a sitting position within 30 seconds [37]. The 2-minute walk test is a feasible method to record the distance (in meters) that is walked over a standardized trail in 2 minutes [38].

Immunological Phenotyping

As the immune system is highly responsive to physical exercise, it has been suggested that structural physical exercise training can improve overall health and may prolong survival in patients with cancer [39]. To exploratively quantify the effect of the preoperative physical exercise training program on the immune system response, blood samples will be taken at baseline and postintervention and analyzed for levels of C-reactive protein, tumor necrosis factor-α, as well as interleukin-6, interleukin-8, and interleukin-10 by multiplex analysis. Moreover, a separate blood sample for each patient will be drawn for storage at –80 °C for future analysis. Blood samples will be stored in the biobank of the participating hospital, for a maximum of 10 years. Future analysis has to be in line with the aims of our ongoing research; if not, informed consent must be retrieved.

Questionnaires

Prior to the start of the physical exercise training program, patients are asked to fill out a perceived fatigue, quality of life, and sarcopenia questionnaire. The level of perceived fatigue is assessed using the Multidimensional Fatigue Index [40], quality of life will be evaluated with the European Organization for Research and Treatment of Cancer Quality-of-life Questionnaire Core 30 (EORTC QLQ-C30) [41], and finally, the strength, assistance with walking, rising from a chair, climbing stairs, and falls (SARC-F) questionnaire [42] is used to screen for sarcopenia in patients. To check for potential improvements in perceived fatigue, quality of life, and sarcopenia, these questionnaires will be repeated after completion of the exercise prehabilitation program.

Study Outcomes

Primary Outcome

The primary outcome of this study is to assess the feasibility of a 4-week, home-based, partly supervised exercise prehabilitation program in unfit patients planned for elective pancreatic surgery. Feasibility is assessed via the participation rate, and by recording reasons for nonparticipation, adherence or compliance and fidelity to the program, dropout rate and reasons for dropout, adverse events during the program, and patient and therapist appreciation.

Secondary Outcomes

Secondary outcomes are to evaluate the patients' responses to exercise prehabilitation on aerobic capacity, functional mobility, muscle strength, body composition, perceived fatigue, quality of life, immune system factors, number of overall postoperative complications within 30 days after surgery, and readmissions within 30 days after discharge. Complications will be graded using the Clavien-Dindo classification and divided into surgical and nonsurgical complications [43,44]. The comprehensive complication index, a continuous scale that also takes into account the number of complications per patient, will be used to summarize complications for each patient [45].

Other Study Outcomes

Data on patient characteristics (eg, age, sex, nutritional status, Charlson Comorbidity Index, American Society of Anesthesiologists score, smoking, location, and type of the tumor) neoadjuvant therapy, and surgical procedure will also be collected for explorative purposes.

Safety

During the preoperative physical exercise training program and 30 days after completion of the program, all adverse events observed by the investigator or his staff or reported spontaneously by the participating patients will be recorded.

Data Analysis

Sample Size Calculation

This study will specifically evaluate the feasibility of a home-based, partly supervised prehabilitation program in unfit patients undergoing elective pancreatic surgery. Thus, the study has a clear explorative character and will analyze individual

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responses to the program. Based on the number of patients undergoing elective pancreatic surgery annually and the relatively short study period (<1 year), 15 patients who are willing to participate in the study will be included per hospital, resulting in a total of 30 patients. Results of this exploratory study will provide information on how to proceed in subsequent effect studies. Furthermore, results can be used to optimize the home-based prehabilitation program in the future.

Procedures for Data Checking and Entering

All data will be handled confidentially according to the General Data Protection Regulation (GDPR). Signed informed consent forms and other traceable data will be stored on a local server secured with a password. Coded data will be collected in an electronic case report form created in Castor (Castor), a program aimed at clinical trial data recording and monitoring. Only the principal and coordinating investigator of each center will have access to uncoded data. Variables will be checked for the number of missing, improbable, or impossible values prior to statistical analysis. In case of impossible or improbable values, the patient's data file will be reviewed.

Statistical Analysis

The R software package (R Foundation for Statistical Computing) will be used for statistical analysis. Collected data on patient characteristics will be presented in tables. Continuous variables will be displayed as mean (SD), while categorical variables will be presented as number (n) and percentage (%). Descriptive statistics will be used to answer the primary study parameter of feasibility. As previously described, feasibility will be presented in tables and based on participation rate (n, %), reasons for nonparticipation (n, %, text), adherence to the program (%), dropout rates (%), reasons for dropout (n, %, text), adverse events (n, %, text), patient motivation (scale 0-10), and appreciation (text). The secondary aim is to evaluate the patients' responses over time in terms of aerobic capacity, muscle function, functional mobility, body composition, perceived fatigue, quality of life, and immune system function. Individual response profiles will be graphically depicted and presented in tables. A repeated measurements analysis will be used to analyze changes over time in continuous variables. *P* values <.05 will be considered statistically significant.

Dissemination Policy

Research results will be disclosed and submitted to a peer-reviewed scientific journal, in case of positive as well as negative results. The investigators will prepare the manuscript together. Coauthorship is preserved for all participating investigators and those who at the discretion of the principal investigator constructively contributed to the study. Disputes on the interpretation of results will not lead to an unnecessary delay in publication.

Ethics Approval

This study was approved by the ethical committee METC azM/UM in the Netherlands (METC20-090, NL75340.068.20, September 2021) and is registered in the ClinicalTrials.gov register (NCT05496777). Informed consent will be obtained from all participating subjects. All methods are carried out according to relevant guidelines and regulations.

Results

Recruitment started in January 2022 and will run until patient inclusion is complete (expected in the summer of 2023) at the Maastricht University Medical Center+ (Netherlands) and the University Medical Center Groningen (Netherlands). After data analysis, results on all relevant study outcomes will be published.

Discussion

Results of this study will provide important clinical knowledge on implementing a supervised (partly direct supervision, partly remote supervision) home-based exercise prehabilitation program for unfit patients scheduled for pancreatic surgery. Any potential barriers that hamper the effective execution of a physical exercise training program will be identified by thoroughly analyzing feasibility outcomes. The resulting scientific knowledge will fill in gaps in this literature and will provide the ability to improve preoperative optimization of unfit patients. Proof of feasibility might ease the path to implementing exercise prehabilitation programs in patients undergoing complex abdominal surgery, such as pancreatic surgery. Ultimately, this may lead to better treatment outcomes in vulnerable patient populations. Apart from future patients being scheduled for pancreatic surgery, we expect participating patients to benefit directly from the physical exercise training program due to an expected increase in preoperative aerobic capacity and subsequently have better treatment outcomes.

Several studies indicated that a VO_2 at the VAT <11 mL/kg/min or a VO_{2peak} <18 mL/kg/min, as determined during a CPET, are accurate cut-off points to identify patients that have a higher risk for postoperative morbidity and mortality [5,8]. Nevertheless, preoperative physical exercise training might also be beneficial for patients with mediocre aerobic capacity undergoing pancreatic surgery [46]. In the Netherlands, the mean waiting time for surgery is 4 to 6 weeks, meaning there is sufficient time for patients to participate in physical exercise training programs. Therefore, we have chosen to include all patients with a VO_2 at the VAT ≤13 mL/kg/min or a VO_{2peak} ≤18 mL/kg/min in their waiting period. Previous studies have clearly demonstrated the beneficial effect of exercise prehabilitation on aerobic capacity in patients scheduled for intra-abdominal surgery [13-16,18]. In high-risk patients scheduled for major abdominal surgery, Barberan-Garcia et al [18] demonstrated a 35% increase in aerobic endurance time and a 51% reduction of postoperative complications after a 6-week course of preoperative high-intensity endurance training. More recently, Berkel et al [16] demonstrated a 10% increase in aerobic capacity (VO_2 at the VAT and VO_{2peak}) and an almost 50% decrease in the incidence of postoperative complications in high-risk patients scheduled for colorectal surgery undergoing a 3-week community-based and personalized preoperative HIIT program. Despite evidence suggesting that exercise prehabilitation is effective, there is a large heterogeneity in design and setting among reported prehabilitation programs. Although most of the reported prehabilitation programs were carried out under supervision in an outpatient clinic, patients

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clearly prefer a home-based prehabilitation program [19]. Nevertheless, home-based prehabilitation programs should be supervised, since a possible disadvantage of unsupervised home-based exercise training could be a lack of adherence of the patient or lack of appropriate exercise intensity and therefore lack of benefit [4]. A supervised and personalized exercise program in a home-based setting might enhance the participation rate, adherence, and motivation of (high-risk) patients, and has been shown to be the preferred method for a prehabilitation program [4,17,47]. This was illustrated by van Wijk et al [17], who recently reported an 83% adherence rate in their partly supervised home-based training program, which led to an increase of respectively 17.8% and 17.2% in VO_2 at the VAT and VO_{2peak} in unfit (VO_2 at the VAT <11 mL/kg/min) patients undergoing liver or pancreatic resection.

Strengths of this study are its clear study design consisting of a supervised home-based prehabilitation program, the ability to thoroughly assess feasibility in a vulnerable patient population, the use of validated measurement instruments, and the personalized training program based on an individual patient's performance at the weekly executed SRT. This study aims to set the standard for home-based exercise prehabilitation programs in pancreatic surgery. Nevertheless, this study will have some limitations. First of all, the physical exercise training program is only partly supervised by a physical therapist. This may lead to a lower patient adherence to the exercise program and subsequently suboptimal training results. However, the advanced cycle ergometer used in this study automatically captures data on training frequency, intensity, and duration. This enables the physical therapist to monitor training progression and compliance in real-time and gives the opportunity to intervene if necessary. Furthermore, as mentioned before, van Wijk et al [17] have reported an acceptable 83% adherence in their partly supervised exercise program. In addition, given that the primary outcome of interest is the feasibility of the training program, noncompletion of training adds valuable information to the data set. Another limitation might be that our study focuses on exercise prehabilitation while most unfit patients might benefit from a multimodal approach, including screening and subsequent treatment of common risk factors associated with postoperative complications. This screening is part of the usual care in both centers. If necessary, nutritional support, treatment of modifiable risk factors (eg, dyslipidemia, smoking, alcohol consumption), and mental support will be implemented within the patient's individual prehabilitation program.

While hospital- and community-based exercise prehabilitation programs encounter significant feasibility issues when enrolling vulnerable unfit patients, this study will offer unfit patients a unique personalized exercise prehabilitation program with adequate supervision in the setting of their own residence. Hence, it is expected that this study will achieve high adherence rates and subsequently high efficacy in improving patients' preoperative aerobic capacity.

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Data Availability

Data sharing is not applicable to this article as no data sets have yet been generated or analyzed.

Authors' Contributions

NDH and AGW prepared the manuscript for publication. BCB, SSR, and MdD performed the ethical approval procedure and communicated with external parties. BCB prepared Figures 1 and 2 and Tables 1-3. BCB, SWMOD, and JMK invented and implemented the protocol. All authors read and approved the final manuscript. All authors reviewed the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

CPET: cardiopulmonary exercise test
CT: computerized tomography
EIT: European Institute of Innovation and Technology
EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality-of-life Questionnaire Core 30
GDPR: General Data Protection Regulation
HIIT: high-intensity interval training
L3: third lumbar vertebra
MFI: Multidimensional Fatigue Index
SARC-F: strength, assistance with walking, rising from a chair, climbing stairs, and falls
SRT: steep ramp test
VAT: ventilatory anaerobic threshold
VO2: oxygen uptake
VO2peak: oxygen uptake at peak exercise
WR: work rate
WR_{peak}: work rate at peak exercise

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Protocol

Twitch Data in Health Promotion Research: Protocol for a Case Study Exploring COVID-19 Vaccination Views Among Young People

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Abstract

Background: Social media platforms have emerged as a useful channel for health promotion communication, offering different channels to reach targeted populations. For example, social media has recently been used to disseminate information about COVID-19 vaccination across various demographics. Traditional modes of health communication such as television, health events, and newsletters may not reach all groups within a community. Health communications for younger generations are increasingly disseminated through social media to reflect key information sources. This paper explores a social media gaming platform as an alternative way to reach young people in health promotion research.

Objective: This protocol study aimed to pilot-test the potential of Twitch, a live streaming platform initially designed for video gaming, to conduct health promotion research with young people. We used COVID-19 vaccination as a topical case study that was recommended by Australian health authorities at the time of the research.

Methods: The research team worked with a Twitch Account Manager to design and test a case study within the guidelines and ethics protocols required by Twitch, identify suitable streamers to approach and establish a protocol for conducting research on the platform. This involved conducting a poll to initiate discussion about COVID-19 vaccination, monitoring the chat in 3 live Twitch sessions with 2 streamers to pilot the protocol, and briefly analyze Twitch chat logs to observe the range of response types that may be acquired from this methodology.

Results: The Twitch streams provided logs and videos on demand that were derived from the live session. These included demographics of viewers, chat logs, and polling results. The results of the poll showed a range of engagement in health promotion for the case study topic: the majority of participants had received their vaccination by the time of the poll; however, there was still a proportion that had not received their vaccination yet or had decided to not be vaccinated. Analysis of the Twitch chat logs demonstrated a range of both positive and negative themes regarding health promotion for the case study topic. This included irrelevant comments, misinformation (compared to health authority information at the time of this study), comedic and conspiracy responses, as well as vaccine status, provaccine comments, and vaccine-hesitant comments.

Conclusions: This study developed and tested a protocol for using Twitch data for health promotion research with young people. With live polling, open text discussion between participants and immediate responses to questions, Twitch can be used to collect both quantitative and qualitative research data from demographics that use social media. The platform also presents some challenges when engaging with independent streamers and sensitive health topics. This study provides an initial protocol for future researchers to use and build on.

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KEYWORDS

twitch; social media; COVID-19; vaccination communication; video gaming; gaming; health promotion; streaming

Introduction

Role of Social Media in Health Promotion

Social media platforms have emerged as influential channels for health communication, facilitating health promotion and information dissemination to social media users. Social media has been effectively used across varied health promotions' areas including health care decision-making and to promote healthy behaviors and interprofessional communication [1-3]. Social media's impact has been the result of several factors including its broad reach, active engagement by users, and support of multimedia content [1,2]. Social media provides an opportunity to support health promotion, with effective data dissemination enabling more cost-effective and wider reaching health campaigns [1]. It also enables the development of live-streamed content and graphics related to health promotion, which may be more engaging for certain populations [2].

For example, Laranjo et al [4] investigated the use of social media in promoting physical activity. The paper illustrated how social media platforms can engage a wide community and facilitate the interactions with users to motivate healthier choices and behavior change. Health interventions on platforms such as Facebook and Twitter were found to have a positive effect on health behavior outcomes. Similarly, Moorhead et al [5] highlights the role of social media in health information dissemination through examining the potential for collaboration between users and health professionals. It provided rapid communication avenues to aid health authorities in a timely and targeted manner, however it requires careful monitoring and guidance to ensure quality, reliability, and privacy [5]. Timely and effective communication is a significant concern during health crises, such as the COVID-19 pandemic. The pandemic illustrated the usefulness of these platforms for rapid dissemination of information, but also the pitfalls of misinformation [6]. Misinformation and antivaccination sentiments have been widespread and infrequently moderated on social media platforms [7], despite the growing rate of people acquiring their news through platforms such as Facebook and Twitter [8,9].

Further, 1 group that may particularly benefit from health promotion via social media are younger people. With an increasing proportion of the younger population accessing and using social media [10,11], modes of health communication need to adapt in order to actively engage with the community. Without social media engagement, health communications may not reach all members of the community.

Potential of Twitch as a Health Promotion Platform

Twitch has been recognized as the most successful and popular web-based streaming platform across the globe [12]. With over 200 million viewers, social media influencers have amassed large audiences for content spanning from gaming to comedy [12]. Although social media has been used by the government in health communications [13,14], Twitch has potential as an effective additional platform to reach young people due to the target demographic of many of the games and activities that are streamed. The 2-way interactions between streamer and viewer on this platform present a new opportunity for research and health promotion.

Woodcock and Johnson [12] conducted a recent analysis of viewers' experiences of parasocial interactions with videogame streamers on Twitch. The research highlights a male-dominated but mixed audience across the platform and how streamers that actively interact with their viewers in a context separate to health are less likely to engage in inflammatory, irrelevant, or disruptive comments [12]. Harpstead et al [15] highlighted the need for understanding the approaches used in social media research and produced a framework for a research toolkit for streaming platforms through a systematic review. This study outlines the primary methods of data acquisition on Twitch such as log data analyses and survey methods and the data types that can be used [15]. They also found a lack of research that studies the relationship between streamers and their audiences [15].

COVID-19 Vaccination as a Topical Case Study

The COVID-19 pandemic has had a huge impact across the world over the last 3 years. While early international border closures and movement restrictions protected Australia at the start of the pandemic before vaccines were available, there were still many deaths after the spread could not be controlled [16]. At a time of low vaccination rates, the 2021 Delta variant started the first large uncontrolled outbreak in Australia, leading to further border closures and lockdowns [17]. Late 2021 and early 2022 saw the COVID-19 response in Australia largely shift toward vaccination as the primary prevention response to the Omicron subvariants [18]. The majority of Australians received their initial vaccination and a second dose [16]. However, booster vaccination dosage rates were much lower [16,17]. Misinformation continued to linger in the web-based community [19,20] and the needs of people with lower health literacy were inadequately met, leaving much to be improved in health communications.[20,21] At the time of this study, this was the most topical case study to use to explore the potential of Twitch for health promotion research.

Aims

Twitch has been under-used for health promotion and research, but presents an opportunity to engage young people and gather unique perspectives on health issues. This protocol study aimed to pilot-test the potential of using Twitch to conduct health communication research with young men, using COVID-19 vaccination as a topical issue at the time of this study.

Methods

Preliminary Discussion and Protocol Development

In preparation to run a session with a streamer, the research team conducted a series of discussions with a Twitch Account Manager to confirm the requirements from the research team and Twitch. Through this iterative process, we established a

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preliminary framework for a protocol that could be used for gathering quantitative and qualitative data from Twitch. This included a strategy to identify an appropriate streamer to run a real time live video session about COVID-19 vaccination, a Twitch protocol for the streamers to run the session and coordination of the retrieval of Twitch data logs. This informed the development of a participant information sheet, consent form, and ethics application to proceed with the live sessions.

Ethical Considerations

Ethical approval was provided by the University of Sydney Human Research Ethics Committee (#2021/880), based on identified Twitch Account Managers who received reimbursement for their time (AUD $100 [US $64.23 on September 21, 2023] voucher), and anonymous stream participants. Managers gave written consent after discussion about this study and reading information about this study. Stream participants were informed of this study at the start of the stream and a representative of the research team was available to answer any questions in the chat. Consent was indicated by participation in the poll and chat. The ethics committee raised some concerns about the potential for children to be identified through public Twitch records, but agreed to approve the protocol if no minors were identified in published quotes through usernames (eg, if birth year was included), and a link to reliable COVID-19 vaccination information was required to be posted at the end of the chat. The link was to the official government information about COVID-19 at the time of this study.

Data Analysis

Once the live stream had been conducted and the Twitch Logs had been retrieved, the chat data was examined to describe the range of comment types provided in response to the poll on COVID-19 vaccination. The Twitch chat log data was pulled by the Twitch Account Manager, which is also available publicly, and sent through to the research team for thematic coding. These data were compiled as an excel sheet with timestamped comments from the stream. It should be noted that these descriptive categories were for data illustration purposes only and detailed thematic analysis was not the aim of this protocol paper. It intends to show the different data types that can be drawn from Twitch for health promotion research. As this project was focused on developing a methodological approach rather than a detailed qualitative analysis, an in-depth analysis was beyond the scope of what was required. However deeper conversation-based analysis could be conducted in future studies.

Results

Overview

In total, 1 session was conducted as a pilot protocol to identify what data types were possible to extract from the stream, followed by a 2 sessions run with a separate streamer to further test the refined protocol. The data gathered from the session can be separated into 3 components: results from the in-stream polls, live chat data from the Twitch logs, and viewer numbers and demographics provided to the streamer. Each is derived through a different mechanism and was discussed with the Twitch Account Manager prior to the live session to coordinate its retrieval.

Participants

Table 1 provides an overview of the sessions that were conducted on Twitch and the usage of the platform.

Table 1. Number of views and chat log responses.

Livestream	Number of viewers (average across vaccine section of stream)	Number of poll responses	Number of chat log responses (relevant responses during vaccine section of stream)
Pilot	11	8	N/A[a]
Livestream 1	23	17	45
Livestream 2	15	9	2

[a]N/A: not available.

Pilot Response

The pilot session was conducted to test the feasibility of the protocol for the live sessions and only included the polling component of the project. This was well received by the pilot session's audience with over 70% (n=34) of viewers across the 3 livestreams responding to the poll (total viewers, n=49). As the stream was primarily a small gaming stream, the number of attendees was small with minimal live conversation, however this step was useful in scoping the visual presentation of a live stream and provided a demonstration of what tools were available. This led to a modified protocol for the live sessions, including prompting the poll to the audience, discussing potential chat starters, and access to stream resources such as demographic data and recording.

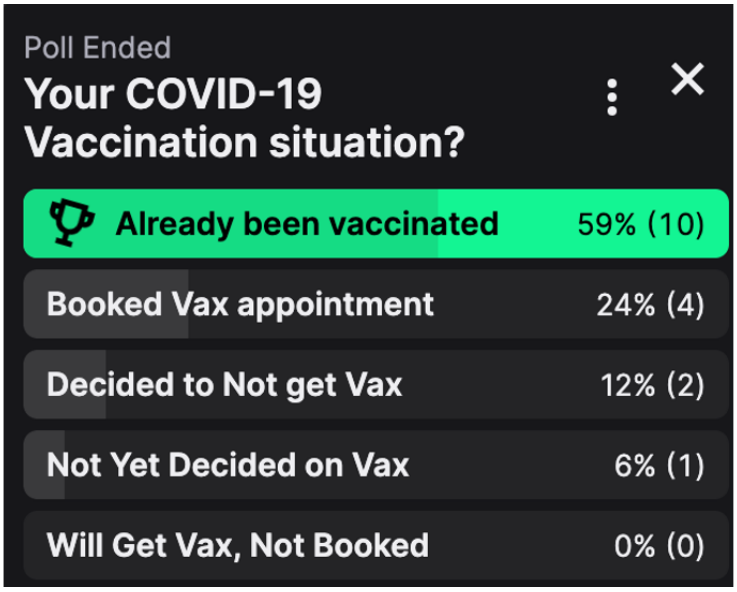
Poll Data

Each live session commenced with a brief introduction from the streamer followed by a poll that was prepared by the Twitch Account Manager to establish the vaccine hesitancy conversation (see Figure 1). The pilot and first session were conducted in August and September 2021, when booster shots had not been fully introduced, resulting in a set of poll questions focused on current vaccination status and intent to vaccinate. These questions ranged from "decided not to get vax" to "already been vaccinated," as seen in Figures 1 and 2. The wording of the poll was discussed with the Twitch Account Manager, where the use of "vax" was interpreted to be easier to incorporate onto the Twitch platform. This set of questions continued over to the first live session and yielded provaccine sentiments (either vaccinated or have already booked vaccination appointment),

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reflecting higher numbers of individuals who had received the vaccination. The new set of poll questions revolved around booster and unvaccinated status to correlate with the shift in COVID-19 context in Australia. Most responders answered with a vaccinated and boosted status.

Figure 1. Example live session poll results.



Chat Log Data

The primary data yielded from both the pilot and live sessions was the Twitch chat log data, which is a recording of each message that is sent to the public livestream (see Textbox 1). This was composed of extracted spreadsheets of responses from Twitch viewers that attended each live session in response to the streamer's questions and comments during a discussion phase. Content of each stream has been limited by setting time parameters on the retrieved spreadsheet. This is a necessary step to filter out content delivered by the streamer that is not relevant to the intervention. Twitch chat logs were not retrieved from the pilot session as the qualitative approach had not yet been developed. However, chat logs from both live sessions were retrieved through the Twitch Account Manager. It was derived from the Twitch Account Manager that this is possible without the support of the Twitch Account Manager; however, this study did not require this. Responses were initiated through the streamer openly discussing their own vaccination status, perspectives, and freely responding to messages delivered in the chat. This created an open-platform discussion and yielded unfiltered perspectives around the vaccine. Overall, Twitch chat logs revealed a range of both positive and negative responses and varying engagement in the health promotion topic. In this case study, response categories included irrelevant comments, false information, comedic and conspiracy responses, vaccine status, provaccine comments, and vaccine hesitant comments. See Table 2 for an example of a chat log extract and the varying categories these quotes fit into.

Textbox 1. Live Twitch session protocol.

- Identify streamer that has interest in participating in this study.
- Participant information sheet to be sent through to the streamer.
- Conduct debrief session with streamer to discuss potential conversations and direction of Twitch live session to cover any issues or concerns from the participant information sheet.
- Researcher to join stream at a coordinated time under Sydney Health Literacy Lab Twitch account. At the start of stream, researcher to send through: "The poll and chat in this stream will be publicly available as per Twitch policy and will be used for research purposes as part of the Sydney Health Literacy Lab COVID-19 project. A summary of the results will be provided here: https://sydneyhealthliteracylab.org.au/projects/."
- Throughout the stream, researcher to monitor the chat but should not intervene so as to influence the direction of the conversation during the livestream.
- At the end of the stream, researcher to send through: "If you have symptoms or questions about COVID-19, call the National Coronavirus Health Information Line on 1800 020 080. If you require translating or interpreting services, call 131 450. You can also find reliable information here: https://www.healthdirect.gov.au/coronavirus."
- Twitch contact to send through an Excel (Microsoft Corp) spreadsheet of Twitch chat log for analysis.

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Table 2. Example Twitch chat log and themes from a 1-minute excerpt first live session.

Theme	Chat log quote
Comedic	His 5g is great now
Provaccine	Novavax coming out in november I think
Vaccine status	Me. Im in wa. I know how science and statistics work.
Irrelevant comments	They and I
Comedic	Can confirm no 5G I am sad
Irrelevant comments	Want to know Y
Vaccine status	Me im not allowed ot get vax yet
Irrelevant comments	It looks like a highlighter
Conspiracy	2009 fine by the FDA. They paid 2.3 BILLION us.

Live Twitch Session Protocol

During the live streams, the streamer replied to polling results as they were submitted. However, responses such as "am vaxxed and boosted. No spicy cough yet" were provided without direct questioning from the streamer, illustrating that the polling visual was sufficient to generate a response. It should be noted that there were some viewers who had difficulty in finding where the poll was, evident in "poll is not on [their] screen." However, Twitch viewers can read and respond to other viewers responses and have the capacity to directly refer to another viewer's response. Furthermore, streamers often read the chat and responded promptly to questions posted in the chat. The streamer for the live sessions outlined where the poll could be found shortly after it was asked and facilitated further discussions where possible. This was further supported by other members in the audience, with some answering "@[username] Poll is at the top of chat." This functionality extended throughout the stream, with viewers frequently replying to each other's responses and questions in a conversational tone, which can be seen throughout the Twitch chat logs. This produced a comprehensive collection of responses and perspectives on COVID-19 vaccines that would otherwise be difficult to retrieve. However, audio discussion was not recorded.

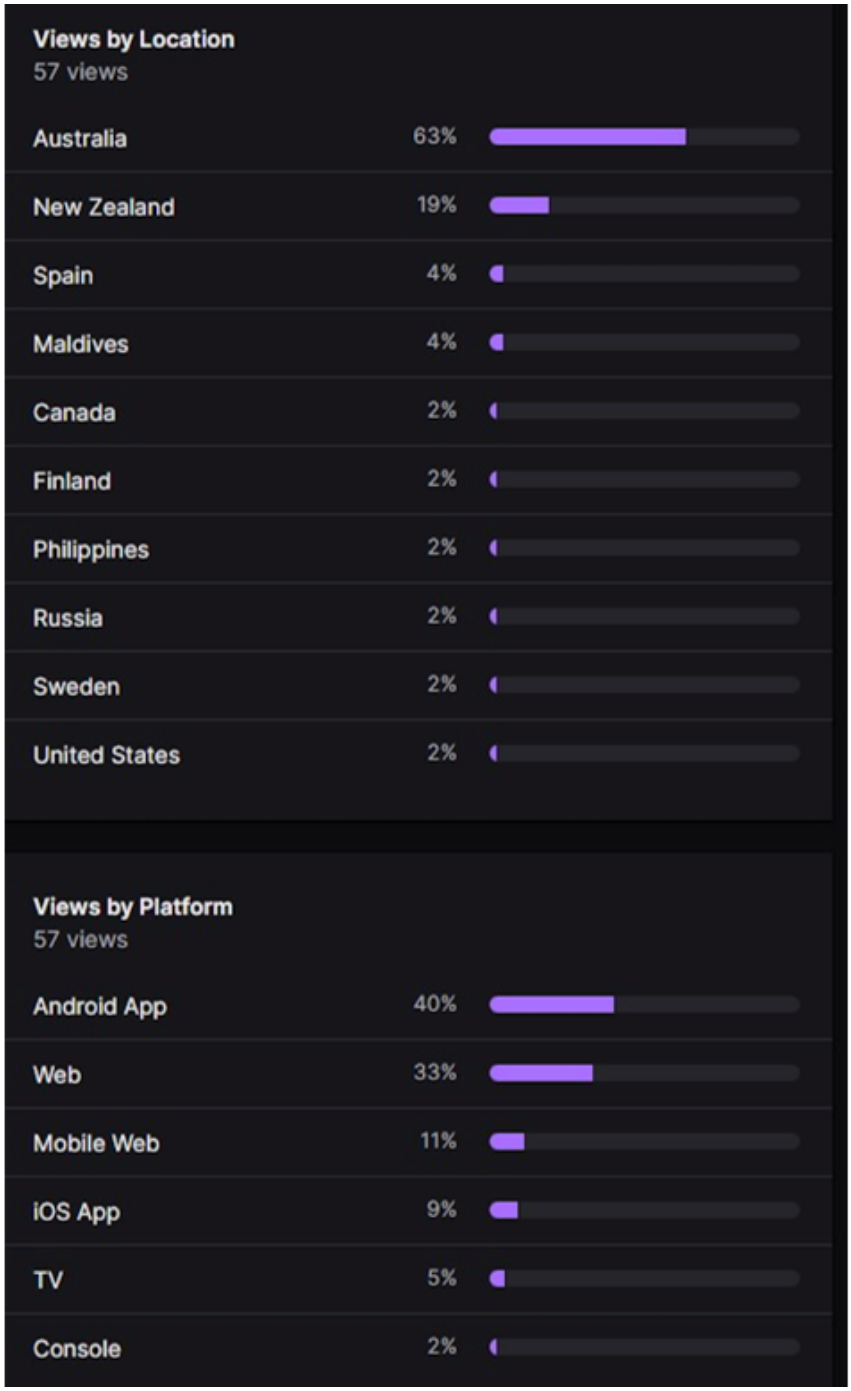
The Twitch chat logs demonstrated a range of responses to the health promotion topic even with the small case study sample. Many responses were irrelevant and directed primarily at other components of the stream, such as "sweet dreams are made of you" and "it looks like a highlighter." These comments are either prompted by the streamer or another viewer. False information (ie, not consistent with official health authority information at the time), comedic and conspiracy responses were also prevalent, including responses such as "I'm taking the vaccine out if my 5G doesn't go up" and "[will get the vaccine when] Pfizer isnt the company that paid the single largest criminal fine." Relevant responses were categorized into vaccine status, pro vaccine, and vaccine hesitant comments and were comprehendible. Examples of vaccine status responses include "been vaccinated for over a month now, Biontech for two months now" and "I chose to get vaxxed but [I don't know why]." Vaccine hesitant comments included "I don't want to get the vaccine because I know it hurts" and "I won't get the vaccine unless I get covid." As there is no filter and minimal chat restrictions, open responses from the audience may lead to difficulty in interpreting results as colloquial abbreviations and terms were used on Twitch such as "idk" or "pog." The Twitch Account Manager was aware of such difficulties and alluded to being able to support in interpreting these responses. Further analysis into these responses could be done in conjunction with videos on demand (VODs) as they will provide the contextual background to the prompt or question being asked by the streamer.

Viewer and Streamer Demographics

The Twitch Account Manager also provided the demographics of live session streams (see Figure 2), providing insights into viewer country and platform that the stream was accessed from, however, this did not provide information on other demographic information such as gender or age. This information was not provided by Twitch to the research team even though this information is required to create an account. Further information on viewer demographics could be gathered by consulting the streamer directly. This was not conducted for this study but could be considered in future studies to ascertain further viewer demographics. Figure 2 is a graphical representation of the demographic data that is automatically collected by the Twitch streaming platform after each stream. These data were collected through the Twitch Account Manager or streamer and is not available to the public. An additional facet that can be considered is the selected streamer. The content available on Twitch is separated into several categories. Provided the limited sample size and potential opportunities, a selection criterion for the streamer was not a major consideration for this study; however, an effort was made to expand potential streamers. Through this process, several different demographics were considered, such as female streamers, gaming streamers, comedians, and "in real life" streamers. This will be explored further in the discussion.

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Figure 2. Demographics screenshot from Twitch Account Manager.



VODs

Recordings of the sessions are saved to the Twitch platform and can be accessed through the streamer's profile page if this function is enabled. For this project, a recording of the session was provided by the Twitch Account Manager through a link which expired shortly after it was received. Due to difficulties in contacting the Twitch Account Manager once they moved to a different role, this was not followed up on as it was not necessary for the purposes of this project. For future studies, this can be avoided by establishing clearer requirements from both Twitch and the research team.

Discussion

Summary of Findings

This study aimed to develop and test a protocol for using Twitch to engage with young people for health promotion research. The live sessions commenced with a poll to establish the conversation, which focused on COVID-19 vaccination as the most topical health promotion issue at the time of this study. The primary data collected were the Twitch chat log data, which demonstrated a range of responses to and engagement with the health promotion topic. The demographics of live session streams provided insights into viewer country and cross-platform usage of the Twitch viewership, which illustrates the reach of

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the session. Recordings of the sessions were saved on the Twitch platform and can be accessed through the streamer's profile page if this function is enabled, however this was not used for the purposes of this study.

Future Potential and Challenges of Using Twitch

Discussions about conducting research on the Twitch platform started with the Twitch Account Manager on Twitter, as there was limited prior research to inform the ethics application and protocol. Several issues needed to be considered, including addressing the fact that children older than 13 years can create an account and view streams. Additionally, there is no age verification procedure on Twitch, making it challenging to ensure minors are not participating. Procedures to minimize engagement with people under 18 through eligibility information can be integrated into this study's design, but they are not foolproof. Ownership of Twitch chat log and VOD data was also an issue that needs to be considered by future researchers. Twitch owns all Twitch data for the first 48 hours after the livestream to promote engagement on the platform. After 48 hours, the data become publicly available and accessible at the streamer's discretion. Access to both the chat logs and VODs could be obtained by communicating with the streamer, but streamers can choose to enable or disable VODs. Therefore, it is important to discuss this with the streamer prior to the session.

Both qualitative and quantitative types of data can be extracted from Twitch live streams. The primary data source explored for this study was open ended discussions and conversations that were recorded in the Twitch chat logs. These data are useful for providing anonymous and unbiased responses from the target population, however more importantly, it provides a platform for health promoters to observe how individuals might interact and respond to others on the internet about a specific topic. This could be used to develop health promotion material using language appropriate to the target group, and can also provide an opportunity for referral to reliable information and health expert input when requested. For research purposes, a link to the research team's website and official government information about the health topic were required for ethical approval. The uptake and impact of such referrals could be explored in future research.

Finally, open-ended responses from communities viewing content on Twitch may lead to inflammatory conversations that could harm the perspectives and emotions of other viewers. The guidelines for managing inflammatory comments on each social media platform varies and can change over time.

Strengths and Limitations

This paper provides a feasible protocol for using a novel method in health promotion research, to inform future research in this area. Several improvements for future researchers were identified during the project. Limitations of the protocol included reliance on the availability of the Twitch Account Manager and streamer, which sometimes led to delays and limits on data access and ownership. When this presents significant barriers to researchers, using publicly available Twitch data from naturally occurring Twitch streams and chats could be considered for analysis. However, this would limit the ability to direct the conversation to a specific health promotion topic.

In future research, the selection of suitable Twitch Account Manager and streamers given this study's aims should be given consideration and prioritized before conducting any live sessions. As this was a case study only, the sample size and diversity of streamers are limited. The Twitch platform provides a variety of contextual and demographic opportunities for future research. For example, responses from a comedy-focused male streamer may differ significantly from those of a gaming-focused female streamer.

Textbox 2 provides a summary of recommendations for future health promotion research using Twitch.

Textbox 2. Recommendations for health promotion research using Twitch.

Recommendations for future research on Twitch

- Minimize communication issues by addressing methodological and ethical concerns (eg, how to deal with inflammatory comments in accordance with the platform policies) prior to engagement with Twitch. Provide resources, forms, and approvals early on to avoid delays.
- Establish communication strategies with the Twitch Account Manager and streamer using appropriate channels such as Discord or Twitter.
- Discuss all requirements, including consent, video on demand recordings, Twitch chat logs, and demographic data before running live sessions. These data should be permanently available and retrieved soon after the livestream.
- Engage a more diverse sample of Twitch Account Managers and streamers to improve the reliability and validity of data gathered.
- Analyze video on demand data in addition to Twitch chat log data to obtain a comprehensive data set including streamer input.

Conclusions

The emergence of new social media platforms has led to the expansion of health promotion strategies beyond traditional methods. This study developed and tested a feasible protocol showing the potential of Twitch as a novel channel for health promotion research with young people. For research, the platform can be used to produce quantitative and qualitative data, but also presents some challenges when engaging with independent streamers and sensitive health topics. This study aims to offer guidance for future research and practice by providing a protocol for researchers to use and build on.

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Acknowledgments

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Conflicts of Interest

None declared.

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Abbreviations

VOD: Video on demand

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Protocol

Developing Health Management Competency for Digital Health Transformation: Protocol for a Qualitative Study

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Abstract

Background: Globally, the health care system is experiencing a period of rapid and radical change. In response, innovative service models have been adopted for the delivery of high-quality care that require a health workforce with skills to support transformation and new ways of working.

Objective: The aim of this research protocol is to describe research that will contribute to developing the capability of health service managers in the digital health era and enabling digital transformation within the Australian health care environment. It also explains the process of preparing and finalizing the research design and methodologies by seeking answers to the following three research questions: (1) To what extent can the existing health service management and digital health competency frameworks guide the development of competence for health service managers in understanding and managing in the digital health space? (2) What are the competencies that are necessary for health service managers to acquire in order to effectively work with and manage in the digital health context? (3) What are the key factors that enable and inhibit health service managers to develop and demonstrate digital health competence in the workplace?

Methods: The study has adopted a qualitative approach, guided by the empirically validated management competency identification process, using four steps: (1) health management and digital health competency mapping, (2) scoping review of literature and policy analysis, (3) focus group discussions with health service managers, and (4) semistructured interviews with digital health leaders. The first 2 steps were to confirm the need for updating the current health service management curriculum to address changing competency requirements of health service managers in the digital health context.

Results: Two initial steps have been completed confirming the significance of the study and study design. Step 1, competency mapping, found that nearly half of the digital competencies were only partially or not addressed at all by the health management competency framework. The scoping review articulated the competencies health service managers need to effectively demonstrate digital health competence in the workplace. The findings effectively support the importance of the current research and also the appropriateness of the proposed steps 3 and 4 in answering the research questions and achieving the research aim.

Conclusions: This study will provide insights into the health service management workforce performance and development needs for digital health and inform credentialing and professional development requirements. This will guide health service managers in leading and managing the adoption and implementation of digital health as a contemporary tool for health care delivery. The study will develop an in-depth understanding of Australian health service managers' experiences and views. This research process could be applied in other contexts, noting that the results need contextualization to individual country jurisdictions and environments.

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KEYWORDS

health care management; health service manager; digital health; health informatics; competency; workforce development; innovation; research protocol; informatics; manager; managers; service; services; delivery; organization; organizational; workforce; management; managerial; qualification; qualifications; focus group; focus groups; interview; interviews; scoping; review methods; review methodology

Introduction

Definitions

For the purpose of this protocol paper, the following definitions are being applied: (1) *health services managers* are the "professional managers charged with the responsibility of leading and managing individual health care services, large healthcare organisations and the overall health system" [1]; (2) *digital health* is "an umbrella term referring to a range of technologies that can be used to treat patients and collect and share a person's health information" [2]; and (3) *digital health services* can be seen as the use of digital tools and processes to provide and support the delivery of health care in a digital society [3].

Background

Overview

The health care system is experiencing a period of rapid and radical change. From a global perspective, the aging population, an escalating burden of chronic disease and pandemics, and increasing community expectations are all placing growing demands on health care services [4]. As a response, innovative service models have been adopted for the delivery of high-quality care to meet this burgeoning need and to improve the efficiency, value, and safety of health service provision [5]. Innovation has included the adoption and implementation of digital health solutions, which were not possible a generation ago. Hence, a health workforce with the requisite skills to support such transformation requires new thinking and new ways of working.

Digital Health Transformation Has Been Witnessed

Digital health services have been shown as crucial to developing just-in-time, tailored, and targeted health care that is accessible, affordable, appropriate, and sustainable [6]. Digital health has become "an umbrella term referring to a range of technologies that can be used to treat patients and collect and share a person's health information" [2]. To ensure success in the digital transformation of health services, digital health solutions need to be designed, developed, and delivered in an effective, efficient, ethical, and evidence-based manner under good governance and management [7-10].

The COVID-19 pandemic saw an acceleration in the uptake of digital health solutions globally. This required health care practitioners and providers to adapt to new ways of working, with the ever-present social distancing and travel restriction requirements becoming commonplace. As an example of the accelerated uptake during the pandemic, digital-first strategies, remote monitoring, and digital care approaches were quickly implemented to enable continuity of health care service without physical interactions [11]. Across Europe, digital health systems enabled critical support of public health policies [12,13] improving the monitoring, surveillance, information, and communication regarding COVID-19 requirements and its impact on health care, as well as the recording and monitoring of vaccination bookings [5]. In the United States, "technology innovations and policy prescriptions" [14] and "right-sizing of regulation" [14] were implemented to support the rapid adoption of innovative, digital health technologies. Furthermore, the web-based medical visit requirements under the HIPAA (Health Insurance Portability and Accountability Act) were also recalibrated [14]. Additionally, the Australian federal government's responses to the pandemic included implementing the necessary policy and funding requirements for innovative digital health solutions to be deployed across the country [15].

Demands on a Skilled Workforce

In response to the fast adoption of digital health technologies, a competent health care workforce with capabilities and confidence in implementing and integrating digital health technologies into health service delivery is essential [6,16]. This includes the management and leadership of health care organizations in the digital health context. Some efforts in addressing the required workforce competencies have occurred. For example, the United Kingdom's National Health Service [17] has responded by instantiating the Graduate Management Training Scheme for leadership development that includes a Health Informatics specialization, which leads to a postgraduate diploma in data analytics.

In Australia, the Australian Digital Health Agency [18] has developed the National Digital Health Workforce and Education Roadmap and recently noted that "there has been significant interest in emerging literature that examines the future of work and the impact digital technologies will have on the health workforce, or indeed are having. However, there has not been as much concentration on the planning, programs and strategies required to improve the digital health literacy of the health workforce." Therefore, in the Australian context, it is imperative to focus on the digital health workforce, management competency, and capability development, with contemporary and contextual training that is relevant and responsive to the current health care environment.

Competency, Context, and Performance

How health service managers plan and manage the increasingly complex digital tools in an ever-changing environment, along with the resultant rise in digital health literacy, requires capabilities and contextual competencies to ensure these new technologies are best used to inform both strategic and operational decision-making [19-23]. This is supported by the growing evidence highlighting the importance of the investment required to develop a competent health service management workforce, including through academic credentialing and professional association certifications [24].

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Although various management competency frameworks have been established to guide the development of management competence for health service managers [25,26], whether these frameworks have adequately captured the competency requirements for health service managers in managing the necessary, fast-paced change and digital transformation of health care is not evident. This highlights a need to articulate the competencies that are necessary for health service managers to acquire to effectively work with and manage in the digital health context. Therefore, confirming the changing competency requirements for health service managers in managing and leading digital health transformation in health care is warranted. This research is being undertaken in the Australian health care setting to contextualize and inform national frameworks, system enablers, and factors that support Australian health service managers in the digital context.

A review of the literature confirmed that the development of competence is context-sensitive [27,28], with performance improvement resulting from competency development. To improve a health service manager's capability in facilitating and implementing digital health transformation, it is desirable that health service managers develop relevant competencies. Providing an environment that enables managers to fulfill their responsibilities is equally important [29].

Preparatory Phase (Phase 1)

Overview

In exploring the theoretical concepts to inform the research design, the initial focus was on the health informatics competencies required for health service managers to perform effectively in today's health care environment, where the use of health informatics and digital tools is the norm [19-23]. Accordingly, preparatory work was undertaken to first explore competencies and what health informatics competencies already existed within the Australasian College of Health Service Management (ACHSM) Master Health Service Management Competency Framework competencies [1] and in the Australian Health Informatics Competency Framework (AHICF) [30], which apply to health service managers in Australia. It should be noted that in the 2022 revision of the AHICF, an international health informatics frameworks review was included that examined changes in the competency frameworks from the United Kingdom, Canada, Saudi Arabia, and the United States.

Second context, health service managers must be able to deliver these competencies in the context of health services management. Third competency (effective performance), health service managers need to be able to demonstrate competency, so what approach is recommended to measure the attainment of health informatics competencies for health service managers?

Digital competence and the demonstration of these competencies are context-sensitive [27,28]. Understanding the requisite knowledge and skills that are necessary to ensure the development of competency in the digital health environment is crucial, particularly in terms of rapid digital transformation. In addition, structural enabling and inhibiting factors to support a health service manager's demonstration of digital competence must be addressed to ensure the efficacy of this competency. Underpinning this understanding is the importance as to how the development of competence can be supported at the organizational level as well as understanding the challenges health service managers face in demonstrating their competence in the digital context. This understanding must be informed by the system level and organizational factors that can support and enable the development and demonstration of competence in this dynamic, digital environment. Consequently, this preparatory work and the initial findings informed the significance of the research study and the final study design.

Research Focus, Research Questions, and Intended Benefits

The original focus of the research was "improving health informatics competencies for health service managers in Australia." The research project was designed in 2019. Since the COVID-19 pandemic, significant developments in digital health have been witnessed. Following the in-depth literature review, ongoing research work, and prevailing industry activities with the Australasian Institute of Digital Health (AIDH), this highlighted that digital health had now become the umbrella term covering health informatics. Digital health is becoming increasingly relevant in the contemporary environment and is the more commonly used lexicon in the industry. The competency frameworks now being developed internationally are increasingly focusing on digital health rather than health informatics alone [31].

The Australian Digital Health Agency [18] has also identified that "digital health is increasingly recognised as an area for research, capability development and investment" [18]. Therefore, expanding the study from health informatics only, to all aspects of digital health, was more relevant to the current health care context and climate.

The research study will contribute to the development of the capability for health service managers in managing health services in the digital health era and enabling digital transformation in the health context by seeking answers to the following three research questions: (1) To what extent can the existing health service management and digital health competency frameworks guide the development of competence for health service managers in understanding and managing in the digital health space? (2) What are the competencies that are necessary for health service managers to acquire in order to effectively work with and manage in the digital health context? (3) What are the key factors that enable and inhibit health service managers to develop and demonstrate digital health competence in the workplace?

Methods

Phase 1

The following initial 2 steps were completed in order to confirm the significance of the study and study design and to develop a conceptual framework as a research guide to answer the 3 research questions.

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Step 1: Competency Mapping

Cognizant of the existing and enduring efforts to support health management competency development in the digital health context, the purpose of this initial step was to comprehend existing structures and factors that can enable competency development and education in digital health management. This guided the primary investigation enumerating the extent to which postgraduate health care management education in Australian universities facilitates the development of informatics competencies. A health care management and informatics competency mapping process was undertaken using industry certification competency frameworks to identify, collect, map, and then distinguish the competencies evidenced in the postgraduate health care management programs. As the leading health informatics competency framework in Australia, the 50 health informatics competency statements from the AHICF were first mapped to the ACHSM Master Health Service Management Competency Framework competencies [1]. These were then mapped to the 21 ACHSM accredited, and the Royal Australasian College of Medical Administrators (RACMA) recognized, postgraduate health care management programs offered domestically in Australia. The ACHSM accredits, and RACMA approves the health care management degrees in Australia. These are voluntary processes that are seen as the recognized industry standard and acknowledgment for higher degrees for health service managers. The mapping process used the "Steps Used to Effectively Map Preexisting Courses to Competency Sets" approach created at the University of Washington School of Public Health's Northwest Center for Public Health Practice, as it has been shown to have a prominent level of assurance in the accuracy of the competency mapping process for university courses [32,33].

Based on the Association of American Medical Colleges' Curriculum Management and Information Tool (CurrMIT) [34], the Competency Mapping Matrix spreadsheet was constructed, which contained the program names, subject or course topic learning objectives, and the 50 AHICF competencies. Each of the 21 postgraduate health care management programs was then reviewed by subject title, learning objectives, and assessments for keywords, competency indicators, and themes that matched with the competency framework. The degree to which the competency was seen as being addressed was then mapped using a four-point criteria scale: (1) not addressed, (2) partially addressed, (3) mostly addressed, and (4) fully addressed. To confirm the reliability and validity of the rating instrument, piloting of the Competency Mapping Matrix spreadsheet was completed with 1 academic and 1 professional services Australian university staff member, both working within health care management postgraduate awards.

An experienced international health informatics academic completed the primary mapping, with a health service management competency specialist and management competency researcher providing oversight. Independent validation was then provided by an expert health informatics competency specialist educator and previous head of a university business school. Interrater reliability of the competency mapping process and tool was used to establish the validity of the mapping itself. Any discrepancies were resolved by a subject matter expert (an Australian professor in health service management) [35].

Step 2: Scoping Review

Overview

The second step was to conduct a scoping review of research literature to confirm the changing competency requirements for health service managers as a result of digital transformation in health care [6]. This published work explored the competencies health service managers need to acquire to effectively manage in the digital health context as well as describing the key factors that enable and inhibit health service managers in demonstrating digital health competence in the workplace. This scoping review of the literature was conducted in 2022 and built on a rapid review undertaken in 2020 [25]. The review was guided by Arksey and O'Malley's five-step framework [36], using the following steps: (1) defining a research question, (2) identifying relevant studies, (3) selecting and confirming empirical studies, (4) data extraction, and (5) collating, summarizing, and reporting results.

Data Sources and Search Strategies

The following databases were searched: PubMed, Scopus, ProQuest, Web of Science, CINAHL, ACM Digital Library, Google Scholar, and ProQuest Dissertations. The following keywords were used: "digital health," "electronic health," "health informatics," "competencies," "capability," "proficiency," "certification," "qualification," "health manager," "health executive," and "health administrator." A PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) approach [37] was used for eligibility screening. The review searched for publications in the English language since the year 2000 that were peer-reviewed, empirical, and from the gray literature, including government white papers and professional institution position papers.

Data Extraction

Data were extracted from eligible publications and included authors, year of publication, country of origin, the aim of the study, target population, methods for data collection, and key findings related to the scoping review objectives. Content analysis was performed on the extracted data to assist in developing an understanding of the content and identifying the principal themes pertinent to the search focus.

The original search conducted in 2020 generated 1212 publications, and after duplicates were removed, 941 publications were included for title screening. This led to 185 papers being included for abstract screening by 2 reviewers. The revised search conducted in 2022 generated 467 publications, and after the removal of duplicates, 403 publications were included for title screening. This led to 114 papers that were included for abstract screening, which resulted in an additional 4 papers that went through full-text review with the initial 185 papers identified. Full-text review confirmed that 81 publications were particularly relevant to digital health competencies and workforce development in the digital health context. From which, 19 papers pertinent to the focus of the scoping review then underwent qualitative content analysis [6].

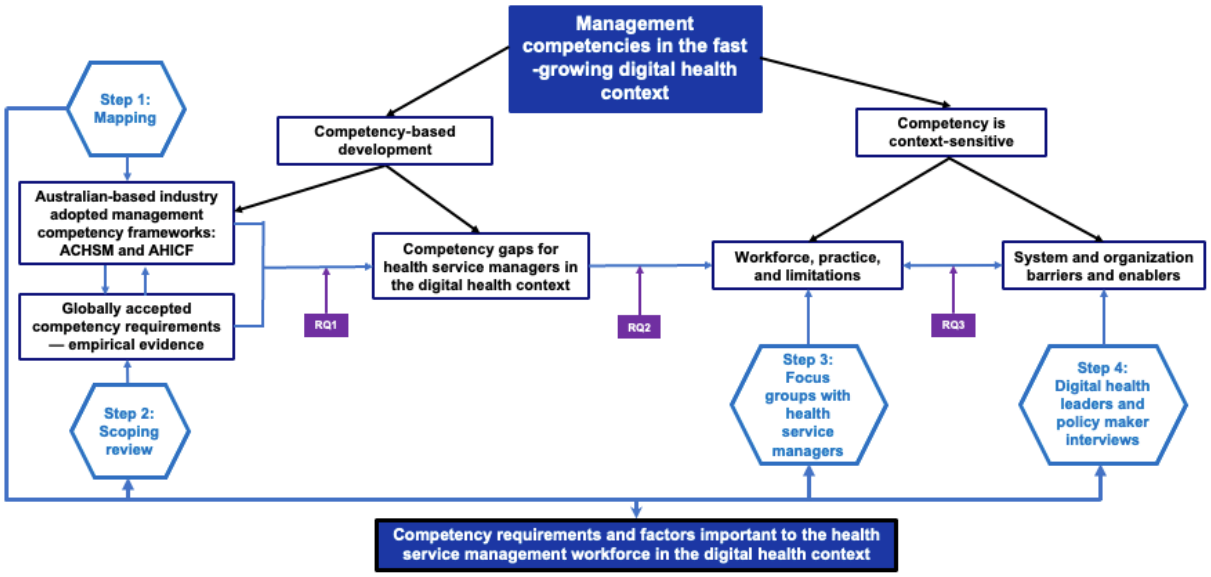
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Phase 2

Overview

Based on the learnings from the competency mapping, the scoping review, and the knowledge gaps identified in the literature, the conceptual framework presented in Figure 1 has been developed to guide the overall design of the study. The framework follows the research process steps (the blue lines) and addresses the 3 research questions (the purple boxes). The study has adopted a qualitative approach, guided by the empirically validated management competency identification process [27], using the following four steps: (1) health management and digital health competency mapping, (2) scoping review of literature and policy analysis, (3) focus group discussions (FGDs) with health service managers, and (4) semistructured interviews with digital health leaders. This approach is also substantiated by consistent evidence in the international literature supporting the use of these data collection methods in identifying and analyzing informatics and digital competencies in health care [38-41].

Figure 1. Conceptual framework—researching digital health competencies for health service managers. Blue lines show the research process. Purple boxes show the research questions (RQs). RQ1: To what extent can the existing health service management competency framework guide the development of competence for health service managers in understanding and managing in the digital health space? RQ2: What are the competencies that are necessary for health service managers to acquire in order to effectively work with and manage in the digital health context? RQ3: What are the key factors that enable and inhibit health service managers to develop and demonstrate digital health competence in the workplace? ACHSM: Australasian College of Health Service Management; AHICF: Australian Health Informatics Competency Framework.



As mentioned earlier, the first 2 steps have been completed as part of the preparation process, and the overall results from these 2 steps provided the foundation for and informed steps 3 and 4 of this research study. Data collection and analysis, including triangulation of data, will be completed by December 2023. Table 1 details the target populations and the proposed number of participants for steps 3 and 4.

Table 1. Details of the qualitative research study focus group discussions and interviews.

Methods	Focus group discussions via videoconference	Semistructured interviews via videoconference
Focus	To explore the competencies that health service managers need to acquire to effectively work with and manage in the digital health context, along with factors that enable and inhibit the acquisition of these competencies.	To validate findings from the focus group discussions in relation to health service manager competencies, barriers, and enablers for managing in the digital health environment. Also exploring issues that influence digital health policy and practice.
Who are the participants?	Mid-level managers who are responsible for the day-to-day operations of Australian public hospitals. These positions may include department directors, unit managers, and ward managers representing level 3 and 4 management[a] from public hospital settings.	Digital health leaders and chief digital health or clinical information officers from national digital health organizations and public health departments who have executive responsibility for digital health.
Participants, n	48 (8 per group×6 focus groups)	15

[a]Management levels are defined by the organizational reporting hierarchy, with level 1 being the chief executive officer, level 2 reporting to the chief executive officer, level 3 reporting to level 2 management, and level 4 reporting to level 3 management.

Sampling

A purposive sampling technique will be used to identify participants for both the focus groups and interviews, as it enables a deliberate selection of a participant due to their characteristics linked to the study variables. This sampling "involves identification and selection of individuals or groups of individuals that are proficient and well-informed with a

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phenomenon of interest" [42]. Furthermore, snowball sampling will be used to assist in locating additional key informants who are information-rich and possess a certain characteristic of research relevance with the target population.

Recruitment

For the FGDs

Potential participants for the FGDs will be invited and recruited from the members of AIDH membership or ACHSM. Invitations of participation will be announced by AIDH and ACHSM in their newsletters and websites. The principal investigator's contact details will be included in the announcement. The announcement will encourage and invite potential participants to contact the principal investigator directly to express their interest to participate. Upon receipt of the expression of interest, the principal investigator will assess the eligibility and contact eligible participants directly via email to provide a formal invitation to participate in the FGD, which will contain a copy of the project information sheet and consent form. The principal investigator will also email those who expressed their interest in participating and who were not eligible and provide them with an explanation as to why they were not selected.

For the Semistructured Interviews

The semistructured interview participants will be invited and recruited from the members of the Digital Health Executive Network AIDH membership or ACHSM membership. Invitations of participation will be announced by AIDH and ACHSM in their newsletters and websites. The principal investigator's contact details will be included in the announcement. The announcement will encourage and invite potential participants to contact the principal investigator directly to express their interest to participate. Upon receipt of the expression of interest, the principal investigator will then assess the eligibility and contact eligible participants directly via email to provide a formal invitation to participate in the semistructured interview, which will contain a copy of the project information sheet and consent form. If there is no response within 5 working days, 1 further email will be sent before the completion of 1 follow-up phone contact. The principal investigator will also email those who expressed their interest in participating and who are not eligible and provide them with an explanation for not being selected.

Ethical Considerations

This research received ethics approval on October 20, 2022, by the James Cook University Human Research Ethics Committee (approval H8877; expiry December 27, 2024). For the focus group and interview participants who respond to the AIDH or ACHSM expression of interest to participate in the general announcement and meet the health service managers' inclusion criteria, an invitation email will be sent to potential participants by the PhD candidate with the participant information sheet and consent form attached to the email. Participants are asked to complete, sign, and return the consent form if they would like to attend the FGD or semistructured interview. The personal information collected will include participant name, position title, name of organization, and email address; however, no names will be retained, participants' identity will not be disclosed, and all information is nonidentifiable. Each participant will be provided with a copy of their FGD or interview transcript, and they can request any specific information in the transcript to be excluded from the analysis. Results of the study will be presented collectively, and no individual information will be used. Participants will volunteer 90 minutes of their time to participate in the FGD or 45 minutes of their time to participate in the semistructured interview; there will be no payment to participate in the research study.

Conducting FGDs and Semistructured Interviews

In total, 6 FGDs will be conducted via videoconference (Microsoft Teams; Microsoft) by the principal investigator and 1 other member of the research team, who will play the role of observer or notetaker. The participants will be 40-50 midlevel managers who are responsible for the day-to-day operations of Australian public hospitals. These positions include department directors, unit managers, program managers, and ward managers, representing level 3 and 4 management from public hospital settings. Management levels are defined by the organizational reporting hierarchy, with level 1 being the chief executive officer, level 2 reporting to the chief executive officer, level 3 reporting to level 2 management, and level 4 reporting to level 3 management. The number of participants is consistent with the qualitative methodology being used to ensure data saturation [43-45]. The FGDs will be conducted for approximately 90 minutes each and digitally captured via the recording functionality of the Microsoft Teams videoconference call. The automatically transcribed text will then be reviewed and proofread for language and readability to provide a full transcript of the discussions.

In total, 15 semistructured interviews will be conducted by the principal investigator via videoconference (Microsoft Teams) with digital health leaders and chief digital health or clinical information officers from national digital health organizations and public health departments, who have executive responsibility for digital health, including authority over all aspects of a significant area of work and accountability for making decisions critical to the organization's success. The number of participants is consistent with the qualitative methodology being used to ensure data saturation [43-45]. Five open-ended questions will guide the interviews. The key informant interviews will be conducted for approximately 45 minutes each and digitally captured via the recording functionality of the Microsoft Teams videoconference call.

For both types of interviews, a person-specific transcription is provided to each participant to amend or delete any of their comments, particularly for validation of accuracy or to clarify a statement, should they wish to do so.

Data Analysis for the FGDs and Semistructured Interviews

All transcripts will be subsequently analyzed using NVivo software (QSR International) or Leximancer software (Leximancer) or other content analysis tools. For the focus group interviews, a thematic analysis will be conducted iteratively with data from the focus groups to develop concepts, categories, and themes. Competencies will then be analyzed and categorized

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against existing national and international health service management and digital health competency frameworks. Enabling and inhibiting factors will also be analyzed using Braun et al [46] 6-phase reflexive thematic analysis approach to identify, organize, analyze, and advance insight into themes or categories of the factors emerging.

Importantly, reflexive thematic analysis enables the researcher to highlight meaning as contextual or situated while simultaneously undertaking analysis of the text for meaning [47,48]. Further, the legitimacy and validity of the researcher's subjectivity are not just acknowledged, but it is also an intrinsic asset, as reflexive thematic analysis supports the active role of the researcher in the knowledge generation process [47]. Using the 6-phase reflexive thematic analysis approach as detailed in Textbox 1 augments the acquisition of text patterns and key terms to reveal patterns that were previously unknown and furnish information with meaning [49].

Textbox 1. The reflexive thematic analysis 6-phase approach guiding data analysis [46].

Familiarization

Moving from data generation to analysis, that is, appreciating the data, by becoming immersed in and connecting with the data in different ways.

Generating codes

Moving to a more in-depth and systematic engagement with the data, that is, making sense of the data, by curating a list of terms, filtering out textual noise, and generating clear patterns to extract more valuable insights [49].

Constructing themes

Moving from codes into overarching themes that accurately and coherently represent the data, that is, creating a story about the data, through latent semantic analysis and singular value determination to uncover themes [49].

Revising themes

Moving to candidate themes and reviewing them to see how each theme relates to the others, that is, telling the overall story about the data.

Defining themes

Moving to clear definitions of each theme by elucidating the essence and scope of each theme, that is, what is meaningful about the data.

Producing the report

Moving to a final test of how well the themes work, both individually in relation to the data set and overall, that is, a logical story with sufficient evidence that the themes are relevant to the data.

The semistructured interview transcripts will then be analyzed using reflexive thematic analysis to triangulate the findings with the themes emerging from the FGDs. This will assist in validating the health service manager's competencies required to manage in the digital health context, as well as generating perspectives on both role development and enhancement needs for a health service manager's digital health competency, and aspirational and professional development requirements for health service managers to lead in the digital health space.

Both the FGDs and semistructured interviews will use the COREQ (Consolidated Criteria for Reporting Qualitative Research) checklist to "promote explicit and comprehensive reporting of qualitative studies (interviews and focus groups)" [50].

Results

Results from phase 1 of the study, which commenced in October 2019, were published in July 2021 [35] and October 2022 [6] and informed the significance of the research study and the final study design, which are presented here.

Competency Mapping Results

By completing the mapping of the 85 ACHSM Master Health Service Management Competency Framework competencies to the 50 health informatics competency statements from the AHICF, it was found that nearly half of this framework's competencies were only partially or not addressed at all by the ACHSM framework. As the ACHSM framework guides accreditation of postgraduate health care management programs offered domestically in Australia and forms part of the RACMA fellowship program, this indicated that the existing formal graduate-level education may not be adequate in developing health service managers' competency in the digital health era [35]. This published work highlighted an important gap to address—developing skills for the health management workforce relies on industry competency framework requirements that guide the curriculum and training endeavors as well as for the university programs, professional organizations, and individual health care institutions.

Scoping Review Results

The scoping review confirmed the five key activities that influence the development of health management workforce competency and capacity, namely: (1) using competency assessment, (2) guided by competency models, (3) supporting formal professional development, (4) including short-term training activities, and (5) using work-based development. Additionally, the following seven key factors that facilitate development of the health management workforce in the digital health context were also identified and included: (1) acknowledgment and recognition of these new digital responsibilities, (2) the organization's capacity to adopt innovation in a supportive environment to embrace digital health, (3) system-level support and political will, (4) specialized digital technology expertise, (5) an investment in the health service management workforce, (6) being underpinned by

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systematic integration in planning, and (7) being used for practice development [6]. How these key activities work in the health care context and how these factors should be addressed require further exploration.

Discussion

Anticipated Findings

Focus Group Discussions

The FGD participants will provide reflections and insights to explore the competencies that health service managers need to acquire to effectively work with and manage in the digital health context along with factors that enable and inhibit acquisition of these competencies. The FGDs will explore the relevance of the additional competencies identified in steps 1 and 2. Findings of the identified list of important competencies from the FGDs will then inform the finalization of the semistructured interview questions.

Semistructured Interviews

The focus of the semistructured interviews is to explore (1) validation of the findings from the FGDs in terms of core health service manager competencies, barriers, and enablers to manage in the digital health environment and (2) in-depth insights affecting digital health influences on digital health policy and practice.

Limitations

It is important to note some limitations associated with a research protocol. The study is qualitative in nature to develop an in-depth understanding of Australian health service manager's experiences and views. The methods described could be applied in other contexts; however, the results may not be generalized to other country contexts. Any recommendations provided in subsequent publications will note these limitations, and suggested findings are contextualized to individual jurisdictions and environments.

Industry Impact

Review of the AHICF competencies was completed by the Certified Health Informatician Australasia Examination Committee in 2022, of which the principal investigator is a member, and version 2.0 of the AHICF [51] now contains 11 leadership and management competencies in domain D, up from the previous 5 management science competencies in domain 4 of version 1.0.

Further, a review of the ACHSM Master Health Service Management Competency Framework was completed by the National Steering Committee in 2022, of which the principal investigator was a member, and version 2.0 [52] now contains 6 digital management competencies in an action domain, whereas no specific digital competencies were articulated in version 1.0.

Conclusions

This study will provide real-time, in-depth insights into the health service management workforce performance and development needs for digital health and will uniquely inform credentialing and professional development requirements for health service management. Further, this will also illuminate the postgraduate programs and continuing professional development requirements for health service management education and training. Developing strategies based on these findings will assist in supporting the health service managers to lead and manage the adoption and implementation of digital health technology and initiatives in the health care sector, including insights into the health care system's digital workforce policy and capacity considerations. This will assist in optimizing the outcomes from adoption of digital health as a contemporary tool for health care delivery and furthering digital transformation outcomes for patients, practitioners, providers, and the public.

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Data Availability

The data sets generated during and analyzed during this study are not publicly available due to ongoing data collection from participants but may be made available from the corresponding author on reasonable request.

Authors' Contributions

MB, with the supervision of ZL, MM, and MW, conceived and designed the study. MB performed the competency mapping and literature search in collaboration with ZL, MM, and MW. The first draft of the paper was prepared by MB. ZL revised it critically for important intellectual content, upon which all authors then conceptually commented. MB, ZL, MM, and MW provided substantial contributions to the conception of the research protocol. MB and ZL finalized the paper, and all authors approved the final version of the paper.

Conflicts of Interest

None declared.

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Abbreviations

ACHSM: Australasian College of Health Service Management
AHICF: Australian Health Informatics Competency Framework
AIDH: Australasian Institute of Digital Health
COREQ: Consolidated Criteria for Reporting Qualitative Research
FGD: focus group discussion
HIPAA: Health Insurance Portability and Accountability Act
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RACMA: Royal Australasian College of Medical Administrators

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Protocol

Empowering Foot Care Literacy Among People Living With Diabetes and Their Carers With an mHealth App: Protocol for a Feasibility Study

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Abstract

Background: Diabetic foot ulcers (DFUs) cause significant morbidity affecting 19% to 34% of people living with diabetes mellitus. DFUs not only impair quality of life but may also result in limb loss and mortality. Patient education has been advocated to raise awareness of proper foot self-care and the necessity of seeking assistance when a foot wound occurs. Modern technologies, including mobile health (mHealth) interventions such as health apps, bring the potential for more cost-effective and scalable interventions.

Objective: This study aims to examine the feasibility and usability of a newly developed mHealth app called Well Feet, which is a diabetes and foot care education app for individuals at risk of developing DFU.

Methods: Well Feet was developed using an evidence-based and expert panel cocreation approach to deliver educational content available in 3 languages (ie, English, Chinese, and Malay) via animation videos and a range of additional features, including adaptive learning. A nonrandomized, single-arm feasibility study using a mixed methods approach with a series of validated questionnaires and focus group discussions will be conducted. In total, 40 patients and carers will be recruited from a tertiary hospital diabetes clinic to receive a 1-month mHealth intervention. The primary outcomes are the usability of the app and a qualitative perspective on user experience. Secondary outcomes include changes in foot care knowledge, self-management behaviors, and quality of life.

Results: Patient recruitment began in July 2023, and the intervention and data collection will be completed by the end of September 2023. This study has been approved by National Healthcare Group Domain Specific Review Board (2022/00614) on February 10, 2023. The expected results will be published in spring 2024.

Conclusions: Through this feasibility study, the Well Feet DFU education app will undergo a comprehensive quantitative and qualitative evaluation of its usability and acceptance for future improvement in its design. With local contextualization, cultural adaptation, and its multilingual functionality, the app addresses a critical aspect of DFU health education and self-management in a multiethnic population. Findings from this study will refine and enhance the features of the app based on user feedback and shape the procedural framework for a subsequent randomized controlled trial to assess the effectiveness of Well Feet.

Trial Registration: ClinicalTrials.gov NCT05564728; https://clinicaltrials.gov/study/NCT05564728

International Registered Report Identifier (IRRID): DERR1-10.2196/52036

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KEYWORDS

digital therapeutics; mHealth; diabetes mellitus; diabetes foot ulcer; feasibility study; mobile phone

Introduction

Background

According to the International Diabetes Federation, 537 million people worldwide (ie, 1 in 10) lived with diabetes in 2021, and this number is expected to rise to 783 million by 2045 [1]. The lifetime incidence of developing a diabetic foot ulcer (DFU) in adults living with diabetes ranges from 19% to 34% [2]. In a 2017 systematic review and meta-analysis, DFU's global prevalence among people with diabetes was estimated to be 6.3%, with Asia having a prevalence of 5.5% [3]. Diabetes-related lower extremity complications affected an estimated 131 million people (1.8% of the total global population) in 2016, with overall age-standardized rates for years lived with disability increasing by 15.9% between 1990 and 2016 [4]. Southern sub-Saharan Africa, South Asia, and Southeast Asia experienced the greatest growth during the period. Despite multiple clinical [5], economic [6,7] and policy [8,9] attempts to address DFU in Singapore, the country is still struggling to combat the rising prevalence of DFU-related complications with a reported 1500 DFU-related lower-limb amputations performed each year [10]. Furthermore, the estimated recurrence rate is 22.1% per person-year [11]. Hence, DFUs impose a significant clinical and economic burden on health care systems around the world as well as significant reductions in the quality of life for those affected [12].

Prevention initiatives, including lifelong patient education and continuous empowerment, are key strategies for successful foot care and management of diabetes, as recommended by evidence-based guidelines [13]. Whether delivered one-to-one or in small groups, diabetes foot health education is resource-intensive and costly—requiring the participation of doctors, nurses, podiatrists, diabetes educators, and allied health professionals. While valuable, foot care and diabetes education sessions lack immediacy, timeliness, access, and flexibility. In Singapore, 36% of patients with diabetes reported receiving no diabetes education [14] and over 51% spend less than a minute checking their feet [15]. Given the unmet need, financial and health workforce constraints, and being in line with modern approaches to education and self-management support, a digitally supported diabetes education mobile health (mHealth) apps using prevention and management of the DFU education program carries the potential to improve health care delivery and increase uptake, equity, and cost-effectiveness of health services related to DFU. Patient-facing technology such as mHealth apps can be blended with face-to-face care to augment the overall delivery of care and health services [16] and impact patients' health outcomes [17].

The other agency that is heavily involved in the management of DFU is the carer. Informal carers are defined broadly as any family member, partner, or friend who provides support to a person having a chronic condition. Carers play a vital role particularly in assisting with wound care, monitoring changes, ensuring foot hygiene, managing medications, offering emotional support, advocating for medical care, and providing education [18]. Carer's involvement improves patient outcomes, prevents complications, and enhances overall DFU care and well-being. For many people with chronic conditions, particularly the elderly, informal carers provide support and take responsibility for many of the care needs. Upskilling informal carers may result in better health outcomes [18]. Training equips them with skills to provide effective wound care, identify issues early, prevent complications, manage medications, offer emotional support [19] and promote timely access to health care. This improves the overall DFU management beyond the hospital walls, which may eventually result in reduction of hospitalizations, lowers costs of health care, and ensures collaborative, sustainable DFU management among patients, carers, and health care professionals.

Related Work

Studies suggest that people living with diabetes show an interest in mHealth apps for preventing and monitoring DFUs [20]. There is a growing body of evidence supporting the potential of mHealth apps to enhance diabetes self-management performance [21]. A few studies have been conducted to assess or validate the potential of an mHealth app for diabetic foot care. Some of them focus on providing wound care trackers [22,23], others on empowering with knowledge on foot-ankle exercises [24], quick tips on foot care and first aid, reminders for medical check-ups, a contacts feature to save health providers' contact information [25], text messaging [26], foot care essentials [27,28], foot care education in 6 animations [29] and tips for self-assessment [30]. Prior to a full trial, feasibility studies are routinely performed to determine whether a future study is feasible [31].

Some of the challenges identified in such interventions include maintaining patient engagement [25], tailoring content to the different stages of complexity of the disease, retaining and applying the knowledge acquired [32]. Thus, there is a need to explore the mechanisms by which evidence-based behavior change techniques and digital features can influence the uptake of digital diabetes and foot care education and ultimately improve diabetes health literacy and self-management behaviors. Even though the validation studies presented promising results, none of the mHealth apps for DFU comprise comprehensive in-depth education on all aspects of foot health, including prevention, inspection, and wound care while concurrently providing support for self-management with tracking features that focus both on feet health and general diabetes care. Additionally, no other tool addresses the need for a multilingual and adaptive solution that fits individual needs, such as the role (patient or caregiver), severity of the condition, and competency levels, concurrently reinforcing learning through notifications and spaced learning. Finally, there is a necessity to understand the user's engagement and app effectiveness in detail using granular click-level data.

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Aim

This is a "proof-of-concept" feasibility study to evaluate a foot health education app for people living with diabetes, Well Feet, among patients and carers. Prior to a full trial, feasibility studies are routinely performed to determine whether a future study is feasible [31].

Methods

Study Design

This study is a nonrandomized, single-arm feasibility study with baseline, end point, and focus-group discussion design. An explanatory sequential mixed methods approach will be used to assess feasibility and usability of the mHealth app, Well Feet. Our study features a 1-month intervention period carefully designed to strike a balance between meaningful observation and participant convenience. This timeframe enables us to assess the feasibility of the intervention on our selected outcomes. All participants will receive Well Feet, and their feedback will be collected through quantitative and qualitative rating measures. Subsequently, focus group discussions will be conducted to provide valuable insights into their experiences. The reporting of this protocol follows CONSORT (Consolidated Standards of Reporting Trials) 2010 statement extension for feasibility studies [33]. This study has been registered at ClinicalTrials.gov (NCT05564728).

Study Participants

Eligibility Criteria

Both patients and carers will be invited to participate in this study. Inclusion criteria for patients are (1) being diagnosed with type 2 diabetes and attending Tan Tock Seng Hospital Diabetes Clinic, (2) being 21 years or older, (3) being able to speak and read English, (4) owning a smartphone or tablet and can download the app, (5) having internet access, (6) being able to provide informed consent, (7) being Singaporeans or Singapore permanent residents. Inclusion criteria for carers are (1) carers who provided care for a patient with type 2 diabetes for the past 6 months, (2) being aged 21 years or older, (3) being able to speak and read in English, (4) owning a smartphone or tablet and being able to download the app, (5) having internet access, and (6) being able to provide informed consent. Exclusion criteria for patients and carers include being (1) pregnant, (2) an inpatient, or (3) having received formal training in medicine or allied health services.

Recruitment

Patients will be recruited through referrals from attending endocrinologists at Tan Tock Seng Hospital. Recruitment will take place during the patients' routine clinic visits at Diabetes Clinic. The endocrinologists will screen for potential participants' eligibility based on this study's inclusion and exclusion criteria before referring them to the appointed research assistant to complete the recruitment process. At the same time, patients will be asked to nominate their carers to participate in this study. The nomination is optional and subject to patients' and carers' willingness. Notwithstanding, patients without a carer can still participate in this study. Potential patients and carers who choose not to participate in this study will be asked an open-ended question about the reasons. It will be highlighted that answering the question is voluntary. The information will be used to inform about the barriers to recruitment and acceptability of the intervention.

Informed Consent

The research assistant will conduct a briefing for all referred patients and carers in a closed space outside of the clinic room. The briefing involves explaining this study's aim and study's inclusion and exclusion criteria. Additionally, potential participants will be briefed thoroughly about this study's procedures, risk exposure, and all the information included in the informed consent form (Multimedia Appendix 1). The research assistant will provide adequate time for the participants to decide. Participants will be allowed to discuss their decisions with family members before participating in this study. The wishes of the participant will be respected if they choose not to participate in the research. The research assistant or site principal investigator will provide a copy of the informed consent form and obtain written consent from the potential study participants. It will be highlighted to the participants that this study is voluntary, and their participation would not affect their clinical care or any benefits that they are entitled to.

Participants will be advised to retain a copy of the signed informed consent form for documentation, they will also receive a WhatsApp (Meta Platforms, Inc) message confirming their enrollment for this study, contact details, and basic information about study design.

Sample Size and Power Calculation

Since this is a feasibility study, a formal sample size calculation is not required [34]. Our target is to recruit a minimum of 30 participants (with a maximum of 40), evenly divided into groups: persons living with diabetes and carers of persons living diabetes, with 15 participants in each group (with a maximum of 20). This approach is based on a previous study that shows a feasibility study requires 30 or more participants to estimate a parameter [35]. An arbitrary sample size of 30 would provide 0.75 (75%) power to detect a medium effect size of 0.5. Alternatively, a sample size of 40 would provide even greater power at 0.87 (87%).

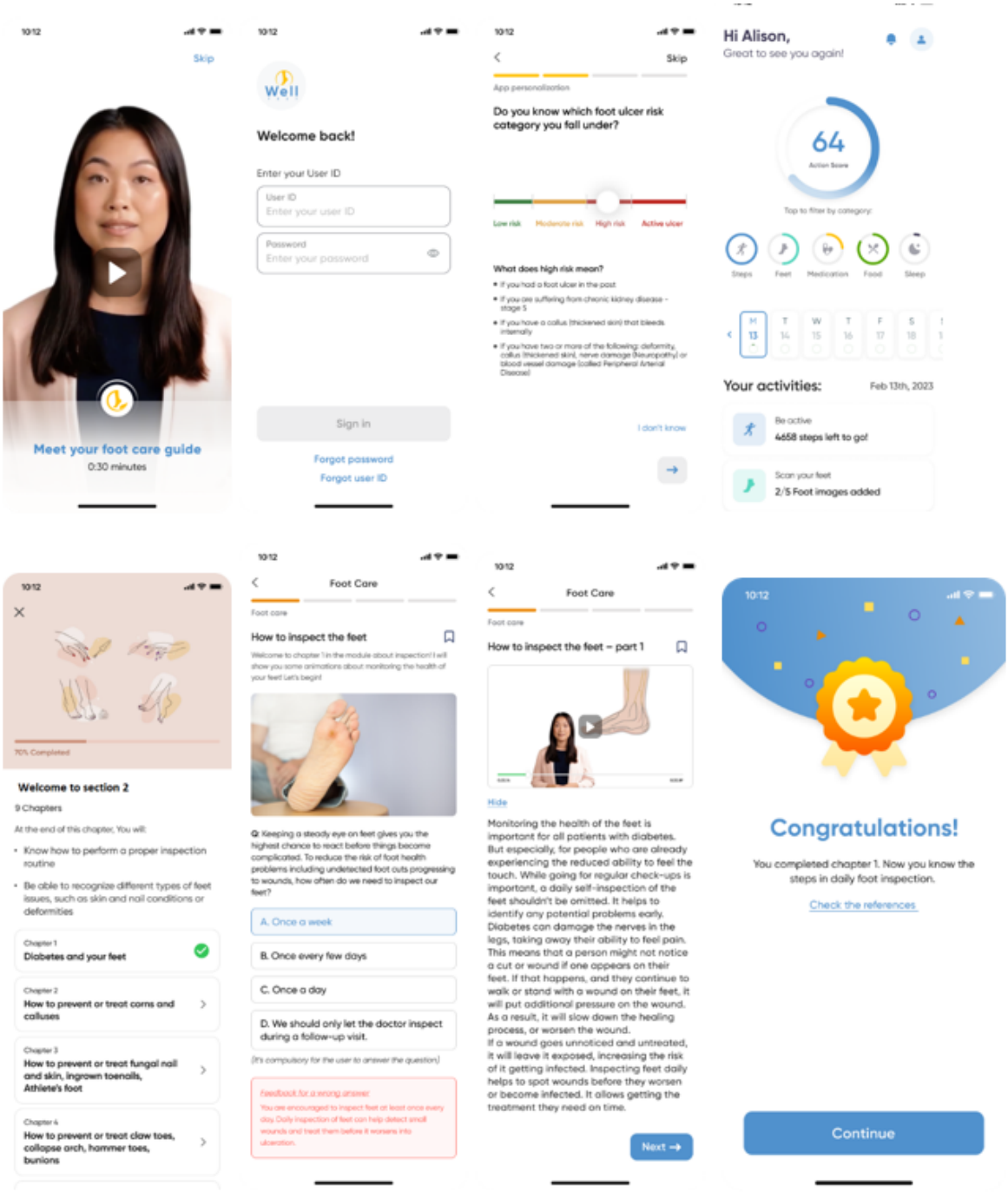
Intervention

Well Feet mHealth App

Well Feet is a diabetes and foot care education mHealth developed by Nanyang Technological University. The technical building process of the app is outsourced to a university-appointed vendor while the content building process was carried out in-house. The app was made available to download both for iOS and Android. Screenshots of Well Feet's main interface and features are shown in Figure 1.

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Figure 1. Selected screenshots from the Well Feet app.



Adaptive Learning Framework

Well Feet is a diabetes and foot care education app and was designed based on an adaptive learning framework to deliver educational modules and action-oriented conversations related to foot care through multilingual (English, Mandarin, and Malay) animations with a deep fake presenter. A total of 21 modules covering 4 themes: introduction, inspection, prevention, and wound care, have been developed by this study's team based on a series of validated and evidenced-based sources including the International Working Group on the Diabetic Foot [36] guidelines as visualized in Textbox 1. The curriculum outline was consulted in 2 rounds in an asynchronous expert panel. Next, the scripts were developed with consideration of readability, cultural relevance, and local context, and were transformed into animations in an iterative design process comprising storyboarding, prototyping, production, and reviews. In total, 54 bite-sized and visually appealing animation videos ranging from 30 seconds to 2 minutes were produced for diabetes foot educational content. The content was prepared in English and translated into Mandarin and Malay. The animations are accompanied by adaptive learning quiz questions that allow us to assess knowledge gaps and trigger spaced learning conversations in case of incorrect answers. The system includes storing an in-depth click-level data which allows a vast analysis of learning and usage analytics.

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Textbox 1. Overview of the 21 modules included in the Well Feet app.

Introduction

- Categories of risk
- Amputation
- Diabetes and your feet: nerves, blood vessels, skin, joints

Inspection

- Visual inspection
- Foot conditions—skin and nails 1 (corns and calluses)
- Foot conditions—skin and nails 2 (fissures or fungal nail and skin [tinea pedis] or dystrophic nail or ingrown toenails)
- Foot conditions—deformities 1 (claw toes or hammer toes or bunions)
- Foot conditions—deformities 2 (Charcot foot)
- Foot conditions—peripheral neuropathy
- Foot conditions—peripheral vascular disease
- Other foot conditions commonly encountered by patients with diabetes
- Professional foot examination

Prevention

- Hygiene
- Diabetes-friendly footwear
- How to trim nails safely
- Skin care
- Simple exercises for the foot or calf
- Practices to avoid

Wound care

- Wound care—basic
- Diabetic foot ulcer
- Wound care—diabetic foot ulcer

Concurrent with curriculum development, the team was working on identifying relevant app features and conceptualizing app mechanics with instructional experience as a focus to connect user flow between features and align it with desirable behavior changes. In total, 3 levels of learning adaptations have been devised: (1) personalization of the content based on the role served, (2) personalization of the order of the modules based on the user's risk stratification identified in the onboarding process, and (3) personalization of the content based on user's knowledge level through knowledge assessment. This personalization forms the basis of learning framework in Well Feet. Additional features such a Frequently Asked Question chatbot, meal diary, feet diary, medication reminders steps, and sleep tracker are further added to enhance user experience. Finally, the app includes an automated notification system which in case of inactivity prompts the user to use the app.

Setting

Due to the nature of the Well Feet intervention being an mHealth app, participants are anticipated to engage with the intervention at their own discretion. Nevertheless, this study's team will remind the participants at the start of this study to engage with Well Feet app throughout this study's period.

Data Collection

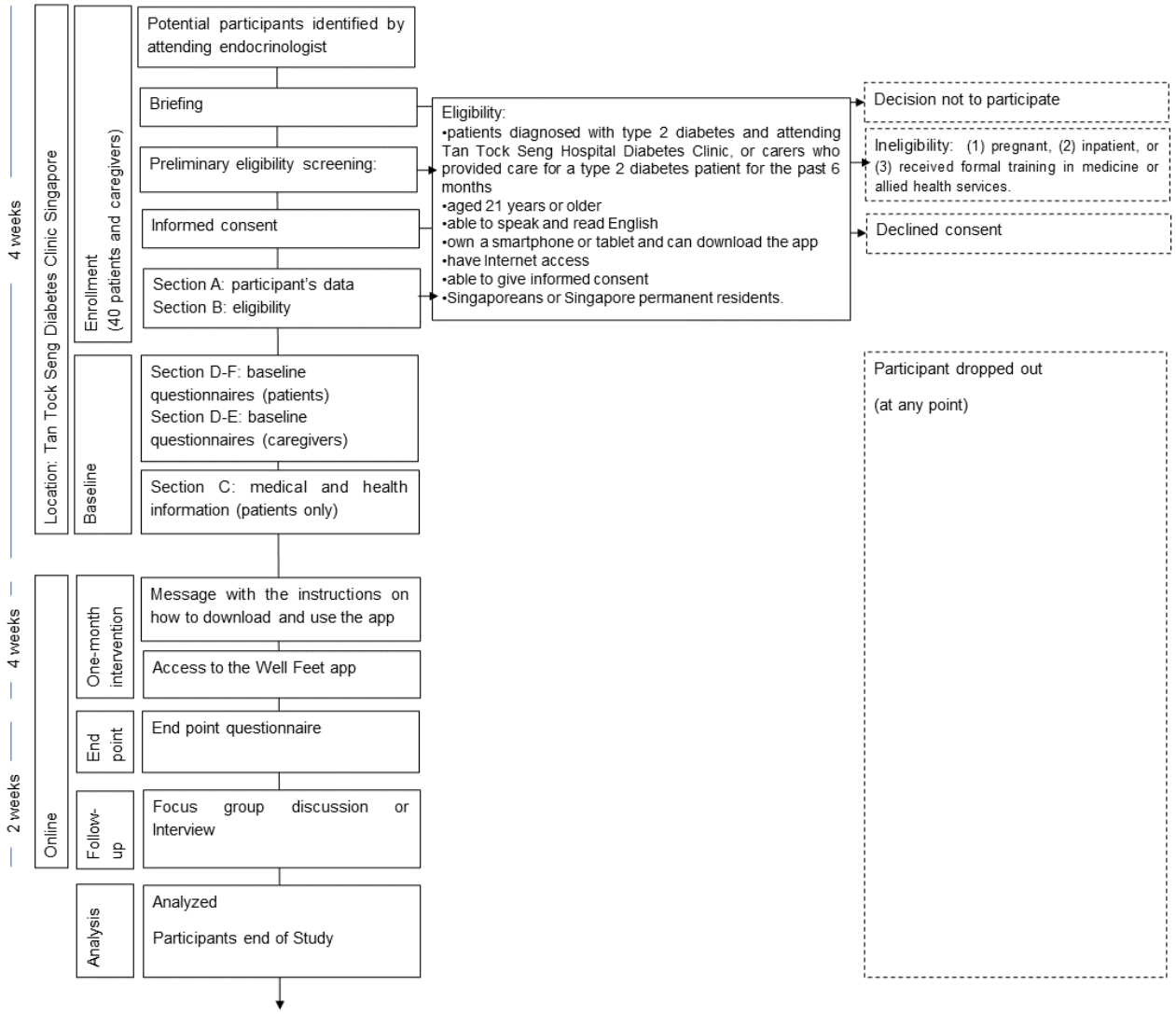
Overview

The participant flow through this study is illustrated in Figure 2. Consenting participants will be assigned with a study ID that will be used as their coded identifier throughout this study. Participants will receive a briefing regarding this study's procedures and will answer a baseline questionnaire using a digital survey platform, REDCap (Research Electronic Data Capture, Vanderbilt University), accessed through a provided tablet. A study ID will be assigned to each participant to keep their answers to the questionnaire anonymous. A research assistant will assist with participants to complete the prescreening and enrollment sections, that is, for the participant's details and eligibility form. The clinical research assistant will access and extract medical records to complete the section with medical and health related information. Participants will complete sociodemographic information and questionnaire sections by themselves. The research assistant may assist the

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participants if help is needed. Additionally, the research assistant will access and extract medical records to complete the section with medical and health related information. Carers will go through the same recruitment and briefing flow as the patients. However, no medical record will be extracted for carers. Completion of the questionnaire is on a voluntary basis. If the participant requests to fill out the questionnaire at their own convenience, the research assistant will send them a link to the questionnaire through their preferred communication medium. The research assistant will also follow-up with a gentle reminder to complete the questionnaire in a case the participant did not fill it out.

Figure 2. Participant flow through this study (CONSORT [Consolidated Standards of Reporting Trials]).



The intervention will begin with the participants receiving the link to the app. The participants will be asked to use the app for up to 1 month. At the end of the period, they will be asked to fill out an end point questionnaire and will be invited to participate in focus group discussions or an interview, in case the participant cannot participate in focus group discussions, as a follow-up. To minimize attrition, prompts will be sent via the participants' chosen mode of contact (eg, via email, telephone, SMS text message, or WhatsApp) to indicate it is time to complete the survey or participate in the focus group discussion.

Outcome Measures

This study's outcomes of interest encompass methodological, procedural, and feasibility questions. Various factors are considered. Table 1 displays the primary outcomes including usability of the app and qualitative perspective on user experience. Multimedia Appendix 2 [37-43] displays secondary outcomes, including changes in foot care knowledge, self-management behaviors, and quality of life. Additionally, usage and learning analytics will be collected from the backend of the app.

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Table 1. Primary outcomes.

Outcome measure	Measure description	Time frame
Primary outcome		
Usability of a health app among patients and carers at the end of the trial (1 month)	A validated questionnaire, MAUQ[a] [44], will be used to determine the usefulness and applicability of an app with a conversational agent or chatbot among patients and carers. The questionnaire consists of 3 subscales, which are ease of use (5 items), interface and satisfaction (7 items), and usefulness (6 items). Participants rate each of the items using a 7-point Likert scale ranging from 1 (strongly disagree) to 7 (strongly agree). The usability of the app is determined by the total and average of all statements—the higher the overall average, the better the usability of the app. However, if the average score is lower than 4, it means that the usability of the app is not good. The MAUQ exhibited strong psychometric characteristics, as evidenced by an overall Cronbach α value of .914 [44].	End-of-trial (1 month)
Qualitative perspective on a conversational agent or chatbot app usage experience among patients and carers at the end of the trial (1 month).	A focus group discussion among the app users will be carried out to collect feedback on the user experience at the end of the trial. Qualitative data on app usability, app applicability, app relevance, and user feedback will be retrieved from the focus group discussion.	End-of-trial (1 month)

[a]MAUQ: mHealth (mobile health) App Usability Questionnaire.

Data Management

All data will be handled according to patient Nanyang Technological University data protection and privacy policy [45] as well as National Healthcare Group, Tan Tock Seng Hospital data protection and privacy policy [46] with all participants assigned a study ID to deidentify data and any personal information about participants will be stored separately from deidentified data. Data collected via digital survey platform, REDCap will be stored on secure servers at Center for Population Health Sciences, Lee Kong Chian School of Medicine, Nanyang Technological University. The data gathered through the app will be stored in a university-approved cloud server as a multiencrypted database with authorization granted for principal investigators and study team members to prevent unauthorized persons from accessing the data. All other physical forms will be stored in a locked filing cabinet in the clinical site and will be accessible only to the site-principal investigator and appointed research assistant. User's interaction within the Well Feet app will be monitored to identify participants' signaling their need for more extensive support.

Ethical Considerations

This study was approved by the National Healthcare Group Domain Specific Review Board (2022/00614) and the Nanyang Technological University institutional review board (IRB-2023-157), ensuring that the welfare and rights of all participants is protected in this study. This study will be conducted in accordance to the Helsinki code of ethics ensuring that patients' confidentiality, integrity, and vulnerability are kept throughout their participation. Informed consent will be collected to ensure participants are aware of this study's procedure and their rights to withdraw from this study without the need to give any reason. Participants will be provided with contact information within the informed consent form should they have any concern regarding the conduct of the feasibility study.

Analysis

Quantitative Analyses

The questionnaires answered by the participants will be summarized using descriptive statistics, and the data will be presented as frequencies, percentages for categorical variables and means, SDs, medians, and IQRs for continuous variables depending on the distribution of the variable. Descriptive statistics will also be used to assess measures of app usage. Differences between groups will be analyzed using chi-squared or Fisher exact test for nominal data and changes within the groups over time (pre-post) will be analyzed using the Wilcoxon signed rank test. R (R Core Team) and Stata (StataCorp) will be used for all analyses.

Qualitative Analyses

All focus group discussions will be recorded on a digital teleconferencing platform (ie, Zoom; Zoom Video Communications, Inc), which will then be transcribed verbatim. Any identifiers in the transcriptions will be removed. Thematic analysis will be used to identify participants' experience, overall acceptance, and feedback. The analysis of the responses will start immediately following the first focus group and transcription. Initial codes will be generated, then collated into themes to identify the key patterns and key themes of the focus group discussions using the procedures suggested by Clarke and Braun [47].

Dissemination

This study's findings will be published in an open access journal and via national and international conference presentations.

Results

This study was funded in October 2019 and received ethics approval in February 2023. Recruitment of this study was done in July 2023 with 40 participants enrolled. Well Feet app is expected to be published at Google Play and iOS testflight at the end of August 2023, followed by a month-long intervention period. Analysis of results is expected to be completed by

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October 2023, and trial results are expected to be published in spring 2024.

Discussion

Principal Findings

This study is designed with the aim to evaluate the feasibility of Well Feet, a mobile health app designed for people living with diabetes and at risk of DFU. This study will provide insights on Well Feet's added values, potential benefits, and challenges of its use among patients and carers. Through a combination of quantitative evaluation using the validated MAUQ questionnaire and qualitative insight from focus group discussions, this study will provide a perspective on the feasibility of Well Feet particularly on how the app facilitates patients and carers engagement in diabetes foot health management. Additionally, analytics derived from Well Feet usage data will provide a clearer picture on user interaction with features of the app.

Studies ranging from early detection and prevention to self-monitoring apps collectively highlight the potential of mHealth in improving patient outcomes, and addressing challenges in diabetes care [48]. We are expecting that similar to other studies a difference in knowledge pretest and posttest knowledge score will be observed [49,50] and that the app will be perceived as valuable [22,24,25,27,28,51]. However, as the learning curriculum included in Well Feet app is much more comprehensive than in other solutions and encompasses multilevel tailoring mechanisms such as notifications for learning reinforcement and adaptive learning pathway for knowledge gaps identification, we are expecting that the foot care knowledge and behavior results will differ from other studies. The qualitative analysis will additionally help to identify specific behavioral changes among study participants going beyond observing frequency of foot checking [20].

Furthermore, in this study we are aiming at in app exploring usage patterns among the participants, especially those who experienced knowledge or behavior change. Ploderer et al [51] has observed 3 usage patterns when evaluating a wound care tracking app: continuous, temporary, and failing usage. In our study, it is expected that some barriers to usage identified by Ploderer et al [51] will overlap, especially the ones leading to temporary usage such as work commitments and health disruptions. As the sample of participants will vary across different risks of developing DFU and will include low and moderate risk patients, the frustration with lack of healing progress might not arise. The usage and learning analytics of click-level data should allow us to further describe exact app behaviors that constitute each group of users. Usage patterns will be juxtaposed with knowledge and behavior questionnaires' results to further reveal engagement patterns and factors influencing the success of foot care education.

Strengths and Limitations

This study comes with a set of strengths and limitations. A structured approach described in this protocol will be used to assess the practicality and viability of a newly developed adaptive diabetes foot health education, Well Feet, before a full-scale development and deployment. The utilization of both quantitative and qualitative measures enhances the depth and breadth of insights gained from this evaluation. By performing a feasibility study, the research team will be able to identify technical, operational, and logistical challenges early in the process, thus potentially saving time and resources when a larger randomized controlled trial is conducted.

However, there are several limitations worth noting. The small cohort of study participants recruited from a single tertiary hospital limits the generalizability of findings. A follow-up multicenter randomized controlled trial is warranted to predict a proper intervention effect. Second, while only patients who owned mobile devices were recruited, no formal assessment of digital literacy was performed during the recruitment process. As smartphone ownership may not be an accurate indicator of proficiency in using basic phone features [52], patient's engagement with Well Feet app may be impacted by limited digital literacy.

Conclusions

Patient-facing digital health technologies such as mHealth apps promise to support self-management of various health conditions, including diabetes and associated risk factors. Such feasibility research, especially when it encompasses user-centered design and evaluation, contributes to health care services transformation aimed at equitability, patient empowerment, and shared decision-making. Gaining growing attention from researchers [53] and patients [15], mHealth interventions pave the road for future health care where digital solutions, including health education, are seamlessly integrated into routine prevention and care. This feasibility study is a step in embracing technological innovations which aim to optimize advancing a DFU prevention and management and care delivery.

Acknowledgments

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Data Availability

Deidentified interview data are available on request. Researchers who wish to obtain further details may contact the corresponding author with a methodologically sound proposal.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Informed consent form.
[DOCX File , 117 KB - resprot_v12i1e52036_app1.docx]

Multimedia Appendix 2
Secondary outcomes.
[DOCX File , 17 KB - resprot_v12i1e52036_app2.docx]

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Abbreviations

CONSORT: Consolidated Standards of Reporting Trials
DFU: diabetic foot ulcer
mHealth: mobile health
REDCap: Research Electronic Data Capture

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Protocol

Exploring Current Practices, Needs, and Barriers for Expanding Distributed Medical Education and Scholarship in Psychiatry: Protocol for an Environmental Scan Using a Formal Information Search Approach and Explanatory Design

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Abstract

Background: Distributed medical education (DME) offers manifold benefits, such as increased training capacity, enhanced clinical learning, and enhanced rural physician recruitment. Engaged faculty are pivotal to DME's success, necessitating efforts from the academic department to promote integration into scholarly and research activities. Environmental scanning has been used to gather, analyze, and apply information for strategic planning purposes. It helps organizations identify current practices, assess needs and barriers, and respond to emerging risks and opportunities. There are process models and conceptual frameworks developed for environmental scanning in the business and educational sectors. However, the literature lacks methodological direction on how to go about designing and implementing this strategy to guide research and practice in DME, especially in the psychiatry field.

Objective: This paper presents a protocol for an environmental scanning that aims to understand current practices and identify needs and barriers that must be addressed to facilitate the integration of psychiatrists from the Dalhousie University Faculty of Medicine's distributed education sites in Nova Scotia and New Brunswick into the Department of Psychiatry, contributing for the expansion of DME in both provinces and informing strategic planning and decision-making within the organization.

Methods: This protocol adopts an innovative approach combining a formal information search and an explanatory design that includes quantitative and qualitative data. About 120 psychiatrists from 8 administrative health zones of both provinces will be invited to complete an anonymous web-based survey with questions about demographics, participants' experience and interest

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in undergraduate, postgraduate, and continuing medical education, research and scholarly activities, quality improvement, and knowledge translation. Focus group sessions will be conducted with a purposive sample of psychiatrists to collect qualitative data on their perspectives on the expansion of DME.

Results: Results are expected within 6 months of data collection and will inform policy options for expanding Dalhousie University's psychiatry residency and fellowship programs using the infrastructure and human resources at distributed learning sites, leveraging opportunities regionally, especially in rural areas.

Conclusions: This paper proposes a comprehensive environmental scan procedure adapted from existing approaches. It does this by collecting important characteristics that affect psychiatrists' desire to be involved with research and scholarly activities, which is crucial for the DME expansion. Furthermore, its concordance with the literature facilitates interpretation and comparison. The protocol's new method also fills DME information gaps, allowing one to identify insights and patterns that may shape psychiatric education. This environmental scan's results will answer essential questions about how training programs could involve therapists outside the academic core and make the most of training experiences in semiurban and rural areas. This could help other psychiatry and medical units outside tertiary care establish residency and fellowship programs.

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KEYWORDS

distributed learning sites; medical education; psychiatry; environmental scan; needs assessment; strategic plan; distributed medical education; rural area; physician; mixed methods approach; education program

Introduction

Distributed Medical Education

The need to recruit physicians into rural areas and regional centers in Canada is well-recognized. According to a report by Pong et al [1], 9.4% of all Canadian physicians were practicing in rural areas compared with 21.1% of Canadians living in rural and small towns. One approach that has been used to successfully recruit and retain trainees in underserved communities is distributed medical education (DME) [2-6]. DME was first used in postgraduate medical education (PGME) in the 1970s to recruit and retain trainees in targeted rural communities. In the intervening years, it has been widely incorporated into undergraduate medical education (UGME) and PGME [7-9]. Studies have shown that longer rural postgraduate training is strongly associated with rural practice among general practitioners [10-12]. Preliminary studies have also suggested that increased exposure to rural practice in psychiatry residency training programs may increase the number of trainees choosing to practice in these communities after graduating [13,14].

In addition to the potential benefit of recruiting physicians, rural training offers trainees unique clinical experiences and provides first-hand knowledge of the health care systems that exist in rural, small, and underserved communities located outside of the academic centers in regional or "satellite" sites [13,15]. There is also the possibility that exposure to smaller communities and community-based practice may encourage generalism [16]. The Royal College of Physicians and Surgeons of Canada defines generalism as "a commitment to a breadth of practice within one's discipline and responsiveness to patient needs" [17] and suggests that specialty training should include rotations in community-based centers in order to expose trainees to generalism and its importance. Adopting a generalist approach enables physicians to manage uncertainty, approach undifferentiated problems, and incorporate a broad understanding of disease prevalence and psychosocial context into the presenting health care concerns and management of patients [18].

While there is strong evidence regarding the value of distributed education, it is important to recognize that the successful implementation of DME involves more than simply sending trainees to distributed sites. In advance of any expansion of training, it is important to develop a comprehensive understanding of the opportunities it will provide and to identify gaps or barriers that may need to be addressed. The general standards for training programs required by external accrediting bodies must be rigorously maintained to ensure trainees can meet all required learning outcomes. In addition, attention must be paid to the quality of the experience and relationships with the local community, as these greatly influence whether a trainee eventually chooses to settle and practice within that community [8,19].

Because physicians and other professionals at distributed sites are essential to implementing DME, academic departments must be respectful and attentive as they engage and integrate distributed faculty into their teaching and scholarly activities [3,20-22]. Careful consideration of community engagement is key when developing DME programming, given the community preceptors' pivotal role in the development, delivery, and ongoing success of DME programming [20,23-27]. Navigating relationships between partners and establishing sound governance structures are essential components of successful DME [3]. Collaborative efforts must incorporate community values, attitudes, and beliefs [28], and all parties should be sensitive to potential challenges that can arise in communications between physicians practicing within the primary academic center and those practicing outside of it [29].

Organizational Context

Dalhousie University's Faculty of Medicine has 2 campuses. Dalhousie Medical School based in Halifax, Nova Scotia, Canada opened approximately 150 years ago in 1868. A regional

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campus Dalhousie Medicine New Brunswick was established in 2010 in Saint John, New Brunswick, Canada. A third distributed campus is planned and will begin accepting students in Cape Breton, Nova Scotia by 2025. Dalhousie University requires anyone completing evaluations of medical trainees to have a faculty appointment, which may be either a continuing appointment or a limited-term appointment.

Clinical training in psychiatry at Dalhousie University comprises both UGME and PGME. In Nova Scotia, there are 2 health authorities where learners may be placed for clinical rotations: IWK Health and Nova Scotia Health. IWK Health provides secondary care to children, youths, and women regionally, tertiary care provincially, and quaternary care for the Maritimes. Nova Scotia Health is divided into 4 geographic zones serving the province: eastern, western, northern, and central. The central zone includes Halifax Regional Municipality, the capital of the province and the largest urban center with a population of 440,000 in 2021 [30]. Dalhousie University's main campus is in Halifax, and this is where the main teaching hospitals are situated. The central zone also contains the majority of the province's psychiatrists. The DME located in New Brunswick provides clinical education through the Horizon Health Network. Preclinical medical education is based in Saint John, and 4 of the province's 7 administrative health zones participate in the clinical education of Dalhousie University's medical students: zones 1 (Moncton), 2 (Saint John), 3 (Fredericton and River Valley area), and 7 (Miramichi).

In both provinces, psychiatrists at distributed sites make valuable contributions to the clinical education of medical students and residents, both psychiatry and nonpsychiatry. Eventually, the department also plans to extend its recently launched international fellowship training program to DME sites in the 2 provinces.

In contrast, psychiatry residency training at Dalhousie University has been more centralized with the majority of time spent in Halifax. While Dalhousie University's psychiatry residents rotate for short periods of time through Saint John, New Brunswick, and Kentville, Nova Scotia, the residency program does not currently meet the rural training requirements as set out by the PGME office, which states 10% of postgraduate training should occur in DME learning sites. To meet this requirement, Dalhousie University's psychiatry residency program has recently expanded its training outside of Halifax to include an inpatient rotation at the Cape Breton Regional Hospital in the eastern zone in their second year of training, a geriatric experience in outpatient clinics in western zone in their third year of training, and a 3-month elective requirement in the Maritimes in their final year of training. Geriatric and child and adolescent psychiatry residency (years 5 and 6) have mandatory DME experiences in rural zones. Nonetheless, the proportion of training outside Halifax is still lower than is desirable.

Greater involvement of distributed sites also offers an opportunity for increasing the training capacity of the residency program. Recently, the Government of Nova Scotia has asked Dalhousie University's Faculty of Medicine to increase the overall number of psychiatry residency training spots in order to address existing vacancies and meet the projected needs of the growing population of Nova Scotia. Similarly, the New Brunswick government is also interested in developing a New Brunswick–based residency program to assist with recruitment and retention of psychiatrists.

These factors (educational needs, institutional requirements, and political priorities) align with the principles underpinning the Dalhousie University Department of Psychiatry's Transformational Plan, which was introduced in 2021. Through this plan, the department seeks to extend its academic mandate to enhance medical education, research, and knowledge translation activities at distributed learning sites in Nova Scotia and New Brunswick.

Environmental Scanning

This paper describes a protocol for an environmental scan of DME sites in Nova Scotia and New Brunswick where the Department of Psychiatry's faculty members are situated. With this environmental scan, we seek to understand the existing resources and determine what is required to fully integrate DME sites into the academic mandate of the Department of Psychiatry.

Environmental scanning has been used as an effective method of gathering information for a variety of purposes. It is defined as "the acquisition and use of information about events, trends, and relationships in an organization's external environment, the knowledge of which would assist management in planning the organization's future course of action" [31]. Gathering, analyzing, and applying information garnered from environmental scans are essential for strategic planning purposes and organizational effectiveness, as it assists with identifying, assessing, and responding to emerging risks and opportunities [32].

There are process models and conceptual frameworks developed for environmental scanning in the business and educational sectors [33-36]; however, the literature lacks methodological direction on how to go about designing and implementing this strategy to guide research and practice in DME. Environmental scanning is crucial in informing strategic planning and decision-making within organizations, and to the best of our knowledge, no framework has been developed to guide this methodological approach in the DME context within psychiatry training. To this end, we have developed a comprehensive environmental scan protocol built upon previous methodologies [31,37].

Methods

Study Design

This study is an environmental scan that adopts a formal information search approach [31] and an explanatory design [37], including quantitative and qualitative data. Formal information search (ie, when a deliberate or planned effort is made to obtain specific information) is often used as an environmental scanning mode [31,33]. The information search is structured according to a pre-established methodology and is focused on systematically finding and retrieving detailed information, usually from sources that ensure data quality and accuracy, in order to provide a basis for developing a decision

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or course of action [31]. The formal information search approach consists of several interrelated processes that determine the relevance of information, how it will be collected, organized, and stored, what products or services will be developed, and how it will be disseminated and used [38].

Due to the lack of standardized recommendations regarding the methodology to be used in environmental scans using a formal information search approach, the explanatory design was added. The overall purpose of this design is to collect qualitative data to help explain or build upon initial quantitative results [37]. This design starts with the collection and analysis of quantitative data followed by a subsequent collection and analysis of qualitative data.

Study Settings and Participants

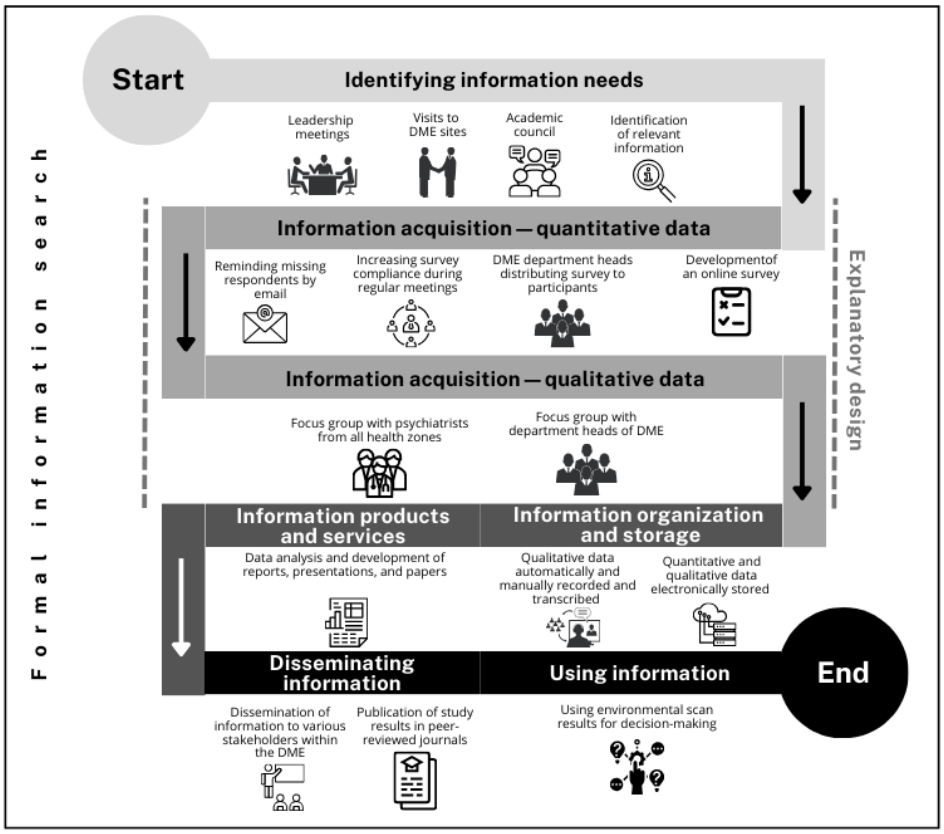
This study will include participants from the 8 administrative health zones (4 in Nova Scotia and 4 in New Brunswick) currently involved in medical education. Dalhousie University Faculty of Medicine DME sites comprise mental health and addiction treatment facilities in the eastern, western, and northern zones of Nova Scotia and 4 health zones of New Brunswick. All psychiatrists at DME sites will be targeted for inclusion in the quantitative study. Based on data obtained from limited-term faculty appointments within the Dalhousie University Department of Psychiatry, it is estimated that approximately 120 psychiatrists are working at DME sites throughout Nova Scotia and New Brunswick. The exact number of psychiatrists working in the central zone of Nova Scotia is unknown, and not all psychiatrists at DME sites in Nova Scotia and New Brunswick have Dalhousie University faculty appointments. Thus, it is difficult to estimate the exact sample size for all psychiatrists working at DME sites in the 2 provinces. A representative sample of psychiatrists working at DME sites, from each health zone in Nova Scotia and New Brunswick, will be invited to participate in the focus group discussions. Purposive sampling will be used to identify subjects for key informant interviews. The distributed sites range in size from small rural communities to medium-sized regional centers, and representing the views of faculty in both types of settings will be an important consideration.

Study Procedures and Data Collection

Overview

The procedures of the environmental scan framework will be organized according to 6 interrelated processes or phases, as proposed by Choo [31] and explained as follows. The explanatory design [37] is integrated into these processes (Figure 1).

Figure 1. Overview of the proposed environmental scan framework. DME: distributed medical education.



Identifying Information Needs

In 2022, a series of meetings were held between the leadership of the Department of Psychiatry and the Faculty of Medicine to generate possible options for increasing residency training capacity. Additionally, the head of the department of psychiatry traveled to the distributed learning sites across Nova Scotia and New Brunswick, meeting with the chiefs of the relevant zones. These tours culminated in the establishment of the Nova Scotia and New Brunswick Psychiatry Academic Council, with membership including the zone chiefs for psychiatry at 8 administrative health zones in the 2 provinces, the chief of

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psychiatry for the IWK Health authority, the directors of education and research, and the chief operating officer for the Department of Psychiatry. Items discussed during the inaugural meeting of the new Psychiatry Academic Council, which was attended by the dean of the Faculty of Medicine at Dalhousie University and the associate dean for Dalhousie Medicine New Brunswick, included the identification and refining of the categories of information that would be needed for this environmental scan. Following this consensus meeting, the categories of information identified as relevant for this environmental scan were demographics, mental health services and scope of practice, medical education, infrastructure, continuing professional development, and research and knowledge translation. These categories are depicted in the Outcome Measures section.

Information Acquisition

Information acquisition is a critical step in the environmental scan process. It involves obtaining relevant data from the right sources that can provide insights into the various factors that may impact an organization's operations, success, and sustainability. Effective information acquisition is essential for conducting a comprehensive and accurate environmental scan. Without access to reliable and relevant data, the scan may miss important trends and risks that could have significant implications for the organization. By contrast, a thorough and well-executed information acquisition process can help organizations stay ahead of emerging risks, take advantage of new opportunities, and make informed strategic decisions [38].

Following are the steps that will be taken during the information acquisition phase of this environmental scan, in which first quantitative and then qualitative data will be collected.

- Acquisition of quantitative data: Based on the information previously identified, a web-based survey was created, piloted, revised, and adopted. A link to the web-based survey will be sent to the clinical department heads for all the administrative health zones, and they will be asked to distribute the survey link to psychiatrists working within their zones. To maximize the survey response rate, engage community-based faculty, and encourage their participation in further program development, the clinical chiefs will be encouraged to set aside 15 minutes of their monthly zone psychiatrists' meetings for their psychiatrists to complete the survey. In this way, the survey can be completed as a group activity, with each psychiatrist given time to complete the survey confidentially on their personal cell phone or computer. For those not attending the meeting, a second electronic reminder will be sent out to ensure survey recipients complete the survey if they have not done so already. The web-based survey is powered by OPINIO (Object Planet), a web-based survey tool that provides a framework for authoring, distributing, and reporting surveys, which is licensed by Dalhousie University; by completing and submitting the anonymous web-based survey, participants agree to participate in this study. A brief study information leaflet and informed consent will be displayed on the initial page of the survey. The survey comprises 64 multiple-choice questions divided into 5 sections: demographics, mental health services and scope of practice, medical education, continuing professional development, and research and knowledge translation. A final section about study participation includes one question, about the willingness to participate in the focus group. The time expected for survey completion is 15 minutes.
- Acquisition of qualitative data: All the zone clinical department heads in New Brunswick and Nova Scotia will be invited by email to participate in a focus group. A second focus group will be organized for a representative sample of psychiatrists working in the zones who are not clinical department heads. For this group, an email will be sent to all the psychiatrists working at distributed learning sites (excluding the clinical department heads), inviting them to consider participating in a focus group. If interest exceeds demand, block random sampling will be used to select 2 representatives from each administrative health zone. Each of the 2 focus groups will be held over Zoom (Zoom Video Communications), recorded and transcribed verbatim. A transcriptionist will be hired to ensure the transcriptions recorded are accurate. If data saturation (ie, the point in data collection where interviews are no longer generating new information) and sufficiency (ie, that takes into account both individuality and the fact that information is shaped by social factors) [39] are not achieved following the analysis of the qualitative data collected through focus group sessions, psychiatrists who did not participate in the group sessions will be invited to participate in individual interviews until data saturation is achieved. The sample selection method for both focus group sessions and individual interviews (if needed) will involve using a purposive sample, entailing all psychiatrists to participate in the activities. The focus group guide comprises 12 questions, divided into 2 sets of 6 questions. The first set of questions addresses education, covering barriers and facilitators in establishing a distributed learning site, needs or gaps related to the proposed rotation, opportunities that a psychiatry postgraduate education site in your zone would offer learners and the local community, ways to promote and measure faculty engagement, and indicators or outcome measures for ongoing quality assurance and program improvement. The second section focuses on research and scholarship, including barriers and facilitators for establishing research programs, the connection between research and clinical care, personal benefits of research participation, methods to promote and sustain research and scholarly work at your site, and indicators or outcome measures for ongoing research initiatives. The same guide will be used in the individual interviews if those are needed.

Information Organization and Storage

During the environmental scan process, it is important to organize and store information so that it can be easily accessed and analyzed to assist with strategic planning and decision-making. When the information is collected electronically (ie, web-based surveys), the organization and storage of the information are superior because it enables easier and more efficient management of the collected large amounts of data. Electronic data can be easily organized, stored, and

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retrieved when necessary, saving time and resources. In addition, electronic data are less susceptible to errors and can be easily shared with team members who may require access. The proposed environmental scan collects quantitative data using the OPINIO platform, an electronic survey platform that enables the collection and management of survey data. OPINIO can generate reports and export data in multiple formats automatically, facilitating data analysis and visualization. Qualitative data from the focus groups and key informant interviews will be generated automatically by the Zoom platform and manually by a transcriptionist. The data will be stored on a secure drive at Dalhousie University, ensuring its safety and confidentiality. Data stored in Dalhousie University's OPINIO server and the university's secure drive are only accessible to authorized users, thereby protecting sensitive data from theft or loss.

Developing Information Products or Services

Developing information products or services entails transforming the data collected during the information acquisition and organization phases into information that can inform strategic planning and decision-making. This step involves analyzing and synthesizing the data collected during the preceding phases into products or services that the organization's decision makers can use. Examples of information products or services that may be developed during this step include reports, presentations, dashboards, and other digital or paper-based visualizations that provide clear and concise information from the environmental scan. This may also involve tailoring the information to the needs of different stakeholders (eg, department heads may require high-level summaries of the key findings, whereas program managers may require more detailed information to support program planning and implementation) [40]. This environmental scan's data analysis strategy will use descriptive and inferential statistics for quantitative data and thematic analysis for qualitative data. The analysis methodology is described in greater detail in the Data Analysis Plan section of this protocol. Following data analysis, PowerPoint (Microsoft Corp) presentations, technical reports, and papers will be prepared by the research team.

Disseminating Information

In the information products and services phase, the aim is to share the developed products or services with the environmental scan participants and other stakeholders to aid strategic planning and decision-making. By spreading information, organizations can raise awareness of critical findings and gain support for necessary actions. Communication channels such as reports, presentations, meetings, newsletters, and intranet sites can be used for internal dissemination. The key findings may also be relevant to external stakeholders, including funders, partners, and regulatory bodies, and sharing them can establish relationships and position the organization as a leader. It is crucial to evaluate the effectiveness of the dissemination procedure to ensure that the key findings have been communicated successfully. Such evaluations can identify areas of improvement for future environmental scans [31-33,38]. Findings from this study will therefore be disseminated to the academic psychiatric and medical community and health and medical education policy makers through technical reports to governments of Nova Scotia and New Brunswick, peer-reviewed publications, and regional, national, and international conference presentations.

Using Information

The use of information is the final step in the environmental scanning process. It entails several analytical and decision-making processes, such as identifying patterns and relationships in data, assessing the implications of different scenarios, prioritizing opportunities and challenges, and developing action plans to address them. To ensure that the environmental scan insights are considered from multiple perspectives, involving a diverse range of stakeholders in using the information is critical. It is also vital to regularly monitor and update the information to ensure the organization is aware of changing trends and emerging risks [41]. Findings from this environmental scan will be used in the second development phase of the expansion of DME that will involve the distributed sites in planning and preparing for potential separate-entry distributed psychiatry residency programs as well as expansion of the Canadian and International Fellowship programs to distributed learning sites in line with the Transformational Plan for the Department of Psychiatry.

Outcome Measures

The environmental scan outcome measures were identified in the initial phase of the environmental scan (ie, identifying information needs). They fall into 6 categories:

- Demographics: Participants will provide their demographic information, including their province and health zone of work, type of medical graduation, type of specialist training, academic appointment within the Department of Psychiatry at Dalhousie University, current academic rank, and gender identity.
- Mental health services and scope of practice: Information about participants' mental health service work, primary and secondary specialization or scope of practice, the practice of psychotherapy, and primary and secondary modes of payment for psychiatric services delivered.
- Medical education: This set of data comprises information about participants' formal medical education training, level of medical education qualification they have received, their knowledge and skills in medical education, areas of medical education they would like to participate in, clinical training and supervision of learners they currently participate in, years of experience providing clinical training or supervision to medical learners, familiarity with the Royal College of Physicians and Surgeons of Canada Competency by Design for residency training, and availability to participate in formal training to facilitate involvement in psychiatry residency training.
- Infrastructure: Opinions on the infrastructure and team set-up for psychiatry resident training, as well as the willingness to participate in clinical training and supervision, offer lectures or skill-based teaching to psychiatry residents and evaluate their skills through skill-based examinations. The barriers that hindered the respondents from contributing to the training and

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supervision of psychiatry residents, as well as the potential benefits of having psychiatry residents train on their service, will also be assessed.
- Continuing professional development: The frequency of attendance to the Department of Psychiatry weekly academic grand rounds and the participants' interest in attending and presenting in the grand rounds will be measured. Participants will also be asked about past and future participation in professional development programs organized by the Department of Psychiatry.
- Research and knowledge translation: The survey will assess the respondents' formal research training, level of research qualification received, interest in exploring opportunities for formal research training, and participation in current and preferred mental health or clinical translational research. The survey also assessed the barriers the participants perceived would hinder psychiatrists from participating in research and knowledge translation activities.

Data Analysis Plan

Data analysis will take place immediately after the phase of information organization and before the development of information products and services.

Quantitative data will be analyzed with SPSS (version 28; IBM Corp) using descriptive and inferential statistics. Demographic data and responses to selected questions will be summarized and presented as numbers and percentages. Depending on the outcome of the descriptive analysis, the chi-square test will be used to assess differences in responses between participants based on their province of work or administrative health zones. Binary or multinomial logistic regression analysis may be used to identify key barriers and enablers for expanding UGME and PGME, continuing medical education, research and knowledge translation at distributed learning sites.

Qualitative data will be analyzed thematically using the NVivo software (version 12; QSR International). Thematic analysis, commonly used in qualitative research, draws upon grounded theory [42] and content analysis [43]. Thematic analysis will be used for identifying and reporting on the major ideas expressed. Initially, transcribed data will be independently coded for themes by 2 investigators. These codes will be reviewed and revised jointly by the 2 investigators through a consensus process and then reapplied to the documents. Themes and subthemes will be created for identified barriers and facilitators for the expansion of UGME and PGME, continuing medical education, research and knowledge translation at distributed learning sites. Verbatim quotes from participants for each of the themes will be provided.

Ethical Considerations

This protocol has been submitted to the Dalhousie University Research Ethics Board and received an exemption from Research Ethics Board oversight according to the Tri-Council Policy Statement Ethical Conduct for Research Involving Humans article 2.5 [41]. Prior to completing the web-based surveys, all participants provided explicit consent. The informed consent presented on the initial page of the web-based survey included an explanation of the voluntary and anonymous nature of participants' participation in the study with a particular emphasis on the use of their data for research purposes covering primary and secondary data analysis.

Results

At the time of paper submission, it was anticipated that the findings from this environmental scan would be available within 6 months from the start of data collection. Fortunately, this timeline has been successfully achieved since data collection took place in February and March 2023, and the data have been thoroughly analyzed. One paper, focusing on results related to the psychiatrists' willingness to participate in scholarly activities, was submitted to a peer-reviewed journal in September 2023. Another paper, which delves into the psychiatrists' willingness to engage in academic research activities, is currently under review by the authors and is scheduled for submission to a peer-reviewed journal by the end of this year, with an anticipated publication date in the upcoming year. Study findings will be used to inform the development of policy options and decisions related to the expansion of the psychiatry residency and fellowship training opportunities at DME sites in Nova Scotia and New Brunswick. Options developed and decisions made during the second development phase will be based on information gathered during this initial or information-seeking phase and stakeholder agreements. With this project, we seek to develop an in-depth understanding of existing needs and factors that must be addressed to ensure the success of the proposed expansion of Dalhousie University’s psychiatry residency and fellowship programs using the infrastructure and human resources at distributed learning sites. By identifying challenges and opportunities in advance of the expansion of psychiatry training into a rural area and defining outcome measures to be tracked over time, it will be possible to design and implement processes and structures that will enhance the educational experience of residents and fellows, encourage faculty engagement, and facilitate ongoing program improvement.

Discussion

This paper describes a protocol for conducting an environmental scan at Dalhousie University's DME sites within the Departments of Psychiatry in Nova Scotia and New Brunswick. It seeks to assess existing resources and determine the necessary steps for the expansion and incorporation of DME sites within the academic framework of the Department of Psychiatry. The chosen method was environmental scanning, well-known for its efficiency in gathering information. Nevertheless, none of the existing frameworks have been designed specifically to guide DME research in psychiatry. As a result, this paper presents a comprehensive environmental scan protocol developed by adapting existing methodologies, combining a formal information search strategy with an explanatory design that includes quantitative and qualitative data.

The protocol holds several strengths that considerably enhance its efficacy and potential impact. Its comprehensive approach facilitates the collection of key factors relating to psychiatrists' willingness to engage in research and scholarly activities, which

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are essential for the expansion of DME. By incorporating diverse viewpoints and experiences, the protocol comprehensively represents the target population. In addition, its consistency with the existing literature provides a firm foundation for interpreting findings and making meaningful comparisons. In addition, the protocol's innovative approach effectively resolves information gaps in the DME field, providing a unique opportunity to discover insights and trends that may influence the future of psychiatric education.

However, it is essential to acknowledge certain limitations of this protocol. Sample selection methods are dependent on the participation and availability of psychiatrists. While efforts will be made to invite all eligible psychiatrists, logistical obstacles or scheduling conflicts may limit the sample size. Another limitation is the use of self-reporting surveys and focus group sessions for data collection. Participants may provide socially desirable responses or incorrect information. In addition, the collected data are contingent on the participants' perceptions, which may not accurately reflect the situation. Despite the protocol's comprehensive data collection and analysis approach, it does not account for unanticipated variables such as health care policy or socioeconomic conditions that may influence the results.

Insights gained from this project will be used to enhance the quality and delivery of DME in Nova Scotia and New Brunswick. In addition, the information gathered will help answer important and timely questions regarding how training programs can engage psychiatrists outside the academic center and optimize semiurban and rural training experiences. This may be valuable information for other psychiatry and medical departments wishing to expand their residency and fellowship programming beyond tertiary care centers.

Data Availability

The data sets generated during or analyzed during this study are available from the corresponding author upon reasonable request.

Authors' Contributions

LH, RdLD, and VIA wrote the original paper. LH, RdLD, ME, PT, NS, AN, S Satyanarayana, S Siddhartha, PA-B, FR, HM, GG, MB, DP, OC, AR, AM, and VIA developed the methodology. RdLD created Figure 1. LH, RdLD, ME, PT, NS, AN, S Satyanarayana, S Siddhartha, PA-B, FR, HM, GG, MB, DP, OC, AR, AM, and VIA reviewed and edited the paper. All authors have read and agreed to the published version of the paper.

Conflicts of Interest

None declared.

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Abbreviations

DME: distributed medical education
PGME: postgraduate medical education
UGME: undergraduate medical education

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Protocol

Minimally Invasive Posterior Spinal Nonfusion Surgery in Patients With Adolescent Idiopathic Scoliosis Using a Bipolar One-Way Self-Expanding Rod System: Protocol for a Single-Center Clinical Cohort Study

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Abstract

Background: The current surgical treatment for patients diagnosed with progressive and severe adolescent idiopathic scoliosis (AIS) consists of the correction of the spinal curvature, followed by posterior spinal fusion (PSF). However, research has uncovered short- and long-term complications of posterior spinal fusion in patients with AIS. Minimally invasive growing rod techniques have successfully been used to treat patients with early-onset scoliosis and neuromuscular scoliosis. It may be questioned if minimally invasive posterior spinal nonfusion (PSnF) surgery with bipolar instrumentation can be used for the treatment of AIS.

Objective: This study will be performed to monitor the efficacy and safety of PSnF surgery by using a commercially available Conformité Européenne-certified spinal implant consisting of bilateral bipolar one-way self-expanding rods (OWSER) for the treatment of patients diagnosed with AIS.

Methods: In 14 selected patients with AIS with Lenke 1-6 curves, minimally invasive PSnF surgery with the OWSER system is performed after the failure of conservative treatment (curve progression of >5° within 1 year). The patients are over 7 years of age, with a major Cobb angle of ≥30°, sufficient flexibility, and a Risser stage of ≤2. Patients will be followed over time, according to the standard medical care. Efficacy will be measured using radiological and patient satisfaction assessments and safety will be determined by the amount of perioperative complications.

Results: Patient inclusion started on November 17, 2021 and we hope to finalize patient inclusion by the beginning of 2025. The first results will be expected by the beginning of 2024.

Conclusions: Minimally invasive PSnF in patients with AIS is presented as a less invasive surgical technique that prevents the progression of the scoliotic curve and that allows minor posture correction of coronal imbalance. This will be the first study to examine whether the PSnF bipolar OWSER instrumentation will be the next generation of surgical instrumentation in AIS.

Trial Registration: ClinicalTrials.gov NCT04441411; https://clinicaltrials.gov/study/NCT04441411

International Registered Report Identifier (IRRID): DERR1-10.2196/47222

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KEYWORDS

adolescent idiopathic scoliosis; minimally invasive; nonfusion; posterior spinal surgery; protocol; one-way self-expanding rod; scoliosis; idiopathic scoliosis; spinal fusion; spinal deformity surgery; nonfusion techniques; surgery; intraoperative; surgical technique; operation; musculoskeletal; orthopedic

Introduction

Adolescent idiopathic scoliosis (AIS) is a 3D deformity of the spine that is clearly associated with the adolescent growth spurt [1]. Up to 10% of patients diagnosed with AIS require some form of treatment, and almost 0.3% will eventually undergo corrective spinal surgery [2]. When the scoliotic curve exceeds 40° to 45°, surgical correction followed by posterior spinal fusion (PSF) is regarded as the standard surgical treatment for AIS [3,4].

Both short- and long-term complications of PSF have been described in relation to AIS, such as spinal imbalance, implant failure, infection and wound complications, degenerative disk disease (16%), postoperative pain, distal adding-on, and proximal junctional kyphosis [5-10]. These complications all result in additional treatment or possibly a reduced quality of life. Therefore, there is a need for a type of minimally invasive spinal surgery that allows natural growth, enables spontaneous spinal balance correction and prevents full spinal fusion to improve the outcomes of patients with AIS.

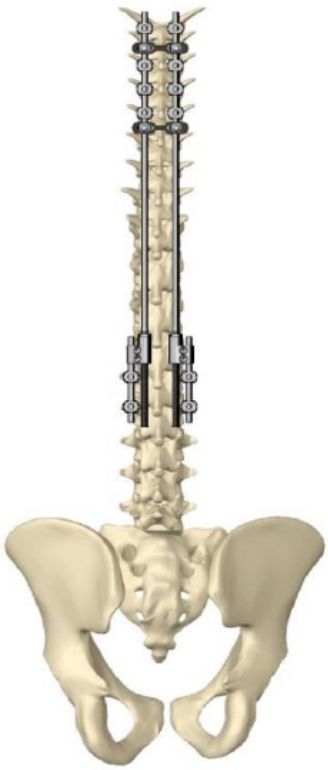
Minimally invasive nonfusion spinal surgery in AIS is not new. Anterior vertebral body tethering and a concave distraction technique (ApiFix) have been used as nonfusion techniques in patients with AIS, although with mixed results and high complication rates [11-13]. In spinal deformity surgery, nonfusion techniques with growing rods have been used for patients diagnosed with progressive early-onset scoliosis (EOS) or neuromuscular scoliosis (NMS) [14-16]. The rods function as an “internal brace” of the spine and aim to control or reduce spinal deformity. These minimally invasive nonfusion surgical techniques have been developed to limit the progression of the curve and to improve the thoracic volume while allowing the spine and thorax to grow along with the natural growth of the patient [17].

Proposed Surgical Technique

The surgical treatment described in this protocol is the standard treatment protocol for scoliosis surgery, including perioperative antibiotic prophylaxis, a supine position on the spine table, and intraoperative motor-evoked potential (MEP) and somatosensory-evoked potential (SSEP) monitoring. Traction is applied to the patient’s head using a Mayfield skull clamp, and distal traction (10% to 15% of body weight) is applied with boots on the legs to achieve intraoperative correction. The level of instrumentation is determined according to the principles developed by Lenke [18,19].

A total of 2 short 5-10–cm midline incisions are placed over the high thoracic and thoracolumbar anchor points. In the high thoracic region, 4 pedicle screws are placed. Additionally, 2 transverse process hooks are placed at the upper-level vertebra to prevent proximal junction kyphosis. At the thoracolumbar anchor region, 4 pedicle screws are placed, including a short rod on both sides (Figure 1).

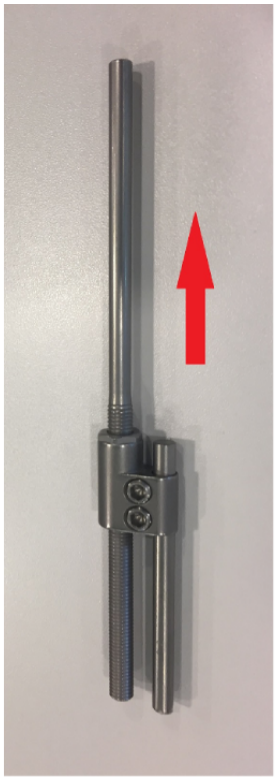
Figure 1. Example of NEMOST growing domino and E-SPINE system construct.



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The one-way self-expanding rods (OWSERs) and domino is a CE-marked commercially available form of instrumentation registered as a NEMOST rod (E-SPINE, Euros; corresponding certificate: N°CE639319; Figure 2).

Figure 2. The one-way self-expanding rod (OWSER) and domino registered as NEMOST rod.



The OWSER is inserted into the subfascial plane between the 2 incisions from the caudal to the cranial region, guided by a cranio-caudal introduced chest tube under the superficial fascia. Subsequently, the OWSERs are fixed to the cranial anchors with an additional cross connector between the 2 rods. After the insertion of the rod, a moderate concave distraction is performed before the OWSER is connected to the laterally positioned small smooth thoracolumbar rods.

The initial correction of the scoliotic curve is obtained via intraoperative traction. The sagittal plane correction is obtained as a result of kyphotic rod contouring before rod insertion. The notched ratchet part of the rod, including the temporarily fixed domino connector that is positioned downward, remains straight to allow future elongation. The one-way self-expanding domino connector slides passively and gradually (1-mm step ratchet) along the notched part of the long rod. Rotation of the rod in the domino connector is prevented by a flat part of the notched rod (Figure 2). Postoperatively, patients have unrestricted mobilization during normal daily activities. Patients have follow-up appointments that adhere to the standard protocol of postoperative scoliosis care (Table 1).

Table 1. Scheme used during clinical care in children treated with nonfusion one-way self-expanding rods.

	Screening (1-2 months preoperative)	30 days preoperative	Preoperative	Postoperative clinic	2 months post surgery	Every 6 months postoperative till 2 years after skeletal maturity
Explanation providing informed consent	✓					
Sign informed consent		✓				
Examination treating MD		✓			✓	✓
X-rays	✓		✓	✓	✓	✓
Clinical picture spine (standing position)		✓				✓
SRS[a] questionnaire		✓			✓	✓

[a]SRS: Scoliosis Research Society.

The minimally invasive nature of the procedure, combined with the system's ability to allow the patient's natural growth while working as an internal brace, holds promise for improvement in the treatment of progressive AIS. This aligns with earlier

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results that have been shown for patients with NMS and EOS [14,20].

To the best of our knowledge, a minimally invasive posterior spinal nonfusion (PSnF) surgery with OWSER has not previously been used in patients with AIS.

This study describes a study protocol for a clinical trial. This study aims to evaluate the efficacy and safety of a nonfusion bipolar self-expanding rod system, here referred to as the "nonfusion OWSER system," in the surgical treatment of patients with progressive AIS. Based on the positive surgical results and relatively low complication rates found when this type of system is used in patients with NMS or EOS [14,16,20], we hypothesize that the minimally invasive surgery using the nonfusion one-way self-expanding rod system (nonfusion OWSER) system is safe and efficient for the surgical correction of progressive AIS.

Methods

Ethical Considerations

The study protocol (version 3, October 29, 2021) describes a single-center cohort study. Ethics approval was granted by the Medical Ethical Committee of the Amsterdam University Medical Center (UMC) in the Netherlands, on May 20, 2020 (METC 2020_023, NL67124.018.19). Due to the COVID-19 pandemic, we were unsure if the study would be able to continue. This has led to a delay in the publication of this study protocol. This study will be conducted according to the principles of the Declaration of Helsinki (2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO). It is registered in the Dutch trial register (NL8659) and the international trial register (NCT04441411). On October 14, 2023, a total of 5 patients have been included in the prospective study.

Participants

All patients will be recruited by 1 single surgeon embedded in a multidisciplinary scoliosis team in the Amsterdam UMC in the Netherlands. Both patients and patients' legal guardians must sign an informed consent form before the patient is included in the study. The inclusion criteria are (1) a diagnosis of AIS, (2) an age of >7 years, (3) a primary Cobb of >30°, (4) failed nonoperative treatment, (5) a Risser grade of ≤2 and a skeletal age of hand and wrist x-rays of ≤14 years, (6) a nonrigid curve, (7) all Lenke types, and (8) no previous spinal surgery.

A patient who meets any of the following criteria will be excluded from participation in this study: (1) nonidiopathic scoliosis: musculoskeletal or neurologic conditions responsible for the cause of the spine curvature (ie, neuromuscular, congenital, or syndromic scoliosis); (2) history of previous spine surgery; (3) Risser grade >2; (3) disease or deformity likely to affect the stability of the device (ie, inadequate anatomy of pedicles, trauma or tumor in fixation region, severe osteoporosis, bone destruction, or poor bone quality); (4) nonreducible scoliosis; (5) known allergy or intolerance to one of the device material; (6) acute or chronic infections, local or systemic; (7) absence or insufficiency of covering tissues; or (8) pathological obesity.

Data Collection and Statistical Analyses

Data will be collected at baseline, directly post surgery, after 2 months, and every 6 months after the operation until 2 years after skeletal maturity (see Table 1).

To describe the included patient group, patient characteristics such as age at surgery, sex, height, weight, medical and surgical history, blood loss during surgery, operative time, length of hospitalization, upper and lower level of fixation, short- and long-term complications (surgical site infections, neurological complications, implant failure, proximal junctional kyphosis, etc), and when applicable, secondary surgery (including the time between the first and second surgery) will be extracted from the patient's medical record. The data will be summarized in tables listing the mean, SD, median, minimum, maximum, and number of subjects for continuous data or in tables listing the quantities and percentages for categorical data, where appropriate.

For the primary goal, to analyze the efficacy of OWSER, the correction of the scoliotic curve will be measured by comparing the preoperative and postoperative Cobb angle with the Cobb angle 2 years after maturity. Radiological parameters will be measured by an orthopedic resident, trained to measure all radiological parameters. Measurements will be randomly verified by a senior experienced spine surgeon. Measured radiological parameters include the main Cobb angle (measured as defined by Cobb [21]), compensatory Cobb angle, correction after surgery, sagittal balance (thoracic kyphosis, lumbar lordosis, and proximal and distal junctional angle), pelvic parameters (pelvic obliquity, sacral slope, pelvic incidence, and pelvic tilt), Risser sign, and vertebral rotation based on full spine standing posterior-anterior and lateral radiographs. Differences between the Cobb angles and growth will be analyzed using repeated ANOVA measures. To correct for possible confounders, a mixed-model regression analysis will be performed including age at surgery, Risser sign, weight, and sex.

Patient satisfaction and function will be assessed using patient appearance (shoulder imbalance and pelvic imbalance) and patient-reported outcome measurements using the Scoliosis Research Society's-22r (SRS-22r) questionnaire. This questionnaire is provided in Dutch and the use of the questionnaire has previously been validated [22]. The safety of the surgical device will be monitored and registered based on (serious) adverse events and complication rates. Radiological and patient-related outcomes will be used to assess the clinical outcomes and with this, the efficiency of the implant. These parameters will be measured at every follow-up moment (Table 1).

In case of missing values at the follow-up, the patient will remain included in the study. Based on the amount of missing values, the patients will be excluded from the calculations from the specific follow-up moment. This will be described in the results section of the specific study. A P value of <.05 will be regarded as statistically significant.

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Adverse Events

Adverse events (AEs) and serious adverse events (SAEs) are documented according to the definition of the Dutch Ethics Committee and will be acted on accordingly. AEs are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the investigational product. These will be actively reported by the subject or observed by the investigator or his staff. All AEs will be recorded throughout the study, and their severity and relation to the investigational device will be determined.

SAEs are documented as any untoward medical occurrences or effects that result in death, are life-threatening (at the time of the event), require hospitalization or the prolongation of existing inpatients' hospitalization, in persistent or significant disability or incapacity, are congenital anomalies or birth defects, or involve any other important medical events that did not result in any of the outcomes listed above due to medical or surgical interventions but that could have been based upon appropriate judgment by the investigator.

The research and treatment team must report any SAEs via telephone or email correspondence within 24 hours after the occurrence of the event to the principal investigator and the delegated medical board of directors. A completed initial SAE report must be sent, as indicated in the study's case report form.

Data Management

All data will be handled confidentially according to the General Data Protection Regulation (GDPR) guidelines. Research subjects will receive a 3-digit ID number upon beginning the study. One patient identification log (Castor electronic data capture will be maintained separately to identify the research subjects and will only be accessible to the principal investigator and the project leader.

Sample Size

To perform a sample size analysis, we compared our study to the study conducted by Miladi et al [23]. The sample size calculation is based on an ANOVA analysis and calculated using the statistical program G*Power (Heinrich-Heine-Universität Düsseldorf) [24,25].

Miladi et al [23] reported the results from the precursor of our OWSER system from the higher thoracic spine to the pelvis in 100 patients with NMS. The mean Cobb angle improved from 89° (range, 25°-149°) to 35° (range, 6°-53°) 3 years after surgery [23]. No SDs were reported. In light of this study, we expect a Cobb angle of 35° at maturity. To use these numbers for the sample size calculation, we assumed a normal distribution of the data; as such, the SDs of the preoperative Cobb angle were 31 and 11.75 for the postoperative Cobb angle [26]. We assumed a correlation of 0.5 and an effect size of 0.4 based on the correction described by Miladi et al [23]. The sample size calculation indicated that 12 patients ought to be included to examine the significant difference between the preoperative Cobb angle and the Cobb angle at the latest follow-up (power: 80%, significance level: 0.05).

Additionally, 20% more patients were included to account for a possible loss of subjects in the follow-up. In conclusion, the highest sample size indicated was 12; therefore, the minimal sample size needed for this study to address the primary goal is 14 patients. After the inclusion is completed, a post hoc power analysis will be performed to conclude if a significant number of patients is included in the study.

Results

Patient inclusion started on November 17, 2021, and we hope to finalize patient inclusion by the beginning of 2025. The first results will be expected by the beginning of 2024. On October 14, 2023, a total of 5 patients have undergone surgical correction with the proposed surgical technique. We aim to publish the 2-year results of these patients in May 2024.

Discussion

Principal Findings

Currently, all patients with AIS and diagnosed with curves exceeding 40° to 45° are recommended surgical correction followed by PSF to fix the patients' spine for the rest of their lives [2,3]. In this study protocol, we describe a protocol to investigate the safety and efficacy of a minimally invasive posterior bipolar nonfusion OWSER for the surgical treatment of patients diagnosed with AIS.

The concept of PSnF for scoliosis surgery is not new. For patients diagnosed with EOS and NMS, multiple successful PSnF options are available and are currently regarded as the standard surgical treatment [16]. However, to the best of our knowledge, this concept has not been used in patients diagnosed with AIS.

The aim of this prospective study is to determine the efficiency and safety of the implant by analyzing radiological parameters (primarily Cobb angle), patient satisfaction scores, and complication rates. The expected primary benefit of this surgical technique is an efficient surgical correction of the Cobb angle without PSF. Because of the minimally invasive character of the surgical procedure, the spinal structures of the apex of the curvature between the thoracic and lumbar anchor points are not altered. Although some cases of auto-fusion have been described when using minimally invasive surgery [14], to the best of our knowledge, no complete full spinal fusion will occur. This might only allow the removal of the nonfusion OWSER at the end of spinal growth in patients in which the curve remains stable for a longer period of time and remains under 30° [27]. In addition, the system allows for a natural correction of the spinal deformity while the correct balance and alignment of the spine are maintained. Because of its self-expanding function, the system allows the patient to follow its final natural growth while functioning as an "internal brace." Finally, due to the minimally invasive nature of the surgical procedure, the overall surgical time and general anesthesia time will be reduced, and the scar length can be limited to two scars that are 5-10 cm in length at the thoracic and lumbar fixation level.

For patients diagnosed with NMS, the positive long-term results of a nonfusion OWSER were described by Gaume et al [20] in 2021. The original nonfusion OWSER provides instrumentation for NMS from T1 to the sacrum. In patients with AIS, however,

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instrumentation is only needed for the length of the structural curve. Therefore, we suggest inserting the notched rod at the end of the caudal part of the construct. Hereby, the thoracolumbar approach is performed using a smaller incision. The OWSER instrumentation elongates and corrects the deformity spontaneously alongside the natural growth of the patient, allowing spinal balance correction; it does not touch the apex vertebrae of the spinal curvature and prevents complete PSF. The OWSER instrumentation can be considered an "internal brace."

Although positive long-term results have been published following PSnF surgery in patients with NMS, complications have been recognized. Gaume et al presented their preliminary results of the use of a minimal invasive OWSER for the treatment of patients with NMS. They found an overall complication rate of 38% (n=8), consisting of 14% (n=3) mechanical complications and 24% (n=5) infectious complications [20]. Although these complication rates seem high, compared to the traditional growing techniques, there is an important decrease in complication rates [28].

All of the included patients were fixed from the high thoracic level up to the pelvis. Our patient population will arguably be fixed over a shorter number of vertebrae, lowering the amount of force distributed over the system. In addition, Gaume et al [20] found a postoperative infection rate of 24% (n=5) directly post surgery. In postoperative patients diagnosed with AIS, this would be unacceptable. However, these results cannot be directly translated to our patient population, as it is known that patients with NMS have poor general status [29]. This makes them more prone to infectious complications as compared to the healthy patients with AIS who will be included in this study.

Other possible complications are an inherent part of spinal surgery, such as intraoperative cardiologic complications and neurological complications. The risk of neurological complications will be minimized using intraoperative neuromonitoring via both MEP and SSEP during the surgical procedure. All AE and SAE are monitored based on the guidelines of the Dutch Ethics Committee, and will help determine the safety of the proposed surgical technique.

The absence of a control group could be seen as a potential limitation. In this study, we do not have a control group as we focus on the efficiency and safety of the surgical device. If the device is proven to be efficient and safe, a follow-up will be proposed to compare the postoperative results between the nonfusion OWSER system and the traditional PSF. In addition, this would allow us to discuss the cost-effectiveness of the PSnF surgery compared to the traditional PSF surgery.

Conclusions

In conclusion, this study is designed to evaluate the efficiency and safety of the surgical treatment with a bilateral bipolar OWSER implant in patients with progressive AIS. We hypothesize that the system is safe and efficient in the surgical treatment of AIS, while it serves as an "internal brace," allowing the patients to follow their natural growth and individual balance. To the best of our knowledge, this is the first study to investigate the potential efficacy and benefits of the use of the nonfusion OWSER in patients diagnosed with AIS who failed conservative treatment.

Data Availability

The data sets generated and analyzed during this study are not publicly available due to the fact that the study has not been finalized and data collection has not been completed yet, but are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

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Abbreviations

AE: adverse event
AIS: adolescent idiopathic scoliosis
EOS: early-onset scoliosis
GDPR: General Data Protection Regulation
MEP: motor-evoked potential
NMS: neuromuscular scoliosis
nonfusion OWSER: nonfusion one-way self-expanding rod system
OWSER: one-way self-expanding rods
PSF: posterior spinal fusion
PSnF: posterior spinal nonfusion
SAE: serious adverse event
SRS-22r: Scoliosis Research Society's-22r
SSEP: somatosensory-evoked potential
UMC: University Medical Center

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Protocol

Comprehensive Ontology of Fibroproliferative Diseases: Protocol for a Semantic Technology Study

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Abstract

Background: Fibroproliferative or fibrotic diseases (FDs), which represent a significant proportion of age-related pathologies and account for over 40% of mortality in developed nations, are often underrepresented in focused research. Typically, these conditions are studied individually, such as chronic obstructive pulmonary disease or idiopathic pulmonary fibrosis (IPF), rather than as a collective entity, thereby limiting the holistic understanding and development of effective treatments. To address this, we propose creating and publicizing a comprehensive fibroproliferative disease ontology (FDO) to unify the understanding of FDs.

Objective: This paper aims to delineate the study protocol for the creation of the FDO, foster transparency and high quality standards during its development, and subsequently promote its use once it becomes publicly available.

Methods: We aim to establish an ontology encapsulating the broad spectrum of FDs, constructed in the Web Ontology Language format using the Protégé ontology editor, adhering to ontology development life cycle principles. The modeling process will leverage Protégé in accordance with a methodologically defined process, involving targeted scoping reviews of MEDLINE and PubMed information, expert knowledge, and an ontology development process. A hybrid top-down and bottom-up strategy will guide the identification of core concepts and relations, conducted by a team of domain experts based on systematic iterations of scientific literature reviews.

Results: The result will be an exhaustive FDO accommodating a wide variety of crucial biomedical concepts, augmented with synonyms, definitions, and references. The FDO aims to encapsulate diverse perspectives on the FD domain, including those of clinicians, health informaticians, medical researchers, and public health experts.

Conclusions: The FDO is expected to stimulate broader and more in-depth FD research by enabling reasoning, inference, and the identification of relationships between concepts for application in multiple contexts, such as developing specialized software, fostering research communities, and enhancing domain comprehension. A common vocabulary and understanding of relationships among medical professionals could potentially expedite scientific progress and the discovery of innovative solutions. The publicly available FDO will form the foundation for future research, technological advancements, and public health initiatives.

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KEYWORDS

fibroproliferative disease; fibrosis; fibrotic disease; ontology; OWL; semantic technology; Web Ontology Language

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Introduction

Fibroproliferative Diseases

Fibroproliferative wound healing, a process that can disrupt normal organ development and lead to increasing fibrosis and eventual organ failure, can affect nearly all organs and tissues. These fibroproliferative or fibrotic diseases (FDs) [1], including lung fibrosis, liver cirrhosis, atherosclerosis, keloids, progressive renal diseases, and systemic sclerosis, represent one of the most prevalent age-related illnesses, impacting over 800 million individuals worldwide [2]. They contribute to over 40% of mortality in developed nations [3,4], a rate that is anticipated to rise with the aging global population, signifying a growing public health concern.

Despite their significance for public health, FDs have received limited attention in both policymaking and research. While these conditions share fundamental biological processes, they are seldom approached collectively in either in vitro studies or clinical settings, constraining effective investigation of shared mechanisms and hindering the formulation of comprehensive public health policies and adequate clinical care [5].

A PubMed search conducted on November 5, 2022, yielded 140, 1674, and 369,557 records for the terms *fibroproliferative diseases*, *fibrotic diseases*, and *fibrosis*, respectively. However, these numbers are inflated by the inclusion of conditions such as *cystic fibrosis*, which is not an FD.

Significant advances have been made in recent years in understanding the molecular details of fibrosis [6,7], the causes and potential therapeutic approaches of various fibroproliferative disorders [8], and in accumulating genomic data on FDs [9]. Insights into epigenetic changes [10], noncoding RNA's role in fibrosis [11], and the escape of fibroblasts from apoptosis [12] have also been unveiled. Promising therapeutic agents, such as dioscin for liver fibrosis and thalidomide and etanercept for lung fibrosis [13,14], are under investigation. Nevertheless, knowledge gaps remain, particularly in areas such as cardiac fibrosis [15], and efficient antifibrotic therapies are still lacking.

The vast and expanding data on FDs remain largely unsystematized and scattered, limiting our understanding of fibrosis mechanisms and hampering the development of comprehensive therapeutic strategies to target fibroproliferative processes.

Ontology on Fibroproliferative or Fibrotic Diseases

In the realm of information technology, an ontology formally defines entities, classes, and relations, providing a structured representation of a knowledge domain [16,17]. In the context of FDs, this domain extends beyond disease nomenclature to encompass hierarchical structures, relationships between diseases, and a host of associated biomedical concepts, such as wound healing pathologies, epithelial-mesenchymal transitions, collagen deposition, involved pathways, genes, proteins, and external factors [18]. Consequently, the FD domain represents a multidimensional and multilevel ecosystem of data, information, and knowledge.

While ontologies have been developed for FD subgroups, such as the classification of fibrotic interstitial lung diseases by Ryerson et al [18] and cross-disease analyses of genetic underpinnings and implicated pathways [19-21], a comprehensive ontology encapsulating the full spectrum of fibroproliferative disorders remains lacking. This contrasts with efforts in other medical fields, such as the National Cancer Institute Thesaurus [22,23].

Clinical ontologies, like the Systematized Nomenclature of Medicine–Clinical Terms (SNOMED CT) [24-26], serve crucial roles in automating decision support tools, standardizing clinical research databases, and ensuring semantic interoperability. In the emerging field of biomedical informatics, domain ontologies enable the structured representation of concepts and entities and their relationships, forming a conceptual scaffold for domain-specific terminologies. These ontologies can be harnessed for tasks such as reasoning, inference, process identification, software enhancement, and community engagement [27-29].

Despite its potential for accelerating scientific progress and enabling novel solutions, no public FDO currently exists. Our review of the MEDLINE, PubMed, and BioPortal databases and the European Molecular Biology Laboratory-European Bioinformatics Institute (EMBL-EBI) Ontology Lookup Service confirmed this lack of a dedicated ontology for FDs [30,31].

Thus, we aim to create and disseminate an FDO as a public resource, fostering collaboration and enabling future development and refinement. This FDO targets several key objectives: sparking interest among stakeholders, facilitating public health initiatives, and supporting knowledge representation, information retrieval, data integration, health information systems, and biomedical research. We believe that a comprehensive FDO will equip researchers and clinicians to navigate the FD domain efficiently and contribute to the evolution of research and therapeutic strategies.

Methods

In the following, we detail the methodology for the development of a comprehensive domain-specific ontology of FDs.

Development of the Fibroproliferative Disease Ontology

The development of the fibroproliferative disease ontology (FDO) will use a top-down approach, starting with the most abstract concepts within the FD domain and then progressively refining toward specific subconcepts. This process integrates (1) findings from our comprehensive literature survey, which includes the results of scoping reviews (detailed subsequently); (2) a review of key classification systems, including the International Classification of Diseases 11th Revision (ICD-11) of the World Health Organization (WHO) SNOMED CT, and Unified Medical Language System (UMLS) Metathesaurus [32], where pertinent; and (3) the significant expertise of experienced clinicians and researchers in the fields of medicine, biomedical informatics, and public health, notably those previously involved in the large-scale Seventh Framework Program of the European Union (FP7-EU) project Resolve

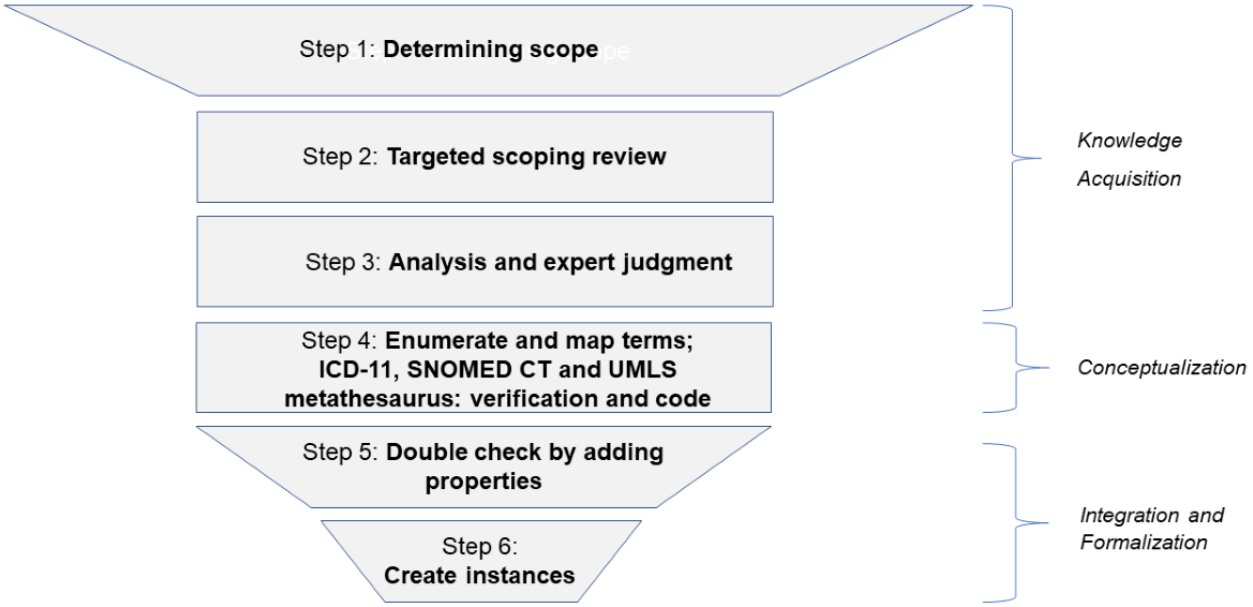
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Chronic Inflammation and Achieve Healthy Aging by Understanding Non-regenerative Repair (RESOLVE) [1]. The ontology will be constructed using the Protégé ontology editor [33] in the Web Ontology Language (OWL) format [34].

The iterative steps for the FDO creation, illustrated in Figure 1, consist of 4 core building blocks (Figure 2) to be systematically applied:

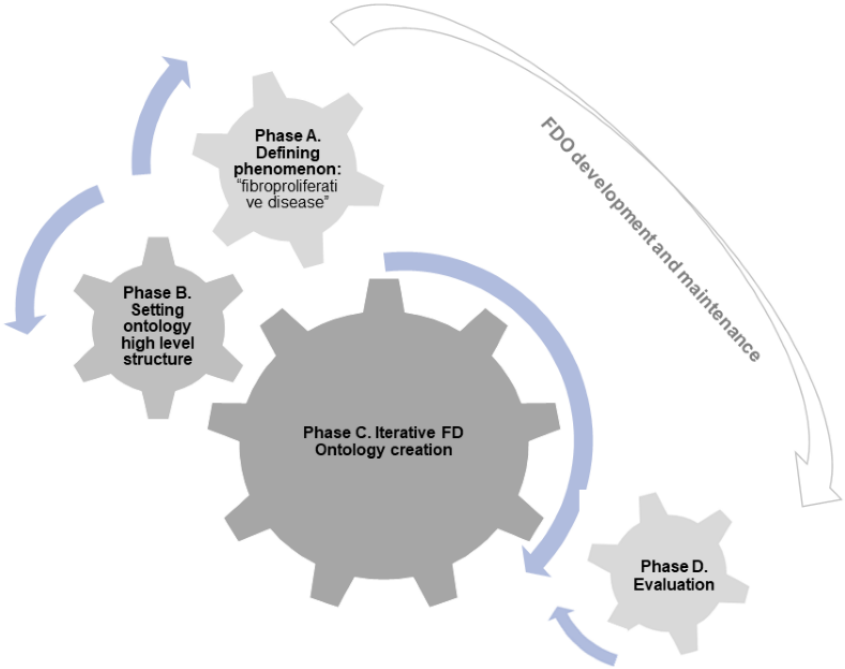
- Building block A will see the expert team delineate the concept of FD, informed by scoping review results and their own professional insight. Here, characteristics specific to FD, including data properties like extracellular matrix (ECM) and collagen deposition and the epithelial-mesenchymal transition (EMT) phenomenon, will be specified. To capture the breadth of the FD phenomenon, the scope will span a range of major biomedical concepts, enriched with synonyms, definitions, and references as driven by scoping review findings and expert judgment. Adherence to SNOMED CT terms and granularity will be sought where feasible, with exceptions made where evidence necessitates exceeding this frame. These defining concepts will be integrated into the FDO as data and object properties unless decided otherwise.
- Building block B focuses on determining the FDO's overall scope, envisioned to encapsulate key categories of FD. Hence, the high-level structure will pivot around body systems and organs, for example, FD of the respiratory system, cardiovascular system, skin, or eye.
- Building block C, contingent on the completion of blocks A and B, will oversee the iterative FDO development. The backbone of this block will involve aligning clinical phenomena with the ICD-11. Additional concepts will be incorporated as data and object properties as the FDO develops, with further refinement driven by future use cases and maintenance needs.
- Building block D will conduct an evaluation module to ensure the ontology's quality and consistency.

Figure 1. Diagram presenting steps to be applied in each phase of creating fibroproliferative or fibrotic disease ontology. Step 1, determining scope of the step based on the expert judgment analysis; step 2, targeted scoping review based on scope search defined in step 2 by experts; step 3, analysis of the scoping review results combined with experts' domain knowledge; step 4, enumerating and mapping identified and included terms, combined with International Classification of Diseases 11th Revision verification, if relevant; step 5, double check, adding properties if relevant; step 6, translating the results into the ontology in a Protégé file by creating instances. ICD-11: International Classification of Diseases 11th Revision; SNOMED CT: Systematized Nomenclature of Medicine–Clinical Terms; UMLS: Unified Medical Language System.



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Figure 2. Building blocks and phases proposed for a methodological grid enabling creation of domain ontologies for complex and interdisciplinary clinical and biomedical phenomena, as exemplified by fibroproliferative or FD ontology creation. Phase A, defining a phenomenon concept, defining "fibroproliferative disease;" phase B, setting the ontology structure—determining high-level scope by expert judgment; and phase C, iterative FD ontology creation. Each of the abovementioned phases is to be implemented in a rigorous iterative row of steps. The final phase D involves an evaluation of the ontology followed by a necessary revision, if needed. Steps 1-3 represent knowledge acquisition; steps 4-5 represent conceptualization; and steps 5-6 represent integration and formalization. The chain-wheel or sprocket-wheel shape of the diagram indicates an iterative and combined approach to FD ontology building. FD: fibroproliferative or fibrotic disease.



Collective Domain Expertise of Experienced Clinicians and Researchers Applied to Determining Scope and Analyses of Targeted Scoping Reviews

A multidisciplinary team of experienced clinicians and researchers will collaborate to determine the scope of this study and analyze the results of our targeted scoping reviews. Drawing on the expertise cultivated during the RESOLVE FP7-EU project [1], among other experiences, this team will convene biweekly throughout the study (see Table 1 for study timelines). The meetings will facilitate iterative refinement of conceptual categories and relationships within the ontology, with each stage involving a critical review of current evidence, method refinement, and a discussion of concept applicability.

Table 1. Overview of study timelines.

Item	Month																			
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Develop protocol	✓	✓																		
Publish protocol			✓																	
Implement protocol				✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓			
Phase A				✓																
Phase B					✓															
Phase C						✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓				
Phase D																	✓			
Submit to BioPortal																		✓		
Publish paper																			✓	✓

To achieve consensus, we will use a modified real time Delphi method [35] when necessary. If the team cannot reach a consensus on a particular issue, we will use a 2-round voting system with straightforward digital tools. The first round entails voting on all proposed opinions, while the second round, if needed, narrows the vote to the 2 highest-ranked options from the initial round.

The scoping review will guide the identification of specific concepts within subdomains, allowing us to map FD concepts across various organs (eg, lung, liver, and kidney) and systems (eg, cardiovascular diseases). These findings will be systematically reviewed by the experts for integration into the FDO development process. We will maintain a cycle of

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information collection, analytical processing, and subsequent integration into the FDO framework.

Scoping Review of Prevalent Concepts and Domain Literature

We will use a scoping review methodology to extract concepts related to the domain of FDs from the PubMed database's peer-reviewed literature [36]. Given the breadth of our research questions and the inclusion of various study types, a scoping review provides an appropriate approach to fulfilling our objectives. The review stages will adhere to the methodological framework by Arksey and O'Malley [37], as revised by Levac et al [38]: (1) population, intervention, comparison, outcomes, and study (PICOS)-based research question formulation [39]; (2) relevant study identification through a MEDLINE and PubMed database search; (3) study screening based on inclusion and exclusion criteria; (4) data charting, including relevant paper review; and (5) collation and summary of findings. Our report will align with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis–Scoping Review (PRISMA-ScR) framework [40].

Search Strategy

For the first phase (phase A), we will systematically search the MEDLINE and PubMed databases using the search strings *fibroproliferative disease* OR *fibrotic disease*. To map FD concepts across different organs and systems, we will pair these terms with the relevant organ and system subdomain (eg, *fibrosis* AND *lung*). Additional terms and Boolean operators may be introduced based on expert judgment and domain knowledge. Domain experts, clinicians, and researchers involved in the FDO's development will decide on the detailed settings for these searches.

We will refine our search string through test searches, identifying appropriate synonyms, medical subject headings (MeSH) phrases, and keywords. We will also manually search the references of pertinent studies.

Inclusion and Exclusion Criteria

Inclusion and exclusion criteria will be established through the PICOS framework, guiding the screening process. We will include any peer-reviewed study conducted on FDs without study design-based exclusions. We will focus on full-text, peer-reviewed research published since 2019 to reflect the field's recent developments and ensure sufficient evidence gathering. Exclusions include non-English papers, editorials, letters to the editor, commentaries, and press articles (see Multimedia Appendices 1 and 2 for eligibility screening form details).

Selection of Studies

The review team, comprising medical, biomedical informatics, and public health experts, will work in pairs to review papers. Each paper will be independently evaluated by 2 reviewers, with disagreements resolved through discussion (see Multimedia Appendices 1 and 2 for screening details).

Charting the Data

Data extraction will occur through a shared Microsoft Office (Microsoft Corp) Excel form (Multimedia Appendix 3), featuring a combination of close-ended and open-ended questions. Open-ended queries will help identify the article's primary aim and crucial results. We will extract key details, including authorship, publication year, domain, objectives, key results, and significant FD-related concepts, facilitating the development of a domain-specific glossary and ongoing model and ontology construction.

ICD-11: Screening Process Ensuring Globally Accepted Naming Standards and Proper Level of Granularity Across the Fibroproliferative Disease Ontology

The ICD-11 is a universally accepted tool, providing over 1.6 million terms for standardized health care information exchange [41]. It is publicly accessible, endorsed by the WHO, and used globally [42].

To ensure the interoperability of our FDO with this internationally recognized nomenclature and to maintain appropriate granularity, we will align all relevant concepts in our FDO with corresponding ICD-11 terms. This process will encompass all FDs and clinical conditions proposed for inclusion in the FDO. Therefore, we will compare the identified names of FDs with those listed in the ICD-11 classification. Each disease included in our FDO will follow ICD-11 naming conventions and be assigned a corresponding ICD-11 code.

Formalization of Ontology Using Web Ontology Language in Protégé

The FDO will be constructed using the Semantic Web standard OWL through Protégé (Stanford University), a leading open-source ontology editor [43]. Drawing from the scoping review findings and the team's expertise, we will incorporate and model various class entities and properties using pertinent OWL axioms, encompassing classes, object properties, data properties, and annotations. Conforming to best practices [44], relevant terms from the ICD-11 will be externally cross-referenced. The ontologies will not be imported given their distinct developmental contexts; specifically, the ICD-11 serves as an exhaustive disease reference terminology, whereas the FDO concentrates on the FD knowledge domain. Upon completion, the FDO will be uploaded to BioPortal [45], the world's most extensive open-source repository of biomedical ontologies, to facilitate annotation and dissemination.

Evaluation

The FDO will undergo evaluation to ensure validation and verification. The assessment will concentrate on the ontology's consistency, clarity, and comprehensive coverage of the FD domain [46]. Consistency checks will occur both during and after the ontology's development, with the open-source semantic reasoner Pellet (Clark and Parsia LLC) used for this purpose [47].

We will involve domain experts for qualitative evaluations. They will devise proficiency questions to examine the ontology's validity and will provide feedback on all FDO concepts and relationships through semistructured interviews, ensuring alignment with current domain knowledge [48]. To ensure the ontology accurately mirrors intended concept meanings and to maintain its coherence, we will eliminate

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irrelevant or incorrect entities, supplement missing terms, and uphold consistency [49].

Fibroproliferative Diseases Ontology Maintenance and Further Development Plan

Like any ontology, the FDO is expected to evolve continually. Realizing a comprehensive ontology for the FD domain is an iterative process, and as such, the FDO must consistently incorporate new concepts and data. It must also stay abreast of knowledge progression or alterations within the domain, ensuring accurate FDO representations. Additionally, regular maintenance by FDO biocurators is essential to rectify any irregularities or errors encountered during FDO use and development [50]. We plan to conduct FDO curation in association with the International Society of Biocuration [51].

The FDO maintenance and development strategy will incorporate 2 major cyclical steps: (1) application of FDO in FD research (use cases) and (2) annual, routine maintenance.

In step 1, subsequent to the initial FDO development, we anticipate its immediate use across multiple use cases. This includes applying FDO to analyze existing FD therapeutic strategies, causative factors, and the role of antimicrobial peptides in FD. Aside from their intrinsic value, these practical FDO applications will contribute to its maintenance and curation by highlighting inconsistencies, irregularities, and nonconformance with current knowledge.

In step 2, FDO biocurators will conduct annual updates, with web-based meetings scheduled each summer.

FDO is designed to accommodate new concepts and properties. Both its maintenance and development will involve ontology population, that is, adding new instances, and ontology enrichment, that is, adding properties to instances [52]. As the primary FDO framework is established and tested in initial use cases, we plan to gradually automate certain tasks related to steps 1 and 2. The progressive integration and reuse of concepts from existing ontologies are also planned as the FDO develops.

Results

The FDO, developed through the methodological framework outlined above, will be made open source, thus becoming a publicly available resource for stakeholders, researchers, and clinicians. The objective of this publication is to ensure transparency and integrity during ontology creation, stimulate domain expert interest, foster acceptance, and encourage continued use once the ontology is released in the public domain. The FDO will be registered and made accessible on BioPortal. Moreover, we plan to showcase the FDO at pertinent scientific conferences through abstracts and presentations. Additionally, the finalized FDO will be disseminated as a peer-reviewed publication.

Discussion

Overview

The protocol we have outlined for the development of the FDO aims to provide a crucial tool for representing and structuring knowledge within the FD domain. The key benefits of representing the FD knowledge domain as an ontology lie in its structured nature, which eases the sharing and dissemination of knowledge and encourages reuse across different research teams, projects, or subspecialties [53]. For example, discoveries in oncology or hematology could spur research in pulmonary medicine. Furthermore, the FDO can facilitate uncovering new relationships or parallels between distinct research findings or identifying knowledge and research gaps [54]. The standardized, interoperable usage of terms will streamline data exchange and integration, potentially accelerating in-depth analysis of general fibroproliferative processes and disease characteristics. Such a structured approach with standardized terminology should also enhance research quality [55]. By leveraging ICD-11 and SNOMED CT terms, we ensure both standardization and consistent granularity across the ontology [56]. This approach is designed to yield a comprehensive ontology of FDs, thereby avoiding the pitfall of incomplete coverage.

However, we anticipate certain limitations with the FDO developed through this protocol, some of which are inherent to biomedical ontologies expressed in OWL description logic [56]. OWL ontologies express relationships between objects, classes, concepts, and their properties, but they do not describe processes or changes occurring over time [57]. This is a significant consideration given that FDs typically involve chronic processes such as pathologies of tissue repair, aging, and senescence. As a workaround, we may consider creating multiple instances to describe a particular FD in the ontology instead of the “one disease, one instance” setting. Despite this, such a workaround introduces other limitations like potential bias, inconsistencies, and increased complexity, which may pose challenges for efficient use and interpretation of the ontology [56].

In conclusion, while the FDO is a promising tool for the representation of the FD knowledge domain, its success hinges on regular updates to keep pace with the evolving understanding of FDs. Therefore, we have planned follow-up activities to ensure that the ontology remains current and relevant.

Conclusions

We will create an FDO as a shared knowledge resource and conceptual framework accessible in the public domain for open usage, including by semantic reasoners and other tools. This facilitates collaboration and promotes ongoing updates and enhancements. The development of the FDO is described as an iterative process involving domain experts, scoping reviews, and the incorporation of existing standardized terminology. Once publicly available, the FDO is anticipated to stimulate research in the FD domain, driving clinical advancements, informing medical research, and influencing public health initiatives. Consequently, it will provide novel insights into the substantial current knowledge gaps in this field of study.

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Acknowledgments

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Data Availability

All data generated or analyzed during this study are included in this published article and its supplementary information files.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Screening phases A and B.
[DOCX File , 48 KB - resprot_v12i1e48645_app1.docx]

Multimedia Appendix 2
Eligibility screening form on the basis of full-text screening in phases A and B.
[DOCX File , 49 KB - resprot_v12i1e48645_app2.docx]

Multimedia Appendix 3
Data extraction: characterization form on the basis of full-text analysis—phases A and B.
[DOCX File , 44 KB - resprot_v12i1e48645_app3.docx]

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Abbreviations

ECM: extracellular matrix
EMBL-EBI: European Molecular Biology Laboratory-European Bioinformatics Institute
EMT: epithelial-mesenchymal transition
FD: fibroproliferative or fibrotic diseases
FDO: fibroproliferative or fibrotic disease ontology
FP7-EU: Seventh Framework Program of the European Union
ICD-11: International Classification of Diseases 11th Revision
IPF: idiopathic pulmonary fibrosis
MeSH: medical subject headings
OWL: Web Ontology Language
PICOS: Population, Intervention, Comparison, Outcomes, and Study
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analysis—Scoping Review
RESOLVE: Resolve Chronic Inflammation and Achieve Healthy Aging by Understanding Non-regenerative Repair
SNOMED CT: Systematized Nomenclature of Medicine–Clinical Terms
UMLS: Unified Medical Language System
WHO: World Health Organization

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Protocol

Targeted Glioblastoma Treatment via Synthesis and Functionalization of Gold Nanoparticles With De Novo–Engineered Transferrin-Like Peptides: Protocol for a Novel Method

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Abstract

Background: Glioblastoma multiforme (GBM) is an aggressive brain tumor with limited treatment options due to the blood-brain barrier's (BBB's) impedance and inherent resistance to chemotherapy. Gold nanoparticles (AuNPs) functionalized with transferrin-like peptides show promise in overcoming these challenges, enhancing drug delivery to the brain, and reducing chemotherapy resistance.

Objective: The primary goal of this study is to establish a detailed protocol for synthesizing and stabilizing AuNPs, functionalizing them with de novo–engineered transferrin-like peptides, and conjugating them with the chemotherapeutic agent temozolomide. This strategy aims to improve drug delivery across the BBB and circumvent chemotherapy resistance. The secondary objective includes an assessment of the safety and potential for in vivo use of the synthesized nanoparticle complex.

Methods: The proposal involves multiple steps with rigorous quality control of AuNP synthesis, stabilization with surfactants, and polyethylene glycol coating. The engineered transferrin-like peptides will be synthesized and attached to the AuNPs' surface, followed by the attachment of temozolomide and O6-methylguanine-DNA methyltransferase inhibitors. The resulting complex will undergo in vitro testing to assess BBB penetration, efficacy against GBM cells, and potential toxicity.

Results: Initial preliminary experiments and simulations suggest successful synthesis and stabilization of AuNPs and effective attachment of transferrin-like peptides. We propose peptide attachment verification using Fourier transform infrared spectroscopy and surface plasmon resonance. Additionally, we will conduct pH stability tests to ensure our functionalized AuNPs retain their properties in acidic brain tumor microenvironments.

Conclusions: The proposed functionalization of AuNPs with de novo–engineered transferrin-like peptides represents a novel approach to GBM treatment. Our strategy opens new avenues for drug delivery across the BBB and chemotherapy resistance reduction. While we primarily focus on in vitro studies and computational modeling at this stage, successful completion will lead to further development, including in vivo studies and nanoparticle design optimization. This proposal anticipates inspiring future research and funding in neuro-oncology, presenting a potentially innovative and effective treatment option for GBM.

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KEYWORDS

gold nanoparticles; glioblastoma; blood-brain barrier; transferrin-like peptides; drug delivery; brain tumor; neuro-oncology; chemotherapy; nanoparticle functionalization; pharmaceuticals

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Introduction

Our previous work demonstrated that pH buffer solutions in biological systems, such as blood and intravascular fluid, are typically maintained at a pH of approximately 7.4 by a carbonic-bicarbonate ion buffering system (accounting for 64% of buffering capacity). However, human blood pH varies between 7.35 and 7.45, indicating that a shift of 0.10 is significant. The hemoglobin-oxyhemoglobin buffering system accounts for approximately 28% of total buffering capacity, making it a critical process in respiration. For medical purposes, it is possible to determine the percentages of dissolved oxygen, nitrogen, carbon dioxide, and carbon monoxide through gas-liquid chromatography or an elemental analyzer. This analyzer includes a flash combustion furnace, a Porapak chromatographic column, and a thermal conductivity detector.

Moreover, the blood pH buffer comprises systems of acidic and basic proteins (about 7% of the total buffering system) and monoacid phosphates or diacid phosphates (roughly 1%). Enzymes, the central chemical agents of life, catalyze essential reactions with high selectivity. However, they are usually sensitive to pH and can function optimally only within a rather narrow pH range. The acidity of aqueous solutions determines which metal ions are soluble, which ones may become hydrolyzed, or which ones may potentially precipitate. As such, the availability of metal ions in the blood is pH dependent [1-3].

Furthermore, the inherent acidity of the brain tumor microenvironment poses a significant challenge for nanoparticle (NP)-based therapies. Thus, pH stability testing is critical to ensure that our NPs maintain their structural integrity and functional capacity in the acidic conditions of the brain tumor microenvironment.

The global burden of glioblastoma multiforme (GBM), a highly aggressive brain tumor, continues to grow due to its resistance to conventional treatment options and difficulty in drug delivery across the blood-brain barrier (BBB) [4,5]. Significant research has been devoted to developing innovative strategies for GBM treatment. One such promising area is the application of gold nanoparticles (AuNPs) [6,7].

AuNPs are increasingly recognized for their unique properties, including their high surface area-to-volume ratio, modifiable surface, and biocompatibility, rendering them potential vehicles for drug delivery [6,8]. Moreover, the functionalized ability to cross biological barriers such as the BBB makes NPs particularly valuable for brain tumor treatment [9-11].

Simultaneously, transferrin, a naturally occurring iron transport protein, has been shown to assist in drug delivery across the BBB due to the high expression of the transferrin receptor on the BBB and cancer cells, including GBM cells [11]. Transferrin-like peptides, engineered from studies on natural transferrin, could potentially enhance the delivery of therapeutic agents to the brain when conjugated to AuNPs [12-14].

Temozolomide, a commonly used chemotherapeutic agent for GBM, struggles with drug resistance and inadequate delivery to the tumor site. Coating AuNPs with temozolomide, coupled with O6-methylguanine-DNA methyltransferase (MGMT) inhibitors to overcome resistance, might provide a more effective strategy for GBM treatment [4,9,15].

Given the potential synergy among AuNPs, transferrin-like peptides, temozolomide, and MGMT inhibitors, we propose the synthesis, stabilization, and functionalization of AuNPs with de novo–engineered transferrin-like peptides and the aforementioned chemotherapeutic agents [7,13,14]. This exploratory proposal aims to outline a novel protocol for a potentially more effective GBM treatment strategy, offering insights and considerations for future researchers in this field.

Methods

Synthesis and Characterization of AuNPs

AuNPs with a diameter between 160 Å and 200 Å and a neutral or slightly negative charge are synthesized and stabilized with surfactants. We characterize the NPs using electron microscopy and spectroscopy techniques to confirm their size, shape, and surface properties [16-18].

Reagents

The following reagents are used: gold (III) chloride hydrate ($HAuCl_4$; Sigma-Aldrich, lot MKBN2548V; 99.999% purity), sodium citrate dihydrate ($Na_3C_6H_5O_7.2H_2O$; Sigma-Aldrich, batch #SLBG6645V; >99.0% purity), Milli-Q Nanopure water (doubly deionized water with a conductance of 5.6×10^{-8} $\Omega^{-1}\cdot cm^{-1}$ and pH 6.0-7.0 from a type D-4744 Nanopure deionization system or Purelab UHQ system to prepare standard and reagent solutions), all other reagents were of the best available analytical grade, and all vessels in contact with samples or reagents were cleaned by soaking in 5.8 M nitric acid (overnight) and repeatedly rinsed with deionized water before use.

Equipment and Materials

The equipment and materials included are a scale (model AY220; Shimadzu), reaction flasks with a 100-mL mouth, oil bath (silicone+glassware), magnetic bar, a laminar flow hood (TROX-100), Heating and stirring plate (model C-MAG HS4; IKA), 50-mL volumetric flasks, 10-mL volumetric flask, 5-mL weighing beakers, spatulas (nonmetallic), a 0.45-µm filter (Chromafil Xtra CA-45/25; Macherey-Nagel), nitrile gloves, 1-mL micropipette, safety glasses, Pasteur pipettes, plastic syringes, Nalgene 10-mL, and 50-mL Teflon tubes.

General Conditions

Beware of Glassware

The glassware must be previously cleaned with a 40% nitric acid solution and Milli-Q Nanopure water (see below Nota bene, Lab-203 rules for washing glassware) and then dried in the TROX-100 hood. Before the beginning of the experiments, the glassware is placed under the germicidal lamp of the TROX-100 hood for 1 hour. Regarding storage, glassware (class A) must be protected from environmental dust in duly clean, closed, and identified containers.

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Nota Bene Glassware cleaning

The method used to clean the glassware is known as drag washing and consists of first washing the glassware with a strong stream of water and letting the tap water overflow when filling the containers. This procedure is repeated at least 5 times. Then, the glassware is immersed in 40% nitric acid for 24 hours and, thereafter, rinsed again with distilled and deionized water until all the acid is removed (at least 4 times, allowing the water to overflow).

Synthesis and Preparation of Solutions

The experiments were carried out at the Catalysis and Interfaces Science Laboratory (LACFI-203) with a controlled temperature of 23±1 °C. The preparation of solutions and the synthesis of NPs should be carried out in the TROX-100 hood (flow 41 and 34.5 m/second). Synthesis should be carried out in a silicone bath. Before starting the experimental procedure, the hood should be sanitized with alcohol, along with all the material that will be placed inside the chapel, for example, supports, micropipettes, and reagent jars.

Experimental Procedure

Heating System

Silicone oil should be previously heated on a heating plate (selector position at 300). In approximately 1 hour, an ideal oil temperature between 110 °C and 120 °C for the experiment is achieved.

Preparation of 10 mL of a 1% (by Weight) Sodium Citrate Solution

Sodium citrate (0.1 g) should be weighed in a 5-mL beaker, completely dissolved in 2-3 mL of water, and transferred to a 10-mL volumetric flask with its volume completely adjusted with distilled water. Thereafter, the 1% sodium citrate solution should be filtered by weight in the 0.45-µm filter (Chromafil Xtra CA-45/25) using a sterile plastic syringe. The solution should be conditioned at room temperature.

Preparation of 50 mL of a 0.01% Gold Solution by Weight

$HAuCl_4$ (0.0050 g) should be weighed in a 5-mL beaker, dissolved completely in 2-3 mL of distilled water, and transferred to a 50-mL volumetric flask. The beaker should be washed with distilled water, and this washing water is transferred to the volumetric flask to remove all $HAuCl_4$ from the walls of the beaker. The volume of the volumetric flask is then completely adjusted with deionized water. The control of Au concentrations follows the methodology described by Fiedler et al [19].

Synthesis of AuNPs

AuNPs with a diameter between 160 Å and 715 Å are prepared as described by Frens [20].

Fifty milliliters of 0.01% gold solution (by mass) should be transferred to the synthesis flask together with a magnetic bar and then placed in a previously heated oil bath. A watch glass should be placed on the mouth of the synthesis flask. In approximately 20 minutes, the gold solution boils, and then the sodium citrate solution should be added as described in Table 1, with stirring (with the stirrer in position 3). Stirring should be carried out for 30 minutes. Thereafter, the heating and stirring should be turned off, and the solution should be allowed to cool to room temperature and transferred to a Teflon tube.

Table 1. Experimental data for the preparation of gold nanoparticles (AuNPs).

Nanoparticle	Sodium citrate (mL)	Diameter (Å)
AuNP size A	1.00	160
AuNP size B	0.75	245
AuNP size C	0.50	410
AuNP size D	0.30	715

Packaging

The solution must be conditioned in a Teflon tube previously washed (as shown in the *Preparation of 10 mL of a 1% [by Weight] Sodium Citrate Solution* section), duly identified at the room temperature of the LACFI-203, and protected from light.

Important Notes (0.01% [By Weight] Gold Solution)

Because it is highly hygroscopic, care should be taken when weighing $HAuCl_4$. The weighted masses are shown in Table 2. The $HAuCl_4$ reagent bottle must be stored in a desiccator [21].

Table 2. Weighted masses for the preparation of solutions.

Nanoparticle	Gold (III) chloride hydrate (g)
AuNP[a] size A	0.0055
AuNP size B	0.0053
AuNP size C	0.0053
AuNP size D	0.0050

[a]AuNP: gold nanoparticle.

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Preparation of 10 mL of a 1% (by Weight) Sodium Citrate Solution

The weight of sodium citrate should be 0.1004 g.

Synthesis of AuNPs

To measure the volume of sodium citrate, the micropipette aligned with the laboratory's quality control was used. An error rate of 4% was tolerated, and the volume was 502.21 µL.

Functionalization of AuNPs

We propose coating AuNPs with polyethylene glycol to enhance their stability and biocompatibility [15,22]. Temozolomide, a chemotherapeutic agent, would be either attached to the surface of the AuNPs or could be encapsulated within them [4,12]. Additionally, the NPs' design has to offer co-delivery of MGMT inhibitors to overcome resistance in GBM cells [7].

More data are needed to reveal the overall integrity of AuNPs post synthesis and post modification to validate successful incorporation of peptides onto AuNPs. Thus, verifying peptide attachment and assessing pH stability are fundamental steps prior to initiating in vitro experimental procedures.

Peptide Attachment Verification

After the synthesis and functionalization of the AuNPs, it is crucial to confirm the successful attachment of peptides onto the NPs. We propose a combination of Fourier transform infrared spectroscopy (FTIR) and surface plasmon resonance (SPR) for this verification.

FTIR can confirm peptide attachment by identifying the characteristic absorption peaks of the peptide-NP bond. After the peptide functionalized AuNPs, samples must be freeze-dried and mixed with potassium bromide. FTIR spectra must be collected in the range of 4000 cm^{-1} to 400 cm^{-1}. The appearance of characteristic absorption bands in the FTIR spectrum, not present in the AuNPs without peptides, would confirm the successful attachment of peptides onto the NPs.

For SPR, we plan to coat a gold chip with a layer of the NPs and flow the peptide solution across the chip. The SPR sensor will monitor the real-time interaction between the NPs and the peptides, as reflected by changes in the resonance angle. A shift in the resonance angle upon the introduction of the peptide solution would confirm the binding of peptides to the AuNPs.

Both these methods can provide complementary information—FTIR would confirm the formation of a covalent bond between the AuNPs and peptides, while SPR will provide real-time information about the binding process and the stability of the peptide-AuNP complex.

pH Stability Test

Given the acidic nature of the tumor microenvironment, it is crucial to ensure that our NPs are stable and retain their functionality under such conditions. We propose conducting pH stability tests to tackle this problem. After verifying peptide attachment, NPs are incubated in solutions of varying pH (ranging from pH 4 to 8 to simulate physiological and tumor microenvironment conditions). We then evaluate the size, shape, and surface charge of the NPs through dynamic light scattering and zeta potential measurements, and the functionality of attached peptides is assessed using FTIR or SPR. This provides a comprehensive view of NP stability and functional integrity in a range of pH conditions.

In Vitro Evaluation

The functionalized AuNPs can be tested in vitro using GBM cell lines to evaluate their cellular uptake, cytotoxicity, and ability to overcome drug resistance [6]. As our current proposal is at an early stage, it focuses on in vitro studies and computational modeling. Upon successful completion of these initial stages, we plan to include in vivo animal studies in future protocols.

Optimization of NP Design

Based on the preliminary results, constant optimization of NP design is needed to enhance their mobility within the brain's extracellular space, their penetration from the cerebrospinal fluid into the brain parenchyma, and their targeting efficiency [8]. Future developments in NP design optimization can involve adjusting NP size and shape to improve mobility and penetration, modifying surface properties for enhanced drug delivery and stability, and potentially incorporating targeting ligands that can increase affinity for GBM cells or specific receptors on the BBB. Each step represents a critical aspect of the research process and will contribute to the development of a more effective treatment for GBM. It is important to note that this complex and challenging project requires a multidisciplinary team of researchers with expertise in NP synthesis, drug delivery, cell biology, neuroscience, and oncology.

Ethical Considerations

Since our proposal is centered on laboratory experiments and computational models, no human subjects or data from human subjects are involved in this research protocol. Therefore, human subjects research ethics review, informed consent, privacy and confidentiality protection, and compensation type and amounts for human subjects research are not applicable to our research proposal. However, should the study progress to the stage of clinical trials, all appropriate ethical considerations will be rigorously applied, including but not limited to obtaining ethical approval from the relevant institutional review board, obtaining informed consent from all participants, ensuring privacy and confidentiality, and providing fair compensation.

Results

This proposal is currently theoretical and does not have reportable results other than structured simulations as listed above, where we found that the protocoled AuNPs have a structure capable of attaching transferrin-like peptides and carrying chemotherapeutics, such as temozolomide and MGMT inhibitors to overcome resistance. The authors do not anticipate proactively obtaining funding in the future due to insufficient resources.

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Discussion

Limitations

While AuNPs are generally considered biocompatible, there could still be potential toxicity or adverse reactions, especially at the high doses for effective treatment [6]. The long-term effects of AuNPs' accumulation in the body are not fully understood. Moreover, GBM tumors exhibit considerable heterogeneity, wherein various regions within a single tumor may display distinct characteristics [4]. This heterogeneity presents a significant challenge, potentially impeding the effectiveness of a singular therapeutic approach to treat the entire tumor.

As an early-stage proposal, our current focus is to establish the feasibility of our approach through computational models and in vitro studies. Moreover, we plan to generate data on AuNPs' stability and delivery accuracy in subsequent studies.

Comparison With Prior Work

In evaluating our proposal relative to recent literature [8], in particular, the study using radiolabeled AuNPs studded with substance P peptides for GBM treatment, it is clear that our approach offers several distinct advantages and complements existing strategies.

First, our work expands on the drug delivery capabilities of AuNPs. While the previous study used AuNPs for delivering radiation therapy, our nanocarrier approach delivers temozolomide and MGMT inhibitors, which are 2 crucial agents in chemotherapy for GBM [7]. The quality of a nanocarrier broadens the therapeutic range of AuNPs and illustrates their potential to transport various types of drugs.

Second, our study also emphasizes the importance of targeted delivery. Our nanocomplex approach (ie, AuNPs with transferrin-like peptides attached), seeks to exploit the upregulated transferrin receptor on GBM cells, thereby improving the specificity of drug delivery and minimizing off-target effects [12].

Another significant advancement in our study is the AuNPs' ability to cross the BBB [4]. This passage is a crucial immune checkpoint and a key factor in neuro-oncologic therapies, which was not addressed in the previous study [8]. A successful BBB traversal by the functionalized AuNPs would suggest a promising strategy for delivering therapeutic agents to the central nervous system [7].

Furthermore, our study's quality control and safety evaluation offers a comprehensive view of the potential impacts of the proposed treatment [6]. By investigating the toxicity of our compound, we could provide valuable insights into its suitability for further development and potential clinical application.

Conclusions

The functionalization of AuNPs with de novo–engineered transferrin-like peptides presents a novel therapeutic approach for GBM. Our work proposes a detailed protocol explaining the synthesis, functionalization, and stability evaluation of AuNPs. Given the acidic nature of the brain tumor microenvironment, maintaining the structural integrity and functional capacity of AuNPs under these conditions is critical; hence, pH stability tests must be conducted accordingly. We demonstrate a potential modification to the surface of AuNPs to overcome current obstacles in GBM treatment. By introducing ligands or peptides—such as the proposed transferrin-like peptides—that target specific transporters or receptors on the BBB and show high affinity for GBM cells, we anticipate an enhanced ability to cross this barrier. Furthermore, we aim to enable accurate payload delivery by leveraging AuNPs as nanocarriers for temozolomide and MGMT inhibitors directly to the tumor site, potentially reducing chemotherapy resistance and systemic side effects. We hope that our rigorous quality control protocol for the synthesis of AuNPs will permit and inspire further research and potential funding in this field, offering an innovative and effective treatment option for GBM.

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Data Availability

All data generated during this study are included in this published article. Data sharing is not applicable to this article as no data sets were generated or analyzed during this study.

Conflicts of Interest

None declared.

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Abbreviations

AuNP: gold nanoparticle
BBB: blood-brain barrier
FTIR: Fourier transform infrared spectroscopy
GBM: glioblastoma multiforme
LACFI-203: Catalysis and Interfaces Science Laboratory
MGMT: O6-methylguanine-DNA methyltransferase
NP: nanoparticle
SPR: surface plasmon resonance

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Protocol

Dietary Temperature's Influence on Energy Balance in Humans: Protocol for a Randomized Controlled Trial and Crossover Design

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Abstract

Background: According to the first law of thermodynamics, energy cannot be created or destroyed in an isolated system. Water has a characteristically high heat capacity, indicating that the temperature of ingested fluids and meals could contribute to energy homeostasis. Citing the underlying molecular mechanisms, we present a novel hypothesis that states that the temperature of one's food and drink contributes to energy balance and plays a role in the development of obesity. We provide strong associations with certain molecular mechanisms that are activated by heat and correlate them with obesity and a hypothetical trial that could test this hypothesis. We conclude that if meal or drink temperature proves to contribute to energy homeostasis, then depending on its contribution and scale, future clinical trials should attempt to adjust this effect when analyzing data. In addition, previous research and established relationships of disease states with dietary patterns, energy intake, and food component intakes should be revisited. We understand the common assumption that thermal energy in food is absorbed by the body during digestion and dissipated as heat into the environment, not contributing to the energy balance. We challenge this assumption herein, including a proposed study design that would test our hypothesis.

Objective: This paper hypothesizes that the temperature of ingested foods or fluids influences energy homeostasis through the expression of heat shock proteins (HSPs), especially HSP-70 and HSP-90, which are expressed to a greater extent in obesity and are known to cause deficits in glucose metabolism.

Methods: We provide preliminary evidence supporting our hypothesis that greater dietary temperatures disproportionally induce activation of both intracellular and extracellular HSPs and that these HSPs influence energy balance and contribute to obesity.

Results: This trial protocol has not been initiated and funding has not been sought at the time of this publication.

Conclusions: To date, no clinical trials are available regarding the potential effects of meal and fluid temperature on weight status or its confounding effects in data analysis. A potential mechanism is proposed as a basis by which higher temperatures of foods and beverages might influence energy balance via HSP expression. On the basis of the evidence supporting our hypothesis, we propose a clinical trial that will further elucidate these mechanisms.

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KEYWORDS

dietary temperature; energy intake; energy conservation; heat shock proteins; clinical trial; design of study

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Introduction

Background

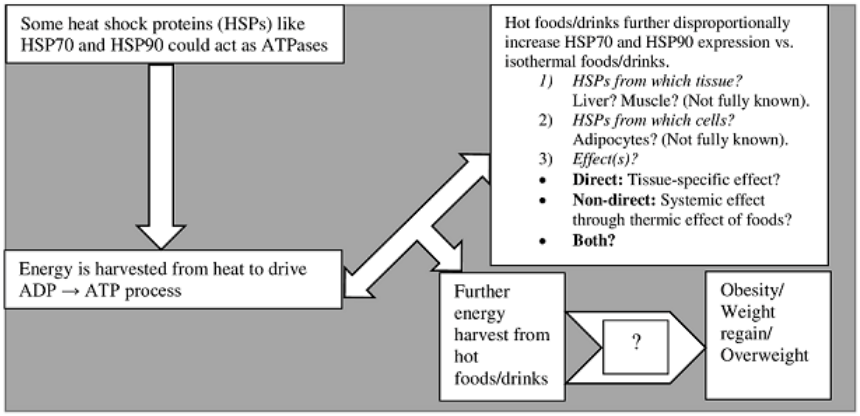
The first law of thermodynamics, also known as the law of conservation of energy, states that energy can neither be created nor destroyed in an isolated system [1]. The human body has its own mechanisms to adapt to changing temperatures; however, it is possible that higher or lower temperatures of food and beverages (referred to as dietary temperature) impose some implications on the energy demands of the body. On the basis of diet composition, chewing habits, and the amount of fluid (and its corresponding temperature) ingested, the human body is exposed to a wide range of temperatures [2,3]. This exposure affects the entire gastrointestinal tract, being greatest at the mouth, followed by the esophagus and stomach, with the latter exposed for a greater time [4-7]. Indeed, there have been several studies relating dietary temperature to gastric function [6], frequency of gastric myoelectrical activity [7], gastric emptying time, gastrin release, gastric acid secretion [8], esophageal cancer [9,10], and intraluminal upper gastrointestinal temperature and motility [5]. Although when it comes to energy metabolism, it has been assumed that higher dietary temperatures are dissipated during digestion and do not contribute to energy balance.

One of the most immediate responses of body cells to higher temperatures is the induction and increased synthesis of heat shock proteins (HSPs), especially HSP-70 [11,12] and HSP-90 [13,14]. HSP-70 [15] and HSP-90 [16] possess N-terminal adenosine triphosphatase fragments at their ends and tightly regulate adenosine triphosphate (ATP) activity and ATP hydrolysis [13,17-19], providing the heat energy to drive the adenosine diphosphate to ATP conversion. Indeed, cells exposed to higher temperatures increase HSP activity [11-14], and the time profile of peripheral blood mononuclear leukocytes HSP-70 response to in vitro heat shock is temperature dependent [11,20]. For instance, under in vitro hyperthermic conditions (40-41 °C), the time course was characterized by a sharp rise in HSP-70 concentration immediately after heat shock treatment ($P<.05$ for 40 °C at 0 hours), followed by a steady and progressive decline over time [11].

We have already shown that HSPs can extract energy from the environment (here, dietary temperatures), thereby contributing to the energy balance. The mathematical calculations are beyond the scope of this paper, and interested readers may read our previous paper [21]. The summary is graphically illustrated in Figure 1.

Importantly, obesity has been linked to HSP expression, specifically for HSP antibodies (HSP-27 [22], HSP-72 [23], HSP-60, HSP-65, and HSP-70 [24,25]). The table in the Multimedia Appendix 1 [22,24-26] lists the studies investigating the relationship between anti-HSP antibodies and indexes of body mass and body composition. Specifically, serum HSP-27, HSP-60, HSP-65, HSP-70, and HSP-72 antibody levels are significantly increased in people with obesity compared to people with a normal weight [22-26]. Furthermore, in the diet-induced obese mouse model of insulin resistance, HSP-90 inhibitors activate the heat shock factor 1 stress response pathway and improve glucose regulation [27]. A similar experiment on diet-induced obese mice supports this hypothesis in which HSP-90β knockdown reverses insulin resistance and improves glucose tolerance [28].

Figure 1. Hypothetic mechanism by which hot meals or drinks may contribute to energy balance. ADP: adenosine diphosphate; ATP: adenosine triphosphate; ATPase: adenosine triphosphatase.



Evidence Supporting Our Hypothesis

Intracellular Versus Extracellular HSPs

HSPs help to maintain cellular homeostasis through a mechanism called thermotolerance. Cells exposed to mild stress induce HSPs, which later protect them against subsequent stress. In cells exposed to severe stress, HSPs promote apoptosis. HSPs meanwhile exist in extracellular fluids and contribute to immunomodulation [29]. It is noteworthy that the intracellular HSP function may be different from that of extracellular HSPs, as the latter appears to manifest a function different from the well-known chaperone role [29]. For instance, intracellular HSP-70 exerts a profound anti-inflammatory effect, whereas extracellular HSP-70 activates proinflammatory pathways [30]. In the case of obesity, both intracellular [31] and extracellular [32] HSP-70 levels are significantly greater in participants with obesity than in lean controls. It has been proposed that the ratio of extracellular medium HSP-70 to intracellular HSP-70 contents may be a determining factor to trigger a chronic proinflammatory status, which leads to insulin resistance and the development of type 2 diabetes mellitus (T2DM) [30].

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Weight Regain and HSPs

In the only published randomized controlled trial (RCT) linking weight regain to HSPs, Roumans et al [33] explored the expression of stress proteins during weight loss and weight maintenance concerning weight regain. They compared the in vivo findings with the results from in vitro cultured human Simpson-Golabi-Behmel syndrome (SGBS) adipocytes. In total, 18 healthy participants participated in an 8-week dietary program with a 10-month follow-up period. They categorized the participants as weight maintainers or weight regainers based on their weight changes during the intervention. Abdominal subcutaneous adipose tissue biopsies were conducted before and after the diet and after the follow-up. In vitro–differentiated SGBS adipocytes were starved for 96 hours with low (0.55 mmol/L) glucose. Weight regainers showed increased expressions of calnexin, β-actin, HSP-27, HSP-60, and HSP-70. Changes in HSP-27 and HSP-70 and β-actin levels were linked to HSP-60, a novel key factor in weight regain after weight loss. SGBS adipocytes manifested increased concentrations of β-actin and HSP-60 after 96 hours of glucose restriction [33]. In another RCT, 20 young overweight men without metabolic syndrome participated in a 3-week residential program on a low-fat diet and moderate aerobic exercise. After 3 weeks of the diet program, significant reductions in BMI, serum lipids and lipid ratios, and oxidative markers were recorded (P<.05), along with the reduced expression of HSP-90 and HSP-27 [34].

There is ample literature on the effects of heat stress on fat deposition [35], insulin sensitivity [36], and the facilitating role of HSPs in adiposity [37-39]. The most direct evidence supporting our hypothesis comes from studies conducted on pigs. Exposure to low or high ambient temperatures directly impacts heat production and energy balance in pigs [40]. Heat stress causes enhanced adiposity [41] and growth performance through reduced energy and nitrogen use [42]. However, it is noteworthy that novel observations challenge this long-held traditional dogma, linking reduced productive output during heat stress to decreased nutrient intake. It is now clear that the heat stress response profoundly changes postabsorptive carbohydrate, lipid, and protein metabolism independently of decreased feed intake through harmonized alterations in fuel supply and use by various tissues [43]. One might argue whether heat stress in pigs is relevant to the effects of food temperature on energy metabolism in humans, especially when there is no direct evidence to show that ingesting hot food raises body temperature to such an extent. In addition, it may be argued that the association of HSPs with obesity does not automatically infer causation, and it is well known that these systems respond to metabolic stress. Therefore, to test this hypothesis, we prepared a short proposal to conduct a clinical trial, as described in the *Methods* section.

Altogether, these trials might provide preliminary evidence that HSPs contribute to obesity and weight regain. There is evidence that other HSPs, that is, HSP-A12A, regulate adipocyte differentiation and diet-induced obesity through positive feedback regulation with PPARγ (peroxisome proliferator-activated receptor gamma) [44].

To explore the mechanism of the effects of heat stress on porcine adipocytes, Qu et al [35] used an in vitro adipocyte differentiation model to determine the cellular responses that occur during adipocyte differentiation in pigs. Stromovascular cells (preadipocytes) were differentiated for 9 days at a normal (37 °C) or heat stress (41.5 °C) temperature under 5% CO_2. They measured the expression of a long list of heat stress genes, such as HSP-27, HSP-60, HSP-70, and HSP-90, as well as cellular triglyceride and ATP concentration. Expectedly, heat stress significantly enhanced the expression of HSP genes but surprisingly had no effect on the level of PPARγ, although C/EBPα was significantly induced. Heat stress leads to the enhanced expression of genes involved in fatty acid uptake and cellular triglyceride synthesis. With the progression of differentiation, the total cellular ATP significantly decreased. However, cells under heat stress had significantly greater cellular ATP than those under control temperature. They concluded that heat stress promoted increased adipocyte triglyceride storage, possibly through the upregulation of genes involved in fatty acid uptake and triglyceride synthesis [35]. It was later determined that the induction of phosphoenolpyruvate carboxykinase expression in adipose tissue by heat stress indicates that increased glyceroneogenesis might also be involved in increased fat storage in pigs under heat stress [38].

Although exposure to a higher dietary temperature is a different form of exposure to higher environmental heat in animals, these animal studies [35,40-42] have invaluable lessons that can be translated into a clinical trial. The temperature range of heat stress applied usually lies between 37 °C and 41.5 °C for in vitro studies [35], which can theoretically simulate physiological responses during eating and drinking of hot meals and drinks, and ranges between 12 °C and 29 °C for exposure to ambient temperature studies [40], which is an acceptable temperature difference range (Δ) to study higher or lower dietary temperatures in humans.

Participants with obesity showed increased expression of HSP-60, HSP-72, HSP-90, and GRP-94 levels, specifically influencing BMI and percent body fat [45], whereas insulin resistance resulted in a decrease in intracellular HSP-70 levels. It also appears that weight loss can reduce HSP activation, as demonstrated in a recent trial where acupuncture in combination with dietary restriction was effective in reducing all immunologic factors (anti-HSP antibodies including anti–HSP-27, anti–HSP-60, anti–HSP-65, and anti–HSP-70) and weight loss [46]. Altogether, these findings indirectly support the hypothesis that a network composed of different HSPs (mainly HSP-70 and HSP-90, but including other HSPs, possibly via modulation of insulin sensitivity or resistance) may alter energy balance and contribute to weight gain and loss, which may have important implications in obesity treatment and prevention.

Thermic Response

Although the higher temperature of ingested meals and fluids may have some overlap with specific dynamic action (SDA), it should be emphasized that these are 2 different concepts; meal or fluid temperature is a subset of SDA, whereas SDA, or thermic response, is a physiological phenomenon, which

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comprises the energy expended on all activities of the body after the ingestion of a meal and leads to a rapid postprandial increase in the metabolic rate. SDA is influenced by the size, type, composition, and temperature of the meal as well as body size, body composition, and multiple environmental factors (such as gas concentration and ambient temperature). In humans, a commonly used estimate of the thermic effect is approximately 10% of the caloric intake; however, the average maximum increase in metabolic rate originating from digestion could reach 25% [47].

However, there is indirect evidence that states that meal temperature might influence energy balance, which is not accounted for by SDA. Meal temperature is one of the determining factors of gastric emptying and absorption of food compositions such as carbohydrates in the duodenum [48], which consequently affects heart rate [8] and thereby metabolic needs. In endotherms, including humans, if meals and fluids are ingested at a temperature lower than the core body temperature, extra heat should be generated to elevate the meal temperature to the body temperature. Thus, the cost of food warming is indicated by the SDA response [47]. The contribution of food warming to SDA should vary as a function of meal temperature and mass. In other words, more energy is expended to warm a large, cold meal compared with a smaller, warmer meal [49]. It might be conjectured that the reverse may hold true for warmer meals and fluids and thereby contribute to energy expenditure and thus energy balance.

The results of direct or indirect calorimetry studies can be criticized; these studies are usually short term and do not account for the influence of between-individual differences in dietary temperatures, neither on the day of calorimetry measurements nor the day before. It might be a good practice to advocate the measurement or control of meal temperature during the day of measurement and at least 1 week before indirect calorimetry. A careful appraisal of the methodology of most laboratory studies shows that, at best, participants are asked to refrain from caffeine and alcohol intake and any vigorous physical activity 1 day before the calorimetry study or a standard diet is prescribed [50-54]. It can also be argued that heat acclimation may partially promote thermoregulatory adaptations in people who consume hot foods and fluids. This might be true; however, this has not been experimentally tested. In addition, there might be an interaction between dietary temperature and some ingredients of food composition (for instance, capsinoids) or some dietary behaviors (such as the frequency of consuming ingredients like capsinoids) that might circumvent thermoregulatory pathways.

In a recent meta-analysis, increases in HSP-70 protein expression after heat acclimation were shown to be moderated by the number of heat acclimation days [12]. In other words, there is a strong possibility that between-individual differences in eating behaviors in terms of the temperature of foods and drinks they consume may influence HSP-70 expression and, if HSP-70 expression contributes to energy balance, then this will confound matching protocols in clinical trials, such as treatment-matching, subject-matching, and data-matching protocols.

Evidence From the Effect of Dietary Temperature on Food and Liquid Intake

Although the current hypothesis is centered on the influence of dietary temperature on HSPs to cause changes in metabolic processes that favor energy storage, a potential confounding effect that may exist is the effect dietary temperature may have on eating behaviors. In an experiment conducted on rats, no interaction was reported between nurture temperature and meal temperature. The food temperature per se had no significant effect on food intake [55]. In contrast, food temperature had an impact on food intake in patients who were hospitalized. The percentage of hospitalized patients who rated the meal temperature as good was higher for those served with isothermal trolleys than those who were not. The amount of food consumed by patients served with isothermal trolleys was significantly greater than that consumed by patients served without the trolleys [56]. Similar results have been obtained in another hospital setting [57]. Furthermore, serving temperature may affect expected satiety and complementary food purchases. Consumers are more likely to choose complementary food items when they consume or intend to consume a food or beverage served cold rather than hot [58], and warm temperature attenuates the preference for savory meals [59]. The dietary temperature may additionally influence executive function and processes associated with obesity, whereas lower executive function acts as a risk factor for increases in specific eating behaviors that play a role in the development of weight management problems [60,61]. Therefore, the dietary temperature may have a complex interaction with total energy consumption, which deserves to be clinically investigated under controlled conditions.

The aforementioned literature justifies the need to conduct a well-controlled clinical trial to test whether higher dietary temperatures interfere with body and cellular energetic states and, thus, influence or confound the results of clinical trials that aim to compare or evaluate dietary interventions.

Methods

Overview

To the best of our knowledge, no studies are available regarding the possible contribution of dietary temperatures to the HSP response. We provide preliminary evidence supporting our hypothesis that higher dietary temperatures disproportionally induce activation of both intracellular and extracellular HSPs and that these HSPs influence energy balance and obesity. In this paper, we outline a protocol to test these hypotheses and elucidate the potential roles dietary temperature plays in obesity development.

A Proposal to Conduct an RCT

A 4-arm randomized design investigating diets served at different temperatures in 5 °C increments (with core body temperature as a reference) in healthy adults would be the first step to elucidate the potential mechanism linking higher meal temperature with energy contribution. The same protocol can be replicated in patients who are overweight and obese or in

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people with T2DM. In addition, a crossover design can be performed with necessary modifications.

Participants: Inclusion and Exclusion Criteria

The participants will include 80 healthy (BMI 25-35 kg/m^2) men and women aged 19-65 years. Entry criteria will include people who are not currently dieting to lose weight and have had no weight loss or gain >2 kg over the past 3 months; not taking any medications (including antifever) that affect energy expenditure or eating; not using tobacco; not pregnant or lactating or planning to become pregnant in the next 12 months; and have no limitations to eating specific foods or to swallowing (eat and drink) a normally estimated range of meal temperatures (37-52 °C). The participants must not have major health problems; known cardiovascular (cardiac, peripheral vascular, and cerebrovascular), pulmonary (chronic obstructive pulmonary disease, interstitial lung disease, and cystic fibrosis), or metabolic (diabetes, thyroid disorders, and renal or liver disease) disease; and severe fever.

Procedures

The day before the experimental session, the participants will be instructed to avoid alcohol, caffeine, and strenuous exercise and to drink plenty of water for 24 hours. On the day of the experimental session, the participants will be asked to arrive at the laboratory adequately rested and will be provided with boluses of soups (each 100 ml) with a predefined temperature to be taken once (to overcome the problem of temperature dissipation).

The energy content of bolus diets (including the thermoneutral diet and temperature-graded bolus diets) will be matched to each of the participant's objectively calculated energy demands [62] and will be provided in the following manner: 20% energy for breakfast, 50% for lunch, and 30% for dinner. This procedure will facilitate the administration of boluses with graded temperatures (eg, +5 °C increments) with a fair precision from 37 °C to 52 °C, which is both ethical and within the optimal drinking temperature of 57.8 °C and <85 °C for the maximum temperature used to serve hot drinks such as coffee [63].

After assuring sufficient hydration (urine-specific gravity <1.025) [64], the participants will be instrumented in a thermoneutral room (approximately 25 °C) and then will be entered into a whole-body calorimeter regulated to 35 °C with approximately 20% relative humidity, where they will rest in an upright seated position for a 30-minute habituation period while steady-state measurements will be obtained.

The dietary temperature will be measured using a noncontact thermometer. All drinks and a standardized diet will be served at room temperature to maximize gastric emptying and fluid uptake while minimizing diuresis. It is expected that by using this metered intake to control for intake pacing, ingestion will be completed between 3 minutes and 5 minutes and will control for heat dissipation of foods and fluids as well. To avoid thermal injury while providing a satisfactory sensation to the participants, the optimum temperature for serving hot fluids and meals will be observed [63].

The drinks and meals will be consumed at a speed that is as rapid as the participants can comfortably manage, which is described elsewhere in detail (mean 11 seconds for 200 mL and 38 seconds for 500 mL) [65,66]. The intraesophageal and intragastric temperatures will be monitored using thermocouples, which is a widely used technique [67]. As currently there is no specific dynamic model for real-time monitoring or measuring of temperature changes of digested meals or drinks along the alimentary tract, inner food and drink temperature will be estimated using the inverse heat conduction problem methodology on surface temperature measurements obtained using thermography [68]. For practical and physiological purposes, considering the applied speed of ingestion, the magnitude of temperature changes along the alimentary tract could be considered as negligible [65-67,69,70].

Measures

All outcome measures will be measured at 0, 6, and 12 weeks. The participants will be asked to follow their assigned diet served at 37 °C, 42 °C, 47 °C, and 52 °C for 12 weeks.

Blood samples will be collected from each participant for analysis after 12-hour fasting, 3 times during the study (at the beginning and 6 and 12 weeks later).

Adipose tissue biopsies, protein isolation, and in vitro cell culture experiments will be performed as described elsewhere [33].

Cellular HSP-70 and HSP-90 levels will be measured to determine the thermic response to feeding, that is, evaluation of the causal relationship among higher dietary temperature, HSP-70/HSP-90 concentrations, and their time profile, as well as measures of obesity, aerobic fitness, resting metabolic rate, and diet-induced thermogenesis.

Food diaries will be analyzed using software to determine energy intake and macronutrient content.

An automated respirometer system plus a whole-body direct calorimeter, as the gold standard, will be used to measure energy expenditure and substrate utilization, aerobic fitness, resting metabolic rate, diet-induced thermogenesis, and markers of protein and fat catabolism to evaluate whether dietary temperature influences metabolism and surrogate end points of obesity in participants, such as weight and waist-hip ratio.

Duration of Study

The optimum length of the study will be 12 weeks, if feasible, and if not, at least 2 weeks would be necessary.

Assignment of Interventions

For treatment allocation, randomization (1:1:1:1) and blinding protocol will be used as described previously [71].

Proposed Outcome Measures

Primary Outcome Measures to Be Assessed

Subset A denotes the change in BMI, total body fat, body weight, percentage body fat, lean body mass, percentage lean body mass, waist circumference, and waist-hip ratio from baseline to 12 weeks (time frame: 0, 6, 12, and n weeks). The

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measurements will be performed with light clothing before breakfast and preferably after voiding.

Subset B denotes changes in HSP-27, HSP-65, HSP-70, HSP-72, and HSP-90 (in plasma and total leukocytes) and anti–HSP-27, anti-HSP-65, anti-HSP-70, anti-HSP-72, and anti-HSP-90 antibodies from baseline to 12 weeks (or whatever time is feasible, time frame: 0, 6, 12, and n weeks).

Subset C denotes changes in motilin, fasting glucose, insulin, C-peptide, 2-hour glucose, and insulin plus homeostasis model assessment–estimated insulin resistance from baseline to 12 weeks (or whatever time is feasible, time frame: 0, 6, 12, and n weeks).

Secondary Outcome Measures to Be Assessed

Changes in total cholesterol, triglycerides, low-density lipoprotein, high-density lipoprotein, reactive oxygen species, reactive nitrogen species, and NF-κB from baseline to 12 weeks (or whatever time is feasible, time frame: 0, 6, 12, and n weeks) are to be assessed.

Other Outcome Measures to Be Assessed

Subset A denotes plasma levels of leptin and adiponectin from baseline to 12 weeks (or whatever time is feasible, time frame: 0, 6, 12, and n weeks).

Subset B denotes possible changes in appetite and food intake (using a 3-day dietary recall questionnaire). Immediately before and after each diet, participants will rate hunger, satiety, and prospective food consumption using 100-mm visual analog scales. Gastric motility will be measured using ultrasound imaging systems.

A Short Proposal to Conduct a Crossover Design

As there are between-individual responses to heat stress [72], there are also interindividual differences in the serum concentration of HSPs [73-75], which may confound statistical analyses when calculating interactions between frequency of drinking or eating hot foods and time elapsed after eating or drinking. To overcome issues with interindividual differences in its broad sense, a crossover design with necessary modifications can be performed. In this case, it will be necessary that participants can eat ad libitum.

A 2-week washout period and thermoneutral diet between conditions will be included, in which participants will eat boluses of soups served at approximately 37 °C. In this case, the order in which participants participate in each treatment will be randomized. The participants will be assigned 4 weeks of each treatment with a 2-week washout period between each of the 4 crossover treatments.

Before starting the second round of the trial, all 3 treatment groups will return to a thermoneutral bolus diet for another 5 weeks (5 weeks of active treatment, 2 weeks of washout period, and 5 weeks of crossover round).

Adipose tissue biopsies and plasma samples will be obtained at 2 time points: before and after dietary treatment diet.

Statistical Analyses

For statistical analysis, Bayesian adaptive approaches [76] will be applied whenever feasible because this approach is more likely to allocate participants to better-performing arms at each interim analysis.

In addition to standard analyses of RCTs, causal mediation analysis can be performed to determine how much of the weight change is mediated by the increase in HSP levels or appetite or both. Future trials should seek to identify alternative mechanisms with the aim of further refining the intervention.

This seminal clinical trial can provide preliminary data for causal mediation analysis to facilitate the exploration of the causal mechanisms underlying possible energy contributions through higher dietary temperatures. Proper methods will be used for this purpose [77,78].

Sample Size Calculation

As the choice of type I errors (α, false positive), type II errors (β, false negative), and effect size may be quite arbitrary [79], we suggest calculating the sample size or power using the *R* value (eHSP-70 to iHSP-70 ratio) for a pilot study (alternatively, owing to feasibility, a preliminary study may be conducted on mice or rats).

Furthermore, as providing a priori sample size calculation is misleading and the presentation of CIs—although serving the same purpose—is superior [80], it would be better to use the CI of the *R* value to calculate the sample size based on the feasibility of a priori assumptions about the study results and available resources. In addition, because foods and drinks may be served and consumed at even wider temperature ranges, it would be instrumental to calculate sample sizes based on wider *R* ranges (approximately 0.2-6).

According to Krause et al [30], assuming the ratio *R* = (eHSP-70) / (iHSP-70) = 1 for the controls (resting and unstimulated) and assuming a moderate-hot meal temperature may produce a shift in *R* to up to 5, which is paralleled by an increase in inflammatory markers and stimulation of cell proliferation, *R* values >5 can be considered as an exacerbated proinflammatory response. However, for a conservative calculation, we suggest using *R*=2. According to Hunter-Lavin et al [81], heat-shocked cells simultaneously measured HSP-70 at 37 °C (*R*=1.00), 39 °C (*R*=1.45), 42 °C (*R*=0.65), 43 °C (*R*=0.48), and 45 °C (*R*=1.97), this later temperature confirms a proinflammatory response.

Note that at 45 °C (*R*=1.97), there is a turning point compared with that at 43 °C. This means that if a study intends to investigate wider ranges of meal temperature, it is necessary to calculate an array of expected *R* values and then choose the maximum calculated sample size. For an *R* value between 0.22 and 1.1, a sample size of 9 participants is needed to achieve 80% power [1], whereas an *R* value between 1.8 and 6 would require 75 participants to achieve 90% power [2].

Changes in the calculation of the *R* value are suggested to be valid during heat exposure, as *R* values are associated with the heat exposure of peripheral blood mononuclear cells to different temperatures within a physiological range [30]. Precautions that

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should be considered could include, but are not limited to, correction for noncompliance of the participants, adjustment for multiple comparisons, and innovative study design.

A total of 80 patients will be randomized equally (1:1:1:1) between the 3 active treatments and the thermoneutral group. Overall, 20 participants will be randomly allocated to the thermoneutral diet group (37 °C): 20 at 42 °C, 20 at 49 °C, and 20 at 54 °C. The primary analysis will be intention-to-treat for the whole study cohort.

It is possible that there are multiple roles of HSPs in body weight, weight regain, and composition, probably related to the exposure time during diet ingestion (and also dietary temperature acclimatization during short-term periods, midterm periods, and long-term periods and presence or absence as well as the degree of insulin resistance in people). Thus, conducting a clinical trial for 12 weeks would provide a sufficient time course to investigate this point.

Further Considerations and Opportunities

Due to HSPs' intertissue differences [30], it would be helpful to obtain samples of plasma, lymphocytes, central adipose tissue, and muscle (and liver tissue in case of animal study), if feasible, to attempt to find correlations between HSPs and other variables. This study will provide a great opportunity to administer an array of questionnaires to determine the quality of life, anxiety, depression, food frequency, physical activity, etc, and these data in combination with regular examinations will also help to decide whether and when this trial should be continued or stopped. As a preliminary study, it might be proposed to conduct an observational study to retrospectively investigate the mean differences in variables and odds ratios between people who report meals as cold and those who report consuming their meals while it is hot, in terms of serum baseline HSP levels. Subjective dietary temperatures should then be defined as objective temperatures with appropriate measures. This proposed trial can be replicated in healthy people, people with obesity, and people with T2DM (and in long-term patients vs newly diagnosed patients).

Further Technical Issues That Need to Be Addressed in the Pilot Clinical Trial

One might argue whether the study discriminates between other possible influences of meal temperature on energy balance mentioned in the paper (eg, effect on gastric emptying and diet-induced thermogenesis). Evidently, these issues should also be controlled. Participants can eat ad libitum during the 12 weeks of intervention and are fed only soups for 3 meals a day for 12 weeks and are supposed to stay in the laboratory during the entire experiment. This can confound the assessment of hunger or satiety obtained using the visual analog scale using different meal sizes. If participants receive standardized and isocaloric meals, it can mask a possible effect on appetite as well. A very important issue regarding meal temperature is the experienced pleasantness of the meal, which can influence food intake. This should be assessed as well. We have proposed an intention-to-treat analysis for the pilot study. Such a long intervention probably might result in a significant dropout rate, so it is questionable if sufficient participants will conclude the study.

Ethical Considerations

As this study involves human participants, the approval by Institutional Review Board (IRB) will need to be obtained before beginning any research activities. This will include an informed consent process, in which participants will be required to provide explicit informed consent for data collection, analysis, and reporting before the inclusion in the study. Such IRB approval will require privacy and confidentiality protection such as the deidentification of participant data, which would be appropriate for this trial. The compensation for participation in research will need to be considered by the specific IRB and research team.

Results

This trial protocol has not been initiated and funding has not been sought at the time of this publication.

Discussion

Principal Findings

Apart from the obvious need to improve weight loss or weight loss maintenance, elucidating the roles that HSP may play in the energy balance is important for future considerations in dietary assessment. The lack of control for dietary temperatures may have produced confounding effects in the data analysis of clinical trials of obesity and medical situations with obesity-related pathology. Dietary assessment tools are widely used in most nutritional and medical studies; therefore, it is critical to have accurate and validated tools. Several meta-analyses and systematic reviews have shown that dietary intake assessment tools have fundamental errors [82-84]; some researchers have proposed that their application in energy balance or obesity and body weight studies must be ceased [85]. It was recently proposed that self-reported energy intake should not be used for the study of energy balance in research on obesity because energy underreporting varies as a function of BMI, and interindividual variability in the underreporting of self-reported energy intake automatically attenuates diet-disease relationships [86]. Furthermore, there is a dispute regarding the validation of dietary assessment tools and the inaccuracy of energy intake measures [87-90]. If dietary temperatures prove to affect energy balance, then future attempts to correct for underreporting and misreporting of diet outcomes cannot avoid taking dietary temperature into account, regardless of whether these tools are kept or abandoned and new tools are developed.

We have presented our hypothesis that dietary temperatures influence energy balance, and we have followed this with a clinical trial that would address this question. The lack of literature regarding possible direct and independent effects of higher dietary temperatures on indexes of obesity warrants a well-designed clinical trial to shed light on the ambiguous role of dietary temperature on daily energy contribution. If meal or drink temperature proves to contribute to energy homeostasis, depending on its contribution and scale, future clinical trials should attempt to adjust this effect when analyzing data. In

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addition, previous research and established relationships of disease states with dietary patterns, energy, and nutrient intake should be revisited.

This hypothetical proposal is important in several ways. Previous studies [69,70] have only examined the effect of water temperature on gastric emptying and thereby appetite and energy intake; however, they did not consider a potential and direct effect of higher meal or drink temperature through body thermodynamics and HSPs expression. Fujihira et al [69] were the first to investigate how different water temperatures impact gastric motility and energy intake. They showed that consuming 500 mL of water at 2 °C can suppress gastric contractions and ad libitum energy intake compared with consuming 500 mL of water at 37 °C and 60 °C. The subjective appetite perception of hunger in their study tended to be lower after consuming 500 mL of water at 2 °C than at 60 °C. They reported that reduced energy intake after consuming cold water (ie, at 2 °C) is accompanied by a change in gastric contractions. These findings suggest that water temperature may modulate gastric motility to influence energy intake. Indeed, the results of well-conducted experiments confirm that liquid and solid meals at 60 °C accelerated gastric emptying compared with those at 37 °C during the initial 30 minutes [66,70]. However, their findings can be simultaneously criticized, as they have not considered the potential biochemical effect of higher dietary temperatures on cell biology and body thermodynamics. For the first time, we argue that dietary temperature may directly influence energy balance through the induction of HSP-27, HSP-65, HSP-70, HSP-72, and HSP-90 expression.

Conclusions

Our hypothetical proposal potentially adds new knowledge to the existing literature that food temperature may directly contribute to energy balance and thereby influence weight management. Our proposal has profound and widespread implications. For instance, if dietary temperatures prove to affect energy balance, future clinical trials involving metabolic studies have to take dietary temperature into account. In addition, the results of many published metabolic clinical trials may need to be revisited. The results of this proposal will have deep implications for dietary recommendations, such as the recommended daily energy intake for different age groups and diet planning in different health and disease states. Efficacy studies of nutritional interventions will also need to consider this point. Furthermore, some cultures are accustomed to consuming hot meals and drinks. Comparative studies, particularly those dealing with weight or metabolism, may need to account for biases created by different dietary temperatures. Our hypothesis may also explain the discrepancies in different studies (that did not control for dietary temperature), despite similar methodologies.

The proposed trial does carry limitations. There is no specific dynamic model for real-time monitoring or measuring of temperature changes of digested meals or drinks along the alimentary tract; therefore, we will have to estimate the inner food and drink temperature using the inverse heat conduction problem methodology, which may influence the precision of the results.

Authors' Contributions

RR conceived the study and wrote the initial draft of the manuscript. KDF contributed to the revision of the paper and critically appraised the paper.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Association between indices of body composition and antibody titers to heat shock protein (HSP)–27, HSP-60, HSP-65, HSP-70, and HSP-90.
[DOCX File , 19 KB - resprot_v12i1e42846_app1.docx]

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Abbreviations

ATP: adenosine triphosphate
HSP: heat shock protein
IRB: Institutional Review Board
PPARγ: peroxisome proliferator-activated receptor gamma
RCT: randomized controlled trial
SDA: specific dynamic action
SGBS: Simpson-Golabi-Behmel syndrome
T2DM: type 2 diabetes mellitus

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Protocol

Cognitive Dysfunction and Affective Mood Disorder Screening in Patients With Chronic Inflammatory Bowel Disease: Protocol for a Prospective Case-Control Study

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Abstract

Background: Mild cognitive impairment (MCI) and Alzheimer's disease (AD) might be more frequent in patients with inflammatory bowel disease (IBD), but the relationship between these 2 entities is yet to be entirely established. Certain blood biomarkers (eg, serum amyloid A [SAA] and serum homocysteine [Hcy], which increase in IBD and MCI; brain-derived neurotrophic factor [BDNF], which decreases in MCI and AD but is not clearly modified in IBD; and S100 calcium-binding protein B [S100B], which increases in the blood-brain barrier and neuronal lesions) might predict the stage of MCI or dementia or progression to a further state. The gut–brain axis (GBA) might be the key to the development of MCI in patients with IBD, along with systemic inflammation and the possible and unknown adverse effects of disease-modifying medication.

Objective: The aim of this study is to investigate whether GBA interactions play a role in MCI development in patients with IBD.

Methods: A case-control study will be conducted on at least 100 patients diagnosed with IBD, matched with 100 healthy individual controls. The matching will include sex, age, and education. Patients will be fully examined, and a full interview and a neurological and cognitive examination will be performed. The primary clinical outcomes will be cognitive test scores (Montreal Cognitive Assessment, Trail Making Test, Digit Symbol Substitution Test, forward and backward digit span testing). Depression, stress, and anxiety screening will also be performed. Blood samples from all participants will be collected, and aliquots will be immediately stored in a biobank. Primary laboratory outcomes will include serum levels of presumed cognitive dysfunction blood biomarkers SAA, Hcy, S100B, and BDNF. Follow-up will be performed at 12, 24, 36, and 48 months.

Results: Data collection started in December 2021 and is ongoing. So far, 53 patients with IBD have been recruited and 50 HC matched. Data collection should end in January 2030. Intermediary analysis will be performed in April 2024. We expect patients with IBD to have lower scores on cognitive testing and a positive correlation between disease length and cognitive impairment level. In addition, the levels of stress, anxiety, and depression should be higher in the IBD group. The serum levels of the 4 biomarkers could correlate or anticorrelate with cognitive scores and serve as predictive factors for MCI or dementia development. A higher level of education, a younger age, the absence of malabsorption, and good disease control might serve as protectors against MCI.

Conclusions: GBA interactions, along with systemic inflammation and the adverse effects of medication, might be a cause of MCI and AD development in patients with IBD. Serum biomarkers could prove cheap and useful predictors of MCI development.

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KEYWORDS

gut–brain axis; gut-brain; cognitive dysfunction; affective mood disorders; depression; anxiety; stress; cognitive; cognition; depressive; mood; dementia; protein; proteins; neurotrophic; blood; serum; IBD; inflammatory bowel disease; bowel; gastrointestinal; inflammation; inflammatory

Introduction

Background

Inflammatory bowel disease (IBD) is a group of chronic conditions characterized by intestinal inflammation. The 2 most common types of IBD are Crohn's disease (CD) and ulcerative colitis (UC) [1,2]. The exact mechanisms underlying the development of IBD are yet to be fully understood, but they are thought to be the result of a combination of genetic, environmental, and immunological factors. IBD is believed to be caused by an abnormal immune response that first appears in the gut, where the body's immune system mistakenly attacks the antigens of the healthy gut bacteria, leading to intestinal inflammation and damage to the intestinal barrier. Exposure to certain environmental triggers, such as a diet high in animal fats, smoking, and, most of all, bacterial or viral infections, may increase the risk of IBD. It is believed that the interplay between these factors leads to a self-perpetuating cycle of inflammation and tissue damage, which contributes to the chronic nature of IBD (a so-called vicious cycle). Systemic inflammation plays a role in IBD pathogenesis, which is proven by the beneficial effect of certain anti-inflammatory medications [3].

Clinical manifestations include common digestive symptoms, such as abdominal pain and cramping, diarrhea (which might be bloody), rectal bleeding, weight loss, fatigue, loss of appetite, anemia, nausea and vomiting, dehydration, and fever. In addition to these digestive symptoms, patients with IBD may also experience extraintestinal manifestations, such as joint pain, skin rashes, eye inflammation, and liver disease. The severity and frequency of symptoms can vary greatly between individuals and can also change over time in the same individual. CD carries a higher risk of extraintestinal manifestations, often believed to be caused by one of its pathogenic mechanisms or malabsorption [1,2].

Mild cognitive impairment (MCI) refers to a decline in cognitive abilities that is greater than that in normal aging but certainly not severe enough to interfere with daily life. MCI is often considered a transitional stage between normal aging and more severe forms of cognitive decline, such as dementia. MCI is most commonly characterized by memory problems, such as difficulty in recalling names and recent events, but it can also involve problems with other cognitive abilities, such as language, decision-making, and attention. The impairment of daily activities is a key criterion to diagnosing dementia and the difference between MCI and dementia [4]. Some of the known risk factors for MCI include age, family history, certain medical conditions, lifestyle factors (eg, smoking and excessive alcohol consumption), and certain medications [4]. There are some modern theories that imply inflammation as a mechanism underlying cognitive impairment [5-8]. A diagnosis is typically made based on a thorough medical and neurological evaluation, as well as a comprehensive assessment of the individual's cognitive abilities. This may involve a battery of tests, such as memory and language tests, as well as brain imaging studies. The most important thing to do when a cognitive impairment is suspected is follow-up over time, as early intervention might stop the progression of the disease [4]. MCI can sometimes progress to Alzheimer's disease (AD) or other types of dementia, depending on the cause, age, and other factors [9]. AD is a progressive brain disorder that affects memory, thinking, and behavior. It is the most common cause of dementia. The symptoms of AD usually start with mild memory loss but eventually progress to affect thinking, communication, and the ability to perform daily activities. As the disease progresses, patients may become increasingly dependent on others for their care [10]. Some studies have revealed a link between IBD and the development of AD [6,7,11,12]. Vascular dementia is a type of dementia that occurs due to problems in the blood supply to the brain. It is caused by damage to the blood vessels that deliver oxygen and nutrients to the brain, leading to brain injury and reduced brain function. It is often caused by conditions such as stroke, high blood pressure, and heart disease. Risk factors for vascular dementia include age, smoking, diabetes, and a family history of stroke or heart disease [13].

"Stress disorder" is a term used to describe a mental health condition that can develop in response to a traumatic or stressful event. Individuals may experience a range of symptoms, including intrusive thoughts or memories of the traumatic event; nightmares; and avoidance of people, places, or activities that are associated with the trauma. They may also experience physical symptoms, such as a racing heart, sweating, and muscle tension [14]. "Anxiety disorder" is a general term that refers to a group of mental health conditions characterized by excessive and persistent feelings of worry, fear, and unease [15]. Depression is a mental health condition characterized by persistent feelings of sadness, hopelessness, and a loss of interest in activities that were once enjoyable. It is a common and serious condition that can have a significant impact on an individual's daily life and overall well-being. In addition to feelings of sadness, depression can also cause a range of physical and emotional symptoms, including fatigue, changes in appetite and sleep patterns, difficulty in concentrating, and thoughts of self-harm or suicide. The exact cause of depression is not fully understood, but it is believed to be related to a combination of

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genetic, biological, environmental, and psychological factors [16-18].

Homocysteine (Hcy) is an amino acid. Studies have shown that individuals with IBD have higher serum concentrations of Hcy compared to healthy controls (HC). The exact reason for this association is not fully understood, but it may be related to nutrient deficiencies caused by the inflammation and malabsorption in the gut that often occur in IBD. There is evidence to suggest that elevated levels of Hcy in the blood are associated with an increased risk of MCI and dementia. High Hcy levels have been linked to damage of the blood vessels in the brain, leading to decreased blood flow and oxidative stress, both of which can contribute to cognitive decline [19-23].

Serum amyloid A (SAA) is an acute-phase protein that is produced by the liver in response to inflammation. Amyloid proteins are abnormal fibrous proteins that can build up in tissues and organs, leading to the formation of amyloid plaques. In some cases, amyloid proteins can also enter the bloodstream and circulate in the body. Elevated levels of SAA can be an indicator of various diseases, such as AD, systemic amyloidosis, and hereditary transthyretin amyloidosis. Studies have shown that SAA can induce neuroinflammation and damage neurons in the brain, which may contribute to the development and progression of AD. In addition, SAA has been found to accumulate in the brain in the form of amyloid plaques, which are a hallmark feature of AD. There is limited research on the relationship between SAA levels and IBD. Some studies have suggested that individuals with IBD may have elevated levels of amyloid proteins in their bloodstream, possibly as a result of chronic inflammation in the gut [24-29].

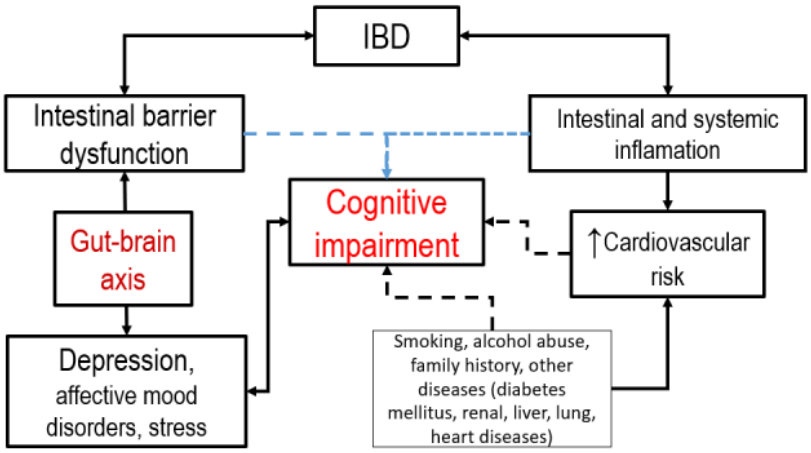
Brain-derived neurotrophic factor (BDNF) is a type of protein that is important for the growth, maintenance, and survival of neurons in the central nervous system. BDNF plays a key role in processes such as neuroplasticity, learning, and memory formation. Low levels of BDNF have been associated with several neurological and psychiatric disorders, including depression and AD. BDNF plays a role in the inflammation associated with IBD. BDNF levels are modified in IBD, but there is little evidence of the direction [30-33].

S100 calcium-binding protein B (S100B) is a protein that is found in a variety of tissues, including the brain, where it has been implicated in several neurobiological processes, including synaptic plasticity, neurogenesis, and neuroinflammation. High serum S100B levels have been associated with a variety of neurological disorders, including traumatic brain injury, stroke, and neurodegenerative diseases. Studies have shown that S100B levels are elevated in the blood and intestinal tissue of patients with IBD, suggesting that the protein may play a role in the development and progression of the disease. In addition, high levels of S100B have been associated with increased inflammation and oxidative stress [34].

In conclusion, IBD is a combination of intestinal barrier dysfunction and intestinal and systemic inflammation. Due to intestinal barrier dysfunction, the intestinal microbiome is affected in the course of the disease or it is the cause of the disease (IBD). Several studies have shown the relationship between the gut–brain axis (GBA) and the development of depression, affective mood disorders, and stress, which might promote the development of cognitive impairment. Systemic inflammation is known to increase cardiovascular risk, which is a risk factor for cognitive impairment. Other risk factors, such as smoking, alcohol consumption, and other diseases, also promote the development of cognitive impairment. Some studies have suggested a link between IBD and cognitive disorders, while other studies have indicated a link between mood disorders and IBD, and still others have suggested a link between mood disorders and cognitive disorders. Therefore, this might be a vicious cycle.

In this study, blood biomarkers, such as SAA (an inflammatory biomarker, a precursor of beta-amyloid plaques in the brain), Hcy (a pro-inflammatory molecule increased in cognitive disorders), S100B (a neuronal structural protein increased in brain injury), and BDNF (decreased in cognitive disorders) were selected in order to validate the hypothesis that these biomarkers could be used as predictive factors for cognitive impairment associated with IBD. As a summary of the basic knowledge that led to the idea of this study, Figure 1 shows the possible implied mechanisms underlying the development of MCI in patients with chronic IBD.

Figure 1. Possible mechanisms underlying the development of cognitive impairment associated with IBD. IBD: inflammatory bowel disease.



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Aim

The aim of this study is to investigate whether GBA interactions play a role in the development of MCI in patients diagnosed with IBD, mainly due to pathological changes at the intestinal level (destruction of the intestinal barrier and pathogenic species in the intestinal microbiome). Presumed cognitive dysfunction blood biomarkers (SAA, Hcy, S100B, BDNF) will be used as predictive factors for the development of MCI or dementia in the study groups. The primary and secondary objectives of the study can be reviewed in Table 1.

Table 1. Primary and secondary objectives.

Objective type	Description
Primary	• To describe the occurrence of MCI[a] in patients with MCI compared to HC[b] • To determine cognitive tests scores for the IBD[c] group compared to HC • To determine serum levels of SAA[d], Hcy[e], BDNF[f], and S100B[g] protein and their association with cognitive testing scores compared to HC • To determine whether there is any correlation between IBD duration, type, blood biomarkers and cognitive scores
Secondary	• To describe the progression of MCI during the follow-up period in both groups • To assess the occurrence of stress and anxiety disorders in the IBD group compared to HC • To assess the occurrence of depression in the IBD group compared to HC • To identify novel biological markers that can predict the stage of MCI or its progression in both groups • To quantify the quality of life of both groups • To identify risk factors for the development of MCI in both groups • To identify the comorbidities of participants in both groups • To quantify the clinical activity scores of the IBD group during patient interviews

[a]MCI: mild cognitive impairment.

[b]HC: healthy controls.

[c]IBD: inflammatory bowel disease.

[d]SAA: serum amyloid A.

[e]Hcy: homocysteine.

[f]BDNF: brain-derived neurotrophic factor.

[g]S100B: S100 calcium-binding protein B.

Methods

Study Design

The study will be a single-center, prospective, observational, analytic study with a group of at least 100 patients with a diagnosis of certainty of IBD and a group of at least 100 HC. The study is part of a PhD thesis, and funding was obtained from the parent university.

Sites, Population, and Case and Control Definitions

The study will take place in Cluj-Napoca, Romania, in the Clinical CF Hospital and the Regional Institute for Gastroenterology and Hepatology “Octavian Fodor.” An agreement was obtained from all the participant clinics.

Two separate groups consisting of at least 100 patients with IBD and at least 100 HC will be recruited. The study will be carried out from May 2021 to January 2030. The HC will be matched with the patients with IBD based on age, sex, and education.

Patients included in the case (IBD) group need to have a clear diagnosis of IBD. For this, a histopathological examination proof will be obtained from the databases of the participant centers or from the personal records of the patients (if the site does not have the original proof diagnosis).

The HC will be recruited from the day care hospital and ambulatory. Their diagnosis must have never been IBD, and they should be in good health at the moment of inclusion.

The inclusion criteria are listed in Table 2 and the exclusion criteria in Table 3.

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Table 2. Inclusion criteria.

Study group	Inclusion criteria
IBD[a]	• Males and females aged over 18 years • Patients with a confirmed IBD diagnosis • Written informed consent obtained
HC[b]	• Males and females aged over 18 years • Good level of health • Written informed consent obtained

[a]IBD: inflammatory bowel disease.

[b]HC: healthy controls.

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Table 3. Exclusion criteria.

Exclusion criteria	Details
Absolute exclusion criteria	
Prior stroke or myocardial infarction or cardiac arrest	Patients with known stroke and myocardial infarction are already known to have an accelerated cognitive decline rate due to a vascular mechanism. Postanoxic encephalitis after cardiac arrest carries an additional risk of cognitive decline.
Severe organ failure	This includes the presence of end-stage respiratory, liver, renal, and cardiac diseases.
Familial AD[a]	Patients with known familial AD develop the disease at an earlier age.
Concomitant past and current neurological disorders	These include epilepsy, encephalopathy due to any cause, history of severe head trauma, history of encephalitis, multiple sclerosis, Parkinson's disease, brain tumor, and dementia due to any cause.
Pregnancy	Pregnant women will not be included because they carry potentially other risks and might be stressed about their situation.
Prior psychiatric disorders and chronic use of neuroleptics and anticholinergic medication	These include all psychiatric pathologies, including depression, anxiety disorder, attention deficit hyperactivity disorder, autism spectrum disorders, posttraumatic stress disorder, schizophrenia, personality disorders, and alcohol and drug abuse. Also in this category is the use of neuroleptics, which are drugs that decrease cerebral function, although they might interfere with cognitive testing, depending on dose. Anticholinergic medication might slow cognitive functioning.
Unclear diagnosis	Patients with an unclear diagnosis will not be recruited as they might have a different pathology.
Involvement in clinical trials	Participation in clinical trials for medication might interfere with the study results because of the unknown side effects of the medication or other factors.
Current and past history of neoplasia	Patients with neoplasms already have a poor performance status, and this might negatively influence the results of this study. in addition, the medication might interfere with cognitive testing.
Use of vitamin B12 and B9 supplements	Vitamin B12 and B9 supplements might decrease serum levels of Hcy[b].
Short bowel syndrome	Intestinal resection carries the risk of malabsorption and might be a cause of cognitive impairment.
Diabetes mellitus	Diabetes mellitus carries an additional risk of MCI[c].
Hypothyroidism	Hypothyroidism leads to decreased brain performance.
Prior diagnosis of atrial fibrillation	Patients with known atrial fibrillation are at greater risk of cognitive dysfunction due to microembolic events.
Uncontrolled arterial hypertension	Patients with uncontrolled hypertension carry an additional risk of cognitive dysfunction.
Relative exclusion criteria	
Acute IBD[d] flares	Acute flares involve a burden of stress and anxiety, which might lead to false-positive results in cognitive testing. Patients will be informed of the possibility of inclusion, and if they agree, testing will be performed after the acute flare is over.
Age over 70 years	Patients aged over 70 years might have age-related cognitive impairment, which might interfere with the study results.

[a]AD: Alzheimer's disease.

[b]Hcy: homocysteine.

[c]MCI: mild cognitive impairment.

[d]IBD: inflammatory bowel disease.

Study Timeline

Patients will be recruited based on the inclusion and exclusion criteria. The recruitment moment will be called "baseline." Follow-up will be performed at 12, 24, and 36 months. A systematization of the procedures is presented in Table 4.

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Table 4. Study timeline.

Objective	Timeline			
	Baseline	12-month follow-up	24-month follow-up	36-month follow-up
Eligibility assessment	X[a]	—[b]	—	—
Signing of informed consent form	X	—	—	—
Exclusion and inclusion criteria reassurance	X	X	X	X
Demographics	X	—	—	—
Relationship status	X	—	—	—
Short cognitive and affective questionnaire	X	X	X	X
Physical examination	X	X	X	X
Medication assessment	X	X	X	X
Medical history assessment	X	—	—	—
Collection of blood sample and storage	X	—	—	—
Detailed risk factor questionnaire	X	—	—	—
Clinical disease activity score	X	X	X	X
Depression, stress, and anxiety screening	X	X		
COVID-19 questionnaire	X	—	—	—
Quality-of-life questionnaire	X	X	X	X
MOCA[c]	X	X	X	X
MIS[d]	X	X	X	X
TMT[e]-A	X	—	—	X
TMT-B	X	—	—	X
DSST[f]	X	—	—	X
FDST[g]	X	—	—	X
BDST[h]	X	—	—	X
ADL[i] questionnaires	X	X	X	X
IADL[j]	X	X	X	X

[a]X: applicable.
[b]—: not applicable.
[c]MOCA: Montreal Cognitive Assessment.
[d]MIS: memory impairment score.
[e]TMT: Trail Making Test.
[f]DSST: Digit Symbol Substitution Test.
[g]FDST: forward digit span testing.
[h]BDST: backward digit span testing.
[i]ADL: activities of daily living.
[j]IADL: Instrumental Activities of Daily Living.

Procedures and Examinations

Clinical procedures and examinations will be performed in a silent room so there is no disturbance to both examiner and participant. Participants will receive information about each test that will be conducted. The scales and questionnaires used in the study are listed in Table 5.

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Table 5. Scales used in the study.

Objective	Scales
Assessment of IBD[a] severity	HBI[b] for patients with CD[c] and SCCAI[d] for patients with UC[e]
Assessment of quality of life	Romanian WHOQOL-BREF[f] questionnaire
Assessment of depression, anxiety, and stress	Romanian DASS[g]-21
Cognitive assessment	Romanian MOCA[h] 7.1, TMT[i]-A and TMT-B, backward digit testing, forward digit testing, DSST[j]
Assessment of COVID-19	Short COVID-19 questionnaire
Assessment of ADL[k]	IADL[l] scale, Katz ADL scale

[a]IBD: inflammatory bowel disease.
[b]HBI: Harvey-Bradshaw Index.
[c]CD: Crohn's disease.
[d]SCCAI: Simple Clinical Colitis Activity Index.
[e]UC: ulcerative colitis.
[f]WHOQOL-BREF: World Health Organization Quality of Life Brief Version.
[g]DASS: Depression-Anxiety-Stress Scale.
[h]MOCA: Montreal Cognitive Assessment.
[i]TMT: Trail Making Test.
[j]DSST: Digit Symbol Substitution Test.
[k]ADL: activities of daily living.
[l]IADL: Instrumental Activities of Daily Living.

The Montreal Cognitive Assessment (MOCA) 7.1 scale includes the Trail Making Test (TMT), drawing, long-term memory testing, verbal fluency tests, short-term memory recall testing, calculus, and spatial and temporal orientation questions. The maximum score obtained is 30 points. The normal range is ≥26 points. An additional point is given to patients who have an education level of ≤12 years.

The memory impairment score (MIS) is derived from the MOCA scale. The maximum score is 15 points. It derives from the short-term memory recall test. Subjects have to recall 5 words to gain points. If they recall the words spontaneously, 3 points are awarded for each word. If any clue is provided, 2 points are awarded if the word is recalled. If variants are provided, 1 point is awarded if the word is recalled. No point is awarded if the word is not recalled.

The TMT involves the subject drawing a trail between 2 points, with the entire operation being timed. It has 2 different parts, TMT-A and TMT-B. TMT-A involves drawing a continuous line between numbers. TMT-B involves drawing a continuous line, alternating letters and numbers. An example of the test is provided before each part. TMT-A has a maximum time of 100 seconds, and 101 seconds means the subject has failed the test. TMT-B has a maximum time of 300 seconds, and 301 seconds means the subject has failed the test.

The Digit Symbol Substitution Test (DSST) involves the subject changing some numbers to symbols as specified in the legend of the test. A training zone is first created. If the training is completed, the subject is given 90 seconds to complete as many substitutions as possible. Correct and incorrect answers are counted.

In forward digit span testing (FDST) and backward digit span testing (BDST), the subject must recall the numbers provided by the examiner in forward order and then in backward order. FDST involves strings of numbers ranging from 2 to 8 numbers, and BDST involves strings of numbers ranging from 2 numbers to 7 numbers. Each string has 2 different variants, and the subject must make a maximum of 1 mistake in these variants, otherwise the test ends.

The Depression-Anxiety-Stress Scale (DASS) is a scale that includes 21 questions split into 3 categories (depression, stress, and anxiety), with 7 questions per category, the questions being interleaved. Each question has a score from 0 to 3, and the result is multiplied by 2.

The Harvey-Bradshaw Index (HBI) and the Simple Clinical Colitis Activity Index (SCCAI) are used for screening the subject. In this study, they are part of the inclusion criteria.

The quality-of-life instruments available in Romania are limited; therefore, the World Health Organization Quality of Life Brief Version (WHOQOL-BREF) will be used in order to determine the quality of life of our participants. The Instrumental Activities of Daily Living (IADL) is an 8-item scale that includes some instrumental daily activities, and it is a useful and essential tool for differentiating MCI from dementia. The Katzl ADL scale is a 6-item scale that includes casual daily activities and is also a useful and essential tool for differentiating MCI from dementia.

A blood sample will be obtained from each participant.

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Outcomes

The first to be mentioned are demographic variables, which will be useful for stratifying our participants; the expected answers are presented in Table 6.

Table 6. Demographic variables.

Demographic characteristics	Expected answers
Education level	Absolute number of years
Current living environment	Rural, urban <10,000 inhabitants, urban 10,000-49,999 inhabitants, urban 50,000-99,999 inhabitants, urban >100,000 inhabitants
Marital status	Married, single, cohabitation, divorced, polygamy, widowed
Employment	Employed full-time, employed part-time, freelancer, retired, student, trainee
Toxic working environment	Yes, no, do not know
Night shifts	Yes, no
Financial status	Enough for a living and saving, enough for a living but not saving, not enough for a living
Monthly wage (average per family member)	<1500 lei (<USD 316.31), 1500-2500 lei (USD 316.31-527.18), 2500-3500 lei (USD 527.18-738.05), 3500-4500 lei (USD 738.05-948.93), >4500 lei (>USD 948.93)

The relationship status is important for affective mood but also for cognitive functioning; therefore, 3 questions will be answered by the participants, listed in Table 7.

Table 7. Current and past relationship data.

Question	Expected responses
Married before diagnosis of IBD[a]	Yes, no, not available
Relationship destabilization due to the disease	Yes, and it caused a broken relationship or divorce; yes, but it did not cause a broken relationship or divorce; no
Helped with the disease by the life partner	Yes, no, not available

[a]IBD: inflammatory bowel disease.

A short cognitive assessment will be performed in order to accommodate the participants in the subsequent questionnaires and tests. Questions are mentioned in Table 8.

Table 8. Short cognitive (long-term memory) and affective assessment.

Question	Expected responses
Trouble with memory in the past month	Yes, occasionally, no
Changes in personality	Yes, no
Difficulties in handling daily activities due to memory changes	Yes, no
Family history of dementia	Yes, AD[a]; yes, other dementia; no; do not know
Current president of Romania	Correct or incorrect answer
The year of the Great Union in Romania	Correct or incorrect answer
Naming a pencil	Correct or incorrect answer
Naming a medical coat	Correct or incorrect answer
Naming a clock	Correct or incorrect answer

[a]AD: Alzheimer's disease.

A short clinical examination will be performed. A full history of IBD will be taken. Variables obtained are mentioned in Table 9. The HBI and SCCAI will be the clinical disease activity scales used in the study, as mentioned in Table 10. Risk factor assessment will also be performed (Table 11).

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Table 9. Physical examination and past medical history.

Variables	Expected responses
Physical examination	
Blood pressure	Value (mmHg)
Pulse	Absolute number (beats/minute)
Respiratory rate	Absolute number (respirations/minute)
Peripheric oxygenation percentage	Value (%)
Medication assessment	All concomitant medications used (international common names and dosing and posology)
IBD[a] history assessment	
Year of diagnosis	Absolute number
Montreal classification	A-L-B[b] for CD[c] patients, E-S[d] for UC[e] patients
Family history of IBD	Yes, no, do not know
Number of flares in the past 12 months	Absolute number
Number of flares since diagnosis	Absolute number
Number of hospitalizations for flares in the past 12 months	Absolute number
History of corticosteroid dependency	Yes, no
Duration of corticosteroid dependency (if the above answer is yes)	Absolute number (months)
Current medication	Name, dose, duration
Past medication	Name, dose, duration
Complications	Enumeration

[a]IBD: inflammatory bowel disease.

[b]A-L-B: onset (A), disease location (L), and disease behavior (B).

[c]CD: Crohn's disease.

[d]E-S: extent (E) and severity (S).

[e]UC: ulcerative colitis.

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Table 10. Clinical disease activity score assessment.

Scales and items	Scoring (points in parentheses)
HBI[a] (0-4 points=remission; 5-7 points=mild disease; 8-16 points=moderate disease; >16 points=severe disease)	
General health	Very well (0), slightly below par (1), poor (2), very poor (3), terrible (4)
Abdominal pain	None (0), mild (1), moderate (2), severe (2)
Liquid or soft stools on the previous day	Absolute number (1 point for each)
Abdominal mass	None (0), dubious (1), definite (2), definite tender (3)
Complications	Arthralgia (1), uveitis (1), erythema nodosum (1), aphthous ulcer (1), pyoderma gangrenosum (1), anal fissure (1), new fistula (1), abscess (1)
SCCAI[b] (0-20 points; ≥5=active disease)	
Bowel frequency	0-3 stools (0), 4-6 stools (1), 7-9 (stools 2), >9 stools (3)
Bowel frequency (night)	0 stools (0), 1-3 stools (1), 4-6 stools (2)
Urgency defecation	No urgency (0), hurry (1), immediately (2), incontinence (3)
Blood in stool	No blood (0p, traces (1), occasionally frank (2), usually frank (3)
General health	Very well (0), slightly below par (1), poor (2), very poor (3), terrible (4)
Extracolonic manifestations	No feature (0), 1 feature (1), 2 features (2), 3 features (3), 4 features (4), 5 features (5)

[a]HBI: Harvey-Bradshaw Index.

[b]SCCAI: Simple Clinical Colitis Activity Index.

Table 11. Risk factor questionnaire.

Detailed risk factor questionnaire	Expected responses
Active smoker status	Yes, no, ex-smoker
Number of smoking years	Absolute number
Number of abstinence years	Absolute number
Daily number of cigarettes	Absolute number
Alcohol drinking rate	Daily, 3-5 times per week, 1-2 times per week, rarer, no drinking, other options (to be mentioned)
30 minutes of physical activity	Daily, 5 times per week, rarer, no physical activity, other frequency (to be mentioned)
Dietary trend	Nonspecific diet, vegetarian, vegan, flexitarian, colitis regimen, other (to be mentioned)
Number of sleeping hours per day (24 hours)	Absolute number
Daytime tiredness	Yes, no
Troubles with maintaining sleep	Yes, no
Troubles with falling asleep	Yes, no

A cognitive assessment must always be preceded by a screening of depression, anxiety, and stress because this may falsely create a diagnosis of cognitive dysfunction. Scales and their interpretations can be seen in Table 12.

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Table 12. Depression, anxiety, and stress screening; COVID-19 impact; current quality of life; and ADL[a] assessment.

Scales and items	Expected responses
DASS[b]-21 scale (7 items each for depression, anxiety, and stress)	Depression (0-9, 10-13, 14-20, 21-27, ≥28 points), anxiety (0-7, 8-9, 10-14, 15-19, ≥20 points), stress (0-14, 15-18, 19-25, 26-33, ≥34 points)
COVID-19 impact questionnaire	
Vaccination status	Yes, no
COVID-19 vaccine (if the above answer is yes)	BNT162b2, NJ-78436735 (Ad26.COV2.S), AZD1222 (ChAdOx1), mRNA[c]-1273, other (mentioned in the questionnaire)
Number of doses	Absolute number
History of infection	Yes, no, do not know
WHOQOL-BREF[d]	Social relationships (4-20 points), environment (4-20 points), physical health (4-20 points), psychological (4-20 points)
ADL	
Katz ADL	0-6 points
IADL[e]	0-8 points

[a]ADL: activities of daily living.

[b]DASS: Depression Anxiety Stress Scale.

[c]mRNA: messenger ribonucleic acid.

[d]WHOQOL-BREF: World Health Organization Quality of Life Brief Version.

[e]IADL: Instrumental Activities of Daily Living

Cognitive assessment will include the baseline scales and follow-up at 12 months. The scoring is shown in Table 13.

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Table 13. Cognitive assessment scoring.

Timeline and scales	Scoring
Baseline	
MOCA[a]	0-30 points: executive function (0-5 points), naming (0-3 points), memory (0-5 points), attention (0-6 points), calculus (0-3 points), language (0-3 points), orientation (0-6 points), abstractization (0-2 points)
MIS[b]	0-15 points
BDST[c]	0-14 points
FDST[d]	0-16 points
TMT[e]-A	0-100 seconds (101 seconds means failed test)
TMT-B	0-300 seconds (301 seconds means failed test)
DSST[f]	Absolute number of correct answers (maximum 90 correct answers), absolute number of incorrect answers (maximum 90 incorrect answers)
12-month follow-up	
MOCA	0-30 points: executive function (0-5 points), naming (0-3 points), memory (0-5 points), attention (0-6 points), calculus (0-3 points), language (0-3 points), orientation (0-6 points), abstractization (0-2 points)
MIS	0-15 points
24-month follow-up	
MOCA	0-30 points: executive function (0-5 points), naming (0-3 points), memory (0-5 points), attention (0-6 points), calculus (0-3 points), language (0-3 points), orientation (0-6 points), abstractization (0-2 points)
MIS	0-15 points
36-month follow-up	
MOCA	0-30 points: executive function (0-5 points), naming (0-3 points), memory (0-5 points), attention (0-6 points), calculus (0-3 points), language (0-3 points), orientation (0-6 points), abstractization (0-2 points)
MIS	0-15 points
48-month follow-up	
MOCA	0-30 points: executive function (0-5 points), naming (0-3 points), memory (0-5 points), attention (0-6 points), calculus (0-3 points), language (0-3 points), orientation (0-6 points), abstractization (0-2 points)
MIS	0-15 points
BDST	0-14 points
FDST	0-16 points
TMT-A	0-100 seconds (101 seconds means failed test)
TMT-B	0-300 seconds (301 seconds means failed test)
DSST	Absolute number of correct answers (maximum 90 correct answers), absolute number of incorrect answers (maximum 90 incorrect answers)

[a]MOCA: Montreal Cognitive Assessment.

[b]MIS: memory impairment score.

[c]BDST: backward digit span testing.

[d]FDST: forward digit span testing.

[e]TMT: Trail Making Test.

[f]DSST: Digit Symbol Substitution Test.

Laboratory Procedures and Outcomes

We will obtain the serum from 5 mL of the blood sample of each participant and quantitatively measure serum SAA, Hcy, S100B, BDNF levels. The blood samples will be obtained at baseline. Other blood measurements will be performed at the hospital's laboratory as part of the visit, and values will be taken from the registry. All the necessary data that will be obtained from blood testing are mentioned in Table 14.

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Table 14. Blood sample outcomes.

Markers	Measurement unit
Presumed cognitive biomarkers (serum levels)	
SAA[a]	mcg/mL
Hcy[b]	µmol/L
BDNF[c]	ng/mL
S100B[d]	mcg/mL
Common biomarkers (taken from the hospital registry from the baseline presentation period)	
C-reactive protein	mg/dL
Total hemoglobin	g/dL
Red blood cell count	number/mm^3
Fecal calprotectin	µg/mg
Triglycerides	mg/dL
Total cholesterol	mg/dL
Low-density lipoprotein (LDL) cholesterol	mg/dL
High-density lipoprotein (HDL) cholesterol	mg/dL
LDL/HDL ratio	fraction
Neutrophile-to-lymphocyte (NLR) ratio	fraction
Erythrocyte sedimentation rate	mm/hour
Mean corpuscular volume (MCV)	%
Basal blood glucose	mg/dL
Fibrinogen	mg/dL
Lactate dehydrogenase (LDH)	IU/L
Creatine kinase (CK)	U/L
CK-MB	% out of total CK

[a]SAA: serum amyloid A.

[b]Hcy: homocysteine.

[c]BDNF: brain-derived neurotrophic factor.

[d]S100B: S100 calcium-binding protein B.

Preparation of Serum Samples

The required materials are a serum collection vaccutainer, a fixed-angle centrifuge for 15 mL tubes, 1.5 mL protein low-binding tubes, 100-1000 µL tips, and a cryogenic box.

For serum preparation, after the blood is collected, the tube will be inverted gently, as indicated in the manufacturer's instructions (in general 5-6 times). The tube will be then left, as indicated in the manufacturer's instructions (in general 30 minutes), at room temperature to form a blood clot. Next, the tube will be centrifuged at 2000× *g* for 10 minutes at 4 °C, as indicated in the manufacturer's instructions, and 500 µL of serum will be aliquoted in 1.5 mL protein low binding tubes. The serum aliquots will be immediately frozen at –80 °C until use. No more than 2 freeze-thaw cycles will be allowed. The tube with the blood clot will be discarded in a biohazard waste container.

Absolute Quantification of Biomarkers

SAA, Hcy, S100B, and BDNF are biomarkers that will be quantified from the serum samples using standardized solid-phase sandwich enzyme-linked immunosorbent assay (ELISA) kits. Table 15 presents the kits that will be used and their related characteristics.

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Table 15. ELISA[a] kits to be used for biomarker quantification.

Biomarker	ELISA kit	Serum volume required (µL)	Kit performance	Assay duration (hours)
SAA[b]	Abclonal catalog # RK04228 or similar	100	Range:0.156-10 ng/mL Sensitivity: <0.071 ng/mL Specificity: 50 ng/mL Intra-assay precision: CV[c]<10% Interassay precision: CV<12%	5.0
Hcy[d]	Assaygenie catalog # HU-FI04768 or similar	50	Range: 7.813-500 pmol/mL Sensitivity: <4.688 pmol/mL Specificity: 50 ng/mL Intra-assay precision: CV<8% Interassay precision: CV<10%	2.5
S100B[e]	Abclonal catalog # RK02234 or similar	100	Range: 46.9-3000 pg/ml Sensitivity: <23.5 pg/mL Specificity: 50 ng/mL Intra-assay precision: CV<10% Inter-assay precision: CV<15%	5.0
BDNF[f]	Abclonal catalog # RK00074 or similar	100	Range: 23.4-1500 pg/ml Sensitivity: <6.3 pg/mL Specificity: 50 ng/mL Intra-assay precision: CV<10% Interassay precision: CV<15%	5.0

[a]ELISA: enzyme-linked immunosorbent assay.

[b]SAA: serum amyloid A.

[c]CV: coefficient of variation.

[d]Hcy: homocysteine.

[e]S100B: S100 calcium-binding protein B.

[f]BDNF: brain-derived neurotrophic factor.

The required materials for this procedure are the serum aliquots, ice, a fixed-angle centrifuge for 2 mL tubes, 1.5 mL protein low-binding tubes, tips, pipettes, 15 or 50 mL tubes (depending on the ELISA kit instructions), a 96-well plate shaker (if mentioned by the ELISA kit manufacturer), a 96-well plate mixer with heating (if mentioned by the ELISA kit manufacturer), and a multiplate reader.

Serum aliquots will be thawed on ice and then mixed gently. Samples will be centrifuged at 13000× *g* for 2 minutes at 4°C to remove the cell debris. The volume indicated in the kit manufacturer's protocol will be taken. The instructions will be used for sample preparation and analysis. Measurements will be made in duplicate.

Calculation of Results

The optical density (OD) of each well will be read using a microplate reader set to 450 nm. The duplicate readings for each standard, control, and sample will be averaged, and the average 0 standard OD will be subtracted. A standard curve will be created by reducing the data using computer software capable of generating a 4-parameter logistic (4-PL) curve fit. Sample concentrations will be calculated from the equation. If samples have been diluted, the concentration read from the standard curve will be multiplied by the dilution factor.

Power Calculation, Statistical Model, and Data Analysis

Based on previous studies, the power of the study, with an α of .05 and a power of 80%, the required number of cases and controls is 52 and 26, respectively, for a mean difference in 2 points (SD 3.0) in MOCA scales.

Statistics will be computed using IBM SPSS software version 28.0.1 or newer. Descriptive analysis of the baseline characteristics of the overall population by gender, age, and education will be conducted. Continuous variables will be presented as the mean (SD) or the median (IQR), and countable data will be presented as numbers and percentages. Comparisons of groups will be conducted using the t-test or the Wilcoxon rank-sum test based on the type of distribution of data and the homogeneity of the variance. The chi-square test or the Fisher exact probability method will be used for counting data, as appropriate.

Multiple linear and logistical regression analyses will be performed to evaluate the association between outcomes and potential risk factors identified in the questionnaires. Participants lost to follow-up will be treated as right-censored data. The Pearson coefficient will be used to assess the correlation between cognitive scores and serum levels of the studied biomarkers. A

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2-sided significance level of .05 will be used for all primary and secondary analyses unless stated otherwise.

Ethical Considerations

The protocol was approved by the Ethics Committees of the Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca (# 52/28.02.2022), the Regional Institute of Gastroenterology and Hepatology "Octavian Fodor" (# 10148/11.10.2022), and the Clinical CF Hospital (# 14/13.07.2022). It was registered with ClinicalTrials (identifier NCT05760729). The study will be conducted in accordance with the ethical principles outlined in the current version of the Declaration of Helsinki of 1975, revised in 2013, and all applicable local regulatory requirements.

All participants will be required to personally sign and date the latest approved version of the informed consent form (ICF) before any study specific procedures are performed. A written version of the participant information and informed consent will be presented to each participant, detailing no less than the exact nature of the study, what it will involve for the participant, the implications and constraints of the protocol, the known side effects and any risks involved in taking part, and the agreement to use the data for primary and secondary data analyses. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, without affecting their legal rights, and with no obligation to provide a reason for withdrawal.

All participants will be allowed as much time as needed to consider the information and an opportunity to question the investigator or other independent parties to decide whether they will participate in the study. Written informed consent will then be obtained by means of a participant-dated signature and a dated signature of the person who presented and obtained the informed consent. A copy of the signed informed consent will be provided to each participant. The original signed form will be retained at the study site.

There will be no participation fee nor any payment to any participant in the study.

Each participant will receive a unique number that will represent their unique ID in the study. Their blood sample will carry the same ID. The database will not include the name of the participants, as they will be deidentified, but their initials and national unique ID will be used to form a code (eg, John Doe with the unique ID 43 will have the code JD_43).

Results

The collection of study data started in December 2021, and it is currently ongoing. Since the start of the study, 53 patients with IBD have been recruited and 50 HC were matched until the moment of this paper being published. The blood samples collected were stored according to the laboratory procedures. Data collection should end in January 2030. Intermediary analysis will be performed in April 2024 after the first 50 patients recruited go through the 12-month follow-up visit. Recruitment will continue until the number of participants in the IBD and HC groups is met (n=100 for each group).

Discussion

Summary

The aim of the study is to evaluate whether there is a correlation between the level of the blood biomarkers studied (SAA, Hcy, S100B, and BDNF) and cognitive scores (MOCA, MIS, FDST, BDST, TMT-A, TMT-B, DSST) in a period of 12-48 months in patients with IBD compared to HC. Previous studies have shown that patients with IBD have lower cognitive scores compared to HC [3,5,8,9,11,12,35]. We expect similar results. Multiple biomarkers have been found modified in patients with MCI but also in patients with IBD; therefore, some reliable biomarkers have been selected for analysis [19-34]. A positive correlation between worse cognitive scores and elevated serum levels is expected to be found.

Perspectives and Clinical Implications

This study might serve as another "brick in the wall" for the question of whether the GBA is involved in the development of MCI. If the results show a correlation between the clinical onset and length of IBD and the risk of MCI development, we could rethink treatment strategies. Serum biomarkers could prove a useful tool for stratifying the risk of MCI development, as their levels can be determined for all patients and the costs are not high.

A possible link between IBD and MCI through the GBA should be further investigated at the molecular level in order to find the underlying pathogenic mechanism. According to the diagnosis criteria of AD, if we find a progression from MCI to AD in patients with IBD, perhaps a clinical study involving the detection of abnormal proteins in the cephalorahidian fluid obtained from a lumbar puncture could be performed in the future. In addition, we could expect some clinical trials involving prevention of the progression from MCI to AD if some more underlying pathogenic mechanisms are found. Furthermore, clinical trials studying the possible prophylactic treatments for the development of MCI must be performed in order to stop this invalidating disease from affecting the population.

Strengths and Limitations

One of the biggest limitations nowadays is the fear of the hospital, a so-called "syndrome" caused by the COVID-19 pandemic. However, this is overcome by the fact that many patients require medical prescriptions monthly or at 2-3-month intervals, so they have to visit the hospital. Language will be a barrier in this study because there are many cognitive tests and questionnaires that have never been validated clinically in Romania, so we have a narrow range to pick from. Neither telephonic nor video testing is available due to language issues. Finance is also a step-back in the development of this study, but it will not limit the results, because it is a prospective and screening study.

Risk of Bias

The risks of bias are negligible because the tests used have clear instructions and interpretations. However, there is a risk that the participants might grow impatient and not correctly complete the questionnaires or might rush them to finish them faster. To

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reduce the risk of bias, the participants will be taken to a silent room and enough time will be provided for them to complete the questionnaires and tests in the best-possible correctly. In addition, clinical data will be obtained before laboratory biomarkers are dosed, so we will not know the results—whether they predict the development of MCI.

Risks and Side Effects

The risks associated with this study are the risks of normal blood collection, which is conducted anyway from time to time when patients visit the hospital for their regular blood analysis. In addition, almost all presentations at the hospital require blood sample collection; therefore, the study should not carry an additional risk. Other minor risks could be found in participants with stress or anxiety, and the fact that they will be interviewed for depression, anxiety, stress, and cognitive function might serve as an aggravating factor. Some patients might not take the tests seriously and might score worse on cognitive testing.

Unexpected Findings

The results may be contrary to the aim of the study. To the best of our knowledge, patients with IBD have a good level of education and this might lead to better cognitive functioning. In addition, patients with IBD are younger in age, and because education is better nowadays, cognitive tests could show better cognitive functioning among well-educated participants. Furthermore, maybe some treatments that are used to control IBD serve as protective factors against MCI, or maybe other medications might be a risk factor for the development of MCI.

Plan for Publication and Future Data Collection

The first phase of the protocol will include 50 patients with IBD and 50 HC, who will be evaluated for 12 months, and the results will be published. Furthermore, we will start applying for others grants in order to continue the clinical study. Details of the enrolled participants will be recorded in a database, and further studies will start based on the results of the first phase. Another study based on the COVID-19 questionnaire will be conducted with participants not included in this protocol (this study includes just partial results). Next, a third study on the quality of life and depression, anxiety, and stress screening will also be conducted with participants not included in this protocol. Finally, a fourth study including results from the first phase with participants not included in this protocol will be conducted.

Conclusion

The GBA might be the link between IBD and the development of MCI associated with systemic inflammation. Mood disorders can be a prodrome for the development of cognitive dysfunction. Serum biomarkers might serve as cheap predictive factors for the development of MCI. Therapies might require adjustments in order to prevent neurological complications of IBD.

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Data Availability

Study data will be available upon reasonable request from the corresponding author. The data will not be published on a public platform for ethical reasons. The pseudonymization of the participants will be removed from the database if a request for access is received.

Authors' Contributions

OS contributed to the investigation, conceptualization, original draft preparation, funding acquisition, and visualization; VV, methodology, data curation, and resources; AS, funding acquisition, visualization, investigation, and resources; MI, software, resources, project administration, and formal analysis; and AIT, supervision, review and editing, validation, and project administration.

Conflicts of Interest

None declared.

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Abbreviations

AD: Alzheimer’s disease
ADL: activities of daily living
BDNF: brain-derived neurotrophic factor
BDST: backward digit span testing
CD: Crohn’s disease
DASS: Depression Anxiety Stress Scale
DSST: Digit Symbol Substitution Test
ELISA: enzyme-linked immunosorbent assay
FDST: forward digit span testing
GBA: gut–brain axis
HBI: Harvey-Bradshaw Index
HC: healthy controls
Hcy: homocysteine
IADL: Instrumental Activities of Daily Living
IBD: inflammatory bowel disease
MCI: mild cognitive impairment
MIS: memory impairment score
MOCA: Montreal Cognitive Assessment
S100B: S100 calcium-binding protein B
SAA: serum amyloid A
SCCAI: Simple Clinical Colitis Activity Index
TMT: Trail Making Test
UC: ulcerative colitis
WHOQOL-BREF: World Health Organization Quality of Life Brief Version

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Corrigenda and Addenda

Correction: A Text Messaging–Based Support Intervention to Enhance Pre-exposure Prophylaxis for HIV Prevention Adherence During Pregnancy and Breastfeeding: Protocol for a Randomized Controlled Trial

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Related Article:

Correction of: https://www.researchprotocols.org/2023/1/e41170

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In “A Text Messaging–Based Support Intervention to Enhance Pre-exposure Prophylaxis for HIV Prevention Adherence During Pregnancy and Breastfeeding: Protocol for a Randomized Controlled Trial” (JMIR Res Protoc 2023;12:e41170), the authors noted a typographical error in one of the senior author’s name.

In the originally published article, this author’s name was incorrectly spelled as:

Jilian Pintye

This has now been corrected to:

Jillian Pintye

The correction will appear in the online version of the paper on the JMIR Publications website on March 17, 2023, together with the publication of this correction notice. Since we have not made any changes to the main paper, we have not resubmitted the article.

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Corrigenda and Addenda

Correction: Evaluating the Acceptance and Usability of an App Promoting Weight Gain Prevention and Healthy Behaviors Among Young Women With a Family History of Breast Cancer: Protocol for an Observational Study

Mary Pegington[1,2], MSc; Alan Davies[3], PhD; Julia Mueller[4], PhD; Rachel Cholerton[5], PhD; Anthony Howell[1,2,6,7], MBBS; D Gareth Evans[2,6,8], MBBS; Sacha J Howell[1,2,6,7], MBBS, PhD; David P French[5,6], PhD; Michelle Harvie[1,2,6], PhD

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Related Article:

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(JMIR Res Protoc 2023;12:e47765) doi:10.2196/47765

In "Evaluating the Acceptance and Usability of an App Promoting Weight Gain Prevention and Healthy Behaviors Among Young Women With a Family History of Breast Cancer: Protocol for an Observational Study" (JMIR Res Protoc 2022;11(12):e41246) the authors noted one error.

Reference 15 originally appeared as:

Cacciamani GE, Aron M, Gill I, Desai M. Re: oncological outcome according to attainment of pentafecta after robot-assisted radical cystectomy in patients with bladder cancer in the multicentre KORARC database. BJU Int 2020 Nov;126(5):644-645. [doi: 10.1111/bju.15222] [Medline: 32870582]

This has been changed to:

Michie S, Johnston M, Francis J, Hardeman W, Eccles M. From Theory to Intervention: Mapping Theoretically Derived Behavioural Determinants to Behaviour Change Techniques. Applied Psychology 2008 July;57(4):660-680. [doi: 10.1111/j.1464-0597.2008.00341]

The correction will appear in the online version of the paper on the JMIR Publications website on April 4, 2023 together with the publication of this correction notice. Because this was made after submission to PubMed, PubMed Central, and other full-text repositories, the corrected article has also been resubmitted to those repositories.

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Corrigenda and Addenda

Correction: The Evaluation of Health Care Services for Children and Adolescents With Post–COVID-19 Condition: Protocol for a Prospective Longitudinal Study

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Related Article:

Correction of: https://www.researchprotocols.org/2023/1/e41010

(JMIR Res Protoc 2023;12:e48338) doi:10.2196/48338

In "The Evaluation of Health Care Services for Children and Adolescents With Post–COVID-19 Condition: Protocol for a Prospective Longitudinal Study" (JMIR Res Protoc 2023;12:e41010) the authors made 5 reference corrections.

In Table 2, column 2, row 13, the reference in the following text:

> *Patient-Reported Outcomes Measurement Information System (PROMIS) Pediatric Short Form version 2.0–Fatigue 10a [35]*

Has been changed to:

> *Patient-Reported Outcomes Measurement Information System (PROMIS) Pediatric Short Form version 2.0–Fatigue 10a [36]*

In Table 2, column 2, row 14, the reference in the following text:

> *DePaul Symptom Questionnaire Focusing on Post-exertional Malaise (DSQ-PEM) [36]*
>
> *Has been changed to:*
>
> *DePaul Symptom Questionnaire Focusing on Post-exertional Malaise (DSQ-PEM) [37]*

In Table 2, column 2, row 15, the reference in the following text:

> *Strength and Difficulties Questionnaire (SDQ) [37], proxy questionnaire (age ≥12 years: self-reported questionnaire)*

Has been changed to:

> *Strength and Difficulties Questionnaire (SDQ) [38], proxy questionnaire age ≥12 years: self-reported questionnaire*

The references in following sentences under Patient-Reported Outcome Measures:

> *The questionnaire comprises 10 items, which are answered on a 5-point Likert scale [35]. A total score is calculated by building the sum of the individual item scores, with higher scores indicating greater fatigue [39]. The DePaul Symptom Questionnaire Focusing on PEM (DSQ-PEM) provides information on the presence of PEM by asking about the frequency and severity of different symptoms [36]. Further, the emotional problems scale of the Strength and Difficulties Questionnaire (SDQ) is used to examine mental health. Items are answered on a 3-point Likert scale. By summing up the individual item scores, a total score is determined that indicates whether a patient shows abnormalities for mental problems, with higher scores implying higher risk for abnormalities [37].*

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Have been changed to:

> *The questionnaire comprises 10 items, which are answered on a 5-point Likert scale [36]. A total score is calculated by building the sum of the individual item scores, with higher scores indicating greater fatigue [39]. The DePaul Symptom Questionnaire Focusing on PEM (DSQ-PEM) provides information on the presence of PEM by asking about the frequency and severity of different symptoms [37]. Further, the emotional problems scale of the Strength and Difficulties Questionnaire (SDQ) is used to examine mental health. Items are answered on a 3-point Likert scale. By summing up the individual item scores, a total score is determined that indicates whether a patient shows abnormalities for mental problems, with higher scores implying higher risk for abnormalities [38].*

In the "Discussion" section, the references in the phrase:

> *To this end, we use extensively evaluated and widely used tools [36,44-46].*

Have been changed to:

> *To this end, we use extensively evaluated and widely used tools [37,44-46].*

The corrections will appear in the online version of the paper on the JMIR Publications website on April 25, 2023, together with the publication of this correction notice. Because this was made after submission to PubMed, PubMed Central, and other full-text repositories, the corrected article has also been resubmitted to those repositories.

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Protocol

Impact of Unmet Social Needs, Scarcity, and Future Discounting on Adherence to Treatment in Children With Asthma: Protocol for a Prospective Cohort Study

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Abstract

Background: Asthma is one of the most prevalent chronic diseases of childhood and disproportionately affects children with lower socioeconomic status. Controller medications such as inhaled corticosteroids significantly reduce asthma exacerbations and improve symptoms. However, a large proportion of children still have poor asthma control, in part owing to suboptimal adherence. Financial barriers contribute to hindering adherence, as do behavioral factors related to low income. For example, unmet social needs for food, lodging, and childcare may create stress and worry in parents, negatively influencing medication adherence. These needs are also cognitively taxing and force families to focus on immediate needs, leading to scarcity and heightening future discounting; thus, there is the tendency to attribute greater value to the present than to the future in making decisions.

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Objective: In this project, we will investigate the relationship between unmet social needs, scarcity, and future discounting as well as their predictive power over time on medication adherence in children with asthma.

Methods: This 12-month prospective observational cohort study will recruit 200 families of children aged 2 to 17 years at the Asthma Clinic of the Centre Hospitalier Universitaire Sainte-Justine, a tertiary care pediatric hospital in Montreal, Canada. The primary outcome will be adherence to controller medication, measured using the proportion of prescribed days covered during follow-up. Exploratory outcomes will include health care use. The main independent variables will be unmet social needs, scarcity, and future discounting, measured using validated instruments. These variables will be measured at recruitment as well as at 6- and 12-month follow-ups. Covariates will include sociodemographics, disease and treatment characteristics, and parental stress. Primary analysis will compare adherence to controller medication, measured using the proportion of prescribed days covered, between families with versus those without unmet social needs during the study period using multivariate linear regression.

Results: The research activities of this study began in December 2021. Participant enrollment and data collection began in August 2022 and are expected to continue until September 2024.

Conclusions: This project will allow the documentation of the impact of unmet social needs, scarcity, and future discounting on adherence in children with asthma using robust metrics of adherence and validated measures of scarcity and future discounting. If the relationship between unmet social needs, behavioral factors, and adherence is supported by our findings, this will suggest the potential for novel targets for integrated social care interventions to improve adherence to controller medication and reduce risk across the life course for vulnerable children with asthma.

Trial Registration: ClinicalTrials.gov NCT05278000; https://clinicaltrials.gov/ct2/show/NCT05278000

International Registered Report Identifier (IRRID): PRR1-10.2196/37318

(JMIR Res Protoc 2023;12:e37318) doi:10.2196/37318

KEYWORDS

asthma; adherence; unmet social needs; behavioral sciences; future discounting; scarcity; pediatrics

Introduction

Background

Asthma is one of the most prevalent chronic diseases of childhood, affecting 1 in 10 children and >3 million Canadians [1,2]. Asthma disproportionately affects children with lower socioeconomic status (SES) [3,4], who not only have a higher prevalence of asthma [5,6] but also have heavier symptom burdens, higher rates of emergency department (ED) visits [7-9], and more hospital admissions [2,4]. The higher burden of disease in these children has several overlapping causes including epigenetic changes related to stress during pregnancy [10], higher secondhand smoke exposure [9,11-13], and greater likelihood of living in environments where air quality is poor [8,14] and allergens are present [15]. Poorer housing quality is also associated with worse asthma control [13,16]. Moreover, families from lower SES have higher perceived barriers to care [17] and are more likely to have unmet care needs [18,19].

Controller medications such as inhaled corticosteroids significantly reduce asthma exacerbations while improving lung function and asthma symptom control [20-22]. Nonetheless, a large proportion of children have poor asthma control, in part owing to suboptimal adherence to inhaled corticosteroids, with objective adherence values ranging from 50% to 70% [23-26]. Previous reports [27-29] suggest that children with lower SES have lower adherence to controller medications, leading to worse asthma control and aggravating health inequities.

Adherence can be hindered by financial barriers that limit access to medication [8,19]. In addition, unmet social needs for food, lodging, and childcare may create stress and worry in parents, negatively influencing medication adherence [30]. Precarious employment, food insecurity, and unstable housing situations are also cognitively taxing and force families to focus on immediate needs [31,32].

Scarcity refers to a state in which one's cognitive resources such as attention and executive control are taxed by living with insufficient resources (money and time) [31]. Individuals may experience scarcity if they have high levels of stress at work, a relative who is acutely sick, or if they are in an unstable housing situation [32]. Although scarcity can affect anyone, those living in poverty may be particularly susceptible, given the financial constraints that require them to carefully balance immediate needs and upcoming expenses [31]. In pediatric asthma, the apparent unpredictable course of the disease is taxing for families. Psychological distress is frequently reported in qualitative studies of children with asthma and their parents [33], and caregiver life stress is associated with a heavier burden of asthma symptoms [34]. The relationship between stress and adherence in pediatric asthma has shown mixed results [35-37], suggesting that other variables such as scarcity may mediate the interaction.

In addition, poverty forces families to attend to immediate needs and makes it more challenging to think about, and invest in, the distant future. Future discounting represents the relative value one assigns to the future compared with the present [38,39]. Poverty is associated with higher levels of future discounting [40], which has been hypothesized to mediate the impact of lower SES on health outcomes [31,41,42]. Lower levels of future discounting (attributing a greater relative value to the future) are associated with several positive health behaviors, including influenza vaccination [43,44], physical activity [44,45], and abstinence from smoking [44,46-49]. In pediatrics, higher levels of future discounting correlate with lower

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medication adherence in type 1 diabetes [50,51]. In asthma, as in other pediatric chronic diseases, parents are asked to administer medications to their children daily to prevent future exacerbations and negative health outcomes. Levels of future discounting correlate with adherence to controller medication in young adults with asthma [52], but whether the same is true in children is unknown. Future discounting may be especially important to study in pediatrics, as medication adherence is a shared responsibility between parents and children [53-59] that evolves with the child's age and developmental stage [53-60]. Children tend to be more present focused than parents [61], which may explain the decreasing levels of adherence to controller medication as the child or adolescent assumes greater responsibility for managing their asthma treatment [62].

In this project, we aim to investigate the relationship between unmet social needs, medication adherence, scarcity, and future discounting in pediatric asthma.

Scientific Objectives

The overall aims of this project are to determine whether scarcity and future discounting are associated with medication adherence in children with asthma and to explore their role in the relationship between unmet social needs and adherence. Using a prospective observational study, we will investigate three primary relationships:

1. The relationship between scarcity, future discounting, and adherence to asthma controller medication;
2. The association between unmet social needs, scarcity, and future discounting; and
3. The potentially mediating role of scarcity and future discounting on the relationship between unmet social needs and adherence to medication in children with asthma.

Our hypotheses related to each of these three primary relationships are the following:

1. We hypothesize that individuals experiencing scarcity and those with higher rates of future discounting will have lower adherence to asthma controller medication.
2. We hypothesize that unmet social needs will be related to scarcity and future discounting in the following ways:
   a. Parents reporting unmet social needs will be more likely to experience scarcity and have greater levels of future discounting;
   b. The number of unmet social needs will correlate with level of scarcity and future discounting; and
   c. Improvements in a family's unmet social needs during the study period will be associated with decreased scarcity and future discounting rates.
3. We expect that scarcity and future discounting will play a mediating role in the relationship between unmet social needs and adherence to medication, with higher levels of both scarcity and future discounting specifically amplifying the impact of unmet social needs on medication adherence.

We will also examine two exploratory aims:

1. Examine whether adherence to medication mediates the association between unmet social needs and asthma outcomes: asthma control, ED visits, and hospitalizations.
2. Document the progression of unmet social needs as the world moves to the next phase of the COVID-19 pandemic.

This project will help understand the relationship between cognitive factors, medication adherence, and unmet social needs, opening the door to developing targeted interventions to improve adherence to medication and, ultimately, children's health outcomes.

Methods

Study Design and Setting

This 12-month prospective observational cohort study will recruit 200 families at the Asthma Clinic of the Centre Hospitalier Universitaire Sainte-Justine, a tertiary care pediatric hospital in Montreal, Canada. The asthma clinic has a routine standardized collection of patient demographics (age and sex), disease (phenotype, control, and triggers), and treatment (dose, format, and frequency) characteristics. With patients' consent, clinical data can be linked with the *Registre de données sur les Medicaments* (reMed) database [63], which collects all data on medication dispensed by all pharmacies in the province of Québec.

Ethics Approval

The study was reviewed and approved by the Institutional Review Board of the Centre Hospitalier Universitaire Sainte-Justine Research Centre (protocol no: 2022-3888) and has been registered (ClinicalTrials.gov ID: NCT05278000).

Participants

Parents of children aged 2-17 years seen at the clinic with a diagnosis of asthma, made according to Canadian national guidelines [64], will be eligible for the study. This age range will help us explore whether the relationships identified vary by the age group of the child (preschool vs school-age vs adolescents).

The inclusion criteria will include (1) children with documented prescription for a controller medication at recruitment visit including at least one of the following: inhaled corticosteroids, long-acting beta-agonists, or leukotriene receptor antagonists and (2) consent to access the reMed database (see section *Study Design and Setting* above).

Participants will be excluded if (1) their child has another chronic pulmonary disease (eg, cystic fibrosis) and (2) parents have insufficient knowledge of French or English to complete the questionnaires.

Potential participants will be identified by a research assistant through prescreening of clinical patient lists. Specifically, the research assistant will prescreen patient lists for the following month and will confirm patient lists using physicians' daily appointment roster upon arrival at the clinic on each day of recruitment.

Recruitment

We will recruit 200 families, stratified to recruit 40 families geographically from each quintile of the Pampalon material deprivation index [65-67]. Refer to the *Power Calculation and*

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Feasibility section for the method of determining the sample size. The Pampalon material deprivation index, measured at the level of the dissemination area and associated with the postal code of the child's primary residence, is a composite of the (1) proportion of persons without a high school diploma, (2) employment:population ratio, and (3) average personal income obtained from the Canadian census [65,66].

Previous evidence suggests that adherence decreases with the age of the child, coinciding with responsibility for taking medication shifting from parents to their children as they age [53-59], whereas evidence for the impact of children's sex is mixed [56,57,62,68,69]. We will stratify our recruitment to ensure equal recruitment between age groups (2-7, 8-12, and 13-17 years), and all analyses will consider the child's age and sex [4].

Consent

Informed consent will be obtained from all participants in the asthma clinic, before enrollment, including consent for follow-up measures and access to clinical data in the reMed database. Consent forms and questionnaires will be administered in French and English according to each participant's preference.

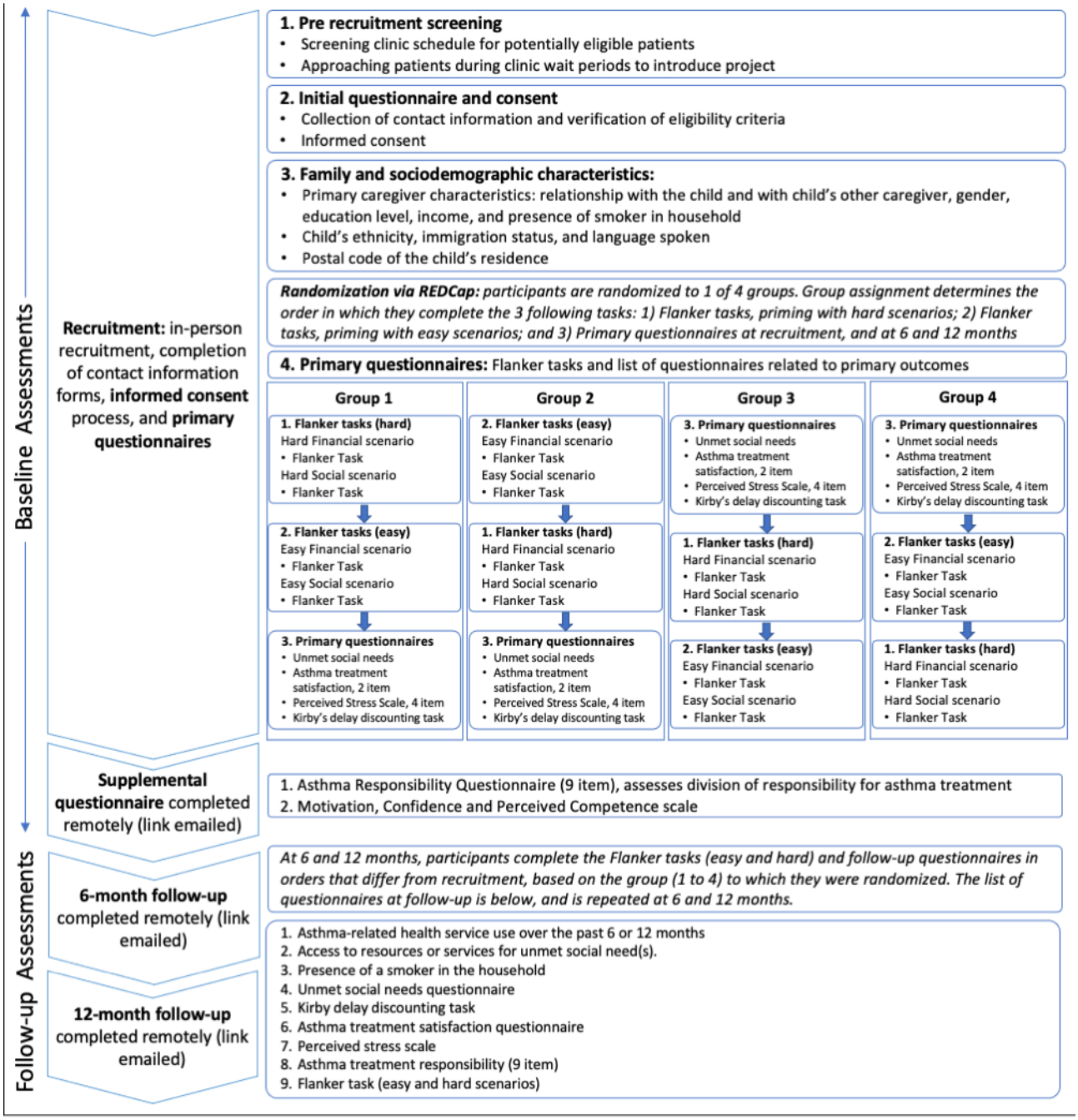
Participants will be approached by a trained research assistant at the time of their clinic appointment. Given the patient flow and clinic organization, participants may be approached in the waiting room before their appointment, between parts of their appointment (ie, after seeing the nurse and before seeing their physician), or after having completed their appointment. The research assistant will approach the patients and describe the project and what their participation would require. Those who express interest in participating will accompany the research assistant to a private room where they will be given the opportunity to read the project consent form, with the research assistant available as needed to explain further or respond to questions. Participants who agree to participate will be asked to sign and date the consent form (either on paper or electronically using the REDCap [Research Electronic Data Capture; Vanderbilt University] database where the survey is hosted) as well as complete the consent form and questionnaire for inclusion in the reMed database, which is required for study participation (given that adherence to medication, obtained from this database, is the primary outcome). Participants will then complete the questionnaire on the REDCap database with guidance from the research assistant throughout.

Follow-up

Participants will be followed prospectively for 12 months after recruitment with measurements at baseline, 6 months, and 12 months (Figure 1). Using the REDCap database, they will be sent the follow-up questionnaires immediately following the baseline questionnaire and at the 6- and 12-month follow-ups. Refer to Figure 1 for the details of each measure.

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Figure 1. Data collection and schedule of events. REDCap: Research Electronic Data Capture.



Outcome Measures

Details of each measure, including operational definitions and data collection methods, are described in the following sections (*Primary Outcome*, *Main Predictors*, *Other Measures and Covariates*, and *Follow-up Measures* sections) and detailed in Table 1.

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Table 1. Overview of measures, data sources, and timeline of measures.

Measure	Measurement details	Data source	Timeline		
			Recruitment	6-month follow-up	12-month follow-up
Primary outcome					
Adherence[a]*:* Proportion of prescribed days covered	Number of days for which the drug was dispensed by a pharmacy divided by the number of days for which it was prescribed [63,70]	Pharmacy claims data (*Registre de données sur les Médicaments*)	—[b]	—	X[c]
Main independent variables					
Unmet social needs	A series of validated questions assessing employment [71], housing stability and ability to pay for utilities, [72-75], financial resource strain [76-78], food security [79], transportation [75], childcare [80], and parent education and health literacy [80,81]	Questionnaire	X	X	X
Scarcity, via executive control—Eriksen flanker task	Speed of response and percentage accuracy [82-84], Δ accuracy between easy and hard condition	In-person computer-based task	X	X	X
Future discounting—Kirby delay discounting task	27-item questionnaire assessing temporal discounting	Questionnaire	X	X	X
Exploratory measures					
Capability	Perceived Competence Scale [85,86]	Questionnaire	X	—	—
Motivation	Treatment Self-Regulation Scale (adapted for adherence) [87]	Questionnaire	X	—	—
Perceived stress: perceived stress scale	4-item measure used to understand how respondents perceive stress and how their feelings are impacted by certain situations [88]	Questionnaire	X	X	X
Asthma severity: PPACI[d]	4-level PPACI assessed in the preceding 6-month period. On the basis of the number of doses per week of short-acting beta-agonists, use of oral corticosteroids within 14 days of a medical claim or hospitalization for asthma, any ED visit for asthma, and any hospitalization for asthma [89]	Medical chart	X	X	X
Access to resources	Whether families accessed resources to which they were referred (social worker at local community health center)	Questionnaire	—	X	X
Asthma treatment satisfaction	Single item inquiring who is primarily responsible for the child's asthma management and 1 question drawn from the Asthma Medication questionnaire [90] adapted to inquire specifically about management of one's child's asthma	Questionnaire	X	X	X
Asthma responsibility questionnaire	10-item measure examining the division of asthma management responsibilities between child and parent [91]	Questionnaire	X	—	X
Covariates					
Child's *age* and *sex*	N/A[e]	Medical chart	X	—	—
Child's *gender*	N/A	Questionnaire	X		
Caregiver's relationship with child	Two items interrogating relationship to the child and whether respondent is the child's legal guardian	Questionnaire	X	—	—
Caregiver's gender	N/A	Questionnaire	X	—	—
Caregiver's marital status and *living situation*	Single items assessing marital status and living situation as it relates to the child	Questionnaire	X	—	—
Postal code of the child's residence	N/A	Questionnaire	X	—	—

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Measure	Measurement details	Data source	Timeline		
			Recruitment	6-month follow-up	12-month follow-up
Caregiver's level of education	Elementary school or less, some high school, high school graduate, some college or technical school, college graduate, or completed a graduate degree	Questionnaire	X	—	—
Household income	One item question based on the Canadian income survey [92]	Questionnaire	X	—	—
Presence of a smoker or e-cigarette user in the house	2 question items investigating use of tobacco products or e-cigarettes in the last month [93]	Questionnaire	X	X	X
Responsibility for asthma management	"Who is responsible for asthma management?"	Questionnaire	X	—	—
Child's ethnicity, immigration status, and *language spoken at home*	Questions using categories from Canadian census [94]	Questionnaire	X	—	—
Class of controller medication received during study period	Inhaled corticosteroids and long-acting beta-agonists of leukotriene receptor antagonists	Medical chart	X	X	X

[a]The name of the variable in question has been italicized.

[b]Em dashes in the timeline signify that data for the associated variable will not be collected at the time point in question.

[c]X in the timeline indicate data collection for the associated variable at the time point (recruitment, 6-month follow-up, or 12-month follow-up) in question.

[d]PPACI: Pediatric Pharmacoepidemiology Asthma Control Index.

[e]N/A: not applicable.

Primary Outcome

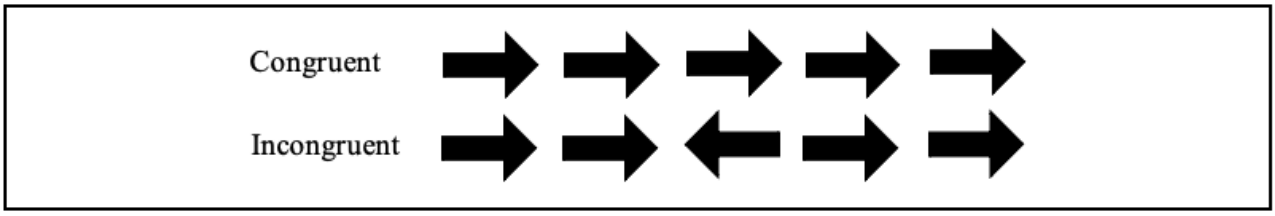
Adherence to controller medication will be measured for the 12 months of follow-up on a scale of 0%-100% by the *proportion of prescribed days covered (PPDC)*, a validated index calculated as the number of days for which the drug was dispensed by a pharmacy divided by the number of days for which it was prescribed [63]. The PPDC accounts for varying durations of physician prescriptions [70] and leads to conservative estimates of adherence, as possession of medication is a prerequisite for adherence but does not confirm its use. The PPDC will be calculated using medical records (prescriptions made by the clinician) and the reMed database [24,63]. reMed collects drug claims for both privately and publicly insured children.

Main Predictors

Scarcity is a state in which individuals' cognitive resources (mental bandwidth) are occupied and taxed by preoccupations, including pressing financial concerns [31]. These worries consume mental bandwidth, leaving less of it available for other tasks. In this study, we will assess scarcity as per the original work in the field [95]. Briefly, participants will be exposed to hypothetical scenarios that are designed to elicit a scarcity mindset in those who are experiencing a state of scarcity. The scenarios bring to the fore participants' scarcity mindset by asking participants to imagine themselves in situations in which they would need to access scarce resources. Specifically, participants will be asked to imagine requiring an urgent car repair, costing either US $1500 in the more taxing, "hard" scenario or US $150 in the "easy" scenario. Similarly, participants will be asked to imagine that their child required either a hospitalization (hard scenario) or an ED visit (easy scenario) for their asthma. After listening to the scenarios, participants will complete the Eriksen flanker task, a widely used, standardized, and validated test of executive function assessing selective attention, information processing, and inhibitory function. The task requires participants to rapidly identify whether a series of arrows, colored boxes, or letters are congruent or incongruent (Figure 2). We will measure both the percentage accuracy and time to complete the task under each condition [31,82,95]. The outcome for each participant will be the difference in accuracy on the flanker test after the easy versus the hard scenarios.

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Figure 2. Flanker task with arrows, illustrating congruent and incongruent series of arrows.



Future discounting will be assessed using Kirby delay discounting task, in which participants are asked to choose between a smaller, immediate financial reward or a larger, delayed reward. From the participant's answers to the 27 choices, a hyperbolic discount parameter (k) is calculated [96].

Unmet social needs will be assessed using validated measures of employment [71], housing stability, ability to pay for utilities [72-75], financial resource strain [76-78], food security [79], transportation [75], childcare [80], parent education, and health literacy [80,81]. We chose these needs as they had published and validated short question items assessing them, had either documented or plausible relationships with asthma, and could be amenable to intervention by social workers.

Families for whom unmet social needs have been identified will be asked whether they are interested in receiving support to address their needs. If they are interested, the study team will ensure referral to a social worker at a *centre locaux de services communautaires* (local community services centers), a service covered by the government's universal health insurance plan. With the participants' consent, their treating clinician will be informed of their unmet social needs and whether they were referred to a local community services center. Participants who agree to be referred to resources to address their unmet social needs at recruitment will be asked at 6 and 12 months if they accessed any resources to help them address their unmet needs and, if so, which ones. In our analysis, among participants with identified unmet social needs, we will explore whether the participants' desire for a referral for social services and, if applicable, access to those resources influenced the relationship between unmet social needs and adherence.

Other Measures and Covariates

Family and sociodemographic characteristics will include the child's age, sex, gender, ethnicity, and immigration status and parent participants' gender, race and ethnicity, level of education, and income. We will also inquire about the presence of a smoker in the household and the languages spoken at home.

Asthma and asthma treatment information will include controller medication type (inhaled corticosteroids, long-acting beta-agonists, or leukotriene receptor antagonists) and frequency (once vs twice daily) retrieved from medical records and asthma disease severity in the 6 months preceding recruitment using the 4-level Pediatric Pharmacoepidemiology Asthma Control Index (PPACI) using data from medical records. The PPACI categorizes asthma control based on the average number of doses per week of short-acting beta-agonists, any use of oral corticosteroids within 14 days of a medical claim or ED visit for asthma, and any hospitalization for asthma [89].

Perceived efficacy of medication will be assessed using a single item on a 5-point scale selected from the Patient Satisfaction with Asthma Medication questionnaire: "Would you recommend your child's asthma medication and its inhaler to someone else with asthma?" [90].

Perceived stress of respondents will be measured using the 4-item version of the Perceived Stress Scale, with each question rated on a 5-point scale [88,97]. The 4-item Perceived Stress Scale has a Cronbach α reliability coefficient of .72.

Capability and Motivation will be measured using a questionnaire based on the Capability, Opportunity, Motivation, and Behavior model [98]. This will serve to evaluate the mechanism by which scarcity and future discounting may influence medication adherence.

Capability will be measured using the 4-point Perceived Competence Scale, validated in adherence to medication as well as in the pediatric population [85,86]. These 4 items inquire specifically about the parent's perceived confidence and capability in ensuring that their child takes their asthma medication as prescribed.

Motivation will be assessed using selected items from the 15-item Treatment Self-Regulation Scale adapted for adherence [87]. The 2 selected items assess the perceived importance that their child takes their asthma medication as prescribed and their confidence in ensuring that they do so. Selected items, rather than the full scale, were chosen to limit participant burden.

Division of asthma treatment responsibility will be assessed using the 10-item Asthma Responsibility Questionnaire, which measures the division of asthma management responsibilities between child and parent [91]. It also measures the parent's degree of satisfaction with the amount of responsibility their child takes for their asthma.

Follow-up Measures

At 6 and 12 months, we will assess health service use, specifically asthma-related ED visits and hospitalizations, via parental reports as well as the patient's hospital file and provincial health insurance data. We will also measure access to resources to address unmet social needs for participants who agreed to be referred to a social worker at their local community services center using a single-item question for each identified unmet social need (eg, "Since you entered this study, have you been in contact with a social worker or someone from the local community services centre to help you access resources for [identified unmet social needs]?")

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Study Procedures

Families will be made aware of the project via a posting in the clinic's regular electronic newsletter and posters in the clinic waiting room. Clinicians will be informed about the study through personalized emails from the study team. A research assistant will be present during each clinic day, prescreen clinic lists for eligible families, and approach primary caregivers for consent at the time of their clinic visit.

Study Assessments

The study flow, including the measurements at each time point, is shown in Figure 1. Measures will be completed on the web via the REDCap platform [99], except for the flanker task, which will be administered via the testable web-based platform.

Baseline

Potential participants will be approached by the research assistant during clinic hours, before their child's appointment with their treating physician. After ensuring that participants are eligible based on the inclusion and exclusion criteria, participants who consent to the study will be randomized to 1 of 4 groups, which determines the order in which they will complete the baseline questionnaire, the flanker task while primed with easy scenarios, and the flanker task while primed with hard scenarios. Details of the questionnaire sequences and randomization groups are shown in Figure 1. The participants will complete the baseline questionnaire on site guided by the research assistant. This includes the following measures (detailed in the *Primary Outcome*, *Main Predictors*, *Other Measures and Covariates*, and *Follow-up Measures* sections above): (1) scarcity assessment (flanker task)—2 rounds, once while primed with "hard" scenarios and once while primed with "easy" scenarios; (2) family and sociodemographic characteristics; (3) unmet social needs; (4) identification of person primarily responsible for the management of the child's asthma and satisfaction with asthma treatment; (5) Perceived Stress Scale; and (6) Kirby delay discounting task to assess future discounting.

To ascertain whether exposure to the scarcity-inducing scenarios and the subsequent completion of the flanker task impact self-reporting of unmet social needs, participants will be randomized to complete the flanker task either before or after having completed the other sections of the questionnaire. Similarly, to determine whether familiarity with the flanker test influences accuracy and speed rather than the type of scenario (easy vs hard), participants will be randomized to start with either the easy or the hard scenarios. A visual representation of the 4 permutations is presented in Figure 1.

Secondary Questionnaire

Immediately after the recruitment visit, participants will be emailed a secure link for a secondary questionnaire including (1) the Asthma Responsibility Questionnaire [91] and (2) questions drawn from the Perceived Competence Scale [85,86] and the Treatment Self-Regulation Scale (adapted for asthma treatment adherence) [87]. This division of the baseline and secondary questionnaire was chosen to limit participant burden and time required at the clinic on the day of recruitment.

Follow-up Questionnaires

Participants will be emailed 6 and 12 months after recruitment to complete the follow-up questionnaires, the contents of which are described in Table 1. Participants will be reminded and offered help to complete the questionnaire if not completed within a week via up to 2 email reminders and 1 phone call from the research assistant.

Participant Compensation

Participants will receive CAD $10 (US $7.50) in compensation for completion of the initial study questionnaire and CAD $10 (US $7.50) at the end of the study if all materials have been completed.

Statistical Analysis

Results will be reported following the recommendations of the Strengthening the Reporting of Observational Studies in Epidemiology Statement for cohort studies [100]. For *aim 1*, we will first perform descriptive statistics for our measures of executive function (accuracy and time to complete the Eriksen flanker task between easy and hard scenarios) at baseline, 6 months, and 12 months and model trajectories using mixed effects regression models. We will then quantify the relationship between both level of scarcity at baseline and trajectories with PPDC in the 12 months following the index visit. We will use unadjusted linear regression models, before adjusting for potential confounders, including sociodemographic factors (eg, child age and sex) and disease characteristics (eg, PPACI at baseline and class and dosing frequency of controller medication). We will perform collinearity diagnostics on potential confounders, and if significant correlation is identified, we will adjust our model accordingly. Exploratory analyses will use logistic and ordinal regression models and the same set of variables to examine any effect of scarcity on health service use (ED visit or hospitalization). We will use the same analysis plan to examine the relationship between future discounting (using Kirby's discount parameter) and PPDC.

For *aim 2*, we will first assess whether scarcity and future discounting scores at baseline differ between families with versus those without unmet social needs. In the subgroup with identified unmet social needs at any time during the study, we will use regression models with time-varying exposure to estimate the effect of referral to social services and access to services on the presence of unmet social needs (ie, determine if referral to social services led to improvement in unmet social needs). We will then use generalized estimating equations to estimate the effect of unmet social needs on cognitive capacity, executive control, and future discounting.

For *aim 3*, we will evaluate whether scarcity is a mediator of the relationship between unmet social needs and adherence with multiple regression models using a recognized approach [101]. We will use a similar analysis for future discounting.

For *aim 4*, we will use multivariable logistic regression models to examine the effect of unmet social needs on ED visits (any vs none) and hospitalizations (any vs none), testing whether there is an interaction between medication adherence and unmet social needs in this relationship (whether better adherence is

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protective in children with unmet social needs). A similar approach will be used for asthma control using an ordinal regression model for the 4-point PPACI.

For *aim 5*, we will use descriptive statistics to document the prevalence of unmet social needs in our sample as well as within families and use logistic regression models to test whether referrals to social services modulate those trajectories.

Power Calculation and Feasibility

Previously published data using the asthma clinic database found a mean PPDC (our measure of adherence and primary outcome) of 68%, with an SD of 33% [24]. In previous studies, a 25% [102] or 1 SD difference [103] in adherence was associated with significant differences in the number of ED visits. As those studies used slightly different measures of adherence, we will be conservative and power our study to detect a 16% difference (half an SD) in PPDC between the participants above and below the median of scarcity and future discounting scores. Using 2-sample *t* tests (2-tailed), an α of .05, and a power of 0.8, this will require us to recruit 135 participants. Accounting for 30.4% (41/135) of missing data (covariates) and loss to follow-up, we will recruit 200 participants. The prevalence of unmet social needs in the clinical population is unavailable; however, in our patient population, 26.59% (335/1260) of children are from the lower quintile of the material deprivation index. In addition, recent Canadian data suggest a food insecurity prevalence of 29% among youth and young adults [104]. Assuming that 25% (50/200) of participants have at least one unmet social need, the proposed sample size will allow 85% power to detect a 16% difference (half an SD) in adherence between those with versus without unmet social needs.

On the basis of preliminary data from the asthma clinic, 87.68% (1139/1299) of patients who were prescribed daily controller medications consented to reMed. In another study (Poitras N et al, unpublished data, August 2023) from our clinic with a similar population and participant burden, 30% of eligible families consented to participate in the study. Using this ratio, we would need to approach approximately 670 families to obtain our desired sample size. There are at least three half-day clinics a week where recruitment could occur, with a minimum of 3 families per clinic. Using a conservative estimate, even if 29.9% (200/670) of families consent to participate, recruiting 200 participants will take 18 months.

Results

This study obtained funding in April 2021. The research activities of this study began in December 2021. Participant enrollment and data collection began in August 2022 and are expected to be completed in 24 months (August 2024). As of February 2023, 100 participants have been recruited and have completed all baseline data. Data analysis will begin once all participants have been recruited and follow-up measures (6-month and 12-month follow-up) are in progress. Primary results of the study are expected to be available in the first months of 2025.

Discussion

Principal Findings

This project will allow us to document the impact of unmet social needs, scarcity, and future discounting on adherence in a diverse population of children with asthma using robust documentation of adherence and validated measures of scarcity and future discounting. The study will also allow us to document ongoing changes in both unmet social needs and adherence to medication in children with asthma in the wake of the COVID-19 pandemic. This research will confirm the potential for scarcity and future discounting as novel targets for either new interventions or improving existing effective interventions to improve adherence to controller medication that may lead to reduced risk across the life course for vulnerable children with asthma. The development of an intervention and assessment of its effectiveness through a randomized trial will be the next stages of this line of research, with potential benefits at both the national and international levels (including in low- and middle-income countries) to ultimately help reduce the disease burden in this population.

Strengths

TTo the best of our knowledge, this study is the first to investigate the relationship between unmet social needs, scarcity, and future discounting in medication adherence. We will use objective measures of adherence, validated questionnaires, and psychometric testing to measure the main independent variables of interest.

We will recruit patients from a clinic with diverse population, representing a broad range of demographic characteristics, including SES and social situations, which we will be able to capture in detail with both our unmet social needs questionnaires and demographic questions. This will allow for important subgroup analyses by age, sex, race and ethnicity, and SES.

Finally, we are performing this study in Canada, where medical care insurance is universal and government-funded and where prescription medication insurance is also universal (either privately or publicly funded). As such, it will help better understand the factors influencing adherence in a setting where financial barriers to either care or prescription medication are lower, especially for low-income populations.

Limitations

Representativeness of the Population

Recruitment from a tertiary pediatric center clinic could, in theory, limit generalizability; however, the clinical population is quite diverse with regard to SES, race, and ethnicity [105]. Previous studies reported lower rates of controller medication prescription in patients with lower SES [106], leading to a potential selection bias. We will limit this bias through stratified recruitment by SES and an analysis of all eligible patients approached to ensure that a similar proportion of patients in each SES stratum were excluded owing to a lack of controller medication prescription.

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Potential Biases

By collecting objective values of adherence using reMed, we will avoid self-reporting bias in adherence, which is our primary outcome. It is possible that objective adherence will be positively influenced by the mere involvement in the research study (Hawthorne effect). Would that occur, it would likely be of similar magnitude for all participants in the study and not substantially influence the associations found. We will also be able to estimate the size of this effect by comparing adherence in this study with previously reported historical data on adherence from other children followed in the clinic [105].

Social desirability may influence parents' report of confidence in managing their child's treatment or other elements on the questionnaire. We attempted to mitigate this potential bias through the selection of previously validated questionnaires as well as an emphasis on the nonjudgmental nature of the questionnaire and the confidentiality of the information they provide. Again, this potential bias would likely be present across our sample and therefore should not influence the relationship found in the study.

Conclusions

Documenting the impact of unmet social needs, scarcity, and future discounting on adherence in a diverse population of children with asthma will provide important data to allow for improved approaches to prescribing and monitoring asthma treatment adherence in children. Understanding and targeting elements especially prevalent in this vulnerable population also has the potential to lead to significant health care cost savings in addition to reducing health inequalities by improving outcomes for populations at highest risk. Finally, our methodological approach to examine scarcity and future discounting and their link to medication adherence has the potential to be applied to a wide range of other chronic diseases (diabetes, cystic fibrosis, heart disease, etc), potentially leading to improvements in health and quality of life for children and adults living with chronic diseases.

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Data Availability

Data for this project will be made available following the conclusion of the study from the corresponding author upon reasonable request for use for noncommercial purposes.

Conflicts of Interest

KL is a member of the Canadian COVID-19 Expert Advisory Panel (Health Canada). She has served on the advisory board or as a consultant for Schering-Plough, Takeda, AbbVie, Almirall, Janssen, GlaxoSmithKline (GSK), Novartis, Boehringer Ingelheim (BI), and Sojecci Inc, has received sponsorship for investigator-generated research grants from GSK and AbbVie, speaker fees from GSK, Astra-Zeneca, Astellas, Novartis, Takeda, AbbVie, Merck, Boehringer Ingelheim, Bayer, Pfizer, Xfacto, and Air Liquide, and has received support for educational materials from Merck, none of which are related to the current article. FMD has received unrestricted research funds from Jamieson, Novartis, Teva, Trudell Medical; research funds from Covis Pharma, GlaxoSmithKline and MEDteq in partnership with Thorasys Inc.; honorarium for consultancy work from Astra Zeneca, Covis Pharma, Ontario Lung Association, Sanofi, Teva, and Thorasys Inc.; honorarium to serve on an advisory board from Sanofi; and honorarium as an invited speaker from Association des Me´decins omnipraticiens du Richelieu Saint-Laurent, Covis Pharma, Fe´de´ration des Me´decins spe´cialistes du Quebec, Sanofi, Thorasys Inc and Trudell Medical International.

Multimedia Appendix 1
Peer review report from the Psychosocial, sociocultural and behavioral determinants of health 2 / Déterminants psychosociaux, socioculturels et comportementaux de la santé 2 - Canadian Institutes of Health Research/Instituts de recherche en santé du Canada.
[PDF File (Adobe PDF File), 618 KB - resprot_v12i1e37318_app1.pdf]

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Abbreviations

ED: emergency department
PPACI: Pediatric Pharmacoepidemiology Asthma Control Index
PPDC: proportion of prescribed days covered
REDCap: Research Electronic Data Capture
reMed: Registre de données sur les Médicaments (data registry for prescribed medications)
SES: socioeconomic status

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Protocol

Effects of the COVID-19 Pandemic on Primary Health Care for Chronic Conditions in Canada: Protocol for a Retrospective Pre-Post Study Using National Practice-Based Research Network Data

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Abstract

Background: Since the COVID-19 pandemic began, there have been concerns that interruptions to the health care system may have led to changes in primary care, especially for care of chronic conditions such as diabetes and heart failure. Such changes may have longer term implications for population health.

Objective: This study aims to describe the impacts of the COVID-19 pandemic on indicators of primary care access, comprehensiveness, and appropriateness among adult patients, as well as on specific indictors of chronic conditions. Additionally, this study aims to determine whether any identified changes were associated with patient sociodemographic characteristics and multimorbidity.

Methods: This is a retrospective, single-arm, pre-post study using Canadian Primary Care Sentinel Surveillance Network (CPCSSN) data. CPCSSN is a research network supported by a primary care electronic medical record database, comprising over 1500 physicians and nearly 2 million patients. We are examining changes in care (eg, frequency of contacts, laboratory tests and investigations, referrals, medications prescribed, etc) among adults. We will also examine indicators specific to evidence-based recommendations for care in patients with diabetes and those with heart failure. We will compare rates of outcomes during key periods of the pandemic between March 13, 2020, and December 31, 2022, with equal time periods before the pandemic. Differences will be examined among specific subgroups of adults, including by decade of age, number of comorbidities, and socioeconomic status. Regression models appropriate to outcome distributions will be used to estimate changes, adjusting for potential confounders. This analysis is part of a mixed-methods study with a qualitative component investigating how patients with diabetes with or without concurrent heart failure perceived the impact of the pandemic on access to primary care and health care–related decisions. This study was approved by the Hamilton Integrated Research Ethics Board (14782-C).

Results: The start date of this study was October 5, 2022, and the prospective end date is January 31, 2024. As of May 2023, the study cohort (n=875,934) is defined, data cleaning is complete, and exploratory analyses have begun. Extended analyses using

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2022 data are planned once the new data becomes available. We will disseminate results through peer-reviewed publications and academic conference, as well as creating evidence briefs, infographics, and a video for policy maker and patient audiences.

Conclusions: This study will investigate whether the COVID-19 pandemic has resulted in changes in the provision of primary care in Canada and whether these potential changes have led to gaps in care. This study will also identify patient-level characteristics associated with changes in care patterns across the COVID-19 pandemic. Indicators specific to chronic conditions, namely diabetes and heart failure, will also be explored to determine whether there were changes in care of these conditions.

Trial Registration: ClinicalTrials.gov NCT05813652; https://clinicaltrials.gov/ct2/show/NCT05813652

International Registered Report Identifier (IRRID): RR1-10.2196/49131

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KEYWORDS

COVID-19; chronic disease; primary health care; electronic health record; health services research; retrospective studies

Introduction

The presence of strong primary care systems has been shown to be associated with superior and more equitable health outcomes in the population [1-6]. Core elements of primary care that contribute to population health outcomes include access, continuity, comprehensiveness, coordination, person focus, and equity enhancement [7]. Chronic diseases are common and represent the leading causes of death worldwide [8]. The core elements of primary care make this setting ideal for managing chronic diseases [4,9], and family medicine and other primary care services provide the majority of care for chronic diseases across the lifespan [4,10]. With increasing age, there is an increasing prevalence of multiple chronic diseases [11], and these patients require careful management to reduce morbidity and mortality and improve quality of life [12]. Life-limiting chronic diseases such as chronic obstructive pulmonary disease, heart failure, and chronic kidney disease [13-15] affect millions of people in Canada and are mostly managed in primary care [16-19]. Other conditions that are risk factors for numerous cardiovascular and cerebrovascular diseases (eg, diabetes and hypertension) are associated with poor health outcomes, and these are also managed in primary care [20].

On March 11, 2020, the World Health Organization declared the circulating SARS-CoV-2 as a pandemic. The SARS-CoV-2 pandemic placed a substantial strain on health care services for care of both COVID-19 illness (the majority of which was provided in primary care without need for hospitalization) and non–COVID-19 illness [8,21]. The documented early impacts of the COVID-19 pandemic were reductions in the number of patients visiting primary care offices [22], dramatic increases in remote care especially for older patients [22,23], and new strategies to maintain care such as implementing wellness checks for high-risk patients [24,25].

Early in the pandemic, there were reductions in visits for chronic condition management [20,26,27], preventive screening and diagnostic testing [28,29], and changes in physician referral behaviors [30]. The limited availability of testing and coordination of prevention services was a concern among Canadian family physicians [31]. Professional organizations recommended continuation of in-person care during the pandemic for complex chronic conditions and when physical examination was required; however, many patients avoided seeking primary care, and clinics experienced decreased attendance relating to the care of serious conditions [32,33]. Although telemedicine strategies can be effective for some chronic disease monitoring, patients who experience lack of equity in access to health care are also likely to experience barriers to using technology [34-36].

The onset of the pandemic worsened existing challenges to the prospects of achieving and maintaining an adequate level of comprehensive primary care in Canada. Understanding the ways in which the core functions of primary care [37-39] were affected by the COVID-19 pandemic is essential for chronic condition management and for system assessment overall. Although there are reports that the volume of primary care in Canada has largely returned to prepandemic levels, it is not clear whether and for whom there is a need to “catch up” on care for chronic diseases. For practices with a tendency for overuse of testing and investigations, these may have declined to more appropriate levels during the pandemic, also highlighting the areas of practice improvement. The objectives of this study are to describe the impacts of COVID-19 on chronic disease care and to determine whether changes were associated with patients’ sociodemographic characteristics and multimorbidity.

Methods

Data Source

The Canadian Primary Care Sentinel Surveillance Network (CPCSSN [40]) is a multidisease electronic medical record (EMR) research and surveillance data repository that securely collects deidentified health information from EMRs of participating primary care clinicians (eg, family physicians and nurse practitioners) who are referred to as “sentinels.” CPCSSN currently brings together 13 primary care research networks for the purposes of research, disease surveillance, and quality improvement, with more networks due to join in the near future. Every 6 months, CPCSSN acquires deidentified patient-level clinical data from primary care EMR systems held by 1583 primary care providers across Canada, with approximately 200 patient encounters per month per physician [20]. CPCSSN acquires most of the data fields in Canadian primary care EMRs with the exceptions of portable document format such as imaging data and the narrative “Subjective, Objective,

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Assessment, and Planning" notes. The acquired data are processed into a standard format and are made available for surveillance and research [41]. The relative frequency, longitudinal format, and comprehensiveness of CPCSSN data are ideal for the study of changes in practice, through time, in response to significant environmental imperatives, such as public health or research initiatives [41]. Numerous case definition validation studies have been completed [42-44], and the data have also been used to evaluate patterns and quality of health care [19,45].

Study Design

This protocol was designed using the RECORD (REporting of studies Conducted using Observational Routinely collected Data) statement [46]. We will conduct a retrospective closed cohort study with a single group using a pre-post design. We will examine prevention and management activities for exemplar conditions on the basis of having a validated CPCSSN case definition [47,48] (ie, diabetes and heart failure), having substantial prevalence in primary care, and either having high morbidity or being risk factors for morbidity if not well managed. Patient-level data extracted from the CPCSSN repository between 2018 and 2022 will be used to investigate changes in rates of presentation and clinical management of various chronic diseases before, and through the phases of, the pandemic.

Study Population

The study population is all patients who were 18 years and older in 2018, and some analyses will focus on subgroups of patients with specific chronic conditions. We will use the 2-year contact population as recommended previously for defining practice populations for primary care [49]. This method uses contacts within encounter, medication, and billing-related data tables, and has been used previously with CPCSSN data to produce national chronic disease estimates [50]. This method will be used in the period from March 13, 2018, to March 13 2020. We will use this population rather than the full CPCSSN patient population data (dating back more than 2 decades for some networks) to limit the size of the data set, while maintaining the patient population that is likely to have a relationship with a primary care practice during the study period. Although this approach may exclude patients who are younger, healthier, and less likely to seek primary care compared with patients with chronic conditions, we do not expect this to have a major impact on findings because this study focuses on the age group where chronic condition prevalence begins to increase and where screening guidelines apply (eg, diabetes). Therefore, this age group is more likely to see a primary care physician regularly.

People who died during the study period will be included up to the point of death using the death date if captured or the presence of a deceased status with date estimated from the most recent contact in CPCSSN data. Patients who were older than 105 years at the start of the COVID-19 pandemic will be excluded as a possible data error.

Variables of Interest

Primary Exposure

The primary exposure is the start of the pandemic in March 13, 2020. This date was selected as it marks the beginning of Canadian provincial governments responding to the formal declaration of the pandemic by the World Health Organization on March 11, 2020, by enforcing sweeping public health and safety measures. The prepandemic time frame used is defined as June 22, 2018, through March 12, 2020. The pandemic time frame used in this study runs from March 13, 2020, through December 31, 2022. In addition to comparison between these 2 periods, 30-day interval rates will also be calculated for selected outcomes and indicators where possible.

Outcome Definitions and Measures

Outcomes were informed by a large primary care trial on improving prevention and management of chronic conditions in primary care [51], a quality index created for primary care with items measurable in EMRs [52], and consideration of data capture across the networks of CPCSSN. We further conceptualized outcomes according to whether they represent aspects of access, comprehensiveness, or appropriateness (Table 1).

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Table 1. Outcomes and outcome measures.

Population	Indicator	Related domain	Data source[a]
Number and types of encounters			Encounter, encounter diagnosis, and billing
All patients in our defined cohort	Overall number of all encounters	Access	
Patients with the CPCSSN[b] case definition of diabetes and HF[c]	Overall number and types of diabetes-related and HF-related investigations	Comprehensiveness	
Diagnoses addressed in encounters		Comprehensiveness and appropriateness	Encounter, encounter diagnosis, and billing
All patients	Number of different diagnoses addressed per patient per year		
Patients with ≥1 condition with the validated CPCSSN case definition	Number and proportion of chronic conditions (ie, CPCSSN case definitions) addressed by physician at least once a year		
Patients with the CPCSSN case definition of diabetes and HF	Overall number and types of diabetes-related and HF-related investigations		
Patients with the CPCSSN case definition of diabetes and HF	Proportion of patients with diabetes-related encounter and HF-related encounter every 6 and 12 months (as appropriate for condition)		
Services provided		Comprehensiveness	Billing, vaccine, and medication
Patients age ≥65 years	Number of patients receiving pneumococcal vaccine and influenza vaccine		
Patients with the CPCSSN case definition of diabetes and HF	Proportion of patients with influenza vaccination		
Procedures performed		Appropriateness	Billing
Patients with the CPCSSN case definition of diabetes	Proportion of patients with foot examinations in last 12 months		
Physical examinations		Appropriateness	Examinations
All patients in our defined cohort; all patients grouped by CPCSSN case definition	Proportion with BP[d] measured every 6 months or every 12 months (as appropriate for condition)		
Referrals made to specialists		Comprehensiveness	Referral
All patients in our defined cohort; all patients grouped by CPCSSN case definition	Overall number and types of referrals; proportion referred to cardiology, endocrinology (as appropriate for condition)		
Investigations performed		Appropriateness	Laboratory
All patients in our defined cohort	Number of vitamin D, CBC[e], eGFR[f], ACR[g], and liver function tests performed		
Patients with CKD[h]	Number with and frequency of eGFR and ACR tests		
Patients without diabetes	Number with HbA_{1c}[i], FBS[j] measured (screening)		
Patients taking or not taking statins	Number with and frequency of lipid panel/LDL[k]		

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Population	Indicator	Related domain	Data source[a]
Patients taking or not taking levothyroxine	Number with and frequency of TSH[l] measured		
Patients with the CPCSSN case definition of diabetes	Proportion with HbA_{1c} measured every 6 months and every 12 months		
Monitoring results		Appropriateness	Examination
All patients in our defined cohort; all patients grouped by CPCSSN case definition and age	Proportion with BP ≤140/90 or ≤130/80 (as appropriate based on chronic conditions and age); proportion of patients in the following sBP[m] ranges: ≤130, 131-140, 141-150, 151-160, and >160		
Medications		Comprehensiveness and appropriateness	Medication and risk factor
Patients with the CPCSSN case definition of diabetes	Proportion of patients with and overall number and frequency of metformin prescriptions, insulin prescriptions, and other oral antidiabetic prescriptions[n]		
Patients with the CPCSSN case definition of HF	Proportion of patients with and overall number and frequency of β-blocker prescriptions, ARB[o] prescriptions, and ACE-I[p] prescriptions		
Patients who smoke	Number of patients with NRT[q] prescription		

[a]CPCSSN data table.

[b]CPCSSN: Canadian Primary Care Sentinel Surveillance Network.

[c]HF: heart failure.

[d]BP: blood pressure.

[e]CBC: complete blood count.

[f]eGFR: estimated glomerular filtration rate.

[g]ACR: albumin-to-creatinine ratio.

[h]CKD: chronic kidney disease.

[i]HbA_{1c}: hemoglobin A_{1c}.

[j]FBS: fasting blood sugar.

[k]LDL: low-density lipoprotein.

[l]TSH: thyroid-stimulating hormone.

[m]sBP: systolic blood pressure.

[n]Other oral antidiabetic medications include classes such as sodium-glucose cotransporter-2 inhibitors, sulfonylureas, meglitinides, dipeptidyl peptidase 4 inhibitors, etc.

[o]ARB: angiotensin receptor blocker.

[p]ACE-I: angiotensin-converting enzyme inhibitor.

[q]NRT: nicotine replacement therapy.

Access to the practice will be measured as the overall number of encounters.

Comprehensiveness refers to primary care addressing "all problems in the population (with short-term referral as needed), except those that are too unusual (generally a frequency of less than 1 or 2 per thousand in the population served) for the primary care practitioner or team to treat competently" [1]. As indicators of comprehensiveness, we will measure number of different diagnoses addressed per patient per year, proportion of patients' chronic conditions addressed at least once a year, number of pneumococcal vaccines and influenza vaccines in patients 65 years or older, and number of prescriptions for nicotine replacement therapy

Appropriateness will be examined in 2 ways: laboratory tests that are indicated for monitoring of chronic conditions but may be ordered more frequently than necessary (eg, hemoglobin A_{1c} in diabetics) and laboratory tests that are frequently ordered routinely (or for screening purposes) but may be overused in certain populations, including thyroid function tests, vitamin D, albumin-to-creatinine ratio, and lipid panel testing [53]. We hypothesize that some of these tests, while indicated at a base frequency, may be commonly overused; thus, their frequency may have declined during the pandemic.

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Diabetes and heart failure are 2 chronic conditions where aspects of care can be reasonably evaluated in CPCSSN. We will describe care across the population in terms of frequency of contacts, laboratory tests and investigations, and medications prescribed that would suggest care that is in step with evidence-based recommendations [54]. For patients with diabetes, we will measure the percentage of patients with a diabetes-related encounter every 6 and 12 months; percent with a foot examination in the last 12 months; percent with a blood pressure measure and hemoglobin A_{1c} test every 6 and 12 months (and results); percent with influenza vaccination; overall number of diabetes-related investigations; percent referred to endocrinology; percent receiving, and number and frequency of metformin, insulin, and other antidiabetic prescriptions. For patients with heart failure, we will measure percentage of patients with heart failure–related encounters every 6 and 12 months; number of investigations (echocardiogram and blood tests); percent with a blood pressure measure every 6 and 12 months (and results); percent with influenza vaccination; percent receiving β-blocker, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers; and percent referred to cardiology and other specialists.

Statistical Analysis and Power

As of 2018, there were 1.13 million adult patients in the CPCSSN database, with 65% (734,500/1,130,000) having at least 1 chronic condition [55]. A sample size of 1276 paired (pre-post) individuals would be required to detect a change from 50% to 55% of patients experiencing an outcome, with a correlation between paired observations of 0.2 [56]. With a correlation between pairs of 0.1, the required sample size would be 1432. We expect to have adequate sample size to examine changes within specific conditions given the approximate prevalence of hypertension (22%), diabetes (10%), chronic obstructive pulmonary disease (4%), and heart failure (4%) among adults in CPCSSN data or other Canadian data [13,55].

Descriptive Analyses

To describe the cohort, continuous or count variables will be analyzed for their mean, median, SDs, and IQRs. For categorical variables, percentages will be calculated. We will present outcomes stratified by sex, age category (40-49, 50-59, 60-69, and ≥70 years), urban versus rural patient address, and neighborhood income quintile (1-2 [lower] vs 3-5 [higher]).

Analyses of Changes Over Time

We will present the proportions of patients experiencing the outcomes for each time period or mean changes for continuous variables and 95% CIs. Statistical significance of changes from pre to post time period will be assessed using the McNemar test for binary variables, the Wilcoxon signed rank test for original variables, and the paired *t* test for continuous variables. Regression models appropriate to outcome distributions will be used to control for potential confounders of age (<70 vs ≥70 years), sex, count of comorbidities (CPCSSN-validated conditions), neighborhood income quintile, and CPCSSN network (corresponding to location within Canada). Interactions will be examined in the descriptive analysis and will be considered for inclusion in models if they are found to be relevant. We will present adjusted estimates and 95% CIs for outcomes and parameter estimates for the independent variable and covariates. Analyses will be completed using SAS (version 9.4; SAS Institute, Inc).

Sensitivity Analysis

To examine whether results are biased because of the nonrepresentativeness of the CPCSSN population, we will conduct the analyses on a sample of patients that is representative of the Canadian population based on age, sex, neighborhood socioeconomic status, and rural or urban residence.

Ethics Approval

This study was approved by the Hamilton Integrated Research Ethics Board on April 11, 2022 (project number 14782-C). Because we will be using deidentified data, no consent is required. This study is also registered with ClinicalTrials.gov (NCT05813652).

Results

Study Timeline

The start date of this study was October 5, 2022, and the prospective end date is January 31, 2024. At the time of writing (May 2023), we have finished data cleaning and begun exploratory analyses. As there are known consistencies with CPCSSN data, having a longer exploratory analysis phase has allowed us to liaise with central CPCSSN data managers in order to prepare data for the main analyses. We have now also defined our study cohort: a total of 875,934 individuals between the ages of 18 and 105 years as of 2018 were included.

Future Analyses

We will attempt to extend our analyses to include the first half of 2022 when data become available if our timelines and resources allow. At the time of writing this protocol (May 2023), data were available up to December 2021. The additional 2022 data will allow us to investigate changes in primary care in the later portion of the COVID-19 pandemic, capturing the Omicron wave, and measure whether any changes identified in the earlier portion of the pandemic were sustained or returned to prepandemic patterns of care.

Dissemination

We plan to share knowledge products for patients and the public with the patient advisory committee being created as part of the David Braley Primary Care Research Collaborative at McMaster University, with whom several authors are affiliated. *For clinicians*, we will create evidence briefs to be shared with the national and provincial colleges of family physicians through social media and our CPCSSN practice-based research network linkages. *For researchers and policy and practice decision makers* (eg, College of Family Physicians of Canada), we will produce peer-reviewed publications and evidence briefs where we will contextualize the new knowledge against recent research relating to pandemic recovery in health care. The 1- to 2-page evidence briefs will be shared with knowledge users involved in the development and implementation of policies and resources

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related to pandemic recovery. *For patients*, we will create infographics and a short video that will raise awareness of the issue of chronic condition care gaps and describe patients' perspectives. These will be circulated via social media and clinical organizations.

Discussion

Key Findings

The aim of this study is to help identify signals of change across several domains of primary care, including access, comprehensiveness, and appropriateness, that may have occurred in response to the COVID-19 pandemic. This will be done by investigating the overall number of primary care encounters during the pandemic compared with prepandemic, as well as potential changes in the number of diagnoses addressed during encounters, number of blood pressure measurements, number of vaccines provided, number of blood tests carried out, and so on. Potential changes in indicators specific to the management of chronic conditions will also be investigated, for example, frequency of HbA_{1c} testing for those with diabetes, number and frequency of visits for monitoring of heart failure, and number of prescriptions for diabetes or heart failure. Potential changes in any of these indicators may indicate that gaps in care are present that may benefit from targeted recovery measures.

However, these potential changes in primary care are not inherently negative. For example, many blood tests, examinations, and procedures are considered overused in certain populations and may be conducted more frequently than necessary [53,57,58]. If decreases in number or frequency of these overused tests are identified during the pandemic, this may be considered more appropriate use when compared to prepandemic levels. Furthermore, decreases in frequency of certain primary care interventions may not be clinically significant or necessarily lead to negative health outcomes. Therefore, it is important that each identified change be carefully considered in a broad clinical context before firm conclusions can be drawn.

Strengths and Limitations

The strengths of this study include the use of a large, multiprovince primary care EMR data source, developed to understand the epidemiology of chronic diseases and care in Canadian primary care. The data set is regularly updated and includes coded information on most aspects of primary care practice. The relative currency, longitudinal format, and comprehensiveness of CPCSSN data are ideal for the study of practice changes, through time, in response to significant environmental imperatives, such as the sweeping public health measures put in place during the pandemic [41]. Numerous case definition validation studies have been completed [42,43], and the data have also been used to evaluate patterns and quality of health care [19,45]. CPCSSN has undertaken extensive data cleaning algorithms to address data quality issues [41].

There are limitations in this study. EMR data are collected for clinical and administrative purposes and are not primarily collected for research, which may result in incomplete capture of information. Furthermore, participating sentinel clinics are overrepresented by academic practices [59], and by extension, we cannot be certain to what extent the patients in the CPCSSN data differ from other Canadian primary health care patients. There may be issues of nonparticipation bias and variation in data quality. This study will not provide information on people who are not attached to a primary care provider. As with primary care patients generally, older adults and female individuals are overrepresented in the CPCSSN database as compared with the national population; however, as this study is about changes in care patterns, this data set is representative of the population of interest [59]. Clinical context for some research based on secondary use of EMR data can be difficult to infer. Detailed information on family and living circumstances, ethnicity, language spoken, education, and socioeconomic status is rarely captured in EMRs, so it is more difficult to conduct equity analyses, relying instead on neighbor-level indicators.

Patient and Public Involvement

This research was initially designed and received funding without patient involvement. When the research team presented the data request to the CPCSSN data access committee (May 2022), a patient advisor on the committee provided input. The advisor noted that the proposal was broad in terms of the scope of chronic diseases to be investigated. In response, we refined our analysis plans to examine diabetes and heart failure in greater detail as exemplar diseases. The advisor also suggested that it would be important to consider the changes in the health care system and behaviors of the public over different phases of the pandemic, especially since the Omicron variant.

Conclusions

We anticipate that this study will provide evidence that will inform whether and in what aspects of primary care the COVID-19 pandemic is associated with interruptions that may require attention. It will also highlight gaps or provide reassurance with respect to chronic condition care for populations who were expected to be disproportionately affected by pandemic health care changes such as those who are older or of lower socioeconomic status.

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Data Availability

The data set from this study is held securely by CPCSSN, and data sharing agreements prohibit the authors from making the data set publicly available. Researchers can request access to CPCSSN data on their website [60].

Authors' Contributions

MH, DM, ND, M-T L, K A-B, AR, and MV were responsible for the study concept. MH, DM, ND, M-T L, KN, K A-B, SH, KF, and JL contributed to the study design. MH wrote the first draft of the manuscript. DM, ND, M-T L, KN, K A-B, SH, KF, JL, and AR critically revised the manuscript. MH, DM, ND, M-T L, KN, K A-B, SH, KF, JL, and AR approved the final manuscript as submitted.

Conflicts of Interest

M-TL declares having received consultation fees from le Collège des médecins du Québec and sits on the board for a small research and communications company. Neither of these have any direct link to this project or manuscript.

Multimedia Appendix 1
Peer review report by Canadian Institutes of Health Research (Canada).
[PDF File (Adobe PDF File), 222 KB - resprot_v12i1e49131_app1.pdf]

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Abbreviations

CPCSSN: Canadian Primary Care Sentinel Surveillance Network
EMR: electronic medical record
RECORD: REporting of studies Conducted using Observational Routinely collected Data

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Protocol

Development of the Preferred Components for Co-Design in Research Guideline and Checklist: Protocol for a Scoping Review and a Modified Delphi Process

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Abstract

Background: There is increasing evidence that co-design can lead to more engaging, acceptable, relevant, feasible, and even effective interventions. However, no guidance is provided on the specific designs and associated methods or methodologies involved in the process. We propose the development of the Preferred Components for Co-design in Research (PRECISE) guideline to enhance the consistency, transparency, and quality of reporting co-design studies used to develop complex health interventions.

Objective: The aim is to develop the first iteration of the PRECISE guideline. The purpose of the PRECISE guideline is to improve the consistency, transparency, and quality of reporting on studies that use co-design to develop complex health interventions.

Methods: The aim will be achieved by addressing the following objectives: to review and synthesize the literature on the models, theories, and frameworks used in the co-design of complex health interventions to identify their common elements (components, values or principles, associated methods and methodologies, and outcomes); and by using the results of the scoping review, prioritize the co-design components, values or principles, associated methods and methodologies, and outcomes to be included in the PRECISE guideline.

Results: The project has been funded by the Canadian Institutes of Health Research.

Conclusions: The collective results of this project will lead to a ready-to-implement PRECISE guideline that outlines a minimum set of items to include when reporting the co-design of complex health interventions. The PRECISE guideline will improve the consistency, transparency, and quality of reports of studies. Additionally, it will include guidance on how to enact or enable the values or principles of co-design for meaningful and collaborative solutions (interventions). PRECISE might also be used by peer reviewers and editors to improve the review of manuscripts involving co-design. Ultimately, the PRECISE guideline will facilitate more efficient use of new results about complex health intervention development and bring better returns on research investments.

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co-design; reporting; guidelines; complex health intervention; scoping review; consensus

Introduction

Health research can often be immaterial when it focuses on questions and outcomes that have limited relevance to the individuals who will ultimately use the research findings, such as patients and clinicians [1]. A scoping study conducted by Oliver and Gray [2] in 2006 found that out of 334 studies, only 9 compared the priorities of researchers with those of patients or clinicians in terms of research and outcomes for assessing treatment effects. If end users, including patients and clinicians, are excluded from the process of establishing research priorities, such as in the selection of research areas or intervention development, irrelevant health research results and interventions might be generated [3].

To address this issue, there has been a notable increase in patient and public involvement (PPI) in health research [4-11]. Acknowledging the significance of incorporating the viewpoints and firsthand knowledge of patients, families, clinicians, and policymakers, many funding agencies have made patient-oriented activities, also referred to as PPI, obligatory [12-14]. According to the Canadian Institutes of Health Research (CIHR), PPI refers to “a continuum of research, from initial studies in humans to comparative effectiveness and outcomes research, and the integration of this research into the health system and clinical practice” [15]. Thus, PPI involves actively involving patients, carers, and members of the public in various stages of research, such as setting priorities, designing studies, collecting and interpreting data, designing interventions, and disseminating findings [14,16,17]. This shift towards PPI signifies a paradigm shift in the research landscape, emphasizing the significance of collaborative and inclusive approaches to better address the needs and preferences of the communities being served [13,18,19]. Thus, researchers are challenged to “do... [PPI] right” [20].

To enact PPI, researchers have used various collaborative and participatory methods and designs [21]. One approach that has garnered significant attention and momentum is co-design, as a specific application and democratization of design that originated from the field of participatory design [22,23]. Co-design entails a process of collective creativity that spans the entire lifecycle of a design project [24]. This approach embraces creativity and flexibility to foster reflective feedback throughout the project [22]. Unlike the traditional expert-led approach, where interventions are designed “for” users, co-design emphasizes designing interventions “with” or “by”

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users. Thus, co-design approaches aim to engage patients and other knowledge users in meaningful and reciprocal collaborations, fostering ownership, empowerment, and shared responsibility [25,26]. During co-design, active collaboration occurs among researchers, designers, developers, and users as experts in their experiences [27,28]. Co-design involves cooperatively exploring and communicating needs and devising solutions as a team [29,30]. Co-design aims for better design based on a richer, deeper understanding of what users know and experience [29]. Co-design in the domain of health services research, specifically in this case, involves multiple end-users, including researchers, designers, developers, and users, including health care workers and patients as experts who contribute their collective input for the purpose of developing a complex health intervention [24,27,29].

There is increasing evidence that co-design can lead to more engaging, acceptable, relevant, feasible, and even effective interventions [25,31]. A systematic review [8] reported examples of practice change from introducing co-designed outputs [31]. Changes included improved consistency in clinician assessment and identification of patient problems that were previously missed [32], revised clinical pathways [33], fewer hospital visits and admissions [32], and a reduction in the number of patients who failed to attend appointments [34]. Additional beneficial outcomes, such as patient satisfaction, were either demonstrated or perceived to be possible [35].

When practicing co-design, most researchers agree that co-design processes begin with understanding users' needs and behaviors and developing concepts that are tested and adapted in simple, fast, and low-cost ways [29,30]. For example, Boyd and colleagues [36] describe a 6-step process that includes engaging, planning, exploring, developing, deciding, and changing. However, there is considerable variation in how co-design is defined and practiced, ranging from feedback and consultation to user testing to web-based collaboration or user research and workshops [25]. Moreover, in practice, the terms co-design, cocreation, and coproduction are often used interchangeably and adopted and described inadequately, collectively termed "coapproaches" [23,31,37-39]. A recent overview of 23 reviews [25] concluded that, while co-design in health care appears to be widely used to develop complex health interventions, it is seldom described or evaluated in detail. The authors further concluded that realizing the potential of research-based co-design might require clearer and more consistent terminology and better reporting of the activities involved [25]. While some of the fundamentals of coapproaches have been described, for example, sharing power, including all perspectives and skills, respecting and valuing all knowledge, reciprocity, and building and maintaining relationships [40], there is limited consistency in understanding how to co-design complex health interventions and report them. Complex health interventions are defined as any effort, activity, or combination of program components that independently and interdependently improve health outcomes. Complex health interventions can be delivered in many settings, including health services, schools, local communities, or national populations. They can be delivered by a variety of individuals, including health care, social care, and public health practitioners, as well as professionals working outside of the health care sector, such as peers [41-43]. An example of a complex health intervention is a self-management program involving educational materials or resources and motivational enhancement delivered via weekly interactions with a peer. Complex health interventions do not include the development of medicines and any invasive interventions (eg, medical or surgical procedures).

In response to the reporting challenges specific to PPI in research, the Guidance for Reporting Involvement of Patients and the Public (GRIPP) [44] and GRIPP2 [45] were developed**.** The use of reporting guidelines can enhance transparency in the methodology presented in research reports and improve the adoption of research findings [45,46]. Reporting guidelines refer to a prescribed set of essential elements that should be included in co-design research reports [47]. These guidelines can be in the form of a checklist, flow diagram, or explicit text to assist authors in accurately reporting specific types of research [47]. The development of guidelines like these follows a well-defined methodology [47]. Hence, reporting checklists have dual applications: they can be used proactively to guide the research design, or retrospectively to evaluate the quality of reporting. Indeed, systematic reviewers have found the endorsement and implementation of guidelines by journals can improve reporting [46,48]. Ultimately, reporting guidelines contribute to the more effective use of new research findings and yield enhanced returns on research investments [46,48].

Despite the contribution of GRIPP2 [45], its guidance is generic and not focused on a particular approach or methodology—this leaves room to develop reporting guidance for particular approaches, including co-design approaches involving patients and other end-users to develop complex health interventions. Additionally, no guidance is provided on the specific designs and associated methods or methodologies involved in the process (eg, needs assessment via qualitative methods to clarify and address gaps in intervention preferences). Furthermore, GRIPP2 does not include guidance on the reporting of values or principles associated with meaningful co-design and how they are enacted or enabled. Thus, new guidelines are needed to promote consistent, transparent, and quality reporting of co-design studies to develop complex health intervention development.

We propose the development of the Preferred Components for Co-design in Research (PRECISE) guideline to enhance the consistency, transparency, and quality of reporting co-design studies used to develop complex health interventions. This aim will be realized by addressing the following objectives: to conduct a scoping review on the models, theories, and frameworks used to co-design complex health interventions to identify their common elements (components, values or principles, associated methods and methodologies, and outcomes); and to use these results to prioritize the co-design components, values or principles, associated methods and methodologies, and outcomes to be included in the PRECISE guideline using a modified Delphi process.

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Methods

Study Design

The development of the PRECISE guideline will follow the methodological framework for developing reporting guidelines, as outlined by the Enhancing the Quality and Transparency of Health Research (EQUATOR) Network [49], and the Guidance for Developers of Health Research Reporting Guidelines [20].

Integrated Knowledge Translation Panel

An integrated knowledge translation (iKT) panel has been formed to codevelop the research protocol, including informing the search strategy, reviewing preliminary results, and planning knowledge dissemination strategies. The iKT panel includes patient partners, caregivers, health care administrators, and journal editors. The formation of the iKT panel aims to codevelop the research protocol, which includes ensuring patient-based data representation in journals, informing the search strategy, reviewing preliminary results, and planning knowledge dissemination strategies, all while fostering a brave space that promotes trust, inclusion, and respect among patient partners, caregivers, health care administrators, and journal editors involved in the process. We will use the reflective exercise titled "SPOREA Reflective EDI Exercise" to promote dialogue and understanding around equity, diversity, and inclusion (EDI) topics amongst all iKT panel members [50]. We will ensure that discussions are conducted in a manner that respects diverse perspectives and experiences. We will compensate patients for their time and expertise according to mutually agreed-upon guidelines, which will be informed by the SPOR Evidence Alliance's policies and procedures [51].

Phase 1: Scoping Review on Models, Theories, and Frameworks in the Co-Design of Complex Health Interventions

Study Design

The methodology for this scoping review was developed following the methodological frameworks of JBI [52] and Khalil and colleagues' [53] suggestions. The protocol for this scoping review was registered on the Open Science Framework Register on June 12, 2023 (osf.io/prd3t). The protocol was guided by and reported according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) [54]. The results of the review will be reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Extension for Scoping Reviews (PRISMA-ScR) checklist [55].

Stage 1: Developing a Search Strategy

An information specialist and health science librarian will create and draft the search strategy using OVID Medline in consultation with the research team. The Population, Concept, and Context framework will be used to guide the search strategy (population: model, theory, or frameworks; concept: co-design studies; context: complex health interventions). Literature search strategies using medical subject headings and text words related to co-design, cocreation, and coproduction and models, theories, and frameworks will be developed. This preliminary search strategy is based on the published search strategies of previous reviews [25,31]. The final search strategy will combine structure database-specific subject headings (as available) and keywords or synonyms. The final search strategy will also undergo peer review using the Peer Review of Electronic Search Strategies (PRESS) statement checklist [56].

The following databases will be searched: Medline, CINAHL, Embase, PsycINFO, ACM Digital Library, and Cochrane Central Register of Controlled Trials. Hand-searching of design-specific publications will also be performed (eg, *Design for Health*, *HERD: Health Environments Research & Design Journal*, and *Health Design*). To help capture any relevant literature, we will also search the reference lists of included studies and those of relevant systematic reviews. The searches will not be limited by study design or languages. The search will capture literature from 1972 to present, consistent with when the term co-design first originated [23,57]. We will also search the gray literature in specialized databases like OpenGrey, Grey Literature Report, and GreyNet International; platforms like arXiv, bioRxiv, and SSRN; and databases like ProQuest Dissertations and Theses. We will search for conference abstracts (full papers) in specialized co-design in health conference proceedings (ie, D4H Proceedings).

Stage 2: Evidence Screening and Selection

All primary studies that have applied a model, theory, or framework for the purpose of co-designing a complex health intervention will be eligible for inclusion. We define a model as the essential elements or variables of a phenomenon or a specific aspect of a phenomenon; a theory as "a set of analytical principles or statements designed to structure our observation, understanding, and explanation of the world;" and a framework as an explanation of a phenomenon by organizing it into a collection of descriptive categories and the relationships between them [58]. We focus on models, theories, and frameworks to identify key components, actions, and mechanisms.

All articles with primary study designs will be included (eg, experimental, quasi-experimental, observational, qualitative, mixed, and multiple methods). Systematic reviews, meta-analyses, editorials, commentaries, and nonspecific conference proceedings will be excluded to focus on including primary results and not preliminary findings or ongoing research; however, the reference lists of relevant reviews will be hand searched for relevant articles.

References for all included studies will be uploaded and managed through EndNote (Niles & Associates) [59] and duplicates will be removed before importing sources into Covidence (developed by an Australian not-for-profit company) [60]. To increase the reliability, a pilot test of the level 1 (title and abstract) screening form based on the criteria outlined above will be conducted on a random sample of approximately 50 papers by the entire team. The descriptions of the eligibility criteria will be revised if deemed necessary by the team or if a low agreement (ie, <70%) [61] is observed to improve the consistent application of the selection criteria**.** Our agreement will be defined by Cohen κ [62]. All screening (ie, levels 1 and 2, full-text) will occur in duplicate and independently. For level 1 screening, reviewers will screen the titles and abstracts for

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inclusion using Covidence. For level 2, the full text of potentially relevant articles will then be collected and screened to determine final inclusion. A pilot test of the level 2 screening will also be performed on approximately 25% of the articles, similar to the process for level 1 screening. When necessary, another reviewer knowledgeable in the research area will be available to resolve conflicts. For studies that are excluded at level 2, the reason for exclusion will be recorded. Evidence screening will be managed using Covidence software [60]. Members of the research team, including members of the iKT panel, will conduct the screening.

Stage 3: Data Extraction

A standardized data extraction form will be developed by the research team, in consultation with the JBI manual data extraction suggestions [52] and the recommendations for the extraction, analysis, and presentation of results in scoping reviews [63]. Extracted data will include study characteristics (eg, year of publication and study design), participant population characteristics (eg, medical condition, age, race, sex, gender, and gender-related variables such as education and health literacy), types of health interventions (eg, in-person support program and apps), and details of the models, theories, frameworks (eg, name, reference, date of initial development, components, values or principles (and how they were enabled or enacted), associated methods and methodologies) that have been used in the co-design of complex health interventions. We will also collect data on how end users were engaged throughout the various stages of the co-design process and outcomes achieved as well as the results of the study. Additional categories will likely be identified through the completion of the search and through discussions with the research team.

To ensure all relevant results are extracted, 2 research assistants will conduct a pilot extraction by trialing the extraction template for 2 to 3 articles. All data will then be extracted in duplicate by 2 independent reviewers. Discrepancies in the extracted data will be discussed and resolved by the 2 reviewers. Quality or risk of bias will not be assessed, as this is not required in scoping reviews [55].

Stage 4: Data Analysis

The bibliographic data from this scoping review will be quantitatively summarized using numerical counts (eg, number of studies from Canada, the United States) and qualitatively using content analysis [64]. These data will be analyzed or coded manually. The data will be grouped by the main components of the model, theories, frameworks, values or principles (and how they were enacted), associated methods (eg, one-on-one interviews), and methodologies. We will also synthesize data on how end users were engaged throughout the various stages of the co-design process, the types of outcomes collected, as well as results. Depending on the included articles, subgroup analyses might be conducted by, for instance, complex health intervention type, sex, gender-related variables, as well as the other PROGRESS-Plus characteristics (eg, race, ethnicity, culture, language, education) [65]. If feasible, we will contact the study authors of the included studies to confirm that all the data collected were included in the article (eg, not excluded due to word count limitations of a journal).

Dissemination

The results of this scoping review will be used to inform the surveys for the Delphi discussions that will be implemented in phase 2, as well as the draft PRECISE guideline. Findings from the scoping review will help to identify which components, values or principles, associated methods and methodologies, and outcomes will be included in the guideline. Other outputs from the scoping review will include a peer-reviewed publication of the results, as well as a newsletter and webinar to promote engagement for phase 2.

Phase 2: Modified Delphi Process to Prioritize Items for the PRECISE Guideline

Study Design

As consensus-building processes are crucial in developing a reporting guideline as per the EQUATOR process [49], the prioritization of the PRECISE guideline items will occur using a modified Delphi process [47]. A modified Delphi process refers to a variation or adaptation of the traditional Delphi method. The Delphi method is a structured and iterative process used to gather insights and perspectives from a panel of experts to reach a consensus or make informed decisions [47,66]. The Delphi process involves repeated surveys to collect previously unknown information from a group of individuals with expertise in a particular area. Participants in a Delphi process are usually given a large number of items that need to be rated or ranked. Consistent with the methods used to develop other reporting guidelines [55], we will conduct this process over 3 rounds. The succeeding iterations of each round of the Delphi process are intended to decrease the number of items based on analyses of participant responses and denote the consensus of these experts.

Identification and Recruitment of Participants for the Modified Delphi Process and Web-Based Consensus Meeting

A multinational, multidisciplinary, and panel of experts specializing in co-design for the development of complex health interventions will be invited to engage in the modified Delphi process. This panel will consist of individuals from various geographical locations, diverse knowledge user types (including patients, caregivers, and members of the public), and a range of research backgrounds and personal characteristics such as sex, gender, and ethnicity. The experts within this panel will actively contribute their insights and recommendations, particularly emphasizing the involvement of specific patient and caregiver knowledge users.

Given the breadth and diversity of expertise and lived experience required for this study, we will use a purposive and snowball sampling strategy to achieve the recommended minimum sample size of 100-150, consistent with other reporting guideline initiatives [67].

Invitations will be extended to potential expert participants via email, accompanied by a comprehensive explanation of the initiative. To ensure inclusivity, individuals facing technological barriers will be offered assistance to facilitate their participation. This may involve conducting surveys over the phone or

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providing participants with necessary devices such as tablets, along with any required training in using the technology.

Data Collection

The round 1 survey will be developed based on the findings of the scoping review. Findings from the scoping review will generate an initial list of PRECISE guideline items that will be reviewed by the researchers and iKT panel. The survey tool will ask participants to rank key concepts in terms of relevance, importance, and comment on the definition of the concept. Pilot testing will be conducted to ensure the content is clear and comprehensible, and necessary revisions will be made before distribution. Participants who complete the round 1 survey will be eligible to participate in the round 2 survey. Likewise, completion of the round 2 survey will determine eligibility for the round 3 survey. Participants in round 2 will be presented with the condensed list of concepts and asked to rank order from most to least important. As with round 1, experts will be asked to comment on the particular concepts listed and add any other categories not identified. This will be repeated for round 3.

During all rounds, participants will be asked to provide demographic and descriptive information, such as sex, gender identity, race, expert participant type, and career stage (if applicable). The web-based survey will be administered using Qualtrics software (Qualtrics XM) for all 3 rounds. This will last 4 weeks, and reminder emails will be sent every 7 days after the initial invitation to encourage participation. Each survey is estimated to take approximately 20 minutes to complete.

Participants will be requested to rate their agreement with the inclusion of each proposed guideline item using a 7-point Likert scale, ranging from “entirely disagree” to “entirely agree.” Surveys will be conducted exclusively in English. Furthermore, each survey item will include an optional text box for participants to provide comments, including suggestions for additions, deletions, aggregations, or refinements of items. This allows for the opportunity to modify and retain items based on participant feedback.

Upon joining the study, participants will be given an exclusive research code for identification purposes. A secure record containing the association between participants’ names and their respective research codes will be maintained on a protected network. Access to this record will be restricted solely to the research administrator responsible for supporting the study.

Analysis

Demographic and descriptive information provided by participants will be analyzed by calculating proportions expressed as percentages. This information will include factors such as sex, gender identity, race, knowledge user type, and career stage if applicable.

Throughout all 3 rounds of the survey, a consensus threshold of 80% agreement will be applied to each guideline item. This means that for an item to be considered as achieving consensus and being kept in the PRECISE guideline, at least 80% of participants must select values of 6 or 7 (mostly or entirely agree with its inclusion) on the Likert scale.

In cases where an item does not meet the 80% agreement threshold, it will be considered discrepant. To gain further insights, potential differences in item agreement will be investigated based on factors such as sex, gender, other aspects of diversity, and knowledge of user type. This analysis will be conducted using chi-square analysis.

Content analysis will be carried out for comments received during the survey [68]. These comments will be summarized and used to inform subsequent surveys. The content analysis process will involve the research team and the iKT panel. These results will be summarized and used to inform subsequent surveys. Furthermore, for the rounds 2 and 3 surveys, participants will be given their individual results as well as the overall group distribution, median, and interquartile range from the previous survey rounds (ie, rounds 1 and 2 surveys). These data will be summarized for transparency and to promote full consideration of discrepant items. In addition, as part of this exercise, in the rounds 2 and 3 surveys, we will ask participants to respond to the question, “After reviewing your survey results with respect to this item (ie, each discrepant item), please comment on why you rated this item the way you did.” Again, content analysis will be conducted on these comments to gain additional insights [68].

Consensus Meeting

After the completion of the 3 rounds of surveys, a web-based 2-day consensus meeting will be organized using Zoom. All expert participants who participated in rounds 1-3 will be invited to attend this meeting. The meeting will begin with a presentation of the summarized results from round 3, including any accompanying recommendations. We will report back demographic differences. Participants will have the opportunity to elaborate on their ratings of discrepant items.

During the consensus meeting, the researchers and iKT panel will draft the PRECISE guideline. This draft will be presented for discussion. Expert participants will collaborate to reach a consensus (ie, 80% agreement) to determine the items to be included in the final version of PRECISE, as well as determine their specific wording. The meeting will also explore the potential recommendation of a core set of items and the linkage of guideline items to checklist items. If appropriate and feasible, the weighting of items will be considered, and both short and long versions of PRECISE will be discussed.

Additionally, the consensus meeting will address how the PRECISE guideline and checklist can promote diverse perspectives and inclusive reporting. Dissemination strategies for the results will also be discussed during the meeting. Detailed records will be kept of all discussions related to the development of the PRECISE guideline and checklist, documenting the decisions made.

Following the consensus meeting, the guideline and checklist will be distributed to the expert participants for their review and to ensure that it accurately reflects the consensus decisions. The final PRECISE guideline and checklist will be tested with approximately 15 researchers or scientists, policymakers, and students by applying it to a study describing the co-design of a

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complex health intervention, as done in the development of other guidelines [55].

Ethical Considerations

Research ethics board approval for this component of the study will be sought by the lead author's primary institution. PRECISE will seek to reflect not just the prioritized components and associated methods or methodologies of co-design, but also the values or principles that drive co-design and how they can be enacted or enabled.

Results

This guideline development is supported by the CIHR (Project Grant). This study will take place from April 2023 to March 2025.

Discussion

Expected Findings

This research will address the need for consistent reporting in the literature regarding the use of co-design in developing complex health interventions. The guidelines developed through this study will play a crucial role in facilitating future synthesis of studies in this field. The PRECISE guidelines will build on the GRIPP/GRIPP2 guidelines by emphasizing equal partnerships between researchers, practitioners, and knowledge users to generate shared knowledge and solutions. By following these guidelines, researchers can report on the authentic engagement of patients, carers, and other knowledge users, moving beyond thinly described coapproaches to describe methods and techniques that can move the field forward, and consequently lead to enhanced involvement and the promotion of inclusion of vulnerable populations to a greater extent in intervention design. The PRECISE guideline can improve the proliferation of the co-design method by providing researchers seeking grant funding a template to work from, improving reporting, and allowing for refinement of the method itself.

Strengths and Limitations

This research protocol has several notable strengths that contribute to its methodological soundness and comprehensiveness. One strength of the scoping review is the inclusion of gray literature, which helps mitigate publication bias and ensures a more comprehensive coverage of relevant information [69]. Similarly, we will use an iterative approach to ensure we capture all studies, using guidance from other published reviews and our iKT panel. Additionally, we will conduct a thorough search of reference lists in the included articles and have the search strategy peer-reviewed to further strengthen the quality and comprehensiveness of the search strategy, ensuring that it is thorough and effectively captures relevant literature. All searches will be performed by an information specialist experienced in scoping and systematic review methodologies including reviews on patient engagement. Due to resource limitations, we have made the decision to only include studies that are available in English as part of our inclusion criteria. However, we recognize that this approach may result in the exclusion of relevant studies published in languages other than English. Moreover, our protocol was developed with the EQUATOR guidelines in mind [49].

Future Directions

We will use a range of passive and active knowledge translation methods to disseminate our research findings. Traditional knowledge translation approaches will involve sharing our findings through local, national, and international meetings, as well as publishing in reputable peer-reviewed journals. Our project will yield open-access publications, including the scoping review itself, and the Delphi process, which will include the PRECISE guideline and checklist along with an explanation and elaboration (E and E) document, consistent with guidance provided by Moher et al [70]. We will widely share the PRECISE guideline and checklist within our networks. Input from our iKT panel and other knowledge users will inform our dissemination strategies and guide the planning of future research initiatives. The research team's strong connections to key journals in this space, such as *Health Expectations*, *Design for Health*, and the *International Journal of Integrated Care*, highlight our ability to disseminate our contributions to the advancement of co-design methodologies and practices.

Conclusions

The collective results of this project will lead to the development of a ready-to-implement PRECISE guideline that outlines a minimum set of items to include when reporting the co-design of complex health interventions. The PRECISE guideline will improve the consistency, transparency, and quality of reporting on studies by researchers and multiple knowledge users in policy and practice, including patients, that use co-design to develop complex health interventions. Additionally, it will include guidance on enacting or enabling the values or principles of co-design for meaningful and collaborative solutions (interventions). PRECISE might also be used by peer reviewers and editors to improve the review of manuscripts involving co-design. Ultimately, the PRECISE guideline will facilitate more efficient use of new results in complex health intervention development and bring better returns on research investments.

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Conflicts of Interest

SM is the Editor-in-Chief of JMIR Rehabilitation and Assistive Technologies and a Guest Co-Editor of Healthcare Transition.

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Abbreviations

CIHR: Canadian Institutes of Health Research
E and E: explanation and elaboration
EDI: equity, diversity, and inclusion
EQUATOR: Enhancing the Quality and Transparency of Health Research
GRIPP: Guidance for Reporting Involvement of Patients and the Public
iKT: integrated knowledge translation
NIHR: National Institute for Health and Care Research
PPI: patient and public involvement
PRECISE: Preferred Components for Co-Design In Research
PRESS: Peer Review of Electronic Search Strategies
PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analysis Extension for Scoping Reviews

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Protocol

Engagement of Older Adults Receiving Home Care Services and Their Caregivers in Health Decisions in Partnership With Clinical Teams: Protocol for a Multimethod Study to Prioritize and Culturally Adapt Decision Aids for Home Care

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Abstract

Background: Older adults (people aged 65 years and older) face many difficult decisions. Patient decision aids (PtDAs) can help them and their families make informed value-congruent decisions. Some PtDAs have been developed for the home care context, but little is known about scaling them for use with older adults in a different culture.

Objective: This study aims to (1) assess the scalability of existing PtDAs for older adults in the home care context; (2) prioritize those that best match the decisional needs of older adults in home care; and (3) culturally adapt the prioritized PtDAs so they can be scaled successfully to the Quebec health care system.

Methods: This multimethod study includes 3 phases. All phases will be overseen by a steering committee of older adults, caregivers, health professionals, decision makers, community organization representatives, and researchers with the needed expertise. In phase 1, we will use the Innovation Scalability Self-administered Questionnaire, a validated scalability self-assessment tool, to assess the scalability of 33 PtDAs previously identified in a systematic review. Based on their scalability, their quality (based on the International Patient Decision Aids Standards), and the importance of the decision point, we will retain approximately a third of these. In phase 2, we will conduct a 2-round web-based Delphi to prioritize the PtDAs selected in phase 1. Using a snowball recruitment strategy, we aim to recruit 60 Delphi participants in the province of Quebec, including older adults, caregivers,

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health professionals, decision makers involved in home care services, and PtDA experts. In the first round, we will ask participants to rate the importance of several PtDA decision points according to various criteria such as prevalence and difficulty on a 5-point Likert scale (1=not important to 5=very important). Approximately 6 of the highest-rated PtDAs will be retained for presentation in the second round, and we will select up to 3 PtDAs judged as having the highest priority for cultural adaptation. In phase 3, using the Chenel framework and user-centered design methods, we will update and adapt the PtDAs to the Quebec health care system and integrate these PtDAs into an interprofessional shared decision-making training program for home care teams. The adapted PtDAs will respect the International Patient Decision Aids Standards criteria.

Results: This study was funded in March 2022 by the Canadian Institutes of Health Research. Data collection for the web-based Delphi began in October 2023. Results are expected to be published in May 2024.

Conclusions: This project will provide relevant and culturally appropriate decision support tools for older adults making difficult decisions and their home care teams that will be ready for scaling across the province of Quebec.

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KEYWORDS

shared decision making; patient-centered care; home care; older adults; caregivers; decision aids; scalability assessment; innovation scalability self-administered questionnaire; interprofessional; team based

Introduction

In Canada, the number of people aged 65 years or older has tripled over the past 40 years, and the current population is expected to grow by 68% by 2037 [1]. In the province of Quebec, Canada, people aged 65 years or older represent 21% of the population and should reach 26% by 2041 [2,3]. While 6.5% of all adults have received home care services in Quebec, this proportion rises to 28% among adults aged 75 years or older [4]. Thus, the demand for health and social services for older adults within the context of home care is likely to increase in the coming years. As older adults lose their autonomy and face increasing health problems, health decisions become more frequent as well as more difficult and decisions faced within the home care context present specific challenges [5].

Shared decision-making (SDM) is a collaborative process whereby clinical teams support individuals and their families to make informed health and social care decisions based on the best evidence and what matters most to them [6,7]. It fosters informed consent [8] and improves care experiences [9,10], health outcomes [10-12], clinical team well-being, and efficiency [13,14]. SDM also reduces the uptake of unproven treatments and, consequently, reduces health care waste [15]. It supports health equity, since the most vulnerable may benefit the most [16-18]. Finally, SDM has been adapted to and successfully tested in the home care context among interprofessional teams [19-21]. It was shown that home care interprofessional teams trained in SDM, along with older adults and their caregivers who had benefited from a decision aid, were more likely to share decisions together about housing transitions [19,20,22-24].

Patient decision aids (PtDAs) are tools that support people in defining the decision to be made, provide information regarding options and outcomes, and help clarify personal values and preferences [25]. They have been successfully used to bolster SDM [26] and to promote the involvement of family members in health decisions [19]. They have been shown to increase participants' knowledge, decrease their decisional conflict, and reduce the number of people who were passive or undecided in decision-making. They also improve patient - clinician communication and patient satisfaction with their decisions [16,18,27].

However, the uptake of SDM and PtDAs in Canada has been disappointing [15]. In a 2018 survey of 1591 Canadians, only 36% of older adults reported that they were always or often offered choices, and only 35% were always or often asked what was important to them. Among them, 8.9% reported receiving home care services, and results showed that they were the least engaged in decisions about their health [28]. In order to address this inequity in decision support, we conducted 2 pan-Canadian surveys and found that older adults in the home care context face numerous difficult decisions that fall under 3 main areas: housing and safety, managing health conditions, and end-of-life care [5,29]. In another survey, health care professionals reported that older adults and their family members needed more help in obtaining information about available options, dealing with peer pressure, and navigating the health care system [30].

We hypothesize that widespread uptake of PtDAs will be more likely if they are adapted to the context in which they will be used [31-33]. Most PtDAs are created to target 1 decision point, 1 defined population, and 1 context or health care system, but when they are scaled to further contexts, they rarely address the specificities of the stakeholders or health care systems into which they will be integrated. Rather than creating a new PtDA for each context, the adaptation of existing PtDAs has numerous benefits: it reduces the duplication of development efforts, optimizes the use of resources, improves relevance and applicability, and engages knowledge users in target locations [34].

Therefore, we propose the ENGAGE (Engagement of Older Adults Receiving Home Care Services and Their Caregivers in Health Decisions in Partnership With Clinical Teams) study: an integrated knowledge mobilization (iKM) scaling project whose aim is to assess the scalability of existing home care PtDAs, prioritize them in relation to the decisional needs of older adults in home care, and culturally adapt them so they can be scaled successfully to the Quebec health care system.

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Methods

Overview of Study Design and Context

The ENGAGE study is a multimethod study with 3 phases: (1) a scalability assessment, (2) the prioritization of existing PtDAs, and (3) cultural adaptation of the most relevant PtDAs to the specificities of the stakeholders and the Quebec health care system. Each phase will use a distinct methodology to meet the objectives.

The ENGAGE study will be conducted within the Quebec health and social care system, 1 of 14 independent health and social care systems in Canada. Each of these systems (1 in each province or territory and 1 at the federal level) is responsible for coordinating, insuring, and managing care and services for the population. Within Quebec, health care services, including home care services, are provided by 18 regional authorities [15,35]. Since the province of Quebec has its own health care system and regulations, and its population is mostly French speaking, PtDAs need careful and culturally sensitive translation and need to be adapted to the Quebec situation, for example, include options available specifically in Quebec, to ensure their uptake by the population [36].

Throughout the project, we will use an iKM approach to strengthen our partnerships with knowledge users and other interested parties [37]. We will form a steering committee of 8-10 persons to oversee the operationalization of the project. The committee will involve older adults, caregivers, health professionals, decision makers in health organizations offering home care services, representatives of community organizations offering services to older adults and caregivers, and representatives of the provincial health ministry. The committee will also include researchers with the expertise needed to conduct the project, that is, experts in PtDAs, the interprofessional SDM approach, Delphi design, scaling, and research with older adults receiving home care services. We will recruit the committee through our networks in 2 regional health authorities (1 rural and 1 urban). We will organize at least 6 meetings over the course of the project to ensure the engagement of committee members in all phases of the project. We will also send quarterly newsletters to all knowledge users and partners to inform them of the project's progress. We will remain attentive to the needs of the knowledge users and will respect the constraints of the managers and workers in the clinical settings as well as the older adults and their families. We will also contribute to capacity building by including trainees in all phases of this project. Finally, considerations of sex, gender, equity, diversity, and inclusion will be considered at all stages of the project using the Canadian Institutes of Health Research (CIHR) guidelines [38,39].

To ensure accurate reporting of the iKM approach, we will report results using the Guidance for Reporting Involvement of Patients and the Public (GRIPP2) checklist [40]. We will also report on the adaptation of PtDAs according to the Guidance for Reporting Intervention Development Studies in Health Research (GUIDED) checklist [41].

Phase 1: Scalability Assessment of the Existing PtDAs

We recently completed a systematic review of PtDAs developed for home care [42]. For them to reach the largest proportion of people who can benefit from them, PtDAs for home care use must be analyzed for their scalability. Scalability is the ability of a health innovation that has demonstrated effectiveness under controlled conditions to be expanded in real-life circumstances to reach a larger proportion of the eligible population while still maintaining effectiveness [43]. Our team developed and tested the Innovation Scalability Self-administered Questionnaire (ISSaQ), a validated evaluation tool for assessing the scaling potential of health innovations that is designed to be used by teams planning to scale health and social services innovations [44,45]. ISSaQ is a list of 37 items covering 12 essential components of scalability, such as evidence on the effectiveness of the innovation, its characteristics, its acceptability, its adaptability, and the quantifiable costs and benefits of scaling (Multimedia Appendix 1, in French only). We will therefore use the ISSaQ to assess the scalability of each of the 33 PtDAs developed for home care that were identified in our systematic review [42].

First, we will retrieve all available information on each of the PtDAs included in our systematic review by searching for publications. A total of 2 team members will then independently extract the characteristics of the PtDAs (eg, type, purpose, decision point, target population) and complete the ISSaQ scalability assessment grid for all 33 PtDAs identified in the literature [42]. Any disagreements will be discussed with a third team member to reach a consensus. The results will be synthesized and discussed with the steering committee. Given the large number of PtDAs identified in the literature review (n=33), the steering committee will then select approximately one-third of the PtDAs based on the relevance of the decision point to home care for older adults in the experience of the steering committee, their scalability, and their quality according to the international criteria established by the International Patient Decision Aid Standards (IPDAS) Collaboration [46]. In order to reach a consensus on the final selection, steering committee members will vote according to all 3 criteria mentioned above, and PtDAs receiving the highest number of votes will be selected for the next phase.

Phase 2: Prioritization of PtDAs Selected in Phase 1

Study Design

We will conduct a web-based Delphi (e-Delphi) study to prioritize the PtDAs selected in phase 1 [47]. The RAND research organization at the University of California at Los Angeles (RAND/UCLA) appropriateness method will be used to judge the prioritization and relevance of the selected PtDAs (maximum of 10 PtDAs) [48]. The decision point criteria deemed necessary for prioritization will be determined by the steering committee. These criteria could include, for example, the prevalence of the decision addressed by the PtDAs, the level of difficulty of the decision, the date at which the evidence was updated, and its potential for scale-up. A questionnaire will then be developed that addresses the various decision point criteria identified as priorities.

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Delphi Participants

Recruitment

We aim to recruit 60 participants in the province of Quebec for this phase of the study to ensure a minimum of 40 participants in both rounds of the e-Delphi study [49,50]. We will use a snowball recruitment strategy, a nonprobability sampling method whereby study participants are asked to recruit future participants from among their social networks [51]. We will recruit older adults, caregivers, health professionals, decision makers involved in home care services (eg, home care team managers, directors of community organizations, managers of health care organizations, and government deputy health ministers or advisers), researchers, and PtDA experts. We aim to recruit a minimum of 8 to 12 participants for each of these categories to ensure representativeness [49]. Inclusion criteria for older adults will be as follows: (1) aged 65 years or older; (2) has home care experience; (3) can participate in the specified timeframe; (4) can read and understand French; and (5) can give informed consent. Inclusion criteria for other categories of participants will be the same except for the following: (1) aged 18 years or older and (2) has home care experience as a caregiver, health professional, decision maker, or expert. We plan to recruit participants using the snowball method with the help of our steering committee members, partners, and knowledge users.

Older Adults and Caregivers

We will ask our partners about the possibility of recruiting potential candidates from their organizations. Our partners in relevant organizations will be invited to share the invitation email with their members and through their social media platforms. The clinical teams in home care working for 2 regional health and social service authorities (1 rural and 1 urban) will also be invited to share the invitation with the older adults and caregivers they meet during their home care appointments. If necessary, with the agreement of the potential participants, the names and telephone numbers of interested individuals may be shared with the research team so that a team member can contact them, explain the project further, and invite them to participate.

Health Care Professionals

Health care professionals will be recruited with the help of managers from the 2 regional health and social services authorities. We will ask them to distribute an invitation email to the health professionals in their organizations. If necessary, we will contact home care managers in other health authorities in the province of Quebec.

Decision Makers

We will solicit our partners who are already in decision-making roles to disseminate the invitation within their networks and help us identify other decision makers.

Other Experts

Finally, members of our research team and collaborating teams will circulate the invitation by email to their respective networks to help us identify potential PtDA experts who can manifest their interest by contacting the team members responsible for the study.

We will make sure all participants understand our research objectives as we prepare and oversee the information provided to them. With a concern for equity, we will also solicit older adults and family members in rural areas, whom we will reach in person if necessary.

Data Collection

The e-Delphi consensus study will be conducted over the web using the REDCap (Research Electronic Data Capture; Vanderbilt University) tools hosted at Université Laval [52,53]. Participants will read and sign a consent form in the REDCap platform before completing the questionnaire. We anticipate that 2 rounds will allow for an acceptable degree of agreement on the PtDAs to be prioritized. There will be an interval of approximately 3 weeks between the 2 questionnaires. Participants who do not have easy access to a computer will be invited to complete the questionnaire during an in-person meeting with a research assistant. For each round, participants will be asked to submit their completed questionnaire within 2 weeks. An email reminder will be sent 48 hours before the end of the 2-week period. In the first round, we will collect participants' sociodemographic information such as age, sex, gender, and education level. For each of the PtDAs selected in phase 1 (maximum of 10 PtDAs), we will present the main characteristics of the PtDAs (eg, decision point addressed, year, and country of development) and an image of each PtDA. Then we will ask participants to rate the PtDA according to the decision point criteria prioritized by the steering committee (eg, prevalence of the decision, level of difficulty of the decision, and potential for scale-up) included in the questionnaire on a 5-point Likert scale (1=not important to 5=very important). Participants will also be able to add free-text comments. We will calculate the overall scores and summarize free-text comments. Results will be synthesized and discussed with the steering committee. The highest-rated PtDAs will be retained for the next round (approximately 6 PtDAs).

In the second round, we will repeat the same procedure, but only the PtDAs prioritized in the first round will be presented (approximately 6 PtDAs). The results of the second round will be summarized and they will be presented and discussed with the steering committee. We will then select up to 3 PtDAs judged as having the highest priority for cultural adaptation (phase 3).

Data Analysis

Descriptive analyses of sociodemographic data will be conducted to profile the participants. Descriptive analyses will also be used to calculate the overall scores for each of the PtDAs after the 2 e-Delphi rounds. Regarding relevance and clarity, if the number of participants giving a score of 4 to 5 for each dimension divided by the total number of participants is greater than 0.80, this will be considered a good score. Regarding necessity, the formula $(Ne - N / 2) / (N / 2)$ will be applied, where Ne is the number of participants indicating an element as important and N is the total number of participants. This indicator varies between –1 and +1, with higher scores indicating

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consensus. Results will be collated using SAS (version 9.0; SAS Institute Inc) to calculate the median score and percentage of agreement. We will summarize the open-ended comments using thematic analysis.

Phase 3: Adaptation of Prioritized PtDAs to the Specificities of the Stakeholders and Health Care Systems Into Which They Will Be Integrated

Chenel et al [54] propose a framework for cultural adaptation of PtDAs in 4 stages: exploration (ie, identification of content to be adapted), adaptation (ie, incorporation of modifications), pilot testing (ie, validation with knowledge users), and field testing (ie, validation in a real-world context). Informed by this framework, we propose to pilot the cultural adaptation of the selected PtDAs using user-centered design methods and to set up a process that will serve as a proof of concept for the adaptation of the PtDAs to Quebec.

Specifically, with the help of the steering committee and the extended knowledge user group involved in this project, we will translate the selected PtDAs into French and identify the content that needs to be adapted, such as evidence updates and local information on available options. The research team will then incorporate these changes into the new versions of the selected PtDAs. We will engage language editors or graphic design services as needed. We will then validate the new versions with the steering committee members and our extended knowledge user team, using a new collaborative web-based platform for designing printable and interactive PtDAs [55]. This user-tested platform (PADA) was developed by an international team and enables the collaborative design, revision, or adaptation of PtDAs for multiple needs and contexts. PADA also facilitates the collection and integration of knowledge users' feedback [56]. Agendas and minutes of each meeting will be produced to document the process of adapting the PtDAs to the Quebec cultural context. The final step will be to integrate the adapted PtDAs into an interprofessional SDM training program. Our team produced and contributed to the first interprofessional model of an SDM training program [57,58] and developed with knowledge users an interprofessional SDM training program for the use of a PtDA for housing transitions that was well received in home care settings [19-21,59]. We will develop a new generic version of this interprofessional SDM training program that can be used in conjunction with the selected PtDAs or any other PtDA.

Ethical Considerations

This project was approved by the ethics committee of the Centre intégré universitaire de santé et de services sociaux de la Capitale-Nationale (MP-13-2023-2848). All stages of this research project will be carried out in accordance with Canadian procedures for informed consent (Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans) [60]. These procedures include disclosure of benefits, risks, and drawbacks of participation, documentation of consent, patient or surrogate competency, plain language, the voluntary nature of the decision, consent for future use of data, confidentiality of data, and data management practices. All participants will give informed consent before participating in the study.

Results

This study was funded in March 2022 by the CIHR. This protocol was initially submitted before any participants were recruited. The steering committee was recruited in June 2023 and is ready to begin its work. The committee consists of 2 older adults or caregivers; 1 representative of an organization whose mission is to improve services for older adults; 2 health professionals who are also decision makers in 2 health organizations offering home care services in the province of Quebec; 1 representative of the provincial health ministry; 1 geriatric internist with expertise in research with older adults receiving home care services; 1 family physician with expertise in SDM, PtDAs, scalability assessment, and e-Delphi studies; and 1 junior researcher with expertise with SDM and PtDAs. The consensus meeting with the steering committee to select the PtDAs to be prioritized in the e-Delphi study was held in September 2023. Data collection for the e-Delphi study began in October 2023. Results are expected to be published in May 2024.

Discussion

This study will provide information about the scalability of PtDAs relevant to home care, a prioritized list of PtDAs for home care, and up to 3 PtDAs culturally adapted to the specificities of the Quebec health care system and stakeholders in the home care context. The study will provide a proof of concept of the process of adapting the PtDAs and integrating them into an interprofessional SDM training program for the home care sector so they can be scaled successfully in the Quebec health care system.

This study has several notable strengths. First, this project was developed as part of a collaboration with knowledge users that dates back to 2007, and its objectives were developed in response to their stated needs [19,20,28,59,61-63]. We have assembled an experienced interdisciplinary team with a long history of collaboration who possess expertise in developing and adapting PtDAs for the home care sector. In addition, the goals of this project are supported by earlier studies conducted by our team since 2007 showing that older adults have unmet needs for support in making shared informed decisions [5,19,20,28-30,59,61-63] and that the engagement of older adults and their families in health and social care decisions is encouraged by the use of PtDAs and training of clinical teams in SDM [19,20,64,65]. Since most PtDAs are in English and were developed in high-income countries, another strength of this study is that it will contribute to the literature on the cultural adaptation of PtDAs, not only for the Canadian context but for any context where languages and cultures differ within the same region or country.

The main limitation is that the PtDAs we will prioritize have been identified in a systematic review of published literature [42]. It is therefore possible that these PtDAs do not represent all the current or emerging difficult decisions faced by older adults, their families, and stakeholders. During the COVID-19 pandemic, different decisional needs emerged among older adults that affected their care, such as "should I delay my

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surgery?" [66,67]. To address this limitation, if participants express a desire for new PtDAs that do not yet exist, we will use the generic Ottawa decision aid to create one that is culturally adapted to the Quebec context [68]. Finally, operational issues could include recruiting enough people for the e-Delphi study. If we are unsuccessful with our current methodology, we will ask the 32 home care teams who participated in our previous home care randomized trials to suggest additional potential members [19,21].

The ENGAGE project is a response to a declared urgent need by the Quebec government to address gaps in home care [69-72], including the need to support and empower older adults and their families in health-related decision-making. This project will provide relevant and culturally appropriate decision support tools for older adults making difficult decisions and their home care teams. The resulting tools will be ready for scaling across the province of Quebec.

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Data Availability

The data sets generated or analyzed during this study are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Innovation Scalability Self-administered Questionnaire (ISSaQ).
[PDF File (Adobe PDF File), 548 KB - resprot_v12i1e53150_app1.pdf]

Multimedia Appendix 2
Peer-review report by the Canadian Institutes of Health Research (CIHR/IRSC, Canada).
[PDF File (Adobe PDF File), 54 KB - resprot_v12i1e53150_app2.pdf]

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Abbreviations

CIHR: Canadian Institutes of Health Research
ENGAGE: Engagement of Older Adults Receiving Home Care Services and Their Caregivers in Health Decisions in Partnership With Clinical Teams
GRIPP2: Guidance for Reporting Involvement of Patients and the Public

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GUIDED: Guidance for Reporting Intervention Development Studies in Health Research
iKM: integrated knowledge mobilization
IPDAS: International Patient Decision Aid Standards
ISSaQ: Innovation Scalability Self-administered Questionnaire
RAND/UCLA: RAND research organization at the University of California at Los Angeles
REDCap: Research Electronic Data Capture
PtDA: patient decision aid
SDM: shared decision-making

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Proposal

Postpandemic Evaluation of the Eco-Efficiency of Personal Protective Equipment Against COVID-19 in Emergency Departments: Proposal for a Mixed Methods Study

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Abstract

Background: The COVID-19 pandemic has had a profound impact on emergency department (ED) care in Canada and around the world. To prevent transmission of COVID-19, personal protective equipment (PPE) was required for all ED care providers in contact with suspected cases. With mass vaccination and improvements in several infection prevention components, our hypothesis is that the risks of transmission of COVID-19 will be significantly reduced and that current PPE use will have economic and ecological consequences that exceed its anticipated benefits. Evidence is needed to evaluate PPE use so that recommendations can ensure the clinical, economic, and environmental efficiency (ie, eco-efficiency) of its use.

Objective: To support the development of recommendations for the eco-efficient use of PPE, our research objectives are to (1) estimate the clinical effectiveness (reduced transmission, hospitalizations, mortality, and work absenteeism) of PPE against COVID-19 for health care workers; (2) estimate the financial cost of using PPE in the ED for the management of suspected or confirmed COVID-19 patients; and (3) estimate the ecological footprint of PPE use against COVID-19 in the ED.

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Methods: We will conduct a mixed method study to evaluate the eco-efficiency of PPE use in the 5 EDs of the CHU de Québec-Université Laval (Québec, Canada). To achieve our goals, the project will include four phases: systematic review of the literature to assess the clinical effectiveness of PPE (objective 1; phase 1); cost estimation of PPE use in the ED using a time-driven activity-based costing method (objective 2; phase 2); ecological footprint estimation of PPE use using a life cycle assessment approach (objective 3; phase 3); and cost-consequence analysis and focus groups (integration of objectives 1 to 3; phase 4).

Results: The first 3 phases have started. The results of these phases will be available in 2023. Phase 4 will begin in 2023 and results will be available in 2024.

Conclusions: While the benefits of PPE use are likely to diminish as health care workers' immunity increases, it is important to assess its economic and ecological impacts to develop recommendations to guide its eco-efficient use.

Trial Registration: PROSPERO CRD42022302598; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=302598

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KEYWORDS

COVID-19; SARS-CoV-2; personal protective equipment; emergency department; health care workers; systematic review; cost-consequence analysis; time-driven activity-based costing; life cycle assessment; ecological footprint

Introduction

Background

The Impact of the Pandemic on Emergency Departments

The COVID-19 pandemic has had a profound effect on emergency care in Canada and around the world. Emergency departments (EDs) have been reconfigured to meet the new demands of the pandemic [1]. Some of the reconfigurations include increased capacity, physical divisions into identified risk zones, changes in care protocols, redefinition of staff tasks, and development of protective measures against COVID-19 nosocomial transmission [2,3].

Personal Protective Equipment

In order to prevent transmission at the peak of the pandemic, personal protective equipment (PPE) was required for all ED care providers (eg, physicians, nurses, and nursing assistants) in contact with patients with proven or suspected COVID-19. PPE encompasses all clothing and other equipment used to protect health care workers from injury or infection [4], and is considered the last step in the hierarchy of controls in infection prevention [5,6]. With respect to the COVID-19 pandemic, the term PPE refers primarily to two options (see Multimedia Appendices 1 and 2) [7]: (1) standard PPE, which includes procedural masks, isolation gowns, nonsterile gloves, and ocular protection; and (2) enhanced PPE which includes respirators (eg, N95), water-repellent gowns, long-cuff nitrile procedure gloves, and face shields. Since the beginning of the pandemic, the understanding of the COVID-19 modes of transmission and the most effective equipment to protect against it have greatly evolved. In many jurisdictions, enhanced PPE was initially reserved for aerosol-generating procedures (eg, endotracheal intubation), that is, aerosolized particles of <5 µm that can remain suspended in the air for extended periods of time and circulate over long distances on air currents [8]. In Canada, in 2021, the use of enhanced PPE with a respirator has gradually become the norm when caring for patients with confirmed or suspected COVID-19 cases, even in the absence of aerosol-generating procedures [9-11].

Conflicting Rules for PPE Use

The rules for PPE use in health care settings have fluctuated greatly and have been a source of uncertainty [8,12]. Often developed as a compromise between incomplete scientific evidence [7,8,13], uncertain PPE supplies [14-16], and staff concerns [12,17], these rules were sometimes so confusing for health care workers that their trust towards the infection control teams and managers was diminished [17]. Although the benefits of PPE for protecting health care workers against SARS-CoV-2 have been demonstrated [7,13,18], the level of evidence is relatively low and its use is more or less influenced by subjective preferences and personal values [19].

New Context, New Rules?

Although the achievement of a certain level of immunity in the population provides significant protection against severe or chronic symptoms of COVID-19 [20], important questions remain; what types of PPE will be needed to protect health care workers as SARS-CoV-2 becomes endemic and circulation in the community continues unabated? Somewhat less discussed since the beginning of the pandemic, the societal consequences of PPE use must also be considered. What will be the opportunity cost for public institutions to pursue the expanded use of PPE [21-23]? What is the ecological cost of continuing on this path [24-27]? More than ever, evidence is needed to evaluate PPE use and to provide recommendations that ensure the clinical, economical, and ecological efficiency of its use.

Hypothesis and Research Goal

With mass vaccination and improvements in several infection prevention components included in the hierarchy of controls, our hypothesis is that the risk of transmission of COVID-19 will be significantly reduced and that wearing fully enhanced PPE for every suspected COVID-19 patient will have economic and ecological consequences that exceed the anticipated benefits. To support the development of optimal rules for PPE use, our research objectives for this project are to (1) determine the clinical effectiveness (reduced transmission, hospitalization, mortality, and work absenteeism) of PPE to protect immune and nonimmune health care workers against COVID-19; (2)

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estimate the financial cost of using PPE in the ED for the management of patients with suspected or confirmed COVID-19; and (3) estimate the ecological footprint of PPE use against COVID-19 in the ED.

Theoretical Framework

Our objectives address a transdisciplinary subject that goes beyond the boundaries of health research and consequently requires a conceptual framework that aggregates complementary theoretical approaches. We therefore propose an extended application of the value-based health care framework, which consists of orienting care practices, decisions, and policies to obtain the best health outcomes at the lowest cost. This model, developed by Porter [28-30] in the 2000s, is now widely used by various organizations [31-35] to improve health services. Optimizing the value of care can, among other things, be achieved by reducing its costs, which can be minimized by eliminating the inappropriate use of resources. The notion of value thus overlaps with the notion of eco-efficiency [36]. The Organization for Economic Cooperation and Development defines it as "a management philosophy that encourages business to seek environmental improvements that are accompanied by economic benefits" [37,38]. Eco-efficiency is closely tied to the appropriate use of resources extracted from the environment and the emissions generated throughout the life cycle in order to increase the economic value of what is ultimately produced. By revisiting these 2 concepts for our research framework, we will define eco-efficiency in health care as the maximization of the clinical benefits of a health care activity while minimizing its costs and its ecological footprint.

Methods

Setting

The project will evaluate the eco-efficiency of PPE use in the 5 EDs of the CHU de Québec-Université Laval (hereafter the CHU) in Québec City (Canada). The CHU is the largest academic hospital in Québec and 1 of the 3 largest in Canada. Its EDs record nearly 240,000 visits annually. They form the same clinical department, use the same protocols, and offer similar care paths. In terms of PPE, the donning and doffing protocols are identical. All CHU wards use disposable PPE. At the beginning of the pandemic, all CHU EDs cleaned and reused protection goggles and face shields. Similarly, one ED site used reusable gowns but has since switched to fully disposable PPE (Multimedia Appendix 3). The CHU's EDs are an ideal setting to conduct the proposed study because (1) several thousand units of PPE are used daily; (2) each of the 5 EDs has cold (non–COVID-19), warm (suspected COVID-19 cases), and hot (confirmed COVID-19 cases) areas; (3) there is a large diversity of patients, from children to elderly, and both medical and surgical cases; and (4) as opposed to high-risk units such as intensive care and COVID-19 units, where infected patients are grouped together and where the wearing of PPE appears more indicated, the majority of patients evaluated in the ED do not have COVID-19, even when the clinical picture is compatible. It is therefore in the ED that an evaluation of the eco-efficiency of PPE use can have the greatest impact on the recommendations for use in a low-risk clientele. Furthermore, since donning and doffing protocols do not differ significantly from one department to another and are very similar in all institutions in Quebec and across Canada, we will be able to infer some of our results from the entire hospital reality in Canada.

Study Design

We propose a mixed methods, multiphase study, merging approaches from epidemiology, biostatistics, industrial engineering, accounting, health economics, mathematics, psychology, and environmental engineering. To achieve our goals, the project will include four phases: systematic review of the literature to assess the clinical benefits of PPE (objective 1; phase 1); cost estimation of PPE use in the ED using a time-driven activity-based costing method (objective 2; phase 2); ecological footprint estimation of wearing PPE during the pandemic using a life cycle assessment approach (objective 3; phase 3); and cost-consequence analysis and focus groups (integration of objectives 1 to 3; phase 4).

For each of these phases, we will propose analyses distinguishing standard and enhanced PPE.

Phase 1: Systematic Review of the Literature (Objective 1)

Protocol and Registration

The protocol for this review is registered in the PROSPERO database of systematic reviews (CRD42022302598) and we will follow recommendations of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines for its reporting [39].

Research Question

What effect does wearing PPE have on health care workers' risk of becoming infected with SARS-CoV-2, being secondarily absent from work, admitted to the hospital or to the intensive care unit (ICU), or die? Table 1 shows the PICOS framework for the systematic review.

Table 1. PICOS (population, intervention, comparison, outcomes, and study design) framework for the systematic review.

Population	Health care workers
Intervention	Standard or enhanced personal protective equipment
Comparison	No or incomplete personal protective equipment
Outcomes	SARS-CoV-2 (COVID-19) infection, hospital admission, intensive care unit admission, mortality, and work absenteeism
Study design	Experimental or observational studies

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Search Strategy

We will search for studies published since December 2019 (identification of SARS-CoV-2 in Wuhan) comparing health care workers' use of disposable or reusable, standard or enhanced PPE to no protection used or a different combination of PPE components. We will use Medline (Ovid), Embase, Cochrane Library, CINAHL, Epistemonikos, ClinicalTrials.gov, MedRxiv, and Web of Science search engines, without language restrictions. The search strategy was developed with the assistance of a qualified librarian and is available in the appendices (Multimedia Appendix 3). This strategy will be executed three times: (1) at the start of the systematic review (May 2022); (2) at the end of the prepublication data extraction (June 2023); and (3) before phase 4 (January 2024) to update the meta-analysis to adequately inform our focus groups.

Article Selection and Eligibility Criteria

Using the Covidence systematic review software (Veritas Health Innovation), 2 independent reviewers will select abstracts, read the articles, and determine their eligibility. All experimental or observational studies (cohort, case-control, or cross-sectional studies) comparing the use of PPE with the absence of PPE with regard to health care workers' risk of SARS-CoV-2 infection, hospitalization (ward or ICU), death, or absence from work, will be included in the review. Studies evaluating the effect of PPE when worn by nonhealth workers, narrative reviews, editorials, modeling studies without original clinical data, and practice guidelines will be excluded. Systematic reviews will also be excluded but will be consulted to identify original articles potentially missed by our search strategy. Bibliographies of selected articles will be reviewed in the same manner.

Data Extraction and Quality Assessment of Selected Studies

In total, 2 independent reviewers will collect data from the selected articles using a previously tested extraction grid. From each article, they will extract, when available, the following variables: authors; title; date and scientific journal of publication; country where the research was conducted; study design; population studied; sample size; age; gender; sex; vaccination or immune status; and comorbidities of the participants, study outcomes, and results. The quality of the selected studies will be assessed by 2 reviewers using the Cochrane Risk of Bias Tool for randomized studies [40] and ROBINS-I for observational studies [41].

Disagreements Among Reviewers

Disagreement between reviewers will be resolved through discussion and consensus. If a disagreement persists, a third reviewer will mediate to reach a final consensus.

Analysis and Synthesis of Results

The results will be presented in tabular and narrative form and will compare the benefits of standard or enhanced PPE to the absence of PPE use. Based on previous systematic reviews, we know that a random effects model meta-analysis is feasible and will then be conducted. According to the original data available, we will calculate estimates of relative risks (RR) or odds ratios (OR) on the risk of transmission of SARS-CoV-2 and of the other outcomes evaluated. The necessary numbers of PPE that must be used (number needed to treat) to prevent one SARS-CoV-2 transmission, admission, or death among staff will be calculated secondarily. Randomized studies will be analyzed separately from observational studies, as recommended by the Cochrane Handbook [42,43]. If studies are in sufficient numbers, we will conduct subgroup analyses by analyzing separately (1) the studies conducted in EDs; and (2) the studies conducted after the start of vaccination in the country where the research took place. Heterogeneity between studies will be assessed using the I^2, a statistic that estimates the percentage of variation in results between studies that are not explained by chance. Thus, an I^2 value between 0 and 40% will be considered to represent a low level of heterogeneity, while values between 30% and 60% represent a moderate level, between 50% and 90% a substantial level, and between 75% and 100% a considerable level [44]. The causes of heterogeneity will be examined by stratifying our outcome measures by (1) the country where the studies were conducted and (2) the clinical departments or units from which the data originated (eg, COVID-19 unit and ICU). We will also conduct a sensitivity analysis excluding studies with a high risk of bias. Finally, the quality of evidence for each outcome (high, moderate, low, and very low) will be assessed using the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach [45].

Phase 2: Cost Estimation of PPE Use (Objective 2)

Concept

The cost of PPE use goes beyond the cost of purchasing its components. Wearing PPE means donning and doffing by care providers who, during this time, cannot engage in direct care, which is a cost to the health care system. Using PPE also incurs costs for material disposal (eg, garbage collection) and overhead (eg, supply management). Therefore, we will estimate the mean cost of wearing PPE in the CHU for contact with a possible case of COVID-19 using a time-driven activity-based costing method [46,47]. This method accounts for all expenditures incurred during direct patient care (eg, staff salaries and medical costs), consumables (eg, masks), and management costs (eg, disinfection service). It uses the duration of care processes to estimate the associated cost; the longer a process (eg, donning PPE) takes to be performed, the higher the cost. It provides a simpler, more accurate, and more reliable way of estimating the cost of health services than other methods frequently used in research or management, such as diagnosis-related group methods (DRG), the level of relative intensity of resource use (NIRRU) or the conventional activity-based costing method (ABC) [48-50]. Time-driven activity-based costing was previously used in many health care settings [48,51-56] and our team successfully adapted it for use in the ED [57-59]. For this project, we will apply this costing method to the care pathway of patients suspected with COVID-19 in the ED. We will analyze the processes involved in PPE use and disposal. The disposal component will include both trajectories of completely disposable PPE versus reusable gowns, as one of our sites used reusable gowns at the beginning of the pandemic. Cleaning of the reusable gowns was done by a subcontractor (Partagec), as

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such, the cleaning cost will be estimated based on the weight of the gowns used as stipulated in the contract with Partagec.

Method Steps

Overview

Time-driven activity-based costing essentially requires two parameters: (1) the cost per minute for each human or material resource involved in care, and (2) the duration in minutes of each care process. To derive these, we will use data from the fiscal year beginning April 1, 2020, through March 31, 2021. We will estimate the average costs of standard and enhanced PPE using the following steps.

Process Maps

We will first map the ED care pathway of suspected COVID-19 cases. We will also map all specific processes performed in the wearing, disposal, recycling, and disinfection of PPE. This will primarily include (1) donning, (2) doffing, (3) disposal, and (4) collection and disinfection or cleaning of reusable components.

Time Measurements

We will estimate the mean time required to complete each mapped process through prospective field measurements at the ED using a time-motion study software (UmtPlus Max, Laubrass).

Resource Costs per Minute

We will calculate the cost per minute (CAD $ per minute; with an average currency exchange rate of CAD $1=US $0.8) of each human or material resource identified in the process maps by dividing its total annual cost for the year 2020-21 by the number of minutes in the same year that the resource was available for care or service. The following is an example from our previous work.



If applicable, a similar calculation will be performed for equipment by considering depreciation and maintenance expenses in the numerator and the number of minutes in service in 2020-21 in the denominator. The cost per minute of emergency physicians will be estimated by the same formula, but the total annual medical expenditures will be estimated using the average annual earnings of an emergency physician as obtained from the regulatory medical associations.

Consumable Costs

We will calculate from the CHU accounting records the average unit cost (CAD $/unit) of each component (gown, gloves, masks, and ocular protection) of PPE purchased by CHU in the financial year 2020-2021 and then break down the specific costs by supplier. The reusable equipment purchase cost will be amortized over the anticipated number of uses.

Overhead Expenses per Minute

Following a formula similar to item 3, we will calculate the cost per minute (CAD $ per minute) of overhead incurred by the CHU for PPE use (eg, rental or transportation of waste containers), by dividing the total overhead related to PPE use in the ED for the year 2020-21 by the number of minutes available for the care of the staff using PPE as part of their work.

Mean Process Costs

We will estimate the mean process costs for PPE by summing the costs of resources, consumables, and overhead according to the calculation presented in the following example based on previous work data and preliminary estimates. Similar calculations will be performed for all PPE-related processes (eg, doffing).



Further details on the method and its practical application can be found elsewhere [60,61].

Analyses

The preceding steps will estimate for each category of ED care providers (eg, nurses and physicians) the mean cost incurred during the pandemic for one standard and one enhanced PPE use, which includes donning, doffing, disposing, and disinfection or cleaning. A set of subanalyses will then estimate (1) the minimum and maximum costs of PPE use based on the minimum and maximum supplier unit costs of the PPE components purchased by the CHU in 2020-2021; (2) the weighted mean cost of PPE use based on the weight of participation of each category of providers in the care pathway, estimated using the mapping of a typical care pathway for COVID-19 in the ED (Multimedia Appendix 4); (3) The total cost of PPE use in the CHU EDs based on the number of suspected COVID-19 cases that consulted since the start of the pandemic, the weighted mean cost of using PPE, and the number of contacts with PPE per episode of care estimated with the mapping; and (4) mean costs based on component costs in the year prior to the pandemic (financial year 2019-2020) to estimate the effect of the shortage on equipment selling prices.

Phase 3: Ecological Footprint Estimation of PPE Use (Objective 3)

Concept

The ecological footprint of standard and enhanced PPE will be estimated through a life cycle assessment that will measure the pollutant load of all material and energy resources used (inputs) and residual materials generated (outputs) by their use (Multimedia Appendix 5 for a typical life cycle diagram). The analysis will assess the environmental impact of the consumables (eg, gloves) and processes (eg, disinfection of face shields) required for PPE use in CHU EDs from cradle to grave, that is, from their design and manufacturing to their final disposal. The life cycle assessment methodology, which is well established in the industrial field, has previously been used in the health field as well [62-64].

Methodology Phases

Overview

The life cycle assessment will follow the ISO-14040/ISO-14044 standards governed by the International Organization for Standardization [65-67]. These international standards are developed through consensus among experts from industry,

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consumer associations, governments, nongovernmental organizations, and universities. The standards that will be used for this project provide a framework for an environmental management system, specifically the realization of a life cycle assessment. We will take the following steps.

Definition of the Objectives and Scope of the Study

The analysis will aim to assess the ecological footprint of one PPE used by a care provider in the ED for contact with a potential or confirmed COVID-19 case (functional unit). We will compare the ecological footprints of standard and enhanced PPE assuming an uneven level of protection that will be measured with the systematic review from the previous phase. Since supplies fluctuated over the course of the pandemic resulting in a very wide variety of equipment at the CHU, we will limit our analyses to those PPE components that were (1) the most frequently used, (2) the most and least costly, and (3) those whose supply contracts predict their predominant use for the foreseeable future.

Emissions and Extractions Inventory

Using the previously developed mappings, we will break down the donning and doffing process as well as the upstream (eg, production) and downstream (eg, disposal) processes to identify the use of consumable or reusable equipment and materials, and their disposition to waste or disinfection units. An inventory of activities and flow of materials, energy, and services will be conducted using data obtained from the CHU and PPE suppliers (eg, raw materials for PPE components and energy consumed at the production plant) and will be scaled to the functional unit level, that is, the use of a single PPE. This inventory will quantify the pollutants emitted and the resources extracted over the entire life cycle using a life cycle database (ecoinvent database, version 3.9.1; ecoinvent) adapted to Québec and data available in the life-cycle assessment literature.

Environmental Impact Analysis

Using the open access software OpenLCA, (version 1.11.0; GreenDelta) each previously collected inventory data on extractions and emissions from PPE use will be translated into potential impacts on environmental issues such as (1) climate change (in kg of CO_2 equivalent emitted), (2) human health (in disability-adjusted life years [DALYs]) [68], (3) resource use (in megajoules of energy—MJ), and (4) ecosystem quality (in PDF·m^2·year, the fraction of species potentially lost from a given area in a year). Conversion of PPE inventory data into impact units for each damage category will be done by the validated IMPACTWorld+ assessment method [67,69]. This method allows for a regionalized analysis by providing continent-specific impact data. An impact measure reflects a sequence of intermediate effects of a product (eg, PPE) production, use, and disposal that, by polluting water, air, soil, or food for example, ultimately affect the environment or human health.

Results Interpretation

The impact results will be interpreted in relation to the functional unit, that is, the use of a single PPE for contact with a suspected COVID-19 case by a care provider. The critical points, that is, the elements of PPE use that account for the greatest proportion of its impact, will be identified. Sensitivity analyses will be conducted to assess the possibility of bias due to incomplete or inaccurate inventory data. Where calculations are performed using proxies from inventory databases rather than original supplier data, we will reanalyze these uncertain variables by applying values for worst- and best-case scenarios.

Phase 4: Cost-Consequence Analysis and Focus Groups (Integration of Objectives 1 to 3)

Cost-Consequence Analysis

The results of the analyses of the previous 3 phases on benefits (OR, RR, and number needed to treat), costs, and ecological footprint will be scaled to a single PPE use for contact with a suspected or confirmed COVID-19 case by a care provider in the ED. They will also be secondarily extrapolated for the full duration of the pandemic from the number of suspected COVID-19 cases assessed in the CHU EDs during this period. Using data from the Institut national de santé publique du Québec on the hospitalization rate of COVID-19 cases in Quebec [70] and the cost of an average hospitalization at the CHU obtained by the Cost per Care Pathway and Service (CPSS) system [71], we will estimate the potentially avoided costs by preventing hospitalizations through PPE. We will do the same by estimating the avoided costs related to staff absenteeism using a human capital approach [72] on the basis of the care providers' salaries identified in phase 2. A cost-consequence analysis will then be carried out by presenting, in parallel, the benefits, costs, and environmental consequences with their 95% CIs in a simple and meaningful disaggregated format. A cost-consequence analysis is a type of economic evaluation that assesses a wide range of costs and consequences associated with an intervention. It can include all types of positive or negative effects of that intervention, including those that are health-related (eg, risk of transmission) and those that are not directly health-related (eg, environmental impact). By presenting the results separately in a nonaggregated manner, it allows stakeholders to determine for themselves the weight and value assigned to the costs and consequences presented for informed decision-making. We believe that cost-consequence analysis is most appropriate for our project because (1) the values and preferences of the stakeholders involved in PPE use are multiple and often divergent, making aggregative ratios or calculations inappropriate (eg the incremental cost-effectiveness ratio [ICER] assesses only one outcome or one benefit) and (2) the economic value of the benefits and consequences of PPE is not clearly elucidated, making cost-benefit analysis (ie, an analysis where all the consequences of intervention are converted into monetary value) problematic.

Focus Groups

The cost-consequence analysis will be presented and discussed in 4 focus groups [73] of 8 participants each [74], via 2 one-hour videoconferences for each group led by a facilitator and a note taker. A third videoconference will be held if not all topics have been covered in the first two. Individual interviews will be offered to participants who prefer this approach or who are unable to attend group meetings. The first group will bring together health care managers responsible for budgets; the second will bring together experts responsible for developing

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recommendations on PPE use in hospitals; the third will gather the perceptions of health care providers, nursing assistants, respiratory therapists, and physicians; and the last group will survey the perspective of patients and citizens. Additional groups of participants will be recruited as needed until the data are saturated. A purposeful sampling strategy will be used to ensure representation of various levels of authority (departmental, regional, local), professions (eg, nurses), regions (urban, semiurban, and rural), and individual characteristics (gender, ethnicity, and age) [75]. Participants will be presented with all the results in a simple, adapted format, after consultation with experts in content (eg, economists and environmental engineers) and information formatting (eg, information designers and knowledge transfer experts). The discussions in each group will be semistructured. The primary objectives of the semistructured discussions will be to (1) analyze the perspective of each group on the study results and (2) identify the cost-consequence analysis results (benefits vs costs vs environmental impact) that participants believe should be prioritized for future recommendations regarding PPE use in the ED. The meetings will be recorded and fully transcribed (verbatim). In total, 2 independent reviewers will code the responses on NVivo 12 (Lumivero) to structure the data and bring out the main themes. Their disagreements will be reconciled by discussion or, if necessary, by the intervention of a third researcher. The analysis will take an inductive approach to capture the different perspectives on PPE use in the ED from the data collected and then develop a theoretical framework.

Ethical Considerations

This trial was approved by the CHU de Québec-Université Laval Research Ethics Board (#2022-6048).

Dissemination Plan

Our dissemination plan has an integrated approach by including co-researchers and knowledge users in strategic positions in our team, including a member of the Québec Nosocomial Infection Committee responsible for defining the rules for the use of PPE (YL) and at the CHU, the infection prevention and control program managers (AD and VD), the assistant director (AG) and the consultant (SC) responsible for sustainable development, the nursing (ST) and medical (IG) managers of the EDs, the clinical and organizational performance director (PL), and the patient experience and partnership expertise office manager (LB). In total, 3 clinicians (IG, EEB, and a collaborator Éric Notebaert) and 2 patient partners (EH and a collaborator Jean-Pierre Gendreau) also participated in our process. All these people have contributed to the development of the concept, will participate in its implementation, will be informed of the results, will interpret them from their perspectives, and will be able to quickly integrate them into their practices. Our dissemination strategy will also include (1) articles in general information newspapers to publicize our initiative; (2) a website to present our team, our results, and our future projects; (3) presentations for the general public in citizen forums or congresses; (4) at least 6 presentations in national (Association des médecins d'urgence du Québec, Association des médecins microbiologistes infectiologues du Québec, Canadian Association of Emergency Physicians, and Canadian Association for Health Services and Policy Research) and international (Society for Academic Emergency Medicine and Infectious Diseases Society of America) scientific conferences; (5) at least 4 publications in recognized peer-reviewed scientific journals; and (6) presentations to our partner organizations, including primarily the Québec Nosocomial Infection Committee, which we plan to meet at least 4 times during the course of the project to share our preliminary results and progress.

Results

Study Preparation

We have assembled a very strong research team composed of patients, clinicians, administrators, and researchers. In addition, 2 patient partners met with us regularly and provided helpful comments to make our research plan patient-centered. From previous studies, our team was able to perform life cycle assessment [76-80] and cost-effectiveness [60,61,81,82] measures. This previous work will help with the proposed study.

Phase 1

Our search strategy for the systematic review, launched on May 10, 2022, and updated on June 7, 2023, has generated a list of 26,591 articles, of which 10,209 duplicates were removed. As of July 9, 2023, a total of 15,539 studies have been screened. Of these, 192 abstracts were retained for full-text review and 74 studies were included.

Phase 2

Our team has made a first draft of the process map of the COVID-19 care pathway in the ED (Multimedia Appendix 6).

Process time measurements were performed in one of the CHU EDs for the donning and doffing of a PPE. Table 2 shows the mean time estimates for the different processes of PPE use. Our team is currently completing financial data collection on care providers' salaries, labor hours, PPE component costs, and overhead. Of these data, the mean total cost of the components for a single use of standard and enhanced PPE was estimated to be CAD $13.30 and CAD $21.50 (US $9.79 and US $15.83), respectively.

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Table 2. Mean donning and doffing time (minutes) for PPE[a] based on field measurements.

Protective equipment	Donning		Doffing	
	n (%)	Mean (SD)	n (%)	Mean (SD)
Standard PPE[a]	63 (60)	1.28 (0.71)	65 (79)	1.10 (0.85)
Enhanced PPE	42 (40)	1.18 (0.43)	17 (21)	0.35 (0.37)
Any PPE	105 (100)	1.19 (0.45)	82 (100)	0.95 (0.84)

[a]PPE: personal protective equipment.

Phase 3

To date, we have begun an inventory of the materials used for each component using attenuated total reflectance-infrared spectroscopy. Additional analyses are performed to further validate the composition of the PPE components in terms of raw materials and the weight of each item. Once these data are obtained, the conversion of inventory into impact categories will be performed and analyzed.

Protocol Endorsement

Our protocol has been endorsed by organizations dedicated to achieving sustainable and eco-efficient health care (Association québécoises des médecins pour l'environnement, CHU de Québec-Université Laval, INSPQ, Ministère de la santé et des services sociaux du Québec, PULSAR). We also have support for our research initiative from an organization in sustainable development (Nature Québec), with life cycle assessment expertise (the International Reference Center for Life Cycle of Products, Processes and Services—CIRAIG) and with national responsibility for the use of PPE (Québec Nosocomial Infection Committee). This broad support demonstrates the importance of addressing the eco-efficiency of health care, particularly the issue of PPE use.

Research Agenda

We propose a 3-year research plan. After receiving funding on October 1, 2021, we have begun the administrative steps, mainly obtaining authorization from the ethics committee and intrainstitutional agreements for access to medico-administrative data. Phase 1 (systematic review) will run from May 2022 to September 2023 (16,401 abstracts screened) and will end with the submission of a paper for publication in December 2023. Phase 2 (cost estimation) and 3 (life cycle assessment) have begun in June 2022, and are expected to be completed in December 2023. Those 2 phases are performed concomitantly as they overlap in process mapping and medical-administrative data collection. Phase 4 will be conducted from January 2024 (preparation) to August 2024 end of focus group phase). Final publications and knowledge transfer activities will be completed in the last 6 months of 2024.

Discussion

Overview

PPE is the last step in the hierarchy of controls in infection prevention, but it has become an essential component of direct care for ED patients potentially infected with COVID-19. As new infection control measures have emerged, primarily from mass vaccination, some advocate for a more eco-efficient use of PPE, that is, one that provides the best possible protection with the least economic and ecological impact. The evidence generated by this study will support the infection control and prevention authorities in Canada and abroad by providing informed guidance for eco-efficient use of PPE in low-risk environments. They will also help us understand the perspective of different stakeholders on this sensitive and fundamental issue where material shortages, the risks to health care staff, the sustainability of the health system, and the protection of the environment are all intertwined.

Beyond this project on PPE, our multidisciplinary team of researchers from different backgrounds aims to initiate a profound change in managerial culture focused on sustainable health within our institutions, particularly in the ED. We propose an innovative conceptual framework, eco-efficiency in health, through which we wish to contribute to the best possible health outcomes in emergency care at the lowest cost and with the least environmental impact. Canada's health care system is among the least eco-efficient in the world, and its environmental impact paradoxically affects Canadians' health [83,84]. A paradigm shift is needed. Unfortunately, clinicians and managers have few tools to understand and act on their services' ecological footprint. Our work incorporating life cycle assessment will help them to (1) provide the best care with the least environmental impact, (2) set realistic targets for reducing their ecological footprint, and (3) optimize interventions to achieve this. Our proposed project on PPE is in fact only the first in a series of analyses of different emergency care activities with the ultimate goal of proposing a model for eco-efficient emergency services [85].

Challenges and Mitigation Strategies

Our project poses a few notable challenges. First, the systematic review will aim to estimate the benefits of using PPE as the risk of SARS-CoV-2 transmission decreases significantly as vaccination is accelerated. The relevance of the results of this phase will depend on the publication of articles that have evaluated the efficacy of PPE in a setting where the population and health care workers have been vaccinated. We have scheduled an update of our systematic review for September 2023, just before the start of our Phase 4 focus groups. Considering the wealth of scientific output on COVID-19 over the past years, we believe it unlikely that by this update, there will be no studies that have assessed the benefits of PPE since the beginning of vaccination. If not, we will use the results of our systematic review for nonimmune personnel and extrapolate the number needed to treat based on the observed rates of

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vaccine protection in the population. Second, our study will be conducted in only one institution, the CHU. However, since supply purchases in Québec are carried out from the same supplier for a group of establishments (eg, eastern Québec), both the costs and the ecological footprint of PPE use in the ED should reflect the reality of all Québec establishments. Similarly, since most PPE suppliers export their products around the world, the results of our analyses will be useful for other health authorities outside Québec. Third, with respect to the life cycle assessment, suppliers of the PPE components studied may not disclose certain information related to the composition of their products and their factory production. In the absence of such data, we will make estimates and use equivalencies from the literature and available life cycle assessment inventory databases. We will disclose the details of these approximations and the uncertainty of the results to transparently inform the resulting organizational decisions.

Conclusions

The World Health Organization recently declared the end of the COVID-19 global health emergency, but acute and emergency care may maintain some habits and behaviors developed and implemented during this health crisis. The intensive use of PPE by care providers to protect patients and themselves from COVID-19 may be one of the pandemic care activities that will require further consideration. While the benefits of PPE use are likely to diminish as health care workers' immunity increases, it is important to assess its economic and ecological consequences so that new parameters and recommendations can be developed to guide its use and ensure eco-efficiency now and in the future.

Acknowledgments

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Data Availability

The data sets generated or analyzed during this study are available from the corresponding author upon reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Standard personal protective equipment.
[PDF File (Adobe PDF File), 280 KB - resprot_v12i1e50682_app1.pdf]

Multimedia Appendix 2
Enhanced personal protective equipment.
[PDF File (Adobe PDF File), 283 KB - resprot_v12i1e50682_app2.pdf]

Multimedia Appendix 3
Literature search strategy.
[PDF File (Adobe PDF File), 112 KB - resprot_v12i1e50682_app3.pdf]

Multimedia Appendix 4
Mapping of care processes and use of personal protective equipment in the emergency department for patients with COVID-19 (influenza-like illness).
[PDF File (Adobe PDF File), 497 KB - resprot_v12i1e50682_app4.pdf]

Multimedia Appendix 5
Life cycle figure.
[PNG File , 160 KB - resprot_v12i1e50682_app5.png]

Multimedia Appendix 6
Canadian Institutes of Health Research grant evaluation.
[PDF File (Adobe PDF File), 117 KB - resprot_v12i1e50682_app6.pdf]

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Abbreviations

ABC: activity-based costing
CIRAIG: International Reference Center for Life Cycle of Products, Processes and Services

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CPSS: Cost per Care Pathway and Service
DALY: disability-adjusted life year
DRG: diagnosis-related group
ED: emergency department
GRADE: Grading of Recommendations Assessment, Development, and Evaluation
ICER: incremental cost-effectiveness ratio
ICU: intensive care unit
OR: odds ratios
PICOS: population, intervention, comparison, outcomes, and study design
PPE: personal protective equipment
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analysis
RR: relative risks

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Protocol

Engaging Black or African American and Hispanic or Latino Men Who Have Sex With Men for HIV Testing and Prevention Services Through Technology: Protocol for the iSTAMP Comparative Effectiveness Trial

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Abstract

Background: Gay, bisexual, and other men who have sex with men (MSM), particularly Black or African American MSM (BMSM) and Hispanic or Latino MSM (HLMSM), continue to be disproportionately affected by the HIV epidemic in the United States. Previous HIV self-testing programs have yielded high testing rates, although these studies predominantly enrolled White, non-Hispanic MSM. Mobile health tools can support HIV prevention, testing, and treatment. This protocol details an implementation study of mailing free HIV self-tests (HIVSTs) nested within a randomized controlled trial designed to assess the benefit of a mobile phone app for increasing the uptake of HIV prevention and other social services.

Objective: This study was a comparative effectiveness trial of innovative recruitment and testing promotion strategies intended to effectively reach cisgender BMSM and HLMSM. We evaluated the use of a mobile app for increasing access to care.

Methods: Study development began with individual and group consultations that elicited feedback from 3 core groups: HIV care practitioners and researchers, HIV service organization leaders from study states, and BMSM and HLMSM living in the study states. Upon completion of the formative qualitative work, participants from 11 states, based on the observed areas of highest rate of new HIV diagnoses among Black and Hispanic MSM, were recruited through social networking websites and smartphone apps. After eligibility was verified, participants consented and were randomized to the intervention arm (access to the Know@Home mobile app) or the control arm (referral to web resources). We provided all participants with HIVSTs. The evaluation of the efficacy of a mobile phone app to support linkage to posttest prevention services that included sexually transmitted infection testing, pre-exposure prophylaxis initiation, antiretroviral treatment, and acquisition of condoms and compatible lubricants has been planned. Data on these outcomes were obtained from several sources, including HIVST-reporting surveys, the 4-month follow-up survey, laboratory analyses of dried blood spot cards returned by the participant, and data obtained from the state health department surveillance systems. Where possible, relevant subgroup analyses were performed.

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Results: During the formative development phase, 9 consultations were conducted: 6 in-depth individual discussions and 3 group consultations. From February 2020 through February 2021, we enrolled 2093 MSM in the randomized controlled trial from 11 states, 1149 BMSM and 944 HLMSM.

Conclusions: This study was designed and implemented to evaluate the effectiveness of recruitment strategies to reach BMSM and HMSM and of a mobile app with regard to linkage to HIV prevention or treatment services. Data were also obtained to allow for the analyses of cost and cost-effectiveness related to study enrollment, HIV testing uptake, identification of previously undiagnosed HIV, sexually transmitted infection testing and treatment, and linkage to HIV prevention or treatment services.

Trial Registration: ClinicalTrials.gov (NCT04219878); https://clinicaltrials.gov/ct2/show/NCT04219878

International Registered Report Identifier (IRRID): DERR1-10.2196/43414

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KEYWORDS

HIV self-testing; HIV self-test; prevention; men who have sex with men; internet; mobile phone

Introduction

HIV testing is the cornerstone of HIV prevention and care and is the starting point for parallel HIV prevention and care continua [1-3]. The Centers for Disease Control and Prevention (CDC) recommends that gay, bisexual, and other men who have sex with men (MSM) test for HIV at least annually and more frequently (eg, at 3- to 6-month intervals) depending on their individual risk factors [4]. However, only about half of the MSM surveyed on the internet and who are not known to be living with HIV meet the minimal recommendation for annual screening [5]. Diagnosing HIV as early as possible, initiating treatment rapidly and effectively to achieve viral suppression, and preventing new HIV infections are the key pillars of the United States Department of Health and Human Services initiative, “Ending the HIV Epidemic in the US” [6]. Thus, interventions are needed for MSM in the United States to increase HIV testing frequency and, for those who are found to be living with HIV, to be promptly linked to HIV care.

Considering the HIV prevention cascade, MSM who obtain a negative HIV test result also have indications for important follow-up prevention services, including sexually transmitted infection (STI) testing [7], provision of prevention commodities (eg, condoms and condom-compatible lubricants), and assessment for pre-exposure prophylaxis (PrEP) initiation [8]. Comprehensive prevention for men who obtain a negative HIV test result should include connecting them with appropriate service providers in the community, identifying sources of commodities if they cannot afford to buy them, and helping them receive other services. The Evaluation of Rapid HIV Self-testing Among MSM Project [9] demonstrated that providing internet-recruited MSM with HIV self-tests (HIVSTs), which could be replenished, resulted in more HIV testing and diagnoses during the study period compared with those who did not receive the HIVSTs. Although there was no statistically significant difference in linkage to care between the 2 arms, men in the HIV self-testing arm reported a lower linkage-to-care rate than those in the control arm. Furthermore, there were no reported differences in the number of sex partners or the number of anal sex partners without condoms among those who received HIVSTs [9]. However, this study had some limitations with external generalizability because Black or African American, non-Hispanic MSM (BMSM) were underenrolled (10%) relative to their representation in the US HIV epidemic (31%), as was the case for Hispanic or Latino MSM (HLMSM; 18% enrolled) relative to the 25% of HLMSM represented in the US HIV epidemic [9-11]. BMSM and HLMSM continue to be disproportionately affected by HIV compared with other groups and, in 2019, accounted for 38% and 35%, respectively, of new HIV diagnoses among MSM in the United States [12]. Research was needed to tailor HIVST delivery to these populations.

To address this gap, we developed a protocol for the Implementation of the Rapid HIV Self-testing Among MSM Project (iSTAMP), with the goal of demonstrating the costs and best practices for reaching BMSM and HLMSM on the internet and providing all participants with free HIVSTs. To ensure prompt linkage to additional HIV testing and care for those with a preliminary positive result and promote linkage to appropriate posttest sexual health care, we provided the intervention arm with a mobile phone app to facilitate linkage to services. We developed methods to enroll BMSM and HLMSM, provide them with HIVSTs, and evaluate the efficacy of a mobile phone app to support linkage to posttest prevention services, including STI testing, PrEP initiation, and acquisition of condoms and compatible lubricants. This paper describes the protocol and enrollment numbers for providing HIVSTs to BMSM and HLMSM enrolled in 11 select US states.

The purpose of this paper is to describe our study procedures and provide recommendations for reaching and distributing HIVSTs to MSM most disproportionately affected by HIV in the United States. In addition, although an HIVST is not designed to link the user to HIV testing and prevention services, we will evaluate the efficacy of a mobile app to increase the linkage to HIV and STI prevention services.

Methods

Overview

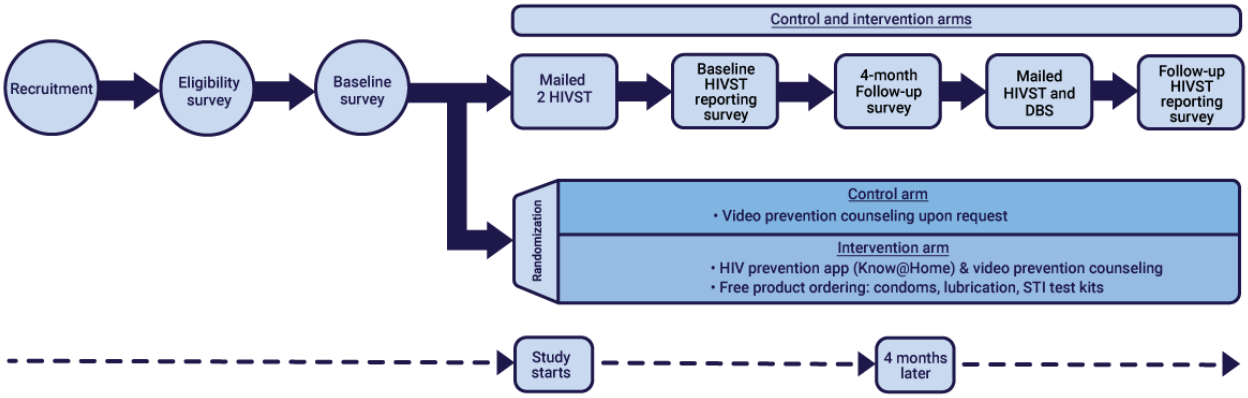
This study was a comparative effectiveness trial of 2093 cisgender MSM living across 11 states in the United States, including 1149 BMSM and 944 HLMSM. We selected these states based on race- and state-specific estimates of the MSM population size previously developed collaboratively by the CDC and Emory University [13]. We selected the 7 states with the highest populations of BMSM, and the 7 states with the

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highest populations of HLMSM, because 3 states were included in both lists (Florida, Louisiana, and Mississippi), and 11 implementation states were included in our study (Alabama, California, Florida, Georgia, Louisiana, Mississippi, Nevada, New York, North Carolina, South Carolina, and Texas).

The study was conducted in 2 phases: phase 1 involved formative discussions with stakeholders to inform the implementation of phase 2. Phase 2 (Figure 1) was a randomized controlled trial, in which participants were recruited through websites and social networking apps. Enrolled participants were mailed 2 HIVSTs (Food and Drug Administration–approved OraQuick In-Home HIV Tests) after providing informed consent, completing a baseline survey, and providing valid contact information. Participants were followed up for 4 months with an additional study assessment at the end of the 4 months. Project staff members discussed the use of HIV surveillance data with the relevant state health departments for the evaluation of the comparative effectiveness of the intervention (access to the Know@Home mobile app) compared with the control (referral to web resources) condition with respect to the linkage of participants to appropriate treatment or preventive services. Phase 2 included obtaining costs for multiple cost-effectiveness analyses related to recruitment; HIV self-testing; and linkage to prevention, treatment, and care services. Recruitment was conducted from February 2020 through February 2021.

Figure 1. Flow and timeline for Implementation of Rapid HIV Self-testing Among MSM Project, a comparative effectiveness trial of Black or African American and Hispanic or Latino men who have sex with men in the United States (2020-2021). DBS: dried blood spot; HIVST: HIV self-test; STI: sexually transmitted infection.



Ethics Approval

This study was approved by the Emory Institutional Review Board (IRB00099710).

Formative Work

To inform the implementation trial recruitment strategy, study procedures, and linkage-to-care protocol, we conducted individual and group consultations to elicit feedback during the Know@Home study planning and app development phase. This formative work solicited feedback from three core groups: (1) HIV care practitioners and researchers, (2) HIV service organization leaders from study implementation states, and (3) BMSM and HLMSM who live within the implementation study states.

One-on-One Consultations With HIV Care Practitioners and Researchers

To gain insight into the nuances of HIV screening among BMSM and HLMSM, 6 HIV care physicians and researchers specializing in working with these populations were invited to participate in one-on-one discussions over video calls. Discussions centered around understanding their experiences of engaging BMSM and HLMSM in HIV research, what advertising venues they found effective for recruiting each population, recommendations for advertising imagery and written content, and approaches to garner trust and foster retention within the project. The notes taken during each discussion were compiled, reviewed by the study team, and assembled into overarching themes. These consultants primarily had experience working with BMSM and had less advice pertaining to HLMSM. There was consensus that dating and hookup apps were the most successful in recruiting BMSM and HLMSM and that images should reflect age, body type, and diversity of skin tone within these populations. Providers working in southern states noted that HIV stigma and distrust of health care and academic institutions were barriers to engaging BMSM in HIV research and prevention and care services. To build confidence, consultants recommended creating relationships with trusted community-based organizations (CBOs) and clinics embedded within these communities. Consultants recommended obtaining support from respected local and state CBOs and clinics to provide study credibility, help keep participants engaged in the duration of the project, and boost linkage-to-care efforts.

Group Consultation With HIV Service Organization Leaders

In an effort to help establish relationships with CBOs and ensure practical research deliverables, 5 directors of HIV service organizations were invited to participate in a consultation over a video call. These CBO directors specialized in providing HIV screening and linkage services for BMSM and HLMSM in Alabama, Florida, Mississippi, New York, and North Carolina. The discussions focused on the types of data that would support the creation and implementation of a web-based HIV self-testing program, strategies for reaching BMSM and HMSM, and considerations for scaling such a program to a local organizational level. The notes taken during the consultation

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were reviewed by the study team, sorted thematically, and assembled into overarching themes. To help create an HIV self-testing program, the CBO directors highlighted their desire for metrics surrounding overall kit distribution, how many results were returned, and how many participants were successfully linked to care. In addition, all directors described the utility of a cost-effectiveness analysis to understand the expenses associated with such a self-testing program in relation to being able to link people who obtained a preliminary positive test result to HIV care. As many of the CBOs had existing laboratory partnerships, the consultants felt that if this program were brought to scale, they would be able to accommodate the processing of returned biospecimens for HIV testing (ie, dried blood spot [DBS] cards) and triple-site bacterial STI testing (ie, pharyngeal swabs, rectal swabs, and urine samples). All directors communicated that their implementation concerns were around staffing and funding, tracking HIVST kits, following up with clients who had a positive test result, and preventing some clients from acquiring more kits than necessary. Finally, CBO directors discussed how having a fully developed protocol for implementing an HIV self-testing program would help them bring a program to scale in their local service provision area.

Group Consultations With BMSM and HLMSM

The last element of the consultations sought to receive developmental input from BMSM and HLMSM regarding our recruitment materials, plans, and study procedures. To enlist BMSM and HLMSM, we asked our consultants (ie, HIV physicians, researchers, and CBO directors) in implementation study states to nominate community members who they felt were engaged with HIV and STI issues. Among the nominations offered, 3 HLMSM from California, Florida, and New York and 3 BMSM from California, Florida, and South Carolina participated. Two separate consultations were conducted via video calls—one with HLMSM and another with BMSM. During each consultation, a PowerPoint (Microsoft Corp) presentation was screen shared to elicit feedback on advertising imagery and content, possible recruitment venues, and strategies for disbursing incentives. The discussions also covered participant retention and study implementation design. Notes taken during each consultation were reviewed by the study team and assembled into a set of themes. Across both groups, community members advised using different dating or hookup apps for advertising in each state, based on their varying popularity, in addition to mainstream social media platforms. Retention issues that were cited included participants moving out of eligible study states during the follow-up period and the low monetary incentive for DBS sample collection. Their recommendations for implementation highlighted the importance of discreet shipment packaging, confidentiality of the result-reporting mechanism, linking those with a positive test result to locally trusted CBOs, and privacy of any study app notifications. Finally, the HLMSM group cautioned about the variability of Spanish dialects across the United States when attempting to offer Spanish-translated resources and materials.

During the 2 consultations with BMSM and HLMSM, feedback was obtained on draft advertisement images and taglines to be used for recruitment purposes. Consultants preferred joyous, light-hearted stock images of men to photos that conveyed solemnness. Consultants rated advertisements higher if they showcased everyday situations and “relatable” models that they felt were recognizable within their communities. Images that felt staged, unnatural, generic, or too commercial were ranked lower. Advertisements that portrayed physical affection and intimacy between men were also favored. Men who were shown hugging, kissing, or cuddling portrayed why HIV self-testing may be relevant to the target audience and related to healthy relationships or partner seeking. However, some images where men appeared too serious with their partners were thought to potentially depict intimate partner violence situations. In terms of race and ethnicity, participants gravitated to photos that included Black or African American and Hispanic or Latino men together and represented diverse skin tones. Finally, consultants endorsed tagline text that incorporated puns or turn of phrases such as “It Pays to Know” to more generic messaging such as “Find out your HIV status.”

Health Department Engagement

After the study states were selected, we contacted each state health department, beginning with HIV surveillance programs, and had multiple group webinars to share the proposed methods for the study and individual calls with some states to discuss the possibility of matching study participants to HIV surveillance records to ascertain the outcomes of testing.

Study Procedures

Eligibility

Study eligibility and exclusion criteria are listed in Textbox 1. We excluded people who were currently taking PrEP, as they would have been receiving regular HIV testing as part of their clinical care. Participants were required to own an Android or iOS smartphone because components of the trial were delivered via an Android or iOS smartphone app.

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Textbox 1. Eligibility criteria for Implementation of Rapid HIV Self-testing Among MSM Project, a comparative effectiveness trial of Black or African American and Hispanic or Latino men who have sex with men in the United States (2020 to 2021).

- Eligibility criteria:
  - Black or African American race, or Hispanic or Latino ethnicity
  - Male sex at birth
  - Currently identifies as male
  - Reported anal sex with at least one man in the past 12 months
  - Aged ≥18 years
  - Has an Android or iOS smartphone
  - Currently resides in a study state (Alabama, California, Florida, Georgia, Louisiana, North Carolina, Nevada, New York, Mississippi, South Carolina, and Texas)
  - Willing to download the study mobile app
  - Willing to provide valid contact information
  - Successful completion of baseline survey
- Exclusionary criteria:
  - Currently participating in another HIV prevention research study or program
  - Had a bleeding disorder
  - Had previously participated in an HIV vaccine study
  - Currently taking pre-exposure prophylaxis for HIV prevention
  - Reported living with HIV
  - Has plans to move out of a study state during the 4-month study period

Recruitment, Screening, Consent, and Enrollment

Potential participants were reached through several web-based avenues, hereafter referred to as *recruitment sources*: (1) general, non–lesbian, gay, bisexual, transgender, and queer (LGBTQ)–oriented social networking websites that were not geared toward sex-seeking (eg, Facebook and Instagram); (2) LGBTQ-oriented websites (eg, Queerty or The Advocate); (3) LGBTQ-oriented mobile social networking apps or dating websites geared toward sex-seeking (eg, Jack'd and Adam4Adam); and (4) other (eg, unknown source, referral from participant, and referral from another research study). Advertisements were placed in these web-based venues and directed users to a web page containing basic study information. Interested individuals were required to complete the web-based consent form and screener, and those who were eligible were required to provide contact information. Those who were determined to be ineligible were asked if they could be contacted for future research. We did not indicate why participants were ineligible to prevent unintentional disclosure of the eligibility criteria or repeated attempts to enroll. All participants who completed the screener were directed to web-based resources for HIV prevention and sexual health. After verification and deduplication by study staff, eligible participants were electronically sent links to the main study informed consent form and the baseline survey. The baseline survey was estimated to be completed in approximately 20 minutes.

Completed baseline responses and participant information were reviewed and checked for duplication by the study team. Web-based screener and baseline survey responses were compared to ensure consistency (eg, date of birth, state of residence, and HIV status), and contact information and IP addresses were compared for duplication, as described elsewhere [14]. Participants were sent an SMS text message and were required to respond by verifying their contact mobile number.

After completing verification, participants were enrolled and assigned in a 1:1 ratio to the intervention or control arms using stratified randomization by race or ethnicity, state of residence, and recruitment source (general social media, LGBTQ-oriented websites, LGBTQ mobile apps or web-based dating platforms, and other), totaling 88 strata. Within the strata, participants were randomly assigned to the next treatment allocation from a randomly permuted block sequence (block sizes were 2 and 4).

Postenrollment Study Period

Participants in both the intervention and control arms were mailed 2 HIVSTs after completing the baseline survey. Participants were encouraged to use the second HIVST to either (1) test again if the first test did not work (eg, an invalid result or sample collection error) or (2) provide the HIVST to someone they thought may benefit from HIV testing (eg, friend or sex partner). After completing the 4-month follow-up survey, participants were mailed 1 additional HIVST along with the DBS self-collection kit. Participants were encouraged to use the HIVST because the results from laboratory tests conducted

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on the DBS card could not be returned to participants. When participants used one or more of the study-provided HIVSTs, they were instructed to report each of their HIVST results and upload a photograph of each HIVST device via a secure web-based survey. Participants who gave HIVSTs to someone not enrolled in the study (referred to as *guests*) were advised to have the guest report their result and upload a photograph of their device via a web-based survey that did not collect any identifiable information. Guests were directed to a landing page with a consent form indicating that they were aged ≥18 years before completing an anonymous survey. At any point in the study, the participants and guests were allowed to stop participating.

Intervention

This study used the Know@Home app, which was built on the HealthMindr mobile health platform [15-17]. We made administrative changes to the functionality and content to match the study's design and updated public health messages. The locator tool was updated to national service locators, including HIV.gov and PrEP Locator [18]. Written feedback on content in the app was solicited from community advisory board members, and their input informed changes such as adding more exclamation points to help the messaging seem friendlier, adding information about undetectable=untransmittable, and streamlining the user experience by changing page order and functionality within the app. The app offers a variety of services related to post-HIV test sexual health care, including locators for PrEP services, STI testing, and postexposure prophylaxis services; tools to schedule periodic HIV testing and receive reminders to test; and PrEP and postexposure prophylaxis eligibility screening tools.

Incentives

Incentives in the form of e-gift cards were provided to participants for completing various study activities totaling up to US $70 over the 4-month study period. Participants received US $20 to complete the baseline survey, US $30 to complete the 4-month follow-up survey, US $10 to report their HIVST results in the baseline test results survey, and US $10 to complete and return their DBS card to Emory University. Participants could complete a web-based survey for the follow-up HIVST; however, they were not compensated for entering the follow-up HIVST result. Guests who used an HIVST provided by a study participant were not compensated for completing the anonymous web-based survey.

Commodity Ordering

Participants in the intervention arm had access to ordering free prevention commodities such as STI self-collection kits, condoms, and condom-compatible lubricants. The delivery of condoms and lubricants was fulfilled by Amazon Fulfillment Services. The delivery of STI self-collection kits was fulfilled by a Clinical Laboratory Improvement Amendments–accredited commercial laboratory. The STI self-collection kits included instructions and materials for participants to collect and return a urine sample, a rectal swab, a pharyngeal swab, a DBS sample, and a microtainer blood sample. The specimens were tested for urethral, rectal, and pharyngeal gonorrhea and chlamydia, and syphilis [19]. Specimens were returned by mail to the originating laboratory, where bacterial STI testing was performed using previously reported methods [20]. Negative STI results were provided to participants through a Health Insurance Portability and Accountability Act (HIPAA)–compliant patient portal, email, or SMS text messages; positive STI results were provided to participants by phone call and the HIPAA-compliant patient portal with referrals to local treatment locations.

Results Monitoring

For all study participants, the project staff monitored the HIVST-reporting survey data daily, Monday through Friday, and once on either Saturday or Sunday. The staff members sought to identify HIV test results that were (1) preliminary positive, (2) invalid, or (3) discrepant, meaning the result reported did not match the result image uploaded. When a preliminary positive result was provided, a staff member attempted to contact the participant to assess their emotional state, elicit existing systems of support, locate nearby HIV testing sites, and create a plan for the next steps. When the staff member identified an invalid result, they attempted to contact the participant about either receiving a replacement HIVST in the mail or providing HIV testing site referrals in their local area. After additional testing had been sought, the study staff member followed up with participants to document their corrected test result. If a discrepant result was identified, the study staff member attempted to contact the participant to verify the result entered in the test result survey, describe the source of the discrepancy, and review the test procedures, if needed. State guidelines for reporting an HIV test result to health departments were followed by study staff. As the guest test result survey (designed for individuals who were not enrolled in the study) did not collect identifiable information, the study staff member was unable to contact guests about their reported test results. Study contact information was listed on the guest test result survey, and guests had the option to schedule video counseling with trained study staff.

Linkage to Care

The study staff member attempted to contact all participants who reported a preliminary positive HIVST result, up to 10 times, by phone call, encrypted email, and SMS text message. Any unencrypted form of communication (ie, standard email or SMS text message) made no reference to HIV testing or their preliminary positive test result. If not successfully contacted by the third attempt, the study staff member sent a list of free or low-cost local HIV testing sites and care providers through an encrypted email. When the study staff member was able to speak to the participant over the phone, they confirmed that the participant was in a private location where they could talk about their result. If the participant was unable to discuss the results at that time, the study staff member asked for another time to call again. Once privacy had been established, the study staff member started by outlining the purpose of the interaction and then transitioned into inquiring about the participant's emotional state after receiving the preliminary positive result. The study staff member discussed the importance of having support from someone and addressed HIV disclosure strategies. The study staff member then discussed additional local HIV testing and

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care options in the context of the participant's insurance status. Additional referrals offered were case management services, mental health support, HIV support groups, housing programs, food assistance, and transportation services. Agreed-upon referrals were sent via encrypted email that included information about the provider's website, their hours of operation, and a Google Maps link to the location. After successfully sending additional HIV testing referrals, subsequent contact attempts inquired if an appointment was made or attended, if the preliminary positive result was confirmed, and if the participant was able to initiate treatment. Additional care and support referrals were assessed at each follow-up contact attempt. Participants with a positive additional HIV test result and those who received an HIV diagnosis, had seen an HIV care provider, and received HIV medication were asked if they would like any additional follow-up from the study staff members. Participants were able to opt out of study linkage-to-care support contacts at any time.

Participants in the intervention arm also had the option of ordering STI self-collection kits that included instructions and materials for collecting and returning samples for gonorrhea, chlamydia, and syphilis testing. For any positive bacterial STI test results, the study staff member attempted to contact the participant up to 10 times, following the same procedures as the HIV test results. If after 3 attempts, the participant was not reachable, the participant was sent an encrypted email with a PDF document detailing the laboratory test results and information on several local free or low-cost STI treatment providers. Participants who had specific samples rejected by the laboratory owing to quality or sample collection issues were offered a replacement STI self-collection kit and a list of local STI testing services. Additional contact attempts by the study staff member assessed whether an appointment concerning the STI results had been made or attended and if any additional referrals were needed. Participants who had seen a care provider and received antibiotic treatment had no further contact from the study staff member.

Video Counseling

Remotely conducted video counseling services were made available to all iSTAMP participants and guests throughout the study. Staff members who provided video counseling were trained in the state health department HIV testing and counseling and were certified following their state guidelines. In addition, staff members were trained in motivational interviewing techniques for HIV risk behavioral change. Sessions were conducted using HIPAA-compliant Zoom Health with meeting passcodes, waiting room requirements, and end-to-end encryption.

Participants were able to schedule a video counseling session for any reason, but session types were advertised as (1) a pretest session where counselors explained how to collect samples and interpret the HIVST result, and for participants in the intervention arm, the STI collection procedures; (2) a facilitated HIV test session where the participant conducted the HIVST during the video call, discussed current HIV or STI prevention behaviors, interpreted results with the assistance of the video counselor, and then discussed next steps; and (3) a posttest session where participants, who have already completed their HIV self-testing or STI self-collection, discussed their results and received appropriate referrals for treatment or prevention services. Because participants were able to schedule a session at any time during the study without describing their needs beforehand, video counselors were trained to respond to any of these standard scenarios and had a detailed knowledge of study procedures to answer participation-related questions.

After their baseline HIVSTs had been shipped, participants received an email describing the video counseling service and a list of available appointment times for that week. A similar video counseling email was sent 4 months later when another HIVST and DBS card had been shipped to participants. Throughout the project, automated email reminders regarding study activities continued to advertise video counseling services. Participants were able to respond to any study-related communication (ie, phone call, SMS text message, or email) to request a video counseling session. Guaranteed video counselor availability was established during standard business hours, Monday through Friday from 9 AM to 6 PM in the eastern time zone. Participants were also able to schedule during evenings and weekends upon request. The study staff member followed telehealth procedures for client setup, provider setup, troubleshooting, and long-distance referrals described elsewhere [21]. To help demonstrate how to use various biological sample collection materials, the study staff members adhered to existing protocols [22].

Data Collection

Cost-effectiveness Data

A comprehensive cost analysis has been initiated to assess the cost of implementing recruitment strategies and the intervention. A microcosting approach was implemented, along with the standard literature practice of itemizing and assigning a dollar value to each component. Three cost-effectiveness analyses have been initiated from the health care payer perspective (the cost to the party implementing the program), which will include the different cost categories.

First, we obtained the costs incurred for the 3 web-based recruitment venue categories on the outcome of study enrollment (defined as the completion of the baseline survey and downloading of the study app). We collected data on the following cost categories: web-based banner advertisement placement and study staff time to (1) manage enrollment, (2) validate participant eligibility, and (3) monitor and evaluate enrollment data.

Second, we obtained cost data for the 3 venue categories on the outcome of HIVST results returned during the study period and the number of participants with a reactive result. We collected data on the costs of enrollment along with HIVST procurement and shipping, staff or personnel time to manage mailing or return of test kits, study staff time to manage monitoring and evaluation of HIV test result data, and study staff time to provide phone counseling to those who reported a preliminary positive HIV test result.

Finally, we obtained costs data for the intervention on linkage to 3 sexual health services (HIV care visit among those who

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tested preliminary positive, PrEP discussion with a provider, and STI testing). We collected data on the costs incurred after the participants are provided with HIVSTs and randomly assigned them to 1 of the 2 study arms.

These analyses have included the cost of study staff time for processing orders, contacting participants, and app management or participant registration and are independent of the prerandomization cost-effectiveness analyses; no cost related to recruitment strategies were included.

Cost data were collected by extraction from accounting and budget records, external contracts, and study or personnel time required to manage the outlined tasks. Data were estimated using Clockify (COING Inc), a free software (both web- and mobile based) that allows personnel to track the time spent on daily tasks. To calculate personnel costs, we multiplied these hours by wage rates plus fringe. Only implementation costs (defined as the ongoing costs of delivering the intervention) were considered, and no costs associated with survey or app development, incentives, or research were included.

Survey Data

A web-based screening survey collected information to determine eligibility, including demographics, sexual behaviors, state of residence, HIV status, and contact information. Participants, if eligible, then completed a web-based baseline survey that collected information on additional demographic characteristics, sexual behaviors, HIV testing history, future preferences for PrEP use, HIV testing intentions, other health service history, internet and mobile app use, medical mistrust, and health literacy. Participants were prompted by email, SMS text message, or phone to take a web-based follow-up survey after 4 months, which covered the same domains as the baseline survey, with reporting limited to the postbaseline period. Additional topics in the follow-up survey included PrEP use, HIV treatment and care, and time and costs. Participants in the intervention arm answered additional questions in the follow-up survey regarding their experiences using the Know@Home mobile app, and individuals who used the video prevention counseling option were asked about their experiences using this service.

Separate test result–reporting surveys were distributed to participants after the baseline and 4-month follow-up surveys, referred to as the baseline test result–reporting survey and 4-month follow-up test result–reporting survey, respectively. The participant and guest surveys asked about their experience regarding (1) receiving HIVSTs, (2) experience using the rapid test, (3) the result of each HIVST, and (4) distributing HIVSTs.

As participants interacted with the Know@Home app, data about the features used, pages visited, functions used, and time spent were captured by the app and stored in the administrative portal.

Laboratory Data

Participants who consented to provide DBS samples for laboratory-based research were provided DBS self-collection kits after completing the 4-month survey. Using the instructions provided, participants prepared and mailed the DBS card for HIV diagnostic testing. Testing included an algorithm with antigen and antibody combination and HIV-1 and HIV-2 differentiation supplemental testing. The DBS samples served both as secondary testing that is more sensitive than the baseline rapid tests and to corroborate or identify new positive HIV results. As a supplemental assessment, participants who returned the DBS card and reported taking HIV medications (PrEP or antiretroviral medications) were sent a microtainer self-collection kit to mail the blood sample to the CDC. The purpose of the microtainer collection activity was to evaluate the feasibility and specimen integrity of self-collected microtainer samples from untrained participants in the United States. The samples were tested for HIV viral load and HIV medications (PrEP or antiretroviral medications).

Health Department Surveillance Data

The state departments of public health receive all reports of reactive HIV diagnostic tests, CD4 counts, and viral load tests performed on patients residing in their jurisdictions through systems such as the electronic HIV and AIDS Reporting System. The study staff member requested HIV surveillance data from state departments of public health following the end of a person's participation in the study. We requested that names and dates of birth of all participants be verified. The goal of this request was to identify participants who received a confirmed reactive HIV test result or entered HIV care for both participants who did or did not report a positive HIV test result during the study.

Other Data

Electronic case report forms (CRFs) were used to capture data for validation and enrollment, HIVST result follow-up communications, STI test result follow-up communications, referrals, and video counseling. For those who engaged in video counseling, data on the length and content of sessions were captured and stored in CRFs, excluding identifiable information.

Planned Analyses

Formative Work

In the first part of the study, we characterized the cultural appropriateness, possible web-based recruitment venues, barriers to engaging BMSM and HLMSM in HIV prevention including HIV testing promotion strategies, and additional considerations for the implementation and potential scale-up of mail-out HIVSTs, following conversations with key stakeholders.

In the second part of the study, we initiated several cost-effectiveness analyses and a comparative effectiveness evaluation of the intervention (Know@Home mobile app) on the linkage of participants to appropriate services (HIV treatment, PrEP, STI testing, additional prevention, and social services).

Cost and Cost-effectiveness Analyses

In primary analyses, we have initiated an evaluation of the cost and cost-effectiveness of the 2 LGBTQ-oriented recruitment platforms and the general, non–LGBTQ-oriented social networking websites for the following outcomes: (1) enrollment in the study defined as completion of the baseline survey, (2) HIVST results returned within 1 month of enrollment, and (3)

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identification of established HIV infections (eg, new diagnoses). The secondary analyses consisted of the cost-effectiveness of the 2 randomized study arms for outcomes of linkage to HIV prevention or HIV care services: (1) HIV counseling and treatment for MSM with HIV, (2) PrEP counseling and uptake for MSM who obtained a negative HIV test result, and (3) STI testing and treatment for MSM. The time horizon used was the time from baseline to follow-up, and both costs and effects will be discounted at an annual rate of 3%. Analyses included the overall study population and were performed separately for the 2 MSM populations (BMSM and HLMSM) enrolled.

Standard methods [23,24] for economic analyses have been used for various HIV prevention interventions [24-26]. Cost and outcome data were entered into a standardized Excel spreadsheet with embedded formulas. The net cost of the recruitment strategies and intervention was calculated along with the incremental cost-effectiveness ratio (ICER) for the recruitment strategies compared with the reference (primary aim) or intervention arm compared with the control arm (secondary aim). For example, using ICER to compare the recruitment venues of LGBTQ-oriented mobile apps or web-based dating websites geared toward sex-seeking versus general, non–LGBTQ-oriented web-based websites not geared toward sex-seeking (the reference) on the outcome of enrollment were calculated as follows: $[(Cost_{\text{sex-seeking apps}} - Cost_{\text{reference}})] / [(Enrollment_{\text{sex-seeking apps}} - Enrollment_{\text{reference}})]$. This value yields the incremental cost per participant enrolled. Where no observed differences in the outcomes of interest by recruitment strategy (primary aim) or study arm (secondary aim) exist, then a cost minimization analysis is planned. One-way sensitivity analyses were planned for all input variables to determine the inputs for which the net costs and ICERs were the most sensitive. We explored the effects of realistic implementation scenarios, including health departments with or without the ability to outsource HIV testing, robust eHealth systems, and tech-savvy staff.

Usage of Test Kits and Counseling and Linkage to Care

Data on use of HIVSTs were collected in multiple surveys. Information on the use of HIVSTs was provided in test result–reporting surveys during the study, and all participants were also asked about their use of study-provided HIVSTs during the 4-month follow-up survey. The date and result of the most recent HIV test before enrollment in iSTAMP were collected at baseline. Participants were asked to report any additional HIV testing and result that occurred outside the study on their 4-month follow-up survey. For the outcome of HIVST use, we report descriptive statistics about the number of HIVSTs distributed or used during the study period, overall and stratified by race or ethnicity, HIV testing history at enrollment, and recruitment source.

We used data collected on CRFs to calculate the number and proportion of people who used the telehealth counseling provided through the study. We used data from counseling CRFs to describe the main reasons for seeking counseling and the types of services used.

Linkage to care is critical for people diagnosed with HIV. We documented the proportion of participants who tested positive for HIV that were linked to care and described the distribution of time from receiving a positive test result to linkage to care, as previously described [9]. We used 3 sources of data to describe linkage to care. First, we used the following data from the study surveys: participants who reported a positive test result were asked if they have seen an HIV care provider and the approximate date of their appointment with that provider. Second, we used notes from CRFs prepared by study staff who talked with participants and assisted with linking them to HIV care. Not all participants requested such assistance, so not every participant who received a positive result has a linkage or counseling CRF. Finally, we have worked with the 11 state health departments to create plans to match our participants to the state surveillance registries. This would allow us to assess the occurrence and timing of additional HIV testing and viral load evaluation and to determine the dates of these services as a marker of linkage to care. We have functioned as a testing provider and reported HIV diagnoses as required (some states require reporting of positive HIV self-test results). We provided feedback to testing providers about the linkage and care outcomes of people that the providers diagnose as a routine function of surveillance programs. Furthermore, we obtained informed consent from the participants to allow for such linkage.

Receipt of Posttest Services by Allocation to App

HIV testing is the entry point for multiple care continua; for those who received a positive test result in this study, their linkage to care was assessed. We assessed the receipt of HIV and STI services during the follow-up period for those who received a negative result or who do not report HIV testing. We also determined whether randomization to the intervention arm (Know@Home app built on the HealthMindr platform [15,16]) was associated with a higher percentage for three outcomes measured at month 4: (1) testing for bacterial STIs in the previous 4 months; (2) receipt of condoms and condom-compatible lubricants in the prior 4 months; and (3) linkage to HIV (PrEP or antiretroviral therapy) services during the study follow-up period. We used an α value of .05 to designate statistically significant intervention effects. Given that we had prespecified 3 primary outcomes, adjustment for multiple comparisons was not necessary [27].

Results

Key Themes in Formative Work

Key themes in formative work among HIV providers and researchers (N=6) indicated that dating and hookup mobile apps have previously been successful in recruiting BMSM and HLMSM for research studies. In addition, HIV stigma and distrust of health care and academic institutions may act as barriers to engaging with these populations. Among HIV organization directors (n=5), primary themes included their desire for cost-effectiveness data for possible implementation of HIV self-testing services and concerns about staffing, funding, and linkage to care for clients who use an HIVST. Among the BMSM (n=3) and HLMSM (n=3) community members, the central findings consisted of their advertising

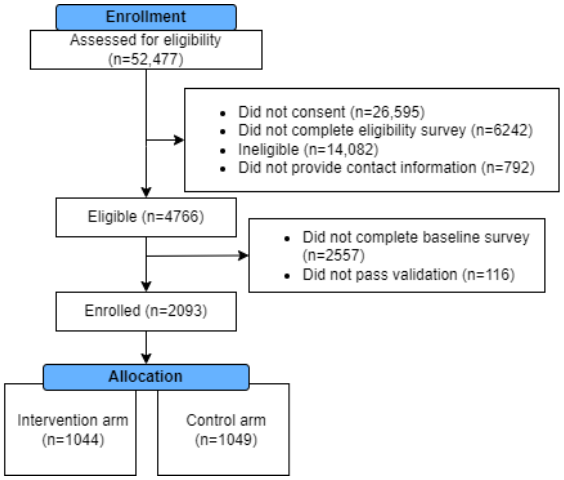
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preferences for noncommercial images, diverse skin tones, and joyous and everyday scenes, accompanied by text that incorporated puns.

Progress to Date

iSTAMP began enrollment in February 2020 and concluded in February 2021, with participant follow-up data completed in September 2021. Of the individuals assessed for eligibility with screening questions, 9.08% (4765/52,481) were considered eligible to join (Figure 2). Of the MSM who consented, 43.92% (2093/4765) completed the baseline survey, passed the validation process, and were enrolled, of whom 45.10% (944/2093) were HLMSM and 54.90% (1149/2093) were BMSM. We randomly assigned 49.88% (1044/2093) participants to the intervention group and 50.12% (1049/2093) to the control group.

Figure 2. CONSORT (Consolidated Standards of Reporting Trials) diagram for Implementation of Rapid HIV Self-testing Among MSM Project, a comparative effectiveness trial of Black or African American and Hispanic or Latino men who have sex with men in the United States (2020-2021).



To examine enrollment proportions relative to state demographic data, we compared participant enrollment numbers with the 2018 Census [10], which estimated the male population in each state, stratified by race or ethnicity (Table 1). Census data were categorized for comparison by including only those who selected single-race Black or African American, non-Hispanic, while iSTAMP allowed for participants included in the Black or African American, non-Hispanic strata to select multiple races.

Table 1. Enrolled study population compared with census-estimated population from 2018 by race or ethnicity for Implementation of Rapid HIV Self-testing Among MSM Project, a comparative effectiveness trial of Black or African American and Hispanic or Latino men who have sex with men in the United States (2020 to 2021).

State	Black NH[a] MSM[b] enrolled (n=1149), n (%)	Black NH men[c] in the state population (11 states; n=8,046,742), n (%)	Hispanic MSM enrolled (n=944), n (%)	Hispanic men in the state population (11 states; n=13,895,483), n (%)
Texas	205 (17.84)	1,220,831 (15.17)	253 (26.8)	3,842,932 (27.66)
South Carolina	42 (3.66)	465,763 (5.79)	14 (1.5)	102,440 (0.74)
North Carolina	102 (8.88)	774,275 (9.62)	46 (4.9)	319,908 (2.30)
New York	137 (11.92)	1,008,059 (12.53)	135 (14.3)	1,330,085 (9.57)
Nevada	18 (1.57)	101,306 (1.26)	17 (1.8)	300,733 (2.16)
Mississippi	43 (3.74)	375,276 (4.66)	7 (0.7)	37,118 (0.27)
Louisiana	55 (4.79)	509,679 (6.33)	12 (1.3)	89,693 (0.65)
Georgia	242 (21.06)	1,121,964 (13.94)	57 (6.0)	344,266 (2.48)
Florida	136 (11.84)	1,157,557 (14.39)	112 (11.9)	2,049,528 (14.75)
California	109 (9.49)	870,988 (10.82)	277 (29.3)	5,408,044 (38.92)
Alabama	60 (5.22)	441,044 (5.48)	14 (1.5)	70,736 (0.51)

[a]NH: non-Hispanic.

[b]MSM: men who have sex with men.

[c]US Census data include those who selected only Black/African American individuals and do not include those who selected multiple races (US Census Bureau. 2019. https://data.census.gov/cedsci/ accessed 2.18.2021).

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Discussion

Public Health Need

Formative research synthesized concrete guidance from stakeholders and community members who informed the methods used to recruit and retain participants in this study. We were able to effectively engage BMSM and HLMSM in this project and share best practices related to recruiting this key population. BMSM and HLMSM are disproportionately affected by HIV [28], and to achieve health equity, it is necessary to develop methods to maximize the opportunities for these communities to access resources such as HIVST distribution. iSTAMP aimed to learn how to effectively reach BMSM and HLMSM and to implement a program for the distribution of free HIVSTs.

Barriers to HIV testing have been described for decades throughout the HIV epidemic in the United States. These include a lack of perception of risk, stigma associated with seeking testing, lack of convenient options for HIV testing, and fear of obtaining a positive test result. Stigma-related concerns may be heightened for BMSM and HLMSM who face intersectional stigmas around race and ethnicity, sexual or gender minority status, and HIV. It is crucial to develop a robust slate of option for HIV testing that will allow MSM at elevated risk for HIV to test as frequently as recommended by the CDC. One approach is by supplementing provider-based testing with HIV self-testing.

Key Innovations

Working closely with the states in which the study was conducted was an important aspect of our study. We conducted this study in states with large populations of BMSM, HLMSM, or both [13]. Involving the state health departments is crucial in planning implementation studies of interventions, because in the United States, with a few exceptions, the primary responsibility for providing prevention services and for following up with those living with HIV falls on state health departments. Thus, state health departments may eventually be implementers of the procedures developed and tested in this study. Including states in the planning phases increases the likelihood that programs can be rapidly and seamlessly implemented by health departments that choose to adopt them.

The cost-effectiveness analyses outlined in this protocol will provide necessary information for providers wishing to implement similar recruitment and testing promotion strategies to reach BMSM and HLMSM, among others. Data on both the cost and impact of such strategies can guide decision-making regarding the efficient allocation of limited resources to increase HIV testing among these populations. Although cost-effectiveness analyses are recognized as an important component of implementation science research, limited data on the cost-effectiveness of varied recruitment, HIV testing, and linkage strategies currently exist. Thus, iSTAMP will make an important contribution to HIV testing and prevention services.

Limitations

Our study had some limitations, including standard biases for randomized controlled trials. The study may be affected by selection bias in that the men who agreed to participate were not representative of all BMSM and HLMSM in the implementation states. Another potential limitation is the differential loss to follow-up between the intervention and control arms. This was mitigated through comprehensive efforts to retain participants in both arms by using multiple modes of contact (phone call, email, or SMS text message), compensating participants for their time to complete study activities, and by allowing all survey and study activities to be completed remotely. There is risk for misclassification bias because we rely, to a large extent, on participant-reported outcomes for the use of tests and linkage to follow-up services. We have taken steps to reduce this bias by allowing participants to complete surveys remotely, using survey tools that have been validated [9], and by measuring key outcomes from multiple sources of data (ie, surveys and communications with the staff). One factor that might influence the results is that this study was primarily conducted during the COVID-19 pandemic [29,30]. A study conducted in 2020 found that during the COVID-19 pandemic, MSM reported fewer sex partners and opportunities to have sex, as well as problems accessing HIV testing, which might have increased the use of HIVSTs [30]. However, because the study had been designed to be conducted entirely remotely, the procedures and protocols for the iSTAMP study did not meaningfully change due to the COVID-19 pandemic.

Public Health Implications

The distribution of HIVSTs is already moving into public health programs. It is critical that we identify and disseminate effective methods to reach BMSM and HLMSM through programs that strive toward health equity for these priority populations. A pilot project in which a community organization partnered with state and local health departments to fulfill orders for free HIVSTs showed that providing HIVST in a "direct-to-consumer" model is feasible and can reach populations with substantial HIV risk and those who have not recently tested for HIV [31]. In 2021, the CDC contracted with Insignia Federal Group, who partnered with Building Healthy Online Communities and Emory University to distribute 100,000 HIVSTs to those who requested an HIVST in the United States or Puerto Rico [32]. The marketing strategy was primarily driven by social media advertising and influencers to reach Black and Latino gay and bisexual cisgender men, transgender women, and Black cisgender women [32] and also included links to the HIVST ordering portal through the HIV testing locator of AIDSVu.org [11]. It is important that these programs continue to monitor the distribution of HIVSTs in the populations most affected by HIV. In the longer term, local or state health departments and CBOs that serve as major sources of public health guidance and provision of services could implement HIV self-testing programs that serve their local populations most affected by the HIV epidemic. The lessons learned in the iSTAMP study will be useful for the planning and budgeting of programs, for anticipating the need for telehealth counseling and linkage services, and for providing examples of program materials to help jump start national, state, or local programs.

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Acknowledgments

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Data Availability

After the primary outcome analyses are completed, deidentified data sets can be made available upon written request to the investigator PSS. Interested parties should propose a specific analytic hypothesis. The data use agreement would be developed to ensure (1) data are used solely for research purposes without attempting to identify individual participants; (2) that there is a clear plan for maintaining the safety and security of data; and (3) commitment to the destruction or return of data after analysis.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer reviewed report by National Center for HIV, STD, and TB Prevention Special Emphasis Panel (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 208 KB - resprot_v12i1e43414_app1.pdf]

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Abbreviations

BMSM: Black or African American, non-Hispanic men who have sex with men

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CBO: community-based organization
CDC: Centers for Disease Control and Prevention
CRF: case report form
DBS: dried blood spot
HIPAA: Health Insurance Portability and Accountability Act
HIVST: HIV self-test
HLMSM: Hispanic or Latino men who have sex with men
ICER: incremental cost-effectiveness ratio
iSTAMP: Implementation of Rapid HIV Self-Testing Among Men Who Have Sex With Men
LGBTQ: lesbian, gay, bisexual, transgender, and queer
MSM: men who have sex with men
PrEP: pre-exposure prophylaxis
STI: sexually transmitted infection

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Protocol

Improving Self-management of Type 2 Diabetes in Latinx Patients: Protocol for a Sequential Multiple Assignment Randomized Trial Involving Community Health Workers, Registered Nurses, and Family Members

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Abstract

Background: The rate of Type 2 diabetes mellitus (T2DM) among Mexican American individuals is 16.3%, about twice that of non-Hispanic White individuals. While a number of education approaches have been developed and shown to improve diabetes self-management behaviors and glycemic control for Spanish-speaking Latinx patients with T2DM, there is little research to guide health practitioners regarding which interventions to apply and when so that resources are used efficiently, and treatment outcomes are maximized.

Objective: This study aimed to describe an adaptive intervention that integrates community mental health workers, diabetes nurse educators, family members, and patients as partners in care while promoting diabetes self-management for Mexican American individuals with T2DM. The project incorporates four evidence-based, culturally tailored treatments to determine what sequence of intervention strategies work most efficiently and for whom. Given the increasing prevalence of T2DM, achieving better control of diabetes and lowering the associated medical complications experienced disproportionally by Mexican American individuals is a public health priority.

Methods: Funded by the National Institute of Nursing Research (National Institutes of Health grant R01 NR015809), this project used a sequential multiple assignment randomized trial and included 330 Spanish-speaking Latinx patients with T2DM. In the first phase of the study, subjects were randomly assigned to an evidence-based diabetes self-management educational program called Tomando Control delivered in a group format for 6, biweekly 1.5-hour sessions, led either by a community health worker or a diabetes nurse educator. In the second phase of the study, those subjects who did not improve their diabetes self-management behaviors were rerandomized to receive either an augmented version of Tomando Control or a multifamily group treatment focused on problem-solving. The primary outcome measure was the "Summary of Diabetes Self-Care Activities." Evaluations were made at baseline and at 3, 6, and 12 months.

Results: This study was funded in June 2016 for a period of 5 years. Institutional review board approval was obtained in November 2016. Between March 2017 and September 2020, a total of 330 patients were recruited from the outpatient primary care clinics of Olive View-UCLA Medical Center, with a brief hiatus between May 2020 and July 2020 due to COVID-19 restrictions. The study interventions were completed in December 2020. Data collection began in March 2017 and was completed in December 2021. Data analysis is expected to be completed in Spring 2023, and results will be published in Fall 2023.

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Conclusions: The results of this trial should help practitioners in selecting the optimal approach for improving diabetes self-management in Spanish-speaking, Latinx patients with T2DM.

Trial Registration: ClinicalTrials.gov NCT03092063; https://clinicaltrials.gov/ct2/show/NCT03092063

International Registered Report Identifier (IRRID): DERR1-10.2196/44793

(JMIR Res Protoc 2023;12:e44793) doi:10.2196/44793

KEYWORDS

community health workers; diabetes education; Latinx; nurses; promotores; type 2 diabetes

Introduction

Background and Rationale

At 53 million people, the Latinx population is the largest minority group in the United States [1]. More than half of these are of Mexican origin, and this group has the lowest median age of any racial or ethnic group in the United States. Despite this, Latinx people living in the United States exhibit a disproportionate burden from type 2 diabetes mellitus (T2DM), with about double the prevalence among non-Hispanic White individuals [2]. A recent review of studies demonstrating an increased prevalence of diabetes and its complications among Latinx individuals compared with non-Hispanic White individuals suggested that low health literacy, lack of access to health care resources, and language barriers are among the main causes of T2DM ethnic disparities in the United States [3].

Over the past 20 years, several diabetes self-management education (DSME) approaches have been developed and shown to improve diabetes self-management behaviors and glycemic control as well as other health outcomes for Mexican American individuals with T2DM [4-9]. Numerous approaches have been developed, many of which share common elements including community involvement, face-to-face encounters, ongoing participation of a multidisciplinary treatment team, targeting the development of skills to promote behavior change, the provision of prompts and reminders, the use of a prior needs assessment to inform intervention design, and an explicit focus on social-contextual issues [10,11]. While each of these evidence-based DSME approaches has demonstrated advantages over usual practices in Mexican American communities, these interventions differ in their format (individual vs group), the type of provider used to deliver the DSME intervention (health professional vs lay community health worker or, in this study, *promotore*), and treatment target (patient vs patient and family). Such differences could be impactful both in terms of overall patient outcomes as well as economic feasibility for health care systems considering their implementation; however, there is little research to date to guide health practitioners regarding which interventions to apply and when in order to maximize treatment outcomes and resource efficiency.

An additional gap in the literature stems from the finding that fewer than 40% of subjects offered these treatments achieved levels of hemoglobin A1c (HbA1c) in accordance with the standards established by the American Diabetes Association [12]. Identifying nonresponding patients early in the treatment process and implementing more culturally appropriate, family-centered approaches could forestall long-term adverse consequences. The rationale of this study is to fill this gap of knowledge by comparing 4 different approaches to enhance diabetes self-management of Hispanic patients with T2DM.

Registered Nurses Versus Community Health Workers

Many educational and management strategies developed and implemented to address the specific needs of the Mexican American population were originally designed to involve registered nurses (RNs), certified diabetes educators, or dietitians as the primary patient educators [6,8,9]. The limited availability of such specialized providers in general, and bilingual or bicultural providers, in particular, prompted many interventions to use *promotores* to handle group educational and skill reinforcement sessions as adjuncts to the primary educators. In some programs, the role of the *promotore* was modified such that the *promotore* became the principal diabetes health educator, thus replacing highly educated personnel such as certified nurses for patient education and long-term case management [13-19].

The evidence regarding the efficacy of *promotore*-delivered interventions is mixed and incomplete. Some studies have found that interventions with community health workers do indeed have an impact when compared to usual clinical practice [8,9,16-18,20]. However, it has also been suggested that this may not be the case [19], and at least one study using focus groups with primarily Mexican American patients found that these patients strongly preferred trained health care professionals like nurses [12]. To date, there has been no study that has directly compared similar DSME interventions delivered by a community health worker (ie, a *promotore*) versus a health care professional such as a nurse.

Family Incorporation

Social support has been recognized as a crucial component of health and behavior change, and family members are the most significant source of that support [21]. Family behaviors and attitudes can support or challenge a patient's adaptation to illness and subsequently a patient's confidence, intent, and willingness to implement disease-management strategies [22], and a recent meta-analysis has suggested that addressing family functioning and problem-solving in addition to teaching diabetes self-management skills is critical to success [23]. Mexican American individuals with T2DM have cited attitudes, perceptions, and preferences of family members as significant barriers to making recommended changes in their diet and exercise patterns [24]. Interventions that target familial support to improve diabetes self-management have been effective within the Mexican American population [25]. Despite this evidence,

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most of the abovementioned interventions designed and tested for Spanish-speaking Hispanic individuals only encourage the involvement of families in DSME interventions; none explicitly target the family or family behaviors.

To date, the literature offers only 2 examples of diabetes interventions that specifically target and address the Mexican American families' collective behaviors. The first was a demonstration project carried out in southern Arizona, which used *promotores* to deliver a 12-week program designed to build and reinforce family communication, collective esteem and efficacy, and family support for appropriate food choices and physical activity behaviors. A pre- versus postintervention comparison indicated a significant increase in diabetes knowledge, family efficacy to change food choices, and actual activity behaviors [9]. The other uncontrolled study enrolled 36 Latinx (predominantly Mexican American) families in rural North Carolina in a similar DSME curriculum but the groups were led by a nurse practitioner rather than a *promotore*. Patients showed significant improvement in diabetes knowledge, diabetes self-efficacy, and higher intake levels of healthy foods (ie, fruits and vegetables), and performance of blood glucose testing and foot inspections, while family members demonstrated improved diabetes knowledge and family support compared to baseline [26].

Group Versus Individual Sessions

The type and setting of these interventions may also be important, and one question that has received some attention is that of group versus individual sessions. One study that tested the "dosing" of an individual DSME found that 16 hours of education with an additional 6 hours of group support was as effective as 52 individual contact hours delivered over 12 months [6]. There are also 4 studies that have directly compared individual with group DSME; three of these led to the conclusion that group education appeared to have a greater impact on diabetes self-management and glycemic control than individual education at 6 and 9 months [27]. However, these were described as poor studies with small numbers and high dropout rates, and there was no significant difference between the interventions at 12 and 18 months. The fourth study did find that patients with T2DM of relatively long duration and HbA1c levels of 7% or higher had improved short-term HbA1c outcomes and a greater likelihood of achieving an HbA1c level below 7% if they were educated using the group approach versus the individual method; however, in this study, the total educator contact time was also greater for the group intervention (8 hours) than for the individual approach (3 hours) [28].

Some families may require extra efforts, such as home visits, telephone reminders, and cultural tailoring, to address the specific obstacles to attendance faced by families [9]. However, other families may need a far more intensive approach to encourage and sustain their participation in DSME, including multifamily groups (MFGs). Two lines of research support the value of MFGs for this purpose. First, randomized controlled studies of MFG in adolescents with type 1 diabetes have shown improvements in diabetes self-care, particularly in patients with poorer glycemic control at baseline [29,30]. Second, the MFG approach has been shown to improve self-management skills in a Mexican American population with chronic mental illness [31]. Given that this study was carried out with a hard-to-reach community of Spanish-speaking Mexican American individuals and that psychiatric symptoms (eg, depression, anxiety, and psychosis) have been identified as major impediments to use diabetes self-management practices [32-35], the results suggest that the MFG approach may be effective in this population.

Primary Objective

The overall objective of this project is to build the science of T2DM self-management for Latinx patients by constructing a family-centered adaptive intervention to help patients and their relatives enhance their diabetes knowledge and beliefs, increase the use of self-regulation behaviors, and foster social facilitation.

Hypothesis

There are 4 main hypotheses this study will test. First, subjects randomized to adaptive interventions that begin with nurse-led groups will show greater increases in diabetes self-management behaviors than those who begin with *promotore*-led groups. Second, among nonresponders to either of the first-line approaches, subjects randomized to a multifamily, problem-solving group will show greater improvements than those assigned to a single-family approach. Third, key relative's participation in treatments will lead to (1) increased patients' and relatives' diabetes knowledge; (2) increased diabetes self-efficacy; (3) increased collaborative goal setting by families with health care providers; (4) increased family support; and (5) increased T2DM self-management behaviors. Fourth, subjects who are older, female, less educated, and less acculturated have an alcohol use or psychiatric disorder or have a longer history and greater severity of T2DM will (1) be less likely to have family members participate in treatment and (2) use diabetes self-management skills less often.

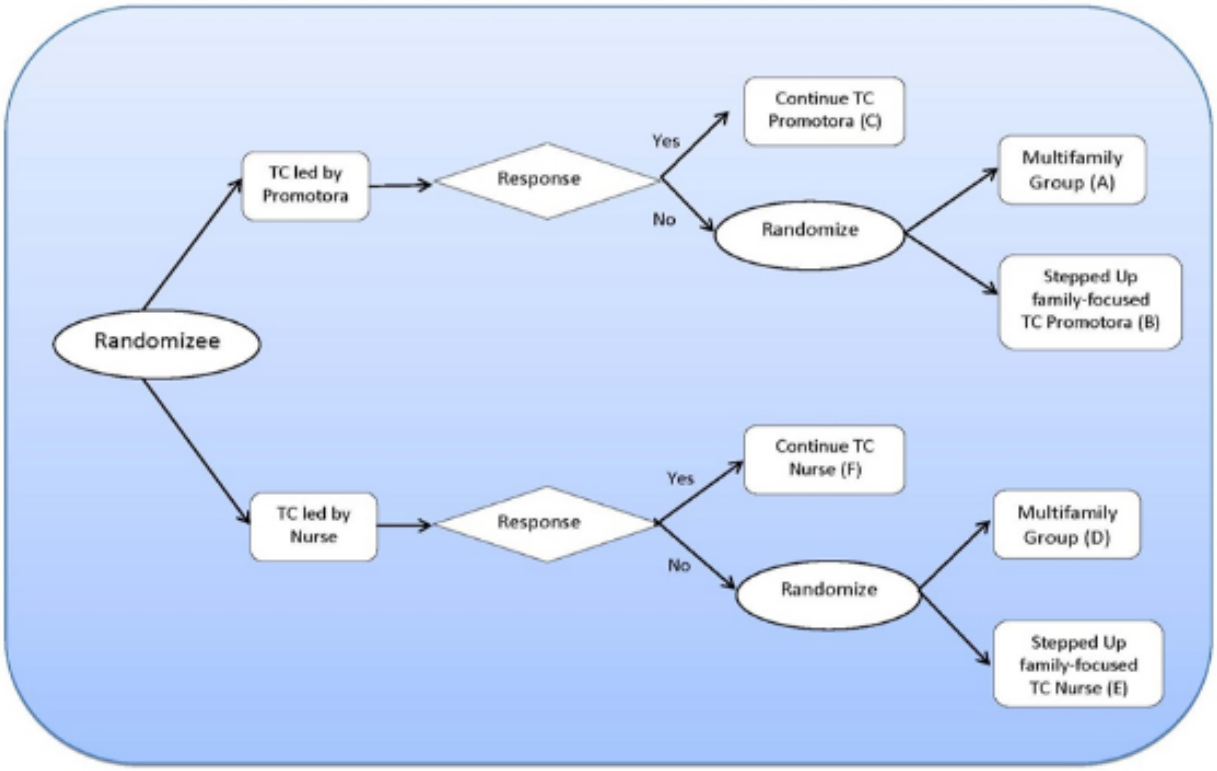
Methods

Study Overview and Design

A sequential multiple assignment randomized trial study design evaluates 2 initial interventions for Hispanic adults with T2DM. Figure 1 indicates the study's procedural flow. First, after baseline assessment, subjects were randomly assigned to receive the *Tomando control* (TC) intervention led either by a community health worker or *promotore* (TC-*promotore*) or by a nurse (TC-nurse). Both of these consist of 6 biweekly 2.5-hour group sessions. After the first 3 intervention sessions (phase 1), preliminary response was measured. Early responders to each intervention continued their same assigned intervention for 3 more sessions. For nonresponders (defined below), participants were rerandomized (phase 2) to receive either an augmented, stepped-up intervention that makes additional efforts to engage family members in the DSME enterprise for 3 more sessions or an MFG intervention designed to individually tailor treatment to address the obstacles encountered in promoting diabetes self-management behaviors. The MFG intervention consisted of 6 additional group sessions.

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Figure 1. Smart design. TC: Tomando control.



Clinical Setting and Patient Population

The study was being conducted in the community served by Olive View-UCLA Medical Center, which is a teaching hospital affiliated with UCLA and part of the Los Angeles County Department of Health Services health care system. It is a safety net facility providing inpatient and outpatient services to the 4 million residents of the San Gabriel, San Fernando, and Antelope Valley regions of Los Angeles County. All patients at Olive View-UCLA Medical Center are under the care of a medical home, which includes full- and part-time staff composed of primary care physicians, residents, interns and medical students, nurses, and nursing assistants. The majority of patients are underinsured or uninsured. Approximately 60% (120,000/200,000) of patients speak Spanish as their primary language, and 60% (120,000/200,000) of patients are of Mexican descent. Among them, over 80% (96,000/200,000) of patients live with their families. The prevalence of T2DM is increased compared to the national average, with 50% (100,000/200,000) of the community affected.

Subject Eligibility and Recruitment Strategy

Inclusion criteria for study participants include the following: (1) aged at least 18 years, (2) being of Latinx origin speaking fluent Spanish, (3) self-report of type 2 diabetes, suboptimally controlled, defined as having HbA1c values of >7.0%, and (4) living with at least 1 adult family member who is willing to participate. Inclusion criteria of family members are as follows: (1) aged 18 years or older, (2) living in the same patient's residence, and (3) being of Latinx origin. Exclusion criteria include (1) type 1 diabetes, (2) pregnancy, and (3) significant cognitive impairment.

Participants were recruited from the outpatient primary care clinics of Olive View-UCLA Medical Center. Recruitment began by advertising the study using flyers in the primary care clinics. Interested individuals notified staff in the primary care clinic or the study coordinator. The study coordinator discussed the study and provided further information about the project. With the individual's permission, key relatives—significant others identified by the individual as among the most important people involved daily in his or her life—were contacted. Both the patient and the family member needed to provide informed consent for either to participate. Subject characteristics at baseline are depicted in Table 1.

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Table 1. Sample characteristics at baseline (n=330).

Variables	Overall	Nurse (n=165)	Promotore (n=165)	*P* value
Age (years), mean (SD)	55.33 (8.39)	55.65 (8.29)	55.01 (8.50)	.48
Education (years), mean (SD)	7.66 (4.21)	7.49 (4.03)	7.84 (4.39)	.46
Sex, n (%)				.27
Male	144 (43.64)	77 (46.67)	67 (40.61)	
Female	186 (56.36)	88 (53.33)	98 (59.39)	
Marital status, n (%)				.38
Never married	92 (27.88)	50 (30.30)	42 (25.45)	
Married	164 (49.70)	78 (47.27)	86 (52.12)	
Divorced	34 (10.30)	14 (8.48)	20 (12.12)	
Widowed	15 (4.55)	7 (4.24)	8 (4.85)	
Separated	25 (7.58)	16 (9.70)	9 (5.45)	
Employment, n (%)				.46
Full-time	41 (12.42)	22 (13.33)	19 (11.52)	
Part time	83 (25.15)	48 (29.09)	35 (21.21)	
Homemaker	64 (19.39)	29 (17.58)	35 (21.21)	
Retired	22 (6.67)	12 (7.27)	10 (6.06)	
Disabled	58 (17.58)	28 (16.97)	30 (18.18)	
Unemployed	62 (18.79)	26 (15.76)	36 (21.82)	

Characteristics and Training of DSME Leaders

The *promotores* were recruited from the workforce of Olive View-UCLA Medical Center (3 women and 1 man). They were of Hispanic origin and spoke fluent Spanish and English. The 3 RNs were employees at Olive View-UCLA Medical Center. All 3 spoke English and Spanish fluently. Two of the 3 RNs were of Hispanic origin. Both *promotores* and RNs were trained and certified in the Stanford Chronic Disease Self-Management program. This training included a 4-day onsite workshop in Palo Alto, California, followed by a cross-training webinar on diabetes self-management education and 2 sets of practice groups conducted at Olive View-UCLA Medical Center designed to ensure fidelity to the treatment model.

Initial Intervention: Tomando Control

The initial intervention, called "Taking Control of your Diabetes" or in Spanish "*Tomando Control de su diabetes*," consisted of 6 biweekly sessions lasting 2.5 hours each led either by 2 trained *promotores* (*promotore*-led group) or by RNs (RN-led group). Each session included 10-12 patients. Patients' families or friends were encouraged to attend sessions, which were held at Olive View-UCLA Medical Center. Each participant received a copy of the companion book, an audio relaxation tape, and an audio exercise tape with a booklet to supplement the material covered during the workshop sessions. The following topics were covered in sessions: (1) techniques to deal with the symptoms of diabetes and associated condition, (2) appropriate exercise, (3) healthy eating, (4) correct use of diabetes medications, and (5) working more effectively with health care providers in a collaborative partnership. Patients were expected to make weekly action plans, share experiences, and help each other solve problems they encountered in creating and carrying out their self-management strategies. The classes were highly participative and allowed participants to show mutual support and develop confidence in their abilities to manage their health. The program is based on the Stanford School of Medicine's Chronic Disease Management Program developed by Lorig et al [36] and culturally adapted by Mauldon et al [37]. Similar program content was delivered in each group, with the only difference being the type of trainer: *promotore* versus RN.

Early response status was determined after the third TC session (ie, 6 weeks after starting the intervention). An independent evaluator blind to study condition used the Summary of Diabetes Self-Care Activities (SDSCA) to assess diabetes self-management behavior. A subject was considered an early responder if he/she showed a gain of 50% over baseline on the SDSCA. Early responders continued to receive the TC intervention that they were originally assigned. Nonresponders, those subjects who did not show a gain of 50% over baseline, were rerandomized to receive either the stepped-up, family-focused TC approach or the MFG. The following sections describe these 2 interventions.

Second Intervention: Family-Focused TC Approach

For those subjects who were randomly assigned to receive the augmented TC, the TC clinician (either a *promotore* or nurse, depending on the original group assignment) conducted up to 3 home visits that were designed to explain the purpose of the TC intervention to a key relative so as to reengage the family member in the group process. Each visit was carefully scripted to address the family's role in helping the family member with

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diabetes. The first home visit was focused on the family's reaction to having a loved one with diabetes and was designed to elicit how the family functioning had changed since the diagnosis was made. The second session aimed to help the family set realistic goals for participation in TC including the length of the groups and the expectations of the family in using the material covered in the group to effect behavior change. Logistical details (eg, which family member would accompany the patient to the group, how they would get to the group, and so on) were identified and obstacles to attendance were resolved. The third session solidified the gains made in the first 2 sessions as well as emphasized to the family that the *promotore* or nurse was available for crises or problem resolution if last-minute difficulties arose prior to the TC group. These engagement strategies have been very effective in increasing the participation of family members in group therapy [38].

Second Intervention: Multifamily Problem-Solving Group Approach

Overview

The other treatment assignment for nonresponders to TC was MFG. As described by McFarlane [39], standard MFG consists of 3 components: three initial "joining" sessions conducted with each of the families separately, a 1-day (6 hours) educational workshop, and ongoing MFG sessions. In the MFG used in this project, the joining sessions and educational workshop were performed as described in the MFG manual. However, the ongoing multifamily sessions in this project differed from standard MFG in which it was explicitly organized around the obstacles to diabetes self-management identified in family interviews. Each MFG session included structured activities that ensured participation by all families in each content area, gave information, carried out problem-solving exercises, and provided skills training focused on increasing individuals' diabetes self-management behaviors.

Joining Sessions

The 3 joining sessions offered each family an individualized approach designed to facilitate the process of engaging in treatment. The sessions were conducted by a bilingual, bicultural *promotore* or nurse, depending on the subject's initial group assignment. The sessions were designed to familiarize all members of the family with the therapists who conducted the ongoing MFG sessions and to educate them about the need for ongoing treatment. The sessions also helped the family identify and overcome the obstacles to successful diabetes self-management. All family members were given the opportunity to describe their understanding of their ill relative's problem and were also given factual information based on current knowledge about diabetes.

Educational Workshop

The educational workshop is a 6-hour program that provides information about the etiology, biology, genetics, symptoms, and treatment of T2DM. Much of this material will be covered in the TC groups; however, the educational workshop was made available to those MFG family members who did not attend the TC sessions. It was conducted by the MFG clinician along with one of the authors (AK). They used the Spanish translation of the standardized videotape and coping skills guidelines developed by the author. The material is presented in basic, elementary school level Spanish with little use of idioms or colloquialisms. Presentations were made both visually and orally, including the use of role plays to allow family members with poor reading skills to adequately assimilate the material.

Ongoing MFG Sessions

Following the joining sessions and educational workshop, each cohort of 5-6 families met twice monthly for 3 months (6 sessions total). All sessions were co-led by the clinicians who conducted the 3 joining sessions. The first MFG session was focused on teaching problem-solving skills. Participants learned the mechanics of the problem-solving method and how to apply it to various problem situations. The method involves 7 steps as follows: define the problem, set goals, generate alternatives, evaluate each, select one, implement it, and evaluate outcomes. The subsequent 5 sessions were structured in the usual MFG fashion. This included a brief sharing period followed by group discussion. The discussion consisted of the sharing of personal experiences, identification of a problem situation, and the use of the problem-solving method to address the situation within the context of general group support. The group ended with review of the gains made by group members that week.

Data Collection and Measures

Table 2 lists the measures to be used at each assessment point. Assessments were done at baseline and at 3, 6, and 12 months. In addition, the primary outcome variable (ie, diabetes self-management behaviors) was measured 6 weeks after the start of the first phase of the study to determine progress over time and the need for a change in treatment strategy. All measures were collected by a research assistant blind to the experimental conditions. Characteristics of the sample were measured at the initial visit including various demographic and clinical information.

The primary outcome is the difference in response scores of the SDSCA between the 4 groups at 3, 6, and 12 months after baseline [40]. The SDSCA is a well-validated instrument with excellent psychometric properties in several languages including Spanish [41,42]. It is the instrument most frequently used for assessing the acquisition of diabetes self-management behaviors [43]. The SDSCA is formatted to ask on how many of the previous 7 days the individual performed recommended self-management activities: eating healthy foods, following a diabetic diet, exercising, self-monitoring of glucose, and caring for one's feet. A weekly self-care score ranging from 0 to 7 is generated, with higher scores corresponding to greater number of days carrying out the recommended behaviors.

Several secondary outcomes were also measured in this study. Diabetes self-efficacy, defined as the confidence of a person with diabetes to manage diet, exercise, track blood glucose levels, and overall control their diabetes, was measured using the 8-item Stanford Self-Efficacy Scale. Scores range from 1 (no confidence) to 10 (total confidence). The internal reliability of the Spanish language version of this measure is 0.85 [44]. Diabetes knowledge was measured using the Spoken Knowledge in Low Literacy Patients with Diabetes scale, a 10-item scale

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that assesses knowledge of glucose management, lifestyle modifications, recognition, and treatment of hyper- and hypoglycemia, and activities to prevent long-term consequences of the disease. Higher scores indicate better knowledge about diabetes, and the measure has been found to have excellent validity and reliability [45]. The patient's degree of family support was measured using the 17-item Diabetes Family Support Behavior Checklist, which uses a 5-point Likert scale to assess the patients' perceptions about their relatives' support in medication taking, glucose monitoring, exercise, and diet [46]. Cronbach αs have been reported between 0.64 and 0.71 in Hispanic subjects with diabetes [26,47]. Collaborative goal setting was measured with the Spanish version of the Patient Assessment of Chronic Illness Care [48], a 20-item survey for evaluating the quality and patient-centeredness of chronic illness care received by the patient according to the Chronic Care Model paradigm [49]. The Spanish language translation of this instrument has demonstrated high reliability, internal consistency, and test-retest reliability [50]. Treatment session attendance was assessed for both patients and their relatives, and the percentage of treatment sessions attended by the key relative was used to analyze relationships with other outcomes. Glycemic control, defined as HgA1c level, was tested using a Bayer A1C NOW kit (Bayer Healthcare) using finger stick blood taken by a phlebotomist. Levels greater than 7.0% are considered poor glycemic control, and levels greater than 10.0% are considered uncontrolled diabetes [51]. Height, weight, BMI, and blood pressure were measured using standard procedures.

Table 2. Study measures.

Variables	Measure	Content	Schedule[a]
Demographics	• UCLA Client Data Inventory • Cuellar acculturation scale • Structured Clinical Interview for DSM-IV (SCID-I)	Age, gender, marital status, work status, educational level, acculturation level, and medical/psychiatric disorders	T1
Diabetes self-management	• Revised Summary of Diabetes Self-Care Activities (SDSCA)	Assesses adherence to diet, exercise, self-monitoring, medications, and foot care	T1-T4 and week 6
Diabetes self-efficacy	• Stanford Self-Efficacy Scale	Measures confidence to self-manage diabetes	T1-T4
Diabetes knowledge	• Spoken Knowledge in Low Literacy Diabetes Patients (SKILLD)	Assesses knowledge of T2DM and its management	T1-T4
Family support	• Diabetes Family Support Behavior Checklist	Assesses family support for T2DM self-management	T1-T4
Collaborative goal setting	• Patient Assessment of Chronic Illness Care (PACIC)	Evaluates quality and patient centeredness of received treatment	T1-T4
Treatment attendance	• Treatment Attendance Log	The percentage of sessions attended by patient/relative	T3
T2DM control	• Bayer A1C NOW kit	Hemoglobin A1c level	T1-T4

[a]Data collection schedule: T1: baseline; T2: 3 months; T3: 6 months; T4: 12 months.

Statistical Analysis

Data analysis will be conducted by intent-to-treat with participants analyzed according to their randomized intervention regardless of attendance. Our primary analytical tool will be the generalized linear mixed model (GLMM) [52,53]. GLMMs accommodate multiple outcome types in a unified framework via an appropriate link function (identity link for continuous normally distributed measures; logistic link for binary measures); allow for both fixed and time-varying covariates; automatically handle missing data, producing unbiased parameter estimates provided observations are missing at random; and appropriately account for the correlations induced by repeated measurements within subjects. We will fit GLMMs with fixed effects for the intercept, time (baseline, 3, 6, and 12 months), group, and a group-by-time interaction term, where the definition of group depends on the hypothesis and an unstructured covariance matrix. Model diagnostics will be used to determine suitability of more parsimonious (eg, autoregressive) correlation structures and nonlinear (eg, quadratic) effects for time. A sample size of 330 patients will provide 90% power to detect a difference of 0.29 in the score of SDSCA between the study groups. Subgroup analysis will be performed to determine if some moderators differentially affect the outcome such as patients' age, gender, educational levels, duration of diabetes, and baseline HbA1c levels.

Ethics Approval

All participants signed an informed consent form. The trial protocol was reviewed and approved by the Institutional Review Board of the David Geffen School of Medicine at UCLA (#16-000434) and the Education and Research Institute of Olive View-UCLA Medical Center (#882988). Initial approvals were received in November 2016, and yearly renewal approvals were received throughout the course of the study. The 1-year follow-up assessments were completed in late 2021.

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Results

This study was funded by the National Institute of Nursing Research in June 2016 for a period of 5 years. Institutional review board approval was obtained in November 2016. Between March 2017 and September 2020, a total of 330 patients were recruited from the outpatient primary care clinics of Olive View-UCLA Medical Center, with a brief hiatus between May 2020 and July 2020 due to COVID-19 restrictions. The study interventions were completed in December 2020. Data collection began in March 2017 and was completed in December 2021. Data analysis is expected to be completed in Spring 2023, and results will be published in Fall 2023.

Discussion

Principal Findings

This paper describes the protocol of a sequential multiple assignment randomized trial to better understand how various factors in the design and implementation of a DSME program can affect the outcomes of participants with T2DM.

The first question we address is whether RNs are more effective than *promotores* in leading DSME programs for Latinx patients with T2DM. This study represents a direct test of the hypothesis that Latinx subjects assigned to RN-led groups will perform more diabetes self-management behaviors than subjects assigned to *promotore*-led groups. The findings of this aspect of the study could have important economic implications, particularly if subjects in RN-led groups do not achieve better outcomes than subjects in *promotore*-led groups because of the greater cost and lower availability of RNs than those of *promotores*.

The design of this study will also further our understanding of the efficacy of interventions that use MFGs and how these are compared with interventions that focus on individual families. The reasons that patients may fail initial DSME interventions are numerous and varied, such that it may be difficult for any individual educator—professionally trained or otherwise—to be able to address all barriers that arise for a patient. The incorporation of multiple families with similar backgrounds in the same community provides the opportunity for participants to offer their combined, cumulative perspectives and experiences in order to problem solve and support their peers. This is important not only because of the increased likelihood of identifying reasonable solutions but also because it could help build a stronger sense of self-efficacy and agency among participants while also decreasing stigma, shame, and isolation. Furthermore, because sessions are intended to address behaviors and beliefs among the entire family, we hope to gain additional insight into how these dynamics influence outcomes for participants in this program.

This study will also measure various demographic variables including age, gender, marital status, working status, educational level, acculturation level, comorbid medical and psychiatric disorders, and severity of diabetes. These will also be analyzed to explore whether particular characteristics of the sample can serve as potential predictors of outcomes.

Comparison to Prior Work

There have been some studies that compared outcomes of patients with T2DM when counseled by RNs versus community health workers (the equivalent of *promotores*). The randomized trial by Babamoto et al directly compared the effectiveness of community health workers with case management and standard provider care in Latinx patients with T2DM for 6 months. In that study, patients in the community health worker group performed better than the other groups in several outcomes, namely higher retention rates, greater reduction in HbA1c concentrations, and medication adherence [16]. Kim et al compared outcomes in Korean Americans with T2DM, finding that patients counseled by community health workers had greater decreases in HbA1c concentrations than RN-counseled patients [54].

Several other studies using different methodological approaches have shown that interventions led by community health workers were cost effective and result in substantial reductions in diabetes complications. Ryabov et al estimated that interventions led by community health workers could result in an absolute reduction in projected probability of lifetime occurrence of nephropathy by 5.9%, neuropathy by 3.4%, retinopathy by 2.6%, and coronary artery disease by 3.8% [55]. Moreover, Brown et al suggested that *promotores* were most cost-effective among Latinx patients aged 50-65 years [56]. The benefits of community health workers extend to other ethnicities. For example, Huang et al found that home visits conducted by community health workers were highly cost-effective in a randomized study of 268 patients with T2DM in American Samoa [57]. We expect that our study will be particularly useful in building on this knowledge because the educational programming is standardized between both groups, with all participants receiving the same evidence-based intervention.

Strengths and Limitations

Strengths of this study include its randomized design and inclusion of enough patients to allow for adequate statistical power and subgroup analysis. This study uses the SDSCA, which is a well-validated instrument to assess diabetes self-management behavior. It is the most widely used self-report instrument for measuring diabetes self-management in US adults [41]. In an appraisal of 26 psychometric tools of diabetes education, Eigenmann et al identified the SDSCA as 1 of 3 tools that met all expected criteria for validity, reliability, relevance, feasibility and acceptability, and responsiveness to change [58].

One potential limitation of this study is that the investigators were aware of the patients' group assignment, and therefore bias in favor of any particular group cannot be excluded. However, every effort was made to ensure blinding. For instance, *promotores* and RNs were not aware of the purpose of the trial. An independent evaluator blind to study conditions was responsible for administering all study measures. A second limitation is the short duration of the trial (ie, 6 sessions over 3 months). However, many years of clinical experience and research data suggest that 6 intervention sessions are sufficient to result in clinically significant changes in diabetes self-management behavior [59].

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Conclusions and Future Directions

The findings of this trial should contribute to our understanding of the roles of community health workers, RNs, and family members in this area and may have important economic implications. Future research will focus on understanding the factors that affect self-management for Latinx patients with T2DM and will provide valuable information toward constructing an adaptive intervention that will help to determine which treatment strategies work to improve diabetes self-management behaviors most efficiently and for whom. Given the ever-increasing prevalence of T2DM, achieving better control of diabetes and lowering the associated medical complications experienced disproportionally by Latinx patients is a public health priority for a group that has long been underserved by current research and practice.

Acknowledgments

This trial was entirely funded by the National Institute of Nursing Research (NIH grant R01NR015809).

Data Availability

Deidentified data will be made available to all appropriate requests from interested researchers at the time of results publication.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review reports from the Nursing and Related Clinical Sciences (NRCS) Study Section - Healthcare Delivery and Methodologies Integrated Review Group - Center for Scientific Review (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 155 KB - resprot_v12i1e44793_app1.pdf]

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Abbreviations

DSME: diabetes self-management education
GLMM: generalized linear mixed model
HbA1c: hemoglobin A1c

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MFG: multifamily group
RN: registered nurse
SDSCA: Summary of Diabetes Self-Care Activities
T2DM: type 2 diabetes mellitus
TC: Tomando control

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Protocol

A Web-Based Decision Aid for Caregivers of Persons With Dementia With Firearm Access (Safe at Home Study): Protocol for a Randomized Controlled Trial

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Abstract

Background: Firearm safety among individuals with Alzheimer disease and related dementias (ADRD) is an underdiscussed and underresearched concern in the United States, especially given the growing population of community-dwelling adults with ADRD. The “Safety in Dementia” (SiD) web-based decision aid was developed to support caregivers in addressing firearm access; the efficacy of SiD is unknown.

Objective: Through the SiD decision aid, the Safe at Home (S@H) study aims to support caregivers in making decisions about home safety that align with their goals and values, and behaviors regarding firearm access for persons with ADRD and firearm access.

Methods: The S@H study is a 2-armed randomized controlled trial to test the effect of the SiD decision aid on caregivers of community-dwelling adults with ADRD who have firearm access. S@H aims to recruit 500 ADRD caregivers (age ≥18 years, fluent in English or Spanish, and in the United States) through online or social media advertisements and through relevant organizations. Participants are randomized to view SiD or a control website at their own pace; all participants complete web-based questionnaires at baseline, 2 weeks, 2 months, and 6 months. The primary outcome is immediate preparation for decision-making; secondary outcomes include longitudinal decision outcomes and self-reported modifications to firearm access. The relative reach

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and effectiveness of each recruitment method (online/social media and through relevant organizations) will be assessed by examining differences in caregiver participation, retention rates, and relative cost.

Results: The study enrollment began in May 2022. As of December 2022, a total of 117 participants had enrolled.

Conclusions: The S@H study is the first randomized trial of a firearm safety decision aid for ADRD caregivers. The results from this study will inform how best to support caregivers in decision-making regarding firearm safety. Further, results may guide approaches for recruiting caregivers and for dissemination of resources.

Trial Registration: ClinicalTrials.gov NCT05173922; https://clinicaltrials.gov/ct2/show/NCT05173922

International Registered Report Identifier (IRRID): DERR1-10.2196/43702

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KEYWORDS

dementia; caregiver; firearms; decision aid decision-making; Alzheimers; ADRD; decision; storage; web-based

Introduction

Background

Approximately 5.8 million Americans—roughly 10% of all adults aged 65 years or older, and 17% of Hispanic older adults [1]—live with Alzheimer disease and related dementias (ADRD) [2]. Almost three-quarters of people with ADRD live in the community [2] supported by an estimated 16 million informal caregivers (eg, spouses or other family members) [2]. Caregivers face myriad concerns and demands, including daily safety considerations, financial management, and long-term goals of care. There is an urgent need for effective, acceptable interventions to support informal caregivers in decision-making and behavior change to act on those decisions, especially regarding home safety. Ideally, the development and dissemination of such interventions—to the broad, diverse community of informal caregivers—could help reduce caregiving burden, delay nursing home placement, and support aging in place [3].

Many ADRD caregivers face difficult decisions about when and how to address the sensitive topic of in-home firearms. In the United States, an estimated 33%-60% of people with ADRD have a firearm in the home [4,5], and 38% of ADRD caregivers identify firearms as an issue to address [4]. Approximately one-third of older Americans (≥65 years) own a gun [6]; yet in a large sample of older firearm owners, only one-fifth reported having a plan for securing, removing, or transferring firearms if they could not handle them safely [7]. For firearm access, caregivers worry about how to take action, questions relate to legal and logistic uncertainties, and lack of guidance [8]. In a national survey of caregivers, although the majority supported ADRD-relevant firearm safety counseling by health care providers, only 5% had ever received it [9]. Caregivers must balance safety concerns (of both the person with ADRD and those around them) with considerations about the person with ADRD's response (eg, anger) and logistics (eg, cost of various options).

Providing resources to caregivers regarding firearm safety is of particular importance due to increased risk of suicide and risk related to behavior changes associated with ADRD. In the United States, 70% of older adult suicides involve a firearm, and suicide risk is elevated among individuals with ADRD, especially in early ADRD [10-12]. The rate of suicide among individuals in a prospective cohort study following individuals in the 12 months after dementia diagnosis was 26.42 per 100,000 person years, totaling 705 deaths by suicide of which 63.3% (nearly 450 deaths) were completed by firearm [13]. Dementia also raises concerns about the safety of others given the behavioral changes that commonly co-occur with ADRD, including confusion and emotional volatility. Violence toward others occurs annually in approximately 1% to 3% of older adults with ADRD [14]. Regarding firearm safety, even among older adults with prior training and safe handling skills, unintentional ("accidental") firearm injuries can also occur due to impairments in judgment, dexterity, and memory [9].

Web-based resources have the potential to reach a broad range of caregivers. More than 75% of American adults aged 30-64 years use at least one social media platform, most commonly Facebook and Instagram among middle-aged and older adults [15]. Web-based support groups are a leading source of health information for people living with or caring for loved ones with chronic disease [16,17]. The National Institute on Aging's (NIA) Informal Caregiving Panel and Alzheimer's Disease Research Summit recommended the development of technologies to integrate evidence-based treatments and support caregivers in the context of ADRDs [18-20]. Internet tools offer the promise of reaching diverse groups across broad geographic regions and allow individualized timing and pace of use [21]. eHealth interventions for informal ADRD caregivers show promise [22-24], are cost-efficient [25], and offer a way to sustain caregiver engagement over time [23]. The privacy afforded by eHealth, already cited as important by ADRD caregivers [23], may be particularly critical for the sensitive topic of firearms. ADRD caregivers may also prefer at-home internet resources or interventions because of limited ability or time to travel to an intervention site (eg, due to being with a home-bound person) [26].

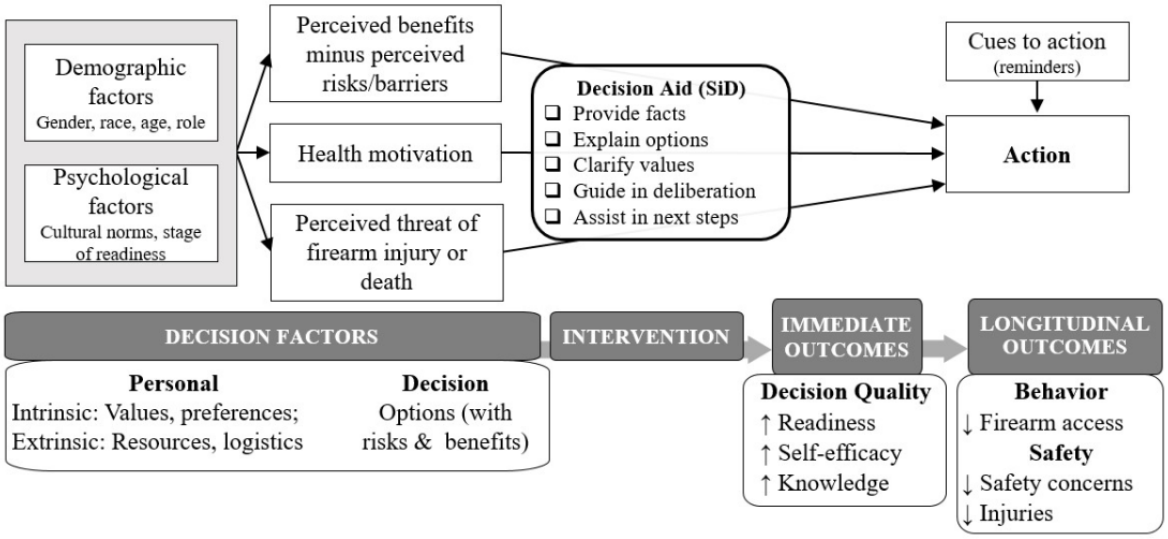
Prior Work

To address caregiver needs related to firearm access, and guided by theory [27-29], our team previously developed the web-based Safety in Dementia (SiD) decision aid [30], which is available for public use at no cost [31]. This web-based tool adheres to the International Patient Decision Aid Standards [29] and recommendations for user-friendly web design for older adults [32-34]. SiD is based on behavior change and decision-making theories [27,28] (Figure 1) and includes content to help

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caregivers understand options (with a balanced presentation of benefits and drawbacks) and then be motivated to take the action that works best for their situation. SiD provides parallel sections regarding driving safety and general home hazards to broaden reach and contextualize firearm safety, and the tool was designed in collaboration with partners from the firearms community. The SiD tool was translated into Spanish using a rigorous translation process including independent back-translation to English by certified translators with adjudication of any discrepancies [35,36]. The pilot trial of SiD, in a national convenience sample of caregivers of community-dwelling people with ADRD, found 44% of caregivers reported safety concerns regarding firearm access and approximately 30% were currently considering options for what to do about firearm access [37].

Figure 1. Theoretical framework of Safety in Dementia (SiD) immediate and long-term impact. Rectangles represent Health Belief Model. Ovals represent Ottawa Decision Support Framework and related measures.



Goal of this Study

The primary goal of the S@H study is to assess the efficacy of the SiD decision aid on caregiver decision-making and behaviors regarding firearm access in the home of the person with ADRD. The study hypothesis is that the decision aid will increase the preparation for decision-making and the self-efficacy of informal caregivers to make and implement decisions that effectively address firearm access, thereby reducing firearm injury risk.

Methods

Study Design

The S@H study is a 2-armed randomized controlled trial. The study protocol follows the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) Guidelines [38]. The trial will be conducted and reported according to 2 checklists: the CONSORT-EHEALTH (Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth; Multimedia Appendix 1) [39] and the SUNDAE (Standards for Universal Reporting of Patient Decision Aid Evaluation; Multimedia Appendix 2) [40].

Theoretical Framework

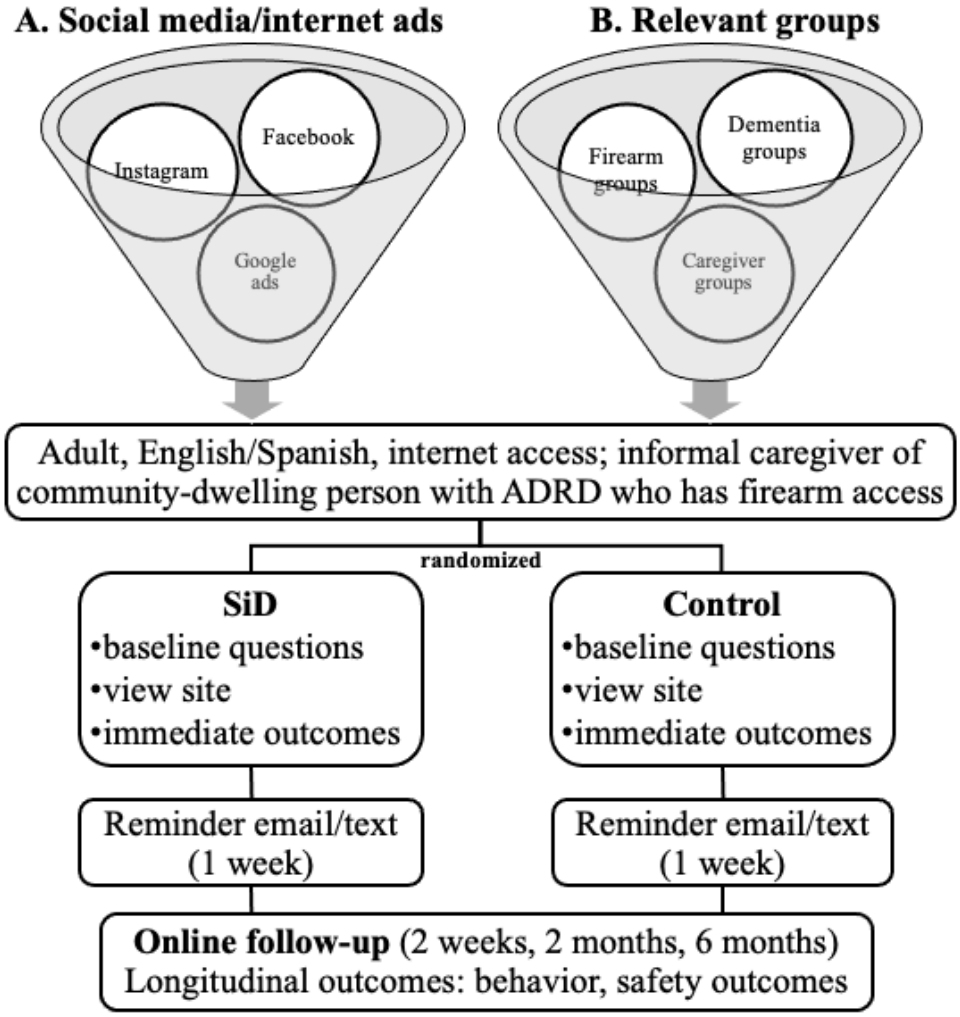
The SiD decision aid and the S@H study are based on the Ottawa Decision Support Framework (Figure 1) [27], which incorporates concepts from psychology, social support, self-efficacy, and decision conflict. The framework suggests that decisional needs (eg, conflict/uncertainty, knowledge, and values) affect decision quality, with a decision being higher quality when it is informed by and reflective of the person's values. Decision aids can increase decision quality by addressing decisional needs, by identifying the decision, by providing a balanced explanation of the risks and benefits of options, by helping clarify personal values, and by activating the individual for decision-making [29,41]. Decision aids improve communication and knowledge and decrease decisional conflict and regret [42]. Application of the Health Belief Model [28] further expands this theoretical framework for how decision aids encourage action.

Eligibility

Participants must be adults aged 18 years or older, who live in the United States, are fluent in English or Spanish, and identify as informal caregivers for a community-dwelling person with ADRD who has firearm access. "Community-dwelling" is defined as a person with ADRD living in a private home and not in any type of caregiving facility (Figure 2). Participants must have internet access but do not need to live in the same home (or state) as the person with ADRD. Those in legal custody or institutionalized are not eligible to participate.

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Figure 2. Study flow. ADRD: Alzheimer disease and related dementias; SiD: safety in dementia decision aid.



Recruitment

The S@H study aims to enroll 500 English- and Spanish-speaking caregivers through social media recruitment (including Facebook, Instagram, and Google ads) and relevant organizations in dementia/caregiver support, aging, and firearms. Social media postings are designed by the study team and then enhanced, implemented, and tracked by a digital marketing organization. Social media advertisement campaign parameters are set and modified to maximize reach and click-throughs, per standard web-based advertising practice; advertisements are iteratively adjusted for adequate gender and age diversity throughout the study.

Recruitment is also conducted via direct email through relevant organizations in dementia/caregiver support, aging, and firearm organizations, including web-based research databases like ResearchMatch and TrialMatch. Direct personal contact is made with relevant organizations by the study team and through the guidance and professional relationships of the Expert Advisory Panel. Study staff post advertisements directly (eg, in ResearchMatch) or send organizational representatives a toolkit with a sample text for inclusion in organization-generated newsletters, listservs, and flyers, on websites, and so on; sample social media content; and social shareables (images and informational graphics). The research team follows up 1 week after sending the media toolkit to inquire about the use of materials and to provide support as needed.

All advertisements contain similar messages and direct individuals to a landing webpage with a description of the study and identification of the lead organization (University of Colorado). The study has separate, identical landing web pages for each recruitment method and subgroup to allow tracking of overall analytics and participation by recruitment modality. There are 12 landing pages in total: 6 pages in English and 6 pages mirrored in Spanish. At each landing page, interested individuals can complete a brief web-based eligibility form. Those who choose to stop participation at any time or who are ineligible are provided with the hyperlink for the control (the NIA Home Safety Checklist for Alzheimer's Disease website, described below [43]).

Potential participants who are eligible based on the web-based form provide their contact information, and study staff then contact them by phone to validate identity (to reduce fraud or bot enrollment) and review eligibility and informed consent (Multimedia Appendix 3). For eligible, interested individuals, a study team member performs the randomization in REDCap (described below) [44,45] and emails or texts, depending upon preference indicated by the participant, the web-based survey link for the baseline assessment. Participants complete the

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survey at a time and in a place of their choosing, on a computer or other web-enabled device, and at their own pace, allowing them to stop and come back to the survey.

Participants complete a set of web-based questionnaires before viewing the SiD decision aid or the control website (Figure 2, Table 1). After reviewing the website for as long as they want, participants complete a second set of web-based questionnaires with questions about the preparation for decision-making, self-efficacy, and knowledge (Table 1). One week after the baseline session, participants receive a text or email reminder (depending on their preference) with a hyperlink to the website to which they were randomized so they may visit it again if desired. Subsequent follow-up (at 2 weeks, 2 months, and 6 months) occurs via web-based surveys that are sent to participants. Participants receive incentives for each completed study survey (US $40 for baseline, US $60 for 2 weeks, and US $40 each for 2 and 6 months).

The study flow follows the SPIRIT template of recommended content for the schedule of enrollment, interventions, and assessments [38].

Table 1. Study flow for caregivers.

	Timepoint[a] (months)					
	Enrollment	Allocation	Postallocation			Close-out
	$-t$	t_0	t_0	$t_{2\ weeks}$	$t_{2\ mo}$	$t_{6\ mo}$
Enrollment						
Web-based eligibility screen	✓					
Phone screen by staff	✓					
Informed consent	✓					
Randomization		✓				
Interventions						
Safety in dementia or control website		✓				
Assessments						
Immediate outcomes						
Preparation for decision-making			✓	✓	✓	✓
Decision self-efficacy scale		✓		✓	✓	✓
Longitudinal outcomes						
Action to reduce firearm access		✓		✓	✓	✓
Firearm access		✓		✓	✓	✓
Subgroups						
Firearm injury/near-injury		✓		✓	✓	✓
Zarit caregiver burden				✓		
Positive aspects of caregiving scale				✓		
Stage of decision-making		✓		✓	✓	✓
Other covariates						
PWD[b] demographics		✓				
PWD characteristics		✓		✓	✓	✓
Revised memory and behavior checklist		✓		✓	✓	✓
Caregiver demographics			✓			
AD8[c] Dementia severity		✓				
Social media usage				✓		

[a]$-t$: pre-screening; t_0: baseline survey; $t_{2\ week}$: 2-week survey; t_{2mo}: 2-month survey; t_{6mo}: 6-month survey.

[b]PWD: person with dementia.

[c]AD8: aging and dementia 8-item scale.

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Randomization and Blinding

Enrolled participants are randomly assigned in equal numbers to the SiD intervention or control arm (Figure 2). Randomization is stratified between recruitment group A (social media or internet) and group B (relevant organizations). To reduce bias and aim for balance across arms, participants are randomized into blocks of undisclosed size. The team biostatistician conceals allocation using a centralized, computer-generated list in REDCap [46]. The study team's principal investigator and one of the biostatisticians are blinded; other members of the study team are unblinded. Participants are blinded to their study arm assignment.

Description of Intervention

In the intervention arm, participants are directed via hyperlink to the SiD decision aid. Participants may view the site in the format they prefer (eg phone, computer, and tablet) and are recommended to view the site for at least 5-10 minutes but may view it for as long as they want. Like other decision aids, SiD guides the participant through the decision process to promote person-centric consideration of values and preferences [47].

Description of Control

In the control arm, participants are directed via hyperlink to the NIA Home Safety Checklist for Alzheimer's Disease website [43]. Similar to the intervention arm, participants in the control arm may view the site in the format they prefer (eg, phone, computer, and tablet). The control (NIA website) represents typical care, as it is an easily accessible website that consistently appears in the top 5 results of a Google search for "home safety dementia" and provides basic education about home safety in the context of dementia [43]. The checklist provides limited guidance on firearms ("*Lock up or remove these potentially dangerous items from the home: ... Guns and other weapons, scissors, knives, power tools, and machinery*") [43] without information about specific locking or disposal options. Unlike the intervention, the NIA website does not guide the individual through the decision or promote person-centric consideration of values and preferences, making it an appropriate control [47].

Primary and Secondary Outcome Measures

Primary Outcome

The primary outcome is the effect of SiD on preparation for decision-making, a core element of the Ottawa Decision Support Framework [27] as a precursor to behavior change (Figure 2). A high-quality decision is defined as an informal caregiver making an informed decision consistent with their values [48,49]. The Preparation for Decision-Making Scale assesses the perception of how useful a decision aid is in preparing for subsequent decision-making. Scores range from 1 to 5, calculated from the average of 10 constructs (each ranging from 1: "strongly disagree" to 5: "strongly agree"). The scale has total test reliability of 0.944 [50].

A secondary immediate outcome is decision self-efficacy (self-confidence or belief in one's capability to make decisions), measured using the decision self-efficacy scale [51], as decision aids typically increase self-efficacy [52]. Transformed scores range from 0 (extremely low) to 100 (extremely high self-efficacy). In the SiD pilot trial, participants had a mean score of 77.6 (SD 17.2) after viewing the SiD firearm section [37] (Table 1).

Longitudinal Outcomes

Additional outcomes, also linked to our theoretical framework (Figure 1), are in Table 1. Firearm access (and actions to reduce access) for the person with ADRD is assessed with existing multipoint scales [52,53], with binary categorization (any access to ≥1 firearm versus no access to any firearms) and progression toward reduced access (eg, locking of additional firearm). This allows the identification of smaller, albeit important, changes. Firearm injury or near-injury in the person with ADRD or others in their home is assessed through questions about recent experiences (including incidents of threats with a firearm or "near-misses") and perceived risks. Caregiver burden is measured by the short-form (3-item) Zarit Burden Interview [24,54,55]. Benefits of caregiving are measured by the Positive Aspects of Caregiving Scale [56-58]; scores range from 0 to 36, calculated from the sum of 9 items (measured on a 5-point scale ranging from 0: "disagree a lot" to 4: "agree a lot"), with higher scores indicating positive experiences.

Other Covariates

Caregiver characteristics include basic demographic characteristics like participation language (English/Spanish) age, gender, race/ethnicity, living situation (marital status, income, and urban/rural), and education. The characteristics of a person with ADRD (as reported by the caregiver) include age, gender, race/ethnicity, and living situation (marital status, income, and urban/rural). Dementia severity and course over time will be measured using the validated caregiver-reported aging and dementia 8-item scale Dementia Screening and Revised Memory and Behavior Checklist. The characteristics of the caregiver relationship to person with ADRD include the type of relationship (eg, spouse and nonrelated friend) and living situation (together or apart; if apart, proximity).

Study measures pertaining to the stages and quality of decision-making are based on validated measures currently available in the literature. Validated measures in Spanish were available for more than half of the English measures. For measures which were not available in Spanish, translation followed a forward and back translation process used throughout the study, incorporating similar phrasing and structure of other validated measures when possible.

Additional Measures

The approximate cost per enrolled participant will be calculated based on advertising costs and fees, and staff time. Website analytics will also be analyzed for each recruitment group and subgroup randomized to SiD, measures will include average time spent on SiD (mean and SD, median, and IQR) and pages viewed.

Data Monitoring

The study team will work with a Data Safety Monitoring Board, along with the IRB and the NIA, to monitor participant safety, evaluate study progress, review procedures for maintaining the confidentiality of data, and ensure the quality of data collection,

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management, and analyses. The following adverse and serious adverse events are monitored: any kind of negative interaction from intervention (eg, verbal disagreement or physical fight), increased stress due to actions taken to reduce firearm access for a person with dementia, physical injury sustained during actions to reduce firearm access for a person with dementia, suicide ideation or attempt in caregiver or individual with dementia, hospitalization due to emotional factors (stress, depression, suicidal, or homicidal ideation or intent), or hospitalization or surgery for a physical injury sustained during actions to reduce firearm access for a person with dementia. Each adverse event is graded by severity and relationship to intervention.

Data Collection

All participant-level data are collected and stored using self-reported, web-based questionnaires through REDCap [22,44,45]. Additional data are obtained through analytic reports provided by the digital marketing firm for each of the unique landing pages and web-based eligibility forms, while these sites will be identical, they will separate the trial participants by their origin of enrollment (group and subgroup). Website analytics will be analyzed at the level of groups or subgroups, as it will not be possible to identify individual participants from their website usage (eg, they do not login to a site or have other markers of identity). For social media and internet advertisements, ad impressions, click-throughs, and enrollment will be tracked and analyzed.

Statistical Analysis

Descriptive statistics will be computed for baseline caregiver characteristics (including key covariates, Table 1), reporting on differences between (1) intervention arm, (2) follow-up status, and (3) recruitment modality. To test the primary hypothesis that SiD increases immediate decision quality compared to control, we will test for a difference in the adjusted mean Preparation for Decision Making score at baseline after viewing SiD or control using multiple linear regression (MLR), with adjustment for baseline characteristics (eg, age, gender, caregiver burden, and severity of ADRD). Other components (decision quality, decision self-efficacy, and knowledge) will be analyzed similarly. To assess longitudinal end points, linear mixed models will replace multiple linear regression to assess changes in self-efficacy and knowledge over time by treatment arm, allowing an interaction of treatment arm and time [59,60]. Substantial efforts will be made to minimize missing data in data collection, and our models will adjust for covariates associated with drop-out to attenuate bias. If necessary, we will also use methods such as multiple imputation, pattern mixture models, or sensitivity analyses, following intent-to-treat principles [61].

To test the secondary hypothesis that SiD increases the odds that action is taken to reduce firearm access, a binomial-family logit-link generalized linear mixed models will be used with subject-specific random effects to account for correlations across measurements from the same individual and with fixed effects to adjust for baseline characteristics. The interaction between intervention and time will be tested to assess if the effect of SiD varies over time. We will use interaction terms to identify potential differential effects of treatment according to age, whether the caregiver lives with the person with ADRD (vs not), and recruitment group. Exploratory heterogeneity of treatment effect will also be conducted by caregiver gender, urban versus rural residence, and language (English vs Spanish). Additionally, we will examine longitudinal change in caregiver burden and reported safety concerns, and how these might affect treatment effects. Both multiplicity-adjusted and unadjusted *P* values will be presented for these comparisons.

We will use analytics from the eligibility screening websites to estimate the proportion of individuals who were eligible by recruitment modality, including separately by language, the proportion of eligible individuals who enrolled, and the rate of recruitment. The cost of recruitment per participant will be calculated based on advertising costs, fees paid to organizations, and estimates of study staff time [62,63]. Finally, among SiD participants, we will compare minutes on-site and trial retention at 6 months across recruitment modalities. Covariates will be included in multivariable models if they are associated with dropout, hypothesized a priori to be adjusted for, or if their inclusion improves the overall model's Akaike information criterion. If there is evidence that normality assumptions have been violated, appropriate transformations will be used, or the appropriate link function (eg, logit link for dichotomized measures).

Power

The target sample size for this study (n=500), which includes recruitment via social media (n=250) and relevant organizations (n=250), was powered conservatively for the primary outcome to allow comparisons by recruitment groups and other participant characteristics. In the pilot trial of 15 caregivers, the mean Preparation for Decision Making scores (using 9 constructs) was 3.9 (SD 0.7) after SiD versus 3.6 (SD 0.2) in the control group; this corresponds to a standardized effect size of 0.42 (3.9 vs 3.6 with a pooled SD of 0.7; d=0.3/0.7=0.42) [37,64]. Based on a *t* test, with the proposed sample size of 500 participants, the analysis will be able to detect a d=0.42 effect size with a very high power of >99% (α=.05) between SiD and control for the primary outcome (preparation for decision-making). Even if the effect is smaller (eg, d=0.30) and the sample size is 80% (400 in total), the power remains high at 84.9%. With a sample size of 500, there will be 125 in each of the final four analytic groups (stratified by recruitment group A vs B, SiD vs control). This sample will yield 80% power to detect any subgroup-specific standardized effect of d=0.36 or greater between SiD and control, including by recruitment group and other participant characteristics (using a *t* test and assuming sample sizes of 125 in each subgroup). Power calculations were computed using R version 4.0.2 (R Foundation for Statistical Computing) [65].

Ethics Approval

This study was approved by the Colorado Multiple Institutional Review Board (COMIRB) (21-4084). All study procedures and documents were reviewed and approved under Expedited Review, Category 7, by COMIRB. COMIRB approved a waiver of written documentation of informed consent and Health Insurance Portability and Accountability Act authorization. The

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S@H trial is registered with ClinicalTrials.gov (ClinicalTrials.gov NCT05173922).

Results

This study was funded in December 2021. Data collection began in May 2022. As of December 2022, 117 participants have been enrolled in the study. This study will test the efficacy of the SiD web-based decision aid in decision-making among ADRD caregivers. Anticipated findings from this study include participant reports of increased preparation for decision-making and greater alignment of decision-making with their goals and values for all study participants; a higher degree of change is anticipated among participants randomized into the SiD decision aid arm. Further, this study anticipates effects on longitudinal decision outcomes including self-reported modifications that caregivers have made to firearm access for persons with ADRD. This study will also contribute to knowledge regarding effective tools for web-based recruitment methods, especially for ADRD caregivers.

Discussion

Principal Findings

This study aims to address the need for access to effective resources to support ADRD caregivers in decisions about firearm safety. Caregivers make important decisions regarding ADRD care, including home safety. Additional guidance—such as through SiD, if it is found effective—could help align decisions with caregiver goals and values, especially regarding difficult and under-discussed topics such as firearm injury prevention.

Strengths and Limitations

Collaborative, nonjudgmental approaches to firearm injury prevention show great promise. A major strength of the SiD decision aid and this study is that they were developed with ideas and recommendations of individuals from the firearms community, including range owners, retailers, and firearm instructors. Such early—and ongoing—stakeholder engagement will help optimize intervention acceptability and effectiveness [66]. Many firearm owners have strong beliefs in self-determination and individual liberty [67,68], which are reflected in many of the same philosophical tenets underpinning shared decision-making more broadly [69]. A culturally sensitive intervention may allow caregivers to more fully and autonomously explore options [70]. An intervention that is responsive to cultural factors and personal values may also have higher acceptability and uptake than historical approaches to promoting firearm safety, which are clinician-delivered and include “one size fits all” recommendations to all firearm users. SiD is the first such tailored intervention for firearm safety in ADRD.

The varied methods of recruitment of ADRD caregivers across the United States is another strength of this study. The prevalence of digital-only or digital/in-person hybrid trials has increased during COVID-19. However, the effectiveness and representativeness of digital recruitment remain under debate. In particular, for sensitive issues like ADRD and firearm safety, it is essential to rigorously evaluate the success and equity of novel recruitment methods. The final sample may not generalize to all ADRD caregivers, given the language restriction (English and Spanish) and the need for access to and ability to use web-based technology. Those who participate in a study may also be different from the general population of ADRD caregivers.

Future Directions

“Designing for dissemination” in interventions can promote real-world use [71]. The SiD decision aid and study design were guided by a desire to disseminate effective, acceptable interventions to support diverse caregivers, and reduce firearm injury among older adults. Translation into real-world application is central to the research design of the S@H study, which aims to evaluate tools and processes that are concurrently easy to implement and responsive to the needs of all involved [72], from caregivers who might use the tool, to older adults with ADRD themselves, to service providers who may recommend it to families, to firearm retailers and advocacy groups seeking to educate their communities [71,73]. Should the tool prove effective in the study, future work should examine its dissemination through formal and informal channels.

Conclusions

The S@H study is the first national randomized trial to evaluate a firearm safety resource for ADRD caregivers. This study will provide information on the efficacy of the SiD decision aid as well as insights on how to recruit caregivers in a national, web-based trial.

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Data Availability

Requests for data from other researchers and the public will be considered, and data will be made available in accordance with local institution policies, Institutional Review Board (IRB) recommendations, local/state/federal laws and regulations, and considerations for publication. Any applicable data sharing will follow Health Insurance Portability and Accountability Act rules.

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Conflicts of Interest

MLR declares the following conflicts: grants from the Center for Disease Control (CDC) and the National Institutes of Health (NIH); unpaid Senior Strategic Advisor to the American Foundation for Firearm Injury Reduction in Medicine (AFFIRM) at the Aspen Institute; unpaid Board of Directors for the NonViolence Institute of Rhode Island 2022.

Multimedia Appendix 1
CONSORT-eHEALTH (V 1.6.1) checklist.
[PDF File (Adobe PDF File), 1106 KB - resprot_v12i1e43702_app1.pdf]

Multimedia Appendix 2
SUNDAE (Standards for Universal Reporting of Patient Decision Aid Evaluation) Checklist for evaluation studies of patient decision aids.
[PDF File (Adobe PDF File), 180 KB - resprot_v12i1e43702_app2.pdf]

Multimedia Appendix 3
Informed consent language.
[DOCX File , 43 KB - resprot_v12i1e43702_app3.docx]

Multimedia Appendix 4
External grant review from the Firearm Injury and Mortality Prevention Research - National Institute on Aging (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 89 KB - resprot_v12i1e43702_app4.pdf]

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Abbreviations

ADRD: Alzheimer disease and related dementias
COMIRB: Colorado Multiple Institutional Review Board
CONSORT-EHEALTH: Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth
NIA: National Institute on Aging
S@H: safe at home study
SiD: safety in dementia decision aid
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
SUNDAE: Standards for Universal Reporting of Patient Decision Aid Evaluation

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Protocol

A Peer-Led Digital Intervention to Reduce HIV Prevention and Care Disparities Among Young Brazilian Transgender Women (The BeT Study): Protocol for an Intervention Study

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Abstract

Background: The HIV epidemic continues to disproportionately burden marginalized populations despite the availability of effective preventive and therapeutic interventions. Transgender women are severely affected by HIV worldwide including in Brazil and other low- and middle-income countries, with evidence of increasing new infections among young people. There is an urgent need for youth-specific HIV prevention and care interventions for young transgender women in Brazil.

Objective: This study aims to (1) address stigma in the Brazilian public health system and (2) reduce barriers to HIV care and prevention with systems navigation among young transgender women aged 18-24 years in Rio de Janeiro, Brazil.

Methods: The *Brilhar e Transcender* (BeT) study is a status-neutral, peer-led, single-arm digital intervention study enrolling 150 young transgender women in Rio de Janeiro, Brazil. The intervention was pilot tested and refined using data from a formative phase. The BeT intervention takes place over 3 months, is delivered remotely via mobile phone and in person by peers, and comprises three components: (1) BeT sessions, (2) digital interactions, and (3) automated messages. Eligibility criteria include identifying as transgender women, being aged 18-24 years, speaking in Portuguese, and living in the Rio de Janeiro metropolitan area in Brazil. The primary outcomes are HIV incidence, pre-exposure prophylaxis uptake, linkage to HIV care, and viral suppression. Primary outcomes were assessed at baseline and quarterly for 12 months. Participants respond to interviewer-based surveys and receive tests for HIV and sexually transmitted infections.

Results: The study has been approved by the Brazilian and the US local institutional review boards in accordance with all applicable regulations. Study recruitment began in February 2022 and was completed in early July 2022. Plans are to complete the follow-up assessment of study participants on July 2023, analyze the study data, and disseminate intervention results by December 2023.

Conclusions: Interventions to engage a new generation of transgender women in HIV prevention and care are needed to curb the epidemic. The BeT study will evaluate a digital peer-led intervention for young transgender women in Brazil, which builds on ways young people engage in systems and uses peer-led support to empower transgender youth in self-care and health promotion. A promising evaluation of the BeT intervention may lead to the availability of this rapidly scalable status-neutral HIV intervention that can be translated throughout Brazil and other low- and middle-income countries for young transgender women at high risk of or living with HIV.

Trial Registration: ClinicalTrials.gov NCT05299645; https://clinicaltrials.gov/ct2/show/NCT05299645

International Registered Report Identifier (IRRID): DERR1-10.2196/44157

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KEYWORDS

youth; transgender women; Brazil; HIV prevention; HIV care; peer-led digital intervention

Introduction

Efforts to end the HIV epidemic by 2030 will not be possible without enhanced efforts to prevent new infections among youths and young adults [1]. Despite the availability of effective HIV care and prevention interventions, reductions in HIV prevalence have stalled, in part, owing to the lack of progress in reducing new infections among youths, especially those in low- and middle-income countries (LMICs) where most new infections are acquired. Innovations in HIV interventions have also failed to adequately reach marginalized populations most affected by HIV [2]. Transgender women are one of the most severely affected populations by HIV worldwide [3]. Brazil has a concentrated HIV epidemic with a 0.4% prevalence in the general population [4] with over 900,000 people living with HIV in the country [5] and the highest prevalence among transgender women who have sex with men [6,7]. Within the population of transgender women, young transgender women are at high risk for HIV and poor HIV care outcomes. The first respondent-driven sampling-based study of HIV risk and pre-exposure prophylaxis (PrEP) awareness among Brazilian transgender women identified that 24.2% of youths aged 18-24 years were living with HIV. Young transgender women also had lower knowledge of HIV prevention strategies (including PrEP) and higher HIV risk than their older peers, with 3 times as many unrecognized infections than adults [8]. These findings are worse than those reported in prior research, suggesting that 1 in 5 young transgender women were infected with HIV before having been aged 25 years [9,10].

Global data reflect a lack of incident infection decline among youths and point to a need for early intervention to curb risk among young transgender women [11]. In a study conducted from 2018 to 2020 using the Limiting Avidity assay as part of a recent infection testing algorithm, the annualized HIV incidence rate was 7% overall and 9% among transgender women [12]. In the largest PrEP demonstration study in Latin America, which enrolled a total of 9509 people, young and transgender participants had lower odds of long-term engagement in PrEP [13].

The Brazilian Public Health System (Sistema Único de Saúde) ensures universal and equitable provision of health care to the whole population; their approach toward the HIV epidemic was human rights–based and science-driven, integrating both prevention and treatment efforts into the Brazilian universal health care system and including a fundamental role of social movements advocacy. Brazilian regulations guide public health services to use social names (ie, names that transgender people use that are different from what is on their government-issued identification) and requested pronouns for them. Despite these protections, discrimination toward transgender people in the Brazilian Public Health System is well documented. For young transgender people, discrimination exacerbates common youth-related barriers to HIV prevention and care. Previous Brazilian research identified stigma as a critical roadblock to HIV prevention and care for transgender women [14,15]. Much like research from the United States, transgender women in our Brazilian study reported experiencing antitransgender stigma in the health care system [6,16-19], and most attributed their underuse of medical care to stigma [6,14]. Transgender people are known to postponing necessary care owing to experiences of and anticipation of discrimination [20,21]. Low health care usage may be the reason underlying very low awareness of PrEP in our US-based research with young transgender women [22]. Young transgender women face the challenge of addressing medical needs related to their gender identity, which compounds typical adolescent development [9,23-25]. For youths, health literacy, systems navigation, and low risk perception are barriers to HIV testing and linkage to HIV care [26-28].

The lack of interventions among young transgender women presents a troubling outlook to the HIV epidemic for young Brazilian transgender women. Overall, most interventions with transgender women focused on those already living with HIV [29]. The few primary prevention interventions are limited to pilot studies of small group sessions that combine didactic and participatory learning, with no information gathered on HIV incidence and risk behavior. Only one intervention has been developed and has shown efficacy for increasing HIV-related preventive behavior among young transgender women [30]. No known interventions have been developed to increase HIV care outcomes among young transgender women. Our data point to an urgent need for youth-specific HIV prevention and care interventions for young transgender women in Brazil. To address limitations in availability of HIV prevention and care interventions for young transgender women, we designed the *Brilhar e Transcender* (BeT [“shine and transcend” in English]) study, which combines a social marketing campaign to address antitransgender stigma in health services toward transgender women and an adapted evidence-based, HIV status–neutral intervention that uses peer-led digital and in-person systems navigation. Our primary aims are to (1) address stigma in the Brazilian public health system, (2) intervene to overcome youth challenges with health care systems navigation, and (3) implement our intervention among young transgender women aged 18-24 years in Rio de Janeiro, Brazil.

Methods

Study Design

The BeT study is one of 8 sponsored research projects chosen to be a part of a Eunice Kennedy Shriver National Institute of Child Health and Human Development–funded Prevention and Treatment through a Comprehensive Care Continuum for HIV-affected Adolescents in Resource Constrained Settings (PATC^{3}H) consortium [31], which conducts clinical research and evaluation of a variety of combination interventions to improve health outcomes among adolescents at risk for HIV

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and youths living with HIV in resource-limited settings. The BeT study is the only PATC^{3}H project conducted in Latin America and among transgender youths and builds on decades of research and community engagement with transgender communities. The BeT study is a peer-led, digital-based intervention study aiming to enroll 150 young transgender women in Rio de Janeiro, Brazil.

Eligibility Criteria

Inclusion criteria are (1) having been assigned the male sex at birth and self-identifying as *travesti*, a transgender woman, or having a gender identity different from identities typically associated with the assigned sex at birth; (2) being aged between 18 and 24 years; (3) providing consent for study participation; (4) living in Rio de Janeiro or the greater metropolitan area; and (5) being sexually active. Additional criteria for HIV-negative individuals include (1) no current PrEP use, (2) PrEP indication per Brazilian standards of care, and (3) no PrEP contraindication. For participants living with HIV, additional inclusion criteria are (1) having a confirmed HIV diagnosis, (2) not currently using antiretroviral therapy (ART) or having a detectable viral load and treatment that is not linked to HIV care.

Exclusion criteria include participation in any HIV prevention or care intervention study in the last year, refusal to undergo HIV testing, or having any health condition that, in the opinion of the investigator, precludes participation in the study or may lead to harm to the participant.

Formative Phase

The study had a formative phase, which comprised developing and implementing an antistigma campaign, and adaptation and pilot testing of the system navigation intervention [32]. The campaign content included information on basic gender definitions (sex, gender identity, gender expression, and sexual orientation), regulations linked to gender and sexual orientation minorities, the medical transition process, overview of mental health and hormone therapy among transgender people, transphobia and violence against transgender people, and HIV among transgender women (Figure 1). The antistigma campaign, focused on health care settings, clinical providers, and support staff, took place at 4 health clinics serving transgender women in Rio de Janeiro, Brazil. We collected pre- and postcampaign qualitative and quantitative data with providers (N=10) to assess whether antitransgender stigma beliefs and attitudes changed among providers and support staff.

We also conducted formative qualitative interviews with 10 young transgender women (mean age 22.2 years) to inform the development of the pilot intervention. The BeT study uses an effective US Centers for Disease Control and Prevention intervention called *Anti-Retroviral Treatment and Access to Services* for system navigation and linkage [33,34]. Three components of the intervention required adaptation: (1) content of the Anti-Retroviral Treatment and Access to Services intervention session plan and asynchronous interactions with young transgender women, (2) adaptation to the cultural context of Brazil, and (3) the digital interface. Ten young transgender women were recruited through community outreach by our community engagement specialists (n=2) and through referrals from other studies at Fiocruz (n=8).

The BeT study pilot-assessed the intervention's preliminary efficacy among 20 participants. Results from the pilot intervention demonstrated preliminary efficacy for improving HIV prevention and care behaviors among young transgender women, as all HIV-negative participants were engaged in PrEP and all but one participant living with HIV became virally suppressed [32]. After the pilot phase, the team refined the intervention, which focused on streamlining the adapted intervention manual to improve peer navigator and participant accessibility. In addition, the team added additional medical monitoring to include important biomarkers of sexual health and HIV as part of the study protocol.

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Figure 1. The antistigma campaign material of the *Brilhar e Transcender* study.



Study Procedures and Measures

Table 1 describes the study procedures. Potential participants are recruited by a community education team, through word of mouth, and via referrals from enrolled participants. Recruitment also occurs at the HIV prevention services based at our site and at an on-site mobile legal unit that offers weekly access to free legal services for transgender people.

Participants have 5 in-person encounters at the National Institute of Infectious Diseases Evandro Chagas, Fiocruz, including a screening and enrollment visit followed by 4 quarterly visits (at weeks 12, 24, 36, and 48). The BeT intervention takes place between the enrollment visit and the 12-week visit and is completed within that time frame. Trained staff conduct interviewer-administered surveys to participants at all study visits.

At baseline, all participants respond to a screening questionnaire and demographic information, after signing the written informed consent form. Baseline and quarterly survey content build upon questionnaires previously developed and tested with transgender women in Brazil and in the United States, as described in Table 2. During follow-up visits, we will collect information on study outcomes: HIV incidence, PrEP uptake and adherence among HIV-negative participants, and linkage to HIV care and viral load suppression among those living with HIV. In addition, we will also collect data on implementation science outcomes: (1) maintenance (pre- and poststudy) for study coordination, feasibility (poststudy) for peer health navigators, and feasibility, acceptability, and appropriateness (poststudy) for study participants.

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Table 1. Measures of the *Brilhar e Transcender* study.

Measures	Time frame	Source
Demographics	Baseline	Grinsztejn et al [6]
Transitioning process	Baseline and quarterly	Grinsztejn et al [6]
Food insecurity	Baseline and quarterly	Adapted from the Food and Agriculture Organization of the United Nations [35]
Substance use		
Alcohol Use Disorders Identification Test for alcohol consumption (3 items)	Baseline and quarterly	Bush et al [36]
Alcohol, Smoking and Substance Involvement Screening Test	Baseline and quarterly	World Health Organization [37]
Stigma and discrimination (including transgender-specific health care discrimination)	Baseline and quarterly	Grinsztejn et al [6], Costa et al [15], and Scandurra et al [38]
Violence	Baseline and quarterly	Grinsztejn et al [6]
Overall health issues	Baseline and quarterly	Grinsztejn et al [6]
Medical mistrust (12-item Group-Based Medical Mistrust Scale)	Baseline and quarterly	Adapted from Thompson et al [39]
Medical avoidance	Baseline and quarterly	Adapted from James et al [40]
HIV knowledge and attitudes (10-item HIV Knowledge Questionnaire adapted to 8 items, HIV testing and counseling attitudes and knowledge)	Baseline and quarterly	Oglesby and Alemagno [41] and Kalichman and Simbayi [42]
Self-efficacy		Adapted from Zhao et al [43]
HIV testing, prevention, and care	Baseline and quarterly	Grinsztejn et al [6]
HIV perceived risk index	Baseline and quarterly	Lauby et al [44]
Testing and diagnosis of sexually transmitted infections	Baseline and quarterly	Grinsztejn et al [6]
Adherence (adapted to antiretroviral therapy and pre-exposure prophylaxis)	Baseline and quarterly	Adapted from Wilson et al [45]
Overall mental health assessment and suicide	Baseline and quarterly	Grinsztejn et al [6] and Jalil et al [46]
The Patient Health Questionnaire for Depression and Anxiety scale	Baseline and quarterly	Kroenke et al [47]
The Primary Care Posttraumatic Stress Disorder scale	Baseline and quarterly	Prins et al [48]
Social support (Multidimensional Scale of Perceived Social Support)	Baseline and quarterly	Zimet et al [49]
Resilience (2-item Connor-Davidson Resilience scale)	Baseline and quarterly	Connor and Davidson [50]
Brazilian political context	Baseline and quarterly	The authors of this study
Sexual behavior	Baseline and quarterly	Adapted from Rocha et al [51]

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Table 2. Schedule of events of the *Brilhar e Transcender* study.

	Baseline	Week 12	Week 24	Week 36	Week 48 or early termination[a]	HIV seroconversion visit
Eligibility	✓					
Measures						
Behavioral, partnership, network, and structural measures	✓	✓	✓	✓	✓	✓
Adverse events		✓	✓	✓	✓	
Social harm		✓	✓	✓	✓	
Implementation science: participants					✓	
Implementation science: coordination	✓				✓	
Implementation science: peer navigators					✓	
Laboratory procedures						
HIV rapid test	✓	✓[b]	✓[b]	✓[b]	✓[b]	✓
$CD4^+$ and $CD8^+$ cell counts	✓[c]		✓[c]		✓[d]	✓
HIV RNA viral load	✓[c,d]	✓[d]	✓[c,d]	✓[d]	✓[c,d]	✓
HIV recency testing	✓[c]					✓
HIV genotyping	✓[c]					✓
Treponemal syphilis rapid test	✓	✓	✓	✓	✓	
Nontreponemal syphilis (venereal disease research laboratory) testing	✓[e]	✓[e]	✓[e]	✓[e]	✓[e]	
Hepatitis B rapid test	✓				✓[f]	
Hepatitis B serology	✓[g]					
Hepatitis C rapid test	✓				✓[h]	
Anti–hepatitis C virus	✓[i]				✓[i]	
Hepatitis C viral load	✓[j]				✓[j]	
Rectal swab (*Chlamydia trachomatis* and *Neisseria gonorrhoeae*)	✓				✓	
Dried blood spot (pre-exposure prophylaxis adherence assessment)	✓[k]	✓[k]	✓[k]	✓[k]	✓[k]	✓[k]
Hormone dispensation	✓	✓	✓	✓	✓	✓
Medical or psychiatric visit	✓[l]	✓[l]	✓[l]	✓[l]	✓[l]	

[a]Withdrawn or discontinued participants before the final visit.

[b]Only for participants with a negative HIV test in the previous visit.

[c]For all participants living with HIV.

[d]Only for HIV-negative participants with recent HIV exposition according to the service guidelines.

[e]Only for those with a positive treponemal test result.

[f]Only for a negative hepatitis B rapid test result.

[g]Only for a positive hepatitis B rapid test result.

[h]Only for those with a negative hepatitis C rapid test result.

[i]Only for those with a positive hepatitis C rapid test result.

[j]Only for those with positive findings on an anti–hepatitis C virus antibody test.

[k]Only for participants receiving pre-exposure prophylaxis, except those initiating pre-exposure prophylaxis at the current visit.

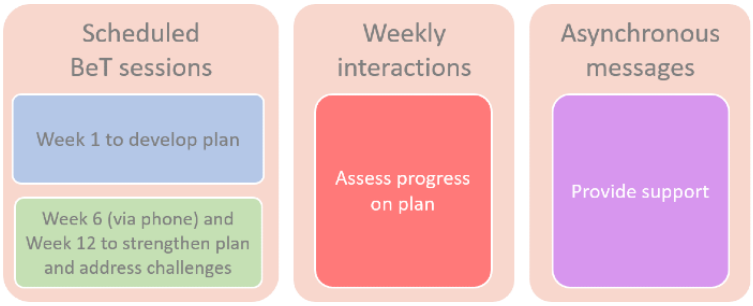
[l]If clinically indicated.

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The BeT Intervention

The 3-month BeT intervention comprises three components: (1) BeT sessions, (2) digital interactions, and (3) automatic messages (Figure 2). During the first BeT session, the participant works with a peer navigator to build a case management plan aimed at meeting HIV prevention and care goals, and getting other needs met to promote health and wellness (BeT plan). BeT sessions 1 and 3 are conducted in person at enrollment and week 12 visits, respectively. BeT session 2 is conducted remotely via a mobile phone. Participants select a preferred app (eg, WhatsApp or Facebook messenger) for communicating asynchronously with the peer navigator during BeT session 2. Asynchronous digital interactions with peer navigators occurs at least weekly for 3 months and can be more frequent based on participant needs. Digital interactions were not restricted to study participation or HIV prevention or care and can include social support, food basket provisions, and guidance on employment, self-care, and other supports. Finally, participants received weekly automatic messages with health information on HIV testing, prevention, and care.

Figure 2. Intervention components of the Brilhar e Transcender study.



Statistical Analysis

Statistical analysis will assess recruitment, baseline, and follow-up data and will describe the rapidity of enrollment of young transgender women, their demographic and risk characteristics, and participation as the percent intervention uptake (ie, the number of participants in the BeT intervention divided by the total number of individuals who were assessed for participation and were preliminarily eligible for the study). We will describe PrEP uptake and adherence and HIV care service linkage at intervention initiation and completion. For the primary endpoint, we will compare PrEP uptake and adherence and HIV care linkage between baseline and follow-up data (ie, before and after the intervention). Primary analyses will test the hypothesis that the odds of PrEP uptake and adherence and HIV care linkage will be higher post intervention relative to baseline data. We anticipate behavior change within 3 instead of 6 months because of our ability to more frequently interact with participants (3 months). In fact, we may achieve a greater dose response and intervention effect in a shorter amount of time because of the possibility for a higher number of encounters. At minimum, participants will engage with their digital navigator 4 to 5 times a week in the form of short digital encounters, and over the course of the intervention, participants will have 48 to 60 short digital encounters in total. We will use a pooled logistic model to estimate treatment effects on time to PrEP uptake and adherence and HIV care linkage.

We will also assess outcomes comparing data from the external comparison group to the BeT intervention group. First, we will conduct sensitivity analyses to compare the demographics of our intervention group to those of the external comparison group. In the analysis, we will focus on comparisons between the BeT intervention group and the external comparison group on measures of PrEP and ART adherence and viral suppression. Primary analyses will involve intention-to-treat analysis without considering adherence to the BeT intervention. This analysis will be a comparison of initiators of PrEP and ART, and we shall adjust for baseline confounders related to age or race. We have chosen to compare initiators of PrEP or ART and not assess PrEP uptake because a comparison of initiators parallels intention-to-treat analysis in which assignment and initiation of the treatment strategies occur together at baseline, regardless of whether individuals continue on the strategies after baseline [52]. We will combine outcome estimates with the cost estimates of the intervention component to calculate cost per participant and roughly estimate costs per HIV infection averted or poor health outcomes based on cohort data being collected in Brazil on HIV incidence and care outcomes.

Antistigma Campaign Evaluation

Data from the baseline and follow-up study surveys will be used to assess whether there were improvements among young transgender women in (1) feeling of safety in health clinics; (2) perceptions of provider, staff, and other patient attitudes toward transgender women; (3) anticipated stigma; (4) medical mistrust; (5) health care participation; and (6) avoidance of health care. We will use repeated measures ANOVA to compare changes in mean stigma scores over the course of time in participating in the intervention (ie, before and after the intervention). In intent-to-treat analyses, we will use generalized estimating equations (GEE) Poisson or negative binomial models with robust SEs to compute the ratio of the single arm intervention rates of change in the mean value of stigma over the study period. GEE methods produce estimates that account for within-subject correlation of stigma scores across time [53]. GEE methods will also be used to assess whether changes in stigma are associated with changes in PrEP uptake and adherence and HIV care linkage over time.

Sample Size and Power Calculation

We propose to enroll 150 participants and have estimated 80% power to detect effects for our primary outcomes using formulas for longitudinal study designs with attrition. These estimates account for an expected attrition of 15% of the sample by 12

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months, as well as adjustment for time-dependent covariates in longitudinal analysis. We will also have 80% power to detect correlations of 0.23 of continuous baseline covariates with baseline responses and changes in study responses from baseline to 6 months.

In the analysis of changes, we will have 80% power in 2-sided tests with a type I error rate of 5% to detect changes from baseline to 12 months of 0.41 to 0.53 SDs in continuous responses, depending on within-subject correlation of the response, and increases of 10-15 percentage points in the frequency of binary responses, depending on baseline frequency as well as within-subject correlation. Thus, this study is powered to detect small to medium effect sizes that are consistent with or smaller than others reported in the literature.

Missing Data

Missing items at any visit should be minimal owing to the electronic data collection protocol described above. However, some loss to follow-up is inevitable. To assess sensitivity to dropout, multiple imputation will be used, under both the standard conditionally missing-at-random assumption, as well as plausible missing not-at-random scenarios. GEE methods can also be weighted to handle missing data.

Laboratory Assessments and Clinical Approach

HIV rapid tests will be performed at baseline for all participants and quarterly for HIV-negative participants. Participants reporting recent anal condomless sex (<30 days) with a negative HIV rapid test will be screened for acute HIV infection through HIV RNA viral load testing. The Limiting Antigen Avidity assay will be used to identify recent HIV seroconversions and may further support the calculation of HIV incidence by providing the timing of seroconversion [54]. Syphilis will be screened using treponemal testing, followed by venereal disease laboratory testing if the former test yields a positive result. Hepatitis B and C will be first screened using rapid tests followed by serology assessments, if needed. All participants will collect rectal swabs at baseline and the 48-week visit for the diagnosis of *Chlamydia trachomatis* and *Neisseria gonorrhea* infections. Sexually transmitted infections will be treated in accordance with Brazilian guidelines [55]. Participants who screened positive for hepatitis B and C will undergo complete the diagnosis algorithm (ie, hepatitis C viral load) [56] and will be referred to treatment. Participants with negative hepatitis B test results who have not been vaccinated will be referred for hepatitis B vaccination. PrEP adherence will be evaluated on the basis of tenofovir diphosphate concentrations in dried-blood spots.

Medical and psychiatric evaluation could occur as needed. Study referrals may include endocrinology, mental health evaluation, and proctology, among others. Participants may also access feminizing hormones on site.

Ethical Considerations

The BeT intervention study was reviewed and approved by the institutional review board of the National Institute of Infectious Diseases, Fiocruz (#CAAE 05018818.0.0000.5262) and the University of California, San Francisco Committee on Human Research (#18-26770) in accordance with all applicable regulations. All participants were asked to sign an informed consent form prior to any study procedure.

Results

Between the study pilot and the study intervention, the COVID-19 pandemic emerged, which caused a substantial impact on the implementation of the study. Study recruitment began in February 2022, initially slowly as Brazil was still facing high numbers of COVID-19 cases and deaths. Nevertheless, we were able to complete study enrollment by early July 2022. To achieve that, we combined prior experience of both the US and the Brazilian teams with transgender communities to new recruitment strategies. The team uses dynamic and multifaceted approaches to community engagement strategies to enhance existing strategies and implement new strategies using field and digital media initiatives for recruitment. The team also encouraged participants to bring other individuals and gave them gifts or reimbursement (eg, peer referrals).

Recruiting and retaining transgender women who are young, early in their gender development, marginalized, and less connected within community poses significant challenges to engagement in the intervention and retention. Therefore, the study team currently has a major focus on retention. Strong supervised peer navigation is important to reach, engage, and retain young transgender women. Regular and meaningful engagement with the community is essential to maintain these connections. Furthermore, we have been providing cell phone credits to the participants retained in the intervention. In addition, we also give participants small gifts, such as study bags, sponge bags, and daily planners, among others, if they achieve some goals (eg, attending study visits in the study window). In addition, we will also conduct raffles of electronic items (such as portable cell phone chargers and earphones) for participants completing the intervention and study visits. Peer navigators also maintain close connections with participants, supporting them in their in-person and remote interactions. Future perspectives are to complete follow-up with study participants by July 2023 and to analyze study data and disseminate intervention results December 2023.

Discussion

The BeT study is a pivotal study that will evaluate a digital peer-led intervention for young transgender women in a LMIC such as Brazil. We anticipate that the BeT intervention will successfully improve HIV prevention and care outcomes among young transgender women. A linkage to prevention intervention is particularly important once oral PrEP is a public health policy in Brazil. Oral PrEP requires strong care linkage, engagement, and retention to reap the prevention benefits. Although oral PrEP has been implemented since 2017 in Brazil, only a small percentage of PrEP users are transgender women [57]. Ancillary services and systems navigation to such services related to PrEP are essential supports to ensure success on PrEP. Among young cis women in Africa, PrEP uptake was facilitated when offered as part of an integrated sexual reproductive health service [58]. Based on the findings of the formative phase [32], BeT

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intervention will be the first intervention tested to meet the needs of the transgender women population in LMICs and may be implemented in resource-constrained settings. We also expect stigma to be reduced over time as participants are engaged in a gender-affirming transgender-centered clinic where an antistigma campaign has been conducted.

The study has some limitations. First, the BeT intervention will not be tested in a randomized clinical trial. Owing to the heightened targeting of transgender people, randomizing BeT participants seemed unethical and impractical in our context. To address this issue, we will assess intervention effectiveness by monitoring changes in intervention outcomes before and after the intervention and comparing outcomes from our cohort to those in an external comparison group. Furthermore, our study will have a convenience sample and our results may not be applicable to all young transgender women. Our study also has some strengths. The study team has extensive experience in conducting transgender-related research. The Brazilian site has a successful history of engaging transgender women in relevant clinical studies owing to historical community engagement efforts that solidified the relationship with the local transgender population.

In the current local adverse political environment, where transphobia is rampant, the implementation of a transgender-specific study is an opportunity to engage a new generation of transgender women in health care. Moreover, peer-led support may empower transgender youth toward their self-care and health promotion. The BeT intervention may be rapidly brought to scale and translated to a relevant, replicable, sustainable, and evidence-based combination HIV prevention intervention for young transgender women in LMICs.

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Data Availability

We and our institutional review board have ethical concerns with releasing our study data publicly owing to the small numbers of transgender persons, the high likelihood that sharing the primary data may expose individual participants, and the possible harm that might befall participants if exposed.

Conflicts of Interest

None declared.

Multimedia Appendix 1
External peer review from the National Institute of Child Health and Human Development Special Emphasis Panel-Eunice Kennedy Shriver National Institute Of Child Health and Human Development (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 205 KB - resprot_v12i1e44157_app1.pdf]

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Abbreviations

ART: antiretroviral therapy
BeT: Brilhar e Transcender
GEE: generalized estimating equations
LMIC: low- and middle-income country
PATC3H: Prevention and Treatment through a Comprehensive Care Continuum for HIV-affected Adolescents in Resource Constrained Settings
PrEP: pre-exposure prophylaxis

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Protocol

Cross-Tailoring Integrative Alcohol and Risky Sexual Behavior Feedback for College Students: Protocol for a Hybrid Type 1 Effectiveness-Implementation Trial

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Abstract

Background: Underage drinking and related risky sexual behavior (RSB) are major public health concerns on United States college campuses. Although technology-delivered personalized feedback interventions (PFIs) are considered a best practice for individual-level campus alcohol prevention, there is room for improving the effectiveness of this approach with regard to alcohol-related RSB.

Objective: The aims of this study are to (1) evaluate the impact of a brief PFI that integrates content on alcohol use and RSB and is adapted to include a novel cross-tailored dynamic feedback (CDF) component for at-risk first-year college students and (2) identify implementation factors critical to the CDF's success to facilitate future scale-up in campus settings.

Methods: This study uses a hybrid type 1 effectiveness-implementation design and will be conducted in 3 phases. Phase 1 is a stakeholder-engaged PFI+CDF adaptation guided by focus groups and usability testing. In phase 2, 600 first-year college students who drink and are sexually active will be recruited from 2 sites (n=300 per site) to participate in a 4-group randomized controlled trial to examine the effectiveness of PFI+CDF in reducing alcohol-related RSB. Eligible participants will complete a baseline survey during the first week of the semester and follow-up surveys at 1, 2, 3, 6, and 13 months post baseline. Phase 3 is a qualitative evaluation with stakeholders to better understand relevant implementation factors.

Results: Recruitment and enrollment for phase 1 began in January 2022. Recruitment for phases 2 and 3 is planned for the summer of 2023 and 2024, respectively. Upon collection of data, the effectiveness of PFI+CDF will be examined, and factors critical to implementation will be evaluated.

Conclusions: This hybrid type 1 trial is designed to impact the field by testing an innovative adaptation that extends evidence-based alcohol programs to reduce alcohol-related RSB and provides insights related to implementation to bridge the gap between research and practice at the university level.

Trial Registration: ClinicalTrials.gov NCT05011903; https://clinicaltrials.gov/ct2/show/NCT05011903

International Registered Report Identifier (IRRID): DERR1-10.2196/43986

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(JMIR Res Protoc 2023;12:e43986) doi:10.2196/43986

KEYWORDS

alcohol-related risky sexual behavior; college students; cross-tailored dynamic feedback; effectiveness-implementation hybrid designs; personalized feedback intervention; underage drinking

Introduction

Overview

Despite declines over the past several decades, underage drinking and related harm continue to be major public health concerns on United States college campuses [1-3]. National data show two-thirds of college students are current drinkers, 1 in 3 reports past-month heavy-episodic drinking (more than 5 drinks in a row), and 1 in 10 reports high-intensity drinking (more than 10 drinks in a row) [1]. Greater college student alcohol consumption and heavy drinking on a given day are linked to increased sexual activity and risky sexual behavior (RSB; eg, unprotected sex and unplanned hookups) [4-9]. Alcohol-related RSB puts college students at risk for negative health outcomes (eg, sexually transmitted infections and unplanned pregnancies) and is a pathway to sexual victimization and escalated drinking [10-14]. Notably, alcohol use is implicated in approximately half of college student sexual assaults [14,15]. Given the high rates of alcohol misuse in college and the association between alcohol use and RSB, prevention efforts that reduce alcohol-related RSB have been identified as a priority area in the National Institute on Alcohol Abuse and Alcoholism (NIAAA) Strategic Plan 2017-2021 [3].

The first weeks of college are referred to as the red zone with escalations in heavy drinking [16-18] and sexual assault [19-23]. Changes in the salience of social and achievement goals and stressors during the transition to college impact alcohol use during this period [24]. Students who drink heavily prior to college are likely to escalate drinking [25], and nondrinkers or light drinkers may consume heavy amounts on occasion, increasing their risk of experiencing serious consequences [26,27]. This coincides with changes in students' sex-related cognitions and behaviors [8,28]. Thus, effective interventions for escalated alcohol use and RSB during this critical period of risk can result in high public health and clinical impacts [29].

Technology-Delivered Personalized Feedback Interventions

NIAAA's College Alcohol Intervention Matrix identifies technology-delivered personalized feedback interventions (PFIs) as a best practice for individual-level campus alcohol prevention [30]. PFIs typically involve a one-time, web-based assessment of an individual's alcohol use behaviors, followed by the provision of a tailored profile based on the assessment of the individual's drinking patterns and strategies to reduce harm [31-33]. The utilization of technology for assessment and feedback allows PFIs to retain key features of efficacious in-person brief motivational interventions without the high costs and need for trained personnel [34]. Many universities now opt for commercially developed PFIs for first-year students (eg, AlcoholEdu for College [35] and eCHECKUPTOGO [36]) [37-42].

Past work from the investigative team [32,43,44] highlights 2 important concerns with PFIs as widely implemented. First, a rather exclusive focus on the assessment and feedback of alcohol use means other health behaviors impacted by alcohol use, such as RSB, are rarely addressed [32]. To address this gap, a PFI with integrated alcohol and RSB content for sexually active, college-aged young adults who regularly drink was developed. The integrated PFI showed promise in reducing alcohol-related sexual outcomes [43]. Second, there is considerable heterogeneity in PFI effects across participants [45] and studies [44,46]. Further, PFIs tend to provide short-term intervention benefits but offer diminished protection to college students beyond 6 months [46,47]. The current intervention is designed to increase and extend the effects of the integrated alcohol and RSB PFI by incorporating repeated and dynamic assessment and feedback.

Extending PFIs With Cross-Tailored Dynamic Feedback

The prevailing approach to technology-delivered PFIs is to provide a single, point-in-time snapshot of one's behaviors and beliefs relative to others, analogous to a "between-person" comparison, which can create initial discrepancy and enhance motivation to change [48]. However, this feedback is limited to a one-time snapshot of individual differences in risk, does not capitalize on the beneficial effects of continued monitoring, and cannot capture dynamic changes in an individual's beliefs or behavior in response to feedback. The proposed PFI and cross-tailored dynamic feedback (CDF) adaptation (PFI+CDF) leverages semester-long diary assessments (once a day for 4 days a week over 12 weeks) to iteratively refine (ie, optimize) initial feedback. The addition of CDF has the potential to amplify the effects of PFIs through the provision of feedback linked to a user's personal, day-to-day trajectory of a target behavior. The integration of adaptive ("just-in-time") and dynamic feedback is designed to bolster and sustain the initial impact of the PFI by creating a unique form of self-monitoring of "within-person" trajectories. In this way, positive behavior change can be acknowledged, and the participant can be redirected when less desirable behaviors are reported. The CDF adaptation of a PFI is intended to develop discrepancy regarding alcohol-related RSB, alcohol use, and other RSB; enhance motivation to change; and boost self-efficacy in one's ability to change. To our knowledge, dynamic optimization of intervention content with rapid deployment and evaluation has never been attempted with alcohol-related RSB interventions.

Designing for Dissemination With an Effectiveness-Implementation Hybrid Design

Over the past 3 decades, researchers have made strides to enhance brief alcohol intervention implementation through a number of key adaptations (eg, extending to different subpopulations [44], altering delivery modality [49], adding

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boosters [50-52], giving students a choice for intervention assignment [53], adding video content [54], and adding substance-free activities [55]). Despite these efforts, a significant proportion of college campuses do not implement evidence-based strategies [56-58]. Although PFIs are a popular choice among campuses that do implement such strategies, little is known regarding strategies they use to encourage stakeholder groups' participation or how PFIs complement other student health efforts.

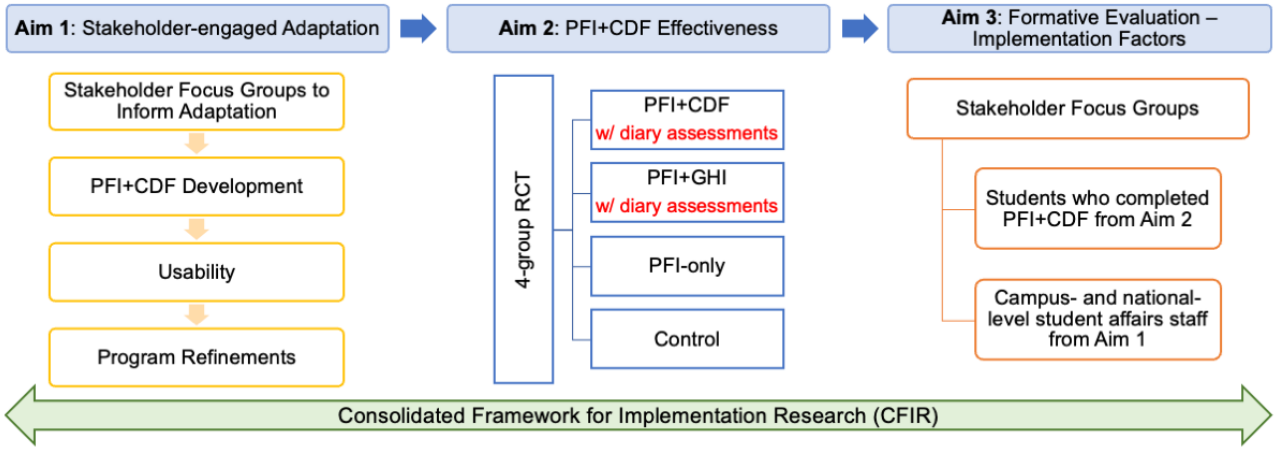
Accordingly, the current intervention study is guided by a hybrid type 1 effectiveness-implementation design to examine PFI+CDF effectiveness and related implementation factors to improve and accelerate translation. Effectiveness-implementation hybrid designs offer a dual focus on both outcomes and process, which can serve to speed up the translation of an intervention if it is effective [59,60]. Process-oriented formative evaluations will be used with stakeholders at multiple levels prior to, during, and after program implementation to better understand implementation context, and barriers and facilitators to implementation [61-64]. It is critical to identify college-specific PFI implementation gaps at both the student level and systems level for the purpose of improving PFI+CDF's acceptance by students and achieving greater adoption on campuses. By engaging multilevel stakeholders at the outset, a "designing for dissemination" approach is followed, using feedback from members of the population of users and organizational adopters [65-68]. In this paper, we provide a description of the proposed hybrid type 1 effectiveness-implementation study protocol.

Methods

Study Design

Figure 1 provides an overview of the 3-phase, multisite hybrid type 1 effectiveness-implementation design to evaluate the effectiveness and understand the implementation of a novel PFI+CDF to reduce first-year college students' alcohol-related RSB. Phase 1 is a focus group-guided PFI+CDF adaptation and usability test. In phase 2, first-year college students who report past-month heavy-episodic drinking (more than 4 or 5 drinks for females or males within 2 hours) or drinking at least 3 times in the past month and who are sexually active without being in a monogamous relationship will be recruited from the University of Kentucky (UK) and the University of North Texas (UNT) to participate in a 4-group randomized controlled trial (RCT) to examine the effectiveness of PFI+CDF in reducing alcohol-related RSB. PFI+CDF will have 3 other comparison conditions: a PFI followed by the 12-week dynamic feedback on general health information (PFI+GHI), a PFI without any additional exposure to intervention (PFI), and assessment-only control (AOC). In phase 3, a qualitative evaluation will be conducted with multilevel stakeholders to better understand relevant implementation factors.

Figure 1. Overview of study design. CDF: cross-tailored dynamic feedback; GHI: generic health information; PFI: personalized feedback intervention; RCT: randomized controlled trial.



Phases 1 and 3 are guided by the Consolidated Framework for Implementation Research (CFIR), a comprehensive set of constructs describing factors influencing implementation across all stages of the implementation process [69,70]. CFIR is commonly used to guide formative investigations within the context of hybrid type 1 designs [61,64]. Constructs are grouped into 5 domains in the current intervention study: intervention characteristics (ie, characteristics of PFI+CDF), outer setting (ie, context surrounding student affairs), inner setting (ie, context within student affairs), individual characteristics (ie, students and student affairs staff), and process (ie, process for implementing PFI+CDF) [69].

Adaptation (Phase 1)

Overview

Phase 1 will focus on adapting the existing integrated PFI to the enhanced PFI+CDF with the following steps: (1) focus groups with multilevel stakeholders, including students and student affairs staff; (2) building the data capture and content platform; (3) usability testing; and (4) program refinements. These 4 key iterative steps of adaptation are crucial in the systematic modification of existing evidence-based interventions to improve their effects and potential for implementation [66]. Furthermore, they ensure that the adaptation of the integrated PFI to PFI+CDF is achieved with the principle of designing for dissemination in mind [65].

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Focus Groups

We will conduct focus groups with stakeholders (ie, students and student affairs personnel) to solicit their perspectives on a prototype of the proposed PFI+CDF intervention. Focus group participants will be students and student affairs professionals (eg, individuals involved with implementation of prevention programming) at UK and UNT, as well as student affairs professionals at the national level, recruited at the annual meeting of NASPA-Student Affairs Administrators in Higher Education, the premier conference in this field [71]. Recruitment and facilitation of focus groups at NASPA will ensure a national perspective on the PFI+CDF intervention.

At UK and UNT, we anticipate a single focus group for staff and 3 focus groups for students, with 5-8 participants per group (32 participants per site, 64 participants total). At NASPA, we will aim for 4 focus groups with 5-8 participants per group, for a total of 32 participants. Development of the focus group interview guide will be informed by the CFIR interview guide tool [72] and will target constructs within the intervention characteristics domain of CFIR (eg, adaptability, complexity, design quality, and relative advantage), exploring barriers and facilitators to implementation at both the student level and systems level [69,73]. Groups will last 60-90 minutes and incentives will be US $50 and US $100 gift cards for students and student affairs staff, respectively.

We will conduct a systematic thematic analysis to identify relevant themes from the qualitative data collections [74]. Focus groups will be transcribed and analyzed using NVivo [75]. A designated subset of the research team will first work independently to identify recurrent themes and important statements specific to intervention content. They will then review the independent coding together, discuss the independent coding with the entire research team, and come to a consensus about the emerging themes. The themes will be compiled into summaries and circulated to the research team to guide discussion of intervention refinement.

Data Capture and Content Development

Overview

Findings from the multilevel stakeholder focus groups will inform the development of an updated version of an existing evidence-based integrated alcohol and RSB feedback profile (PFI) and the addition of CDF content, as well as an assessment and delivery platform necessary to populate and house the PFI and CDF content.

PFI and CDF Delivery Platform

The PFI and CDF content will be housed in a website application platform that offers flexibility in reach and accessibility but is optimized for viewing across device types (eg, computer, tablet, and phone). For example, links to PFI and CDF content can be sent to participants via multiple channels (eg, SMS text message and email) to access feedback. The assessment and content platform will be built as an integrated system, essential for scale-up for several reasons: (1) survey responses inform both the PFI and CDF content and are a necessary part of the system, (2) it allows for a built-in evaluation mechanism, and (3) it creates one overall system that is portable for hosting at other sites. The underlying programming will be conducted in HTML5 to ensure flexibility for future adaptations to other platforms. The web-based app will run on common web browsers on iOS and Android smartphones, tablets, and on iOS and Windows personal computers. A backend tracking program will record user progress.

Intervention Content: PFI

Consistent with prior work, PFI content will be generated from responses to a baseline assessment and offer participants integrated feedback on both alcohol use and RSB across the following content domains: a behavioral profile, normative comparisons, blood alcohol content, expectancies, perceived risk, likelihood of engaging in future risk behaviors, and protective behavioral strategies. In addition to integrated alcohol and RSB content, the PFI will include an option to view feedback on alcohol use behaviors only, as pilot data indicated separate alcohol-focused content was necessary to reduce alcohol use not specific to sexual behavior.

Intervention Content: CDF

CDF content will be generated from weekly diary-style surveys (Friday to Monday) in which students report their alcohol use and RSB, as well as their preferences when interacting with CDF content. Participants will receive dynamic feedback on their own behaviors for 12 weeks of the fall semester, allowing them to see their behaviors over time and receive feedback on their behavior changes (ie, “within-person” feedback). Although the overall system and specific design features will be created in consultation with students and technology developers, and subsequently refined following the usability testing, it is anticipated that the CDF content will include (1) a brief and updated behavior profile, (2) normative feedback on their current weekly drinking and related sexual behavior pattern, (3) positive reinforcement for improving behaviors within weekly and monthly time frames in figures, (4) brief updated intervention content topics (eg, individual-specific protective strategies that they can use in the following week) along with an option to see a full version, and (5) alerts for potential areas for improvement and referral information, if needed.

Usability Testing and Program Refinement

Usability testing will focus on (1) soliciting feedback on users’ experience with the enhanced PFI+CDF and (2) troubleshooting the CDF diary surveys and dynamic weekly feedback methodology. The usability test will be conducted with the methodology, assessments, and timing of the RCT procedures for the PFI+CDF group (see phase 2 description below), with the exception that the testing does not need to start at the beginning of the academic year or include follow-up surveys. Participants (n=100, 50 per site) will provide standard ratings of the acceptability [76] (eg, attractiveness, comprehension, relevance, and persuasive value) and usability [77] (eg, ease and efficiency of use) of the PFI+CDF intervention and respond to open-ended questions regarding most and least liked features. We will create a summary of participants’ impressions, commonly referenced problems, and acceptability and usability ratings, and use this information for one last round of program refinement, as recommended in systematic adaptation approaches.

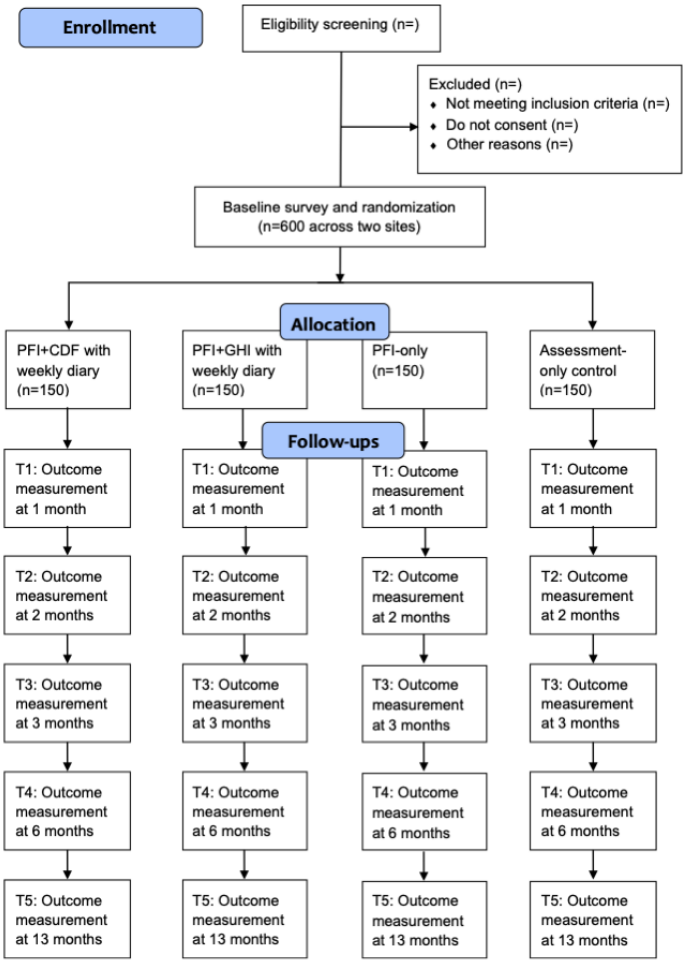
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Effectiveness Trial (Phase 2)

Overview of RCT Design

We will conduct a multisite, 4-group RCT to evaluate the intervention (Figure 2). Participants (N=600 total, 300 per site) will be randomized to 1 of 4 groups: (1) PFI+CDF with weekly diary surveys; (2) PFI+GHI (generic health information) with weekly diary surveys; (3) PFI-only, no weekly diary surveys; and (4) AOC, no weekly diary surveys. All participants will complete a baseline survey during the first week of the semester, be randomly assigned to 1 of the 4 groups, and complete follow-up surveys at 1, 2, 3, 6, and 13 months post baseline. The staggered design allows for comparison of the enhanced PFI+CDF relative to the PFI+GHI, which may be consistent with a "treatment-as-usual" comparison group (eg, of the universities that have adopted an evidence-guided alcohol intervention program for their campus, many currently deliver commercialized alcohol-focused PFIs to incoming first-year students) [35,36]. Providing weekly GHI in the comparison group allows for an equal number of "exposures" between PFI+CDF and PFI+GHI, analogous to an attention control group, offering a clearer understanding of the overall impact of the PFI+CDF adaptation. The inclusion of 2 PFI conditions, 1 with weekly diary assessments and 1 without, allows us to control potential assessment reactivity that might result from the diary-style assessment approach. This design is intended to allow a separation of the "true" intervention effect of the CDF above and beyond the effect of assessment reactivity. The PFI-only versus AOC group comparison will provide a test of the integrated PFI that has been adapted based on stakeholder feedback.

Figure 2. Randomized controlled trial workflow diagram. CDF: cross-tailored dynamic feedback; GHI: generic health information; PFI: personalized feedback intervention.



Recruitment

Contact information for a random sample of first-year college students between the ages of 18-20 years will be drawn from the registrar's office at each study site. Students will be sent a prenotification letter on the university letterhead describing the study and inviting their participation. The letter will inform them to check their email on the study start date for more details and be followed by an email that reiterates study details, invites their participation, and includes a web link and personal identification number to access a web-based consent form and screening survey. Other recruitment methods will supplement this recruitment from the registrar's office, including direct emails to interested students, advertisements in newspapers, on websites and social media, and postcards and fliers distributed at various on-campus locations. Eligibility criteria are shown in Textbox 1. Eligible students will be required to give informed consent before being directed to the baseline survey. Those who decline to consent and those who are not eligible will be directed out of the survey and removed from the participant list. Students

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will receive email reminders over the course of the following week. We will oversample underrepresented groups (n=300, 50% non-White and n=300, 50% White students) and maintain an equal ratio of men and women at each site.

Textbox 1. Eligibility criteria for the randomized controlled trial.

Eligibility criteria

- First-year student
- 18-20 years of age
- Past 30-day heavy-episodic drinking (more than 4 or 5 drinks for females or males within 2 hours) or 3 or more drinking occasions within the past month
- Sexually active (oral, anal, or vaginal sex within past 12 months)
- Not in a monogamous relationship (single, not dating, or dating, not serious) or in a monogamous relationship (dating only 1 person) for less than 3 months or in a monogamous relationship but open to cheating
- Not pregnant or planning to become pregnant

Procedures

Following the baseline survey, participants randomized to 1 of the 3 PFI conditions will immediately be linked to their PFI, which will also be sent via email and SMS text message. A 2-week window is allotted at the beginning of the semester for participants to complete their baseline assessment and, if applicable, view their PFI content. Following that period, participants in the PFI+CDF and PFI+GHI will be sent prompts via email and SMS text message to complete diary surveys on Friday through Monday of each week. On Tuesdays, participants in the PFI+CDF group will receive a link to access their CDF corresponding to that week's behavior, via text and email, and those in the PFI+GHI group will receive a link to access health topics relevant to college students guided by the American College Health Association website (eg, nutrition, mono, exercise, and immunizations) [78]. These procedures will continue for a total of 12 weeks. All participants will be asked to complete web-based 1-, 2-, 3-, 6-, and 13-month follow-up assessments and receive up to US $100 (US $15 per survey, with an additional US $10 bonus for the 13-month follow-up). Participants in the diary conditions will receive an additional payment up to US $96 (US $2 per day×4 days×12 weeks=US $96).

Intervention Assessments and Other Measures

Table 1 shows a list of self-report measures, including primary and secondary outcomes, demographics, and covariates. Primary and secondary outcomes and content-specific measures will be assessed at baseline and in all follow-up surveys. Measures will be adapted for weekly diary assessments along with items related to daily drinking context, consistent with our prior work. We anticipate baseline and follow-up surveys to be approximately 20 minutes in length, and daily surveys will be 5 minutes in length. Participants will be made aware of the importance of the data, the confidential nature of their responses, and we will follow procedures to secure their privacy.

Table 1. Self-report measures.

Construct	Description
Primary outcomes	
Alcohol-related sexual behavior	Number of times that alcohol was consumed during or before sex, quantity of alcohol consumed before sex [79]
Alcohol-related consequences—sexual	Sexual consequence scale [80]
Secondary outcomes	
Alcohol use behavior	Daily drinking questionnaire [81], heavy-episodic drinking, and high-intensity drinking
Alcohol-related consequences—nonsexual	Young adult alcohol consequences questionnaire [82]
Sexual behavior	Frequency of sex (including oral, vaginal, or anal), number of casual sexual partners, and number of times that a condom was used during sex [79,83]
Demographics and covariates	
Background demographics	Birth sex, gender identity, sexual orientation, race and ethnicity, height and weight (for blood alcohol content calculation)
Alcohol use history	Lifetime alcohol use, age of drinking and intoxication onset, and family history
Sex history	Age of first sex and history of sexual behavior

In addition to self-report measures, participant behavior analytics will be captured to help ensure intervention fidelity and be included as covariates in analyses. Analytics include (1) whether or not participants accessed their PFI, CDF, or GHI; (2) the

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number of times each PFI, CDF, or GHI was accessed; (3) time spent viewing each PFI, CDF, or GHI; and (4) time spent viewing each topic area within the PFI, CDF, or GHI. These data will be captured through tracking routines programmed on the website. We will examine the depth of college students' engagement with intervention content to assess the effects of program exposure (ie, dose) based on the level of access to content (eg, ranging from students who looked at PFIs and all weekly CDF and GHI content vs those who engaged in some or none of the content) and time spent on various intervention components. These data will provide intervention acceptability metrics and allow us to control each participant's exposure to the PFI, CDF, or GHI content in outcome analyses.

Sample Size Justification

Power analyses to detect intervention main effects were conducted using Optimal Design Plus Version 3.01 software and the "power determination approach." Based on past research, we assumed a standardized effect size of 0.3 (a small to medium effect size) from the repeated measures RCT with 5 follow-ups over 13 months. To examine the effect of the PFI+CDF and PFI interventions, compared to the control, a minimum of 452 participants are required for a power of 0.8 at an alpha level of .05. To examine the effect of the PFI+CDF intervention (vs PFI+GHI or PFI-only intervention), at least 350 participants are required. Based on this power analysis, there is sufficient power (≥0.89) to detect a small to medium effect size for the integrated interventions (PFI+CDF, PFI+GHI, and PFI only) versus control and sufficient power to detect the small effect of the PFI+CDF intervention compared to the PFI+GHI or PFI-only intervention over time. Although the overall effect size was conservatively assumed to fall between small and medium in size, due to the fine-grained assessment approach within the time period where most changes are likely to occur, followed by a long-term 13-month follow-up assessment, we anticipate that the proposed study is sufficiently powered.

Statistical Analysis

For study phase 2, we will use a multilevel model for the main outcome analysis where the participant is defined at the highest level of the model (level 2), and observations (level 1) are nested within the participant. We will assume that the observation-level (level 1) residual error term and participant-level (level 2) intercept coefficients (ie, random effects) are each normally distributed with mean zero and a variance that is estimated from the data, while intercept and slope coefficients are multivariate normally distributed with mean zero for each, and a covariance matrix that is estimated from the data. Intervention groups will be tested as a fixed effect. Given that many outcomes of our interest are count outcomes with excessive zeros, we will utilize appropriate models to accommodate a zero-inflated outcome distribution with overdispersion [44,84]. The 2 sites can be entered as a random effect (level 3) or a fixed effect in a 2-level model. We will include an interaction term to test whether PFI+CDF is similarly effective for men and women. The intercept and growth slopes will be appropriately specified to maximize information.

We will use a parallel process growth model to test the codevelopment of correlated processes (eg, alcohol use and RSB) and a parallel process growth mediation model. This allows for the examination of 2 potentially dependent reduction trajectories, which are altered by intervention. We expect that those who reduce alcohol misuse more rapidly in response to intervention will also exhibit a trajectory in which one's likelihood of engaging in RSB decreases, which can be tested by comparing a model where the 2 slope terms are correlated with a null model where its correlation is constrained to be zero. Intervention effects can be explicitly tested by adding intervention membership as an external covariate that changes these coupled processes. Intervention effect modifiers or moderators will be tested in a confirmatory (eg, sex) or exploratory investigations.

Implementation (Phase 3)

A qualitative postintervention assessment of intervention implementation will be conducted with multilevel stakeholders, including students and both campus- and national-level student affairs staff. The goals are to better understand (1) participating students' experiences with the intervention; (2) barriers and facilitators to implementation, guided by CFIR; (3) potential program sustainability; and (4) necessary modifications for other sites for scale-up.

Focus group participants will be a subset of students from the PFI+CDF arm of the RCT, as well as campus- and national-level stakeholders who also participated in preimplementation focus groups. Participants in the PFI+CDF condition will be asked if they are interested in participating in a follow-up study after the 13-month follow-up. We will randomly select up to 48 students who indicate interest in participating (n=24 per site) at varying levels of engagement with the intervention (as guided by program analytic measures) for a maximum of 3 focus groups per site (5-8 participants per group). Campus student affairs staff will be contacted via phone and email for staff focus groups (1 focus group per site for student affairs staff with 5-8 participants per group). At the national level, we will conduct 4 focus groups, with 5-8 participants per group, yielding a total of up to 32 participants. All focus groups will last 60-90 minutes with US $50 and US $100 gift card incentives for students and staff, respectively. The analytic plan for phase 3 qualitative data will mirror phase 1.

Ethics Approval

The study underwent review and approval by the UK Institutional Review Board (IRB #62769), which serves as the single IRB of record for this study. All participants will sign an approved consent form in accordance with the ethical standards of Helsinki.

Results

Recruitment and enrollment for phase 1 began in January 2022. The findings of phase 1 will inform the development and build of integrated PFI+CDF. It is anticipated that phase 2 will begin in August 2023, and phase 3 will begin in October 2024. Data will be shared in the NIAAA Data Archive twice a year (April 1 and October 1), starting from October 1, 2023. Findings will

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be published in peer-reviewed journals and presented at international, national, or regional professional meetings and conferences.

Discussion

Overview

This project aims to fill a gap highlighted in the NIAAA Strategic Plan 2017-2021 [3] by advancing an intervention that integrates alcohol misuse and RSB. It also directly addresses the 2 primary areas of foci underlying a recent NIAAA workshop to advance the science on evidence-based brief interventions for young adult populations: (1) optimizing intervention design and (2) implementation and scale-up [85]. To the best of our knowledge, the use of dynamic feedback based on individual behavior trajectories to optimize PFI content with rapid and sustained deliveries and ongoing evaluations has never been attempted with this population and area of study. Understanding the impact of a dual-risk behavior PFI that incorporates novel, cross-tailored between- and within-person feedback profiles can help inform best practices for the delivery of prevention interventions relevant to college students. If successful, our approach could influence how PFIs are developed and delivered in other populations and settings for maximum benefit. In addition, employment of a hybrid type 1 effectiveness-implementation design for this population, behavior, and campus setting is also the first of its kind and is expected to yield broadly informative outcomes through its rigorous randomized trial design testing intervention effectiveness and multilevel stakeholder engagement pre- and postimplementation.

Limitations

There are several potential limitations that need to be acknowledged. First, the emphasis on first-year college students may be restrictive. We chose to focus on first-year students because they are at risk for alcohol use and RSB [16-26], but older students also experience alcohol-related harms. Many college campuses require students to complete a brief alcohol intervention at the start of college and often use existing commercialized PFIs, providing a built-in audience for the adapted PFI+CDF intervention [35,36]. We encourage future studies to explore PFI+CDF in other at-risk populations, such as older students and young adults not in college. Second, the PFI+CDF intervention approach is intensive and could lead to concerns about student engagement. However, our past work on integrated PFIs indicates that participants engaged with feedback content and viewed it multiple times [86]. We demonstrated that increased personalization leads to a stronger program effect, potentially mediated through increased attention to content [32]. By involving students in the design process in phase 1, we should enhance their interest [59,87,88]. Students also reported favorable reactions to the proposed study methods. Thus, we anticipate high levels of engagement, but will also examine program engagement in phase 2 analyses and phase 3 focus groups. Third, there are alternatives to a web-based app platform. Technology changes rapidly, with many other options for content delivery (eg, native mobile apps, smartwatches, social media). Our goal was to create a flexible system to deliver content in multiple ways (email and SMS text message), increasing the likelihood of engagement. Native mobile apps require more programming than web apps to operate across smartphone types and operating systems. Social media offers opportunities (eg, user-generated interaction and content) but also its own challenges (eg, spread of misinformation). Alternate delivery platforms will be explored during focus groups, and we anticipate the need for content to be portable to other platforms in future implementation.

Conclusions

This innovative, multisite hybrid effectiveness-implementation study will (1) evaluate the impact of a PFI that integrates content on alcohol use and RSB and is adapted to include an innovative CDF component for at-risk first-year college students and (2) identify implementation factors critical to its success to facilitate future scale-up in campus settings. The findings of this study will improve existing evidence-based alcohol programs and bridge the gap between research and practice at the university level.

Acknowledgments

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Data Availability

Data sharing is not applicable to this paper as no data sets have been generated or analyzed. Once generated, this study will submit and share data with National Institute on Alcohol Abuse and Alcoholism (NIAAA) Data Archive, a data repository housed within the National Institute of Mental Health Data Archive (NDA).

Conflicts of Interest

DBB receives a salary from Klein Buendel, Inc. His spouse is an owner of Klein Buendel, Inc.

Multimedia Appendix 1

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Peer-reviewer report from the Interventions to Prevent and Treat Addictions Study Section - Risk, Prevention and Health Behavior Integrated Review Group (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 144 KB - resprot_v12i1e43986_app1.pdf]

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Abbreviations

AOC: assessment-only control
CDF: cross-tailored dynamic feedback
CFIR: Consolidated Framework for Implementation Research
GHI: generic health information
IRB: Institutional Review Board
NIAAA: National Institute on Alcohol Abuse and Alcoholism
PFI: personalized feedback intervention
RCT: randomized controlled trial
RSB: risky sexual behavior
UK: University of Kentucky
UNT: University of North Texas

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Protocol

Strengthening Addiction Care Continuum Through Community Consortium in Vietnam: Protocol for a Cluster-Randomized Controlled Trial

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Abstract

Background: A chronic condition, drug addiction, requires long-term multipronged health care and treatment services. Community-based approaches can offer the advantages of managing integrated care along the care continuum and improving clinical outcomes. However, scant rigorous research focuses on sustainable, community-based care and service delivery.

Objective: This protocol describes a study aiming to develop and test an intervention that features the alliance of community health workers and family members to provide integrated support and individualized services and treatment for people who use drugs (PWUD) in community settings.

Methods: Based on the National Institute on Drug Abuse's Seek-Test-Treat-Retain (STTR) framework, an intervention that provides training to community health workers will be developed and piloted before an intervention trial. Trained community health workers will conduct home visits and provide support for PWUD and their families. The intervention trial will be conducted in 3 regions in Vietnam, with 60 communities (named communes). These communes will be randomized to either an intervention or control condition. Intervention outcomes will be evaluated at baseline and at 3, 6, 9, and 12 months. The primary outcome measure is PWUD's STTR fulfillment, consisting of multiple individual fulfillment indicators across 5 domains: Seek, Test, Treat, Retain, and Health. The secondary outcomes of interest are the community health workers' service provision and family members' support. The primary analysis will follow an intention-to-treat approach. Generalized mixed-effects regression models will be used to compare changes in the outcome measures from baseline between intervention and control conditions.

Results: During the first year of the project, we conducted formative studies, including in-depth interviews and focus groups, to identify service barriers and intervention strategies. The intervention and assessment pilots are scheduled in 2023 before commencing the trial. Reports based on the baseline data will be distributed in early 2024. The intervention outcome results will be available within 6 months of the final data collection date, that is, the main study findings are expected to be available in early 2026.

Conclusions: This study will inform the establishment of community health workers and family members alliance, a locally available infrastructure, to support addiction services and care for PWUD. The methodology, findings, and lessons learned are expected to shed light on the addiction service continuum's implementation and demonstrate a community-based addiction service delivery model that can be transferable to other countries.

Trial Registration: ClinicalTrials.gov NCT05315492; https://clinicaltrials.gov/ct2/show/NCT05315492

International Registered Report Identifier (IRRID): DERR1-10.2196/44219

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KEYWORDS

addiction service; community consortium; drug addiction; health care worker; health; family; Vietnam

Introduction

Drug addiction, such as opioid use disorder, is one of the most significant public health issues globally [1]. Medication-assisted therapies (MAT), including methadone and buprenorphine or naloxone, are in place to prevent opioid-related overdose and the spread of infectious diseases [2-5]. However, substantial barriers exist to the provision and use of MAT because of the shortage of addiction specialists to prescribe and monitor MAT, especially in remote areas [6,7]. For example, community MAT programs require community members' support and resources to train community health care workers [6,7].

Mobilization of community-based systems in the service delivery model has been advocated as a desirable strategy to reduce the current gap in MAT [8-12]. In addition, drug addiction, as a chronic condition, requires long-term multipronged health care [13,14]. Community-based approaches can offer the advantages of managing integrated care along the care continuum and improving clinical outcomes [15-18]. However, there is a lack of research focusing on the systematic implementation of MAT and its related service delivery in community care settings [18].

Commune Health Centers (CHCs) are grassroots health care facilities in rural Vietnam, where essential preventive care, initial diagnosis, and referral services can be accessed by residents [19]. Vietnam is one of the first countries to decentralize MAT delivery from centralized treatment sites to community settings [20,21]. However, its CHC-based MAT programs face challenges, such as community health workers (CHWs) lack of capacity in treatment services, misconceptions of harm reduction, and stigmatizing attitudes toward PWUD [22]. Hence, adherence to MAT has been suboptimal, and the patient dropout rates are alarmingly high [23,24].

In Vietnam, the family presents a critical source of support for people who use drugs (PWUD) [25-27]. Families are commonly the source of daily care and financial, emotional, tangible, and informational support for opioid users' care seeking. The support given by family members can significantly impact the health care use and outcomes of PWUD [28,29]. At the same time, close family members of PWUD often struggle with mental health issues, impaired social adjustment, poor work relations, decreased social participation, and increased intrafamily dysfunction [30,31]. These challenges have jeopardized the family's capacity to support PWUD in care seeking and adherence.

Current health care infrastructure and culture in Vietnam provide an opportunity to test a community-based service delivery model for addiction care and treatment. We plan to develop and test an intervention that features the alliance of community health workers and family members to provide integrated support and individualized treatment services for PWUD in community settings.

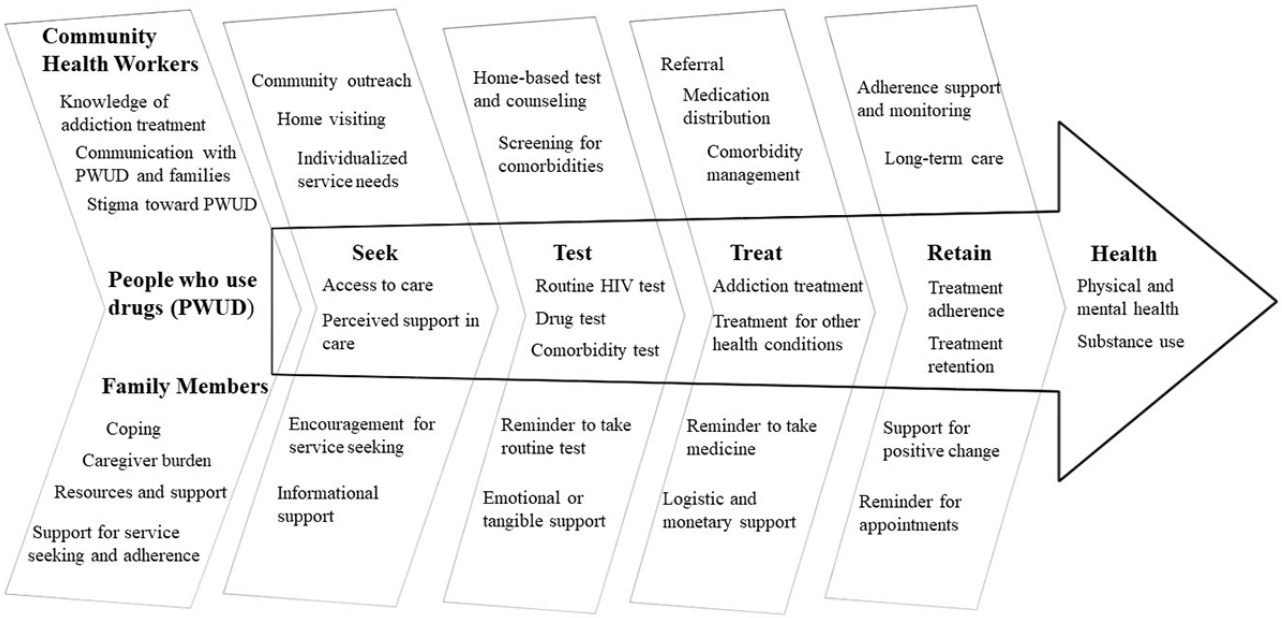
Methods

Theoretical Framework

The National Institute on Drug Abuse's Seek-Test-Treat-Retain (STTR) initiative provides a framework to guide the delivery of addiction services [32,33]. This approach requires reaching out to PWUD and understanding their health needs (Seek), engaging them in routine physical examinations and laboratory testing (Test), initiating MAT and treatment of comorbidities (Treat), and facilitating treatment adherence and long-term, uninterrupted care (Retain). Based on the theoretical framework, we plan to synergize the support from CHWs and family members as two of the most essential enabling factors to build a respectful, accepting, and supportive addiction care continuum for PWUD (Figure 1). Specifically, CHWs will be trained to provide individualized care with a nonstigmatizing attitude. In addition, family members will be mobilized to give continuous support to PWUD's service seeking and adherence. The coalition between CHWs and family members will provide a locally available infrastructure to support addiction treatment services, resulting in effective and sustainable outcomes.

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Figure 1. Theoretical Framework.



Intervention Development and Pilot

Formative studies, including focus groups and in-depth interviews, will inform intervention development and implementation plan. A total of 3 CHW focus groups and 3 focus groups with community representatives focus on identifying service gaps and effective local strategies to address the challenges. In-depth interviews with PWUD and family members will identify the needs in support, barriers, and facilitators to maintaining service engagement and retention. Following the formative studies, a multidisciplinary work group will be formed and go through 3 steps: (1) reviewing the problem and identifying intervention outcomes, (2) adapting evidence-based strategies to local infrastructure and culture, and (3) developing the intervention implementation and evaluation plan. A pilot version of the intervention program will be produced and followed by an intervention pilot study. The pilot will include a full implementation of intervention activities. In-depth interviews with participants and intervention team members will be conducted to refine the intervention. We will also finalize recruitment procedures and assessment batteries in this phase.

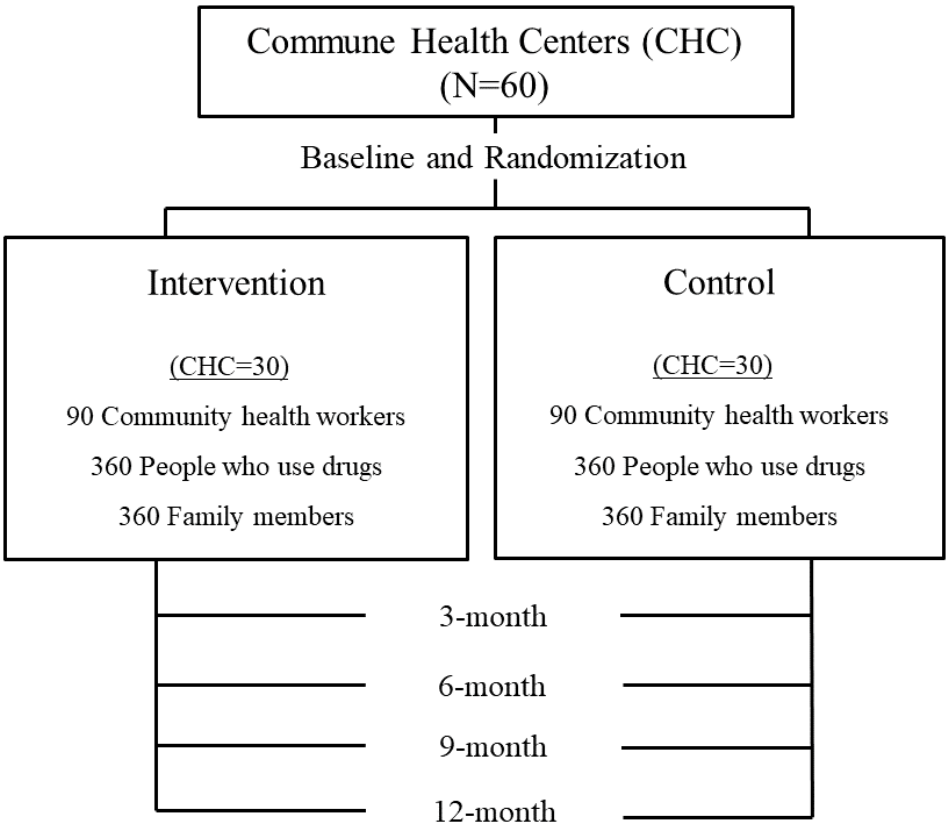
Cluster-Randomized Controlled Trial

Study Design

The intervention trial aims to test the efficacy of the intervention, primarily with PWUD outcomes, and secondly, at family members and CHW levels. We hypothesize that (1) the intervention will improve PWUD's service fulfillment along the addiction service continuum, as well as their health outcomes; (2) the intervention will enhance CHWs' provision of addiction-related service provision for PWUD and support of their family members; and (3) the intervention will improve family members' support for PWUD's engagement in the addiction continuum. The trial will be conducted in 3 regions in Vietnam. These regions represent geographical variations in the country. The trial will include 60 CHCs, randomized to either an intervention or control condition. We propose to enroll 720 PWUD and 720 family members (12 families per CHC) as well as 180 CHWs (3 per CHC). Intervention outcomes will be evaluated at baseline and every 3 months after that (Figure 2). We plan to select communes with the highest number of PWUD in each region to ensure adequate participants. The selected CHC in each region will be paired based on the number of PWUD. Within each pair, the CHC will be randomized after baseline.

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Figure 2. Study design.



Eligibility and Recruitment

To recruit PWUD, we will post project recruitment flyers in major community activity sites, such as local commune culture centers, hospitals or pharmacies, and other places where local PWUD usually gather. PWUD interested in the study can contact our recruitment staff using the information printed on the flyers. Recruitment staff will meet with potential participants individually to screen for eligibility. Eligibility criteria include (1) age of 18 years and older, (2) having a history of drug use, (3) having disclosed the drug-using status to at least one of the family members and being willing to invite the family member to our study, and (4) currently residing in the selected communes. Written informed consent and consent to contacting a pointed family member will be obtained.

The consented PWUD will be asked to choose a family member in the order of closeness, usually starting from spouse, mother, father, sibling, to other relatives. The inclusion criteria for a family member are (1) age of 18 years and older, (2) being an immediate or extended family of the PWUD, and (3) knowing the PWUD's drug-using behavior. Our recruitment staff will work with the PWUD to arrange a private meeting with the nominated family member. If the nominated family member also has a history of drug use, he or she will be enrolled as a PWUD participant, and another family member will be recruited from the family. All family member participants will sign a written informed consent.

Eligibility criteria for CHWs include age of 18 years and older and being a CHW (including doctors, assistant doctors, and nurses) who regularly provides health services to community residents. Supporting staff, including cleaners, accountants, and security personnel, will be excluded. There are usually 3 to 5 eligible CHWs in each CHC, and they will be invited to participate in the study. Written informed consent will be obtained.

Intervention Implementation

Based on our literature review and intervention research experience, we plan to implement an intervention that combines CHWs' in-person group training sessions, online support groups, CHW-delivered home visits, and mobile phone text messages for PWUD and their family members. The group training sessions will be conducted with participating CHWs in the intervention arm. We anticipate conducting 2 group sessions, each lasting approximately 90 minutes. The training topics will concentrate on community-based addiction service delivery. After the initial group training sessions, online support groups will be formed to facilitate continued skill building, information sharing, networking, and problem-solving. As part of the intervention requirement, trained CHWs will work as a team to deliver individualized addiction services to PWUD and family members in the community. For each participating PWUD and their family, the trained CHW team will conduct home visits to identify PWUD's specific needs and gaps, offer referrals, and provide social and mental health support. During the home visits, activities will be conducted with family members to release the caregiver burden, enhance family support, and address other barriers. As a supplement to the home visits, mobile phone text messages will be delivered periodically from trained CHWs to PWUD participants for health promotion and

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service engagement. The text messages will be adaptive to individual needs and preferences.

We will collect process evaluation data to monitor and improve intervention implementation, that is, evaluator observation, intervention activity tracking, and participant self-evaluation. For the in-person group sessions, facilitators will keep records of participants' attendance and activities conducted in each session. The investigators and field directors will observe training sessions and use a predesigned checklist to rate the adherence to session contents, time allocation, core elements, techniques, clarity, and responsiveness. For the online group discussion, the frequency and format will be tracked. Each group member's activity, including the initiation of threads, comments, and reactions, will be captured to determine the level of engagement. In addition, all CHWs in the intervention will be given a user-friendly service log to document their experiences and feedback on the program.

Data Collection

The intervention assessments will consist of self-report questionnaires and medical or service records. We will collect the information at baseline and at 3-, 6-, 9-, and 12-month follow-ups. CHWs will be surveyed using the Computer-Assisted Self-Interview method, as PWUD and family members will be assessed using the Computer-Assisted Personal Interview method. We will ask PWUD participants at each assessment to donate a urine sample to test. PWUD's service records will be chart reviewed, and their service encounters with providers, laboratory testing dates and results, and treatment status will be collected.

Outcome Measures

The primary outcome measure is the PWUD's STTR fulfillment score, which is a comprehensive score that integrates medical, behavioral, and psychosocial indicators to evaluate PWUD's health and service engagement profile. The score consists of multiple fulfillment indicators across 5 domains: Seek, Test, Treat, Retain, and Health. Most of the indicators were suggested by the STTR Data Collection and Harmonization Initiative [14,32] and adapted to the context of Vietnam. The secondary measures of interest include CHWs' service provision, support to PWUD and their family members, and family members' support of PWUD's service engagement. Other relevant indicators are listed in Figure 1. All the measures will be piloted before the trial.

Sample Size

The study will randomize 60 CHCs (clusters) to intervention and control conditions with a 1:1 ratio. The sample size calculation was based on the primary outcome measure. We propose enrolling 720 PWUD (360 per condition) to ensure we have 80% power at 5% significance level to detect a standardized effect size of 0.41 when comparing the mean change scores of the primary outcome between intervention and control conditions. The proposed sample size accounts for the commune-level clustering, repeated observations within PWUD, and an attrition rate up to 8% for PWUD.

Data Analysis

All participants will be analyzed on an intent-to-treat basis. Descriptive statistics, frequencies for demographic and baseline characteristics, and all the outcome measures will be summarized at baseline by intervention condition. For each study population, generalized linear mixed-effects regression models with appropriate link functions will be used to compare the changes in the primary outcome from baseline between intervention and control groups. Each regression model will include commune- and participant-level random effects to account for dependence within communes and repeated observations within participants. The main effects included in each model are intervention condition, visit, and a condition-by-visit interaction term. Intervention effects on the primary outcomes will be estimated using model contrasts. The preselected demographic and background characteristics (covariates) will be added to evaluate whether the intervention effects on primary outcomes remain significant. The same analytical approach will be applied to each STTR domain score and the secondary outcomes of interest. We also plan to conduct several exploratory data analyses to (1) examine the intervention effect on each STTR fulfillment indicator by subgroup, (2) explore the interrelationship among PWUD's STTR domains or indicators to identify service gap, and (3) explore the interconnectedness of intervention effects on CHW, PWUD, and family members.

Ethics Approval

The study protocol was reviewed and approved by the Institutional Review Board of the University of California, Los Angeles (UCLA IRB#20-001594-AM-0001) and the Institutional Review Board in Bio-Medical Research, National Institute of Hygiene & Epidemiology in Vietnam (NIHE IRB VN01057/IORG 0008555; No: NIHE IRB - 28/2022).

Results

The intervention and assessment instruments have been developed based on the findings from formative studies (in-depth interviews and focus groups). The pilot activities are scheduled for 2023 and followed by the main trial. For the assessment of trial outcomes, we are scheduled to collect data at baseline and at 3-, 6-, 9- and 12-month follow-ups. We will distribute reports based on the baseline data in early 2024. The intervention outcome results will be available within 6 months of the final data collection date, that is, the main study findings are expected to be available by early 2025.

Discussion

Expected Outcomes

We anticipate the intervention to be feasible and provide community stakeholders, health professionals, and policy makers with insights for the future establishment and implementation of a community-based addiction service continuum. Community-based service delivery model has been considered a desirable strategy, and the scale-up of accessible and community-led harm reduction services is a global priority [34]. The existing primary health care system in Vietnam provided

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an opportunity and platform to test an intervention that features the alliance of CHWs and family members to provide a continuum of addiction services for PWUD. If tested effective, the delivery strategies in this study can potentially serve as an example to provide community-based addiction services in other countries. For example, the CHW training package can offer a transferable tool for training primary care providers in addiction disorders in a global context.

Compared to prior work on community-based service delivery models, this study focuses on community partnership rather than each target population, such as PWUD, family members, or CHWs, respectively. We anticipated that improving CHWs' capacity through intervention training will strengthen their support for PWUD and family members, which will in turn improve addiction service engagement and retention. With the capacity building in the community, we anticipate that the trained CHWs will focus on adapting services across the care continuum to reflect different conditions of individuals and families, potentially enhancing community service delivery with sustainable outcomes.

Another strength of this study is to pay special attention to the vulnerability of family members and the role of family support. We have learned from the existing literature and previous studies that family can be mobilized to become a locally available, trustful, and sustainable support system. We anticipate that our intervention effort will form a partnership between CHWs and family members. Our intervention aims to address the impact of addiction and stigma on families and the burden and challenges faced by family members. The study findings would contribute to the growing body of literature on the role of family support in community-based addiction services and care.

This study has some limitations. First, considering that we integrate various components (eg, in-person sessions, online groups, home visits, and text messages) in the intervention, we will not have the opportunity to assess the effect of each strategy. Second, the intervention program in this study is designed to use the capacity-building approach to train CHWs. The process of training health workers to improve their knowledge and skills to enhance care and services could be too complex to be identified. Third, although the intervention aims to mobilize community health workers and PWUD's family members to strengthen community partnerships to support addiction services, the study's outcome assessments and measures are mainly at the individual level.

Dissemination Plan

The dissemination of study findings will include articles in both Vietnamese and English journals, international conference presentations, and other scholarly channels. Also, we will disseminate study findings to stakeholders to support the development and implementation of health care policies in Vietnam. We will make the intervention training guides, tools, manuals, and materials available to other interested organizations and agencies.

Acknowledgments

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Data Availability

All data collected will be accessible by the study investigators, who have the right to analyze and publish data. After the publication of the primary findings, deidentified and individual-level data can be available upon reasonable requests by graduate students and research scholars. Data requests can be submitted to the investigators at both participating agencies in Vietnam and the United States.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Peer review report by the National Institute on Drug Abuse - Community-Level Health Promotion Study Section - Healthcare Delivery and Methodologies Integrated Review Group - Center for Scientific Review (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 101 KB - resprot_v12i1e44219_app1.pdf]

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Abbreviations

CHC: commune health center
CHW: community health worker
MAT: medication-assisted therapy
PWUD: people who use drugs
STTR: Seek-Test-Treat-Retain

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Protocol

Biological Mechanisms in Pregnant Women With Anxiety (Happy Mother-Healthy Baby Supplement Study): Protocol for a Longitudinal Mixed Methods Observational Study

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Abstract

Background: Anxiety and depression are common in the perinatal period and negatively affect the health of the mother and baby. Our group has developed "Happy Mother-Healthy Baby" (HMHB), a cognitive behavioral therapy–based psychosocial intervention to address risk factors specific to anxiety during pregnancy in low- and middle-income countries (LMICs).

Objective: The purpose of this study is to examine biological mechanisms that may be linked to perinatal anxiety in conjunction with a randomized controlled trial of HMHB in Pakistan.

Methods: We are recruiting 120 pregnant women from the Holy Family Hospital, a public facility in Rawalpindi, Pakistan. Participants are assessed for at least mild anxiety symptoms using the Hospital Anxiety and Depression Scale (ie, a score ≥8 on the anxiety scale is necessary for inclusion in the anxiety groups and <8 for inclusion in the healthy control group). Women who meet the criteria for an anxiety group are randomized into either the HMHB intervention group or an enhanced usual care (EUC) control group. Participants receive HMHB or EUC throughout pregnancy and undergo blood draws at 4 time points (baseline, second trimester, third trimester, and 6 weeks post partum). We will assess peripheral cytokine concentrations using a multiplex assay and hormone concentrations using gas chromatography and mass spectrometry. The statistical analysis will use generalized linear models and mixed effects models to assess the relationships across time among anxiety, immune dysregulation, and hormone levels, and to assess whether these biological factors mediate the relationship between anxiety and birth and child development outcomes.

Results: Recruitment started on October 20, 2020, and data collection was completed on August 31, 2022. The start date for recruitment for this biological supplement study was delayed by approximately half a year due to the COVID-19 pandemic. The trial was registered at ClinicalTrials.gov (NCT03880032) on September 22, 2020. The last blood samples were shipped to the United States on September 24, 2022, where they will be processed for analysis.

Conclusions: This study is an important addition to the HMHB randomized controlled trial of an intervention for antenatal anxiety. The intervention itself makes use of nonspecialist providers and, if effective, will represent an important new tool for the treatment of antenatal anxiety in LMICs. Our biological substudy is one of the first attempts to link biological mechanisms

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to antenatal anxiety in an LMIC in the context of a psychosocial intervention, and our findings have the potential to significantly advance our knowledge of the biological pathways of perinatal mental illness and treatment efficacy.

Trial Registration: ClinicalTrials.gov NCT03880032; https://clinicaltrials.gov/ct2/show/NCT03880032

International Registered Report Identifier (IRRID): DERR1-10.2196/43193

(JMIR Res Protoc 2023;12:e43193) doi:10.2196/43193

KEYWORDS

antenatal anxiety; perinatal anxiety; pregnancy; cognitive behavioral therapy; inflammation; allopregnanolone; Pakistan; randomized controlled trial

Introduction

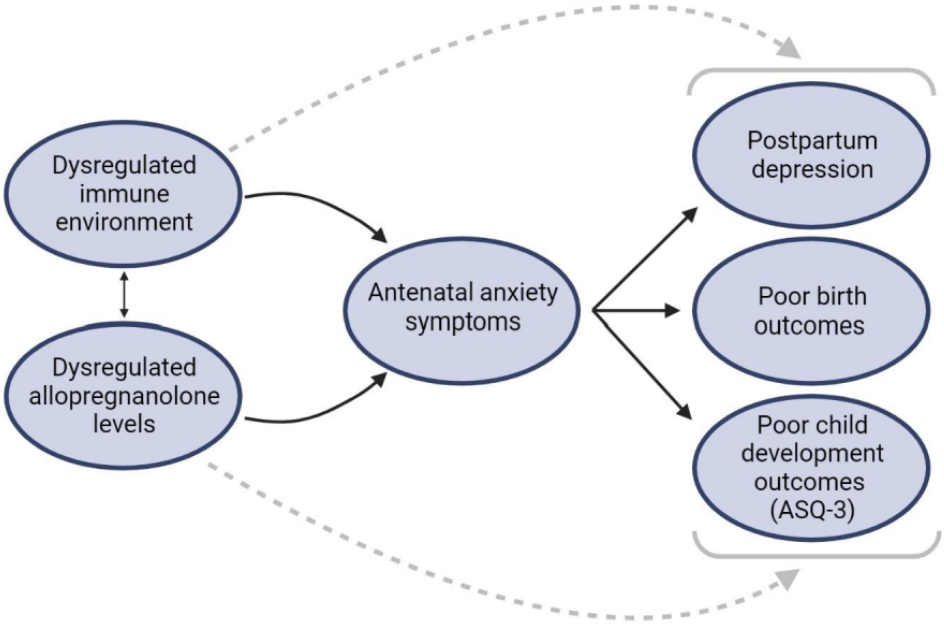
Common perinatal mental disorders such as depression and anxiety occur frequently, are underdiagnosed, and negatively affect the health of both the mother and baby [1]. While the majority of epidemiological data is focused on perinatal depression, peripartum anxiety is equally prevalent, if not more so, yet remains largely understudied [2]. In Pakistan, for example, between one-third and one-half of pregnant women experience anxiety during pregnancy [3,4]. Despite the known morbidity associated with antenatal anxiety (ie, high risk of later anxiety or depression, risk of suicide [5-8], a range of poor birth outcomes [9-11], ill child health [12], and host of child development problems [13-17]), the biological underpinnings of antenatal anxiety remain unknown. In low- and middle-income countries (LMICs), the treatment gap for anxiety disorders exceeds 75%, largely due to the absence of specialists to provide evidence-based psychological interventions [18]. To address this gap, our group developed a cognitive behavioral therapy–based psychosocial intervention called "Happy Mother-Healthy Baby" (HMHB), delivered by nonspecialists and tailored to address risk factors specific to anxiety during pregnancy. HMHB is the subject of an ongoing randomized controlled trial in Rawalpindi District, Pakistan [19,20]. In conjunction with this larger study, our group has designed an observational study to examine biological factors that may be linked to perinatal anxiety, with a particular focus on immune dysregulation and sex hormones. Any such alterations can inform plausible mechanisms that can then be used in the development of other interventions, either psychosocial or biological (for example, anti-inflammatory nutritional approaches or exercise interventions).

The connection between anxiety and immune dysregulation outside of pregnancy is well-established [21,22], including studies showing heightened anxiety symptoms in women with inflammatory diseases such as colorectal cancer and irritable bowel syndrome [23-25]. There are several mechanisms by which increased inflammation could be related to fear and anxiety. For example, exposure to stressful stimuli has been shown to activate immune cells to release cytokines and other peripheral inflammatory markers [26-29]. This increased inflammation can be related to hypothalamic-pituitary-adrenal axis dysregulation and, in turn, to behavioral manifestations and clinical symptoms of anxiety [26-32]. Such changes may be especially important in pregnancy, as maternal immune activation has been implicated as a risk factor for child developmental outcomes such as altered neurobehavioral functioning [33,34]. Even a healthy pregnancy is a time of immune dysregulation [35-37]. Prior research has identified a distinct "cytokine fingerprint" in normal pregnancy—a pattern of relative changes in cytokine levels across time, despite individual differences in absolute levels—due in large part to hormonally driven decreases in both innate and adaptive immunity [37-40].

The neuroendocrine system is centrally related to the immune response in pregnancy. Progesterone (P4) and its metabolites, including allopregnanolone (ALLO), rise dramatically in healthy pregnancy [41], and there is bidirectional feedback between P4 metabolites and the immune system [42-46]. Higher levels of ALLO have been linked to decreased production of inflammatory mediators by microglia, reduced cytokine production by macrophages, and diminished lymphocyte proliferation [47]. Low levels of ALLO have also been linked to anxiety outside of pregnancy [48]. There is some evidence of a relationship between ALLO and psychiatric symptoms in the perinatal period as well [2,49-51]. A theoretical model outlining these possible connections is given in Figure 1.

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Figure 1. Proposed theoretical model. In our study, we will measure the relationship between the dysregulated immune and endocrine environment, their influence on antenatal anxiety symptoms, and the direct and indirect influence on associated outcomes (postpartum depression, poor birth outcomes, and poor child development outcomes). ASQ-3: Ages and Stages Questionnaire.



The proposed study aims to investigate the biological mechanisms that underlie antenatal anxiety in women enrolled in the HMHB psychological intervention in Pakistan. This study sets out to answer the following research questions: (1) whether there is a pattern of immune dysregulation common to women with antenatal anxiety, (2) whether there is a relationship between ALLO and concurrent anxiety symptoms or future symptoms of postpartum depression, (3) whether immune dysregulation is related to dysregulation of ALLO, (4) whether these biological mechanisms are mediators of the association between antenatal anxiety and poor birth outcomes, and (5) if biological markers of anxiety are associated with infant neurodevelopment at 6 weeks of age as measured by the Ages and Stages Questionnaire (ASQ-3).

While the evidence concerning the role of such biological factors is increasing, no study has yet examined them in the context of a psychological intervention in pregnancy in an LMIC, where anxiety and depression rates are high and psychosocial intervention can make a meaningful difference [52]. This manuscript describes the design and implementation of one such study.

Methods

Study Design and Setting

Pregnant women are recruited from the Holy Family Hospital (HFH), a public facility in Rawalpindi, Pakistan.

Recruitment

The study is embedded in the main trial of the HMHB intervention, for which the recruitment of 1200 women started in April 2019 [20]. Recruitment for this supplemental biological study began in October 2020. Recruitment is carried out by a female assessment team based in the outpatient Gynecology and Obstetrics Department. The team describes the HMHB study to all pregnant women who fulfill the initial screening criteria (see next paragraph for details on level 1 screening) and their families visiting the department for their initial prenatal visit at or before 22 weeks' gestation (approximately 600 women monthly). For this biological supplement study, women are included if they are ≤12 weeks of gestation. All women eligible for the main study are offered the opportunity to participate in the supplemental study, and we anticipate enrollment of 120 participants over 18 months (30 from each arm of the main study and another 60 pregnant controls who are neither depressed nor anxious as assessed by the Hospital Anxiety and Depression Scale [HADS]); this rate of recruitment is slower than for the main study, due to the reluctance of many women to undergo blood draws, as well as stricter inclusion criteria related to gestational age and absence of anemia.

Screening Procedure and Eligibility Criteria

We use 3 levels of inclusion and exclusion screening criteria that occur at the same time at enrollment. For level 1 screening, we determine if the woman is at ≤12 weeks' gestation, ≥18 years old, resides ≤20 km from HFH, and understands Urdu. If they fulfill these criteria, women expressing initial interest are asked to provide informed consent for completing the next stage of screening. At level 2 screening, we determine from self-reports if women have (1) life-threatening health conditions, including suicidal ideation, (2) past or current serious learning disability, (3) past or current psychiatric disorder other than anxiety (eg, bipolar disorder or schizophrenia) or psychiatric treatment (eg, current use of anxiolytic drugs or other psychotropic drugs), (4) medical disorders or severe maternal morbidity that require current inpatient management, or (5) intensive care unit admission (for treatment, not solely for assessment). If not excluded on this basis, potential participants undergo level 3 screening, which includes assessment for the presence or absence of at least mild anxiety on the anxiety subscale of the HADS (ie, a score ≥8 is necessary for inclusion

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in the anxiety groups and <8 on both the anxiety and depression subscales for the healthy controls). The HADS is a validated screening tool for depression and anxiety and has been used in research settings [53]. Women who score ≥8 on the HADS anxiety subscale move onto level 4 screening, which includes an interview with a qualified psychiatrist who conducts a Structured Clinical Interview for DSM V Diagnoses; women meeting criteria for a major depressive episode are excluded.

Randomization

Participants with anxiety are randomly assigned to a group using a pseudo-random number generator, which assigns a random sequence via permuted blocks of sizes 4, 8, 12, and 16. The list of assignments is printed out, and each step in the sequence is stored apart from the others in an opaque envelope; the envelopes are numbered sequentially with a 7-digit code. Participants are assigned to control or intervention according to the next available envelope after consent. All members of the on-site trial team, as well as the trial statistician, principal investigator, and coinvestigator leading the biological study, are blinded to the allocation.

Participant Groups

To enhance participation in the study and adherence to study protocols, all participants are reimbursed for transportation and for as many ultrasounds as are medically indicated at HFH during pregnancy.

Intervention Group

Women allocated to this group receive the HMHB intervention, a cognitive behavioral therapy–based treatment focused on anxiety and culturally adapted and tailored to a low-literacy population during the initial research phase [19,54]. Core principles include the mother's psychosocial well-being, preparation for birth, relationship skills, and psychosocial support [19]. HMHB includes 6 core weekly sessions and anywhere from 2 to 6 booster sessions, depending on the timing of enrollment and individual needs. The final core session is in the third trimester of pregnancy. HMHB is presented as a "mother-to-be" program (to combat the stigma associated with mental health issues), and family members are encouraged to participate in 3 sessions. The intervention is delivered by nonspecialist research therapists, who are university graduates with a master's degree in psychology but no experience delivering mental health care [55]. Prior to the start of the study, research therapists receive a 6-day classroom training, followed by field training and weekly group supervision. Competency is assessed by role plays during training and by direct observation of 15% of their sessions by independent assessors using the ENACT (Enhancing Assessment of Common Therapeutic Factors) rating scale for global training and supervision in mental health [56].

Enhanced Usual Care (EUC) Control Group

Women with anxiety allocated to the control condition are receiving EUC in the Obstetrics Department. The target number of visits is 8, as recommended by the World Health Organization (WHO) for a positive pregnancy experience [57]. Visits involve evaluating health status, discussing any concerns, and performing routine exams consistent with the stage of pregnancy.

Healthy Controls

The healthy control group consists of 60 women who have low or no anxiety or depressive symptoms (<8 on both the anxiety and depression subsections of the HADS). This will allow us to compare biological processes between women with anxiety (both those receiving the intervention and those in the EUC) and healthy controls.

Timing of and Measures for Data Collection

All participants in the main study with anxiety (either in the intervention group or receiving EUC) will undergo the same visits and psychological measures. The measures received by the healthy controls are indicated in the final column of Table 1. The timelines of visits and measures used are outlined in Table 1 and Figure 2, and details of these measures are described in the trial protocol paper for the main study [20].

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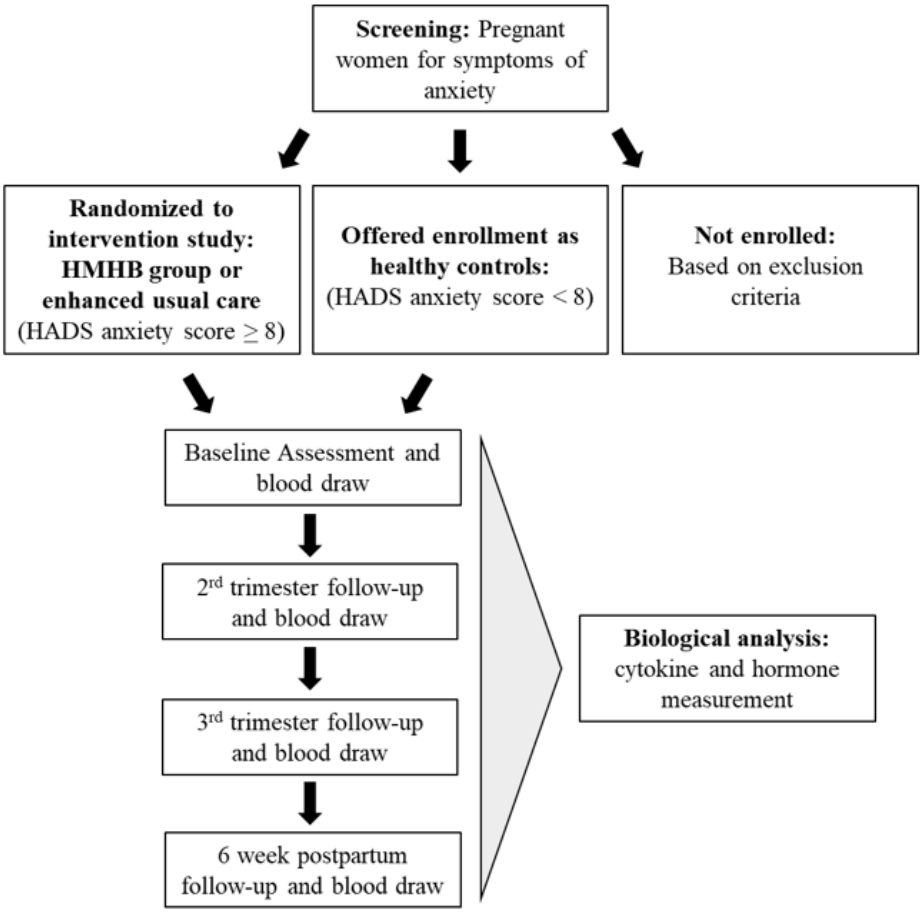
Table 1. Timing of data collection.

	Measured in anxious women (intervention and anxious controls)					Measured in healthy controls
	Screening or baseline[a] (time 1)	Second trimester (time 2)	Third trimester (time 3)	Birth (time 4)	6 weeks post partum (time 5)	Time-matched
Assessments						
Sociodemographic questions	✓					✓
PSS-10[b] (stress)			✓		✓	
PES-Brief[c] (pregnancy anxiety)	✓		✓			
PHQ-9[d] (depressive symptoms)					✓	
HADS[e] depression (subscale)	✓				✓	✓
HADS anxiety (subscale)	✓	✓	✓		✓	✓
MDE[f] diagnosis (from SCID[g])	✓				✓	
MSPSS[h] (social support)	✓		✓		✓	
MRQ[i] (relationships)	✓		✓		✓	
Empowerment	✓				✓	
Pakistan Demographic Health Survey interpersonal violence questions					✓	
Breastfeeding					✓	✓
PBQ[j] (bonding)					✓	
MIRI[k] (maternal responsiveness)					✓	
MSEQ[l] (maternal self-efficacy)					✓	
Blood draw for biological factors	✓	✓	✓		✓	✓
ASQ-3[m]					✓	✓
Primarily from medical records						
Pregnancy conditions			✓			✓
Birth outcomes: SGA[n], PTB[o], LBW[p]				✓		✓
Medications	✓		✓		✓	✓

[a]Baseline assessment may be the same day or up to 2 weeks after screening.
[b]PSS-10: Perceived Stress Scale 10 items.
[c]PES-Brief: Pregnancy Experience Scale-Brief version.
[d]PHQ-9: Patient Health Questionnaire 9 items.
[e]HADS: Hospital Anxiety and Depression Scale.
[f]MDE: Major Depressive Episode.
[g]SCID: Structured Clinical Interview for DSM Disorders.
[h]MSPSS: Multidimensional Scale of Perceived Social Support.
[i]MRQ: Motivations for Reading Questionnaire.
[j]PBQ: Postpartum Bonding Questionnaire.
[k]MIRI: Maternal Infant Responsiveness Instrument.
[l]MSEQ: Maternal Self-Efficacy Questionnaire.
[m]ASQ-3: Ages and Stages Questionnaire.
[n]SGA: small for gestational age.
[o]PTB: preterm birth.
[p]LBW: low birth weight.

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Figure 2. Study design and setting. HADS: Hospital Anxiety and Depression Scale; HMHB: Happy Mother-Healthy Baby.



Biological Sample Collection

Participants have their blood drawn (up to 20 ml) at 4 visits by a phlebotomist who was trained on the study protocol. Target times for sampling blood are at baseline (between 10 and 22 weeks' gestation), during the second trimester (between 22 and 26 weeks' gestation), during the third trimester (between 34 and 38 weeks' gestation), and between 4 and 8 weeks post partum. Each participant is scheduled as close as possible to the same time and during morning hours for all 4 blood draws (as blood is drawn in HFH between 8 AM and 1 PM), allowing us to account for diurnal variation in cytokine levels. Blood is centrifuged within 8 hours of collection using low-density gradient centrifugation via a Z326 High Performance Centrifuge. Plasma is immediately frozen in cryovials in a ThermoScientific Revco RLE Ultra-Low Lab Freezer at –80 °C and stored at the National Institute of Health Laboratory in Pakistan until it is shipped to Baltimore.

Shipping of Samples

Plasma samples (approximately 1280 cryovials) are being shipped from Pakistan to Baltimore, United States, in multiple shipments throughout the trial using courier services. Blood is kept frozen at a maximum temperature of –20 °C throughout shipment using standard cold packs, dry ice, or liquid nitrogen as required by local regulations and the standards of the courier services. All plasma samples are then stored at –80 °C in a ThermoScientific Revco RLE Ultra-Low Lab Freezer at Johns Hopkins to await analysis together at the end of the study to avoid batch effects.

Analysis of Biological Samples

Cytokine Analysis

Plasma cytokines will be measured using the Meso Scale Discovery (Gaithersburg, MD) Ultrasensitive Pro-inflammatory multiplex kit. The Meso Scale Discovery multispot array will be run according to the manufacturer's protocol. Calibration curves will be prepared. Plates will be read using the MS2400 imager. Samples for cases and controls will be assayed adjacently but in random order and replicated; the technician performing analyses will be unaware of the case status. To determine assay reliability, we will calculate the coefficient of variation for each woman's replicates when both have concentrations above the limit of detection [58].

Hormone Analysis

All hormone analyses will take place at the same time at the end of the study. Samples will be stored at –80 °C and run in 1 batch. Extraction, derivatization, and gas chromatography and mass spectrometry analyses of ALLO will be performed as previously described [59,60]. After the samples are extracted with ethyl acetate and lyophilized, the steroids of interest will be purified and separated by high-performance liquid chromatography. Tritiated neuroactive steroids will be added to monitor the high-performance liquid chromatography retention profile, while deuterated internal standards consisting of 2 pmol of deuterium-labeled neuroactive steroids will be

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used to allow quantitation of the compound of interest and correct for procedural losses. Each steroid of interest will then be derivatized for gas chromatography and mass spectrometry [59,60]; mass spectrometry analysis will be performed in the standard electron impact mode for both ALLO and its isomers and P4 measurements. The quantity of each neuroactive steroid of interest will be calculated by dividing the area under the peak of the neuroactive steroid in the sample by the area under the peak of the deuterated internal standard.

Statistical Analysis

Aim 1: Immune Dysregulation and Anxiety

Models for Immune Marker Patterns

Initially, we will perform exploratory cross-sectional analyses at each time point, both for quality assurance and to attain a better understanding of the distributions of the outcome variables for use in subsequent analyses (eg, the need for any transformations), followed by the longitudinal analyses. Specifically, the distribution of cytokine values will be explored at each time point to assess the frequency of missingness (including the number of observations below the limit of detection) and summarized using descriptive statistics. Longitudinal models will be fit to the cytokine data to describe the average trajectory over the course of pregnancy. Generalized linear mixed-effects models (GLMMs) will be fit with random intercepts for women to account for within-woman correlation of the measurements over time. The basic model will include time, group (intervention, EUC, and healthy control), and their interaction, and will address whether cytokine trajectories differ between groups. This basic model will be extended to include a random slope for time if the exploratory analysis shows large variability in individual woman-specific cytokine trajectories over time. Additionally, nonindependent residual correlation structures will be explored to assess any leftover correlation after accounting for the random-effect structure. The main model will include log-transformed cytokine values; however, other distributions for the dependent variable will be used, such as multilevel Tobit models that account for the lower limit of detection for these measurements. GLMMs account for "missing at random" missingness, that is, women with missing data at some time points are not excluded, and missing cytokine values are assumed to depend on observed data: prior values and covariates in the model [61]. These models allow us to estimate each woman's trajectory as a deviation from the average trend using all their available data by borrowing information within and between women. However, in the case of substantial dropout, we will explore pattern mixture models where the "missing at random" assumption might not be adequate. These models allow us to estimate model coefficients for each pattern of drop-out or missing data and obtain overall estimates by averaging over the patterns [62]. Standard model checking will be performed, and the most parsimonious model will be selected based on the Bayesian information criterion.

Immune Dysregulation and Anxiety

To characterize the relationship between anxiety symptoms and peripheral markers of inflammation, we will assess the associations between cytokine levels as independent variables and the level of anxiety (as measured by the HADS-anxiety) as the dependent variable. The level of anxiety will be considered from the following perspectives: (1) dichotomous (HADS-anxiety score ≥8 or <8) and (2) continuous. In both analyses, we will compare women with anxiety against healthy controls to evaluate whether there is a positive association between cytokines and anxiety at different time points during pregnancy. In the exploratory analyses, we will also compare the distribution of demographic, medical, and pregnancy history characteristics across the 3 study groups to assess for potential confounding.

We will add anxiety measured as an independent variable to the model identified in the first set of analyses for cytokines as a dependent variable. The models will adjust for baseline symptom severity and other patient characteristics that are differentially distributed across the 3 study arms.

Aim 2: ALLO and Anxiety

To determine the relationship between levels of ALLO in pregnancy and anxiety symptoms, we will follow the same approach as for longitudinal modeling immune dysregulation, with ALLO levels as the independent variable and anxiety as the dependent variable. The model will include group and time as well as interactions of ALLO with group (to test whether the relationship between ALLO and anxiety differs by group) and ALLO with time (to test whether the relationship between ALLO and anxiety differs by time). The model will use concurrent values and lagged values for ALLO and anxiety to test whether the ALLO levels at prior time points are associated with the current value of anxiety scores.

Finally, because anxiety in pregnancy is a major risk factor for postpartum depression and our previous work has shown a relationship between ALLO in pregnancy and future postpartum depression [2,51], we will repeat all analyses using the development of postpartum depression as the dependent variable.

Aim 3: Immune Dysregulation and ALLO

We will evaluate the associations between ALLO levels and immune markers across time during pregnancy by disease group using exploratory analytic techniques, including visual displays to inform modeling. Using a similar GLMM framework, we will fit a separate model for each immune marker with ALLO levels as the independent variable, in addition to group, time, and other characteristics identified as potential confounders. Cytokine-specific models can be combined in 2 ways: (1) by creating a composite cytokine score for each woman, and (2) by fitting a multilevel model with crossed random effects that include random intercepts for women and immune markers to "borrow information" across multiple immune markers within the woman.

Aim 4: Mediation Analysis by Biological Measures

Estimated anxiety trajectories and ALLO levels (ie, random slope estimates from the GLMMs) will be used as candidate independent variables in generalized linear models (GLMs) for risk of pregnancy and birth outcomes: pre-eclampsia, gestational diabetes, preterm birth (PTB), small for gestational age (SGA),

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and low birth weight (LBW). GLM with a Poisson distribution will be used to model risk for rare outcomes. The cross-validated area under the curve will be used to assess model discrimination and determine which model is the best fit for our data.

The next analysis will focus on the association of antenatal anxiety and birth outcomes, comparing anxious to nonanxious women. We will specifically assess mediation by biological factors in both cross-sectional and longitudinal analyses, partitioning the total effect of anxiety on birth outcomes as direct and indirect, through a change in cytokine and hormone levels.

Aim 5: Infant Neurodevelopment

The final analysis will examine the association between biological indicators of anxiety and infant neurodevelopment at 6 weeks post partum using the ASQ-3, comparing both groups of women with symptoms of anxiety (those who received the intervention and those who did not) to the healthy controls and controlling for ALLO and immune dysregulation. The same type of GLM described in the previous section will be used with appropriate distributions, such as Gaussian for continuous or normally distributed outcomes or Poisson for binary outcomes. We will also examine whether the severity of anxiety symptoms modifies the effect. Because the ASQ-3 can be used as both a dichotomous and continuous scale, we will examine it using both binary and continuous techniques.

Sample Size and Power

A sample size of 60 participants in each group, women with anxiety and healthy controls, will give us at least 80% power to detect a difference in the means of log-transformed cytokines across groups with an effect size of 0.3 to 0.5. This calculation assumes 4 repeated measurements with an exchangeable covariance structure, a correlation of 0.6, and an =.05. Sample size calculations were performed using the PASS Sample Size Software program (NCSS Statistical Software) [63]. Prior studies in our clinic in Baltimore have an attrition rate of up to 20%, but the attrition rate for this type of study in Pakistan is unknown.

Ethics Approval

Institutional Approval

This study was reviewed and approved by the Johns Hopkins Bloomberg School of Health Institutional Review Board, Baltimore, United States (IRB No. 9177/MOD1879), the Human Development Research Foundation Ethics Committee, Islamabad, Pakistan (IRB/001/2017), the RMU Institutional Research Forum, Rawalpindi, Pakistan (IRB/RMU-20/12/20190), the National Bioethics Committee of Pakistan, Islamabad, Pakistan (IRB No.4-87/NBC-536/20/881), and the National Institute of Mental Health (NIMH)–appointed Global Mental Health Data Safety and Monitoring Board from the United States.

Consent Procedures

Following WHO guidelines [64], full study information is provided in Urdu before any study participant is asked to provide written informed consent. In cases of illiteracy, information is read aloud in the presence of a witness (not affiliated with HMHB), and oral consent is witnessed. These procedures as alternatives to written informed consent are routine and culturally acceptable in Pakistan.

Care and Referrals

Detailed ethical procedures have been established for the main trial. These procedures are the same for the extra 60 healthy (nonanxious) controls added for this substudy. Any woman showing severe depression or suicidality at any point during the study will be referred directly for psychiatric or psychological care. For non–life-threatening but high-symptom levels of anxiety or depression, the obstetrician or primary care provider will be alerted to undertake further assessment and to make appropriate referrals. Based on any report of intimate partner violence (IPV), during assessments, or reports of IPV in answer to a screener asked (at baseline and the third trimester) or on questions about emotional and physical violence taken from the Pakistan Demographic Health Surveys asked at 6 weeks post partum, women who report IPV will be referred to the Institute of Psychiatry, Rawalpindi Medical College, for social services.

Dissemination

The HMHB intervention is designed to reduce symptoms of anxiety during pregnancy, which has the potential to affect the development of common maternal postpartum perinatal mental disorders, including postnatal depression and anxiety, as well as intrauterine growth, as reflected in SGA, LBW, and PTB. The findings from this study will describe the biological mechanisms through which antenatal anxiety may be linked to future maternal psychiatric risk as well as how these biological markers may relate to birth and child development outcomes. The principal investigator and coinvestigators, both in the United States and the host country, will be given access to the cleaned data sets. The deidentified project data from the study will be posted on ClinicalTrials.gov and the NIMH data archive. The study results will be disseminated through peer-reviewed journals and conferences.

Results

Recruitment started on October 20, 2020, and data collection was completed on August 31, 2022. The start date for recruitment for this biological supplement study was delayed by approximately half a year due to the COVID-19 pandemic. The trial was registered at ClinicalTrials.gov (NCT03880032) on September 22, 2020. The last shipment of blood samples was shipped to the United States on September 24, 2022, where they will be processed for analysis. At the time of this submission on November 27, 2022, data had been collected but biological and data analysis had not yet begun.

Discussion

This study is an important addition to the HMHB randomized controlled trial of an intervention for antenatal anxiety. The intervention itself makes use of nonspecialist providers and, if effective, will represent an important new tool for the treatment of antenatal anxiety in LMICs. Our biological substudy is one of the first attempts to link biological mechanisms to antenatal

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anxiety in an LMIC in the context of a psychosocial intervention, and our findings have the potential to significantly advance our knowledge of the biological pathways of perinatal mental illness and treatment efficacy.

Expected Principal Findings

We hypothesize that anxious women will exhibit increased innate immune activity in late pregnancy compared to healthy controls. We further hypothesize that pregnancy ALLO levels will be negatively correlated with anxiety and that low ALLO in early- and midpregnancy will predict increased immune activation in late pregnancy. Lastly, we hypothesize that adverse birth outcomes will be positively correlated with immune activation and negatively correlated with pregnancy ALLO and that the neurobehavioral functioning of babies born to women with anxiety will be correlated with biological indicators when compared to infants born to healthy controls.

Comparison to Prior Work

These hypotheses are centered on our previous work finding elevations of innate immune cytokines in women with anxiety during pregnancy and early postpartum and our work finding that low ALLO in pregnancy is associated with current and future symptoms of anxiety [1,2,65]. These prior studies were carried out in extremely different populations (both in a high-income country, one with largely low-income Black and Hispanic participants and the other with largely high-income White participants). Should we find alterations in immune and/or neurosteroid activity, we will advance the field's understanding of the biological mechanisms that may underlie perinatal mood and anxiety disorders and pave the way for future research into new methods of treatment to address these potential mechanisms.

Strengths and Limitations

Our study involves research teams on 3 continents and the training of a substantial number of nonspecialist providers. It is complex to begin with. Nevertheless, recruitment for both the main study and the supplement study has been steady. The biggest logistical challenge has been the COVID-19 pandemic (combined in Pakistan with waves of dengue fever). These public health crises delayed the start of the study due to the lockdown and have greatly reduced our ability to recruit during the rest of the study period. Pregnant women in Pakistan have been reluctant to come into the hospital even for standard prenatal care due to the pandemic, and there have been misconceptions and misinformation about the role of public hospitals in COVID-19 [66]. These logistical challenges have resulted in a scaling back of our study design. We had originally planned to recruit larger numbers (N=300) into this substudy, which would have allowed us to examine not only differences between anxious and healthy women but also whether those differences were mitigated by our psychosocial intervention. These latter questions will now await a follow-up study.

Future Directions

Our next step for this research is to analyze the biological samples collected. Future studies may include additional secondary biological analyses and the design of future studies involving other maternal and infant biological systems.

Trial Status

This article reports on the first version of our protocol; recruitment began in October 2020 and ended in January 2022; study visits ended on August 31, 2022.

Acknowledgments

The authors wish to acknowledge all participants involved in the study. They wish to thank members of the Osborne Lab at Johns Hopkins University for their assistance in coordinating sample shipments and study protocols. All work in this manuscript, including design, data collection, analysis, and interpretation, was supported by the NIMH at the US National Institutes of Health grant RO1 MH111859-01. LMO's time was additionally supported by NIH-NIMH K23 MH110607 and MLS' by NIH-NIAID T32 AI007417.

Data Availability

The HMHB intervention is designed to reduce symptoms of anxiety during pregnancy, which has the potential to affect the development of common maternal postpartum perinatal mental disorders, including postnatal depression and anxiety, as well as intrauterine growth, as reflected in SGA, LBW, and PTB. The findings from this study will describe the biological mechanisms through which antenatal anxiety may be linked to future maternal psychiatric risk as well as how these biological markers may relate to birth and child development outcomes. The principal investigator and coinvestigators, both in the United States and the host country, will be given access to the cleaned data sets. The deidentified project data from the study will be posted on ClinicalTrials.gov and the NIMH data archive. The study results will be disseminated through peer-reviewed journals and conferences.

Authors' Contributions

MLS drafted the original manuscript. PJS and LMO are the lead investigators on this project and edited the manuscript. All other authors are involved in the study team and edited the manuscript. All authors approved the final version of the manuscript.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-reviewer report from Biobehavioral Mechanisms of Emotion, Stress and Health (MESH) Study Section - Biobehavioral and Behavioral Processes Integrated Review Group - Center for Scientific Review (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 171 KB - resprot_v12i1e43193_app1.pdf]

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Abbreviations

ALLO: allopregnanolone
ASQ-3: Ages and Stages Questionnaire
EUC: enhanced usual care
GLM: generalized linear model
GLMM: generalized linear mixed-effects models
HADS: Hospital Anxiety and Depression Scale
HFH: Holy Family Hospital
HMHB: Happy Mother-Healthy Baby
IPV: intimate partner violence
LBW: low birth weight
LMIC: low- and middle-income country
NIMH: National Institute of Mental Health
P4: progesterone
PTB: preterm birth
SGA: small for gestational age
WHO: World Health Organization

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Protocol

Using User-Centered Design to Facilitate Adherence to Annual Lung Cancer Screening: Protocol for a Mixed Methods Study for Intervention Development

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Abstract

Background: Lung cancer is the leading cause of cancer-related death in the United States, with the majority of lung cancer occurrence diagnosed after the disease has already metastasized. Lung cancer screening (LCS) with low-dose computed tomography can diagnose early-stage disease, especially when eligible individuals participate in screening on a yearly basis. Unfortunately, annual adherence has emerged as a challenge for academic and community screening programs, endangering the individual and population health benefits of LCS. Reminder messages have effectively increased adherence rates in breast, colorectal, and cervical cancer screenings but have not been tested with LCS participants who experience unique barriers to screening associated with the stigma of smoking and social determinants of health.

Objective: This research aims to use a theory-informed, multiphase, and mixed methods approach with LCS experts and participants to develop a set of clear and engaging reminder messages to support LCS annual adherence.

Methods: In aim 1, survey data informed by the Cognitive-Social Health Information Processing model will be collected to assess how LCS participants process health information aimed at health protective behavior to develop content for reminder messages and pinpoint options for message targeting and tailoring. Aim 2 focuses on identifying themes for message imagery through a modified photovoice activity that asks participants to identify 3 images that represent LCS and then participate in an interview about the selection, likes, and dislikes of each photo. A pool of candidate messages for multiple delivery platforms will be developed in aim 3, using results from aim 1 for message content and aim 2 for imagery selection. The refinement of message content and imagery combinations will be completed through iterative feedback from LCS experts and participants.

Results: Data collection began in July 2022 and will be completed by May 2023. The final reminder message candidates are expected to be completed by June 2023.

Conclusions: This project proposes a novel approach to facilitate adherence to annual LCS through the development of reminder messages that embrace content and imagery representative of the target population directly in the design process. Developing effective strategies to increase LCS adherence is instrumental in achieving optimal LCS outcomes at individual and population health levels.

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KEYWORDS

health information processing; intervention design; lung cancer; lung cancer screening; LCS; mixed methods; photovoice; user-centered design

Introduction

Background

Lung cancer is the leading cause of cancer-related deaths in both men and women in the United States [1,2] and is expected to account for approximately 21% of all cancer deaths in 2022 [2]. Most lung cancer occurrences are diagnosed at advanced stages, after the cancer has metastasized, directly contributing to the deadliness of the disease [2]. Lung cancer screening (LCS) with low-dose computed tomography (LDCT) can detect lung cancer in the early stages when curative and less-invasive treatment options exist [3,4]. LCS received a B recommendation from the United States Preventive Services Task Force (USPSTF) in late 2013, prompting private insurance companies to cover the cost of the service for high-risk individuals, defined as individuals aged 55 to 80 years, with a minimum tobacco smoking exposure history of 30 pack-years and currently smoking or have quit within the past 15 years [5]. The Centers for Medicare and Medicaid Services (CMS) subsequently approved reimbursement for LCS in 2015 for Medicare beneficiaries, although they recommended stopping screening at 77 years of age [6]. Recently, the LCS eligibility criteria were expanded by lowering the recommended starting age to 50 years and tobacco exposure to 20 pack-years [7,8]. The USPSTF implemented these recommendations in 2021, followed by Medicare in early 2022.

The efficacy evidence for implementing LCS in routine clinical practice is based on the results of 2 large randomized trials: the National Lung Screening Trial [3] and the Dutch-Belgian Lung Cancer Screening Trial [4]. The results from these trials showed that LCS can reduce lung cancer–specific mortality by at least 20% when performed annually. Importantly, both trials diagnosed more early-stage cancers on follow-up rounds of screening than on the first baseline LDCT scan [3,9], highlighting the importance of sustained engagement with LCS programs. Adherence to multiple rounds of screening exceeded 90% in both clinical trials, further demonstrating the importance of annual screening to maximize the effectiveness of LCS [3,9]. Unfortunately, the translation of yearly LCS participation has emerged as one of the core threats to fully achieving the population health benefits of early lung cancer detection, with real-world annual adherence rates as low as 22% [10]. There is an urgent need for individual- and system-level interventions that focus on increasing the annual adherence rates.

The American College of Chest Physicians recommends that LCS programs develop strategies to maximize compliance with annual screening, including mechanisms to communicate with screening participants [11]. Community and academic LCS programs have reported using reminder letters to address adherence [12-14], and the Community Preventive Services Task Force (established by the United States Department of Health and Human Services in 1996) strongly recommends client reminders for breast cancer screening with mammography and colorectal cancer screening with fecal occult blood test [15]. Research supporting this recommendation found that any type of reminder (live telephone call, automated telephone call, letters, and postcards) increased adherence rates over no reminders, and targeted and tailored materials were superior to generic materials for continued screening participation [16,17].

Although research on established cancer screening modalities serves as a starting point for understanding interventions for reminder preferences, modes, and frequency, the needs and context of the LCS-eligible population must be considered during intervention development. For optimal impact, the unique elements of the LCS and the eligible community must be used to inform efforts to build and sustain engagement with the LCS process. At the center of this milieu is the stigma surrounding cigarette smoking and lung cancer, which is deeply embedded in all levels of society and presents as a barrier for some LCS-eligible candidates to participate in screening [18]. In addition, individuals eligible for LCS often face additional health care disparities, as cigarette smoking is linked to indicators of low socioeconomic status such as rural residence, individuals with Medicaid or being uninsured, and racial and ethnic minority groups [19]. Furthermore, health messages that contain pictures are processed more efficiently [20], highlighting another integral component of LCS communication. Understanding the informational needs and imagery considerations of the LCS-eligible population is crucial for messaging in reminder intervention development.

Objectives

This paper describes an iterative, mixed methods study that uses the principles of user-centered design and participatory research methods to develop a reminder message intervention specific to annual LCS. This research study will (1) determine how LCS participants process health information regarding screening to identify possible options for reminder message content targeting and tailoring, (2) pinpoint imagery options that engage LCS participants, and (3) use these data to develop adherence to reminder messages for individuals who participate in LCS. Accordingly, the aims of this study are as follows:

- Aim 1: to determine key reminder preferences and demographic and clinical characteristics associated with LCS-specific health processing, informed and facilitated by Cognitive-Social Health Information Processing (C-SHIP) model constructs to guide reminder message content and options for message targeting and tailoring.
- Aim 2: to identify engaging graphic themes drawn from photos selected by LCS participants to facilitate annual adherence aided by meaning and visual appeal.
- Aim 3: to develop and evaluate a pool of candidate reminder messages for multiple platforms (postcard, letter, and SMS text messaging) integrating visual imagery based on LCS experts and participant feedback using the principles of user-centered design.

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Methods

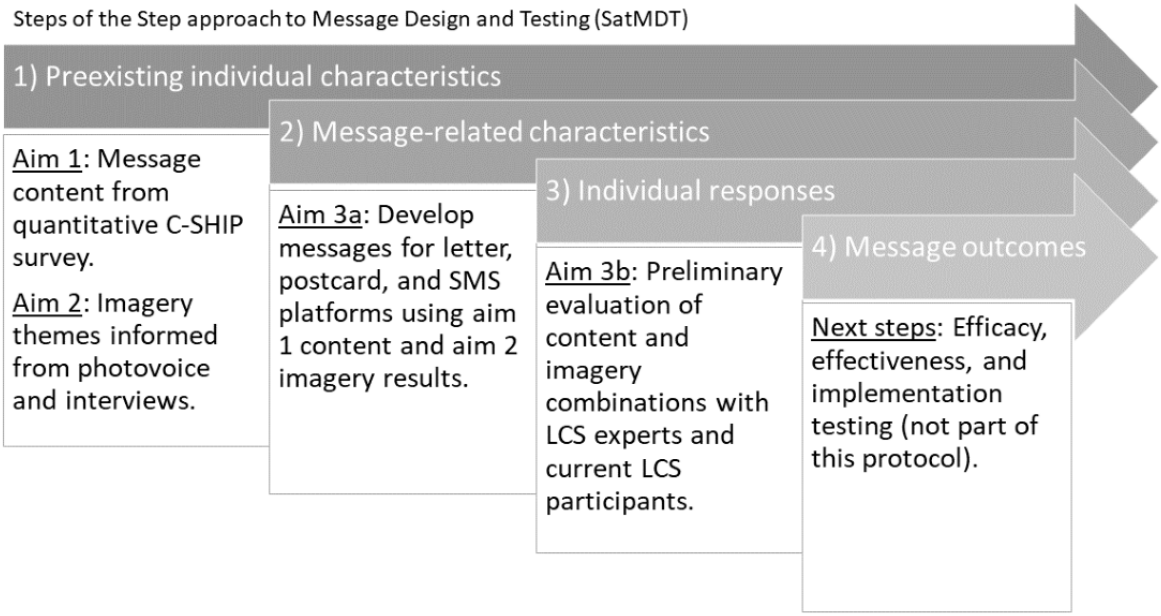
Design Overview

The goal of this research is to use a theory-informed, multiphase, and mixed methods approach with LCS experts and participants to develop a set of clear and engaging reminder messages to support LCS annual adherence. In a 3-step process, survey data (step 1) and themes for imagery informed by LCS participant photovoice and key informant mixed method interviews (step 2) will inform the development of a pool of candidate reminder messages (step 3) for usability evaluation and testing with LCS experts and participants. This research will be guided by methodological, theoretical, and conceptual frameworks and principles to direct the steps needed to design and evaluate reminder message content, provide guidance to measure relevant constructs about how LCS participants process health information, and inform message context and imagery through engagement with LCS participants.

Methodologic Framework

This research study will be guided by the Step approach to Message Design and Testing (SatMDT), a four-step conceptual process—(1) preexisting individual characteristics, (2) message-related characteristics, (3) individual responses, and (4) message outcomes—that will guide the overall reminder message development, from content identification to outcome evaluation [21]. As shown in Figure 1, step 1 of the SatMDT corresponds to study aims 1 and 2, informing the selection of relevant message content identified from quantitative survey data and further guiding reminder message imagery selection through the photovoice and interview activity. Aim 3 operationalizes SatMDT steps 2 and 3 by first using content results from aim 1 and imagery results from aim 2 to develop 10 to 12 reminder messages with varying visual combinations for each reminder type (ie, letter, postcard, and SMS text messaging). Second, it conducts preliminary testing of the message content and imagery combinations with rapid, iterative feedback with LCS experts and participants. SatMDT step 4 is outside the scope of this study. However, future studies will evaluate the efficacy and effectiveness of reminder messages to improve LCS annual adherence rates in clinical trials and real-world settings and on implementation testing to measure the acceptability and feasibility of using the reminder system in busy clinical settings.

Figure 1. Study approach as guided by the Step approach to Message Design and Testing (SatMDT). C-SHIP: Cognitive-Social Health Information Processing Model; LCS: lung cancer screening.



Theoretical Framework

To find informative and appealing content for the reminder messages that can further be targeted and tailored to the intended recipients, the C-SHIP model [22] will be applied to identify, contextualize, and operationalize the content of the reminder messages for the aim 1 quantitative survey. The C-SHIP model draws from several theoretical frameworks within the fields of health, cognitive, clinical, social, and behavioral psychology to identify health information seeking and processing behaviors, with the main premise detailing that health decision-making processes are the result of an interaction between the individual and the environment [22]. Aim 1 survey data informed by C-SHIP will be collected to assess how LCS participants process health information aimed at health protective behavior to develop content for the reminder messages and pinpoint options for message targeting and tailoring.

Conceptual Framework and Guidance

Additional research methodology will be guided by user-centered design and participatory photovoice to identify relevant content and imagery through engagement with LCS-eligible individuals and assessing preliminary usability testing. User-centered design is an intervention design approach that encompasses information about the individuals that will be using the intervention in the development and testing processes [23]. The goal of user-centered design is to maximize the usability of the intervention among the population of interest

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in a real-world context [23]. User-centered design will be used to (1) design the reminder intervention based on the characteristics of LCS participants and (2) refine message content and imagery based on rapid testing and feedback from LCS experts and participants. Consideration of the needs and emotions of LCS participants is vital for effective adherence reminder messaging.

Photovoice is a participatory research method that invites participants to take pictures representing an area of research within their community, allowing areas of concern to be documented and contemplated [24]. Traditional photovoice is completed by providing participants with a camera to capture the visual representation of the concern or research question and is then discussed through critical dialog in focus groups [25]. In this research project, photovoice will be used to invite participants to identify images that represent LCS to them and to identify themes for reminder message imagery through mixed methods interviews with the photovoice participants to understand the selection, likes, and dislikes of each photo.

Aim 1—Participant Health Information Processing Survey to Inform Message Content

Participants

The study participants will be recruited from three established LCS programs across the Colorado Front Range: (1) UCHealth University of Colorado Hospital in Aurora, Colorado; (2) UCHealth South in Colorado Springs, Colorado; and (3) UCHealth North in Fort Collins, Colorado. All LCS participants screened at these sites that meet the CMS or USPSTF eligibility guidelines, are English speaking, and have a screening-specific LDCT scan with results recommending 1-year (annual) follow-up (Lung-RADS 1 or 2) will be invited to complete the aim 1 health information processing survey 1 to 2 weeks after their LDCT. LCS participants who do not agree or consent to complete the survey or whose screening LDCT recommends shorter-term follow-up (Lung-RADS 3 or 4) will be excluded.

Procedure

Recruitment

All LCS participants that are screened in the 3 recruitment programs and have LDCT results recommending annual screening follow-up will be identified from clinical databases used to manage each program (Powerscribe Lung Cancer Screening developed by Nuance or Lung Cancer Screening Eon Patient Management developed by Eon Health). Additional variables, including Lung-RADS score, sex, race, ethnicity, smoking status, and pack-year information, will be abstracted from the clinical database to describe the study population and to report any differences between respondents and nonrespondents.

Survey Distribution

Potential study participants will be emailed a link for a REDCap (Research Electronic Data Capture; Vanderbilt University; electronic data capture hosted at University of Colorado Anschutz Medical Campus) web-based survey if an email is available in the electronic health record or a mailed paper version of the survey if only a postage address is available. The Tailored Design Method [26] will be used to maximize the response rate; specifically, enrolled participants will be contacted on multiple attempts if records indicate that the survey has not been completed, and respondents will receive US $40 compensation on the completion of the survey. Potential participants who received the survey by email will be contacted up to 4 times, 3 times by email and once by postal mail. This strategy has been reported to help increase survey response rates for individuals who do not respond to web-based surveys. Potential study participants who receive the survey by postal mail will be contacted up to 3 times.

Interested participants will be asked to acknowledge the contents of the informational consent form before proceeding with the survey. By completing the survey, respondents will agree to participate in the research study.

Sample Size

Using a 2-sample proportion test and assuming a minimum sample size of 125 survey respondents, there will be 80% power to detect a minimum difference of 20% for a χ^2 test with 1 *df* or 28% for a χ^2 test with 2 *df* between C-SHIP constructs (dependent) and survey respondent characteristics (independent) at an α level of .05. Power calculations were performed using PASS 11 (NCSS, LLC) [27]. A minimum of 125 complete surveys will be an achievable goal because the Tailored Design Method [26] will be used to optimize the response rate by offering multiple modes of survey delivery, making multiple contact attempts to nonrespondents, and offering US $40 compensation on the completion of the survey.

Measures

Relevant constructs from each C-SHIP domain have been chosen as a foundation for survey questions based on an extensive LCS literature review and identification of how C-SHIP has been applied to breast, cervical, and prostate cancer research [22,28,29]. Multimedia Appendix 1 [30-43] shows each LCS construct relevant to each C-SHIP domain and the scale or measure that will be used to measure each construct. Standardized scales were chosen wherever possible during the development of the aim 1 quantitative survey (LCS Health Beliefs Scale [30], Health Information National Trends Survey [31], Health Perceptions Questionnaire [32], Self-Regulatory Questionnaire for LCS [33], LCS Knowledge Survey [34], Cataldo Lung Cancer Stigma Scale [35], Revised Powe Fatalism Inventory [36], Health Behavior Scale for Cancer Patients [37], Medical Minimizer Maximizer Scale 1 [38], BRIEF Health Literacy Scale [39], Subjective Numeracy Scale [40], 9-item Shared Decision-Making Questionnaire [41], and radiology results from Woolen et al [42]).

The survey instrument contains all close-ended questions and comprises eight sections: (1) health-relevant encodings, (2) health beliefs and expectancies, (3) affects (emotions), (4) health goals and beliefs, (5) self-regulatory competencies, (6) previous screening LDCT and shared decision-making experience (satisfaction and stigma), (7) reminder preferences (timing, modality, and frequency), and (8) demographic and clinical information. The principles of the Tailored Design Method [26] (using simple words, complete sentences, as few words as

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possible, logical question organization, and easily understood concepts) were used to develop the survey to reduce common survey biases. The survey takes approximately 30 minutes to complete.

Analysis

All data from the aim 1 survey will be quantitative, mainly using Likert-type scales. Survey responses that occur more frequently will be prime candidates for reminder message content. Differences in C-SHIP constructs between demographic and clinical characteristics will guide reminder message content, with any statistically significant differences becoming a focus for message targeting and tailoring. To test for differences between C-SHIP constructs and respondent characteristics, the normal distribution of all variables will be evaluated with quantile-quantile plots. Variables with a normal distribution will be treated as continuous, whereas nonnormally distributed data will be categorized or analyzed using nonparametric tests. Univariate differences between the constructs and characteristics will be assessed with a 2-tailed *t* test or ANOVA for continuous variables (or nonparametric tests using ranks) and the chi-square test for categorical variables. The quantitative data collected in aim 1 will directly inform and influence the development of the reminder message content in aim 3.

Aim 2—Participant Photovoice and Interviews to Inform Themes for Message Imagery

Participants

Participants for aim 2 will be recruited from the same LCS programs used for the aim 1 survey. This sampling of participants will be recruited both independently and as a continuation of the aim 1 sample. As the purpose of aim 2 (to inform the imagery that will be selected for reminder messages) is separate from that of aim 1, no bias is expected from involving the same participants for both aims 1 and 2. Participants who completed an LCS LDCT within the past 12 months with results of Lung-RADS 1 or 2 with recommended 1-year (annual) follow-up and are English speaking will be eligible for aim 2. Sampling will be purposive, with emphasis placed on accruing heterogeneous participants (eg, males and females, race and ethnicity, and individuals that currently and formerly smoked cigarettes) for the photovoice activity and subsequent interviews. Participants who do not agree or consent to the photovoice activity and interview or whose screening LDCT recommends shorter-term follow-up (Lung-RADS 3 or 4) will be excluded from aim 2.

Procedure

Recruitment

The recruitment strategies will be similar to those of aim 1. Participants eligible for aim 2 will have completed an LCS LDCT that recommends 1-year (annual) follow-up within the past 12 months. Potential participants who represent a wide range of demographics and demographic characteristics (purposive sampling) will be sent an informational letter about aim 2 with directions to return the response card in the postage paid addressed envelope if only a postal address is available in the electronic health record or respond to the email to receive more information about participation.

The research team will follow-up with interested individuals using the contact information provided on the response card or email with additional information about participation in aim 2. Owing to the ongoing COVID-19 pandemic, enrollment will be limited to individuals who have access to computers with internet and video and audio capabilities. Participants will be asked to agree to an information sheet and consent electronically in REDCap to participate in aim 2.

Participant Photovoice Procedures

After obtaining informed consent, aim 2 participants will be asked to find 3 photos that represent LCS to them and to upload them into a REDCap database to later be used for the interview portion. This approach will use a modified photovoice component for participants to visually capture their idea of LCS by taking photos or finding photos using Google Images. Photovoice is a visual research methodology that traditionally supplies participants with a camera to take a picture that captures the essence of a cultural phenomenon or problem [24]. Photovoice is meant to facilitate community engagement in research and invoke a *voice* for self-perception in a research problem [24]. Using photovoice for LCS adherence will help pinpoint visual imagery that is attractive to a population traditionally stigmatized at individual and societal levels. The photovoice activity instructions will provide prompts about participating in LCS to help them think thoughtfully when choosing photos (Multimedia Appendix 1 [30-43]).

Interview Guide, Procedures, and Measures

Photovoice interviews will be conducted via Zoom and will be guided by a semistructured interview guide and use both open- and close-ended questions. Close-ended questions will yield quantitative data, and the open-ended questions will provide qualitative data. Participants will be shown the images they chose for the photovoice component one at a time on Zoom and asked questions about why they chose the image, what the image means to them, and likes and dislikes about the image. The interview questions were modified from the SHOWeD technique, which is commonly used in photovoice studies to help participants discuss the photos they captured [43] (Multimedia Appendix 1 [30-43]). Interview participants will also be asked to rate the image on a scale of 0 to 10, where 0 is "I don't like this photo" and 10 is "I really like this photo." At the end of the interviews, participants will be shown images commonly used in current LCS communications (cigarettes, lungs, and smoke) and will be asked about their thoughts, likes, dislikes, and ratings of each image on a scale of 0 to 10 (Multimedia Appendix 1 [30-43]). Probing questions will be used when appropriate. Interviews will be audio recorded and transcribed verbatim. Interview participants will receive US $60 as compensation on the completion of the interview.

Sample Size

The participants photovoice aim involves conducting approximately 20 debriefing interviews to reach saturation for photo visual appeal and thematic content. Interviews will be stopped early if saturation is reached before 20 interviews or

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will continue beyond 20 if the research team concurs that saturation has not been reached.

Analysis

Aim 2 interviews will use qualitative and quantitative data collected in parallel from the same interview guide, as described earlier. Following a parallel convergent mixed methods design [44], quantitative and qualitative data will be analyzed separately and then merged to make final conclusions about themes for reminder message imagery. Quantitative data from the closed-ended rating questions will be recorded in a matrix in Microsoft Excel (Microsoft Corporation), and similar responses will be categorized and ranked in order of frequency. Qualitative data from open-ended questions will be analyzed using thematic analysis [45]. Coding will be completed by 2 coders for the first 5 interviews to establish intrareader reliability, calculated using Pearson correlation or κ statistics. Coding will be inductive, meaning that the research team will use codes that emerge from the data. Standardized codes from the first 5 interviews will also be used to inform the development of a codebook that will be used to code the remaining interviews. The study team will meet weekly during the coding process to review and categorize themes and to determine when saturation has been reached. Finally, the team will integrate the results from the qualitative and quantitative data to make rich, multiangled inferences for the determination of the final imagery themes. The integration of the 2 data types will be done using a matrix analysis, in which the quantitative imagery ratings are compared with the qualitative themes. It is expected that the data types will corroborate, with higher-rated imagery containing positive and encouraging themes and lower-rated imagery associated with themes about lower-rated pictures. The matrix design will also offer the opportunity for qualitative data to explain the quantitative ratings and highlight the specific aspects the participants did or did not like regarding high- or low-rated imagery.

Aim 3—Development and Preliminary Evaluation of Reminder Messages

The purpose of aim 3 is 2-fold: first, to develop a group of reminder message candidates for 3 platforms (ie, letter, postcard, and SMS text messaging) with differing content and imagery combinations, and second, to conduct preliminary usability testing of the messages with LCS experts and participants. Evaluative testing will consist of rapid, iterative feedback cycles, with the refinement of messages occurring after each cycle of 3 experts or participants.

Development of Reminder Message Candidates

Reminder messages and content will be developed by the principal investigator (EAH), with final message candidates reviewed and finalized by the full research team. Messages will likely focus on conveying the benefit ("gain-framed") of annual LCS adherence [46]. Gain-framed messages have been shown to lead to greater knowledge and message recall [47]. Options for reminder message visual imagery based on themes from aim 2 will be chosen to accompany the message text. Messages that include a combination of verbal and visual cues are processed more efficiently than those with text alone [20]. Message content will be guided by messages that have led to increased adherence to repeat mammography [48,49] and messages developed for LCS awareness campaigns [50]. Overall, 10 to 12 reminder messages with differing visual appeals for each reminder type (postcards, letters, and SMS text messages) will be developed to achieve engagement for LCS-eligible individuals. Differences between health information processing constructs by demographic or clinical characteristics found to be statistically significant from aim 1 will be the focus of message targeting and tailoring.

Preliminary Testing by LCS Experts

Expert review of the reminder message candidate combinations (content and imagery) will be completed by LCS experts to gauge the message content from a clinical and implementation perspective.

LCS Expert Study Participants

Experts will be prespecified by the research team before the survey invitation and will include pulmonologists, radiologists, primary care clinicians, advanced practice providers, medical oncologists, and implementation scientists with expertise in LCS. Experts who agree to complete the evaluative survey will be included in aim 3. LCS experts who do not agree to participate in the rating process will be excluded.

LCS experts will be selected a priori based on the knowledge and contacts of the research team. Experts will be contacted via email to introduce the study and ask about their willingness to participate. Every effort will be made to have a balanced panel of experts (ie, pulmonologists, radiologists, advanced practice coordinators, primary care providers, medical oncologists, and implementation specialists). Informed consent will be obtained electronically using REDCap.

LCS Expert Survey Distribution and Follow-up Procedure

Expert surveys will be closed-ended and administered on the REDCap electronic platform. Respondents will be presented with a mock-up of each message-type and a brief clinical vignette with targeting and tailoring characteristics (if applicable) and asked to rate each message on 6 categories adapted from the Centers for Disease Control and Prevention (CDC) Health Communication Playbook [51] and the National Institutes of Health (NIH) Health Literacy Online [52] guidelines. Message ratings will use a 7-point Likert scale, where 1 is "very poor" and 7 is "very good," to rate the following categories specific to LCS annual adherence: (1) relevance of the message content, (2) readability of the message content, (3) accuracy of the message content, (4) intent of the message content (conveying screening benefit), (5) memorability of the visual appeal, and (6) overall rating of the message content and visual imagery combination (Multimedia Appendix 1 [30-43]). Experts will be asked to evaluate each message candidate, 10 to 12 for each message-type platform (letter, postcard, and SMS text messaging), or 30 to 36 messages in total.

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LCS Expert Sample Size

Rapid, iterative feedback and refinement of messages will be completed in cycles comprised of 3 experts. It is expected that usability testing will consist of 3 to 4 iterative cycles, with a total of 9 to 12 LCS experts.

LCS Expert Analysis Plan and Message Refinement

Data from the expert survey will be quantitative. Responses will be entered into a matrix in Microsoft Excel, and similar responses will be categorized and ranked in the order of frequency. Messages with lower ratings will be revised accordingly. Message candidates will be refined based on the feedback of each feedback cycle.

Preliminary Evaluation by LCS-Eligible Participants

In addition to expert review, further evaluative testing of the reminder messages will be performed with LCS participants who are close to their annual screening to determine the usefulness, desirability, and value of the reminder message content and imagery combinations.

LCS-Eligible Study Participants

Message evaluation participants will be recruited solely from the UCHealth University of Colorado Hospital LCS program, with emphasis on participants who are close to their annual screening LDCT (Lung-RADS result of 1 or 2). This sampling of participants will be separate from the aims 1 and 2 samples. The focus for this aim will be on participants within 4 to 6 weeks of their recommended annual screening LDCT. Participants will be eligible for annual screening by CMS or USPSTF guidelines, English speaking, and due for their annual LDCT scan within 4 to 6 weeks. Participants who do not agree or consent to participate in the reminder evaluation interviews or are not eligible for annual screening (aged out of screening age, >15 years since quitting smoking, or competing comorbidities) will be excluded from this study.

LCS-Eligible Participant Recruitment

Participants eligible for aim 3 will be due for their annual screening within 4-6 weeks. These participants will be identified in the database that is used to clinically manage the screening program at the University of Colorado Hospital. Recruitment strategies and informed consent procedures will mirror those used for aim 2.

LCS-Eligible Participant Interview Guide and Procedures

Evaluation interviews will be conducted on the Zoom platform, with participants shown each reminder message content and imagery combination during the interview. The interview guide will include both open- and closed-ended questions and is based on prior research work in adherence for mental health appointments [53]. A total of 3 questions will focus on the understanding of the message content, 3 questions will ask about the message appeal (likes and dislikes), and 1 question will ask about how wording or content could be improved (Multimedia Appendix 1 [30-43]). Interview procedures and participant compensation will be parallel to those used in the aim 2 photovoice interviews. Participants will be asked to evaluate approximately 20 to 25 message candidates, 7 to 8 for each message-type platform (letter, postcard, and SMS text messaging). The interviews are expected to last approximately 60 minutes, and participants will receive US $60 as compensation on the completion of the interview.

LCS-Eligible Participant Sample Size

Rapid, iterative feedback and refinement of messages will be completed in cycles comprised of 3 participants. It is expected that usability testing will consist of 3 to 4 iterative cycles, with a total of 9 to 12 LCS participants.

LCS-Eligible Participant Evaluation Analysis Plan

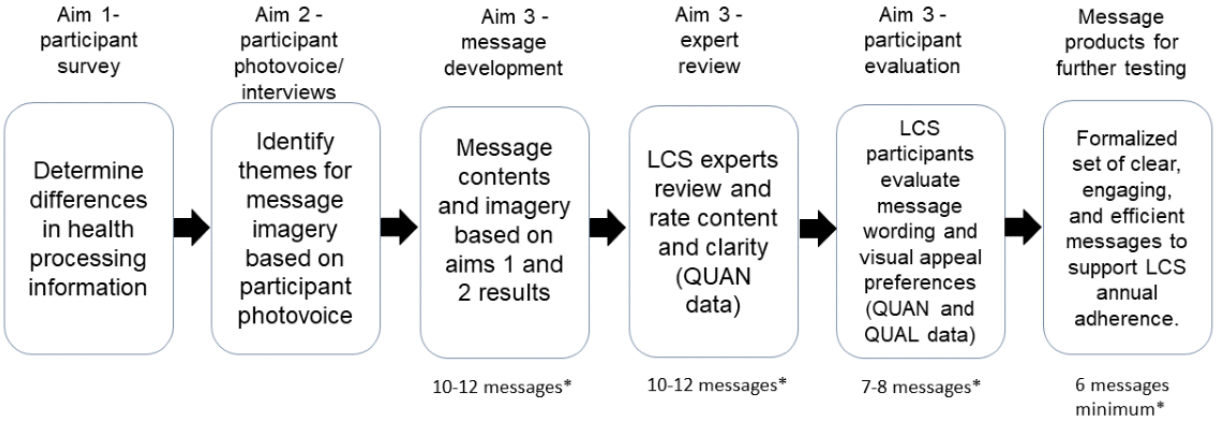
The participant evaluation will use qualitative and quantitative data collected from the same survey instrument and will therefore be completed using the same procedures as in the aim 2 analysis. Quantitative and qualitative data will be analyzed separately and then merged to make final inferences and recommendations for further reminder message refinement. It is expected that the data types will corroborate one another, with higher-rated messages and visuals containing positive and encouraging themes and lower-rated messages associated with themes about confusion or misunderstanding of the message. The matrix design will also offer the opportunity for the qualitative data to explain the quantitative ratings and highlight the specific aspects the participants did or did not like about high- or low-rated messages.

Refinement and Determination of Final Reminder Messages for Further Testing

The determination of the final reminder messages for each reminder type and matched visual picture will be driven by 3 main criteria: understanding, appeal rating, and anticipated impact. Difficulties in understanding the core message or with specific words will be used to refine the wording. Final message determination will consider results from both the usability expert survey and participant interviews by comparing the concordance or discordance between overall message ratings. Study team consensus will determine the final message set. The entire message development process is illustrated in Figure 2. The study team expects to have a minimum of 6 messages per communication type ready for robust testing in busy clinical settings.

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Figure 2. Summary of the message development process. *Per message-type (letter, postcard, and SMS text messaging). LCS: lung cancer screening; QUAL: qualitative data; QUAN: quantitative data.



Ethics Approval, Informed Consent, and Participation

This study was approved by the Colorado Multiple Institutional Review Board (COMIRB #21-3881) with full waivers of informed consent and Health Insurance Portability and Accountability Act of 1996 authorization to use LCS clinical databases and electronic health records to identify potential participants. In addition, a waiver of written documents for informed consent was obtained to allow for the ease of the consent process in REDCap. Participants in all aims will agree to the contents of an informational consent form containing details about the study purpose, procedures, confidentiality, and use of data before the initiation of any study procedures.

Results

The estimated milestones for study completion include (1) six months for setup (institutional review board approval, initiating procedures at accrual sites, updating the literature review for survey and interview guide development), which was completed in July 2022; (2) nine months for aim 1 survey recruitment, data collection, and analysis (expected completion: March 2023); (3) four months for aim 2 recruitment, data collection, and analysis (expected completion: March 2023); and (4) three months for aim 3 development of reminder message content and imagery combinations, recruitment, data collection, analysis, and refinement of final message candidates (expected completion: June 2023).

Discussion

Expected Outcomes

This project proposes a novel approach to facilitate adherence to annual LCS through the development of reminder messages that embrace content and imagery representative of the target population directly in the design process. Developing effective strategies to increase LCS adherence is instrumental in achieving optimal LCS outcomes at individual and population health levels. Engaging participants in yearly screening will ultimately increase the number of early-stage lung cancers detected, leading to improved outcomes and quality of life. Interventions aimed at addressing this critical need must be designed with the unique LCS population and context in mind and eliminate stigmatizing and biased content and imagery.

This research will develop message content based on health information processing theory conceptualized with the C-SHIP model, which recognizes health protective behavior decisions are the result of an interaction between the individual and their environment [22]. C-SHIP provides a broad framework to describe the characteristics of LCS-eligible individuals and constructs that may influence decisions to adhere to annual screening and to explore options for message targeting and tailoring. This project also aims to pinpoint imagery that is visually appealing and engaging in the LCS-eligible population. Imagery is often considered a significant component of health messaging and is even more important for individuals with low health literacy [54]. Specific to LCS, previous qualitative research in individuals at high risk for lung cancer found that images with cigarettes and lungs are ineffective in informational campaigns [55], highlighting the importance of identifying appropriate imagery for LCS communication. Finally, the resulting reminder messages will be iteratively tested with both LCS experts and participants to refine the message accuracy, understandability, and value of the content and imagery combinations.

Limitations

Although this approach will leverage the strengths of participatory research and user-centered design methods, there are limitations that must be acknowledged using the available settings and resources. First, we will not be able to assess social cognitive theory for all LCS populations that experience health disparities and could benefit from message targeting and tailoring (eg, lesbian, gay, bisexual, transgender, queer or questioning persons or those with mental and substance disorders). Second, Colorado's population lags the US population with regard to African American representation but exceeds the national average of individuals with Hispanic ancestry [56]. These demographic differences may compromise the generalizability of the initial development and testing of the message combinations. Finally, the efficacy and generalizability of these messages to clinical and health care settings are unknown. Despite these limitations, the design choices are appropriate to stimulate collaborative development of interventions directed specifically at improving LCS annual

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adherence and to highlight important areas of the future to strengthen the healthy equity reach and future efficacy, effectiveness, and implementation of the intervention.

Acknowledgments

This work is supported by a National Cancer Institute F99/K00 Predoctoral to Postdoctoral Fellow Transition Award (F99CA264409, principal investigator: EAH; Multimedia Appendix 2). This research was supported by National Institutes of Health (NIH) and National Center for Advancing Translational Sciences Colorado Clinical and Translational Science Awards grant UL1 TR002535.

Conflicts of Interest

JLS has provided consultation with the J&J Lung Cancer Initiative and the Lung Ambition Alliance and serves as the Scientific Advisory Committee for the Go2 Foundation for Lung Cancer and the Steering Committee for the National Lung Cancer Roundtable, which is currently funded by the National Cancer Institute (R01254734), the Bristol-Myers Squibb Foundation, Golfers Against Cancer, and the American Cancer Society. EAH reports grants from the National Institutes of Health (NIH) and National Cancer Institute (F99CA264409) and nonfinancial support from the NIH and National Center for Advancing Translational Sciences (UL1 TR002535).

Multimedia Appendix 1
Key questions and instructions for aims 1, 2, and 3.
[DOCX File , 29 KB - resprot_v12i1e46657_app1.docx]

Multimedia Appendix 2
Peer review report by National Cancer Institute Special Emphasis Panel - National Cancer Institute - NCI Predoc to Postdoc Fellow Transition Award (F99/K00) (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 145 KB - resprot_v12i1e46657_app2.pdf]

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Abbreviations

CDC: Centers for Disease Control and Prevention
CMS: Centers for Medicare and Medicaid Services
C-SHIP: Cognitive-Social Health Information Processing
LCS: lung cancer screening
LDCT: low-dose computed tomography
NIH: National Institutes of Health
REDCap: Research Electronic Data Capture
SatMDT: Step approach to Message Design and Testing
USPSTF: United States Preventive Services Task Force

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Protocol

Enhancing Nonverbal Communication Through Virtual Human Technology: Protocol for a Mixed Methods Study

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Abstract

Background: Communication is a critical component of the patient-provider relationship; however, limited research exists on the role of nonverbal communication. Virtual human training is an informatics-based educational strategy that offers various benefits in communication skill training directed at providers. Recent informatics-based interventions aimed at improving communication have mainly focused on verbal communication, yet research is needed to better understand how virtual humans can improve verbal and nonverbal communication and further elucidate the patient-provider dyad.

Objective: The purpose of this study is to enhance a conceptual model that incorporates technology to examine verbal and nonverbal components of communication and develop a nonverbal assessment that will be included in the virtual simulation for further testing.

Methods: This study will consist of a multistage mixed methods design, including convergent and exploratory sequential components. A convergent mixed methods study will be conducted to examine the mediating effects of nonverbal communication. Quantitative (eg, MPathic game scores, Kinect nonverbal data, objective structured clinical examination communication score, and Roter Interaction Analysis System and Facial Action Coding System coding of video) and qualitative data (eg, video recordings of MPathic–virtual reality [VR] interventions and student reflections) will be collected simultaneously. Data will be merged to determine the most crucial components of nonverbal behavior in human-computer interaction. An exploratory sequential design will proceed, consisting of a grounded theory qualitative phase. Using theoretical, purposeful sampling, interviews will be conducted with oncology providers probing intentional nonverbal behaviors. The qualitative findings will aid the development of a nonverbal communication model that will be included in a virtual human. The subsequent quantitative strand will incorporate and validate a new automated nonverbal communication behavior assessment into the virtual human simulation, MPathic-VR, by assessing interrater reliability, code interactions, and dyadic data analysis by comparing Kinect responses (system recorded) to manually scored records for specific nonverbal behaviors. Data will be integrated using building integration to develop the automated nonverbal communication behavior assessment and conduct a quality check of these nonverbal features.

Results: Secondary data from the MPathic-VR randomized controlled trial data set (210 medical students and 840 video recordings of interactions) were analyzed in the first part of this study. Results showed differential experiences by performance

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in the intervention group. Following the analysis of the convergent design, participants consisting of medical providers (n=30) will be recruited for the qualitative phase of the subsequent exploratory sequential design. We plan to complete data collection by July 2023 to analyze and integrate these findings.

Conclusions: The results from this study contribute to the improvement of patient-provider communication, both verbal and nonverbal, including the dissemination of health information and health outcomes for patients. Further, this research aims to transfer to various topical areas, including medication safety, informed consent processes, patient instructions, and treatment adherence between patients and providers.

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KEYWORDS

human technology; MPathic-VR; nonverbal communication behavior; patient-provider communication; virtual human

Introduction

Overview

The most important component of the patient-provider encounter is communication [1,2]. This finding has been reinforced by the National Cancer Institute model of patient-centered communication [3]. A recent meta-analysis of randomized controlled trials found a statistically significant effect (Cohen *d*=0.11; *P*=.02) on patient outcomes [4], consistent with other systematic reviews [5,6]. Poor patient-provider communication represents a pressing public health issue associated with increased medical errors and malpractice [1,7-11]. Communication has been shown to be a driver of patient satisfaction and outcomes and is closely connected with patient-centered care [9,10,12]. Collectively, these reports stress the public health importance of health communication and the need for interventions to improve providers' health communication.

Research on verbal health communication has led to important insights into information dissemination in the patient-provider encounter. However, less is known about nonverbal communication despite its equal importance [4]. Mehrabian and Ferris [13] reported that only 7% of emotional communication is conveyed verbally, 38% is conveyed by voice tone and inflections, and 55% is transferred by facial expressions [1,14,15]. Health issues, such as cancer, evoke fear, anxiety, and uncertainty. Patients are keen on subtle cues communicated both verbally and nonverbally [16]. For example, increased direct clinician body orientation is associated with increased patient satisfaction and understanding [17]. Inconsistency between verbal and nonverbal communication is detrimental to patient-centeredness because patients likely perceive these inconsistencies as disingenuous [1]. Henry et al's [18] systematic review of nonverbal communication found an association between nonverbal communication (global affect, warmth, negativity, listening, etc) and patient satisfaction. Connection to patient outcomes was less clear but also less researched, potentially due to the lack of a systematic assessment of nonverbal behavior. The authors called for developing consistent and validated measures of nonverbal communication and urged that "studies of facial expression might analyze patients' and clinicians' expressions at the dyadic rather than the individual level" with dyadic data analysis [18]. Thus, better assessment of nonverbal communication and application of appropriate dyadic statistics are needed.

Communication interventions directed at providers tend to provide communication skills training in a variety of formats, such as courses, workshops, or training videos [6]. One promising informatics-based educational strategy is virtual human training. Technology-based avatars and virtual humans have been developed to address cognitive tasks [19], such as verbal communication [20,21] and reasoning for diagnosis and therapy [22]. However, this body of literature is relatively nascent, particularly related to health communication. Research on virtual humans to enhance health communication has the potential to train medical students and nurses [23,24], as virtual humans offer a unique advantage by providing an authentic, safe simulated environment to learn with the appropriate level of challenge [25]. Users perceive virtual human interactions as real [26], and learners feel a social presence that can enhance learning and engagement [25,27,28]. After receiving feedback, the professional can immediately practice and implement the feedback, which is crucial to developing communication skills [29]. In contrast to human-standardized patients, virtual humans offer needed training without becoming fatigued. As a result, interactive and engaged virtual human informatics–based interventions demonstrate promise in enhancing communication.

Improving communication skills requires a reliable and valid method to assess them. Many communication assessments focus on verbal communication. These methods involve coding recorded interactions, such as the evidence-based Roter Interaction Analysis System (RIAS) [30], which has 41 categories, including a global affect rating (eg, voice tone) and the use of standardized patients instructors (SPIs) in simulated interactions [31] to evaluate performance. A nonverbal assessment is the Facial Action Coding System (FACS), which delineates observable components of facial movement into action units [32,33]. However, these are typically used for summative assessment of interventions or competence. Virtual human and informatics simulations have the potential to use assessment formatively by assessing behavior, providing automated feedback to the user, and giving further opportunities to practice. Educators often distinguish "assessment for learning" (ie, formative) with "assessment of learning" (ie, summative) because strategic use of formative assessment provides a more tailored, engaging experience with better outcomes [34,35]. Unfortunately, with few exceptions

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[23,36,37], interventions tend to rely on verbal assessment and standardized patients as a summative assessment only, rather than feeding results into the intervention as a formative assessment.

Standardized patients are widely used but are also costly, fatigue-prone, and have reliability concerns. SPIs have been used in objective structured clinical examinations (OSCEs) to assess verbal and nonverbal communication and provide feedback to learners. SPIs and OSCEs are a gold standard in communication assessment and are used in many interventions, including the MPathic–virtual reality [VR] trial, to assess primary outcomes. Yet, the cost of developing the scenarios, finding and hiring SPIs to conduct 1 OSCE, training to reach interrater reliability, and ongoing maintenance training is high. Published costs were estimated at US $35 per student in the United States in 1994 [38] and more recently in 2011 at US $90 per student in a European study [39]. The personnel time required for 1 OSCE has been reported as 104 hours for supervision, monitoring, logistics, and evaluation [39]. Finally, SPIs are prone to fatigue and excessive mental workload, which limits their ability to correctly identify and report on critical conversational and behavioral cues [40]. Therefore, SPIs are costly and best suited for summative assessment.

These informatics-based interventions to improve communication have primarily focused on verbal aspects. A recent innovation is an automated nonverbal feedback and detection system based on teleconferencing with an SPI, as reported by researchers in an Australian medical school [37]. The researchers demonstrated the utility of automated feedback on nonverbal behavior. In a randomized crossover trial, they found the system useful for enhancing medical communication and a statistically significant improvement over the standard curriculum component based on assessments by an SPI. Mpathic-VR, a virtual human simulation, has also assessed nonverbal communication by providing instructions to the user and by collecting sensor data (unanalyzed to date and a focus of this study) on nonverbal behaviors demonstrated. It also included an assessment of nonverbal behavior as 1 of 4 domains in a follow-up OSCE about 1 week post intervention, which indicates training transfer. It is important to note that communication may vary across in-person and telehealth visits. For example, clinicians tend to display more dominant behaviors, fewer empathy utterances, and portray an increased sense of urgency in telehealth visits [41].

One area that remains unclear is how nonverbal behavior is a mediating factor in communication competence, the accuracy of this nonverbal assessment, and whether the assessment is patient-centered. As a mediating factor, a potential path is that the system provides instruction on nonverbal communication (ie, stimulus), which prompts the learners to follow those instructions, leading to improved nonverbal communication as assessed by the Mpathic-VR and the follow-up OSCE. A path model is needed to test these assumptions, beginning with the extent to which the learner followed instructions. Although the data exist in this data set to test that path model, it has not yet been investigated. Understanding the mediating influence of nonverbal communication is essential to fully integrate nonverbal aspects into virtual human technology.

Conceptual Frameworks

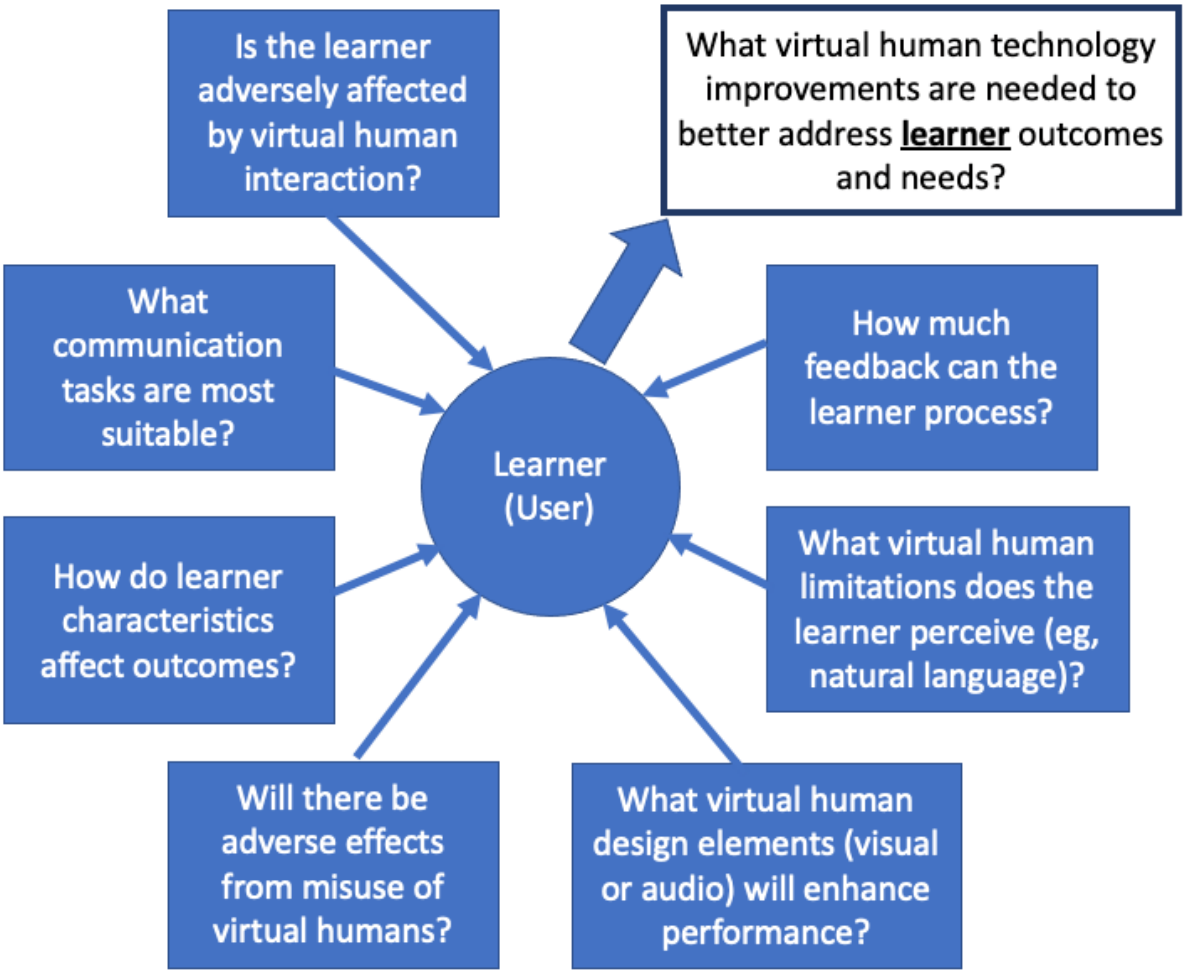
This study is guided by several conceptual frameworks, including frameworks for analysis of human factors and virtual human intervention.

Conceptual Framework for Analysis of Human Factors

Two models help guide the analysis of the human-computer interaction with the virtual human and the understanding of the mediation of nonverbal behavior. Stanney et al's [42] human factors in virtual environments (Figure 1) provide a model for systematic informatics research to harness the potential of virtual environments [42]. Second, the Activity Theory–based Model of Serious Games posits 3 interrelated activities contribute—instructional (what MPathic intrinsically teaches), learning (communication outcomes), and gaming (interacting with MPathic) [43]. This model is a framework for analyzing the relationship between the virtual human and educational goals. Teaching communication principles is not enough, and MPathic incorporates audit and feedback principles to reinforce lessons and promote sustained change [44]. A major outcome of this study is to better understand computer-human interaction to ensure a realistic experience that drives behavior change.

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Figure 1. Human factors in virtual human environment. Adapted from Stanney et al [42].



Conceptual Framework for the Virtual Human Intervention

Previous work has developed broad models of patient-centered communication (Figure 2) that guide the virtual human's instructional tasks. The National Cancer Institute's model of Patient-Centered Communication in Cancer Care [3] posits that patient-centered care and clinicians skilled in communication lead to improved health communication, which leads to improved health outcomes. Effective communication requires that patients and clinicians have "knowledge, understanding, and self-awareness of what is required to communicate effectively" and the skills to do so. In the Patient-Centered Communication model and consistent with educational theory [45], motivation of all parties is necessary to enhance communication skills. Additionally, health outcomes improve with attention to 6 core communication functions: (1) responding to emotions, (2) exchanging information, (3) making decisions, (4) fostering healing relationships, (5) enabling patient self-management, and (6) managing uncertainty. Nonverbal behavior can be mapped onto these core functions. An intervention that targets these core functions—both verbal and nonverbal aspects—to develop skills and attend to motivation through an engaging learning experience may overcome the limitations of these training models.

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Figure 2. Conceptual model of core functions of patient-clinician communication. Adapted from Epstein and Street [3].



Study Aims

This research aims to improve providers' dissemination of health information and related health outcomes for patients through an enhanced conceptual model of patient-centered communication that not only describes core communication functions but also presents a directional model of the interrelationships between those components. That conceptual model will be critical to incorporate into the technology to address verbal and nonverbal communication more comprehensively. Finally, this research will build the nonverbal assessment and automated feedback directly into the virtual human simulation for testing. This research has implications for a wide range of disease areas and broad applicability to medication safety, informed consent processes, patient instructions, and treatment adherence.

Methods

Overview

This research will use a multistage mixed methods design that includes convergent and exploratory sequential components (Table 1). The first phase will use a convergent design that merges [47] qualitative and quantitative MPathic-VR data to better understand the mediating influence of nonverbal communication (aim 1). Next, an exploratory sequential design will follow that begins with a qualitative grounded theory exploration through patient interviews. This information will be used to build [47] an automated nonverbal communication behavior assessment (aim 2). These findings will be used to develop the virtual human software's nonverbal assessment and conduct a quality control check as a small pilot of the enhanced system (aim 3).

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Table 1. Summary of research design: data sources, analysis, and outcomes of each phase.

Aim	Data collection procedures	Data analysis procedures	Product or outcome
(1) Mediating effects nonverbal communication	• Quantitative: MPathic game scores, Kinect nonverbal data, OSCE[a] communication score, RIAS[b] and FACS[c] coding of video • Qualitative: video recording of MPathic-VR interactions, student reflections	• Dyadic data analysis, path modeling • Thematic analysis of video data, followed by data transformation to quantify it	Understand what elements of the nonverbal behavior construct are most important in the human-computer interaction
(2) Develop model of nonverbal communication	• Interviews with oncology providers about intentional nonverbal behaviors (eg, mirroring, silence, and nodding)	• Grounded theory qualitative analysis: open coding and relating components to develop the model	Model of nonverbal communication; function to include in virtual human
(3) Add and validate a new automated nonverbal communication behavior assessment in MPathic-VR	• Qualitative findings inform development of assessment along with FACS and RIAS models; Providers use MPathic-VR and assess if the system detects nonverbal behavior	• Mixed methods to build assessment: codes → variables, quotes → item language, interrater reliability analysis; code interactions, dyadic data analysis	Updated virtual human with new automated nonverbal communication behavior assessment; initial quality control data

[a]OSCE: objective structured clinical examination.

[b]RIAS: Roter Interaction Analysis System.

[c]FACS: Facial Action Coding System.

Convergent Mixed Methods Design

Overview

A mixed methods convergent design [48] will be used that integrates qualitative nonverbal assessment and student reflections with quantitative MPathic-VR game data and OSCE communication skill scores. The results generated from the convergent mixed methods design will help identify the mediating influence of nonverbal behavior and what nonverbal elements of the intervention were most important.

Data Collection

Data will be collected from the MPathic-VR to investigate the mediating influence of nonverbal behavior in virtual human intervention. Although results from the trial indicated a positive effect, it is imperative to understand what aspects of nonverbal communication were most predictive of outcomes. To address this, a large amount of data will be gathered from 210 participants in the MPathic-VR intervention arm (that has not yet been previously analyzed) to understand the extent and mechanism by which nonverbal communication influenced outcomes. Data include video recording MP4 files for each of 4 interactions (840 videos), MPathic-VR scores (continuous data) that reflect the path through the system and responses for each participant, a warehouse of nonverbal sensor data (binary data) recorded by the Microsoft Kinect sensor for 4 nonverbal behaviors (eg, nodding, shaking head, smiles, and proximity), OSCE performance scores (5-point rating for 4 domains and a continuous global score), and qualitative written reflections from the medical students.

Data Analysis and Integration

Data will be analyzed using several methods. Specifically, instances of nonverbal behavior displayed by the learner and the virtual human will be coded, and dyadic data analyses will be carried out to examine the extent to which the learner mirrored the behavior of the virtual humans. Then, interactions using the RIAS and FACS will be coded. Another aspect that will be investigated is how participants responded to each virtual human after their action review by using the feedback in their second attempt at the scenario. Thus, it is necessary to test the relationship between the nonverbal behavior the learner demonstrated, and the assessment scores focused on that behavior (ie, if a learner demonstrates nonverbal behavior through the scenario, do the assessments detect it?). These will be tested in a structural equation model that will be compared to the qualitative data.

Importantly, analyzing video and individual-level data will help explain the extent to which participants followed instructions regarding nonverbal behavior and connect it to communication skills outcomes. The R-squared of nonverbal behavior relative to verbal behavior by learners on the OSCE outcome will be calculated to guide virtual human simulations. Data will be integrated by merging the qualitative and quantitative data, which will yield new insight into the particular mechanisms of nonverbal behaviors related to OSCE outcomes. Integration aims to generate meta-inferences, that is, integrated conclusions, beyond what either database alone could determine. The outcomes will provide a better understanding of human-computer interaction with virtual humans, which will inform future informatics interventions and identification of variables to assess nonverbal communication for inclusion in the virtual human.

Exploratory Sequential Design

Overview

To develop a new conceptual model of nonverbal communication to inform virtual human-based training (aim 2) and develop new nonverbal functionality into the MPathic-VR

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virtual human simulation by creating an automated nonverbal communication behavior assessment for health care providers (aim 3), an exploratory sequential design will be carried out. First, a qualitative study using grounded theory methods [49] will be conducted to explore patient-provider communication, in addition to drawing from existing models. The follow-up quantitative strand will assess how well the system detects added features of nonverbal behavior through a quality control check.

Data Collection

For the qualitative grounded theory phase of this exploratory sequential design, data sources will include findings and video data from the MPathic-VR trial (aim 1). Interviews will also be conducted with providers focused on understanding intentional nonverbal communication (eg, mirroring, silence, distance, smiling, nodding, and leaning). Specifically, using theoretical, purposeful sampling [49] of providers (eg, physicians, nurse practitioners, and physician assistants) actively seeing oncology patients, 20 providers will be recruited from the University of Michigan health system, seeking variation in terms of cancer specialty, years since training, gender, and other demographics. The ultimate sample size will be determined by data saturation—the point at which the theory is developed, and new information is not emerging [50]. It is necessary to obtain the providers' perspectives firsthand of intentional nonverbal communication to develop a patient-centered model. The quantitative strand will consist of video recordings that will allow for comparisons of nonverbal behaviors from provider participants between the system-recorded (Kinect) responses and manually scored records.

Data Analysis and Integration

Patient-provider interviews will be analyzed following Corbin and Strauss' [49] constant comparative method, including open and focused coding, to develop a theory of the process of patient-provider nonverbal communication. This model will provide a theoretical basis for the subsequent automated nonverbal communication behavior assessment I will develop. The outcomes will be a new model of nonverbal communication that refines models of patient-centered communication and novel nonverbal elements to include in MPathic-VR for testing.

The qualitative data analysis, including coding of nonverbal behavior, provider interviews, and the FACS and RIAS models of communication assessment, will inform the development of a novel automated nonverbal communication behavior assessment that will be tested. Specifically, qualitative findings will be incorporated using building integration to systematically use the qualitative findings to develop the assessment. Themes will inform assessment features, and qualitative codes will inform variables to measure in the automated nonverbal communication behavior assessment [51]. The video recordings will be used to assess the reliability of the assessment by calculating Cronbach α using .8 as a standard for internal consistency and will be compared with OSCE nonverbal behavior ratings to gather initial evidence of construct validity. Finally, the manually coded video data will be compared to the Kinect sensor data, both dichotomously scored for each encounter, to gather further evidence of the validity of the assessment. As described above, this existing nonverbal data recorded whether or not 4 nonverbal behaviors (eg, smiles, nods, body lean, and eyebrow raises) occurred for each participant interaction. The new automated nonverbal communication behavior assessment will be programed into the MPathic-VR intervention for quality testing.

A prospective quality check will be conducted to test and refine the new automated nonverbal communication behavior assessment of the MPathic-VR's ability to capture and assess nonverbal communication using the newly added features. This testing is needed to ensure the virtual human software is assessing clinically meaningful nonverbal behavior. Especially, it will be critical to test whether the system can recognize predefined aspects of nonverbal behavior by comparing system-recorded (Kinect) responses to manually scored records for predefined nonverbal behavior produced by provider test participants (n=30).

All data will be dichotomous (Yes/No) for each nonverbal behavior. Participants will be directed in advance to produce certain behaviors during the scenarios. Then, 2 analysts (principal investigator and research assistant) blinded to the directions will code behavior for each interaction from a video recording using the nonverbal communication behavior assessment, the RIAS, and the FACS. Because the manual recording will be considered the standard, the principal investigator and second independent reader will score manually to account for and investigate variability in manual coding. An interrater reliability analysis of the system-recorded responses with manually scored responses will be conducted. Dyadic data analysis techniques will also be applied to examine recorded nonverbal behaviors.

Based on accepted interrater reliability of SPIs [52,53], κ=0.6 will be considered adequate interrater reliability and κ=0.8 optimal using Cohen statistic [54,55]. Using the most conservative estimate of detecting κ=0.6 and a 2-tailed test of the null hypothesis of 0 agreement, a sample of 30 is needed for 90% power to assess the reliability [55]. If reliability falls below κ=0.6, we have 2 alternative procedures: (1) identify the lowest-performing cue and delete it to improve reliability, or (2) when 1 cue performs poorly, seek new technology, and repeat the analysis with the new technology, and compare to manually-coded assessment data from the MP4 recording. The outcome of this aim will be a refined virtual human software that includes the automated nonverbal communication assessment and initial quality control check data. Aim 3 will be critical to prepare for a subsequent R01 intervention to refine and test the revised virtual human system that contains novel scenarios assessing and automating both nonverbal and verbal communication after action review feedback.

Ethical Considerations

This study has been approved by the University of Michigan's institutional review board (HUM00134766). Informed consent will be requested electronically from each participant interested in participating in the study.

Privacy and Security

Given the large amount of video data that will be used in this study, several steps will be taken to ensure the security of these

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documents. For example, all data will be stored on University-approved Box and Dropbox secure storage systems using password-protected security and encrypted computers.

Results

Data collection for this study started in 2019 by accessing secondary data of the MPathic-VR randomized controlled trial data set (210 medical students and 840 video-recordings of interactions) [56]. These data have been analyzed and are expected to be published in 2023. After analyzing these data, recruitment for the qualitative phase of the exploratory sequential design followed in 2021. We expect to complete data analysis for the qualitative phase by July 2023.

Discussion

Principal Findings

This study aims to improve providers' dissemination of health information and related health outcomes for patients through an enhanced conceptual model of patient-centered communication. This study will not only describe core communication functions but also present a directional model of the interrelationships between those components. This conceptual model will be critical to incorporate into the technology to address verbal and nonverbal communication more comprehensively. It is expected that the resulting conceptual model will be able to capture differences in verbal and nonverbal communication behaviors based on the delivery format (eg, in-person or telehealth visits). Finally, the project will build the nonverbal assessment and automated feedback directly into the virtual human simulation for testing. In doing so, we anticipate learners will be able to incorporate the program feedback and improve their nonverbal behaviors.

We expect to find changes across learners interacting with virtual humans on nonverbal behaviors, including those emphasized by the MPathic-VR (eg, eyebrow raise, nodding, and smiling), as well as other facial expressions (eg, furrowed eyebrows, lip corner puller, lower eyelid raise, and oblique eyebrows slight lip press) [57], and head and body orientation (eg, eye gaze toward virtual human, forward lean, and head tilting). Specifically, we would expect to find an increase in the frequency of nonverbal behaviors across learners after repeated interactions with virtual humans. We also anticipate that feedback from the virtual human will contribute to an increased awareness of learners' nonverbal behaviors. Dissemination of research findings will occur through conferences and articles.

Limitations

It is important to consider some limitations of this study. First, a team of researchers will be involved in coding a large number of video recordings to analyze learners' nonverbal behaviors. As a result, coder drift can occur, and discrepancies across coders can arise. To mitigate potential issues of coder drift, the team will meet regularly to discuss any discrepancies throughout the coding process. Second, the role of culture is critical to the assessment of nonverbal behaviors. Nevertheless, a previous study assessing the effectiveness of the MPathic-VR for teaching intercultural and interprofessional communication among medical students demonstrated that the MPathic-VR helped to increase students' scores after repeated exposure, thus leading to increased awareness of cultural components [36]. Moreover, previous research found significantly higher scores on cultural conversational verbal and nonverbal behaviors for participants exposed to a virtual human condition compared to using illustrations as guides [58]. Thus, the use of virtual humans has been shown to enhance cultural awareness across interactions.

Conclusions

This research has implications for a wide range of disease areas and broad applicability to medication safety, informed consent processes, patient instructions, and treatment adherence. One of the main strengths of this study is the potential to advance understanding of key aspects of nonverbal communication that can be used to develop informatics-based interventions and ultimately improve patient-provider communication. Using a multistage mixed methods design consisting of convergent and exploratory sequential components, we will be able to more thoroughly understand the nonverbal elements that lead to skill enhancement, develop a model, and automate nonverbal communication behavior assessment. These results will be needed for further virtual human simulation development and will help advance biomedical informatics.

Acknowledgments

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Data Availability

Deidentified data will be made available to all appropriate requests from interested researchers at the time of results publications.

Conflicts of Interest

MDF has stock options in Medical Cyberworlds and FWK serves as president of Medical Cyberwords, which develops MPathic-VR. The University of Michigan Conflict of Interest Office considered potential for conflict of interest and concluded that no formal management plan was required.

Multimedia Appendix 1

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Peer review report from the National Library of Medicine Special Emphasis Panel - Conflict of Interest and Career Awards (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 145 KB - resprot_v12i1e46601_app1.pdf]

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Abbreviations

FACS: Facial Action Coding System
OSCE: objective structured clinical examination
RIAS: Roter Interaction Analysis System
SPI: standardized patients instructor

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Protocol

Assessing the Feasibility of Economic Approaches to Prevent Substance Abuse Among Adolescents: Protocol for a Mixed Methods Study

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Abstract

Background: Adolescent alcohol and drug use (ADU) is a significant public health challenge. Uganda, one of the poorest countries in Sub-Saharan Africa (SSA), has the second-highest rate of per capita alcohol consumption in SSA, and over one-third of Ugandan adolescents have used alcohol in their lifetime (over 50% of them engage in heavy episodic drinking). These estimates further increase in fishing villages, a key HIV-vulnerable population, where ADU is normative. However, few studies have assessed ADU among adolescents and youths living with HIV despite their increased risk for ADU and its impact on engagement in HIV care. Moreover, data on risk and resilience factors for ADU are scarce as only few studies evaluating ADU interventions in SSA have reported positive outcomes. The majority have been implemented in school settings, potentially excluding adolescents in fishing communities with high school dropout rates, and none have targeted risk factors including poverty and mental health, which are rampant among adolescents and youths living with HIV and their families, undermine their coping skills and resources, and have been associated with increased risk for ADU among them.

Objective: We propose a mixed methods study with a sample of 200 adolescents and youths living with HIV (aged 18-24 years) seen at 6 HIV clinics in southwestern Uganda's fishing communities to (1) examine the prevalence and consequences of ADU and identify the multilevel risk and resilience factors associated with ADU among them and (2) explore the feasibility and short-term effects of an economic empowerment intervention on ADU among them.

Methods: This study comprises four components: (1) focus group discussions (FGDs) with adolescents and youths living with HIV (n=20) and in-depth qualitative interviews with health providers (n=10) from 2 randomly selected clinics; (2) a cross-sectional survey with 200 adolescents and youths living with HIV; (3) a randomized controlled trial with a subgroup of adolescents and youths living with HIV (n=100); and (4) 2 postintervention FGD with adolescents and youths living with HIV (n=10 per group).

Results: Participant recruitment for the first qualitative phase has completed. As of May 4, 2023, ten health providers from 6 clinics have been recruited, provided written consent to participate, and participated in in-depth qualitative interviews. Two FGDs was conducted with 20 adolescents and youths living with HIV from 2 clinics. Data transcription, translation, and analysis of qualitative data has commenced. The cross-sectional survey will commence shortly after and dissemination of the main study findings is targeted for 2024.

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Conclusions: Our findings will advance our understanding of ADU among adolescents and youths living with HIV and inform the design of future interventions to address ADU among them.

Trial Registration: ClinicalTrials.gov NCT05597865; https://clinicaltrials.gov/ct2/show/NCT05597865

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KEYWORDS

adolescents living with HIV; alcohol; Sub-Saharan Africa; substance use; Uganda

Introduction

Overview

Adolescent alcohol and drug use (ADU) is a growing public health concern globally, especially in low-resource settings such as Sub-Saharan Africa (SSA), where the epidemics of ADU and HIV/AIDS are co-occurring. ADU plays a significant role in the epidemiology of HIV among adolescents and young adults in SSA, who accounted for over 40% of new infections globally in 2019 [1]. ADU is associated with higher rates of HIV risk behaviors, such as condomless sex [2] and lower rates of HIV testing [3-5]. Among adolescents and youth living with HIV, ADU is a significant barrier to achieving positive HIV treatment outcomes, including enrollment and retention in HIV care [6], adherence to antiretroviral therapy (ART) [7-9], and viral suppression [8,10]. Among HIV-infected adults, it has been shown that alcohol and drug misuse increase AIDS mortality, even among virally suppressed and medication-adherent persons [11-13]. Uganda, one of the poorest countries in SSA, has high rates of HIV/AIDS (6.2%) [14] and alcohol use [15], and illicit drug use is on the increase [16]. Previous studies have reported high rates of alcohol consumption among adults living with HIV [17-19]. Fishing communities, a key vulnerable population in Uganda [20], have high levels of ADU, including among adolescents and youths [16,21-23], which lead to poor HIV prevention and care outcomes.

ADU onset typically occurs in adolescence as an experimental behavior that may escalate into problematic use and disorders [24,25]. Adolescence is a period characterized by the exploration of new roles, identities, and behaviors, including experimentation with ADU [26]. A multitude of factors influence ADU, and these include individual factors (eg, sensation seeking, impulsivity, and mental health) [27-32], interpersonal factors (eg, peer pressure, parental drug use, and poor parental monitoring) [33-43], and structural factors (eg, availability of alcohol and drugs, exposure to ADU marketing, community drug use attitudes, laws and policies, and structural barriers that contribute to poverty) [33,38]. Adolescents and youths living with HIV also experiment with ADU, which may escalate into problematic ADU.

Adolescents and youths living with HIV face numerous HIV-related psychosocial challenges, including HIV stigma, bereavement, chronic pain, relationship stress, and poverty, which heighten their risk for ADU [44-46]. Indeed, research reports indicate a higher burden of mental health problems among adolescents and youths living with HIV [45,47-50], which may lead to ADU. The co-occurrence of mental health problems and ADU is common, including among adolescents and youths living with HIV [49,51-57]. Both ADU and mental health difficulties are associated with nonadherence to ART [48,58-60] and risky sexual behaviors among adolescents and youths living with HIV [59,61-63], which could lead to secondary transmission of HIV and ART resistance due to nonadherence [64-66]. Poor mental health and poverty, which are rampant in poor countries, are significant risk factors for ADU. Poor mental health [54,67,68] and poverty [69-71] are rampant among HIV-affected households, and both are significant risk factors for acquiring HIV [72] and for poor HIV treatment outcomes [73,74]. Adolescents and youths living with HIV living in poverty-stricken households face greater challenges in accessing and sustaining HIV treatment due to economic factors, such as lack of money preventing access to transportation to clinics [75,76] and insufficient resources to afford food leading to inadequate meals to support medication adherence [77-79], which could lead to psychological distress and consequently, ADU [80]. Poverty adversely affects the quality of family relationships, including parent-child communication, involvement [81-83], and parenting skills [84,85], which increases susceptibility to emotional and behavioral challenges and increases risk for ADU [41,43,82,86-90].

Several studies have examined the risk and resilience factors for ADU [91] but few interventions targeting ADU have been tested in SSA. Efforts to prevent ADU are rooted predominantly in the substance use risk reduction and protection enhancement model [91] and require understanding of the risk and resilience factors for ADU. These interventions largely target individual and interpersonal risk factors for ADU, with a focus on providing participants with information on ADU and its consequences or building life skills. In SSA, only 1 intervention targeted the family [92], an important developmental context for adolescents, with a focus on enhancing parenting skills. Yet, none of these interventions has targeted risk factors, such as poverty and mental health, that are widespread in SSA and may undermine the resources and coping skills of adolescents and youths living with HIV.

Despite our knowledge of the higher risk for ADU among adolescents and youths living with HIV [93-96], there is lack of evidence-based interventions targeting ADU risk among adolescents and youths living with HIV. Only 10 ADU interventions have been evaluated in SSA [27,92,97-104] and only a few have been successful [27,98,99,101,103,104]. Most have been ineffective in preventing or reducing ADU, and none of these interventions have targeted adolescents and youths living with HIV. The majority of these interventions are largely

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school-based [27,100-104], which may exclude adolescents in fishing communities that have high rates of school dropout. These interventions also focused on individual and intrapersonal risk factors for ADU without paying attention to structural risk and resilience factors for ADU. The few existing studies on ADU among adolescents and youths living with HIV have been conducted in high-income countries. These studies focused on younger adolescents, yet ADU typically emerges and escalates in middle-to-late adolescence. Further, these studies rely on self-reports of ADU, which can be undermined by underreporting of ADU.

Economic empowerment (EE) interventions have the potential to prevent ADU among adolescents and youths living with HIV by reducing poverty and its associated mental impacts and bolster adolescents and youths living with HIV and their families' resources to overcome the challenges associated with HIV. In our previous studies, we have used EE strategies to reduce poverty and improve mental health and HIV care outcomes (eg, medication adherence) among adolescents and youths living with HIV and other AIDS-affected adolescents in Uganda [73,82,105-108]. In this application, we propose to build on this growing evidence by examining the feasibility of using EE to address ADU among adolescents and youths living with HIV.

This study will investigate the epidemiology, underlying risk, and resilience factors for ADU among adolescents and youths living with HIV and evaluate the effects of an EE intervention on ADU among adolescents and youths living with HIV. The specific aims of the study are as follows.

Aim 1a: Examine the prevalence and consequences of ADU in a cohort of 200 adolescents and youths living with HIV (aged 18-24 years) seen at 6 HIV clinics in southwestern Uganda. We will use adolescent self-reports and biological measures of ADU (urine).

Aim 1b: Using a mixed methods approach, identify the multilevel (individual, interpersonal, community, and structural) factors associated with ADU among adolescents and youths living with HIV.

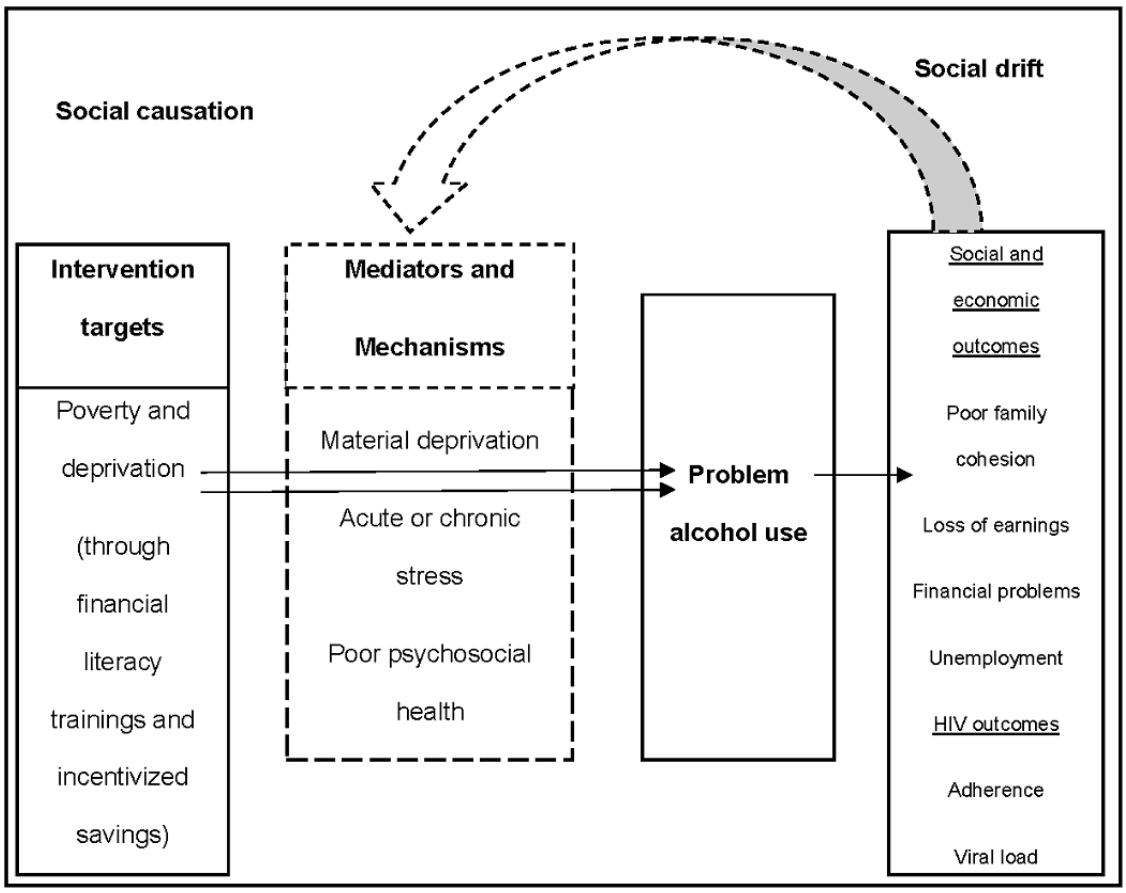
Aim 2: Using a subset of the sample, explore the feasibility and short-term effects of an EE intervention on ADU among adolescents and youths living with HIV.

Theoretical Framework

Our conceptual approach is informed by the socioecological model (SEM) [109], social causation and drift theories [110], and asset theory [111,112]. We have applied the SEM as a basis for investigating the contextually relevant risk and resilience factors for ADU. SEM posits that environmental factors fall into 4 broad domains: micro-, meso-, exo-, and macrosystems, and interactions within and between these domains determine behavior. This model has demonstrated effectiveness in identifying risk and resilience factors for prevention planning and intervention for ADU [113-117]. Social causation and social drift theories suggest that alcohol consumption problem may be both a response to and a driver of poverty [118]. Acute and chronic stress associated with living in a poverty-impacted environment increases the likelihood of ADU, which causes further material and economic deprivation, hence fueling the cycle of alcohol misuse, and contributing to downward social mobility. Our conceptual framework describes the hypothesized relationship among the intervention targets, poverty, poor mental health, and alcohol use. This has been adapted from Jones and Sumnall [119] (Figure 1)**.** Research in Uganda has reported a higher burden of alcohol and drug abuse among poor populations [120], and many poverty-impacted Ugandan households engage in informal alcohol production for income-generating purposes [121]. Impoverished youths are burdened with hopelessness due to lack of opportunities for improvement in their economic well-being [122,123]. As a result, for impoverished adolescents and youths living with HIV, they may be inclined to spend on instant pleasures, such as alcohol and drugs, as a coping mechanism since they are less likely to believe they can afford the costs associated with accessing and maintaining long-term care for HIV. Our proposed EE intervention is based on Asset theory [124] and is intended to improve economic well-being, relieve poverty and its related consequences, such as poor mental health [106,125], and create a more hopeful and optimistic outlook for the future, thus reducing engagement in risk-taking behaviors like ADU by adolescents and youths living with HIV. The proposed EE will be one of the first studies to examine the impact of EE interventions on reducing ADU among adolescents and youths living with HIV in poverty-impacted communities.

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Figure 1. Conceptual model.

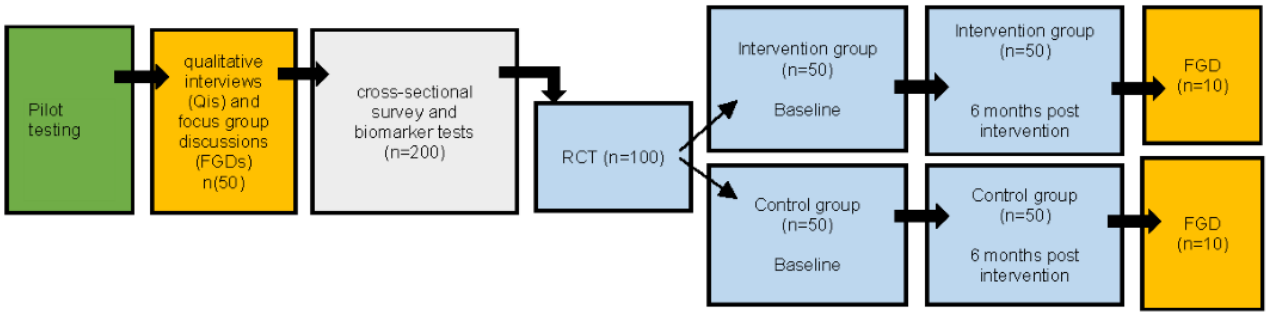


Methods

Overall Study Design

This mixed methods study comprises the following four components: (1) focus group discussions (FGDs) with adolescents and youths living with HIV (n=20) and in-depth qualitative interviews (QIs) with health providers (n=10) from 2 randomly selected clinics; (2) a cross-sectional survey (CS) with 200 adolescents and youths living with HIV; (3) a randomized controlled trial (RCT) with a subgroup of adolescents and youths living with HIV (n=100); and (4) 2 postintervention FGDs with adolescents and youths living with HIV (n=10 per study group). Figure 2 depicts the study components and expected number of participants in each component.

Figure 2. Study components and participant flow through the study. RCT: randomized controlled trial.



Study Sites and Participants

The study will be conducted in 6 randomly selected HIV clinics located in fishing districts within the Greater Masaka region of Southwestern Uganda—a region heavily affected by HIV (12% prevalence vs 6.2% national average) [126] with high rates of household poverty and alcohol use [127,128]. The target populations for this study are adolescents and youths living with HIV and health care providers at the selected HIV clinics. We

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will specifically target HIV clinics located in fishing districts with known HIV hot spots that are accredited by the Uganda Ministry of Health as a provider of ART and currently have established services for adolescents and youths living with HIV.

Inclusion Criteria

For the overall study, the inclusion criteria for adolescents and youths living with HIV are: (1) male or female adolescents and youths living with HIV aged 18-24 years; (2) medically diagnosed with HIV and aware of their HIV status; and (3) enrolled in care at one of the selected HIV clinics. Additionally, we will recruit 1-2 health care providers (psychosocial counselors, nurses, clinical officers, or doctors) from each of the selected clinics. For the RCT, a subsample of adolescents and youths living with HIV (n=100) with a positive self-report for ADU will be randomly selected and randomly assigned at the clinic level (3 clinics per group) to either the intervention group (n=50) or control group (n=50). A subsample of adolescents and youths living with HIV from both the control (n=10) and intervention groups (n=10) will be selected to participate in 2 FGDs at the end of the intervention. Overall, we will exclude any potential participant with significant cognitive impairments that interfere with their understanding of the informed consent process or who is unable or unwilling to consent. For the RCT and postintervention FGDs, we will exclude any adolescents and youths living with HIV with a negative self-report for ADU. However, given the minimum and maximum detection times for different drugs of abuse in the urine, we will not exclude those with a positive self-report but negative urine test results from being included in the RCT.

Participant Recruitment and Consent

Recruitment strategies will build on Reach the Youth Uganda (local implementing partner) and ICHAD's (International Center for Child Health and Development) long-standing relationships (>15 years) with 39 health clinics in the greater Masaka region. We will capitalize on recruitment procedures tested in previous SUUBI (Luganda word for Hope) studies that involve collaborating with health clinics in the region (namely Suubi+Adherence: 1R01HD074949-01, Suubi+Adherence-R2: R01HD074949-07, and Suubi4Stigma: R21MH121141) [129-131]. All participants will be recruited from the selected HIV clinics. For the CS, 200 adolescents and youths living with HIV will be recruited from across 6 clinics located in the greater Masaka region. The designated study contact at each health clinic will present the project to all eligible adolescents and youths living with HIV aged 18-24 years during their clinic visits. If there is interest, they will provide verbal consent to be contacted by the research study team. The study coordinator will contact interested adolescents and youths living with HIV to inform them about the required extent of participation, the risks and benefits of participating, and to ask any questions. Written informed consent will be obtained from adolescents and youths living with HIV aged 18-24 years and from health care providers aged more than 18 years to participate. The written consent documents will emphasize the following elements: (1) participation in the study is voluntary; (2) responses to study questions are confidential; (3) participants can terminate their participation at any time, and their decision to withdraw from the study will not affect their access to services they are currently receiving in any way; and (4) participants may be contacted to participate in the RCT if eligible. A screening tool will be developed to assess whether participants meet the study inclusion criteria.

Ethics Approval

We have obtained approval for the study procedures from the institutional ethics and institutional review boards at the Washington University in St. Louis (202301145) on January 31, 2023 (with an amendment approved on March 2, 2023); the University of Michigan (HUM00223732) on February 23, 2023 and from the in-country local institutional review boards in Uganda: Uganda Virus Research Institute (GC/127/933) on January 16, 2023, and Uganda National Council of Science and Technology (HS2683ES) on March 2, 2023. The study has been registered with ClinicalTrials.gov (NCT05597865) as of October 28, 2022. The dissemination of the main study findings is targeted for 2024. Participants' data will be protected by a certificate of confidentiality, which protects the privacy of research subjects by prohibiting the disclosure of identifiable, sensitive research information to individuals not involved in the research unless the participant consents.

Data Collection and Assessments

After pilot testing of data collection interview tools, 2 separate FGDs will be conducted with adolescents and youths living with HIV (n=20) and in-depth QIs will be conducted with health providers (n=10). Adolescents and youths living with HIV will be recruited from 2 randomly selected clinics, with 10 participants per FGD. The FGDs and QIs will explore participants' perceptions of the multilevel risk and resilience factors associated with ADU and recommendations for culturally appropriate ADU interventions for adolescents and youths living with HIV. Data from the qualitative phase will inform assessments to be conducted in the CS. For the CS, 200 adolescents and youths living with HIV will complete an interviewer-administered survey comprising questions assessing their alcohol and drug consumption patterns and frequency, as well as exposure to multilevel (individual, interpersonal, community, and societal) factors that may be associated with risky and hazardous drinking and drug use among adolescents and youths living with HIV. To reduce social desirability bias, questions on ADU will be self-administered using audio computer–assisted interviewing. We refer to the social ecological framework [132] to guide data collection on the multiple levels of influence that are associated with harmful alcohol and drug use among adolescents and youths living with HIV (see Table 1 for socioecological framework and additional measures that will be collected at each time point). Questions assessing the presence of common mental disorders and other physical health conditions will be included.

Urine tests for ADU will be conducted for all 200 adolescents and youths living with HIV who participate in the CS and for the 100 who participate in the RCT (at the 2 time points: baseline and postintervention). A trained research assistant will collect and test a urine specimen from each participant. The urine sample will be tested for up to 16 classes of the most commonly abused illicit drugs using the T-Cup 16 panel

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Compact Instant Drug Test Cup at the study site. The T-Cup can detect alcohol in the urine from as early as 8 hours to up to 80 hours after consumption. Minimum and maximum detection times for illicit drugs of abuse range from 1 hour to 40 days, depending on the drug.

Table 1. List of measures and time points collected during the study.

Category	Measure	Time point
Individual level of socioecological framework	Sociodemographic: gender, age, orphanhood status, education, income and unemployment, food insecurity [133], experienced homelessness, refugee, day and boarding school, and urban and rural residence. Mental health: depression [134], hopelessness [135], optimism [136], stress [137], pain [138], and history of substance abuse [139].	Cross-sectional survey, qualitative interview, focus group discussion, randomized controlled trial
Interpersonal and relationship levels of socioecological framework	Loneliness [140], number of close friends, bullying, interpersonal violence [141,142], social support [143], family cohesion [144,145], childhood abuse and trauma [146], family history of substance abuse [139], and sexual risk-taking [147]	Cross-sectional survey, qualitative interview, focus group discussion, randomized controlled trial
Community level of socioecological framework	Community norms and access to alcohol and illegal drugs	Cross-sectional survey, qualitative interview, focus group discussion, randomized controlled trial
Society level of socioecological framework	Educational campaigns, price and supply of alcohol, and social stigma [148]	Cross-sectional survey, qualitative interview, focus group discussion, randomized controlled trial
Biomarkers	Urine alcohol and drug tests	Cross-sectional survey, randomized controlled trial
Savings deposits	Savings	Randomized controlled trial
Assessments	Self-reported alcohol and drug use [139], viral load from clinic records, self-reported adherence [149], depressive symptoms [134], hopelessness [135], physical health conditions, and sexual risk-taking [147]	Randomized controlled trial

Randomized Controlled Trial: Intervention Conditions

For the RCT, 100 adolescents and youths living with HIV with a positive self-report or urine ADU test (based on data from the CS) will be randomly recruited from the 6 clinics and randomly assigned at the clinic level (3 clinics per group) to either the control (n=50) or intervention (n=50) group. The intervention will be delivered over a period of 6 months, with assessments at baseline and 6 months (end of intervention). Upon completion of the RCT, adolescents and youths living with HIV will be randomly selected to participate in 2 FGDs (n=10 from control group and n=10 from intervention group). Adolescents and youths living with HIV in the intervention group will share how the intervention affected their alcohol and drug use as well as their recommendations on how to improve the intervention to be more culturally appropriate and effective in reducing ADU among adolescents and youths living with HIV in Uganda, while adolescents and youths living with HIV in the control group will share their experiences with ADU risk reduction sessions and how this influenced their ADU.

Description of the Control Condition

Adolescents and youths living with HIV in the control condition will receive 4 ADU risk reduction sessions tailored for adolescents and youths living with HIV. Working with author JM (consultant), we plan to adapt, expand, and tailor the Program for Appropriate Technology in Health (PATH) Life Planning Skills curriculum (Unit 11 on substance use) [150] to include issues specific to adolescents and youths living with HIV. We will train research assistants, using an adapted facilitator's manual, to deliver the adapted curriculum. As part of the RCT, adolescents and youths living with HIV will complete a questionnaire (at baseline and at the end of the intervention) on their alcohol and drug use behaviors (self-reported and biologically measured) and risk and resilience behaviors.

Description of the Intervention Group

In addition to the adapted ADU training module that the control group will receive, adolescents and youths living with HIV in the intervention arm will receive 4 financial literacy training sessions and a youth development savings account (YDA) for long-term savings. Although akin to conditional cash transfer interventions, which have become increasingly popular in the social development field by enabling individuals to meet basic needs while incentivizing prosocial behaviors [82,107,151-153], EE interventions that apply matched savings accounts go beyond incentivizing behavior. They emphasize long-term investment and promote lifelong financial inclusion by forming savings habits and establishing partnerships between the participants and local financial institutions and the actual intervention program. For the proposed study, the EE intervention will be in the form of a YDA, where savings are housed at a local bank and deposits made by the adolescent are matched by the intervention to encourage savings. YDAs yield positive effects, including creating a greater sense of security, self-confidence, and future orientation for young people [82,107,151-153]. Each adolescent and youth living with HIV in the EE intervention will receive a YDA held in their own name in a bank registered by the Central Bank (Bank of Uganda). We will form partnerships with national banks operating in the study area. The account will then be matched with money from the program.

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The maximum adolescent's contribution to be matched by the program will be an equivalent of US $20 per month per adolescent or US $120 for the 6-month intervention period. Our previous studies indicate that the partner financial institutions have multiple and easily accessible deposit locations in the study area and that participants can save these amounts [82,107,151-153]. Therefore, adolescents and youths living with HIV who save the maximum amount will have a total of US $240 at the end of the intervention (US $120 in savings and US $120 from the match: a 1:1 match).

As in the studies that inform this application, each month a bank account statement will be generated for every adolescent and youth living with HIV to note their accumulated savings. The statements are intended to act as "moral boosters" for the enrolled adolescents and youths living with HIV. Unique to this study is our innovative spending model, which empowers participants to make informed financial decisions. During the intervention period, adolescents and youths living with HIV will have direct access to both their personal savings deposited in the accounts as well as the match provided by the study. This is different from our previous studies that required the participants' own savings and the match to be maintained in separate accounts and to get approval by the research team to access the match [82,107,151-153]. This added unconditional component provides adolescents and youths living with HIV with a safety net to address short-term medical needs and financial and consumption emergencies if they arise. Participants will be provided with financial literacy sessions and mentorship tailored specifically to the needs of adolescents and youths living with HIV and ADU. We expect adolescents and youths living with HIV to be equipped with the knowledge to make well-informed consumption and expenditure decisions but also to feel supported in case of immediate medical needs. The research team will monitor, but not restrict, how participants spend their money. Additionally, the study team will have access to and review participants' bank statements to ascertain deposit and withdrawal frequency. Participants will be encouraged to use financial diaries to record their expenditures.

Analysis of CS Data

Frequency distributions and summary statistics for the outcome and all predictor variables will be derived. The prevalence of ADU from both biological tests and self-reports, assessed using the Smoking and Substance Involvement Screening Test (NIDA-Modified ASSIST) [139] among adolescents and youths living with HIV, will be calculated by dividing the number who tested positive for ADU by the total number of participants tested and dividing the number screened to be of moderate or high risk in self-reported data by the total number of participants who completed the survey. To determine which multilevel factors are associated with substance misuse, we will fit logistic regression models comprising the outcome (ADU) and potential risk factors with standard errors adjusted for clustering by clinics.

Analysis of RCT Data

Primary Outcome Measures

Our primary outcomes are feasibility and acceptability of the intervention. Feasibility will be determined by the proportion of participants who enrolled or refused to participate in the intervention. In addition, we will measure the willingness of local partners to assist with recruitment, reasons for refusal, enrollment, and ineligibility. Acceptability will be determined by measuring retention rates at 6 months, the proportion of participants that adhered to study procedures, intervention attendance and engagement, and the extent to which the intervention is acceptable and appealing to study participants.

Secondary Outcome Measures

Changes in ADU and mental health functioning are our secondary outcomes. Our primary hypothesis is that participants in the intervention group will have a lower odds of ADU compared to participants in the control group at the end of the intervention. Our secondary hypothesis is that adolescents and youths living with HIV in the intervention group will have better mental health outcomes, including lower levels of depressive symptoms, less hopelessness, improved adherence, better viral suppression, and improved economic outcomes than adolescents and youths living with HIV in the control group. To test these hypotheses, we will fit 3-level mixed-effects models. Each model will comprise the outcome and fixed categorical effects for study group (intervention vs control), time (baseline and 6-months), and a group-by-time interaction term. Random intercepts will be fitted at the clinic and person levels, with unstructured correlations among subjects' repeated measures. Robust Huber-White standard errors and test statistics will be computed for each model. We will assess the omnibus effects of study group, time, and their interaction. Postestimation analyses will be conducted to assess time within group simple effects and group within time simple effects.

Qualitative Data Analysis

Interviews will be transcribed and uploaded to NVivo 12 (QSR International) [154]. Analytical induction techniques [155] will be used for coding. Ten interview transcripts will be randomly selected, read multiple times, and independently coded by the team using sensitizing concepts to identify emergent themes (open coding) [156]. Broader themes will be broken down into smaller, more specific units until no further subcategory is necessary. Analytic memos will be written to further develop categories, themes, and subthemes and to integrate the ideas that emerge from the data [156,157]. Codes and the inclusion and exclusion criteria for assigning codes will be discussed as a team to create the final codebook in NVivo 12. Each transcript will then be independently coded by 2 investigators using the codebook. Intercoder reliability will be established. A level of agreement ranging from 66% to 97% based on level of coding indicates good reliability [158]. Disagreements will be resolved through team discussions. The secondary analysis will compare and contrast themes and categories within and across groups to identify similarities, differences, and relationships among the findings. Member checking, peer debriefing, and an audit trail will be used to ensure rigor [159].

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Results

Recruitment of participants for the first qualitative phase has commenced. As of May 4, 2023, ten health providers from 6 clinics have been recruited, provided written consent to participate, and participated in in-depth QIs. Two FGDs was conducted with 20 adolescents and youths living with HIV from 2 clinics. Data collection for the qualitative phase has completed and transcription, translation, and analysis of qualitative data will commence immediately thereafter. The CS will begin shortly after the qualitative phase. Data collection will continue over the next year, and dissemination of the main study findings is targeted for 2024.

Discussion

This will be one of the first studies to examine the impact of EE interventions on reducing alcohol and drug use among adolescents and youths living with HIV in poverty-impacted communities. This study will advance our understanding of the epidemiology, underlying risk factors, and consequences of ADU among adolescents and youths living with HIV in high-risk environments and evaluate a culturally tailored intervention that could prevent harmful ADU and improve the overall and long-term health and well-being of adolescents and youths living with HIV. We specifically target adolescents and youths living with HIV living in fishing communities—known HIV hot spots that typically have high levels of poverty as well as ADU. Study findings will contribute to our understanding of the epidemiology, risk and resilience factors, and consequences of ADU among adolescents and youths living with HIV in order to inform the development of effective ADU prevention interventions. We envision that the findings will also inform the design of longitudinal studies to evaluate the long-term effects of an EE intervention on ADU among adolescents and youths living with HIV.

There is a scarcity of evidence-based interventions for addressing ADU among youth in resource-limited settings. Only a few ADU interventions evaluated in SSA have targeted the family context [92]. No study has targeted poverty and its attendant impacts (eg, mental health) as a risk factor for ADU. In this proposal, we will examine the feasibility, acceptability, and short-term effects of an EE intervention to reduce and prevent risky and hazardous alcohol and drug use. Our intervention targets the most commonly occurring risk factors for ADU (ie, poverty and mental health problems). This will be one of the first studies to examine the impact of EE interventions on reducing alcohol and drug use among adolescents and youths living with HIV in poverty-impacted communities. The proposed EE intervention is based on Asset theory [124] and is intended to improve economic well-being, create a more hopeful and optimistic outlook for the future, and thus reduce engagement in risk-taking behaviors by adolescents and youths living with HIV, including ADU. However, our findings should be interpreted with some limitations. Given our target population, our findings may not be generalizable to adolescents and youths living with HIV populations in more urban or developed areas, and to younger or older age groups. This is a small feasibility study, so our study is not powered to detect significant changes but will provide preliminary data for a larger-scale study with sufficient power.

Acknowledgments

We would like to thank our staff and volunteers at the International Center for Child Health and Development (ICHAD) Uganda and Reach the Youth Uganda for their respective contributions to study preparation. In addition, we are grateful to the participating health care clinics and participating youth for agreeing to participate in the study. The study outlined in this protocol is supported by the National Institute on Alcohol Abuse and Alcoholism (NIAAA) under award number 1R21AA030225-01 (multiple principal investigators: MM, PhD and RB, PhD). NIAAA has no role in the study design, data collection, analysis, interpretation of findings, and manuscript preparation. The content is solely the responsibility of the authors and does not necessarily represent the official views of NIAAA or the National Institutes of Health.

Data Availability

Data sharing is not applicable to this study as no data sets were generated or analyzed during this study. However, the data sets generated during this study will be available in the National Institute of Mental Health Data Archive.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Summary statement for grant reviewed by Center for Scientific Review Special Emphasis Panel Member Conflict: HIV/AIDS Related Behavioral Research.
[PDF File (Adobe PDF File), 137 KB - resprot_v12i1e46486_app1.pdf]

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Abbreviations

ADU: alcohol and drug use
ART: antiretroviral therapy
CS: cross-sectional survey
EE: economic empowerment
FGD: focus group discussion
ICHAD: International Center for Child Health and Development
PATH: Program for Appropriate Technology in Health
QI: qualitative interviews
RCT: randomized controlled trial
SEM: socioecological model
SSA: Sub-Saharan Africa
YDA: youth development savings account

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Protocol

Adapting and Testing the Care Partner Hospital Assessment Tool for Use in Dementia Care: Protocol for a 2 Sequential Phase Study

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Abstract

Background: Research and policy demonstrate the value of and need for systematically identifying and preparing care partners for their caregiving responsibilities while their family member or friend living with dementia is hospitalized. The Care Partner Hospital Assessment Tool (CHAT) has undergone content and face validation and has been endorsed as appropriate by clinicians to facilitate the timely identification and preparation of care partners of older adult patients during their hospitalization. However, the CHAT has not yet been adapted or prospectively evaluated for use with care partners of hospitalized people living with dementia. Adapting and testing the CHAT via a pilot study will provide the necessary evidence to optimize feasibility and enable future efficacy trials.

Objective: The purpose of this paper is to describe the study protocol for the adaptation and testing of the CHAT for use among care partners of hospitalized people living with dementia to better prepare them for their caregiving responsibilities after hospital discharge.

Methods: Our protocol is based on the National Institutes of Health Stage Model and consists of 2 sequential phases, including formative research and the main trial. In phase 1, we will use a participatory human-centered design process that incorporates people living with dementia and their care partners, health care administrators, and clinicians to adapt the CHAT for dementia care (ie, the Dementia CHAT [D-CHAT]; stage IA). In phase 2, we will partner with a large academic medical system to complete a pilot randomized controlled trial to examine the feasibility and estimate the size of the effect of the D-CHAT on care partners' preparedness for caregiving (stage IB). We anticipate this study to take approximately 60 months to complete, from study start-up procedures to dissemination. The 2 phases will take place between December 1, 2022, and November 30, 2027.

Results: The study protocol will yield (1) a converged-upon, ready-for-feasibility testing D-CHAT; (2) descriptive and feasibility characteristics of delivering the D-CHAT; and (3) effect size estimates of the D-CHAT on care partner preparedness. We anticipate that the resultant D-CHAT will provide clinicians with guidance on how to identify and better prepare care partners for hospitalized people living with dementia. In turn, care partners will feel equipped to fulfill caregiving roles for their family members or friends living with dementia.

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Conclusions: The expected results of this study are to favorably impact hospital-based care processes and outcomes for people living with dementia and their care partners and to elucidate the essential caregiving role that so many care partners of people living with dementia assume.

Trial Registration: ClinicalTrials.gov NCT05592366; https://clinicaltrials.gov/ct2/show/NCT05592366

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KEYWORDS

dementia; caregiving; health care; systems; co-design; randomized control trial

Introduction

People living with dementia experience frequent and costly hospitalizations, which are associated with poor health outcomes. Compared to other older people, people living with dementia have twice as many hospitalizations and stay nearly a day longer [1]. Moreover, evidence indicates that people living with dementia discharged from hospitals are at higher risk for readmission within 30 days [2,3], urinary tract infections, pressure areas, pneumonia, and delirium [4]. The total costs of these hospital services are more than 3 times greater for people living with dementia than for those without dementia [5]. Further, hospitalizations also hasten the cognitive decline of people living with dementia [6]. Care partners (a traditional family, partner, or other support person designated by the older adult care recipient) have the potential to mitigate these adverse outcomes for people living with dementia when included in care processes during hospitalization.

While more than 11 million care partners of people living with dementia provide nearly 15 billion hours of unpaid care annually [6], many hospitals fail to integrate care partners in the care delivery processes of people living with dementia [7]. Care partners are not included despite our knowledge that frontline approaches to reducing adverse outcomes rely on their unique knowledge of the preferences and functional abilities of people living with dementia [7,8]. In fact, a recent study investigated compliance with the Caregiver Advise, Record, and Enable (CARE) Act, which requires hospitals to (1) provide admitted patients the opportunity to identify and record the name of a care partner; (2) inform the care partner when discharge is to occur; and (3) prepare care partners to fulfill caregiving roles to be performed in the home, like complex medical and nursing tasks [9]. Analyses of more than 200 direct observations and 13,000 patient electronic health records for the first 6 months after implementation of the CARE Act in 1 health care system revealed the following: (1) 53% of patients identified a care partner on admission, 23% declined, and 8% were not asked by a clinician; (2) 97% of care partners identified on hospital admission were not notified of the patient's upcoming discharge; and (3) only 19% of care partners received preparation on tasks to be performed in the home during the patient's hospital stay [10,11].

Further, a systematic review of the needs of care partners of people living with dementia across care settings [12] found limited available evidence for identifying and preparing care partners for their caregiving tasks in settings other than the home and community; no studies focused on acute care settings. These findings highlight missed opportunities to individualize care for people living with dementia and to prepare their care partners to fulfill caregiving tasks post hospital discharge. Despite their essential role, care partners who are poorly integrated into hospitalizations and inadequately prepared to fulfill dementia caregiving tasks are at high risk of experiencing excess burden, chronic stress, and depression [13,14].

Clinical decision-support tools offer a valuable resource for addressing this gap in practice as they enable multidisciplinary teams to navigate complex care processes (eg, care partner identification) using structured yet flexible guidance [15]. Common uses of clinical decision-support tools include timely screening for preventable conditions or medical events and ensuring accurate diagnoses [15]. Yet, a recent systematic review uncovered no clinical decision-support tools to guide the systematic identification and preparation of care partners for hospitalized people living with dementia [16].

In response to this gap, we developed and validated a standardized decision-support tool to facilitate the timely identification and preparation of care partners for cognitively unimpaired adult patients during their hospitalization. The Care Partner Hospital Assessment Tool (CHAT) has strong content and face validity and is endorsed as appropriate by clinicians and care partners in the hospital setting [17,18]. Guided by the widely used and effective decision-support model of Screening, Brief Intervention, and Referral to Treatment [19,20], the CHAT applies a sequential screening and referral pathway that (1) identifies care partners and their preferences for involvement in the patients' hospital care and (2) tailors referrals to address their stated preferences and unmet needs for postdischarge preparedness.

Because there is a great need for a novel decision-support tool in hospital-based dementia care, we will (1) adapt the CHAT for dementia (ie, the Dementia Care Partner Hospital Assessment Tool (D-CHAT)), and then (2) test the feasibility and estimate the size of the effect of the D-CHAT compared to usual care. D-CHAT has the potential to improve hospital-based care processes and outcomes for people living with dementia and their care partners. In addition, findings from this study will further elucidate the essential caregiving role that so many care partners of people living with dementia assume.

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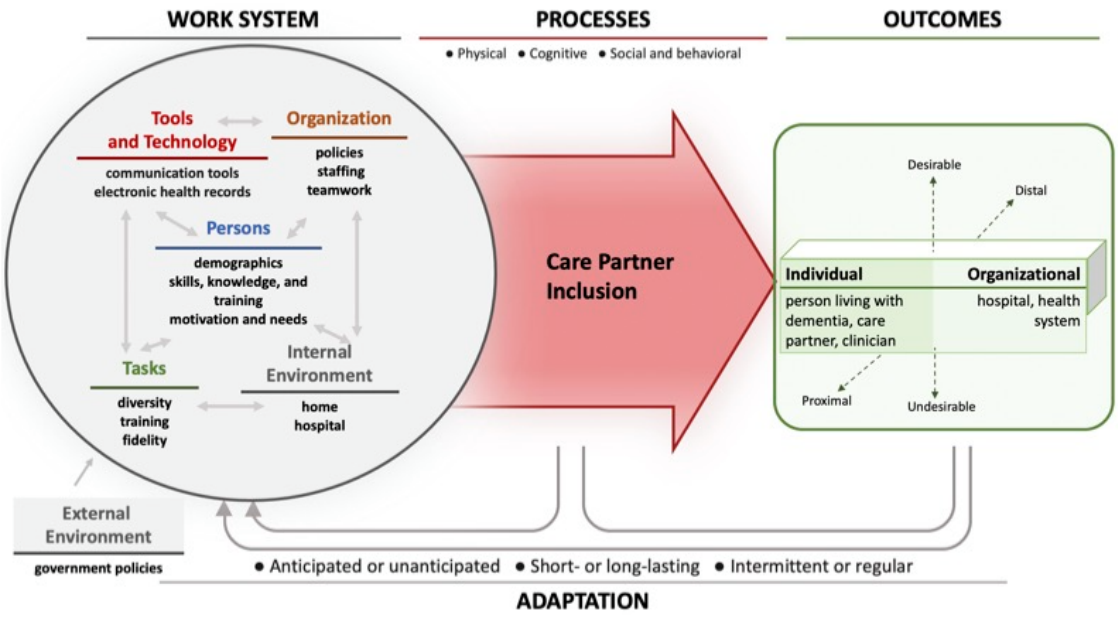
Methods

Design and Conceptual Framework

The study is based on the National Institutes of Health Stage Model approach [21] to intervention development, focusing on stage 1, and will be conducted in 2 phases: formative research and the main trial. During the formative research phase, we will use a participatory human-centered design process that incorporates people living with dementia and their care partners, health care administrators, and clinicians to refine and adapt the CHAT for hospital-based dementia care (stage IA). During the main trial phase, we will conduct a pilot randomized controlled trial to examine the feasibility and estimate the size of the effect of the D-CHAT on care partners' preparedness for caregiving tasks (stage IB).

The System Engineering Initiative for Patient Safety 2.0 model (Figure 1) will guide our data collection and analysis to ensure the identification of components influencing the adaptation and delivery of the D-CHAT across all health care system components. This model emphasizes a working system that includes interacting components (ie, people, tasks, tools or technology, organization, and physical environment) that influence health care processes and outcomes [22-24].

Figure 1. System Engineering Initiative for Patient Safety 2.0 model.



Ethics Approval

The study was approved by the institutional review board on April 11, 2023 (2022-0352). All protocol modifications will be reviewed and approved by the institutional review board as needed.

Phase 1—Formative Research

Sample

Based on established relationships with health system and community partners, we will purposefully select interested parties for two groups: (1) health care administrators and frontline clinicians, and (2) people living with dementia and their care partners that meet eligibility criteria (see Table 1). Each group will form a design team and have 5-7 participants, which is within the standard range used in participatory design research [25]. The small number of participants in groups reduces the potential for groupthink (ie, by having products from one group evaluated by the other) and ensures that all participants have ample time to provide their perspectives [26].

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Table 1. Sampling plan (N=10-14).

Group	Reason for inclusion	Eligibility criteria
Group 1 (n=5-7)		
Health care administrators	Knowledge and expertise related to the day-to-day operations of hospital, patient eligibility, enrollment, claims, and payment of health services	• Have at least 5 years of professional experience in their respective position • Speak and understand English
Clinicians	Knowledge and expertise related to the delivery of health services	• Have at least 5 years of professional experience in their respective position • Speak and understand English
Group 2 (n=5-7)		
People living with dementia	Knowledge and experience related to receiving hospital care	• Have experienced a hospitalization • Have some form of dementia • Identified a care partner
Care partners of people living with dementia		• Provide unpaid care to a relative or partner living with dementia to help them take care of themselves • Be at least 18 years or older • Speak and understand English

Data Collection

Teams will complete 5 co-design videoconference sessions occurring in parallel across 4 months, with 2-3 weeks between each session. In session one, we will present the original CHAT. We will lead discussion, interpretation, and respectful debate among design team members to begin to generate the needs of dementia care partners and health care system process changes to optimize their involvement in care. We will ensure progress toward solution convergence from session to session. The design teams will conduct sessions independently, but in between sessions, they will swap solutions and provide feedback, which we will summarize and present in subsequent sessions. Each web-based session will last approximately 90 minutes and will be audio recorded for subsequent analysis. The design process can be conceptualized as a funnel in which we start with divergent ideas and then work toward convergence through the sessions. Participants will receive US $20 after completing each session.

Data Analysis

Within the 2-3 weeks between each session, we will review audio recordings as well as any team and participant observation notes, case scenarios, and sketches. Two members of our team will use the Rapid Identification of Themes From Audio Recordings (RITA) method [27] to identify design specifications. The same 2 team members will then combine the themes from the RITA with the synthesized team and participant observation notes, use of case scenarios, and sketches to provide as inputs to participants at the following design session. Following the design session's completion, we will adapt the CHAT for dementia care, applying input from the final design session, and performing member checking by reviewing changes with members from the groups. This process will produce a converged-upon D-CHAT that is ready for stage 1B feasibility testing [21].

Phase 2—Main Trial

Setting and Sample

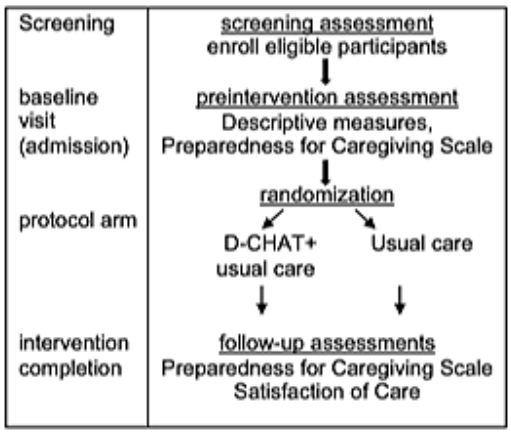
This single-blind pilot randomized controlled trial [28] will occur on medical and surgical units at a large academic health care system in the Midwest. This system serves more than 700,000 patients each year with approximately 1849 physicians and 21,000 staff at 7 hospitals. Care partners will be asked to participate if they meet the following inclusion criteria: (1) provide unpaid care to a hospitalized adult relative or partner to help them take care of themselves because of a dementia diagnosis, (2) be at least 18 years or older, and (3) speak and understand English. Care partners of hospitalized adult relatives or partners that are observation or same-day stay patients will be excluded. There will be no exclusion based on sex, gender, race, or ethnicity.

Training, Informed Consent, and Screening

Before recruitment begins, we will provide training on the D-CHAT to clinicians in medical and surgical units. To reduce contamination [29], we will instruct trained clinicians to not use the D-CHAT when treating those in the control arm and to not discuss details of the D-CHAT with nontrained clinicians. Once this training is completed, a member of the study team will work with unit coordinators to schedule morning, afternoon, and evening shifts for data screening, consent, and data collection. Institutional review board approval will be obtained to access electronic health records of hospitalized people living with dementia. We will use electronic health records to identify patients who have a documented care partner (or legally authorized representative). Someone who is part of the patient's care team will then approach the patient's present care partners to determine their interest in the study. If a care partner expresses interest in participating, a study team will then share study details, obtain written consent, and complete the baseline visit (see Figure 2). A member of the study team will monitor protocol deviations like unintended crossovers by completing weekly, in-person check-ins with the trained clinicians.

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Figure 2. Main trial flow diagram. D-CHAT: Dementia Care Partner Hospital Assessment Tool.



Baseline Visit

The baseline visit will be completed in a designated room in the hospital to limit distractions. After completing consent, participants will complete descriptive measures and the primary clinical outcome measure (see Table 2). All measures will be administered by a trained, blind assessor. Immediately after these procedures, participants will be randomized to either the intervention or control group, and the clinical team will be notified of the assignment. These efforts will minimize bias and increase internal validity [28].

Table 2. Measures.

Study measures	Instrument	Collection method	Time points	
			1[a]	2[b]
Clinical outcomes				
Preparedness for caregiving	The Preparedness for Caregiving Scale	Self-report	✓	✓
Satisfaction of care	Hospital Consumer Assessment of Health care Providers and Systems	Self-report		✓
Burden	Zarit Burden Interview	Self-report	✓	✓
Depression	Patient Health Questionnaire-2	Self-report	✓	✓
Descriptive measures				
Demographic characteristics	Patient and care partner sex, age, race or ethnicity, education, employment status	Self-report	✓	
Admission status	Patient reason for patient admission	Medical record	✓	
Dementia characteristics	Patient type and stage of dementia	Medical record	✓	
Caregiving context characteristics	Care partner relationship to patient, hours providing care, living situation	Self-report	✓	
Feasibility measures				
Recruitment	Number of care partner contacts, screened, consented, and enrolled	Study records		✓
Attrition	Reasons for absence and attrition	Study records		✓
Safety	Adverse events from completing the D-CHAT[c]	Study records		✓
Time to complete measures and D-CHAT	Minutes	Study records	✓	
Adherence	Reasons for not following the D-CHAT protocol	Self-report		✓
Implementation satisfaction	Clinician questionnaire	Self-report		✓

[a]Time point 1: preintervention—within 24 hours of the patient's admission.

[b]Time point 2: follow-up—within 72 hours of the patient's discharge.

[c]D-CHAT: Dementia Care Partner Hospital Assessment Tool.

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Intervention

Care partner participants randomized to the intervention group will receive the D-CHAT and usual care delivered through the patient's care team. Aftercare partners complete the D-CHAT, and their responses will be given to the unit coordinator to review and make suggested referrals to specified clinicians. These clinicians then use the responses to develop and complete information and skill preparation with the care partners. For example, the D-CHAT could reveal that a care partner does not have the necessary diabetes knowledge or skill set to help give her husband living with Alzheimer disease and diabetes his insulin injections. Information gleaned from the D-CHAT would trigger a diabetes care and education specialist to address the care partners' caregiving needs.

Usual Care Control

The comparison condition will be the usual care that hospitalized people living with dementia and their care partners receive as part of the large academic health care system. No standardized clinical decision-support tool that facilitates the identification and preparation of care partners is currently used for routine hospital-based dementia care. These care partner participants will complete the same measures as participants in the intervention condition on the same timeline using identical assessment procedures.

Measures

Participants will be assessed on the measures listed in Table 2. Participants will be compensated US $25 after each time point is completed. Baseline measures will be collected in person at the hospital, and follow-up assessments will be administered via phone by a study team member. The primary clinical outcome we will measure is a change in care partner preparedness. The Preparedness for Caregiving Scale [30] is a self-rated measure that consists of 8 items that ask care partners how well prepared they believe they are for multiple domains of caregiving. Preparedness is defined as perceived readiness for multiple domains of the caregiving role, such as providing physical care, providing emotional support, setting up in-home support services, and dealing with the stress of caregiving. Responses are rated on a 5-point scale, with scores ranging from 0 (not at all prepared) to 4 (very well prepared). The scale is scored by calculating the mean of all items answered with a score range of 0 to 4. The higher the score, the more prepared the care partner feels for caregiving. The items have an internal consistency rating of 0.88 to 0.93. We will also collect secondary outcome measures, including satisfaction of care, caregiving burden, and depression, using standardized measures.

Sample Size Justification

An estimated sample size of 128 will be recruited for the main trial based on the 95% CI width around the effect of the D-CHAT on care partner preparedness as measured by the Preparedness for Caregiving Scale [31]. Since this is a novel tool that will be adapted as part of phase 1, the variability of the response is unknown, and therefore justification is based on general terms of SD. With 64 subjects in both groups, the 95% CI width of the estimated effect will be 0.35 × SD. We expect to see a medium effect size (Cohen d=0.5). With this 95% CI width and expected effect size, we will have a sufficiently narrow CI of the true effect size to apply toward the planning of the future efficacy trial. If there was a ≈12% loss to follow-up such that 56 in each group have follow-up data, the 95% CI width would only increase to 0.375 × SD.

Data Analysis

Analyses will be conducted using SAS (SAS Institute Inc) [32]. We will screen univariate distributions for normality and influential outliers and confirm that the randomization process balanced demographic characteristics between groups. We will also document the number of participants who are lost in each group, the reasons for the loss, and unintended crossovers. This information will influence the design of a future trial, including the frequency and mode of communication with clinicians and participants. The effect of the D-CHAT on care partner preparedness will be estimated as the difference in mean change from baseline to study completion between groups. The 95% CI will be calculated using a t distribution. Cohen d effect size will be calculated as the effect of the D-CHAT divided by the pooled standard deviation. This will give us a sense of the magnitude of the effect in terms of SDs. If normality assumptions in the raw data are not met and a simple transformation of the data (logarithmic or square root) does not sufficiently normalize the distribution, then we will use a nonparametric equivalent methodology [33]. If greater than 10% of the participants are noncompliant with their group assignment, then a per-protocol sensitivity analysis will be conducted to assess how influential the noncompliance was on the results of the study. Noncompliance is based on whether the group assignment was followed.

Results

We anticipate this study to take approximately 60 months to complete, from study start-up procedures to dissemination. The 2 phases will take place between December 1, 2022, and November 30, 2027. We expect the following results:

- Phase 1—formative research: Results will provide a converged-upon, ready-for-feasibility testing, D-CHAT, to guide clinicians' identification and preparation of care partners in hospital care of people living with dementia. The D-CHAT will include caregiving domains unique to dementia caregiving and discipline-specific treatment to meet the needs of care partners.
- Phase 2—main trial: A total of 128 eligible care partners of hospitalized people living with dementia will be randomized into either the D-CHAT plus usual care or usual care-only groups. Descriptive and feasibility characteristics for delivering the D-CHAT will be collected. We expect that care partners who receive the D-CHAT will demonstrate larger improvements in caregiving preparedness than those in the usual care group.

Findings from both studies will be disseminated following best practices throughout the conduct of this research. The study is registered at ClinicalTrials.gov in accordance with current National Institutes of Health (NIH) policies and federal regulations (NCT05592366). Results will be posted to

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ClinicalTrials.gov within 12 months of study completion. Across all stages of the research, we will publish peer-reviewed papers and present our findings at conferences attended by researchers and clinicians in diverse and relevant fields. We will also share the results of this study directly with relevant and interested parties by developing infographics. These will be distributed through dementia caregiving networks and established partnerships.

Discussion

Lack of caregiving preparedness is prominent and persistent among care partners of people living with dementia and is associated with increased risk for adverse clinical outcomes for people living with dementia [2,3] and increased levels of burden, depression, and morbidity for care partners. While clinical decision-support tools offer a valuable resource for addressing this gap in practice, no tool exists to guide the systematic identification and preparation of care partners for hospitalized people living with dementia [16].

We will involve a broad range of individuals in the participatory co-design process to create a converged-upon, ready-for-feasibility testing D-CHAT. Moreover, we will use the novel clinical decision-support tool to facilitate the timely identification and preparation of care partners during hospital-based care delivery processes. This work will help bridge the gap between recommendations or policy and practice by providing clinicians with guidance on how to identify and better prepare care partners for hospitalized people living with dementia.

The control group will be randomized to usual care delivered by medical and surgical acute care teams at 1 large academic medical system. While we realize that these teams could prepare care partners for people living with dementia without intervention, we consider the D-CHAT to be more of an individualized care approach that systematically and comprehensively identifies and prepares care partners to fulfill their caregiving responsibilities after the patient discharges from the hospital. The intervention may be seen as burdensome by some clinicians. Our protocol has plans in place to train clinicians on the D-CHAT to ease workflow demands prior to beginning the main trial phase. We are also aware of the potential for measurement bias in the study design (ie, care partners may underreport caregiving needs and preparedness). Therefore, this issue will be discussed during the formative research phase and brought up in the co-design process to develop the best approaches to minimize these potential concerns. We also recognize that hospitals may enforce visiting restrictions at any given point because of the COVID-19 pandemic. For this reason, we have collaborated with research directors and clinical nurse scientists at the academic medical system to identify ways to adapt our data collection and communication approach so that we minimize the potential risks to both hospitalized people living with dementia and their care partners.

Engaging diverse and interested parties to adapt the standardized CHAT for hospital-based dementia care will expand its potential reach. Further, findings from this pilot randomized controlled trial will enable future efficacy trials to advance the refinement and implementation of the decision-support tool that can enhance caregiving preparedness and improve health outcomes after hospital discharge [34]. We anticipate that the resultant D-CHAT will provide clinicians with guidance on how to identify and better prepare care partners for hospitalized people living with dementia. In turn, care partners will feel equipped to fulfill caregiving roles for their family members or friends living with dementia.

Acknowledgments

We especially acknowledge the considerable influence of Drs. Juleen Rodakowski, Richard Schulz, Lauren Terhorst, and Ms. Madelyn Carbery on the development of the Care Partner Hospital Assessment Tool. This work is supported by the National Institute on Aging (1K23AG080068-01). We want to thank the University of Wisconsin Hospitals and Clinics, the Center for Aging Research and Education, and the Alzheimer Disease Research Center for partnering with us in this work. We also want to thank Anne Mortensen for her ongoing support in project management.

Data Availability

The data sets generated during or analyzed during this study will be available from the corresponding author upon reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review report by the Career Development for Clinicians/Health Professionals Study Section - National Institute on Aging Initial Review Group (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 773 KB - resprot_v12i1e46808_app1.pdf]

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Abbreviations

CARE: Caregiver Advise, Record and Enable
CHAT: Care Partner Hospital Assessment Tool
D-CHAT: Dementia Care Partner Hospital Assessment Tool
RITA: Rapid Identification of Themes From Audio Recordings

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Protocol

Feasibility of a Career Development Intervention for Veterans in Vocational Rehabilitation: Protocol for a Pilot Randomized Controlled Trial

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Abstract

Background: Veterans with psychiatric disorders want additional career development services to support their recovery and pursuit of meaningful employment. However, no career counseling programs have been designed for this specific population. We developed the Purposeful Pathways intervention to fill this need.

Objective: This study protocol aims to (1) evaluate the feasibility and acceptability of the Purposeful Pathways intervention for veterans living with psychiatric disorders and (2) explore preliminary clinical outcome data.

Methods: A total of 50 veterans who are participating in transitional work vocational rehabilitation services at a Veterans Affairs hospital will be randomized to either treatment as usual or the augmented treatment condition (treatment as usual plus Purposeful Pathways). Feasibility will be assessed via recruitment rates, clinician fidelity to treatment, retention rates, and acceptability of randomization procedures. Acceptability will be assessed via client satisfaction at treatment termination using quantitative and qualitative data collection. Preliminary clinical and vocational outcomes will be assessed at baseline, 6 weeks, 12 weeks (treatment termination), and a 3-month follow-up via quantitative measures assessing vocational functioning, vocational process, and mental and physical functioning.

Results: This pilot randomized controlled trial is beginning recruitment in June 2023 and is expected to continue through November 2025. Data collection is expected to be completed by February 2026, with full data analysis completed by March 2026.

Conclusions: Findings from this study will provide information on the feasibility and acceptability of the Purposeful Pathways intervention, as well as secondary outcomes related to vocational functioning, vocational process, and mental and physical functioning.

Trial Registration: ClinicalTrials.gov NCT04698967; https://clinicaltrials.gov/ct2/show/NCT04698967

International Registered Report Identifier (IRRID): PRR1-10.2196/47986

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(JMIR Res Protoc 2023;12:e47986) doi:10.2196/47986

KEYWORDS

psychiatric disorders; career development; vocational rehabilitation; randomized controlled trial; transitional work; veterans; mental health; employment

Introduction

Background

Meaningful employment is consistently associated with the health and well-being of individuals living with mental health conditions [1-3], yet veterans living with psychiatric or substance use disorders often experience high levels of unemployment or underemployment [4-7]. To address this problem, the Veterans Health Administration (VHA) offers robust vocational rehabilitation programming that has helped countless veterans with psychiatric disorders obtain competitive employment. The most widely used vocational rehabilitation service within VHA is transitional work (TW) [8]. While the TW intervention varies across Veterans Affairs (VA) health care settings, it usually provides veterans with rapid access to time-limited, paid work experiences provided by VA departments, other federal agencies, or community employers through partnerships with the VA. Positions are typically housed in the VA (eg, housekeeping, grounds, kitchens, and construction) but are sometimes located in the community. To be eligible for TW, a referral needs to be made by a health care provider, and the veteran must have a vocational and clinical problem.

Research examining participation outcomes in TW has demonstrated that consumers are more likely to engage in paid activity, work more total hours, work more weeks, and earn more in total wages compared to individuals receiving state-funded vocational rehabilitation services [9]. However, research also finds that TW may not be effective at helping veterans find and secure competitive employment, even though this is a goal of the TW program [8,9]. A recent study of national TW data (N=38,199) found that only 34.8% of veterans participating in TW at a community-based job site, and 30.3% of veterans participating in TW at a VA-based site, were competitively employed at discharge [8]. Additional interventions may be needed for veterans in TW to support their employment functioning.

Ancillary vocational services such as prevocational assessment and job clubs have been shown to increase the odds (1.12 and 1.32 odds ratios, respectively) of veterans securing competitive employment when paired with a main VHA Vocational Rehabilitation Services program such as TW [8]. Given this finding, researchers recommend evaluating the impact of ancillary vocational interventions on competitive employment outcomes of veterans when paired with TW [8]. This recommendation is aligned with the voices of veterans living with psychiatric disorders who report wanting ancillary vocational services such as vocational assessment and career planning to help support their pursuit of meaningful employment and their mental health and substance use recoveries [10,11].

The overarching goal of this study is to develop and evaluate a career counseling protocol to promote vocational outcomes for veterans living with psychiatric disorders. This study consists of three phases: (1) treatment development, (2) treatment refinement through an open trial, and (3) evaluating feasibility through a pilot randomized controlled trial (RCT). The first 2 phases of this study were completed between April 2021 and February 2023 and are discussed below.

Prior Work

During the first phase of this treatment development and evaluation project, our team conducted qualitative focus groups among veterans in TW (n=6), as well as among TW providers (n=7), to better understand the career development needs of veterans engaged in vocational rehabilitation services [12]. An advisory panel of practitioners, researchers, academic scholars, and administrators with expertise in vocational rehabilitation, career development, or treatment manualization (n=12) reviewed the findings from these focus groups and synthesized the results across the best available research and clinical practice. Collectively, four major treatment mechanisms emerged: (1) career exploration, (2) goal clarity, (3) job-searching skills, and (4) self-regulation skills.

A preliminary treatment manual was developed to address the 4 major treatment mechanisms identified. The preliminary manual was then reviewed by the 7 TW providers who previously participated in 1 of 2 focus groups. These providers offered suggestions for editing the manual. These suggestions were reviewed by the principal investigator (PI), a coinvestigator, and a research assistant and then used to revise the treatment manual. Modifications included developing additional handouts and worksheets for veterans to complete during treatment, offering more clinical case examples within the manual, and using more inclusive language.

During the second phase of our project, we conducted an open trial in which 10 veterans in TW received the newly developed career development intervention. The PI provided the treatment and maintained process notes on each session. After study completion, veterans provided qualitative feedback to a research assistant about their experiences in the intervention. In total, 7 veterans completed this exit interview, with 3 lost to follow-up. Generally, veterans provided positive feedback about the intervention. Minor adjustments were made to the manual based on their feedback, which focused on helpful counselor qualities and approaches rather than the intervention content. The PI completed a final version of the treatment manual in consultation with 2 expert consultants who previously participated on the treatment development advisory panel.

Description of the Purposeful Pathways Intervention

Purposeful Pathways is a manualized intervention to assist veterans in aspiring and pursuing meaningful employment.

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Purposeful Pathways is an individual counseling protocol delivered weekly for up to 12 sessions (50 minutes per session). The intervention is divided into three sections: (1) introductory sessions (up to 3 sessions), (2) middle sessions (up to 8 sessions), and (3) discharge planning sessions (at least 1 session). In the introductory sessions, the counselor engages the veteran in developing a therapeutic bond and collaboratively developing a treatment plan. During these sessions, the counselor focuses on introductions, reviewing the context of the treatment, establishing the treatment orientation, providing psychoeducation on career development, gathering a comprehensive vocational history, exploring the veteran's desired vocational outcomes, and collaborating on a shared understanding of the goals of their work together. In the middle sessions, the counselor and client work on 1 or all 4 of the following: career development tasks, career exploration, goal clarity, job-searching skills, and self-regulation skills. The choice of interventions is collaboratively decided upon between the counselor and veteran based on the veteran's needs and preferences. The counselor uses cognitive behavioral therapy and motivational interviewing strategies throughout the implementation of the various interventions, such as open-ended questions, affirmations, reflections, summaries, and motivating behavior change. Career exploration includes identifying the veteran's preferences, connecting the veteran's preferences to the world of work, identifying needed occupational accommodations, and working through indecision. Goal clarity includes developing a visual goals map (ie, developing a plan for achieving one's occupational goals). Job-searching skills include job-searching strategies, resume writing, and interviewing skill-building. Self-regulation skills include recognizing distractions, opportunities, and roadblocks to reaching employment goals, skills for sustaining career development over time, immediate coping skills for managing distress during recovery, and developing a vocational coping plan (ie, a plan for managing distress on a worksite). The final section of the manual, the Discharge Planning section, focuses on helping a veteran synthesize what they have learned in therapy and planning for their recovery once therapy ends. Discharge planning includes reviewing therapist and veteran perceived progress made toward goals, planning for booster sessions, and facilitating warm handoffs to additional treatment, as needed.

This Study

This protocol represents the third and final phase of this treatment development and evaluation study. This third phase aims to (1) evaluate the feasibility and acceptability of the Purposeful Pathways intervention among veterans living with psychiatric disorders and (2) explore preliminary clinical outcome data. To accomplish this aim, we will conduct a pilot RCT comparing Purposeful Pathways to a treatment as usual (TAU) control condition with a 3-month follow-up. This study has received approval from a local VA Institutional Review Board, and the protocol has been registered with clinical trials and will begin recruitment in June 2023.

Methods

Recruitment

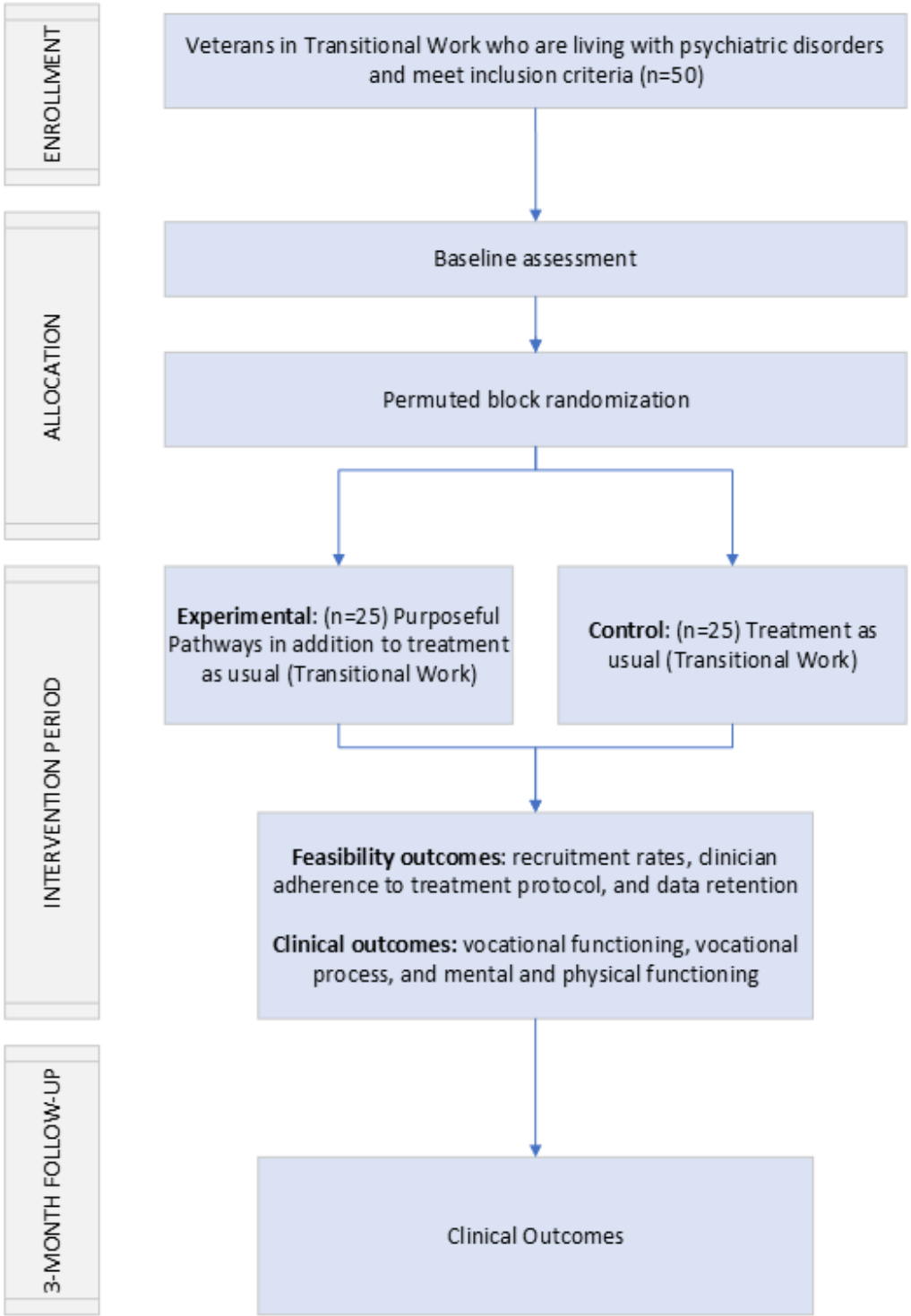
In total, 50 veterans participating in a VHA TW vocational rehabilitation program will be recruited for this study. Inclusion criteria will include (1) eligible for and planning to enroll in TW, or within 16 weeks of having enrolled in TW; (2) the presence of a current psychiatric disorder, such as posttraumatic stress disorder, mood disorders (eg, bipolar disorders and major depression), anxiety-related disorders (eg, generalized anxiety disorder, panic disorder, agoraphobia, and obsessive compulsive disorder), psychotic disorders (eg, schizophrenia and schizoaffective disorder), substance use disorders (eg, alcohol, opioid, cannabis, cocaine, sedative, hypnotic or anxiolytic, and other stimulants), which is indicated by an International Classification of Diseases-10 diagnosis encounter in the participants' VA medical record within the last 6 months, inputted by a licensed mental health provider (psychiatrist, psychologist, licensed clinical social worker, and psychiatric nurse practitioner); (3) self-identification as either unemployed, underemployed (self-report of falling into 1 of 5 categories: overeducated, job-education mismatch, skill underuse, being involuntarily engaged in part-time, temporary, or intermittent employment [ie, hours underemployed], or earning wages in a job that are 20% less compared to a previous job, or for recent college graduates, earning wages that are 20% less compared to graduating peers of similar education or training [ie, pay underemployment] [13]), or self-report that they are employed but functioning poorly at work as a result of mental illness or substance use; (4) self-identification as not being on leave from a job for which there are arrangements to return to their job following the completion of TW; (5) having plans to work for 3 years beyond the end of this study; and (6) competency to provide written informed consent.

Exclusion criteria will include (1) acute suicide or homicide risk requiring treatment focused on safety to self or others based on self-report of current and active thoughts of harm to self or others with intent and plan that requires crisis stabilization in an acute psychiatric unit; (2) being not otherwise eligible for TW services; (3) current enrollment in compensated work therapy supported employment services; (4) Symptom Checklist-6 [14] score greater than 26; (5) Veterans RAND-12 physical component score [15] less than 12, and Veterans RAND-12 mental composite score [15] less than 8; (6) improbability that participant will complete the study for the following reasons: expected deployment, expected incarceration, expected long-term hospitalization, or expected relocation from the vicinity of the participating VA during the study period; and (7) unwillingness to engage in a weekly career development intervention.

Veterans who are eligible and complete the informed consent procedures will be randomized to 1 of 2 study arms: the treatment condition (n=25) or the control condition (n=25). An overview of the design of this pilot RCT is presented in Figure 1.

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Figure 1. CONSORT (Consolidated Standards of Reporting Trials) diagram of the work trial.



Randomization Procedures

To ensure equal distribution across the intervention and control conditions, a permuted block randomization method will be used. Randomization will use computer-generated numbered lists, one for each condition (treatment and control). The lists will be generated through a block design where the block sizes are randomly selected among block sizes of either 4 or 6. There will be 5 rounds of each block size to randomize the 50 veterans into either the treatment or control condition. With this approach, every study arm assignment on the randomization list will consist of an even number of treatment or control assignments in random order. This approach has been discussed by previous researchers as guaranteeing balance in the 2 conditions while also ensuring that researchers are unable to predict the treatment sequence as they will not know if the block size is 4 or 6 [16]. This procedure will result in 25 participants per condition, which is in line with the recommendations of Rounsaville and colleagues [17], who suggest that each treatment condition in a stage 1b clinical trial should have at least 15 subjects. Subjects randomized to the treatment group will receive the Purposeful

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Pathways intervention in addition to TAU. Subjects randomized to the control group will only receive TAU.

Participation in TAU

Both the experimental and the control condition will participate in TAU through TW. Upon admission into TW, veterans are quickly placed into a paid work setting, either at the VA hospital or in the community. There are minimal formal assessment or other vocational services prior to a veteran being placed into a worksite. TW program staff, which can range from peer support staff to master's-trained vocational counselors, provide some on-site and off-site job coaching to help veterans maintain their TW placement, in addition to some guidance on competitive job searching. TW program staff tend to have caseloads of 25-40 veterans [9].

Experimental Intervention

Veterans randomized to the experimental condition will augment their experience in TW with the Purposeful Pathways intervention. This intervention will be delivered to the veteran by a master's-level mental health clinician. This intervention will be delivered on an individual basis for up to 12 sessions (depending on the unique needs and experiences of the veteran-client). The intervention has been designed to be delivered face-to-face or through web-based telehealth platforms, depending on the preferences of the veteran-client.

Therapist Recruitment and Training

The PI will recruit and train at least 4 master's- or doctoral-level mental health clinicians in the delivery of Purposeful Pathways (2 clinicians per 15 months). Clinicians will have specialized training in clinical social work, counseling, or clinical psychology. Before implementing Purposeful Pathways, therapists will participate in a 6-hour training workshop held over 2 or 3 days. The training workshop will be facilitated by the PI of the study.

Therapist Adherence

There will be multiple fidelity checks to ensure treatment adherence among study clinicians. After completing the initial 6-hour training workshop, study clinicians will be required to attend weekly group consultations with the PI (1 hour per week) for the first 3 months of providing treatment to address technical issues in the provision of the manual. Additionally, all Purposeful Pathways sessions will be video recorded, and these sessions will be reviewed and rated (on a variable time schedule) for treatment adherence by 2 staff researchers using a fidelity checklist system, which includes both process and content variables necessary for treatment. Once a session is rated, researchers will provide in-person, individual feedback to clinicians.

Assessment Measures and Timeline

A variety of clinical outcomes will be assessed at baseline, 6 weeks, 12 weeks (treatment termination), and at a 3-month follow-up. Subjects will be compensated US $40 for completing the baseline assessment, US $40 for the completing assessment at week 6, US $80 for completing the assessment and exit interview at treatment termination or week 12, and US $40 for completing the assessment at a 3-month follow-up for a possible total compensation of US $200. Table 1 provides an overview of the administration schedule for the planned measures. Descriptions of each measure are provided after Table 1.

A demographic questionnaire will be used at the screening to gather basic demographic information. Information gathered will include age, gender, race, level of education, service-connected percentage, service-connected condition, receipt of disability pensions, housing stability, and history of substance abuse.

A vocational functioning questionnaire will gather common employment outcome information. The following employment outcomes will be assessed: (1) the mean number of jobs acquired, mean duration of each job acquired, mean pay rate, and total pay per job; (2) the total weeks worked and total hours worked during the follow-up period (if relevant); and (3) the total earned income.

Table 1. Timeline of measures.

Measure	First session	6 weeks	12 weeks	3 months
Demographic questionnaire	✓			
Vocational functioning questionnaire	✓	✓	✓	✓
Confidence and importance rulers	✓	✓	✓	✓
Job-Search Intensity Scale	✓	✓	✓	✓
Career Adapt-Abilities Scale	✓	✓	✓	✓
Vocational Identity Scale	✓	✓	✓	✓
Decent Work Scale	✓	✓	✓	✓
Work Needs Satisfaction Scale	✓	✓	✓	✓
Quality of Life Enjoyment and Satisfaction Questionnaire	✓	✓	✓	✓
Sheehan Disability Scale	✓	✓	✓	✓
Client Satisfaction Questionnaire-8			✓	
Qualitative exit interview			✓	

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Confidence and importance rulers are common tools used in motivational interviewing and cognitive behavioral therapy protocols to assess levels of confidence and importance related to a specific goal. For the purposes of this study, the specific goal would be to "find meaningful employment." On a scale of 1-10, participants will be asked to rate their level of confidence from 0 ("not at all confident") to 10 ("extremely confident") and the level of importance to them from 0 ("not at all important") to 10 ("extremely important") to find meaningful employment. Evidence of reliability and validity has been documented by others [18].

The Job Search Intensity Scale [19] will be used to assess the level of time one spends on various job-search activities. This 9-item measure asks respondents about the following job-search activities: preparing or revising resumes, reading classified or help wanted advertisements, looking for jobs on the internet, talking with friends or relatives about job leads, speaking with previous employers or business acquaintances about job leads, contacting employment agencies, making inquiries to prospective employers, sending out application letters, and preparing and going on job interviews. Responses to each activity are measured on a 5-point Likert-type scale to assess the amount of time spent on each activity. Possible scores for each item range from 1 ("no time at all") to 5 ("very much time"). A previous study found this measure to be valid and reliable [19].

The Career Adapt-Abilities Scale [20] will be used to measure one's level of career adaptability, a commonly used measure of career readiness. This is a 24-item measure that is grouped into 4 different subscales that capture total adaptability along with 4 dimensions—concern, control, curiosity, and confidence. Respondents are asked to rate how strongly they have developed each of these strengths using a 5-point Likert-type scale. Responses range from 5 ("strongest") to 1 ("not strong"). This is a widely used measure in the fields of vocational psychology and career development, with evidence of good validity and reliability [20].

The Vocational Identity Scale (VIS) [21] will measure the extent to which an individual possesses a clear and stable understanding of his or her goals, interests, and talents as related to vocational decisions. The VIS consists of 18 true or false items that ask respondents to identify whether the statement is mostly "true" or mostly "false." A respondent's total number of "true" responses makes up their final score (range 0-18), with higher scores indicating greater career indecision and lower scores indicating more crystallized vocational decidedness. The VIS is extensively used in vocational psychology literature and has undergone extensive psychometric analysis that has demonstrated validity and reliability as a measure of career indecision [22] and has been used in other studies among individuals with psychiatric disorders [23].

The Decent Work Scale [24] will be used to assess the quality of one's job with respect to (1) physically and interpersonally safe working conditions, (2) access to health care, (3) adequate compensation, (4) hours that allow for free time and rest, and (5) organizational values that complement family and social values. The scale is comprised of 5 subscales (based on the factors of decent work just described) and a total scale score. This self-report measure consists of 15 items on a 7-point Likert scale, ranging from "strongly disagree" to "strongly agree" with higher scores indicating greater levels of decent work. The Decent Work Scale has evidence of reliability and validity among employed adults [24].

The Work Needs Satisfaction Survey [25] will be used to measure one's satisfaction with their employment in terms of meeting their survival or power, social connection, and self-determination needs. This is a 20-item measure that prompts respondents to rate an item on a 7-point scale ranging from "strongly disagree" to "strongly agree." Evidence of validity and reliability was demonstrated by the scale developers [25].

The Quality of Life Enjoyment and Satisfaction Questionnaire–Short Form [26] will be used to measure general psychiatric functioning. The Quality of Life Enjoyment and Satisfaction Questionnaire–Short Form is a 16-item self-report measure of perceived functioning and is one of the most widely used outcome measures in psychiatric research. Reliability and validity of this measure have been extensively documented.

The Sheehan Disability Scale [27] will measure the level of functional impairment due to mental health and medical impairments. This self-report measure asks raters to how much their work or school, social life, and home life or family responsibilities are impaired by mental and medical symptoms. This is a 5-item measure using a 10-point visual analog scale. The Sheehan Disability Scale has received extensive psychometric testing for validity and reliability [27].

The Client Satisfaction Questionnaire–8 (CSQ-8) [28] will be used to measure satisfaction, perceived quality, and effectiveness of the treatment. This self-report questionnaire consists of 8 items, scored 1-4, with higher scores indicating higher satisfaction with treatment. The CSQ-8 has been used in mental health and other health centers and has acceptable internal consistency (α=.83 to .93) [28].

In addition to the above measures, subjects will complete a semistructured 30-minute exit interview at treatment termination or 12 weeks. This semistructured interview will be conducted by a researcher not involved in the delivery of treatment. These interviews will be recorded and transcribed for later analysis. The following content areas will be assessed through this interview: (1) general thoughts or experiences with treatment, (2) perceived benefits of participating in treatment, (3) specific changes and outcomes obtained because of participating in treatment, (4) perceived limitations of the treatment, and (5) recommendations for enhancement and improvement of services. We will also ask open-ended questions about the usability of measures and assessments.

Data Analysis

Primary analyses will involve the examination of the feasibility and acceptability. Feasibility will be verified by adequate (1) recruitment rates (ie, 2-3 veterans per month), (2) >90% fidelity of clinician adherence to the treatment protocol, and (3) data retention (ie, ≥70% of participants who attend at least 6 sessions of Purposeful Pathways. An acceptable level of attrition will be 30% in each condition). We will also examine the

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willingness of veterans to be randomized with a goal of 80% of those approached who agree to randomization, the number of referrals from clinicians, ease of recruitment based on the average number of contacts needed to get consent, and the number of eligible participants from the pool of potential participants. We will compare veteran acceptability between groups by conducting an independent samples *t* test on the CSQ-8 [28]. We will compare attrition rates (<30% vs >30%) between the 2 groups using a chi-square and logistic regression analysis.

Qualitative data gathered during the exit interviews will be analyzed using the Hamilton Rapid Turn-around Analytic Approach [29]. This technique is suited to short-term projects using targeted interview guides. It improves on past rapid procedures through its systematic, rigorous approach, yielding results that are slightly less nuanced but more efficient. The PI will develop an analytic template organized by the topic areas from the semistructured interview guiding qualitative interviews. The PI and at least 2 other researchers will apply the template to summarize 2 interviews to test the usability and relevance of the template to the transcripts. The research team will then meet to establish consistency in how the template is used to summarize the transcripts. From here, all focus groups will be individually summarized (each focus group will be analyzed by at least 2 researchers to ensure reliability). The PI will then transfer all the summary points into a master matrix (respondent × topic area). Next, the PI will condense the summaries in the master matrix by identifying and organizing recurring themes. The other members of the research team will review the condensed matrix to the original master matrix to confirm all central themes have been identified and ensure consensus.

Finally, we will examine differences in our clinical and vocational measures to identify empirical targets for further refinement of the treatment and inform the design of future, fully powered efficacy trials. Based on the intent-to-treat principle, all participants randomized to treatment will be included in analyses. We will run descriptive statistics as well as internal reliability (Cronbach α) for all measures. We will additionally examine the Pearson *r* to look at relationships between variables, Cohen *d* for any continuous measures, and Cramer *V* for any categorical measures to look at effect size. We will also look at individual trajectories of response to gain better insight into which participants do particularly well (or poorly) in the 2 interventions. Effect sizes and 95% CIs will be used as only 1 element to estimate the power and sample size needed for future efficacy trials.

Ethical Considerations

All phases of this study were approved by the institutional review board of the VA Bedford Health Care System Research and Development Committee in Bedford, Massachusetts, United States, with initial approval granted in February 2021. This pilot trial was registered at ClinicalTrials.gov (NCT04698967).

Results

This study was funded in October 2020, with a project start date of April 2021. Participant recruitment for this phase 3 pilot RCT began in June 2023. We anticipate study recruitment to be completed by November 2025 and primary data analysis completed by March 2026.

Discussion

Anticipated Findings

This pilot randomized control trial will provide feasibility and acceptability data for the Purposeful Pathways intervention, a manualized intervention to assist veterans in aspiring and pursuing meaningful employment. This pilot RCT will also provide data regarding the feasibility of the protocol procedures, which can help inform future efficacy trials. Finally, the findings will produce preliminary data regarding significant effects on specific outcome measures, which will inform further refinement of the treatment protocol and the development of future efficacy trials.

Conclusions

Meaningful employment is associated with the health and well-being of individuals living with psychiatric disorders [1-3]; however, the benefits gained from meaningful employment extend to few veterans, who as a group face high levels of un- and underemployment [4-7]. While previous research has shown that an integration of services like vocational assessment along with a primary VHA vocational rehabilitation program improves the likelihood of veterans obtaining competitive employment [8], there remains a gap in our knowledge of evidence-based approaches to such services. This pilot study addresses this critical need for evidence-based career counseling and development services for veterans living with psychiatric disorders. The trial will serve as the first step in testing whether enhancing VA vocational rehabilitation services with a concurrent, targeted career counseling and development protocol is feasible and acceptable for veterans with psychiatric disorders, as well as initial estimates of potential benefits.

Acknowledgments

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Data Availability

Owing to privacy and ethical considerations, final data sets underlying publications resulting from this research will not be publicly shared outside the Department of Veterans Affairs. On request and with principal investigator (BS) permission, a deidentified,

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anonymized data set will be created and shared pursuant to a data use agreement, appropriately limiting the use of the data set and prohibiting the recipient from identifying or reidentifying (or taking steps to identify or reidentify) any individual whose data are included in the data set.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review report by the Career Development Program - Panel II - Rehabilitation Research and Development Parent IRG (RRD9) - Office of Research & Development (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 139 KB - resprot_v12i1e47986_app1.pdf]

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Abbreviations

CSQ-8: Client Satisfaction Questioannaire-8
PI: principal investigator
RCT: randomized controlled trial
TAU: treatment as usual
TW: transitional work
VA: Veterans Affairs
VHA: Veterans Health Administration
VIS: Vocational Identity Scale

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Protocol

Using Wearable Passive Sensing to Predict Binge Eating in Response to Negative Affect Among Individuals With Transdiagnostic Binge Eating: Protocol for an Observational Study

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Abstract

Background: Binge eating (BE), characterized by eating a large amount of food accompanied by a sense of loss of control over eating, is a public health crisis. Negative affect is a well-established antecedent for BE. The affect regulation model of BE posits that elevated negative affect increases momentary risk for BE, as engaging in BE alleviates negative affect and reinforces the behavior. The eating disorder field's capacity to identify moments of elevated negative affect, and thus BE risk, has exclusively relied on ecological momentary assessment (EMA). EMA involves the completion of surveys in real time on one's smartphone to report behavioral, cognitive, and emotional symptoms throughout the day. Although EMA provides ecologically valid information, EMA surveys are often delivered only 5-6 times per day, involve self-report of affect intensity only, and are unable to assess affect-related physiological arousal. Wearable, psychophysiological sensors that measure markers of affect arousal including heart rate, heart rate variability, and electrodermal activity may augment EMA surveys to improve accurate real-time prediction of BE. These sensors can objectively and continuously measure biomarkers of nervous system arousal that coincide with affect, thus allowing them to measure affective trajectories on a continuous timescale, detect changes in negative affect before the individual is consciously aware of them, and reduce user burden to improve data completeness. However, it is unknown whether sensor features can distinguish between positive and negative affect states, given that physiological arousal may occur during both negative and positive affect states.

Objective: The aims of this study are (1) to test the hypothesis that sensor features will distinguish positive and negative affect states in individuals with BE with >60% accuracy and (2) test the hypothesis that a machine learning algorithm using sensor data and EMA-reported negative affect to predict the occurrence of BE will predict BE with greater accuracy than an algorithm using EMA-reported negative affect alone.

Methods: This study will recruit 30 individuals with BE who will wear Fitbit Sense 2 wristbands to passively measure heart rate and electrodermal activity and report affect and BE on EMA surveys for 4 weeks. Machine learning algorithms will be developed using sensor data to distinguish instances of high positive and high negative affect (aim 1) and to predict engagement in BE (aim 2).

Results: This project will be funded from November 2022 to October 2024. Recruitment efforts will be conducted from January 2023 through March 2024. Data collection is anticipated to be completed in May 2024.

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Conclusions: This study is anticipated to provide new insight into the relationship between negative affect and BE by integrating wearable sensor data to measure affective arousal. The findings from this study may set the stage for future development of more effective digital ecological momentary interventions for BE.

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KEYWORDS

affect; binge eating; heart rate; heart rate variability; electrodermal activity; ecological momentary assessment; wearable sensors; ecological momentary intervention

Introduction

Binge eating (BE), characterized by perceived overeating accompanied by a subjective sense of loss of control over eating [1], is a public health crisis associated with significant psychological and physical morbidity [2-6]. The frontline treatment for BE, cognitive behavioral therapy, fails to produce remission in 40%-70% of individuals [7,8]. There is a clear need to better understand specific risk factors for BE that could be targeted to improve outcomes.

The affect regulation model of BE posits that affect dysregulation (ie, difficulty tolerating or regulating negative emotional states) is a significant, momentary risk factor for BE, as BE is negatively reinforced by the alleviation of negative affect that it facilitates [9-11]. Although the affect regulation model of BE has been substantiated in extant literature [12-14], there remain several unanswered questions about the role of affect in BE.

Existing literature examining affect as a momentary predictor of BE has exclusively used ecological momentary assessment (EMA) [12,13,15-20]. EMA methodologies for BE typically involve completing multiple daily surveys on a smartphone to report binge episodes and contextual risk factors for BE. Although EMA allows for the examination of within-day relationships between affect and BE, these surveys are completed only every few hours, which precludes the examination of minute-to-minute changes in affect [21]. The field has already identified some inconsistent findings on the role of affect in predicting BE that have been attributed to the inability to measure proximal changes to affect before and after BE with EMA [14-16,18-20,22,23]. For example, an individual may experience rapid-onset negative affect related to an event (eg, intense anxiety or sadness upon hearing bad news) and engage in BE to quell the negative affect within the span of minutes, in contrast to the hours-long timescale on which the relationship between EMA-measured affect and BE is typically examined. Thus, it is critical to examine continuously measured affect to uncover the timescale on which negative affect increases BE risk.

Existing research using EMA to study BE has also focused on only 1 of the 2 key aspects of affect, affective valence (ie, the extent to which an affective state is pleasant or unpleasant). Measuring markers of affective arousal (ie, the degree of associated physiological activity) alongside affect valence may improve prediction of BE, as affect arousal may increase eating-related disinhibition [24] and the aversiveness of negative affect states [25].

A novel data collection method that could address the limitations of EMA is ambulatory passive sensing. Sensors are likely to augment EMA for the real time measurement of affect as they permit objective, continuous, and passive measurement of biomarkers of affective arousal. The use of sensors to measure physiological correlates of affect will allow for the observation of affect trajectories immediately before, during, and after EMA-reported binge episodes. Sensor data may also be able to detect negative affect before the individual is consciously aware of it, potentially facilitating earlier detection of risk for BE. Passive sensors also require substantially lower user engagement than EMA, which may produce higher compliance with data collection and reduce the requisite frequency of EMA.

Established biomarkers of affect that can be measured by ambulatory sensors include heart rate, heart rate variability, and electrodermal activity [26,27]. These features are measures of sympathetic nervous system arousal (eg, elevated heart rate, increased electrodermal activity) and parasympathetic nervous system inactivation (eg, decreased heart rate variability), which are hallmarks of affective arousal. A substantial number of studies have identified reliable changes in heart rate, heart rate variability, and electrodermal activity associated with negative affect [28-35], but only 2 studies have used ambulatory sensors to assess heart rate variability prior to BE [36,37]. These studies found that heart rate was elevated, and heart rate variability decreased prior to loss of control eating episodes relative to nonloss of control eating episodes, offering preliminary evidence that these variables may be biomarkers of affect that confer BE risk [36,37]. However, these studies were conducted among adolescents and retrospectively compared heart rate indices prior to loss of control and nonloss of control eating episodes, rather than examining the accuracy of using heart rate data patterns to predict engagement in BE. Using passive sensors to collect momentary, naturalistic affective data is likely to improve our understanding of the role of affect in maintaining BE and our capacity to accurately predict future BE.

One challenge to the use of passive sensors to measure affect is that physiological arousal may also be elevated during some high-arousal positive affect states in addition to negative affect states. Some previous research using sensors to measure affective arousal has identified distinct physiological features associated with negative affect such as longer duration of physiological arousal [38], greater changes in electrodermal activity and heart rate, and greater variability in interbeat

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intervals associated with negative affect compared to positive affect [27,35,39,40]. Furthermore, models have been developed that can distinguish negative and positive affect based on physiological parameters in healthy individuals [41,42]. Given the incredibly large and dimensional data sets yielded by sensors, these previously developed models have used machine learning, an analytic approach well-suited to predict an output (ie, negative or positive affect) based on several input variables (eg, heart rate variability and electrodermal activity). However, the capacity for these models of sensor data to distinguish negative and positive affect has not yet been established among individuals with BE. Existing research using psychophysiological sensors among individuals with BE has demonstrated elevated autonomic reactivity to psychological stress in these individuals [43-45]. However, obesity, which affects 28%-42% of individuals with BE [3], has been associated with reduced sympathetic activity [46,47]. Given these contradictory findings, it is important to establish whether sensors can distinguish negative and positive affect in this specific population. If passive sensors can distinguish between positive and negative affect states, these sensors will provide information about both the occurrence of negative affect and the intensity of physiological arousal associated with that affective state. Even if passive sensors cannot distinguish positive and negative affect, information about the intensity of affective arousal may still improve the capacity to detect risk for BE above EMA alone.

Importantly, the use of sensor technologies to improve the field's capacity to predict risk for BE offers transformative potential to power momentary interventions that target negative affect. Improved prediction of BE could facilitate the development of more effective just-in-time adaptive interventions that promote the use of therapeutic skills (eg, emotion regulation skills) when an individual is at identified risk for BE. Accordingly, this study will use psychophysiological sensors and EMA to measure negative affect to improve the prediction of BE. The study will evaluate whether the features extracted from passive sensor data can distinguish positive and negative affect in individuals with BE (aim 1). Consistent with previous research using sensors to distinguish positive and negative affect in healthy populations, we hypothesize that sensor features will distinguish between EMA-reported negative and positive affect with ≥60% accuracy [33]. Second, the study aims to develop and compare machine learning algorithms using sensor- and EMA-measured negative affect to predict BE episodes. We hypothesize that the combined sensor- and EMA-based machine learning algorithm will be more accurate for predicting BE than the algorithm using only EMA data. Based on past findings using sensors to predict emotional eating and dietary lapses, we hypothesize that the combined sensor and EMA algorithm will classify the occurrence of BE episodes with ≥70% accuracy [48,49].

Methods

Study Design

This study will use an observational design to examine real-time associations between affect (measured by psychophysiological sensors and EMA) and BE.

Participants

Participants will be 30 individuals with recurrent BE (defined as at least 12 BE episodes in the past 3 months); we will enroll participants with objective binge episodes, subjective binge episodes, or a combination of both, as both behaviors are hypothesized to be maintained via the affect regulation model. Participants will be eligible for this study if they are 18-65 years old, have a BMI of ≥18.5 kg/m^2, own a smartphone, and are willing to wear a smartwatch and complete EMA surveys for the 4-week study protocol. Exclusion criteria include inability to speak, read, and write English fluently, current eating disorder–focused treatment, and current, severe psychopathology that would inhibit engagement in study protocols (eg, active suicidality, psychosis, and substance use disorder). As antecedents for BE episodes are similar in bulimia nervosa, binge eating disorder, and other specified feeding and eating disorder diagnoses, individuals with any of these diagnoses will be eligible for the study provided they meet all other inclusion or exclusion criteria. We will aim to enroll 15 female (50%) and 15 male participants (50%). Furthermore, given that individuals with minoritized racial and ethnic identities have been underrepresented in eating disorders research, we aim to enroll at least 15 participants (50%) belonging to minoritized racial or ethnic groups.

Study Recruitment and Procedures

Participants will be recruited from across the United States using social media and radio advertisements and ResearchMatch. Participants will complete an initial phone screen, followed by a baseline assessment to confirm eligibility. Participants will complete the Eating Disorder Examination, a diagnostic interview, at the baseline assessment to confirm eligibility and assess BE frequency [50]. Once eligibility is confirmed, participants will be enrolled in the study and begin the data collection protocol. Participants will be oriented to the use of the smartwatch and completion of EMA surveys at the baseline assessment. Participants will then complete EMA surveys and wear the Fitbit Sense 2 smartwatch daily for 28 days. Participation will be fully remote, with assessments conducted using Drexel Health Insurance Portability and Accountability Act–compliant Zoom platform and Fitbit Sense 2 sensor watches mailed to and returned by participants via prepaid shipping labels. Informed consent will be obtained from all participants.

Ethics Approval

Study procedures have been approved and will be overseen by Drexel University's institutional review board (approval received September 2022; protocol number 2207009376). All procedures will be conducted in accordance with the Helsinki Declaration.

Measures

Psychophysiological Sensors to Measure Affect

Fitbit Sense 2 watches are wrist-worn devices that include several psychophysiological sensors, including photoplethysmography sensor, accelerometer, galvanic skin response sensor, and infrared thermopile. The heart rate features extracted from data collected by the photoplethysmography

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sensor will include time domain features, including average heart rate and root mean square of successive differences between normal heart beats (a measure of average variability in heart rate), and frequency domain features, including high-frequency heart rate variability (a measure of parasympathetic activity), and low-frequency heart rate variability (a measure of sympathetic arousal). These components were selected as they have been shown to change during conditions of elevated affective arousal among individuals with BE in laboratory and ambulatory studies [36,43,45,51,52]. Electrodermal activity features to be extracted from galvanic skin response data are tonic skin conductance level (average skin conductance level) and skin conductance responses (number of spikes in skin conductance), as these indices increase during periods of elevated negative affect among individuals with EDs characterized by BE [52-54]. The Fitbit Sense 2 watches contain sensors similar to devices that have demonstrated high validity for the measurement of heart rate indices and acceptable validity for the measurement of electrodermal activity during stressors [54-56].

EMA-Measured Eating Behaviors and Affect

Participants will complete signal-contingent and event-contingent EMA surveys during waking hours to report affect and the occurrence of BE and non-BE episodes (see Multimedia Appendix 1 for EMA questions). Signal-contingent surveys will be sent 6 semirandom times per day via Ethica EMA software (Ethica Data) [57]. Participants will be instructed to complete event-contingent surveys whenever they engage in BE (defined as overeating accompanied by a sense of loss of control). Consistent with BE EMA literature [12,22,58], all surveys will include ratings of positive and negative affect using the Short-Form Positive and Negative Affect Schedule modified to also include guilt, joy, excitement, and satisfaction [59]. Guilt will be included, given its established relevance to risk for BE [18] and joy, excitement, and satisfaction will be included as these items have high face validity with positive emotions individuals endorse, do not overlap with already included positive and negative affect schedule items, and have been used in previous EMA research on BE [60]. These items will be rated on a 5-point scale (1=very slightly or not at all to 5=extremely) and instances where a participant rates an item greater than 1 SD above their mean level (computed from all EMA ratings across the full study period) will be considered an instance of high negative affect or positive affect.

Statistical Analyses

Aim 1

To evaluate aim 1, instances of high positive and high negative affect will be identified from EMA data; instances of concurrent high negative and high positive affect (if observed) will be excluded from analysis for aim 1, as binary classification machine learning models require mutually exclusive, binary outcomes [61]. Sensor features from the 30-minute period surrounding (15 minutes before and 15 minutes after) EMA surveys with high positive or negative affect ratings will be included in the machine learning models. This time frame was selected, given prior research indicating that affective states typically last ≥30 minutes [62,63]. The 30-minute period will be split into six 5-minute moving windows, for which heart rate, heart rate variability, and electrodermal activity indices will be computed.

Supervised binary classification machine learning models will be developed using heart rate, heart rate variability, and electrodermal activity indices to distinguish instances of high negative affect from high positive affect. Lasso regression will be used to select features that distinguish instances of high positive and high negative affect. Machine learning models (eg, support vector machines, classification and regression trees, and neural networks) using the selected parameters will be developed using the first 3 weeks of data collected (training data) and will be evaluated for accuracy using the last week of data (test data) collected from all participants. The last week of data will be excluded from algorithm development to ensure that the algorithms can be evaluated on previously unseen data to select the most accurate algorithms and avoid overfitting. Both group-level and individual-level algorithms will be generated to reduce model variance and bias, thereby addressing concerns about both over- and underfitting [61]. This approach will balance the need for accurate prediction with developing a group-level algorithm that substantiates the general capacity to predict BE using negative affect. Given the greater importance of identifying all instances of negative affect-related risk for BE to power a future intervention than correctly classifying instances without negative affect, minimum model sensitivity thresholds of 70% will be prescribed. The best performing models will be selected by maximizing sensitivity while maintaining adequate (eg, >50%) specificity and the average accuracy will be computed for the best performing models.

Aim 1 Power

Previous studies conducted by our team using EMA to measure negative affect among individuals with BE indicate that these individuals endorse high negative affect at 22%-32% of surveys and high positive affect at 12%-34% of surveys. Previous EMA research on BE suggests overall rates of missing data of 9.7%-32.6% [12,22,58]. Conservatively estimating that approximately 20% of surveys will include high negative affect, 20% of surveys will include high positive affect, and 30% missing data, we expect at least 529 instances each of high negative and positive affect in the training data (~0.2×6 surveys per day×21 days×30 participants×0.7 compliance). Simulation studies have indicated that supervised machine learning models using highly dimensional data require ≥150 observations in each class to be powered at 0.80 to detect a small to medium effect, which 529 exceeds [64].

Aim 2

Two sets of supervised binary classification machine learning models will be developed to predict BE, 1 set using only EMA-reported negative affect data and the other integrating both EMA- and sensor-measured negative affect. Due to the dearth of research examining the timescale on which negative affect increases risk for BE, sensor patterns across several timescales (ie, 5-, 15-, 30-, and 60 minutes prior to the binge episode) will be included in the models, and the timescales that maximize model sensitivity will be retained. These time periods will be divided into 5-minute moving windows, for which heart

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rate, heart rate variability, and electrodermal activity indices will be computed. Sensor features computed for each 5-minute window within the selected timescale will be included as predictors in each machine learning algorithm examined. As in aim 1, both group- and individual-level algorithms will be generated, and the algorithms will be developed using the first 3 weeks of data (training data) and evaluated on the last week of data (test data). Sensitivity will be set a priori >70% and the best fitting model for EMA-reported negative affect alone and for the combined data will be selected by maximizing sensitivity while maintaining adequate specificity.

Aim 2 Power

Previous studies conducted by our team and others have identified an average of 2-6 BE episodes per week per participant, with most episodes occurring on separate days [12,22,65,66]. Conservative estimates of 3 binge episodes per week will yield approximately 189 BE episodes (~3 episodes per week×3 weeks×30 participants×0.7 compliance) and 1134 non-BE episodes (~18 episodes per week×3 weeks×30 participants×0.7 compliance) in the training data. As in aim 1, since the number of observations in each class exceeds 150, the supervised machine learning models will be sufficiently powered [64]. 95% bootstrap CIs will be constructed for each set of models (combined and EMA-only) to evaluate their accuracy; if the intervals do not overlap, this indicates that 1 model is significantly more accurate. For the bootstrap CI comparison, a power analysis conducted in G*Power (version 3.1; Heinrich-Heine-Universität) (power=0.80; α=.05) indicated that ≥77 total test observations are required to detect a medium effect. Aim 2 will therefore be fully powered, given 63 binge episodes (~3 episodes per week×1 week×30 participants×0.7 compliance) and 378 anticipated non-BE episodes (~18 episodes per week×1 week×30 participants×0.7 compliance) in the test data [67].

Results

This study received funding from the National Institute of Mental Health (award number F31MH131262) for the period of November 2022 through October 2024. Recruitment began in January 2023 and is expected to continue through March 2024; as of April 2023, a total of 7 participants have been enrolled. We anticipate that data collection will be completed by May 2024, and all analyses will be conducted by July 2024.

Discussion

Principal Findings

We anticipate that findings from this study will clarify whether features extracted from passive sensor data can distinguish between positive and negative affect among individuals with BE and provide an estimate of the accuracy with which these features can distinguish these emotional states. Furthermore, the study findings will identify which features are useful for distinguishing positive and negative affect states, which we anticipate will include both heart rate and electrodermal activity features. The findings from the study will also clarify the extent to which sensor-measured negative affect improves upon EMA-measured negative affect for the accurate prediction of BE episodes and provide an estimate for the accuracy of machine learning algorithms using these data sources to predict BE.

If our hypotheses are supported, our findings will replicate previous algorithms using sensor data to distinguish positive and negative affect states in a population of individuals with BE [33]. Furthermore, this study will build upon previous research using psychophysiological sensors to measure autonomic indices of emotional arousal [28-35] and to assess autonomic activity prior to BE [36,37] among individuals with BE by using these sensors to predict ecological BE in real time.

Study Implications and Future Directions

This study will use an innovative data collection method to detect real-time risk for BE, potentially providing a new avenue to study the role of affect in BE. This study may set the stage for a future sensor-integrated momentary intervention system, a technological innovation that could enhance the efficacy of mobile health tools. The findings from this study will be disseminated via presentation at scientific conferences and publication in a peer-reviewed journal.

Strengths and Limitations

This study is strengthened by the use of psychophysiological sensors and EMA to measure affect and eating behavior in an ecologically valid way. The inclusion of a transdiagnostic sample and a high proportion of men and individuals of minoritized racial and ethnic identities will increase the generalizability of our findings to groups that are underrepresented in research on BE. This study is limited by the possibility of reactivity to wearing the sensors or completing EMA surveys and the potential impact of limited participant insight and social desirability on reporting affect and BE on EMA.

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Data Availability

The data sets generated during this study will be available from the corresponding author on reasonable request.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Ecological momentary assessment questions.
[DOCX File , 18 KB - resprot_v12i1e47098_app1.docx]

Multimedia Appendix 2
Peer-review report by the National Institutes of Health Center for Scientific Review Special Emphasis Panel Fellowships: Risks, Prevention, and Health Behavior.
[PDF File (Adobe PDF File), 150 KB - resprot_v12i1e47098_app2.pdf]

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Abbreviations

BE: binge eating
EMA: ecological momentary assessment

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Protocol

Epidemiology of Motoric Cognitive Risk Syndrome in the Kerala Einstein Study: Protocol for a Prospective Cohort Study

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Abstract

Background: The southern India state of Kerala has among the highest proportion of older adults in its population in the country. An increase in chronic age-related diseases such as dementia is expected in the older Kerala population. Identifying older individuals early in the course of cognitive decline offers the best hope of introducing preventive measures early and planning management. However, the epidemiology and pathogenesis of predementia syndromes at the early stages of cognitive decline in older adults are not well established in India.

Objective: The Kerala Einstein Study (KES) is a community-based cohort study that was established in 2008 and is based in the Kozhikode district in Kerala state. KES aims to establish risk factors and brain substrates of motoric cognitive risk syndrome (MCR), a predementia syndrome characterized by the presence of slow gait and subjective cognitive concerns in individuals without dementia or disability. This protocol describes the study design and procedures for this KES project.

Methods: KES is proposing to enroll a sample of 1000 adults ≥60 years old from urban and rural areas in the Kozhikode district of Kerala state: 200 recruited in the previous phase of KES and 800 new participants to be recruited in this project. MCR is the cognitive phenotype of primary interest. The associations between previously established risk factors for dementia as well as novel risk factors (apathy and traumatic brain injury) and MCR will be examined in KES. Risk factor profiles for MCR will be compared between urban and rural residents as well as with individuals who meet the criteria for mild cognitive impairment (MCI). Cognitive and physical function, medical history and medications, sociodemographic characteristics, lifestyle patterns, and activities of daily living will be evaluated. Participants will also undergo magnetic resonance imaging and electrocardiogram investigations. Longitudinal follow-up is planned in a subset of participants as a prelude to future longitudinal studies.

Results: KES (2R01AG039330-07) was funded by the US National Institutes of Health in September 2019 and received approval from the Indian Medical Council of Research to start the study in June 2021. We had recruited 433 new participants from urban

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and rural sites in Kozhikode as of May 2023: 41.1% (178/433) women, 67.7% (293/433) rural residents, and 13.4% (58/433) MCR cases. Enrollment is actively ongoing at all the KES recruitment sites.

Conclusions: KES will provide new insights into risk factors and brain substrates associated with MCR in India and will help guide future development of regionally specific preventive interventions for dementia.

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KEYWORDS

motoric cognitive risk; Kerala; India; dementia; cognitive decline; neuroimaging

Introduction

Background

India's older adult population (≥60 years old) currently is comprised of 146 million people and is expected to increase to 179 million people by 2030 [1]. Southern India (including the state of Kerala) has the highest number of older adults—one-quarter of India's older adults [2]. Kerala has had the highest life expectancy rates since the 1970s when compared with all other Indian states (Kerala: 75.2 years; India: 69.7 years) [3]. Kerala has the highest prevalence of older adults (16.5%) among all Indian states, and this number is projected to increase to 20.9% by 2031 [4]. High literacy rates, access to health care, and a relatively strong public health system in Kerala have been hypothesized to play important roles in this demographic profile.

The increase in the older adult population in Kerala is expected to be accompanied by an attendant increase in chronic age-related diseases, including dementia [5]. Only a few studies have examined the prevalence of dementia in Kerala, with prevalence rates ranging from 3.2% to 8.7% [6-9]. A dementia prevalence of 4.9% was reported in adults aged 55 years and older in Thiruvananthapuram, the capital city of Kerala [6]. Independent studies carried out in urban and rural areas of Ernakulam district in Kerala reported dementia prevalence rates of 3.36% (≥65 years old) and 3.39% (≥60 years old), respectively [7,8]. The Harmonized Diagnostic Assessment of Dementia for the Longitudinal Aging Study in India, the first cross-national study of dementia in India, reported higher dementia prevalence rates of 7.8% and 8.7% in urban and rural areas in Kerala, respectively [9]. A 10-year follow-up study in Kerala reported incidence rates per 1000 person-years for Alzheimer disease of 11.67 (95% CI 10.9-12.4) for those aged ≥55 years and 15.54 (95% CI 14.6-16.5) for those aged ≥65 years [10].

Recognizing the need for a comprehensive study of cognitive decline in this population, the Kerala Einstein Study (KES) was established in 2008 to understand the epidemiology of and risk factors for cognitive decline, Alzheimer disease, and related dementias [11-13]. The primary phase of recruitment of this study spanned from 2008 to 2016. During this initial phase, we successfully developed a clinical research center in Baby Memorial Hospital (BMH) [14] in Kozhikode City in Kerala, validated culture-fair cognitive tests, identified new dementia risk factors (eg, depression, polypharmacy, cardiovascular disease, and small vessel disease [SVD]) [12,15-17], and established magnetic resonance imaging (MRI) protocols and processing pipelines [18,19]. KES (2R01AG039330-07) was renewed by the National Institutes of Health in September 2019 and received approval from the Indian Council of Medical Research (ICMR) to start the study in June 2021.

In this KES project, we target risk factors and brain substrates of predementia syndromes, especially the motoric cognitive risk syndrome (MCR). MCR is a predementia syndrome characterized by cognitive complaints and slow gait, proposed by Verghese and colleagues in 2013 [20], and validated in multiple countries [13,21-23]. MCR predicts both Alzheimer disease and vascular dementia even after accounting for overlap with mild cognitive impairment (MCI) [13,20,21]. MCR is common; the prevalence was 9.7% in our 17-country study (including KES) [13]. Unlike MCI, complex cognitive tests or assays are not needed to diagnose MCR [13,20,21], increasing its clinical utility in resource-poor low- and middle-income countries (LMIC) like India. We have identified several potentially modifiable risk factors (depression, sedentary lifestyle, and obesity) for MCR in high-income countries [21], but their association with MCR in LMIC is unknown. In this KES project, we will study 2 novel risk factors for predementia syndromes in KES: apathy and mild traumatic brain injury (TBI). Recent investigations highlighted apathy as a separate entity from depression and uniquely associated with cognitive decline [13]. Although TBI is a leading cause of disability in LMIC, its role as a contributor to late-life cognitive decline in LMIC is underrecognized. We hypothesize that apathy and TBI will be associated with MCR and that these associations will be moderated by early-life (years of schooling) and late-life participation in cognitive activities. We also aim to explore commonalities and differences in risk factors for predementia syndromes such as MCR in urban (Kozhikode City) and rural (Kakkodi village) communities in Kozhikode district, Kerala (Figure 1).

Figure 2 shows the conceptual framework of the KES. This study will identify relationships between different risk and protective factors for MCR in this southern Indian population. This study will have a major impact on building sustainable research capacity in this region. The extensive data collected as part of this study will act as a rich resource for discovery as well as validation of risk factors of other age-associated phenotypes and syndromes.

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Figure 1. Kerala Einstein Study research site in Kozhikode, Kerala, India.

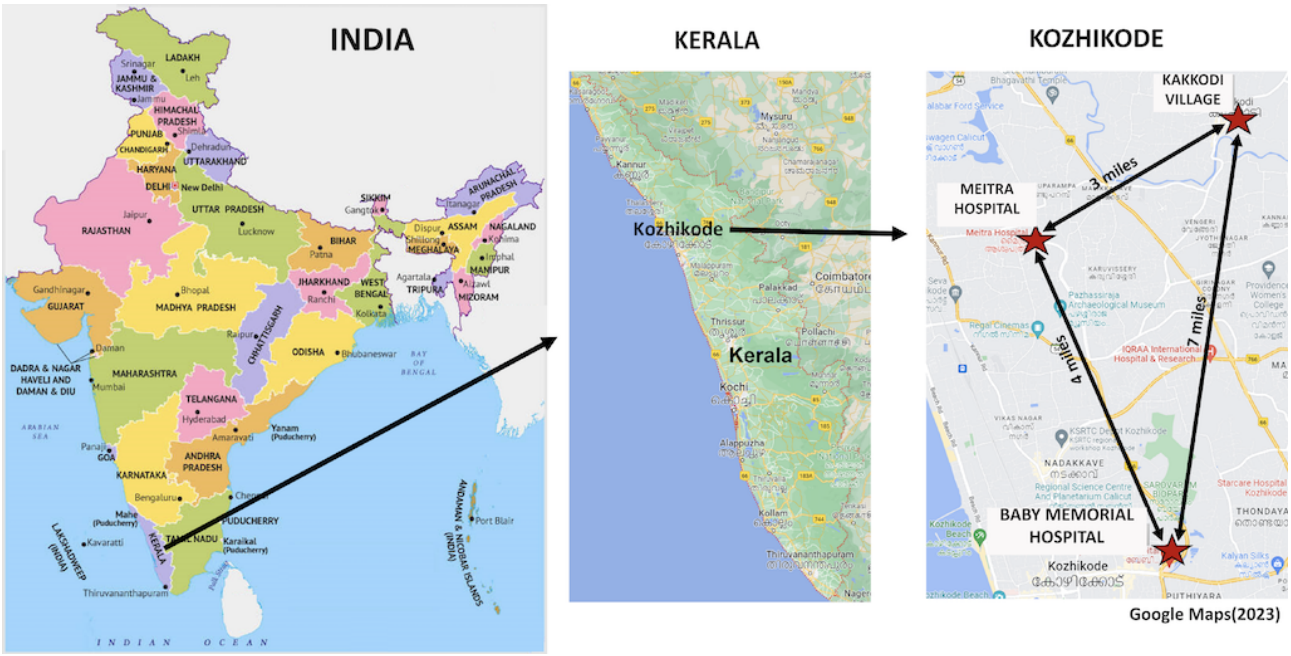
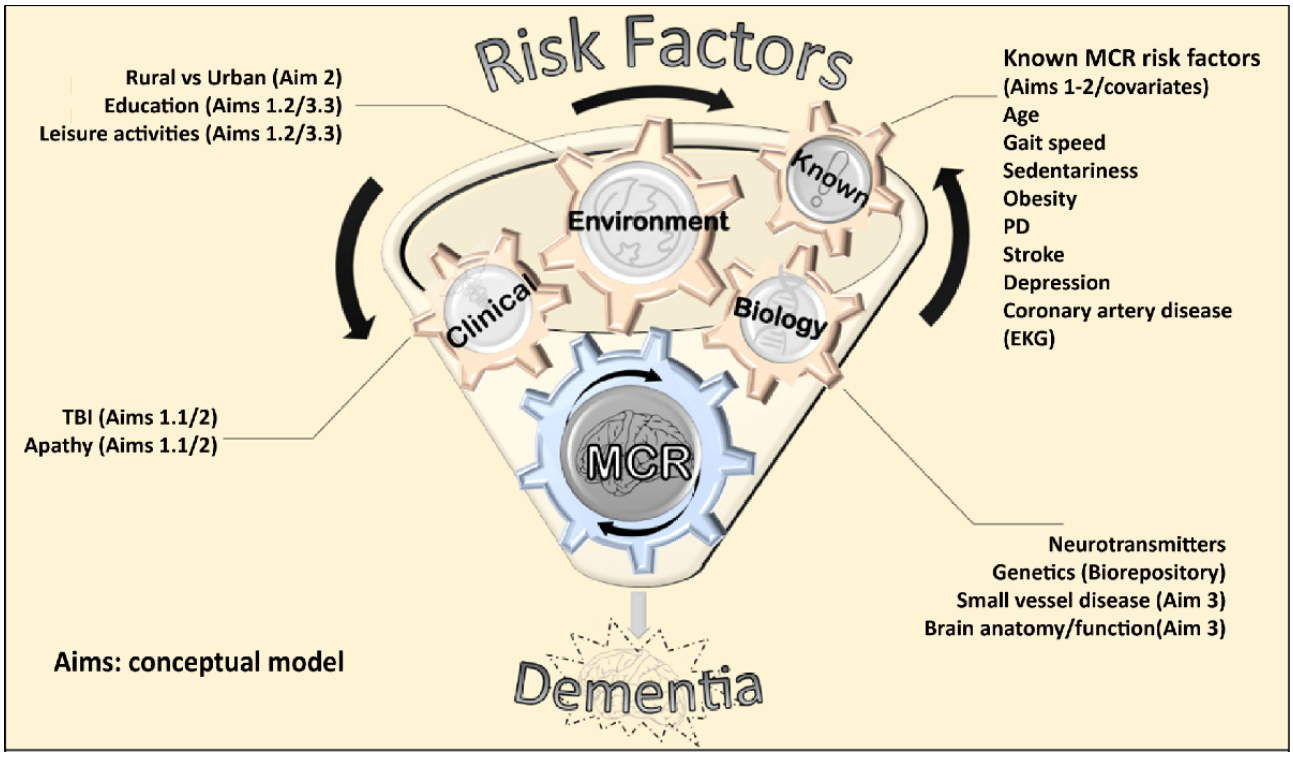


Figure 2. Conceptual framework of the Kerala Einstein Study. EKG: electrocardiogram; MCR: motoric cognitive risk syndrome; PD: Parkinson disease; TBI: traumatic brain injury.



Study Aims

The main aims of this observational study are threefold. First, the study aims to examine clinical risk factors for predementia syndromes (MCR and MCI) in 1000 older adults from Kerala: 200 already recruited in phase 1 of KES and 800 new recruits from urban and rural sites (Aim 1). The following will be conducted to support this aim:

- Examine the association of potentially modifiable risk factors previously identified in high-income countries as well as novel risk factors (apathy and TBI) with MCR and MCI in 1000 Kerala seniors (Aim 1.1)
- Examine if the relationship between apathy or TBI and MCR or MCI is moderated by early-life (years of schooling) and late-life participation in cognitive activities (Aim 1.2)

Second, we will explore commonalities and differences in risk factors for predementia syndromes in rural and urban Kerala older adults (Aim 2). Third, we will establish brain substrates and pathologies of MCR in Kerala older adults (Aim 3). The following activities will support this aim:

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- Examine structural brain abnormalities (gray matter atrophy, reduced structural connectivity) and SVD pathologies in adults with MCR compared with healthy aging controls (Aim 3.1)
- Examine the relationship between structural brain abnormalities and MCR and the role of SVD in mediating this association (Aim 3.2)
- Examine the impact of early-life and late-life participation in cognitive activities on the association between structural brain abnormalities and MCR (Aim 3.3)

Methods

Study Design and Population

We propose a cross-sectional survey of 1000 older adults in urban and rural locations in Kozhikode district. We also propose follow-up assessments at 12-month intervals with participants at our rural site. This will be the first epidemiological survey of predementia syndromes from this region and will provide preliminary data to develop new biological hypotheses. The KES project is based in Kozhikode, a northern district in Kerala state with a metropolitan population of more than 2 million people, making it the 19th largest urban agglomeration in India. The initial phase (2008-2016) of the KES was based in BMH—one of the leading providers of medical care in Kozhikode City [14]. Participants (n=200) were identified from patients and caregivers attending the neurology clinic at BMH.

An additional 800 new participants will be recruited in this phase of KES. Brain MRI will be performed with 400 participants (180 completed in the initial phase of KES and 220 new studies in this project), and up to 154 repeat MRIs will be obtained at 12-month intervals. Large-scale neuroimaging investigations are limited in India. The KES will create a unique MRI database to examine brain substrates of cognitive decline in this population.

A new component included in this KES study is the addition of rural and exurban recruitment sites in Kozhikode district. The rural site will be in Kakkodi village (population: 42,866 people) [24]. Kakkodi village differs from Kozhikode City in several indicators such as socioeconomic status (lower), occupational types (agricultural and household work are the major occupations), health care access (no hospitals nor specialty clinics), educational institutions (only primary school and middle school), and transportation (limited bus service and no trains). These rural-urban differences disproportionately affect rural-dwelling older adults who may be less mobile. There are no hospitals in Kakkodi, but BMH maintains a community health center where 500 to 600 Kakkodi adult residents receive routine medical care annually. Patients with more acute or serious complaints are referred to BMH and other hospitals in Kozhikode City. We will utilize this BMH community health center to recruit rural-dwelling older adults. The second new site will be Meitra Hospital [25], located in an exurban (beyond the suburbs) location outside Kozhikode city. As in BMH, potential participants will include patients attending neurology and other specialty clinics as well as older caregivers or family members who meet KES eligibility criteria. Meitra Hospital is a multidisciplinary institution with outpatient and inpatient facilities. Although BMH and Meitra Hospital are in urban and exurban locations, respectively, the patient population in both hospitals includes a mix of urban and rural patients who are referred from all over Kozhikode district as well as neighboring districts. We will track urban or rural residency for our analyses (regardless of study site) based on participants' home addresses.

Inclusion and Exclusion Criteria

Inclusion criteria are (1) age of 60 years or older and (2) being able to provide informed consent. Exclusion criteria are (1) refusal to complete the study tasks (ie, we had <5% refusal rate in the initial KES phase), (2) previous physician-diagnosed dementia, and (3) presence of acute or terminal illnesses or (4) presence of severe auditory or visual loss that would make it difficult for the participant to complete cognitive tasks. In addition, for neuroimaging studies, standard exclusion criteria apply, such as presence of pacemakers; aneurysm clips; artificial heart valves; ear implants; and metal fragments or foreign objects in the eyes, skin, or body.

Data Collection and Measures

Study protocols were collaboratively developed by the KES team in India and the United States over the past decade. Study procedures, testers, and supervision will be uniform and harmonized across all 3 field centers in Kozhikode district. Several culturally appropriate strategies approved by the local institutional review board (IRB) are in place to optimize recruitment and retention. For instance, all testing will be administered in Malayalam (local language) or English, as preferred by participants [11,26-28]. Results of electrocardiogram (ECG) and neuroimaging studies will be provided to the participants to share with their medical providers.

Once participants provide informed consent, they and their caregiver, if appropriate, will complete a standardized interview with the research assistant (RA) to obtain demographic characteristics, comprehensive medical history including TBI history, current medications, functional status, and mood states. Participants also complete robust measures of cognitive and physical functioning and undergo ECGs. Those who consent for the neuroimaging substudy will also complete MRIs of the brain. KES assessments are described in detail in the following sections.

Cognitive Tests and Self-reported Measures

Neuropsychological measures will be completed to evaluate cognitive function and to diagnose cognitive impairment or dementia in this cohort. Table 1 provides a catalog of the neuropsychological tasks conducted in KES. All KES tests have established Malayalam and English versions.

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Table 1. Tests conducted in the Kerala Einstein Study—local language (Malayalam) versions of all tests are available.

Category and measure	Instrument(s)
Cognition	
General	• Addenbrooke Cognitive Examination (ACE) [26,28]
Memory	• Picture-based memory impairment screen [11] • Verbal Learning Test [29,30] • Modified Taylor Complex Figure recall [29-31]
Attention and executive function	• Digit Symbol Substitution Test [32] • Verbal fluency [27,29] • Trail Making Test-Black and White [29,30,33] • WMS-R[a] Digit Span [26,34]
Visuospatial	• Modified Taylor Complex Figure [29,31]
Mood	• Geriatric Depression Scale-15 [35] • Generalized Anxiety Disorder-7 [36]
Function	
ADL[b]	• Kerala ADL scale [37]: Instrumental/basic
Social	
Network support	• Social Network Index [38] • Social Support Survey [39]
Illness	
Comorbid index	• Charlson Comorbid Index [40] • Clinical interview
Vascular	
Coronary artery disease	• Electrocardiogram [12,41] • Clinical interview

[a]WMS-R: Wechsler Memory Scale-Revised.

[b]ADL: activities of daily living.

The Addenbrooke Cognitive Examination (ACE) [28] and picture-based memory impairment screen [11] will be used to provide estimates of global cognition and memory function, respectively. For those participants who agree to complete more comprehensive testing, neuropsychological measures will include those chosen from the ICMR-Neurocognitive Toolbox (NCTB), a validated battery created in India and translated into various Indian languages including Malayalam [42]. The following ICMR-NCTB measures will be selected: Verbal Learning Test (verbal learning and memory), Modified Taylor Complex Figure Test (visuospatial and visual memory), Trail Making Test Black and White (A and B; visuospatial attention, cognitive speed, and set-shifting), Category Fluency Test (verbal fluency), and Phonemic Fluency Test (verbal fluency). The Wechsler Memory Scale-Revised Digit Span Task, which was previously used and validated in Kerala, will be used to assess auditory attention and working memory [43].

Participants will complete validated self-report questionnaires assessing depressive symptoms (Geriatric Depression Scale-30 [GDS-30] [42]), anxiety (Generalized Anxiety Disorder [GAD-7] [36]), apathy (Apathy Evaluation Scale [AES] by Marin et al [44]), social networks (Social Network Index [45] and Medical Outcomes Study Social Support Survey [46]), happiness (Subjective Happiness Scale [39]), and current leisure activities (Leisure Activity Scale [47]).

Level of independent functioning will be measured using the Instrumental Activities of Daily Living Scale for elderly people, which was developed in Kerala as a scale of functional abilities [37]. Subjective cognitive complaints will be operationalized using the 20-item Cognitive Change Index [48] and Subjective Cognitive and Motoric Complaint Questionnaire**.** The latter instrument was developed by our team to ascertain participant concerns regarding their cognition and motoric function.

All cognitive tasks and questionnaires will be administered by KES RAs, trained and supervised by the KES clinical neuropsychologists (EFW and MS). RAs in Kerala are trained in the administration and scoring of neuropsychological measures via televideo by a licensed clinical neuropsychologist (MS) based in the United States. Training includes review and explanation of each of the neuropsychological measures, modeling of test administration, and practice administration and scoring. RAs will be cleared by the neuropsychologist (MS) to evaluate participants following acceptable televideo practice

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administration. Quality control measures include regular meetings with the neuropsychologist (MS) and RAs to refresh and review procedures as well as periodic review of scored protocols by the neuropsychologist. In addition, all study protocols are double scored by a single dedicated RA (who did not administer the tests) to ensure consistency in scoring across RAs and to identify and correct any observed errors in administration and/or scoring procedures.

Physical Tests

Gait

Timed walks at a normal pace over a fixed distance (10 feet) will be completed by participants. Use of any walking aid will be noted. We have reported that older adults with MCI had slower walking times compared with cognitive normal controls in KES [49].

Unipedal Stance

The unipedal stance test is a widely used clinical test of balance. Participants will be timed as they stand on 1 leg (participant will choose which leg) for a maximum of 30 seconds [50]. "Failure" is defined as shifting the stance foot or placing the lifted foot on the floor [50]. The test is stopped and considered normal at 30 seconds.

Grip Strength

A Jamar handgrip dynamometer will be used to objectively measure grip strength as the maximum voluntary contraction in the dominant hand. Grip strength is used to define frailty and is a validated marker of physical function [51].

Repeated Chair Rise

To test leg strength and endurance, participants will perform the repeated chair rise test using a standard padded chair [52]. Participants are instructed to stand and sit down on the chair 5 times as quickly as they can with their arms folded across their chest. Time taken to complete the 5 trials will be recorded.

Neuroimaging: MRI Protocol and Assessment

Image Acquisition

Overview

All images are acquired on a 3T Siemens MAGNATOM-Skyra at Meitra Hospital. T1-weighted whole head structural images are acquired using axial 3D-MP-RAGE parameters over a 256 mm field of view (FOV) and 1.0 mm isotropic resolution (echo time [TE]=2.26 ms, repetition time [TR]=2300 ms, α=80). Diffusion-weighted images are acquired at b=1000 s/mm^2 for 64 gradient directions. In addition, 6 b=0 s/mm^2 volumes are collected, one-half with opposing phase encoding directions to correct for distortions. 3D fluid-attenuated inversion recovery (FLAIR) images are acquired over a 256 mm FOV with 0.89 mm resolution (TE=387 ms, TR=4,500 ms, inversion time=1800 ms). Finally, 3D-susceptibility-weighted images (SWIs) are acquired over 216x256 FOV with a 0.86 mm resolution (TE=20 ms, TR=27 ms). The Meitra Hospital neuroradiologist reviews each MRI scan. Any significant neuroradiological abnormality is communicated to the KES neurologists by the neuroradiologist for consideration of further action. The MRI reports are shared with the participant. Each MRI examination takes approximately 1 hour including safety screening, set up, and scanning.

Gray Matter Volume and Cortical Thickness: Preprocessing

Parcellation of the T1-weighted data into anatomical brain regions is important for examining gray matter volume and cortical thickness patterns associated with MCR and is a necessary step in processing data for examining structural connectivity associated with MCR. Each participant's structural T1-weighted image will be reconstructed using FreeSurfer v 7.2 [53]. The accuracy of FreeSurfer's subcortical segmentation and cortical parcellation has been reported to be comparable to manual labeling [54]. Gray matter segmentation and longitudinal alignment will be performed with the FreeSurfer longitudinal pipeline [53], which is robust to initialization points and avoids biasing toward any one time point by generating a median template for each participant based on the T1-weighted images at both time points using cubic spline interpolation in FreeSurfer [55]. Several processing steps, such as skull stripping, Talairach transforms, and atlas registration as well as spherical surface maps and parcellations will then be initialized with common information from the participant-specific template, significantly increasing reliability and statistical power. The gray matter volumes of 68 different regions extracted from the FreeSurfer processing pipeline are entered in subsequent statistical analyses.

Structural Connectivity: Preprocessing

Preprocessing of diffusion-weighted images consists of field distortion correction using topup distributed as part of the Functional Magnetic Resonance Imaging of the Brain Software Library (FSL; [56]) and eddy current and movement correction using the eddy tool in FSL. To evaluate any white matter changes as a function of MCR status, we will use Tracts Constrained by Underlying Anatomy (TRACULA) distributed as part of the FreeSurfer v 7.2 library. TRACULA uses probabilistic tractography to extract 42 major white matter tracts. The software performs informed automatic tractography by incorporating anatomical information from a training data set, provided by the software, with the anatomical segmentation of the T1 image of the current data set, thus increasing the accuracy of the white matter tract placement for each participant by incorporating each participant's anatomical data into the tractography algorithm. Parcellation results from the FreeSurfer longitudinal stream will be applied to TRACULA to increase sensitivity to longitudinal changes in white matter tracts. The software outputs white matter integrity measures for each voxel inside the 42 tracts with a mean of about 500 voxels per tract. Thus, for each participant, voxel-wise white matter integrity measures for 42 tracts at baseline and follow-up will be used to test the association with MCR.

Lacunes with presumed vascular origin are defined (consistent with recent consensus criteria) as round or ovoid, subcortical, fluid-filled cavity, 3-15 mm diameter, with a surrounding rim [57]. Infarcts located in white matter must be hypointense on T1-weighted and FLAIR images to distinguish from white matter hyperintensities (WMH).

WMH are automatically quantified from 3D FLAIR images using the lesion segmentation toolbox [58], which will be implemented with SPM12/MatLab [59]. The lesion segmentation

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tool pipeline provides us with overall WMH lesion count and volume, as well as a voxel-based WMH probability map that can be entered into subsequent analyses.

Microbleeds are identified on SWI, a 3D T2* sequence attuned to detecting hemorrhage [60-63]. SWI was shown to detect 67% more microbleeds than conventional T2 [64,65]. Longitudinal tracking of microbleeds on SWI correlates with cognitive decline [64,65]. We will use the Microbleed Anatomic Rating Scale (MARS) to quantify microbleeds by number and location on SWI [66]. The MARS quantifies microbleeds in the following 9 regions: frontal, parietal, temporal, occipital, infratentorial (brain stem and cerebellum), basal ganglia, thalamus, capsule, and corpus callosum. Regional and overall number and presence of microbleeds will be examined. MARS was used in our MCR study based in KES.

ECG

A standard 12-lead ECG (Tricog Health) will be performed by a certified cardiac physiologist at BMH and Meitra Hospital [12,41]. Standard 12-lead ECG will be analyzed following the Minnesota code classification by a study clinician, blinded to neurological status including normal, MCR, or dementia diagnoses. Based on our previous KES projects, the following abnormalities will be reported: rhythm abnormalities, left ventricular hypertrophy, significant ST and T wave changes, Q waves, heart block, and bundle branch block [12]. Major ECG abnormalities are defined as the presence of any one of the following: Q-QS wave abnormalities, left ventricular hypertrophy, Wolff-Parkinson-White syndrome, complete bundle branch block or intraventricular block, atrial fibrillation or atrial flutter, or major ST-T changes.

Phenotypes of Interest

MCR

MCR is our primary outcome of interest and is algorithmically diagnosed using the criteria by Verghese et al [13,20,21] in KES participants who meet all 4 of the following criteria: (1) subjective cognitive complaint, (2) slow gait, (3) no functional decline, and (4) no dementia [13,20]. Assessment of the key MCR criteria is summarized in the following paragraphs.

Subjective cognitive complaints are assessed based on participant positive (abnormal) responses to standardized questions in the Subjective Cognitive and Motoric Complaint Questionnaire [67].

Consistent with prior MCR studies, including KES [13,21-23,68,69], slow gait is defined as a gait speed 1 SD below age and sex-specific means. Although gait is multifactorial with neurological and non-neurological causes (eg, arthritis) [70], multiple studies have shown that, irrespective of causes, slow gait predicts dementia, which supports the robustness of this sign [71,72].

MCI

We have implemented the following established criteria for MCI [73] in the KES [15,16,18]: (1) score 1.5 SD below age and education-adjusted means on any cognitive test (Table 1), (2) cognitive complaints, (3) no functional decline [37], and (4) no dementia.

Dementia

Diagnosis of dementia is made by consensus of study clinicians (neurologist and neuropsychologists) and research staff following review of all available clinical evaluations, neuropsychological test results, functional assessments, and medical history. The Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) criteria for diagnosis of dementia will be used [74]. Dementia at baseline is an exclusion criterion for the KES.

TBI

Mild TBI is being examined as a novel predictor of MCR in the Kerala population. We will use the American Congress of Rehabilitation Medicine definition of mild TBI that is widely used in clinical and research practice [75]. Mild TBI results in ≤30 minutes of unconsciousness (cf >30 minutes in moderate/severe TBI), and the posttraumatic amnesia period is <24 hours. We will use a local adaptation of the Brain Injury Screening Questionnaire (BISQ) [76], a structured questionnaire that characterizes incidence and severity of lifetime exposure to head trauma and TBI [77-79]. The BISQ provides a profile of symptoms in the following 4 domains: attention and memory; depression, anxiety, and mood; aggression and impulsivity; and physical [78,79]. The BISQ may be completed via interview or self-administration. The BISQ has good-to-excellent test-retest reliability [76,78,79].

Apathy and Depressive Symptoms

Apathy has been reported to predict risk of developing predementia syndromes including MCR in the United States [80,81]. We will measure depression and apathy utilizing the GDS-30 [25] and the AES, respectively [44]. Confirmatory factor analysis has shown apathy-withdrawal to be a distinct domain of the GDS [82]. The GDS-3A is the apathy subscale of the GDS, consisting of the following 3 items (score range 0-3) [83]: (1) “Have you dropped many of your activities and interests?” (2) “Do you prefer to stay at home, rather than going out and doing new things?” and (3) “Do you feel full of energy?” A score of 2 or more indicates presence of apathy. Reported sensitivity and specificity of the GDS-3A varied from 29% to 69% and from 89% to 93%, respectively, in 3 large European cohorts of older adults [83,84]. GDS-3A has been used to measure apathy in our Bronx-based cohorts [85]**.** The AES [44], an 18-item questionnaire, assesses apathy symptom severity and 3 domains of apathy (behavioral, emotional, and cognitive). AES scores range from 18 to 72, with higher scores indicating greater severity [44]. The AES has been reported to have higher sensitivity than the GDS-3A, as well as excellent test-retest and inter-rater reliability [44,86]. The AES is recommended for evaluation of people with dementia [87,88] but has not been widely used in aging cohorts [44]. We will develop a local language version of the AES and pilot it in our new sites as an alternate apathy assessment. As the GDS-30 is more widely used, we will also use confirmatory factor analysis of the GDS-30 to partition out apathy from depression in order to

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develop a more robust measurement model, which we will compare with the AES.

Statistical Analysis

Outcomes

The primary outcome of interest is MCR (and MCI) status. Predictors are continuous and categorical measures including apathy, mild TBI, cognitive reserve (education and leisure activities), and neuroimaging variables. We will examine modifiable predictors for MCR (identified in the United States) such as obesity and sedentariness [21] as well as novel risk factors that we associated with the presence of cognitive impairment or MCI in KES such as ECG abnormalities, apathy, and TBI [12,41]. Baseline distribution of variables will be examined using appropriate graphical procedures and summary statistics before analyses. Transformation of continuous biomarkers will be considered if severe skewness in distributions is detected. We will also address sex in our analyses, both adjusting for it as a covariate and conducting stratified analyses by sex. Cross-sectional associations between both established and novel predictors and MCR/MCI will be evaluated using logistic regression models. All models will adjust for age, gender, education, and other confounders including but not limited to medical illnesses, anthropometric measures, residency status, recruitment source, and global cognition (ACE score). We will compare risk factors for MCR/MCI between urban and rural older adults using logistic regression models in the overall sample as well as separately.

Gray matter volumes and cortical thickness of 84 brain regions will be extracted from the FreeSurfer processing pipeline and entered in linear mixed effects models (LMEMs) adjusted by standard covariates (age, sex, education, total intracranial volume, global health score, and MCI) to detect differences by MCR status. To evaluate white matter integrity or structural connectivity associated with MCR, voxel-wise white matter integrity—fractional anisotropy—measures for 42 tracts at each time point will be entered into LMEMs adjusted by standard covariates (age, sex, education, total intracranial volume, and global health score) to detect differences by MCR status. Finally, the influence of SVD in general as well as specific SVD pathologies (lacunes, WMH, and microbleeds) will also be examined in subsequent LMEMs adjusted by standard covariates (age, sex, education, total intracranial volume, and global health score) to detect differences by MCR and non-MCR status.

Power

With a proposed sample size of 1000 and estimated MCR prevalence of 15% [13], we can detect an odds ratio of 1.33, corresponding to a 1 SD increase in worsening apathy and TBI, with 80% power at a significance level of .05. Prevalences of modifiable risk factors for MCR in KES ranges from 10% to 70%, which allows a detection of odds ratios of 1.69 to 2.24 on the associations of these risk factors with MCR and MCI with 80% power [15,16,18].

Power (Neuroimaging)

With 400 participants with neuroimaging measures and a prevalence of 15% for MCR or MCI, we can detect a difference of 0.45 SD in structural brain abnormalities between participants with and without MCR or MCI with 80% power. For comparison, we derived a structural brain network of MCR in 267 participants [19].

Timeline

Over the 5 years of this project, we will seek to recruit approximately 400 urban-dwelling and 400 rural-dwelling participants. Of the 800 new participants, 220 from all sites will undergo neuroimaging, which, along with the 180 studies from the first KES phase, will provide a database of 400 neuroimaging studies. Participants from all 3 sites will be recruited for imaging studies. Given the restricted geographic location of our rural site (Kakkodi village) and very low rates of out-migration by older residents, we propose to follow up rural participants every 12 months. In our urban sites, we will attempt to conduct 12-month follow-up assessments with all participants undergoing neuroimaging. Given the larger catchment area, follow-up will be more challenging, but we will also consider home assessments to improve retention.

Ethics and Procedures

This study will be conducted in accordance with the Helsinki Declaration. The informed consent and recruitment processes follow local socially and culturally appropriate practices. The assessments and procedures have been approved by the IRB at BMH (BMH/IEC/02/2022), which also served as the local IRB for the first phase of KES. In addition, study design and consent procedures have also been approved by the ICMR (2020-10058), which is a requirement for epidemiological and experimental studies conducted in India. The study protocols have also been reviewed and approved by the Albert Einstein College of Medicine IRB (2006-368).

Results

We had recruited 433 participants as of May 17, 2023. The basic characteristics of the recruited participants at each of the research sites in Kozhikode are shown in Table 2. As the recruitment is ongoing, formal statistical group comparisons were not conducted. Most of the recruited participants are men (255/433, 58.9%), as noted in previous KES publications [12,13,15,16,18,49]. Most participants (293/433, 67.6%) recruited thus far, including those from BMH and Meitra Hospital, have rural residency. Of the 433 participants recruited thus far, 58 (13.4%) met the criteria for MCR, and 89 (20.6%) met the criteria for MCI.

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Table 2. Demographic characteristics of participants recruited in the Kerala Einstein Study as of May 17, 2023.

Characteristics	Total (N=433)	BMH[a] (n=194)	Mietra Hospital (n=102)	Kakkodi (n=137)
Age (years), mean (SD)	68.89 (5.48)	68.46 (5.24)	70.89 (5.22)	68.02 (5.66)
Sex (female), n (%)	178 (41.1)	81 (41.8)	30 (29.4)	67 (48.9)
Residence, n (%)				
Rural	293 (67.6)	107 (54.9)	61 (59.8)	125 (91.2)
Urban	137 (31.7)	87 (44.6)	39 (38.2)	12 (8.8)
Education (years), mean (SD)	9.20 (3.65)	9.35 (3.76)	9.91 (3.93)	8.47 (3.13)
Addenbrooke Cognitive Examination (ACE) score, (range 0-100), mean (SD)	78.37 (13.07)	77.56 (14.73)	77.58 (11.42)	80.10 (11.51)
Picture-based Memory Impairment Screen (range 0-8), mean (SD)	6.95 (1.90)	6.94 (1.98)	6.12 (2.36)	7.59 (0.94)
Geriatric Depression Scale (range 0-30), mean (SD)	7.76 (6.06)	7.55 (6.71)	9.03 (4.83)	7.13 (5.81)
Generalized Anxiety Disorder (range 0-21), mean (SD)	3.56 (4.54)	2.30 (4.03)	6.49 (3.96)	3.15 (4.67)
Social Network Index, number of high-contact roles (range 0-12), mean (SD)	5.27 (1.26)	5.37 (1.09)	5.04 (1.28)	5.32 (1.43)
Social Network Index (number of people in the social network), mean (SD)	18.92 (8.38)	18.59 (7.91)	17.22 (7.15)	20.57 (9.49)
Social support score, mean (SD)	3.92 (0.65)	3.85 (0.61)	3.66 (0.49)	4.17 (0.70)
MCI[b], n (%)	89 (20.6)	37 (19.1)	40 (39.2)	12 (8.8)
MCR[c], n (%)	58 (13.4)	38 (19.6)	9 (8.8)	11 (8)

[a]BMH: Baby Memorial Hospital.

[b]MCI: mild cognitive impairment.

[c]MCR: motoric cognitive risk syndrome.

Discussion

KES aims to understand the risk factors associated with MCR in the Kerala population. The initial phase of KES has already played a key role in defining and establishing risk factors and pathologies for MCR and MCI in India [13,18]. In this new project, our focus will shift to studying the role of apathy and TBI (risk factors) as well as cognitive reserve (protective factor) on the pathogenesis of cognitive decline and predementia syndromes in Kerala. Research on predementia syndromes such as MCR in LMIC such as India is scarce [89,90]. Emerging evidence emphasizes the interactions among ethnicity, genetics, environment, culture, and neurobiology in influencing manifestations of dementia [90]. We will make use of the interdisciplinary expertise of the KES team, local research infrastructure established since 2008, access to unique populations, and strong foundation of research to address our research questions focusing on predementia, especially MCR. This study also lays down a strong foundation of neuroepidemiological research in this region. The Kerala population is homogenous in terms of race, language, and culture. Hence, any observed findings should also apply to the broader Kerala older adult population.

Apathy is one of the prevalent and challenging behavioral symptoms associated with dementia [91]. Our recent study of a cohort based in the United States has shown apathy to be associated with incident MCR but not MCI [81]. Mild TBI is a novel risk factor that we address in this project. Although severe TBI-related injuries and deaths are common in India, mild TBI has not been established as a risk factor for late-life cognitive decline in Indian older adults. Neuroimaging studies to understand the association of TBI and other neuroimaging correlates (SVD, WMH, lacunes, microbleeds, gray matter volume, cortical thickness, and structural connectivity) with predementia syndromes including MCR have been scarce in this part of the world. Hence, this new KES project will provide new insights into the nature of cognitive decline in the growing older Indian population.

KES's main strength is the extensive clinical data being collected from a unique population, which provides opportunities to carry out research focusing on cognitive decline as well as geroscience. This will also be the first as well as the largest organized study of predementia syndromes and cognitive decline in Kerala state. The research infrastructure established in past and current KES projects will be key to initiating future spin-off studies to understand other clinical and biological aspects of cognitive decline and aging. KES data can also be utilized to understand multiple other age-associated phenotypes and syndromes such as frailty and depression in the older adult population in this region.

The cross-sectional design of KES does not permit causal inferences. However, this will be overcome with the longitudinal study design, which will be initiated in this phase and expanded in the future. We have not proposed biological specimen

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collection. We will explore local collaborations with the goal of establishing a biorepository facility in Kozhikode, which will aid in conducting genetic and bioassays.

This KES project builds on the foundation of our past successful collaboration. Recruitment for the new KES project has started and is going well. We expect to achieve our recruitment goals and aims within the proposed project period. This KES project will be a major step toward understanding risk factors and neuroimaging correlates associated with MCR in Kerala and will help improve identification of older individuals at risk of dementia as well as guide future development of preventive strategies for dementia in India and elsewhere.

Acknowledgments

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Data Availability

The data set generated in this study is available from the corresponding author on reasonable request and with completion of the data user agreement.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-reviewer report from the National Institute on Aging and Fogarty International Center.
[PDF File (Adobe PDF File), 162 KB - resprot_v12i1e49933_app1.pdf]

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Abbreviations

ACE: Addenbrooke Cognitive Examination
AES: Apathy Evaluation Scale
BISQ: Brain Injury Screening Questionnaire
BMH: Baby Memorial Hospital
DSM-IV: Diagnostic and Statistical Manual of Mental Disorders IV
ECG: electrocardiogram
FLAIR: fluid-attenuated inversion recovery
FOV: field of view
FSL: Functional Magnetic Resonance Imaging of the Brain Software Library
GAD: Generalized Anxiety Disorder
GDS: Geriatric Depression Scale
ICMR-NCTB: Indian Council of Medical Research-Neurocognitive Toolbox
IRB: institutional review board
KES: Kerala Einstein Study
LMEM: linear mixed effects model
LMIC: low and middle-income countries
MARS: Microbleed Anatomic Rating Scale
MCI: mild cognitive impairment
MCR: motoric cognitive risk syndrome
MRI: magnetic resonance imaging
RA: research assistant
SVD: small vessel disease
SWI: susceptibility-weighted imaging
TBI: traumatic brain injury
TE: echo time
TR: repetition time
TRACULA: Tracts Constrained by Underlying Anatomy
WMH: white matter hyperintensities

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Protocol

The Role of Emotion Regulation, Affect, and Sleep in Individuals With Sleep Bruxism and Those Without: Protocol for a Remote Longitudinal Observational Study

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Abstract

Background: Sleep bruxism (SB) is an oral behavior characterized by high levels of repetitive jaw muscle activity during sleep, leading to teeth grinding and clenching, and may develop into a disorder. Despite its prevalence and negative outcomes on oral health and quality of life, there is currently no cure for SB. The etiology of SB remains poorly understood, but recent research suggests a potential role of negative emotions and maladaptive emotion regulation (ER).

Objective: This study's primary aim investigates whether ER is impaired in individuals with SB, while controlling for affective and sleep disturbances. The secondary aim tests for the presence of cross-sectional and longitudinal mediation pathways in the bidirectional relationships among SB, ER, affect, and sleep.

Methods: The study used a nonrandomized repeated-measures observational design and was conducted remotely. Participants aged 18-49 years underwent a 14-day ambulatory assessment. Data collection was carried out using electronic platforms. We assessed trait and state SB and ER alongside affect and sleep variables. We measured SB using self-reported trait questionnaires, ecological momentary assessment (EMA) for real-time reports of SB behavior, and portable electromyography for multinight assessment of rhythmic masticatory muscle activity. We assessed ER through self-reported trait questionnaires, EMA for real-time reports of ER strategies, and heart rate variability derived from an electrocardiography wireless physiological sensor as an objective physiological measure. Participants' trait affect and real-time emotional experiences were obtained using self-reported trait questionnaires and EMA. Sleep patterns and quality were evaluated using self-reported trait questionnaires and sleep diaries, as well as actigraphy as a physiological measure. For the primary objective, analyses will test for maladaptive ER in terms of strategy use frequency and effectiveness as a function of SB using targeted contrasts in the general linear model. Control analyses will be conducted to examine the persistence of the SB-ER relationship after adjusting for affective and sleep measures, as well as demographic variables. For the secondary objective, cross-sectional and longitudinal mediation analyses will test various competing models of directional effects among self-reported and physiological measures of SB, ER, affect, and sleep.

Results: This research received funding in April 2017. Data collection took place from August 2020 to March 2022. In all, 237 participants were eligible and completed the study. Data analysis has not yet started.

Conclusions: We hope that the effort to thoroughly measure SB and ER using gold standard methods and cutting-edge technology will advance the knowledge of SB. The findings of this study may contribute to a better understanding of the relationship among SB, ER, affect, and sleep disturbances. By identifying the role of ER in SB, the results may pave the way for the development of targeted interventions for SB management to alleviate the pain and distress of those affected.

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KEYWORDS

sleep bruxism; emotion regulation; ecological momentary assessment; rhythmic masticatory muscle activity; heart rate variability; wrist actigraphy

Introduction

Background

Sleep bruxism (SB) is an oral behavior [1] characterized by high levels of repetitive jaw muscle activity during sleep, known as rhythmic masticatory muscle activity (RMMA), and expressed as teeth grinding and clenching [2]. When its occurrence is frequent and associated with oral damage, pain, or sleep or neurological comorbidities, it can be classified as a sleep-related movement disorder. With a general population prevalence of 5.5% to 16% [3,4], SB varies on a spectrum of frequency, severity, and awareness, with many experiencing subclinical levels of teeth grinding [5]. Despite its detrimental outcomes, including jaw pain and fractured teeth as well as impaired sleep, function, and quality of life, there is currently no cure for SB [6].

SB can be measured in terms of self-reported or physiological measures at either trait or state timescales. Self-reported individual-difference questionnaires ask about perceived symptoms over weeks or months to assess trait-level SB [7]. Momentary questionnaires probe current pain or teeth grinding during the preceding sleep period to assess state-level SB [8]. Although relatively inexpensive, self-reporting sleep behavior limits the validity of this method of assessing SB because individuals are not aware of the behavior unless told by an observer. Physiological measures have the advantage of unobtrusively assessing SB while the individual is asleep. In-laboratory polysomnography is considered the gold standard of objective sleep measurement [9], but it is not feasible for multiple nights. Alternatively, portable physiological devices are optimal for a multinight assessment within a participant's home because they are relatively inexpensive to purchase, easy to distribute, and ideal for self-application [10,11].

SB and Emotion Regulation

The etiology of SB is not yet well understood. It is widely thought to have multiple predisposing factors [6], including maladaptive personality traits, neurotransmitter imbalance, and psychosocial impairments. Recent research implicates negative emotions as a likely factor. Tensing of the jaw muscles can be part of an emotional motor response [12], and acute wake-time negative emotions can increase RMMA [13]. SB has also been associated with impaired affect regulation, either diminished use of adaptive regulation strategies or increased use of maladaptive regulation strategies [14-17]. However, this relationship remains unclear [18].

Emotion regulation (ER) is defined as "attempts to influence which emotions we have, when we have them, and how those emotions are experienced and expressed" [19]. Individuals can regulate their emotions by implementing ER strategies [19] such as cognitive change (generating alternative interpretations of an event to change its affective impact [eg, cognitive reappraisal]), attentional deployment (directing one's attention to other aspects of the situation [eg, distraction]), and response modulation (controlling experiential, behavioral, or physiological emotional reactions [eg, expressive suppression]). Cognitive change and attentional deployment are considered generally adaptive strategies, whereas expressive suppression is more so a generally maladaptive or harmful strategy [20]. One core aspect of ER is how frequently individuals use a specific ER strategy (ie, ER frequency or use). Another core aspect of ER is how individuals perceive their ability to successfully use an ER strategy to achieve the goal of the ER attempt (ie, ER self-efficacy or effectiveness) [21].

Similar to SB, ER can be measured in terms of self-reported or physiological measures at either trait or state timescales. Self-reported trait questionnaires and momentary assessments of ER strategy use tap into the domain of deliberate, reflective, and consciously accessible information, whereas physiological measures provide access to relatively unconscious and automatic processes [22] and circumvent the numerous limitations of self-report. Such limitations include response biases, limited insight, and one's motivational level. Research has shown a positive association between ER effectiveness and both resting and 24-hour heart rate variability (HRV) [23,24].

SB and Affective and Sleep Disturbances

Although affective and sleep disturbances play a prominent role in SB, there have been mixed patterns of findings in the current literature. In the domain of affective disturbances, depression, anxiety, negative affect, and perceived stress are key variables that have been related to self-reported, clinician-diagnosed, or physiologically based SB. Depression has been associated with self-reported [25] but not polysomnography-based measurements of SB [26]. Trait anxiety has been linked with self-reported [27] and physiological [28] measures of SB. Negative affect has been found to be greater in individuals with clinician-diagnosed SB than in those without in 1 study [29] but not in another study [25]. Perceived stress has been associated with self-reported or physiological measures of SB in some studies [16,30] but not in others [31,32].

In the sleep domain, sleep quality and sleep efficiency represent key variables that have been related to SB. Self-reported sleep quality, hereinafter referred to as sleep quality, integrates perceived experiences reflecting sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, the use of sleeping medication, and daytime dysfunction [33]. Some studies have found worse trait sleep quality with self-reported [34] or physiological measures (including polysomnography) [35] of SB, but this was not the case in another multimeasure study

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[32]. Worse state sleep efficiency (the ratio of time spent in bed asleep to the total amount of time spent in bed) has been found for both self-reported or clinically diagnosed [34] and home-based electromyography (EMG) [36] SB measures but not in a polysomnography sleep laboratory study [37].

The mixed patterns of results of SB in relation to affective and sleep disturbances suggest that an underlying cause may exist. We propose that ER may play this role. In fact, ER is a transdiagnostic factor in affective and sleep disorders [38]. This study proposes to phenotype ER in SB with both self-reported and physiological trait and state measures of SB and ER collected longitudinally in the context of a 14-day ambulatory assessment while controlling for affect and sleep.

Hypotheses and Objectives

We hypothesize that the effect of ER in those with SB remains when adjusting for associations with affect and sleep variables. Therefore, we expect that for those with greater (vs lower) self-reported or physiological trait or state SB, there will be a lower self-reported trait and state use of cognitive reappraisal and distraction (hypothesis 1a [H1a]), a greater self-reported trait and state use of expressive suppression (H1b), a lower self-reported trait and state effectiveness of cognitive reappraisal and distraction (H2a), a greater self-reported trait and state effectiveness of expressive suppression (H2b), and a lower physiological trait and state HRV (H2c).

The primary objective of this study is to test whether ER is associated with SB, while controlling for affect and sleep variables. As outlined in *Methods* section, we operationalized the core variables of SB, ER, affect, and sleep in terms of self-reported and physiological assessment modalities and trait and state temporal modalities. The secondary objective of the study is to test cross-sectional and longitudinal mediation pathways in the bidirectional relationships among SB, ER, affect, and sleep.

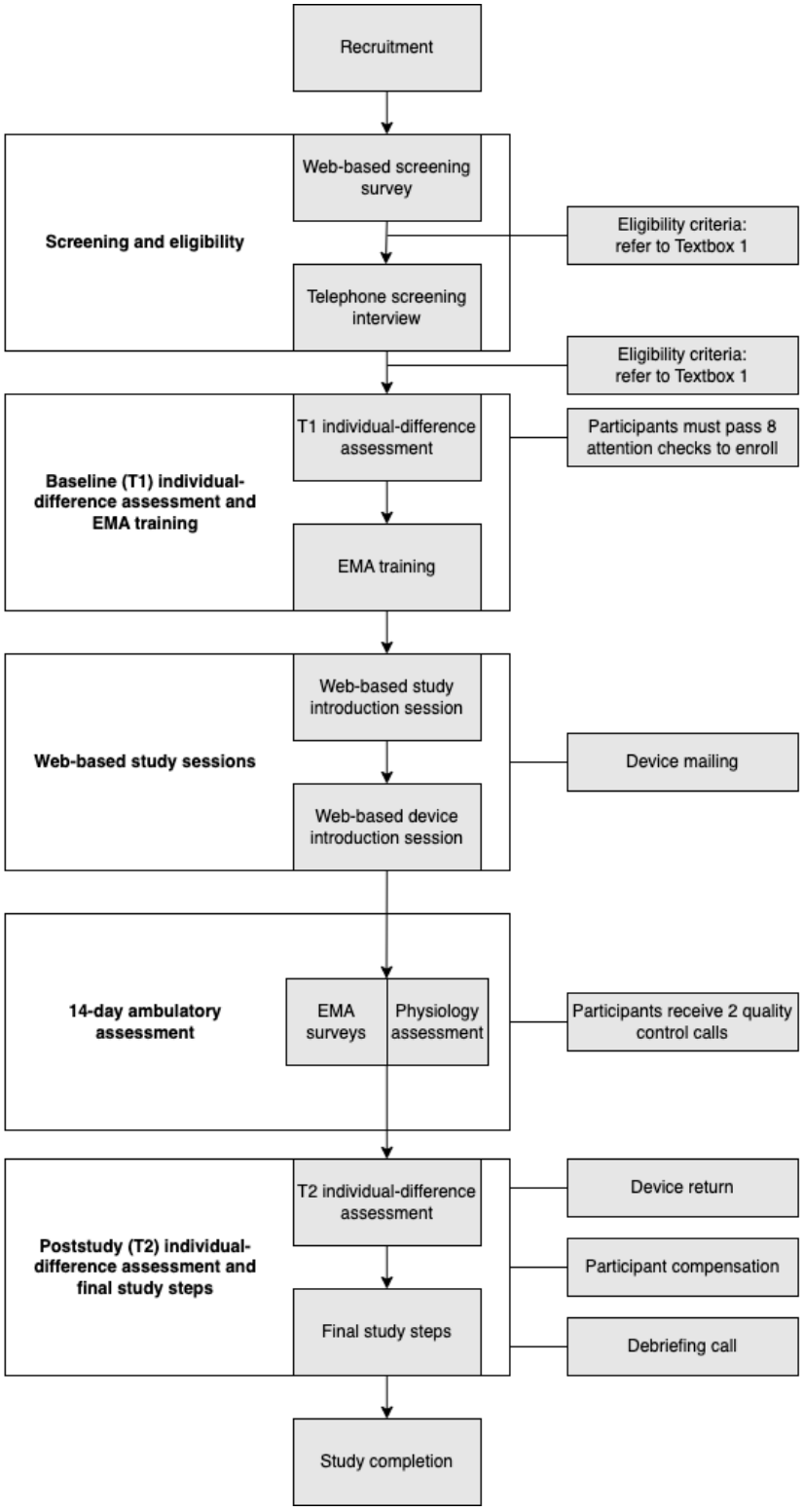
Methods

Study Design

This study applied a repeated-measures observational design. It did not use randomization, blinding, or assignment. As Figure 1 shows, participants went through a fully remote 5-step procedure, including screening and determination of eligibility, an assessment of individual differences, 2 web-based study sessions, the 14-day ambulatory assessment, and an abbreviated assessment of individual differences. As defined by the National Institutes of Health (NIH), this study is a basic behavioral science study at stage 0. It was preregistered at the National Institute of Dental and Craniofacial Research [39] of the NIH on July 8, 2020 (1R01DE026771-01, version 0.1).

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Figure 1. Study design. As indicated in the white boxes, participants underwent 5 task components; criteria and additional procedures are noted to the right of these white boxes. EMA: ecological momentary assessment.



Ethics Approval

The protocol of this study was submitted to, and approved by, Institutional Review Board 7 of Stanford University, Stanford, California, United States (FWA00000935; protocol #50342).

Informed Consent and Risk Mitigation

Participants were informed of, and consented to, the study's potential risks, although the overall evaluation of risk was low owing to the use of noninvasive procedures and precautionary measures such as (1) measures taken to preserve participant confidentiality (eg, anonymous participant IDs, a password-protected database, separation of data and identifiable information, and access restrictions to data sets), (2) measures to mitigate risk of suicidal ideation (eg, the use of scripts assessing the severity of suicidality and following referral plans in the case of detected suicidal ideation), (3) measures to

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mitigate the risk of uncovering an unknown health condition (eg, through the consent form stating that study team members are not responsible for communicating medical diagnoses to participants), (4) measures to mitigate experiencing minor skin irritation from electrodes (eg, the use of clinical-grade gels and adhesives, instructing participants to discontinue use in the case of a reaction, creating an explicit electrode removal and reapplication schedule, sending reminder emails and conducting check-in calls, and requesting participants to contact the study team at the first sign of potential skin irritation), and (5) measures mitigating the risk of negatively affecting participants' psychological well-being (eg, including a consent statement that explains risks and informs participants of their right to voluntarily withdraw from the study at any time).

Recruitment and Participants

A minimum sample size of 236 participants was determined by power analyses (G*Power; Heinrich Heine University Düsseldorf) [40]. The calculations were based on the detection of typical effect size estimates of prior studies investigating affect regulation in SB (Cohen d >0.21) [14-18], with at least 80% power for 2-tailed pairwise comparisons at Cronbach $\alpha \leq .05$.

Enrollment and data collection took place from August 2020 to March 2022. Participants were recruited through Facebook advertisement campaigns, research registries, web-based forums, web-based classroom visits, university email mailing lists, and flyers posted at medical clinics and on university campuses on the West Coast. We sought to enroll 275 participants approximately evenly distributed across SB severity and sex, as well as racial and ethnic diversity representative of that in the United States. Racial and ethnic details were collected via the web-based screening survey (Multimedia Appendix 1) that was used to determine study eligibility. We completed intermittent distribution checks to assess the need for targeted recruitment. Participants who completed all steps of the study were compensated with a US $80 gift card as well as a comprehensive sleep report.

Inclusion and Exclusion Criteria

The inclusion and exclusion criteria are presented in Textbox 1.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Living in the United States
- Aged between 18 and 49 years
- High school graduate
- At least 5 natural teeth per quadrant
- Normative bedtime (ie, bedtime no later than 1 AM and wake time no later than 10 AM)
- Refrain from consuming alcohol as well as nicotine and cannabis
- Refrain from consuming caffeine after 12 PM
- Maintain a stable bedtime routine (see 5th point in inclusion criteria)
- Pass at least 8 of 9 attention checks in the 90-minute baseline individual-difference assessment
- Have reliable access to the internet

Exclusion criteria

- Reporting as having health conditions other than sleep bruxism (SB), especially physical, mental, and sleep disorders known to affect SB or sleep
- A history of skin allergies
- Any traveling during the 14-day ambulatory assessment that affects circadian rhythm and thus bedtime routine
- Undergoing SB treatment
- Intake of any of the disqualifying medications (ie, antidepressants, anxiolytics, antipsychotics, antihypertensives, thyroid medications, antiasthmatics, anti–Parkinson disease medications, anticonvulsants, antihistamines, triptans, stimulants, and sleep medicines)
- Significant exposure to nicotine or cannabis products
- Caffeine use disorder
- Current pregnancy or pregnancy within the past year or the presence of infants aged <12 months
- Stomach sleeping or uncommon sleeping arrangement that would prevent the application of sensors

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Screening and Eligibility

Web-Based Screening Survey

Potential participants were directed through a link from the recruitment medium to the 30-minute web-based screening survey.

Telephone Screening Interview

Potential participants who met the inclusion criteria assessed at the web-based screening survey completed a telephone interview to screen for psychiatric (Mini International Neuropsychiatric Interview) [41] and sleep disorders (Duke Structured Interview for Sleep Disorders) [42].

Materials

Study data were collected and managed using the electronic data capture tool REDCap (Research Electronic Data Capture; Vanderbilt University) hosted at Stanford University [43]. The ecological momentary assessment (EMA) training was presented, and the EMA surveys were collected, using the Qualtrics survey software and platform (versions 09-2020 to 04-2022; Qualtrics). The EMA surveys were delivered using a web application built by our research team (Multimedia Appendix 2). The study sessions were conducted via laptop computers running the secure Zoom software for videoconferencing (version 5.9.1, package 3506; Zoom Video Communications, Inc).

Baseline Individual-Difference Assessment and EMA Training

Baseline Individual-Difference Assessment

After the screening process and before enrolling in the study, participants completed the 90-minute baseline (T1) individual-difference assessment.

EMA Training

Upon completion of the T1 individual-difference assessment, participants were directed to the 30-minute EMA training via a web-based link.

Web-Based Study Sessions and Device Mailing

Web-Based Study Introduction Session

In the 30-minute study introduction session, participants were guided through signing the consent form to enroll in the study. Research assistants identified a timetable with the participant with SMS text messaging for the ambulatory assessment, considering the participant's wake, sleep, and general life schedule.

Device Mailing

After the study introduction session, the research team mailed the study equipment to the participants. The package included (1) an RMMA device with 18 pregelled adhesive pads (Butler GrindCare; Sunstar Suisse SA) and 14 alcohol swabs; (2) an electrocardiography (ECG) device (Vivalink VS-US4 - ECG Multi-Vital-Monitor; Vivalink, Inc) with 8 ECG device adhesives (Vivalink Hydrogel Adhesive [VSA-1, A13]; Vivalink, Inc), 10 skin-barrier film wipes (SNS80775; Safe n Simple), and 10 alcohol prep pads (CUR45585RBZ; Curad); and (3) an actigraphy wristwatch (Respironics Actiwatch Spectrum Plus; Philips), configured for the participant's data collection using the Actiware software (Philips), an instructional brochure, and a return envelope that participants were to use to return the devices to the study team. Each physiology device was fully charged and sanitized before we mailed it out. The study team kept a mailing protocol and recorded the serial numbers of all equipment sent out to participants on a device tracking form.

Web-Based Device Introduction Session

The 45-minute device introduction session took place after the participant had received the physiology devices. A research assistant instructed participants on device application, charging, and troubleshooting. The ambulatory assessment began at the end of this session and ended 14 days (336 hours) later.

14-Day Ambulatory Assessment and Quality Assurance

EMA Surveys

During the 14-day ambulatory assessment, 5 daily EMA surveys were sent to participants: 1 morning diary, 1 evening diary, and 3 daytime surveys (Multimedia Appendix 3 [44,45]). The EMA surveys were delivered using a web application built by our research team. The web application allows research assistants to enroll new participants and create a schedule for when EMA SMS text message reminders with the survey link are delivered to them. This system was hosted on a server (Amazon Web Services, Inc) that provides an on-demand cloud computing platform and application programming interfaces. EMAs were delivered through an automated SMS text messaging system (Twilio). The web application sent an application programming interface request to Twilio at the scheduled times, and Twilio sent predefined EMA SMS text messages to participants. Participants were instructed to complete the morning survey 15 minutes after getting out of bed, the evening survey 30 to 40 minutes before going to bed, and the 3 daytime surveys as soon as possible after they received the SMS text messages. The 3 daytime surveys were spaced at least 3 hours apart. All 5 surveys were set to arrive within a 30-minute window (jittered ±15 minutes from the scheduled time) to prevent the timing of the assessment from being a confounding variable. Participants were given a maximum of 3 hours to complete the surveys and received a follow-up SMS text message after approximately 30 minutes if no response was received. If there were no responses to the EMA surveys for >24 hours, the research team contacted the participant to ensure that there were no technical issues keeping them from completing the EMA surveys.

Physiology Assessment

Concurrently with the EMA surveys, participants wore 3 physiological devices for 14 consecutive days and nights (Multimedia Appendix 4). Participants were instructed to apply a facial EMG device each evening at bedtime and remove and charge it each morning after waking; continuously wear an ECG device, except for an approximately 4-hour charging period every 3 days; and continuously wear an actigraphy device. The EMG device was referred to as *Sleep Buddy* in communications with participants to avoid affecting RMMA behavior through expectations.

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Quality Assurance

Research assistants followed a quality assurance protocol to monitor participant safety and data completeness during the ambulatory assessment, which involved participants receiving 2 quality control calls during the 14-day ambulatory assessment (Figure 1).

Poststudy Individual-Difference Assessment and Final Study Steps

Poststudy Individual-Difference Assessment

The day after their ambulatory assessment ended, participants completed an abbreviated poststudy (T2) individual-difference assessment with questionnaires about affect and sleep.

Device Return

At the end of the study, participants were instructed to mail back the physiology devices to the study team with the provided return envelope (Multimedia Appendix 5). Upon receipt, a research assistant exported and saved the data from the devices and remote servers.

Participant Compensation

Once data completeness status had been established, a research assistant issued participant compensation (Multimedia Appendix 5).

Debriefing Call

Research assistants administered a debriefing call to participants at the end of the study.

Monitoring of Data Collection

Stopping Guidelines

We stopped data collection upon reaching one of the stopping guidelines: (1) 275 participants had been enrolled in the study or (2) the enrollment window of April 1, 2022, had passed.

Premature Termination or Suspension of Study

Participants were able to stop participating at any point. The participation of a participant in the study could be terminated by the principal investigator, the institutional review board, or the funder in case of unexpected, significant, or unacceptable risk to participants [46]; insufficient adherence to protocol requirements; or insufficiently complete and evaluable data.

Measures

We present the core outcome measures among sleep- and affect-related constructs in Tables 1 and 2. At a minimum, participants had to complete the T1 individual-difference assessment, respond to 2 of the 5 EMA surveys each day on 7 of the 14 days, and wear the actigraphy device for 7 of the 14 days.

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Table 1. Operationalization of sleep-related core constructs through dependent variables.

Core construct, assessment modality, temporal modality, assessment time point, and time frame	Measurement tool
Sleep bruxism	
Self-report	
Trait	
Baseline (T1) individual-difference assessment	
Past 6 months	Sleep Bruxism Questionnaire
Past 7 days	PROMIS[a] Pain Intensity-Short Form 3a v1.0
Last year	Oral Health Impact Profile 14
State[b]	
Morning diary survey	
Past sleep	Single EMA[c] item on teeth grinding or clenching
Morning (current)	Single EMA item on jaw pain or soreness
Evening diary survey	
Past day	Four EMA items adapted from Oral Behavior Checklist on frequency of teeth contact, jaw muscle tensing, teeth clenching, and tongue thrusting
Physiology	
Trait	
Ambulatory assessment	
Multinight	Butler GrindCare device (Sunstar Suisse SA) for RMMA[d] of anterior frontalis muscle bursts
State[b]	
Ambulatory assessment	
Nightly	Butler GrindCare device for RMMA of anterior frontalis muscle bursts
Sleep	
Self-report	
Trait	
Baseline (T1) and poststudy (T2) individual-difference assessment	
Past month	Pittsburgh Sleep Quality Index, sleep quality scale; and Pittsburgh Sleep Quality Index, sleep efficiency scale
State[b]	
Morning diary survey	
Past sleep	The Expanded Consensus Sleep Diary for Evening, morning portion on sleep quality; and The Expanded Consensus Sleep Diary for Evening, morning portion on sleep efficiency
Physiology	
Trait	
Ambulatory assessment	
Multinight	Respironics Actiwatch Spectrum Plus (Philips) and Actiware software (Philips) for sleep efficiency
State[b]	
Ambulatory assessment	
Nightly	Respironics Actiwatch Spectrum Plus and Actiware software for sleep efficiency

[a]PROMIS: Patient-Reported Outcomes Measurement Information System.

[b]Repeated daily, momentary, and continuous state measures may be averaged over multiple items and assessment time points to form trait measures.

[c]EMA: ecological momentary assessment.

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[d]RMMA: rhythmic masticatory muscle activity.

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Table 2. Operationalization of affect-related core constructs through dependent variables.

Core construct, assessment modality, temporal modality, assessment time point, and time frame	Measurement tool
Emotion regulation	
Self-report	
Trait	
Baseline (T1) individual-difference assessment	
Lifetime	Emotion Regulation Questionnaire, frequency of cognitive reappraisal use subscale; Emotion Regulation Questionnaire, frequency of expressive suppression use subscale; frequency of distraction use; Emotion Regulation Questionnaire, self-efficacy of cognitive reappraisal effectiveness; Emotion Regulation Questionnaire, self-efficacy of suppression; and self-efficacy of distraction
State[a]	
Morning diary survey	
Presleep	Single EMA[b] item on emotion regulation use and single EMA item on emotion regulation effectiveness
Daytime survey	
Past 3 hours	Single EMA item on cognitive reappraisal use, single EMA item on expressive suppression use, single EMA item on distraction use, and single EMA item on emotion regulation effectiveness
Physiology	
Trait	
Ambulatory assessment	
Multiday	Vital Scout ECG[c] device (Vivalink) and Kubios HRV Premium software (Kubios Oy) for HRV[d] (emotion regulation effectiveness)
State[a]	
Ambulatory assessment	
24 hours	Vital Scout ECG device and Kubios HRV Premium software for HRV (emotion regulation effectiveness)
Resting state	Vital Scout ECG device and Kubios HRV Premium software for HRV (emotion regulation effectiveness)
Affect	
Self-report	
Trait	
Baseline (T1) and poststudy (T2) individual-difference assessment	
Past 7 days	PROMIS[e] Short Form v1.0-Depression 8a and PROMIS Short Form v1.0-Anxiety 8a
Past 14 or 7 days (T1 and T2)	Positive and Negative Affect Schedule, positive affect subscale; and Positive and Negative Affect Schedule, negative affect subscale
Past month	Perceived Stress Scale
State[a]	
Morning diary survey	
Current	Single EMA item on positive affect and single EMA item on negative affect
Evening diary survey	
Current	Single EMA item on positive affect and single EMA item on negative affect
Past day	Single EMA item on positive affect, single EMA item on negative affect, and single EMA item on perceived stress
Daytime survey	
Current	Single EMA item on positive affect and single EMA item on negative affect

[a]Repeated daily, momentary, and continuous state measures may be averaged over multiple items and assessment time points to form trait measures.

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[b]EMA: ecological momentary assessment.

[c]ECG: electrocardiography.

[d]HRV: heart rate variability.

[e]PROMIS: Patient-Reported Outcomes Measurement Information System.

Demographics

We collected information on self-reported sex, age, ethnicity, race, and marital and socioeconomic status in the T1 individual-difference assessment.

SB Measures

Individual-Difference Assessment

We measured self-reported trait SB as follows (Multimedia Appendix 6 [33,47-53]).

The Sleep Bruxism Questionnaire, which was created by our research team based on prior questionnaires [54-56], assesses the perceived experience of SB.

The Patient-Reported Outcomes Measurement Information System (PROMIS) Pain Intensity-Short Form 3a v1.0 [47] measures subjective pain in the past 7 days and at present. It has a Cronbach α value of .906 and demonstrates high construct validity [57,58]. This questionnaire was adapted to ask about (1) orofacial pain and (2) other pain throughout the body.

The Oral Health Impact Profile-14 [48] is a short-form version that measures self-reported dysfunction and distress stemming from one's oral condition. It has a Cronbach α value of .880 and has strong construct validity [48].

Morning and Evening Diary Surveys

We measured self-reported state SB through morning diary surveys composed of single-item questions about past-night teeth grinding and current jaw pain in combination with evening diary surveys composed of 4 questions about teeth behaviors throughout the day that were adapted from the Oral Behaviors Checklist [44] (Multimedia Appendix 3).

Ambulatory Assessment

We measured physiological trait and state SB in terms of RMMA using Butler GrindCare (Sunstar Suisse SA), a portable single-channel EMG device (Multimedia Appendix 4). Past research supports the device's reliability and validity for assessing SB, consistent with gold standard measurement of SB through polysomnography [10,11,59].

ER Measures

Individual-Difference Assessment

We measured self-reported trait ER use and effectiveness as follows (Multimedia Appendix 6).

Two versions of the Emotion Regulation Questionnaire were used. The original version [49] assesses habitual use or frequency of ER strategies in terms of cognitive reappraisal (Cronbach α >.880) and expressive suppression (Cronbach α >.750) with strong overall validity [60]. The additional version assesses habitual use of distraction.

A derived measure [49] assesses the perceived self-efficacy of ER strategy use via reappraisal and suppression subscales (Cronbach α >.870) [61]. The other version assesses self-efficacy of distraction use.

Morning Diary and Daytime Surveys

We measured self-reported state ER use and effectiveness through the morning diary survey, which contained questions pertaining to presleep ER. Using the daytime survey, we measured the response to a negative event that had occurred since the last survey (within the past 3 hours) in terms of cognitive reappraisal, distraction, and expressive suppression (Multimedia Appendix 3).

Ambulatory Assessment

We measured physiological trait and state ER effectiveness using continuous ECG from a medical-grade wearable and reusable ECG sensor: VS-US4-ECG (Vivalink Inc) (Multimedia Appendix 4). This device has been demonstrated to be reliable and valid [62].

Affect Measures

Individual-Difference Assessment

We measured self-reported trait affect as follows (Multimedia Appendix 6 and 7).

The PROMIS Short Form v1.0-Depression 8a [50] assesses depression in terms of emotional distress caused by depressed mood in the last 7 days. The measure's Cronbach α values range from .920 to .980 [58], and it demonstrates strong validity [57].

The PROMIS Short Form v1.0-Anxiety 8a [50] assesses anxiety in terms of fear, anxious misery, hyperarousal, and somatic symptoms related to arousal in the last 7 days (Cronbach α=.950) [50], and the tool has strong validity [57].

The Positive and Negative Affect Schedule [51] assesses positive and negative affect over the past 2 weeks via 2 scales. The measure's Cronbach α values range from .860 to .900 and .840 to .870 for positive and negative affect scales, respectively; it has good validity [51].

The Perceived Stress Scale [52] assesses perceived stress in terms of appraisal of stress in daily life in the past month, where Cronbach α >.700 was reported with adequate validity [63].

Morning and Evening Diary and Daytime Surveys

We measured self-reported state affect through single-item questions about current positive and negative affect. We also administered single-item questions about past-day positive and negative affect and perceived stress (evening diary) (Multimedia Appendix 3).

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Sleep Measures

Individual-Difference Assessment

We measured self-reported trait sleep quality and efficiency with the Pittsburgh Sleep Quality Index [33], which is composed of seven subscales: (1) subjective sleep quality, (2) sleep latency, (3) sleep duration, (4) habitual sleep efficiency, (5) sleep disturbances, (6) use of sleep medication, and (7) daytime drowsiness (Multimedia Appendix 6 and 7). The measure has a Cronbach α value of .830 and possesses strong validity [33].

Morning and Evening Diary Surveys

We measured self-reported state sleep quality and efficiency with *The Expanded Consensus Sleep Diary for Evening* morning and evening portions, respectively [45] (Multimedia Appendix 3). Research supports the Consensus Sleep Diary as a psychometrically sound daily assessment tool [64].

Ambulatory Assessment

We measured physiological trait and state sleep efficiency by recording activity, measured as movement, using the Actiwatch Spectrum Plus (Multimedia Appendix 4). Actigraphy has been found to be a reliable and valid indicator of sleep behavior compared with polysomnography in healthy adults [65].

Data Reduction and Preprocessing

For all data types, data will be cleaned by examining and applying necessary corrections for outliers, variable normality, and missing data in accordance with standard recommendations [66]. Self-report data will be scored, physiology data will be processed by response channel, and data aggregates will be calculated.

Data Analysis

Statistical analyses will be performed using R software (R Foundation for Statistical Computing) [67].

Preliminary Analyses

The incidence of missing data and technical or compliance deviations will be reported. Descriptive statistics will be presented using frequency tables for categorical variables and means and SDs or SEs of the mean for continuous variables. Pertinent group differences will be tested with chi-square tests, Mann-Whitney *U* tests, 2-tailed *t* tests, or analyses of variance.

Preliminary analyses will address the (1) evaluation of reliability and validity of core outcome measures; (2) evaluation of temporal convergence of core outcome measures based on T1 and T2 individual-difference assessments; (3) evaluation of construct convergence of core outcome measures based on self-reported and physiological state and trait measures; and (4) characterization of the sample regarding demographics and core outcome measures based on self-reported and physiological trait and state measures, including means, subgroups, internal reliability, and temporal variability.

Analyses for Testing Core Hypotheses

Preregistered analyses will address the primary objective of testing for ER impairment in those with SB and the secondary objective of testing for mediation pathways in the bidirectional relationships among SB, ER, affect, and sleep.

To address our primary objective, we will test our hypotheses by using SB measures such as self-reported and physiological trait and state SB (Table 1) as predictors and ER measures such as self-reported and physiological trait and state ER (Table 2) as outcomes in targeted contrasts based on the general linear model.

Control analyses will test whether the relationship between SB and ER remains when adjusting for the influences of affective and sleep measures, that is, self-reported and physiological trait and state affect (Table 2) and self-reported trait and state sleep (Table 1). To identify potential control variables, we will test for group differences and associations of SB and ER each with affective and sleep measures. Using the responses from web-based screening surveys, we will additionally test for associations with demographic variables, including sex, age, ethnicity, race, and marital and socioeconomic status. We will include in the primary-objective analyses those variables for which group differences or associations were identified using appropriate statistical methods [68].

To address our secondary objective, we will use cross-sectional and longitudinal mediation analyses on self-reported and physiological trait and state measures of SB, ER, affect, and sleep for contrasting various competing models of directional effects.

Results

This research received funding in April 2017. Data collection took place from August 2020 to March 2022. A total of 9378 participants were recruited, of whom 237 (2.53%) were eligible and completed the study. Data analysis has not yet started. We expect the first results to be published by the end of 2023.

Discussion

Expected Findings

This study seeks to examine the roles of ER, affect, and sleep in individuals with SB and those without through a remote longitudinal observational study. Although existing data on the association between SB and ER are conflicting and limited [14], our aim is to better phenotype ER in SB by (1) testing whether ER is impaired in SB while adjusting for the potential control variables of affect and sleep and (2) testing mediation pathways in the bidirectional relationships among SB, ER, affect, and sleep. We anticipate that the findings from this study will provide insights into the intricate interplay among these factors and their potential implications for understanding and managing SB.

Strengths and Limitations

This study has several strengths: the longitudinal at-home design enables more representative data collection and ecological validity of the night-to-night variable expression of SB than 1 or 2 nights in a sleep laboratory. This study also involves a large sample size of >200 participants, EMA that eliminates memory

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bias, and ambulatory assessment of physiological data as objective indicators of SB, ER, and sleep.

This study also has limitations: first, it conducted data collection during the COVID-19 pandemic. The experience of the pandemic likely affected participants' SB [69], emotion generation and regulation [70], HRV [71], and sleep [72]. Second, this study used a descriptive observational protocol and no experimental manipulation, precluding causal inference. Third, although the remote nature of our study is novel, it presents unique challenges, increasing the risk of noncompliance and technical difficulties. Fourth and last, the EMA surveys may have caused participants to consider and process their emotions more frequently or in different ways than usual, potentially altering their typical SB, ER, affect, or sleep.

Conclusions

SB is a prevalent oral behavior that, if overexpressed, can be a disorder in susceptible individuals, with a significant negative impact on well-being for those affected [1,6]. The findings of this study may contribute to a better understanding of the relationship among SB, ER, affect, and sleep disturbances. If, as hypothesized, we find maladaptive ER in participants with SB, then this study will represent a meaningful step toward developing treatments for SB through ER intervention. Future studies will need to demonstrate a causal role of impaired ER in SB through extended longitudinal and experimental laboratory studies. We hope that the effort to thoroughly measure SB and ER using gold standard methods and cutting-edge technology will advance the knowledge of SB as well as initiate more effective interventions through ER to alleviate the pain and distress of those affected.

Acknowledgments

This study was preregistered at an independent institutional registry: the National Institute of Dental and Craniofacial Research (NIDCR) [39] of the National Institutes of Health (NIH). The authors thank the peer reviewers from the NIH involved in peer reviewing the study protocol (Multimedia Appendix 8). This work was supported by the NIDCR in part by grant R01DE026771 awarded to the principal investigator, JJG. The coordinating group includes AKA, ASB, JJG, Leah Harris, SDK, Hanqiu Li, SSL-G, Olivia Magaña, and Hannah Overbye. The steering committee consists of JJG, Clete A Kushida, GJL, and RM. The data management team consists of ASB and SDK. Study oversight is provided by NIDCR program officials (Dr Melissa Riddle, Medical Monitor Oversight Report-Quality Management Reporting Committee) and NIDCR Clinical Research Operations and Management Support. The authors thank research assistants Ella Becker, Alexander Bruckhaus, Yishu Chen, Victoria Costa, Isabel Gao, Addison Gills, Anusha Goyal, Rachel Hokanson, Rachel Huynh, Norhan Khafagy, Sewit Kidane, George Lausten, Gordon Luu, Olivia Magaña, Charlotte Ostrow, Priti Patel, Zoey Pham, Lorena Portillo, Yasamin Sadeghi, Sohrab Sami, Ann-Kathrin Schwientek, Purnima Seshadri, Elian Mateo Valencia, Michael Wicklein, Jocelyn Wilmore, and Sawyer Wisniewski for help with the data collection; Olivia Magaña and Yasamin Sadeghi for help with summarizing the literature; and Danny Nguyen for editorial support.

Data Availability

Study materials, data, and analysis code will be available through an Open Science Framework repository [73].

Conflicts of Interest

None declared.

Multimedia Appendix 1
Web-based screening survey.
[PDF File (Adobe PDF File), 148 KB - resprot_v12i1e41719_app1.pdf]

Multimedia Appendix 2
Ecological momentary assessment software screenshots.
[PDF File (Adobe PDF File), 244 KB - resprot_v12i1e41719_app2.pdf]

Multimedia Appendix 3
Ecological momentary assessment.
[PDF File (Adobe PDF File), 96 KB - resprot_v12i1e41719_app3.pdf]

Multimedia Appendix 4
Physiological assessment devices.
[PDF File (Adobe PDF File), 124 KB - resprot_v12i1e41719_app4.pdf]

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Multimedia Appendix 5
Study completion.
[PDF File (Adobe PDF File), 2132 KB - resprot_v12i1e41719_app5.pdf]

Multimedia Appendix 6
Baseline (T1) individual-difference assessment.
[PDF File (Adobe PDF File), 139 KB - resprot_v12i1e41719_app6.pdf]

Multimedia Appendix 7
Poststudy (T2) individual-difference assessment.
[PDF File (Adobe PDF File), 87 KB - resprot_v12i1e41719_app7.pdf]

Multimedia Appendix 8
National Institutes of Health peer-review report.
[PDF File (Adobe PDF File), 201 KB - resprot_v12i1e41719_app8.pdf]

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Abbreviations

ECG: electrocardiography
EMA: ecological momentary assessment
EMG: electromyography
ER: emotion regulation
HRV: heart rate variability
NIH: National Institutes of Health
PROMIS: Patient-Reported Outcomes Measurement Information System
REDCap: Research Electronic Data Capture
RMMA: rhythmic masticatory muscle activity
SB: sleep bruxism

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Protocol

Effect of Technology and Digital Media Use on Adolescent Health and Development: Protocol for a Multimethod Longitudinal Study

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Abstract

Background: Technology and digital media (TDM) use is integral to modern adolescence; adolescents have been labeled as "digital natives," since they have had exposure to digital technology for their entire lives. Previous evidence has illustrated TDM's connections with adolescent risk behaviors such as increased alcohol use and social media exposure, as well as relationships with adolescent well-being such as improved socioemotional health and social media connections with peers. Although several recent review articles have described both the benefits and risks of technology use, most individual studies adopt a singular risk-centered approach. In addition, reviews suggest that little evidence exists on the potential mediating and moderating factors between TDM use and well-being and health outcomes, which limits our understanding of what influences the outcomes of interest. Therefore, there is an urgent need to fill these gaps.

Objective: This protocol addresses the need to understand how TDM exposure and use affect multiple developmental domains and health outcomes. We address the fragmented nature of previous research, the common focus on single behaviors or conditions, and the typical narrow lens on risks. Our approach further aligns with reviews that called for studies identifying and investigating the factors that moderate the relationships between social media and health behaviors and outcomes.

Methods: We will address our objective by longitudinally examining over a 2-year period a common set of adolescent participants (N=400, aged 13-15 years) across 3 studies that adopt a multimethodological approach. Study 1 will use TDM to understand the mechanisms behind adolescent health and risk behaviors. Study 2 will use functional magnetic resonance imaging to understand how positive and negative TDM experiences relate to mental and behavioral health in a subsample of 150 adolescents. Study 3 will use a mixed methods design to evaluate self- and other-generated TDM content as the predictors of socioemotional well-being in sexual and gender minority and non–sexual and gender minority adolescents.

Results: Recruitment is ongoing, and the initial results from the first wave of recruitment are expected in 2024.

Conclusions: This integrated approach to longitudinal data collection from a shared adolescent participant pool will lead to novel analyses and findings, allowing for the examination of the health and well-being risks and benefits associated with TDM use and factors that moderate these relationships. The findings from this study will advance conceptual models and inform new interventions to improve adolescent health.

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KEYWORDS

social media; adolescents; teenagers; health; well-being; risk behavior; brain; functional magnetic resonance imaging; fMRI; mobile phone

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Introduction

Background

Technology and digital media (TDM) use is integral to modern adolescence; adolescents have been labeled as "digital natives," since they have had exposure to digital technology for their entire lives [1-3]. The 2022 Pew Internet and American Life Project [4] estimated that 95% of US adolescents have their own personal smartphone. These rates have increased from 2014 to 2015, when 73% of adolescents reported personal smartphone access [5]. Moreover, teenagers have begun obtaining their first phone at a younger age, with most adolescents owning a phone by the age of 13 years [6,7]. The nearly ubiquitous and thus dominant form of TDM use among adolescents is social media use. Web 2.0 led to what has been called social media, which is also called immersive or interactive media.

Social media represents a set of Web 2.0 tools that are centered on interaction and sharing of content with others, although users may also consume content passively. In the world of social media, adolescents have become both creators of self-generated content and consumers of other-generated content. Messages and content can flow in all directions, from peers to other users, among other users, and across platforms through a seemingly endless array of potential paths. Social media is used for a variety of activities, including sharing information, interacting with peers, and developing an identity [8]. Most adolescents report the ownership of at least 1 social media account or profile, and most maintain them on several platforms [9]. Thus, today's adolescents have an increased capacity to interact with each other and the larger world using media, enhanced opportunities to explore and experiment via media, and an increased likelihood of being influenced by media experiences. The recent social isolation and disrupted school schedules experienced by adolescents during the COVID-19 pandemic have highlighted the diverse uses and values of TDM for adolescents [10].

Given that adolescents' development includes identity development, peer relationships, and independence, the tools offered by social media seem almost perfectly aligned with this period [11]. Research supports the idea that youths use TDM to achieve critical developmental tasks [12], such as seeking a coherent sense of self via self-presentation and experimenting with identity. This social media–based identity development may be even more important for adolescents who identify as part of minority groups, such as the lesbian, gay, bisexual, trans, queer, or intersex community [13,14], and for adolescents with chronic illnesses [15]. Further, social media can offer the opportunity to engage in aspirational development, providing a place to reflect on, complement, and reinforce offline relationships [16], practices, and behaviors [17]. Social media combines peer and media effects and thereby represents a powerful motivator of behavior, whether through self-generated or other-generated (ie, consumed) content. Social media brings together the power of interpersonal persuasion with the reach of mass media and led to a new concept of "mass interpersonal persuasion," which is "the most significant advance in persuasion since radio was invented in the 1890s" [18].

Many studies on adolescent TDM use have focused solely on risks and negative outcomes. Previous studies have illustrated that TDM use is associated with negative outcomes such as impaired sleep [19-21], decreased physical activity [20,22,23], problematic internet use [24-26], and risk for depression [27]. Although several recent review articles have described both the benefits and risks of technology use [8,28], most individual studies adopt a singular risk-centered approach [29,30]. The benefits of social media include increased social capital [31], safe identity exploration [32], social support, and an opportunity for self-disclosure [33]. Specifically, in the area of adolescent health, previous studies have shown that TDM offers opportunities to provide novel interventions for pediatric patients [34], advance reproductive and sexual health [35,36], and provide new approaches to mental health support [37]. Those who experience isolation, stress, and unmet needs in their offline worlds may find corrective experiences or buffering effects by going on the web [38,39]. For example, a qualitative interview study found that young people naturally and organically developed close-knit communities of close friends, often in the form of private Instagram (Meta Platforms, Inc) accounts, in which privacy was a priority and emotional disclosure was safe and commonplace [40].

This Protocol

Overview

In this protocol, we will address the fragmented nature of previous research, the common focus on single behaviors or conditions, and the typical narrow lens on risks. Although scholars have called for comprehensive approaches considering the benefits and risks of technology use [8,28], most existing studies focus on risks [29,30]. Our approach is aligned with a previous review that called for studies identifying and investigating the factors that moderate the relationships between social media and health behaviors and outcomes [8]. This approach is further highlighted in the 2023 US Surgeon General's Advisory on Social Media and Youth Mental Health, which calls for research examining the benefits and risks associated with specific social media designs, features, and content [41]. Studies in this protocol will incorporate a particular emphasis on 2 key attributes of adolescent development: identity development and social development.

Identity Development

Social media offers the opportunity for identity exploration and development via the creation of personal profiles and the sharing of self-generated content. A previous study found that adolescents who communicated more on the web had greater self-concept clarity, the ability to understand oneself clearly and stably [42]. For adolescents using social media to explore their identity, social media may provide a conducive environment for receiving positive or negative social feedback on their identity. Another aspect of web-based identity development is impression management [43]: adolescents use social media for impression management by using their self-representation to control or influence other people's perceptions of who they are and how they act. In all 3 studies in this protocol, evaluations will incorporate adolescents' self-generated content on social media.

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Social Connection

Social connectedness and inclusion are essential for well-being during adolescent development. Social media offers adolescents the capacity to build peer connections by sharing content, endorsing each other's content, and communicating publicly and privately. By viewing their peers' content, adolescents may engage in social comparison [44] and potentially emulate behaviors or internalize the ideas seen in social media posts. Other-generated content may thus be persuasive through both peer and media effects. In all 3 studies in this protocol, we will incorporate evaluations of other-generated content consumed by adolescents via TDM.

Methods

Project Overview

Our overall objective for the 3 studies in this protocol is to understand the aspects of behavior and socioemotional well-being, alongside neurocognitive correlates, and how self-generated (ie, created) and other-generated (ie, consumed) social media content influence and associate with them. This comprehensive approach to investigation across multiple dimensions of health and technology use focuses on an integrated research strategy and interdisciplinary expertise. This protocol describes a program of research across 3 studies that leverage a shared participant pool and data to examine the health risks and benefits associated with social media use over a 2-year period during adolescence. Our long-term goal is to use the findings from this synergistic protocol to enhance health messaging campaigns, improve big data surveillance approaches, develop innovative interventions, and advance conceptual models. This program protocol includes the following 3 studies.

Study 1

Study 1 will focus on TDM use to understand the mechanisms behind adolescent health and risk behaviors. Health behaviors will include behaviors that advance adolescent physical and mental health, including physical activity and sleep. Risk behaviors will focus on substance use, including the use of 10 categories of substances most often used by adolescents (eg, alcohol, tobacco, and marijuana). Substance use is connected with the major causes of morbidity and mortality in adolescents: accidents (particularly motor vehicle accidents), homicide, and suicide. Study 1 will include a 2-year data collection process, wherein social media data created by adolescents will be triangulated with self-reported health attitudes, social norms, intentions, and behaviors (aim 1). Study 1 will also include an assessment of other-generated TDM content reported by adolescents via an ecological momentary assessment (EMA) approach to capture real-time exposure to health and risk behavior content on TDM (aim 2). This study will also examine the persuasive elements of self-generated and other-generated content via functional magnetic resonance imaging (fMRI; aim 3). This project will include technology importance and parent involvement as moderators.

Study 2

Study 2 will use fMRI to understand how neural correlates associated with positive and negative TDM experiences relate to mental and behavioral health. Drawing on social media use data on health and risk behaviors and well-being, from studies 1 and 3, study 2 will assess reactivity (ie, neural activity) in reward-processing regions during social inclusion and reactivity in social pain regions during social exclusion at 2 time points, during middle school (time 1; 13 and 14 years of age) and after the transition to high school (time 2; 15 and 16 years of age). For study 2, aim 1 will include fMRI data collection at time 1 to examine whether the main effects of reactivity to social inclusion and exclusion predict health and risk behaviors and well-being at times 1 and 2. Aim 2 will include fMRI data collection at time 1 to examine whether neural reactivity to social inclusion and exclusion moderates the relationship between social media use (ie, likes, comments, number of friends or followers) and health and risk behaviors and well-being at times 1 and 2. Aim 3 will include fMRI data collected at times 1 and 2 to examine whether changes in reactivity to social inclusion and exclusion are associated with changes in one's social media environment (ie, positive valence peer interactions vs negative valence peer interactions) during the transition from middle school to high school, health and risk behaviors, and well-being, including technology importance and parent involvement as moderators, at time 2.

Study 3

Study 3 will use mixed methods to evaluate self- and other-generated TDM content as predictors of socioemotional well-being in sexual and gender minority (SGM) and non-SGM adolescents. Socioemotional well-being will include concepts of self-esteem, loneliness, stress, emotional difficulties, and subjective well-being, all of which are contributors to the overall mental health and subsequent morbidity and mortality in adolescents. Study 3 will involve data collection over 2 years to test a cross-lagged panel model of the relationships among self-generated social media content (aim 1), other-generated social media content (aim 2), and socioemotional well-being. Socioemotional well-being will be assessed through validated self-report instruments at baseline, 1 year, and 2 years. Self-generated social media content will be assessed using ethnographic observation and coding of participants' social media accounts for common patterns to create latent variables of self-generated content types. Other-generated content will be assessed through the direct observation of social media profiles that are followed by participants, which will be coded for common patterns and triangulated with participant interview data to create latent variables of other-generated content types. Study 3 will also examine self-generated and other-generated social media content of SGM participants, which will be qualitatively compared with the social media content of non-SGM participants (aim 3). SGM adolescents are at an increased risk for threats to socioemotional well-being and are also high-frequency users of TDM, warranting additional exploration of their social media experiences.

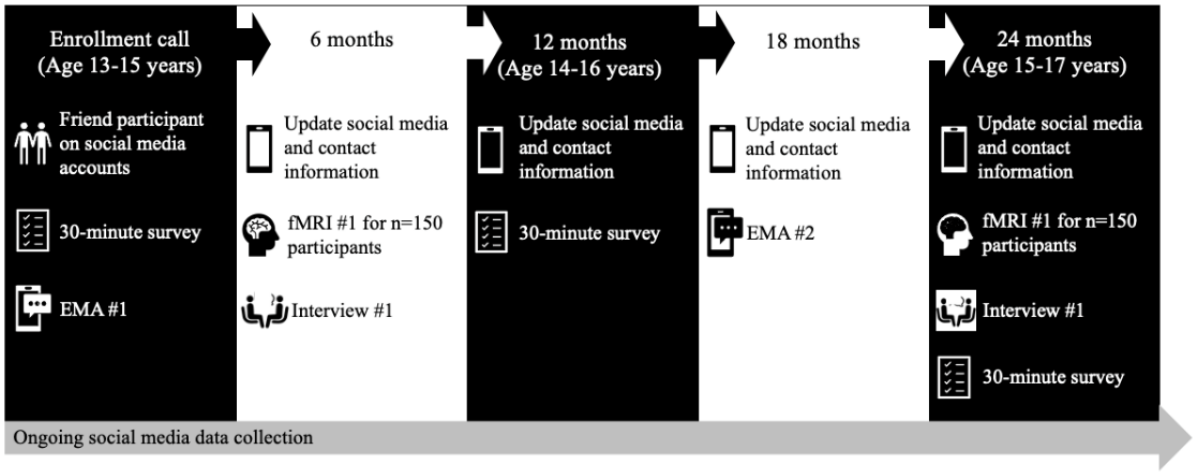
Study Design

This multimethodological protocol will recruit 400 adolescents aged 13 to 15 years to take part in a 2-year study on a rolling basis. Eligible participants will have at least 1 active social media account (ie, Instagram, Facebook [Meta Platforms, Inc],

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Twitter [Twitter, Inc], or TikTok [ByteDance]). A subsample of 150 participants who meet the fMRI criteria will be recruited to participate in a 2–time point fMRI study in addition to the primary study. After gaining written informed assent from participants and consent from a parent or guardian, researchers will friend the social media accounts of participants to track their social media data over the 2-year enrollment period. Researchers will conduct a check-in at 6, 12, 18, and 24 months to update the research team on the current social media platform use. In addition, participants will complete a series of web-based self-report measures regarding health behaviors, well-being, and demographic information at the beginning of the study (0 mo), 12 months, and 24 months. Participants will also complete an EMA about health behaviors and social media content exposure at 0 and 18 months. Finally, participants will complete interviews at 6 and 24 months about their well-being and social media use. Participants enrolled in the fMRI portion of the study will also be asked to complete neuroimaging appointments at 6 and 24 months to collect neural responses associated with social connection (ie, self- vs other-generated social media posts, peer feedback, social influence, and social inclusion and exclusion) and self-reported individual difference measures and health behaviors. The study activities and participant experience timeline are summarized in Figure 1.

Figure 1. Study activities and participant experience timeline. On the basis of the shared participant pool, synergy in measures, and integration of data collection approaches, participants will have the same study experience even when starting at different time points. EMA: ecological momentary assessment; fMRI: functional magnetic resonance imaging.



Participants

Inclusion and Exclusion Criteria

Our inclusion criteria will include 400 adolescents living in Wisconsin who are aged 13 to 15 years at enrollment. Adolescents must own and maintain at least 1 social media profile on any of the social media platforms covered in our study (Facebook, Instagram, Twitter, and TikTok) at the time of enrollment. A social media profile will be defined as an individual (not a group or an organization) profile that the adolescent logs into and interacts with at least weekly. Participants must be able to speak, post content, and read in English.

A total of 150 participants (aged 13 and 14 years) from the 400 participants in the shared participant pool will be invited to take part in fMRI data collection. All fMRI participants will be right handed, not have claustrophobia, not currently be taking any psychoactive medications, have no history of psychiatric or neurological disorders, have normal (or corrected to normal) vision, not have metal in their body that is contraindicated for fMRI, and not currently be pregnant. Finally, participants should be in eighth grade at the time of the first scanning appointment to examine whether the social transition into high school alters neural function during development.

Recruitment and Enrollment

Participants will be recruited using a variety of methods (eg, on the web, mailers, recruitment ambassadors, speaking events, and pediatric clinics) from the state of Wisconsin, with efforts focused on the regions of and surrounding Madison, Green Bay, Beloit, and Milwaukee. To achieve our recruitment goal of including participants who represent communities of interest, we will use a quota sampling approach [45-47] and prescreen potential participants before enrollment. Screening will involve a brief demographic survey assessing age, race, ethnicity, gender identity, socioeconomic status (SES), and the identified sexuality. After screening, we will assess whether participants meet the criteria for recruitment based on the availability within each study quota. If a participant meets the recruitment criteria, we will proceed with consent and assent and recruitment.

The current protocol aims to recruit a sample reflective of the demographics of the United States in terms of sex, race, ethnicity, and SES. These demographics include, as of 2020, sex (50% female), ethnicity (18.7% Hispanic and Latino), and race (61.6% White, 12.4% Black, 6% Asian, 1.3% American Indian and Native Hawaiian or Pacific Islander, and 10.2% more than 1 race) [48]. Regarding SES, we will ask at screening whether an adolescent has free or reduced-price lunch at school. This proxy measure for SES will be useful for adolescents who are screened in the absence of a parent and may not know their household income. From 2019 to 2020, 52.1% of the students were eligible for free or reduced-price lunch [49]. Regarding

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SGM status, given study 3's focus on SGM social media activities (aim 3), we will oversample individuals who identify as SGM. To reach theoretical saturation for qualitative analyses, we aim to recruit a minimum of 30 gender minority youths and 50 sexual minority youths. These estimates are based on our team's prior experiences with qualitative sampling.

Sample Size Calculations

Separate sample size calculations were performed for each of the 3 studies in this protocol based on the primary analyses that will be implemented. The primary hypothesis for study 1 is that adolescents' health and risk behavior displays will have a high positive predictive value (PPV) in identifying behaviors. In our previous work, self-generated alcohol displays were consistently and significantly positively associated with self-reported alcohol behaviors [50,51]. In our previous study, self-reported marijuana users had 1.7 higher odds of displaying marijuana use on social media compared with nonusers. For this study, a target sample size of 400 participants is proposed. A PPV of ≤60% for self-generated risk behavior displays will be considered unacceptably low. Hence, the null hypothesis that the PPV is at most 60% will be tested against the alternative hypothesis that the PPV is greater than 60%. Alcohol use has consistently been the most common risk behavior displayed on social media as well as reported by adolescents in our studies and national surveys. On the basis of the results of our previous study, it is estimated that at least 15% of participants will display alcohol use on social media over the period assessed. With the proposed sample size of 400 participants and an alcohol display rate of approximately 15%, the null hypothesis that the PPV is at most 60% will be rejected with 93% power at the 1-sided .05 significance level, assuming that the true PPV for alcohol display is 80% and an attrition rate of up to 15%. Furthermore, the proposed sample size will provide 55% to 78% power for detecting PPVs for less prevalent risk behavior displays (eg, marijuana use), assuming risk behavior display prevalence rates ranging from 5% to 10%, which is the lower end of prevalence we have seen in studies of older adolescents [52].

The primary goal of study 2 (fMRI) is to examine how the neural correlates of social TDM behavior relate to health and well-being outcomes in a within-participant design. A power analysis was conducted using G*Power based on a prior study that examined whether neural activity in the negative affect network during negative social feedback was related to behavior change (effect size=0.30; P=.05; power=0.95). The results indicated that a sample of approximately 110 participants would be large enough to detect a relationship between neural activity and behaviors outside the scanner within participants. In addition, a power analysis aimed at detecting neural differences between 2 time points was conducted based on a study examining reward activity differences within participants between 2-time points (mean of the paired difference 0.09, SD of the paired difference 0.26; P=.05; power=0.95). The results indicated that a sample size of 92 would be large enough to detect neural differences within participants. Therefore, a sample of 150 participants should be appropriate for the current design and will compensate for attrition and missing data.

Study 3 will incorporate ethnography and content analysis with data collected monthly. Research staff will immerse themselves in the self-generated content of the participant and take field notes on the participant's self-generated content using a template comprising the descriptions of the participant's posts as well as responses to their posts (eg, comments and the participant's responses to those comments). In addition, notes will be taken on the participant's overall profile, which may include the content they have been tagged in by others and personal information they use to self-describe. Profile and posts will also be coded for the type and themes of media content presented. Participant content will be assigned to the same research staff each month so that field notes can reflect the context of observable trends and changes within participants over time.

Social Media Data Collection

Platform Selection

We have selected social media platforms based on an affordance approach. Affordances are described as properties of artifacts that can be recognized by users and contribute to their functions or items that present an action possibility [53-55]. The goal of this framework is to increase the likelihood that an assessment or future intervention will hinge on replicable technological qualities as opposed to a platform's current popularity. This protocol design will focus on platforms with high identity affordances. Identity affordances include key attributes such as the use of individuals' names and personal photos and support sharing personal content, such as health behaviors [56]. Thus, higher identity affordances are an ideal approach to identify personal disclosures and behaviors. Of the platforms used by adolescents, Instagram, Twitter, and Facebook have been identified in previous studies as high–identity affordance platforms [57,58] and will be the focus of this protocol. TikTok, a newer platform, is widely used by adolescents and has identity affordances that are used to different degrees by adolescents based on whether they post content as an alter ego (eg, cosplay) or themselves. Thus, we will also include this platform for the evaluation of identity-focused content in this protocol.

Study Approaches to Social Media Data Collection

Social media data collection will occur over the 2-year enrollment period. This will be data collection through passive observation that requires no ongoing input from participants. With each 6-month check-in, participants will update the study team on their current social media platform use. Given that adolescents typically maintain several platforms and can change them over time, this will allow us to follow these patterns and observe data over the 2-year period. Social media observational data will be integrated into the 3 studies.

In study 1, we will perform a criterion-based content analysis using monthly profile assessments for health behaviors and risks. The main outcomes will be the frequency, prevalence, and content of health and risk behavior displays on social media, and the secondary outcome will be PPV for these displays associated with self-report.

Study 2 will examine social connectedness on social media by examining the number of friends or followers, conversion rates (number of comments/post), applause rate (number of

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likes/post), and amplification rate (number of shares/post) [59]. In addition, a content analysis will be conducted on peer comments to determine how supportive (ie, positive valence) versus unsupportive (ie, negative valence) peer connections are on social media and the types of support provided, emotional support (eg, expressions of empathy and love), instrumental support (eg, aid and service), informational support (eg, advice and suggestions), and appraisal (eg, information for self-evaluation). The content and network interaction data can be combined to examine the sentiment and support provision, which can even allow for distinctions between message expression and reception [60,61].

Study 3 will incorporate ethnographic field notes collected monthly during the 2-year data collection period. During the monthly observation periods, the research staff will immerse themselves in the self-generated content of the participant for the previous week. The staff will take field notes on the participant's self-generated content using a template developed for web-based ethnography in our laboratory. The field note template comprises descriptions of the participant's posts as well as responses to their posts (eg, comments and the participant's responses to those comments). In addition, notes will be taken on the participant's overall profile, which may include the content they have been tagged in by others and personal information they use to self-describe. Participant content will be assigned to the same research staff each month so that field notes can reflect observable trends and changes within participants over time. In the field notes template, research staff will reflect on their own interpretations of the participant's self-generated content as well as any outstanding questions they have about the participant.

Self-Report Data Collection

The web-based self-report survey measures will be collected at 0, 12, and 24 months. This survey includes measures of demographics, health and risk behaviors, well-being, TDM exposure and use, and parental involvement. These measures will be used across all 3 studies included in this protocol. Full details are reported in Table 1.

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Table 1. Self-report data collection.

Category	Measure
Well-being measures	• RSES[a] [62,63] • UCLA[b] Loneliness Scale [64] • Perceived Stress Scale [65] • Warwick Edinburgh Wellbeing Scale [66]
Mental health measures	• PHQ-9[c] [67,68] • GAD-7[d] [69]
Risk behavior measures[e]	• Substance use attitudes [70] • Substance use social norms [71] • Substance use behavioral intentions [72] • Substance use current and lifetime [73] • Substance use quantity and frequency [74,75]
Health behavior measures	• Physical activity [76]
Parent involvement measures	• Household media rules [77] • Parent-adolescent relationship [78]
Learning disability measures	• Diagnosed learning disabilities • IEP[f]
TDM[g] use and experience measures	• Emotional responses to social media experiences • Preferences for web-based social interactions • ADTI[h] [13,79] • Rosen Media and Technology Usage and Attitudes Scale (subscales: Usage and Attitudes) [80]
Demographic measures	• Age • Race • Ethnicity • School (grade, public vs private, and web-based vs in person) • Birth sex • Gender identity • Sexual orientation

[a]RSES: Rosenberg Self-Esteem Scale.

[b]UCLA: University of California, Los Angeles.

[c]PHQ-9: Patient Heath Questionnaire-9.

[d]GAD-7: General Anxiety Disorder-7.

[e]Web-based self-report measures were collected at 0, 12, and 24 months. Risk behaviors will examine the use of cigarettes, chewing tobacco, vaping tobacco, cannabis, vaping cannabis, alcohol, cocaine, hallucinogen, opiate, amphetamine, club drugs (methylenedioxy-methamphetamine, ecstasy, and molly), inhalants (nitrous oxide and whippets), and prescription drugs (for nonmedical reasons).

[f]IEP: Individualized Education Program.

[g]TDM: technology and digital media.

[h]ADTI: Adolescents' Technology Importance and Interactions Scale.

EMA Data Collection

EMA data will be collected at 0 and 18 months to measure exposure to content about health and risk behaviors. EMA, also called the experience sampling method, is characterized by a collection of data in real-world environments. These assessments focus on an individual's current or very recent behaviors and are particularly effective for behaviors that occur intermittently [81,82]. EMA avoids the reliance on retrospective reports, which may be subject to biases that challenge their reliability and validity [83]. To measure daily time spent using TDM and content exposure using EMA, surveys will be designed to be brief (<3 min) and allow responses via an SMS text message. Each brief SMS text message survey will begin with the following question: "When you got this text, were you using a digital device?" If participants respond "Y" for yes, these questions will follow: (1) "How long were you on the device in minutes?" (2) "Were you looking at a post or video? (Y or N)" (3) "Please list every topic that was in the post or video (this message is sent with an image that illustrates 9 topics of interest)." To describe their current content exposure, participants can enter all applicable options from the following predetermined content list: E=exercise, A=alcohol, F=food and cuisine, C=cannabis, L=lifestyle and self-improvement,

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T=tobacco and nicotine, D=drugs, S=shows and entertainment, and O=other. If participants respond "N" to the first prompt, these questions follow: (1) "Have you seen a post or video since we messaged last? (Y or N)" and (2) "Please list every topic from the last post or video you remember" (this message is paired with the topic list image). After completing the survey, participants will receive this message: "Thanks for completing this prompt! Your answers are a contribution to science!"

Interview Data Collection

We will use a qualitative phenomenological approach to interviews, enabling us to capture individual lived experiences [84]. Our open-ended, semistructured interview method encourages the exploration of concepts important to the participant and provides the researcher with the ability to ask follow-up questions based on the participant's experience and let their narrative guide the interview process. This creates an opportunity for concepts that might not be detected through other, more structured methods to be introduced [85]. Research staff will conduct in-person or video interviews with participants 6 months after study enrollment and at study conclusion. During these interviews, the research staff will question participants about the social media accounts that they follow, reasons for following the accounts, and how the content from the accounts' feeds makes them feel. Participants will be encouraged to take out their device and use specific examples from their feed in real time to elicit the nature of each account from their perspective. Our laboratory has piloted similar interviews with adolescents in which study staff reviewed participants' own social media content in real time, and we have found that adolescents are open with interviewers and eager to teach them about the social media content they see. The data from these interviews (key quotes, observations, and insights) will be analyzed using a constant comparative approach. These findings will be collected and grouped by themes, culminating in a summary that captures key insights, frameworks, and principles to be triangulated with the study team codebook and applied to each participant's larger list of accounts they are following.

Neuroimaging Data Collection

fMRI Data Acquisition

Brain imaging data will be collected using the 3T magnetic resonance imaging scanner (GE Healthcare MR750) and include longitudinal relaxation time (T1) and transverse relaxation time relaxometry using steady-state sequences (multicomponent Driven Equilibrium Single Pulse Observation of T1 and transverse relaxation time) [86,87]. Structural imaging of anatomical detail for morphometric analyses will be performed using a custom magnetization-prepared rapid acquisition gradient echo sequence, which removes the intensity variations from inhomogeneities in the coil sensitivities. Functional blood-oxygen-level-dependent images may be recorded using a reverse spiral sequence (repetition time=1000 ms, time to echo=32 ms, flip angle=60°, 56 sagittal slices, field-of-view=208 mm, slice thickness=2.5 mm, and voxel size=2.5×2.5×2.5 mm). Each sequence will take 1 to 10 minutes, and the total scan time will be 60 minutes.

Collecting Self-Generated TDM Content

Aim 3 of study 1 is to examine whether self-generated versus other-generated TDM content is processed differently and whether neural activity is associated with self-reported health behaviors. To collect self-generated posts, participants will be asked to complete a self-report survey during EMA data collection, which will ask participants to create self-posts that they have or would upload to social media. Participants will upload a picture and create a text post for 25 posts (20 posts will be used in the associated fMRI task). In addition, participants will be asked whether they have already posted the content on social media.

Scanning Session

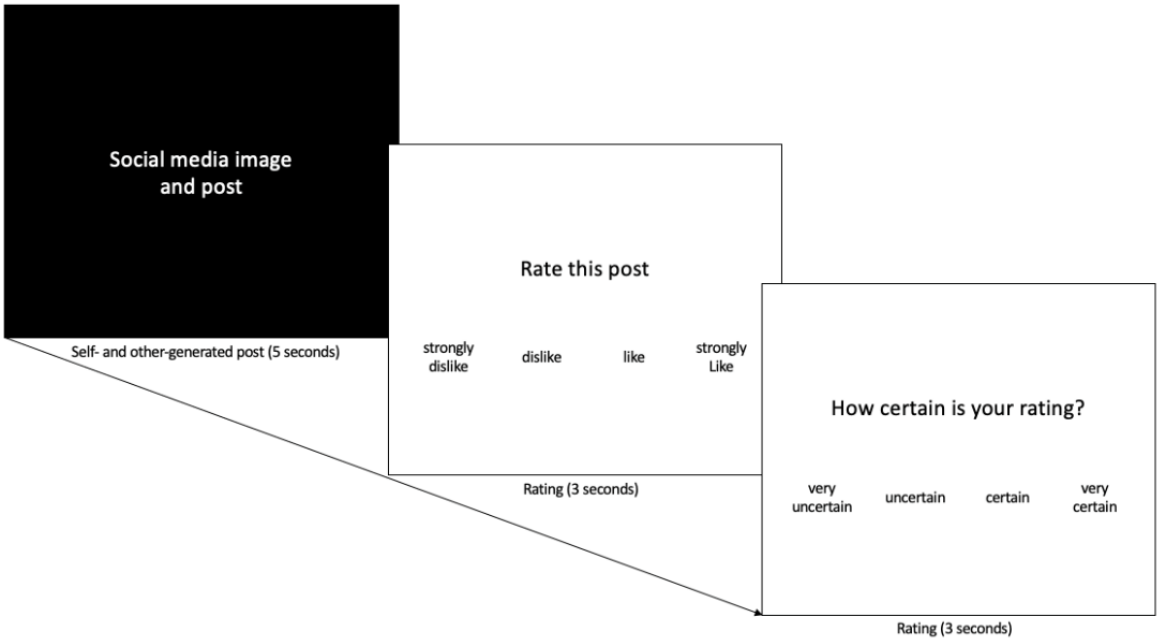
Participants taking part in the fMRI portion of the protocol will complete neuroimaging appointments at 6 and 24 months. Both neuroimaging appointments will consist of 4 neuroimaging tasks aimed at examining the neural processes associated with social connections. Before the scan, participants will be asked to complete a fMRI safety screening form and a series of self-report measures, including measures of well-being and health and risk behaviors. Next, participants will be trained on the fMRI tasks they will be asked to complete during the scanning session. Details regarding the 2 primary functional tasks (ie, self and other messages and Cyberball) are provided in the subsequent paragraphs. Details regarding the 2 secondary functional tasks (ie, peer feedback and social influence) and secondary self-report measures are provided in Multimedia Appendix 1 [70-75,88-107].

The Self and Other Message Task

Participants will first complete the self and other message task as part of study 1 aim 3. Participants will be exposed to 65 social media posts targeting health or risk behaviors. Messages (5 s/message) will be either self-generated using participants' own data provided in the survey detailed earlier (20 messages) or peer generated (45 messages; categories: vaping tobacco [5], alcohol [5], cannabis [5], exercise [5], nutrition [ie, high-caloric foods; 5], self-image [ie, idealized bodies wearing provocative clothing; 5], civic engagement [5], and generic or neutral [ie, everyday events, such as studying and hanging out with friends; 10]). The other-generated messages will be created by the study team and will be the same stimuli set for each participant. Following each message, participants will answer the question "how would you rate this post on social media" by pressing their pointer finger for 1 star (strongly dislike), middle finger for 2 stars (dislike), ring finger for 3 stars (like), or pinky for 4 stars (strongly like; 3 s). Next, they will rate their preference certainty (on a 4-point scale from 1="very uncertain" to 4="very certain;" 3 s). Ratings will be followed by a jittered fixation period (mean 3 s; range 1-5 s), which will serve as an implicit baseline (Figure 2).

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Figure 2. Self and other message task. The self and other message task will measure neural activity during exposure to self-generated and other-generated social media posts.

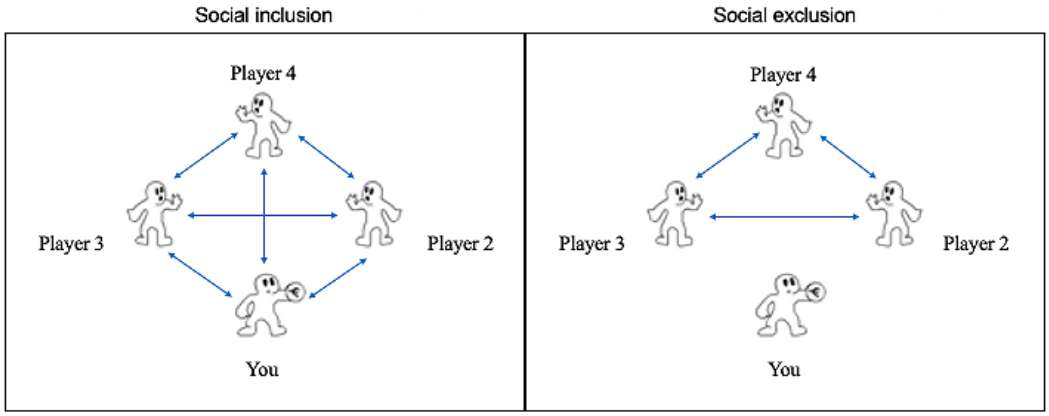


The Cyberball Task

In addition, participants will complete a social inclusion and exclusion task (Cyberball). Cyberball is a game that allows the simulation of both inclusion and exclusion in an fMRI environment [108,109]. In this task, during the first fMRI session, participants will be told that they are engaging in a web-based ball-tossing game with 3 confederate participants playing the game on the web at a remote location. In reality, a preset computer program will control the other 3 players. Before the scan, participants will be shown screenshots of the web-based ball-tossing game and given instructions on how to throw the ball. In addition, they will be told that the only rule for the game is that you can throw the ball to any player; however, you cannot just hold the ball and do nothing. During the first part of the game, the other players will throw to one another and to the participant equally (social inclusion). In the second round, the other players will stop throwing the ball to the participant and only throw to one another (social exclusion).

The 2 rounds of Cyberball will each last 178 seconds. The social inclusion round will always be played first, in which all participants will receive the ball equally often. This will be followed in the social exclusion version of the game. The round of social inclusion will always be the first to preserve the psychological experience across participants. These rounds will be preceded by a period in which participants visually track a star as it moves on the screen (105 s). Each round will be separated by a 16-second dot-fixation rest period. This task will always be the final task during the fMRI session. Following the scanning session, participants will complete the Needs Threat Scale to measure self-reported distress following social exclusion in Cyberball [110] and will take part in an interview regarding the study to alleviate any stress experienced from Cyberball. Participants will not be debriefed on the true nature of the Cyberball task after the first scanning session to avoid contaminating the results during the second scanning session (Figure 3).

Figure 3. Cyberball task. The Cyberball task is a web-based ball-tossing game that measures neural activity during exposure to social inclusion and social exclusion.



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Data Analysis

Study 1

Aim 1

Aim 1 is to determine the frequency and content of self-generated displays of health and risk behaviors on social media profiles. Aim 1a is to test the predictive value of self-generated health and risk behavior content on adolescents' social media profiles to represent attitudes, social norms, intentions, and behaviors. Hypothesis 1a is that adolescents' self-generated health and risk behavior content will have a high PPV in identifying behaviors. Aim 1b is to test the moderators of the relationship between self-generated health and risk behavior content and self-reported health and risk behaviors, including parenting involvement and the perceived importance of technology. Hypothesis 1b is that parenting and the importance of technology will serve as moderators such that the associations between self-generated health and risk behavior content on TDM and self-reported health and risk behaviors will be stronger for those with lower parenting involvement and greater technology importance.

In these analyses, the outcome measures will be self-reported behaviors, and predictor variables will be self-generated displays. Measures will be dichotomized based on established threshold values. We will use a generalized linear mixed-effects model with participant-specific random effects and an autoregressive correlation structure to account for repeated measures over time to identify and examine the factors of self-generated displays that predict the corresponding self-reported outcomes. Both univariate and multivariate analyses will be conducted. Study participants' baseline characteristics, including demographic variables and health and risk behavior variables, will be included as covariates in the multivariate analyses. The least absolute shrinkage and selection operator method for the variable selection of generalized linear mixed-effects models will be used to identify parsimonious models with independent predictors. To test the moderators of the relationship between social media displays and self-reported cognitions (eg, attitudes, social norms, and intentions) and behaviors, we will test interaction effects between social media displays and the moderators of parent involvement and technology importance and include significant moderators in these models. In exploratory analyses, we will examine possible differences in PPV by platform across health and risk behaviors.

Aim 2

Aim 2 is to determine adolescents' real-time TDM exposure to self-generated and other-generated health and risk behavior content using EMA and to test the association between TDM exposure to health and risk behavior content and self-reported health attitudes, social norms, intentions, and behaviors. Hypothesis 2 is that adolescents' exposure to other-generated health and risk behavior content will have positive associations with attitudes, social norms, and intentions, moderated by technology importance.

The association between TDM content exposure and self-reported intentions and behaviors will be evaluated using a generalized linear mixed-effects model with subject-specific random effects. The moderation effects will be evaluated by conducting a series of univariate and multivariate analyses with the corresponding predictor and median variables, and the Sobel test will be used to formally test for moderation effects [111]. As an additional exploratory analysis, we will determine an accurate measure of adolescents' daily TDM use. We will not ask participants to attempt to recall a full day or "typical time spent" on TDM because of strong evidence that these measures are inaccurate owing to response and recall bias. Instead, EMA data will be used to calculate daily TDM time as a measure of the quantity of use, which will be reported as descriptive data or incorporated into models across projects as appropriate. First, raw data for the duration of TDM use will be summarized using mean, SD, median, and range from the self-reported data. Second, we will calculate the proportion of time that participants mention that they were using TDM across each participant's responses of "Y" to indicate that they were actively using TDM. We will use a similar approach to investigate the frequency of content types they are exposed to via TDM. These proportions will be estimated using a generalized linear mixed-effects model with a logit link function and subject-specific random effects. To account for the correlations between time points, an autoregressive correlation structure of order one will be used. Third, we then will use a multilevel modeling approach that captures both within-participant and between-participant variations of the EMA data [112]. This includes subject-specific random effects and an autoregressive correlation structure to account for the correlations within each participant among the repeated measures over time in addition to the covariate of the percentage of time the participant mentions that they were on the web. If the distribution of the time spent is skewed, the data will be log-transformed before conducting the analysis to satisfy the normality assumption.

Aim 3

Aim 3 is to use fMRI to examine whether self-generated TDM content versus other-generated TDM content are processed differently and whether neural activity is associated with self-reported health behaviors. Hypothesis 3a is that the ventral medial prefrontal cortex (VMPFC) will show greater activation for self-generated messages compared with other-generated messages. Hypothesis 3b is that sharing more self-generated content on TDM will be associated with increased VMPFC activity compared with sharing more other-generated content. Hypothesis 3c is that VMPFC activity at time 1 will be associated with increased health and risk behaviors reported at time 2.

Data will be modeled at the participant-subject level using the general linear model, as implemented in Statistical Parametric Mapping version 12 (SPM12; Wellcome Department of Cognitive Neurology, Institute of Neurology). Details regarding fMRI data analysis can be found in study 2. The persuasion task will consist of 2 phases: message exposure (5 s), where participants will be exposed to self- versus other-generated messages, and then they will rate the effectiveness of each message (3 s) and provide confidence ratings (3 s), which will be used as baseline ratings for the social influence task. We will model the 5-second period during which participants will be exposed to the persuasive messages as a boxcar. Specifically,

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we will cross the message source using 2 regressors, self and other, with whether the participant rated the messages as effective. In other words, we will have 2 regressors for each persuasive message condition noted earlier, depending on whether the participant rated the message as effective for that trial, resulting in 4 focal regressors crossing message condition and message effectiveness. Region of interest (ROI) analyses will be performed using independent sample 2-tailed *t* tests and linear regression. The primary ROIs will be regions associated with positive valuations [113], including the VMPFC. The ROIs will be constructed using the association test map in Neurosynth using the search term "valuation." Individual difference scores will be calculated for the positive valuation network based on a percent signal change score. This score will be created by dividing the average time-series signal (activation) across all voxels within the ROIs during the condition of interest by the baseline condition. The persuasion task will consist of examining differences in neural activity between the following conditions (self-generated>other-generated; self-generated+persuasive>other-generated+persuasive; self-generated+persuasive>self-generated+unpersuasive; other-generated+persuasive>other-generated+unpersuasive). Parallel whole-brain analyses will be performed to determine whether neural regions outside of our a priori ROIs are associated with self-generated versus other-generated content and health behaviors.

Study 2

Quality Checking

Quality checking of the brain data will be done before and after the preprocessing step to ensure that the results are not driven by abnormalities related to data acquisition or preprocessing (eg, scanner artifacts). All the brain images will be visually inspected for signal dropout or other abnormal data. In addition, motion parameters from SPM12 will be examined, and no runs displaying greater than 3 mm (translation) or 2 degrees (rotation) of head movement during a task run will be used.

Preprocessing

Functional data will be preprocessed and analyzed using SPM12. To allow for the stabilization of the blood oxygen level–dependent signal, the first 4 volumes (8 s) of each run will be discarded before analysis. Functional images will be despiked using the 3dDespike program as implemented in the Analysis of Functional NeuroImages toolbox. Next, data will be corrected for differences in the time of slice acquisition using sinc interpolation; the first slice will serve as the reference slice. Data will then be spatially realigned with the first functional image. We then will coregister the functional and structural images using a 2-stage procedure. First, in-plane T1 images will be registered to the mean functional image. Next, high-resolution T1 images will be registered to the in-plane image. After coregistration, high-resolution structural images will be skull stripped using the Computational Anatomy Toolbox 12 for SPM12 and then normalized to the skull-stripped Montreal Neurological Institute template provided by the Oxford Centre for Functional Magnetic Resonance Imaging of the Brain Software Library ("MNI152_T1_1mm_ brain.nii"). Finally, functional images will be smoothed using a Gaussian kernel (8-mm full width at half maximum). Following the preprocessing steps, motion parameters from SPM12 will be examined, and no participants who display greater than 3 mm (translation) or 2 degrees (rotation) of head movement during a task run will be included.

Construction of ROI

In both primary fMRI tasks (ie, self and other messages and Cyberball), the primary ROIs will be neural regions associated with social pain [108] and reward processing [114]. ROIs will be constructed using the association test maps in Neurosynth using the search terms "negative affect" and "reward." Individual difference scores will be calculated for the social pain and reward networks based on a percent signal change score. This score will be created by dividing the average time-series signal (activation) across all voxels within each ROI during the condition of interest by the baseline condition.

Primary Task (Cyberball)

Statistical Modeling

Data will be modeled at the single-subject level using the general linear model, as implemented in SPM12. The Cyberball (version 5) task consists of 3 phases: social inclusion (178 s), social exclusion (178 s), and visual tracking (105 s), and all 3 phases will be modeled as blocks and convolved with the synthetic hemodynamic response as provided by SPM12. For all tasks, the 6 rigid-body translation and rotation parameters derived from spatial realignment will also be included as nuisance regressors. Data will be high-pass filtered with a cutoff of 128 seconds. Volumes will be weighted according to the inverse of their noise variance using the robust weighted least squares toolbox [115]. The Cyberball task will involve examining neural activity in the contrast (social exclusion>social inclusion).

ROI Analyses

To examine neural reactivity to social inclusion and exclusion and its relationship with social media use, well-being, and health behaviors, we will conduct a series of linear regressions and moderation analyses. The specific hypotheses and analyses for each aim are outlined in the following paragraphs.

Aim 1

To test whether participants who show greater reactivity in social pain regions during social exclusion will be associated with poorer well-being and risk behaviors at time 1 (hypothesis 1a) and at time 2 (hypothesis 1b), we will test whether social pain activity during social exclusion compared with social inclusion is associated with subjective measures of well-being and risk behaviors at times 1 and 2. Next, to test whether participants who show greater reactivity in reward regions during social inclusion will be associated with better well-being and health behaviors at time 1 (hypothesis 1c) and at time 2 (hypothesis 1d), we will test whether reward activity during social inclusion compared with exclusion is associated with subjective measures of well-being and health behaviors at times 1 and 2.

Aim 2

To test whether the relationship between social media use and well-being and health behaviors will depend on the reactivity

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of participants' brains to social pain during social exclusion at time 1, we will examine whether social pain activity during social exclusion compared with social inclusion moderates the relationship between social media use (ie, social connectedness measures) and subjective measures of well-being and health and risk behaviors at time 1 (hypothesis 2a) and time 2 (hypothesis 2b). In addition, we will examine whether reward activity during social inclusion compared with social exclusion moderates the relationship between social media use (ie, social connectedness measures) and subjective measures of well-being and health and risk behaviors at time 1 (hypothesis 2c) and time 2 (hypothesis 2d).

Aim 3

To test whether changes (time 2–time 1) in reactivity to social inclusion and exclusion will be associated with increased risk behaviors and worse well-being for those who have unsupportive social media experiences over time (hypothesis 3a) and associated with better health behaviors and well-being for those who have a more supportive social media experience over time (hypothesis 3b), we will examine whether changes in social pain activity during social exclusion compared with social inclusion and reward activity during social inclusion compared with social exclusion from time 1 to time 2 moderate the relationship between the social media environment (ie, support measures) and subjective measures of well-being and health and risk behaviors at time 2.

Study 3

Overview

We will run descriptive statistics and transform skewed outcome variables as necessary to ensure normality. We will address missing data by applying advanced statistical techniques, such as *multiple imputations*, using the multiple imputation procedure in the Statistical Analysis Services and Imputation and Variance Estimation Software Statistical Analysis Services macro. Bivariate analyses will be performed to examine potential covariates and covariates significantly associated with the predictor, and our outcomes will be included in the model.

We will begin by conducting an exploratory factor analysis using principal axis factoring with Promax rotation to examine how social media activities identified through the web-based ethnography load onto latent factors. We will then run a confirmatory factor analysis to establish whether the emerging latent factors are nested into our hypothesized higher-level factor structure, specifically self-generated content and other-generated content. Finally, we will conduct factorial invariance tests using the approach suggested by Kühne [116] to establish whether the same factor structure emerges at all measurement time points and between SGM and non-SGM adolescents.

Aim 1

Aim 1 is to test bidirectional relationships between self-generated TDM content and socioemotional well-being. Hypothesis 1a is that TDM engagement with peers (higher vs lower) will be predictive of socioemotional well-being (higher and lower, respectively) at times 1 and 2. Hypothesis 1b is that socioemotional well-being (higher vs lower) will be predictive of TDM engagement with peers (higher and lower, respectively) at times 1 and 2.

Aim 2

Aim 2 is to test the bidirectional relationships between other-generated TDM content and socioemotional well-being. Hypothesis 1a is that the consumption of TDM content connected with offline life (higher vs lower) will be predictive of socioemotional well-being (higher and lower, respectively) at times 1 and 2. Hypothesis 1b is that socioemotional well-being at baseline (higher vs lower) will be predictive of the consumption of TDM content connected with offline life (higher and lower, respectively) at times 1 and 2.

To test the direct and indirect associations of self-generated content and other-generated content with socioemotional well-being (aims 1 and 2), we will conduct a cross-lagged panel analysis (ie, a type of structural equation model), with unweighted data and a full information maximum likelihood estimator, using Mplus 8.4 [117]. As illustrated in Figure 1, self-generated content, other-generated content, and socioemotional well-being at *time 0 (baseline)* will be allowed to simultaneously predict these same variables at *time 1* and then again predict these same variables at *time 2*. In cross-lagged models, each person serves as their own control, and results can be interpreted as pertaining to within-person changes; therefore, it is not necessary to include control variables [118]. This analysis will allow us first to investigate the cross-sectional relationships between the variables of interest at *time 0*, *time 1*, and *time 2* (ie, to what extent self-generated and other-generated content are related to well-being), thus adding to prior cross-sectional research. More importantly, it will allow us to examine lagged relationships or relationships between our variables of interest over time (ie, to what extent self-generated and other-generated content at one time point predicts well-being at the next time point, controlling for well-being at the initial time point). These lagged relationships make it possible to longitudinally test whether well-being is (1) an outcome of self-generated or other-generated content (eg, if self-generated and other-generated content at *time 0* predicts well-being at *time 1* and *time 2*), (2) a predictor of self-generated or other-generated content (eg, if well-being at *time 0* predicts self-generated and other-generated content at *time 1* and *time 2*), (3) both (eg, if well-being at *time 0* predicts self-generated and other-generated content at *time 1 and* self-generated and other-generated content at *time 1* predict well-being at *time 2*), or (4) neither (ie, no relationships are statistically significant).

In other words, the lagged analyses will enable us to ascertain the direction of causality between well-being and self-generated and other-generated content on social media. An additional benefit of this statistical approach is the ability to tease out between-person effects (ie, group-level differences) from within-person effects (ie, individual-level differences). Of primary interest to us are within-person effects, which refer to how changes in an individual's activities affect their well-being over time (and vice versa). Thus, we will be able to investigate whether an adolescent's social media activities affect their well-being over time and whether an adolescent's well-being

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affects the type of social media activities they engage in over time.

In cross-lagged designs, all variables are correlated with each other, resulting in just-identified models. Thus, model fit indices are not informative and do not need to be reported [118]. In addition, further tests of scalar invariance (ie, mean differences across groups in the latent construct) are not appropriate, given that the latent factors at the 3 time points are not independent of each other [119].

From the cross-lagged panel models, all mediated effects of interest will be estimated and tested using bootstrapping. Both the magnitude and statistical significance will be reported, with the significance level set at 2-sided α=.05.

Aim 3

Aim 3 is to compare the self- and other-generated TDM experiences of SGM adolescents with those of non-SGM adolescents. This exploratory aim will involve the use of qualitative comparison groups for future hypothesis generation.

Ethics Approval

This protocol is approved by the University of Wisconsin-Madison institutional review board (2022-1280).

Data Management

For eligible individuals who decide to participate in the study, all identifying information will be removed from the brain image files, survey, EMA, and interview data, and they will be labeled with a study code before they are transferred for storage or used in data analyses. Only trained research staff will analyze the data. Any forms that contain identifying information will be locked in file drawers or stored in password-protected files and accessible only to this study's research staff. There may be publications as a result of this study, but no identifying information will be included. Survey data will be collected through the use of REDCap (Research Electronic Data Capture; Vanderbilt University), and fMRI brain images will be collected on the Waisman Center server during the scanning session. Data will be permanently stored on a secure server run by the Department of Pediatrics. Only the study staff, who all have human participants certification, will have access to the data on these servers.

Reviewer Feedback

Reviewer feedback on the grant and author responses have been provided in Multimedia Appendix 2 [120-122].

Results

Data collection began in March of 2023 and is ongoing. Our long-term goal is to use the findings from this synergistic protocol program to enhance health messaging campaigns, improve big data surveillance approaches, develop innovative interventions, and advance conceptual models. This protocol will (1) include interdisciplinary studies of TDM use across adolescence using multilevel assessments of neurodevelopment to examine interrelated developmental changes in brain structure and function and complex behavior, (2) examine real-time measures of TDM exposure and use and how this use regulates adolescents' behavior, and (3) conduct research using converging methodologies to assess the relationship between TDM exposure and sensitive periods in brain development.

Discussion

Overview

This protocol will establish a fully integrated interdisciplinary program of research studies that are essential for developing a fundamental understanding of the complex interplay between adolescent health and development and TDM. Previous evidence has illustrated TDM's connections with adolescent risk behaviors such as increased alcohol behavior and social media exposure, as well as relationships with adolescent well-being such as improved socioemotional health and peer social media connections. The goal of the studies described in this protocol is to address the urgent need to understand how TDM exposure and use affect multiple developmental domains and health outcomes. Study 1 will use TDM to understand the mechanisms behind adolescent health and risk behaviors. Study 2 uses fMRI to understand how positive and negative TDM experiences relate to mental and behavioral health. Study 3 will use a mixed methods design to evaluate self- and other-generated TDM content as predictors of socioemotional well-being in SGM and non-SGM adolescents. Each study uses a 2-year longitudinal design and draws from a shared participant pool. Across studies, observed and measured data will be collected, including observed social media content and fMRI data, self-reported participant experiences and perceptions from surveys and interviews, and EMA for capturing real-time TDM exposure. This protocol prioritizes the dissemination of findings, both to scientific audiences and to the communities across Wisconsin to reach those who participated in this research. Thus, the protocol will enhance the ideas and outcomes obtained through the interactions of the 3 studies. This protocol will provide the scientific approach necessary to advance data-informed theories and conceptual models addressing how TDM exposure and use impact the developmental trajectories and health outcomes of adolescents. Because of the broad potential for advancing research and possible clinical translation of the results, these connected studies portend an opportunity to improve prevention and intervention approaches for adolescent health and TDM.

This project's data hold exciting potential in four areas:

1. Messaging campaigns: an understanding of key messages regarding health and risk behaviors or socioemotional well-being may inform prevention messaging campaigns. Using data from this protocol, targeted messages (such as tailored advertisements) could be made to automatically pop up
on social media when a specific type of risk-related post is present, providing a link to health education or a web-based intervention.
2. Surveillance: by identifying keywords or phrases associated with health and risk behaviors or well-being, big data approaches could be used to identify or track social media posts focusing on health and risk behaviors or well-being across a larger population or different social media platforms.

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3. Intervention approaches: health behavior intention posts may represent an individual's consideration of behavior change or openness to intervention. Studies support that adults who are considering behavior change have more motivation and willingness to engage in alcohol interventions [123]. Identifying the markers of adolescents' intention to improve health may allow for novel intervention approaches tailored to this particular stage of development and intentionality.
4. Conceptual models: the findings from this study have the potential to enhance or update conceptual models focused on adolescent technology use, such as the Media Practice Model [124], which supports the idea that adolescents choose to interact with media based on who they are or who they aspire to be. The data from this protocol may also contribute to the development of new models.

Potential Limitations

A central benchmark of success for our protocol will be our capacity to recruit and retain a shared participant pool of 400 participants for the 3 studies. There are several reasons that support the planning and success of this study. First, authors MAM and ES bring experiences that span projects 1 to 3 in recruiting and retaining adolescent populations. Second, we will pursue recruitment and retention via recruitment ambassadors, who will provide us with a warm and familiar connection with adolescents and families during recruitment. We will leverage both intrinsic motivation, such as promoting emotional connection with the study by providing participants with appealing branded materials, and extrinsic motivation via escalating incentives to retain adolescents. Our investigator team collaboratively designed participant recruitment to occur on a rolling basis over the first 2 years of the protocol period. If recruitment is an issue, we will use alternative approaches, such as targeted social media advertisements and Qualtrics (Qualtrics International Inc) panel–based recruitment, to achieve recruitment goals. If we have retention issues, we will engage our recruitment ambassadors to obtain insights into continued engagement with the participant population. Given that our rolling recruitment efforts will extend over 2 years, we will also have the flexibility to recruit additional participants if early dropouts occur.

A second critical aspect of our study will be to build trust in participants to support their willingness to provide ongoing data in this longitudinal study. Our investigator team will use several evidence-based approaches to optimize adolescents' trust and comfort in this longitudinal study, including conducting frequent touch points via check-ins every 6 months and providing incentives with every touch point. We will work with trained staff who have centered their research career work on the adolescent population and have training in working with this study population.

Critical Considerations for Social Media Data Collection

Although adolescents may use other social media platforms, we focus on the selected 4 social media platforms based on several factors. First, authors MAM and ES selected these platforms based on the conceptual approach of affordances, and given this study's focus on the process of identity development, these 4 platforms represent venues that have strong identity affordances [125,126]. Further, these 4 platforms are popular and used across diverse adolescent demographic groups. Given the length of our planned protocol, there could be a rise of a new popular social media platform or a decline of a planned study platform. If a new platform aligns with promoting identity affordances, we would consider adding it to our study protocol. Content analysis (study 1) and digital ethnography (study 3) procedures require staff training and attention to the coding quality, both tasks that MAM and ES are familiar with owing to past projects. Although big data techniques allow text-based scraping from large data sets, they are limited in that they cannot assess hashtags or all types of photos. Further, big data approaches cannot always ascertain whether content is self-generated or other generated, which are central concepts in this proposal. For this study, we will rely on establishing a *friend* link between our research team profiles and our participants' profiles. We have several points of evidence to suggest that this approach will work. First, social media users' desire to accumulate more friends provides an incentive for them to *friend* our research team, as this number is associated with increased social capital [31]. Second, we have used this approach before in several studies to inform friending approaches [127] and collect data [120,128,129]. If a participant wanted to *defriend* us at some point in the study, we would consider this a voluntary withdrawal. On the basis of our previous longitudinal studies, we anticipate that this loss would be <5% of participants.

Acknowledgments

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Data Availability

Data from this protocol will be deposited into the Eunice Kennedy Shriver National Institute of Child Health and Human Development Data and Specimen Hub repository.

Conflicts of Interest

ES is on the scientific board for Google/YouTube Kids. YouTube is not one of the platforms being examined in this study and no funding was received from Google for this study.

Multimedia Appendix 1
Secondary functional magnetic resonance imaging data collection.
[DOCX File , 239 KB - resprot_v12i1e50984_app1.docx]

Multimedia Appendix 2
Peer-review report by the National Institute of Child Health and Human Development Special Emphasis Panel Impact of Technology and Digital Media (TDM) Exposure/Usage on Child and Adolescent Development (P01 Clinical Trial Optional).
[PDF File (Adobe PDF File), 240 KB - resprot_v12i1e50984_app2.pdf]

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Abbreviations

EMA: ecological momentary assessment
fMRI: functional magnetic resonance imaging
PPV: positive predictive value
REDCap: Research Electronic Data Capture
ROI: region of interest
SES: socioeconomic status
SGM: sexual and gender minority
SPM12: Statistical Parametric Mapping version 12
T1: longitudinal relaxation time
TDM: technology and digital media
VMPFC: ventral medial prefrontal cortex

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Protocol

Advancing Understanding of Just-in-Time States for Supporting Physical Activity (Project JustWalk JITAI): Protocol for a System ID Study of Just-in-Time Adaptive Interventions

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Abstract

Background: Just-in-time adaptive interventions (JITAIs) are designed to provide support when individuals are receptive and can respond beneficially to the prompt. The notion of a just-in-time (JIT) state is critical for JITAIs. To date, JIT states have been formulated either in a largely data-driven way or based on theory alone. There is a need for an approach that enables rigorous theory testing and optimization of the JIT state concept.

Objective: The purpose of this system ID experiment was to investigate JIT states empirically and enable the empirical optimization of a JITAI intended to increase physical activity (steps/d).

Methods: We recruited physically inactive English-speaking adults aged ≥25 years who owned smartphones. Participants wore a Fitbit Versa 3 and used the study app for 270 days. The *JustWalk JITAI* project uses system ID methods to study JIT states. Specifically, provision of support systematically varied across different theoretically plausible operationalizations of JIT states to enable a more rigorous and systematic study of the concept. We experimentally varied 2 intervention components: notifications delivered up to 4 times per day designed to increase a person's steps within the next 3 hours and suggested daily step goals. Notifications to walk were experimentally provided across varied operationalizations of JIT states accounting for need (ie, whether daily step goals were previously met or not), opportunity (ie, whether the next 3 h were a time window during which a person had previously walked), and receptivity (ie, a person previously walked after receiving notifications). Suggested daily step goals varied systematically within a range related to a person's baseline level of steps per day (eg, 4000) until they met clinically meaningful targets (eg, averaging 8000 steps/d as the lower threshold across a cycle). A series of system ID estimation approaches will be used to analyze the data and obtain control-oriented dynamical models to study JIT states. The estimated models from all approaches will be contrasted, with the ultimate goal of guiding rigorous, replicable, empirical formulation and study of JIT states to inform a future JITAI.

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Results: As is common in system ID, we conducted a series of simulation studies to formulate the experiment. The results of our simulation studies illustrated the plausibility of this approach for generating informative and unique data for studying JIT states. The study began enrolling participants in June 2022, with a final enrollment of 48 participants. Data collection concluded in April 2023. Upon completion of the analyses, the results of this study are expected to be submitted for publication in the fourth quarter of 2023.

Conclusions: This study will be the first empirical investigation of JIT states that uses system ID methods to inform the optimization of a scalable JITAI for physical activity.

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International Registered Report Identifier (IRRID): DERR1-10.2196/52161

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KEYWORDS

just-in-time adaptive intervention; JITAI; just-in-time; JIT; walking; physical activity; needs; opportunity; receptivity; mobile phone

Introduction

Background

There is great interest in the promise of just-in-time adaptive interventions (JITAIs) to support behavioral medicine. A JITAI is a behavioral intervention that is designed to (1) provide interventions and support during *just-in-time (JIT) states*, defined as times when a person would have a *need for support*, an *opportunity to act* in accordance with the support, and *be receptive* to support [1]; and (2) adapt over time to a person's changing needs with the use of adaptation algorithms that strive toward enabling a person to meet clinically meaningful behavioral targets (eg, national recommendations for a given behavior) while accounting for the person's current capabilities and constraints. Although there is a lot of interest in this type of intervention, more work is needed to advance the understanding of the foundational concepts implied by JITAIs, particularly the JIT state. The JIT state concept is inherently context dependent, dynamic, and likely to manifest differently for different people over time. Given this complexity, much of the work on JITAIs has focused on either creating interventions that are theory driven in terms of specifying JIT states according to a priori decision rules or through more data-driven approaches such as reinforcement learning. An important gap is the lack of a conceptual understanding of JIT states, which could be achieved by conducting rigorous theory-testing protocols designed to test dynamic hypotheses about JIT states.

The purpose of this paper is to describe a research protocol for a National Institutes of Health–funded Smart and Connected Health study (R01LM013107) explicitly designed to produce rigorous empirical evidence to study JIT states in the context of a physical activity (PA) JITAI. The structure of the paper is as follows. First, background information is provided about JITAIs that is necessary to understand the motivation for our system ID protocol. Next, a description of the system ID experimental protocol is provided, including the specific goals of the project, experimental design procedures, measurement approach, and analysis plan. Finally, a discussion and the implications of this work are offered in terms of future research on JITAIs.

Improving Understanding of JIT States Within a Digital Health PA Intervention

There is convincing evidence indicating that PA is valuable for reducing the risk of colon, breast, endometrial, lung, and pancreatic cancers [2,3] and cardiovascular disease [4] and improving glycemic control [5]. With an aging population, step interventions could help prevent chronic diseases, reduce health care costs, and improve functional life years and quality of life [2-18]. The clinical guidelines for steps suggest 8000 steps per day for adults [19,20], but only one-third of this group meets the guidelines [21-31]. Across PA interventions for adults (eg, human-delivered and digital), results show increases of 496 steps per day achieved above baseline levels of 5000 steps per day, and even high-impact interventions peak at 1363 steps per day above baseline; both result in activity that is still below the guidelines. Even among interventions that produce an effect, maintenance is rarely measured, and when it is, it is not achieved by many participants [32-35]. Our long-term goal is to create a model-predictive controller-driven JITAI to increase walking that, we hypothesize, will be more effective than current PA interventions at supporting individuals in achieving and maintaining national guideline recommendations of at least 8000 steps per day averaged across a week [19,20].

Although there are many possible algorithmic approaches to achieve this, such as reinforcement learning [36] or recommender systems [37], this research effort is focused on the use of a model-predictive controller approach [38]. A model-predictive controller is an adaptation algorithm that uses time-series data from an N-of-1 unit [39,40] to support decisions over time in dynamic, often complex situations, such as dynamically providing support to a person to increase their PA. As the name implies, a central feature is a computational dynamical model, which is a series of mathematical equations that encode previous domain knowledge and include parameters that are estimated from data derived from each N-of-1 unit (ie, a person in this context), thus enabling the controller to account for individual differences in predictions. These computational models, similar to weather or climate forecasting models, enable rigorous simulations of a person's likely responses to different types of support provided both now and in the future. For example, the model could be used to simulate a person's

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response to the provision of a notification meant to nudge them to walk within the next 3 hours. The model would generate predictions on the likelihood that a person will walk after receiving the notification at each moment. In addition, the model can be used to simulate the potential synergistic or antagonistic effects that might occur because of different decisions that could be made. For example, using the model, predictions could be made on the potential diminishing effects of providing notifications over time owing to habituation or growing annoyance, particularly if notifications are sent when a person does not need them.

As this description implies, model-predictive controller-driven JITAIs are complex and, thus, are difficult to create using theory alone, which, historically, was the dominant way in which adaptive behavioral interventions were developed [41,42]. Instead, JITAIs require robust experimentation that enables empirical optimization of their elements, particularly the generation of the computational dynamical models that the controller uses to run simulations and, by extension, make dynamic decisions. As described in previous work [43], the empirical estimation and validation of dynamical models occur through system ID.

The system ID study described in this paper had 2 complementary but distinct aims. First, it aimed to gather empirical evidence on the concept of JIT states. By varying whether a notification is provided when the person is thought to be in a state of need, when they have an opportunity to walk, when they are thought to be receptive, or combinations of these 3 states, the experiment collected initial evidence for which aspects of the JIT state are most important for supporting the effectiveness of JIT interventions and whether this changes over time.

Second, the experiment was designed to collect the data needed to optimize a digital health intervention, *JustWalk JITAI*. The goal was to estimate and validate dynamical models that can be used to construct a model-predictive controller that can make decisions on the provision of support in given moments to achieve and sustain clinically meaningful PA targets. Prior work was used as a foundation to achieve these aims, particularly a dynamic model of social cognitive theory (SCT) that encapsulates domain knowledge about behavioral processes that influence PA [44-46]. The SCT models were refined using the newly collected data both to help us better understand JIT states and to develop models that can be incorporated into a multitimescale model-predictive controller.

Methods

Overview

Aims

The aim of this study was to conduct a system ID experiment to empirically assess the conceptual elements of a JIT state and estimate and validate dynamical computational models relevant to JIT states. This work was conducted to inform the development of a future model-predictive controller-driven JITAI. We had three broad hypotheses: (1) walking bout planning prompts that are provided when the system determines that individuals meet all 3 conditions of a JIT state—have a need, have an opportunity to walk, and are receptive to intervention notifications—will be more effective than when such prompts are provided when only some or none of those conditions are met; (2) idiographic computational models (ie, models developed by and for individual participants) can be produced that are effective at predicting contexts in which suggestions to go for a walk will be effective and how such suggestions and adaptive step goals combine to support a person in achieving both daily step goals and sustained engagement in steps per day; and (3) nomothetic analyses (ie, insights gleaned from data aggregated across participants) will reveal meaningful clusters for different types of contextual patterns and trajectories of change across participants. These clusters will enable the selection of initial dynamical model parameters and, by extension, the development of a generic semiphysical model that can be used as a starting point for new participants in a future model-predictive controller-driven JITAI. In aggregate, these results will also be used to empirically test the added value of previous domain knowledge, as encapsulated in previous computational models, for improving model prediction and response, with a basic autoregressive model with external input as a reference model that only accounts for previous domain knowledge in the form of variable selection but not the structure of their relationships.

Study Design Overview

Building on prior work, including the mobile health app *HeartSteps* (which was relabeled *JustWalk JITAI* for this study to continue on the control systems side of JITAI development) [47,48], we conducted a system ID experiment designed to study the theoretical concept of JIT states as a tool for fostering behavior change. The system ID experiment focused on two key intervention components: (1) notifications delivered up to 4 times per day designed to increase a person's steps within the next 3 hours via either increased awareness of the urge to walk or via bout planning and (2) adaptive daily step goals. Both types of notifications prompting short walks within the next 3 hours were experimentally provided or not across variations of *need* (ie, whether daily step goals were previously met), *opportunity* (ie, the next 3 h are a time window when a person has an opportunity to walk based on their previous step data), and *receptivity* (ie, the person received <6 messages in the last 72 h and walked after notifications were sent). In addition, the suggested daily step goals also varied systematically across time rooted in a person's baseline levels of steps per day (eg, 4000 steps) and gradually increasing until they met clinically meaningful targets (at least 8000 steps/d on average). Participants wore a Fitbit Versa 3 and used the study app for 270 days.

Technology

Wearable Sensor

The Fitbit Versa 3 is a wrist-worn, watch-style activity tracker that records participants' steps and minutes of moderate or vigorous PA (*active minutes* in the language used by Fitbit) that the tracker detects based on accelerometer and heart rate data. The Fitbit tracker records the step and activity data, automatically synchronizes with the Fitbit server, and pushes

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to the *JustWalk JITAI* servers using Fitbit's subscription application programming interface (API). It was recommended to participants to set the Fitbit to use one of the market-available watch faces with the following features: (1) always visible information about the current step count, daily step goal, and progress toward meeting the goal and (2) positive reinforcement (in the form of a fireworks display and vibrations) when the daily step goal is met. The list of watch faces that met these requirements was provided by the staff.

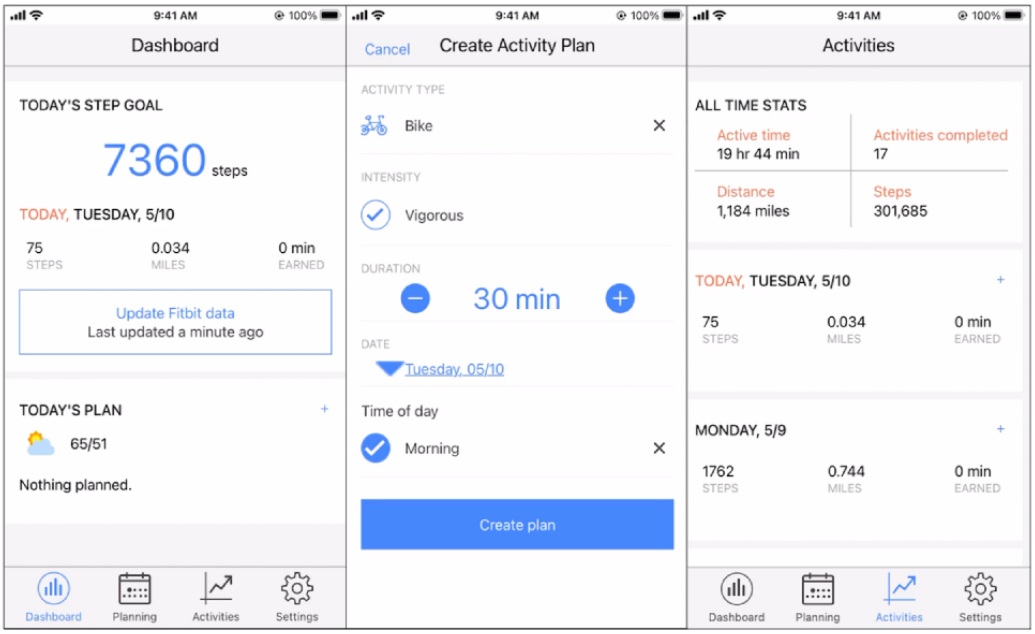
Mobile App

The *JustWalk JITAI* app contained (1) *pull* components that participants could access at any time by opening the *JustWalk JITAI* app (Figure 1), (2) *push* components that were sent to the participants as app notifications based on system-based rules (these were our key experimental manipulations and are described in the *Interventions and System ID Experimental Design* section and Figure 2), and (3) ecological momentary assessment (EMA) questions (described in the *Measures* section).

The *JustWalk JITAI* app consisted of 3 *pull components*, which were drawn from the *HeartSteps* app [48]. These were accessible through tabs along the bottom of the app screen (Figure 1; left):

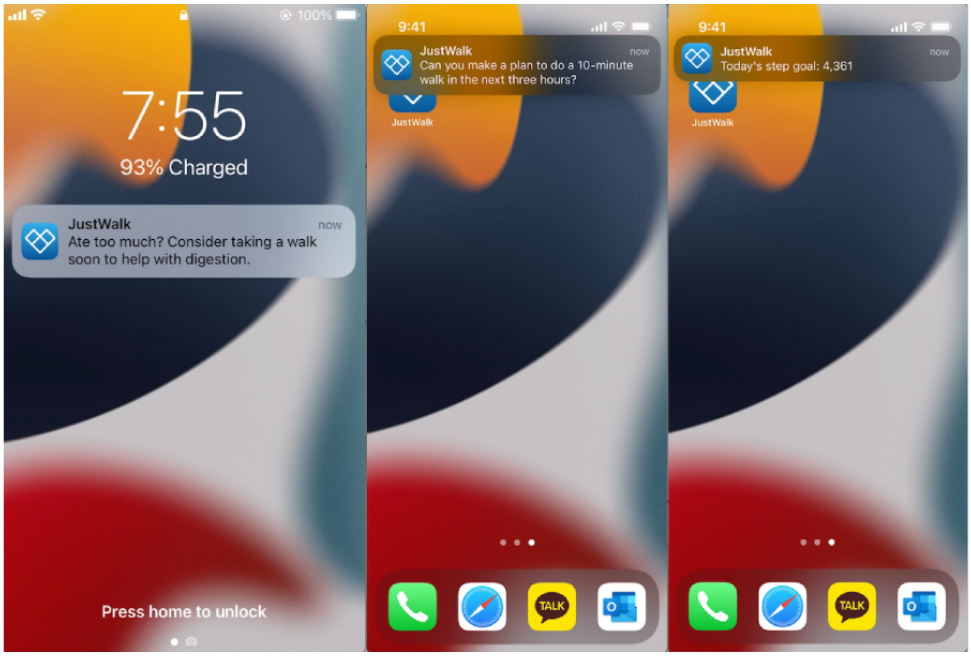
1. *Dashboard*: the dashboard was the home screen of the app and was displayed whenever a participant entered the app or finished interacting with a *JustWalk JITAI* notification. The dashboard implemented 3 behavior change techniques [49,50]: self-monitoring, feedback on goal progress, and reminders of activity plans. At the center of the dashboard, a participant's progress toward their daily step goal was shown as feedback. If participants created an activity plan for the day, the dashboard also displayed this plan for the participants.
2. *Planning*: through the planning tab (Figure 1; center), participants could identify when they would plan to exercise that week. The planning tool was designed to operationalize the behavior change technique implementation intentions [51,52] by enabling participants to identify when they would be active and for how long and identify a specific activity to engage in.
3. *Activity log* (Figure 1; right): participants could see an activity summary for the last 2 weeks, including steps walked and distance covered each day, as well as the types of activities that the Fitbit tracker detected automatically or the user logged manually (eg, running, hiking, walking, and yoga). In addition, the activity log displayed Fitbit-derived active minutes for each day. Finally, the tab displayed the participants' all-time statistics—hours of active time, total distance walked, total counts of activities (detected or manually logged), and total number of steps recorded since the user started using the JustWalk JITAI system. These all-time statistics were intended to provide longer-time-frame feedback on what the participant accomplished over the duration of the study.

Figure 1. JustWalk JITAI app screenshots (left: app dashboard; center: planning tab; right: activity log tab).



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Figure 2. JustWalk JITAI app notification screenshot on the locked screen and background status.



Participant Procedures

Recruitment

Participants were recruited nationally using a noncontact approach. Participants were recruited mainly through university mailing lists and word of mouth. The targeted number of participants was 50, with a final fully enrolled sample of 48 as 2 participants never showed up to preintervention meetings.

Eligibility

Inclusion criteria were participants who (1) were aged ≥25 years; (2) were inactive, defined as engaging in <60 minutes per week of self-reported moderate-intensity PA; (3) owned either an iPhone with iOS 11 or above or an Android phone with Android 5.1 or above; (4) stated a commitment to follow study protocols, including regularly carrying a mobile phone, using the *JustWalk JITAI* app, answering phone-based questionnaires, and wearing the Fitbit Versa 3 activity tracker at least 8 hours a day; and (5) were fluent in English.

The exclusion criteria were participants who (1) were incapable of providing informed consent or (2) had a psychiatric disorder that limited their ability to follow the study protocol, including psychosis and dementia.

Screening, Informed Consent, and Onboarding Meeting

All participant interactions occurred remotely. Recruitment materials directed participants to the study website, which included a contact entry form. Upon completion, participants were automatically sent a link to an eligibility screener, which asked about age and PA levels (as reported using the Global Physical Activity Questionnaire [53] and the revised Physical Activity Readiness Questionnaire [54]). The staff reviewed the survey responses to confirm eligibility.

Eligible participants were offered time slots for an informed consent meeting. Ineligible participants were informed of their ineligibility.

During the informed consent meeting, the following activities took place: (1) the study was described in detail via a guided read-through of the consent form, (2) participants were provided with a list of reasons to and reasons not to take part in the study, (3) participants were invited to develop a list of their own pros and cons for taking part in the study, and (4) participants were given time to ask any questions they had. If participants verbally agreed, the study staff asked them to sign the consent form via DocuSign (DocuSign, Inc).

Consented participants were asked for a mailing address to send a Fitbit. Participants were also sent instructions on how to set up the Fitbit and the app via email. Once confirmation of delivery of the Fitbit was received by the staff, a follow-up email was sent to participants inviting them to pick a time slot for the preintervention meeting.

During the onboarding internet-based meeting, participants were instructed on the following topics: (1) instructions on how to install and use the Fitbit and study app, (2) information on the 10-day baseline, (3) information on what to expect after the 10-day baseline period, (4) direction to complete a baseline survey, and (5) instructional videos with corresponding notes about how to use and maintain the Fitbit (eg, strategies to keep it charged and reminders to clean it to reduce skin irritation). All meetings between the participants and the staff took place via Zoom (Zoom Video Communications), and the interviews took place within 2 weeks after the time slots were sent.

Incentives

Participants received the following incentives: (1) Fitbit Versa 3 (received at study enrollment; US $229 in value), (2) US $25 gift cards provided to them up to 3 times (US $75 in total) if they completed at least 80% of the daily EMA items within each 3-month period, and (3) US $25 gift cards if they attended an optional postintervention interview.

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Study Timeline

During the 10-day baseline, participants were asked to engage in their normal level of steps or PA and always wear the Fitbit except while charging. No interventions were provided, and no EMA questions were asked during the baseline period. When participants opened the app, 10 circles were shown designating the number of days they had met the minimal wear time requirements (ie, 8 h/d). If the participant did not wear the Fitbit for at least 8 hours a day, the circles did not fill up. Once all 10 circles were filled, the app automatically transitioned to the intervention phase, displaying a dashboard.

In the intervention phase, all app features were delivered, including the 2 push intervention components (ie, walking prompts and adaptive suggested step goals) and the daily EMA questions. The participants also gained access to other parts of the *JustWalk JITAI* app such as activity logs and planning support. Participants were asked to interact with the app whenever it sent them notifications and were told that they could open the app at any time if they wanted to access pull components and found them useful. Total interaction time with the app from push interventions and EMA notifications does not exceed 10 minutes each day, but participants may choose to spend more time on the app accessing other features. The interactions participants were prompted to do occurred in response to four types of notifications: (1) daily step goal notifications, (2) walking suggestion notifications, (3) prompts to complete the daily EMA battery, and (4) experience sampling prompts (ie, if Fitbit detected an activity) to complete EMA items throughout the day and in relation to the notifications to either increase the urge to walk or plan (for details about EMA, see the *Measures* section).

Interventions and System ID Experimental Design

System ID Overview

This study used a system ID approach to manipulate 2 intervention components experimentally: *walking suggestions* and *daily step goals*. To achieve the desired dynamics on the timescale of interest, we used 2 input signals, one for each of the 2 components. Although our study design enables traditional statistical analyses to examine the impact of intervention components on behavioral outcomes, that is not the primary focus of a system ID experiment. The primary goal of a system ID experiment is to estimate and validate dynamical computational models that are validated based on their ability to predict the future responses of each individual's behavior across time. These aims are achieved by having different intervention components—suggestions to walk in the next 3 hours and adaptive goal setting—delivered at different timescales and orthogonally, that is, statistically independent of each other. Our approach is analogous to a within-person factorial experiment (and, indeed, can be treated as such with all relevant nomothetic statistics used on the developed data set, which the team plans to perform as secondary analyses). The critical difference is that, in system ID studies, the designed input signals achieve statistical independence through orthogonality as verified in the frequency domain. Orthogonality enables separate study and estimation of the dynamics and impact of each intervention component. One can think of frequencies as different repeating rhythms across time, such as the notion of a minute-by-minute, daily, or weekly frequency. The study was designed to ensure that the intervention signals were disambiguated across time (via delivery at different frequencies). This enables a rigorous independent study of dynamical responses to both intervention components within the same experiment and, indeed, within each person, both proximally (eg, immediate responses following intervention delivery) and distally (eg, continued or delayed effects up to several days after any notification).

Specifically, both signals are designed to follow the guidelines presented in the study by Rivera et al [55], in which equation 1 is highlighted to define the effective frequency range of the input signal based on a priori knowledge of the dominant system time constant.

Equation 1 is the equation used to define the effective frequency range of the input signals of the *JustWalk JITAI* study based on a priori knowledge:



 and  represent the higher and lower bounds for the estimated dominant time constant of the system, meaning the range in which signals relevant to walking would occur naturalistically. α_s and β_s dictate the input signal's content of high and low frequency, respectively. The orthogonality of our intervention components was confirmed via the use of cross-correlation analysis (the appropriate approach for testing orthogonality via frequency domains) to the designed input signals.

Sample Size Considerations

The number of participants has little impact on the power estimate for system ID studies as system ID approaches mostly use dynamic models that consider individual-level changes over time [43]. Instead, different methods, such as study length and validation analysis, can be used to establish the equivalent notion of *power* [56]. A multisine signal's *cycle*, or predetermined time interval, serves as the foundation for the power calculation [57]. By dividing the cycles into estimation and validation data sets, this type of design maximizes the signal-to-noise ratio and aids in the evaluation of model fits.

Previous research has demonstrated that 3 independently excited harmonics per cycle can achieve a sufficient excitation to deliver dynamically meaningful data in relation to daily frequencies. This can be performed with 3 sinusoids per cycle, resulting in a cycle that lasts at least 12 days [58]. Estimating and comprehending the multitimescale dynamics of behavior change are the goals of this effort. A total of 9 excited harmonics were revealed through simulations to be necessary to provide persistence of excitation across relevant frequencies [59]. The result is that each cycle lasts 26 days. From this, the final study length was set at 10 cycles (260 d).

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Intervention Design

Overview

An overview of the *JustWalk JITAI* intervention elements is provided in Textbox 1.

Textbox 1. Summary of the JustWalk JITAI intervention elements

Wearable sensor

- Fitbit Versa 3

Mobile app

- *HeartSteps* [47] (renamed *JustWalk JITAI*)

Walking notifications

- Walking notifications were pushed up to 4 times a day starting at the participant-set time (eg, 7 AM or 8 AM), with 3-h gaps between each possible notification (eg, 7 AM, 10 AM, 1 PM, and 4 PM as possible decision points for sending notifications).
- Notification texts were randomly chosen from a library of 50 messages that included 24 messages meant to inspire participants to plan a time when they would walk in the next 3 h and 26 messages meant to invite participants to become aware of internal urges that could inspire them to walk (Figure 2 and Multimedia Appendix 1).
- The experimentation setting used 4 just-in-time (JIT) definitions: (1) full JIT (need [N], opportunity [O], and receptivity [R]), (2) N+R, (3) N+O, and (4) random, with each element defined as follows:
  - *N*: on track to meet the daily step goal accounting for time of day when assessed (eg, 50% of steps accrued halfway in a person's day, using their self-selected start time as a reference and assuming 12-h windows)
  - *O*: next 3-h time window was predicted to have an 80% likelihood that someone could take steps using a previously published algorithm [60]
  - *R*: participant received <6 notifications and responded (ie, walked) to at least 50% of notifications sent to them within the previous 72 h

Adaptive step goals

- Each morning, participants were provided with a suggested daily step goal.
  - The notification also included a single-item ecological momentary assessment whether it was helpful or not.
- Daily step goals were calculated using the following procedures:
  - For the first cycle, median steps/d were used as a personalized reference to guide adaptive step goal suggestions. For cycle 1, a participant's personalized reference (ie, median steps/d) was calculated from their 10-d baseline period excluding nonwear days.
  - For all subsequent cycles, their personalized reference (ie, median steps/d) was calculated from the previous 26-d cycle (eg, cycle 2's median steps/d were calculated using all step/d data from cycle 1 excluding nonwear days).
  - Participants were provided with a step goal that ranged between their personalized reference (median steps/d) up to their personalized reference+4000 steps.
  - A multisine signal design that ranged from 0 (personalized reference) to 1 (personalized reference+4000 steps) was used. For example, if a person's median steps/d during the baseline period were 5000 steps/d, they would receive step goal suggestions between 5000 and 9000 steps/d.
  - Maximum step goals were set at 12,000 steps/d, and minimum step goals were 2000 steps/d.

Walking Notifications

Overview

The first component of the *JustWalk JITAI* was notifications meant to inspire short (eg, ≥10 min) walking bouts within 3 hours after receiving the notification. This component had two variations that targeted different behavioral processes: (1) an invitation for a person to create a microimplementation intention on when, where, and how to fit in a ≥10-minute walk in the next 3 hours—we label these suggestions as *bout planning*—and (2) an invitation for a person to become aware of interoceptive experiences and signals (eg, stiff muscles and lethargy) that may inspire them to go for a walk—we refer to these messages as *cultivating an urge*. Both types of walking notifications were drawn from a library of 50 messages (n=24, 48% on bout planning and n=26, 52% on cultivating an urge). Walking notifications were provided in the form of push notifications from the *JustWalk JITAI* app. The notification could be sent 4 times a day (ie, decision points) starting at the user-defined *start of day* time, which was gathered during the onboarding processes. Starting from the participant's self-described *start of the day*, the walking notification decision points occurred every 3 hours. For example, if a participant's day started at 8 AM, their decision points would be 8 AM, 11 AM, 2 PM, and 5 PM. For each participant, on each day of the study at each of the 4 decision times, the *JustWalk JITAI* system decided whether to send a walking notification based on the system ID procedure described in the following section.

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Operationalization of JIT States

JIT states were experimentally varied via the use of different rules to define a *JIT* state. By nudging participants when they were in *JIT* states, the hypothesis is that the effect of the walking notifications should increase while maintaining a low level of burden on participants, thus minimizing notification fatigue.

A JIT state has been previously conceptualized [1] as a state in which a person is receptive to support (eg, if a notification is sent, a person would appreciate receiving said notification) and has the opportunity to engage in the desired behavior (or vulnerability to a negative behavior). Building on this theoretical formulation, a third theoretical parameter was added: the need for intervention support. For example, if someone is already meeting their daily step goals, they likely do not need additional intervention prompts to walk. For the purposes of this study, JIT states were operationalized as follows:

1. *Need (N)*: a person is defined as in a state of need if they did not meet the previous day's step goal (for the first decision point) or if they are not making steady progress toward that day's goal (for all other decision points). Sufficient progress was defined as the goal prorated to the current time of day:



2. *Opportunity (O)*: a person is deemed to be in a state of opportunity when they can feasibly walk. To operationalize this, a predictive algorithm described in the study by Park et al [60] used a threshold of 80% probability that, within the next 3 hours, a person may walk. We used the high threshold of 80% so that even a slight nudge to walk could effectively achieve short-term behavior change (note: whether notification is needed at such a high moment of opportunity is a question that we will be able to study retrospectively).
3. *Receptivity (R)*: a person is deemed to be receptive when they have received ≤6 messages in the last 72 hours *and* have responded (ie, walked in the following 3 h) after ≥50% of the walking notifications sent in that period.

The operationalizations of these 3 facets of a JIT state allow us both to define a full JIT state—that is, when need, opportunity, and receptivity are *all* present—and to empirically test how different operationalizations of JIT states (eg, states when only some of these components are present) influence walking notification effectiveness. Specifically, daily decision rules were tested that embodied four different levels of being in a JIT state:

1. *Full JIT state*: need, opportunity, and receptivity are present.
2. Partial JIT state (2 forms): *N+O* (only need and opportunity are present) and *N+R* (only need and receptivity are present).
3. *Not in a JIT state (random)*: notifications are randomized each time at 50% probability.

How and when each of these rules for defining JIT states was varied experimentally is described in the following section.

Previous Observations and Theoretical Considerations That Guided Our Study Design to Test JIT States

This specific study design was created based on data from the original *HeartSteps* trial [47] followed by engaging with previous domain knowledge, including behavioral theory and our previously developed SCT dynamical model [61], to guide the final study design such that this study could provide robust data for supporting computational model testing.

Concerning previous observations, in the *HeartSteps* trial related to the notifications designed to inspire bouts of walking, 3 empirical observations guided our understanding of JIT states. First, as reported previously [47], notifications had a diminishing proximal impact on the total number of steps taken within the 30-minute window after the notification. These results indicated a theorized diminishing value-to-burden ratio of the prompts, namely, a dynamic concept that balances, for each instance, a person's perceived value that they receive from an intervention compared with the perception of the level of burden of the intervention. This dynamic hypothesis, which conformed to the data, was that the value-to-burden ratio would diminish over time, with initial notifications being perceived as more valuable than burdensome; however, by the end of the study, this would shift toward a low or negative value in relation to the burden.

Second, it was observed that, if <2 notifications were sent on a given day, even later in the 6-week trial, then the bout notifications resulted in significantly improved steps taken within the 30-minute window after the notification. We interpreted this dynamic observation as representing a hypothesized *autorecovery* that could take place on a person's value-to-burden ratio. One could think of this as analogous to a neuron. Once a neuron fires, if new signals come in, the neuron will not fire again until it has sufficient time to recover, but this recovery process is automatic. It was hypothesized that a similar dynamic takes place regarding notifications. Namely, if notifications are sent at a rate that is faster than a person's autorecovery rate, habituation will set in and the notifications will be ignored (again, similar to a neuron not firing). If, in contrast, *sufficient time* has passed for autorecovery to take place (eg, such as a neuron re-establishing itself as ready for the next signal), then a notification sent would be more likely to be attended and reacted to by a participant. Previous data guided us to a population-based starting point of, on average, 2 notifications in a day, providing sufficient time for autorecovery. With that said, it was postulated that this autorecovery may vary among individuals. This study design enables us to study these individual differences in temporal responses.

Finally, it was observed that there was a trend in the daily timescale or frequency. Specifically, it was observed that there was an overall trend of increased steps per day over the 6-week intervention period. This third observation was translated into a hypothesized *internalization* process of the knowledge, skills, and practices that the intervention was meant to cultivate. This third dynamic hypothesis is the most critical target for designing an effective JIT intervention. Specifically, the goal is to create a JITAI that would enable a person to develop internalized knowledge, skills, and practices that could be maintained after

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the cessation of the intervention while accounting for the likely diminishing value-to-burden ratio and the need for *recovery* between notifications. This complex, interactive dynamic hypothesis, which postulates 3 different underlying dynamics that interact together, is what is primarily being studied in this experiment. Most critically, it was hypothesized that *internalization*, observed in the form of increases in steps per day in a time series, would take place more often when notifications or interventions were provided using JIT states compared with times when notifications were offered without taking account of JIT states.

System ID Experiment Design via Simulation Studies

With these empirical observations as a foundation, previous behavioral literature was reviewed to (1) look for previous domain knowledge that could be used to guide the understanding of these dynamics and (2) support us in better operationalizing the dynamic expectations we hypothesize to be observed, particularly if interventions could be provided consistently taking account of JIT states. A computational model was developed guided by these empirical observations and building on principles drawn from operant learning and cognitive science, which is described elsewhere [62]. A set of simulations was run to model anticipated responses to receiving PA notifications during positive and negative JIT states. A key focus of the simulation work was to determine whether the models could produce the dynamics observed in *HeartSteps*, described previously, and to guide the anticipated length of time needed to observe a possible overall step per day increase across days when notifications are repeatedly delivered during positive JIT states. In this context, a positive outcome was operationalized as a person taking at least 1000 steps (as a proxy for 10 min) within the 3-hour window after receiving a walking notification. Overall, it was hypothesized that a greater number of positive outcomes when using the full JIT state operationalization (N+O+R) would be observed, with increased overall steps per day occurring across days during those times (accumulative internalization). In contrast, it was hypothesized that a relatively steady steps per day response would occur during times when notifications were sent at random (which was a replication of the original *HeartSteps* study and intentionally did not consider JIT states; thus, it was hypothesized that the random signals would replicate the observations from the original study). A set of additional simulations was run based on the SCT model [61], with the results of the simulation reported elsewhere [59] to further refine our study design.

On the basis of the simulation results from both models, a system ID study was devised that experimentally varied the use of different definitions of JIT states but did so in a way that would enable the study of possible accumulation or degradation of the dynamic effects across days. Specifically, 4 days was set as the minimal length of days needed to observe the effects of successive full JIT rules. It was anticipated that stabilization to degradation of effects would start to occur within 1 day of sending non-JIT notifications based on our simulation studies. With that said, given the highly novel study design and limited robust empirical data to guide this subtle study of dynamics, longer periods were used, particularly for the full JIT state (N+O+R). In other words, the experiment compared decision rules that range from not trying to intervene in a JIT state to trying to intervene in a full JIT state over a sustained period that, based on simulation studies, would be sufficiently long to detect accumulative effects if they occurred.

This resulted in a categorical 4-level design. To construct this categorical 4-level input signal, a pseudorandom binary sequence (PRBS) was used (for full justification and details, see the study by El Mistiri et al [59]). This base signal compares JIT with some form of partial JIT or random (ie, non-JIT) states. To incorporate the exploratory examination of differences between JIT operationalizations, a random multilevel sequence was superimposed over one of the PRBS binary levels to compare the 2 incomplete JIT decision rules (N+O and N+R) with the randomly sent walking notifications [59]. The input signal design parameters for the PRBS were chosen as =3 days, =3.5 days, α_s=2,β_s=2, which was done to cover the frequency range of interest based on the guidelines provided in equation 1. This resulted in a 60-day cycle with n_r=4 shift registers and switching time T_{sw}=4 days (Figure 3). This 60-day cycle enabled the team to (1) study the hypothesized dynamic, positive accumulative effect on steps within 3 hours of notification times, and steps per day when walking notifications were sent during theoretically defined JIT states; (2) compare these dynamics with the hypothesized dynamic degradation across days when walking notifications were delivered during partial or negative JIT states (ie, at random); and (3) as an exploratory aim, study if the dynamics vary across different JIT state operationalizations. In total, 4 cycles of a 60-day PRBS signal were generated to support both estimation and validation of the dynamical models that operationalized the hypothesized dynamics, which results in a 240-day period followed by a final period of full JIT state level to match the full study period (260 d), which was constrained by adaptive step goal cycles (26 d × 10 cycles).

Figure 4 provides a visualization of the spectral power density as it relates to the walking notifications. This visualization provides insights into the degree to which the theorized dynamics will be appropriately excited, enabling the detection of effects if they occur across various frequencies and, thus, the study of the proposed dynamic hypotheses. The results suggest sufficient persistent excitation by the number of harmonics included in the effective frequency range between 0.14 and 0.67 rad per day. This frequency range, determined by the time constant guidelines in equation 1, ensures that the appropriate slow dynamics (ie, low frequencies) and fast dynamics (ie, high frequencies) of the system are captured.

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Figure 3. The designed decision rules signal for the walking notification component of the intervention in the time domain in the JustWalk JITAI study. Each level represents one of the decision rules. The 4 signal levels were obtained by superimposing a 3-level random multilevel sequence (RMLS) signal on the base pseudorandom binary sequence (PRBS) signal. JIT: just-in-time; N+O: need and opportunity; N+R: need and receptivity.

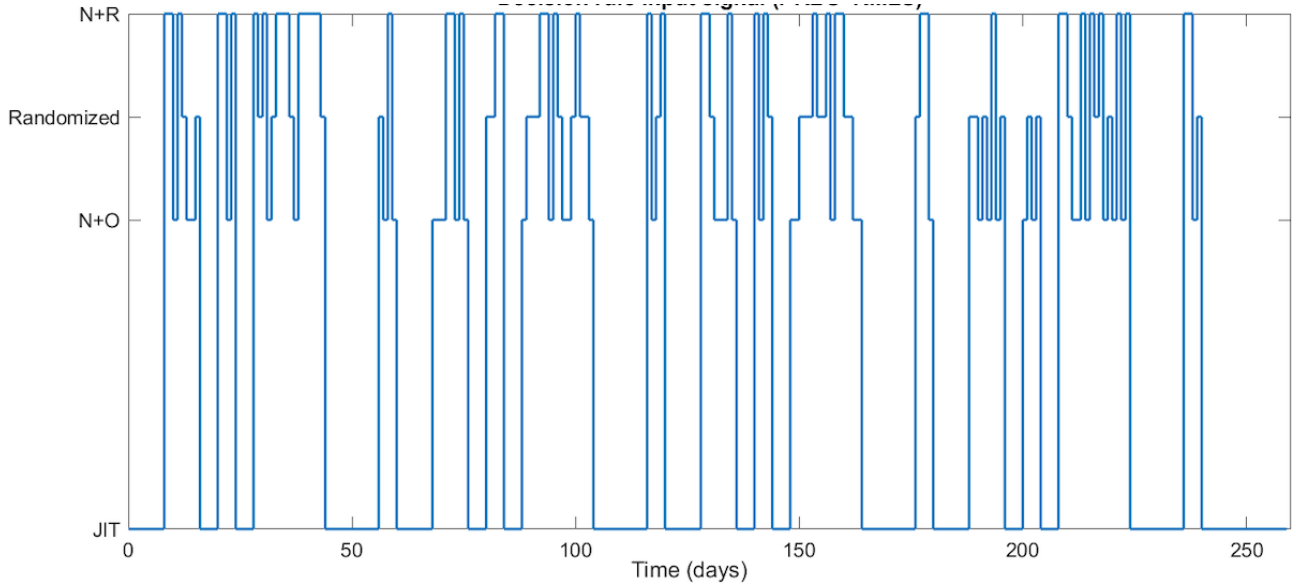
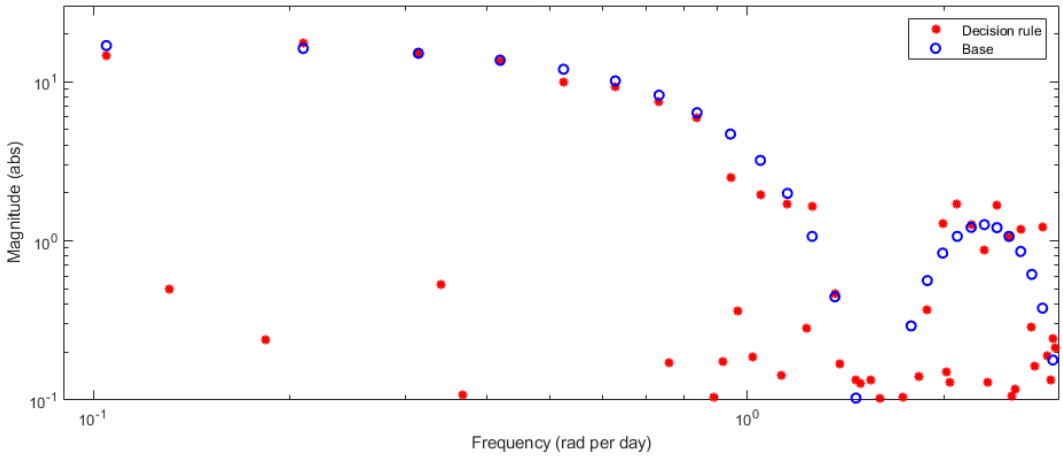


Figure 4. Spectral power density of the designed decision rule input signal of the JustWalk JITAI study. It is shown to determine whether sufficient excitation across key frequencies is established within the trial.



Adaptive Step Goals Intervention Component

Overview

The adaptive daily step goal component follows a similar structure to that of a previous system ID experiment whereby participants were given a specific suggested step goal to target each day [63]. Similar to this previous design, a key consideration is to design a *cycle*, which is a deterministic, repeatable pattern that defines the provision of intervention options to an individual. Intervention options can be provisioned to mimic randomness via pseudorandom signal designs that achieve the valuable properties of randomness for causal inference while still being deterministic and, thus, repeatable. This provides valuable properties for a system ID experiment as it enables a more robust comparison between cycles (for more details, see prior work [38]). In this study, the same basic logic of prior work was followed, specifically, using a pseudorandom signal design that varied step goals between an *achievable* target up to a plausibly *ambitious* target (how goals are assigned each day is described in greater depth in prior work [59]).

The definition of an *achievable* step goal was personalized to each participant, which was labeled as a personalized reference, defined as a person's median steps per day calculated from the previous 26-day cycle period [59]; note that, for the first cycle only, the personal reference was the 10-day-baseline period. Each morning, participants received a notification informing them of their targeted step goal for the day. The updated goal was also available to them on the *JustWalkJITAI* dashboard and was automatically synced by the *JustWalkJITAI* server to the participant's Fitbit account so that the feedback on the Fitbit app and the participant's Fitbit tracker always showed the correct goal progress each day. To further facilitate goal pursuit, participants were instructed to install a watch face providing the step goal number and a goal progress bar to enable always visible goal progress feedback. Fitbit's native visual and haptic feedback was used when the participant completed the daily step goals (ie, fireworks animation and vibrations).

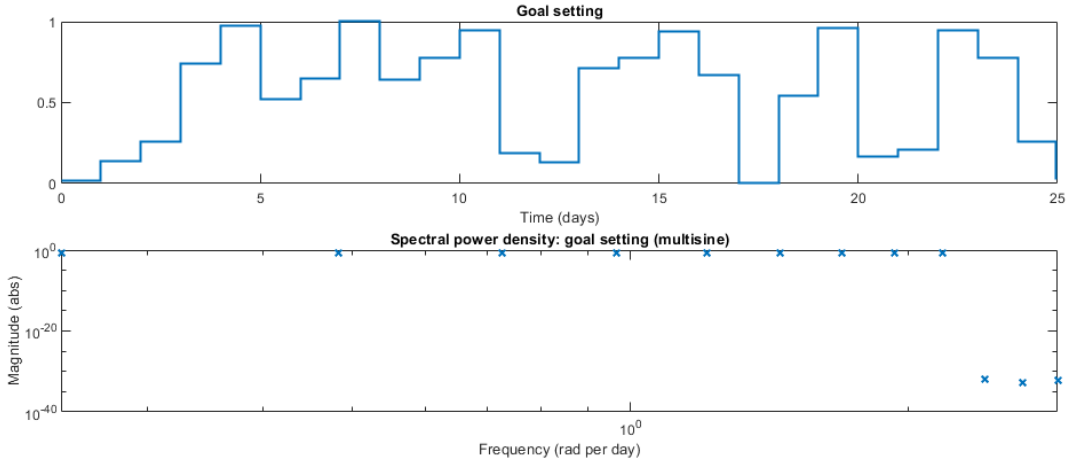
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Experimental Manipulation: Input Signal Design

To define a cycle for this component, a multisine signal was used. The input signal design parameters (=1 day, =2 days, α_s=2,β_s=2), as described in equation 1, were chosen based on the results from previous work and the simulation studies we conducted in preparation for staging this system ID experiment [59]. The design parameters result in a cycle length of 26 days, as shown in Figure 5. For each participant, a personalized realization of the multisine signal generates the daily goals throughout the 260-day intervention across 10 cycles by determining, for each day, the factor by which the 4000 steps per day range is multiplied and then added to the participant's personalized reference (ie, median steps/d), as described in Textbox 1.

The effective frequency range of the signal is related to the design parameters through equation 1, which yields the persistence of excitation between ω_*=0.25 rad per day and ω^*=2 rad per day approximately for the designed multisine signal, as it is highlighted in the power spectrum of the signal shown in Figure 5. This showcases that the designed input signal for goal setting creates variability in the relevant dynamical ranges of interest.

Figure 5. One cycle of the designed multisine input signal for the goal setting component of the JustWalk JITAI intervention in both the time (top) and frequency (bottom) domains. The multiplier factor varies between 0 and 1 over time. The spectral power density plot highlights the number of excited harmonics at the frequencies of interest.



Measures

Baseline Survey

The baseline survey includes (1) demographic information, including age, height, weight, ethnicity, gender, race, marital status, household size, employment status, and level of education; (2) personal characteristics related to the study (ie, how the participants spend their time and information about their routine and their neighborhood); (3) self-perception (ie, personality [64] and perceived stress [65]); and (4) life habits [66] and PA [67] (ie, how they feel about PA, how they engage in exercise, how much they intend to exercise, and how they notice the effects of exercise).

Continuous Measurement of Activity and Heart Rate

Steps per minute and minute-level heart rate were measured using the Fitbit Versa 3, a wrist-worn, consumer-level activity tracker that uses triaxial accelerometry to measure movement. Further details are provided in the next subsection. Moderate or vigorous PA was measured in four ways: (1) automatically triggered objective measurement (the Fitbit Versa 3 automatically detects vigorous movement [68] if the activity is sufficiently vigorous and long), (2) manually initiated objective measurement (the Fitbit Versa 3 or the Fitbit app on the smartphone has an *activity* tab to log activity manually), (3) manual logging in the Fitbit app, and (4) manual logging on the study app using the *activity* tab (which was also populated with any reporting on the Fitbit app). The Fitbit assesses steps, PA intensity levels, energy expenditure, start or end time point and type of activity, distance traveled, and number of floors. Prior work shows that Fitbits likely underestimate heart rates and, by extension, total activity, but they do so reliably, thus establishing a meaningful within-person comparison [69], which is the focus of this study.

EMA Items

Psychological constructs and process variables were asked daily for inclusion in our targeted, dynamic models via EMA conducted at 7 PM local time. The EMA items included concepts of (1) self-efficacy for walking, (2) self-efficacy for problem-solving, (3) positive context for walking, (4) negative context for walking, (5) supportive routine, (6) drive to walk, (7) relationships supportive of walking, (8) interoceptive awareness of cues that could inspire walking (eg, stiffness and fatigue), (9) negative reinforcement of walking, (10) behavioral repertoire, and (11) typical supportiveness for walking. Detailed items are included in Multimedia Appendix 2. Items 1 to 6 were asked daily, items 7 to 10 were asked every 4 days to minimize the burden of responding, and item 11 was asked every day for the first week of each month (ie, 7 times/mo).

In total, 2 other types of EMA question items were sent. Triggered by completed PA, the participants were asked if they felt healthy, fatigued, energized, and discomfort. We also asked if the participants thought that they could meet the daily goal.

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Weather

Daily weather data (current weather and weather forecasts) were gathered from the public weather database API [70]. No actual location GPS data were gathered; instead, a self-reported home zip code was used to gather weather data.

Postintervention Interviews

After the 260-day intervention, participants were asked to fill out a brief postintervention survey and were also given the option to participate in a postintervention interview. During the postintervention interviews, participants were asked about their overall reactions, including both positive and negative aspects of using the app and any suggestions to improve the intervention. The interviews were audio recorded and transcribed.

The participants were also given a choice to either stop the use of the *JustWalk JITAI* intervention or continue to use it, in which case the data past the study end date would not be used in the analyses.

Treatment Fidelity Monitoring Procedures

Mobile App Use Logs

Mobile app use was recorded with time stamps for every page viewed in the *JustWalk JITAI* app, including opening notifications, opening the app, viewing pages within the app, and opening surveys. The one piece of information that could not be logged owing to operating system limitations was whether notifications (eg, walking notifications) were seen without being opened, such as when they automatically expanded on the iOS lock screen.

Monitoring the JustWalk JITAI Systems

The *JustWalk JITAI* server was automatically monitored every 10 minutes throughout the study period using a separate program to check for 5 performance and stability targets: the web server, the database server, the security firewall, the software framework for the server, and the Fitbit API. If the server stopped working or took too long to respond (>3000 ms), the program sent SMS text messages and emails to the study staff. The monitoring program was separately overseen by another program to ensure that monitoring was conducted properly. If any data operations failed (eg, if the Fitbit server was not responding), the study staff were immediately notified via email. If there was an error in the Fitbit data synchronization, when the data connection resumed, all the missing data were refetched to fill up any missing period.

Data Collection Monitoring

Data collection was monitored by the study staff on a weekly basis with automated visualizations to ensure that there were no technical errors that may compromise the study.

Study Adherence

Study adherence was monitored automatically using the *JustWalk JITAI* server. During the preintervention meetings, participants were asked to wear the Fitbit for a minimum of 8 hours a day, but it was suggested that they wear the Fitbit all day, even at night. Fitbit devices typically synchronize with the Fitbit server via the Fitbit phone app every 15 minutes. This synchronization stops if the Fitbit device runs out of battery or is not worn for several days. The *JustWalk JITAI* server regularly checks whether a participant's device has stopped syncing with the Fitbit server, and if so, it sends an adherence SMS text message to the participant.

As an operationalized protocol, at 15 minutes before the first decision point for walking notifications (eg, 6:45 AM local time for most participants), if a participant had no Fitbit app synchronization records for 60 minutes (eg, since 5:45 AM local time for most participants), the server sent an automated adherence SMS text message including an approximate length of the period for which the updates were missed (eg, a few hours, a day, or a while) to invite participants to recharge and synchronize their Fitbit on the Fitbit app.

This approach helped avoid making the mistake of responding too immediately to the problem of data drops caused by accidental battery discharges. As it can be assumed that people do not carry their Fitbit charger around during the day, sending an immediate *charge it now* message when data updates stop during the day is unlikely to be an effective remedy. In addition, given that it only takes approximately 30 minutes to charge a Fitbit from fully depleted to lasting more than a day, it was assumed that sending these reminders before the start of the day would give participants a chance to charge their Fitbit.

Modeling and Data Analysis

A series of system ID estimation approaches will be used to analyze the data and obtain control-oriented dynamical models to study JIT states. General data analysis will start with examining the cross-correlation of the data to verify the hypothesized structure of the system as operationalized via the computational models described previously. Nonparametric estimation methods such as correlational analysis and spectral analysis [71] will be used to obtain preliminary information about the responses of each individual (ie, time constants, gains, and orders). The knowledge gained from the nonparametric estimation methods will be used to obtain ideographic models through prediction error modeling approaches such as autoregressive with external input and output error [71] estimation and more elaborate gray box methods using the SCT model structure. In addition, the model-on-demand [72,73] estimation will be used to estimate more flexible models that address nonlinearities in the system. The estimated models from all approaches will be contrasted with one another, and the advantages or disadvantages of each will be assessed to inform future efforts.

Ethical Considerations

The study was approved by the University of California, San Diego, institutional review board (protocol 800132) and was preregistered on ClinicalTrials.gov (NCT05273437).

Results

Simulations

The input signal design for the 2 intervention components in this study involved an iterative procedure that relied on a priori knowledge and simulation results for different types of

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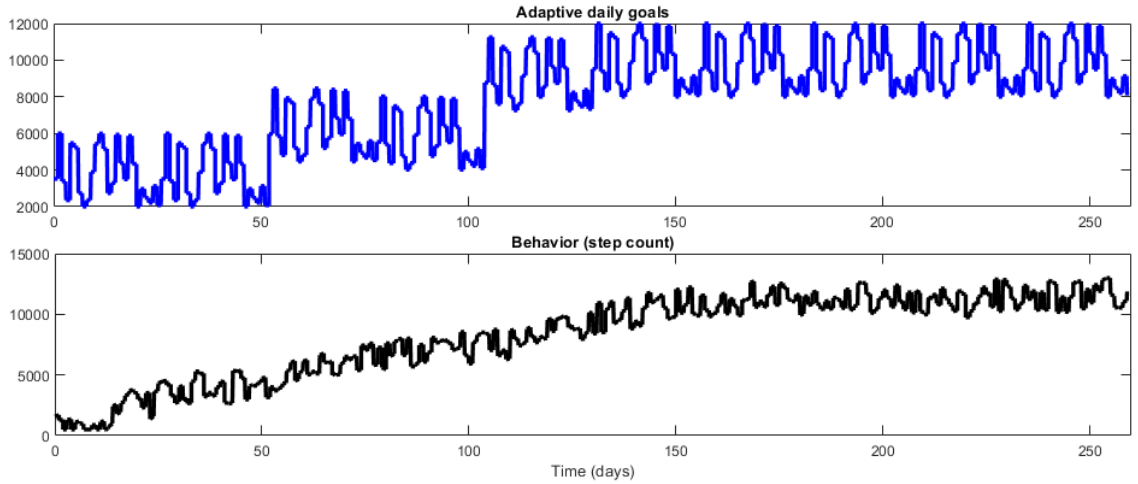
anticipated participants to guide the efforts. The simulations were based on a dynamic SCT model derived from a fluid analogy, which provided the means to guide specific conditions for the JIT states considered in the decision rules to ensure that both the number of notifications sent per day and the overall number of notifications sent throughout the intervention were not burdensome for the participants. Furthermore, the simulation framework with diverse scenarios provided insights into the *ambitious yet achievable* range of adaptive goals provided in each goal setting cycle. A detailed account of the model used in the simulations, technical details of the designed input signals, and simulation results that guided the design are provided in the study by El Mistiri et al [59]. In this section, the results for a hypothetical adherent participant are presented to illustrate the dynamic nature by which the daily goals adapt to the participant's performance, as well as the effectiveness of the JIT decision rules in limiting the provision of support only to times that are hypothesized to be beneficial.

Figure 6 [59] shows the implementation of the designed daily goal signal in a simulation setting. In this case, the goals in each cycle are adjusted to the performance of the participant in the previous cycle, as described in Textbox 1. Note that, in this case, a hypothetical adherent participant is capable of achieving the daily goals given to them in each cycle; consequently, the median of the participant's performance increases, which leads to an increase in the goals provided in subsequent cycles. As a result, the daily goals gradually increase over the span of the intervention, from a low of 2000 steps per day in the first 2 cycles of the intervention (the first 52 d) to a high of 12,000 steps per day in the last 5 cycles. This simulation result illustrates that the input signal design for this component is working as intended by adapting the daily goals to each participant in a personalized manner while nudging the participant toward higher levels of PA through a combination of *ambitious* and *achievable* goals.

Figure 7 [59] shows the walking notification component of the intervention in the simulated scenario for the hypothetical adherent participant. As shown in the figure, the decision rules work as intended in terms of dictating the nature of the notifications sent to the participant. At the beginning of the intervention, when the participant does not achieve the daily goals (hence, the need condition of the decision rules is met), the number of notifications sent to the participant is high across all levels of the decision rules. Later in the intervention, as the participant adopts healthier behaviors and meets the daily goals, the number of walking notifications sent on a daily basis is significantly lower. Furthermore, note that, on days when the receptivity condition is considered, the number of notifications sent follows the notification budget mentioned in Textbox 1.

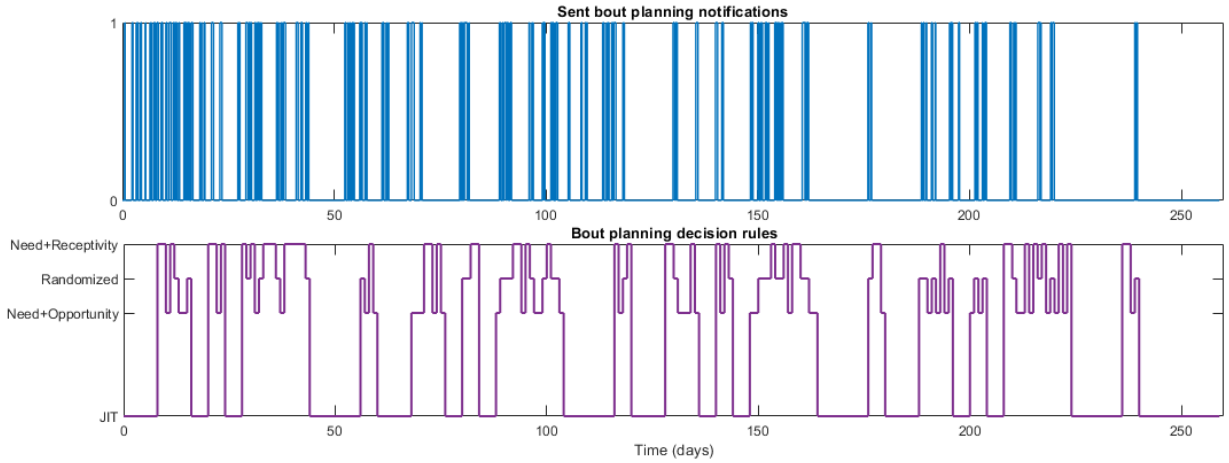
Finally, as the need condition is not met by the participant toward the end of the intervention, walking notifications are only sent on days with fully randomized notifications. This design allows for comparing the impact on the participant of fully randomized notifications with that of notifications that are guided by JIT state conditions that should make them more beneficial. From these simulation results, the rate at which notifications are sent (ie, notifications or decision point) on full JIT state days is the lowest at 0.084, followed by days of need and opportunity (N+O) conditions at 0.148 and need and receptivity (N+R) conditions at 0.176. The highest rate of notifications is observed on days with fully randomized walking notifications at 0.488.

Figure 6. Simulation results illustrating the implementation of adaptive daily goals (top) in reaction to the performance of a hypothetical adherent participant in terms of daily step count (bottom) in the JustWalk JITAI study (adapted from the study by El Mistiri et al [59]).



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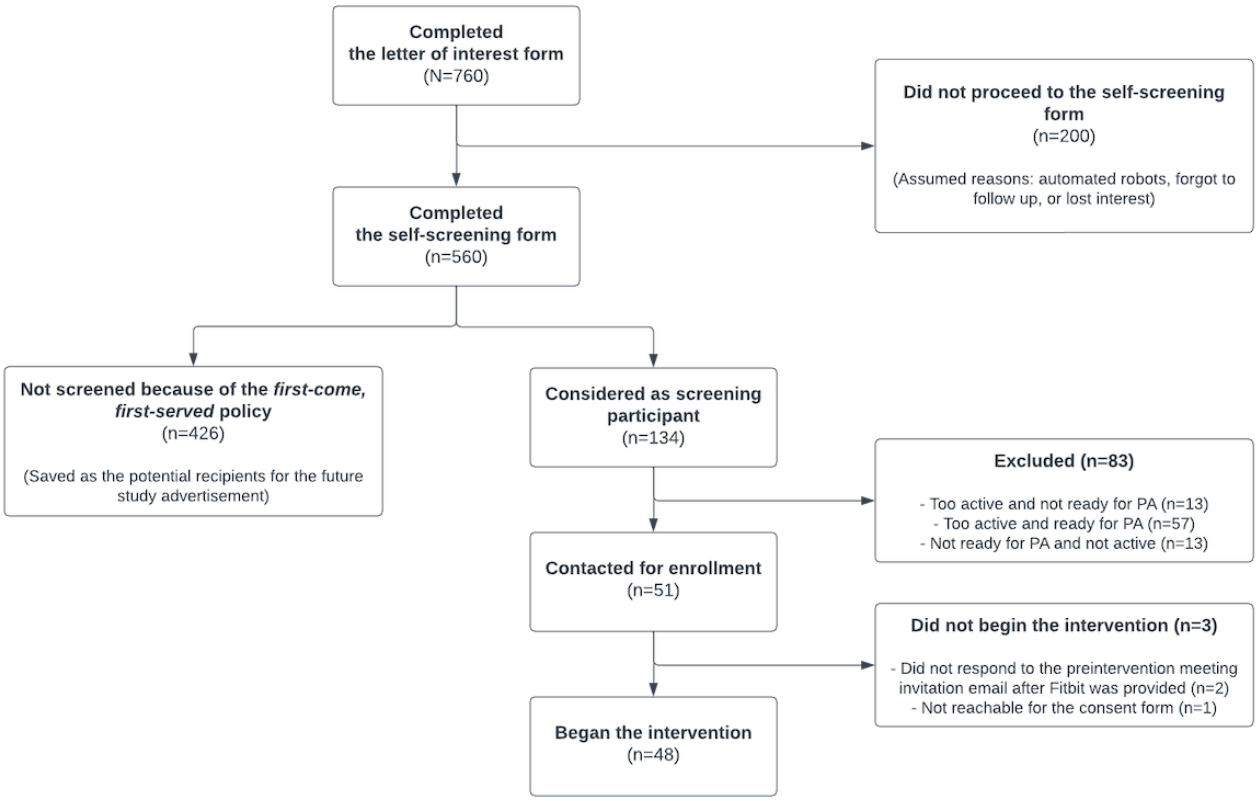
Figure 7. Simulation results for a hypothetical adherent participant illustrating the expected walking notifications (top) sent based on the designed decision rules signal (bottom) of the JustWalk JITAI study. For the sent notifications signal at the top, a 0 value implies that no notifications were sent at that decision point, whereas a value of 1 implies that a notification was sent (adapted from the study by El Mistiri et al [59]). JIT: just-in-time.



Recruitment

Enrollment began in March 2022 and ended in July 2022. In total, 761 potential participants submitted a letter of interest, and 48 (6.3%) were enrolled in the study. Figure 8 shows the CONSORT (Consolidated Standards of Reporting Trials) diagram [74]. The intervention was completed in April 2023. The data were gathered without major incidents. The source code for the server and the app is publicly available on the project's GitHub repository [75].

Figure 8. CONSORT (Consolidated Standards of Reporting Trials) recruitment diagram for the JustWalk JITAI study. PA: physical activity.



Discussion

This is a study protocol to investigate 3 JIT states (ie, need, opportunity, and receptivity) empirically and enable the empirical optimization of a JITAI intended to increase PA (steps/d) in adult populations with an inactive lifestyle.

There is well-documented evidence suggesting that digital health interventions to date have not lived up to their intended potential [76-78]. From issues of poor adherence; results that only produce limited effects; and questionable scalability, particularly among those with less access to digital devices, the potential of digital health interventions has not yet translated to a real-world impact [76,77,79]. A pathway for improving this is to focus on

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producing evidence directly targeting and seeking to improve the fundamental shortcomings of digital health interventions [77,78].

In this study, our primary focus was to rigorously examine the notion of JIT states. To date, JIT states used to formulate intervention decision rules have either been assumed to be correctly defined—typically based on guidance from behavioral theory—but not empirically tested or they have been derived using data-driven approaches such as reinforcement learning whereby previous domain knowledge and understanding is underemphasized and, instead, there is hope that useful insights about intervention timing will emerge from data collected in intervention studies [80]. Although we believe that both of these paths have merit, this study protocol offers a middle ground whereby previous domain knowledge is encapsulated into computational models, which, through simulation studies, can then be used to guide the careful generation of evidence that can test dynamic hypotheses about the nature of JIT states.

This is important as a JIT state, conceptually, is an inherently nonlinear causal phenomenon [81]. There is no one causal factor that makes a given moment a JIT state, but instead, it is a mixture of different factors such as time of day, a person's current motivational levels, their relationships, recent experiences with the types of support given, and the degree to which support is well matched to a person's current needs. Such factors combine at a given moment to influence the decision to engage—or not—in the target behavior. This study protocol recognizes the inherent nonlinear causal nature of the phenomenon under study and provides a rigorous approach to gathering the data needed to make progress in the context of such complexity. By varying whether a notification is provided when the person is thought to be in a state of need, when they are thought to have an opportunity to walk based on their personal historical step data, and when they are thought to be receptive, or combinations of these 3, the experiment will collect initial evidence for which aspects of the JIT state are most important for supporting the effectiveness of JITAIs and whether this changes over time. Using this information, particularly when linked with slow dynamic processes of change (ie, daily goal setting), the experiment produces data needed to empirically optimize a digital health intervention, *JustWalk JITAI*. Specifically, this work will result in individualized, empirically validated dynamical models that can be used to predict each individual's response to the intervention options offered to them. These individualized or idiographic dynamical models can be applied to optimal personalized behavioral interventions through sophisticated control algorithms such as model-predictive control [43,82]. These model-predictive control–driven JITAIs could have the potential to work more effectively than previous digital health interventions.

The key limitations of this study stem from the high novelty of the overall experiment and its approach. To the best of the authors' knowledge, no system ID experiment of this sophistication for studying human behavior has ever been conducted. On the basis of this, there was very little robust previous evidence and examples that we could draw upon to guide study design decisions. Although we did compensate for this by drawing on some relevant data (largely from our own work, as already described) and via a number of simulation studies, overall, there are potential risks and limitations to our approach. For example, given the novelty of this experiment, it is unknown how well the assumptions we used to guide the experiment will hold up. With this, it is unclear exactly how informative those data will be for studying JIT states. Second, given the novelty of this experiment, it was unclear what an appropriate sample size should be. This point is critical for determining the degree to which any patterns or insights gleaned about JIT states from this sample will be transportable to other populations or settings.

With that said, the primary focus of any system ID experiment is the study and articulation of computational models that are predictive and foster robust control decisions for each *system*. In this context, a *system* is a person. This is critical to note because, as flagged previously, the notion of *statistical power* as is used in the classic frequentist inferential statistics used most commonly by health scientists does not have any direct translation or use within system ID experiments. Indeed, the key focus of system ID experiments is to work within each system to gain a deep understanding of its dynamics. This focus makes sense particularly for a concept such as JIT states, which, definitionally, will likely manifest idiosyncratically. The critical question is not whether some general pattern of JIT states can be inferred but, instead, whether the same algorithmic development processes can be conducted ideographically and in a replicable and scalable fashion to enable the insights that the algorithm can produce to guide intervention decision-making. This is the primary focus of our work. Thus, the limitation is less one of *statistical power* and more akin to what arises with regard to the right training data sets for machine learning algorithms. It is unclear at this time what variations across people, places, and time could occur in real-world contexts that would render our approach nonfunctional. With a sample of only 48 participants, a key limitation is that we very likely did not have diversity across variations in people and places where this type of algorithm could be used to test the robustness of our approach. With that said, given the great novelty of our overall approach, we contend that this is an appropriate trade-off. Most critically, it is likely that, even in the sample of 48 participants, we will discover some individuals from whom we can create computational models that are informative and others from whom we cannot. That will be the type of initial data we could use to then develop more rigorous hypotheses about the transportability of our methods, which can then guide future experimentation.

Overall, this work could feasibly be a key step in filling the gap between the hope of digital tools and current realities in terms of limited long-term impact and engagement based on the evidence. Although this is all still quite hypothetical, this trial is a critical step in testing the potential benefits of this overall approach for intervention optimization.

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Data Availability

The study materials and analysis code will be available through a public repository. The data set generated in this study will be available from the corresponding author upon reasonable request and with completion of the data user agreement.

Authors' Contributions

MEM, RK, LG, GC, DER, PK, and EH performed theoretical foundation work and simulations. JP, MK, MEM, RK, DER, PK, and EH developed the intervention. JP and PK developed the technical systems, including the server and mobile app. Patrick Neggie, Rahul D'Costa, and Nick Reid supported the development and operation of the technical systems. JP, MK, RK, and SB conducted recruitment and interviews and worked on the trial logistics (eg, sending out Fitbits). JP and MK monitored the participants, communicated with them if necessary, and executed the adherence protocol. MEM, RK, and DER developed system ID programs. DER, PK, and EH provided guidance at each stage of the study. All authors contributed to the writing of the manuscript.

Conflicts of Interest

JP is an employee of the Ministry of Health and Welfare, Korean National Government. LG is an employee of Lufthansa Industry Solutions.

Multimedia Appendix 1
Walking suggestion notification messages and their classification into 2 categories of messages.
[DOCX File , 19 KB - resprot_v12i1e52161_app1.docx]

Multimedia Appendix 2
Ecological momentary assessment items.
[DOCX File , 17 KB - resprot_v12i1e52161_app2.docx]

Multimedia Appendix 3
National Institutes of Health peer review report.
[PDF File (Adobe PDF File), 183 KB - resprot_v12i1e52161_app3.pdf]

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Abbreviations

API: application programming interface
CONSORT: Consolidated Standards of Reporting Trials
EMA: ecological momentary assessment
JIT: just-in-time
JITAI: just-in-time adaptive intervention
PA: physical activity
PRBS: pseudorandom binary sequence
SCT: social cognitive theory

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Protocol

Ecological Momentary Assessment of Midlife Adults' Daily Stress: Protocol for the Stress Reports in Variable Environments (STRIVE) App Study

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Abstract

Background: Daily stressors are associated with cognitive decline and increased risk of heart disease, depression, and other debilitating chronic illnesses in midlife adults. Daily stressors tend to occur at home or at work and are more frequent in urban versus rural settings. Conversely, spending time in natural environments such as parks or forests, or even viewing nature-themed images in a lab setting, is associated with lower levels of perceived stress and is hypothesized to be a strong stress "buffer," reducing perceived stress even after leaving the natural setting. However, many studies of daily stress have not captured environmental contexts and relied on end-of-day recall instead of in-the-moment data capture. With new technology, these limitations can be addressed to enhance knowledge of the daily stress experience.

Objective: We propose to use our novel custom-built Stress Reports in Variable Environments (STRIVE) ecological momentary assessment mobile phone app to measure the experience of daily stress of midlife adults in free-living conditions. Using our app to capture data in real time will allow us to determine (1) where and when daily stress occurs for midlife adults, (2) whether midlife adults' daily stressors are linked to certain elements of the built and natural environment, and (3) how ecological momentary assessment measurement of daily stress is similar to and different from a modified version of the popular Daily Inventory of Stressful Events measurement tool that captures end-of-day stress reports (used in the Midlife in the United States [MIDUS] survey).

Methods: We will enroll a total of 150 midlife adults living in greater Indianapolis, Indiana, in this study on a rolling basis for 3-week periods. As those in underrepresented minority groups and low-income areas have previously been found to experience greater levels of stress, we will use stratified sampling to ensure that half of our study sample is composed of underrepresented minorities (eg, Black, American Indian, Hispanic, or Native Pacific Islanders) and approximately one-third of our sample falls within low-, middle-, and high-income brackets.

Results: This project is funded by the National Institute on Aging from December 2022 to November 2024. Participant enrollment began in August 2023 and is expected to finish in July 2024. Data will be spatiotemporally analyzed to determine where and when stress occurs for midlife adults. Pictures of stressful environments will be qualitatively analyzed to determine the common

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elements of stressful environments. Data collected by the STRIVE app will be compared with retrospective Daily Inventory of Stressful Events data.

Conclusions: Completing this study will expand our understanding of midlife adults' experience of stress in free-living conditions and pave the way for data-driven individual and community-based intervention designs to promote health and well-being in midlife adults.

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KEYWORDS

activity trackers; built environment; ecological momentary assessment; heart rate monitoring; life stress; physical activity; spatial analysis; wearable technology

Introduction

Daily stressors are associated with cognitive decline and increased risk of heart disease, depression, and other debilitating chronic illnesses for midlife adults [1-5]. Daily stressors tend to occur at home or at work and are more frequent in urban versus rural settings [6-8]. Conversely, spending time in natural environments such as parks or forests, or even viewing nature-themed images in a lab setting, is associated with lower levels of perceived stress and is hypothesized to be a strong stress "buffer," reducing perceived stress even after leaving the natural setting [9-12]. The role that natural environments can play in reducing stress arousal is particularly important when considering that neighborhoods with high poverty rates and higher proportions of racial or ethnic minorities have less access to green space and higher exposure to stressful elements such as abandoned buildings and crime [13-15]. However, many studies of daily stress have not captured environmental contexts and relied on end-of-day recall instead of in-the-moment data capture. With new technology, these limitations can be addressed to enhance knowledge of the daily stress experience [16].

In the United States, midlife adults are staying in the workforce longer and are engaging in higher levels of physical activity than previous generations, potentially extending their interactions with elements of the built and natural environments that influence their experience of daily stress [17,18]. Recent evidence has revealed that age-related linear increases in perceptions of well-being observed during past periods of economic prosperity have not continued during more recent, less economically prosperous times [19]. The seismic and unpredictable economic and social changes brought about by the COVID-19 pandemic have greatly altered the experience of daily stressors in the built and natural environment, a trend that is likely to continue well into the future [20].

In the midlife adult population, stress (or the lack thereof) plays an important role in the aging process. The relationship between various types of stress and alterations in cognitive functioning has been well documented, and there is growing evidence showing a relationship between daily stress in midlife and cognitive decline [2,3,21]. Perceived stress in midlife adults has also been closely linked with physical disability later in life [22,23]. A growing body of research has also found that perceived stress, particularly in the workplace, is closely related to heart disease [24]. Furthermore, while individual health and wellness in midlife is no doubt important, longitudinal studies have shown that the health and wellness of midlife adults is also pivotal to others in their workplace, society in general, and in the lives of those in younger and older generations who often are socioeconomically dependent on midlife family members [25].

Midlife adults of different socioeconomic statuses and races are subject to structural inequality in their living environments. Those living in urban environments with higher levels of poverty and violence experience higher levels of environmental stress than those living in suburban or rural environments [15]. In particular, it is well documented that underrepresented minorities are exposed to environmental stressors more than nonunderrepresented minorities [26,27]. One explanation for racial differences in exposure to stressors is residential segregation, resulting in a predisposition for low-income minorities' exposure to environmental stressors such as traumatic events, urban decay, and poverty [28]. Minority and low-income midlife adults' exposure to environmental stressors has been linked to unhealthy behaviors like cigarette smoking [29], as well as myriad negative health outcomes [30].

In response to this research gap, we propose to use our novel custom-built Stress Reports in Variable Environments (STRIVE) ecological momentary assessment (EMA) mobile phone app to measure the experience of daily stress of midlife adults in free-living conditions. Using our app to capture data in real time will allow us to determine (1) where and when daily stress occurs for midlife adults, (2) whether midlife adults' daily stressors are linked to certain elements of the built and natural environment, and (3) how EMA measurement of daily stress is similar to and different from a modified version of the popular Daily Inventory of Stressful Events (DISE) measurement tool that captures end-of-day stress reports (used in the Midlife in the United States [MIDUS] survey) [31].

Completing this study will expand our understanding of mid-life adults' experience of stress in free-living conditions and pave the way for data-driven individual and community-based intervention designs to promote health and well-being in midlife adults. Potential interventions that could stem from our data include technology-based "just-in-time" interventions that account for spatiotemporal location, mindfulness-based interventions that incorporate environmental stress triggers, and community-based interventions designed to eliminate

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environmental stressors that are commonly experienced by midlife adults (eg, congested areas).

Methods

Overview

In this stage 0 (of the NIH Stage Model for behavioral intervention development) study, we propose an interdisciplinary mixed method approach to examine the occurrence of daily stressors in the moment they occur for midlife adults in the built and natural environment using mobile and wearable technology. A total of 150 midlife adults will be enrolled in this study on a rolling basis for 3-week periods. Participants will meet with a researcher in person at the start and end of their 3-week study period. They will be provided with a smartphone preloaded with the STRIVE app and a Polar Unite smartwatch. They will be instructed to carry the phone and wear the watch for the 3-week duration of the study. Each enrolled participant will use one or more daily stress measurement tools in any given week, randomized to account for participant priming. In 1 week of participation, participants will complete the DISE by the Research Electronic Data Capture (REDCap; Vanderbilt University) survey every evening. In another week of participation, participants will use the STRIVE app to report daily stressors in real time and complete the DISE every evening. In another week of participation, participants will only report stressors in real time through the STRIVE app. Automated SMS text messages will be sent to participants each day to remind them of what they need to do to remain active in the study and provide survey links when needed.

Participants will be recruited from the greater Indianapolis area in Indiana. As those in underrepresented minority groups and low-income areas have previously been found to experience greater levels of stress, we will use stratified sampling to obtain a sample that is racially and socioeconomically diverse (Table 1). Income levels are defined as the bottom, middle, and top third of household incomes based on 2020 US Census percentiles (low income: <US $39,535; middle income: US $39,535-$85,076; high income: >US $85,076) [32]. Participants will be recruited with the assistance of the Indiana Clinical and Translational Sciences Institute recruitment concierge services and their community partnerships. Recruitment materials will be posted on community-based social media pages, on paper flyers in public community spaces, and through all communication channels operated by community health partners.

Table 1. Study sample stratified by race and household income (N=150).

Race	Low income, n (%)	Middle income, n (%)	High income, n (%)
Black, American Indian, Hispanic, Native Pacific Islanders	25 (16.6)	25 (16.6)	25 (16.6)
White or Asian	25 (16.6)	25 (16.6)	25 (16.6)

Measurement of Stress With the STRIVE App

Study participants will be asked to carry the researcher's provided Android mobile phone with them at all times. The STRIVE app passively records the participant's GPS coordinates every 60 seconds throughout the data collection period (Table 2). Research participants are informed that their location is being tracked by the app. When participants experience a daily stressor, they are asked to open the app and provide a rating of their stress level, a description of the stressor, their preferred coping strategy, and optionally take a photograph of the environment where they experienced stress (Figure 1). Data input is kept to a minimum to reduce participant burden and burnout [33].

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Table 2. All study measures.

Measurement tools	Measure
Pretest survey	
CDC[a] Healthy Days [34]	• Overall health
Godin Leisure-Time Exercise Questionnaire [35]	• Physical activity level
Portion of Behavioral Risk Factor Surveillance (BRFSS) [36]	• Substance use and abuse
Social Provisions Scale [37]	• Social support
UCLA[b] Loneliness Scale [38]	• Loneliness
Patient Health Questionnaire-9 (PHQ-9) [39]	• Depressive symptoms
Adverse Childhood Events Scale (ACES) [40]	• Early life stress
Economic Strain Model [41]	• Financial strain
Neighborhood Disorder Scale [42]	• Neighborhood safety
Real time measurements (all time-stamped)[c]	
STRIVE[d] app	• Per 60 second GPS coordinates (continuous) • Self-reported stress level (7-point scale) • Self-reported stressor (text-based) • Self-reported coping response (text-based) • Photo of stressful environment (JPEG)
Polar Unite Smartwatch	• Heart rate (continuous) • Activity level (continuous)
End-of-day recall DISE[e] measurements[c]	• Self-reported overall stress level (7-point scale) • Self-reported stressor type • Self-reported stress level by stressor (7-point scale) • Self-reported date

[a]CDC: Centers for Disease Control and Prevention.

[b]UCLA: University of California, Los Angeles.

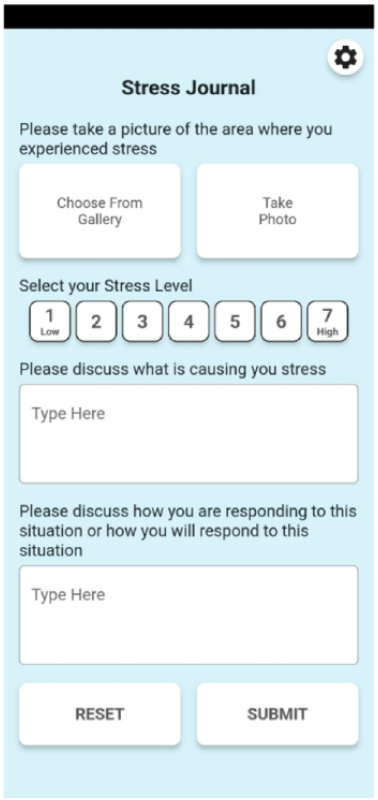
[c]Additional measurements include demographics and health history.

[d]STRIVE: Stress Reports in Variable Environments.

[e]DISE: Daily Inventory of Stressful Events.

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Figure 1. The Stress Reports in Variable Environments (STRIVE) app.



We have created a protocol to promote the safety of research participants during their reporting of daily stressors with the STRIVE app. If they cognitively appraise themselves as stressed and are in a situation in which it is unsafe to use their phones (eg, driving a car), they are asked to proceed to the nearest safe location before recording their experience. Participants will be asked to indicate when and where the stressor occurred if they are not reporting from the location in which the stress occurred in their later description of it. Many people go through a day without experiencing a stressor [43]; for days when this is the case, participants will be asked to indicate on their app that they had not experienced stress but were still actively participating in the study.

Measurement of Stress With the Modified DISE Tool

The DISE is recommended by the National Institute on Aging funded Stress Measurement Network for daily stress measurement. A modified version of the DISE will be administered through the REDCap survey each evening for 2 weeks of the study period. The modified version of the DISE includes questions about the number of times participants felt stressed over the course of the day, their overall stress level, and questions about specific stressor categories (eg, had an argument and had work stress) and how stressful each of those experiences was for the participant. The DISE was modified to allow for direct comparisons between STRIVE and DISE.

Geospatial Analysis

We will fit spatiotemporal regression models to determine the impact of specific elements of the built and natural environment on daily stressors. Given the nature of our spatially dependent data, traditional regression-based approaches (eg, Poisson or negative binomial regression) violate the independence assumption required for generalized linear models. Ignoring the dependence of spatial data can underestimate standard errors, resulting in overly narrow confidence interval estimates and, consequently, incorrect statistical inference [44]. Thus, we will use spatiotemporal models that can simultaneously account for dependence (autocorrelation) in geospatial locations and temporal measurements. We will do this using Integrated Nested Laplace Approximation (INLA) models. Specifically, we will fit zero-inflated negative binomial INLA models, as these models can account for the many instances where stress experiences are not recorded (zero inflation) while still adjusting for the spatial and temporal autocorrelation of each measurement [45,46]. Importantly, the INLA modeling approach is robust as it can incorporate individual-level characteristics and group-level (ie, neighborhood) characteristics while adjusting for the spatial and temporal autocorrelation [47]. INLA uses a Bayesian paradigm, can fit offsets for any necessary weightings (eg, population size or number of measurements), is able to handle both point process (ie, singular latitude and longitude locations) and irregular lattice data (ie, polygons of parks and census tracts), and can analyze the individual impact of temporal, spatial, and spatiotemporal effects [46]. Through this analysis, we can identify the magnitude, direction, and impact of participant attributes (including data collected through the pretest survey and real-time collection of heart rate and activity level data from the Polar Unite watch), neighborhood features, and location characteristics on daily stressors.

Qualitative Analysis of Reported Stressors

We will conduct an analysis of data reported through the STRIVE app in a 2-step process including open and axial coding [48]. Open coding will be conducted twice: first to code stressors into stressor types and second to code mentions of elements of

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the built and natural environment that played a role in the stressful experience. This open coding process will be conducted on qualitative responses to the question, "Please discuss what is causing you stress." In this open coding process, researchers will be versed in previous research categorizing daily stressors to identify themes in the data that may overlap with commonly experienced daily stressors identified in previous research [49]. Any new themes that emerge will be given new names and detailed descriptions. In the second axial coding step, researchers will analyze stressor and environmental characteristic themes to look for those that may be related to identify linkages, creating meta-categories for daily stressors that may be similar in nature. Then, the open and axial coding processes will be conducted on participant photographs that accompany stressor reports. Characteristics of the environment in which stress occurs will be coded for each participant photograph, allowing for triangulation among themes generated by text-based responses and participant photographs**.** This data triangulation will allow us to understand how daily stressors are related to specific elements of the built and natural environment.

Comparison of STRIVE and DISE Stressor Data

We will compare the number of stressors reported, the type of stressors reported, and the subjective severity of stressors reported by the same individual using the DISE and STRIVE app across 3 time periods. The 3 time periods are designed to differentiate between stand-alone use of each instrument and concurrent use of both instruments, as there is potential for these instruments to be complementary in terms of the scope and depth of data captured. Thematic coding of stressors reported through the DISE and STRIVE app will be conducted to allow for comparison between the two. All stressors will be coded into 7 categories specified by the DISE to retain consistency. Stressful events are categorized into 1 of 7 broad classifications organized by interpersonal tensions, work or education, home, finances, health or accident, network, and miscellaneous. As the unit of analysis of the DISE is the "day," we will conduct a repeated measures ANOVA to compare the number of stressors reported per day, the average subjective severity of stressors per day, and the type of stressors reported per day across the 3 modes of daily stress reporting, including an interaction of group (STRIVE or DISE) and mode (using only one or both together) to test if there is any effect on the reported stressors by use. A factor will also be included for the order receiving the conditions to account for carryover effects. Models will also be adjusted by demographic variables.

Ethics Approval

This study has been approved by the Indiana University Institutional Review Board (study number 1910712088). Informed consent has been and will be obtained from all research participants. A special document outlining when and where it is appropriate and safe to take photographs of stressful environments will be provided to all research participants, with a focus on protecting the privacy of others. Further, a document highlighting that study participants are not to report stressors in dangerous situations (eg, while driving a car) will be provided. Although we will make efforts to deidentify study data as much as possible, certain elements of data collected (eg, pictures and GPS coordinates) could be used to identify participants. Participants are informed of this risk and may choose not to report stressors or take pictures in situations where they are concerned about their confidentiality. Each study participant will be paid US $150 for their participation in the study.

Results

This study will take approximately 24 months to complete and will take place between December 2022 and November 2024. Enrollment began in August 2023 and is expected to be completed by July 2024. We expect the following study findings:

1. A better understanding of where and when stressors occur for midlife adults in free-living conditions. We hypothesize that the quantity of stressors reported, type of stressors reported, and subjective severity of stressors reported by midlife adults will differ by location (eg, at home vs at a park) and time (eg, morning vs evening) throughout the built and natural environment.
2. An understanding of specific elements of the built and natural environment that contribute to midlife adults' daily stress. We hypothesize that distinct environmental characteristics (eg, abandoned buildings) will emerge as contributors to stress through the qualitative analysis of stressor descriptions and pictures of stressful environments.
3. An understanding of how the STRIVE-based EMA of daily stress is supplementary or complementary to the DISE. We hypothesize that, when reporting through the STRIVE app compared with when reporting through the DISE, midlife adults will report a greater number of daily stressors, a lower average stressor severity, and different types of stressors.

Throughout the study, we will present our research findings at relevant academic or professional conferences and publish peer-reviewed papers. We will also share our study findings with partner governmental organizations and nongovernmental organizations in the state of Indiana. These organizations will likely find our data useful for future community planning.

Discussion

Daily stress contributes to myriad negative health outcomes. Midlife adults are staying in the workforce longer than previous generations and are likely subject to greater environmental stressors than in the past. Technological advances, including smartphones and wearable technology, allow us to measure stress in situ, painting a clearer picture of how stress is experienced in real time. Our custom-built STRIVE EMA app allows us to reduce recall bias and geospatially locate stressors while simultaneously collecting health data (eg, heart rate, sleep, and physical activity), allowing for a clear picture of the role the built and natural environment play in the daily stress of midlife adults.

Completing this study will expand our understanding of midlife adults' experience of stress in free-living conditions and pave the way for data-driven individual and community-based

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intervention designs to promote health and well-being in midlife adults: (1) technology-based "just-in-time" therapeutic interventions that account for spatiotemporal location, (2) mindfulness-based interventions that incorporate environmental stress triggers and stimuli, and (3) community-based interventions designed to eliminate environmental stressors that are commonly experienced by many midlife adults (eg, abandoned buildings, areas that often become crowded or congested, or other yet undiscovered stressful elements of the environment).

Acknowledgments

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Data Availability

The data sets generated or analyzed during this study will be available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review report from the Community Influences on Health Behavior Study Section, Healthcare Delivery and Methodologies Integrated Review Group, CENTER FOR SCIENTIFIC REVIEW (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 151 KB - resprot_v12i1e51845_app1.pdf]

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Abbreviations

DISE: Daily Inventory of Stressful Events
EMA: ecological momentary assessment
INLA: Integrated Nested Laplace Approximation
MIDUS: Midlife in the United States
REDCap: Research Electronic Data Capture
STRIVE: Stress Reports in Variable Environments

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Protocol

The Mood, Mother and Child Study: Protocol for a Prospective Longitudinal Study and Randomized Controlled Trial

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Abstract

Background: Perinatal depression affects >400,000 mother-child dyads in the United States every year and is associated with numerous adverse maternal and child developmental outcomes. Previous research implicates the dysregulation of oxytocin and the hypothalamic-pituitary-adrenal (HPA) axis functioning in mothers and children as potential mechanisms mediating or moderating the transmission of risk associated with maternal depression.

Objective: The Mood, Mother and Child study will examine the psychobiological sources of risk and resilience within mother-child dyads affected by maternal depression. This manuscript describes (1) the study rationale and aims, (2) the research design and procedures and how they were altered in response to the COVID-19 pandemic, and (3) the data analysis plan to test the study hypotheses.

Methods: This is a prospective longitudinal study with an embedded randomized controlled trial that examines (1) correlations among postpartum depression and anxiety symptoms, maternal and child oxytocin and HPA axis functioning, and child developmental outcomes and (2) the causal relationship between exogenous oxytocin and HPA reactivity. This study is funded by the National Institute of Child Health and Human Development with institutional review board approval.

Results: Recruitment and data collection have commenced, and the expected results will be available in 2024. Analyses are presented for testing the proposed hypotheses.

Conclusions: The unique combination of a prospective longitudinal research design with an embedded randomized controlled trial will allow the Mood, Mother and Child study to apply a developmental lens to the study of maternal depression and anxiety symptoms from birth to middle childhood and the psychobiological mechanisms promoting risk and resiliency for both mother and child outcomes. This will be the first study that simultaneously evaluates (1) the role of oxytocin using multiple methodologies, (2) the causal relationships between exogenous oxytocin and HPA axis functioning among mothers with differing levels of depression and anxiety symptoms, and (3) the multiple mediating and moderating roles of parenting behaviors and maternal and child psychobiological characteristics. The goals of these aims are to provide insights into the psychobiological effects of oxytocin in women and inform future clinical trials to treat perinatal mood disorders.

Trial Registration: ClinicalTrials.gov NCT03593473; https://classic.clinicaltrials.gov/ct2/show/NCT03593473

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KEYWORDS

maternal depression; oxytocin; hypothalamic-pituitary-adrenal axis; HPA axis; parenting; executive functioning; socioemotional development

Introduction

Background and Study Design Considerations

Overview

Perinatal depression (PND) is a common, morbid condition affecting >400,000 mother-child dyads in the United States each year [1]. In addition to the direct effect of PND on mothers' health and well-being, it presents challenges for early child development, including reduced maternal sensitive caregiving [2]; impaired parent-child attachment relationships; and compromised child emotion regulation abilities [3,4], socioemotional development [5,6], and executive functioning (EF) [7,8]. These effects may occur even when mothers receive medication or psychotherapy for depressed mood [9], and they may extend well into adolescence and early adulthood [10,11]. Research has implicated the dysregulation of the oxytocin system [12] and the hypothalamic-pituitary-adrenal (HPA) axis [13] in the context of maternal depression as potential contributors to individual and parent-child relational dysfunction that increases the risk of nonoptimal child outcomes. The Mood, Mother and Child (MMC) study (funded by the National Institutes of Health; grant R01HD093901; grant review provided in Multimedia Appendix 1) addresses specific aims regarding the complex roles oxytocin functioning plays within the mother-child dyad, including the role of maternal oxytocin and HPA axis functioning as predictors of postpartum depression and anxiety symptoms (PDAS) and parenting behaviors and the role of child oxytocin functioning as both an outcome, mediator, and moderator of exposure to maternal depression and maladaptive parenting behaviors. This paper provides a brief synopsis of these goals and a detailed description of the MMC study protocol.

Both the severity and chronicity of maternal depression are associated with child developmental outcomes [14,15], and this association is (in part) mediated by dysregulated dyadic interactions between mother and child [16]. Symptomatic mothers are more likely to display withdrawn or intrusive behaviors when interacting with their infants in the first postpartum year [17,18], and these associations persist through early childhood, with the lowest levels of sensitive caregiving observed among mothers with chronic depression [19,20]. Building on previous research demonstrating the developmental risk associated with exposure to maternal depression, the MMC study will examine PDAS and associated parenting behaviors across early childhood as predictors of a variety of biopsychosocial outcomes in middle childhood, including EF, general cognitive development, and socioemotional adjustment. However, far less is known about the biopsychosocial processes underlying the manifestation of depressive symptoms in mothers and the transmission of risk in offspring. To address this gap, the MMC study will examine the roles of maternal and child oxytocin functioning, heart rate variability (HRV), and HPA axis functioning as potential sources of psychobiological risk and resilience.

Maternal Oxytocin Functioning, Depression, and Parenting

A subset of systems contributing to the biopsychosocial process underlying experiences of PND may include oxytocin and its effects on HPA functioning. Research suggests that PND is associated with dysregulation of the HPA axis [21] and that this association may (in part) be driven by dysregulated oxytocin functioning [22]. Previous studies on this topic—including research by the authors of this paper—have been mixed, including research demonstrating (1) no association between oxytocin during breastfeeding and PND [23], (2) an inverse association between oxytocin during breastfeeding and maternal symptoms of depression and anxiety at 2 months post partum [12], and (3) that oxytocin levels differentially predicted HPA axis reactivity in women with or without mood symptoms [13]. There are also candidate gene studies reporting correlations between oxytocin-related genetic variants and maternal depression [24] as well as oxytocin-related variants that predict developmental risk factors associated with maternal depression, such as stress reactivity [25,26], empathetic functioning [27], and parenting behaviors [28-30]. In addition, there is mixed evidence that exogenous administration of oxytocin can alter parenting behaviors [31-33] (for a systematic review, see the study by Szymanska et al [34]), although we are unaware of studies examining oxytocin administration and depressive symptoms. Furthermore, research on oxytocin and the psychobiology of PND has largely been conducted on mothers of infants and toddlers, with little empiricism on these topics in subsequent years of development. The MMC study will examine oxytocin functioning, oxytocin-related genetic variants, and HPA axis functioning as predictors of PDAS and parenting behaviors. This will be done using both a passive longitudinal design and a placebo-blinded trial examining the effects of exogenous administration of oxytocin on HPA axis functioning for mothers with and without depression diagnoses.

Child Oxytocin Functioning as a Potential Moderator and Mediator of PND

There is mixed evidence from candidate gene studies of oxytocin-related genetic variants functioning as moderators of the associations between adverse developmental exposures and subsequent child outcomes. For example, oxytocin receptor (OXTR) rs53576 G allele carriers who had experienced childhood maltreatment reported more depressive symptomatology compared with AA homozygotes, suggesting that the G allele confers increased vulnerability to stressors [35]; however, contradictory findings have reported that A allele carriage increased intergenerational transmission of maternal depression to child depressive symptomatology [36]. Meanwhile, a study of OXTR rs2254298 suggested that carriers of the A allele have increased developmental risk of anxiety and depression in the context of exposure to early-life adversity

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[37,38]. Finally, several studies indicate that these associations may vary by child sex [39,40] in the form of both sex-specific diathesis-stress and differential susceptibility models of gene × environment interaction. The MMC study will examine oxytocin-related candidate genes (as well as child sex) as potential moderators of child exposure to PDAS and maternal parenting behaviors with respect to a variety of outcomes in middle childhood, including EF and socioemotional adjustment.

In addition to the genetic-based moderation of exposure to PDAS and parenting behavior, there is evidence suggesting that epigenetic alterations in children's oxytocin-related gene systems may mediate the associations between these exposures and child outcomes. Exposure to maternal depression is associated with differences in glucocorticoid receptor (NR3C1) methylation, which are thought to mediate associations between early-life adversity and subsequent psychopathology [41-45]. Furthermore, a recent genome-wide methylation study of children aged 1 year of mothers with or without major depressive disorder found differences across the epigenome [46]. It is also possible that the association between PDAS, maternal sensitivity, and child changes in epigenetic form may vary by child sex with respect to oxytocin functioning. Although speculative, research suggests that circulating oxytocin levels are comparable across boys and girls during the first 5 years of life [47,48]; however, oxytocin responsiveness to stress is significantly greater for girls who have a history of parental maltreatment as compared with girls without maltreatment or boys in either condition [49]. This alteration in functioning in girls may be a product of epigenetic changes in response to an extreme and maladaptive environment that accelerates reproductive development and individual fitness in the context of a dangerous environment; as such, if female individuals are genetically more sensitive to such environments, it is possible that markers of epigenetic change will be stronger for girls than for boys even at the age of 5 years. The MMC study will examine oxytocin-related changes in the epigenome from early infancy to middle childhood as potential mediators of associations between exposure to PDAS and parenting behavior and developmental outcomes, as well as the potential moderation of this pathway by child sex.

MMC Study Aims and Hypotheses

The MMC study will address 3 specific aims. The first aim is to examine the role of oxytocin in the prediction of PDAS and other biopsychosocial maternal outcomes (eg, stress reactivity and parenting behaviors)—and specifically to examine the causal relationships between exogenous oxytocin and HPA reactivity. The following three hypotheses will be addressed as part of aim 1: (1) more severe PDAS will be associated with oxytocin and HPA axis dysregulation in correlational analyses, and causal relationships between oxytocin activity and HPA axis reactivity will be evidenced through a placebo-blinded trial of intranasal oxytocin effects on serum cortisol levels in response to a social challenge (hypothesis 1a); (2) genetic variation in maternal oxytocin-associated pathways will predict PDAS severity (hypothesis 1b); and (3) genetic variation will moderate associations among depression and anxiety symptoms, maternal oxytocin and HPA axis physiology, and parenting behaviors (hypothesis 1c).

The second aim is to examine the associations between PDAS and child biopsychosocial outcomes (eg, child epigenetics, EF, and cognitive and socioemotional development). The following four hypotheses will be addressed as part of aim 2: (1) more severe PDAS will predict more adverse child biopsychosocial outcomes during early elementary school years (hypothesis 2a); (2) high stress reactivity and maladaptive parenting behaviors will mediate associations between more severe PDAS experienced during the first year post partum and adverse child biopsychosocial outcomes in years 5 to 7 (hypothesis 2b); (3) the direct and indirect effects of PDAS on externalizing behaviors at ages 5 to 7 years will be stronger for boys, the direct and indirect effects of PDAS on internalizing behaviors at ages 5 to 7 years will be stronger for girls, and the direct and indirect effects of PDAS on early elementary cognitive outcomes will be comparable across boys and girls (hypothesis 2c); and (4) the effects of PDAS on early childhood outcomes will persist even after accounting for concurrent maternal depression and anxiety symptoms (hypothesis 2d).

The third aim is to examine the associations from the previous aim as moderated by child oxytocin-related genotype and mediated by child oxytocin-related epigenetic changes over time. The following five hypotheses will be addressed as part of aim 3: (1) child genetic variation in oxytocin-associated pathways will moderate the associations between PDAS and child biopsychosocial outcomes (hypothesis 3a); (2) child genetic variation in oxytocin-associated pathways will moderate the associations between maternal parenting behaviors and child biopsychosocial outcomes (hypothesis 3b); (3) child sex will moderate relationships among child oxytocin genetic variation, PDAS, parenting behaviors, and child biopsychosocial outcomes (hypothesis 3c); (4) child epigenetic changes underlying oxytocin functioning between the ages of 2 months and 5 years will mediate the associations between PDAS exposure and parenting behaviors and child biopsychosocial outcomes (hypothesis 3d); and (5) the associations between PDAS or parenting behaviors and child epigenetic changes will be stronger for girls than for boys (hypothesis 3e [exploratory hypothesis]).

Methods

Overview

The MMC study recruits mother-child dyads who previously participated in the Mood, Mother and Infant (MMI) study [50]. Although MMC study data collection focuses on mothers and children during the middle childhood period (age of approximately 6 y), using this existing sample will provide for longitudinal analyses spanning from the prenatal period to the current age of the child. Participation involves completing 2 laboratory-based data collection visits along with web-based surveys completed outside the visit (typically at home before the final visit). The first visit involves data collection using a double-blinded randomized experimental design and involves only the biological mother. During this visit, nonpregnant mothers are randomized to either the nasal oxytocin or placebo condition (based on a randomization table created using a random number generator from the University of North Carolina

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at Chapel Hill investigational drug service). The second laboratory visit involves data collection with mothers and children for the purpose of hypothesis testing within the passive longitudinal design.

Data collection began on February 7, 2019, and was scheduled to continue until the spring of 2022. However, data collection was interrupted by the COVID-19 pandemic. On March 14, 2020, data collection was halted entirely and did not resume until August 25, 2020, at which point an adapted protocol was implemented for the safety of participant families and research staff. On April 21, 2021, the original protocol was largely reinstated and will be implemented until the completion of the project (participants continued to wear masks beyond this date, and the order of the child data collection protocol remained the same as during the pandemic). Descriptions of the data collection protocols for the pre– and post–COVID-19 periods and the protocol during the COVID-19 period are provided in the following sections.

Participants

Participants for the MMC study are recruited from the MMI sample (N=222). Table 1 provides a summary of descriptive information for this sample. Mothers in the MMI study were initially recruited in the third trimester of pregnancy and had a singleton pregnancy, and all reported intention to breastfeed (this was relevant because of the centrality of breastfeeding to the oxytocin assessments and hypotheses in the MMI study). The sample was enriched with women at a high risk of depression or anxiety such that 87 (39.2%) had a Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)–verified current diagnosis of depression or anxiety or were in active treatment with psychotherapy or antidepressants, 64 (28.8%) had a past diagnosis of depression or anxiety, and 71 (32%) were low risk with no history of depression or anxiety. After completing the final in-person data collection visit at 12 months of child age, mothers were invited to participate in web-based follow-up questionnaires every 6 months until the child was aged 4 years. Of these mothers, 92% (138/150) chose to participate in ongoing data collection, leading to a projected enrollment of 150 dyads for the MMC study. Owing to additional attrition and suspension of data collection because of the COVID-19 pandemic, the MMC enrollment target has been reduced to 110 dyads.

Table 1. Demographic information on the original Mood, Mother and Infant study.

	Depression diagnosis		
	Current (n=71)	Previous but not current (n=64)	Never (n=87)
Primiparous	37 (52)	22 (34)	40 (46)
Race or ethnicity			
Asian	5 (7)	3 (5)	4 (5)
Black	11 (15)	9 (14)	8 (9)
Hispanic or Latino	9 (13)	6 (9)	7 (8)
American Indian or Alaska Native	1 (1)	1 (1)	3 (4)
White	59 (83)	52 (81)	76 (87)
Married	59 (83)	52 (81)	66 (76)
Education			
<4 y of college	12 (17)	17 (26)	26 (30)
4 y of college	27 (38)	21 (33)	18 (21)
Postgraduate	32 (45)	26 (41)	43 (49)

Procedures

Visit 1: The Randomized Controlled Trial Administration

Pre– and Post–COVID-19 Protocol

Following the mother's arrival and informed consent procedures, each participant provides a urine sample used immediately for pregnancy testing, and only nonpregnant participants proceed with the oxytocin randomized controlled trial (RCT) visit. Research staff apply MindWare cardiovascular sensors (MindWare Technologies LTD) to monitor HRV and the cardiac pre-ejection period (PEP), a SunTech Tango monitor (SunTech Medical, Inc) assesses blood pressure and heart rate, and an antecubital intravenous catheter is placed for interval blood sampling. Next, the mother is left to adapt to the testing chamber for a 10-minute habituation period [51,52]. Following the habituation period [53-56], participants are randomized by risk level in a 1:1 allocation to either 24 international units of nasal oxytocin or a placebo nasal spray in an identical bottle. Both participants and study team members are blinded to allocation. The study drug and placebo are obtained from Apotheke Roter Ochsen. A total of 40 minutes after the nasal spray administration, mothers participate in the Trier Social Stress Test (TSST). The TSST includes a speech performance task and a math performance task, which reliably induce large and consistent HPA and cardiovascular responses [52,57]. Following the guidelines for examining HPA stress reactivity, intravenous blood samples are collected at baseline; at 20 and 40 minutes

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of the post–nasal spray rest period; during the speech and math tasks; and at 10, 20, and 30 minutes of the post-TSST recovery period [52,58]. Across these 8 samples, a total blood volume of 113 mL is collected. Each maternal blood sample is collected into prechilled vacutainer tubes, immediately cold centrifuged, aliquoted into prechilled cryotubes, and stored at −80 °C. Owing to conflicting evidence regarding the optimal timing of stress testing [59,60], visits are scheduled for 1 PM to increase the likelihood of detecting a stress response unopposed by the circadian influence [22]. Previous findings suggest that the possible menstrual cycle phase does not affect TSST results [61,62]; therefore, although the date of the last menstrual period and hormones are not used for scheduling data collection visits, these data are recorded for analytic control purposes. Staff also conduct the nonpatient version of the Structured Clinical Interview for the DSM-IV (SCID-NP), to assess the mother's current psychiatric symptoms [52] at this visit.

Protocol Amendments Owing to COVID-19

During the months affected by the COVID-19 pandemic, the MMC study visit 1 protocol was amended as follows. First, participants completed informed consent protocols over the phone using DocuSign (DocuSign, Inc). The research staff reviewed a COVID-19 information sheet and symptom screening before arriving at the study visit. Participants were also screened for symptoms upon arrival. Second, the SCID-NP was conducted via phone call instead of in person. Finally, research staff and participants further enhanced safety protocols by requiring masking for all, limiting contact by leaving the testing chamber when possible, keeping the door open for increased air circulation, and remaining a minimum of 6 feet away as much as possible. The TSST committee members were seated >6 feet away from the participant and from each other. These protocol amendments will be implemented for the remainder of the study.

Visit 2: Mother and Child Data Collection for Hypothesis Testing

Pre–COVID-19 Protocol

Following the mother's arrival and informed consent procedures, MindWare cardiovascular sensors were placed on the mother and child, 6 cheek cell swabs were collected from the child, and the child's height and weight were recorded. After a 5-minute habituation period to the testing chamber, the mothers were taken into a neighboring room, and the children remained in the assessment room with the research staff. The children were then assessed for EF ability using the EF Touch assessment (a computerized EF battery validated for use in children aged 4 to 7 y). This lasted for approximately 30 to 45 minutes (including practice, administration, and breaks between tasks). Finally, child IQ was assessed using the 6 subscales of the Wechsler Preschool and Primary Scale of Intelligence that comprise the full-scale IQ (FSIQ) measure [56]. While the children completed the EF and IQ assessments, the mothers were asked to complete a series of computer-based EF assessments from Inquisit, including the Wisconsin Card Sorting Test, Visual Simon Task, Symbol Search, Simple Visual Reaction Time Task, Self-Ordered Pointing Task, Digit Symbol Substitution Task, Counting Span Task, Stroop Task, and Tower of London Task, which took approximately 45 minutes. Mothers then completed the Child Behavior Checklist (CBCL) and a recorded speech for which they were instructed to talk for 5 minutes about their child.

Once the mothers and children were done with their separate tasks, a maternal antecubital intravenous was placed for interval blood sampling. The dyad was then reunited for an additional 5-minute baseline rest period. After this period, the mother and child participated in a set of 3 parent-child interaction tasks designed to assess parent and child behaviors within a dynamic interaction context [63]. Three 5- to 10-minute tasks were used in this interaction. The first was a tower-building task in which the dyad was instructed to recreate a large wooden block tower using smaller, differently shaped wooden blocks. The dyad was instructed that the task was for the child to complete but the mother could provide any assistance she chose. The second task involved a simple card game with a standard deck of playing cards divided evenly between the mother and child. Each was instructed to simultaneously turn over a card and place it face up in the space between them. This continued until one of the cards was a jack, at which point the first person to slap the jack card won all the cards that had accrued to that point. The goal of the game was to win as many cards as possible. For the third interaction task, the dyad was provided with an Etch A Sketch toy (Ohio Art Company) and a line picture of a sailboat. Mothers were instructed to use one of the Etch A Sketch knobs, and the children were instructed to use the other; their goal was to recreate the picture of the sailboat on the Etch A Sketch by working cooperatively with each using a separate turning knob on the toy. These parent-child interaction tasks were recorded for later behavioral coding. Maternal blood was collected before and immediately after the parent-child interaction tasks; a total blood volume of 59 mL was collected. Each maternal blood sample was collected into prechilled vacutainer tubes, immediately cold centrifuged, aliquoted into prechilled cryotubes, and stored at −80 °C. Once participants were deinstrumented, research staff collected hair samples from the mother and child for cortisol analysis.

Post–COVID-19 Protocol

During the months affected by the COVID-19 pandemic, the MMC study visit 2 protocol was amended as follows. First, we suspended maternal blood sampling, mother and child MindWare data and hair sample collection, and child cheek cell collection to reduce contact between staff and participants. Second, upon arrival (after completion of wellness screening), mothers and children were directed into a cleaned, unoccupied room without research staff where they could remove their masks to complete the parent-child interaction tasks (cameras were operated remotely for recording). These safety accommodations were important as it was necessary to observe these interactions without masks to code mother and child facial affect. Once the parent-child interaction tasks were complete, mothers and children resumed mask wearing. Suspended protocols were gradually reintroduced as COVID-19 restrictions were reduced. On April 21, 2021, cheek cell collection resumed. On August 23, 2021, MindWare data collection for the children and the baseline rest period were reintroduced. On June 26, 2022, hair samples were reintroduced and moved to the beginning of the protocol. Maternal blood collection and

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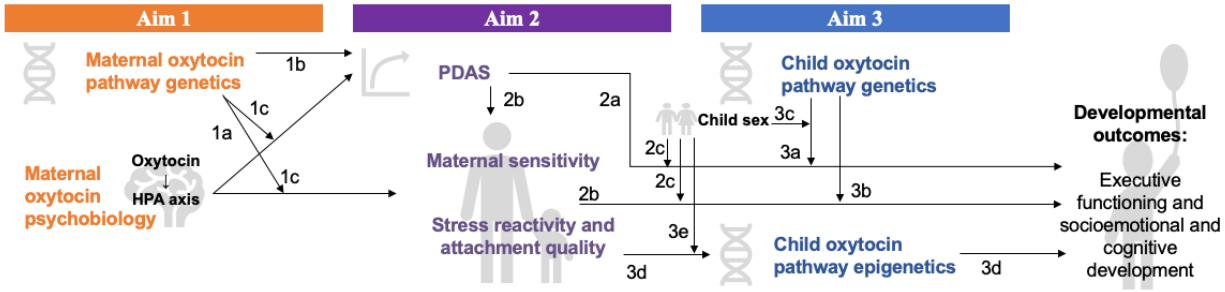
MindWare data collection were not implemented for the remainder of the study. Owing to this, the second baseline rest period was never reintroduced, either. The research staff reviewed a COVID-19 information sheet and symptom screening before arriving at the study visit. Participants were also screened for symptoms upon arrival. Research staff and participants increased safety protocols, including required masking for all, limiting contact by leaving the chamber when possible, keeping the door open for increased air circulation, and remaining a minimum of 6 feet away as much as possible. These protocols will be implemented for the remainder of the study.

Measures

Overview

MMC study measures are presented in the following sequence. First, measures pertinent to the RCT examining oxytocin and HPA axis functioning are presented. Next, measures pertinent to testing the hypotheses in aims 1, 2, and 3 are presented in order of appearance in the passive longitudinal design (Figure 1). This begins with maternal oxytocin functioning and oxytocin genetics as primary predictors (maternal oxytocin psychobiology and oxytocin genetics) followed by maternal biopsychosocial outcomes (PDAS and maternal parenting behaviors) and then child biopsychosocial outcomes (child oxytocin epigenetics, stress reactivity, and cognitive and socioemotional outcomes). Summaries of potential moderators and control variables are also provided.

Figure 1. Conceptual model for the Mood, Mother and Child Study. HPA: hypothalamic-pituitary-adrenal; PDAS: postpartum depression and anxiety symptoms.



RCT Measures

Independent Variable: Intranasal Oxytocin Administration

Mothers in the experimental condition are administered 24 international units of nasal oxytocin, and mothers in the placebo condition are administered an equivalent volume of an inert nasal spray. After a rest period, mothers are trained and observed to self-administer 6 separate nasal spray inhalations at approximately 30- to 60-second intervals, alternating between the right and left nostril.

Dependent Variable: HPA Axis Functioning

Maternal blood samples from the first laboratory visit (including baseline; during the TSST speech and math tasks; and at 10, 20, and 30 min of the recovery period following the TSST) will be assayed for adrenocorticotropic hormone in ethylenediaminetetraacetic acid–treated plasma and serum cortisol using commercially available radioimmunoassay reagents from MP Biomedicals.

Primary Predictors: Maternal Oxytocin Functioning

Maternal Oxytocin Secretion

Oxytocin in ethylenediaminetetraacetic acid–treated plasma, with aprotinin added to prevent peptide degradation, will be determined through enzyme immunoassay with extraction (Enzo Life Sciences), as previously described [64]. Interpretation of the oxytocin literature is complicated by controversies in the assay technique [65] as many studies report results for unextracted samples. These results are difficult to interpret given that Szeto et al [66] found no correlation between the extracted and unextracted oxytocin values. A key strength of our study is that we will use the extracted oxytocin for all measures.

Maternal Oxytocin Genetics

DNA extracted from maternal blood collected during the MMI study will be used for genotyping. Genome-wide single nucleotide polymorphism (SNP) arrays will be used to identify genetic variations in individual genes (in addition to clusters of genes) whose products interact in pathways that have been implicated in maternal depression, stress reactivity, and parenting behaviors (such as oxytocin). To estimate genetic ancestry in our diverse population, we will apply both structure and Eigensoft SmartPCA to linkage equilibrium-pruned array data.

Maternal Biopsychosocial Outcomes

Maternal Depression and Anxiety

Depression and anxiety symptoms are measured at multiple times (Table 2), including the SCID-NP [53] in the third trimester of pregnancy (for the MMI study) and again at the first data collection visit at 5 years of child age in the MMC study. The Structured Clinical Interview for the DSM-IV is a semistructured interview for assessment of major DSM-IV axis-I diagnoses and is considered the gold standard instrument for rigorous assessment of lifetime and current psychiatric illness (the nonpatient version was specifically developed for use in research studies). In addition, monthly assessments were conducted during the first year of life using the Edinburgh Postnatal Depression Scale [67]; assessments at 2, 6, and 12 months were conducted using the Beck Depression Inventory–II [68] and the Spielberger State-Trait Anxiety Inventory [69];

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and all 3 measures were collected every 6 months thereafter from the ages of 1 to 4 years and then again at the current MMC study visit.

Table 2. Maternal depression and anxiety measurement over time.

	Prenatal—third trimester	Year 1 (month)												Year 2 (month)		Year 3 (month)		Year 4 (month)		Years 5-7—month 60 onward
		1	2	3	4	5	6	7	8	9	10	11	12	18	24	30	36	42	48	
SCID[a]	✓																			✓
EPDS[b]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
BDI[c]	✓		✓				✓						✓	✓	✓	✓	✓	✓	✓	✓
SSA[d]	✓		✓				✓						✓	✓	✓	✓	✓	✓	✓	✓

[a]SCID: Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition.

[b]EPDS: Edinburgh Postnatal Depression Scale.

[c]BDI: Beck Depression Inventory.

[d]SSA: Spielberg State-Trait Anxiety Inventory.

HRV Measure

Mobile Impedance Cardiographs (MindWare Technologies LTD) are used to measure cardiac rate, interbeat interval, and PEP in mothers and children. MindWare HRV software will be used to derive respiration and calculate high-frequency HRV and respiratory sinus arrhythmia from the interbeat interval series as indexes of parasympathetic activity. Respiratory rate will be used in all HRV analyses. MindWare Impedance Cardiography Analysis software will calculate cardiac time intervals, stroke volume, and cardiac output. PEP will index sympathetic activation.

Chronic HPA Activation

Hair cortisol will be assayed from 20 to 25 strands of hair [70] collected from mothers and children using a commercially available immunoassay with chemiluminescence detection (IBL-Hamburg) that has been validated using liquid chromatography mass spectrometry.

Parenting Behaviors

Video recordings of parent-child interactions collected at visit 2 will be coded by a team of trained and certified researchers led by WRM-K. Ratings of maternal sensitivity, detachment, intrusiveness, positive regard, negative regard, stimulation of cognitive development, and animation will be made using a 5-point Likert scale (ranging from 1 as *not at all characteristic* to 5 as *highly characteristic*). On the basis of previous empirical findings and theoretical models of parenting dimensions, we anticipate that these scales will load onto 2 broad dimensions of maternal parenting behavior—*overall sensitivity* (comprising sensitivity, detachment [reversed], stimulation, positive regard, and animation) and *negative-controlling behaviors* (negative regard and intrusiveness). The ultimate creation of parenting dimensions will be guided by factor analyses comparable with those in previous studies by WRM-K [71].

Child Biopsychosocial Outcomes

Child Epigenetics

DNA extracted from child cheek swabs at the ages of 2 months and 5 years will be used to assess genome-wide DNA methylation using the Illumina MethylationEPIC BeadChip. This platform interrogates 850,000 methylation sites across the genome at single-base resolution; target gene regulatory regions include enhancers, CpG islands, promoters, and open chromatin sites. Methylation probes are dropped from the analysis for bad genome mapping, missingness (>0.01), and low detection (<0.05). Raw microarray signal intensity (SI) data are first corrected using the Illumina probe type, followed by individual methyl and nonmethyl channel quantile normalization using the *limma* package in Bioconductor. The methylation status of each CpG site is then calculated as the β value based on the following definition: β value = (SI of the methylation detection probe) / (SI of methylation detection probe + SI of non–methylation detection probe + 100). Cell type composition will be estimated as a covariate for association analyses using the *minfi* package in Bioconductor. Interindividual DNA methylation trajectories will be identified from the age of 2 months to 5 years. Although all relevant methylation sites will be examined, particular emphasis will be placed on oxytocin pathways and their effects.

Child EF

Children's EF is assessed at visit 2 via performance on the EF Touch instrument, which is a computerized battery of EF tasks using a capacitive touch screen monitor to record child responses [72]. Working memory is assessed using the Working Memory Span Task [73] and the Pick the Picture Game [74,75]; inhibitory control is assessed using the Silly Sounds Stroop [76], Spatial Conflict Task [77], and animal Go or No-Go Task [78]; and attention shifting is assessed using the Something's the Same Game [79]. Each of these 5 tasks takes 3 to 7 minutes to complete. For complete descriptions of these tasks and extensive psychometric and reliability information, see the study by Willoughby et al [80].

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Child IQ

Child IQ was assessed at visit 2 using 6 subscales of the Wechsler Preschool and Primary Scale of Intelligence that comprise the FSIQ composite. These include the Block Design (assessing spatial reasoning), Information (assessing cultural knowledge), Matrix Reasoning (assessing visual processing), Bug Search (assessing speed of processing), Picture Memory (assessing working memory), and Similarities (assessing logical thinking) subscales. The FSIQ composite is considered the most reliable and representative measure of broad cognitive functioning in middle childhood [81].

Child Maladaptive Behaviors

Mothers completed the CBCL for school-age children [82]. The CBCL is a highly used instrument that assesses emotional and behavioral problems in children and produces broad-band (internalizing problems, externalizing problems, and total problems) and narrow-band (eg, attention problems, sleep problems, anxiety or depression, and aggressive behavior) scales with standardized T scores.

Potential Moderating Variables

Child Sex

Maternal report of child sex at birth will be used as a moderating variable in hypotheses 2c, 3c, and 3e.

Child Oxytocin Genetics

DNA extracted from child cheek swabs will be used for genome-wide SNP arrays to identify (1) aggregate genetic risk (eg, genetic risk scores for psychiatric outcomes) and (2) genetic variation of individual genes (in addition to clusters of genes) associated with oxytocin functioning; these data will be used as moderating variables in hypotheses 3a and 3b.

Potential Control Variables

In addition to demographic controls (eg, maternal or child race and ethnicity and maternal education, age, and family income), additional control variables will be collected and used as appropriate for specific hypothesis testing. For example, analyses of child EF and IQ outcomes will include control variables for maternal EF [55]. Child temperament (assessed using the Children's Behavior Questionnaire [83]) will be used to control for genetic confounds between mothers and children as well as passive gene-environment correlations within the family system. Current psychiatric treatment for maternal depression and anxiety (both pharmacological and nonpharmacological) will be included as appropriate.

Data Analysis Plan

Characterizing PDAS

We plan to integrate PDAS measures obtained from repeated assessments of the Edinburgh Postnatal Depression Scale, Beck Depression Inventory–II, and State-Trait Anxiety Inventory by constructing a hierarchical confirmatory factor analysis (HCFA) model with a general PDAS factor giving rise to anxiety and depression subdomains (Figure 2). We will incorporate orthogonal method factors (not shown in the figure) to account for the scale of origin. The HCFA model will be estimated using 1 randomly drawn observation from each mother's first year of postpartum data. Once we have obtained a good-fitting HCFA model, we will use the parameter estimates from the calibration model to generate time-varying maternal PDAS factor score estimates—1 per month during the first year post partum [84].

Once time-varying PDAS scores have been obtained, we will determine the optimal method for characterizing maternal PDAS. We will consider three approaches: (1) latent mean, (2) growth parameters, and (3) growth mixture classes. We describe each of these approaches in the following paragraphs.

First, we will generate spaghetti plots to examine the shape and heterogeneity of PDAS scores over time. We will use linear mixed models to construct univariate growth models for PDAS to determine empirically whether scores follow a linear, quadratic, or cubic average trajectory and whether there is significant individual heterogeneity in change over time. The following set of equations presents an example of a quadratic growth trajectory for PDAS, where i=1...N indexes individuals and t=0...12 indexes time in months, starting immediately post partum. Time is centered at 6 months post partum in the equation. The b parameters are the fixed effects that characterize the PDAS trajectory for the average participant. The u parameters are individually varying random effects that define each participant's unique PDAS trajectory. We assume that the u terms follow a multivariate normal distribution centered at 0 and that the residual error is normally distributed at each time point. The residual error is assumed to be uncorrelated with the random effects.

$$PDAS_{ti} = b_0 + b_1 \times (t - 6) + b_2 \times (t - 6)^2 + u_{0i} + u_{1i} \times (t - 6) + u_{2i} \times (t - 6)^2 + r_{ti} \quad (1)$$

If we do not find a significant fixed effect of time (ie, if b_1 and b_2 are not significantly different from 0), we will output empirical Bayes estimates of the random intercept and use these scores to represent each participant's average PDAS score . We refer to this first approach as the latent mean approach.

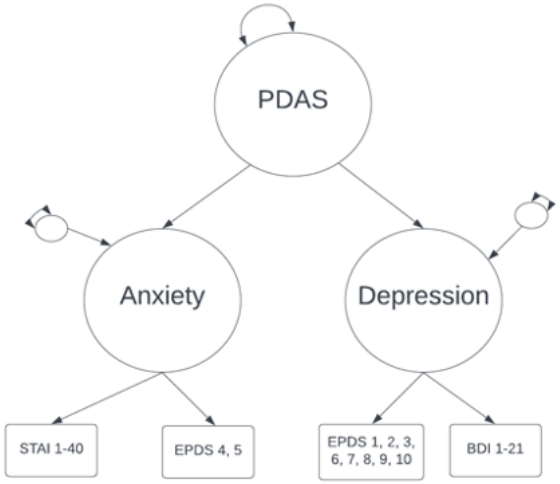
If individual trajectories follow the same general form (eg, all linear but with continuously varying slope values), we will output empirical Bayes estimates of mother-specific intercepts ($int_i = b_0 + u_{0i}$, representing the average PDAS at 6 mo post partum) *and* slopes ($slope_i = b_1 + u_{1i}$, representing the direction and rate of change over time). In this "growth parameter" approach, we will represent PDAS trajectories using a combination of 2 or more growth parameters.

Finally, if we find visual and empirical evidence of substantial heterogeneity in the *shape* of PDAS change over time, we will use growth mixture models to estimate a small number of prototypical PDAS trajectory shapes and then use posterior probability scores to assign participants probabilistically to a trajectory class. This third approach will allow for a small number of different trajectories (eg, 1 stable trajectory, 1 increasing linearly, and 1 decreasing to a plateau). Each participant will receive a posterior probability of membership

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to each trajectory class. Once PDAS trajectories have been operationalized as (1) latent means, (2) growth parameters, or (3) growth mixture classes, we will use the resulting measures to address the study hypotheses.

Figure 2. Hierarchical confirmatory factor analysis model of postpartum depression and anxiety symptoms (PDAS) factor. Numbers reflect child age (in months) at time of assessment. BDI: Beck Depression Inventory; EPDS: Edinburgh Postnatal Depression Scale; STAI: Spielberg State-Trait Anxiety Inventory.



Aim 1 Hypothesis Testing

First, we will use a general linear model to test the hypothesis that participants who are randomized to receive nasal oxytocin experience lower HPA reactivity during the TSST to evaluate this proposed causal pathway (hypothesis 1a). Next, we will also evaluate whether observed oxytocin functioning or genetic variation in oxytocin-associated pathways correlates with PDAS and will then use structural equation modeling (SEM) to assess whether mothers' HPA functioning mediates the association between oxytocin variation and PDAS (hypotheses 1a and 1b). The SEM framework will enable us to model uncertainty in the growth parameters or latent class membership while simultaneously estimating the 2 mediation pathways (oxytocin to maternal HPA functioning [*a* path] and maternal HPA functioning to PDAS [*b* path]). We will use bootstrapped SEs to conduct significance tests for the indirect effects.

Finally, multigroup SEM will be used to examine the potential of moderated mediation, with maternal genetic variation in oxytocin-related pathways moderating the associations between maternal oxytocin and HPA functioning and PDAS (hypothesis 1b). We will also test whether maternal genetic variation moderates the associations between PDAS and maternal HPA functioning, oxytocin functioning, and parenting behaviors (hypothesis 1c). Significant moderation effects will be probed following procedures outlined by Preacher et al [85] to obtain estimated effect conditions on genetic variation within the range of our data.

Aim 2 Hypothesis Testing

Our next step of analysis will be to evaluate the extent to which PDAS predicts more adverse child biopsychosocial outcomes during early elementary years (hypothesis 2a), whether high stress reactivity or maladaptive parenting behaviors mediate this association (hypothesis 2b), whether the direct effects of PDAS on child outcomes remain significant after accounting for concurrent maternal depression and anxiety severity (hypothesis 2b), and whether sex moderates the associations between PDAS and child outcomes such that the effects of PDAS on child externalizing are stronger for male individuals and the effects of PDAS on child internalizing are stronger for female individuals. We will continue within an SEM framework for aim 2 analyses as this approach allows for the simultaneous modeling of mediation, moderation, and a variety of response distributions.

In addition to demographic control variables, we will include child temperament (assessed in infancy and concurrently at the age of 5 y) to control for genetic confounds between mothers and children as well as passive gene-environment correlations within the family system.

Aim 3 Hypothesis Testing

For aim 3, we will conduct SEM analyses in two ways: (1) including estimated risk scores and (2) stratified by child OXT and OXTR genotypes to determine if child genotype moderates the associations between PDAS and developmental outcomes (hypothesis 3a) and between maternal sensitivity and developmental outcomes (hypothesis 3b). Next, we will test whether the pathways tested in aims 1 and 2 vary by child sex by introducing 2-way interactions between PDAS and child sex and parental sensitivity and child sex and probing significant effects. We will test whether the methylation status of oxytocin-related genetic regions mediates associations among PDAS exposure, sensitivity, attachment quality, and developmental outcomes (hypothesis 3d). Finally, we will conduct exploratory analyses using multigroup models to examine whether the effects of PDAS and maternal sensitivity on epigenetic changes in child oxytocin functioning are stronger for girls than for boys (hypothesis 3e). We will use bootstrapped SEs to conduct significance tests for the indirect effects. Moderation effects will be probed following the procedures outlined by Preacher et al [85].

Missing Data

The proposed study design incorporates extensive repeated assessments. Growth models and SEMs are estimated using full

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information maximum likelihood, which permits the assumption that missing data are missing at random conditional on observed measures. We will rely on this assumption when data are missing exclusively on endogenous variables. We will use multiple imputation for all analyses involving missing covariates to avoid listwise deletion of cases with missing exogenous variables.

Power Analysis

As described previously, attrition and suspension of data collection because of COVID-19 resulted in a lower enrollment in the MMC study than we had hoped; however, we anticipate enrolling 110 dyads from the original sample. With this sample size and a type-I error rate of Cronbach α=.05, we will have 80% power to detect a correlation of $r \geq 0.26$, a mean difference of Cohen $d \geq 0.5$, and an odds ratio of ≥2.02. Thus, broadly, we expect to have the power to detect moderate, clinically meaningful effects; however, we will have limited power to detect smaller effect sizes that tend to occur in mediation and moderation analyses.

Ethics Approval

This project received ethics approval from the University of North Carolina at Chapel Hill institutional review board (21-0421).

Results

The trial was registered with ClinicalTrials.gov on July 20, 2018 (NCT03593473). The study began in September 2018 and continues through August 2024. Recruitment and data collection have commenced; as of June 1, 2023, a total of 102 participants have been enrolled. Study results should be available in 2024.

Discussion

Previous research has documented associations between PND and offspring developmental outcomes in middle childhood [30,86] and evidenced the role of oxytocin in PND [87]. However, no study has evaluated the role of oxytocin using multiple methodologies (eg, circulating oxytocin, exogenous oxytocin administration, SNP, and epigenetic analyses) in mothers and children using a longitudinal design spanning infancy to middle childhood. Our unique combination of methodologies will allow for potential attributions of causality with respect to oxytocin administration while allowing us to unpack the psychobiological processes underlying these effects with the ongoing longitudinal design. These results will provide unique insights into the psychobiological effects of oxytocin in women and may inform future clinical trials to treat perinatal mood disorders [88]. Furthermore, we will be the first to report on interindividual measures of oxytocin-related DNA methylation in children as a function of maternal depression and parenting experiences [89]. Previous studies have approached these topics in a piecemeal fashion within time and across single levels of analysis, whereas our integrated, multilevel, multi-method longitudinal approach will elucidate the role of oxytocin in dyadic development and identify psychosocial, genetic, and epigenetic markers that can be leveraged to cultivate resilience across 2 generations.

Acknowledgments

The Mood, Mother and Infant and Mood, Mother and Child studies are funded by the National Institute of Child Health and Human Development (R01HD073220 and R01HD093901). They have institutional review board approval from the University of North Carolina at Chapel Hill (institutional review board study 12-2061) and are registered with ClinicalTrials.gov (NCT03593473). The authors are grateful especially to the participants and their families for their time and effort in being part of this study.

Data Availability

The data sets generated from this study are not publicly available because of ongoing data collection protocols but will be available at the conclusion of this study from the corresponding author upon reasonable request following guidelines stipulated by the National Institutes of Health.

Authors' Contributions

AMS (principal investigator), WRM-K (principal investigator), KG, NGO, SEM-B, and JDG are investigators on the Mood, Mother and Child study; each made significant contributions to the grant proposal funded by the National Institute of Child Health and Human Development to support this study. BP and CGS are key research associates; each made significant contributions to the final design and execution of this study. WRM-K wrote the first draft of the paper with significant assistance from each coauthor. All the authors approved the final version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Final National Institutes of Health grant proposal review.
[PDF File (Adobe PDF File), 231 KB - resprot_v12i1e51132_app1.pdf]

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Abbreviations

CBCL: Child Behavior Checklist
DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
EF: executive functioning
FSIQ: full-scale IQ
HCFA: hierarchical confirmatory factor analysis
HPA: hypothalamic-pituitary-adrenal
HRV: heart rate variability
MMC: Mood, Mother and Child
MMI: Mood, Mother and Infant
OXTR: oxytocin receptor
PDAS: postpartum depression and anxiety symptoms
PEP: pre-ejection period
PND: perinatal depression
RCT: randomized controlled trial
SCID-NP: nonpatient version of the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
SEM: structural equation modeling
SI: signal intensity
SNP: single nucleotide polymorphism
TSST: Trier Social Stress Test

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Protocol

Testing a Culturally Tailored Advance Care Planning Intervention (MY WAY) for an American Indian Tribe: Protocol for a Quasi-Experimental Waitlist Control Design

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Abstract

Background: American Indian and Alaska Native peoples experience poor end-of-life care, including more hospitalizations and lower use of hospice and do-not-resuscitate orders. Although advance care planning (ACP) can improve end-of-life care, ACP rates are disproportionately low in American Indians and Alaska Natives.

Objective: We culturally tailored and delivered an existing evidence-based ACP program for an American Indian tribal community. Here, we present the protocol for assessing the intervention's feasibility and efficacy.

Methods: We measured feasibility via participant recruitment, participants' evaluation (acceptability, appropriateness, comprehension, and satisfaction), and intervention fidelity. Recruitment was measured with participant screening, eligibility, enrollment, and retention. Participant's evaluation of the intervention was measured with surveys. Fidelity was measured with direct observation and the Make Your Wishes About You (MY WAY) Fidelity Checklist Tool. To assess the intervention's efficacy, we used a quasi-experimental waitlist control design with 2 cohorts who were surveyed each on three separate occasions. The intervention's efficacy was assessed by the following: ACP barriers and facilitators as well as ACP self-efficacy, readiness, and completion.

Results: A total of 166 participants were screened for eligibility; 11 were deemed ineligible, and 155 participants were enrolled in the study. Of those enrolled, 113 completed the intervention and will be included in subsequent analyses. We finalized data collection in January 2023, and analyses are underway. Study enrollment was successful, and we expect that participants will report high levels of acceptability, appropriateness, comprehension, and satisfaction with the intervention. We expect that the intervention was implemented with fidelity and will demonstrate decreases in ACP barriers and increases in ACP facilitators, self-efficacy, readiness, and completion.

Conclusions: Enrolling over twice as many participants as we had hoped suggests that members of this tribal community are willing to engage in end-of-life ACP. We were able to implement a waitlist study design to show that a culturally tailored ACP program for a tribal community is feasible.

Trial Registration: ClinicalTrials.gov NCT05304117; https://clinicaltrials.gov/study/NCT05304117

International Registered Report Identifier (IRRID): DERR1-10.2196/50654

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KEYWORDS

American Indian or Alaskan Native; advance care planning; end-of-life care

Introduction

Background

American Indian and Alaska Native peoples experience poor end-of-life care, including a higher likelihood of being hospitalized at the end of life; receiving futile treatment at the end of life; and lower rates of hospice [1], palliative care, do-not-resuscitate orders [2-4], and advance care plans [3,5]. Advance care planning (ACP) is a process that allows people to make health care decisions if they are unable to speak for themselves because of serious or terminal illness. ACP is associated with goal-concordant care, decreased anxiety about end-of-life decision-making, and reduced stress among primary caregivers [6].

ACP rates are disproportionately low among American Indians and Alaska Natives. Research with 270 American Indian and Alaska Natives in the Northwest Plains found that none had heard of palliative care and 93% had never heard of a living will [4]. When compared to non-Hispanic White people, American Indians and Alaska Natives were half as likely to have a living will or a health care power of attorney [3]. A medical chart review of a New Mexico Indian Health Service facility found that information about advance directives, as required by the Patient Self-Determination Act, was in only 20% of charts [7]. Despite being twice as likely to die from type 2 diabetes and 4 times as likely to die from chronic liver disease than non-Hispanic White people [8], little work has been done to increase opportunities for American Indians and Alaska Natives to express their end-of-life care wishes. To date, there are no randomized controlled trials (RCTs) that have demonstrated the efficacy of ACP for American Indians and Alaska Natives [5], and there are limited other ACP research studies with American Indians and Alaska Natives [2,3,9-11].

The lack of ACP among American Indians and Alaska Natives is not a reflection of unwillingness to engage in conversations about death [4,9,12]. Rather, American Indians and Alaska Natives are presented with formidable barriers to ACP including lack of access to such opportunities and experiences of health care professionals' stereotypes that American Indians and Alaska Natives do not want to engage in end-of-life conversations [13]. Further, typical ACP models may be unsuitable for many American Indians and Alaska Natives because they are conventionally delivered by health care professionals in clinical settings that American Indians and Alaska Natives have historically valid reasons for not trusting [11,13-16]. ACP approaches for American Indians and Alaska Natives should be developed with guidance and input from the intended community [11,17] and incorporate culturally relevant values [18] as well as beliefs and practices concerning the end of life and death, which vary within and across Indigenous populations [19].

A previous RCT study demonstrated that the program, Make Your Wishes About You (MY WAY), increases ACP self-efficacy, readiness, and completion rates for patients with chronic kidney disease [20,21]. However, as the Consolidated Framework for Implementation Research asserts, interventions that are not tailored to a population of interest are usually a poor fit [22]. To deliver interventions that are sensitive to a group's worldview, language, cultural meanings, and values, a systematic approach to tailoring is suggested [23,24]. Tailoring includes modifying the intervention delivery, that is, the delivery person, channel, or location, and modifying content, such as certain information in the intervention materials [25].

Objectives

The objective of our study was to use a community-based participatory research (CBPR) approach to culturally tailor the existing MY WAY [21] for a tribal community. Specifically, our study had three aims: (1) culturally tailor MY WAY for a specific tribe, (2) assess the feasibility of the culturally tailored MY WAY, and (3) examine the efficacy of the culturally tailored MY WAY. At the successful completion of this project, we expect to develop a feasible, culturally tailored MY WAY that, through a quasi-experimental waitlist control design, shows promise as an efficacious program. Here, we describe the protocol for assessing the feasibility and efficacy of the culturally tailored MY WAY.

Methods

Ethical Considerations

The project received approval from our institutional review board (blinded to protect confidentiality; #2022-01-24-01-02), a tribal institutional review board, and a tribal council (resolution #412-2021).

Conceptual Framework

Our approach relied on the Consolidated Framework for Implementation Research, which provides a practical structure for complex, interacting, multilevel, and momentary constructs by consolidating key elements from implementation theories [22]. The framework's main premise is that for implementation to be effective, the following domains must be considered: intervention characteristics, setting, individuals involved, and implementation process. Methodologically, our approach also adhered to the CBPR principles, including recognizing the community as a unit, building on strengths and resources within the community, facilitating collaborative partnerships in all phases of the research, integrating knowledge and action for the mutual benefit of all partners, promoting a co-learning and empowering process that attends to social inequalities, involving a cyclical and iterative process, and disseminating knowledge gained to all parties [2,26].

Setting

Our study was conducted with a federally recognized tribe whose lands span five rural counties with approximately 16,000 enrolled members (personal communication with the personnel at the tribal enrollment office, May 23, 2023; the name of person and tribe deidentified for confidentiality).

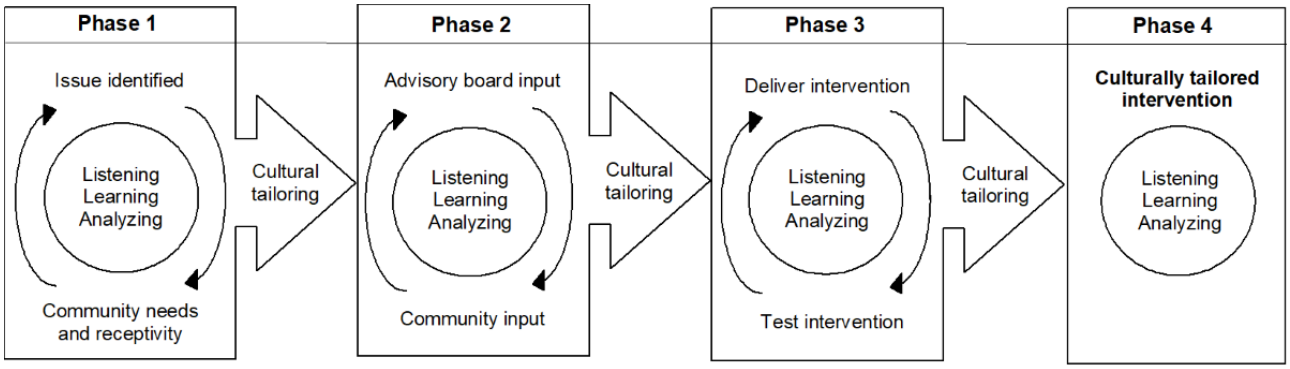
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Intervention Characteristics

Overview

The original MY WAY project developed and used *Planning Today for Tomorrow's Healthcare*, an ACP patient guide, and *A Curriculum Guide for ACP* to assist health care providers in having ACP discussions with patients in a nephrology clinic. Both guides are grounded in the stages of change theory and use motivational interviewing techniques [21]. The previous RCT demonstrated that the MY WAY curriculum was effective in increasing self-efficacy, readiness, and completion of ACPs when used with a trained coach, especially in ACP "conversation ready" health care settings [27]. For the cultural tailoring effort, we were guided by the Consolidated Framework for Implementation Research and were informed by community engagement. Our approach included a cyclical process of listening, learning, and analyzing at each phase. The framework is shown in Figure 1 and described below.

Figure 1. Cultural tailoring framework.



In phase 1 of the cultural tailoring process, we identified community needs and receptivity through collaboration with local leaders and health care providers, and by holding two listening sessions. This phase also included tailoring the delivery of the program to create a 2-step intervention: (1) community information sessions and (2) one-on-one sharing sessions with project staff (support stars) who were trained to deliver the intervention. At the end of this phase, we applied for and received National Institutes of Health funding in response to PAR 19-0587 entitled "Strategies to Provide Culturally Tailored Palliative and End-of-Life Care for Seriously Ill American Indian and Alaska Native Individuals."

Phase 2 included the greatest number of activities. First, we created a community advisory board (CAB) and a professional advisory board (PAB). In CAB and PAB meetings, we shared data from the listening sessions and discussed ways to incorporate the feedback. We also hosted four additional listening sessions to obtain feedback on the original MY WAY materials. We used a grounded theory approach to analyze the listening session data to guide subsequent tailoring. We held an additional meeting with the CAB and PAB to share findings and elicit feedback that was used to further tailor MY WAY.

After the first revisions of MY WAY materials, we met individually with 7 of the listening session participants to solicit their reactions to the materials' usability and acceptability. We then met the CAB and PAB for a third time to share the interview findings and incorporate additional revisions to further tailor MY WAY. In phase 2, we also used the process, as described by Lynn [28], to quantitatively evaluate the content validity of the culturally tailored materials. A self-administered web-based survey was sent to all CAB and PAB members that included items about the personal and curriculum guides concerning the appropriateness of the images and language, and if the content was culturally relevant, culturally sensitive, respectful, and clear. If a respondent indicated an issue, they were then prompted for suggestions as to how to address it.

Phase 3 included implementing, delivering, and testing the culturally tailored MY WAY. First, participants attended a community information session on ACP, which was held at a venue within the tribal community. After attending a community information session, participants scheduled a one-on-one meeting or a sharing session. Topics covered in the community information session and sharing session included an overview of the project, health care agents, future health care wishes, writing an ACP, sharing the ACP, and Physician Orders for Life Sustaining Treatment (POLST) forms. The sharing sessions allowed participants to ask personal and private questions of the support star. These sessions were held in a location of the participant's choice (eg, their home or community club), and they were encouraged to bring family members. The support star also notarized ACPs, if desired, at any point in the process. The implementation phase lasted approximately 10 months. Finally, in phase 4, the investigators met again to conduct a final tailoring of the materials based on impromptu feedback that was received during implementation (phase 3). This included eliminating the term "healthcare agent" and adding information on how participants can share their notarized ACP with their health care provider. More information on the cultural tailoring can be found elsewhere (Goins, Haozous, Anderson, and Winchester, unpublished data, under review).

Research Design

Feasibility

Assessing feasibility was a primary objective for this study as there are no clinical trials on ACP interventions for American Indians and Alaska Natives and limited other work for ACP with this population. Although American Indians and Alaska Natives are willing to talk about and plan for end-of-life events, it was still necessary to assess whether there were other reasons

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that American Indians and Alaska Natives have lower than usual ACP rates. Conceptually, feasibility was measured with participant recruitment, participant evaluation (acceptability, appropriateness, comprehension, and satisfaction), and the fidelity of the intervention.

Efficacy

In addition to determining feasibility, we also sought to measure the efficacy of the culturally tailored intervention to address the disproportionate rates of ACP for this population. We used a quasi-experimental waitlist control study design to test the hypothesis that the intervention participants would experience decreased ACP barriers and increased ACP facilitators, self-efficacy, readiness, and completion rates. Rather than deny a portion of our sample the intervention, as in a traditional RCT, we planned to implement both steps of the intervention twice such that our intervention group, cohort 1, would comprise those who participated in the first round of both the community information sessions and sharing sessions. Our comparison group, cohort 2, would comprise those who participated in the second round of both the community information sessions and sharing sessions. To test the efficacy, we used the combined 2-cohort sample of those who participated in both steps of the intervention and compared intervention baseline measures to those measured post program.

Study Population and Sample Size

Eligibility criteria for the study population included tribal members, spouses of tribal members, tribal first descendants, and other American Indians and Alaska Natives residing in the tribal community, aged ≥18 years, and residing within the tribe's service area. Participants with cognitive impairments were excluded. Participants were recruited via purposive sampling. Existing collaborative relationships established in the tailoring phase helped the recruitment process. Recruitment efforts included numerous in-person announcements at tribal venues at events, a video on the local television station, social media postings, and several billboards.

Based on the risk ratio of completing an ACP indicated in the previously implemented MY WAY intervention (1.79, 95% CI 1.18-2.72) and using 90% power as a threshold, we used G*Power (Axel Buchner) with 3 predictors and the primary outcome of ACP completion to estimate that we would need at least 60 participants to find effects. As effect sizes for ACP self-efficacy and readiness were smaller in the original intervention, our goal was to enroll a total of 70 participants with 35 in each cohort.

Procedure

Overview

Feasibility

Recruitment was measured by documenting the number of potential participants in attendance and completing each intervention event or measure. Participant's evaluation of the intervention was measured twice: once at the end of the community information session with a self-administered survey and once 1 week after the sharing session with a telephone interviewer-administered survey. We conducted fidelity checks on 40% of the community information sessions and 18% of the sharing sessions.

Efficacy

Procedures varied across cohorts. Cohort 1 completed intervention baseline surveys immediately before the intervention and completed postprogram surveys about 9 weeks after the intervention. Cohort 1 also completed follow-up surveys approximately 6 months after their intervention baseline surveys. Cohort 2 completed a control baseline survey approximately 4 months before the intervention, and a second intervention baseline survey right before the second set of community information sessions. Cohort 2 then completed a postprogram survey approximately 3 months later. Table 1 describes the data collection schedule by cohort.

A timeline describing the steps of the intervention and data collection is shown in Figure 2.

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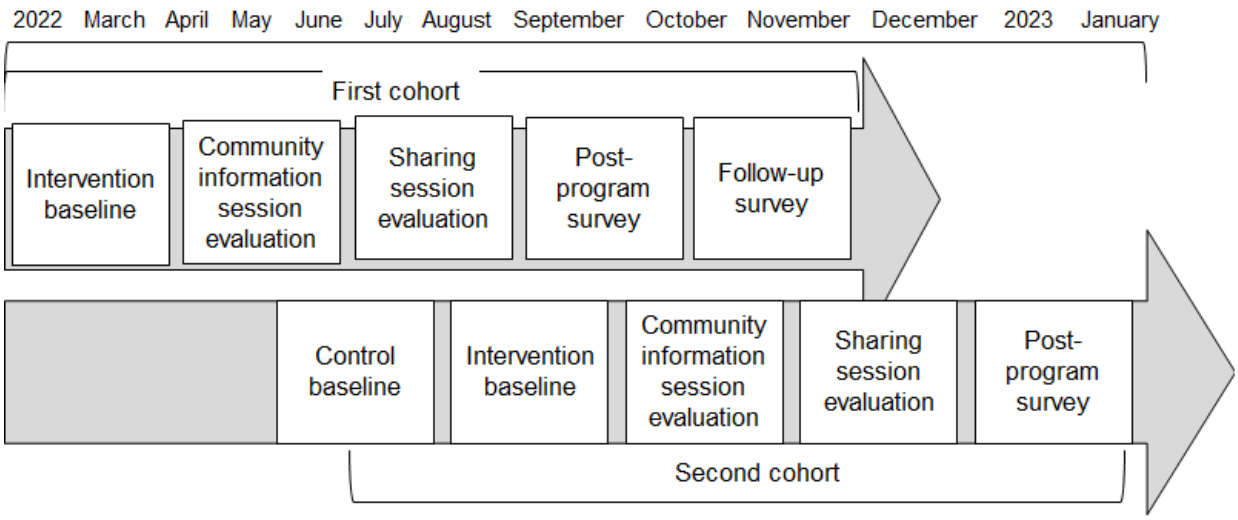
Table 1. Data collection schedule by cohort.

Data collection	Timeframe	Format
Cohort 1		
Intervention baseline	≤1 week before CIS[a]	Interviewer-administered in person
Community information session		
CIS evaluation	Immediately after on site	Self-administered paper/pencil
Sharing session		
SS[b] evaluation	1 week post SS	Interviewer-administered telephone call
Postprogram survey	9 weeks post CIS	Interviewer-administered telephone call
Follow-up survey	6 months post CIS	Interviewer-administered telephone call
Cohort 2		
Control baseline	4 months before CIS	Interviewer-administered in person
Intervention baseline	≤1 week before CIS	Interviewer-administered in person or telephone call
Community information session		
CIS evaluation	Immediately after on site	Self-administered paper/pencil
Sharing session		
SS evaluation	1 week post SS	Interviewer-administered telephone call
Postprogram survey	12 weeks post CIS	Interviewer-administered telephone call

[a]CIS: community information session.

[b]SS: sharing session.

Figure 2. Cohorts' timeline.



Measurement

Feasibility Measurements

Recruitment

Recruitment was captured by documenting the number of potential participants who were screened, deemed eligible, enrolled, and engaged in the full intervention, and the retention rates (number who completed the entire intervention, number who completed postprogram surveys from both cohorts, number in cohort 1 who completed the follow-up survey, and the number who dropped out from the control baseline to the intervention baseline in cohort 2).

Participant Evaluation

Acceptability, appropriateness, comprehension, and satisfaction of the intervention experience were assessed with a self-administered survey immediately following the community

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information sessions. Sharing session evaluations measuring the same concepts were administered by interviewers via telephone. Acceptability and appropriateness of the community information sessions and the sharing sessions were captured with the Acceptability of Intervention Measure and the Intervention Appropriateness Measure [29]. Comprehension and satisfaction were assessed with eight items, with response options ranging from strongly agree to strongly disagree, and a single item about how they rated the session, with response options ranging from excellent to poor.

Implementation Fidelity

Implementation fidelity was measured with the MY WAY Fidelity Checklist, which was developed and used in the MY WAY RCT. This checklist tool was a modified version of the Treatment Adherence Fidelity Tool [30], which allowed us to assess the adherence to the intervention delivery and content, intervention pacing, participant responsiveness, intervention delivery quality index, and support stars' competence level in judgment and delivery.

Efficacy Measurements

Barriers and Facilitators

We also used the ACP Facilitators and Barriers survey instrument [31] used in the original MY WAY RCT [27]. Barriers and facilitators were created based on findings from a former study [31] that found barriers to be related to perceptions of relevancy, personal barriers, relationship concerns, information needs, time constraints, and problems with the advance directives.

Self-Efficacy and Readiness

We used the 9-item ACP engagement survey instrument, including measures of self-efficacy and readiness as identified in behavior change theory [32,33]. Self-efficacy and readiness items have Likert responses of "not at all, a little, somewhat, fairly, extremely" and have good reliability and discriminant validity [32,33].

ACP Completion

ACP completion at baseline was operationalized with the number of participants who answered yes to the following question on the baseline survey (intervention and control): "Do you have an advance care plan?" The project coordinator confirmed a survey self-report of ACP completion by reviewing documentation as to whether the support star had notarized the advance care plan, which was confirmed with the official notary records.

Analyses

At the time of this publication, analyses for this study were not complete. Below, we report on our planned analysis.

Feasibility

Recruitment will be reported in raw counts. Participant evaluation and fidelity will be analyzed using descriptive statistics (mean, SD, and frequency scores for each).

Efficacy

Participant demographic characteristics will be examined using descriptive statistics and stratified analyses (eg, by demographics, attendance, and ACP completion) to examine the association between demographics and intervention outcomes. Since there may likely be significant attrition from community information sessions to sharing sessions, we will also run Heckman selectivity analyses to determine if there were differences between those who completed both intervention steps and those who completed only baseline measures for community information sessions. If there are differences in attrition, we plan to include the inverse Mills ratio. The comparison of measures between each cohort's intervention baseline scores will ensure that there are no significant differences between the cohorts that would keep them from being combined. ACP barriers, facilitators, self-efficacy, readiness, and ACP completion will then be compared between those who do and do not engage in both intervention steps and between cohorts 1 and 2. The comparison analysis will consist of Student *t* tests or a similar nonparametric test for differences in means if necessary.

After these preliminary analyses, the cohorts will be combined to examine changes in ACP outcomes (barriers, facilitators, self-efficacy, readiness, and completion) from the intervention baseline to the postprogram survey results. In the full sample of participants who experienced both steps of the intervention, the intervention baseline results for cohort 1 will be combined with the intervention baseline results for cohort 2 (as both occurred immediately before the intervention began) and compared to the combined sample of the postprogram surveys. Repeated measures of ANOVA will be used to compare these outcomes before and after the intervention. We will also assess changes in cohort 1's ACP outcomes from the intervention baseline to the postprogram survey and compare them to changes in cohort 2's ACP outcomes from the control baseline to the intervention baseline. Cohort 2 received no intervention between the control baseline and the intervention baseline, making this comparison analysis a control for natural variations over time. To ensure that changes can be attributed to the intervention and not the result of the passage of time or contamination from participants hearing about ACP in the community, we will measure two changes: (1) the change in cohort 1's intervention baseline to postprogram scores and (2) cohort 2's change from the control baseline to the intervention baseline.

Results

This project was funded in March 2021 and the cultural tailoring process began immediately. The cultural tailoring of the delivery and content of MY WAY has been completed and the intervention has been delivered to both cohorts. Data collection for the intervention began in February 2022 and ended in January 2023. A total of 166 participants were screened for eligibility, and we enrolled 155 participants in the study, including 114 participants in cohort 1 and 41 in cohort 2. A total of 113 participants (cohort 1: n=81; cohort 2: n=32) completed both steps of the intervention and data collection. Data analyses of the intervention's feasibility and efficacy have

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begun and are expected to be completed in the fall of 2023. During the project, we have kept our study participants informed through a periodic project newsletter. The culturally tailored MY WAY curriculum and personal guides are available for free on the project website.

Discussion

Principal Findings

There is a dearth of research on ACP interventions with American Indians and Alaska Natives and no culturally tailored ACP interventions for American Indians and Alaska Natives, despite having a high occurrence of chronic diseases such as diabetes [8], high rates of preventable hospitalizations [34], high premature mortality rates [35], and low hospice use rates compared to White people [2,36]. This study culturally tailored an existing evidence-based ACP program for an American Indian tribe. Though our data analyses have not been finalized, we were able to enroll over twice the number of participants (n=155) as hypothesized (n=70). Further, we successfully implemented a waitlist control design with this population.

Interpretations, Implications, and Comparisons

Our study's success at enrolling 155 participants and completing the waitlist design suggests that members of this tribal community were willing to engage in end-of-life discussions and ACP. Prior studies have indicated that providers often believe American Indians and Alaska Natives are reluctant to engage in end-of-life care or that discussions about the end of life are taboo [11-14]. We hypothesize that this study will show that tailored ACP interventions can increase facilitators; decrease barriers; and demonstrate increases in self-efficacy, readiness, and completion rates [4,12]. Tailoring interventions is believed to generate greater buy-in, acceptance, and ultimately the intended outcomes, and is considered preferable when working with populations in which the evidence-based program was not originally tested.

Limitations

This study has several limitations, most specifically in that it only represents 1 of 574 federally recognized tribes [37], each with its own set of values and preferences concerning the end of life. However, the process of culturally tailoring and engaging the community can be replicated so that other tribal nations and their members can benefit from ACP. Like other CBPR studies, our approach required flexibility with the community's needs, which created challenges in adhering to the strict timeline for the RCT. Instead, we adopted the waitlist approach. Additional cultural tailoring and testing of the MY WAY ACP intervention will be needed to test its effectiveness with other American Indian and Alaska Native tribes. However, this study will be the first to report on the effectiveness of a culturally tailored ACP intervention with an American Indian tribe. Our study results will provide valuable information for the health care community about American Indian readiness and confidence to engage in culturally tailored ACP. If more American Indians and Alaska Natives can express their health care wishes related to the end of life, it could lead to decreased suffering and hospitalization, increased hospice use, goal-concordant care, and increased patient and family satisfaction [6].

Potential Problem and Alternate Plans

Recruitment for cohort 2 proved challenging. Many participants were unwilling to wait approximately 6 months to receive the intervention. This challenge led to a large difference in the number of participants enrolled in cohort 1 compared to cohort 2. Our planned analyses should determine if there are any differences between the cohorts, however, which will account for this discrepancy.

Acknowledgments

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Data Availability

The data sets generated or analyzed during this study are not publicly available due to tribal institutional review board restrictions. Readers interested in accessing the data can contact the corresponding author on how to initiate tribal institutional review board permission.

Conflicts of Interest

None declared.

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Abbreviations

ACP: advance care planning
CAB: community advisory board
CBPR: community-based participatory research
MY WAY: Make Your Wishes About You
PAB: professional advisory board
POLST: Physician Orders for Life Sustaining Treatment
RCT: randomized controlled trial

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Protocol

Reducing Premature Coronary Artery Disease in Malaysia by Early Identification of Familial Hypercholesterolemia Using the Familial Hypercholesterolemia Case Ascertainment Tool (FAMCAT): Protocol for a Mixed Methods Evaluation Study

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Abstract

Background: Familial hypercholesterolemia (FH) is predominantly caused by mutations in the 4 FH candidate genes (FHCGs), namely, *low-density lipoprotein receptor (LDLR)*, *apolipoprotein B-100 (APOB-100)*, *proprotein convertase subtilisin/kexin type 9 (PCSK9)*, and the *LDL receptor adaptor protein 1 (LDLRAP1)*. It is characterized by elevated low-density lipoprotein cholesterol (LDL-c) levels leading to premature coronary artery disease. FH can be clinically diagnosed using established clinical criteria, namely, Simon Broome (SB) and Dutch Lipid Clinic Criteria (DLCC), and can be identified using the Familial Hypercholesterolemia Case Ascertainment Tool (FAMCAT), a primary care screening tool.

Objective: This study aims to (1) compare the detection rate of genetically confirmed FH and diagnostic accuracy between the FAMCAT, SB, and DLCC in the Malaysian primary care setting; (2) identify the genetic mutation profiles, including novel variants, in individuals with suspected FH in primary care; (3) explore the experience, concern, and expectation of individuals with suspected FH who have undergone genetic testing in primary care; and (4) evaluate the clinical utility of a web-based FH Identification Tool that includes the FAMCAT, SB, and DLCC in the Malaysian primary care setting.

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Methods: This is a mixed methods evaluation study conducted in 11 Ministry of Health primary care clinics located at the central administrative region of Malaysia. In Work stream 1, the diagnostic accuracy study design is used to compare the detection rate and diagnostic accuracy of the FAMCAT, SB, and DLCC against molecular diagnosis as the gold standard. In Work stream 2, the targeted next-generation sequencing of the 4 FHCGs is used to identify the genetic mutation profiles among individuals with suspected FH. In Work stream 3a, a qualitative semistructured interview methodology is used to explore the experience, concern, and expectation of individuals with suspected FH who have undergone genetic testing. Lastly, in Work stream 3b, a qualitative real-time observation of primary care physicians using the "think-aloud" methodology is applied to evaluate the clinical utility of a web-based FH Identification Tool.

Results: The recruitment for Work stream 1, and blood sampling and genetic analysis for Work stream 2 were completed in February 2023. Data collection for Work stream 3 was completed in March 2023. Data analysis for Work streams 1, 2, 3a, and 3b is projected to be completed by June 2023, with the results of this study anticipated to be published by December 2023.

Conclusions: This study will provide evidence on which clinical diagnostic criterion is the best to detect FH in the Malaysian primary care setting. The full spectrum of genetic mutations in the FHCGs including novel pathogenic variants will be identified. Patients' perspectives while undergoing genetic testing and the primary care physicians experience in utilizing the web-based tool will be established. These findings will have tremendous impact on the management of patients with FH in primary care and subsequently reduce their risk of premature coronary artery disease.

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KEYWORDS

mixed methods evaluation; study protocol; familial hypercholesterolemia; diagnostic accuracy; qualitative methods; FAMCAT; Simon Broome criteria; Dutch Lipid Clinic Criteria; genetic diagnosis; primary care; Malaysia

Introduction

Familial hypercholesterolemia (FH) is an autosomal dominant genetic disorder characterized by elevated low-density lipoprotein cholesterol (LDL-c) that leads to premature atherosclerotic cardiovascular disease, particularly coronary artery disease (CAD) [1,2]. Genetic mutations in 3 FH candidate genes, namely, *low-density lipoprotein receptor* (*LDLR*), *apolipoprotein B-100* (*APOB-100*), and *proprotein convertase subtilisin/kexin type 9* (*PCSK9*), are responsible for the autosomal dominant form of FH [2], while other rare mutations in the *LDL receptor adaptor protein 1* (*LDLRAP1*) gene and *apolipoprotein E* (*APOE*) gene have been reported to be responsible for the recessive form of FH [3,4]. Mutations in the *ATP-binding cassette subfamily G members 5* and *8* (*ABCG5 and ABCG8*, respectively) genes have been associated with sitosterolemia, an autosomal recessive disorder characterized by increased plant sterol levels [5].

Phenotypically, FH presents in the form of either heterozygous FH (HeFH) or homozygous FH (HoFH) [1,2]. An estimated 70%-90% of cases are HeFH, while HoFH is less common [6,7]. Individuals with HeFH typically present with LDL-c levels of more than 4.9 mmol/L, whereas those with HoFH present with LDL-c levels of more than 13 mmol/L [6,7]. If left untreated, men with FH have a 50% risk of developing CAD by the age of 50, and women with FH have a 30% risk of developing CAD by the age of 60 [8]; however, most individuals with HoFH experience severe CAD before the age of 20 and generally do not survive beyond 30 years of age [6]. Early detection of FH and treatment with lipid-lowering therapies can effectively prevent premature CAD by extending CAD-free life up to 18 years, compared with untreated individuals [9].

Globally, the prevalence of HeFH ranges from 1 in 200 to 1 in 500 in various populations [10], while the prevalence of HoFH is estimated to range from 1 in 160,000 to 1 in 300,000 [6]. In Malaysia, a recent study [11] has estimated that the prevalence of clinically diagnosed FH was 1 in 100. Based on the current total population of 32 million people, a staggering 320,000 individuals are estimated to have FH [11]. A majority of these cases were previously undiagnosed and lipid-lowering medications were prescribed to 30.5%-54.5% of these individuals, but none of them achieved the therapeutic LDL-c target [11]. The under-detection and under-treatment of FH in the Malaysian population resulted in lost opportunities to prevent premature CAD [11]. This common autosomal dominant condition has undeniably contributed to the high prevalence of premature CAD which accounted for 10%-15% of acute coronary syndrome in Malaysia [12]. According to a national report, 23.8% of patients admitted with acute coronary syndrome were younger than 50 years old [13]. Among patients with confirmed premature CAD, 45.5% had clinically diagnosed FH [14]. Therefore, identifying and treating FH early, and subsequently reducing the incidence of premature CAD is a key national priority in Malaysia [15].

Improving FH identification in primary care has been recognized as a cost-effective strategy to reduce premature CAD [16]. In Malaysia, primary care physicians (PCPs) are ideally positioned at the forefront of primary care service where they manage common atherosclerotic cardiovascular disease risk factors such as hypercholesterolemia, hypertension, obesity, and diabetes [17]. However, substantial gaps in knowledge regarding FH have been identified, including knowledge on prevalence, inheritance, and risk of CAD as well as on awareness of FH clinical guidelines and diagnostic criteria [18]. These gaps in knowledge, awareness, and practice regarding FH among PCP could be a significant contributing factor to the poor detection

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of FH in Malaysia [18]. Efforts are currently being undertaken to address these gaps through a partnership with the FH Ten Countries Study to improve awareness of FH among PCP in Malaysia [10,18].

Currently, individuals with FH tend to be discovered incidentally in primary care practice. It has been suggested that primary care should be the key target area to increase identification of new FH index cases and to initiate cascade screening [19-22]. Researchers in the United Kingdom have shown that early identification of FH is achievable in primary care [23-26]. However, the 2 established clinical criteria, namely, Simon Broome (SB) and Dutch Lipid Clinic Criteria (DLCC), are of limited use for case-finding in primary care [24]. These clinical diagnostic criteria were originally developed from secondary care FH registries. Furthermore, these criteria would require a comprehensive physical examination (tendon xanthoma and arcus cornealis), recording of family history, and genetic mutation testing, which are not routinely assessed or inadequately documented in primary care. As a consequence, researchers in the United Kingdom have developed a new tool, the Familial Hypercholesterolemia Case Ascertainment Tool (FAMCAT), based on a risk prediction algorithm developed and validated using primary care databases [26].

The FAMCAT has been shown to perform well as an initial case ascertainment tool to identify FH in the UK primary care setting when it was tested among 3.7 million British patients with cholesterol measurements in primary care electronic health records [25]. Compared with other established diagnostic criteria, the FAMCAT is 20% more accurate in identifying FH than SB criteria and 15% more accurate than DLCC [25,26]. Targeted case-finding for FH in the primary care setting has already been shown to be cost-effective by prioritizing those with the highest likelihood of having FH for further assessment and genetic testing in secondary care [27-29]. This measure would efficiently allocate resources toward those who would benefit the most [27,29].

The performance of the FAMCAT in the United Kingdom has been well recognized [23-26]. However, its performance in the Malaysian primary care setting remains unknown. To improve identification of patients with FH in the Malaysian primary care, we developed a web-based FH Identification Tool to collect key information to identify individuals with suspected FH using the FAMCAT, DLCC, and SB criteria. Using these criteria, patients were screened for features of FH. Those who were suspected to have FH clinically were offered genetic testing. Genetic testing is not routinely available in Malaysia. However, it can be offered if resources are available as it is the gold standard to diagnose FH [30]. We hypothesize that the rate of detection of genetic mutations using the FAMCAT will be higher compared with the SB criteria and DLCC score, thus showing better performance.

Overall, this study aims to enhance detection of individuals with high probability of FH in the Malaysian primary care setting who can then be genetically tested and subsequently referred for further clinical management and cascade screening of family members in multidisciplinary specialized lipid clinics, maximizing efficient use of limited resources. The specific objectives of this study are to (1) compare the detection rate of genetically confirmed FH and the diagnostic accuracy between the FAMCAT and the established clinical diagnostic criteria (SB and DLCC) in the Malaysian primary care setting; (2) identify the genetic mutation profiles, including novel variants, in individuals with suspected FH in the Malaysian primary care setting; (3) explore the experience, concern, and expectation of individuals with suspected FH who have undergone genetic testing in the Malaysian primary care setting; and (4) evaluate the clinical utility of a web-based FH Identification Tool that includes the FAMCAT, SB, and DLCC in the Malaysian primary care setting.

Methods

Study Overview

This is a mixed methods evaluation study that used both the quantitative and qualitative research methods to answer complex research questions, and to understand the process and to strengthen the impact evaluation [31]. Methodologically, this study was divided into Work streams 1, 2, and 3. In Work stream 1, the diagnostic test accuracy study design is used to compare the detection rate of genetically confirmed FH and discriminatory accuracy between the FAMCAT, SB, and DLCC in the Malaysian primary care setting. In Work stream 2, the targeted next-generation sequencing (NGS) is used to identify the genetic mutation profiles among individuals with suspected FH in the Malaysian primary care setting. In Work stream 3a, a qualitative semistructured interview methodology is used to explore the experience, concern, and expectation of individuals with suspected FH who have undergone genetic testing in the Malaysian primary care setting. Lastly, in Work stream 3b, a qualitative real-time observation of PCPs using the "think-aloud" methodology is applied to evaluate the clinical utility of a web-based FH Identification Tool containing the FAMCAT, SB, and DLCC in the Malaysian primary care setting.

Work Stream 1: Comparing the Detection Rate and Diagnostic Accuracy of Genetically Confirmed FH in the Malaysian Primary Care

Study Design and Setting

This is a diagnostic test accuracy study. The study was conducted at 11 Ministry of Health (MOH) primary care clinics located in the urban and suburban areas at the central administrative region of Malaysia (in the states of Selangor, Kuala Lumpur, and Putrajaya). These areas were chosen due to their commutable proximity to the Universiti Teknologi MARA (UiTM) Lipid Specialist Clinic where patients who are genetically confirmed to have FH are referred for further management and cascade screening of their family members.

Site Selection

To be eligible for selection, the clinics must be equipped with an electronic medical record (EMR) system, have minimum attendance of 500 patients per day, and be led by a family medicine specialist (FMS).

In total, there were 21 MOH primary care clinics (15 clinics in Selangor and 6 clinics in Kuala Lumpur and Putrajaya) that

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fulfilled the aforesaid selection criteria. The FMS leading these 21 clinics were invited for a briefing to introduce the study. Out of the 21 clinics, 11 clinics were interested in participating and therefore were included in the study (6 are located in Selangor and the other 5 are located in Kuala Lumpur and Putrajaya).

The site selection for this study was completed in February 2020. Table 1 shows the demographic characteristics of the study sites. All the clinics are located in the urban and suburban areas. The population served ranged from approximately 78,000 to 500,000, with most from the low to middle household income groups. All the clinics have multidisciplinary team members consisting of doctors (FMS and medical officers), assistant medical officers, nurses, dietitians/nutritionists, and pharmacists.

Table 1. Demographic characteristics of the study sites.

Number	Clinic name	Area	Total number of populations served, n	Description of populations served	Total number of multidisciplinary team members, n
1	Precinct 18, Putrajaya	Suburban	91,900	• Middle to high income • Majority are civil servants	180
2	Section 7, Shah Alam	Urban	511,153	• Low to middle income • Majority are working in the private sector	103
3	Sungai Buloh	Suburban	466,163	• Low to middle income • Majority are unemployed and self-employed	183
4	Jinjang	Urban	132,272	• Low to middle income • Majority are self-employed and unemployed	205
5	Pandamaran	Urban	150,000	• Low to middle income • A mixture of private sector workers and civil servants	200
6	Kelana Jaya	Suburban	180,000	• Low to middle income • A mixture of private sector workers and civil servants	171
7	Taman Ehsan	Suburban	78,693	• Low to middle income • A mixture of private sector workers and civil servants	103
8	Selayang Baru	Urban	212,164	• Low to middle income • A mixture of private sector workers and civil servants	150
9	Tanglin	Urban	400,000	• Low to middle income • A mixture of private sector workers and civil servants	170
10	Kuala Lumpur	Urban	105,000	• Middle income • A mixture of private sector workers and civil servants	217
11	Batu Muda	Suburban	180,000	• Low to middle income • A mixture of private sector workers and civil servants	158

Study Population

Patients registered at the 11 MOH primary care clinics were recruited according to the inclusion and exclusion criteria. This study included patients aged 18 years or older and who had an LDL-c level of 4.0 mmol/L or more recorded in their EMR. Those who were previously diagnosed with FH by genetic testing, were pregnant, or did not have the mental capacity to provide informed consent were excluded.

Study Tool and Variables

This study used the FAMCAT web-based FH Identification Tool, developed by and based at the University of Nottingham, UK. This web-based tool contains 3 index tests, namely, the FAMCAT, SB, and DLCC. Figure 1 shows the interface of the FAMCAT web-based FH Identification Tool. Table 2 shows the variables needed to identify patients with suspected FH using the FAMCAT web-based FH Identification Tool.

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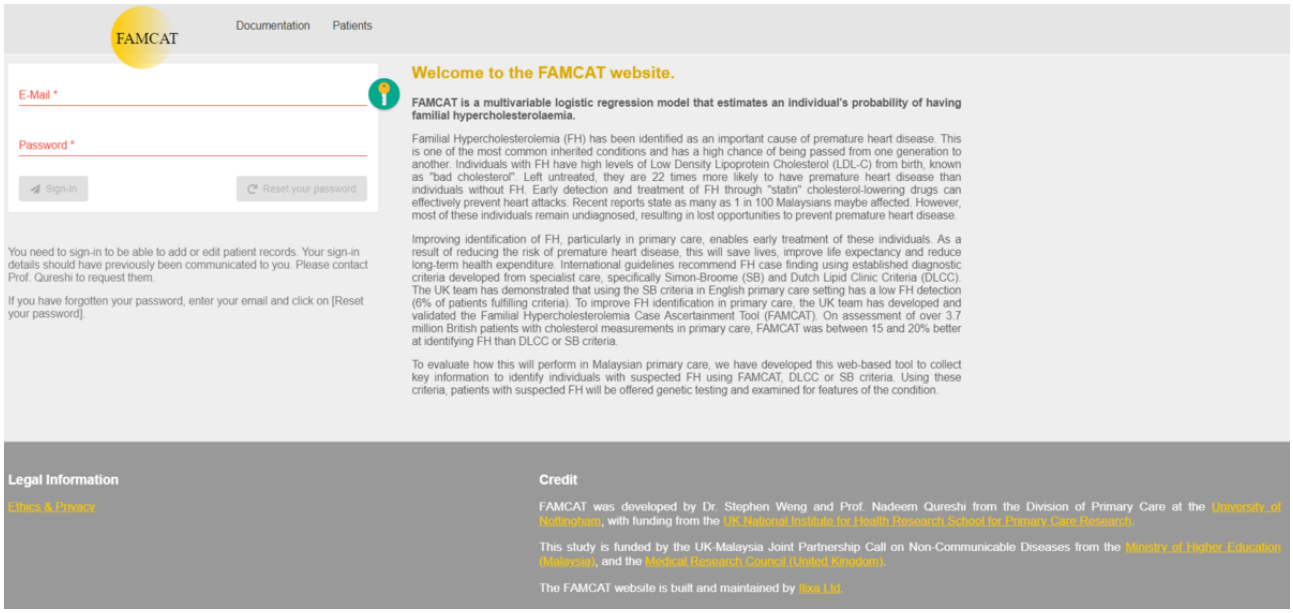
The variables entered into the FAMCAT web-based FH Identification Tool identified patients with suspected FH who were indicated to have genetic testing based on either one of the following definitions:

- The FAMCAT algorithm relative risk score >1 (high probability of FH).
- Clinical diagnosis of “definite” or “possible” FH by SB criteria.
- DLCC score ≥6 (clinical diagnosis of “definite” or “probable” FH by DLCC).

The disease of interest is the HeFH and the reference standard for diagnosis is genetically confirmed HeFH determined by targeted NGS of pathogenic variants (PVs) in 4 FH candidate genes (ie, *LDLR*, *APOB-100*, *PCSK9*, and *LDLRAP1*).

Full details of the genetic testing methods are presented in Work stream 2. The laboratory staff analyzing the samples and the specialist interpreting the genetic test results were blinded to the index tests results.

Figure 1. Interface of the FAMCAT web-based FH Identification Tool.



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Table 2. Clinical diagnostic variables for the FAMCAT[a], SB[b], and DLCC[c].

Index tests	SB criteria	DLCC	FAMCAT
Lipid levels	• Total cholesterol >7.5 mmol/L • LDL-c[d] >4.9 mmol/L	• LDL-c ≥4 mmol/L	• The highest LDL-c ever measured • The highest total cholesterol ever measured • Triglycerides during LDL-c measurement • Age during LDL-c measurement • Lipid-lowering treatment during LDL-c measurement
Physical examination	• Tendon xanthomas	• Tendon xanthomas • Corneal arcus <45 years of age	• Nil
Personal history	• Nil	• Personal history of premature CAD[e], cerebrovascular accident, or peripheral vascular disease (<55 years in men, <60 years in women)	• Personal history of premature myocardial infarction (<55 years in men, <60 years in women) • Diagnosis of diabetes • Diagnosis of chronic kidney disease
Family history	• Tendon xanthomas in a first- or second-degree relative • Family history of premature myocardial infarction <60 years in a first-degree relative or <50 years in a second-degree relative • Family history of elevated total cholesterol >7.5 mmol/L in a first- or second-degree relative • Family history of elevated total cholesterol >6.7mmol/L in a child or siblings ≤16 years old	• A first-degree relative with tendon xanthomas or corneal arcus • A first-degree relative with premature CAD, cerebrovascular accident, or peripheral vascular disease (<55 years in men, <60 years in women) • A first-degree relative with LDL-c >95th percentile • Children <18 years with LDL-c >95th percentile	• Family history of premature myocardial infarction (<55 years in men, <60 years in women) • Family history of familial hypercholesterolemia

[a]FAMCAT: Familial Hypercholesterolemia Case Ascertainment Tool.

[b]SB: Simon Broome.

[c]DLCC: Dutch Lipid Clinic Criteria.

[d]LDL-c: low-density lipoprotein cholesterol.

[e]CAD: coronary artery disease.

Patients Recruitment and Sampling Method

Patient recruitment was conducted by the research assistants (RAs) under the supervision of clinician investigators, who were the FMS. A list of patients with LDL-c levels of 4.0 mmol/L or more was extracted from the EMR. These patients were then stratified into 4 groups (≥7.0 mmol/L, 6.0-6.9 mmol/L, 5.0-5.9 mmol/L, and 4.0-4.9 mmol/L). Patients in these 4 groups were invited to participate via social media messaging service. This comprised a concise invitation message and a flyer containing information about the study. Invitations were sent to all patients in the highest LDL-c groups of 7.0 mmol/L or more and 6.0-6.9 mmol/L. Equal numbers of patients in the other 2 groups (5.0-5.9 mmol/L and 4.0-4.9 mmol/L) were invited to participate. If the patient did not respond to the invitation message sent via the social media messaging service, the RA followed up with a telephone call. Those who agreed to participate were given an appointment to be screened according to the inclusion and exclusion criteria at the primary care clinic.

At the primary care clinic, the patients received the study information sheet and informed consent form. This is available in either Malay or English language according to patients' preference. It contains important information pertaining to the study and included background; purpose; benefit and risk; information regarding participation, including possibility of genetic testing (if indicated), study procedure, confidentiality status, and contact information. The RA gave the information verbally when the patients required further information or clarification.

Those who verbally consented to participate were screened for eligibility according to the inclusion and exclusion criteria. Screening for the eligibility criteria was conducted by the RA through structured interviewing of the patients. Those who fulfilled the eligibility criteria and agreed to participate were recruited; and written informed consent was obtained by the RA.

Patients were recruited until the sample size was achieved. Sample size calculation for this study is described later in this manuscript.

Data and Sample Collection Procedures

Data collection at the primary care clinics was conducted by the RA under the supervision of the clinician investigators. Prior to data collection, a training workshop for the RA and the clinician investigators was conducted to ensure standardization of study procedures. The training included physical examinations to identify tendon xanthomata and corneal arcus, and taught the participants how to use the FAMCAT web-based

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FH Identification Tool. At the primary care clinic, the RA also had an on-site hands-on training on how to interview patients, review the EMR, identify clinical signs of FH, and enter data into the FAMCAT web-based FH Identification Tool. During the first 2 months of the study, the clinician investigator directly observed the RA during the data collection and physical examination procedures. Further, they were trained on how to counsel patients for genetic testing.

Data were collected using the data collection form and standardized questionnaires, both of which have been translated into the Malay language. Participants were requested to fill in the sociodemographic data (age, ethnicity, education level, marital status, household income) and the Family History Questionnaire [32]. Clinical data (ie, significant medical history, medication history, and previous lipid profile results [total cholesterol, triglycerides, and LDL-c]) were retrieved from the EMR in the presence of the patients. Physical examination to identify tendon xanthomata and corneal arcus was performed by the RA, supervised by the clinician investigators. To identify patients who may need immediate medical attention, the WHO Rose Angina Questionnaire [33] and Edinburgh Claudication Questionnaire [34] were administered.

All of the variables that were collected on paper were double entered by the RA into a Microsoft Excel spreadsheet and the FAMCAT web-based FH Identification Tool to identify patients with suspected FH who were indicated for genetic testing. The criteria for genetic testing have previously been described in the "Study Tool and Variables" section.

Patients with suspected FH who were indicated to have genetic testing were given another set of patient information sheet and informed consent form in either Malay or English language. It contains important information pertaining to genetic testing. Participants were counseled regarding their risk of having FH, the pattern of inheritance, the genetic testing procedure, confirmation of diagnosis after the genetic testing, further management, and the need for cascade screening of family members once they are genetically diagnosed. Written informed consent was obtained from those who agreed to participate. Approximately 4 mL of venous blood sample was collected from each participant into an ethylenediaminetetraacetic acid (EDTA) tube. These samples were kept in a temperature-controlled container and were delivered to the Institute of Pathology, Laboratory and Forensic Medicine (I-PPerForM) Genetic Laboratory within 3 hours.

Sample Size Calculation

A previous study, in a UK population, found the detection rate for genetically confirmed FH using the FAMCAT to be 28% [35]. Therefore, a sample size of 310 will allow for a single proportion of 28% to be estimated with a 95% confidence level within a 5% margin (ie, from 23% to 33%).

Study Outcomes and Process Measures

Primary Outcomes

- Comparison of detection rate of genetically confirmed FH between the FAMCAT, SB, and DLCC.

Secondary Outcomes

- Sensitivity and specificity;
- Area under the curve;
- Positive and negative predictive values;
- Diagnostic odd ratio.

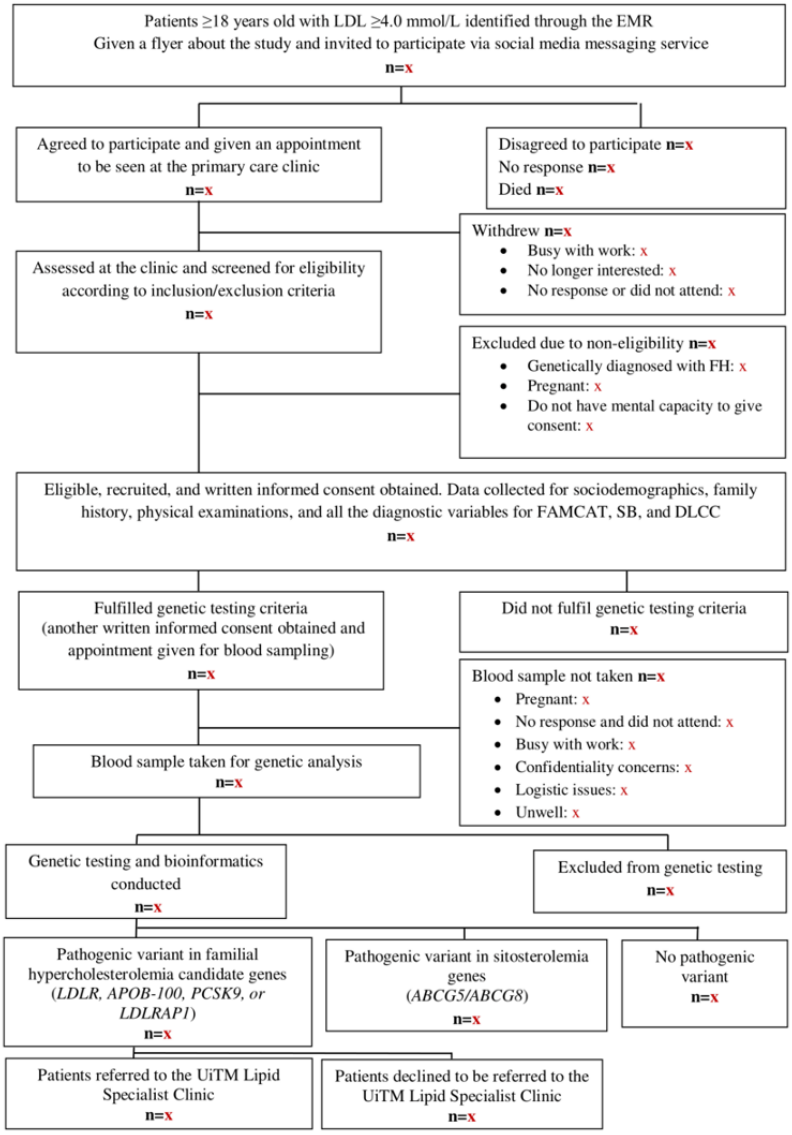
Process Measures

- Number of patients who are screened through the EMR and invited to participate.
- Number and proportion of patients who disagree to participate or do not respond (out of those invited).
- Number and proportion of patients who agree to participate and are given appointment to be seen at the primary care clinic (out of those invited).
- Number and proportion of patients who withdraw after being given an appointment (out of those given an appointment).
- Number and proportion of patients who are assessed for eligibility according to the inclusion/exclusion criteria at the primary care clinic (out of those given an appointment).
- Number and proportion of patients who are excluded due to noneligibility (out of those who are assessed at the clinic).
- Number and proportion of patients who are eligible, recruited, and for whom written informed consent was obtained (out of those who are assessed at the clinic).
- Number and proportion of patients with complete diagnostic variables data entered into the web-based FH Identification Tool (out of those who are eligible and recruited).
- Number and proportion of patients who fulfilled the genetic testing criteria (out of those who are eligible and recruited).
- Number and proportion of patients who give consent and have blood sample taken for genetic analysis (out of those who fulfilled the genetic testing criteria).
- Number and proportion of patients who are identified to have PV in any of the 4 FH candidate genes (out of those who have blood sample taken for genetic analysis).
- Number and proportion of patients who agree to be referred to the lipid specialist for further care (out of those who have PV in any of the 4 FH candidate genes).

Figure 2 shows the flowchart of participants screening and recruitment at the primary care clinics.

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Figure 2. Flowchart of the participants screening and recruitment.



Statistical Analysis Plan

The demographics and clinical characteristics of the participants included in the study will be reported using descriptive measures, where frequencies (with percentages) will be used for categorical outcomes and either means (with SDs) or medians (with IQRs) will be used for continuous outcomes. Measures of diagnostic accuracy (detection rate, sensitivity, specificity, positive and negative predictive values, area under the curve, and diagnostic odds ratio) for each of the 3 index tests will be reported with their corresponding 95% CIs, with genetic testing as the reference standard. The diagnostic accuracy of the FAMCAT compared with SB and DLCC will be conducted using paired analyses by constructing a joint classification table and estimating the relative diagnostic odds ratio and relative likelihood ratios, with corresponding 95% CIs. Stratified analyses will be conducted to assess the impact of ethnicity (genotyping profile) and sensitivity analyses will be conducted excluding people with hypothyroidism. Process outcome measures will be reported as frequencies (with percentages).

Work Stream 2: Identifying Genetic Mutation Profiles of Individuals With Suspected FH

Study Design and Setting

Targeted NGS of the 4 FH candidate genes (FHCGs), namely, *LDLR*, *APOB-100*, *PCSK9*, and *LDLRAP1*, and 2 hypercholesterolemia-associated genes (HCAGs), namely, *ABCG5* and *ABCG8*. The study is performed at the I-PPerForM Genetic Laboratory located in UiTM Sungai Buloh Campus, Selangor, Malaysia.

Sample Collection

The EDTA tubes containing venous blood samples were delivered in a temperature-controlled container from the primary care clinics to the I-PPerForM Genetic Laboratory within 3 hours. Once received, the whole blood was stored in a freezer at –20°C before further analysis.

DNA Extraction

The DNA extraction was conducted by an RA who was blinded to the index tests results (FAMCAT, SB, and DLCC) using standardized method [36]. The frozen blood samples were

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thawed at room temperature before being subjected to DNA extraction using MasterPure DNA Purification Kit for Blood Version II (Lucigen Corporation). A total of 200 µL whole blood and red cell lysis solution (600 µL) were pipetted and mixed in a microcentrifuge tube. The mixture was incubated at room temperature for 5 minutes and then briefly vortexed. After centrifuging for 25 seconds, the supernatant was removed, leaving approximately 25 µL of pellet (white blood cells). The white blood cells were resuspended in 300 µL tissue and cell lysis solution by pipetting. RNase A (1 µL) was added and thoroughly mixed. The samples were then incubated for 30 minutes at 37°C. The samples were placed on ice for 3-5 minutes, followed by addition of the MasterPure Complete protein precipitation reagent (175 µL) into the lysed sample. The mixture was vigorously vortexed for 10 seconds. The debris was pelleted by centrifugation for 10 minutes at 10,000*g* or more in a microcentrifuge. The supernatant was transferred to a clean centrifuge tube and the pellet was discarded. Isopropanol (500 µL) was added to the recovered supernatant. The DNA was pelleted by centrifugation at 4°C for 10 minutes in a microcentrifuge. The isopropanol was carefully removed, without dislodging the DNA pellet. The DNA pellet was rinsed 2 times with 70% ethanol (EtOH; Fisher Scientific), without dislodging the pellet. All the residual EtOH was removed. Approximately 3-9 µg of DNA was acquired, which was then resuspended in 35 µL of Tris-EDTA (TE) buffer (Sigma). The DNA was then quantitated. The extracted DNA was stored in a –20°C freezer to preserve its integrity.

Quantification and Quality Control

QuickDrop Quantification

The concentration and purity of samples were determined using the SpectraMax QuickDrop Micro-Volume Spectrophotometer (Molecular Devices). TE buffer (1 µL) was then used as the blank and 1 µL sample was pipetted onto the sample port. The reading for the concentration (ng/µL) and purity were recorded. Samples with concentration of 20 ng/µL or more and purity of A260/A280=1.70-2.00 were subjected to electrophoresis that was performed to clarify the intactness of DNA.

Qubit Quantification

The Qubit dsDNA HS (High Sensitivity) Assay Kit (Thermo Fisher Scientific) was used to further assess DNA quality. Samples with concentration of 50 ng/µL or more based on the QuickDrop readings were diluted to 18-30 ng/µL in case the reading was underestimated before proceeding to Qubit quantification.

The Qubit working solution was prepared by diluting the Qubit dsDNA HS Reagent in the Qubit dsDNA HS Buffer with a ratio of 1:200. The Qubit dsDNA HS assay requires 2 standards for calibration. The standards were prepared by mixing 190 µL Qubit working solution and 10 µL of each Qubit standard. The solution was then mixed by vortexing for 2-3 seconds. For sample preparation, 2 µL of the sample was added to 198 µL of the Qubit working solution. The solution was then mixed by vortexing for 2-3 seconds. The tubes were allowed to incubate at room temperature for 2 minutes before being read by the fluorometer. The actual concentration of DNA was obtained by calculating the readings from Qubit and times with the number of dilutions.

Ethanol Purification

One part of sodium acetate solution (3.0 M; pH 5.2; Sigma) and 2 parts of cold absolute EtOH were added to 10 parts of the DNA sample volume. The mixture was vortexed for 10 seconds and kept in a –70°C freezer for 20 minutes. The mixture was then transferred into a column tube and centrifuged for 10 minutes, at 14,000*g* in 4°C. The supernatant was carefully discarded without moving the DNA pellet, which was later washed with 500 µL of 70% EtOH, followed by centrifugation for another 10 minutes, at 14,000*g* in 4°C. The supernatant was discarded and the washed pellets were air dried. The pellets were resuspended in 40 µL elution buffer (EB) buffer and requantified using QuickDrop, followed by agarose gel electrophoresis and Qubit fluorometer reading.

Next-Generation Sequencing

Custom Targeted Gene Sequencing

The NGS [37] was run using an AmpliSeq Custom DNA panel (Illumina), which was designed using the Illumina DesignStudio Sequencing Assay Designer. The targeted NGS employed the amplicon sequencing method, where PCR primers were used to amplify the sequences of interest. Samples used for amplicon sequencing were transformed into libraries and enriched via PCR amplification individually and barcoded by ligating the indexes into the amplicons. The libraries were then pooled and analyzed using a bench-top sequencer. The panel in this study was designed to identify the 4 FHCGs, namely, *LDLR*, *APOB-100*, *PCSK9*, and *LDLRAP1*, and the HCAGs, namely, *ABCG5* and *ABCG8*, with an overall gene coverage of 98.61% [38-40].

Quantification and Dilution of DNA

The samples were diluted to an intermediate concentration of about 20-50 ng/µL using low TE followed by requantification using the Qubit fluorometer. The samples were then further diluted into the desired final concentration of 3.5 ng/µL using low TE.

Amplification of DNA Targets

For each sample, 7 µL of 5× AmpliSeq HiFi Mix and 10.5 µL DNA samples (3.5 ng/µL) were combined in a fresh 1.5-mL microcentrifuge tube to bring the total volume of the master mix to 17.5 µL. About 5 µL of the master mix was transferred into a 96-well PCR plate. Because of the complexity of the panel design, each sample was separated into 3 different wells and separately added with different 5 µL of 2× AmpliSeq Custom DNA Panel Pool (the primer pool). In total, each well contained 5 µL sample master mix and 5 µL primer pool for a total of 10 µL per well. The plate was properly sealed and briefly centrifuged. The plate was placed in a preprogrammed thermal cycler and run with the following settings: preheat lid option, 105°C; reaction volume, 10 µL; 99°C, 2 minutes; 19 cycles of –99°C for 15 minutes and –60°C for 4 minutes; and 10°C for up to 24 hours.

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Partial Digestion of Amplicons

After PCR, the 3 separated products amplified from the same sample were then combined into 1 well, making the total volume per sample as 30 µL. Then, 3 µL of the FuPa reagent was added to each combined sample. The plate was sealed, briefly vortexed at 1600 rpm for 1 minute, followed by centrifugation at 280*g* for 1 minute. The plate was placed in the thermal cycler and run with the following settings: preheat lid, 105°C; reaction volume, 33 µL; 50°C for 10 minutes; 55°C for 10 minutes; 62°C for 10 minutes; and 10°C for up to 1 hour.

Ligate Indexes

Switch solution (6 µL), AmpliSeq CD indexes (3 µL), and finally DNA ligase (3 µL) were added sequentially into each well containing the digested amplicons (33 µL) to a total volume of 45 µL for each sample. The plate was then sealed, vortexed, centrifuged, and placed into the thermal cycler and run with the following settings: preheat lid, 105°C; reaction volume, 45 µL; 22°C for 30 minutes; 68°C for 5 minutes; 72°C for 5 minutes; and 10°C for up to 24 hours.

Cleanup Library

A total of 45 µL of AMPure XP beads were added to each library. The plate was then sealed, vortexed, centrifuged, and incubated at room temperature for 5 minutes. The plate was then placed on a magnetic stand until the mixture became clear (approximately 2 minutes). While still on the magnetic stand, the plate was unsealed, and the supernatant was carefully pipetted out from each well. The beads were washed by adding 150 µL freshly prepared 70% EtOH to each well, followed by incubation at room temperature until the solution became clear (approximately 30 seconds). Without disturbing the pellets, the supernatant was again discarded from each well. The washing step was repeated once again. The plate was sealed, briefly centrifuged, and placed on the magnetic stand in the same position as before. The plate was unsealed and all residual EtOH was removed from each well.

Amplify Library

In a fresh 1.5 µL microcentrifuge tube, 1125 µL of 1× Lib Amp Mix was combined with 125 µL of 10× Library Amp Primers for a total of 1250 µL amplification master mix. The master mix was vortexed and centrifuged briefly. The plate was removed from the magnetic stand and 50 µL of the master mix was added to each well and the plate was sealed again, vortexed, centrifuged, and placed into the thermal cycler and run with the following settings: preheat lid, 105°C; reaction volume, 50 µL; 98°C for 2 minutes; 7 cycles of 98°C for 15 seconds and 64°C for 1 minute; and 10°C for up to 24 hours.

Second Cleanup

About 25 µL of AMPure XP beads were added to each well containing approximately 50 µL library and the plate was sealed again. The library was vortexed, centrifuged briefly, and incubated at room temperature for 5 minutes. The plate was placed on the magnetic stand for another 5 minutes until the liquid is clear and the plate was unsealed. The entire supernatant that contains the desired amplicon library (approximately 75 µL) was transferred to a new plate and 60 µL of AMPure XP beads were added to each well in the new plate. The plate was briefly vortexed, centrifuged, and incubated at room temperature. After 5 minutes, the plate was placed on the magnetic stand for another 5 minutes until the liquid cleared. The plate was unsealed. Without disturbing the beads, the supernatant was discarded from each well. The beads were washed by adding 150 µL freshly prepared 70% EtOH to each well, followed by incubation at room temperature until the solution became clear (approximately 30 seconds). Without disturbing the pellets, the supernatant was discarded from each well. The washing step was repeated once again. All residual EtOH was pipetted out, and the plate was air dried on the magnetic stand for 5 minutes. Low TE (30 µL) was added to each well and mixed well. The plate was sealed again, vortexed, and centrifuged briefly to disperse the beads. It was then placed on the magnetic stand until the liquid cleared and then unsealed. About 27 µL supernatant that contains the amplicon library was transferred to a new plate.

Libraries Checking

Each library was subjected to Qubit quantification to ensure the concentrations were approximately 1-10 ng/µL.

Bioanalyzer Reading

Each sample was diluted to 0.5-1.0 ng/µL before the bioanalyzer step. Size distribution of the library was checked using the Agilent High Sensitivity DNA Kit (Agilent Technologies). Nearly 15 mL of high-sensitivity DNA dye concentrate was added to a vial containing high-sensitivity DNA gel matrix. The mixture was vortexed and transferred to a spin filter, and subsequently centrifuged to obtain the elution. The gel-dye mix elution was allowed to equilibrate to room temperature for 30 minutes before use. A high-sensitivity DNA chip was put on the chip priming station. About 9 µL of the gel-dye mix was pipetted into the loading well on the chip. A priming plunger was used to push the gel-dye mix to the entire sample wells on the chip. About 5 µL marker was pipetted into each sample well and a ladder well. Nearly 1 µL high-sensitivity DNA ladder was also pipetted in the ladder well. Then, 1 µL sample was also pipetted into each sample well. The chip was vortexed for 1 minute at 2400 rpm, and then run in the Agilent 2100 Bioanalyzer instrument (Agilent Technologies) within 5 minutes after its preparation. Each library size was recorded in a Microsoft Excel sheet and the average library size measured was determined. The molarity of the library was calculated using the following formula [41]:

$$\text{Molarity (nM)} = [(\text{ng}/\mu\text{L}) \times 10^6]/[660\ (\text{g/mol}) \times \text{average library size (bp)}]$$

Dilution of the Library to the Starting Concentration

Samples (about 5 µL) were pipetted into separate microcentrifuge tubes. EB-0.1% Tween 20 mix was pipetted into each sample tube, where the volume varies so the final molarity of each sample was 4 nM. Next, 5 µL of each library was pooled into a single microcentrifuge tube. The library pool was subjected to Qubit to confirm the 4 nM concentration.

Sequencing

The Illumina iSeq 100 is a benchtop high-throughput sequencer, measuring 1 ft^3 in size. This sequencer is useful for sequencing

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small genome, transcriptome, long amplicon, and targeted resequencing applications, generating up to 1.2 Gb data per run.

The cartridge was first thawed overnight in a water bath (20-25°C) in its foil bag. When the cartridge is ready, 4 nM library pool was diluted to 50 pM loading concentration using EB. About 10 nM of PhiX (control library) was diluted to 50 pM using EB. Then, 2 µL of PhiX (50 pM) was added to 98 µL library pool (50 pM), making the final pool volume as 100 µL.

The cover of the loading reservoir on the thawed cartridge was first teared using a pipette tip. Then, 20 µL final pooled library was pipetted into the bottom of the reservoir. Flow cell was inserted into the cartridge. Then, the cartridge-flow cell assembly was inserted into the iSeq 100 tray. Run was initiated using instrument control software. The total runtime was up to 17.5 hours.

Bioinformatics Analysis

The iSeq100 run monitoring was executed using BaseSpace Sequence Hub (Illumina) cloud-based software, where GRCh37 hg19 human reference assembly [42] was used to map genomic sequences. Variant calls and differential expression results for amplicon panels were produced using BaseSpace Sequence Hub and Local Run Manager (on-board).

The variant call format (VCF) files were extracted and downloaded from BaseSpace Sequence Hub. Variants with minor allele frequency of 0.05 or less, based on either the gnomAD or 1000 Genome database, were considered as rare gene mutations.

Variant Call Format Analysis

The VCF files were outsourced (BioEasy Sdn Bhd) for data cleaning and bioinformatics interpretation [43]. Gene filtering for *LDLR, APOB-100, PCSK9, LDLRAP1, ABCG5,* and *ABCG8* was conducted by coordination using the BED format file downloaded from the UCSC Genome Browser, and each VCF format file was subjected to gene filtering using BCFtools. The overlapping list of variants was merged into 1 single list of variants consisting of 1 sample per column using BCFtools. Consistent gene annotation was performed using the SnpEff and Genome Analysis Toolkit/GATK. The cumulative allele frequency and the global minor allele frequency (GMAF) values were annotated using BCFtools. REVEL scores for hg19 were prepared for annotation using BCFtools. The SIFT annotation was performed using the SIFT4G annotator program, while PolyPhen-2 annotation was prepared using BCFtools. Variants with no GMAF values and GMAF ≤5% were separated into different files.

Pathogenicity Interpretations

The cleaned and combined VCF files were further analyzed for variant pathogenicity using modified American College of Medical Genetics and Genomics guidelines [44,45]. The American College of Medical Genetics and Genomics guidelines classify variant pathogenicity based on the type of mutation and other clinical evidence such as medical history, population frequency, in silico prediction, functional study, and segregation data. Additional reliable sources of references were identified using ClinVar [46] and Leiden Open-source Variation Database [47] websites. The variants were ultimately classified into "pathogenic" (PV), "likely pathogenic," "benign variant," or "variant of unknown significance." The RA, Genetic Laboratory staff, and the lipid specialists who were involved in analyzing and interpreting the genetic results were blinded to the index tests results (FAMCAT, SB, and DLCC) and the relevant variables collected in Work stream 1.

Delivery of the Genetic Results

The genetic analysis results for individual patients will be delivered by the clinician investigators. Patients who are genetically confirmed to have FH will be counseled regarding the nature of the genetic mutations, mode of inheritance, the need for pharmacological management, and cascade screening of first- and second-degree relatives. The importance of adherence to lifestyle modification and pharmacotherapy will also be emphasized. Lipid-lowering treatment for each patient will be reviewed and uptitrated to achieve an LDL-c target of <1.8 mmol/L [48,49]. Patients will also be supported psychosocially on how to adapt with the condition. They will be referred to the UiTM lipid specialists for further management and cascade screening of family members.

Work Stream 3a: Exploring the Experience, Concern, and Expectation of Individuals With Suspected FH

Study Design, Setting, Population, and Method

This is a nested qualitative study performed in MOH primary care clinics. The study population included patients with suspected FH who have undergone genetic testing. Semistructured interviews and thematic analysis of data are performed.

Sampling Method

Patients with suspected FH who have received their genetic analysis results are purposefully sampled to reflect their social, ethnic, and educational diversity, and range of results including those who are genetically confirmed to have FH and those with negative results. Written informed consent is obtained from the participants.

Data Generation

Semistructured in-depth interviews are conducted face-to-face or virtually using the online platform Google Meet (Google LLC/Alphabet Inc.) by an RA, supervised by a Malaysian lead qualitative co-investigator (SAR) who is an expert in qualitative study methods. A topic guide developed for the interview (Multimedia Appendix 1) is used to help explore patients' experience and concern of being identified with suspected FH, of undergoing FH genetic testing, and understand their experience of receiving the results and undergoing follow-up assessment and referral processes [50]. The interviews are conducted for up to 45 minutes, and they are audio- and video-recorded. Recruitment and data generation will continue until saturation of themes. This is expected to be achieved by interviewing approximately 10-15 patients [51,52].

Data Analysis

Data from the interviews will be transcribed verbatim and translated into English. Data will be organized using NVivo

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qualitative software (QSR International) [53], and analyzed thematically by JK, SAR, and LC. Coding and development of analysis will involve a minimum of 2 qualitative researchers (SAR and LC).

Work Stream 3b: Evaluating Clinical Utility of the Web-Based FH Identification Tool in Malaysian Primary Care

Study Design, Setting, Population, and Method

This is a nested qualitative study conducted in MOH primary care clinics. The study population included PCPs working at the MOH Primary Care Clinics. The "think-aloud" interview method [54] is applied.

Sampling Method

PCPs are purposefully sampled to reflect their varied lengths of clinical experience, and range of use of the FAMCAT web-based FH Identification Tool in practice. Written informed consent is obtained from the participants.

Data Generation

Interviews are conducted using the "think-aloud" method [54] in which participants are required to talk aloud while using the FAMCAT web-based FH Identification Tool. A user manual and task scenarios (Multimedia Appendix 2; also see [26,55,56]) have been created to assist clinicians in performing clinical tasks simulation using the web-based tool. The clinical scenarios are standardized for all participants, regardless of their level of clinical experience. The task scenarios are reviewed by the research team members, including experienced and practicing PCPs, to ensure that the content, format, and presentation are representative of real clinical use and addressed the major functional components of the application.

The "think-aloud" interview method generates direct data on participants' ongoing thought processes during task performance. The underlying assumption of "think aloud" is based on human cognition where it is postulated that only information capable of being verbalized in situ is being actively processed in the working memory and so is taken as an active representation of task performance [54]. The output of this process is called a verbal protocol, which is then transcribed and systematically analyzed to develop a model of the persons' task behavior.

Video-based observational data are collected to record the participants' interaction with the interface and functionality of the FAMCAT web-based FH Identification Tool. These data are time-locked for analysis to the verbal protocols. Following the end of the task simulations, participants complete a short questionnaire to capture a subjective measure of their user satisfaction with the interface and functionality of the FAMCAT web-based FH Identification Tool. Recruitment and data generation will continue until saturation of themes and this is expected to be achieved by interviewing approximately 10-15 participants [51,52].

Data Analysis

Each verbal protocol will be transcribed and coded using a predefined coding scheme following the categories of interest. Similarly, the audio-video–recorded simulation will provide a range of images on all of the tasks including time to completion, types of clinical knowledge, resources accessed, participants' statements, and the tasks associated therewith. Two qualitative researchers will independently map the statements made by participants and the video observations, identifying both "positive" and "negative" mental heuristics; the former demonstrating potential features that are acceptable to the needs of participants, and the latter to determine whether there are any possible refinements that might be made to the FH Identification Tool.

Ethics Approval

This study protocol was approved by the respective research ethics committees in Malaysia, namely, the UiTM Research Ethics Committee [(REC/03/2020) (FB/48)] and the Medical Research Ethics Committee of the Ministry of Health Malaysia [NMRR-20-272-52797 (IIR)].

Results

The recruitment for Work stream 1 and blood sampling and genetic analysis for Work stream 2 were completed in February 2023. The data collection for Work stream 3a and 3b was completed in March 2023. Data analysis for Work streams 1, 2, 3a, and 3b is projected to be completed by June 2023, with the results of this study anticipated to be published by December 2023.

Discussion

Expected Findings

To the best of our knowledge, this is the first study to assess the diagnostic accuracy of different clinical diagnostic criteria (SB, DLCC, and FAMCAT) in identifying FH in the Malaysian primary care setting, with molecular diagnosis targeting the 4 FHCGs (*LDLR*, *APOB-100*, *PCSK9*, and *LDLRAP1*) as the gold standard. The findings will also include molecular analysis of the 2 HCAGs (*ABCG5* and *ABCG8*). The full spectrum of genetic mutations in these 6 genes including novel PVs will be identified. This study also included nested qualitative research exploring the experience, concern, and expectation of patients with suspected FH who have undergone genetic testing and also real-time observation of PCPs using the "think-aloud" method to evaluate the clinical utility of the FAMCAT web-based FH Identification Tool in the Malaysian primary care setting. In a nutshell, it is a comprehensive mixed methods study that uses both quantitative and qualitative research methods to answer complex research questions, understand the process, and strengthen the impact evaluation [31].

A previous diagnostic accuracy study that included 755 individuals with an LDL-c level of 4.0 mmol/L or more from secondary care clinics and community health screenings in Malaysia showed that the SB criteria appeared to be the most useful in identifying FH compared with the Japanese FH Management Criteria and the US Make Early Diagnosis to Prevent Early Deaths criteria, when assessed against the DLCC as the gold standard [57]. However, unlike this study, genetic testing was not performed in the previous study.

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Recent studies have shown that NGS is the method of choice [58,59] and is cost-effective in the genetic diagnosis of FH in primary care [60-62]. The targeted NGS method [37] that is being used in this study is robust and efficient in terms of speed, read length, and throughput, designed to identify the 4 FHCGs and the 2 HCAGs, giving an overall gene coverage of 98.61% [38-40].

The nested qualitative research exploring the patients' perspectives while undergoing genetic testing and the PCPs experience in utilizing the web-based tool will add tremendous value in developing a clinical care pathway that is patient-centered [63]. A recent qualitative study [64] showed that the main benefit of genetic diagnosis from the patients' perspective lies in its ability to provide accurate information to their younger family members to undergo screening, and subsequently receive timely management to reduce their risk of having premature CAD. In the United Kingdom, patients and practitioners reported a positive experience when genetic testing was introduced with electronic case-finding for FH in primary care [63].

Implications on Clinical Practice

The findings from this study will be shared through scientific publications, conference presentations, and through a resource impact report with the key stakeholders. The resource impact report will include a patient-centered clinical care pathway that will be implemented by the stakeholders in primary care. FH management training modules for primary care providers will also be developed and delivered through online webinars or face-to-face workshops, to enhance their knowledge and skills in managing FH. Dissemination of knowledge regarding FH and its genetic causes will also be made available to the general public through public health campaigns using various mass media channels and social media platforms. All of these imperative measures will accelerate early FH identification in the Malaysian primary care setting and subsequently reduce the risk of premature CAD.

Limitations

This study has several limitations. First, the selection of sites was limited to the clinics located in the urban and suburban conurbations that can access genetic testing facility at the I-PPerForM Genetic Laboratory. Future research should include a wider selection of clinics including those in the rural parts of Malaysia. Second, only those clinics with EMR were invited to participate as the screening for patients with elevated LDL-c levels was conducted through the EMR. This could potentially cause selection and recruitment bias. To minimize this bias, purposive sampling was conducted by targeting those with the highest LDL-c levels, with study invitations sent to all patients in the highest LDL-c groups of 7.0 mmol/L or more and 6.0-6.9 mmol/L, while an equal number of patients were invited from the lower LDL-c groups of 5.0-5.9 mmol/L and 4.0-4.9 mmol/L.

Third, this study will provide insights into the nature of mutations in the 6 targeted genes, but it does not include functional studies to validate the pathogenicity of the potential PV, which is warranted in future studies. The polygenic hypercholesterolemia genes were also not included as they are not within the scope of this study. Therefore, future studies are warranted to evaluate the impact of polygenic hypercholesterolemia genes on patients with clinically suspected FH without any PV. Additionally, the targeted NGS method used in this study was not able to detect large gene rearrangements, which may account for a small proportion of PV in patients with FH [65,66].

Fourth, the molecular analysis was performed only in index cases. Cascade screening of family members will be conducted and they will be clinically diagnosed with SB or DLCC. Unfortunately, we are not able to offer genetic testing to the family members due to financial constraints and this is also beyond the scope of this study.

Conclusions

This comprehensive mixed methods study will provide objective evidence on which clinical diagnostic criterion is the best to detect FH in the Malaysian primary care setting against molecular diagnosis as the gold standard. The full spectrum of genetic mutations in the 6 targeted genes including novel PVs will be identified. Patients' perspectives while undergoing genetic testing and the PCPs experience in utilizing the web-based tool will be established in this study. These findings will have a tremendous impact in advancing the scientific knowledge and skills on the clinical and genetic diagnosis of patients with FH in primary care and subsequently reduce their risk of premature CAD.

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the nurses at the MOH primary care clinics, and all the staff at the I-PPerForM Genetic Laboratory for their assistance rendered in data collection and performing the genetic analysis.

Data Availability

Raw data are kept at the Institute of Pathology, Laboratory and Forensic Medicine (I-PPerForM), Universiti Teknologi MARA, Selangor, Malaysia and encrypted data are kept at the University of Nottingham, United Kingdom in secured databases. Unidentified data will be shared by the corresponding authors upon request after all the results of this study have been published; and the data are subjected to the data protection regulations of Malaysia and the United Kingdom.

Authors' Contributions

This study was conceptualized and designed by ASR, NQ, HAH, JK, and HN. The funding for the study was acquired by ASR and NQ. ASR is the Principal Investigator for Malaysia and NQ is the Principal Investigator for the United Kingdom. ASR, NQ, HAH, and HN contributed to the project administration. The data were curated by AK and JDK, with supervision provided by ASR, SAR, MSMY, NB, SFBS, and AFAA. NSS conducted the genetic analysis supervised by HN, AAK, YAC, NAMK, and SHSAK. LC and SAR lead the qualitative study. RKA will conduct the formal analysis of the quantitative data. ASR, NQ, HAH, LC, LS, RKA, YAC, AAK, and JLB drafted the manuscript. All authors contributed to the critical revision and editing of the manuscript and have read the final version of this manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Topic guide to explore the experience, concerns and expectations of individuals with suspected Familial Hypercholesterolaemia.
[PDF File (Adobe PDF File), 174 KB - resprot_v12i1e47911_app1.pdf]

Multimedia Appendix 2
The FAMCAT Web-Based Familial Hypercholesterolaemia Identification Tool user manual and task scenarios for primary care physicians.
[PDF File (Adobe PDF File), 1020 KB - resprot_v12i1e47911_app2.pdf]

Multimedia Appendix 3
MRC UK peer-review reports and grant offer letter.
[PDF File (Adobe PDF File), 498 KB - resprot_v12i1e47911_app3.pdf]

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Abbreviations

ABCG5: ATP-binding cassette subfamily G member 5
ABCG8: ATP-binding cassette subfamily G member 8
APOB-100: apolipoprotein B-100
APOE: apolipoprotein E
CAD: coronary artery disease
DLCC: Dutch Lipid Clinic Criteria
EB: elution buffer
EMR: electronic medical record
FAMCAT: Familial Hypercholesterolemia Case Ascertainment Tool

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FH: familial hypercholesterolemia
FHCG: familial hypercholesterolemia candidate gene
FMS: family medicine specialist
GMAF: global minor allele frequency
HCAG: hypercholesterolemia-associated gene
HeFH: heterozygous familial hypercholesterolemia
HoFH: homozygous familial hypercholesterolemia
LDL-c: low-density lipoprotein cholesterol
LDLR: low-density lipoprotein receptor
LDLRAP1: low-density lipoprotein receptor adaptor protein 1
MOH: Ministry of Health
NGS: next-generation sequencing
PCP: primary care physician
PCSK9: proprotein convertase subtilisin/kexin type 9
PV: pathogenic variant
RA: research assistant
SB: Simon Broome
UiTM: Universiti Teknologi MARA
VCF: variant call format

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Protocol

Community-Based Public Health Vaccination Campaign (VaccinateLA) in Los Angeles' Black and Latino Communities: Protocol for a Participatory Study

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Abstract

Background: The COVID-19 pandemic has significantly affected Los Angeles County and disproportionately impacted Black and Latino populations who experienced disparities in rates of infection, hospitalizations, morbidity, and mortality. The University of Southern California (USC), USC Keck School of Medicine, Southern California Clinical and Translational Science Institute, USC Mann School of Pharmacy and Pharmaceutical Sciences, Annenberg School for Journalism and Communication, and Children's Hospital Los Angeles will launch a collaborative public health campaign called VaccinateLA.

Objective: VaccinateLA will implement a community-based, community-partnered public health campaign that (1) delivers culturally tailored information about COVID-19 and available vaccines; and (2) addresses misinformation and disinformation, which serves as a barrier to vaccine uptake. The campaign will be targeted to communities in Los Angeles with the highest rates of COVID-19 infection and the lowest vaccination rates. Using these criteria, the campaign will be targeted to neighborhoods located in 34 zip codes in the Eastside and South Los Angeles. The primary aim of VaccinateLA will be to design and deliver an evidence-based multimedia public health campaign tailored for Black and Latino populations. A secondary aim will be to train and deploy community vaccine navigators to deliver COVID-19 education, help individuals overcome barriers to getting vaccinated (eg, transportation and challenges registering), and assist with delivering vaccinations in our targeted communities.

Methods: We will use a community-based, participatory research approach to shape VaccinateLA's public health campaign to address community members' attitudes and concerns in developing campaign content. We will conduct focus groups, establish a community advisory board, and engage local leaders and stakeholders to develop and implement a broad array of educational, multimedia, and field-based activities.

Results: As of February 2023, target communities have been identified. The activities will be initiated and evaluated over the course of this year-long initiative, and dissemination will occur following the completion of the project.

Conclusions: Engaging the community is vital to developing culturally tailored public health messages that will resonate with intended audiences. VaccinateLA will serve as a model for how an academic institution can quickly mobilize to address a pressing

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public health crisis, particularly in underrepresented and underresourced communities. Our work has important implications for future public health campaigns. By leveraging community partnerships and deploying community health workers or *promotores* into the community, we hope to demonstrate that urban universities can successfully partner with local communities to develop and deliver a range of culturally tailored educational, multimedia, and field-based activities, which in turn may change the course of an urgent public health crisis, such as the COVID-19 pandemic.

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KEYWORDS

community engagement; COVID-19; vaccine; vaccination; public health; population health; health equity; social media; vaccine hesitancy

Introduction

The COVID-19 pandemic significantly affected Los Angeles County [1] and disproportionately impacted Black and Latino populations in Los Angeles who experienced disparities in rates of infection, hospitalizations, morbidity, and mortality. [2,3].

In response, the University of Southern California (USC), USC Keck School of Medicine, Southern California Clinical and Translational Science Institute, USC Mann School of Pharmacy and Pharmaceutical Sciences, and Annenberg School for Journalism and Communication, and Children's Hospital Los Angeles will launch a collaborative year-long public health campaign called VaccinateLA. Given the size and diversity of Los Angeles County (ie, more populous than 42 other US states), we will focus this campaign on communities with the highest rates of infection and the lowest rates of vaccination. Using these criteria, the campaign will be delivered in neighborhoods located in 34 zip codes located in the Eastside and South Los Angeles. The overarching aim of VaccinateLA will be to design and deliver an evidence-based multimedia public health campaign tailored for Black and Latino populations. A secondary aim will be to train and deploy community vaccine navigators (CVNs) to deliver COVID-19 education, help individuals overcome barriers (eg, transportation and challenges registering) to becoming vaccinated, and assist with delivering vaccinations in our targeted communities. In this paper, we describe VaccinateLA, including our planned approach to partnering with the community to develop and implement a broad array of evidence-based educational, multimedia, and field-based activities.

Methods

Approach

The overarching goal of VaccinateLA is to implement a community-based, community-partnered public health campaign intended to deliver culturally tailored information about COVID-19 and available vaccines, as well as to address misinformation and disinformation, which can serve as barriers to vaccine uptake. The difference between misinformation and disinformation is intent [4]. Misinformation is erroneous information reported as fact, whereas disinformation is a form of misinformation that is intended to deceive or mislead [4]. The aims of VaccinateLA will be accomplished through a range of public health campaign strategies.

Conceptual Model

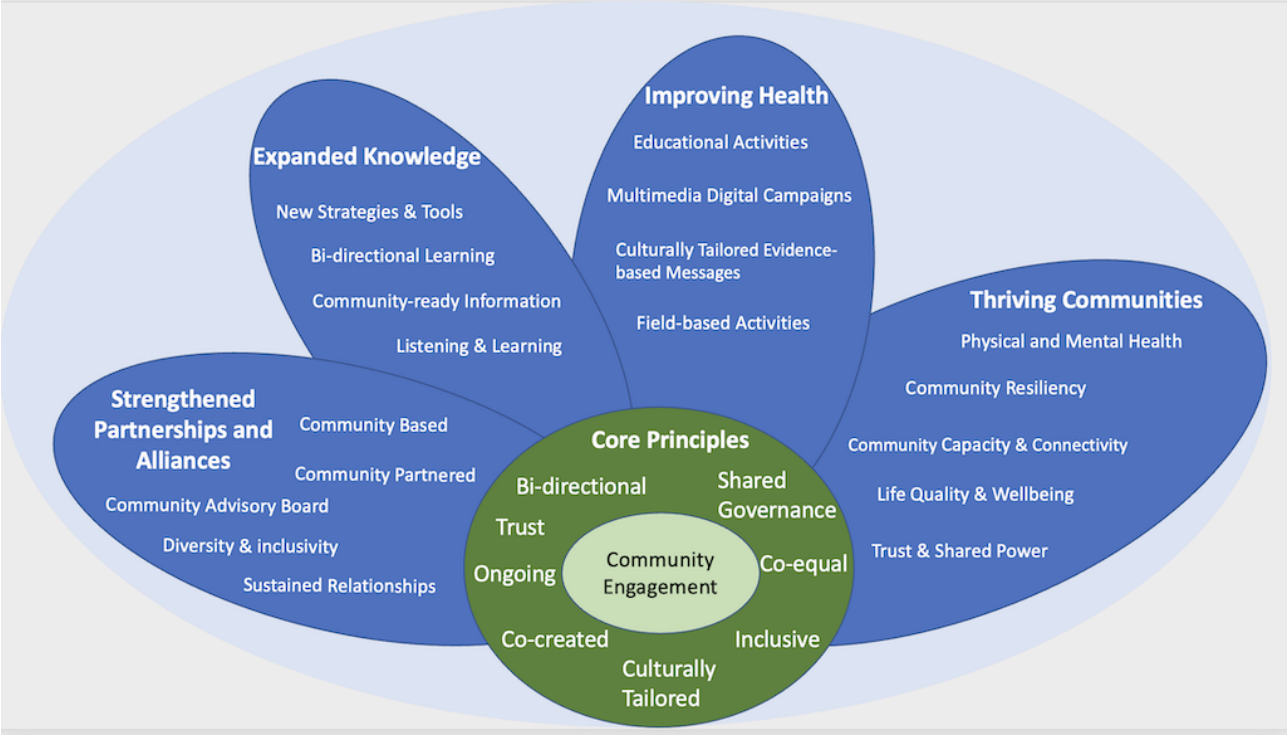
Through VaccinateLA, we seek to strengthen existing partnerships and forge new relationships in our targeted communities, as well as to engage the public health community and other key stakeholders throughout the greater Los Angeles County area (eg, with the Los Angeles County Departments of Public Health, Health Services, and Mental Health).

We plan to use a community-based, participatory research approach to shape VaccinateLA's public health campaign. Our work will be guided by a conceptual model that was adapted from a framework developed by the National Academy of Medicine's Leadership Consortium: Collaboration for a Value & Science-Driven Health System [5]. Our conceptual model, titled *VaccinateLA Public Health Campaign: Building Health Equity Through Community Engagement*, takes a holistic approach to engaging multiple communities and key stakeholders to promote equity (Figure 1).

Our core principles of community engagement include work that is bidirectional, inclusive, culturally tailored, and co-equal and has shared governance to build trusting relationships. When developing a public health campaign, the work should be cocreated and ongoing. Our goals are to *strengthen community partnerships and alliances* and *expand our knowledge* through bidirectional learning (eg, listening to community members and learning from them about their experiences and needs will guide our work), with the goal of being able to develop effective, resonant, and community-ready messages, strategies, and tools. We will be able to succeed through the sustained relationships that are developed through this process, which includes a diverse and inclusive community advisory board (CAB). VaccinateLA intends to develop culturally tailored evidence-based messages and a multimedia digital educational campaign and launch education and field-based activities to *improve the health of our targeted communities*. Trust and shared power will help guide this community-based, community-partnered initiative, resulting in our ability to promote *thriving communities*. By engaging multiple communities and key stakeholders, we can increase community connectivity and the capacity to develop and sustain beneficial public health programs that address physical and mental health, ideally improve quality of life and overall well-being, and ultimately support and enable community resiliency

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Figure 1. Conceptual model, titled VaccinateLA Public Health Campaign: Building Health Equity Through Community Engagement.



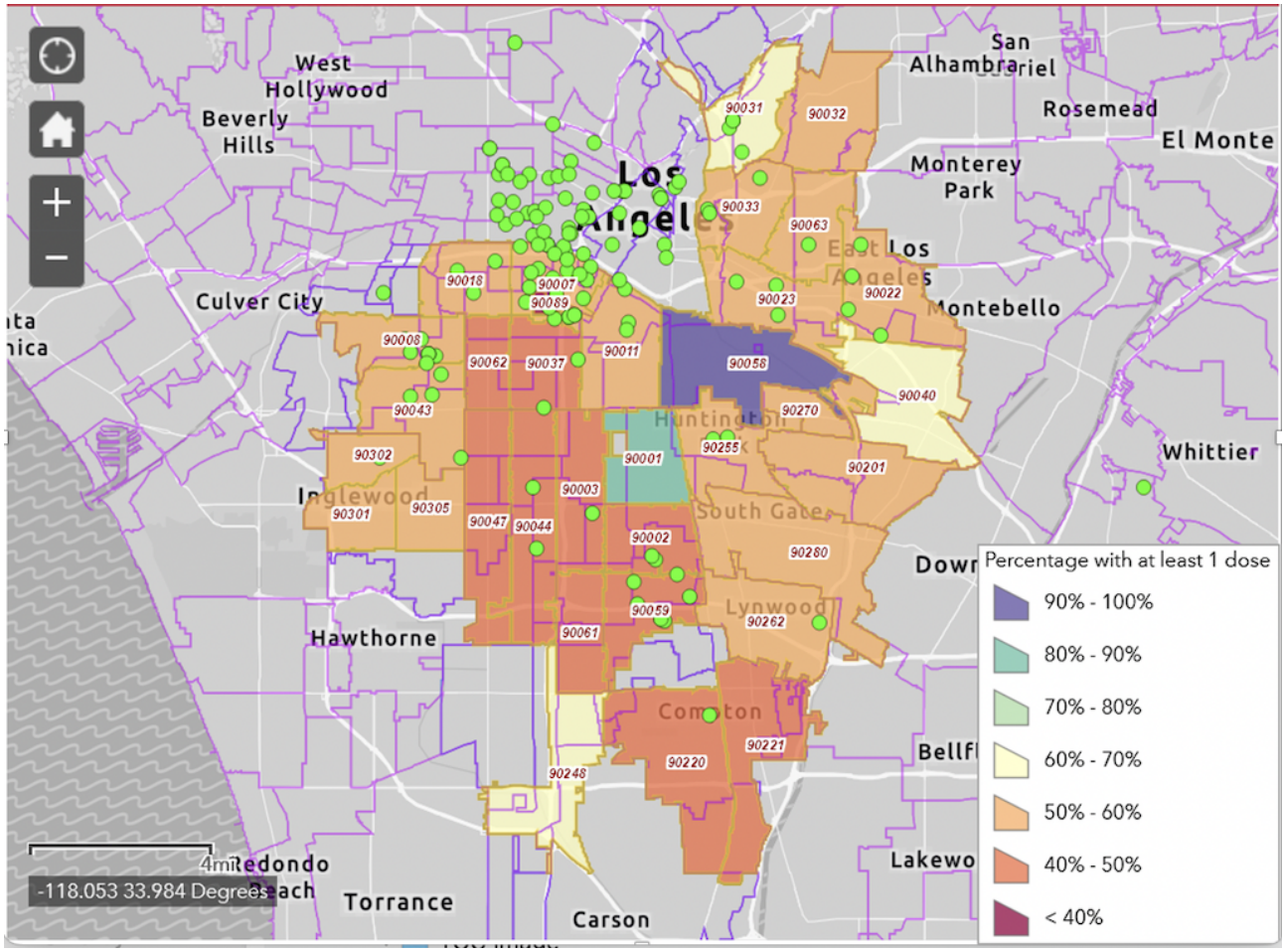
Description of Our Targeted Communities and Populations

Community Overview

Los Angeles County is a large and diverse county that is more populous than 42 states in the United States. In Los Angeles County, 185 languages are spoken and 42% of residents are Spanish speakers [6]. Given the sheer size of Los Angeles County, we plan to target the campaign to communities with the highest rates of infection and the lowest vaccination rates. Using these criteria, we identified 34 zip codes located in the Eastside and South Los Angeles. A map of neighborhoods in these zip code areas (based on vaccination rates from May 2021) is shown in Figure 2. The goal will be to work closely with existing partners and forge new partnerships in these same communities. The campaign will target to five distinct segments of the population: (1) Latino and Black residents of South Los Angeles; (2) Latino and Black residents in the Eastside of Los Angeles; (3) members of the lesbian, gay, bisexual, transgender, and queer (LGBTQ+) community; (4) parents of school-age children, both vaccinated and unvaccinated; and (5) community health workers in Spanish-speaking communities, called *promotores de salud*.

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Figure 2. VaccinateLA map of targeted zip codes and vaccination rates. The green dots represent our 160 community partners.



South Los Angeles Community

This area has historically been predominantly Black; however, approximately 28% of current South Los Angeles residents are Black. Low-wage, temporary jobs are common in this area, as is poverty and unemployment [7].

East Los Angeles Community

East Los Angeles is historically a predominantly Latino area, and approximately 96% of current residents in this area identify as Hispanic or Latino. Spanish is the first language for most residents aged 5 years and older [8]. The median household income is just over US $46,000, and approximately 20% of the population live at the poverty line [8].

Parents

The pandemic's effect on parents included hardships such as facilitating online learning, new safety measures at school, and an overwhelming amount of information about vaccine and booster eligibility. Balancing multiple priorities at work and at home, caring for sick family members, and experiencing loss and unemployment also take a toll.

LGBTQ+ Community

The LGBTQ+ community is also facing challenges and barriers to getting vaccinated. In California, 5.3% of the population identify as gender and/or sexual minority individuals [9]. Reliable statistics for county-level data could not be identified. These individuals regularly experience challenges in accessing medical care, are often stigmatized and discriminated against, and experience high rates of violence [10].

Community Health Workers

Our final group of interest is *promotores de salud* [11]. We will partner with an organization, called Vision y Compromiso, which provides comprehensive and ongoing leadership development, capacity building, advocacy training, and support to over 4000 *promotores* throughout the State of California and in a region within Mexico [12]. We will conduct a focus group with *promotores* to understand the challenges that local communities experience during the pandemic.

VaccinateLA Public Health Campaign Strategies

As a starting point, we will first establish a CAB and then initiate a *listening tour* using a semistructured interview guide to listen to and learn from the community. Then, in partnership with the community, we will develop and deliver a combination of *educational* (town halls and workshops), *multimedia* (radio, local newspapers, social media campaigns, and project website), and *field-based activities* (pop-up vaccination clinics, deployment of a cadre of embedded community workers, and restorative circles). The following provides a description of each of these activities, the sequencing of which can be found in Table 1.

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Table 1. Project timeline.

Activity	Month											
	1	2	3	4	5	6	7	8	9	10	11	12
Develop VaccinateLA website	✓[a]											
Community advisory board	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Conduct focus groups	✓	✓	✓	✓						✓	✓	
Town halls	✓	✓			✓			✓	✓	✓		
Educational workshops		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Print and digital fotonovela				✓	✓							
Culturally tailored short films		✓	✓	✓	✓							
#ShareYourWhy testimonials		✓	✓			✓	✓			✓	✓	✓
Public service announcements									✓	✓	✓	✓
Social media campaign		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Pop-up vaccination clinics	✓	✓	✓	✓	✓	✓						
Community vaccine navigators	✓	✓	✓									
Restorative circles			✓	✓	✓							

[a]✓: denotes the timepoints at which these activities will be completed.

Establishing a CAB

The CAB will consist of 10-15 members, including trusted and respected community leaders, social service providers, and residents from our targeted communities. The CAB will include both men and women and a diverse racial/ethnic representation; the CAB will be chaired by a member of the board. The CAB will meet virtually on a monthly basis or more, based on what is needed. CAB members will receive an electronic gift card in the amount of US $25 to compensate them for their time and effort. The aim of the CAB is to provide valuable insight and important feedback to inform our outreach activities, multimedia educational materials, and dissemination strategies. CAB members will also help introduce us to new community partners and provide guidance on how to liaise with the community. Representatives from the Los Angeles County Department of Public Health and the Los Angeles Unified School District will also be invited to serve on the CAB.

Focus Groups to Listen to and Learn From the Community

We will begin by conducting a series of focus groups with various segments of the community to understand sources of concern, vaccine hesitancy, and barriers to becoming vaccinated. We will then conduct additional focus groups to inform our educational campaign. These focus groups will be conducted with various segments of the population, including community leaders and key stakeholders, young adults, older adults, members of the LGBTQ+ community, parents of vaccinated and unvaccinated children, community health workers in the Latino community (ie, *promotores de salud*), and community residents from 2 large public housing developments.

We plan to conduct a total of 40 to 45 focus groups, each with 7 to 8 participants. These focus groups will be conducted in both English and Spanish depending on the primary language of the participants. The groups will be conducted virtually using a semistructured interview guide with questions that focus on barriers, misinformation, and experiences at vaccination sites. These sessions will last 60-120 minutes. Following each session, discussions and comments will be transcribed, deidentified, and coded by researchers trained in qualitative research. Findings will then be summarized to inform real-time, culturally tailored educational campaign messages. Focus group participants will receive US $50 to compensate them for their time and effort.

Educational Activities

Town Halls

A series of virtual townhall events for community members will be delivered. The format will be to have 1 or 2 guest speakers offer short presentations (approximately 10 minutes), followed by up to 60 minutes for questions and answers. Our guest speakers will include trusted community leaders, local physicians, pediatricians, and other health care providers. Guest speakers will provide up-to-date information about the pandemic, infection rates in local communities, and the safety and efficacy of available vaccine/boosters. Information about available resources will also be presented (eg, how and where to access vaccinations/boosters). Town hall events will also be offered to specific segments of the population, including parents of children eligible for the vaccine and booster, Spanish-speaking parents, members of the LGBTQ+ community, and congregations within the faith community. We will advertise and promote these events through email listserves, targeted outreach to community partners, flyers, and social media. The flyer will include information about how to RSVP online, as well as how to submit questions in advance of the event. After each townhall event, we will develop frequently-asked-question sheets based on the questions asked by the community.

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Workshops

Educational workshops will be offered virtually to smaller groups, allowing for more focused discussions as well as more time allotted to address attendees' questions/concerns. These workshops will be delivered by *promotores* on our staff. Workshops will be offered multiple times per week and regularly updated to reflect the most recent data and information regarding vaccine and COVID-19 regulations and requirements. Due to the skills and background of our *promotores*, workshops can be developed quickly to meet the evolving educational needs of the community. Attendees will be asked to provide feedback after each workshop to help inform future workshop topics.

Multimedia Digital Educational Campaign

Overview

We will work with local artists, content creators, and film makers to develop and produce a variety of still images and messages for social media, public service announcements (PSAs), brief #ShareYourWhy testimonial videos, short films, and a fotonovela. In addition to partnering with the local community, we will also be partnering with Wondros, a creative design and production agency, to help us craft engaging messages to address common fears, misinformation, and questions about the safety and efficacy of the vaccines. Once developed, we will solicit input from community leaders and CAB members before the products are disseminated. With each product, individuals will be directed to the VaccinateLA website for more information [13]. Most importantly, the website will also include links to additional information and resources, such as a list of local vaccination sites, a link to make a vaccination appointment, and a way to request assistance from a vaccine navigator. The following provides more information about the planned multimedia campaign.

Print and Digital Fotonovela

We will work with the USC Mann School of Pharmacy and Pharmaceutical Sciences to develop a bilingual fotonovela entitled *Infectious Rumors*. We will partner with La Opinión, a popular local newspaper, to print and distribute 40,000 copies to their subscribers as an insert in their paper; an additional 10,000 copies will be distributed to community partners, pediatric offices, and schools and at vaccine pop-up clinics. Fotonovelas are print versions of telenovelas, which use storytelling as an educational tool and are popular among Latino populations [14].

Culturally Tailored Short Films

We will partner with the USC's Annenberg School for Journalism and Communication and USC School of Cinematic Arts to produce two 8-minute films. These will be coproduced and directed by local Black and Latino filmmakers, who will assist with storyboarding, planning, filming, and editing. One film, called *Happy Birthday Granny*, will feature a birthday celebration of a Black family. A second film, called *Of Reasons and Rumors*, will feature 2 young Latinas discussing rumors and misinformation associated with the vaccine (in both English and Spanish). Both films will use the art of storytelling as an approach to deliver evidence-based information about COVID-19, routes of transmission, and the safety and efficacy of the vaccine, as well as to address common misinformation and disinformation about COVID-19 and the vaccines. The videos will be posted on the VaccinateLA's website, on project-dedicated YouTube and Vimeo accounts, on social media accounts created for VaccinateLA, and with organizations such as the American Association of Public Health and the National Alliance for Hispanic Health with its 15 million Latino members nationwide.

#ShareYourWhy Testimonials

Local leaders, community members, physicians, nurses, and pediatricians will be asked to share their experiences and reasons for why they chose to be vaccinated; these testimonials will be recorded and edited into short 1-minute videos, called #ShareYourWhy. The #ShareYourWhy videos will be produced by a local video production and editing company, called Everyone Can Eat.

PSAs

We will partner with USC's Hollywood, Health & Society to produce multiple PSAs. USC's Hollywood, Health & Society will also partner with LifeNoggin, to develop an animated video to be titled, *What if everyone got the COVID vaccine?* LifeNoggin is a YouTube channel that uses animation to deliver scientific content to its more than 3.26 million subscribers.

Social Media Campaign

The VaccinateLA team, with assistance from Wondros and Everyone Can Eat, will launch a full-scale social media campaign on Facebook, Instagram, Twitter, and YouTube. We will create original content in both English and Spanish using still images, reels, and short videos with captions and video end cards directing individuals to our website to learn more or schedule an appointment. Data analytics will be reviewed to ensure we successfully reach our targeted audiences

Field-Based Activities

Pop-up Vaccination Clinics

We will partner with the USC Mann School of Pharmacy and Pharmaceutical Sciences, to offer pop-up vaccination clinics in locations chosen by the community (eg, church parking lots, health fairs, local YMCAs, places of employment, and other local venues). At pop-up clinics, we also will host food banks, back-to-school backpack distributions, and tables with information and access to resources such as housing assistance and employment. We will coordinate with social services, such as Women, Infants, and Children and rent relief resources, to distribute essential products such as diapers, personal protective equipment, and personal hygiene and household products such as detergent and shampoo. In addition, we will provide preventive health screenings such as blood pressure screenings and wellness counseling. Members of our team and CVNs will staff these events. Toolkits with advice on how to replicate such pop-up vaccine clinics will be developed and available on the VaccinateLA website.

CVNs in Targeted Communities

We will train and deploy community-embedded health workers and *promotores* to be CVNs in our targeted communities. This

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virtual training will involve 6 to 8 hours of teaching and instructor-led educational content over multiple days, culminating in a 4.5-hour experiential field training. CVNs will learn about COVID-19 transmission, risk mitigation, how to identify and refer people to credible sources, vaccine efficacy, and how to schedule vaccine appointments on someone's behalf. At the end of their training, each CVN will receive a toolkit to reinforce the training. In South Los Angeles, we will partner with the Southern California National Council of Negro Women, Inc. to deploy CVNs. We will be partnering with Vision y Compromiso to train and deploy CVNs in our targeted Latino communities.

Restorative Circles

We intend to conduct in-person restorative circles facilitated by community partners with Black men aged 18 to 35 years and individuals who identify as LGBTQ+. A restorative circle is an intentional gathering of people who have a shared, often traumatic or painful, experiences. These circles serve as a safe space for sharing struggles and expressing grief and trauma, ideally providing a path to healing and connection with others who may have had similar experiences. They are designed to address the longstanding historical trauma and pain around topics such as medical and institutional racism and police brutality against people of color and gender and sexual minority groups, which have worsened and been made more visible during the pandemic. Meals will be provided, and each participant will be offered a parting gift designed by the facilitator, such as journals, pens, and additional information about self-care, mental health, and domestic services in the Los Angeles area.

Ethics Approval

Data collection protocols for the proposed qualitative focus group interviews have received approval from Children's Hospital Los Angeles' Institutional Review Board (CHLA-21-00152). All participants will be identified through community outreach; screened for eligibility; and if eligible, invited to participate. All participants will provide written informed consent using DocuSign during a virtual consenting visit with project staff. Participants will be consented in both English and Spanish and will be provided a hardcopy of their signed consent form.

Results

As of February 2023,target communities have been identified. The activities will be initiated and evaluated over the course of this year-long initiative, and dissemination will occur following the completion of the project. The activities will be sequenced according to the project timeline in Table 1.

Discussion

Universities are in a unique position to leverage their immense resources and partner with local communities to respond to emerging community and public health crises [15]. This is especially true in underresourced urban communities [15]. To build trust, it is critical to develop meaningful partnerships with local leaders and other key stakeholders. It is through these partnerships and authentic community engagement that public health messages can be developed and delivered in a culturally tailored and culturally responsive way [16].

Our work and the VaccinateLA campaign will build upon a growing literature that describes best practices to forging academic-community partnerships. This literature demonstrates that local communities welcome the opportunity to partner with academic, health, and public health institutions if the goal is to improve community health [16,17]. Moreover, our work will be grounded in a framework recently developed by the National Academy of Medicine [5].

VaccinateLA will be a true academic-community–partnered initiative designed to respond to a public health crisis. A crucial first step will be to listen to and learn from the community. Findings from a variety of data-gathering activities (ie, focus groups, feedback during workshops, and the CAB) will in turn be analyzed and used to help determine *who the right messengers are*, *what are the right messages*, and *how these messages should be delivered* to reach individuals living and working in our targeted, high-impact communities. We will evaluate this effort to determine if VaccinateLA's educational and multimedia campaigns were successful at reaching our intended audience, encouraging individuals to become vaccinated, and if CVNs and field-based activities helped to reduce practical barriers to becoming vaccinated. Ultimately, we hope to demonstrate that VaccinateLA did successfully increase rates of vaccinations in our targeted communities.

It is our hope that the proposed VaccinateLA initiative might also have important implications for other public health campaigns. Indeed, we believe that VaccinateLA will serve as a model for how academic institutions can quickly mobilize and respond to a pressing public health crisis, particularly in underrepresented and underresourced communities. Additionally, we hope to demonstrate that such an academic-community partnership can successfully engage with and be responsive to the local needs in underresourced communities. Furthermore, it is our hope that VaccinateLA will serve as a model for how to develop and deliver culturally tailored evidence-based messages that might also be generalizable and potentially used to address other acute public health crises and chronic health conditions (eg, cancer screening, diabetes prevention and care, and asthma prevention).

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Conflicts of Interest

None declared.

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Abbreviations

CAB: community advisory board
CVN: community vaccine navigator
LGBTQ+: lesbian, gay, bisexual, transgender, and queer
PSA: public service announcement
USC: University of Southern California

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Protocol

Participatory System Dynamics Approach Targeting Childhood Health in a Small Danish Community (Children's Cooperation Denmark): Protocol for a Feasibility Study Design

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Abstract

Background: Improving childhood health is complex due to the multifactorial nature and interaction of determinants. Complex problems call for complex intervention thinking, and simple one-size-fits-all solutions do not work to improve childhood health. Early awareness is important, as behavior in childhood often is manifested across adolescence and into adulthood. To facilitate shared understanding of the complex structures and relationships that determine children's health behavior, participatory system approaches in, for example, local communities have shown promising potential. However, such approaches are not used systematically within public health in Denmark, and before being rolled out, they should be tested for their feasibility within this context.

Objective: This paper describes the study design for Children's Cooperation Denmark (Child-COOP) feasibility study that is aiming to examine the feasibility and acceptability of the participatory system approach and the study procedures for a future scale-up controlled trial.

Methods: The feasibility study is designed as a process evaluation of the intervention with the use of both qualitative and quantitative methods. A local childhood health profile will provide data for childhood health issues, for example, daily physical activity behavior, sleep patterns, anthropometry, mental health, screen use, parental support, and leisure-time activities. Data at system level are collected to assess development in the community, for example, readiness to change, analysis of social networks with stakeholders, rippled effects mapping, and changes in system map. The setting is a small rural town in Denmark, Havndal, with children as the primary target group. Group model building, a participatory system dynamics method, will be used to engage the community, create consensus on the drivers of childhood health, identify local opportunities, and develop context-specific actions.

Results: The Child-COOP feasibility study will test the participatory system dynamics approach for intervention and evaluation design and survey objective measures of childhood health behavior and well-being among the ~100 children (6-13 years) attending the local primary school. Community-level data will also be collected. We will assess the contextual factors, implementation of interventions, and mechanisms of impact as part of a process evaluation. Data will be collected at baseline, at 2 years, and 4 years of follow-up. Ethical approval for this study was sought and granted from the Danish Scientific Ethical Committee (1-10-72-283-21).

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Conclusions: s: The potential of this participatory system dynamics approach includes opportunities for community engagement and local capacity building to improve children's health and health behavior, and this feasibility study holds the potential to prepare an upscaling of the intervention for effectiveness testing.

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KEYWORDS

system dynamics; community-based participatory research; feasibility; childhood health; community; design; acceptability; intervention; evaluation; implementation; effectiveness; testing

Introduction

Children's health and well-being are of great concern worldwide [1], with decreasing levels of physical activity, more sedentary time, emerging rates of childhood obesity, and more children living with mental health problems [1-5]. Childhood health is closely related to the socioeconomic status of the family, for example, children raised in families with low socioeconomic status more often have mental health problems, obesity, and a sedentary behavior [2,3,6]. Several studies suggest that it is possible to improve childhood health despite inequalities in health [2,3,7-10], and early interventions have shown to be important in childhood health promotion [11]. Childhood health is a result of a complex interplay between many factors at individual, family, and society levels. Hence, declining childhood health must be viewed as a complex problem and calls for multilevel interventions and broader societal awareness [12]. Within childhood obesity, interventions building on community-based participatory research, and system dynamics have shown promising results in addressing complex health problems of children [13] by involving whole of communities in complex problem-solving at multiple levels of actions. Researchers have highlighted such participatory and system dynamic approaches as a potential way forward [14,15], addressing complex health problems in communities [13,16].

However, before applying a full-scale participatory system dynamics intervention in Denmark, feasibility testing is needed to underpin decisions about whether or not and how to progress [16]. The 2021 Medical Research Council (MRC) framework for complex interventions stresses the importance of considering the phases of intervention development in an iterative manner, from development, testing, and evaluating to implementation of interventions. Moreover, it identifies important core elements such as context, engage stakeholders, and development of a program theory [16].

Building on Australian experience with the participatory system dynamics approach [13] and the MRC framework as guidance [14], this paper describes the Children's Cooperation Denmark (Child-COOP) feasibility study design that is aiming to examine the feasibility and acceptability of the participatory system dynamics approach [17] and the study procedures intended for a future larger scale-up controlled trial.

Methods

Design

The Child-COOP feasibility study will apply a participatory system dynamics approach, and the MRC framework [16] informs the design of the feasibility study and guidelines for applying feasibility studies [18]. As suggested by the MRC, feasibility studies should be designed to assess the intervention and evaluation design.

The Community

The Child-COOP feasibility study will be tested and evaluated in a small community in a rural town area (Havndal) with approximately 900 citizens, located in the northeastern part of a large Danish Municipality, Randers. Including the surrounding area, the local community consists of approximately 2000 citizens. The community holds an integrated school and kindergarten "The Child Village" with approximately 100 children in grades 0 to 6 and approximately 40 children in the kindergarten. A few shops such as a local fitness provider, leisure-time sport provider, and a relatively small business environment exist within the area.

Populations

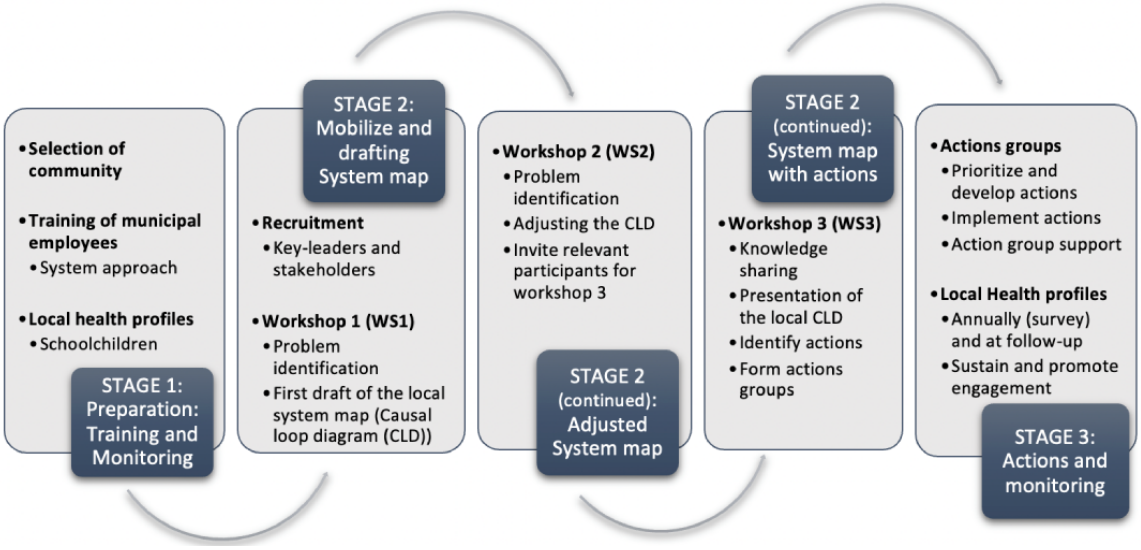
The target population is primary school–aged children (grades 0 to 6, 6-13 years of age; n=110), and all children attending the local primary school will be invited to participate in the health monitoring (described later in "Childhood Health: Outcome and Data Collection" section). Another target population is the key stakeholders of the local community, the local stakeholders, and municipality leaders and staff working within the community. These could include local politicians, grocery owner, chairperson of sports clubs, school board leader and members, local parents (with children at the school), leader of the municipality health department, and other municipality leaders, among others. The town of Havndal is one of the areas in Randers Municipality with the lowest social class and highest unemployment rate.

Intervention

The Child-COOP feasibility study will apply a participatory system dynamics approach and consists of several elements illustrated in Figure 1 and described in the following sections.

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Figure 1. Illustration of the participatory system dynamics approach including the group model building processes. CLD: Causal loop diagram.



Monitoring

A local childhood health profile will be generated at baseline, for example, daily physical activity behavior, sleep patterns, anthropometry, mental health, screen use, parental support, and leisure-time activities (Table 1).

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Table 1. Outcome measurements at child level in the Children's Cooperation Denmark feasibility study.

Concept	Outcomes of interest	Instrument or measure	Method	Data collection
Anthropometry	• Height • BMI • Fat mass • Prevalence of overweight	• Tanita Leicester transportable height measure • InBody 230 multifrequency body composition (bioelectrical impedance analysis)	Individual measurement	Examination at baseline and after 2 and 4 years
Physical activity and sedentary behavior	• Minutes per day spent on moderate and vigorous physical activity and sedentary activity • Minutes per day spent on • Step counts	• Accelerometer (Axivity AX3)	Individual measurement	7 days at baseline and after 2 and 4 years
Physical literacy	• Motivation and confidence • Physical competence • Daily behavior • Knowledge and understanding	• A Danish version of the Canadian Assessment of Physical literacy	Individual measurement of physical competence (including motor skill test, aerobic capacity run, and torso strength test) and daily behavior (self-report weekly participation in moderate- to vigorous-intensity physical activity and objectively measured average step count for 1 week). Survey of motivation or confidence and knowledge or understanding.	Baseline and after 2 and 4 years
Mental health	• General well-being • Social relations—peers • Loneliness • Bullying • Stress	• Børnungeliv.dk	Survey	Baseline and after 2 and 4 years
Sleep	• Hours of sleep • Time of sleep week days or weekends • Quality of sleep • Use of electronic devices	• Børnugeliv.dk and accelerometer (Axivity AX3)	Survey and individual measurement	Baseline and after 2 and 4 years
Leisure time	• Participation in sport and other activities • Use of computer, tablet, and other electronic devices	• Børnungeliv.dk	Survey	Baseline and after 2 and 4 years
Body and movement	• Active transport to school • Time spent on physical activity in school • Frequencies of high-intensity activity • Physical fitness level • Facilities for sports and play in the neighborhood • Body satisfaction	• Børnungeliv.dk	Survey	Baseline and after 2 and 4 years
Food and meals	• Breakfast, lunch, and dinner • Cooking at home • Intake of fruit and vegetable, sugar-sweetened beverage, candy, and cake	• Børnungeliv.dk	Survey	Baseline and after 2 and 4 years

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Concept	Outcomes of interest	Instrument or measure	Method	Data collection
Family relations	• Siblings • Country of origin (child and parents) • Relation to parents • Place of residence	• Børnungeliv.dk	Survey	Baseline and after 2 and 4 years

Recruitment of Key Leaders and Local Stakeholders

A coordinator from Randers Municipality together with the research team identify and recruit key leaders (eg, local politicians, department heads, and municipality leaders) and local stakeholders (eg, school board members, school principal, school nurse, and sport club representatives). Key leaders and local stakeholders will be selected based on the authority and capacity to initiate actions that are likely to influence the children's health behavior across sectors and organizations. During this stage, key leaders must commit to allocating resources to ensure subsequent implementation. The aim is to recruit 12-15 key leaders and local stakeholders from the community.

Group Model Building Process and System Mapping

A total of 3 group model building (GMB) workshops (WS1, WS2, and WS3) will be held during the 3 stages of the process (see Figure 1). The GMB method is an evidence-based method for solving complex challenges [13]. During WS1, the local childhood health profile will be presented, and based on this information, key stakeholders will discuss what health-related topic they find most important to their community (eg, obesity, physical activity, and mental health). In WS1 and WS2, the key leaders and stakeholders will map the system by creating a causal loop diagram (CLD) to understand how the perceived local system affects the prioritized childhood health topic in their community. For developing the CLD, the web-based software tool Systems Thinking in Community Knowledge Exchange (STICKE; version 3.0.14; Deakin University) was used [13]. STICKE stands for Systems Thinking in Community Knowledge Exchange and is developed to facilitate community knowledge exchange to foster shared understanding of complex problems.

In WS3, all community members willing to engage in changing the local system will be invited to identify priority areas for action based on the developed CLD from WS1 and WS2.

Actions and Support

The output of WS3 is the formation of local working groups that will focus on implementing the chosen actions using cocreation ideals [13]. The working groups will be supported and supervised by a backbone office formed by the Child-COOP municipality coordinator and the research team. A follow-up workshop will be held with the key stakeholders 6 months after the completion of WS3 to review the consolidated priority actions. To increase and maintain motivation and actions in the local community, subsequent follow-up meetings will be held with the working groups when needed after WS3.

Assessment of the Evaluation Design

The feasibility study of the evaluation design for Child-COOP will involve multiple levels and perspectives with a focus on key aspects such as recruitment, data collection tools and processes, analysis, and unintended outcomes [16]. In Child-COOP, the evaluation design will include both quantitative and qualitative methods. The evaluation design includes (1) evaluation of childhood health and (2) evaluation of community readiness to change, social network, actions implemented, and system changes.

Child-COOP will be considered feasible if it meets the following criteria: (1) The GMB sessions were conducted as planned. (2) Working groups are formed and active in implementing interventions arising from GMB. (3) Outcome measures were collected and considered complete (>75% considered acceptable at baseline). (4) Response rate considered acceptable (>75% considered acceptable at baseline).

Childhood Health: Outcome and Data Collection

Overview

All measurement instruments are listed in Table 1 and briefly explained. The measures will be conducted over 2 test days at the local school to assess the health of the children and test the data collection procedure. On day 1, children in grades 4, 5, and 6 are invited to participate, and on day 2, those in grades 0, 1, 2, and 3 are invited to participate. All children available on the day of data collection, whose parents have given written consent, will be included. A team of trained data collectors will collect the data on the test days with assistance from the class teachers. The longitudinal design makes it possible to study the changes over time within the local community, with limited effectiveness testing due to the limited power, as this is a feasibility study.

Anthropometry

All included children will have height, weight, and fat mass measured, wearing light clothes and barefoot, by the school nurse (Table 1).

Physical Activity and Sedentary Behavior

Physical activity and sedentary behavior will be measured continuously over a 7-day and -night period using Axivity AX3 accelerometers (Table 1). The accelerometer will be attached to the skin on the medial front of the right thigh using skin tape. The procedure is described in detail elsewhere [19]. The accelerometer is water-resistant, and the skin tape is intended to be water-resistant; thus, the accelerometer can be worn when swimming and bathing. The OMGui software (version 1.0.0.43; GitHub Inc), which is available on the internet, will be used for instrument initialization and data download [20].

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Physical Literacy

The Danish version (DAPL) of the Canadian Assessment of Physical Literacy [21] will be used to measure physical literacy for children in grades 1 to 6 [22]. Grade 0 children will not be included in the assessment tool and have neither been used nor validated, as we consider these children too young for the assessment [22].

Self-reported Health and Well-being

The children will fill a questionnaire at school with assistance from their teacher and trained data collectors, more questions for children in grades 4 to 6 and less for children in grades 0 to 3. The parents will also fill a questionnaire about their child's health and well-being with more questions for children in grades 0-3 and less for children in grades 4-6.

We will use a Danish-validated questionnaire instrument (Danish: BørnUngeLiv, English: ChildYouthLife) developed by researchers and practitioners from the municipalities to use in the municipalities of Denmark to assess the health and well-being of children [23]. Topics that will be covered in the questionnaires are mental health, sleep, leisure-time activities, body and movement, food and meals, and family relations (see Table 1).

System Level: Outcomes and Data Collection

Data at system level will be collected continuously from baseline and with 2- and 4-year follow-up. All outcomes and measurement instruments are listed in Table 2 and briefly explained.

Table 2. Community outcome measurements in the Children's Cooperation feasibility study.

Item	Outcomes of interest	Instrument or measure	Method	Data collection
Readiness to change	Baseline and change in: • Community knowledge about child obesity • Existing community efforts • Community knowledge of the efforts • Leadership • Community attitudes • Resources related to child obesity	• The community readiness model	• One-to-one interviews	• 12 interviews of 45-75 minutes • Collection before WS1[a] • 1-year follow-up
Social network	Strength and importance of relationships • Density • Centrality • "Opinion leader" And change over time	• Social network dynamics	• Survey • Semistructured interviews	• Survey delivered to stakeholders • Collection before WS1 • 1-year follow-up • 2-year follow-up
Actions implemented	• Number of actions implemented • Place of influence within the CLD[b] • Stakeholders	• REM[c] • Add action variables within system dynamics software (STICKE[d])	• Ongoing communication with working groups after WS3[e] • Semistructured interviews with working group leaders	• Using REM as a method to track actions developed • 1-year follow-up • 2-year follow-up • 4-year follow-up
Change in system maps	• CLD	• CLD using STICKE	• Monitoring CLD • Focus groups • Adjustment of CLD	• CLD at WS3 • Collection of focus groups at • 2-year follow-up • 4-year follow-up • Based on focus groups

[a]WS1: workshop 1.

[b]CLD: causal loop diagram.

[c]REM: rippled effects mapping.

[d]STICKE: Systems Thinking in Community Knowledge Exchange.

[e]WS3: workshop 3.

Readiness to Change

To assess whether changes occur in the community's readiness and capacity for making system changes, we use the community readiness model [24] forward-and-back translated to Danish [25]. Community capacity and readiness here refer to a "community's ability to identify, mobilize and address public health problems" [26]. Responses will be used to measure the changes in community capacity by scoring the descriptive responses on anchored scales [24,25]. Data will be collected

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from key leaders in the community including school principal and staff, local government leaders, parent representatives, among others. It is hypothesized that Child-COOP will change the readiness to change in the local community.

Social Network Analysis

Social network analysis will be used to assess the development of relationships between people and organizations [27]. Social network analysis can calculate network statistics including density and centrality and "opinion leader" positions [13]. Furthermore, social network dynamics will be applied with longitudinal network models in mind to determine how the networks change over time and the role of the network in the diffusion information, knowledge, and practice [28]. Data will be collected using the COMPACT Stakeholder-driven Community Diffusion Survey [29] adapted to a Danish context. It is hypothesized that Child-COOP will change and connect more people within the community's social networks.

Actions Implemented

Proxy indicators of system change will be actions initiated by the community, and these will be monitored from baseline and followed up annually using the STICKE software [30]. The number of community actions will be tracked as proxies of community-level engagement [13]. Semistructured interviews with working group leaders will also be used to understand and provide deeper information on the actions implemented (eg, goal, content, and setting) [31]. To track the actions developed and implemented in the local community, we will use "ripple effect mapping" (REM) [32]. REM is a method used to better understand the complex, dynamic nature, and wider impacts of system dynamics intervention [33]. Unlike traditional evaluation designs, REM is aimed at understanding contribution; how may an intervention, action, or policy contribute toward changing a larger system? [32-34] During the workshops, participants (stakeholders, citizens, municipality employees, etc) visualize the impacts of the actions and how these impacts may go beyond those, which Child-COOP was designed to achieve [32].

Change in System Map

Tracking of change in the CLD and the communities' responses to the participatory system dynamics approach will be monitored through a revised system map at 2 and 4 years post the initial CLD [13]. The STICKE software [30] will be used to track changes in the system and the interaction among key actors, actions, and the system.

Assessment of the Intervention: Process Evaluation

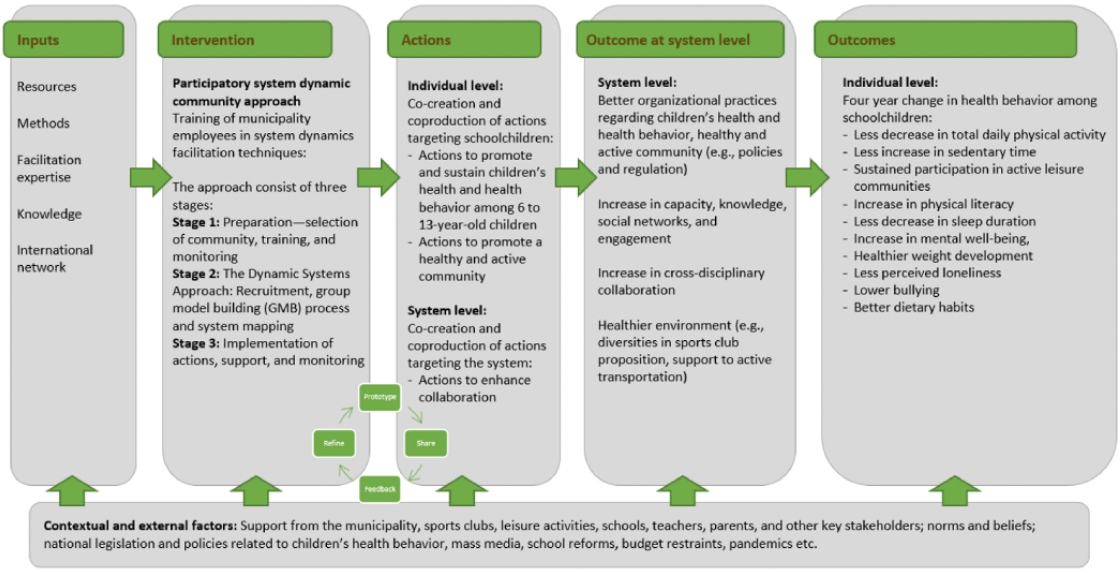
The process evaluation aims to understand the functioning of an intervention by examining mechanisms of impact, implementation, acceptability, and context.

Through analyses, crosscutting qualitative and quantitative results on the implementation (adherence, dose, quality of delivery, participant responsiveness, and reach), mechanism of impact, acceptability, and context will be synthesized to gain knowledge on how the participatory system dynamics approach was delivered and implemented and inform a final program theory.

Mechanism of Impact

What are the change mechanisms for Child-COOP and how do they align with program theory? These questions will be addressed through 12 semistructured interviews with key stakeholders and the municipal coordinator, addressing the research questions: *What are the mechanisms of change associated with the participatory system dynamics approach? What hinders or enables implementation of the participatory system dynamics approach?* Our program theory is a tentative developed program theory for the overall study (see Figure 2), while the developed CLD will be considered a form of logic model [16].

Figure 2. Child-COOP tentative program theory for feasibility study in Havndal, Denmark. Child-COOP: Children's Cooperation Denmark.



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Implementation

What is delivered in Child-COOP? Here, we aim to understand how the "implementation" is done locally in the community assessing (1) fidelity (is the participatory system dynamics approach delivered as intended?); (2) dose (who is reached by the participatory system dynamics approach and to what strength?); (3) adaptions (have any significant changes to the participatory system dynamics approach been made?); (4) reach (how many are part or affected by the participatory system dynamics approach?); and (5) process (understanding the implementation process?). These elements are sought to understand through structured observations by registration and participation (number of participating stakeholders or established working groups or initiated actions) and a questionnaire for stakeholders.

Acceptability and Context

How is "acceptability" of the Child-COOP approach among the participants? Through 12 semistructured interviews with key stakeholders and participants, we will collect data aiming to understand the following: *How do participants involved in workshops and implementation of actions react to and engage in the Child-COOP approach?* Furthermore, we aim to conduct follow-up phone interviews with dropout key stakeholders to provide a realistic perspective.

Ethics Approval

This study will be carried out in accordance with the Declaration of Helsinki. Ethical approval for the study has been granted by The Regional Scientific Ethics Committee of the Central Denmark Region, Danish National Committee on Health Research Ethics (1-10-72-283-21). Any protocol amendments will be reported and submitted to the Ethics Committee. Anonymity and confidentiality of participants will be ensured by assigning a study ID number to all participants. Informed consent will be obtained from parents in order to include the children in the health assessments. No results of the anthropometric measurements will be visible to, or available for, the children to reduce risk of the bullying and stigmatizing.

Consent for Publication

Informed consent will be collected from parents on behalf of the children taking part in the study. Informed consent will be collected from all participants in the workshops.

Results

The Child-COOP feasibility study has officially started with baseline measures in September 2021, recruitment of participants and delivery of the GMB phase started in 2021-2022. The 2-year follow-up will be the next step and will reveal the first results of the study—this is expected in 2023. Furthermore, process evaluation is underway and will be concluded at the 2-year follow-up in 2023. The project will conclude with the 4-year follow-up, which will provide the final results—these are expected in 2025. In September 2022, a large grant was given for the Child-COOP Denmark project, focusing on children's physical activity behavior. This project will include 5 municipalities and 10 communities, building on the experiences of the Child-COOP feasibility study. It will begin immediately after the conclusion of the process evaluation of the Child-COOP feasibility study in late 2023 or early 2024.

Discussion

Expected Findings

The Child-COOP feasibility study will provide new knowledge on the potential to implement a participatory system dynamics approach targeting childhood health in a Danish context. Childhood health is a complex health problem and evidence points to system science as one of the best means of identifying and addressing such complex and dynamic problems [13]. The approach will be tested out in a small disadvantaged community in Denmark, and therefore, it may be applicable in similar settings upon a positive feasibility assessment.

Strengths of the Study Design

Interventions building on a participatory system dynamics approach as Child-COOP have already been suggested as a feasible way to address complex problems, as they combine the current evidence base on prevention, best practice, and local wisdom to achieve new knowledge and create solutions [16,34]. The participatory system dynamics approach in Child-COOP based on the co-creation and close collaboration between the municipality, community, and facilitating research team will most certain be a strength of the Child-COOP feasibility study. In addition, this study builds upon existing evidence and shows a positive effect of a participatory system dynamics approach in improving the childhood health and obesity rates [13]. Furthermore, to investigate the complex relationship of childhood health drivers in the community, the active involvement of the local community in mapping, developing action plans, and maintaining the efforts may provide sustainability and empower the local community [13]. The extensive evaluation design using multiple methods for data collection at the individual level as well as the system level also serve as a strength of this study.

Potential Challenges

Potential challenges of the study include the long-term engagement of the local community, which may decline over time; however, this feasibility study will provide insight into the magnitude of the support from the research team, local leaders, or coordinators to develop, facilitate, and support the working groups to continue to implement and adjust actions in their local community. Moreover, a potential challenge is that the community will not take the chance to change and influence the local system affecting the health and well-being of the children.

In addition, external factors may challenge the implementation of the intervention, for instance, the COVID-19 pandemic or local and municipality economic challenges. However, the participatory system dynamics approach is flexible and can be adapted to be conducted largely on the internet while still representing the local context. Finally, we acknowledge that a whole of system approach for evaluation may never be fully achievable, as changes in a complex system will always give rise to more uncertainties than a single evaluation can

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satisfactorily capture [34,35]. However, with our feasibility assessment, we focus on the most important areas of uncertainty and to justify decisions of which assessment of impact can be expected to be meaningful at a system level.

Conclusions

In conclusion, the Child-COOP feasibility study is crucial in evaluating the potential for a full scale-up study in a Danish context. If feasible, this participatory system dynamics approach in Child-COOP provides opportunities for the application of local capacity building by applying a practical approach to complex health problems in a local community [34]. This study will be able to inform both the content of the participatory system dynamics approach and the future larger-scale evaluation design. Furthermore, the community outcomes included may help to better understand the changes in the community and the mechanisms leading to changes in childhood health within communities [13]. If proven feasible, the Child-COOP study will be scaled and tested for the effectiveness in relation to improving childhood health in a Danish context.

Acknowledgments

We like to thank Stine Klitgaard and Ulla Skov Aldahl from Randers Municipality on their tireless engagement in the project in the municipality and the local community. We also thank Annette Nejmann-Laursen, principal at “Børnebyen,” for her great help in assisting the project. Last but not least all children and citizens in Havndal, Denmark.

Authors' Contributions

KR, JNØ, and HK adapted and designed the intervention, prepared the first drafts of the paper, revised the manuscript, and approved the final submission. SA and HTM contributed to the design of the intervention, revised the manuscript, and approved the final submission. SA contributed to the education of the research group. CB and ASEA revised the manuscript and approved the final submission.

Conflicts of Interest

HK and JNØ are employed at Steno Diabetes Center Aarhus, a public hospital and research institution situated in Central Denmark Region, which is partly funded by an unrestricted grant from the Novo Nordisk Foundation. HTM is employed at Steno Diabetes Center Copenhagen, a public hospital and research institution situated at the Capital Region of Denmark, which is partly funded by an unrestricted grant from the Novo Nordisk Foundation.

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Abbreviations

Child-COOP: Children's Cooperation Denmark
CLD: causal loop diagram
GMB: group model building
MRC: Medical Research Council
REM: ripple effect mapping
STICKE: Systems Thinking in Community Knowledge Exchange

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Protocol

Combining Outreach and Cross-sectional Research to Gather Children's Soil Values in Aotearoa New Zealand: Protocol for the Mixed Methods Soilsafe Kids Program

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Abstract

Background: Soil underpins most terrestrial systems; hence, its degradation should concern everyone. In 2021, Soilsafe Aotearoa surveyed the adult population of New Zealand about how they value soil, particularly values related to how they care about and are concerned about soil. Pursuant to this study, Soilsafe Kids (the outreach branch of Soilsafe Aotearoa) developed a combined research and outreach program to collect a supplemental data set of children's soil values, so both adults' and children's voices can be considered when understanding the implications of different practices and how to care for presently "uncared for" or neglected soils in the future.

Objective: The program not only asks primary school students about their soil values but also aims to teach them about soil from many disciplinary perspectives to enhance their understanding and awareness of soil, and, more broadly, for knowledge production.

Methods: Here we describe the research protocol used in this Soilsafe Kids program. This program uses surveys (in the form of worksheets), focus groups (introduced as group discussions), and art projects to learn what children think about soil in Tāmaki Makaurau Auckland. We have received ethics approval from the University of Auckland's Human Participants Ethics Committee (reference number 23556) on March 25, 2022, for 3 years.

Results: We have begun recruiting participants and delivering the Soilsafe Kids program in schools across Tāmaki Makaurau Auckland. Our data collection is ongoing with final student engagement in the first quarter of 2023. We expect to analyze data at the start of 2023 and to disseminate results later this year.

Conclusions: Once this study is complete, we will disseminate the final results to the research community, stakeholders, and the local community through conference presentations, journal articles, hui (meetings), on our website, and in art exhibits. We note that although Tāmaki Makaurau Auckland is home to the majority of people living in Aotearoa New Zealand, the Auckland region only represents a small portion of Aotearoa New Zealand's land, and findings are not generalizable to Aotearoa New Zealand as a whole.

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soil values; environmental education; child-centric research; child-centered teaching and learning; transdisciplinary; Tāmaki Makaurau Auckland; soil; school; student; child; environment; nature; natural

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Introduction

While encounters with soil tend to be everyday and be mundane, many of us do not think deeply, or much at all, about its connections or its diverse values (eg, as calculative, emotive, or utilitarian). Soil underlies spaces we interact with and is a medium in which animate entities grow. Additionally, soil is a site of biodiversity and recreation and has its own intrinsic value. Particularly important for the context of this study are Māori Indigenous values of soil and the broader environment, with vital connection to the *whenua* (land) and *atua* (creators) [1], and the context of largely conventional "valuation" of soil taking place by way of settler-colonial knowledge frameworks, with soil being both *tī puna* (ancestor) and stolen land simultaneously. Globally, soil quality is decreasing for reasons such as its use as a platform for development, its overuse in food and resource productivity, and as a deliberate or accidental sink of waste, holding contaminants such as metals and pesticides. Nonetheless, soil is a foundation to human settlements, we relate to it in diverse ways, and food is generated out of soil. In fact, some of us produce that food at home. Domestic and community gardening has long been a solution for populations in Tāmaki Makaurau (Auckland), and Aotearoa New Zealand (hereinafter "NZ"), to gain access to affordable, adequate, and culturally appropriate food supply [2]. Of concern, then, is the significant scholarship that discuss soil degradation as the number 1 threat to food security and environmental sustainability; for example, Krzywoszynska [3] and Osman [4,5].

In particular, there is concern for soil degradation in the form of soil metal contamination. Lead is one metal of notoriety in urban soils because of its toxicity, persistence, and ubiquity in cities [6,7]. In urban locations, there is a legacy of leaded petrol use in vehicles, industrial pollution, waste incineration, and leaded paint usage [8-11]. While the use of paints containing lead was outlawed in New Zealand between 1965 and the early 1980s (different paints were banned at different times), older homes may still therefore contain lead-based paint [12], and house paint that is poorly maintained will flake into surrounding soil. Contaminated garden soils are a global problem [13], as demonstrated in Canada [14], Denmark [15], France [16], Hungary [11], Italy [16,17], and the United States [18,19]. Other heavy metals—such as mercury, arsenic, chromium, and cadmium—have also been found in soils, including soil that is used for growing food, thus creating an exposure pathway for metal absorption by humans [20]. Soil contamination can also be a multigenerational problem, where the contamination does not "go away" but rather is retained in situ within soils until disturbed or mobilized (eg, through water, by wind, manually by humans, or where it is taken up by plants). There are numerous links to the importance of children learning about soil quality, including potential sources of contamination and an appreciation of less documented benefits that soil brings that relate to its intrinsic (nonutilitarian) and well-being values [21].

Soilsafe Kids is a research and outreach project that sits under the umbrella of Soilsafe Aotearoa [22]. Soilsafe Aotearoa launched in 2021 in NZ as a program to examine diverse soil values, including those that are scientific, cultural, ecological, economic, political, and artistic. After a year of learning about why the public values soil and their concerns about soil, Soilsafe Aotearoa launched a citizen science project to test domestic garden soils for metal contaminants, free of charge, in response to the concerns raised [22], including a study on gardening values (eg, EL Sharp, F Porter, N Strawbridge et al, unpublished data, January 2023) and matters of soil care and concern. All respondents in this study of soil care and concern were adults.

This leads us to question "Who are the *public*?" Nearly a quarter of NZ's population is younger than 15 years [23,24]. Although children spend more time outdoors than adults [25], we know very little about what children think, feel, or know about soil. In order to understand what the *broader* public values about soil, it is paramount that we understand what children value, not just adults; further, the diversity in the known and unknown perspectives of adults and children, rather than just an adult-child binary, is of interest here.

Soilsafe Kids launched in 2022, with keystone activities including a research study gathering "soil values" parallel to that undertaken by Soilsafe Aotearoa with adults, instead of children, and the opportunity for the families of the participating children to take part in Soilsafe Aotearoa's heavy metals soil testing, along with an in-class educational component to teach children about factors that might lead to the risk of soil contamination or human exposure to contamination. Ultimately, this information would guide *whānau* (families) in their decision-making about whether their gardens are safe places to grow food, and, if not, what to do about it to reduce contaminant exposure, including government guidance regarding practices such as eliminating sources of contamination depending on the metal, growing food in commercially available soils that are brought to the site (not growing in ground soil), moving the location of the food garden, or reducing food or hand-to-mouth exposure to contaminants.

The delivery of a combined educational and research program offers diverse benefits to children, their communities, and researchers. First, it establishes a reciprocal relationship with participants, where we provide knowledge and demonstrations of practice as well as obtaining data from participants [26], demonstrating the value of the knowledge imparted to us. Second, it prioritizes and highlights the value of knowledge dissemination in ethical research practice by emphasizing children's right to be heard and seriously considering their views in relation to policy and planning [27]. Third, educational and research activities offered jointly mean that knowledge can be coproduced in the community and knowledge previously produced can be returned to communities who can use it. The aforementioned benefits of combining teaching and research into 1 program, as the Soilsafe Kids program does, are important given children's increasing roles and participation in contemporary issues, as evidenced by the COVID-19 pandemic [28] and the climate crisis [29].

This Soilsafe Kids program is intended to run over 2-3 days depending on the context of the individual school's needs. Our research question is, "what do children (aged 6-10 years) think about soil, and how do they value it?"

The program is composed of 8 workshops designed and run by social, physical, and health scientists with support from scientists

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from the New Zealand Crown Research Institutes GNS Science and AgResearch, charities Oke and Garden to Table Trust, 2 community artists, a Māori tikanga advisor, and a Royal Society of New Zealand Te Apārangi Teaching Fellow. The benefits of this type of transdisciplinary research—that encourages children to raise awareness in their communities through environmental activism—include unique educational opportunities [28] and embracing education as a driver for sustainable development [30].

To address our research question, the program is planned to include surveys at the beginning and end of the program, supplemented with focus groups and drawings throughout the workshops. Here, we describe our study design and outline how we will analyze our data and disseminate our findings, allowing us to consider the potential impact of this work.

Methods

Soilsafe Kids aims to understand what children know about soil and how they value it. This takes a child-centered approach [31,32] throughout our workshop series with 8 primary school classes in Tāmaki Makaurau Auckland. Class sizes are planned for approximately 30 students, resulting in a convenience sample of ~240 participants. Data collection and student engagement began in 2022 and is intended to last approximately 9 months, with dissemination of results intended for early 2023.

Ethical Considerations

The University of Auckland's Human Participants Ethics Committee approved this study (reference number 23556) on March 25, 2022, for 3 years. Principals, teachers, and families will provide informed consent via written consent forms; all children (ie, "the participants") will provide assent by signing forms as their reading level precludes truly informed consent. As required by ethics approval processes, Soilsafe Kids has developed participant information sheets (PIS), consent forms (CF), assent forms, and recruitment posters with specific wording and sections of information [33]. When writing the student versions, we were cognizant that we would be working with students who may have rudimentary reading skills, so these documents have larger text, less text, and a limited vocabulary to ensure that the information is child-friendly. During our first interactions with principals, we have received a few comments about the amount of reading that will be required of families. While the PIS and CF are a page each (front and back), they are dense documents. Even though these forms are a standard part of the ethics approval process, this has led to discussions about how to make the recruitment stage more approachable in the future. In each of these forms, we acknowledge that we will maintain the confidentiality of all participants in research outputs but that we cannot guarantee anonymity as participation will occur in a public manner (ie, in a classroom setting).

Our program was designed before young students were eligible to be vaccinated against COVID-19. To help ensure that we minimize the risk of introducing COVID-19 into classes, our in-school team is fully vaccinated and boosted against the virus. Although NZ's vaccine mandate for teachers and staff has since dropped, we are maintaining a vaccination requirement for our in-school team to enter schools. We also respect that schools may not want visitors during periods of high COVID-19 transmission. Thus, we have the ability to transition our program fully outdoors or remotely—this would allow for students to learn about soil in an environment that prioritizes their health.

Although we strongly prefer that students participate in Soilsafe Kids' research component, we understand that some families and students may not want to. Because Soilsafe Kids has both research and educational outreach objectives, we will ensure that students can partake in the educational component without participating in the research component. We have designed each workshop to accommodate this preference. For example, multiple focus groups will be held simultaneously with some groups being recorded as data while others being carried out as unrecorded discussions. Through simultaneous focus groups with the same topics and structure, looking around the classroom will not indicate who is and is not participating in the research. Such choices will help make our lessons more accessible to all students, regardless of their and their families' feelings about participating in research.

All participants (including students, families, teachers, and principals) will have several opportunities to learn about our results. We will send a summary of school-specific results of the children's values of care and concern for soil back to the principal within a few weeks of the final workshop. At the end of the year, we will host a webinar to describe our combined findings about children's collective soil values. This format will enable our results to be disseminated, irrespective of people's locations or the COVID-19 restrictions at the time, thus allowing us to highlight students' communication outputs. Additionally, all participants will have the opportunity to request the study results in written form. By offering multiple ways of summarizing the study results, we hope to be able to reach a wider audience that is able to engage in a way that is appropriate to them. Results of the citizen science metal testing of home garden soil, as per the Soilsafe Aotearoa's own protocol, are only shared back to the citizen science participant and not the wider public. While this protocol is counter to many citizen science movements that are working toward "open" science, data, and access, the choice to manage data in this way was made because of the risks of this openness [34]—in this study, the politics and potential harmful effects of particular locations being labeled as "contaminated places." Despite the plans to communicate this, there is awareness that some may choose not to participate, given the unequal impacts of this type of environmental monitoring, as well as the known reduced participation of more marginalized communities in community science due to limitations of time and resources and possible surveillance and engagement fatigue concerns among Indigenous communities [34].

All participating schools were given gift cards worth NZ $500 (US $316.89 [exchange rate as on February 14, 2023, is indicated here]) of gift cards, while each student in the participating class (regardless of research participation status) received a NZ $30 (US $18.83) gift card to Booksellers Aotearoa New Zealand. By providing every student with a gift card, we ensure that we do not disclose the participation (or nonparticipation) status of a student.

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Participant Recruitment

Participant recruitment is planned in 3 stages at each school. Initially, using a combination of our networks and cold approaches to schools, principals are approached with a recruitment flier, a PIS, and a study protocol document [33]. This targeted recruitment approach will ensure that our sample is composed of a range of geographical locations and settings, communities of low and high socioeconomic status, and an ethnic distribution that reflects Tāmaki Makaurau Auckland. At this point, we are happy to address any questions either electronically or in person as in keeping with the NZ Ministry of Health's COVID-19 public health measures. Once the principal or school's board of trustees has decided that their school will participate and signed a CF, we will share a recruitment flier, PIS, and the study protocol with the principal and request that their front office share these documents with appropriate teachers. These second-stage documents will provide teachers general information about Soilsafe Kids and address how students can be part of the teaching and research components of the program, just the teaching components, or abstain altogether. With a signed teacher CF, the third stage of recruitment will commence and focus on families and students. Teachers will be provided with recruitment fliers, PIS, and consent and assent forms to distribute to parents and potential student participants.

As the potential student participants will be early readers, we have developed documentation equivalent to the adult documentation to build students' confidence and responsibility. To ensure that learner-appropriate vocabulary has been used, a registered and student teacher both assessed all documents [35,36]. Students are participants if their principal, teacher, and caregiver all return signed CFs and have signed an assent form.

Accessibility

Traditionally, schools in close proximity to research centers have more opportunities to work with researchers [37,38]. While this is convenient, it also means that students attending schools farther away have fewer interactions with researchers and are less likely to imagine themselves as researchers [39]. With this in mind, we will begin recruitment by reaching out to principals of suburban and rural schools first. We hope that this will provide different students an opportunity to participate in research and humanize researchers.

Data Collection

This program is composed of 8 workshops that will be led by a team of researchers and expert practitioners. Each workshop is designed and will be led by a social, natural, or health scientist, an artist, or local charity. This diversity of backgrounds ensures that students gain a transdisciplinary understanding of soil. When possible (see the *Discussion* section for more information), the person who designed the workshop will also deliver it with support from other researchers.

The topics addressed on the first day of workshops include the following: an introduction, te ao Māori (the Māori worldview) on soil, composting, and how to sample soil for heavy metal analysis, as well as information on reducing exposure or introduction of contaminants into backyard soil. The topics addressed on the second day of workshops include the following: soil as an artistic medium, soil characteristics from a Western soil science perspective, and the relationship between food and soil. The second day ends with a science communication workshop in which students then create an output sharing the importance of soil and how to keep it healthy. Depending on the communication method, the Soilsafe Kids team will return for a third day to help the students share their soil messaging with their communities.

During the workshops, data are collected in the form of surveys presented as worksheets, art projects, focus groups that are labeled as "small group discussions," a hands-up survey, and an interview with the teacher. As the students participating in Soilsafe Kids are still in early primary school (aged between 6 and 10 years), they may not be proficient readers or writers, so many of our activities revolve around art tasks. The Soilsafe Kids team will also write a critical researcher reflection, using the framework developed by Fook and Gardener [40] at the end of each day.

Results

One of the goals of this program is to center students in knowledge production, so they realize their agency in the world. Thus, the final format of the data will be decided by the students. We anticipate using NVivo [41] to conduct automated and manual thematic analysis [42] to analyze the qualitative data [43], which will supplement our previous data set of adults' soil values.

Public Involvement

Local practitioners and stakeholders are central to the formation and operation of Soilsafe Kids. We have partnered with local practitioners, and stakeholders from Soilsafe Kids' inception and will continue to involve them in the conduct of workshops, depend on them as advisors in the data analysis phase, and provide inputs regarding the dissemination of the results and knowledge transfer stages of the project.

When we were initially designing this program, our artists, local charities, and Royal Society Te Apārangi Teaching Fellow helped decide and shape our workshop series. The Teaching Fellow's guidance and 2 of the authors' teacher education training help ensure that Soilsafe Kids is aligned with the local curriculum. These partnerships have continued to evolve and grow as we have developed the Soilsafe Kids program.

To help foster relationships with the schools, we intend on offering meetings with all principals, boards of trustees, and teachers who might want to run the Soilsafe Kids program. Our aspiration is that the people we meet with will become ambassadors for the program during family and student recruitment. We will request that teachers make the first approach to families to minimize the transfer of personal information and ensure that a known contact makes first contact with families.

This program was designed for students who are familiar with school formats, who may not yet see themselves as having the authority to teach others in their community. Our workshops

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will aim to shift this view, especially in the final science communication workshop. This is important because these students not only are providing their current views on soil but also will inherit values of caring for the environment and soil. Actions taken now will affect the state of the soil that they have to work with in the future, so children need to view the soil as something they can influence now, not just later on.

Dissemination

Our anticipated dissemination can be categorized as targeting the research community, stakeholders (eg, Auckland Council, the Ministry of Education, schools, students and their families, environmental education groups, Auckland Regional Public Health, Auckland District Health Board, and environmental artists), and the local community. Our results will be disseminated to the research community at academic conferences and through peer-reviewed academic journal publications. We maintain relationships with stakeholders and offer periodic updates in meetings and by sharing our research results. To transfer our new knowledge to communities, we will conduct a webinar for participants and partners and post updates on our blog. Our lessons also aim to empower students to share their learnings with their communities about soil, which is why our last workshop focuses on science communication. Additionally, Soilsafe Aotearoa held several soil-themed art exhibitions in 2021. We would like to use students' artistic outputs to host such galleries for the public in the future. Finally, we will invite students to participate in Soilsafe Aotearoa's soil testing for heavy metals. The results from this testing will be disseminated back directly to students' families who contributed soil samples with a special child–friendly insert explaining their results in child-friendly terms. The results will only be shared back to the citizen science participant who takes part in this project and not the wider public, as explained in the *Ethical Considerations* section above.

Data Storage

Paper consent forms will be stored in a locked cabinet in the locked office assigned to one of the Soilsafe Kids coleads (Sophia Tsang, Victoria Egli, or Emma Sharp). All data for this project will be stored digitally to ensure that the entire research team has access and that data are regularly saved and backed up. Given that we have many Indigenous participants, the guidelines set out by Te Mana Raraunga | the Māori Data Sovereignty Network [44] have shaped our data storage processes. This includes only using document transfer and backup systems that have domestic servers. To ensure that none of our data are transferred offshore, we will use the University of Auckland's Webdropoff Service and local (ie, internal to the University of Auckland) storage. More information about our data storage can be found in our data management plan [45].

Discussion

Expected Findings

The Soilsafe Kids program is unusual due to its transdisciplinary nature while also combining educational outreach and research aims. This protocol describes our considerations as we designed the program to teach early to middle primary school students in NZ about soil. This will enable us to use mixed methods to gather student soil values that can supplement ongoing Soilsafe Aotearoa work that investigates adult soil values.

This program was designed to be accessible to schools in rural areas and to students with low reading levels during the COVID-19 pandemic (2020 to present). While accessibility and the pandemic guided the development of this program, we also were focused on ensuring that we provide students with an age-appropriate experience that supports their developing leadership potential, which all students could participate in the educational program without the research component without having their nonparticipation status disclosed to classmates, and that we followed best practices as laid out by Te Mana Raraunga | the Māori Data Sovereignty Network [44]. In line with the transdisciplinary Soilsafe Kids team, we will collect both quantitative and qualitative data to be analyzed, and we aim to share our results widely among academic circles, policy makers, and the public. To do so, we will disseminate our work in a variety of manners.

Limitations

Everyone's opinions and values are influenced by our contexts irrespective of whether they are spatial, temporal, cultural, or many others. We recognize that the results of Soilsafe Kids are not generalizable for 2 primary reasons related to the students we are working with. Although Tāmaki Makaurau Auckland is the largest population center in NZ, it is very urban compared to the rest of the country. While we aim to include more rural schools than in most programs, our results will not be representative of the country as a whole due to the schools' proximity to Tāmaki Makaurau Auckland. Additionally, students who are currently in early to middle primary school will be shaped by current events and contemporary culture; a student who is currently 8 years old likely views the world and soil differently than a 15-year-old. Thus, additional work must be designed and undertaken to increase the robustness of our data set to students of different backgrounds including settings and ages.

Conclusions

The Soilsafe Kids Three-Day program is a comprehensive way to ask children to consider the soil under their feet thinking through multiple worldviews. Through this program, we will gather students' soil values while also encouraging them to participate in Soilsafe Aotearoa's heavy metals soil testing. This not only will provide students a better understanding of the health of their soil at home but also ensures that they know if their home gardens are safe places to be growing food. By testing each students' soil individually and communicating their results back with considerations and suggestions for improvement where necessary, students and families can make informed decisions about their gardens and if the plants they would like to grow could pose a health concern due to heavy metal uptake.

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Data Availability

An extended protocol document can be found in Tsang et al's study [33].

Authors' Contributions

ST, VE, and ES conceptualized the Soilsafe Kids program and drafted the original manuscript. ST and BCM developed the study's methodology and resources. ST, VE, ES, BCM, and LEM are carrying out the detailed investigation. MK serves as a scientific mentor for Soilsafe Kids. All authors reviewed and edited this article.

Conflicts of Interest

None declared.

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Abbreviations

CF: consent form
NZ: Aotearoa New Zealand
PIS: participant information sheet

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Protocol

Safe Medication in Nursing Home Residents Through the Development and Evaluation of an Intervention (SAME): Protocol for a Fully Integrated Mixed Methods Study With a Cocreative Approach

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Abstract

Background: Medication safety is increasingly challenging patient safety in growing aging populations. Developing positive patient safety cultures is acknowledged as a primary goal to improve patient safety, but evidence on the interventions to do so is inconclusive. Nursing home residents are often cognitively and physically impaired and are therefore highly reliant on frontline health care providers. Thus, interventions to improve medication safety of nursing home residents through patient safety culture among providers are needed. Using cocreative partnerships, integrating knowledge of residents and their relatives, and ensuring managerial support could be beneficial.

Objective: The primary aim of the Safe Medication of Nursing Home Residents Through Development and Evaluation of an Intervention (SAME) study is to improve medication safety for nursing home residents through developing an intervention by gaining experiential knowledge of patient safety culture in cocreative partnerships, integrating knowledge of residents and their relatives, and ensuring managerial support.

Methods: The fully integrated mixed method study will be conducted using an integrated knowledge translation approach. Patient safety culture within nursing homes will first be explored through qualitative focus groups (stage 1) including nursing home residents, their relatives, and frontline health care providers. This will inform the development of an intervention in a multidisciplinary panel (stage 2) including cocreators representing the medication management process across the health care system. Evaluation of the intervention will be done in a randomized controlled trial set at nursing homes (stage 3). The primary outcome will be changes in the mean scale score of an adapted version of the Danish "Safety Attitudes Questionnaire" (SAQ-DK) for use in nursing homes. Patient safety–related outcomes will be collected through Danish health registers to assess safety issues and effects, including medication, contacts to health care, diagnoses, and mortality. Finally, a mixed methods analysis on patient safety culture in nursing homes will be done (stage 4), integrating qualitative data (stage 1) and quantitative data (stage 3) to comprehensively understand patient safety culture as a key to medication safety.

Results: The SAME study is ongoing. Focus groups were carried out from April 2021 to September 2021 and the workshop in September 2021. Baseline SAQ-DK data were collected in January 2022 with expected follow-up in January 2023. Final data analysis is expected in spring 2024.

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Conclusions: The SAME study will help not only to generate evidence on interventions to improve medication safety of nursing home residents through patient safety culture but also to give insight into possible impacts of using cocreativity to guide the development. Thus, findings will address multiple gaps in evidence to guide future patient safety improvement efforts within primary care settings of political and scientific scope.

Trial Registration: ClinicalTrials.gov NCT04990986; https://clinicaltrials.gov/ct2/show/NCT04990986

International Registered Report Identifier (IRRID): DERR1-10.2196/43538

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KEYWORDS

protocols and guidelines; medication safety; cocreation; user involvement; health and safety within primary care; research in nursing home care; mixed methods

Introduction

Background

Medication Safety in Nursing Homes

Despite years of focus, medication safety is still troubling patient safety globally, with increasing demands on health care systems challenged by aging populations [1]. Physical and social environments constitute system factors that are thought to be the main factors influencing health of older adults [2]. Medication errors and unsafe medication practices are the leading causes of avoidable harm in health care, playing a key role in jeopardizing patient safety. Nursing home residents constitute a marginalized, medically complex, and underresearched group who are in high risk of experiencing preventable medication-related harm [3]. Worldwide, older adults in need of specialized health care delivery through primary care, including nursing home care, is expected to increase [2,4]. In terms of improving medication safety in primary health care settings, focus on the most dangerous aspects of systems and the people who are most at risk have been suggested [5]. Highest rates of preventable medication harm have been found in older adult patient care settings [6]. Moreover, nursing homes provide health care for the older adults who are most at risk of experiencing risk factors of medication errors [3,7-9]. In 2021, an 11% increase in adverse events, with a total of 326.416 adverse events, was reported by the Danish Patient Safety Authority in Denmark, and approximately 60% of the events were related to medication errors. A substantial proportion of this increase is reported from municipality health care settings, including nursing homes. This is supported by international findings regarding medication errors in European nursing homes and community care context [7,8,10]. Thus, focus on the interventions to improve medication safety of older adults living in nursing homes is needed. Moreover, multiple work system factors, including persons (resident and staff), organization, tools and technology, tasks, and environment, have been found to affect medication safety in nursing homes. One of the organizational factors, namely, interprofessional collaboration was reported as a relevant factor [11]. These findings reflect recent suggestions for taking a systems approach with focus on organizational issues in terms of minimizing mistakes related to the medication management process [12]. Managing medication of nursing home residents is a highly complex task, often implicating a relatively invisible, multidisciplinary, and cross-sectoral team of health care professionals, providers, as well as the residents and their relatives [13]. However, existing literature remain sparse, heterogenous, and inconclusive when it comes to interventions to improve medication safety in nursing homes [14].

Complexity of Context in Primary Care—Toward a Safety II Theoretical Perspective

Absence of accidents and incidents is often referred to as *safety*, which is, ensuring that things do not go wrong. The theoretical underpinning can be defined as Safety I theory, which has been the primary driver of safety improvement efforts globally [15]. Nevertheless, as primary health care constitutes a complex system structure, safety cannot be hypothesized to be achieved through measuring errors to avoid them from reoccurring. The human ability to adapt to varying conditions, thereby increasing resilience within health care systems, cannot be overruled. In theoretical terms this can be defined as Safety II theory, where understanding why things go right most of the time becomes the primary investigatory question to answer [15]. Safety II theory has recently been suggested as a guidance to avoid harm in health care [16], thus enabling prevention of errors through determining underlying mechanisms and resources already in play before errors happen and improving patient safety through no-blame cultures in nursing homes [17]. However, there are no specific evidence-based guidelines on how to realize such safety culture [18,19]. Knowledge on the effects of quality improvement initiatives and interventions to improve medication safety in primary care is based on sparse, highly heterogenous evidence [20,21]. In Denmark, nursing homes are under the responsibility of municipalities who constitute an important part of primary health care. The nursing home setting is highly complex, being both a private home and a center of health care delivery for the residents.

Interventions to Improve Medication Safety in Nursing Homes

Development and evaluation of interventions fit to the complex context of nursing homes in large-sample, longitudinal studies have been suggested beneficial to obtain positive, long-lasting effects on medication safety [22]. Within hospital settings, multifaceted approaches and inclusion of stakeholders has been found to be associated with a decrease in medication errors and a positive change in patients' satisfaction [23]. This supports earlier studies arguing that future interventions targeting medication safety could benefit from being based on

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multidisciplinary teams focusing on quality as a shared commitment; being multifaceted; and involving all stakeholders, including residents and their relatives [24,25]. Nevertheless, findings are contradictory. A recent study investigating a multifaceted intervention to improve medication safety of nursing home residents did not find positive effects on the health status of nursing home residents [22], contrary to a study aimed to improve medication safety in a hospital setting through a multifaceted interventional strategy [23]. Overall, studies on interventions to improve medication safety in residential health care for older adults are heterogenous in terms of methodologies with inconclusive results [14]. This corresponds to findings of a review on the interventions to optimize medication use within nursing homes [26].

Thus, medication errors and unsafe medication practices continue to concern health care systems worldwide, including nursing home settings. However, earlier research clearly reflects a gap in the knowledge about interventions to improve medication safety in nursing home settings. Patient safety culture is acknowledged as a key to patient safety, both in terms of improvement and effect evaluation [16,27-29] and has been associated with medication errors, also showing improvement potential [19,30]. In 2021, a guiding report on avoiding harm in health care added the importance of focus on primary health care settings, involvement of stakeholders, and cocreation to conquer the challenge of patient safety, including medication safety [16]. Moreover, safety cultures were recommended to be integrated within research designs and as for efforts within health care organizations [16]. This is in alignment with the most recent health work paper by the Organization for Economic Cooperation and Development stating patient safety culture as a recognized factor of importance at all levels of health care. Moroever, instruments to measure patient safety cultures are already in use in 20 of 24 member countries [20].

Patient Safety Culture

Patient safety culture is a complex phenomenon that is thought as a subclass of organizational cultures referring to the safety culture related to patients [21]. It is defined as "the values shared among organization members about what is important, their beliefs about how things operate in the organization, and the interaction of these with work unit and organizational structures and systems, which together produce behavioral norms in the organization that promote safety" [31]. Instruments that aim to capture reflections of patient safety cultures have been developed and validated [20,32], with one of the most widely translated and adapted being the "Safety Attitudes Questionnaire" (SAQ), originally developed in the United States in 2006 [33]. The SAQ can be used with dualistic perspectives both to compare different health care employees perceptions and to monitor changes over time [32]. In addition, it allows for comparison between large numbers of sites across settings [33]. Although evidence is sparse and contradictory [34], there is evidence indicating that SAQ is a proper proxy measure of patient safety [35]. SAQ scores have been reported to be directly associated with patient outcomes [32]. The SAQ has been adapted and validated for use in both secondary care and primary care settings [36-40], including Western European nursing homes [38,41] and Danish hospital settings [36].

Prior Work

International studies have found lower measures of patient safety culture in nursing homes compared with hospital settings [42,43]. Importantly, no single instrument can capture the complexity of safety culture [44], which is regarded a multilayered construct. Outermost layers are considered to be visible and measurable (layers 1 and 2), whereas the deepest layer holding the essence of a culture is measurable only through qualitative means (layer 3) [45]. Layer 3 has not been reflected by earlier research [46], resulting in evidence on patient safety culture in nursing homes being mainly based on quantitative studies. This gap in knowledge could weaken medication safety improvement initiatives [45] and implies a need for in-depth exploration of patient safety culture, including qualitative methods [44-46]. An integrative mixed methods approach to analysis could further strengthen results to gain comprehensive understanding of patient safety culture as a target of intervention to improve medication safety [47].

Study Objective and Research Questions

Therefore, the primary objective of the Safe Medication in Nursing Home Residents (SAME) study is to develop and evaluate an intervention to improve medication safety of nursing home residents through patient safety culture. First, we aim to develop an intervention to improve medication safety of nursing home residents in a cocreative process, including (1) exploration of patient safety culture as perceived at the frontline of nursing homes (stage 1) and (2) development of a knowledge-based intervention in a multidisciplinary panel informed by findings from focus groups interviews exploring patient safety culture (stage 2). Second, we aim to evaluate the intervention in a randomized controlled trial (RCT) set at nursing homes (stage 3), including a register-based study on patient safety–related outcomes in nursing home residents. Finally, we aim to perform an integrative mixed methods analysis on patient safety culture in nursing homes to comprehensively understand patient safety culture as a complex phenomenon and target of medication safety improvement (stage 4). This could potentially drive a new theory on patient safety culture to guide future efforts to improve medication safety of older adults living in nursing homes. Using an integrated knowledge translation (IKT) approach, we aim to enhance knowledge translation from research into practice through generation of partnership-based, meaningful, acceptable, and feasible results to address medication safety in nursing homes, incorporating the voices of nursing home residents and their relatives. As no current golden standard exists for IKT approach in research, and as the existing guiding tool is based on general assumptions toward cocreativity and knowledge creation, we chose to pragmatically use the 8 guiding principles of IKT [48] that was recently developed to guide research on spinal cord injury, but follow general assumptions and definitions concerning cocreation and knowledge generation, to frame the overall research process of the SAME study. In addition, the IKT project proposal worksheet [49] based on the Canadian Institutes of Health Research's merit review criteria [50] will be used in the secondary objectives, which are to (1) explore and identify patient safety culture perceived by knowledge users at the frontline of nursing homes, including health care providers and

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receivers, and find out whether it is possible to explicitly describe implicit, core elements of patient safety culture through in-depth qualitative explorative analysis; (2) cocreate an intervention within existing resource frame to increase medication safety in nursing homes by including stakeholders and knowledge users, and it is based on patient safety culture as perceived at the frontline and guided by Safety II theory; (3) explore the impact of cocreativity in the development of an acceptable and feasible complex intervention to improve medication safety through patient safety culture in nursing homes; (4) develop new, comprehensive understanding of patient safety culture as a complex target to improve medication safety within high-risk complex primary care settings through mixed methods integrative analysis including both in-depth qualitative data on patient safety culture and quantitative data on patient safety climate in nursing homes; and (5) describe the impact of the intervention on quantitative health-related outcomes for safety assessment.

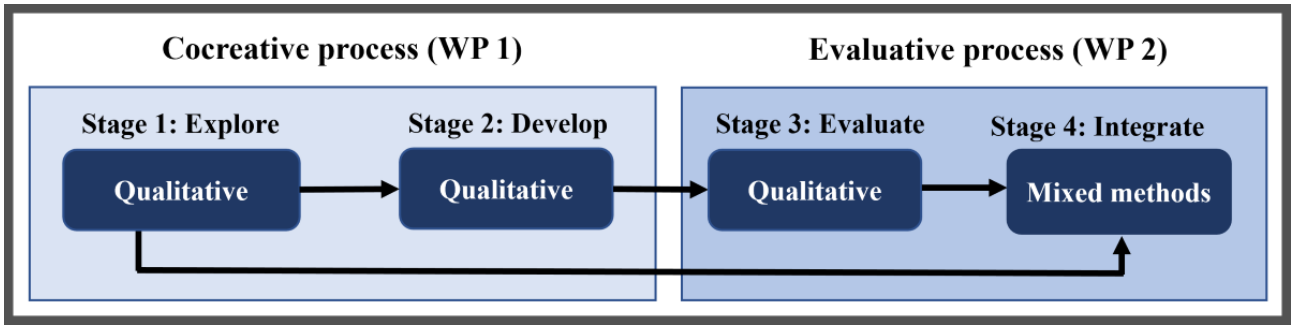
Methods

Study Design

Overview

The SAME study applies an overall theory-informed, fully integrated mixed methods study design that includes an exploratory sequential and IKT-guided research process, integrating 2 work packages including a cocreative intervention developing process (stages 1 and 2) and an evaluative process, including RCT (stage 3) and mixed methods integrative analysis of the intervention (stage 3 and 4). Integration will occur at design, method, and reporting levels to reach comprehensive understanding of patient safety culture as a target to improve medication safety. The SAME study aims to reach partnership-developed results through an IKT approach, thereby increasing the chances of achieving translation of research into practice with a focus on the empowerment of stakeholders, end users, and decision makers to generate useful, meaningful, acceptable, and feasible results. Thus, shifting roles of knowledge users to cocreators will be of primary focus throughout the study (Figure 1). To follow current political recommendations to shift perspective in terms of patient safety, Safety II theory [15] will inform data collection.

Figure 1. Safe Medication of Nursing Home Residents Through Development and Evaluation of an Intervention overall study design: a fully integrated, mixed methods study following sequential stages covering a cocreative process and a randomized controlled trial to develop and evaluate an intervention to improve medication safety of nursing home residents (black arrows indicate points of data integration). WP: work package.



Setting

Nursing homes registered within the Municipality of Aalborg, The North Denmark Region, Denmark, constitute the main setting of the SAME study. A nursing home is defined as "a facility with a domestic-styled environment that provides 24-hour functional support and care for persons who require assistance with activities of daily living and who often have complex health needs and increased vulnerability" [51].

Recruitment

A purposive sampling strategy will be followed through all the stages of SAME, conducted in partnership between the research team and municipal advisory board. The municipal advisory board will actively take part in recruitment through establishing contact with eligible cocreators (stages 1, 2, and 3) and participants (stage 3), including those employed at nursing homes, by sending out information material electronically (email). The research team will be responsible for the recruitment of cocreators not directly employed within municipal settings, including an external consultant in cocreativity and communication, risk managers at hospitals, and volunteers representing nursing home residents and their relatives.

Overall Eligibility Criteria

Participants will be eligible for inclusion in the SAME study according to the following criteria: (1) sufficient knowledge of spoken Danish language, (2) being directly or indirectly implicated in the medication management process of nursing home residents, (3) being employed for >2 months at a nursing home registered within the Municipality of Aalborg, and (4) being actively engaged in older adult health care at political or societal level within the Municipality of Aalborg. To represent nursing home residents, we aim to include volunteers from "the senior-council Aalborg" and "The council of elderly" (Table 1); both the groups are characterized by independent, voluntary participation.

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Table 1. Cocreators of the Safe Medication of Nursing Home Residents Through Development and Evaluation of an Intervention study: subgroups, definitions, and roles.

Subgroup	Definition	Role
Knowledge users		
Municipal management advisory board	Municipal management of the Department of Care for the Elderly and Disabled and Unit of Quality and Innovation	• Knowledge on practice • Decision makers • Feasibility
Nursing home managers	Nursing home managers and assistants	• Knowledge on practice • Empowerment • Feasibility
Nursing home care staff	Nursing home care staff (social and health assistants and helpers and home care and nursing home nurses)	• Knowledge on practice • Empowerment • Acceptability • Feasibility • Scope
Hospital risk managers	Employed as risk manager at Aalborg University Hospital or employed within the Municipality of Aalborg	• Knowledge on practice • Feasibility • Scope
General practice dedicated to nursing homes	NH-GP[a]	• Knowledge on practice • Empowerment • Acceptability • Feasibility • Scope
Representatives of residents and relatives	Actual relatives of nursing home residents of included nursing homes within the Municipality of Aalborg and representants of "The Senior-council, Aalborg" and "DaneAge Association"	• Knowledge on practice • Empowerment • Acceptability • Feasibility • Scope
Stakeholders		
Researchers	A multidisciplinary research group will ensure expertise in fields, including qualitative, quantitative, and mixed methods designs in addition to focus on general practice, nursing, and clinical pharmacology	• Scientific knowledge • Knowledge translation: merging theory and practice
External consultant in cocreativity and communication	An external expert will play an active part in the research team in the qualitative study stages, from facilitation to data analysis	• Knowledge translation: actual practice of cocreativity within municipalities • Empowerment of cocreators
VELUX FONDEN	Noncommercial foundation with grant areas including scientific, environmental, social, and cultural purposes in Denmark and internationally	• Funding

[a]NH-GP: Nursing home general practitioners

Patient and Public Involvement

We aim to achieve active engagement and empowerment of patients, health care professionals, decision makers and other stakeholders through developing partnerships, with emphasis on equal power but acknowledgment of different roles and responsibility (Table 1). To do so, an overall iterative IKT approach will be applied. IKT is viewed as "an approach or set of processes that can lead to the generation of knowledge for optimizing health care delivery systems and improving health system performance and associated outcomes" [52]. A total of 8 IKT guiding principles are available to support meaningful research, mitigating risk of tokenism. Although relatively recent, the IKT approach has been found useful in other research areas [48] and is in broad terms similar to other collaborative research approaches, including aiming at true partnerships rather than simple engagement; focusing on essential components and processes rather than labels; enabling collaborative research orientations rather than research methods, core values, and principles; and extensive time and financial investment [53]. Thus, in the SAME study, we aim to shift participants and researchers to the role of cocreators following an IKT approach. For practical implication, cocreators include the term "knowledge user" referring to "…an individual who is likely

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to be able to use the knowledge generated through research to make informed decisions about health policies, programs and/or practices" and "stakeholders" as "individuals, groups or organisations with shared interest in the research; may be in the geographic locality of the research setting or it may be affected by the environmental effects of the research but may not necessarily use the generated knowledge" [54]. To describe and evaluate the level of participation, we will use the International Association for Public Participation Spectrum of Public Participation [55].

Thus, we aim to develop an intervention that will improve medication safety of the older adults with frailty living in nursing homes, and it will be based on coknowledge, generating results perceived as meaningful, useful, acceptable, and feasible by those affected by the research to inform clinical practice. This could help support the ongoing development of sustainable, accessible, and equitable health care systems [56], making room for positive change.

SAME Study Cocreators

Table 1 shows an overall presentation of participants in the SAME study. We aim to achieve equally powered partnerships between participants and researchers, shifting participants and researchers into the role of cocreators [53] divided into subgroups following the SAME study IKT approach [57].

Work Package 1: A Developing Cocreative Process

To reach the overall aim of the SAME study, an intervention to improve medication safety of nursing home residents is aimed in a 2-staged cocreative process (Figure 1). Safety II theory will be used to obtain recommended shift in perspectives in facing health care issues [15,16]. The overall IKT approach of the SAME study will guide the development of cocreators. (Table 1).

Stage 1: Qualitative Exploration of Patient Safety Culture in Nursing Homes

The primary objective of stage 1 is to explore patient safety culture in nursing homes, with the perspectives of frontline health care providers being the primary focus. Experienced knowledge will inform the development of the intervention (stage 2) collected through semistructured focus group interviews [58,59]. In addition, field notes will be used as a data source. The medication management process of nursing home residents will be integrated in the development of the semistructured interview guide to ensure the development through medication safety lens of the SAME study.

Semistructured Focus Group Interviews

Focus group interviews can be used to gain in-depth understanding of a topic and to identify group norms and cultural values and minimize risk of discrimination regarding reading and writing abilities. Thus, using focus groups to explore patient safety culture could be beneficial with the aim of reaching in-depth knowledge, which is not achieved through quantitative methods [58-60]. All focus group interviews will be facilitated by the external consultant in cocreativity and communication (Table 1). In addition, a researcher (Table 1) will attend to observe and write field notes (Table 1). The first focus group interview will be set to ensure space for the needed adjustments before proceeding with data collection. The municipal risk manager (Table 1) will be invited as an observant of this interview and for a short reflection session at the end of each of the following interviews of approximately 15 minutes.

Semistructured Interview Guide

A semistructured interview guide will be developed in collaboration with the research group and an external partner in cocreativity and communication (Table 1). The latter will focus on presentability and general structure of the interview guide, whereas the researchers will account for theoretical information–based and evidence-based outline. To reach in-depth results, 9 intangible domains of organizational culture defined in a recent umbrella review on patient safety culture [44] will inform the interview guide development that will be structured based on Schein's model of safety culture [45]. Duration of each focus group will be ≤3 hours. This decision was made to face medication safety as a risk area with an expected need for slowly developing a "safe space" for knowledge users not expected to be formerly involved in similar projects, increasing the chance of reaching in-depth results.

Study Sample and Size

To help ensure that subgroup norms do not affect data generation negatively and allowing for intimacy, we aim to include a minimum of 3 and ≤5 participants in each focus group. Focus groups will therefore be formed by defined professional subgroups. We aim to include 4 to 6 focus groups, including social and health care assistants, social and health care helpers, general practitioners dedicated to nursing homes, home care nurse and nursing home nurses, and representatives of nursing home residents and their relatives (Table 1). Focus on organizational subgroups could minimize potential negative effects of possible existing hierarchical structures.

Outcomes

The primary outcome of stage 1 will be qualitative themes.

Data Analysis

Qualitative data will be both field notes and audio recordings that will be transcribed and stored according to current law. Themes will be generated following a triangulated in-person process including researchers with expertise in both qualitative and quantitative methods as well as a representant of end users in the sense of the external consultant in cocreativity and communication, representing cocreators of the SAME study (Table 1). Data analysis will be done following the principles of analyzing in the present [61]. Further validation of the generated themes will be sought through individual triangulation by including researchers representing relevant clinical functions and expertise, including a pharmacist, a nurse, a general practitioner, a qualitative expert, and a quantitative expert.

Stage 2: Development of a Knowledge-Based Intervention

In stage 2, the design of the new intervention will be formed. This will be done in a 2-phased process embedded a co-designing process. First, we aim to develop idea generation in a multidisciplinary panel representing a systems view in terms

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of the medication management process of nursing home residents, and the panel includes nursing home residents and their relatives as well as decision makers. Second, triangulation of ideas will be done with focus on research knowledge. To meet the possibility of using an inadequate number of cocreators to reflect the entire system, the cocreative process will include the investigation of acceptance and usefulness of the intervention through semistructured qualitative focus group interviews with knowledge users and stakeholders in stage 3. The municipal advisory board will play an essential role in stage 2, acting not only as partners in idea generation but also as decision makers in relation to the final intervention design.

Data Sources—Collection and Analysis

Data will be qualitative and collected as electronic recordings. Also, a collaborative field note worksheet will be written by facilitators after the workshop. Data analysis will be informed pragmatically by the Delphi method and through a process of data triangulation including stakeholders.

Phase 1: Multidisciplinary Panel Workshop

In this phase, we aim to generate ideas based on shared knowledge as an innovative base and to include systems perspective. Experiential knowledge on patient safety culture perceived by nursing home care staff, nursing home residents, and their relatives (Table 1; stage 1, Figure 1) will inform this phase. This will ensure the presence of voices of all knowledge users and minimize potential negative effects of power hierarchical structures. We will ensure acceptable, useful, and meaningful consensus through the presentation of the experiential knowledge from stage 1 as paradoxes by integrating multiple views and possible heterogeneity in the cocreated process. The workshop will be facilitated by the external consultant in cocreativity and communication and 3 representants of the research group (Table 1). The workshop will run over a full working day.

Study Sample and Size

A purposive sampling strategy to recruit a multidisciplinary, cross-sectoral panel consisting of knowledge users (Table 1) will be used. This will visualize the relatively invisible team who function in everyday practice and who are implicated in the medication management process of nursing home residents across professions, departments, and health care sectors, including the following:

1. Social assistants and health assistants (n=2)
2. Social helpers and health helpers (n=2)
3. Municipal management (n=2)
4. Nursing home management (n=2)
5. Nursing home general practitioners (n=2)
6. Home care nurses and nursing home nurses (n=2)
7. Risk managers employed at hospital and by the municipality (n=2)
8. Relatives of nursing home residents (n=2)
9. Representants of nursing home residents (“DaneAge association” and “Senior-council, Denmark”; n=2)

Outcome, Data Sources, and Collection

The primary outcome of phase 1 will be generation of ideas to improve medication safety, focusing on shared knowledge. A part of a cocreative process, data collection methods have not been predefined but will be developed as part of the research process. The external consultant in cocreativity and communication (Table 1) will play a key role. Both electronic records and field notes will be used as data sources. Results will inform phase 2.

Phase 2: The Co-designing Process—Data Sources, Collection, and Analysis

Data will be qualitative and collected as electronic recordings. In addition, a collaborative field note worksheet will be written by facilitators during and after the workshop. Data analysis will be done in a process of data triangulation including relevant stakeholders.

First, a preliminary intervention will be co-designed based on ideas generated at the workshop. Qualitative data will be analyzed guided by “analyzing in the present” [61] based on a triangulated process between participating facilitators after the workshop, following the cocreative approach including the external consultant in cocreativity and communication (Table 1).

Second, a co-designing phase including researchers and decision makers (Table 1) will be done to undertake an organizational and contextualized perspective. This will increase feasibility and acceptability potential of the final intervention design to be evaluated in the RCT (stage 3). Purposely sampled cocreators will be consulted in person through the presentation of the preliminary intervention, thereby leaving room for revision and correction. We aim to include cocreators having expertise in general practice, nursing, and pharmacology, in addition to those from qualitative and quantitative research fields in this phase.

Third, the municipal advisory board will be consulted, as their knowledge concerning organizational factors implicating the intervention will be essential to ensure a local contextualized, final intervention design.

Finally, the intervention will be designed by the research team in terms of explicating the decisions made by all the cocreators. The final intervention will be presented to the municipal advisory board, minimizing the risk of misinterpreted information and increasing the potential for adaptability through management support.

Work Package 2: Evaluation of Intervention and Understanding of Patient Safety Culture

Stage 3: Quantitative Evaluation of the New Intervention in an RCT

In stage 3, we will evaluate the new intervention in a randomized controlled study set at nursing homes. Data on primary outcome will be collected at baseline before rollout of the intervention and at 6-month to 9-month follow-up according to intervention rollout at individual participating nursing homes. Data on secondary outcomes will be collected during the intervention period.

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Study Sample and Size

A total of 36 public nursing homes were registered within the Municipality of Aalborg in 2021. We expect to recruit a minimum of 22 nursing homes to participate in this phase. Inclusion criteria are the following: to be eligible for inclusion within this study, nursing homes must be supported by a general practitioner registered by the Municipality of Aalborg. Exclusion criteria are the following: if a conflict appears, for example, in relation to other initiatives targeting medication, the Municipality will ensure exclusion of specific nursing homes. Nursing home care staff will be included according to the overall eligibility criteria and definitions defined in Table 1.

As no other studies have investigated the effect of a complex intervention in a mixed methods study design in primary care on SAQ, the sample size cannot be based exclusively on previous study outcomes. We aim to recruit as many respondents as possible from the included nursing homes.

Based on previous studies focusing on related health care setting and culture, we expect mean scale scores of SAQ of 32 to 75 [62,63], and we expect to find an increase of at least 4.0. We expect a lower SD than that reported in previous studies, as these studies have investigated more variable groups of professions. The overall SD (all domains) in home care services have been reported as 9.8 [62]. Thus, with a power of 0.8, significance level (α) of .05, and an expected SD of 9.8, it has been estimated that 192 respondents (96 respondents in the intervention group and 96 respondents in the control group) will be sufficient.

Outcomes

The initial problem statement that emerged from the Municipality of Aalborg was that adverse events were increasingly reported, yielding a legally bound challenge that is not yet overcome. Thus, the Municipality sought help for lowering the number of medication errors and unsafe medication practices through collaboration. Although reporting adverse events is an intended goal in safety terms in Denmark, the number of adverse events is not a proper estimate of medication safety.

As a proxy for the overall medication safety, including medication errors, the SAQ has been suggested. A Danish reliable and valid version is available (Danish Safety Attitudes Questionnaire, SAQ-DK). An increase in SAQ-DK would indicate a decrease in medication errors, whereas a decrease would indicate a worsening. We are aware of using the SAQ-DK as the primary outcome with precaution, as the intended increase in reporting adverse events within primary care is still an ongoing issue. However, to the best of our knowledge, no other more suitable measure is available, and therefore, we chose the SAQ as the most reliable and relevant proxy for medication safety in the SAME study.

The primary outcome will be focused on the nursing home frontline, including nursing home care staff's and nursing home managers' (Table 1) self-reported perceptions of patient safety culture measured as mean scale SAQ-DK score [36]. The SAQ-DK will be adapted for use in Danish primary health care settings, including nursing homes following the cocreative approach of the SAME study.

Secondary outcomes will include the following: qualitative—perceptions of patient safety culture of relevant cocreators collected through semistructured focus group interviews or individual interviews, depending on the results of the research process; quantitative—register data; that is, sociodemographic data and data on health-related outcomes will be collected at baseline and at follow-up. Data will be collected from relevant Danish registries.

Statistical Analysis

An evaluation of the new intervention will be done through comparison of primary outcomes and secondary outcomes between the intervention group and control group of the trial at baseline and 12-month follow-up. Results will be presented as SAQ-DK mean scale scores and SD, using Poisson regression statistical modeling.

Qualitative data will be transcribed and stored according to the current law. A structured codebook will be generated to guide thematical analysis [64]. Analysis will be performed by a junior researcher triangulating findings with a senior researcher with expertise in the qualitative research field, using NVivo (QSR International) [65].

Quantitative data will be registered and stored in REDCap [66] subsequently being transferred for analyses in Stata (StataCorp).

Safety Assessments and Effects

Patient safety–related outcomes will be analyzed through quantitative data collected through national registers; these data include (1) medication (number and type); (2) contacts to a health care system (hospital, nursing home general practitioner, and out-of-hour general practitioner); (3) diagnoses (somatic and psychiatric 10th revision of the International Statistical Classification of Diseases diagnoses); and (4) mortality. Descriptive statistics will be used to compare groups.

Stage 4: Mixed Methods Integrative Analysis of Patient Safety Culture: Mixed Methods Analysis

Through a mixed methods integrative analysis, the SAME study aims to gain comprehensive understanding of patient safety culture as a multilayered construct and target of medication safety intervention (stage 4) via different data sets, including (1) a quantitative questionnaire on nursing home care staff and nursing home management's (Table 1) self-reported perceptions of patient safety climate (SAQ-DK), (2) qualitative data on patient safety culture, and (3) qualitative data from individual interviews with knowledge users. The different sets of data will be collected and analyzed separately for final integration through use of "joint display of data" [67] in a mixed methods analysis. Results could lead to the development of a new theory on patient safety cultures in Danish nursing homes, informing future research and clinical practice in the area.

Ethics Approval

The North Denmark Region Committee on Health Research Ethics has reviewed and deemed the SAME study exempt according to the study design and the emphasis on the sole use

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of survey, interview, and national register methodology (2020-000992). The study was registered at and approved by the institutional data protection department, Department of Research Data and Statistics, Aalborg University Hospital (2021-015) and in ClinicalTrials.gov (NCT04990986). Participation will be voluntary, and informed consent will be obtained and can be withdrawn at any point in time. The SAME study will be conducted according to the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013).

Results

The SAME study is ongoing. Idea groups and experience groups (stage 1) were carried out from April 2021 to September 2021 and the workshop in September 2021. Baseline SAQ-DK data were collected in January 2022, with expected follow-up in January 2023. We expect to finish data analysis in spring 2024.

Discussion

Principal Findings

Mixed Methods

To impact decision-making, research could benefit from including multiple ways of understanding complex concepts leading to new understanding [68]. Thus, study designs combining mixed methods with participatory approaches could improve research outcome with increasing complexity of the area under investigation, allowing for a deeper understanding of complex phenomena [69-72]. Although sparse, mixed methods studies have been reported, underpinning the benefits in the development and evaluation of interventions [73-75]. Community-based organizations are important stakeholders in health systems, often called upon to use research evidence to inform health care delivery [76]. Consulting key stakeholders and service users, therefore, seems crucial to allow for evidence that is "probably more realistic, acceptable and likely to produce more change" [68]. Combining mixed methods with participatory research approach can help the translation of research into practice and may facilitate meaningful, evidence-based change [69]. Moreover, integration can occur at the level of knowledge. Thus, it is expected that integrative mixed methods analysis including in-depth qualitative exploration will provide a more comprehensive understanding of the complex phenomenon of patient safety culture within high-risk primary care settings, minimizing risk of generating misleading results to guide future clinical practice.

IKT Approach

IKT can be used to identify a problem and be able to implement the research recommendations through collaborative research processes. This will form partnerships between researchers and service users [57] aiming to produce meaningful, useful, acceptable, and effectful results [52,57,77]. Importantly, perspectives of representants of an entire organization should be accounted for in terms of investigating safety cultures [44]. Patient participation in the medication process has been stated essential in preventing adverse events, including medication errors [78]. This supports the acknowledgment of patient involvement to avoid harm in health care [16]. Moreover, a scoping review on the IKT approach reported by few studies that included patients who are knowledge users as partners, whereas decision makers were highly represented. Thus, it is anticipated that the IKT approach of the SAME study will increase the chance of identifying and acting upon needs and priorities of knowledge users, including decision makers, nursing home care staff, nursing home residents, and their loved ones, who are rarely integrated as active partners within research on patient safety culture.

Overall Discussion Resume

The SAME study will provide insight and knowledge to bridge the gap between research and clinical practice on medication safety strategies targeting older adults with frailty, with emphasis on cocreation. Moreover, understanding patient safety culture through an integrative method could lead to new opportunities of using and analyzing results based on instruments already in play. Including the SAQ as a primary outcome will help generate comparable results. This could increase learning potential across national borders, health care sectors, and local health care organizations and departments as a key to meet the global challenge of patient safety [20]. There is a possibility that results generated could guide the development of a novel framework to facilitate cocreation to improve medication safety in nursing homes.

Limitations

Systems and nursing home organizational–related factors such as political changes, time schedules, and resources could be limitations in all stages of the SAME study. Moreover, engagement in a knowledge user-researcher partnership is complex, nonlinear, and changeable, presenting a limitation of this study in terms of generalizability, transparency, and feasibility.

Conclusions

With growing aging populations, there is an increasing scope to analyze medication safety as one of the challenges facing patient safety. The SAME study will help generate evidence on patient safety culture that could help inform and guide future improvement efforts within primary care settings within both political and scientifical scopes.

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Data Availability

Data sharing not applicable to this study, as no data sets were yet analyzed during this study.

Authors' Contributions

AEO, JKK, ALS, and SPJ drafted the study design and applied for the funding of the study. MHJ, AEO, JKK, ALS, and SPJ planned the detailed study design and study protocol. MHJ drafted the manuscript and revised it based on comments from all authors. All authors approved the final version of the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

IKT: integrated knowledge translation
RCT: randomized controlled trial
SAME: SAfe MEdication in nursing home residents
SAQ: Safety Attitudes Questionnaire
SAQ-DK: Danish Safety Attitudes Questionnaire

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Protocol

Establishing Novel Antiretroviral Imaging for Hair to Elucidate Nonadherence: Protocol for a Single-Arm Cross-sectional Study

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Abstract

Background: Adherence to antiretroviral (ARV) therapy is critical for achieving HIV RNA suppression in people living with HIV and for preventing HIV infection in uninfected individuals using preexposure prophylaxis. However, a high level of adherence can be challenging to achieve for people living with HIV on lifelong ARVs and for HIV-negative individuals using daily preexposure prophylaxis who are not at daily risk for HIV infection. Current biological measures of adherence are invasive and use bioanalytical methods that do not allow for real-time feedback during a clinic visit. This study was designed to test the feasibility and acceptability of using MedViewer, a novel, minimally invasive, hair-based assay that measures longitudinal ARV drug adherence in real time and provides an output for provider-patient discussion.

Objective: The primary objectives were to investigate the feasibility of delivering the MedViewer results as planned, the acceptability of participation in a discussion of the MedViewer results, and the appropriateness of using MedViewer for adherence counseling. The secondary objectives were to investigate additional dimensions of feasibility, acceptability, and appropriateness of using the MedViewer test during a routine clinic visit for people with HIV.

Methods: The proposed study was a single-arm cross-sectional study among patients receiving HIV care and providers of HIV care in a southeastern infectious disease clinic. The study originally planned to implement the MedViewer test with 50 eligible patients who were living with HIV across 2 viral load strata (undetectable or detectable plasma HIV RNA over the previous 2 years), administer brief visit-specific questionnaires to all patient and provider participants, and conduct qualitative in-depth interviews and quantitative end-line questionnaires with a subsample of patient participants (n=30) and all provider participants.

Results: The Establishing Novel Antiretroviral Imaging for Hair to Elucidate Nonadherence study was funded by the National Institute of Allergy and Infectious Diseases and approved by the local institutional review board on November 4, 2019. Provider participant enrollment began on January 17, 2020, and patient participant enrollment began on January 22, 2020. Participant enrollment was halted on March 16, 2020, because of the COVID-19 pandemic (16 providers and 10 patients on study). Study activities resumed on February 2, 2021, with COVID-19 modifications approved by the local institutional review board. Participant enrollment closed on October 8, 2021, and data collection closed on November 15, 2021. In total, 36 unique patient participants, representing 37 samples, and 20 provider participants were enrolled. Data analysis and manuscript writing will take place throughout 2023.

Conclusions: We anticipate that the data collected through this study will provide important insights regarding the feasibility, acceptability, and appropriateness of incorporating new real-time longitudinal, minimally invasive adherence tests into routine clinical care and identify potential barriers to medication adherence among patients.

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KEYWORDS

HIV; AIDS; adherence; hair; infrared matrix–assisted laser desorption electrospray ionization; IR-MALDESI; antiretroviral therapy

Introduction

Background

HIV RNA suppression in blood plasma is a key factor in controlling the HIV epidemic. Adherence to antiretroviral (ARV) therapy (ART) is an effective way to achieve viral suppression, maintain good health for people living with HIV, and prevent the transmission of HIV to uninfected individuals [1]. However, it can be challenging to maintain adherence to lifelong drug therapy. Poor adherence to ARVs can result in the development of viral resistance and worsened patient morbidity and mortality [2]. Having an accurate measure of ARV adherence for patients and providers can facilitate early interventions to improve adherence. Blood plasma or intracellular ARV concentration monitoring has been considered the "gold standard" for biological measures of adherence. However, this approach has its own set of limitations, including being invasive, requiring advanced processing (eg, intracellular measures) or specific storage conditions, being a short-term measure of drug-taking behavior (depending on the half-life of the analyte), and requiring long turnaround times [3]. Therefore, valid noninvasive longitudinal measures of adherence such as hair analysis are critical for optimizing ARV effectiveness.

In this study, we proposed a novel solution to bridge the gap in adherence monitoring to improve clinical outcomes based on hair. Hair is unique in that it has the potential to provide information about drug intake over a longer period compared with other biological fluids, including plasma [4], blood cells [5], and urine [6]. Recent studies have used sensitive analysis of hair strands through liquid chromatography–mass spectrometry to evaluate ARV concentrations. These studies have demonstrated that ARV drug concentrations scale proportionally with dose frequency [7] and can predict virologic success [8]. Liquid chromatography–mass spectrometry methods typically evaluate hair segments of ≥1 cm; this length corresponds to at least a month of hair growth. Our approach uses infrared (IR) matrix–assisted laser desorption electrospray ionization (MALDESI) technology for mass spectrometry imaging (MSI) to visualize and quantify ARV concentrations longitudinally over the previous month of hair growth. An IR-MALDESI MSI method has been validated for the quantification of emtricitabine (FTC) and dolutegravir (DTG) in hair strands. As part of this validation, we have determined the lower limits of quantification for each of these 2 ARVs (FTC: 0.27 ng/mg; DTG: 0.04 ng/mg) using a series of prepared hair standards and ensured that our sensitivity is within the range of incurred samples we have evaluated as part of study aim 1. The benchmarking of this IR-MALDESI MSI longitudinal ARV profiling has been conducted through a 3-phase (single dose, daily dose, and dose proportionality) directly observed therapy study with FTC+tenofovir and DTG (ClinicalTrials.gov NCT03218592). Our preliminary results suggest that this method has potential value in measuring longitudinal drug exposure [9] and distinguishing between different adherence patterns [10].

Objectives

For ease of communicating regarding the IR-MALDESI MSI approach with patients and providers, we named this approach "MedViewer" and will refer to it as such throughout this protocol paper. In preliminary studies, we demonstrated that MedViewer can rapidly and accurately provide noninvasive and longitudinal evidence of drug ingestion and thereby has the potential to provide clinicians, researchers, patients, and study participants with feedback on adherence performance [3]. However, little is known about how such a tool would be accepted as an adherence-enhancing intervention by patients or providers or how best to implement it feasibly in the context of a clinic setting. The primary objectives of this study were to investigate the feasibility of delivering the MedViewer analysis as planned, the acceptability of discussing the MedViewer results, and the appropriateness of MedViewer use for adherence counseling. Secondary objectives of this study were to investigate additional dimensions of feasibility, acceptability, and appropriateness of using MedViewer to provide feedback to people living with HIV regarding longitudinal patterns of medication adherence. The goal of this work was to develop a simple, rapid, noninvasive, longitudinal monitoring tool of ARV adherence that will provide useful feedback for clinicians and patients to improve ARV adherence. As this was a feasibility study, of note, no change in clinical care was initiated based on information assessed with the intervention.

Methods

Intervention

The study intervention included four components: (1) a standardized training session for medical providers; (2) an informational video for patients; (3) the hair sample, MedViewer test, and accompanying MedViewer report (patient and provider versions); and (4) communication aids for providers.

All research activities were conducted in as private a setting as possible.

All medical providers that consented to participate in this study attended a standardized training session. Training sessions were offered in person and in a web-based format. The training sessions lasted between 30 and 60 minutes and were held at the start of the study as well as at various points throughout the study (for providers who were new or had not enrolled at the

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study start). The training introduced the providers to the MedViewer patient video (described in the following paragraph), the MedViewer test and report, and provider communication aids. The training also prepared providers to incorporate the delivery of the investigational MedViewer test results into discussions with patients during routine HIV care appointments by providing an opportunity to practice interpreting and discussing MedViewer results with patients using an example MedViewer report. The training session was required for all enrolled providers participating in the study before they could be scheduled to see enrolled patients for visits to review their MedViewer report. Supplemental training sessions with the same training materials were offered as needed. Although providers used the investigational MedViewer reports during their conversations with patients about ARV adherence, provider participants still only used currently accepted measures of ARV adherence (eg, plasma HIV RNA, HIV genotyping, and plasma therapeutic drug monitoring of ARVs) for making clinical decisions.

An 8-minute informational video was used to introduce patients to the MedViewer test, the hair collection process, and how test results can be useful for conversations between patients and providers about adherence. More specifically, the video explained (1) how ARVs are processed in the body and end up in the hair, (2) what the hair sample collection process would be like, (3) how the hair sample would be processed and how data and reports would be generated, (4) how the hair sample would be disposed of, (5) how the provider might review the results with the patient, and (6) how the test results could inform conversations about the patient's adherence. The video also addressed potential patient concerns about the test (as identified in a formative study conducted as part of intervention development) [11]. Potential concerns included but were not limited to whether it was painful to provide a hair sample and how patient privacy would be protected. This video was part of the informed consent process for patient participants to facilitate their understanding of the MedViewer aspect of the study. Eligible and interested patients watched the video during the informed consent process either in a private room in the research center or clinic or via an institutional review board (IRB)–approved videoconferencing call. Patients had the opportunity to watch the video multiple times as needed.

After providing informed consent, patient participants provided a hair sample for MedViewer testing. Hair sample collection took place in the research center or clinic initially. After the pandemic, hair sample collection could also take place in a private remote location where the patient participant felt comfortable, such as their home, to minimize study participants' exposure to the clinic environment. To collect the sample, a trained clinical research staff member used tweezers to pluck 5 strands of hair from the back of the patient's head. The research team member then placed the hair on a foil package and affixed the distal end of the hair with a label. The folded foil was placed into a resealable biohazard bag in a closed container and then transported promptly to the laboratory for testing in accordance with local environmental, health, and safety policies. The date and time of sample collection and transportation were documented on a paper case report form. At the laboratory, the laboratory scientist placed the sample in the IR-MALDESI instrument to run the test [3].

As suggested by our formative research findings [11,12], after the hair sample was run in the IR-MALDESI instrument, the laboratory scientist generated 2 distinct visual reports of the results intended for patients (Figure 1) and providers (Figure 2). The patient version presented a calendar indicating whether the IR-MALDESI output from each day achieved a sufficient threshold consistent with daily dosing, whereas the provider version displayed more detailed quantification of the IR-MALDESI output with a bar chart. The laboratory scientist then sent both reports via secure email to the research team, who printed the reports and delivered a hard copy or electronic version to the appropriate provider participant in the infectious disease (ID) clinic. The laboratory scientist that ran the test recorded the time the analysis process was started and the time the report was available for the research team on the same paper case report form. These times were used to assess the duration of this component of the intervention.

Before seeing the patient, the provider reviewed the provider and patient reports. During the patient's regularly scheduled appointment at the ID clinic, the provider and patient viewed the patient version of the report together and used them to have a conversation about the patient's ARV medication adherence. If the provider thought that the patient would be interested in the more detailed provider report, the provider could elect to also review that report with the patient. If the MedViewer report was not available during the patient's regularly scheduled ID clinic appointment, the provider and patient participants had the option to discuss them during a separately scheduled MedViewer appointment within 4 weeks of hair sample collection. The provider participants did not follow a standardized script to discuss the results with the patient; rather, the provider conducted the appointment based on their clinical judgment and discretion, drawing on information from the provider training session and communication aids, medical expertise, and their clinical judgment regarding the individual needs and circumstances of the patient participant (Figure S1 in Multimedia Appendix 1). If the provider chose to follow suggested communication strategies listed in the MedViewer intervention reference sheet, they could discuss MedViewer reports with patients by explaining the summary statistics printed with the results or pointing out any patterns of insufficient drug concentrations and adherence successes, asking patients about event-level or chronic and psychosocial causes of missed doses, asking patients about successful adherence strategies, working with patients to identify personalized strategies that could help them overcome causes of missed doses in the future or to replicate successes, offering encouragement for good adherence, and working with patients to set goals for improving future adherence.

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Figure 1. Example patient MedViewer report. ARV: antiretroviral; IRB: institutional review board.

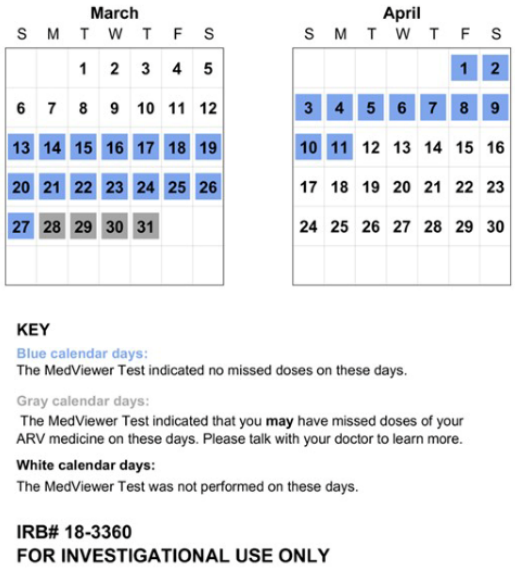
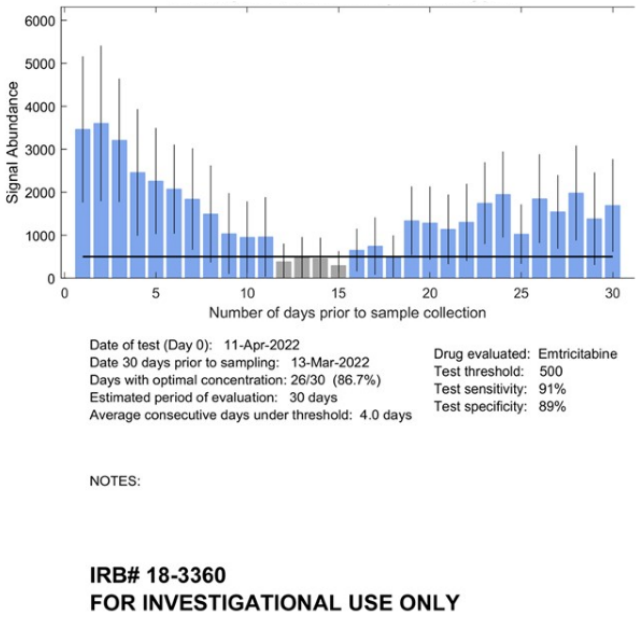


Figure 2. Example provider MedViewer report. IRB: institutional review board.



Owing to their investigational nature, the MedViewer reports were not entered into the patients' electronic health records, did not become a formal part of the clinical patient record, and were not used for clinical decision-making. After the provider and patient reviewed the MedViewer reports, both versions of the report were destroyed in accordance with standard medical document destruction procedures. A copy of each was stored in the research record. The research team documented receipt of the MedViewer report by the provider on the study forms.

Recruitment

Recruitment and Retention Strategies for Patient Participants

We planned to enroll 50 patient participants from a large hospital-based outpatient ID clinic in the southeastern United States. Data collection occurred in the clinic, in a clinical research center, or at remote locations to minimize exposure to the clinic environment in response to the COVID-19 pandemic. The ID clinic has a full-time research screener to assess patient eligibility for open research projects. Of all the patients in the ID clinic who are living with HIV, approximately 95% have consented to having their patient information available in a secure clinic database from which it can be viewed by a research screener to identify potential eligibility for open research studies and to being notified of studies for which they are potentially eligible (as per IRB form 99-MED-408). Patients in the database have indicated all the methods of contact to which they have and have not agreed for contact by researchers for potential participation. We used an IRB-approved screening process that has been used in the ID clinic for >10 years whereby the clinic screener or a trained research team member prescreened patients scheduled for an appointment in the upcoming week in the clinic database. After using the clinic database to identify potential patients, the screener or trained research team member assessed the patients' electronic health record for eligibility criteria under

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an IRB-approved limited waiver of the Health Insurance Portability and Accountability Act (HIPAA). At regular intervals, the clinic screener shared with the research team the list of scheduled patients who met eligibility at prescreening.

Using the list of potentially eligible study participants, the research team contacted patients by phone before their next scheduled HIV appointment using an IRB-approved phone screening questionnaire to notify them about the study and assess their interest. Phone calls were conducted in a private room to prevent inadvertent disclosure of participant information. Participants could also contact study staff in response to IRB-approved study recruitment flyers. For participants who expressed interest on the phone, the researchers continued with the phone contact to verify their eligibility using a brief standardized IRB-approved script and screening form (with questions pertaining to patient age, amount of time as a patient at the University of North Carolina at Chapel Hill [UNC] ID clinic, HIV appointments in the last year, current and past prescribed ARV medications, and length of caput hair), and if confirmed to be eligible for a screening visit and the patient agreed, they provided basic demographic data needed to schedule their appointment in the clinical research management system. This was done under an IRB-approved limited HIPAA waiver. Full HIPAA and informed consent occurred during the first patient participant visit. All contact attempts were documented in a recruitment log.

To ensure a sufficient number of patients with a history of detectable viral loads (VLs; who represented a minority in the clinic), we enrolled participants into 2 VL groups with a target of 25 participants in each group. Group A included those with plasma HIV RNA below the limit of quantification (<40 copies per million) over the previous 2 years with documentation of at least one test in the previous 6 months. Group B included those who had had at least one plasma HIV RNA result above the limit of quantification within the previous 2 years. We anticipated enrolling an average of 7 patients per month over the course of 7.5 months (33 weeks) to reach our target of 50 total participants. We screened and enrolled patients of all gender identities, racial identities, ethnicities, and ages (>18 years) such that the demographic distribution of screened participants reflected that of patients at the UNC ID clinic who are living with HIV.

Recruitment and Retention Procedures for the In-depth Interview Subsample of up to 30 Patient Participants

We also planned to enroll a subsample of up to 30 patient participants (up to 15 per VL group) enrolled in the larger study, to participate in a follow-up study visit including an in-depth interview (IDI) and brief end-line questionnaire. We invited every enrolled patient to participate.

Recruitment and Retention Procedures for Provider Participants

We aimed to recruit and enroll all (up to 30) medical providers who provided care to patients in the ID clinic (eg, attending physicians, fellows, nurse practitioners, physician assistants, nurses, and pharmacists) during the study period.

Most of our initial provider participant contacts were completed through email, wherein an IRB-approved email invitation to attend the provider training and participate in the study was sent. If the provider was willing to participate, they scheduled their training with the research team and completed the informed consent process before the training. Full informed consent and screening occurred before the provider training.

Ethics Approval

This study received ethical approval from the University of North Carolina at Chapel Hill instituional review board (reference ID 336881).

Informed Consent, Compensation, and Confidentiality

The investigators obtained informed consent from each patient and provider participant before starting any study procedures according to the standards set forth in the International Conference on Harmonization Good Clinical Practice guidelines and per local standard operating procedures. The process included reviewing consent forms with potential participants in a confidential setting and explaining all risks and benefits associated with participation in the study. The IRB-approved consent form was read with the participant in a private space, after which questions were solicited from the participant. The participant was allowed time alone to rereview the form and questions were again solicited. To ensure understanding, study staff asked questions of the participants regarding study procedures. The consent forms used language sufficiently simple for lay persons to comprehend. Participants were not coerced into taking part. Children aged <18 years, adults with impaired decision-making skills, and non-English speakers were not enrolled in this study. Each participant was provided with a photocopy of all the documents they signed. The informed consent process covered all elements required by research regulations. In addition, the process specifically addressed the following topics of importance to this study: (1) the unknown safety and unproven efficacy of the study interventions, (2) the importance of patients in both study groups to the success of the study, (3) the importance of adherence to the study visit and procedure schedule, (4) the potential medical risks of study participation (and what to do if such risks were experienced), (5) the potential social harms associated with study participation (and what to do if such harms were experienced), (6) the limited benefits of study participation, (7) the distinction between research and clinical care, and (8) the right to withdraw from the study at any time.

During the consent process, the patient participants watched the aforementioned short, IRB-approved video describing MedViewer. Participants who were not able to demonstrate adequate understanding of key concepts after exhaustive educational efforts were not enrolled in the study. The informed consent process included an assessment, through a series of questions, of each potential participant's understanding before enrollment and sequential assignment of concepts identified by the protocol team as essential to the informed consent decision.

Finally, the participants were offered the opportunity to sign the consent form or provide verbal consent for follow-up IDI study visits using an IRB-approved verbal consent process. All

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participants also reviewed and signed a HIPAA form approved by the IRB.

Participants were compensated for all parts of the study that they completed. Payment was provided in the form of Visa gift cards, and the amount per activity was reviewed and approved by the local IRB to not be coercive. Patient participants received US $5.00 for providing a hair sample, US $15.00 for providing a blood sample, US $20.00 for completing the baseline questionnaire, and US $10.00 for completing the postvisit questionnaire. When study operations were resumed after the COVID-19 pandemic, patient participants were provided with an additional US $20.00 to cover any telephone minutes or internet data they may have had to purchase to complete study activities. If a patient participant did not complete all parts of the study, their payment was adjusted. If the patient participant agreed to participate in the subsample, they were compensated for these activities as well. Patient participants received US $30.00 for taking part in the IDIs and US $10.00 for the questionnaire administered at the end of the interview. As these interviews were conducted in a web-based format after the COVID-19 pandemic, an additional US $20.00 was added to the gift cards to cover any telephone minutes or internet data they may have had to purchase to complete study activities. Provider participants received US $20.00 for attending the provider training session and completing all baseline questionnaires, US $30.00 for completing the postvisit questionnaires for all MedViewer patient visits they conducted during the study, US $20.00 for completing the IDI, and US $10.00 for completing the end-line questionnaire.

Confidentiality was maintained throughout the study by storing all specimens for current and future use with a unique identifying number, which was linked to the participant's name, social security number, address, telephone number, and hospital medical record number. The principal investigators and study staff were the only people with access to the identifying information. Any information provided to other people working on this study was given with the study ID number, not other identifying information. The records were secured in a locked file cabinet in a locked room in a badge access–only office suite of the principal investigator.

All electronic data for this study were stored on a dedicated university server with extensive protections and securities that exceed the standards of the UNC privacy of electronic information policy.

Participant confidentiality and privacy were strictly held in trust by the participating investigators, their staff, and the sponsors and their interventions. This confidentiality was extended to cover testing of biological samples in addition to the clinical information related to participants. Therefore, the study protocol, documentation, data, and all other information generated were held in strict confidence. No information concerning the study or the data was released to any unauthorized third party without previous written approval of the sponsor.

The study participants' contact information was securely stored at each clinical site for internal use during the study. At the end of the study, all records continued to be kept in a secure location for as long a period (6 years after completion of the research) as dictated by the reviewing IRB, institutional policies, or sponsor requirements. The period of 6 years is consistent with the requirements of Title 45 of the Code of Federal Regulations 46.115(b) and Title 21 of the Code of Federal Regulations 56.115.

To further protect the privacy of study participants, a Certificate of Confidentiality was issued by the National Institutes of Health. This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

Study Objectives and End Points

The study objectives and end points are outlined in Table 1.

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Table 1. Objectives and end points for the study.

Objectives	End points	Justification for end points
Primary		
• Investigate the feasibility of delivering the MedViewer intervention as planned, the acceptability to patients of participation in the MedViewer intervention, and the appropriateness of MedViewer use for adherence counseling	• Feasibility: proportion of participants receiving the MedViewer report during their provider visit as planned (ie, the results are delivered to the designated research staff member within 2 hours of initiation of hair processing and the results are discussed with the provider or pharmacist within 4 weeks of hair collection) • Acceptability: proportion of contacted patients who are eligible for a screening visit (not including inclusion criterion 9) who agree to participate in the MedViewer intervention pilot study • Appropriateness: perceived usefulness of the MedViewer intervention for adherence counseling	• Evaluation of these implementation domains will indicate the potential for future application of MedViewer in routine care and help identify needed modifications to the MedViewer intervention to improve delivery. The framework by Proctor et al [13] for outcomes in implementation research indicates the importance of assessing feasibility, acceptability, and appropriateness.
Secondary		

• Investigate additional dimensions of feasibility, acceptability, and appropriateness of using hair IR[a]-MALDESI[b] MSI[c] (MedViewer) to provide patients living with HIV with feedback regarding longitudinal patterns of medication adherence	• Feasibility:
	  • Reasons for patients' nonreceipt of the MedViewer report during a visit with the provider or pharmacist within 4 weeks of hair collection (if applicable)
	  • Reasons for nondiscussion of the MedViewer report with the provider or pharmacist (if applicable)
	  • Length of time (in minutes) from initiation of hair processing to MedViewer report delivery to the designated research staff member
	• Acceptability:
	  • Provider-reported likelihood of recommending MedViewer to future patients
	  • Patient-reported likelihood of agreeing to future MedViewer use
	  • Patient comprehension of the MedViewer report
	• Appropriateness:
	  • Perceived usefulness of MedViewer to promote ART[d] adherence
	  • Perceived impact of MedViewer use on patient-provider communication and relationship
		• Evaluation of these implementation domains will indicate the potential for future application of MedViewer in routine care and help identify needed modifications to the MedViewer procedure to improve delivery. The framework by Proctor et al [13] for outcomes in implementation research indicates the importance of assessing feasibility, acceptability, and appropriateness.

Exploratory		

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Objectives	End points	Justification for end points

• Assess exploratory aspects of MedViewer feasibility and acceptability and patient and provider views of and experiences with the MedViewer test
• Explore the impact of adherence counseling using MedViewer on ART adherence and hypothesized mechanisms of change (adherence information, motivation, and behavioral skills)
	• Feasibility:
	  • Patient-reported maximum out-of-pocket cost willing to pay for MedViewer
	  • Cost of MedViewer delivery per person
	  • Compatibility of MedViewer with current clinic practices
	• Acceptability:
	  • Patient-reported reasons for declining participation in the MedViewer intervention pilot study
	  • Reasons why participants would or would not agree to (patient-reported) or recommend (provider-reported) future MedViewer use
	  • Acceptability of specific components of the MedViewer procedure:
	  • Sufficiency of provider training and materials
	  • Sufficiency of patient education (video)
	  • Provider satisfaction with results delivery (discussion format and content)
	  • Patient satisfaction with results delivery (person, discussion format, and content)
	• Adherence-related:
	  • ART adherence measured via self-reported assessment of 3-, 7-, and 30-day adherence
	  • Adherence information (qualitative assessment of information and understanding gained of patient adherence resulting from use of MedViewer)
	  • Adherence motivation (quantitative and qualitative assessment of adherence motivation resulting from use of MedViewer)
	  • Adherence behavioral skills (quantitative and qualitative assessment of adherence behavioral skills and self-efficacy resulting from use of MedViewer)
		• Preliminary assessment of MedViewer's impact on the intended behavioral outcome (ART adherence) and hypothesized mechanisms of influence (based on the Information–Motivation–Behavioral Skills model) will be used to inform the design of a future randomized trial to evaluate the effect of MedViewer on these end points [14].

• Further explore the accuracy of the MedViewer test as an adherence measure	• ARV[e] concentrations in blood collected for first patient study visit and follow-up patient study visit when applicable • Patient viral load assessed with a clinical care visit linked to a patient-provider MedViewer visit and abstracted from the medical record by study staff • log10 ARV drug response in hair via IR-MALDESI collected for first patient study visit and follow-up patient study visit when applicable	• These end points will allow for comparison of reported concentrations of medication in hair with recent ART adherence, as measured via Mitra and current viral load. These comparisons will provide further evidence to assess MedViewer accuracy (in addition to that gathered in aims 1 and 2) among a larger group of patients.

[a]IR: infrared.

[b]MALDESI: matrix-assisted laser desorption electrospray ionization.

[c]MSI: mass spectrometry imaging.

[d]ART: antiretroviral therapy.

[e]ARV: antiretroviral.

Assessments

Data Collection Procedures

Patient and provider participants were administered IRB-approved questionnaires at different points during their study participation to assess outcome measures (Figures 3 and 4). These questionnaires were designed by trained qualitative researchers. Patient participants were administered a baseline computer-assisted self-interviewing (CASI) questionnaire after providing informed consent but before receiving and discussing the MedViewer reports with their provider. This questionnaire contained items asking about self-rated health, patient sociodemographic information (time to travel from home to the ID clinic, age, sex assigned at birth and gender identity, sexual orientation, race and ethnicity, current marital status, education level, income in the previous year, current employment status, health insurance status and type, and method of paying for ARVs), comprehension and sufficiency of video content,

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self-reported ARV adherence over the previous 30 days, and adherence motivation and self-efficacy. After receiving and discussing the MedViewer report with their provider, patient participants were administered a postvisit CASI questionnaire. This 13-item questionnaire comprised questions regarding experience receiving and discussing the MedViewer report, with whom they had discussed the report, their comprehension of the report, and acceptability of the process.

Figure 3. Patient participant study schema. Sequence of the Establishing Novel Antiretroviral Imaging for Hair to Elucidate Nonadherence study activities for patient participants. Note: MedViewer Report review can be conducted up to 28 days from hair sample collection if not completed at day 1 clinic visit with providers.

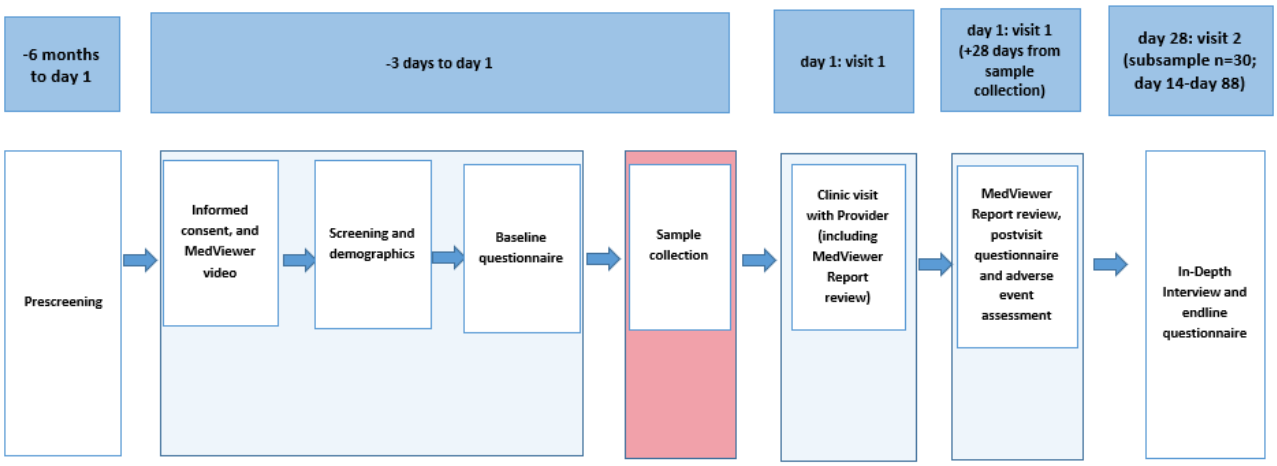
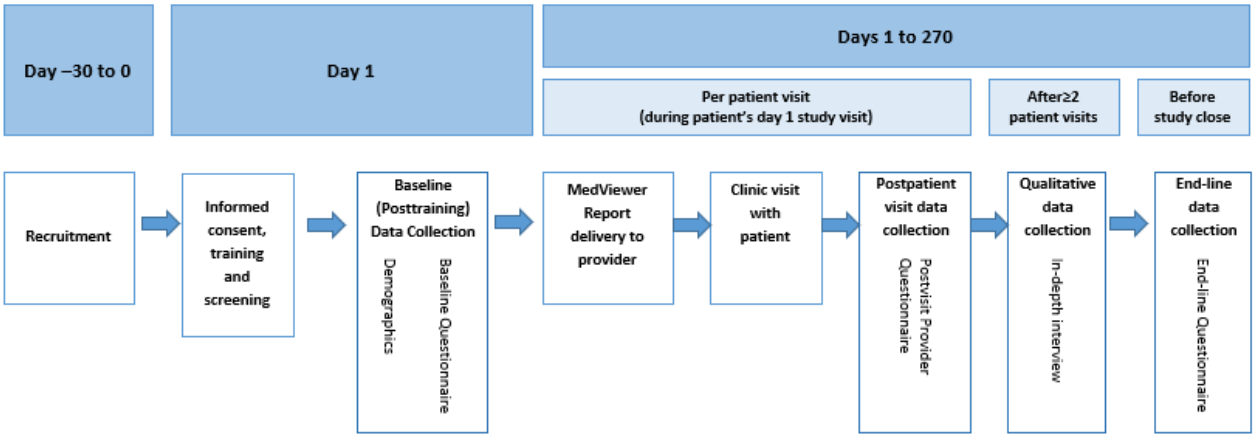


Figure 4. Provider participant study schema. Sequence of the Establishing Novel Antiretroviral Imaging for Hair to Elucidate Nonadherence study activities for provider participants.



The subsample (up to 15 from each VL group) of patient participants who returned for an IDI completed semistructured IDIs either in person or remotely via an IRB-approved videoconference. Interview topics included perceived usefulness of the MedViewer report for adherence counseling; reasons why the patient participant would or would not use MedViewer in the future if available; satisfaction with the patient education video; comprehension of the MedViewer report; satisfaction with adherence counseling discussion using the MedViewer report; attitude toward wait time and hair sample collection process; anticipated effect of regular MedViewer report use on patient-provider relationships and communication; and perceived effect of the MedViewer report on comprehension of own adherence behavior, adherence motivation, and adherence behavioral skills. All IDIs were approximately 1 hour in length. Trained research staff experienced in qualitative research conducted the IDIs using a semistructured interview guide that included open-ended questions corresponding to each qualitative outcome. Interviewers had the flexibility to probe patient responses and pursue discussion diverging from the initial interview questions if relevant to the outcomes of interest. Each interview was digitally recorded and transcribed verbatim for analysis. After completing the IDI, patient participants also completed a brief CASI questionnaire pertaining to their perceived adherence over the previous 3, 7, and 30 days as well as their adherence motivation and maximum out-of-pocket cost that they would be willing to pay for future MedViewer reports.

After completing the provider training session, provider participants were asked to complete a short baseline questionnaire. The questions pertained to their satisfaction with the training quality, content, perceived knowledge gained of the MedViewer test and study procedures, and self-efficacy to deliver the MedViewer report to patients. Each time a provider saw a patient participant for a MedViewer report discussion, they were asked to complete a postvisit questionnaire. These questionnaires assessed if the MedViewer reports were discussed, how long the discussion took, their perception of the

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patient's comprehension of the MedViewer report, and their perceived usefulness of the MedViewer report as an adherence tool. All provider participants enrolled in the study were asked to complete an IDI with research staff either after having reviewed the report with at least 2 patients or before study close, depending on which occurred first. The topics of the provider IDIs included the usefulness of the MedViewer report in encouraging patients to sustain or improve adherence, reasons why they would or would not recommend future MedViewer use, their satisfaction with the MedViewer report and adherence counseling using the report, perceived ease of delivering and discussing MedViewer results during a typical appointment, perceived level of disruption to clinic flow by MedViewer procedures, and the anticipated effect of regular MedViewer use on patient-provider communication and relationships. All provider IDIs were audio recorded with participant consent, and the audio file was transcribed for analysis. At the end of a provider's participation in the study, they were asked to complete an end-line questionnaire. The items on this questionnaire pertained to the likelihood of recommending MedViewer to other patients, satisfaction with adherence counseling discussions using the MedViewer report, perceptions of the most appropriate clinician for future MedViewer counseling, perceived usefulness of the MedViewer report in encouraging patients to sustain or improve adherence, and the influence of the MedViewer report on patient-provider communication and relationships.

Outcome Variables and Measures

Primary Outcomes

Feasibility

- Proportion of Patient Participants Receiving the MedViewer Report During Their Clinic Visit as Planned

This primary feasibility outcome is the proportion of participants who both (1) had their MedViewer report delivered to the designated research staff member within 2 hours of initiation of hair processing and (2) discussed the results with a provider (ie, their medical provider or the HIV care pharmacist) within 4 weeks of hair collection. To assess this primary feasibility outcome, the numerator was calculated using 2 separate data sources. First, to assess whether the designated research staff member received the patient's MedViewer report within 2 hours of initiation of hair processing, a study tracking log was maintained by the study team on which the following times were recorded: hair collection, hair transport, hair processing, and delivery of the report to the designated research staff member. The patient participants were asked to indicate on the self-report postvisit questionnaires whether the MedViewer report was discussed following clinic visits with their medical provider or the HIV care pharmacist; the study team also noted which clinician reviewed the report with the patient participant. As a backup data source, providers were also asked in their postvisit questionnaire if they discussed the report with the patient. The numerator of the primary feasibility outcome was a single dichotomous (yes or no) measure. Patients were counted in the numerator of the primary outcome if (1) the study team member indicated on the tracking log that, yes, study staff received the patient's results within 2 hours of initiation of hair processing in the laboratory—this was determined by subtracting time 1 (when hair processing was initiated) from time 2 (when the results were delivered to the designated research staff member—and (2) the patient self-reported on the postvisit questionnaire that, yes, they discussed the results with the provider. The proportion of enrolled participants who achieved the primary feasibility outcome will be estimated. An estimated proportion and corresponding 95% Wilson-Score CI was used to analyze this outcome and all similar dichotomous (ie, binary) outcomes.

Acceptability

The acceptability primary outcome was assessed based on the proportion of contacted patients who were eligible and agreed to participate in the MedViewer intervention feasibility study. Data for this outcome were obtained from the recruitment log. This was a single dichotomous (yes or no) measure for each individual participant. To create this measure, the denominator included all potential patient participants who were contacted and found to be eligible for the study as documented on their prescreening questionnaire. The numerator was those who agreed to participate in the study as documented by their informed consent form. The acceptability primary outcome is descriptive. The proportion of potential patient participants eligible for a screening visit who achieved the acceptability primary outcome (accepted enrollment) was estimated. An estimated proportion and corresponding 95% Wilson-Score CI was used to analyze this outcome.

Appropriateness

The appropriateness primary outcome (perceived usefulness of MedViewer for adherence counseling) was assessed using data obtained from the IDIs.

Secondary Outcomes

Feasibility

- Reasons for Patient's Nonreceipt of the MedViewer Report During a Visit With Provider or Pharmacist Within 4 Weeks of Hair Collection

This secondary feasibility outcome was only assessed for the subsample of patient participants for whom nonreceipt of the MedViewer report was reported (either by a provider in the provider postvisit questionnaire or by a research team member in a study activity tracking log). Reasons for nonreceipt were assessed using a 1-item multiple-choice question with a "check all that apply" approach in the provider postvisit questionnaires and an open-ended response on study tracking forms completed by the research team.

- Length of Time (in Minutes) From Initiation of Hair Processing to MedViewer Report Delivery to Designated Research Staff Member

This secondary feasibility outcome was defined as the amount of time elapsed (in minutes) from the time of initiation of hair processing in the laboratory to the time the results were delivered to the designated research staff member. This variable was determined by subtracting time 1 (when hair processing was initiated) from time 2 (when the results were delivered to the designated research staff member). This variable was

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measured using the study visit hair sample tracking log. The log was maintained by the study team, who reported the time at which each study activity occurred.

Acceptability

- Provider-Reported Likelihood of Recommending MedViewer to Future Patients

This secondary acceptability outcome was assessed using a single Likert-type item among providers in a self-reported end-line questionnaire administered by study team members. Providers were asked to rate their likelihood of recommending MedViewer, if available for regular use, to other patients in the future. This item was rated on a 4-point scale (*definitely would not recommend* to *definitely would recommend*). We calculated the proportion of providers reporting each response category (count/denominator and percentage).

- Patient-Reported Likelihood of Agreeing to Future MedViewer Use

This secondary acceptability outcome was assessed among patients in the self-reported postvisit questionnaire administered by the study team members after the participant had received and discussed their MedViewer report with their provider (or completed their visit without a discussion). This was measured using a Likert-type item. Participants were asked to rate their future likelihood of agreeing to MedViewer use if recommended by a provider. This item was rated on a 4-point scale (*definitely would not use* to *definitely would use*). We calculated the proportion of patients reporting each response category (count/denominator and percentage).

- Patient Comprehension of MedViewer Report as Perceived by Patients and Providers

This secondary acceptability outcome was assessed in postvisit questionnaires and IDIs. In the postvisit questionnaire following the MedViewer report discussion, patients were asked to rate their comprehension of the information presented in the report. Providers completed a parallel item in their postvisit questionnaire to assess their view of how well patients understood the information in the MedViewer report. The patient item was rated on a 4-point scale (*very difficult to understand* to *very easy to understand*). The provider item was rated on a 5-point scale (*understood poorly* to *understood excellently*). We calculated the proportion of patients reporting each response category (count/denominator and percentage). We calculated similar proportions for provider responses regarding their perception of each patient's comprehension as a proportion of patients. Patient comprehension of the report was also assessed qualitatively—during the patient IDIs, we conducted a cognitive interview to assess patient comprehension of adherence information presented in the MedViewer report. We used the data from the IDIs to summarize the extent to which patients understood the content of the reports and describe the primary content and formatting features of the report that were poorly understood by participants, if applicable.

Appropriateness

- Perceived Usefulness of MedViewer to Promote ART Adherence

This secondary appropriateness outcome was measured in the patient postvisit questionnaire administered by the study team members following the MedViewer discussion, in the provider postvisit questionnaire following each visit with an enrolled patient, in the patient and provider end-line questionnaires, and in the patient and provider IDIs. Participants were asked to rate their agreement with statements regarding MedViewer's usefulness in promoting adherence over the following 30 days, adherence motivation, skills, and strategies to avoid missed doses. These items were rated on a 5-point scale (*not at all useful* to *extremely useful*). For each item, we calculated the proportion of patients and providers reporting each response category (count/denominator and percentage).

- Perceived Impact of MedViewer Use on Patient-Provider Communication and Relationship

This secondary appropriateness outcome was assessed using the postvisit questionnaires for patients and the end-line questionnaires for providers as well as through questions during the IDIs. In the postvisit questionnaires administered to patients following the MedViewer visit, patients were asked to rate the comparative satisfaction with the patient-provider interaction during the MedViewer visit as compared with a typical visit. In the end-line questionnaires administered to providers, they were asked to rate the effect of using MedViewer on their relationships with their patients. The patient questionnaire item was rated on a 5-point scale (*much less satisfied than usual* to *much more satisfied than usual*), and the provider questionnaire item was rated on a 5-point scale (*very negatively affected relationships* to *very positively affected relationships*). For each questionnaire item, we calculated the proportion of patients and providers reporting each response category (count/denominator and percentage). During the patient and provider IDIs, participants were asked to discuss the anticipated effect of regular MedViewer use on patient-provider communication and relationships.

Statistical Analysis of Quantitative Data

General Approach

As this was a feasibility study, our analytic approach focused on calculating precise estimates of the outcomes. Descriptive statistics of categorical variables (eg, race, sex, gender identity, and VL cohort) were presented as counts and percentages, and descriptive statistics of continuous variables (eg, age) were presented as means with SDs or median, IQR, and ranges. We plotted and visually inspected the distribution of continuous variables. Generally, we did not anticipate variable transformations other than those prespecified in the Study Objectives and End Points and Outcome Variables and Measures sections (eg, $\log_{10}$ VL).

Statistical Analyses

With respect to estimation, a maximum likelihood estimate will be presented together with a 95% CI for the proportion or arithmetic mean of a continuous variable. Estimated proportions will be presented with a corresponding 95% Wilson-Score CI, and estimated means will be presented with a corresponding t-distribution 95% CI. If an estimated proportion is unexpectedly

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near the 0 or 1 boundary (eg, <0.1 or >0.9), an exact Clopper-Pearson 95% CI will be used as a sensitivity analysis.

Main protocol analyses will be conducted within the 2 enrolled VL strata separately as the strata sample sizes were selected for stratum-specific estimation and precision. We anticipate that patients in group B will be oversampled for study participation compared with the general clinic population. At the time of final analysis, data from the clinic cohort database will be used to define weights for each VL stratum such that a combined, weighted analysis can be used to generalize back to the clinic population. Details of a combined analysis will be prespecified in a separate analysis plan with consideration of additional patient characteristics such as gender, race and ethnicity, and age. Some exploratory analyses may be conducted using the 2 VL groups.

Qualitative Data Analysis

Data analysis consisted of 4 key steps. The first was reading for content. We began with data reading until the content became intimately familiar. As data were reviewed, emergent themes were noted. The second step was coding. A list of structural codes related to the interview questions was developed. Code definitions were documented in a codebook. Qualitative research assistants were trained to apply the codes using software for qualitative analysis. The codebook was piloted with 5 interview transcripts—each transcript was double coded to reconcile code application, and codes and rules for their application were modified as needed. To ensure intercoder reliability, 100% of the data were double coded. Independent coders reviewed areas of discrepancy until complete agreement was achieved on coded text. The third step was data reduction. We summarized participant responses pertaining to each interview topic and described variation in responses between individuals or among subgroups. We worked with the data related to each code to identify principal subthemes that reflected finer distinctions in the data. The fourth step was data display. Matrices and tables that categorize and display data were used to help facilitate comparisons (eg, across VL strata).

Primary Sample Size Consideration

We estimated the probability that participants would have their hair sample–based MedViewer report delivered as planned (for primary feasibility) within each VL strata with a corresponding 95% Wilson-Score binomial CI. The same approach was used for acceptability, appropriateness, and additional binary end points. A sample size of 50 would enable sufficient precision for a feasibility study to estimate main and secondary outcomes as well as sufficient power for exploratory data analyses.

Results

The Establishing Novel Antiretroviral Imaging for Hair to Elucidate Nonadherence study was approved by the local IRB on November 4, 2019. Provider participant enrollment began on January 17, 2020, and patient participant enrollment began on January 22, 2020. Participant enrollment was halted on March 16, 2020, because of the COVID-19 pandemic. When participant enrollment was halted, there were 16 provider participants and 10 patient participants on study. Study activities resumed on February 2, 2021, with COVID-19 modifications approved by the local IRB. Participant enrollment closed on October 8, 2021, and data collection was closed on November 15, 2021. In total, 36 unique patient participants, representing 37 samples, and 20 provider participants were enrolled. Data analysis and manuscript writing will take place into 2023.

Discussion

Expected Findings

Over the past 10 years, hair analysis has gained importance in forensic sciences, drug testing [15,16], toxicology investigations [17], and drug adherence [18]. Hair is unique in that it has the potential to provide information about drug intake over a longer period compared with other biological fluids, including plasma [4], blood cells [5], and urine [6]. Advances in bioanalytical technology have transitioned hair analysis from gas chromatography–mass spectrometry methods to more efficient and sensitive liquid chromatography triple-quadrupole mass spectrometry (LC-MS/MS) methods. However, several limitations exist. Some ARVs require collecting a thatch of up to 100 strands of hair [19]. As no one multiplex LC-MS/MS method exists to measure all ARVs in a single sample, multiple thatches are required for complete ARV evaluation. This can be a considerable deterrent for individuals with short hair, those who require hair collected between braids, or those who object to the collection of large amounts of hair for cultural reasons [20]. Although sensitive and specific, LC-MS/MS data require at least 7 steps to process hair for analysis, including segmentation, washing and decontamination, cutting or grinding, extracting, and purifying before analysis can occur [21].

Conversely, our IR-MALDESI MSI method uses single hair strands for analysis. Our method can also determine the identity and distribution of multiple drugs and their metabolites in biological matrices with 1 test without complicated labeling approaches [22-24]. IR-MALDESI MSI requires minimal sample processing, allowing sample analysis to be completed within 2 hours of collection.

Poor medication adherence is widespread among those living with HIV and on lifelong ART [25]. Research, including our statewide survey of North Carolina HIV health care providers, has found that physicians face challenges when counseling their patients about ART adherence [26-34] and that health care professionals would benefit from additional support to effectively address adherence [34-36]. Our research, and that of others, has demonstrated that counseling with accurate adherence feedback can enhance medication adherence [25,37-42].

Therefore, this paper described the rationale and method of a new adherence-enhancing intervention that is based on a novel measure using IR-MALDESI MSI of a hair sample to generate a longitudinal ARV adherence report as objective feedback during a routine clinic visit. This technique is noninvasive and can show daily medication response for the previous month depending on the length of the hair tested. In this study, we aimed to transform these medication responses into easily digestible visual aids for both patients and providers.

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Our model is unique in that it assesses both the IR-MALDESI assay and the social behavioral impact of the intervention on the patient's motivation to adhere to their medication. Furthermore, the study measures the perceived impact on providers' abilities to counsel their patients and their ability to implement MedViewer in the clinic.

We anticipate that the data collected in this study will provide important insights regarding the feasibility and acceptability of incorporating this new tool into routine clinical care and accentuate potential barriers to medication adherence among patients.

Limitations

This study allowed participants to self-report data about hair treatments (which could make them ineligible), medication adherence, and social behaviors. Self-report measures in research may present social desirability biases as well as recall bias. On patient and provider questionnaires, respondents may have underreported socially undesirable attitudes or answered questions in a favorable manner. To mitigate social desirability bias, questionnaires were self-administered on computers or tablets whenever possible, and the confidentiality of responses was made clear to participants. On the basis of statistical power calculations, 50 patient participants were anticipated to enroll in this pilot study. This limited sample size may limit our ability to detect differences for exploratory comparisons per strata. Another limitation of this study was the recruitment challenges surrounding patients in group B (detectable VL). Barriers included cancellations, no-shows, lost contact, and a very small number of patients with detectable plasma HIV RNA in the clinic. Hair sampling also has limitations, including needing to exclude patients with bald or shaved heads. A total of 6.7% (10/150) of potentially eligible patients were ineligible because of either having insufficient hair on their head or having recently treated their hair with chemical products. Of the eligible patient participants contacted about taking part in the study, 16% (24/150) declined participation for various reasons, including time constraints, distance lived from clinic, and no longer wanting to participate in research as a whole. Of the eligible providers contacted about study participation, 16% (5/32) declined to take part and 28% (9/32) never responded to contact attempts.

The COVID-19 pandemic presented unique challenges that required a protocol amendment after the first 27% (10/37) of patient participants were enrolled in the study. The remaining 73% (27/37) of patient participants were enrolled using the methods in the protocol amendment. The amendment was designed to limit in-person contact and ensure the safety of patients, research staff, and providers. Revisions to our methodology included redefining a real-time visit as "delivery of the report to the designated research staff member within 2 hours of initiation of hair processing" rather than "...within 2 hours of hair sample collection." Furthermore, hair collection during study visit 2 (IDIs) was removed from the protocol. Thus, patient adherence over time was not assessed via hair during the pandemic. To increase safety and flexibility, patient visits were conducted in a web-based format, and telehealth visits were available to patients and providers. Web-based data collection may have affected the results. The nature of the pandemic may have also created interpersonal challenges that discouraged patients from being contacted, seeking care, or expressing interest in participating in research.

Conclusions

To advance the understanding of adherence issues and help inform future research, this project provides insights on the feasibility, acceptability, and appropriateness of integrating MedViewer as an adherence monitoring tool into real-time clinical visits. A strength of this study is that it includes both patient and provider participants to measure the impact on patient behavior and whether it assists providers in their discussions with patients.

This project will contribute to the knowledge gap in the HIV adherence literature and have an effect on ending the HIV and AIDS epidemic. It will advance research by shaping important goals of public health, improving patients' medication adherence, and facilitating a semistructured method for providers to counsel their patients regarding adherence. Data from this study will determine whether having a broader, more comprehensive picture of how well a patient has adhered to their medication approximately 30 days before a routine clinic visit provides patients and their providers with a motivational tool with detailed information to engage in or sustain medication adherence.

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Data Availability

This study was conducted in accordance with the National Institutes of Health (NIH) public access policy, the NIH data sharing policy, the policy on the dissemination of NIH-funded clinical trial information, and the clinical trials registration and results

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information submission rule. As such, this trial was registered at ClinicalTrials.gov, with results archived on ClinicalTrials.gov. In addition, results were published in peer-reviewed journals and archived on PubMed Central.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Provider communication aids.
[DOCX File , 1078 KB - resprot_v12i1e41188_app1.docx]

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Abbreviations

ART: antiretroviral therapy
ARV: antiretroviral
CASI: computer-assisted self-interviewing
DTG: dolutegravir
FTC: emtricitabine
HIPAA: Health Insurance Portability and Accountability Act
ID: infectious disease
IDI: in-depth interview
IR: infrared
IRB: institutional review board
LC-MS/MS: liquid chromatography triple-quadrupole mass spectrometry
MALDESI: matrix-assisted laser desorption electrospray ionization
MSI: mass spectrometry imaging
UNC: University of North Carolina at Chapel Hill
VL: viral load

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Protocol

Determining the Impact of the COVID-19 Pandemic on Availability, Use, and Readiness of Family Planning and Contraceptive Services at Selected Primary Health Care Facilities in Africa and Asia: Protocol for a Mixed Methods Study

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Abstract

Background: The COVID-19 pandemic and the associated social restrictions may have disrupted the provision of essential services, including family planning (FP) and contraceptive services. This protocol is adapted from a generic study protocol titled "Health systems analysis and evaluations of the barriers to availability and readiness of sexual and reproductive health services in COVID-19 affected areas," conducted by the World Health Organization (WHO) Department of Reproductive Health and Research.

Objective: This study aims to assess the availability and use of FP and contraceptive services in primary health facilities during and after the COVID-19 pandemic; assess the risk perceptions of COVID-19 stigma, barriers to access, and quality of services from clients' and providers' perspectives in the COVID-19–affected areas; and assess the postpandemic recovery of the facilities in the provision of FP and contraceptive services.

Methods: In-depth interviews will be conducted with clients—women in the reproductive age group and their male partners who visit the selected health facilities for FP and contraceptive services—and health providers (the most knowledgeable person on FP and contraceptive service provision) at the selected health facilities. Focus group discussions will be conducted with clients at the selected health facilities and in the community. The in-depth interviews and focus group discussions will help to understand clients' and health service providers' perspectives of FP and contraceptive service availability and readiness in COVID-19–affected areas. A cross-sectional health facility assessment will be conducted in all the selected health facilities to determine the health facility infrastructure's ability and readiness to provide FP and contraceptive services and to capture the trends in FP and contraceptive services available during the COVID-19 pandemic. Scientific approval for this study is obtained from the WHO Research Project Review Panel, and the WHO Ethics Review Committee has given ethical approval in the 3 countries.

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Results: Using a standardized research protocol will ensure that the results from this study can be compared across regions and countries. The study was funded in March 2021. It received ethics approval from the WHO Ethics Review Committee in February 2022. We completed data collection in September 2022. We plan to complete the data analysis by March 2023. We plan to publish the study results by Summer 2023.

Conclusions: The findings from this study will provide a better understanding of the impact of the COVID-19 pandemic on FP and contraceptive services at the facility level, which will help policy makers and health managers develop and strengthen FP policies and services in health facilities to be more responsive to community needs.

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KEYWORDS

contraception; family planning; stock-out; COVID-19; facility assessment

Introduction

Background

COVID-19 was first reported in December 2019 and has since spread rapidly around the globe, being declared a pandemic by the World Health Organization (WHO) on 11 March 2020 [1]. The pandemic led to an unprecedented increase in demand on health systems to care for people infected with COVID-19.

Lessons from the Ebola and Zika virus outbreaks have highlighted the severe disruptions in sexual and reproductive health (SRH) services that expose women and girls in particular to preventable health risks [2]. The United Nations Population Division has suggested that the COVID-19 pandemic can result in 60 million fewer users of contraceptive methods worldwide, with projected declines expected to be most significant for injectables (–20%), condoms (–10%) and the pill (–10%) [3]. It is expected that during the pandemic, access to family planning (FP) services will disproportionately affect the rural populations, as supply lines and services are more thinly distributed and contraceptive methods that require medical consultations will have particularly noticeable falls, whereas methods that can be used independently will be less affected [3,4]. According to the United Nations Population Fund, overwhelmed with COVID-19 cases, clinical staff may not have the time or personal protective equipment needed to provide FP counselling and commodities [5]. Women refrain from visiting health facilities due to movement restrictions or fears about COVID-19 exposure. Meanwhile, supply chain disruptions are limiting the availability of contraceptives in many places [6]. It is anticipated that significant levels of lockdown-related disruption over 6 months could leave 47 million women in low- and middle-income countries unable to use modern contraceptives, leading to a projected 7 million additional unintended pregnancies [7]. Furthermore, studies have modelled the potential impacts, showing that even a 10% reduction in essential SRH services could lead to an estimated 15 million unintended pregnancies, 3.3 million unsafe abortions, and 29,000 additional maternal deaths during the next 12 months [7-9].

There is some scientific evidence on the impact of COVID-19 on FP and contraceptive services. A recently published scoping review [10] included 55 studies on the impact of COVID-19 on contraceptive services in low- and middle-income countries. Nearly all studies reported a decline in contraceptive service provision of varying magnitudes, but severe disruptions were relatively uncommon or of limited duration. Most included studies showed declines in at least some indicators of access to contraceptive services during the COVID-19 pandemic. Another scoping review on the global impact of the COVID-19 pandemic on SRH services included 24 studies that showed a decrease in access or use of contraceptive services, especially long-acting reversible contraception, evenly distributed across various contexts and populations [11]. A systematic review reported substantial decreases in contraceptive access and use in all 5 included studies on the impact of the COVID-19 pandemic and the associated lockdowns [12].

This research protocol details a mixed methods study to evaluate the impact of the COVID-19 pandemic on the primary health system's capacity to provide FP and contraceptive services and the perceptions of clients and health care providers about the access and use of FP and contraceptive services in 3 countries: India, Nigeria, and Tanzania. This protocol has been adapted from a generic study titled "Health systems analysis and evaluations of the barriers to availability and readiness of sexual and reproductive health services in COVID-19 affected areas" conducted by the WHO Department of Reproductive Health and Research [13].

Study Aims and Objectives

The study aims to assess the availability of FP and contraceptive services in primary health facilities during the COVID-19 pandemic. The specific study objectives are the following:

- To explore the availability of FP and health facilities' readiness to provide FP and contraceptive services in regions most affected by the COVID-19 pandemic.
- To assess the risk perceptions of COVID-19 stigma as well as barriers to access, use, and quality of services from clients' and providers' perspectives in the COVID-19–affected areas.
- To assess the postpandemic recovery of the facilities in the provision of FP and contraceptive services.

Methods

Study Design

This is a mixed methods study that uses both quantitative and qualitative methods. In-depth interviews (IDIs) and focus group discussions (FGDs) will be used to understand clients' and

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health service providers' perspectives of FP and contraceptive service availability and readiness in COVID-19–affected areas. A cross-sectional health facility assessment will be conducted to determine the health facility infrastructure's ability and readiness to provide FP and contraceptive services and to capture the trends in FP and contraceptive services availability during the COVID-19 pandemic. Table 1 summarizes the study design, analysis plan, and the expected outcomes.

Table 1. Overview of study methodology.

Study type and method	Respondent	Study setting	Study tools	Analysis plan	Variable measured
Qualitative study					
In-depth interview	• Women of reproductive age • Men of reproductive age	Health facility	• Semistructured interview guide for women • Semistructured Interview guide for men	Computer- assisted thematic analysis using NVivo or ATLAS.ti	• Knowledge of COVID-19 • Gaps in service provision • Risk perception, beliefs, and concerns • Enablers and barriers in availing services
In-depth interview	• Health care providers	Health facility	• Semistructured interview guide for health care providers	Computer- assisted thematic analysis using NVivo or ATLAS.ti	• Knowledge of COVID-19 • Gaps in service provision • Risk perception, beliefs, and concerns • Recovery in service availability
Focus group discussion	• Women in reproductive age • Men in reproductive age	Health facility	• Focus group discussion topic guide for women • Focus group discussion topic guide for men	Computer- assisted thematic analysis using NVivo or ATLAS.ti	• Knowledge of COVID-19 • Gaps in service provision • Risk perception, beliefs, and concerns • Enablers and barriers in availing services
Focus group discussion	• Women in reproductive age	Community	• Focus group discussion topic guide for women	Computer- assisted thematic analysis using NVivo or ATLAS.ti	• Knowledge of COVID-19 • Gaps in service provision • Risk perception, beliefs, and concerns • Enablers and barriers in availing services
Quantitative study					
Health facility assessment	• Senior Health care provider or administrator	Health facility	• Health facility assessment questionnaire	Database will be developed. SPSS will be used for descriptive analysis.	• Knowledge of COVID-19 • Gaps in service provision • Risk perception, beliefs, and concerns • Recovery in service availability
General client information	• All men and women who participate in Focus group discussions and in-depth interviews	Health facility	• General client questionnaire	Database will be developed. SPSS will be used for descriptive analysis.	• Sociodemographic information

Study Setting

This study will be conducted in India, Nigeria, and Tanzania by the Indian Council of Medical Research—National Institute of Research in Reproductive and Child Health, the University of Ilorin Teaching hospital, and the Ifakara Health Institute, respectively. These 3 countries are selected as they are a part of the WHO FP Accelerator project [14], and we leveraged the support from the project funds to support the research. Other criteria included the willingness of the Ministry of Health to participate in the study as well as the capability and capacity of research institutions in the 3 countries.

In each country, the research team will select study sites based on geographical location (ease of access and areas with a high incidence of COVID-19 cases), organization of FP and contraceptive services, and epidemic status, where the COVID-19 pandemic is likely to have significantly affected service delivery.

Study Population

The study population will be women and their male partners who visit the selected primary health facilities for FP and contraceptive services during the study period. It also includes health providers who provide FP and contraceptive services at

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the selected health facilities. In countries where it is not customary for men to accompany their partners when they seek FP and contraceptive services, other options will be used to recruit male partners.

Health Facility Selection

The minimum criteria should be the selection of primary health care facilities providing FP services and the availability of human resources qualified to provide FP and contraceptive services. Rural and urban representation of the primary health facilities in each region will be ensured.

Qualitative Study

Selection of Women and Male Clients

Women and their male partners seeking FP and contraceptive services at the selected facilities will be approached to participate in the IDIs and FGDs. The women and men will be purposively selected, if they fulfil the following criteria: (1) being of reproductive age (18-49 years), (2) having sought or received FP and contraceptive services from the selected primary health facilities, and (3) being comfortable discussing their experience seeking FP and contraceptive services in a group (for FGDs).

A health provider from the selected health facility, who is not a part of the study, will help identify potential participants based on the inclusion criteria and ascertain their willingness to participate in the study. Participants will be purposively selected to obtain a sample of women and men from all socioeconomic backgrounds in the area. The health provider will identify potential participants from among the women visiting the facility for FP and contraceptive services and will ask the women their age and willingness to participate in an FGD using screening questions to check for eligibility. The provider will approach the clients after they have been attended to or while waiting to be attended. The screening will occur in a private room selected by the provider and agreed upon by the study team. Clients who agree to participate will be introduced to the study research team. All participants will be given comprehensive information about the study, and all their questions and concerns will be addressed. Written informed consent will be obtained from all participants.

To provide a holistic picture of the knowledge and perceptions about FP and contraceptive services during the COVID-19 pandemic in the community, FGDs will be conducted with women in the community who have not obtained FP and contraceptive services from the selected public health facility but may have sought FP services from other private or public facilities. The community health workers will help identify participants for this FGD. Interested women will be asked to contact the study team.

The study will recruit a purposive sample of 10 to 15 women (or until saturation) and 6 to 12 male partners (or until saturation) per health facility for the IDIs. At each health facility, one FGD will be conducted with women clients, one with male partners, and one with women in the community.

Selection of Health Care Providers

Health care providers will be purposively selected to participate in the IDIs. Health care providers need to fulfil the following inclusion criteria: (1) those who deliver FP and contraceptive services, (2) are knowledgeable about the readiness and availability of FP and contraceptive services, and (3) are stationed in the FP clinic and have been working at the clinic for at least six months before the pandemic started. The health care provider will be selected after obtaining information from the facility in charge. Participation will be voluntary, and only the health care providers who accept to participate after talking with the study gatekeepers will be referred to the study team for interviews. Approximately 1 to 2 health care providers per health facility will be selected to participate in the IDIs. Depending on the norms and standards for providing FP services in different country contexts, they will include medical doctors, nurses, midwives, nurse assistants, allied health professionals, and other cadres.

Quantitative Study

A general questionnaire for clients will be used to collect sociodemographic data from all participants of the qualitative study. The most knowledgeable person on FP and contraceptive service provision in each selected health facility (senior health care provider or administrator) will be selected to assist in completing the health facility assessment.

Data Collection

Qualitative Study

Qualified researchers with experience in conducting IDIs and FGDs will be selected and trained to ensure the validity of data collection, build trust with participants, and protect participants' privacy and confidentiality. Male facilitators will facilitate the IDIs and FGDs with men, and female facilitators will facilitate FGDs and IDIs with women. The interviews will be conducted in a place that is convenient and safe for the participants to discuss the subject matter freely. The interviews will commence after the introduction and informed consent processes are completed. To ensure all information is captured, interviews will be audio-recorded. The researcher will also take notes on the participant's nonverbal communication during the interview. We expect each IDI to last approximately 40-60 minutes and each FGD to last 60-90 minutes.

To guarantee the anonymity of the participants, any personal or family identifiers will be removed. After each IDI or FGD, the moderators will send the recording to the team supervisor, who will store them securely for transcription. To protect the data from unintended use, the audio files will be encrypted and sent to an electronic database, which will also be shared with the WHO. Therefore, only the research team will be authorized to listen to the recordings. These audio recordings will be retained until the researcher has transcribed and checked them for accuracy, after which they will be destroyed.

Quantitative Study

The health facility assessment survey will be implemented using a cross-sectional survey design. All facilities identified in the selection phase will be assessed. The assessment will include

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a review of health facility records of FP and contraception to assess the availability, type, and range of commodities offered prior to, during, and after the pandemic. Records for 6 months prior to the start of the pandemic will be reviewed to determine the recovery in service availability and readiness in health facilities. The assessment will also highlight gaps or service delivery issues during the COVID-19 pandemic. The quantitative data will be collected on paper in India and electronically in Nigeria and Tanzania.

Pilot studies will be conducted in all 3 study sites to ensure the validity of the questionnaires in the local context.

Data Collection Tools

The qualitative study includes 5 data collection tools: (1) IDI topic guide for women, (2) IDI topic guide for men, (3) IDI topic guide for health care providers, (4) FGD topic guide for women, and (5) FGD topic guide for men. These tools will help understand the psychosocial effects of COVID-19 on fertility desires, knowledge of COVID-19, risk perceptions and concerns about the COVID-19 effects on SRH, care-seeking behaviors, experiences and barriers in accessing FP and contraceptive services, the influence of men on access to FP services, and the role the male partners play when their partners require contraception.

The quantitative study includes 2 data collection tools: (1) a general questionnaire to collect sociodemographic information from all participants of the qualitative study and (2) a health facility assessment questionnaire. The health facility assessment questionnaire follows and adopts the WHO's Service Availability and Readiness Assessment tool [15] and the health facility checklist developed by the WHO Health Emergency department [16] for assessment of infrastructure and services. This will help to understand how health systems delivered FP and contraceptive services during the emergency response to the COVID-19 pandemic. The following indicators will be used to assess the availability and readiness of health facilities in the provision of FP and contraceptive services: (1) policies and plans, (2) services maintenance and referrals, (3) infrastructure, (4) commodities, and (5) human resources.

The data collection tools will be translated into local languages: Yoruba and Hausa in Nigeria, Kiswahili in Tanzania, and Hindi and Marathi in India.

Data Analysis

The audio-recorded data will be transcribed verbatim and deidentified using ID numbers. Interviews conducted in local languages will be translated to English and back-translated to ensure there is no distortion of information. The data will be analyzed using general content analysis approach according to the suggested steps by Elo and Kyngäs [17]. This will involve reading through the verbatim transcripts and notes to understand what was being expressed by the participants, noting down emerging themes and patterns in the data, and condensing the data into codes. The codes will be used to generate categories and condensation of related categories into themes that convey the meaning of the data. The coding method and progress will be systematically discussed between the researchers and the project coordinator. The analysis will be done using NVivo software (version 12; QSR International). Two researchers will analyze the same data set and be guided by general questions, specific questions, and comparisons. The analysis will begin while data collection is ongoing to assess progress and determine any data collection problems and patterns.

Quantitative data from the facility assessment survey will be entered into an electronic database using SPSS (IBM Corp). Descriptive analysis will be used to illustrate the basic characteristics of the different facilities, including the monthly number of clients, types of procedures provided, number of medical staff, and stocks of drugs. In Tanzania, the Open Data Kit platform will be used to collect data digitally on tablets, and the KoboCollect App will be used in Nigeria on the research staff's phones for data collection.

Ethics Approval

Scientific approval for this study in 3 countries has been obtained from the WHO Research Project Review Panel. The WHO Ethics Review Committee has given ethical approval for this study in 3 countries (protocol IDs CERC.0103K, CERC.0103J, and CERC.0103I). Each study site is required to obtain ethical approvals based on the specific requirements in each country.

Results

We expect to gain more insight into the impact of the COVID-19 pandemic on FP and contraceptive services at the primary health care level and the trends in contraceptive uptake during and after the pandemic. The study was funded in March 2021 and approved by the WHO Ethics Review Committee in February 2022. Data collection was completed between April and September 2022. The project is ongoing. Expected results will be published in summer 2023.

Discussion

Expected Outcomes

This paper outlines the design of a multicountry study determining the impact of the COVID-19 pandemic on FP and contraceptive services at the primary health care level in India, Nigeria, and Tanzania. This study will explore the availability of FP and health facility readiness to provide FP and contraceptive services; it will assess the risk perceptions of COVID-19 stigma and barriers to access and use services as well as their quality from clients' and providers' perspectives; it will also assess the postpandemic recovery of the facilities in the provision of FP and contraceptive services.

A cross-sectional study was conducted across 10 states of Nigeria to determine the impact of the COVID-19 pandemic on the provision of SRH services at primary health facilities [18]. Findings showed that 97.7% of the 307 primary health centers offered FP services before the pandemic and lockdown, which decreased to 95.8% during the lockdown and reduced to 92.5% after the lockdown. A rapid qualitative study among young men and couples in 2 districts from 2 states of India (Bihar and Uttar Pradesh) showed a marked increase in the demand and use of condoms compared to pre–COVID-19 times,

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while women avoided the use of oral contraceptive pills due to the misperception of its ill effects on their health [19]. A mixed methods study in 3 purposively selected districts from 3 regions of Tanzania (Unguja, Pemba, and Dar es Salaam) revealed low uptake of FP services because of changes in clinic schedules, fear of COVID-19 infection, and unavailability of contraceptives [20]. Additionally, the quantitative analysis of FP use between January and March in 2019, 2020, and 2021 showed a decrease in FP use in 2020 for continuing clients, whereas an increased trend was noted for new clients in 2020 and 2021. A web-based survey among 51 clinicians and stakeholders in 29 countries showed that 86% perceived access to contraceptive services was less or much less because of the pandemic [21]. On the other hand, a population-based survey in 4 sub-Saharan African countries (Burkina Faso, Democratic Republic of the Congo, Nigeria, and Kenya) showed that among the 7245 women surveyed, there were no deleterious effects of the pandemic on contraceptive access and use [22].

In the scoping review by Polis et al [10], the study design of most of the included studies (69%) were cross-sectional or longitudinal surveys, and many were conducted on the web or by phone due to the pandemic [10]. However, our study uses a mix of quantitative and qualitative methods to assess the health facilities' availability and readiness to provide these services and clients' and providers' perceptions of the availability and readiness of these services in COVID-19–affected areas. Data in our study will be collected in person.

Polis et al [10] report the reasons for the change in the contraceptive demand as lack of awareness that contraceptives were provided during the pandemic, preferences for methods accessible with no or fewer visits to health facilities, use of condoms to attempt prevention of COVID-19 transmission, and the stigma that respondents perceived or experienced at health facilities. The reasons for disruptions in the provision of contraceptives were reported as reduced availability or stock-outs, not being able to offer provider-administered methods, health providers advising FP clients not to seek services at health facilities, fewer clients permitted in clinics due to social distancing measures, and service disruptions across multiple humanitarian contexts due to mandatory restrictions, lockdowns, and curfews. Key barriers to accessing contraceptive services during the pandemic included fear of infection in general and in health facilities, lack of transport or travel-related restrictions, costs, increased waiting times, limited home visits by health workers who would normally provide contraceptive services, lack of supplies, and for adolescents in humanitarian settings, the compounding effect of other pandemic challenges, such as being out of school and isolated from peers [10].

Limitations

We anticipate certain limitations for this study. The study focuses on primary health care facilities and only in a few sites per country. The information gained might not be generalizable to the situation in other public facilities and private facilities as well as all over the country. However, information on FP access at this level is necessary because it indicates the situation the most vulnerable in the society are facing and would call for prompt intervention. The use of a standardized research protocol can ensure that the results from these studies can be compared across regions and countries and will potentially improve the quality of observational studies by identifying and minimizing biases. Since most of the countries are out of the pandemic, there can be recall bias because participants would be reproducing the experiences from the past 2 years. However, as the pandemic and lockdowns are rare events, many might remember their personal experiences.

Conclusions

The findings from this study will provide a better understanding of the impact of the COVID-19 pandemic on FP and contraceptive services at the subnational and facility level, which will help policy makers and health managers develop and strengthen policies and services to be more responsive to community needs. These policies and services will ensure the availability of a contraceptive method mix that is accessible, affordable, and women-centered during emergency situations like the COVID-19 pandemic.

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Authors' Contributions

RK, KPA, JK, BJ, EE, and TMA were involved in the conception and study design. TMA, BJ, EE, AO, DT, RKP, MR, and DS are responsible for assuring the quality of data acquisition and will be responsible for data analysis and interpretation.

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RK and KPA worked on the draft manuscripts and the final manuscript. All authors were involved in manuscript revisions. All authors have reviewed and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

FGD: focus group discussion
FP: family planning
IDI: in-depth interview
SRH: sexual and reproductive health
WHO: World Health Organization

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Protocol

Care Partner Inclusion of People Hospitalized With Alzheimer Disease and Related Dementias: Protocol for a Mixed Methods Systems Engineering Approach to Designing a Health Care System Toolkit

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Abstract

Background: Research and policy demonstrate the value and need for the systematic inclusion of care partners in hospital care delivery of people living with Alzheimer disease and related dementias (ADRD). Support provided to care partners through information and training regarding caregiving responsibilities is important to facilitating their active inclusion and ultimately improving hospital outcomes of people living with ADRD. To promote care partners' active inclusion, a toolkit that guides health systems in the identification, assessment, and training of care partners is needed. User-centered approaches can address this gap in practice by creating toolkits that are practical and responsive to the needs of care partners and their hospitalized family members and friends living with ADRD.

Objective: This paper describes the study protocol for the development and refinement of the ADRD Systematic Hospital Inclusion Family Toolkit (A-SHIFT). A-SHIFT will provide health care systems with guidance on how to effectively identify, assess, and train care partners of hospitalized persons living with ADRD.

Methods: The A-SHIFT study protocol will use a 3-aimed, convergent mixed method approach to iteratively develop and refine the toolkit. In Aim 1, we will use a systems-engineering approach to characterize patterns of care partner inclusion in hospital care for people living with ADRD. In Aim 2, we will partner with stakeholders to identify and prioritize health care system facilitators and barriers to the inclusion for care partners of hospitalized people living with ADRD. In Aim 3, we will work with stakeholders to co-design an adaptable toolkit to be used by health systems to facilitate the identification, assessment, and training of care partners of hospitalized people living with ADRD. Our convergent mixed method approach will facilitate triangulation across all 3 aims to increase the credibility and transferability of results. We anticipate this study to take 24 months between September 1, 2022, and August 31, 2024.

Results: The A-SHIFT study protocol will yield (1) optimal points in the hospital workflow for care partner inclusion, (2) a prioritized list of potentially modifiable barriers and facilitators to including care partners in the hospitalization of people living

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with ADRD, and (3) a converged-upon, ready for feasibility testing of the toolkit to guide the inclusion of care partners of people living with ADRD in hospital care.

Conclusions: We anticipate that the resultant A-SHIFT will provide health systems with a readiness checklist, implementation plan, and resources for identifying, assessing, and training care partners on how to fulfill their caregiving roles for people living with ADRD after hospital discharge. A-SHIFT has the potential to not only improve care partner preparedness but also help reduce health and service use outcomes for people living with ADRD after hospital discharge.

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KEYWORDS

caregiving; co-design; dementia; health care; systems; mixed methods

Introduction

Persons living with Alzheimer disease and related dementias (ADRD) experience not only poorer health outcomes, but more hospital admissions and readmissions, longer hospital stays, and higher health care costs than older people who have not been diagnosed with ADRD [1-6]. Research and policy call for the systematic inclusion of care partners of people living with ADRD in hospitalizations to improve these health service use outcomes**.** Care partner inclusion has been associated with reduced readmissions and increased net savings [7,8]. Furthermore, when included in care, care partners report feeling more satisfied and less burdened [9]. Moreover, the policy has been mandated to better assist care partners in the hospital setting, including the Caregiver Advise, Record, and Enable Act. Across 44 states, hospitals are required to (1) provide patients with the opportunity to identify a care partner; (2) inform the patient and care partner when the discharge is to occur; and (3) provide the patient and care partner training regarding the discharge care plan [10]. Despite the supporting research and policy, care partners often report feeling unprepared to fulfill caregiving roles during and after a hospitalization of a family member or friend living with ADRD [11,12]. This is problematic as the 2022 National Strategy to Support Family Caregivers outlines federal, state, and local actions to help strengthen care partner services, including “recognizing them as essential partners in care teams of the person to whom they are providing support” (Outcome 2.1) [13].

Although research and policy work endorse the need for inclusive care practices, to our knowledge, no toolkit exists to guide health care systems when working with care partners of people living with ADRD [14]. To address this gap, in accordance with the National Institutes of Health Stage Model for Behavioral Intervention Development [15], we propose to conduct the critical Stage 0 and IA activities to develop the ADRD Systematic Hospital Inclusion Family Toolkit (A-SHIFT). We will use a user-centered approach to address each stage and to (1) uncover key hospital workflow intervention points, (2) identify and prioritize barriers and facilitators to care partner inclusion at multiple system levels (Stage 0), and (3) guide the transformation of these factors through stakeholder co-design into a comprehensive toolkit to help facilitate the inclusion of care partners of hospitalized people with ADRD, which is adaptable for use by different health systems (Stage IA). The following specific aims will be accomplished:

- Aim 1: describe the current practices around care partner identification, assessment, and training for hospitalized people living with ADRD.
- Aim 2: identify and prioritize health care system facilitators and barriers to the inclusion of care partners of hospitalized people living with ADRD.
- Aim 3: collaborate with stakeholders to co-design an adaptable toolkit to facilitate the inclusion of care partners of hospitalized people living with ADRD.

Toolkits, such as A-SHIFT can provide health care systems practical guidance regarding how to systematically include, assess, and train care partners of hospitalized people with ADRD. Further, A-SHIFT will be scalable to health care systems across the United States, providing the foundation for fulfilling the needs of care partners and alleviating their feelings of being unprepared to provide care following discharge.

Methods

Design and Conceptual Framework

Our interdisciplinary team will use a convergent mixed method approach [16] using systems engineering methods to conduct the necessary Stage 0 and IA activities of the National Institutes of Health Stage Model [15] to develop A-SHIFT across 3 aims (Figure 1). Our aims are guided by the System Engineering Initiative for Patient Safety (SEIPS) 2.0 model (Figure 2) [17]. SEIPS 2.0 has been used to design and implement health care processes in myriad health care settings [18-23]. SEIPS 2.0 expands upon Donabedian’s structure-process-outcome model [24] by providing a detailed and expanded structure (ie, work system) of interacting components (people [or teams]; tasks; tools and technology; organizational factors [eg, policies and teamwork]; physical environment [lighting, noise]; and external environment) that influence health care processes (eg, identify, assess, and train care partners of hospitalized people living with ADRD) and outcomes [4]. The model depicts a system that adapts to process changes and outcomes. SEIPS 2.0 will be used to guide data collection and analysis to ensure the identification of factors influencing care partner inclusion across all system components.

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Figure 1. Overview of specific aims. EHR: electronic health record.

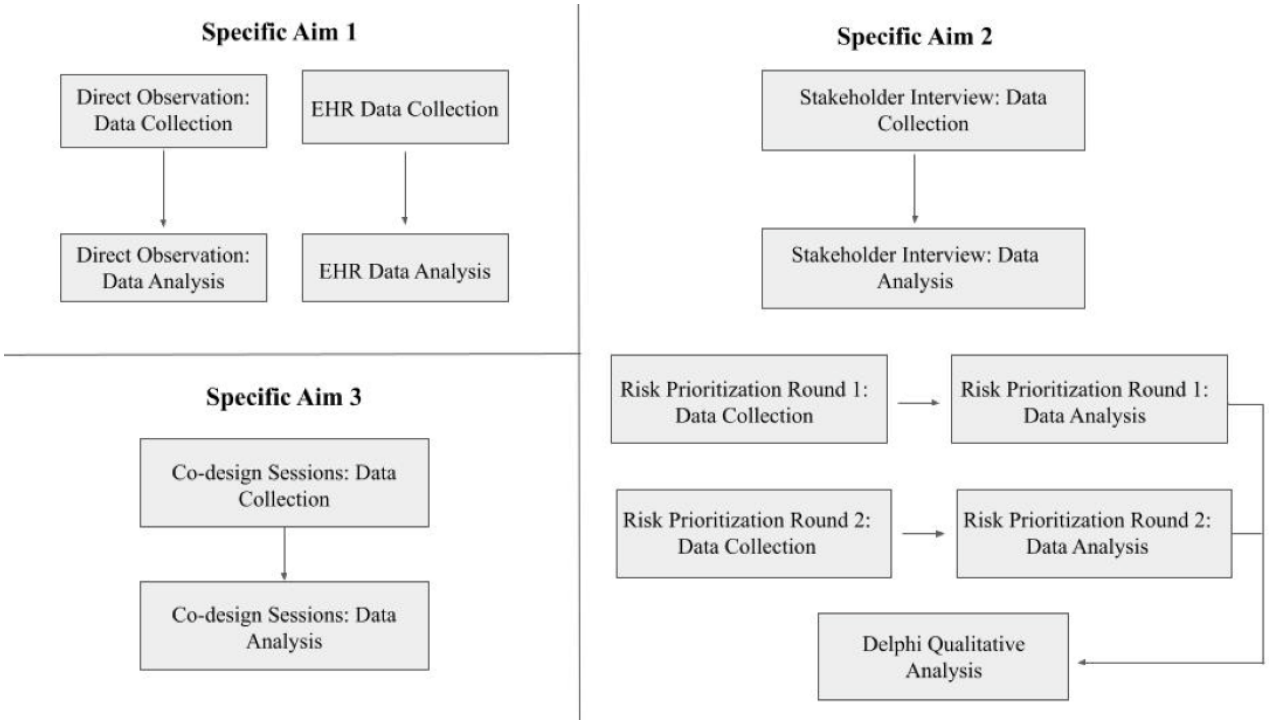
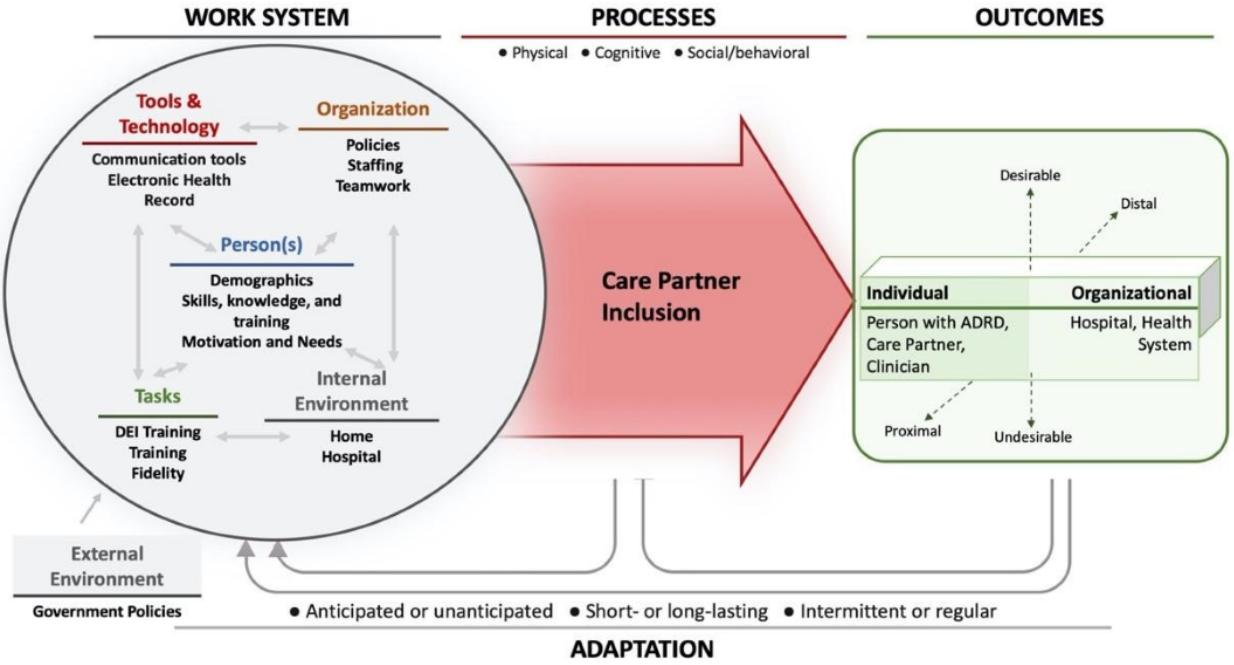


Figure 2. System Engineering Initiative for Patient Safety 2.0. ADRD: Alzheimer disease and related dementias; DEI: Diversity, Equity, and Inclusion.



Aim 1: Using Direct Observation and Electronic Health Record Data to Characterize Patterns of Care Partner Inclusion in Hospital Care for People Living With ADRD

Setting

We will collect observation and electronic health record (EHR) data from a large academic health care system in the Midwest. This system serves more than 600,000 patients each year with approximately 1750 physicians and 2100 staff at 7 hospitals and more than 80 outpatient sites. A major focus of this health care system is to put patients and their families, health plan members, employees, and community at the center of everything they do and create a model that ensures patient and family-centered care.

Direct Observation Sample

We will purposively select 4 diverse inpatient units from this health care system for direct observations, such as a trauma or medical surgical unit, an orthopedic unit, a family practice unit, and a neuroscience or stroke unit. These units allow for more

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heterogeneity of admitted patient conditions, providing us greatest exposure to various care partner needs.

EHR Sample

We will purposively select EHRs for patients across all hospitals in the health care system who meet our selection criteria: (1) aged >18 years with an ADRD diagnosis, (2) admitted to an inpatient unit, and (3) care partner identification, assessment, or training documented during patients' hospital stay. To enhance rigor and reproducibility, there will be no exclusion based on sex, race, ethnicity, or HIV status. Records will be excluded for same-day surgery patients and patient discharge disposition that is not home (eg, skilled nursing facility).

Direct Observation Data Collection

We will capture care partner interactions on each selected unit using a structured SEIPS 2.0-based observation guide in Vosaic Software (Table 1) [25]. Observations will be conducted across 3 days in each unit. Each observation session will consist of a 3-hour block of time that represents morning, afternoon, and evening shifts to maximize understanding of different care points and care partners' availability. In total, we will collect 27 hours of direct observations of direct care experiences (3 hours×3 days×3 units). Research team members will be trained to use the observation guide on department-owned laptops stored in a locked room. Training will consist of at least 2 meetings with the PI and research team members to discuss example observations for each code and review consent processes. Before starting data collection, the unit director will give a brief overview of the project to the clinicians on the unit and introduce the research team members. The team members will complete the observation guide for each interaction a clinician has with an admitted patient and any present care partners. Within a given interaction, team members will use Vosaic Software [25] to record each time they witness a code in the observation guide. To increase trustworthiness in our observations, each team member will create memos describing their observations of patient care and care partner inclusion, in addition to using the observation guide.

Table 1. Observation and electronic health record (EHR) data collection examples.

SEIPS[a] component	Observation protocol	EHR fields
Work system organization internal environment	• Are care partner policies, education, or trainings posted? • What is the staff/patient ratio? • Are there designated areas for care partners?	• Hospital location (suburban, urban, and rural), size of unit
Work system personnel	• Do providers invite care partners into patient interaction? • How many providers did the care partner interact with?	• International Classification of Diseases (ICD)-10 code, length of stay, discharge disposition, patient age, Patient sex, marital status, reason for admission
Process care delivery	• At what point in the stay is the observation occurring: admission; during stay; discharge • How do providers involve care partners: assessment; hands-on demonstration; verbal instruction; written instruction • Were care partners notified of upcoming patient discharge?	• Medical service (ie, provider type), patient or care partner education topic (eg, prescriptions, pain management, food and fluids, and preventing infections), patient or care partner taught (eg, patient, child, and spouse), patient or care partner education method (eg, oral instruction, demonstration, printed materials, and teach back)
Outcome patient	• Do patients and care partners seem satisfied with their care experiences?	N/A[b]
Work system technologies	• Do care partners have access to EHRs or other tools? • Did providers document care partner interactions?	N/A

[a]SEIPS: System Engineering Initiative for Patient Safety.

[b]N/A: not applicable.

Direct Observation Data Analysis

Data will be summarized as frequencies and proportions, as appropriate. Frequencies will represent the number of times our study team observed a given phenomenon, such as the use of a care partner assessment by a provider. Proportions will provide a nuanced picture of the relative frequencies of certain codes, such as how often care partner education was initiated by the provider versus the care partner themselves. We will then create a SEIPS 2.0-based process map of the current hospital workflow to include care partners using both observation and memo data. We have developed methods for using SEIPS 2.0 to create process maps that simultaneously depict workflow and the system barriers associated with each stage of the workflow [26].

EHR Data Collection

We will select EHR fields that align with SEIPS 2.0 domains (Table 1). Data will be obtained from January 2019 to August 2022 to capture care practices before and during the COVID-19 pandemic. This time frame will allow us to better understand

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the impact of any visitor restrictions on care partner inclusion practices.

EHR Data Analysis

To calculate the sample size, we conducted an a priori power analysis using G*Power 3.1 [27]. For a chi-square goodness-of-fit test with a small effect size of 0.3, an α level of .05, a power level of 0.80, and 10 degrees of freedom (the maximum for any of our variables), a sample size of 181 was determined. We anticipate identifying several thousand patients in the hospital system who meet our inclusion criteria. We will not be able to gather EHR data from the same patients we observe due to the time it can take to record, process, and submit documentation for billing purposes. We will use SAS 9.4 [28] for data management and statistical analysis of the EHR data. We will conduct descriptive analyses of means, SDs, medians, and frequencies for all project variables.

Merging the Observation and EHR Data

We will use our direct observation data to identify ways in which to stratify the EHR care partner inclusion characteristics. For example, our direct observations may indicate that clinicians tend to include care partners in hospital care in distinct ways. We may also learn from our direct observations that patients with certain admitting conditions (ie, ICD-10 code) are more likely to have their care partners included in care. Depending on how we stratify care partner inclusion characteristics, we will use bivariate analyses: *t* test or ANOVA (continuous variables) and chi-square tests (categorical variables). We will also use classification and regression tree analysis to look for patterns in care partner inclusion across competing prediction variables. Classification and regression tree produces clear classification criteria and a visual "tree" showing the hierarchical relationships between variables within subgroups of the sample, which facilitates interpretation and direct translation to practice.

Aim 2: Using Stakeholder Interviews and Risk Prioritization Methods to Identify and Prioritize Health Care System Facilitators and Barriers to the Inclusion of Care Partners of Hospitalized People Living With ADRD

Setting

Based on established relationships with UW Health, the University of Pittsburgh National Center on Family Support, and the Johns Hopkins University School of Medicine, we will recruit stakeholders from 3 geographical locations, Wisconsin, Pennsylvania, and Maryland. These locations will provide increased exposure to various health care system facilitators and barriers to the inclusion of care partners of hospitalized people living with ADRD.

Sample

Stakeholders will be purposefully selected from the following groups: (1) health care administrators and payers, (2) frontline clinicians (eg, hospital-based physicians, nurses, pharmacists, and therapists), and (3) hospitalized patients with ADRD and their care partners. These groups were selected because they will help our research team better understand dementia care in the hospital setting based on direct experiences. In each geographical location, we will recruit 5 health care administrators and payers, 5 frontline clinicians, and 5 patient and care partner dyads that meet eligibility criteria (Table 2).

Table 2. Sampling plan.

Stakeholder	Reason for inclusion	Eligibility criteria	Target, n
Health care administrators and payers	Knowledge and expertise related to the day-to-day operations of hospital, patient eligibility, enrollment, claims, and payment of health services	• Have at least 5 years professional experience in position • Speak and understand English	15
Frontline clinicians	Knowledge and expertise related to the delivery of health services	• Have at least 5 years professional experience in their position • Speak and understand English	15

Patients with ADRD[a] and their care partners	Knowledge and experience related to receiving hospital care	• Patient:
		  • Admitted to, or recently (within the last year) discharged from a hospital
		  • Diagnosed with some form of dementia
		  • Identified a care partner
		• Care partner:
		  • provide unpaid care to a relative or partner with ADRD
		  • be at least 18 years of age or older
		  • speak and understand English
			15 dyads

[a]ADRD: Alzheimer disease and related dementias

Stakeholder Interviews Data Collection

We will conduct semistructured interviews either face-to-face or over the telephone with stakeholders. The semistructured interview guide will be developed based on SEIPS 2.0 (Table 3) and will be tailored to each stakeholders' experiences and responsibilities. Interviews will last up to 60 minutes and will be audio recorded, transcribed verbatim using department desktops in a locked lab space, and analyzed in NVivo 12 [29].

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Table 3. Example System Engineering Initiative for Patient Safety (SEIPS) 2.0–guided interview questions.

SEIPS 2.0 domain	Stakeholder	Interview questions
Work system (Organization and Environment)	Health care administrators	In what ways, if any, does your organization demonstrate patient and family-centered care?
Process (Care Delivery)	Frontline clinicians	In what ways, if any, do you communicate discharge plans with care partners?
Outcome (Patient)	Patient and care partner dyad	In what ways do you feel you were prepared to carry out health care tasks once home?
Work system (Technologies)	Frontline clinicians	In what ways, if any, are care partner inclusion practices documented within the EHR[a]?
Outcomes (Organizational)	Wisconsin-based payers	In what ways, if any, are care partner inclusion practices evaluated?

[a]EHR: electronic health record.

Stakeholder Interviews Data Analysis

We will perform directed content analysis [30] guided by SEIPS 2.0. The research team will review a subset (ie, 2-3) of interview transcripts and use SEIPS 2.0 to develop high-level codes of facilitators and barriers to the systematic inclusion of care partners in hospital care. For example, under the high-level code of "tools and technology," there will be a subcode for barriers and for facilitators. We will use these codes as guides to review subsequent transcripts and revise codes as needed until the codebook is formalized. Two team members will apply the codebook to independently code 20% of the data. We will then use the coding comparison query function in NVivo 12 to measure intercoder reliability. A threshold will be set at 80% agreement based on suggested values of intercoder reliability [16]. The team members will discuss disagreements and continue to code 2-3 interviews independently until this threshold is reached. Once the threshold is met, team members will finish the remaining coding. After the qualitative coding of interviews is completed, frequencies of code usage and percentages of all coded texts will be computed to quantify the degree to which certain aspects of SEIPS 2.0 were represented.

Risk Prioritization Data Collection

We will use a modified Delphi approach [31] where the same stakeholders who participated in interviews will conduct risk prioritization ratings in 2 rounds. We will conduct the first round of the Delphi over a 1-month period. Each group of stakeholders will be sent a web-based questionnaire using the Qualtrics survey platform. They will be asked to rate each barrier and facilitator identified from the stakeholder interviews on the following three categories, each on a 5-point scale: (1) frequency of occurrence (very high frequency to very low frequency), (2) level of importance in influencing the inclusion of care partners in hospitalizations (very high importance to very low importance), and (3) likelihood that the factor is modifiable (very high to very low). We will also provide an optional free-text field for each entry so that stakeholders can provide comments about each barrier and facilitator or their rating decision. Stakeholders will also be able to enter suggestions for additional content that they think is missing and important to add. The free-text data will allow for an in-depth understanding of the rationale underlying ratings and will also serve as a member-checking process to ensure validity of the data. Following the same procedures from round 1, we will conduct round 2 of the risk prioritization. In this round, stakeholders will be provided with a reminder of what their ratings were in round 1, and will also be provided with, and asked to consider, the combined responses from all other stakeholders in round 1.

Risk Prioritization Data Analysis

We will use descriptive statistics to summarize responses. We will then assign each potential item an overall prioritization score by multiplying the individual scores from each category. Factors that received over 75% consensus among stakeholders will be considered to have met consensus in round 1. Items will be considered to have met consensus when at least 75% (34/45) of stakeholders agree within 1 point on the Likert scale, for example, over 75% of participants rate an item as likely (4) or extremely likely (5). Factors that receive less than 75% consensus will be used in the second round of ratings. A systematic review of Delphi studies indicated that 75% was the median threshold for percent agreement-based consensus across studies [32]. Factors that do not reach over 75% consensus after round 2 will not be included in the prioritization index. However, factors not reaching consensus will be presented for consensus discussion by design teams in Aim 3.

The free-text data will be uploaded to NVivo 12 for qualitative analysis. We will use an interdisciplinary team-based thematic analysis [33] to identify themes related to stakeholders' rationale for ratings. Coding will be performed by research team members independently, and themes will be developed iteratively following the 6 phases outlined by Clarke and Braun [33]. In phase 1, we will familiarize ourselves with the data from both rounds of risk prioritization. In phase 2, we will thoroughly code the data using a systematic process guided by SEIPS 2.0. Team discussions will be used to reach a consensus on codes throughout this phase [34]. We will then move into phase 3, which involves a generation of initial, or candidate, themes and an exploration of relationships between themes. This phase will produce a thematic map to display these relationships. In phase 4, we will assess our candidate themes against the coded data to evaluate how well the themes fit the coded data. If a good fit is determined, the research team will assess candidate themes against the entire data set, editing the themes as needed. This process will continue until the research team members have come to a consensus and are satisfied with the definitive themes. Phase 5 will involve generating definitions for each theme. This process will conclude with phase 6, which consists of writing up the findings of this analysis [33].

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Aim 3: Using a Co-design Process to Iteratively Develop an Adaptable Toolkit to be Used by Various Health Care Systems to Facilitate the Inclusion of Care Partners of Hospitalized People Living With ADRD

Setting and Sample

We will convene 2 co-design groups using the same recruitment settings and stakeholders from Aim 2. One group will consist of patient or care partner dyads and the other group of health care administrators, payers, and clinicians. Each design team will have approximately 5 to 7 stakeholders, which is within the standard range of stakeholders used in participatory design research [35]. The odd number of stakeholders allows for a tie-breaking perspective in the groups. The small number of stakeholders in groups (ie, rather than 10-14 in one group) reduces the potential for groupthink (ie, by having products from 1 group evaluated by the other) and ensures that all stakeholders have ample time to provide their perspectives [36].

Co-design Data Collection

Design teams will complete 5 co-design videoconference sessions occurring in parallel across 4 months, with 3 weeks between each session. The design process can be conceptualized as a funnel [6] in which we start with myriad divergent ideas and then begin to work toward convergence through the sessions. In session 1, we will present the teams with the prioritized list from our risk prioritization process completed in Aim 2. We will lead discussion, interpretation, and respectful debate among design team members to begin to generate health care system process changes to optimize the inclusion for care partners of hospitalized people living with ADRD. We will ensure progress toward solution convergence from session to session. The design teams will conduct sessions independently, but in between sessions will swap solutions and provide feedback, which we will summarize and present in subsequent sessions. Each session will last up to 90 minutes. Sessions will be audio recorded for subsequent analysis. Sessions will be held virtually to support retention using our established web-based process for participatory design, which has been a successful alternative to in-person design sessions.

Co-design Data Analysis

Analysis of design session outputs such as sketches, use of case scenarios, ratings, research team memos, and stakeholder notes will occur both within and between sessions. Within sessions, we will guide stakeholders in generating, grouping, and converging upon design solutions. Within the 3-week period between sessions, we will review the audio recording of the session and use the rapid identification of themes from audio-recordings method [37] to identify design specifications. We will combine the themes from the rapid identification of themes from audio recordings with synthesized outputs from the session (eg, sketches and ratings) to provide inputs to stakeholders at the following design session. Following the design session completion, we will continue to refine the A-SHIFT, applying input from the final design session, and performing member checking by reviewing changes with the stakeholder groups [38].

Ethics Approval

The study was approved by the Institutional Review Board (IRB) at the University of Wisconsin-Madison on March 23, 2023 (approval no. 2022-0024). All protocol modifications will be reviewed and approved by the IRB as needed. We will obtain a waiver of signed consent using a process that employs an IRB-approved information sheet.

Results

We anticipate this study to take 24 months to complete. All 3 aims will take place between September 1, 2022, and August 31, 2024. We expect the following results:

- Aim 1 expected results: observations and EHRs will provide 2 views of care partner interactions—whether care partners are included in hospital care and how inclusion is documented. Analyses are in progress and will result in the identification of optimal points in the hospital workflow for care partner inclusion that will be presented during stakeholder interviews in Aim 2.
- Aim 2 expected results: a prioritized list of potentially modifiable barriers and facilitators to including care partners in hospitalization of people living with ADRD will be presented to the Aim 3 co-design teams. This information will provide the basis for designing A-SHIFT.
- Aim 3 expected results: results will provide a converged-upon, ready for feasibility testing of A-SHIFT to guide inclusion of care partners in hospital care of people living with ADRD. We anticipate that the A-SHIFT will include strategies on when and how to identify care partners in hospital care, tools for assessing the needs of care partners and their caregiving preparedness, methods for how to train care partners to fulfill caregiving roles for people living with ADRD after hospital discharge, a health care system readiness checklist and implementation plan, and suggested measures of successful implementation.

Study results will be disseminated in peer-reviewed journals and presented at annual scientific meetings. We will also share the results of this study directly with stakeholders by developing infographics. These will be distributed through dementia caregiving networks and established partnerships.

Discussion

Despite research and policy calling for the systematic inclusion of care partners in hospitalizations to improve outcomes of persons living with dementia, no toolkit exists to guide health care systems on how to effectively identify, assess, and train care partners.

We will be using a user-centered, systems engineering approach to develop A-SHIFT that is well-suited to address real-life barriers to care partner inclusion in health systems. Our systems-engineering approach to development increases the likelihood of the successful implementation of A-SHIFT in health systems. In using SEIPS 2.0, we will acquire a comprehensive understanding of the work systems, processes, and outcomes related to care partner inclusion that will enable us to create a toolkit that addresses barriers in each of these

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areas. SEIPS is an inherently user-centered model, which places the people at the center, and as such, promotes the design of systems that optimally support the people in the system. Additionally, we will use a mixed methodology in our data collection, which will provide us with a rich understanding of current practices of care partner inclusion that quantitative and qualitative methods could not provide on their own. Most importantly, our methodology involves stakeholders from multiple disciplines, sites, and geographical areas, which will increase the likelihood of A-SHIFT being implemented across a range of health systems. Our user-centered approach, including engaging stakeholders as co-designers, has been recognized as an important approach by the World Health Organization [39], the National Institute of Standards and Technology [40-42], and the International Standards Organization [43,44]. The user-centered approach is the epitome of person-centered methodologies [45] and is critical to the design of an A-SHIFT that meets the needs of all stakeholders.

We may find that stakeholders will not wish to participate in this study, or that we cannot retain them as expected. We have infrastructure, however, for successfully recruiting and retaining stakeholders, and strong partnerships to expand recruitment strategies. For example, our team has secured funding to provide stakeholders compensation and we have access to technology support. We have also designed our approach to reduce stakeholder burden. In particular, we will use phone and videoconferencing to conduct interviews and design meetings and we will mail stakeholders remuneration. Although we have adapted our risk prioritization methods to be delivered using a Delphi approach as a COVID-19 precaution, we recognize that this approach is slower than traditional in-person focus groups or meetings. Our research team has also fostered collaborative partnerships with representatives from 3 different health care systems to increase the generalizability of A-SHIFT. Although the direct observations and EHR data from Aim 1 will only represent 1 academic medical setting, these results will serve as a basis for discussion with stakeholders from all 3 systems in Aims 2 and 3.

A-SHIFT will provide diverse health care systems guidance on how to identify, assess, and train care partners of hospitalized people living with ADRD. Our inclusion of stakeholders from health systems in different geographical locations will promote the creation of a toolkit that is more generalizable across health systems. The development and refinement of A-SHIFT are critical for the next planned R-series grant proposals, which will address Stage 1B feasibility testing followed by hybrid efficacy or effectiveness testing of A-SHIFT's effectiveness at improving care partner preparedness and reducing avoidable hospital readmissions by people living with ADRD. Care partners that are well-prepared have the potential to increase their own well-being and also help optimize health and service use outcomes for people with living ADRD after hospital discharge. Furthermore, we hope our study protocol can be used as a model for researchers to develop additional toolkits to target key areas of concern across health care systems. Our comprehensive, systems-engineering approach promotes the creation of user-centered toolkits that meet all stakeholder needs to foster sustainable change in health care system processes to ultimately improve patient and care partner outcomes.

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Data Availability

The data sets generated and analyzed during this study will be available from the corresponding author on reasonable request.

Conflicts of Interest

AS receives royalties from Wolters Kluwer, Taylor Francis Publishers, and Thieme Publishers.

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Abbreviations

ADRD: Alzheimer disease and related dementias
A-SHIFT: ADRD Systematic Hospital Inclusion Family Toolkit
EHR: electronic health record
IRB: institutional review board
SEIPS: System Engineering Initiative for Patient Safety

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Protocol

Canada's Student Mental Health Network: Protocol for a Comprehensive Program Evaluation

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Abstract

Background: Prevalence estimates for mental health–related problems, including above-average stress, psychological distress, and symptoms of mental illnesses have increased significantly among Canadian postsecondary students. As demand for downstream mental treatment has surpassed many institutions' abilities to deliver timely care, there is a need for innovative upstream supports that foster mental health promotion and mental illness prevention among this population.

Objective: Supported by an extensive network of student volunteers, Canada's Student Mental Health Network is a virtual, one-stop shop for centralized mental health education and evidence-based resources tailored to postsecondary students. This article describes a protocol for the comprehensive evaluation of the Network.

Methods: Development of the Network was developed using a participatory action research framework. Network content is created and curated by students and reviewed by subject matter experts. The proposed program evaluation will include both a formative process evaluation and a summative impact assessment to determine the feasibility, acceptability, and utility of the Network in addition to assessing change in the 3 primary outcomes of interest: mental health literacy, perceived social support, and help-seeking behavior. Participants will be recruited directly from the Network website using a "rolling" recruitment approach to allow for continuous data collection and evaluation. A combination of qualitative (ie, interviews) and quantitative (ie, surveys) methods of data collection will be used.

Results: The process of evaluation of the Network will begin in September 2022, collecting data for 1 year. In September 2023, the impact evaluation will begin using the same follow-up schedule. Data collection will then remain ongoing to facilitate the continued evaluation of the Network. Reports detailing evaluation data will be released annually.

Conclusions: The Network is a novel and innovative method of delivering universal mental health promotion to Canadian postsecondary students by providing centralized and freely accessible mental health education and resources, created by students and validated by subject matter experts. The continued creation and curation of resources for the Network will be ongoing to meet the evolving needs of the target population.

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KEYWORDS

health promotion; higher education; mental health; postsecondary; program evaluation; stress; students; university; well-being

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Introduction

Background

Prevalence estimates for above-average stress, psychological distress, and symptoms of mental illnesses have increased significantly among Canadian postsecondary students over the past several years [1]. Excessive stress has been linked to a number of negative academic (ie, decreased performance and decreased motivation) and health (ie, anxiety and depression) outcomes among students [2,3]. Indeed, data collected from Canadian postsecondary institutions through the 2019 National College Health Assessment II survey revealed large proportions of students feeling hopeless (63.6%), overwhelmed (88.2%), and anxious (68.9%) within the past 12 months [4].

Existing research has highlighted the variety of stressors students experience within the postsecondary setting [5,6]. The COVID-19 pandemic produced additional, novel stressors, with national data suggesting postsecondary aged Canadians were the most likely to report increased symptoms of anxiety and depression throughout the pandemic [7]. Over the past decade, demand for downstream mental health services (ie, counseling and pharmacotherapy) has surpassed institutions' capacities to deliver timely care [8]. In the wake of the pandemic and its mental health-related fallout, there is reason to believe that this demand will only continue to increase [9]. Placing additional focus on upstream mental health supports (ie, those that aim to intervene before the development of psychological distress) may contribute toward alleviating the bottleneck currently observed at the downstream level. Upstream supports can help to bolster students' resilience and well-being by providing them with the skills and resources required to monitor and respond to the changes in their mental health, as well as providing education around appropriately aligning level of help seeking with level of need.

While some form of mental health promotion is offered by many institutions, a national review of mental health and well-being services on Canadian postsecondary campuses found that only 70% of respondents felt students were well-informed about available resources on campus, and about mental health issues in general [10]. Many respondents (84%) also indicated that they felt there was room for improvement in the mental health promotion supports currently offered on their campus [10]. One of these barriers is the cost associated with accessing some forms of mental health education. For example, many institutions now offer for-credit mental health courses, but students must be formally registered at a substantial cost. Training courses such as Mental Health First Aid, SafeTALK, and others sometimes also require a registration fee. The second barrier lies in the reality that some institutions have more available budget than others to put toward campus mental health supports. Larger schools tend to have more funding and can therefore offer more robust mental health support to students compared to smaller schools. At most institutions, the majority of the mental health budget is skewed toward downstream services, typically leaving upstream supports to operate on more limited resources. Finally, accessibility and logistics barriers are another consideration. Many mental health promotion supports provided by institutions take the form of on-campus workshops and events. This poses a barrier for some groups of students who may be left out (ie, web-based students, students studying abroad, and students who commute to campus), as well as students with multiple competing priorities to manage (ie, coursework, extracurricular activities, sports, and employed work). These observed gaps demonstrate a need for cost free, universally accessible mental health promotion.

Introducing Canada's Student Mental Health Network

Canada's Student Mental Health Network (hereafter, "the Network") is a virtual, one-stop shop for mental health education and evidence-based resources, tailored specifically to postsecondary students. Development of the Network's website began in 2020, using a participatory research design wherein members of the target population work alongside researchers as contributors, helping to provide a deeper understanding of their thoughts, needs, and experiences [11]. In line with this approach, all content on the Network is created and curated by students and reviewed for validity by subject matter experts (ie, researchers and health care practitioners) using a collaborative approach to the cocreation and translation of knowledge. Based on the extant literature consistently highlighting mental health education, social support, and help seeking as major predictors of positive mental health outcomes for students, the Network targets these 3 areas as primary objectives: (1) to improve mental health literacy; (2) to encourage the development of strong social support networks; and (3) to improve awareness of available resources and encourage appropriate help seeking. The content on the website is aligned with these objectives, centered around 3 pillars: learn, connect, and access.

Learn

Mental health literacy (MHL) refers to "understanding how to obtain and maintain positive mental health; understanding mental illnesses and their treatments; decreasing stigma related to mental illnesses; and enhancing help-seeking efficacy (knowing when and where to seek help and developing competencies designed to improve one's mental health care and self-management capabilities)" [12]. MHL has been identified as a foundational component in mental health promotion and mental illness prevention [12]. Improved mental health education not only enables an individual to recognize changes in their mental health and well-being, but also empowers them to respond appropriately [13,14]. Given that MHL is context specific, it is important for resources to be tailored appropriately to the target population (ie, students) and the postsecondary setting [14]. The *learn* section of the Network facilitates access to free and evidence-based mental health education. Education is provided in an interactive, accessible, and aesthetically appealing format. Some features in this section include: a series of web-based mental health education modules, created by Network volunteers and validated by subject matter experts; a curated library of informational and educational TedTalks; a library of free, web-based mental health courses; and a library of detailed toolkits, providing guidance on topics including financial literacy, relationship management, and an introduction to cognitive-behavioral therapy techniques.

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Connect

The development of strong social support networks is a key predictor of positive mental health outcomes and overall well-being across the course of life, but particularly during adolescence and early adulthood [15,16]. The majority of Canada's postsecondary students are "emerging adults," defined as ages between 18 and 25 years [16]. Students navigate a number of major transitions during this time, including the transition to a postsecondary setting, integration into a new social environment, and increased autonomy and responsibility. A lack of social support when faced with these adjustments can lead to social isolation, loneliness, and homesickness [17]. In fact, many students struggle to form new, meaningful friendships at university or college and can find it difficult to maintain pre-existing relationships, such as those with their parents or childhood friends [18,19]. Together, the breakdown of previous social ties and difficulty finding a new social support network at school can result in mental health deterioration [20]. Social support has also been found to be a protective factor against student burnout [21]. Burnout is common in students in academic settings and is linked to psychological distress and perceived stress [22,23].

The *connect* section of the Network encourages students to develop healthy social support networks by providing access to resources designed to encourage peer connection. Some features in this section include: a clubs portal, which provides single-click access to student club listings for every university and college across Canada; the Student Mental Health Network podcast, featuring interviews with subject matter experts and students on a variety of topics relevant to student mental health, including sharing lived experiences; and a library of web-based forums designed to foster peer connection.

Access

Commonly perceived barriers to help seeking for mental health-related problems among students include a preference for self-management [24], a lack of time [24,25], perceived stigma [26-28], and a lack of awareness around availability of resources [27]. Structural barriers also exist; students are sometimes surprised to learn of the mental health–related services and supports available to them through their institution and frequently report not knowing where to physically access them [29]. This is particularly evident on sprawling campuses, where health supports are split across several different buildings rather than in a centralized location [29]. Additionally, some students are predisposed to structural barriers as a result of socioeconomic status, race or ethnicity, or gender [30]. Increasing awareness of available services and supports both on and off campus, as well as educating students about aligning their level of mental health need with the level of mental health support sought, is essential to supporting the mental health and well-being of the postsecondary population [30].

Rather than provide services, the goal of the *access* pillar of the Network is to improve students' awareness of existing resources and services available to them, as well as to improve education regarding appropriate levels of help seeking. These resources include: (1) a mental health resource bank, which includes one-click access to Student Wellness Services websites for every university and college across Canada, as well as a library of community mental health resources (both in person and web-based) at the provincial and national levels; (2) a library of evidence-based and physician recommended mental health mobile apps; (3) an interactive mental health services map detailing locations of mental health support on Canadian campuses across the country; and (4) a bank of stress management resources tailored specifically to postsecondary students based on the stressors measured by the Postsecondary Student Stressors Index [31].

Methods

Project Overview

The overall goal of the Network is to reduce barriers and facilitate universal access to upstream mental health supports for postsecondary students across Canada. This study describes a protocol for a comprehensive evaluation of the Network, including a formative process evaluation and a summative impact assessment. The key objectives of this evaluation are to determine the feasibility, acceptability, and utility of the Network in addition to assessing change in the 3 primary outcomes of interest aligning with website content: mental health education, perceived social support, and help-seeking behavior.

Study Design

The proposed program evaluation will include a formative process evaluation and a summative impact assessment. The logic model we have developed for the purposes of evaluating the Network can be found in Multimedia Appendix 1. Process evaluations are intended to assess 2 key components of program function: (1) whether the program is reaching the intended targeted population (*acceptability*) and (2) whether its delivery and function is consistent with program design specifications (*feasibility*) [32]. Impact assessments are intended to assess the observed change in the outcomes of interest and estimate the degree to which that change may have occurred in the absence of the intervention (*utility*) [33]. Alignment of evaluation design with initiative life span is imperative. For example, conducting an impact assessment when a program is too "young" for observable change to have occurred in outcomes of interest may lead to the incorrect conclusion that the program or initiative is not effective. Given that the Network is a newly developed initiative, we will begin with a formative process evaluation that focuses on the user experience in terms of feasibility and acceptability. A summative impact assessment will be conducted after the Network has been in operation for a minimum of 1 year.

Increasingly, mixed methods approaches to studying complex public health problems have been recommended, as the use of qualitative and quantitative methodologies in tandem provides a more holistic and thorough understanding than either approach individually [32]. A concurrent mixed methods study design will be used to facilitate a comprehensive evaluation of the Network, where both quantitative and qualitative data will be used to facilitate both depth and breadth of understanding.

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Measures

Process Evaluation

Data for the process evaluation phase of this project will be drawn from 2 sources: (1) Google Analytics and (2) cognitive interviews (Table 1). To collect information regarding the reach of the Network in terms of website engagement and user experience, we will analyze website metrics collected through Google Analytics. These metrics include total number of users, average number of users (weekly, monthly, and annually), average engagement time (time spent on each component of the website), user "stickiness" (average length of visits), page views, event counts (clicks and file downloads), and user region.

We will use individual cognitive interviews employing a "think aloud" technique [34] to further evaluate the user experience and highlight gaps in content. Participants will be asked to screen share over Zoom as they navigate through the Network website and talk us through their navigation, identifying content-related issues or preferences as well as any navigational challenges. The interviews will include questions related to sociodemographic characteristics, important website attributes, and perceived acceptability and feasibility (Table 1). Collecting this additional in-depth qualitative data on website attributes and navigation will augment the quantitative data collected through Google Analytics and allow us to identify gaps and areas for improvement to ensure the best possible user experience.

Table 1. Process evaluation measures.

Mode of data collection and component	Measures/item	Qualitative/quantitative
Cognitive interviews		
Sociodemographic characteristics	• Age • Gender • Ethnicity • Year of study • Level of study • Area of study • International student (Y/N)[a] • First generation student (Y/N) • Identify as a visible minority (Y/N) • Identify as a person with a disability (Y/N) • Self-reported SES[b] • Grade Point Average • Current self-rated mental health • Mental health diagnoses (lifetime) • Impact of COVID-19 on mental health • Previous access of mental health supports and type	Quantitative/qualitative
Website attributes	• Appearance • Content • Interactivity • Inclusivity and representation • Accessibility	Qualitative
Google Analytics		
Website engagement and user experience	• Total number of users • Average number of users (weekly, monthly, and annually) • Average engagement time • Page views • User stickiness (average length of visits) • Event counts (visits, clicks, scrolls, and file downloads) • User location (country, region, and city)	Quantitative

[a]Y/N: yes/no.

[b]SES: socioeconomic status.

Impact Assessment Evaluation

Data for the impact assessment evaluation of the Network will be drawn from 2 sources: (1) web-based surveys and (2) interviews (individual and group) (Table 2).

The impact assessment survey will include questions related to sociodemographic information (eg, age, gender, ethnicity, year of study, level of study, area of study, and estimated grade point average) and important website attributes (eg, appearance, content, interactivity, inclusivity or representation, and accessibility). However, the survey will also include several validated instruments designed to evaluate change in each of the outcomes of interest (eg, scales evaluating mental health literacy, perceived social support, and help-seeking behaviors). The majority of the survey will consist of closed-ended, quantitative questions, with a few open-ended, qualitative response options. More in-depth descriptions of each of the

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selected measures and their associated psychometric properties can be found in Multimedia Appendix 2.

Web-based interviews will be held in both individual and focus group formats, depending on recruitment. A semistructured interview guide will be used to assess students' perspectives on changes in the outcomes of interest as well individual understandings of mechanisms that may have contributed to the change (eg, improved mental health literacy due to completion of Network modules). Interviews will be used to evaluate students' experiences engaging with the website, as well as their perceptions of potential mechanisms through which they observed change in their mental health education, connections with members of their social support network, and help-seeking attitudes and behaviors.

Table 2. Impact assessment evaluation measures.

Mode of data collection and component	Measure/item	Qualitative/quantitative
Web-based survey		
Sociodemographic characteristics	• Same as process evaluation	Quantitative/qualitative
Mental health	• Perceived stress scale, 4-item [35] • Kessler Psychological Distress Scale, 6-item [36] • Brief-postsecondary student stressors index [6]	Quantitative/qualitative
Mental health literacy	• Mental health literacy scale, adapted [37] • Social distance subscale of OMS-WA[a] [38]	Quantitative/qualitative
Social support and resilience	• Multidimensional scale of perceived social support [39] • Connor-Davidson Resilience Scale (10-item) [40]	Quantitative/qualitative
Help seeking	• Barriers to care evaluation, revised [41] • Self-stigma of seeking help scale [42] • General help seeking questionnaire [43]	Quantitative/qualitative
Interviews		
User experience and impact of website engagement	• User experience • Website navigation • Perceived impact	Qualitative

[a]OMS-WA: Opening Minds Scale–Workplace Attitudes.

Procedure

Participants and Recruitment Strategy

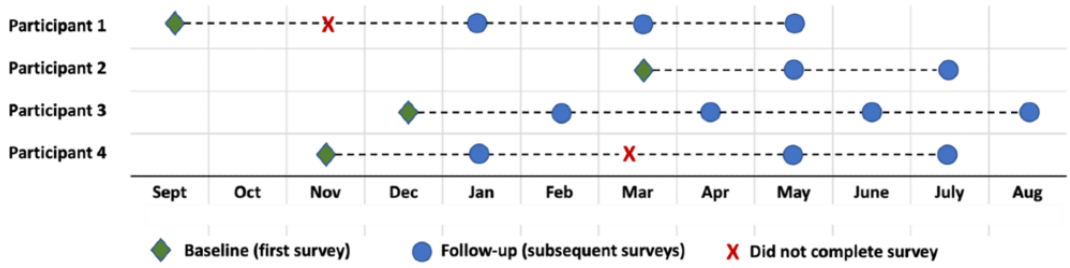
Canadian postsecondary students who have engaged with the Network are the target population for the proposed evaluation. Students attending any type of postsecondary institution (ie, college, university, etc) will be eligible to participate. Participants will be recruited through 3 possible avenues: (1) directly from the Network website through a posted call for participants; (2) through the Network's social media channels; or (3) through a snowball sampling method. Network contributors will communicate the opportunity to become involved in the evaluation study through word-of-mouth as the first point of contact. To avoid bias, contributors themselves will not be eligible to complete the impact assessment survey. Participants who complete the survey will have the opportunity to refer 5 other students to complete it in exchange for 1 entry into our raffle draw per completed survey submitted by a referral.

The process evaluation, recruitment, and data collection period will take place between May 2022 and May 2023, allowing for a formative assessment of the first year of operation. A "rolling" recruitment approach (Figure 1) will be used for the impact assessment, allowing participants to complete the survey at any time within the data collection period of September 2023 to September 2024. This approach will allow for continued data collection as new users engage with the Network over time. Rolling recruitment approaches have been shown to reduce recruitment delays and improve statistical power by minimizing the effects of loss to follow-up [44]. Students may participate in process evaluation, impact evaluation, or both.

The appropriate sample size for the process evaluation interviews will be determined by the length of time it takes to reach saturation. For the impact assessment survey, we will aim to obtain a total sample size of 10,000 respondents. Statistics Canada data for the latest academic year (2020-2021) indicates that a total of 2.2 million students are enrolled in a postsecondary program [44]. Our goal will be to obtain responses from students across Canada, with relative contributions by region (Western ~30%, Atlantic ~5%, and Central Canada ~65%) in order to obtain a sample that is generalizable to the broader Canadian postsecondary population. We determined the relative contributions by region using Statistics Canada's Postsecondary Student Education Dashboard [35].

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Figure 1. Visual depiction of rolling recruitment strategy.



Data Collection and Processing

Google Analytics data will be continually collected from the website over the lifetime of the Network for program monitoring purposes. Cognitive interviews will be conducted, recorded, and transcribed through Zoom [36]. Participants will be compensated for their participation in a cognitive interview with a US $14.97 electronic gift card to Amazon.

Web-based surveys will be administered through Qualtrics survey software [37]. A letter of information (LOI) for the evaluation will appear as the first page of the survey, communicating the purpose of the evaluation, survey content, incentives to participate, process for withdrawing submitted responses, data deidentification and confidentiality, and consent for use of data in future analyses. After reviewing the LOI, participants will indicate their informed consent before being granted access to the survey questions. The only identifying information on the survey will be students' institutional email addresses used to link their responses across surveys. Emails will be permanently deleted and replaced with numeric participant numbers at the end of the data collection period (September 2024), effectively deidentifying data. The impact assessment survey will consist of approximately 30 close-ended questions and is expected to take around 30 minutes to complete. Following the submission of their first survey, participants will be invited to submit a brief follow-up every 2 months, enabling us to track their responses over time. Participants who "miss" a follow-up will continue to be invited to complete a survey every 2 months throughout the data collection period, unless they choose to opt out of receiving additional surveys. Data will be linked between survey iterations wherever possible.

Participants will be compensated for their submission of each survey with an entry into a prize draw for a chance to win 1 of several electronic gift cards. They will also be provided with an additional entry into the raffle for every individual they refer who completes the survey, per the snowball sampling strategy outlined above. Prize draws will be completed at the end of each academic term.

At the end of the survey, participants will be asked whether they would be interested in participating in an interview to further discuss their engagement with the Network. Participants who express interest will be contacted by email to indicate their preference for either a one-on-one interview or a focus group interview, depending on recruitment numbers. We will attempt to place students from the same region in focus groups together to encourage participants to draw on common experiences and promote idea sharing. Participants will be provided with a letter of information and asked to verbally consent to keeping discussions confidential as well as to interviews being recorded and transcribed. Individual interviews will be 1-hour in length, while the length of focus group interviews will depend on the number of participants included. All interviews will be facilitated over Zoom to accommodate collaboration with participants across Canada. Participants will be compensated for their participation in interviews with a US $20 electronic gift card to either Amazon or Starbucks.

Risk Mitigation

The risk associated with the proposed evaluation is low. However, to mitigate any feelings of elevated stress or emotional distress participants may feel after completing a survey, an interview, or both, we will refer participants to the access section of the Network which includes contact information for campus Student Wellness Services across the country as well as other evidence-based resources.

Analysis

Process Evaluation

Quantitative data and website metrics collected through Google Analytics will be analyzed through the use of descriptive statistics (eg, frequencies, measures of central tendency, and dispersion) using R statistical software [38]. Cognitive interview data will be analyzed through the use of the problem codes displayed in Table 3, which were adapted from those proposed for use in the evaluation of new survey tools [39,40]. Following each interview, corrective action will be taken to assess the identified problems, ensuring that each interview provides maximum value to the improvement of the Network. In the event that a new issue arises that is not captured by existing problem codes, a new code will be added to the list for use in subsequent interviews. After problem codes have been applied, interview transcripts will also be coded using a thematic analysis framework [41,42]. A total of 2 research assistants will independently review interview data and generate initial codes, subsequently meeting to share interpretations and develop a codebook. A third researcher will be available to break ties where disagreements arise. Research assistants will then return to the data to generate initial themes and categories.

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Table 3. Cognitive interviewing problem codes.

Problem code	Description	Corrective action
1. Clarity	Participant was confused by website content	Revise content
2. Relevance	Respondent felt that website content was not relevant to postsecondary student mental health and well-being	Revise content/remove content
3. Redundancy	Respondent felt that website content was repetitive or redundant, or could be combined with another content piece	Revise content/remove content
4. Bias	Respondent felt the presentation of website content was biased or leading in some way	Revise content/remove content
5. Missing	Respondent felt there was content missing from the website	Add content
6. Navigation	Respondent felt website content was difficult to navigate or locate	Optimize navigation/revise content organization
7. Accessibility	Respondent felt website content was not accessible	Optimize accessibility
8. Representation	Respondent felt website content did not represent all equity-deserving group	Optimize representation/revise content

Impact Assessment

Both descriptive (eg, frequencies, measures of central tendency, and dispersion) and inferential statistics will be calculated for quantitative data collected through the impact assessment survey using R statistical software. We will explore (1) relationships between sociodemographic variables and outcomes of interest (ie, mental health literacy, perceived social support, and help seeking), (2) the degree of change in outcomes of interest over time, and (3) the relationship between degree of engagement with the Network and degree of change observed in outcomes of interest. Trend analyses examining changes in stress, mental health, and the primary outcomes of interest over time will be conducted once enough data has been collected to facilitate these analyses.

Transcripts derived from individual and focus group interviews will be coded in NVivo [43] using a thematic analysis framework [42] using the approach described above. Qualitative interview data will be triangulated with participants' quantitative survey data, with qualitative data used to provide more context and facilitate a more in-depth understanding of the user experience and the mechanisms of change in outcomes of interest.

Ethical Considerations

The Tri-Council Policy Statement TCPS2 regarding ethical conduct for research involving humans states that Research Ethics Board (REB) approval is exempted in cases of program evaluation activities normally administered in the ordinary course of operation (Article 2.5) [45]. Moving forward, should the research team choose to conduct additional secondary data analyses to answer emergent research questions, REB approval will be sought. Despite the program evaluation being exempt from REB approval, participants will still be provided with a LOI to obtain their informed consent to participate through survey completion.

Results

Phase 1 of this project entailed the development of the Network website, including the curation and creation of relevant resources for the web-based space. Moving forward, content developed for the Network will continue to be informed by the evolving needs of our target population. Phase 2 entails the formative process evaluation, the data collection period for which is from May 2022 to May 2023. Data analysis and the dissemination of a freely available web-based report will take place in summer 2023. For the final phase of the project, the summative impact assessment, data collection will take place between September 2023 and September 2024. Following this period, the results of the evaluation will be made publicly available through the Network, in addition to being published and presented at academic conferences.

Discussion

The anticipated main findings of the proposed evaluation are that the Student Mental Health Network will fill existing gaps in the mental health promotion supports currently provided at postsecondary institutions across Canada. In doing so, we hypothesize that engagement with the Network will result in improvements in mental health education, the ability to develop strong social support Networks, and awareness of available help-seeking resources. Further, improving students' access to effective upstream mental health promotion supports may contribute toward alleviating the long wait times and general overwhelm that downstream mental health services currently face by increasing students' awareness of the spectrum of available services from low- to high-intensity options and helping students access services that align with their level of mental health need.

The accessibility of the Network is vital to its utility and is an important strength of the project; it is available to all postsecondary students on the internet at no cost. The "for-students, by-students," participatory approach to development ensures that content is meaningful and tailored to the target audience while maintaining relevance and timeliness. Given the nation-wide accessibility of the Network and recruitment for the participatory research design, we hope to obtain a wide sample variation spanning postsecondary institutions across the country. This may allow for the identification of inequities in the outcomes of interest between

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regions. Further, relationships between sociodemographic variables and these outcomes of interest will be investigated, and findings may be used to tailor the development of future website content to combat identified inequities. Lastly, although the Network takes an upstream health promotion-focused lens, it also serves to connect a generation of students with an interest in mental health and well-being. Through the provision of information and facilitation of social connection, the Network may empower collective action to advocate for institutional, political, and service-level change in current approaches to postsecondary mental health—"for-students, by-students." The Network is a first-of-its-kind initiative that aims to fill the urgent, evidence-supported gaps in student mental health through an innovative, collaborative design.

Importantly, the overarching goal of the Network is to provide opportunities for knowledge translation and exchange that will support postsecondary students' mental health and well-being. To that end, a technical report detailing evaluation results as well as a summary of Network resources will be made publicly available on an annual basis, with reports released in August. Network users will be invited to sign up for a mailing list, through which they will receive a copy of each report as it becomes available. We will also seek to share our annual reports through organizational connections such as the Best Practices Network [46] and the Center for Innovation in Campus Mental Health [47]. Transparency in the communication of the results of our evaluation of the Network will contribute toward a positive community impact by allowing institutions to examine the efficacy of the Network as a universal mental health promotion initiative. Results may also inform improvements to campus-specific mental health promotion and mental illness prevention resources and programming.

The novelty of the Network is both a strength and a limitation, as there is currently no set process for developing or evaluating this form of content. It is challenging to predict what uptake of the site will look like, but website usage statistics and social media interactions have demonstrated that the Network is receiving increasing attention from students since it was made public in May 2022. In terms of the analysis, it is not possible for residual confounding to be eliminated and observed changes in outcomes will not be attributable to the Network alone. There will also inevitably be some loss to follow-up, although a rolling recruitment strategy and raffle entry with each completion of the survey will be used to limit the effect on study power. Content on the Network is in English, and thus may be less accessible to French-dominant parts of Canada, international students, immigrants, and other groups who do not speak English as their first language. Further, not all students have equitable access to technology and social media or the time to navigate the Network and participate in voluntary surveys, which may result in some degree of selection bias.

Conclusion

Strategies to address postsecondary mental health have emerged at the national, provincial, and institutional levels [10]. Over the past decade, many postsecondary institutions have attempted to improve students' mental health by offering both upstream and downstream mental health supports, though typically the majority of resources are placed downstream [5,10]. Bolstering upstream supports like mental health promotion may help alleviate the current bottleneck observed at the downstream service level. Many students default to seeking help from high-intensity downstream services (ie, counseling and pharmacotherapy) when their level of mental health need does not necessarily align with this level of help seeking (ie, those who have not yet become symptomatic or reached a clinical threshold). There is a need to increase both the provision and awareness of lower-intensity upstream supports available on campuses to provide options for students experiencing a lower level of mental health need. This will in turn alleviate the pressure on downstream campus mental health services and ensure more timely downstream care for students who require it [29,30].

The Student Mental Health Network is a first-of-its kind web-based one-stop shop for mental health education and evidence-based resources, targeted specifically toward postsecondary students and uniquely developed using a participatory "for-students, by-students" approach. The Network will fill gaps in existing upstream mental health promotion supports provided by postsecondary institutions across the country, including eliminating fees and facilitating universally accessible mental health promotion for postsecondary students across Canada. The evaluation described here will allow us to assess the feasibility, acceptability, and utility of the Network, in addition to its effectiveness in improving the 3 primary outcomes of interest—mental health education, perceived social support, and help-seeking behavior—which are each proven predictors of positive mental health outcomes among students. This initiative has the potential to improve the mental health and well-being of postsecondary students across the country by providing access to the tools and resources required to build resiliency and respond to changes in one's mental health.

Acknowledgments

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Data Availability

Evaluation data will be made publicly available in a repository following the data collection period.

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Conflicts of Interest

All authors have a nonfinancial competing interest as founding members of the Student Mental Health Network.

Multimedia Appendix 1
Logic model.
[DOCX File , 193 KB - resprot_v12i1e41521_app1.docx]

Multimedia Appendix 2
Included measures.
[DOCX File , 38 KB - resprot_v12i1e41521_app2.docx]

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Abbreviations

LOI: letter of information
MHL: mental health literacy

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OMS-WA: Opening Minds Scale – Working Attitudes
REB: Research Ethics Board
SES: socioeconomic status
TCPS2: Tri-Council Policy Statement 2

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Protocol

Culturally Adapting a Digital Intervention to Reduce Suicidal Ideation for Syrian Asylum Seekers and Refugees in the United Kingdom: Protocol for a Qualitative Study

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Abstract

Background: The conflict in Syria has produced the largest forced displacement crisis since the Second World War. As a result, Syrians have experienced various stressors across the migratory process, putting them at an increased risk of developing mental health issues, including, crucially, suicidal ideation (SI). Despite their high rates of SI across Europe, there remain various barriers to accessing treatment. One way to increase access is the use of culturally adapted digital interventions, which have already shown potential for other minority populations. To culturally adapt the intervention, further research is needed to better understand Syrian asylum seekers' and refugees' cultural conceptualizations, coping strategies, and help-seeking behavior for SI. To do so, this study will use a unique cultural adaptation framework to intervene at points of lived experience with the migratory process where Syrian culture and signs of psychopathology converge. Likewise, co-design events will be used to adapt points of experience with the intervention where Syrian culture and the intervention conflict. As the first cultural adaption of a digital SI intervention for Syrian asylum seekers and refugees, this study will hopefully encourage further development of culturally sensitive interventions for the largest refugee population in the United Kingdom and the world.

Objective: The objective of the study is to increase access to mental health treatment for Syrian asylum seekers and refugees in the United Kingdom by culturally adapting a digital intervention to reduce SI.

Methods: The study will use experience-based co-design, an action research method, to culturally adapt a digital intervention to reduce SI for Syrian asylum seekers and refugees in the United Kingdom. This will involve conducting 20-30 interviews to understand their lived experiences with the migratory process, cultural conceptualizations of mental health and SI, coping strategies, mental health help-seeking behavior, and perceptions of digital mental health interventions. In addition, 3 co-design events with 6 participants in each will be held to collaboratively adapt the intervention. Touchpoints and themes extracted from each phase will be prioritized by a community panel before adapting the intervention.

Results: The study began in November 2022 and will continue until the last co-design event in August 2023. The results of the study will then be published by December 2023.

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Conclusions: Access to treatment for some of the most severe mental health issues is still limited for Syrian asylum seekers and refugees in the United Kingdom. Cultural adaptations of digital interventions developed for general populations have the potential to increase access to treatment for this population. Specifically, adapting the intervention for Syrian asylum seekers' and refugees' experiences with SI in relation to their lived experience with the migratory process may enable greater recruitment and adherence for users of various cultural and ethnic subgroups and levels of SI.

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KEYWORDS

cultural adaptation; digital mental health; suicidal ideation; refugee mental health; Syrian refugee; experience-based co-design; mental health; suicide; suicidal; refugee; immigrant; ethnic minority; asylum; user experience; cultural; Syria; Syrian; refugees

Introduction

Background

Since 2011, the civil war in Syria has resulted in the loss of over half a million lives and the largest forced displacement crisis since the Second World War [1]. By recent estimates, this includes 6.7 million displaced within Syria and 6.8 million refugees living abroad [2]. Of those displaced, over 1 million Syrians have reached Europe. As asylum seekers and refugees, they are likely to experience high rates of mental health issues, including major depressive disorder, posttraumatic stress disorder, and suicidality [3]. It is therefore important to improve the understanding and care of mental health for Syrian asylum seekers and refugees arriving in the United Kingdom.

Suicidal Ideation

One of the most concerning mental health issues for asylum seekers and refugees across Europe is suicidal ideation (SI), with research showing high rates in Sweden, 33.9% [4] and 48% [5]; Switzerland, 42.1% [6] and >30% [7]; and the United Kingdom, 40.9% [8]. Asylum seekers' and refugees' elevated rates of SI may be explained by their experiences of the migratory process [9]. While in their countries, they are often exposed to bombings, torture, and bereavement [1,3,10]. The journey to their first country of asylum often involves encountering human traffickers [11], unsafe modes of transport including inflatable boats and closed containers [12], and harsh living conditions in refugee camps [13]. Upon arriving in the first country of asylum, asylum seekers may face punitive immigration control policies [12] or a prolonged asylum application process [14]. After receiving refugee status, they may continue to experience stressors associated with a loss of social networks and environmental mastery [3,15,16], with acculturation, with discrimination, and with mental health services based on dominant models of illness in Western developed countries [17]. Thus, in order to develop acceptable and effective treatments, more research is needed to understand the specific determinants of SI for asylum seekers and refugees, and in particular Syrians, the largest refugee population globally and in the United Kingdom.

Despite asylum seekers' and refugees' elevated risks for SI, they still underuse mental health services [18-21]. Some of the barriers to accessing treatment include a lack of knowledge about mental health services, a lack of culturally competent treatment, fears about confidentiality, limited proficiency in English, and logistical issues such as transport difficulties and immigration status [21]. Again, further research is needed to understand the specific barriers and facilitators of mental health help-seeking among Syrian asylum seekers and refugees in the United Kingdom.

Cultural Adaptation

As a complex problem, reducing SI among asylum seekers and refugees in the United Kingdom will inevitably require complex structural interventions. However, reducing SI can start with the short-term individual adoption of simple clinical interventions [22]. Specifically, treatment for SI among Syrian asylum seekers and refugees in the United Kingdom may be improved with culturally adapted digital mental health interventions [23,24], which already seem promising for ethnic minorities [25], refugees in general [26,27], and Syrian refugees specifically [28].

Cultural adaptation involves "the systematic modification of an evidence-based treatment...or intervention...protocol to consider language, culture, and context in such a way that it is compatible with the client's cultural patterns, meanings, and values" [29]. Based on the universality of emotional expression, Bernal and colleagues' [29] framework of cultural adaptation asserts that while mental health beliefs and help-seeking behavior differ across cultures, the distinct signs and symptoms of psychopathology are universal. They therefore hold that cultural adaptations should attempt to maintain the integrity of the original intervention as much as possible. Conversely, Horrell [30] asserts that rather than adapting existing interventions, entirely new interventions should be developed for different cultural groups. Although her framework is more situated, it still does not acknowledge the dynamic nature of culture within cultural groups. These contrasting frameworks can perhaps be integrated by identifying the signs of psychopathology through shared experiences that give rise to core affect, including hedonic valence and physical arousal, and conceptual knowledge [31]. Thus, an embodied and experience-based approach to emotions will allow one to use changes in experience [32] to predict a person's core affect and core beliefs [33]. Importantly, where cognitive behavioral therapy (CBT) commonly involves challenging distorted core beliefs through cognitive reconstruction, in some circumstances, mental health issues may arise as a result of experiential challenges to a person's core beliefs, such as the inherent value of one's life and safety. In which case, challenges to the core belief could result in identity crisis [33] and suicidal behavior [34]. Thus, the cultural

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adaptation process can be simplified by focusing on points of lived experience with the migratory process at which signs of psychopathology such as SI and Syrian culture coincide [35]. In addition, due to Syrian education policies, Syrian ethnic and linguistic groups are only able to read and write in Modern Standard Arabic [35]. Therefore, based on a lived experience paradigm, the intervention will be adapted for Modern Standard Arabic but will identify and adapt marked language use. A possible research approach to simplify the cultural adaptation process is experience-based co-design (EBCD) [36]. Specifically, this will entail identifying crucial moments, known as touchpoints, that make a difference in Syrian asylum seeker and refugee experiences with the migratory process such as their experiences of SI in response to torture or the asylum process. After culturally adapting the intervention using the themes and touchpoints identified during interviews, Syrian asylum seekers and refugees will participate in co-design events to collectively identify and adapt touchpoints of the intervention at which Syrian culture and the intervention's core mechanisms of change conflict.

Digital Intervention

This study will build on Eylem and colleagues' [24] cultural adaptation of the Leven onder Controle (literally "Living under Control") intervention, a guided 6-week CBT-based digital intervention to reduce SI developed by van Spijker and colleagues [37]. The intervention includes 6 modules: thinking about suicide, dealing with thoughts and feelings, thinking about the future, thinking about the self, thinking about others, and repetition and relapse. Randomized controlled trials of the intervention have found it to be effective in reducing SI compared to treatment as usual—an information website—for general Dutch (d=0.2) [38] and Belgian populations (d=0.34) [39], but not for Australian populations [40].

Based on Bernal and colleagues' [29] cultural adaptation framework, Eylem and colleagues [24] adapted the intervention for Turkish immigrants in the United Kingdom and the Netherlands by including cultural metaphors, treatment concepts, and goals, as well as the context and methods of the intervention. Although largely successful in culturally adapting the intervention, Eylem and colleagues [24] were unable to recruit enough participants for a full randomized controlled trial. They therefore suggested a need for further optimization of the recruitment process and intervention including culturally appropriate strategies for recruitment, identifying the determinants of SI, and a diversity of case studies both in terms of culture and SI severity.

Aims

This research aims to improve the understanding and treatment of SI among Syrian asylum seekers and refugees arriving in the United Kingdom. As the research has shown varying rates of SI among asylum seekers and refugees [4-8], lived experience data will help to identify the determinants of SI across the migratory process and specifically for Syrian asylum seekers and refugees in the United Kingdom. Moreover, EBCD will help simplify the cultural adaptation process and increase access to treatment for SI for a greater number of Syrian cultural, ethnic, and linguistic subgroups.

Objectives

The first phase of the study will involve one-to-one semistructured interviews to (1) identify touchpoints across the 3 stages of migration (pre-, peri-, and postmigration); (2) explore how Syrian refugees conceptualize, cope with, and seek help for mental health and SI; (3) identify cultural, linguistic, and structural barriers and enablers for seeking help for mental health and SI; and (4) understand Syrian refugee perceptions of digital mental health interventions. The second phase will include community panel discussions and co-design events to (5) prioritize touchpoints and themes extracted from interview data with a community panel to adapt the intervention; (6) conduct co-design events to identify touchpoints to culturally adapt the intervention; and (7) prioritize touchpoints and themes from the co-design events with the community panel to adapt the intervention.

Methods

Study Design

In this study, an accelerated version of EBCD will guide the cultural adaptation process of a digital intervention to reduce SI for Syrian asylum seekers and refugees in the United Kingdom. EBCD is an action research method for collaboratively improving health care services and interventions [36]. Although traditionally used to improve existing services, EBCD has more recently been used to incorporate users' lived experiences of mental health problems into digital interventions [41]. For example, Lewis and colleagues [41] used EBCD to develop a mental health mobile app for health care workers affected by COVID-19. They conducted photo interviews with up to 30 health care workers to understand their mental health needs and lived experiences. The photos were used to draw out touchpoints related to health care workers' experiences during the pandemic and the effects on their mental health. Touchpoints were then further explored during co-design workshops to develop content for the app. Similarly, this study will involve semistructured interviews to gather Syrian asylum seeker and refugee lived experiences with the migratory process. Given the traumatic nature of some asylum seeker and refugee experiences, the 3 phases of migration, pre-, peri-, and postmigration, will be used to structure interviews and draw touchpoints instead of using photos. The interviews will also explore their cultural conceptualizations, coping strategies, and help-seeking behavior for mental health and SI, as well as their perceptions of digital mental health interventions. The study will be accelerated by focusing data collection on specific stakeholders, Syrian asylum seekers and refugees in the United Kingdom, rather than mental health professionals whose role was more important during the initial development of the intervention. Instead, touchpoints and themes identified in the interviews will be prioritized by a community panel during group meetings before adapting the intervention in preparation for co-design events. The community panel will consist of researchers, mental health professionals, and cultural brokers associated with the Syrian community in the United Kingdom. Similar to Lewis and colleagues' [41] study, the cultural adaptation process will include co-design events where participants will be presented with the partially adapted

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intervention and collectively identify and adapt touchpoints related to the intervention. The use of co-design events to empower participants to directly culturally adapt the intervention is another methodological innovation of the study, with previous attempts having only involved participants indirectly [24]. Again, the community panel will meet after touchpoints and themes are extracted from the co-design events to balance any need for cultural adaptation with maintaining the integrity of the intervention's core mechanisms of change.

Setting

As Syrian asylum seekers and refugees are dispersed across the United Kingdom, interviews and co-design events will be held on the web to lower barriers to participation.

Participants

In total, 40-50 male or female Syrian asylum seekers and refugees in the United Kingdom, aged 18 years and older will participate in one-to-one semistructured interviews and 3 focus groups (co-design events). Recruitment objectives include 20-30 participants for interviews and 18 participants for 3 focus groups with 6 participants in each group. The participants will include different genders (male and female), age groups (18-39 years and 40 years and older), ethnicities (Arab, Kurdish, and other), religious groups (Muslim, Christian, and other), and refugee status (asylum seeker or refugee). Previous research has shown that most of the information is revealed in the first 5-6 interviews [42]; however, due to the stigma associated with suicide, participants may underreport their experiences with SI. Therefore, 20-30 participants will be recruited to increase the likelihood of identifying participants with experiences of SI. Likewise, a minimum level of SI will not be set for inclusion but rather individuals with serious SI, defined as a score of 4 and above on the SI subscale of the Columbia-Suicide Severity Rating Scale, will be excluded from participation [43,44]. This decision was made to avoid risks of harm to the participants and has thus far not resulted in the exclusion of any participants. To reduce the time spent on recruitment, interview participants will be asked to participate in a co-design event focus group.

Sampling

The study will use purposive sampling to recruit participants from various demographic backgrounds including age, gender, religion, ethnicity, and refugee status. Participants will be recruited via correspondence with nongovernmental organizations and charities and adverts on social media. At the time of writing, 16 participants have already been recruited through Syrian cultural brokers with no participants from NGOs or charities. The main barrier to recruitment through NGOs and charities has most often been low capacity. As suggested by Eylem and colleagues [24], cultural brokers can increase recruitment capacity where certain organizations produce an institutional barrier for subgroups of migrants [45]. In fact, this may be true for all Syrians who, due to government-sanctioned repression, have understandably developed a mistrust for authority structures in general [46].

Data Collection

Lived Experience Interviews

The first phase of the study will involve one-to-one semistructured interviews with Syrian asylum seekers and refugees in the United Kingdom. The interviews will follow a topic guide including open-ended questions about participants' lived experience with the migratory process and the effects it has had on their mental health; their cultural and personal conceptualizations of mental health and SI; the ways in which they cope with mental health and SI; the barriers and facilitators for seeking help for mental health and SI; and their perceptions of digital mental health interventions (programs). Given the stigma attached to mental health [21], semistructured interviews that focus on Syrian refugees' mental health in relation to their experiences with the migratory process are more likely to encourage participation and also reduce researcher bias. Touchpoints will be extracted from the interviews to better understand the mechanisms by which SI arises for this population and provide culturally relevant and appropriate case examples in the intervention. Previous cultural adaptation work on this intervention conducted by Eylem and colleagues [24] found case examples over emphasized SI and traditional values. Therefore, focusing on Syrian asylum seekers' and refugees' experiences with the migratory process should provide a shared paradigm for a culturally diverse population with varying levels of SI. Since asylum seekers and refugees are dispersed across the United Kingdom, interviews will be conducted remotely using Microsoft Teams or over the phone. Prior to conducting the interviews, participants will provide oral consent, which will include consenting to being audio-recorded and indirectly quoted in any publications. Participants' consent will be recorded by the researcher on an oral consent form, and only digital copies will be kept by the researcher and participant. Digital case report forms will also be used to collect data about the participants age, gender, ethnicity, religion, refugee status, and general practitioner registration. Subsequently, the interviews will be conducted for 30-45 minutes, which will be voice recorded and then transcribed and translated into English.

Co-Design Events

The co-design events will involve collecting data through 3 focus groups with 6 participants in each. This will involve bringing participants of diverse backgrounds together to identify key touchpoints of the intervention for cultural adaptation. The adaptation will build on Eylem and colleagues's [24] Turkish cultural adaptation of van Spijker and colleagues' [37] 6-week guided CBT-based web-based intervention to reduce SI. Prior to the focus group, participants will be given access to 2 modules that have already been translated and partially adapted. Modules will be paired based on the order in which they are provided in the intervention. The 2 modules will be presented again at the beginning of each focus group. Subsequently, participants will be asked to identify the main touchpoints and ways to adapt the modules. The focus groups will be conducted on the web using Microsoft Teams to facilitate participation from various locations across the United Kingdom. Prior to conducting the focus groups, participants will provide oral consent in the same manner as the interviews. Digital case report forms will also be

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used to collect demographic data including age, gender, ethnicity, religion, refugee status, and general practitioner registration. The focus group will then be conducted for no longer than an hour and a half, which will also be voice recorded, transcribed verbatim, and translated into English for analysis.

Data Analysis

Semistructured interviews will be transcribed verbatim, and thematic analysis will be used to identify themes, as well as touchpoints of participants' lived experience with the migratory process to culturally adapt the intervention. Thematic analysis was chosen for its epistemological flexibility [47]. Analysis will combine both realist and social constructionist paradigms. Braun and Clarke [47] describe thematic analysis as identifying semantic themes for specific areas of interest in the data or latent themes spread across the data. Moreover, they assert that semantic themes are revealed through description, whereas latent themes only arise after interpretation. However, the distinction between semantic and latent meaning disregards the primary roles of intentions and context in meaning interpretation and construction [48]. In other words, what is obvious in one context may be latent in another and vice versa, hence, the need for cultural adaptation. For example, mental health issues may be latent in discussions about mental health but obvious in discussions about lived experiences with the migratory process. Additionally, mental health issues may be latent during the premigration phase and more obvious in the postmigration phase. Thus, to combine both epistemologies, the analysis will be inductive but will be bound by the objectives of the study. The code system and themes will be developed in accordance with the 6 phases outlined by Braun and Clarke [47] and will be checked by another member of the research team. The stages include data familiarization, generating initial codes, searching for themes, reviewing themes, defining and naming themes, and producing the report. Internal reliability will be ensured by an iterative review of themes as well as checking for consistency between members of the research team [49]. Where irreconcilable differences in interpretations arise, preference will be given to the interpretation in line with participants' shared lived experience and the objectives of the study. Such differences are likely to arise due to an analyst's background knowledge either as a researcher or from lived experience. Therefore, adherence to the objectives of the study and the participants' lived experiences in analysis is as essential to the cultural adaptation process as adherence to the intervention's mechanisms of change and participants' lived experience is to maintaining implementation fidelity. Internal validity will be ensured by iteratively checking for correspondence between the thematic map and the data set [49]. Given the study involves semistructured qualitative data, this will involve comparing the thematic map to the original codes before structuring them into themes. The use of a thematic map to guide the analysis is also important as NVivo, a qualitative analysis software produced by Lumivero, mostly supports the representation of linear and not complex relationships. The co-design events will also help to determine the credibility of the analysis through participant validation of lived experience case examples, coping strategies, and help-seeking behavior [49]. The co-design event data will be analyzed using the same methods, and themes will be prioritized by a community panel before the final adaptation of the intervention.

Ethics Approval

Ethics approval has been provided for the study by the Central University Research Ethics Committee at the University of Oxford (R81752/RE001).

Informed Consent

Eligible participants will receive a participant information sheet for either an interview or focus group. This will describe, in both Arabic and English, the goals and limitations of the study, the way interviews and focus groups will be performed, the way data will be collected and handled, and any risks involved in participating. Participants will be informed that they are free to withdraw from participation at any time, for any reason, without consequence, and are not obliged to provide the reason for their withdrawal. The contents of the participant information sheet will be explained verbally by the DPhil researcher, OB, or one of the members of the research team before conducting the interview or focus group, and participants will have the opportunity to ask questions. Oral informed consent will then be obtained from participants before screening for inclusion and exclusion criteria and participating in an interview or focus group. Informed consent will be recorded on an oral informed consent form on behalf of the participant, and digital copies will be given to the participant and kept on university servers for at least 3 years from the time of publication.

Safety Protocol

Although the study will not necessarily involve the recruitment of participants directly experiencing SI, if OB suspects that any participants are at risk of harming themselves or in need of help, he will encourage them to contact their local general practitioner and provide them with information for alternative sources of help. Likewise, participants will be informed in the participant information sheet that confidentiality could be broken where there is a risk of harm to themselves or others. In which case, OB will report any risk of harm to the principal investigator, KB, who will in turn review the circumstances and act according to his judgment. If there is a risk of immediate harm, the emergency services will be contacted via 999. If further steps are necessary, the matter will be referred to the Multi-Agency Safeguarding Hub within 1 working day of first receiving the information from the participant. The local area designated officer will then advise on the next appropriate steps to take.

Data Management

Access to personal data will be restricted to only authorized individuals. Personal names will be replaced with unique participant numbers on consent forms and audio recordings and transcriptions of interviews. Focus group audio recordings and transcriptions will be given a unique focus group number and individual electronic case report forms will be labeled with the participant's initials. All audio recordings will be deleted once they have been transcribed. The remaining data will be kept on university servers for 3 years from the time of first publication in accordance with Oxford University policy and then deleted by the principal investigator.

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Dissemination

The findings of this study will be disseminated through publication and web-based Syrian asylum seeker and refugee communities. Likewise, the feasibility and acceptability of the culturally adapted intervention will be assessed in a later study as part of OB's dissertation research.

Results

The first phase of the study, lived experience interviews, was initiated in November 2022. Since commencing, 16 participants have been recruited and interviewed. The second phase of the study, co-design events, will commence in June 2023. The study, including the write-up period, is expected to end in December 2023.

Discussion

Expected Findings

This paper describes the study protocol for the cultural adaptation of a digital SI intervention for Syrian asylum seekers and refugees in the United Kingdom. The main aim of the study is to improve the understanding and treatment of SI among Syrian asylum seekers and refugees arriving in the United Kingdom. Accordingly, the study will consist of two phases: (1) semistructured interviews and (2) co-design events. First, interviews will be conducted to explore the lived experiences of Syrian asylum seekers and refugees in the United Kingdom with the migratory process; their mental health and SI conceptualizations, coping strategies, and help-seeking behavior, including cultural, linguistic, and structural barriers; and their perceptions of digital mental health interventions. This integrative approach to cultural adaptation identifies lived experience as the source of both psychopathology and their subsequent cultural interpretations and help-seeking. Specifically, this includes touchpoints, crucial moments that make a difference to Syrian asylum seeker' and refugee' experiences with the migratory process. Importantly, touchpoints can highlight the ways implicit boundaries of lived experience such as refugee status impact mental health. Second, co-design events will be held to enable Syrian asylum seekers and refugees to collaboratively and culturally adapt the intervention. While digital evidence-based interventions have generally been effective in reducing SI, most studies have revealed low adherence rates, with participants completing only half of the intervention [50-52]. Thus, rather than evaluating intervention outcomes, the study will help achieve greater access to treatment for this population by optimizing the recruitment process and the intervention.

Limitations

While the cultural adaptation of a digital mental health intervention for Syrian asylum seekers and refugees is aimed at reducing barriers to treatment for SI, it nonetheless will not affect their ongoing lived experiences with the migratory process. It is therefore hoped that digital mental health interventions will help Syrian asylum seekers and refugees in the United Kingdom cope with the asylum process, which will often involve reopening the wounds caused by their experiences of conflict in Syria. It is also important to acknowledge the difficult ethical dilemma of balancing the need to explore their lived experiences and the effects it might have on their mental health. This study is therefore indebted to the Syrian asylum seekers and refugees who have already shared their experiences with the expectation that this research will be used for the benefit of their community. While digital SI interventions may have limited capacity for systems change, their most substantial contribution is to help preserve the lives and mental health of those who must live in them. The study design is also limited to culturally adapting the digital intervention; however, its feasibility and acceptability to Syrian asylum seekers and refugees in the United Kingdom experiencing SI will be assessed in a future study.

Conclusions

The conflict in Syria has resulted in the largest forced displacement crisis since the Second World War [1]. As a result, Syrian asylum seekers and refugees have been exposed to several stressors throughout the migratory process, including dangerous journeys and a prolonged asylum process [9]. Their experiences have put them at an increased risk of developing mental health issues including crucially SI [3]. Despite their elevated rates of SI, Syrian asylum seekers and refugees often fail to seek treatment due to language barriers, the lack of culturally competent services, mental health stigma, and the fear of deportation [18-21]. Thus, access to treatment for SI among Syrian asylum seekers and refugees in the United Kingdom may be improved with culturally adapted digital mental health interventions [23]. In this study, this will involve using EBCD, an action research method for collaboratively improving health care services and interventions, to culturally adapt a digital SI intervention developed for the general population [36]. Syrian asylum seekers and refugees in the United Kingdom will be interviewed to explore their cultural conceptualizations, coping strategies, and help-seeking behavior for SI in relation to their lived experiences with the migratory process. They will then collaboratively and culturally adapt the intervention during 3 co-design events to reduce any negative consequences of the cultural adaptation and improve engagement. Cultural adaptation frameworks have traditionally consisted of various components [29], and therefore, EBCD was chosen for its focus on experience touchpoints. Touchpoints of lived experience will not only provide signs of psychopathology behind cultural interpretations and responses but points at which both interact. Co-design events will also enable participants to identify shared touchpoints in the intervention in a similar way to their lived experience with the migratory process. Studies that include opportunities for co-design not only facilitate engagement but could also increase mental health literacy among their target population. Finally, it is hoped that the cultural adaptation of a digital SI intervention for Syrian asylum seekers and refugees in the United Kingdom provides an example of procedural fairness in facilitating equal access to mental health care.

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Data Availability

The data sets generated during and/or analyzed during this study are not publicly available due to the vulnerable nature of the participants but are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

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Abbreviations

CBT: cognitive behavioral therapy
EBCD: experience-based co-design
SI: suicidal ideation

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Protocol

Dynamic Modelling of Mental Resilience in Young Adults: Protocol for a Longitudinal Observational Study (DynaM-OBS)

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Abstract

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Background: Stress-related mental disorders are highly prevalent and pose a substantial burden on individuals and society. Improving strategies for the prevention and treatment of mental disorders requires a better understanding of their risk and resilience factors. This multicenter study aims to contribute to this endeavor by investigating psychological resilience in healthy but susceptible young adults over 9 months. Resilience is conceptualized in this study as the maintenance of mental health or quick recovery from mental health perturbations upon exposure to stressors, assessed longitudinally via frequent monitoring of stressors and mental health.

Objective: This study aims to investigate the factors predicting mental resilience and adaptive processes and mechanisms contributing to mental resilience and to provide a methodological and evidence-based framework for later intervention studies.

Methods: In a multicenter setting, across 5 research sites, a sample with a total target size of 250 young male and female adults was assessed longitudinally over 9 months. Participants were included if they reported at least 3 past stressful life events and an elevated level of (internalizing) mental health problems but were not presently affected by any mental disorder other than mild depression. At baseline, sociodemographic, psychological, neuropsychological, structural, and functional brain imaging; salivary cortisol and α-amylase levels; and cardiovascular data were acquired. In a 6-month longitudinal phase 1, stressor exposure, mental health problems, and perceived positive appraisal were monitored biweekly in a web-based environment, while ecological momentary assessments and ecological physiological assessments took place once per month for 1 week, using mobile phones and wristbands. In a subsequent 3-month longitudinal phase 2, web-based monitoring was reduced to once a month, and psychological resilience and risk factors were assessed again at the end of the 9-month period. In addition, samples for genetic, epigenetic, and microbiome analyses were collected at baseline and at months 3 and 6. As an approximation of resilience, an individual stressor reactivity score will be calculated. Using regularized regression methods, network modeling, ordinary differential equations, landmarking methods, and neural net–based methods for imputation and dimension reduction, we will identify the predictors and mechanisms of stressor reactivity and thus be able to identify resilience factors and mechanisms that facilitate adaptation to stressors.

Results: Participant inclusion began in October 2020, and data acquisition was completed in June 2022. A total of 249 participants were assessed at baseline, 209 finished longitudinal phase 1, and 153 finished longitudinal phase 2.

Conclusions: The Dynamic Modelling of Resilience–Observational Study provides a methodological framework and data set to identify predictors and mechanisms of mental resilience, which are intended to serve as an empirical foundation for future intervention studies.

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KEYWORDS

resilience; stress; stressor reactivity; resilience factors; mental health; stress disorders; longitudinal; prospective; neuroimaging; ecological momentary assessment; mobile phone

Introduction

Background

Stress-related disorders, such as depressive disorders, anxiety disorders, posttraumatic stress disorder, and addiction, are highly prevalent globally and pose a significant burden on individuals, the economy, and society in general [1-4]. Years lost to disability owing to mental disorders have increased by 45.2% from 1990 to 2016 [3], and mental disorders are associated with a reduced life expectancy by a median of 10.1 years [5]. Mental and substance use disorders are particularly prevalent in people in their 20s, and anxiety disorders and major depression have a high long-term stability [6]. Many mental health studies have focused on the mechanisms and predictors of vulnerability (risk) and dysfunction. However, we and others have argued that a focus on resilience, aiming to investigate factors and mechanisms contributing to the maintenance and recovery of mental health despite adversity [7], is a complimentary, helpful approach to reveal novel intervention targets and to help avert (chronic) mental health problems before they develop. Here, we describe the protocol of a longitudinal study designed to gain a better understanding of resilience.

Resilience is the maintenance of, or quick recovery toward, mental health during and after times of adversity, such as trauma, difficult life circumstances, challenging life transitions, or physical illness [8,9]. It is becoming increasingly clear that resilience is the result of a dynamic process of successful adaptation to stressors [9-14]. Besides person-environment interactions and the activation of dispositional coping strategies, there is accumulating evidence that individuals *change* while they successfully cope with stressors. These adjustments can manifest at various levels, such as altered perspectives on life [15], the emergence of new strengths or competencies [16], partial immunization against the effects of future stressors [17-19], or epigenetic alterations and modified gene expression patterns [20,21]. Neurobiological studies in animal models indicate that adjustments at the brain level are causal for the preservation of normal behavior [22-25]. From a dynamic perspective, resilience results from change and not just inertia, insensitivity to stressors, or merely a passive response to adversity.

Consequentially, resilience should no longer be understood as a fixed personality trait or predisposition (the *resilient personality*) that will determine successful coping independent

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of other factors. Rather, we should take a dynamic stance and investigate the complex, interactive, and time-varying processes (*resilience processes*) that lead to a positive long-term outcome relative to the number of stressors to which an organism is exposed. These processes will partly be determined by individual dispositions, including traits, habits and skills, beliefs, genotype, brain architecture, and physical constitution ("resilience factors"). Although some of those will be quite stable and define a person's typical coping patterns throughout a stressful life period, other resilience factors may themselves undergo change, for instance, by increasing their effectiveness or frequency of use. The latter would constitute allostatic resilience processes, in which the system learns to change its mode of operation to remain stable. Allostatic adjustment is more likely when an external perturbation (a stressor) taxes the system. In contrast, homeostatic resilience processes are defined as mental stability in the absence of individual change [13].

By definition, resilience as an outcome cannot be measured through any one-time (cross-sectional) assessment (eg, a questionnaire, brain scan, and genotype) performed before adversity occurs, as the trait-like conceptualization of resilience implies. Instead, resilience can only be determined by assessing both stressors and mental health longitudinally, thus capturing the dynamic nature and time course of the stressors, as well as the changes in mental health that these stressors may or may not induce [9,11]. This should be complemented by assessing potential resilience factors at study baseline and, ideally, also repeatedly during the course of observation [13]. Moreover, the factors and processes of resilience should ideally be studied at different levels of organization, from the molecular (including genetic), physiological, neural, and cognitive levels to behavioral, experiential, and social levels [26].

This Study

The observational study Dynamic Modelling of Resilience–Observational Study (DynaM-OBS) of the Consortium "DynaMORE (Dynamic Modelling of Resilience)," funded by the European Union Horizon 2020, is designed to unravel such multilevel mechanisms of outcome-based resilience. The targeted sample is young students who find themselves in the transition from family and school life to work or academics—a life period characterized by new unfamiliar environments and demands, which is associated in some individuals with the exacerbation of existing, or the onset of new, stress-related psychological problems. The rationale of focusing on young people is that many mental disorders have their first onset or even peak during this critical life transition phase [27], and stress-related mental problems appear to be a particular problem in the student population [28-33]. To enrich our sample with at-risk individuals, we added two further inclusion criteria: participants must (1) have a history of at least 3 adverse life events [34] and (2) score in the mid-to-high range in the General Health Questionnaire (GHQ), a self-report instrument for internalizing symptoms [35], in addition to being a student or undergoing an apprenticeship. The study started in October 2020, when the second wave of the COVID-19 pandemic began in Europe, which formed an additional general stressor to the sample population at the time of data assessment [36].

DynaM-OBS is a longitudinal study with a baseline assessment, a dense observation period of 6 months (longitudinal phase 1), and a subsequent less dense observation period of 3 months (longitudinal phase 2) for each participant. DynaM-OBS features four core components: (1) an extensive baseline characterization (baseline battery) measuring potential social, psychological, and biological resilience factors; (2) a biweekly web-based assessment of stressor exposure and mental health during phase 1; (3) repeated measurement of a subset of potential resilience factors at different time points during the study; and (4) every 4 weeks, 1-week–long ecological momentary assessments (EMAs) and ecological physiological assessments (EPAs) of mood and stress reaction patterns during real life conducted using smartphones and wristbands, respectively.

The DynaM-OBS biweekly stressor and mental health assessments (study core component 2) apply the frequent stressor and mental health monitoring (FRESHMO) paradigm introduced recently to operationalize and measure resilience in longitudinal studies [13]. In the data analysis, we will use normative modeling of stressor reactivity (SR) as an approximation of resilience. Specifically, we will regress participants' average mental health problem score from all assessment time points in phase 1 over their average stressor exposure score from the same time points, and thus, we will establish the sample's normative stressor exposure–mental health problem relationship during the study. At any single assessment time point or series of subsequent time points, the deviation of a participant's (average) mental health problem score from the norm relationship (its regression residual) expresses the participant's individual mental health reactivity to stressor exposure during that time window. A positive SR score reflects higher than predicted reactivity, whereas a negative SR score reflects lower than predicted reactivity. Importantly, SR scores inherently correct for different degrees of stressor exposure between individuals and can thus be compared between them.

On this basis, the inverse of the SR score calculated from the average stressor exposure and mental health problem scores over the entire longitudinal phase 1 time window of the study can be considered a dimensional measure of a participant's outcome-based resilience over these 6 months. We will also build within-participant time courses of SR scores by building the score in sliding windows of several averaged biweekly stressor exposure and mental health problem measurements. This permits us to index temporal fluctuations in reactivity and to detect potential substantial changes that would be a strong indicator of allostatic adjustment at the level of resilience factors, without which relevant increases or decreases in reactivity are difficult to imagine.

Thus, the time series–based approach to SR assessment goes beyond the mere prediction of a longer-term resilience outcome (here, the inverted 6-month SR score of phase 1) from a single measurement of more or less stable resilience factors (here, DynaM-OBS baseline battery, study core component 1). In combination with repeated measurement of resilience factors (DynaM-OBS core component 3)—some biweekly and some at study entry and study exit—the approach allows for relating changes in the outcome to potentially underlying allostatic

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changes in resilience factors (toward the good or bad). Another more distal source of change in the outcome may lie in the stressor exposure itself, which may increase to a degree that the system reacts allostatically by ideally strengthening the existing or developing new coping mechanisms, which then, in turn, improve SR [13].

Core component 4 of DynaM-OBS (EMA and EPA) serves to examine whether stressor exposure, mental health, and SR measured using web-based questionnaires over periods of weeks or months (refer to component 2) are reflected in individuals' patterns of SR measured at a higher temporal frequency in real life. EMA combined with EPA will allow us to quantify, among others, the frequency of self-reported real-life stressors, the magnitude of mood or physiological changes in response to these stressors, the speed of recovery, and the alterations of recovery speed.

Relation to Other Studies

The FRESHMO paradigm [13] in its combination with repeated resilience factor measurement is or has been used in several other longitudinal studies by our consortium and partners, including the studies "MARP (Mainz Resilience Project)" (study protocol in preparation, functional magnetic resonance imaging [fMRI] battery and results published by Kampa et al [37,38]), "LORA (Longitudinal Resilience Assessment)" [39], and "DynaCORE-L (The DynaMORE Longitudinal Study on Psychological Resilience to the Mental Health Consequences of the Corona Crisis)" [40]. MARP and LORA are ongoing since 2016 and are monitoring stressors and mental health every 3 months and resilience factors approximately every 1.5 years over many years of participants' lives (refer to the publication by Kalisch et al [13]). DynaCORE-L was conducted over 6 weeks during the early phase of the COVID-19 pandemic in 2020 and involved weekly stressor, health, and resilience factor monitoring. Similar to DynaM-OBS, all studies also include baseline resilience factor assessment. DynaM-OBS thus covers a time range lying in between MARP and LORA on the one hand and DynaCORE-L on the other hand. A similar approach is also used in the ongoing Healthy Brain Study, which uses 3 waves of assessments to calculate dynamic resilience scores [41].

In DynaCORE-L, we observed that several baseline resilience factors prospectively predicted average SR over the full monitoring period, whereas week-to-week changes in resilience factors were not predictive of SR changes in the subsequent week [42]. This indicates that allostatic adaptation processes may occur over longer timescales. Another possibility is that the relatively mild stressor exposure in DynaCORE-L, which occurred after the first wave of the pandemic had subsided, permitted homeostatic coping. Owing to its longer time range and more severe at-risk constellation, DynaM-OBS should be more sensitive than DynaCORE-L in detecting allostatic processes. At the same time, DynaM-OBS allows us to test the generalizability of the baseline resilience factors discovered in DynaCORE-L to a different sample. Another source of hypotheses is the unpublished preliminary analyses of the MARP and LORA data sets. In synopsis with the anticipated results from these long-term studies, DynaCORE-L and DynaM-OBS will yield a good picture of the temporal dynamics of allostatic resilience processes.

DynaCORE-L had further detected that week-to-week changes in stressor exposure predate subsequent changes, specifically in the resilience factor of active behavioral coping, which were, however, not translated into improvements in SR. Again, this may have been the consequence of the limited duration or limited exposure severity in the study. With DynaM-OBS we, therefore, also aim to detect mediated relationships between stressors, resilience factors, and SR. The addition of EMA and EPA is intended to detect potential relationships at much higher (within-week and within-day) temporal resolution, which is possible neither in DynaCORE-L nor in MARP and LORA.

In addition to answering questions about resilience factors and processes, a purpose of DynaM-OBS is to establish a methodological framework for a subsequently planned intervention study (DynaMORE intervention study [DynaM-INT]) that aims to find new ways to prevent stress-related mental illness in at-risk individuals with the help of mobile training apps targeting specific resilience factors. In the context of such interventions, regular monitoring of SR and resilience factors can provide information on the desired outcome (lastingly reduced SR) and potential working mechanisms (lastingly strengthened resilience factors), whereas a baseline battery of both resilience and risk factors (RFs) may inform us about the individual characteristics that predict intervention success.

Statistical Methods Development

The conceptual framework and the types of data generated by DynaM-OBS require new analysis methods. Although the time-sensitive regression models used in DynaCORE-L were appropriate for analyzing time point–to–time point (week-to-week) effects, they were also limited. Notably, they only tested each of the multiple, partially correlated resilience factors in a separate model, and they did not consider interrelations between resilience factors; they did not test for time-lagged effects between either stressors and resilience factors or resilience factors and SR extending beyond 1 week; and they did not test for changes or change points in the time series of stressor exposure, resilience factors, or SR. Therefore, we also use DynaM-OBS (together with the other mentioned studies) as a test bed for new methodological developments. These include regularized regression methods [36,43], network models [12], landmarking methods [13], and individualized deep dynamic methods in combination with deep generative models, allowing, for example, additional quantification of resilience, multiple imputation, and dimension reduction [43]. We will also use the data for potential improvements in the calculation of SR scores, including partial least squares methods [44], serving notably to improve the mental health problem variance explanation by stressor exposure and the better integration of stressors of various sources into stressor exposure [13]. Thus, DynaM-OBS has a strong exploratory character from a methodological perspective.

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Research Questions and Hypotheses

Nevertheless, we formulate a set of hypotheses that will be tested using established methods, as described in the *Methods* section. A major theoretical background of DynaM-OBS is Positive Appraisal Style Theory of Resilience (PASTOR) [9,45]. Positive appraisal style (PAS) is the tendency to appraise potential threats to one's goals and needs (stressors) in a way that avoids unnecessarily negative but also highly unrealistically positive (delusional) appraisals. Instead, appraisals typically produced by individuals exhibiting PAS range from realistic to slightly unrealistically positive appraisals. Therefore, positive appraisers generate appropriate, optimally regulated stress reactions that are sufficient to cope with a threat but do not use more resources than necessary and have more time for recovery and rebuilding of resources and more opportunity to make growth experiences than individuals who are inclined toward catastrophizing, pessimism, or helplessness.

Questionnaires

DynaM-OBS uses a PAS self-report questionnaire developed to assess the cognitive processes or mental operations that lead to positive appraisal contents (Perceived Positive Appraisal Style Scale—process focused [PASS-process]; refer to the *Methods* section) in its baseline battery, its biweekly web-based monitoring, and in the exit questionnaire battery applied in month 9 of the study. We hypothesize (a) that the baseline PASS-process negatively predicts the SR score covering the first 6 months of the study (phase 1, henceforth: SR_1), (b) that changes in PASS-process from time point to time point in the biweekly monitoring inversely cofluctuate with the corresponding SR score, (c) that such changes also negatively predict time-lagged changes in SR (where the duration of the PASS-process change necessary to entail SR changes and the duration of the time lag are to be explored), and (d) that changes in PASS-process from study baseline to study exit are negatively related to the SR score covering the entire study period (phases 1 and 2, SR_{1+2}).

An alternative PAS self-report instrument used in the DynaM-OBS baseline and exit batteries focuses on positive appraisal content instead of focusing on the processes that generate such appraisals (Perceived Positive Appraisal Style Scale–content focused [PASS-content]; refer to the *Methods* section). Hypotheses a and d, therefore, analogously apply to PASS-content.

In this manner, we will also test other baseline and exit questionnaires that specifically assess positive appraisal tendencies on single threat appraisal dimensions, namely, the dimensions of threat probability (optimism), threat coping potential (general self-efficacy and control), and threat magnitude and costs (inverted anxiety sensitivity score).

In the combined multivariate analysis using regularized regression of the PAS scales and the latter instruments, we will also address the question of which of these scores are best in explaining SR. In a complementary approach using factor analysis, we will ask whether there are interpretable latent variables across questionnaires that can be considered dimension-reduced representations of the PAS construct and whether these predict SR.

Finally, we will ask whether PAS (assessed with the "winning" instrument or instruments in the comparative multivariate analysis or, alternatively, with suitable cross-questionnaire factors) mediates the effects of perceived social support on SR and whether its effect on SR is in turn mediated by perceived good stress recovery (refer to the studies by Kalisch et al [9] and Veer et al [36] for rationale). For these mediation analyses, we will again use either baseline scores (for explanation of SR_1; hypothesis a) or baseline-to-exit change scores (for explanation of SR_{1+2}; hypothesis d).

The complete battery of RFs assessed in the baseline and exit questionnaires will be evaluated for its ability to explain SR scores in a more exploratory manner, using the abovementioned and potential newly developed methodological approaches.

Neuroimaging

In the development of PASTOR, we have emphasized the problems associated with self-report assessment in general (which knows various sources of bias) and self-report assessment of appraisal processes and contents in particular (not all of which may be accessible to consciousness and be verbally reportable) [9]. Therefore, we also use a complementary approach, namely, to indirectly index the effectiveness and efficiency of participants' positive appraisal processes through objective measures of their behavioral, physiological, or neural reactions to stressors in the laboratory or in real life. To this end, we generated a baseline neuroimaging battery where fMRI tasks are (partly) accompanied by behavioral and physiological recordings. The battery includes tasks from the corresponding MARP battery (reward sensitivity, differential fear conditioning, and situation-focused volitional reappraisal [37]), all of which provide reproducible imaging data [38] and were either found to be predictive of SR in initial analyses in MARP (unpublished) or were retained because of their special theoretical interest (refer to the study by Kampa et al [37] for task rationales in the context of PASTOR). A purely behavioral stress reactivity and recovery task in the MARP battery is replaced in the DynaM-OBS battery using a dedicated neuroimaging variant [46,47]. To link the battery with other neuroimaging cohort studies, a frequently used implicit emotional processing task is also used [48,49]. These tasks are complemented by structural and resting-state fMRI measurements.

For the neuroimaging data, we hypothesize (based on initial MARP findings and PASTOR) that SR_1 will be negatively predicted by activity related to (a) high gain anticipation (gain>zero anticipation contrast), (b) low loss anticipation (loss>zero anticipation contrast), (c) high threat safety discrimination during the processing of fear-conditioned stimuli (CS) (threat-predictive CS+ > non–threat-predictive CS- contrast), (d) low threat generalization (CS- contrast), (e) high volitional reappraisal (R>NR contrast). Finally (f), we hypothesize that SR_1 will inversely correlate with amygdala-ventromedial prefrontal functional connectivity during implicit emotion processing as measured using a faces versus shapes matching paradigm [50]. For details on contrasts, refer

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to the studies by Kampa et al [37] and Wackerhagen et al [50]. Similar to the questionnaire measures, PASTOR-related neuroimaging measures will be additionally analyzed using multivariate regression and factor analysis to identify best or latent predictors, respectively, of SR. We will also attempt cross-modality analyses including both questionnaires and neuroimaging measures.

Similar to longitudinal resilience data, the neuroimaging data will be used for the development of analysis methods.

Other Data Modalities and Hypotheses

PASTOR claims that the effects of other social, psychological, and biological resilience factors on resilience are mediated by how they shape PAS [9]. In this framework, we used a range of additional questionnaires, neuropsychological tests, and biological samples (blood for genotyping, DNA methylation, plasma proteome analysis, and also cytokines at 1 site; stool for gut microbiome analysis; and saliva for cortisol analysis). Well-known risk factors and sociodemographic variables were also assessed. The latter will be included as covariates in several planned analyses, along with other potentially confounding factors such as the study site.

Methods

Study Centers and Study Period

The data were acquired in a multicenter setting at 5 research sites: Charité–Universitätsmedizin Berlin, Department of Psychiatry and Psychotherapy in Berlin, Germany; Universitätsmedizin Mainz, Neuroimaging Center (NIC) in Mainz, Germany; Donders Centre for Cognitive Neuroimaging (DCCN) in Nijmegen, The Netherlands; Sagol Brain Institute, Tel Aviv University (TAU) and Tel Aviv Soursaky Medical Center, Tel Aviv, Israel; and University of Warsaw, Faculty of Psychology in Warsaw, Poland. Each site's official language was used to communicate with the participants, as well as in the study materials (informed consent form, tasks, questionnaires). Participants enrolled in the study between October 2020 and September 2021, which was during the second wave of the COVID-19 pandemic, as indicated in the details provided in Multimedia Appendix 1. Phase 1 assessments were completed in March 2022, and phase 2 assessments were completed in June 2022.

Participants

A total of 250 mentally healthy male or female participants who were studying or in vocational training at the time of recruitment were planned to be included at the 5 research sites (n=50 each). The exact number of participants per site will be reported in the follow-up reports. The permitted age range was 18-25 years at all sites, except for TAU, where the age range was 18-27 years because most young adults in Israel complete 2 to 3 years of military service and spend 1 year abroad before entering vocational training or university. Participants were included if they had experienced ≥3 stressful life events [34], which they rated as burdening, and if they reported an elevated level of general psychopathology (internalizing symptoms), defined by a score of >20 in the GHQ-28 [35]. The complete list of the inclusion criteria is provided in Table 1.

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Table 1. List of inclusion criteria and format in which they were assessed. Participants who were found eligible for criteria 1 to 10 in the anonymous web-based screening were invited to an on-site interview to check eligibility for criteria 9 to 13, to receive written and verbal information about the study, and to provide written informed consent.

Number	Criterion	Format
1	Age between 18 and 25 years (18 and 27 years at Tel Aviv University)	Web-based
2	≥3 life events rated as burdening	Web-based
3	GHQ-28[a] score of ≥20	Web-based
4	BMI between 18 and 27	Web-based
5	No hormonal treatment and no consumption of steroids or treatment with steroids	Web-based
6	Proficiency in the official language of the country of study enrollment (minimum level of C1 in the Common European Framework of Reference for Languages)	Web-based
7	Eligibility to participate in ecological physiological assessment using a wearable device (no skin disease in the wrist or chest area, no medical condition that increases the risk of infection through electrodes, and no medication with phototoxic side effects)	Web-based
8	Eligibility to participate in the fear conditioning task (no skin allergy or allergy to adhesive electrodes)	Web-based
9	No lifetime diagnosis of any severe mental or organic disorder that affects neurodevelopment owing to its pathological mechanism or treatment (eg, schizophrenia, bipolar disorder, anorexia or bulimia nervosa, attention-deficit hyperactivity disorder, autism spectrum disorder, meningitis, epilepsy, multiple sclerosis, stroke, brain cancer, brain concussion, or coma)	Web-based and interview
10	Eligibility for undergoing the functional magnetic resonance imaging protocol (normal or corrected-to-normal eyesight, no hearing impairment, no claustrophobia, no nonremovable ferromagnetic metal in or on the body, not pregnant, and no large tattoo on the head or neck area)	Web-based and interview
11	No diagnosis within 9 months before inclusion of any mental disorder other than a mild depressive episode (ICD-10[b] F32.1), tobacco abuse or dependence (ICD F12), or substance abuse, as assessed by trained psychologists using the Mini-International Neuropsychiatric Interview [51]	Interview
12	No consumption of any psychoactive drug or substance up to 4 weeks before the first psychological assessment and before the magnetic resonance imaging assessment	Interview
13	The participant has received all relevant information about the study, is able to obtain full insight and is fully contractually capable, is willing and able to comply with the protocol, and agrees to participate by giving written consent	Interview

[a]GHQ-28: General Health Questionnaire.

[b]ICD-10: International Classification of Diseases, Version 10.

Ethics Approval and Consent to Participate

The study was reviewed and approved by the local ethics committees of all participating sites: the ethics committee of Charité–Universitätsmedizin Berlin, Germany (ethics approval number [EAN] EA1/319/19); the ethics committee of Radboud University Medical Center, Nijmegen, The Netherlands (Commissie Mensgebonden Onderzoek Arnhem-Nijmegen; EAN 2019-5613); the ethics committee of TAU, Tel Aviv, Israel, and the Helsinki committee of Tel Aviv Souraski Medical Center (EAN 0055-19-TLV); the ethics committee of the State Medical Board of Rhineland-Palatinate, Mainz, Germany (EAN 2019-14731_1); and the Ethics Committee for Scientific Research at Faculty of Psychology, University of Warsaw (Komisja Etyki Badań Naukowych Wydziału Psychologii Uniwersytetu Warszawskiego; EAN 03/04/2020), Warsaw, Poland. All study participants provided written informed consent.

Materials

Self-Report Variables

Self-report variables included demographic characteristics, stressor exposure, mental health, potential psychological resilience, and, to a lesser extent, risk factors. RFs are grouped into primary and secondary RFs. Primary RFs are of main interest in this study based on previous findings and the theoretical background of our consortium [9,36,40], whereas secondary RFs are based on hypotheses drawn from the literature. Where available, validated versions of the questionnaires and their translations into the site-specific languages were used. Self-developed questionnaires are provided at the Center for Open Science, Open Science Framework (OSF) [52]. Refer to Tables 2-5 for an overview of all questionnaires and Table S1 in Multimedia Appendix 2 [37,53-55] for an overview of all collected sociodemographic information. Refer to Multimedia Appendix 3 for an overview of validation studies of all questionnaires and their translated versions used at the different study sites.

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Table 2. List of self-report questionnaires on stressor exposure. Please note that only the original publications are cited here and not the validation studies of versions translated into the 4 study languages. Self-developed questionnaires are provided at the Center for Open Science [52].

Name	Construct
Life Events Questionnaire	A total of 28 stressful life events (eg, death of a friend or family member, separation or divorce of the parents, and illness or injury). For each event, participants indicate whether and at what age it has occurred and how positive or burdensome it has been experienced [34].
List of COVID-19–related stressors	A list of 23 stressors specific to the COVID-19 pandemic (eg, being at increased risk for an infection, loss of social contact, and having COVID-19 symptoms), for which participants report whether the situation occurred and how burdensome it was perceived on a 5-point scale. The list was self-developed in March 2020 for the DynaCORE[a] studies on psychological resilience during the COVID-19 pandemic [36,40].
Mainz Inventory of Microstressors	A total of 58 minor stressors of daily life (eg, loss or displacement of an object, conflict, bad weather, and traffic). Participants report whether the events have occurred and how straining they were experienced on a 5-point scale [56].

[a]DynaCORE: DynaMORE Study on Psychological Resilience to the Mental Health Consequences of the Corona Crisis.

Table 3. List of self-report questionnaires on mental health status. Please note that only the original publications are cited here and not the validation studies of versions translated into the 4 study languages.

Name	Construct
General Health Questionnaire	Symptoms of anxiety, depression, insomnia, social problems, and somatic symptoms. This inventory is designed to capture the inability to carry out normal functions and the appearance of new and distressing phenomena in the general population (28 items) [35].
Revised Symptom Checklist 90	Psychological distress in terms of 9 primary symptom dimensions including somatization, obsessive-compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, and psychoticism (90 items) [57].
WHO[a] Disability Assessment Schedule	Functioning and disability in accordance with the International Classification of Functioning, Disability, and Health (12 items) [58].

[a]WHO: World Health Organization.

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Table 4. List of self-report questionnaires used to assess primary resilience and risk factors. Please note that only the original publications are cited here and not the validation studies of versions translated into the 4 study languages. Self-developed questionnaires are provided on the Open Science Framework website [52].

Name	Construct
Brief Resilience Scale	The subjective ability to cope with and recover from stress (10 items) [59].
Cognitive Emotion Regulation Questionnaire	Different strategies of emotion regulation such as self-blame, other blame, rumination, catastrophizing, positive re-focusing, planning, positive reappraisal, putting into perspective, and acceptance (18 items) [60].
Coping Orientation to Problems Experienced Inventory	Emotion regulation strategies such as self-distraction, active coping, denial, substance use, use of emotional support, use of instrumental support, behavioral disengagement, venting, positive reframing, planning, humor, acceptance, religion, and self-blame (28 items) [61].
General Positive Appraisal Style Scale–content based	General style of positive appraisal in stressful situations, focusing on appraisal contents (29 items; self-developed). Validation and condensation into a PASS-content[a] in progress.
General Self-Efficacy Scale	Perceived ability to cope with a variety of difficult demands in life (10 items) [62].
Internal External Locus of Control-4	Degree to which individuals perceive themselves the outcomes of their behavior to be determined by their own actions or by forces outside their control (4 items) [63].
Life Orientation Test–Revised	Dispositional optimism and pessimism (10 items) [64].
NEO[b]-Neuroticism	Neuroticism scale of the NEO Five Factor Inventory (12 items) [65].
Oslo 3 Item Social Support Scale	Degree to which participants perceive themselves as surrounded by people who are close, concerned, and supportive [66].
Perceived Positive Appraisal Style Scale—process based	Assessment of positive appraisal style focusing on cognitive processes that generate positive appraisal contents in stressful situations (as opposed to assessment of the resulting appraisal contents themselves, as in PASS-content above in this section). PASS-process[c] includes correlated items of the Brief COPE[d], the CERQ[e] short, as well as 2 own-formulated items on distancing (detachment), which are all readily interpretable as indexing processes leading to positive appraisals (distancing, positive reappraisal, acceptance, putting into perspective, and humor). A previous version is referred to as PASS[f] in the study by Veer et al [36].
Psychological Flexibility Questionnaire	Subjective psychological flexibility, assessed via 5 factors including positive perception of change, characterization of the self as flexible, self-characterization as open and innovative, a perception of reality as dynamic and changing, and a perception of reality as multifaceted (20 items) [67].

[a]PASS-content: Perceived Positive Appraisal Style Scale—content focused.

[b]NEO: Neuroticism: Extraversion Openness.

[c]PASS-process: Perceived Positive Appraisal Style Scale—process focused.

[d]COPE: Coping Orientation to Problems Experienced Inventory.

[e]CERQ: Cognitive Emotion Regulation Questionnaire.

[f]PASS: Perceived Positive Appraisal Style Scale.

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Table 5. List of self-report questionnaires used to assess secondary resilience and risk factors. Please note that only the original publications are cited here and not the validation studies of versions translated into the 4 study languages. Self-developed questionnaires are provided at the Center for Open Science [52].

Name	Construct
Anxiety Sensitivity Index	Beliefs of negative implications of anxiety experiences (18 items) [68].
Bem Sex Role Inventory	Subjective gender roles (30 items) [69,70].
Body Awareness Questionnaire	Subjective attentiveness to nonemotive body processes, such as the sensitivity to body cycles and rhythms, the ability to detect small changes in normal functioning, and the ability to anticipate bodily reactions (18 items) [71].
Connor-Davidson Resilience Scale	Subjective ability to cope with stress (10 items) [72].
Dimensional Anhedonia Rating Scale	Multiple facets of hedonic function such as desire, motivation, effort, and consummatory pleasure across hedonic domains (17 items) [73].
Emotion Regulation Questionnaire	Habitual use of the emotion regulation strategies “cognitive reappraisal” and “expressive suppression” (10 items) [74].
Green Space Questionnaire and geographic information	Self-developed questionnaire assessing the degree to which participants have access to and make use of green spaces (parks and forests) in their living environment. In combination, geographic analysis of a participant’s address data is used to determine the degree of green space in their living environment (12 items).
Maltreatment and Abuse Chronology of Exposure	Abuse and neglect during development (52 items) [75].
Perceived Social Status Scale	Subjective socioeconomic status by means of a drawing of a ladder with 10 rungs, described to represent where people stand in society. Participants are instructed to indicate the rung that best represents where they stand on the ladder. In addition, the same question is asked for the dimensions of academic and occupational status [76].
Ruminative Thought Style Questionnaire	Components of ruminative thinking including problem-focused thoughts, counterfactual thinking, repetitive thoughts, and anticipatory thoughts (15 items) [77].
Sensitivity to Punishment and Sensitivity to Reward Questionnaire	Tendency for aversive and appetitive behavior (48 items) [78].
State Trait Anxiety Inventory	Symptoms of anxiety as a state and as a general trait (40 items) [79].
Toronto Alexithymia Scale	Deficiency in understanding, processing, or describing emotions (20 items) [80].

Neuropsychological Measures

The neuropsychological test battery included paper-pencil paradigms such as the Trail Making Test [81,82] to assess visual attention and task switching speed, the Hamburg-Wechsler-Intelligenztest für Erwachsene (HAWIE) Matrices to assess nonverbal logical reasoning [83], and the HAWIE Digit Symbol Test to assess processing speed [83]. Furthermore, a computer-based paradigm, the Stab/Flex task [53,54], was administered to assess cognitive flexibility (refer to section 1 and Figure S1 in Multimedia Appendix 2).

Neuroimaging

Magnetic Resonance Imaging Data Acquisition

At all sites except for Warsaw, brain imaging data were acquired using identical models of 3 Tesla MAGNETOM Prisma systems (Siemens Healthineers) with 32-channel head coils (at TAU 64-channel head coil) using the following settings: multiband gradient-echo echo planar imaging (EPI) sequences (repetition time [TR]=800 ms, time to echo [TE]=37 ms, flip angle=52°, field of view [FOV]=208 mm, voxel size=2.0 × 2.0 × 2.0 mm, 72 slices, multiband acceleration factor=8, and phase-encoding direction=posterior to anterior [PA]) from the Center for Magnetic Resonance Research, University of Minnesota, as adopted from the Human Connectome Project, were used for blood oxygen–level dependent fMRI [84]. Before each task, a pair of blip-up and blip-down EPI sequences were acquired (TR=8000 ms, TE=66 ms, flip angle=90°, FOV=208 mm, and voxel size=2.0 × 2.0 × 2.0 mm), 1 with an anterior to posterior phase-encoding direction and 1 with a PA phase-encoding direction. Furthermore, a T1-magnetization-prepared rapid gradient echo (MPRAGE) sequence (TR=2500 ms, TE=2.22 ms, flip angle=8°, FOV=256 mm, and voxel size=0.8 × 0.8 × 0.8 mm), a fluid-attenuated inversion recovery (FLAIR) sequence (TR=9000 ms, TE=83 ms, flip angle=150°, FOV=220 mm, and voxel size=0.7 × 0.7 × 3.0 mm), and 2 diffusion-weighted imaging sequences (1. TR=3600 ms, TE=92 ms, flip angle=78°, FOV=210 mm, voxel size=2.0 × 2.0 × 2.0 mm, 50 directions b=1000, 50 directions b=2000, 5 b0 volumes, multiband acceleration factor=3, phase-encoding direction=anterior to posterior and 2. TR=3600 ms, TE=92 ms, flip angle=78°, FOV=210 mm, voxel size=2.0 × 2.0 × 2.0 mm, 6 directions b=2000, multiband acceleration factor=3, phase-encoding direction=PA), adopted from the UK Biobank scan protocol [85], were acquired.

In Warsaw, a 3 Tesla MAGNETO Trio system was used. There, multiband gradient-echo EPI sequences were acquired with the following settings: TR=1410 ms, TE=30.4 ms, flip angle=56°, FOV=210 mm, voxel size=2.5 × 2.5 × 2.5 mm, 60 slices, multiband acceleration factor=3, and phase-encoding direction=PA. Blip-up and blip-down EPI sequences before each task (identical settings as other sites, except for voxel

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size=2.5 × 2.5 × 2.5 mm), T1-MPRAGE (TR=1100 ms, TE=3.32 ms, flip angle=7°, FOV=256 mm, voxel size=1.0 × 1.0 × 1.0 mm), a FLAIR sequence with identical settings as described in the previous paragraph, and 2 diffusion-weighted imaging sequences (identical settings as above, except TE=97 ms) were acquired as well.

Head movement was restricted by foam pads and a tape on the forehead. All task paradigms were presented using the software Presentation (Neurobehavioral Systems) [86] on a monitor placed behind the scanner bore via a mirror that was fixed on the head coil.

Reward Sensitivity

To capture neural responses during reward and loss anticipation, an adapted version of the monetary incentive delay task [87] was used, as described in detail by Kampa et al [37]. Participants were instructed that they can win or lose a small amount of money if they pressed a button fast enough as soon as the target stimulus appeared on the screen. Before the target appeared, participants were presented with a cue for 2 seconds, which indicated whether they could win or lose money in the current trial (+€3, 12, or zł12; +€0.5, 2, or zł2; ±0; −€0.5, 2, or zł2; and −€3, 12, or zł12). The conversion rates at the time of study enrollment were €1=US $1.17, 1=US $0.29, and zł1=US $0.26. The cue was followed by a jittered anticipation phase of 2 to 2.5 seconds, after which participants had to press a button as soon as a target stimulus (white star) appeared on the screen. Each trial ended with a 2-second numeric feedback on the participant's trial outcome and the overall gain. To ensure that the reward experience did not differ between participants depending on task performance, an adaptive algorithm was applied that changed the target duration for the participant within each condition based on their past performance. If the participant's hit rate was <66%, the target duration was increased by 25 ms; otherwise, it was reduced by 25 ms. Reaction times and hit rates were collected as behavioral outcomes. A graphical depiction of the task design is provided in Figure S2 in Multimedia Appendix 2.

Differential Fear Conditioning

We used the fear conditioning part of a safety learning and memory paradigm, as described by Kampa et al [37]. Three different geometrical shapes (squares, circles, and triangles) served as the CS. Electrotactile stimuli delivered to the back of the right hand were used as the unconditioned stimuli. Two background images of different conference rooms were inherited from the original paradigm in which they served as context variables. Each background image showed a screen on which the CS were depicted to make them part of the scene in a naturalistic way (Figure S3 in Multimedia Appendix 2). Before the main experiment, a short training session was given during which the different stimuli and the rating scale were shown, but no electric stimuli were delivered. During the experiment, 2 of the CS were paired with an unconditioned stimulus in 100% of the trials. These stimuli worked as CS+. The other stimulus (CS−) was never paired with an unconditioned stimulus. Each CS trial lasted for 6 seconds. During the first 4.5 seconds of the trial, participants rated their fear of receiving an electric stimulus between 1 and 100 using a visual analog scale at the bottom of the screen. The intertrial intervals lasted from 9 to 15 seconds. The background images and stimuli were counterbalanced across participants.

The stimulus intensity was calibrated beforehand using a calibration procedure developed to reach a stimulus level that was highly unpleasant but not painful. Participants received an initial stimulus at the lowest level (1) and were asked to rate its severity on a scale ranging from 1 (not unpleasant at all) to 5 (painful). The desired rating was 4. Stimulus intensity was adapted after each stimulus according to a predefined scheme (Figure S4 in Multimedia Appendix 2).

Stimulation was performed using 2 sticky electrodes (INVISATRACE Adult electrocardiography (ECG) Electrode) placed on the back of the hand. Except for the DCCN, all sites used a Digitimer DS7A stimulator. One electrical stimulation consisted of a train of 3 square-wave pulses of 2-ms duration each, with an interval of 50 ms apart from each other. The electric potential was 400 V, and the current varied with the calibration, starting at a minimum of 10 mA. At the DCCN, the electric stimuli were delivered using an Innostim Tens 2000 (formerly named MAXTENS2000, Bio-Protech Inc) [88]. The stimulus duration was 200 ms, and the intensity ranged between 0 V to 40 V and 0 mA to 80 mA.

At TAU, the electric stimulus was replaced by white noise with a duration of 50 ms. The volume was maximized to create a startle response. All the other conditions (background and reinforcement schemes) remained the same. A pilot study at TAU revealed similar activation patterns as the typical activation patterns found using an electric stimulus.

Situation-Focused Volitional Reappraisal

In this task, participants were instructed to positively reinterpret or just view photographs that are either negative, positive, or neutral and to rate their affective state on a nonverbal scale. The paradigm has been previously described by Kampa et al [37] and was adapted from the study by Kanske et al [89]. Stimuli were selected from the International Affective Picture System and EmoPics [90] based on normative ratings of valence and arousal [91]. In a fully balanced, 3-by-2 factorial design, the 3 types of picture valences were combined with either situation-focused reappraisal or viewing the pictures as a control condition (Figure S5 in Multimedia Appendix 2).

Implicit Emotion Processing

To assess neural responses during implicit emotion processing, we used an adaptation of the face matching task [48,49]. In each trial, participants were presented with a trio of pictures and were instructed to select the matching pair by pressing a button. In the emotion condition, the trios contained grayscale photographs of Ekman faces [92] with angry or fearful expressions, counterbalanced for sex and emotion valence. In the control condition, the trios contained geometric shapes (circles, horizontal ellipses, and vertical ellipses). Four blocks per condition were presented in alternation. Each block consisted of 1 instruction (2 seconds) and 6 trials (5 seconds each; refer to Figure S6 in Multimedia Appendix 2 for the task design).

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Resting State

A resting-state scan was acquired before and after the stress task, during which participants were instructed to keep their eyes open and to focus on a fixation cross on the screen.

Social Stress

To examine brain activation and cortisol levels in response to stress, an adaptation of the ScanSTRESS paradigm was used [93-95]. In this task, the participants were instructed to perform mental rotation and arithmetic subtraction exercises. During the performance, task speed and difficulty were automatically adjusted so that the participants fail most of the tasks. Furthermore, participants were presented with a live video screen showing the face of the experimenter observing and giving negative nonverbal feedback on the performance. Thus, the task involves both social evaluative threat components (verbal and nonverbal feedback from the experimenter) and uncontrollable components (task difficulty, time constraints, and mock feedback of poor performance). The original version of the task is composed of 2 runs, both containing control (no feedback and no video) and stress (feedback and live video of experimenters) blocks, 1 run before and 1 after negative verbal feedback by the experimenter. Here, we used the adapted version by Sandner et al [47], in which all stress blocks are presented in one run and all control blocks in another run, both presented before and after negative verbal feedback by the experimenter. However, we shortened this version by discarding the control runs and using only stress runs. Specifically, a shorter practice run of stress blocks was presented first, followed by negative verbal feedback, after which a full run of stress blocks was presented during scanning. Brain responses to the stress paradigm are estimated by comparing task blocks with baseline (fixation cross). An overview of the task design is provided in Figure S7 in Multimedia Appendix 2.

Biosamples

Blood was collected for the purpose of DNA extraction from whole blood (to determine participants' genotype and DNA methylation patterns using next-generation sequencing) and—at 2 sites only—for blood plasma preparation (to perform proteome analyses using immunoassays). Additional blood collected at 1 site was used to determine interleukin (IL)-10, IL-6, tumor necrosis factor α (TNF-α), and C-reactive protein levels. Stool samples were collected for the purpose of gut microbiome analysis by 16S rRNA profiling. Saliva samples were collected to determine cortisol and α-amylase levels. Details of the analyses performed will be provided in individual publications.

Ambulatory Assessments

During monthly burst weeks (6 days) in phase 1, EMA and EPA were measured.

EMA Technique and Design

At the beginning of each burst week, participants received a smartphone (Motorola Moto E6 Play) with the app "RADAR-active RMT (Remote Assessment of Disease and Relapse Remote Monitoring Technology)" for EMA data collection [96]. Questionnaires were sent 10 times per day during the participants' usual wakening hours using push notifications ("beeps"). Notifications were scheduled to appear within 90-minute blocks semirandomly, that is, for all participants, the notifications appeared at the same time. Similarly, 2 notifications never occurred closer than 15 minutes to each other (refer to Table S2 in Multimedia Appendix 2 for the beep schedule). The participants received a reminder notification 5 minutes after the initial notification. The EMA questionnaire remained available for 10 minutes after the initial push notification. Every beep questionnaire (approximately 3 minutes) included in-the-moment self-assessments of mood, (virtual) social context, physical context, event appraisal, substance use, and anticipation of pleasure. In addition, participants were instructed to start a separate morning questionnaire (approximately 1 minute) about the previous night's sleep immediately after waking up. Immediately before going to bed, participants were instructed to start an evening questionnaire (approximately 2 minutes) about the evaluation of the day, the most negative and positive event of the day, stress anticipation for the upcoming day, and whether the questionnaire influenced their mood during that day. All EMA items are shown in Figures S8 and S9 in Multimedia Appendix 2.

EPA Technique

EPA was measured for 23 hours a day during each burst week using the Chill+ wristband developed by Interuniversity Microelectronics Centre [97]. The wristband measures the photoplethysmography-based heart rate, galvanic skin response, skin temperature, and movement through a 3-axis accelerometer and 3-axis gyroscope. Furthermore, participants were instructed to press a button on the wristband to actively report stressful events.

Procedure

Overview

Participants underwent a screening for inclusion criteria, 2 assessment days at baseline (Table 6), and longitudinal follow-up assessments (phase 1 and phase 2; Multimedia Appendix 4). Before each on-site appointment, a short screening interview about potential COVID-19 symptoms including measurements of or questions regarding body temperature was conducted to minimize the risk of transmission. The participants and experimenters wore filtering facepiece masks (level 2) or surgical masks, used disinfectants, and maintained a distance of at least 1.5 m.

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Table 6. Procedure steps at baseline days 1 and 2. Note that, before each functional magnetic resonance imaging sequence, a field map scan was acquired. The total duration of the imaging battery was approximately 2 hours.

Procedure step and task/interview/test	Self-ratings	Duration[a] (mm:ss)
Day 1		
On-site screening interviews		
Informed consent	__[b]	—
MINI[c]	—	—
Drug screening	—	—
Neuropsychological tasks		
StabFlex	—	—
Trail making test	—	—
Digit symbol test	—	—
Matrices test	—	—
Biological samples		
Blood	—	—
Stool instruction	—	—
Postassessment interviews		
Longitudinal schedule	—	—
Online questionnaire briefing	—	—
Emotional disturbances interview	—	—
Day 2		
Pre MRI[d]		
Drug screening	—	—
MRI training	—	—
MRI battery		
Saliva sample 1	Perceived stress	—
Reward sensitivity task	—	08:26
Saliva sample 2	Perceived stress	—
Fear conditioning calibration	—	—
Fear conditioning task	—	12:10
Saliva sample 3	Perceived stress	—
T1 weighted image	—	06:54
Reappraisal task	Performance	13:06
Saliva sample 4	Perceived stress	—
Faces matching task	—	04:34
FLAIR[e]	—	02:44
Preresting state	Perceived stress	—
Resting state 1	—	07:10
Saliva sample 5	Perceived stress	—
ScanSTRESS training	—	—
ScanSTRESS task	—	06:26
Post ScanSTRESS	Perceived stress	—
Resting state 2	—	07:10

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Procedure step and task/interview/test	Self-ratings	Duration[a] (mm:ss)
Saliva sample 6	Perceived stress	—
DTI[f]	—	06:32
Out of scanner	—	—
Post MRI		
Saliva sample 7	Perceived stress	—
MRI exit interview	—	—
EMA[g]/EPA[h] briefing	—	—
Saliva sample 8 (20 minutes after Saliva sample 7)	Perceived stress	—
Saliva sample 9 (20 minutes after Saliva sample 8)	Perceived stress	—
MRI debriefing	—	—

[a]Durations are reported in the format minutes:seconds and are only mentioned for the MRI tasks, which had exactly the same durations for all participants.
[b]Self-ratings are only mentioned where applicable.
[c]MINI: Mini-International Neuropsychiatric Interview.
[d]MRI: magnetic resonance imaging.
[e]FLAIR: fluid-attenuated inversion recovery.
[f]DTI: diffusion tensor imaging.
[g]EMA: ecological momentary assessment.
[h]EPA: ecological physiology assessment.

Recruitment and Prescreening

Participants were recruited via web-based advertisements in mailing lists and on social media platforms. After receiving brief information about the study purpose, methods, and prerequisites, participants were invited to anonymously fill in a web-based screening survey via the platform SoSci Survey [98], in which the eligibility criteria (Table 1) of the study were checked using an automated algorithm. When starting the screening survey, participants were instructed to generate an anonymous code, which they later provided to the study staff in case of their inclusion, to link their screening data to their participant ID. The screening data of nonincluded participants remained anonymous. After completing the web-based screening questionnaire, eligible participants received an invitation to participate and a request to contact their study site. The complete study information material was then sent to the participants via email, and an on-site appointment was made.

On-site Screening

During the on-site appointment, the participants received verbal information about the study and provided written informed consent. Then, further inclusion criteria were assessed in a standardized interview with trained researchers (Mini-International Neuropsychiatric Interview [MINI] [51]). Afterward, a urine-based drug screening test (SureStep Multi-Drug One Step Screen Test Panel, Innovacon Inc) for amphetamine, barbiturates, benzodiazepines, buprenorphine, clonazepam, cocaine, fentanyl, heroin, ketamine, cannabis, methadone, methamphetamine, methylenedioxymethamphetamine, morphine, opiate oxycodone, phencyclidine, propoxyphene, tramadol, and tricyclic antidepressants was administered, after which participants who were included started with the baseline assessment (baseline day 1).

Baseline Day 1

Baseline assessments were distributed across 2 appointments on 2 days (Table 1).

Neuropsychological Assessments

During neuropsychological assessments, 1 participant per session was assessed by 1 study assistant. The participant was placed at a desk with a computer in a room with minimized potentially distracting stimulation (eg, noise, visual distractions, and other people). Telephones were muted or in airplane mode. The first task (Stab/Flex) was presented on the computer, and all other tasks were instructed verbally and executed in a paper-and-pencil format (refer to the *Materials* section).

Blood Sampling

One blood sampling was performed at baseline day 1 or baseline day 2, and another one was performed at month 6 (Multimedia Appendix 4). Nine milliliters of blood (10 at DCCN) was drawn from each participant into an ethylenediaminetetraacetic acid (EDTA) tube (red monovette; Sarstedt) and stored as whole blood at −20 °C or colder until assay of DNA and DNA methylation. At the study sites NIC and DCCN, an additional 9 mL (NIC) or 10 mL (DCCN) of blood was sampled into EDTA tubes for proteomic analyses. At these sites, all blood was drawn between 12:30 PM and 3:30 PM, and participants arrived at least 5 hours sober to limit the influence of metabolism or diurnal oscillations on proteomics measurements. Blood samples for the proteomics assay were centrifuged, and serum was divided into 8 to 16 aliquots (depending on volume), which were stored at −80 °C until assay. At TAU, 2 additional tubes (1 EDTA and 1 VACUETTE TUBE 3.5 mL coagulation

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activator tube Serum Separator Clot Activator) of blood samples were taken between month 1 and month 6 to derive IL-10, IL-6, TNF-α, and C-reactive protein.

Stool Sampling

Stool samples were collected using an OMNIgene-gut feces kit (OM-200, DNAgenotek). Participants received a test kit, an instruction sheet about the collection procedure, the Bristol Stool Scale [99], and verbal instructions from the test leader. Participants were instructed to collect the stool sample as close as possible to the appointment, to take several small samples from different locations in the stool material, to fill out the Bristol Stool Scale, and to store the sample in a dark place without direct sunlight. Participants brought the sample to the study center at the next appointment, where it was stored at −20 °C until the assay of the gut microbiome, or, at DCCN, directly shipped to the laboratory processing the microbiome.

Postassessment Procedures

After the baseline day 1 assessments, a personalized schedule was created with the participant, indicating the upcoming magnetic resonance imaging (MRI) appointment and timings of the upcoming phase 1 and phase 2 assessments. Furthermore, participants received all necessary information about the web-based questionnaires and were introduced to the web-based survey platform SoSci Survey [98] by filling out a dummy questionnaire. Finally, to ensure the participant's well-being, they were asked if they have experienced emotional disturbances triggered by any questions asked during the preceding session in a standardized interview. If they reported emotional disturbance and a need for help, they were directed to a clinician associated with the study.

Baseline Day 2

Overview

At baseline day 2, neuroimaging and a briefing about ambulatory assessments were performed. Before testing, participants returned their stool sample (except for DCCN), and another urine-based drug screening test (refer to the description for baseline day 1) was conducted. Participants with a negative test result then received a brief training session on MRI paradigms. During the training, they were given an on-screen presentation of the tasks, and the experimenter explained the tasks and asked questions to ensure that the participants understood the instructions. To account for diurnal or metabolism-related variations in cortisol levels, all scanning took place between 12:30 PM and 5 PM. Participants were instructed to get up from bed at least 4 hours before the appointment; not to eat, smoke, or drink beverages containing caffeine or sugar at least 2 hours before starting the MRI; to refrain from physical exercise that day; and not to drink alcohol within 24 hours before the appointment. They were reminded of these instructions via email before the appointment.

Physiological and Subjective Measures During Neuroimaging

During all fMRI sequences, the participants' heart rates were assessed using a wireless pulse oximeter (Siemens Healthineers). Furthermore, to assess salivary cortisol levels in response to the MRI tasks, 9 saliva samples were collected before, in between, and after the scanning sequences using Salivette collection kits (Sarstedt). For each saliva sample, the participant's subjective level of distress was assessed on a scale from 0 (not stressed) to 10 (extremely stressed). Before scanning, the participants were introduced to the saliva sampling technique while donating their first saliva sample. The participant received a plastic tube containing a cotton swab and was instructed to put the cotton swab into their mouth without touching it with their fingers. They were instructed to moisten the cotton swab for 1 minute and to put it back into the plastic tube. This procedure was repeated for 8 times, of which the participant was inside the scanner 5 times (Table 6).

Neuroimaging

When placed in the MRI scanner, the participants were provided with earplugs. To respond to tasks during functional MRI scans, participants operated a 4-button Inline Fiber Optic Response Pad (Current Designs; home-designed system in Warsaw [100]) with their right hand. Further, an electrode for the fear conditioning task was attached to the back of the right hand. A wireless pulse oximeter was attached to the index finger of their left hand. Via a mirror placed on the head coil, they were presented with the visual stimulation of the tasks on a monitor placed behind the scanner bore. Before and after each task, the test leader provided verbal instructions via an intercom system and received feedback from the participant. Specific instructions were repeated verbally on the screen and by the test leader before each task. An overview of the procedure steps during neuroimaging and further details of the tasks are provided in Table 6 and Multimedia Appendix 2. After scanning, participants were asked to fill in an MRI exit interview questionnaire (paper-pencil), which asked about the experiences and potential difficulties with the fMRI tasks.

EMA and EPA Briefing

After scanning, the participants were thoroughly briefed on the EMA and EPA devices and procedures. Contraindications for using the wristband collecting EPA (skin disease around the wrist area, wounds or skin allergies, and medication with phototoxic side effects) were ruled out. The devices (mobile phone, wristband, and chargers) were handed to the participants, and their functions were explained. Furthermore, the purpose of EMA and EPA, the app, and questionnaires were explained, and it was discussed with the participant how to ensure that beeps are not missed in everyday life. Further details are provided in the *Materials* section and Multimedia Appendix 2.

Post-MRI Debriefing

After donating their last saliva sample, participants were debriefed about the stress task (refer to the *Materials* section) and were informed that the task was programmed to adapt to the participant's performance and induce stress, instead of measuring their cognitive performance. Furthermore, identical to baseline day 1, participants were interviewed about emotional disturbances triggered by any questions asked during the preceding session in a standardized fashion. If they reported emotional disturbance and a need for help, they were offered counseling by a clinician associated with the study.

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Longitudinal Phase 1

In the first week after the baseline day, a baseline battery of questionnaires was administered on the web. Longitudinal phase 1 spanned from month 1 to month 6 and contained the web-based monitoring for the FRESHMO paradigm [13]. In biweekly web-based questionnaires, stressor exposure, mental health problems, and process-based PAS (PASS-process) were assessed on the web. For this, participants received a link to the SoSci Survey platform at the beginning of each web-based monitoring week and had 1 week to complete the questionnaire. Furthermore, 1-week EMA and EPA assessments took place in the second week of each of the 6 study months, for which participants received 10 beeps per day (Multimedia Appendix 4).

Before and after the EMA and EPA weeks, the participants came to the laboratory to pick up or return the devices used for EMA and EPA (smartphones and wristbands). During these appointments, the participants were again interviewed about potential emotional disturbances to ensure their well-being. At months 3 and 6, further stool samples were collected. At month 6, a second blood sample was collected (Multimedia Appendix 4).

Longitudinal Phase 2

In longitudinal phase 2, which spanned from month 7 to 9, assessments of stressor exposure, mental health problems, and PASS-process took place only once a month, and no EMA and EPA was conducted. The final questionnaire battery at month 9 contained additional assessments of the resilience factors (Multimedia Appendix 4).

Remuneration

Complete participation in all assessments was remunerated with €290 (1224 in Tel Aviv and zł1200 in Warsaw). Participants could win about €10, 40, or zł40 on average during the reward task in the neuroimaging battery. Furthermore, those who completed all assessments until month 6, week 3, were included in a lottery to win 1 out of 3 additional awards of €100, 400, or zł400. To maintain compliance throughout the longitudinal assessments, money was disbursed in tranches at different timepoints throughout the study (Table S3 in Multimedia Appendix 2). The conversion rates to at the time of study enrollment were €1=US $1.17, 1=US $0.29, and zł1=US $0.26.

Results

Participant inclusion started in October 2020, and data acquisition was completed in June 2022. A total of 249 participants completed baseline days 1 and 2, whereas 209 completed the EMA part of longitudinal phase 1, and 153 completed longitudinal phase 2. At the time of manuscript submission, preprocessing and quality checks of the data are ongoing. First results are expected to be published by the end of 2023.

Discussion

Aims of This Study

DynaM-OBS targets a gap in resilience research: providing a dense longitudinal database to assess resilience as a long-term outcome and the underlying resilience processes. This approach and framework offer new possibilities to test current hypotheses about putative resilience factors as well as to explore novel ones. Specifically, our main hypothesis is that a PAS is both contemporaneously and prospectively predictive of resilience, operationalized as SR. Moreover, we expect several secondary predictors of resilience, ranging from specific brain network configurations during acute stress to high reward sensitivity, threat safety discrimination, and volitional reappraisal processes, among others.

Strengths and Limitations

Despite its strengths, which are mainly reflected in the study's richness of longitudinal and multimodal data on resilience factors, processes, and outcomes, DynaM-OBS also has several limitations. Although we were trying to be exhaustive in our assessment of stressors (including potential life events, a large number of microstressors in a wide range of life domains, and pandemic-related stressors), we cannot exclude the possibility that some relevant types of adversity were missed. For example, we did not collect information on parental traumatic exposure, which may transmit to children, and did not ask specific questions on the exposure of participants to stressors that only became more apparent over the course of data collection (eg, Russia-Ukraine war). Moreover, because of the multicenter nature of our study, we could not entirely rely on previously validated questionnaires for each study site's language and therefore translated some questionnaires ourselves, without validating them. This may pose a threat to the construct equivalence and validity between the nonvalidated and validated versions of the questionnaires. Another consequence of the multicenter nature of DynaM-OBS is that different COVID-19 restrictions applied at the different sites. Among other things, this led to the interruption of participant inclusion at Charité–Universitätsmedizin Berlin from mid-December 2020 to the end of February 2021, although all other study sites continued participant inclusion. For the interested reader, we present an overview of the general COVID-19 situation at all sites over the course of data collection in Multimedia Appendix 1.

Conclusions

Despite these limitations, the dense investigation of the most important resilience factors and resilience processes and the multi-modal database generated in DynaM-OBS have the potential to serve as a foundation for future studies on interventions and trainings aiming to enhance resilience factors and adaptive processes in at-risk individuals.

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Acknowledgments

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Data Availability

Self-generated questionnaires are available at the Center for Open Science [52].

Authors' Contributions

CW, IMV, JMCL, ZR, RK, and HW drafted the manuscript. RK, HW, IMV, AA-V, BK, DK, EJH, HB, IM-G, JT, KR, KSLY, MM, OT, SP, TH, and WdR conceptualized and designed the study. CW, JMCL, ZR, AR, SB, NM, AL, JM, LP, AU, MZ, GK, JW, and KSLY acquired the data. All authors contributed to critical editing and revision of the manuscript. All authors have approved the submitted version of this manuscript. All authors have agreed to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even those in which the author was not personally involved, are appropriately investigated and resolved and that the resolution is documented in the literature.

Conflicts of Interest

RK receives advisory honoraria from JoyVentures, Herzlia, Israel. All other authors declare that they have no conflicts of interest.

Multimedia Appendix 1
Overview of the COVID-19–related situation during data acquisition per country.
[XLSX File (Microsoft Excel File), 23 KB - resprot_v12i1e39817_app1.xlsx]

Multimedia Appendix 2
Supplementary information.
[DOCX File , 1559 KB - resprot_v12i1e39817_app2.docx]

Multimedia Appendix 3
Overview of questionnaire validations for the different study languages.
[XLSX File (Microsoft Excel File), 24 KB - resprot_v12i1e39817_app3.xlsx]

Multimedia Appendix 4
Overview of the measures used and the days (d), weeks (w), and months (M) from baseline at which they are assessed (x).
[DOCX File , 37 KB - resprot_v12i1e39817_app4.docx]

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Abbreviations

CS: conditioned stimuli
DCCN: Donders Centre for Cognitive Neuroimaging
DynaCORE-L: The DynaMORE Longitudinal Study on Psychological Resilience to the Mental Health Consequences of the Corona Crisis
DynaM-INT: DynaMORE intervention study
DynaM-OBS: Dynamic Modelling of Resilience–Observational Study
DynaMORE: Dynamic Modelling of Resilience
EAN: ethics approval number
EDTA: ethylenediaminetetraacetic acid
EMA: ecological momentary assessment
EPA: ecological physiological assessment
EPI: echo planar imaging
FLAIR: fluid-attenuated inversion recovery
fMRI: functional magnetic resonance imaging
FOV: field of view
FRESHMO: frequent stressor and mental health monitoring
GHQ: General Health Questionnaire
HAWIE: Hamburg-Wechsler-Intelligenztest für Erwachsene
IL: interleukin
LORA: Longitudinal Resilience Assessment
MARP: Mainz Resilience Project
MINI: Mini-International Neuropsychiatric Interview
MPRAGE: T1-magnetization-prepared rapid gradient echo
NIC: Neuroimaging Center
OSF: Open Science Framework
PA: posterior to anterior
PAS: positive appraisal style
PASS-content: Perceived Positive Appraisal Style Scale—content focused
PASS-process: Perceived Positive Appraisal Style Scale—process focused
PASTOR: positive appraisal style theory of resilience
RF: resilience and risk factors
SR: stressor reactivity
TAU: Tel Aviv University
TE: time to echo
TNF-α: tumor necrosis factor α
TR: repetition time

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Protocol

Indigenous Women and Their Nutrition During Pregnancy (the Mums and Bubs Deadly Diets Project): Protocol for a Co-designed mHealth Resource Development Study

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Abstract

Background: Nutrition in pregnancy is pivotal to optimizing infant growth and maternal well-being. The factors affecting Indigenous people's food and nutrition intake are complex with a history of colonization impacting the disproportionate effect of social determinants to this day. Literature regarding the dietary intake or dietary priorities of Indigenous women in Australia is scarce, with supportive, culturally appropriate resources developed for and with this group rare. Research suggests mobile health (mHealth) tools are effective in supporting health knowledge of Indigenous people and positive health behavior changes when designed and developed with the expertise of Indigenous communities.

Objective: This study seeks to build the body of knowledge related to nutrition needs and priorities for Indigenous women in Australia during pregnancy. Further, this project team and its participants will co-design an mHealth digital tool to support these nutrition needs.

Methods: The Mums and Bubs Deadly Diets study recruits Indigenous women and health care professionals who support Indigenous women during pregnancy into 2 phases. Phase 1 (predesign) uses a mixed methods convergent design using a biographical questionnaire and social or focus groups to inform phase 2 (generative). Phase 2 will use a participatory action research process during co-design workshops to iteratively develop the digital tool; the exact actions within a workshop will evolve according to the participant group decisions.

Results: To date, this project has undertaken phase 1 focus groups at all Queensland sites, with New South Wales and Western Australia to begin in early to mid-2023. We have recruited 12 participants from Galangoor Duwalami, 18 participants from Carbal in Toowoomba, and 18 participants from Carbal in Warwick. We are expecting similar numbers of recruits in Western Australia and New South Wales. Participants have been both community members and health care professionals.

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Conclusions: This study is an iterative and adaptive research program that endeavors to develop real-world, impactful resources to support the nutrition needs and priorities of pregnant Indigenous women in Australia. This comprehensive project requires a combination of methods and methodologies to ensure Indigenous voices are heard at each stage and in all aspects of research output. The development of an mHealth resource for this cohort will provide a necessary bridge where there is often a gap in access to nutrition resources for women in pregnancy in Indigenous communities.

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KEYWORDS

co-design; community-based participatory research; mHealth; Aboriginal and Torres Strait Islander; maternal health; pregnancy; nutrition; Indigenous women; diet; health literacy; Indigenous; Indigenous people; mobile phone

Introduction

Pregnancy is an opportune time for promoting nutrition and health behaviors given the nutritional needs of rapid mental growth and development [1,2]. Inadequate intake of key nutrients during pregnancy can have lifelong effects on brain function and in childhood. It can lead to stunting and increased risk of chronic disease in adulthood, including obesity, cardiovascular, metabolic, and endocrine diseases [3]. Globally, it has been reported that women commonly find it challenging to meet the pregnancy nutrition targets [4]. In 2019, the National Health and Medical Research Council of Australia sought applications for a Targeted Call for Research that specifically addressed nutrition in Aboriginal and Torres Strait Islander Peoples with one of the identified areas identified for research being mothers and their children.

The factors affecting Aboriginal and Torres Strait Islander (hereinafter respectfully referred to as Indigenous) people's food and nutrition intake are complex. Colonization of Australia by European settlers since the late 18th century has created a legacy of trauma and dispossession for many members of Indigenous communities [5]. Traditional cultural practices that included ceremony, language, and the hunting, fishing, and gathering of diverse and rich animal and plant food sources were banned or greatly restricted by the colonizers, which has continued to impact the health of Indigenous communities nationally to this day [6]. Food insecurity, often linked to the introduction of Western diets, limited access to traditional food sources, and the prohibitive expense of and lack of access to nutritious foods in many homeland communities is an ongoing concern for Indigenous communities [5]. Social determinants, including housing, education, economic status, and access to services all impact on health. Indigenous Australians are disproportionately affected by food insecurity and socioeconomic determinants that can contribute to unhealthy food patterns (ie, the affordability of fast food) and development of diet-related chronic diseases [7]. For instance, Indigenous adults in Australia experience type 2 diabetes at a rate 3.3 times higher than non-Indigenous adults, this increases further in remote and very remote areas [8]. Lee and Ride [9] also reported that nutrition-related chronic conditions (diabetes, cardiovascular, and kidney diseases) account for at least 75% of the mortality gap between Indigenous and non-Indigenous adults.

In Australia, very few studies have explored what Indigenous Australian pregnant women are consuming or the quality of their dietary intake [9,10]. Further, there is a dearth of information regarding nutritional knowledge during pregnancy for Indigenous women; particularly lacking is literature describing Indigenous Australians' worldviews on their needs and priorities around pregnancy nutrition [11]. Lee and colleagues [10] published the first report on an Australian Indigenous cohort (n=56; the Gomeroi Gaaynggal cohort) exploring the nutritional adequacy of maternal dietary intake during pregnancy. When compared to the Australian Guide to Healthy Eating food groups serving recommendations, the analysis found that none of the women in this cohort met the recommended daily food group servings. In addition, of the 5 key nutrients for optimal reproductive health (folate, iron, calcium, zinc, and fiber), the nutrients with the highest percentage of pregnant women achieving the nutrition reference values were zinc (77.6%) and folate (68.9%), whereas iron was the lowest (1.7%) [10,11]. The authors recognized the low generalizability of the study, though called for urgent strategies to optimize the dietary patterns of pregnant women in this cohort. Iron, iodine, and folate are critical nutrients for growth and development, yet intakes are often reported as inadequate in general populations of pregnant women [11].

The use of digital tools such as mobile apps or websites to aid in knowledge sharing or tracking of health is defined as mobile health (mHealth). Often, Indigenous communities in Australia lack access to traditional health care, and mHealth has been successfully used to bridge this gap in some communities [12]. These instruments can be effective in supporting the health knowledge of Indigenous people and aid positive health behavior changes when designed and developed with the expertise of Indigenous communities [13]. A recent study of Aboriginal and Torres Strait Islander women aged 16 to 49 years found 89.2% owned a smartphone and 93.1% had access to the internet at home [14]. Furthermore, research suggests when development of mHealth tools is led by Indigenous peoples for inclusion of Indigenous participants, the outcomes are improved [12,15,16]. Though many existing mHealth options for Indigenous Australians focus on general health behaviors or mental health [13], to date, this form of health tool is currently underused for nutrition and pregnant women alike [15,17]. This project offers a unique opportunity for the co-design and development of an mHealth app or digital tool that enhances community members' understanding of health issues and actively engages women in

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the planning and management of their own nutrition during pregnancy. As part of ensuring that this project is easily identified by Indigenous community members as a culturally safe project, the title "Mums and Bubs Deadly Diets" has been chosen. In Australian slang, the term *bub* is often used for baby, and *deadly* is well-known slang within Australian Indigenous communities to mean something is excellent, wonderful, and community-driven.

This project team seeks further understanding of the behaviors of Indigenous women who are pregnant across approximately 7 sites of Australia. A mixed methods biographical survey and social or focus groups in phase 1 deliver the predesign phases of intervention and behavior stage mapping, while co-design workshops in phase 2 will address the digital tool elements necessary for program production and implementation. Ultimately, the goal is to create a digital tool that supports the provision of nutritional information and access to resources Indigenous Australian women require during pregnancy and to operate within holistically embedded Indigenous research values and principles.

Methods

Aim

The aim is to further build the body of knowledge related to diet intake, food insecurity, and nutrition support needs, which may include behavior change strategies relevant for Indigenous women from diverse urban, rural, and remote communities in Australia. This team will co-design a specification document and with further funding, an mHealth app or digital tool to support the nutrition needs of Indigenous women during pregnancy.

Study Design

This study comes from an Indigenous standpoint and is underpinned by critical self-reflexive practices that are aligned with a number of Indigenous research methods, including Aboriginal participatory action research [18]. The project will be undertaken in 2 phases that will use both mixed methods and co-design methodologies. The method builds on Sanders and Stappers [19] co-design framework, with a particular focus on the "predesign phase" (phase 1) and the "generative phase" (phase 2). Phase 1 will use a mixed method convergent design following an adapted shortened biographical narrative interpretive method (BNIM). The methods for phase 1 are based on the BNIM, which reconstructs data to understand a topic through 2 tracks of a participant's perspective [20]. First, how they lived their life, and secondly, how they interpret the relevant events as told through their personal stories within the focus group.

Findings from the focus groups in phase 1 will inform phase 2. Phase 2 will use a participatory action research process during co-design workshops with participants. This phase adopted the Kaupapa Māori method for phase 2 workshops [21]. Kaupapa Māori clearly speaks to the goals of the co-design process. This method will be adapted as needed for the Indigenous Australian context but the concept of creating meaning together, enabling research by Indigenous peoples, for Indigenous peoples, and with Indigenous peoples is inherent within the Kaupapa Māori approach [21]. Due to the nature of this method (co-design) and the Aboriginal participatory action approach that is being undertaken, the exact actions within a workshop will evolve according to the participant groups' direction.

Governance and Ethics

Governance

Study governance includes the research team of both Indigenous and non-Indigenous academics from a broad cross-section of academic backgrounds (research team), the Indigenous Steering Committee (ISC), and partner organizations. The study has been closely developed with the Aboriginal community–controlled health sector, and the project is partnered with Galangoor Duwalami Primary Healthcare Service (Maryborough, Queensland), Carbal Medical Services (Toowoomba and Warwick, Queensland), Pius X Aboriginal Corporation (Moree, New South Wales), and Moorditj Koort in the Perth metropolitan area in Western Australia.

The investigatory team are committed to the concept of making meaning together and have developed the governance with the ISC, an integral part of the project. Each partner site has nominated members to the ISC who are recognized as having appropriate cultural, community, and nutritional knowledge to be representing their community. Additionally, Indigenous members of the research team are active members of the ISC and anticipate that this facilitates strong relationships across the project. The ISC will meet quarterly and have an active role in project management, data storage and retention, data analysis, publications, and dissemination.

Ethics Approval

The project has been approved by ethics committees aligned with the principles in the Australian Institute of Aboriginal and Torres Strait Islander Studies (AIATSIS) Code of Ethics for Aboriginal and Torres Strait Islander Research (2020) as follows: Mater Misericordiae (62512), University of Queensland (2021/HE002031), Aboriginal Health and Medical Research Ethics Committee of New South Wales (1966/22), and Western Australia Aboriginal Health Ethics Committee (HREC1102). Indigenous ways of knowing, practices, and cultural expressions are fully incorporated into the study methods as per the AIATSIS Code of Ethics for Aboriginal and Torres Strait Islander Research (2020) [22].

Settings

This project is being undertaken across 3 states (Queensland, New South Wales, and Western Australia) to ensure that the project is broadly representative of the views and needs of Indigenous women across Australia. It is not feasible to work with every Aboriginal or Torres Strait Islander nation of Australia, but these sites were chosen for their diversity in cultural community, community sizes, socioeconomic status (measured by Socio-Economic Indexes for Australia; SEIFA), and rurality (measured by the Modified Monash Model). The average community SEIFA score is 1000, where SEIFA measures the relative level of socioeconomic disadvantage or advantage based on a range of community characteristics taken

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from the national census. As the index decreases from 1000, so too does the socioeconomic index; likewise, as it increases above 1000, the affluence of the community increases. It is worth noting that the SEIFA score shown for the communities in Table 1 is for an entire community or town and is only an indication for a region. To reflect the economic diversity of the participants, we will also be asking about their household income in our surveys. The Modified Monash Model scale from 1 to 7 defines the rurality of a community, whereby 1 is a major city and 7 is a very remote community [23]. Table 1 shows the characteristics of the sites for this study and highlights the diversity of population size, rurality, and socioeconomic status.

Table 1. Demographic characteristics of study locations.

Site	Primary cultural identification	Total population, n (significant urban area according to ABS[a]) [24]	Indigenous population [24], %	Modified Monash Model scale [23]	SEIFA[b] score [25]
Queensland					
Toowoomba: Carbal Aboriginal Medical Services	Jagera, Giabal, and Jarowair [26]	173,204	5	2	989
Warwick: Carbal Aboriginal Medical Services	Githabul [27]	12,294	8	4	976[c]
Maryborough: Galangoor Duwalami Primary Healthcare Service	Butchulla [28]	27,489	6.3	6	912
New South Wales					
Moree: Pius X Aboriginal Corporation	Kamilaroi [29]	9346	21.5	4	917
Western Australia					
Midland: Moorditj Koort	Whadjuk Noongar [30]	5972	5.3	1	900
Armadale: Boodjari Yorgas	Whadjuk Noongar [30]	79,602	2.5	1	994
Joondalup: Aboriginal Women's Health Service	Whadjuk Noongar [30]	154,445	0.6	1	1078
Northbridge: Aboriginal Women's Health Service	Whadjuk Noongar [30]	1307	0.8	1	1016
Cockburn: Moorditj Koort	Whadjuk Noongar [30]	104,473	1.5	1	1033

[a]ABS: Australian Bureau of Statistics.

[b]SEIFA: Socio-Economic Indexes for Australia.

[c]SEIFA score available for Local Government Area.

Participant Recruitment

Participant recruitment strategy has been determined in collaboration with each site. Each organization has prominently displayed posters (on their noticeboards and electronic sites) and has flyers available for potential participants, with a QR code included on both documents leading to detailed participant information and contact information for the research team if potential participants have any questions. Some participating sites, Carbal (Warwick) and Galangoor Duwalami (Maryborough), have indicated the study is an ideal activity for existing community groups within their organizations, including women's groups, mother and baby groups, and Elder groups. In these instances, the research team has attended these organizations' community groups in advance to deliver a short presentation to group members about the study and answer questions asked by potential participants. Following the research team presentation to the site and to potential participants, the site arranged a time for data collection with the group of participants who consented. All participants are advised that only deidentified data will be used for this project and are given a full explanation of how data will be stored safely.

Consent forms are signed by all participants upon arrival at the data collection activity following a further opportunity for participants to clarify any concerns of consent. In recognition of the commitment by participants to the study, participants involved in phase 1 and phase 2 are offered a gift or voucher to the value of Aus $50 (US $33.45) for each phase as advised by the partner organizations.

Inclusion and Exclusion Criteria

This study is recruiting 2 different types of participants. We are specifically recruiting women who identify as having Aboriginal and Torres Strait Islander heritage. These women may either be currently pregnant or have raised children in their lifetime. The study also includes women who are older community members or Elders to ensure that experiences of all women in the community are represented. Additionally, health care professionals from Aboriginal community–controlled health organizations who support women's health are being

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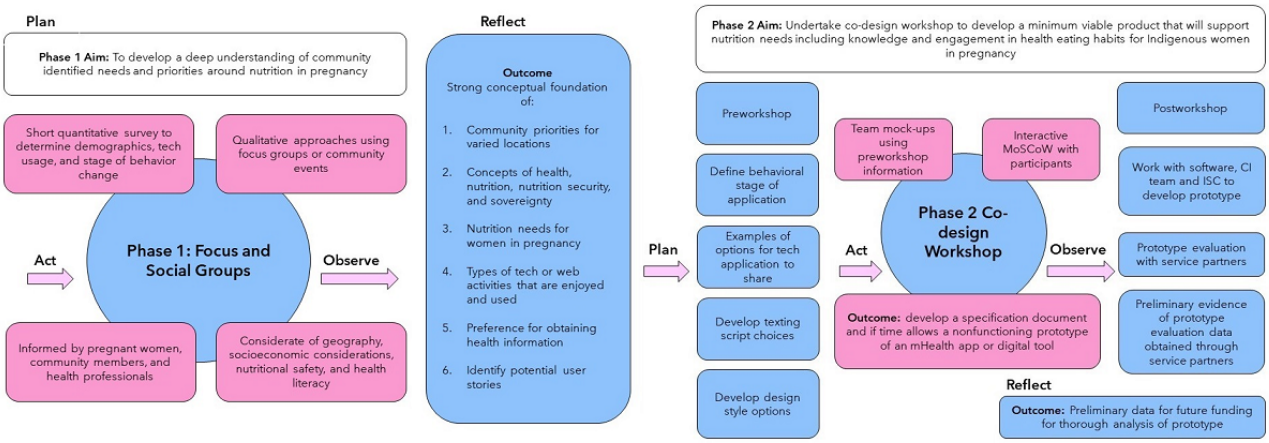
recruited. This participant group can include either male or female participants who may or may not identify as having Aboriginal and Torres Strait Islander heritage. Aside from health care professionals, this study will exclude male community members. The digital tool is designed to be used during pregnancy; therefore, men are not appropriate participants for the project.

Approach

Overview

Phase 1 and phase 2 will occur as face-to-face discussions unless during the current pandemic health advice suggests otherwise. The project takes the holistic approach precedented by Chamberlain et al [31] using intervention mapping and action research cycle as shown in Figure 1. This study uses Aboriginal participatory action approaches discussed by Dudgeon et al [18] and also draws upon the guidelines to co-design mHealth systems developed by Noorbergen et al [32].

Figure 1. Co-design methods used and the integration of information from the phases 1 and 2 research cycle. CI: Chief Investigator; ISC: Indigenous Steering Committee; mHealth: mobile health; MoSCoW: must have, should have, could have, and would not have.



Phase 1: Understanding Community Worldview (Predesign Phase)

Overview

Focus and social groups will be held with at least 2 members of the research team. One member will be the primary group facilitator, and the other attendee will be there to assist with consent and survey paperwork. The other attendee will also take field notes during the discussions. The facilitator and other research team members will introduce themselves at the start of the focus group and spend some time talking informally to give participants time to relax prior to the start of the group.

Focus groups with community members and health professionals will use similar prompt questions (Textbox 1) with the facilitator rephrasing these as appropriate for each group. To further aid discussion, visual aids are used to generate conversation during the social and focus groups and are placed around the room and to be used by participants throughout the discussion (Figure 2).

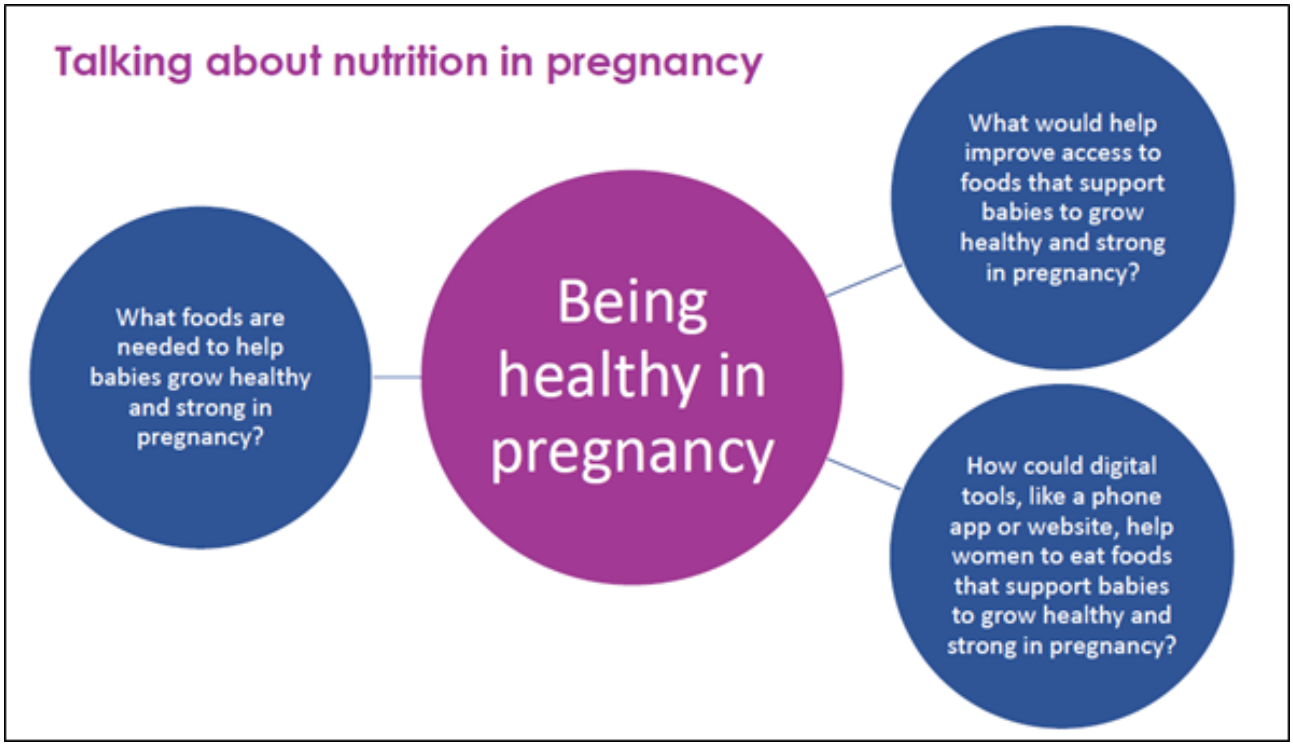
All participants attending will complete a short-answer survey designed by the research team. This will be completed at either the start or end of the group discussion. The survey contains standard demographic questions, current nutrition issues and food access experiences, and questions regarding current use of mobile phone apps, access to the internet, computers, and the types of activities used on the phone. When designing this survey, the team were aware that many research participants can feel that some questions have no relevance to the study. They made a conscious effort to only include questions that were directly related to the study outcomes and would be used in the data analysis for this study, and for which they could justify the use of the data to a participant who may query its purpose. Group discussions are between 1 and 2 hours depending on the group.

Textbox 1. Discussions with both women from the community and health care professionals are centered around the same prompts, reworded to suit their context.

- What are the foods you or your community need to help babies grow healthy and strong in pregnancy?
- What would help you and your community to access foods that support babies to grow healthy and strong in pregnancy?
- How could digital resources, like a mobile phone app or a website, help you and your community to eat foods that support babies to grow healthy and strong in pregnancy?

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Figure 2. Social and focus group visual aid.



Data Analysis

Survey data will primarily be assessed using descriptive statistics and later integrated with qualitative results in matrices. All focus groups are audio-recorded with participant permission and transcribed verbatim with thematic analysis undertaken. Transcripts and audio recordings are cross-checked for accuracy prior to analysis. Both deductive and inductive analyses will be undertaken. Analysis of the literature will provide a set coding framework (the deductive approach) that will be used across all sites and focus group transcripts by the research team. The inductive approach will develop site- or community-specific knowledge, while the deductive approach will provide a clear analysis framework that can be used for all sites that is specific to the objectives of the project. Inductive qualitative evaluation of the transcripts will use thematic techniques and insights to this cohort outlined by Sherriff et al [33] to guide the interpretation, thematic analyses, and reporting of this data. Using NVivo (version 12, 2018; QSR International Pty Ltd) qualitative data analysis software, identified themes will be compiled into a coding frame and, as new themes emerge, they will be compared against the initial coding frame and either added as new themes or used to expand and modify existing themes, until all data are accounted for.

The ISC will be enlisted to assist in the coding framework and contribute their understanding of any themes represented in the data using a chunk-by-chunk analysis format. Data analysis will be undertaken using constant comparison methods, and matrix displays will be used to explore similarities and differences across groups on key themes.

Prephase 2 (Generative Phase)

Data analysis of phase 1 will be completed from all sites prior to undertaking the phase 2 co-design workshops. Additionally, many resources to inform the co-design workshops will be compiled or developed by the research team based on the findings from phase 1.

Development of the workshop resources will occur in an active partnership with the ISC. Personas of potential users of the app will be determined and included in the developed presentation. The behavior stages of these potential personas will be identified to assess where the cohort's understanding may be regarding a topic, ranging from precontemplation, contemplation, planning and preparation, action, and maintenance [34,35]. The team will compile initial concepts and themes for the app or tool and design or feature ideas to test and refine in co-design workshops with participant groups.

Phase 2: Co-design Workshop (Generative Phase)

Overview

Co-design workshops will be held with participants from phase 1 who can attend. However, it is expected that there will be a reduction in participant numbers as phase 2 workshops will take several hours. The start of co-design workshops will include additional introduction of new research team members attending and a short presentation of findings from phase 1 (likely delivered by the phase 1 facilitators). It is likely that this workshop will have 3 to 4 research team members attending throughout the workshop.

An additional interactive presentation will be delivered that will include mock-ups, ideas, and other information developed by the research team and the ISC during the prephase preparation. This will include a suite of technology probes (eg, screenshots of existing or relevant mHealth technology). The research team will discuss personas they have developed with the participants to consider if the target audience of the mHealth app or digital tool is appropriate. A facilitator from the research team will

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follow this with a 1-hour interactive discussion to build on feedback on these initial concepts with participants.

Regular breaks will be held throughout the workshop. Following a break, a further co-design activity will be undertaken with participants. This will be facilitated by one of the research team and it will include a strong focus on MoSCoW (must have, should have, could have, and would not have) activities [36]. This method is used in software development to assess how potential elements should be prioritized depending on participant opinion and is an ideal way of progressing from an idea through to the minimum viable product needed in mHealth product developments [36]. For a minimum viable product, such as the Mums and Bubs Deadly Diets project, the focus will be on the development of the "must haves" and "should haves." Participants will be able to identify other desirable elements for the tool, with the research team ensuring that participants are aware of the timeline and budgetary considerations that can impact on the inclusion of these elements. In this case, elements will be identified in workshop activities such as a sticky notes exercise. Ideally, this workshop would have all participants and facilitators in 1 room throughout; however, with pandemic restrictions, the research team will be guided by health advice.

Data Analysis

Data collected in this phase includes audio recordings, transcripts, observer field notes as well as the collection of participant-developed workshop materials such as sticky notes and flip charts. The analysis of phase 2 is dependent on the outcomes of the co-design workshops and nature of workshop-developed materials. Using the aspects of interpretive phenomenological consensus analysis [37], the goal of this assessment is to identify exactly what these participants want in the project outcome. This may be the type of mobile technology, how it can be used, and the elements it contains, including nutrition knowledge and aspects related to health behavior change.

Data Ownership and Management

Data management of this project has been undertaken to ensure that it reflects the 8 Indigenous Data Sovereignty principles identified by Trudgett et al [38]: ownership, control, accessibility, custodianship, accountability to Indigenous people, amplify the voice of the community, relevant and reciprocal, and sustainably self-determining. For the purposes of this study protocol, data refer to voice recordings, transcripts, survey responses, and files arising from the focus or interview recordings, including field notes and observations. The data arising directly from the participants of the study remain owned by the individuals; however, the analysis arising from the participants' contributions is owned by the research team.

To ensure ownership and control, participants will have the option for their data to be handled in one of three ways after the project is complete, specifically 5 years after the final action of the project: (1) the data can be disposed of appropriately, (2) the survey and focus group data can be donated back to the community organization, or (3) all data can be donated to the AIATSIS data repository. This decision will be individual for survey data but must be unanimous for focus groups and workshops. Where a unanimous decision cannot be made, disposal of data will be the default. Whether data are returned to the community organization or AIATSIS, it will be sustainably held with Indigenous custodianship and appropriately accessible to the community.

During the life of the project, deidentified aggregate reports of initial findings will be shared with each site after each phase. These reports will be provided as an act of reciprocity to assist service strategic planning and amplify the voice of the participants.

Dissemination of Results and Publications

This project seeks to follow the Consolidated Criteria for Strengthening the Reporting of Health Research Involving Indigenous Peoples (CONSIDER) statement [39]. This statement, developed through a meta-synthesis of international guidelines by a working group, identifies 8 key domains to guide the appropriate reporting of health research involving Indigenous peoples.

Results will be disseminated in several ways to meet the needs of the community and research team, including forums for the partner organizations and community members. Individual participants will be provided study outcomes and will also be encouraged to attend any public forums and research presentations. Publication of the outcomes from this work and this goal are embodied and enacted through the collaboration and Terms of References for the ISC and agreements made with partner organizations that include how the sharing and publication of material will occur.

Results

To date, this project has undertaken phase 1 focus groups at all Queensland sites with New South Wales and Western Australia to begin in early to mid-2023. We have recruited 12 participants from Galangoor Duwalami, 18 participants from Carbal in Toowoomba, and 18 participants from Carbal in Warwick. We are expecting similar numbers of recruits in Western Australia and New South Wales. Participants have been both community members and health care professionals. Despite not asking specific questions about stages of behavior change, both community members and health professionals have raised this in a number of ways. Women and mothers have identified the things that they are currently practicing in their diets as well as areas where they are seeking further information and strategies, while health professionals have identified specific nutrition information that is challenging to explain related to pregnancy needs and highlighted the types of clients that would benefit and how best this information could be used in their practice. This will form part of the findings to inform phase 2. Preliminary findings have been disseminated to each of the Queensland sites as planned. Analysis is underway in preparation for phase 2.

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Discussion

Principal Findings

This study has been designed using a combination of methodologies and methods to ensure such a major program is iterative, holistic, and culturally appropriate. A critical component to Indigenous research practice and more specifically the iterative nature of this project was reflexivity. This process encouraged shared understandings between the research team members and other collaborators, encouraging the positioning of Indigenous perspectives central to the project, allowing the research to remain ethical, meaningful, and useful throughout the many learnings and changes throughout the project [40].

The project takes a similar approach as that by Chamberlain et al [31] using intervention mapping and action research cycles to frame a co-design project from predesign and generation to implementation. Phase 1 will include the first 3 steps of intervention mapping: logic modeling of the problem, logic modeling of the change, and program design. Phase 2 will then address program production and some implementation concerns, though full implementation of evaluation will be addressed with future funding [41]. The action research cycle is used to intertwine the 2 phases in an iterative manner as highlighted in Figure 1. The dual cycle steps of "plan, act, observe, and reflect" among the 2 phases are linked, so the findings from surveys and group discussions of phase 1 inform phase 2.

The phase 1 biographical survey informs the lived life track through BNIM methods so that we may use the qualitative information to focus on the told stories track. Field notes and observations will be assessed to identify moments in the group conversation dynamics, linking transcripts to reality, emotions, and relationships. This process was adopted to allow this phase the in-depth understanding required to set the foundations for this project.

As highlighted by Noorbergen et al [32], prior to phase 2, the findings from phase 1 will have developed an intimate understanding for the research team of nutrition priorities for women during pregnancy. This will aid in determining what stages of behavior change the digital tool should focus on or may be added at each stage to support the journey of pregnant mothers. The behavioral stages identify where a person or cohort's understanding may be regarding a topic [34,35]. This is an important component to designing the digital tool in a way that targets the correct level of comprehension and commitment of the target user. Although questions related to behavior change were not included in focus group guides, our preliminary analysis of phase 1 shows health professionals and community members have identified that they have distinct needs and varied stages of behavior change that they would like to address in the mHealth tool. This will encourage true engagement and retention with the information.

Prior to the workshops, the research team and the ISC will consider the types of user (persona) who will likely use this nutrition mHealth tool to ensure that each of these users is represented within its usage. For example, a technology tool focused on pregnancy nutrition for Indigenous women could be used by a woman during her pregnancy or used by a health professional to support health education during pregnancy. It will only be during the phase 1 that the team will be able to identify what needs are important for the community.

During phase 1, participants identify how they currently use their phones and consider how these could assist them with nutrition needs. These findings will assist in compilation of suitable technology approaches that can be shared, types of design options, as well as texting and script options that will be presented in phase 2 workshops. Feedback on probes will help to uncover types of technology and functions likely to be most effective in addressing the nutrition needs and priorities of Indigenous communities. The activities included are important to determine what aspects of the app must be standalone and what can be uploaded when an internet connection is available. It also helps with determining how diverse the activities within the app can or should be. For example, should it just contain written material, or are videos and pop quizzes more suitable to engage participants?

Kaupapa Māori concepts will be used throughout data analysis from phase 1 and during the co-design workshops in phase 2. This framework originally resonated with the research team due to these underpinning values that encapsulate the concepts of similar Indigenous Australian research concepts including Aboriginal participatory action research methods [18,42]. Embedding Kaupapa Māori principles positions the project within a research paradigm of epistemic self-determination. Indigenous Australian values, knowledge, and voices influence all aspects of the project.

Phase 2 has specifically been identified to require more research team members present, as differing areas of expertise will be required on the day. To ensure best outcomes from the workshops, all efforts will be made by the research team to relax participants, so that participants feel comfortable and confident to voice their opinions throughout. Breaks will no doubt be needed; however, they serve the dual purpose of people chatting informally and getting to know one another, which will aid in participation from all.

Strengths and Limitations

The study's priority is to inform and co-design a culturally appropriate digital tool to support nutrition needs of Indigenous women in pregnancy. The strength of this study is the co-design methods and approaches to "making meaning together" with Indigenous governance and partnered communities across the country. The consolidation of the co-design method, the development of an Indigenous governance structure, and the research team comprising Indigenous researchers and leaders ensure the study is culturally safe.

As a priority, this study endeavors to include sites across Australia in order to truly include the end users in the development of this tool and seeks to be respectful of Indigenous communities in Australia and their incredibly diverse values, traditions, and customs [12,16,43]. It is not possible to include every single Indigenous country of Australia (there are over 250 individual Aboriginal and Torres Strait Islander nations contained within Australia); therefore, these results may not be

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generalizable to all Indigenous Australian women. However, the spread across rural, coastal, and metropolitan communities and cultural groups will provide diversity to develop the mHealth product.

The COVID-19 pandemic continues to be a distinct limitation for this project. Local lockdowns and restrictions meant delays to project timelines, and significant modifications have been made to community engagement plans. Initial engagement meetings were moved to web-based platforms, which limited the ability to develop rapport with partner organizations and delayed the start of the study. Further, many community members have reduced their attendance to organized programs such as mothers groups, creating early challenges to recruitment. However, as we move further away from the major pandemic waves, we hope that COVID-19-related challenges are reduced.

The predicted users of this tool would be pregnant Indigenous women and potentially their health care professionals. As such, we felt it reasonable to limit our cohort to these 2 groups. However, participants have mentioned they would like their male partner or their children's fathers to be engaged in the conversation as they may rely on them to do nutrition tasks within the home. The restriction of the study cohort to women may be a limitation of this study; however, they are the target intended users. Future research could consider including the entire family unit in these conversations.

Conclusions

The Mums and Bubs Deadly Diets study is an iterative and adaptive research program that endeavors to develop real-world, impactful resources to support the nutrition needs and priorities of pregnant Indigenous women in Australia. This project addresses a problem from beginning to end, which requires a combination of methods and methodologies to ensure Indigenous voices are heard at each stage and in all aspects of research output. A mixed methods biographical survey and social or focus groups in phase 1 will deliver the predesign phases of intervention mapping, while co-design workshops in phase 2 will address the digital tool elements necessary for program production and implementation. The development of an mHealth resource for this cohort will provide an essential bridge, where there is often a gap in access to nutrition resources for women in pregnancy in Indigenous communities.

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Data Availability

In line with ethics approval, the data collected as a part of this study will not be publicly available. However, the data may be made available upon request for specific purposes to the corresponding author and with the agreement of the Indigenous Steering Committee.

Conflicts of Interest

None declared.

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Abbreviations

AIATSIS: Australian Institute of Aboriginal and Torres Strait Islander Studies
BNIM: biographical narrative interpretive method
ISC: Indigenous Steering Committee
mHealth: mobile health
MoSCoW: must have, should have, could have, and would not have
SEIFA: Socio-Economic Indexes for Australia

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Protocol

Advance Care Planning Website for People With Dementia and Their Family Caregivers: Protocol for a Development and Usability Study

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Abstract

Background: Web-based tools for people with dementia and their family caregivers have considerably increased over the years and offer promising solutions to several unmet needs such as supporting self-care in daily life, facilitating treatment delivery, or ensuring their ability to communicate. The use of web-based tools in the field of advance care planning (ACP) for people with dementia and their family caregivers has yet to be explored and requires careful consideration, given the sensitive topic and the specific needs of people with dementia and their families.

Objective: This paper reports the protocol for a study aiming to develop and simultaneously test the usability of an ACP website designed for, and with, people with dementia and their families.

Methods: The development of the website is based on a process map for the development of web-based decision support interventions and on the Medical Research Council framework for complex intervention development and evaluation. Additionally, we apply a user-centered approach in combination with patient and public involvement (PPI) throughout the development process. We describe our iterative development approach to the website. Participants and a PPI group give feedback on 4 prototypes of the ACP website. For each iteration, we aim to include 12 participants (3 people with dementia, 3 family caregivers, and 3 dyads) in usability testing. In the first 3 iterations, usability testing includes (1) a think-aloud exercise, (2) researcher observations, and (3) the System Usability Scale questionnaire. The last iteration of usability testing is composed of a semistructured interview assessing the layout, content, face validity, and readability of the website. Qualitative data from the think-aloud exercises and interviews are analyzed using thematic analysis. Mean scores are calculated for the System Usability Scale questionnaire.

Results: This study received approval from the Ethical Review Board of Brussels University Hospital of the Vrije Universiteit Brussel. Recruitment began in October 2021. The target date for paper submission of the results of the development and usability testing will be in 2023.

Conclusions: The methods in this protocol describe a feasible and inclusive approach to the development of an ACP website together with people with dementia, their family caregivers, and other stakeholders. We provide a clear overview of how to combine PPI input and user-centered development methods, leading to a transparent and reliable development process. This protocol might stimulate the active participation of people with dementia, their caregivers, and regional stakeholders in future studies on web-based technologies. The results of this study will be used to refine the design and create a relevant and user-friendly ACP website that is ready to be tested in a larger evaluation study.

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KEYWORDS

advance care planning; people with dementia; technology; development; usability testing; dementia; caregiver; web-based tools; digital health; user-centered approach

Introduction

Background

Web-based tools for people with dementia have considerably increased over the years and offer promising solutions to several unmet needs [1,2]. Many web-based tools have targeted the different needs of people with dementia by, among others, supporting self-care in daily life, facilitating treatment delivery, or facilitating communication [3]. Further, many people with dementia are enthusiastic and positive about using technologies to facilitate their independence [4]. However, the use of web-based tools in the field of advance care planning (ACP) for people with dementia has yet to be explored. To the best of our knowledge, no web-based ACP tool has been developed for people with dementia.

ACP has been defined as an ongoing process that enables individuals to explore and identify their values, reflect upon the meanings and consequences of serious illness scenarios, and define goals and preferences for future care and medical treatment [5,6]. ACP encourages people to discuss these preferences with family and health care providers, appoint a proxy decision maker, and record these preferences and choices [5,6]. We adopt a public health approach to ACP. This approach originated from an ongoing shift in the ACP concept; going from a clinician-led and documentation-focused process that highlights the need of advance directives to a broader concept of ongoing communication among patients, family, and health care providers about several aspects of future care and treatment planning [7,8]. The public health approach to ACP highlights the need to normalize and reconfigure the way decisions are made by reframing ACP as a health-promoting activity through public education and engagement. Underlying this approach is the need to have conversations about end-of-life preferences, death, and dying not only within a medical context (between patients and health care providers) but also within the family context.

Considering the progressive decline in cognitive and functional abilities associated with dementia, ACP can be particularly relevant for people living with dementia, as they become more vulnerable and more dependent on others throughout the disease trajectory [9,10]. Yet, research has shown that ACP is not a widespread practice among people with dementia [11]. People living with dementia and their families are often not well informed about ACP, as they might not be aware of ACP at all or there might be many uncertainties concerning this complex topic, which can be due to a lack of familiarity with the process or with the specific content of ACP [12-14]. Talking about ACP has been found to be complicated as people with dementia and their families experience tensions and perceive this as emotionally difficult conversations [15]. Moreover, people with dementia have quite specific needs in terms of ACP compared to other illnesses. They have a need for a clear understanding of the dementia disease trajectory and what ACP can achieve or not [14]. Furthermore, the more the disease advances and cognition declines (in a nonlinear gradual way), the more family plays a crucial role in ACP in this population [16]. As their condition evolves, many people with dementia may require a surrogate decision maker or legal representative [17].

In other patient groups than dementia, many ACP tools have been developed that are not web-based, such as trainings for professionals or documentation booklets. These have generally aimed to facilitate engagement in ACP discussions by helping patients and family caregivers in reflecting about or making decisions for future care and treatment in coordination with health care professionals [18]. However, web-based tools can have many advantages over paper-and-pencil or face-to-face tools. Web-based ACP tools can be accessed on the internet at any preferred time and place, can be used at everyone's own pace, with or without the presence of a health care professional or family caregiver, and can reach a larger audience [19]. Additionally, one of the most important features of web-based tools is the use of interactive elements allowing for tailoring to the specific needs and preferences of individuals, which seems particularly relevant for dementia [20]. A recent systematic review identified 10 existing web-based ACP tools published in international peer-reviewed literature. However, they were mostly developed in and limited to the United States [21]. None were designed for people with dementia or tested with people with dementia, despite the specific needs of this population.

Objectives

In this paper, we describe the protocol of a study that aims to develop and test the usability of an ACP website especially designed for, and with, people with dementia and their families. Furthermore, the website should be user-friendly, interactive, and accessible at any preferred time, so that people with dementia and family caregivers can use the ACP website at their own pace and within the family context.

Methods

Development Overview

The methods selected for the development of the ACP website are based on a process map for the development of web-based decision support interventions for a specific audience as proposed by Elwyn and colleagues [22] and follow the Medical Research Council (MRC) framework for the development of complex interventions [23]. Given the complexity of the intervention, combining these approaches is warranted for the development of a website that is both evidence- and theory-informed.

This study focuses on the development stage of the MRC framework for the development of complex interventions [23]. Within the development stage of the MRC framework, we use

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the process map for the development of web-based decision support interventions, which provides a clear development approach for digital interventions especially. It is composed of main steps such as (1) content specification, with an emphasis on considering patients' perspectives in addition to synthetizing the current scientific evidence, and (2) creative design, including storyboarding and field and usability testing [22]. Furthermore, as recommended in the MRC framework, we build in theory and integrate continuous stakeholder engagement. Thus, in the first content specification phase, we specify the information that should be included in the ACP website by identifying relevant existing evidence and conducting an assessment of needs among people with dementia, family caregivers, and dementia experts. In the second creative design phase, prototypes of the ACP website are developed and revised in several iterations.

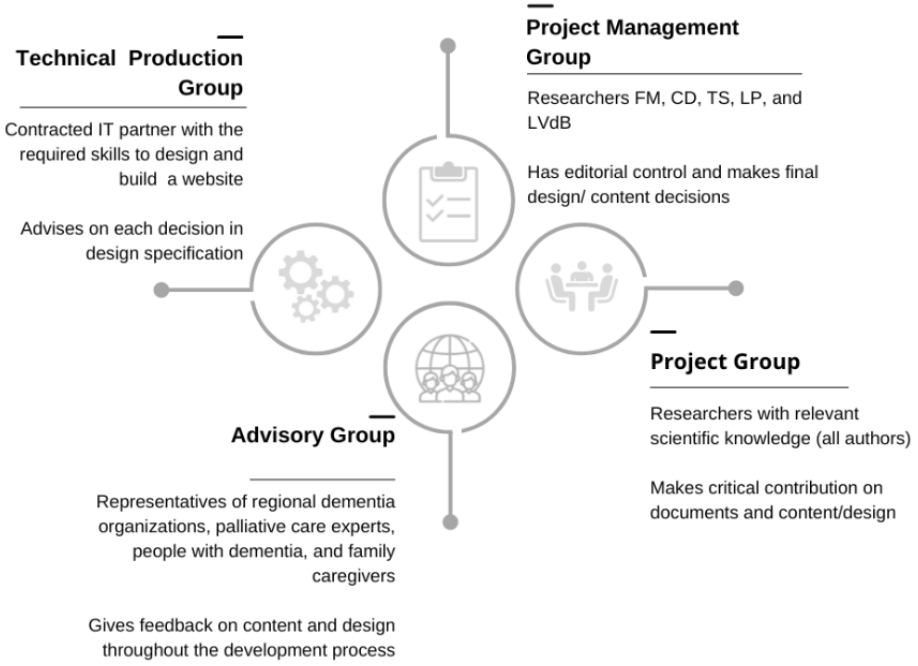
User-Centered Design and Patient and Public Involvement

In all phases of the development process, we incorporate user views as recommended in recent literature reviews on the development of technological interventions [4,24]. We adopt a user-centered approach throughout the development of the ACP website. User-centered design is a recognized method for complex intervention development [23] and is an evidence-based approach that emphasizes the importance of the needs of end users during the development [25]. Additionally, as advocated by Alzheimer Europe, we integrate meaningful patient and public involvement (PPI) consultation sessions at different stages of the development process to enhance the quality and relevance of the ACP website [26]. PPI sessions are conducted with an advisory group composed of people with dementia, family caregivers, representatives from local dementia associations, and palliative care experts (nurse and consultant for ACP). This group is consulted throughout the development process, in parallel to user testing with study participants, through online meetings and emails.

Stakeholder Groups Involved in the Development Process

The development of the ACP website is supported by 4 groups as suggested by Elwyn et al [22]: a project management group (composed of FM, CD, LVdB, LP, and TS), a project group (composed of all authors of this paper), an advisory group (a PPI group composed of representatives of regional dementia and palliative care organizations and experts in Flanders, people with dementia, and family caregivers), and a technical production group (contracted IT partner). Figure 1 gives an overview of each group's responsibilities.

Figure 1. Overview of the stakeholder groups involved in the development process.

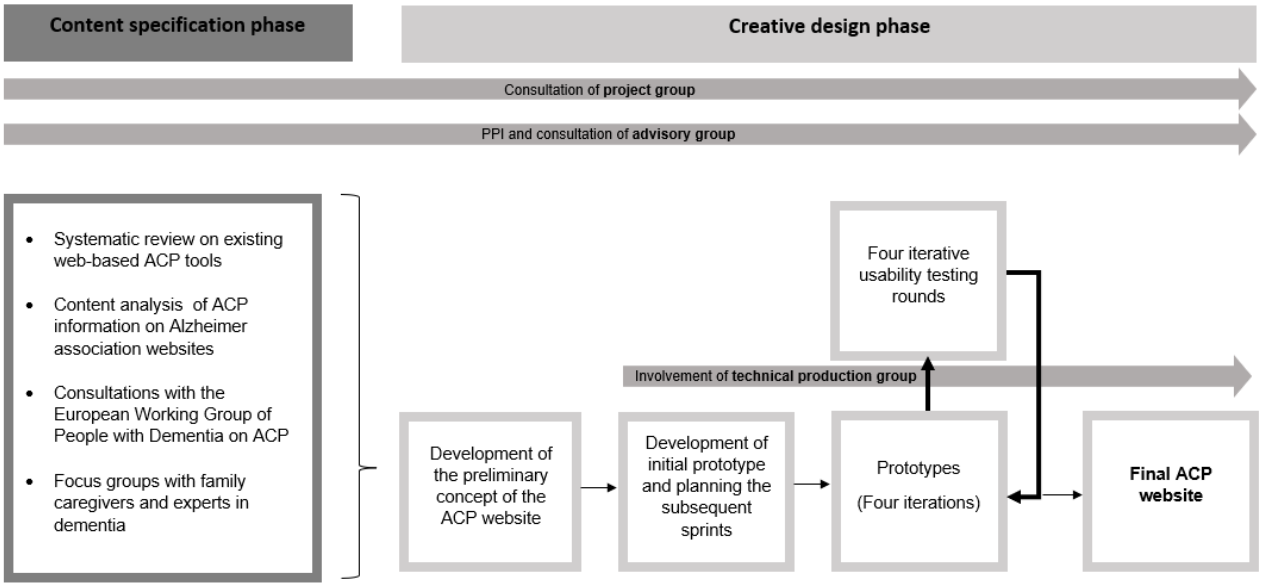


Content Specification Phase of the ACP Website

In this phase, we specify the information that should be included in the ACP website by identifying relevant existing evidence and conducting an assessment of needs among people with dementia, family caregivers, and dementia experts. An overview of the activities conducted in this phase and their main output is presented in Figure 2. Results from the research activities in the content specification phase are reported separately [27-29]. In this content specification phase, we summarize the evidence from these activities. This includes ensuring the content and structure of the website are in line with previous research on a web-based ACP tool, the information already provided on the internet by dementia associations, and the needs expressed by people with dementia and their families for ACP and an ACP website, as well as with the opinion of experts in the field.

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Figure 2. Overview of the development process and usability testing of the ACP website [28,29]. ACP: advance care planning.



Creative Design Phase of the ACP Website

Results from the content specification phase inform the design phase of the ACP website. The findings from the evidence base and the user needs assessment are used to build the first concept of the website. An overview of this study, its aims, and all involved groups is shown in Figure 2.

We adopt an agile development approach to build the ACP website. This approach is characterized by an iterative and dynamic development process while collaborating with several groups of stakeholders. It is based on the principles of continuous design improvement and testing based on rapid feedback and change and allows for high-quality adaptive software [30,31]. Such an approach is thus in line with a user-centered approach. Within the agile development approach, we use the Scrum method, as it particularly emphasizes the role of feedback loops. The core characteristic of the Scrum method is the sprint, which is a short development timeframe of approximately 4 weeks [32]. Each sprint requires careful preparation from recruitment of participants to meetings with the advisory group and the technical production group. Based on the complexity of website development and previous work using a Scrum in the development of health-related interventions [33], we estimate that the development of the ACP website will be conducted in 5 successive stages, including 4 sprints. An overview of the sprints is shown in Table 1.

In the presprint, the project management group summarizes and synthetizes the evidence found in the content specification phase. Then, the preliminary concept of the ACP website is discussed in a meeting with the advisory group. The project management group drafts a specification document based on the evidence synthesis and the discussions of the advisory group. Based on this specification document, the technical production group develops the first prototype of the ACP website.

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Table 1. Overview of the sprints executed during the iterative development process.

Sprints	Objective	Content	User testing	
			Data collection	Participants, n
Presprint	Development of the first prototype	• Development of initial prototype • Planning of the subsequent sprints	• Feedback from advisory group and project group	N/A[a]
Sprint 1	Evaluate the usability of the first 3 features	• Usability testing of the home page, structure of the website	• Think-aloud method • Survey • Feedback from advisory group	12 participants (3 people with dementia, 3 family caregivers, and 3 dyads)
Sprint 2	Evaluate usability of the following 3 features	• Usability testing of the informational part of the website	• Think-aloud method • Survey • Feedback from advisory group and project group	12 participants (3 people with dementia, 3 family caregivers, and 3 dyads)
Sprint 3	Evaluate usability of the remaining features	• Usability testing of the communication part of the website and the web-based tools	• Think-aloud method • Survey • Feedback from advisory group and project group	12 participants (3 people with dementia, 3 family caregivers, and 3 dyads)
Sprint 4	Test the content, face validity, and readability of the tool, and its layout and ease-of-use	• Content, face validity, and readability of the whole website	• Semistructured interviews • Feedback from advisory group and project group	12 participants (3 people with dementia, 3 family caregivers, and 3 dyads)

[a]N/A: not applicable.

Usability Testing

We follow the definition of the International Organization for Standardization of usability (ISO 9241-11), that is, "how well users can learn and use a product to achieve their goals and how satisfied they are with that process" [34]. This includes the evaluation of the ease of learning, efficiency of use, memorability, error frequency, and satisfaction [35].

People with dementia, family caregivers, and dyads evaluate several versions of the prototype of the ACP website. Based on their input as well as feedback from the advisory group, the technical production group adapts and extends the tool in several iterations (sprints). After 3 usability sprints (sprints 1 to 3), the latest prototype of the ACP website is evaluated by people living with dementia, their main family caregivers, and dyads in terms of content, face validity, readability, and layout (sprint 4). The findings are used to develop the final prototype of the ACP website. An overview of the usability testing is provided in Table 1. The following sections explain the procedure in more detail.

Participants

We aim to include 48 participants in total. We organize the testing with people with dementia, family caregivers, and dyads. For each iteration (sprint), we aim to include 12 participants (3 people with dementia, 3 family caregivers, and 3 dyads) who are asked to test the prototype and fill in the System Usability Scale (SUS) questionnaire. For every sprint, we seek to enroll new participants. For people with dementia, the inclusion criteria were being aware and informed of their diagnosis, having an interest in and being willing to test an ACP website (including using a computer and the internet), speaking and understanding Dutch, being able to understand the information about this study, and being able to sign a written informed consent form. For family caregivers, the inclusion criteria were as follows: being the main or primary caregiver of a person formally diagnosed with dementia, having an interest in and being willing to test a web-based ACP tool, being 18 years of age or older, and speaking and understanding Dutch.

Recruitment

We ask participants to use a computer and the internet, which can be challenging, as one needs to have a certain level of computer literacy. The topic of ACP can also be sensitive and can evoke emotional reactions. Therefore, we use a process of active volunteering in our recruitment, that is, potential participants have to indicate themselves if they want to participate in this study. Thus, it is a self-assessment of willingness to participate and interest in the topic.

We recruit participants through different organizations such as the Flemish Alzheimer Liga, memory clinics, or Belgian sickness funds. Individuals who are interested in participating are asked to contact one of the researchers, who in turn sends an information letter and an informed consent form about the study through email. Potential participants are asked to reply to the email or send back the forms if they still want to participate in the study after reading the study information letter and informed consent.

Data Collection

Sprints 1 to 3

The usability tests are conducted in individual sessions with people with dementia, family caregivers, and dyads. Each session is conducted according to a pretested protocol, in the

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following order: (1) a think-aloud exercise on a set of predefined tasks [36], (2) researcher observations, and (3) a usability questionnaire. The aim of combining these methods is to gather more diverse data. The same type of session is performed with the participants in the sprints 1 to 3. The sessions are conducted in a familiar setting, for instance, the location where they are recruited or in the homes of the participants.

First, we ask the participants to fill in a demographics questionnaire. We give them tasks and oral instructions on how to go through the features of the ACP website prototype. People with dementia, their family caregivers, and the dyads are asked to navigate through each prototype version using a "think-aloud" method. This involves asking participants to verbalize their thoughts, impressions, and feelings while engaging with the tool. A researcher is present to observe and note the participants' physical cues, successes in tasks, mistakes, difficulties, or comments [36]. Guidance or interference from the researcher is kept to a minimum to investigate whether the ACP website prototype is intuitive. However, if the participants fall silent for too long (eg, if the researcher notices that a participant has silently moved on to a new task or is experiencing difficulties without expressing them), the researcher reminds them to keep thinking aloud using prompts [36].

In addition, participants' perspectives on usability are further assessed through the SUS questionnaire [37]. The SUS is a widely used and a simple, reliable, and validated 10-item scale that measures subjective usability and that has already been used by people with dementia [36,37]. The SUS score measures users' perception of the usability of the prototype in terms of effectiveness, efficiency, and satisfaction. Each item is scored on a 5 - point Likert scale (strongly disagree = 1 and strongly agree = 5). Higher scores (range 0 - 100) represent better usability [37].

Sprint 4

We ask all participants to fill in a demographics questionnaire. Then, we ask people with dementia, family caregivers, and dyads to navigate the ACP website and answer questions in a semistructured interview about the content, face validity, and readability of the website, as well as about its layout.

Data Analysis

The data from the think-aloud sessions and interviews are audio-recorded and transcribed verbatim. The field notes from the observations serve to further support the data collected during the think-aloud exercise. From sprint 1 to 3, the think-aloud sessions are analyzed through thematic analysis of the notes taken by the researchers and, if the notes were not sufficient, we listen back to the audiotapes to complete the notes. After sprint 4, the data from the transcript are analyzed using thematic analysis [38]. The data are coded by 2 researchers to identify key themes. The researchers meet and discuss the preliminary codes before agreeing on a final list of codes. Disagreements are resolved through discussion.

The data from the SUS questionnaire complements the findings from the think-aloud sessions and interviews. Data are analyzed with SPSS (version 25; IBM Corp). The SUS score is calculated by summing the score contributions of each item. For items 1, 3, 5, 7, and 9, the score contribution is the scale position minus 1. For items 2, 4, 6, 8, and 10, the score contribution is 5 minus the scale position. To obtain the overall value of the SUS score, the sum of the scores must be multiplied by 2.5. Mean scores are calculated, and comparisons between types of participants are considered. A score of 68 or above will be deemed acceptable [39]. Descriptive statistics are used to describe participant demographic characteristics.

Ethics Approval

This study received approval from the Ethical Review Board of Brussels University Hospital of the Vrije Universiteit Brussel on June 26, 2021 (BUN 1432021000437). To determine the ability of people with dementia to give informed consent, we ask them to read the informed consent form out loud. We ask them per line if they understand their rights and whether they understand what is asked of them. One of the researchers (CD) ensures participants with dementia understand what they sign by discussing the statements formulated in the informed consent form with them. A family caregiver is also present to help the researcher assess the understanding of the person with dementia. If everything is clear, they are asked to sign the informed consent. We also ask the family caregivers to sign the informed consent form of the persons with dementia as witnesses, as recommended by the Alzheimer's Association National Board of Directors [40]. All data are coded anonymously, and pseudonyms are used when quoting participants.

Results

We began recruitment of participants in October 2021, and participant enrollment has been completed. A total of 48 participants took part in the usability testing across 4 prototypes of the ACP website, and we conducted a total of 6 advisory group meetings. Data analysis has not started.

Dissemination of the results will be led by the authors and will include presentations at international conferences and publications in scientific peer-reviewed journals and the creation of best practice guidance for the development of technology for people with dementia. Results from the development and usability study will be published in 2023. A larger evaluation study will also be conducted. After evaluation and further adaptation where needed, the ACP website will be made freely available as a resource for people with dementia and their family caregivers, if it is evaluated as acceptable and useful by users, and no negative effects are noticed. The website will be disseminated via the dementia organizations that were involved in our advisory group and is expected to be publicly launched in 2024.

Discussion

Principal Findings

User involvement and PPI are recognized as critical components in the development of eHealth and digital solutions, as they can help ensure that interventions meet user needs [41,42]. Involving users in the development of technology has been suggested as an important component for improving technology acceptance, especially for older people [43]. The involvement of people

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living with dementia in particular has been highly advocated for in the development of technology both in research and by groups such as Alzheimer Europe [24,26,44]. Yet, studies providing a detailed description of user involvement in technology development are scarce. A particular strength of this protocol relates to the step-by-step description of our development process and how we approached the involvement of multiple key stakeholders in all phases of the website development. We particularly emphasize the combination of PPI input and user-centered development methods, leading to a transparent and reliable development process. The development process of the ACP website brings together researchers, regional stakeholders in the fields of dementia and palliative care, as well as people living with dementia and family caregivers to support people with dementia and their families in engaging in ACP.

Furthermore, this protocol describes in detail a unique combination of approaches consisting of the MRC framework for the development of complex interventions [23], the process map for the development of web-based decision support interventions [22], and an agile development approach rooted in user-centered design. The findings of the content specification phase, which are based on rich and extensive input from people with dementia, family caregivers, and dementia experts, as well as up-to-date research evidence on ACP in the field of dementia, have informed the design and content of the ACP website. The iterative development process adopted in the creative design phase facilitated the provision of feedback from the end users. This combination of methods can support researchers and designers in the development of web-based technologies, as well as understanding and considering user needs early on and throughout the development process. We hope that our efforts to describe this research approach will inspire researchers to integrate PPI and user-centered approaches in their own studies.

We strongly encourage the active participation of people with dementia, their caregivers, and regional stakeholders in research on the development of web-based technologies for dementia care.

One of the challenges anticipated in the study described in this protocol is that our sample may not be very heterogeneous. In particular, one of the inclusion criteria was to have an interest in testing a website regarding ACP; thus, our sample may be composed of people with generally higher computer skills and who are already familiar with the topic of ACP. Therefore, we may lack different types of perspectives, which could influence the content and design of the ACP website. This study is the first step before a larger evaluation study, which will involve a larger sample and where we will aim for variability in the sample in terms of age, gender, type of dementia, and dyad composition (eg, partners or a parent and child). Additionally, continuous technical support should be organized to encourage the participation of people with lower computer skills.

Conclusions

The methods put forth in this protocol describe a feasible and inclusive approach to the development of an ACP website. The results from this study will be used to refine the design of the ACP website for a future larger evaluation study to assess the ACP website's acceptability by people living with dementia and their family caregivers and the effects on people with dementia and family caregivers' knowledge of ACP, attitudes toward ACP, and intention to engage in ACP. We hope that the findings of the development and usability of the ACP website for people with dementia and their family caregivers will contribute to the design and development of future studies involving the development of web-based technologies for people with dementia.

Acknowledgments

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Data Availability

Data sharing is not applicable to this paper as no data sets were analyzed for the creation of this study protocol.

Conflicts of Interest

None declared.

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Abbreviations

ACP: advance care planning
MRC: Medical Research Council
PPI: patient and public involvement
SUS: System Usability Scale

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Protocol

Developing A Mobile App With a Human-Centered Design Lens to Improve Access to Mental Health Care (Mentallys Project): Protocol for an Initial Co-Design Process

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Abstract

Background: Co-design is one of the human-centered design approaches that allows end users to significantly and positively impact the design of mental health technologies. It is a promising approach to foster user acceptance and engagement in digital mental health solutions. Surprisingly, there is a lack of understanding of what co-design is in this field. In this paper, co-design is approached as a cocreation process involving persons with a lived experience of mental health problems, health professionals, and design experts who lead and facilitate the overall creative process.

Objective: This paper describes an initial co-design research protocol for the development of a mobile app that aims to improve access to mental health care. It highlights the characteristics of a co-design approach in e–mental health rooted in human-centered design and led by design experts alongside health experts. The paper focuses on the first steps (phase 1) of the co-design process of the ongoing Mentallys project.

Methods: This Mentallys project will be located in Montréal (Quebec, Canada). The method approach will be based on the "method stories," depicting the "making of" this project and reflecting adjustments needed to the protocol throughout the project in specific situations. Phase 1 of the process will focus on the desirability of the app. Targeted participants will include people with a lived experience of mental health problems, peer support workers and clinicians, and 3 facilitators (all design experts or researchers). Web-based sessions will be organized because of the COVID-19 pandemic, using Miro (RealtimeBoard Inc) and Zoom (Zoom Video Communications, Inc). Data collection will be based on the comments, thoughts, and new ideas of participants around the imaginary prototypes. Thematic analysis will be carried out after each session to inform a new version of the prototype.

Results: We conducted 2 stages in phase 1 of the process. During stage 1, we explored ideas through group co-design workshops (divergent thinking). Six co-design workshops were held: 2 with only clinicians (n=7), 2 with peer support workers (n=5) and people with a lived experience of mental health problems (n=2), and 2 with all of them (n=14). A total of 6 facilitators participated in conducting activities in subgroups. During stage 2, ideas were refined through 10 dyad co-design sessions (convergent thinking). Stage 2 involved 3 participants (n=3) and 1 facilitator. Thematic analysis was performed after stage 1, while analytic questioning is being performed for stage 2. Both stages allowed several iterations of the prototypes.

Conclusions: The design of the co-design process, the leadership of the design expertise throughout the process, and the different forms of co-design activities are key elements in this project. We highly recommend that health researchers partner with professional designers or design researchers who are familiar with co-design.

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KEYWORDS

co-design; human-centered design; e-mental health; design expertise; user engagement; patient-centered design; imaginary prototype

Introduction

Background

Digital mental health technologies promise greater access to services, improved quality of care, reduced cost, reduced distance and isolation, and enhanced data quality and accessibility [1-3]. However, there are few examples of successful implementation [2], and 2 systematic reviews reveal that few users are using mental health apps for a long period of time [4,5]. One of the reasons for low user engagement is the lack of user perspective in the design of eHealth solutions [6-8]. In the design of sustainable solutions in health care, we should embrace a human-centered design approach at every level of the design process [9].

Human-centered design refers to a wide range of creative approaches that do not belong to engineering design and that allow end users to significantly and positively impact the design of technologies [10,11]. Co-design is one of them [12]. In co-design, end users are not only considered; they also take part in the creation of solutions alongside researchers, designers, and stakeholders [13]. By engaging them in the creative process, co-design can better address end users' needs and potentially improve user engagement [7,14]. Co-design can also contribute significantly to social change and social innovation [15].

Yet co-design remains an umbrella term, as evidenced by the diversity of initiatives in the scientific literature [16]. There is even a broad range of relationships between actors, from denigration to learning as one [17]. First, it is important to distinguish co-design and participatory design from collaborative design. In collaborative design, participants are "experts operating in their own domain of expertise on a shared problem" [18]. Even if the team is composed of a broad range of expertise, the activities are typically carried out in design teams [19]. The distinction between participatory design and co-design is harder to find in the scientific community, with both terms often being used as synonyms. However, participatory design is a term used in various disciplines to refer to a wide range of participatory activities that are not necessarily related to human-centered design principles and in which there is an irregular and sporadic involvement of end users during the design process. Halskov and Hansen [20] identified fundamental aspects of participatory design: people who are affected by a decision should have an opportunity to influence it; people play critical roles in design by being experts in their own lives; the use situation is the fundamental starting point for the design process; participatory methods are means for users to gain influence in design processes; the goal of participation is to design alternatives to improve quality of life [20]. These aspects also apply to co-design.

In a previous study, we suggested differentiating the 2 terms and reserving the term co-design for a specific form of participatory design rooted in human-centered design [11]. We need to define exactly what it consists of from a research protocol perspective. We consider co-design as a co-creation process at the center of 3 dimensions: collaboration, design, and participation [16]. Potential users are an essential component of any co-design approach, and the quality of the participatory experience offered to them is crucial [14]. Few studies in mental health report using co-design in the development of their applications [11,21], and even fewer embrace its principles [7,22,23]. Most studies in digital mental health simply conduct participatory workshops at specific points during development [24]. Participants usually have the opportunity to provide feedback on the developed solutions, but real cooperation and co-creation remain a challenge [22,25]. Moreover, the role of the expert designers in the development process is often unclear, and in most studies, there is no explicit mention of the presence of designers in the "design" team [11].

However, we have identified a small number of e–mental health studies, still very rare, that assign design and designers an important role in their team, with promising and effective results [26-28]. Co-design requires design. Following the perspective of Manzini, "expert design" (design that comes from people trained in design) is as much a part of a co-design process as "diffuse design" (design that comes from people not trained in design) [29]. The role of the design experts is to design the co-design experience and, as co-design facilitators, to provide conditions conducive to expanding the capabilities of nondesign-trained participants to fully contribute to the co-creation of the solution. People not trained in design bring their natural creativity and experiential knowledge, while design experts bring original ideas and visions, practical design tools, and a structured human-centered design approach derived from their experience [29].

We need to understand what co-design is in e–mental health and how we can implement it. For instance, people not trained in design can be people with a lived experience of mental health problems, families, peer support workers, clinicians, and health professionals. All of them can have their say in the creation process of a digital mental health solution. Therefore, in this paper, we will use this working definition of co-design in e–mental health: a 2-sided human-centered design approach in which (1) end users are engaged from day 1 as partners in the design of the solution and (2) design experts, alongside health researchers, play a key role as facilitators of the overall process and activities.

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Objective

This paper describes an initial co-design research protocol for the development of a mobile app that aims to improve access to mental health care. This protocol highlights the characteristics of a co-design approach in e–mental health rooted in human-centered design and led by design experts alongside health experts. This paper focuses on the first steps of the co-design process for the Mentallys project.

Methods

Study Context

Methodological Approach and Principles

We want to position this paper in line with the approach of "method stories" in co-design [30,31]. Method stories focus on what the designers actually did with methods in particular circumstances [31]. It focuses not only on the results of co-design sessions but also on the way a method has been used and adjusted in a specific situation [30]. Thus, we will first depict the "making of" the method to be used in this project (see section Study Preparation). In addition, our research protocol for co-design claims a certain flexibility that is directly related to design thinking as a cognitive style [32-35]. Designers alternate between phases of divergent thinking (generating multiple ideas in an exploratory way) and convergent thinking (choosing the best ideas and making choices) [36]. They investigate the problem space more for new possibilities and are more open to a variety of prototyping materials and tools [37]. This leads to adjusting the process several times and adapting it to new creative insights that arise, especially in the early stages. Therefore, the protocol we present in this paper shows the basic structure of our co-design process but, since it is led by design, assumes that adjustments along the way can take place to support flexibility in ideation.

Setting

Our study is based on the Mentallys project, located in Montréal (Quebec, Canada). The aim of this project is to improve access to mental health care on a large scale through a mobile app (Mentallys) intended to be distributed for free to the population of a given territory. It is developed from the outset using a co-design process that involves persons with a lived experience of mental health problems, peer support workers, health care professionals (eg, social workers, nurses, psychologists, psychiatrists, and health managers), researchers, design experts, and design students. The Mentallys app will gradually take shape through several steps of co-design, prototyping, and real-world testing in an iterative loop of continuous improvement.

Study Preparation

The Mentallys project officially took shape in 2019, prior to the COVID-19 pandemic, and funding and ethics approval were obtained in 2020. Because of the lockdowns and remote work, we had to develop a system of 100% web-based workshops. To this end, we partnered with a design studio specialized in service design and co-design. Due to health restrictions, they had already started this type of practice. One designer (SR) from their team joined us and helped us prepare and initiate stage 1 of the co-design.

First, we set the objective: to explore ideas and desirable features for the Mentallys app. Second, we designed and implemented the co-design experience. The following design experts participated in this step: (1) one social design researcher from another university, (2) one service designer (SR) from the design studio we partnered with, and (3) 5 design researchers and students from our internal co-design team. Their contributions are detailed below.

1. The external social design researcher was Prof Philippe Gauthier, who is highly experienced in co-design practice for Montreal public libraries. We conducted an unstructured interview with him to gather his feedback and advice, particularly on how to initiate the co-design process in the most engaging way possible for participants. The interview highlighted the importance of what Dr Gauthier and his colleagues call "imaginary prototypes," "starting fictions," or "possible concepts," which they have shown to play a structuring role in fostering collective ideation, engagement in co-creation, and the organization of co-design workshops [38]. Gauthier and colleagues sometimes refer to these imaginary prototypes as "martyr concepts" to emphasize that they are typically inadequate concepts that participants are invited to criticize [39]. We prefer to think of them as provocative concepts or heuristic provocations, in the sense that they provoke reactions and promote the discovery of new ideas. This led us to build our co-design workshops with imaginary prototypes of the Mentallys app screens, presented as low-fidelity wireframes (having the appearance of being quickly drawn by hand). Workshop participants would then discuss and comment on these imaginary prototypes.
2. The service designer (SR) from the design studio we partnered with is one of the studio's founders and is the fifth author of this paper. When we contacted her in June 2020, she was already experienced in web-based co-design workshops, which was something relatively new in the early days of the COVID-19 pandemic. With her and thanks to her, we considered a structured co-design process able to take place entirely on the internet via a visual collaboration platform. As part of this process, each co-design workshop will have its own visual dashboard in which collaborative spaces will be organized, allowing each participant to comment on an imaginary prototype using web-based post-it notes (Figure 1). The process will rely on the role of several design experts acting as facilitators of co-creation with the participants. These designer-facilitators will act on several levels: stimulating individual and collective ideation, inspiring and moderating the conversation, supporting the visual formatting of ideas, and helping with the use of the software. Our partner service designer (SR) will participate as a cofacilitator in the first 2 co-design workshops to help us fine-tune the method, and our internal co-design team will then conduct the rest of the workshops alone.
3. Our internal co-design team was initially composed of 3 people (SV, SB, and SR) and then evolved to 5 people to meet the expected needs for facilitation (4 facilitators on

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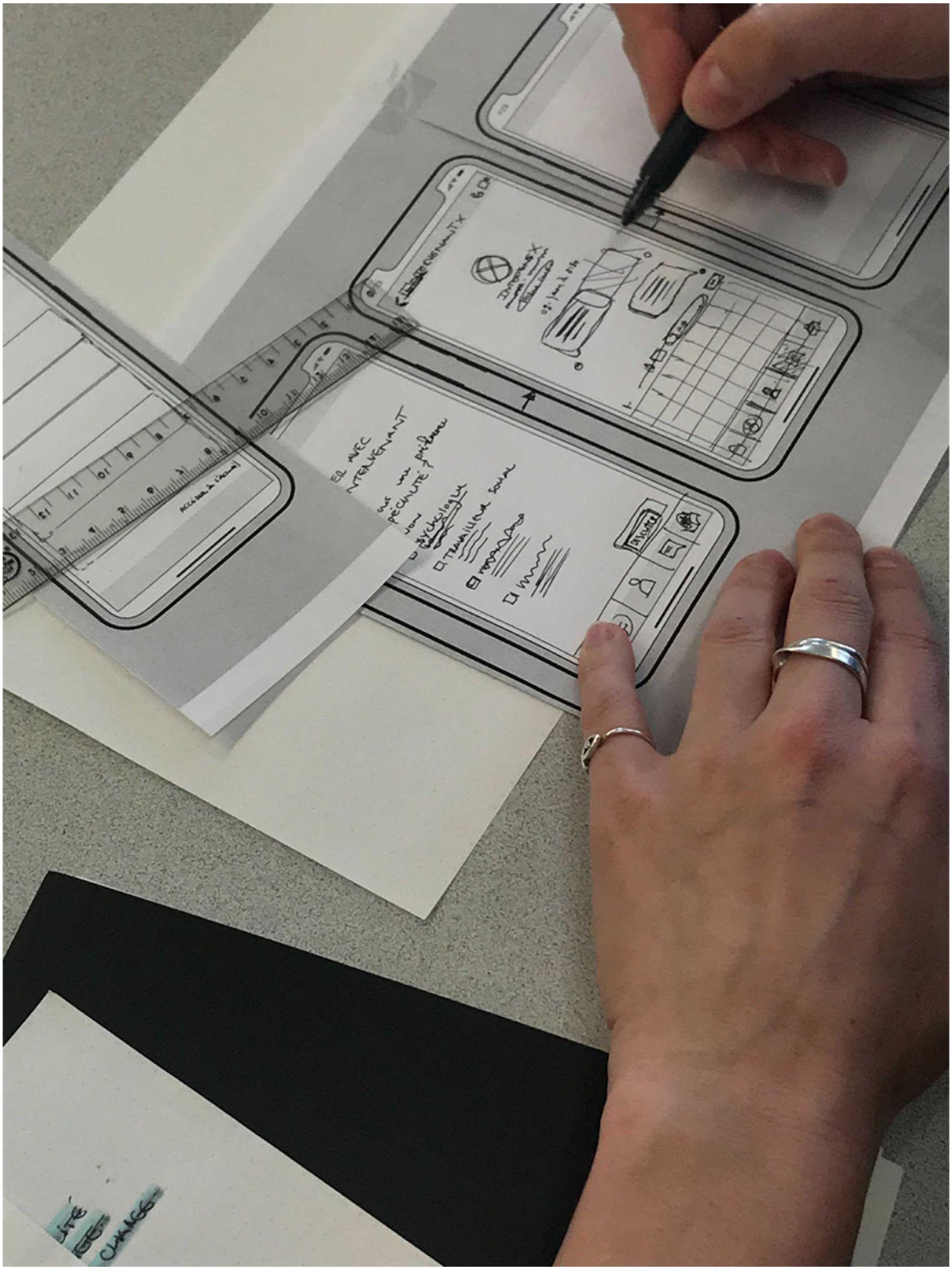
average per workshop): 1 design researcher (SV) experienced in interaction design with a background in clinical psychology and philosophy (principal investigator); 1 postdoctoral researcher (SB) with a background in industrial design and research expertise in co-design; 1 researcher in occupational therapy (MD) familiar with new technologies and participatory design; 1 doctoral student in service design with expertise in interaction design; and 1 master's student in design with expertise in graphic design and with personal experience of mental health problems. Highly experienced in design and familiar with the subject of mental health, our team will adopt the co-design method from the first workshops and then develop, adapt, and customize it through subsequent workshops. This will include the continuous design work of the co-design experience between workshops (Figure 2).

Figure 1. Screenshot of a collaborative space for commenting on an imaginary prototype.



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Figure 2. A preliminary sketch of an imaginary prototype in between 2 workshops.



Study Design

Our study is based on the core concepts of design thinking. Originally described as a cognitive style [33,34,40], design thinking is now widely recognized as an organizational resource for innovation [41]. It was popularized by American design agency IDEO, especially its former CEO Tim Brown, and defined as a methodology for innovation with a human-centered design ethos [42]. Our study design is inspired by design thinking as integrating thinking composed of 3 dimensions: desirability, feasibility, and viability [43]. Desirability relates to "what is desirable from a human point of view," that is, people's needs; feasibility relates to "what is technologically feasible," and viability relates to "what is economically viable" [44].

In an e–mental health context, we assume that (1) desirability relates to what is desirable and acceptable for people with a lived experience of mental health problems, families, peer

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support workers, clinicians, and health professionals, which takes into account their needs, expectations, frustrations, and concerns; (2) feasibility relates to what is digitally and organizationally feasible within the health system; and (3) viability relates to what is economically acceptable for all stakeholders (business model) and environmentally sustainable.

Based on these 3 dimensions, we are planning 3 design phases: phase 1, focusing on exploring desirability, phase 2 exploring feasibility, and phase 3 exploring viability. In this study, we present only phase 1, desirability, since it will be entirely focused on co-design.

Recruitment

After obtaining an ethical certificate for the Mentallys project, we will launch a call for participation through our channels for the 3 types of participants: persons with a lived experience of mental health problems (n=10), peer support workers (n=10), and health professionals (n=10). Eligibility criteria in terms of age and language will be the same for all participants: Age (18-65 years) and being able to communicate in French. A diverse representation of ages, genders, and ethnicities will be sought.

For those with lived experience, additional eligibility criteria will be added: having experienced at least one anxiety or depressive episode in adulthood and within the past 2 years that has fully resolved or is currently at the mild to moderate level.

Ethics Approval

This project has been approved by the Institutional Human Research Ethics Committee of the Université du Québec à Montréal (No. 4425_e_2020).

Participants will sign an information and consent form, giving their free and informed consent to the research and publication, including their participation. They will be well informed that all personal information collected about them during the study will be coded to ensure confidentiality. This data will be kept under lock and key by the study leader for a period of 5 years after the end of the validity period of the research grant obtained, after which it will be destroyed. During this period, only members of the research team will have access to them. If the results of this research are presented or published, they will not be identified. All participants will receive monetary compensation (ranging from US $55 to US $75) for each time they participate.

Data Collection and Analysis

Textbox 1 shows the initial data collection and analysis strategy.

Participants will be divided into subgroups of 4 or 5 participants (1 subgroup per facilitator) and led by the facilitators to comment freely, generate thoughts, and share new ideas around the imaginary prototypes while being asked reflective questions by the facilitator. Imaginary prototypes will be delivered to participants in the form of wireframes. Well-known in the web industry, wireframes are visual schematics or screen blueprints that help represent and communicate the content and features of an app or website. Most often, wireframes are made with a low-fidelity design, that is, imitating a quick drawing by hand or a simple design with minimal graphic details (Figure 3).

Participants will directly comment on wireframes through the collaborative visual platform, mostly using web-based post-its (a different color for each participant; Figure 3). If necessary, a designer-facilitator with expertise in interaction design will be able to create a wireframe in real time based on the ideas shared by the participants using other annotation tools (Figure 4).

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Textbox 1. Plan for the Mentallys co-design process (phase 1).

Dimension

- Desirability

Objective

- Exploring ideas and desirable features for the Mentallys app

Nature of activities

- Group co-design workshops

Number of activities

- 5

Expected duration

- 3 months

Participants

- 10 clinicians
- 10 people with lived experience of a mental health problem
- 10 peer support workers

Facilitators

- 1 service designer from a partner design studio (SR)
- 1 design researcher experienced in interaction design (SV)
- 1 postdoctoral researcher in design and co-design (SB)

Modality

- Online

Data to be collected

- Participant verbatim comments on prototypes (audio data)
- Participant verbatim discussions (audio data)
- Web-based post-its and comments on prototypes (visual or textual data)

Data collection tools

- Video conferencing software (Zoom; Zoom Video Communications, Inc)
- Visual collaboration platform (Miro; RealtimeBoard Inc)

Data analysis

- Thematic analysis [45]

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Figure 3. Sample of low-fidelity wireframes used for imaginary prototypes.

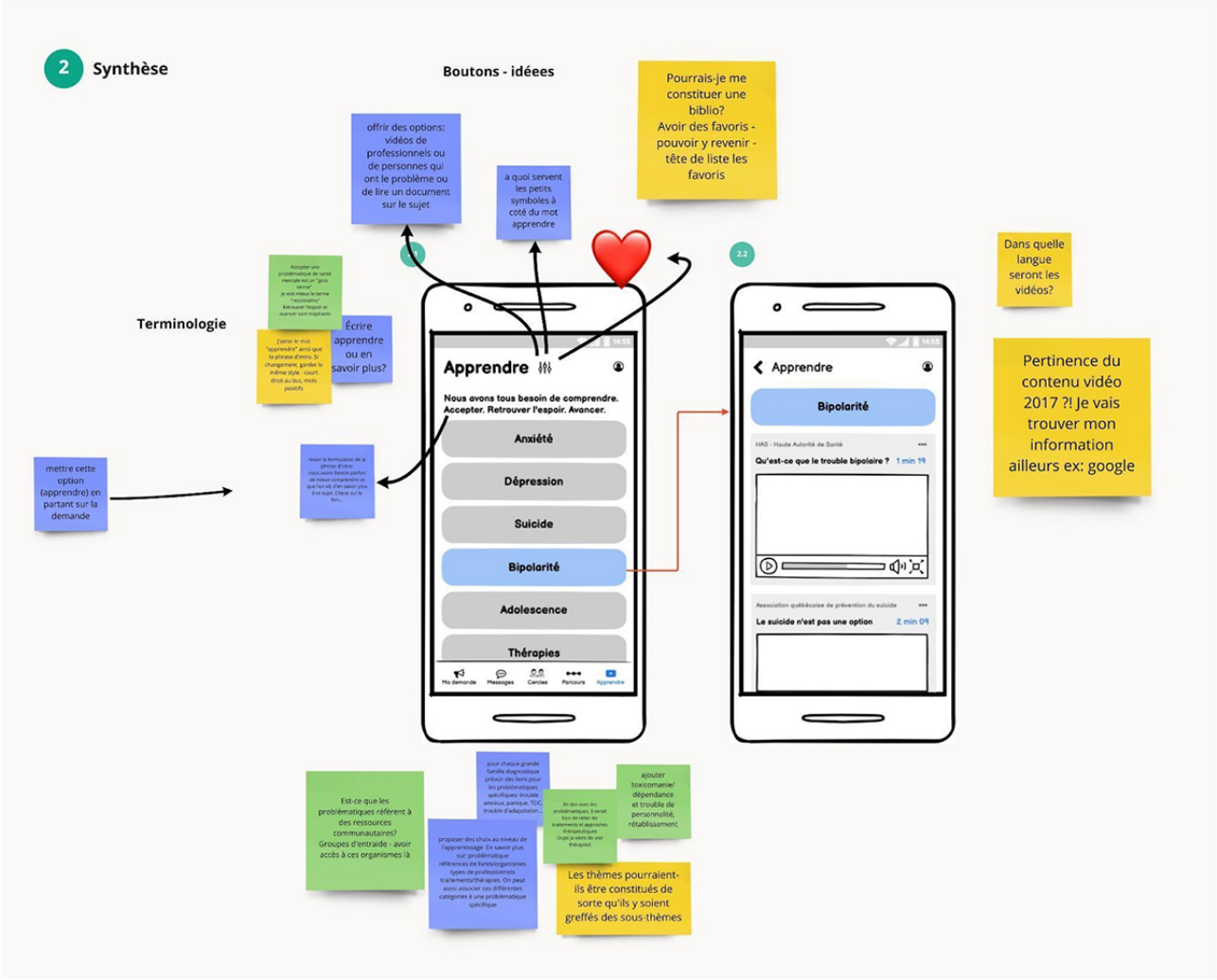


Figure 4. Sample of a wireframe incorporating participants' ideas created in real time during a workshop.



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All the collected data will be analyzed through a thematic analysis. Thematic analysis is essentially a method for identifying and synthesizing the themes present in a corpus. In accordance with Paillé and Mucchielli [45], themes will be assigned to ideas, questions, and challenges that emerge from the workshop. They will then be grouped into categories. The process will be conducted jointly by the second author (SB) and a research assistant (a doctoral student) familiar with this process. The differences will be discussed between analysts in order to reach an interrater agreement.

Results

Overview

Our study received funding on June 2, 2020, from the Fonds de recherche du Québec (#2021-AUDC-283359). It received ethical approval on December 1, 2020, from the "Comité institutionnel d'éthique de la recherche avec des êtres humains" at the Université du Québec à Montréal (certificate number: 4425_e_2020). Recruitment began immediately, in December 2020, and lasted until the end of January 2021.

Here, we present the status of the co-design process for the Mentallys project. Consistent with the flexible methodology principle, the co-design activities have been conducted in 2 stages so far: one stage in group co-design workshops (February 2021 to June 2021) and one stage in dyad co-design sessions (April 2022 to July 2022). Only some of the participants from stage 1 participated in stage 2, since stage 2 required a very small number of people (Table 1).

Table 1. Sociodemographic data of the participants in both stages.

Variable	People with a lived experience of a mental health problem (n=2)	Peer support workers[a] (n=5)	Clinicians (n=7)
Gender, n (%)			
Women	2 (100)	4 (80)	4 (57)
Men	0 (0)	1 (20)	3 (43)
Age range (years), n (%)			
18-24	0 (0)	0 (0)	0 (0)
25-34	0 (0)	0 (0)	0 (0)
35-44	1 (50)	0 (0)	1 (14)
45-54	1 (50)	4 (80)	2 (28)
55-65	0 (0)	1 (20)	4 (58)
Geographical distribution, n (%)			
Montréal	1 (50)	2 (40)	4 (58)
Other regions in Quebec	1 (50)	3 (60)	1 (14)
France	0 (0)	0 (0)	2 (28)

[a]Peer support workers are also people with a lived experience of a mental health problem.

Stage 1: Exploring Ideas Through Group Co-Design Workshops

Stage 1 took place from February 2021 to June 21, 2021. We recruited 14 end users (see table 1). Participants have been divided into 2 groups. Group A included 7 clinicians (5 psychologists and 2 psychiatrists), and group B included 7 people with lived experience of a mental health disorder and peer support workers. We conducted 6 co-design workshops (rather than 5, as planned). Two workshops were held with group A, 2 workshops were held with group B, and 2 workshops were held simultaneously with both groups (Textbox 2).

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Textbox 2. Results summary of co-design (stage 1).

Thinking

- Divergent

Dimension

- Desirability

Objective

- Exploring ideas and desirable features for the Mentallys app
- Collecting user experiences and issues

Nature of activities

- Group co-design workshops

Number of activities

- 6

Duration

- 5 months

Data collection period

- February 2021 to June 2021

Participants

- 7 clinicians (5 psychologists, 2 psychiatrists)
- 2 people with lived experience of a mental health problem
- 5 peer support workers

Facilitators

- 1 service designer from a partner design studio (SR)
- 1 design researcher experienced in interaction design (SV)
- 1 postdoctoral researcher in design and co-design (SB)
- 1 researcher in occupational therapy experienced in participatory design (MD)
- 1 PhD student in service design with a background in interaction design
- 1 master's student in design with lived experience of a mental health problem

Modality

- Online

Prototypes (medium)

- Imaginary (wireframes)

Data types

- Participant verbatim comments on prototypes (audio data)
- Participant verbatim discussions (audio data)
- Web-based post-its and comments on prototypes (visual or textual data)
- Additional prototypes made in real time by facilitators (images)
- Ad hoc diagrams and visual maps (images)

Data collection tools

- Video conferencing software (Zoom; Zoom Video Communications, Inc)

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- Visual collaboration platform (Miro; RealtimeBoard Inc)

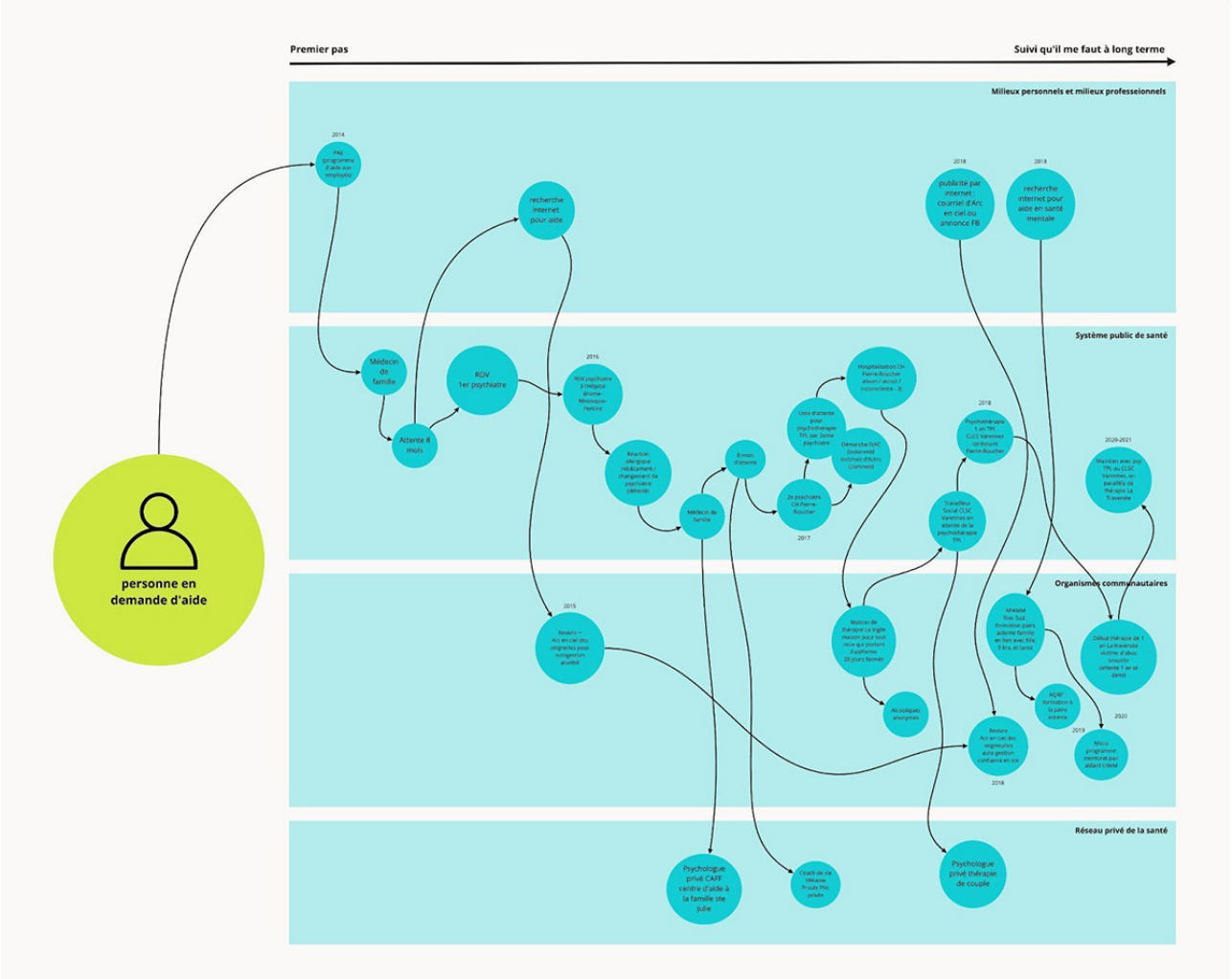
Data analysis

- Thematic analysis [45]

This stage encouraged divergent thinking with the goal of generating ideas and identifying desirable features for the Mentallys app through imaginary prototypes and social conversations with different types of end users. Six facilitators were involved in the co-design activities, as it turned out that small groups were more appropriate for web-based workshops.

As planned, audio feedback from participants on the prototypes was collected and analyzed using thematic analysis. Moreover, visual data were eventually collected during a workshop with group B as we realized that we did not sufficiently understand their reality, which hindered the co-design process. Participants were invited to create care pathway maps (Figure 5), adjusting the initial protocol according to our flexible methodological approach. Those data have been analyzed using qualitative and quantitative content analysis [46].

Figure 5. Sample of a care pathway map.



Stage 2: Refining Ideas Through Dyad Co-Design Sessions

Stage 2 ran from April to July 2022. Two participants continued their involvement (1 peer support worker and 1 person with a lived experience of a mental disorder), and 1 health professional was recruited (a medical resident). The co-design activities did not take the usual form of group workshops but were rather conducted as dyad sessions, again adjusting for specific situations according to our flexible methodological approach (Textbox 3). This was necessary in order to explore sensitive and confidential topics while respecting the privacy of the participants and building trust. A total of 10 dyad co-design sessions were conducted for 3 months: 5 web-based sessions with the person with lived experience of a mental health problem, 2 web-based sessions with the peer support worker, and 3 in-person sessions with the medical resident.

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Textbox 3. Results summary of co-design (stage 2).

Thinking

- Convergent

Dimension

- Desirability

Objective

- Making choices among possible features
- Refining and validating key features of the Mentallys app

Nature of activities

- Dyad co-design sessions

Number of activities

- 7

Duration

- 3 months

Data collection period

- April 2022 to July 2022

Participants

- 1 clinician
- 1 person with lived experience of a mental health problem
- 1 peer support worker

Facilitators

- 1 design researcher (principal investigator)

Modality

- Online

Prototypes (medium)

- Real (graphic, interactive, clickable)

Data types

- Participant verbatim comments on prototypes (audio data)
- Participant verbatim discussions (audio data)
- Facial expressions and body language (video data)
- Web-based post-its and comments on prototypes (visual or textual data)
- Additional prototypes made in real time by facilitators (images)
- Ad hoc diagrams and visual maps

Data collection tools

- Video conferencing software (Zoom; Zoom Video Communications, Inc)
- User Interface (UI) design prototyping software (Figma; Figma, Inc)
- Research diary

Data analysis

- Analytic questioning [45]

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This stage encouraged convergent thinking with the goal of validating ideas that can satisfy end users in the real world through real prototypes. One facilitator (SV) was involved in all sessions. For each session, the objective was to refine and validate a set of features through real, clickable, and testable prototypes shared on screen using a collaborative design and prototyping tool. End users could either verbally comment on the features or suggest new features in real time (Figure 6) or think about it at home and bring ideas to the next session (Figure 7).

Audio feedback from participants on the prototypes was collected and is being analyzed using an analytic questioning method inspired by Paillé and Mucchielli [45]. In this method, research questions are further developed and used as a framework to analyze the data. This is the most suitable approach when answers to a certain number of explicit questions are sought [45], which is the case for this convergent stage.

Figure 6. High-fidelity prototype being commented on and improved in real time through screen sharing.

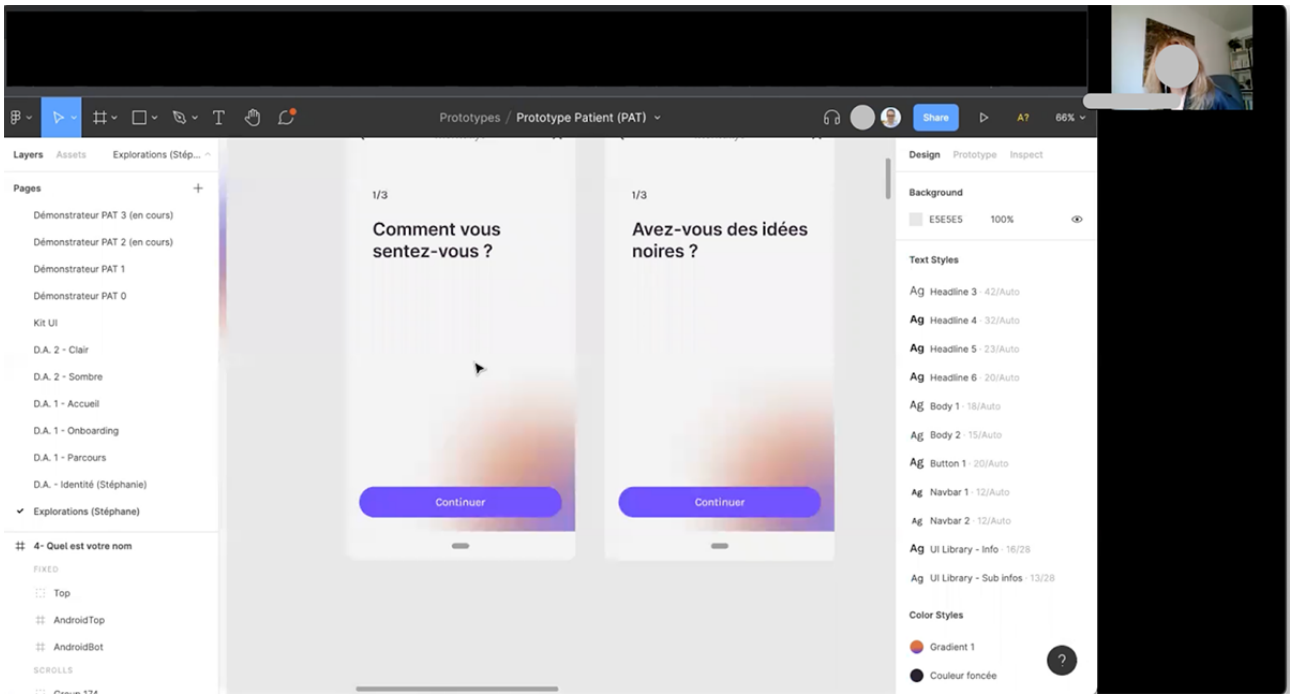
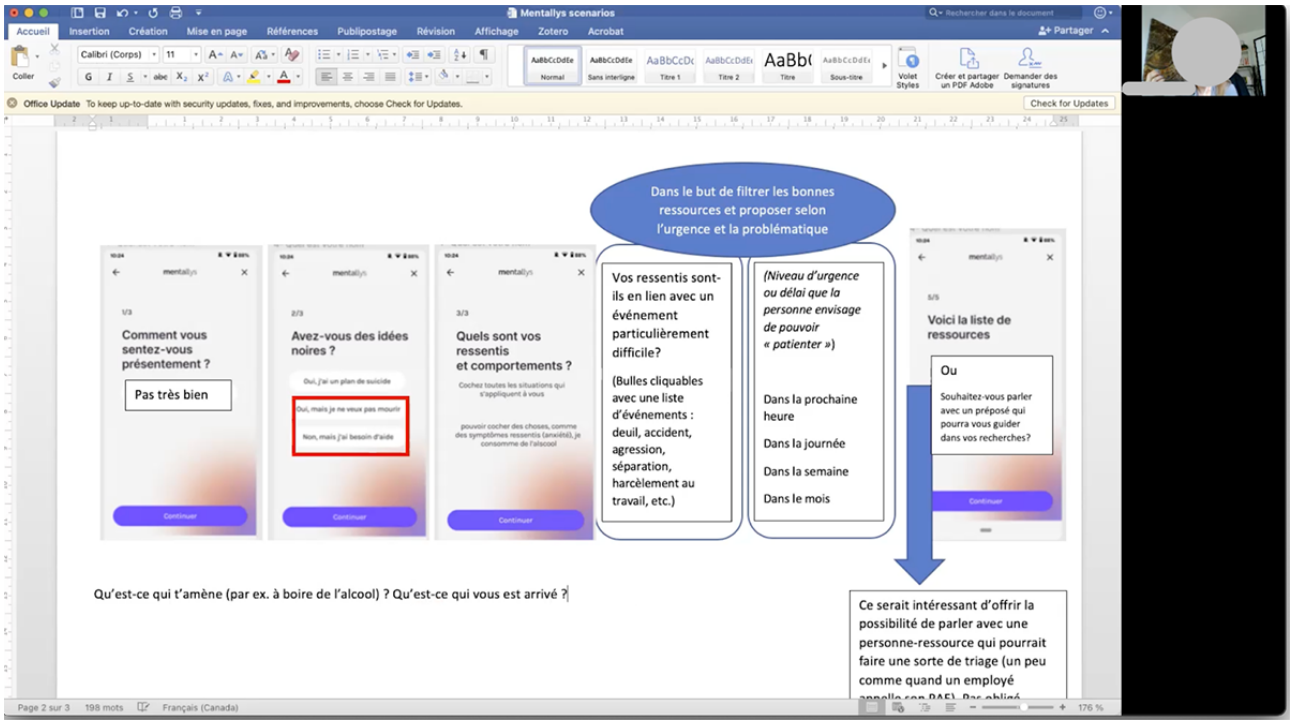


Figure 7. Mix of high-fidelity prototypes and new ideas generated by the participant in a Word document.



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Discussion

Principal Findings

In this study, we described the characteristics of a co-design research protocol in e–mental health rooted in human-centered design and led by design experts alongside health experts. This protocol focused on initializing the co-design process and centered on exploring the desirability of a mobile app that aims to improve access to mental health care by collecting data on the needs, expectations, frustrations, and concerns of people with lived experience of mental health problems, peer support workers, and clinicians. We successfully implemented a 2-stage protocol, with group co-design workshops in the first stage and dyad co-design sessions in the second. For both stages, the role of expert design facilitators was crucial. In this discussion, we want to highlight a few challenges and lessons learned.

Initiating the Co-Design

Our preliminary design work on the co-design experience was critical to the implementation and success of the process, especially partnering with a design studio specialized in service design to help us structure the approach and become familiar with the best-suited tools. This allowed us to prepare and conduct the first workshops according to the best practices in human-centered design and, afterward, to continue doing so independently. We now have the full capacity to devise and manage further co-design stages thanks to the skills our team has acquired. These skills are necessary to create a positive group dynamic that encourages each participant's creativity. In co-design, co-designers participate with different perspectives, which can lead to frustration and conflicts among participants who do not always understand each other [47-49]. By structuring activities using a human-centered design perspective, optimizing collaboration by orienting the process toward positive and constructive interactions among participants, and leading participants into a creative design thinking mode, facilitators can create this positive dynamic and foster creativity [14]. Expert design skills are also needed to ground the co-design process in concrete prototypes from the start, which become mediators of conversation and ideation. Prototypes are a useful co-design tool to engage participants in the design conversation. Prototypes allow opposite opinions to exist and are socio-material, welcoming a neutral space and facilitating the negotiation of issues [50]. In this project, where the subjects discussed were often very sensitive, prototypes played a significant mediator role to ensure constructive conversation.

Adapting the Process Along the Way

Even when highly organized and structured, co-design is a creative process that inevitably involves unforeseen ideas and insights. Unique to each design process, this characteristic is known as the "creative leap" [51]. To facilitate a co-design process, one must be attentive to these creative leaps, be able to welcome them, and integrate them into the process along the way. This involves moving away from the rigidity of traditional methodological protocols in research in order to be able to adapt the protocol as it unfolds. The difficulty lies in maintaining a balance between following the planned protocol and making the necessary adjustments resulting from creative leaps. In this study, creative leaps led us to focus first on 1 major phase (desirability) instead of tackling all 3 phases from the outset (desirability, feasibility, and viability), which were itself divided into 2 stages (group co-design and dyad co-design). Therefore, we could only study the desirability dimension, as it turned out to require much more time. Indeed, rather than the 3 months planned, this study lasted a total of 8 months (5 months for stage 1 and 3 months for stage 2). Other similar studies also mentioned that some stages of the co-design process took longer than expected [52].

Doing Co-Design in Dyads

Our study suggests that co-design can be dyadic. During stage 2, we organized the co-design sessions in dyads, that is, one-to-one meetings, instead of the standard group workshops. Even if it was not a group activity, it was true collective creativity. Since co-design is a collaboration between diffuse design and expert design [29], it can start with 2 people, provided one of them is a design expert. As a specific point of co-creation, co-design is collective creativity that can be shared "by two or more people" [53]. In our protocol, each dyad session was a conversation between a person not trained in design (the end user) and a member of our team with design expertise (the principal investigator). Both were equal speakers, each able to bring his or her points to the table. The 3 main aspects of co-design, that is, collaboration, design, and participation [16], were present but manifested dyadically. Through the accumulation of dyadic sessions, a mass effect in data collection occurs that is comparable to that of a larger group. In-depth analysis of the results will provide a better understanding of the contribution of dyadic sessions to the design process.

Leading Co-Design Thanks to Design Expertise

Our co-design research protocol focused on a close and effective collaboration between experts in design and end users throughout the process. While other e–mental health research projects have shown less involvement on the part of the designers in their process, we aimed at creating a continuous collaboration environment between designers and users. In fact, very few studies mention the presence of designers on their teams and mostly focus on involving end users [11]. The challenge in these types of projects is how to properly incorporate users' needs into the project, redefine them properly, and bridge them while the project evolves. Design expertise leadership is a key component in achieving that goal since design practice and research focus on users' unmet needs through well-understood and applied inclusive design approaches coming from design expertise [54]. Designers are sensitive to how care is received through user-centered practices [55] and can use a variety of flexible methods and tools to enhance communication about the project.

Limitations and Future Work

While co-design is central to our approach, we recognize that other elements must be taken into account to ensure the development of a mental health app that meets the needs of users and is likely to be adopted. Close collaboration with the software development team is important, as is usability testing of the app [56] or user experience design [57]. One should also

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assess the viability of the solution, develop a business model for the app, and plan the implementation of the technology [42,58]. This points to the importance of transdisciplinary work in the development of e–mental health solutions from a human-centered design perspective [59]. This is why the Mentallys project relies on other research and development activities complementary to co-design: a full design team, including branding design experts and user experience and user interface designers; a business accelerator program and business model definition coaching; a partner technology company that cosupervises the software development; and several partner health institutions to conduct real-world testing.

Conclusions

This paper presented a research protocol rooted in human-centered design related to the Mentallys project. More precisely, we sought to present how a co-design approach can be used to initiate the design and development of a mental health mobile app. The preliminary design of the co-design process, the leadership of the design expertise throughout the process, and the different forms of co-design activities are key elements in this project. We expect that this process can lead to the development of an app that is more engaging and better meets the important needs of people seeking access to mental health services. Overall, this research protocol may inspire other research teams that want to integrate co-design as a more user-centered approach to the development of e–mental health solutions. For this purpose, we highly recommend that health researchers partner with professional designers or design researchers who are familiar with co-design.

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Data Availability

The data sets generated during this study are not publicly available since the research is still ongoing, but they are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

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Protocol

Using Wearable Devices and Speech Data for Personalized Machine Learning in Early Detection of Mental Disorders: Protocol for a Participatory Research Study

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Abstract

Background: Early identification of mental disorder symptoms is crucial for timely treatment and reduction of recurring symptoms and disabilities. A tool to help individuals recognize warning signs is important. We posit that such a tool would have to rely on longitudinal analysis of patterns and trends in the individual's daily activities and mood, which can now be captured through data from wearable activity trackers, speech recordings from mobile devices, and the individual's own description of their mental state. In this paper, we describe such a tool developed by our team to detect early signs of depression, anxiety, and stress.

Objective: This study aims to examine three questions about the effectiveness of machine learning models constructed based on multimodal data from wearables, speech, and self-reports: (1) How does speech about issues of personal context differ from speech while reading a neutral text, what type of speech data are more helpful in detecting mental health indicators, and how is the quality of the machine learning models influenced by multilanguage data? (2) Does accuracy improve with longitudinal data collection and how, and what are the most important features? and (3) How do personalized machine learning models compare against population-level models?

Methods: We collect longitudinal data to aid machine learning in accurately identifying patterns of mental disorder symptoms. We developed an app that collects voice, physiological, and activity data. Physiological and activity data are provided by a variety of off-the-shelf fitness trackers, that record steps, active minutes, duration of sleeping stages (rapid eye movement, deep, and light sleep), calories consumed, distance walked, heart rate, and speed. We also collect voice recordings of users reading specific texts and answering open-ended questions chosen randomly from a set of questions without repetition. Finally, the app collects users' answers to the Depression, Anxiety, and Stress Scale. The collected data from wearable devices and voice recordings will be used to train machine learning models to predict the levels of anxiety, stress, and depression in participants.

Results: The study is ongoing, and data collection will be completed by November 2023. We expect to recruit at least 50 participants attending 2 major universities (in Canada and Mexico) fluent in English or Spanish. The study will include participants aged between 18 and 35 years, with no communication disorders, acute neurological diseases, or history of brain damage. Data collection complied with ethical and privacy requirements.

Conclusions: The study aims to advance personalized machine learning for mental health; generate a data set to predict Depression, Anxiety, and Stress Scale results; and deploy a framework for early detection of depression, anxiety, and stress. Our long-term goal is to develop a noninvasive and objective method for collecting mental health data and promptly detecting mental disorder symptoms.

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KEYWORDS

machine learning; speech analysis; Depression, Anxiety, and Stress Scale; DASS21; depression; anxiety; stress; mood disorders; mental health; voice; smartwatches; wearables

Introduction

Overview

The Quantified Self movement proposes that self-tracking, measurement, and quantification of one's daily life using technology can lead to personal insights that can help individuals improve their behaviors and health. Recent advances in sensors and their embedding in many wearables and mobile devices have made this idea extremely easy to adopt [1]. Currently, affordable consumer devices contain sensors that continuously and unobtrusively track one's activity, sleep, heart rate, and stress levels. Furthermore, many mobile apps enable individuals to record multimedia throughout their day, such as media, images, audio, and video. Hundreds of MBs of data can be collected from an individual every day [2], thus creating a data stream amenable to machine learning algorithms that can capture patterns related to different behavioral, cognitive, and mental states. In this project, we investigate the usefulness of activity trackers and voice recordings as data sources through which models of mental health indicators can be extracted. More specifically, we are interested in examining how personalized models, constructed from long-term individual data streams, compared with population-level models, learned from population-level data in terms of their ability to predict mental health conditions accurately.

We developed a special-purpose app to collect voice, physiological, and activity data for this study. Physiological and activity data are provided by various off-the-shelf fitness trackers, which record steps, active minutes, duration of sleeping stages (rapid eye movement, deep, and light sleep), calories consumed, distance walked, heart rate, and speed. In addition, our study app collects 2 types of voice recordings: the former is a recording of the user reading a specific text, and the latter is a recording of the user responding to an open prompting question, chosen randomly from a set of open questions, without repetition. Finally, the app collects the users' answers to a standard psychological instrument, the Depression, Anxiety, and Stress Scale (DASS21) [3], which quantifies the severity of these 3 mental disorders based on the emotional states during the past week, and the results allow us to set the dependent variable of the machine learning algorithm for its classification.

The data collected through our study have already been used for detecting depression, anxiety, and stress [4]. Smartwatch activity data [5-8] and voice [9-11] have been demonstrated to predict depression, anxiety, and stress with high levels of accuracy. The novelty of our study lies in three pillars:

1. First, our study is designed to collect longitudinal data from each participant. In contrast, previous studies about detecting depression from voice relied on data sets consisting of a single data point per participant for a one-size-fits-all model. In addition, each data point includes 2 different voice samples, 1 text reading and 1 personal response to a prompt. This design enables us to analyze the complete data set to train the classifiers of the DASS21 scores and construct personalized models from each participant's data.
2. Second, besides voice data, our study includes physiological and activity data collected by any number of off-the-shelf fitness trackers, relying on the core subset of common data collected by most such devices today. So far, no study has fused these 2 types of data streams.
3. Third, we are recruiting both English-speaking and Spanish-speaking participants because we aim to develop a language-agnostic, data processing and analysis pipeline.

This paper aims to describe the design of the experiment to capture data from participants and define the study's objectives for analysis to advance research in mental health disorder detection and personalized machine learning in computing science.

Background

Personalized machine learning involves using algorithms trained on user data to automatically learn models and use this knowledge to make predictions from new data. Unlike traditional machine learning methods, the results of these models are tailored to an individual and not to a population [12].

Applications of personalized machine learning include heart rate profiling [13], personalized sleep monitoring [14], personalized chronotherapy [13], and studies that predict risk factors for a particular illness [15,16]. A similarity among the previous applications is that the studies have been longitudinal. Longitudinal studies are particularly useful in personalized machine learning, as they permit researchers to track individual data over time and gather data from various factors affecting the changes observed in the results. In these studies, multidimensional data are collected from individuals, and a model is created for each individual.

Typically, models are constructed for predicting one among a set of alternative future states of interest using a classification technique. For example, Feng et al [17] used binary classification to predict whether a specific drug combination would result in a therapeutic response. Webb et al [18] analyzed data from individuals with major depressive disorders and built a model to predict their likelihood of response to antidepressants. Regression models may be developed to forecast a variable's specific interest value. For example, Bertsimas et al [19] used a k-nearest neighbors regression model to predict blood sugar levels based on individual data from patients with type 2 diabetes. By leveraging the user's features, the learning

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algorithms capture specific behaviors of the individual, and their performance is optimized for that particular person.

Early indicators of mental health disorders could motivate early treatment, potentially preventing more severe symptoms that could affect the quality of life of an individual. Preventing these diseases could reduce the symptoms' recurrence and associated disabilities [20]. These indicators could motivate people to seek the advice of a health professional and receive a prompt and correct diagnosis that could prevent severe depression symptoms in the future. Symptoms are usually diagnosed based on the patient's description and mental state. Hence, creating a tool to detect early signs of mental diseases is essential to take the necessary measures to prevent major onsets of these diseases.

Therefore, one must address two key questions: (1) *What types of data convey information relevant to extracting indicators of mental-health conditions?* and (2) *How can one collect ground truth on whether the individual is experiencing mental-health challenges?* There is substantial evidence to support the idea that the onset of mental health disorders often coincides with changes in the individual's daily activity patterns [21]. This information can be realistically captured by the data collected through activity trackers. Although significant studies have been conducted about extracting mental health indicators from activity trackers [4,8], our study aims to use this information without considering the brand, as we strive to compare traditional machine learning methods with personalized modeling. This approach may allow more widespread and accessible data collection, providing more comprehensive insights into mental health. Furthermore, recent studies have established that sound features and content from speech capture relevant information that can be exploited to recognize mental health conditions. This is why our study envisions a regular collection of 2 types of voice recordings: one recording of the users reading a standard text and a second recording of the user responding to a prompting question. To collect the ground truth about our participants' mental health status, we used the DASS21 instrument, validated for depression, anxiety, and stress [22]. Finally, recognizing that activity data and voice features may exhibit different patterns across individuals, our study is designed to construct personalized models in addition to cohort-based models. We anticipate that these personalized models could improve the accuracy of detecting mental health disorders.

Related Studies

Machine learning algorithms have been increasingly used for detecting depression, anxiety, and stress in recent years. Several studies have explored machine learning techniques, including deep learning and parametric and nonparametric techniques, to identify patterns in data from physiological measures, self-reported symptoms, and social media posts [23-25]. These studies have shown promising results in accurately predicting mental health outcomes, indicating the potential for machine learning to improve the detection and management of depression, anxiety, and stress.

Personalized machine learning has been increasingly used in health care to provide tailored interventions to individuals based on their unique characteristics and health status. Several studies have demonstrated the potential of personalized machine learning in improving health outcomes, such as predicting patient outcomes, personalized treatment recommendations, and identifying at-risk populations [26,27]. In mental health care, customized machine learning has been used to identify individuals at high risk for suicide and to provide personalized interventions based on individual characteristics and needs [28].

Wearable devices, such as smartwatches and fitness trackers, have emerged as a promising tool for detecting mental health conditions. Several studies have investigated wearables data in combination with machine learning algorithms to detect various mental health conditions, such as depression, anxiety, and bipolar disorder, by analyzing physiological data, such as heart rate and sleep patterns [29,30]. These studies have shown that wearables can provide a discreet and objective way to monitor mental health, allowing for early detection and personalized treatment. However, most studies are performed in clinical setups or with specific features found only with unique equipment. We address this issue by acquiring the core subset of common features among 3 major brands (Fitbit, Samsung, and Garmin) of fitness trackers for framework flexibility.

Using voice and machine learning to detect mental health issues is an active research area. Dematties et al [31] used speech features extracted from recorded interviews to distinguish between individuals with and those without major depressive disorder. Chen et al [32] analyzed the speech of patients with schizophrenia and found that certain speech features indicated the severity of their symptoms. Wang et al [33] used a machine learning algorithm to predict depression and anxiety from speech data obtained during therapy sessions. These studies suggest that voice and machine learning can potentially be valuable tools for the early detection and management of mental health issues. However, the analyzed data consist of a single data point per participant and language. Thus, the resulting data set could provide great insight into multilingual machine learning models and a deep analysis of mood over time.

Hypothesis and Research Questions

Our study is designed to investigate the following hypothesis: basic activity tracking, in combination with regularly and consistently captured speech data, can provide the basis for extracting accurate indicators of several prevalent mental health conditions, in this case, depression, anxiety, and stress.

Our focus is to comprehend the relative usefulness of the 2 data streams. We aim to investigate the significance of speech data when the user is reading a neutral text versus reflecting about their daily life experiences. In addition, we aim to compare the accuracy of personalized machine learning models with population-level models and evaluate the robustness of these models across various languages.

Our study will answer the following research questions:

1. How does voice modality affect predictive machine learning models, specifically comparing the impact of voice from a neutral text reading against that of voice from open questions about life experiences?
2. What critical predictive features exhibit strong association with DASS21 responses from participants?

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3. To what extent does personalized machine learning demonstrate superior predictive power in mental health compared with traditional, one-size-fits-all models in the context of DASS21 responses?

Methods

Study Overview and Design

The study analyzes and applies machine learning models to behavioral data extracted from sensors embedded in wearable devices and voice to predict DASS21 results in participants. The data consist of two principal components: (1) sensors embedded in standard smartwatch devices (brands: Samsung, Fitbit, and Garmin) and (2) voice recordings.

Modern sensing technologies in wearable devices continuously measure the body's autonomic response. These responses include continuous heart rate, daily steps, speed, burned calories, and sleeping patterns (minutes in rapid eye movement sleep, deep sleep, and light sleep) and are monitored daily for the duration of the study. The voice data are collected using 2 methods: the first one is a text reading, which stays consistent with all participants, and the second one is a free-form speech (1 open question is asked). For 2 months, every third day, the participant submits voice samples and DASS21 answers.

The data will show variational patterns that could explain the DASS21 results, and machine learning algorithms can capture these consistent patterns that allow us to predict depression, anxiety, and stress.

Data Collection

Overview

Data collection for this study is ongoing. We expect to collect multidimensional data from at least 50 participants attending 2 major universities—the University of Alberta and Tecnológico de Monterrey, the former from the campus in Edmonton, Alberta, Canada, and the latter from 2 campuses in Mexico, Monterrey and State of Mexico campuses.

The selection criteria considered students aged between 18 and 35 years, with no chronic physical illnesses, high levels of chronic pain, or motor disability and who confirmed not being pregnant. Given that informed consent was required, the study excluded individuals with communication disorders, acute neurological diseases, or a history of brain damage.

Each participant contributes data over 2 months. Participants are assigned an alias as an identification number and are asked to download a mobile app on their mobile phones. The app was developed by the researchers in this study and included the mechanisms to collect the voice recordings and DASS21 questionnaires. Once collected, all data are stored in a repository inside the servers of the University of Alberta associated with this ID. Activity data are collected using Fitbit, Samsung, and Garmin smartwatches, and the app was made available only for Android mobile devices to collect voice and DASS21 answers and upload the smartwatch data.

After this initial assessment, the app regularly (every 3 d) prompts the participants to perform the following tasks. We have chosen 3 days as the app use period to collect samples on different days of the week; this could aid in reflecting the effect of day-to-day stress and workload.

Guided Reading

The participants are prompted to read out a paragraph. This task aims to capture as much phonetic variety as possible. For this task, we considered using established English and Spanish text snippets for speech analysis, such as the Calling Stella passage [34].

Free-Form Speech

In this task, the participants are asked 2 questions, randomly selected from a list of questions, to answer freely. This includes describing their hobby, city, favorite person, or memorable event. In addition to intonation, these data will enable us to analyze speech-to-pause ratio and durational features, which may correlate with their psychological condition.

Smartwatch Data

The participant downloads the data from the smartwatch (we provide the instructions depending on the model and brand) and then uploads the data to the app. The number of attributes and amount of data varies depending on the model and brand of the participant's smartwatch. However, we have identified and selected common base attributes of each smartwatch model.

Finally, once the abovementioned recordings are complete, participants are prompted to complete a mental health questionnaire (DASS21). The questionnaire gives us a valid indicator of their anxiety, depression, and stress levels to label the audio recordings.

The app lists the mental health resources available to the students of the University of Alberta and encourages them to seek help if they feel stressed, anxious, or depressed. For participants of Tecnológico de Monterrey, it provides a list of mental health resources available at their campus in Mexico.

Ethical Considerations

The protocol was reviewed and approved by the Research Ethics Office of the University of Alberta (Pro00116909). All participants provided written informed consent after being briefed about the study's goals. The data are collected using secure transfer mechanisms to comply with ethical and personal data privacy requirements.

Data Analysis

Overview

One of the first steps in data analysis is data exploration. Exploratory analysis is a crucial step in data science, as it helps uncover insights and patterns in the data that can inform subsequent analyses and models. It involves summarizing and visualizing the data, identifying relationships between variables, detecting outliers and missing values, and checking for data quality issues. It also helps to identify potential biases or confounding factors that may influence the results of subsequent analyses.

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The purpose of our investigation is to address the abovementioned research inquiries. This section presents our analysis and approaches to examine each question.

Question 1

What is the effect of voice modality on predictive machine learning models, specifically comparing the impact of voice from a neutral text reading against that of voice while answering open questions about life experiences?

This question aims to perform a comparative analysis between 2 different voice data sets. These data sets include 2 recordings taken every third day and the answers to the DASS21 questionnaire. The DASS21 questionnaire result is the independent variable we want to predict. DASS21 adopts a dimensional perspective of a psychological disorder rather than a definite one, and it is designed to measure the severity of depression, anxiety, and stress. The scale consists of a numerical value ranging from 0 to 63. The higher the value, the higher the severity of depression, anxiety, and stress.

For this objective, we aim to train 2 machine learning models: one containing the data of a neutral text reading and the other with the voice while answering open questions. We must extract numerical features that quantitatively represent the audio to train the models. These features include but are not limited to language-agnostic linguistic features (eg, number of words, words/min, lemma/token ratio, and verbs/utterance) and perceptual features such as loudness, brightness, pitch, timbre, and rhythm. We will use ensemble methods, such as random forest and support vector machine for the machine learning algorithms that have been demonstrated to have good performance to detect mood disorders using these features [10], and deep learning methods, such as convolutional neural networks and recurrent neural networks [10,35]. We will test both approaches of machine learning tasks, binary classification and regression. For the classification task, the cutoff points are defined based on the DASS21 scale. All scores above mild scores are considered to be indicative of depression, anxiety, or stress for the classification task.

To validate our results, we will use leave-one-out, stratified cross-validation. This method assures us that by tuning the hyperparameters of our model, these will help to avoid overfitting the models. Several metrics can be used to compare the results, and for evaluating the task as a regressor, we use root mean squared error and R^2. For the classification task, we compare area under the curve and F_1-scores.

Question 2

Overview

What are the key predictive features that exhibit strong association with DASS21 responses from participants?

We aim to perform a feature selection process to identify the variables with the strongest association with the result of DASS21. This step involves selecting a subset of the most relevant features from a large set of potential predictors. It aims to simplify the model and reduce the risk of overfitting. Our data set will contain 3 different variable types: audio, text, and numeric variables. We will use other methods for each variable type to extract features and select the most significant ones.

Audio Features

In the case of audio features, this step will involve feature extraction techniques such as mel-frequency cepstral coefficients and discrete wavelet transform to extract the applicable features from the recordings. These techniques will help us transform the audio signal into a more meaningful representation that can be used as input for our machine learning model.

Text Features

In addition to extracting the audio signal, we aim to extract the transcript from the audio recordings and identify relevant semantic text features using word embeddings. The idea behind using word embeddings is to group similar words in a high-dimensional space, where words with similar meanings and emotional tones are close to each other. Our approach is to input the word vectors as sentences to the machine learning model to classify the emotional tone of the individuals' responses to the open questions.

Numeric Features

We will use wrapper methods to select the most relevant features in our numeric attributes subset, such as recursive feature elimination. This method will evaluate the performance of our machine learning model with different subsets of features by considering the interaction between the distinct variables and their relationship with the target variable.

Finally, after extracting meaningful representations of the audio and text columns in our data set and compressing the numeric features, we will use dimensional reduction techniques such as principal component analysis to reduce the number of features further, while preserving the most critical information, allowing us to visualize the data in 2 or 3 dimensions.

Question 3

To what extent does personalized machine learning demonstrate superior predictive efficacy in mental health compared with traditional, one-size-fits-all models in the context of DASS21 responses?

Personalized machine learning aims to fill the gap of one-size-fits-all models when assessing mental health disorders in people. The collected features could have significant variability among individuals with equal DASS21 assessment. Hence, we aim to supply individual machine learning models trained with personal data to provide personal activity and a baseline to assess whether personalized models outperform cohort-trained models.

We should consider careful preprocessing to clean the data to train a machine learning model. First, we need to consider the presence of outliers. Outliers could bias or influence the decision of our trained algorithms. Hence, applying Mahalanobis distance to our numerical attributes obtained from the activity tracker can aid us in identifying abnormal points of data and treating them. We could cap the score to treat the outliers at a particular value above the 90th or below the 10th percentile. The imbalanced data set is another issue while applying machine

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learning for classification tasks. If the number of instances where one class label is significantly lower than the others, it could bias the model toward the majority class. Therefore, we should consider oversampling or undersampling techniques to remove this bias. Finally, we will consider removing background noise for voice analysis.

For personalized modeling, we should consider using multitasking learning techniques. These techniques leverage data from across the population with deep neural networks and hierarchical Bayesian models [36]. We could also consider implementing ensemble learning, such as random forest and gradient boosting, by training the models with the different data types for each person and using a voting regressor performance to select the most accurate model. The more data we obtain through time from the individual, the more the model will capture the patterns of the individual by retraining the models to adjust to the new data.

After training the models with the leave-one-out technique, we will compare the performance of the regression or classification models to draw our conclusions.

Results

The data collection process started in June 2022. So far, 67% (29/43) of the participants have completed the study protocol, and 33% (14/43) are in the process. The study results will be available at the end of 2023 and published in scientific journals.

Discussion

Expected Findings

This study aims to describe the data collection experiment to capture the mood and activity of students in Canada and Mexico. This data set will consist of longitudinal data from each participant, allowing us to observe our participants' behavior extensively. Each data set entry is labeled with the DASS21 questionnaire, enabling us to apply machine learning algorithms for prediction or classification. The data set includes physiological and activity data from some popular fitness trackers. This allows us to identify a subset of the common underlying data from these trackers. In addition, as we recruit English-speaking and Spanish-speaking participants, the data set will include 2 significant languages, allowing for rich analysis and comparison.

Overall, the high-level objective of this study aims to advance state-of-the-art personalized machine learning for mental health; generate a valuable data set that could be used to predict DASS21 results by applying algorithms of machine learning; and finally, deploy a framework that detects the onset of depression, anxiety, and stress to alert the user and prompt them to consult a professional. Moreover, we aim to compare traditional, cohort, machine learning methods against personalized methods and propose a methodology to detect multiple mood disorders not limited to depression, stress, and anxiety. Finally, we will compare the relative value of 2 speech data sources, free speech and simple text reading, for mood analysis.

Limitations

When interpreting the results of the study, various limitations need to be taken into account. Our experiments are exclusively conducted on students within graduate and undergraduate environments. This decision was mainly based on the available resources and will narrow the conclusions of our study for this specific group.

Another limitation is the challenge regarding the participant's adherence to the protocol and consistency of the data. The periodicity of the data might not be consistent for all the participants; thus, we require them to deliver 20 full days of complete data. However, we are planning to consider these gaps as part of the behavioral information that could lead us to the objective of personalized machine learning for DASS21 predictions.

Our methodology relies on the assumption that participants will provide true signals about their daily behavior and mental status. In principle, it is possible that they will remove their wearable devices during the study or that they may not respond truthfully to the DASS21 questionnaire. This is a potential flaw with all studies collecting and analyzing self-reported data, and it is almost impossible to eliminate. Nevertheless, we believe that our study protocol is designed in a manner that diminishes the likelihood of this problem. First, participation in our study is voluntary, and the monetary incentive was calculated to recognize the time that participants spend in following our protocol. Second, all data outside the consent form are anonymous and associated only with a nickname, which should alleviate any concerns that participants may have about being associated with the "stigma" of mental health challenges that might lead them to not answer truthfully. Furthermore, it is important to note that the DASS21 questionnaire has been extensively used and validated for Spanish-speaking and English-speaking users and adopted for depression, anxiety, and stress diagnosis.

Conclusions

In this paper, we have described a protocol for collecting physiological data using wearable and mobile devices, which will be used in a subsequent study to predict depression using machine learning algorithms. The project is designed to collect physiological signals, such as heart rate variability, sleeping patterns, voice, and activity levels, which are reliable indicators of depression, anxiety, or stress. The noninvasive protocol consists of simple steps for the participants to follow. In this paper, we have outlined the procedures to ensure informed consent and data collection in a standardized and secure manner.

With the increasing prevalence of anxiety and depression disorders, this study has significant implications for developing a noninvasive and objective method for collecting and joining DASS21 results and data from wearables and mobile devices. The availability of the data set for the scientific community could motivate new and better ways for prompt detection of mood disorders. The proposed methods emphasize the importance of proper participant recruitment and data storage, collection, and processing. However, we recognize the limitations of our study, including the small sample size and

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need for further validations using more extensive and diverse populations, adherence of the participants to the study, and fidelity of the provided data. Further studies will be conducted to validate these findings and explore this technology's potential for predicting other mental health disorders.

Acknowledgments

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Data Availability

The data are not publicly available because the collection is ongoing and it has not been appropriately formatted. However, the data collection tools are available upon request from the corresponding author.

Conflicts of Interest

None declared.

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Abbreviations

DASS21: Depression, Anxiety, and Stress Scale

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Protocol

Implications of Agile Values in Software Engineering for Agility in Breast Cancer Treatment: Protocol for a Comparative Study

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Abstract

Background: Breast cancer treatment has been described as a dynamic and patient-centered approach that emphasizes adaptability and flexibility throughout the treatment process. Breast cancer is complex, with varying subtypes and stages, making it important to tailor treatment plans to each patient's unique circumstances. Breast cancer treatment delivery relies on a multidisciplinary team of health care professionals who collaborate to provide personalized care and quick adaptation to changing conditions to optimize outcomes while minimizing side effects and maintaining the patient's quality of life. However, agility in breast cancer treatment has not been defined according to common agile values and described in language comprehensible to breast cancer professionals. In the rapidly evolving landscape of breast cancer treatment, the incorporation of agile values from software engineering promises to enhance patient care.

Objective: Our objective is to propose agile values for breast cancer treatment adopted and adapted from software engineering. We also aim to validate how these values conform to the concept of agility in the breast cancer context through referencing past work.

Methods: We applied a structured research methodology to identify and validate 4 agile values for breast cancer treatment. In the elicitation phase, through 2 interviews, we identified 4 agile values and described them in language that resonates with breast cancer treatment professionals. The values were then validated by a domain expert and discussed in the context of supporting work from the literature. Final validation entailed a domain expert conducting a walkthrough of the 4 identified agile values to adjust them as per the reported literature.

Results: Four agile values were identified for breast cancer treatment, and among them, we validated 3 that conformed to the concept of agility. The fourth value, documentation and the quality of documentation, is vital for breast cancer treatment planning and management. This does not conform to agility. However, its nonagility is vital for the agility of the other values. None of the identified agile values were validated as partially conforming to the concept of agility.

Conclusions: This work makes a novel contribution to knowledge in identifying the first set of agile values in breast cancer treatment through multidisciplinary research. Three of these values were evaluated as conforming to the concept of agility, and although 1 value did not meet the concept of agility, it enhanced the agility of the other values. It is anticipated that these 4 agile values can drive oncology practice, strategies, policies, protocols, and procedures to enhance delivery of care. Moreover, the identified values contribute to identifying quality assurance and control practices to assess the concept of agility in oncology practice and breast cancer treatment and adjust corresponding actions. We conclude that breast cancer treatment agile values are not limited to 4.

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KEYWORDS

agile breast cancer treatment; breast cancer; breast cancer treatment; agile; software engineering; agile software engineering; oncology; agile values; multidisciplinary research; agility in health care; agile oncology practice

Introduction

Background

Breast cancer is the most frequent cancer diagnosis and the main cause of cancer mortality in women globally [1]. Through the 2 past decades, traditional breast cancer treatment (BCT) has been the standard of care and has led to significant improvements in patient outcomes [2]. However, the lack of consideration of the unique characteristics of each patient's cancer can lead to ineffective and nontargeted therapy with adverse and toxic side effects, reduced quality of life, and, in some cases, a resulting delay in detecting progression [2-4]. Thus, today, BCT is shifting toward more personalized approaches that enhance the patient experience while considering their diverse characteristics and evolving conditions [3,5-7].

Different treatment strategies may be required for each subtype of breast cancer, and genetic variation within tumors may complicate aspects of treatment. Developing tailored medicines that target certain genetic alterations or molecular subtypes is one of the main challenges in BCT [8]. Treatment planning has become more difficult as a result of the increased emphasis on personalized medicine, which calls for adjusting plans depending on a patient's genetic profile [8]. Optimizing therapeutic results and reducing the risk of treatment resistance require customizing therapies to fit the genetic features of each patient's tumor [9]. A patient's values and preferences must be taken into account in addition to clinical factors while deciding on the best course of action [10].

Further complication arises from managing treatment side effects and maintaining a patient's quality of life, particularly with regard to the level of depression both before and after treatment, as highlighted in the work of Salibasic and Delibegovic [11] and Breidenbach et al [12]. It can be difficult to strike a balance between a treatment's effectiveness and possible effects on the patient's well-being. Additionally, there are obstacles associated with the timing and order of various treatment modalities, including radiation therapy, hormone therapy, immunotherapy, chemotherapy, and surgery. A multidisciplinary approach to care is necessary to determine the most effective sequence and combination of therapies, which necessitates a comprehensive evaluation of the tumor characteristics, patient's overall health, and adverse side effects [13].

In the literature, all these reported treatment challenges, efforts, and strategies lack consideration and identification of their respective agility values. According to the *Oxford Dictionary*, the word *agility* means "the ability to move quickly and easily" [14]. *Value* means "the quality of being useful or important" or "beliefs about what is right and wrong and what is important in life" as a meaning related to *principle* or *standard* [15]. Thus, to improve BCT approaches and strategies and to overcome these challenges, it should be assessed whether they meet agility values and to what extent. This calls for identifying standards for the ability to move quickly, easily, and effectively in this complex disease, that is, defining *agility values* for BCT. Although the literature emphasizes addressing some agility values, such as patient-centric processes, personalization, and a multidisciplinary approach to decision-making and treatment plan design, there is still no validated definition of agility values for BCT. The complexity of BCT, shaped by factors ranging from tumor characteristics to patient preferences, highlights the need to identify common agile values to help in overcoming the above challenges. By identifying and promoting these values, health care organizations can create an agile culture of interactions, continuous learning, and improvement.

Multidisciplinary research has inspired individuals and communities, offered knowledge returns to individuals, and improved environment outcomes. In order to improve BCT and research, the different domains of software engineering and BCT may complement each other in a number of ways. Recent software development projects are adopting the agile approach to produce high-quality, useful software, in contrast to the traditional approach, which has limited flexibility, low user involvement, a long and delayed time-to-market cycle, late detection of errors, and high cost [16,17]

The concept of agility has been successfully described in the software engineering field over decades [17]. In software engineering, agility is a mindset, and its 4 values are not solid rules to follow [18]. In this context, it is possible to use the 4 agile values of software engineering for providing a shared framework for BCT teams to work together effectively and deliver value to their stakeholders while adapting to changing circumstances in complex environments and improving collaboration for better decision-making through a human-centric approach. Agile values emphasize the importance of individuals and interactions. This human-centered approach helps in building collaborative and motivated teams. The 4 agile values in software engineering are "individuals and interactions over processes and tools," "working software over comprehensive documentation," "customer collaboration over contract negotiation," and "responding to change over following a plan" [18]. The agile approach has enhanced value delivery to customers when user-centered experience and design are considered in the work of agile teams [19-21]. The agile approach has been used in the health care sector to translate the delivery of care from traditional methods into personalized ones, making care patient-centric, involving the patient in decision-making, enhancing continuous improvement and learning, and encouraging collaboration [22-26].

The creators of the agile values and principles have placed collaboration and people front and center, as the success or failure of a software project is highly dependent on them and not on the processes, tools, or the technology invested in it. Similarly, in the BCT process, the patient can be placed at the center of care by developing a personalized treatment plan considering the patient's preferences, values, and circumstances

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and engaging their families to develop accurate and well-conceived plans [18].

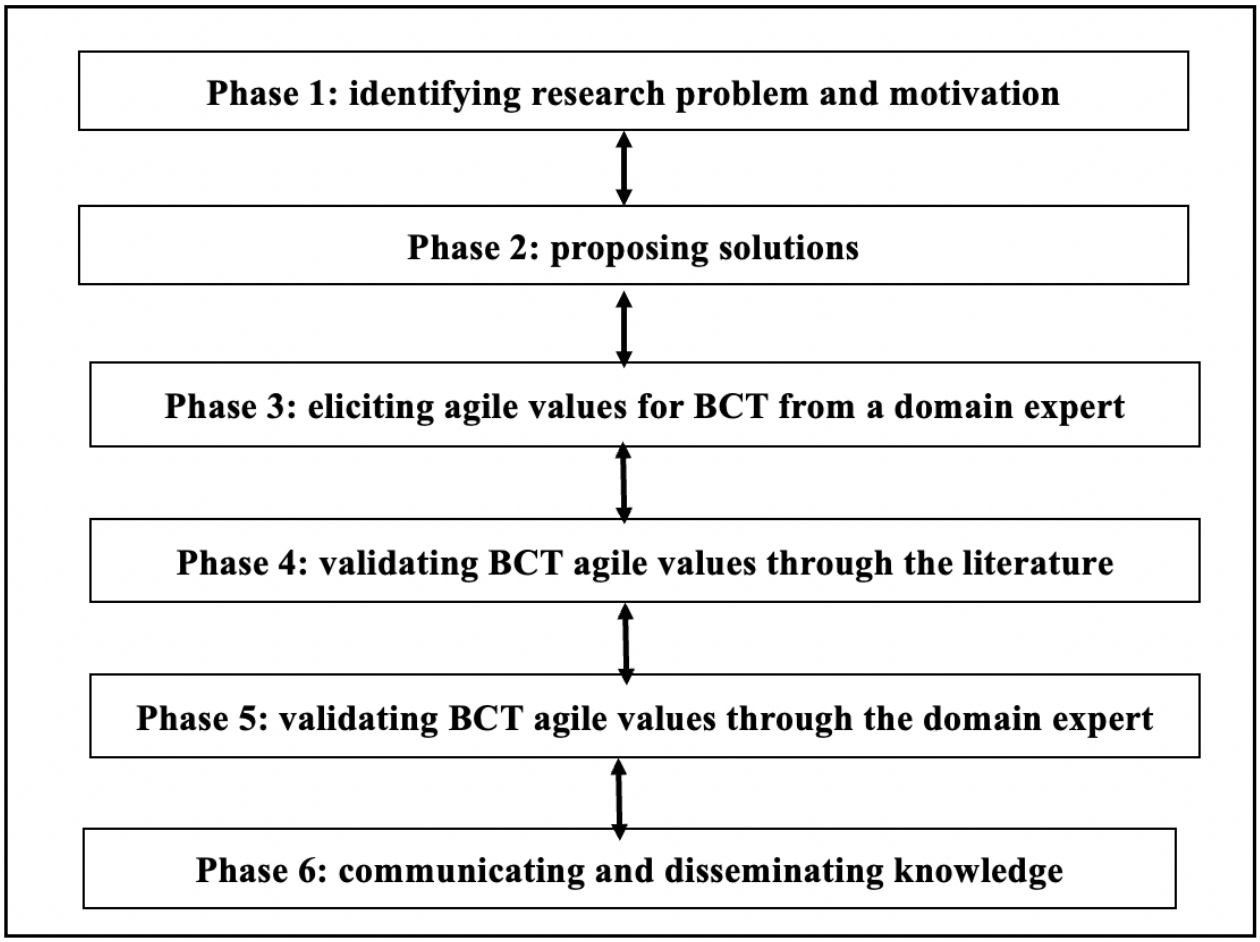
Aim of the Study

In this paper, we aim at identifying agility values in BCT to drive the BCT journey and ensure that patients receive appropriate and responsive care that considers their unique needs and preferences, ultimately leading to improving the effectiveness and efficiency of BCT strategies and approaches. The 4 identified agile values are adopted and adapted for BCT from the software engineering field. Also, we aim to investigate and validate how these values conform to the concept of agility in the breast cancer context through work reported in the literature. This should allow us to assess how they conform to the concept of agility in comparison with agile values in the field of software engineering. The reason behind adopting and adapting agility values from software engineering is that this discipline was founded to engineer effective solutions for complex problems while considering different aspects of continuous change. According to a domain expert, this is a noted similarity to the BCT discipline.

Methods

Here, the applied research methodology has 6 overlapping phases (Figure 1). This encourages researchers to actively engage with the problem-solving process, resulting in outcomes that align with the identified and validated agile values for BCT; this is anticipated to have a direct impact on BCT, health care, and society. As the methodology is described as a problem-solving process, it starts by identifying the research problem and the associated motivation. This leads to identifying the desired solution, which allows identifying the corresponding BCT agile values. Then, an elicitation phase is conducted to elicit the agile values for BCT from the domain expert after reviewing and amending the software engineering agile values into language that is reasonable for BCT professionals. In the fourth phase, we review the literature to provide references with the aim of validating these values. In the fifth phase, the domain expert conducts a walkthrough of the 4 BCT agile values as a final validation before communicating them to the research community in phase 6.

Figure 1. Research methodology.



Phase 1: Identifying Research Problem and Motivation

According to a literature review, there is a gap in promoting the agility of BCT with respect to well-identified values, although the literature reports huge efforts in patient-centered and personalized BCT. It is essential for patients to have open, transparent, and personalized communication with their care team professionals and health providers about their treatment approach and whether it is agile or not. Patients are empowered when they are aware of how BCT is delivered, particularly if agile mindsets are leading the journey. This encourages them to take an active role in making decisions about their care, ask

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pertinent questions, and advocate for the appropriate treatment options that meet their individual needs and circumstances. Having initial BCT agile values would pave the way to more flexible and personalized protocols, polices, and procedures to move closer to deliver patient-centric care. This also motivates policymakers to specify quality assurance processes that measure and indicate the extent of compliance to agility. Overall, this motivates health care providers to improve their care outcomes and increases patient satisfaction.

Phase 2: Proposing Solutions

To our knowledge, there is a lack of a validated definition of agile values for BCT, although BCT professionals strive to adhere to agility, as reported in the literature. The authors seek to propose and identify BCT agile values that are adopted and adapted from the software engineering field.

Phase 3: Eliciting Agile Values for BCT From a Domain Expert

The 4 agile values of software engineering were reviewed and rearticulated into language that is tailored to BCT professionals through 2 interview elicitation sessions conducted with a BC oncologist. The outcome here was the 4 identified BCT agile values, which are discussed below in phase 4 through work referenced from the literature. The outcomes of this phase are the following:

- Value 1: Individuals and interactions over processes and tools
- Value 2: Documentation and quality of documentation is as high priority as delivering an appropriate patient-centered treatment plan
- Value 3: Patient collaboration over treatment plan design agreement
- Value 4: Responding to change over following a plan

Phase 4: Validating Breast Cancer Treatment Agile Values Through the Literature

In this phase, we aim to reference work from literature that supports the articulation of the BCT agile values, as defined in phase 3. Below, each of the 4 BCT agile values is supported with work reported in the literature to enhance the validation.

Value 1: Individuals and Interactions Over Processes and Tools

In software engineering, this agile value highlights the fact that people and the communication behind developed processes and tools for achieving software development success are more important than these processes and tools themselves. Even if the team has the best, most appropriate tools, having the right people along with effective communication is still of greater importance. Regarding language for BCT professionals, this value is maintained as it is, without changing any of its wording [18,20].

In the BCT context, “working together is much more than policies, strategies, structures and processes” [27]. This can be seen in the shared decision-making (SDM) process for BCT, where the patient and everyone else is involved in delivering valuable information and reducing any mismatch between information that is delivered and the information that is needed in the complex treatment process [28]. When a patient is involved in SDM, it permits consideration of the patient’s preferences in the treatment, increasing their satisfaction and transforming the treatment process into a patient-centered one [29]. Improving patients’ engagement skills, using elicitation, performing clarification exercises for their preferences, and using formal and informal coaching are recommended to increase patients’ engagement in SDM in the BCT lifecycle. However, lack of time and resources are the biggest barriers mentioned regarding SDM [29]. This would prioritize individuals and their interactions over the tools [26,28,29]. Patient-centered communication and education, as well as coordination of care, are vital components for achieving the triple aims defined by the Institute for Healthcare Improvement that aim to improve the care experience for patient and family, improve the population’s overall health, and reduce health care capital costs [30]. According to research findings, the effectiveness of communication changes depending on the stage of the disease, and, for it to be effective, it must be adapted to the changing requirements and preferences of breast cancer patients [31,32]. Even after cancer treatment, regardless of the channel used, communications and interactions are still necessary. For example, a storytelling support group was run over the internet to break the social isolation that follows cancer [33,34].

In cancer care, the multidisciplinary team is a core central point of communication and collaboration. The National Health Service in the United Kingdom defines the multidisciplinary team (MDT) as “a group of health and care staff who are members of different organizations and professions (e.g. GPs, social workers, nurses, anesthesiologist, radiologist, pathologist, etc.,) that work together to make treatment and related services decisions of individual patients. MDTs are used in both health and care settings” [35]. In BCT planning, individuals in the MDT and their interventions can optimize care planning. For example, a nurse can stimulate interdisciplinary strategic planning that satisfies the clinical setting and improves outcomes through playing a key role in assessing the patient’s holistic needs [36]. A breast radiologist plays a vital role in the assessment and management of pain while leveraging patient communication and education, can add significant value to the care delivery process and patient care, and can improve outcomes [37]. Breast cancer patients who participated in a well-organized MDT contributed to facilitating a clear definition of their needs related to diagnosis, treatment, surveillance, and monitoring. This significantly enhanced breast cancer care planning, clarifying SDM in terms of booking appointments, referring procedures, and allocating respective roles and their responsibilities for patient care [38-40]. As a result, this MDT communication approach with the patient enhances survival rates and improves quality of life [40-44]. Although the research community reports that the MDT and patient interaction are prioritized over processes, some barriers may still hinder the effectiveness of these interactions; these are reported to include absence of leadership, individual personalities, cultural and belief systems, the need for regular clinical meetings, health care workers with double positions, availability of the workforce, specific goals of care, implementation in national

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health insurance, hospital bureaucracy, issues with hospital infrastructure, patients themselves, and high turnover [44-46]. In the BCT context, collaborative decision-making constitutes far more than relying on factual information, as patient communication may generate a decision that contradicts the evidence; the evidence may suggest a different plan. This highlights the reality that communication between the MDT and patient allows for the consideration of all factors [47].

Effective tools and processes, such as value-based breast cancer care, cannot be effectively addressed without interactions [48]. This does not neglect the role of tools and processes in the BCT context. Tools and processes should be used to improve the provision of patient-centered BCT planning and interactions [18]. The National Coalition for Cancer Survivorship (NCCS) provides the Cancer Survival Toolbox, a tool that aids cancer patients to learn how to communicate, obtain information, make decisions, negotiate, and speak up for their patient rights as they manage their cancer treatment [49].

When a person is diagnosed with breast cancer, it not only affects the individual but also has a significant impact on their family members. According to some studies, it is viable and beneficial to shift care delivery toward person- and family-centered care to clarify and address patient preferences, legitimize care-partner contributions, and grant appropriate access to information for family members and other care partners who are key players in enacting high-quality cancer care [50]. Research indicates that involving family members as care partners in communication intervention at the point of care increases patient understanding of illness, patient access to and use of the patient portal, and viewing of clinician visit notes among patients with more actively engaged care partners [50].

In conclusion, the agility of this BCT value fully conforms to the corresponding software engineering value. This leads us to classify this BCT value as achieving agility.

Value 2: Documentation and Quality of Documentation is as High Priority as Delivering an Appropriate Patient-Centered Treatment Plan

This software engineering agile value places "working software over comprehensive documentation." This indicates that it is a higher priority to rapidly deliver functioning software than to spend great attention and effort on documentation tasks [18]. This does not neglect the importance of documentation. The aim is to improve future software releases through obtaining feedback quickly [18]. This value is translated into BCT language as follows: "Documentation and quality of documentation is as high priority as delivering an appropriate patient-centered treatment plan."

Documentation is vital for medical records and legal purposes in parallel to the patient's health and immediate needs. Patient-centered treatment planning's main objective is to involve patients and their families in meaningful and in-depth conversations with their medical professionals to develop an accurate, well-thought-out treatment plan that appropriately uses all available medical information while also taking the medical, social, and cultural needs and preferences of the patient and family into account [26]. The treatment plan is designed, developed, communicated, and executed based on the patient's individual characteristics, preferences, and responses to treatment in collaboration with an MDT that includes members with different specialties, thus ensuring that their best interests are considered and the best benefits are delivered. Therefore, all this necessary information should be documented as required by the MDT [26].

The documentation of a breast cancer patient may require up to 20 distinct professional groups. Across these different professions, most of this paperwork is normally completed by resident doctors [51]. Across different medical specialties, most of the documentation is carried out by gynecologists or gynecological staff. Most of the time dedicated to paperwork is required for therapy [51]. All this necessary information from different resources is required to be documented for organization, doctor-patient communication, quality assurance and management, managing future changes (as changes are inevitable during BCT), and, mostly, for diagnostic needs and follow-up after each therapy [51].

In a study carried out by the American Society of Clinical Oncology (ASCO), a treatment plan and summary template increased communication between patients and their health care providers among almost 90% of assessed patients and health care professionals [52]. This highlights the importance of documentation for communication and demonstrates not only the need to prioritize documentation but also the need to prioritize documentation quality requirements [51].

Thus, the agility of this BCT value does not conform with the corresponding agile value in software engineering.

Value 3: Patient Collaboration Over Treatment Plan Design Agreement

In software engineering, this agile value places "customer collaboration over contract negotiation." It highlights that contracts do not clearly detail customer needs; rather, customers themselves do. Thus, continuous feedback loops are a priority in this agile value to ensure that the developed product is effective and useful as per the customer's needs. This indicates that agile development is customer-centric. However, this does not neglect the role of contracts. This value can be translated into BCT language as follows: "patient collaboration over treatment plan design agreement."

BCT professionals interpret patients' collaboration based on continuous feedback from them. This is observed in patient collaboration and in visits that begin early in the BCT process and should happen frequently. This close collaboration culture with patients has been reported to lead to significant benefits for them, particularly when they are unable to make decisions [44]. Close collaboration helps oncologists and their teams ensure they are delivering an effective, useful treatment solution to patients. When they talk to patients and their families, they build feedback into the treatment cycle and reduce risks [28,29,41].

Encouraging patient collaboration can be achieved through providing them the care and information they need according to their stage of breast cancer, as each stage varies in the aspects of information and associated delivery of care [31,32]. What

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was effective at one stage may not produce similar effectiveness in another stage. Therefore, it is highly recommended to look for communication alternatives that meet needs and preferences at each stage [53]. Sharing a treatment plan and summary template enhances patients' and their families' collaboration [52].

In conclusion, this leads us to classify this BCT value as achieving agility.

Value 4: Responding to Change Over Following a Plan

The world is not static. Therefore, a workable plan should never be static. This software engineering agile value highlights that changes in software development happen due to changes in the market, customer preferences, priorities, project management conditions, and business needs [18]. Thus, the agile mindset encourages reviewing and readjusting the plan based on new, emerging information. Regarding the BCT context, this value can be maintained as it is without changing any of its wording.

Changes in a BCT plan are inevitable and can occur for several reasons. Changes involve but are not limited to diagnosis results, follow-up assessments, surgical outcomes, health conditions, tumor characteristics, treatment response, side effects and tolerance, structural changes, resources, policies, disease recurrence, drug resistance, monitoring assessments, new research, and others. All these alert us to the need for a personalized response to the changes as a priority over following a static plan. For example, changing the sequence of treatment, in terms of radiotherapy and surgery, could improve outcomes and reduce side effects in terms of treatment complications and address safety and technical feasibility [54]. Lifestyle changes that involve exercise, diet, smoking, and alcohol have empowered patients psychologically and reduced the risk of recurrence and death [55-57].

Breast cancer is a complex disease in which not all patients can benefit from the same treatment. Thus, it is essential to go beyond conventional BCTs [58]. Changes in BCT may require developing a novel treatment that could be described as personalized [58]. Changes to the treatment plan could happen if the aim has changed. Aims could include preventing cancer recurrence, slowing growth of cancer, and managing symptoms of incurable cancer [59]. Accordingly, changes entail allocating roles that are put into place to address the aim of BCT and provide referral to clinical trials that are regulated to effectively address the desired treatment aim with minimum side effects [60]. Furthermore, a change may require halting the treatment to recover from adverse side effects [60].

Managing BCT entails evaluating the patient's response to treatment from the perspectives of surgery, imaging, and medical oncology. Adjuvant treatment is guided by an appropriate surgical and pathological assessment and follow-up care that concentrates on identifying recurring illness with the goal of enhancing long-term survival [61]. Whatever the change that requires a response, the BCT team will strive to improve the patient's quality of life.

Magnetic resonance imaging (MRI) is used to accurately identify stages of breast cancer by assessing the size and extent of the tumor within the breast and evaluating if it has spread to nearby lymph nodes or other structures [62]. This information is essential in determining an appropriate treatment approach that is ready to respond to changes. A major change in the treatment plan may involve the need for surgery and additional treatment [62-64].

In BCT, personalized treatment is a means of responding to a change and delivering patient-centric medicine. Knowing the molecular characteristics of breast cancer subtypes is necessary to create a tailored therapy and diagnosis [65]. It is necessary to establish molecular profiles and metrics for tailoring the appropriate treatment and evaluating its benefits and risks. Dose ratios and regimens are likely to change according to an identified combination therapy [66]. BCT decisions are based not only on the assessment of prognostic factors but also on the assessment of pathological and clinical findings. A multitopic-based integrated data approach to address many breast cancer risk variables can bring tremendous insight and promises to change treatment for the better [67].

In conclusion, this BCT agile value shows how change is necessary for the benefit of the patient.

Phase 5: Validating Breast Cancer Treatment Agile Values Through the Domain Expert

In this phase, the domain expert conducted a walkthrough of the output generated from the previous phase as a form of final validation. This was to ensure that the BCT agile values identified in phase 3 are consistent with the respective reported literature as shown in phase 4.

Phase 6: Communicating and Disseminating Knowledge

The research knowledge obtained from this paper is disseminated in this open access journal to increase its availability and accessibility to the scientific community, policymakers, practitioners, and the public. In addition, the article is published to enhance collaboration between multidisciplinary fields for better BCT strategies. The authors also aim to deliver a public seminar about the ideas delivered in this article to increase community awareness of promoting agility in BCT for better care values, strategies, and delivery.

Ethical Considerations

No ethical considerations are required for this study, as it does not involve human subjects. The statements for human subject research ethics review, exemptions, and approvals, as well as descriptions of informed consent (for the institutional review board), privacy and confidentiality protection, and compensation type and amount are not applicable. The study does not include any clinical setting for recruitment, not even recruitment procedures.

Results

In this study, we have identified BCT agility values and showed how they conform to the concept of agility in the field of software engineering. Our validation was conducted through a comprehensive review of the existing literature and interviews

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with a breast cancer oncologist. This work has resulted in 4 BCT agility values, which are specified below:

1. Individuals and interactions over processes and tools (conforms)
2. Documentation and quality of documentation is as high priority as delivering an appropriate patient-centered treatment plan (does not conform)
3. Patient collaboration over treatment plan design agreement (conforms)
4. Responding to change over following a plan (conforms)

In summary, our analysis indicates that BCT has made significant strides in aligning with the concept of agility through the identification of the 4 values that were reconfigured from the software engineering field. These values focus on how individuals interact, collaborate, and welcome changes. However, the quality of documentation is as high priority as delivering a patient-centered treatment plan. These values have been integrated into various aspects of breast cancer care, from treatment planning and delivery to ongoing support and survivorship care. However, there is still room for improvement, and ongoing efforts to enhance these values in BCT will continue to benefit patients, families, BCT professionals, and health care providers.

Discussion

The work has delivered a novel contribution to knowledge in identifying the first set of agile values in the BCT context adopted from the software engineering field. We conclude that only 3 of the 4 identified agile values in BCT conform, in terms of agility, with the 4 agile values in software engineering. The 3 BCT agility values are "individuals and interactions over processes and tools," "patient collaboration over treatment plan design agreement," and "responding to change over following a plan." However, the second BCT agile value did not conform to agility, as it is vital that documentation not only be comprehensive but also have high quality and have high priority for delivering an appropriate patient-centered plan. None of the agile values were recorded as partially conforming to agility; this addresses the aim of this paper to identify BCT agile values and compare their conformance to agile values in the software engineering field.

In the first BCT agility value, the priority of collaboration has emerged as a fundamental aspect of BCT that is interpreted in the SDM and MDT approaches. MDTs consisting of oncologists, radiologists, surgeons, nurses, and other health care professionals work closely together to ensure comprehensive patient care. Furthermore, the involvement of patients in SDM has promoted collaboration between health care providers, patients, and those managing the treatment. Collaboration and ongoing interactions appear early in the BCT lifecycle and continue even after survival, emphasizing the significance of these interactions and implying that quality of life requirements are increasing and leading to more patient-centric processes. For the second BCT agility value, the design of BCT plans respects the personalized characteristics of each patient. All kinds of collaborations and interactions between the patient and the MDT to discuss and design an effective and safe BCT plan should be based on high-quality documentation. Therefore, it is a priority to allocate enough time to facilitate documentation work to attain agility in the remaining values. In the third agile value, patient collaboration is a higher priority than following a rigid treatment plan; this leads to better treatment decisions via continuous feedback throughout the BCT lifecycle. Regarding the fourth agile value, effective and safe changes are always welcomed to interrupt a BCT plan for the patient's benefit, with or without minimizing impacts on quality of life, thereby leading to closer, patient-centric, and better treatment outcomes, as well as minimized side effects.

Attempts to address BCT agile values are limited and constrained by cultural mindsets, the availability of resources for implementation, the availability of quality standards that support agility, and interoperability of health care systems. Patients' efficient participation is constrained by the quality of their education and their health literacy in terms of understanding risks, benefits, overall quality of life, and adherence to their treatment plans and medication regimens.

The authors do not claim that these are the only BCT agile values, as they are not limited to 4. Instead, the values proposed here constitute the first version of a BCT agile values manifesto. The implication of having BCT agile values shared among administration and BCT professionals is broader than the specific interpretation behind each identified BCT agile value. The identified agile values focus on effective and efficient collaboration between the patient and MDT in SDM, with consideration to continuous response to change, which will contribute to increasing the patient's activity level and forming a more personalized BCT process that drives patient-centric therapy decisions. Moreover, this contributes to eliminating waste, in other words, unneeded activities or tasks that may involve tests, procedures, and treatments. Hence, this contributes to more cost-effective, time-saving, and efficient care. Rather than just following strict protocols, BCT agile values increase the flexibility of these protocols, allowing for more personalized care with respect to patients' characteristics, preferences, and needs. The identified BCT agile values highlight the necessity of specifying quality assurance processes that aim at investigating the extent to which they conform to the concept of BCT agility. Health care systems are anticipated to become more flexible, patient-focused, and efficient by adopting agile values in BCT and care. This will eventually enhance patient outcomes and experiences and promote a change from inflexible, one-size-fits-all methods of care to ones that are tailored to the specific requirements of each patient and the rapidly advancing fields of medicine and technology. Finally, this holds the potential to revolutionize the way we approach oncological care. This endeavor reflects a commitment to embracing innovation, collaboration, and patient-centeredness, mirroring the very essence of the agile philosophy.

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Acknowledgments

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Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during this study.

Authors' Contributions

The first author (YO) contributed to research conceptualization, methodology, formal analysis, investigation, resources, data curation, writing—original draft preparation, writing—review and editing, visualization, and supervision. The second author (MAB) contributed to research validation, investigation, resources, data curation, and writing—review and editing.

Conflicts of Interest

None declared.

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Abbreviations

ASCO: American Society of Clinical Oncology
BCT: breast cancer treatment
MDT: multidisciplinary team
MRI: magnetic resonance imaging
NCCS: National Coalition for Cancer Survivorship
SDM: shared decision-making

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Protocol

Impact of the COVID-19 Health Crisis on Key Populations at Higher Risk for, or Living With, HIV or Hepatitis C Virus and People Working With These Populations: Multicountry Community-Based Research Study Protocol (EPIC Program)

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Abstract

Background: Information concerning the impact of the COVID-19 health crisis on populations most affected by HIV and hepatitis C virus (HCV; or key populations [KP]), and those working with these populations in community settings, is limited. Community-based organizations working in the field of HIV and viral hepatitis are well placed to identify and meet the new needs of KP owing to the health crisis.

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Objective: This study aims to describe the development and implementation of an exploratory and descriptive multicountry, community-based research program, EPIC (*Enquêtes Pour évaluer l'Impact de la crise sanitaire covid en milieu Communautaire*), within an international network of community-based organizations involved in the response to HIV and viral hepatitis. The EPIC program aimed to study the impact of the COVID-19 health crisis on KP or people living with HIV or HCV and people working with these populations at the community level (community health workers [CHWs]) and to identify the key innovations and adaptations in HIV and HCV services.

Methods: A general protocol and study documents were developed and shared within the Coalition PLUS network. The protocol had a built-in flexibility that allowed participating organizations to adapt the study to local needs in terms of the target population and specific themes of interest. Data were collected using surveys or interviews.

Results: From July 2020 to May 2022, a total of 79 organizations participated in the EPIC program. Across 32 countries, 118 studies were conducted: 66 quantitative (n=12,060 among KP or people living with HIV or people living with HCV and n=811 among CHWs) and 52 qualitative (n=766 among KP or people living with HIV or people living with HCV and n=136 among CHWs).

Conclusions: The results of the EPIC program will provide data to describe the impact of the health crisis on KP and CHWs and identify their emerging needs. Documentation of innovative solutions that were put into place in this context may help improve the provision of services after COVID-19 and for future health crises.

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KEYWORDS

COVID-19; key populations; health; crisis; HIV; mobile phone

Introduction

Context

Numerous COVID-19 research and epidemiological surveillance data have shown that certain populations are disproportionately affected by the COVID-19 health crisis not only in terms of mortality and morbidity but also in terms of the social and economic consequences of the crisis [1-4]. This is notably the case among the homeless and people living in inadequate or poor housing conditions, which makes the implementation of prevention measures such as social distancing and frequent hand washing difficult or unfeasible [5]. In addition, key populations (KP; such as men who have sex with men [MSM], people who inject drugs, sex workers [SWs], transgender women, and migrants) who are exposed or living with HIV or hepatitis C virus (HCV) may also experience compounding effects of the health crisis in terms of infringement on their human rights and exacerbation of preexisting health inequalities.

International organizations and community-based associations have alerted public authorities to the susceptibility of these marginalized groups in the early phase of the COVID-19 pandemic and the consequences on the HIV response [6]. The HIV epidemic is largely concentrated within KP: MSM, people who inject drugs, SWs and their clients, and transgender women [7]. The lack of consideration or consultation with KP has resulted in further social exclusion [3] and greater susceptibility to violence and human rights abuses [6]. For example, governmental measures such as lockdowns have exposed SWs to great economic instability, forcing them to put their health in danger [8]. The crisis may also have an important impact among transgender populations in terms of reinforcing preexisting inequalities with regard to access to health care, including gender affirming care and social and mental support [9]. Disruptions in access to drug services and clean drug consumption-related equipment were experienced early in the pandemic, possibly increasing the risk of infection with SARS-CoV-2 in addition to HIV and hepatitis B and C among people who use drugs [10-12]. Increased alcohol and drug consumption because of distress may also be a consequence of the crisis, and whether this persists after COVID-19 is of concern [5,13]. Among MSM, and likely other KP, a reduction in sexual activity was observed early in the pandemic owing to lockdowns and distancing measures, which may have resulted in a lower uptake of prevention tools such as preexposure prophylaxis and HIV testing [14,15]. It is thus important to ensure the necessary support and access to services when sexual activity resumes. Finally, disruptions in treatment and other services for people living with HIV and people living with HCV could lead to significant increases in new infections and mortality in the coming years, hindering global elimination efforts [16-18].

The COVID-19 crisis thereby represents a threat to the global progress against HIV and viral hepatitis and has consequently highlighted the importance of engaging or re-engaging and maintaining KPs, people living with HIV and people living with HCV in the HIV and HCV prevention and care pathway. The crisis has in many ways served as a catalyst for the development of innovative solutions for health service delivery since the beginning of the COVID-19 pandemic. For example, many in-person services moved to the web [19], and although this may be a viable solution for some individuals, there remains a concern that remote delivery of care will further exacerbate social gradients of health owing to limited or no access to internet, technological resources, and technological literacy [20]. Efforts to maintain harm reduction services despite lockdowns and other restrictions created an opportunity in some countries to develop or expand multimonth dispensing of opioid agonist treatment, unsupervised dosing and diversification of points of dispensation (pharmacy, vending machines), and

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take-home naloxone, where they were previously not permitted [21,22]. Similarly, home delivery, multimonth dispensing, and "fast track" antiretroviral therapy refills were solutions put into place in some countries to maintain antiretroviral therapy services [23].

Many of these innovative solutions were put into place by community-based organizations (CBOs), who were notably at the forefront in the early days of the pandemic [21,24-26]. However, studies of the other epidemics have shown a negative impact (depression and stigmatization) of health crises on health workers [27,28]. Given their proximity to KP, and their essential role in the provision of support, prevention, and treatment for these populations, it is equally important to study the impact of the COVID-19 health crisis on community health workers (CHWs) [29].

The COVID-19 pandemic has thus reinforced the necessity of community engagement to provide adapted responses to the specific needs of KP. Community organizations worldwide have effectively led initiatives to provide COVID-19 information and share expertise [24]; however, data regarding these initiatives are limited. Therefore, it is important to document the new solutions put in place during the COVID-19 health crisis and to document the perceptions and experiences of CHWs.

Objectives

The EPIC (*Enquêtes Pour évaluer l'Impact de la crise sanitaire covid en milieu Communautaire*) community-based research program aimed to understand how the COVID-19 health crisis affected the populations at higher risk for, or living with, HIV and viral hepatitis and the people working with these populations at the community level, and to identify the key innovations and adaptations in HIV- and hepatitis-related services. In the following sections, we describe the general framework of the EPIC program, which was implemented in 32 countries across the world in partnership with local CBOs involved in the fight against HIV and viral hepatitis. The program was developed by Coalition PLUS, an international union of CBOs involved in the fight against HIV and viral hepatitis, in partnership with external scientific partners. Founded in 2008, Coalition PLUS unites 16 member organizations and >100 partner organizations in 52 countries. These organizations are grouped into 6 regional networks (Middle East and North Africa [MENA], West Africa, Central and East Africa, Indian Ocean, Americas-Caribbean, and Europe), 2 thematic networks (RIGHT PLUS [research] and AGCS PLUS [advocacy]), and a linguistic (Lusophone) network.

Methods

General Design and Study Development

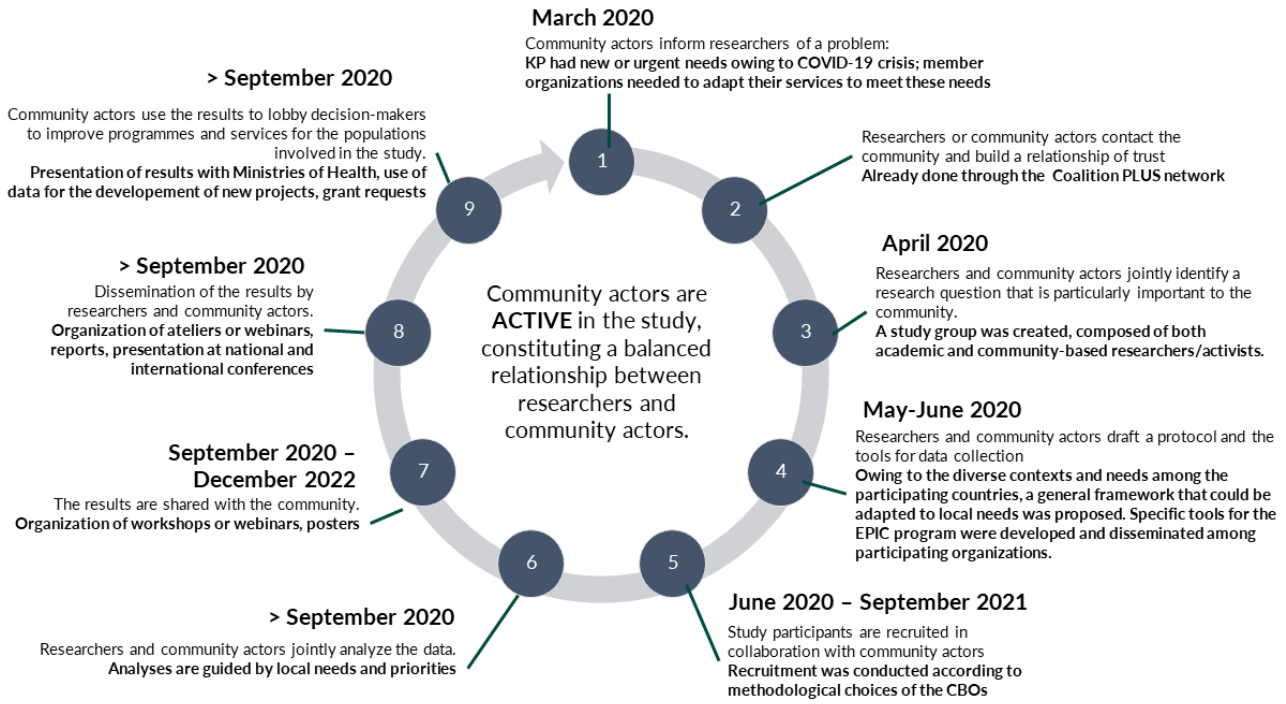
EPIC is an exploratory and descriptive multicountry, cross-sectional, and community-based program that uses mixed methods: qualitative and quantitative. To accommodate the diverse themes of interest and target populations, as well as the exceptional circumstances, the study was customizable at the local level, and there was a common basis for all organizations implementing EPIC. However, data collection tools were adjustable depending on the target population or populations and specific themes of interest, which were determined by the implementing organizations. Other considerations such as human and financial resources and technical capacity of the implementing organizations were also taken into consideration. The adaptative methods of the EPIC program thus resulted from an urgent need to document the COVID-19 crisis within the Coalition PLUS network and adapt to the realities of the field within the context of an ongoing pandemic. This decision was in line with the community-based approach and with Allport [30] when he postulated that "we should adapt our methods so far as we can to the object, and not define the object in terms of our faulty methods." Following the community-based approach [31], many CBOs, members or partners of Coalition PLUS, actively participated at all stages of this research project (Figure 1).

Starting in March 2020, Coalition PLUS members and partners mobilized to respond to the COVID-19 crisis within their organizations and countries. These CBOs were confronted with new needs such as supplying CHWs and beneficiaries with protective equipment and information regarding prevention measures, adapting services to respect governmental measures (lockdowns, distancing, and mobility restrictions), and provision of basic needs such as food for beneficiaries. In this context, there was a growing concern that KP at higher risk for HIV or HCV, and people living with HIV or HCV, were likely to have the greatest difficulty adapting to public health measures and most likely to experience negative impacts of the COVID-19 crisis.

On April 23, 2020, the Community-based Research Laboratory (CBRL) at Coalition PLUS organized a web-based Zoom (Zoom Video Communications, Inc) meeting with representatives from each of the regional, thematic, and linguistic networks as well as external scientific partners (hereafter, the EPIC study working group). A total of 18 people participated in this meeting and an additional meeting was held on April 28, 2020, with 5 people who were unable to join the first meeting. The aim of these meetings was to set the objectives of the project and the methodology that was best adapted to the current context and timeline. To better identify the needs within the various Coalition PLUS networks, the working group then consulted with the member and partner organizations of their respective networks to identify common themes. The feedback of these consultations informed the draft proposal of the research project, which was shared at a web-based Zoom meeting held on May 13, 2020. A total of 24 people participated in this meeting. Following this meeting, and individual exchanges with the working group members, the final study documents were finalized and shared on June 12, 2020.

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Figure 1. Stages of a community-based research project adapted to the EPIC (*Enquêtes Pour évaluer l'Impact de la crise sanitaire covid en milieu Communautaire*) program. CBO: community-based organization; KP: key populations.



Objectives

The EPIC program had 3 main objectives:

1. To study the impact of the COVID-19 health crisis on KP at higher risk for, or living with, HIV or HCV (people who use or inject drugs, SWs, MSM, transgender people, and migrants)
2. To study the impact of the COVID-19 health crisis on people working with these populations at the community level (peer educators, CHWs)
3. To identify the key innovations and adaptations in HIV and HCV services that could be maintained and extended beyond the COVID-19 health crisis.

Study Population and Inclusion Criteria

The inclusion and exclusion criteria of the EPIC program are presented in Textbox 1.

Textbox 1. EPIC (Enquêtes Pour évaluer l'Impact de la crise sanitaire covid en milieu Communautaire) program inclusion and exclusion criteria.

Inclusion criteria

- Part of at least one of the eligible study populations: people living with HIV or hepatitis C virus, people who use or inject drugs, sex workers, men who have sex with men, transgender people, migrants, community health workers
- Above the age of the majority in the recruitment country
- Accept to participate and provide informed consent

Exclusion criteria

- Not a part of one of the eligible study populations
- Below the age of the majority in the recruitment country
- Refuse to participate or provide informed consent

Nomenclature

As the implementation of the EPIC protocol varied among the participating countries, based on target population, themes of interest, and methodology used, the overall project is referred to as the EPIC program. EPIC study or studies refer to the local implementation of the program among a specific target population. Therefore, in countries with multiple target populations, the studies were referred to as EPIC-(Methodology) (Country name) (Target Population).

Data Collection Tools

Quantitative Data

Two structured questionnaires were designed to collect quantitative data: one questionnaire targeted KP and the other targeted CHWs. Both questionnaires were organized into

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different modules so that each organization had the option to implement modules corresponding to their specific interests and target populations. Textbox 2 describes the modules of each questionnaire. There was one mandatory module in the KP questionnaire and 3 mandatory modules in the CHWs questionnaire. Additional questions could be added by each participating organization to collect information on a specific topic that was not already covered by the questionnaire or questionnaires. It was not possible to change the wording of the questions or the proposed responses.

To centralize all the quantitative EPIC data, both questionnaires were created in the Voxco survey software, offering not only web-based but also offline data collection (via a tablet or smartphone app). Organizations that collected data using paper questionnaires entered the data into the Voxco software.

Textbox 2. Modules of the key populations and community health workers questionnaires.

Key populations

- Sociodemographic, general impact of COVID-19 and intention to vaccinate against COVID-19 (mandatory module)
- Sexual activity and prevention strategies for HIV and other sexually transmitted infections
- Experience and application of lockdown or barrier measures
- Socioeconomic needs and responses in relation to the COVID-19 health crisis
- Representations and perception of the COVID-19 risk
- Well-being and resilience
- Access to health care
- COVID-19 impact on pre-exposure prophylaxis
- People who use or inject drugs
- People living with hepatitis C virus
- People living with HIV
- Sex workers
- Migrant

Community health workers

- Sociodemographic, general impact of COVID-19 and intention to vaccinate against COVID-19 (mandatory module)
- Experience of the COVID-19 crisis at work (mandatory module)
- Experience and application of lockdown or barrier measures
- Relationship with beneficiaries (mandatory module)
- Representation and perception of COVID-19 risk
- Well-being and resilience

Qualitative Data

Two semistructured interview guides were designed to conduct individual interviews with the KP of member and partner organizations and with the CHWs of these organizations. An additional interview guide was designed for CHWs who also belonged to or identified with a KP group. Individual interviews aimed to explore in greater detail the experiences and needs of KP communities during the COVID-19 crisis. Textbox 3 describes the main areas of interest covered by the interview guides.

Interviews were conducted in different ways to accommodate the local restrictions in effect during the data collection period: face to face, on the web (with or without video), or by phone.

All interviews were conducted by trained CHWs, members of the Coalition PLUS community-based research team, or by a local consultant. The interview guides were translated into local language or languages in collaboration with local partners. Interviews were conducted in the local language or languages and recorded using a voice recorder. Voice recordings were transcribed verbatim and translated into French or Spanish, if necessary, for analysis. To guarantee the confidentiality and the anonymity of the interview, external consultants conducted all the interviews among CHWs.

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Textbox 3. Main topics covered by the interview guides for key populations, community health workers, and community health workers who identify with a key population.

Key populations

- COVID-19 knowledge, risk perception, and experience of the COVID-19 crisis (in terms of stigma, emerging needs)
- Attitudes toward COVID-19 vaccination
- Experience of lockdown and other governmental measures
- Overall health care access
- Relations with the Coalition PLUS member or partner structure

Community health workers

- Personal experience of the COVID-19 crisis within the professional sphere
- Attitudes toward COVID-19 vaccination
- Impact of the COVID-19 health crisis on the beneficiaries

Community health workers who identify with a key population

- Personal experience of the COVID-19 crisis within the professional sphere
- Attitudes toward COVID-19 vaccination
- Impact of the COVID-19 health crisis on the beneficiaries
- Experience of lockdown and other governmental measures

Complementary Data

A country information sheet concerning local policies, government measures taken during the health crisis, and COVID-19–related data (eg, incidence at study launch) was created to gather information about the context in which the quantitative or qualitative data were collected. Similarly, an organizational information sheet was created to collect general information about organizations that implemented EPIC among CHWs (eg, size of the organization, KP reached, and regular and COVID-19–related activities).

Sample Size

Given the COVID-19 context and the exploratory and descriptive aims of the project, convenience samples were more adapted to the uncertain pandemic context than samples based on statistical criteria. Indeed, the aim was to gather information about the impact of the COVID-19 crisis on KP and CHW in many Coalition PLUS members and partner organizations. Each organization has its own specificities regarding the COVID-19 crisis at the local level, number of beneficiaries or users reached, and number of CHWs involved. However, before the implementation of the EPIC study, each organization provided an estimation of the sample size to be recruited on the basis of their context and their experience with the target populations to be included in the qualitative or qualitative studies. This sample size estimation was important to orientate or validate the methodological choices through technical support from the Coalition PLUS research team. As a general guide, a minimum of 100 respondents was recommended for quantitative studies and 10 for qualitative studies. Organizations that targeted <100 persons for quantitative studies were encouraged to switch to a qualitative methodology.

Ethical Considerations

Regarding data protection regulations, the EPIC protocol was registered at the French National Commission of Informatics and Liberties (registration #2218347 v 0).

Local ethics approval was obtained in each participating country before study implementation (Multimedia Appendix 1).

Before taking part in the study, participants were provided information regarding the research objectives, how the data were collected, managed, and by whom, as well as the participant's rights. For web-based participation, this information was available on the landing page of the EPIC questionnaire in Voxco. Participants had access to the questionnaire once they provided their consent to participate. For face-to-face participation, oral consent was obtained after this information was delivered and before starting the questionnaire or the interview. Face-to-face interviews were conducted in places that guaranteed anonymity and privacy.

All participating organizations signed a cooperation agreement to guarantee the security of the data collected in compliance with both French data protection regulations and local ethics and data protection requirements. The cooperation agreement also detailed collaborative research guidelines and operating rules for teams involved in the study, such as guaranteeing the place of communities in the research process, use of Voxco software, and the EPIC program logo.

General Coordination of the EPIC Program

The overall coordination of the EPIC program was assured by the Coalition PLUS CBRL, which initially comprised 7 people in 2020, including the principal investigator of the EPIC program and the Director of the Laboratory, 1 research manager, 4 research officers, and 1 biostatistician. By 2021, the team expanded to include an additional research manager, 6 research

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officers, and 1 data manager for a total of 15 team members. One research officer was dedicated full-time to the coordination of the EPIC program, whereas the other team members worked on the EPIC program in addition to other studies. The follow-up of all participating organizations, in terms of presentation of the study protocol and other documents, development of local adaptation of the study tools, and overall technical support throughout the entire research process was provided by the CBRL team. In 2020, each participating organization was followed through regular Zoom calls and email exchanges by 2 members of the initial team. The addition of the new members in 2021 allowed a more local follow-up of participating organizations as 5 research officers were based in 5 Coalition PLUS regional networks (MENA, West Africa, Central and East Africa, Indian Ocean, and Americas-Caribbean).

Local Implementation and Data Collection

Following the community-based approach, and within the framework of the capacity-building mission of Coalition PLUS, each member or partner organization willing to locally implement EPIC was assisted by at least one person of the CBRL to guide, check, and validate all steps of the study implementation. Regarding quantitative data collection, each participating member or partner organization was trained on the Voxco software from the CBRL to learn the basic functionalities of the software, for example, how to modify a questionnaire, make it available on the web, and follow-up recruitment. All questionnaires were checked and validated by a member of the CBRL before the survey was launched. Regarding qualitative data collection, all CHWs who conducted interviews received training through a video conference from a qualitative researcher from the CBRL. Each local organization that used qualitative methods sent the first audio interviews and transcriptions to CBRL to check the quality of the interviews. If needed, additional support was provided by the CBRL to improve the quality.

It was crucial that the implementation of the research study did not become a barrier to the continuity of member and partner organizations' services during the health crisis. Therefore, implementation had to match the organization's needs in terms of data collection and topics of main interest while considering their local constraints (available human resources, contact with KP, COVID-19 prevention measures, etc). The local design and implementation of the EPIC protocol was documented in the EPIC implementation document. Textbox 4 describes the main sections of the implementation document and its content. The completed implementation document was used as a basis for the local EPIC protocol and was submitted to the local ethics committee in addition to the general protocol.

Once the implementation document was completed, the participating organizations translated all the EPIC study tools into the local language when necessary. The CBRL provided the EPIC main study documents (questionnaires, including web-based questionnaire in Voxco, interview guide, informed consent, etc) in 4 languages: English, French, Portuguese, and Spanish. The study documents were shared with external scientific partners upon request.

Each participating organization was responsible for the survey promotion and the entire data collection process, including data storage when not using the Voxco software (pen-and-paper questionnaires, voice recordings, etc).

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Textbox 4. Content of the EPIC (Enquêtes Pour évaluer l'Impact de la crise sanitaire covid en milieu Communautaire) implementation document.

Section and main information of the section

1. Collaborators

- Local reference person responsible for the local implementation of the EPIC study
- Name and roles of all involved collaborators
- Budget (if any)

2. Local context

- General introduction and rationale of the project: COVID-19 situation, affected population, etc
- Brief presentation of the organization: history, key populations, etc
- Reasons for implementing EPIC, target populations, etc

3. Objectives

- Selection of the objectives to be used by the organization

4. Study population: List of all key populations to be surveyed by the organization, among

- People who use or inject drugs
- Sex workers
- Men who have sex with men
- Transgender people
- People living with HIV
- People living with hepatitis C virus
- Migrant people
- Community health workers

5. Inclusion criteria

- Be a part of the study population, above the national age of majority, and accept to participate and provide informed consent

6. Ethics committees

- French National Commission of Informatics and Liberties and local ethics committee approvals

7. Survey methods

- Quantitative surveys:
  - Study population or populations
  - Modules of the questionnaire to be used and additional questions (if any)
  - Administration of the questionnaire: face-to-face (pen-and-paper and tablet offline), self-administered (pen-and-paper, tablet offline, and web-based questionnaire)
  - Recruitment strategies: promotion (specific venues and on the web), key persons to be contacted and involved, places of recruitment, other channels for promotion or recruitment
  - Estimated time of recruitment and expected sample sizes
- Qualitative surveys
  - Target population or populations
  - Expected sample sizes
  - Recruitment strategies
  - Interview characteristics: who will conduct the interviews, where, face-to-face or remotely, etc

8. Informed consent

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Brief note presenting the survey and participants' legal rights (voluntary participation, right to drop out at any moment, anonymity and privacy, and data storage)

- Ways to obtain consent: oral, voice recorded, or tick box

9. Data management

- Places where the data will be stored
- People granted with access to these data

Data Management

Overview

All data (quantitative, qualitative, and complementary) were centralized at Coalition PLUS and were securely stored and transferred. No personal data were collected to ensure anonymity of the study participants. The European General Data Protection Regulation requirements in terms of data protection are complied with regard to data processing and storage.

Quantitative Data

Quantitative data that were not collected through Voxco (ie, pen-and-paper questionnaires) were entered into Voxco by the corresponding organization, and hard copies of the questionnaires were stored in a secure place with restricted access. All databases generated by Voxco were then cleaned by the CBRL and shared with each participating organization. All databases are stored on a secured server with access restricted to the CBRL biostatistician and data manager. Each participating organization had access to its own data. The global or subset of the global database may be accessed if a formal demand to perform multicountry analyses is approved by the EPIC study group team.

Qualitative Data

Voice recordings, verbatim transcripts, and translations (when necessary) were sent by a secure link to the CBRL and stored.

Analyses

Overview

In general, local level analyses are prioritized as the overall aim of this study was to collect information regarding the impact of the COVID-19 crisis on KP and to identify specific needs to inform local or national interventions or adaptation of services. Analyses at the global and regional levels, and within specific populations, will also be conducted.

Quantitative Analyses

All participating organizations were provided with a cleaned database and descriptive tables of all their data, which were prepared by the CBRL. Technical assistance may also be proposed for conducting more in-depth analyses. Participating organizations are also encouraged to seek partnerships with local universities if support is needed for the analyses.

Country-level analyses will be conducted so that participating organizations can build on national results. When possible, multicountry analyses will be conducted, grouping countries by language, geographical region, key issues (eg, health care access), or targeted KP.

Descriptive analyses will be conducted to first characterize the needs of the participants. Three validated scales were used in this study: Patient Health Questionnaire-9 for depression [32] and the Generalized Anxiety Disorder-7 for anxiety [33] and the 6-item Brief Resilience Scale (BRS) for resilience.

Qualitative Analyses

According to the quality of qualitative data collected, 2 analysis methods are planned:

1. For corpus with a good quality of data collection, a thematic content analysis will be conducted on the transcripts of the interviews by the local consultant or consultants or CBRL in close collaboration with the local partners. The objective of the analysis will be to identify most relevant themes to describe the impact and experiences of the COVID-19 crisis in collaboration with the partners. The validity of the analysis will be checked with the interviewers or local consultant or consultants.
2. For corpus with difficulties in qualitative data collection (concerning several local organizations for which this was their first time using qualitative methods), a descriptive of the results will be provided by the CBRL based on quotes and summary themes. In addition, this experience will be used to strengthen partners' abilities in qualitative methods through working sessions to discuss the lessons learned and identify points of improvement.

The quality of the interviews was evaluated by the CBRL based on the transcriptions received. The criteria used were (1) the respect of the interview guide, (2) the quality of the exchanges (interviewers follow the semistructured method and had nonjudgmental and nondirective attitude during the interview), and (3) the quality of the transcription (all the interactions were transcribed).

Publications and Scientific Dissemination

All participating organizations are strongly encouraged to disseminate the results of the EPIC studies through various formats and channels of communication that are best adapted to the local context and target audience (including but not limited to the concerned communities and other stakeholders). EPIC data will be disseminated through webinars, in-person workshops, national reports (eg, detailed study reports and infographics), and scientific publications (article and conference presentations). Knowledge management documents that explore the EPIC program as an example of the community-based

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research approach, and its implementation, during this health crisis are also under development.

Results

General Results

The first EPIC surveys were deployed by the CBOs AIDES (France), the Association de lutte contre le Sida (ALCS; Morocco), Asocia ia Română Anti-SIDA (ARAS; Romania), and Grupo de Ativistas em Tratamentos (GAT; Portugal) in the summer of 2020. To date, the EPIC program has been implemented by 79 organizations in 32 countries worldwide. In total, 118 country-level surveys were conducted, including 66 quantitative studies and 52 qualitative studies. The details on the number of participants, studies, and countries per target population are described in Tables 1-3.

In addition to Coalition PLUS member and partner organizations, external scientific partners (n=2) integrated specific questions or entire modules from the EPIC questionnaires into dedicated or follow-up questionnaires within the framework of ongoing studies. The data from one of these studies may or may not be included in the global database (and the global analyses) depending on the ability to fusion this specific database with the global database and confirmation that there is no risk of duplication. The study, which was implemented in Togo, Burkina Faso, Mali, and the Ivory Coast, has therefore been excluded from the numbers presented here (Tables 1 and 3).

Quantitative data collection completed on March 15, 2022, and qualitative studies completed on May 31, 2022. A total of 13,773 participants participated in the EPIC program (n=12,871, 93.5% participants for the quantitative studies and n=902, 6.5% participants for the qualitative studies).

To date, all participating organizations have received their cleaned database and descriptive tables. Although some countries have already started to disseminate initial results and work on more advanced analyses, many are starting to conduct or discuss the preliminary analyses. Regarding the diffusion of the results, at least 27 organizations have created infographics with a selection of descriptive data from their EPIC studies, which have also served as a basis for feedback to the concerned communities during dedicated meetings. Organizations are also working on national reports or other documents that will summarize the collected data at the national level. The EPIC data have also been used as an evidence base for discussions with local ministries of health or other governmental institutions.

Description of the EPIC program structure and preliminary global results have been presented at regional or international conferences (n=7). Reflections on the development of the EPIC program as a community-based research study in the context of a pandemic have been published [34].

Table 1. Distribution of collected quantitative data by targeted study population (N=12,871 respondents; 66 studies in 29 countries)[a].

Targeted study population[b]	Respondents (n=12,871), n (%)	Different studies (n=66), n (%)	Countries implicated, n	Countries (n=29)
Community health workers	811 (6.3)	10 (15.2)	9	Benin, Burkina Faso, Burundi, Colombia, Guatemala, Malaysia, Mali, Senegal, Spain
People living with HIV	3923 (30.5)	15 (22.7)	15	Brazil, Burkina Faso, Burundi, Canada (Quebec), Cape Verde, Chile, Guinea-Bissau, Mali, Mauritania, Mauritius, Mozambique, Portugal, Romania, São Tomé and Príncipe, Senegal
Men who have sex with men	2965 (23)	11 (16.7)	10	Algeria, Benin, Burkina Faso, Guatemala, Lebanon, Mali, Peru, Portugal, Senegal, Tunisia
Sex workers	2589 (20.1)	15[c] (22.7)	15[c]	Argentina, Algeria, Angola, Brazil, Burkina Faso, Cape Verde, France, Guinea-Bissau, Mali, Morocco, Mozambique, Portugal, São Tomé and Príncipe, Senegal, Spain
People who use drugs	1364 (10.6)	10 (15.2)	9	Algeria, Burkina Faso, Cape Verde, Colombia, France, Malaysia, Mozambique, Portugal, Senegal
Migrants	554 (4.3)	2 (3)	2	Colombia, Portugal
Transgender people	324 (2.5)	2 (3)	2	Benin, Timor
Key populations (including sex workers, people living with HIV, men who have sex with men, migrants)[d]	341 (2.7)	1 (1.5)	1	Colombia

[a]Excludes participants from 4 countries (Togo, Burkina Faso, Mali, and Ivory Coast) who participated in the EPIC program within the framework of an ongoing cohort study (CohMSM PrEP). The integration of the data from this study with a global database must be determined. Associations in Mali and Burkina Faso also implemented EPIC studies outside the cohort study and were therefore included in this study.

[b]None of the participating organizations specifically targeted people living with hepatitis C virus for their studies.

[c]Includes study (HIVITS-TS-COVID) conducted in Spain.

[d]No specified target population within the key populations.

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Table 2. Distribution of collected qualitative data by targeted study population (N=902 respondents; 52 studies in 25 countries).

Targeted study population[a]	Respondents (n=902), n (%)	Different studies (n=52), n (%)	Countries implicated, n	Countries (n=25)
Community health workers	136 (15.1)	9 (17.3)	9	Burkina Faso, Benin, Brazil, Burundi, Guatemala, Lebanon, Malaysia, Mauritania, Senegal
People living with HIV	154 (17.1)	9 (17.3)	9	Algeria, Angola, Cape Verde, Guinea-Bissau, Morocco, Portugal, Tunisia, São Tomé and Príncipe, Mozambique
Men who have sex with men	120 (13.3)	8 (15.4)	8	Angola, Benin, Guatemala, Lebanon, Morocco, Peru, Portugal, São Tomé and Príncipe
Sex workers	186 (20.6)	10 (19.2)	10	Bolivia, Brazil, Canada (Quebec), Cape Verde, Guinea-Bissau, Mozambique, Portugal, São Tomé and Príncipe, Spain, Tunisia
People who use drugs	114 (12.6)	8 (15.4)	8	Algeria, Angola, Canada (Quebec), Cape Verde, Guinea-Bissau, Malaysia, Mozambique, Portugal
Migrants	64 (7.1)	2 (3.8)	2	Colombia, Portugal
Transgender people	39 (4.3)	3 (5.8)	3	Benin, Peru, Timor
Key populations (including sex workers, people living with HIV, men who have sex with men, people who inject drugs, migrants)[b]	89 (9.9)	3 (5.8)	3	Burkina Faso, France, Senegal

[a]None of the participating organizations specifically targeted people living with hepatitis C virus for their studies.

[b]No specified target population within the key populations.

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Table 3. Distribution of collected quantitative and qualitative data by country[a].

Countries	Quantitative data (N=12,871), n (%)	Qualitative data (N=902), n (%)
Algeria	481 (3.74)	57 (6.32)
Angola	101 (0.78)	50 (5.54)
Argentina	256 (1.99)	N/A[b]
Benin	888 (6.9)	48 (5.32)
Bolivia	N/A	29 (3.22)
Brazil	246 (1.91)	60 (6.65)
Burkina Faso	838 (6.51)	60 (6.65)
Burundi	432 (3.36)	30 (3.32)
Canada (Quebec)	182 (1.41)	19 (2.11)
Cape Verde	292 (2.27)	30 (3.32)
Chile	300 (2.33)	N/A
Colombia	842 (6.54)	54 (6)
France	347 (2.69)	10 (1.11)
Guatemala	436 (3.39)	49 (5.43)
Guinea-Bissau	533 (4.14)	40 (4.43)
Lebanon	118 (0.92)	30 (3.32)
Malaysia	305 (2.37)	30 (3.32)
Mali	1168 (9.07)	N/A
Mauritania	151 (1.17)	10 (1.11)
Mauritius	260 (2.02)	N/A
Morocco	119 (0.92)	40 (4.43)
Mozambique	705 (5.48)	30 (3.32)
Peru	476 (3.7)	19 (2.11)
Portugal	1381 (10.73)	49 (5.43)
Romania	103 (0.8)	N/A
São Tomé and Príncipe	599 (4.65)	40 (4.43)
Senegal	623 (4.84)	45 (5)
Spain	437 (3.4)	29 (3.22)
Timor	100 (0.78)	10 (1.11)
Tunisia	152 (1.18)	34 (3.77)

[a]Excludes participants from 4 countries (Togo, Burkina Faso, Mali, and Ivory Coast) who participated in the EPIC program within the framework of an ongoing cohort study (CohMSM PrEP). The integration of the data from this study with a global database must be determined. Associations in Mali and Burkina Faso also implemented EPIC studies outside the cohort study and were therefore included in this study.

[b]N/A: not applicable.

Capacity Building Through the EPIC Program

A total of 139 people were trained during 38 training sessions, amounting to 54 hours of training. Specifically, 29 sessions concerned training on the Voxco platform and the use of its offline functionality, and 2 quantitative data analysis trainings were conducted. Three qualitative training sessions were conducted among 7 associations with 11 people.

Furthermore, several webinars have been organized to encourage sharing of experiences and mutual capacity building between the organizations implementing EPIC such as a webinar among all Spanish-speaking organizations to share experiences and tips regarding practical implementation and recruitment and another webinar for participating organizations in the MENA region, which focused on qualitative methodology and data collection. During the 11th Francophone Conference on HIV/AIDS, AFRAVIH, which was held in Marseille from April 6 to 9, 2022, a round table was organized for participating organizations and academic and community-based researchers to discuss the EPIC program, its implications, and the lessons learned.

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Discussion

Principal Findings

In response to the COVID-19 health crisis, a general community-based research protocol was rapidly developed and made available to CBOs within the Coalition PLUS network. The research protocol was also adapted by external scientific partners to document the impact of the crisis among their ongoing studies. The aims of the global EPIC program were to identify and respond to the specific needs of KP at higher risk for, or living with, HIV or HCV, as well as those who work with these populations.

With a total of 66 surveys (12,871 respondents) and 52 qualitative studies (902 respondents), the EPIC program may largely be considered a success because of the mobilization of an unprecedented number of member and partner organizations across different networks within Coalition PLUS. The EPIC research program will contribute to wider reflections on developing and implementing research projects that respect the community-based research principles within a pandemic context [35]. Furthermore, the program has collected a consequential amount of data among populations who are not represented in general population survey data, who are often not adequately reached by traditional health structures, and who have specific needs [1,25,36].

Although the analysis of the study data is ongoing, we can reflect on some key elements and lessons learned from the implementation of the EPIC program.

Community-Based Research

Following the community-based research approach [31], the EPIC program was initiated based on information from CBOs of the emerging and urgent needs of KP at the start of the COVID-19 health crisis. CBOs were, and continue to be, involved at every step of the research study process as detailed in Figure 1.

Although the development and implementation of the EPIC program followed the stages of a community-based research project, this process was accelerated owing to the urgency of the COVID-19 health crisis (7 weeks between the initial meeting of the EPIC study working group and the validation and availability of the final study documents). The experience of the stakeholders involved in the project, regarding the specificities of EPIC as a community-based research project and the context of a global health crisis, will be explored in a knowledge management project led by the knowledge management department at Coalition PLUS.

Mobilization, Capacity Building, and Coordination

Several key factors related to the structure of Coalition PLUS and its mission may explain the reach and the anticipated breadth of the EPIC program data. The established geographic, thematic, and linguistic networks were advantageous to efficiently channel and coordinate information from the field. Through 2 programs (*convention programs*) that aim to structure and reinforce the local capacities of 5 geographical networks in terms of services, research, and advocacy, and cofunded by the Agence Française de Développement (AFD), local coordinators, and CBRL team members, had a key role in centralizing and communicating information regarding the EPIC program. The CBRL team members based in the 5 geographical regions were able to closely follow the local implementation with the participating organizations. The CBRL also provided support for member organizations that are not part of these 5 geographical networks, including the research network, RIGHT PLUS, and the (linguistic) Lusophone network.

Although most of the organizations have previously participated in research studies, or have had a coordinating role, for some organizations, EPIC was a first-time experience having an active and lead role in the implementation of a research study. This is the case for the association Bésyp in Benin, which collected quantitative data from >200 transgender people, >600 MSM, and >50 CHWs through EPIC surveys. However, it is important to note that most of the participating organizations had extensive experience in conducting research and were instrumental in sharing their experiences and good practices within their regional networks. Such exchanges among the partner and member organizations are fundamental to knowledge sharing and capacity building within and across the Coalition PLUS networks. As the coordinating organization of the Lusophone network, Grupo de Ativistas em Tratamentos in Portugal, had a lead role in training and providing technical support for the organizations and overall coordination of the EPIC studies within the network. Importantly, the EPIC program represented not only a first experience with community-based research for many of the Lusophone network organizations but also an opportunity to collectively work on a research project, and in turn reinforce the structuration of the new network (created in 2019) and collaboration with Coalition PLUS. The ALCS in Morocco, one of the founding members of Coalition PLUS and coordinating organization of the MENA geographical network, was the first to conduct an EPIC study in the region. The ALCS was therefore able to share first-hand experience regarding study implementation during the webinar on qualitative methods with the other partners who were still in the preparatory phase of the study.

A project to capitalize on the EPIC program is currently underway to study and document the achievements and results obtained, lessons learned and good practices, the specificity of this research project compared with an academic research project, and to identify the key factors that contributed to the success of the project at the level of the association, at the level of the regional, thematic, or linguistic networks as well as within Coalition PLUS.

Innovation but Not Without a Cost

For the CBRL, this was the first experience in developing a community-based study within the context of a pandemic as well as developing a general study protocol that was made available to the members and partners of Coalition PLUS. As described elsewhere [34], the EPIC program was launched without a clear idea of how many organizations would implement the study or the human resources and financing needed to assure the technical support and follow-up generated from the high demand. Although the flexibility of the EPIC's

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methodology likely explains, in part, its high uptake within the Coalition PLUS network, it also adds complexity to the overall study coordination and follow-up. The global coordination of the study necessitated the mobilization of all 15 members of the research team, in addition to the coordinating organizations of the Coalition PLUS networks. Depending on the level of experience of the participating organizations, customized support regarding training on good study practices, data collection and management, and analysis were provided. The technical support provided by the Coalition PLUS CBRL will continue as participating organizations prepare to disseminate the results. Other Coalition PLUS departments, such as advocacy, knowledge management, and services, will have greater roles as results are used to inform recommendations and better practices.

Another significant factor to be considered is the fact that the development of the study protocol and its implementation in 2020 was possible largely because of the Coalition PLUS' or partner organizations' own funds. The number of participating countries greatly expanded in 2021 thanks to a reallocation of funds to pandemic efforts within the context of the *convention-programs* financed by the AFD [34]. Although 4 attempts were made to obtain research grants, success was limited because of the innovative methodology and the fact that research funding bodies were reluctant to fund studies that had already been launched at the time of the grant application. Research funding bodies also insisted on a justification for the choice of participating countries, the study populations, and sample sizes. This community-based research study was therefore evaluated within the framework of traditional research studies and not within the context of an ongoing pandemic, which explained the necessity to implement a flexible methodology and certain choices regarding the study population and size. The balance between keeping the research focus on responding to local needs during the health crisis and limiting local implementers' potential exposure to COVID-19 while assuring scientific rigor has been touched upon elsewhere [35]. In addition to cofunding from the AFD, funding from the French Agency for Research on AIDS and Viral Hepatitis (*ANRS-Maladies infectieuses émergentes*) was secured to cofinance the qualitative data collection, analysis, and scientific dissemination of the EPIC program in the MENA region. Finally, funding was also secured from the Robert Carr Fund for the organization of 3 workshops for the presentation and discussion of the EPIC results from the West African and MENA regions. Minor local financing or other support for the EPIC program was obtained by some participating organizations through national institutions or through the contribution of resources from universities.

Strengths and Limitations

Impelled by the urgency to identify and document emerging needs among KP at the start of the COVID-19 health crisis, the EPIC research program was developed following alerts from Coalition PLUS member and partner organizations. It was a research program guided by the principles of community-based research at its start and will continue to be throughout the research process. In line with the community-based research approach, the study populations and themes covered in the questionnaire or interviews were determined by the partner organizations in accordance with local needs. Therefore, the major strength of this program is the relevance of the study results to the local context. In addition, data regarding the impact of the COVID-19 crisis among KP at the local, regional, and global levels are particularly important to provide visibility to populations that are rarely represented in general population surveys. Furthermore, the EPIC data will capture precious information regarding the innovations or solutions that were put into place to maintain services during the crisis. This information could help support the sustainability of these solutions outside the COVID-19 crisis. The Coalition PLUS geographical and thematic networks aided in the (regional) coordination and implementation of the study. The collection of quantitative and qualitative data will provide more robust data to explore the experiences of KP and CHWs. Finally, implementation of this study, particularly by organizations that had little or no prior experience leading the local implementation of a research study, provided an opportunity for capacity building in research among the Coalition PLUS member and partner organizations.

The development and implementation of the EPIC program during a global pandemic has created several limitations that should be considered. COVID-19–related restrictions resulted in delays for ethics approvals and complicated data collection for some partners, sometimes resulting in a data collection period that spanned several months. Information regarding the state of the COVID-19 pandemic (eg, the epidemiological situation and governmental measures in place) at the time of data collection will be considered in the analyses to minimize potential bias. As each participating organization was able to construct their questionnaire or questionnaires according to local needs, there may be some limitations regarding the themes that can be explored in the global analyses. Thematic, regional, and global analyses will be performed whenever possible. Finally, some analyses will be limited owing to the sample size. Although it may not be possible to perform advanced data analyses in such situations, descriptive analyses will be performed and nonetheless will contribute important contextual information to broader common themes [37]. Analysis may also be limited owing to the quality of the collected data, particularly for qualitative data collection as it was a first-time experience in qualitative methods for many participating organizations. Although the literature on the implementation of multicountry qualitative research studies by previously untrained local implementors is limited, previous work suggests that implication of the local agents at the start of the study and continued support through the research process (including analysis) will help bolster the quality of the results [38]. In situations where the quality of EPIC data is not sufficient for in-depth analysis, efforts will be made to provide detailed feedback to the participating organizations to identify better practices.

Conclusions

The multicountry community-based EPIC program was developed by various stakeholders, including and with the continued engagement of communities at all stages of the research process. With the challenge of documenting the impact of the global health crisis among KP and the CHWs who work

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with these populations, a general protocol was developed with a built-in flexibility that allowed the adaptation of the study to meet local needs. The deployment of this community-based research program within the Coalition PLUS network created the opportunity to not only collect data on the COVID-19 crisis but also to develop or reinforce capacity-building initiatives among the participating organizations through trainings, experience sharing, and continued technical support.

The EPIC program will provide essential information regarding the impact of the health crisis on KP at higher risk for HIV who are still little or not represented, depending on the geographical area, in the scientific literature. These results will therefore enhance community responses by capitalizing on new adaptations and innovations to HIV and viral hepatitis prevention and care services that may be pertinent beyond the current health crisis.

Finally, these data will also be essential to carry out national and international advocacy to ensure that KP are not forgotten in public responses to the current and future health crises. Thanks to the community expertise acquired in the field of HIV and hepatitis, it is anticipated that these data will show that the community-based response can be complementary to the public health response in a pandemic context and can continue to provide pertinent solutions for KP.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Ethics approval obtained by each participating organization.
[DOCX File , 14 KB - resprot_v12i1e45204_app1.docx]

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Abbreviations

AFD: Agence Française de Développement
ALCS: Association de lutte contre le Sida
CBO: community-based organization
CBRL: Community-based Research Laboratory
CHW: community health worker
EPIC: *Enquêtes Pour évaluer l'Impact de la crise sanitaire covid en milieu Communautaire*
HCV: hepatitis C virus
KP: key populations

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MENA: Middle East and North Africa
MSM: men who have sex with men
SW: sex worker

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Corrigenda and Addenda

Correction: Impact of a Postintensive Care Unit Multidisciplinary Follow-up on the Quality of Life (SUIVI-REA): Protocol for a Multicenter Randomized Controlled Trial

Diane Friedman[1], MD; Lamiae Grimaldi[2], MD, PhD; Alain Cariou[3], MD, PhD; Philippe Aegerter[2], MD, PhD; Stéphane Gaudry[4], MD, PhD; Abdel Ben Salah[5], MD, PhD; Haikel Oueslati[6], MD, PhD; Bruno Megarbane[7], MD, PhD; Nicolas Meunier-Beillard[8,9], PhD; Jean-Pierre Quenot[10], MD, PhD; Carole Schwebel[11], MD, PhD; Laurent Jacob[6], MD; Ségloène Robin Lagandré[12], MD; Pierre Kalfon[5]; Romain Sonneville[13], MD, PhD; Shidasp Siami[14], MD, PhD; Aurelien Mazeraud[15], MD, PhD; Tarek Sharshar[15], MD, PhD

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Related Article:

Correction of: https://www.researchprotocols.org/2022/5/e30496

(JMIR Res Protoc 2023;12:e47929) doi:10.2196/47929

In "Impact of a Postintensive Care Unit Multidisciplinary Follow-up on the Quality of Life (SUIVI-REA): Protocol for a Multicenter Randomized Controlled Trial" (JMIR Res Protoc 2022;11(5):e30496) the authors made three clarifications.

In the sample size section of the manuscript, the passage:

Therefore, we estimated that at least 50% had a very poor outcome, combining death and moderate to severe impairment of at least one EQ5D dimension

has been corrected to:

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Therefore, we estimated that at least 50% had a very poor outcome, combining death and severe to extreme impairment of at least one EQ5D dimension.

In the sample size section of the manuscript, the passage:

The study was then powered to detect a decrease from 50% to 37% of patients with very unfavorable outcome with a power of 90% and a 2-sided 5% alpha risk, assuming this rate would be 50% in the control arm.

has been corrected to:

The study was then powered to detect a decrease from 50% to 37% of patients with very unfavorable outcome with a power of 80% and a 2-sided 5% alpha risk, assuming this rate would be 50% in the control arm.

In the "statistical methods" section of the manuscript, the passage:

The 1-year survival rate without major deterioration in QoL (main endpoint, defined as reporting of an extreme problem" level in 1 of the 5 dimensions studied) will be compared between both arms using a piecewise exponential model considering any censorship and the repeated nature of observations, prohibiting the use of conventional methods of analysis of censored data

has been corrected to:

The 1-year survival rate without major deterioration in QoL (main endpoint, defined as reporting of death or a severe to extreme problem" level in 1 of the 5 dimensions studied) will be compared between both arms using a piecewise exponential model considering any censorship and the repeated nature of observations, prohibiting the use of conventional methods of analysis of censored data.

The correction will appear in the online version of the paper on the JMIR Publications website on April 14, 2023, together with the publication of this correction notice. Because this was made after submission to PubMed, PubMed Central, and other full-text repositories, the corrected article has also been resubmitted to those repositories.

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Corrigenda and Addenda

Correction: The Efficacy, Safety, and Efficiency of the Off-Label Use of Bevacizumab in Patients Diagnosed With Age-Related Macular Degeneration: Protocol for a Systematic Review and Meta-Analysis

João Estarreja[1*], PharmD; Priscila Mendes[1*], MSc, PharmD, PhD; Carina Silva[1,2*], BSc, MSc, PhD; Pedro Camacho[1*], BSc, MSc, PhD; Vanessa Mateus[1,3*], MSc, PharmD, PhD

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Related Article:

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In "The Efficacy, Safety, and Efficiency of the Off-Label Use of Bevacizumab in Patients Diagnosed With Age-Related Macular Degeneration: Protocol for a Systematic Review and Meta-Analysis" (JMIR Res Protoc 2023;12:e38658) the authors noted a missing Acknowledgments section. The Acknowledgments section has now been added to the published paper as follows:

> *H&TRC authors gratefully acknowledge the FCT/MCTES national support through the UIDB/05608/2020 and UIDP/05608/2020.*

The correction will appear in the online version of the paper on the JMIR Publications website on July 4, 2023, together with the publication of this correction notice. Because this was made after submission to PubMed, PubMed Central, and other full-text repositories, the corrected article has also been resubmitted to those repositories.

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Corrigenda and Addenda

Correction: Acceptability and Feasibility of a Return-to-Work Intervention for Posttreatment Breast Cancer Survivors: Protocol for a Co-design and Development Study

Karine Bilodeau[1,2], PhD; Marie-Michelle Gouin[3], PhD; Alexandra Lecours[4], PhD; Valérie Lederer[5], PhD; Marie-José Durand[3], PhD; Kelley Kilpatrick[2,6], PhD; David Lepage[7], MSc; Lauriane Ladouceur-Deslauriers[7], MSc; Tomas Dorta[8], PhD

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Related Article:

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In "Acceptability and Feasibility of a Return-to-Work Intervention for Posttreatment Breast Cancer Survivors: Protocol for a Co-design and Development Study" (JMIR Res Protoc 2022;11(4):e37009) the authors noted an error.

The following sentence and reference [55] were deleted from the manuscript:

> *Participants will be instructed to not work on existing or unappreciated resources for people affected by cancer, such as a pamphlet or a website that already exists in Canada [55].*

All subsequent references have been renumbered accordingly.

The correction will appear in the online version of the paper on the JMIR Publications website on July 18, 2023, together with the publication of this correction notice. Because this was made after submission to PubMed, PubMed Central, and other full-text repositories, the corrected article has also been resubmitted to those repositories.

Reference

55. Cancer and work. Cancer and Work. URL: https://www.cancerandwork.ca [accessed 2022-04-12]

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Corrigenda and Addenda

Correction: Effectiveness of Silver Diamine Fluoride for Early Childhood Caries Among Children Aged 24 to 72 Months: Protocol for a Randomized Controlled Trial

Amitha Basheer N[1*], MDS; Praveen S Jodalli[2*], MDS, PhD; Namratha Nayak[3*], MDS; Aparna K S[2*], MDS; Avinash R Badekkila[2*], MDS

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Related Article:

Correction of: https://www.researchprotocols.org/2023/1/e46144

(JMIR Res Protoc 2023;12:e50744) doi:10.2196/50744

In "Effectiveness of Silver Diamine Fluoride for Early Childhood Caries Among Children Aged 24 to 72 Months: Protocol for a Randomized Controlled Trial" (JMIR Res Protoc 2023;12:e46144) the authors noted two errors.

1.) In the originally published manuscript, affiliation 2 appeared as follows:

> *Department of Public Health Dentistry, Manipal College of Dental Sciences Mangalore, Manipal Academy of Higher Education, Mangalore, India*

This has been corrected to:

> *Department of Public Health Dentistry, Manipal College of Dental Sciences Mangalore, Manipal Academy of Higher Education, Manipal, India*

2.) In the originally published manuscript, the postal code for the Corresponding Author address appeared as follows:

> *Mangalore, 575001*

This has been corrected to:

> *Manipal, 5756104*

The correction will appear in the online version of the paper on the JMIR Publications website on July 26, 2023, together with the publication of this correction notice. Because this was made after submission to PubMed, PubMed Central, and other full-text repositories, the corrected article has also been resubmitted to those repositories.

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Corrigenda and Addenda

Correction: Effects of Aerobic Exercise on Cardiorespiratory Fitness, Cardiovascular Risk Factors, and Patient-Reported Outcomes in Long-Term Breast Cancer Survivors: Protocol for a Randomized Controlled Trial

Tormod Skogstad Nilsen[1*], PhD; Mali Sæter[2,3*], MD; Sebastian Imre Sarvari[3], MD, PhD; Kristin Valborg Reinertsen[4], MD, PhD; Sara Hassing Johansen[1], MSc; Elisabeth Rustad Edvardsen[1], MSc; Jostein Hallén[1], PhD; Elisabeth Edvardsen[1,5], PhD; May Grydeland[1], PhD; Cecilie Essholt Kiserud[4], MD, PhD; Hanne Cathrine Lie[6], PhD; Paul André Solberg[7], PhD; Torbjørn Wisløff[8], PhD; Adam Philip Sharples[1], PhD; Truls Raastad[1], PhD; Kristina Hermann Haugaa[2,3], MD, PhD; Lene Thorsen[4,9], PhD

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Related Article:

Correction of: https://www.researchprotocols.org/2023/1/e45244

(JMIR Res Protoc 2023;12:e54462) doi:10.2196/54462

In "Effects of Aerobic Exercise on Cardiorespiratory Fitness, Cardiovascular Risk Factors, and Patient-Reported Outcomes in Long-Term Breast Cancer Survivors: Protocol for a Randomized Controlled Trial" (JMIR Res Protoc 2023;12:e45244) the authors made two corrections.

The affiliations for authors Mali Sæter and Kristina Hermann Haugaawere originally published as:

> *[2] ProCardio Center for Innovation, Department of Cardiology, Oslo University Hospital, Oslo, Norway*

And have been changed to:

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>
> *[3]ProCardio Center for Innovation, Department of Cardiology, Oslo University Hospital, Oslo, Norway*

The subsequent affiliation numeration has been adjusted to accomodate for this change. The correction will appear in the online version of the paper on the JMIR Publications website on November 15, 2023 together with the publication of this correction notice. Because this was made after submission to PubMed, PubMed Central, and other full-text repositories, the corrected article has also been resubmitted to those repositories.

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Corrigenda and Addenda

Correction: Community-Led, Cross-Sector Partnership of Housing and Health Care to Promote Aging in Place (Unite Health Project): Protocol for a Prospective Observational Study

Lesli Skolarus[1], MSc, MD; Erica Thrash-Sall[2], MBA; Abby Katherine Hellem[3], MPH; Michael Giacalone Jr[4], MD; James Burke[5], MSc, MD; Chun Chieh Lin[3], MBA, PhD; Sarah Bailey[6], MA; Casey Corches[3], MPH, OTR; Mackenzie Dinh[7], MSc; Amanda Casetti[3], BSc; Maria Mansour[3], BSc; Kaitlyn Bowie[7], BSc; Rylyn Roth[3], BSc; Candace Whitfield[7], BSc; Anne Sales[8,9], RN, PhD

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Related Article:

Correction of: https://www.researchprotocols.org/2023/1/e47855

(JMIR Res Protoc 2023;12:e54662) doi:10.2196/54662

In "Community-Led, Cross-Sector Partnership of Housing and Health Care to Promote Aging in Place (Unite Health Project): Protocol for a Prospective Observational Study" (JMIR Res Protoc 2023;12:e47855) the authors noted one error.

Multimedia Appendix 1 was initially published as follows:

> *Multimedia Appendix 1. Peer review report by the Community-Level Health Promotion (CLHP) Study Section - Healthcare Delivery and Methodologies Integrated Review Group - Center for Scientific Review (National Institutes of Health, USA).*

This file has been removed from the article. Accordingly, the boiler plate text was changed from:

> *The proposal for this study was peer-reviewed by: Community-Level Health Promotion (CLHP) Study Section - Healthcare Delivery and Methodologies Integrated Review Group - Center for Scientific Review (National Institutes of Health, USA). See the Multimedia Appendix for the peer review report;*

To the following:

> *The proposal for this study was peer-reviewed by: Community-Level Health Promotion (CLHP) Study Section - Healthcare Delivery and Methodologies Integrated Review Group - Center for Scientific Review (National Institutes of Health, USA);*

The correction will appear in the online version of the paper on the JMIR Publications website on November 21, 2023 together with the publication of this correction notice. Because this was made after submission to PubMed, PubMed Central, and other full-text repositories, the corrected article has also been resubmitted to those repositories.

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Corrigenda and Addenda

Authorship Correction: Voice-Based Screening for SARS-CoV-2 Exposure in Cardiovascular Clinics (VOICE-COVID-19-II): Protocol for a Randomized Controlled Trial

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In "Voice-Based Screening for SARS-CoV-2 Exposure in Cardiovascular Clinics (VOICE-COVID-19-II): Protocol for a Randomized Controlled Trial" (JMIR Res Protoc 2023;12:e41209) the authors noted the following error:

In the author list, the first two authors Emily Oulousian and Seok Hoon Chung had contributed equally but this was not listed. In the corrected version the first two authors have been listed as:

Emily Oulousian; Seok Hoon Chung**

**these authors contributed equally*

The corrections will appear in the online version of the paper on the JMIR Publications website on November 23, 2023, together with the publication of this correction notice. Because this was made after submission to PubMed, PubMed Central, and other full-text repositories, the corrected article has also been resubmitted to those repositories.

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Original Paper

Parents' and Health Care Professionals' Perspectives on Prevention and Prediction of Food Allergies in Children: Protocol for a Qualitative Study

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Abstract

Background: Food allergy in children is increasing in prevalence in the western world and appears to become an important health problem. Parents of children at risk of food allergy live with the fear of allergic reaction, especially when the children are very young. The paradigm shift in allergy prevention in the last decade—away from allergen avoidance toward a tolerance induction approach—challenges both parents and health care professionals, as they have to deal with changing information and new evidence that often contradicts previous assumptions. Yet, research on health information–seeking behavior and needs of parents on primary prevention of food allergy in children as well as on prediction and prevention strategies of German health care professionals is lacking.

Objective: The aim of the study is to explore and understand parents' and health care professionals' perspectives on the prediction and prevention of food allergies. We are particularly interested in information needs, information seeking, and health care usage and place a special focus on families' experiences when their child is at risk or diagnosed with food allergies. Furthermore, food allergy prediction and prevention strategies of health care professionals will be explored.

Methods: This study is part of the NAMIBIO (food allergy biomarker) app consortium, which aims to identify early predictors for the development of food allergy in children and develop apps to guide health care professionals and parents of children with a high risk of food allergy toward prevention and timely tolerance induction. The study uses a qualitative approach with topic-guided interviews and focus groups with parents of children (0-3 years) and health care professionals. Data collection will continue until theoretical saturation is reached. The qualitative content analysis will be used according to Kuckartz to identify overarching themes toward information needs and seeking behavior as well as usage of health care and health care professionals' predictive and preventive strategies. In addition, a constructivist grounded theory approach will be used to explore and understand parents' experiences, interactions, and social processes in families in daily life.

Results: Recruitment and data collection started in February 2022 and is still ongoing.

Conclusions: The qualitative study will provide insight into parents' information-seeking behavior and needs regarding the prevention of food allergy in children, parents' use of pediatric primary care, and health care professionals strategies for the prediction and prevention of food allergies in children. We assume that our results will highlight the challenges associated with the paradigm shift in allergy prevention for both parents and health care professionals. The results will be used to make practical recommendations from the user's perspective and inform the development of the NAMIBIO apps.

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KEYWORDS

parents; health care professionals; content analysis; grounded theory; food allergy; children; allergic reaction; information needs; information seeking; prevention; prediction; risk factors

Introduction

Background

Food allergies (FAs) are an important public health issue affecting children and adults and have been increasing in prevalence in the last 2 to 3 decades [1-3]. The estimated prevalence of food allergy in children (FAIC) in the western world is around 6%-8% [4]. The symptoms can vary from mild to severe, and in extreme cases, FA can lead to a life-threatening allergic reaction (anaphylaxis) [1]. Therefore, it is important to identify children at increased risk before the onset of clinical symptoms and prevent the development of FA. Genetic, epigenetic, and environmental risk factors are increasingly being clarified. This offers a potential for improved prevention and treatment strategies for at-risk groups and possibly all children [2,5]. Insights on pathophysiology reveal a complex interplay of the epithelial barrier, mucosal and systemic immune response, route of exposure, and microbiome among other influences resulting in allergy or in tolerance [6].

Currently, there is no cure for FAs [2]. Avoidance of allergens is the mainstay of management, along with patient education and provision of emergency medication (adrenaline auto-injectors) [2,7]. Prevention approaches based on new research highlight that a strict diet avoiding allergenic foods such as milk, egg, fish, or nuts is not a sensible allergy prevention intervention during pregnancy, breastfeeding, and complementary feeding. The aim is rather to introduce potentially allergenic foods at an early stage in order to promote tolerance induction [4,8].

This paradigm shift in allergy prevention—away from allergen avoidance toward a tolerance-induction approach [8-10]—challenges both parents and health care professionals (HCPs) as they have to deal with changing information and new evidence that often contradicts previous assumptions. Thus, different knowledge of (changing) guidelines, attitudes, and beliefs about FA may result in heterogeneous counseling practices [11] and prevention strategies [12] in pediatricians.

In Germany, pediatricians and midwives are an important source of information on newborn care and allergy prevention for parents [13]. However, parents also seek information from other sources, for example, websites and social media, which can lead to confusion when deciding which recommendation to follow [14,15]. In particular, those with limited access and information-seeking skills, as well as a lack of critical evaluation skills, have been identified as being disadvantaged when searching for health information on the internet [16,17].

Previous studies from other countries (the United Kingdom, Canada, and Australia) showed that parents' information needs regarding FA are often not met [18-20]. Hu et al [20] found that information needs and information-seeking behavior of parents with a child diagnosed with FA changed over the course of the disease. In particular, in the period after the diagnosis, parents wanted extensive information [20]. Other studies identified a strong parental need for recommendations on how to manage FA and on how to cope with fear and anxiety associated with the disease [18,19].

Chang et al [12] studied the beliefs and practices of general pediatricians from the United States regarding early peanut introduction. Physicians perceived important barriers to the implementation of the recommendations of the guideline. Among other things, they did not fully agree with the content of the guideline and also anticipated that parents would be skeptical. This corresponds to surveys from the United States, Brazil, and Canada, which revealed that awareness and implementation of guidelines on FA prevention varied widely among physicians [21-23].

Until now, there is no research on information-seeking behavior and needs of parents regarding the primary, early childhood prevention of FA as well as on FA prediction and prevention strategies of German HCPs.

Objectives

The objectives of the study are to (1) identify, conceptualize, and systematically describe (a) parental information needs, information seeking, and health care usage regarding prediction and prevention of FAIC and (b) HCPs' strategies on prediction and prevention of FAIC and (2) explore and understand how parents experience family life with children at risk of FA or with an existing FA.

Methods

Research Context

The study is a subproject of the Nahrungsmittelallergie biomarker (NAMIBIO) app consortium, funded by the German Federal Ministry of Education and Research (01EA2108A-E). The consortium aims to identify early predictors for the development of FAIC and to develop 2 applications to guide HCPs and parents of children at high risk of FA toward prevention and timely tolerance induction. NAMIBIO is a German acronym for Nahrungsmittelallergie biomarker ("food allergy biomarker"). The planned NAMIBIO digital health apps, "Parent app" and "Professional app," will provide an algorithm for individual prediction of children's FA risk and help parents of children at high risk of FA and their HCPs to manage their information needs and prevention efforts [24]. While there is an increasing availability of mobile health technology that focuses on FA management [25], to the best of our knowledge, until now, there is no app that focuses on the prediction and prevention of FAIC.

The results of this study will inform the development of the NAMIBIO apps.

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Research Team and Reflexivity

Our subproject is jointly led and conducted by members of the Otto von Guericke University Magdeburg, Faculty of Medicine, Institute of Social Medicine and Health Systems Research and the University Children's Hospital Regensburg (KUNO) at the St. Hedwig Clinic, Hospital of the Order of St. John, University of Regensburg.

The project team consists of 2 leads (CA and SB), 4 research assistants with master's degrees (Public Health, Psychology, Sociology, and Social Work in the Aging Society, female), 1 postdoctoral researcher (Nursing Science, female), and 2 student research assistants (female). All team members have previous research experience and training in conducting qualitative research. In order to develop a common understanding of qualitative methods, we shared our prior qualitative research experience in a joint workshop during the elaboration of the study protocol. In this process, interviewing skills were further discussed and practiced as well as prejudices and preassumptions with regard to recruitment, data collection, and results were exchanged and recorded.

We are aware that qualitative research interviewers influence the interaction of the interviews. As interviewers, we want to display self-confidence in what we do, trust in the interview situation and what the participants will share with us, as well as inner tranquility that communicates interest and attention [26]. The participants will be informed about the reasons and aims of this study. We will also inform them that we (the interviewers) are part of the research team and where we are located (institute or university). We will not actively disclose personal information such as professional and research background and family situation (eg, children). Our credibility comes from active listening and asking relevant questions which are meaningful to our participants [26].

Study Design

The study uses a qualitative approach with topic-guided interviews and focus groups (Table 1). The qualitative content analysis approach according to Kuckartz will be used [27,28] and Charmaz constructivist grounded theory will be followed to develop a theory [29] of family life with children at risk of or diagnosed with FA.

Table 1. Study design.

Characteristics	Parent group	Health care professionals group

Participants	• Parents of children (0-3 years)
	  • Diagnosed with a FA[a]
	  • At risk of FA
	  • Without a known risk of FA
		• Health care professionals
		  • Pediatricians
		  • Allergists
		  • Pediatric dermatologists
		  • Gynecologists or obstetricians
		  • Midwives
		  • Nurses

Study design	• Qualitative approach	• Qualitative approach
Data collection	• Topic-guided interviews • Approximately 30 interviews	• Topic-guided interviews and focus groups • Approximately 15 interviews and 2-4 focus groups
Data analysis	• Qualitative content analysis according to Kuckartz [27,28] • Constructivist grounded theory according to Charmaz [29]	• Qualitative content analysis according to Kuckartz [27,28]
Dissemination	• Recommendations for the development of the NAMIBIO[b] apps	• Recommendations for the development of the NAMIBIO apps

[a]FA: food allergy.

[b]NAMIBIO: Nahrungsmittelallergie biomarker/food allergy biomarker.

Theoretical Framework

Within the social constructivist perspective, we work with sensitizing concepts from the social sciences, for example, "doing family" [30-32], "health literacy" [33], "the social amplification and attenuation of risk framework" [34], "burden of illness" [35], "access to health care" [36,37], "peer support among patient communities" [38], and "guilt" [39].

These concepts are preliminary tools and repeatedly stimulate our thinking about the topic (eg, raising questions for the topic guides) and the generated data (eg, while analyzing processes and actions or interactions). We will dispense with particular sensitizing concepts, if they prove to be irrelevant [29].

Participants

We focus on 2 different target groups—parents and HCPs: (1) The parent group includes caregivers (mothers or fathers) of children between the ages of 0 and 3 years diagnosed with FA, at risk of FA, or without a known risk of FA (Textbox 1). Participating parents receive 30€ (US $32.7) to compensate for their time and efforts. (2) The HCP group includes pediatricians, allergists, pediatric dermatologists, gynecologists or obstetricians, midwives, and nurses. Participation is remunerated with 80€ (US $87.2; Textbox 2).

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Textbox 1. Inclusion criteria (parent group).

- Parents of children (0-3 years) diagnosed with a food allergy
- Parents of children (0-3 years) at risk of food allergy
  - Risk factors for food allergy in children
    - Preexisting allergies or allergic diseases, for example, allergic asthma and hay fever
    - Preexisting atopic eczema, especially one that starts early in life and is severe
    - Genetic or environmental risk factors for food allergy, for example, food allergy, atopic eczema, allergic asthma, or hay fever in the family history (first generation)
- Parents of children (0-3 years) without a known risk of food allergy
- Living in Germany
- Written consent form

Textbox 2. Inclusion criteria (health care professionals group).

- Health care professionals: Pediatricians, allergists, pediatric dermatologists, gynecologists or obstetricians, midwives, and nurses
- Working in an inpatient or outpatient setting in Germany
- Written consent form

Recruitment Process

Figures 1 and 2 display the strategies for the recruitment of participants for the parents and the HCPs group.

We first established field access through personal contacts (in our families and professional environment) at the 2 projects sites in Germany—Magdeburg and Northern Saxony-Anhalt and Regensburg and Eastern Bavaria—which differ in sociodemographic and structural characteristics [40]. It was ensured that there is no personal relationship between the interviewer and the interviewee.

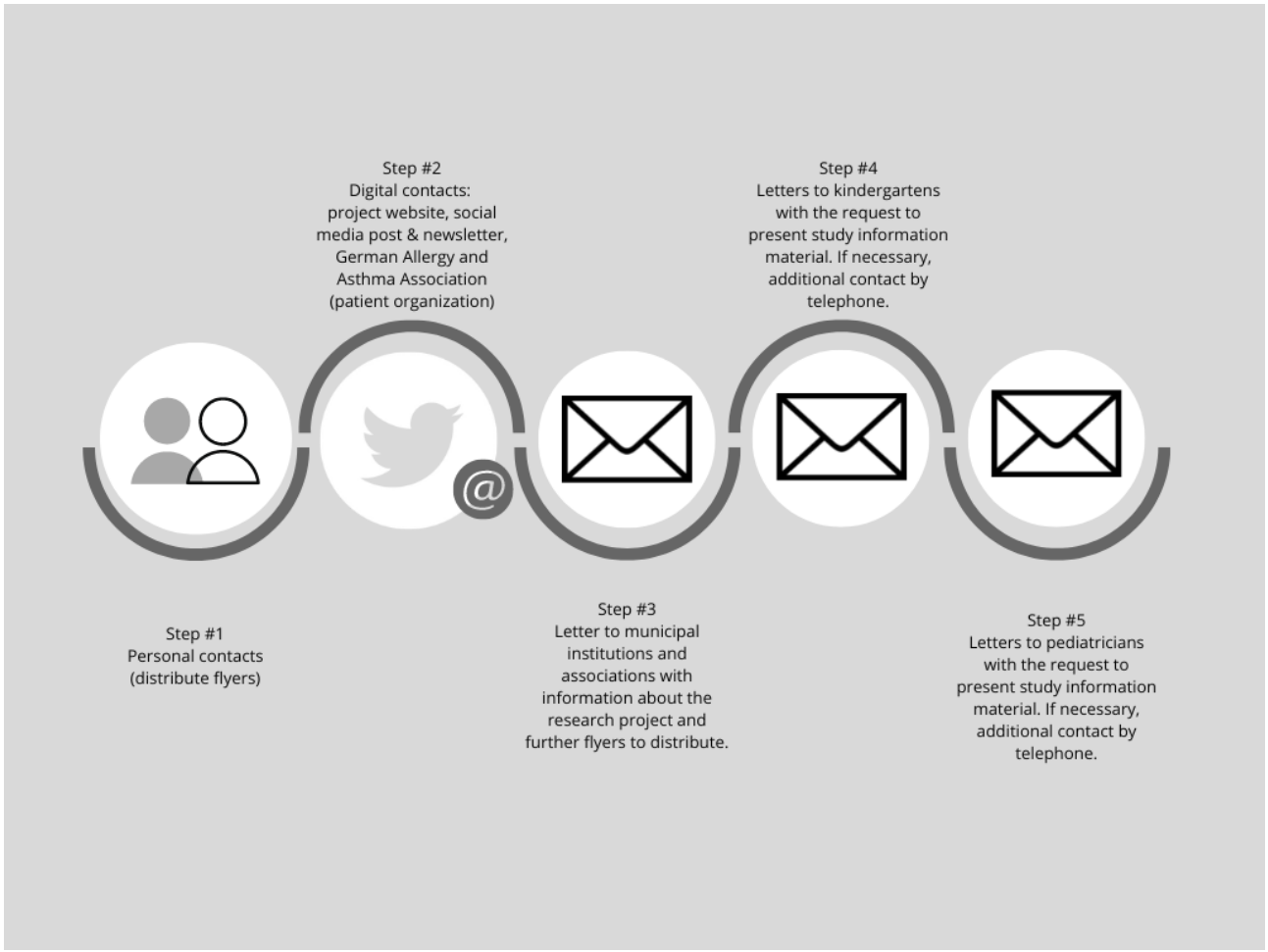
Afterward, we recruited through a snowball sampling, followed by theoretical sampling.

The snowball sampling provides a point of departure to find relevant material for the study. This offers first insights into different (perhaps opposing) perspectives of the field, for example, parents of children without known risk of FA and parents of children diagnosed with FA or pediatricians and allergists. In addition, snowball sampling can prepare the theoretical sampling in a narrower sense [41]. The selection of further “cases” (theoretical sampling) is primarily concerned with the elaboration and contrasting of the phenomena found. Accordingly, the criteria for initial sampling may differ from those we use while sampling theoretically. The goal is to collect information from different perspectives in order to arrive at a vivid and comprehensive representation of the phenomenon of interest [42].

The size and composition of the 2 target groups (parents and HCPs) are not precisely defined. We anticipate about 30 interviews with parents, as well as about 15 interviews with HCPs and 2-4 focus groups. We aim for theoretical saturation of our data. “Saturation” means that collecting fresh data no longer leads to new theoretical insights and does not reveal new characteristics of the core theoretical categories [29].

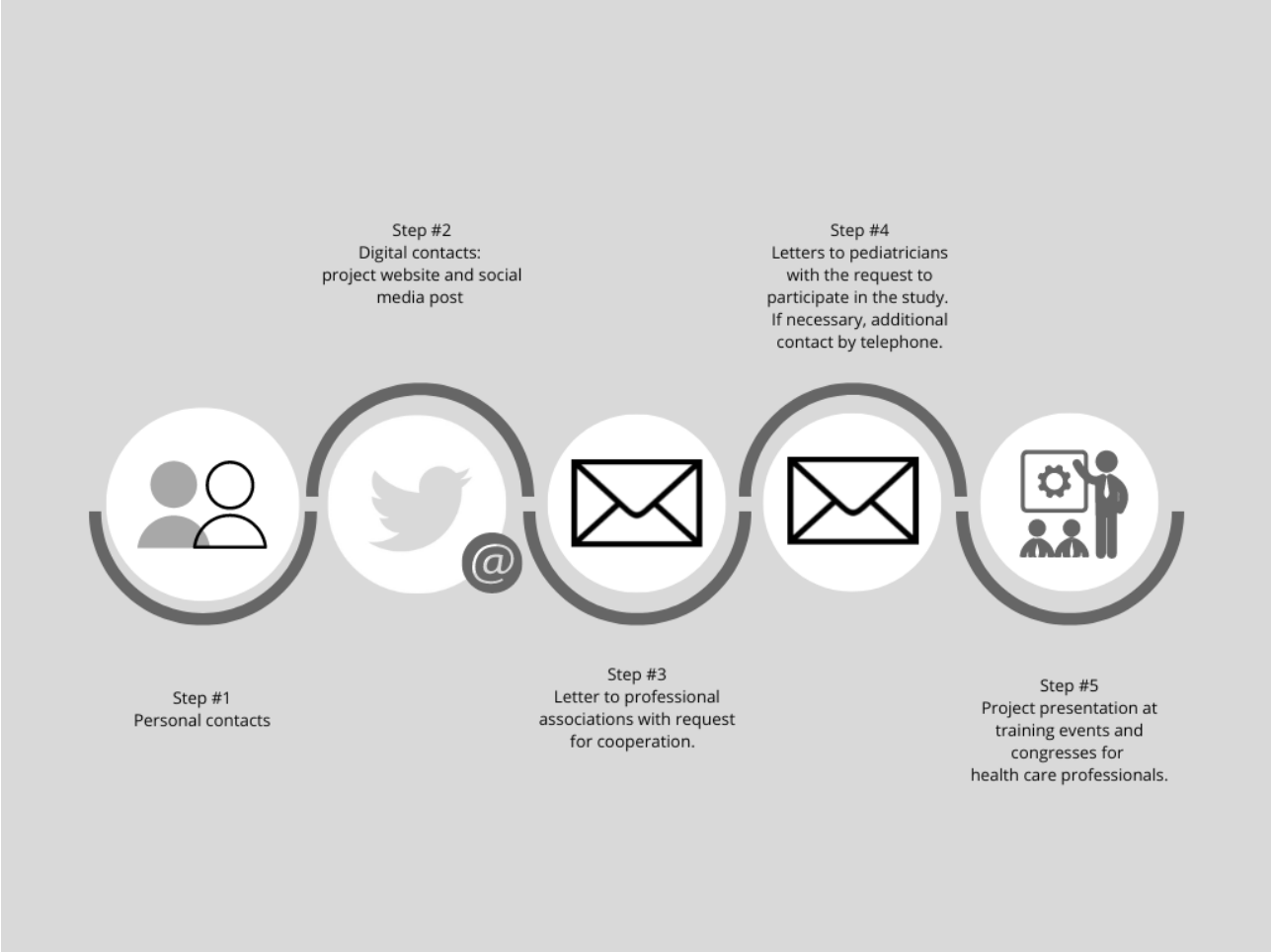
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Figure 1. Recruitment strategy parents.



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Figure 2. Recruitment strategy health care professionals.



Setting

Interviews and focus groups are conducted in person, by telephone, or via privacy-compliant videoconferencing systems (Webex, Cisco), and in light of applicable COVID-19 regulations. Parent interviews are conducted individually (mother or father) or as a parent or family interview according to participants' preferences.

Data Collection

The topic guides were developed for the interviews with parents and focus groups [43] with HCPs (Multimedia Appendices 1 and 2). The questions were phrased openly to provide only as much guidance in the narrative flow as is needed [44] and yet support the interviewers in data collection. In the focus groups, case vignettes were used (Multimedia Appendix 2) to stimulate narratives at the beginning. The short presentations represent hypothetical case descriptions to foster discussion among the participants.

The German Allergy and Asthma Association (patient organization) provided feedback on themes and questions. We will adapt the guiding questions as needed during data collection, for example, to check hunches about categories, clarify relationships between emerging categories, or identify variations within a process (theoretical sampling) [29].

Audio data are recorded as mp3 files. To better contextualize the insights gained from the interviews and focus groups, parents' sociodemographic data (year of birth, sex, nationality, marital status, country of birth, living situation, highest school or university degree, and employment or occupational status) as well as information on the HCPs' career (qualification and professional experience) were gathered. In addition, field notes were written after the interviews and focus groups, which provide space for the researchers' observations, perceptions, and further information.

Data Analysis and Reporting

The interviews and focus groups are transcribed verbatim. MAXQDA Analytic Pro 2022 (VERBI software for qualitative and mixed methods research) is used to support us in managing and coding the data.

For answering our first research question, we will identify, conceptualize, and systematically describe relevant themes on parental information needs and seeking as well as health care usage and HCPs' strategies on prediction and prevention of FAIC. A qualitative content analysis according to Kuckartz [27,28,45] will be applied. Kuckartz [27,28,45] describes different phases of data analysis that will be performed (Textbox 3). The procedure is rule governed and thus intersubjectively verifiable [27,45].

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Textbox 3. Qualitative content analysis approach according to Kuckartz [27,45].

Step 1: Preparing the data, initiating text work, including attentive reading and marking interesting parts of the text, noting special features and evaluation thoughts, and creating initial case summaries
Step 2: Forming main categories corresponding to the research questions
Step 3: Coding data with the main categories
Step 4: Compiling text passages of the main categories and forming subcategories inductively on the data material; assigning text passages to subcategories
Step 5: Category-based analyses and presenting results
Step 6: Reporting and documentation

The second research question (investigating the family's experiences with children at risk of or diagnosed with FA) will be answered by using grounded theory methodology, which focuses on social processes and actions and interactions. Constructivist grounded theory [29] highlights shared meaning constructed by both participants and researchers. We use the 2 main types of coding of grounded theory: (1) initial coding, a strategy that helps us to conceptualize our ideas and (2) focused coding, which allows us to separate, sort, and synthesize our data. During initial coding, we study our transcripts line-by-line, (inter)action-to-(inter)action, or we adopt the narratives of our participants from time to time as in vivo codes [29]. Memoing on the interpretation and constant comparative analysis within and between interviews are used to confirm similarities and differences and push the analysis forward [29].

Weekly interpretative meetings including all researchers ensure an iterative process of data collection and analysis. Interpretations in groups are a discursive form (communicative validation) to establish intersubjectivity and comprehensibility [46,47]. At present, no respondent validation is planned.

Reportings will be based on COREQ checklist—consolidated criteria for reporting qualitative research [48]—that also guides the structure of this protocol.

Ethics Approval and Data Protection

The ethics approval was obtained for the study from the Ethics Committee of the University Medicine Magdeburg (184/21). Participation in the interviews and focus groups is voluntary. Participants receive information about the aims and contents of the study as well as data protection at the time of initial contact and afterward by email or post. They provide written informed consent prior to participation. All study activities are conducted in strict compliance with the European Union's General Data Protection Regulation and in accordance with the Declaration of Helsinki [49].

We are storing the data from the interviews and focus groups in a pseudonymized way. An independent trusted third party at the Medical Faculty of the Otto von Guericke University of Magdeburg manages data containing personally identifiable information (consent forms) and stores these data separately from the study data.

Results

The project was funded from June 2021. Data collection started in February 2022. Depending on theoretical sampling, data analysis will continue until spring 2023.

Discussion

The qualitative study will provide an in-depth insight into parents' information-seeking behavior and needs regarding the prevention of FAIC, how parents use pediatric primary care, and what strategies HCPs' use for prediction and prevention toward FAIC. The research team anticipates that the results will reveal challenges associated with the paradigm shift in allergy prevention for both parents and HCPs. We hope to be able to derive practical recommendations for the development of the NAMIBIO apps. Only by understanding the users' perspective and the family's experience with children who are at risk or diagnosed with FA, apps can be developed that correspond to the users' everyday needs and accepted by them.

The results will be disseminated through scientific publications, social media (Instagram and Twitter), and at national and international conferences of health services research and allergy.

When we started the recruitment for our study, it was assumed that potential participants might have difficulties understanding the overall goal of the NAMIBIO app consortium. Since there is no direct objective-added value from participating in the study, we expected that it would be easier to recruit informed and engaged people to participate in the study. We assumed that mothers with a high level of education would be more likely to feel addressed in the recruitment process. In addition, we also anticipated difficulties in recruiting HCPs, especially because of both a lack of time and interest.

By now, we were able to recruit a diverse sample of parents and pediatricians in terms of age and personal or occupational experiences, capturing a variety of different perspectives. Our in-depth interviews and focus groups lasted up to 90 minutes. We followed all the steps of the recruitment strategies. Currently, it appears very difficult to recruit parents with a migration history and low level of education, especially fathers.

For this reason, the recruitment process is still ongoing. While we may not be able to overcome these challenges completely, we have launched a social media channel (Instagram: namibioapp) and ensured that we address organizations that have special access to the groups relevant to our study, in

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particular family and childcare institutions. Furthermore, we have adjusted the recruitment material. To gain better access to parents whose child has no known risk of FA, a broader approach focusing on general child health is used. In a preliminary contact, we inform about our study and ask about the risk factors for FAIC. In addition to German, the flyers are now also available in English, Turkish, Arabic, and Russian.

Acknowledgments

The Federal Ministry of Education and Research (01EA2108B/D) funds this study.

Data Availability

The data sets generated and analyzed during this study are available from the corresponding author upon reasonable request.

Conflicts of Interest

CA is a Grant Holder Scientific Representative of the Core Outcome Measures for Food Allergy Action (COMFA, European COST Action 18227).

Multimedia Appendix 1
Topic guide for parents.
[DOCX File , 865 KB - resprot_v12i1e41436_app1.docx]

Multimedia Appendix 2
Case vignette and topic guide: health care professionals and focus group.
[DOCX File , 122 KB - resprot_v12i1e41436_app2.docx]

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Abbreviations

FA: food allergy
FAIC: food allergy in children
HCP: health care professional
NAMIBIO app: Nahrungsmittelallergie biomarker application (food allergy biomarker application)

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Protocol

Perceptions of Global Health Engagements in Relation to the COVID-19 Pandemic Among Health Care Workers and Administrators in Western Kenya: Protocol for a Multistage Qualitative Study

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Abstract

Background: There has been significant interest in global health in low- and middle-income countries (LMICs) among individuals living in high-income countries (HICs) over the past 30 years. Much of the literature on global health engagements (GHEs) has been presented from the perspective of individuals from high-income countries. Local stakeholders such as health care workers and health care administrators represent critical constituencies for global health activities, yet their perspectives are underrepresented in the literature. The purpose of this study is to examine the experiences of local health care workers and administrators with GHEs in Kenya. We will explore the perceived role GHEs play in preparing the health system to address a public health crisis, as well as their role in pandemic recovery and its aftermath.

Objective: The aims of this study are to (1) examine how Kenyan health care workers and administrators interpret experiences with GHEs as having advantaged or hindered them and the local health system to provide care during an acute public health crisis and (2) to explore recommendations to reimagine GHEs in a postpandemic Kenya.

Methods: This study will be conducted at a large teaching and referral hospital in western Kenya with a long history of hosting GHEs in support of its tripartite mission of providing care, training, and research. This qualitative study will be conducted in 3 phases. In phase 1, in-depth interviews will be conducted to capture participants' lived experience in relation to their unique understandings of the pandemic, GHEs, and the local health system. In phase 2, group discussions using nominal group techniques will be conducted to determine potential priority areas to reimagine future GHEs. In phase 3, in-depth interviews will be conducted to explore these priority areas in greater detail to explore recommendations for potential strategies, policies, and other actions that might be used to achieve the priorities determined to be of highest importance.

Results: The study activities commenced in late summer 2022, with findings to be published in 2023. It is anticipated that the findings from this study will provide insight into the role GHEs play in a local health system in Kenya and provide critical stakeholder and partner input from persons hitherto ignored in the design, implementation, and management of GHEs.

Conclusions: This qualitative study will examine the perspectives of GHEs in relation to the COVID-19 pandemic among Kenyan health care workers and health care administrators in western Kenya using a multistage protocol. Using a combination

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of in-depth interviews and nominal group techniques, this study aims to shed light on the roles global health activities are perceived to play in preparing health care professionals and the health system to address an acute public health crisis.

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KEYWORDS

global health; global health engagements; GHEs; health care workers; local perspectives; low- and middle-income countries; LMICs

Introduction

Background

Over the past 30 years, there has been growing interest in global health volunteering and service-learning trips in low- and middle-income countries (LMICs) among individuals living in high-income countries (HICs) [1,2]. This is reflected in a large increase in the number of colleges, universities, and medical schools that offer programs of study and experiences in global health to their students. Across the United States, educational institutions of all sizes have begun offering global health programs to undergraduates and graduate students [3,4]. The desire for global health experiences is also observed among American medical students, 31% of whom reported having a global health experience in medical school in 2015, up from just 15% in 1998 [5].

Global health activities taking place in LMICs vary widely, with short-term clinical services being among the most commonly described in the literature, particularly among medical trainees [6,7]. The terminology used to describe these programs also varies considerably, with "international medical electives," "short-term medical missions," and "short-term experiences in global health" being just a few terms used to describe these activities [8-13]. The term "global health engagements" (GHEs) perhaps describes these activities in more comprehensive and inclusive terms and provides consideration to the fact that interest in global health has not been limited to the boundaries of higher education, or to those with specialized clinical skills. Religious organizations, civic clubs, nongovernmental organizations, corporate groups, and even for-profit volunteer placement companies have offered GHEs for those without specialized skillsets to participate in global health volunteering abroad [14]. As such, opportunities abound for both skilled health professionals and nonskilled lay people to travel to LMICs to participate in global health activities, including medical missions, service-learning projects, and a wide range of volunteer service activities [15,16]. Ranging from a few days to several weeks, GHEs take place in LMICs around the world with varying degrees of coordination with local stakeholders [7,11,14]. A core challenge of GHEs is that traveling volunteers often lack adequate training and preparation to work in the environment, regardless of their educational background or prior training, and are frequently sent into LMIC settings without formal needs assessments having been conducted nor adequate consultation with in-country stakeholders regarding local needs. This implies that many global health interventions may be subjective solutions posed by HIC participants rather than bidirectional efforts to address local needs and priorities [17-20].

GHEs are big business. Fueled by a growing awareness of global issues and participant motivations of "giving back" and "doing good," annual expenditures on GHEs have been estimated to be well in excess of US $3 billion from the United States alone [10]. A significantly increased interest in GHEs in recent years has prompted increased scientific inquiry and academic analysis on the subject. GHEs have been generally portrayed as providing value to the health care systems of LMICs, although objective assessments of these activities are infrequent [11]. A common critique of GHEs focuses on ethical concerns, in that they might allow an opportunity for students and nonskilled volunteers to "practice on the poor" by providing care beyond their skillset [21]. Recently, experienced global health practitioners have sought to bring greater awareness of this and other ethical concerns and have called for the development of guidelines for ethics training, predeparture preparation, and management of participants to improve the otherwise largely unregulated activities in GHEs [4,11,22,23]. Recent critiques of these questionable practices have also brought attention to inequities in global health activities. It has been argued that GHEs perpetuate colonial mindsets and power asymmetries between HIC and LMIC individuals and organizations [24,25]. In recent years, there has been growing awareness to examine these inequities in an effort to "decolonize" global health practices in favor of more equitable practices, including greater decision-making regarding the management of GHEs. Despite increased interest to critically evaluate global health practices through the lens of decoloniality, much of the scientific literature on global health efforts and GHEs has been presented in overwhelmingly positive terms, and largely from the perspective of HIC participants [11,14].

Examples of recent studies focused on HIC individuals participating in GHEs include those examining satisfaction and motivations for participation among volunteers; the impact on long-term career paths for students; and cultural competency skills development [26-29]. In addition to allowing HIC individuals to build their resumes, engagement in GHEs provides participants (particularly medical trainees) the ability to see tropical diseases firsthand or to develop cross-cultural communications skills in an effort to promote themselves as well-rounded and experienced candidates in the job market [4,15]. HIC participation in GHEs has also been shown to influence career choices, leading participants to choose careers in public service [30-32]. Although examining GHEs from the perspective of HIC participants is important, these individuals make up only a small portion of the total number of stakeholders

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involved with global health activities occurring in LMICs. Local stakeholders, such as health care workers and health care administrators, represent a critical component of GHE activities, yet research focused on their perspectives is far less common. A recent literature review revealed only 31 studies reporting local stakeholder perspectives from LMICs, mostly consisting of multicountry surveys from LMICs around the world, although none focused solely on Kenya, despite the regular occurrence of GHEs in this setting. Studies of GHEs have shown that LMICs are often recipients of GHEs due in part to longstanding social, cultural, and political ties between institutions and communities within the host country and the sending country [6,14,15]. Since 1964, Kenya has maintained favorable and consistent diplomatic relations with the United States following its independence from Britain in December 1963 [33]. This long history has no doubt contributed, at least in part, to many Americans' perception of Kenya as a safe and stable country—a factor also known to attract GHEs [14]. Kenya's status as an English-speaking country and a top-notch safari destination are possible considerations that make Kenya an attractive location for some individuals pursuing GHEs, while others may be drawn to global health "hotspots" on the African continent due to (perhaps misguided) perceptions of needs related to poverty or health crises [15]. Whatever the motivations, Americans and other HIC individuals pursuing GHEs have maintained a notable and sustained presence in Kenya in recent decades.

COVID-19 Global Pandemic

The advent of the COVID-19 global pandemic significantly disrupted day-to-day activities around the world, including global health activities in Kenya [34]. This unprecedented shift has impacted local health care workers, health care administrators, and the health systems in which they work. Like in many other countries, health care workers in Kenya have experienced increased stressors, anxiety, insomnia, depression, and burnout [35-37]. Although occupational challenges are being increasingly well documented, far less is known about the potential new understandings health care workers and health care administrators are gaining as they make meaning of their work, the health care system, and the role of global health activities in relation to the COVID-19 pandemic in Kenya. We developed our study protocol to leverage the unique and unprecedented opportunity to explore how health care workers and health care administrators understand their new reality working in an environment where GHEs, which were previously ubiquitous, have greatly declined over a significant period of time. In this study, we will ask participants to reflect on their history with GHEs and consider how prior experience with these activities may have shaped them professionally, and the health system broadly, to provide care in the face of the COVID-19 pandemic. Findings from this study may contribute to the field of global health research by providing a more nuanced understanding of the roles—expected or actual—GHEs play in the professional lives of those working within LMIC health systems, as well as their perceptions of the functioning of the system itself. The paucity of current research on local LMIC stakeholder perceptions of GHEs means that far less is known about how individuals make meaning of these activities in comparison to their HIC colleagues. Understanding the local perspectives of GHEs and global health inequities is of increased importance in the era of the COVID-19 pandemic. Further research to examine GHEs from the local perspective is necessary to paint a more complete picture of how these activities are perceived by those who host and manage global health activities in Kenya, particularly in the context of the pandemic.

Study Aims and Objectives

The purpose of this study is to examine local health care workers' and administrators' experiences with GHEs in Kenya and the role they are perceived to play in preparing individuals and the health system to address the COVID-19 public health crisis and their unfolding role in pandemic recovery and its aftermath. The primary aim of this study is to examine how Kenyan health care workers and administrators interpret experiences with GHEs as having advantaged or hindered them and the local health system to provide care during the COVID-19 pandemic.

Our study protocol is guided by the following research questions: (1) In what ways have GHEs affected health care workers' and administrators' professional lives and their perceptions of the local health system? (2) How have previous experiences hosting GHEs positioned these individuals and the health system to deliver care during the COVID-19 crisis? and (3) What are stakeholder priorities with regard to the design, implementation, and management of GHEs in Kenya in the future?

To achieve the primary aim of our study, one-on-one in-depth interviews will be conducted among health care workers and administrators in the fields of pediatrics, adult medicine, and mental health care. Interviews will explore how participants make meaning of prior experiences of GHEs in relation to their work in a health system under the stress of a public health crisis. Their reflections may reveal new insight into the role GHEs may play in strengthening the capacity of the health care system as well as those who work within it.

A secondary aim of this study is to identify stakeholder priorities and explore recommendations for future GHEs to achieve maximum benefit in the health care system after the COVID-19 pandemic. We will achieve this aim by using a group consultation process, nominal group techniques (NGTs), followed by one-on-one in-depth interviews. NGTs use a highly prescriptive, multistep process that engages each group participant individually and gives equal voice across the group, thereby minimizing opportunities for stronger personalities to dominate conversations and influence group dynamics. NGTs were chosen in lieu of focus group discussions for several reasons. Primarily, NGTs offer a high level of efficiency in achieving group consensus in comparison to focus groups, which can be significantly impacted by group dynamics, dominant personalities, and biases of participants and researchers [38]. Equally important in the selection of NGTs is their proven use in research in health care research, including among individuals working in health care in the African context [39-43]. In our study, NGTs will be used to generate a prioritized list of recommendations among health care workers and administrators, which will be examined further in subsequent in-depth

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interviews. In-depth interviews will identify potential strategies to implement recommendations generated during NGT activities. Together, these methods will result in stakeholder-identified priorities as well as actionable strategies necessary to implement recommended innovations for future GHEs in Kenya.

Methods

Study Design

Qualitative methods are particularly well-suited to understanding disruptive social events, including disasters and crises, to explore meaning-making and the experiences of those living through these events [44]. Using 2 qualitative methods, our study will explore the perceptions of GHEs among individuals and groups from 2 key stakeholder groups who were particularly impacted by the COVID-19 public health crisis: health care workers and health care administrators. Conducted in 3 phases, our study will ask participants to reflect on their experiences working in the health care system prior to and during the COVID-19 pandemic to examine how their understandings of GHEs have shifted. Participants will be asked to consider how the presence of GHEs or lack thereof may have benefited, or disadvantaged, them to provide care during an acute public health crisis. Our research will also explore participants' opinions, views, and perspectives on the essential elements of GHEs that are beneficial, as well as identify the aspects of these activities in which innovations can be made to improve their design, implementation, and management in the future.

Using in-depth interviews, phase 1 of the study will explore perceptions of, and experiences with, GHEs among frontline health care workers (eg, nurses and physicians) and health care administrators (eg, individuals responsible for decision-making and the day-to-day management of health care facilities). The research team will use NGTs in phase 2 to develop a stakeholder-prioritized list of actions and recommendations that can be used in future GHEs in Kenya. Similar to focus groups, NGTs are used to gather input from stakeholder groups regarding a specific topic of interest. Unlike focus groups, which rely on group discussions guided by a facilitator, NGTs use a highly structured protocol where participants are individually asked to generate ideas, discuss them as a group, and rank or score those ideas. This results in building consensus on the discussion topics, which can be used to determine priorities for action to solve problems. This is a useful method to compare the viewpoints and priorities of stakeholder groups. Two NGTs will be conducted in this study, 1 for each of the 2 stakeholder groups (ie, health care workers and health care administrators). Phase 3 will use another set of in-depth interviews to further explore potential recommendations identified in phase 2 regarding the design, implementation, and management of GHEs in pandemic recovery and beyond. The findings will offer insight from the local perspective regarding the role GHEs play in local health systems in Kenya and provide critical stakeholder input on the management of future GHEs.

Study Setting

Participants will be recruited from the flagship hospital of a network of health care facilities, which regularly hosts a wide variety of global health activities, headquartered in the Kenyan city of Eldoret, in Uasin Gishu county [45,46]. The network of health care facilities began with a single facility through a partnership of universities in Kenya and the United States. Established in the early 1990s in response to the HIV/AIDS crisis in Kenya, it now comprises a network of more than 800 care facilities across western Kenya. Today, this system provides primary and specialized health care to more than 8 million people, including more than 150,000 in its flagship HIV/AIDS program, and pursues a tripartite mission of providing health care and training and conducting research in partnership with many universities across North America [47]. For the past 30 years, this health system has had a consistent flow of North American faculty, researchers, clinicians, students, and affiliated personnel to participate in global health service and learning opportunities in the fields of medicine, pharmacy, dentistry, nursing, child health, and myriad other health professions. The constant presence of these HIC individuals over the past 3 decades makes this setting ideal to study local perspectives on GHEs and perceived impact of the COVID-19 pandemic on the health system.

Ethics Approval

The research procedures presented in this study protocol have been approved by the Northern Illinois University Institutional Review Board (HS21-0286) and Moi University's Institutional Review and Ethics Committee (IREC059/2021). Protocols were also reviewed by the study site's research working groups, which are responsible for vetting research conducted at the network's facilities prior to ethics reviews. Protocols have been approved by the behavioral and social science and public health and primary care working groups for primary and secondary review, respectively. A national research permit was also secured from Kenya's National Commission for Science, Technology, and Innovation (NACOSTI/P22/16944).

Study Participants

Health care workers and health care administrators were selected as the 2 primary categories of stakeholders of interest for this study because they offer 2 very important, yet potentially different perspectives, on GHE activities at health care facilities in western Kenya. This cross-sectional approach has been commonly used in health science research in African settings, including Kenya, and was chosen because it creates opportunities for a more comprehensive exploration of a broad range of perspectives than otherwise possible from a singular cadre of stakeholders [48,49]. First, as decision-makers and managers, health care administrators stand to offer viewpoints rooted in leadership and organizational perspectives, particularly in relation to carrying out activities and achieving the health care network's tripartite mission. Their "30,000-foot view" can provide insight into the design and implementation of GHEs as well as the "how and why" decisions are made regarding them. In contrast, health care workers and other frontline staff offer different, much more granular perspectives of GHEs and can provide an up close and personal look at these activities. Frequently working alongside individuals pursuing GHEs, individuals in this stakeholder category have firsthand knowledge of the challenges and opportunities created by these activities and understand how they influence clinical

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environments for both patients and local providers. Collectively, both of these stakeholder groups offer an opportunity to explore perceptions on GHEs in Kenya during the COVID-19 pandemic.

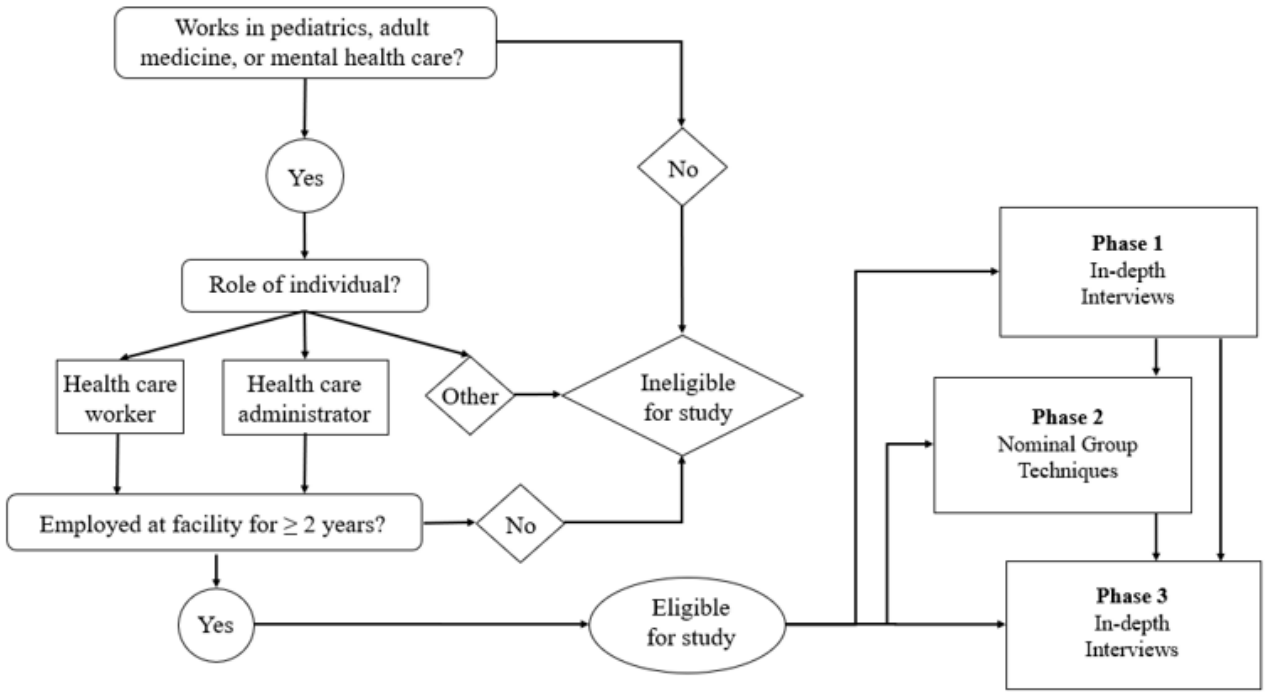
We will recruit participants aged 18 years or older who are proficient in English, have worked at target facilities for a minimum of 2 years, and have either direct interaction with global health activities or have firsthand knowledge of their impact on their clinical facility and wider network's system. Inclusion criteria include being a health care worker (eg, nurse, physician, and other clinical staff) or a health care administrator (eg, "in-charge" staff, facility leadership and management, other administrative staff) working in facilities providing pediatric, adult medicine, or mental health care services. Exclusion criteria include those aged younger than 18 years; those without the ability to speak English; individuals working at the target health facilities for less than 2 years; those without direct experience with, or knowledge of, global health activities in the facility; individuals who do not fall into the 2 stakeholder categories (ie, health care workers and health care administrators); and those working outside of pediatrics, adult medicine, and mental health care services.

Recruitment Procedures

To elicit a range of perspectives, participants will be recruited from among individuals working in the fields of pediatrics, adult medicine, and mental health care. Recruitment flyers will be posted in staff areas of targeted facilities and at selected staff gatherings (eg, staff meetings), where members of the research team will briefly share information on the purpose of the study and provide contact details. Interested parties will be invited to contact members of the research team to arrange eligibility screenings and to discuss study activities. Once eligibility has been established, potential participants can be recruited into 1 or more phases of the study based on the individual's interest and the study's ongoing recruitment needs. Simultaneous recruitment for all 3 study phases is intended to provide greater flexibility, improve efficiencies, and counterbalance potential challenges due to the attrition of participants over the course of study activities. Purposive sampling will be used to achieve a balanced range of perspectives of participants across stakeholder categories as well as gender [50]. As such, male and female participants will be recruited into the study in roughly equal numbers into each of the 2 stakeholder categories (ie, health care administrators and health care workers).

Figure 1 shows the recruitment eligibility decision tree for basic recruitment and eligibility guidelines for study participation.

Figure 1. Recruitment eligibility decision tree.



Informed Consent

All research activities, including the informed consent process, will take place in a private room and informed consent will be obtained prior to eligible individuals' engagement in any study activity. A member of the research team will provide eligible individuals with an overview of the nature of the study including that their participation is voluntary. Potential participants will be provided with all pertinent information including the study's purpose, procedures, risks, and benefits. A member of the research team will explain how confidentiality will be maintained, including the management and storage of data for future use. The individual will be provided with information on their rights as a study participant, including that their participation in the research study is entirely voluntary and that participation can be withdrawn at any point during study activities.

After being given the overview of the study and their rights as a participant, the individual will be given ample opportunity to ask questions and to seek clarification on any points that require

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additional information. The potential participant will then be assessed to determine whether they understand the study. The research team member will assess the individual's understanding of the goals of the study by asking "Can you tell me what this study is about?" The individual will then be asked (1) to name things they will be expected to do during the study; (2) to explain what they would do if they no longer wished to participate in the study; and (3) to identify potential risks and benefits of participating in the study. Respondents will be enrolled only if they are able to provide clear and correct answers to each item.

The individual will then be given a copy of the informed consent document to read in full. After the person is done reading the document, they will be asked if they understand the form and will be given the opportunity to ask clarification questions. After satisfying any remaining questions, the individual will be asked if they would like to participate in the study. The individual will be enrolled in the study by signing, dating, and returning the informed consent document to the research team member. The participant will be given the option to have a copy of the informed consent form to keep for their own records.

Compensation

Eligible Kenyan health care workers and health care administrators will receive compensation for their time. Participants will receive 550 Kenyan shillings (approximately US $5) for each study component (ie, interviews and NGTs) in which they participate. Cash payments will be made at the completion of each interview or group activity.

Data Collection Procedures

Overview

All data collection activities will be administered by a team of trained Kenyan research assistants experienced in qualitative research methods. All one-on-one interviews and NGTs will be audio-recorded and transcribed verbatim. Transcripts will then be verified and deidentified by members of the research team. All study records will be assigned a unique identification number and will be uploaded and stored in password-protected files on a cloud-based encrypted file storage service.

Phase 1

One-on-one in-depth interviews will be conducted to capture participants' lived experience in relation to their unique histories and perspectives regarding GHEs and the local health system. Interviews will be conducted by Kenyan research assistants in order to facilitate an environment conducive to elucidating candid responses from participants. This is of particular importance given that previous research on stakeholder perspectives on GHEs suggests that participants are reluctant to make overly critical statements, particularly among HIC partners, for fear of losing access to resources and opportunities [51,52].

In-depth interviews will be conducted for the 2 stakeholder categories of interest: health care workers (target sample size: n=5) and health care administrators (target sample size: n=5). All in-depth interviews will be conducted in a private setting within the research areas of the study site, which is a teaching and referral hospital. In-depth interviews will be audio-recorded and will last approximately 1 hour. Interviews will conclude when questions or talking points (as outlined in research protocols) have been exhausted. Textbox 1 below outlines sample interview questions. Participants will be queried about their past experiences with GHEs and will be asked to provide their perspectives (beliefs, opinions, and viewpoints) on GHEs in Kenya. Participants will also be asked to reflect on how these activities have professionally shaped them, as well as the health system, to provide care during the COVID-19 pandemic (Textbox 1).

Textbox 1. Phase 1: sample interview questions.

- What have you learned about the Kenyan health system during the COVID-19 pandemic?
  - Probe: Strengths?
  - Probe: Weaknesses?
- In your view, how has the prior history of global health activities shaped the local health system to face events such as the COVID-19 pandemic?
  - Probe: Prepared the health system?
  - Probe: Hindered the health system?
- How has your own prior history with global health activities shaped you professionally to face events such as the COVID-19 pandemic?
  - Probe: Prepared you?
  - Probe: Hindered you?

Phase 2

Group discussions using NGTs will be conducted in phase 2 of the study. NGTs are administered through a structured, multistep process in which participants are asked to (1) generate ideas, (2) share ideas in round-robin format, (3) clarify ideas presented, and (4) rank the ideas presented. This consensus-building research method is used to determine stakeholder priorities for action to solve problems among communities of interest. NGTs are similar to focus group discussions; however, they have unique strengths, namely the ability to equalize groups of participants and minimize opportunities for individual participants from dominating or influencing the group dynamic. Using the round-robin format, NGT facilitators engage each

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participant to speak one by one, creating an equal voice across the group and minimizing opportunities for stronger personalities to dominate the conversation [53]. Additionally, NGTs are noted for their usability and outputs, typically prioritized lists of actions, and can be a useful method to compare viewpoints and priorities of stakeholder groups [39]. NGT methods have also been shown to reduce researcher bias and have been applied frequently in health research, particularly among health care workers—including in sub-Saharan Africa [39-43,54].

A total of 2 NGTs will be conducted, 1 for health care workers (target sample size: n=8) and 1 for health care administrators (target sample size: n=8). Each NGT is anticipated to last between 2 and 3 hours and will be audio-recorded. NGTs will conclude after completing the steps of nominal group activities. The 8 steps outlined below describe the NGT process developed for this study:

1. Explain the process for NGTs: In the first step, facilitators will outlay expectations and answer questions participants may have regarding the process.
2. Silent idea generation: Participants will be asked to recall their past experiences with global health activities prior to the COVID-19 pandemic to reflect on aspects (eg, characteristics, policies, and management) to recall how these activities impacted them and their work, both positively and negatively. Participants will then be presented with the following prompt: "What changes do you feel are necessary for global health activities after the COVID-19 pandemic is over?" and will be asked to silently and independently generate ideas for 5 minutes.
3. Round-robin idea sharing: Participants share their ideas one at a time, 1 participant at a time. Participants may think of new ideas during this phase but can only share them at their designated turn. Ideas are recorded on a flip chart until no new ideas are uncovered.
4. Clarification: A brief discussion of ideas may follow for clarity of purpose for the ideas presented. Participants may ask questions of facilitators and other participants to clarify the ideas presented. Similar or overlapping ideas are grouped together and are discussed until all participants understand each concept presented.
5. Idea ranking: Participants are then asked to consider all the ideas presented and to vote in rank order based on their subjective determinations of importance. Participants are given a piece of paper to anonymously assign scores to the top 5 ideas according to their preferences. Scores will then be tallied by the facilitators and presented to the group for discussion. The number of ideas to be discussed will vary depending on how many ideas were generated in the second and third stages.
6. Discussion: Tallied scores are then presented to the group for a detailed discussion regarding the results. Participants will be invited to share their thoughts on the results. Participants can provide additional context to why certain ideas may have received higher scores and may ask questions of one another for clarification and to foster robust discussion. No new ideas will be introduced or discussed at this stage.
7. Reranking: After discussing results, participants will be asked to anonymously rank the ideas once more based on the discussion of the results from ranking in step 5. Participants will again assign scores to their top 5 ideas according to their preference in light of the recent discussion. Participants may remain consistent with their ranking selections or can change their selections according to changes in their opinions based on the discussion.
8. Sharing of results: Final scores will be tallied and presented to the group. The top-scoring ideas will be used as themes to explore in more detail through one-on-one in-depth interviews in phase 3.

Conventionally, NGTs are drawn to a close after a single round of ranking or voting and scores have been tallied (corresponding to step 5 in this study) [39]. Our study adds additional steps to include participants in a peer-to-peer discussion to further explore potential motivations behind their selections. The additional step for discussion (step 6) was added to this study to allow participants to engage with one another in dialogue similar to that of focus groups to share greater detail regarding their preferences for certain ideas over others. A second round of ranking (step 7) will provide participants with the opportunity to reassess their individual priorities in consultation with their peers. Collectively, these additional steps are intended to gather robust data to provide further insight into the groups' interests in prioritizing key areas of action in relation to GHEs.

Phase 3

One-on-one in-depth interviews will be conducted based on the ranked priorities identified in phase 2. A semistructured interview guide will be used to further explore the priority areas identified in NGTs. These in-depth interviews will serve as a means to closely examine the similarities and differences of ranked priorities between health care workers and health care administrators, as well as to explore the contextual nuances of NGT discussions. Phase 3 participants will be recruited into groups of key informants, health care workers (target sample size: n=5), and health care administrators (target sample size: n=5). All in-depth interviews will be conducted in a private setting, will be audio-recorded, and last approximately 1 hour. Interviews will conclude when questions and talking points have been exhausted. Participants will be asked to share their perspectives on potential innovations identified in phase 2 regarding the implementation and management of global health activities in the future. Data collected in phase 3 will provide insight into recommendations for potential strategies, policies, and other actions that might be used to achieve the priorities ranked with highest importance among the 2 stakeholder groups.

Data Analysis

The analytical plan will be conducted in 2 steps. First, trained qualitative researchers will conduct open coding of transcripts to identify emergent themes. Members of the research team will read all transcripts and develop an initial list of codes independently. In the open coding process, researchers will identify broad categorical themes that emerge among frequently used words and key phrases in the data. The researchers will then compare emergent codes during regular research meetings to eliminate duplicates and collapse overlapping codes.

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Discrepancies in coding decisions will be discussed to determine consensus. Upon reaching a consensus, a codebook will be developed, which will be used to purposefully analyze the data. Qualitative analysis will be conducted by independent coders to explore the nuances of the data to develop themes and examine phenomena of interest to generate new concepts [55]. This approach is ideal for studies, such as this one, exploring under-researched areas of inquiry such as local perspectives on GHEs in Kenya [56]. Researchers will independently code approximately 20% of the transcripts and then compare the independently coded data. Interrater reliability will be established by achieving Cohen κ coefficient ≥80%. All qualitative analyses will be conducted using qualitative analysis software (NVivo; QSR International).

Results

The study activities commenced in late summer 2022, with the recruitment of participants began in August 2022. All 3 phases of this study, including 10 in-depth, one-on-one interviews in phase 1, 2 nominal group activities in phase 2, and 10 in-depth, one-on-one interviews in phase 3 were conducted between September 2022 and February 2023. In each phase, data collection and analysis were conducted concomitantly. The results are expected to be published in 2023.

Discussion

This qualitative study examines the perceptions of GHEs in relation to the COVID-19 pandemic among Kenyan health care workers and health care administrators working at a facility with a long history of hosting global health activities. It is one of the small but growing number of studies that examine the perceptions of GHEs in LMICs from the local host perspective, and this is the first study to our knowledge to do so in relation to the COVID-19 pandemic. The purpose of this study is to examine participants' experiences with GHEs in Kenya and the role they are perceived to play in preparing individuals and the health system to address the COVID-19 crisis and their unfolding role in pandemic recovery and its aftermath.

Data collected in this study will be critical to understanding participants' current and evolving perspectives on GHEs in relation to their work against the backdrop COVID-19 pandemic. Our multiphase study will examine how participants interpret their experiences with GHEs as having advantaged or disadvantaged them and the health system to provide care during a public health crisis, using one-on-one in-depth interviews in phase 1. The second and third phases of the study aim to identify stakeholder priorities and explore recommendations for future GHEs to achieve maximum benefit in the health care system going forward, using NGTs in phase 2, followed by one-on-one in-depth interviews in phase 3, respectively.

Applying a lens of decoloniality to global health research, our study elevates the voices of 2 stakeholder groups that are frequently involved in management and hosting activities associated with GHEs yet are currently underrepresented in global health perceptions literature [11,52]. The findings may reveal areas of strength and potential areas of growth for global health approaches in Kenya and perhaps other LMIC settings. Furthermore, the findings may provide critical data that can inform improved practices to overcome well-documented challenges in global health activities, including issues of equity in global health collaborations as well as sustainability and the effectiveness of programs [20,25].

This study has several strengths and limitations. A key strength of this study is its data collection methodology, which will use highly experienced Kenyan qualitative researchers for data collection to reduce potential bias. Another strength is the inclusion of 2 additional steps in the NGT process. Steps 6 and 7 in phase 2 of this study aim to elicit additional data to garner greater insight into reasoning and decision-making with regard to prioritizing key recommendations to be explored in phase 3. Limitations of this study relate to the contextual aspects of the study setting and its participants, which may limit the generalizability of study findings to other settings. The study site is the flagship hospital of a large, fairly well-resourced network of health facilities, which is not reflective of the wider Kenyan health care system. This could influence the perspectives shared by participants in this study. Likewise, participants will be recruited into 2 broad categories (ie, health care workers and administrators) from among individuals working in disciplines of mental health care, adult medicine, and pediatrics—it is unclear how individuals' professional views or occupational environments might influence the data. Therefore, the findings from this study may be specific to the local reality and may not be generalizable to other contexts elsewhere in Kenya, sub-Saharan Africa, or other LMICs.

In summary, this exploratory qualitative study will engage 2 key groups of Kenyan stakeholders to gain insight into the role GHEs are perceived to have played in preparing the health care system, and those who work within it, to provide care in an acute public health crisis. Informed by calls to decolonize global health, this study will provide valuable stakeholder-identified priorities and insight into improved practices for the management and accountability of GHEs going forward. The implications of which may provide greater clarity regarding the expected roles and intended purpose of GHEs in Kenya among those who are frequently involved in hosting these activities. A better understanding the role that GHEs play in the professional lives of LMIC stakeholders may shed light on the challenges inherent in hosting GHEs, ultimately informing the development of models for more equitable engagement of LMIC partners.

Acknowledgments

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Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during this study.

Authors' Contributions

EA conceived the idea for the study as well as the research design and methods with necessary input from VN, SB, and BH. EA, SB, and BH obtained funding to execute and publish the research. EA is responsible for study coordination and subsequently overseeing data analysis. EA wrote the article with input from SB, BH, and VN. All authors reviewed the article for relevant content. All authors have read and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

GHE: global health engagement
HIC: high-income country
LMIC: low- and middle-income country
NGT: nominal group technique

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Protocol

Effects and Limitations of a Unique, Nationwide, Self-Exclusion Service for Gambling Disorder and Its Self-Perceived Effects and Harms in Gamblers: Protocol for a Qualitative Interview Study

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Abstract

Background: Voluntary self-exclusion from gambling is a common but underdeveloped harm reduction tool in the management of gambling problems or gambling disorders. Large-scale, multi-operator, and operator-independent self-exclusion services are needed. A recent nationwide multi-operator self-exclusion service in Sweden (Spelpaus), involving both land- and web-based gambling sites, is promising, but recent data have revealed limitations to this system and possibilities to breach one's self-exclusion through overseas web-based gambling. More knowledge is needed about the benefits and challenges of such an extensive self-exclusion service, and its effects as perceived by gamblers.

Objective: This study protocol describes the rationale and design of a qualitative interview study addressing the effects and limitations perceived by individuals with gambling problems and their concerned significant others. The study aims to provide an in-depth experience of this novel self-exclusion service and to inform stakeholders and policymakers in order to further improve harm reduction tools against gambling problems.

Methods: Individuals with gambling problems will be recruited primarily through social media and also from a treatment unit, if needed, for a qualitative interview study. Recorded interview material will be analyzed through content analysis, and recruitment will continue until saturation in the material is reached. This study will provide in-depth information about a harm reduction tool that is promising and commonly used, but which has proven to be breached by a significant number of users, potentially limiting its efficiency. The aim is to interview a sufficient number of gamblers until saturation has been obtained in the interview material. Saturation will be considered through a continuous analysis, comparing recently collected data to previously collected data.

Results: Results will be reported as the themes and subthemes identified after the thorough analysis and coding of the transcribed text material and will be accompanied by citations representing relevant themes and subthemes. Results are planned to be provided before the end of 2023.

Conclusions: This study will likely provide new insights into user perspectives on a multi-operator self-exclusion service that involves both web- and land-based gambling operators, and which according to previous literature attracts many gamblers but also appears to have limitations and challenges in the target group of individuals with gambling problems. Policy and legislation implications, as well as clinical implications for treatment providers, will be discussed. Results and conclusions will be disseminated to policy makers in Sweden and internationally, as well as to peer organizations, treatment providers, and the research community.

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KEYWORDS

gambling disorder; problem gambling; behavioral addiction; self-exclusion; Spelpaus; gambling; management; data; online gambling; harm; harm reduction tool; recruitment; qualitative interview study; gambler

Introduction

Gambling disorder (GD) is an addictive condition known to cause overindebtedness, mental health consequences, and psychosocial problems in affected individuals and their concerned significant others. GD is the first addictive condition not involving a substance, and it is defined both in the diagnostic manual of the American Psychiatric Association, the DSM-5 (the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition) [1], and in the International Classification of Diseases (ICD) manual of the World Health Organization [2]. GD typically involves problematic gambling on either chance-based gambling modalities such as land- or web-based casinos, bingo or lotteries, sports or horse race betting, and poker or other card gambling. Severe consequences for family relationships are common [3], and psychiatric comorbidity is very common in individuals suffering from GD [4]. Likewise, GD is associated with overindebtedness [5] and with an increased risk of suicidal behavior including completed suicide [6,7]. GD can be treated using a psychotherapeutic approach, typically involving cognitive behavioral therapy, or through brief or more extensive motivational interventions or normative feedback interventions. Furthermore, pharmacological treatment strategies are applied, most commonly involving opioid antagonists. In addition, psychiatric comorbidities are fundamental to identify and treat [3]. However, treatment-seeking is typically low, and many patients with GD experience barriers against seeking treatment [8].

Voluntary self-exclusion from gambling venues or from web-based gambling sites is one preventive or harm-reducing strategy often applied. The concept behind this is the desire of individuals with gambling problems to control or discontinue their gambling behavior, that is, the voluntary choice to apply external control on gambling, in individuals who perceive a lack of control in their own behavior. Voluntary self-exclusion from gambling can be chosen by individuals regardless of whether they seek treatment or not. In addition, although people who choose self-exclusion typically may experience a gambling problem that they wish to control, self-exclusion may theoretically also be chosen by individuals without gambling problems. Previous data have revealed that individuals who choose to self-exclude have—in most but not all cases—gambling problems [9]. Thus, it is theoretically possible, although hitherto poorly demonstrated, that individuals without any gambling problems may wish to prevent themselves from developing potential gambling problems.

In many cases, self-exclusion services involve only one or a few land-based gambling venues or involve one or a few web pages of web-based gambling operators. Thus, a typical scenario is that a person with a GD chooses to self-exclude from that individual's most common gambling sites or as many sites as possible but may relapse into gambling on other gambling sites. One part of this challenge is the fact that self-exclusion services are often operator-based and therefore involve only the gambling services of a specific gambling operator. Thus, breaching one's own voluntary self-exclusion historically has been a challenge strongly limiting the efficacy of this harm reduction tool [10-13]. The highly diverse designs of such programs across countries and settings have been pointed out as a major limitation of this type of harm-reducing intervention [14]. In recent years, more transparent self-exclusion programs, easier to access, have been called for [15].

Based on these limitations, a new type of self-exclusion service, the Spelpaus service (literally "gambling break") was introduced in Sweden in 2019, as part of the introduction of a new gambling market. The new gambling legislation allowed for a large number of gambling operators, previously often operating over the internet from overseas settings, to obtain a license to operate in Sweden, provided they adhere to this national self-exclusion system and other responsible gambling practices [16]. Spelpaus is a unique self-exclusion service, as it (1) is nationwide; (2) involves all licensed gambling operators, both web- and land-based (currently around 80 different operators are licensed to operate in Sweden); and (3) is independent of the operators themselves, administered by a governmental institution and therefore possible to access without any contact with gambling operators.

The actual effects of the Spelpaus service have not been assessed in research. However, it has been documented that Spelpaus attracts a large number of people; around 95,000 people on a given day are reported to be self-excluded from gambling through this system [17]. Thereby, the number of people self-excluded through this service clearly surpasses the number of people believed to experience a GD at a given time (which may, despite discrepancies between methods of measure, reach a number in the order of 30,000) [18]. Thus, this service appears to attract many people [19,20], both in the general population and among people attending a GD treatment unit [21].

However, one experience of Spelpaus is the emerging data indicating that despite the multi-operator, nationwide nature of this service, breaching the self-exclusion appears to be common in individuals with a GD. This type of breaching typically involves access to overseas, unlicensed web-based gambling operators [21]. In one web-based survey study, 38 percent of self-excluded individuals reported that they had continued to gamble during the self-exclusion period, and web-based casinos were the most common gambling type reported by individuals who relapsed in that context [22]. Furthermore, in patients with a GD, gambling under another person's identity has been reported as a different way of breaching one's self-exclusion [21].

Thus, Spelpaus appears to be a potentially effective harm reduction tool in order to prevent gambling in patients with GD

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or in people at risk of such problems, but major challenges regarding gambling outside of the jurisdiction appear to potentially limit the value of this service. However, given the popularity of this service, and the need to optimize harm-reducing interventions against GD, there is reason to study the effects and limitations of the self-exclusion service further. Hitherto, the experience of this new, unique self-exclusion tool is primarily based on quantitative research [19-22], whereas qualitative research may provide deeper knowledge about the lived experience of Spelpaus self-exclusion in individuals affected. Furthermore, the experience of concerned significant others has been little understood so far, and there is reason to suspect that the relationship of gamblers with their concerned significant others may change if they self-exclude in order to discontinue a problematic gambling pattern. Theoretically, the negative experience of concerned significant others from the gambling of their loved ones may be partly relieved if an external barrier can prevent the gambler from gambling further. In line with this, previous research has demonstrated that the choice of a person to self-exclude often involves the communication of this decision to the person's loved ones, or sometimes is even part of measures required by the family [9].

The study aims to describe the experience of the Spelpaus service in gamblers, in order to deepen the understanding of the utility and challenges of this harm reduction tool. The study will use a semistructured interview design, in order to obtain a deeper knowledge than can be achieved in quantitative survey studies.

Methods

Study Procedure

This is a semistructured, qualitative interview study including individuals who gamble and who have an experience of Spelpaus self-exclusion. Interviews will be carried out primarily over the internet (or in exceptional cases face-to-face). Interviews will be recorded and transcribed verbatim, and the text will be analyzed using a content analysis on a descriptive level [23]. Interviews will be carried out by the second author of this paper, who has extensive clinical experience in psychiatric nursing and experience in qualitative research interviewing. The interview structure has been tested, and thereafter adapted (Textbox 1), in a pilot interview conducted with a respondent with a history of gambling problems and involved in peer support of patients with GD.

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Textbox 1. Semistructured interview guide. The interview guide is meant to guide the qualitative interview, and therefore, the conversation is likely to move away slightly from the exact wording of the questions, based on the responses and associations made by the interviewee. Closed-ended questions will be asked as if they introduce a potential topic into the interview, and will not be handled, in the interview situation, as dichotomous quantitative study items.

General introduction to one another, introduction to the topic of the research, etc.

- How old are you?
- Your gender (male, female, or other)?
- Your marital status (married, cohabitating, partner, or unmarried living alone)?
- What is your occupation?
- Which gambling types has/have been problematic for you? On how many gambling operators?
- Have you ever been in treatment for gambling problems? Which type of treatment?
- Have you ever had any problems related to the misuse of alcohol or drugs?
- Have you ever been in treatment (therapy or medication) for any kind of poor mental health?
- Tell me a little bit about your gambling problem. Why did you start gambling, and for how long have you had a problem? Which types of gambling have been involved, and on how many operators? Have you ever sought treatment, now or before? What type?
- How has your gamble influenced your concerned significant others (CSOs)?
- Tell me about your choice to self-exclude through Spelpaus? Which factors led to that?
- Did any of your CSOs have any influence on your decision to self-exclude?
- Do you have previous experience of other self-exclusion from gambling, before Spelpaus existed?
- How many times have you self-excluded, and for how long periods? Why did you choose those periods of time? Are you self-excluded right now, and for what duration?
- Tell me about your experience of Spelpaus. What has it meant to you, and to your CSOs? Do you believe it changed something for you? Did it reduce the inflow of gambling advertising, and how did that affect you? Which factors of Spelpaus have been favorable, and unfavorable, respectively?
- If you have received treatment for gambling problems, how has the Spelpaus self-exclusion affected that?
- Has your relationship with other people changed after your self-exclusion? How?
- Have you gambled during the Spelpaus self-exclusion? If no, which factors prevented you from that?
- After how long time of self-exclusion did you relapse into gambling? In what gambling types? Which were the factors in life that led to this gambling or which made it more difficult? In what way?
- Were you able to tell people that you had relapsed into gambling? How did that affect your relationship with these people?
- What's your general impression of Spelpaus? What works and what does not? What could be improved in this system?
- Is there anything you feel we have forgotten to ask, and that you would like to add when it comes to your own and your CSO's impressions of Spelpaus?

The analysis will be a content analysis, more specifically involving a text analysis of transcribed text, in order to interpret and provide an understanding of the narrative of the study participants. The analysis will be conducted according to the following sequence: (1) repeated reading of the entire transcribed text material, (2) coding of meaning units, (3) categorization of identified themes and subthemes, (4) provision of citations describing the categories, (5) calculation of the number of times a theme appears in the transcribed material, (6) comparison of interviews and identification of differences and similarities between them, and (7) the search for explanations to such differences. Analyses will be carried out by the second and third authors of this paper. The analytic procedure and discussions within the study group will aim to optimize trustworthiness in the analyses [24].

Study Questions

What is the lived experience of users who have been self-excluded through the Spelpaus service? Which have been the major advantages and the major disadvantages of self-exclusion in gamblers, and in which way has this been affected by the possibility of breaching one's self-exclusion through gambling on overseas gambling sites? Which potential improvements can be made to the Spelpaus self-exclusion service, according to users? What is the lived experience of gamblers who have self-excluded at Spelpaus, regarding how this has changed their relationship with their concerned significant others?

Study Participants

Study participants will be recruited through purposeful sampling. Individuals will be recruited because they are either (1) individuals recruited from social media advertising and who

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have a gambling problem and experience of the Spelpaus self-exclusion service or (2) patients with a GD at the Gambling Disorder Unit of Region Skåne and who have experience of the Spelpaus self-exclusion service. Participants will primarily be recruited through social media recruitment. In case of a slow recruitment procedure, patients at the treatment unit will also be addressed with a question about their interest in taking part in the study. Participants receive a smaller economic compensation, in the format of cinema ticket gift cards. The study aims to recruit a sufficient number of gamblers for saturation to be obtained in the data material. This will include the aim to include participants with a wide variety of experiences concerning the Spelpaus service, including different reasons for self-excluding, and involving both women and men.

Saturation will be considered through a continuous analytic procedure, where collected data material is compared to previously collected data. Thus, no exact number of expected interviews can be decided and reported beforehand, and given the continuous process of assessing saturation, this may require the research group to add additional participants during ongoing analysis. However, based on our experience from previous studies, and based on the intention to assess potentially diverse experience and potentially experience in women and men, it has been reported in the ethics application that the final number of included clients may reach 20. Thus, despite this uncertainty, we expect the final number of participants to be in the range of 12-20.

Setting

The outpatient Gambling Disorder Unit in Region Skåne, Sweden, from which a minority of participants may be recruited, is one of very few units treating GD in a health care setting in Sweden, and has been described previously [21,25]. The unit is part of the Region Skåne Competence Center Addiction, which is a research and development unit closely related to an addiction medicine research group. This treatment unit welcomes patients aged 18 years and older, who experience gambling problems (typically diagnosed with GD [25]) and who live in the Skåne county, a region with a population of 1.4 million inhabitants. The facility is located in the city of Malmö, which is the most urban center of the region.

Ethical Considerations

The study has been approved by the Swedish Ethical Review Authority (overall project approved, file number 2022/06933-01, and amendment number 2023/01684-02 regarding change of interview guide and social media route of recruitment).

Study Preregistration

The study has been preregistered at ClinicalTrials.gov (NCT05693155).

Results

Results from this study are scheduled to be presented before the end of 2023. Findings will be reported as themes and subthemes, which will be identified after transcribing and coding the text material. Results will be accompanied by citations which will be selected to represent relevant themes and subthemes.

Discussion

Principal Findings

This study will be the first to examine, in a qualitative in-depth research design, the experiences of the present self-exclusion system, which is novel and relatively unique in international comparison. Given the novelty of the service, the study may have the potential to guide improvements in this self-exclusion service and the regulations around it.

Findings from this study will be disseminated both within the research community and to peer organizations addressing individuals with GD and their concerned significant others. In addition, findings will be discussed formally and informally with policymakers in government settings, public authorities, and with treatment providers and organizations involved in the prevention and early detection of addictive disorders. Furthermore, findings from this qualitative study are likely to inspire upcoming quantitative studies that can quantify and follow, over time, key aspects of gambling self-exclusion identified through this research.

Strengths

The possibility to address more detailed aspects of different reasons for self-excluding, other than what can be obtained through closed-ended quantitative study items, is one advantage of the qualitative study design. Another strength of this study is that it is the first to assess the present type of nationwide, multi-operator system which involves both land-based, traditional gambling types, and web-based gambling sites. In addition, it is conducted in a situation where web-based gambling, either within or without the jurisdiction in which the system is introduced, is likely a larger challenge than ever. Therefore, this study has the potential to add updated information about a novel type of system that meets challenges that have been less significant in older similar systems.

Limitations

Limitations of the study may be related to the recruitment procedure. As it is hitherto largely unknown which features may characterize individuals who self-exclude from the present type of self-exclusion service, other than people with manifest gambling problems, it is a challenge to reach the full variety of reasons for self-excluding or types of self-exclusion–related experiences. Therefore, wide social media recruitment has been chosen, although patients with a known GD at a treatment facility may also be added, in case of a slow recruitment procedure through the open social media channel. Thus, given the lack of knowledge so far, we have chosen a wide recruitment method but still, the inclusion of participants may potentially be biased by features of social media users and users who are specifically attracted by this type of study advertising. These aspects will be of importance to discuss in the analyses and the results reported in upcoming publications.

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Acknowledgments

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Data Availability

The data sets generated or analyzed during this study are not publicly available due to requirements of confidentiality in line with the present ethics permission and can be made available from the corresponding author on reasonable request, in an aggregated nonidentified form, and after review by the ethics authority.

Conflicts of Interest

AH declares funding for other projects from the state-owned gambling operator of Sweden, as well as from its research council and from the research council of the Swedish alcohol monopoly. None of these organizations had any role in - or influence on - the present project.

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Abbreviations

DSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
GD: gambling disorder
ICD: International Classification of Diseases

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Protocol

The Provision of Texture-Modified Foods in Long-term Care Facilities by Health Professionals: Protocol for a Scoping Review

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Abstract

Background: Malnutrition among older adults with dysphagia is common. Texture-modified foods (TMFs) are an essential part of dysphagia management. In long-term care (LTC) facilities, health professionals have implemented TMFs, but their application has not been fully elucidated, making them heterogeneous.

Objective: We aim to explore the implementation of TMFs in LTC facilities, particularly focusing on the role of health professionals in nutritional care involving TMFs (eg, deciding the type of food, preparing and giving the food, and evaluating the outcomes).

Methods: A scoping review using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) methodological approach will be performed. A comprehensive search for published literature will be systematically performed in PubMed, CINAHL, MEDLINE, ProQuest, PsycINFO, and Science Citation Index (Web of Science). Data screening and extraction will be performed by 2 reviewers independently. The studies included will be synthesized, summarized, and reported, following the preferred reporting items of the Mixed Methods Appraisal Tool. Our review will consider the following study designs: mixed methods, quantitative, and qualitative. Studies with patients who are not older adults will be excluded.

Results: Data extraction will be completed by February 2023. Data presentation and analyses will be completed by April 2023, and the final outcomes will be completed by June 2023. The study findings will be published in a peer-reviewed journal.

Conclusions: Our scoping review will consider studies related to TMF interventions for older adults in LTC residential facilities, with no exclusion restrictions based on country, gender, or comorbidities. Studies on interventions that address TMF-related issues, such as deciding the type of food, preparing and giving the food, and evaluating the outcomes, are qualified for inclusion.

Trial Registration: OSF Registries 79AFZ; https://osf.io/79afz

International Registered Report Identifier (IRRID): PRR1-10.2196/44201

(JMIR Res Protoc 2023;12:e44201) doi:10.2196/44201

KEYWORDS

aged; diet; dysphagia; health professional; texture-modified foods; residential care

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Introduction

Background

Malnutrition is prevalent among the older adult population. The prevalence of malnutrition among older adults has been reported to be between 1.3% to 47.8% in the community [1], but in long-term care (LTC) facilities, the prevalence of malnutrition is much higher, ranging from 30% to 60%, and malnutrition has a significant negative impact on the health of older adults [2-4]. Malnutrition in older adults is often associated with dysphagia [5]. The prevalence of dysphagia among older adults ranges from 12% to 60% [6-8]. Texture-modified foods (TMFs) are commonly prescribed for older adults to address the problem of dysphagia [9,10].

Although standardized terminology and international terminology for TMF have been established [11-13], the implementation of TMF is still reported as a public health concern and has resulted in adverse events [14-16]. The implementation of TMF in LTC facilities is related to many factors, including health professionals' knowledge, health facility financing, infrequent dysphagia screening, and the misunderstanding of TMF calories. To understand the gap in TMF implementation, the exploration of TMF implementation by health professionals needs to be reviewed to understand future directions.

Previous studies have reported on the implementation of TMF in LTC facilities [17-19]. However, relatively little research that explores complete information on TMF implementation by health professionals in LTC facilities has been conducted [20]. TMF implementation, the frequency of giving TMFs, target patients, the types of TMFs used, and the implementers of TMF in LTC facilities need to be explored to improve TMF implementation and identify research gaps in TMF implementation within LTC facilities.

An international framework for the implementation of TMF has been developed [13,21]. However, there is no existing literature review on TMF implementation in LTC facilities [22]. There are no clear rules regarding the implementation of TMF in LTC facilities, how to implement TMF, and who should implement TMF. We conducted a preliminary search of PubMed, and no current or underway scoping reviews and systematic reviews on the topic were identified.

The objective of our scoping review is to explore the implementation of TMF in LTC facilities, particularly focusing on the role of health professionals in nutritional care involving TMF.

Review Questions

Our scoping review will address the following research question, mainly focusing on the role of health professionals in nutritional care involving TMF (eg, deciding the type of food, preparing and giving the food, and evaluating the outcomes): how is the implementation of TMF in LTC facilities?

Participants

Our scoping review will consider studies describing the implementation of TMF in LTC residential facilities. Older adults will be defined in our study as those aged ≥60 years [23]. No exclusions will be made based on country, gender, or a specific medical condition.

Intervention

Health professionals have implemented TMF in LTC facilities. Health professionals undertake remunerated work for which formal education is required (eg, nurses, dietitians, physicians, speech therapists, and paramedical workers). They are classified based on the International Standard Classification of Occupation [24,25]. Studies will be excluded if the roles of health professionals in the provision of TMF are not clearly defined. We aim to explore the implementation of TMF in LTC facilities, mainly focusing on the role of health professionals in nutritional care involving TMF (eg, deciding the type of food, preparing and giving the food, and evaluating the outcomes).

Concept

The concept of interest is any implementation of TMF. TMFs and thickened drinks are commonly used to reduce choking risks and aspiration [26]. Studies on the implementation of TMF will be considered eligible if they explain who implemented TMFs in LTC facilities; how to implement TMF; and at least one of the following: how to decide the type of TMF, how to prepare and give TMFs, how to improve nutritional support in geriatrics through TMFs, how to evaluate the implementation of TMFs, or how to address any other TMF-related issues. Our study will include older adult–reported outcomes and health professional–reported outcomes described by the authors. Studies will be eligible if they include at least one TMF-related implementation.

Context

We will select studies set in LTC facilities. LTC facilities are designed institutions that provide formal (paid) accommodation and include health or social LTC facilities [27]. Studies will be included if their contexts suit this LTC facility description. Studies will be included regardless of the registration, orientation, type, or scope of the LTC facilities or the qualifications of health care professionals. Studies will be excluded if patients were cared for without health care professionals working in LTC facilities. Studies will also be excluded if institutionalized care was conducted as home care. Studies conducted in diverse facilities will be included if findings from LTC facilities can be identified [28].

Types of Sources

Mixed methods, quantitative, and qualitative study designs are eligible for inclusion in our review. We will include studies published from database inception to the date of the search. Documents will be considered eligible only if the full text is available. Only articles available in English, Japanese, and Bahasa Indonesia will be considered for inclusion due to limited resources that do not allow for the screening and translation of studies in other languages. The search process will include a filter for participants aged ≥60 years.

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Methods

Overview

The final scoping review will be reported based on the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) [29]. A preliminary search was carried out on Google Scholar on September 3, 2022, using keywords (*texture modified food*, *health professional*, and *long term care*). There is no existing review that addresses a similar aim as that of our review. Our scoping review is registered in Open Science Framework (registration number: 79AFZ).

Search Strategy

The comprehensive search of bibliographic databases will use PubMed, CINAHL, MEDLINE, ProQuest, PsycINFO, and Science Citation Index (Web of Science). Our search strategies will use the following process [30,31]. First, the scoping review protocol constructs will be identified with an initial logic grid that aligns with the participants, intervention, concept, and context of interest. Second, a pilot search of 2 databases—PubMed and Web of Science—will be conducted. An author will analyze the titles and abstracts of retrieved papers and then confirm the index terms used to describe the articles. Third, the initial logic grid will be reorganized, using all identified keywords and index terms for all included databases (Textbox 1). Fourth, the databases will be screened in the last search for potentially relevant records that were missed in the previous search. The full texts of retrieved review articles will also be reviewed to identify additional potentially relevant documents. An example of the search strategy is presented in Table 1. The pilot search was completed between August and September 2022.

Textbox 1. List of search terms.

Search terms related to participants

- *Older adults, Elderly, Aged, and Senior*

Search terms related to intervention

- *Health professionals; Personnel, Health; Health Care Providers; Health Care Provider; Provider, Health Care; Healthcare Providers; Healthcare Provider; Provider, Healthcare; Healthcare Workers; Healthcare Worker; Health Care Professionals; Health Care Professional; and Professional, Health Care*

Search terms related the concept

- *Texture modified foods, Texture modified, Texture food, and Texture modified diet*

Search terms related to the context

- *Long-term care, Care residential facilities, Residential care, Residential facilities, Residential care institutions, Nursing homes, Elderly homes, Care homes, Assisted living facilities, and Skilled nursing facilities*

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Table 1. Example of the search strategy for PubMed (date of search: September 2022).

Search query number	Query	Records retrieved, n
1	*((((older adults)) OR (elderly)) OR (Aged)) OR (Senior)*	5,963,158
2	*(((((((((Long$term care) OR (Care residential facilit*)) OR (Residential care)) OR (Residential facilit*)) OR (Residential care institution*)) OR (Nursing home*)) OR (Elderly home*)) OR (Care home*)) OR (Assisted living facilit*)) OR (Skilled nursing facilit*)*	464,315
3	*(((Texture$food*) OR (Texture$diet)) OR (Texture$modified)) OR (Texture modified food*)*	12,282
4	Query 1 *OR* query 2	6,178,105
5	Query 4 *AND* query 3	1145
6	*(((((“Health professional*”) OR (“Health personnel”)) OR (“Health$Care Provider*”)) OR (“Health Care Professional*”)) OR (“Healthcare Worker*”)) OR (“Health Care Professional”)*	315,421
7	Query 5 with the following filters: English, Indonesian, and Japanese	1064
8	*((((((older adults)) OR (elderly)) OR (Aged)) OR (Senior)) OR ((((((((((Long$term care) OR (Care residential facilit*)) OR (Residential care)) OR (Residential facilit*)) OR (Residential care institution*)) OR (Nursing home*)) OR (Elderly home*)) OR (Care home*)) OR (Assisted living facilit*)) OR (Skilled nursing facilit*))) AND ((((Texture$food*) OR (Texture$diet)) OR (Texture$modified)) OR (Texture modified food*))* (filters: English; participants aged ≥65 years, ≥80 years, and >80 years; and middle-aged participants [ie, 45-64 years])	783
9	*((((((older adults)) OR (elderly)) OR (Aged)) OR (Senior)) OR ((((((((((Long$term care) OR (Care residential facilit*)) OR (Residential care)) OR (Residential facilit*)) OR (Residential care institution*)) OR (Nursing home*)) OR (Elderly home*)) OR (Care home*)) OR (Assisted living facilit*)) OR (Skilled nursing facilit*))) AND ((((Texture$food*) OR (Texture$diet)) OR (Texture$modified)) OR (Texture modified food*))*	1173

Study Selection

Reference management software (Mendeley [Elsevier]) will be used to manage the retrieved sources and identify duplicate references. The full-text version of an article will be reviewed if the article's eligibility is unclear based on the abstract. Two independent reviewers will screen the full texts of selected studies based on the inclusion criteria. The exclusion of references will be recorded and reported in the scoping review. Any disagreements between reviewers will be resolved through discussion or with the help of a third reviewer.

Data Extraction

The extraction of qualitative data will be carried out in 2 stages. First, the reviewers will read the studies and identify different opinions in the paper, such as original statements from the study participants (ie, first-order constructs) and their interpretations by the researchers or authors (ie, second-order constructs) [32]. Second, the reviewers will reread the studies to extract all raw data. The Excel (Microsoft Corporation) database program will extract the papers included in the review process (Multimedia Appendix 1). The Excel data will include information about the characteristics of the publications, residential facilities, older adults, and health professionals; the implementation of TMF; and the assessment of TMF implementation. The data extraction form will be modified if needed and detailed in the full scoping review. Further, 2 researchers will independently extract the data, 2 researchers will confirm the consistency of the extraction, and 1 reviewer and 1 verifier will review all papers. Any disagreements among reviewers will be resolved through discussion. If a paper has missing data or needs additional data, we will contact the authors of the paper. Such papers will be omitted or described as papers that are missing data if the papers' authors do not respond in 14 days.

Data Presentation

A thematic analysis approach will be used to synthesize the data. The data synthesis will consist of the following three stages: (1) synthesizing, (2) summarizing, and (3) reporting the papers reviewed. The stages will follow the preferred reporting items of the Mixed Methods Appraisal Tool [33,34]. A synthesis of analytical themes will be performed. Appropriate information will be reported for our conclusions, including study types, aims, characteristics, types of providers, types of recipients, and information on the implementation of TMF. The study will provide descriptive data (eg, number of studies included, types of study designs, and characteristics of study populations). The implications of the study for future research priorities will be defined.

Results

Data extraction will be completed by February 2023. Data presentation and analyses will be completed by April 2023, and the outcomes will be completed by June 2023. The main results of our investigation will be presented in a narrative form, focusing on research results to date regarding TMF implementation by health professionals. Additional data on publication years, countries, study designs, populations, and settings will be presented in diagrams or in tabular format.

Discussion

Anticipated Findings

The results from our scoping review will explore the implementation of TMF in LTC facilities, particularly focusing on the role of health professionals in nutritional care involving TMF (eg, deciding the type of food, preparing and giving the

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food, and evaluating the outcomes). Health professionals play a vital role in TMF-related intervention and decision-making within LTC facilities. To our best knowledge, our study will be the first review of the implementation of TMF in LTC facilities, and it will mainly focus on the role of health professionals in nutritional care involving TMF.

We propose that the results of our study will support the development of existing feeding policies in LTC facilities, especially by identifying current knowledge on the role of health professionals in TMF implementation. Several literature reviews have been performed regarding TMF [22,35,36], including a recent review that focused specifically on the unique challenges in LTC.

The implementation of TMF is tightly related to the quality of care in LTC facilities. Older adults' safety while eating is an essential part of standard safety care in LTC facilities [37]. However, choking incidents in LTC facilities still have low levels of attention, although they may be recognized and understood by health professionals [38]. TMF is provided clinically to reduce choking risk among older adults [13,22,39]. This knowledge may help to improve the design and implementation of future TMFs in LTC facilities, so that their benefits become clear and valuable to older adults.

A limitation of our study might be the concepts of LTC facilities among countries and papers. The country-specific terminology about LTC facilities that has been used relates to goals, providers, activities, and target groups [27,40,41]. Comparing types of LTC facilities is beyond the aim of our study. Therefore, our scoping review will define *LTC facilities* as designed institutions that provide formal accommodation and health or social LTC services for older people.

Conclusion

To our knowledge, our review will be the first systematic scoping review to provide knowledge about the implementation of TMF in LTC facilities, particularly focusing on the role of health professionals in nutritional care involving TMF. Our study will address the evidence-practice gap regarding nutritional sustenance in LTC facilities. The policy makers, decision makers, and health professionals in LTC facilities have insight on TMF implementation. This knowledge may help to improve the design and implementation of future TMFs in LTC facilities. The review will also seek to identify further research gaps and the possible need for further study on TMF.

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Data Availability

All data that have been generated or analyzed during the study are included in this published research protocol (and its supplementary information files). The main outcome analyses are being conducted at the time of publication of this protocol, but specific data sets might be available from the corresponding author upon reasonable request.

Authors' Contributions

DWS and GEA wrote the manuscript and designed figures. RI, FF, MT, and ER contributed to drafting the protocol and were responsible for the conception of the study. All authors read the paper, provided feedback, and approved the paper for submission.

Conflicts of Interest

None declared.

Multimedia Appendix 1
The proposed data extraction form.
[DOCX File , 14 KB - resprot_v12i1e44201_app1.docx]

Multimedia Appendix 2
Peer-review reports in Indonesian and English from the Kementerian Pendidikan, Kebudayaan, Riset, Dan Teknologi - Universitas Airlangga - Lembaga Penelitian Dan Pengabdian Masyarakat / Institute for Research and Community Service (Surabaya, Indonesia).
[PDF File (Adobe PDF File), 556 KB - resprot_v12i1e44201_app2.pdf]

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Abbreviations

LTC: long-term care
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews
TMF: texture-modified food

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Protocol

Mapping the Evidence for Opioid-Mediated Changes in Malignancy and Chemotherapeutic Efficacy: Protocol for a Scoping Review

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Abstract

Background: Numerous reports contend opioids can augment or inhibit malignancy. At present, there is no consensus on the risk or benefit posed by opioids on malignancy or chemotherapeutic activity. Distinguishing the consequences of opioid use from pain and its management is challenging. Additionally, opioid concentration data is often lacking in clinical studies. A scoping review approach inclusive of preclinical and clinical data will improve our understanding of the risk-benefit relationship concerning commonly prescribed opioids and cancer and cancer treatment.

Objective: The aim of the study is to map diverse studies spanning from preclinical to clinical regarding opioids with malignancy and its treatment.

Methods: This scoping review will use the Arksey six stages framework to (1) identify the research question; (2) identify relevant studies; (3) select studies meeting criteria; (4) extract and chart data; (5) collate, summarize, and report results; and (6) conduct expert consultation. An initial pilot study was undertaken to (1) parameterize the extent and scale of existing data for an evidence review, (2) identify key factors to be extracted in systematic charting efforts, and (3) assess opioid concentration as a variable for its relevance to the central hypothesis. Six databases will be searched with no filters: MEDLINE, Embase, CINAHL Complete, Cochrane Library, Biological Sciences Collection, and International Pharmaceutical Abstracts. Trial registries will include ClinicalTrials.gov, Cochrane CENTRAL, International Standard Randomised Controlled Trial Number Registry, European Union Clinical Trials Register, and World Health Organization International Clinical Trials Registry. Eligibility criteria will include preclinical and clinical study data on opioids effects on tumor growth or survival, or alteration on the antineoplastic activity of chemotherapeutics. We will chart data on (1) opioid concentration from human subjects with cancer, yielding a "physiologic range" to better interpret available preclinical data; (2) patterns of opioid exposure with disease and treatment-related patient outcomes; and (3) the influence of opioids on cancer cell survival, as well as opioid-related changes to cancer cell susceptibility for chemotherapeutics.

Results: This scoping review will present results in narrative forms as well as with the use of tables and diagrams. Initiated in February 2021 at the University of Utah, this protocol is anticipated to generate a scoping review by August 2023. The results of the scoping review will be disseminated through scientific conference proceedings and presentations, stakeholder meetings, and by publication in a peer-reviewed journal.

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Conclusions: The findings of this scoping review will provide a comprehensive description of the consequences of prescription opioids on malignancy and its treatment. By incorporating preclinical and clinical data, this scoping review will invite novel comparisons across study types that could inform new basic, translational, and clinical studies regarding risks and benefits of opioid use among patients with cancer.

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KEYWORDS

opioid; opioid receptor; drug; cocaine; crack; prescription opioid; opium; war on drug; cancer; chemotherapy; drug-drug interaction; malignancy; treatment; oncology; tumor; survival; antineoplastic; cancer cell; scoping; chemotherapeutic; librarian; library science; antineoplast; cancer cell survival; cancer cell growth; addict; addiction

Introduction

This project stems from a multidisciplinary team approach to better understand the consequences of drug interactions known to occur commonly in the management and care of patients with cancer. In contrast with typical scoping review methodology comprised exclusively of clinical data, this study incorporates a more comprehensive mapping of the literature, inclusive of preclinical data. In many clinical studies, it is difficult or impossible to disambiguate patient outcomes related to opioid use from the consequence of pain or pain management. This is because opioid use is often the measure by which pain is assessed. Therefore, our approach will enable a new perspective on an old and controversial problem.

Opioid analgesics are among the most frequently administered drugs for patients with cancer, and their use often coincides with active chemotherapeutic regimens [1]. The intended target for opioid analgesics is the μ-opioid receptor (μOR) expressed within the central nervous system [2]. However, the μOR is also present in diverse cancer types [3]. In cancer cells, μOR activity can stimulate intracellular signal cascades that regulate processes of cell survival and death and can coincide with the same signal cascades triggered by cytotoxic chemotherapy [3-12]. Some clinical studies for specific cancer types have identified the μOR as a negative prognostic factor and associated with chemotherapy resistance [3,13-23].

Paradoxically, opioids have demonstrated potential to both augment and inhibit cancer cell growth and survival as well as chemotherapeutic activity. For some types of cancers, opioid use is linked to metastasis, proproliferative effects, and decreased patient survival, while in other cancer types, opioids are associated with improved cancer cell killing and improved patient outcomes [16-19,21-47]. At present, there is no consensus on the risk or benefit posed by opioids in the context of malignancy and its treatment.

While multiple clinical studies have been conducted to evaluate the relationship between malignancy and its treatment with the μOR and analgesic opioid use, interpreting the risks or benefits of opioid use on tumor growth remains challenging and often confusing. Public response to some literature reports has led to surges in demand for opioids as potential antineoplastics. In contrast, other published data have led to concern that opioids will be withheld in the presence of suffering for fear of promoting malignancy [11,48,49]. Therefore, an improved understanding of the effects routinely prescribed opioids can have on any neoplasm, cancerous lesion, or malignancy and its treatment is an urgent public health need. A scoping review approach can help meet this need by organizing the existing clinical and preclinical evidence in a manner suitable to better distinguish clinically meaningful patterns and identify key knowledge gaps.

By examining both clinical and preclinical evidence together, 3 major challenges found in interpreting the clinical literature can begin to be addressed. First, clinical studies typically have a small n and focus on a specific cancer subtype, and among these, they differ in experimental design, intervention (eg, type, timing, and route of opioid administration), and patient population. Second, clinical opioid concentration data are lacking. Opioid concentration data are critical to establish the consequences of opioid use in the context of malignancy. As opioids are characterized by high inter- and intraindividual pharmacokinetic (PK) variability, the common practice of using opioid dose as a surrogate is a highly flawed means of estimating tumor tissue concentrations [50,51]. Finally, clinical studies seeking to assess the risks and benefits of opioids related to disease progression are frequently confounded by the role of pain and pain management on patient outcomes [41,52]. Preclinical studies have the potential to fill gaps in knowledge regarding opioid effects for certain cancer models at known concentrations and are not influenced by pain.

It is to be expected that the relationship between heterogeneous forms of cancer, μOR expression, and the clinical use of various analgesic opioids (routes of administration, formulations, and patterns of use) will be complex. Nonetheless, a scoping study approach can map evidence from both clinical and preclinical studies that will augment one another in the detection of meaningful associations between analgesic opioid exposure and the potential risks or benefits to patients with cancer.

Our objective is to map preclinical and clinical study data on therapeutically relevant concentrations of opioids effects on tumor growth or survival, or alteration on the antineoplastic activity of chemotherapeutics. We will map and evaluate published evidence regarding (1) opioid concentration data from human subjects with cancer, yielding a “physiologic range” to better interpret available preclinical data, (2) patterns of opioid exposure and disease and treatment-related patient outcomes, and (3) the influence of opioids and μOR activity on cancer cell survival and growth, as well as changes in susceptibility to

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clinically used chemotherapeutics. Apparent contradictions and clinically relevant knowledge gaps concerning the risks or benefits of analgesic opioid use in the context of malignancy can be better understood and clarified by using a systematic approach to catalog and examine existing literature from a pharmacologic perspective.

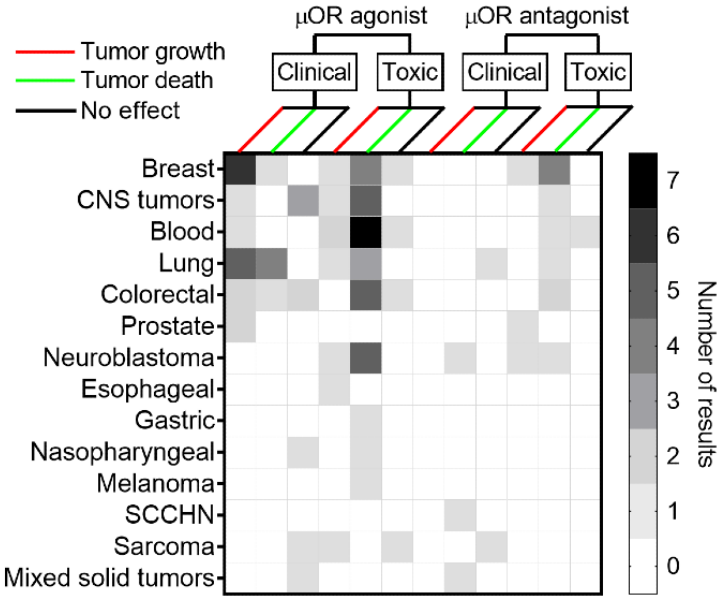
A search for existing evidence reviews or protocols on topic has been conducted (TC) in PROSPERO and MEDLINE (Ovid) on February 6, 2021. None were identified by the team as being on topic.

Prior to developing the scoping methodology protocol, a pilot study was undertaken to evaluate existing clinical and preclinical data concerning the effects of analgesic opioids on malignancy and its treatment (JEC). The central research question proposed for this study has been sought before and remains the source of much controversy. However, as the pilot study demonstrated, harnessing both clinical and preclinical information can bring into focus central concepts, such as the use of physiologic versus supraphysiologic opioid concentrations and biologic context. These concepts are often absent in the broader discussion of opioids and malignancy yet essential to solving some of the seeming contradictions. As this prestudy data, using an inclusive approach, revealed novel and informative patterns, we anticipate, a full scoping review will provide a new framework to view existing evidence and therefore, its interpretation.

The pilot study used MEDLINE (Ovid) for years 1946-2021, titles and abstracts were screened for inclusion (full publication). References of included studies were additionally assessed for relevancy and potential inclusion. Study data were collected and managed using Excel (Microsoft Corp) and GraphPad Prism (version 9; GraphPad Software, Inc). Data elements extracted were manuscript information (journal, title, authors, and year), study type (clinical [human subjects], including ex vivo), preclinical (in vivo [animal model] or in vitro), malignancy (type, subtype, model, or cell line), ligand (μOR agonist [ie, most analgesic opioids], antagonist, and partial agonist) and concentration information (eg, IC_{50}), any coinciding antineoplastic treatment, and predominant effect reported (ie, promotion or inhibition of tumor growth or chemotherapeutic activity). For ex vivo or in vitro data, "clinical" concentrations of μOR agonists were based on human subject studies reporting maximal peak concentrations experienced by adult patients with cancer receiving opioids as part of the standard of care: morphine (≤350 nM), fentanyl (≤10.8 nM), methadone (≤3.2 μM), and oxycodone (≤320 nM), and antagonists: nalmefene, methylnaltrexone, naltrexone, and naloxone (≤1 μM).

Data were extracted from 94 studies found to meet the pilot study criteria. From each study, findings were categorized as "tumor growth," "tumor death," or "no effect." A given study could report multiple findings, for instance, morphine (μOR agonist) could be found to stimulate cancer cell proliferation in a breast cancer cell line, while naloxone (a μOR antagonist) may be found to induce cancer cell apoptosis. Aggregated findings of opioid-associated effects on cancers are presented in Figure 1 [7-10,12,17-23,30,31,33-40,42,46,52-121].

Figure 1. Summary data from in vitro, in vivo, and clinical studies of opioids at "clinical" or "toxic" concentrations grouped by cancer type. μOR: μ-opioid receptor; CNS: central nervous system; SCCHN: squamous cell carcinoma of the head and neck.



The following conclusions have been drawn:

- The magnitude of the literature makes a scoping approach feasible, with fewer than 100 total clinical and preclinical studies found to meet the pilot study criteria for inclusion.
- Clinical studies evaluating opioid effects on malignancy are typically retrospective, and opioid concentration data among patients with cancer are scant.
- Preclinical studies often use opioids at concentrations exceeding those considered safe for humans. Additionally, preclinical studies which use opioid concentrations reflecting physiologically relevant concentration ranges for humans, on the basis of comparison with existing clinical concentration data, can offer important dose-response information but pose challenges for clinical interpretation.

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- Important patterns emerged, including confirming the hypothesis that for cancer tissue, opioid concentration is a critical dimension to understand the effect. Clinically relevant μOR agonist concentrations were often associated with cancer growth, while "toxic" or supraphysiologic concentrations were associated more often with cancer cell killing. Concentration is a critical, but often overlooked, dimension of opioid influence on malignancy and emphasizes the need for PK data in patients with cancer.
- The expression profiles of the μOR are poorly understood for many cancer types.

Methods

Study Design

We will conduct our scoping review with guidance from the latest version of the *JBI Manual for Evidence Synthesis* [122]. Using the framework as outlined by Arksey [123] and expanded by Peters [124], we will conduct our scoping review with Arksey's [123] six stages: (1) identifying the research question; (2) identifying relevant studies; (3) study selection; (4) charting the data; (5) collating, summarizing, and reporting the results; and (6) expert consultation involving oncologists, pain management specialists, and basic and translational scientists with expertise in pharmacology and cancer biology. Consultations will be held to inform the process of project conception, protocol development, study design and conduct, and finally, the interpretation of data, including discovery and description of key knowledge gaps [123,124]. For transparency and reproducibility, we will adhere to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) reporting guidelines in reporting our results [125].

We will use Covidence (Veritas Health Innovation), a web-based systematic reviewing platform, to screen and select studies. Citation management and duplicate detection and removal will be accomplished with EndNote (Clarivate Analytics). Research Electronic Data Capture (REDCap) tools hosted at the University of Utah will be used for data capture and charting [126].

Literature Searching

Overview

A librarian (TC) will develop and translate search strategies for the web-based databases using a combination of keywords and controlled subject headings unique to each database. Peer review of the strategies will be conducted by an information specialist (MMM) using the Peer Review of Electronic Search Strategies guidelines [127]. Preliminary searches by 2 reviewers (JEC and VY) resulted in pilot data of 94 studies, which will be used by the librarian to harvest search terms.

Electronic Sources

We will search the following databases: MEDLINE (Ovid) 1946-2022, Embase 1974-2022, CINAHL Complete (Ebscohost) 1937-2022, Cochrane Library 1898-2022 including CENTRAL 1898-2022, Biological Sciences Collection (ProQuest) 1946-2022, and International Pharmaceutical Abstracts (Ovid) 1970-2022.

Other Sources

Trial registries will include ClinicalTrials.gov, Cochrane CENTRAL Register of Controlled Trials (Wiley), International Standard Randomised Controlled Trial Number registry, European Union Clinical Trials Register, and World Health Organization International Clinical Trials Registry.

No gray literature will be designated for searching. For studies meeting inclusion criteria, references will also be evaluated for relevancy and potential inclusion.

Study Selection (Eligibility Criteria)

Inclusion Criteria

Participants

Patients in clinical studies diagnosed with any type of malignancy will be included.

Concept

We will assess the use of therapeutic opioids or assessment, direct or indirect, of opioid receptors or any other proposed mechanism for opioid action.

Context

For preclinical studies, any investigation involving any cancer cell lines, xenografts, ex vivo specimens, or relevant in vitro models of cancer related to clinically used opioids, opioid receptors, opioids purported to act upon, bind to, or influence cell processes via known or unknown targets will be included.

For clinical studies, patients diagnosed with, or survivors of, any type of cancer may or may not have received opioids at any time. Studies including patients with cancer but without opioid exposure will be included, if the study concerns biomarkers, outcomes, or other parameters related to opioid receptor or opioid influence on a malignancy or its treatment.

English-language studies will be preferred. We will chart non–English-language studies meeting or appearing to meet inclusion criteria.

Exclusion Criteria

Conference abstracts, studies exclusive to the topic of opioid addiction and abuse and not involving a cancer diagnosis or containing opioid concentration data, and those exclusive to the topic of pain and pain management and do not involve a cancer diagnosis or contain opioid concentration data will be excluded.

Team

Reviewers (JEC, VY, and KJ) will screen, independent of each other, the titles and abstracts of search results. Reviewers will then review the full text, also independent of each other's vote. Consensus will be reached through discussion among the reviewers. Any ties will be decided by a fourth independent reviewer (KMW, CSL, EYE, or RSL).

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Quality Assessment

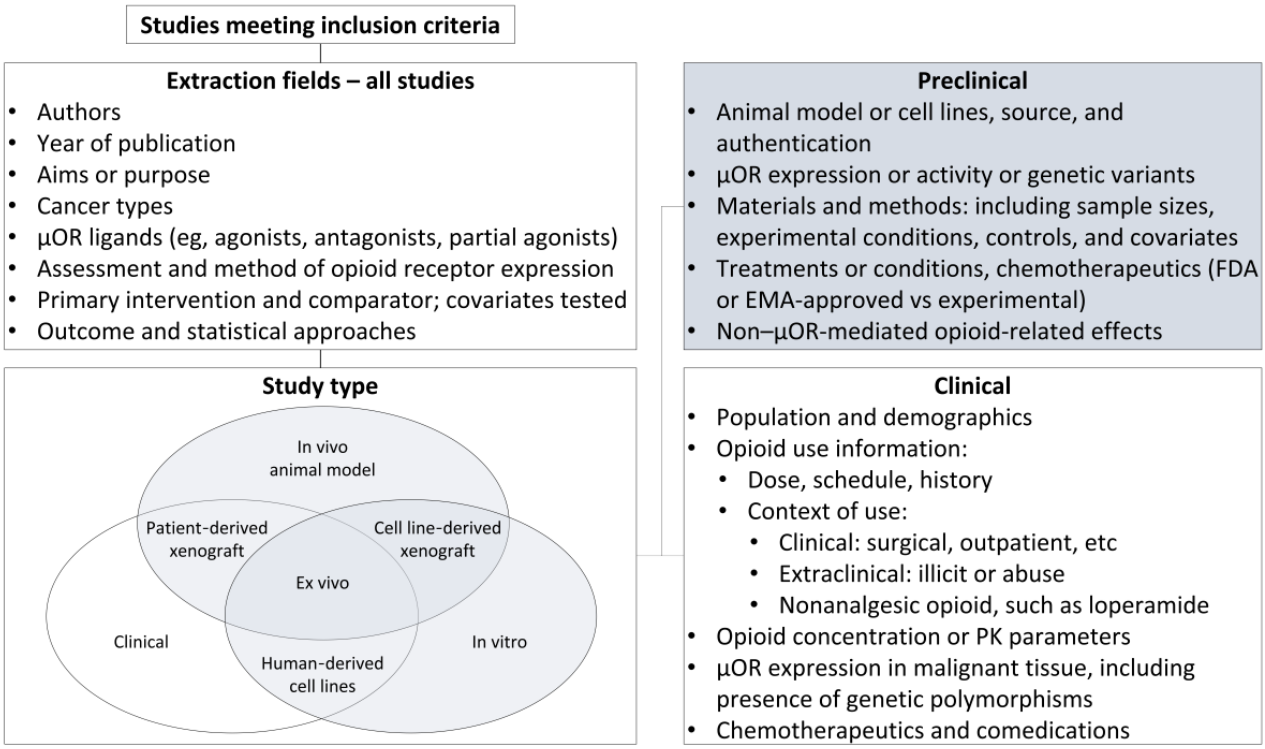
In compliance with scoping review methodology, no quality assessment of included studies will be performed as our goal is to rapidly map the literature.

Data Extraction: Charting the Data

Study data will be collected and managed using REDCap tools hosted at the University of Utah [126]. REDCap is a secure, web-based application designed to support data capture for research studies, providing (1) an intuitive interface for validated data entry, (2) audit trails for tracking data manipulation and export procedures, (3) automated export procedures for seamless data downloads to common statistical packages, and (4) procedures for importing data from external sources [126].

Extraction fields were developed based on the initial prescoping review pilot study to adequately address the primary research question (Figure 2). This includes extraction and charting of general manuscript information as well as adopting strategies to facilitate disaggregation of studies dependent upon data type (eg, clinical vs preclinical) for analysis.

Figure 2. Data extraction and charting. Studies concerning the influence of clinically used opioids on malignancy and its treatment do not align with a strictly "clinical" versus "basic" science dichotomy. Capturing data elements from across the spectrum of study types will provide a more holistic view to benefit the goals of this scoping review and distinguishes it from other reviews. µOR: µ-opioid receptor; EMA: European Medicines Agency; FDA: U.S. Food and Drug Administration; PK: pharmacokinetic.



Analysis of Evidence

Overview

A descriptive analysis will be used across all studies (eg, retrospective, clinical trial, and in vitro) and be inclusive of reported outcomes. For each cancer subtype, a descriptive synopsis of opioid-related data will be compiled, including conditions or variables associated with opioid or µOR activity influencing malignancy or its treatment. The analysis will be split into 2 main components based on the "Research question."

Component 1: Do Therapeutically Relevant Concentrations of Opioids Affect Tumor Growth and Survival?

Data extracted from clinical and basic research studies will be aggregated by µOR ligand and cancer type. µOR ligands will be categorized by class (agonist, antagonist, and partial agonist) as well as by individual entity (morphine, oxycodone, etc) and by measures of µOR ligand exposure (eg, concentrations, PK parameter estimates, dosage, and route of administration) or exposure-response (eg, IC_{50}).

For basic (animal, in vitro) study results, µOR ligands will be categorized according to effect on malignancy (ie, no effect, promotes, or inhibits malignancy), and for clinical study results, µOR ligands will be categorized according to effect on malignancy, chemotherapeutic activity via clinical indices, or patient outcome (eg, minimal residual disease and progression-free survival). Clinical data will be further categorized by covariates such as sex, age range (pediatric vs adult), new diagnosis, or relapse.

Due to differences in study design, direct comparisons between studies are not feasible. Data will be aggregated by category, and a count of results will be conducted. An illustration: consider a study that demonstrates that morphine administered in high doses, generating supraphysiologic blood concentrations (considered toxic for humans), stimulated metastases, as compared to controls, in a xenograft murine model of breast cancer. This study result would be tabulated as breast cancer,

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μOR agonist, supraphysiologic exposure, promotes cancer. If, in addition, to the experimental conditions above, morphine was administered to generate clinically relevant blood concentrations, and these were associated with diminished tumor growth, this would be tabulated as breast cancer, μOR agonist, physiologic exposure, inhibits cancer.

Component 2: Do Therapeutically Relevant Concentrations of Opioids Alter the Antineoplastic Activity of Chemotherapeutics?

Data extracted from clinical and basic research (preclinical) studies, incorporating μOR ligand use coinciding with chemotherapeutics used to induce malignant cell death will be aggregated by μOR ligand, cancer type, and chemotherapeutic class.

Chemotherapeutics and μOR ligands will be classified by class as well as by individual entity. Chemotherapeutics will include conventional (anthracyclines, antimetabolites, alkylating agents, mitotic spindle inhibitors, topoisomerase inhibitors, antitumor antibiotics, platinum-based agents, corticosteroids, biologicals [enzymes], or nitrosoureas), targeted (kinase inhibitors, proteasome inhibitors, and antibodies), and agents undergoing clinical trials or considered experimental.

Measures of chemotherapeutic agent or μOR ligand exposure (eg, concentrations, PK parameter estimates, dosage, and route of administration) or exposure-response (eg, IC_{50}) will be considered.

For basic (animal, in vitro) study results, μOR ligands will be categorized according to effect on chemotherapeutic activity (ie, no effect, antagonism, or synergism). For clinical study results, μOR ligands will be categorized according to the effect on chemotherapeutic activity via clinical indices and patient outcomes studies attribute to or suggest as being related to changes in treatment efficacy. Clinical data will be further categorized by covariates such as sex, age range (pediatric vs adult), new diagnosis, or relapse.

As with component 1, it is anticipated that differences in study design and experimental conditions will preclude direct comparisons between data generated across studies. As above, data will be tabulated by category, including chemotherapy type, and a count of results will be conducted.

Ethical Considerations

This study does not require ethical approval as data and information collected, using scoping review methodology, has previously been made available through publication. The results of this scoping review will be submitted for publication in a relevant peer-reviewed journal as well as disseminated through presentations at scientific conferences. Any changes from our protocol during the conduct of the scoping review will be acknowledged and defined in the manuscript.

Results

The results of this scoping review will be presented using a descriptive narrative form as well as graphical and tabular representations. The results will be structured, as appropriate, to emphasize the effects of prescription opioids by cancer classification as well as chemotherapy type. Additionally, study results concerning data classified as preclinical, translational, and clinical will be presented distinctly to facilitate comparison. The protocol for the scoping review was initiated in February 2021 at the University of Utah and is expected to be completed in August 2023. The results of the scoping review will be disseminated through regional and national scientific conference proceedings and presentations, stakeholder meetings, and by publication in a peer-reviewed journal.

Discussion

This scoping review will map diverse studies spanning from preclinical to clinical regarding the intersection of opioids with malignancy and its treatment. The interpretation of opioid-malignancy interactions within a clinical context is often confounded by pain and its management. It is therefore both novel and necessary to include preclinical study data to identify key knowledge gaps, begin to reconcile seeming conflicting data (eg, opioids foment cancer growth vs opioids kill cancer cells) by setting a context to parse the biologic and molecular complexities of opioid impact on malignancy and its treatment, and ultimately, inform patient treatment algorithms to optimize outcomes. The knowledge presented in the scoping review will help to inform and improve the design of studies to assess the unmet medical need to understand the risks and benefits associated with opioids extending to the potential to impact cancer and its care.

This scoping review study has several strengths. First, our scoping review approach will be inclusive of studies spanning the spectrum of published data available from clinical to in vitro. Popular opinion and clinical judgment regarding the potential for opioids to affect malignancy have been deeply influenced by the publication of basic (in vitro or ex vivo) studies. Therefore, expanding this review to include both clinical and preclinical studies provides a new perspective on the topic, acknowledges that basic studies impact clinical care and shape patients' attitudes, and addresses limitations specific to the opioid-malignancy question in the context of clinical studies. Current clinical studies examining the opioid-malignancy question, often retrospective, are confounded by pain and the management of pain. Adequate pain management is associated with improved patient survival; therefore, interpretation of the potential effects of opioid use on the malignancy itself is challenging to interpret. Finally, despite the intense attention the topic has received, the key dimension of opioid concentration is often not addressed. Therefore, incorporating data from clinical and preclinical studies into this review with an emphasis on systemic opioid exposures (concentration) is warranted, and based on the preliminary data collected, aids in clarifying seemingly contradictory findings pointed to in existing reviews.

This scoping review also has limitations. Specifically, no quality assessment of the included studies will be performed. Relevant data may be missed, as we are searching for published studies only. We selected several sources and developed sensitive search strategies to increase the discovery of eligible studies.

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The topic of opioid impact on cancer and its treatment is not new but remains controversial and clinically relevant. This scoping review seeks to encompass preclinical and clinical studies to generate a comprehensive landscape for interpreting the existing literature within pathophysiologic and pharmacologic contexts. We hope this study will be used to identify key knowledge gaps and advance future studies aimed at improving patient outcomes.

Acknowledgments

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Data Availability

Data sets will be presented in the main manuscript and as additional supporting files or made available upon request.

Authors' Contributions

JEC wrote the manuscript and provided data, VY conceptualized the project as a scoping review, TC aided in methodologic approach for scoping protocol development, and MMM provided oversight for scoping review protocol development. All authors helped in the preparation, critical review, and revision of the scoping protocol.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review reports.
[PDF File (Adobe PDF File), 144 KB - resprot_v12i1e38167_app1.pdf]

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Abbreviations

μOR: μ-opioid receptor
PK: pharmacokinetic
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews
REDCap: Research Electronic Data Capture

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Protocol

Nurses' Perceptions of Climate Change: Protocol for a Scoping Review

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Abstract

Background: Climate change is a major threat to human health. Nurses are in contact with patients suffering from the effects of climate change in their daily work. Therefore, they need to be involved in combating it at both the individual and collective levels. However, there is still very little known about nurses' perception of climate change and their role toward it. A few recent studies have embarked on the process of examining the perceptions of these health professionals relative to climate change, but no exploratory review of the literature has been conducted on nurses' perception of this phenomenon.

Objective: The purpose of this protocol is to develop a research strategy for an exploratory review of the literature focused on identifying nurses' perceptions of climate change.

Methods: Firstly, with the help of a specialized librarian, we defined keywords and their combinations, using an iterative process, to develop a documentary search strategy. This strategy was tested in the following four bibliographic databases: MEDLINE (PubMed), CINAHL, Embase, and Web of Science. A search of the grey literature will also be conducted to supplement the results of the bibliographic database search. The next step will be for 2 members of the research team to carry out a 2-stage selection process using the web-based systematic review software Covidence. They will carry out this selection process independently, with the aim of identifying relevant studies that meet the inclusion criteria for our exploratory review. Finally, data on year of publication, authors, geographic area, article type, study objectives, methodology, and key findings will be extracted from selected articles for analysis. The data will be analyzed by the research team based on an in-depth examination of the findings and will be directed toward answering the research question and fulfilling the study's objective.

Results: The results will help in defining nurses' perceptions of climate change more clearly as well as the role they can play and what they need to be able to bring forward solutions to this phenomenon. The findings should also serve to guide the health sector and nursing faculty's interventions aimed at preparing health professionals to act on the potential threats associated with climate change.

Conclusions: The preliminary search suggests a possible gap between the importance of the nursing role in addressing the health impacts of climate change and the nurses' lack of knowledge and awareness on this matter. The results will allow for raising nurses' awareness of their role in the fight against climate change and the ways to address its health effects. This study

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will also open up new research perspectives on how to equip nurses to better integrate response to climate change issues into their professional practice.

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KEYWORDS

perception; climate change; nurse; scoping review; review method; environment; nursing; perspective; search strategy; global warming; health care professional

Introduction

Climate change represents one of the greatest threats to human health in the 21st century [1-4]. The new report from the Intergovernmental Panel on Climate Change indicates that climate change is already affecting the physical health and well-being of many people around the world [5]. This is reaffirmed by a recent Health Canada report, which states that climate change is already having a negative impact on the health of Canadians due to increased temperatures, extreme heat, forest fires, and the geographic spread of zoonotic diseases such as Lyme disease [6]. Climate change affects the physical and mental health of populations in direct and indirect ways. Examples of the direct health effects of climate change include extreme weather events, such as storms, wildfires, floods, or drought; increased exposure to pollens; and heat waves [7]. Moreover, a 2011 study published in the journal *Science* found that the frequency of such events is expected to increase by a factor of 5 to 10 over the next 40 years [8]. Examples of indirect effects include air pollution (causing respiratory and heart diseases), water pollution (causing gastroenteritis), changes in ecosystems and in the geographic distribution of vector-borne diseases, food insecurity, population displacement, conflict, and mental health [7,9-12]. The World Health Organization estimates that climate change could cause approximately 250,000 additional deaths per year between 2030 and 2050 due to malnutrition, malaria, diarrhea, and heat stress [13].

Health professionals have an important role to play in combating health threats related to climate change [14]. Nurses, who make up a significant portion of health professionals engaged in improving the health and well-being of individuals [15-17], have a critical role to play in responding to and reducing health issues stemming from climate change [18]. Because they benefit from a high degree of public trust [19], nurses can play a leadership role in the health sector both by increasing awareness of climate change as an important health issue and by spearheading action and advocacy in the fight against climate change [20]. In their daily work, nurses also have an advocacy role toward their patients experiencing the effects of climate change, especially those who are the most vulnerable. Therefore, nurses need to be involved in combating climate change at both the individual and collective levels. However, there is still very little known about nurses' perception of climate change and of their role toward it. A few recent studies have examined nurses' perceptions of climate change and health [16,17,21-23]. In addition, two exploratory reviews of the literature have been conducted. The first, conducted in 2018, focused on health professionals' knowledge, attitudes, perceptions, and practices related to climate change and its health impacts [14]. The second, conducted in 2022, concerns awareness and attitudes among nursing students and educators related to sustainability and climate change [24]. To the best of our knowledge, no study has yet been conducted for the purpose of identifying and synthesizing nurses' perceptions of climate change in an exploratory literature review. The 2018 study considers health care professionals in general, and the 2022 study focuses on nursing students and educators.

The purpose of this protocol is to develop a research strategy for an exploratory literature review aimed at identifying nurses' perceptions of climate change.

Methods

Overview

The exploratory literature review will be conducted in 5 steps, as described by Arksey and O'Malley [25] and refined by Levac et al [26]. These steps are as follows:

1. Identification of the research question
2. Identification of relevant studies
3. Selection of relevant and reliable studies
4. Charting the data from the included studies
5. Collating, summarizing, and reporting the findings

Identification of the Research Question

As recommended by Levac et al [26], the question we wish to answer through this exploratory review has been clearly articulated and focused. The question under study in this exploratory literature review is, "what are nurses' perceptions relative to climate change?" This question is justified by the need to advance knowledge about nurses' perceptions of climate change to better prepare them to tackle these climate issues [16,20,22,23].

Identification of Relevant Studies

We first developed a search strategy with the help of a specialized librarian using an iterative process. Searches were conducted in the following four bibliographic databases targeting biomedical and interdisciplinary topics: MEDLINE (PubMed), CINAHL, Embase, and Web of Science. Two concepts were used to identify keywords for the literature search strategy: climate change (concept 1) and nurses' perceptions (concept 2). Once identified, the keywords were classified into free-text search terms and controlled vocabulary to define a search strategy specific to each database. The characteristics of free-text and controlled vocabulary searches in the databases used are presented in Table 1.

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Table 2 presents the keywords (free-text search terms) and thesauri terms (controlled vocabulary) for each of the four databases for each of the two concepts defined previously. An example of a preliminary MEDLINE (PubMed) search strategy is shown in Table 3.

Table 1. Free-text and controlled vocabulary search characteristics for databases used for this study.

Selected databases	Search vocabulary
MEDLINE via PubMed	• Free text: title/abstract or tiab (advanced) • Controlled vocabulary: MeSHa
CINAHL Plus with full text (EBSCO)	• Free text: title + abstract, ti+ab (two separate searches) • Controlled vocabulary: CINAHL descriptors
Embase	• Free text: title, abstract, keyword, ti,ab,kw (quick search) • Controlled vocabulary: EMTREE
Web of Science	• Free text only: topic (includes title, abstract, author keywords, and Keywords Plus).

[a]MeSH: Medical Subject Headings.

Table 2. Free-text search terms (keywords) and controlled vocabulary.

Concepts and free-text search terms (Keywords)	Controlled vocabulary (thesaurus terms in electronic bibliographic databases)		
	MEDLINE (PubMed)	CINAHL Plus with Full Text (EBSCO)	Embase
Concept 1: climate change			
"Climate change*" OR "global warming" OR "climate crisis" OR "climate warming" OR "climate issue*" OR "Climate vulnerabilit*" OR "Climate Emergenc*" OR "Greenhouse Effect" OR "climate action"	"Climate Change"[Mesh[a]] OR "Greenhouse Effect"[Mesh]	(MH "Climate Change") OR (MH "Greenhouse Effect")	'Climate change'/exp OR 'greenhouse effect'/de
Concept 2: nurses' perceptions			
(Nurse OR nurses OR nursing) AND (attitude* OR perception* OR awareness OR perspective* OR belief* OR views OR behavior* OR opinion* OR concern* OR understanding OR knowledge*)	("Nurses"[Mesh]) OR "Nurse's Role"[Mesh]) AND ("Perception"[Mesh:NoExp] OR "Attitude"[Mesh:NoExp] OR "Attitude of Health Personnel"[Mesh:NoExp] OR "Awareness"[Mesh] OR "Knowledge"[Mesh] OR "Behavior"[Mesh:NoExp])	(MH "Nurse Attitudes") OR ((MH "Nurses+") OR (MH "Nursing Role")) AND ((MH "Attitude") OR (MH "Perception") OR (MH "Knowledge") OR (MH "Nursing Knowledge") OR (MH "Behavior"))	'Nurse attitude'/de OR ('nurse'/exp OR 'nursing role'/de) AND ('perception'/de OR 'attitude'/de OR 'awareness'/de OR 'knowledge'/exp OR 'beliefs'/de OR 'behavior'/de)

[a]MeSH: Medical Subject Headings.

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Table 3. Example of a search strategy in MEDLINE (PubMed); # represents the different sequences of the search.

#	Query	Search details
10	#3 AND #6 AND #9	(“Climate change*”[Title/Abstract] OR “global warming”[Title/Abstract] OR “climate crisis”[Title/Abstract] OR “climate warming”[Title/Abstract] OR “climate issue*”[Title/Abstract] OR “climate vulnerabilit*”[Title/Abstract] OR “climate emergenc*”[Title/Abstract] OR “Greenhouse Effect”[Title/Abstract] OR “climate action”[Title/Abstract] OR (“Climate Change”[MeSH[a] Terms] OR “Greenhouse Effect”[MeSH Terms])) AND (“Nurse”[Title/Abstract] OR “Nurses”[Title/Abstract] OR “nursing”[Title/Abstract] OR (“Nurses”[MeSH Terms] OR “Nurse’s Role”[MeSH Terms])) AND (“attitude*”[Title/Abstract] OR “perception*”[Title/Abstract] OR “Awareness”[Title/Abstract] OR “perspective*”[Title/Abstract] OR “belief*”[Title/Abstract] OR “views”[Title/Abstract] OR “behavior*”[Title/Abstract] OR “opinion*”[Title/Abstract] OR “concern*”[Title/Abstract] OR “understanding”[Title/Abstract] OR “knowledge*”[Title/Abstract] OR (“Perception”[MeSH Terms:noexp] OR “Attitude”[MeSH Terms:noexp] OR “Attitude of Health Personnel”[MeSH Terms:noexp] OR “Awareness”[MeSH Terms] OR “Knowledge”[MeSH Terms] OR “Behavior”[MeSH Terms:noexp]))
9	#7 OR #8	“Attitude*” [Title/Abstract] OR “perception*” [Title/Abstract] OR “awareness” [Title/Abstract] OR “perspective*” [Title/Abstract] OR “belief*” [Title/Abstract] OR “views” [Title/Abstract] OR “behavior*” [Title/Abstract] OR “opinion*” [Title/Abstract] OR “concern*” [Title/Abstract] OR “understanding” [Title/Abstract] OR “knowledge*” [Title/Abstract] OR “Perception” [MeSH Terms:noexp] OR “Attitude” [MeSH Terms:noexp] OR “Attitude of Health Personnel” [MeSH Terms:noexp] OR “Awareness” [MeSH Terms] OR “Knowledge” [MeSH Terms] OR “Behavior” [MeSH Terms:noexp]
8	“Perception”[Mesh:NoExp] OR “Attitude”[Mesh:NoExp] OR “Attitude of Health Personnel”[Mesh:NoExp] OR “Awareness”[Mesh] OR “Knowledge”[Mesh] OR “Behavior”[Mesh:NoExp]	“Perception”[MeSH Terms:noexp] OR “Attitude”[MeSH Terms:noexp] OR “Attitude of Health Personnel”[MeSH Terms:noexp] OR “Awareness”[MeSH Terms] OR “Knowledge”[MeSH Terms] OR “Behavior”[MeSH Terms:noexp]
7	Attitude*[Title/Abstract] OR perception*[Title/Abstract] OR awareness[Title/Abstract] OR perspective*[Title/Abstract] OR belief*[Title/Abstract] OR views[Title/Abstract] OR behavior*[Title/Abstract] OR opinion*[Title/Abstract] OR concern*[Title/Abstract] OR understanding[Title/Abstract] OR knowledge*[Title/Abstract]	“Attitude*”[Title/Abstract] OR “perception*”[Title/Abstract] OR “awareness”[Title/Abstract] OR “perspective*”[Title/Abstract] OR “belief*”[Title/Abstract] OR “views”[Title/Abstract] OR “behavior*”[Title/Abstract] OR “opinion*”[Title/Abstract] OR “concern*”[Title/Abstract] OR “understanding”[Title/Abstract] OR “knowledge*”[Title/Abstract]
6	#4 OR #5	“Nurse”[Title/Abstract] OR “Nurses”[Title/Abstract] OR “nursing”[Title/Abstract] OR “Nurses”[MeSH Terms] OR “Nurse’s Role”[MeSH Terms]
5	“Nurses”[Mesh] OR “Nurse’s Role”[Mesh]	“Nurses”[MeSH Terms] OR “Nurse’s Role”[MeSH Terms]
4	Nurse[Title/Abstract] OR nurses[Title/Abstract] OR nursing[Title/Abstract]	“Nurse”[Title/Abstract] OR “nurses”[Title/Abstract] OR “nursing”[Title/Abstract]
3	#1 OR #2	“Climate change*”[Title/Abstract] OR “global warming”[Title/Abstract] OR “climate crisis”[Title/Abstract] OR “climate warming”[Title/Abstract] OR “climate issue*”[Title/Abstract] OR “climate vulnerabilit*”[Title/Abstract] OR “climate emergenc*”[Title/Abstract] OR “Greenhouse Effect”[Title/Abstract] OR “climate action”[Title/Abstract] OR “Climate Change”[MeSH Terms] OR “Greenhouse Effect”[MeSH Terms]
2	“Climate Change”[Mesh] OR “Greenhouse Effect”[Mesh]	“Climate Change”[MeSH Terms] OR “Greenhouse Effect”[MeSH Terms]
1	“Climate change*”[Title/Abstract] OR “global warming”[Title/Abstract] OR “climate crisis”[Title/Abstract] OR “climate warming”[Title/Abstract] OR “climate issue*”[Title/Abstract] OR “Climate vulnerabilit*”[Title/Abstract] OR “Climate Emergenc*”[Title/Abstract] OR “Greenhouse Effect”[Title/Abstract] OR “climate action”[Title/Abstract]	“Climate change*”[Title/Abstract] OR “global warming”[Title/Abstract] OR “climate crisis”[Title/Abstract] OR “climate warming”[Title/Abstract] OR “climate issue*”[Title/Abstract] OR “climate vulnerabilit*”[Title/Abstract] OR “climate emergenc*”[Title/Abstract] OR “Greenhouse Effect”[Title/Abstract] OR “climate action”[Title/Abstract]

[a]MeSH: Medical Subject Headings.

Selection of Relevant and Reliable Studies

For this step, studies identified by the database search were first imported into the bibliographic management software EndNote and then transferred to Covidence (Veritas Health Innovation) to remove duplicates and facilitate the sorting and selection of relevant studies based on previously defined inclusion and exclusion criteria.

Once the duplicates were removed, an initial selection was begun based on the titles and abstracts, by 2 members of the research team (TD and AB) working independently. Studies

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focused on nurses' perceptions of climate change will be retained. No date limits will be applied. All studies that address an environmental issue other than climate change, concern health professionals other than nurses, or are published in a language other than English or French will be excluded. Any disagreement regarding inclusion or exclusion will be resolved by consensus and, if necessary, by consultation with a third team member.

Once this initial stage of selection is completed, a second stage of selection will determine which articles will be included in the final analysis, based on their full text. This stage will be carried out by the same 2 researchers performing the initial selection. Studies whose full text is not available, studies that do not provide the authors' names or publication dates, or those that constitute expert opinions or commentaries will be excluded. Accordingly, only empirical studies will be considered. Once again, any disagreements will be resolved by consensus between the 2 reviewers. A third reviewer will be consulted to establish consensus if the 2 reviewers' opinions diverge.

The results of the selection process will be presented in a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) diagram [27], showing the number of studies selected at each stage of selection.

Charting the Data From the Included Studies

This step consists of extracting the data from the full-text articles selected. For this purpose, a Microsoft Excel table will be developed. It will include the following sections: title, authors, year of publication, geographic area, study objectives, methodology, and key findings.

Collating, Summarizing, and Reporting the Findings

The data extracted in the previous step will be analyzed by the research team. This analysis may include an informed discussion based on an in-depth examination of the findings and directed toward answering the research question and fulfilling the study's objective. Quantitative and qualitative data will be analyzed altogether and categorized according to the type of perception to which it refers (eg, perception of nurses' role toward climate change or perception of their needs regarding climate change).

Grey Literature Search

To supplement the results of the bibliographic database search, we plan to also conduct a search of the grey literature. To this end, we will consult the websites of associations and organizations related to nursing and those focused on the environment. Social media searches or reporting were not considered. We targeted nursing associations and organizations in the province of Québec, those at the federal level in Canada and the United States, and those at the international level. The following associations in Table 4 were identified through the scientific literature [18,28,29] and through a Google search using a combination of keywords related to nursing associations or organizations, climate change, and geographic area of interest (ie, Canada, United States, or international).

Table 4. Nursing associations and organizations identified for grey literature search.

Location and name of the association or organization	Website
Province of Québec	
Quebec Nurses' Association	[30]
Ordre des infirmières et infirmiers du Québec	[31]
Canada	
Canadian Nurses Association	[32]
Canadian Association of Nurses for the Environment	[33]
Canadian Federation of Nurses Unions	[34]
Canadian Nurse Educator Institute	[35]
Canadian Association of Schools of Nursing	[36]
United States	
American Nurses Association	[37]
American Association of Colleges of Nursing	[38]
American Academy of Nursing	[39]
Alliance of Nurses for Healthy Environments	[40]
National Student Nurses' Association	[41]
International	
World Health Organization	[42]
International Council of Nurses	[43]
Secrétariat international des infirmières et des infirmiers de l'espace francophone	[44]
Nurses Climate Challenge	[45]

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Three approaches will be used to search the grey literature. The first approach will consist of searching by navigating the websites of the various associations and consulting their different sections, such as the section on publications; the second approach will involve using the search function of the websites to search for the keywords that were defined for the bibliographic database searches; finally, the third approach will consist of searching on Google by combining the name of the association with the keywords defined for the bibliographic database searches. The data will be extracted into an Excel spreadsheet that will contain the following sections: date of search, site searched, type of search performed (referencing one of the three approaches listed above), number of results found, number of results retained, and comments. For searches conducted by navigating the sites, the sections consulted will be specified, and for keywords searches, the terms or expressions used in searches will be specified.

Results

The results will allow us, firstly, to ascertain how nurses perceive climate change; and secondly, to analyze these perceptions in relation to nurses' contexts (personal or professional), the roles they can play, and what they require to better address this phenomenon.

The results will be gathered and shared according to the type of perception they refer to (eg, perception of climate change's causes and impacts, perception of nurses' role toward climate change, and perception of their needs regarding climate change).

We hope that the results will point toward targeted climate change awareness, raising interventions for nurses and guide new interventions aimed at improving nursing practice in a climate change context. In addition, with climatic hazards, such as extreme heat episodes and floods, expected to become increasingly frequent in coming years, a better understanding of climate issues among nurses will enable them to better assess risks and provide patients with appropriate advice and care. The results may also move forward engagement and dialogue on this important topic among nurses as well as raise awareness in nursing faculty to include these important issues in the education of future nurses. The findings will also open avenues for future research on the potential of nursing involvement in the mitigation, adaptation, and resilience of communities in the context of climate change.

Discussion

Expected Outcomes

To our knowledge, this study is the first exploratory review of the literature aiming to identify nurses' perceptions of climate change. Its relevance comes from the fact that studies have been conducted in recent years that address nurses' perceptions of climate change [16,17,21-23] but have not been compared and interpreted as a body of literature. The preliminary results of this exploratory literature review suggest that nurses could be preoccupied about climate change to a certain extent [20] but could lack knowledge about climate change, its causes, and its impacts on health [15,20,22]. The perceptions of their role in the fight against climate change as well as concrete ways to include the fight against climate change in their daily work despite constraints seems also unclear [17,22]. The full results of this review of the literature will allow us to cross-reference the different perceptions nurses have of climate change, as described in the various studies, and to develop an overall portrait of these perceptions. These results will allow us to identify ways to fill the possible gap between the importance of the nursing role in addressing the health impacts of climate change and the lack of knowledge and awareness of nurses in this matter. Therefore, this study should also help nursing organizations, educational institutions, and policy makers to better identify the elements that would help prepare these health care workers to face this climate crisis and the subsequent impacts on the health and well-being of the communities and populations they serve. Research could also help better identify promising strategies to empower nurses to fully carry out their advocacy role toward their patients who are the most vulnerable to climate change.

One of the strengths of the search strategy is that it targets diverse interdisciplinary databases in which articles from different fields, such as biomedical sciences and social sciences, are indexed. This will give us a broader view of the scope of the existing literature. In addition, this search is supplemented by a search of the grey literature, which will allow us to find relevant documents that cannot always be found in current bibliographic databases.

Review Limitations

One of the limitations of this exploratory review of the literature is that it only includes publications in French and English, which means that all publications in other languages that may be relevant to the topic will not be taken into consideration. Nevertheless, as the vast majority of scientific publications are written in English, our findings should be of interest. Another limitation is that we do not plan to assess the quality of studies. However, this step is optional in the case of a scoping review [25].

Conclusions

The full results will be disseminated through various means, such as international nursing conferences and articles, including an article in a nursing association journal. Authors will also publicize the published articles in their respective professional network. This dissemination strategy hopes to reach nurses and raise awareness toward their role in the fight against climate change and the ways to address its health effects.

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Conflicts of Interest

None declared.

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Abbreviations

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

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Protocol

Examining Drug-Resistant Tuberculosis Stigma Among Health Care Workers Toward the Development of a Stigma-Reduction Intervention: Protocol for a Scoping Review

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Abstract

Background: Drug-resistant tuberculosis (DRTB) is an increasing threat to human health and economic security worldwide. Exacerbating the severity of DRTB is the low rate of service delivery, leading to increased community transmission of the disease, further amplified by stigma. Health workers are on the front line of service delivery; their efforts in all areas of disease control are suspected of having resulted in stigmatization, impacting patient-centered care. As a growing concern, attention to addressing the DRTB stigma confronting health workers is required. However, little is known about stigma among health workers delivering services to patients with DRTB. This scoping review will provide an overview that could help inform appropriate responses toward stigma-reduction interventions for these health workers.

Objective: This scoping review protocol articulates a methodology that will examine the facets of DRTB-related stigma confronting health workers in high TB- and DRTB-burdened countries. This scoping review will (1) summarize stigma barriers and facilitators contributing to stigmatization among health workers delivering services to patients with DRTB, (2) identify the most common stigma barrier and facilitator, and (3) summarize the stigma-reduction intervention recommendations in the studies.

Methods: Guided by Arksey and O'Malley's framework and the recommendations of Munn et al, we will conduct a scoping review of relevant literature providing evidence of DRTB-related stigma among health workers from countries with a high burden of tuberculosis (TB) and DRTB. We will search published articles written in English from 2010 onward in electronic databases using Medical Subject Headings and keywords. Our search will apply a 3-step search strategy and use software tools to manage references and facilitate the entire scoping review process. The findings of our review will be presented following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Scoping Reviews checklist. Our study is registered with Open Science Framework Registries.

Results: This scoping review is part of a bigger project that will critically investigate stigma among health workers delivering services to patients resistant to TB medications. This study began in November 2021 and is expected to finish in 2023. The study has retrieved 593 abstracts out of 12,138 articles searched since February 2022 from the identified databases. The findings of this study will be published in a peer-reviewed journal.

Conclusions: This review will provide an outline of the aspects of DRTB-related stigma confronting health workers. The findings of this review could help inform appropriate responses toward stigma-reduction interventions for these health workers. This is significant because interventions addressing related TB (and DRTB) stigma in the workplace are lacking.

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KEYWORDS

drug-resistant tuberculosis; health workers; stigma; tuberculosis stigma; TB stigma; DRTB stigma

Introduction

Background

Tuberculosis (TB) exists in every part of the world. Approximately 25% of the world's population has latent TB and is at risk of developing the disease during their lifetime [1]. Accordingly, about 10 million people fall sick with this disease each year, two-thirds of whom are in Bangladesh, China, India, Indonesia, Nigeria, the Philippines, and South Africa [1]. Meanwhile, drug-resistant tuberculosis (DRTB) is the highest in China, India, and Russia, while 9 of the 30 countries with the highest DRTB burden are within the European region [1].

With over a million people becoming ill with DRTB each year, the disease is considered a significant contributor to drug resistance worldwide [2]. In 2021, overall, 3.6% of new TB cases and 18% of previously treated patients were resistant to at least 1 anti-TB drug [3]. However, DRTB has become more challenging as the number of people previously treated for the disease had declined because of COVID-19 pandemic–related disruptions to TB service delivery. In 2021, the burden of DRTB increased by 3%, with 450,000 new cases [3]. As the increasing incidence of DRTB burdens public health, the country's economic security is threatened. Treatment of DRTB is prolonged and requires new-generation drugs, making it financially burdensome [4]. Additionally, the DRTB treatment success rate is lower than for new TB cases.

Ending the TB epidemic by 2035 is one of the priority goals of global health organizations. However, attaining this goal requires an urgent action that will accelerate efforts to diagnose, treat, and prevent TB (including DRTB). Such efforts can be achieved strategically by focusing on cutting-edge research and innovation, improving drug resistance surveillance, and strengthening public-private partnerships [3]. In the community, essential services such as case finding, diagnosis, treatment, health promotion and education, and psychosocial support are among the current strategies used to reduce the disease burden [1]. Central to these activities are the health workers, where DRTB essential services are integrated into community health services and directed toward patient-centered care [5]. Patient-centered care involves clinical service delivery and provides support for the patient's social and economic conditions that increase the burden of DRTB, such as malnutrition, poor housing, and financial and geographic barriers to health care access. In addition, it provides a holistic approach by incentivizing patients, treatment supporters, and health care providers [6].

The burden of DRTB is a multifaceted health challenge and social issue [6,7]. Medications for DRTB are more toxic and expensive [8], and the risks and treatment outcomes are influenced by various determinants and are commonly associated with stigma [9,10]. Stigma is the negative evaluation of oneself tainted by a particular attribute, making one constantly unsure how others will identify or receive it [11]. In terms of stigma in health, patients and communities distinguish and label various health conditions, views, and perceptions differently. As such, stigma influences community norms, interpersonal relations, and health institutions' culture [12,13].

A growing area of research has evidenced the stigma associated with DRTB. Datiko et al [14] posited that stigmatization of TB (including DRTB) affects prevention, care, and treatment. As a result, TB-related stigma contributes to the increasing DRTB burden and is a crucial predictor of its high incidence [15], and thus, warrants reduction interventions [9]. Tackling DRTB stigma is significant because it affects the quality of life of people affected by the disease and, in part, confronts health workers [16-18]. In health care, for health workers delivering essential services, the stigma surrounding TB (in general) is commonly associated with the "dirty work" stigma [19]. Hughes (1962) referred to dirty work as tasks and occupations perceived by the community as disgusting or degrading.

Current literature reviews on TB-related stigma suggest that most studies are geared toward understanding stigma among patients and their families. For example, in their qualitative review, Juniarti and Evans [20] explored stigma and the impact of either having TB, or a family member having TB. Craig et al [21] mapped TB stigma research and found that the majority of studies aimed to assess the knowledge, attitudes, and beliefs regarding TB (including DRTB) in low-incidence countries. The review of Sommerland et al [22] evaluated TB stigma–reduction interventions within the community. Notably, their reviews generally highlight the impact of TB stigma on individuals and communities. However, the growing evidence of DRTB-related stigma among health workers requires attention. There is a need to better understand the stigma surrounding the disease and how it is currently addressed in health facilities.

We conducted a preliminary search of MEDLINE, the Cochrane Database of Systematic Reviews, and Joanna Briggs Institute (JBI) Evidence Synthesis and found no current systematic reviews or scoping reviews underway on DRTB-related stigma among health workers. Using Arksey and O'Malley's [23] methodological framework and the recommendations of Munn et al [24], we will conduct a scoping study to examine the literature about the stigma of health workers delivering services for DRTB, explicitly examining the facets of disease stigma. Stangl et al [25] mentioned that the facets of stigmatization primarily constitute drivers and facilitators (eg, government policies, institutional support, and exaggerated fear) that influence disease outcomes among affected populations, organizations, and institutions. This scoping review will provide an overview of the aspects of DRTB-related stigma confronting

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health workers and other relevant information. The result of this review could help inform appropriate responses toward stigma-reduction interventions for these health workers. This is significant because interventions addressing related TB (and DRTB) stigma in the workplace are lacking [9]. Nyblade et al [26][26] stated that it is crucial to sustainably address this issue, from national to facility levels, because it undermines the delivery of quality health care and successful health outcomes.

Review Question

Based on our objective, the overarching research question in this review is: "What aspects of DRTB-related stigma are confronting health workers in high TB- and DRTB-burden countries?" We will consider subquestions:

- What are the stigma drivers confronting the health workers, and what is the most common stigma driver?
- What are the stigma facilitators confronting the health workers, and what is the most common stigma facilitator?
- What stigma-reduction interventions are recommended in the study?

Methods

We will apply the JBI scoping review methodology and use the features and functionalities of the JBI System for the Unified Management, Assessment, and Review of Information (SUMARI) [27] web-based software tool throughout the review process. The scoping review is registered with OSF Registries.

Inclusion and Exclusion Criteria

Our review will apply the Participants/Concept/Context criteria recommended by Peter et al [28]. The eligibility criteria for this review will be as follows.

Participants

The participants in the study are health workers, including physicians, nurses, midwives, medical technologies, pharmacists, and other allied professionals in health care settings such as hospitals, clinics, community centers, and TB treatment facilities delivering DRTB services such as case-finding, screening, diagnosis, treatment, and prevention.

Concept

This review will include evidence of the stigma of health workers delivering services to patients with DRTB. Concepts to be examined are stigma drivers and facilitators, including but not limited to beliefs, fears, lack of awareness about the DRTB and stigma, inability to clinically manage the condition, negative attitudes, and institutionalized procedures or practices.

Context

This review will consider available data from countries identified in the World Health Organization's list of high TB- and DRTB-burden countries (Table S1 in Multimedia Appendix 1). Any article whose study participants are not included in the list will not be considered. To be eligible, stigma confronts the health worker delivering services to patients with DRTB. Studies in which the context of stigma relates to drug-susceptible TB (DSTB), DRTB patients, and their families will be excluded from the review. We will also exclude sources coming from opinion articles, commentaries, or editorial reviews.

Types of Sources

We will consider qualitative, quantitative, and mixed study designs, including descriptive observational studies, case reports, and gray literature on stigma confronting health workers delivering essential services to patients with DRTB. Peters et al [29] noted that one crucial point in scoping reviews is to draw upon data from any source of evidence and research methodology; thus, identifying articles for a scoping review will be less restrictive. As a result, an appraisal of the methodological quality of the available evidence on health workers' stigma in this scoping review will not be performed. As mentioned, we could not find any systematic or scoping reviews on this topic. However, if any review is found as a result of a rigorous literature search in this study, those that meet the inclusion criteria will also be considered, depending on the research question.

Search Strategy

This review will locate published articles using the 3-step search strategy recommended by the JBI scoping review guidelines [28]. We first conducted a pilot search of the PubMed and EBSCO databases to identify articles on the topic using Medical Subject Headings terms and keywords. In the next step, we will create a search protocol using the identified text terms in the titles, abstracts, and keywords and use the protocol to develop a full search strategy for CINAHL and MEDLINE (Table S2 in Multimedia Appendix 1). To enhance our search strategy, we will seek expert advice from university librarians to develop a search protocol that will be used to retrieve potentially relevant articles from the databases. The search strategy will be applied to Cochrane, ProQuest, Scopus, Web of Science, and other databases and information sources. Finally, we will search for gray literature and additional resources in electronic sources such as Google Scholar, ProQuest Dissertation, Open Access Theses and Dissertations, Networked Digital Library of Theses and Dissertations, and researchgate.net.

Study Selection

After the initial search, all identified citations will be collated and uploaded to EndNote X9, de-duplicated, and imported to JBI SUMARI. Two independent reviewers will subsequently screen the titles and abstracts to assess the inclusion criteria for the review. We will retrieve potentially relevant sources for full-text screening to confirm the eligibility of the study for analysis. Any study that includes stigma associated with DRTB and health workers will qualify for the analysis. The bibliographies of studies meeting the inclusion criteria will be scanned to identify additional articles eligible for inclusion. Any disagreements between the reviewers at each stage of the selection process will be resolved through discussion or with an additional reviewer. The scoping review will record and report reasons for excluding sources of evidence in the full text that do not meet the inclusion criteria.

Data Charting

We developed a draft extraction chart (Table S3 in Multimedia Appendix 1) that will be piloted to examine results from 3 to 5

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articles. The piloting is aimed to ensure that the extraction chart captures all relevant information to satisfy the scoping review objectives and questions. The data extraction chart includes specific details about the participants, concept, context, study methods, and key findings relevant to the review questions. Henceforth, to ensure comprehensive coverage in the literature search, the search process will be iterative and require reviewers to engage reflexively [23]. We will have an opportunity to modify and revise the data extraction chart at this stage to suit our needs. Once all the reviewing team members are satisfied with the pilot charting, the 2 independent reviewers will use the finalized chart to extract relevant data from the identified studies. The reviewers will detail the modifications in the scoping review. If appropriate, we will contact the authors of papers to request missing or additional data, where required.

Data Analysis and Presentation

We will use the Preferred Reporting Items for Systematic Reviews and Meta-analyses extension for scoping review flow diagram [30] to report the review search and inclusion pathway. First, the details of the included articles will be summarized and presented in tabular form outlining the authors, year of publication, settings, outcome measures, and main descriptions of the results to provide an overview of the extent, nature, and distribution of the studies in this scoping review. Second, we will present a summary list of findings with illustrations and narratives. Third, we will thematically synthesize the key findings of the studies and will present a graphic diagram following the aspects of DRTB stigma (stigma drivers and facilitators) identified in the research questions of this scoping review. Lastly, we will provide a summary of our findings and describe how the results relate to the objectives and questions of this scoping review.

Results

This study commenced in October 2021. After conception, this scoping protocol was registered in OSF to promote transparency in our research and prevent duplication by others. The protocol refinement was completed in December 2021, and soon after, a pilot search of the PubMed and EBSCO databases was performed to inform the search strategy's development. The study has retrieved 593 abstracts out of 12,138 articles searched since February 2022 from the identified databases. This study is expected to finish in 2023. The findings of this study will be published in a peer-reviewed journal.

Discussion

Principal Findings

The stigma surrounding DRTB is a growing concern. Research has shown that frontline health care workers delivering DRTB services are affected by such stigma, so it requires attention [9]. In scanning the literature, gaps emerged as most interventions were geared toward patients with DRTB and their families, less toward health workers. Also of note was the focus of reviews on DSTB-associated stigma in health facilities. As of yet, no literature review summarizing the stigma surrounding DRTB among health workers has been found.

Addressing the multiple facets of stigma from national to facility levels is important for a sustainable response to stigma. At the facility level, there is increasing recognition to target the primary factors—the drivers and facilitators—that constitute the stigmatization process. Akin to stigma-reduction interventions for patients and their families that primarily result from an understanding of the factors contributing to the stigma process, DRTB stigma–reduction interventions for health workers likewise require critical analysis of what drives and facilitates the stigmatization. However, unlike patients and their families, where beliefs and lack of knowledge of the disease are common stigma factors, the stigma among health workers could be originated from a range of other factors. Such factors could include innate disease characteristics (eg, being a potent version of TB), and certain features from within the health facilities (eg, institutional policies) and from individual health workers (eg, attitudes and behaviors) [25]. Without an analytic study, intervention reduction efforts for health workers could be undermined.

This scoping review is part of a bigger project that will critically investigate stigma among health workers delivering services to patients resistant to TB medications in the Philippines. This study will provide an overview of the health workers' stigma surrounding DRTB by explicitly examining the available literature regarding drivers and facilitators contributing to disease stigma, and how it is currently addressed. The findings of this review will offer insights that could help inform appropriate responses toward stigma-reduction interventions for these health workers. Moreover, being part of a bigger project, this review's findings could also be valuable in the translation and implementation of stigma-reduction measures.

A limitation of this review is its inclusivity in time, language, and place of study; thus, it will only capture part of the picture regarding the stigma associated with DRTB and health workers. Also, the methodological quality of the searched literature will not be assessed. However, the results of this review will inform knowledge users, researchers, DRTB program managers, and implementers to identify key factors leading to stigma among health care workers. The findings of this scoping review will be disseminated through conference and webinar presentations and peer-reviewed journal publications. Should there be modifications to the protocol after its publication, we will provide the details and rationale for the changes, including the dates.

Conclusions

This review will provide an outline of aspects of DRTB-related stigma confronting health workers. The findings of this review could help inform appropriate responses toward stigma-reduction interventions for these health workers. This is significant because interventions addressing related TB (and DRTB) stigma in the workplace are lacking and such interventions are likely to have a positive impact on both patient care and patient outcomes.

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Acknowledgments

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Data Availability

All data sets generated and analyzed in this current study will be made available on the Open Science Framework (OSF) website.

Authors' Contributions

LA conceived the paper, conducted the initial search, designed the search strategy, and drafted the protocol. KA, RAM, and PG will verify the articles, and review and edit the manuscript. All authors contributed to the revision and finalization of this manuscript. All authors have read and approved this manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
DRTB scoping. DRTB: Drug-resistant tuberculosis.
[DOCX File , 20 KB - resprot_v12i1e43084_app1.docx]

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Abbreviations

DRTB: drug-resistant tuberculosis
DSTB: drug-susceptible tuberculosis
JBI SUMARI: Joanna Briggs Institute System for the Unified Management, Assessment, and Review of Information
OSF: Open Science Framework
TB: tuberculosis

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Protocol

Analyzing the Perspectives of Health Professionals and Legal Cannabis Users on the Treatment of Chronic Pain With Cannabidiol: Protocol for a Scoping Review

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Abstract

Background: Medical cannabis is one of the most commonly reported treatments for chronic pain. The wide acceptance and research in alternative medicine have put medical cannabis in the limelight, where researchers are widely examining its therapeutic benefits, including treatment of chronic pain.

Objective: The purpose of this scoping review is to provide an overview of the perspectives on cannabidiol as an alternative treatment for chronic pain among health professionals and legal cannabis users.

Methods: The framework of Arksey and O'Malley guides the design of this scoping review, and the elements reported use the recommended guidelines of the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews). A comprehensive literature search accessed the databases CINAHL Complete and MEDLINE via EBSCO, Australia/New Zealand Reference Centre, PsycINFO, Ovid Emcare, Wiley Online Library, Scopus, Informit New Zealand Collection, and Google Scholar for published literature, and then it was extended to include gray literature. Gray literature searches included searching the databases Australia/New Zealand Reference Centre, Informit New Zealand Collection, INNZ: Index New Zealand, ProQuest Dissertations & Theses Global, and AUT Tuwhera Research Repository, and the website nzresearch.org.nz. The studies included in this scoping review were assessed for eligibility for inclusion using the following criteria: published in English after 2000, conducted in New Zealand (NZ) or Australia, and aimed to investigate the perspectives of health professionals and medical cannabis users using interviews for data collection. Studies were screened for inclusion using Covidence, a software tool to filter search results, and the risk of bias was assessed using the Critical Appraisal Skills Programme tool. Although this is not a required step for scoping reviews, it added an element of strength to this scoping review. Data will be analyzed using thematic analysis guided by Braun and Clarke. The findings from the data analysis will be presented in a table, which will then inform the key themes for discussion.

Results: The database search started in October 2021 and was completed in December 2021. The total number of studies included in this review is 5 (n=5). Studies included were conducted in NZ or Australia and examined the perspectives using participant interviews. This scoping review is anticipated to be submitted for publication in December 2022.

Conclusions: Using perspectives is a valuable tool to understand the challenges experienced by health professionals and medical cannabis users associated with medical cannabis treatment. Addressing these challenges through interventions that are highlighted through perspectives such as educating health professionals to increase access to medical cannabis in NZ may aid in policy

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reformulation for medical cannabis in the context of NZ. Thus, this scoping review highlights the importance of medical cannabis research and suggests recommendations to guide and inform medical cannabis policy in the context of NZ.

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KEYWORDS

CBD; cannabidiol; medicinal cannabis; medical cannabis; chronic pain; pain; perspectives; opinions; health professionals; medical professionals; users; medicinal cannabis users; medical cannabis users; New Zealand; NZ

Introduction

Overview

Medical cannabis is one of the most reported treatments for chronic pain [1,2]. Chronic pain is one of the most disease-burdening conditions in the world [3,4], which is estimated to affect 1 in 5 adults of the world's general population [5]. Opioids are currently the preferred method of treatment, trusted by physicians to manage chronic pain [6]. However, although opioids are readily attainable and a preferred method of treatment, there is excessive use of opioids globally as more people access opioid prescriptions for chronic pain management [7]. The commonly reported reasons for researching opioid alternative treatments are opioid-related drug abuse, overdosing, associated risks, and high prescription rates [8].

Medical cannabis, or *Cannabis sativa* L. (*C sativa*), is a plant of the Cannabaceae family, which has properties that are particularly interesting to researchers for their therapeutic benefits as alternative treatments for varying chronic conditions including chronic pain [9]. It comprises 2 elements: delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD). THC is the psychoactive compound, consuming which produces a "high" as it alters the functioning of the central nervous system (CNS). CBD, however, tends to be the focus of modern-day research for its medical benefits when consumed in small doses. The exact mechanism of how CBD works in the body is unclear. However, it is known to activate the body's internal endocannabinoids via the endocannabinoid system [10]. It is suggested that the neurotransmitters emitted from the CBD products bind to the cannabinoid receptors in the body's CNS and activate signals. The activated signals cause signal blocking, which results in relief from discomfort caused by medical conditions [10].

Background

In 2018, New Zealand (NZ) legalized medical cannabis by amending the Misuse of Drug Act 1975 to control the use of cannabis as medicine. In April 2020, the Medical Cannabis Scheme was implemented in NZ. The Medical Cannabis Scheme aims to allow qualifying users to access quality medical cannabis products. Currently, qualifying users are limited to only those diagnosed with multiple sclerosis [11]. However, chronic pain management is one of the more commonly proposed reasons to use medical cannabis [3,4]. While some studies show improvements when using medical cannabis for chronic pain [12,13], others have emphasized their apprehensions with study designs and research affiliations with pharmaceutical companies suggesting more positive applications [8,14-16]. Others explain that studies investigating the relationship between medical cannabis and chronic pain have a high prevalence of reporting bias, over-reporting of results, small sample sizes, short-duration outcomes, and short follow-up periods [8]. These concerns are further justified by similar concerns voiced by researchers who strongly argue for the need to expand research on medical cannabis and its use for chronic pain [16]. Overall, the findings from studies suggesting the effectiveness and efficiency of using medical cannabis as a treatment for chronic pain are considerably low, and therefore, further research is required [4].

Rationale

In addition to literature highlighting the inconsistencies of medical cannabis as an alternative treatment for chronic pain, seeking the opinions of health professionals and medical cannabis users may add another dimension to this body of evidence. The studies exploring the perspectives of health professionals and legal cannabis users using a government-standardized CBD product are limited. Previously, studies explored the perspectives of health professionals and medical cannabis users using surveys without performing participant interviews. Therefore, this scoping review adds a methodological dimension too [17-19]. Furthermore, when these studies were conducted, medical cannabis was not legal in NZ. Therefore, these studies have not examined a form of standardized CBD treatment legal for use in NZ. This highlights a possible limitation as the participants would have reported outcomes consuming substances from the black market.

For this reason, study results cannot be directly linked to chronic pain treatment with CBD, considering the unknown concentrations of CBD, THC, and other contaminants in black market substances. The perspectives of individuals with chronic pain who use medical cannabis and the perspectives of health professionals who prescribe medical cannabis are essential and should contribute to the clinical, social, economic, and political discussion of medical cannabis in NZ. This scoping review aims to examine the perspectives surrounding medical cannabis use to treat chronic pain among health professionals and legal cannabis users. This scoping review is being performed as part of a qualification intended for achievement by the primary author (PK), which is not reported in this scoping review protocol.

Overall Aim

This scoping review aims to provide an overview of the perspectives on CBD as an alternative treatment for chronic pain among health professionals and legal cannabis users.

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The specific objectives are as follows:

1. To search and synthesize literature on the perspectives of health professionals and legal cannabis users in treating chronic pain with CBD
2. To provide literature that will add to the current knowledge that may inform policy regarding prescribing CBD treatment for chronic pain in NZ.

Methods

Overview

The framework of Arksey and O'Malley [20] guides the design of this scoping review, and the elements reported will use the recommended guidelines of the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) [21]. Scoping reviews have become a popular tool for synthesizing evidence. Similar to a systematic review, a scoping review follows a structured process. A scoping study is practical when providing an overview of what is already known about a particular topic or in circumstances where the literature volume is broad and detailed. The most common reason to perform a scoping review is to identify and map the currently available evidence [20,22]. A useful aspect of performing a scoping review is when studies aim to identify themes and concepts reported and discussed in the literature on a particular topic. To address the purpose of this review, a scoping review is a better suited approach compared with a systematic review as it seeks to examine the perspectives of health professionals and legal cannabis users while identifying and mapping the currently available literature on medical cannabis and chronic pain [23].

Developing the Research Question

The search protocol was developed using the PICO(T) tool, developed by Richardson and Wilson [24], which comprises the components People, Intervention, Comparison/Control, Outcome, and Time. Scoping reviews have broad questions, as the general aim of a scoping review is to map the literature available on a topic. Therefore, 2 elements of the PICO(T) tool were used to formulate a broad question sufficient to perform a scoping review. The 2 elements of the tool that were used in formulating the question for this scoping review are population/problem (P) and intervention (I) [25].

Research Question

What are the perspectives of health professionals and legal cannabis users (population) about the use of medical cannabis (intervention) in treating chronic pain (problem)?

Searching the Literature

The literature search was performed from October to December 2021. In the initial stages of searching, there was no restriction on searching by geography; however, because of the number of results that were present for each search, the supervisors were consulted to narrow the search to studies limited to NZ and Australia. To our knowledge, this is the first scoping review to explore the perspectives of health professionals and legal cannabis users restricted to NZ and Australia. The decision to restrict the literature search by geographical location was taken given the nature of the study to explore the perspectives of health professionals and legal cannabis users where studies were limited. This scoping review also aims to add knowledge through a wider qualification to aid policy changes in NZ. Therefore, it is vital to explore the perspectives of health professionals and legal cannabis users to ensure informed policy change decisions in NZ. As a result, the literature search for this scoping review was restricted to NZ and Australia. In addition, reviewing the availability of literature without a geographical restriction is beyond the capability of the primary researcher in the time allocated for the completion of the intended qualification.

The databases that were searched included the following: CINAHL Complete and MEDLINE via EBSCO, Australia/New Zealand Reference Centre (EBSCO), PsycINFO, Ovid Emcare, Wiley Online Library, Scopus, Informit New Zealand Collection, and Google Scholar.

In addition to the databases listed above, gray literature was searched using platforms dedicated to this purpose. The platforms that were used to search gray literature included the databases and website listed as follows: Australia/New Zealand Reference Centre, Informit New Zealand Collection, INNZ: Index New Zealand, ProQuest Dissertations & Theses Global, AUT Tuwhera Research Repository, and nzresearch.org.nz.

The keywords and phrases used to search were kept the same for consistency. The keywords were often combined with truncation and Boolean search techniques. An example of the search string is presented in Textbox 1, and the full search string can be found in Multimedia Appendix 1. All the keywords used to modify the search during the database, gray literature, and website searches are presented in Textbox 2.

Textbox 1. An example of the search string used to search databases, gray literature, and websites.

Example of the search string used to search

CBD OR Cannabidiol* OR (Medical Cannabis) AND Pain OR (Chronic Pain) AND Perspective* OR Opinion* OR Experience* AND Professional* OR (Health professional*) AND (New Zealand) OR Aotearoa OR Australia

Example 1 of the search string used to search websites

Medical cannabis AND Pain

Example 2 of the search string used to search websites

CBD AND Pain AND New Zealand OR NZ

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Textbox 2. The search terms that were used to perform the database and gray literature search

CBD
CBD, Cannabidiol, Medical cannabis, Medicinal cannabis, Medical marijuana, Medicinal marijuana
Pain
Pain, Chronic pain, Neuropathic pain, Chronic condition, Non cancer chronic pain
Perspectives
Perspective, Opinion, Attitude, View, Experience, Lived experience, Knowledge User experience, Professional experience
Population
Professional, Health professional, Medical professional, User, Patient, Doctor, Nurse, Pharmacist
Geography
New Zealand, NZ, Aotearoa, Australia, Aus, Auz

Eligibility Criteria

Eligible studies were those published in English between 2000 and 2021 and were either qualitative or mixed methods studies using interviews. The recruited participants were 18 years or older and used medical cannabis for chronic pain, or chronic pain in conjunction with another condition. Also, studies were eligible to be included if they were conducted in either NZ or Australia and must have aimed to investigate the lived experience, perspectives, or opinions of health professionals of all categories, for example, general practice, mental health professionals, nurses, and medical cannabis users, specifically CBD.

Exclusion Criteria

Studies were excluded if they were conducted outside of NZ or Australia, did not use interviews, and used other methods of analyzing perspectives such as surveys. Studies focusing on medical cannabis for mental health–related disorders, those examining the efficacy of cannabis treatment, and recreational cannabis studies were also excluded from this review.

Screening or Selecting the Studies

After the search was completed in each database, the search results were exported as an RIS file into the reference manager EndNote X9. After all search exports from each database were completed, a final XML file was exported from EndNote X9 and imported into Covidence, a web-based software tool useful when performing a type of comprehensive literature review [26]. The purpose of the software is to aid in screening studies, data extraction, and quality assessment required to perform a full review [26,27]. The software Covidence was used in all stages to screen titles and abstracts for the first screen, the full-text screening stage where studies were either included or excluded, data extraction, and quality assessment of the studies included. The primary researcher (PK) completed the initial screening and selected the articles to be screened in the abstract screening stage. The second reviewer, also the secondary supervisor in this research project (DW), also individually screened the titles for abstract screening in Covidence. Although an appraisal of the literature is not required to be included in a scoping review, articles included in our scoping review will be critically appraised using the Critical Appraisal Skills Programme (CASP) tool. Appraising literature that is included in the review will aid in further identification of research gaps.

The quality assessment was performed in Covidence. At this stage, the template provided by Covidence was customized to suit the data present in qualitative studies, adapting it to the CASP checklist for qualitative studies [28]. The CASP tool is a simple tool that can be used to appraise the strengths and limitations of qualitative research methodology. CASP is commonly chosen among novice researchers as the tool is user friendly and easy to understand. It was created for appraising health-related research and is endorsed by Cochrane and the World Health Organization for use in qualitative evidence synthesis [29,30]. It is for these reasons that CASP was selected as the most appropriate tool to be used in this scoping review.

The full-text screening was completed by both the primary researcher (PK) and the second reviewer (DW) in December 2021. Data extraction and CASP were initially completed by the primary researcher (PK) and reviewed by the second reviewer (DW). The third reviewer, also the primary supervisor of this project (CM), was assigned to resolve conflicts after discussions at each stage. However, no conflicts were present throughout the stages of progress. Therefore, the third reviewer's involvement was not required in the process. At the completed full-text screening stage, five studies met the eligibility criteria to be included in the review (Figure 1). Considering the low number of studies (n=5) to be included, the researcher consulted with supervisors to seek advice to proceed. The consensus was reached to expand to include more gray literature. The search results yielded from the gray literature search and selection process of results are shown in Figure 2.

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Figure 1. PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) flow diagram of the study selection process from databases.

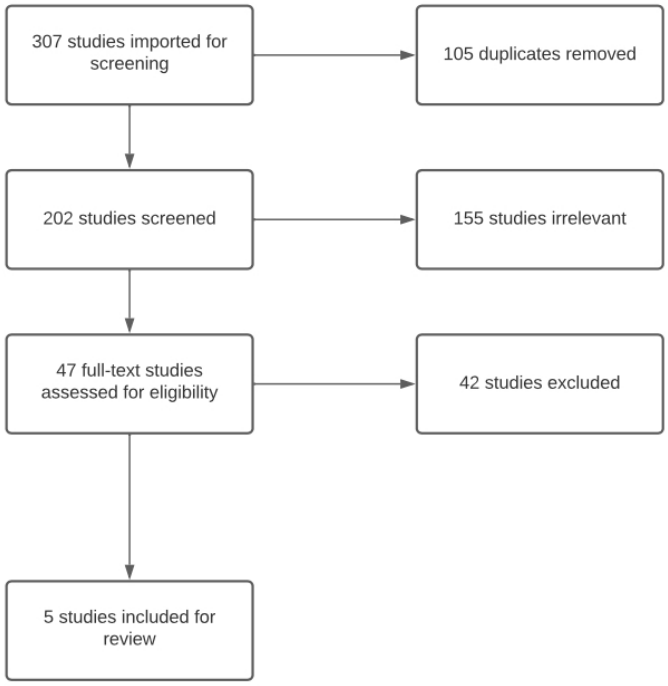
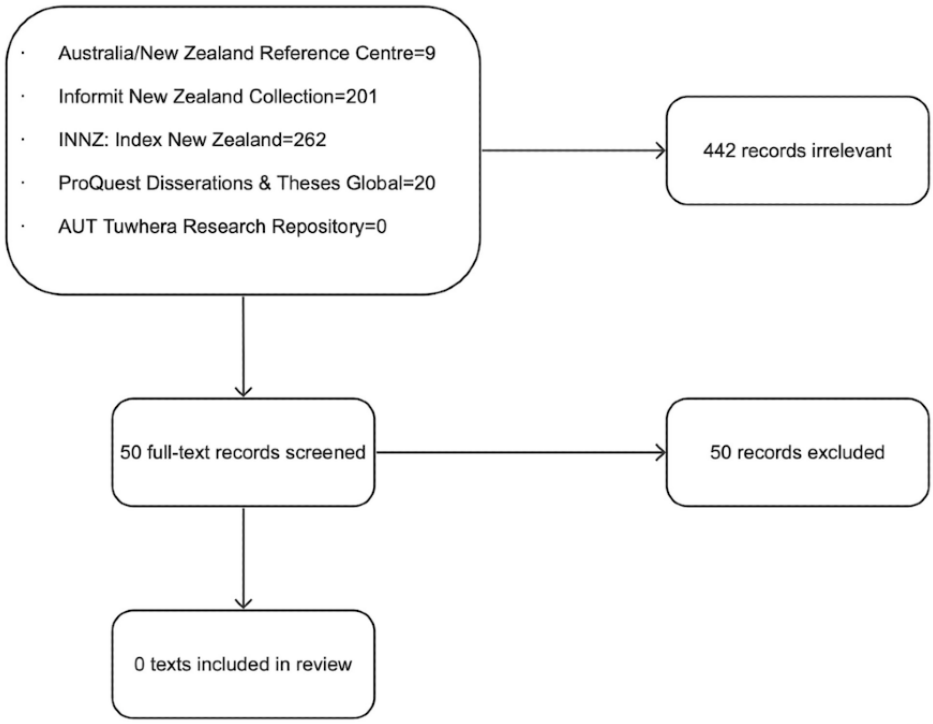


Figure 2. Flow diagram of the study selection process from gray literature.



Data Analysis and Presentation

The findings of this scoping review will be presented in a tabular format. The articles included in the review will be summarized and displayed in categories describing the studies included in the full review. Analysis of the results will consist of a narrative synthesis to link the results and research objectives using thematic analysis guided by Braun and Clarke [31], a commonly used technique suitable for analyzing qualitative literature. The data analysis will be carried out by the primary researcher (PK) and will be validated by the primary (CM) and secondary (DW) supervisors. The template to extract the relevant data from the included studies and the description of information that will be extracted are presented in Textbox 3.

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Textbox 3. Template for data extraction.

Study
Description of information being extracted: the title and reference of the study
Country
Description of information being extracted: identify the country in which the study was conducted
Design
Description of information being extracted: details of the study design, methodology, and research frameworks
Participants
Description of information being extracted: details of the participants, number of participants, age, etc.
Main findings
Description of information being extracted: results of the study, highlights, limitations, and conclusions

Results

An initial search of the databases was conducted in October 2021. After consulting with the supervisory team (CM and DW) for this project to continue, the search was completed in December 2021. We anticipate that the full scoping review will be completed in December 2022, as this scoping review is part of a qualification that the researcher PK is currently undertaking. The full scoping review is anticipated to be submitted for publication in December 2022.

The scoping review includes 5 articles in the initial review. The process of finding the articles to be included in the review is presented in Figure 1, which shows the PRISMA-ScR flowchart. Of the final articles included, one article is a study performed in NZ, while the others were performed in Australia. All five studies included in the scoping review were qualitative studies conducted by interviewing participants and had the common aim of understanding perspectives. Four of the articles explored medical cannabis–related perspectives, while one explored the use of opioids in the population of pharmacists. Although this study is not directly related to medical cannabis perspectives for pharmacists, the themes present in the study are associated with the aim of this scoping review and will contribute valuable insights to the discussion.

The databases Australia/New Zealand Reference Centre, Informit New Zealand Collection, INNZ: Index New Zealand, ProQuest Dissertations & Theses Global, and AUT Tuwhera Research Repository were searched along with the website nzresearch.org.nz. This website enabled searching of theses, dissertations, and academic articles produced at educational institutes throughout NZ. The databases did not reveal relevant information specific to this scoping review. The search for gray literature was performed after consultation with supervisors to find more texts relevant to the aim to be included in the full review. However, the search results were unable to yield results related to the topic of this review (n=0). Given the limited timeframe to complete the scoping review as part of a qualification for the primary author (PK), the supervisory team agreed that data saturation was reached at this stage of the literature search.

Discussion

To our knowledge, this is the first scoping review to explore legal cannabis users and health professional perspectives to treat chronic pain with medical cannabis in NZ and Australia since the rollout of medical cannabis in both countries. Studies that have been previously conducted on medical cannabis occurred before medical cannabis legalization and mostly used surveys [17,32-36]. This makes our review focusing on regulated and prescribed medical cannabis products using interviews unique as it examines perspectives to develop themes that highlight the research gaps and challenges to accessing medical cannabis relevant to NZ. The developed themes discussed in this scoping review may highlight why medical cannabis users prefer medical cannabis over other first-line treatments and aid in improving medical cannabis treatment for chronic pain in NZ.

This scoping review highlights the current barriers for patients using medical cannabis through their health system experience. These outlined barriers may assist in proposing recommendations that may guide policy shifts in NZ and suggest future study directions. These suggestions will be formed from the themes that arise from this scoping review results, such as spillover effects of medical cannabis, the impact of medical cannabis on the youth, the existing barriers to accessing medical cannabis treatment, for example, the associated treatment costs, the limited knowledge of health professionals to recommend medical cannabis treatment, and the stigma associated with medical cannabis use.

The suggestions and recommendations in this review will focus on highlighting and addressing the barriers identified through perspectives to improve the future of accessing medical cannabis in NZ. Suggestions may include improvements to education of health professionals in other countries and the effects of education in medical practice, for example, achieving higher prescription rates to access medical cannabis for users through the health system that may improve access to medical cannabis. Increasing education among health professionals and increasing access to medical cannabis using the health system may also reduce the stigma surrounding medical cannabis use. Other suggestions may include conducting a study examining the perspectives of health professionals and legal CBD users in NZ to understand the reasons for using medical cannabis. A future

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study in this direction may highlight the challenges experienced by health professionals and medical cannabis users in NZ. Therefore, studying the perspectives of health professionals and medical cannabis users to suggest recommendations may aid in informing knowledge for NZ policy makers that may provide better access to medical cannabis and guide future policy making on medical cannabis in NZ.

The future directions of this study will include suggesting the current research that the primary author (PK) is undertaking, which includes interviewing medical cannabis users and health professionals to examine CBD user perspectives in NZ and highlight their experiences of using medical cannabis through the NZ health system. This research will follow the suggestions of this scoping review and interview participants that may provide valuable information to guide policy reformation of medical cannabis in NZ.

Limitations

The inclusion criteria for this scoping review are limited to studies that use qualitative methods. Therefore, the results may not represent the broader population of perspectives studied using other methods, for example, surveys. However, this scoping review will recommend a future study in NZ that uses interviews to add knowledge that examines the reasons for using medical cannabis in NZ. We also recognize that limiting the scoping review to include studies from only NZ and Australia may not represent the body of knowledge that exists on medical cannabis user and health professional perspectives globally. However, it is essential to note that this scoping review aims to provide suggestions for policy recommendations in NZ. Therefore, it contributes to the currently limited evidence for the country for which recommendations are being suggested.

Conclusions

The conclusions of this scoping review will summarize the importance of medical cannabis and the reasons for its use among medical cannabis users and health professionals using perspectives. A summary of the evidence discussed will be an important component to reinforce the success of addressing the overall aim. The challenges highlighted through the discussions of this scoping review include access to medical cannabis due to the associated treatment costs, the limited knowledge of health professionals to recommend medical cannabis treatment for chronic pain, and the stigma associated with its use.

These elements indicate that using perspectives to understand the reasons for medical cannabis use may enforce policy changes that address the current challenges in NZ for chronic pain treatment with medical cannabis. Through this scoping review, the importance of implementing interventions that educate health professionals to increase access to medical cannabis using the health system may address a significant barrier, for example, the limited knowledge of health professionals to prescribe medical cannabis. Additionally, this scoping review may suggest introducing a wider selection of medical cannabis products into the NZ market. Introducing new products may reduce the associated costs of treatment through competition and will increase product variety for consumers that are currently limited.

Highlighting the concerns raised by health professionals and medical cannabis users may reinforce the importance of medical cannabis research using perspectives. The same is demonstrated through the overall aim of this scoping review that highlights the importance of understanding perspectives to contribute to effecting a positive change for the future policy reformation of medical cannabis in the context of NZ. Future research directions undertaken by the primary author (PK) will be summarized. The summary will acknowledge the contribution of the research currently being undertaken as a valuable contribution to advancing medical cannabis research using perspectives in NZ that may contribute to future policy reformation for medical cannabis in NZ.

Acknowledgments

This protocol and the subsequent review will contribute toward the primary author's (PK) Master of Public Health degree. The wider project that is being undertaken by the primary author (PK) is being supported by a research budget from the Auckland University of Technology and the dedication and guided direction of the primary (CM) and secondary (DW) supervisors.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search string used to perform the search for published literature in electronic databases.
[PDF File (Adobe PDF File), 40 KB - resprot_v12i1e37697_app1.pdf]

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Abbreviations

CASP: Critical Appraisal Skills Programme
CBD: cannabidiol
CNS: central nervous system
NZ: New Zealand
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews
THC: delta-9-tetrahydrocannabinol

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Protocol

Updating the Data on Malaria Vectors in Malaysia: Protocol for a Scoping Review

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Abstract

Background: Malaria is still a public health threat. From 2015 to 2021, a total of 23,214 malaria cases were recorded in Malaysia. Thus, effective intervention and key entomological information are vital for interrupting or preventing malaria transmission. Therefore, the availability of malaria vector information is desperately needed.

Objective: The objective of our study is to update the list of human and zoonotic malaria vectors in Malaysia. This work will include (1) the characterization of the key behavioral traits and breeding sites of malaria vectors and (2) the determination of new and potential malaria vectors in Malaysia. The findings of our scoping review will serve as decision-making evidence that stakeholders and decision makers can use to strengthen and intensify malaria surveillance in Malaysia.

Methods: The scoping review will be conducted based on the following four electronic databases: Scopus, PubMed, Google Scholar, and Science Direct. A search strategy was conducted for articles published from database inception to March 2022. The criteria for article inclusion were any malaria vector–related studies conducted in Malaysia (with no time frame restrictions) and peer-reviewed studies. The PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) will be used to guide our systematic approach. Data from published research literature will be extracted by using a standardized data extraction framework, including the titles, abstracts, characteristics, and main findings of the included studies. To assess the risk of bias, articles will be screened independently by 2 reviewers, and a third reviewer will make the final decision if disagreements occur.

Results: The study commenced in June 2021, and it is planned to be completed at end of 2022. As of early 2022, we identified 631 articles. After accessing and evaluating the articles, 48 were found to be eligible. Full-text screening will be conducted in mid-2022. The results of the scoping review will be published as an open-access article in a peer-reviewed journal.

Conclusions: Our novel scoping review of malaria vectors in Malaysia will provide a comprehensive evidence summary of updated, relevant information. An understanding of the status of *Anopheles* as malaria vectors and the knowledge generated from the behavioral characteristics of malaria vectors are the key components in making effective interventions for eliminating malaria.

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KEYWORDS

malaria vector; Anopheles; Malaysia; scoping review; malaria; vector; transmission; prevention; entomology; eliminating malaria

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Introduction

Malaria is still a public health threat. The World Health Organization (WHO) recorded a total of 241 million malaria cases and 627,000 malaria deaths worldwide in 2020 [1]. Further, Malaysia recorded 23,214 malaria cases from 2015 to 2021, of which 87% were zoonotic cases [1]. Malaysia is facing increasing cases of zoonotic malaria due to *Plasmodium knowlesi*. The number of *P knowlesi* cases increased from 1960 to more than 4000 between 2016 and 2018. This number declined slightly in 2019 and 2020 (to 3213 and 2609 cases, respectively), but *P knowlesi* infection still resulted in 6 and 5 deaths in 2019 and 2020, respectively [1].

Malaria is caused by parasites of the genus *Plasmodium*. These parasites harm not only humans but also other vertebrate species, including birds, reptiles, and mammals. *Plasmodium* species that naturally infect humans and cause malaria in large areas of the world were limited to the following four: *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium malariae*, and *Plasmodium ovale* [2]. However, studies conducted by Cox-Singh et al [3], Piera et al [4], Siner et al [5], and Yek et al [6] confirmed that there is a fifth *Plasmodium* species responsible for zoonotic malaria—*Plasmodium knowlesi*.

Malaria is a vector-borne disease transmitted by *Anopheles* mosquitoes [7-9]. The WHO recorded 4500 species of mosquitoes worldwide in 34 genera from the family Culicidae, the order Diptera, the class Insecta, and the phylum Arthropoda [10]. Interestingly, only 70 species of anophelines were confirmed as malaria vectors around the world [10]. A total of 434 mosquito species have been recorded in Malaysia [11], including 75 species of *Anopheles* mosquitoes [12]. Previous studies recorded the following nine species of *Anopheles*, which were established as malaria vectors in Malaysia: *Anopheles balabacensis*, *Anopheles maculatus*, *Anopheles campestris*, *Anopheles sundaicus*, *Anopheles letifer*, *Anopheles donaldi*, *Anopheles dirus*, *Anopheles leucosphyrus*, and *Anopheles flavirostris* [12,13]. It is important to investigate potential malaria vectors when developing new technology for species complex identification. A potential malaria vector is defined by the vectorial capacity of a vector population to transmit malaria [14].

Malaysia is working toward eliminating malaria and preventing malaria re-establishment [15]. Effective entomological surveillance tools are the most important tools for interrupting malaria transmission [16-18], which can be achieved by designing a targeted control intervention based on the behavioral characteristics of malaria vectors [17,19-21]. For example, *Anopheles balabacensis* rests outdoors after feeding [22]. Therefore, vector control tools need to be developed for and applied on the walls of houses, tree trunks, bushes, or any possible resting places of *Anopheles balabacensis*, and existing outdoor vector control interventions should be strengthened. Our review will serve as a resource for informing entomologists, malaria personnel, and physicians about malaria vectors in Malaysia. Entomological information accelerates the process of malaria elimination by enhancing the impact and efficacy of the intervention needed [18]. The objectives of our study are to establish protocols for determining new and potential malaria vectors and to update the list of existing human and zoonotic malaria vectors in Malaysia.

Methods

Protocol Design

Our study will broadly cover the subject area—the nature of research activity on malaria vectors—in accordance with the 6-stage framework of Arksey and O'Malley [23], which was refined by Levac et al [24]. The six stages of the review process are as follows: (1) identifying the research question; (2) identifying relevant studies; (3) selecting studies; (4) charting the data; (5) collating, summarizing, and reporting the results; and (6) consulting with relevant stakeholders. The scoping review will adhere to the 22-item PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Review) checklist [25].

Stage 1: Identifying the Research Questions

In order to develop and identify the research questions, the subject area—the nature of research activity on malaria vectors—was examined. Thus, the following research questions were identified: (1) what are the established malaria vectors in Malaysia and (2) what are the potential malaria vectors in Malaysia?

Stage 2: Identifying Relevant Studies

A search strategy was conducted for articles published in scientific journals and peer-reviewed publications, using the following electronic databases: PubMed, Scopus, Google Scholar, and Science Direct. Relevant research websites, such as Portal Data Terbuka Malaysia [26], WHO websites, and Ministry of Health Virtual Library, were also searched.

Articles were identified by using Medical Subject Headings and keywords. Using a systematic approach, titles, abstracts, and keywords were searched, screened, and reviewed, and data were extracted. The search was not restricted by year or language. All selected search results were imported into Mendeley software (Elsevier) and Microsoft Excel spreadsheets (Microsoft Corporation) to manage references and duplicates.

Stage 3: Study Selection

All entomological research conducted in Malaysia will be included in the study, including longitudinal studies, cross-sectional studies, observational studies, and descriptive reports. The literature search was only conducted for peer-reviewed articles published from database inception to March 2022. The exclusion criteria for the scoping review are gray literature, annual reports, and bulletins. First, inclusion and exclusion criteria will be used to determine the eligibility of articles based on their titles during the screening portion of the review process. Any articles with titles indicating that the research was conducted outside of Malaysia will be excluded. Second, titles and abstracts will be selected based on eligibility criteria. Only abstracts that fulfill the inclusion criteria will be further analyzed. Finally, full-text articles that are selected based on their abstracts will be reviewed and included in the study if they are considered significant and relevant studies.

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Stage 4: Charting the Data

The significant study characteristics of published research literature will be extracted by using a standardized data extraction framework. Two independent reviewers will conduct the data extraction, and they will discuss any discrepancies or disagreements with a third reviewer. A data extraction framework was developed to guide the extraction and charting process for the data from the articles. It will consist of standard bibliographical information (title, author, journal, year of publication, language, location of the study, and study objectives). Additional information, such as the type of study, the primary outcome, and other valuable information, will be included as well. The framework will provide an overview of the significant information about the studies and facilitate data analysis.

Stage 5: Collating, Summarizing, and Reporting the Results

Our scoping review intends to present an overview of the study area, unlike a systematic review, which requires meta-synthesis reporting. Thus, we will report on the information we gather based on the selection criteria. Our study will summarize all of the data and information from relevant articles and will emphasize the scope of malaria vectors in Malaysia. Furthermore, gaps in research regarding specific study areas will be identified and determined. The study will use the PRISMA-ScR reporting guidelines to accurately report the scoping review and search results.

Ethical Considerations

Ethical approval is not required, as our study does not involve collecting data from human participants.

Dissemination

An article detailing the findings of the scoping review will be submitted to a scientific journal for publication. Study findings will be disseminated via open-access publications in peer-reviewed journals, presentations to stakeholders, relevant meetings, conferences, and continuous medical education at the department level, as well as future seminars and workshops. The published article will be included as part of a dossier for the Malaria Elimination Program of Ministry of Health Malaysia.

Results

The literature search was conducted in March 2022, yielding 631 malaria vector–related articles. A total of 48 studies were found to be eligible after accessing and evaluating the articles. As of early 2022, our scoping review reached the data synthesis stage. Results are expected to be published by the end of 2022 in a peer-reviewed journal.

Discussion

Malaria is incredibly harmful to very young children and low-income individuals [27]. The eradication of malaria is among the best returns on investments in public health and is very cost-effective [27]. In endemic nations, including Malaysia, initiatives for preventing and eventually eradicating malaria are increasingly seen as high-impact strategic investments that will benefit public health, reduce poverty, advance equity, and advance overall development [28].

Vector control is a crucial part of malaria prevention, control, and eradication programs due to its tremendous potential to improve personal protection and reduce disease transmission [29]. The ability of vectors to transmit parasites and their susceptibility to vector control techniques vary by mosquito species and are impacted by regional ecological parameters. Vector control must be implemented on the basis of local epidemiological and entomological data. Entomological surveillance and monitoring of the coverage and effects of vector control interventions must be included in national surveillance systems in order to provide an efficient vector control response [30].

The distribution of mosquitoes in Malaysia was last reviewed in 1997, with a focus on *Anopheles* mosquitoes, by Rahman et al [12], but their focus was not specifically on malaria vectors. Later, Vythilingam and Hii [13] outlined the malaria vectors in Malaysia, focusing on human malaria. The desired elimination of malaria is thought to be affected by extended delays in updating information on vectors. A systematic study conducted by Bertola et al [31] on the occurrence and bionomics of potential malaria vectors successfully supported the identification of 3 new potential vectors in Europe, along with a study conducted by Sinka et al [32]. Our scoping review will provide up-to-date insights on established and potential human and zoonotic malaria vectors, which we believe will contribute to the development of strategies for achieving malaria elimination in Malaysia. However, it is crucial that Malaysian researchers continue to study malaria vectors in order to make decisions about vector control measures that will help to eradicate the disease.

The lack of current information on malaria vectors in Malaysia indicates the need for more extensive research and the systematic compilation of entomological data. The development of effective malaria interventions, such as tools for selecting vector control options and strategies and managing vector control, as well as the acceleration of the certification of malaria eradication, can benefit from such information. However, a limitation of our study is the exclusion of any unpublished data, as we aim to ensure that the sources on which our findings are based are reputable by only including peer-reviewed studies in our scoping review.

Our novel scoping review of malaria vectors in Malaysia will provide a comprehensive evidence summary of the updated status of malaria vectors. An understanding of the status of *Anopheles* as malaria vectors and the knowledge generated from the behavioral characteristics of malaria vectors are the key components in making effective interventions for eliminating malaria.

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Acknowledgments

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Data Availability

Data sharing is not applicable to this article, as no data sets have been generated or analyzed during the study at this time.

Authors' Contributions

RA contributed to the study concept, developed the research questions and study methods, was involved in the data extraction process, and contributed to the drafting and editing of the manuscript. WNWMA was involved in the data extraction process and the editing of the manuscript, while PWP supervised the writing of the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews
WHO: World Health Organization

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Protocol

Occupational Health Hazards Among Traffic Police in South Asian Countries: Protocol for a Scoping Review

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Abstract

Background: Occupational health hazards and injuries are an alarming concern among traffic police. Occupational injuries affect the physical, social, and mental well-being of police personnel, which has various public health implications. The evaluation of occupational health and safety policies and regulations for the traffic police relies on their occupational exposure and health hazard statistics and assessments.

Objective: The purpose of this scoping review is to systematically explore, analyze, and describe relevant findings from all studies conducted on occupational exposure and associated health hazards among traffic police in South Asia.

Methods: The scoping review will include studies that assessed occupational exposure prevalence, types, knowledge, predisposing factors, and prevention strategies. Databases like PubMed, Springer Link, EBSCOhost, the Cochrane library, and Google Scholar will be used to obtain both published and unpublished works in the English language. Relevant gray literature, including governmental and international organization reports, will be examined. After removing duplicates and screening titles and abstracts, the full-text analysis will begin. Arksey and O'Malley's methodology framework for scoping reviews will be followed. According to Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews, the scoping review will be reported. Two qualified reviewers will independently conduct article screening and data extraction. The extracted data will then be tabulated and accompanied by an explanation to facilitate comprehension. We will extract relevant article results using NVivo (version 10; QSR International) and thematic content analysis. The included articles will be evaluated using the mixed methods appraisal tool (version 2018).

Results: The scoping review will provide insight into how occupational health hazards affect traffic police physically and psychologically in South Asia. The theoretical conceptualization of different aspects of the occupational health of traffic police will emphasize future studies in this region, which will inform policy makers to revise their occupational health and safety policies and principles. It will have implications for taking necessary preventive measures in the future to reduce occupational injuries and fatalities resulting from different types of occupational hazards.

Conclusions: This scoping review will describe the overview of occupational hazards among South Asian traffic police and will provide insights for policy makers to implement changes and to adapt new strategies.

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KEYWORDS

traffic police; occupational health hazards; occupational injuries; occupational exposures; South Asia; occupational; injury; psychosocial; well-being; prevention; database; policy

Introduction

Where there is unplanned urbanization, occupational- or work-related health risks related to environmental pollution have become a serious public health problem [1]. Workplace health risks include injuries, illnesses, and diseases that originate from a particular occupation and chronic exposure to certain chemicals or progressive physical actions. According to the International Labour Organization, 2.3 million individuals are injured at work every year. Moreover, each day, more than 6000 individuals die as a consequence of workplace accidents [2]. Occupational risks can cause fatalities and prolonged absences from work. Occupational hazards are estimated to cost the global economy 4% of the gross domestic product each year [3].

Traffic police perform crucial actions in maintaining the country's law, regulations, order, and safety-security. They are actively involved in managing the city's commutation system. They ensure that automobiles may travel freely on the road. Their responsibilities include controlling traffic on cross streets, settling roadside traffic disputes, and collecting penalties for breaking traffic regulations. Traffic police officers are continuously compromising their health for the general public and are more exposed to occupational hazards. Since occupation is a major determinant of health, traffic police personnel face multiple occupational hazards, and it has become a serious public health concern. Thus, duty-bound personnel like traffic police are continuously exposed to occupational health risks and hazards and experience severe related health problems [4]. A Canadian study reported that 42% (n=1500) of working Canadians had hazardous occupational noise exposure and 80% (n=373) of them used to wear hearing protection [5]. They are constantly and concurrently exposed to vehicular pollution, noise from vehicle honking, harsh weather conditions, and interpersonal tension between drivers and pedestrians. Traffic police can also get injured or killed due to car accidents and assaults. These can happen while driving, patrolling, or when police are dealing with violence, particularly in the context of South Asia. The possible occupational hazards for traffic police include respiratory illness, noise-induced hearing loss or impairment, skin diseases brought on by UV radiation, musculoskeletal disorders or backaches, psychological issues, occupational cancer, and other diseases [6].

Traffic police encounter a variety of occupational dangers, as one’s occupation is a major driver of one’s health [7]. A systematic review of 36 global studies among police officers concluded that traffic police officers were exposed to noise-induced hearing loss, dermatitis, cancer, posttraumatic stress disorder, and musculoskeletal disorders [8]. Another systematic review revealed that traffic police officers are one among those who are at risk of developing lung cancer due to environmental exposure to polycyclic aromatic hydrocarbons, benzene, and so forth [3]. According to a European study, air pollution is responsible for 6% of all deaths, whereas vehicular pollution is responsible for 50% of all deaths caused by air pollution [7]. Similarly, noise is one of the world's most common occupational health hazards, and the connection between excessive noise levels and noise-induced hearing loss (NIHL) is widely established. As traffic police officers spend most of their day exposed to noise and air pollution and remain in close proximity to the smoke and fumes emitted from vehicles, they experience air- and noise-induced illness. A cross-sectional study was conducted on the respiratory health status of traffic police in Dhaka, Bangladesh, and reported 84.4% of the respondents had different types of respiratory problems, such as cough, whistling problems, and breathlessness. About 3.1% of the traffic police had been experiencing asthma, and 9.1% of respondents had a history of parental lung disease [9]. A study in Mangaluru city, India, found that the prevalence of respiratory morbidity, eye symptoms, and ear problems were 51.2%, 61.6%, and 47.5%, respectively [4]. Research conducted in Patiala, India, showed that out of 100 traffic policemen, 68% had a frequent cough, 22% had shortness of breath, and 36% had irritation in the respiratory tract [10]. Another study conducted in Gujarat, India, studied the different disease prevalence in traffic police personnel and revealed that about 7% of traffic police personnel experience eye problems, 35.5% from blocked ear sensations, and 51.50 % from mild hearing loss, 13.6% from moderate and 0.90% from severe hearing loss. The most common physical problems include joint problems (62.65%), burning soles (42.37%), back pain (20.3%), and disturbed sleep patterns (16.3%) [11]. A study conducted among traffic police in Kathmandu found that 72.3% of the respondents had a complaint of burning eyes or tearful eyes. Ear ringing was reported by 37.8% of the study subjects [12]. Therefore, skin, respiratory, and eye problems were the most common physical problems seen among traffic police reported in another study in Kathmandu [13]. A Malaysian study reported that traffic police experience hypo- or hyperthermia, skin cancer, depression, lower back pain, asthma, NIHL, and so forth due to occupational exposure to major environmental hazards [14]. A study conducted in Hong Kong has assessed that 80% of traffic constables have reported exposure to environmental tobacco smoke, and the odds ratio of having respiratory systems is 20.4 times more in men as compared to women [15].

While dealing with heavy traffic congestion, traffic police become mentally and physically exhausted, making them susceptible to physical and mental stress, increasing with the duration of employment [6]. A study conducted in Kathmandu, Nepal, revealed a significant prevalence of mental health problems, such as depression (41.3%), anxiety (47%), and stress symptoms (44%), among traffic police officials. This study also

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reported that smoking and longer working hours were significantly associated with depression, anxiety, and stress [16]. About 73% of traffic police were reported with anxiety, while stress-related problems were identified among 40.6% in another study conducted in Kathmandu [13]. Poor pay, workload, and irregular working hours were stress factors causing psychological hazards among Malaysian traffic police [14].

Cardiovascular disease and cancer risk are also linked to traffic pollution [17]. The leukocyte telomere length might reduce in persons exposed to traffic pollution, resulting in early biological aging and an increased risk of developing coronary heart disease, heart failure, diabetes, cancer, and osteoporosis [18]. The time-weighted average exposure to benzene, a carcinogen, was generally higher for traffic police than indoor workers [19].

Many traffic police officers experience work-related musculoskeletal diseases, particularly in the lower back, neck, and shoulders [20]. Musculoskeletal issues related to work are the leading cause of absenteeism and decreased productivity [21]. Standing in a static posture for lengthy periods exposes them to ergonomic issues [22]. Overall, 12% (n=24) of the traffic police in Nepal were found experiencing varicose veins due to long-standing working hours [23]. Another study in Bengaluru, India, reported 60% of study participants had varicose veins associated with long standing hours [24]. An Indian study on traffic police officers reported disorientation in working schedule, fear of being vulnerable to disease, and pressure of maintaining law and order during the COVID-19 lockdown increased their stress level [25]. Job conflict, lack of autonomy, and organizational policies were found to significantly affect burnout among Islamabad traffic police officials [26].

This implies that traffic enforcers' occupational health and safety (OHS) is a critical public health issue, especially in South Asian countries.

Occupational health hazards may be preventable, and the majority of people are ignorant of them. As a consequence, a safety culture must be developed in the workplace. Occupational infection prevention and control training programs are developed at a local level by hospitals or at a national level by Ministry of Health and Professional Organizations in the United States and Australia [27]. New Delhi traffic police have various preventive measures and safety recommendations. They have extensive safety and skill training, they exercise often to stay fit and limit the risk of injury, they use personal protective equipment or other barriers for the duty, and they learn safe lifting techniques. They follow a recommended shift work pattern to protect themselves from the consequences of continuous long shifting hours. They receive first aid training to combat any emergency situation. Blood pressure checkups, cholesterol tests, and psychiatric screenings are provided as part of the Health Surveillance program to ensure general well-being of traffic police officers in New Delhi. Baseline health assessments are carried out before starting training or deployment to a specialty police duty [28]. According to another study conducted in Ahmedabad, traffic officers standing for a long period of time in hot and humid weather and their traffic intersections are not equipped with shade and existing uniform material for traffic police diminish the effectiveness of sweating. In order to deal with the heat, traffic officers drink lemon water, sugarcane juice, and buttermilk. They cover their faces with a handkerchief, which they also use to protect themselves from smoke from car exhaust [29].

In India, regarding OHS policies, key activities include reviews of the labor administration system at the national and state levels, and conduction of workshops to promote ratification of the International Labour Organization conventions on OHS [30]. Control measures being implied among traffic police through the OHS policy of Malaysia were job rotation, using earplugs if necessary to prevent NIHL, counseling by Religious and Counseling Division of the Royal Malaysian Police to prevent psychological hazards, following self-hygiene practices such as handwashing, using face masks, and so on [14]. In Bhutan, though the OHS laws are in place, the Department of Labour is still incompetent to implement the legislation fully. The situation is impaired resistance from employers and employees to comply with the OHS legislation and to adopt a safety culture [31]. The enforcement of OHS laws is being carried out through inspections, emphasizing on the prevention, protection, and promotion. Although the National OHS policy of Bangladesh has gaps, it includes multiple clauses based on international labor policy such as workplace safety, accident prevention, workplace environment and prevention of hazards, disease prevention, and safeguards. The policy stipulates the need to ensure workplace safety and health protection in the light of international conventions, to develop a strategy and action plan to ensure proper implementation of national laws, and to include OHS issues in the policies and programs of all related ministries and agencies [32].

Therefore, directly or indirectly, traffic police face a wide variety of health hazards at their working environment, namely, physical, biological, psychosocial, chemical, and ergonomic hazards. Thus, duty-bound personnel like traffic police get exposed to various occupational hazards with different work-related injuries or diseases that have profound public health implications. These identified impacts pose severe health and safety problems and require inculcating a safety culture in the workplace. After a careful search, limited studies were found focusing on occupational health hazards among traffic police officers in South Asian countries. However, a few relevant studies regarding OHS practices, and guidelines for traffic police officers were conducted in this region. Hence, the conduct of this scoping review is imperative to explore the knowledge gaps, prevalence, possible risk factors, and control or preventive measures of occupational health hazards among traffic police in South Asia.

The suggested scoping review will include studies conducted on the occupational health of traffic police. It will cover all aspects of health, including the physical, psychological, social, and environmental components in this vulnerable group related to their occupational exposure. Furthermore, risk factors causing these exposures, such as insufficient knowledge and preventive measure, will be explored. This study is directed to come up with a complete evaluation of the evidence on occupational hazards among South Asian traffic police.

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We will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) guidelines, use reliable tools to assess study quality [33,34], and propose a method to query the literature about the occupational exposures and health hazards among South Asian traffic police.

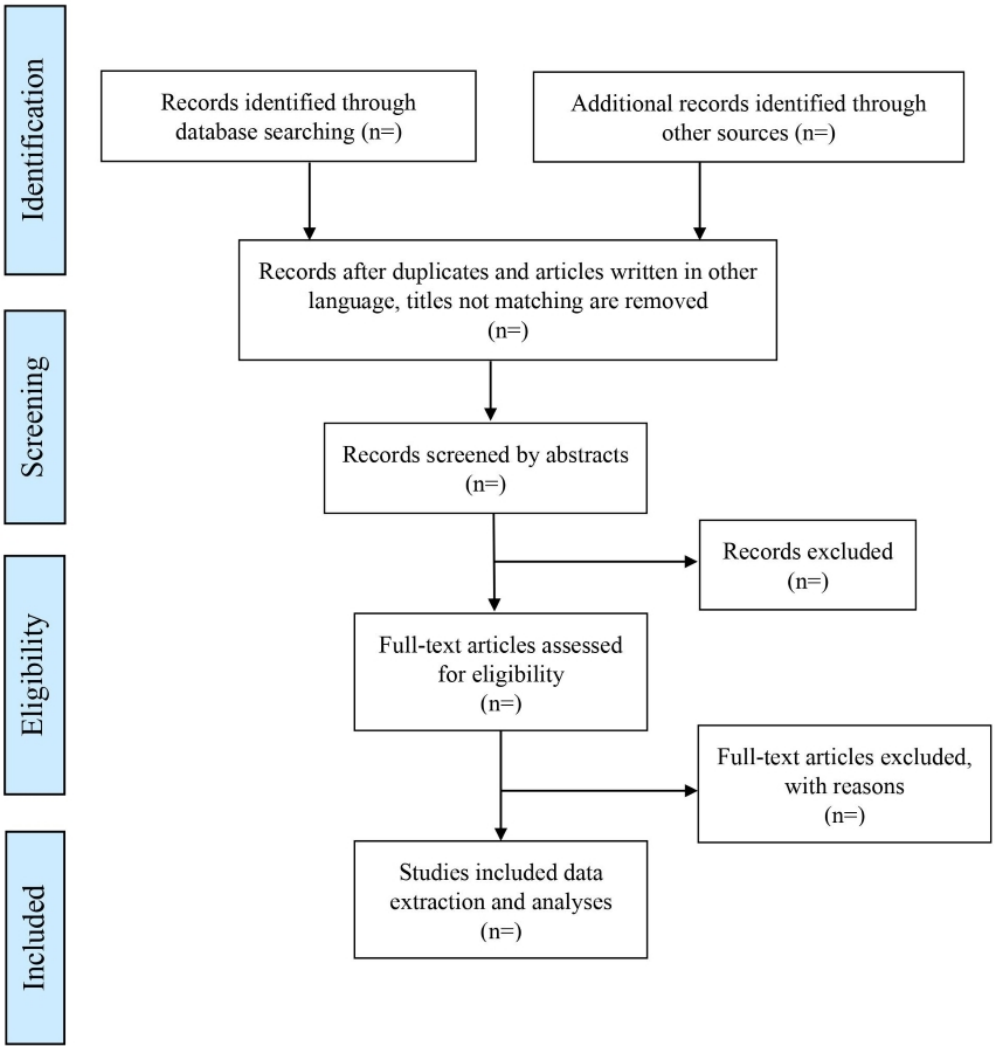
Methods

Protocol Design

This scoping review will synthesize all available information by systematic research, selection, and amalgam of current knowledge. The conceptual framework developed by Arksey and O'Malley [35] will be followed to develop this protocol. The development of a scoping review will involve six steps: (1) identifying research question; (2) identifying suitable publication or studies; (3) selection of studies; (4) data charting; (5) collating, summarizing, and reporting results; and (6) quality appraisal.

To assess the quality of the articles incorporated in the review, the mixed methods assessment tool, 2018 will be used [34]. NVivo (version 10) [36] will be used to obtain meaningful outcomes for thematic content analysis. After the observations are input into NVivo, information about occupational health risks among traffic police will be coded. The findings on the number of studies retrieved from the search and the total number of studies excluded at each screening stage guided by the Preferred Items for Systematic Reviews and Meta-Analyses extension for scoping reviews will be reported and is outlined in Figure 1 [33]. Therefore, scoping review will give an outline relevant to our interest, allowing for the clarification of key concepts and the identification of gaps. This scoping review will be used to help us choose an appropriate arena for a future systematic review.

Figure 1. Study selection process.



Eligibility of Research

Studies will be selected according to the population, exposure, and outcomes framework outlined below (Textbox 1).

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Textbox 1. Structure to determine eligibility for the research question.

Population

- Traffic police in South Asia

Exposure

- Occupational exposure (air pollution, noise pollution, exposure to chemical substances, and negative workplace exposure)

Outcomes

- Types
  - Physical hazards: noise-induced hearing loss
  - Chemical hazards: cancer
  - Biological hazards: blood-borne diseases
  - Ergonomic hazards: musculoskeletal disorders
  - Organizational hazards: burnout
  - Psychological hazards: anxiety, depression, insomnia, and posttraumatic stress disorder
- Prevalence
- Level of knowledge
- Predisposing factors or risk factors
- Preventive measures
- Usage of preventive measures

Identifying Research Questions

Overall, the research questions are as follows: what is the current status of occupational health hazards among South Asian traffic police? Based on this research question, the following questions are specified: (1) what kind of occupational health hazards do traffic police face, and how common are they? (2) What are the traffic police's understanding or knowledge of the occupational hazards related to their jobs? (3) What are the potential risk factors that put traffic police at risk for health hazards related to their occupation? (4) What are the preventive strategies accessible for use by traffic police to avoid occupational health outcomes? (5) What preventive steps the traffic police might use to avoid workplace health risks or hazards? (6) Is there awareness of various protocols for occupation-related injuries or chronic disease management?

Identifying Suitable Studies

The scoping review also aims to compare patterns, prevalence, and characteristics of occupational hazards of South Asian countries (India, Pakistan, Bhutan, Bangladesh, Nepal, and Sri Lanka) in which there will be a search for common patterns in regard to occupational health hazards as well as comparison of patterns, characteristics, and prevalence of occupational health hazards by country. We assume that there could be a common culture, common characteristics of the occupational health hazards among the traffic police, and even there could be a similar pattern of environmental exposures as these countries belong to the same subcontinent. On the other hand, there could be variance in prevalence, national policies, and preventive measures in different countries of South Asia. Moreover, most of the studies were conducted on various types of occupational health hazards among traffic police in different countries of South Asia. There are very few studies, which are focused on occupational health hazards of traffic police, thus generalizing findings for South Asia. Therefore, there will be an inclusion of all types of studies conducted on occupational health hazards of traffic police in countries as well as a whole of South Asia to identify the root causes behind prevalent occupational health hazards and also to have a clear picture on the emergence of tailoring any program for traffic police to prevent occupational health hazards.

Another goal of this review is to discover a wide range of literature including published studies, policy reports, newspapers, gray literature, and so on. The following electronic databases will be searched for keywords: PubMed, Springer Link, as well as EBSCO host, the Cochrane library, and Google Scholar (Multimedia Appendix 1). In addition, investigators will also look for appropriate research in gray literature, such as dissertations, as well as reports from governmental and international organizations such as World Health Organization and abstracts from conferences as there are very limited published studies focused on this topic in South Asia available in web-based sources. Finally, investigators will examine the reference lists of the incorporated research for related articles. During database searches and article retrieval, assistance from North-South University library services will be sought. The following are the keywords that will be used to find these databases: traffic police, occupational health hazards, prevalence, types, level of knowledge, predisposing factors or risk factors, preventive measures, and level of use of preventative measures (Multimedia Appendix 1). While searching, Boolean terms (AND, OR) will be used to separate

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relevant keywords. Additionally, MeSH terms will also help to specify the search. As each database has a distinct search method, the result of database searches will be transferred to the Mendeley library for additional screening of abstracts and complete articles. Every search will have its own specific documentation, which will include all details of the literature such as the search terms, the date of the search, the search engine used, the total number of articles found, and so on Research teams, important stakeholders, and knowledge consumers working in this field, such as health care professionals, university professors, will be polled to choose the search terms that will be used by the search strategy. Search terms or strategy will be changed based on the comments of other partners. In order to avert any risk of bias while selecting publications, the final step of the search process will be conducted in complete anonymity.

Study Selection

The review approach will consist of two screening steps: (1) A title and an abstract and (2) a full-text evaluation.

Two nonpartisan investigators will review the titles and abstracts of manuscripts to determine whether or not they meet the minimal set of inclusion as well as exclusion criteria.

Inclusion criteria are as follows: (1) studies carried on traffic police; (2) studies conducted on job-related exposures to biological and nonbiological hazards, prevalence, different kinds of hazards, risk factors, knowledge levels, and preventative methods; (3) studies carried out in South Asian countries (Bangladesh, Bhutan, Pakistan, India, Nepal, and Sri Lanka); (4) studies that are based on cohorts, case-control studies, cross-sectional studies, randomized controlled trials, and nonrandomized controlled trials; and (6) scholarly work published in English as well as in other languages with an English translation.

Exclusion criteria are as follows: (1) studies that did not focus on traffic police and occupational health hazards, (2) studies published in languages other than English, and (3) qualitative studies.

Before the actual review of article abstracts, the minimal inclusion and exclusion criteria will be evaluated on a sample of abstracts to make sure they are robust enough to include any studies on occupational exposures among traffic police in South Asia. Articles matching the inclusion criteria will be chosen for a full-text review. Based on the sample review, the inclusion and exclusion criteria will be finalized. In the subsequent step of the process, out of 2 investigators, each will conduct their own independent evaluation of the complete texts of the publication using the study criteria. If reviewers disagree with any article, it will be given a second look, and any further disagreements about the article's eligibility will be discussed with a third investigator. In order to provide a comprehensive record of the review procedure, a flowchart known as the PRISMA-ScR [33] will be constructed (Figure 1).

Data Charting

The relevant data will be drawn out using an extraction form. Specific details such as year of publication with date, study design, population, study aim, study title, study setting, intervention, proportions, result of the study, key findings pertinent to the study questions, and observations will be extracted and will be used to organize the data of all analyzed studies using a codebook. An extraction sample is provided in Textbox 2. Alterations will be made to the data extraction form on a regular basis. The given data extraction instrument will be then adjusted and adapted as needed while processing data from a source of evidence. Two independent reviewers will extract data from the submitted data separately. Extracted data from the reviewers will then be analyzed and compared. To ensure data accuracy and integrity, any inconsistencies will be addressed. In order to assure data validity and coding, all extracted data will be compiled in a single Excel (Microsoft) document.

Textbox 2. Data charting form.

- Name of author, date of publication
- Study title
- Objective of the study or research question
- Population
  - Sample size
  - Characteristics of participants
- Geography of the study
- Study design
- Recruitment setting
- Sampling strategy
- Most relevant and significant findings
- Conclusions

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Collating, Summarizing, and Reporting Results

The objective or goal of the scoping review is to outline the existing evidence and give a comprehensive summary of occupational health risks and hazards among traffic police in South Asian countries. It will not only incorporate the prevalence of hazards but also ensure the usage of preventive strategies. It will also serve as a guide to identify the risk factors. According to Arksey and O'Malley methodology [35], the investigators will use thematic content analysis to extract data linked to the research objectives and code them using NVivo software (version 10) [36]. The full-text papers will subsequently be analyzed for documented evidence on occupational health concerns among traffic police. Through coding, all data on occupational health hazards among traffic police will be collected from the included publications. Lastly, an overall interpretation of how the various concepts relating to the research topic and thematic areas relate to one another will be undertaken.

Quality Appraisal

For the quality evaluation, evidence from various research will be evaluated. This will be performed to confirm that the research strategy is suitable for the study's objectives and to limit the likelihood of bias. The 2018 version of the mixed methods appraisal tool (MMAT supported by the Canadian Institutes of Health Research) will be applied to evaluate the standard of the study's chosen articles [36]. Using this instrument, researchers will be able to evaluate the objective, methodology, research design, recruitment of study participants, data collection, data analysis technique, description of study outcomes, and authors' debates and conclusions. It will also help to evaluate the quality of primary research. Due to the necessity of making judgments, this technique requires the participation of 2 independent reviewers. Reviewers will adhere to the scoring manual included in the MMAT 2018 version. The overall percentage score for quality will be calculated for each study evaluation, scores below 50% will be regarded as poor and scores between 51% and 75% will be considered average. A score between 76% and 100% will be considered as of good quality.

Ethical Considerations

This scoping review requires no ethical approval as it does not involve human subjects; yet, it might have some limitations. Limited studies are conducted regarding this topic in this region. Again, this review will only consider published and gray literature written in English.

Results

A preliminary search of the primary databases has been conducted. Electronic database searches will be completed by October 2022. Disseminating the findings from this scoping review in a scientific peer-reviewed journal has been envisaged. It is anticipated that the theoretical conceptualization on different aspects of occupational health of traffic police will emphasize future studies in this region, which will inform policy makers to revise their OHS policies and principles. Additionally, it will have implications on taking necessary preventive measures in the future to reduce occupational injuries and fatalities resulting from different types of occupational hazards.

Discussion

Principal Findings

The scoping review aims to systematically explore, analyze, and describe relevant findings on occupational exposures and their associated health hazards among traffic police in South Asia. However, a few relevant studies regarding OHS practices, policies, and guidelines for traffic policies were conducted in this region. Hence, this scoping review will explore the knowledge gaps, prevalence, possible risk factors, and control or preventive measures of occupational health hazards among traffic police in South Asia.

The scoping review will outline and perform a detailed discussion on occupational exposure focusing on the physical, psychological, and environmental aspects of health affecting traffic police in the South Asian region. The extracted data will be provided in a tabular format and a descriptive summary will explain how the results relate to the scoping review's goals and objectives. The scoping study is expected to shed light on the information and evidence that are currently available on occupational exposure and health hazards for South Asian traffic police, and the summary will also be evaluated, interpreted, and compared considering the existing literature. The review may have far-reaching implications for future projections of occupational exposures and for revising the current policy if needed. It may also reveal different research areas into multiple aspects of occupational exposure and occupational health hazards among traffic police in South Asia.

The findings of this scoping review will be impactful as it will explore in detail the health hazards associated with this profession, and an evidence-based review of the current status of occupational health safety policy and preventive measures as well as interventions will be explained.

The study will explain the need for occupational safety and health strategy for traffic police with the overall vision of providing a healthy, safe, and productive working environment, which should be implemented by all the relevant agencies such as government, industry, and general public. This study will inform policy as well as management principles and interventions. When a strategy on the OHS of traffic police is well developed and implemented, there will be effectiveness on how the traffic police keep themselves safe from occupational health hazards.

Strengths and Limitations to the Scoping Review

This scoping review will describe its findings in accordance with the Preferred Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews guidelines. Five electronic databases and gray literature, such as unpublished theses and dissertations will be used as a primary source of relevant studies. All articles will be screened by 2 independent researchers using a minimum set of inclusion and exclusion criteria. The study will evaluate the quality of included studies in accordance with an established MMAT. However, there is a

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possibility to overlook some relevant studies as only English-language publications will be considered and reviewed.

Authors' Contributions

IJ, MASK, and AM conceptualized the study and prepared the draft proposal. IJ, AM, MAH, and SS contributed to the development of the background, the research questions, and study methods. IJ, MASK, MH, and MUR planned the output of the research and contributed meaningfully to the drafting and editing. SS, MUR, MMAH, and MHN aided in developing the research questions and critically reviewed the study methods. IJ, AM, MASK, MDHH, MHN, and MAH wrote the first draft of the manuscript. All authors read and approved the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Data search strategy.
[DOCX File , 13 KB - resprot_v12i1e42239_app1.docx]

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Abbreviations

MMAT: mixed methods appraisal tool

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NIHL: noise-induced hearing loss
OHS: occupational health and safety
PRISMA-ScR: Preferred Reporting Items for Systematic Review and Meta-Analysis extension for scoping reviews

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Protocol

Possible Pathophysiological Roles of Neurotransmitter Systems in Men With Lifelong Premature Ejaculation: Protocol for a Scoping Review

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Abstract

Background: Lifelong premature ejaculation (LPE) is a rare sexual condition believed to be caused by genetic neurobiological disorders. In the field of LPE, 2 main types of research have been conducted: direct genetic research and pharmacotherapeutic interference of neurotransmitter systems that can relieve the symptoms of LPE in male patients.

Objective: We aim to provide an overview of studies on neurotransmitter systems as the pathophysiological cause of LPE by investigating direct genetic research or pharmacotherapeutic interference that relieves the main symptom of LPE in male patients.

Methods: This scoping review will use the PRISMA-ScR tool (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews). In addition, this study will use a peer-reviewed search strategy. Systematic searches will be conducted using 5 scientific databases (Cochrane Database of Systematic Reviews, PubMed or MEDLINE, Cumulative Index to Nursing and Allied Health Literature [CINAHL], EMBASE, and Epistemonikos). Additionally, pragmatic searches for relevant information in gray literature databases will be performed. Two reviewers will independently include relevant studies in a 2-stage selection strategy. Finally, data will be extracted from the studies and charted to summarize relevant study characteristics and key findings.

Results: As of July 2022, we completed the preliminary searches according to the PRESS 2015 guidelines and started to determine the final search terms that we will use in all selected 5 scientific databases.

Conclusions: This scoping review protocol is the first to focus on neurotransmitter pathways in LPE by combining the results from the genetic and pharmacotherapy studies. The results could help identify potential research gaps or target candidate proteins and neurotransmitter pathways in LPE for further genetic research.

Trial Registration: Open Science Framework 10.17605/OSF.IO/JUQSD; https://osf.io/juqsd

International Registered Report Identifier (IRRID): PRR1-10.2196/41301

(JMIR Res Protoc 2023;12:e41301) doi:10.2196/41301

KEYWORDS

drug therapy; genetic research; lifelong premature ejaculation; scoping review

Introduction

Premature ejaculation (PE) is a common sexual problem among men, with a prevalence of 20%-40% when using a broad definition of the term [1-4]. To obtain valuable standardized and reproducible research on PE, a sharp demarcation of the research field and a clear definition of PE are needed. A distinction can be made between the different types of PE. As defined by a panel of experts at an International Society for Sexual Medicine (ISSM) meeting in 2013, the internationally

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accepted definition of lifelong premature ejaculation (LPE) and acquired premature ejaculation is as follows [5,6]: (1) Ejaculation that always or nearly always occurs prior to or within about 1 minute of vaginal penetration (LPE) or a clinically significant and bothersome reduction in latency time, often to about 3 minutes or less (acquired premature ejaculation); (2) the inability to delay ejaculation on all or nearly all vaginal penetrations; (3) negative personal consequences, such as distress, bother, frustration, or the avoidance of sexual intimacy.

LPE is a subtype of PE with a prevalence of <4% in the general population [7]. The other suggested subtypes of PE include variable PE and subjective PE. Since these variants are not part of the genetic LPE, they fall outside the scope of this scoping review.

In 1943, Schapiro discovered a possible genetic component in the occurrence of LPE in men [8]. Waldinger further elaborated on this result and thus extended the field of genetic research since 1998 [9]. Thereafter, several studies have examined multiple genes and associated them with the occurrence of LPE [10-27]. Although a clear cause of LPE has not yet been revealed, Schapiro [8] reported that patients responded well to sedatives. Other successful treatments for LPE have been described since 1973 and have been further developed in the past 20 years [28-31]. Some drugs, such as dapoxetine, were specifically registered for the treatment of PE [32]. Additionally, neurobiological causes for LPE are supported by the findings that demonstrate that single-psychotherapeutic treatments or sex therapy is not effective for a significant remission of symptoms [5,33-36]. It has been pointed out that neurotransmitter pathways have multiple complex mechanisms, multiple families, and subtypes of receptors, all of which affect one another, making one polymorphism unlikely to be the sole cause of LPE [10,12,37,38]. It is therefore likely that a subset of polymorphisms in one or more neurotransmitter systems may lead to LPE.

In the field of LPE, 2 main types of research have been conducted. These include genetic research and pharmacological mechanisms that successfully prolong intravaginal ejaculation latency times (IELTs) through pharmacotherapeutic treatment. It is therefore possible to collect evidence on specific neurotransmitter systems. To study neurotransmitter pathways in relation to LPE in this manner, one or more targets can be identified to conduct a targeted strategy for conducting genome-wide association studies (GWAS) and ultimately resolve the cause of LPE.

A preliminary search for the existing scoping and systematic reviews on this topic was conducted on the January 12, 2022, in the following journals, databases, and search platforms: JBI Evidence Synthesis, Cochrane Database of Systematic Reviews, CINAHL (Cumulative Index to Nursing and Allied Health Literature), PubMed or MEDLINE, Embase, and Epistemonikos. Scoping reviews that combined pharmacological evidence with genetic causes were not available.

The objective of this scoping review is to provide an overview of studies on neurotransmitter systems as the pathophysiological cause of LPE by investigating direct genetic research or pharmacotherapeutic interference that relieves the main symptom of LPE in male patients.

Methods

Overview

This scoping review will be conducted from April 2022 in 6 stages using the methodology outlined in Levac et al [39], Peters et al [40], and the JBI Manual for Evidence Synthesis [41]. All sections will be reported in accordance with the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses-extension for Scoping Reviews) guidelines [42]. Any amendments will be uploaded on the Open Science Framework public page of this study.

Identifying the Review Questions

What evidence is currently available that could explain the potentially affected neurotransmitter systems in the pathophysiology of LPE?

The following evidence can be referred: (1) genetic variation correlated with the occurrence of LPE in affected versus unaffected men or (2) successful neuro-targeted pharmacologic treatment of LPE.

Identifying Relevant Studies

Studies will be collected from the Cochrane Database of Systematic Reviews, PubMed or MEDLINE, CINAHL, Embase, and Epistemonikos databases. Additionally, references of studies will be checked for relevancy and, if eligible, added to this scoping review (snowballing). The reference list of reviews found through the electronic search will be checked to ensure that relevant articles are included in the scoping review. Finally, we will perform pragmatic searches in gray literature databases for relevant information. These include the Grey Literature Report, OpenGrey, Web of Science Conference Proceedings, and local, national, and international organization websites. For inclusion websites should comply with the eEurope 2002 quality criteria [43].

A publication timeline or language restriction will not be set. A systemic search term will be developed using keywords and MeSH terms with the Boolean operators “AND/OR.” Search terms will be applied to the titles and abstracts of the relevant studies. An example of the initial search terms is included in Multimedia Appendix 1. The generated search terms will be peer-reviewed according to the Peer Review of Electronic Search Strategies 2015 guidelines [44]. Google translate will be used as a supportive tool for screening and including non-English studies [45]. Eventually, all included studies will be imported into the Mendeley research software. Studies collected from different sources will be deduplicated in EndNote [46].

Study Selection

Study selection will occur in 2 stages. The first inclusion will be based on eligibility by screening the title and abstract. Articles that are classified as relevant will be included for full-text review and for final inclusion in the scoping review. The Rayyan software tool will be used for the blind systematic

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inclusion and exclusion of studies [47]. Studies will be independently selected by 2 individual reviewers. Reviewers will meet when approximately 10%, 50%, and 90% of the studies have been screened to discuss dissent regarding study selection. A PRISMA-ScR flow diagram will be used to describe the study selection process. The diagram will be added to the publication of this scoping review.

All inclusion and exclusion criteria are displayed in Table 1.

Table 1. Search strategy using inclusion and exclusion criteria based on the patient population, intervention, comparison, outcomes, and study designs.

Parameter	Inclusion criteria	Exclusion criteria
Patient	Adult males with LPE[a] (aged ≥18 years)	Populations not matching with one of the following definitions: ISSM[b] 2007, ISSM 2013, DSM-5[c], or Definition 1[d]
Intervention	Genotyping or pharmacotherapy treatment	Pharmacotherapy studies using a topical anesthetic or locally active agents or with traditional or herbal medicine
Comparison	Males without LPE in genotype studies or drug naïve or washed-out patients with LPE in pharmacotherapy studies	N/A[e]
Outcome	Comparison of genotype or gene's or *x*-fold increase in sIELTs[f] by drug treatment	N/A
Study design	In pharmacotherapy studies: RCTs[g], cross-over drug studies, single-arm trials with a baseline sIELT, or case reports with a baseline sIELT	N/A

[a]LPE: lifelong premature ejaculation.

[b]ISSM: International Society for Sexual Medicine.

[c]DSM-5: Diagnostic and Statistical Manual of Mental Disorders.

[d]Definition 1: studies using a cut-off IELT of approximately 1.5 minutes after vaginal penetration, measured using the stopwatch method. Symptoms must be present from the first sexual encounter to all sexual partners.

[e]N/A: not applicable.

[f]sIELTs: stopwatch-measured intravaginal ejaculation latency time.

[g]RCT: randomized controlled trial.

Inclusion Criteria

Patient Population

Studies qualify for inclusion if the patient population meets the criteria for LPE, as stated in the ISSM 2007-2013 definition or in the 2013 Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [5,7,48]. IELTs must be measured using the stopwatch method that is the standardized outcome method demanded in drug registration by the European Medicine Association [49]. As these criteria were defined in 2007, the studies performed before this time have a risk of diagnosing patients with LPE with vague terminology or less reliable parameters such as self-reported estimated ejaculatory latency times (eIELTs) using questionnaires [30,50,51]. However, by rejecting the studies executed before 2007, we may overlook useful data; we have therefore designed a secondary inclusion term for the studies performed before 2007. These terms approach the ISSM 2007 or DSM-5 definition as closely as possible. The prior and post-2007 definitions used in the DSM-III [52], DSM IV [53], DSM-IV-TR [54], ICD-9 [55], ICD-10 [56,57], and ICD-11 [58] or the definition used by the American Urological Association Guideline on the pharmacologic management of PE [59] have been found to be inferior to correctly diagnosed LPE [1,60].

Studies before 2007 are eligible if they use a cutoff of approximately 1.5 minutes after vaginal penetration, measured using the stopwatch method. Symptoms must be present from the first sexual encounter to all sexual partners. This additional definition is based on the proposals for definitions published by Waldinger et al in 2006 [1].

Pharmacotherapy Studies

We will include the pharmacotherapy studies that meet the following criteria: (1) randomized placebo-controlled trials; (2) cross-over designs; (3) single-arm trials with a baseline stopwatch measuring intravaginal ejaculation latency time (sIELT); and (4) case reports with a baseline sIELT.

Exclusion Criteria

The exclusion criteria here are pharmacotherapy studies using traditional or herbal medicines and local topical anesthetic agents, as these drugs do not interfere with the central neurotransmission systems.

Charting the Data

Data will be collected by the research team with research software that is yet to be specified. Data will be collected as an iterative process, in which reviewers extract and update data continuously. Data will be collected as shown in Figure 1. To test whether the framework matches the research question and aim of the study, 2 reviewers will independently use the data charting form using the data extracted from the first 5 articles.

If any data are unclear or incomplete, the corresponding authors will be contacted for additional details on the performed studies. If additional information will not be obtained, a comment on this issue will be placed in the charting table.

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Figure 1. Example of data charting form. LPE: lifelong premature ejaculation; sIELTs: stopwatch-measured intravaginal ejaculation latency time; Tx: drug therapy; wk: week(s).

Agent/ polymorphism	Author/ year	Origin/ country of origin	Aim(s)	Study design	LPE definition	Primary outcome	Secondary outcome measure(s)	Number of subjects	Age	Duration (wk)	Pre-Tx sIELT	Post-Tx sIELT	ΔsIELT (fold)	Key finding(s) related to the scoping review questions	Notes

Collating, Summarizing, and Reporting the Results

The key findings of the included studies will be summarized. A distinction will be made between genotype research studies and pharmacotherapeutic drug studies, ordered by the targeted neurotransmission protein subtype. Quantitative data will include, for example, a factor-fold increase in sIELTs by pharmacotherapy or a correlation with specific gene types. This will provide an overview of evidence in the field and could help identify potential research gaps or target protein and neurotransmitter pathways for further genetic research.

Results

As of July 2022, we completed the preliminary searches according to the PRESS 2015 guidelines and started to determine the final search terms that we will use in all selected 5 scientific databases.

Discussion

This scoping review protocol is the first to focus on neurotransmitter pathways in LPE by combining the results from the genetic and pharmacotherapy studies. The results could help to identify potential research gaps or target candidate proteins and neurotransmitter pathways in LPE for further genetic research. This could ultimately lead to an improvement in therapy for patients with LPE.

In this scoping review a sharp demarcated definition of LPE will be used to prevent inclusion of non-LPE males by overdiagnosis. Furthermore, the method of this scoping review complies with the most recent guidelines using the PRISMA-ScR tool. In addition, this study will use a peer-reviewed search strategy without language restrictions; therefore, a robust and systematic foundation for thorough scientific research is laid. The final scoping review will be published in a peer-reviewed journal and information will be disseminated in scientific meetings.

This scoping review is limited to wide evidence collection; the quality of evidence of studies will only be partly evaluated since it is not a standard element of scoping review methods. In LPE research the quality of studies is widely discussed [51,61-63]. Confounded published studies are not excluded in advance because this scoping review focusses mainly on wide evidence collection as input for a targeted strategy in a GWAS. To assess potential confounders or outcome differences by ethnicity, patient characteristics and social information of studies will be charted and discussed.

To date several reviews on LPE have been conducted. However, this will be the first scoping review focusing on neurotransmitter pathways in LPE by combining the results from the genetic and pharmacotherapy studies. With this protocol a scoping review could be conducted systemically leading to further input for future candidate gene studies or GWAS and ultimately improve LPE care.

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Authors' Contributions

PKCJ is the guarantor. JJVR took the lead in writing and shaping the protocol. PKCJ provided feedback.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Preliminary search terms.
[DOCX File , 14 KB - resprot_v12i1e41301_app1.docx]

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Abbreviations

CINAHL: cumulative Index to Nursing & Allied Health Literature DSM-5: Diagnostic and Statistical Manual of Mental Disorders
GWAS: genome-wide association study
IELT: intravaginal ejaculatory latency time
ISSM: International Society of Sexual Medicine
LPE: lifelong premature ejaculation
PE: premature ejaculation
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses-extension for Scoping Reviews

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Protocol

Health Experiences of Sexual and Gender Minority People Living With Dementia and Their Care Partners: Protocol for a Scoping Review

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Abstract

Background: People living with dementia and their care partners who identify as a sexual and gender minority (SGM) often experience specific health inequities and disparities due to discrimination related to age, cognitive impairment, and being SGM.

Objective: The purpose of this scoping review is to identify, explore, and synthesize the state of the science regarding the health and health care experiences of SGM people living with dementia and their care partners. This review also aims to identify gaps in research and set forth key recommendations to improve the health and health care experiences of SGM people living with dementia and their care partners by advancing health equity through research, policy, and practice.

Methods: The protocol follows the guidelines set forth by Joanna Briggs Institute protocol for scoping reviews. Steps of this framework that will be followed include (1) identifying the research question; (2) identifying relevant studies; (3) study selection; (4) charting the data; (5) collating, summarizing, and reporting the results; and (6) consultation. This scoping review will explore several electronic databases, including MEDLINE, Embase, CINAHL, AgeLine, PsychINFO, and Scopus. Health librarians will conduct the initial search for articles that are in English, include people living with dementia who identify as SGM, SGM people living with dementia and their care partners, or SGM care partners caring for people with dementia. Studies must be peer reviewed and focus on the phenomenon of interest, which is the health and health care experiences of participants. Covidence will be used to review abstracts and full-text articles and to screen articles. After the search has been completed, 2 independent reviewers will screen article titles and abstracts to identify eligibility. Discrepancies will be discussed and decided upon by the 2 reviewers. Relevant studies will be collected, and data will be extracted and charted to summarize key findings. Key findings will be presented to a community stakeholder group of SGM care partners and people living with dementia, and a listening session will be convened.

Results: This scoping review will identify the state of the science of health and health care experiences of people living with dementia and their care partners who identify as SGM. We will identify gaps and provide recommendations to inform future research, policy, and practice to improve health and health care experiences of SGM people living with dementia and their care partners.

Conclusions: Little is known about people living with dementia and their care partners who identify as SGM. This scoping review will be one of the first to identify the health and health care experiences of people living with dementia and their care partners who identify as SGM. The results of this review will be used to guide future interventions and to inform future policy and practice to improve health care and reduce health disparities in this population.

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KEYWORDS

lesbian, gay, bisexual, transgender, and queer; LGBTQ; dementia; caregiver; identity; gender minority; health inequity; vulnerable population; health care; health disparity; scoping review protocol; sexual minority

Introduction

Older adults are often at the intersection of multiple minoritized identities due to stigma surrounding aging and age-related conditions [1]. Older adults who identify as lesbian, gay, bisexual, transgender, queer, as well as other sexual or gender minority (SGM) identities are known to experience unique, compounding stressors and resultant disparities in health outcomes (eg, depression, anxiety, posttraumatic stress disorder, cognitive impairment, cardiovascular disease, hypertension, and diabetes) due to discrimination, stigma, and structural inequities [2-5]. Prior research supports older adults living with dementia and their care partners experience disparities in health outcomes due to individual (eg, grief, comorbid conditions, as well as limitations with physical and cognitive abilities) [6-8] and social stressors (eg, declining social networks and relationship strain) [9-11] that are distinct from the already complex, stigmatized process of aging [12]. People living with dementia and their care partners who identify as SGM represent a unique intersecting population at risk of experiencing health disparities and care inequities due to longstanding false beliefs and discrimination surrounding aging, cognitive impairment, and SGM status.

Many SGM older adults experience health care access barriers, including nonaffirming providers that can delay pursuit of general and specialist care [2]. Care partners of SGM older adults also experience barriers to providing optimal care due to discrimination, providers that may not acknowledge nontraditional partnerships, and health care systems and interventions that do not promote health equity or address social determinants of health [13,14]. Although such barriers are known to affect health outcomes among SGM older adults, little is known about the unique health and health care experiences of SGM people living with dementia and their care partners. This knowledge gap is especially concerning considering that the number of SGM people living with dementia and those providing care to them is anticipated to rise in the coming decades as the population ages [15].

Understanding the health and health care experiences of SGM people living with dementia and their care partners is critical to elucidating health disparities and inform targeted strategies to better support families living with dementia. To date, no prior review has synthesized the evidence surrounding people at the intersection of being SGM and living with dementia or caring for someone with dementia. Foundational knowledge and recommendations to inform policy initiatives that promote health equity for SGM people living with dementia are needed [16,17]. The purpose of this scoping review is to identify, explore, and synthesize the state of the science regarding the health and health care experiences of SGM people living with dementia and their care partners. This review also aims to identify gaps in research and set forth key recommendations to advance health equity by improving the health and health care experiences of SGM people living with dementia and their care partners through research, policy, and practice.

Methods

Procedure

A scoping review framework will be used broadly to explore the state of the science pertaining to SGM people living with dementia and their care partners, which represent a historically underexamined group of older adults [18]. The Joanna Briggs Institute protocol for scoping reviews [19], which is informed by the advancing methods of Levac, Colquhoun, and Peters will be used to guide the scoping review process [20,21]. Steps of this framework that will be followed include (1) identifying the research question; (2) identifying relevant studies; (3) study selection; 4) charting the data; (5) collating, summarizing, and reporting the results; and (6) consultation. Consultation is an optional step of the framework that will be addressed in this review. Adherence to the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) guidelines will be used to promote rigor in this review [22].

Step 1: Identifying the Research Question

This review is guided by the following research questions:

- What is the extent and nature of research relating to the health and health care experiences of SGM people living with dementia and their care partners?
- What gaps exist in the evidence surrounding health and health care experiences of SGM people living with dementia and their care partners?
- What areas in research, policy, and practice warrant further exploration to advance health equity by improving the experiences of SGM people living with dementia and their care partners?

Step 2: Identifying Relevant Studies

Relevant studies will be identified through a comprehensive database search conducted by health librarians. Two reviewers will independently screen titles and abstracts and review full-text articles to identify relevant studies using predefined eligibility criteria.

Eligibility Criteria

Eligible studies will include participants living with dementia who identify as SGM, SGM people living with dementia *and* their care partners, or SGM care partners caring for people living with dementia. Dementia will be broadly defined as any self-report or medical diagnosis of dementia of any type or severity. Studies focused on mild cognitive impairment will not be included. Studies will focus on the phenomenon of interest, which is the health and health care experiences of participants. The studies must be in English; the 2 researchers conducting the review are English speakers. Studies will not be excluded based on research methods (eg, qualitative, quantitative, and

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mixed), setting (eg, hospital, long-term care, and community), or publication date. Dissertations, conference proceedings, working papers, and non-English studies will be excluded.

Search Strategy

The following databases will be searched to identify relevant studies: MEDLINE (PubMed), Embase (Elsevier), CINAHL (EBSCOhost), AgeLine (EBSCOhost), PsychINFO (EBSCOhost), and Scopus (Elsevier). These databases were selected by the authors with guidance of a health librarian to ensure that a wide variety of publications from various fields are located. A combination of keywords and database-specific subject headings for the concepts of gender or sexuality and dementia will be used. No restrictions will be placed by date in the database search. A health librarian will assist in developing the keyword search and conduct the search strategy. A draft of what the search might look like for PubMed with relevant combinations of Medical Subject Headings and keywords is included in Table 1. Additionally, a health librarian will conduct a separate search of the grey literature to identify relevant policy papers, white papers, blog posts, and op-eds [23]. Electronic database searches will occur within the same week and extracted into Covidence (Veritas Health Innovation) software [24]. Covidence will be used to organize, review, and remove duplicate citations.

Table 1. Draft PubMed search strategy.

(1) Gender or sexuality key terms	"Bisexuality"[Mesh[a]] OR "Homosexuality, Male"[Mesh] OR "Homosexuality"[Mesh] OR "Homosexuality, Female"[Mesh] OR "Sexual behavior"[Mesh] OR "Sexual and Gender Minorities"[MeSH Terms] OR "Transgender Persons"[Mesh] OR "Health Services for Transgender Persons"[Mesh] OR 'Intersex Persons"[Mesh] OR "Transsexualism"[Mesh] OR MSM[tiab] OR BMSM[tiab] OR "men having sex with men"[tiab] OR "men who have sex with men"[tiab] OR "men who have sex with other men"[tiab] OR "women having sex with women"[tiab] OR "women who have sex with women"[tiab] OR "women who have sex with other women"[tiab] OR bisexual[tiab] OR bisexuals[tiab] OR bisexuality[tiab] OR homosexual[tiab] OR homosexuals[tiab] OR homosexuality[tiab] OR "homo sexual"[tiab] OR "homo sexuals"[tiab] OR gay[tiab] OR gays[tiab] OR lesbian[tiab] OR lesbians[tiab] OR lesbianism[tiab] OR sexuality[tiab] OR Trans[tiab] OR transgender[tiab] OR transgenders[tiab] OR transgenderism[tiab] OR transgendered[tiab] OR transsexual[tiab] OR transsexualism[tiab] OR transsexuals[tiab] OR transsexuality[tiab] OR transvestite[tiab] OR transvestites[tiab] OR transvestism[tiab] OR transman[tiab] OR transmen[tiab] OR transwoman[tiab] OR transwomen[tiab] OR Intersex[tiab] OR intersexuality[tiab] OR intersexual[tiab] OR intersexuals[tiab] OR "Inter sex"[tiab] OR "inter sexuality"[tiab] OR "inter sexual"[tiab] OR "inter sexuals"[tiab] OR "two spirit"[tiab] OR "two-spirit"[tiab] OR "two nature"[tiab] OR "two-nature"[tiab] OR hijra[tiab] OR "third gender"[tiab] OR "third sex"[tiab] OR nonbinary[tiab] OR non-binary[tiab] OR "non binary"[tiab] OR "same sex"[tiab] OR "same-sex"[tiab] OR asexual[tiab] OR asexuals[tiab] OR asexuality[tiab] OR Pansexual[tiab] OR pansexuals[tiab] OR pansexuality[tiab] OR polyamory[tiab] OR polyamorous[tiab] OR polysexual[tiab] OR polysexuals[tiab] OR polysexuality[tiab] OR queer[tiab] OR queers[tiab] OR genderqueer[tiab] OR non-heterosexual[TIAB] OR "non-heterosexual"[TIAB] OR "non heterosexuals"[TIAB] OR nonheterosexuals[TIAB] OR LGBT[tiab] OR LGBTQ[tiab] OR LGBTQIA[tiab] OR LGBTQIA+[tiab] OR GLBT[tiab] OR TGNB[tiab] OR ((transition[tiab] OR transitioning[tiab] OR transitioned[tiab] OR transitions[tiab]) AND (female[tiab] OR male[tiab] OR woman[tiab] OR women[tiab] OR men[tiab] OR man[tiab] OR females[tiab] OR males[tiab])) OR ((Gender[tiab] OR sexual[tiab]) AND (behavior[tiab] OR behaviors[tiab] OR behaviour[tiab] OR behaviours[tiab] OR "non conforming"[tiab] OR "non-conforming"[tiab] OR fluid[tiab] OR orientation[tiab] OR presentation[tiab] OR identity[tiab] OR identities[tiab] OR minority[tiab] OR minorities[tiab] OR diverse[tiab] OR diversity[tiab] OR dysphoria[tiab] OR dysphoric[tiab] OR dysphorias[tiab] OR disorder[tiab] OR disorders[tiab] OR change[tiab] OR affirmation[tiab] OR confirmation[tiab] OR reassignment[tiab] OR reassigned[tiab] OR change[tiab] OR changed[tiab] OR changes[tiab] OR changing[tiab] OR expansive))
(2) Dementia key terms	"AIDS Dementia Complex"[Mesh] OR "Alzheimer Disease"[Mesh] OR "Aphasia, Primary Progressive"[Mesh] OR "Primary Progressive Nonfluent Aphasia"[Mesh] OR "Creutzfeldt-Jakob Syndrome"[Mesh] OR "Dementia, Vascular"[Mesh] OR "Dementia, Multi-Infarct"[Mesh] OR "Diffuse Neurofibrillary Tangles with Calcification"[Mesh] OR "Frontotemporal Lobar Degeneration"[Mesh] OR "Frontotemporal Dementia"[Mesh] OR "Primary Progressive Nonfluent Aphasia"[Mesh] OR "Huntington Disease"[Mesh] OR "Kluver-Bucy Syndrome"[Mesh] OR "Lewy Body Disease"[Mesh] OR dementia[tiab] OR dementias[tiab] OR Alzheimer[tiab] OR alzheimers[tiab] OR alzheimer's[tiab] OR aphasia[tiab] OR aphasias[tiab] OR creutzfeldt-jakob[tiab] OR "creutzfeldt Jakob"[tiab] OR CADASIL[tiab] OR "diffuse neurofibrillary tangles"[tiab] OR "frontotemporal lobar degeneration"[tiab] OR "frontotemporal lobar degenerations"[tiab] OR "huntington disease"[tiab] OR huntingtons[tiab] OR huntington's[tiab] OR kluver-bucy[tiab] OR "kluver bucy"[tiab] OR "lewy body"[tiab] OR amentia[tiab] OR amentias[tiab]
(3)	1 AND 2
(4)	3 NOT (Editorial[pt] OR Letter[pt] OR Comment[pt])

[a]MeSH: Medical Subject Headings.

Step 3: Study Selection

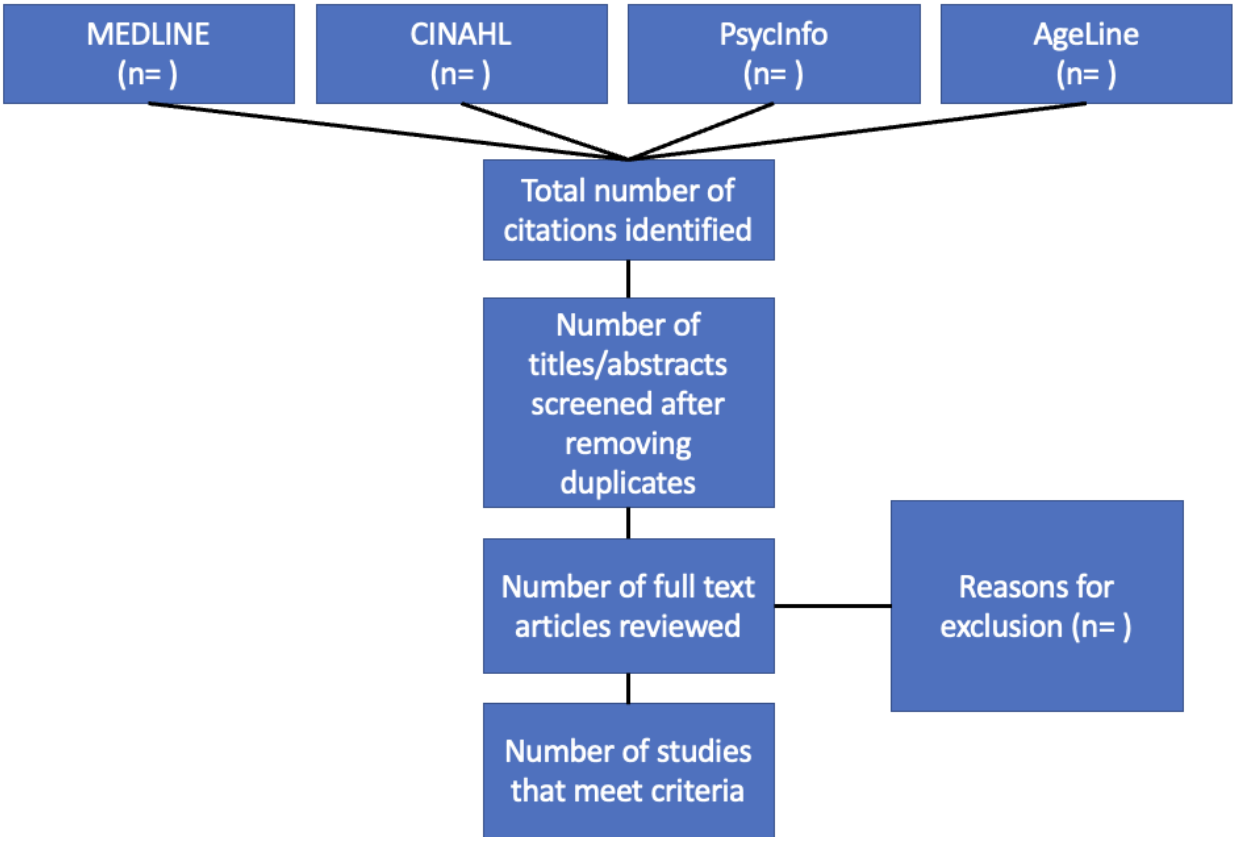
Titles and abstracts will be reviewed independently by 2 reviewers (JTM and MLH) according to the defined eligibility criteria. Weekly meetings will be held to resolve discrepancies and reach consensus on final titles and abstracts. Each author will then independently review all full-text articles to determine eligibility. Discrepancies will be resolved through discussion between the 2 reviewers.

Step 4: Charting the Data

Covidence will record the number of articles included, excluded, and the reasons for exclusion, which will be used to develop a PRISMA-ScR flowchart (Figure 1).

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Figure 1. PRISMA flow diagram of the studies to be included in the scoping review.



Data Extraction

A data extraction tool will be used to collect publication details, and information pertaining to study characteristics, findings, and author conclusions of included studies. Textbox 1 shows information to be included in the data extraction tool. The tool will be modified as needed during the data extraction phase; these changes will be reported in the final scoping review.

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Textbox 1. Information gathered using data extraction tool.

Publication details

- Author
- Year of publication
- Country of origin
- Publication type

Study characteristics

- Aims or purpose
- Study design
- Methods used
- Participants
- Sample size
- Setting
- Recruitment strategy

Key findings

- Qualitative findings
- Quantitative results
- Context to which the findings apply (health or health care experiences? Community vs health care system?)

Author conclusions

- Study limitations
- Implications
- Recommendations for research
- Recommendations for policy
- Recommendations for practice

Data Management

The 2 reviewers will independently extract data manually from each study and chart it in Microsoft Excel spreadsheets. Data extraction tables will be compared through regularly scheduled team meetings.

Step 5: Collating, Summarizing, and Reporting Results

Data Analysis Procedure

Following data extraction, we will use the data extraction tables to identify key information that will be collated in a comprehensive summary table. The summary table will include author and year, study aims or purpose, study design and methods, country, sample, key findings, limitations, implications, and recommendations. In the summary table, a brief description will be added regarding the sociopolitical climate surrounding SGM populations for each study's country of origin. This information will be gathered from the article itself and by analyzing survey data reports from reputable sources like Pew Research Center and The Williams Institute at University of California, Los Angeles School of Law. Content and structure of the summary table may change based on the results of the data extraction process.

Data Analysis

To further synthesize results of the included studies, each reviewer will independently analyze each study and the tabulated summary data to identify common concepts and themes across studies. Concepts and themes will be discussed through regular team meetings, and discrepancies will be resolved through discussion. Reviewers will finalize and define each concept and theme together. A table of themes, concepts, definitions, and exemplars (eg, qualitative findings, quantitative results, and key statements) from the included studies to support each theme will be developed (Table 2 is an example of a themes table).

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Table 2. Example of a table depicting themes, concepts, definitions, and exemplars identified through thematic analysis.

Major theme name 1 (theme definition, as defined by thematic analysts MLH and JTM)			
Concepts	Concept definition	Support or exemplars	Paper
• Concepts identified through thematic analysis	• Defined by thematic analysts (MLH and JTM)	• Raw quantitative data or results • Qualitative quotes and themes or subthemes • Key statements from author conclusions	• Author and year

Step 6: Consultation

The final step in the Joanna Briggs Institute protocol for scoping reviews is consultation. With support and guidance from the authors' institutional Community-Engaged Research Initiative, a stakeholder group of SGM care partners and people living with dementia will be developed, and a listening session will be convened. Stakeholders will be recruited from, for example, SGM-friendly church organizations, SGM and dementia care support groups, and SGM or dementia community organizations. Stakeholder participants will be compensated for their time with a gift card. The listening session will include a presentation of the scoping review themes, followed by open discussion for stakeholders to provide feedback on the findings. Stakeholders will be asked to discuss whether the themes resonate with their personal experiences, and they will be asked to identify topics that were left out of the scoping review themes. They will then be asked to propose key recommendations for future research, policy, and practice initiatives based on their own lived experiences and the scoping review themes. Stakeholder feedback provides those who are affected by these experiences with relevant research and findings [25].

Detailed notes will be kept by 2 trained notetakers during the listening session. MLH and JTM will compare and contrast the topics discussed or the notes taken during the listening session with the original themes identified through thematic analysis. A series of meetings will be held to refine and synthesize themes, gaps, and recommendations based on the combined results of the thematic analysis and listening session. The themes table (Table 2) will be updated based on results of the synthesis meetings. Findings generated through this consultation process are anticipated to inform future research, policy, and practice initiatives focused on SGM people living with dementia and their care partners.

Results

Results of this review will include a PRISMA-ScR flow diagram to illustrate results of the database search and the final included studies. Key study information for all included studies will be presented in narrative and tabular format. Integrated findings from the thematic analysis and listening session will be presented through a narrative synthesis with detailed description of the final themes, gaps, and recommendations. Finalized themes, definitions, and exemplars from the thematic analysis and listening session will also be depicted in a table. We will present a discussion regarding the significance of the findings of this scoping review as well as concrete recommendations to inform future research, policy, and practice to improve health and health care experiences of SGM people living with dementia and their care partners.

Discussion

Overview and Expected Outcomes

Older adults living with dementia and their care partners who identify as SGM are at the intersection of several identities associated with disparities in health outcomes and health care provision [2-4,26]. Understanding the health and health care experiences of individuals and families living at the intersection of such identities is critical to inform practice and policy initiatives to address health disparities and advance health equity. No prior reviews have focused on synthesizing the evidence relating to the health and health care experiences of SGM people living with dementia and their care partners. This review will characterize the extent and nature of the research surrounding SGM people living with dementia and their care partners and identify meaningful gaps that warrant future examination. Findings of this review are anticipated to act as a stepping stone to inform a future program of action-oriented research aimed to address health inequities experienced by SGM people living with dementia and their care partners.

The innovation of this review is the use of community-engaged methods to address the consultation step of the scoping review framework, which is currently considered an optional component [27]. Engaging members of a target population early in the research process is pivotal to uncovering the experiences and needs of groups that have historically been socially and economically marginalized. Given the focus of this review on members at the intersection of multiple stigmatized identities, convening a listening session with stakeholders who identify as SGM and are living with or caring for someone with dementia will be critical to not only identify disparities but also elucidate potential paths to advance health equity. Integrated findings from the scoping review and the community-engaged listening session are likely to yield concrete recommendations and areas to explore to address health inequities experienced by this population. Other strengths of this review include collaboration with health librarians in building and conducting the database search, searching multiple databases across several disciplines (medicine, nursing, and gerontology), and including 2 independent reviewers in the screening process.

Potential limitations of this review include the lack of critical appraisal of included studies, which would provide deeper insight into the overall quality of research. Additionally, this review will not contribute essential data to advance equity; it will instead focus on synthesizing the extent and nature as well as gaps in this area of research. Finally, although a comprehensive database search will be conducted, it is still possible that studies will be missed, as the grey literature and non-English studies will be excluded. These limitations

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notwithstanding, findings of this review will be the first to summarize the research focused on SGM people living with dementia and their care partners, and they are likely to yield concrete areas to explore through future efforts in research, policy, and practice.

Future Directions

Findings from this review will be used to inform a future program of research focused on advancing equity for SGM families living with dementia. Based on what is learned in relation to the state of the science, further exploration through qualitative inquiry to understand disparities may be warranted, while recommendations from key stakeholders will be used to directly inform action-oriented pilot studies aimed at addressing gaps in health and health care of this population. Community-engaged methods used in this review will provide a foundation to inform the design of future studies as well as policy initiatives focused on advancing health equity for aging adults.

Conclusions

In this scoping review, we aim to understand the health and health care experiences of SGM people living with dementia and their care partners. This study may provide a deeper understanding of the health disparities and challenges navigating the health care system for this population. We hope to gain insight for future studies and the development of interventions that advance health equity for SGM people living with dementia and their care partners.

Acknowledgments

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Data Availability

Data sharing is not applicable to this paper, as no data sets were generated or analyzed during the current study.

Conflicts of Interest

None declared.

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Abbreviations

PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews
SGM: sexual and gender minorities

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Protocol

Older Adults, the "Social Admission," and Nonspecific Complaints in the Emergency Department: Protocol for a Scoping Review

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Abstract

Background: Older adults have a higher visit rate and poorer health outcomes in the emergency department (ED) compared to their younger counterparts. Older adults are more likely to require additional resources and hospital admission. The nonspecific, atypical, and complex nature of disease presentation in older adults challenges current ED triage systems. Acute illness in older adults is often missed or commonly disguised in the ED as a social or functional issue. If diagnostic clarity is lacking or safe discharge from the ED is not feasible, then older adults may be labelled a "social admission" (or another synonymous term), often leading to negative health consequences.

Objective: This scoping review aims to describe and synthesize the available evidence on patient characteristics, adverse events, and health outcomes for older adults labelled as "social admission" (and other synonymously used terms), as well as those with nonacute or nonspecific complaints in the ED or hospital setting.

Methods: A literature search of MEDLINE, Embase, Scopus, PsycINFO, and CINAHL was completed. Relevant reference lists were screened. Data have been managed using EndNote software and the Covidence web application. Original data have been included if patients are aged ≥65 years and are considered a "social admission" (or other synonymously used term) or if they present to the ED with a nonacute or nonspecific complaint. Two review team members have reviewed titles and abstracts and will review full-text articles. Disagreements are resolved by consensus or in discussion with a third reviewer. This review does not require research ethics approval.

Results: As of January 2023, we have completed the title and abstract screening and have started the full-text screening. Some remaining full-text articles are being retrieved and/or translated. We are extracting data from included studies. Data will be presented in a narrative and descriptive manner, summarizing key concepts, patient characteristics, and health outcomes of patients labelled as a "social admission" (and other synonymously used terms) and of those with nonacute and nonspecific complaints. We expect the first results for publication in Spring 2023.

Conclusions: Acute illness in the older adult is not always easily identified. We hope to better understand patient characteristics, adverse events, and health outcomes of older adults labelled as a "social admission," as well as those with nonacute or nonspecific complaints. We aim to identify priorities for future research and identify knowledge gaps that may inform health care providers caring for these vulnerable patients.

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KEYWORDS

social admission; failure to thrive; failure to cope; acopia; community emergency; geriatric emergency; emergency medicine; geriatric; older adults; elderly; hospital; visit; admission; non-medical; non-acute; social; reasons

Introduction

Background

In recent years, visits to the emergency department (ED) by older adults (generally those aged ≥65 years) have significantly increased [1-3]. Between 2021 and 2050, the global population of older adults is expected to double [4], likely exacerbating the already existing problem of ED overcrowding [5]. The ED often serves as a "point of entry" for older adults, particularly for those without access—or perceived lack of access—to primary care [6,7]. Compared to younger counterparts, older adults in the ED have a higher visit rate and a longer length of stay and are more likely to be admitted to the hospital [3,8,9]. Older adults who visit the ED have a high mortality rate and increased likelihood of dependence for instrumental and basic activities of daily living [1,2].

The nonspecific and atypical nature of disease presentation in older adults presents a challenge in the ED. For example, issues may be missed at triage (ie, undertriaged), as many triage tools do not identify atypical, nonspecific, or multisystem complaints commonly seen in older adults [10-12]. Furthermore, older adults may present with no apparent acute medical reason for their visit, or at least none that can be quickly identified [13,14]. However, it is known that older adults who present with nonspecific complaints, such as "fatigue," "weakness," or "feeling unwell," are at risk for serious conditions (ie, acute coronary syndrome, metabolic or endocrine disturbances, transient ischemic attack, urinary tract infection, dehydration, etc) [15,16]. Older adults may also present with a combination of acute, chronic, social, or functional issues [17-20]. If diagnostic clarity is lacking or if patients are unable to be safely discharged—but they also do not seemingly require a hospital bed—they are often labelled as a "social admission" [17,19]. Other synonymous labels include "failure to cope/thrive" [13,21]; "community emergencies" [22]; or other colloquial terms based on local hospital policy, culture, or media [19,21]. There is no single common term used to describe this older adult population. However, it is known that these patients are at high risk for inappropriate disposition and adverse outcomes [23].

Older adults typically present with geriatric syndromes, including delirium, falls, poorly managed pain, malnutrition, depression, functional decline, sensory impairment, and incontinence [17,19]. If older adults present with poorly controlled or multiple geriatric syndromes, then a "social admission" may occur if no specific diagnosis can be identified [21]. Not infrequently, these patients cannot return to their prior place of residence without additional support, which may require extensive discharge liaison and planning. Examples of these discharge predicaments include the need for additional home supports (including nursing and/or social supports), home equipment or structural remodeling to accommodate physical decline, or placement in a care facility, among others.

Many of these older patients present to the ED in the later stages of their complex health issues and may not return home [21]. There are a few potential contributing factors that may lead to a "social admission," which include patient (eg, multimorbidity, polypharmacy, frailty, medication adverse events, or progression of or poorly managed health conditions), family/informal caregiver (eg, caregiver burnout, lack of a "back-up" plan, or time and financial constraints for caregiver), peer group (ie, social isolation), institutional (eg, single-system complaints or barriers to formal caregivers), or societal and policy (eg, government policy, accessibility, or age-friendly activities) factors [17,24-29]. If admitted, many health care providers may continue to view these patients as "bed blockers" or "inappropriate admissions" [19,28]. In addition, community-based health care professionals lack the resources, collaborative networks, and organizational infrastructure necessary to provide medical, social, and functional support outside of the hospital setting [30-32]. Thus, these patients continue to use the ED [33,34] and are at risk for further decline (eg, pressure ulcers, sleep deprivation, or delirium) once there [2,35-37]. Several studies also report high mortality rates among older adults with "acopia" (22%) [13], "failure to thrive" (32.5%) [38], and nonspecific chief complaints (20.2%) [39] that present to the ED.

Ideally, alternative pathways to care should exist outside the hospital setting, but our health care systems have not adapted to the demographic changes and increased health care needs of older adults [40]. Thus, many EDs remain ill-equipped to provide adequate care for these patients [40,41]. Historically, medical education systems train physicians and health care systems are designed with a focus on single-system complaints. However, this approach does not effectively meet the needs of older adults with nonacute, nonspecific, or multifactorial complaints [19,21]. The issue is perpetuated when ED health care professionals lack the expertise or comfort in managing these complex patients, while ED trainees often prefer to focus their efforts on more acute presentations [19]. ED-trained health care professionals are not equipped to manage these patient presentations from a time, training, or resource perspective [19,21].

While many EDs have implemented programs or interventions for older adults, they do not specifically target the older adults that present as a "social admission," "failure to cope/thrive," or "community emergency" [22,42]. There is a paucity of data around the patient characteristics, adverse events, and health outcomes of these patients that present to the ED. In this scoping review, we hope to describe what is currently known about these patients and identify knowledge gaps that may direct future research or interventions to potentially improve health outcomes.

Review Aim and Objectives

The aim of this scoping review is to describe older adults (aged ≥65 years) who present to the ED and are labelled as a "social admission" (or other synonymous terms) or present with

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nonspecific complaints or without an apparent acute medical reason for their visit. The review objective is to summarize patient characteristics, adverse events, exposures, interventions, and disposition from the ED/hospital from the included study population.

Methods

Overview

The protocol was developed based on the proposed framework from the Joanna Briggs Institute for scoping reviews [43], which builds on the framework previously described by Arksey and O'Malley [44]. The PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) checklist has guided the reporting of this protocol and will guide the future reporting of the review itself [45] (see Multimedia Appendix 1).

A scoping review was felt to be the most appropriate to (1) map key concepts and evidence available, (2) summarize current evidence, and (3) identify knowledge gaps in the literature. We also recognize the need for a scoping review to be iterative and that the protocol may deviate to obtain the best results. If a study author identifies the need for a protocol update, other authors will be notified and involved in the process. A consensus will be reached between authors. Protocol deviations will be reported to *JMIR Research Protocols*.

Inclusion and Exclusion Criteria

The inclusion and exclusion criteria are described in Table 1. The criteria are not exhaustive and may be modified throughout the search process, as necessary. If a study author identifies a search term, type of participant, variable, or outcome that they deem potentially relevant, other authors will be notified. A consensus will be reached between authors on whether to update the inclusion and exclusion criteria.

Table 1. Inclusion and exclusion criteria.

Criteria	Description

Types of participants	• Inclusion criteria
	  • All patients who present to the emergency department (ED) without an apparent acute medical reason for their visit or a combination of acute, chronic, functional, or social issues (ie, nonacute or nonspecific complaints)
	  • Labelled as a "social admission" or other synonymous term (ie, failure to thrive/cope, community emergency, etc) or with clinically relevant presentation
	  • Male or female
	  • Aged ≥65 years
	• Exclusion criteria
	  • Aged <65 years
	  • Not labelled as a "social admission" or other synonymous term or with nonacute or nonspecific complaints

Variables and outcomes	• We will collect data, as available, to include: • All types of patient characteristics[a] • All exposures in the ED/hopsital[a] • All adverse events in the ED/hospital[a] • All interventions in the ED/hospital[a] • Disposition from the ED/hospital[a] • All other measured outcomes reported in included studies[b]
Setting	• ED • Hospital
Types of evidence sources	• Original journal articles (no systematic reviews or meta-analyses) • Observational studies (cohort, case control, or cross-sectional), descriptive studies, case series, case reports, opinion pieces, and letters to the editor[c]

[a]See Textbox 1 for details.

[b]When an outcome is identified by an author as being potentially relevant, that author will notify the other authors. All authors involved in the title and abstract review, full-text review, and data extraction processes will be informed, and a decision will be made via consensus.

[c]Any opinion piece or letter to the editor that contains original research data will be included.

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Textbox 1. Variables for data extraction.

- Publication details (ie, author, journal, year of publication, country, and grey or peer-reviewed)
- Methodological data (ie, study type, sample size, etc)
- Patient characteristics (ie, age, past medical history, presenting complaint, triage score, arrival mode, place of residence, recent admissions, recent emergency department visits, etc)
- Adverse events (ie, falls, delirium, pain, infection, etc)
- Exposures (ie, infectious diseases, antipsychotic medication use, etc)
- Interventions (ie, antibiotics, intravenous fluids, new medications, etc)
- Other measured health outcomes
- Disposition (ie, home, home with supports, nursing homes, long-term care, etc)

Search Strategy

A research librarian, in collaboration with the review team, developed search strategies to identify potentially relevant articles for screening. The following databases will be searched: (1) MEDLINE, (2) Embase, (3) Scopus, (4) PsycINFO, and (5) CINAHL. The search strategies are presented in Multimedia Appendices 2-6. Search dates are from 1946 to November 8, 2022. Some of the search terms included are “social admission,” “social patient,” “acopia,” “bed blocker,” geriatric emergenc*,” and “community emergency,” among others (see Multimedia Appendix 1). The search strategies were piloted by ensuring that they captured a few key articles that are likely to be included in the final review. Records will be exported to EndNote software (Clarivate Analytics) [46] for deduplication and citation management and then into Covidence [47] for article screening. A final search will be repeated prior to the draft of the manuscript. Searches of the databases will be supplemented by manual searches through the references lists of original journal article publications, as well as citation searching when appropriate. If a relevant review or meta-analysis is identified, we will manually search the associated reference list.

Study Selection Process

Two reviewers will independently screen titles and abstracts identified by all electronic databases against the predetermined inclusion and exclusion criteria (see Table 1) and document their findings in Covidence [47]. To ensure interrater reliability, 10% of the titles and abstracts were piloted before starting the formal screening process. A flow chart will be used to report the study selection process according to the PRISMA-ScR statement. Any disagreement of the titles and abstracts identified between reviewers will be resolved via consensus between reviewers or via arbitration by a third reviewer if consensus is not achievable.

Next, articles that are deemed relevant will be reviewed in full and screened according to the inclusion and exclusion criteria. Any disagreement of the full-text review between reviewers will be resolved via consensus between reviewers or via arbitration by a third reviewer if consensus is not achievable. When a duplicate study is identified, the data will be extracted from the most informative study sample, but all published articles will be included in the reference list. When important data are missing, the authors of all eligible studies will be contacted.

Data Charting, Analysis, and Synthesis

Reviewers will use standardized pro forma data extraction Microsoft Excel sheets to independently extract relevant data from included studies. To ensure interrater reliability, we will pilot 10 studies prior to formally starting the data collection process using the data extraction sheets. Variables and data to be extracted are listed in Textbox 1. Other key information related to the review objectives may also be collected. Further data points may be added if unforeseen, useful data can be extracted. We will provide a narrative synthesis of study data. Text and tables will be used to provide a descriptive summary of included studies and study characteristics.

Risk of Bias (Quality Assessment)

As this is a scoping review of the available evidence, no quality assessment will be performed.

Results

Our search strategies were applied to the 5 databases as described above (see *Search Strategy*). Prior to starting data collection, 2 authors (KRF and KOD) piloted 100 studies to review their titles and abstracts. Disagreement was identified for 8 (8%) studies. All disagreements were resolved via consensus between the 2 reviewers (KRF and KOD). A third reviewer was not required.

In total, 1860 titles and abstracts were identified for screening after the removal of 115 duplicate articles. Thus far, 30 full-text articles were identified for inclusion. As of January 2023, we have completed the title and abstract screening. The full-text review is ongoing as we await the retrieval of some texts and translation of others. A manual reference search has been completed. We are currently extracting data from identified studies for inclusion. We will present data in a narrative and descriptive manner. We expect the first results for publication in Spring 2023.

Discussion

Expected Findings

The results of this scoping review aim to inform ED physicians and other ED health care practitioners about this population.

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We hope that appropriate stakeholders and policy makers can adapt their approach to the population labelled as a "social admission" and with nonacute, nonspecific complaints. We aim to describe the characteristics of this population, how they present, and any exposures or adverse events experienced during their ED stay or "social admission." It is expected that this population may demonstrate frailty, comorbidity, and polypharmacy. We expect the reasons for presentation to include nonspecific complaints, such as "weakness" or "generally unwell," but to also include functional or social reasons that are difficult for ED physicians to navigate. We expect acute medical illnesses to be missed and for disposition and discharge planning to be difficult. We also expect adverse events, revisit, admission, and mortality rates to be high, if documented.

To date, several original journal articles have been published in this area. However, the terms used to describe this population varies greatly between institutions and over decades. To our knowledge, this is the first review to be conducted on this topic with the intention of including all synonymous and colloquial terms in the literature equivalent to "social admission" and nonacute and nonspecific complaints in the ED. Strengths of our study include our broad-scope search strategies and the inclusion of a wide range of study designs. We chose to conduct a scoping review and not a systematic review as we wanted to focus on the state of research that exists for this emerging topic, not necessarily its quality. Limitations may include the inability to make evidence-based recommendations for clinical guidelines and a lack of risk of bias assessment for included full-text studies.

Dissemination Plans

We hope that this scoping review identifies priority areas for future research. Dissemination will help practitioners and the public understand this patient population. A multidisciplinary approach will help guide the dissemination of results at local hospitals and clinical sites. We plan to publish our results in a peer-reviewed academic journal and present at national and international conferences.

Acknowledgments

This research study is partially funded from the Carbonear Institute for Rural Reach and Innovation by the Sea (CIRRIS).

Data Availability

The data sets generated during and/or analyzed during the current study will be available from the corresponding author on reasonable request.

Authors' Contributions

All authors contributed to the protocol writing and revisions. AF formulated and modified the search strategies. KRF and KOD screened titles and abstracts and reviewed full-text articles. KRF and KOD will perform manual reference searching and extract relevant data.

Conflicts of Interest

None to declare.

Multimedia Appendix 1
PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) checklist.
[DOCX File , 84 KB - resprot_v12i1e38246_app1.docx]

Multimedia Appendix 2
MEDLINE search strategy.
[DOCX File , 14 KB - resprot_v12i1e38246_app2.docx]

Multimedia Appendix 3
Embase search strategy.
[DOCX File , 14 KB - resprot_v12i1e38246_app3.docx]

Multimedia Appendix 4
Scopus search strategy.
[DOCX File , 13 KB - resprot_v12i1e38246_app4.docx]

Multimedia Appendix 5
PsycINFO search strategy.
[PDF File (Adobe PDF File), 144 KB - resprot_v12i1e38246_app5.pdf]

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Multimedia Appendix 6
CINAHL search strategy.
[PDF File (Adobe PDF File), 154 KB - resprot_v12i1e38246_app6.pdf]

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Abbreviations

ED: emergency department
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews

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Protocol

Developing the Next Generation of Nursing Disciplinary Leaders in Higher Education: Protocol for a Sequential Mixed Methods Study

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Abstract

Background: Leading nurse education and research in the higher education (HE) sector has become increasingly challenging over the last decade with many universities in Australia and New Zealand having undergone academic restructuring. The future of HE faces many challenges including recruitment of suitably qualified staff to lead teaching and research and advance professional disciplines. Increasing cultural diversity of the Nursing workforce and the communities' nurses serve, and the identification of cultural attributes in the context of racial inequities exposed by the pandemic and the climate emergency suggest different forms of leadership may be required in the future by those leading nurse education in the HE sector. Currently, there is a dearth of research evidence that identifies the qualities, behaviors, and characteristics (collectively identified as core attributes) required by nurse academic leaders.

Objective: This research aims to identify an evidenced based set of core attributes that are required to lead the discipline of Nursing in the Australian and New Zealand HE sectors.

Methods: This research is using a 2-phase sequential mixed methods design incorporating a scoping review; and Delphi technique. In phase 1, a scoping review will be undertaken to identify the qualities, behaviors, and characteristics that can influence the evolution of the next generation of academic nurse leaders. A set of draft statements and questions will be prepared based on analysis of findings from the review. Phase 2 uses Delphi technique consisting of e-survey rounds with experts in leading nursing faculties in Australia and New Zealand. An Expert Advisory Group will consider the initial set of draft statements and questions from phase 1. Consistent with Delphi technique, a series of "rounds" will then occur using an e-survey method. Established leaders (Professors and Associate Professors who are members of the Council of Deans Australia and New Zealand) will rate their level of agreement to statements on the qualities, behaviors, and characteristics required to lead the discipline of nursing in the HE sector in Australia and New Zealand.

Results: The findings of the scoping review will identify what is currently known about the qualities, behaviors, and characteristics of academic nurse leaders. Quantitative and qualitative results from the Delphi study will initially be reported in separate manuscripts for publication. It is projected that a final paper will be prepared from aggregated research data and outline how the findings can inform the preparation of future academic nurse leaders.

Conclusions: The generation of an evidenced-based set of core attributes will serve to inform the next generation of academic nurse leaders including informing recruitment processes and postgraduate nurse leadership programs. It is anticipated that the data sets and findings will be transferrable to other disciplines within HE to aid in future-proofing discipline-based expertise and leadership in the context of academic restructure.

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KEYWORDS

academic; attributes; behaviors; characteristics; higher education; leadership; nursing; qualities

Introduction

Background

Nurse leaders exist across the professional spectrum including clinical practice, education, management, policy, and research. Nursing is now a well-established discipline in higher education (HE) in Australia and New Zealand, creating knowledge through research inquiry and producing graduates for employment in health through accredited program pathways. However, there are now significant challenges in HE to growing the next generation of academic nurse disciplinary leads [1]. A key focus of the nursing profession remains the commitment to teaching, supervision of students, and assessment to develop the nursing workforce across the professional spectrum [2]. Where once academic appointments in HE were seen as an attractive option for RNs seeking to move away from clinical practice to a well-remunerated workplace setting with autonomy and flexible working arrangements, this is no longer the case. As an applied profession, there is the expectation that registered nurses **(**RNs) working in HE have significant years of clinical experience to effectively mentor students and provide the next generation of nurses with foundation knowledge on which they can safely commence their careers in industry [3]. Despite these high expectations, there is a disparity between health industry salaries that sit significantly higher than a commensurate salary of a Lecturer (or level A and B academic). In contrast, a career in HE requires a postgraduate qualification and for advancement, doctoral preparation is often an essential criterion. As an applied discipline, nurses employed in the HE sector to teach nursing theory and practice in Australia are required to be an RN and hold a qualification higher than the program level that they are teaching into or have equivalent professional experience [4]. These requirements are embedded in Standard 3.14 of the current Registered Nurse Accreditation Standards 2019 through the Australian Nursing and Midwifery Accreditation Council on behalf of the Nursing and Midwifery Board of Australia. In New Zealand, individuals employed as a nurse academic must be an RN and hold a relevant master's degree (or have a professional development plan in place to obtain a master's degree within 4 years of initial appointment), have completed a program in adult teaching and learning within 2 years of appointment, and be involved in research and scholarship activities. These requirements are embedded in Standard 3.10 of the current RN Education Programme Standards (2021) [5]. Commitment to gaining the requisite qualifications for a career in HE can present as a financial burden and requires a considerable time commitment. For these reasons, RNs with the potential to be excellent academic nurse leaders may not find a move to HE as an attractive alternative to staying in clinical practice.

COVID-19–induced cost-saving measures in HE have compounded the need for fiscal restraint measures and have placed additional pressures on university staffing budgets [6]. While now in a recovery phase staff recruitment is a growing concern across the sector raising questions as to how the next generation of nurse academics and leaders in HE will be supported into a sustainable career pathway.

The HE sector in Australia and New Zealand is at a crossroad. As a key contributor to the Australian and New Zealand economies, the HE sector holds a significant role in ensuring workforce supply needs are met and graduates meet diverse employability requirements. The past 15 years have seen a change in the global economy resulting in streamlining of service delivery to reduce operational costs and a stronger dependence of local society on the income brought about through education. This altering climate has been at the forefront of structural changes across Australian and New Zealand HE. The key considerations of HE in the 21st century include internationalization, student learning outcomes, diversification, racial inequities and gender equity, societal need, and strategic planning [7-11]. There are also challenges for leaders going forward in the context of racial inequities shown during the pandemic and climate emergency. Leaders into the future may need to demonstrate different forms of leadership and have additional skill sets that recognize these significant challenges.

For many RNs working within the HE sector, career advancement is another challenge. Structural challenges and changes have become increasingly common, with some nursing schools losing standalone "disciplinary" status as they become part of larger multidisciplinary cognate units led by nonnurses. With such significant structural changes there has been an increase in the number of fixed-term (nontenured) teaching specialist positions; an increased reliance on a casualized workforce; and in many instances fewer senior nurse academic leadership roles, or these roles have cross-disciplinary implications.

Aim

This research aims to identify the qualities, behaviors, and characteristics that exist within academic nurse leaders (senior, established leaders) to provide the evidence in which to develop a set of core attributes to support the development of emerging leaders. Core attributes comprise the key qualities, behaviors, and characteristics that exemplify the essence and culture academic staff should emulate [12].

Objectives

This research will identify the qualities, behaviors, and characteristics (core attributes) that are exhibited by exceptional nurse leaders who are associate professors or professors (levels D and E) in Australian and New Zealand HE schools and faculties of nursing. These concepts will be explored as the foundation to developing a successful career pathway for emerging academic nurse leaders. This research is using a 2-phase sequential mixed methods design incorporating a scoping review and the Delphi method. In phase 1, a scoping review will be undertaken to identify the qualities, behaviors, and characteristics that can influence the evolution of the next generation of academic nurse leaders. Phase 2 uses the Delphi technique consisting of e-survey rounds with experts in leading

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nursing faculties in Australia and New Zealand. An Expert Advisory Group consisting of past or current Deans or Heads of nursing faculties will consider the initial set of draft statements and questions arising from the analysis of the scoping review findings. Consistent with the Delphi technique, a series of "rounds" will then occur using the e-survey method. Established leaders (professors and associate professors who are members of the Council of Deans of Nursing and Midwifery [Australia & New Zealand]) will rate their level of agreement via a Likert scale to statements on the qualities, behaviors, and characteristics required to lead the discipline of nursing in the HE sector in Australia and New Zealand. The questions for each round will be based on the findings of the previous round until consensus (set at 90% agreement) has been achieved. Participants will also have the opportunity in the e-survey to provide qualitative comments.

Primary Research Question

What are the core attributes (qualities, behaviors, and characteristics) required to succeed in the role of academic nurse disciplinary lead?

Methods

Study Design

Overview

Mackenzie and Knipe [13] argued the existence of a "pragmatic paradigm" that is not committed to a particular view of the world. Pragmatist researchers focus on the "what" and "how" of the research problem [14]. Pragmatism is seen as the paradigm that provides the underlying philosophical framework for mixed methods research [15,16]. The pragmatic paradigm places the research problem as central and applies all approaches (methods) to understanding the problem [14]. With the research question "central," data collection and analysis methods are chosen as those most likely to provide insights into the question with no philosophical loyalty to any alternative paradigm [13]. To achieve the research objectives, the research design must capture the qualities, behaviors, and characteristics that are required to succeed in the role of academic nurse leader (qualitative data) and must also capture the degree to which established senior academic nurse leaders and the Expert Advisory Group believe these are agreeable (quantitative data). This is to ensure that the data captured meet the expectations of those who make employment-related decisions (ie, senior leaders) and resonate with the emerging leaders who are looking to pursue a career pathway in nurse academe. A sequential mixed methods approach with 2 clearly defined methods has been chosen as the research will be an iterative process, specifically with the scoping review findings informing the Delphi method [17]. This approach requires flexibility and adaptability while maintaining the research question as central to the design.

Phase 1: Scoping Review

A scoping review of the literature will be undertaken to identify qualities, behaviors, and characteristics that are considered desirable in academic nurse leaders. A scoping review method has been chosen as it enables the mapping of a wide-ranging set of relevant literature and key concepts underpinning the research topic [18]. While an initial review of published research showed a gap in this area, there were surmountable findings to support a search of the literature that specifically targeted the qualities, behaviors, and characteristics that support career success. This approach allowed for consideration of published and gray literature and the identification of a range of potential qualities, behaviors, and characteristics and the development of an early set of core attributes that will be presented to an Expert Advisory Group (phase 2, round 1). The scoping review aligns to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Extension for Scoping Reviews (PRISMA-ScR) published in 2015 by Peters et al [19]. Specific questions pursued during the scoping review included: What are the qualities, behaviors, and characteristics required for a nurse disciplinary lead? What are the qualifications required to work as a nurse disciplinary lead? What are the intrinsic and extrinsic factors that may affect an individual's ability to succeed as an academic nurse leader? Does mentorship have a positive impact on academic nurse leadership skill development? What type of framework could assist supporting nurses into the role of academic nurse leader? Searches for MEDLINE, Embase, Emcare, ProQuest Dissertations and Theses Global, and Open Access Theses and Dissertations were undertaken. An extraction table was created to identify and analyze how each article addressed one or more of the research questions and a content analysis was conducted [20]. The findings of this review will be written up as a qualitative data set informing an early list of qualities, behaviors, and characteristics that will be built on and refined through phase 2.

Phase 2: Delphi Method

A Delphi method will be conducted to establish consensus on the core attributes required for future academic nurse leaders. The Delphi technique has been chosen due to the ability to refine the thoughts and ideas of a large cohort of experts to form a consensus view, defined at ≥90% agreement on a set of core attributes [17,21,22]. While agreement of ≥80% is deemed sufficient to validate content, the researchers have set an agreement of ≥90% to ensure a high level of validity [22].

Round 1: Expert Advisory Group

In round 1 of the Delphi method, an Expert Advisory Group will be sought to confirm the broader understanding and application of the preliminary list of key qualities, behaviors, and characteristics for academic nurse leader success as informed by the scoping review in phase 1. The research will specifically target senior leaders from Schools of nursing within Table A or public universities throughout Australia and New Zealand [23]. These Table A or public universities have been chosen due to their strong research divisions, participation in the development of nursing academe (through the Council of Deans of Nursing and Midwifery [CDNM; Australia & New Zealand]), and their support of "balanced" academic positions—where individuals are required to attend to both teaching, research, and professional engagement duties to maintain their academic skill sets. Senior leaders have been identified to participate in this Expert Advisory Group due to their significant experience within academe, their influence and

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insight in developing staff, and the distinctive understanding and views they hold of academic hierarchy having succeeded in the role of associate professor or professor. Analysis of these traits, followed by further testing with established leaders, will assist in the creation of a set of agreed core attributes to support succession planning and growing the next generation of academic nurse disciplinary leads. Such measures are necessary to address a potential future shortage of transformational nurse leaders who are able to influence future academic leadership roles in HE during a time where many universities are undergoing restructure. Disciplinary leads are the leaders who hold decision-making, executive roles within Table A or public universities and are responsible for leading the Discipline [24]. Participants will be invited to an internet-based meeting and asked to review the list of qualities, behaviors, and characteristics determined in phase 1, identify definitions for terms with multiple meaning, identify gaps, and address these gaps. As an iterative process, the data will then lead to the undertaking of round 2.

Rounds 2 and 3: Delphi e-Survey

In round 2 of the Delphi method, the refined data from round 1 will be tested through at least 2 rounds of the Delphi e-survey targeting all established leaders. The Delphi e-survey has been chosen to facilitate the collation of information beyond the Expert Advisory Group as it facilitates the easy circulation of survey material and collation of high-quality data across Australia and New Zealand at the convenience of the research participant (ie, no restraint due to time zones or travel required) [21]. The Delphi e-survey will aim to further refine any areas of ambiguity in the list of qualities, behaviors, and characteristics while also gauging prioritization to inform the development of a final list of core attributes. Content analysis will be undertaken after round 2. In round 3, the findings of round 2 will be presented to the participants of round 2. Participants' reactions to the findings will be sought. Consensus on the list of core attributes will be defined as ≥90% agreement [22,25]. The number of rounds of the Delphi method will be dependent on the establishment of consensus [25].

Round 4: Achieving Consensus

In round 4, the Expert Advisory Group will test the consensus opinion of the established leaders. The purpose of testing this research with the Expert Advisory Group is to ensure the proposed attributes and steps toward the research objectives meet the practical requirements of the role and end user—the future academic nurse disciplinary leads. As round 4 of the research will be an iterative process, the number of rounds will be dependent on the establishment of consensus and, if needed, further refine the core attributes. Content analysis will be used to further validate if consensus has been met across the participants in terms of the accuracy and resonance of the final list of core attributes and any further areas for considerations or areas for investigation. Consensus on the final list of core attributes will be defined as ≥90% agreement [22,25].

Mixed Methods Approach

The qualitative data captured throughout the Delphi method will be synthesized through content analysis. Content analysis is advantageous in this research design as it allows for the analysis of qualitative data while also quantifying its importance [20]. Content analysis is suitable to provide simple reporting of common issues identified in the data, which will likely be necessary to refine the qualities, behaviors, and characteristics into a list of core attributes for consideration in round 2 of the Delphi method. Content analysis allows for coding of the data to assume a quantitative measure—or weight—to which the qualities, behaviors, and characteristics can be measured in degree of importance or value [26,27].

Setting

It is noted that in some instances, schools or faculties of nursing in Australia include Midwifery to provide a multidisciplinary school reflective of a single regulatory board for both professions [28]. Universities in New Zealand do not have this "merged" model as Nursing and Midwifery have separate regulatory authorities, that is, the Nursing Council and the Midwifery Council [29,30]. This research will focus on the discipline of nursing. Although some nurse leaders may also be registered as a Midwife, midwifery has been excluded from this research to maintain comparable data specific to nurse leadership within academe. In examining qualities, behaviors, and characteristics exclusively within the discipline of nursing, this study will take on a similar approach to the research conducted by Carryer et al [31] in 2007, which explored the core role of nurse practitioners specifically within a clinical setting in Australia and New Zealand. Carryer and colleagues' study [31] recruited participants through the Nurses Board or Council of each respective country and excluded midwifery. A similar approach was again taken by Gardner and colleagues [32] in 2016. In this research, specific steps will be taken to ensure trans-Tasman distribution of participation through improving accessibility (eg, using ZOOM) and consideration of terminology to target both Australian and New Zealand HE sectors' requirements.

Participants

Overview

This study will focus on the recruitment of a sample population from within schools and faculties of nursing at identified Table A or public universities in Australia and New Zealand. These public universities have been chosen due to their strong research divisions, delivery of education in the nursing discipline, participation in the development of nursing academe (through the CDNM), and their support of "balanced" academic positions—where individuals are required to attend to both teaching and research duties to maintain their academic skill sets. Thirty-three Australian universities and 5 New Zealand universities have been identified—although it is noted that there have been significant changes in discipline delivery in some universities over the past 2 years and this may impact inclusion at the time of phase 2.

Participation for rounds 1 and 4 (Expert Advisory Group) will target senior leaders. The commitment of a participant to the Expert Advisory Group is likely to reflect their interest and involvement with the issue being addressed [22]. Recruitment of this Expert Advisory Group will be through direct invitation,

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initially made via email (through the CDNM) and then followed up by telephone. Representatives from Australia and New Zealand will be chosen because of the similarities in the standards of practice and regulatory structures for nursing.

Inclusion Criteria

The inclusion criteria are as follows: (1) well-renowned and recognized senior leaders who have currently or previously represented their institution as the named Member of the CDNM (Australia and New Zealand); (2) currently or previously employed as a dean, head of school, or head of discipline; and (3) actively working within Table A or public universities in Australia and New Zealand.

Exclusion Criteria

The exclusion criteria are as follows: (1) designated proxies to the CDNM (Australia and New Zealand) and (2) members of the PhD candidate's supervisory panel who would meet the inclusion criteria.

Recruitment

Overview

A minimum threshold of 5 participants has been set for the Expert Advisory Group to establish initial priorities. Prospective participants will be recruited through email contact from the researcher, outlining the purpose of the research, participation requirements, and consent. If available, the researcher will also approach the CDNM for their support in promoting the research initiative to improve the likelihood of participation.

Participation for rounds 2 and 3 (Delphi e-survey) will target established leaders.

Inclusion Criteria

The inclusion criteria are as follows: (1) established leader within the discipline of nursing, including those responsible for leading nursing programs; (2) employed as an associate professor (level D or E); (3) actively working within Table A or public universities in Australia and New Zealand; (4) is an active member of the CDNM (Australia and New Zealand); and (5) is a designated proxy to the CDNM (Australia and New Zealand).

Exclusion Criteria

The exclusion criterion is not participating in CDNM (Australia and New Zealand).

Recruitment: Rounds 2 and 3

A minimum threshold of 15 participants has been set for rounds 2 and 3 of the Delphi method to refine and test the resonance of the qualities, behaviors, and characteristics to create the draft list of core attributes. Prospective participants will be recruited through similar means to round 1 (direct email contact through the CDNM); however, they may also be recruited through referral from round 1 participants or through advertising, to ensure a broad capture of evidence.

Ethical Considerations

Approval

Ethics approval was obtained for all phases of this study from the University of South Australia's Human Research Ethics Committee (HREC) on April 30, 2020 (202862). Phase 1 of the research was a scoping review and as a literature-based form of inquiry it did not require ethics approval; however, the researchers noted that there are still some considerations regarding scoping review methods that include studies wherein the researchers have included human participants without approval of a duly constituted ethics committee. Key ethical considerations for phase 2 of this research are obtaining informed consent, ensuring that participants' details are treated in a manner that ensures an appropriate degree of privacy, and the safe storage of confidential data collected within the research.

Consent

Participants in phase 2 of the research will be provided a Participant Information Sheet (PIS) specific to the phase of research. The PIS details the purpose of the research including the aim, objectives, and potential outcomes. The PIS provides prospective participants with details on participation, including what participation would involve, potential benefits, potential risks, confidentiality, and strategy for managing any adverse events. If prospective participants have any unanswered questions, the contact information of the research team is provided within the PIS, thereby further enabling informed decision-making and consent.

Participants' Safety and Withdrawal

In the unlikely event a participant suffers an adverse event as a result of participating in the research, the research will be suspended while investigation into the occurrence is considered and risk analysis is completed, inclusive of HREC advice being obtained and acted upon. Prospective participants will be advised that participation is voluntary and they may withdraw their interest and participation at any time. This information is documented in the PIS. If a participant withdraws after their contribution has been deidentified, the contribution or data will be unable to be extracted from the study.

Confidentiality

Participants will offer their voluntary consent to the research team using data to inform the research. Any information obtained in connection with the research that may identify participants will remain confidential.

Data Management

All data will remain confidential to the researcher and stored on a password-protected computer, and in the University of South Australia's Research Data Storage and University of South Australia server. Access to data will be limited to the research team. Expert Advisory Group data may potentially be individually identifiable through voice recognition if recordings of Zoom contributions are made. These recordings may be required to ensure accurate documentation of participant contributions in a busy meeting setting. The researcher will undertake to deidentify this data at the point of transcription.

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Results

This research will identify an agreed set of core attributes required to develop and support successful disciplinary nurse leaders in academe.

Discussion

Anticipated Findings

It is anticipated that the findings of this study will inform the design and delivery of postgraduate nurse leadership programs and assist senior nursing faculty in HE to support the development of the next generation of academic nurse leaders. The findings will contribute to recruitment strategy, including succession planning and job description development. Upon completion of this research it is anticipated that the data sets and findings will be transferrable to other disciplines within HE to aid in future-proofing discipline-based expertise and leadership in the context of academic restructure.

Limitations

The scoping review process will align to the PRISMA-ScR, and the selection of studies will be guided by a protocol reviewed by the research team with expertise in conducting scoping reviews and prospectively published on the Open Science Framework [19]. While the researchers aim to ensure the rigor of the scoping review design is upheld, potential limitations include relevant articles published in languages other than English that may be missed, the exclusion of articles that focus on clinical leadership, and characterization and interpretation bias. A data extraction tool will be used to ensure that the selected studies are independently mapped to the research questions by two of the researchers with conflicts reviewed by the third researcher [18].

The Delphi method has been adopted due to the ability to refine the thoughts and ideas of a large cohort of experts to form a consensus view; however, the limitations of this method include timeliness and the potential complexities of conducting multiple rounds to achieve agreement among participants [22,33]. The validity of the Delphi studies can be called into question due to the varied definitions of “consensus” [33]. While agreement of ≥80% is deemed sufficient to validate content, the researchers have set an agreement of ≥90% to ensure a high level of validity and increase the rigor of this study [22]. The researchers will use e-surveys to improve accessibility for participants in an effort to increase participation in and improve the validity of the study [33]. The use of e-surveys also reduces the likelihood of bias developing through participants who may seek to demonstrate the same view as the majority [33].

Conclusions

The development of a set of agreed core attributes will assist current disciplinary leads to support early career trajectory identification and fast-tracking of the next generation of nursing disciplinary leaders in Australian and New Zealand HE institutions. It is anticipated that the findings of this research will inform postgraduate nurse leadership programs and assist senior nursing faculty in HE to effectively implement recruitment strategies, including succession planning and job description development. Ensuring the next generation of nursing disciplinary leaders hold or are supported to grow the qualities, behaviors, and characteristics that will empower them to succeed will assist in future-proofing discipline-based expertise and leadership in the context of academic restructure.

Acknowledgments

This proposed research is being undertaken as a PhD degree and the candidate and supervisors will all contribute to the research.

Data Availability

Data sharing is not applicable to this article as it outlines a prospective research protocol and therefore at this stage no data sets have been generated.

Conflicts of Interest

None declared.

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Abbreviations

CDNM: Council of Deans of Nursing and Midwifery
HE: higher education
HREC: Human Research Ethics Committee
PIS: participant information sheet
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analysis Extension for Scoping Reviews
RN: registered nurse

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Protocol

Factors Influencing the Clinical Adoption of Quantitative Gait Analysis Technologies for Adult Patient Populations With a Focus on Clinical Efficacy and Clinician Perspectives: Protocol for a Scoping Review

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Abstract

Background: Quantitative gait analysis can support clinical decision-making. These analyses can be performed using wearable sensors, nonwearable sensors, or a combination of both. However, to date, they have not been widely adopted in clinical practice. Technology adoption literature has highlighted the clinical efficacy of technology and the users' perspective on the technology (eg, ease of use and usefulness) as some factors that influence their widespread adoption.

Objective: To assist with the clinical adoption of quantitative gait technologies, this scoping review will synthesize the literature on their clinical efficacy and clinician perspectives on their use in the clinical care of adult patient populations.

Methods: This scoping review protocol follows the Joanna Briggs Institute methodology for scoping reviews. The review will include both peer-reviewed and gray literature (ie, conference abstracts) regarding the clinical efficacy of quantitative gait technologies and clinician perspectives on their use in the clinical care of adult patient populations. A comprehensive search strategy was created in MEDLINE (Ovid), which was then translated to 4 other databases: CENTRAL (Ovid), Embase (Ovid), CINAHL (EBSCO), and SPORTDiscus (EBSCO). The title and abstract screening, full-text review, and data extraction of relevant articles will be performed independently by 2 reviewers, with a third reviewer involved to support the resolution of conflicts. Data will be analyzed using content analysis and summarized in tabular and diagram formats.

Results: A search of relevant articles will be conducted in all 5 databases, and through hand-searching in Google Scholar and PEDro, including articles published up until December 2022. The research team plans to submit the final scoping review for publication in a peer-reviewed journal in 2023.

Conclusions: The findings of this review will be presented at clinical science conferences and published in a peer-reviewed journal. This review will inform future studies designed to develop, evaluate, or implement quantitative gait analysis technologies in clinical practice.

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KEYWORDS

quantitative gait analysis; clinical adoption; clinical efficacy; clinician perspectives; barriers; facilitators; adults

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Introduction

Gait impairments increase risk of falls and the level of disability, thus negatively influencing a person's involvement in society and quality of life. There are many causes of gait impairments, including neurological, musculoskeletal, and other health conditions. Gait assessments are an important aspect of a clinical assessment because they provide clinicians with information to support diagnosis, risk assessment, and treatment planning, with the goal of optimizing a person's independence and physical function. In clinical practice, gait assessments are primarily performed using observational gait analysis, which involves a clinician's visual assessment of the patient's gait [1,2]. This analysis can also be supported by outcome measures such as the Functional Gait Assessment in the adult patient population [3]. However, the reliability of observational gait analysis has been questioned [4], with the amount of experience performing this analysis influencing reliability [5]. Additionally, observational gait analysis may lack precision in identifying the subtle nuances of gait that are important for treatment planning, understanding treatment outcomes, and clinical decision-making. Quantitative gait analysis can provide clinicians with objective measurements of the gait cycle that can help them assess and monitor changes in gait, thus better informing clinical decision-making. Quantitative gait analysis makes use of wearable sensors, nonwearable sensors, or a combination of both (eg, hybrid systems) [6]. Wearable sensors are attached to the patients themselves and allow for monitoring within or outside of a controlled environment [6-9]. Nonwearable sensors allow for the monitoring of gait within a controlled environment [6]. Examples of common wearable and nonwearable gait technologies are shown in Textbox 1.

Textbox 1. Common quantitative gait analysis technologies.

Wearable [6-9]

- Inertial sensors (eg, accelerometers and gyroscopes)
- Force sensors (eg, instrumented insoles)
- Electromyography
- Flexible goniometers
- Ultrasonic sensors

Nonwearable [6,7]

- Pressure sensor mats
- Force plates (eg, ground reaction force plates)
- Motion capture
- Vision-based gait assessment [10]

Research on quantitative gait analysis technologies has increased nearly 10-fold over the last 10 years [11], with a nascent but expanding literature in support of the clinical efficacy of gait technologies. For example, 2 retrospective studies highlighted the role of gait technologies in guiding and optimizing treatment plans for people with stiff knee gait and spinal cord injury [12,13]. Both studies provide preliminary evidence for using gait technologies to enhance patient care. Moreover, guidelines for gait assessments [14-16] have been developed and can help support the use of these technologies in practice. However, despite this preliminary evidence of clinical efficacy, quantitative gait analysis technologies have yet to be widely adopted into clinical practice [2,17].

There are many factors that influence technology adoption [18-20], with evidence for clinical efficacy (ie, efficacy and effectiveness) only being a piece of the puzzle [20,21]. Instead, consideration must also be given to clinicians' perspectives on using technology in their practice. The Technology Adoption Model suggests that 2 key factors influence users' attitudes toward using a technology: perceived usefulness and perceived ease of use [18]. Perceived usefulness is defined as "the degree to which an individual believes that using a particular system would enhance his or her job performance" [18] (ie, perceived facilitator to usefulness) or the degree to which an individual believes that using the technology would not enhance his or her job performance (ie, perceived barrier to usefulness). Perceived ease of use is defined as "the degree to which an individual believes that using a particular system would be free of physical and mental effort" [18] (ie, perceived facilitator to ease of use) or the degree to which an individual believes that using the technology is not free of physical and mental effort (ie, perceived barrier to ease of use). Previous studies have used perceived usefulness and perceived ease of use to study technology acceptance in health care [22,23]. Beyond clinicians' perspectives on ease of use and usefulness of technology, thought must also be given to their perspectives on factors that exist beyond ease of use and usefulness, such as whether they believe their workplace would support their use of the technology [20,24].

In applying these learnings to the clinical adoption of quantitative gait analysis technologies, we then consider some factors that influence their successful adoption to be clinical efficacy and effectiveness, and clinicians' perspectives on the use of gait technologies in practice (ie, perceived barriers or facilitators to ease the use and usefulness of the technology, and beyond). As there are many different gait analysis technologies, consideration must be given to how and whether the above factors differ between each respective technology,

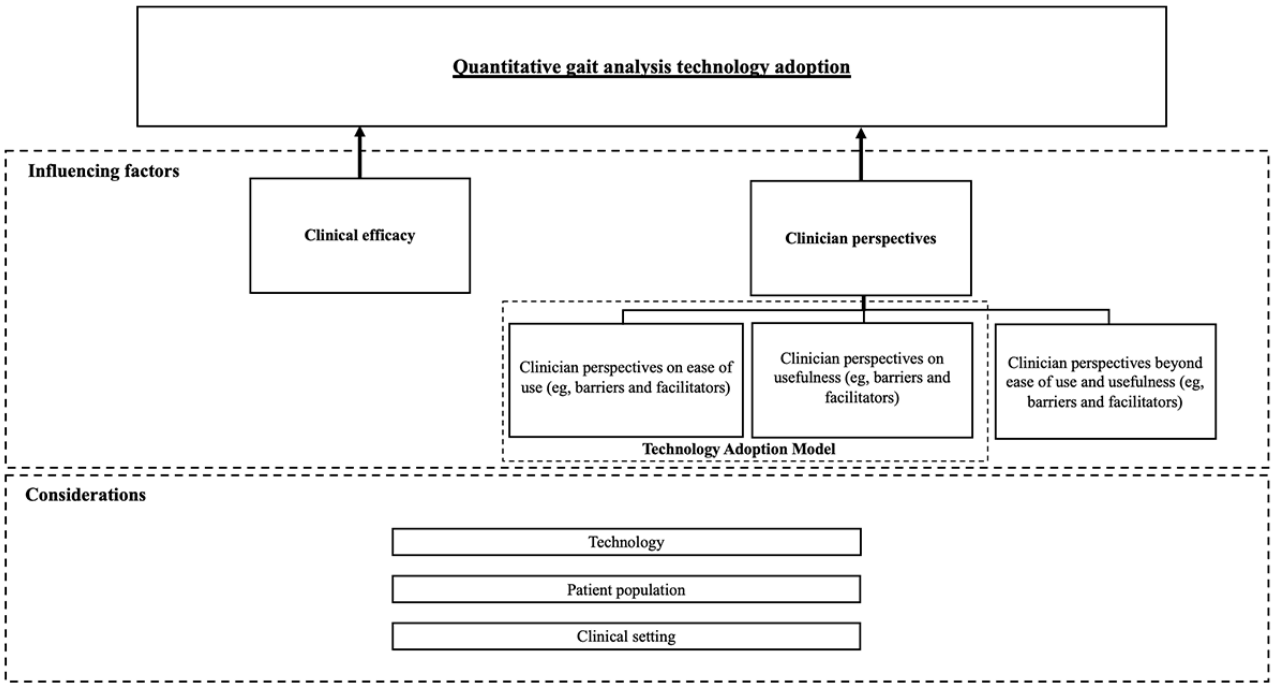
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patient population, and clinical context. A visual representation of how we consider these factors to influence the clinical adoption of quantitative gait technologies in the care of adult populations is shown in Figure 1.

To our knowledge, no previous review has synthesized the evidence for clinical efficacy and a clinician's perspective that influences the use of gait technologies in the clinical care of adult patient populations. A preliminary search for similar existing scoping and systematic reviews was conducted up until April 2021 in PubMed and Google Scholar. Two related systematic reviews were published in 2011 [25,26]. Bergmann and McGregor [25] focused on clinician and patient preferences for wearable technologies. This review addressed wearable technologies broadly and did not examine gait analysis specifically. Wren et al [26] investigated the clinical efficacy of quantitative gait analysis in a review of studies up until 2009, which was recently updated in 2020 [11]. This review investigated the clinical efficacy of gait technologies across 6 categories: technical efficacy, diagnostic accuracy efficacy, diagnostic thinking, treatment efficacy, patient outcomes efficacy, and societal efficacy. However, this review did not consider clinicians' perspectives on the ease of use and usefulness of gait technologies, and the recent update solely focused on 3D motion capture technologies.

The objective of this scoping review is to describe the factors influencing the clinical adoption of quantitative gait analysis technologies with a focus on their clinical efficacy, and clinicians' perspectives on their use in the clinical care of adult patient populations. We will also explore how these components differ across gait technology types, patient populations, and clinical contexts. A scoping review approach has been chosen to explore the extent of literature on this broad topic and is a necessary step in identifying how gait technologies can be integrated into clinical practice.

Figure 1. Factors influencing the clinical adoption of quantitative gait analysis technologies.



Methods

Overview

This scoping review protocol follows the recommendations outlined in the Joanna Briggs Institute (JBI) methodology for scoping reviews [27].

The conduct and reporting of results will conform to the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) checklist [28].

Inclusion and Exclusion Criteria

A list of inclusion and exclusion criteria can be seen in Textbox 2.

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Textbox 2. Inclusion and exclusion criteria.

Inclusion criteria

- All adult patient populations (18 years and older)
- All health care professionals
- Quantitative gait analysis technologies
- Clinical efficacy studies (ie, efficacy and effectiveness)
- Clinician perspectives on the use of gait technologies in practice
- Clinical setting

Exclusion criteria

- Gait training technologies
- Gait technologies used solely to measure movement or activity levels
- Gait technologies in the development or preliminary validation phase

Types of Participants

There are 2 categories of participants included in this review. The first category of participants includes all adult patient populations (18 years and older), and the second category of participants includes all health care professionals. There will be no restrictions with regards to gender, sex, or ethnicity.

Concept

There are three components to the concept of this scoping review: (1) quantitative gait analysis technologies, (2) clinical efficacy (ie, efficacy and effectiveness), and (3) clinicians' perspectives on the use of gait technologies in practice (eg, perceived barriers or facilitators to ease of use and usefulness of technology or factors beyond ease of use and usefulness). First, gait analysis technologies are defined as those used to quantitatively measure the different phases of gait for the purpose of assessment or monitoring changes in gait. This can include collecting kinetic or kinematic measures or muscle function data. By this definition, articles studying gait training technologies or technologies used solely to measure movement or activity levels (eg, number of steps per day) will be excluded. Additionally, studies focused on gait technology development or preliminary validation will be excluded from this review. Second, we define clinical efficacy similarly to the "diagnostic thinking and treatment efficacy" and "patient outcomes" categories as outlined by Wren et al [26]. This includes studies that investigate how clinicians use gait technologies (eg, treatment planning) with patient populations and what impact, if any, there is on patient outcomes. Both efficacy and effectiveness trials were included in this review. However, for simplicity, the term clinical efficacy will be used throughout this protocol. Third, clinicians' perspectives on the use of gait technologies in practice encompass their perception of ease of use and usefulness of the technology and barriers or facilitators beyond ease of use and usefulness that they perceive to impact the use of gait technologies in practice. Barriers or facilitators beyond ease of use and usefulness include a clinician's perception of how factors about themselves or their surroundings (eg, supportive environment, training, experience) influence the use of gait technologies in practice. The components of clinical efficacy and clinician perspectives do not need to occur within a given paper, but rather these components are combined using "OR" (eg, gait analysis technologies AND (clinical efficacy OR clinician perspectives)). How these components differ between the type of technology, patient population, and clinical context will also be examined in this review.

Context

There are no restrictions on geographical location or cultural factors in this review. The context of this scoping review includes "clinical care," which encompasses a wide range of settings, including but not limited to hospitals, homes, community-based locations, and private health clinics. Because we are investigating clinician perspectives, it is likely that many of the articles will be qualitative in nature. Thus, the context of these papers may include interview or focus group settings.

Types of Evidence Sources

Primary research studies of all designs, including both quantitative and qualitative work, as well as gray literature (ie, conference abstracts), will be included in this review. Secondary research studies (eg, systematic reviews) and other gray literature (eg, textbooks and dissertations) will be excluded from this review. Additionally, articles and conference abstracts will be excluded if there are no reported results.

Search Strategy

A 3-step search strategy was performed as outlined by the JBI methodology for scoping reviews [27]. First, a preliminary search of relevant sources consisted of hand-searching primary research articles that met the above inclusion criteria in PubMed and Google Scholar. Search terms included: Gait technologies AND clinician perspective, gait technologies AND clinical care, gait analysis AND barriers. A thorough analysis of the keywords included in the title and abstracts of selected articles was then conducted. Second, a comprehensive search strategy was created in MEDLINE (Ovid) based on the list of keywords and subject headings derived from the previous analysis and synonyms found by the first author. Boolean operators were used in the search strategy in two separate ways: (1) to combine all keywords that describe a single concept using "OR" and (2) to

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combine all 3 concepts using "AND" to develop a final search. The MEDLINE (Ovid) search strategy was created in collaboration with an information specialist at the University Health Network. Search terms were tested, and adjustments to the search strategy were made based on the identification of new keywords. Between March and April 2021, the final MEDLINE (Ovid) search strategy was translated to 4 other databases: CENTRAL (Ovid), EMBASE (Ovid), CINAHL (EBSCO), and SPORTDiscus (EBSCO). Engineering databases are excluded from this search because this review considers technology applications in a clinical context. The list of keywords and subject headings used in the MEDLINE (Ovid) search string was modified (eg, synonyms found) to suit the search capacity of the other databases. In the SPORTDiscus (EBSCO) database, subject headings from the MEDLINE (Ovid) search were omitted as no synonyms were found. The search will be iterative in nature, with adjustments being made to the search strategy in all databases as new keywords are identified. The third search strategy involved scanning the reference list of included literature and relevant review articles. To add to the breadth of the search strategy, supplemental searching through PEDro and Google Scholar was performed. If the full text of the included articles cannot be found, the reviewers will contact the primary authors for this information.

Only articles written in the English language will be included in this review because that is the language understood by the authors. Both peer-reviewed and gray literature (ie, conference abstracts) discussed in the above 3-step search strategy will be included in this review. Conference abstracts are included to increase the comprehensiveness of this review and will be searched in Embase (Ovid) and CENTRAL (Ovid). These 2 databases were chosen because conference proceedings are indexed in Embase (Ovid), with some also being found in CENTRAL (Ovid). There is no date limit on the articles included in this review, because to our knowledge, no other scoping review has addressed this specific question. An information specialist at the University Health Network was involved in the development and review of the search strategies created in all 5 databases. The complete MEDLINE (Ovid) search strategy can be found in Multimedia Appendix 1.

Description of Source Selection

Covidence (Veritas Health Innovation) systematic review software will be used for the management of the articles identified in the search strategy. Prior to performing the formal selection process, pilot testing will be completed with 4 reviewers (YS, LC, AI, and KKP). In accordance with the JBI methodology for scoping reviews, 25 titles and abstracts will be chosen for the reviewers to screen based on the inclusion criteria previously mentioned [27]. Inconsistencies found during the pilot testing will result in further refinement of the inclusion criteria. The formal screening process will begin once there is a 75% or greater agreement among reviewers on the chosen 25 titles and abstracts [27].

During the formal screening process, 2 reviewers (YS and LC) will independently perform title and abstract screening. Both reviewers must agree on the inclusion of the article for it to be processed in the full-text review stage. Conflicts between the 2 reviewers at this stage will be resolved by a third reviewer (AI). Once title and abstract screening is complete, pilot testing for the full-text review stage will begin with the same 4 reviewers (YS, LC, AI, and KKP). Similar to the pilot testing for title and abstract screening, all 4 reviewers will independently read 5 full-text articles and assess them for inclusion. Any discrepancies during the pilot testing will result in further refinement of the inclusion criteria. The formal full-text review process will begin once 75% agreement or more is reached during pilot testing. Once the pilot testing is complete, both reviewers (YS and LC) will independently read the full-text articles for inclusion. Where articles are agreed upon for exclusion but the chosen exclusion criteria differ between reviewers, both reviewers (YS and LC) will decide on the most appropriate exclusion criteria by consensus. A third reviewer (AI) will resolve conflicts as they pertain to including and excluding articles. The complete review process will be illustrated using a flow diagram and included in the appendices of the scoping review. A short explanation regarding the inclusion and exclusion of sources of evidence will also be included in the appendices of the scoping review.

Critical Appraisal

This review will also include a critical appraisal of all full-text articles included in this review. The critical appraisal will be used to assess the quality of the study design, methods, and analysis of the included literature. The JBI critical appraisal tools will be used, as this is recommended to authors who are conducting reviews following JBI guidelines [29]. JBI critical appraisal tools will be chosen based on the study design of the literature and may include checklists for cross-sectional studies, case control studies, case reports, case series, cohort studies, qualitative studies, quasi-experimental studies, and randomized controlled trials [30-33]. The JBI critical appraisal tools will be piloted by both reviewers (YS and LC) on 3 studies: a randomized controlled trial, a qualitative study, and a case report. The remaining articles will be divided between both reviewers; one will critically appraise the evidence source, and the other will review the appraisal for accuracy. The results of the critical appraisal will not be used to determine the inclusion or exclusion of literature in this review. This is because the authors consider including papers of all methodological quality to be valuable to the research community because it shows the state of the literature in this field and whether higher-quality evidence is warranted. No scoring system will be used during critical appraisal. Authors will report on the quality of the articles by sharing the results of the critical appraisal in tabular format in the final review. This will allow readers to see how each study attempted to limit bias in the design, conduct, and data analysis.

Data Extraction

A draft data extraction form has been created in accordance with the JBI methodology for scoping reviews [27]. Information retrieved from the included sources will include the following as available: study characteristics (eg, authors, year of publication, location of where the article was published or conducted, aims or purposes, population or sample size, type of population or sample), methods or methodology (eg, tradition

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of inquiry or quantitative design), intervention (if any), and findings as they address the scoping review question (eg, clinical efficacy or clinician perspectives). In situations where conference abstracts are associated with a full text, the reviewers will only extract data from the full text. In cases where there is no full text associated with the conference abstract, the abstract itself will be used for data extraction.

The data extraction form will be piloted by both reviewers (YS and LC) on 3 articles to ensure that relevant information is being extracted. Pilot testing will involve both reviewers (YS and LC) extracting data from 3 articles. The first reviewer (YS) will check for consistency in the extracted information between both reviewers. Both reviewers will then meet to discuss whether additional modification of the data extraction form is needed. Recognizing that the development of the data extraction form is iterative, modifications may be made throughout the extraction process by both reviewers. For modifications to be made, both reviewers will need to agree upon the added information categories. If disagreements arise, a third reviewer (AI) will be involved. The included literature will be divided between both reviewers (YS and LC); one will complete data extraction and the other will review the extraction for accuracy.

Analysis of the Evidence

The results of this scoping review will be synthesized and presented using both quantitative and qualitative methods. Quantitative methods will include counts of the number of unique clinical uses, clinician perspectives, types of gait analysis technologies used, patient populations, and clinical contexts. Qualitative methods will be used to organize the findings into Figure 1. We will use a combination of deductive and inductive content analysis in this review. Deductive content analysis will be used to code the literature, similar to the visual representation outlined in Figure 1. Inductive coding will be used to describe how and whether the clinical efficacy of gait technologies and clinician perspectives (eg, ease of use, usefulness, and factors beyond ease of use and usefulness) differ depending on the type of gait technology, patient population, and clinical context. This process involves coding the data, developing categories, and forming concepts [34]. The first author (YS) will be responsible for completing all stages of the content analysis process. NVivo (version 12, QSR International Pty Ltd) software will be used as the data management system for the qualitative content analysis. To ensure the trustworthiness of the analysis, the first author will provide justifications for how the literature was organized into the components outlined in Figure 1. The first author will also meet with the research team throughout all stages to receive team feedback for further refinement of the content analysis process.

Ethical Considerations

This scoping review does not require research ethics board approval.

Patient and Public Involvement Statement

There was no patient or public involvement in the development of this protocol.

Results

Results of this proposed scoping review will be presented in both a tabular format and a diagram. The table will display the quantitative analysis of the results. Results of the critical appraisal for each study will be shared within the text of the scoping review as well as in tabular format. The diagram will display the qualitative results and be similar to what is shown in Figure 1. In summarizing the results both quantitatively and qualitatively, this review will highlight the gaps in the literature surrounding how gait analysis technologies are used in practice and what supports or hinders their clinical adoption.

A search of relevant articles will be conducted in all 5 databases and through hand searching in Google Scholar and PEDro, including articles published up until December 2022. The research team plans to submit the final scoping review for publication in a peer-reviewed journal in 2023. If we experience any delays to the timeline (eg, a greater number of papers to screen than expected), we will recruit others to assist with screening and data extraction.

Discussion

Impact

Preliminary research suggests gait analysis technologies have a role in clinical decision-making [12,13]. Despite this potential value, gait analysis technologies are not commonly found in clinical practice. This review will describe the factors that influence the clinical adoption of quantitative gait analysis technologies with a focus on clinical efficacy and clinicians' perspectives on their use in the clinical care of adult patient populations. To be comprehensive, this review will also highlight how these components differ across gait technology types, patient populations, and clinical settings.

To our knowledge, this will be the first review to synthesize the evidence on the clinical efficacy and a clinician's perspective on the use of gait technologies in the clinical care of adult patient populations. This review differs from related systematic reviews [11,25,26] for several reasons. First, this review focuses on gait analysis technologies (ie, wearable and nonwearable) and how these technologies impact clinical decision-making or patient outcomes. Lastly, this review also takes into consideration the perspectives of clinicians on the use of gait technologies in practice.

Limitations

This review has some limitations. First, this review will only consider conference abstracts as a source of gray literature, and second, this review will only consider studies written in the English language. Thus, relevant articles may be missed if written in another language.

Conclusions

We anticipate that this review will provide insights into the clinical adoption of quantitative gait analysis technologies by highlighting their role in clinical decision-making and clinician perspectives on using gait technologies in practice. The results of this review can also be used to inform and guide future work

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focusing on facilitating the translation of technologies into practice. Recognizing the role of this review in technology adoption and clinical sciences, the results will be disseminated at clinical science conferences and through publication in a peer-reviewed journal.

Acknowledgments

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Authors' Contributions

YS led the development of the search string and protocol. LS was the second reviewer on the scoping review and provided feedback to the protocol. KKP provided feedback on the protocol and is the cosupervisor of the first author. AI provided feedback on the search strategy and protocol and is the primary supervisor of the first author.

Conflicts of Interest

None declared.

Multimedia Appendix 1
MEDLINE search string.
[DOCX File , 34 KB - resprot_v12i1e39767_app1.docx]

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Abbreviations

JBI: Joanna Briggs Institute
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews

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Protocol

Public Transport Accessibility for People With Disabilities: Protocol for a Scoping Review

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Abstract

Background: Transportation is essential for people of all ages and backgrounds to live a fulfilling and satisfying life. Public transport (PT) can facilitate access to the community and improve social participation. However, people with disabilities may encounter barriers or facilitators in the whole travel chain that can lead to negative or positive perceptions in terms of self-efficacy or satisfaction. These barriers may be perceived depending on the nature of the disability. Few studies have identified PT barriers and facilitators experienced by people with disabilities. However, findings were focused mainly on specific disabilities. Access requires broader considerations of barriers and facilitators for various types of disabilities.

Objective: This scoping review aims to describe the barriers and facilitators to the use of PT experienced by people with various disabilities in the whole travel chain and to explore perceived experiences, self-efficacy, and satisfaction when using PT.

Methods: A scoping review will be conducted using Arksey and O'Malley's framework and the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) checklist. The literature search will be conducted using the electronic databases MEDLINE, Transport Database, and PsycINFO via Ovid platform, Embase, and Web of Science from 1995 to 2022. Two reviewers will independently identify studies based on inclusion (published in English or French, outcomes on PT accessibility for people with disabilities, peer-reviewed or guideline reports or editorials) and exclusion (no full text, focused on a technology system, outcome validation study, study on no-fixed route PT accessibility, etc) criteria and extract the data. When a study has addressed the accessibility of multiple modes of PT, including fixed-route PT, it will be retained. However, only data on fixed-route PT will be extracted. Any related systematic reviews identified through the search will be retained, and the reference lists will be hand-searched and screened for inclusion criteria.

Results: The search we performed on July 21, 2022, in the databases mentioned above allowed us to retrieve 6399 citations. Of these citations, 31 articles were identified, and data extraction was performed. As of March 11, 2023, we have started data analysis. The findings will be synthesized narratively to summarize the barriers and facilitators to PT, perceived experiences with PT, self-efficacy for using PT, and satisfaction with PT according to the Human Development Model-Disability Creation Process conceptual framework.

Conclusions: The results of this scoping review could lead to a better understanding of the potential barriers and facilitators to the use of PT by people with various types of disabilities and how negative or positive experiences throughout the travel may influence their self-efficacy and satisfaction. The results may be used to provide recommendations to PT providers and policy makers to work together to make PT accessible, usable, and inclusive for all people with disabilities.

Trial Registration: Open Science Framework OSF.IO/2JDQS; https://osf.io/2jdqs

International Registered Report Identifier (IRRID): DERR1-10.2196/43188

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KEYWORDS

accessibility; public transport; disability; experience; self-efficacy; satisfaction; scoping review

Introduction

On the basis of the 2010 global population estimates, the World Health Organization (WHO) and World Bank [1] report that more than 1 billion people live with some form of disability, including motor, sensory, and cognitive; intellectual; or mental disabilities. This represents approximately 15% of the world's population, which is 5% more than a previous WHO estimate from the 1970s. More than 46% of people 60 years and older have disabilities and more than 250 million older adults experience moderate to severe disabilities [2].

Given their disability or aging-related health conditions, many people may experience restrictions in accessing transportation. In transportation modes, public transport (PT) is essential for people of all ages and backgrounds to live a fulfilling and satisfying life. For example, PT plays a vital role in many aspects of daily life including access to employment, education, health care, shopping, social occasions, and multiple recreational activities [3]. Thus, it may facilitate participation in community activities and employment if it is accessible to people with disabilities. PT is a system of vehicles such as buses and trains that operate at regular times on fixed routes and are used by the public [4]. Accessible PT enables people with disabilities to live independent lives and means having access to transport services that are available where and when one wants to travel, being informed about the services, knowing how to use the services, being able to use the services, and having the means to pay for them [5]. This suggests that the accessibility of PT involves more than simply boarding and disembarking. To ensure access, an understanding of all the elements that make up the travel chain is required [6], such as leaving the home to wait for the transport at the stop or station, availability of timetable information, boarding, moving within the transport, disembarking, the use of sidewalks, and the attitudes of drivers and other passengers toward people with disabilities [7]. Thus, people with disabilities may encounter barriers or facilitators related to any element of the travel chain that can lead to negative or positive perceptions in terms of self-efficacy or satisfaction, and these may, in turn, affect their willingness to use PT.

Defined as the belief in one's ability to perform a specific task [8], self-efficacy has been identified as the most important predictor of travel behavior change [9]. Self-efficacy is determined by factors such as past experiences or accomplishments and emotional reactions [8,10,11]. Past accomplishments that are interpreted as the result of a skill developed in the past [12] have been found to be the most important in influencing self-efficacy [10]. Emotional reactions can improve or reduce self-efficacy. Thus, positive experiences with PT use may generate positive emotions that can enhance feelings of personal efficacy toward PT use. Conversely, negative experiences can induce negative emotional reactions such as anxiety and doubt, which in turn may impact self-efficacy for using PT. Therefore, low self-efficacy may be a barrier to PT use [9].

Satisfaction is described as an intrinsic positive consequence emerging from a behavior that fulfills the expectations of an individual [13]. Satisfying experiences have been shown to increase intrinsic motivation, which increases the likelihood to continue the behavior. Consequently, experiencing satisfaction during interventions is assumed to increase the likelihood that the individual will sustain the behavior change [9]. The most relevant features of the transportation system, such as trip duration, accessibility, fare, network connectivity, information, comfort, safety, and employees' kindness, may influence user satisfaction. Satisfaction with travel can have a significantly positive effect on the frequency of PT use [14]. Indeed, the more satisfied PT users are with their travel experience, the more they tend to use PT for their work commute [14].

We are interested in all PT modes including buses, trains, tramways, subways, and ferries because people with disabilities travel less frequently and rely on PT more than the general population [15]. Long before the adoption of the United Nations Convention on the Rights of Persons with Disabilities (UN-CRPD) in 2006 [16], many countries including the United States, Canada, and Australia developed regulations, codes, and standards to regulate the practices related to the accessibility of PT [17]. Indeed, in 1990, the Americans with Disabilities Act (ADA) qualified accessible and usable transportation as a qualified civil right [5]. In Australia, the Disability Standards for Accessible PT 2002 (as amended in 2010) were enforced to provide transport operators and providers with information on their obligations under the Disability Discrimination Act (DDA). Under the Canada Transportation Act (1996), the Canadian Transportation Agency was made responsible for removing obstacles to mobility in all federally regulated (air, rail, marine, and interprovincial bus) transportation services and facilities. Despite these efforts, many people with disabilities continue to face barriers including physical and social barriers [3,18-24] that limit their use of PT.

Recently, Unsworth et al [20] examined, in their systematic review, the evidence that solely investigated the use of PT by mobility device users, which largely comprised people with mobility disabilities. The study identified problems encountered by mobility devices users, such as uneven pavement surfacing, lack of dropped curbs, steps instead of ramps, narrow doorways, controls for pedestrian lights or lift access that are too high, and badly designed street displays; problems with information being placed out of reading reach, inappropriate spaces for wheeled mobility devices, and lengthy wait times with little shelter [20]. Since the study excluded other types of disabilities such as visual; hearing; autism; and cognitive, mental, or intellectual disabilities, its findings cannot be generalized to all people with disabilities. Identification of needs related to PT of people with other types of disabilities is also important. For example, people with mental health conditions might not use certain services because of the existing social barriers, such as stigma [1], which differ from physical barriers commonly encountered by people with mobility impairment.

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This study primarily aims to examine barriers and facilitators to the use of the PT (buses, trains, tramways, ferries) by people with different types of disabilities in the whole travel chain, where disability is defined as the interaction between individuals with a health condition (could be physical or mental) with personal and environmental factors including negative attitudes, inaccessible transportation and public buildings, and limited social support, etc [25]. For the purpose of this review, the definition includes older adults, as people with disabilities are aging with the increase of level of disabilities, and older adults commonly experience disabilities because of various age-related health conditions [26]. Second, this study aims to highlight the perceived experiences of individuals with disabilities when using PT in terms of their self-efficacy and satisfaction.

Methods

Design

A scoping review will be conducted using the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) checklist [27]. The extent, range, and the nature of research activity will be explored to determine the value of undertaking a full systematic review, to summarize and disseminate research findings, and to identify research gaps in the existing literature [28]. For this scoping review, the methodological framework described by Arksey and O'Malley [28] will be used. It includes five stages: (1) identifying the research question; (2) identifying relevant studies; (3) study selection; (4) charting the data; and (5) collating, summarizing, and reporting the results. This last stage is described in the Results section.

Identifying the Research Question

This phase involved a discussion among the authors (CRM, KLB, and FR) to identify the relevant research that arises from the gaps in the existing literature on the topic of this scoping review. The main research questions identified by the authors to guide the scoping review process were as follows: What are the different barriers and facilitators to the use of PT experienced by people with various types of disabilities including older persons? Second, what is their perceived experience in terms of satisfaction or self-efficacy when using PT? These questions emerge from a preliminary search of the literature using Google Scholar.

Identifying Relevant Studies

An extensive literature search of both peer-reviewed and gray literature databases will be performed to identify relevant information about the topic. To conduct this research robustly, we will seek the collaboration of a librarian (MG) who specializes in the use of databases related to the rehabilitation and accessibility of PT by people with disabilities. Given that PT accessibility should consider several fields such as biomedical, transportation, psychological, and human and social sciences, the literature search will be conducted in 5 relevant databases including MEDLINE, Transport Database, PsycINFO (from Ovid platform), Embase, and Web of Science from 1995 to 2022. 1995 date was selected as the start date because very little literature was published in the field prior to this time [20]. The keywords and terms that will be used are as follows: (((Aged or ag?ing or old*) ADJ2 (person* or adult* or people or individual* or man or men or woman or women or user*)) or elder* or geriatric*).ti,ab,kw OR ((mental* or intellectual*) ADJ2 (retard* or deficien* or ill or illness)).ab,ti,kw OR ((physical* or hearing or visual* or cogniti*) ADJ2 (deficien* or impair* or challenge*)).ab,ti,kw OR (disabled or disabilit* or Handicap*or blind* or "hard of hearing" or deaf*).ab,ti,kw OR (((walking) ADJ2 (frame or stick)) or wheelchair* or scooter* or walker* or rollator* or crutche* or cane* or brace*).ti,ab,kw OR ((mobility or walking) adj2 (difficult* or limitation*)).ti,ab,kw AND ("Public transport* accessibility" or bus or buses or tramway* or train or trains or subway* or metro or underground or ferry or ferries).ti,ab,kw AND (satisfaction or "self-efficacy" or "self-efficacy" or confiden* or experience or "quality of life").ti,ab,kw. Since the quality of life includes many aspects of life, such as psychological factors, we inserted this term just for optimizing the search function. This search function could be modified, if necessary, by switching from one database to another. A special mention has to be made for the Web of Science database. Indeed, we will activate the exact search from the advanced search to limit the lemmatization of the results. All retrieved literature will be imported into Covidence (Veritas Health Innovation), which is a software in which all the steps of a knowledge synthesis can be completed, where the duplicates will be removed from the selection of articles for the extraction of obtained data. The literature that meets the criteria presented in Textbox 1 will be included in our scoping review. Moreover, when a study has addressed the accessibility of multiple modes of PT, including fixed-route PT, it will be retained. However, only data from fixed-route PT will be considered in this study. In addition, when any systematic review related to the topic of this scoping review will be identified, we will count the number of studies included in the review that potentially meet our inclusion criteria and will note how many studies are not present in our search [27].

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Textbox 1. Inclusion or exclusion criteria.

Inclusion criteria

- Original peer-reviewed manuscript
- Guideline report
- Editorial
- Concerned with PT (public transport; bus, train, tramway, ferry) accessibility or confidence and satisfaction with PT for people with disabilities including older people
- Published from 1995 to 2022
- Published in English or French

Exclusion criteria

- Article for which the full text is not available
- Article focuses on the use of technology while using the PT system
- Article generally discusses universal design or transportation
- Validation study of measurement tools assessing PT accessibility or travel confidence or travel satisfaction for people with disabilities
- Study on no-fixed route PT accessibility (eg, adapted school bus for students with disabilities, paratransit)

Study Selection

Two reviewers (CRM and SG) will independently select the literature to be included in the scoping review in the 2 steps of screening provided in the Covidence platform, based on the inclusion and exclusion criteria. The first step, after removing duplicates, will consist of screening the title and abstract for each document by examining how they are related to the topic. The second step will be reviewing the remaining full articles. All reasons for exclusion will be recorded in the Covidence platform, and cases of disagreement will be resolved through discussion between at least 2 reviewers. To prevent errors and reduce the risk of discrepancies between the 2 reviewers, each screening phase will start with a calibration exercise. In case of persistent disagreement, a third evaluator will be involved.

Charting the Data

This stage involves the use of a data-charting form to extract relevant information from the reviewed literature [28]. For this scoping review, the data-charting form will be jointly developed by 2 reviewers to determine which variables to be extracted. The same reviewers (CRM and SG) will independently chart the data, discuss the results, and continuously update the data-charting form in an iterative process [29] by using Covidence. Information, such as author names and year of publication, setting of the study, study objective, sample, study design, intervention (if applicable), outcomes, and relevant findings to the research questions, will be extracted.

Ethical Considerations

Research ethics approval is not required for this scoping review as the study will not include human or animal participants. Data will be sourced only from peer-reviewed and gray literature.

Results

The search we performed on July 21, 2022, in the databases mentioned above allowed us to retrieve 6399 citations. Of these citations, 31 articles were identified, and data extraction was performed. As of March 11, 2023, we have started data analysis. Relevant findings related to barriers and facilitators, as well as the perceptions of people with disabilities in terms of self-efficacy and satisfaction when using PT, will be presented in tables. In addition, a narrative report will allow us to summarize the relevant findings from the key terms. For this purpose, a brainstorming session that involves all authors will be organized. The results will be described according to the Human Development Model-Disability Creation Process (HDM-DCP) conceptual framework [30] with respect to the research questions, and the aims of this scoping review. This conceptual framework addresses situations of disability that occur when personal and environmental factors restrict life habits, thereby decreasing social participation. Any gap or limitation in the existing literature will be identified and highlighted. We expect to complete this scoping review by June 2023.

Discussion

Expected Findings

This scoping review aims to examine the barriers and facilitators to the use of TP (buses, trains, tramways, and ferries) by people with various disabilities in the whole travel chain and highlight their perceived experiences in terms of satisfaction and self-effectiveness during their travel in PT. Since barriers and facilitators differ between people with disabilities, focusing on the literature on these indicators of PT use by people with various disabilities might help to provide recommendations for making PT more accessible and usable equitably by all passengers. Accessibility and use of PT ensure the participation and social inclusion of people with disabilities. In contrast, an inaccessible mode of PT will never be used by people with disabilities, and therefore may lead to their isolation and social exclusion. To better understand the issue of barriers and facilitators to the use of PT, Iwarsson and Ståhl [6] proposed

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the concept of the travel chain in PT. The travel chain suggests that any given travel starts at the origin of the users (eg, their home) and ends at the final destination. Thus, travel needs to be considered an indivisible whole rather than singling out each element. Jensen et al [31] underlined taking a sustained look at all the problems that people with disabilities might experience along an entire route, not simply considering the physical accessibility of PT vehicles. In this way, the elements of the travel chain mentioned above, including drivers' and passengers' attitudes, cannot be considered individually. For example, encountering a sidewalk lacking a curb cut for a wheelchair user is similar to a nondisabled person who encounters an impassable brick wall along their route to the bus stop. Minimally, such barriers can cause distress to the individual with a disability involved, and in the worst case, they can lead to journeys not being made [7]. Any barrier to all or part of the chain of PT use, and negative experiences, may affect the self-efficacy and satisfaction levels of people with disabilities, and therefore their willingness to travel. In return, these psychological factors may enhance travel behavior if PT is accessible and people with disabilities experience positive emotions throughout the travel.

This review will contribute evidence on the multiple barriers and facilitators that may be encountered by people with various forms of disabilities or in situations of autonomy loss (eg, older adults) throughout the fixed-route PT. Barriers and facilitators to PT may be experienced differently by people with disabilities depending on their individual situation of disability (eg, physical, intellectual, cognitive, visual, or hearing disability). It is therefore important to review the scientific literature that addresses PT issues to provide recommendations for best practices in PT to transport providers and policy makers to work together to make PT accessible, usable, and inclusive for people with all types of disabilities. Modifications to the environment (eg, installation of ramps) and interventions (eg, staff awareness and education, training in the use of PT for people with disabilities) may facilitate accessibility and use of PT by people with disabilities. Improved use of PT may develop access to the community and community-based services. Therefore, improved use of PT may facilitate social inclusion, participation, and well-being for people with disabilities.

Limitations

This scoping review may exclude some studies. Indeed, the keywords to be used in the search strategy are broad and may not identify all specialized studies in PT accessibility for people with disabilities. Moreover, the fact of having considered only English and French as the languages of publication could exclude papers that are relevant for our scoping review.

Conclusion

The identification of barriers and facilitators to the use of PT by people with disabilities is an important step that may help policy makers and transport operators around the world to develop and implement interventions to facilitate access, use, and inclusion of this mode of transport, as the experiences of people with disabilities when using this mode of transport have an impact on their well-being. The results of this scoping review could lead to a better understanding of the potential barriers and facilitators to the use of PT by people with various disabilities and how negative or positive experiences throughout the travel may influence their self-efficacy and satisfaction.

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Data Availability

The data sets generated or analyzed during this study are available from The Open Science Framework (OSF; registration DOI: https://doi.org/10.17605/OSF.IO/2JDQS).

Authors' Contributions

CRM, FR, and KLB contributed to the conceptualization of the study. CRM prepared the draft protocol under the supervision of FR and KLB. MG refined the search function. CRM, FR, KLB, and SG contributed to the development of the background, design of the study, and planned outcomes of the research. CRM prepared the manuscript, and FR, KLB, and SG reviewed it. The authors read and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

ADA: Americans with Disabilities Act
DDA: Disability Discrimination Act
HDM-DCP: Human Development Model-Disability Creation Process
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews
PT: public transport
UN-CRPD: United Nations Convention on the Rights of Persons with Disabilities
WHO: World Health Organization

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Protocol

Platform-Based Patient-Clinician Digital Health Interventions for Care Transitions: Protocol for a Scoping Review

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Abstract

Background: With the increased adoption of technology, the use of digital health interventions in health care settings has increased. Patient-clinician digital health interventions have the potential to improve patient care, especially during important transitions between hospital and home. Digital health interventions can provide support to patients during these transitions, thereby leading to better patient outcomes.

Objective: This scoping review aims to explore the available literature, specifically (1) to examine the impact of platform-based digital health interventions focused on care transitions on patient outcomes, and (2) to identify the barriers to and enablers for the uptake and implementation of these digital health interventions.

Methods: This protocol was developed based on Arksey and O'Malley's, Levac and colleagues', and JBI scoping review methodologies, and it has been reported according to the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement for the Scoping Reviews) format. The search strategies were developed for 4 databases: MEDLINE, CINAHL, EMBASE, and the Cochrane Central Register of Controlled Trials by using key words such as "hospital to home transition" and "platform-based digital health." Studies involving patients 16 years or older that used a platform-based digital health intervention during their hospital to home transition will be included in this review. Two reviewers will independently screen articles for eligibility by using a 2-stage process (ie, title and abstract screening and full-text screening). We expect to refine the eligibility criteria during the title and abstract screening process as we anticipate retrieving a significant number of articles. In addition, we will also perform a targeted search of the grey literature, as well as data extraction. Data analysis will consist of a narrative and descriptive synthesis.

Results: The review is expected to identify research gaps that will inform the development of future patient-clinician digital health interventions. We have identified a total of 8333 articles. Screening began in September 2022, and data extraction is expected to commence in February 2023 and end by April 2023. Data analyses and final results will be submitted to a peer-reviewed journal in August 2023.

Conclusions: We expect to find a wide variety of postcare interventions, some gaps in the quality of research evidence, as well as a lack of detailed information on digital health interventions.

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KEYWORDS

care transitions; digital health; targeted patient/client communication; scoping review protocol; patient care; patient support; hospital-to-home transition; hospital discharge; implementation; barriers

Introduction

Patient-clinician digital health interventions have been described by the World Health Organization as "targeted patient/client communication" [1] and have become increasingly popular in health care settings [2]. Such interventions can support patients and caregivers in navigating a complex health system by utilizing information technologies to facilitate communication between parties [1,3]. Digital health interventions that use platform-based technology to facilitate communication and information-sharing between patients and clinicians have the potential to improve care coordination and outcomes during care transitions.

Specifically, asynchronous digital platforms such as web-based or mobile applications contain information that is shared or stored between patients and clinicians. These digital platforms often include patient information and education for discharge planning, follow-up appointments and services, patient empowerment and engagement, and health status updates [1]. In a recent scoping review by Zhang and colleagues [4], the role of digital health interventions for patients with hip fractures was examined. Results of the scoping review indicated that digital health interventions were generally used to support health care providers in the care of such patients. In another systematic review by Free and colleagues [3], digital health interventions were shown to have increased the engagement of patients in their health care journey and a corresponding reduction in hospital admissions.

Engaging patients in their care through digital health interventions is possible given the widespread use of internet-based personal communication devices [5] and the effective use of such interventions with patients and their clinicians. Although asynchronous digital platforms can sometimes be challenging, especially in relation to technological issues [6], successful use of these platforms has been described with patients living with diabetes [7,8], cardiovascular disease [9,10], chronic obstructive pulmonary disease [11], and patients recovering post surgery [12-14].

The multi-service and multi-sector coordination of care after an acute event or diagnosis can be complicated for patients and caregivers to navigate. After acute care admission, patients often receive inadequate information about discharge instructions [15], whereas others have unanswered questions [16]. Some studies have described how patients may experience poor retention of verbal instructions during post-discharge periods [17,18], and how effective education and written discharge instructions may help improve a patient's understanding and facilitate transition from hospital to home [19-23]. A critical gap that has been identified is poor communication between clinicians and patients and their caregivers [24,25]. Digital health interventions can provide opportunities for ongoing support from clinicians to patients and their caregivers [12], which can improve the overall level of communication and lead to better adherence to care instructions [26].

The emerging research highlighting the benefits of patient engagement [27] reinforces the importance of developing patient-centered discharge planning processes [28]. This may include education for patients and their caregivers regarding their health conditions, medication, and common symptoms; a mechanism for exchanging questions and obtaining feedback from patients; and guidance on when to seek appropriate medical care or follow-ups. Using integrated [29] and holistic patient and caregiver interventions [19-23,30], and digital platforms [31] in particular, can help minimize avoidable readmissions and other challenges with the transition of patients from hospital to their homes. Digital health interventions should be inclusive and consider unique patient characteristics such as age, disability, and level of cognition to optimize success [32]. The usability of digital health interventions for patients and clinicians is also crucial for their successful uptake [33].

Despite the widespread development and use of information technology [5], the desire of patients and caregivers for readily available information [34], and the need for better engaging patients in their care process to optimize patient outcomes, only limited research has examined the specific platform-based patient-clinician digital health interventions that are in use for discharge and care transitions.

Our goal is to explore the available literature, specifically (1) to examine the impact of platform-based digital health interventions specific to care transitions on patient outcomes, and (2) to identify the barriers to and enablers for the uptake and implementation of these digital health interventions. The findings from this work would inform future work on the "MyPath to Home" digital health intervention [35].

Methods

Protocol Design

This protocol was developed based on Arksey and O'Malley's [36] methodology, elaborated by Levac and colleagues [37] and JBI Manual for Evidence Synthesis [38], which involves the following stages: (1) identify the research question; (2) identify relevant studies: (3) select studies; (4) chart the data; and (5) collate, synthesize, and report results. For this protocol, we also followed the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement for the Scoping Reviews) reporting format [39].

Stage 1: Identify the Research Question

The research questions guiding this scoping review are as follows:

1. What is the impact of platform-based patient-clinician digital health interventions used for discharge or care transitions on patient outcomes?

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2. What are the barriers to and enablers for the uptake and implementation of these interventions for clinicians and patients transitioning from hospital to home?

Stage 2: Identify Relevant Studies

A comprehensive search strategy will be developed by an information specialist relevant to MEDLINE, CINAHL, Embase, and the Cochrane Central Register for Controlled Trials. The MEDLINE strategy will be peer-reviewed by another information specialist according to the PRESS (Peer Review of Electronic Search Strategies) guidelines [40]. The search strategies are available in Multimedia Appendix 1.

Once the searches have been completed, the results will be exported to Covidence [41] for storage, removal of duplicates, and screening. In addition, we will conduct a manual search of the references from the included studies and a targeted grey literature search of ClinicalTrials.gov [42] and the International Clinical Trials Registry Platform Search Portal [43], as well as key digital health technology websites.

Stage 3: Select Studies

Preliminary inclusion criteria are defined following the Population, Concept, Context (PCC) format:

- Population: Patients (16 years or older) recruited before hospital discharge;
- Concept: Postcare interventions (eg, self-care, symptom monitoring, pain control and management, mobilization, follow-up appointments, ability to ask questions) using any asynchronous digital platforms such as web-based or mobile applications where information is shared or stored between patients and clinicians; and
- Context: Discharge episode from hospital to the community.

We will include primary studies (ie, randomized controlled trials [RCTs], quasi-experimental studies, pilot or feasibility studies, observational studies [case-control, cohort, cross-sectional, and descriptive studies], and qualitative studies) published between 2012 and 2022. Preliminary exclusion criteria will include: (1) pediatric, newborn care, mental health, and cancer populations; (2) synchronous non–platform-based digital health care interventions (eg, chat platform, wearable devices, prosthetics, robotics, medical imaging technology such as x-rays and ultrasounds, interventions only using a standard telephone); and (3) nonprimary studies (eg, commentaries, editorials, study protocols, and policy briefs).

Study selection will be performed independently by two reviewers (AF and RP) in two steps: (1) screening of abstracts and titles and (2) screening of full-text articles. Any disagreement in screening decisions will be resolved through discussion among the reviewers or by a third reviewer (CB). A list of the excluded studies from the full-text review will be reported using the PRISMA-ScR reporting format [39].

Stage 4: Chart the Data

Two reviewers (AF and RP) will independently pilot the data extraction by using a form designed in Microsoft Excel (Microsoft Corp.). These reviewers will then independently extract the data from the eligible studies. Data extracted will include authors, year of publication, study location, purpose, study design, theoretical approach, study population, description of intervention (and comparator), data analysis, and study results or outcomes (eg, patient outcomes, barriers, and enablers). To describe the interventions, we will follow recommendations from the Template for Intervention Description and Replication checklist [44], comprising brief name of the intervention; why; materials used; procedures; who provided; how; where; when and how much; tailoring; modifications; how well (planned); and how well (implemented).

Stage 5: Collate, Synthesize, and Report Results

We will conduct a narrative data synthesis, including quantitative descriptive analyses for quantitative studies and thematic analyses for qualitative studies. We will group data into tables by type of intervention, and by outcomes or findings.

For the barriers and enablers analysis, we will group the findings using the 14 domains of the Theoretical Domain Framework: knowledge, skills, social or professional role and identity, beliefs about capabilities, optimism, beliefs about consequences, reinforcement, intentions, goals, memory, attention, and decision processes, environmental context and resources, social influences, emotion, and behavioral regulation [45-47]. Specifically, the analysis will follow 3 steps. First, two reviewers (AF and RP) will independently map the findings to each of the Theoretical Domain Framework domains. Second, similar findings will be themed and grouped together. Third, each theme will be coded as either a barrier or an enabler. We will report the top barriers and enablers using descriptive statistics (eg, frequency and percentage for each barrier and enabler). Disagreements will be discussed and resolved by the two reviewers (AF and RP) or by consulting a third reviewer (CB).

Results

The scoping review began in September 2022 and is expected to be completed in August 2023. We have identified a total of 8333 articles. The screening process took place between September 2022 and February 2023, and data extraction is expected to be completed in April 2023. Data analyses and final results will be submitted to a peer-reviewed journal in August 2023.

Through this review, we intend to provide an overview of the current state of research on platform-based, patient-clinician digital health interventions for care transitions, including a discussion of the different types of platforms and interventions that have been studied, the evidence for their effectiveness, and the barriers to and enablers for future research in this area.

Discussion

Overall, we will provide a comprehensive picture of the current state of knowledge on the use of digital health interventions in care transitions, and the potential for these interventions to improve patient outcomes. We expect to find a wide variety of postcare interventions, some gaps in the quality of the research evidence, as well as a lack of detailed information on the digital health interventions. Our results will include an overview of patient-clinician digital health interventions for discharge or

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care transitions, as well as barriers to and enablers for their implementation. In addition, this review is expected to identify research gaps that will inform the development of future patient-clinician digital health interventions.

Our review has several strengths and limitations. We designed an in-depth a priori protocol. The search strategy was developed and peer-reviewed by a research librarian with extensive knowledge in scoping and systematic reviews. However, we anticipate that the digital health interventions will be heterogeneous, making it more difficult to make comparisons and draw specific conclusions.

The results of our review would be beneficial to various stakeholders such as researchers, clinicians, administrators, and policymakers. We will disseminate our findings through publication in a peer-reviewed journal as well as by presenting our results at a scientific conference.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Search strategies.
[DOCX File , 22 KB - resprot_v12i1e42056_app1.docx]

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Abbreviations

PCC: Population, Concept, Context
PRESS: Peer Review of Electronic Search Strategies
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement for the Scoping Reviews

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Protocol

Understanding Intersectional Ageism and Stigma of Dementia: Protocol for a Scoping Review

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Abstract

Background: Ageism and stigma reduce the quality of life of older adults living with dementia. However, there is a paucity of literature addressing the intersection and combined effects of ageism and stigma of dementia. This intersectionality, rooted in the social determinants of health (ie, social support and access to health care), compounds health disparities and is, therefore, an important area of inquiry.

Objective: This scoping review protocol outlines a methodology that will be used to examine ageism and stigma confronting older adults living with dementia. The aim of this scoping review will be to identify the definitional components, indicators, and measures used to track and evaluate the impact of ageism and stigma of dementia. More specifically, this review will focus on examining the commonalities and differences in definitions and measures to develop a better understanding of intersectional ageism and stigma of dementia as well as the current state of the literature.

Methods: Guided by Arksey and O'Malley's 5-stage framework, our scoping review will be conducted by searching 6 electronic databases (PsycINFO, MEDLINE, Web of Science, CINAHL, Scopus, and Embase) and a web-based search engine (ie, Google Scholar). Reference lists of relevant journal articles will be hand-searched to identify additional articles. The results from our scoping review will be presented using the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Scoping Reviews) checklist.

Results: This scoping review protocol was registered with the Open Science Framework on January 17, 2023. Data collection and analysis and manuscript writing will occur from March to September 2023. The target date for manuscript submission will be October 2023. Findings from our scoping review will be disseminated through various means, such as journal articles, webinars, national networks, and conference presentations.

Conclusions: Our scoping review will summarize and compare the core definitions and measures used to understand ageism and stigma toward older adults with dementia. This is significant because there is limited research addressing the intersectionality of ageism and stigma of dementia. Accordingly, findings from our study may provide critical knowledge and insight to help inform future research, programs, and policies to address intersectional ageism and stigma of dementia.

Trial Registration: Open Science Framework; https://osf.io/yt49k

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KEYWORDS

stigma; dementia; ageism; definitions; measures; older adults; quality of life; social inclusion; health care access

Introduction

Background

Ageism and stigma reduce the quality of life of marginalized older adults, including those living with dementia. Research shows that ageism and stigma are associated with higher rates of discrimination, lifetime victimization, social exclusion, and poorer physical and mental health [1]. Older adults are often stigmatized because of stereotypes and negative beliefs associated with old age. This type of stigma related to aging is often referred to as age stigma or ageism [2]. Ageism, like other types of stigmas (eg, stigma based on disability or a health condition, such as dementia), can exist at the individual, community, and policy levels. Ageism can occur internally or externally [2,3]. For example, ageist stereotypes can be self-internalized and create barriers to accessing health care and support services, especially for older adults with dementia. Specifically, older adults living with dementia can face intersectional or combined stigma of ageist stereotypes that overlap with dementia myths. For example, misinformation about dementia is often exacerbated by ageist stereotypes and inaccurate beliefs that dementia is a normal part of the aging process [3]. However, these myths and ageist stereotypes are harmful as they can delay a timely dementia diagnosis required for accessing support services and planning for the future. Despite this knowledge, there is a lack of understanding about the intersection and combined impact of ageism and stigma of dementia [2-4]. Accordingly, this intersection of ageism and stigma of dementia may exacerbate existing health inequities grounded in the social determinants of health, such as access to health care and support services.

Ageism and stigma of dementia are complex constructs that are often embedded within deep-rooted societal issues. More specifically, different forms of stigma (eg, stigma based on age, health condition, and disability) often converge and intersect (ie, intersectionality) to create health inequities and reduce health outcomes at the population level [5-7]. Accordingly, stigma toward individuals based on their age cannot be addressed separately from stigma based on individuals' health conditions, such as dementia.

Any intervention designed to mitigate the combined effect of ageism and stigma of dementia requires knowledge of the core definitions, indicators, and measures used to track and evaluate their outcomes. Currently, there is a paucity of literature and no scoping review examining both ageism and stigma. However, a review is necessary to provide evidence-informed research of key measures to identify, monitor, and evaluate the impact of ageism and stigma of dementia. Accordingly, our scoping review will focus on understanding the core definitions and measures used to address ageism and stigma toward older adults living with dementia.

Stigma

In Goffman's renowned work, "Stigma: notes on the management of spoiled identity" [8], stigma is defined as attributes or characteristics that are socially discrediting. In comparison, Corrigan and Watson [9] describe stigma in terms of stereotypes (negative beliefs), prejudice (agreement with beliefs), and discrimination (discriminatory actions or behaviors) against themselves (self-stigma) or a group of people (public stigma). Corrigan and Watson [9] further explain that prolonged exposure to stigma contributes to the internalization of self-stigma. Link and Phelan [10] suggest that stigma involves components of stereotyping, labeling, and categorization of separation between "us" and "them," which can lead to social exclusion, rejection, and discrimination. Although several definitions of stigma exist, there remains little consensus on a shared definition of stigma [11]. Without a shared definition, it is difficult for researchers to compare, monitor, and evaluate the impact of stigma on dementia.

Ageism

The term ageism was first coined by Robert Butler [12] to define structural stereotypes and discrimination against older adults based on perceived old age. Ageism is often described in terms of negative beliefs, discriminatory actions, and stereotypes (e., severely impaired) toward older adults held by young, middle-aged, and older adult age groups [5,13,14]. Issues of ageism transcend our societal fabric through cultural values, beliefs, and media [15]. Research shows that ageism negatively impacts the health equity and outcomes of older adults. Specifically, ageism is linked to reduced physical health, poorer mental health, and earlier mortality [16,17]. Ageism is also associated with risky behaviors that impact health outcomes, such as excessive alcohol consumption, smoking, addiction, poor diet, and a reduced quality of life [5,18].

Rationale

Ageism and stigma toward older adults can lead to serious consequences, including depression, social isolation, feelings of shame, and social exclusion [5,19]. More specifically, research shows that older adults with disabilities are often shunned, excluded, and stripped of their social status [20]. Despite this knowledge and the fact that dementia is one of the major causes of disability, few studies examine the intersection of ageism and stigma toward older adults with dementia [5]. However, to address the intersectionality of ageism and stigma of dementia, a comprehensive understanding of the definitional components and measures is required. Accordingly, the objective of this scoping review will be to identify the existing definitions and measures used to track and evaluate the impact of ageism and stigma on older adults with dementia. More specifically, this review will explore the commonalities and differences in definitions and measures to develop a better understanding of intersectional ageism and stigma of dementia.

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Methods

Scoping Review Framework

Guided by Arksey and O'Malley's [21] scoping review framework, our review will include the following five steps: (1) identification of the study's aim; (2) examination of relevant studies; (3) study selection; (4) extraction of the data; and (5) collating, summarizing, and reporting the research findings. Arksey and O'Malley [21] propose an optional consultation process (step 6) involving key stakeholders to provide input in the scoping review (eg, references, interpreting the findings, and dissemination strategies). However, due to limited time and financial resources, this step will not be included in our study.

Step 1: Identification of the Study's Aim

The aim of the scoping review will be to synthesize the current state of the research by identifying the definitional components, indicators, and measures used to track and evaluate the impact of ageism and stigma of dementia. More specifically, this review will examine the commonalities and differences in definitions and measures to gain a better understanding of intersectional ageism and stigma of dementia.

Step 2: Identification of Relevant Studies

Studies will be retrieved by searching various electronic databases, including PsycINFO, MEDLINE, Web of Science, CINAHL, Scopus, Embase, and Google Scholar. In addition, reference lists of relevant studies will be searched to identify any additional journal articles. The initial keywords that will be included in our search strategy are outlined in Table 1. We will also consult with a research librarian to inform our search strategy and provide expertise to ensure that no relevant databases or search words are missed. More specifically, each database (eg, MEDLINE) may require its own search strategy using Medical Subject Heading terms, which may greatly improve our search results. Our search timeline will focus on peer-reviewed journal articles published from January 1, 2008, to January 1, 2023. This time frame was selected to ensure that our findings are representative of relevant theories and methods that are currently being used to define and measure ageism and stigma of dementia.

Table 1. Keyword search strategy. Databases and search engines used were PsycINFO, Web of Science, MEDLINE, CINAHL, Embase, and Google Scholar.

Concept	Keywords
Older adult	Older adult* OR Older adulthood* OR Aged* OR Aging
Dementia	Dementia* OR Cognitive impairment* OR Alzheimer's disease* OR Parkinson's disease* OR Cognitive aging*
Stigma OR Ageism	Stigma* OR Ageism* OR Attitude* OR Stereotype* OR Discrimination* OR Bias* OR Prejudice*
Definition	Define* OR Definition*
Measure	Measure* OR Indicator*

Our inclusion criteria will focus on the following four parameters: (1) articles that are written in the English language; (2) full-text, peer-reviewed journal articles; (3) studies that include a definition of ageism and stigma or includes measurements to study the psychometric properties of ageism and stigma; and (4) research that focuses on older adults living with dementia (aged ≥60 years). Given that young onset dementia only occurs in approximately 2%-8% of people before the age of 65 years, we have decided to focus our review specifically on older adults with dementia [22].

Step 3: Study Selection

We will use Rayyan [23], a leading software tool, to help manage our data and organize our reviews. Following our inclusion criteria, 2 reviewers will independently conduct title and abstract screening. The 2 reviewers will be delegated to oversee the full-text screening of the articles. Any questions on the inclusion of articles will be resolved by discussion with a third reviewer. However, any remaining issues of uncertainty will be resolved through consensus with the full research team. Reasons for study exclusion will be documented and reported in our scoping review publication. The results of our scoping review will be presented using the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Scoping Reviews) checklist [24].

Step 4: Data Extraction

Data will be extracted from the included studies using a systematic extraction approach. More specifically, a standardized data extraction form will be developed and used to chart data from the included studies. Our data extraction form will focus on collecting information on the definitions and measurements for ageism and stigma of dementia as well as identifying any similarities or distinctions between ageism and stigma of dementia (ie, in intersectionality or in assessment measures). The following data may also be included in the form: authors, date of publication, study objective, sample size, sample characteristics (eg, age and gender), study design, and study results. This data extraction form will be pilot-tested with a small number of included studies and revised as necessary. Any modifications or revisions to our data extraction form will be described in our scoping review paper. To reduce errors and ensure consistency in data extraction, one author will oversee the data extraction process. All data collected and analyzed during our scoping review will be made available on an open repository (eg, Open Science Framework) and included as supplementary files with our scoping review manuscript.

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Step 5: Collating, Summarizing, and Reporting the Findings

The analysis will synthesize the evidence based on the existing literature of ageism and stigma toward older adults with dementia. Guided by the work of Arksey and O'Malley [21], our scoping review will not evaluate the methodological quality and rigor of the included studies. Using tables, findings will be presented to showcase the summarized results based on our data extraction findings. Moreover, our findings will highlight research gaps that remain underinvestigated and require further investigation.

Results

This scoping review was registered with the Open Science Framework on January 17, 2023, prior to any title and abstract screening. Data collection and analysis and manuscript writing is scheduled to occur from March to September 2023. The target date for manuscript submission will be October 2023.

Discussion

Principal Results

Addressing issues of intersectional ageism and stigma are critical to improving the quality of life of older adults with dementia. To our knowledge, our research will be the first scoping review to examine and compare the definitional components and measures of ageism and stigma of dementia. However, developing interventions to mitigate intersectional ageism and stigma of dementia requires evidence-informed research of the existing definitions and measures. This scoping review will provide a comprehensive synthesis of the commonalities and differences of the definitions and measures used to address ageism and stigma of dementia. Moreover, this review will shed light on the existing knowledge gaps and the current state of the research, which may help to inform future research, programs, and policy responses.

Our knowledge translation and dissemination strategies will focus on a range of methods, including peer-reviewed journal articles, webinars, and conference presentations. We will also collaborate with our national research networks to disseminate our review's findings. The reach of our webinars and networks will enable us to develop widespread knowledge dissemination to inform policy, practice, and research.

Although we will aim to conduct a comprehensive scoping review, it will not be without limitations. For example, an important limitation of scoping reviews is that they focus on mapping and synthesizing data rather than evaluating the strength of the evidence or assessing risk of bias in the research. Thus, further research is required to evaluate and assess the quality of the existing studies on ageism and stigma of dementia. Another limitation is that our scoping review will only include peer-reviewed journal articles; as such, it is possible that relevant grey literature may be missed and excluded from our findings. Moreover, articles that are not written in the English language will also be excluded from our scoping review. Consequently, additional research examining grey literature and non-English articles may be useful for developing further insight on intersectional ageism and stigma of dementia.

Conclusions

This review will synthesize and compare the core definitions and measures used to examine ageism and stigma of dementia. To our knowledge, this study will be the first scoping review to examine ageism and stigma toward older adults living with dementia. Our study will shed light on the existing knowledge gaps and the current state of the research. This knowledge will enable researchers, clinicians, and policy makers to better understand ageism and stigma of dementia. Consequently, the findings from our review may provide pertinent knowledge and insight to inform future research, programs, and policies to address issues of intersectional ageism and stigma of dementia.

Acknowledgments

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Data Availability

All data collected and analyzed during our scoping review will be available on the Open Science Framework repository and included as supplementary files with our scoping review publication.

Authors' Contributions

MEO, AK, JM, ALC, JDB, and SF conceived the research focus and scoping review approach with support from the Canadian Consortium on Neurodegeneration in Aging's Stigma and Social Inclusion (SSI) working group. JDB wrote the first draft of the scoping review protocol with support from AK and JM. SF, ALC, and MEO provided revisions and critical review of the paper. All authors reviewed the final manuscript.

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Conflicts of Interest

None declared.

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Abbreviations

PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Scoping Reviews

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Protocol

Decolonization in Sexual and Reproductive Health Research Methods: Protocol for a Scoping Review

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Abstract

Background: As researchers and implementors begin to acknowledge the repercussions of institutionalized colonialism on community and individual health, the need to decolonize research has become clear. Despite this, there is neither a singular definition of decolonizing methodologies nor an overview of the shared principles and characteristics of decolonized research needed to codify this work as common practice in global health.

Objective: The review will identify papers that reference principles of decolonization and identify shared characteristics between them. The aim of this scoping review is to review decolonized research methodologies through the lens of sexual health as a step in creating a shared understanding of best practices. We will further examine the tools and methods used to collect and analyze data within the included studies.

Methods: The protocol for this scoping review was developed using the framework from the Joanna Briggs Institute and the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews). The search strategy will comprise a search of electronic databases (JSTOR, Embase, EMCare, MEDLINE [Ovid], Global Health Database, Web of Science), gray literature sources, and key studies. Titles and abstracts will be reviewed by 2 or more independent reviewers against inclusion criteria. Bibliometric details, study design, methodology, community involvement, and other indicators will be collected using a data extraction tool developed for this review. Extracted data will be analyzed using descriptive statistics and qualitative analysis of content and themes to identify common practices in decolonized methodologies within sexual health. Narrative summaries will be used to describe results in relation to the research question, and identified gaps will be discussed.

Results: The initial title or abstract review of 4967 studies identified by the search strategy was completed in November 2022. In total, 1777 studies met initial inclusion criteria and were sent to a second round of title or abstract review, which was completed in January 2023. In total, 706 studies were downloaded for full-text inclusion, which is expected to be completed by April 2023. We aim to complete data extraction and analysis by May 2023 and expect to publish the findings by the end of July 2023.

Conclusions: There remains a gap in the research on the meaning and application of decolonized research strategies, particularly within sexual and reproductive health. The findings of this study will contribute to a shared definition of decolonized methodologies and how they can be applied as a common practice in global health research. Applications include the development of decolonized frameworks, theoretical discourses, and methodologies. The study will inform the design and implementation of future decolonized research and evaluation strategies, particularly around sexual and reproductive health.

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KEYWORDS

sexual and reproductive health; decolonized research; decolonized methodologies; community-centered research; indigenous research; scoping review; electronic database; colonialism; decolonization; indigenous peoples; decolonizing methodologies; decolonizing method; human sexuality, reproduction; reproductive health; sexual and reproductive health; Aboriginal

Introduction

Background

As researchers and implementors in the global health and development sector begin to acknowledge the repercussions of institutionalized colonialism, the call for the decolonization of research has grown [1]. Indigenous peoples globally have felt the othering effects of traditional research and implementation strategies. These strategies often frame them as numbers in a study designed by those operating within a dominant culture rather than individuals with unique perspectives and experiences. The colonialization of research manifests itself through the identification of funding priorities and recipients, academic imperialism, methodological imperialism, dominant culture definitions of success, and not least through the prominent use of western research ideals in research design and implementation. Funding for global health originates primarily in high-income countries where it shapes research priorities and establishes the measures and indicators of success without the involvement of communities of focus [2]. Western research paradigms, such as positivism or constructivism, as well as individualist roots, have shaped the way research and knowledge are conducted and perceived, superseding culturally relevant indigenous worldviews, learning, and language [3].

This approach to research serves to undermine indigenous knowledge and extracts data from communities without the intent of directly benefitting them [1], often removing them from accessing and using the information gathered. Relying exclusively on the western paradigm may also result in the use of evaluation and research tools that do not collect accurate and valid responses [4]. A unified definition of decolonizing methodologies and an overview of their shared principles and characteristics (or lack thereof) are necessary to codify this work as a common practice in global health research. This review will examine the meaning of decolonizing research by reviewing research methods, designs, and evaluation strategies through the lens of sexual health to identify the strategies used to implement and measure decolonized research.

Decolonization of Research

The premise of decolonization is one of critiquing existing power structures and dominant culture at multiple levels. The approach is not centered specifically on human rights, sexual autonomy, or social justice. Instead, decolonization is a method of centering research, methodology, and practice within indigenous communities rather than rooting research in colonized institutions and epistemologies [5]. This scoping review defines decolonizing research as the prioritization of the needs and voices of indigenous communities in research, methodology, and practice in order to improve the caliber of assessment, analysis, and evaluation [6]. As authors such as Battiste [7] and Smith [5] emphasize, to decolonize research, it is of the utmost importance that indigenous communities and their ways of knowing lead research and that their voices are central to the process. Research paradigms should align with localized and indigenous ways of knowing to reclaim research and knowledge for indigenous peoples [3]. The decolonization of research methods will lead to indigenous research methods and provide a critique of dominant culture methodologies [5]. Decolonized research does not inherently mean oppositional to western methods but rather learning equally from dominant culture and indigenous methods in order to identify what is most applicable to a specific community.

While the need to decolonize research and practice has been identified and entered into the academic discourse, there is neither a clear definition for what a decolonized research methodology should entail or what elements these methodologies share nor an existing strategy to enter decolonized research methods into practice or best practice recommendations [8]. In particular, there is a need to identify these commonalities so that research strategies may be developed alongside communities to fit their specific needs, based on a body of foundational learning around decolonizing methodologies [9].

Research that is not rooted in decolonization can, and often will, result in the continued oppression of indigenous communities. These practices result in researchers and implementors entering communities and taking what they want, leaving behind little to no positive change and othering that community as a source of information rather than centering them in the work [10].

Defining Indigenous

This research frequently uses the term indigenous in reference to the communities and populations who would initially benefit from the process of decolonizing research. While there is no universally agreed-upon definition of indigenous, the United Nations proposes “those which, having a historical continuity with pre-invasion and pre-colonial societies that developed on their territories, consider themselves distinct from other sectors of the societies now prevailing on those territories, or parts of them” [11]. Based on this commonly used definition where indigenous peoples are those who existed precolonial intervention, this research uses the terminology indigenous to refer to all of the first peoples of colonized nations.

The term indigenous is also often used to refer to a minority population or a population whose practices and social norms differ from the dominant culture. In the context of decolonization, it is important to acknowledge that colonialism

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has had lasting repercussions on the educational systems, research institutions, and governing bodies of the majority of the world. The argument can easily be made that the dominant culture and the institutions which uphold it do not reflect the cultures of even majority indigenous peoples. Colonialism has also had a lasting impact not only on indigenous peoples but also on formerly enslaved peoples who continue to live in spaces where colonial history has systemic ramifications on their health and well-being.

This review wishes to acknowledge the importance of indigenous research and knowledge within the context of decolonized research while still making an important distinction between the two. For the purpose of this work, indigenous research methods provide location or community-specific strategies and relationships to knowledge and data collection. Decolonization of research itself is the process of acknowledging and subsequently counteracting historical systems of power within and through the research being conducted. The two are linked, and in many scenarios, inextricable, but by no means the same.

Sexual and Reproductive Health

The recognition of colonial history, the need to decolonize research methods, and the importance of centering the voices of the community in research are of particular importance when it comes to sexual and reproductive health (SRH). Colonialism and its institutions have historically oppressed women and sexual minorities, removing the capacity for choice and agency in family planning. Colonial powers have a history of the oversexualization of indigenous women [12], gynecological experimentation, eugenics, forced sterilization [13], population control [14], homophobia [15], and more, all of which are echoed in an ongoing culture of medical experimentation in previously colonized nations [16]. This history of oppression has ramifications today in the form of perceptions around access to SRH services, reliability of institutions, discrimination in service delivery, and desire to access SRH services. As such, reproductive justice and freedom of choice are critical areas of focus for decolonization research [17].

SRH rights and services are a broad range of fundamental health rights that apply to the physical and mental health of all individuals. SRH applies to a variety of topics that include access to family planning services, sexual health information, autonomy of sexual health decision-making, pregnancy and prenatal care, access to a trained health physician throughout pregnancy and birth, prevention and treatment of sexually transmitted infections, prevention of gender-based violence, abortion services [18], the ability to freely express sexual and gender identities [19], menstrual health education and access to products, and community information on menstruation and other sexual health subjects [20]. Lack of access to SRH services can result in poor mental and physical health outcomes.

SRH is divided by sex and gender and riddled with challenging power dynamics. Gender inequality and norms affect the ability of certain populations, particularly those who identify as women or gender nonconforming, to access equitable service delivery [21]. Specific SRH outcomes, such as teenage pregnancy, unintended or complex pregnancies, underage marriage, or domestic violence, predominantly affect those who identify as women or have uteruses [22].

Colonialism is a key determinant of health outcomes and therefore must be explicitly acknowledged in research methodologies [23]. To conduct relevant and effective research on sexual health in previously colonized nations, the needs of indigenous communities must be prioritized, which require clear acknowledgment of the presence of colonialism and the ongoing ramifications of colonial intervention in communities, infrastructure, institutions, and research, in order to mitigate centuries of oppression.

There is a need to decolonize research, implementation, and evaluation design in order to ensure that the work being done is sustainable and effective, and the data collected are ethical, reliable, and replicable [24]. There is a lack of information and research on the shared characteristics of decolonized methodologies and the tools and measures of outcomes and success. This review will not assess the “efficacy” of programming in comparison with other research methodologies but rather seek to identify shared (or differing) research and data collection methods, evaluation strategies, outcome measurement, and other indicators and outcomes, and how effectively they incorporate community voices. This is the first step in developing a shared understanding of best practice in decolonized sexual health research.

An initial scan of PROSPERO, MEDLINE, Open Science Frameworks, and Joanna Briggs Institute (JBI) Database of Systematic Reviews and Implementation Reports has been conducted, and there are no past or ongoing reviews on shared characteristics of decolonized research methodologies in the context of SRH. While there have been reviews of the characteristics of specific indigenous research methodologies [25] and models of service delivery [26], participatory action research for SRH [27], and meta-reviews of the different forms of community-engaged scholarship [9], there still remains a gap in the assessment of what it means to decolonize SRH research and what tools and assessments of success researchers are using.

Objectives

There is no shared understanding of the characteristics that decolonized research methodologies share. We will address this gap in the literature by identifying the different characteristics of decolonized SRH research and interventions and the designs and methodologies on which they are based. The researchers will identify and map the tools used to define, measure, and analyze program outcomes and success in this context. Summarizing research strategies and findings will enable the researchers to identify not only recommendations for future research but also the space where there is room for growth in researching and designing decolonized SRH studies.

Review Questions

Through this scoping review, the researchers will answer the following question: What are the characteristics of decolonized research methodologies in SRH research?

The primary outcome of this research will be to identify the shared characteristics of these methodologies, including a

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specific focus on the tools used to collect and analyze data. Secondary outcomes will include the specific measures and definitions of success, and how they are identified across geographic regions.

Methods

This protocol was designed using the framework for scoping review from the JBI [28] and referred back to the reporting framework of PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) [29].

Search Strategy

The search strategy will aim to locate peer-reviewed published studies (including ongoing studies) and gray literature on decolonized SRH research or program implementation and evaluation published between January 2012 and December 2022. The decision to use this time frame was based on the increasing recognition of various decolonizing methodologies over the last decade [9]. This decade of research will cover a great deal of relevant research conducted while ensuring an equal representation of research based on recent methodological ideologies and trends. There will be no geographic exclusion criteria, as decolonized research can be undertaken in any location. Abstracts, posters, book reviews, and blog posts will not be included.

A 3-step search strategy will be used to ensure that the strategy is comprehensive and collects as many appropriate studies as possible. The search strategy was developed in cooperation with a librarian scientist at McMaster University. First, a preliminary limited search of 2 web-based databases (eg, MEDLINE [Ovid] or JSTOR) will be conducted (Multimedia Appendix 1). Second, an analysis will be done of the text words in the title, abstract, and index to develop an updated search strategy. This search strategy using these terms will be adapted and applied to each relevant database. The databases searched include Embase, EMCare, MEDLINE (Ovid), Global Health Database, and Web of Science. Gray literature sources include Advanced Google, World Health Organization (WHO), United Nations Children's Fund (UNICEF), United Nations Population Fund (UNFPA), Guttmacher Institute, and Médecins Sans Frontières (MSF). Finally, the resource lists of identified reports and papers will be reviewed for additional relevant studies.

Study Selection

Following the search, all identified citations will be uploaded into DistillerSR: Literature Review Software (Evidence Partners), and duplicates will be removed. Titles and abstracts will then be reviewed by 2 or more independent reviewers for assessment against the inclusion criteria for review. Potentially relevant sources will be retrieved in full and uploaded to DistillerSR for subsequent review. The full text of the citations will be assessed against the inclusion criteria by the reviewers. Reasons for the exclusion of sources of evidence will be recorded and validated by another reviewer and reported in the full scoping review. If there are any disagreements during this process, they will be resolved through discussion or by involving additional reviewers. If any existing systematic or scoping reviews are identified during the screening, relevant studies will be extracted and added to the review if not already present. The results of the search and the study inclusion process will be reported in full in the final scoping review and presented in a PRISMA-ScR flow diagram to demonstrate the process of paper inclusion or exclusion.

Data Extraction

The data extraction process for reporting will first take a quantitative approach, which will allow reviewers to identify key themes for exploration. These themes will subsequently be reported in narrative form. The reporting will be compliant with the PRISMA-ScR checklist.

The reviewers will use a data extraction tool developed by them for this scoping review. The data extracted will include bibliometric details, geographic location of primary institution, geographic location of research, study design, methodology, and community involvement, as well as key findings relevant to the study question. A draft data extraction form is provided in Multimedia Appendix 2. The draft data extraction tool will be modified and revised as necessary during piloting, and all changes will be detailed in the final scoping review. The piloting process will involve researchers gathering to discuss the data extraction form, testing individually on papers selected from the preliminary research search, and making adjustments for usability. Once approved, this will be entered into DistillerSR into at least 3 levels of analysis.

Any disagreements between reviewers will be resolved through discussion. If no consensus can be reached, a third reviewer will adjudicate. Data will also be subject to quality control checks. If necessary, authors of papers will be contacted to request missing or additional data.

Analysis and Reporting

We will conduct quantitative analysis of the extracted data including descriptive statistics regarding areas of publication, institutions, income level and geographic location, and qualitative analysis of content and themes. The results will be presented in tables, charts, and figures, and a narrative summary of findings will represent the primary analysis and reporting.

Paper details will be presented in a table showing authors names, year research was published, location of research, aim or objective of study, methodology, and results. Charts and visualizations developed via descriptive statistics will be used to represent geographic location of lead author affiliations, location of funding institution, location of research, and comparison of these three. A narrative discussion of the results around shared characteristics between methodologies, data collection methods, study outcomes, community engagement strategies and leadership, development of data collection tools, and determinations of success will also be included. Thematic synthesis may be required to discuss these elements. If so, the reviewers will extract the key concepts from the text, develop descriptive codes for themes that carry across studies, and produce final analytical themes from this process [30]. The authors will further use these data to comment on unexpected findings, identified gaps, and implications for research and practice.

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A narrative summary will accompany the charted results and will describe how the data relate to the stated objective and question, namely identifying shared characteristics of decolonized SRH findings. The summary will also discuss the ways in which the voices of the community of focus are centered and prioritized as well as other thematic areas that emerge over the course of the research. The team will work together to identify gaps in the research and present recommendations for future research and work in this area.

Ethics and Dissemination

Ethics approval is not required for a scoping review as the materials being used are publicly available. Dissemination will be done through conference presentation, publication in a peer-reviewed open-access journal, and dissemination among researchers and policy makers in the field of SRH research and practice. Input from leaders and practitioners in this field will be requested to support dissemination. Findings will also be available as an element of a doctoral thesis.

Results

The search strategy netted an initial 4967 studies for title or abstract review after the removal of duplicates. This initial review was conducted on Covidence and was completed in November 2022. In total, 1847 studies were marked for inclusion and exported to DistillerSR where a subsequent 70 duplicates were identified. The remaining 1777 studies were sent to a second round of title or abstract review, which was completed in January 2023. In total, 706 studies have been downloaded for full-text inclusion, which is expected to be completed by April 2023. We aim to complete data extraction and begin data analysis by May 2023. The final manuscript is expected to be submitted for publication by the end of July 2023.

Discussion

Principal Findings and Implications

The results from this scoping review will inform researchers and implementors as to the shared characteristics that decolonized methodologies in sexual health research share. In particular, in the field of SRH, where power and oppression play a critical role in the delivery and receipt of health care services, understanding how current interventions acknowledge and address this through their methodologies will provide guidance on future work. Findings from this study will provide guidance as to where there are gaps in defining and implementing decolonized research methodologies throughout the research process. Findings will also show where there are well-established methodologies for decolonizing traditional research practices, providing the first step toward the development of clear guidance for others hoping to replicate and expand on this style of research.

As the importance of decolonizing research evolves and expands, it will become important for a broad range of stakeholder groups to have access to a set of standards or recommendations regarding best practice. The findings from this scoping review will help to identify the commonalities that unite various forms of decolonized research and create a foundation for research strategies to be designed and used alongside communities of focus. Knowledge from this review may also inform researchers in the design and implementation of their own work as a point of reference for application of the strategies identified therein. Findings from this scoping review will support the existing theoretical literature from scholars such as Battiste [7] and Smith [5], who describe and identify the need for decolonized methodologies, and set the agenda for future work.The results of this analysis will support the findings of other literature which identifies the shared characteristics of related research methodologies [25] and identifies common strategies to guide researchers in the implementation of specific approaches [27], to create consensus. The findings from this review will add to the growing body of work describing and supporting the practical uses of new theories and methodologies [31].

Limitations

The primary limitation of this work is the challenge of uncovering interventions and research that may not have been conducted within the guidelines of dominant culture publication and academic authorship. A significant limitation of the search strategy was that the structure of a scoping review and the academic language used may limit the inclusion of materials outside of academic institutions. While open-source databases and other web-based resources were accessed in an attempt to identify non–peer-reviewed materials, community-led and organized interventions are less likely to have been identified and included based on how data on these projects are published and shared.

Conclusions

There remains a gap in the research on the meaning and application of decolonized research strategies, particularly within SRH. The findings of this study will contribute to a shared definition of decolonized methodologies and how they can be applied as a common practice in global health research. The study will inform the design and implementation of future decolonized research and evaluation strategies, particularly around SRH. Potential stakeholders who may use these findings include researchers, community-based organizations, and individuals within communities of focus.

Acknowledgments

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Thanks to AP for his diligent work as an independent researcher.

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Data Availability

The data sets that will be generated and analyzed during the course of the study will be attached as a supplementary document to the final study or if the size of the data set makes this challenging will be available from the corresponding author on reasonable request.

Authors' Contributions

MSU drafted the manuscript. LM is the guarantor and contributed comments to the manuscript. All authors read and approved the manuscript of this protocol.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search strategy.
[DOCX File , 14 KB - resprot_v12i1e45771_app1.docx]

Multimedia Appendix 2
Data extraction framework.
[DOCX File , 18 KB - resprot_v12i1e45771_app2.docx]

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Abbreviations

JBI: Joanna Briggs Institute
MSF: Médecins Sans Frontières
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews
SRH: sexual and reproductive health
UNFPA: United Nations Population Fund
UNICEF: United Nations Children's Fund
WHO: World Health Organization

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Protocol

Indigenous Food Systems Changes and Resiliency: Protocol for a Scoping Review

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Abstract

Background: Indigenous food systems (IFS) consider the complex relationships and connections between land, animals, plants, water, and people. These food systems may differ between regions, Indigenous cultures, and history; however, given the similar colonial histories and policies influencing Indigenous groups in Canada, the United States, Australia, and Aotearoa (New Zealand), the IFS changes and responses in these regions may follow similar trends. Climate change and pollution continue to impact the environment in catastrophic ways, and this, in turn, impacts IFS. However, to date, there has been no review of the literature on IFS, how they are changing, and how communities are responding to these changes.

Objective: In this scoping review, we will summarize primary research in Canada, the United States, Australia, and Aotearoa related to IFS addressing the following questions: (1) What changes are IFS experiencing in the context of climate change and pollution? (2) What actions have been taken in response to IFS changes? (3) What are the characteristics of IFS research in peer-reviewed academic literature?

Methods: We will use the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines for scoping reviews and the Joanna Briggs Institute reviewer's manual to inform the review process. MEDLINE, SCOPUS, International Bibliography of the Social Sciences, Sociological Abstracts, and the Bibliography of Native North Americans are the databases included in this review search. All screening and extraction have been supported by Covidence software (Veritas Health Innovation) with 2 independent reviewers conducting the abstract and full-text screening. We will map concepts and themes related to the research questions to contribute to the understanding of IFS within the academic literature and provide a narrative review of the outcomes.

Results: The electronic database searches for this review were conducted in May 2021. Screening and full-text review were initially completed in the winter of 2022. We are currently in the process of compiling results and aim to share findings in 2023.

Conclusions: This review will provide valuable insight into current IFS needs by summarizing the peer-reviewed literature on how IFS are changing because of climate change and pollution and how communities are responding to these changes. The results of this review will be shared with Indigenous communities, through academic publications, community conversations, and conference presentations.

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KEYWORDS

Indigenous; food systems; Indigenous health; scoping review; traditional foods; colonization; climate change; pollution; environment

Introduction

Indigenous food systems (IFS) refer to the connections between Indigenous groups and the land; however, climate change, colonization, and pollution have resulted in detrimental impacts to the environment and access to it [1]. This influences food sovereignty and security for Indigenous groups in Canada, the United States, Aotearoa (New Zealand), and Australia in similar ways due to the shared impacts of Western-European colonization [2,3]. Food sovereignty refers to the sovereign rights of Indigenous Peoples to self-determine their own food systems, connecting with land, history, language, and ways of life [4]. Disruptions to food sovereignty can result in food insecurity, an issue disproportionately impacting Indigenous communities with prevalence rates consistently above 25% in Canada, the United States, Australia, and Aotearoa [5-7]. Additionally, inconsistent definitions and measures of food insecurity between regions and institutions may lead to underestimations of food insecurity among Indigenous communities [8].

Household food insecurity has several health implications including a greater prevalence of diabetes, heart disease, asthma, musculoskeletal diseases, intestinal disorders, and mental health disorders [9,10]. Food insecurity is more prevalent in households with children [5], and therefore it is important to consider health concerns throughout the lifespan. For example, children and adolescents in homes experiencing food insecurity are more likely to have suicidal ideation, mood disorders, and asthma [10,11]. Although much of the research to date has focused on physical and mental health implications, food insecurity is a complex public health concern that is deeply intertwined with Indigenous spiritual and emotional health and overall well-being [12].

To date, there have been no systematic explorations of IFS changes in the peer-reviewed literature. Therefore, this scoping review will characterize recent trends in peer-reviewed research concerning IFS changes and Indigenous food sovereignty with the objective of understanding the experiences of Indigenous Peoples living in Canada, the United States, Australia, and Aotearoa and how communities have observed and responded to changes in their traditional lifeways. IFS changes refer to broad adaptations to market and land-based food systems including both positive and negative impacts. For example, an IFS change could be the reduction of an animal population or a response to the loss of hunting skills where a community is educating youth through on-the-land hunting activities. This review will discuss the potential impacts of climate change and pollution on IFS, provide information on the significance of IFS, and explore how IFS have been changing in similar and different ways in these regions. Although each food system lies within a unique context, there is considerable similarity in the experiences of Indigenous Peoples within these regions, particularly as it relates to colonization [2,3]. This review will help identify those points of similarity and difference to generate a better understanding of the issues in IFS and facilitate connections between Indigenous communities and their shared experiences. The following research questions are of interest: (1) What changes are IFS experiencing in the context of climate change and pollution? (2) What actions have been taken in response to these IFS changes? and (3) What are the characteristics of IFS research in peer-reviewed academic literature?

Methods

Ontological Origins

This scoping review emerged from discussions between Indigenous scholars, academics, Elders, and community members who were focused on IFS as part of a proposed partnership between the University of Toronto, Canada and Moi University, Kenya. The creation of this review is tied to the goals of this partnership and informed by initial feedback from the community of practice in 2020 and 2021. In accordance with Indigenous communal decision-making traditions in Canada, all decisions were open to input from members of the community of practice with the goal of collective consensus on the direction of the project. Solicitation of feedback was facilitated by regular group meetings and the dissemination of project updates via email by those who were unable to attend meetings.

Eligibility Criteria

The eligibility criteria (Textbox 1) were amended following initial screening and calibration due to the significant number of citations involved. To maintain a focused scope, we excluded work that focused on colonization as a driver of environmental change and only included papers that primarily described climate change and pollution as influencing environmental changes. Works that only discussed environmental revitalization were also excluded as these papers differed significantly from the others and may require a separate review. We retained papers specific to colonization and revitalization so that we could do an additional review and synthesis if desired at a later date, as we recognize the value in these topics.

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Textbox 1. Eligibility criteria.

Inclusion criteria

- Directly related to Indigenous Peoples living in Canada, the United States, Australia, or Aotearoa
- Related to Indigenous food systems or Indigenous food sovereignty
- About Indigenous food systems changes or actions to protect or revitalize Indigenous food systems related to climate change or pollution
- Primary research
- Published between 2016 and 2021
- Written in English
- Available electronically

Exclusion criteria

- Not related to Indigenous Peoples or Indigenous Peoples specifically residing in Canada, the United States, Australia, or Aotearoa
- Not related to Indigenous food systems or food sovereignty
- Not related to Indigenous food systems changes or actions to protect or revitalize Indigenous food systems related to climate change or pollution
- Not primary research (does not include data collection)
- Not published between 2016 and 2021
- Not available in English
- Papers that only document Indigenous foods (ethnobotany)
- Papers that only document the food consumption of Indigenous Peoples
- Papers that only document food literacy of Indigenous People
- Papers about teaching Indigenous Peoples how to grow or cook non-Indigenous foods or use capitalist market-based retail environments
- Papers focused on food security or insecurity for Indigenous Peoples without discussing Indigenous food systems and experiences or changes related to climate change or pollution
- Papers about Indigenous environmental management unless it explicitly includes information about Indigenous food systems

Information Sources

This protocol was developed using the methodological framework for scoping reviews outlined in the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) guidelines [13] and informed by the Joanna Briggs Institute Reviewers' Manual [14]. An electronic search was conducted in the following databases: MEDLINE, SCOPUS, International Bibliography of the Social Sciences, Sociological Abstracts, and the Bibliography of Native North Americans for academic literature relating to IFS across the globe. The search strategy was developed to find journal articles focused on IFS changes or the protection or revitalization of IFS, and with the knowledge that the language used to describe those ideas can vary between countries and disciplines. Index terms were used for each database where index terms were available. Additionally, some databases may use terms that are no longer in use to refer to Indigenous Peoples, which is a limitation of the search functions. We took great care to find the articles within the limits of the databases despite knowledge of the outdated terms. All database searches were conducted on June 1, 2021. Citations obtained from the searches were exported to Covidence for the removal of duplicates and used for screening and data extraction [15]. Reference lists will not be searched for additional citations due to capacity limits. Documentation of the search strategy can be found in Multimedia Appendix 1.

Selection of Sources of Evidence

Two independent reviewers completed both the abstract and full-text screening using Covidence software [15] to facilitate the process, aligning with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. A sample of 10 papers was assessed by authors ECH and EVS to test the validity of the eligibility criteria, after which the 2 reviewers compared the screening results to calibrate the criteria and ensure a high level of rater interreliability. After calibration, screening proceeded until complete. The full-text review was completed by authors HM, ECH, YS, and EVS. All conflicts were resolved by meeting among the reviewers and reaching a consensus. Disagreements were solved by consensus, and if consensus could not be reached, the disagreements were resolved by a third reviewer.

Data Charting Process

Data extraction will be completed using a detailed template, and pilot testing will be completed with the team prior to moving forward with all data extraction. Once the data extraction tool has been adjusted, the data extraction will proceed independently. Should any clarifications be required throughout the process, the team will meet to ensure consistency with extraction. Textbox 2 provides detail on the data extracted for this review.

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Textbox 2. Data extraction tool details (the data extraction tool collected information from 4 main categories with specific information represented below them).

Paper information

- Title
- First author
- Publication year
- Positionality of authors or researchers
- Additional notes

Location

- Country
- Specific Location details (ie, province)
- Type of region (ie, remote)
- Type of climate (ie, Boreal Forest)
- Additional notes

Study details

- Aim and objective
- Study design
- Dates and time
- Funding sources
- Indigenous community or organization
- Indigenous group/People
- Name of the nonhuman population (ie, Geese)
- Number of participants
- Indigenous engagement (yes/no and explain)
- Additional notes

Results

- Food system category (ie, food acquisition)
- Food system disruptors (ie, pollution)
- Food system changes
- Are food system changes the primary focus? Elaborate
- Policy recommendations
- Knowledge dissemination and translation
- Impact on community

Data Items

We are interested in collecting information on how the studies were conducted, where the study was done and with or for whom, the details describing the IFS, the changes related to the environment (eg, climate), and the community perspective and response to the food systems changes. The data extraction template addresses each of these key topics to enable us to answer the research questions of interest. Studies that only discuss changes related to colonization and community responses without describing specific IFS changes will not be captured in this review.

For this review, "Indigenous Peoples" are defined as those who self-identify as Indigenous. In Canada, Indigenous groups may include Inuit, Métis, and First Nations, including any of the over 600 First Nations communities. In Aotearoa, the Māori people are the Indigenous Peoples of the land, in the United States, Native American Peoples, American Indians, and Alaska Natives, and in Australia, this includes Aboriginal and Torres Strait Islanders. We recognize that not all Indigenous groups identify with the same terminologies, and so we aim to be inclusive and respectful of local terminology; however, previous publications included in this review may use outdated terms.

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We will aim to use the most up-to-date terminology even if it differs from language used in previous publications.

"Indigenous food systems" (IFS) are any traditional foods and foodways that any self-identified Indigenous group living on the lands known today as Canada, the United States, Aotearoa, and Australia defines as such. Generally, these systems are deeply connected to the lands and environments from which they emerged within these regions.

Synthesis of Results

Results will be presented both quantitatively and qualitatively by providing numerical and descriptive details of the papers included. We will map the findings and conceptualizations of this work, and present the number of studies screened, included, and excluded at each stage of this review using tables and diagrams. The results will be mapped into categories based on research objectives (ie, climate change) and themes will be described. In addition to mapping and describing the outcomes specific to environmental changes and community responses to these changes, we will compare the methodologies used and discuss these approaches in detail. In addition, it is important to note that we will include Indigenous community and scholar involvement in the interpretation and mapping of this work.

Ethical Considerations

All data in this review will be gathered through database searches of primary research and does not include identifiable individual data. Only secondary analyses will be conducted; therefore, no research ethics approval is required for this scoping review. This protocol was registered with the Open Science Framework on January 13, 2022 (10.17605/OSF.IO/XRJ87).

Results

The electronic database searches for this review were conducted in May 2021. Screening and full-text review were initially completed in the winter of 2022. We are currently in the process of compiling results and aim to share findings in 2023.

Discussion

We describe the protocol for a scoping review of academic, peer-reviewed literature about IFS changes and Indigenous food sovereignty in Canada, the United States, Australia, and Aotearoa. To our knowledge, no review of the literature on IFS changes and community responses related to climate change and pollution has been completed to date. We will provide a description of the research area and identify gaps for future investigation, as well as lay the basis for future comparative work in IFS research on a global scale. We anticipate that this scoping review will provide knowledge about IFS changes and experiences related to climate change and pollution, actions taken to protect IFS, and characteristics of IFS. This focus on the impacts of environmental changes on IFS and responses to these changes is important in understanding community-driven solutions, which we hope will benefit Indigenous public health and provide knowledge for future research with Indigenous Peoples for IFS.

Through this review, we will help identify current demographic and methodological priorities and clarify what kinds of questions, methodologies, and conclusions are proliferating in the research area. Peer-reviewed academic literature is generally privileged in funding and dissemination, and therefore it is crucial to understand what messages are being sent about IFS through academic publications [16,17]. This is particularly important work as Indigenous voices have traditionally been excluded from institutional knowledge production [18].

In addition to the value of this review, our protocol is robust and limits bias by including various subject-specific databases, 2 independent reviewers, and consideration of region-specific terminology. However, this protocol is limited in that there are additional databases that could be included to expand the search. Our work also only includes primary research published in peer-reviewed journals; therefore, community projects that are published elsewhere are not included and may limit findings. While we do our best to use appropriate and context-specific terminology in our searches, it is possible that outdated terminology is included through database indexing and previous publications, and work using other terminology is missed.

Dissemination of this work will be completed through both academic publications and community conversations to ensure that communities can benefit from this knowledge. This review is important in understanding the primary research completed to date and areas for further exploration in the future. Ultimately, completing this review benefits not only academics but also Indigenous Peoples seeking to revitalize IFS for the health of their communities and future generations and will help to inform global climate policy directions.

Acknowledgments

For advice in the construction of the scoping review methodology, we would like to thank Jenaya Webb (Research Librarian, University of Toronto) and Desmond Wong (Outreach Librarian, University of Toronto). We also acknowledge the conceptual contributions of Erica Di Ruggiero, Paula Braitstein, and Kimberly Fairman.

With respect to the conventions of Indigenous literature, author positionality statements are offered to assist readers in understanding the worldviews contributing to this protocol (ie, its ontological origins) with additional details provided in the Authors' Contributions. HM is a registered dietitian with a PhD in Nutritional Sciences from the University of Toronto and is of Scottish, Irish, French, German, and English settler ancestry. ECH is a PhD student in Rehabilitation Science at the University of Toronto of Irish settler ancestry. YS is a Master of Medical Science candidate at the University of Toronto, with a focus on population health research. She is a settler of Iranian background. EVS is a research assistant of white settler ancestry who holds an MSc in Anthropology from the University of Toronto with a Collaborative Specialization in Indigenous Health. AMP is an Algonquin

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Assistant Professor and the Associate Director of the Waakebiness-Bryce Institute for Indigenous Health, Dalla Lana School of Public Health, University of Toronto.

Data Availability

Our search strategy is available in Multimedia Appendix 1. Journal articles at each of the review stages and review results will be published and available upon request.

Authors' Contributions

HM began providing support to this review after the initial database search and then guided the full-text screening and data extraction, providing a significant contribution to the writing and registration of this protocol. ECH began supporting this review during the database searches and provided guidance throughout the duration of the project. YS assisted with the full-text screening, data extraction, and writing stages of the scoping review. EVS was recruited to the project based on experience with scoping study methodology; she had a significant role in conceptualizing the objectives of the review, developing search strategies, and supervising initial search strategy implementation. AMP developed the project and assisted with the protocol for the scoping review.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Scoping review search string documentation.
[DOCX File , 43 KB - resprot_v12i1e41627_app1.docx]

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Abbreviations

IFS: Indigenous food systems
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews

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Protocol

The Use of Spatial Analysis in Syphilis-Related Research: Protocol for a Scoping Review

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Abstract

Background: Latin America, Africa, and Asia have high incidences of syphilis. New approaches are needed to understand and reduce disease transmissibility. In health care, spatial analysis is important to map diseases and understand their epidemiologic aspects.

Objective: The proposed scoping review will identify and map the use of spatial analysis as a tool for syphilis-related research in health care.

Methods: This protocol was based on the Joanna Briggs Institute manual, guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR). We will conduct searches in Embase; Lilacs, via the Virtual Health Library (Biblioteca Virtual en Salud; BVS), in Portuguese and English; Medline/PubMed; Web of Science; Cumulative Index to Nursing and Allied Health Literature (CINAHL); and Scopus. Gray literature will be searched for in Google Scholar, the Digital Library of Theses and Dissertations, the Catalog of Theses and Dissertations of the Coordination of Improvement of Higher Education Personnel (Coordenação de Aperfeiçoamento de Pessoal de Nível Superior; CAPES), Open Access Theses and Dissertations, ProQuest Dissertations and Theses Global, and the Networked Digital Library of Theses and Dissertations. The main research question is “How has spatial analysis been used in syphilis-related research in health care?” Studies are included if they have the full text available, address syphilis, and use geographic information systems software and spatial analysis techniques, regardless of sample characteristics or size. Studies published as research articles, theses, dissertations, and government documents will also be considered, with no location, time, or language restrictions. Data will be extracted using a spreadsheet adapted from the Joanna Briggs Institute. Quantitative and qualitative data will be analyzed using descriptive statistics and a thematic analysis, respectively.

Results: The results will be presented according to the PRISMA-ScR guidelines and will summarize the use of spatial analysis in syphilis-related research in health care in countries with different contexts, factors associated with spatial cluster formation, population health impacts, contributions to health systems, challenges, limitations, and possible research gaps. The results will guide future research and may be useful for health and safety professionals, managers, public policy makers, the general population, the academic community, and health professionals who work directly with people with syphilis. Data collection is projected to start in June 2023 and end in July 2023. Data analysis is scheduled to take place in August and September 2023. We expect to publish results in the final months of 2023.

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Conclusions: The review may reveal where syphilis incidence has the highest incidence, which countries most use spatial analysis to study syphilis, and whether spatial analysis is applicable to syphilis in each continent, thereby contributing to discussion and knowledge dissemination on the use of spatial analysis as a tool for syphilis-related research in health care.

Trial Registration: Open Science Framework CNVXE; https://osf.io/cnvxe

International Registered Report Identifier (IRRID): PRR1-10.2196/43243

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KEYWORDS

treponema pallidum; syphilis; infectious diseases; spatial distribution; systems of geographic information; spatiotemporal analysis; health care; surveillance; spatial analysis; geographic information; policy maker

Introduction

Spatial analyses are techniques performed on geographic data that describe an entire geographic region or a single point in space [1] to measure, interpret, and explore characteristics and associations [2]. These analyses are an important tool in health care for mapping diseases and understanding their epidemiology [3,4].

The evolution of computer science has improved and expanded software development, increasing the applicability and accessibility of spatial analysis [2]. Visualizing geographic areas has enabled the mapping of disease distribution, risks and correlated factors, and the physical and human structures of health services. Spatial analysis is a useful tool to visualize areas with the greatest epidemiological pressure and infer associations between the studied phenomenon and sociopolitical and economic factors that contribute to it [5,6]. Therefore, spatial analysis contributes to planning, implementing, and assessing global health policies [3,4].

In the context of health care, it is equally important to consider the location and characteristics of where people seek care. Thus, spatial epidemiology has evolved rapidly in recent years. Research has developed to include geocoding, distance estimation, residential mobility, record linking, data integration, spatial and spatiotemporal clustering, small area estimation, and Bayesian applications for disease mapping. Computer-based geographic information systems for integrating and analyzing geographic data are applicable in epidemiology, contributing, for example, to disease mapping, rate smoothing, cluster or hot spot analysis, and spatial modeling [2].

Documenting the role of the geographic environment where individuals live and interact (often called “activity spaces”) will improve our understanding of health outcomes. This is because the place where an individual lives or works can be considered as a potential determinant of disease; this has profound political implications for local health interventions and resource-allocation decisions and will ultimately lead to a reduction in health disparities [2].

Previous research has used spatial analysis to map disease distribution (eg, for multiple sclerosis [7], HIV [8], and COVID-19 [9]), and spatial analysis could also guide health strategies against syphilis [10], which has a high incidence and represents a problem for public health worldwide, especially in Latin America, Africa, and Asia [11,12].

Syphilis spreads via sexual or vertical transmission. It can be asymptomatic, can manifest as spots on hands and feet, and can affect the functioning of several organs (in the systemic phase). Gestational syphilis and congenital syphilis directly impact reproductive and child health. During pregnancy, syphilis may lead to abortion, stillbirth, premature birth, neonatal death, and early or late congenital manifestations [13].

A previous study used spatial analysis to assess the epidemiological status of congenital syphilis in Brazil and found that the most affected municipalities were those with a large migratory flow, those bordering other countries, and those with many tourists [10]. Clusters of congenital syphilis were even identified in municipalities with prenatal care [14].

In China, researchers reported spatiotemporal changes in the incidence of syphilis; eastern coastal provinces showed a declining trend, whereas inland provinces showed an increasing trend, suggesting an association between epidemiological and economic issues [15]. In Italy, a study pointed out that women diagnosed with syphilis were more likely to be non-Italian, while men were more likely to be Italian [16]. Strategies to provide support services for accessing treatment have been implemented in Colombia for HIV and syphilis testing among Venezuelan migrants [17]. In Africa, the implementation of self-tests for HIV and syphilis in men’s workplaces can be thought of as an approach to increase the availability of and access to tests among men and provide linkage to treatment and prevention services [18].

New strategies are needed to reduce syphilis transmission, such as spatial analysis, which has previously been applied in syphilis-related research [10,14,15,19]. However, due to a lack of studies, how and to what extent this tool is being used is unclear. A search was conducted in July 2022 of the Joanna Briggs Institute, Cochrane Library, Web of Science, PubMed, Prospero, and Open Science Framework databases. The search found no review studies or protocols that used spatial analysis in syphilis-related research, highlighting this knowledge gap.

A scoping review identifying and globally mapping the application of spatial analysis in syphilis-related research would help researchers, managers, and health policy makers manage methodologies for disease control. Thus, this study describes a protocol for a scoping review to identify and map the use of spatial analysis in syphilis-related research in health care.

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Methods

Overview

This is a protocol for a scoping review to answer broad research questions based on defined selection criteria [20]. We used the guidelines of the *Joanna Briggs Institute Reviewer's Manual* [20], based on the theoretical framework proposed by Arkey and O'Malley [21], updated by Levac et al [22], and guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) [23].

The stages of the scoping review include (1) definition and alignment of research objectives and questions; (2) development and alignment of inclusion criteria; (3) description of the search for evidence, selection and extraction of data, and presentation of evidence; (4) the search for evidence; (5) selection of evidence; (6) extraction of evidence; (7) analysis of evidence; (8) presentation of the results; and (9) a summary of the evidence, conclusions, and the implications of the findings [20].

Stage 1: Definition and Alignment of Research Objectives and Questions

The mnemonic PCC (population, concept, context) underlay formulation of the research question. This model allows broadly mapping information to identify knowledge gaps, present key concepts, quantify aspects of interest, and expose practices and evidence of a particular theme [20]. We defined the population as people diagnosed with syphilis, the concept as spatial analysis, and the context as health care. Thus, the research question is "How has spatial analysis been used in syphilis-related research in health care?"

Stage 2: Development and Alignment of Inclusion Criteria According to Research Objectives and Questions

Studies will be included if the full text is available, they address syphilis, and they use any geographic information systems software and spatial analysis technique. Studies will be included independently of sample characteristics and size. Studies published as research articles, theses, dissertations, and government documents will be considered with no location, time, or language restrictions. An external translator will be used when needed.

Studies will be excluded if they are literature reviews, debates, documents, editorials, expert opinions, comments, opinion articles, or conference or poster abstracts. Studies that do not have syphilis as the primary outcome, have an insufficient methodological description, or do not answer the research question will also be excluded.

Stage 3: Description of the Search for Evidence, Selection, Extraction of Data, and Presentation of Evidence

The search strategy will be conducted in 3 steps to reach the largest number of publications possible.

First Step: Identification of Descriptors and Keywords

An exploratory search on PubMed and the Virtual Health Library (Biblioteca Virtual en Salud; BVS) was conducted to identify the main medical subject heading (MeSH) terms and health sciences descriptors (Descritores em Ciências da Saúde; DeCS) related to the topic. The search strategy was built using 4 controlled health vocabularies, including DeCS, MeSH, Emtree, and the Tesauro Cumulative Index to Nursing and Allied Health Literature (CINAHL), to identify relevant studies and expand the results in different databases.

A search was conducted to identify synonyms and keywords. The search strategy was then expanded, checked, and improved by a librarian. Descriptors were combined with natural language [24,25] to increase sensitivity and expand the search results. The construction of the search strategy used the extraction, conversion, combination, construction, and use model [24]. This model increases the sensitivity of the search strategy by following complementary steps. Table 1 shows the conversion of mnemonic elements into the main keywords.

Multimedia Appendix 1 shows the complete search strategy built for Medline/PubMed.

Table 1. Definition of the PCC (population, concept, context) mnemonic elements.

Mnemonic elements	Definition	Keywords
Population	People diagnosed with syphilis	Syphilis; treponema pallidum; treponema infections
Concept	Spatial analysis	Spatial analysis; geographic information system; geographic information systems; disease hotspot; spatiotemporal analysis; spatiotemporal analysis; geographic mapping
Context	Health care	Identification by document reading

Second Step: Database Definition for Data Collection

After defining a search strategy with high sensitivity, data collection will be performed in the following databases: Embase, Lilacs (in Portuguese and English) via the BVS, Medline/PubMed, Web of Science, CINAHL, and Scopus.

For a gray literature search, we will consult Google Scholar, the Digital Library of Theses and Dissertations, the Catalog of Theses and Dissertations from the Coordination of Improvement of Higher Education Personnel (Coordenação de Aperfeiçoamento de Pessoal de Nível Superior; CAPES), Open Access Theses and Dissertations, ProQuest Dissertations and Theses Global, and the Networked Digital Library of Theses and Dissertations.

Third Step: Browse Additional Sources in Selected Publication References

The reference lists of selected articles will be searched to track down eligible sources not retrieved with the search strategy.

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Authors of the included studies will be consulted by email for any additional information if needed.

Stage 4: Search for Evidence

The search strategy will be adapted to each database. The free version of Rayyan (Qatar Foundation) [26] will be used for duplicate removal and study selection. Two reviewers (JdCD and YTP) will conduct a pilot test to reduce biases, standardize the selection process, and verify agreement with the study protocol. Each author will select 25 studies and read the titles and abstracts; the screening will follow the eligibility criteria. The team will then discuss any discrepancies and make necessary changes to the criteria and definitions. The screening will start only after 75% agreement is reached [20].

After the pilot test, 2 blind reviewers (JdCD and YTP) will use Rayyan [26] to read the titles and abstracts of all identified studies, evaluating them according to the inclusion criteria. In cases of disagreement, a third reviewer (RARdS) will be consulted.

Stage 5: Selection of Evidence

After reading the full text, potentially eligible publications will be retrieved in full via their titles and abstracts and exported to a Microsoft Excel database (2020 version; Microsoft Corp). Full texts will be analyzed and reasons for exclusion will be recorded. Information regarding the selection of publications, eligibility criteria, and reasons for inclusion and exclusion will be reported in the PRISMA-ScR flowchart [27].

Stage 6: Extraction of Evidence

Data will be extracted using a spreadsheet built in Microsoft Excel (Table 2). Two trained reviewers (JdCD and YTP) will extract the data.

Two reviewers will map the application of spatial analysis in syphilis-related research using geographic data and by identifying where the study was performed. The map will be developed using a Google spreadsheet.

Table 2. Data extraction variables.

Variable	Standardized method
First author and year of publication	Identify the first author and year of publication of the study
Objective	Detail the study objective
Study design	Detail the study design described by the author or authors
Data collection procedures	List the data collection technique or techniques used
Geographic extent	Identify the city, state, region, or country where the study was conducted
Syphilis, gestational syphilis, congenital syphilis	Identify the classification of syphilis
Period (in years) of the collected data	Identify the period of data collection
Visualization software	Identify the geographic visualization software
Spatial analysis method	Describe the methodology developed in the spatial analysis
Results	Describe the main study results
Challenges and limitations	Describe the main study challenges and limitations mentioned by the authors related to using spatial analysis

Stage 7: Analysis of Evidence

Results will be interpreted qualitatively and quantitatively and presented using a PRISMA-ScR flowchart [27]. SPSS (version 24.0; IBM Corp) will be used for statistical analysis. The quantitative analysis will use descriptive statistics with the absolute frequency and percentage. Thematic analysis will be used in the qualitative analysis due to its flexibility in identifying patterns in research questions [28,29]. A thematic analysis will categorize the application of spatial analysis in syphilis-related research in health care. The results will be discussed using the literature and research objectives and questions.

Stage 8: Presentation of Results

The final report guided by PRISMA-ScR will include the results in flowcharts, graphs, or figures [23]. We will use images to help readers understand the results of the studies. As the theme of the presented protocol involves spatial analysis, it is very likely that some of the results will be shown in map images.

Stage 9: Summary of Evidence, Conclusions, and Implications of Findings

After carrying out the previous steps, we will prepare a summary of the results of the scoping review linked to the objective of the study. This way, the conclusion of the study will be grounded and presented effectively. We will highlight knowledge gaps that may arise in the development of the scoping review to provide direction for future studies.

Results

This protocol will guide a scoping review to identify and map the use of spatial analysis as a tool in syphilis-related research in health care. The results will be presented according to the PRISMA-ScR guidelines [23] and summarized regarding (1) the use of spatial analysis in syphilis-related research in health care in countries with different contexts, (2) factors associated with the formation of spatial clusters, and (3) impacts on population health; contributions to health systems, challenges, limitations, and possible research gaps will also be summarized

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to guide future research. In addition, the results of this scoping review may be useful for public health and safety professionals, managers, public policy makers, the general population, the academic community, and health professionals who work directly with people with syphilis.

This protocol will enable method replication following the principles of open science [30], minimizing the risk of bias.

Data collection is projected to start in June 2023 and end in July 2023. Data analysis is scheduled to take place in August and September 2023. We expect to publish the results of the scoping review in the final months of 2023.

Discussion

Principal Findings

This protocol will guide a scoping review to identify and map the use of spatial analysis as a tool in syphilis-related research in health care. Spatial analysis in health care research can identify the spatial distribution of high-incidence diseases, identify associations in their distribution with determining factors, and support direct health planning and actions [31-33].

The United Nations proposed the elimination of congenital syphilis by 2030, reducing its incidence to 0.5 cases per 1000 live births [34]. Strategies to prevent syphilis are a concern of authorities worldwide and are included in the sustainable development goals. Therefore, this review will help develop specific health strategies to control syphilis.

The research team involved in this protocol has experience studying syphilis and spatial analysis and has knowledge and experience in scoping reviews. A librarian helped develop the high-sensitivity search strategy, which is based on a combination of 4 vocabularies and will expand the results and allow access to the literature; an especially important point is the lack of time and language restrictions.

A test search with terms for epidemiology, treatment, prevalence, and incidence was performed in the thematic context group (on the use of spatial analysis in health care). However, the search had restricted results and directed the research question to a certain type of technique, creating bias. Thus, we left the "context" field empty and searched for all possibilities for using spatial analysis in health care.

Limitations

The study limitations will include the lack of a search for institutional sites in all countries (ie, for gray literature at these sites), but this should not affect study development. We will select essential databases to minimize this limitation. The use of descriptors and search terms in only English and Portuguese may be another limitation of the study.

Conclusions

This study protocol presents the main methodological steps that will guide the proposed scoping review and identify and map studies that use spatial analysis as a tool in syphilis-related research in health care. The review may reveal areas with the highest incidence of syphilis, identify which countries most use spatial analysis to study syphilis, and determine the applicability of the technique for syphilis research in each continent.

The results will be published in open access and peer-reviewed journals, favoring the dissemination of knowledge in the scientific community.

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Authors' Contributions

JdCD contributed to conception of the study; JdCD, RHL, and RARdS contributed to study methodology; JdCD, RHL, and RARdS contributed to data management; JdCD, RHL, YTP, and CdSRM contributed to formal analysis; RARdS contributed to administration and supervision; JdCD and RHL contributed to original writing; and JdCD, RHL, YTP, CdSRM, and RARdS contributed to writing, review, and editing of the manuscript. All authors read and agreed with the final version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Table S1. Complete strategy for searching Medline/Pubmed.
[DOCX File , 14 KB - resprot_v12i1e43243_app1.docx]

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Abbreviations

BVS: Biblioteca Virtual en Salud
CAPES: Coordenação de Aperfeiçoamento de Pessoal de Nível Superior
CINAHL: Cumulative Index to Nursing and Allied Health Literature
DeCS: Descritores em Ciências da Saúde
JBI: Joanna Briggs Institute
PCC: population, concept, context
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses: Extension for Scoping Reviews
PROSPERO: International Prospective Register of Systematic Reviews

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Protocol

The Impact of Secure Messaging in the Treatment of Patients With Diabetes Within a Primary Care Setting: Protocol for a Scoping Review

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Abstract

Background: Diabetes—a high-burden chronic disease—requires lifetime active management involving the use of different tools and health care resources to improve patient health outcomes. Recent studies have demonstrated promising results regarding the impact of the use of virtual care technology on the treatment of chronic diseases, such as diabetes. However, it is unclear whether the use of technologies, such as secure messaging, improves the quality of care and reduces diabetes-related costs to the health care system.

Objective: The purpose of our scoping review is to explore what is known about the use of secure messaging in the treatment of diabetes within the primary care setting and how its impact has been assessed from the patient and health system perspectives. Our review aims to understand to what extent secure messaging improves the quality of diabetes care.

Methods: Our scoping review will follow the 6-step Arksey and O'Malley methodological framework, as well as the Joanna Briggs Institute methodology for scoping reviews and their recommended tools. The tools to guide the development and reporting of the review in a structured way will include the Population, Concept, and Context framework and the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) guidelines and checklist. The search strategy was developed iteratively in collaboration with a professional information specialist. Furthermore, a peer review of electronic search strategies was also conducted by an independent, third-party, professional information specialist. A systematic literature search will be conducted against databases, including Ovid MEDLINE ALL, Embase, APA PsycINFO, Cochrane Library on Wiley, CINAHL on EBSCO, and PubMed. Grey literature sources will also be searched for relevant literature. Literature on the use of secure messaging in the treatment of diabetes (types 1 and 2) within a primary care setting will be included. Two reviewers will review the literature based on the inclusion criteria in the following two steps: (1) title and abstract review and (2) full-text review. Discrepancies will be discussed to reach consensus where possible; otherwise, a third reviewer will resolve the dispute.

Results: The results and a final report are expected to be completed and submitted to a peer-reviewed journal in 6 months.

Conclusions: The review will examine existing literature to identify the impact of secure messaging in diabetes treatment within primary care settings. Research gaps will also be identified to determine if there is a need for further studies.

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KEYWORDS

secure messaging; secure message; text messaging; security; privacy; chronic disease; chronic condition; primary care; health outcome; diabetic; diabetes; virtual care; scoping review; review methodology; health care system

Introduction

The prevalence of diabetes worldwide is expected to continue to rise. From 2010 to 2030, the prevalence of diabetes among individuals aged 20 to 79 years will likely increase from 6.4% to 7.7% worldwide and from 11.6% to 13.9% in Canada [1].

Diabetes is an endocrine disorder that arises from the body's inability to produce insulin, effectively use it, or both, resulting in an unhealthy rise in blood sugar levels. Insulin is a hormone that is produced by the pancreas to regulate blood sugar. Consequences of unmanaged diabetes include pain, nerve damage, amputation, the failure of different organs, cardiovascular diseases, and more. Complications of this disease are very serious and can lead to death [2,3].

Canada's public health care system spends billions of dollars annually in the treatment of chronic diseases, and this cost is rising due to population growth and improvements in screening, diagnosis, and care. Diabetes Canada estimated the direct cost of diabetes to the Canadian health care system to be about CAD $32 billion (approximately US $24 billion) in 2023 and predicted it to reach about CAD $39 billion (approximately US $29 billion) by 2028 [3]. The province of Alberta spends approximately twice as much money on patients with diabetes compared to the amount of money it spends on those without it [4].

The recent COVID-19 pandemic has acted as a catalyst for the adoption of virtual care technology and services around the world, including Canada. The Canadian government continues to invest in virtual care technology (eg, secure messaging technology, videoconferencing technology, and other tools), in addition to the billions of dollars already invested in digital health [5]. *Virtual care* is defined as "[a]ny interaction between patients and/or members of their circle of care occurring remotely, using any form of communication or information technology with the aim of facilitating or maximizing the quality of patient care." *Secure messaging* is a virtual care modality defined as "the asynchronous exchange of information between providers and patients, or between providers, through electronic platforms (e.g. texting, e-mail) that adhere to the standards of safety and privacy" [6]. Effective diabetes treatment involving the tracking and monitoring of diet, blood sugar, and physical activities that involve using technology together with active treatment is shown to be cost-effective in reducing complications. The provision of remote health care services by using a variety of virtual care tools is identified by Diabetes Canada as a delivery mechanism that can improve patient outcomes by providing timely and interdisciplinary care [3]. In contrast with other outcomes of conventional diabetes treatment, the use of virtual care offers benefits, such as improved access to services in rural or remote areas, reduced wait times, the avoidance of clinician and patient travel, cost efficiencies, and even reduced carbon emissions [3,7,8]. It is unclear to what extent the use of virtual care technology in health care helps to facilitate or maximize the quality of care for patients.

Our preliminary literature scan found many studies on the use of one or another form of digital health technology (telehealth, telemedicine, telemonitoring, videoconferencing, SMS text messages, electronic health records, etc) to improve diabetes management and patient outcomes, but only a small proportion are on the use of secure messaging for diabetes management. Similar findings were also suggested by a scoping review on the costs and benefits of eHealth applications that support the independent living of older adults [9]. A literature scan on virtual care evaluations, which was conducted by the Canadian Agency for Drugs and Technologies in Health in 2021, noted that studies tend to assess combined virtual care modalities (eg, video and telephone), making it difficult to provide informative evidence on the impact of a specific modality [10].

There is some evidence suggesting that the use of virtual care technology in the management of diabetes and other chronic diseases is associated with positive clinical outcomes that, in some cases, are comparable to those of in-person care [11-15]. Moreover, the use of asynchronous electronic communications tools is shown to improve primary care providers' access to specialists, minimize unnecessary referrals, and reduce call volumes to providers [3,16-19]. However, negative impacts on clinicians' workloads and mixed inconclusive impacts on certain clinical outcomes (eg, blood pressure and cholesterol) and aspects of the quality of care have also been reported [11,15,19-22].

We find that literature on the impact of secure messaging in diabetes management tends to focus on discrete outcomes, such as biomedical outcomes, cost, adoption, patient satisfaction, and workflows, among others. We posit that there is a research gap on studies that assess the impact of secure messaging in primary care through a more holistic quality of care lens (ie, safety, effectiveness, efficiency, timeliness, and patient centricity, as defined by the Institute of Medicine [23]). A recent systematic review of patient portal functionalities and outcomes of patients with diabetes also identified similar gaps and the need for further studies to understand how the use of patient portals by patients with diabetes improves health outcomes [15].

To continue investing in virtual care services, health care policy makers need evidence on both the clinical outcomes and the health system outcomes to inform their decisions. The purpose of our scoping review is to explore what is known about the use of secure messaging in the treatment of diabetes within the primary care setting and how its impact has been assessed from the patient, health system, and quality of care perspectives.

Our scoping review will contribute to existing literature by examining the literature for evidence on the impact of secure messaging in the treatment of diabetes from a more holistic quality of care perspective that includes both clinical outcomes and health system outcomes.

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Methods

Study Design

Our review will be based on the Arksey and O'Malley methodological framework for scoping reviews, which includes the following six steps: (1) identifying the research question; (2) identifying the relevant studies; (3) defining the study selection criteria; (4) charting the data; (5) collating, summarizing, and reporting the results; and (6) optionally consulting with peers for additional feedback and the validation of findings [24].

Our approach will result in the wide coverage of the literature. The decision to narrow down the literature will be made once the reviewers have a sense of the volume and general scope of the literature and gain familiarity with the literature and the field, after conducting the search [24]. The tools recommended by Levac et al [25] and the Joanna Briggs Institute [26-28], which are grounded on Arksey and O'Malley's [24] earlier work, will be leveraged to conduct and report our scoping review in a structured way. These tools include the Population, Concept, and Context (PCC) framework and the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) guidelines and checklist.

Stage 1: Identifying the Research Question

Our scoping review aims to address the following research questions:

1. How is secure messaging used in the treatment of diabetes within the primary care setting?
2. Which outcome measures are used?
3. What is the impact of using secure messaging on the quality of care?
4. What are the facilitators, risks, and challenges of adopting secure messaging for diabetes care?

Stage 2: Identifying Relevant Studies

The PCC framework was utilized to identify the main concepts of the research questions (Table 1). Initial iterative searches in MEDLINE were conducted by the principal investigator (AL) to identify relevant articles and subject headings.

Table 1. Population, Concept, and Context framework and search terms.

	Main concept keywords	Alternative keywords	Medical Subject Headings
Participants	• *diabetic patients*	• *Diabetes Mellitus*	• *Diabetes Mellitus*
Concept	• *secure message*	• *secure messaging* • *secure communication* • *secure email* • *virtual care* • *virtual health* • *telehealth* • *telemedicine* • *e-visits data* • *mhealth* • *patient portal*	• *Electronic Health Records* • *Communication* • *Telemedicine* • *Patient portal* • *Personal Health Records* • *Computerized Medical Records Systems* • *Electronic Mail*
Context	• *Primary healthcare setting*	• *Primary care setting* • *Community setting* • *Outpatient setting*	• *Primary Health Care* • *Community Health Services* • *Outpatient*

Further iterative searches against MEDLINE were conducted in collaboration with a professional information specialist, resulting in a more refined search strategy that produced 4972 results (Multimedia Appendix 1). This search strategy was then submitted to a second information specialist for a peer review assessment and the validation of the quality and comprehensiveness of the search strategy, in accordance with the PRESS (Peer Review of Electronic Search Strategies) 2015 guideline [29]. Comments were reviewed, and adjustments were made to the strategy as deemed appropriate.

The intervention of interest is secure messaging use in the treatment of diabetes within primary care settings. The care settings will comprise noninstitutionalized and nonhospital settings. This aligns with the definitions of *primary care* by the World Health Organization [30] and Health Canada, whereby primary care is considered an "element within primary health care that focusses on health care services, including health promotion, illness and injury prevention, and the diagnosis and treatment of illness and injury" [31].

Our strategy utilizes a combination of controlled vocabulary (eg, *Diabetes Mellitus*, *Telemedicine*, and *Patient Portals*) and free-text terms (eg, *NIDDM*, *virtual consult*, and *secure email*). Using the Ovid platform, we will search Ovid MEDLINE ALL, Embase, and APA PsycINFO. We will also search the Cochrane Library on Wiley, CINAHL on EBSCO, and PubMed. Vocabulary and syntax will be adjusted across the databases. No language or date limits will be applied, but animal-only records will be removed where possible. Results will be downloaded and deduplicated by using EndNote 9.3.3 (Clarivate Plc) and uploaded to Covidence (Veritas Health Innovation Ltd).

The reference lists of all included studies will also be hand searched to identify additional literature that may not be captured through the database search. Additional grey literature will also be identified through an existing network of reviewers, relevant

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journals, organizations, conferences, and a community of practices across the globe. EndNote software will be utilized to manage references.

Stage 3: Defining the Study Selection Criteria

Based on the research questions and objectives, the inclusion and exclusion criteria shown in Table 2 will be used to initially guide the review. The further refinement of these criteria will occur in an iterative manner as the reviewers gain a better understanding of the scope of available literature. In alignment with the PCC framework, the initial inclusion criteria will include those for the population (patients with diabetes), concept (secure messages), and context (primary and community care settings). The use of secure messaging for patient-provider, caregiver-provider, and provider-provider communications will be included. The initial exclusion criteria will be patients with gestational diabetes, other virtual or digital health interventions, and institutionalized or hospital settings.

Table 2. Inclusion and exclusion criteria.

	Inclusion criteria	Exclusion criteria
Year of publication	• No limit	• N/A[a]
Language	• English	• All other languages
Population	• Patients with diabetes (types 1 and 2)	• Patients with gestational diabetes
Concept or intervention	• Secure message	• Other virtual care modalities (videoconferences and phone calls)
Context and setting	• Primary health care setting • Primary care setting • Outpatient setting • Community setting	• Hospital setting • Inpatient setting • Institutionalized treatment within acute care setting
Study design	• Studies that contain defined impacts and outcomes of secure messaging for diabetes treatment	• Studies that do not contain defined impacts of secure messaging for diabetes treatment • Commentaries • Opinions • Summary articles • Clinical trial recruitments • Scoping or systematic review protocols • Abstracts
Outcomes	• All patient-related clinical outcomes and health system outcomes (eg, patient experience, patient clinical outcomes, health system outcomes, health care utilization, quality of life outcomes, health status, emergency room visits, follow-up visits, etc)	• Nonclinical outcomes and outcomes unrelated to health systems

[a]N/A: not applicable.

Stage 4: Charting the Data

The review team consists of the following three reviewers: the principal investigator (AL), the supervisor (DM), and the cosupervisor (TS). Due to its convenience, Covidence will be used by the reviewers to independently screen the articles, based on the inclusion and exclusion criteria, in the following two steps: (1) title and abstract review and (2) full-text review of the full-text articles and documents. To be more inclusive and reduce the risk of excluding relevant studies, any articles that reviewers are unsure of during the title and abstract scan will be moved forward to the full-text review stage.

Data extraction will be conducted outside of Covidence, using a charting form (Multimedia Appendix 2) that we initially created based on Arksey and O'Malley's [24] recommendations, which include the following elements: author(s), year of publication, study location, intervention type, comparator (if any), duration of the intervention, study populations, aims of the study, methodology, outcome measures, and important results.

Two reviewers will pilot the data extraction form on the first 30 articles to identify the need for modification. The review team will further revise the form, as needed, during the data extraction process as new relevant data types and themes are encountered.

Stage 5: Collating, Summarizing, and Reporting the Results

The review team will utilize the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) chart and PRISMA-ScR checklist [27] to report their findings in a clear, transparent way (Multimedia Appendix 3 [28] and Multimedia Appendix 4 [27]).

A narrative summary of findings will be developed based on the elements of the data extraction form and guided by the context of the research question and study objectives.

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Throughout the course of the review, if other criteria or elements are uncovered, the authors will decide on other additional formats (eg, graphs, tables, and diagrams) for presenting the study findings.

Stage 6: Peer Consultation for Feedback and Validation

At different stages, experts will be consulted to review and provide feedback. In stage 2, prior to executing the final search, the search strategy will undergo a peer review by a qualified librarian to ensure relevance and achieve more holistic search results. Other experts within the field will also be drawn from our networks to ensure that relevant findings are captured and reported in a clear manner. In stages 3 to 5, experts will also be consulted to suggest additional literature and provide feedback on the data extraction form.

The experts we consult will include researchers and practitioners within the digital health field and decision makers from publicly funded payer organizations.

Ethical Considerations

Neither ethics approval nor participant consent is required, as our scoping review will not include human or animal participants. Data will be collected from published literature.

Results

The systematic literature search of databases has been conducted, and the title and abstract review is planned to commence in early September 2022.

An article of the scoping review findings will be submitted for publication in a peer-reviewed journal. The final version of findings and the full-text article will be shared with a panel and wider stakeholder organizations.

Discussion

Overview

Our scoping review will explore what is known about the use of secure messaging in the treatment of diabetes within the primary care setting. The review will contribute to knowledge on this topic by examining how the impact of secure messaging has been assessed from the patient, health system, and quality of care perspectives. To our knowledge, this has not been the focus of previous reviews [11,15,22,23].

The findings of the scoping review will inform health care policy makers' decisions on virtual care services.

Strengths and Limitations

Our scoping review will use an established framework and a comprehensive systematic search to identify and review existing literature on the use of secure messaging in the treatment of diabetes to date. The search strategy is peer-reviewed, and the grey literature search and the review will be informed and guided via consultation with experts. Although the findings will be useful in understanding the state of the literature and potential research gaps, the study does not aim to conduct a full assessment of the quality of the evidence in the literature uncovered.

Acknowledgments

The study design, conceptualization, and manuscript were developed by AL, under the supervision of DM and TS, who reviewed and approved the draft and final version of the review protocol. EA reviewed the draft and provided input and feedback on research objectives, definitions of key terms, and accompanying literature sources.

The authors consulted with Simon Hagen (Canada Health Infoway), who provided guidance on sources of grey literature for consideration.

We thank Kaitryn Campbell, MLIS, MSc (St. Joseph's Healthcare Hamilton/McMaster University), for peer reviewing the MEDLINE search strategy.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search strategy.
[DOCX File , 21 KB - resprot_v12i1e42339_app1.docx]

Multimedia Appendix 2
Data extraction form.
[DOCX File , 24 KB - resprot_v12i1e42339_app2.docx]

Multimedia Appendix 3
PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 flow diagram template [28].
[DOCX File , 66 KB - resprot_v12i1e42339_app3.docx]

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Multimedia Appendix 4
PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) checklist [27].
[DOCX File , 109 KB - resprot_v12i1e42339_app4.docx]

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Abbreviations

PCC: Population, Concept, and Context
PRESS: Peer Review of Electronic Search Strategies
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews

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Protocol

Rehabilitation Approaches and Strategies in the Management of Adult Patients Following Pelvic Fractures: Protocol for a Scoping Review

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Abstract

Background: Pelvic fractures can lead to disability and a poor health-related quality of life, thereby contributing to the burden of disease in South Africa. Rehabilitation plays an important role in improving the functional outcomes in patients with pelvic fractures. However, there is limited published research that presents optimal interventions and guidelines to improve outcomes in affected individuals.

Objective: The purpose of this study is to examine and map the range of and gaps in rehabilitation approaches and strategies used by health care professionals globally in the management of adult patients with pelvic fractures.

Methods: The synthesis of evidence will follow the framework outlined by Arksey and O'Malley and supported by the Joanna Briggs Institute. The identification of research questions; the identification of relevant studies; the selection of eligible studies; charting data; collating, summarizing, and reporting of the results; and consultation with relevant stakeholders will be undertaken. Peer-reviewed articles written in English; from quantitative, qualitative, and mixed methods studies; and searched through Google Scholar, MEDLINE, PubMed, and Cochrane Library will be considered. Studies eligible for selection will be full-text articles written in English about adult patients with pelvic fractures. Studies on children with pelvic fractures and on interventions following pathological pelvic fractures as well as opinion papers and commentaries will be excluded from the study. Rayyan software will be used for title and abstract screening to determine inclusion in the study and to improve collaboration between the reviewers. The Mixed Methods Appraisal Tool (version 2018) will be used to appraise the quality of the studies.

Results: This protocol will guide a scoping review to examine and map the range of and gaps in rehabilitation approaches and strategies used by health care professionals globally in the management of adult patients with pelvic fractures, irrespective of level of care. Impairments, activity limitations, and participation restrictions in patients with pelvic fractures will be highlighted, which will give an indication of the rehabilitation needs of the affected individuals. Results of this review might provide evidence for health care professionals, policy makers, and scholars to aid rehabilitative care and further integration of patients into health care systems and community.

Conclusions: The rehabilitation needs of patients with pelvic fractures will be drawn from this review and will be presented in a flow diagram. Rehabilitation approaches and strategies in the management of patients with pelvic fractures will be identified to guide health care professionals in the promotion of quality health care for these patients.

Trial Registration: OSF Registries osf.io/k6eg8; https://osf.io/k6eg8

International Registered Report Identifier (IRRID): PRR1-10.2196/38884

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(JMIR Res Protoc 2023;12:e38884) doi:10.2196/38884

KEYWORDS

rehabilitation approaches; rehabilitation strategies; adult patients; pelvic fractures; polytrauma; integrated health care; early intervention

Introduction

Pelvic fractures are mainly due to trauma [1] and can lead to disability and a poor health-related quality of life, thereby contributing to the burden of disease in South Africa [1]. The burden of disease hinders development and delays the attainment of sustainable development goals. Pelvic fractures may be complex injuries due to their association with polytrauma as a result of high-velocity impact [2]. The majority of individuals in India and South Africa who sustain pelvic fractures, secondary to motor vehicle accidents, are young male adults from both low and middle socioeconomic classes [3-5]. However, pelvic fractures in older adults are commonly associated with low-velocity impact in the United Kingdom [2].

The rate of survival of patients with pelvic fractures has increased significantly [6]. However, patients present with impairments and disabilities that affect their participation in the activities of daily living in their homes, society, and the community at large. Pelvic fractures present a challenge to the trauma and orthopedic surgeons due to their complexity [2]. They are further complicated by the associated injuries, which can lead to poor outcomes following management [3]. Poor outcomes were reported by patients following the management of pelvic fractures between 2008 and 2013 from different academic hospitals in Tshwane, South Africa (Sobantu, Skaal, and Tshabalala, unpublished data, 2017).

The aforementioned study explored the perspectives of patients on their health-related quality of life, following management of their pelvic fractures. Some of the challenges that were reported by the participants were poor mobility, chronic pain, lack of vitality, sexual dysfunction, and urinary and bowel incontinence. These challenges affected their day-to-day functioning at home, in society, in their communities, and at their workplaces. All these disabling outcomes resulted in low levels of physical health; psychological strain; poor social relations; and loss of independence in patients with pelvic fractures, regardless of the type of fracture. Pelvic fracture malunion leads to permanent disability in more than 65% of patients [7]. Some of the limitations in patients with pelvic fractures include gait abnormalities and chronic pelvic and back pain [8].

The increased survival rate of patients with pelvic fractures has been attributed to improved multidisciplinary health care management [9]. However, there is limited published research that presents optimal interventions and guidelines to improve outcomes in affected individuals. Patients with pelvic fractures commence their rehabilitation programs very late. Some patients even get discharged from hospitals before receiving rehabilitation. Health care professionals focus on the impairments that patients present with whilst hospitalized. Activity limitations and participation restrictions, which are more noticeable once the patient has been discharged, are rarely addressed. There is limited use of outcome measurement tools in these patients, especially by the rehabilitation team, to guide their progress.

Early appropriate care optimizes health care and results in fewer complications in patients following pelvic fractures [10]. The provision of early appropriate care has been a challenge in most health institutions due to limited human resources and few hospital beds. Few hospital beds lead to the early discharge of patients. These challenges lead to some patients not receiving optimum, integrated health care, including rehabilitation. Loss of continuity in health care can occur due to patients being discharged without home programs or relevant referrals for outpatient rehabilitation. Loss of continuity leads to an increase in long-term disabilities in these patients.

Even though pelvic fractures are a challenge to manage due to their complexity, no standardized comprehensive guidelines have been published to address the problems associated with them [11]. Guidelines and models are important in providing clear strategies to health care professionals involved in the management and rehabilitation of patients with pelvic fractures. Guidelines and models can assist in guiding the rehabilitation of patients with pelvic fractures within the biopsychosocial model of care, as guided by the International Classification of Functioning, Disability and Health framework [12]. An integrative rehabilitation approach will improve patient health outcomes and reduce the incidence of residual disabilities. Physiotherapists play a major role in the rehabilitation of patients with pelvic fractures. They work toward reducing pain, improving joint mobility, strengthening muscles, addressing pelvic dysfunction, and promoting function. The aforementioned aims are achieved by using therapeutic exercises, manual therapy, and electrotherapy.

Therefore, the aim of this scoping review is to examine and map the range of and gaps in rehabilitation approaches and strategies used by health care professionals globally in the management of both in- and outpatients with pelvic fractures, irrespective of level of care.

Methods

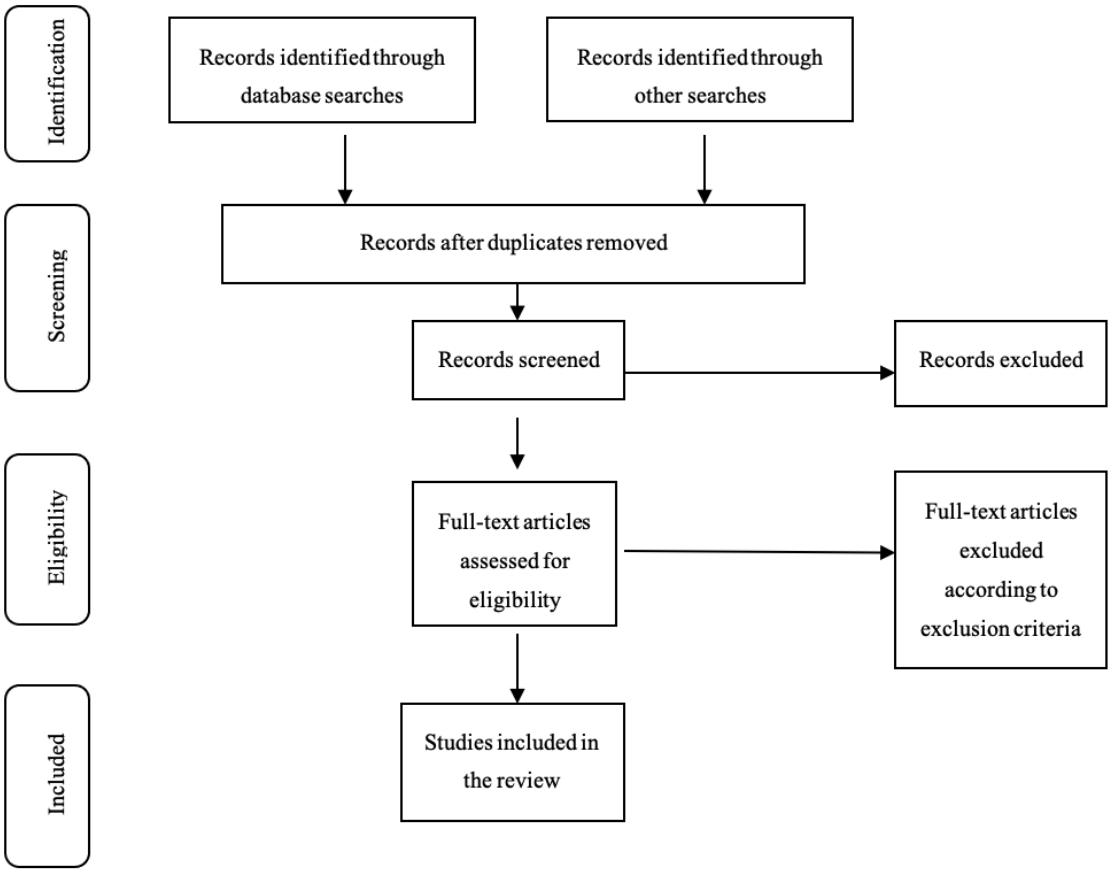
Overview

This protocol has been registered with the Open Science Framework (osf.io/f9w3z). This study protocol follows the reporting guidelines provided in the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) statement [12] and the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews; Figure 1; Multimedia Appendix 1) [13]. Literature on rehabilitation approaches and strategies in the management of adult patients following pelvic fractures will be reviewed. This review will be guided by Arksey and

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O'Malley's methodological framework [14]. The framework identifies 6 stages that must be considered when developing a scoping review. The 6 stages are as follows: identification of the research question; identification of relevant studies; selection of eligible studies; charting the data; collating, summarizing, and reporting the results; and consulting with relevant stakeholders. The stakeholders include the orthopedic surgeon, urologist, psychologist, physiotherapist, dietician, orthopedic nurse, occupational therapist, social worker, orthotist, and prosthetist, and general or trauma surgeon. Results of the scoping review will be sent by email to the stakeholders for critiquing and reflecting on the evidence. Virtual meetings may be arranged as a follow-up to emails should the need arise. Stakeholders will have an opportunity to provide possible solutions to develop a fit-for-purpose interprofessional education and collaborative practice model. The purpose of including the stakeholders is to ensure that the best quality of evidence is collated and implemented.

Figure 1. PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) flow diagram [13].



Identifying the Research Question

The research question underpinning the review is "What rehabilitation approaches and strategies have been integrated in the management of adult patients with pelvic fractures?"

Subquestions that will guide the review are as follows:

- What evidence exists on the rehabilitation approaches and strategies for skeletal stabilization of pelvic fractures, globally?
- What evidence exists on the rehabilitation approaches and strategies for associated injuries (eg, rectal and urogenital, chest and abdomen, and other musculoskeletal systems) in adult patients with pelvic fractures?
- What evidence exists on rehabilitation interventions for impairments (eg, pain, joint mobility and function, as well as emotional and psychological challenges) experienced by adult patients following pelvic fractures?
- What evidence exists on rehabilitation interventions for functional disabilities, including mobility, urinary and bowel incontinence, and sexual dysfunction experienced by adult patients following pelvic fractures?

Information Sources and Search Strategy

Identification of studies relevant to this review will be achieved in accordance with the Joanna Briggs Institute search strategy [15]. A search for relevant literature will be conducted on the following electronic databases from 2002 to 2022: Google Scholar, MEDLINE, PubMed, and Cochrane Library. Keywords relevant to each search parameter will be separated by the Boolean terms "AND," "OR," and "NOT." A draft search strategy in PubMed is documented in Multimedia Appendix 2. The reference section of the selected studies will also be explored to identify further, potentially relevant studies that could have been missed in the initial search.

A pilot search using keywords to determine the feasibility of the study will be conducted (Multimedia Appendix 2). The search strategy will be adjusted for each database.

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Eligibility of Research Studies

The study will incorporate the Population, Concept, and Context (PCC) model to align the study selection with the research question [15]. The Population, Concept, and Context model is a well-formulated model that improves scientific rigor for scoping review questions. Studies will have to include globally published articles on adult patients with pelvic fractures focused on rehabilitation approaches and strategies used during management. Rehabilitation approaches and strategies used to address skeletal stability, associated injuries, as well as impairments and disabilities in adult patients with pelvic fractures will be included. Articles on the functional outcome measurements used, home programs, and advice and education that can be given to adult patients with pelvic fractures will also be included. Peer-reviewed journal articles written in English will be included. Quantitative, qualitative, and mixed methods studies will also be included. All health care systems, including primary, secondary, and tertiary systems, will be included. Titles, abstracts, and full texts will be screened by 2 reviewers (MDT and NAS). Discrepancies and disagreements will be resolved by discussions between the 2 reviewers and a third reviewer (VC). Rayyan software will be used for title and abstract screening to determine inclusion in the study and to improve collaboration between the reviewers [16,17].

Inclusion and Exclusion Criteria

The Inclusion and exclusion criteria for studies eligible for selection are presented in Textbox 1.

Textbox 1. Inclusion and exclusion criteria for study selection.

Inclusion criteria

- Articles about adults (aged ≥18 years) with pelvic fractures
- Global articles on rehabilitation approaches and strategies used during management
- Full-text studies
- Articles written in English

Exclusion criteria

- Articles on children with pelvic fractures
- Articles on interventions following pathological pelvic fractures
- Opinion papers
- Commentaries

Charting of the Data

A data charting template (Textbox 2) will be used to extract and capture information from studies through each phase of the review. The information will be about rehabilitation approaches and strategies used by the health care team in the management of patients with pelvic fractures. The chart will be continually and regularly updated by the reviewers through the scoping process to capture all possible results for the research question. Two reviewers will chart the data independently, discussing the results and updating the chart.

Textbox 2. Data charting form.

Data charting information

- Author(s)
- Year of publication
- Origin or country of origin (where the study was published or conducted)
- Aims or purpose
- Study population
- Sample size (if applicable)
- Methodology or methods
- Intervention
- Details of interventions (if applicable)
- Outcomes (if applicable)
- Details of these of outcomes (eg, how measured, if applicable)
- Key findings that relate to the scoping review question(s)
- Conclusions that relate to the scoping review questions

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Collating, Summarizing, and Reporting Results

The data extracted from the studies will be guided by the research questions and subquestions. This will include evidence that exists on the rehabilitation approaches and strategies for each impairment as well as activity limitations and participation restrictions in adult patients with pelvic fractures. The stages of the scoping review promote transparency and allow reproducibility of the study by reducing the risk of bias and data duplication [14,18]. The extracted data will be summarized in the final write-up using a thematic analysis with flexibility in the capturing of data, as in the scoping review [18]. The results will be interpreted and described according to the research question and subquestions.

Quality Appraisal and Bias

Quality appraisal will be undertaken in this scoping review to ensure that strong evidence is collected, which will help to create a trustworthy guide for follow-up research projects. Performance of quality appraisal is informed by a study by Daudt et al [19] who underlined the importance of assessing the quality of studies and conducting a trial of the method before starting with the charting process, if the research is to be used to inform policy makers. The Mixed Methods Appraisal Tool (MMAT; version 2018) will be used to assess the quality of the studies from the search strategy, described above [19]. Moreover, MMAT will be used to assess and report bias from quantitative, qualitative, and mixed methods studies [20]. MMAT is suitable as the study excludes articles such as commentaries and opinion papers. The process requires critical appraisal, and therefore, 3 reviewers will be involved in the appraisal process. One reviewer has experience in MMAT application and will add rigor to the appraisal. The MMAT method allows for the inclusion of qualitative studies, quantitative randomized controlled trials, quantitative nonrandomized trials, and quantitative descriptive and mixed methods studies. Methodological quality criteria will be captured as per the MMAT by 2 reviewers, with the third reviewer overseeing the process.

Results

This protocol will guide a scoping review to examine and map the range of and gaps in rehabilitation approaches and strategies used by health care professionals globally in the management of both in- and outpatients with pelvic fractures, irrespective of level of care. Impairments, activity limitations and participation restrictions in patients with pelvic fractures will be highlighted, which will give an indication of the rehabilitation needs of the affected individuals. Results of this review might provide evidence for health care professionals, policy makers, and scholars to aid rehabilitative care and further integration of patients into health care systems and community.

Discussion

Expected Outcomes

These guidelines will inform the scoping review of examining the range of and gaps in the literature on the rehabilitation approaches and strategies for the management of patients with pelvic fractures. The rehabilitation needs of patients with pelvic fractures will also be drawn from the results of this review and presented in a flow diagram. This study might be used to inform health care professionals of the important aspects to be included in the assessment, management, and rehabilitation of patients with pelvic fractures. The results of this study might also be used to improve the physiotherapy curriculum. Approaches to health care management by health care professionals might be guided by the findings of this review. Health care professionals might be aware of the impact of pelvic fractures on the physical, mental, psychological, and socioeconomic status of the affected individuals. Health care professionals might be able to draw up relevant and patient-centered ward and home programs that can promote health-related quality of life in patients who had sustained pelvic fractures.

This scoping review is the first phase of a study that seeks to develop an interprofessional model of care for patients with pelvic fractures. It is hoped that this review will create awareness of the health care needs of patients with pelvic fractures. This awareness might prompt the health care professionals to set goals that will address most of the patients' needs. The rehabilitation approaches and strategies used by the health care professionals globally as well as gaps in the literature will be identified [21]. This information will be crucial in informing the envisaged model with the best practical evidence, especially pertaining to physiotherapy practice, for patients with pelvic fractures.

The findings of the study will also provide evidence for health care policy makers to assist the stakeholders in addressing the needs of this population by rendering quality health care.

Conclusions

This scoping review protocol outlines steps that will guide the scoping review. This review will also identify and map studies that indicate the rehabilitation approaches and strategies in the management of patients with pelvic fractures. The results of this study may promote circulation of information and knowledge among health care professionals at various levels of health care.

Limitations

Some articles might not be available in the databases that will be included in the study. Literature might also be limited since only articles written in English and available in full text will be considered for the study.

Acknowledgments

The authors acknowledge the support provided by Levin Chetty and the librarian Nomgcobo Ntsham during the development of the search strategy and literature search from the databases.

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Data Availability

Articles that will be included in the study will be deposited into the university repository and will be made available when necessary.

Authors' Contributions

NAS and MDT conceptualized the study; NAS, MDT, and VC refined the methodology and drafted, reviewed, and edited the manuscript. All authors agreed to publish this paper.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Data search strategy.
[DOCX File , 106 KB - resprot_v12i1e38884_app1.docx]

Multimedia Appendix 2
PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) fillable checklist.
[DOCX File , 13 KB - resprot_v12i1e38884_app2.docx]

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Abbreviations

MMAT: Mixed Methods Appraisal Tool
PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews

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Protocol

Black Health in Canada: Protocol for a Scoping Review

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Abstract

Background: Black Canadians experience poor health care, poor health outcomes, and a greater burden of health inequalities, much of which is rooted in the unequal distribution of social determinants of health. Despite Canada's emphasis on social inclusion, Canada's Black population faces substantial social inequities that affect their health and well-being. These disparities may specifically be attributed to racial discrimination, immigration status, precarious housing, underemployment, and increased poverty among Black Canadians.

Objective: This paper describes a protocol for a scoping review that aims to understand the range and nature of research conducted on the health of Black Canadians as well as the gaps in this literature.

Methods: Arksey and O'Malley's methodological framework guided the conduct of the scoping review. We searched electronic databases (CINAHL, Embase, Global Health, MEDLINE, PsycINFO, Scopus, Sociological Abstracts, and Web of Science) and grey literature sources for peer-reviewed articles and grey reports on the health of Black Canadians. Six reviewers independently screened the abstracts and full text of studies to determine eligibility for inclusion. According to the PRISMA-ScR (Preferred Reporting Items for Systematics Reviews and Meta-Analyses extension for Scoping Reviews) guidelines, the findings will be synthesized quantitatively and qualitatively through thematic analysis.

Results: Title, abstract, and full-text screening concluded in October 2022. Data collection is in progress and is expected to be completed by April 2023. Data analysis and drafting of the manuscript will be done thereafter. Findings from the scoping review are expected to be provided for peer review in 2023.

Conclusions: This review will collect important data and evidence related to the health (mental, reproductive, and sexual; social determinants of health) of the Black population in Canada. The findings could help identify existing gaps in the health of Black individuals in Canada and inform future research paradigms. The findings will further inform the development of a knowledge hub on Black Canadians' health.

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(JMIR Res Protoc 2023;12:e42212) doi:10.2196/42212

KEYWORDS

Black people; inequities; mental health; reproductive and sexual health; HIV; social determinants of health; Canada

Introduction

Background

Canada is a racially and culturally diverse country, much of which has been fueled by immigration and settlement of racial minority groups from Asia, the Caribbean, and Africa since the 1960s [1,2]. Today, Canada is one of the most popular immigrant destinations globally, with a growing inflow of Black migrants from sub-Saharan African and Caribbean nations [3]. Black people are the third-leading minority group in Canada, nearing 3.5% of the country's total population, with a projected increase to 5.6% by 2036 [4]. Despite persistent attempts to

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support multiculturalism and racial equality in Canada, race-based social and health inequalities are still widespread [5,6]. The social, economic, and political conditions in which people grow, live, and work are largely responsible for the observed inequalities [4,7,8]. For this scoping review, we will adopt the World Health Organization's definition of health: "Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity" [9]. Therefore, health is broadly defined to include disease conditions; physical, mental, emotional, and spiritual well-being; access to and utilization of health care; barriers and facilitators to health; health interventions, etc.

Black people in Canada are disproportionately affected by social and health inequalities, including poor access to quality health care, education, employment, housing, and mental health support [10-13]. The inequities produced by these social determinants of health are exacerbated by Black people's experiences of precarious immigration status, poverty, and racial discrimination at both interpersonal and institutional levels [4,8,14,15]. Yet, Black people aged 25 to 54 years are more likely to have a bachelor's degree or higher (41.1%) than their nonvisible minority or non-Indigenous counterparts (34.2%) [16]. In 2018, the proportion of the Black population in Canada who resided in rented dwellings (n=695,900, 52%) was twice that for the overall population (n=9,749,700, 27%); furthermore, of those who lived in rented dwellings, the proportion of Black individuals living in unsuitable housing (n=209,800, 30%) was notably higher than that of the overall population (n=1,808,900, 19) [17].

The prolonged exposure to trauma caused by oppression, colonialism, racism, and segregation among Black people in Canada has resulted in them being underprivileged with respect to access to health services and social support systems [13]. Black Canadians experience disparities in health outcomes when compared to other ethno-racial groups in Canada [18]. For instance, heart disease and stroke are among the prominent causes of death in Canada, and Black populations are among those with the highest rate of risk factors for these conditions [4]. In addition, the proportion of Black Canadians aged 18 years and older who rated their health status to be either fair or poor was higher (14.2%) than that of their White Canadian counterparts (11.3%) [4]. About 64% of young Black women between the ages of 12 and 17 years described their mental health to be "excellent" or "very good," which is substantially lower than the 77.2% reported by their White counterparts [4]. Black Canadians experience notable social and economic difficulties that have deleterious consequences on their mental health [19]. This includes disparities in access to mental health services among Black Canadians, which may be attributed to having few Black mental health service providers in the health care system. Indeed, Black Canadians have indicated their interest in accessing mental health care services with Black service providers [20]. The mental health of youth and children in Canada has become a public health problem and has been attributed to the inaccessibility of mental health care services [21]. The Black community in particular has emphasized the need to tackle the mental health issues that are prevalent among youth and children in their communities [22]. Finally, the Black population in Canada has been disproportionately burdened with HIV in the last 20 years. In 2017, a total of 25% of reported HIV cases were among the Black population, which is noteworthy as Black people only account for 3.5% of Canada's total population; in contrast, their White counterparts, who make up almost 75% of Canada's population, represent only 35% of reported cases [23]. Timely access and provision of health care services are major determinants of health for people living with HIV; however, Black populations face inequities that hinder their access to health care services [24].

These disparities suggest a need for innovative research focusing on Black Canadians' health. A scoping review of the literature chronicling existing research on the health of Black Canadians is a critical step in this regard. This project will synthesize this literature and explain the nature and breadth of research on the health of Black Canadians, as well as gaps to be addressed by future research. The findings from the scoping review will inform the creation of a knowledge hub on Black health in Canada. The purpose of this scoping review is thus to map out the scope of the literature on health (including disease conditions; physical, mental, emotional, and spiritual well-being; access to and utilization of health care; barriers and facilitators to health; health interventions, etc).

Objectives

The review will address two specific objectives:

1. To identify the extent, range, and nature of the literature on the health of Black Canadians; and
2. To identify gaps in the literature on the health of Black Canadians.

Methods

Stage 1: Identifying the Research Questions

Arksey and O'Malley [25] proposed an iterative process for developing research questions, where each modification is based on intensifying familiarity with the literature. Thus, the research question was as follows: What is known in the existing literature about the health of Black individuals in Canada?

Stage 2: Identifying Relevant Studies

Bibliographic database searches were conducted in June 2022. At this stage, we developed a search strategy, including the keywords to use, and searched the following databases: CINAHL, Embase, Global Health, MEDLINE, PsycINFO, Scopus, Sociological Abstracts, and Web of Science (Multimedia Appendix 1). We completed a search for grey literature by searching Google and the websites of agencies.

Stage 3: Study Selection

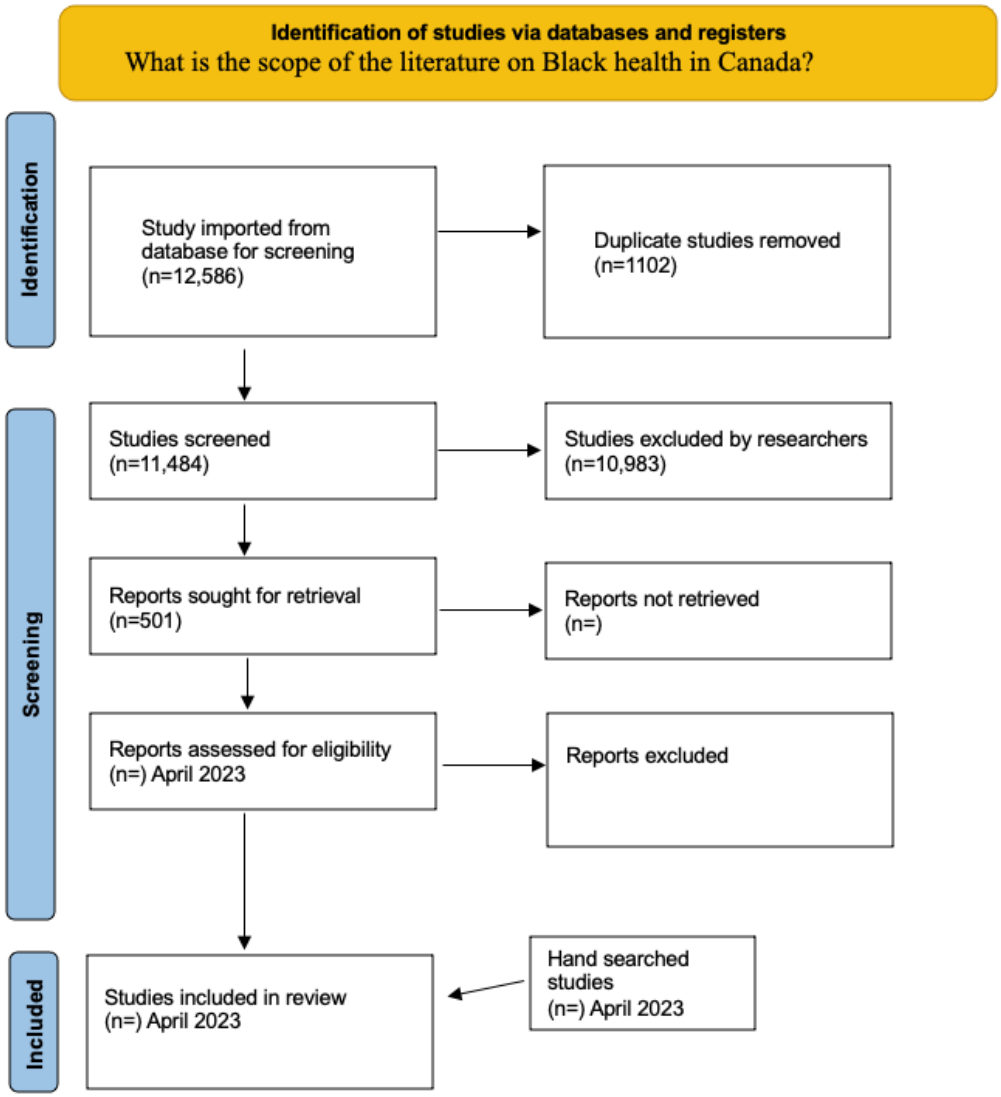
Search Strategy

A total of 12,586 articles were retrieved, of which 1102 were duplicates. A total of 11,484 citations were downloaded from the bibliographic databases into an Endnote library (Endnote 20) and, from there, exported into Covidence where titles and abstracts were reviewed independently by 2 research assistants. Studies that did not meet the inclusion criteria (n=10,983) were excluded. The full text versions of the remaining 501 articles

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have been retrieved and are being independently reviewed by 2 research assistants to determine the eligibility of the articles. A third researcher will resolve disagreements between the 2 research assistants at all review stages. Reference lists of included articles will be scanned for any additional articles that meet the study's inclusion criteria (Figure 1).

Figure 1. PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) 2020 flow diagram: Black health in Canada. Adapted from Page et al [26].



Inclusion Criteria

Participants

The participants will include any Black/African individuals, populations, and communities living in Canada. We define Black Canadians as "People of African descent and those who define themselves as such, who are now residents/citizens of Canada" [27].

Concept

For this scoping review, we define health as "a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity" [9]. A broader range of languages will be considered, and language translators will be engaged with articles published in other languages. The review team will include Black Canadians to ensure that the review is culturally sensitive and inclusive.

Geographical Location

Studies conducted in Canada will be included.

Types of Sources

Eligible study designs will include qualitative, quantitative, and mixed methods study designs. In addition, unpublished theses and dissertations will be included in this scoping review.

Exclusion Criteria

Exclusion criteria will include the following:

- Study types: secondary literature (scoping reviews, literature reviews, systematic reviews, and meta-analysis), letters to the editor, protocols, and case series
- Concept: studies that did not target the health of Black Canadians

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Stage 4: Charting the Data

A data extraction sheet will be developed and used for extraction (Multimedia Appendix 2). It is anticipated that the data categories will include standard information such as author name(s), year of publication, the purpose of the study, study population, methods, results/findings, and comments/implications. Two trained research assistants will independently read each article and extract data. A third reviewer will verify a sample of the extraction for completeness and accuracy. We will ensure that methodological quality checks are conducted to ensure the consistency, accuracy, and thoroughness of the information extracted.

Stage 5: Collating, Summarizing, and Reporting the Results

Quantitative data will be analyzed through a numerical summary. Qualitative studies will be analyzed using thematic analysis to synthesize and categorize the findings of the included studies into themes (drawing from Braun and Clarke [28]). To do so, we will read the included articles several times and familiarize ourselves with the data. Subsequently, we will compile codes into potential themes, group all data relevant to the potential theme, and compare data across the coded excerpts and the entire data set.

Results

We started this project in June 2022 with the development of the search strategy and literature search. As of October 2022, the study team has completed the title, abstract, and full-text screening of imported citations. The articles selected to be represented in the table are important because they meet the inclusion criteria and contribute to the understanding of the health, quality of life, and well-being of Black Canadians. Articles that survive the screening process will provide valuable evidence on the topic of interest. As the study team is expected to complete data collection by April 2023 and the analysis of data and drafting of manuscripts will be done thereafter, this study may provide timely and relevant information to inform the development of the knowledge hub on the health of Black Canadians.

Discussion

Expected Findings

This research protocol aims to guide the researchers in conducting research using a method that entails exploring and mapping literature and identifying research gaps in the health of Black Canadians.

Several study protocols or reviews have been published on the health of Black Canadians. However, these tend to focus too narrowly on specific aspects of health and often neglect a more comprehensive picture. Nguemo et al [29] performed a scoping review of substance use disorders among Black Canadians and found that low income, economic deprivation, unemployment, the lack of health education, immigration, and limited access to treatment services intensified the rate of substance use among Black Canadians. Jefferies et al [30] described food security in African Canadian communities and indicated that food access and food availability are associated with an increase in the rate of dietary acculturation. Similarly, Lofters et al [31] noted that findings from a future review would help in the implementation of human papillomavirus self-sampling and the improvement of uptake of cervical cancer screening among women from African countries who resides in Ontario. Finally, Dogba et al [32] published a scoping review protocol to identify obstacles and enablers to participation by diabetic ethnocultural minority immigrants in retinopathy screening as well as generate results that would help in developing intervention schemes for behavioral modification.

The scoping review will evaluate various disease prevention strategies, access to and utilization of health care, and facilitators to health in Black individuals and communities in Canada. We will explore the resistance of Black Canadians in relation to the barriers they face in accessing health care services and other health intervention programs. Additionally, the impacts of social determinants of health and intersections of dimensions such as gender identity, sexual orientation, age, disabilities, language, educational attainment, and immigration status on the health of Black Canadians will be evaluated.

The completed scoping review will inform research, programs, and services as well as identify potential areas to facilitate and improve the health and well-being of Black Canadians. The findings will be relevant to a variety of audiences, such as researchers, policy makers, stakeholders, health care providers, clinicians, and governments who strive to better understand the health, quality of life, social determinants of health, and well-being of Black Canadians.

Limitations

One limitation of this scooping review is the wide range of inclusion criteria. Therefore, the hand searching of the literature by the research team may result in individual interpretation of the criteria. The lack of critical appraisal and the chance of omitting relevant studies have been reported as major challenges in conducting scoping reviews [33,34]. We acknowledge some biases such as the possibility of omitting studies not captured by our search terms or databases. As there is potential disagreement among reviewers in determining the eligibility of studies, a third reviewer will resolve disagreements at all review stages.

Implications

Our review will address the absence of a comprehensive review on the health of Black Canadians by taking a broader view of health than previous efforts. We will identify the full range of research on the health of Black Canadians and categorize such work into themes reflecting specific topical areas of health and well-being. We will synthesize the literature and identify trends and knowledge gaps in each category of research articles. This effort will contribute to the development of a knowledge hub on the health of Black Canadians that will serve as a resource for the Black communities, policy makers, stakeholders, health care providers, and the government at large. Our findings will also be disseminated in peer-reviewed manuscripts and at conferences.

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Authors' Contributions

BS is the project lead; she conceptualized the idea and designed the study. AOA wrote the protocol and conducted article selection. DA reviewed several versions of the manuscript, and BS provided critical feedback and gave the final approval of this manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search strategy for Black people's health in Canada.
[DOCX File , 27 KB - resprot_v12i1e42212_app1.docx]

Multimedia Appendix 2
Data extraction instrument.
[DOCX File , 15 KB - resprot_v12i1e42212_app2.docx]

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Abbreviations

PRISMA-ScR: Preferred Reporting Items for Systematics Reviews and Meta-Analyses extension for Scoping Reviews

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Protocol

Impact of Cultural and Linguistic Maintenance on Mental Health Outcomes in Migrant Adolescents: Protocol for a Scoping Review

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Abstract

Background: There is no consensus on how the disruption or maintenance of heritage culture and language affect mental health outcomes in adolescents with a migrant (also known as “immigrant” or “international migrant”) background. Even though previous literature reviews have investigated the association between acculturation and mental health in migrants, none have explicitly focused on adolescents.

Objective: The aim of the scoping review described in this protocol is to understand (1) the focus, scope, and nature of quantitative empirical research investigating heritage cultural maintenance, including linguistic maintenance, and mental health outcomes in adolescents with a migrant background worldwide and (2) the potential effects of cultural and linguistic maintenance or disruption on migrant adolescent mental health outcomes.

Methods: A total of 11 key electronic health, medical, social science, and language databases (APA PsycArticles Full Text; Embase Classic+Embase; Ovid MEDLINE All and Epub Ahead of Print, In-Process, In-Data-Review and Other Non-Indexed Citations and Daily; Ovid MEDLINE All; APA PsycInfo; University of Melbourne full-text journals; Science Citation Index Expanded; Social Sciences Citation Index; Arts & Humanities Citation Index; Scopus; Linguistics and Language Behavior Abstracts) were searched. Databases were searched without time restrictions from the beginning of their coverage. Publication date, location, and quantitative study design (except for literature reviews) were not restricted; however, the search was only conducted in English. Data from included studies will be extracted using a template with predefined data items, and results will be summarized in a structured, narrative summary.

Results: A search was conducted on April 20, 2021, returning 2569 results. We are currently at the final stages of screening titles and abstracts of our search results, which will be followed by a full-text review and the data extraction of included studies. We expect to submit the full review for publication by the end of 2023.

Conclusions: The scoping review aims to provide a better understanding of existing research on the association between cultural (including linguistic) maintenance and mental health in migrant adolescents. It will help identify gaps in the existing literature and develop hypotheses that could inform future research, eventually facilitating the development of targeted prevention initiatives and improving migrant adolescents’ well-being.

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KEYWORDS

PRISMA; PRISMA-ScR; PRISMA-P; youth; risk factors; protective factors; suicide; depression; culture; language knowledge; acculturation; heritage

Introduction

Background

The World Migration Report 2022 stated that 1 in 30 people globally resides in a country that differs from their birth country and that this number has increased over the last 5 decades [1]. With most migration streams flowing from low-income to high-income countries [1], many migrants experience differences between their heritage and host cultures.

Previous research into acculturation (ie, the impact of interacting with other cultures on an individual) has highlighted 2 key issues. First, the issue of cultural maintenance, which is the extent to which heritage cultural identity is considered important and practices are continued. Second, the issue of deciding on the extent of contact and participation (ie, interacting with the host culture or remaining within heritage cultural groups) [2]. Based on these 2 issues, Berry and Sam [2] proposed four acculturation strategies: (1) integration (whereby heritage culture is maintained while seeking to interact with other groups), (2) assimilation (whereby heritage culture is not maintained while interactions with other groups are sought), (3) separation (whereby heritage culture is maintained while wishing to avoid interactions with other groups), and (4) marginalization (whereby cultural maintenance is perceived as difficult, and little interest is demonstrated in interacting with other groups).

A considerable amount of research has examined the association between acculturation and mental health outcomes, including several systematic reviews [3,4] and meta-analyses [5,6]. However, despite age being identified as a key component of the association between acculturation and mental health [6], no review to date has examined how cultural maintenance affects mental health outcomes in migrant adolescents (aged 10-24 years [7]).

Marked as the transition into adult life, adolescence is a life phase of great change. Adolescence has been identified as "a second sensitive developmental period in which puberty and rapid brain maturation lead to new sets of behaviours and capacities that trigger or enable transitions in family, peer, and educational domains, and in health behaviours" [8]. As these transitions affect a child's future health outcomes [8], understanding factors shaping adolescents' mental health outcomes is important to support their healthy development.

Even though Viner and colleagues [8] caution that their ecological analysis does not imply causality, they found that "national wealth, inequality, and education had the largest effect sizes...and were associated with the largest range of health outcomes in young people." They further identified that similar factors, related to family, peers, and education, can help protect adolescents' health across countries [8].

Adolescents with a migrant background—specifically, first- or second-generation migrants—are faced with the added complexity of navigating this intense transitional phase within a multicultural or multilingual context. In fact, some research has identified a migrant background to be a predictor of poor mental health outcomes in adolescents [9]. A study in a regional child and adolescent mental health service in Australia reported that the majority of mental health support was needed by Aboriginal youth, followed by Asian-European heritage youth, with the researchers pointing at the role loss and disconnection from heritage culture may play in poor mental health outcomes [10]. Hallett and colleagues [11] had even more poignant findings related to Indigenous cohorts, identifying native language knowledge as correlating with a reduction in Indigenous youth suicide in Indigenous communities in Canada. The extent to which a similar effect of language or culture maintenance on mental health outcomes may be evident among adolescents with a migrant background remains unknown.

There is a large body of adolescent mental health research studying the effectiveness of interventions [12], help-seeking behaviors [13,14], and the applicability of information technologies [15]. Müller and colleagues [16] conducted a scoping review on the effect bilingualism has on family and child well-being, which provides valuable insights. However, rather than specifically looking at bilingualism, we are interested in research investigating the association between heritage culture or language knowledge and mental health outcomes in migrant adolescents.

This scoping review will provide a better understanding of migrant adolescents' ecological systems and identify modifiable risk factors associated with optimal mental health outcomes. This knowledge will inform future research leading to improved interventions and policies that contribute to improved mental health outcomes in migrant adolescents.

Objectives

This protocol outlines the methodology of a scoping review that will address the following questions:

(1) What is the focus, scope, and nature of quantitative empirical research investigating heritage cultural maintenance, including language maintenance, and mental health outcomes in adolescents with a migrant background worldwide?

(2) What effects, if any, do cultural and linguistic maintenance or disruption have on migrant adolescent mental health outcomes?

Methods

Protocol Development

This protocol adheres to relevant sections of the Preferred Reporting Items for Systematic Review and

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Meta-Analyses–Protocols (PRISMA-P) [17], which we provide in the form of a checklist [18] in Multimedia Appendix 1.

Scoping Review Methodology and Reporting

We conduct the scoping review following the methodological framework outlined by the Joanna Briggs Institute [19], which is based on the Arksey and O'Malley framework [20] and Levac and colleagues' [21] elaborations. Reporting will follow the PRISMA Extension for Scoping Reviews (PRISMA-ScR) [22].

For an overview of the scoping review's inclusion and exclusion criteria, please refer to Textbox 1.

Textbox 1. A summary of inclusion and exclusion criteria.

Inclusion Criteria

- Published, peer-reviewed empirical studies.
- Any language (however, the search was only conducted in English, which indirectly excluded all studies without an English title, abstract, or keywords).
- Any publication date.
- Any study location.
- Adolescent study participants between 10 and 24 years.
- Studies focused on mental health outcomes, symptom severity, and diagnosis.
- Studies measuring mental health outcomes, specifically depression, anxiety, self-harm, suicide, substance misuse, and schizophrenia.
- Studies measuring any nondominant heritage culture or language.

Exclusion Criteria

- Qualitative studies, literature reviews, book chapters, dissertations, conference papers, conference abstracts, and editorials.
- Participants younger than 10 years, or those who are 25 years or older.
- Studies focused on help-seeking, or interventions in mental health dimension.
- Studies measuring trauma, self-esteem, life satisfaction, or well-being.
- Studies measuring the uptake of host language or culture without considering heritage language and cultural maintenance; studies measuring ethnic identity.

Eligibility Criteria

Participants

We include empirical studies examining the effect of cultural maintenance, including linguistic maintenance, on mental health outcomes in migrant adolescents. Participant age is limited to 10-24 years, in line with the contemporary definition of adolescence [7].

Outcome Measures

The scoping review is interdisciplinary in nature and included studies must measure mental health and cultural or linguistic maintenance outcomes. Appropriate mental health outcomes include depression, anxiety, self-harm and suicide, substance misuse, and schizophrenia. Studies measuring only trauma, self-esteem, life satisfaction, or well-being are excluded. Studies measuring mental health outcomes without measuring culture or language maintenance are also excluded. Studies examining help-seeking or interventions are also not included.

Heritage language or cultural maintenance must be measured for studies to be included. We do not include studies that examine only the uptake of the host language or culture without examining heritage culture or language maintenance, but we consider findings related to host cultural orientation if heritage cultural orientation is measured.

Study Design

We include published, peer-reviewed empirical studies measuring cultural or linguistic maintenance and mental health outcomes in migrant adolescents. We exclude qualitative studies, book chapters, dissertations, conference papers, conference abstracts, and editorials. We do not include literature reviews as they may include studies that do not meet our inclusion criteria. However, we will screen and review the reference lists of relevant literature reviews to identify studies not identified during our searches.

Information Sources

A total of 11 electronic databases were searched on April 20, 2021, from the beginning of each database.

The electronic databases are APA PsycArticles Full Text (coverage from 1894); Embase Classic+Embase (from 1947); Ovid MEDLINE All and Epub Ahead of Print, In-Process, In-Data-Review and Other Non-Indexed Citations and Daily (from 1946); Ovid MEDLINE All (from 1946); APA PsycInfo (from 1806); University of Melbourne full-text journals; Science Citation Index Expanded (from 1900); Social Sciences Citation Index (from 1900); Arts & Humanities Citation Index (from 1975); Scopus (from 1970); Linguistics and Language Behavior Abstracts (from 1973).

We will also screen reference lists to identify relevant studies that the electronic search might not have identified.

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Search Strategy

The search strategy was shared with a university librarian, who provided feedback to further tailor the search strategy to each database. After the search of the electronic databases, the search results' titles and abstracts are screened in a Microsoft Excel (Microsoft Corp) spreadsheet, applying the inclusion and exclusion criteria as outlined by this protocol. To be eligible for inclusion, studies must fulfill all 4 categories (coded in the search query with "AND"). Within each category, studies must meet at least 1 search term (coded in the search query with "OR"). The search query syntax was adjusted to meet specific database requirements. An example of the search command used for Ovid MEDLINE All is provided in Table 1.

Table 1. Ovid MEDLINE All search strategy.

Category	Operators	Search field	Fields
1. Linguistic and cultural component	N/A[a]	"language maintenance" OR "language knowledge" OR "language transmission" OR "cultural maintenance" OR "cultural knowledge" OR "cultural transmission"	All fields
2. Mental health outcome	AND	"mental health" OR suicid* OR depress* OR anxiet* OR anxious* OR self-injur* OR self-harm OR nssi OR "non-suicidal self-injury" OR "substance abuse" OR "drug abuse" OR "substance use" OR "substance misuse" OR "substance-related disorder" OR "substance use disorder" OR "SUD" OR resilien* OR schiz* OR vulnerab*	All fields
3. Age group	AND	adolescen* OR "young person" OR teen*	All fields
4. Immigrant background	AND	refugee* OR cald OR "culturally and linguistically diverse" OR immigrant OR migrant OR aborigin* OR indigenous OR "Torres Strait"	All fields

[a]N/A: not applicable.

Study Records

Data Management and Selection Process

AH exported and consolidated all electronic database study results' titles and abstracts into a single Microsoft Excel spreadsheet before removing duplicates. AH is currently finalizing the screening of titles and abstracts, applying the inclusion and exclusion criteria, and recording reasons for inclusion or exclusion. JH and RB are involved in the screening of search results, checking 20% of included and excluded studies to test the validity of the approach and discuss potential alterations.

In the next stage, AH will download the full text of studies whose title and abstract appear relevant or unclear in answering the research question into citation management software Zotero (Corporation for Digital Scholarship). Each study will be read in full and assessed against each inclusion criterion using a simple charting form covering each of the 4 search categories. AH will consult the appropriate expert in the team to discuss studies that she is unsure about. If they cannot agree, the third team member will decide. JH and RB will review all included studies and at least 20% of excluded studies to detect and correct potential errors.

Data Collection Process and Data Items

AH will collect data using 2 separate spreadsheets. In the first spreadsheet, AH will record extracted information for each included study: authors, year, final sample size, other included cohorts (eg, parents), participant information (age, heritage, and culture), and geographical location.

In the second spreadsheet, AH will code data in a binary table, which will allow sorting and comparing study characteristics. Expected information categories that will be coded at the top level will be related to frameworks, the terminology used, cultural or linguistic measures, mental health outcomes measured, scales used, as well as key findings about this paper's second research question. These findings will be shared, reviewed, and discussed with JH and RB.

Outcomes and Prioritization

The primary focus of this review is to understand the research investigating the association between cultural or linguistic maintenance and mental health outcomes in migrant adolescents. As we are investigating a multidisciplinary field of study, there is a possibility of studies having heterogeneous research perspectives and findings. We aim to be rigorous in including only studies that fulfill all 4 search categories. When studies meet criteria in all 4 categories, we will also report on findings that may directly or indirectly affect the association between cultural maintenance and mental health outcomes, such as the effect of host cultural orientation, as well as moderating or mediating factors. This will allow us to understand the identified phenomena better.

Data Synthesis

We will provide a descriptive overview of included studies, stating sample size, age, and location, as well as mental health outcomes and cultural or linguistic maintenance factors measured. We will then provide a structured, narrative summary of study findings about our second research question in text and—depending on feasibility—table form. We will report commonalities and differences in findings, explore potential hypotheses, and identify gaps in the research. We will not assess the quality or bias of studies, grade evidence, or include a quantitative synthesis of evidence.

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Ethical Considerations

Our review does not require ethical approval, as it reports on findings from published studies that have already obtained ethics approval. We will disseminate the findings of the scoping review through a peer-reviewed journal article and national and international conference presentations.

Results

Applying the methodology outlined in this protocol, we conducted a search in April 2021, which returned 2569 results. We are in the process of screening titles and abstracts of these results. We expect to submit the scoping review for publication by the end of 2023.

Discussion

Overview

This scoping review protocol outlines a rigorous and replicable methodology for the review of empirical research investigating cultural maintenance, including language maintenance, and migrant adolescent mental health outcomes. To our knowledge, no comparable study has been conducted. The search conducted in April 2021 returned 2569 results.

We will report results in the scoping review following the PRISMA-ScR. Our search strategy included 11 relevant academic databases, as well as a grey literature search. We are screening titles and abstracts and will extract data from included studies using predefined charting items. This will allow us to compare the nature of study elements and identify trends and gaps in the existing literature.

We will also extract relevant findings to address our second research question and present the results in a narrative summary, which will possibly result in the suggestion of hypotheses or research questions that could inform future research or systematic reviews. The preliminary review of literature has shown that rather than inferring causality, it is important to interpret findings considering adolescents' context. Some studies use an ecological approach [23] and, depending on our results, we are planning to use a similar approach to contextualize results.

Some existing reviews that were not adolescent-specific identified biculturalism to be advantageous on adjustment [5], and child well-being benefiting from bilingualism at home [16]. Our study will contribute to the existing literature, providing a better understanding of language or cultural maintenance, while specifically focusing on mental health outcomes in migrant adolescents who are and will constitute large cohorts within society.

Even though we conducted the search worldwide, we used only English search terms, limiting our results to studies with English titles, abstracts, and keywords. Included results that were written in another language are reviewed by a researcher proficient in the language. Another limitation of this study is that evidence will not be quantitatively synthesized in this review, as we will not do a quality or bias assessment of studies. Moreover, this highly multidisciplinary field of study leads to heterogeneous results from various disciplines (ie, psychology, adolescence research, and linguistics), which slows down the review process.

Conclusion

The scoping review outlined by this protocol will provide a more cohesive understanding of existing multidisciplinary research into cultural and linguistic maintenance and mental health outcomes in migrant adolescents. This will provide a more comprehensive understanding of how youth mental health outcomes and cultural factors, including linguistic factors, have been investigated to date, and what future investigations may be required. The outlined scoping review therefore plays an important part in improving migrant adolescents' mental health outcomes.

Acknowledgments

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Data Availability

All data generated or analyzed during this study will be included in the published article (and its supplementary information files).

Authors' Contributions

RB and JH developed the original research proposal and obtained funding to conduct the review. AH contributed to the design of the project. AH, RB, and JH developed the search strategy. AH wrote the initial draft protocol, and RB and JH contributed significantly to drafting and editing the manuscript. All authors approved the final manuscript for submission.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA-P checklist.

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[PDF File (Adobe PDF File), 144 KB - resprot_v12i1e40143_app1.pdf]

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Abbreviations

PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analyses Protocols
PRISMA-ScR: Preferred Reporting Items for Systematic Review and Meta-Analyses extension for Scoping Reviews

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Protocol

Trauma-Informed Care in Digital Health Technologies: Protocol for a Scoping Review

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Abstract

Background: The use of digital health technologies is becoming increasingly common across the globe as they offer immense potential to enhance health care delivery by promoting accessibility, flexibility, and personalized care, connecting patients to health care professionals, and offering more efficient services and treatments to remote residents. At the same time, there is an increasing recognition of how digital health can inadvertently foment psychological trauma. This phenomenon has led to the adoption of trauma-informed care in designing and deploying digital health technologies. However, how trauma-informed care is defined and characterized, and the various trauma-informed care strategies used in designing and deploying digital health technologies remain unexplored.

Objective: This scoping review aims to explore and synthesize the literature on how trauma-informed care is defined and characterized in digital health and the various trauma-informed care principles, strategies, or recommendations used in designing and deploying digital health.

Methods: This review will draw on the Joanna Briggs Institute's updated methodological guidance for scoping reviews. A search will be conducted on CINAHL, PubMed, Embase, Compendex Engineering Village, Web of Science, Scopus, and PsycINFO. This review will consider published research studies and unpublished work (gray literature). Studies will be included if they applied trauma-informed care in designing or deploying digital health for patients across all geographical locations or provide trauma-informed recommendations on how web developers should develop digital health. Studies will be limited to publications within the past 10 years and studies in all languages will be considered. Two independent reviewers will screen the titles and abstracts, and then perform a full-text review. Data will be extracted into a data extraction tool developed for this study.

Results: The scoping review was undergoing a full search as of April 2023. The main results will synthesize the peer-reviewed and gray literature on adopting trauma-informed care practices in digital health research and development. The study is expected to be completed by December 2023 and the results are expected to be published in a peer-reviewed journal.

Conclusions: This review is expected to provide the knowledge base on the adoption of trauma-informed care in designing and deploying digital health. This knowledge can lead to more engaging, and likely, more effective digital health interventions that have less potential for harm. A synthesis of the various trauma-informed care strategies in digital health will also provide a trauma-informed language by enabling researchers and digital health developers to consider trauma as a critical factor in each stage of the design process.

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KEYWORDS

clinical intervention; digital health technologies; digital health; psychological trauma; stress; trauma; trauma-informed care

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Introduction

Overview

Trauma is a term used to describe the challenging emotional and psychological consequences associated with an individual after going through a distressful event [1]. This definition of trauma is specific to emotional and psychological trauma, which is different from physical trauma (ie, injuries or body wounds produced by sudden physical injury from impact, violence, or accident). According to the World Health Organization, approximately 70% of people across the globe have experienced at least one traumatic event with varying emotional and psychological sequelae [2]. The number of reported cases of trauma increased across several countries during the COVID-19 pandemic [3]. Living through the COVID-19 pandemic has heightened the degrees of trauma with symptoms that can eventually harm a person's sense of safety and distort their ability to regulate emotions and navigate relationships [4]. At the same time, the outbreak of the pandemic saw an accelerated adoption of digital health for various clinical and public health services across the globe. In the United States, telemedicine appointments through "Plush Care" and "American Well" increased by 70% and 150% respectively [5]. In Canada, the number of people using digital health interventions increased from a prepandemic level of 72% to approximately 86% in some provinces during the peak of the pandemic [6,7]. Technologies such as Skype, WhatsApp, and FaceTime were adapted as alternative and complementary methods of health care delivery and health care access across Australia and various European countries [8,9]. While digital health is convenient and cost-effective, there are legitimate concerns about how the digital transformation of health care can lead to unintended consequences, including triggering or perpetuating trauma among end users [10]. The likelihood of perpetuating unintended consequences like trauma through digital technologies may be higher in patient-facing digital health interventions than in clinician-facing technologies. This is possible because, unlike technologies in clinical settings, patient-facing technologies (eg, patient portals, mHealth, and health-related websites) are more likely to be unregulated and unmoderated. Bonell et al [11] termed this the "dark logic" of interventions where digital health could result in unintended trauma-related consequences despite a generally virtuous intention.

Technology-Mediated Trauma

Trauma resulting from the use of digital health technologies (herein known as technology-mediated trauma) is becoming common with the increasing use of digital health interventions [12-14]. While technology-mediated trauma started emerging in social media platforms [15-17], emerging evidence shows that digital health technologies, especially patient-facing digital health technologies can also trigger or facilitate technology-mediated trauma depending on its' interface design [18,19]. Indeed, technology-mediated trauma perpetrated through digital health platforms may produce worse outcomes due to the potentially vulnerable nature of people who uses such technologies (ie, patients).

Technology-mediated trauma can occur in various forms. For instance, interventions delivered through web platforms that unexpectedly expose people's information or identities can cause reputational and psychological damage with associated trauma-related symptoms. Also, digital health technologies (eg, HIV/AIDS web-based platforms and social networking sites for people with mental health problems) that expose people to sextortion, identity theft, cyberbullying, and web-based scams, including the purchase of fake health products, could result in short-term or long-term emotional traumatic consequences, and sometimes, suicidal thoughts [20,21]. Other forms of digital communication channels embedded within digital health platforms, such as chatrooms, user subscription channels, forums and bulletin boards, social networking sites, and other platforms that enable information sharing, may also be used unscrupulously to victimize, and expose users of digital platforms in a manner that could result in technology-mediated trauma-related experiences [22-26]. While youth with mental health challenges found the use of social networking sites to be highly usable, engaging, and supportive [27], such sites could also pose avenues for web-based victimization and bullying with the potential consequences for trauma-related experiences [28]. For instance, cyberbullying activities perpetrated through web-based social networking sites for mental health patients, including negative forum posts and negative comments, have been shown to result in technology-mediated trauma experiences and other forms of mental health challenges among adults [28,29]. Web-based practices such as advertisements carried out on digital platforms like sexual health–related websites can inadvertently foment stigma [30]. For instance, discriminatory advertising on maternal health websites can inadvertently perpetuate trauma when a woman who just experienced a miscarriage is not able to opt out of pregnancy adverts when using such a platform [31]. Technology-mediated trauma experiences can result in devastating sequelae for people's overall psychological and physical well-being [32]. The negative effects of technology-mediated trauma on psychological well-being were demonstrated in a recent systematic review that revealed a negative association between digital technology use and emotional well-being outcomes among teenagers during the COVID-19 pandemic [33].

The pervasive and potentially negative impact of technology-mediated trauma on end users made it necessary within the digital health community to rethink "the usual way of doing business" by incorporating trauma-informed care in the design and deployment of digital health interventions. Some researchers subsequently coined the term "trauma-informed design" to denote the application of trauma-informed care in developing interactive technologies, including digital health platforms.

Trauma-Informed Care in Digital Health

Trauma-informed care in interactive digital technologies is a new concept that started appearing as blog posts among user interface and user experience practitioners across the United States, the United Kingdom, and Australia. The concept of trauma-informed design became prominent in the later parts of 2020 [34]. Since then, researchers have been actively engaged in developing approaches in which trauma-informed principles,

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approaches, or practices can be translated into the design of digital health technologies to make them emotionally safer. Trauma-informed care recognizes the effects of trauma on users of digital health technologies and provides theoretical approaches and practical guidance for how such technologies can be designed to be emotionally safe and empowering for all users [34]. Indeed, several digital health interventions have adopted trauma-informed approaches in designing and developing digital health interventions or produced trauma-informed recommendations that can be used to adapt old interventions or develop new digital health services [35-38]. Other researchers have developed trauma-informed web heuristics for designing human-centered information systems, including digital health [39].

While trauma-informed care is gradually gaining ground in the digital health community, how the concept is defined and characterized, and the various trauma-informed care strategies used in designing and deploying digital health technologies remain unexplored and ill-understood. The purpose of this review is two-fold: (1) to explore and synthesize the current state of the literature that has defined and characterized trauma-informed care in digital health and (2) to synthesize the literature on various trauma-informed care strategies, practices, principles, or approaches that are used in designing and deploying digital health. A preliminary search was conducted in February 2023 in Cochrane Databases, the Joanna Briggs Institute (JBI) Evidence Synthesis, and PROSPERO to identify any possible reviews that might have been conducted on the topic. The search results did not reveal any scoping or systematic review that has been conducted on our proposed topic. However, the search did return relevant articles that were used in formulating our search terms [13,35-38].

Review Questions

1. How is trauma-informed care defined and characterized in the digital health literature?
2. What trauma-informed care principles, strategies, or recommendations are currently used in designing and deploying digital health technologies?

Methods

Overview

This proposed review will draw on the JBI updated methodological guidance for the conduct of scoping reviews [40]. We will use the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-analyses Extension for Scoping Reviews) framework to report the findings of this review [41]. Because trauma-informed care in digital health is an emerging area with varied sources of evidence, we consider a scoping review to be more appropriate in providing conceptual clarity on the topic than a systematic review.

Inclusion and Exclusion Criteria

The inclusion and exclusion criteria for this proposed review will adopt the JBI criteria of population, concepts, and context outlined by Peters et al [40]. The details of each criterion are outlined below.

Population

This review will include 2 distinct populations. These include (1) digital health technology designers (eg, software developers, content creators, and user interface and user experience professionals) and (2) patients who use digital health technologies (without consideration to a type of patient or disease or age). For the first population, studies will be included if they provide trauma-informed strategies or recommendations for developers or designers of digital health technologies. For the second population, studies will be included if they explore ways in which trauma-informed care principles or strategies can be applied in designing or deploying digital health technologies for patients. Studies will also be included if they explore how trauma-informed care can be applied to digital technologies to improve patients' health outcomes. A patient in this study is used to refer to anyone who uses a digital health intervention for health-related purposes. Digital health technology studies on posttraumatic stress disorder (PTSD) that adopt trauma-informed care approaches or provide trauma-informed care recommendations will be included. However, digital health technology studies on PTSD that did not adopt or recommend trauma-informed care approaches will be excluded.

Concepts

This review aims to map the evidence on how trauma-informed care is defined and characterized in digital health and to synthesize the literature on trauma-informed care in designing and deploying digital health. Therefore, the review will include two major concepts: (1) trauma-informed care and (2) digital health technologies. Based on these concepts, we will consider studies that discussed the definitions and characteristics of trauma-informed care in digital health. We will also consider studies that provided trauma-informed care strategies, practices, approaches, or recommendations for designing and deploying digital health. Studies that provide trauma-informed care strategies which are not focused on designing or deploying digital health technologies will be excluded. In this review, trauma is limited to psychological trauma at the personal and interpersonal levels. Other forms of trauma, such as physical trauma, group trauma, community trauma, or mass trauma or casualties, are beyond the scope of this review. Digital health in this review is used to refer to patient-facing technologies, including mHealth, wearable devices, health-related websites, patient portals, social networking sites, etc. Digital health technologies that are focused on health care professionals (eg, electronic health records and clinical decision support systems) will be excluded from this review. We decided to exclude clinician-facing technologies because such technologies are more likely to be regulated and might have fewer chances of causing trauma among patients compared to patient-facing technologies.

Context

This review will include studies that are conducted with individuals in all age groups in any geographical location. Our search will not be limited to any specific gender or sex group, a particular disease condition, and a specific user group or population. We aim to include all outpatient or nonclinical

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settings that explore how trauma-informed care can be applied in designing or deploying digital health technologies (community health centers, social service organizations, etc), and industry (technology design companies). We will also consider digital technology developers (eg, User Experience research centers) that have discussed, developed, or applied trauma-informed care principles in designing digital health.

Types of Evidence

This scoping review will include all types of peer-reviewed studies on trauma-informed care in digital health, including primary research studies (quantitative, qualitative, and mixed methods research) and review papers (systematic reviews or meta-analyses). We will also consider gray literature on trauma-informed care in digital health, including theses, editorials, commentaries, government reports, industry-sponsored works, guidelines, book chapters, and blogs. Abstracts, letters to editors, and short papers will be excluded. Gray literature is considered important because trauma-informed care strategies or recommendations for designing digital health may be developed and published outside traditional academic publishing and distribution channels. These include industry-sponsored works that may provide trauma-informed recommendations (software designers, software engineers, etc) but may not necessarily be published in peer-reviewed journals. Due to the emerging nature of the field and the rapid advancements in digital health technologies in the past decade [42], this review will be limited to studies conducted within the past 10 years.

Search Strategy

A strategy was developed in consultation with a university librarian at the University of British Columbia. Following Pollock's [43] practical guide to conducting scoping reviews, a preliminary search was conducted in Cochrane Databases, the JBI Evidence Synthesis, and PROSPERO to determine if any reviews were conducted on the topic and to identify additional words and phrases to inform the search strategy. Given the multidisciplinary nature of the topic (ie, trauma-informed care and digital health), we formulated a search strategy that reflected each dimension of the topic. The search strategy for the gray literature will be iterative depending on the emerging evidence. Using the refined search strategy, a literature search will be conducted on a variety of databases, including CINAHL, PubMed, Embase, Compendex Engineering Village, Web of Science, Scopus, and PsycINFO. These databases were selected because they covered a broad range of published literature that reflected the topic in nursing, medicine, psychology, allied sciences, engineering, and computer science. A reference list of articles that meet the inclusion criteria will be manually screened to identify additional eligible studies that were not returned by the search strategy. Using different search terms, we will also search for gray literature through Google and Google Scholar. We will open individual web links that contain blogs or industry materials on trauma-informed care in digital health. Multimedia Appendix 1 contains the detailed search strategy as well as the data extraction guide for both published and grey literature.

A preliminary search conducted on the 2 databases for gray literature produced results of less than 5 pages each. Since we do not expect these databases to produce results that exceed 10 pages by the time the review is completed (ie, December 2023), we are limiting the data from Google and Google Scholar to the first 100 results. Consistent with JBI recommendations, we will not apply language restrictions to our search. We will use translation services for eligible studies that fall outside the proficiency of the authors. Where necessary, the authors of relevant publications, blogs, and opinion pieces will be contacted to get additional information or seek clarification regarding their publications. As an emerging area of research, it is possible that some latest evidence might have been published after our literature search. To identify any latest publication, we will repeat the search strategy (but limited to the specific time frame) before the final manuscript is submitted for publication.

Study Selection

Search results from all databases will be exported into Endnote X9 (Clarivate, 2020). Search results from Google and Google Scholar will be manually added and duplicates will be removed accordingly. Two independent reviewers will then screen the titles and abstracts using the inclusion and exclusion criteria outlined under the population, concepts, and contexts. Studies that meet the inclusion criteria will undergo a full-text review by the 2 independent reviewers. Any discrepancies that result from either the title, abstract, or full-text review between the 2 reviewers will be solved through a discussion with a third reviewer.

Data Extraction

Specific information from the included studies will be extracted by the 2 independent reviewers. The data will be summarized on an Excel spreadsheet developed in line with the JBI guidelines for data extraction [43]. The data extraction sheet will contain specific information about each study, including the authors' names, the study's title, the year of publication, geographical location, the study population, type of digital health technology, target population, sample size (if applicable), purpose, and the findings of each study. Where applicable, information from each paper will be entered into the respective portion of the spreadsheet. We will also extract information specific to each of the 2 populations (ie, health technology developers and patients). For studies related to how technology developers adopt trauma-informed care, we will extract data related to the specialty, and place of work or origin (eg, industry and research). For studies on patient populations, we will extract data on age groups, sex and gender, socioeconomic status, and health issues. The data extraction tool will be amended for gray literature and will be iterative depending on the kind of emerging evidence. To reduce biases and ensure consistency and comprehensiveness of the data extracted, the 2 reviewers will each conduct independent data extraction on the first 4 papers (both published and gray literature). These preliminary data will be compared, contrasted, and discussed with a third reviewer to resolve any disagreements before they are applied to the rest of the papers. The remaining data extraction will occur through an ongoing team discussion and disagreements will be resolved by discussion with a third reviewer.

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Data Analysis and Presentation

The search results as well as the inclusion and exclusion pathways for various studies will be reported in line with the PRISMA-ScR flow diagram [44]. The extracted data and the themes will be presented as narrative summaries. This will be augmented by numerical summaries to report each high-level domain that is common across the papers. Such numerical summaries may include the number of papers that adopt trauma-informed approaches and the number that provide trauma-informed recommendations. It may also include a summary of the number of trauma-informed guidelines and their area of focus in the digital health lifecycle (ie, the needs assessments, design, evaluation, or deployment phases of digital health). Research and gray literature will be grouped accordingly and papers that reflected the 2 research questions will also be grouped in the numerical summaries. To answer the research questions, the included papers will be analyzed thematically using inductive coding by 2 reviewers. Depending on the number of papers that meet the inclusion criteria, 3 papers will be reviewed and coded independently by 2 reviewers for each research question. The different coding frameworks will then be discussed among the reviewers to arrive at a final coding structure for each research question. The coding structure will then be applied to the rest of the papers to identify emerging themes. The emerging themes will then be clustered into major themes that represent the definitions of trauma-informed care in digital health and trauma-informed care strategies for designing and deploying digital health technologies.

Results

The scoping review was undergoing a comprehensive literature search at the time this protocol was being published. This will be followed by tile and abstract screening and then full data extraction. The scoping review is expected to be completed and the manuscript submitted to a peer-review journal by December 2023.

Discussion

Overview

Trauma-informed care in digital health is an emerging area of research that sought to explore various trauma-informed approaches in developing and deploying digital health interventions that limit the potential for further harm to end-user patients. There are several systematic and scoping reviews on trauma-informed care in various aspects of health care as well as in the built environment [37,45]. Despite an increasing application of trauma-informed care principles in digital health research, no reviews summarizing the definitions or characterization of trauma-informed care approaches in digital health were found. This scoping review was conceptualized in October 2022 to summarize the current state of the literature on trauma-informed care in digital health. This scoping review will form an evidence base for an emerging program of research on trauma-informed design in digital health. The results of this scoping review are expected to provide researchers with an extant knowledge of how trauma-informed care is defined, characterized, and adopted in digital health while providing directions for future research on the topic. Digital health technologies are increasingly developed for managing various traumatic stress and PTSD [46,47]. Therefore, we believe that this review will provide trauma-informed recommendations for designing health technologies that have the least chance of causing harm while ensuring emotional safety to end users.

Limitations

Abstracts, letters to editors, and short papers that might have been relevant to the topic will be excluded. Secondly, the methodological quality of this review will not be assessed. Therefore, we cannot conclude whether the trauma-informed strategies that would be synthesized from this review are indeed effective or applicable to digital health. While we acknowledged these limitations, we believe that they would not diminish the quality of our review because scoping reviews by their nature do not assess the methodological quality of studies.

Conclusions

This review is expected to provide the knowledge base on the definition, characterization, and adoption of trauma-informed care in designing and deploying digital health interventions. This knowledge can lead to more engaging, and likely, more effective digital health interventions by enabling researchers and digital health developers to consider trauma as a critical factor in each stage of the design and deployment process. A synthesis of the various trauma-informed care strategies used in digital health will also provide a trauma-informed language for developing digital health technologies that have less potential for harm.

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Authors' Contributions

AFA conceived the idea for the scoping review, wrote the initial draft of the manuscript, revised the manuscript, and performed a supervisory role. HN, EG, FA, and EB refined the search strategy in consultation with AFA and the librarian and all authors contributed to writing and revising the manuscript.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Search terms and data extraction.
[DOCX File , 30 KB - resprot_v12i1e46842_app1.docx]

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Abbreviations

JBI: Joanna Briggs Institute
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-analyses extension for scoping review
PTSD: posttraumatic stress disorder

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Protocol

Conceptualizing Interprofessional Digital Communication and Collaboration in Health Care: Protocol for a Scoping Review

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Abstract

Background: Effective communication and collaboration among health professionals are essential prerequisites for patient-centered care. However, interprofessional teams require suitable structures and tools to efficiently use their professional competencies in the service of high-quality care appropriate to the patient's life situation. In this context, digital tools potentially enhance interprofessional communication and collaboration and lead to an organizationally, socially, and ecologically sustainable health care system. However, there is a lack of studies systematically assessing the critical factors for successfully implementing tools for digitally supported interprofessional communication and collaboration in the health care setting. Furthermore, an operationalization of this concept is missing.

Objective: The aim of the proposed scoping review is to (1) identify factors influencing the development, implementation, and adoption processes of digital tools for interprofessional communication in the health care sector and (2) analyze and synthesize the (implicit) definition, dimensions, and concepts of digitally supported communication and collaboration among health care professionals in the health care setting. Studies focusing on digital communication and collaboration practices among health care professionals, including medical doctors and qualified medical assistants, in any health care setting will be included in this review.

Methods: To address these objectives, an in-depth analysis of heterogeneous studies is needed, which is best achieved through a scoping review. Within this proposed scoping review, which adheres to the Joanna Briggs Institute methodology, 5 databases (SCOPUS, CINAHL, PubMed, Embase, and PsycInfo) will be searched for studies assessing digital communication and collaboration among various health care professionals in different health care settings. Studies focusing on health care providers or patient interaction through digital tools and non–peer-reviewed studies will be excluded.

Results: Key characteristics of the studies included will be summarized through descriptive analysis, using diagrams and tables. We will synthesize and map the data and conduct a qualitative in-depth thematic analysis of definitions and dimensions of interprofessional digital communication and collaboration among health care and nursing professionals.

Conclusions: Results from this scoping review may help in establishing digitally supported collaborations between various stakeholders in the health care setting and successfully implementing new forms of interprofessional communication and collaboration. This could facilitate the transition to better coordinated care and encourage the development of digital frameworks.

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KEYWORDS

digital technologies; interdisciplinary communication; intersectoral collaboration; nurse; physician; collaboration; interdisciplinary; scoping review; communication; interprofessional

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Introduction

Overview

Efficient communication and collaboration among health care professionals are essential prerequisites for high-quality patient-centered care [1]. Among other things, this reduces readmission rates, improves patient health outcomes, increases time efficiency, partially improves clinical processes, and reduces health care costs [2-4].

Interaction among health care professionals can be denominated as inter-, multi- or transprofessional. Although the definition of each term is not uniform, they decipher different degrees of collaboration between professions [5]. In this review, we will use the term "interprofessional communication and collaboration" (ICC) to refer to any type of interprofessional interaction among health care professionals, from pure information exchange to collaborative working.

Key enablers for ICC are trust and respect, shared visions, as well as respectful and constant communication [6]. Barriers to ICC include a lack of funding and inadequate reimbursement, poor definitions of roles and responsibilities, insufficient training, a lack of time, hierarchical differences, and divergent communication styles [7-9]. Communication styles can be classified as either formally structured, such as team meetings or clinical rounds, or informal and opportunistic, such as hallway consultations [10].

Within our scoping review, we focus on 1 specific part of ICC, which is characterized by the use of digital tools to support its effectiveness [9,11]. Research shows that digitally supported interprofessional communication and collaboration (DICC) lead to better division of tasks; improve the definition of responsibilities; increase the accessibility, efficiency, and safety of clinical information transfer; and partly replace time- and resource-consuming face-to-face multidisciplinary meetings [2,12-15]. Despite the benefits, implementation of DICC is complex and challenging, with studies assessing critical factors for the successful implementation and use of DICC being scarce [16].

Although various definitions and conceptualizations of DICC are available in the literature, they largely neglect the technical dimension [16,17]. Greenhalgh et al [16] proposed the Nonadoption, Abandonment, Scale-up, Spread, and Sustainability (NASSS) framework, which helps predict and evaluate the success of a technology-supported health or social care program. Successful implementation of DICC tools depends on the material and technical features, the knowledge generated, the support and knowledge needed to use the tools, as well as their substitutability and sustainability. A definition of DICC that includes these dimensions may guide research activities and support implementation projects, improving the probability of success for DICC. Therefore, we aim to conduct a scoping review on the (implicit) definition and dimensions of DICC across health care settings and its driving factors.

A preliminary search of PubMed returned some systematic reviews on facilitators of and barriers to ICC [6,8,11,18] as well as a handful of scoping reviews on DICC in the primary health care system and for specific disease groups [19-24].

However, no current or ongoing PROSPERO-registered systematic or scoping review on our research aim was identified in previous primary and review studies.

Aim and Review Questions

This review aims to (1) identify the factors that influence the development, implementation, and adoption processes of DICC and (2) elicit, analyze, and synthesize the (implicit) definition, dimensions, and concepts of DICC among health care professionals.

Subquestions driving the analysis include the following:

- How can DICC be operationalized?
- How do DICC complement or interfere with existing ICC practices and pathways?
- What barriers and solutions exist in the use of DICC?
- How does the health care setting (eg, primary care or secondary care) impact key concepts of DICC practices?

Methods

Search Strategy

To be able to conduct an in-depth analysis of the literature, we will draw upon a broad range of heterogeneous types of primary research, which can best be obtained through a scoping review. To standardize the approach, we will adhere to the Joanna Briggs Institute methodology [25].

In accordance with the methodology, we adopted a 3-step approach for including articles. To start with, an initial screening of titles, abstracts, and index terms of relevant articles in PubMed was used to identify possible keywords and refine our final search strategy (Table 1). Specific instant messenger apps, such as WhatsApp and WeChat, were included in the search if they were demonstrably the most popular messenger apps in at least one country and were specific to the search, meaning we discarded Line and imo due to their ambiguity [26]. Table S1 (Multimedia Appendix 1) details the hits per search string in PubMed. In a second step, we adapted the search strategy to each database (ie, CINAHL, PubMed, Embase, PsycInfo, and Scopus; Table S2 in Multimedia Appendix 1). Search strings were tested across all databases for conclusiveness. Our third step will be to manually screen all references of the included full texts for additional studies according to the snowball technique described by Greenhalgh et al [27]. Due to the rapid development of digital technologies, we will limit the studies included to those conducted from 2012 onward and include studies in English, French, German, Portuguese, and Spanish.

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Table 1. Search strategy on MEDLINE via PubMed and SCOPUS.

Participant, concept, and context scheme	#	Search string	Hits on PubMed (December 11, 2022)	Hits on SCOPUS (December 11, 2022)
Communication and collaboration among different health care provider groups	1	trans-disciplin*[a] OR transdisciplin*[a] OR cross-disciplinar*[a] OR crossdisciplinar*[a] OR inter-disciplin*[a] OR interdisciplin*[a] OR multi-disciplin*[a] OR multidisciplin*[a] OR multi-profession*[a] OR multiprofession*[a] OR inter-profession*[a] OR interprofession*[a]	185,543	392,636
	2	"knowledge transfer"[a] OR information*[a] OR Health Information Exchange[b] OR cooperat*[a] OR co-operat*[a] OR collaborat*[a] OR communicat*[a]	2,089,524	7,334,822
	3	"integrated care"[a] OR Intersectoral Collaboration[b] OR Interdisciplinary Communication[b]	26,343	33,558
	4	(# 1 AND #2) OR 3#	75,493	144,245
Digital tools	5	Health Information Systems[b] OR Ambulatory Care Information Systems[b] OR Information Technology[b] OR technolog*[a] OR sociotechni*[a] OR sociotechni*[a] OR mHealth[a] OR eHealth[a] OR digit*[a] OR Electronic Health Records[b] OR Public Health Informatics[b] OR messag*[a] OR messeng*[a] OR app[a] OR video*[a] OR phone[a] OR E-Mail*[a] OR "E Mails"[a] OR "E Mail"[a] OR Email*[a] OR "electronic mail"[a] OR "electronic mails"[a] OR "social media"[a] OR WhatsApp[a] OR Facebook[a] OR Viber[a] OR WeChat[a] OR Telegram[a] OR Kakotalk[a]	1,254,069	5,992,856
Health care setting	6	Health*[a] OR hospital*[a] OR care*[a] OR caring[a]	5,596,504	7,922,757
Combined	7	#4 AND #5 AND #6	7261	11,056
Filters	8	#7 + English, French, Spanish, Portuguese, German, from 2012 onward	5694	8216

[a]Title or abstract.

[b]Medical Subject Headings term for PubMed search string and title, abstract, or keyword for SCOPUS search string.

Eligibility Criteria

We defined several eligibility criteria based on formal issues, such as article type or language of publication, and issues related to the content of the manuscript, such as participants and context. These eligibility criteria are listed in Table 2 and described in detail below.

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Table 2. Inclusion and exclusion criteria.

Feature	Inclusion criteria	Exclusion criteria
Article type	Any of the following published in a peer-reviewed journal: • Primary research approach and study design • Opinion pieces • Guidelines • Reviews • Meta-analyses • Meta-syntheses	• Unpublished studies • Non–peer-reviewed research papers • Grey literature • Conference abstracts • Editorials • Book chapters • Records for which we are unable to obtain the full text • Studies that focus on students of health care professions
Language	• English • French • German • Spanish • Portuguese	• All other languages
Participants	• DICC[a] among health care professionals, including medical doctors and nursing staff	• Studies focusing on DICC between patient groups and health care practitioners • Studies focusing on individuals in the same health care profession within the same setting
Concept	• DICC involving either at least two different groups of health care professionals • DICC among health care professionals working in similar roles but in different health care settings	• All other DICC among health care professionals
Context	• Any geographic and demographic health care setting	N/A[b]

[a]DICC: digitally supported interprofessional communication and collaboration.

[b]N/A: not applicable.

Participants

The scoping review will include studies that focus on DICC among health care professionals, including medical doctors and nursing staff. Studies focusing on DICC between patient groups and health care practitioners as well as among individuals of the same health care profession within the same setting will be excluded.

Concept

We will consider DICC either involving at least two different groups of health care professionals or among health care professionals working in similar roles but in different health care settings.

Context

The study will include any geographic and demographic health care setting, as understandings of DICC may vary among different groups and settings, such as primary and secondary health care systems. We will include sources, but not limit them to such, assessing the implementation, piloting, and adoption of new DICCs.

Types of Sources

We will consider any type of primary research approach and study design, opinion pieces, guidelines, reviews, meta-analyses, and meta-syntheses published in a peer-reviewed journal. We will not include any unpublished studies, non–peer-reviewed research papers, or grey literature. We will further exclude conference abstracts, editorials, and book chapters, as well as all records for which we are unable to obtain the full text. Furthermore, studies that focus on students of health care professions will be excluded.

Study or Source of Evidence Selection

For screening, review, and data extraction, the web-based review manager Covidence (Veritas Health Innovation) will be used. We will upload all identified records and remove duplicates. Following the Joanna Briggs Institute methodology, all authors will independently screen the title and abstract of the first 50 records sorted by first author's last name. Any discrepancies will be discussed to ensure a uniform understanding of the inclusion and exclusion criteria. All remaining records will be screened by 2 independent reviewers. Potentially relevant sources will be retrieved in full, and their details will be imported into Covidence. Two independent researchers will assess the full text against the inclusion criteria and note reasons for exclusion. Any discrepancies between reviewers' decisions will be settled by an additional reviewer throughout all stages of the screening process. The results of the search and the study inclusion process will be reported in full in the final scoping review report and presented in a PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) flow diagram [28].

Data Extraction

Data will be extracted from all included records by 1 reviewer using MAXQDA (version 2022; CERBI GmbH). Specific categories for data extraction are predefined (Table 3) and include details about the study setting, participants, and key

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findings relevant to the review questions. The draft data extraction tool will be modified and revised as necessary during the process of data extraction. All modifications will be detailed in the scoping review.

We will extract data for sources that define DICC based on another reference ("secondary record") into a second data extraction sheet—if the secondary record is available to the researcher. No further inclusion or exclusion criteria will be applied to secondary records.

Table 3. Categories for data extraction.

Category	Item
Source details	• Journal • Year • Country of study setting • Study type

Details or results extracted from source of evidence	• Aim or purpose
	• Definitions (communication, collaboration, and digital tool)
	• Health care setting
	• Participants
	• NASSS[a] framework:
	  • Domain 1: the condition or illness
	  • Domain 2: the technology
	  • Domain 3: the value proposition
	  • Domain 4: the adopter system
	  • Domain 5: the organization
	  • Domain 6: the wider context
	  • Domain 7: embedding and adaptation over time
	• Other remarkable results

[a]NASSS: nonadoption, abandonment, scale-up, spread, and sustainability.

Analysis

The NASSS framework will be used as the basis for data analysis [16,17]. It consists of 7 domains, as follows: condition or illness, technology, value proposition, adopter system (intended users), organization(s), and wider context (especially regulatory, legal, and policy issues). The seventh domain, which is crosscutting, considers how the domains interact and change over time [16]. Through the NASSS framework, researchers can identify and explain the complex manifestations in technology-supported change efforts. Using the dimensions of the NASSS framework as predefined analytical themes, we will analyze the extracted data following a thematic analysis approach [29]. If necessary, we will inductively establish new themes or subthemes alongside the data analysis process.

Results

We will characterize the extracted data of all primary and secondary records by means of descriptive analysis, using diagrams and tables, accompanied by a narrative account of the findings, with a focus on the questions of this scoping review. A qualitative in-depth thematic analysis of definitions, dimensions, and concepts will be carried out, and data will be synthesized and mapped.

The scoping review was initiated in October 2022 with a protocol. Screening started in December 2022 and the analysis will be concluded in August 2023. We expect to submit the final scoping review manuscript by October 2023

Discussion

Contribution to Digital Health

The definitions and dimensions identified might have the potential to assist in the design, development, implementation, and evaluation process of DICC. They might further aid in understanding the barriers encountered in interprofessional use of DICC and identifying solutions. Furthermore, the results might help to advance new forms of interprofessional communication and to establish collaborations among different stakeholders in the health care setting. This might support a transition toward more coordinated care and help create digital frameworks for integrated patient care. Furthermore, the results might inform stakeholders from different backgrounds, including health care providers, health authorities and management staff, as well as entities developing DICCs.

Limitations

Our results will need to be interpreted with caution, as our search is limited in terms of language and publication time, which may have led to the exclusion of relevant literature. However, we deem the inclusion of manuscripts written in one of five languages to be quite extensive. In addition, we will not include any grey literature, as we want to address the current gaps in scientific literature. However, including non-peer-reviewed interventions and experiences assessing DICCs may provide further insights.

Conclusions

To the best of our knowledge, this is the first scoping review synthesizing definitions and dimensions of DICC among health

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care professionals as described in peer-reviewed studies. Closing this definition gap will provide a differentiated definition system, informing future research activities and implementation projects alike. We additionally expect to identify areas that merit further research in the form of primary or review studies.

Acknowledgments

This study is undertaken without external funding.

Data Availability

All data supporting the results of the scoping review will be reported in the manuscript, and the entire raw data sets that support the findings will be made available by the authors.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Supplementary material.
[DOCX File , 29 KB - resprot_v12i1e45179_app1.docx]

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Abbreviations

DICC: digitally supported interprofessional communication and collaboration
ICC: interprofessional communication and collaboration
NASSS: nonadoption, abandonment, scale-up, spread, and sustainability
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews

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Protocol

The Past, Present, and Future of Psychotherapy Manuals: Protocol for a Scoping Review

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Abstract

Background: Psychotherapy manuals are critical to the dissemination of psychotherapy treatments. Psychotherapy manuals typically serve several purposes, including, but not limited to, establishing new psychotherapy treatments, training providers, disseminating treatments to those who deliver them, and providing guidelines to deliver treatments with fidelity. Yet, the proliferation of psychotherapy manuals has not been well-understood, and no work has aimed to assess or review the existing landscape of psychotherapy manuals. Little is known about the breadth, scope, and foci of extant psychotherapy manuals.

Objective: This scoping review aims to identify and explore the landscape of existing book-based psychotherapy manuals. This review aims to specify the defining characteristics (ie, foci, clinical populations, clinical targets, treatment type, treatment modality, and adaptations) of existing book-based psychotherapy manuals. Further, this review will demonstrate how this information, and psychotherapy manuals more broadly, has changed over time. This project aims to make a novel contribution that will have critical implications for current methods of developing, aggregating, synthesizing, and translating knowledge about psychotherapeutic treatments.

Methods: This scoping review will review book-based psychotherapy manuals published from 1950 to 2022.This scoping review will be informed by guidance from the Joanna Briggs Institute Scoping Review Methodology Group and prior scoping reviews. Traditional search and application programming interface–based search methods will be used with search terms defined a priori to identify relevant results using 3 large book databases: Google Books, WorldCat, and PsycINFO. This review will leverage machine learning methods to enhance and expedite the screening process. Primary screening of results will be conducted by at least 2 authors. Data will be extracted and double-coded by research assistants using an iteratively defined codebook.

Results: The search process produced 78,600 results, which were then iteratively deduplicated. Following deduplication, 50,583 results remained. The scoping review is expected to identify common elements of psychotherapy manuals, establish how the foci and content of manuals have changed over time, and illustrate coverage and gaps in the landscape of psychotherapy manuals. Results from this scoping review will be critical for future work focused on developing, aggregating, synthesizing, and disseminating knowledge about psychotherapeutic treatments.

Conclusions: This review will provide knowledge about the vast landscape of psychotherapy manuals that exist. Findings from this study will inform future efforts to develop, aggregate, synthesize, and translate knowledge about psychotherapeutic treatments.

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KEYWORDS

psychotherapy; manual; protocol; primer; evidence-based treatment; scoping review; review methodology; mental health; scoping; manual; guideline; guidelines; book based; manuals; knowledge translation

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Introduction

Psychologists have long disseminated therapeutic knowledge and procedures through writings such as books and papers. For example, Freud first published *The Interpretation of Dreams* in 1899. However, the origins of the psychotherapy manual are unclear, and what qualifies as the first psychotherapy manual has not been well-established. Previous work has endorsed different publications as the first psychotherapy manual, including Wolpe's [1] 1958 *Psychotherapy by Reciprocal Inhibition*, Kelerman and Neu's [2] 1973 (unpublished) *Interpersonal Approach to Treating Depression*, Paul's [3] 1966 *Insight vs. Desensitization in Psychotherapy*, and Beck's [4] 1979 *Cognitive Therapy for Depression*. Though the origins of manuals are not well-understood, psychotherapy manuals have evolved to play an important and prominent role in clinical research, education, and practice.

Since their emergence, the value of psychotherapy manuals for the field has been widely and contentiously debated, receiving both praise and criticism [5-11]. Critics have argued against the use of manuals for being prescriptive, difficult to apply to real-world clinical practice, antagonistic to clinician intuition, harmful to therapeutic alliance, and detrimental to the impactful delivery of therapeutic skills and techniques [5,6]. By contrast, proponents highlight the numerous functions that psychotherapy manuals serve. First, they are essential for conducting research and establishing evidence-based psychotherapeutic treatments as they provide a protocol for treatments to test and evaluate treatment efficacy [2,7-11]. Second, creation of a manual legitimizes new and emerging psychotherapy treatments, such that without a manual, it is difficult to disseminate new treatments to practicing clinicians [9-12]. Third, manuals provide a structure that can be used to understand and evaluate fidelity or adherence to treatment [2,7,9,10]. Fourth, manuals aid in the training and development of clinicians [2,7-10,13]. Throughout their careers, clinicians can use manuals to learn new practices or improve their own practice. Indeed, research has indicated that practicing clinicians have read multiple manuals [14]. Finally, manuals are used to communicate information about treatments and enhance the legitimacy of psychotherapy practice to outside stakeholders (ie, policymakers and consumers). Because of these benefits, manuals have become the primary method of disseminating psychotherapeutic treatments, and their proliferation has been extensive over the past half-century [11].

Despite the prominence of manuals in psychotherapy research and practice, what constitutes a psychotherapy manual is not well-defined [15]. Clarity about what defines psychotherapy manuals is also mixed among those who use them, as demonstrated through empirical research with clinicians [7,14]. Previous works have attempted to define the psychotherapy manual and its necessary components [2]. Common components include a theoretical basis for treatment, a historical overview of treatment, a guide for delivering treatment, an overview of information about delivering treatment, troubleshooting information, patient or client dialogue, case or vignette examples of treatment, and supporting resources for delivering treatment (eg, assessment tools, fidelity checklists, client worksheets, case vignettes, and session outlines) [7,14]. The form of psychotherapy manuals is also not strictly defined, with "psychotherapy manuals" being disseminated as multiple forms, including books, individual book chapters, journal papers, gray literature, theses or dissertations, government publications, and more. However, books remain a popular method for disseminating psychotherapy manuals.

Given that psychotherapy manuals have become the predominant method for disseminating psychotherapy techniques outside of direct face-to-face supervision, a review of existing book-based manuals is critical for understanding the evolution in foci and content of manuals over time, the elements of psychotherapy manuals, and the current coverage and gaps of specific topics in extant psychotherapy manuals. A scoping review is the optimal approach to review the landscape of existing psychotherapy manuals. Scoping reviews focus on mapping existing knowledge on a topic, and they can be particularly advantageous when all relevant information on a topic is infeasible or impossible to attain. Given the decentralization and unknown breadth of psychotherapy manuals, a scoping review is the ideal design for understanding this landscape and addressing this problem [16].

Although scoping reviews have typically relied on manual search, screening, and data extraction procedures, machine learning has increasingly been used to support the review process [17]. Conducting reviews is resource-intensive [17], and as the body of literature gets larger, the labor associated with conducting reviews increases. Previous work has illustrated that the disparity in size between search results and the final sample is vast, with an average inclusion rate of ~3% of search results [18]. To address this problem, machine learning has been used to efficiently and effectively aid the review process [17]. Previous work has illustrated the use of machine learning techniques in the search, title or abstract screening, full-text screening, and information extraction phases [19]. While rapidly expanding, current machine learning techniques are only recommended for certain phases of the process, including, particularly, the screening phase [19,20]. Review platforms themselves have also increasingly leveraged machine learning components within their own software [20-22].

Leveraging machine learning techniques, this scoping review will be the first to perform a high-level review of book-based psychotherapy manuals. Currently, there is no systematic or even quasi-systematic knowledge about the psychotherapy manuals that exist. Given the large role of psychotherapy manuals in training, practice, and research in clinical psychology, this is a critical gap in knowledge that this scoping review will fill. This review will address several aims. Primarily, this review will aggregate and synthesize information about a large portion of manuals that exist. Within this aim, this review will specify the foci, clinical populations, clinical targets, treatment type, treatment modality, and adaptations of existing manuals. Further, this review will demonstrate how psychotherapy manuals have changed over time. The findings from this review will also support future efforts to develop, aggregate, synthesize, and translate knowledge about psychotherapeutic treatments. This paper delineates the protocol and methods used to address these aims.

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Methods

Study Design

This scoping review will be informed by guidance from the Joanna Briggs Institute Scoping Review Methodology Group [23] and previous literature on scoping reviews [20]. Specifically, this scoping review will use a modified form of the scoping review framework outlined by Peters and colleagues [16]. Slight modifications to this framework will be necessary to capture information specific to psychotherapy manuals in book form.

Search Strategy

Search terms and search strategy were developed collaboratively with the research team and subject matter librarians. The full search approach can be found in Multimedia Appendix 1. PsycINFO, Google Books, and WorldCat were searched for this review, searched in July 2022. These databases were selected based on (1) catalog size, (2) availability of relevant data for review, and (3) feedback from study authors and subject matter librarians. Some traditional scholarly databases, such as PubMed, do not consistently index psychotherapy books and thus were not used for this review. For PsycINFO, traditional database search methods were used. A search statement was developed for PsycINFO that combined both treatment and format language. Search terms for PsycINFO consist of "(psychotherap* OR therap* OR clinic* OR treat* OR interven* OR practi* OR counsel*) AND (manual OR protocol OR guide OR handbook OR primer)." PsycINFO offers over 5 million bibliographic records across numerous disciplines [24]. Search terms for PsycINFO included the aforementioned search statement as well as additional terms to include books but exclude book chapters (see Multimedia Appendix 1). Application programming interfaces (APIs) were used to search Google Books and WorldCat. As of October 2019, Google Books maintained a catalog of over 40 million books [25]. As of November 2022, WorldCat maintained a catalog of over 542 million bibliographic records [26]. APIs allow for the large-scale aggregation of search results that is unavailable through other methods. Compound search terms were created from the predefined search statement for the Google Books API. More specifically, permutations were created from terms from both sides of the search statement's "AND" to create briefer search terms (ie, "therap* manual," "therap* handbook," "clinic* primer," and "clinic* protocol") that were more feasible for API search methods (see Multimedia Appendix 1). Search strategy for WorldCat leveraged specific subject headings for the search process (see Multimedia Appendix 1). WorldCat search procedures were conducted by subject matter librarians from the University of California, Irvine. All initial search processes for this review were conducted in July 2022. Additional search processes will occur following the coding phase and be based on included results. This additional search process will be a snowball search based on bibliometric information of included results. Data from API queries were extracted and formatted to citations.

Deduplication was conducted in Python through an iterative duplication process. Deduplication focused on deduplicating by multiple parameters, given that some results may have the same titles (ie, books of different editions) or authors. Multiple rounds of deduplication were performed. First, deduplication by URL was performed to ensure that equivalent results from the same source were removed. Next, deduplication by ISBN identifiers was performed to ensure that duplicate results based on ISBN-10 or ISBN-13 numbers were removed. Finally, deduplication by a combination of title, description, AND year was performed, as well as a combination of title, author, AND year. Manual deduplication will be conducted throughout the later review phases, if necessary. Citations will be managed in reference management software.

Identification and Screening

Inclusion criteria were developed by study authors and subject matter librarians. First, manuals must be in the English language. Second, manuals must be a published book as this review focuses on books (ie, print books and electronic books), rather than other publication forms (ie, unpublished manuscripts, book chapters, journal papers, and research documents). Third, manuals must have been published between 1950 and 2022, as this reflects a broad time period that includes the creation of a vast majority of modern psychotherapies (ie, cognitive behavioral therapy and rational emotive behavior therapy). Additionally, this encompasses the time period in which previously identified "first" manuals were published [1-4]. Fourth, manuals must consist of a majority of instructional content about how to deliver a psychotherapeutic treatment or treatment components. This is defined as at least 50% or more content dedicated to instruction about delivering techniques or interventions. In cases where this is unclear, other resources may be used to assist with verification, such as book previews and freely available copies of books. Screening decisions will be made based on the information provided through titles or descriptions. After screening decisions have been completed, trained coders will code each included resource. For the coding process, more information may be sought through identified sources (ie, scholarly book reviews, publisher websites, and other book databases). If the additional information referenced during the coding process reveals that a manual should have been excluded, the manual will be excluded at this stage. This information may result in included resources being excluded during the coding process. Full information regarding inclusion or exclusion decisions at each stage will be outlined in the subsequent scoping review [16]. Fifth, manuals must be intended for use by a mental health professional (ie, psychologist, social worker, counselor, nurse, or physician). While some manuals have been previously addressed to consumers or lay providers, this review opts to focus on manuals that can be used by professionals to deliver mental health care. Results were excluded if they were a thesis or dissertation, another form of gray literature, or did not meet established inclusion criteria.

Screening of book descriptions and titles will be conducted in Rayyan (Rayyan Systems) [21]. Due to the size of this review, Rayyan's machine learning enhanced ranking system will be used as a form of active learning. Rayyan uses a support vector machine prediction system based on previous inclusion or exclusion decisions and text features (ie, unigrams and bigrams) [21]. Following an initial introductory period where eligibility

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screening is conducted by the research team, Rayyan's ranking system will gradually "learn" the parameters (ie, lexical patterns in titles and descriptions) of results that are receiving certain decisions (ie, "included" and "excluded"). Rankings of results with no decision will be regenerated by KW on a regular basis throughout the screening process. Results will be screened in accordance with this ranking system, with highly ranked results (ie, those most likely to be included) prioritized for screening. Approximately 15%-20% of all results will be screened by KW and a member of the screening team. The remaining records will be screened for inclusion by machine learning enhanced inclusion or exclusion and supplemented input by KW, mirroring previous work and recommendations [20-22].

Screening fidelity (ie, 80% agreement) will be met through multiple rounds of test screening across the screening team and AZ. Results that will be screened by the screening team will receive 2 decisions, 1 made by KW and 1 made by another author. Screening decisions will be made on the basis of information provided (ie, book title and book description). All disagreements will be resolved through consensus discussions between screeners for each result in conflict.

Coding Process

A codebook will be devised by input from all authors. An initial codebook will be created by KW and AZ. Feedback on the codebook will be solicited from the screening team to ensure that codes reflect relevant and extractable information from results. Additionally, the codebook will be further iteratively defined through the test coding process, with additional codes proposed, discussed, and agreed upon by the coding team, KW, and AZ. Coding will be performed for all included manuals. Fidelity will be established through 3 rounds of test coding prior to the beginning of coding. The coding team will code each result based on the information provided through bibliometric information (ie, book title and book description) as well as open-access information such as scholarly book reviews, freely available published portions of the book, and information provided via official sellers (ie, publisher websites, Amazon, and scholarly databases). Information outside of bibliometric data will be used when coding cannot be adequately performed on the information provided. Scholarly databases will be used to search book reviews when more information is necessary for coding purposes. Code disagreements will be addressed through consensus discussion or adjudication of disagreements by KW.

The initial codebook includes bibliometric information (ie, title, author, publisher, and date published), edition number, clinical target, clinical population, treatment name, treatment orientation, treatment notes, mental health provider target, treatment delivery setting, type of treatment (ie, individual, group, couples, family, and parent-child), age of treatment target, as well as dichotomous codes for several potential adaptations to treatment based on gender identity, race or ethnicity, culture, physical illness or disability, religion, employment or role, and other adaptations that are not covered by previous categories.

Results

This scoping review is currently being conducted. Initial search across all sources was completed in July 2022. The search process produced 78,600 results, which were then iteratively deduplicated. Following deduplication, 50,583 results remained. Nearly 14.2% of results (n=7171) have been screened. A portion of included results (n=775) have been coded. Full results from this review will be submitted for publication in peer-reviewed journals.

Discussion

Principal Results

The proposed review will be the first to synthesize information about the existing landscape of psychotherapy manuals with the goal of addressing critical and unanswered questions. More specifically, we aim to identify the features of existing manuals (ie, foci, clinical populations, clinical targets, treatment type, treatment modality, and adaptations), illuminate the ways in which psychotherapy manuals have evolved over time, and highlight current resource allocation and gaps evidenced by existing manuals. The findings from this review will be critical for future efforts to develop, aggregate, synthesize, and translate knowledge about psychotherapeutic treatments.

Comparison With Prior Work

Prior work that has focused on reviewing psychotherapy manuals has been narrowly limited to a specific treatment type, treatment focus (ie, eating disorders) [27], or manual format (ie, manuals from randomized controlled trials) [28]. This work has been impactful for the field, but critical gaps remain as to the broader landscape and evolution of psychotherapy manuals. Digital methods have become increasingly important for conducting research across myriad disciplines [29]. Past scholarship in digital humanities and digital history has called for the use of digital technologies to supplement psychology research, particularly in the history of psychology [29], and this scoping review aims to build on this work.

Limitations

There are several limitations to this work. Psychotherapy manuals can be disseminated through myriad forms and methods. Because of the disparities in how psychotherapy manuals are published and disseminated, the ability to systematically aggregate all knowledge related to this topic is arguably impossible. Therefore, we limited the search strategy to books to capture the predominant method by which manuals are disseminated. This will exclude psychotherapy manuals disseminated through peer-reviewed papers and gray literature, for example.

Certain books used as psychotherapy manuals may not meet our inclusion criteria. For example, providers have previously used client-facing (ie, "self-help") books as psychotherapy manuals, yet these resources will be excluded from this review. This was decided by the authors to limit the inclusion of materials that are not focused on providing instruction to mental health professionals about treatments and treatment delivery.

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Additionally, providers may use other types of books or resources to inform their clinical practice that do not focus directly on delivery of an intervention (eg, books focused on how to improve 1 specific technique within a treatment such as assigning homework, books on how to practice culturally competent care across many treatment modalities for specific populations, and books focused on developing therapeutic alliance across modalities). While these resources may be beneficial to delivery of psychotherapeutic treatments, they do not focus on instructing mental health professionals on how to deliver treatment.

Given the history of psychotherapy manuals and psychotherapy more generally, this scoping review aims to be informed by the changing definitions and ontologies in psychotherapy research. However, it is likely that through this scoping review, a modern qualitative coding may not encompass the changing definitions of psychotherapy treatments and the language used to describe them. Coding will be performed based on the bibliometric data, which is inherently reflective of the contemporary definitions in which a manual was produced. For example, the changing understanding of "behaviorism" and "behavioral treatments," as well as what constitutes "cognitive therapy" then versus now, may not be completely understood through the results from this review.

It is possible that the databases used within this review may not have a comprehensive list of psychotherapy manuals; however, the selected databases have extensive and growing catalogs [24-26]. Data quality may also differ widely within large databases. For some results, full information may be available, others may have gaps in information provided. Further, database entries may not be fully accurate, as some databases allow for manual entry of book information. Because of this, included references will be cross-checked with other sources (ie, scholarly book reviews, other databases, and publisher information), when possible. Finally, leveraging machine learning to expedite the screening process may result in increased false positives (ie, manuals that were included that should not have been included) and false negatives (ie, manuals that were excluded that should not have been excluded) [30]. Previous work using machine learning in title or abstract screening has demonstrated strong performance in not only accelerating the screening process but also doing so with high accuracy when combining with individual review [20,30].

Conclusions

Notably, this review will have numerous strengths. Although this is a scoping review, significant efforts will be taken to ensure that a wide variety of manuals will be included, increasing the potential representativeness of the results. Further, the use of these novel methods within this review will expand upon the growing literature on the use of machine learning to enhance reviews [17]. Most importantly, to our knowledge, this is the first large-scale review of book-based psychotherapy manuals. Thus, the benefits and implications of this work will be far-reaching for the development, dissemination, and implementation of psychotherapy knowledge. Given that a review of this topic and focus has yet to be done, this study will provide necessary information for the field's understanding of the landscape of psychotherapy manuals. Accomplishing this will not only provide critical information on the evolution of the treatment manual, but also how treatment manuals may be improved to meet the needs of users going forward. Previous work has indicated that use of manuals may vary across different types of users [14,31]. This review has particular use in identifying current resource allocation and extant gaps, as well as how this has shifted over time. With this information, future work will be able to better address those gaps, synthesize treatment-specific knowledge, and engage in the development of more effective methods of dissemination of psychotherapy.

Acknowledgments

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Data Availability

The data sets generated during and/or analyzed during this study are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search approach.
[DOCX File , 13 KB - resprot_v12i1e47708_app1.docx]

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Abbreviations

API: application programming interface

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Protocol

Designing and Evaluating IT Applications for Informal Caregivers: Protocol for a Scoping Review

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Abstract

Background: A growing number of informal caregivers in many countries are important for effective functioning of health care in our society. Hence, they must receive the required support and services to continue providing care. IT applications can be used to support informal caregivers in their caregiving activities. However, evidence-informed guidelines for developing such IT applications and their evaluation are scarce. Hence, this scoping review can aid researchers and designers by providing design recommendations for IT apps for caregivers and potentially improve the design of IT applications for caregivers to meet their needs better.

Objective: This study aims to describe the proposal for a scoping review of current practices and recommendations in designing and evaluating IT applications for informal caregivers. The scoping review will also discuss the opportunities and challenges in designing these IT applications.

Methods: We will use a 5-step scoping review methodology to map relevant literature published as follows: (1) identify the research question, (2) identify relevant studies, (3) select relevant studies for review, (4) chart the data from selected literature, and (5) summarize and report results. A structured search will be conducted in PubMed, Scopus, IEEE digital library, Web of Science, and ACM Digital Library databases. In addition, hand searches of reference lists and keyword searches in Google Scholar will also be conducted. Inclusion criteria will be researched (journal and conference) articles focused on IT applications designed for use by informal caregivers and study type to be qualitative studies. Two reviewers will independently identify articles for review and extract data. Conflicts will be discussed, and a third reviewer will be consulted if a consensus cannot be reached. These data will be analyzed using thematic analysis.

Results: The results from this scoping review will be presented in a narrative form, and additional data on study characteristics will be presented in diagrams or tabular format. Uppsala University first initiated this scoping review protocol in December 2021 as part of the European Union–funded project ENTWINE. This work was also supported by the Swedish Research Council and the Swedish Cancer Society. The results will be presented in August 2023 and will be disseminated through a report to the European Union and a peer-reviewed journal publication. In addition, the team plans to share its findings on various public platforms, including social media, blog posts, and relevant conferences and workshops.

Conclusions: This is, to our knowledge, the first study to map the literature on the design and evaluation of IT applications for informal caregivers. The scoping review's results will detail the requirements, design suggestions, and user preferences, as well as the usability criteria and features of IT applications for informal caregivers. A mapping of studies could inform the design and implementation of future IT applications for informal caregivers.

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KEYWORDS

burnout; caregiver; caregiving activity; design guidelines; design; development; digital health; digital resources; effectiveness; evaluation; health care services; implementation; informal caregiver; IT applications; long term care; mobile app; smartphone; usability; work-life balance

Introduction

Overview

Informal caregivers voluntarily provide care for a relative or a friend facing illness, disability, or any condition requiring particular attention [1]. They are essential to the health care sector, providing critical care and support to those in need [2]. Informal caregivers play an important role in providing long-term care in people's homes and ensuring the quality of life for millions of individuals [3]. They must receive recognition and access to resources to help them better manage their responsibilities. Caregiving can be a burdensome role with negative consequences on the physical and emotional health of the caregiver [3]. Studies have consistently shown that informal caregiving is often associated with a sense of burden, resulting in psychiatric and physical illnesses and mortality [1,4,5]. Lack of choice in becoming a caregiver is often associated with a higher subjective burden [1,6]. Informal caregivers may experience burnout due to their role, which is characterized by feelings of exhaustion, lack of motivation, and difficulty concentrating [1]. This burnout can be caused by factors such as a lack of support from family and friends, financial strain, and feeling overwhelmed by the demands of caregiving [1]. The impact of informal caregiving on caregivers' health has been studied extensively. Informal caregivers face several challenges, including limited personal time, difficulty navigating the health care system, and care recipients with a higher awareness of needs [7]. Organizations have introduced digital tools to address these challenges to support caregivers [8]. Additionally, recognizing and acknowledging their role is important for providing adequate support [8].

IT applications can benefit informal caregivers by assisting with their caregiving activities, among other things. IT applications for informal caregivers are technology-based tools that aim to provide support, resources, and assistance to individuals who provide care for family members or friends with chronic illnesses, disabilities, or aging-related issues. These applications can range from mobile apps to web-based platforms, for instance, the mobile app and web-based application CareHeroes [9]. They can provide educational information, help remember doctors' appointments, and coordinate care among all involved parties [10]. Smartphone apps can deliver timely and personalized health information to families and friends of chronically ill adults living in the community [11]. Digital resources, such as webinars, handbooks, and more, can educate caregivers about conditions and improve care quality. IT applications can also support informal caregivers by streamlining the process of building an informal care team of friends and family members. By making it easier to share information, ask for help, and create sign-ups, tasks can be easily delegated from the informal caregiver to a wider network. Access to current information is essential for informal caregivers. They could benefit from technological services that provide up-to-date information on their loved one's condition [12]. However, it is important to note that not all IT applications effectively support informal caregivers. A previous scoping review found that IT applications focus more on supporting caregivers in their caregiving role than their private and professional life [13]. Therefore, it is important to identify IT applications that cater to the primary caregiving and personal need domains of informal caregivers. This means developing IT applications that not only support caregivers in their caregiving roles but also address their personal and professional lives, such as managing their health, work-life balance, and social connections leading to better well-being. Overall, there is a need to investigate the design guidelines and principles for IT applications that go beyond addressing the caregiving role and cater to the personal and professional lives of informal caregivers, as well as to the specific needs of different caregiver groups.

It is important also to evaluate the usability of IT applications for informal caregivers to ensure they are effective and useful. Research has shown that most applications offer limited evidence of effectiveness. This highlights the importance of conducting rigorous usability evaluations of IT applications to ensure that they are meeting the needs of their users and achieving their intended goals. Still, those evaluated have been found to help provide educational information, remember doctors' appointments, coordinate care among all caregivers, manage behavior problem checklists, provide alerts for care providers, and offer information about available services [10,14]. Evaluating IT applications for informal caregivers is important in identifying and addressing usability issues and ensuring that they are effective and useful for their intended purpose [14]. Caroço et al [15] and Gomes et al [16] report on the usability studies of Help2Care, an eHealth platform that provides digital training materials for informal caregivers. Both studies found that the platform had less usable aspects, such as navigation flow and design elements, which were identified through usability tests. Držanič et al [17] evaluated the usability of a smartphone telecare app for informal caregivers and found that users perceived the app as high in usability and user experience. Xiao et al [18] designed and evaluated web interfaces for informal caregivers in senior monitoring and found that combining evaluation methods is important in identifying usability issues. Overall, these papers suggest that usability evaluations are important in identifying and addressing usability issues in IT applications for informal caregivers.

There are some reviews in the field of IT applications for informal caregivers that have been discussed in recent literature. Sala-González et al [10] conducted a systematic review of mobile apps for helping informal caregivers, finding that most of the studies assessed caregivers' needs before designing

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mobile apps to adapt them to the needs of their users which has proved useful. Martínez-Alcalá et al [19] and Powell et al [20] found that IT applications were useful in improving the life of informal caregivers. However, it was found that there were some challenges to deploy these IT solutions for informal caregivers, and Hassan [21] conducted a scoping review and provided recommendations for the deployment of IT applications for informal caregivers. Guessi Margarido et al [11] investigated the nature and extent of native smartphone apps for informal caregivers of chronically ill patients and found that most apps targeted a single chronic condition, with Alzheimer and other dementia being the most common. Meyer et al [22] conducted a systematic review of novel technology as a platform for interventions for caregivers and individuals with severe mental health illnesses and found that none of the studies focused on caregivers, and the ones identified using mobile or web-based apps were just for patients and not their relatives. While previous reviews have explored the effectiveness of IT applications and the challenges and recommendations for their deployment, our proposed scoping review aims to contribute to the existing literature on IT applications for informal caregivers by identifying and summarizing knowledge about the design recommendations and usability of such applications.

Study Objectives

The objective of the proposed scoping review is to identify and summarize knowledge about the design recommendations of IT applications and the usability of IT applications by informal caregivers. The scoping review will also discuss the opportunities and challenges in designing these IT applications. Design recommendations for IT applications refer to best practices and guidelines that can be followed by software designers and developers to ensure that the applications they create are user-friendly, efficient, and effective. For instance, a relevant design recommendation could be accessible information; the application should provide concise and relevant information that is easily accessible and available in different formats, such as text, audio, and video, to cater to the different learning styles and needs of informal caregivers.

Usability refers to the degree to which an IT application is easy to use, learn, and understand. A usable IT application is designed with the end user in mind, allowing users to complete their tasks quickly and efficiently without encountering unnecessary obstacles or confusion. Many IT applications are designed for caregivers based on identified unmet needs through interviews and focus groups. However, to the best of our knowledge, this literature has not been compiled. This scoping review can aid researchers and designers by providing design recommendations for IT applications for caregivers and potentially improve the design of IT applications for caregivers to meet their needs better.

Methods

Study Design

Arksey and O'Malley's [23] methodological framework for scoping reviews will be used for the proposed scoping review. The research topic addressed here includes a wide range of study designs and various support platforms and solutions for informal caregivers caring for a wide range of illnesses and care-recipient types carried out in multiple countries. Moreover, designing effective solutions for informal caregivers has been carried out in multiple fields like information systems, human-computer interaction, and health informatics. A scoping review methodology was considered suitable as this is an emerging topic where evidence is scarce and scattered. There is a need to bring results from these different fields of designing IT support together to generate a common knowledge pool, which is a major research gap. This scoping review methodological framework outlines the following five stages: (1) identification of the research question; (2) identification of relevant studies; (3) selection of relevant studies; (4) charting the data from the selected literature; and (5) collating, summarizing, and reporting the results.

We will follow the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analysis Extension for Scoping Reviews) guidelines [24] to complement the conduct and reporting of the results.

Step 1: Identifying the Research Questions

The focus of the proposed review was identified through a preliminary scan of the extant literature. Initially, the focus was the design recommendations for IT applications for informal caregivers. However, upon initial inquiry, it became clear that to have effective and user-friendly design recommendations, the review would benefit from also looking at the evaluation of IT applications for informal caregivers. The research question was also discussed, and feedback was obtained from experts from Uppsala University and the eHealth research group at the University of Twente. Based on multiple rounds of brainstorming, the following questions were developed for the scoping review:

1. What are the design recommendations for developing IT applications for informal caregivers?
2. How are these IT applications perceived and evaluated by informal caregivers?

Step 2: Identification of Relevant Studies

The literature search was conducted in collaboration with a health psychology information specialist at the University of Twente and some sessions with the university librarian at Uppsala University. Search terms focused on three components of the research question: (1) informal caregivers, (2) IT applications, and (3) design or evaluation. Terms related to caregivers were based on previous reviews on this topic from Lambert et al [25,26] and included terms, such as "home nursing," "informal caregiver," "family caregiver," "informal carer," "family carer," "caregiver," and "carer." Terms related to IT solutions included "mobile application," "ICT solution," "ICT," "e-coaching system," "coaching system," "digital solution," and "IT solution." Terms related to design and evaluation included "design," "evaluation," "effectiveness," "usability," "requirements," "needs," "perspective," and "user experience." Table 1 provides an overview of the different groups of keywords.

Studies included both conference papers and journal articles as publication types. The databases searched were PubMed,

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Scopus, IEEE digital library, Web of Science, and ACM Digital Library. EndNote 12 was used to store the search results and remove duplicates. The quality of the searches was confirmed by verifying that the results contained relevant studies identified before the formal search.

Table 1. Keywords for the search string.

Keywords	Search terms
Group 1: informal caregiver	"Home nursing" OR "informal care*" OR "family care*"
Group 2: IT solution	"Mobile application*" OR "ICT solution*" OR "ICT" OR eHealth OR "e-coaching system*" OR "* coaching system*" OR "digital solution*" OR "IT solution*" OR "internet-based interventions*" OR telehealth*
Group 3: design or evaluation	Design OR evaluation OR effectiveness OR usability OR requirements OR needs OR perspective OR "user experience*"

Step 3: Selection of Relevant Studies for the Review

The initial screening of titles and abstracts was done only by the first author (SP) and was guided by the inclusion criteria using the web-based screening tool Rayyan [27]. At present, SP has also completed the full-text screening stage, while the second author (AA) will soon start full-text screening of all the articles. In the event of conflicts, a discussion will be held between the authors, and a third reviewer will be consulted if a consensus cannot be reached. Studies will be included if they are peer-reviewed conference articles, journal articles, or early-access articles. As the scoping review is restricted to peer-reviewed articles, the next stage includes removing proceedings, editorial and opinion papers, news articles, books and book chapters, theses, and clinical case papers. The inclusion and exclusion criteria to be used are summarized in Textbox 1. The study selection process is illustrated in Figure 1. The number of articles in each stage indicates the numbers from the first review. These numbers are expected to change based on the second review and further discussions.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria:

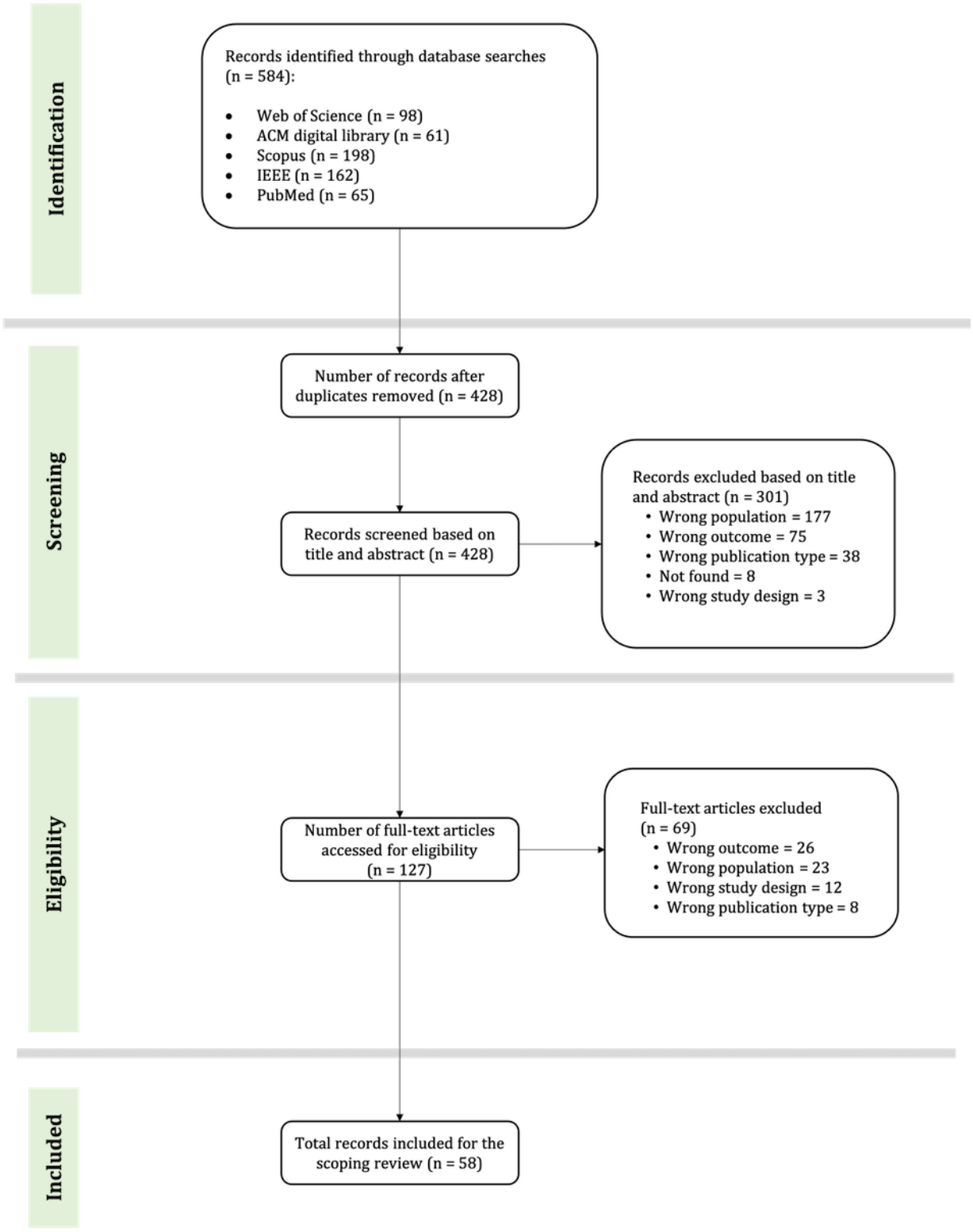
- Publication type: conference articles, journal articles, and early access articles
- Studies regarding usability tests of IT apps or platforms
- Studies describing user needs or requirements for IT apps for informal caregiving
- Studies that describe the evaluation of IT apps focusing on what works or what is preferred along with user experience
- Studies describing the development process of IT apps for informal caregiving
- Studies on IT apps to train informal caregivers in their caregiving activities

Exclusion criteria:

- Study type: review articles, editorial and opinion papers, news articles, books and book chapters, theses, and clinical case papers
- Descriptive or quantitative studies assessing the adoption of a system or criteria for adoption based on a theoretical model
- Studies focused on care recipients and formal caregivers
- Studies on IT apps targeted at patients, but developed with interviews with patients and informal caregivers along with health care professionals

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Figure 1. Study selection flow diagram.



Step 4: Charting the Data

The following information regarding the included studies will be extracted and stored in Excel (Microsoft Corp): authors, year of publication, the purpose of the paper or study and innovation, study location and context (setting and end users of innovation), study design, outcomes measured, main findings, and lessons learned used. Once the analysis and writing of the scoping review manuscript are finished, the articles used for the review will be accessible on the open science framework platform [28]. While submitting the scoping review manuscript, full citations of the included articles will also be added as supplementary files.

Step 5: Collating, Summarizing, and Reporting the Results

A descriptive-analytical narrative method was used to extract and chart the data from the selected articles. Using the same

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process of team consultation, data from the selected articles were first extracted onto a data charting form developed by the research team using an iterative process. Charts were used to collate, summarize, and share data for team review and decision-making. Data entered included the following: authors, year of publication, the purpose of the paper or study and innovation, study location and context (setting and end users of innovation), study design, outcomes measured, main findings, and lessons learned. A coding scheme (framework) will be created under three thematic categories: (1) design and development, (2) evaluation, and (3) opportunities and challenges. Full articles were imported as PDF files into NVivo 12 (QSR International), a software program for qualitative analysis, for more detailed data extraction and coding. The authors applied the coding scheme to all pertinent text, and then further coded the data under emergent themes using an iterative process.

Results

The findings of our scoping review will be presented in a clear and coherent narrative, supplemented by relevant data on the study characteristics in diagrams or tables. The results can be broadly categorized into 2 main sections: design recommendations and usability criteria. Under the design recommendations category, we may have subcategories that address specific conditions or that are based on the type of system or caregiver characteristics. This will provide a more tailored approach to designing eHealth applications for informal caregivers that take into account their unique needs and circumstances. Similarly, the usability criteria category may also have subcategories that are specific to certain types of systems or caregivers. By considering the context in which caregivers use these applications, we can identify usability criteria that are most important to their overall experience. The presentation of our results will provide valuable insights for researchers and designers working in the field of eHealth applications for informal caregivers. The subcategories will help to further refine our understanding of the needs and preferences of this population and guide the development of more effective and user-friendly applications. The scoping review will also discuss the opportunities and challenges in designing these IT applications.

Uppsala University first initiated this scoping review protocol in December 2021 as part of the European Union–funded project ENTWINE. This work was also supported by the Swedish Research Council and the Swedish Cancer Society. The scoping review is being undertaken to delve into the potential design recommendations and usability criteria for IT applications catering to informal caregivers. The main objective of this scoping review is to produce 2 comprehensive lists: one comprising design recommendations and the other focusing on usability criteria for IT applications targeted toward informal caregivers. The first list will serve as a solid foundation for designers who are keen to develop IT applications for informal caregivers and will provide the answers to the first research question. If the chosen articles address both design recommendations and usability criteria for IT applications, the team will be able to effectively gauge whether these design recommendations are well-received by the caregivers. However, if some included papers only discuss usability criteria, the resulting list would still serve as a starting point for designers, as it would provide a comprehensive set of usability criteria for designing IT applications for caregivers and also help answer the second research question.

The results of the scoping review will be presented in August 2023 and will be disseminated through a report to the European Union and a peer-reviewed journal publication. In addition, the team plans to share its findings on various public platforms, including social media, blog posts, and relevant conferences and workshops.

Discussion

In this proposed scoping review, we will provide an overview of the current state of research on the design and usability evaluations of IT applications for informal caregivers. The review will identify the types of IT applications, their design recommendations, and the usability criteria. This information can guide the development of new IT applications or improve existing ones. The scoping review will also provide an opportunity to reflect on the challenges and opportunities associated with designing and evaluating IT applications for informal caregivers. To our knowledge, no previous studies have explicitly highlighted these factors. While Hassan's [21] study addressed the challenges and recommendations for the practical implementation of IT applications for informal caregivers, it solely focused on the caregivers of older adults. On the other hand, our study seeks to broaden the scope and delve into the factors essential for designing and evaluating IT applications for all informal caregivers.

The potential benefits of IT applications for informal caregivers are numerous [29,30]. They can provide support tailored to the individual caregiver's needs [2,31]. For example, an IT application could provide personalized reminders to take breaks or offer suggestions for self-care activities. IT applications can also connect caregivers to support networks, such as other caregivers or health care professionals [32,33]. This can help reduce the social isolation that is often associated with being an informal caregiver. Such apps can provide support for caregivers in the form of information, education, communication, and coordination of care. They also offer solutions for specific caregiver challenges, such as medication management and self-care. Moreover, these apps can potentially reduce caregiver burden, stress, and burnout, thereby improving the quality of care provided to the care recipients.

However, designing and evaluating IT apps for informal caregivers is a complex and challenging task. Many factors must be taken into account, such as the needs and preferences of caregivers, the technological capabilities of the target population, and the ethical and privacy considerations involved [21,34,35]. Additionally, evaluating the effectiveness of IT applications for informal caregivers requires using appropriate iterative evaluation methods that consider the unique characteristics of this population [29,36].

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Our scoping review thus provides a comprehensive overview of the unique challenges and opportunities associated with designing and evaluating the usability of IT applications for informal caregivers across all age groups. The findings of our study will help researchers and developers create more effective and efficient eHealth interventions that cater to the diverse needs of informal caregivers.

Acknowledgments

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Data Availability

Once the analysis and writing of the scoping review manuscript are finished, the articles used for the review will be accessible on the open science framework platform. While submitting the scoping review manuscript, full citations of the included articles will also be added as a supplementary file.

Authors' Contributions

SP is the principal author of this manuscript. SP designed the review, identified the research questions, worked with the search strategy, did the title and abstract screening and full-text screening, and wrote the manuscript. AA wrote parts of the manuscript. PÅ contributed to the study design. ÅC, PÅ, and LvGP critically revised the manuscript drafts. All authors approved the final draft of the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analysis Extension for Scoping Reviews

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Protocol

Strategies for Alleviating the Burden Experienced by Informal Caregivers of Persons With Severe Mental Disorders in Transitional Countries: Protocol for a Scoping Review

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Abstract

Background: Caregiver burden is highly prevalent among the informal caregivers of persons with severe mental disorders (SMDs). As such, strategies to support informal caregivers are necessary to enable them to cope with their caregiving role. Currently, there is limited evidence on the extent of existing strategies for supporting informal caregivers of persons with SMDs in transitional countries.

Objective: This study presents a scoping review protocol to identify and describe the extent and type of evidence on the existing strategies for alleviating caregiver burden among informal caregivers of persons with SMDs in transitional countries.

Methods: This scoping review will be conducted using the Joanna Briggs Institute's methodology for scoping reviews. The participants, concept, and context framework will be used to select relevant studies. This review will include studies on strategies for addressing caregiver burden among informal caregivers, with a specific focus on studies outlining caregiver interventions, caregiver support, and policies with strategies for supporting informal caregivers of persons with SMDs. Relevant studies conducted in transitional countries will be considered for inclusion. There will be no restrictions on publication type or design. Published literature will be accessed by searching electronic databases, including PubMed, MEDLINE, CINAHL, and PsycINFO; ProQuest will be used to access gray literature. Additionally, the reference lists of key studies will be reviewed to identify studies for inclusion. The search will be restricted to articles published between 2011 and 2021. Two reviewers will work independently to screen all abstracts and full texts for inclusion in line with the set inclusion criteria. Extracted data will be categorized and described using descriptive qualitative content analysis.

Results: This protocol will guide a scoping review to identify and describe the extent and type of evidence on the existing strategies for alleviating caregiver burden among informal caregivers of persons with SMDs in transitional countries. The main results of this scoping review will synthesize evidence from peer-reviewed and gray literature sources outlining various services and interventions for supporting informal caregivers of people with SMDs in transitional countries. In addition, existing gaps in the literature will be identified to inform future studies.

Conclusions: The increase in caregiver burden among informal caregivers in mental health warrants the development and implementation of strategies for alleviating the burden. This scoping review aims to increase awareness on the various services and intervention strategies for alleviating burden among informal caregivers in transitional countries.

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KEYWORDS

burden; caregiver burden; caregiver care; caregiver intervention; caregiver stress; caregiver; developing country; guidelines; implementation strategy; informal carers; mental disorder; mental well-being; review method; rural; scoping review; support strategies

Introduction

Severe mental disorders (SMDs) are disabling, chronic psychiatric conditions with a substantial burden on the patients and their caregivers [1]. These disorders include schizophrenia spectrum and other psychotic disorders, bipolar and related disorders, and depressive disorders [2]. People who are diagnosed with SMDs often exhibit long-term symptoms that compromise their ability to fulfill occupational and social roles [3]. For example, depressive disorder is characterized by prolonged feelings of sadness and guilt and reduced energy levels, which hinder participation in activities of daily living and work-related activities [4-7]. Those diagnosed with schizophrenia spectrum and other psychotic disorders often exhibit psychotic behavior, apathy, social withdrawal, and cognitive impairments, which all lead to a deterioration of social and occupational functioning [2,8]. Similarly, people with bipolar and related disorders are likely to experience considerable impairments at work and in their family lives and often struggle to form and maintain social relationships [9,10]. Given the chronic nature of SMDs, the symptoms are often persistent and thus require sustained care and management [11,12].

In resource-constrained settings in transitional countries, the care and management of those with SMDs relies on informal caregivers, making them instrumental in bridging the treatment gap [13]. Informal caregivers can be a family member, a friend, a neighbor, or any good Samaritan within the community responsible for providing care to a person with a chronic condition [14,15]. Informal caregivers assume responsibility for the health and well-being of those with mental disorders [16]. They are expected to manage the patient's behavior, structure their routines, and monitor their treatment [17-19]. To fulfill these responsibilities, most informal caregivers are obligated to live with the mental health care user 24 hours a day, every day of the year, to support them [16]. Fulfilling the responsibilities of caregiving and dealing with the recurring symptoms of SMDs result in high caregiver burden, stress, a decline in health and well-being, and a decreased sense of support [18].

Informal caregivers of persons with SMDs require ongoing access to information, guidance, and support to enable them to cope with their caregiving responsibilities. Various strategies for supporting and alleviating caregiver burden among the informal caregivers of persons with SMDs have been proposed in developed countries, including the United States and the United Kingdom. These strategies include the provision of family-based interventions and support programs. Family-based interventions encompass different combinations of psychotherapeutic strategies, including psychoeducation, stress management, cognitive appraisal, and problem-solving skills [20].

Psychoeducation is described as a systematic and structured psychotherapeutic intervention that contains a brief introduction to the mental disorder, presenting symptoms, and information on signs of early relapse [21]. This intervention aims to inform persons with SMDs and their caregivers about the available treatment with details on efficacy, safety, common side effects, cost, and methods to identify burden and coping strategies [17]. To ensure effectiveness, psychoeducational sessions can initially be offered weekly and later once a month [15]. Similarly, cognitive behavioral therapy (CBT) involves training informal caregivers to develop cognitive and behavioral skills to enable them to cope with current stressors [20]. This makes CBT suitable for addressing the complex demands and stresses attached to the caregiving role [20]. The cognitive skills gained through CBT address dysfunctional thoughts that may arise from a negative appraisal of the caregiving role, and the behavioral skills aim to increase pleasure when performing the caregiving activities [21]. This intervention seeks to promote positive attitudes such as empathy, affective support, and changing verbal communication patterns between the caregivers and the care recipients [21]. CBT can be offered individually or in a group through diverse platforms, including face-to-face, web-based, and phone-based modes [22]. CBT has been found to be beneficial in reducing burden among caregivers of persons with schizophrenia [23].

Most family-based interventions have been developed and tested in Western countries. The American Psychiatric Association and the United Kingdom's National Institute for Health and Care Excellence (NICE) guidelines for schizophrenia recognize the importance of family-based interventions for caregivers [24,25]. To ensure the effectiveness of these interventions, it is recommended that caregivers be involved in a minimum of 10 sessions over a period of 3 months to 1 year [26,27]. These interventions can be offered to caregivers individually or in a group session. Traditionally, a trained therapist or health care professional is required to offer these interventions to single or multiple families. Several randomized controlled trials conducted in the United States and the United Kingdom yielded positive results related to the effect of psychoeducation on families' social function and caregiver burden in those with psychotic disorders [28]. Additionally, these interventions have been shown to increase the quality of life for caregivers and care recipients and are associated with positive patient outcomes, including increased medication compliance, which reduces relapses and hospitalization [14,29].

Peer-led support groups have been identified as another strategy to alleviate caregiver burden among the informal caregivers of persons with SMDs. Peer-led support groups, such as the National Alliance on Mental Illness (NAMI), were established in the United States as part of the larger social movement of self-help [30]. These support groups are meant to address the needs of service users and their caregivers that are not adequately addressed by standard health care services. They

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provide a platform through which informal caregivers can share and re-examine their own caregiving difficulties and challenges with other caregivers in similar situations. Additionally, it gives informal caregivers an opportunity to learn from others by exchanging information on SMDs and the experiences of caregiving [31]. Peer-led support groups are useful for improving caregiver attitudes, emotions, and empathy. Subsequently, they help improve effective communication and relationships among caregivers and their care recipients [32,33]. They are commended for being flexible and taking a more client-centered approach to enable caregivers to cope with the demands of their caregiving [28]. Previous studies conducted in the United States, the United Kingdom, and China demonstrated that peer-led support groups for informal caregivers of persons with SMDs can reduce caregiver burden and improve the caregivers' knowledge and stress management [32,33].

Although most research on strategies for alleviating caregiver burden among informal caregivers originated in Western countries, including the United States and the United Kingdom, there has been a phenomenal increase in studies conducted in transitional countries [34]. There has been an emergence of randomized controlled trials in transitional countries, including China, India, Iran, Pakistan, Thailand, and Malaysia, over the last decade [31,35-38]. The growing body of knowledge from studies outlining strategies for alleviating caregiver burden among informal caregivers in transitional countries calls for a review of the literature in this area. Currently, no scoping reviews have been published on strategies for alleviating caregiver burden among informal caregivers of persons with SMDs. This scoping review will therefore present available evidence on strategies for alleviating informal caregiver burden. Published and gray literature from caregiver burden studies, caregiver intervention and caregiver support studies, and mental health policy documents will be reviewed to allow for the synthesis of available evidence in transitional countries.

Methods

Overview

This protocol is a systematic scoping review of the literature reporting on strategies for alleviating caregiver burden among the informal caregivers of persons with SMDs in transitional countries. A scoping review method was selected to present an outline of the evidence that exists in the area of interest and the gaps for further research [39]. The proposed scoping review will be conducted in accordance with the Joanna Briggs Institute's (JBI) methodology for scoping reviews [39]. This methodology is based on 5 stages that guide the development of the protocol and the scoping review, which include identifying the research question and the relevant studies, selecting the studies, charting the data, and assembling the results to identify the relevant implications for policy, practice, and research [39].

First Stage: Identifying the Research Question

The main research question is: "What strategies exist for alleviating caregiver burden among informal caregivers of persons with SMDs in transitional countries?"

The Research Aims

The research aim is to present existing literature on strategies for alleviating caregiver burden among informal caregivers of persons with SMDs in transitional countries.

The Research Objectives

This study has the following research objectives:

1. To identify existing strategies for alleviating caregiver burden among informal caregivers of persons with SMDs in transitional countries.
2. To describe the characteristics of the strategies used to alleviate caregiver burden among informal caregivers of persons with SMDs in transitional countries.

This study will use the participants, concept, and context (PCC) framework (Textbox 1) to guide the selection of relevant studies and ensure alignment with the research question.

Textbox 1. The participants, concept, and context (PCC) framework for eligibility of studies.

Criteria and determinants

- Population
  - Informal caregivers of persons with severe mental disorders in transitional countries
  - Informal caregivers include family, friends, neighbors, or community members, often unpaid, to providing care
- Concept
  - Caregiver burden
  - Caregiver strain
  - Caregiver stress
  - Caretaker role fatigue
- Context
  - Transitional countries (including Africa, Asia, Latin America, and the Caribbean)
  - Lower- to middle-income countries

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Second Stage: Identifying the Relevant Studies

This scoping review will consider both published and unpublished studies detailing strategies for supporting informal caregivers in mental health in transitional countries. The 3-step search strategy process will be used to identify relevant studies. An initial limited search of PubMed, MEDLINE, CINAHL, and PsycINFO will be undertaken to identify relevant articles published over the last 10 years. This will be followed by the analysis of text words contained in the titles and abstracts of relevant articles and of the index terms used to describe the articles. The initial key words will include [informal caregiver/s OR caregiver/s] AND [caregiver burden OR caregiver stress] AND [support strategy/ies OR intervention/s] AND [severe mental disorder/s OR mental illness] AND [developing country/ies OR underdeveloped country/ies]. The second search will include all keywords and index terms identified and revised with the assistance of a librarian at the University of the Witwatersrand. The search strategy will be adapted for each included database and information source (Multimedia Appendix 1). For unpublished or gray literature, a targeted search of dissertations, theses, and conference abstracts will be conducted on "ProQuest Dissertations and Theses Global" and public health and conference databases. Lastly, the reference lists of all included sources of evidence will be screened for additional studies.

Third Stage: Selection of Studies

The PCC framework (Textbox 1) provides detailed eligibility criteria to ensure that the content of relevant studies aligns with the research question (Textbox 2).

Textbox 2. Inclusion and exclusion criteria.

Inclusion criteria

- Contain details on strategies for alleviating caregiver burden among the informal caregivers of persons with mental disorders in transitional countries as classified by the World Bank
- Contain strategies for informal caregivers, which includes family, friends, neighbors, or community members, often unpaid, to provide ongoing care to a person with a mental disorder
- Contain strategies for caregivers of persons with severe mental disorders (SMDs), including schizophrenia spectrum and other psychotic disorders, bipolar and related disorders, depressive disorders, and personality disorders
- Contain strategies targeted towards alleviating caregiver burden, caregiver strain, caregiver stress, and caregiver role fatigue
- Include documents on caregiver intervention and caregiver support and mental health policy documents outlining relevant strategies
- Were published in the last 10 years, that is, between 2011 and 2021
- Be primary and secondary studies with both quantitative, qualitative, and mixed methods research approaches

Exclusion criteria

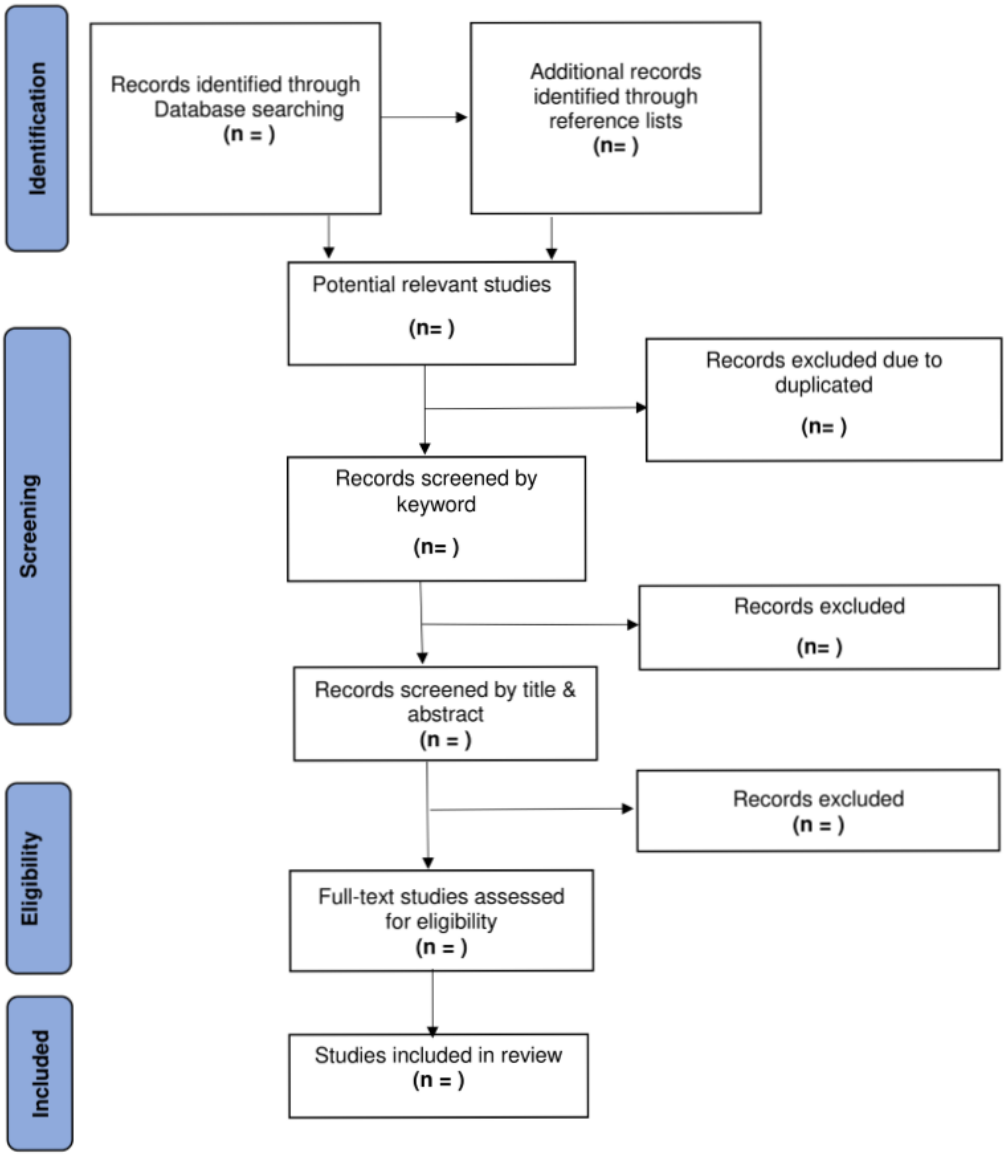
- Those outlining strategies for supporting caregivers who are paid to provide care
- Strategies that focus only on care recipients
- Strategies for informal caregivers of persons with intellectual disabilities, Alzheimer disease, and dementia

The search strategy will be piloted to check the appropriateness of the identified keywords and databases. All eligible articles will be uploaded on Mendeley Reference Manager. The identified articles will then be uploaded to Covidence, and duplicates will be removed. Covidence is a web-based primary screening and data extraction tool used to streamline the systematic review process. The author will be responsible for searching and uploading the identified studies, and the author and co-reviewer will be responsible for screening the titles, abstracts, and full texts of the identified studies.

The initial search and screening of titles and abstracts will commence in September 2021, and this will be followed by the second search and screening of titles, abstracts, and full texts in January-March 2022. In April-May 2022, the reviewers plan to conduct a full text review for additional studies identified in the references of the included studies. Throughout the process, all attempts will be made to obtain the full texts of the eligible studies by searching the University's library guides and the internet and by collaborating with a librarian at the University of the Witwatersrand Faculty of Health Sciences. The author and identified co-reviewer will be responsible for conducting a full text review of the identified studies. All excluded studies, along with the reasons for exclusions, will be tracked on Covidence. All identified conflicts will be resolved through constant discussions between the 2 reviewers and a web-based meeting will be held biweekly. The degree of agreement between the reviewers will be calculated on Covidence and reported in the findings. The results of the search and the study inclusion process will follow the recommendations in the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) checklist (Multimedia Appendix 2) [39]. This will be mapped using the PRISMA-P (PRISMA Extension for Protocols) chart (Figure 1).

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Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram for the scoping review process [39].



Fourth Stage: Charting the Data

The data will be charted using an electronic data extraction form [39] on the Covidence software. A total of 2 separate data extraction forms will be used for the research articles (Table S1 in Multimedia Appendix 3) and the policy and guideline documents (Table S2 in Multimedia Appendix 3). This is useful for capturing the relevant information from each included study.

A total of 2 independent reviewers based at separate tertiary institutions will carry out the data extraction. Communications regarding consensus will be facilitated through regular web-based meetings and face-to-face meetings when necessary. Before using the data extraction forms, piloting will be done to ensure the standardization and relevance of the extracted information. This process will be conducted at the end of the initial limited search phase of the scoping review. This process is essential to ensure efficient, meaningful extraction of data from all included papers. This process will be conducted at the end of the initial limited search phase of the scoping review. A sample of 10 included papers meeting the eligibility criteria will be selected to test the quality and validity of the data extraction tools [40]. First, the included studies will be purposely sampled, and second, data will be extracted from the included studies. The sample synthesis will then be conducted after the data analysis process, which is outlined in the data analysis and presentation. The results from the synthesis will be used to inform the modification of the data extraction form. This process is essential to ensure efficient and meaningful extraction of data from all included papers. To ensure the quality and validity of the modified data extraction form, the piloting process will be repeated at the end of the second search.

Fifth Stage: Data Analysis and Presentation

A descriptive qualitative content analysis will be conducted inductively using NVIVO software to code the characteristics of the extracted data into overall categories [39]. This method of analysis is selected as it allows for rich meanings and insights to be derived from text by interpreting the manifest and latent content of the text, which is done through rigorous analysis and an understanding of a phenomenon's critical processes [41]. The outcome of this scoping review will inform the development of interview guides for the subsequent studies, and therefore, a

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rigorous data analysis is required. A PRISMA-ScR flowchart (Figure 1) will be used to show the number of identified included and excluded studies. The various strategies for alleviating informal caregiver burden and their outcomes will be tabled under the different identified categories, including, but not limited to, the type of support strategies and interventions, the outcomes of the strategies and interventions used, and the challenges related to the implementation of these strategies and interventions [39]. Graphs and tables will be provided to enhance clarity. Existing gaps identified in the support strategies and interventions for informal caregivers in mental health, as well as the outcomes and challenges encountered will be identified to draw conclusions on the scoping review.

Ethics Approval

This scoping review forms part of a PhD project aimed at developing guidelines to alleviate caregiver burden among informal caregivers of persons with SMDs in South Africa, a transitional country. Ethical clearance (M200957) was obtained from the University of the Witwatersrand Human Research Ethics Committee.

Results

This protocol guides a scoping review aimed at identifying and describing the extent and type of evidence on the existing strategies for alleviating caregiver burden among informal caregivers of persons with SMDs in transitional countries. The initial search and screening of titles and abstracts commenced in September 2021, and this was followed by the second search and screening of titles, abstracts, and full texts from January to March 2022. A full-text review of the additional studies identified from the included studies was conducted from April to June 2022. Overall, 44 studies were identified for inclusion in the main study. The data were analyzed and written up for publication in September 2022. The scoping review article was submitted for consideration in a peer-reviewed journal, and the authors expect publication by the end of 2023. The results of this scoping review are useful to policy makers, mental health managers, health care professionals, and informal caregivers in mental health since they present the services and practical strategies that can be implemented to alleviate caregiver burden among informal caregivers. Additionally, existing gaps in the literature have been identified to inform future studies.

Discussion

Principal Findings

This protocol will guide a scoping review to identify and describe the extent and type of evidence on the existing strategies for alleviating caregiver burden among informal caregivers of persons with SMDs in transitional countries. There is acknowledgment of the unique role informal caregivers play in the care and management of people with SMDs within transitional countries and the subsequent burden arising from occupying this role [13,42,43]. A supported informal caregiver is likely to provide quality care, which is critical for the recovery of a person with a SMD [44]. The synthesis and analysis of existing literature on the various services and intervention strategies for alleviating caregiver burden forms a basis through which the development and implementation of these strategies can be facilitated within transitional countries where such evidence is lacking. Three researchers who have knowledge and experience in the JBI scoping review methodology developed the protocol. A librarian helped develop a comprehensive search strategy to allow for broad access to existing literature sources. To the best of our knowledge, there is no synthesis of literature in this area; this review therefore adds to the body of knowledge on the support for informal caregivers in mental health.

Limitations

The scoping review is limited to studies conducted in transitional countries; thus, the scope excludes studies conducted in developed countries, limiting the extent of the evidence on the strategies for supporting informal caregivers in mental health. Additionally, the review only includes studies conducted in English, creating a bias in the scope of the collated evidence. While the scoping review intends to include both peer reviewed and gray literature, it may not cover the entire existing evidence; as a result, studies in indexed databases may not be identified. The current review focuses on strategies for alleviating caregiver burden in SMDs, which locates it within the traditional Western medical health system paradigm. It is critical to acknowledge culture-bound syndromes, particularly within transitional countries; however, in other transitional countries, these syndromes are still classified under SMDs, which is within the Western medical terminology.

Conclusions

Informal caregivers are the backbone of recovery for persons with SMDs, and thus, strategies for alleviating their caregiver burden are critical, especially in resource-constrained transitional countries. With the growing research on the need for strategies aimed at supporting informal caregivers in their role, it is necessary to understand the extent of the burden and characteristics of these strategies in transitional countries. This scoping review will generate evidence to raise awareness on the various services and intervention strategies that can be developed and implemented to alleviate burden among informal caregivers in mental health within transitional countries.

Acknowledgments

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with support from the Developing Excellence in Leadership, Training, and Science in Africa (DELTAS Africa) program. The statements made and views expressed are solely the responsibility of the Fellow.

Data Availability

The data sets generated during and analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

All authors contributed to the development of the protocol. OS drafted the manuscript and search strategy. NGN and FA reviewed the draft manuscript and search strategy. OS incorporated the feedback from the authors for publication.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search terms.
[PNG File , 154 KB - resprot_v12i1e44268_app1.png]

Multimedia Appendix 2
Preferred Reporting Items for Systematic Reviews and Meta-analyses extension for scoping review (PRISMA-ScR) checklist.
[DOCX File , 23 KB - resprot_v12i1e44268_app2.docx]

Multimedia Appendix 3
Data extraction tables adapted from Peters et al [39].
[DOCX File , 20 KB - resprot_v12i1e44268_app3.docx]

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Abbreviations

CBT: cognitive behavioral therapy
JBI: Joanna Briggs Institute
NAMI: National Alliance on Mental Illness
NICE: National Institute for Health and Care Excellence
PCC: participants, concept, and context
PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Protocols
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews
SMD: severe mental disorder

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Protocol

The Role of Social Media for Identifying Adverse Drug Events Data in Pharmacovigilance: Protocol for a Scoping Review

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Abstract

Background: Adverse drug events (ADEs) are a considerable public health burden resulting in disability, hospitalization, and death. Even those ADEs deemed nonserious can severely impact a patient's quality of life and adherence to intervention. Monitoring medication safety, however, is challenging. Social media may be a useful adjunct for obtaining real-world data on ADEs. While many studies have been undertaken to detect adverse events on social media, a consensus has not yet been reached as to the value of social media in pharmacovigilance or its role in pharmacovigilance in relation to more traditional data sources.

Objective: The aim of the study is to evaluate and characterize the use of social media in ADE detection and pharmacovigilance as compared to other data sources.

Methods: A scoping review will be undertaken. We will search 11 bibliographical databases as well as Google Scholar, hand-searching, and forward and backward citation searching. Records will be screened in Covidence by 2 independent reviewers at both title and abstract stage as well as full text. Studies will be included if they used any type of social media (such as Twitter or patient forums) to detect any type of adverse event associated with any type of medication and then compared the results from social media to any other data source (such as spontaneous reporting systems or clinical literature). Data will be extracted using a data extraction sheet piloted by the authors. Important data on the types of methods used (such as machine learning), any limitations of the methods used, types of adverse events and drugs searched for and included, availability of data and code, details of the comparison data source, and the results and conclusions will be extracted.

Results: We will present descriptive summary statistics as well as identify any patterns in the types and timing of ADEs detected, including but not limited to the similarities and differences in what is reported, gaps in the evidence, and the methods used to extract ADEs from social media data. We will also summarize how the data from social media compares to conventional data sources. The literature will be organized by the data source for comparison. Where possible, we will analyze the impact of the types of adverse events, the social media platform used, and the methods used.

Conclusions: This scoping review will provide a valuable summary of a large body of research and important information for pharmacovigilance as well as suggest future directions of further research in this area. Through the comparisons with other data sources, we will be able to conclude the added value of social media in monitoring adverse events of medications, in terms of type of adverse events and timing.

International Registered Report Identifier (IRRID): PRR1-10.2196/47068

(JMIR Res Protoc 2023;12:e47068) doi:10.2196/47068

KEYWORDS

adverse event; pharmacovigilance; social media; real-world data; scoping review; protocol; review method; pharmacology; pharmaceutics; pharmacy; adverse drug event; adverse drug reaction

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Introduction

Adverse drug events (ADEs) cause significant harm by influencing morbidity and mortality and increasing the economic burden on the health care system [1,2]. Furthermore, patients may prematurely discontinue treatment or hesitate to begin new drug treatments due to ADEs, depriving them of the potential beneficial treatment [3]. Not all adverse drug reactions can be detected before a drug is marketed; therefore, continuous surveillance and monitoring of their safety are important.

Traditionally, postmarketing pharmacovigilance for drug safety signals has relied on spontaneous reporting to regulatory agencies. Conventional pharmacovigilance systems have many limitations; most notably, the underreporting of ADEs experienced [4-7]. The low rate of reporting to these agencies has prompted researchers to examine other potential data resources to fill the gap in reporting.

Social media data analysis and monitoring have been investigated for its application in health research including health outcomes research, disease surveillance, and patient perspectives [8-10]. However, the most commonly studied outcome is that of safety [8-10]. Indeed, social media has been identified as a content-rich resource of patient reports of ADEs [11]. Given the volume, velocity, and variety of social media big data across platforms, using social media as a type of supplementary data source may be invaluable to provide perspectives of patients who are otherwise not usually reached through traditional pharmacovigilance channels. The combined use of different data sources may increase the representativeness and comprehensiveness of ADE synthesis by including ADEs experienced and reported by social media users, part of whom can belong to medically underresourced communities that tend to be neglected in regulatory agencies' reporting programs.

Researchers began exploring the potential value of retrieving drug safety data from social media as early as 2010 [11]. It was believed that social media data could be used to identify new signals or signals earlier than conventional methods [12]. To cope with the enormous amounts of text-based information posted on social media, natural language processing (NLP) and machine learning (ML) methods for automatic detection of mentions are continually being developed [13,14]. These methods have to overcome many challenges, for instance, the language in social media is highly informal, and user-expressed concepts are often nontechnical, descriptive, and challenging to extract [15,16]. NLP has been particularly instrumental in overcoming some of the barriers to identify adverse event mentions [13,14]. However, while the technological methods have advanced, the use of social media in identifying adverse events has not been sufficiently demonstrated, and thus, the debate as to whether (and if so, how) social media can enhance pharmacovigilance is still not resolved.

While many papers have concluded that social media has the potential to improve pharmacovigilance, others have argued that this is not the case, including the well-known Web-Recognizing Adverse Drug Reactions study [17]. These papers have tended to rely on case studies and the selection of these case studies, and the comparative analysis used may have impacted the results. The question that needs answering may be more complex and nuanced than whether or not social media can be used in pharmacovigilance, necessitating not a binary yes or no answer. The question may rather be how and in what circumstances social media can improve pharmacovigilance and when social media is less appropriate or even not appropriate in pharmacovigilance.

In total, 7 systematic reviews have been published from 2015 to 2021 that attempted to evaluate the potential use of social media in pharmacovigilance by either focusing on detection, such as safety signals, or the frequency of adverse event reports [12,18-23] (Table 1). These reviews, despite including over a hundred papers, largely concluded that the research is still in its infancy and that more research is required. Some of the reviews, however, did highlight that social media was more appropriate for mild symptomatic ADEs and for gaining patient perspectives of salient events and their impact or identifying adverse event signals earlier than regulatory agencies. The methods used to extract data from social media are continuously improving, and many more studies have been published since these reviews were published. These reviews also focused on ADE detection for pharmacovigilance or extraction methods, but they did not compare the types of drugs or the specific adverse events for which social media may prove more successful.

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Table 1. Systematic or scoping reviews of the use of social media for pharmacovigilance.

Author (year)	Date searched	Included studies, n	Studies with comparison	Main focus of included studies	Review conclusions
Golder et al (2015) [18]	2015	51	29	ADE[a] detection	• Higher frequency of adverse events was found in social media and that this was particularly true for symptom-related and mild adverse events. Reliability or validity not thoroughly evaluated.
Lardon et al (2015) [23]	2014	24	6	ADE detection (11 papers) and extraction methods (13 papers)	• Detection: studies failed to accurately assess the completeness, quality, and reliability of the data. • Extraction: no study proposed a generic approach to easily adding a new site or data source. Additional studies are required.
Sarker et al (2015) [19]	2015	22	10	Extraction methods	• Annotated data are publicly available in a still very limited amount. As indicated by the promising results obtained by recent supervised learning approaches, there is a strong need to make such data available to the research community.
Tricco et al (2018) [12]	May 2016	70	19	ADE detection	• Social media is potential to supplement data from regulatory agency databases; it can capture less frequently reported AEsb and identify AEs earlier than official alerts or regulatory changes, but the use and validity of the data source remain understudied.
Convertino et al (2018) [20]	December 2017	38	38	ADE signal detection	• Poorer information quality as compared with spontaneous reporting databases. Rarely allows the evaluation of causal relationships. Proto signals had the potential of anticipating prespecified known signals in only 6 studies. Social media is not currently recommended for pharmacovigilance.
Pappa and Stergioulas (2019) [21]	Early 2018	100	Not reported	AE signal detection	• Developed new classifications of social data sources and taxonomies for social data, identified key challenges, and extracted new insights in terms of potential for practical applications.
Lee et al (2021) [22]	January 2021	14	14	ADE signal detection	• Assessed the time interval between signals detected on social media and regulatory authority action, revealing that most studies reported that meaningful signals could be identified 3 months to 9 years before regulatory authorities take action.

[a]ADE: adverse drug event.

[b]AE: adverse event.

We propose to undertake an updated analysis that allows us to validate the necessary conditions and methods to harness adverse event reports from social media as a complement to other sources. Given the wide breadth of studies conducted in this area and our objective to summarize the literature, we propose to undertake a scoping review using the Arksey and O'Malley [24] framework to answer the following questions: (1) what recent research has been undertaken into the detection of adverse events from social media at a large scale? (2) What types of drugs and adverse events have been studied to date with what findings? (3) How do the types and frequency of ADEs identified from social media differ from those identified from other sources, such as regulatory data or clinical trials? (4) What extraction methods are used to identify ADE data from social media and what impact may this have on the results?

Methods

Study Design

This scoping review protocol is reported in line with the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) checklist [25]. The inclusion and exclusion criteria present in Textbox 1 will be used in order to provide an understanding of the volume of the research in this area.

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Textbox 1. Inclusion and exclusion criteria for studies on identifying adverse drug events data from social media.

Inclusion criteria

- Population
  - Any person (including pregnant women and young and older adults) with or without any condition or disease type (chronic or acute) states that they have taken any drug intervention (including vaccines) used in diagnosis, treatment, or prevention (as defined by the Food and Drug Administration [FDA]) and experienced an adverse event.
- Interventions
  - Any type of social media defined as any computer-mediated tools for users to create, share, or exchange information, ideas, or content via text, images, and audio (eg, message postings, pictures, and videos) in web-based communities and networks (such as message boards, social networks, patient forums, Twitter, Reddit, blogs, and Facebook).
- Comparators
  - Any data source other than social media (such as spontaneous reporting systems of the FDA or the Medicines and Healthcare products Regulatory Agency, clinical trials, or summary of product characteristics) is eligible as a comparator.
- Outcomes
  - Primary outcomes: Data on the type and frequency of adverse drug events (such as muscle aches, headaches, or rashes) are required from social media and at least one other data source.
  - Secondary outcomes: Data on the application of the adverse drug events (such as pharmacovigilance and hypothesis generation).
- Study design
  - Any type of assessment.
- Limits
  - Published 2017 onward in English, Spanish, French, or Chinese or in any language with an English translation available.

Exclusion criteria

- Population
  - Reports by health care professionals.
  - People reporting diagnosis, treatment, or prevention with a nonmedical intervention (such as medical devise, surgery, supplements, or natural remedy). People not reporting experience of an adverse event.
- Interventions
  - Simple, nonsocial internet-based interventions (ie, web 1.0).
  - Studies using social media to recruit participants.
- Comparators
  - No comparison undertaken to any nonsocial media data source.
- Outcomes
  - We are concerned with the properties of interventions under normal use. We therefore will not consider papers where the primary aim was to assess events such as intentional and accidental poisoning (ie, overdose), drug abuse, errors, or noncompliance. Drug-drug interactions are not eligible where they are the primary objective of the paper due to the different techniques required in identifying interactions as opposed to adverse events under normal use.
  - Papers focused on identifying patient perspectives of adverse events (such as fear or impact on quality of life) and papers on subsequent patient behaviors as a result of adverse events are also ineligible.
- Study design
  - Discussion papers, purely technical papers, and papers that only contain examples of posts from social media.
- Limits
  - Anything published before 2017 and anything published since 2017 that is not in English, Spanish, French, or Chinese or in another language with no available English translation.

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Search Methods

In total, 11 databases covering a range of topic areas, including health and medical sciences, nursing, information and computer science, and gray literature will be searched. We will also search Google Scholar; however, due to the immense number of hits this will retrieve, we will only sift the first 300 records [26]. Searching databases may not retrieve all relevant available studies as there are delays in indexing, they may not have been indexed adequately (particularly where the database does not index using full text or uses automated methods) or they may have a lack of detail in titles and abstracts. We will, therefore, conduct handsearching of the most common journal titles from a previous review [18]: Drug Safety; Journal of Medical Internet Research, and Pharmacoepidemiology and Drug Safety (Textbox 2).

Textbox 2. Sources to be searched.

Databases

- ACM Digital Library
- Conference Proceedings Citation Index—Science
- Emerging Sources Citation Index
- Embase
- IEEE Xplore
- Library, Information Science & Technology Abstracts
- MEDLINE
- OpenDissertations
- ProQuest Dissertations & Theses: United Kingdom and Ireland
- PsycINFO
- Science Citation Index Expanded

Internet search engine

- Google Scholar (first 300 records will be sifted)

Handsearching of journals

- *Drug Safety* (2017-2023)
- *Journal of Medical Internet Research* (2017-2023)
- *Pharmacoepidemiology and Drug Safety* (2017-2023)

The database search strategies will have 2 facets—"social media" and "adverse events" (see Multimedia Appendix 1 for draft search strategy in Ovid MEDLINE, which will be translated for other databases and interfaces as necessary).

A publication date restriction of 2017 onward will be placed on the searches as this review updates 7 previous reviews [12,18-23], the most recent of which is more focused than our review [22]. No language restrictions will be placed on the searches, although financial and logistical restraints will not allow translation from all languages; therefore, this review will be likely to focus more on papers published in English, Spanish, French, or Chinese and other languages for which an English language translation is available. We will also undertake forward and backward citation searching by checking the references of all included studies and forward citation searching using CitationSearcher to identify papers that have cited key papers we identify. Searches will be rerun before conducting the final analysis to retrieve any further includable studies.

The results of all the searches will be entered into an EndNote (Clarivate) library with the duplicates removed. Title and abstract screening will be undertaken independently by 2 reviewers in Covidence (Covidence) with any disagreements resolved by discussion or if necessary, a third reviewer. Full-text screening will again be undertaken in Covidence by 2 independent reviewers.

Data Extraction

A data extraction spreadsheet will be designed and piloted for this review. The form will record study characteristics of existing papers on using social media data to identify potential ADEs. Two reviewers will extract descriptive data independently, with findings compared and agreed. The following data will be extracted from included studies if available: (1) details on the type of social media platform used; (2) details on the primary aim of the study; (3) brief details of the methods used to extract data from social media including which drugs or adverse events are searched for and how and for what time period; (4) whether the study distinguished between personal and nonpersonal mentions, and whether it accounted for the influence of bots or nonindividual accounts; (5) the type and frequency of adverse events data identified for each drug and which drug; (6) comparator data sources along with any comparisons of the data collected; (7) conclusions of the original investigators; and (8) finally, whether code or annotated or raw data are made available by the authors.

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As this is a scoping review, we will not assess the methodological quality (risk of bias assessment) of the studies or conduct any evidence synthesis. Nevertheless, we will summarize an array of NLP and ML (artificial intelligence) methods used for this task and synthesize the studies' self-reported performances and if available, scalability per method.

Ethical Considerations

Since the scoping review methodology consists of reviewing and collecting data from publicly accessible materials, this study does not require ethics approval.

Results

Unlike a systematic review, a scoping review does not "synthesize" the evidence or aggregate results from the included studies [24]. Although this scoping review does not involve raw data synthesis summary across all studies to be reviewed, descriptive statistics with each study as a unit of analysis will be used. Tables, graphs, and charts will be provided when applicable regarding the range of social media platforms evaluated, the frequency and types of adverse events and drugs identified, the types of methods used (including data collection), the types of data comparisons made, the data source compared to, as well as the results and conclusions. We will also require some form of analytic framework. The literature will be organized by type of comparison made (eg, spontaneous reporting systems, clinical literature, and summary of product characteristics). We will also seek to summarize our analysis by type of social media, type of adverse events, and type of ADE detection or extraction methods if applicable.

We will compare our results of studies from 2017 onward to the results of the 7 systematic reviews identified. Any discrepancies between the results will be investigated in terms of methods used and any other possible explanations.

Discussion

Principal Findings

Through the use of ML and NLP techniques, the automatic detection and extraction of ADEs from social media have been the focus of much research to refine the methods, including shared task competitions in the community [27]. This review will update and build upon previous reviews in this rapidly evolving field. Especially, the contributions to the current literature will be surrounding 2 contextual questions we asked in the beginning, namely, how and in what circumstances social media can improve pharmacovigilance and when social media may be less appropriate or even not appropriate in pharmacovigilance. Therefore, part of this review's objective is to suggest to fellow researchers the optimal use of social media data for ADE detection. Without suggesting that social media is a better or worse approach to pharmacovigilance than alternative data sources, we set this review to assist future research in this area in improving study design, validity, scalability, and reproducibility. We will also provide evidence-based discussions on the conceptual challenges we have identified through this review, the possible solutions to them, and future research directions.

We will review the latest research allowing us to elucidate how recent advances in the fields of ML and NLP are being used to advance discoveries in this research area. We will also address any patterns in the findings related to the methods and drugs and adverse events studied. Additionally, the results will objectively inform the debate regarding the value of social media in identifying adverse events and bring us nearer to a consensus. By systematically evaluating the comparisons made to other sources, we will be able to identify the similarities and differences in what is reported in social media, and by extension, identify the burden of ADEs from the patient's perspective. We will also highlight any gaps in the evidence and priorities for future research.

We will also discuss any issues that may have risen in terms of access to data subsequent to the time at which the studies were conducted. This will be particularly relevant given the new restrictions some social media platforms have placed on their data or application programming interface availability. For example, whether the data from the selected social media platforms are still available to access, and whether it is free to access or based on a commercial license. We will also discuss our results in the context of user privacy concerns, commercial interests, and barriers to social media research. This review is expected to be of particular use to regulatory agencies, and researchers wanting to prioritize research on suspected adverse events or monitor adverse events.

Strengths and Limitations

There are 2 main strengths to this study. First, different experts in the fields of NLP, ML, systematic review methodology, and information science will participate in the planning and development of the study. Second, we have already identified 7 previous systematic reviews or scoping reviews on which we can build our methods. The main limitations of our study are the exclusion of studies published in languages other than English, French, Spanish, or Chinese and the use of Anglo-dominated databases. This is also a fast-paced area of research meaning that the applicability of our findings may change over time.

Conclusions

This scoping review protocol outlines steps that will guide our scoping review. This review will also identify and map studies that indicate the value of social media in detecting adverse events and improving pharmacovigilance. The results of this study may help inform current recommended practices and the future direction of research in this area.

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Data Availability

The full search strategies for all the databases, the data extraction sheets, and a full list of the included and excluded studies will be made available in the completed scoping review.

Authors' Contributions

SG, KO, YW, and GGH contributed to the development of the protocol. SG was in charge of developing the search strategy. SG, KO, YW, and GGH will develop the rest of the tasks of the scoping review.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Draft search strategy for Ovid MEDLINE.
[DOCX File , 16 KB - resprot_v12i1e47068_app1.docx]

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Abbreviations

ADE: adverse drug event
ML: machine learning
NLP: natural language processing
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews

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Protocol

Data Quality– and Utility-Compliant Anonymization of Common Data Model–Harmonized Electronic Health Record Data: Protocol for a Scoping Review

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Abstract

Background: The anonymization of Common Data Model (CDM)–converted EHR data is essential to ensure the data privacy in the use of harmonized health care data. However, applying data anonymization techniques can significantly affect many properties of the resulting data sets and thus biases research results. Few studies have reviewed these applications with a reflection of approaches to manage data utility and quality concerns in the context of CDM-formatted health care data.

Objective: Our intended scoping review aims to identify and describe (1) how formal anonymization methods are carried out with CDM-converted health care data, (2) how data quality and utility concerns are considered, and (3) how the various CDMs differ in terms of their suitability for recording anonymized data.

Methods: The planned scoping review is based on the framework of Arksey and O'Malley. By using this, only articles published in English will be included. The retrieval of literature items should be based on a literature search string combining keywords related to data anonymization, CDM standards, and data quality assessment. The proposed literature search query should be validated by a librarian, accompanied by manual searches to include further informal sources. Eligible articles will first undergo a deduplication step, followed by the screening of titles. Second, a full-text reading will allow the 2 reviewers involved to reach the final decision about article selection, while a domain expert will support the resolution of citation selection conflicts. Additionally, key information will be extracted, categorized, summarized, and analyzed by using a proposed template into an iterative process. Tabular and graphical analyses should be addressed in alignment with the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) checklist. We also performed some tentative searches on Web of Science for estimating the feasibility of reaching eligible articles.

Results: Tentative searches on Web of Science resulted in 507 nonduplicated matches, suggesting the availability of (potential) relevant articles. Further analysis and selection steps will allow us to derive a final literature set. Furthermore, the completion of this scoping review study is expected by the end of the fourth quarter of 2023.

Conclusions: Outlining the approaches of applying formal anonymization methods on CDM-formatted health care data while taking into account data quality and utility concerns should provide useful insights to understand the existing approaches and future research direction based on identified gaps. This protocol describes a schedule to perform a scoping review, which should support the conduction of follow-up investigations.

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KEYWORDS

EHR; electronic health record; data quality; common data model; data standard; data privacy models; data anonymization

Introduction

The anonymization of health data is a key approach for preserving patient anonymity during the secondary use of relational (ie, tabular) electronic health record (EHR) data [1]. However, to overcome the challenges related to the considerable heterogeneity in clinical data source systems (eg, due to diverse medical data coding frameworks, heterogeneous definitions of laboratory data values, or disparate setting- or task-dependent metadata), the use of common data models (CDMs) has been proposed and discussed [2]. Converting structured or unstructured source data to CDM standards helps to reach an understanding of commonly harmonized data into collaborative network research [3] and hence facilitates the cross-institutional exchange of medical data by using appropriate CDM metadata [2]. By approaching this, anonymization of CDM-converted EHR data promises patient privacy–secured sharing and analysis of harmonized data, which requires specific data anonymization components.

Extensive efforts describing the conduction [1,4-13] of data anonymization exist, and it is essential to differentiate and properly address 3 major aspects when dealing with relational data anonymization (anonymization of tabular data). This includes privacy models, data transformation models, and data utility models for assessing and ensuring the fitness of anonymous data for use. In terms of proposed privacy models, the k-anonymity privacy model [1,7] is one of the most widely used models. It consists of placing at least *k* patients in an equivalence class with the same patient-identifying data element values (so-called quasi-identifiers; eg, birthdate and zip code), so that the probability of reidentifying a patient becomes *1/k*. The value of the threshold *k* is determined by the data owner (eg, a hospital department sharing the data) depending on the size of the data and privacy protection level [1]. Because of the limitations of this model for fully protecting sensitive information (eg, patient health insurance and treating medical doctor), the *l*-diversity privacy model [1,8] was proposed. This ensures that at least *l*-"well-represented" values for sensitive data elements are presented within each equivalent class. Furthermore, additional data privacy models including the *t*-closeness privacy model [9] (for preventing linkage of the record and data elements) and the differential privacy model [10] (for preventing table linkage and probabilistic attacks) were also addressed. The strengths and limitations of these models were discussed in depth and extensively by Majeed and Lee [1] and Lei et al [11]. For implementing the data privacy models on data, a corresponding data transformation model is required, which may include a variety of technical operations. These comprise, for instance, generalization (by replacing some data values with parent values), suppression (implementing data record, value, or cell suppression), permutation (partitioning data records into dissociated groups), perturbation (partly or totally replacing original data with synthetic data), or anatomization (dissociating the relationships among patient-identifying data elements) [1,11,13]. Implementing the privacy- and data transformation models mentioned above leads to high impact on the quality of anonymous data in terms of utility. Nonetheless, utility models including metrics such as accuracy or error rate, the *F*-measure, precision, and recall have been proposed to assess the utility of anonymous data for special purposes [1]. Furthermore, the weighted certainty penalty, generalized information loss, the global loss penalty, relative error, or information theoretical metrics have also been recommended to estimate the utility of anonymous data for general purposes [1,12,13]. In addition, further evidence-based recommendations on how to assess and report on EHR data quality have been proposed [14-18] (eg, 3×3 data quality assessment guidelines [16], the framework of Kahn et al [15], or that of Fox et al [18]), and tools for data anonymization, transformation, and utility models have been proposed and discussed [4].

Among others, by using CDM standards in the clinical context, related source data can be more efficiently reused, organized, described, validated, searched, and queried [2]. International standards such as Fast Health Interoperability Resources (FHIR) [19] and CDM frameworks including the Informatics for Integrating Biology & the Bedside (i2b2) TranSMART CDM [20], the Observational Medical Outcomes Partnership's Observational Health Data Sciences and Informatics (OMOP OHDSI) CDM [21], the Patient-Centered Outcomes Research network (PCORNet) CDM [22], and the Clinical Data Interchange Standards Consortium's (CDISC's) Operational Data Model (ODM) [23] therefore gained widespread attention in the scientific community in the last decades. For instance, the Medical Informatics in Research and Care in University Medicine (MIRACUM) consortium of the German Medical Informatics Initiative [24,25] presents an illustrative deployment of some of these CDMs.

While the interoperable conversion and querying of source EHR data into multiple CDM formats has been demonstrated [26], it is nonetheless worth noting that an entire transformation of health care data from the original data format to CDMs, or from one CDM to another one, is barely practicable [2]. This leads to potential challenges related to data completeness in the context of the use of CDM-converted health care data. Moreover, the relational anonymization of CDM-converted data by using the k-anonymity or *l*-diversity privacy models might build an interesting lever to allow patient privacy–preserved sharing of harmonized health care data as shown by Almeida et al [6] and in a recent study by Pitoglou et al [27]. Nonetheless, the anonymization of health care data can disproportionally affect the quality of resulting anonymous data sets due to

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information loss, and hence their suitability for medical research, as investigated by Langarizadeh et al [28] and Ferrão et al [29]. Especially in the case of CDM-converted data, anonymization may affect both cardinalities and completeness requirements of the respective CDM data models. This can be observed, for example, by the suppression of mandatory fields or by generalization through entering of ranges (eg, age range) into fields that only allow numeric values (not interval). Moreover, once CDM-converted data have been anonymized, it would be relevant to ensure whether the generated anonymous data may at all be stored in conformity with the CDM structures, or if it would be necessary to adapt the CDM specifications (eg, through some slicing in FHIR specifying both the exact and range-based anonymous age). This indicates the need for a thorough investigation of the suitability of CDM databases to record anonymized data in a quality-compliant format.

This raises problems related to how anonymization-assisted preservation of patient privacy in using or sharing of CDM-harmonized health care data with a reflection of anonymous data utility is addressed, and whether CDMs differ in terms of their ability to record anonymized data. Despite the large range of studies performed in the fields of relational data anonymization [1,4-13], CDM standards [19-22,30,31], and frameworks for medical data quality assessments [15-17,32], little attention has been paid to an extensive review of the existing literature addressing these questions. Reviewing the existing evidence concerning these issues might aid in identifying, describing, and understanding how relational data are anonymized, evaluated, and documented into specific CDM databases and to what extent the utility and quality of the obtained anonymous data are addressed. There could be some gaps in data utility research to be considered when anonymizing specific CDM-transformed clinical data for specific data mining scenarios such as predictive analysis or machine learning for improving health care quality. The evidence and identified gaps should serve as support for further investigations in the field of utility-compliant anonymizing of harmonized health care data.

Given this research scope, we plan to conduct a scoping review that aims to identify and describe (1) the current status and challenges of implementing formal privacy models (eg, k-anonymization, *l*-diversity, differential privacy, or *t*-closeness) on CDM databases (including i2b2, OMOP, CDISC, PCORnet, and FHIR), (2) the strategies used there to ensure the quality and utility of anonymized data, and (3) the differences in multiple CDM standards in relation to their suitability to record and document anonymized data.

Methods

Ethical Considerations

No ethics approvals are required since the planned study is only concerned with the assessment of the literature within a specific domain. Hence, no sensitive patient-identifying data will be processed.

Schedule

For conducting this scoping review study, we will use the methodological framework of Arksey and O'Malley [33], which recommends an analysis process based on 5 steps: step 1—identifying the research question, step 2—identifying the relevant studies, step 3—selecting studies, step 4—extracting and charting data, and step 5—collating, summarizing, and reporting the results. Below, we describe the methodology's stepwise concepts and the planned and already implemented in-between steps.

Step 1—Identification of the Research Questions

As a prelude, an initial exploration of the literature was manually carried out to gain an overview of the issues regarding data quality and data anonymization as well as to determine the appropriate keywords to be included. A search was undertaken using a combination of the search terms "data quality," "anonymi*ation," and "deidentification," and by querying the literature platforms PubMed and Web of Science Core Collection. The most relevant articles were selected and analyzed upon full-text reading. To form the final research questions, we additionally addressed an explicit focus on the most internationally adopted CDMs (including i2b2 TranSMART, OMOP OHDSI, PCORnet, and CDISC ODM) and the FHIR standard. The research questions were derived by considering both the research objectives stated above.

In doing so, the planned scoping review investigation will address the following 3 research questions: how are formal anonymization methods carried out with CDM-converted health care data and which challenges are observed? How are data quality and utility concerns considered during the anonymization of CDM-converted health care data? How does anonymization affect the specifications of different CDM data models, and which differences are observable in the CDMs regarding their suitability for recording and documenting anonymized data?

Step 2—Identifying the Relevant Studies

Overview

To identify the most relevant articles matching the research questions, we will explore a large set of articles by taking into account the literature databases to be used, language considerations, key concepts for retrieving the literature items, and construction of the search query. Additionally, here we show the designed query we tentatively implemented on Web of Science.

Literature Databases

The literature search should be performed by querying the literature engines PubMed and Web of Science Core Collection. These literature search engines cover an extended range of medical and health informatics–related studies, and the latter additionally includes the fields of biomedical sciences and engineering, which are of high relevance for retrieving relevant data anonymization of related papers. Similar review projects considered the Web of Science Core Collection database as well [34,35].

Article Language Considerations

We will include articles published in English for facilitating the selection and screening of identified literature items.

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Key Concepts and Search Terms

To efficiently find suitable articles, we have proposed 3 categories (concepts) of search terms, reflecting each of the relevant investigation domains of the study objective. The proposed set of search terms can be extended and documented, if necessary, during the literature extraction process.

While the first category (A) relates to data anonymization methods, the second one (B) captures the field of medical CDMs and data standards, and the last one (C) covers the domain of data quality and utility assessment. Table 1 provides an overview of the key concepts and the explicit search terms.

Table 1. Key concepts.

Key concepts	Search terms	Investigation domains
A	• Deidentification/ De-identification • k-anonymity • t-closeness • l-diversity • Differential privacy • De-identified • Data masking • Data generalization • Data perturbation • Data permutation • Data suppression • Data anatomization	Formal data anonymization
B	• i2b2 • TranSMART • OMOP • OHDSI • CDISC ODM • PCORnet • FHIR	Medical research CDMs[a] or data standard
C	• Data quality • Data accuracy • Data utility • Data fidelity • Fitness for use • Fitness for purpose	Assessment of quality or utility of data

[a]CDM: common data model.

Search Query Construction

Based on the defined key concepts and search terms, we built a search string by combining the domain of formal data anonymization with those of CDM standards and data quality by using corresponding “AND” and “OR” Boolean operators.

The final search string is built using the following key concept combination:

Search query = A AND (B OR C)

The proposed citation search query is documented in Multimedia Appendix 1.

Step 3—Study Selection

After the collection of articles meeting the eligibility criteria, a diligent selection process will be followed. This will be based on independent reviews by 2 experts, while a third expert will ensure that a compromise is achieved in case of selection conflicts. Two major stages will constitute this paper selection process.

First, a general screening review based on the title and abstracts of each article will be carried out in order to exclude all references not useful to achieve the targeted research objective.

In the second phase, a content review will be conducted via a full-text reading of each remaining citation included, to determine their final eligibility by considering their relevance for responding to the research questions. In addition, we will document and provide a list of all excluded articles in a complementary appendix.

These 2 phases will be implemented independently by the 2 citation reviewers by using the free web-based application Rayyan [36]. This application supports the traceable management of the inputs of the different contributing stakeholders and transparent conflict management [36]. Thus, any conflict regarding the final decision about the inclusion or exclusion of a reference will be discussed and decided under consideration of the both reviewers’ viewpoints and input from the independent expert; this will be followed by interactive literature explorations within the Rayyan platform in a nonblinded form. Finally, a detailed description of the literature selection process and conflict management will be provided using a PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) flowchart [33].

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Step 4—Extracting and Charting the Data

We will extract from each of the selected articles all relevant information (including metadata) and record these into a template-based documentation, so that a subsequent descriptive analysis (including information visualization) can be performed by using an appropriate statistics package. A general template has been provisionally proposed (see Table 2) considering approaches from similar review projects [34]. Updates on this template will be iteratively and collaboratively integrated, in accordance with requirements during the review, taking into account the concrete relevance for responding to the research objectives.

Table 2. Template to extract key information form the included articles.

Metadata	Description
Citation details	Name of first author and coauthors, digital object ID, and journal name
Year of publication	Year of publication of the article in a valid year format (eg, YYYY)
Study type	Use case, framework development, evaluation, etc
Study location	Continent, country, or city hosting the study
Institute	Research institution of the first author
Funding source	Public, industry, or missing
Aims of the study	Objective of the study
Methodology (including technical implementation)	Methods, techniques, models, framework, or approach implemented to achieve the research aims
Study populations (if described in the article)	Targeted research cohort, built on the basis of corresponding eligibility criteria
Summary of outcome measures	Summarizing the study results
Limitations or gaps	Strength and limitations of the study
Important results associated with research question 1	Description of formal relational data anonymization processes on CDM[a]-converted health care data
Important results associated with research question 2	Description of existing evidence to address anonymous data quality and utility: description of implemented strategies and description of observable gaps
Important results associated with research question 3	Description of differences in CDMs regarding how data anonymization modifies the specified table's granularity and how anonymized data are there recorded

[a]CDM: common data model.

Step 5—Collating, Summarizing, and Reporting the Results

We will carry out a narrative quantitative analysis of findings using a 2-way analytical framework [33], which will include a descriptive and thematic-based approach. This will generate comprehensive results, outlining the current evidence and research gaps related to the research questions. In doing so, we will first describe the implementation of data anonymization on FHIR- and CDM-formatted data, which include i2b2 TranSMART, OMOP OHDSI, PCORnet, and the CDISC. This will be accompanied by an analysis of deployment to ensure strategies for quality and utility assessment of anonymous data obtained, to present the current state of the art, and identify open research aspects. In addition, the effects of data anonymization on CDM specifications will be presented and discussed.

Furthermore, corresponding comparison tables and graphs (PRISMA-ScR model–oriented) will be presented. Second, the findings will be organized, analyzed, and discussed in accordance with the 2 research questions. A thematically oriented illustration will be additionally generated.

Results

Following the methodological elements, outlined in steps 2 (identifying the relevant studies) and 3 (study selection), we were able to generate a set of search keywords and design an appropriate literature search query. Furthermore, a tentative execution of this query on Web of Science resulted in the detection of 507 matching publications. In alignment with the presented methodology, these articles will be interactively scrutinized by the experts in order to gain relevant information regarding the research questions. This preparatory work will support the transparent execution of this scoping review study. In doing so, we intend to implement the full extraction of the literature and to proceed with the full execution of the review study by the end of the fourth quarter of 2023.

Discussion

During the planning stage, we designed and implemented a query allowing the identification of potentially eligible publications, in order to investigate the current status of evidence regarding data quality–preserving relational anonymization of

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CDM-converted health care data. The considerable amount of eligible literature obtained from Web of Science showed that useful information could be found to describe how relational data anonymizations are performed in the context of CDM-transformed health data and to what extent the quality and utility of obtained anonymous data are addressed in consideration of CDM specifications.

However, a more detailed analysis of these citations should support (1) investigating how the several privacy models, data transformation techniques, and utility models [1] are applied on CDM-converted health data, and (2) document the findings into the CDM databases. Moreover, the obtained set of literature could cover a wide range of current formal anonymization techniques, technologies related to Extraction-Transformation-Load processes for converting source data to the CDM format, or numerous data quality assessment frameworks. This requires a meticulous literature analysis strategy to include the most pertinent citations, which should enable answering the research questions. By following up on the systematic review of Fernández-Alemán et al [37], revealing the necessity of complementary work concerning the security and privacy of EHR data systems, and the investigation by Majeed and Lee [1], presenting the quantification of both utility and privacy of anonymized sensitive data for some scenarios as a challenging task, this scoping review should serve as a response to these questions, capture and describe the current evidence about utility-preserving anonymization of tabular CDM-based health data, and help identify potentially existing research gaps. This aspect is adequately in line with some of the main goals for conducting a scoping review as proposed by Arksey and O'Malley [33], which are to summarize and disseminate research findings and to identify research gaps in the existing literature.

Nevertheless, the planned scoping review might include some restrictions. Regarding the scope of the intended literature review, just a focus on formal data privacy models should be addressed, including, for instance, the k-anonymization, *l*-diversity, differential privacy, and *t*-closeness privacy models. Moreover, only the relational (table-based) data anonymization methods should be approached due to their frequent application for anonymizing tabular data in the medical context. A follow-up review including further anonymization frameworks such as social network– or graph-based data anonymization [1] in the clinical context could be subsequently initiated. However, to address the four-eyes principle on the proposed literature search string early, we will proceed with the validation of the search query by a librarian from the licensed library of Medical Faculty Mannheim, Heidelberg University, in order to correspondingly mitigate any potential conceptual or technical issues in the query.

Among other aspects, it is pertinent to point out that the anticipated definition of the study's specifications is an essential approach for limiting decision conflicts and providing transparency in the completion of this literature review. This should foster a reproducible and transferable methodology and disseminate reliable insights necessary to enhance and to better understand the approaches for preserving patient privacy and data quality in the secondary use of harmonized health care data.

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Data Availability

Scripts for the technical implementation of citation visualization based on statistical software such as RStudio [38], as well as files containing the collected literature and other study documents, will be made available on an open publicly available repository such as Zenodo [39]. These data will be available in an anonymized format for facilitating more transparency and for offering the possibility to reproduce the literature extraction, charting, and analysis processes.

Authors' Contributions

All authors commented on the draft and approved the final manuscript version.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Revised literature search query.
[TXT File , 1 KB - resprot_v12i1e46471_app1.txt]

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Abbreviations

CDISC: Clinical Data Interchange Standards Consortium
CDM: common data model
EHR: electronic health record
FHIR: Fast Healthcare Interoperability Resources
i2b2: Informatics for Integrating Biology & the Bedside
MIRACUM: Medical Informatics in Research and Care in University Medicine
ODM: Operational Data Model
OHDSI: Observational Health Data Sciences and Informatics
OMOP: Observational Medical Outcomes Partnership
PCORnet: Patient-Centered Outcomes Research network
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews

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Protocol

Assessing the Well-Being at Work of Nurses and Doctors in Hospitals: Protocol for a Scoping Review of Monitoring Instruments

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Abstract

Background: Well-being at work can be defined as "creating an environment to promote a state of contentment which allows an employee to flourish and achieve their full potential for the benefit of themselves and their organisation." In the health care context, well-being at work of nurses and doctors is important for good patient care. Moreover, it is strongly associated with individual- and organization-level consequences. Relevant literature presents models and concepts of physical, mental, and social well-being. This study uses the 6 elements of the job demands-resources (JD-R) model to interpret well-being at work (job demands, job resources, personal resources, leadership, well-being, and outcomes) as part of a Netherlands Federation of University Medical Hospitals program to find ways to improve and monitor health care professionals' well-being in Dutch hospitals. Many instruments exist to measure well-being at work in terms of population, setting, and other aspects. An overview of available and eligible instruments assessing and monitoring the well-being of nurses and doctors is currently missing.

Objective: We will perform a scoping review aiming to provide an overview of validated instruments assessing and monitoring the well-being of nurses and doctors at work.

Methods: We will perform a search of published literature in the following databases: Medline, Embase, and CINAHL. Studies will be eligible if they (1) assess well-being at work of nurses and doctors employed in hospitals; (2) describe an evaluation of an instrument or review an instrument; (3) measure well-being at work or aspects of well-being at work according to the elements of the JD-R model, and (4) were published in English from 2011 onwards. Title/abstract screening according to the eligibility criteria will be followed by full-text screening. Data extraction of included studies will be conducted by 3 reviewers independently. Reviewers will use standardized data extraction forms that include study characteristics, sample characteristics, measurement instrument details, and psychometric properties. The analysis will be descriptive. When synthesizing the data, a distinction will be made between comprehensive instruments and common instruments.

Results: This scoping review identifies instruments that have been developed and validated for monitoring the well-being of nurses and doctors at work. Studies were searched between September and December 2021 and screened between December 2021 and May 2022. A total of 739 studies were included.

Conclusions: Timely screening of well-being at work may be beneficial for individual health care workers, the organization, and patients. There is often a substantial gap and mismatch between employer perceptions of well-being and well-being interventions. It is important to develop and implement suitable interventions adapted to the needs of nurses and doctors and their health or other problems. Well-being screening should be timely to gain insight into these needs and problems. Moreover, to

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determine the effectiveness of well-being interventions, measurement is mandatory. The results will be critical for organizations to select a monitoring instrument that best fits the needs of employees and organizations.

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KEYWORDS

well-being at work; well-being; well being; health care professionals; doctors; nurses; monitoring; assessment; measure; scale; instruments; scoping literature review; occupational health

Introduction

Well-being at work for nurses and doctors employed in hospitals is an important condition for achieving effective, safe, and good patient care [1-3]. Moreover, well-being at work is strongly associated with serious consequences at an individual level, such as poor work-life balance [3,4], obesity [3], reduced quality of life of the health care worker [3,5], substance abuse, and suicide [3,6]. At an organizational level it is related to high staff turnover [3,6], absenteeism [3,7], and high health care costs [3].

The Chartered Institute of Personnel and Development defines well-being at work as "creating an environment to promote a state of contentment which allows an employee to flourish and achieve their full potential for the benefit of themselves and their organisation" [8]. Well-being comprises psychological well-being, physical well-being, and social well-being [9]. Also, a variety of published literature presents models and concepts of well-being. Deci et al [10] reported the self-determination theory. The self-determination theory suggests that both employees' performance and their well-being are affected by the type of motivation they have experienced [10]. For medical students, the "coping reserve tank" was illustrated [11]. This is a coping reservoir that can be replenished or drained by various factors, such as stress, mentorship, time demands, and support [11]. Potential outcomes were described as resilience versus burnout [11]. Schaufeli [12] developed the job demands-resources model (JD-R model) facilitating communication about "work and well-being." In essence, the JD-R model integrates 2 processes: the stress process, which is sparked by excessive job demands and lack of resources, and a motivational process, which is triggered by abundant job resources and may lead to positive outcomes, such as organizational commitment, intention to stay, and work performance [12]. Thus, different components, including resources (eg, support, development opportunities, team atmosphere), demands (eg, stress, workload, conflicts), and personal resources (eg, leadership, intrinsic motivation, resilience), contribute to positive well-being (eg, job satisfaction) or negative well-being (eg, burnout). Abundant resources and reasonable demands will result in positive outcomes (eg, performance, commitment); the reverse will lead to negative outcomes (sickness, absenteeism) [12].

Measuring well-being at work among doctors and nurses is not easy, since this multidimensional concept encompasses diverse elements [8,13]. Instruments to measure well-being at work vary in specific professions [14] and specific settings [15] or include only one or two aspects of well-being at work [12,16]. This study is part of a program of the Netherlands Federation of University Medical Hospitals (NFU) about finding ways to improve and monitor health care professionals' well-being in Dutch hospitals. Strikingly, there is often a substantial gap and mismatch between employer perceptions of well-being and well-being interventions [8]. It is important to develop and implement suitable interventions adapted to the needs of nurses and doctors and their health and other problems [8,17]. Well-being screening should be timely to gain insight into these needs and problems. Moreover, measurement to determine the effectiveness of well-being interventions is mandatory [8,17].

To summarize, when hospitals assess and monitor the well-being of nurses and doctors with validated instruments, they can, in a timely manner, design and start tailored interventions to prevent negative well-being in the workplace, thereby contributing to sustainable employability and quality of care [18,19]. An overview of available and eligible instruments assessing and monitoring the well-being of nurses and doctors is currently missing. Scoping reviews are helpful to explore broad, complex, and heterogeneous literature [20]. For this study, a scoping review is planned to obtain an overview of the field of well-being instruments and identify its breadth.

Methods

Aim

This scoping review aims to identify instruments monitoring the well-being at work of nurses and doctors working in hospitals. The Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) [21] and the 6-stage framework of Arksey and O'Malley [22] for conducting scoping reviews will be used.

Information Sources

A priori, possible previous reviews of this topic were checked. Published articles will be searched in the following electronic databases: Medline, Embase and CINAHL. To avoid including outdated literature, we will include only articles published after 2011 [23]. To identify instruments that are applied in present clinical practice, preference is given to more-frequent, lower-volume searches to fit the exponentially changing field of health care [24,25]. Gray literature will not be used as an information source.

Search Strategy

The search strategy was created by AB with assistance by an information specialist and the research team. Several terms derived from the research aim were identified to develop search strings to find relevant literature. Keywords and Medical Subject Heading (MeSH) terms related to the domain (nurses and doctors

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working in hospitals), the determinants (instruments for monitoring), and the outcome (well-being at work) will be used. The first draft of the search string was based on 5 relevant, previously published "golden bullets," sample articles that had to be found in the data set. Afterwards, a test data set was screened by the first author to optimize the search string. After this screening, the data set turned out to be too large (more than 17,000 studies), so to ensure the feasibility of the study it was decided to make the search more specific. For the search strategy see Tables 1, 2, and 3.

Table 1. Search strategy for Medline.

ID	Query	Results
1	("Health care professionals" or Caregivers or "Health care providers" or Practitioners or Doctor or nurse? or physician? or resident? or "health care worker" or "health staff").ti. or exp *"physicians"/ or exp *"Medical staff"/ or *"Residents"/ or exp *"Nurses"/ or exp *"Nursing Staff"/	461,194
2	(instrumentation or methods).fs. or exp "psychometrics"/ or psychometr*.ti,ab. or clinimetr*.tw. or clinometr*.tw. or exp "Health Status Indicators"/ or survey?.ti,ab. or score.ti,ab. or scale.ti,ab. or subscale.ti,ab. or (measurement adj 3 instrument).ti,ab. or subscale*.ti,ab. or item-discriminant.ti,ab. or interscale correlation*.ti,ab. or "ceiling effect."ti,ab. or "floor effect."ti,ab. or "Item response model."ti,ab. or Rasch.ti,ab. or "Differential item functioning."ti,ab. or "item bank."ti,ab. or (item adj3 (correlation* or selection* or reduction* or bank)).ti,ab.	6,142,766
3	Validation Studies.pt. or exp "observer variation"/ or observer variation.ti,ab. or exp "reproducibility of results"/ or exp "discriminant analysis"/ or valid*.ti,ab. or (cronbach* adj3 (alpha or alphas)).ti,ab. or interrater.ti,ab. or inter-rater.ti,ab. or intrarater.ti,ab. or intra-rater.ti,ab. or intertester.ti,ab. or inter-tester.ti,ab. or intratester.ti,ab. or intra-tester.ti,ab. or interobserver.ti,ab. or inter-observer.ti,ab. or intraobserver.ti,ab. or intraobserver.ti,ab. or interexaminer.ti,ab. or inter-examiner.ti,ab. or intraexaminer.ti,ab. or intra-examiner.ti,ab. or interindividual.ti,ab. or inter-individual.ti,ab. or intraindividual.ti,ab. or intra-individual.ti,ab. or kappa.ti,ab. or kappa?s.ti,ab. or kappas.ti,ab. or ((replicab* or repeated) and (measure or measures or findings or result or results or test or tests)).ti,ab. or concordance.ti,ab. or (intraclass and correlation*).ti,ab. or (uncertainty and (measurement or measuring)).ti,ab. or "standard error of measurement."ti,ab. or sensitiv*.ti,ab.	2,822,376
4	exp Burnout, Psychological/ or exp Personal Satisfaction/ or exp Mental Health/ or (satisfaction or well-being or fulfilment or burnout or ((psychological or mental) adj health) or thriving or environment or ethic*).ti,ab,kf.	1,122,990
5	1, 2, 3, and 4	3301

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Table 2. Search strategy for Embase.

ID	Query[a]	Results
S1	S17 AND S10 AND S4 AND S3	1329
S2	S17 AND S10 AND S4 AND S3	229
S3	S9 OR S8 OR S7 OR S6 OR S5	46,447
S4	S25 OR S24 OR S23 OR S22	421,434
S5	TI(satisfaction or well-being or fulfilment or burnout or ((psychological or mental) N1 health) or thriving or environment or ethic*)	145,799
S6	AB(satisfaction or well-being or fulfilment or burnout or ((psychological or mental) N1 health) or thriving or environment or ethic*)	36,566
S7	(MH “Mental Health”)	44,106
S8	(MH “Job Satisfaction”) OR (MH “Personal Satisfaction”)	35,259
S9	(MH “Burnout, Professional”)	12,506
S10	S15 OR S14 OR S13 OR S12 OR S11	502,496
S11	TI(valid* or (cronbach* N3 (alpha or alphas)) or interrater or inter-rater or intrarater or intra-rater or intertester or inter-tester or intratester or intra-tester or interobserver or inter-observer or intraobserver or intraobserver or interexaminer or inter-examiner or intraexaminer or intra-examiner or interindividual or inter-individual or intraindividual or intra-individual or kappa or kappa?s or kappas or ((replicab* or repeated) and (measure or measures or findings or result or results or test or tests)) or concordance or (intraclass and correlation*) or (uncertainty and (measurement or measuring)) or “standard error of measurement” or sensitiv*)	80,499
S12	AB(valid* or (cronbach* N3 (alpha or alphas)) or interrater or inter-rater or intrarater or intra-rater or intertester or inter-tester or intratester or intra-tester or interobserver or inter-observer or intraobserver or intraobserver or interexaminer or inter-examiner or intraexaminer or intra-examiner or interindividual or inter-individual or intraindividual or intra-individual or kappa or kappa?s or kappas or ((replicab* or repeated) and (measure or measures or findings or result or results or test or tests)) or concordance or (intraclass and correlation*) or (uncertainty and (measurement or measuring)) or “standard error of measurement” or sensitiv*)	417,988
S13	(MH “Kappa Statistic”)	17,505
S14	(MH “Reproducibility of Results”)	67,821
S15	(MH “Interrater Reliability”)	27,493
S16	S25 OR S24 OR S23 OR S22 OR S21	82,033
S17	S20 OR S19 OR S18	753,761
S18	TI(clinimetr* or clinometr* or psychometr* or survey? or score or scale or subscale or (measurement N3 instrument) or subscale* or item-discriminant or interscale correlation* or “ceiling effect” or “floor effect” or “Item response model” or Rasch or “Differential item functioning” or “item bank” or (item N3 (correlation* or selection* or reduction* or bank)))	12,483
S19	AB(clinimetr* or clinometr* or psychometr* or survey? or score or scale or subscale or (measurement N3 instrument) or subscale* or item-discriminant or interscale correlation* or “ceiling effect” or “floor effect” or “Item response model” or Rasch or “Differential item functioning” or “item bank” or (item N3 (correlation* or selection* or reduction* or bank)))	694,621
S20	(MH “Psychometrics”) OR (MH “Measurement Issues and Assessments”)	32,107
S21	AB(“Healthcare professionals” or Caregivers or “Healthcare providers” or Practitioners or Doctor or nurse? or physician? or resident? or “healthcare worker” or “health staff”)	556,739
S22	TI(“Healthcare professionals” or Caregivers or “Healthcare providers” or Practitioners or Doctor or nurse? or physician? or resident? or “healthcare worker” or “health staff”)	296,467
S23	(MM “Nurses+”)	141,674
S24	(MM “Medical Staff, Hospital+”)	3977
S25	(MM “Physicians+”)	64,766

[a]The following abbreviations are applicable to the queries: T1: title; N1: adjacency of 1 word; AB: abstract; MH: mesh heading; MM: major mesh.

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Table 3. Search strategy for CINAHL.

ID	Query[a]	Results
S1	S17 AND S10 AND S4 AND S3	1329
S2	S17 AND S10 AND S4 AND S3	229
S3	S9 OR S8 OR S7 OR S6 OR S5	46,447
S4	S25 OR S24 OR S23 OR S22	421,434
S5	TI(satisfaction or well-being or fulfilment or burnout or ((psychological or mental) N1 health) or thriving or environment or ethic*)	145,799
S6	AB(satisfaction or well-being or fulfilment or burnout or ((psychological or mental) N1 health) or thriving or environment or ethic*)	36,566
S7	(MH “Mental Health”)	44,106
S8	(MH “Job Satisfaction”) OR (MH “Personal Satisfaction”)	35,259
S9	(MH “Burnout, Professional”)	12,506
S10	S15 OR S14 OR S13 OR S12 OR S11	502,496
S11	TI(valid* or (cronbach* N3 (alpha or alphas)) or interrater or inter-rater or intrarater or intra-rater or intertester or inter-tester or intratester or intra-tester or interobserver or inter-observer or intraobserver or intraobserver or interexaminer or inter-examiner or intraexaminer or intra-examiner or interindividual or inter-individual or intraindividual or intra-individual or kappa or kappa?s or kappas or ((replicab* or repeated) and (measure or measures or findings or result or results or test or tests)) or concordance or (intraclass and correlation*) or (uncertainty and (measurement or measuring)) or “standard error of measurement” or sensitiv*)	80,499
S12	AB(valid* or (cronbach* N3 (alpha or alphas)) or interrater or inter-rater or intrarater or intra-rater or intertester or inter-tester or intratester or intra-tester or interobserver or inter-observer or intraobserver or intraobserver or interexaminer or inter-examiner or intraexaminer or intra-examiner or interindividual or inter-individual or intraindividual or intra-individual or kappa or kappa?s or kappas or ((replicab* or repeated) and (measure or measures or findings or result or results or test or tests)) or concordance or (intraclass and correlation*) or (uncertainty and (measurement or measuring)) or “standard error of measurement” or sensitiv*)	417,988
S13	(MH “Kappa Statistic”)	17,505
S14	(MH “Reproducibility of Results”)	67,821
S15	(MH “Interrater Reliability”)	27,493
S16	S25 OR S24 OR S23 OR S22 OR S21	82,033
S17	S20 OR S19 OR S18	753,761
S18	TI(clinimetr* or clinometr* or psychometr* or survey? or score or scale or subscale or (measurement N3 instrument) or subscale* or item-discriminant or interscale correlation* or “ceiling effect” or “floor effect” or “Item response model” or Rasch or “Differential item functioning” or “item bank” or (item N3 (correlation* or selection* or reduction* or bank)))	12,483
S19	AB(clinimetr* or clinometr* or psychometr* or survey? or score or scale or subscale or (measurement N3 instrument) or subscale* or item-discriminant or interscale correlation* or “ceiling effect” or “floor effect” or “Item response model” or Rasch or “Differential item functioning” or “item bank” or (item N3 (correlation* or selection* or reduction* or bank)))	694,621
S20	(MH “Psychometrics”) OR (MH “Measurement Issues and Assessments”)	32,107
S21	AB(“Healthcare professionals” or Caregivers or “Healthcare providers” or Practitioners or Doctor or nurse? or physician? or resident? or “healthcare worker” or “health staff”)	556,739
S22	TI(“Healthcare professionals” or Caregivers or “Healthcare providers” or Practitioners or Doctor or nurse? or physician? or resident? or “healthcare worker” or “health staff”)	296,467
S23	(MM “Nurses+”)	141,674
S24	(MM “Medical Staff, Hospital+”)	3977
S25	(MM “Physicians+”)	64,766

[a]The following abbreviations are applicable to the queries: T1: title; N1: adjacency of 1 word; AB: abstract; MH: mesh heading; MM: major mesh.

Inclusion Criteria

Studies will be eligible if they (1) assess well-being of nurses and doctors working in hospitals; (2) describe an evaluation of an instrument or review an instrument; (3) measure well-being at work or aspects of well-being at work according the elements of the JD-R model and (4) were published in English in or after 2011.

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Exclusion Criteria

Studies will be excluded if they (1) describe only the development of the instrument but not its evaluation or (2) have a sample that consists only of students, without employees.

Data Management

Records and data will be managed by using the software Endnote (version 20.1; Clarivate Analytics), Rayyan (Rayyan Systems), EPPI-Reviewer (EPPI-center) and Mendeley Reference Manager (version 2.590; Elsevier).

Selection Process

Study screening and selection will be conducted independently by AB, KvdB, and NA using Rayyan. After the removal of duplicate records identified by the search strategy, articles will be screened on titles and abstracts for the inclusion and exclusion criteria. To ensure consistent screening, the first 100 articles will be pilot-screened by all 3 researchers until consensus is reached. After validation, the hits will be allocated to 1 of the 3 researchers. Eligible articles will then be assessed on their full text. To ensure consistent full-text screening, the first 18 articles will be pilot-screened by all 3 researchers until consensus is reached. After validation, the full texts will be subdivided among the 3 researchers. Justification for study inclusion and exclusion will be reported. Inclusion reasons and exclusion reasons will be marked with a label. Uncertainty in selection and the data extraction process will be resolved by consensus [12]. The JD-R model will be used to assess if the reported instruments appropriately measured well-being or aspects of well-being at work (job demands, job resources, engaged leadership, personal resources, employees' well-being, outcomes) [12]. The energy compass of the JD-R model includes all aspects of well-being at work and is applicable to different employees in different settings [12]. Included instruments will be categorized according to the 6 domains of the JD-R model. The domain "job demands" contains the categories "qualitative job demands," "quantitative job demands," and "organizational demands." The domain "job resources" contains the categories "social resources," "work resources," "organizational resources," and "developmental resources." The domain "engaged leadership" contains the categories "inspiring," "strengthening," and "connecting." The domain "personal resources" contains the categories "resilience," "self-efficacy," "optimism," flexibility," "setting one's own limits," "productivity," "goal direction," and "self-development." The domain "well-being" contains the positive and negative categories "burnout," "work engagement," "psychological distress," "boredom," "sleep problems," and "job satisfaction." The domain "outcomes" contains the categories "commitment," "employability," and "performance." Study search and selection will be illustrated using the PRISMA flow diagram.

Data Collection Process

Data extraction and full-text screening will be conducted at the same time. AB, KvdB, and NA will independently use the standardized data extraction form, which will be developed a priori in Excel (Microsoft Corp). The elements that will be charted for each article are (1) study characteristics, including year, authors, country, study ID, and study aim (validation study, measuring variables, both, other); (2) sample characteristics, including type of health care professionals (nurses, doctors, other), setting (hospital, partly hospital), and sample size; (3) measurement instrument, including the name of the instrument, main construct measured, subconstructs measured, job demands, job resources, leadership, personal resources, well-being, and outcomes; and (4) psychometric properties, including validity, reliability, responsiveness, and quality references. The aim of this study is not to evaluate psychometric properties but include only the evaluated instruments. Therefore, information about psychometric properties (whether validity, reliability, and responsiveness are tested) will be extracted. When no psychometric properties are reported, the references mentioned for evaluation will be extracted. Table 4 shows further details.

All instruments meeting the inclusion criteria will be extracted from studies. If more than one instrument has been described, instrument details will be extracted separately for each instrument. The data extraction form will be tested by AB, KvdB, and NA on 18 studies to ensure adequacy of the extraction. Disagreements will be discussed, and the form will be refined, if necessary, after the pilot phase with the 18 studies.

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Table 4. Defining variables.

Item	Definition
1. Study characteristics	
Year	Picklist • Years from 2011, up to and including 2021
Authors	Last name, initials
Country	Country where participants are recruited
Study ID	Unique code to identify the study, found in Eppi-reviewer
Study aim	Picklist • Validation study: the study tests or evaluates instruments • Measuring variables: the study uses instruments to measure variables • Both: studies that both validate instruments and measure variables • Other: studies in which the above is not described (eg, study protocols)
2. Sample characteristics	
Health care professionals	Picklist • Nurses (exclusively or mixed with other types of participants): all kinds of nurses providing direct patient care in hospitals (eg, intensive care nurses and pediatric nurses) • Doctors (exclusively or mixed with other types of participants): all kinds of doctors providing direct patient care in hospitals (eg, residents, medical assistants, and medical specialists in various specialties) • Both: studies in which both nurses and doctors are described
Setting	Picklist • Hospital: full sample works in hospital • Partly in hospital: a part of the sample works in a hospital; any kind of hospital will be included (eg, psychiatric hospitals, general hospitals, and academic hospitals)
Sample size	Full sample size: if only part of the sample works in a hospital, the full sample needs to be reported
3. Measurement instrument	
Name of instrument	Full name of the instrument, including any abbreviations (eg, Professional Quality of Life Scale, version 5; ProQol-5).
Main construct measured	Main construct intended to be measured (eg, professional quality of life)
Subconstructs measured	Subthemes intended to be measured (eg, compassion satisfaction, secondary traumatic stress, burnout)
JD-R[a] demands	Picklist • Job demands: the outcome fits with “job demands” according to the JD-R model. • N/A[b]: the outcome does not fit with “job demands” according to the JD-R model
JD-R resources	Picklist • Job resources: the outcome fits with “job resources” according to the JD-R model • N/A: the outcome does not fit with “job resources” according to the JD-R model
JD-R leadership	Picklist • Engaged leadership: the outcome fits with “engaged leadership” according to the JD-R model • N/A: the outcome does not fit with “engaged leadership” according to the JD-R model
JD-R well-being	Picklist • Employee well-being: the outcome fits with “employee well-being” according to the JD-R model • N/A: the outcome does not fit with “employee well-being” according to the JD-R model
JD-R outcomes	Picklist • Outcomes: the outcome fits with “outcomes” according to the JD-R model • N/A: the outcome does not fit with “outcomes” according to the JD-R model

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Item	Definition
4. Psychometric properties	
Validity	Picklist • Valid: the instrument is tested and proven valid in the study (eg, content validity, construct validity, criterion validity) [26] • N/A: validity is not tested in the study
Reliability	Picklist • Reliable: the instrument is tested and proven reliable in the study (eg, internal consistency, reliability, measurement error) [26]
Responsiveness	Picklist • Responsiveness: the instrument is responsive (the ability of the instrument to detect relevant changes in health status when they exist) [26] • N/A: responsiveness is not tested in the study
Quality reference	Only for reference(s) to the original evaluation study; formatted as author; year

[a]JD-R: job demands-resources.

[b]N/A: not applicable.

Risk of Bias

Evaluating evidence quality is not applicable for scoping reviews [22,27]. AB, KvdB, and NA are junior researchers with relatively little experience in conducting scoping reviews on the topic of the well-being of nurses and doctors, but they are supervised by senior researchers with ample experience. The variety of backgrounds, opinions, experiences, and perspectives within the interdisciplinary research team supports self-reflectivity about the subjective values, biases, and inclinations of the researchers. In addition to the medical doctors, other health care professional types are also represented within the research team and have experience with the well-being topic. The first author is a nurse and KvdB has a physiotherapy background. Likewise, LH specializes in the methodology of reviews.

Data Analysis

This scoping review will determine the size and nature of the evidence base for instruments evaluating well-being at work. The analysis will be descriptive and findings will be assimilated, synthesized, and described. The plan is to summarize validated well-being instruments in tables and figures according to the elements of the JD-R model. Additionally, we will report how often instruments have been extracted, which aspects of well-being are measured, and which types of health care professional are targeted. Synthesizing the data, a distinction will be made between comprehensive instruments and common instruments. The more JD-R domains an instrument encompasses, the more comprehensive (measuring entire well-being) the instrument will be considered to be. Most common instruments are instruments occurring frequently. Results will help readers interpret and choose fitting instruments.

Ethical Considerations

This study does not require ethical approval since it is a literature review.

Results

Studies were searched between September 2021 and December 2021. Studies were screened between December 2021 and May 2022. A total of 739 studies were included. Thereafter, data extraction and full text screening were conducted at the same time. The protocol was submitted for publication in October 2022. Before submission, we carried out our search and started screening and extracting data from relevant articles but had no insight into the overall data and had not yet performed data analysis.

Discussion

This scoping review gives an overview of instruments that have been developed and validated for monitoring the well-being of nurses and doctors at work.

Published research shows a great variety in concepts and measures of well-being at work in terms of target population (professions), settings, and aspects of well-being at work. However, a critical, overarching analysis of these concepts and measures is missing in the scientific literature. There is often a substantial gap and mismatch between employer perceptions of well-being and well-being interventions [8]. It is important to develop and implement suitable interventions adapted to the needs of nurses and doctors and their health or other problems [8,17]. Timely screening of well-being is necessary to gain insight into these needs and problems. Moreover, it is necessary to determine the effectiveness of well-being interventions [8,17].

Our study has some limitations that need to be considered. First, the articles will be divided among 3 researchers because of the amount of data. Consequently, data screening and extraction will be performed once. In order to avoid bias, pilot sets will be screened until consensus on eligibility criteria and JD-R classification is reached. Additionally, an audit trail is used to describe and link thoughts, doubts, and methodological choices.

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This study is distinctive in that it does not focus specifically on one instrument but provides an overview of many instruments. By using the JD-R model, we are able to determine which instruments fit in the construct of well-being. By categorizing the instruments according to the elements of the JD-R model, the reader will be supported in selecting instruments appropriate to their context.

Data Availability

All data generated or analyzed during this study will be included in the published article or its supplementary information files.

Authors' Contributions

AB designed the research protocol and will carry out the data screening, extraction, and analysis. KvdB provided feedback on the protocol, including the methodological choices, will carry out data screening and extraction, and will be involved in the analysis and writing process. NA provided feedback on the protocol and will contribute to the screening and selection phase. LH, GW, AF, and MvdL provided critical feedback on revisions and methodological choices and approved the final version of the paper for publication. All the authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflicts of Interest

None declared.

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Abbreviations

JD-R: job demands-resources
MeSH: Medical Subject Heading
NFU: Netherlands Federation of University Medical Hospitals
PRISMA-ScR: Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews

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Protocol

Changes in Documentation Due to Patient Access to Electronic Health Records: Protocol for a Scoping Review

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Abstract

Background: Internationally, patient-accessible electronic health records (PAEHRs) are increasingly being implemented. Despite reported benefits to patients, the innovation has prompted concerns among health care professionals (HCPs), including the possibility that access incurs a "dumbing down" of clinical records. Currently, no review has investigated empirical evidence of whether and how documentation changes after introducing PAEHRs.

Objective: This paper presents the protocol for a scoping review examining potential subjective and objective changes in HCPs documentation after using PAEHRs.

Methods: This scoping review will be carried out based on the framework of Arksey and O'Malley. Several databases will be used to conduct a literature search (APA PsycInfo, CINAHL, PubMed, and Web of Science Core Collection). Authors will participate in screening identified papers to explore the research questions: How do PAEHRs affect HCPs' documentation practices? and What subjective and objective changes to the clinical notes arise after patient access? Only studies that relate to actual use experiences, and not merely prior expectations about PAEHRs, will be selected in the review. Data abstraction will include but will not be limited to publication type, publication year, country, sample characteristics, setting, study aim, research question, and conclusions. The Mixed Methods Appraisal Tool will be used to assess the quality of the studies included.

Results: The results from this scoping review will be presented as a narrative synthesis structured along the key themes of the corpus of evidence. Additional data will be prepared in charts or tabular format. We anticipate the results to be presented in a scoping review at a later date. They will be disseminated at scientific conferences and through publication in a peer-reviewed journal.

Conclusions: This is the first scoping review that considers potential change in documentation after implementation of PAEHRs. The results can potentially help affirm or refute prior opinions and expectations among various stakeholders about the use of PAEHRs and thereby help to address uncertainties. Results may help to provide guidance to clinicians in writing notes and thus have immediate practical relevance to care. In addition, the review will help to identify any substantive research gaps in this field of research. In the longer term, our findings may contribute to the development of shared documentation guidelines, which in turn are central to improving patient communication and safety.

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KEYWORDS

electronic health record; patient-accessible electronic health record; patient portal; electronic portal; scoping review; patient access; documentation change; natural language processing; patient-clinician relationship; online record access; review method; library science; librarian

Introduction

Background

Electronic health records (EHRs) are common in almost all areas of health care and are an indispensable tool for saving and sharing information between health care professionals (HCPs) [1]. A more recent development focuses on opening clinical notes or entire EHRs for patients [2] and their proxies [3-7]. These so-called patient-accessible electronic health records (PAEHRs) are well established internationally, especially in Scandinavian countries and the United States, but are not yet fully embedded even among high-income countries [8-11]. An essential part of patients' online record access (ORA) through a PAEHR is access to the clinical free-text notes written by clinicians. Giving patients access to these notes is often referred to as "open notes" in the literature [2].

Research shows that HCPs are often skeptical about giving patients ORA [12,13], and many of their concerns relate to how PAEHR use might impact their clinical routines, workload, and patient safety [11,13-20]. Regarding documentation, many HCPs anticipate changing the content and tone of their notes when patients have ORA, which, it is feared, might ultimately compromise the integrity of their records [11,19,21]. For example, a tendency to avoid technical terminology to facilitate patient understanding could have a negative impact on multidisciplinary communication within the team [21-24]. Also, some HCPs feel that they may be less detailed or less candid in their documentation and need to omit information or even start using parallel documentation (a "shadow record") to protect patients from information that they consider as potentially harmful or disruptive [14,15,20,25-27]. In contrast, however, there are other voices that assume the introduction of PAEHRs could make notes more patient-friendly by using a more patient-centered and less stigmatizing language and could also stimulate communication between HCP and patients [22].

As Blease et al [11] noted, while most studies explore subjective changes after introducing open notes, there are few studies demonstrating objective changes, and where these studies exist, they offer inconclusive results [22,28,29] and are often hampered by methodological limitations. There is a growing body of qualitative research [30] as well as research using natural language processing approaches to explore the language used by clinicians in their records, including the potential for stigmatizing language [31]. However, it is unclear from these studies whether access affects, or indeed, even improves the quality of recordkeeping with the knowledge that patients may read what the clinician has written [31]. Despite the increasing scientific interest and debate within medicine, little is currently known about how far sharing EHRs with patients affects clinical documentation [11,32].

Study Objectives

The objective of the proposed scoping review is to identify, collate, and evaluate possible changes of documentation after implementing patient access to EHRs. The scoping review focuses exclusively on studies including postimplementation data, such as experiences of the stakeholders (HCPs, patients, policymakers and designers of EHRs or patient portals), while excluding expectations prior to implementation.

As outlined, HCPs are often reluctant, or even critical of giving patients ORA, and expect an additional documentation burden through their introduction. To address these obstacles to implementation, it is timely and appropriate to review the existing body of literature and summarize what is currently known regarding PAEHR documentation change. This scoping review is intended to increase knowledge for stakeholders about the kinds of documentation changes that might arise with PAEHRs, illuminate how this relates to documentation practices, provide recommendations for future clinical practice, and identify further research gaps.

Methods

Scoping Review

Compared with the systematic review method, which is guided by a strongly focused research question, a scoping review aims to open up the spectrum of the available evidence on a relatively new field of research, so that its breadth and depth become visible [33]. We will conduct a scoping review following the framework proposed by Arksey and O'Malley [33]. Their approach consists of the following five stages: (1) identifying the research question, (2) identifying the relevant studies, (3) selecting eligible studies, (4) collecting data, and (5) summarizing data and synthesizing results. The review will be reported following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) Extension for Scoping Reviews checklist [34,35]. Any subsequent modification of the study design will be highlighted in the final publication, which is aimed at being published in a JMIR journal.

Stage 1: Identifying the Research Question

Through discussions with the research team, we decided on the following research questions: Does clinical documentation change after the introduction of ORA for patients? If so, what objective and subjective changes arise after PAEHR implementation? By objective, we mean such differences that can be demonstrated by a direct quantifiable comparison of clinical notes before and after implementation of PAEHRs. By

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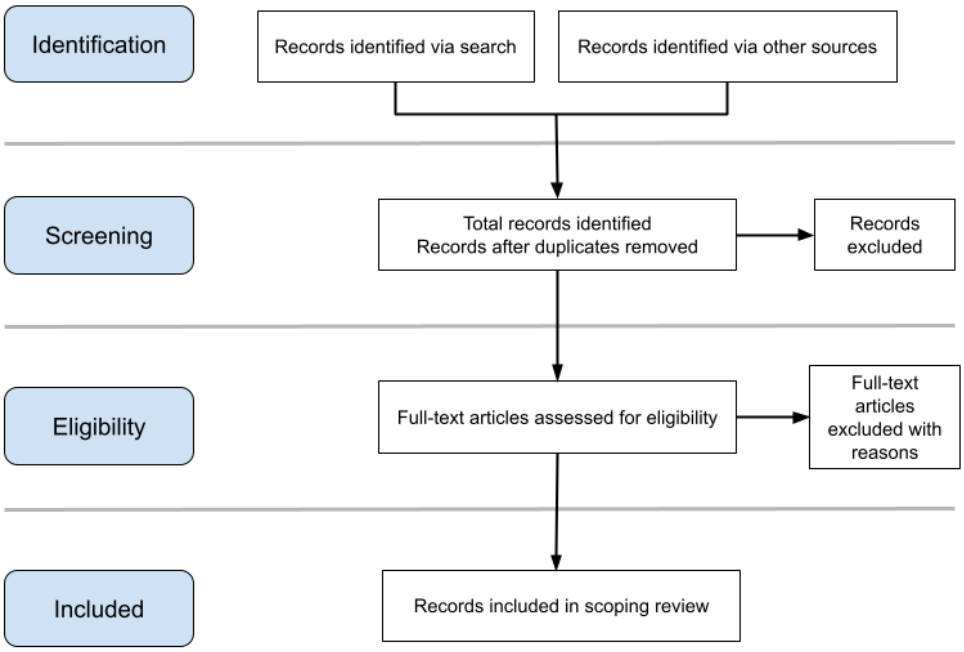
subjective, we refer to clinicians' perceptions of how they write their notes after PAEHR implementation. In the context of this scoping review, we define PAEHR to be any channel in which patients have electronic access to their patient record (eg, through the internet or via patient portals and apps).

Stage 2: Identifying Relevant Studies

The process of identifying relevant studies is outlined in the flowchart (see Figure 1). The deduplication process will be carried out by an experienced research librarian at Uppsala University, Sweden. In advance, the research team will conduct a rigorous manual search to obtain a basic overview of the available evidence and to refine the scope of the review as well as the search strategy as Popay et al suggest [36].

The literature search in the following 4 databases will be conducted by the librarian Malin Barkelind from Uppsala University: APA PsycInfo, CINAHL, PubMed, and Web of Science Core Collection. The search strategy was developed in collaboration with the Uppsala University library and consists of three key concepts: (1) EHRs, (2) sharing EHRs with patients, and (3) changes in documentation, which were combined with the Boolean AND (Textbox 1). The search terms were adapted according to different databases. The complete search string is stored in Multimedia Appendix 1. In addition, we will include individual relevant records from the hand search conducted previously.

Figure 1. Flowchart describing the multistage screening process.



Textbox 1. Key concepts of the search strategy.

Electronic health record search string

- "inpatient portal*" OR "open notes" OR opennotes OR PAEHR OR "patient portal*" OR "patient web portal*" OR "Electronic Health Records"
- "clinic notes" OR "clinical notes" OR "progress notes" OR "doctors notes" OR EHR OR "health record*" OR "health care record*" OR "medical record*" OR "mental health notes" OR "patient record*" OR "psychiatric notes" OR "psychotherapy notes" OR "visit notes"

Sharing electronic health records with patients search string

- "guardian access" OR "parental access" OR "parents access" OR "patient access*" OR "patients access*" OR "patient online access" OR "patients online access" OR "proxy access" OR "shared medical record*" OR "shared health record*"

Documentation changes search string

- "Language"[Mesh] OR "Attitude"[Mesh] OR "Comprehension"[Mesh]
- accura* OR ambigu* OR characteristics OR characters OR clarity OR content* OR completeness OR comprehend* OR comprehensibl* OR comprehension* OR correctness OR dialog* OR express* OR directness OR impression* OR inaccura* OR incomplete* OR incomprehen* OR incorrectness* OR intelligib* OR interpret* OR intuitive* OR language OR length OR linguistic* OR misconception* OR misinterpret* OR misread* OR misunderstand* OR monolog* OR negative* OR pattern* OR positive* OR pronoun* OR readab* OR style* OR simplicity OR terminolog* OR transparen* OR truthful* OR unambigu* OR understand* OR untruthful* OR veracity OR wordcount* OR words OR writing
- OR attitude* OR emotion* OR experience* OR perception* OR satisfact*
- OR adopt* OR alter* OR censor* OR change* OR changing OR difference* OR introduc* OR implement* OR modif* OR postimplement*

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Stage 3: Selecting Eligible Studies

Inclusion and Exclusion Criteria

Inclusion and exclusion criteria (Textbox 2) were defined by the entire research team and will be applied in the study selection process. Due to the limited number of publications available on the subject, there will be no restrictions on the study type. As PAEHRs are only gradually being implemented in various countries, we will refrain from any location restrictions. A wide variety of approaches exist to make clinical notes available to patients electronically [37]. We will include all studies examining the actual implementation and the use of patient ORA regardless of the digital device used (eg, web-based and mobile apps). Varieties of studies exploring the sharing of hard copies of patients' clinical records will be excluded.

Textbox 2. Inclusion and exclusion criteria.

Inclusion criteria

- Study design: all study types
- Publication: original, peer-reviewed work including empirical data published between January 1, 2005, and June 30, 2023 in English
- Study location: all medical disciplines, all health care settings, no location restrictions
- Study participants: patients and health care professionals of all ages
- Studies that examine actual use by stakeholders and their experiences with patient-accessible electronic health records

Exclusion criteria

- Paper-based, disc, or USB sharing of patients' records
- Papers without empirical data (eg, comments, editorials, news)
- Gray data (websites, tweets, blogs)
- Studies that exclusively investigate expectations about patient-accessible electronic health records

Study Selection Process

We will use Rayyan Software (Rayyan Systems, Inc) for conducting a collaborative, blinded title and abstract screening [38]. All members of the research team will participate in this process and each record of the result set will be evaluated by at least 2 people. Discrepancies will be discussed, taking the full texts of the corresponding studies into account. In case of disagreements that cannot be resolved, a third reviewer will be involved and entrusted with the decision of including or excluding the study.

Stage 4: Collecting Data

After selecting the studies to include, metadata (eg, title, authors, and publication year) of the remaining records will be exported and summarized in a Google Sheets (Google LLC) spreadsheet for further processing. To extract and organize relevant data from included studies, the spreadsheet will be extended by the following and other parameters based on the studies' full text: country, study design, sample, characteristics of study participants (eg, gender, age, ethnicity, type of stakeholder), treatment setting and medical specialty, and study purpose. Data extraction will be performed involving all members of the research team. Furthermore, the first author will check the data extraction for correctness and completeness. To assess the quality and methodological rigor of the studies, the Mixed Methods Appraisal Tool (MMAT) will be used [39]. Two researchers will independently conduct the MMAT grading of all studies and consent their results. If no agreement can be reached, a third independent researcher will be consulted.

Stage 5: Summarizing Data and Synthesizing Results

Narrative Synthesis

Study results will be extracted from the full texts by the lead author and summarized in (1) a reduced format within a textbox, providing an overview of the findings from all included studies, and (2) a detailed version for narrative synthesis. The latter will be analyzed independently by at least 2 researchers using thematic analysis [40]. Objective and subjective changes of HCPs' documentation practices after the introduction of patient ORA will be used as guiding deductive themes and are informed by the research question but may change in the analytical process. As Levac et al [35] suggest, we aim to identify patterns and relationships within and across studies to identify potential factors influencing documentation after PAEHR implementation. In assessing the methodological rigor of the studies, we also envisage the potential to identify research gaps; for example, we predict there may be a preponderance of survey research investigating clinicians' perceptions about documentation changes rather than studies investigating objective markers of any such documentation changes. While the former studies may be useful, they may be compromised by responder biases. Results will then be discussed and approved by the entire research team.

Assessing the Robustness of the Synthesis

As Popay et al [36] state, the robustness of the narrative synthesis depends on the quality of included studies as well as on the trustworthiness of the synthesis. In order to minimize bias, we will conduct the study quality appraisal through MMAT to ensure that studies of equal technical quality are given equal weight. To provide a high level of trustworthiness in our review, reviewers will have detailed information about the eligibility

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criteria and the type of intervention (PAEHR) in order to provide sufficient information for replication.

Ethical Considerations

Since we will use only publicly available data material with the scoping review methodology, this study is not subject to ethical approval.

Results

The main results from our analysis will be presented in a narrative form, focusing on subjective and objective changes in clinical notes as well as on changes in HCPs' documentation after sharing EHRs with patients. Additional data on year, country, study design, characteristics of study participants, setting, sample, medical specialty, and study purpose will be presented in diagrams or tabular format.

Discussion

Research indicates that HCPs have concerns regarding the effects of ORA on clinical routines, workload, and patient safety as patients increasingly gain access to medical information on the internet [11-20]. Although a limited number of studies have examined alterations in documentation practices following the implementation of policies, these studies have primarily focused on subjective evaluations rather than objective assessments [11]. Furthermore, the few studies attempting to investigate objective changes in documentation have yielded inconclusive results that are further restricted by methodological limitations [22,28,29].

Although there are already a few reviews that address the use of patient ORA [32,41-43], no review specifically addresses the potential changes to clinical documentation that may result from the implementation and use of PAEHR. Our scoping review aims to map current research into documentation changes and to potentially raise awareness among many different involved parties about the risks and opportunities of PAEHR use.

A potential limitation of the study is a reduced depth of the analysis due to the broader nature of the scoping review. In addition, due to exclusion of gray literature, it is possible that some studies will be overlooked. Nevertheless, we defined our search strategy to identify the most comprehensive and high-quality evidence.

Dependent on the findings, this study may offer important insights on how to support effective documentation practice in the future. For example, the findings may provide a basis for a widely demanded "documentation training" that could better prepare HCPs and patients on how to read and write notes [20]. The scoping review will strive to identify any existing research gaps and to indicate directions for further studies in this field. The growing body of evidence on natural language processing in relation to documentation changes after PAEHR introduction will be explored.

Acknowledgments

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Data Availability

The data used for the scoping review are openly available and can be retrieved from the following databases: APA PsycInfo, CINAHL, PubMed, and Web of Science Core Collection.

Authors' Contributions

EM-D wrote the manuscript and designed Figure 1. JS contributed to drafting the protocol. CB and JS were responsible for the conception of the study. All authors read, provided feedback, and approved the paper for submission.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Adapted search strategies for each database.
[DOCX File , 19 KB - resprot_v12i1e46722_app1.docx]

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Abbreviations

EHR: electronic health record
HCP: health care professional
MMAT: Mixed Methods Appraisal Tool
ORA: online record access

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PAEHR: patient-accessible electronic health record
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

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Protocol

Gender Equality Training for Students in Higher Education: Protocol for a Scoping Review

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Abstract

Background: The principles of gender equality are integral to the goals, targets, and indicators of all sustainable development goals. Higher education institutes can be powerful agents for promoting gender equality, diversity, and inclusion not only in the higher education context but also in society as a whole. To address and overcome gender inequality in the higher education environment, experts posit that change needs to occur from day 1 of the student's academic experience. To this end, training is required. A preliminary review of the literature indicates that multiple gender equality–based training programs or initiatives for students have been designed and evaluated in second and third-level education settings. Examples of educational activities undertaken include delivery of didactic teaching, participation in a face-to-face collaboration project, site visits, case studies, and coaching. Yet, our initial search indicated that, to date, a comprehensive review collating the available evidence on gender equality training for third-level students has not yet been carried out.

Objective: Our review seeks to identify and explore the existing literature on gender equality training interventions for third-level students, with a particular emphasis on training content, methodology, and outcome evaluation.

Methods: This scoping review will be structured using the Arskey and O'Malley's 5-stage framework and will consider empirical research and other relevant published works that address gender equality training. Systematic searches will be carried out in 6 research databases and the gray literature using key search terms. Inclusion and exclusion criteria have been defined, and a data charting tool created to methodically extract information from selected literature. The free web software Rayyan will be used for primary screening where each reference will be screened in duplicate first by title, then abstract, and finally by full text.

Results: This review forms part of the LIBRA (Balance) study and has received peer-reviewed grant funding from the Irish Higher Education Authority. LIBRA aims to use simulation-based education to develop a gender equality leadership training program for student leaders in higher education. The findings will be summarized in tabular form, and a narrative synthesis produced to inform curriculum development.

Conclusions: This review seeks to inform curriculum design by reporting on the gender equality–enabling skills and leadership skills necessary to foster gender equality. This paper should inform recommendations for training and catalyze future research in this rapidly evolving area.

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KEYWORDS

gender equality; student leaders; simulation-based education; communications skills; training; higher education; sustainable goal; scoping; review method; PRISMA; Preferred Reporting Items for Systematic Reviews and Meta-Analyses; search strategy; gender; equality; equalities; inclusion; diversity; postsecondary; student; teaching; coaching; teacher; educator

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Introduction

Background

Higher education institutions (HEIs) can be powerful institutions for promoting gender equality, diversity, and inclusion not only in the higher education context but also in society in general; however, universities remain both gendered and gendering organizations [1]. Recent statistical reports on gender equality data in the European Union show that female students make up the majority of the undergraduate population in HEIs, yet several published reports highlight ongoing cultural, institutional, and structural barriers inhibiting gender equality from true realization in this sector [2]. Despite the global feminization of the third-level student population, women are not progressing at the same rate as men in their academic careers. Male students remain a majority among postgraduates [2] and at leadership level, women accounted for only 24% of professorial chairs and 22% of heads of institutions in the higher education sector across the European Union in 2017 [1]. This gender imbalance is replicated in senior leadership in Irish third-level institutions [3,4].

Institutional structures involuntarily erect barriers against the recruitment, retention, and career progression of women. The fact that overt discrimination has been replaced with less obvious, primarily implicit preconceptions and prejudices against women makes gendered working circumstances even more difficult to change (eg, women have less career motivations, an assumed lack of confidence, and less ambition to take on leadership positions) [5]. Evidence suggests female researchers were disproportionately affected by the COVID-19 pandemic in terms of unequal distribution of childcare, elderly care, and other kinds of domestic and emotional labor reflected by a sudden drop in the number of female authors of scientific publications [6].

The National Surveys of Student and Staff Experiences of Sexual Violence and Sexual Harassment in Higher Education revealed over one-quarter of HEI staff did not feel safe from sexual harassment and 60% reported sexist hostility in the workplace. Among students, one-third or less felt safe socializing at night on campus or in the local community. In total, 66% of students reported experiencing sexist hostility [7].

A comprehensive review of state interventions to tackle gender inequality in Irish HEIs in Ireland from 2014 to 2019 indicated the ongoing presence of barriers impacting women's opportunity to occupy academic or managerial positions of formal power [8]. The authors acknowledge that the impact of several state interventions is not yet clear; however, they advocate for the continuation of a multifaceted approach, which addresses this issue at "the state (macro), the HEI (meso), and the situational (micro)-level simultaneously." To address and overcome gender inequality in the higher education environment, Acai et al [9] posit that change needs to occur from day 1 of the student's academic experience. Gender equality and fairness training in third-level institutions are important steps toward creating a more inclusive and equitable learning environment for all students, regardless of their gender identity. Promoting gender equality and fairness in higher education is a complex issue that requires a multifaceted approach. Barriers contributing to the shortage of women in academics and academic leadership are numerous, including a shortage of role models and mentors [10]. Training is a critical tool for addressing gender inequality and promoting gender equality in higher education. The importance of gender-sensitive training material and nondiscriminatory education and training has been highlighted [11]. Appropriate and timely training has the potential to help students, faculty, and staff to recognize and address unconscious biases, stereotypes, and discriminatory practices that may exist within the institution. It can also help to promote a culture of respect, dignity, and mutual understanding among members of the campus community.

A recent study highlighted the gender inequality that exists in student leadership, demonstrating that although females made up 55% of the student body, they represented only 33% of the leadership in student organizations [12]. The Irish Higher Education Authority has emphasized a need to train both male and female student leaders in gender equality to increase awareness and nurture competences in order to actively address gender inequality. Such training will have an impact on the wider HEI community [3]. According to the European Institute for Gender Equality, gender equality training should enable and empower participants to (1) define and understand gender equality principles, (2) identify gender inequalities in their field, (3) be aware of gender in their planning and policy implementation, (4) monitor progress, and (5) review and assess their work from a gender perspective. Developing competence in gender equality means identifying and changing gender stereotypes and gendered roles, thereby creating a more equal society [13].

Similarly, UN Women identifies gender-equality competence as possessing the "awareness, knowledge, commitment and capacity necessary to incorporate gender perspectives into substantive work among professional staff." At the heart of gender equality training lies transformation; to realize gender equality is to transform power sharing, control of resources, and decision-making to promote equal gender relations [14]. According to UN Women, gender equality training is not an event but a process. European Institute for Gender Equality and UN Women emphasize the necessity of *gender mainstreaming*, whereby individuals are provided with tools and training in gender equality competence-development and awareness-raising, but gender equality is simultaneously realized at an institutional and legal level [8,9].

At the heart of UN Women's approach to gender equality training is the theory of change, which acknowledges that training plays an integral role in enhancing participants' knowledge, motivation, and ability to promote gender equality, but that a long-term institutional commitment is also necessary to realize change. To optimize gender equality training, UN Women advises using Myra Marx Ferree's Knowledge, Desire, and Ability model. Applying this approach recognizes that participants require all 3 components in order to enact change, including a knowledge and understanding of gender equality principles and gender inequalities, the desire and motivation to implement changes and address gender inequalities, and the tools and competences required to bring about change. The

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theory of change also encompasses engaging in reflexive practices to develop an awareness of one's own thinking and behavior to become a self-reflexive learner and to foster gender equality over time. UN Women notes that the theory of change should be recognized as both a process and a product in empowering people and institutions to bring about gender equality [14].

Study Aims

A preliminary literature review indicates that multiple gender equality–based training programs or initiatives for students have been designed and evaluated in second- and third-level education settings. Examples of educational activities undertaken include the delivery of didactic teaching, participation in a face-to-face collaboration project, site visits, case studies, and coaching [15-17]. Yet, our initial database searches indicated that, to date, a comprehensive review collating and synthesizing the available evidence on gender equality training for third-level students has not yet been carried out. Our review seeks to fill this gap.

This review will form part of the LIBRA study, which uses simulation techniques to develop a gender equality leadership training program for student leaders in higher education. This project is guided by the Irish Higher Education Authority's Gender Equality Task Force recommendations under *integrating the gender dimension into teaching and learning by embedding the gender dimension into undergraduate or postgraduate education* [18]. In carrying out a review, we aim to identify and explore the existing literature on gender equality training and gender equality interventions for third-level students, with a particular emphasis on training content, methodology, and outcome evaluation. Second, the review seeks to construct a consensus on gender equality–enabling skills and leadership skills necessary to foster gender equality.

Study Design

We considered a variety of approaches for analyzing the existing literature and deemed a scoping review most suitable for the requirements of this study. Arskey and O'Malley [19] list four principal reasons for conducting a scoping review, including (1) to explore the extent, range, and nature of available research on a specific topic; (2) to summarize and disseminate findings from the existing literature; (3) to identify a potential need for a systematic review; and (4) to identify gaps in the research literature. In line with these reasons, a scoping review will provide an appropriate methodology to explore the extent and nature of the existing research on gender equality training for third-level students. In designing the LIBRA gender equality simulation program, it will be essential that this process is informed by an evidence-based approach and uses the most up-to-date research regarding gender equality training in higher education. Leadership plays an integral role in the LIBRA program in order to empower student leaders to promote gender equality. This review also seeks to identify potential gaps in the literature regarding gender equality leadership training for third-level students.

Peters et al [20] explain that a scoping review is useful in clarifying key concepts and definitions in the literature. This will be particularly relevant within the LIBRA project to consolidate a definitive skills framework that outlines key competences required to promote gender equality and challenge gender inequality. Research questions informing a scoping review are typically wide in breadth, and researchers can draw on a diverse and heterogenous range of sources and study designs in carrying out the review. Conversely, the systematic review requires a detailed research question and generally includes a narrow range of quality-assessed studies [19-21]. This review will explore and present an overview of the existing literature on gender equality training, as opposed to ascertaining the efficacy of a specific intervention, so we deemed a scoping review the most suited approach for this study.

Methods

Overview

The review will be structured using Arskey and O'Malley's [19], 5-stage framework, which involves (1) identifying the research question, (2) identifying relevant studies, (3) selecting the studies, (4) charting the data, and (5) collating, summarizing, and reporting the results. The scoping reviews' systematic approach will also be informed by 3 additional studies, each of which has contributed depth and detail in advancing Arskey and O'Malley's [19] original framework, including Levac et al [22], Peters et al [20], and Tricco et al [21].

Identifying the Research Question

Tricco et al [21] list a variety of models to facilitate the development of a research question, including population, intervention, control, and outcomes tool and an adaption of the sample size, phenomenon of interest, study design, evaluation, research type tool. However, Peters et al [20] argue that the population, concept, and context mnemonic are more suited to crafting a research question suited to the exploratory and descriptive nature of the scoping review. The population, intervention, control, and outcomes model, in contrast, facilitates the development of focused and explanatory research questions more suited to a systematic review [20]. In forming the research question for this review, we selected the population, concept, and context approach: the population will include students in higher education, the concept will include gender equality training, and the context will encompass all HEIs.

The principal aims of this scoping review will be to (1) produce a descriptive overview of gender equality training and gender equality interventions for students in higher education or postsecondary education, including their core aims, key content areas, implementation methodology, and outcome evaluation, and (2) construct a consensus on skills and competences required to promote gender equality. A secondary aim of this study is to review the extent to which leadership is incorporated into gender equality training.

The principal research question for the review is: what is the current nature and scope of interventions promoting gender equality competences among students in higher education? The secondary research questions include (1) how is gender equality training delivered to students, and what are the key topics included in the intervention? (2) What specific skills and competences are taught to students to enable them to promote

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gender equality? (3) How is gender equality training evaluated? (4) To what extent is the concept of leadership included in gender equality interventions, and how are gender equality leadership skills fostered among students?

Identifying Relevant Studies

The search strategy was designed in consultation with an experienced librarian. The search terms will comprise three thematic combinations, including (1) gender equality training, (2) HEIs, and (3) students, each separated with the Boolean operator AND. Within each thematic combination, search terms will be separated with the Boolean operator OR. Wildcards will be used to ensure the inclusion of plurals and variation in spelling across the search terms. The search will be limited to studies and other sources published between January 2011 and November 2021. Based on preliminary database searching, the majority of publications on gender equality training for second- and third-level students have been published in the last 10 years. Systematic searches will be carried out in 6 databases, CINAHL Plus and APA PsycInfo (accessed on Ebscohost), Embase, MEDLINE (Ovid), Web of Science (Science and Social Citation Indexes accessed on Clarivate), and Scopus (accessed on Elsevier). Textbox 1 provides an example of the search strategy, which will be applied. We will also carry out searches using MedEdPortal, MedEdPublish, and Open Grey to identify any gray literature that could further inform the review. The search will be limited to titles, abstracts, and keywords to ensure the search terms collate papers and sources whose focus relates to these topics.

Textbox 1. An example of search strategy applied for APA PsycInfo and CINAHL databases.

1. TI (gender N2 training OR bias N2 training OR discrimination N2 training OR diversity N2 training OR equality N2 training OR inclusion N2 training OR sexuality N2 training) OR AB (gender N2 training OR bias N2 training OR discrimination N2 training OR diversity N2 training OR equality N2 training OR inclusion N2 training OR sexuality N2 training)
2. TI (gender N2 course$ OR bias N2 course$ OR discrimination N2 course$ OR diversity N2 course$ OR equality N2 course$ OR inclusion N2 course$ OR sexuality N2 course$) OR AB (gender N2 course$ OR bias N2 course$ OR discrimination N2 course$ OR diversity N2 course$ OR equality N2 course$ OR inclusion N2 course$ OR sexuality N2 course$)
3. TI (gender N1 program* or bias N1 program* or discrimination N1 program* OR diversity N1 program* or equality N1 program* OR inclusion N1 program* OR sexuality N1 program*) OR AB (gender N1 program* OR bias N1 program* OR discrimination N1 program* OR diversity N1 program* OR equality N1 program* OR inclusion N1 program* OR sexuality N1 program*)
4. TI (gender N1 awareness* or gender N1 bias or gender N1 equality OR gender N1 inclusion OR gender N1 equity OR sex N1 bias) OR AB (gender N1 awareness* or gender N1 bias or gender N1 equality OR gender N1 inclusion OR gender N1 equity OR sex N1 bias)
5. 1 OR 2 OR 3 OR 4
6. TI (“higher education” OR “third level education” OR “tertiary education” OR university* OR college$) OR AB (“higher education” OR “third level education” OR “tertiary education” OR university* OR college$)
7. TI (Undergraduate$ OR postgraduate$ OR student$) OR AB (Undergraduate$ OR postgraduate$ OR student$)
8. 1 AND 2 AND 3
9. LIMIT 8 to 2010-2021

Literature searches to be carried out in APA PsycInfo, CINAHL, Embase, MEDLINE (Ovid), Scopus, and Web of Science databases. Searches using MedEdPortal, MedEdPublish, and Open Grey will be carried out to identify gray literature to further inform the review. The search was limited to studies and other sources published between January 2011 and November 2021.

Study Selection

The search will be carried out by the librarian and subsequently prepared for screening in an EndNote library (EndNote, version 20.2.1; Clarivate Analytics), and duplicates removed. The EndNote library will be exported to Rayyan (Rayyan), which will be used to collaboratively complete paper screening. Rayyan is a web-based tool designed to speed up the screening process of systematic reviews, scoping reviews, and other knowledge synthesis projects [23]. The principal investigator and research assistant will each carry out the title and abstract screening. Tricco et al [21] advise establishing an agreed standard for reviewing texts prior to commencing the formal screening process. We will use the following inclusion and exclusion criteria as our agreed framework for paper screening. In line with the study’s research questions, our inclusion and exclusion criteria will be applied as detailed in Textbox 2.

Throughout the course of the screening process, the inclusion and exclusion criteria will be adapted and developed in an iterative fashion. Researchers will resolve disagreements through discussion and develop a finalized list of abstracts to be reviewed. If consensus is not reached on particular sources, one of the coauthors will act as a third party in finalizing the selection decision. All authors will collectively review the first 10 texts screened for applicability to the research questions and use group discussion to add depth and detail to the inclusion and exclusion criteria. The remainder of the texts to be reviewed will be divided among 3 groups, with each group consisting of 2, 2, and 3 authors, respectively. A collaborative and discursive process will be applied to resolve disagreements at the full-text screening phase, and the collective work and consensus among each group will form the finalized list of full texts to be included in the scoping review. Throughout the screening phase, the authors will use a reflexive approach in reviewing papers and consolidating the inclusion and exclusion criteria, given the iterative nature of this process [20].

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Textbox 2. The inclusion and exclusion criteria.

Inclusion criteria

- Undergraduate or postgraduate students in higher education
- Interventions (eg, campaign or workshop) promoting gender equality awareness or gender equality competences:
  - Interventions inside or outside of the academic curriculum
    - for example, project within a module or exercise within a module
    - for example, course or program external to course of study
  - Papers or sources focusing on the experience of participation in an intervention
  - Interventions do not have to focus solely on gender equality; interventions can also focus on other aspects of equality, diversity, and inclusion (EDI) training; as long as gender equality is included in the intervention, it can be included
  - Interventions involving gender equality in terms of gender diversity (transgender, nonbinary, and gender-diverse students)
  - Teacher training
- Third-level education institutions
- Published between January 2010 and September 2021
- Publications such as peer-reviewed literature and gray literature (dissertations, conference papers, corporate documents, government reports, preprints, proceedings, research reports, and periodicals)
- Any relevant papers cited in literature, systematic, and scoping reviews focusing on similar subject matters
- Studies in English

Exclusion criteria

- Primary or secondary students, higher education staff, general public
- Papers or sources focusing on:
  - Measuring gender balance in higher education courses
  - Strategies to promote greater equality among applicants to particular courses
  - Experiences of gender or gender inequality among students
  - Impact of gender on subject-specific competences, for example, programing or spatial awareness
  - Recruitment or retention of female students in academic courses
  - Gender equality in health care
  - Mentorship programs
  - Diversity or EDI programs that do not include a gender dimension
  - Gender studies modules
  - Papers focusing on a whole-of-campus institutional change
  - Experiments on students' attitudes—unless these form part of a specified intervention.
- Papers referring to primary- or secondary-level school interventions, youth services, community services programs
- Published prior to January 2010
- Publications such as books, film reviews, and websites
- Studies for which no English translation is available

Reference lists of the included texts will be hand-searched for further relevant studies and sources, as will literature reviews identified in the database search. As per the exploratory nature of a scoping review, a variety of study designs and sources will be used to gather data, including empirical peer-reviewed research, periodicals, dissertations, conference abstracts, magazines, periodicals, and research reports. Appropriate gray literature will also be searched in the reference lists of selected texts. Quality appraisal will not form part of the screening and selection process. A scoping review principally seeks to identify, explore, and map existing literature on a given topic, so assessing the methodological and academic quality of the studies will not be applicable or necessary [20,22].

Finally, to optimize the comprehensiveness of the search, Levac et al [22] and Paez [24] recommend consulting experts in the field to inform and guide the review. We will liaise with several

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experts in the field of gender equality and leadership training via email. Experts will be asked to review the list of papers selected, provide feedback, and identify any further papers or ongoing studies that should be included. We aim to liaise with a variety of organizations in informing the review, including the UN Women Training Centre, the European Institution for Gender Equality, the Gender Equality Academy, RCSI Institute of Leadership, Technology University Dublin Equality, Diversity, and Inclusion Unit, University College Cork (UCC) Equality, Diversity, and Inclusion Unit, UCC Business School, the Irish Management Institution UCC, Aurora Management, 30% Club, and Advance Higher Education. The study selection process will be laid out using a flow diagram as per the PRISMA-ScR (Preferred Reporting Items for Systematic reviews and Meta-Analyses Extension for Scoping Reviews) Statement to make the search strategy and selection process transparent and auditable [19,21].

Ethical Considerations

This review will involve the analysis of publicly available empirical research and the production of secondary data, so ethical approval will not be required.

Results

Overview

The extracted data will be collated, and a narrative summary will accompany the results to explain how the results relate to the reviews' objectives. The findings will be discussed as they relate to higher education. Gaps and limitations of this literature will also be identified and presented.

Charting the Data

A data-charting form will be used to collect key information from each study using Word (Microsoft Corp) documents and Excel (Microsoft Corp). MP developed the original data-charting form, which will be expanded and refined in an iterative fashion by all authors during the full-text screening process. The researchers will independently chart the data and update the data-charting table as they see necessary. Group discussion will be used to address disagreements and create the final standardized data-charting table. Arskey and O'Malley [19] explain that data charting differs from the data extraction process used in systematic reviews and meta-analyses, where data extraction is specific and may involve statistical techniques, data charting within scoping reviews involves a broader approach and includes narrative information, capturing how the study was carried out.

Peters et al [20] explain that the information documented in the data-charting table should align with the research aims and research questions of the review. As such, the data collected for this scoping review will include study details (author or year), location, context, type of source, study aims or intervention aims, participant details and sample size, research questions addressed, study design, gender equality theories used, intervention style and duration, intervention content, intervention methods and format, outcome evaluation measures, key findings, interesting observations, incorporation of gender equality and leadership, incorporation of intersectionality, and incorporation of transgender and gender-diverse inclusivity.

Collating, Summarizing, and Reporting the Results

Levac et al [22] recommend dividing this final stage into 3 distinct components. To collate and summarize the results, we will use descriptive numerical summary analysis. The data will be mapped and presented in tabular format to make it easier to respond to the study questions. Basic descriptive analysis is both sufficient and the most suited approach of data analysis for the exploratory nature of the scoping review [21]. Finally, Levac et al [22] advise the researcher to consider the meaning of the findings in relation to the overarching purpose of the study. A narrative summary will accompany the results and will describe how the results relate to the review objective. Gaps and limitations of this literature will also be identified and presented.

Discussion

Principal Findings

HEIs have the potential to amplify gender equality through training for the betterment of society at large. We are undertaking this scoping review as part of a need assessment to provide the best evidence to inform intervention design and prioritize content for an educational program.

We aim to first synthesize the existing literature on training that supports gender equality in HEIs providing conceptual, theoretical, and evidentiary clarity on the current state of the art. Second, we aim to identify gaps and areas for future research to help define the research agenda for gender equality training in HEIs going forward.

Study Dissemination

Research findings will be disseminated using a variety of mediums, including publication in a peer-reviewed academic journal and presentation of the findings at national and international conferences and other academic events. The findings will also be used to inform the pilot study for the LIBRA gender equality–based training program, with the goal of a subsequent national roll-out across Irish HEIs. Further afield, the findings will be available to be used by other universities or institutions of education to inform the development of gender equality training for students in higher education.

Strengths and Limitations

To the best of our knowledge, this is the first review of the literature focusing on gender equality training and interventions for third-level students. The search strategy was comprehensively developed by all authors, with the support of an experienced librarian, which will facilitate a thorough and extensive database search. The university in which this study is being carried out is a medical and scientific institution, which will necessarily limit the full scope of databases available to the authors in carrying out the search. Following consultation with our librarian, hand-searching reference lists of the included papers and texts was considered sufficient to identify other important studies and gray literature in the event that they were

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not retrieved in the database search. We originally intended to incorporate Google and Google Scholar searching into the search strategy; however, given time limitations within the allocated funding period, we decided to focus specifically on academic databases when carrying out the search. This review is limited to papers written in English or which have an English translation available, which may bias the evidence.

It is also important to note that there may be a lack of relevant literature available in this particular field, given the niche topic on which this review will focus. However, this finding in itself may encourage further research on the topic as it would highlight a significant gap in the literature following a comprehensive search of the databases. Excluding studies focusing on gender equality in health care, mentorship programs, and gender studies modules may lead to the exclusion of useful information, both within the review itself and later informing the LIBRA study. Yet, following the preliminary database searching and screening, we concluded that these particular studies did not fully align with the research questions.

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Conflicts of Interest

None declared.

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Abbreviations

HEI: higher education institution
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews
UCC: University College Cork

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Protocol

Digital Rights and Mobile Health in Low- and Middle-Income Countries: Protocol for a Scoping Review

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Abstract

Background: Digital technology is a means to uphold or violate human rights in various domains, including business, military, and health. Given the pervasiveness of mobile technology in low- and middle-income countries (LMICs), mobile health (mHealth) interventions present an opportunity to reach remote populations and enable them to exercise civil and political rights and economic, social, and cultural rights, such as the right to health and education. Simultaneously, the ubiquity of mobile phones involves processing sensitive data which can threaten rights, including the right to privacy and nondiscrimination. Digital health is often promoted as advancing human rights and health equity; however, digital rights are underexplored in the literature on mHealth in LMICs. As such, creating an understanding of the digital rights topics covered in the 2022 literature is important to avoid exacerbating existing inequities relating to digital health design, use, implementation, and access.

Objective: This scoping review aims to identify digital rights topics in the 2022 peer-reviewed literature on mHealth in LMICs.

Methods: The Arksey and O'Malley framework for scoping reviews guides this review. Searches were performed across 7 electronic databases (Web of Science, Scopus, Ovid, ACM Digital Library, IEEE Xplore, ProQuest, and PubMed). The screening processes were guided by the research question "What digital rights topics have been explored in the 2022 literature on mHealth in LMICs?" Only papers addressing mHealth in LMICs and digital rights topics were included. Data extraction will include publication title, year, and type; first author's affiliation country; LMICs implicated; infrastructure challenges; study aims, design, limitations, and future work; health area; mHealth technology, functions, purpose or application, and target end users; human or digital right terms used; explicit rights topics cited; and implied rights topics. The results will be reported using the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) checklist.

Results: This scoping review was registered in Open Science Framework (December 22, 2022). Title and abstract screening and full-text paper screening were completed in 2023. This resulted in 56 papers being included in the study. The target date for completing data extraction and publishing a case study of the initial findings is the end of 2023. The full scoping review findings are expected to be disseminated through various pathways benefiting academia, practice, and policy making by the end of 2024. These include journal papers, conference presentations, publicly available toolkits for research and practice, public webinars, and policy briefs with evidence-based policy recommendations emerging from this review.

Conclusions: The planned scoping review will identify digital rights topics in the 2022 literature at the intersection of mHealth and LMICs. Furthermore, it will highlight the importance of patient empowerment, data protection, and inclusion in mHealth research and related policies in LMICs.

Trial Registration: Open Science Framework osf.io/7mz24; https://osf.io/7mz24

International Registered Report Identifier (IRRID): DERR1-10.2196/49150

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(JMIR Res Protoc 2023;12:e49150) doi:10.2196/49150

KEYWORDS

human right; digital right; mobile health; mHealth; smartphone; mobile phone; digital health; scoping review; health equity; patient empowerment

Introduction

Background

In 2022, the European Commission signed "The Declaration on Digital Rights and Principles," acknowledging the power of digital technologies as enablers and inhibitors of human rights [1]. Further, it reshapes and applies existing human rights to the digital space (eg, the right to the protection of their personal data on the internet and the right to freedom of expression in the internet-based environment). Likewise, in 2020, the United Nations put forward the "Roadmap for Digital Cooperation," which acknowledged that digital technology, as a tool, is a means to exercise human rights and violate them [2,3]. Similarly, "the resolution on the promotion, protection, and enjoyment of human rights on the internet" in 2016 [4] affirmed the importance of protecting and realizing human rights on the internet and other information and communications technology. Clearly, human rights relating to the digital environment, or digital rights, are an emerging and evolving topic that concerns 2 key areas. First, the extension, realization, and protection of existing human rights in the digital space and over personal, digitized data (eg, freedom of expression). Second, the discussion around emerging human rights to access, use, and participate in the digital space (eg, the right to internet access) [5]. For this study, digital rights are all existing and emerging human rights that extend to, and relate to accessing and protecting, participation in the digital space.

The internet as an enabling technology is often at the center of the discussion around digital rights, with arguments made for the right to internet access [6-8]. Although the European Commission and United Nations do not explicitly identify internet access as a right, they proclaim necessary internet access protections for the sake of safeguarding, or at least not intentionally stifling, human rights [1,2,9]. So far, several countries have recognized the right to internet access, including Greece [10] and India [11]. Yet, the status of this right is still being discussed at the international level [12]. Beyond internet access considerations, the topic of digital rights also concerns the broader information and communications technology environment and addresses, for instance, health care systems and respect for human dignity [13], automation and the right to work [14], and surveillance technologies and the right to freedom of movement [15].

Low- and Middle-Income Countries

Digital rights discourse often focuses on high-income countries in which, in most cases, users enjoy significant digital access and considerable rights and legal protections [16]. This work seeks to explore low- and middle-income countries (LMICs) instead, which are more at risk of digital rights violations (eg, state-sanctioned internet shutdowns and internet-based censorship) [17-19] and where user rights are inadequately regulated [20,21].

Mobile Health

This study examines the underexplored digital rights concerns relating to mobile health (mHealth) in LMICs. mHealth refers to "the use of mobile and wireless technologies to support the achievement of health objectives" [22], categorizing various devices such as mobile phones, wearable and implantable devices, tablet computers, and personal digital assistants [23]. Digital health, including mHealth, is often promoted as advancing human rights and promoting "health equity, if implemented in partnership with communities and based on core values of local autonomy, fairness and ecological sustainability" [24]. However, to what extent the literature on mHealth in LMICs engages with digital rights topics is currently underexplored. Exemplary digital rights topics concerning mHealth in LMICs include the impacts of mandatory Subscriber Identity Module registration mobile app download taxes, cyberviolence over mobile phones, and internet-based censorship, as well as gender disparities and the gender digital divide, internet-based surveillance and the right to privacy, and prolonged data retention and the right to be forgotten [25-28]. To create knowledge in this underexplored space, this scoping review aims to identify digital rights topics in the 2022 peer-reviewed literature on mHealth in LMICs.

Methods

Scoping Review

This review follows the scoping review framework outlined by Arksey and O'Malley [29] and recommendations by Levac et al [30]. This involves adhering to and reporting the following six steps: (1) identifying the research question; (2) identifying relevant studies; (3) study selection; (4) charting the data; (5) collating, summarizing, and reporting results; and (6) consultation [29]. The PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) checklist will be used to report the review results. This review commenced in November 2022 and is expected to conclude by the end of 2023.

Step 1: Identifying the Research Question

The guiding question of this review is "What digital rights topics have been explored in the 2022 literature on mHealth in LMICs?" To limit the scope to digital rights, this review will not investigate well-explored mobile access topics (eg, infrastructure, literacy, connectivity, and cost) except in instances relating to digital rights. Further, the scope is limited to literature published in 2022 based on resource limitations and the saliency and engagement of digital rights topics in recent years.

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Step 2: Identifying Relevant Studies

Searches were performed across 7 electronic databases. A preliminary search was performed on November 25, 2022, across 6 electronic databases: Web of Science, Scopus, Ovid, ACM Digital Library, IEEE Xplore, and ProQuest. The search strategy (Multimedia Appendix 1) consisted of terms considered to capture the nature of the research question. Multimedia Appendix 1 reports the numerous variations and abbreviations of terms used, as well as the search string adapted according to the requirements of each database. A second series of searches were performed on March 9, 2023, in the same databases to identify any papers published after the initial search date. On August 16, 2023, PubMed was added to the list of databases and searched. Search results were imported into Covidence (Veritas Health Innovation), a web-based tool for collaborative paper screening, reviewing, and data collection. Duplicate citations were removed using Covidence functions.

Step 3: Study Selection

The inclusion and exclusion criteria applied to the study selection process are described in Textbox 1.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Paper type: Peer-reviewed papers.
- Language: English.
- Publication date: 2022.
- Subjects of interest: Mobile health (mHealth) in low- and middle-income countries (LMICs) and digital rights topics.

Exclusion criteria

- Paper type: Not peer-reviewed papers (eg, unpublished work and gray literature).
- Language: All other languages.
- Publication date: Before or after 2022.
- Subjects of interest: Not mHealth in LMICs (eg, reviews on health technology in LMICs not covering mHealth) and not digital rights topics specifically (eg, mobile phone accessibility topics such as cost and digital literacy).

Papers were screened by 2 reviewers (coauthors AP and YJCS) to assess relevance to the research question over two iterations: (1) title and abstract screening and (2) full-text paper screening. To aid in both screening iterations, the authors developed a screening form and integrated it into Covidence. Following recommendations by Levac et al [30], the reviewers regularly met during the screening process to resolve emerging conflicts related to study selection. An arbiter (coauthor EFV) settled the conflicts that could not be resolved in the reviewers' discussions.

Initially, during the search and title abstract screening, no limits were put on the publication date. However, the criteria were revised post hoc only to include publications from 2022 based on resource limitations and familiarity with the literature. As such, the search and title and abstract screening included papers published on any date, and only after the title and abstract screening were papers published before 2022 excluded. Post hoc, iterative revisions to the eligibility criteria are not uncommon [29,31] and are appropriate "to ensure that abstracts selected are relevant for full paper review" [30]. However, they should be reported with justification for transparency [32], as done here. The post hoc excluded papers will be retained for a later, larger review.

Step 4: Charting the Data

For the included papers, 2 authors (AP and YJCS) independently piloted the data extraction process with 5 papers to reach a consensus and check for consistency. Afterward, data extraction of the remaining papers will be conducted by one reviewer (AP). Data will be extracted using a data chartering form integrated into Covidence, initially developed by the authors before the data collection process and later revised by 3 coauthors (AP, YJCS, and HML) after the data extraction pilot. Data items included in the form were publication title, year, and type; first author's affiliation country; LMICs implicated; infrastructure challenges noted; study aims, design, limitations, and future work proposed; health area addressed through mHealth; mHealth technology, functions, purpose or application, and target end users; human or digital right terms used; explicit digital or human rights topics cited; and implied digital or human rights topics.

Step 5: Collating, Summarizing, and Reporting Results

All data will be exported from Covidence and collated in a single spreadsheet on Excel (Microsoft Corp) for frequency and content analysis. Descriptive statistics will be calculated to summarize the general characteristics of the included literature. Content analysis will be used to interpret the extracted data. These methods are typical and recommended in scoping reviews [30].

Step 6: Consultation

No consultation outside of the primary author's wider research team will be performed in the design of this scoping review.

Ethical Considerations

As this scoping review will not include human or animal participants, neither ethics approval nor participant consent is required. Only secondary analyses will be conducted on data collected from published literature.

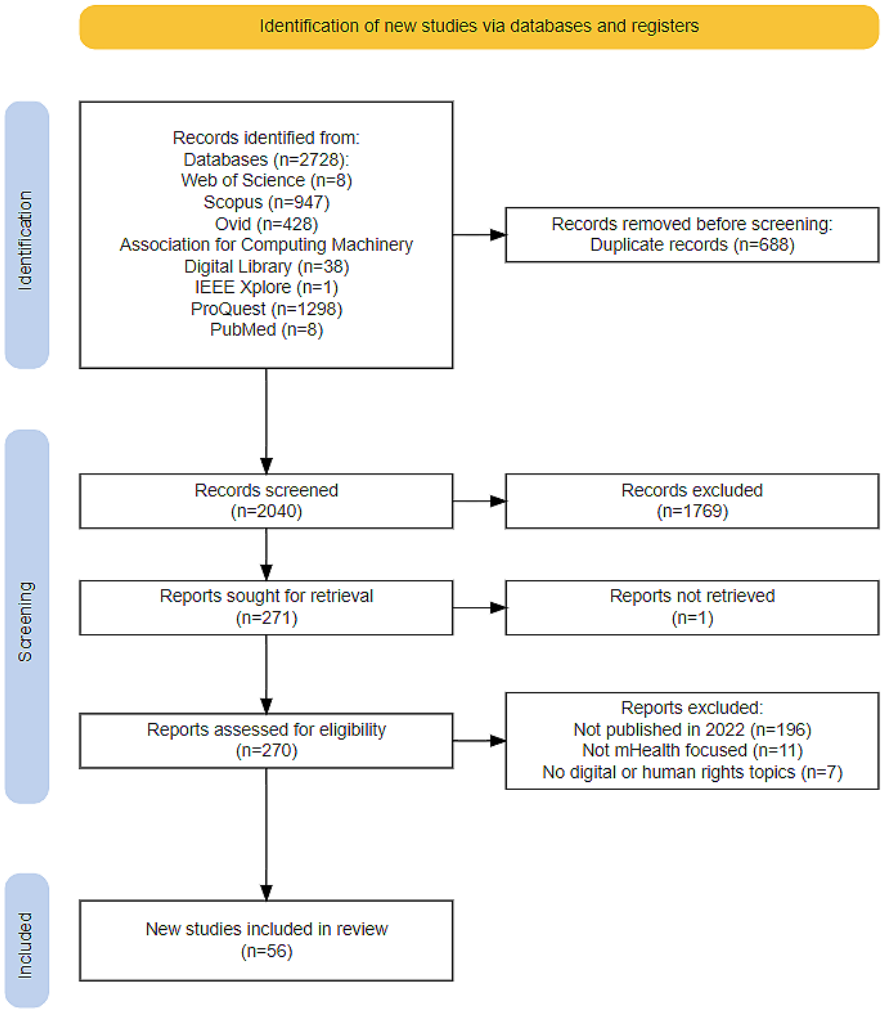
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Results

The database searches yielded 2728 papers. After duplicates were removed, 2040 papers underwent title and abstract screening. This resulted in 271 papers being considered eligible for full-text screening. However, only 270 were retrieved for full-text screening (one was inaccessible and therefore excluded). Post hoc eligibility criteria were applied before full-text screening, excluding 196 not published in 2022. The post hoc excluded papers will be retained for a larger review to be completed in the future. The remaining 74 papers were considered eligible for inclusion. Following full-text paper screening of 74 papers, which excluded papers not focusing on mHealth (n=11) and not addressing digital or human rights topics (n=7), 56 papers were included in this scoping review. Figure 1 reports the scoping review process using the PRISMA-ScR flow diagram.

Data extraction is underway and expected to be completed by the end of 2023. Further, by the end of 2023, the initial findings of selected studies are expected to be published as a case study. The full scoping review findings are expected to be published by the end of 2024.

Figure 1. PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) flow diagram of the scoping review process.



Discussion

Principal Results

This planned scoping review is designed to identify and map digital rights topics explored in the recent literature addressing mHealth in LMICs. Furthermore, it is projected to examine to what extent the literature engages with digital rights considerations relating to mHealth interventions; that is, whether digital rights topics are explicitly or implicitly deliberated. The review findings are expected to draw attention to the importance of data protection, inclusion, and patient empowerment in mHealth solutions and associated policies in LMICs to avoid exacerbating existing inequities relating to digital health design, use, implementation, and access. Moreover, this review is positioned to reveal existing knowledge and policy gaps relating to digital rights, which could help inform future mHealth research directions and relevant policy. The dissemination of findings will be varied, including journal papers, conference presentations, and publicly available research toolkits. Policymakers will be engaged through, for instance, webinars and policy briefs with evidence-based policy recommendations.

Due to the ubiquity of mobile phones in LMICs and continued interest in mHealth research in these contexts, this review will likely interest digital health researchers, making them aware of

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digital rights considerations when realizing and investigating digital health interventions. Furthermore, the findings of this review may benefit policy makers in LMICs by adding to the emerging discussion about digital rights protections and violations in these settings, which may impact digital health access.

Limitations

This scoping review will follow well-established methods established by Arksey and O'Malley [29] and Levac et al [30]; yet, limitations will exist. First, scoping reviews lack formal bias and quality assessment methods, risking potential bias in the selection of included papers and derived conclusions [33]. Second, only peer-reviewed, English-language papers will be included in the review, thus excluding possible insights from the gray and non–English-language literature. As such, further research is needed to evaluate the quality of existing literature in this space and widen the scope of the included literature. Yet, acknowledging the strength of scoping reviews in providing an initial assessment of the size and scope of the available research literature, this review will provide the groundwork for research addressing digital rights and mHealth in LMICs going forward.

Conclusions

This scoping review will identify digital rights topics in the 2022 peer-reviewed literature on mHealth in LMICs. Moreover, it will highlight the importance of data protection, patient empowerment, and inclusion in mHealth research and related policies in LMICs. In addition to creating knowledge about the digital rights topics currently deliberated or implied in the recent mHealth research literature, the review findings will identify to what extent researchers engage with those topics. Furthermore, the results will identify knowledge and policy gaps and future research directions relevant to mHealth in LMICs research. The findings may advantage digital health researchers and policymakers operating in LMIC contexts, improving understanding of pertinent digital rights considerations relating to mHealth.

Acknowledgments

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Data Availability

The data sets generated and analyzed during this study will be made available from the corresponding author upon reasonable request.

Authors' Contributions

IBH and YJCS were integral in securing funding to support the study. The study was designed by AP, YJCS, HML, OI, and MA. AP, YJCS, and EFV contributed to data collection. Scientific oversight and guidance were provided by IBH and HML to ensure that all activities were conducted responsibly. All authors contributed to and approved the final paper.

Conflicts of Interest

IBH is the Codirector, Health and Policy at the Brain and Mind Centre University of Sydney. The Brain and Mind Centre operates an early-intervention youth service at Camperdown under contract to headspace. He is the Chief Scientific Advisor to, and a 3.2% equity shareholder in, InnoWell Pty Ltd which aims to transform mental health services through the use of innovative technologies. HML is a section editor for JMIR Aging but does not receive any financial benefit nor preferential treatment in the review process. AP, YJCS, EFV, OI, and MA have nothing to disclose.

Multimedia Appendix 1
Search strategy.
[DOCX File , 16 KB - resprot_v12i1e49150_app1.docx]

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Abbreviations

LMIC: low- and middle-income country
mHealth: mobile health
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews

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Protocol

Coadaptation Between Smart Technologies and Older Adults Over Time: Protocol for a Scoping Review

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Abstract

Background: The Internet of Things (IoT) has gained significant attention due to advancements in technology and has potential applications in meeting the needs of an aging population. Smart technologies, a subset of IoT, can support older adults in aging in place, promoting independent living and improving their quality of life. However, there is a lack of research on how older adults and smart technologies coadapt over time to maximize their benefits and sustain adoption.

Objective: We will aim to comprehensively review and analyze the existing scientific literature pertaining to the coadaptation between smart technologies and older adults. The primary focus will be to investigate the extent and nature of this coadaptation process and explore how older adults and technology coevolve over time to enhance older adults' experience with technology.

Methods: This scoping review will follow the methodology outlined in the Joanna Briggs Institute Reviewer's Manual and adhere to the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analysis Extension for Scoping Reviews) guidelines for reporting. Peer-reviewed articles will be searched in databases like Ovid MEDLINE, OVID Embase, PEDro, OVID PsycINFO, EBSCO CINAHL, the Cochrane Library, Scopus, IEEE Xplore, Web of Science, and Global Index Medicus. The research team will create a data extraction form covering study characteristics, participant characteristics, underlying models and frameworks, research findings, implications for technology coadaptation, and any identified study limitations. A directed content analysis approach will be used, incorporating the Selection, Optimization, and Compensation framework and Sex- and Gender-Based Analysis Plus theoretical framework.

Results: The results of this study are expected in January 2024.

Conclusions: This scoping review endeavors to present a thorough overview of the available evidence concerning how smart technologies interact with older adults over an extended period. The insights gained from this review will lay the groundwork for a research program that explores how older adults adapt to and use smart technologies throughout their lives, ultimately leading

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to improved user satisfaction and experience and facilitating aging in place with tailored support and user-centered design principles.

International Registered Report Identifier (IRRID): PRR1-10.2196/51129

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KEYWORDS

scoping review; review methods; review methodology; knowledge synthesis; scoping; coadaptation; older adults; older adult; gerontechnology; technology; smart technology; smart technologies; smart; geriatrics; elderly; elder; geriatric; scoping literature review; protocol; internet of things; IoT; ageing; aging; PRISMA-ScR; user-centered design

Introduction

In recent years, the Internet of Things (IoT) has gained significant attention from researchers, health service providers, entrepreneurs, and technology developers [1,2]. The IoT refers to the interconnection of various devices, objects, and systems through the internet, enabling them to collect and exchange data and perform intelligent actions [1]. The rapid growth of IoT has been fueled by advancements in connectivity, sensors, data analytics, and artificial intelligence [3]. Concurrently, researchers have recognized the potential of various technologies in meeting the needs of a rapidly expanding aging population [2,4,5]. These technologies aim to enhance the quality of life, foster independent living, and address the challenges associated with aging in place.

Older adults (aged 55 years or older) are expected to make up 16% of the global population by 2050 [6]. Ensuring effective support for older adults who choose to "age in place," meaning they prefer to live independently in their own homes rather than relocating to institutionalized care facilities such as nursing homes, is of utmost importance [7-9].

Smart technologies are believed to have the potential to help older adults successfully age in place [10]. Smart technologies refer to a wide range of devices, systems, and applications that use sensors to collect data that can influence the machines' "decision-making," that connect with and share data with other systems, that use processors to run algorithms based on predefined rules or prescriptive models, and that have a user interface of some kind. Lyardet and Aitenbichler [11] define them as having "computational power, information and sensing capabilities into everyday objects and environments." These systems leverage technology to enhance functionality, automation, and interactivity [12] and are increasingly viewed as tools that expand both capability and capacity to support older adults, many of whom live with multiple chronic conditions and age in their homes [13].

Older adults can benefit from smart technologies to promote independent living [4,14]. Smart technologies can also be customized to a degree to the unique needs and preferences of older adults [15,16] and are increasingly used to support occupational and leisure activities in various aspects of daily life [14,17]. To date, research has demonstrated that smart technologies can promote independent living, enhance health and well-being, and help to improve the quality of life in older adults and their caregivers [14,18-21]. For example, smart wearable devices can serve as fall detection and prevention tools, providing alerts or notifications in case of a fall or sudden changes in movement patterns that can help older adults with their self-management and active engagement [22,23]. Other studies have explored the use of voice-activated virtual assistants like Amazon Alexa or Google Assistant by older adults [24,25]. For example, such assistants can help older adults with their exercise routines, engage in digital leisure, and support self-management of their health and well-being [24-27].

The literature exploring the interaction between smart technologies and older adults, from the young old (65-74 years old) to the oldest old (>85 years old), is limited. However, it is crucial to understand this interaction in order to maximize the benefits these smart technologies can provide. While several studies have explored older adults' use of smart technologies [14,15,28-30], fewer studies have explored how older adults coadapt to and with these technologies [31-35]. In the context of smart technologies and older adults, coadaptation refers to the process by which both older adults and the technologies they use adapt and adjust to each other over time [36-38]. As an example, a recent longitudinal study of Google Home suggests that patterns of use and benefits experienced by older adults from these technologies change as they get more used to its features and increase their confidence and digital literacy [39].

However, most existing studies fail to consider how older adults coadapt technologies over time to meet their evolving needs. Understanding how older adults adapt to and interact with smart technologies over an extended period is essential for the development of effective and sustainable technological solutions. Moreover, this is important to understand how to sustain adoption as we know from previous research that some abandon it after trial [40]. A recent qualitative systematic review and meta-synthesis explored the existing qualitative data on older adults' perspectives, opinions, and experiences regarding wearable devices [41]. The review synthesized the perspectives of 349 participants, ranging in age from 51 to 94 years, who wore smart devices for durations ranging from 3 days to 24 months [41]. Among other factors, the authors emphasized the importance of the technology's ability to adapt to user's preferences over time, as this was found to play a crucial role in determining the long-term adoption of smart technologies by older adults [41].

This scoping review protocol aims to address the existing research gap and to better understand the current body of scientific literature that explores the interaction between smart technologies and older adults over time. Furthermore, the review

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will explore how their interactions coadapt to optimize user experiences and the benefits they may accrue from their use. This study will support further research on how older adults compensate for declines as they age, how to tailor artificial intelligence–enabled technologies for specific needs, inform the development of more intuitive technologies, alleviate caregiver stress, and develop policies that promote independent living.

Methods

Study Design

A scoping review was chosen as the systematic method for synthesizing knowledge [42-44] to comprehensively map the available evidence and provide a broad overview of the literature on the interaction between smart technologies and older adults, considering the diverse range of study designs, methodologies, and sources in this research area [44]. This scoping review protocol was guided by the PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Protocols) guidelines [45,46]. Our proposed study will use the methods outlined in the Joanna Briggs Institute manual for knowledge synthesis [47] and will be reported following the PRISMA-ScR (PRISMA Extension for Scoping Reviews) guidelines [48]. Our study will not involve evaluating the quality of the included studies as scoping reviews seek to identify and map all relevant evidence rather than assessing the strength or validity of individual studies [43]. The study will be conducted in 2023.

Ethical Considerations

Ethics review board is not necessary for this particular study as all literature will be publicly available. The public was not involved in the design of this scoping review protocol. This scoping review protocol has undergone registration in the Open Science Framework [49].

Theoretical Lens

This study will be informed by 2 theoretical frameworks. This study will be informed by the Selection, Optimization, with Compensation (SOC) framework [50,51] that suggests as individuals age, they use adaptive strategies to maintain or enhance their well-being and achieve their goals, despite changes in cognitive and physical abilities [50,51]. This can be applied to understand how older adults coadapt with smart technology as they age. The selection aspect of the SOC framework refers to the process of choosing goals, activities, and resources that align with one's capabilities and priorities, whereas optimization involves actively engaging in practices to enhance performance and maximize benefits [50,51]. Compensation in the SOC framework refers to the adaptation strategies individuals use to overcome limitations or challenges in achieving their goals, such as using alternative approaches or tools to compensate for declines in cognitive or physical abilities [50,51]. Over the life span, there are 3 main functions associated with ontogenetic development, namely growth, maintenance, and the regulation of loss. The ability to manage weakening functionality and intellectual capacity using SOC lessens as we age, increasing the importance of research into scientific and cultural innovations that will extend the optimization of development and independence later into the lifespan [50].

The study will also incorporate the Sex- and Gender-Based Analysis Plus (SGBA+) theoretical framework [52]. SGBA+ draws on intersectionality frameworks and was specifically chosen to examine sample characteristics, including biological sex and various social positions of older adults, such as ethnicity, income, age, race, education, and gender within the existing body of research [52,53]. This framework was chosen based on the growing recognition that there are significant differences and disparities in older adults' technology use and adoption experiences related to socioeconomic, demographic, physical, cultural, and psychological factors [54,55].

Review Questions

What is the extent and nature of the existing scientific literature exploring the coadaptation between smart technologies and older adults and how do older adults and technology coevolve over time to enhance older adults' experience with the technology?

Subquestions are (1) what have been the outcomes of the coadaption between older adults and smart technology? (2) What specific outcome measures have been used in studies investigating the experiences of older adults in terms of coadapting with technology over time? (3) What specific strategies or approaches have participants used to adapt to the changing circumstances, challenges, or opportunities in their environment, and what process do they follow when making adaptive decisions? (4) What are the key characteristics of older adult participants who have been involved in studies examining the coadaptation between smart technologies and older adults? (5) What methodological strengths, limitations, and recommendations have been documented in the literature regarding the exploration of coadaptation between smart technologies and older adults? (6) What research models and theories contribute to the conceptualization of coadaptation?

Inclusion Criteria

Overview

We used the Population, Concept, and Context (PCC) framework to determine the elements of our inclusion criteria [47].

Participants

The participants included in this study will consist of individuals aged 55 years or older and living independently in the community. We operationalize independent living as individuals aging in place, that is, living within houses, apartments, and retirement communities (ie, not institutional care settings [56]). Thus, this review will encompass a diverse population with varying health conditions and levels of independence.

Concepts

The concepts of interest are smart technologies, interactions and coadaptations, and experiences and outcomes. Smart technologies, in the context of this study, refer specifically to wearables and voice-activated virtual assistants [57]. Older adults, as end users of smart technologies, gain a progressively

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refined understanding of the technology's functionalities, operational nuances, and potential utilities [38]. Simultaneously, the technology itself assimilates and accommodates user preferences, habits, and behaviors through machine learning algorithms and adaptive interfaces [36]. In the context of older adults, it is notable that the iterative coadaptation process fosters an environment of familiarity and trust, resulting in reduced cognitive load and an enriched user experience [58,59]. As postulated by Melenhorst et al [60], further research should delve into the intricate interplay of individual differences, cognitive aging, and the evolution of technology in the context of sustained coadaptation over time. Thus, our concepts focus on the dynamic process of interaction between older adults and smart technologies and involve an exploration of how older adults engage with and adapt to the use of these technologies over time. We define coadaptation as the reciprocal adjustments and changes that occur in both older adults and smart technologies as they interact and learn from each other [36,37,61-63]. We will include any study that has explored coadaptation using older adults as the human component of the system. This includes, but is not limited to, quality of life, well-being, social connectedness, independence, and overall user experience.

Context

This review aims to encompass a wide range of contexts, settings, disciplines, and fields without imposing limitations. We will include articles from diverse areas such as clinical sciences, public health, social sciences, engineering, and policy. By adopting such a transdisciplinary approach, the review aims to provide a comprehensive understanding of the topic by incorporating insights from various domains and disciplines.

We will limit the search to literature published since 2000, in part to ensure the review can prioritize studies that are more likely to reflect current knowledge, practices, and technologies related to the topic of interest.

Types of Sources

Our sources will consist of peer-reviewed scientific literature that presents empirical study designs (eg, quantitative research studies, qualitative research studies, mixed methods studies, experimental studies, observational studies, case-control studies, cohort studies, and cross-sectional studies). We will also include conference proceedings and dissertations. By incorporating diverse empirical study designs, the review aims to gather a comprehensive range of evidence and perspectives on the topic, allowing for a more nuanced understanding of the interaction between smart technologies and older adults. Literature reviews and grey literature will be excluded.

Search Strategy

The search strategy for this scoping review will be developed by an information specialist (Centers for Disease Control and Prevention). The following subject headings and terms related to the following concepts may be included in the search: (1) aged, seniors, older adults, elderly, people with disabilities, cognitive and physical disabilities; (2) wearable electronic devices, voice recognition, artificial intelligence, smart technology, smart assistive technology, virtual reality, ambient intelligence; (3) coadaptation, double-loop learning, coevolution, human-computer interface, human-environment interaction, interaction design, personalization, customization, tinkering, crafting, redesign, modification, sensemaking, hacking, accommodation, mutual adaptation, symbiotic evolution, reciprocal adjustment, interactive iteration, user-technology synergy, dynamic interface refinement, adaptive coevolution, concurrent learning, and bidirectional refinement.

These terms will be combined using Boolean operators (such as AND and OR) to construct search queries tailored to specific databases or search engines.

An initial search will be conducted in Ovid MEDLINE, using text words in article titles and abstracts, as well as index terms, to identify relevant articles. This strategy will undergo press peer review to minimize biases and ensure comprehension prior to being finalized [64]. Once the strategy is finalized in Ovid MEDLINE by the research team, it will be translated and adapted for other databases including OVID Embase, PEDro (Physiotherapy Evidence Database), OVID PsycINFO, EBSCO CINAHL, IEEE Xplore, Web of Science, the Cochrane Library, Scopus, and Global Index Medicus by the information specialist. The aim is to ensure comprehensive coverage of relevant literature by searching multiple databases. The retrieval period for the search will span from January 2000 to August 2023.

The final search will be reported following the PRISMA-S (PRISMA literature search extension)—an extension to the PRISMA Statement for Reporting Literature Searches in Systematic Reviews [65]. To identify any studies that may have been missed during the search process, we will conduct a hand-search of the reference lists of the included articles [44] and conduct forward and backward searching [66]. Additionally, we will consult with experts in the field (eg, authors of the included paper) to gather their insights and recommendations on potentially relevant studies that should be included in the review.

Study Selection

The search results will be combined in EndNote reference management software and duplicates will be removed [67]. The deduplicated records will be imported into Covidence (Veritas Health Innovation Ltd), a tool for managing and documenting studies during the review process [68]. Screening will occur in 2 phases: level 1 for title and abstract screening and level 2 for full-text screening. To ensure consistency, a pilot test will be conducted on 10 titles and abstracts by all members of the research team to evaluate agreement among reviewers. Any discrepancies and ambiguity regarding the inclusion and exclusion criteria will be resolved through discussion, and another pilot test will be conducted until a consensus is reached. Following the pilot testing, the titles and abstracts will be screened by 2 reviewers against the predetermined inclusion criteria. The authors will use Covidence to vote yes, no, and maybe. Abstracts with uncertainty will undergo full-text review. Potentially relevant sources will be assessed at the full-text stage by the same 2 independent reviewers. Any disagreements in voting between reviewers will be resolved through discussion with the senior responsible investigator at both levels of screening. The reviewers will meet weekly with the research

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team to discuss the screening process. The following inclusion criteria will be used to screen the literature: (1) be published in the English language in a peer-reviewed journal and include primary data on wearables and voice-activated virtual assistants as the primary smart technology interventions; (2) examine the interaction between smart technologies and older adults over a period of 6 months or more; (3) involve study samples of participants only aged 55 years or older.

Study Extraction

The research team will create a data extraction form to extract data related to the study aims and questions. Thus, the data extraction process will cover various categories, such as study characteristics (eg, the author's name, year of publication, country of origin, study purpose or aim, study design, data collection methods, sample size, and study setting), participant characteristics (ie, sex, gender, and other identity constructs), underlying models, theories and frameworks used to inform the research, findings, implications for the coadaptation of technology process, and any quality or limitations identified in the study. We will look for instances of shifts in user behavior patterns over time, reflect on adjustments in interactions with smart technologies, and identify instances where both users and technologies engage in reciprocal feedback loops, thereby leading to iterative adaptations.

Three reviewers (KK, AG, and JM) will first pilot the extraction tool on a subset of the articles. The data extraction tool will be modified and revised as needed during the extraction process for each study included. Any disagreements between the reviewers will be resolved through discussion or by involving additional reviewers if necessary. Next, 1 author (KK) will extract data from the included studies. All relevant data from the studies included will be extracted using free text. By extracting data using free text, the reviewers can capture a wide range of details and nuances, providing a detailed overview of the studies' content and enabling a thorough analysis of the research findings. The senior responsible investigator will then review all extracted data for accuracy.

Data Analysis and Presentation

The scoping review will use 3 reporting and presentation strategies to provide an overview of the literature.

First, a basic numerical account will be provided, presenting information on the number of included records, the year of publication, the types of study designs included details of included participants, and the outcome measures, among other relevant factors. This numerical summary will give a quantitative overview of the body of literature.

Next, a directed content analysis [69] will be conducted on the included literature, focusing on the purpose of coadaptation techniques used over time, study findings related to outcomes and experience, and implications for technology design and future research. The content analysis will involve inductive and deductive categories. Deductive categories will be informed by the SOC model to examine how older adults use the 3 strategies of selection, optimization, and compensation [51] in their interactions with smart technologies and the coadaptation process over time. We can examine how these strategies influence their satisfaction, experiences, and outcomes with technology. In addition, the model can help identify any gaps or areas where further support or intervention may be needed to enhance the coadaptation process.

To do so, all authors will read over the extraction to become familiar with the content related to older adults' experiences with smart technologies and coadaptation. The authors will then look for instances where older adults engage in selection, optimization, or compensation strategies in their interactions with smart technologies. This will help us identify key concepts derived from the research objectives, research questions, and the SOC. Once we have identified several initial concepts, we will group them into broader categories that align with the three strategies of the SOC model—selection, optimization, and compensation. This step involves organizing similar categories together based on their conceptual similarity. Through team discussion, these categories will be included in a codebook [70]. One author (KK) will then apply the coding framework to the extracted data and return to the full text of the articles if needed for more context [70]. Once the data have been coded, we will organize the coded content based on the patterns, frequencies, and variations within and across the categories to identify common themes [70]. As we explore themes, we will consider differences in various forms of technology [71]. Through team discussions, we will consider the implications of the findings in relation to the research objectives and research questions.

Finally, participant characteristics will be synthesized by having the first author (KK) map the findings into deductive categories informed by the SGBA+ framework [72], including age, patient population, race and ethnicity, sex and gender, sexual orientation, education, geography disability, language, and technology access and comfort [73].

Thus, the descriptive synthesis will also highlight any study limitations, identify knowledge gaps, and suggest opportunities for future research related to the inclusion of participants and gaps in knowledge.

Results

The results of this study and the submission of a manuscript for peer review are expected in January 2024.

Discussion

Preliminary Findings

The scoping review outlined in this protocol will serve as a foundation for a broader program of research exploring the experiences of older adults and smart technology over time. By expanding upon the proposed work in the scoping review, there is potential to leverage innovative technological solutions and evaluation to support optimized independent aging at home or in other environments such as the workplace, for diverse older adults. Additionally, we anticipate that the results of this scoping review will offer methodological clarity and guidance for exploring the development of coadaption features for technology in this context. The findings from the scoping review will be disseminated through a peer-reviewed scientific journal and conference presentations.

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Limitations

One limitation is that the quality of the studies included will not be assessed. Moreover, we will only include articles that describe empirical evidence and have been published in English over the last 23 years. It is important to acknowledge this limitation as it may bias included studies to those conducted in western countries. Thus, readers of our review must interpret the findings of the review with caution, recognizing that the quality and generalizability of the included studies may vary. The terms coadaptation and smart technologies exhibit significant variation in their usage. During the development of our search strategy, we worked with an information specialist to conduct pilot tests using various terms to ensure comprehensive coverage. However, despite these efforts, there remains some uncertainty as to whether all relevant search terms will be included. As such, it is important to acknowledge that despite our best efforts, which include hand searching and expert consultation, there may still be some risk of missing articles in this rapidly evolving field.

Conclusions

This scoping review aims to present a comprehensive overview of the existing evidence concerning the interaction between smart technologies and older adults over time. The outcomes of this review will establish the basis for a research program investigating how older adults engage with and adapt to smart technologies across various contexts and throughout their lives. Recognizing the unique requirements of older adults, offering suitable assistance, and integrating approaches that prioritize user needs can substantially enhance the satisfaction and overall experience of older adults who aim to age in their preferred environment with the aid of smart technologies.

Acknowledgments

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Data Availability

The data sets generated and analyzed during this study are available from the corresponding author upon reasonable request.

Conflicts of Interest

None declared.

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Abbreviations

IoT: Internet of Things
PCC: Population, Concept, and Context
PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Protocols
PRISMA-S: Preferred Reporting Items for Systematic Reviews and Meta-Analyses literature search extension
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analysis Extension for Scoping Reviews
SGBA+: Sex- and Gender-Based Analysis Plus
SOC: Selection, Optimization, with Compensation

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Protocol

Relationship Between Depression and Falls Among Nursing Home Residents: Protocol for an Integrative Review

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Abstract

Background: Aging exposes individuals to new health disorders and debilitating chronic diseases, yet most older adults, even in functional decline, do not want to leave their homes. Nevertheless, for many, institutionalization in a nursing home (NH) may become essential to ensure their continued safety and health. Depression is one of the most common psychiatric disorders among older adults, especially among those who are institutionalized. Depressed NH residents face a high risk of future functional decline and falls, decreasing their quality of life. The relationship between depression and falls is complex and bidirectional. Previous reviews have focused on home-dwelling older adults or explored the relationship between antidepressant drugs and falls. To the best of our knowledge, no integrative literature reviews have explored the relationship between depression and falls among NH residents.

Objective: Analyze studies on the relationship between depression and falls among NH residents.

Methods: We will conduct an integrative literature review of published articles in relevant scientific journals on the relationship between depression and depressive symptomatology and falls among NH residents. As usually defined, we will consider NH residents to be people aged 65 years and older who can no longer live safely and independently in their homes. We will also consider older adults on short-term stays in an NH for rehabilitation after hospital discharge. Retrieved articles will be screened for eligibility and analyzed following previously reported steps. The most pertinent bibliographical databases will be examined for qualitative, quantitative, and mixed methods studies, from inception until August 31, 2023, thus ensuring that all relevant literature is included. We will also hand-search the bibliographies of all the relevant articles found and search for unpublished studies in any language. If appropriate, we will consider conducting a meta-analysis of the studies retrieved.

Results: A first round of data collection was completed in March 2023. We retrieved a total of 2276 references. A supplementary literature search to ensure the most up-to-date evidence is ongoing. We anticipate that the review will be completed in late September 2023, and we expect to publish results at the end of December 2023.

Conclusions: This integrative review will increase knowledge and understanding of the complex relationship between depression and falls in NH environments. Its findings will be important for developing integrated, multidisciplinary models and care recommendations, adaptable to each NH resident's situation and health status, and for creating preventive interventions to help them maintain or recover optimal health stability.

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KEYWORDS

depression; falls; nursing homes; nursing home residents; older adults; fall risk; intervention

Introduction

Overview

The world's population is aging fast. The World Health Organization predicts that about 2 billion people will be aged 65 years or older in 2030 [1-3]. For various biological, psychological, and societal reasons, older adults are at greater risk of developing psychopathologies such as depression and dementia, conditions which lead to further loss of autonomy and functional decline [4,5]. A recent study estimated a prevalence of depression of 7% among community-dwelling older adults [6]. A depressive episode can be defined as a mood disorder (a common mental and behavioral disorder) that persists for at least 2 weeks [7]. Depression can present at different levels of clinical severity—mild, moderate, or severe—and can occur on 1 unique occasion during a life course or be recurring or chronic [7]. Older adults enduring severe depression and other associated psychiatric diseases face a significant risk of planned or unplanned admission to a nursing home (NH) [8,9]. Several studies have reported that planned and unplanned institutionalization in an NH is often associated with debilitating medical comorbidities, a reduced ability to perform the activities of daily living, problems with mobility, and cognitive impairment [9]. NH residents, mostly older adults, are defined as people aged 65 years and older [10]. However, it is not easy to apply a strict definition because people age biologically at different rates, so, for example, someone aged 75 may be healthier than someone aged 65 [11]. NHs are facilities that provide 24-hour functional support for older adults who require assistance with the activities of daily living or the instrumental activities of daily living and have recognized health needs. They are staffed with health care professionals and provide long-term care and rehabilitation as part of hospital avoidance or to facilitate early hospital discharge; they do not function as hospital wards and are not hospital-based, and they may play a role in providing palliative and hospice care at the end of life [12]. We will also accept studies examining older adults staying in NHs for short-term rehabilitation after hospital discharge. However, most NH residents live there permanently because they have ongoing physical or mental conditions that require constant care and supervision [12].

The reported prevalence of depression among NH residents varies from 15%-48%, with variations caused by the diversity in methodological approaches and measurement instruments used [6,13-15]. Depressed NH residents often become less able to function, and the condition sometimes speeds them toward functional disability, with an increased risk of falls [16]. NHs implement person-centered care as best as they can, considering individuals' needs and striving to avoid functional and mental decline (including disease- and drug-related fall risks) to ensure the best possible level of overall physical, emotional, and mental well-being for their residents [17,18]. However, most care is aimed at residents' somatic complaints: even though psychiatric disorders are prevalent, particularly clinical depression, they frequently remain unidentified by health care staff [19,20]. Furthermore, concerning functional decline, it seems that falls are one of the most significant associated dangers faced by NH residents [21-25]. Multiple causes can contribute to heightening the risk of falls, including frailty, psychopathological disorders, and their pharmacological treatments—all of which are common among NH residents [26-28]. They can even include an NH resident's new, spacious surroundings, involving more distance to cover along corridors or less furniture to hold onto [29-31]. However, with any of these factors, a predicted higher or lower risk may be underestimated or overestimated, creating the false reassurance that something is being done about falls. Falls often have severe consequences for NH residents, and between half and three-quarters of them may take a fall in any given year. Recent research reported that 10%-20% of falls result in serious injury, and a significant fraction of NH residents die from fall-related injuries [32]. Numerous factors can contribute to falls [31,33]. (1) Many NH residents are prescribed antipsychotics, antidepressants, Z-drugs, benzodiazepines, and other drugs to abate neuropsychiatric symptomatology; however, these substances can cause confusion, unsteady gait, and loss of balance. (2) Inadequate or insufficient NH staffing, especially at night, can cause problems when residents need to get up but no one is immediately available to help them. (3) An absence of sufficient adaptive equipment for mobility-impaired NH residents. (4) Existing health conditions, such as orthostatic hypotension, Parkinson disease, Alzheimer disease, and other neuropsychiatric diseases, can result in an unsteady gait that leads to falls. (5) An absence of any comprehensive fall prevention plan for mobility-impaired NH residents at risk of falls.

Depression and falls have a significant bidirectional relationship [34]. Excessive fear of falling, which is frequently associated with depression, increases the risk of falls [35,36]. Both depression and fear of falling are associated with impaired gait and balance, an association that is mediated through cognitive, sensory, and motor pathways. Our integrative review will explore the relationship between depression and falls. The relationship between the variables will determine whether the right conclusions are reached. In our review, a relationship is defined as the existence of a correspondence between the 2 variables of depression and falls—it is a complex and bidirectional relationship. The relationship between depression and falls could be positive or negative associations, symmetrical, causal, linear, or nonlinear [37]. We will also consider these relationships according to their nature or pattern. A relationship suggests that as 1 variable changes, the other also tends to change. For example, 2 variables may have a quadratic relationship. Moreover, depression will be considered as an independent risk factor for falls. Previous studies of prospective cohorts have shown that depression increases the risk of future falls. A recent meta-analysis summarized the findings of 17 prospective studies and found an odds ratio for the association of depression with falls of 1.63 (95% CI 1.36-1.94) [37]. Retrospective studies have reported 4 determinants of falls: postural sway, history of falls, handgrip strength, and depressive

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symptoms [38,39]. Symptoms of depression may have individual direct roles in promoting falls. Poor appetite and weight loss are commonly seen in geriatric depression, and nutritional deficiencies in vitamin D and folate may be related to falls [39]. The relationships between depression, cognitive performance, motor performance, and the risk of falls were illustrated by a recent study that found that the association between depression and slowed-choice stepping reaction time was mediated by 2 variables—quadriceps strength and executive function—that influenced choice stepping reaction time via simple reaction time and balance [40,41]. Depression and falls are also linked indirectly through several common risk factors. Functional decline, history of falls, and cognitive impairment has each been linked separately to both depression and falls. Poor physical health is also a notable risk factor for depression and falls. Vascular disease, in particular, and its related burden of white matter lesions, may produce concurrent changes in balance, gait, and mood [40]. The interaction between depression and falls may also be self-perpetuating. Depressive symptoms are particularly high among recurrent fallers, which may be related to the demoralizing effect of repeated falling [42]. Prospective cohort studies have reported that increased depressive symptoms were associated with increased falls [43]. Conversely, a lower rate of falls was associated with improved morale scores over the follow-up period. The depressive cognitive-affective symptoms seen in repeat fallers include a lower sense of self-efficacy and negative expectations of the future. Restricted activity and decreased social participation can be a complication of recurrent falls: the resulting social isolation is known to be a significant risk factor for depression among older adults [44].

Managing depression in fall-prone individuals is challenging since antidepressant medications can increase the risk of falls, selective serotonin reuptake inhibitors may increase the risk of fragility fractures, and data are lacking about the effect of fall rehabilitation programs on clinically significant depression [45]. Antidepressant medications are indicated to treat moderate to severe depression in fall-prone individuals, but this should include appropriate precautions, including a low starting dose and slow dose titration, the use of psychotropic monotherapy whenever possible, and monitoring for orthostatic hypotension [45-47]. Treating depressed NH residents at risk of falls is a major concern in those settings and deserves our full attention. There is a need to expand current knowledge about the potential relationship between falls and depression among NH residents.

Review Aims and Objectives

This review sought to analyze the literature examining the relationship between depression or depressive symptomatology and falls among NH residents.

Research Question

This integrative review will explore the following question: “What is the relationship between depression and falls among nursing home residents?”

Methods

Design

This integrative literature review aims to synthesize the literature reporting on the relationships between depression or depressive symptomatology and falls among NH residents receiving or not receiving treatment with antidepressant medication. The review will be conducted based on the guidelines contained in Coleen’s *Step-by-Step Guide to Conducting an Integrative Review* [48] in the following order: (1) formulation of a review question, (2) systematic literature search, (3) critical appraisal of the research retained, (4) literature analysis and synthesis, (5) discussion on new knowledge, and (6) preparing a dissemination plan for findings [49].

Types of Participants

The review will consider studies focusing on older adults with a mean or median age of 65 years or older living in a geriatric or psychiatric NH.

Eligibility Criteria

Textbox 1 presents the eligibility criteria for the types of information that publications retained in this integrative review should contain. These criteria were based on an exploratory literature review of sociodemographic features, long-term care facilities and rates of depression among NH residents. We also included NH residents’ contextual and empirical experiences. This review will consider NH’s skilled nursing facilities and long-term care facilities as synonyms, providing a wide range of health and personal care services.

A patient fall is defined as an unplanned descent to the floor, with or without injury [50]. The review will not consider publications reporting on the nonfatal falls of residents receiving antidepressant medication without a diagnosis of depression.

We will include mixed methods studies and use the Mixed Methods Appraisal Tool scale to assess their quality and bias [51], as reported on the Equator Network website.

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Textbox 1. Inclusion and exclusion criteria for the population, phenomena of interest, type of publication, health care setting, and language.

Inclusion criteria

- Population: Older adults (65 years or older) living in nursing homes
- Depression criteria: Depression (diagnosed by a physician) and depressive symptomatology (reported by health care professionals using validated scales), whether treated or not treated with antidepressants
- Falls: Incidence, prevalence, or occurrence of falls; recurrent falls; and reported or assessed risk of falls
- Setting: Long-term geriatric or psychiatric nursing home o nursing home
- Article types: Original prospective research studies with a descriptive, correlational, or cohort design; retrospective cohort studies; and mixed-methods studies
- Language: No restrictions

Exclusion criteria

- Population: Adults younger than 65 years
- Depression criteria: Nursing home residents prescribed antidepressant medication but without recognized depression or depressive symptomatology
- Falls: Near falls (not reported in most publications)
- Setting: Intrahospital or private nursing home contexts (older adults' houses or apartments, assisted living apartments, and community care living)
- Article types: Meeting abstracts; conference abstracts; posters; guidelines, commentaries, editorials, opinion papers, and book reviews and case reports; literature reviews, whether narrative, rapid, scoping, or meta-syntheses, and systematic and meta-analyses

Types of Studies

This integrative review will include studies addressing depressive conditions or symptomatology and may include other types of neuropsychiatric symptomatology. Studies examining concepts surrounding falls and falling will also be associated with the literature search strategy to respond to the research question. Eligible studies will include prospective research studies with a descriptive, correlational or cohort design, retrospective cohort studies, and mixed methods studies.

Types of Sources

The integrative review's searches will consider original articles to identify the prevalence of falls among NH residents and their relationships with depression or depressive symptomatology. We will consider publications in any language but will focus on those identified in languages that the research team masters. In cases where the study language is not mastered, we will contact the authors and ask them to complete this study's data extraction and quality assessment forms. The articles retrieved have been screened, and the review was completed in August 2023.

Search Strategy

The search strategy is developed in collaboration with a medical librarian (JRA). The following bibliographic databases will be examined for qualitative, quantitative, and mixed methods studies to ensure that all the relevant literature is included: Ovid MEDLINE ALL, Embase, CINAHL with Full Text, APA PsycInfo Ovid, Web of Science Core Collection, ProQuest Dissertations & Theses A&I, and Cochrane Library. All searches will be conducted without language or date restrictions. Textbox 2 presents an example of the equation developed in Embase.

Textbox 2. Example of the Embase search strategy.

('nursing home'/exp OR 'nursing home patient'/exp OR 'long term care'/de OR 'assisted living facility'/exp OR 'home for the aged'/exp OR ((nursing NEXT/2 home*) OR "skilled nursing facilit*" OR ("long term" NEXT/3 care) OR "care home*" OR "assisted living facilit*" OR ("assisted living" NEAR/2 resident*) OR "extended care facilit*" OR "intermediate care facilit*" OR "medical home*" OR (institutionali* NEXT/2 elderly) OR "geriatric homes" OR "home for the elderly" OR "homes for the elderly" OR "home for the aged" OR "homes for the aged"):ab,ti,kw) AND ('aged'/exp OR 'elderly care'/de OR 'geriatric care'/exp OR 'geriatric patient'/de OR 'geriatrics'/exp OR 'home for the aged'/exp OR (elder* OR eldest OR geriatr* OR "old age*" OR (older NEXT/1 (patient* OR people OR subject* OR age* OR adult* OR man OR men OR woman OR women OR population* OR person*)) OR aging OR ageing OR senior* OR "late life" OR "oldest old*" OR "very old*" OR "home for the aged" OR "homes for the aged" OR geronto* OR psychoger*)) AND ('falling'/exp OR 'fear of falling'/exp OR 'fall risk'/exp OR (fall OR falls OR falling):ab,ti,kw) AND ('mood disorder'/de OR 'depression'/exp OR 'antidepressant agent'/exp OR (depress* OR "mood disorder*" OR "affective disorder*" OR "mood decline" OR antidepress*):ab,ti,kw) NOT [conference abstract]/lim

Data Management

Selection Process

All the titles and abstracts identified in the searches will be independently screened by 2 reviewers (AMQ and HV) to assess which studies met the inclusion criteria. Disagreements will be resolved through discussions, and in cases where no agreement could be found, a consensus was reached after discussions with the coauthors (AvG and MMM). In addition, the reviewers will independently assess the full-text articles to see if they met the literature review's inclusion criteria. Again, the coauthors discussed and resolved disagreements (HV, AvG, and MMM). The integrative review selection process flowchart will be drawn in accordance with the guidelines in the 2020 PRISMA

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(Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement [52] to present the number of articles identified at each step of the review selection process.

Data Extraction

Data extraction will use a specially designed and structured data extraction form. The following information will be collected from each study finally included in the review: (1) study authors, year of publication, study duration, and country location; (2) study characteristics, including setting, design, and sample size; (3) participants' characteristics, including sex and mean (SD) age; (4) types of results, such as the prevalence of depression or depressive symptoms, depression evaluation tools, the prevalence of antidepressant use, and the prevalence of falls; (5) statistical results; and (6) the studies' recommendations.

Assessment of the Risks of Bias in the Studies Included

The risks of bias in all the cross-sectional, retrospective, and prospective cohort studies; mixed methods studies; and pragmatic or randomized and nonrandomized controlled trials will be independently assessed by 2 reviewers (AMQ and HV). Disagreements will be resolved through discussion and consultation with coauthors (MMM and AvG). We will use the validated Robins-I tool for assessing the risk of bias in nonrandomized studies of interventions [53]: (1) preintervention and at intervention (bias due to confounding, bias in the selection of study participants, and bias in the classification of the intervention), and (2) postintervention (bias due to deviations from intended interventions, bias due to missing data, bias in the measurement of outcomes, and bias in the selection of the reported results) [53]. Bias in cohort and case-control studies will be assessed using the Newcastle-Ottawa Quality Assessment Form for Cohort Studies (NOSGEN) [54] and the Appraisal tool for Cross-Sectional Studies (AXIS) [55]. The NOSGEN tool covers two dimensions of bias and seven domains through which that bias might be introduced into nonrandomized studies of intervention: (1) preintervention and at intervention (bias due to confounding, bias in the intervention, bias due to deviations from intended interventions, bias due to missing data, bias in the measurement of outcomes, and bias in the selection of the reported results) [54]. The AXIS tool assesses study quality and risk of bias, but it does not provide a numerical scale for assessing that quality—a degree of subjective assessment is required [55]. How the tool is used thus has implications for interpreting the results as there will be differences in individuals' judgments. However, it has been argued that numerical scales for quality can be problematic as the outputs from assessment checklists are not linear and, as such, difficult to sum up or weigh, making them unpredictable for assessing study quality.

Our search strategy will include being very careful to select original research papers only, and it will try to avoid duplicates of published data reappearing in longitudinal studies. Additionally, our data extraction sheet will pay special attention to longitudinal cohort studies and any secondary analyses of published results.

Statistical Analyses

We will compute descriptive statistics of the review population's mean and median age, the distribution of men and women, and the number of falls recorded in the studies retained. Additional descriptive statistics will be computed to report differences between NH residents' profiles and types of NHs.

We will consider whether it is appropriate to combine the numerical results from all the studies retained—or at least 2 of them—in a meta-analysis to yield overall statistics (together with their CIs) summarizing the relationship between depression and falls based on risk ratios. For dichotomous outcomes, average intervention effects will be calculated as relative risks or odds ratio with 95% CIs using a random effects model [56]. A random effects model will also be used on continuous data to calculate weighted mean differences with 95% CIs. If required, we will calculate SDs from the SEs or 95% CIs presented in the articles. Heterogeneity will be quantified using the I^2 and chi-square tests. Funnel plots will be drawn, and Egger tests will be computed to explore the possibilities of publication bias [57]. Reasons for effect estimate heterogeneity will also be sought via meta-analyses [58]. To explore the possible determinants of heterogeneity, we will conduct subgroup analyses according to selected study characteristics (eg, participants' age and sex). Furthermore, sensitivity analyses will be calculated by (1) excluding relatively small studies (with fewer than 20 participants) and (2) restricting analyses to the best-quality studies. These data will also be analyzed using SPSS (version 29.0; IBM Corp).

Results

A first round of data collection was completed in March 2023. Our search in Ovid MEDLINE ALL (n=385), Embase (n=810), Cinahl with full text (n=303), APA PsycINFO Ovid (n=178), Cochrane Library (n=123), Web of Science (n=455), and ProQuest Dissertations and Theses A&I (n=22) returned 2276 references. A supplementary literature search to ensure the most up-to-date evidence is ongoing. Studies will be screened independently by 2 research team members. The inclusion and exclusion criteria will be rigorously respected throughout the study selection. Disagreements in article selection will be resolved through discussion. We anticipate that the review will be completed in late September 2023, and we expect to publish results at the end of December 2023.

Discussion

Principal Findings

This literature review will investigate original work on the sometimes complex and bidirectional relationship between depression or depressive symptomatology and falls or fall risks among NH residents. Depression will be considered an independent risk factor for falls, one that may lead to increased fall risks through behavioral, neuromuscular, or psychopathological pathways, as demonstrated in prospective cohort studies [59-61]. We will retrieve studies reporting on depression and falls identified as risks among NH residents, mostly presenting poor physical and mental health and producing concurrent changes in balance, gait, and mood. The review will explore studies indicating any evidence of the bidirectional relationship between depression and falls due to

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deficits in executive function, poor nutritional status, and cognitive disorders. Factors related to falls will be highlighted if they are documented in the publications retrieved. Although the risk factors identified do not always contribute directly to falls, our review will assess whether these factors are useful for detecting fall risks among NH residents.

Limitations of the Literature Review

Although antidepressant medication can mitigate depression or depressive symptoms, which should lower fall risks, it can also increase fall risks independently of depression. We will not consider the contributing factor of antidepressant medication as an independent risk factor for falls within the relationship between falls and depression.

Conclusions

The researchers anticipate that this integrative literature review will increase overall knowledge and understanding of the complexity of the phenomena of depression and falls in NH environments. Indeed, most preceding reviews have focused on home-dwelling older adults or research into antidepressant drugs and fall. The proposed study's findings will be important for developing integrated, multidisciplinary models and recommendations of care that can be adapted to each NH resident's situation and health status, and for creating preventive interventions to enable them to maintain or recover optimal health stability.

Data Availability

The data sets generated during this study are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

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Abbreviations

AXIS: Appraisal tool for Cross-Sectional Studies
NH: nursing home
NOSGEN: Newcastle-Ottawa Quality Assessment Form for Cohort Studies
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

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Protocol

HIV and Black People in Canada: Protocol for a Scoping Review

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Abstract

Background: Race-based health information is necessary to address disproportionate barriers racial communities face and to achieve optimal health outcomes. In Canada, Black people are disproportionately affected by HIV. There is an emerging body of literature on this topic, but a concise summary is lacking. There is a need to collectively and critically analyze research on HIV in the Black population in Canada to identify knowledge gaps and address this disproportionate burden.

Objective: The aim of this scoping review is to summarize the evidence on HIV and Black people in Canada. The main outcomes of interest are HIV prevalence, access to care, HIV prevention and treatment, the HIV care cascade, and related HIV outcomes. Through this scoping review, we aim to provide a comprehensive overview of the existing literature and highlight topics that need more investigation in future research.

Methods: We will conduct a scoping review of electronic databases using a systematic search strategy for qualitative, quantitative, or mixed methods studies reporting on HIV and Black people in Canada. We will conduct our searches in MEDLINE, Embase, CINAHL, Web of Science, EBSCO, and Google Scholar for literature published between 1985 and 2023. Gray literature, including government reports, dissertations, and other reports, will be included. Search results will be screened, and the full text of relevant literature will be retrieved. The extraction of data will be conducted independently by 2 reviewers. Consensus meetings will be held to resolve conflicts. Our results will be reported according to the PRISMA-ScR (Preferred Reporting Items for the Systematic Reviews and Meta-Analyses Extension for Scoping Reviews).

Results: The initial title and abstract review identified 447 articles. These articles will be critically appraised, and relevant information will be extracted. Information from these articles will be compared using charts and tables. Screening will start in November 2023, and we anticipate publishing the scoping review in June 2024.

Conclusions: The findings from this scoping review will help inform policy, practice, and research on HIV and Black people in Canada.

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KEYWORDS

African; barrier; Black community; Black research; Canada; Caribbean; community; conflict; HIV; mixed methods; public health; qualitative; quantitative; race; racial community; racial; scoping review

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Introduction

In 2021, it was reported that the HIV epidemic had led to over 80 million people being infected and over 40 million deaths globally [1]. The World Health Organization reported in 2021 that approximately 38.4 million people worldwide are living with HIV [1]. In Canada, 4.5 people per 100,000 were diagnosed with HIV in 2021 [2]. For over 4 decades, the Black community has been disproportionately impacted by HIV [3]. Although the Black community makes up less than 5% of Canada's total population, 25% of new HIV infections are Black people [3-5]. Additionally, in 2023, Statistics Canada reported higher HIV-related mortality rates among Black Canadians when compared with other ethnicities [6].

In 2014, the Joint United Nations Programme on HIV/AIDS organization, a global initiative aimed at eradicating HIV, developed the 95-95-95 approach (where 95% of people living with HIV are diagnosed, 95% of those diagnosed are on treatment, and 95% of those on treatment have a suppressed viral load) [7]. The Government of Canada aims to end the transmission of HIV by 2030 by adopting the 95-95-95 approach [8,9]. Canada's action plan includes tracking prevalence, increasing access to HIV care and treatments, and focusing on prevention and the care cascade [3,9]. It is unclear how this goal will be fulfilled in the Black community, although Canada's Federal Initiative to Address HIV/AIDS aims to address inequities. In 2016, the results of a Canada-wide census illustrated lower educational attainment, housing access, income, and employment in the Black population when compared with the White population [10]. A study by Husbands et al [11] found that Black Canadian participants were less likely to be tested for HIV if they had racist experiences. Systematic disadvantages, lower income, poorer living conditions, higher rates of unemployment, stigma, precarious work, and many other socioeconomic factors plague the Black community and impact the effectiveness of HIV control and care [3,5,12]. These factors also affect Black people's ability to achieve and maintain viral suppression, which is necessary to end transmission [13].

In addition to behavioral modifications to prevent HIV infection, preventive treatment options for persons at high risk of acquiring HIV include pre-exposure prophylaxis, a combination of antiretroviral drugs [3]. On the other hand, people living with HIV can achieve viral suppression through antiretroviral therapy, therefore decreasing the risk of transmission [3]. Although these options are available, there are still many barriers to accessing them for people in the Black community [8]. A study conducted by Etowa et al [14] identified multilevel barriers, including those at the individual and health system levels that require community-level, health policy, and intersectional interventions. Barriers also remain at other stages of the cascade, such as diagnosis, adherence to antiretroviral therapy, and sustaining care over time [8]. Black French speakers living in predominantly English-speaking provinces also face additional language and communication barriers in HIV diagnosis and treatment [15]. Black people in Canada living with HIV may also be overlooked in surveillance data due to a lack of ethnicity- and race-based data [5]. Therefore, it is beneficial to review the available health literature pertaining to the people living with HIV in the Black community to capture the overall progress toward achieving the 95-95-95 and equitable care.

Some researchers are concerned that once the government of Canada meets the 95-95-95 target, investments in HIV care and research may wane, thus compromising outcomes for the Black community and other subgroups of people who have not met these targets [3]. Identifying the gaps in Black health literature related to HIV is necessary as it will help us better understand the specific vulnerabilities to HIV infection faced by Black people and identify how Black people living with HIV can be better supported. Additionally, having this knowledge can help in the development of a more inclusive HIV response plan and provide the necessary information to fulfill Canada's Federal Initiative [16].

Although several studies have investigated HIV in Black people, this evidence has not been synthesized in a systematic way, and therefore the state of the evidence is unknown and knowledge gaps have not been thoroughly mapped. This scoping review will highlight areas of HIV research that require further evaluation and identify gaps in the current research regarding HIV and Black people in Canada. A preliminary search was conducted using the Cochrane Database of Systematic Reviews and MEDLINE; no scoping or systematic reviews were found on this topic. The purpose of this scoping review is to inform health policy makers, HIV organizations, and researchers on the state of the evidence on the disproportionate burden of HIV on the Black community in Canada and its impact on their lives.

Methods

Overview

This scoping review will use the approach of Peterson et al [17] to inform current HIV research, policies, and education. In contrast to a systematic review, which aims to answer a research question, this scoping review will appraise a wide range of information to illustrate how HIV impacts the Black community in Canada.

This scoping review will be conducted and reported according to PRISMA-ScR (Preferred Reporting Items for the Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) guidelines [18]. The data will be summarized in tables and described narratively. Where possible, we will use means (SD) or counts (percent) to summarize the data from the included studies. Key findings from the studies will be summarized narratively, and the data will be interpreted to identify knowledge gaps, challenges, and opportunities for evidence generation on HIV in the Black community in Canada.

Collaboration

The public and patients were not involved in this review.

Eligibility Criteria for Articles

Types of Studies

Qualitative, quantitative, mixed methods, experimental, and observational study designs will be considered. Additionally, systematic reviews and gray literature will be considered. To fulfill the eligibility criteria, a study must include data on HIV

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and Black people in Canada and address an outcome of interest. Literature in English and French will be included, as our reviewers are not fluent in other languages (Textbox 1).

Textbox 1. Eligibility criteria.

Inclusion criteria

- Qualitative, quantitative, mixed methods, experimental, observational studies, systematic reviews, and government reports, dissertations, and gray literature
- Articles in English and French
- Prevalence, access to care, prevention, treatment, the care cascade (initiation of treatment, adherence to medication, and retention in care), and other HIV-related health outcomes

Exclusion criteria

- Other articles and websites
- Articles in other languages
- Other topics, whether related to Black people in Canada or not

Outcomes

The outcomes of interest are prevalence, access to care, prevention, treatment, the care cascade (initiation of treatment, adherence to medication, and retention in care), and other HIV-related health outcomes.

Search Strategy

We will conduct a comprehensive and exhaustive search of studies on HIV and Black people in Canada. The search strategy is shown in Textbox 2.

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Textbox 2. Search strategy outlining concepts and alternate search terms.

Black ethnicity and racial groups

- minority health/ or exp Minority Groups/ or minority.mp.
- minorit*.mp.
- communit*.mp.
- Africa*.mp.
- Afrique.mp.
- exp Caribbean Region/ or Caribbean*.mp.
- Black or blacks.mp.
- Black canadian*.mp.
- Mixed race*.mp.
- 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9

Canadian provinces and territories

- Canada.tw.
- Canad*.tw.
- 11 or 12
- Newfoundland and Labrador.mp.
- Prince Edward Island.mp.
- lile du prince Edouard.mp.
- Nova Scotia*.mp.
- la Nouvelle-ecosse.mp.
- New Brunswick.mp.
- le Nouveau-Brunswick.mp.
- Quebec*.mp.
- le Quebec.mp.
- Ontario or Ontarian*.mp.
- lOntario.mp.
- Manitoba*.mp.
- le Manitoba.mp.
- Saskatchewan*.mp.
- la Saskatchewan.mp.
- Alberta*.mp.
- lAlberta.mp.
- British Columbia*.mp.
- la Colombie-Britannique.mp.
- Yukon.mp. or Yukon Territory/
- Le Yukon.mp.
- Northwest Territories.mp.
- les Territoires du Nord-Ouest.mp.
- Nunavut.mp.
- le Nunavut.mp.
- Health canada.mp.
- Sante canada.mp.

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- CIHR.mp.
- 14 or 15 or 16 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41

HIV

- HIV Infections/ or HIV-1/ or HIV Antigens/ or HIV Seropositivity/ or HIV Testing/ or exp HIV/ or HIV.mp. or HIV Seroprevalence/ or HIV Seronegativity/ or HIV-2/
- HIV infect*.mp.
- seroconversion/
- 44 or 45 or 46
- 10 and 13 and 42 and 46

Electronic Search

We will search MEDLINE, Embase, CINAHL, Web of Science, and Google Scholar from 1985 (the date HIV surveillance began in Canada) to 2023 [19]. Key terms will be searched in combination with each other. Some examples include HIV, Black, African, Caribbean, and Canada.

Reference Lists

The list of references of the included studies will be examined for relevant articles.

Gray Literature

We will search various government reports, dissertations, and other reports that are significant to this scoping review. Relevant organizations and authors will be contacted.

Screening

Citations collected from the search will be collated in EndNote [20]. After updating the references and removing the duplicates, we will use the DistillerSR platform (DistillerSR Inc), literature review software, to process the articles [21]. We will first screen titles and abstracts. Only the articles that meet our eligibility criteria will be retained. Articles in languages other than English and French will be excluded, as our reviewers are fluent in those languages. Potentially relevant articles will be downloaded as full text for further screening.

A pilot of the eligibility criteria search strategy will be conducted by 2 reviewers. A sample data collection of 50 abstracts will be done to ensure consistency in the search strategy and approach. Interrater reliability will be measured using the Kappa statistic [22]. The screening will progress when there is at least 80% consensus. The process of screening will be as follows: examining titles and abstracts, analyzing full text for relevance, and then completing data extraction and quality review by 2 reviewers simultaneously.

Data Extraction

We will extract data from the full text of included articles, including bibliometric information (author, year, and language), study design, province, source of funding, main objectives, participants, sample size, proportion of females, outcome, community involvement, outcomes reported, and key findings. We will pilot our forms on 5% of the data to ensure that they are clear and can be used consistently. All data processing (title and abstract screening, full-text screening, and data extraction) will be conducted by 2 independent reviewers. Disagreement will be resolved by consensus, and if consensus cannot be reached, a third senior reviewer will adjudicate. Agreement will be measured using the Kappa statistic [22]. Data referring to HIV prevalence in the Black community and related statistics will also be extracted. The data extraction framework is shown in Table 1.

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Table 1. Data extraction framework.

Main category and subcategory	Description
Authors	The institution where authors are based and country of primary affiliation
Lead author	The institution where author is based and country of primary affiliation
Funders	Funder country of origin
Year of publication	The year the research was published
Aims or objectives of study	Stated aim of the study
Methodology	
Study design: subcategory of quantitative, qualitative, or mixed methods	Study design of research within stated category (eg, cross-sectional, ethnography, etc)
Population	Eligibility criteria to participate in the study
Data collection method	Methods of data collection
Data collection and evaluation tools	Types of tools used if applicable and if developed or adapted specifically for this study
Outcome measures	Primary and secondary outcomes (where applicable), or selected measures of success (eg, how were objectives of the study measured)
Community involvement	Was the community involved in the development of methods or data collection tools (eg, key stakeholder involvement in design), co-designing activities
Data analysis	The method of data analysis
Results	
Reported outcomes	Key HIV outcomes or quantitative or qualitative results related to primary stated outcomes
Key findings	Summarize any key findings that report on HIV and Black people in Canada

Ethical Considerations

This study does not require human participants. Only secondary data from publicly available sources will be used, and thus ethics approval is not required. The findings will be disseminated through a peer-reviewed manuscript, conferences, abstracts, and an MSc thesis.

Results

We have identified 447 articles as of May 2023. A critical appraisal of the articles collected will be conducted for the extraction of relevant information. Tables and charts will be used to illustrate similarities and differences in data from various articles. Screening will start in November 2023, and we anticipate publishing the scoping review in June 2024.

Discussion

Overview

The current data and health information related to HIV in the Black population in Canada have not been synthesized systematically. There is a need to identify knowledge gaps in order for future research to fill those gaps. This is significant as it can help us understand how and why the Black population in Canada continues to have disproportionately higher HIV infection rates, HIV mortality, and limited access to HIV treatments and care. The lack of HIV health policies and approaches in Canada that are focused toward disproportionately burdened communities, such as the Black community, is concerning. The results of this scoping review will have implications for the development of health policy and how HIV organizations can better support Black people in Canada. As this scoping review is conducted, data will be critically analyzed to ensure that interpretations, comparisons, and implications are reported and concluded accurately.

Limitations

The Canada-focused approach in this study is the first limitation of this review, as the findings cannot be accurately generalized to global circumstances. However, there is potential for theoretical generalizations to Black communities in countries facing similar dilemmas. A second limitation of this review is that our eligibility criteria exclude articles that are not in English or French. There is a possibility that articles with important information will be left out of our review.

Acknowledgments

This scoping review is being contributed towards a thesis paper for a Master of Health Research Methodology at McMaster University (TG). This review will be supervised by Dr Lawrence Mbuagbaw, an Associate Professor and Research Methods Scientist in Clinical Epidemiology and Biostatistics at McMaster University.

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Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during this study.

Conflicts of Interest

None declared.

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Abbreviations

PRISMA-ScR: Preferred Reporting Items for the Systematic Reviews and Meta-Analyses Extension for Scoping Reviews

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Protocol

e-Learning Evaluation Framework and Tools for Global Health and Public Health Education: Protocol for a Scoping Review

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Abstract

Background: There has been a significant increase in the use of e-learning for global and public health education recently, especially following the COVID-19 pandemic. e-Learning holds the potential to offer equal opportunities, overcoming barriers like physical limitations and training costs. However, its effectiveness remains debated, with institutions unprepared for the sudden shift during the pandemic. To effectively evaluate the outcomes of e-learning, a standardized and rigorous approach is necessary. However, the existing literature on this subject often lacks standardized assessment tools and theoretical foundations, leading to ambiguity in the evaluation process. Consequently, it becomes imperative to identify a clear theoretical foundation and practical approach for evaluating global and public health e-learning outcomes.

Objective: This protocol for a scoping review aims to map the state of e-learning evaluation in global and public health education to determine the existing theoretical evaluation frameworks, methods, tools, and domains and the gaps in research and practice.

Methods: The scoping review will be conducted following the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) guidelines. The initial search was performed in PubMed, Education Resource Information Center, Web of Science, and Scopus to identify peer-reviewed articles that report on the use of evaluation and assessment for e-learning training. The search strings combined the concepts of e-learning, public health, and health science education, along with evaluation and frameworks. After the initial search, a screening process will be carried out to determine the relevance of the identified studies to the research question. Data related to the characteristics of the included studies, the characteristics of the e-learning technology used in the studies, and the study outcomes will be extracted from the eligible articles. The extracted data will then undergo a structured, descriptive, quantitative, and qualitative content analysis to synthesize the information from the selected studies.

Results: Initial database searches yielded a total of 980 results. Duplicates have been removed, and title and abstract screening of the 805 remaining extracted articles are underway. Quantitative and qualitative findings from the reviewed articles will be presented to answer the study objective.

Conclusions: This scoping review will provide global and public health educators with a comprehensive overview of the current state of e-learning evaluation. By identifying existing e-learning frameworks and tools, the findings will offer valuable guidance for further advancements in global and public health e-learning evaluation. The study will also enable the creation of a comprehensive, evidence-based e-learning evaluation framework and tools, which will improve the quality and accountability of global health and public health education. Ultimately, this will contribute to better health outcomes.

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KEYWORDS

computer-assisted instruction; disaster medicine; disaster; e-learning; educational assessment; global health; medical education; public health; evaluation; scoping; review methods; review methodology; education; educational

Introduction

Even before COVID-19, health systems around the globe were confronted with multiple challenges that necessitated strengthening health systems based on the primary health care approach and maintaining a good balance between public health and clinical care. The shortage in the health workforce, including public health professionals, is among the challenges that hinder the achievement of global health goals [1-3]. Still, the medical education literature addressing public health is scarce [4].

e-Learning (also known as digital education or technology-enhanced learning, among other synonymous terms) is a promising educational strategy to address the shortage of skilled health professionals through strengthening education [2]. The electronic-based approach to learning and education uses different forms of electronic devices, applications, or processes. The internet is the commonly used mode to deliver e-learning content, though non–internet-based delivery, such as via CD-ROM, audiotape and videotape, satellite broadcasts, stand-alone computers, and interactive televisions, are also being used [5,6].

In higher education, including medical education, the use of e-learning began in the 1990s and has been documented in the scientific literature since 2000 [7,8]. Structuring learning outcomes around clinical or public health competencies is a common approach to classifying and reporting e-learning interventions [2]. However, the usefulness and effectiveness of e-learning in medical education have long been debated [9-11]. Nevertheless, a well-designed and implemented e-learning program has the potential to provide equal opportunities for medical education by maintaining flexibility, and at the same time, overcoming multiple barriers to building health workforce capacity, such as physical barriers and training delivery costs [2,3,12].

More recently, the COVID-19 pandemic pushed education toward a distance structure and stimulated the exponential growth of e-learning education [8,13]. Unfortunately, many institutions around the globe were not prepared for the digital transformation [14,15]. Moreover, the effectiveness of e-learning depends on many factors that go beyond the e-learning intervention [16,17].

Hence, a pressing need to evaluate the different dimensions of e-learning interventions has emerged. To do so, a standard and rigorous approach to evaluating e-learning is essential. Existing evidence suggests that e-learning is associated with high satisfaction and improvement in knowledge and skills [18,19], and the effectiveness of e-learning for health professionals is comparable to that of traditional educational interventions. However, the existing literature in medical education is usually limited to measuring e-learning outcomes and comparing e-learning with traditional methodologies. Further research is needed, particularly focusing on its impact on trainees' behaviors and patient outcomes [18,20].

Additionally, the validity of such evaluations is threatened by the dearth of literature that reports the use of standardized assessment tools [21,22] and theoretical foundations, which are essential to explain what and how learning can be facilitated [23-25]. Moreover, the methodological diversity among studies hampers the clear interpretation of the findings [26]. To establish a more definitive understanding of the benefits and limitations of e-learning in the health care sector, additional investigation and standardization of methods are essential.

The aim of the systematic scoping review will be to map the theoretical frameworks and models that explain the underlying concepts, domains, and constructs, as well as the assessment tools required, of rigorous e-learning evaluation. This will enable evidence-based practice as a means of ensuring accountability and validity in education.

It is worth noting that evaluation and assessment are often used interchangeably in the literature. In this paper, however, we will refer to evaluation as the process of obtaining information about any aspect of an educational program for subsequent judgment and decision-making. On the other hand, assessment will refer to the instruments that measure the learner's achievements, which comprise an essential component of the evaluation. To understand what is known about how public health e-learning is being evaluated, the scoping review will aim to identify and synthesize the available evidence on the evaluation frameworks and tools. The study will identify, describe, and discuss the theoretical frameworks and tools that are being used to evaluate public health e-learning. The PICO (Population, Intervention, Comparison, and Outcome) essential elements framework guided the development of the research questions (Table 1). Specifically, in the context of public health education, this study aims to answer the following questions: (1) How is e-learning evaluation conceptualized? (2) What are the existing theoretical models or frameworks to evaluate e-learning and what do they aim to evaluate? (3) How is e-learning evaluation investigated or measured? (4) Are there validated tools for evaluating e-learning? (5) What outcomes do these tools evaluate?

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Table 1. PICO (Population, Intervention, Comparison, and Outcome) framework for the systematic scoping review.

Element	Description
Population	Health professionals or students
Interest	e-Learning evaluation and assessment frameworks and tools
Context	Public health and public health-related education
Outcome	Reporting the evaluation framework or tools

Methods

The scoping literature review involved a systematic search following the PRISMA-ScR (Preferred Reporting Items for Systematic reviews and Meta-Analyses Extension for Scoping Reviews) checklist [27]. Unlike systematic reviews, which address a relatively narrow range of quality-assessed studies, a systematic scoping review addresses broad questions, mapping the key concepts underpinning a research area and the main sources and types of evidence with a range of methodologies, and does not undertake quality assessment.

Inclusion and Exclusion Criteria

The articles selected in this review aim to describe or use a framework or tool to evaluate e-learning used for public health education. The e-learning target group could be undergraduate, graduate, or continuing education programs. All types of study designs of peer-reviewed, original studies that were published after 2000 in English will be included. See Textbox 1 for further details about inclusion and exclusion criteria.

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Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Population
  - Includes health professionals or students at any level (undergraduate, graduate, or continuing education programs).
- Interest
  - Articles addressing public health or public health–related fields (eg, global health, international health, One Health, planetary health, humanitarian health, disaster medicine or disaster management).
- Outcome
  - Articles that describe evaluation frameworks or tools for e-learning.
- Article type
  - Peer-reviewed original literature.
  - Empirical and theoretical articles, including those with experimental and quasi-experimental study designs, descriptive and analytical observational study designs, and qualitative studies.
  - Studies may or may not include comparison with conventional or other e-learning.
- Language, date, and availability
  - Articles published after 2000.
  - Articles written in English.
  - Articles for which the full text is available.

Exclusion criteria

- Population
  - The evaluated population did not include health professionals or students.
- Interest
  - Articles that did not address public health or public health–related education.
  - Articles focused on clinical skill evaluation.
  - Articles focused on medical education topics related to individualistic clinical care, diagnostics, or basic health science.
- Outcome
  - Articles that did not describe or use evaluation frameworks or tools.
- Article type
  - Non–peer-reviewed grey literature.
  - Secondary literature, such as reviews and meta-analyses.
  - Opinion articles, theses, dissertations, book chapters, protocols, and editorials.
- Language, date, and availability
  - Articles published before 2000.
  - Non-English articles.
  - Articles for which the full text is not available.

Information Sources and Search Strategy

On January 31, 2022, a preliminary limited search of the PubMed database was conducted to identify relevant articles and keywords. On July 31, 2023, an updated search was conducted in the PubMed, Web of Science, Education Resource Information Center, and Scopus databases for studies published from January 1, 2000, onward. The search was limited to the English language. Search terms included the concepts of e-learning, public health, and health science education and evaluation, frameworks, and tools using “text word searching,” which involves searching for a word or phrase appearing

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anywhere in the document using Boolean operators and truncations (Table S1 in Multimedia Appendix 1).

Study Selection and Screening

The identified records will be imported into Rayyan [28] to streamline the screening process. Duplicates will be removed before titles and abstracts are reviewed independently by 2 authors for the inclusion criteria. We will use the standard PRISMA flow diagram to provide the study selection process. The articles included in the review must report the use of evaluation or assessment for e-learning training within the specified inclusion criteria for the population, topics, and level of education. After initial review, the reviewers will go through the complete text and apply the inclusion criteria.

Data Extraction and Data Items

Data from eligible studies will be extracted by 2 reviewers. The following data will be extracted and charted from each paper: (1) descriptive data of the included study profile, (2) study characteristics data, (3) e-learning and technology characteristics, and (4) the study outcome, including evaluation framework, evaluation methods, and evaluation tools (Table S2 in Multimedia Appendix 1). The data extraction tool will be tested and may be adjusted and amended during the process, and any changes will be documented in the final report. The summary table will improve transparency and reproducibility by showing what types of data were extracted from which studies.

Analysis

The data will be synthesized using structured, descriptive, quantitative, and qualitative content analysis of the main themes and an overview will be provided for the current scope of the literature. In addition, the research team will analyze findings regarding the studies' overall purpose and evaluate the implications for future research, practice, and policy.

Ethical Considerations

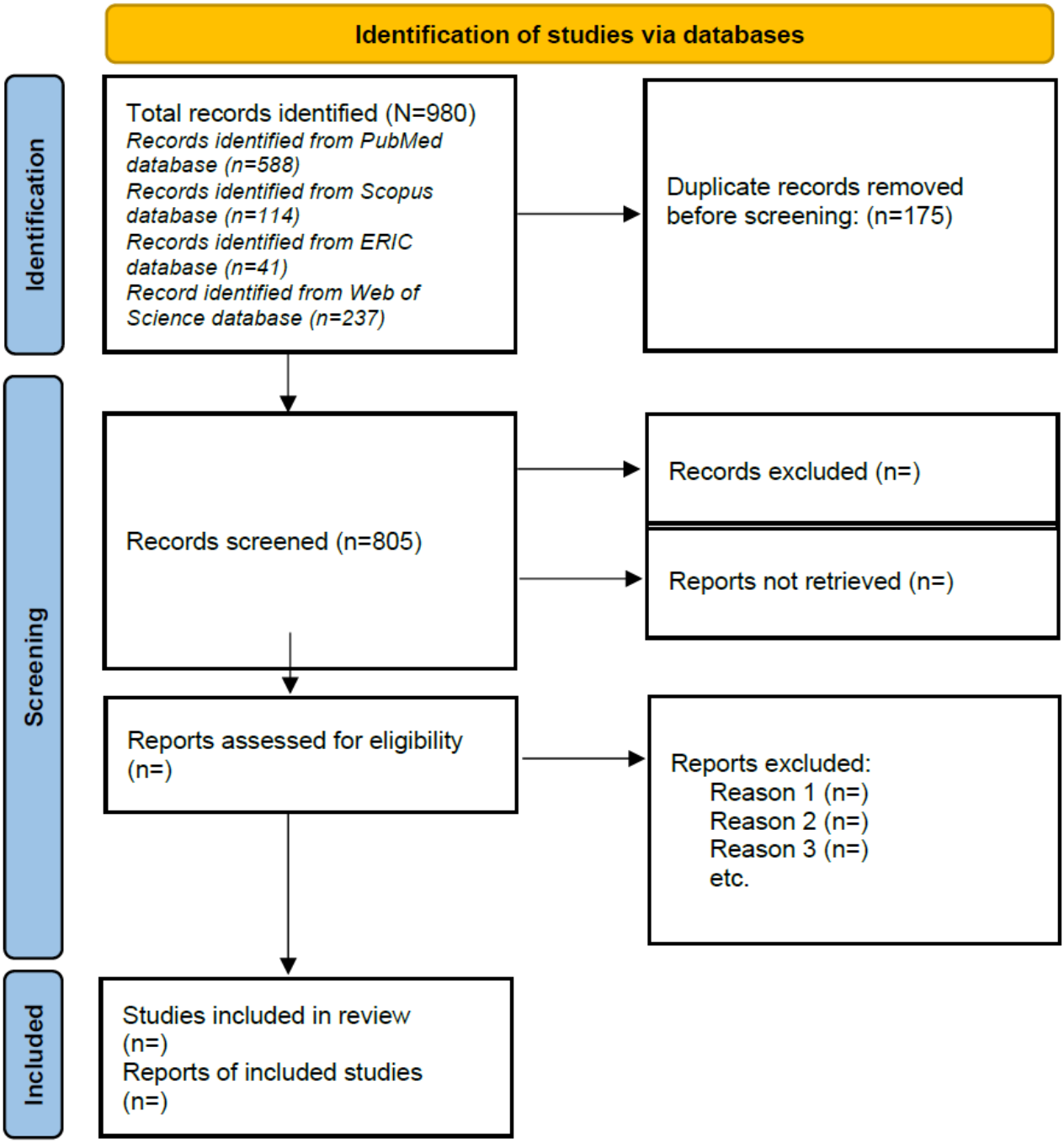
No ethical board approval is necessary to conduct this scoping review.

Results

Targeted searches were conducted in January 2022 to inform the development of a comprehensive search strategy for electronic database searches. This strategy was iteratively developed for and tested in PubMed. Iterative refinements to the scoping review protocol and formalization of the methods were completed by July 2022 and updated on July 31, 2023. The final search was conducted in the PubMed, Scopus, Education Resource Information Center, and Web of Science databases. The initial database searches revealed 980 studies. The database searches were completed in August 2022, duplicates were removed, and title and abstract screening of 805 extracted articles is currently underway. Study selection, data extraction and analysis, and drafting of the manuscript to report the results of the scoping review will be conducted throughout 2023. Any changes to the methods reported here will be documented and reported. The PRISMA flowchart will be used to describe the research selection procedure (Figure 1), and the scoping review's findings relevant to the study objectives will be presented.

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Figure 1. Flowchart diagram of the study selection process based on PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).



Discussion

Expected Findings

Comprehensive multifaceted evaluation of e-learning in the context of public health and global health training is essential to make an evidence-based decision about the future investment in health workforce capacity building. This scoping review is expected to identify existing evaluation frameworks and tools for evaluating public health e-learning.

To the best of our knowledge, this will be the first systematic scoping review to address public and global health as a growing field of medical education. While previously published reviews did not focus on medical education [29] or were limited in scope [29-31], this study will identify the theoretical framework, methods, and domains commonly used in the evaluation of public and global health e-learning. Thus, the study will underline the existing gaps in the scope and practice of e-learning evaluation.

A previous systematic review for e-learning evaluation identified 8 themes [29]. Most of these studies focused on only one or two aspects. Moreover, the representation of evaluation themes varied among different disciplines, technologies, and educational levels. Some of these themes were applied more than others, while others were underrepresented [29]. Still, previous reviews lacked or underrepresented information about public health and global health education [1]. Moreover, the proliferation of e-learning and related literature in the past few years necessitates reviewing the current status of the literature in the field. In

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addition, previous systematic reviews revealed that educational theories and theoretical learning frameworks rarely guided e-learning evaluation, raising concerns about the quality and validity of training evaluation.

Strengths and Limitations

The review will adhere to a robust methodology following the recommended standards for conducting scoping reviews [27,32] that allows transparency and replicability.

The limitations of scoping reviews, which also apply to this review, will be noted. The literature search was applied to 4 relevant search engines. Due to limited time and resources, the search was restricted to English and peer-reviewed articles. Hence, some articles may be missed from the review. Since the scoping review aims to understand the status of evaluating e-learning rather than measuring effectiveness, we will not use a quality appraisal or bias assessment for the included studies.

Future Directions

The lack of comprehensive and robust guidance on e-learning evaluation is an obstacle for educators to ensure the quality and accountability of public health e-learning [3,33]. Hence, the results of this review will allow public health and medical educators to understand how public health e-learning is being evaluated from theoretical and practical points of view. The discussion will reflect on the current status of e-learning evaluation in public health education and compare the findings to the existing body of knowledge. Moreover, the results can guide the development of an evidence-based, field-specific, multifaceted, integrated model for e-learning evaluation and recommend the most appropriate evaluation methods, and tools, as well as domains to be evaluated.

Conclusion

In conclusion, this review will enhance our knowledge about the current practice of e-learning evaluation in global and public health education. The findings will inform the development of a comprehensive field-specific evaluation framework and tools, with the ultimate aim of improving the quality and accountability of global and public health e-learning.

Data Availability

All data generated or analyzed during this study are included in or alongside this article.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Supporting information regarding the search strategy and data items for extracting information from eligible articles.
[DOC File , 66 KB - resprot_v12i1e49955_app1.doc]

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Abbreviations

PICO: Population, Intervention, Comparison, and Outcome
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews

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Protocol

eHealth Tools Supporting Early Childhood Education and Care Centers to Assess and Enhance Nutrition and Physical Activity Environments: Protocol for a Scoping Review

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Abstract

Background: Many children today are growing up in environments that predispose them to develop noncommunicable diseases. While no single preventive solution exists, evidence supports interventions in childcare settings for establishing good nutrition and physical activity behaviors as a "critical window" that could reduce the risk of developing noncommunicable diseases later in life. Emerging eHealth tools have shown potential in promoting best practices for nutrition and physical activity environments in early childhood education and care (ECEC) settings.

Objective: The primary objective of this review is to map the breadth of available evidence on eHealth tools currently available to assess and support best practices for nutrition, physical activity, or both in ECEC settings and to highlight potential research directions.

Methods: This scoping review will be conducted in accordance with the *Joanna Briggs Institute Manual for Scoping Reviews* with adherence to the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) checklist guidelines. Eligibility is based on the Population, Concept, and Context criteria as follows: (1) early childhood educators (population); (2) eHealth (digital) technology, such as websites, smartphone apps, email, and social media (concept); and (3) measurement and intervention tools to support best practices for nutrition, physical activity, or both in ECEC settings (context). The information sources for this review are the bibliographic databases PubMed, Scopus, CINAHL Plus, ERIC, and Embase in English and French with no date restrictions. Following this, a scan of gray literature will be undertaken. The electronic search strategy was developed in collaboration with two librarians. Two independent reviewers will screen the titles and abstracts of all relevant publications against inclusion criteria, followed by a full-text review using a data extraction tool developed by the reviewers. A synthesis of included papers will describe the publication, assessment, and intervention tool details. A summary of the findings will describe the types of eHealth assessment tools available, psychometric properties, eHealth intervention components, and theoretical frameworks used for development.

Results: Preliminary searches of bibliographic databases to test and calibrate the search were carried out in May 2023. Study selection based on titles and abstracts was started in August 2023. The developed search strategy will guide our search for gray literature. The findings will be presented in visualized data map format, waffle chart, or tabular format accompanied by a narrative discussion. The scoping review is planned for completion in 2024.

Conclusions: A structured review of the literature will provide a summary of the range and type of eHealth tools available for ECEC programs to assess and improve nutrition environments, physical activity environments, or both in order to identify gaps in the current evidence base and provide insights to guide future intervention research.

Trial Registration: Open Science Framework XTRNZ; https://osf.io/xtrnz

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KEYWORDS

early childhood education and care; childcare; nutrition; physical activity; healthy eating environment; eHealth; digital technology; health technology; digital public health; eating; diet; dietary; exercise; child; children; childhood; pediatric; pediatrics; digital health; early childhood educators; ECEC; knowledge synthesis; review methods; review methodology; scoping; mobile phone

Introduction

Background and Rationale

Noncommunicable diseases (NCDs) are on the rise and represent the leading cause of disability and death worldwide [1]. In Canada, approximately 60% of deaths are due to chronic illnesses [2]. The latest statistics show that 1 in 3 Canadian adults live with at least one chronic disease, placing a significant physical, emotional, and financial burden on patients in addition to significant societal costs [3,4]. NCDs are largely preventable and share at least one predisposing risk factor related to unhealthy lifestyles, including physical inactivity and poor nutrition [5]. Thus, one avenue of prevention or treatment could be achieved through lifestyle modification of approaches such as good nutrition and physical activity.

Many children are growing up in environments that may predispose them to developing NCDs later in life. Research suggests that many preschool-aged children consume higher energy diets and do not meet the recommended intake for vegetables and fruits and have low levels of physical activity [6-10]. These findings are troubling, as lifestyle behaviors that contribute to the development of chronic diseases, such as eating habits and physical activity habits, are formed in the early years and often track into adulthood [11-13]. While the significance of early child development on adult health and lifelong outcomes is well acknowledged [14], health-promoting behavior interventions focused on healthy eating and physical activity in early childhood settings are an important area for critical inquiry to clarify optimal preventative strategies for support [15].

Early childhood education and care (ECEC) programs have been recognized as ideal settings to promote healthy behaviors. This is because an increasing number of children spend time in care during these formative years, and this represents a significant component of a young child's weekly waking hours [16-18]. Evidence from a review on children's physical activity correlates illustrates that on average physical activity levels are significantly associated with the ECEC setting they attend [19]. The influence on the development of eating behaviors and dietary intake in young children is also strongly influenced by educators and the ECEC setting [20-22]. As a result, ECEC centers are in a unique position to encourage and facilitate healthy behaviors in young children and represent a rich opportunity for interventions aiming at fostering healthier habits in children [23]. Moreover, recent studies suggest that professional development for childcare providers on nutrition and physical activity best practices can positively influence health-related practices and outcomes in children [24].

The proliferation of the internet along with the rapid growth and availability of digital technologies has provided a new platform for health interventions. eHealth refers to the use of information technology, including the internet, digital gaming, virtual reality, and robotics, in the promotion, prevention, treatment, and maintenance of health [25]. eHealth tools include digital technologies such as the web, smartphone apps, SMS text messaging, and social media modalities that may be used for measurement or intervention within a health improvement paradigm [26]. Among studies aiming at fostering healthier habits, many have adopted the eHealth modalities, including interventions targeting ECEC eating and activity practices. eHealth tools are becoming more popular as they can deliver information in various forms and have the potential to reach large audiences at low cost [27,28].

A preliminary search of PROSPERO, PubMed, the Cochrane Database of Systematic Reviews, and *JBI Evidence Synthesis* was conducted, and no current or in-progress scoping reviews or systematic reviews in the area of eHealth tools in the ECEC setting were identified. Previous reviews have primarily focused on examining the effectiveness of preschool-focused nutrition and physical activity interventions delivered face-to-face [29] or eHealth interventions in children and adolescents but not in preschool-aged children [27]. A previous review looked into health behavior resources for childcare educators but limited the focus to the Canadian context and did not consider international evidence [30]. Additionally, the authors explored both print and web-based materials [30]. With the rapid development of digital interventions, Prowse and Carsley [31] emphasize the need to examine those interventions to establish best practices for eHealth nutrition interventions for younger children. Hence, the specific focus of our review is on eHealth technologies. Furthermore, previous reviews emphasize the role of settings in the successful implementation of health promotion interventions [32,33]. For instance, in their review evaluating the success of childhood obesity interventions by setting, Flynn et al [32] found that interventions aimed at improving the food environment delivered in the ECEC setting were effective in improving childhood outcomes. Another important construct to consider is the theoretical basis of interventions. In a recent review conducted by Kracht et al [27] examining eHealth and mobile health interventions in children and adolescents, the authors underscored the importance of reporting on the theoretical underpinnings of eHealth interventions. The use of a theoretical framework in behavior change interventions was associated with increased effectiveness and maintenance of the desired behavior [28,31,34]. Additionally, the use of theory was noted as enabling potential replication for future intervention development [35]. Consequently, this underpins the importance of reporting and identifying the theoretical basis used to develop a given eHealth tool.

Rationale and Objectives

For these reasons and given that no reviews on the use of eHealth tools developed for educators in ECEC settings were

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found, we are undertaking a scoping review in this area. This scoping review will allow a broad examination of the literature in this emerging field and provide directions for future systematic reviews.

Our broad objective is to explore which eHealth tools are available to assess and support best practices for nutrition, physical activity, or both in ECEC environments and to highlight potential future research directions. To map the breadth of the available evidence, the scoping review will address the following specific objectives: (1) to identify the existing eHealth tools that are used to assess or improve nutrition environments, physical activity environments, or both in ECEC centers; (2) to describe the components of the eHealth tools, including technology type (eg, websites, smartphone apps, and social media) and health purposes (eg, nutrition evaluation and movement promotion); (3) to describe the psychometric evidence provided; (4) to report the theoretical foundations used in developing the eHealth tools; and (5) to identify any evidence gaps.

Methods

Study Design

This scoping review will be conducted in accordance with the Joanna Briggs Institute methodology for scoping reviews [36] and follows the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) guidelines [37].

Ethical Considerations

No ethics approvals are required since the planned study is an assessment of the literature and will not include human or animal participants.

Protocol and Registration

This protocol was written before the study commenced (ie, before the electronic literature search was performed). The protocol for this scoping review is registered on Open Science Framework (XTRNZ) [38].

Eligibility Criteria

Overview

The eligibility for our scoping review is based on the Population, Concept, and Context framework (Textbox 1).

Textbox 1. Eligibility criteria for the scoping review.

Inclusion criteria

- Population: early childhood educators within early childhood education and care (ECEC) centers
- Concept: eHealth (digital) tools
- Context: nutrition and physical activity ECEC environment
- Study type: primary studies with any design or data type
- Study focus: eHealth tool is the primary focus of the resource
- Publication status: peer-reviewed journals and gray literature
- Publication language: English or French
- Full text accessible

Exclusion criteria

- Data only collected on children within the ECEC centers
- eHealth technology is a minor component of the assessment or intervention
- Family-based childcare, preschool programs operating less than 4 hours, and before- or after-school care
- Publication language other than English or French
- Full text not available

Participants or Population

This review will consider studies that include early childhood educators within ECEC programs, publicly or privately operated, providing full-day care for children aged 0-5 years. Studies will be excluded if educators work in a family-based setting, preschool programs where children attend less than 4 hours per day, or before- or after-school care.

Concept

This review will consider studies that explore eHealth tools that aim to support nutrition environments, physical activity environments, or both in the ECEC setting. eHealth tools may be defined using any of the constructs displayed (Textbox 2). eHealth tools include digital technologies that (1) measure and (2) deliver interventions to improve nutrition environments, physical activity environments, or both. Additionally, eHealth tools that assess the ECEC environment must provide feedback to ECECs. We will consider all types of eHealth modalities

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including but not limited to web-based tools, mobile apps, SMS text messages, social media, and gamification. We will only include studies where the eHealth tool is an essential assessment or intervention component. The eHealth tool should be the predominant mode of assessment or intervention delivery. We will exclude studies in which the eHealth modality constitutes a minor component, for example, if the majority of the assessment or intervention is conducted in person.

Textbox 2. Definitions of the inclusion criteria in the scoping review.

Population: early childhood educators within early childhood education and care (ECEC) centers

- Educators include the staff within an ECEC center with any responsibilities for the care of children aged 0-5 years, which includes teachers or center directors.
- Studies will be excluded if educators work within family-based care, before- and after-school care, or preschools where children attend less than 4 hours per day.

Concept: eHealth (digital) tools

- eHealth tools are digital technologies that are noninvasive and used to assess and track the health of a patient or consumer.
- eHealth assessment is used as a term to indicate eHealth tools that measure and evaluate ECECs' nutrition environment, physical activity environment, or both, policies, knowledge, and practices.
- eHealth intervention is used as a term to indicate eHealth tools that support ECEC centers to improve their nutrition environment, physical activity environment, or both, policies, knowledge, and practices.
- eHealth modalities are eHealth tools such as websites, mobile or smartphone (SMS text messages and apps), emails, digital games, and social media.
- Studies will be excluded if the digital technology is only a minor part of the assessment (ie, web-based survey without feedback to participants) or intervention.

Context: nutrition and physical activity environment within ECEC centers

- Focused on the domain of nutrition and physical activity related to child health
- Nutrition environments will be defined in the physical context (eg, availability of healthy food and dramatic play center toys) or the social context (eg, adult-child interactions during meals and ECEC mealtime policies).
- Physical activity environments will be defined in the physical context (eg, space for movement activities and time dedicated to activity) or the social context (eg, adult-child interactions during the outdoor time and ECEC physical activity policies).

Context

This review will consider the nutrition and physical activity environments in the ECEC setting as the context. We will focus on both the physical and social environment in ECECs.

Information Sources

The information sources for our scoping review include bibliographic databases PubMed, Scopus, CINAHL Plus (EBSCOhost), ERIC (EBSCOhost), and Embase (OVID). These databases were chosen because they host the most relevant literature in public health digital technologies within the education domain. We will also conduct a scan of the gray literature in accordance with Godin et al [39] that includes (1) the gray literature database ProQuest, (2) a customized Google search, and (3) targeted websites to identify unpublished studies and gray literature. This scoping review will consider all relevant literature including quantitative, qualitative, and mixed methods study designs. Systematic reviews, text, and opinion papers will be considered for inclusion in the proposed scoping review if identified.

Search Strategy

To ensure a comprehensive search, our search strategy will follow the 3-step search strategy from Peters et al [36]. First, an initial limited search of PubMed and Scopus will be undertaken to identify papers on the topic. The text words contained in the titles and abstracts of relevant papers and the index terms used to describe the papers will be used to develop a refined search strategy for PubMed (Multimedia Appendix 1). Second, the search strategy, including all identified keywords and index terms, will be adapted for each included information source. Third, the reference list of retrieved papers will be examined for additional relevant sources. Papers published in English and French with no limit on publication date will be included in this review.

Study Selection

Following the search, Covidence (Veritas Health Innovation) will be used to upload search results and identify and remove duplicates. A pilot test of 10 papers will be conducted by 2 independent reviewers to assess agreement regarding the relevance of titles and abstracts. Following the pilot test, the reviewers will conduct title and abstract screening against eligibility criteria to determine whether to include the study in the review. In the following step, a full-text screening of selected citations will be done by 2 independent reviewers, and a third reviewer will be consulted in the case of disagreements that cannot be resolved by discussion. Reasons for exclusion of full-text papers that do not meet the inclusion criteria will be recorded and reported in the scoping review. The results of the search will be reported in full in the final scoping review and

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presented in a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram [40].

Data Extraction

Data will be extracted from papers included in the scoping review by 2 independent reviewers using a data extraction tool developed by the research team. The data extracted will include specific details about the population, concept, context, methods, and key findings relevant to the review question. The research team will use a data extraction tool adapted from the template provided in the Joanna Briggs Institute methodology for scoping reviews [36]. The data extraction form will include paper information (author, publication year, and country), study design and aim, study setting, participant information, inclusion or exclusion criteria, sample size, recruitment method, eHealth modality used, eHealth tool components, psychometric validation, theoretical underpinning, and outcome measures (Multimedia Appendix 2). For the gray literature, the extracted data will include (1) resource details (eg, title of document, author or organization, country, year, resource type, purpose, and participants) and (2) eHealth tool details (eg, type of eHealth tool, tool components, psychometric properties, and nutrition or physical activity measured or improved). The data extraction form will be piloted before implementation to ensure agreement in capturing relevant information. The data extraction form will be revised as necessary as the data extraction proceeds. Modifications will be detailed in the full scoping review. Any disagreements that arise between the reviewers that cannot be solved by discussion or consensus will be resolved by a third reviewer.

Methodological Quality Appraisal

Methodological quality or risk of bias will not be appraised, which is consistent with guidance on scoping review conduct [36]. This work will inform the next steps on a decision to conduct a systematic review where methodological quality appraisal will be conducted.

Results

The extracted data will be graphically presented in tables and charts in line with the objective of this scoping review. The presentation of results will be organized by each review question. First, a table of all included studies will be presented providing information on authorship, year of publication, country of origin, study design, aims, participants, and outcomes (Table S1 in Multimedia Appendix 3). A second table will display characteristics of the eHealth tools including eHealth modality used, tool components, and psychometric evidence (Table S2 in Multimedia Appendix 3). Data about the use of theoretical framework will be presented in a third table (Table S3 in Multimedia Appendix 3). A narrative summary will describe the results for each research question and will accompany the tabulated results. Data analysis and presentation will depend on data extraction and thus will be subject to change in case of potential modification of the data extraction form. Any changes will be documented in the review.

This study commenced in May 2023. The scoping review protocol was registered in the Open Science Framework to promote transparency and help avoid unintended duplication of reviews. The search strategy was developed in June 2023 in collaboration with 2 university librarians and was refined in August 2023. The title and abstract screening started in August 2023 and is ongoing. The final results will be submitted to an open-access peer-reviewed journal in 2024.

Discussion

Overview

Using eHealth tools can facilitate the evaluation of ECEC environments and the delivery of interventions aimed at enhancing nutrition and physical activity practices within those settings. The synthesis and analysis of existing literature are useful to characterize the current scope of evidence and identify opportunities for future reviews and studies. This protocol will guide a scoping review to identify the extent, range, and characteristics of available evidence [36] on eHealth tools in ECEC settings and to identify any gaps and limitations. This scoping review is also examining the use of theory in the development of the eHealth tools. This information can support the replication of effective tools and inform future intervention development. The results of this scoping review will be disseminated through publication in a peer-reviewed journal.

Strengths and Limitations

While we aim to conduct a comprehensive scoping review, some limitations should be considered. First, only studies written in English or French will be included. Second, this scoping review is limited to full-time day care centers and excludes home day cares and after-school cares. Family or home day cares are excluded due to the scarcity of formalized information available for this group, and after-school cares are excluded as they do not typically serve children aged 0 to 5 years.

This review has several strengths. First, the search strategy was reviewed by 2 librarians with extensive knowledge in scoping and systematic reviews. Second, our search strategy targets diverse databases that are known to host relevant peer-reviewed literature in public health digital technologies within the education domain. Additionally, the search will be supplemented by gray literature that will broaden the scope of the review. Lastly, this scoping review is the first to synthesize the eHealth tools that assess or improve the nutrition and physical activity environment in early learning settings. The results of this scoping review will provide valuable insights into the potential of eHealth tools to promote healthier environments in early learning settings.

Conclusions

This scoping review will identify the types of eHealth technologies in the context of health promotion within early learning settings. This knowledge could guide further research on how eHealth technologies can support the promotion of healthy practices in childcare settings and ultimately inform the development of evidence-based interventions to improve health behaviors and outcomes in children.

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Acknowledgments

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Authors' Contributions

All authors have read and approved the final paper. JH and LMZL participated in the conceptualization and paper composition and developed the data extraction form. All authors participated in piloting the extraction form.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search strategy.
[DOCX File , 22 KB - resprot_v12i1e52252_app1.docx]

Multimedia Appendix 2
Data extraction instrument.
[DOCX File , 22 KB - resprot_v12i1e52252_app2.docx]

Multimedia Appendix 3
Data presentation tables.
[DOCX File , 26 KB - resprot_v12i1e52252_app3.docx]

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Abbreviations

ECEC: early childhood education and care
NCD: noncommunicable disease
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews

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Protocol

Methods for the Clinical Validation of Digital Endpoints: Protocol for a Scoping Review Abstract

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Abstract

Background: Clinical trials often use digital technologies to collect data continuously outside the clinic and use the derived digital endpoints as trial endpoints. Digital endpoints are also being developed to support diagnosis, monitoring, or therapeutic interventions in clinical care. However, clinical validation stands as a significant challenge, as there are no specific guidelines orienting the validation of digital endpoints.

Objective: This paper presents the protocol for a scoping review that aims to map the existing methods for the clinical validation of digital endpoints.

Methods: The scoping review will comprise searches from the electronic literature databases MEDLINE (PubMed), Scopus (including conference proceedings), Embase, IEEE (Institute of Electrical and Electronics Engineers) Xplore, ACM (Association for Computing Machinery) Digital Library, CENTRAL (Cochrane Central Register of Controlled Trials), Web of Science Core Collection (including conference proceedings), and Joanna Briggs Institute Database of Systematic Reviews and Implementation Reports. We will also include various sources of gray literature with search terms related to digital endpoints. The methodology will adhere to the Joanna Briggs Institute Scoping Review and the Guidance for Conducting Systematic Scoping Reviews.

Results: A search for reviews on the existing evidence related to this topic was conducted and has shown that no such review was previously undertaken. This review will provide a systematic assessment of the literature on methods for the clinical validation of digital endpoints and highlight any potential need for harmonization or reporting of methods. The results will include the methods for the clinical validation of digital endpoints according to device, digital endpoint, and clinical application goal of digital endpoints. The study started in January 2023 and is expected to end by December 2023, with results to be published in a peer-reviewed journal.

Conclusions: A scoping review of methodologies that validate digital endpoints is necessary. This review will be unique in its breadth since it will comprise digital endpoints collected from several devices and not focus on a specific disease area. The results of our work should help guide researchers in choosing validation methods, identify potential gaps in the literature, or inform the development of novel methods to optimize the clinical validation of digital endpoints. Resolving these gaps is the key to presenting evidence in a consistent way to regulators and other parties and obtaining regulatory acceptance of digital endpoints for patient benefit.

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KEYWORDS

digital endpoint; digital biomarker; mobile health technologies; mobile health; mHealth; remote monitoring; wearable technology; scoping review; review method; validate; validation; outcome measure; sensor; wearable

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Introduction

Background

Digital technologies such as smartphones, wearables, implantables, digestibles, and other biosensors present new opportunities to collect and analyze health data [1,2]. They enable more accurate and reliable identification and quantification of different aspects of one's health [3]. A wide range of parameters can be collected by digital devices such as physiological, anatomic, and pathological, as well as behavioral-, social-, or activity-related characteristics [3]. The patient can use the device in everyday life while data are passively collected or can perform assessments at the clinic [4]. Before clinicians and researchers can use data acquired by digital technologies, algorithms transform the data into metrics designated as digital endpoints [4].

In clinical care, digital endpoints may increase diagnostic accuracy and improve treatment decisions, as the clinicians can be provided with more information about the patient's status and treatment response in everyday life [2]. In clinical trials, digital endpoints can be used as replacements or as a proxy for outcome measures. This new type of endpoint consists not only of traditional endpoints assessed in a new way but also endpoints that were not previously possible to obtain [5]. By being collected automatically outside the clinic, digital endpoints enable more frequent or continuous data collection while requiring fewer staff and fewer clinic visits and reducing the need for patients to respond to so many questionnaires [6-9]. Despite the concerns that digital literacy may restrict patients' access to clinical trials [8], many argue that technology can support increased trial participation and retention [6]. In addition, it is not consensual whether using digital endpoints will increase the efficiency and effectiveness of clinical trials [1]. Regardless of these concerns, pharmaceutical and technological companies have turned their attention toward digital endpoints, incorporating them into clinical trials as study endpoints [10,11]. So far, 436 clinical trials using digital endpoints have been registered in the Digital Medicine Society Library of Digital Endpoints, out of which 205 (47%) consisted of drug studies, 175 (40.1%) were device-related studies, 30 (6.9%) were biological products, 1 (0.2%) was genetic, and 25 (5.7%) were other medical products [3].

Digital endpoints have yet to be accepted to support new medical product (or new applications of medical products) approvals [12]. There appears to be a global regulatory consensus on using digital devices in clinical trials [1,7,12], but only validated digital endpoints will be suitable for supporting safety and efficacy claims in applications to regulatory authorities [13]. The same applies to digital endpoints intended to be medical products [13]. However, the current need for a well-defined methodology for the clinical validation of digital endpoints poses a critical limitation [13].

The V3 framework, which combines software and clinical development, establishes the foundation for evaluating digital clinical endpoints [13]. Clinical validation is defined in the V3 framework as an evaluation of whether digital endpoints "acceptably identifies, measures or predicts a meaningful clinical, biological, physical, functional state, or experience, in the stated context of use (which includes a specified population)" and takes place after both the verification and analytical validation processes [13]. This assessment evaluates the association between a digital endpoint and a clinical condition. It is subject to similar principles of research design and statistical analysis of clinical validation of traditional tests, tools, and measurement instruments [13,14]. In general terms, clinical validation comprises the assessment of content validity, reliability, and accuracy (which validates the digital endpoint against a gold standard) and the establishment of meaningful thresholds [12,15].

Some approaches have been suggested, such as the Food and Drug Administration Guidance on patient-reported outcomes [16] or the Clinical Trials Transformation Initiative Recommendations for endpoints generated by mobile technology [5], but no standardized framework for clinical validation is currently available. Standardization is challenging; indeed, there is a wide variety of digital endpoints [13]. If we consider bodily functions captured, a few examples include diverse parameters such as heart rate, cognition, lung function, and gait. If we divide digital endpoints by type of devices, we have, for example, smartphones, wearables, implantables, and digestibles. Adding to that, and similarly to traditional endpoints, the clinical goal of the digital endpoints (diagnostic, safety, response, monitoring, prognostic, risk, and predictive) also determines variations in methods of clinical validation.

A search for reviews on the existing evidence related to this topic was conducted and has shown that no such review was previously undertaken. This study aims to map the literature on the methods for validating digital endpoints used or proposed. A scoping review is a suitable approach to synthesize such a complex topic comprehensively [17-19]. We hypothesize that in a scoping review, important patterns of methods for clinical validation of digital endpoints grouped by bodily functions, type of devices, and clinical application goal will emerge. The results of this work will guide researchers and identify potential gaps in the literature, which in turn can inform the development of novel methods to optimize the clinical validation of digital endpoints.

Review Question

The main research question addressed by the scoping review will be "What methodologies have been employed or proposed for clinical validation of digital endpoints?"

Methods

Overview

This protocol is reported in line with the Joanna Briggs Institute (JBI) Scoping Review Protocol [8]. The scoping review will be conducted and reported following the methodology for scoping reviews by the JBI Scoping Review [8] and the Guidance for Conducting Systematic Scoping Reviews [9].

Search Strategy

An exploratory search of MEDLINE (PubMed) was performed to retrieve sentinel papers and identify text words contained in

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the title and abstract and the index terms in the description of those papers to compile a list of terms to inform our search strategy. The search strategy for PubMed was drafted by the first author and further refined through team discussion with the remaining authors. In total, 2 librarians translated and adapted the search strategy for other electronic databases and ran the searches. The final search strategy is reported in Multimedia Appendix 1.

We ran the search query in MEDLINE (PubMed), Scopus (including conference proceedings), Embase, IEEE (Institute of Electrical and Electronics Engineers) Xplore, ACM (Association for Computing Machinery) Digital Library, CENTRAL (Cochrane Central Register of Controlled Trials), Web of Science Core Collection (including conference proceedings), and JBI Database of Systematic Reviews and Implementation Reports. We included databases indexing research related to life sciences and biomedicine and other databases of traditional engineering journals because digital medicine is a highly interdisciplinary field.

The search strategy was first developed for PubMed and then adapted to each additional database, including Boolean operators, various combinations of text words (including truncation), index terms related to digital endpoints for use in clinical practice and clinical trials, and validation studies methodologies. The search in electronic scientific databases will be supplemented by searching gray literature in Google Scholar, ClinicalTrials.gov, and at least 1 national and 2 international nonindexed conference proceedings using free text in the title and abstract related to digital endpoints and validation. This search aims to find conference papers, theses, dissertations, ongoing studies, white papers, academic and industrial reports, expert group documents, regulatory entity documents, blog posts, etc, of potential interest. These sources are essential to consider that information may be in various formats due to the novelty of the theme.

No time or language restrictions will exist, provided an English or Portuguese title and abstract are available. Relevant papers identified in languages other than English or Portuguese will be translated. Additionally, the reference lists of retrieved studies meeting the inclusion criteria will be manually searched to identify additional relevant studies. The final search results will be imported into the professional version of Rayyan [20], a web-based platform for literature review management hosted at NOVA Medical School–Universidade NOVA de Lisboa, and duplicates will be removed. In addition, we will cross-check authors' names across gray literature and results from electronic databases to identify and remove potential duplicates.

Study Selection and Eligibility Criteria

Study screening and selection will be performed using Rayyan [20] as it facilitates collaborative screening of papers while ensuring reviewers do not see each other's selections. The software logs reasons for exclusion and lists disagreements between reviewers. In total, 2 reviewers will independently perform the study selection process. Blinding will be switched off for reviewers to see papers with disagreements, which will be resolved by consensus. If consensus is not possible, a third reviewer will assess the discussed abstracts or full texts and provide a decision. Reviewer agreement will be calculated using the κ coefficient and reported in the scoping review paper.

Study selection will be undertaken in 3 phases: pilot testing, title and abstract screening, and full-text review. The first phase, a pilot, will involve the screening of the same random 20 publications (title and abstracts) by all reviewers, followed by a discussion to ensure consistency and that all relevant data were captured. Any resulting changes to the inclusion and exclusion criteria will be documented and reported. In the second phase, both titles and abstracts will be assessed.

For studies to be included, they must meet the inclusion criteria (Textbox 1), which were defined based on the "Population–Concept–Context (PCC)" framework recommended by the JBI for scoping reviews [9]. Studies will be excluded if they have any characteristics listed as exclusion criteria (Textbox 1).

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Population: Human adults.
- Concept: Scientific methodologies used or proposed to validate digital clinical endpoints.
- Context: The review will include all study designs published in journals, conferences, theses, or dissertations, as well as clinical trials registered in platforms, white papers, academic and industry reports, opinion papers, blog or website or forum posts, letters, guidelines, book chapters, editorials, commentaries, papers or guidelines by an expert group, regulatory entities, or others; there will be no date and language restrictions.

Exclusion criteria

- Studies describing verification or analytical validation of digital endpoints.
- Studies describing clinical validation of surrogate endpoints.

In the third stage, the full texts of the selected publications will be reviewed for further assessment against the inclusion and exclusion criteria. Reasons for excluding sources of evidence at the full-text review will be recorded and reported. As an iterative approach to study selection is recommended [21], changes to this protocol may be made and reported accordingly in the scoping review.

Data Extraction

Reviewers will independently collect data from the full text of each included study using a structured extraction form adapted

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by authors from the review of Polhemus et al [22] with an explanation for each data item. Our team will internally assess the appropriateness and comprehensiveness of the data extraction form. Then, following the "Updated methodological guidance for the conduct of scoping reviews" [21], all reviewers will pilot the extraction form on at least 3 (same) random studies to ensure consistency in data extraction. If a level of agreement indicated by a κ of at least 0.8 is achieved, the data extraction begins; and if not, a second (or more) round of the pilot is conducted. Modifications to the form identified through the pilot, including rewriting sentences for clarity and adding or removing items to the initial list of study characteristics, will be discussed by reviewers. The draft extraction form will include information about each included study, such as authors, year and type of source, and the key findings relevant to the review questions for original papers (Table 1) and regulatory guidelines, viewpoints, expert group recommendations, or other sources (Table 2).

Table 1. Preliminary data items to extract from original papers.

Data items	Explanation
Publication details	
Authors and reference	Who conducted the research? Include the reference.
Year	When was the study published?
Type of source	In what type of literature was the study published (journal, conference, or gray literature—conference, thesis or dissertation, clinical trials registry platform, white paper, book chapter, or others)?
Country or region	In which country or region did the study take place?
General details	
Study design	What was the study's design?
Study aims	What were the study's aims?
Population	What population was studied? What were the inclusion or exclusion criteria (eg, age, disease, and disease severity)?
Study size	How many people participated in the study?
Sampling method	What method was used for sampling?
Study limitations	What were the limitations of the study?
Validation method limitations	What were the limitations of the method used for clinical validation?
Digital endpoint details	
Digital endpoints	Which digital endpoints were measured? How and in what setting were the digital endpoints calculated?
Analytical methods	How did the authors measure the relationship between clinically relevant outcomes and digital endpoints? What association measure was used?
Clinically relevant methods	What clinically relevant endpoints were studied?
Type of clinical application	Which type of clinical application of the digital endpoints concerning the studied outcome? Diagnostic, safety, response, monitoring, prognostic, risk, or predictive?
Study endpoints	Was the digital endpoint used as a primary, secondary, or exploratory endpoint? What other primary, secondary, and exploratory endpoints were measured?
The device used for the collection of digital endpoints	Which devices were used to collect digital endpoints?

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Table 2. Preliminary data items to extract from regulatory guidelines, viewpoints, expert group recommendations, and other similar sources.

Data items	Explanation
Publication details	
Authors and reference	Who wrote the paper? Include the reference.
Year	When was the paper published?
Type of source	In what type of literature was the paper published (journal, conference, gray literature—conference, thesis or dissertation, clinical trials registry platform, white paper, academic and industry report, opinion paper, blog or website or forum post, letter, guideline, book chapter, editorial, commentary, paper or guideline by expert group, regulatory entity, or others)?
Country or region	In which country or region was the paper written? To which regions do the recommendations apply (which country or region, global)?
General details	
Sampling size	What is the recommended or used sample size?
Sampling method	What method is recommended or used for sampling?
Study design	What study design is recommended or used for clinical validation?
Digital endpoint details	
Clinical application of digital endpoints	What is the clinical application of digital endpoints (diagnostic, safety, response, monitoring, prognostic, risk, or predictive)?
Type of validation methods	Which type of validation method is recommended? The trial, simulation, expert opinion, model-centered, and other?
Analytical methods	What methods are recommended to measure the relationship between clinically relevant outcomes and digital endpoints? What association measures should be used?
Analytical methods	Is there any consideration for using the digital endpoint as a primary, secondary, or exploratory endpoint?

Further refinement may be made to the extraction form at the review stage, and the final version will be included in the scoping review. If relevant missing or additional data are necessary, the studies' corresponding authors will be contacted. The data extraction process will involve 2 reviewers to minimize the chance of errors and bias [21]. Disagreements will be solved through consensus, and if that is not achieved, a third reviewer will provide the final decision. Reviewers will use the Rayyan [20] software to access the full texts of eligible studies and register the information extracted in a Microsoft Excel spreadsheet file.

Results

A narrative synthesis will be produced to summarize the extracted data and present a comprehensive overview of the methods for the clinical validation of digital endpoints. The study will be reported following the "Preferred Reporting Items for Systematic Reviews and Meta-Analysis: Extension for Scoping Reviews (PRISMA-ScR)" [19]. The search strategy and selection process results will be described, and a PRISMA-ScR flow diagram will be presented [23]. Moreover, the results relevant to this scoping review's objectives and research question will be described [23], namely, the methods for the clinical validation of digital endpoints, structured around the patterns identified per device, digital endpoint, and clinical application goal. Findings will be compiled in tables and figures where appropriate. We will also identify gaps in the evidence to inform areas of future research.

Discussion

This scoping review will map the methods for the clinical validation of digital endpoints. It will be unique in its breadth since it will comprise digital endpoints collected from several devices and not focus on a specific disease area. However, we expect to be able to derive more robust trends and patterns of clinical validation of digital endpoints generated from movement, physiological (electrical, optical, and imaging), and biochemical sensors.

Digital clinical endpoints are a new and rapidly growing research field [24]. Research studies assessing the clinical validity of digital clinical endpoints do not accompany the volume of studies reporting the development of digital endpoints [24], likely due to clinical validation being the last phase of the V3 framework, following verification and analytical validation. As research on digital clinical endpoints is a new field, the initial focus is the development phase. Moreover, it has been reported that deployment studies have been conducted without prior clinical validation, therefore not establishing fit-for-purpose and trustworthiness [24]. This can result in either resource wastage or harm [24]. The lack of a standardized methodology is likely a significant reason for the reduced proportion of clinical validation studies of digital endpoints. Without a well-defined and standardized method, more effort and time are required for each study. Hence, patterns must be identified so researchers can rapidly have a reference to guide clinical validation studies of digital clinical endpoints.

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There is an asymmetry in the number of publications for body functions, diseases, or conditions, with a predominance of studies assessing digital endpoints derived from movement, physiological (electrical), physiological (optical and imaging), and biochemical sensors [24]. Those endpoints are most commonly used to answer clinical questions and are most common among studies promoted by pharmaceutical companies to support medical product development [11,24,25]. Thus, we may be able to examine better trends and patterns of digital endpoints. We may also be able to identify gaps in the literature, informing the need for further research in specific types of digital endpoints.

This scoping review study will conform with the recommended standards for conducting scoping reviews, which contributes to a robust methodology as well as transparency and reduced risk of bias. However, some limitations are expected. First, we will not undertake a methodological appraisal or risk of bias assessment of the studies included in the scoping review, as that neither is recommended in scoping reviews [21] nor would be adequate for all sources of evidence we are expecting to retrieve (eg, letters, guidelines, website, or blog posts). However, we are aware that the lack of methodological appraisal in scoping reviews is not consensual [26], with some authors defending that it prevents identifying gaps in the literature regarding the low quality of research and using the results to make recommendations for policy or practice [26]. Second, there is a heterogeneity of terms used to describe endpoints generated by digital technology. We included several terms in our search strategy, informed by a pilot search in PubMed we have conducted, but more may be needed to capture all existing studies exhaustively. In addition to that, digital endpoints can be identified using terms related to the technology (eg, inertial sensors, smartwatch, and smartphone), disease (eg, rheumatic diseases), or bodily function (eg, sleep, gait, and hemodynamic). We attempted to create an extensive list of appropriate search terms for all available technologies and bodily functions. Still, the search strategy retrieved a colossal number of results, making a scoping review unfeasible. Following expert advice, we maintained only some of the terms related to technology and the terms related to digital endpoints, expecting a low possibility that additional information of interest may be missed.

We believe this work will be relevant to various researchers, including those designing and developing clinical studies using digital endpoints and those involved in applications for marketing approval of either drugs assessed in clinical trials using digital endpoints or developing digital health technologies to collect data remotely and seeking regulatory approval. It will also inform health care professionals supporting the modernization and acceleration of clinical trials and those interested in integrating digital endpoints in their clinical practice. The study findings could further be used by regulators developing regulations and guidelines for clinical trials and medical devices. Therefore, we plan to disseminate the results of this scoping review through publication in an international peer-reviewed scientific journal and present the main findings in a workshop of the European project COTIDIANA [27] to a diverse group of stakeholders.

Acknowledgments

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Data Availability

Data sharing does not apply to this paper, as no data sets were generated or analyzed during this study.

Authors' Contributions

SR and FN conceptualized the study as a scoping review. AMR and FN provided oversight for scoping review protocol development. SR drafted the protocol. ARH, AMR, and FN helped to review and edit the protocol. SR, ARH, SSS, and TC drafted the search strategy and ran the search on electronic databases. All authors read and approved the final paper.

Conflicts of Interest

AMR Received independent grants or support from Amgen, Astrazeneca, Novartis, Abbvie, Pfizer, MSD, Lilly, and Boehringer Ingelheim.

Multimedia Appendix 1
Search strategy.
[DOCX File , 18 KB - resprot_v12i1e47119_app1.docx]

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Abbreviations

ACM: Association for Computing Machinery
CENTRAL: Cochrane Central Register of Controlled Trials
IEEE: Institute of Electrical and Electronics Engineers
JBI: Joanna Briggs Institute
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analysis: Extension for Scoping Reviews

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Protocol

Robotics in Nursing: Protocol for a Scoping Review

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Abstract

Background: Globally, health care systems are challenged with the shortage of health care professionals, particularly nurses. The decline in the nursing workforce is primarily attributed to an aging population, increased demand for health care services, and a shortage of qualified nurses. Stressful working conditions have also increased the physical and emotional demands and perceptions of burnout, leading to attrition among nurses. Robotics has the potential to alleviate some of the workforce challenges by augmenting and supporting nurses in their roles; however, the impact of robotics on nurses is an understudied topic, and limited literature exists.

Objective: We aim to understand the extent and type of evidence in relation to robotics integration in nursing practice.

Methods: The Joanna Briggs Institute methodology and the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) checklist will guide the scoping review. The MEDLINE (Ovid), Embase (Ovid), CINAHL Plus with Full Text (EBSCOhost), Scopus, Cochrane Library, and IEEE Xplore electronic bibliographic databases will be searched to retrieve papers. In addition, gray literature sources, including Google Scholar, dissertations, theses, registries, blogs, and relevant organizational websites will be searched. Furthermore, the reference lists of included studies retrieved from the databases and the gray literature will be hand-searched to ensure relevant papers are not missed. In total, 2 reviewers will independently screen retrieve papers at each stage of the screening process and independently extract data from the included studies. A third reviewer will be consulted to help decision-making if conflicts arise. Data analysis will be completed using both descriptive statistics and content analysis. The results will be presented using tabular and narrative formats.

Results: The review is expected to describe the current evidence on the integration and impact of robots and robotics into nursing clinical practice, provide insights into the current state and knowledge gaps, identify a direction for future research, and inform policy and practice. The authors expect to begin the data searches in late January 2024.

Conclusions: The robotics industry is evolving rapidly, providing different solutions that promise to revamp health care delivery with possible improvements to nursing practice. This review protocol outlines the steps proposed to systematically investigate this topic and provides an opportunity for more insights from scholars and researchers working in the field.

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KEYWORDS

automation; robots; nursing; nursing robots; nursing robotic technologies

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Introduction

Background

Globally, health care systems are challenged with the shortage of health care professionals, particularly nurses. Nurses and midwives account for nearly 50% of the global health care workforce [1], with the same proportion bearing out in the Canadian health care system [2]. It has been projected that by 2035, there will be a global deficit of 12.9 million health care professionals, with nurses and midwives making up half of the health care workforce shortage [1,3]. Several factors account for the increasing decline in the nursing workforce, including increased workload, insufficient resources, chronic burnout, stress, early retirement, understaffing, job dissatisfaction, work-related and musculoskeletal injuries, and low remuneration [4-10]. Other factors include post–COVID-19 discontentment, disease and patient acuity increase, and the aging population and workforce [4,7,11,12]. The COVID-19 pandemic exacerbated the already existing nursing shortage crisis.

Nurses undertake multiple and complex activities within any care setting, and their most central role is to provide efficient and effective patient-centric care [13]. Research shows increased staffing leads to greater job satisfaction and retention, reduced mortality and associated injuries among nurses and patients [14]. Nonetheless, about one-third of nurses' time is often spent on administrative and nonpatient care activities and auxiliary tasks that could be completed by other staff, such as nursing aides, assistants, or administrative staff [15,16]. Among health care professions, nurses are ranked with the highest prevalence of musculoskeletal pain and injuries [17] and an annual prevalence of work-related musculoskeletal diseases of 77.2% [18]. The results from these injuries are absenteeism, sick leaves, health-related problems, and disabilities, affecting the quality of health and putting added pressure on the health care workforce [19]. In addition, there is a significant rise in error rates among nurses resulting from physical and mental exhaustion, compromising patient and nurses' safety [20]. Nurses' time and skills are highly valuable, as they have specialized knowledge essential to achieving optimal health outcomes. Identifying alternative solutions that can decrease nurses' time lost in undertaking noncritical tasks is therefore necessary. Robotics is 1 solution that is gaining growing attention due to the many activities that robots can undertake to support nursing practice, strengthen health care delivery, improve overall health outcomes and the quality of care, and fill current and projected gaps in the workforce needed to meet population health needs [21]. When thoughtfully and appropriately integrated, robotics could also save money for the health care system and free up time for nurses to focus on patient care, thereby mitigating negative impacts on patients and the mental well-being of nurses [22]. On the other hand, robotics integration in nursing also raises inquiries regarding the methodologies, technologies, and ethics of developing robots to support the work of nurses and other health care professionals [23].

In broad terms, robots in health care are classified into surgical, rehabilitation, medical assistants, and hospital service robots [24]. These robots are referred to as assistive robots because they provide users with assistance and are subcategorized as physically and socially assistive robots [25,26]. Physically assistive robots are those robots that assist end users through physical interaction and may be designed to perform tasks without much physical human input, such as exoskeletons, intelligent wheelchairs, robotic manipulators, and walking assistive robots [26-30]. On the other hand, socially assistive robots are physical or digital entities capable of social interaction functions that promote users' psychological, emotional, cognitive, and overall well-being [26,31,32]. Socially assistive robots, such as Nao and Pepper robots, are used to provide affective therapy, social facilitation, companionship, and physiological therapy in patients [28,30,33]. The socially assistive robots have proved useful in caring for older people, assisting with activities of daily living such as medication reminders, undertaking household tasks, health monitoring to enhance safety, supporting independence and aging in place, and overall users' well-being [34]. Multimedia Appendix 1 provides a visual representation of classifications of the different types of robots used in health care.

The boundaries between the areas of application of robots in nursing are somewhat fluid. Different names are given to robots used by nurses in health care facilities, such as nurse assistants, hospital service robots, delivery care robots, and nurse robots. These names are based on their specification and practical use in care settings. For this review, the robots used in the nursing practice will be referred to as nursing robots. Nursing robots combine the features and functions of medical assistant robots and hospital service robots. The nursing robots are specifically designed to perform activities to supplement nurses' work at hospitals, long-term facilities, and home care [26]. These robots are socially and physically assistive and can be categorized into humanoids and nonhumanoid robots, including telepresence robots. Since nursing robots can provide assistance with complex activities within care settings, they can support nurses in providing services to patients unrelated to medical functions [24].

The surge in the interest in using nursing robots in health care is because of the technological capacity to strengthen health care delivery and improve quality health outcomes [21]. Nursing robots can complement nurses' efforts by undertaking repetitive work such as retrieving and delivering supplies, providing ambulation services, medication delivery services, assisting in patient transfers, lifting, and assisting with standardized approaches to care management [30,35,36]. In addition, robots can enhance nurses' work by monitoring patients' condition and vital signs and providing patient reminders [26,31]. Furthermore, nursing robots can serve as frontline actors during emergency response and routine care to prevent or reduce nurses' physical contact and exposure to hazardous substances, infections, or contamination. These tasks are usually physically and mentally demanding. They are routine activities that can be assigned to a nonhuman entity, thereby reducing the physical and mental stress for nurses, saving money for the health care system, and freeing up nurses’ time to focus on patient care [22]. To this end, nursing robots can decrease the physical demands of nurses' work and reduce the rate of injuries and human errors, thereby

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increasing job satisfaction and improving patient care quality and outcomes [37,38]. For nurses, incorporating nursing robots in health care means improved workflow, increased work quality and productivity, and reduced workload. To health systems, robots could be an ideal solution to the wicked problem of nurse shortage.

To identify published literature reviews on the use of robotics or robots in nursing practice, a preliminary literature search was conducted (April 13, 2023) in CINAHL Plus with Full Text database, and 4 reviews were located. Ohneberg et al [35] focused their review on assistive robotic systems and their application areas in nursing practice. The other reviews focused on identifying the different tracks in which robots are used in nursing, barriers to implementation, and the outcomes of robots and other automated devices on nurses' activities [31,37,39]. Based on the findings from these reviews, the authors proposed that further research studies are needed to explore the acceptance and impact of robotics systems on nursing practice and examine facilitating factors and ethical concerns of implementing robots [35]. In addition, the authors suggested examining research designs used for undertaking studies in nursing robotics to ascertain the consistency and rigour of the quality of the studies [39] and evaluate which devices and functions will improve and support nurses' work [37]. Further, the authors noted the need to examine the human-robot interactions, focusing on monitoring robots and exploring psychological barriers that need to be overcome to influence and increase the acceptance of robots [31].

Despite the 4 reviews published on this topic, there remains a pressing need to map out the extant literature to better understand the current research discourses on the influence of robots (regardless of their type) on nurses and nursing practices across clinical care settings. A clear picture of what has and has not been attended to in terms of both (1) the robot's ability to reshape, reconstitute, and reconvene nursing practices, as well as (2) their influence on the nurse's mental, physical, and overall well-being is necessary to generate and inform future research. Scoping reviews are appropriate for examining emerging areas where little is known about a phenomenon of interest [40]. Broadly, this scoping review aims to understand the extent and type of evidence in relation to robotics integration in nursing practice. More specifically, the review will (1) identify the available evidence reporting on robots used in supplementing nursing and their related tasks in direct clinical care, (2) identify the benefits and challenges associated with their use, and (3) understand nurses' perceptions of the impact of robots on their work, and patient and clinical care.

Research Questions

The overarching question guiding this review is, what is the current evidence on the integration and impact of robots and robotics into direct nursing care? The following subquestions will be examined: (1) what are the types of robots and robotic technologies available to support nursing care? (2) What is the range of tasks (nursing and nonnursing related) that robots and robotic technologies can assist nurses with in providing direct clinical care? (3) What are the benefits and challenges associated with robotic integration in nursing? (4) What are nurses' perceptions and views on the impacts of robots and robotic technologies on nurses' work, patient care, and health systems that can be achieved when robots are used to supplement nursing practice from process, structure, and outcome perspectives?

Methods

Study Design

The Joanna Briggs Institute methodology and the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) checklist for scoping reviews will guide the scoping process [41,42]. We will review existing literature, examine the extent, scope, and nature of research activities to identify gaps and summarize and disseminate research findings [42]. An initial search (January 05, 2023) in the Open Science Framework revealed that no study of this nature had been registered; hence, this review will be registered in the Open Science Framework registry, which is a platform where researchers register prospective scoping reviews to inform other researchers interested in undertaking similar work, hence minimizing the risk for duplication.

Inclusion Criteria

The Joanna Briggs Institute's participants, concept, and context framework will be applied to guide the decision-making about the inclusion and exclusion of studies for the review, eliminate studies that are not essential to the central research questions, and maintain the consistency of the review process [42].

Participants

This review will focus on nurses working in different roles, including licensed practical nurses, registered practical nurses, registered nurses, registered psychiatric nurses, community health nurses, and nurse practitioners providing direct care within a variety of practice settings. Unless nurses are included as part of the study population, studies that report on other health professionals and patients will be excluded because they are not the participants of interest.

Concept

The authors recognize the differences in the classification of nursing robots; therefore, all papers that report on the use of nursing robots used in nursing practice, irrespective of the reported outcomes or the clinical context, will be included. In addition, any paper that does not report on robot use within the nursing practice or the use of socially assistive robots that focus on patient care will be excluded.

Context

This review will consider studies that examine robot use in all nursing practice settings, including long-term, primary care, acute care, rehabilitation, community care, and health care settings. In addition, the review will not be limited to any geographical location as the authors want to evaluate nursing robots from an international perspective and be comprehensive in the search.

Types of Sources

This review will consider all study types, including qualitative, quantitative, and mixed methods research, except for published

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reviews on the topic, including systematic reviews, scoping reviews, narrative or traditional literature reviews, meta-analyses, and integrative reviews. Excluded reviews may be used later for discussion and comparison of results. In addition, studies that report on theoretical and methodological approaches will also be examined for relevance and considered for inclusion. Gray literature in the form of guidelines, theses, dissertations, discussion papers, white papers, reports, brief reports, specific guidelines, and unpublished papers that report on nursing robots or robotic technologies in nursing practice will be included. Blogs and internet research sites that report on the piloting of robots relevant to nursing practice will also be considered for inclusion. Conference proceedings and publications, opinion pieces and commentaries will be excluded as they might not provide in-depth information for analysis. Studies will be limited to the English language due to the lack of funding to support the translation of the materials, and reviewers can only speak English. Since the area of robotics in nursing is novel and evolving, the year of publication will be from the beginning of indexed papers in databases to the current search date. This will enable an assessment of the development of robots or robotics in nursing practice and their evolution over time.

An eligibility form for screening the papers will be used to guide the screening process (Multimedia Appendix 2), making the screening process clearer to the reviewers and maintaining the robustness of decision-making regarding the inclusion and exclusion of studies [43]. In total, 2 reviewers will independently screen data using the eligibility form provided and record the results. The kappa statistic, sometimes called Cohen kappa, a robust statistical method used most frequently, will be used to measure interrater reliability between the reviewers [43,44]. The kappa statistic method is applicable when two or more reviewers make decisions at various points in a study's screening and data extraction process [43,44]. Interrater reliability is important to ensure that data collected in the study are correct depictions of the variables measured [43].

Search Strategy

A comprehensive search strategy will be developed using predefined search terms in consultation with a health science librarian. A search was conducted in 1 database (CINAHL Plus with Full Text) to determine the appropriateness and effectiveness of the search terms and strategy (Multimedia Appendix 3) proposed for this review on September 26, 2023. The following Boolean operators and keywords proposed and identified will guide the search of the published and unpublished (grey literature) relevant to the topic: Automat* OR Robot* AND Nurs* AND Patient* OR In-patient* OR Hospital* OR "Nursing Care" OR "Clinical Care" OR "Direct Care," in four electronic bibliographic health databases, one interdisciplinary database and one electronic engineering database: Medline (Ovid), EMBASE (Ovid), Cumulative Index to Nursing and Allied Health Literature (CINAHL) Plus with Full Text (EBSCOhost), Scopus, Cochrane Library, and IEEE Xplore. The health science databases are appropriate for researching the topic because nursing papers are published in these databases. Whereas the IEEE Xplore database publishes papers from computer science, electrical engineering, and other technological disciplines, nursing robots are found in this database. The search strategy will be further refined and adapted to the remaining databases as necessary. In addition, the reference lists of all included studies retrieved from studies databases, and gray literature will be checked to ensure relevant papers are not missed.

For the gray literature, Google Scholar, dissertations, theses, registries, blogs, and relevant organizational websites will be searched to identify papers relevant to nursing robots. The gray literature provides studies that might not have been peer-reviewed or indexed in databases, thereby providing balanced evidence on the subject matter. Finally, the search strategy will use an iterative process until the search becomes robust to retrieve all related papers. The authors expect to begin the data searches in late January 2024.

Study Selection

The PRISMA-ScR checklist will be used as a guide in reporting the scoping review [45]. In addition, database search results will be exported to the Mendeley reference manager to keep track of search results, organize references and bibliographies, and facilitate collaboration among all authors [46]. Retrieved studies will then be exported into Covidence Management Software (Covidence) to remove duplicates and support organizing and screening the studies into a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) chart.

In total, 2 reviewers (EMD and GL) will screen the studies independently at each stage of the screening process. Stage 1 involves the title and abstract screening, where eligible studies are passed to stage 2 for full-text screening. In stage 2, the developed eligibility criteria form will be used to assess the eligibility of the papers for either inclusion or exclusion. Studies marked for exclusion will be assigned a reason for the exclusion to help keep track of and report on them in the findings. When conflicts arise due to disagreements between reviewers on studies during the full-screening stage, a third reviewer (MK), a content expert, will be invited to help resolve the conflicts. An interlibrary loan request will be sent to the library if full-text papers cannot be retrieved. Further, if possible, a request will be sent to the authors or journals to obtain more information about a study, as needed and feasible. If attempts made to retrieve papers are unsuccessful, the studies will be excluded and documented in the PRISMA diagram and reported in the findings.

Data Extraction

An Excel (Microsoft Corp) sheet extraction table will be developed and piloted to record essential information in the included studies to allow for transparency and clarity among reviewers. Each reviewer will independently extract the following data characteristics from the included studies grouped under the participants, concept, and context domains: study citation details (author's name, year of publication, country of publication, and title), study design, study purpose, participants (population and sample size), context (study settings), concept (types and range of tasks undertaken by the robots, benefits and challenges, nurses' views, and perceptions), and outcomes

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(Multimedia Appendix 4). The identified extracted characteristics will support answering the research questions and in identifying the gaps in the literature. The extraction template is iterative; hence, it will be piloted on n=10 of the papers and may undergo refinement during the review and extraction stages to capture information based on how researchers reported information.

In total, 2 reviewers (EMD and GL) will undertake the data extraction process independently to reduce the chance of bias and errors [41]. Data extraction information will be compared for agreements and differences. In the event of discrepancies among the reviewers, a consensus will be reached by inviting a third reviewer (MK) and having a discussion for reconciliation. In scoping reviews, missing data are not usually dealt with, but the authors will decide how to proceed where possible. Scoping reviews do not aim to assess the quality of evidence, the robustness, or the generality of the evidence [40] but rather to identify literature that addresses the topic of interest. Therefore, the study quality will not be appraised in this scoping review.

Data Analysis

Data in this review will be systematically examined to minimize bias in interpreting the information abstracted from the included studies. Basic descriptive statistics will be applied to describe, aggregate, and report the findings in numerical values to enable a comprehensive evaluation of study characteristics such as the geographic distribution of included studies, populations studied, and publication time lines [47,48]. Content analysis will be applied to capture relevant information from each individual study to answer the research questions of interest in this review [49,50]. All team members will be involved in the data analysis to ensure a robust and timely analytical process.

Results

Information related to the characteristics of the included studies will be reported in the PRISMA chart to provide an overview of the body of the literature available, included and excluded studies, and the data sources used. This will be followed by a description of the characteristics of the included studies, using both a narrative and a tabular format. Graphs may also be used where appropriate to further illustrate the findings visually. A list of the excluded studies will also be provided with reasons for exclusion. To answer research questions 1 and 2, data related to the types of robots and robotic technologies available to support nursing care, the names of those robots and the different terminologies used to describe them in the literature, and the different tasks that these robots can assist nurses with will be reported in a tabular format to map out this literature. To answer research questions 3 and 4, abstractions from each included study in relation to the benefits and challenges associated with robotics integration, nurses' perceptions, and views on the impacts of robots and robotic technologies on nurses' work, patient care, and health systems will be summarized and reported narratively. Specific outcomes discussed in the literature will be noted and further organized according to the conceptual framework (structure, process, and outcome) proposed by Donabedian to facilitate a synthesis of these findings [51,52] to answer the research questions.

Discussion

Principal Findings

This scoping review aims to understand the extent and type of evidence in relation to robotics integration in nursing practice. Prior work has focused on investigating assistive robotic systems and their application areas in nursing practice [35]. Also, some reviews have identified the different tracks in which robots are used in nursing, barriers to implementation, and the outcomes of robots and other automated devices on nurses' activities [31,37,39]. The findings from these reviews reveal more research is needed to explore other areas of robotics in nursing practice, including human-robot interactions, and evaluating the robotics that supports nurse's work [31,35,37]. Building on the evidence, this review will (1) identify the available evidence on robots being used to supplement nursing and their related tasks in direct clinical care, (2) identify the benefits and challenges associated with their use, and (3) understand nurses' perceptions of the impact of robots on their work, patient care, and the health system.

The results from this review will be discussed in detail and in alignment with each research question. Furthermore, the results will be compared against what is already reported in the literature about robotics in nursing to help address the identified knowledge gaps and reveal new areas of research that have yet to be explored. In addition, other relevant literature sources, such as publications about digital health and health service research, will also be reviewed and used where appropriate. The discussion will also include detailed recommendations and implications relevant to nursing practice, education, research, and policy. The findings will also be published in a journal and disseminated at conferences, seminars, workshops, and web-based platforms.

Limitations

Only papers written in English will be included; hence, there is a possibility of missing out on other papers written in other languages. Furthermore, despite the comprehensive and extensive inclusion criteria, there is also the possibility of missing some relevant sources of information. Since the included studies will not be critically appraised, the rigor and trustworthiness of included studies cannot be ascertained; however, this scoping review may help provide a general assessment of the overall quality of research available and outline areas of research warranting further investigation.

Conclusions

This scoping review aims to investigate the current evidence on the integration and impact of robots and robotics nursing. By conducting a comprehensive search of peer-reviewed and nonpeer-reviewed sources, this scoping review will systematically map out and describe the current evidence about nursing robots and add to the body of knowledge on robots' integration in nursing. The scoping review is an appropriate method because the searches and inclusion of evidence are broad and unlimited to investigate an emerging area of science, identify knowledge gaps, and provide a direction for future research. Considering the novelty of robotics integration in

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health care, the findings from this review will be instrumental in expanding the scholarly discourse about robotics as one of the emerging technologies that will have significant implications for patient care and nursing practice in the short and long term. This review protocol outlined the steps proposed to systematically investigate this topic and provide an opportunity to gain more insights on conducting the proposed review from scholars and researchers working in the field.

Acknowledgments

We want to express our gratitude toward Megan Kennedy, the health science librarian at the University of Alberta, for her valuable contribution to developing the search strategy for this review. It is also important to note that the authors wrote the paper without any assistance from generative artificial intelligence apps. We relied exclusively on our knowledge, literature, and experience while writing the paper.

Data Availability

All data used in this review, including the extraction table, the search strategy, and eligibility criteria, will be attached as appendices in the final paper. Any other document will be made available upon request to the corresponding author.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Classification of the different types of health care robots.
[DOC File , 87 KB - resprot_v12i1e50626_app1.doc]

Multimedia Appendix 2
Robotics in nursing: a scoping review eligibility form.
[DOC File , 39 KB - resprot_v12i1e50626_app2.doc]

Multimedia Appendix 3
Search strategy.
[DOC File , 31 KB - resprot_v12i1e50626_app3.doc]

Multimedia Appendix 4
Extraction table: characteristics of included studies.
[DOC File , 35 KB - resprot_v12i1e50626_app4.doc]

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Abbreviations

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews

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Protocol

Digital Rehabilitation Interventions in Sub-Saharan Africa: Protocol for a Scoping Review

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Abstract

Background: Estimations show that at least one in every 3 people in the world needs rehabilitation at some point in the course of their illness or injury. Access to rehabilitation services is an essential part of the continuum of care and is integral to achieving universal health coverage. However, most of the world's population living in low- and middle-income countries, especially in the sub-Saharan African region, does not have access to adequate rehabilitation services. Wider adoption of digital solutions offers opportunities to support and enhance access to rehabilitation services in sub-Saharan Africa. A region where there is a greater burden and need for these services. There is also little published research about digital rehabilitation in sub-Saharan Africa, as it is an underexamined topic in the region.

Objective: This scoping review aims to provide a comprehensive picture of the current evidence of digital interventions in rehabilitation implemented in any health, social, educational, or community setting in the sub-Saharan Africa region.

Methods: We will conduct a scoping review using Arksey and O'Malley's methodological framework and follow the Joanna Briggs Institute methodology for scoping reviews. We will develop search strategies for a selected number of web-based databases, search for peer-reviewed scientific publications until September 2023, and screen the reference lists of relevant articles. We will include research articles if they describe or report the use of digital interventions in the rehabilitation of patients with any health problem or disability in sub-Saharan Africa. For selected articles, we will extract data using a customized data extraction form and use thematic analysis to compare the findings across studies.

Results: The preliminary database search in MEDLINE (EBSCO) was completed in May 2023. The research team will conduct a search of relevant articles in the autumn. The results will be synthesized and reported under the key conceptual categories of this review, and we expect the final scoping review to be ready for submission in early 2024.

Conclusions: We expect to find gaps in the research and a lack of detailed information about digital rehabilitation interventions in sub-Saharan Africa, as well as potential areas for further study. We will identify opportunities to inform the development of digital rehabilitation interventions.

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KEYWORDS

digitalization; rehabilitation; scoping review; sub-Saharan Africa; telerehabilitation

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Introduction

Background

Anyone with a health condition who experiences difficulties in any area of their life might need rehabilitation. According to the World Health Organization (WHO) [1], rehabilitation is defined as "a set of interventions designed to optimize functioning and reduce disability in individuals with health conditions in interaction with their environment." By aiming to optimize functioning, rehabilitation can help an individual be as independent as possible in everyday activities and support individuals to participate in education, work, recreation, and other meaningful life roles [2-4].

It is estimated that at least one in every 3 people in the world needs rehabilitation at some point in the course of their illness or injury [4]. According to the Global Burden of Disease study [4], the need for rehabilitation has increased by 63% since 1990, rising from 1.48 billion to 2.41 billion people [4]. Thus, the demand for rehabilitation services already exceeds availability, leaving a large unmet need, especially in low- and middle-income countries (LMICs) [5]. This provides strong evidence to prioritize rehabilitation and address the functioning needs of the population.

Rehabilitation has been effective in improving functioning outcomes in different health conditions in low-income and lower-middle-income countries, but it has not been prioritized in some of these countries and is underresourced [4]. Strengthening and reforming systems for health and collaborative practice requires a reconsideration of the role of the "patient." Patients are moving from being passive recipients to service and knowledge users, drivers, and partners in a shared approach to services, a person-centered framework. This requires collaboration, shared decision-making, and shared budgets to deliver services where the person is truly at the center [6,7].

Rehabilitation targets an individual's needs and priorities in functioning across the continuum of care and throughout the individual's life span. As countries move toward integrated person-centered care, it is imperative that quality rehabilitation be embedded in service delivery models [8]. The complexity of functioning should be acknowledged in relation to the context in which a person is striving to fulfill their life roles and goals [9,10]. There is a need for interprofessional, person-centered approaches within integrated community-based services to reform the rehabilitation and education of the health workforce [11]. By using technology, people with disabilities can share their functioning in their environment and make an impact by identifying their specific needs, both at an individual and population level [10,12]. Innovative technology, interprofessional teamwork, task shifting, and task sharing are recommended as catalysts for the reform.

Digital technologies are considered an essential solution to health services in countries with limited resources around the world, including those in sub-Saharan Africa [13,14]. Sub-Saharan Africa is home to approximately 1.2 billion people, half of whom are expected to be 25 years or younger by 2050. The region has the world's largest free trade area, is diverse, and offers human and natural resources that have the potential to yield inclusive growth. Sub-Saharan Africa is composed of 48 low, lower-middle, upper-middle, and high-income countries from Central, Eastern, Southern, and Western Africa, 22 of which are fragile or conflict-affected [15].

In the global context, rehabilitation models are costly and based on professionally delivered services. Most LMICs do not have a sufficiently educated rehabilitation workforce, leading to a situation where services do not meet demand [3]. Digital rehabilitation interventions hold significant potential to address key rehabilitation challenges [16], such as reduction in health care costs [17] and improving treatment adherence, functioning, and quality of life [18]. Strategically leveraging these interventions to address the needs of users directly and equipping different social and health systems with rehabilitation expertise could increase access. This will make present health care systems, especially in low-resource settings, more scalable, inclusive, and resilient in situations where systems become ineffective, overloaded, or do not meet demand [19].

Goal of This Study

We consider digital rehabilitation as an umbrella term, including different digital technologies that are used by rehabilitation professionals or self-driven service users as part of the rehabilitation process in its different phases (assessment, goal setting, intervention, reassessment, and secondary prevention). These include, but are not limited to, the use of tele- and distance rehabilitation applications and services [20] and the use and design of emerging technologies, such as artificial intelligence–powered conversational agents, wearable devices, emails, video, speech, and text messaging solutions. Digital rehabilitation aims to optimize functioning and reduce disability in individual's interaction with their environment. Digital rehabilitation has a strong link with the empowerment of individuals and communities (adapted from WHO [1]). The core is connecting and empowering persons and populations to improve functioning and well-being and managing rehabilitation needs.

A multidisciplinary approach considers the person and their entire needs. Rehabilitation is simply not a health issue but includes education, social, livelihood, and empowerment-related efforts [21]. If considered from the professionals' perspective, it means all professional groups related to rehabilitation, such as physiotherapists, occupational therapists, prosthetist-orthotists, speech therapists, and social workers.

Wider adoption of digital solutions has the potential to improve access to rehabilitation services and avail more research opportunities, especially in LMICs where there is a greater burden and need for rehabilitation services [22,23]. Some of the challenges hindering the adoption of digital rehabilitation identified in sub-Saharan African countries include inadequate and underdeveloped infrastructures for power supply, internet coverage, and transport; the need to train more professionals and enhance patient literacy; the financial implications of transitioning to digital services for health institutions; and the affordability of smart devices for patients [14,24]. However, the extent of research on digital solutions for rehabilitation in the region has not been mapped. There are also a limited number

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of studies in LMICs about using digital services in rehabilitation. For example, in a review about the use of mobile health applications for stroke, healthy aging, Parkinson disease, and multiple sclerosis, only 5 studies out of more than 130 were from Africa [22].

We conducted a preliminary search of MEDLINE, the Cochrane Database of Systematic Reviews, and JBI Evidence Synthesis and did not identify current or ongoing systematic or scoping reviews on the topic. Unlike Kipruto et al's [25] ongoing scoping review aiming to map the digital health landscape and the stage of development in sub-Saharan Africa, our study specifically focuses on peer-reviewed digital rehabilitation research not limited to health contexts but includes social, educational, and community settings as well. A recent scoping review by Nizeyimana et al [26] investigated the feasibility and cost-effectiveness of telerehabilitation in a global context. The review focused on both high-income countries and LMICs, considering the accessibility of rehabilitation services and the facilitators and barriers of telerehabilitation.

Therefore, the objectives of this scoping review are to identify the scope and types of evidence of digital rehabilitation solutions and to examine how research about digitally delivered rehabilitation interventions is conducted in sub-Saharan Africa. We expect the review to summarize the available evidence of digital rehabilitation interventions and identify potential research gaps and avenues for development. We chose a scoping review to explore the extent of literature on the topic and as a necessary step in identifying how digital rehabilitation technologies can be integrated into primary health care.

Methods

Overview

We will conduct this review according to Arksey and O'Malley's [27] framework with the 5 mandatory stages and the Joanna Briggs Institute methodology for scoping review guidelines [28]. According to the framework, the stages in a scoping review include (1) identifying the research question, (2) identifying relevant studies, (3) selecting studies, (4) charting the data, and (5) summarizing and reporting the results. A scoping review is used to identify the key concepts relating to the research question, understand the conceptual boundaries of the research topic, and clarify definitions [29].

Review Question

The main research question guiding this review is: "What is the scope of research related to digital interventions used for rehabilitation in sub-Saharan Africa, and how is the research conducted?"

Eligibility Criteria

Overview

To select relevant studies, we have developed eligibility criteria (Textbox 1). These criteria are structured according to the population, concept, and context categories for scoping reviews suggested by Peters et al [28].

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Textbox 1. Eligibility criteria structured according to the population, concept, and context domains. These outline the study population, the concept of digital rehabilitation, and sub-Saharan Africa as the locations of interest.

Inclusion criteria

1. Population: health professionals and patients
   - Social, health, and other professionals delivering rehabilitation services
   - Persons using or in need of rehabilitation services
2. Concept: use, experiences, and issues of integrating digital services in rehabilitation
   - Studies describing the use of digital interventions in rehabilitation
   - Studies evaluating the effectiveness of various types of digital rehabilitation interventions
   - Studies reporting the problems and barriers to integrating digital services into rehabilitation
3. Context: digital rehabilitation interventions adapted, piloted, and deployed in sub-Saharan Africa
   - Studies conducted in health, social, educational, and community settings in sub-Saharan Africa
4. Types of sources
   - Peer-reviewed articles, including research protocols
5. Other considerations
   - Published in English
   - Full article is available on the internet

Exclusion criteria

1. Concept
   - Studies reporting digitalization of health services other than rehabilitation
2. Types of sources
   - Editorials
   - Opinion and perspective articles
   - Abstracts only
   - Literature reviews

Population

The review will include studies involving patients of all ages receiving treatment through digital rehabilitation interventions delivered by multidisciplinary rehabilitation professionals.

Concept

The concepts of interest in this review are the use and effectiveness of digital rehabilitation interventions and how these interventions are implemented and evaluated in research. For the purposes of the review, we will only include digital rehabilitation interventions, such as telerehabilitation, wearable devices, robotics, virtual and augmented reality, smart device apps, and gamified mobile and web-based interventions.

Context

Studies conducted within any rehabilitation setting in sub-Saharan Africa will be eligible for inclusion.

Evidence Sources

The search strategy will be limited to peer-reviewed literature. Primary research studies of all designs, including both quantitative and qualitative, will be included in this review. Secondary research studies (eg, systematic reviews) will not be included.

Search Strategy

We planned a search strategy to identify a comprehensive list of research literature specific to digital solutions used for rehabilitation in sub-Saharan Africa. Text in the title and abstracts of relevant articles, and the index terms used to describe the articles, were used to develop a full search strategy for MEDLINE (EBSCO; Multimedia Appendix 1). We will adapt the search strategy with assistance from an information specialist for each included database and information source. We will search databases (MEDLINE [EBSCO], CINAHL, Cochrane Library, and Scopus) for peer-reviewed scientific publications. The reference list of all identified sources will be screened for additional studies.

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Source of Evidence Selection

We will collate and upload identified citations from all databases into Covidence (Veritas Health Innovation) [30] and remove duplicates. Following a pilot test, 2 or more independent reviewers will screen the title and abstract of all retrieved citations for assessment against the inclusion criteria for the review. In the second step, 2 or more independent reviewers will then assess the full-text articles against the inclusion criteria. We will report reasons for the exclusion of sources of evidence in the full text that do not meet the inclusion criteria in the scoping review. We will resolve any disagreements that arise between the reviewers at each stage of the selection process through discussion or with additional reviewers. The results of the search and the study inclusion process will be reported in full in the final scoping review and presented in a PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Review) flow diagram and checklist by Tricco et al [31].

Data Extraction

The research team will develop a data extraction tool to record the key information from the studies. Data will be extracted from papers included in the scoping review by 2 or more independent reviewers using the data extraction tool. The data extracted will include specific details about the participants, concept, context, study methods, and key findings relevant to the review question. These include author, publication year, publication type, country of origin, aims, population sample size and characteristics, methodology or methods, intervention type, outcomes and details of these, and other key findings that relate to the review's question as suggested by the Joanna Briggs Institute [28]. A draft extraction sample is provided in Textbox 2.

The research team will review the data extraction form and pretest it before implementation to ensure it is capturing relevant information. We will make modifications to the form after testing if necessary and state these modifications in the review. The extraction strategy will also be updated according to the categories emerging as the review progresses. We will resolve any disagreements that arise between reviewers through discussion and consensus, or with additional reviewers. The authors of the original papers will be contacted to request missing or additional data when required.

Textbox 2. Data extraction form.

1. Name of author, date of publication
2. Aims of the study and research question
3. Population
   - Characteristics of participants
   - Sample size
4. Country of origin (geography of the study)
5. Methodology
   - Study design
   - Recruitment setting
   - Intervention type, comparator, and details of these (eg, duration of the intervention; if applicable).
   - Sampling strategy (if applicable)
6. Key findings relating to the research question.
7. Conclusions

Data Analysis and Presentation

We will summarize the results using descriptive statistics. Descriptive statistics will be used to report the number of studies under each general category and additional conceptual categories, such as the study design, type of intervention, and the challenges and barriers to integrating digital solutions.

A narrative summary will accompany the tabulated and charted results and will describe how the results relate to the review's objectives and questions. Thematic analysis conducted according to Braun and Clarke's [32] outline will be used to contextualize the findings and describe the evidence and scope of the digital solutions. The process consists of developing initial coding ideas from the data, manually coding and matching codes to extracts, and sorting the codes into potential themes. Then analyzing the relationships between the themes, reviewing and refining them, and finally tabulating all codes under the final themes [32].

Ethical Considerations

We will collect all data through searches of web-based scientific databases. No information on individuals will be collected, so approval from a research ethics committee is not required. The study follows the ethical principles of Jamk University of Applied Sciences.

Results

The protocol was registered and submitted for publication in May 2023. Databases will be searched in September 2023.

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Based on the preliminary search (Multimedia Appendix 1), we expect to have a reasonable number of references for screening. Screening and data extraction will be done between October and December 2023. The results will be synthesized and reported under the key conceptual categories of this review, and we expect the final scoping review to be ready for submission in early 2024.

Discussion

Overview

The review will examine published peer-reviewed research about digital solutions for rehabilitation to establish the extent of their use. This will provide a comprehensive picture of the current knowledge on the use of digital rehabilitation interventions in sub-Saharan Africa and the potential for these interventions to improve patient outcomes. The review extends previous research by Kipruto et al [25] and Nizeyimana et al [26] by emphasizing the "multimodal, patient-centered, and collaborative process" [33] of rehabilitation in a broader health care context, focusing on services to address the health care needs of individuals [1,8,33]. Unique to the present study is the focus on digital solutions for multidisciplinary rehabilitation in low-resource settings, which represents an underexamined topic.

This work is the initial step in a research project aiming to develop evidence-based, person-centered, and context-specific digital rehabilitation services in LMICs in East Africa and Southeast Asia. In the project, we aim to propose a digital-first multidisciplinary approach to address the challenges of access to rehabilitation services in low-resource settings. A digital-first approach will assist in delivering services directly to patients or through the primary health care system instead of solely through rehabilitation professionals, as is the case with the practice in high-income countries.

Limitations

A potential limitation is the availability of full-text articles. Some relevant articles may not yet be accessible during the search process; thus, limiting the reviewers' ability to give a summary that reflects all available evidence of digital rehabilitation. Lack of relevant studies because of the sole focus on peer-reviewed research is another limitation. As the digital landscape goes through rapid changes, there may be limited information about studies related to digital rehabilitation interventions in the sub-Saharan context if they, for example, do not progress beyond the trial phase of a project after deployment. Focusing solely on English-only articles also limits the review, as there may be relevant publications in other languages spoken in the sub-Saharan African region, such as French or Portuguese.

We expect the review to give us insights to develop the digital-first rehabilitation model proposed in the project. In addition, we expect it to outline research gaps and the implications for future research, policy, and practice. Other researchers, health professionals, and policy makers will benefit from the results. We will disseminate our findings through different channels, including peer-reviewed publications, presentations at scientific conferences, and web-based blogs.

Acknowledgments

This study is part of the project Co-innovation for Digital Rehabilitation in the Global Marketplace, funded by Business Finland (grant 6169/31/2021). The funders had no role in the review.

Data Availability

The data sets generated and analyzed during this study will be included as multimedia appendices in the resulting manuscript.

Authors' Contributions

KK is the research lead for the project. MO drafted the initial manuscript; MO and EA revised the search strategy; EA conducted the search and refined the strategy. MO and EA wrote the final manuscript in consultation with KK, JG, and DKT, who reviewed and approved the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search strategy for Medline (EBSCO).
[PDF File (Adobe PDF File), 116 KB - resprot_v12i1e48952_app1.pdf]

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Abbreviations

LMIC: low- and middle-income country
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Review
WHO: World Health Organization

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Protocol

Circular Business Model for Digital Health Solutions: Protocol for a Scoping Review

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Abstract

Background: The circular economy reshapes the linear “take, make, and dispose” approach and evolves around minimizing waste and recapturing resources in a closed-loop system. The health sector accounts for 4.6% of global greenhouse gas emissions and has, over the decades, been built to rely on single-use devices and deal with high volumes of medical waste. With the increase in the adoption of digital health solutions in the health care industry, leading the industry into a new paradigm of how we provide health care, a focus must be put on the amount of waste that will follow. Digital health solutions will shape health care through the use of technology and lead to improved patient care, but they will also make medical waste more complex to deal with due to the e-waste component. Therefore, a transformation of the health care industry to a circular economy is a crucial cornerstone in decreasing the impact on the environment.

Objective: This study aims to address the lack of direction in the current literature on circular business models. It will consider micro, meso, and macro factors that would impact the operational validity of circular models using the digital health solutions ePaper label (medical packaging), smart wearable sensor (health monitoring devices), smart pill box (medication management), and endo-cutter (surgical equipment) as examples.

Methods: The study will systematically perform a scoping review through a database and snowball search. We will analyze and classify the studies from a predetermined set of categories and then summarize them into an evidence map. Based on the review, the study will develop a 2D framework for businesses to follow or for future research to take a standpoint from.

Results: Preliminarily, the review has analyzed 26 studies in total. The results are close to equally distributed among the micro (8/26, 31%), meso (10/26, 38%), and macro (8/26, 31%) levels. Circular economy studies emphasize several circular practices such as recycling (17/26, 65%), reusing (18/26, 69%), reducing (15/26, 58%), and remanufacturing (8/26, 31%). The value proposition in the examined business model is mostly dominated by stand-alone products (18/26, 69%) compared to product as a service (7/26, 27%), involving stakeholders such as health care professionals or hospitals (20/26, 77%), manufacturers (11/26, 42%), and consumers (9/26, 35%). All studies encompass societal (12/26, 46%), economic (23/26, 88%), and environmental (24/26, 92%) viewpoints.

Conclusions: The study argues that each digital health solution would have to be accessed individually to find the optimal business model to follow. This is due to their differing life cycles and complexity. The manufacturer will need a layered value proposition, implementing several business models dependent on their respective product portfolios. The need to incorporate several business models implies an ecosystem perspective that is relevant to consider.

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KEYWORDS

business model; circular economy; digital health solution; digital health; digital tool; digital; healthcare; life cycle; MedTech device; monitoring device; technology

Introduction

Overview

A circular economy is a system that has been evolving in theory and practice for decades, with a core focus on minimizing waste and reprocessing products in a closed-loop system [1-4]. Grounded in a circular economy, a circular business model follows the same core fundament by emphasizing the creation and capture of value [2,5]. Businesses in resource-intensive industries, such as health care, can find a lot of value in implementing circular business models for their products to decrease their environmental footprints and become more resource efficient. Although circularity is not a mainstream model, several sectors have successfully started incorporating circular practices, especially in the utilities and consumer goods industries [6,7]. Yet with the advancement of circular models, health care seems to lag in the implementation of circular practices compared to other industries [8].

As global technological advancement continues, the health care industry has witnessed a surge in the adoption of digital health solutions across hospitals, health care professionals, and patients [9]. Given the increased production and use of digital health solutions, they have become a good use case for circular business models and could serve as a pivotal tool for reshaping the health care supply chain and business models. These intricate products are resource-intensive, comprising diverse materials such as metals, plastics, glass, and electronic components, all handled in the current linear waste management system. A waste management system refers to a strategy for how companies dispose of, reduce, and reuse waste [10,11]. Waste management in health care is often complex, especially in hospitals, with multiple streams of high volumes of waste generated daily [10-12]. Although several studies have delved into incorporating circular practices in hospital or home care waste management systems [10,11], research on a broader system-level viewpoint incorporating the supply chain, its stakeholders, and their interconnectedness is lacking [13]. Therefore, the main focus of this review will not be the patient but rather the system and its stakeholders. Nevertheless, as patient focus is at the core of all health care operations, this should be done while acknowledging and considering the role and importance of the patient in it.

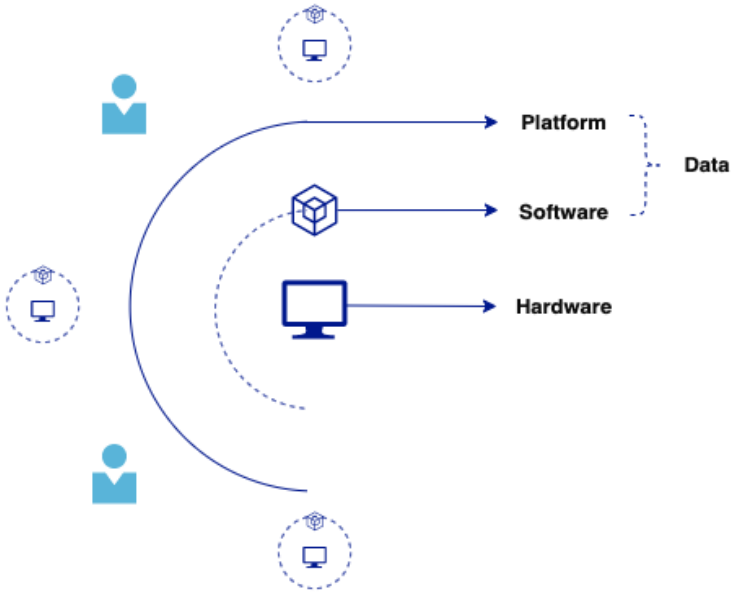
The current literature landscape's lack of consensus on how to develop a circular business model in health care does not arise due to disagreements on how circular waste management should be introduced but rather stems from a lack of knowledge and research on the topic. This conundrum could hint toward current circular business model solutions being too generalized and not considering the specificities of the health care industry and digital health to be implemented. Circularity must thus be implemented on a product- or industry-specific level to succeed [7].

For instance, 2 crucial characteristics of digital health solutions would make the implementation of a generic circular model fail. First, the term digital health "solution" is used on purpose instead of "device" because the product not only contains hardware but also software and data components (Figure 1). Apart from the circular practices of the solution's hardware, we must also consider the waste of data, both in terms of the climate impact data storage has through embedded CO_2 emissions due to electricity use and the continuous use as well as the repurposing of data. Even within digital health solutions, a distinction must also be made between the different types of life cycles the solutions have due to their varying use. Some digital health solutions never leave the hospital, in which case it can be easier to control their reprocessing, while other solutions are owned by the patients, which can leave uncertainties on take-back schemes in a circular business model. Second, the contamination risk of medical solutions adds an additional layer of regulatory and operational complexity that also must be considered in the operations of the circular model. You need to ensure the product does not spread or contain harmful elements impacting human health and the environment. The motivation behind developing an industry-specific model forms the purpose of this scoping review: to theoretically develop a framework that businesses can take as a standpoint [7]. This fills the call for research combining circularity and digital health in health care and bridging the research gaps by merging the concepts.

To develop concepts for tailored circular business models for digital health solutions, this scoping review examines existing circular models in the health care industry and of other similar products in other industries. To make the analysis concrete, 4 product categories will be used as examples: medical packaging (ePaper label), health monitoring devices (smart wearable sensor), medication management (smart pill box), and surgical equipment (endo-cutter). These 4 products are representative of medical versus nonmedical, as well as single-use versus recurrent-use products.

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Figure 1. Illustration of components in a digital health solution.



Unit of Analysis

The unit of analysis in the scoping review is the circular business model. This is due to it being the core concept that motivates and justifies the performance of the study. The units of analysis can be broken down into circular and business models. Circularity will be defined through the concept of the 4 R's (recycle, reuse, reduce, and remanufacture) and the MacArthur butterfly model [2] and hence refers to the concept of creating a closed-loop system where resources are remanufactured, reused, and recycled instead of being disposed of after use. The 4 R's and the butterfly model both emphasize the importance of reducing waste and creating a circular economy. The second part of the unit of analysis, the business model, is a framework that describes how an organization creates, delivers, and captures value [14]. It is a conceptual tool that helps businesses articulate and communicate their strategy, operations, and revenue models in a concise and structured manner [5,14].

Theoretical Boundaries

A set of theoretical boundaries will guide the scoping review. First, as the research on circular business models in health care is limited, the search does not solely focus on the health care industry but also related industries such as wellness. To avoid a scope that is too broad, it is important to narrow down the types of solutions to be examined and only include products that have similar components (Figure 1) or business models to a digital health solution. The study will therefore include specific types of products that contain hardware, software, or data and preferably are part of a highly regulated industry. Second, the study will not only take into account traditional business model factors such as revenue stream and value proposition but also the environmental and societal impact of the circular model being examined. This would involve a comprehensive analysis of the economic, environmental, and social benefits and costs of the circular model being proposed or implemented, as well as any potential trade-offs that may arise.

Relevance

The scoping review will provide valuable information for future research in the circular economy as well as within the European Union (EU)–funded Digital Health in Circular Economy (DiCE) project and the stakeholders involved [15]. The adoption of circular economy principles by businesses developing digital health solutions has the potential to align with the United Nations' Sustainable Development Goals (SDGs) [16]. The scoping review addresses SDG 3 on good health and well-being and SDG 9 on industry, innovation, and infrastructure [16]. Furthermore, the circular economy can also support economic growth and job creation. Lastly, the research is also relevant to SDG 12, as part of the business model comes from the value of returned materials, both in economic terms and in more environmental settings, to avoid depleting scarce resources [15].

Methods

Overview

The scoping review will follow a systematic framework and best practices developed by Arksey and O'Malley [17], Durach et al [18], and the Joanna Briggs Institute scoping review manual [19]. To establish guidelines for the data collection, the protocol is outlined below before conducting the review. The process and data collection will be structured around the following steps: identify the research question, determine the required characteristics of relevant studies, search strategy, study selection, synthesize the literature, and report the results.

Identify the Research Question

The scoping review and its research question will be built around the unit of analysis and on the defined research boundaries listed. As the research question has an exploratory objective as well as an evaluation perspective on current circular business models, the following research question has been formulated: "How can circular business models be adapted and remodeled to digital health solutions?"

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The research question will synthesize the literature on circular business models with a health care–oriented lens. To support the research question, a set of subquestions has been created to guide the analysis.

1. What are the barriers and enablers of implementing circular economy practices in the digital health market, and how can they be addressed? (This question will enlighten why traditional circular practices do not apply to the digital health market and where the existing models should be adapted.)
2. How are value and cost both negatively and positively redistributed in implementing a circular business model and impacting its key targets and performance indicators? (This question will discover how the business model of the solutions will change in terms of value. Value can be seen as financial, epistemic, ethical, service, and reputation.)
3. How would operating systems and data gathered by the solutions be affected positively or negatively by circularity? (This question focuses specifically on the software and data management parts of the solutions to ensure circularity is not only observed from the hardware perspective.)

Determine the Required Characteristics of Relevant Studies

To identify a relevant set of studies, the following inclusion and exclusion criteria (Textbox 1) have been chosen.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Studies focusing on one or more of the components in the solutions being hardware, software, and data
- Studies including health care or related industries such as fitness and wellness
- Studies including one or several stakeholders in a circular business model
- Studies illustrating environmental or societal impact by implementing circular business models

Exclusion criteria

- Studies that do not focus on economical, societal, or consumer outcome
- Studies published before the year 2010 [4,20]
- Non–peer-reviewed articles
- Editorials and commentaries
- Non-English studies

Search Strategy

In the literature search, 2 search strategies will be implemented: keyword search and snowball search. The keyword search will be performed in Scopus and Web of Science. Furthermore, a separate cross-checking search in PubMed has been done to ensure the databases include studies within the industry of interest, health care. Scopus and Web of Science have been chosen for several reasons. First, they both cover interdisciplinary results, thus fitting the scope of the scoping review into circularity, business model, and health care. Second, the databases have similar search functions, making the standard search protocol easier to follow without too much adaptation from one database to another. Third, they are some of the biggest databases and have a broad reach. Following the research protocol, a set of search criteria and search strategies have been applied when searching in the mentioned databases.

The snowball search will be performed by screening the reference list of selected studies and their references. The dual search approach will help ensure a more comprehensive scoping review and provide a complete understanding of the topic. The keywords have been chosen by testing the number of hits for each keyword and using the snowball search technique to choose relevant keywords.

A total of 3 search queries have been created to enlighten the different layers of the research question (Table 1). One topic is the life cycle and supply chain of digital health solution. No relevant results appeared when searching for explicit terms of digital health. Therefore, the first search has a broader level and focuses on products in health care, wellness, fitness, or medicine and will be manually sorted based on whether they are or resemble digital health solutions. The second and third topics are the solution's individual components, which are hardware, software, and data.

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Table 1. Search queries.

Topic	Search query
Circular economy and processes	AB= (circul* OR “closed loop” OR “waste management” OR “Waste disposal”) AND AB= (“Business model*” OR “Operation*” OR “Value creation*” OR strateg*) AND AB= (“Supply chain*” OR “supply network” OR “process” OR “value chain” OR “life cycle” OR Logistic*) AND AB=(Healthcare OR Wellness OR fitness OR Medical))
Circular economy and hardware	((((AB=(circul* OR “losed loop” OR “waste management” OR “Waste disposal”)) AND AB=(“Business model*” OR “Operation*” OR “Value creation*” OR strateg*)) AND AB=(“Supply chain*” OR “supply network” OR “process” OR “value chain” OR “life cycle” OR Logistic*)) AND AB=(metal* OR plastic* OR e-waste OR “electronic waste” OR ceramics OR polymers OR glass OR composite))
Circular economy, data, and software	AB= (circul* OR “closed loop” OR “waste management” OR “Waste disposal” OR green OR sustain*) AND AB= (“Business model*” OR “Operation*” OR “Value creation*” OR strateg*) AND AB=(“Supply chain*” OR “supply network” OR “process” OR “value chain” OR “life cycle” OR Logistic*)) AND AB= (“information” OR data) AND (tech* OR platform OR Software OR system OR program*)

Study Selection

In the study selection, all duplication of records is removed before a screening of the topic is performed. Furthermore, the inclusion and exclusion criteria will be used to reduce the final selection of studies. The results from the keyword search will be manually screened by 2 independent researchers to be able to compare and discuss the final study selection. The tool Rayyan (Qatar Computing Research Institute) will be used for this procedure. This method ensures the screening is less biased by the researchers’ different fields of expertise. In the data extraction process, the data will be inserted into the reference manager Zotero (Corporation for Digital Scholarship).

Both empirical qualitative and quantitative studies, as well as literature reviews, conceptual pieces, and modeling research, will be considered to enlighten the topic from different methodological perspectives. Table 2 has been created to guide the study selection.

Table 2. Patient or population, intervention, comparison, and outcomes (PICO) model.

Criteria	Description
Unit of analysis	Users of digital medical solutions or users of similar products
Intervention	Noninterventional study. The study will observe business models of a digital health solution.
Comparison	Circular versus linear business models[a]
Outcome	Positive and negative outcome are accepted

[a]Linear model refers to a “take-make-dispose” operational practice [21].

Synthesize the Literature and Report the Results

The selected studies will be coded through an emerging and a priori coding structure to find relevant relationships between variables. With a priori code, we mean predetermined categories will be screened for when reporting the results. It will in addition extract relevant details on the studies such as title, author, publication details, and methods.

The results will be analyzed and summarized through a statistical view in tables and graphs as well as a narrative method. An evidence map will be created, with the set of categories that have been chosen below to categorize the data and find similarities and differences among the results to discuss (Table 3). The categories have been chosen to cover circular elements, characteristics of the unit of analysis, description of their business model, and their added value. At last, the results will be presented through both a descriptive analysis and a thematic analysis.

In addition to the categories chosen in the evidence map, the 3 levels, micro, meso, and macro, will be the structure of the discussion and help find the current research gaps in the literature.

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Table 3. Evidence map categories described.

Categories and types	Description
Circularity industry focus	
General perspective	Circularity of any relevant product or process
Health care perspective	Circularity within the health care industry and its products
Level of circular adoption	
Micro	Product and single firm level
Meso	Network of firms
Macro	Regional, national, or European Union level
Butterfly model	
Technical cycles	Nonbiodegradable materials such as metals. The main strategy is maintaining or reusing the materials
Biological cycles	Biodegradable materials such as biodegradable plastic
4 R's	
Recycle	Collecting and processing materials into a new product instead of throwing them away
Reuse	Finding new ways to use products and materials to extend their life span and reduce waste
Reduce	Minimizing the use of resources, product, and packaging
Remanufacture	Rebuild or restore a product
Governance of the device	
Owned by consumer	The consumer has full ownership of the product and the use or disposal of it
Owned by intermediaries such as HCPs[a] or hospitals	The organizations buy the product from the manufacturer and use it or lease or lend out the product for a certain period of time to the consumer
Owned by manufacturer	The manufacturer lends or leases out products to HCPs or patients
Not applicable	Governance of product not specified
Value creation for stakeholders	
Manufacturer	A company that produces and sells the product
Consumer	The end-client or patient actively using the products
Government	Regulating and overseeing health care policies and practices
Intermediaries such as HCPs or hospitals	Organizations that operate between the manufacturers and end consumers
Value impacts	
Societal	Actions or events that are harmful or beneficial on the society
Economical	Actions or events that lead to a decline or growth in economic prosperity
Environmental	Actions or events harmful or beneficial to natural environment
Digital health solutions	
Single-use devices	Devices that are used a single time and thereafter obsolete, such as syringes, needles, etc
Imaging	Devices with the purpose of creating scanning or images of patients' body parts such as ultrasounds
Medical equipment	Devices used to monitor patients such as a wearable
Software	A computer system often used in collaboration with hardware, and can be used for diagnosing, monitoring, storing data, etc
In vitro diagnostics	Products used that come in contact with human tissue such as a glucose meter
Personal protective equipment	Worn by medical staff or used by patients as masks, gowns, and gloves
Surgical and laboratory instruments	Devices used in surgeries such as endocutters and endoscopes

[a]HCP: health care professional.

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Ethical Considerations

This scoping review does not require ethical approval as it solely uses published articles with no research involving humans, medical records, patient information, or observations of public behaviors. Therefore, the term “not applicable” applies. Any deviations from this protocol will be disclosed in the following scoping review publication. Additionally, the outcomes will be disseminated in the research community, such as through conference participation.

Results

Overview

A preliminary description of the results has been performed. The results have been ranked according to the hierarchy of evidence to assess how likely they are to incorporate a systematic bias. There are 7/26 (27%) systematic reviews, 18/26 (69%) controlled studies, and 1/26 (4%) expert opinion. The results are well distributed among the 3 levels that will be analyzed: micro (8/26, 31%), meso (10/26, 38%), and macro (8/26, 31%). The reporting of results is divided into the unit of analysis, the circular business models, and the type of product analyzed in the studies.

Unit of Analysis

Circular Economy

Most studies incorporate 2 or more R’s in their analysis (18/26, 69%). Reuse (18/26, 69%), recycle (17/26, 65%), and reduce (15/26, 58%) are covered in most studies, with remanufacture being the least covered (8/26, 31%).

Business Models

Most studies focused on a stand-alone value proposition (18/26, 69%). Product as a service is mentioned in 27% (7/26) of the results. The main stakeholders covered by the studies are health care professionals or hospitals (20/26, 77%), manufacturers (11/26, 42%), and consumers (9/26, 35%).

Type of Product

The majority (17/26, 65%) of the studies have a product-specific focus, and 9/26 (35%) studies have a system-oriented focus. Out of the 17 studies that focus on a product, most of these are single-use devices (5/26, 19%) and medicine (5/26, 19%).

A more in-depth report of the results will be performed.

Discussion

Preliminary Findings

The review outlined will serve to understand and offer insights into the factors that influence the adoption of circular business models in health care. The findings within the micro level are expected to shed light on the product design and principles to design after. The findings within the meso level will focus on the role of stakeholders, the set of skills they must have, and key factors when collaborating. At last, the macro level will adopt broader legislation and guideline perspectives on the circular economy within health care at the national and EU levels. The findings from the review will be disseminated through a peer-reviewed scientific journal and conference presentations.

Limitations

A total of 2 main limitations have been identified. First, as the review’s macro level focuses partially on EU legislation, there may be an overrepresentation of European studies, and the review might oversee interesting legislative initiatives in a global context. Second, in the literature search, the review only focuses on studies from 2010 onward. Therefore, older, important articles might be missed and not included in the review, which the readers should be aware of.

Conclusion

The conclusion and outcome of the review will show that a circular business model for digital health solutions will be very specific to what kind of product it is. This will in the future require manufacturers to have a clear end-of-life management plan for their product and incorporate a layered value proposition. Furthermore, to make the value proposition and end-of-life management of the products successful, the review implies they must engage in an ecosystem with several actors to close the circular loop.

Acknowledgments

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Data Availability

All data generated or analyzed during this study are included in this published paper (and its supplementary information files).

Authors' Contributions

CR and DF conceived the study, and CR wrote the first draft. AM, CL, AW, AS, and PL have commented on and approved the contents.

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Conflicts of Interest

None declared.

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Abbreviations

DiCE: Digital Health in Circular Economy
EU: European Union
SDG: Sustainable Development Goal

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Protocol

Airway Sequelae After Mechanical Ventilation for COVID-19: Protocol for a Scoping Review

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Abstract

Background: The epidemiology, morbidity, and burden of disease related to airway sequelae associated with invasive mechanical ventilation in the context of the COVID-19 pandemic remain unclear.

Objective: This scoping review aims to summarize the current knowledge regarding airway sequelae after severe SARS-CoV-2 infection. This knowledge will help guide research endeavors and decision-making in clinical practice.

Methods: This scoping review will include participants of all genders, and no particular age group who developed post–COVID-19 airway-related complication will be excluded. No exclusion criteria will be applied from country, language, or document type. The information source will include analytical observational studies. Unpublished data will not be completely covered as gray literature will be covered. A total of 2 independent reviewers will participate in the process of screening, selection, and data extraction, and the whole process will be performed blindly. Conflict between the reviewers will be solved through discussion and an additional reviewer. The results will be reported by using descriptive statistics, and information will be displayed on RedCap (Research Electronic Data Capture).

Results: The literature search was conducted in May 2022 in the following databases: PubMed, Embase, SCOPUS, Cochrane Library, as well as LILACS and gray literature to identify observational studies; a total of 738 results were retrieved. The scoping review will be finished by March 2023.

Conclusions: This scoping review will describe current knowledge on the most frequently encountered laryngeal or tracheal sequelae in patients exposed to mechanical ventilation due to SARS-CoV-2 infection. This scoping review will find the incidence of airway sequelae post COVID-19 and the most common sequelae such as airway granuloma, vocal fold paralysis, and airway stenoses. Future studies should evaluate the incidence of these disorders.

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KEYWORDS

airway; sequelae; COVID-19; mechanical ventilation; SARS-CoV-2; scoping review; pulmonary; mortality; voice production; health care cost; health intervention

Introduction

Airway sequelae can be due to several etiologies and cause disability by problems related to breathing, deglutition, and voice production [1-3]. Since the early decades of the twentieth century, when orotracheal intubation (OTI) became popular in clinical practice, the most frequent etiology of airway sequelae is iatrogenic and secondary to invasive mechanical ventilation

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(IMV) [1]. The duration of IMV not only positively correlates with the probability of developing airway sequelae but also with severity [2,3]. These sequelae include the need for alternative airway (ie, tracheostomy), and the development of cicatricial lesions. For instance, according to Johnson et al [4], in the United States for 2016, the nationwide estimated incidence of laryngotracheal stenosis at 45 days from discharge among patients exposed to IMV was 1.98 cases per 1000 discharges. Current knowledge on airway sequelae in SARS-CoV-2 infection survivors exposed to IMV is limited. A preliminary search of PROSPERO, MEDLINE, the Cochrane Database of Systematic Reviews, and Joanna Briggs Institute (JBI) Evidence Synthesis was conducted, and no current or in-progress scoping reviews or systematic reviews on the topic were identified.

The COVID-19 pandemic has imposed great challenges to humanity, representing the most important public health concern in recent times. Although most people recover from SARS-CoV-2 infection, many are left with sequelae [5]. Every COVID-19–related death could result in 5 quality-adjusted life-years lost, and at least 30% of the burden of the disease could be attributable to disability [6]. While the economic impact of adult laryngotracheal stenosis has been described [7], it remains unclear in the setting of the COVID-19 pandemic. A survey on 488 patients at day 60 after discharge from 38 hospitals in Michigan [8] found that 188 (38.5%) did not return to normal activities, 45 (9.2%) did not return to work due to health issues, 75 (15.4%) reported persistent cough, 193 (39.5%) reported dyspnea, 34 (7%) used continuous positive airway pressure, and 32 (6.6%) required supplementary oxygen. Although the authors did not discuss the possibility of airway sequelae in some of the surveyed patients, their findings may raise concerns about that possibility.

The pathophysiology of airway lesions associated with IMV is believed to involve processes ranging from the initial insult (ie, the exerted pressure by the endotracheal tube pressure on the respiratory mucosa, traumatic intubation, etc) causing tissue damage, through the mechanisms of repair (ie, inflammation, scarring, keloid formation, etc) [9]. Several risk factors for developing airway sequelae associated with IMV have been recognized [4,10-13], many related to pathophysiological processes. These can be categorized into sociodemographic characteristics, comorbidities, medications, and other variables related to the intubation-extubation process. Interestingly, there is some evidence that SAR-CoV-2 may have direct effects on the airway mucosa, such as cytopathic insult [14-17]. Perhaps, airway sequelae could develop in SARS-CoV-2 infection survivors exposed to noninvasive mechanical ventilation.

The proportion of patients with COVID-19 requiring IMV varies across different reports. In the HIFLO clinical trial, 18.7% of the 652 confirmed severe cases required IMV [18]. A study from Seattle, WA, reported that 75% of 24 patients with respiratory failure required IMV [19]. Other authors from China reported that 47.2% of 36 intensive care unit–admitted patients required IMV [20]. Another study from New York analyzed 2634 hospitalized patients, from which 12.2% required IMV [21]. One Italian study describes that 88% of 1300 intensive care unit patients required IMV [22]. Although the proportion of patients requiring IMV is not described, other Chinese researchers reported 44,415 cases, from which 14% were severe and 5% critical [23]. In a prospective cohort of 1357 confirmed patients with COVID-19 from Brazil [24], 421 (31%) required IMV, and from these, only 172 (40.9%) survived and were discharged. From those who survived, 95 (55.2%) were followed by video endoscopy at approximately day 100 after extubation; 38 of these patients presented laryngotracheal lesions, resulting in an incidence of 40%, with 6.3% of the cases being severe. The authors suggest that major risk factors for developing laryngotracheal lesions after surviving IMV for severe COVID-19 include larger endotracheal tubes, prone position, duration of intubation, increased leucocyte count, and coagulopathy as determined by elevated D-dimer or PT/INR [25,26]. In addition, widely used pronation maneuvers may increase the chance of laryngotracheal trauma as higher endotracheal pressure may be required, increasing the chances of airway trauma [27].

In patients with prolonged IMV (>96 h) [28], since prepandemic times, early tracheostomy (at days 7-14 after OTI) was widely accepted to be associated with better clinical outcomes, including lower complication rates, such as airway sequelae, among others [29]. However, COVID-19 guidelines recommend waiting for this procedure to avoid SARS-CoV-2 spread among health care workers, resulting in prolonged IMV up to 4 weeks [15]. In a preliminary report on clinical outcomes in 543 patients with post–COVID-19 tracheostomy from the United Kingdom, by November 2020, the number of days between OTI and tracheostomy ranged between 0 and 35 (median 16, IQR 13-22) [16]. Early on in the pandemic in Italy, the world was alerted to expect a surge in the incidence of airway sequelae because of the overwhelming number of critical patients who would be exposed to prolonged IMV [17].

The epidemiology, morbidity, characteristics, and burden of the disease related to airway sequelae associated with mechanical ventilation in the context of the COVID-19 pandemic remain unclear. The purpose of this study is to perform a scoping review based on a systematic literature review to summarize current knowledge regarding these conditions. Putting in perspective this knowledge will help guiding research endeavors and decision-making in clinical practice.

Methods

The proposed scoping review will be conducted in accordance with the JBI methodology for scoping reviews [30].

Review Questions

The research questions for this study are as follows:

- What is the current state of knowledge on airway sequelae in patients after mechanical ventilation for severe COVID-19?
- What is the epidemiology?
- What are the most common features of the lesions?
- What is the most common approach to treatment?
- What are the knowledge gaps and future insights?

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Eligibility Criteria

Participants

This review will consider studies of any design reporting airway sequelae encountered in patients of both sexes and all ages who survived after exposure to mechanical ventilation in the context of an infection with the SARS-CoV-2. Studies describing patients exposed to both invasive and noninvasive mechanical ventilation will be considered.

Inclusion Criteria

The following studies will be selected for this review:

- Studies including patients with airway sequelae after SARS-CoV-2 infection describing frequency, clinical features, and complications.
- Studies providing information about the effects and extent of complication in airways after mild, moderate, and severe SARS-CoV-2 infection.
- Studies providing information about the medical management of patients with airway sequelae after SARS-CoV-2 infection.

Exclusion Criteria

The exclusion criteria were as follows:

- Lack of full-text availability.
- Manuscripts describing an airway sequela before the COVID-19 pandemic.
- Review, state of the art article, comments, or expert opinions were not considered in this scoping review.
- Other SARS-CoV-2 infection sequelae, which do not include the airway, were not considered for the present scoping.

Concept

Airway sequelae developed after exposure to mechanical ventilation as part of the treatment for SARS-CoV-2 infection. These conditions may include the need for an alternative airway (ie, trachestomy) and cicatricial lesions, such as fistulae, granulomas, synechiae, malaciae, and other causes of stenosis, among others. This scoping review will include patients with early airway intervention after discharge and minor surgical interventions to address early post-tracheostomy complications and long-term sequelae for this group of patients with and without intervention. Finally, the scoping review will not be limited by the time frame of the airway complication after the SARS-CoV-2 infection.

Context

This review will consider studies that were published in the context of the COVID-19 pandemic. The scoping review would not be limited by language, but it will focus on the COVID-19 pandemic time frame from early 2020 to 2023.

Types of Sources

The scoping review will include any source of scientific evidence. It may be quasi-experimental and observational in nature. It will not discriminate among quantitative, qualitative, and mixed methods study designs. In addition, systematic reviews as well as text and opinion papers will be considered for inclusion in the proposed scoping review.

The proposed scoping review will be conducted in accordance with the JBI methodology for scoping reviews [31] and in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) [32].

Search Strategy

The search strategy is intended to locate published scientific studies that meet the inclusion criteria. A preliminary search was performed by a librarian on May 17, 2022. An initial search of Ovid MEDLINE identified the following keywords and index terms: covid-19, SARS-CoV-2, long COVID, coronavirus disease 2019, post-acute covid, covid sequelae, sequelae, and airway. Using these keywords and index terms, a second search on Ovid MEDLINE, PubMed, Scopus (Elsevier), Embase, Cochrane Library, Web of Science, LILACS, and gray literature resulted in 738 article references. A detailed search strategy is provided in Multimedia Appendix 1.

The search strategy included all identified keywords and index terms. All the key terms were adapted for each included database and information source. Search terms will be created by the entire team of reviewers, though the search will be conducted by 1 person. The reference list of all included sources of evidence will be screened for additional studies. Studies published in any language will be included.

Study or Source of Evidence Selection

The 738 article references were collated and uploaded to EndNote 20 (Clarivate Analytics), and 255 duplicates were removed. This resulted in a total of 483 references. Titles and abstracts will be screened by 2 independent researchers. Potentially relevant papers will be retrieved in full, and their citation details imported into the JBI System for the Unified Management, Assessment, and Review of Information. Articles published in languages different from English or Spanish will be initially translated through Google Translate, and, if deemed to meet the inclusion criteria, the full text will be professionally translated.

The full text of selected citations will be assessed in detail against the inclusion criteria by the same 2 independent researchers. Reasons for exclusion of full-text papers that do not meet the inclusion criteria will be recorded and reported in the scoping review. Any disagreements that arise between the researchers at each stage of the selection process will be resolved through discussion or with a third researcher. The results of the search will be reported in full in the final scoping review and presented in a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram [33].

Data Extraction

Data will be extracted from papers included in the scoping review by 2 independent researchers using a spreadsheet to include the following variables: title, authors, year of publication, origin or country of origin (where the source was published or conducted), aims or purpose, population and sample size within the source of evidence (if applicable), methodology

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or methods, intervention type, comparator and their details (eg, duration of the intervention; if applicable), duration of the intervention (if applicable), outcomes and their details (eg, how measured; if applicable), and key findings that relate to the scoping review questions.

The draft spreadsheet will be modified and revised as necessary during the process of extracting data from each included paper. Modifications will be detailed in the full scoping review. Any disagreements that arise between the researchers will be resolved through discussion or with a third researcher. Authors of papers will be contacted to request missing or additional data, where required.

Data Analysis and Presentation

A narrative description of the findings will be discussed in the framework of the review questions. The data will be summarized and presented in tables.

Reference Searches

Citation tracking criteria will be used to identify important articles relevant to the topic of interest; this will also be done by using the reference list of a paper or citations of a paper by other articles to identify additional manuscripts relevant to the topic of the study, as it was previously mentioned by Diaz-Ordoñez et al [34]. Following that, papers from the list that have already been examined will be removed. If a paper meets the inclusion criteria, potential new manuscripts will be identified by checking the reference list of the included paper [35].

Results

The search was performed on May 17, 2022, in MEDLINE, LILACS, the Cochrane Library, ScienceDirect, and OpenGrey; a total of 214 results were retrieved. Complete review of the manuscripts is expected in August 2022. All potential manuscripts will be imported into the reference management software Rayyan QCRI 23 [36]. The results of this scoping review will identify and describe the epidemiology, clinical characteristics, classification, and management of upper airway sequelae after SARS-CoV-2 infection.

Discussion

Airway sequelae due to SARS-CoV-2 infection are described in most observational studies, most from the United States and Europe. The compromise of the upper airway was related to mechanisms to prevent the spread of the virus; as these interventions increased, the lesions became more severe. In the following years, the pressure over climate change increases the cross-species transmission of their associated viruses an estimated 4000 times [37], which may increase the chance of pandemics such as COVID-19. For this reason, all the lessons learned about it should change how the following epidemics will be addressed. For example, developing more efficient strategies with the help of technology or artificial intelligence to contain the respiratory virus would decrease the sequelae among patients and the related cost.

At the beginning of the pandemic, interventions began not only thinking about the well-being and recovery of patients but also about avoiding the transmission of the virus to health personnel. However, the involvement of the upper airway was related to the mechanisms used to prevent the spread of the virus [38]; as these interventions increased, injuries became more prevalent and more severe [17]. These sequelae are complications that, given the high need to perform the causal procedures, are a problem that will increase in the coming years. Otorhinolaryngologists and head and neck surgeons should know them in depth to make a diagnosis and timely treatment to reduce the high disease burden of affected patients evidenced in our review. Airway sequelae due to SARS-CoV-2 infection are described in most observational studies, most from the United States and Europe. The compromise of the upper airway was related to mechanisms to prevent the spread of the virus; as these interventions increased, the lesions became more severe.

Some of the frequent airway sequelae documented in the literature include the development of tracheal and laryngotracheal stenosis after prolonged intubation and subsequent tracheostomy [14,39,40]. Other articles reported aerodigestive complications, which include vocal fold paralysis and paresis, muscle tension dysfunction, laryngotracheal hypersensitivity, and laryngopharyngeal reflux [41]. Allisan-Arrighi et al [41] reported a broad spectrum of respiratory, swallowing, and voice difficulties, which cause distress in patients recovering from COVID-19 infection. The sequelae included structural and anatomic inflammatory changes of the upper airway trachea with the following frequency: 16.13% for tracheal stenosis, 16.13% arytenoid ankylosis, and 16.13% posterior subglottic stenosis [41]. In other articles, authors report airway granulomas as a frequent complication of severe COVID-19 infection [42]. In addition, Guarnieri et al [43] reported a high incidence of tracheomalacia after tracheostomy in patients with severe SARS-CoV-2 infection, as the tracheostomized patient had a longer intensive care unit and hospital stay [43]. In their study, Guarnieri et al [43] showed a 5% incidence of tracheomalacia, which is 10 times higher than the reported literature [43].

In the following years, the environmental and physiological stress to which the animals are subjected translates into an alteration in their immune system that provides greater susceptibility not only to being hosts of the microorganism but also to promoting its replication and therefore increasing the risk of a zoonotic overflow [44]. Environmental issues may be associated with pandemic occurrence [44]. For this reason, all the lessons learned in this regard should change how the following epidemics will be addressed; for example, by developing more efficient strategies [45] and artificial intelligence to contain the respiratory virus. These strategies would decrease the sequelae between patients and the high cost. Patients with pre-existing airway disease are thought to be at a higher risk of developing severe outcomes from acute COVID-19 [46]. Most of the evidence reports these effects on lower airways, and the effects on upper airways may start to be reported in the next few years.

This study has several limitations, including the following: a summary of results that would not reflect the entirety of the

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literature available needs to be included. Additionally, the scoping review does not consider the risk of bias assessment [47]. For that reason, some included studies may incur bias. In our case, the data synthesis needs to address the weight of the evidence. We performed a narrative summary of the results and a descriptive form of the quantitative data. Finally, the broad search would dilute some specific results essential to the main objective of the scoping review.

Authors' Contributions

EC conceived this study. EC, OAV, JTA, FQ, DFIP, WV, and LFT developed the study and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search strategy.
[DOCX File , 18 KB - resprot_v12i1e41811_app1.docx]

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Abbreviations

IMV: invasive mechanical ventilation
JBI: Joanna Briggs Institute
OTI: orotracheal intubation
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews
RedCap: Research Electronic Data Capture

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Protocol

Implementation of Competency-Based Education for Quality Midwifery Programs in Africa: Protocol for a Scoping Review

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Abstract

Background: Competency-based education (CBE) for midwifery programs is a system of academic instruction and evaluation that aims to achieve proficiency in midwifery student learning outcomes, which is based on students' ability to demonstrate the knowledge, attitudes, self-perceptions, and skills of a predetermined set of educational activities in theory and practice. CBE focuses on ensuring that midwifery students can develop critical thinking abilities, values, and the clinical decision-making abilities needed for the delivery of safe care in future practice.

Objective: The objective of this scoping review is to map and synthesize existing literature on the implementation of CBE for midwifery programs and its sustainability in Africa.

Methods: We will use the Arksey and O'Malley approach for scoping reviews for the research methodology. The 3-stage search process, proposed by the Joanna Briggs Institute, will be used to determine the eligibility of published and unpublished studies. PubMed, Science Direct, Web of Science, CINAHL, PsycINFO, and Scopus will be searched to screen published articles. ProQuest Dissertations and Theses and Google Scholar will be used to search for unpublished studies. Findings will only apply to studies conducted in Africa from 2010 to the present year in English. The 2 reviewers will work independently to carefully screen and compare the full text of the selected citations to the inclusion criteria. In the event of any disagreements between the 2 reviewers at any stage of the selection process regarding the inclusion of an article, this will be settled by discussion or consultation with a third reviewer. The extracted data will be presented using a PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Review) flow diagram with an attached narrative summary. The review will summarize and disseminate findings on the implementation of the CBE for midwifery programs and its sustainability in Africa.

Results: It is intended that this scoping review will be completed within 6 months following the publication of this protocol.

Conclusions: The conclusions from this scoping review will inform midwifery educators, institutions, policy makers, and other stakeholders on the strategies to implement and sustain CBE for midwifery programs in Africa.

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KEYWORDS

Africa; competency-based education; implementation; midwifery programme; protocol; scoping review; sustainability

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Introduction

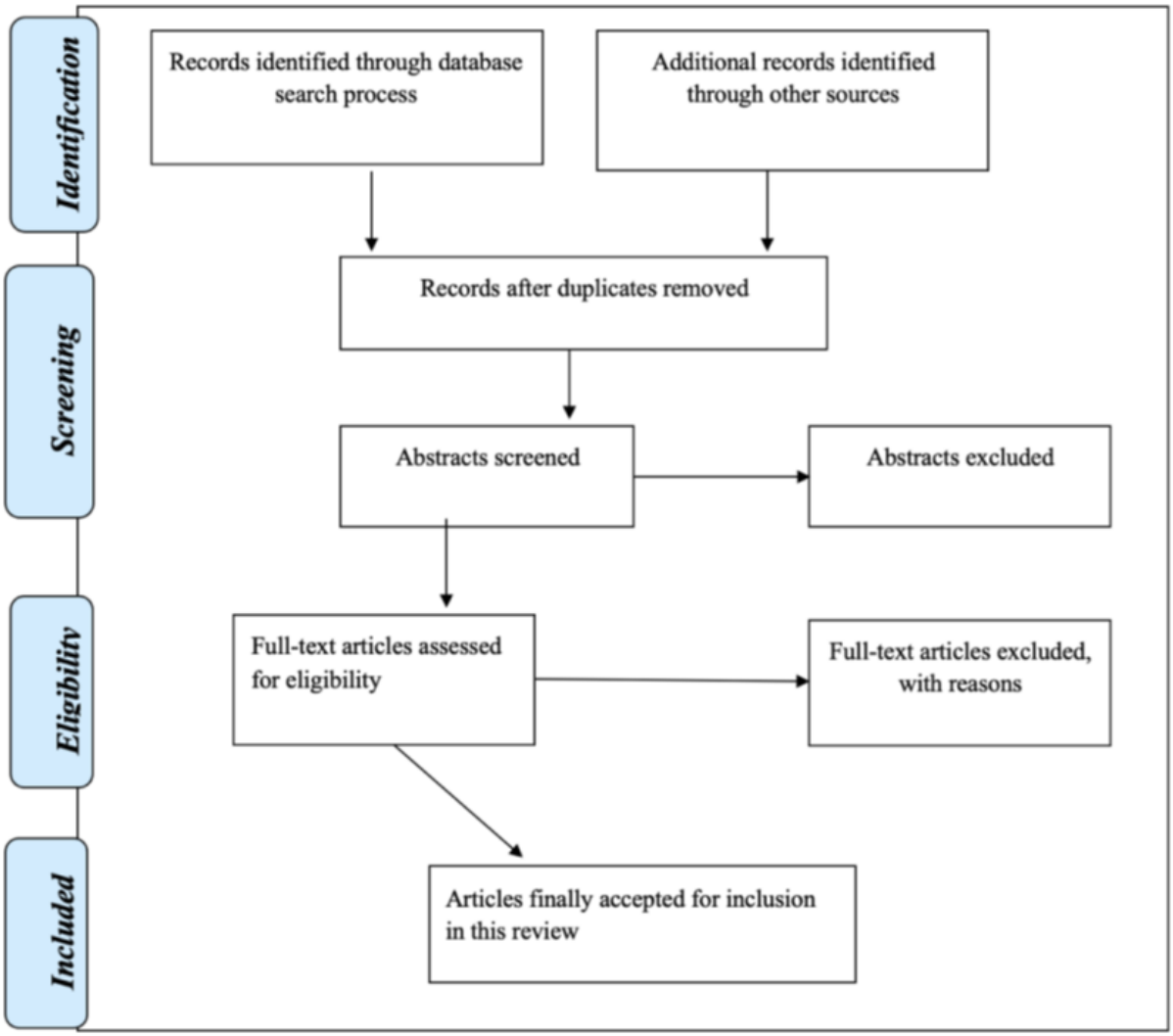
The past few decades have witnessed a rapid and worldwide reform in traditional education toward competency-based education (CBE) at all levels and types of education [1,2]. The competency-based approach to education focuses on addressing positive educational outcomes that align with the needs and expectations of the workforce, employers, and the population they serve [3,4]. CBE places strong emphasis on learner-centered learning, which encourages better adaptability and accountability [5,6]. Through CBE, graduates can critically think, communicate effectively, and work collaboratively with others to provide solutions to problems [7]. This teaching and learning strategy differs from the traditional approach, which consists of time-based training, evidence of academic degrees, and the assessment of student progress based on lessons taught [8,9]. This paradigm shift evolved in an attempt to bridge the gap between students having completed their educational program yet still being unable to perform competently in the workplace or being inadequate to proceed to the next level of education [8,10], despite the immeasurable efforts, time, and resources invested in this traditional education without achieving positive outcomes [10].

The World Health Organization (WHO) and the International Confederation of Midwives (ICM) also adopted this educational trend in the education of midwives and other health professionals by using the term "core competencies" [11,12]. Core competencies, also known as essential competencies, are a set standard for preparing the health workforce to be current and responsive to dramatic health advances geared to meeting clients' expectations [13,14]. The midwifery set of competencies was created and published by the ICM in 2002 [15]. Since then, the competencies have undergone reviews and updates based on scientific evidence [16,17]. The updated competencies are arranged in a framework of 4 interconnected categories, including general competence, which applies to all aspects of a midwife's practice, and competencies that are particular to care throughout prepregnancy, antenatal care, labor, delivery, and the postpartum period [18]. These competencies represent the requirement for preservice education in midwifery and its intended outcomes [17]. CBE for the midwifery profession is, therefore, a system of academic instruction and evaluation that aims to achieve proficiency in midwifery student learning outcomes based on students' ability to demonstrate all the essential competencies for basic midwifery practice [18].

CBE aims at developing critical thinking abilities, values, and the clinical decision-making abilities needed by midwifery students for the delivery of safe care in future practice [10,14]. The design of CBE for teaching and learning activities should comply with standards by integrating knowledge, skills, values, and attitudes within each competency [19]. Midwife educators, midwifery regulatory bodies, midwifery institutions, and others involved in the development and implementation of preservice midwifery education are expected to adopt and adapt CBE to curricula [12,14,20]. However, reports on the integration of competency-based curricula and the approach to ensure sustainability are yet to be well documented, especially in Africa [14], whereas countries and institutions in which the CBE approach has been fully adopted have recorded positive outcomes in their education programs. Outcomes include, but are not limited to, producing competent and confident graduates and improved quality care for clients, contributing to improved family health [8,21-23]. Previous reviews on CBE in Africa focused on challenges regarding the implementation of CBE [24,25]. This review will, however, explore and synthesize existing literature on the implementation of CBE for midwifery programs and its sustainability in Africa.

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Figure 1. PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Review) flow diagram showing the phases of the literature search and selection procedures of studies for the review.



Methods

Overview

The Arksey and O'Malley [26] approach for scoping reviews will be used for the research methodology. The Arksey and O'Malley [26] framework comprises the following steps: (1) identify the research question; (2) identify relevant studies; (3) perform study selection; (4) extract and chart the data; and (5) collate, summarize, and report the results. This framework will direct the scoping review methodology, and, if applicable, the protocol will adhere to the pertinent PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Review) guidelines [27].

Step 1: Identify the Research Question

The following research questions will guide this study:

1. What is the existing evidence on implementing CBE in midwifery education in Africa?

2. How has CBE for midwifery education been sustained in Africa?

Inclusion Criteria

The participants, concept, and context (PCC) framework will guide the inclusion of eligible studies in this scoping review [28].

Participants

Studies that include midwifery students, midwifery educators, midwives, obstetric nursing, obstetrics and gynecology nursing, and maternal and child health nursing relating to CBE will be included in this study, while studies on CBE relating to other health professions such as nursing, medicine, pharmacy, and allied health professions will be considered irrelevant to this study.

Concept

Studies that discuss the implementation of competency-based midwifery education in Africa will be considered in this scoping review. The concept of interest is competency-based curriculum and teaching and learning strategies used in theory and clinical practice. These strategies include the lecture method, demonstration, simulation, role play, etc. Competency-based

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curriculum content includes the ICM competency framework, that is, prepregnancy, pregnancy, labor and childbirth, and the postpartum period.

Context

The context covers academic settings, including, but not limited to, schools, colleges, polytechnics, universities, and hospitals facilitating the teaching and learning of midwifery education programs. These settings where CBE is integrated into theory and practice will be considered in this review. Studies that relate to Africa, published from 2010 onward, will be considered.

Step 2: Identify Relevant Studies

The 3-stage search process proposed by Joanna Briggs Institute will be used to determine the eligibility of published and unpublished studies [29]. To develop a comprehensive search strategy, a preliminary limited search of PubMed and EBSCOhost will be performed to scrutinize text words found in the titles and abstracts, including any index keywords. Second, a second search across PubMed, EBSCOhost, Science Direct, and Scopus will be carried out using all specified keywords and index terms. Third, the reference lists of all accessed articles will be checked for additional studies and included, if considered eligible. Furthermore, ProQuest Dissertations and Theses and Google Scholar will be used to search for unpublished studies that would not have been easily accessed through conventional databases. Findings will only apply to studies conducted in Africa from 2010 to 2024, presented in English.

Step 3: Perform Study Selection

The aggregate citations found will be uploaded into EndNote (version 9; Clarivate Analytics) after the search, while duplicates will be deleted manually. Titles and abstracts will then be screened by 2 independent reviewers (WBI and OA) to assess eligibility using the PCC framework. The full text of potentially relevant articles that fulfill the eligibility requirements will be retrieved, and their citation information will be imported into Rayyan (Qatar Computing Research Institute). WBI and OA will work independently to carefully screen and compare the full text of the selected citations to the inclusion criteria. The reasons for the exclusion of the full text of articles not considered will be documented and reported in the scoping review. In the event of any disagreements at any stage of the selection process regarding the inclusion of an article between WBI and OA, this will be settled by discussion or consultation with WBN (the third reviewer). The final scoping review will include a narrative report on the search and study selection procedure and a diagrammatic presentation using a PRISMA-ScR flow diagram [27].

Step 4: Extract and Chart the Data

All eligible studies' data will be extracted and processed using data charting. A data charting table will be created using Excel (Microsoft Corp) to extract and chart relevant information. The team of reviewers will pilot the data charting form on 5-10 articles to ensure that vital information is completely extracted. All publications meeting the inclusion criteria will have their data extracted by 2 independent reviewers, and the data will then be validated by a third reviewer. The reviewers will independently draft and later compare the form for consistency, using the PCC framework of the review objectives and questions, and may also consider including emerging relevant variables that may arise during the process. These variables currently consist of (but are not limited to) the type of study, year, setting or context, aims, study population, research design, research techniques, and summary of findings. If applicable, this draft will be modified and revised.

Step 5: Collate, Summarize, and Report the Results

The aim of this study is to map existing evidence on the implementation of competency-based midwifery education across the various studies in Africa. The extracted data will be presented using a PRISMA-ScR flow diagram with an attached narrative summary. Descriptive statistical analysis (eg, frequencies) will initially be used to quantitatively summarize the extracted data. The reviewers will further analyze the data using a qualitative content analysis using the Graneheim and Lundman [30] approach to find new themes and present a narrative report and descriptive analysis of the studies included. This identified theme will be coded independently by the reviewers using NVivo software (version 12; QSR International) with reference to the variables mentioned earlier during the data extraction stage. To ensure validity and credibility, the team will discuss and cross-validate the findings, that is, the codes and emerging themes. The team will also address the implications for future research, clinical practice, and policy while critically evaluating the findings' significance to the study's primary objective.

Results

It is intended that this scoping review will be completed within 6 months following the publication of this protocol. The findings will be presented as outlined above.

Discussion

The purpose of this scoping review is to map and synthesize existing literature on the implementation of CBE for midwifery programs and its sustainability in Africa. The discussion of the findings will be contextualized based on previous studies on CBE for midwifery programs, its implementation, and the strategies used to sustain the implementation of CBE for midwifery programs in Africa. The scoping review is limited to midwifery education, which means other health care professionals' education will be excluded. The review is also limited to studies conducted in Africa in the English language. The findings of the review will be significant in identifying gaps in knowledge and research on this topic of interest. It is anticipated that understanding CBE for midwifery programs may contribute to strengthening midwifery education and advancing the standard of maternity care. The conclusions from this scoping review will inform midwifery educators, institutions, policy makers, and other stakeholders on the strategies required to implement and sustain CBE for midwifery programs in Africa. The results of this scoping review will be published in a reputable journal and presented at local and international conferences.

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Acknowledgments

WBI and WBN conceptualized the scoping review protocol**.** WBI and OA developed the search strategy and prepared the draft manuscript of the scoping review protocol, with appraisal, review, and editing completed by them under the supervision of WBN. All authors have read and approved the final version of the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

CBE: competency-based education
ICM: International Confederation of Midwives
PCC: participants, concept, and context
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Review
WHO: World Health Organization

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Protocol

Transformation and Articulation of Clinical Data to Understand Students' and Health Professionals' Clinical Reasoning: Protocol for a Scoping Review

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Abstract

Background: There are still unanswered questions regarding effective educational strategies to promote the transformation and articulation of clinical data while teaching and learning clinical reasoning. Additionally, understanding how this process can be analyzed and assessed is crucial, particularly considering the rapid growth of natural language processing in artificial intelligence.

Objective: The aim of this study is to map educational strategies to promote the transformation and articulation of clinical data among students and health care professionals and to explore the methods used to assess these individuals' transformation and articulation of clinical data.

Methods: This scoping review follows the Joanna Briggs Institute framework for scoping reviews and the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) checklist for the analysis. A literature search was performed in November 2022 using 5 databases: CINAHL (EBSCOhost), MEDLINE (Ovid), Embase (Ovid), PsycINFO (Ovid), and Web of Science (Clarivate). The protocol was registered on the Open Science Framework in November 2023. The scoping review will follow the 9-step framework proposed by Peters and colleagues of the Joanna Briggs Institute. A data extraction form has been developed using key themes from the research questions.

Results: After removing duplicates, the initial search yielded 6656 results, and study selection is underway. The extracted data will be qualitatively analyzed and presented in a diagrammatic or tabular form alongside a narrative summary. The review will be completed by February 2024.

Conclusions: By synthesizing the evidence on semantic transformation and articulation of clinical data during clinical reasoning education, this review aims to contribute to the refinement of educational strategies and assessment methods used in academic and continuing education programs. The insights gained from this review will help educators develop more effective semantic approaches for teaching or learning clinical reasoning, as opposed to fragmented, purely symptom-based or probabilistic approaches. Besides, the results may suggest some ways to address challenges related to the assessment of clinical reasoning and ensure that the assessment tasks accurately reflect learners' developing competencies and educational progress.

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KEYWORDS

clinical reasoning; semantic qualifiers; discourse; linguistics; education; natural language processing; scoping review; clinical data; educational strategy; student; health care professional; semantic transformation

Introduction

Overview

Health care professional education has made significant progress in teaching clinical reasoning, a fundamental competency for professional practice. Clinical reasoning encompasses the cognitive and metacognitive processes necessary for clinical decision-making [1,2]. These processes enable health care professionals to understand the meaning of clinical data, make accurate decisions, and develop appropriate treatment plans [3,4]. Clinical reasoning is deeply intertwined with the context and environment in which it occurs rather than being disembodied from clinical situations [5].

Insufficiently developed clinical reasoning poses a risk of incidents or errors, which can negatively impact the quality and safety of care [6-8]. Therefore, promoting the development of clinical reasoning in both education and practice is crucial to ensure safe and effective care [2]. In that sense, many efforts have been made to develop different educational strategies aiming to foster the development of clinical reasoning (eg, case studies, concept mapping, simulation, and serious games) [9] and to assess competency (eg, scoring rubrics used during an objective structured clinical examination [OSCE] or a think-aloud exercise) [10]. However, the complexity lies in understanding how these educational strategies and assessment methods can stimulate or simulate the complex cognitive operations involved.

One such cognitive operation is transforming and articulating clinical data, where “raw” data from clinical situations are analyzed, transformed, and expressed using specific professional vocabulary [11]. Translating what students or health professionals hear, see, or perceive into specific professional vocabulary is essential for them to recognize the salient features of a situation and make connections between clinical data and professional knowledge [11]. This cognitive operation is vital in ensuring the consistency and efficiency of oral or written information exchanges between professionals, thus contributing to safe practice [12].

Despite its significance, there are still unanswered questions regarding effective educational strategies to promote the transformation and articulation of clinical data while teaching and learning clinical reasoning. While the analysis of the discourse of students or health care professionals can have a didactic value to promote learning or teaching of clinical reasoning and its assessment, the methods used to achieve this are less clear. In other words, what are the conceptual and methodological tools for analyzing the quality of health care professionals’ discourse? How can we ensure that educational choices are anchored in recognized theories of clinical reasoning to promote the development of professional knowledge structures? How other theories or approaches, particularly on language and health care professionals’ discourse, can support the learning or teaching and assessment of clinical reasoning?

Additionally, understanding how the cognitive process of transformation and articulation of clinical data can be analyzed and assessed is crucial, particularly considering the rapid growth of natural language processing (NLP) in artificial intelligence. NLP aims to develop machines capable of modeling and reproducing human language capabilities [13-16]. Applications of NLP include language translation aids, chatbots (eg, ChatGPT [OpenAI]), and voice-controlled technologies [13]. In clinical practice, for example, NLP can extract relevant information, categorize data, and identify patterns from large volumes of text in electronic health records. In education, NLP enables realistic interactions between students and simulated patients in training software.

Furthermore, challenges persist for educators’ assessment of clinical reasoning, in an educational context where machines attempt to replicate competencies such as clinical reasoning. These could support learning or, on other occasions, present threats to the validity or veracity of students’ cognitive efforts in the assigned tasks assigned to them. [17]. Assessment-related challenges include operationalizing the necessary validity and reliability standards and ensuring that the assessment tasks accurately reflect learners’ developing competencies and educational progress.

Thus, understanding how the teaching and learning of clinical reasoning align with learners’ NLP, specifically the transformation and articulation of clinical data, becomes crucial. Therefore, this scoping review protocol aims to map educational strategies to promote the transformation and articulation of clinical data among students and health care professionals. A secondary objective is to explore the methods used to assess these individuals’ transformation and articulation of clinical data.

Background

Research addressing the quality of language and discourse in clinical reasoning grew in the 1990s when George Bordage [11,18,19] introduced prototype theory. According to this cognitivist theory, the characteristics of clinical cases (eg, signs and symptoms, diagnosis, and treatment) are not directly stored in long-term memory. Instead, these characteristics undergo a process of abstraction, generating a set of generic characteristics or a brief, typical description of the case known as a prototype.

Prototypes play a significant role in health education as they facilitate creating and consolidating unit-meaning knowledge networks in long-term memory [12]. This allows students and health care professionals to decode the characteristics of a problem. These characteristics will be correlated or contrasted with those from other clinical problems in similar and different contexts [20], leading to densifying the scripts of students and health professionals, thus promoting the development of clinical reasoning. Professional knowledge and in-depth understanding of these prototypes in terms of pathophysiology, concomitant factors, evolution, and so forth, are therefore essential to the clinical reasoning process [21]. In line with prototype theory,

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the theory of scripts postulates that well-organized knowledge networks and units of meaning stored in the memory of students and health professionals enable effective clinical reasoning [2,22]. Continuing, deliberate clinical practice allows them to densify their scripts by encountering diverse patients and cases.

It was through the use of conceptual and methodological tools derived from structural semantics that Lemieux and Bordage [20,23] analyzed the quality of clinical reasoning, in particular the capacity to diagnose. Issued from linguistics and semiotics (the study of signs and symbols in language), the object of structural semantics is to study the systems of meaning comprised in discourse [20,23]. According to medical semiotics, signs and symptoms represent 2 constituting units of clinical reasoning, highlighting that they must be interpreted in their contexts [24,25]. In structural semantic analysis, the discourse is therefore examined according to the linear and vertical dimensions. The linear dimension relates to the syntactic order, before and after, of the terms used (eg, signs and symptoms) [20,23]. The vertical dimension refers to the underlying semantic structures that allow a student or a health care professional to classify the meaning of clinical data into multiple levels of signification called semantic axes. The semantic axes represent logical levels of abstractions where the student or health professional uses qualitative semantic properties, which are structured on an axis into opposition pairs. Opposition pairs refer to various concepts, such as temporality (constant or intermittent and sudden or gradual), body space (left or right and proximal or distal), degree of impairment (low, moderate, or high), and the quality of the signs and symptoms (apparent or insidious) [20,23].

According to their approach, it is from the constituent units (signs and symptoms) and their forms (eg, syndrome, affected systems, processes, and predisposing factors) that the clinical discourse of students and health professionals can be analyzed, integrating cognitive operations in the latter (eg, being able to decode or define signs and symptoms, to classify them or associate them with others, and to prioritize data). Analyzing the students' and health professionals' discourse provides insight into their knowledge's richness and organization. The semantic component of discourse involves semantic qualifiers, which reflect the intelligible organization of knowledge into meaning units [11,18]. These semantic qualifiers, such as "acute" versus "chronic" pain or "proximal" versus "distal" region, serve as building blocks for organizing knowledge and function as cue mechanisms in long-term memory. Qualifiers can be seen as "useful adjectives" that characterize clinical data abstraction in a situation [12,26].

The syntactic component of discourse is linked to its richness and structure, as it mirrors the richness and organization of one's knowledge repertoire [11,18]. It refers to the associative competence between the constituent units (signs and symptoms) of the discourse as opposed to a simplistic enumeration of signs and symptoms without creating meaning or relationships between them [20,23]. In this sense, discourse can also appear scattered or reduced when there is an apparent lack of or insufficiently developed knowledge to understand and respond effectively to a situation. Bordage [11,18] proposed a discourse classification system that examines the organization of knowledge and the ability to contrast diagnostic hypotheses using clinical data. These categories are (1) reduced: discourse that lacks any effort of semantic transformation, with no connections between patient data and knowledge; (2) scattered: discourse that exhibits limited semantic transformation and disordered hypotheses, which do not reference the obtained data and are listed without contrasting; (3) elaborated: discourse with numerous semantic transformations used judiciously to contrast hypotheses; and (4) compiled: the individual immediately recognizes a semantic data set associated with a clinical hypothesis.

The semantic and syntactic components of discourse are important because they reflect the elaboration and organization of clinical knowledge in the minds of students and health care professionals [11,18]. Semantic qualifiers, integral components of professional vocabulary, are crucial in clearly communicating a patient's condition in the clinical setting. By mastering these qualifiers, students can effectively convey relevant clinical information and enhance their ability to participate in meaningful clinical discussions [12].

While the semantic competence of students and health professionals should be enhanced to understand, analyze, and develop or evaluate clinical reasoning, the question is how it is solicited or simulated in the educational strategies and evaluation methods used in health education.

Methods

Overview

This scoping review will be based on the methods described by Arksey and O'Malley [27]. A scoping review is a knowledge synthesis method to address exploratory research questions by mapping key concepts, types of evidence, and gaps in a research area. This scoping review will identify the extent and range of evidence [28-30] regarding the articulation and transformation of clinical data to guide educational practices and propose avenues of research.

The scoping review will follow the 9-step framework proposed by Peters et al [28] of the Joanna Briggs Institute. This framework includes several consecutive steps that are (1) developing and registering the protocol, (2) formulating the objective and research questions, (3) developing inclusion criteria, (4) identifying relevant studies, (5) selecting relevant studies, (6) charting the data, (7) analyzing the data, (8) reporting the results, and (9) summarizing the results. We will use the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension of Scoping Reviews) checklist [31] to report findings.

Developing and Registering the Protocol

A preliminary search was performed to assess the existing literature and ensure that no other reviews with the same focus were published. We then developed a protocol based on the 9-step framework mentioned above [28]. The protocol was registered on the Open Science Framework. Furthermore, publishing the protocol in a peer-reviewed journal aims to increase transparency [31].

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Formulating the Objective and Research Questions

In this phase, the 2 primary tasks that are undertaken are (1) identifying research questions that provide a roadmap for the subsequent steps and (2) establishing the scope of inquiry, which encompasses defining the concept, the target population, and the context. The objectives of this scoping review are (1) to map the educational strategies to promote the transformation and articulation of clinical data by students and health professionals and (2) to examine the methods to assess the transformation and articulation of clinical data by students and health care professionals. We have developed the following research questions: (1) what educational strategies are used to promote the transformation and articulation of clinical data among students and health care professionals? and (2) what methods are used to assess the articulation and transformation of clinical data by students and health professionals?

Developing Inclusion Criteria

Peters et al [28] recommended that inclusion criteria are based on the Population-Concept-Context framework instead of the Population-Intervention-Comparator-Outcomes framework suggested in the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) [32]. Textbox 1 summarizes the inclusion and exclusion criteria.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Studies on students and health professionals
- Studies reporting educational or assessment strategies involving semantic transformation and articulation of clinical data
- Studies written in French or English
- All primary studies, regardless of study design and geographic areas
- Studies conducted in both academic and clinical settings across all geographic areas

Exclusion criteria

- Studies in fields other than health education programs, unlicensed health care providers, personal care providers, and caregivers
- Studies without a description of educational or assessment strategies; studies focusing on the developments and applications of intelligent or clinical decision support systems
- Studies in languages other than English or French
- Conference abstracts, protocols, editorials, expert opinions, commentaries, letters, book reviews, blogs and social media

For the population, we will consider literature that discusses educational strategies to foster the development of clinical reasoning among students and health professionals across various academic levels (eg, pregraduates and postgraduates) and disciplines. The included studies will encompass a range of health disciplines, such as medicine, midwifery, occupational therapy, speech-language therapy, and nursing. Conversely, we will exclude studies involving populations outside the field of health, unlicensed health care providers, personal care providers, and caregivers.

The central concept of this review will be the semantic transformation and articulation of clinical data during clinical reasoning [11]. This cognitive operation involves converting “raw” data from a clinical situation into specific professional vocabulary to describe the situation [11]. By organizing clinical data into meaningful units, this cognitive operation helps to understand the situation and generate clinical hypotheses. Clinical reasoning is a cognitive process underlying clinical judgment and decision-making [1,2,33]. These terms, often used interchangeably in the literature [1,4], will also be considered in the search strategy.

For the context, we will consider sources reporting on educational strategies or assessment methods involving the semantic transformation and articulation of clinical data in the context of clinical reasoning. These educational strategies may include, for example, case studies, concept mapping, and simulation. The assessment methods refer to the scoring grid used during OSCE or a think-aloud exercise, and so forth [10]. This review will consider studies conducted in both academic and clinical settings across all geographic areas. Studies examining the developments and applications of intelligent or clinical decision-support systems will be excluded, as technical or engineering procedures could be difficult to analyze and would deviate from the objectives of the review.

We will consider primary studies with quasi-experimental (eg, before and after studies and interrupted time series), experimental (eg, randomized controlled trials), observational (eg, cohorts, case-control, and cross-sectional), qualitative, and mixed methods designs. We will also include grey literature such as theses, dissertations, conference proceedings, and research reports. To focus on scientific literature with sufficient content to help answer our questions, the following will be excluded: conference abstracts, protocols, editorials, expert opinions, commentaries, letters, book reviews, blogs, and social media. Studies written in French or English will be included. The search will span the period from 1990 to the present, that is, after Bordage introduced semantic qualifiers in the 1990s. The objective is to comprehensively examine the literature on clinical reasoning in health professional education during this timeframe.

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Identifying Relevant Studies

As recommended by Peters et al [28], a comprehensive 3-step search strategy was implemented with the support of a health science librarian. Initially, an exploratory search was performed in CINAHL and PubMed to identify keywords and medical subject headings from articles about the review topic. Subsequently, a thorough literature search was conducted in November 2022 using 5 databases: CINAHL (EBSCOhost), MEDLINE (Ovid), Embase (Ovid), PsycINFO (Ovid), and Web of Science (Clarivate). The search strategy was first developed in CINAHL and later adapted to other databases (see Multimedia Appendix 1). Considering the possibility of articles being present in fields other than health care, such as education or linguistics, the review team decided to manually select articles that specifically focused on students or health professionals to ensure relevance to the research topic.

In the future, we plan to use a hand search approach to review the reference list of the included records. This approach will help identify any additional relevant studies that may have been missed during the initial database search. Furthermore, we intend to search for unpublished studies using the ProQuest dissertations and theses electronic database and the ProQuest TDM studio tool and conduct targeted searches on Google Scholar. For the Google Scholar searches, we will use specific search string queries such as “semantic transformation and clinical reasoning,” “diagnostic reasoning and semantics,” and “semantic qualifiers and differential diagnosis.” We will analyze Google Scholar’s top 100 search results to identify additional studies aligning with the review questions and objectives.

Selecting Relevant Studies and Charting the Data

After conducting the initial database search, the retrieved references were imported into Covidence (Veritas Health Innovation) to facilitate the screening process and identify duplicate records. To ensure consistency and establish a shared understanding, 3 reviewers independently assessed the eligibility of a randomly selected sample of 25 articles based on the predefined inclusion and exclusion criteria. In all, 2 meetings were conducted to refine the selection criteria to improve agreement rates.

The screening of titles, abstracts, and full texts was carried out independently by 2 reviewers, following the predefined selection criteria. In the event of any disagreements, a third reviewer was involved. The reasons for excluding studies at the full-text stage were documented and will be reported accordingly.

In the upcoming phase of the scoping review, 2 independent reviewers will extract relevant data from all included studies. A structured data extraction form developed by the reviewers will be used to record the information. Microsoft Excel will be used for data management. The extraction form proposed by Peters et al [28] will serve as a foundation, encompassing article characteristics such as the first author’s name, year of publication, and country of origin, as well as study methods, including the aim, study design, and population. Additionally, we will create codes under the following categories: the transformation and articulation of clinical data to facilitate learning or capture clinical reasoning; educational strategies; any referenced theoretical framework; methods or tools used to analyze the articulation and transformation of clinical data; relevant results; and authors’ recommendations.

Following the recommendation of Peters et al [28], the extraction form will undergo a testing phase by the reviewers, who will extract data from 5 selected studies. This process will help ensure the effectiveness and consistency of the form. Based on their feedback, the reviewers will collaboratively refine the extraction form and create a comprehensive list of codes if any adjustments or modifications are required.

Subsequently, 1 reviewer will perform data extraction, and a second reviewer will independently review the results to ensure accuracy and reliability. In the event of any discrepancies, the reviewers who performed the data extraction will engage in discussion to reach a consensus. A third reviewer will be consulted to finalize the extracted data if a consensus cannot be reached.

Analyzing the Data and Reporting and Summarizing the Results

Extracted data will be processed using content analysis techniques inspired by Miles et al [34]. This data analysis method involves three steps, which are (1) data condensation, (2) data display of similarities and differences, and (3) drawing and verifying conclusions. Based on the review questions, relevant findings pertaining to the characteristics of the included studies will be presented in tables, along with insights into the transformation and articulation of clinical data for educational and assessment purposes. In addition, a narrative report will be used to summarize the key findings from the articles. For this purpose, a brainstorming session involving all reviewers will be organized. The findings will be described with respect to the research questions and the objectives of this scoping review. Additionally, gaps or limitations in the existing literature will be identified and highlighted to provide insights for future research. The search results and the study inclusion process will be reported comprehensively in the final report using a PRISMA-ScR flow diagram [31].

Ethical Considerations

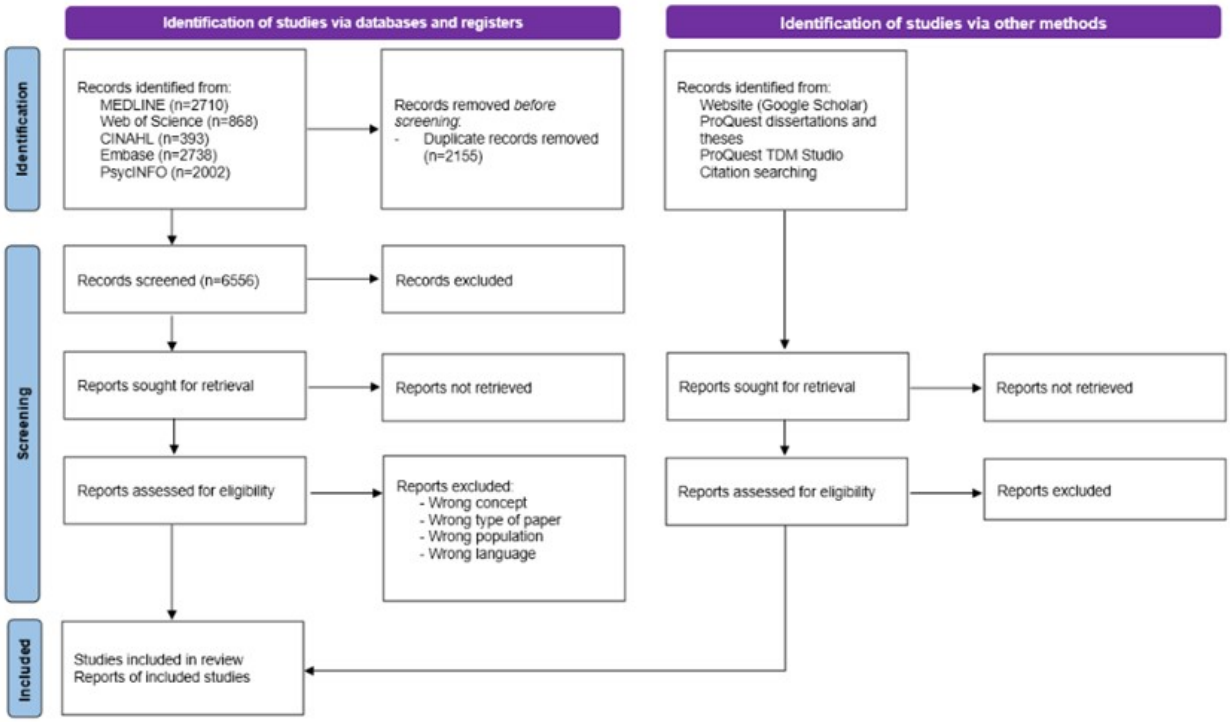
All data will be collected from published and grey literature. Ethics approval is, therefore, not a requirement. We will present our findings at relevant conferences and submit them for publication in peer-reviewed journals.

Results

Database searches were conducted in November 2022. A total of 8711 results were retrieved, of which 2155 were duplicates. Figure 1 shows a flow diagram of the records identified. The review will be completed by February 2024.

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Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram.



Discussion

Principal Findings

The proposed scoping review aims to provide a comprehensive overview of the existing evidence on semantic transformation and articulation of clinical data during clinical reasoning education. The initial literature search yielded substantial results, totaling 6656 after removing duplicates.

Various educational strategies have been identified thus far. These include summary statements with simulated patients, verbal analysis of thoughts related to vignettes, tests to assess the association between clinical data and diagnoses, and examining written reports in actual or simulated contexts. Furthermore, the review has uncovered the presence of rubrics that incorporate both the semantic and syntactic dimensions of students' and health professionals' discourse, providing a framework for evaluating clinical reasoning. These findings highlight the diversity of educational strategies and assessment tools used in the field. Based on the review's preliminary findings, an initial evaluation of the theories about the articulation and transformation of clinical data has been formulated.

Despite a robust review design, some limitations can be identified in this protocol. This scoping review may exclude relevant studies as it will mainly include peer-reviewed journal articles. As such, some relevant grey literature may be excluded from our findings. Excluded studies examining developments and applications of intelligent or clinical decision support systems could contain some additional information to answer the review questions. Indeed, the keywords used in the search strategy are broad and may not identify all specialized studies. Moreover, only considering English and French as the languages of publication could exclude papers relevant to our scoping review written in other languages.

Conclusions

By synthesizing the evidence on semantic transformation and articulation of clinical data during clinical reasoning education, this review aims to contribute to the refinement of educational strategies and assessment methods used in academic and continuing education programs. The insights gained from this review will help educators develop more effective semantic approaches for teaching or learning clinical reasoning, as opposed to fragmented, purely symptom-based or probabilistic approaches. Besides, the results may suggest some ways to address challenges related to the assessment of clinical reasoning and ensure that the assessment tasks accurately reflect learners' developing competencies and educational progress.

Acknowledgments

This study was funded by Équipe FUTUR, a research infrastructure subsidized by the Fonds de Recherche du Québec—Société et Culture and by Social Sciences and Humanities Research Council of Canada Institutional Explore grants (PVX20020). The content is solely the responsibility of the authors. The funders had no role in the study design, the data collection and analysis, the decision to publish, or the preparation of the study.

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Data Availability

The data sets generated and analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

All authors contributed to the study's conceptualization, including the background development, design of the study, and planned outcomes of the research. MFD prepared the draft protocol with PL, NF, KL, and MEC. MFD prepared the study with the support from PL, NF, KL, and MEC, and DA and TCM reviewed it. The authors read and approved the final study.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search strategy.
[DOCX File , 22 KB - resprot_v12i1e50797_app1.docx]

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Abbreviations

NLP: natural language processing
OSCE: objective structured clinical examination
PRISMA-P: Preferred reporting items for Systematic Review and Meta-Analysis Protocols
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews

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Protocol

Pilot-testing a Multiplayer HIV and Sexually Transmitted Infection Prevention Video Game Intervention for Black Adolescent Girls: Protocol for a Randomized Controlled Trial

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Abstract

Background: Black adolescent girls aged between 14 and 19 years are more likely than White girls to be diagnosed with a sexually transmitted infection (STI). As STI diagnosis is associated with an increase in the risk for HIV acquisition, an early intervention specifically tailored to Black adolescent girls is warranted. A web-based video game intervention has the potential to reach this demographic. Because studies of social and behavioral determinants of disease demonstrate the protective role of peer group structures on individual outcomes, a multiplayer game can facilitate opportunities to exchange and evaluate information, learn social norms, develop behavioral skills, and allow peers to influence attitudes and behavior. No prior research has examined the feasibility of a web-based multiplayer game intervention for this population.

Objective: This study describes the protocol for a randomized controlled trial (RCT) pilot-testing the feasibility, acceptability, and limited efficacy of a multiplayer game–based intervention for increasing HIV and STI testing and condom use in Black adolescent girls.

Methods: We enrolled 79 Black adolescent girls aged 14 to 19 years residing in the United States into a 2-arm parallel RCT. The intervention is a theory-based, community-informed, multiplayer game that can be played with peers on the web using videoconferencing software. The goal of the game is to empower Black adolescent girls to make healthy decisions regarding dating, relationships, and sex, thus reducing HIV and STI infection. Control condition participants received a list of resources after playing a time and attention control game. All study procedures were conducted via the internet. We conveniently sampled Black adolescent girls using web-based advertisements. Study assessments occurred at enrollment, 1 week, 1 month, and 4 months after enrollment. The primary outcome of this study is increased HIV and STI testing by Black adolescent girls. Secondary outcomes include increased condom use, self-efficacy to use condoms, positive attitudes toward condom use, intentions, harm perceptions, HIV and STI and pre-exposure prophylaxis knowledge, positive sexual norms, sexual communication with partners, and reduced incidence of sexual risk behaviors associated with HIV and STI transmission. Secondary outcomes also included assessment of intervention feasibility and acceptability.

Results: From February to April 2022, a total of 79 Black adolescent girls were enrolled, with 40 (51%) having been randomized into the intervention condition and 39 (49%) into the control condition. At baseline, participant ages ranged from 14 to 19 (mean 16.4, SD 1.23) years.

Conclusions: Web-accessible game interventions overcome common impediments of face-to-face interventions presenting a unique opportunity to reach Black adolescent girls and improve their sexual health and self-efficacy. Trial data will provide information about the limited efficacy of the intervention and inform future web-based studies and a larger RCT aimed at improving the sexual health of Black adolescent girls.

Trial Registration: ClinicalTrials.gov NCT04108988; https://clinicaltrials.gov/ct2/show/NCT04108988

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International Registered Report Identifier (IRRID): DERR1-10.2196/43666

(JMIR Res Protoc 2023;12:e43666) doi:10.2196/43666

KEYWORDS

black; adolescent; female; video games; feasibility studies; HIV prevention; randomized controlled trial; sexual health; condom use; self-efficacy; pre-exposure prophylaxis; PrEP

Introduction

Background

Despite advances in HIV prevention efforts, Black adolescents continue to be disproportionately affected by HIV in the United States, comprising 54% of all new HIV diagnoses in 2016 [1]. In the United States, Black adolescent girls aged between 14 and 19 years have higher rates of sexually transmitted infections (STIs) than other ethnic minority girls and are more than twice as likely to be diagnosed with an STI than their White peers [2-5]. Racist, sexist, and classist views significantly disadvantage Black adolescent girls' achievement of positive health outcomes relative to White girls [6]. Indeed, mounting evidence implicates the role of gendered-racist stereotypes on increases in Black girls' sexual risk behaviors [7,8], indicating a need for the development of HIV and STI prevention strategies specifically tailored for Black adolescent girls.

A recent systematic review noted that many existing sexual health promotion interventions for Black youth are not specifically tailored for Black adolescent girls or made to account for their unique experiences because of the intersection of race and gender [9]. Because increased knowledge about HIV and HIV prevention strategies is associated with protective sexual behaviors such as condom use and HIV testing among adolescents of color [10,11], there exists a critical need for the development of more interventions specifically designed for Black adolescent girls that increase the knowledge about HIV and STI prevention and emphasize resisting and challenging gendered-racist stereotypes [12]. Although the recent systematic review identified 15 effective HIV and STI prevention programs that have been used with Black adolescent girls, only 4 were created specifically for this population [9]. In addition, challenges regarding implementation and fidelity of interventions have been a concern. Studies have cited several barriers to the implementation of HIV and STI prevention interventions, including access to adequately trained providers, staff turnover, resource constraints of agencies, and fidelity of the interventions [13-15].

One possible method for intervention delivery is through the creation of a self-contained video game, which can provide consistent fidelity, and places little demand on program resources [16,17]. Game interventions have demonstrated efficacy in increasing knowledge and affecting behaviors related to health promotion and disease management across domains [18]. Successful game interventions have focused on health topics ranging from asthma management, healthy diets, medication adherence, and even sexual health promotion through risk behavior reduction [19-22]. Because 83% of adolescent girls play video games on computers, web, phone, or console [23], a game-based HIV and STI prevention intervention specifically tailored for Black adolescent girls will likely be an acceptable and enjoyable means of delivering the material.

Among adolescent girls, social or multiplayer games are among the most popular and frequently played video games [24]. Because interactions within peer groups offer opportunities for individuals to exchange and evaluate information, learn social norms, develop behavioral skills, and influence each other's attitudes and behavior [25], an HIV and STI prevention initiative that targets peer groups by leveraging adolescent girls' preference for multiplayer gaming experiences has the potential to have benefits above and beyond an intervention designed for a single individual. Indeed, research suggests that peers often serve as a valuable source of information about HIV and as role models for prevention strategies such as condom use [26]. For instance, a community-based pilot study demonstrated a 72% increase in the number of individuals getting tested for HIV and STI when peers recruited others through their social network [27]. Similarly, a recent study of at-risk Black and Hispanic youth aged 13 to 24 years found that a female friendship network method of engagement was successful with increasing HIV testing rates by 90% [28].

Although Boyd et al [29] found that Black and Latinx adolescents who learned about HIV from their friends were *less* likely to get tested for HIV, the researchers note that youth surveyed in their study likely perceived the HIV-related knowledge gleaned from friends as unreliable. Therefore, to take advantage of the benefits that peer group structures can have on individual determinants of health, it is important that a multiplayer intervention create a shared experience where the information provided is known by all to be both factual and relevant to the players' lived experiences. Adopting this strategy in the creation of an HIV and STI prevention multiplayer video game specifically tailored for Black adolescent girls allows for conversations between players to occur in real time during gameplay, which deepens engagement with the material and provides girls the opportunity to positively influence attitudes, beliefs, and perceptions around serious topics. Moreover, the game environment encourages a safe and playful space where peer groups can normalize discussions about sex and safe sex practices. Because most research on Black girls' sexuality and sexual health is focused on the reduction of risky behaviors rather than fostering safe and healthy sex and sex positivity [12,30], a game-based sex positive intervention represents a novel strategy. Such an intervention has the potential to impact the sexual self-efficacy of Black adolescent girls, high levels of which have been associated with HIV-risk mitigation strategies such as consistent condom use by adult Black women [31].

In light of the COVID-19 pandemic, efforts to recruit groups of Black adolescent girls to gather in person for multiple

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gameplay sessions were stymied. Thus, rather than continue to delay data collection, the research team used their extensive experience working with youth and decided to pivot to web-based data collection by following a model previously found successful in the collection of focus group data that served as the foundation for the development of this study's video game intervention [32,33]. This decision was made with knowledge from conducting numerous randomized controlled trials (RCTs) with schools and informed by processes that we developed to accommodate remote data collection.

With the ubiquity of the videoconferencing software Zoom (Zoom Video Communications, Inc) and recent reports that "gamified videoconferences" facilitated both connection and learning during periods of social isolation [34], the research team embraced the opportunity to recruit a sample of Black adolescent girls from across the United States, rather than wait for the resumption of in-person learning at local school partner sites. Although web-accessible game interventions overcome many common barriers of face-to-face interventions and offer a unique opportunity to reach Black adolescent girls across the United States, no previous studies have examined the use of multiplayer game interventions delivered remotely to this population. Therefore, pilot-testing the limited efficacy of this specifically tailored multiplayer game intervention is necessary to understand the acceptability of the gaming experience such that future expansions and adaptations can be created. Moreover, results of this pilot limited efficacy test can be used to estimate variability and precision to power a future larger RCT.

Study Aims

Primary Aim

Our primary aim of this study is to evaluate the feasibility and acceptability of a multiplayer game–based intervention designed to increase HIV and STI testing and condom use among adolescent Black girls.

Feasibility of this intervention is assessed by collecting data on the number of intervention sessions completed by participants and retention rates. We hypothesize that the intervention will have high completion and retention rates across survey time points (>80%).

Acceptability of the intervention condition is assessed via self-reported survey at the postgameplay time point using the game experience and satisfaction questionnaire, which is a 15-item scale with 4-point Likert-type responses ranging from 1 (strongly disagree) to 4 (strongly agree) [22,35-37]. Example questions include "I enjoyed playing the game" and "I would make decisions in life like I made them in the game." We hypothesize that in response to the question as to whether a participant would be interested in playing the game again and whether they would recommend the game to their friends, ≥75% of participants will "agree" or "strongly agree" that they would like to play the game again and ≥75% will "definitely" or "very probably" recommend the game to their friends.

Secondary Aim

Our secondary aim of this study is to determine the preliminary impact of the intervention on knowledge, intentions, beliefs and attitudes, self-efficacy, social norms, and behavioral skills related to HIV and STI testing, condom use, and sexual risk behavior reduction. We hypothesize that compared with control participants, participants in the intervention group will have greater improvements in all proximal outcomes.

Exploratory Aim

This study includes an exploratory aim designed to evaluate participants' real time responses to the game through the content analysis of audio recordings of gameplay sessions. We will investigate participant perceptions of research procedures and game content to analyze suggestions for the improvement of both. We will also explore whether connection to one's ethnic identity may be a protective factor against sexual risk behavior [38]. Because the exploratory aim concerns implementation procedures and the adaptation and expansion of the game, there are no a priori hypotheses.

Methods

Ethics Approval

All the procedures were approved by the Yale University Institutional Review Board (ID #2000026487). In addition, a Data Safety and Monitoring Board consisting of 2 experts in clinical trials in adolescents and in statistical analysis of clinical trials was formed to oversee the safety and data integrity of this study. The Data Safety and Monitoring Board also periodically reviewed the progress of the study. The following personally identifying and medical information were collected: email ID, phone number, self-reported HIV and STI testing status, test results, and sexual activity status. All data collected from the assessments were entered by participants directly into the secure web-based system, Qualtrics (Qualtrics International Inc), which is Yale's enterprise-wide data management system. This ensured participant confidence that their data would remain confidential. Study participation incentives were sent via email as Amazon e-gift cards. Written consent was obtained via digital signature from all the participants before their participation, as detailed in the section Study Population and Study Flow.

Study Design

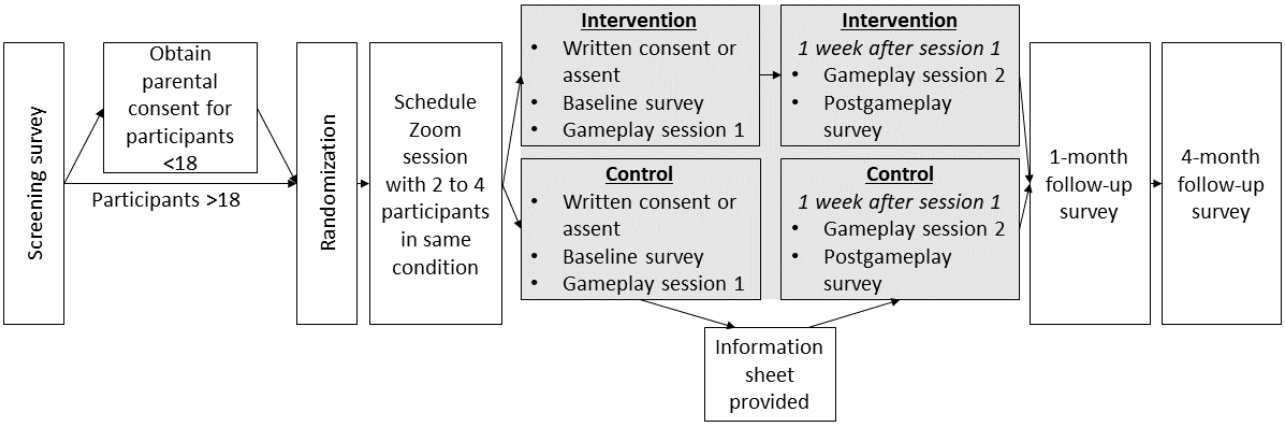
This study is a pilot of a 2-arm RCT designed to evaluate the feasibility and acceptability of a multiplayer game–based intervention designed to increase HIV and STI testing and condom use among adolescent Black girls. The study is led by a team with expertise in conducting research with youth, as well as extensive experience with the design and evaluation of game-based health promotion interventions, including interventions specifically designed for HIV and STI prevention [22,37]. Our multiplayer video game intervention prototype and research protocol were developed through extensive collaboration with partners including a specialist in strength-based approaches to understanding HIV and STI disparities among girls and women of color, a biostatistician, and a professional game development company, PreviewLabs, Inc.

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Study Population and Study Flow

All study procedures including screening, consenting, and surveying were conducted through Qualtrics, a secure Health Insurance Portability and Accountability Act–compliant website for managing web-based surveys and databases. Study participant flow is depicted in Figure 1.

Figure 1. Two-arm randomized controlled trial design and data collection schedule.



First, to determine eligibility, respondents completed a brief web-based self-reported screening questionnaire, the link to which was displayed on the social media advertisements. Respondents were eligible if they met the following eligibility criteria: they must (1) be aged between 14 and 18 years; (2) identify as Black; (3) identify as female; and (4) identify as straight (ie, heterosexual), bisexual, or pansexual. Once ≥3 prospective participants signed up for a single study session, the project manager or research assistant emailed those 3 prospective participants the Zoom link for the study session and a description of the procedure, which included recommendations for equipment (a PC for Zoom and cell phone for gameplay). Respondents under 18 years of age were also required to provide an email address for a parent or guardian.

All the eligible respondents were assigned a participant number and were randomly assigned to either the experimental or control condition (full descriptions of conditions are provided in later sections). Eligible respondents then received an email from the project manager or research assistant with details about the study and exclusion and inclusion criteria, and for respondents under the age of 18 years, the parental information sheet and a link to the informed consent document was emailed to the parent or guardian using the address provided in the screening survey. Prospective participants who were 18 years old and respondents whose parent or guardian digitally signed the informed consent document were then invited to sign up for a study session.

Separate study sessions for experimental and control participants were determined each week by the project manager and research assistant. Prospective participants were instructed to indicate their availability for as many study sessions as possible. Respondents provided their email address and had the option to provide a cell phone number if they preferred to receive text messages for study communication. If additional prospective participants later indicated availability for a study session for which links had already been distributed, those participants were similarly provided with the Zoom link and study procedure description. Invitations to study sessions were capped at 8 prospective participants per session.

Adolescent assent for participants under 18 years and informed consent for participants aged 18 years were obtained at the start of each Zoom study session. After explaining the risks and requirements of the study in general terms, the researcher provided each participant a link to the full consent or assent document via Qualtrics. Participants were given ample time to fully read through the document and asked to provide their digital signature if they agreed to participate. The researcher was available to answer all the questions regarding the consent and assent document. Following consent procedures, the baseline survey was administered (full description of the baseline survey is provided in a later section). Once all participants had completed the baseline survey, the researcher launched the video game according to condition (intervention game vs control game; both described in detail in a later section). Throughout gameplay, participants were encouraged to use Zoom's chat feature to discuss the game.

Upon conclusion of the first gameplay session, participants were emailed an Amazon gift card worth US $30 and a second gameplay session at the same time in the following week was scheduled. Participants who were unable to attend a second gameplay session at the same time in the following week were scheduled for a different second gameplay session with another group via email. For all the participants, the second gameplay session began with playing either the control or the experimental game, followed by the completion of the postgameplay survey (full description of the postgameplay survey is provided in a later section). Once all the participants submitted their postgameplay survey, a second Amazon gift card worth US $30 was emailed to all participants.

The first follow-up survey was emailed to all the participants 1 month after their second gameplay session. The second follow-up survey was emailed to all the participants 3 months after the completion of their first follow-up survey. For each follow-up survey completed, participants received a US $30 Amazon gift card via email. Participants who did not complete either follow-up survey within 5 days of receiving the survey were reminded to complete the survey via email. An additional email reminder was sent 1 week after the first reminder.

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Participants who asked to be contacted via text message additionally received survey links and reminders through text message.

Recruitment

Participants were conveniently sampled and recruited throughout the United States using advertisements on Facebook and Instagram. Instagram was our primary recruitment site because it is possible to target individuals of a particular age (14-18 years) and gender (female) through the advertising platform. Moreover, Instagram is used by approximately 71% of adolescents, making it an appropriate platform to reach our target demographic [23]. We created an advertisement and recruited participants from Facebook using the same advertisement and targeting criteria. An individual who was interested in participating clicked on the advertisement and was directed to the Qualtrics screening survey.

Assessments

To evaluate the multiplayer game–based intervention we collected assessment data at 4 time points during the study: baseline, after the gameplay, 1-month follow-up, and 4-month follow-up. The assessments administered at each time point are depicted in Table 1.

Table 1. Assessments and time of administration.

Assessment	Baseline	Postgameplay time point	1-month follow-up	4-month follow-up
Participant demographics (ie, gender, age, and sexual orientation)	✓			
Self-reported HIV and STI[a] testing rate (1 item)	✓	✓	✓	✓
Sexual Risk Behaviors and Sexual communication—self-reported measures of sexual intercourse with or without condoms and frequency of safe sex discussions with partners (27 items)	✓	✓	✓	✓
CUSES[b] (11-item Likert scale)	✓	✓	✓	✓
HIV and STI KQ[c] (12 items true or false questions adapted from HIV-KQ and STD-KQ)	✓	✓	✓	✓
PrEP[d] knowledge and attitudes (11 items)	✓	✓	✓	✓
Microbehaviors: discussing condoms with partners, purchasing condoms, and discussing testing with partners (4 items)	✓	✓	✓	✓
MEIM-R[e] (6-item Likert scale)	✓			✓
Self-efficacy in sexual risk behaviors—SRBBS[f] (27-item Likert scale)	✓	✓	✓	✓
Gameplay experience and satisfaction; *intervention participants only* (12-item Likert scale)		✓		
Game experience reflection; *intervention participants only* (4 items)			✓	✓

[a]STI: sexually transmitted infection.

[b]CUSES: Condom Use Self-Efficacy Scale.

[c]KQ: Knowledge Questionnaire.

[d]PrEP: pre-exposure prophylaxis.

[e]MEIM-R: Multigroup Ethnic Identity Measure—Revised.

[f]SRBBS: Sexual Risk Behavior Beliefs and Self-efficacy.

Materials

Control Materials

Participants randomized into the control condition attended live Zoom sessions with up to 4 other control participants and a researcher, who facilitated gameplay of the non–health-related attention and time control condition multiplayer video game. Players in control Zoom sessions played 1 of 2 Jackbox (Jackbox Games, Inc) games (Fibbage or Drawful), which were selected for use as attention and time control games for their similarity in game structure to the intervention game. Participants randomized to the control condition received a short list of links to resources with HIV- and STI-related general information, prevention, testing locations searchable via zip code, and suggestions for talking with partners about HIV and STI testing and prevention strategies such as condom use via email. Finally, after completion of the final 4-month follow-up survey, control participants were offered access to a web page that contained the information and resources provided in the intervention. Participants in the control condition played 2 full games of Jackbox during each gameplay session, resulting in 100 to 120 minutes of total playtime.

Intervention Materials

Participants randomized into the intervention condition attended live Zoom sessions with up to 4 other intervention participants and a researcher, who facilitated gameplay of the multiplayer intervention video game, *InvestiDate*. The design and story content of the intervention video game was based on information the research team gathered through focus groups with 27 Black

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adolescent girls in which participants discussed their experiences with sex, dating, the use of social media to inform partner selection, and participants' experiences of gendered-racist stereotypes and how these experiences influenced their own sexual decision-making [32,33]. In addition, 7 participants from the focus groups further volunteered to guide the development of the video game by forming a Board of Advisors that oversaw the writing of game dialogue and creation of character storylines, as well as provided feedback on character art and design. The characters and background images in *InvestiDate* were designed and illustrated by a young Black female graphic artist. The educational content of the intervention game was determined through the examination of other HIV and STI prevention programs, existing literature, and through the creation of a Game Playbook [39] guided by theories of behavior change [40,41]. Game development was achieved through collaboration with professional educational game developers. A typical game takes between 30 and 45 minutes to complete. Participants in the intervention condition played 1 to 2 games during each gameplay session, resulting in 70-130 minutes of total intervention exposure.

Game Development

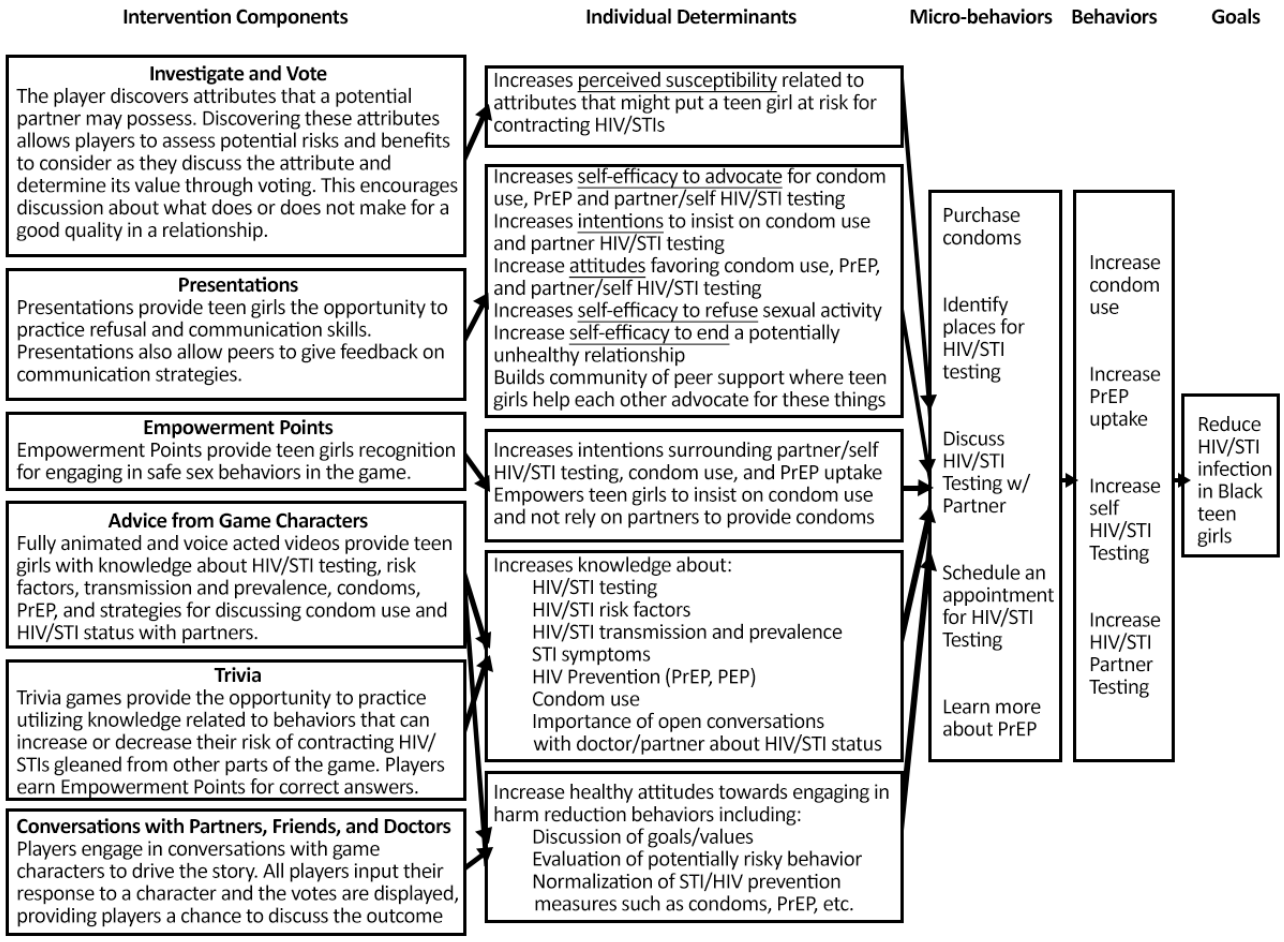
InvestiDate is based on a theory-driven and evidenced-informed HIV and STI prevention social card game designed for young Black women [37]. The video game adaptation was developed in collaboration with PreviewLabs, Inc, a rapid prototyping and game development company located in New Haven, Connecticut, United States. The video game intervention is a multiplayer and feminist take on a traditional dating simulation (sim) game and is dialogue based, containing no explicit sexual imagery or descriptions. Dating sim games are typically dialogue heavy and involve the building and maintenance of a relationship with one or more characters, with game outcomes largely dependent on statistics. The intervention game adds a social component to the dating sim genre by pitting players against one another in a race to develop relationships with the datable characters. Furthermore, an element of icebreaker games is added in that players are encouraged to predict each other's reactions to game events. The intervention game also borrows structural components form the hit social game series Jackbox, in that game action takes place on a single shared screen, which runs on desktops and laptops with Windows (Microsoft Corp) or Mac (Apple Inc) operating systems while players input gameplay decisions on separate internet-capable devices through a web-based interface.

Theoretical Underpinnings

The conceptual model of the game intervention depicted in Figure 2 is based on well-established behavior change theories, including social cognitive theory [40] and health belief model [42]. Social cognitive theory [43,44] posits that behavior change occurs through the development of self-efficacy and skill acquisition and that learning is expedited through the observation of behavior carried out by others similar to the observer. Self-efficacy can be achieved through behavioral rehearsal and feedback, and the observation of behavior is simulated through the inclusion of roleplaying storylines based on the lived experiences of Black adolescent girls who participated in the formative focus groups. The health belief model posits that if a person perceives a benefit from a particular change in behavior, they will be more likely to adhere to the change [42]. In the video game, players earn points for behaviors like testing for HIV and STI, insisting on condom use, and communicating with partners extensively. These vicarious learning opportunities model beneficial behavior for players.

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Figure 2. Game intervention conceptual model. PrEP: pre-exposure prophylaxis; STI: sexually transmitted infection.



Gameplay

At the beginning of the game, the players are introduced to "Chelsea" and "Brandon," 2 nonplayable characters who serve as guides throughout the game by providing instructions and verbal prompts to capture and direct player attention. In addition to learning a bit about the 2 host characters, all the players must pick 5 goals from options such as "talk to your doctor about PrEP," "convince a guy to use a condom during sex," "answer 9 trivia questions correctly," and "get tested for HIV and STIs," all with varying amounts of points awarded for completion. The game concludes when the first player reaches 300 points, and goal achievement provides the highest point awards. Figures 3-6 depict screenshots from the game and provide examples of actions players can take during the game to achieve goals.

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Figure 3. Players, represented by emojis on the left of the screen, choose whom to "follow" based on biography and profile image and whom to investigate based on traits revealed on previous turns.

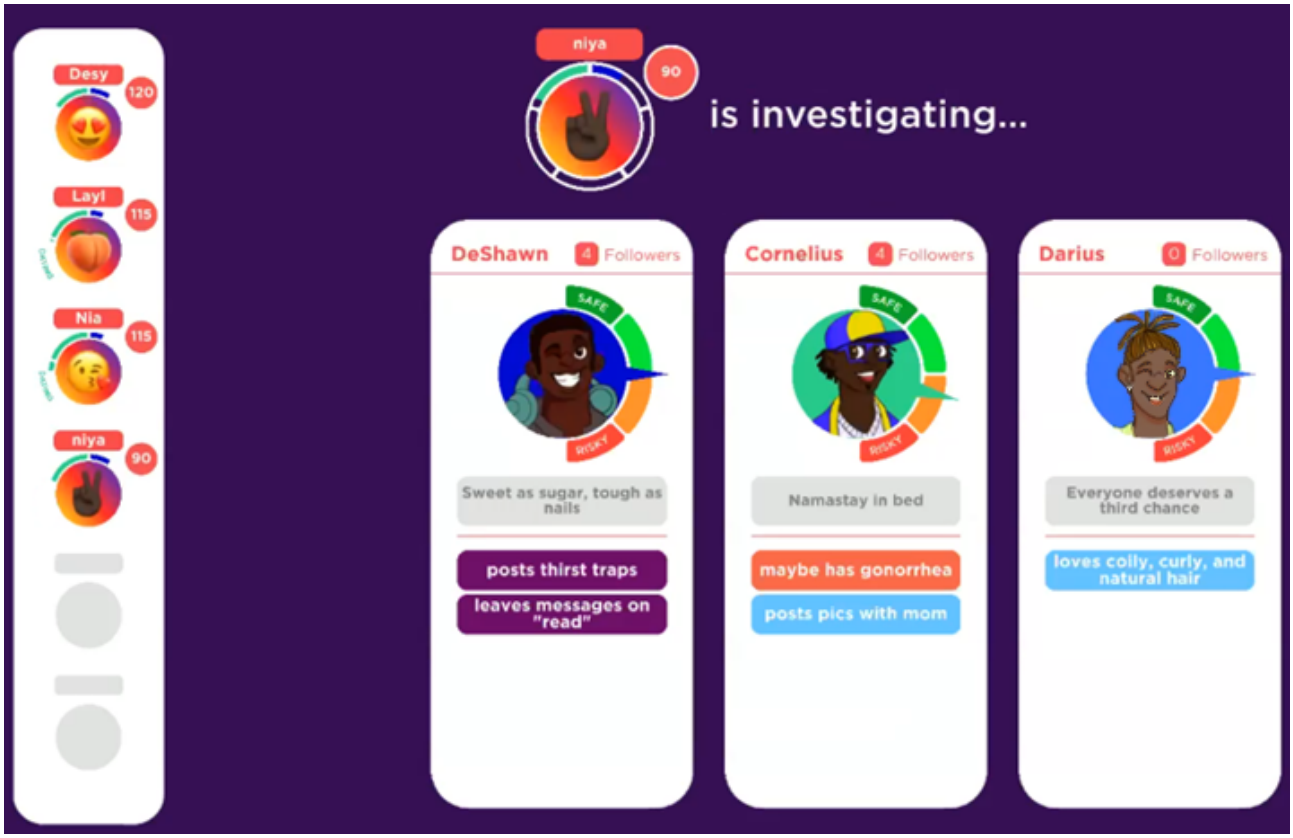
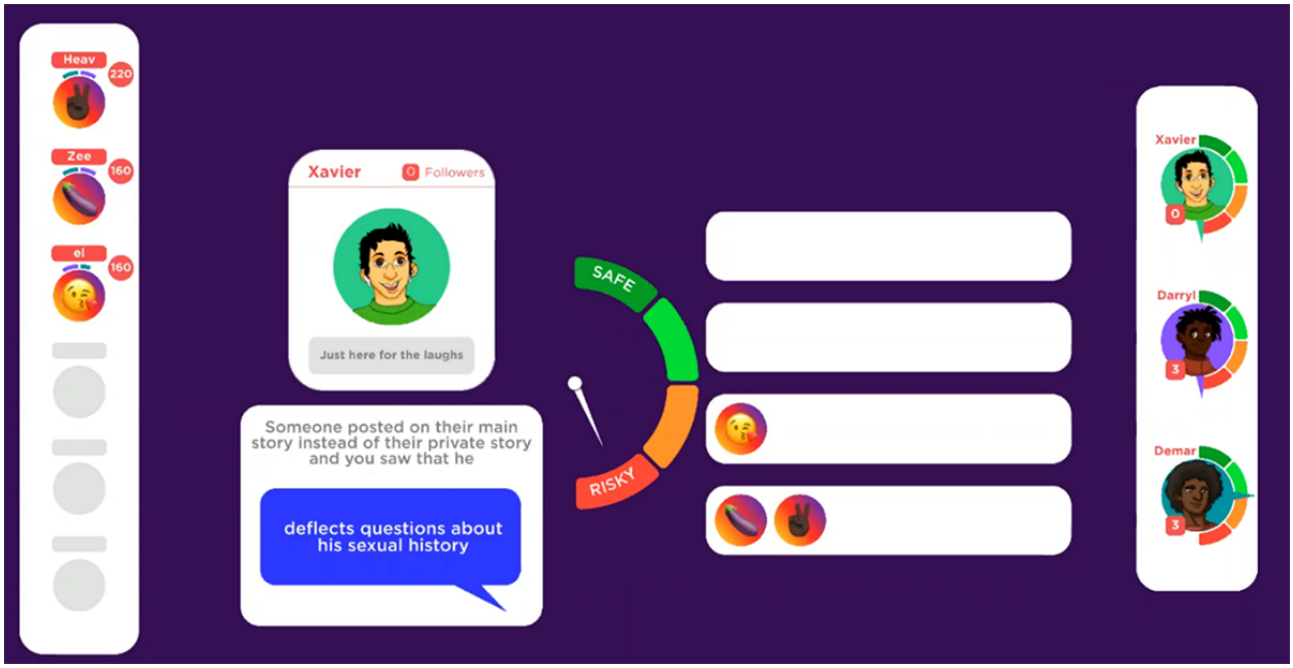


Figure 4. Players investigate datable characters and then vote on traits on a scale from safe-risky (pictured below) and cool-lame. Dating more risky characters increases the likelihood of a player becoming diagnosed with HIV or another sexually transmitted infection (STI).



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Figure 5. The character Chelsea explains sexually transmitted infection (STI) prevalence in the United States in an animated voice-acted video.

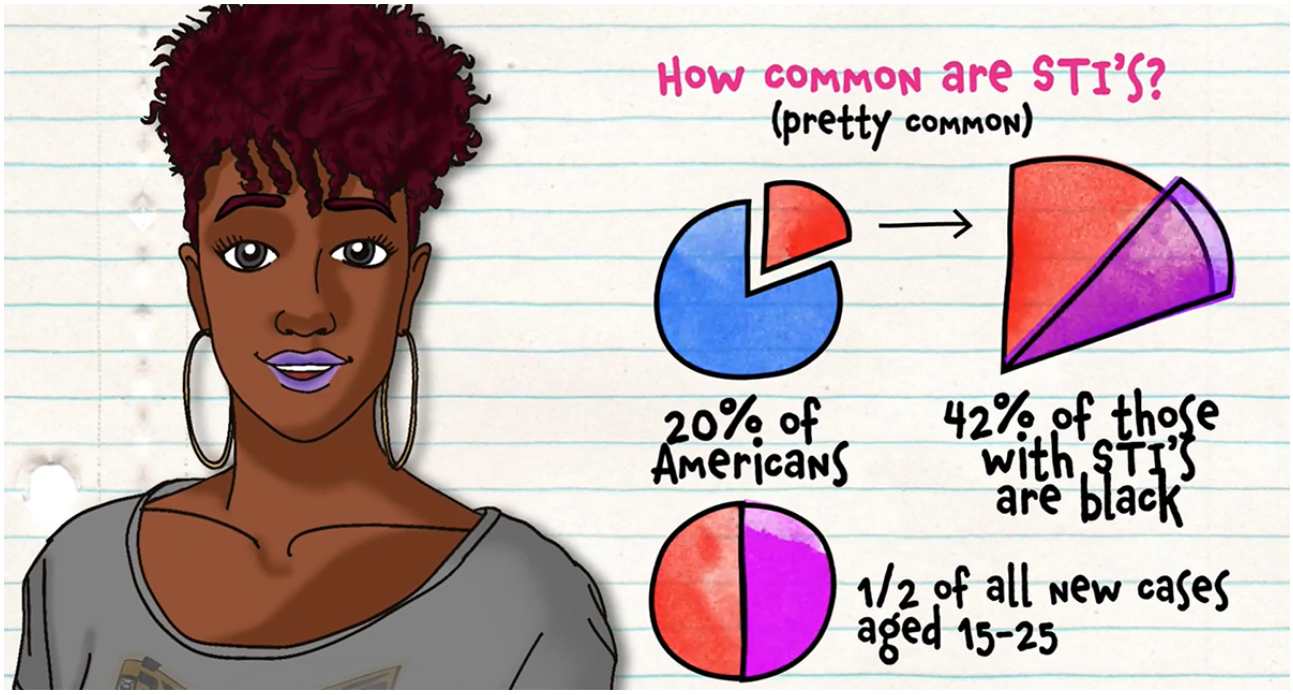


Figure 6. A conversation about HIV and sexually transmitted infection (STI) testing with a doctor.



Data Collection

Data were collected in 2 unique ways. First, all the assessments were self-administered via Qualtrics, which allows participants to complete assessments on their computer, phone, or tablet. Participants completed the baseline and postgameplay assessments during a live Zoom session with the researcher, which ensured that participants could ask questions of the study personnel as they arose. The 1-month and 4-month follow-up assessments were emailed to participants and completed by participants on their own time. Second, recordings of all gameplay sessions allow for the transcription of game content and player interactions during the game for qualitative analysis.

Outcomes

Primary Outcomes

The primary outcome of this study is to evaluate the feasibility and acceptability of a multiplayer game–based intervention designed to increase HIV and STI testing and condom use among Black adolescent girls. Intervention feasibility and acceptability will be examined through the number of sessions completed by participants and participant retention rates throughout the study.

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Secondary Outcomes

Our secondary outcome is to increase Black adolescent girls' HIV and STI testing; use of condoms; self-efficacy to use condoms; positive attitudes toward condom use; intentions to use condoms; harm perceptions; HIV, STI, and pre-exposure prophylaxis (PrEP) knowledge; positive sexual norms; sexual communication with partners; and reduced incidence of sexual risk behaviors associated with HIV and STI transmission. We hypothesize that participants in the intervention condition will demonstrate greater improvements in the above outcomes when compared with the control participants. We will also measure whether changes are sustained across the follow-up periods of 1- and 4 months, as well as intervention feasibility and acceptability. Table 1 lists the surveys used to evaluate our secondary aim.

Across all time points, HIV and STI knowledge is evaluated with 12 true or false statements such as "having an STI like herpes can put a person at greater risk for getting HIV" or "chlamydia and gonorrhea cannot be cured," and recoded as correct or incorrect. The 12-item assessment is based on the validated 45- and 27-item HIV- and STI-Knowledge Questionnaires [45,46] and is available in Multimedia Appendix 1 [45,46]. Participants have the option to select "I don't know," which is scored as incorrect. A cumulative knowledge score will be created for each participant, with a maximum score of 12. CUSES (Condom Use Self-Efficacy Scale) is measured with a 10-item adaption of the scale designed by Brafford and Beck [47] and includes questions like "If my partner didn't want to use a condom, I feel confident that I could convince him that it was necessary" and "I feel confident in my ability to put a condom on my partner" to which participants could respond 1 (strongly disagree) to 5 (strongly agree). SRBBS (Sexual Risk Behavior Beliefs and Self-efficacy) is measured with a 27-item Likert scale questionnaire that includes questions like "Most of my friends believe people my age should wait until they are older before they have sex" or "If you decided to have sex, how sure are you that you could have a condom with you when you needed it?" to which participants respond on a 5-point scale [48]. PrEP knowledge and attitudes were assessed with questions regarding participant familiarity with PrEP, whether they would approve of friends or partners taking PrEP, and whether they believed friends and partners would approve if they were to take PrEP. Finally, sexual risk behavior was assessed with self-report questions based on the Youth Risk Behavior Survey [49]. We hypothesize that participants in the intervention condition will have greater changes or improvements in the above outcomes when compared with the control participants and that these changes will be sustained across time points.

Exploratory Outcomes

An exploratory outcome is included to evaluate participants' real-time responses to the game through the content analysis of audio recordings of gameplay sessions. We will investigate participant perceptions of research procedures and game content to analyze suggestions for the improvement of both. An additional exploratory analysis seeks to determine whether there is a relationship between participant responses on the 6-item MEIM-R (Multigroup Ethnic Identity Measure—Revised) and other outcome measures. The connection between ethnic identity and self-esteem, for example, is well known [50]. We will explore whether connection to one's ethnic identity may be a protective factor against sexual risk behavior [38]. Because the exploratory aim concerns implementation procedures and the adaptation and expansion of the game, there are no a priori hypotheses.

Statistical Analysis

All statistical analyses will be conducted on an intention-to-treat sample using SPSS Statistics (IBM Corp) packages. Baseline characteristics will be analyzed using descriptive statistics. We will use baseline, postgameplay, 1-month, and 4-month data to estimate effect sizes for the primary outcomes. We will test the hypothesis that individuals who play *InvestiDate* will report more HIV and STI testing and communication with partners about testing in comparison to the control condition. We will conduct a longitudinal analysis using a hierarchical linear mixed models approach to compare participants in the intervention group to participants in the control group on reported participant HIV and STI testing from baseline across all follow-up assessments (ie, baseline, 1 month, and 4 months). Hierarchical modeling will allow us to account for the fact that the data are nested, as the participants will play the game in groups. An advantage of mixed models is that participants with missing data need not be excluded as all available data are used in estimating parameters. We will also use logistic regression models to determine if any relevant baseline variables, including ethnic identity, are associated with improvement in reported HIV and STI testing (constructed as a binary outcome [yes or no]). We plan to evaluate the prognostic significance of a small set of predictor variables (eg, attitudes, self-efficacy, ethnic identity, and knowledge) and use them as covariates in the primary analysis. Given the limited sample size (n=79), we anticipate that the power of this study to identify small but significant effect sizes will be low. A strength of this design is that it provides a number of perspectives from which to view treatment effects, including a treatment condition, a control condition, and a follow-up period. The results will inform the sample size calculation for a subsequent larger RCT.

Qualitative Analysis

The transcripts and chat logs from *InvestiDate* gameplay sessions (experimental group only) will be reviewed by members of the research team jointly who will perform data coding. These codes will be created in a step-wise fashion [51], beginning with the creation of an initial code structure from the first 2 transcripts that are independently reviewed by each team member. To enhance interrater reliability, gameplay transcripts will be independently reviewed and coded by each researcher and coding will be compared for agreement. Manual coding will then be electronically applied to the textual data using Dedoose (SocioCultural Research Consultants), a software program designed to facilitate the analysis of qualitative data. Data collected will be used to inform subsequent iterations of the video game, *InvestiDate*, and will similarly be used to provide exploratory evidence for the success of the intervention at achieving primary outcomes such as normalization of

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conversations about sex and safe sex practices such as testing and condom use.

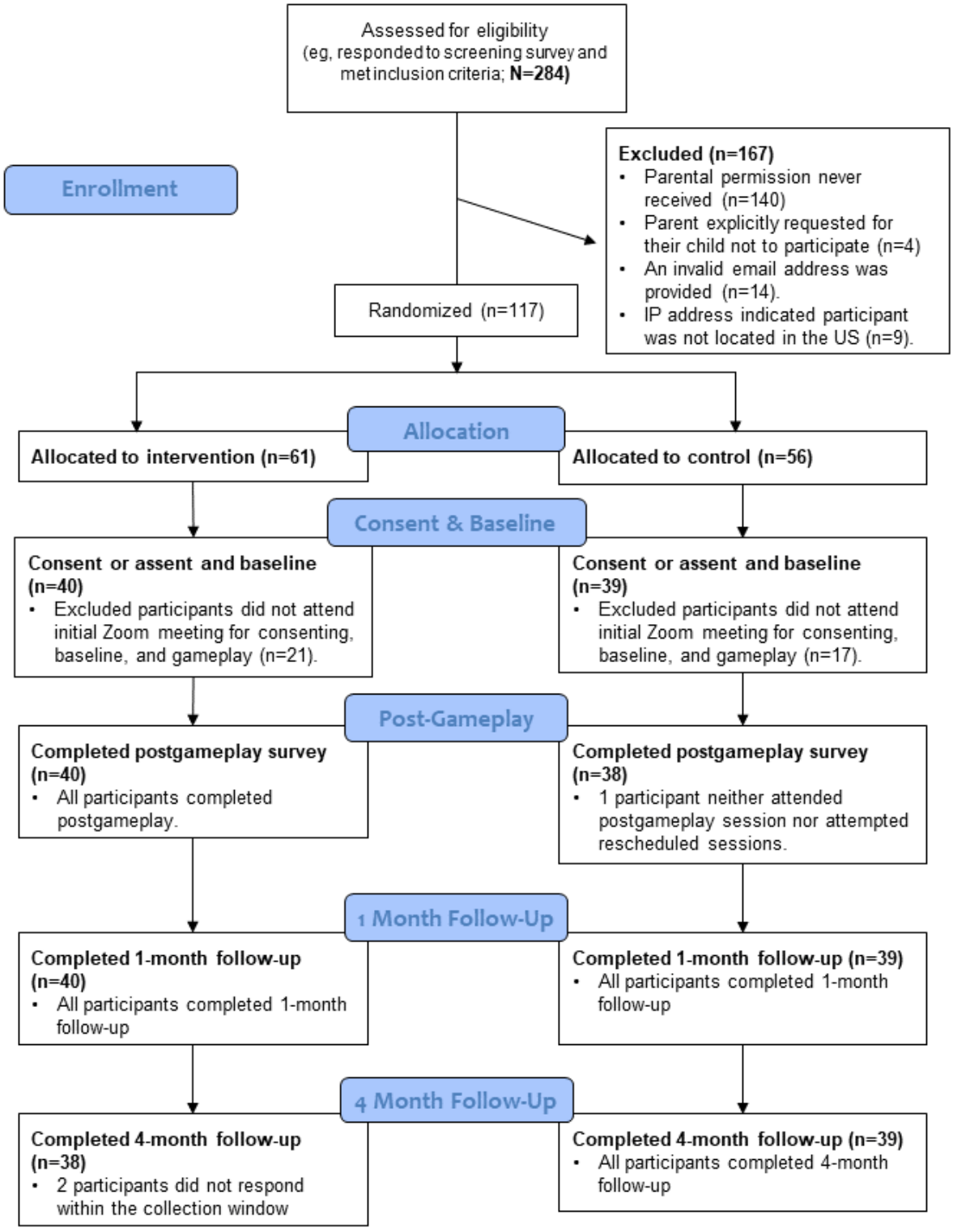
Results

Enrollment and Randomization

Overall, 1497 individuals clicked the link to the screening survey. In total, 47.43% (710/1497) of individuals completed the screening questionnaire, 40% (284/710) of which met the eligibility criteria; 9.5% (27/284) of eligible respondents were 18 years old at the time of recruitment, and we received parental consent for an additional 31.7% (90/284) of individuals to participate. Of those 117 prospective participants, 79 (67.5%) girls attended the first gameplay session, consented to participate, and were enrolled. Subsequently, 51% (40/79) of the enrolled participants were randomized into the intervention condition, and 49% (39/79) of the participants into the control condition. Figure 7 shows the CONSORT (Consolidated Standards of Reporting Trials) flow diagram that depicts participant retention at all time points [52]. All 79 participants were enrolled into the RCT between February 2022 and April 2022. All 39 participants in the control condition and 38 participants in the intervention condition completed the final survey in September 2022.

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Figure 7. CONSORT (Consolidated Standards of Reporting Trials) flow diagram depicting participant enrollment and retention across all study time points. US: United States.



Sample Demographics

At baseline, there were no significant differences in demographic characteristics between intervention and control condition participants. At baseline, participant ages ranged from 14 to 19 years (mean 16.4, SD 1.23). One participant turned 19 during the week that elapsed between recruitment and the first gameplay session. Although the screening survey excluded participants who identified as having a sexual orientation other than straight (ie, heterosexual), bisexual, or pansexual, at baseline 10.1% (8/79) of participants identified as questioning or unsure, 1.2% (1/79) as queer, and 1.2% (1/79) as asexual, with the remaining 55.6% (44/79) of the participants identifying as straight or heterosexual and 32.9% (26/79) of the participants as bisexual or pansexual.

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Discussion

Overview

In this pilot RCT of a multiplayer game–based intervention designed to increase HIV and STI testing and condom use among adolescent Black girls, we enrolled and randomized 79 participants. All participants were recruited through Instagram or Facebook, and there were no significant demographic differences between participants randomized to the intervention and control conditions. Notably, we chose to expand our inclusion criteria from strictly heterosexual-identifying participants to include individuals who identified as bisexual or pansexual in response to high numbers of participants who self-identified as something other than heterosexual. This observation is consistent with recent data from the Adolescent Behaviors and Experiences Survey in which 1 in 5 high schoolers identified as something other than straight or heterosexual [53].

This study protocol offers several strengths and novel strategies that can inform future gender- and culturally tailored HIV and STI prevention interventions as well as inform efforts to collect data for RCTs remotely using extant platforms like Zoom. Our video game intervention specifically addresses the intersectional identities of Black adolescent girls by incorporating the lived experiences of focus group participants into game story lines. In addition, the video game fosters a sense of social support by allowing Black adolescent girls to interact with each other, which is an important protective factor for sexual health [38]. It is among the first targeted interventions that is sex positive and harnesses the power of peer interactions through multiplayer gameplay to deliver HIV and STI prevention material. Because the video game intervention is self-contained, it has the potential to overcome common barriers to existing HIV prevention interventions, including access to adequately trained providers and intervention fidelity. Finally, data were successfully collected remotely during the global COVID-19 pandemic when in-person interactions were restricted. The procedures developed for data collection in this intervention can be adopted and used in other web-based studies involving multiple synchronous participants and may also be useful for the collection of larger nationally distributed samples.

Limitations

There are some limitations to this study protocol. In particular, participants were conveniently sampled through social media advertising, which may have resulted in selection bias. To participate in the study, participants were required to be available for gameplay sessions during weekday evenings, have a strong internet connection, and had to have access to 2 separate internet-capable devices (one to use the Zoom platform and one to play the game). These requirements may have discouraged participants with full evening schedules such as afterschool activities, part-time jobs, or family responsibilities from participating, as well as participants with low socioeconomic status. Finally, although the game was intended to be a social experience, game audio (such as background music and video game character dialogue) made communication between players difficult during many game sequences. Decreased social interaction in the multiplayer game may impact both participant ratings of gameplay satisfaction and acceptability, as well as intervention outcomes. In future iterations, we will examine whether in-person gameplay is more satisfactory than remote play over Zoom.

Conclusions

Black adolescent girls have the highest rates of STI among ethnic minority girls and are more than twice as likely to be diagnosed with an STI than their White peers, but there are very few HIV and STI prevention interventions specifically tailored for this group. This paper describes our protocol for a pilot RCT of a multiplayer game–based intervention designed to increase HIV and STI testing and condom use in Black adolescent girls. The aims of this pilot study are to assess the feasibility, acceptability, and preliminary efficacy of the game intervention. This protocol directly informs the development of a future larger RCT testing the efficacy of the video game intervention, *InvestiDate*, and can serve as an example for other researchers seeking to collect data over Zoom from multiple synchronous participants distributed nationally.

Acknowledgments

This project would not have been possible without our partnership with game prototype developer, PreviewLabs, Inc. The authors would also like to thank our sound engineer, Andrew Schartmann, PhD, who created the *InvestiDate* soundtrack and audio. The authors would like to thank our Board of Advisors and all the focus group participants who contributed to the development of this project, as well as Ms Alex Evans who provided her talents as a voice actor for the game. The study is funded by the Eunice Kennedy Shriver National Institute of Child Health and Human Development at the National Institutes of Health (1R21HD098031-01) and is registered as a clinical trial (NCT04108988).

Data Availability

The data generated during this study will be available from the corresponding author on reasonable request.

Authors' Contributions

KH, VW, IO, SH-R, and BS designed the intervention. VW, MB, and BS collected the data. IO, LD, and CSFF contributed to the design and selection of the assessments. VW drafted the manuscript, and IO and KH revised and critically reviewed the

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manuscript for important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Conflicts of Interest

KH is the principal investigator for this study and has a significant relationship with the video game prototype company, PreviewLabs Inc, that is currently developing the video game intervention based on the findings of this research study. This relationship is extensively managed by KH and her academic institution. All other authors declared no potential conflicts of interest.

Multimedia Appendix 1
A 12-item assessment based on the validated 45- and 27-item HIV and sexually transmitted infection (STI) Knowledge Questionnaires.
[PDF File (Adobe PDF File), 109 KB - resprot_v12i1e43666_app1.pdf]

Multimedia Appendix 2
Peer review report by Behavioral and Social Science Approaches to Preventing HIV/AIDS (BSPH) Study Section AIDS and Related Research Integrated Review Group Center for Scientific Review (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 156 KB - resprot_v12i1e43666_app2.pdf]

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Abbreviations

CONSORT: Consolidated Standards of Reporting Trials
CUSES: Condom Use Self-Efficacy Scale
MEIM-R: Multigroup Ethnic Identity Measure—Revised
PrEP: pre-exposure prophylaxis
RCT: randomized controlled trial
SRBBS: Sexual Risk Behavior Beliefs and Self-efficacy
STI: sexually transmitted infection

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Protocol

Developing Early Markers of Cognitive Decline and Dementia Derived From Survey Response Behaviors: Protocol for Analyses of Preexisting Large-scale Longitudinal Data

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Abstract

Background: Accumulating evidence shows that subtle alterations in daily functioning are among the earliest and strongest signals that predict cognitive decline and dementia. A survey is a small slice of everyday functioning; nevertheless, completing a survey is a complex and cognitively demanding task that requires attention, working memory, executive functioning, and short- and long-term memory. Examining older people's survey response behaviors, which focus on how respondents complete surveys irrespective of the content being sought by the questions, may represent a valuable but often neglected resource that can be leveraged to develop behavior-based early markers of cognitive decline and dementia that are cost-effective, unobtrusive, and scalable for use in large population samples.

Objective: This paper describes the protocol of a multiyear research project funded by the US National Institute on Aging to develop early markers of cognitive decline and dementia derived from survey response behaviors at older ages.

Methods: Two types of indices summarizing different aspects of older adults' survey response behaviors are created. Indices of subtle reporting mistakes are derived from questionnaire answer patterns in a number of population-based longitudinal aging studies. In parallel, para-data indices are generated from computer use behaviors recorded on the backend server of a large web-based panel study known as the Understanding America Study (UAS). In-depth examinations of the properties of the created questionnaire answer pattern and para-data indices will be conducted for the purpose of evaluating their concurrent validity, sensitivity to change, and predictive validity. We will synthesize the indices using individual participant data meta-analysis and conduct feature selection to identify the optimal combination of indices for predicting cognitive decline and dementia.

Results: As of October 2022, we have identified 15 longitudinal ageing studies as eligible data sources for creating questionnaire answer pattern indices and obtained para-data from 15 UAS surveys that were fielded from mid-2014 to 2015. A total of 20 questionnaire answer pattern indices and 20 para-data indices have also been identified. We have conducted a preliminary investigation to test the utility of the questionnaire answer patterns and para-data indices for the prediction of cognitive decline and dementia. These early results are based on only a subset of indices but are suggestive of the findings that we anticipate will emerge from the planned analyses of multiple behavioral indices derived from many diverse studies.

Conclusions: Survey response behaviors are a relatively inexpensive data source, but they are seldom used directly for epidemiological research on cognitive impairment at older ages. This study is anticipated to develop an innovative yet unconventional approach that may complement existing approaches aimed at the early detection of cognitive decline and dementia.

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KEYWORDS

dementia; mild cognitive impairment; early markers; survey response behaviors; epidemiology

Introduction

Dementia, a syndrome characterized by a progressive cognitive decline that interferes with independent functioning, affects a large and growing number of older adults. With increases in life expectancy in the population, the individual, family, and societal burdens associated with dementia are expected to accelerate rapidly, making the disease one of the major public health challenges of this century [1]. It is increasingly recognized that the identification of preclinical markers that are predictive of the future transition from healthy cognition to dementia is of paramount importance [2,3]. Such markers could allow earlier intervention and even modest delays in disease onset or progression, which would have a substantial impact on incidence rates and health care costs.

Despite existing efforts to discover biomarkers of cognitive decline and dementia [4,5], there is a need to develop and investigate nonbiological, behavioral markers that can be turned to when using biomarkers is impractical [6]. Accumulating research has shown that subtle alterations in daily functioning, for example, telephone or computer use, managing finances, and completing forms, are among the earliest and strongest signals that predict cognitive decline and dementia [4,5,7-9]. Reductions in the efficiency, speed, and consistency of performing these and other cognitively demanding activities can be observed up to a decade before diagnosis [3,7]. Accordingly, recommendations by the US National Institute on Aging and Alzheimer's Association highlight the need to identify and validate new neurobehavioral measures, including assessments of very early deficits in functional performance, that could detect preclinical manifestations of the disease [2,3].

We propose to develop indicators of functioning that can be gleaned from the way older people complete survey assessments, that is, questionnaires and computer-administered assessments. Surveys are ubiquitous in research and clinical practice, and many large-scale national and international longitudinal panel surveys on aging are presently in the field. A survey is a small slice of everyday functioning; nevertheless, completing a survey is a complex and cognitively demanding task that requires attention, working memory, executive functioning, and short- and long-term memory. Research on the psychology of survey methods confirms that answering survey questions requires considerable cognitive effort: respondents are expected to interpret the meaning of each question, retrieve relevant information from memory, integrate it into a summary judgment, and map their judgment onto the provided response alternatives [10]. As a result, examining older people's survey response behaviors, which focus on how respondents complete surveys irrespective of the content being sought by the questions, may represent a valuable but often neglected resource that can be leveraged to develop behavior-based early markers of cognitive decline and dementia that are cost-effective, unobtrusive, and scalable for use in large population samples.

The purpose of this paper is to describe the study protocol of the "Testing Early Markers of Cognitive Decline and Dementia Derived from Survey Response Behaviors" study. The study has the following 3 specific aims:

1. Aim 1 will develop questionnaire answer patterns and para-data indices of potential functional deficits based on survey response behaviors observed in a number of longitudinal aging studies.
2. Aim 2 will evaluate the validity and clinical utility of the indices and synthesize validity results across multiple longitudinal studies using meta-analytic principles.
3. Aim 3 will determine the optimal combination of survey response behavior indices for the prediction of subsequent mild cognitive impairment and dementia onset.

Methods

Overall Design

This study will develop early markers of cognitive decline and dementia from 2 types of indices summarizing different aspects of older adults' survey response behaviors. One category is comprised of indices that can be directly computed from the pattern of answers in questionnaires. These questionnaire answer pattern indices can be generated from participants' responses in a number of population-based longitudinal aging surveys, providing a repository of archival data that allows for predictions of current cognitive function from response behavior data collected many years ago. Examples of these questionnaire answer pattern indices are skipping questions, agreeing or disagreeing with statements regardless of content, errors due to nondifferentiation among questions or response options, or giving contradictory responses. The second category is comprised of so-called para-data indices, that is, auxiliary information unobtrusively collected alongside people's responses in surveys that are collected electronically (eg, on the web). Examples of such para-data indices are participant response times for survey questions, mouse movements, and keystrokes.

Ethics Approval

The study is approved by the University of Southern California Institutional Review Board (UP-22-00147) and the University of Surrey Research Integrity and Governance Office (FHMS 21-22 216 EGA).

Data Sources

Data for Creating Questionnaire Answer Pattern Indices

Existing longitudinal studies on aging are screened to identify data sets suitable for creating questionnaire answer pattern indices. Inclusion criteria are (1) a minimum of 3 waves of data collection (to estimate change over time) in which (2) participants complete a minimum of 40 multi-item rating scale questions at each assessment occasion (to achieve a sufficient

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body of questionnaire answers to construct the indices), (3) respondents are 50 years of age or older (studies that include younger participants are truncated or only later waves are used), and (4) availability of objective tests of cognitive functioning. The criteria for inclusion in these studies are intentionally broad to enable the construction and examination of questionnaire answer pattern indices under a wide range of conditions. Excluded are studies that are cross-sectional, focus on younger adults, or administer questionnaires on a single occasion.

Table 1 shows the 15 longitudinal studies that we have identified as of October 2022 as eligible data sources for creating questionnaire answer pattern indices. The combined sample size in these studies is >50,000, including over 300,000 assessment time points. Multiple self-report scales of varying content are administered at each measurement occasion in all studies, including personality, mental health, attitudes, beliefs and values, quality of life, and emotional experience, which are used for generating the questionnaire answer pattern indices. Each study provides multiple cognitive functioning measures at each assessment wave, including the Mini-Mental State Examination [11], the Telephone Interview for Cognitive Status [12], and formal clinical assessments of dementia status.

Table 1. Eligible longitudinal aging studies for creating questionnaire answer pattern indices.

Study	First wave[a]	Sampling interval (years)	Waves, n	Minimum age (years)	Approximate sample size, n	Survey items (note[b]), n	Dementia status ascertained
Health and Retirement Study	2006	2	>6	50	12,000	>100	T[c]
English Longitudinal Study of Ageing	2002	2	>8	50	8000	>100	M[d], T
Longitudinal Aging Study Amsterdam	1992	3	>7	55	3100	>100	M
Irish Longitudinal Study on Ageing	2010	2	>4	50	5000	>100	M, T
Memory and Aging Project	2004	1	>15	65	1700	60	C[e], M
Australian Longitudinal Study of Ageing	1992	3-4	>7	65	1100	80	M
Canberra Longitudinal Study	1990	4	4	70	1000	50	C, M
Sydney Memory and Aging Study	2005	2	>7	70	1000	80	C, M
Minority Aging Research Study	2005	1	>14	65	950	60	C, M
Einstein Aging Study	2004	1	>7	70	800	80	C, M
Swedish Adoption or Twin Study of Aging	1986	3	>7	50	600	>100	C, M
Octogenarian Twins Study	1991	2	5	79	300	80	C, M
Longbeach Longitudinal Study	1994	3	5	50	150	40	C
Mexican Health and Aging Study	2012	3	>3	50	15,000	40	T
Survey of Health, Aging, and Retirement in Europe	2004	2	>7	50	20,000	40	M, T

[a]Years indicate the first assessment wave to be used in the analyses.

[b]Minimum number of available individual questions from multi-item rating scales at each assessment occasion.

[c]T indicates that dementia status is ascertained by validated cutoffs from Telephone Interview for Cognitive Status [13,14].

[d]M indicates that dementia status is ascertained by Mini-Mental State Exam cutoffs [15,16].

[e]C indicates that dementia status is ascertained by formal clinical assessment.

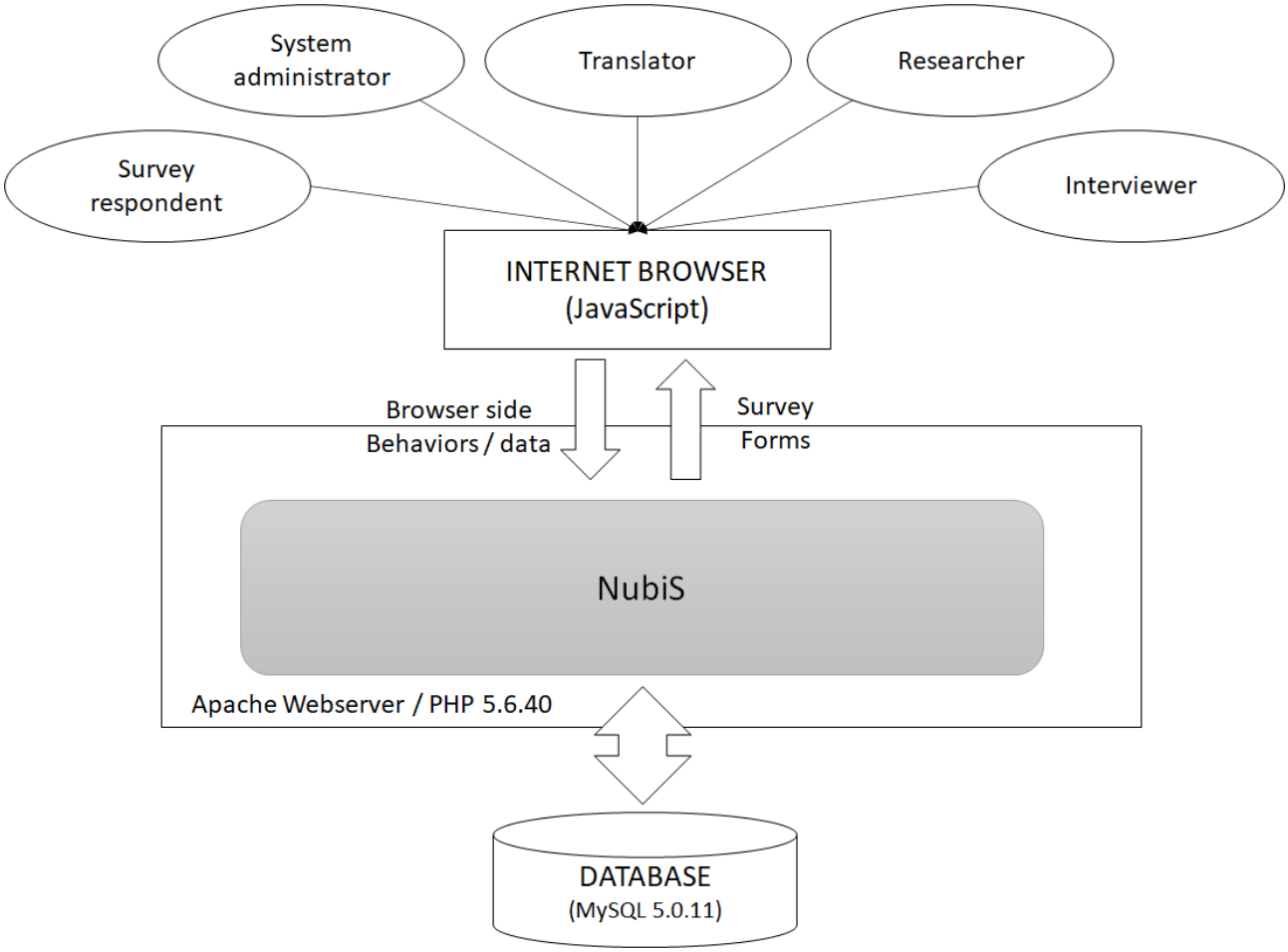
Data for Creating Para-Data Indices

To create para-data indices, para-data are identified from the backend server of the Understanding America Study (UAS). The UAS is a probability-based web-based panel launched in 2014 that comprises 10,000 panel members, of whom about 5000 are aged 50 years or older. Panel members are randomly selected through address-based sampling and are compensated based on the estimated time spent on each survey. Panel members without prior access to the internet are provided with a tablet computer and internet access. Since its launch, the UAS has conducted over 400 surveys of varying length. Details about the UAS can be found on the UAS website [17].

Surveys in the UAS are conducted and managed by using an internally developed web-based software called NubiS (Centre for Economic and Social Research, University of Southern California), whose development was co-led by author BO. Figure 1 illustrates the system architecture of NubiS. The software runs on an Apache Webserver 2.4.10 with PHP version 5.6.40 and provides a role-based web interface for user groups such as survey respondents and system administrators. NubiS has the capability to capture and store both survey responses and browser-side behaviors, including mouse clicks, keys pressed, errors, leave, return, or progress in surveys, and user platform information using JavaScript.

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Figure 1. The system architecture of NubiS.



There are seven types of raw para-data pertaining to the survey response process on NubiS: (1) "timing" records the time spent per screen, defined as the time from which the server outputs the survey screen to the browser to the moment that the respondent uses the back or next button; (2) "error" records errors detected on the browser side; (3) "key pressed" records keys pressed on the browser side; (4) "mouse click" records mouse clicks or touch events on the browser side; (5) "leave/return to survey" records the leaving or returning to the browser tab that contains the survey; (6) "survey invitation/response" records survey nonresponse and the times of survey invitation, uptake, and completion; and (7) "platform information" records the type of device, operating system, and browser type of the device used by the respondent.

Procedures for Creating Survey Response Behavior Indices

We periodically conduct literature searches in the areas of aging and cognition, psychometrics and survey methodology, computer use behaviors among older adults, and the psychology of survey response to identify publications describing questionnaire answer pattern indices and para-data indices that may be useful for research on cognitive decline and dementia. SAS macros are developed to compute the identified indices. For indices that require different analysis software, like R (R Foundation for Statistical Computing) or M*plus* (Muthén & Muthén), macros are developed to execute these external analysis steps in batch mode from within the SAS environment. The generated indices are matched to the survey waves or scales of each eligible aging study and stored for analysis. As of October 2022, we have identified a total of 20 questionnaire answer pattern indices (Table 2) and 20 paradata indices (Table 3). We will periodically refresh our literature search and update the list of response behavior indices.

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Table 2. List of questionnaire answer pattern indices.

Index	Description
Item nonresponse	
• Proportion of skipped items [18]	This index measures the proportion of skipped items in a multi-item survey, which has been suggested to be associated with cognitive functioning [18].
Response styles	
• Acquiescence ("yea-saying") • Disaquiescence ("nay-saying") • Extreme response tendency • Midpoint responses	These indices are based on detecting abnormal response styles to identify respondents with cognitive impairment. Emerging evidence has suggested that certain response styles, such as acquiescence and an extreme response tendency, may be predictive of cognitive impairment or associated with important risk factors for cognitive impairment like low education in older adults [19,20].
Expressions of uncertainty	
• Proportion of "don't know" answers • Response uncertainty parameter [21]	These indices capture the extent to which participants express uncertainty about their answers in the surveys.
Classical Test Theory indices of improbable responses	
• Multivariate outlier rate [22] • Person-total correlation [23] • Psychometric synonyms [24] • Psychometric antonyms [24]	These indices are based on detecting improbable or implausible responses to identify respondents with cognitive impairment. Cognitive impairment has been suggested to result in improbable answers [24].
Item Response Theory person-fit statistics	
• Polytomous l_z index [25] • Normed Guttman errors [26] • *U*3 index [27]	These indices are also designed to detect improbable or implausible response patterns, based on modern test theory approaches.
Random errors or noise in responses	
• Individual test reliability • Inter-item standard deviation [28]	These indices capture unreliable answer patterns to capture random variability in attention or fluctuating cognitive performance.
Response inertia	
• Residual autocorrelation across consecutive responses [29] • Long-string analysis [24]	These indices measure carry-over effects in people's response patterns, which may express an inability to adapt responses to changing question contents.
Response pattern drift within a survey	
• Improvement or worsening in missing, stylistic, outlying, misfitting, or random response patterns within a survey • Change-point analysis of weighted residuals [30]	These indices measure trends in response patterns over the course of a survey. Worsening response behaviors as a participant completes multiple questions in succession may indicate mental fatigue or lower sustained attention ability.

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Table 3. List of para-data indices.

Index	Description
Survey completion	
• Time lag from invitation to survey uptake • Time of day survey was taken • Missed survey • Time from uptake to complete the survey	This category of indices measures aspects of survey completion, such as whether a survey is incomplete and the time spent on completing a survey. Emerging evidence suggests that these indices may be predictive of cognitive impairment [31].
Response time	
• Median browser-side response time • Deviations from the median browser-side response time • Variability in response times across questions • Autocorrelation (inertia) of response times across questions • Item response theory person-fit statistics response time patterns • Pause rate (no response for >20 seconds) • Median pause duration	This category of indices measures aspects of response times such as the median response times, variability, and autocorrelations. A growing number of studies suggest that response times and their derived measures may be associated with cognitive impairment [32,33].
Errors and corrective behaviors	
• Proportion of corrected or changed answers • Rate of error messages received (eg, invalid entry) • Rate of “back” button use • Rate of “next” button use without a completed response	This category of indices measures aspects of errors and corrective behaviors in answering web-based surveys.
Mouse and touch efficiency	
• Number of mouse clicks per page (median) [34] • Variability of mouse clicks across screens [34] • Total pixel count (inefficiency in movement: “wandering around on screen”) [34]	This category of indices measures aspects of mouse clicks and inefficiencies in mouse movement behaviors.
Keystrokes	
• Median time between keystrokes (for text entries) [34] • Variability of time between keystrokes (within a text entry) [34]	This category of indices measures temporal rhythms of keystrokes from keyboard entries by respondents for survey questions.

Data Analysis Procedures

Validity and Clinical Utility of the Proposed Indices

We will conduct in-depth examinations of the properties of the generated questionnaire answer pattern and para-data indices for the purpose of evaluating their concurrent validity, sensitivity to change, and predictive validity in each study, as well as the replicability and robustness of their performance across different studies and survey contents. We first evaluate the cross-sectional correlations between the survey response behavior indices and cognitive functioning scores. We then evaluate each generated index for its sensitivity to change in 3 aspects, including the average rate of change with age (ie, whether an index reflects a decline in performance with age), differential change with age (ie, the extent to which some people change more rapidly than others with age), and correlated changes (ie, the extent to which changes in an index correlate with changes in a cognitive test score). In addition, we evaluate prospective relationships between the generated indices and subsequent changes in cognitive functioning measures. We examine the lagged effects between the indices and subsequent cognitive test scores across the measurement occasions in each study. We also test the ability of the survey response behavior indices at baseline (ie, the first measurement occasion) to predict the later onset of dementia in time-to-event (survival) analyses. To ensure robustness and replicability of the variables’ performances, we repeat the analyses across all eligible longitudinal aging studies. As for the paradata indices, we repeat the analyses for different surveys in the UAS.

Synthesis of Indices Across Studies

Methods of individual participant data meta-analysis are used to analyze and aggregate results across different studies. These methods have been considered state-of-the-art for study comparison and integration, and the research team has successfully implemented them in prior research projects [35,36]. Given that the different panel studies vary in data structure (eg, number and spacing of measurement occasions) and do not administer exactly the same instruments (eg, cognitive functioning tests), we do not harmonize the data across studies or combine them into a single large data set. Instead, analyses are first carried out separately for each data set (ie, for each study) using identical data-analytic models. The resulting effect sizes are then synthesized across data sets using meta-analytic techniques. This method preserves the heterogeneity of effect sizes across studies, and, because it synthesizes effect sizes without directly pooling data into a single data set, it can accommodate the integration of results from diverse studies. Thus, individual participant data meta-analysis enables us to generate a cumulative evidence-base

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of the performance and validity of the survey response behavior variables with great efficiency.

Selection of the Optimal Combination of Indices

We use feature selection methods to determine the optimal subset of survey response behavior indices that are most predictive of subsequent dementia onset when combined with each other. Feature selection is a machine learning technique that is particularly well-suited for determining those indices that jointly optimize a prediction equation for individuals while identifying and discarding those indices that are irrelevant or provide redundant predictive information. Among the multiple approaches considered, we use a regularized survival modeling method that uses a path-based algorithm for the Cox proportional hazards model, regularized by elastic net penalties, to rank and select the most predictive indices [37]. The model penalizes the regression coefficients of the survival model, effectively causing many coefficient estimates to shrink to zero. The predictive power of each index is then ranked based on shrinkage speed, with the slowest shrinking index having the strongest predictive power. Overall model accuracy is assessed with common measures of model performance such as sensitivity, specificity, and area under the receiver-operating curve.

Results

As mentioned in the previous section, we will have identified 15 longitudinal ageing studies as eligible data sources for creating questionnaire answer pattern indices by October 2022 (Table 1). We have identified a total of 20 questionnaire answer pattern indices (Table 2) and 20 paradata indices (Table 3). We have conducted a preliminary investigation to test the utility of the questionnaire answer pattern indices for the prediction of cognitive decline and dementia. The tested indices included the proportion of skipped items [18], the multivariate outlier rate [22], the normed Guttman errors [26], the inter-item standard deviation [28], and the person-total correlation [23] derived from the 2006/2008 waves in the Health and Retirement Study (N=12,554). Survival analyses (using the Fine and Gray competing-risk model [38]) were used for each index to examine whether it predicted dementia onset in the subsequent 8 years, while statistically controlling for age and education and while taking death into account as a competing event. Dementia status was ascertained using the criteria by Langa and Weir, which categorize respondents as cognitively normal, cognitively impaired (not dementia), or having dementia. The classification is based on cognitive test scores with cutoffs calibrated against in-person clinical assessments in the Aging, Demographics, and Memory Study [13]. It is not a clinical diagnosis but has proven useful for research purposes. As shown in Table 4, the hazard rates of dementia onset are between 1.52 and 2.25 times as high in respondents with questionnaire answer patterns that suggested cognitive problems (highest tertile) as for those in the lowest tertile (P<.001 for each index), and the middle tertile fell between the lowest and the highest. Details on the results of these analyses have been published elsewhere [39].

To assess the predictive power of the para-data indices, we derived participants' response times to survey items in 15 UAS surveys that were fielded from mid-2014 to 2015. We examined whether they were predictive of subsequent cognitive functioning measured in 2016 and of cognitive function change from 2016 to 2018. The response times to UAS survey items were log-transformed to reduce skewness. Cognitive functioning was evaluated by using the verbal analogies test, an executive functioning and analogical reasoning task with good specificity and sensitivity in discriminating normal controls from probable dementia patients. The analysis included 3829 UAS panelists 50 years and older and examined both zero-order associations and associations controlling for age and education. As shown in Figure 2, longer response times on 14 of the 15 surveys were significantly correlated at the 0.05 level with lower subsequent cognitive test scores in 2016 as well as with worsening cognitive functioning from 2016 to 2018. The significance and direction of these associations did not change after controlling for age and education.

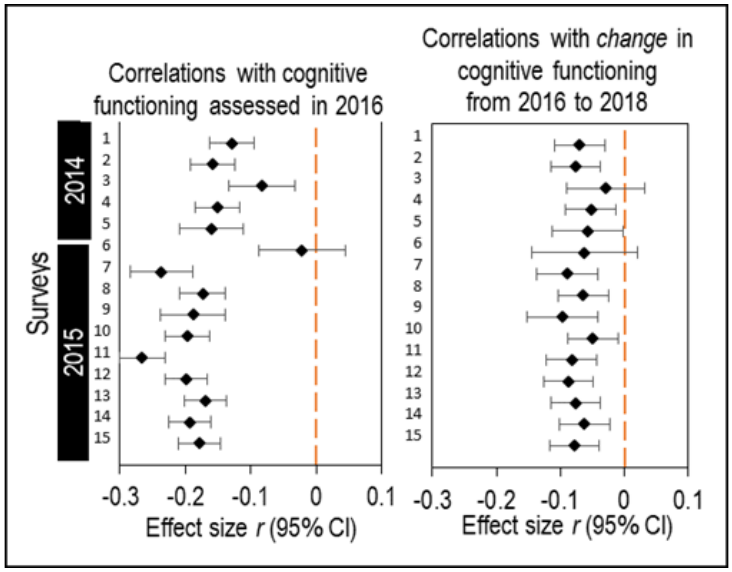
Notably, these early results are based on only a subset of questionnaire response patterns and para-data indices but are suggestive of the findings that we anticipate will emerge from the planned analyses of multiple behavioral indices derived from many diverse studies.

Table 4. Hazard ratios (95% CI) for associations between selected questionnaire answer pattern indices and subsequent dementia risk in the Health and Retirement Study (N=12,554).

Tertile for each variable	Proportion of skipped items	Multivariate outlier rate	Normed Guttman errors	Interitem SD	Person-total correlation
Low	Reference	Reference	Reference	Reference	Reference
Middle	1.34 (1.15-1.56)	1.38 (1.12-1.71)	1.43 (1.18-1.76)	1.28 (1.05-1.57)	1.40 (1.14-1.71)
High	1.52 (1.24-1.86)	2.25 (1.84-2.75)	2.09 (1.73-2.53)	1.93 (1.61-2.34)	2.03 (1.68-2.46)

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Figure 2. Relationships between survey response times and subsequent cognitive functioning in the Understanding America Study.



Discussion

This paper describes the protocol of a multiyear research project that aims to develop early markers of cognitive decline and dementia from survey response behaviors. The project plans to develop 2 types of indices, known as questionnaire answer pattern indices and paradata indices, summarizing different aspects of older adults' survey response behaviors. The project will examine the psychometric properties of the created indices and create predictive models of cognitive decline and dementia using the indices. Preliminary results are suggestive of the predictive power of survey response behavior indices for forecasting cognitive decline and dementia. To the best of our knowledge, this study is the first multiyear funded project aspiring to develop nonbiological early markers of cognitive decline and dementia from large-scale survey response behavior data at older ages.

If successful, the study may open novel opportunities for advancing research on health care for cognitive decline and dementia. Indices derived from survey response behaviors that could serve as preclinical markers of cognitive decline could greatly enhance the usefulness of questionnaires collected in large-scale surveys for epidemiological research on the risk and protective factors of dementia. Questionnaires are also routinely collected in medical care settings, and it is possible that survey response behavior indices extracted in these settings could potentially supplement information from standardized cognitive tests. In clinical trial research, the Food and Drug Administration recommendations for early-stage Alzheimer disease trials encourage the development of novel approaches for the evaluation of preclinical functional deficits [40], and response behavior indices extracted from questionnaires administered in clinical trials might potentially supplement core clinical measures that serve as trial endpoints. Furthermore, the survey response behavior indices may be useful as a proxy for cognitive impairment in aging survey research where standardized cognitive functioning measures are not assessed.

Survey response behaviors are a relatively inexpensive data source, but they are seldom used directly for epidemiological research on cognitive impairment at older ages. This innovative yet unconventional approach may complement existing approaches aimed at the early detection of cognitive decline and dementia.

Acknowledgments

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Data Availability

The Health and Retirement Study data supporting the findings in this paper are openly available in the study's website [41]. The Understanding America Study data supporting the findings in this paper are openly available in the study's website [17].

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review report for the project.
[PDF File (Adobe PDF File), 148 KB - resprot_v12i1e44627_app1.pdf]

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Abbreviations

UAS: Understanding America Study

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Protocol

An Online Acceptance and Mindfulness Intervention for Chronic Pain in Veterans: Development and Protocol for a Pilot Feasibility Randomized Controlled Trial

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Abstract

Background: In the veteran community, chronic pain is particularly prevalent and often debilitating. Until recently, veterans with chronic pain were offered primarily pharmacological intervention options, which rarely suffice and can also have negative health consequences. To better address chronic pain in veterans, the Veterans Health Administration has invested in novel, nonpharmacological behavior interventions that target both pain management and chronic pain–related functional issues. One approach, acceptance and commitment therapy (ACT) for chronic pain, is supported by decades of efficacy evidence for improving pain outcomes; however, ACT can be difficult to obtain owing to issues such as a lack of trained therapists or veterans having difficulty committing to the time and resources needed for the full clinician-led ACT protocol. Given the strong ACT evidence base combined with access limitations, we set out to develop and evaluate Veteran ACT for Chronic Pain (VACT-CP), an online program guided by an embodied conversational agent to improve pain management and functioning.

Objective: The aims of this study are to develop, iteratively refine, and then conduct a pilot feasibility randomized controlled trial (RCT) of a VACT-CP group (n=20) versus a waitlist and treatment-as-usual control group (n=20).

Methods: This research project includes 3 phases. In phase 1, our research team consulted with pain and virtual care experts, developed the preliminary VACT-CP online program, and conducted interviews with providers to obtain their feedback on the intervention. In phase 2, we incorporated feedback from phase 1 into the VACT-CP program and completed initial usability

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testing with veterans with chronic pain. In phase 3, we are conducting a small pilot feasibility RCT, with the primary outcome being assessment of usability of the VACT-CP system.

Results: This study is currently in phase 3; recruitment for the RCT began in April 2022 and is expected to continue through April 2023. Data collection is expected to be completed by October 2023, with full data analysis completed by late 2023.

Conclusions: The findings from this research project will provide information on the usability of the VACT-CP intervention, as well as secondary outcomes related to treatment satisfaction, pain outcomes (pain-related daily functioning and pain severity), ACT processes (pain acceptance, behavioral avoidance, and valued living), and mental and physical functioning.

Trial Registration: ClinicalTrials.gov NCT03655132; https://clinicaltrials.gov/ct2/show/NCT03655132

International Registered Report Identifier (IRRID): DERR1-10.2196/45887

(JMIR Res Protoc 2023;12:e45887) doi:10.2196/45887

KEYWORDS

chronic pain; randomized controlled trial; usability; acceptance and commitment therapy; embodied conversational agent

Introduction

Background

Among the most complicated medical conditions to manage, chronic pain refers to pain lasting longer than 3 to 6 months that persists beyond the healing of an initial injury or disease; in fact, it can often last for years or decades [1,2]. Chronic pain is a highly prevalent problem in the United States, with 50 million (20.4%) American adults experiencing daily chronic pain [3]. Military veterans aged ≥20 years are at a particularly high risk because they are 11.4% more likely to have chronic pain than nonveterans of the same age [4]. American veterans, with higher rates of chronic pain and more severe pain than nonveterans, are substantially affected in terms of general functioning and well-being [5-7]. In an effort to reduce chronic pain in this population, pharmacological treatments such as long-term opioid therapy were routinely prescribed and considered standard of care for chronic pain [8]. However, although patients with chronic pain report some relief from short-term use of opioids, there are concerns about long-term opiate use [9], which can lead to substance use and abuse, as well as death [10,11].

To adequately address chronic pain, it is imperative to look beyond pharmacological treatments and encourage the use of behavioral approaches that can enhance self-management of chronic pain. Over the past decade, the Veterans Health Administration (VHA) has strongly promoted a holistic approach to chronic pain treatment that promotes behavioral, therapeutic, and holistic interventions for pain management [12]. Research has shown that addressing factors promoting resilience and psychological well-being can be particularly helpful for individuals with chronic pain [13]. One promising therapeutic framework for pain that emphasizes behavior change and promotes resilience is acceptance and commitment therapy (ACT) for chronic pain, which focuses on mindfulness, value-based goal setting, and psychological flexibility [14]. More than 15 randomized controlled trials (RCTs) to date have shown greater efficacy of ACT for chronic pain than cognitive behavioral therapy, educational and support control groups, medical treatment as usual, or a waitlist control [15,16]. For veterans specifically, ACT for chronic pain has shown effectiveness in improving functioning [17], pain interference, pain-related anxiety, and depression [18].

ACT, similar to other behavioral approaches, requires considerable support from both the health care system (in terms of clinician training and appointment availability) and the patient (in terms of time and effort needed to complete the full treatment protocol). Even when veterans are interested in behavioral interventions for their chronic pain, they may not find it easily or locally accessible. Behavioral treatment for chronic pain requires considerable clinician time and training and, as a result, is less accessible to veterans who are not close to a large Veterans Affairs (VA) medical center. In fact, fewer than half of the veterans diagnosed with chronic pain receive mental health treatment [19], and half of VA facilities do not have any pain-focused behavioral therapy services [20].

To bridge this access gap, technology-assisted pain management interventions are increasingly appealing because remote treatment options can improve the VHA's ability to reach patients, are cost-effective, and can increase overall clinical impact [21,22]. Web-based behavioral interventions are relatively easy to implement across clinical settings after initial development, compared with in-person interventions, because they do not require training new practitioners to implement a treatment or monitor treatment fidelity [23,24]. In addition, online interventions have the potential to reach many veterans with chronic pain in their homes because 85% of veterans report having access to the internet in their homes [25].

Recent systematic reviews have concluded that technology-delivered ACT is both feasible and effective in managing chronic pain [26]. However, although technology-supported health care interventions are increasing in popularity and are often noninferior to in-person treatment, sustained engagement in these treatments continues to lag [21]. Research has suggested that existing online interventions can increase engagement by adding in more interactive, personalized, and user-tailored feedback [27]. For years, developers of online pain self-management systems have also reported that users become most engaged when the systems provide intelligent responses to the user's input information related to their pain experiences, concerns, goals, and target behaviors [28]. It should be noted that very few online interventions are able to provide this level of interaction between

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the user and the system, and even fewer evaluate the impact of personalized features on health outcomes [29] or sustained engagement [23,30]. Consequently, there is still room to improve online pain treatment by developing and testing a more user-centered, interactive, and engaging online pain management experience.

One way to increase engagement with online behavioral interventions is by using embodied conversational agents (ECAs), which are computer-animated characters that simulate interactive dialogue with patients [31]. An ECA can act as a responsive, humanistic, and nonjudgmental coach to guide patients through treatments such as health behavior change interventions, social skills training, and mindfulness-based stress reduction [32-35]. Interacting with ECAs that guide behavior interventions has been associated with positive outcomes such as higher use of stress management skills [33] and healthier eating behaviors in older adults [35]. Clinical trial participants—in particular, individuals with lower levels of health literacy [31]—have also expressed greater satisfaction with interventions that use ECAs than with educational content delivered by other means [33]. By using an ECA as a digital coach for delivering module-based ACT for chronic pain, we aim to provide a fully remote, accessible, and engaging option for at-home pain treatment for veterans with chronic pain.

Objectives

We are conducting a 3-phase project that will culminate in a pilot feasibility RCT of ECA-delivered ACT for chronic pain. The online program, Veteran ACT for Chronic Pain (VACT-CP), will use a weekly 7-module protocol to guide veterans with chronic pain to decrease behavioral avoidance and increase pain acceptance and valued living to improve their functioning. Using the principles of user-centered design, the aims of this research project are to (1) develop the VACT-CP system with feedback from mental health and other clinical professionals who treat chronic pain; (2) assess the usability of the VACT-CP system via iterative usability testing and development from veteran feedback; and (3) assess the usability of the complete VACT-CP website, as well as describe differences between the VACT-CP group and a waitlist plus treatment-as-usual (WL+TAU) control group on secondary outcomes related to treatment satisfaction, pain outcomes (pain-related daily functioning and pain severity), ACT processes (pain acceptance, behavioral avoidance, and valued living), and mental and physical functioning.

Methods

Phase 1: Consultation, Development, and Gathering Provider Feedback

Objective

The aim in phase 1 was to gather qualitative feedback on the VACT-CP system from 10 to 12 chronic pain clinical care providers, as well as identify barriers and facilitators for VACT-CP referrals and implementation in the VA Bedford Healthcare System.

Participant Recruitment

In phase 1, we conducted semistructured interviews with clinical care providers (n=10) at the VA Bedford Healthcare System, whose work is at least partially related to issues of chronic pain. Participants were recruited using flyers posted around the facility in areas that serve veterans with chronic pain as well as snowball recruitment methods. To ensure a representative mix of clinical care pain providers, we aimed to recruit 2 to 3 psychologists, 2 to 3 nurses, 2 to 3 physicians, and 2 to 3 psychiatrists. The inclusion criteria were as follows: (1) currently working at the VA Bedford Healthcare System or one of its affiliated community-based outpatient clinics in a clinical capacity and (2) currently seeing veterans to assist in their management of chronic pain. The exclusion criterion was any cognitive or physical impairment (eg, auditory or sight issues) that would interfere with aspects of study participation that require using a computer or giving verbal feedback.

Provider Feedback Session Procedure

Interested individuals were briefly screened by telephone for eligibility and scheduled for their hour-long session. After providing informed consent, eligible participants completed a quantitative survey and a qualitative interview. The quantitative survey included a brief (5-minute) questionnaire related to their work background and individual demographics. The qualitative interviews were audio recorded for formative assessment of the potential benefits, concerns, and institutional VHA dissemination issues for the VACT-CP intervention using a semistructured interview guide and a *think-aloud* strategy for intervention review.

Measures

The demographics questionnaire included basic, nonidentifying information, including participant age, ethnicity, race, and education. The work history survey included questions created specifically for this study related to working with patients who have chronic pain, including the provider's current position, past experiences as a health or mental health provider specific to working with patients with chronic pain, length of time in their current position, past specialized training on treating chronic pain, and information related to making any prior referrals to online or technology-mediated health interventions or resources. The qualitative interview included open-ended questions related to palatability of the intervention; feasibility of engagement with veterans with chronic pain; interest in, or potential concerns regarding, referring veterans to such a program; and reactions to a short walk-through of the intervention. Questions about palatability were based on the "organizational perspective" components of the Practical, Robust Implementation and Sustainability Model [36] (Multimedia Appendix 1).

Data Analysis Plan

After data collection, we used provider feedback to (1) understand the acceptability and potential usability of the platform in other settings (eg, at the veteran's home), (2) examine provider attitudes toward the VACT-CP system, (3) address any technological or system-specific concerns, and (4) modify potential plans for the future VACT-CP phase 2 usability

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assessment. Modifications to the interface and protocol were based on (1) acceptability and feasibility of the VACT-CP platform and potential treatment components and (2) qualitative feedback obtained from providers. Individual qualitative interviews will be analyzed at the end of the full study via the consensual qualitative research (CQR) approach. The initial codebook will be used by 2 to 3 coders throughout the data analysis process to foster multiple perspectives until consensus is reached among the coders about the meaning of the data. In addition, at least 1 auditor will check the work of the primary team of coders and serve to minimize potential bias.

We will report the frequency of emerging domains and themes. Themes will then be categorized according to the following CQR groupings: general (include all or all but one of the cases), typical (include more than half of the cases up to the cutoff for general), and variant (at least 2 cases up to the cutoff for typical). We will use these data to discuss broader scientific and implementation-related barriers and facilitators for interventions for patients with chronic pain within the VA system. Full data for this phase will be analyzed at the end of the completed study.

Phase 2: Veteran Usability Assessment

Objective

The objective in phase 2 was to conduct an iterative usability assessment by pilot-testing VACT-CP components, including the format, digital ECA guide (*Coach Anne*), and system via field-based iterative usability testing (3 waves; n=4-5 per testing wave, total goal: N=12-15).

Participant Recruitment

Veteran participants for phase 2 were recruited through a variety of methods, including through providers who shared information about the study with potential participants, posting flyers throughout the hospital, and sending mailers to veterans who received treatment for chronic pain within the past 6 months as identified via a medical chart review. The inclusion criteria were as follows: (1) veteran aged ≥18 years; (2) current diagnosis of noncancer chronic pain; (3) competent to provide written informed consent; and (4) has a working, high-speed wireless internet connection at home or is willing to access the website at the VA Bedford Healthcare System using a provided laptop computer in a secure space. The exclusion criterion was any cognitive or physical impairment (eg, auditory or sight issues) that would interfere with aspects of study participation that require using a computer or giving verbal feedback.

Usability Testing Procedure

We aimed to have 3 different usability testing waves, with at least 1 week between each wave to allow enough time to iteratively address any functionality issues or concerns with the user interface. The choice of 4 to 5 participants per wave was based on the finding that approximately 80% of usability problems can be detected using a sample of 4 to 5 participants [37]. Usability sessions were conducted remotely using a secure videoconferencing platform or in person at the Bedford VA medical center, if preferred by the participant. The goals of phase 2 were to (1) obtain further feedback on the VACT-CP treatment by gathering information from veterans via usability testing designed to assess interest in, satisfaction regarding, and usability of the online VACT-CP treatment; and (2) iteratively address any technological concerns. We first completed a telephone screen to assess whether veterans were eligible according to our inclusion and exclusion criteria. After the intake assessment, eligible participants were scheduled for a single 2-hour usability testing session. After providing verbal informed consent, participants completed a pre–usability testing survey battery. Subsequently, they were provided with a hyperlink and their precreated account information and asked to complete the first and second modules (combined) of the VACT-CP system, guided by Coach Anne. Participants were instructed to *think aloud* as they completed the module and provide their first reactions to the program. VACT-CP usability was evaluated along four dimensions: (1) usefulness: whether users can successfully complete designated tasks on the website, (2) effectiveness: whether users can accomplish tasks quickly and easily, (3) learnability: whether users meet predetermined site navigation goals within a specified period of time, and (4) satisfaction: how users feel about the website. Objective measures included usability scales related to content, perceived usefulness, visual appeal, and overall usability of the system. A qualitative interview was conducted after the think-aloud session to gather additional feedback, identify which aspects of the program were the most or least helpful, and review any suggested changes. Participants received a US $40 gift card for their 2-hour digital research session.

Measures

Demographics, Functional Health, and Pain Measures

Demographic measures included questions on pain type and duration, age, gender identity, race, ethnicity, and education level. Additional measures will include the Patient Health Questionnaire-9 [38] and Posttraumatic Stress Disorder Checklist [39], as well as pain interference (Brief Pain Inventory) [40] and the Veterans RAND 36-Item Health Survey (VR-36) [41]. These measures will be used to describe the demographic and health-related characteristics of the sample.

Media and Technology Use and Attitudes Scale

The Media and Technology Use and Attitudes Scale [42] is a 16-item measure of attitudes toward technology with a 10-point frequency scale, from 0=never to 10=all the time, that assesses comfort level, attitudes toward new technology, and use patterns for mobile technology. This scale is completed before the VACT-CP interaction session and will be used to describe the technology attitudes and perceptions of the sample.

System Usability Scale

The System Usability Scale (SUS) [43] is a 10-item measure that uses a 5-point Likert scale from 1=strongly disagree to 5=strongly agree to assess the usability of a technology. The SUS, a globally used scale, generates a subjective evaluation score to determine whether the technology system in its current form is sufficiently usable. An SUS score of >68 is regarded as above average usability, and an SUS score of >80 is regarded as high; when people rate a technology product with an SUS score of >80, they are likely to recommend it to friends [43].

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Intrinsic Motivation, Usability, and Perceived Usefulness Scales

The usability survey items are adapted from an existing set of usability questions to make the questions specific to the VACT-CP treatment and are informed by the Unified Theory of Acceptance of Technology [44,45] and the Wilson and Lankton [46] model, which combines the Technology Acceptance Model [47] and motivational model of technology acceptance [48]. The survey items assess the following factors: intrinsic motivation to use the VACT-CP system, perceived ease of use, perceived usefulness, and behavioral intention to use the system. Each item is assessed using a 5-point Likert scale, and participants are asked to indicate their level of agreement with each item on a scale from 1=strongly disagree to 5=strongly agree. Scale scores (agreement ratings averaged across items for each construct) are then calculated for each of the following constructs: intrinsic motivation, ease of use, perceived usefulness, and behavioral intention to use the VACT-CP system.

Qualitative Combined Usability and Contextual Interview

Participants were observed while working with the VACT-CP system, including being video recorded and asked questions by an interviewer. The interview guide (Multimedia Appendix 2) includes specific questions related to the different parts of the system (eg, the digital coach design, structure of the modules, and feedback system). In addition, interviewers query participants for feedback or information when participants seem to be confused or report difficulties with the system (eg, What are you trying to get to from this page? and What could be better about how this is set up?). All questions are open-ended and ask about multiple areas of usability and content, such as problems accessing and using the VACT-CP treatment, the perceived usefulness or importance of VACT-CP areas of treatment, and whether the participant would recommend this treatment to a fellow veteran.

Intervention Revision

Between each wave of testing, information specific to usability issues was gathered and analyzed to address any technological issues and revise content. Modifications to the website, module structure, and overall VACT-CP website framework were made between each wave based upon acceptability and feasibility of the online treatment and qualitative feedback obtained from patients.

Data Analysis Plan

Similar to phase 1, the video recordings and notes made during the qualitative portion of user testing will be transcribed and analyzed using Excel (Microsoft Corp). The quantitative data from the SUS and usability survey will be used to obtain scale scores that describe each veteran's general perceptions and opinions of the usability and content of the VACT-CP system. This feedback will then be reported in conjunction with qualitative usability and acceptability data, which will be analyzed using the modified CQR approach also planned for in phase 1. In phase 2, the themes generated by these qualitative data will be used to identify user system issues, general trends in use of the website, content issues, how well users can complete an assigned task on the VACT-CP system, and where they are encountering problems. Using this method, we will classify all general comments regarding usability as necessary to include in iterative development and site changes, whereas variant and typical usability concerns will be discussed within the research group to decide upon potential ways to incorporate this feedback into future intervention refinement. Full analysis of these data is ongoing, although initial general usability issues have been resolved, and suggestions for website refinement have already been integrated into the VACT-CP system.

Phase 3: Small Pilot Feasibility RCT

Objective

We will conduct a stage IB pilot feasibility RCT to assess the usability, feasibility, and acceptability of the VACT-CP system compared with a WL+TAU control group. This will include (1) evaluating the usability of the VACT-CP system; (2) assessing the relative feasibility and acceptability of the VACT-CP intervention procedure and WL+TAU control, including ease of recruitment, retention in each condition, treatment receptivity, attrition and retention in each condition, sustained VACT-CP website use, and the assessment process; and (3) describing changes in pain acceptance, valued living, mental and physical functioning, pain-related interference in daily functioning, and behavioral avoidance for each group. This trial has been registered on ClinicalTrials.gov (NCT03655132).

Participant Recruitment

We aim to recruit and complete baseline assessments for up to 60 participants over 15 months to allow for the required 40 participants to be screened as eligible and successfully randomized. Participants will be screened based on the inclusion and exclusion criteria. The inclusion criteria will include (1) veteran aged ≥18 years; (2) current diagnosis of noncancer chronic pain (as noted in the phase 2 inclusion criteria); (3) has a working, high-speed wireless internet connection at home or is willing to access the website over the 7-week intervention at the VA Bedford Healthcare System using a provided laptop computer in a secure space; and (4) competent to provide written informed consent. The exclusion criteria will include (1) any current or lifetime Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), psychotic disorder; (2) current or recent (within 1 month of study entry) DSM-5 alcohol or drug use disorder; (3) current use of any other chronic pain–related behavioral or psychological treatment; (4) any cognitive impairment that would interfere with study participation; (5) clinically significant suicidality within the past year; (6) presence of any clinical features requiring a higher level of care (inpatient or partial hospital treatment); and (7) any cognitive or physical impairment that would interfere with aspects of study participation that require using a computer and providing feedback. Participants with >1 pain diagnosis or comorbid mental health diagnoses other than those already listed will not be excluded.

RCT Procedures

Potential participants will be prescreened by telephone to determine whether study eligibility criteria are met. Individuals who remain eligible after the telephone prescreen will be

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scheduled for a baseline session during which staff will obtain informed consent and confirm clinical eligibility through the Structured Clinical Interview for DSM-5 to assess for potential psychosis, substance use disorders (SUDs), or clinically significant suicidality. Eligible participants will complete self-report measures via an online or mailed paper survey, and after completion of the survey, they will be randomized in a 1:1 ratio into 4 randomly permuted blocks (10 per block) to either the VACT-CP condition or the WL+TAU control condition. Veterans randomized to the VACT-CP condition will receive 7 online weekly modules to be accessed using a desktop or laptop computer within a secure space at the VA Bedford Healthcare System. Veterans in the WL+TAU control group will be provided with a list of common pain resources and encouraged to connect to their local VA pain clinic if interested in pain management care. All participants will complete the 4 surveys. At the conclusion of the study, participants in the WL+TAU condition will be provided with the VACT-CP website as an optional pain management resource, but they will not be asked to use it and will not be followed as research participants. Participants will be compensated US $60 for the baseline assessment (approximately 1 hour), US $40 at the midpoint (week 3; approximately 45 minutes), US $60 at the end of treatment (week 7; approximately 1 hour), and US $40 for the week 11 (1-month follow-up; approximately 40 minutes) for a total possible compensation of US $200.

VACT-CP Treatment Content and Structure

Table 1 shows the treatment components that will be emphasized in the VACT-CP program based on previous manualized ACT for chronic pain treatments and workbooks [15,49-52].

Table 1. Veteran Acceptance and Commitment Therapy for Chronic Pain (VACT-CP) timeline and intervention description.

Timeline	Module focus	Intervention components
Week 1	Introduction to the VACT-CP program	The introductory module assesses the nature of the veteran's pain, past treatments, and experience with acceptance and mindfulness. Coach Anne provides information on ACT[a] and assesses the veteran's values and goals to help them set a weekly goal.
Week 2	Behavioral change and triggers	This module focuses more broadly on pain psychoeducation and pain management. Veterans complete exercises on dealing with cognitive barriers with the goal of changing their own self-identified obstructions to living a meaningful life.
Week 3	Acceptance and mindfulness	This module uses metaphors and a veteran narrative story to explain and explore concepts of acceptance and mindfulness, and the veteran completes an acceptance exercise linked to previously identified values.
Week 4	Cognitive defusion	This module focuses on the ACT concept of cognitive defusion using psychoeducation about the nature of language and cognitive barriers to valued living. Metaphors, mindfulness, and ACT exercises are included.
Week 5	Willingness	This module explains the ACT concept of willingness and discusses willingness to experience discomfort as a means to pursuing important valued living goals. The veteran creates and applies a willingness hierarchy to identify a goal for the week that embodies values-driven willingness.
Week 6	Committed action	This module focuses on the ACT concept of committed action. Coach Anne helps the user to identify personal barriers to committed action and strategies for dealing with these perceived barriers.
Week 7	Valued living wrap-up	The final session provides an overview of ACT processes, a review of goals achieved, and reinforces progress made during the program. This session ends with planning for the "lifelong assignment" of fully engaging in one's life.
Additional modules	Mindfulness exercises module	This module introduces the topic of mindfulness and provides a series of questions to route users to use exercises that align with their goal for the mindfulness experience. This module is accessible any time after completing the first module.
Additional modules	Additional resources	This module provides additional information, links, and resources for care options within the VHA[b] for pain, psychiatric conditions, and physical health management.

[a]ACT: acceptance and commitment therapy.

[b]VHA: Veterans Health Administration.

The 7 online modules that participants will receive as weekly sessions feature Coach Anne as a digital treatment guide (Figure 1). The website is currently only accessible on desktop and laptop computers; it is not available as a mobile-enabled website for mobile phones. Seven modules were chosen, consistent with reviews of module-based online ACT that suggested that 7 to 8 modules are sufficient to allow users to experience all aspects of ACT [26]. All content is presented interactively through text-based 2-way conversations with Coach Anne. Veterans hear what Coach Anne *says* and can respond to her queries using forced-choice text options that will trigger different responses from Coach Anne as the conversation progresses, allowing the system to responsively interact in a personalized manner with the veteran (for an example of our video introduction, refer to Multimedia Appendix 3). The modules also use videos (eg, veteran narratives and metaphors), in-module assessments (eg, values assessments), and interactive exercises for goal setting. Each week, the user is reminded via an encrypted email to complete their next online module.

Once a module has been completed, the next week's module opens 5 days later to allow for more flexible completion of the 7 sessions. Thus, the shortest duration over which a user can complete the VACT-CP protocol is 35 days. The system

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prevents the user from completing the next week's module immediately because they must wait 5 days for the next module to open. This was incorporated to provide the user with several days to meet self-created goals, practice skills, and use other resources provided through the website as desired. Participants will be contacted via telephone at week 3 and week 5 to check in on any usability issues and potential concerns, as well as to assess for any possible risk related to mood, physical health, or suicidal ideation. Users can access the website for their entire participation time (11 weeks).

Figure 1. Screenshot of the Veteran Acceptance and Commitment Therapy for Chronic Pain website program.



Measures

Demographics, Functional Health, and Pain Measures

We will use many of the same surveys from phase 2 in our phase 3 data collection, including the Patient Health Questionnaire-9, Posttraumatic Stress Disorder Checklist, Brief Pain Inventory, VR-36, Intrinsic Motivation and Perceived Usefulness Scales [53], and SUS [54]. In addition, we will collect the information encapsulated in the following sections.

Feasibility and Acceptability Measures

Feasibility outcomes will include information on recruitment rates, retention rates within each condition, completion rates, how often each veteran accesses the website, and any reported problems with the website. This information will be collected through open-ended survey items, website data, and through use of a semistructured post–VACT-CP qualitative interview (Multimedia Appendix 4).

Pain-Related Daily Functioning

The Pain Outcomes Questionnaire-Short Form [55] is a 19-item inventory that assesses a patient's ability to engage in functional activities related to daily living that may be affected by pain interference. Each item is rated on an 11-point (0-10) Likert-type scale and yields an overall average score of all 20 items, resulting in a total score between 0 and 10. In addition, the scale contains a pain numeric rating scale item and 5 subscales measuring (1) activities of daily living, (2) negative affect, (3) mobility, (4) vitality, and (5) fear.

Pain Acceptance

The Chronic Pain Acceptance Questionnaire-Revised [56] is 20-item survey measuring recognition that pain does not prevent one from living a valued life. The questionnaire consists of two subscales: (1) activity engagement (11 items), or the degree to which one engages in life activities regardless of the pain; and (2) pain willingness (9 items), or an individual's willingness to experience pain. In addition, a total score is created by summing all items [57]. The scales have shown adequate reliability and validity and are substantially related to the other measures of patient functioning [58].

Valued Living

The Chronic Pain Values Inventory [59] is a 12-item self-report measure of the extent to which a patient is living in accordance with their values in areas such as work, health, and family, and which is related to lower perceived disability and pain-related anxiety, as well as greater reported patient functioning, even in the context of high levels of pain.

Behavioral Avoidance

The Multidimensional Experiential Avoidance Questionnaire (MEAQ) [60] is a 62-item self-report measure of experiential avoidance, including subscales on behavioral avoidance, distress aversion, procrastination, distraction and suppression, repression and denial, and distress endurance. The MEAQ has shown good internal consistency across all subscales, with Cronbach α averaging .83 across multiple samples [60,61].

Patient Satisfaction With Treatment

The Client Satisfaction Questionnaire-8 [62] is an 8-item scale that measures global treatment satisfaction based on perceived treatment quality and effectiveness of the intervention. This scale has been used at mental health and other health centers and has acceptable internal consistency (Cronbach α=.83-.93).

Planned Analyses

Sample Size Considerations

Consistent with the recommended stage model for development of behavioral therapies, the aim of this stage IB pilot feasibility RCT is to inform future treatment development and evaluation. Given that prior investigations of ACT have reported effect sizes in the large-to-medium range, we expect that the VACT-CP intervention will also produce at least a medium

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treatment effect. To have a power of 0.80 to detect differences at a 2-tailed α level of .05, a medium effect would require 125 participants. This was beyond the objective and scope of this preliminary stage IB pilot feasibility RCT. A total sample size of 40 (n=20, 50%, per group) is consistent with the recommendation by Rounsaville et al [63] of 15 to 30 participants per condition for stage IB behavioral treatment development. For phase 3, the total goal for enrollment and randomization is 40 participants (n=20, 50%, per group) for the 7-week VACT-CP intervention and WL+TAU control groups. Assuming an attrition rate of 30% after randomization based on past attrition rates for online behavior interventions [30], we plan to enroll up to 60 participants to meet our goal of 40 successfully randomized participants.

Primary Analyses

Usability of the VACT-CP system as assessed through the SUS is the primary outcome for the RCT. Scores for those in the VACT-CP group will be aggregated and described according to these metrics, with an SUS score of >68 interpreted as above average and a score of >80 as high and reflective of a system that participants are likely to recommend to others [64]. We will also describe changes on the Usability Survey Scales from before to after the intervention. Additional feasibility and usability data will be provided by the semistructured qualitative interviews and tracking of any telephone calls or emails to research staff with concerns. Similar to phases 1 and 2, phase 3 analysis of postintervention interview transcripts will use CQR techniques (eg, coding for and extracting major themes) to assess both barriers and facilitators for use of the VACT-CP system, as well as individual demographic user factors that affect use and perceived usefulness. Finally, we will assess intervention feasibility by measuring the proportion of individuals who successfully complete at least 5 (71%) VACT-CP modules of the total 7, which would be slightly above the mean percentage of completed sessions observed in previous online behavior interventions [30].

Secondary Analyses

Secondary exploratory analyses will describe satisfaction with the VACT-CP system and the potential impact of the intervention on treatment outcomes related to pain-related interference in daily functioning and severity (Pain Outcomes Questionnaire-Short Form), pain acceptance (Chronic Pain Acceptance Questionnaire-Revised), behavioral avoidance (MEAQ), valued living (Chronic Pain Values Inventory), and mental and physical functioning (VR-36 Mental Component Score and VR-36 Physical Component Score). On the basis of the intent-to-treat principle, all participants enrolled and successfully randomized will be included in these analyses, and the principal investigator will conduct preliminarily analyses and descriptively report on the pilot RCT outcomes of the VACT-CP intervention to inform further refinements to it. Descriptive measures (means and SDs) will be reported for all outcomes of interest. We anticipate that, for VACT-CP participants, we will observe increases in the mean scores for pain acceptance, valued living, and mental and physical functioning, as well as a decrease in pain-related interference in daily functioning and behavioral avoidance. In addition, we predict that there will be small-to-no changes in mean pain severity levels, given research suggesting that behavior interventions do not change pain levels for participants with chronic pain. Given imprecise estimations owing to the pilot's small sample size and a lack of power, we will not report estimates of effect sizes for these specific predictions. However, we will report descriptive outcomes (means and SDs) between before and after the intervention as well as between the groups and use nonparametric testing to report changes in secondary outcomes at the individual and group levels (pain acceptance, valued living, and mental and physical functioning, as well as pain-related interference in daily functioning and behavioral avoidance).

Ethics Approval

All 3 phases of this study were approved by the institutional review board of the VA Bedford Healthcare System Research & Development Committee in Bedford, Massachusetts, United States (1598754), with initial approval granted in September 2018.

Results

Participant recruitment for phase 3 began in April 2022 and is currently ongoing. We expect that recruitment will be complete by April 2023, data collection completed by October 2023, and primary data analyses completed by late 2023.

Discussion

Potential Applications

Online programs and at-home treatments for chronic pain are increasingly popular, but there is room to improve the breadth and efficacy of remote treatment options and to create a more engaging user experience. The intended outcome product, online VACT-CP, requires this multiphase project to successfully apply user-centered design best practices in developing our proposed intervention. Good usability and acceptability research should highlight the biggest needs for the proposed end product, but we cannot know all requirements before beginning the design processes. Consequently, by having multiple stages of feedback across multiple stakeholder groups, we will be able to develop and continually improve on the initial proposed VACT-CP system. Given the existing research base for our preliminary system, we believe that this online, ECA-delivered intervention may be a promising treatment option for chronic pain for the veteran population.

Limitations and Future Directions

This study includes limitations specifically related to its small sample size and, therefore, generalizability. However, our proposed sample size aligns with prior research on the number of participants needed to assess usability and feasibility. In addition, the format of the website requires a person to have access to a laptop or desktop computer because the current website is not mobile-device enabled. However, as a proof-of-concept design, successful findings from this study could be leveraged to further revise the site to allow for mobile options. In addition, excluding participants with an active SUD is a limitation. This comorbidity is common among veterans

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with chronic pain, and this online intervention could potentially assist in both their pain management and substance use owing to the transdiagnostic nature of ACT interventions. However, for this preliminary study, such an exclusion is warranted to ensure that participants are medically stable and not reporting clinical symptoms that would require a higher level of care. In the future, it would be useful to allow participants with an active SUD to participate if interested and as part of their SUD treatment. Finally, this study will include a majority of veterans living in 1 region of the country. Further testing could include multiple sites, including other VA medical centers that serve more rural populations that would potentially benefit from efficacious remotely delivered treatments for chronic pain.

Conclusions

This research project has the potential to create an easily disseminated and highly accessible pain treatment option, VACT-CP. In addition, the online intervention is potentially more engaging, accessible, and cost-effective than other existing versions of ACT for chronic pain. An interdisciplinary research team, comprising experts in ACT interventions, chronic pain, and technology-assisted health care assessment and delivery, will create and refine the VACT-CP system. Multiple stages of testing with veterans will further refine the intervention as well. Overall, it is expected that this 3-phase research project will lead to the development of a veteran-centered pain management website that helps users to better manage pain-related symptoms and focus on valued living domains. This study will provide preliminary feasibility data on whether the VACT-CP system is usable and acceptable. The final online program would allow all veterans with a home computer and internet access the option of an engaging, user-centered pain intervention. The VACT-CP system may also be particularly well received by, and of interest to, patients with chronic pain, given the lasting impact of COVID-19 on increased acceptance of, and interest in, remotely delivered interventions. After completion of this project, we will evaluate whether a future study is warranted in the form of a larger-scale VACT-CP efficacy trial to investigate whether the intervention improves pain-related functioning and quality of life.

Acknowledgments

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Data Availability

Owing to privacy and ethical considerations, the final data sets underlying publications resulting from this research will not be publicly shared outside of the Department of Veterans Affairs. On request and with principal investigator (EDR) permission, a deidentified, anonymized data set will be created and shared pursuant to a data use agreement, appropriately limiting the use of the data set and prohibiting the recipient from identifying or reidentifying (or taking steps to identify or reidentify) any individual whose data are included in the data set.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Phase 1: Veteran Acceptance and Commitment Therapy for Chronic Pain provider interview protocol.
[PDF File (Adobe PDF File), 192 KB - resprot_v12i1e45887_app1.pdf]

Multimedia Appendix 2
Phase 2: Usability and contextual interview protocol.
[PDF File (Adobe PDF File), 164 KB - resprot_v12i1e45887_app2.pdf]

Multimedia Appendix 3
Introductory tutorial video of the Veteran Acceptance and Commitment Therapy for Chronic Pain online program.
[MP4 File (MP4 Video), 27003 KB - resprot_v12i1e45887_app3.mp4]

Multimedia Appendix 4
Phase 3: Veteran Acceptance and Commitment Therapy for Chronic Pain postintervention feedback interview.
[PDF File (Adobe PDF File), 150 KB - resprot_v12i1e45887_app4.pdf]

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Multimedia Appendix 5
Summary statement by Career Development Program Panel II - Rehabilitation Research and Development Parent IRG - Office of Research & Development (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 149 KB - resprot_v12i1e45887_app5.pdf]

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Abbreviations

ACT: acceptance and commitment therapy
CQR: consensual qualitative research
DSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ECA: embodied conversational agent
MEAQ: Multidimensional Experiential Avoidance Questionnaire
RCT: randomized controlled trial
SUD: substance use disorder
SUS: System Usability Scale
VA: Veterans Affairs
VACT-CP: Veteran Acceptance and Commitment Therapy for Chronic Pain
VHA: Veterans Health Administration
VR-36: Veterans RAND 36-Item Health Survey
WL+TAU: waitlist plus treatment-as-usual

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Protocol

Focus Group Study of Medical Stakeholders to Inform the Development of Resilient Together for Dementia: Protocol for a Postdiagnosis Live Video Dyadic Resiliency Intervention

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Abstract

Background: Alzheimer disease and related dementias (ADRD) are increasingly common conditions that disrupt the lives of persons living with dementia and their spousal care partners. At the time of ADRD diagnoses, many couples experience challenges that produce emotional distress and relationship strain. At present, there are no interventions to address these challenges early after diagnoses to promote positive adjustment.

Objective: The study protocol described here is part of the first phase of a larger program of research that aims to develop, adapt, and establish the feasibility of Resilient Together for Dementia (RT-ADRD), a novel dyadic skills-based intervention to be delivered over live video early after diagnosis, with the goal of preventing chronic emotional distress. This study will elicit and systematically summarize perspectives of ADRD medical stakeholders to inform the procedures (eg, recruitment and screening methods, eligibility, timing of intervention, and intervention delivery) of the first iteration of RT-ADRD prior to pilot-testing.

Methods: We will recruit interdisciplinary medical stakeholders (eg, neurologists, social workers, neuropsychologists, care coordinators, and speech language pathologists) from academic medical center clinics in the departments treating persons living with dementia such as neurology, psychiatry, and geriatric medicine via flyers and word-of-mouth referrals from clinic directors and members of relevant organizations (eg, dementia care collaboratives and Alzheimer disease research centers). The participants will complete electronic screening and consent procedures. Consenting individuals will then participate in a 30- to 60-minute qualitative virtual focus group, held either via telephone or Zoom, using an interview guide designed to assess provider experiences with postdiagnosis clinical care and to gather feedback on the proposed RT-ADRD protocol. The participants will also have the

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opportunity to participate in an optional exit interview and web-based survey to gather additional feedback. Qualitative data will be analyzed using a hybrid inductive-deductive approach and the framework method for thematic synthesis. We will conduct approximately 6 focus groups with 4-6 individuals in each group (maximum N=30 individuals; until saturation is reached).

Results: Data collection began in November 2022 and will continue through June 2023. We anticipate that the study will be completed by late 2023.

Conclusions: The results from this study will inform the procedures of the first live video RT-ADRD dyadic resiliency intervention focused on the prevention of chronic emotional and relational distress in couples shortly after ADRD diagnoses. Our study will allow us to gather comprehensive information from stakeholders on ways to best deliver our early prevention–focused intervention and gain detailed feedback on study procedures prior to further testing.

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KEYWORDS

dementia; stakeholders; focus group; intervention; video; telehealth

Introduction

Background

Alzheimer disease and related dementias (ADRD) are a common cause of death and disability that have a substantial impact on individuals, families, health care systems, and society. By 2030, over 78 million individuals will be living with ADRD, leading to global health care costs of over US $2.8 trillion [1,2]. There are no available disease-modifying treatments or cures for ADRD [2,3]. ADRD symptoms (eg, forgetfulness, communication challenges, loss of recognition of places, time, and routines) are progressive in nature and continually undermine the independence of persons living with dementia [2]. In the months and years following diagnosis, these symptoms lead to heightened stress, clinically elevated emotional distress, burden, and relationship strain for persons living with dementia and their family care partners—many of whom are spouses or other forms of committed partners [4-7]. The timely diagnosis, care, and management of ADRD is critically important because these can each facilitate positive adjustment and preserve quality of life for couples [8,9].

Recent research advancements have enabled the earlier diagnosis of ADRD, creating the potential to meaningfully engage persons living with dementia in psychosocial interventions early after diagnosis during the "window of opportunity" before cognitive symptoms progress [9]. However, there are no established psychosocial interventions available at the time of diagnosis for persons living with dementia and their partners to support them in developing a shared understanding of the diagnosis, learning to collaboratively address early challenges, expressing personal needs, and collaboratively planning for the future [10,11]. Evidence suggests persons living with dementia and partners are interested in participating in interventions together (ie, "dyadic interventions"), early after diagnosis [10-14], and prior work has demonstrated that dyadic interventions are more effective avenues for promoting positive adjustment than those focused on individuals or care partners alone [15,16]. Dyadic interventions deployed during the later stages of ADRD have demonstrated feasibility and some positive effects on the dyads' relationships [17], including those delivered via telehealth approaches (eg, Zoom; Zoom Video Communications) [18-20].

Early dyadic interventions have the potential to promote positive adjustment to ADRD by improving the dyads' individual and interpersonal *resiliency* (ie, the ability to adjust effectively to significant adversity) [21] and can provide persons living with dementia and their partners with skills and support to actively contribute to care planning, preserve autonomy for persons living with dementia, and help both partners to express their needs and preferences [22,23]. The members of our team have developed dyadic programs with procedures that can be adapted to address the dyads' needs early after ADRD diagnoses. Specifically, the Recovering Together program is a brief dyadic resiliency intervention that demonstrates feasibility and preliminary efficacy at preventing chronic emotional distress in patients and informal care partners (ie, unpaid family members and friends) shortly after intensive care unit admission for acute neurological illnesses (eg, traumatic brain injury and stroke) [24,25]. The Recovering Together program was iteratively developed as part of a larger multidisciplinary partnership with patient–care partner dyads and medical stakeholders involved in patient care [26]. Prior research indicates that psychosocial interventions for ADRD are poorly integrated into medical treatment settings, have inconsistent methods of delivery, and are poorly aligned with participant and medical stakeholder preferences [14,27]. Therefore, there is a missed opportunity to integrate dyadic psychosocial interventions into the postdiagnosis support clinical infrastructure, and to design interventions that consider the perspectives of participants and medical stakeholders involved in patient care. Gathering feedback from individuals who will adopt, deliver, and use interventions is a necessary first step of developing early psychosocial interventions to improve adjustment to ADRD diagnoses for persons living with dementia and their care partners [28,29].

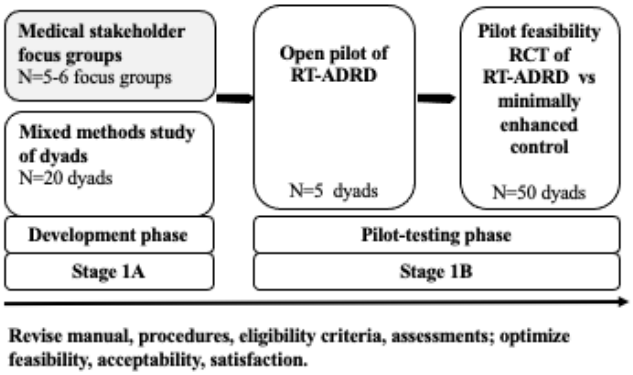
This Study

The purpose of this paper is to describe the protocol for our qualitative focus group study involving ADRD medical stakeholders that will inform the development of the procedures of the first version of a dyadic intervention. The study protocol described here is part of the first phase of a larger 5-year program of research (Figure 1) that aims to use the methodology, program content, and procedures of the Recovering Together program as a basis for developing a novel postdiagnosis dyadic

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resiliency intervention for ADRD called Resilient Together for Dementia (RT-ADRD). RT-ADRD will be developed using our team's theoretically and empirically derived framework for transdiagnostic dyadic interventions [30]. Our approach to intervention development will follow the National Institutes of Health stage model for intervention development [31], including the following: (1a) qualitative interviews with dyads and (1b) qualitative focus groups with ADRD medical stakeholders to understand population needs and develop the first iteration of the program; (2) an open pilot study to assess and refine RT-ADRD content and procedures; and (3) a feasibility pilot randomized controlled trial to further refine RT-ADRD content and test feasibility, acceptability, and preliminary efficacy of RT-ADRD relative to a minimally enhanced usual care condition (Figure 1). Through this study, we will gather detailed information from heterogeneous groups of medical stakeholders and develop procedures (eg, recruitment, screening, eligibility, timing of intervention, and intervention delivery) that are feasible, acceptable, and capable of meaningfully improving adjustment to ADRD for persons living with dementia and their partners.

Figure 1. Proposed iterative development of Resilient Together for Dementia (RT-ADRD). RCT: randomized controlled trial. RT-ADRD: Resilient Together for Dementia.



Methods

Ethics Approval

This study was approved by the Massachusetts General Independent Review Board (2022P001510).

Study Design

We will conduct a qualitative focus group study involving medical stakeholders (eg, neurologists, geriatricians, geriatric psychiatrists, social workers, neuropsychologists, care coordinators, and cohabiting speech language pathologists) involved in the care of persons living with dementia around the time of diagnosis (target N=up to 30 stakeholders in up to 6 focus groups). This study is designed to gather ADRD stakeholders' perspectives on the following: (1) postdiagnosis challenges and psychosocial support needs of persons living with dementia and their partners, (2) factors that may promote or inhibit couples' suitability and interest in a postdiagnosis dyadic intervention, and (3) proposed recruitment procedures and ways of optimizing recruitment support from ADRD stakeholders.

Inclusion and Exclusion Criteria

We plan to include up to N=30 adult participants (18+ years old) who are currently employed in 1 of 2 academic health care settings and provide outpatient care for individuals diagnosed with ADRD around the time of diagnoses. Recruitment began in November 2022 and will continue until June 2023. Eligible participants will be (1) fluent in English, (2) willing and able to participate in a live video interview or focus group, and (3) employed in a position relevant to ADRD care. Focus groups will be conducted separately for each of the 2 recruitment sites in order to understand potential differences by clinic setting. Our team will use purposive, convenience sampling from both sites and construct focus groups in an iterative manner based on ongoing data collection and rapid data analysis, consistent with prior studies [32].

Recruitment and Screening

We will recruit participants actively involved in ADRD clinical care from clinics within relevant departments (eg, neurology, psychiatry, and geriatric medicine) at 2 academic medical centers with comprehensive research and clinical programs dedicated to the treatment of ADRD (Massachusetts General Hospital in Boston, MA and Mount Sinai Hospital in New York, NY). We will recruit via flyers, presentations, and word-of-mouth referrals. Interested individuals will respond to a brief survey on a secure Research Electronic Data Capture platform and provide their name, contact information (email or phone number), current employment site, and current position. The survey will also contain an information sheet and form for eligible individuals to provide electronic consent to participate in the study. A research assistant will contact the individual to confirm eligibility and discuss scheduling for a focus group or individual interview. All recruitment, screening, and consent procedures will be performed remotely via telephone, electronic survey, email, and over a live video platform (ie, Zoom).

Data Collection

We will conduct a series of focus groups comprising medical stakeholders. Focus groups will include approximately 4-6 participants to encourage discussion while maximizing participant comfort, consistent with guidelines for virtual focus groups [33]. Stakeholders who are unable to attend the focus group sessions will be invited to participate in an individual interview. Focus groups and individual interviews will last

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approximately 30-60 minutes in total. Focus group participants will have the opportunity to participate in an optional exit interview immediately following the conclusion of the focus group to provide any additional information that they did not have time to share or did not feel comfortable sharing in the group setting.

Focus groups will be cofacilitated by a PhD-level clinical psychologist with expertise in qualitative research methods and a trained research assistant. The clinical psychologist will lead the focus group, and the research assistant will provide technical support and document observations using a rapid data analysis template developed by the research team. The rapid data analysis template will be used to inform formal coding and includes observations within key interview domains, poignant participant quotes, researcher reflexivity, and other notes or observations (Multimedia Appendix 1) The clinical psychologist will work to generate information on convergent and divergent perspectives regarding the dyads' experiences early after ADRD diagnoses and feedback surrounding the proposed intervention procedures and content. Exit interviews will be led by trained research assistants and volunteers using a live video conference breakout room tool.

Prior to the focus groups, participants will receive a document with potential discussion topics and guidelines for participating in the focus group with other individuals. The focus group discussion will follow an interview guide with open-ended prompts and questions surrounding domains including the following: (1) perceptions of clinical care early after ADRD diagnosis, (2) feedback on the proposed intervention procedures and content, and (3) ways of maximizing feasibility and acceptability outcomes (Multimedia Appendix 2). The clinical psychologist will follow general prompts with questions and probes to develop a more comprehensive understanding of the participants' perspectives.

Data Analyses

Audio data will be transcribed verbatim using a transcription service and deidentified. Deidentified transcripts will be uploaded into Dedoose software [34] for formal analysis. We will use a combination of deductive and inductive approaches to data analysis for our key research aims. Specifically, our *deductive* approaches will serve as the basis for our interview guide, rapid data analysis template, and coding framework (ie, codebook domains), which will be influenced by (1) prior research on the dyads' early psychosocial challenges and unmet needs following ADRD diagnoses and (2) the findings from on our prior studies focused on dyadic intervention development [35]. For example, we will include prompts in the interview guide that assess perspectives of the proposed delivery context (eg, current available psychosocial resources and ways of screening and referring dyads) on the rapid data analysis template and initial codebook domains.

Following the organization of the initial codebook domains, our approach to data analysis will involve rapid data analysis and be primarily *inductive* in nature. During data collection, our research assistant will document observations using the rapid data analysis template in a generative manner based on focus group discussion. These observations will be used to refine our initial codebook prior to formal data analysis and to assess when thematic saturation is reached [36]. Next, we will analyze the transcribed interviews in a collaborative and iterative fashion guided by the framework method [37]. Members of our research team involved in data analysis will begin with a line-by-line review of transcripts for 1-2 focus groups and openly code any relevant observations. These codes will be organized into categories within the a priori determined domains and refined through team discussion to create a revised codebook that will be used for formal coding in Dedoose. Two members of the research team will then code 25% (n=1-2 focus groups) of the transcripts using the initial codebook and will resolve discrepancies in discussions with the larger research team to refine the codebook. We will ensure a high agreement between the coders before they individually complete the remaining focus group transcriptions. We will then iteratively refine coded data into themes and subthemes within each domain through individual review and team discussions.

Results

This study is funded by the National Institute on Aging grant 1K23AG075188-01A1. Recruitment began in November 2022. Data collection is anticipated to begin in January 2023 and be completed by June 2023, and data analysis is anticipated to be completed by August 2023.

Discussion

ADRD are increasingly common conditions due to the aging population and have a considerable negative impact on persons living with dementia and their spousal care partners. At present, these dyads have little psychosocial support to address postdiagnosis challenges and positively adjust to ADRD and progressive symptoms at the time of diagnosis. Dyads are interested in participating in interventions together early after diagnosis [10-14], and prior research suggests that existing interventions [24,25] can be adapted to effectively and efficiently address the dyads' challenges to promote dyadic adjustment [15,16]. To effectively adapt such programs, it is necessary to first gather comprehensive feedback from individuals who will adopt, deliver, and use interventions [14,27]. This approach can help promote alignment with patient, caregiver, and medical stakeholder perspectives and is recognized as an important step toward optimizing clinical care for ADRD [28,29].

This paper describes a study design that is part of the first phase of a larger project focused on the development of a novel postdiagnosis dyadic resiliency intervention for couple dyads navigating ADRD. We provide details on the study aims and the recruitment, screening, data collection, and data analysis procedures. This information is valuable for future studies involving medical stakeholders treating ADRD shortly following diagnosis and for the development of intervention programs and procedures that are tailored to address the postdiagnosis experience of persons living with dementia and their care partners.

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The results of this trial will critically inform the development of the proposed RT-ADRD intervention and procedures. Our findings will also benefit the broader field, as we will gain perspectives to further understand common experiences and challenges before and after ADRD diagnoses. In addition, using direct feedback from a variety of stakeholders, we will be able to highlight commonly identified ways of integrating interventions within the existing clinical infrastructures, as well as areas of disagreement across stakeholder groups and clinic sites. Taken together with feedback obtained from dyads at the time of diagnosis gathered from a separate study, our findings will be used to refine our approach prior to pilot-testing, consistent with the National Institutes of Health Stage Model guidelines [31].

In summary, this study will be the first to gather comprehensive feedback from medical stakeholders on experiences, unmet needs, and perceptions of helpful intervention approaches and procedures for persons living with couple dyads early after ADRD diagnoses. Our findings will inform the design, procedures, and content of the novel Resilient Together for Dementia program, and we will gather feedback to inform subsequent clinical trials and implementation efforts. The results from this study will also have the potential to directly inform other efforts to increase the dyads' postdiagnosis support, with implications for other chronic and progressive neurological conditions.

Acknowledgments

We would like to thank the members of the Massachusetts General Hospital CHOIR lab members and the Massachusetts General Hospital "K club" led by Dr Ana-Maria Vranceanu for their feedback on proposed focus group procedures.

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Data Availability

Data collection and analysis instruments are available in the Multimedia Appendices. The data sets generated or analyzed during this study are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Rapid data analysis template.
[DOCX File , 25 KB - resprot_v12i1e45533_app1.docx]

Multimedia Appendix 2
Focus group guide.
[DOCX File , 26 KB - resprot_v12i1e45533_app2.docx]

Multimedia Appendix 3
Peer-review reports from the Career Development for Clinicians/Health Professionals Study Section - National Institute on Aging Initial Review Group - National Institute on Aging (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 140 KB - resprot_v12i1e45533_app3.pdf]

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Abbreviations

ADRD: Alzheimer disease and related dementias
RT-ADRD: Resilient Together for Alzheimer disease and related dementias

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Protocol

The Electronic Surviving Cancer Competently Intervention Program—a Psychosocial Digital Health Intervention for English- and Spanish-Speaking Parents of Children With Cancer: Protocol for Randomized Controlled Trial

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Abstract

Background: The psychosocial needs and risks of children with cancer and their families are well-documented including increased risk of parental distress, posttraumatic stress, and anxiety. There is a critical need to provide evidence-based psychosocial care to parents and caregivers of children with cancer. Digital health interventions are important to address many barriers to in-person intervention delivery but are not widely used in pediatric psychosocial cancer care. The COVID-19 pandemic has reinforced the need for flexible, acceptable, and accessible psychosocial digital health interventions. The Electronic Surviving Cancer Competently Intervention Program (eSCCIP) is an innovative digital health intervention for parents and caregivers of children with cancer, delivered through a combination of self-guided web-based content and supplemented by 3 telehealth follow-up sessions with a trained telehealth guide. A Spanish language adaptation of eSCCIP, El Programa Electronico de Intervencion para Superar Cancer Competentemente (eSCCIP-SP), has been developed. The self-guided web-based cores of eSCCIP/eSCCIP-SP are a mix of didactic video content, multifamily video discussion groups featuring parents of children with cancer, and hands-on web-based activities.

Objective: The objective of this study is to test eSCCIP/eSCCIP-SP in a multisite randomized controlled trial, compared to an internet-based education control condition consisting of information specifically focused on concerns relevant to parents and caregivers of children with cancer.

Methods: Using a randomized controlled clinical trial design, 350 eligible parents and caregivers of children with cancer will be randomly assigned to the intervention (eSCCIP/eSCCIP-SP) or an education control condition. Data will be collected at 3 time points: preintervention (prior to randomization), immediately post intervention (after 6 weeks), and at a 3-month follow-up (from baseline). Participants randomized to either condition will receive study material (eSCCIP/eSCCIP-SP intervention or education control website) in English or Spanish, based on the primary language spoken in the home and participant preference.

Results: The primary study end point is a reduction in acute distress from baseline to postintervention, with secondary end points focused on reductions in symptoms of posttraumatic stress and anxiety, and improvements in coping self-efficacy and cognitive coping. An additional exploratory aim will be focused on implementation strategies and potential costs and cost-savings of eSCCIP/eSCCIP-SP, laying the groundwork for future trials focused on dissemination and implementation, stepped-care models, and intervention refinement.

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Conclusions: This trial will provide necessary data to evaluate the efficacy of eSCCIP/eSCCIP-SP. This intervention has the potential to be an easily scalable and highly impactful psychosocial treatment option for parents and caregivers of children with cancer.

Trial Registration: ClinicalTrials.gov NCT05294302; https://clinicaltrials.gov/ct2/show/NCT05294302

International Registered Report Identifier (IRRID): PRR1-10.2196/46339

(JMIR Res Protoc 2023;12:e46339) doi:10.2196/46339

KEYWORDS

pediatric cancer; digital health; parents; caregivers; psychosocial intervention; family systems; cultural and linguistic adaptation

Introduction

Background

Parents and caregivers of children with cancer are at risk for negative psychosocial sequelae following their child's cancer diagnosis [1-3]; yet, few evidence-based options exist for improving psychosocial outcomes. This is particularly discouraging because the Standards for Psychosocial Care for Children with Cancer and Their Families specifically recommend that parents and caregivers of children with cancer have access to such interventions to decrease the risk of adverse psychosocial outcomes, including acute distress, posttraumatic stress symptoms (PTSSs), anxiety, depression, and decreased family functioning [1,4]. Parent, child, and family-level functioning are closely linked, and parent distress is linked to impaired family functioning and child maladjustment across the cancer trajectory [2,5-8]. Providing evidence-based psychosocial support to parents and caregivers of children with cancer is a clear, actionable strategy to prevent adverse outcomes and improve individual and family functioning following a pediatric cancer diagnosis [9,10].

Individuals identifying as Latinx represent the largest minority group in the United States and are also the fastest-growing segment of the population in the United States, representing 18% of the total population and contributing over half (52%) of the population's growth between 2010 and 2019 [11]. Parents and caregivers of children with cancer, who are of Latinx descent, are at especially high risk for negative psychosocial sequelae because they are overrepresented in the United States in terms of being affected by multiple, negative, systemic, and sociodemographic factors, including low socioeconomic status and limited English proficiency [12]. Socioeconomic status has been found to mediate survival outcomes in pediatric cancer, with worse outcomes for Latinx and racially diverse children [13-15]. Moreover, parents and caregivers of children with cancer of Latinx descent often report high levels of distress following their child's cancer diagnosis [12,13]. Although there is some evidence that culturally adapted interventions are effective in improving health and well-being outcomes for these populations [16-19], cultural and language adaptations of psychosocial evidence-based interventions for the Latinx population are scarce [1,12,20]. As the Latinx population in the United States continues to grow, there is an urgent need to provide evidence-based psychosocial care to this at-risk subset of parents and caregivers of children with cancer.

Access to technology and the internet is widespread in the United States and is often used to seek health care information and support [21,22]. Latinx and non-Latinx populations report internet use at comparably high levels, with recent data showing that 93% of White adults, 91% of Black adults, and 95% of Hispanic adults use the internet [23]. Trends in internet usage over time have demonstrated that the "digital divide" in the United States is shrinking across race and ethnicity, so the need for psychosocial interventions that adapt to this new reality is critical.

Intervention Development and Adaptation

Several studies have laid the groundwork for the proposed randomized controlled trial (RCT). The Electronic Surviving Cancer Competently Intervention Program (eSCCIP) was developed as a brief, psychosocial digital health intervention for parents and caregivers of children with cancer to reduce negative psychosocial sequelae following pediatric cancer diagnosis and improve family functioning [24]. The theory and content of eSCCIP were adapted from 2 prior in-person interventions for parents and caregivers of children with cancer: the Surviving Cancer Competently Intervention Program [25] and the Surviving Cancer Competently Intervention Program—Newly Diagnosed [26]. To provide parents and caregivers of children with cancer with the accessibility and flexibility of a digital health intervention, eSCCIP was initially developed in 2015 using best practice methodology from the digital health literature. In addition to its foundation in both cognitive behavioral and family systems principles, eSCCIP is guided by the Ritterband Behavior Change model for internet interventions, which explains change as occurring through a pattern of unique, nonlinear interactions in 9 steps, including the users, the environment, and the web-based tool [27]. eSCCIP is further guided by the Pediatric Preventative Health Model [28,29], a social ecological model conceptualizing how families should receive psychosocial support based on individual needs, strengths, and risk factors. Following the conceptualization and initial development of eSCCIP, the intervention was refined using think aloud usability testing, collaboration with community stakeholders, and small-scale beta testing [24]. Recent preliminary studies evaluating the eSCCIP intervention have demonstrated high acceptability and feasibility, as well as preliminary evidence of efficacy [30]. Additional revisions and iterations have been made to eSCCIP to modernize and scale up for a larger RCT. To fill a critical need in the field, a Spanish-language adaptation of eSCCIP, El Programa Electronico de intervencion para Superar Cancer Competentemente (eSCCIP-SP) [31], was also developed using

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best practices for cultural and linguistic intervention development [32]. Refer to Figure 1 for a visual overview of the eSCCIP/eSCCIP-SP work to date.

Figure 1. Overview of eSCCIP/eSCCIP-SP development. eSCCIP: Electronic Surviving Cancer Competently Intervention Program; eSCCIP-SP: El Programa Electronico de Intervencion para Superar Cancer Competentemente.



Study Objectives

The purpose of this study is to test eSCCIP/eSCCIP-SP in a multisite RCT to build off existent pilot work and establish a strong base for the efficacy of the intervention. With the exception of the present intervention and a web-based adaptation of the Bright IDEAS Maternal Problem-Solving Skills Training Intervention [16,33,34], we are not aware of any additional psychosocial digital health interventions for parents and caregivers of children with cancer, so establishing a strong evidence base for this intervention is both timely and imperative in addressing the psychosocial needs in this population. The specific aims of this study are as follows:

1. Specific aim 1 evaluates the efficacy of eSCCIP/eSCCIP-SP in a multisite RCT comparing eSCCIP/eSCCIP-SP with an education control website in "real-world" clinical settings. The primary hypothesis is that eSCCIP/eSCCIP-SP will be more efficacious than an education control in decreasing acute distress post intervention. A secondary hypothesis is that eSCCIP/eSCCIP-SP will be more efficacious than an education control in decreasing PTSS and anxiety and improving coping self-efficacy and use of positive cognitive coping strategies post intervention.
2. Specific aim 2 describes the patterns of user engagement and identifies clinical and psychosocial factors associated with eSCCIP/eSCCIP-SP treatment gains. A component of this aim is to identify clinical, demographic, and psychosocial protective factors and risks predictive of maximum eSCCIP/eSCCIP-SP participation benefit. Potential differences in outcomes for English-speaking and Spanish-speaking parents and caregivers of children with cancer will also be explored.
3. Specific aim 3 explores preliminary eSCCIP/eSCCIP-SP implementation strategies and costs and cost savings. We will conduct qualitative interviews with oncology health care providers (psychosocial and medical/nursing staff) and intervention participants using the Consolidated Framework for Implementation Research (CFIR) paradigm to identify barriers and facilitators of eSCCIP/eSCCIP-SP uptake and completion. We will also estimate the costs and potential cost savings of delivering eSCCIP/eSCCIP-SP.

Methods

Ethics Approval

The MD Anderson Cancer Center Office of Human Subjects Protection serves as the central institutional review board for this study. Study procedures have been approved (protocol # 2021-0988).

Study Design

This study is a multisite RCT that will enroll participants at 3 geographically diverse pediatric hospitals, which are subsequently anonymized as sites A, B, and C. Participants will be randomized to one of two treatment conditions: (1) eSCCIP/eSCCIP-SP (depending on primary language or preference) or (2) education control.

Randomization

Randomization will be conducted at the family level according to a 1:1 ratio between groups, in permuted blocks of 6, stratified by site and language preference. The study data analyst at site A will use an Excel (Microsoft Corp) spreadsheet with a randomization scheme created by the study biostatistician to randomize families. This spreadsheet will be inaccessible to any members of the study team aside from the data analyst. It is not possible for study telehealth guides to be blinded to the intervention condition because of the in-person contact required for eSCCIP/eSCCIP-SP; however, study investigators and research coordinators (RCs) not involved in intervention delivery will not have access to random assignment information. After randomization, participants will be instructed on the procedures within their assigned group. All outcome measures will be completed directly on the web by study participants, further reducing the risk of bias.

Participants

Participants will be parents or caregivers of a child with cancer who speak English or Spanish between ages 0 and 18 years.

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Parents and caregivers of children with cancer must have access to the internet (including access exclusively via cellular data or access via a borrowed institutional device). The only disease-based exclusion criteria are known poor or uncertain prognosis at the time of approach (child not expected to live longer than 6 months). In families with 2 caregivers, both will be eligible to participate in the study, including receiving the intervention and completing study measures; however, 1 caregiver will be asked to identify as the primary participating caregiver at study enrollment.

Sample Size

Based on the power analyses discussed below, 350 parents and caregivers of children with cancer will be recruited to account for a conservative 25% attrition rate. Of note, although multiple caregivers from each family are eligible to participate, the target sample size of 350 parents and caregivers of children with cancer refers specifically to 350 primary participating caregivers from unique families. Data from nonprimary participating parents will be used only for exploratory analyses. Based on the results from pilot studies, we expect approximately 20% of the 350 families recruited to include a second participating parents and caregivers of children with cancer. Recruitment, retention, and engagement strategies have been an explicit focus of previous eSCCIP research, and strategies generated from this research and the literature inform the recruitment plan [35,36]. Recruitment targets are feasible based on the number of children with cancer treated annually at sites A, B, and C (1000 per year across sites), as well as the number of English-speaking and Spanish-speaking parents and caregivers of children with cancer at each site. We expect 40%-50% of the sample to be Spanish-speaking parents and caregivers of children with cancer. Previous eSCCIP studies have had high recruitment rates (64%-70%) [24,36] as well as retention rates of over 70% in eSCCIP pilot work. Estimating 25% study attrition is an appropriately conservative approach; however, recruitment targets will be evaluated frequently and adjusted accordingly if attrition is higher than expected, given previous work.

To specifically address aim 3, parents and caregivers of children with cancer will be identified from each study site using purposive sampling across demographic groups. We will initially target 10 participants from each site (n=30), comprising 6 parents and caregivers of children with cancer (3 English-speaking and 3 Spanish-speaking), 2 psychosocial providers, and 2 oncology providers, but final recruitment will be dependent upon data saturation. We will complete interviews until no new ideas are shared, consistent with best practices for reaching saturation in qualitative research [37].

Study Conditions and Delivery

eSCCIP Intervention

The content of eSCCIP/eSCCIP-SP has 4 web-based, self-directed cores designed for parents and caregivers of children with cancer to complete over 1 month during their child's active cancer treatment (including maintenance therapies) or shortly after completion of treatment. Each core is a unique mix of original video content and web-based activities and is complemented by a brief telehealth follow-up with an eSCCIP-trained clinical interventionist (ie, guide). Cores 1-3 include novel content derived directly from evidence-based cognitive behavioral concepts and family system principles modeled from components of the in-person predecessor of eSCCIP; core 4 is designed as a wrap-up core to summarize intervention content. All cores incorporate family systems theory to maintain an interpersonal focus and normalize the family's experiences. All intervention materials exist in English and Spanish, and telehealth sessions are delivered in English or Spanish, depending on enrollment in eSCCIP or eSCCIP-SP.

Video content falls into two distinct categories: (1) the multifamily video discussion groups, which were initially created for the Surviving Cancer Competently Intervention Program—Newly Diagnosed protocol, consist of recorded and edited conversations between a group of 17 parents and caregivers of children with cancer that serve as a powerful family systems proxy of participants' interaction with other parents and (2) skill-building videos, where foundational cognitive behavioral intervention skills, such as cognitive reframing, are introduced. The multifamily video discussion groups capture themes common among parents and caregivers of children with cancer (eg, anger, guilt, and emotional exhaustion), examples of coping (eg, putting things in perspective), and the impact on the family over time (eg, siblings, grandparents, and thinking about the future). The skill-building videos feature interviews with parents and providers, as well as graphics and narration illustrating foundational intervention skills. Web-based activities provide opportunities for caregivers to practice the skills they have learned.

All web-based activities are securely captured by the program, allowing the guide to view data entered by participants (eg, free text responses) and integrate participant responses into telehealth follow-up sessions. The telehealth follow-ups after cores 1-3 are the only component of eSCCIP that is scheduled with a trained guide. The telehealth follow-up sessions follow a flexible manualized format to ensure standardization across guides and appropriate delivery of key intervention principles.

Education Control

Parents and caregivers of children with cancer randomized to the patient education control condition will be given a unique log-in to access a website with information about psychosocial functioning, coping, and PTSS related to pediatric cancer. This website will be available in both English and Spanish and will consist of information modified from CopingSpace [38], an evidence-informed website developed by Ryan's Case for Smiles, a national organization dedicated to supporting families impacted by pediatric cancer and other chronic diseases. Topics include age-appropriate explanations and coping strategies for children, the siblings' unique experience and needs, warning signs a child is not coping well, techniques to reduce your stress and anxiety, and practical tips for managing meals and family needs. Unlike eSCCIP/eSCCIP-SP, the education control website will not include instruction in the cognitive behavioral skills taught in eSCCIP/eSCCIP-SP nor will it include access to the videos or telehealth follow-up sessions in eSCCIP/eSCCIP-SP. The high-quality information provided to

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parents and caregivers of children with cancer makes this a valuable and meaningful comparator condition.

Study Platform

The eSCCIP/eSCCIP-SP and education control programs have been built in the most recent version of the Research Infrastructure Containing e-interventions system developed and maintained by the University of Virginia Center for Behavioral Health and Technology. This platform provides the tools to both deliver robust digital health interventions as well as to manage participants in research trials. The system is designed to support projects that contain protected health information and are subsequently subject to compliance with federal and state regulations regarding data of this type. eSCCIP/eSCCIP-SP has been designed to be delivered as a fully automated program, but also it has the functionality to incorporate human support components (eg, facilitate communication between participant and guide). It includes 4 cores and 3 telehealth visits, with the cores automatically made available to the participant over time. After completion of the first core, the first telehealth visit is scheduled for a time in the upcoming week. The second and third cores are available 1 week after the completion of the previous core and include a subsequent telehealth visit. The fourth and final core concludes the intervention with a review of the program. Participants access the intervention through a secured portal, and all data are captured and maintained consistent with Health Insurance Portability and Accountability Act's guidelines.

Study Procedure

Potential participants will be screened for eligibility using a brief, web-based screening questionnaire that is accessible by direct contact with a member of the study team or through the study interest website. Once screened, an RC will confirm eligibility and instruct participants about the consent process. Web-based consent procedures will be conducted via DocuSign or a similar secure software. Once web-based consent is complete, participants will receive a unique username and password to log onto their randomized condition (eSCCIP/eSCCIP-SP or education control). Study questionnaires will be completed through this web platform. As there are no required components of the education control, automated or RC-directed text and email reminders to use the program will not be required for individuals randomized to the education control.

After completion of the initial web-based assessment battery, participants in the intervention condition will schedule their initial telehealth session using an automated scheduling tool available through the platform hosting eSCCIP/eSCCIP-SP. Participants will be notified that the overview core and core 1 need to be completed prior to the telehealth session. Automated reminders will be sent at regular intervals to encourage participation in study cores. Manual follow-up by RCs will also be initiated in cores that are not completed. Cores will automatically unlock at 1-week intervals, and telehealth sessions will be scheduled directly with the participant. A total intervention completion window of 4-6 weeks will be anticipated by the study team for each participant, building in some additional time for start-up and potential scheduling delays. A similar process has been successfully implemented in eSCCIP pilot studies [24,30]. Because eSCCIP/eSCCIP-SP cores and the education control website are delivered digitally, all parents and caregivers of children with cancer will have convenient access to their respective condition's content anywhere the internet is available.

Treatment Fidelity

The administrative interface of the intervention platform collects several metrics that will be used to record the intervention and monitor participation, including generating a comprehensive activity record of core use (ie, a record of completion of each activity and a record of all free-response answers). Fidelity checklists and session outlines have also been developed for the telehealth follow-up sessions. The designated Fidelity Consultant, a pediatric psychologist with extensive experience delivering psychosocial intervention to families, will watch and code 15% of all telehealth sessions for each guide using the fidelity checklists as a measure of treatment fidelity to strengthen study rigor.

Study Outcomes

Data will be collected at 3 time points: prior to beginning the intervention (T1), postintervention (after 6 weeks; T2), and at 3-month follow-up (3 months after baseline; T3). Outcome measures include the Psychosocial Assessment Tool (PAT) [39,40], the Multidimensional Scale of Perceived Social Support [41], the Kessler Psychological Distress Scale (K-6) [42,43], the COVID-19 Exposure and Family Impact Scale [44], the Coping Self-Efficacy Scale [45], the Cognitive Emotion Regulation Questionnaire [46], Distress Thermometer [47], the Patient-Reported Outcomes Measurement Information System Short Form (PROMIS Short Form v1.0—Anxiety-8a) [48], the posttraumatic stress disorder checklist [49], as data on previous psychosocial service usage. Individuals randomly assigned to the intervention condition will also complete a questionnaire at T3 measuring satisfaction and acceptability with the intervention, which has been used in all prior eSCCIP studies. Measure description and schedule for data acquisition are provided in Table 1.

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Table 1. Outcome measures and assessment timing schedule.

Domain or measure	Description	T1[a]	T2[b]	T3[c]
Chart review	Review of patient medical record			
Demographic variables of parents and caregivers of children with cancer	Demographic variables of enrolled parents and caregivers of children with cancer	✓		
Previous psychosocial service usage	Questionnaire to measure contact and work with social work, psychology, psychiatry, pastoral care, community, and hospital-based services for all members of the family	✓	✓	✓
PAT[d]	Brief parent report screener of psychosocial risk [39,40]	✓		
MSPSS[e]	Questionnaire to measure perceived social support from family, friends, and significant other [41]	✓	✓	✓
K-6[f]	Questionnaire to measure acute distress [42,43]	✓	✓	✓
CEFIS[g]	Questionnaire to measure the extent to which a family has experienced or been "exposed" to COVID-19–related potentially traumatic events (eg, economic changes, illness in family) and the impact of these events on the family's functioning and well-being [44]	✓	✓	✓
CSES[h]	Questionnaire to measure the perceived ability to cope effectively with challenging situations across 3 domains (use problem-focused coping, stop unpleasant emotions and thoughts, and get support from friends and family) [45]	✓	✓	✓
CERQ[i]	Questionnaire to identify cognitive coping strategies used after a negative event or situation. Measures of 9 different cognitive coping strategies [46]	✓	✓	✓
Distress thermometer	Single-item indicator of psychosocial distress that is widely used in the oncology literature [47]	✓	✓	✓
PROMIS[j] Short Form v1.0—Anxiety-8a	Questionnaire measuring symptoms of anxiety [48]	✓	✓	✓
PCL-5[k]	Questionnaire to assess for symptoms of posttraumatic stress disorder in the civilian population [49]	✓	✓	✓
eSCCIP[l] Evaluation Questionnaire	Questionnaire to measure intervention acceptability		✓	✓

[a]T1: preintervention (baseline).

[b]T2: postintervention (after 6 weeks).

[c]T3: follow-up (3 months after baseline).

[d]PAT: Psychosocial Assessment Tool.

[e]MSPSS: Multidimensional Scale of Perceived Social Support.

[f]K-6: Kessler Psychological Distress Scale.

[g]CEFIS: COVID-19 Exposure and Family Impact Scale.

[h]CSES: Coping Self-Efficacy Scale.

[i]CERQ: Cognitive Emotion Regulation Questionnaire.

[j]PROMIS: Patient-Reported Outcomes Measurement Information System.

[k]PCL-5: posttraumatic stress disorder checklist.

[l]eSCCIP: Electronic Surviving Cancer Competently Intervention Program.

Power Analyses and Sample Size Consideration

The primary end point of the study is to compare posttest differences in distress post intervention between intervention and education control groups. In a recent pilot study of 14 participants, we detected a mean change of 1.71 (SD 2.09) in distress on the distress thermometer at 1 month in the English version of the questionnaires. In standardized form, the effect size is 0.82. We do not have an estimate of the impact of the education control group on our primary end point; however, we expect no more than a modest to medium effect (0.2 to 0.5). Therefore, we are planning a sample size to detect a difference in effects between the groups of at least 0.3. Power analyses based on the analysis of covariance (ANCOVA) model and assuming a correlation of at least 0.5 between pretest and posttest scores suggest that a sample size of 350 individual parents and caregivers of children with cancer (175 in each group) can detect a difference of ≥0.3 in standardized mean distress reduction between intervention and education group conditions with a power of at least 80% at the level of significance of .05 and assuming an attrition rate of 25%. Therefore, a sample size of 350 is planned for this study.

Data Quality

Data quality will be monitored throughout intervention implementation and data collection. The research team will routinely generate data quality reports (via built-in functionality) and meet biweekly to review the reports, discuss any identified

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issues (eg, missing data), and outline remedial actions. For the education control website, data from CopingSpace.org will be migrated to the same server that will host eSCCIP/eSCCIP-SP for ease of tracking and standardization. Once data collection is complete, a rigorous data cleaning, description, and covariate screening process will be carried out prior to analysis. Data will be first inspected for erroneous, outlying, or potentially high-leverage values, and missing data patterns tabulated and visualized. Data from the 3 recruiting study sites will then be pooled for analyses in 2 different versions of the data set separating participants who provide data for at least 1 measurement visit from participants who provide data at all time points. Multiple imputations will be used to handle missing data, including determination of a primary missing data mechanism, appropriate selection of auxiliary variables (if applicable), and sensitivity analyses to check for robustness of underlying assumptions (eg, MNAR selection models, pattern mixture models) [50]. Efficacy analyses will be carried out for both sets, thus providing a complete picture of whether and how missing data impact analysis results.

Planned Statistical Analyses

Aim 1: Analyses

The primary end point of specific aim 1 is the change in acute distress as measured by the K-6 distress scale over 1 month (immediately post intervention). To test whether eSCCIP/eSCCIP-SP is more efficacious in decreasing acute distress relative to the education control (hypothesis 1), an ANCOVA model will be estimated, which has repeatedly been shown to provide optimal estimate precision, power, and CI coverage among pretest-posttest analysis alternatives in RCTs [51,52]. The ANCOVA model will be used to test for group differences in K-6 distress scores, controlling for preintervention distress scores. Covariates will be incorporated if baseline differences are identified across site-specific, program delivery, and demographic variables. As participants may be nested within providers at each site, we will explore the need for specifying a mixed-effects model, contingent upon the size of the provider effect (eg, design effect, impact on model standard errors) and the number of providers available in the data set. With regard to families with 2 participating parents and caregivers of children with cancer, methodological research has shown poor model performance of mixed-effects dyadic models if the proportion of singletons (dyads with only 1 member) is high, as is expected for this study; therefore, primary analyses will be conducted only on primary participating caregivers [53]. We do not expect treatment effects to differ by dyad status and will test this assumption with data obtained from nonprimary participating parents analyzed in exploratory analyses. Model assumptions will be checked and alternative robust will be methods used, for instance, robust SEs, bootstrapping, or generalized linear models, if applicable [54,55]. Secondary end points (eg, PTSS and anxiety) in specific aim 1 will be analyzed in the same manner. All tests will be 2-tailed at a .05 level of significance; the Benjamini-Hochberg method will be used to adjust for multiple testing [56].

Aim 2: Analyses

Specific aim 2 analyses will further probe the eSCCIP/eSCCIP-SP user experience, intervention effects, and boundary conditions. First, descriptive summaries and data visualizations will be used to explore user engagement variables, such as the number of cores completed. Next, potential risk and protective factors will be examined by introducing interaction effects to the models previously described for specific aim 1, including all primary and secondary end points. Interaction terms will be formed between intervention assignment and each potential moderator variable, tested in separate models under the Benjamini-Hochberg control method. Follow-up inferential and graphical procedures will be used to interpret significant interaction effects [57]. Variables selected as potential moderators are participant characteristics guided by the Behavior Change Model for Internet Interventions (eg, race, gender, and socioeconomic status) and family risk variables guided by the Pediatric Preventative Health Model (eg, COVID-19 Exposure and Family Impact Scale score, PAT baseline score). Of primary importance is the potential moderating effect of intervention language, which will similarly be tested. Additional exploratory analyses will be carried out to answer key auxiliary questions and maximize the use of the data collected. First, we will examine any possible persisting effects of eSCCIP/eSCCIP-SP at the 3-month follow-up time point, based on longitudinal analysis models designed for randomized pretest-posttest-follow-up designs [58]. Similarly, we will also explore whether treatment effects differed between parents and caregivers of children with cancer from families with 1 or 2 participating caregivers, as well as examine trends in data provided by nonprimary participating caregivers.

Aim 3: Analyses

Qualitative interviews will be coded and analyzed using the CFIR framework, a widely used implementation science framework. An initial codebook will be generated using different domains of the CFIR framework, focusing on the constructs within each domain that are most related to the implementation of eSCCIP/eSCCIP-SP (eg, adaptability, cost, patient needs and resources, and self-efficacy). Discrepancies will be identified and resolved by consensus among the investigators. To strengthen the rigor of the analysis, a primary and secondary coder will be assigned as the analysis continues with the secondary coder checking the coding of the primary coder as well as completing a summary of data on each category within that case (group) and across all cases (groups). The case summaries and samples of the coding process will be reviewed in regular meetings of the study team. Through this content analysis process, codes will be transformed into categories and categories into themes according to national standards that identify and refine strategies for the implementation of the intervention. Themes that result from this process will be translated into implementation and sustainability strategies organized around the 5 major domains of the CFIR framework. We will explore intervention characteristics, inner and outer settings, characteristics of individuals, and the implementation process.

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The incremental (ie, beyond the cost of an education control website) costs and cost-savings analysis will follow best practices. We will estimate incremental costs associated with eSCCIP/eSCCIP-SP treatment, costs per participant, and marginal costs per unit of acute distress reduction. All costs will be estimated and evaluated in constant dollars using the appropriate index for price adjustment. Those resources that rise at the rate of general inflation will be corrected for inflation with the consumer price index, while medical costs will be adjusted with the medical component of the consumer price index. Due to the efficacy trial nature of this project, we will conduct a partial economic evaluation to document the cost information of the eSCCIP/eSCCIP-SP and estimate a preliminary cost-effectiveness regarding the primary outcome (ie, acute distress reduction). We will evaluate the intervention costs from health care provider perspective; therefore, the nonresearch-related cost/resource will be those health care provider–related ones, which will include intervention labor costs for hourly wages including fringe benefits of delivery staff for a different component of the program (ie, website regular maintenance staff, and telehealth guide). During all phases of development and implementation, we will document what was performed, by whom, the length of execution, and the use of any nonhuman resources. Cost collection instruments will be modified based on the eSCCIP guide/research team templates and behavioral intervention templates. Care will be taken to accurately separate research-based costs (eg, costs of follow-up assessments) from actual worksite program implementation costs. We will estimate separate costs for eSCCIP and eSCCIP-SP to provide the information needed to compare differences and provide evidence for predicting costs based on patients' ethnicity distribution. To capture cost savings from a health care provider's perspective, we will use electronic patient record to track control group patients' related health care service usage, which provides the relevant information to estimate potential cost savings patients in the treatment group could have used if there is no eSCCIP/eSCCIP-SP. A full-scale cost-effectiveness analysis will be out of the scope of this efficacy study. We will calculate incremental cost-effectiveness ratios and will use bootstrapping methods to account for the uncertainty around the incremental cost-effectiveness ratios but recognize that the limited scope of this study: only collecting partial information on program costs, especially on implementation costs [59]. We will calculate net benefits, benefit-cost ratio, and return on investment (return on investment=net benefits/costs×100). Bootstrapping will be used for CIs construction around those measures. Generalized linear models will be applied to estimate the relationship between program incremental costs and the characteristics of participants, providers, and programs. Appropriate link function and distribution family will be chosen to fit the data. A 2-part model will be used to examine and handle sample selection and nonrandom attrition.

Results

This RCT was funded by the National Cancer Institute (1R01CA258668) in March 2022. Recruitment is planned to begin by February 2023 and will continue for 3 years.

Discussion

Principal Findings

This study protocol details an RCT to evaluate the psychosocial efficacy of eSCCIP/eSCCIP-SP, a novel digital health intervention for parents and caregivers of children with cancer. The development of eSCCIP and eSCCIP-SP was thoughtfully guided by the psychology, culturally competent care, and technology literature. Considering the recent and ongoing COVID-19 pandemic, the need for flexible, acceptable, and accessible psychosocial digital health intervention is more apparent than ever before to provide evidence-based psychosocial care for parents and caregivers of children with cancer. We hypothesize that the intervention will be more efficacious than an education control at decreasing negative symptoms of acute distress, anxiety, and PTSS symptoms while demonstrating improvements to coping self-efficacy and positive cognitive coping strategies.

Comparison With Prior Work

Despite the well-documented and established psychosocial needs of parents and caregivers of children with cancer as well as challenges to in-person engagement, exceedingly few digital health options have been evaluated to provide care to this population. To our knowledge, the web-based adaptation of the Bright IDEAS Maternal Problem-Solving Skills Training Intervention [16,33,34] is the only existent psychosocial digital health intervention for parents and caregivers of children with cancer. This intervention provides education to improve problem-solving skills.

The proposed study is innovative for several key reasons. The availability of an evidence-based, psychosocial digital health intervention for parents and caregivers of children with cancer available in English and Spanish is novel, especially given its hybrid format of including both self-guided web-based content and live telehealth sessions with a trained interventionist. This format capitalizes on recommendations from prior electronic adaptations of manualized psychosocial support for parents and caregivers of children with cancer, which has suggested that web-based content may be most effective when combined with in-person contact and support [33]. The eSCCIP/eSCCIP-SP intervention has been rigorously designed and developed and is now ready for large-scale testing. Second, the development of eSCCIP/eSCCIP-SP used a systematic participatory process with multiple groups of stakeholders at all stages of design and initial testing, increasing the likelihood that the intervention is responsive to participant needs and reflects the "true" needs of the target population. In addition to working closely with parents and caregivers of children with cancer, we also partnered with trained medical interpreters and experts in cultural intervention adaptation when developing the eSCCIP-SP. Although this type of participatory research is increasingly important and well used in social and behavioral research, it is not yet commonplace in pediatric psychosocial oncology and further serves to distinguish our tools and approach. Third, the eSCCIP-SP is innovative, given the lack of resources available to the high-risk population of parents and caregivers of children with cancer, who are of Latinx descent, and the potential of the intervention to reduce

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systemic health care disparities related to psychosocial services. Fourth, eSCCIP/eSCCIP-SP can be used anywhere with an internet connection (including cellular telephone data access or Wi-Fi) and is adaptable/responsive to devices (eg, mobile phones), decreasing barriers to access and making the intervention highly amenable to eventual broad and rapid dissemination. While delivering web-based psychosocial interventions itself is not altogether novel, these interventions are largely unavailable for parents and caregivers of children with cancer. This is especially timely given the recent rise and acceptability of telehealth and video platforms for health care service delivery during the COVID-19 pandemic. Fifth, we will use an advanced platform to closely track engagement metrics, which will allow us to develop and quickly implement stepped care plans for future implementation studies. This platform has been developed by the Center for Behavioral Health and Technology at the University of Virginia and is used successfully to manage numerous behavioral and psychosocial digital health intervention trials, including large studies in adult oncology and adolescent oncology [60-62].

Limitations

It is possible that the sample of parents and caregivers of children with cancer who opt to participate in our research are self-selected and may not fully represent the population of caregiving individuals of children with cancer. To identify and more broadly implement successful recruitment, retention, and engagement strategies, the primary study team recently published a manuscript describing qualitative data from focus groups and interviews [36]. The sample included past eSCCIP participants and parents and caregivers of children with cancer who were naïve to eSCCIP (but viewed some intervention content prior to participating). By implementing these strategies broadly over the course of the study, a wide range of potentially eligible parents and caregivers of children with cancer will be targeted for inclusion. We will monitor recruitment and enrollment rates closely over the course of the study, adjusting recruitment strategies if indicated. It is also possible, given both the duration of the study follow-up and randomization procedures, that participants may drop out or be lost to follow-up. Efforts by research staff to maintain participation in the study and to obtain postintervention measures for all participants will be made, including participants providing multiple means of contact to aid in follow-up as well as receiving study payments after completion of each data collection time point. In eSCCIP development trials, close tracking and monitoring procedures led to high retention rates for participants who begin the intervention, and the addition of automated reminders and a stepped care approach to communicate with participants will bolster these efforts. The characteristics of completers versus noncompleters will also be examined for systematic differences, and we will use an intent-to-treat design for data analyses.

Second, since the intervention involves an active intervention component, including telehealth follow-up with a trained guide for participants allocated to eSCCIP/eSCCIP-SP, blinding of guides is not possible. However, study team members not involved in intervention delivery will not have access to random assignment information. After randomization, participants will be instructed on the procedures within their assigned group. All outcome measures will be completed directly on the internet by study participants, further reducing the risk of bias.

Finally, it is also important to acknowledge that care at study sites includes access to psychosocial support; however, the use of these services is likely to be equivalent across intervention and control group participants, and no participant in either condition will be discouraged from accessing any available psychosocial support. While usual care may include work with a licensed psychologist, novel aspects of eSCCIP are unique to the intervention and not a component of routine care. We will also collect information on mental and psychosocial health services used by all participants during the study period to understand the context in which eSCCIP/eSCCIP-SP was received and control for other psychosocial services in analyses if indicated.

Dissemination Plan

Data will be disseminated and shared with the scientific community through peer-reviewed publications and academic conference presentations. Furthermore, the results will be shared with participants through annual updates. Continual efforts to disseminate study progress and results are valued to maintain productive and collaborative relationships with institutional care teams and relevant stakeholders. A summary of study results will be submitted to ClinicalTrials.gov within 1 year of the trial's primary completion date.

Conclusions

Despite advances and improved medical outcomes for childhood cancer, parents and caregivers of children with cancer are at known risk for negative psychosocial sequelae, including increased risk for Latinx, Spanish-speaking parents and caregivers of children with cancer [1,2,12]. Established standards of care recommend access to high-quality psychosocial support for parents and caregivers of children with cancer and, while digital health interventions may address many logistical barriers to in-person participation in this population [63], few options exist at this time. The results from rigorous development, refinement, and pilot testing of eSCCIP and eSCCIP-SP have demonstrated the potential to deliver an effective and easily disseminatable intervention, decreasing barriers to care, and improving psychosocial outcomes. Data obtained from this RCT will be instrumental in evaluating the efficacy of the eSCCIP/eSCCIP-SP intervention as an evidence-based tool to support parents and caregivers of children with cancer across the cancer trajectory.

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official views of the National Institutes of Health. Publication made possible in part by support from the Nemours Grants for Open Access from Library Services.

Data Availability

We would be happy to share deidentified study data upon request with other research groups who request access or valid research purposes. Dissemination of study results to the scientific and lay community is described in the Dissemination Plan subsection of the main manuscript text.

Conflicts of Interest

None declared.

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Abbreviations

ANCOVA: analysis of covariance
CFIR: Consolidated Framework for Implementation Research
eSCCIP: Electronic Surviving Cancer Competently Intervention Program
eSCCIP-SP: El Programa Electronico de Intervencion para Superar Cancer Competentemente
K-6: Kessler Psychological Distress Scale
PAT: Psychosocial Assessment Tool
PROMIS: Patient-Reported Outcomes Measurement Information System
PTSS: posttraumatic stress symptom
RC: research coordinator
RCT: randomized controlled trial

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Protocol

A Digital Mental Health App Incorporating Wearable Biosensing for Teachers of Children on the Autism Spectrum to Support Emotion Regulation: Protocol for a Pilot Randomized Controlled Trial

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Abstract

Background: As much as 80% of children on the autism spectrum exhibit challenging behaviors (ie, behaviors dangerous to the self or others, behaviors that interfere with learning and development, and behaviors that interfere with socialization) that can have a devastating impact on personal and family well-being, contribute to teacher burnout, and even require hospitalization. Evidence-based practices to reduce these behaviors emphasize identifying triggers (events or antecedents that lead to challenging behaviors); however, parents and teachers often report that challenging behaviors surface with little warning. Exciting recent advances in biometric sensing and mobile computing technology allow the measurement of momentary emotion dysregulation using physiological indexes.

Objective: We present the framework and protocol for a pilot trial that will test a mobile digital mental health app, the *KeepCalm* app. School-based approaches to managing challenging behaviors in children on the autism spectrum are limited by 3 key factors: children on the autism spectrum often have difficulties in communicating their emotions; it is challenging to implement evidence-based, personalized strategies for individual children in group settings; and it is difficult for teachers to track which strategies are successful for each child. KeepCalm aims to address those barriers by communicating children's stress to their teachers using physiological signaling (emotion dysregulation detection), supporting the implementation of emotion regulation strategies via smartphone pop-up notifications of top strategies for each child according to their behavior (emotion regulation strategy implementation), and easing the task of tracking outcomes by providing the child's educational team with a tool to track

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the most effective emotion regulation strategies for that child based on physiological stress reduction data (emotion regulation strategy evaluation).

Methods: We will test KeepCalm with 20 educational teams of students on the autism spectrum with challenging behaviors (no exclusion based on IQ or speaking ability) in a pilot randomized waitlist-controlled field trial over a 3-month period. We will examine the usability, acceptability, feasibility, and appropriateness of KeepCalm as primary outcomes. Secondary preliminary efficacy outcomes include clinical decision support success, false positives or false negatives of stress alerts, and the reduction of challenging behaviors and emotion dysregulation. We will also examine technical outcomes, including the number of artifacts and the proportion of time children are engaged in high physical movement based on accelerometry data; test the feasibility of our recruitment strategies; and test the response rate and sensitivity to change of our measures, in preparation for a future fully powered large-scale randomized controlled trial.

Results: The pilot trial will begin by September 2023.

Conclusions: Results will provide key data about important aspects of implementing KeepCalm in preschools and elementary schools and will provide preliminary data about its efficacy to reduce challenging behaviors and support emotion regulation in children on the autism spectrum.

Trial Registration: ClinicalTrials.gov NCT05277194; https://www.clinicaltrials.gov/ct2/show/NCT05277194

International Registered Report Identifier (IRRID): PRR1-10.2196/45852

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KEYWORDS

digital mental health; just-in-time adaptive intervention augmentation; JITAI; autism; heart rate tracking; emotion dysregulation; challenging behavior; evidence-based strategies; student progress monitoring; mobile phone

Introduction

Background

Children on the autism spectrum can exhibit challenging behaviors, such as aggression, self-injury, and property destruction [1-3], which occur in as much as 80% of children [4]. These behaviors can have a devastating impact, negatively affect personal and family well-being [5], contribute to teacher burnout [6], and even lead to hospitalization [7]. Challenging behaviors may stem from a culmination of physiological and psychosocial stress when children are unable to regulate their stress, that is, when they do not have a repertoire of emotion regulation strategies to call on to defuse their stress [8,9]. Emotion dysregulation—difficulties with monitoring, evaluating, and modifying emotional responses to environmental demands [10]—is thought to serve as a mediator between stress and challenging behaviors in autism [11,12]. Consistent with this notion, recent literature has documented that challenging behaviors in children and adolescents with autism spectrum disorder are more likely to surface in response to situations placing demands that exceed their emotion regulation skills [13]. Individuals on the autism spectrum are more likely to experience stressful events compared with their peers owing to their difficulties with communicating, understanding others' behaviors, and responding to demands; sensitivities to sensory stimuli; insistence on sameness; and social expectations that might be perceived as emotionally overwhelming [9]. These difficulties or factors can be particularly pronounced in the school setting [14]. Therefore, these difficulties with emotion dysregulation, in addition to frequently experienced stressors, place children on the autism spectrum at high risk for frequent challenging behavior episodes.

Evidence-based strategies for managing challenging behaviors and supporting emotion regulation in schools include proactive (antecedent) and reactive (consequent) strategies [1,15,16]. Proactive strategies, such as setting routines and tailoring the environmental or instructional design to prevent challenging behaviors, are typically preferred to reactive strategies, such as punishment and planned ignoring [1,15,16]. However, even when proactive strategies are well implemented, challenging behaviors still occur, with parents and teachers often reporting that they occur without warning [11,12]. In children on the autism spectrum, triggers can be difficult to determine even with expertise in functional behavioral assessment (which is not standard training for the teaching force) [17], as children on the autism spectrum often have trouble in communicating their stress [18]. Therefore, it is critical to understand the stress-related triggers that lead to the onset of challenging behaviors. Early detection of rising stress can allow for the implementation of proactive strategies targeting stress reduction or emotion regulation, such as emotion regulation training; mindfulness-based strategies; the prompting of cognitive reappraisal; functional communication training; or other antecedent-based strategies, such as providing access to sensory stimuli or offering choices.

A way to know when a child may be experiencing stress before a challenging behavior, and thus intervene early, is by measuring the physiological state; physiological state is a well-recognized index of stress, which may be captured using many physiological channels, including heart rate (HR) [19-24]. Many theoretical frameworks point to a causal pathway between physiological stress and challenging behavior [8,25-27], and previous studies have shown elevated HR before the onset of a challenging behavior in adults on the autism spectrum [28,29]. In our previous study, we found that there is often a >22% increase in HR in the 58 seconds immediately preceding the challenging behavior and that this increase has moderate utility in predicting challenging behaviors (area under the curve [AUC]=0.72;

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P<.001) [30]. We replicated this finding in 2 samples of children aged 8 to 12 years on the autism spectrum, finding that 33% to 36% increase in HR in the preceding 76 to 80 seconds was associated with challenging behaviors (AUC=0.75-0.82). These results were again replicated in another data set including both children and adolescents on the autism spectrum (AUC=0.71) [31]. These studies suggest that responding to early HR increases may be a more direct approach to identifying the need for emotion regulation strategies, which may support the identification of behavioral triggers.

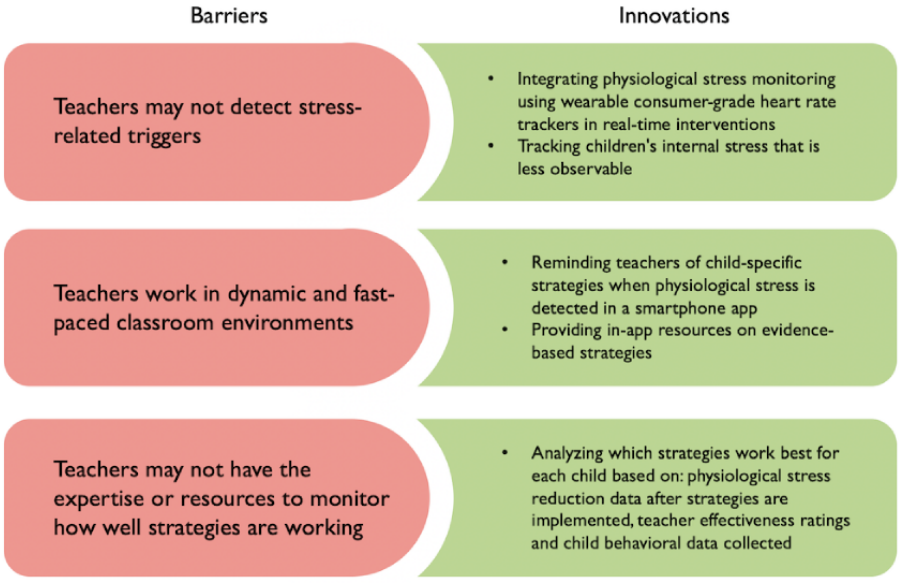
Timely identification of stress may help prevent emotion dysregulation and challenging behaviors. In addition, children on the autism spectrum may be less equipped to deal with this stress, as many have well-documented difficulties in independently using emotion regulation strategies and instead more frequently rely on maladaptive or ineffective strategies, such as rumination or shutting down [32-37]. Thus, difficulty in emotion regulation is likely a mechanism by which stress contributes to challenging behaviors, and teaching emotion regulation is critical. However, there are 3 barriers that limit the use of emotion regulation strategies for managing challenging behaviors in children on the autism spectrum in school settings. First, teachers may not detect children's stress-related triggers or their rising stress, with or without training, as children on the autism spectrum often do not express emotions verbally or in clear, observable ways using nonverbal communication channels [18]. Therefore, the detection of stress by teacher's observation alone may be sometimes ineffective or unreliable.

Second, teachers work in dynamic and fast-paced classroom environments. Even when teachers are sensitive to behavioral triggers and evidence-based behavior plans are in place, teachers have multiple demands on their attention and may not recognize a trigger or recall the best strategies to use with each student in the moment of crisis. In addition, teachers' own stress during episodes may interfere with this recall, as their stress has been found to interfere with delivery of evidence-based practices in schools [38,39]. Therefore, teachers need support to implement emotion regulation interventions with children on the autism spectrum.

Third, teachers may not have the training or resources to monitor how well the strategies are working. Many teachers do not receive training in program monitoring and analysis that is required to refine children's behavioral plans, limiting their ability to make data-informed decisions about which strategies work for a given child. Even when teachers have training in outcome measurement and monitoring, they may be unable to systematically monitor the success of strategies owing to competing demands. They may not have the time, personnel, or technological resources to determine which strategies are the most effective. Our proposed mobile health (mHealth) app, KeepCalm, is designed to address these 3 barriers and reduce or prevent challenging behaviors in children on the autism spectrum (Figure 1; app development and features are described in the *Methods* section).

The KeepCalm app is designed as a real-time electronic clinical decision support tool, otherwise known as a *just-in-time adaptive intervention* (JITAI) augmentation, a term coined in mHealth [40]. JITAI augmentations are intervention supports designed to provide the right type or amount of support at the right time by adapting to a person's changing internal and contextual state (eg, by tracking physiological stress, sleep quality, exercise or activity, temperature, and location). Most JITAI technologies are designed to support the individual client directly (eg, check-in messages and resources for clients with alcohol use disorder, triggered by GPS data showing that they are near a predetermined risk location, such as a local bar) [41]. However, the KeepCalm app is one of the first (also refer to the studies by Juarascio et al [42] and Clausen et al [43]) to support the provider (in this case, teacher or aide) directly, so that they may in turn best support their client (in this case, student).

Figure 1. Barriers and the KeepCalm app's corresponding proposed innovations to be tested.



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Objectives

We present the framework and protocol for a pilot randomized waitlist-controlled field trial that aims to examine the implementation of a digital mental health app, the KeepCalm app (refer to the *Materials* section for details about the app), designed for children on the autism spectrum with challenging behaviors of any IQ or speaking ability. Given that >95% of digital mental health apps have not actually been studied [44,45], an overarching goal of the project is to test the KeepCalm app systematically. We expect the KeepCalm app to score high on usability, acceptability, feasibility, and appropriateness. We also predict satisfactory proximal efficacy (>80% clinical decision support success rates and <20% false positive and negative rates), high technical reliability (the removal of artifacts and offline mode activation success), and the use of the KeepCalm app to result in low severity and frequency of challenging behaviors and emotional dysregulation in children on the autism spectrum after the trial relative to baseline.

Methods

App Development Work

We have used user-centered design [46,47] methods to develop the mHealth KeepCalm app by involving key stakeholders in each phase of development and testing [47-49]. As part of the early stages of the project, we have already conducted needs assessments with school personnel and parents to understand their needs in managing children's challenging behaviors and supporting their emotional regulation. We are in the process of completing 5 cycles of rapid cycle prototyping (so far, 4 cycles have been completed, including 2 with the live app prototype). App feedback gathered through this testing has directly informed future app iterations. We have also gathered data showing high usability, feasibility, acceptability, and appropriateness of the KeepCalm app and data from associated HR trackers and accelerometry devices to examine in the context of regulatory and ethical educational frameworks [50]. Alongside this work, we conduct expert advisory board meetings with a board composed of relevant experts in the community (the autism support coordinator from the School District of Philadelphia, teachers, teacher coaches, parents, and adults with autism). The board meets every few months to gather their feedback about and support for every aspect of the project, including app features and design, in-app evidence-based strategy resources, study methods, and recruitment. All previous work will inform the final KeepCalm app to be tested in this pilot randomized waitlist-controlled field trial.

Design

We will conduct a pilot randomized waitlist-controlled field trial of the KeepCalm app (refer to the *Materials* section for details about the KeepCalm app) in which participants will either be randomized to the KeepCalm app for a period of 3 months or will be included in a waitlist and will trial the app for 3 months after an initial 3-month waiting period. In this trial, the KeepCalm app will be tested for usability, feasibility, acceptability, and appropriateness, and we will also collect some preliminary proximal and distal efficacy data to inform a future, fully powered randomized field trial.

Participants and Recruitment

Overall, 20 educational teams comprising a preschool or elementary school student on the autism spectrum, their parent, their teacher, and their aide (if they have one) will be recruited. If a child does not have an aide or their aide declines to participate, their speech therapist, occupational therapist, or another educational team member may participate instead. Therefore, at a minimum, teacher-child or parent dyads will be consented, with some teams forming a triad with an aide or other member of the educational team. Teachers may participate with 1 to 2 of their students on the autism spectrum.

Inclusion Criteria

Children must have an educational classification of autism, verified using the Social Communication Questionnaire [51], a parent-reported measure. They must also exhibit challenging behaviors (ie, behaviors dangerous to the self or others, behaviors that interfere with learning and development, and behaviors that interfere with socialization). Examples include aggression, self-injury, escape behavior, property destruction, loud noises, and rigid or inflexible behavior (if at least one of the challenging behavior criteria mentioned previously applies).

Participants will be recruited from the School District of Philadelphia and private preschools or schools in the Philadelphia area using several recruitment methods including emailing teacher listserves or email lists, through the center participant registry, through the study's expert advisory board, and through projects led by HJN or DM. We will also send Parent Permission-to-Contact forms home from school via students, along with the study flyer. If parents sign the form and send it back to school, we will reach out to them to invite them into the study. We also include a version of the flyer and Parent Permission-to-Contact form in Spanish. We may also use study flyers sent through various relevant organizations and listserves, newsletters, internet postings, social media (Facebook and Twitter), and other recruitment tools as needed, and we may attend parent workshops and autism-related events to recruit participants. If study participation is initiated by parents, after consenting parents, we will send the referral contact forms to schools via parents to recruit the child's teachers or reach out to the schools directly to invite teachers to participate, after obtaining letters of support from school principals or directors, if required. Then, parents and teachers who agree to be contacted will be contacted by the research team to explain the study and invite them to participate. In addition, once teacher consent is completed, classroom aides will also be invited to participate. If no aides are available to participate, we will invite their speech therapist, occupational therapist, or any other educational team member identified by the parent or teacher.

To help characterize the children in the study, we will obtain the child's IQ from their Individual Education Program, if this was derived from a standardized test battery. If such an IQ score is not available on the child's Individual Education Program, the research team will administer the Stanford Binet Abbreviated Scales [52] test battery to obtain an IQ score.

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Materials

Overview of the KeepCalm App

The KeepCalm app is designed to be an interactive learning and data collection tool to facilitate a team approach to support emotion regulation in students. It integrates wearable HR tracking to identify and alert educators about heightened stress in their students and remind them about evidence-based strategies for de-escalating stress, supporting proactive coping, and preventing challenging behaviors. Refer to Figure 2 for the KeepCalm causal model, which shows that the pathway from stress to challenging behaviors via emotion dysregulation is "rescued" with the KeepCalm app, via teacher-assisted emotion regulation, whereby the teacher supports their student to reattain autonomic equilibrium (ie, physiological baseline or resting state) via stress communication (ie, child HR signaling to teacher), along with individualized recommendations about strategies to keep calm.

The KeepCalm app offers 3 innovations (to be tested) that address the 3 barriers described in the *Introduction* section (Figure 1). First, it incorporates physiological stress data into treatment delivery by capitalizing on recent advances in wearable biosensing [22,53,54]. The selected consumer-grade trackers are accurate [53,55,56] and have high technical reliability [55,57] for measuring HR (beats per minute) and HR variability (interbeat interval), making them inexpensive and scalable alternatives to medical-grade devices. In previous studies, we found that 85% of children on the autism spectrum will wear these trackers without complaint and rate them high on comfort and low on exacerbating sensory sensitivities [55,57].

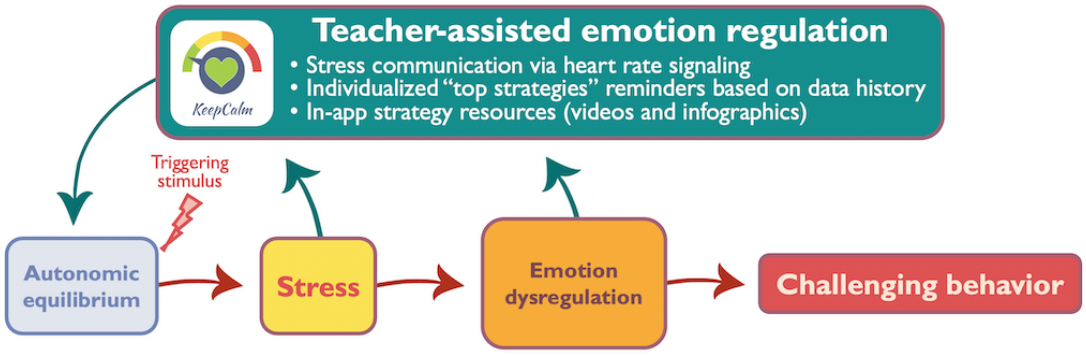
Second, KeepCalm reminds teachers about child-specific strategies when physiological stress is detected. Computerized clinical decision support systems have been found to be related to higher fidelity in evidence-based practices and better patient outcomes among providers who work in chaotic environments, such as ambulatory clinic staff [58-61]. Despite the promise of this technology, such systems have not been linked with HR monitoring for decision support during behavioral interventions or therapy. The KeepCalm app gives pop-up notifications about top emotion regulation and behavior management strategies identified for each child and contains a comprehensive easy-to-access list of proactive and reactive strategies to support teacher training and ongoing in-class coaching in these strategies by the center's teacher coaches. Additional coaching will be conducted as needed.

Third, it has a feature to track and tailor strategy recommendations based on stress reduction data. The app captures HR data before and after strategy implementation, allowing for calculation of physiological stress reduction based on each strategy. These data allow for the calculation of the "Top 3 Strategies" for each child. These are included in push notifications linked with HR alarms, accessible via an app dashboard, and sent to teams on a daily or weekly basis via email, so that everyone can stay up to date with which strategies work best for each child. Thus, the technology gives teachers a tool to assess strategy effectiveness in restoring emotion regulation. This is adaptive and will allow teachers to tailor future use of strategies, thus supporting personalized treatment.

This app is aligned with the strategic plan of the Interagency Autism Coordinating Committee [62], which calls for maximizing the potential for technology-based intervention supports to improve the lives of individuals on the autism spectrum and developing technology-based treatments deployable in community settings to increase treatment access. In addition, our previous pilot data from parents and children show that they think that an app using HR signaling could be "extremely useful" for managing stress in students on the autism spectrum; they "strongly agree" that such a system would help prevent challenging behaviors, and they "strongly agree" that this offers advantages over current practices [63]. Figure 3 shows the main features and design of the KeepCalm app.

The KeepCalm app offers several features designed to make it easy to know when and how to intervene with children to support their proactive coping and emotion regulation development.

Figure 2. KeepCalm causal model.



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Figure 3. KeepCalm app design.



HR Stress Zone Tracking

The KeepCalm app pairs with selected commercially available HR trackers (refer to the *HR Trackers* section) that children wear to allow moment-by-moment physiological arousal tracking by educators. After recording a baseline HR for each child, educators are given pop-up notifications to alert them about moderate stress levels, along with individualized top strategies that can be used to reduce their stress. As HR is an index of stress levels [22-24], an increase in HR may index rising stress in children. HR above baseline (ie, HR at rest) is arranged in a stress zone rainbow in the KeepCalm app, with green representing baseline, yellow representing small increase in HR above baseline (+10%), orange representing medium increase in HR above baseline (+20%), and red representing large increase above baseline (+30%). Educators can track the child's HR, so that they can intervene at moderate stress levels (ie, orange-zone HR) to prevent challenging behaviors associated with high stress levels or HR of approximately 30% above baseline [30] (ie, red-zone HR). In doing so, the educator creates emotion regulation learning opportunities for the child. Increase in HR may occur for other reasons, including increased physical exertion; however, accelerometry data movement thresholds ensure that increases in HR owing to child movement are not reflected in the HR stress zone tracking (refer to the *Offline Mode* section).

Individualized Child Behavior, Skills, Triggers, and Strategies Tracking

The KeepCalm app is designed to help educators and parents track children's individualized education programs in a centralized manner. Teams can create custom profiles for each child for individualized tracking of challenging behaviors, skills, behavioral triggers and antecedents, and strategies for that child and sync data entry across the team.

Top Strategy Notifications

The KeepCalm app offers individualized "top strategy" suggestions from an up-to-date list of evidence-based strategies for supporting emotion regulation and preventing challenging behaviors in children on the autism spectrum. The top strategies are individualized for the child based on previous data collection and HR tracking and sent out when a child enters the orange or red stress zones.

Offline Mode

"Offline mode" is activated when a child's average movement (acceleration) over the past 5 seconds is ≥1 m/s^2. This threshold was selected to screen out the effect of vigorous movement on the top strategy notifications triggered by the child entering the orange or red stress zones.

Evidence-Based Strategy Resources

The app provides resources (infographics and videos) about the implementation of evidence-based strategies to help support emotion regulation and prevent challenging behaviors in children on the autism spectrum. These strategies are based on the research team's comprehensive systematic review of the literature [64].

Day View

The KeepCalm app includes a "Day View" tab with a daily report including 2 versions. The first is a detailed day view that includes each data entry in list and figure format, and the second is a summary day view that includes a narrative description of the day including the top strategies used that day. This downloadable report is autogenerated at the end of each day and sent to the team via pop-up notification to support frequent team communication.

Custom Reports

The KeepCalm app includes a "Reports" tab where teams can produce clear and concise tables and figures to present data about each child's challenging behaviors, skills, behavioral triggers and antecedents and strategies for upcoming education team meetings and to share with parents. These downloadable reports may be used to help with noticing trends and for evidence-based programming to support children's development.

Functional Behavioral Assessment Mode

The KeepCalm app includes a functional behavioral assessment mode to help teams collect data to determine the function of or

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reason for new or emerging challenging behaviors, to help decide on strategies for these behaviors. Behavioral analysts can be added to the child's KeepCalm team for easy sharing of functional behavioral assessment data.

Team Messaging

The KeepCalm app offers a team messaging platform to aid team communication, which is important for consistency of strategy use across school teams and at home. Teams can also contact the app development team in real time for troubleshooting.

To sign up to the app, school personnel and parents will enter their name, email, phone numbers, and their child's nickname or ID, so that they can identify the child. Teams will record triggers, behavior and skills, and strategies in the app, and HR and accelerometry data will be recorded from child participants. Only the child's team members and the research team will have access to this information. The app does not collect any other information from participants' mobile devices.

HR Trackers

We will use 2 HR tracker models previously tested for accuracy, reliability, validity, and comfort [55]—the Mio Fuse (Mio Global) wristband and Polar H7 (POLAR) chest strap. These models are highly accurate (correlation with wired electrocardiogram: Mio Fuse: mean r=0.91, 95% CI 0.882-0.929; Polar H7: mean r=0.99, 95% CI 0.987-0.991) [53,56] and reliable (they meet quality thresholds on spike rate—Mio Fuse: 100%; Polar H7: 87.4%-89.4% and sampling fidelity—Mio Fuse: 96.2%-97.1%; Polar H7: 96.6%-100%) [55] for measuring HR and HR variability. We found that children on the autism spectrum rated both devices in the comfortable range [55], and in our pilot study, they were able to wear one of the 2 HR trackers during 5 school days.

Accelerometer

We will also use belt-clip accelerometers (mBient MetaMotionRL or another suitable model) to measure child movement, so that stress zone alerts are not sent out during period of high child movement but instead put the child's notifications in "offline mode" (refer to the *Offline Mode* section for more details). In our pilot study, teachers were asked to use the mBient trackers with child participants during 5 school days.

Measures

Primary Outcome Measures

Usability

Teacher and parent perceptions of usability will be measured using the System Usability Scale [65]. The scale consists of 10 items rated on a 5-point Likert scale ranging from 1 ("Strongly disagree") to 5 ("Strongly agree"). Responses are transformed to obtain a total value from 0 to 100, with higher scores indicating greater perceptions of usability. This scale will be administered at the end of the trial, 3 months after baseline.

Feasibility

Feasibility of the app will be assessed through teacher and parent report using the Feasibility of Intervention Measure [66]. The measure consists of 4 items rated on a 5-point Likert scale ranging from 1 ("Completely disagree") to 5 ("Completely agree"). The score is calculated by summing all items to yield a total score ranging from 4 to 20, with higher scores indicating greater feasibility of the app. Participants will complete this scale at the end of the trial, 3 months after baseline.

Acceptability

Acceptability of the app will be measured through teacher and parent report using the Acceptability of Intervention Measure [66]. The measure consists of 4 items rated on a 5-point Likert scale ranging from 1 ("Completely disagree") to 5 ("Completely agree"). The score is calculated by summing all items to yield a total score ranging from 4 to 20, with higher scores indicating greater acceptability of the app. Participants will complete this scale at the end of the trial, 3 months after baseline.

Appropriateness

Appropriateness of the app will be assessed through teacher and parent report using the Intervention Appropriateness Measure [66]. The measure consists of 4 items rated on a 5-point Likert scale ranging from 1 ("Completely disagree") to 5 ("Completely agree"). The score is calculated by summing all items to yield a total score ranging from 4 to 20, with higher scores indicating greater feasibility of the app. Participants will complete this scale at the end of the trial, 3 months after baseline.

Interview Feedback

Following participation in the study, teachers, aides, and parents will complete a 30-minute interview, where we will gather more context about the usability, feasibility, acceptability, and appropriateness of the KeepCalm app. We will also gather feedback, suggestions, and general impressions about the app. This feedback will also focus on the issue of alarm fatigue, that is, if teachers were overwhelmed, annoyed, or otherwise felt negatively toward the number of notifications received from the app during the day.

Secondary Outcome Measures

Proximal Preliminary Efficacy Outcomes

Clinical decision support success: We will additionally obtain information from teachers to measure the clinical decision support success of the app. This will be calculated from the proportion of alarms and emotion regulation strategy push notifications that result in timely implementation, as measured through in-class observation sessions (if possible, given the COVID-19–related school policies and teacher preferences) and remotely through data entry on the app.

False positives and false negatives: False positives and false negatives will be calculated as the proportion of alarms that appear to not be associated with an oncoming challenging behavior (eg, child movement) or challenging behaviors that occurred without an alarm, respectively. This will be measured through in-class observation sessions (if possible, given the COVID-19–related school policies and teacher preferences) and remotely through data entry on the app.

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Distal Preliminary Efficacy Outcomes

Challenging behaviors: Challenging behaviors will be assessed using 3 measures: 2 measuring challenging behavior severity—the School Situations Questionnaire (SSQ [67]), completed by teachers, and the Open-Source Challenging Behavior Scale [68], completed by parents—and 1 measure of challenging behavior severity—the Institute for Basic Research Modified Overt Aggression Scale (IBR-MOAS [69]), completed by teachers and parents.

The SSQ assesses challenging behaviors within the school context. The scale assesses both the presence and the severity of challenging behaviors, with items assessing whether a given behavior occurs for a child and the severity ratings. The scale yields 2 summary scores. The first is the number of problems score, which is a sum of the number of challenging behaviors endorsed, ranging from 0 to 8, with higher scores indicating greater number of problems endorsed. The second is the mean severity, calculated as the mean severity for the items endorsed, ranging from 1 to 9, with higher numbers indicating more severe problems (1-3=mild severity, 4-6=moderate severity, and 7-9=significant severity). Participants will complete this measure at baseline and 3 months after baseline.

The Open-Source Challenging Behavior Scale measures the severity of challenging behavior episodes across contexts (eg, school and home), from the parent's perspective. The scale includes 18 questions rated on a 5-point Likert scale (1=not at all a problem, 2=mild problem, 3=moderate problem, 4=severe problem, and 5=very severe problem). Participants will complete this measure at baseline and 3 months after baseline.

The IBR-MOAS measures the frequency and severity of aggressive behavior episodes. The scale is divided into five subscales: (1) verbal aggression toward others, (2) verbal aggression toward self, (3) physical aggression against other people, (4) physical aggression against objects, and (5) physical aggression against self. Items are rated on frequency on a 5-point Likert scale: never=never happens, rarely=averages about once a year to once a month, sometimes=averages about several times a month to several times per week, often=averages about daily to several times a day, and U=used to happen but not in the past year. For our analyses, we will code U ratings as equivalent to never. Unlike the original Overt Aggression Scale and other modified versions, a weighted scoring system was not used. We will adapt the measure to include other challenging behaviors of interest (eg, escape, climbing furniture, and meltdowns). Participants will complete this measure at baseline and 3 months after baseline.

Emotion dysregulation: Emotion dysregulation will be measured through parent and teacher reports using the Emotion Dysregulation Inventory (EDI), either the original version [70-72] or the young child version [73], depending on the child's age. The scales consist of 30 items (original version) or 22 items (young child version) for raters to indicate how much of a problem certain emotions and behaviors are for the individual, being rated on a 5-point Likert scale ranging from 0 ("Not at all") to 4 ("Very severe"). The EDI produces scores for reactivity (rapidly escalating, intense, and poorly regulated negative affect) and dysphoria (sadness, low positive affect, and unease). Raw scores are summed and converted to standardized scores with clinically elevated cutoffs, based on a large autism sample, and scoring information from a US census–matched sample of 1000 youths provides clinical cutoffs. Participants will complete this measure at baseline and 3 months after baseline.

Technical Outcomes

Artifact removal: The total number of "artifacts"—interbeat HR intervals (also known as RR intervals) >200 ms [55] detected during the testing period will be calculated throughout study participation.

Offline mode activations: The proportion of time for which "offline mode" (refer to the Offline Mode section for more details) is activated over the testing week based on the accelerometry data threshold will be calculated throughout study participation.

Adverse Events

We will use a brief Adverse Events Checklist to be administered to teachers and parents in the treatment group weekly throughout the trial, which may include items related to teachers experiencing stress triggered by monitoring their student's stress levels. This checklist will be reviewed by the expert advisory board for the study before trial commencement.

Ethics Approval

The trial is approved by the University of Pennsylvania institutional review board (829690) and the School District of Philadelphia research review committee (2022-12-1071).

Procedure

The trial is registered at ClinicalTrials.gov (NCT05277194). After screening for eligibility, the 20 teams (at a minimum, teachers-parents and child dyads; at a maximum, teachers-parents and child-aide [or other educational team member] triads) will be randomized to the waitlist (n=10, 50%) or treatment group (n=10, 50%). The treatment (and later, the waitlist) group will use the app for 3 months. After a dyad or triad has signed up for the study, participants will complete a conferencing software-based intake meeting, during which they will be individually briefed about the KeepCalm app and complete the baseline assessments.

School personnel will then complete an in-app training session either remotely or in the classroom, during which they will receive access to the KeepCalm app, HR tracker, and accelerometer. The research team will also show or instruct teachers about how to put the HR tracker and accelerometer on the child or assist or instruct the child in putting them on themselves. Participants will download the app onto their own phones or, if they do not have an iPhone, an iPhone will be lent to them for their participation in the project. A member of the research team will also help the school personnel to customize the app for their student by showing them how to add the child's profile and their triggers, behaviors and skills, and strategies. Standard but editable lists will be programmed into the app for each student, including evidence-based proactive and reactive strategies for reducing challenging behaviors and supporting emotion regulation [64]. All teachers recruited will have had

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professional development and in-class coaching in these strategies by coaches in our center. The research team will administer a fidelity assessment tool to teachers to understand their proficiency in implementing these strategies and provide additional coaching or resources for strategies, as needed.

Following this training, school personnel participants will begin testing the app within the classroom. They will initially record at least one baseline HR of the child, which will be used to calibrate the app's stress zone notifications for the child. Baseline HR is recorded over a 5-minute period, during which the child will be engaged in a relaxing activity. We recommend that teachers take 2 to 3 baseline measurements to ensure accuracy. Students will then wear the HR tracker and accelerometer each day during the 3-month testing period. School personnel will be able to track the student's HR and movement; enter child data about triggers and antecedents, challenging behaviors and skills, and intervention strategies; view the daily report; export the child's data; and message others on the student's team. School personnel will receive SMS text message support from the study team during the testing period and will be able to ask questions and troubleshoot any issues that arise during this period. Parents will be able to view the autogenerated daily report for the child, export and build figures of the child's data, access the intervention strategy resources, and use the app's messaging features. The research team will remotely monitor each participant's use of the app during their respective testing period.

Following the app testing period, teachers, aides, and parents will provide feedback about their experience with the app during a brief interview with a member of the research team that will cover various themes including usability, acceptability, feasibility, appropriateness, and any adverse event that may have occurred (the latter will be in addition to the previously mentioned Adverse Events Checklist that will be administered weekly throughout the trial). Measures will be taken at eligibility determination, baseline, throughout the trial, and after the trial as per Table 1. A demographic survey will also be administered at baseline, including a question on the child's current medications, as some are known to affect HR. If possible, given the COVID-19–related school policies and teacher preferences, the research team will perform in-class observations to obtain a first-hand look at the use of the KeepCalm app in the classroom and to track clinical decision support success and false positives and false negatives (as described in the *Measures* section).

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Table 1. Timeline for data collection.

Construct and measure	Respondent or assessor	Timeline					
		Baseline		Throughout the trial (3 months)		After the trial	
		WL[a]	TX[b]	WL	TX	WL	TX
Eligibility							
SCQ[c]	Parent	✓	✓				
IQ							
Any standardized IQ battery, as reported on the child's IEP[d] (if not available, Stanford Binet ABIQ[e])	Investigator, if required	✓	✓				
Primary outcome measures							
SUS[f] (usability)	Teacher and parent						✓
AIM[g] (acceptability)	Teacher and parent						✓
FIM[h] (feasibility)	Teacher and parent						✓
IAM[i] (appropriateness)	Teacher and parent						✓
Qualitative interview	Teacher, aide, and parent						✓
Technical reliability							
Artifact removal success	Investigators (app data metrics)				✓		
Offline mode activations	Investigators (app data metrics)				✓		
Proximal preliminary efficacy							
Implementation success	Investigators (classroom observation)				✓		
False positives and false negatives	Investigators (classroom observation)				✓		
Distal preliminary efficacy							
SSQ[j] (CB[k] severity)	Teachers	✓	✓			✓	✓
OS-CBS[l] (CB severity)	Parents	✓	✓			✓	✓
IBR-MOAS[m] (CB frequency)	Teachers and parents	✓	✓			✓	✓
EDI[n] (dysregulation)	Teachers and parents	✓	✓			✓	✓
Adverse events							
Adverse events checklist	Teachers and parents				✓		✓

[a]WL: waitlist group.
[b]TX: treatment group.
[c]SCQ: Social Communication Questionnaire.
[d]IEP: Individual Education Program.
[e]ABIQ: Abbreviated Battery IQ.
[f]SUS: System Usability Scale.
[g]AIM: Acceptability of Intervention Measure.
[h]FIM: Feasibility of Intervention Measure.
[i]IAM: Intervention Appropriateness Measure.
[j]SSQ: School Situations Questionnaire.
[k]CB: challenging behavior.
[l]OS-CBS: Open-Source Challenging Behavior Scale.
[m]IBR-MOAS: Institute for Basic Research Modified Overt Aggression Scale.

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[n]EDI: Emotion Dysregulation Inventory.

Data Analysis

Primary Outcomes

This trial is designed to test usability, acceptability, appropriateness, and feasibility data rather than efficacy; therefore, primary outcome data analyses will use descriptive statistics of the survey measures on usability (System Usability Scale), acceptability (Acceptability of Intervention Measure), feasibility (Feasibility of Intervention Measure), and appropriateness (Intervention Appropriateness Measure) of the KeepCalm app, as outlined in the *Measures* section.

We will also examine usability, acceptability, feasibility, and appropriateness through a qualitative interview and examine barriers to and facilitators of using the KeepCalm app in classrooms with students on the autism spectrum. Audio recordings of the interviews will be transcribed, and all transcripts will be loaded into Dedoose for data management and analysis. Thematic analysis will be guided by an integrated approach that includes identification of a priori attributes of interest (usability, acceptability, feasibility, and appropriateness). This integrated approach uses an inductive process of iterative coding to identify recurrent themes, categories, and relationships in qualitative data. After exploring the data, a comprehensive coding scheme will be developed and applied to produce a descriptive analysis. A team of coders will separately code the transcripts and compare the results to assess the reliability of the coding scheme. Any disagreements in coding will be resolved by team consensus. After the coding scheme is finalized, coders will be required to code 2 transcripts in a row at a high level of agreement with the lead coder (k>0.70) before independent coding of the rest of the transcripts. Following this, the lead coder will code 20% of the transcripts in duplicate for the reporting of interrater reliability.

Quantitative and qualitative data about usability, acceptability, feasibility, and appropriateness will be integrated by examining the qualitative data from the participants who responded in the lowest versus highest quartile on the quantitative measures of each construct. Data analysis will inform our understanding of the usability, acceptability, feasibility, and appropriateness of the KeepCalm app and will provide a list of feature updates to be included in the app before the following fully powered randomized controlled trial.

Secondary Outcomes

To examine technical reliability, we will use descriptive statistics of artifact removal success and offline mode activations. To examine proximal preliminary efficacy, we will use descriptive statistics of clinical decision support success rates and false positive and negative rates. To examine distal preliminary efficacy, we will also conduct a preliminary examination of the efficacy of KeepCalm on challenging behavior (SSQ and IBR-MOAS) and emotion dysregulation (EDI) using an exploratory (underpowered) repeated measures ANOVA to assess the 2 groups (waitlist and treatment) at baseline and posttrial periods. Given the sample size, this analysis will be underpowered.

Power

For the study's pilot randomized controlled trial, the analyses will focus on feasibility, usability, and implementation (descriptive) data but will include some preliminary efficacy inferential analyses. In this study, 50% (10/20) of the teams will be randomized to the treatment condition and 50% (10/20) of the teams will be randomized to the waitlist control condition. The sample size was not based on power analysis but rather a need to obtain pilot data that will support an app for a fully powered trial.

Results

We anticipate that recruitment for the randomized controlled trial will begin in September 2023. The analysis of data will begin following the trial, which we expect to be completed in the second half of 2024. We expect to publish the results of the trial in 2025.

Discussion

In this paper, we described the protocol of an innovative pilot randomized waitlist-controlled field trial to investigate the usability, acceptability, feasibility, and preliminary efficacy of an app to detect and manage challenging behaviors in children on the autism spectrum. We aim to address current barriers that limit the use of emotion regulation strategies with children on the autism spectrum by developing this evidence-based strategy implementation tool based on objective, physiological measurements. This study offers several innovations to be tested. First, it tests an app that integrates physiological stress monitoring, to track children's internal stress that is less observable, with real-time intervention suggestions. Second, the intervention suggestions provided by the app are individualized to each child. It reminds teachers about child-specific emotion regulation strategies and provides in-app resources about evidence-based strategies to help parents and teachers learn strategies that may be more effective to use with the child. Finally, the app will analyze which strategies work best for each individual child based on physiological stress reduction data, teacher's ratings of strategy effectiveness, and child's behavioral data.

The mHealth KeepCalm app is an app designed to target challenging behaviors in children on the autism spectrum using biosensing technology. The main limitation we anticipate facing in this trial is that, owing to the small sample size of only 20 teams, we will lack sufficient power to determine the efficacy of the app in preventing and reducing challenging behaviors. However, this trial will be aimed at gathering usability, acceptability, feasibility, and appropriateness data and information about barriers and facilitators to prepare for a large randomized controlled trial to gather data about effectiveness, which will be conducted later.

We are not aware of any other digital health app for children on the autism spectrum that uses physiological biosensing to monitor physiological arousal and support the implementation

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of evidence-based practices for children on the autism spectrum. Although there are many other types of technological innovations to support individuals on the autism spectrum and despite the range of digital mental health apps that are commercially available, there is little evidence about their efficacy [74]. However, as mentioned previously, >95% of them have not actually been studied, and there is a lack of studies in this field regarding efficacy, especially relative to studies of web-based mental health programs [44,45].

Current implementation of strategies to manage challenging behaviors or emotion dysregulation by school teams is limited by difficulties in detecting rising stress levels in children on the autism spectrum who struggle to communicate their emotions, chaotic and stressful classroom environments that make it difficult to recall the best emotion regulation strategies per student, and difficulty in tracking the effectiveness of these strategies for ongoing program refinement. The mHealth KeepCalm app seeks to address these barriers with new biosensing technology and takes a personalized medicine approach to reduce the impact of significant challenging behaviors in children on the autism spectrum.

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Data Availability

Data sharing is not applicable to this paper, as no trial data sets have been generated or analyzed at this time. Data that will be collected in the trial described in this paper, which will be published in a future manuscript, will adhere to the established rules set forth by the National Institutes of Health for public sharing of data.

Conflicts of Interest

HJN consults with 2 digital health companies, Songbird Therapy and Pletly. CAM receives royalties from Oxford University Press and is on the scientific advisory board for the Brain and Behavior Foundation. JCM consults with Customer Value Partners, Bridgebio, Determined Health, and BlackThorn Therapeutics; has received research funding from Janssen Research and Development; serves on the Scientific Advisory Boards of Pastorus and Modern Clinics; and receives royalties from Guilford Press, Lambert, and Springer. RSB is the principal at Implementation Science & Practice, LLC. She receives royalties from Oxford University Press and consulting fees from United Behavioral Health and OptumLabs and serves on the advisory boards for Optum Behavioral Health, AIM Youth Mental Health Foundation, and the Klingenstein Third Generation Foundation. All are outside the scope of the submitted work. All other authors have no conflicts of interest to declare.

Multimedia Appendix 1
Peer-review report from the Center for Scientific Review Special Emphasis Panel - National Institute of Mental Health (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 238 KB - resprot_v12i1e45852_app1.pdf]

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Abbreviations

AUC: area under the curve
EDI: Emotion Dysregulation Inventory
HR: heart rate
IBR-MOAS: Institute for Basic Research Modified Overt Aggression Scale
JITAI: just-in-time adaptive intervention
mHealth: mobile health
SSQ: School Situations Questionnaire

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Protocol

Community-Led, Cross-Sector Partnership of Housing and Health Care to Promote Aging in Place (Unite Health Project): Protocol for a Prospective Observational Study

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Abstract

Background: For many older Americans, aging in place is their preferred living arrangement. Minoritized and socioeconomically disadvantaged older adults are up to 3 times more likely to experience disability than other groups, which increases their likelihood of being unable to age in place. Bold ideas to facilitate aging in place, particularly among vulnerable populations, are needed. One such idea is the Unite care model, a community-initiated, academic-supported, cross-sector initiative that combines 2 sectors: housing and health care. The Unite care model colocates a federally qualified health center clinic on an older adult affordable housing campus in Flint, Michigan.

Objective: There are two aims to this study. Aim 1 is to evaluate the implementation of the Unite care model in terms of acceptability, adoption, and penetration. Aim 2 is to determine which older adults use the care model and whether the care model promotes aging in place through risk factor reduction and improvement in the physical and social environment.

Methods: We will assess the care model using a concurrent, exploratory mixed methods design. For aim 1, acceptability will be assessed through semistructured interviews with key stakeholder groups; adoption and penetration will be assessed using housing and health care records. For aim 2, residents residing in the Unite clinic building will participate in structured outcome assessments at 6 and 12 months. Risk factor reduction will be measured by change in systolic blood pressure from baseline to 12 months and change in the physical and social environment (item counts) will also be assessed from baseline to 12 months.

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Results: Data collection for aim 1 began in July 2021 and is anticipated to end in April 2023. Data collection for aim 2 began in June 2021 and concluded in November 2022. Data analysis for aim 1 is anticipated to begin in the summer of 2023 and analysis for aim 2 will begin in the spring of 2023.

Conclusions: If successful, the Unite care model could serve as a new care model to promote aging in place among older adults living in poverty and older Black Americans. The results of this proposal will inform whether larger scale testing of this new model of care is warranted.

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KEYWORDS

aging in place; stroke prevention; hypertension; blood pressure; social determinants of health; affordable housing; older adults; community-based participatory research; implementation evaluation

Introduction

Background

Aging in place, defined as the ability to stay in one's current residence by securing necessary support in response to evolving needs, is overwhelmingly preferred among older adults [1-3]. Aging in place also provides health benefits for older adults [4], via sustaining established social networks and care services [5,6]. Furthermore, aging in place is overwhelmingly favored by policy makers because it may delay or avoid the costly option of institutional care; 1 year of nursing home care costs about US $80,000 [7]. For many older Americans, aging in place is their only option as assisted living facilities require significant out-of-pocket spending. Thus, strategies to support aging in place are critical, particularly among low-income Americans.

Disability is the strongest predictor of nursing home admissions [8]. Over 25% of older adults experience activity limitations and cognitive impairment [9-11]. Disability disproportionately impacts Black people and low-income Americans and negatively impacts aging in place. Minority and socioeconomically disadvantaged older adult populations are up to 3 times more likely than other groups to experience disability [12-14]. Furthermore, Black people have the highest incidence of Alzheimer disease and Alzheimer disease–related dementias (AD/ADRDs) with a 2-fold greater incidence compared with White people [15-19].

Efforts to reduce disability and optimize the environment may help facilitate aging in place. Hypertension is the most important modifiable cardiovascular risk factor [20-24] and a predictor of nursing home admission [8]. Hypertension treatment reduces the incidence of stroke [25] and may reduce the incidence of AD/ADRDs [26], which are the leading causes of disability and strongest predictors for not aging in place [27-29]. Therefore, hypertension treatment, complemented by physical and social environment optimization, may promote aging in place by reducing informal caregiving needs, unmet needs, falls, and disability [30-33].

Unite Care Model

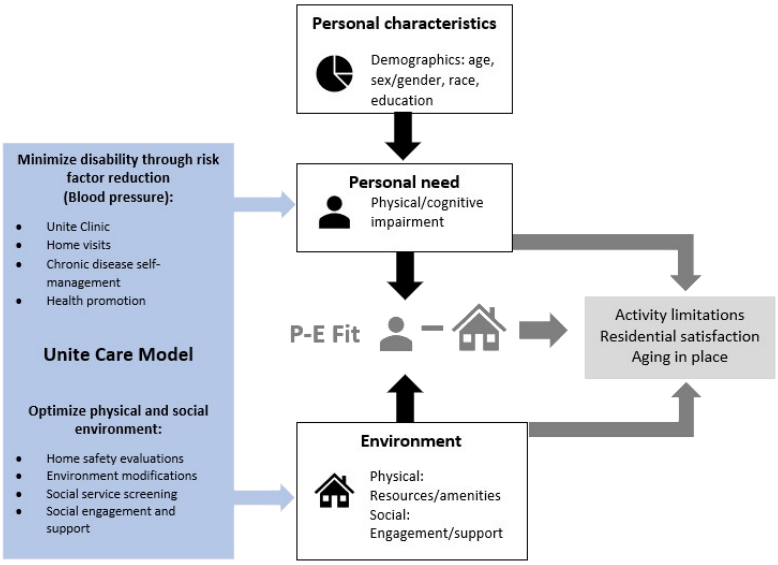
The Unite care model is a community-initiated and led, academically supported, cross-sector initiative that combines housing and health care to promote aging in place by addressing personal needs and optimizing the physical and social environment. The Unite care model includes a federally qualified health center clinic on an older adult affordable housing campus in Flint, Michigan, home to over 700 predominately Black older adults. The Unite clinic is located within the largest older adult congregate housing building, home to about 300 older adults.

The Unite care model is comprised of 3 components: Colocation of a federally qualified health center clinic on the affordable housing campus, home medical visits, and community health worker–supported care. The Unite care model will promote aging in place by optimizing (1) medical care including onsite clinic and home visits; (2) the social environment through clinic referrals for home safety evaluations and facilitating environmental modifications; and (3) the social environment by community health worker–led social engagement and support. Figure 1 depicts this care model. Overall, the Unite care model flips the paradigm that asks the most vulnerable older adults to seek out the medical safety net. Instead, the Unite care model will bring the safety net to older adults to support aging in place.

The Unite care model builds on Community Aging in Place—Advancing Better Living for Elders (CAPABLE), a randomized trial of home occupational therapy and nursing sessions, and home repairs to reduce disability and promote aging in place through physical environmental optimization compared to controls. The CAPABLE group experienced a 30% (4.00 to 2.22) decrease in disability scores compared to controls at 5 months but was not sustained at 1 year [34]. Booster visits, social service screening, and community health worker support were identified by the research team and other researchers as mechanisms that could improve sustainability [34,35]. The Unite care model builds on the CAPABLE trial by expanding the intervention to provide medical care to reduce disability risk factors and community health workers to optimize the social environment.

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Figure 1. Unite care model.



Aims and Objectives

This study will evaluate the Unite care model through 2 aims.

- Aim 1: To assess the implementation and impact of the Unite care model in terms of acceptability, adoption, and penetration among key stakeholder groups using an exploratory mixed methods design
- Aim 2: To determine which older adult residents who reside in the Unite clinic building use the Unite care model and whether the model promotes aging in place through cardiovascular risk factor reduction and improvement in the physical and social environment

Methods

Study Design

A concurrent exploratory mixed methods approach will be used to evaluate the implementation of the Unite care model.

Ethics Approval

This study is approved by the University of Michigan Institutional Review Board (HUM00197049).

Study Setting

Flint, Michigan is a community with a large burden of chronic disease and poverty. Flint is recovering from the water crisis, where the city's drinking water was contaminated with excessive levels of lead for over 18 months. Flint has a population of about 80,000, 57% of which are Black; 40% live in poverty and is ranked 80 out of 83 Michigan counties on Robert Wood Johnson Foundation County Health Rankings [36].

The Unite care model takes place at a heavily charity-subsidized older adult (55 years and older) affordable apartment complex in Flint, Michigan. The apartment complex is situated within a broader, informal, older adult housing campus. Within a 3-square mile radius of the apartment complex, an estimated 700 independently living older adults reside at a public housing apartment building, a US Department of Housing and Urban Development senior living building, and single-family homes. About 75% of the older adults are Black, many earning less than US $12,000 annually.

Aim 1: Assessing the Implementation and Impact of the Unite Care Model

Overview

We will determine how much and for whom (ie, adoption and penetration) and how well (ie, acceptability) the Unite care model is implemented. These implementation outcomes are necessary preconditions to understand the effectiveness of the Unite care model [37].

Acceptability

To measure the acceptability of the Unite care model, stakeholders from three different groups: (1) housing and health care administrators, (2) providers, and (3) older adult residents will be recruited to participate in semistructured interviews based on the theoretical framework of acceptability [38], theoretical domains framework, and Proctor's definition of acceptability [37]. Interview guide questions will explore constructs including affective attitude, burden, perceived effectiveness, ethicality, intervention coherence, opportunity costs, and self-efficacy. Interview guides will be tailored to each population, given acceptability is distinct among those who received the care model compared to those who deliver the care model [38]. Sample interview guide questions for each group are shown in Table 1.

Housing and health care administrators (n=9) will be interviewed at the time of the clinic opening (baseline) and again at 18 months. Snowball sampling will be used to identify all key administrators. Providers (n=5) will be interviewed at 12 months and will include Unite clinic staff (nurse practitioner and medical assistant) and housing employees who provide wraparound services to residents (resident wellness director, resident service coordinator, and community health worker). Older adult residents (n=36) will also be interviewed at 12 months. Older adult positive and negative opinion leaders will be purposely sampled across three subgroups: (1) older adult residents who use the clinic (n=12), (2) older adult residents who have

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attempted to use the clinic (n=12), and (3) older adult residents who do not use the clinic (n=12). We will identify older adults pertaining to each subgroup based on structured survey responses (aim 2) and notes kept by the research team. Interviews will be conducted in person as possible at a location convenient to the participant, with the alternative of video or telephone calls given the individual's availability, preference, and COVID-19 restrictions. Participants will receive US $40.

Semistructured interviews will be audio recorded, professionally transcribed, and reviewed by the research team for accuracy. We will use ATLAS.ti (ATLAS.ti Scientific Software Development GmbH), a qualitative data analysis and research software, to facilitate qualitative analysis. We will perform direct content analysis using the theoretical framework of acceptability and theoretical domains framework as a template. Two members of the research team will independently code each transcript, compare their coding, discuss discrepancies, and agree on final codes. Several strategies will be used to enhance the reliability and validity of the analysis including member checks, peer debriefing, and concurrent data collection and analysis described below.

Table 1. Overview of aim 1 interviews.

Population	Participants, n	Timeline	Sample questions
Housing and health care administrators	9	• Baseline (clinic opening) • 18 months	• Now, as the Unite clinic is about to open, how are you feeling about participating in this project? (affective attitude) • How has the clinic impacted your daily workload? (burden and barriers)
Providers	5	• 12 months	• How are things going at the clinic? (positive and negative affect) • What do residents say about the clinic? (social norms)
Older adults	36	• 12 months	• How do you feel about the clinic? or What do your friends think about the clinic? (positive/negative affect) • What do you think would happen if you went to the clinic? (outcome expectations)

Adoption

Adoption, defined as the Unite care model uptake by older adult residents, will be quantified by the number of provider home visits and community health worker or resident service coordinator interactions. The number of home visits will be self-reported. Community health worker or residence service coordinator interactions will be sampled daily for 1 week per month via a Qualtrics survey completed by the community health worker. The survey will assess the number of residents served that day as well as the services provided to each resident.

Penetration

Penetration is defined as the proportion of people who participate in a given program. We will explore the role of clinic proximity as a predictor of Unite care model usage. The research team will obtain data from the Unite clinic electronic health record, including patient-level data (addresses, demographics, and comorbidities). Patient addresses will be geocoded using Google's interface to identify if the patient resides on the older adult affordable housing campus and specifically in the Unite clinic building.

The primary outcome is the proportion of older adults who reside on the older adult affordable housing campus who are cared for by the Unite clinic. The research team will make 2 types of comparisons between older adults who reside in the Unite clinic building compared to older adults who reside on the campus but not in the Unite clinic building. First, for measures that can only be defined in aggregate (ie, number of new patient visits), the research team will compare mean per-patient usage measures between populations. Specifically, we will compare the mean of each usage variable divided by the number of patients living in each setting using *t* tests and the proportion of new and return visits using chi-square tests across settings. Second, for measures where individual-level data can define the population at risk (number of missed appointments and appointment timeliness), we will fit appropriate regression models to predict the usage measures (dependent variable) accounting for residence (Unite clinic building vs other older adult campus) and demographics known to predict missed appointments (age, race, and sex), comorbidities and dual eligibility (independent variables).

Integration of Qualitative and Quantitative

The qualitative (acceptability) and quantitative data (adoption and penetration) will be collected and analyzed during the same time. Integration will merge the qualitative and quantitative data after their respective analyses are complete [39]. We will merge the data through narrative integration, whereby the qualitative results are presented followed by the quantitative results and jointly displayed in a table. Conceptually, the research team believes that the Unite care model must be found to be acceptable by stakeholders as a precursor to adoption and penetration. Thus, the qualitative data will be presented first. The research team will also assess the concordance of the data integration. If discordance is identified, additional data may be gathered.

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Aim 2: Determining Which Older Adults Residing in the Unite Clinic Building Use the Unite Care Model and Whether the Model Promotes Aging in Place

Overview

We seek to understand the usage of the Unite care model and to assess the impact of the components of the person-environment fit model, hypertension as a predictor of disability, and the environment. This is a prospective observational study with baseline, during, and post-Unite care model initiation assessments.

Study Population Recruitment and Enrollment

Residents of the Unite clinic building (n=300) will be recruited to complete in person, prospective observational assessments in which they will be asked structured interview questions and have their blood pressure taken. Residents will be recruited from building central locations, including community and recreation rooms, in addition to fliers, word-of-mouth, and door-to-door knocking. Recruitment will continue until all residents have been contacted and provided the opportunity to consent or decline. The housing staff will aid the research team in contacting hard-to-reach residents. Residents who do not respond to the research team and housing staff after multiple contact attempts will be considered a decline. We will use our ongoing successful retention strategies, which include maintenance of contact and obtaining alternate contact information, including those of family members, in the event of change in contact information. The assessments will take place in a private space in the Unite clinic building. Participants will be given US $20 at baseline and US $25 for each outcome assessment.

Baseline assessments will begin at the time of the Unite clinic opening, with 6- and 12-month outcome assessments. The assessments will measure resident cognition, activity limitations [40-42], blood pressure, Unite clinic usage, physical [43] and social environment [44], health-related social needs [45], and housing transition information. Blood pressure will be measured by research staff using the OMRON 7 series upper arm blood pressure monitor (OMRON Healthcare, Inc) in accordance with national standards for measurement. Housing status transition will be obtained from the Unite clinic building records including 2 years prior to the start of the Unite care model. Participant responses and blood pressure measurements will be stored in a Research Electronic Data Capture database (Vanderbilt University). Table 2 depicts which measures are assessed at each outcome assessment.

Table 2. Comparison of aim 2 measures by outcome assessment.

	Baseline	6 months	12 months
Sociodemographics	✓		
Comorbidities	✓		
Self-rated health	✓		✓
Activity limitations	✓		
Cognitive impairment	✓		
Unite care model usage		✓	✓
Blood pressure measurement	✓	✓	✓
Physical environment	✓		✓
Social environment	✓		✓
Housing status	✓	✓	✓

Data Analysis

The primary analysis is the change in systolic blood pressure (SBP) from baseline to 12 months. Meta-analyses have found that for a given blood pressure, SBP predicted over 90% of the risk of ischemic heart disease and stroke and that a 2 mm Hg decrease in SBP could reduce stroke and ischemic heart disease mortality [46]. Analysis will fit a linear regression model with the outcome of 12-month SBP, including baseline SBP and a binary predictor of Unite care model patient (yes vs no) as independent variables.

Other secondary analysis end points will include determining whether functional and cognitive limitations are associated with care model usage, change in physical and social environment, and moves out of the Unite clinic building. To determine if functional and cognitive limitations, including activity limitations and AD/ADRD are associated with Unite care model usage, the research team will build a logistic regression model predicting Unite utilization, including age, sex, race, ethnicity, AD/ADRD status, level of functional disability, self-reported health, and baseline hypertension as independent variables. Change in physical and social environment (item counts) will be assessed using a Poisson regression with an outcome of 12-month values, adjusting for baseline values and including an intervention indicator. Moves out of the clinic building will be assessed by comparing moves out of the building in the 2 years prior to the Unite care model compared to year 2 of the Unite care model.

Of the 300 older adults residing in the Unite building, we estimate that 5% will elect not to enroll, resulting in a study population of 285 older adults. We estimate that we will have 89% power to detect a 2-point change in SBP within older adults assuming a mean baseline SBP of 162 mm Hg and SE of change in SBP over time of 10 mm Hg, based on prior data in this

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community and community studies [47,48], and a 10% loss to follow-up using an analogous test to our primary analysis. If loss to follow-up increases to 20%, power to detect a 2-point change in SBP would decrease to 85%. The effect may be larger. We will have 100% power to detect a 4-point SBP change if loss to follow-up were 20%.

Overall Assessment of Unite Care Model

After executing these aims, true to our community-engaged approach, our advisory board comprised of older adults, Unite partners (housing and health care), insurance, and local government stakeholders will review the results. Our evaluation of the care model will be holistic and require considerable judgment as no single metric nor combination of metrics is likely to capture the complexities of the initial Unite experience. The panel will then judge whether the Unite care model is sufficiently promising to justify efforts to develop similar models of care.

Results

This study was funded by the National Institutes of Health-National Institutes on Aging in April 2021 and received institutional review board approval from the University of Michigan in May 2021. Semistructured interviews for aim 1 began in July 2021 and are anticipated to end in April 2023, with an anticipated total 45 stakeholders, including administrators, providers, and older adult residents. Structured interviews for aim 2 began in June 2021 and ended in November 2022. For aim 2, at baseline, 265 residents were approached, of which 179 residents enrolled. In total, 149 residents completed 6-month outcomes and 131 residents completed the final 12-month outcome. Data analysis for aim 1 is anticipated to begin in summer 2023; analysis for aim 2 will begin in spring 2023.

Discussion

Anticipated Findings

We anticipate the following outcomes: (1) among older adults residing in the Unite clinic building, those with functional and cognitive limitations (ie, activity limitations, AD/ADRD) will be more likely to use the Unite care model than those without limitations; (2) among older adults residing in the Unite clinic building, those who receive care through the Unite care model will have reduced SBP compared to those who do not receive care through the Unite care model; and (3) Among older adults residing in the Unite clinic building, those who receive care through the Unite care model will have an increase in physical environment modifications and a decrease in social isolation compared to those who do not receive care through the care model.

Strengths and Limitations

The evaluation of the Unite care model is at the intersection of community engagement and implementation science. The Unite care model is a community-led and community-implemented intervention where the academic partners are supporting the initiative by conducting the analysis. Cross-sector collaborations such as Unite where housing and health care are partnering is 1 approach to addressing adverse social determinants of health. Often, investment in 1 sector accrues benefits in another sector while increasing the costs and resource usage in the investing sector [49-51]. In this case, the Unite care model is initiated and led by both housing and health care stakeholders, a cross-sector partnership promoting a shared assessment of value [52]. Multilevel interventions, such as the Unite care model, may interact to create synergistic effects, but rigorous assessments are rarely completed [53,54]. Our robust, holistic assessment of the Unite care model will inform whether larger scale testing of this new care model is warranted.

Potential challenges include recruitment and retention of participants in aim 2. We will employ our long-standing community recruitment and retention practices to reduce this barrier. Another potential pitfall lies in the study duration. The 2-year study timeframe may not be long enough to accrue outcomes of interest including aging in place and change in physical and cognitive impairment. Long-term follow-up of the Unite population could occur in subsequent research.

Conclusions

Understanding the impact of combining older adult housing and health care will inform future cross-sector collaborations. Additionally, overlaying an implementation science-centered evaluation on a community-led initiative is an example of how academic teams can fully support their community partners.

Conflicts of Interest

None declared.

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Abbreviations

AD: Alzheimer disease
ADRD: Alzheimer disease–related dementia
CAPABLE: Community aging in place-advancing better living for elders
SBP: systolic blood pressure

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Protocol

Studying Movement-Related Behavioral Maintenance and Adoption in Real Time: Protocol for an Intensive Ecological Momentary Assessment Study Among Older Adults

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Abstract

Background: Older adults struggle to maintain newly initiated levels of physical activity (PA) or sedentary behavior (SB) and often regress to baseline levels over time. This is partly because health behavior theories that inform interventions rarely address how the changing contexts of daily life influence the processes regulating PA and SB or how those processes differ across the behavior change continuum. Few studies have focused on motivational processes that regulate the dynamic nature of PA and SB adoption and maintenance on microtimescales (ie, across minutes, hours, or days).

Objective: The overarching goal of Project Studying Maintenance and Adoption in Real Time (SMART) is to determine the motivational processes that regulate behavioral adoption versus maintenance over microtimescales, using a *dual process framework* combined with ecological momentary assessment and sensor-based monitoring of behavior. This paper describes the recruitment, enrollment, data collection, and analytics protocols for Project SMART.

Methods: In Project SMART, older adults engaging in at least 30 minutes of moderate-to-vigorous intensity PA per week complete 3 data collection periods over 1 year, with each data collection period lasting 14 days. Across each data collection period, participants wear an ActiGraph GT3X accelerometer (ActiGraph, LLC) on their nondominant waist and an ActivPAL micro4 accelerometer (PAL Technologies, Ltd) on their anterior thigh to measure PA and SB, respectively. Ecological momentary assessment questionnaires are randomly delivered via smartphone 10 times per day on 4 selected days in each data collection period and assess reflective processes (eg, evaluating one's efficacy and exerting self-control) and reactive processes (eg, contextual cues) within the dual process framework. At the beginning and end of each data collection period, participants complete a computer-based questionnaire to learn more about their typical motivation for PA and SB, physical and mental health, and life events over the course of the study.

Results: Recruitment and enrollment began in January 2021; enrollment in the first data collection period was completed by February 2022; and all participants completed their second and third data collection by July 2022 and December 2022, respectively. Data were collected from 202 older adults during the first data collection period, with approximate retention rates of 90.1% (n=182) during the second data collection period and 88.1% (n=178) during the third data collection period. Multilevel models and mixed-effects location scale modeling will be used to evaluate the study aims.

Conclusions: Project SMART seeks to predict and model the adoption and maintenance of optimal levels of PA and SB among older adults. In turn, this will inform the future delivery of personalized intervention content under conditions where the content will be most effective to promote sustained behavior change among older adults.

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KEYWORDS

physical activity; sedentary behavior; aging; multiburst design; ambulatory assessment; experience sampling method; accelerometers; stage of change; dual process; motivation; mobile phone

Introduction

Background

By 2035, the number of older adults is expected to outnumber children for the first time in the United States [1]. As our society ages, strategies are needed to promote the health and well-being among older adults. Physical activity (PA) offers many physical and mental health benefits [2], yet adults aged ≥60 years are the least active and most sedentary segment of the population [3,4]. Accelerometer-derived data suggest that the average older adult engages in no more than 10 minutes of moderate-to-vigorous intensity PA per day [5]. In addition, most older adults spend 60% to 85% of their waking hours (approximately 9.4 hours each day) engaged in sedentary behavior (SB) [6]. Although short-term interventions have increased PA or decreased SB, individuals often struggle to sustain new behavior patterns in the long term [7,8]. The fact that interventions often fail to have enduring effects on long-term behavior change represents a substantial challenge to health promotion in older adulthood.

Limitations of Contemporary Theoretical Frameworks

The lack of sustained intervention effectiveness is partly because health behavior theories that inform interventions rarely address how the changing contexts of daily life influence the processes regulating PA and SB or how those processes differ across the behavioral sequence from adoption to maintenance [9]. These are necessary considerations because (1) PA and SB occur within and across days, with optimal levels of these behaviors ideally maintained across the life span, and (2) these behaviors are partly driven by temporal and situational cues such as location, social context, and affective states that rapidly change over time [10]. Moreover, there is a growing body of research that suggests that different pathways guide behavior adoption and maintenance [11-13]. Thus, there is a critical gap in understanding the factors that drive adoption versus maintenance within the context of PA and SB as dynamic, time-varying behaviors. Understanding microtemporal factors (ie, factors that unfold over minutes, hours, and days) within everyday life and how the temporal dynamics of motivational processes contribute to health behavior adoption and maintenance is essential for developing effective behavioral interventions [14].

Dual Process Models

Dual process models represent a viable framework for investigating microtemporal processes regulating behavioral adoption and maintenance. These models categorize behavioral determinants as either *reflective processes* (intentional, deliberative, slow, and effortful) or *reactive processes* (nonconscious, automatic, fast, and effortless) [15-17]. Reflective processes encompass motivational factors central to many contemporary health behavior theories (eg, attitudes toward a behavior, confidence to perform a behavior, and self-monitoring of goals) [18]. Reflective processes often rely on self-regulation (eg, regulating emotions, coping with stress, managing demands, or exerting self-control) to override a dominant, unwanted behavioral response and translate intentions into goal-directed behavior [19]. Reactive processes represent automatic associations spontaneously activated by stimuli within one's environment (eg, physical location, surrounding people, and affective state) [20,21].

To adopt a new behavior, a person would likely need controlled effort; willpower and ultimately, a conscious decision to replace the habitual, undesired behavior in a given context. The deliberative overriding of cues and the undesired habitual response would require considerable self-control resources and self-regulatory skills [22,23]. Therefore, strong reflective processes are needed when adopting a new behavior [24-26]. However, once a behavior is well learned and automatic, reactive processes likely dominate the motivations underlying the behavior [27,28], thus promoting behavioral efficiency and making long-term continued behavioral engagement more likely [29,30]. Strong reactive processes are likely needed to maintain engagement in a behavior [11,12].

Studying Maintenance and Adoption in Real Time

To address existing knowledge gaps, Project Studying Maintenance and Adoption in Real Time (SMART) was designed to test a dual process model mapping the microtemporal mechanisms regulating PA and SB along the continuum from adoption to maintenance in older adults. To accomplish the overall objective, ecological momentary assessment (EMA) methodology and sensor-based monitoring of behavior will be used to intensively capture motivation and behavior over microtimescales and to examine differences in the microtemporal processes underlying the adoption and maintenance of older adults' PA and SB. Specific research questions to be addressed in this study include the following:

1. To what extent do momentary reflective and reactive motivational processes differentially predict subsequent PA and SB among behavioral adopters and maintainers?
2. To what extent do subject-level patterns in reflective and reactive motivational processes predict behavioral adoption versus maintenance at each wave and across the entire year?
3. How do reflective and reactive motivational processes and behavioral patterns predict change in adopter or maintainer status from wave to wave?

The purpose of this paper is to present the protocol for Project SMART.

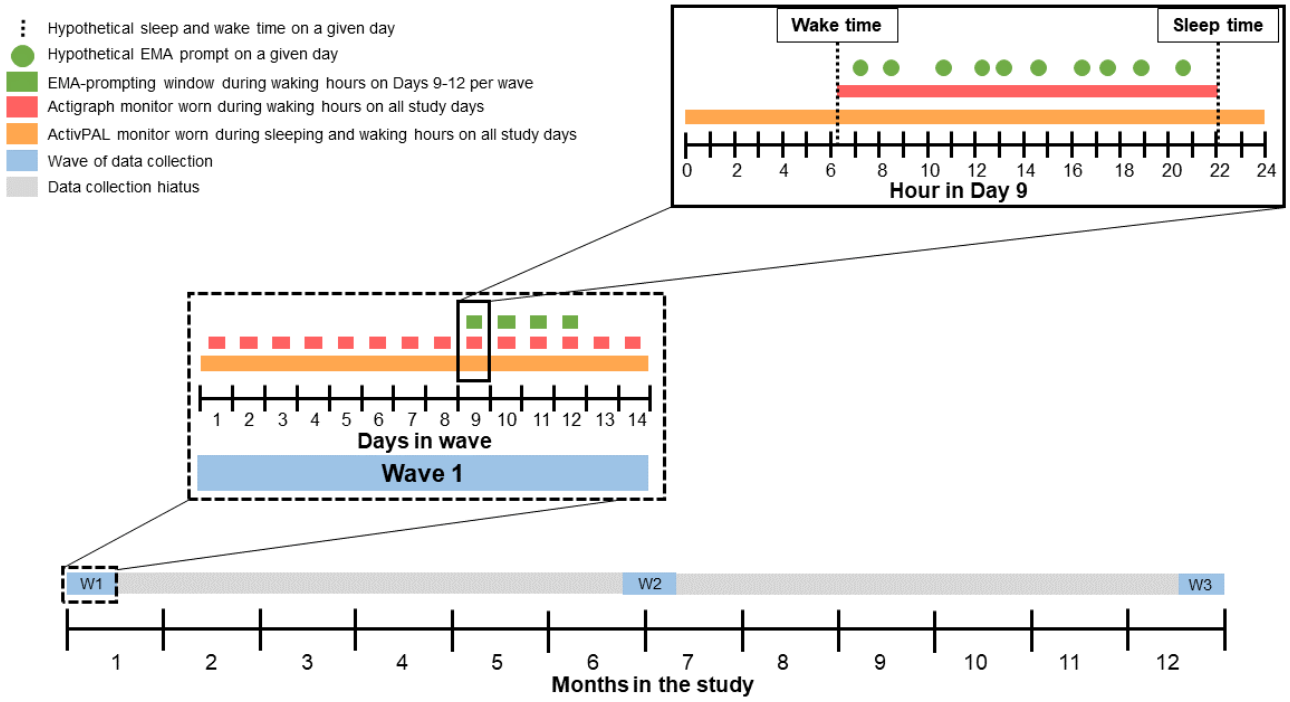
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Methods

Project Overview

Project SMART is a measurement burst design of physically active older adults living in Guilford County, North Carolina. Participants complete three 14-day data collection periods spaced out over the course of 1 year. For the duration of each data collection period, waist-worn and thigh-worn accelerometers measure participants' PA and SB, respectively. In addition, on days 9 to 12 of each data collection period, participants complete an EMA protocol in which they use a loaned smartphone to answer 10 brief questionnaires per day assessing current behavior, context, feeling states, demands, and motivation to engage in PA and limit SB over the next hour. Figure 1 provides an overview of the study's design and procedures. Project SMART began enrolling participants in January 2021.

Figure 1. Overview of the study design. EMA: ecological momentary assessment.



Target Population and Eligibility

We aimed to enroll 200 older adults who are aged >60 years; living in Guilford County, North Carolina; and currently engage in ≥30 minutes of moderate-to-vigorous intensity PA. Within that sample, we aimed to have approximately 50% (100/200) of older adults classified as PA adopters and 50% (100/200) of older adults classified as PA maintainers through initial and back-end classification (details about the classification are provided in the following sections). We chose minimum levels of PA as the inclusion criteria for behavioral adopters and maintainers rather than levels of SB, because of the relatively high volume and normal distribution of SB in older adults [3,6]. By prioritizing PA adopters and maintainers, we can ensure adequate group numbers, given the frequent low levels of PA among older adults. Adopter or maintainer status classification is repeated at each wave. Exclusion criteria for all participants are the following: (1) unable to speak or read English fluently, (2) functional limitations that prevent older adults from standing or walking on their own for at least 10 consecutive minutes, (3) unable to use a smartphone's basic functions, (4) unable to hear the auditory signal on the study smartphone, (5) planning to move outside of Guilford County within the next year, or (6) a score indicating impaired cognitive status on a consolidated mental status screener [31].

Sample Size, Recruitment, and Retention

Sample estimation was performed using Monte Carlo simulations [32], with the expected parameter values derived from aim 1 and aim 2 models fit using our preliminary data (39 participants; 10 observations/day; 4 days). Although missing data in EMA studies of older adults are typically low (ie, almost 90% of EMA studies in older adults achieve compliance of ≥80%) and our preliminary data showed a 96% EMA compliance rate, we conducted simulations using varying patterns of missingness (0%-30%) at varying likelihoods (5%-80%). If missingness occurs at the highest anticipated limits—70 participants per behavioral status group, providing 5 to 7 observations per day over 4 days—we would still obtain 20 to 28 observations per person at each wave. For the study, α was set at .05, and minimum acceptable power was set to 0.80. Given a maximum sample size of 200 participants per model (with simulation sample sizes ranging from 140-200 participants), we achieved power >0.90 for each outcome. To account for possible attrition of up to 30% in both the PA adopter and maintainer groups, we aimed to recruit 100 PA adopters and 100 PA maintainers.

Recruitment efforts targeted fitness centers and older adult programming available within Guildford County, North Carolina. A recruitment method was the electronic distribution of a brief study description with links to videos posted on

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YouTube that further explained the study, showed the necessary study equipment, and addressed frequently asked questions through cooperating organizations' listserves. The second major recruitment method was making in-person announcements at exercise classes geared toward individuals aged ≥60 years. In addition, recruitment efforts were conducted through local media coverage of the study and word of mouth. Depending on the recruitment method, participants' contact information was collected (eg, in-person announcements) or study contact information was provided to individuals.

Owing to the longitudinal nature of this study, retention plans were developed, including (1) obtaining phone numbers, email addresses, and home and mailing addresses of participants and up to 3 other individuals (in case we are unable to reach the participant); (2) scheduling participants for their next data collection period during the current data collection period and providing an appointment reminder card or email after scheduling; (3) sending birthday postcards to participants; and (4) sending study newsletters at 4-month intervals, which are customized to each participant to remind them about their next scheduled data collection period.

Procedures

Interested individuals complete a telephone screening with a research staff member to determine eligibility. Eligible individuals receive additional details about the study and are able to ask any questions to a research staff member. Participants are then scheduled to attend an introductory session. A week before an introductory session, participants receive a link to a questionnaire via email to provide electronic consent for the study and complete a baseline assessment of their motivation for PA and SB, self-reported levels of PA and SB, and demographic and contact information. Participants are asked to complete the baseline assessment before their introductory session.

An introductory session is conducted on day 1. Introductory sessions are conducted every 3 weeks, and as a result, participants are scheduled on a rolling basis. A research staff member meets with individual participants (or participants from the same household) in person on campus, at a community location, or via Zoom (Zoom Video Communications), depending on the participant's preference. Participants meeting via Zoom receive study equipment in person at a community location, or study equipment is delivered to their home. During the introductory session, the research staff member reviews the consent document with the participant and answers any questions. Then, participants are familiarized with the study procedures and trained on 2 accelerometers to be worn for the next 14 days. Accelerometers include an ActiGraph GT3X-BT accelerometer to be worn on their nondominant waist during all waking hours (except when swimming or bathing) to provide a device-based measure of PA and an ActivPAL3 micromonitor to be worn on their thigh during all sleeping and waking hours to provide a device-based measure of SB. Participants begin wearing the activity monitors at the introductory session. Participants are given a sleep and wake time log and an activity monitor log to complete over the 14-day study period. On the sleep and wake time log, participants indicate for each day the time they got out of bed to start their day (ie, wake time) and the time they began trying to fall asleep at the end of the day (ie, sleep time). On the activity monitor log, participants report any waking times during which they were not wearing their activity monitor and a brief explanation of the reason. These logs will be used to validate activity monitor nonwear algorithms.

A week later, on day 8, a research staff member meets the participant or participants again (in person or via Zoom) to train them on how to use a smartphone preloaded with a commercially available, app, MovisensXS, on which they answer brief EMA questionnaires. To ensure that the MovisensXS app is functioning as intended, all participants are loaned a Motorola Moto G Power mobile phone, a compatible device for the MovisensXS app. Participants receive a practice questionnaire at 7:30 PM that same evening to practice accessing the questionnaire and familiarizing themselves with the questions and response formats. The practice questionnaire will not be included in the analytic data set.

On days 9 to 12, participants receive prompts to complete the EMA questionnaire 10 times per day as part of the study procedures. Participants select 1 of 3 EMA prompting schedules for the data collection period based on their self-reported usual wake time. Available EMA prompting schedules deliver questionnaires between 7 AM and 9 PM, between 8 AM and 10 PM, or between 9 AM and 11 PM. Across all prompting schedules, the day is divided into intervals of 1 hour and 25 minutes. Participants receive 1 EMA prompt randomly during each interval. There is an imposed minimum 30-minute buffer period between the random EMA prompts. Participants are alerted to the EMA prompt via an auditory signal. Participants can adjust the mobile phone volume but are encouraged, when able, to have the mobile phone volume turned up to maximum. Upon hearing a prompt, participants are asked to complete a brief EMA questionnaire on the mobile phone. If no entry is made, the app emits up to 3 reminder signals at 5-minute intervals. If a signal occurs during an incompatible activity (eg, driving or sleeping), participants are instructed to ignore it or complete that activity before answering. Each EMA questionnaire contains 20 items and is expected to take 2 to 3 minutes to complete (refer to the *EMAMeasures* section for details). Upon going to bed on day 12, participants will have completed the EMA protocol but continue to wear their activity monitors until waking on day 15.

On day 15, participants return their equipment at an in-person appointment or mail the equipment back to the research team using a prepaid United Parcel Service envelope provided to them. Participants also complete a post–data collection period questionnaire, which assesses life events, affective experiences during movement behaviors, behavior over the data collection period, and feedback about the data collection period.

Study procedures are identical for each data collection period, except that, at the second and third data collection periods, participants are given the option to complete a 1-hour, condensed training session reviewing both the activity monitors and smartphone on day 1 as opposed to 2 separate 1-hour training sessions spaced through the data collection period.

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For their participation in the study, participants can earn up to US $100 for each data collection period. Participants are compensated with US $60 for completing the data collection period. If participants answer at least 80% of the questionnaires on the smartphone, they receive US $40 as bonus. If participants complete all 3 data collection periods, they receive US $40 as bonus at the third data collection period. Therefore, participants can earn up to US $340 for this study.

Measures

Adopter and Maintainer Status

Overview

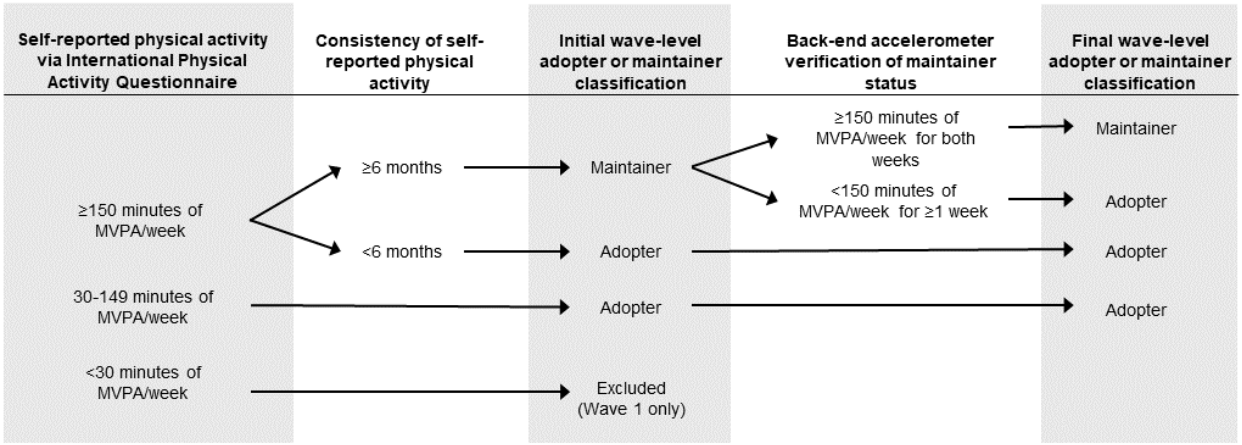
To determine adopter and maintainer status, we use a staged classification model using self-reported behavior initially, with subsequent selective verification via accelerometer. Overall, 2 weeks of accelerometer data will be collected to more reliably differentiate adopters and maintainers, given that self-report measures are subject to recall biases and social desirability [33] and having only 1 week of accelerometer data may not provide an accurate representation of participants' typical levels of PA and SB.

PA Adopter and Maintainer Status

Initial eligibility based on PA level is determined during the telephone screening before study enrollment using items assessing moderate-to-vigorous intensity PA from the International Physical Activity Questionnaire Short Form [34]. Items include the number of days in the past 7 days in which participants engaged in moderate-to-vigorous intensity PA and the typical amount of time spent engaged in that activity on one of those days. Individuals engaging in <30 minutes of moderate-to-vigorous intensity PA over the past 7 days are excluded. Here, 30 minutes was chosen as the minimum level of PA to increase the likelihood of capturing moments of PA during the wave (to minimize the extent to which we have a skewed distribution for data analysis where PA serves as the outcome).

Then, during the administration of the baseline electronic questionnaire, participants will complete the Physical Activity Stage of Change Questionnaire [35], where they indicate whether they are currently engaging in 150 minutes of PA per week and, if so, how long they have been engaging in that level of PA. Individuals indicating <150 minutes of moderate-to-vigorous intensity PA per week will be classified as adopters. Those indicting that they engage in ≥150 minutes of moderate-to-vigorous intensity PA but for <6 months will also be classified as adopters. Those indicating ≥6 months of that PA level will be categorized as maintainers. As overestimation of PA is a common methodological weakness associated with self-reported, retrospective measures of PA [33], PA maintainer status will be confirmed via accelerometry. On the back end of each wave of data collection, maintainer status will be confirmed by examining ActiGraph-derived minutes of moderate-to-vigorous intensity PA during the wave. Participants who meet the 2018 US Federal PA guidelines according to ActiGraph-derived data during both weeks of data collection will remain as maintainers. Those who do not meet 2018 US Federal PA guidelines according to ActiGraph-derived data for one or both weeks are recategorized as adopters. The staged classification model is depicted in Figure 2. This initial and back-end classification will be performed at each data collection period.

Figure 2. Overview of adopter or maintainer classification procedures at each data collection period. MVPA: moderate-to-vigorous intensity physical activity.



SB Reduction Adopter and Maintainer Status

Although our inclusion criteria are based on PA adopter and maintainer status, we also determine SB reduction adopter and maintainer status via the baseline questionnaire before each data collection period using items from the International Physical Activity Questionnaire [34], assessing weekday and weekend-day SB. Those indicating sitting for >8 hours per day will be considered as SB reduction adopters. Individuals indicating sitting for ≤8 hours per day for <6 months are also categorized as adopters; those sitting for ≤8 hours per day for ≥6 months are classified as maintainers. We confirm SB reduction adopter or maintainer status using ActivPAL-derived data and follow similar recategorization procedures for PA. We chose sitting for ≤8 hours per day as the cutoff for adopter or maintainer status because older adults who sit for >8 hours per day have high risk for premature death and other chronic conditions [36].

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EMA Measures

EMA measures real-time experiences of reflective and reactive factors (refer to Multimedia Appendix 1 for details about reflective and reactive EMA items). EMA data are stored on the study-provided mobile phone after each entry and uploaded to a secure server when a participant enters a Wi-Fi–enabled area. If a participant does not have access to Wi-Fi, all responses are stored on the mobile phone until uploaded by a research assistant upon completion of the data collection period. All EMA items are either taken directly or modified from established measures. Construct-general (instead of behavior-specific) reflective EMA items begin with the stem, "Right before the phone went off..." to capture momentary reports. Each construct-general reflective factor is assessed using a single item appearing in every EMA prompt. Construct-general reflective EMA items will assess momentary self-efficacy [37], deliberation [38], self-control [39], demands [40], stress coping [41], and emotion regulation [42]. In addition, we also assess behavior-specific reflective factors through EMA. Behavior-specific reflective factors include single-item assessments of intentions, self-efficacy, and planning to engage in PA and reduce SB over the next hour [43,44]. At each EMA prompt, 2 items assessing behavior-specific reflective factors are randomly delivered to participants. Therefore, each behavior-specific reflective factor will be assessed 3 to 4 times per day. Reactive EMA items will assess current positive and negative affect. Positive and negative affect assessments each use a domain-specific approach assessing 5 affective domains; however, each EMA prompt will only contain 3 affect-related items randomly delivered. The average of the available items for each construct will be used to create momentary positive and negative affect composite scores. Additional reactive factors include current functional stability of habits (1 item), physical context (2 items), and social context (1 item) at each EMA prompt [45,46]. Each EMA prompt is date and time stamped to assess the temporal context. Temporal context data will be used to create dummy-coded variables related to the day of week (ie, weekend day vs weekday) and time of day (eg, morning vs other times of day). Participants also self-report their behavior at every EMA prompt (2 items). Each EMA prompt contains 20 items and takes 2 to 3 minutes to complete.

Device-Based PA and SB

The ActiGraph GT3X-BT accelerometer provides a device-based measure of PA. Participants are instructed to wear the ActiGraph device on their nondominant waist during all waking hours. If participants engage in activities where the monitor could get wet (eg, swimming and showering or bathing), they are instructed to remove it. Data are collected in 30-second epochs. The ActiGraph has been used extensively in large epidemiologic studies to assess PA and validated in both laboratory and field settings [3,5]. Existing count-based intensity thresholds inform time spent in specific intensities of PA. The count threshold for moderate-to-vigorous intensity PA (≥2020 counts/min) was designed and validated specifically to assess PA in populations across the adult life span and has been used extensively in epidemiologic studies and intervention trials [3]. PA is operationalized as the total time spent engaged in moderate-to-vigorous intensity PA in the 60 minutes after the EMA prompt. Any occasion where the ActiGraph records 0 minutes of valid wear time in the 60 minutes after the EMA prompt will be considered as nonwear and coded as missing data. Accelerometer recordings will be date and time stamped to link with EMA data.

The ActivPAL3 microaccelerometer provides a device-based measure of SB. Participants will be instructed to wear it on their anterior thigh during all sleeping and waking hours. Participants' ActivPALs are waterproofed using heat-sealed polymer plastic tubing to ensure that wearing it during water-based activities does not damage the monitor. Owing to the placement of the ActivPAL on the thigh, the monitor is better able to detect different postures (ie, sitting, lying, and standing) compared with waist-worn accelerometers such as the ActiGraph [47]. The ActivPAL has been used in large epidemiologic studies and intervention trials and has undergone validation in both laboratory and field settings [4,48,49]. ActivPAL uses proprietary algorithms to categorize behavior in 15-second epochs as time spent in SB. SB is operationalized as total time spent engaged in SB in the 60 minutes after the EMA prompt. Any occasions where the ActivPAL was not worn for the entire 60 minutes after the EMA prompt will be considered as nonwear and coded as missing data.

Data Analysis Plan

Overview

An overview of key study measures and their role in data analysis is presented in Table 1.

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Table 1. Overview of key study measures and their role in data analysis.

Construct	Measure	Aim 1	Aim 2		Aim 3
			Hypothesis 2a	Hypothesis 2b	
Reflective factors	• EMA[a] (10 prompts/day)	Predictor	• Stage 1—outcome • Stage 2—predictor	• Stage 1—predictor	Predictor
Reactive factors	• EMA (10 prompts/day)	Predictor	• Stage 1—outcome • Stage 2—predictor	• Stage 1—predictor	Predictor
Physical activity	• ActiGraph GT3X-BT	Outcome	• N/A[b]	• Stage 1—outcome • Stage 2—predictor	Predictor
Sedentary behavior	• ActivPAL3 micro	Outcome	• N/A	• Stage 1—outcome • Stage 2—predictor	Predictor
Adopter or maintainer status	• Initial self-report classification—International Physical Activity Questionnaire • Back-end accelerometer classification—ActiGraph GT3X-BT and ActivPAL3 micro	Moderator	• Stage 2—outcome	• Stage 2—outcome	Outcome

[a]EMA: ecological momentary assessment.

[b]N/A: not applicable.

Aim-1 Analytic Plan

Hierarchical linear modeling [50] will be used to determine the extent to which momentary reflective and reactive motivational processes are associated with subsequent PA and SB in the 60 minutes after the EMA prompt. Separate, 2-level (observations within participants) random effects models will be estimated for both PA and SB, with only 1 reflective or reactive factor tested at a time, resulting in a total of 18 reflective factor models and 10 reactive factor models. Reflective and reactive variables will be person-mean centered at level 1 and grand-mean centered at level 2 to partition variance in outcomes owing to within-subject changes and between-subject differences, respectively [51]. Maintainer status at baseline will be entered as a person-level covariate; both within-level and cross-level interactions with reflective and reactive variables will be tested. In addition, it is not uncommon for PA data to be positively skewed. Should model assumptions concerning normality be violated, we will log transform dependent variables and refit the model or models or shift to hierarchical generalized linear modeling should a non-Gaussian link function be more appropriate [50]. The fixed effects for interactions between maintainer status and reflective and reactive variables on PA and SB will be of primary interest in investigating this aim. It is because of our specific interest in these interactions that we will not include multiple reflective and reactive factors in the same model. Finally, given the number of model parameters to be estimated across all models, we will use false discovery rate to maintain a type-1 error rate within acceptable levels (0.05) while limiting commensurate type-2 error inflation that occurs with other techniques used to control family-wise error rates (eg, Bonferroni correction) [52].

Aim-2 Analytic Plan

Aim 2 is designed to determine the extent to which subject-level patterns in reflective and reactive motivational processes predict behavioral adoption versus maintenance. Analyses for aim 2 will use a novel, 2-stage approach for each hypothesis using the stand-alone program, MixWILD [53]. In stage 1, mixed-effects location scale modeling [54,55] is used to model between-subject and within-subject variability in momentary reflective and reactive motivational processes. With heterogeneous variability, mixed-effects location scale modeling extends the typical hierarchical linear model to allow the incorporation of covariates in the modeling of between-subject and within-subject variability. Thus, we will estimate separate 2-level random effects models, controlling for relevant demographic and temporal covariates (refer to information about covariate screening in the previous section). We will estimate effects of random within-subject means (ie, subject-level average of a given construct based on all available occasions of data—location effect), variance (ie, subject-level degree of intraindividual variability on a given construct across all available occasions of data—scale effect), and slope (ie, subject-level average strength of an association between 2 variables across all available occasions of data). Within-subject mean, variance, and slope random effect estimates generated in stage 1 will be retained for use in the stage-2 analysis.

In stage 2, the within-subject mean, variance, and slope estimates of reflective or reactive variables will serve as predictors of likelihood of categorization as a behavioral adopter or maintainer (coded as 0 or 1, respectively) in single-level logistic regression models [53]. Separate single-level logistic regressions will be tested for each wave and for the entire year,

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with associated location and scale estimates incorporated as covariates. The dependent variables will be maintainer status at the end of each wave (for single-wave models) and whether participants retained the classification as a maintainer across all 3 waves (year model). In addressing each hypothesis associated with aim 2, model refinement will be informed by the magnitude and significance of individual beta coefficients and the impact on omnibus model performance assessed via change in –2 log likelihood. Final conditional models will be examined for improvement in classification accuracy over null models and for the individual performance of subject-level mean and variance effects in reflective and reactive factors and subject-level slopes regarding associations between reflective and reactive factors and subsequent behavior in predicting maintainer status. Again, we will use false discovery rate in each stage to control type-2 error rates [52].

Aim-3 Analytic Plan

Aim 3 is designed to investigate the extent to which reflective and reactive motivational processes and behavioral patterns predict change in adopter or maintainer status from wave to wave. For this exploratory aim, we will apply latent Markov modeling to examine predictors of individuals' status change over waves (ie, adopter to maintainer or maintainer to adopter) [56]. Specifically, we will estimate adopter or maintainer status using observed status and test whether subject-level mean, variance, and slope random effects generated in aim-2 analysis can be used to predict the likelihood of transitioning from one status category to another. Given the power concerns and the exploratory nature of this aim, we will test each reflective or reactive variable within a separate model.

Ethics Approval

All study procedures were approved by the University of North Carolina Greensboro institutional review board (20-0216) in January 2020.

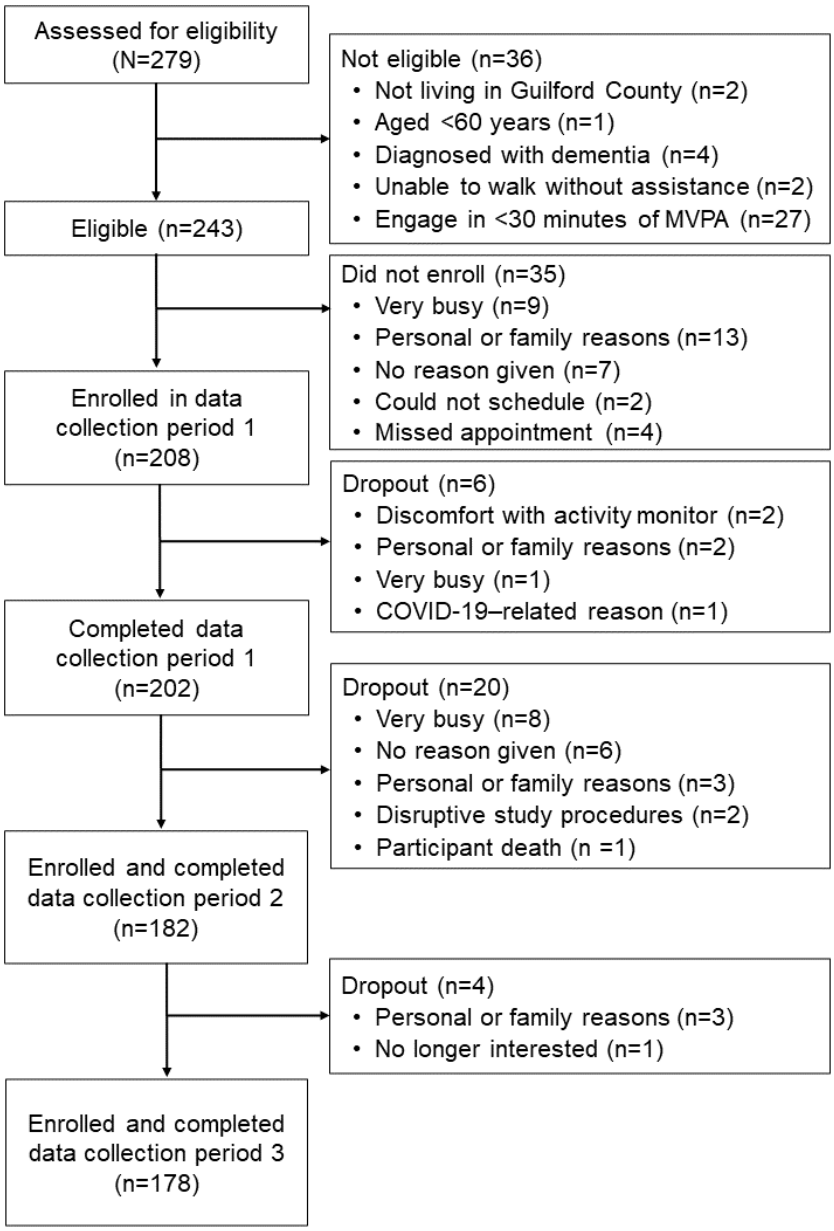
Results

Funding for Project SMART was awarded in April 2020. Additional COVID-19 protocols were approved by the University of North Carolina Greensboro's Office of Research Engagement in December 2020. Participant recruitment and enrollment began in January 2021. As of February 2022, a total of 202 participants enrolled and completed the first data collection period. As of July 2022, overall, 90.1% (182/202) of participants completed their second data collection period. As of December 2022, overall, 88.1% (178/202) of participants completed the third and final data collection period. Among those who dropped out of the study between data collection period 1 and 2 and between 2 and 3 (n=24), reasons for attrition included no longer being interested in the study (n=1, 4%), personal or family reasons (n=6, 25%), being very busy (n=8, 33%), having found the smartphone protocol to be disruptive (n=2, 8%), or no reason was given as they were unable to be contacted (n=6, 25%). A participant (1/24, 4%) also passed away during a scheduled break from data collection between data collection periods 1 and 2. A flow diagram showing participant progress through the recruitment, screening, enrollment, and data collection processes is shown in Figure 3.

Of those who enrolled in and completed the first data collection period and provided relevant information, most identified as female (female: 142/199, 71.4%; male: 57/199, 28.6%) and White (Asian: 1/199, 0.5%; Black or African American: 47/199, 23.6%; White: 148/199, 74.4%; and ≥2 races: 3/199, 1.5%). The average age of the sample was 69.9 (SD 5.7; range 60-85) years. Most participants were overweight (61/194, 31.4%) or obese (49/194, 25.3%; mean BMI 27.1, SD 5.5 kg/m^2). The median annual income in the sample was US $60,000 to US $79,999. Approximately 22.6% (45/199) of the participants reported <US $40,000, and 21.1% (42/199) reported >US $100,000 as annual income. After back-end classification, approximately two-thirds (127/201, 63.2%) of the sample were classified as PA adopters, and the remaining (74/201, 36.8%) were classified as PA maintainers.

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Figure 3. CONSORT (Consolidated Standards of Reporting Trials) flow diagram. MVPA: moderate-to-vigorous intensity physical activity.



Discussion

Summary

Project SMART will determine the motivational processes that regulate behavioral adoption versus maintenance over microtimescales, using a dual process framework combined with EMA and sensor-based monitoring of behavior. Applying a within-subject approach permits a refined examination of motivation-behavior relations as naturally occur in everyday life across the behavior change continuum. This paper describes our approach to understanding these relations.

Methodological Challenges and Decisions

To enhance the likelihood of capturing moments of PA during data collection periods, this study requires that older adults currently engage in at least 30 minutes of self-reported PA per week. There are many older adults who engage in <30 minutes of self-reported PA per week. An important direction for future studies is to examine the motivational processes at play in inactive and insufficiently active older adults. Such studies would complement the proposed study by identifying microtemporal motivational processes regulating health behaviors among older adults at other key points in the behavior change continuum such as contemplation (ie, intending to change behavior in the next 6 months) or preparation (ie, intending to change behavior in the next 30 days and sporadically engaging in desired health behavior) [57]. Future studies expanding our approach to additional points in the behavior change continuum would enable temporally sensitive and context-sensitive interventions applicable to a wide range of older adults. Minimum levels of PA are used as an inclusion criterion rather than levels of SB because of the relatively high volume and normal distribution of SB in older adults [4,6].

In this study, participants are loaned Motorola Moto G Power mobile phones to complete the EMA protocol. This decision was made for several reasons. First, the MovisensXS app is

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available only on Android devices. As most smartphone owners in the United States use an iOS device [58], the research team did not want to exclude a large proportion of potential participants owing to the operating system of the personal device. Second, MovisensXS tests specific devices and operating systems to determine their potential for app performance. The Moto G series of devices has been shown to perform well in executing various features of the MovisensXS app. Furthermore, the MovisensXS app currently requires an operating system of Android 4 or higher. Providing a loaned mobile phone ensures that the recommended operating system is in use and that the device is optimized for performance. Finally, evidence suggests that adults have improved compliance when completing an EMA protocol on a loaned mobile phone as opposed to one's personal device [59]. This may be because participants are more sensitive to novel app-based notifications from a new device as opposed to their personal device on which they may be used to ignoring notifications. In this study, the research team weighed the costs and limitations associated with buying a limited number of devices (n=30) and the benefits associated with optimal app performance. Another important consideration for providing participants with devices is that introducing a novel device may require additional training, depending on the participant population. In this study, because of the need to meet with participants (in person or over Zoom) to train them on wearing the activity monitors, there was a built-in opportunity to train them on the smartphone device as well.

Strength of Project SMART

Previous studies that aimed at understanding the motivational processes regulating movement-related behaviors in older adults have used retrospective or summary-based questionnaires, which may be prone to recall biases and misremembering, to capture typical levels of behavior [10]. Unlike these traditional (between-person) methods, our approach recognizes that movement behaviors change within individuals and across days and that the pattern of variation in movement behaviors may differ between people. Furthermore, this study addresses those methodological weakness by pairing EMA of older adults' current motivation, affect, and contexts with device-based movement behavior. This study capitalizes on the fact that mobile phones have become ubiquitous and easy to use in daily life, even among older adults [60]. Previous studies have documented that smartphone-based EMA studies of movement-related behavior are feasible, acceptable, and valid among diverse groups of older adults [61,62]. However, this is the first known movement behavior EMA study to intensively assess older adults 10 times per day. This study will enhance our knowledge about how EMA can be used among older adults in combination with other types of real-time behavioral measures (ie, accelerometers) to capture momentary, within-day effects of reflective and reactive motivational processes on older adults' PA and SB.

This study will help to generate more definitive conclusions about how reflective and reactive processes operate to influence PA and SB from adoption to maintenance. In addition, this study will not only explore the role of specific levels of constructs (eg, degree of confidence) or the presence of a particular construct (eg, alone vs not alone) but also explore patterns of stability (or instability) in reflective and reactive processes and the influence those patterns have on behavior across the behavior change continuum. This study is a necessary and fundamental step toward refining health behavior theories to predict health behaviors more accurately as they unfold over everyday life [14].

In summary, Project SMART is well suited to address gaps in the current understanding of the motivational processes that regulate movement behaviors along the continuum of adoption to maintenance. By intensively assessing movement behaviors and motivational antecedents, Project SMART aims to generate a great understanding of the within-person, reflective, and reactive motivational processes regulating behavior and thus will provide information to identify intervention targets in the context of everyday life. Specifically, novel intervention approaches such as just-in-time approaches [63] that can respond to participants in real time based on passively collected or participant-reported data may benefit from our more ecologically valid, real-time approach. Ultimately, this study is necessary to develop behavioral interventions that deliver personalized intervention content (eg, motivational messages and prompts to increase PA or reduce SB) under the temporal and contextual contexts when that content will be most effective to promote sustained behavior change among older adults.

Acknowledgments

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Data Availability

The data sets generated and analyzed during this study are available from the corresponding author upon reasonable request.

Authors' Contributions

JPM, LKM, and JDL conceptualized the study. JPM, DJH, KMB, and BLH led data collection. JPM conducted analysis and wrote the manuscript. All authors provided feedback about the draft and reviewed the final manuscript.

Conflicts of Interest

None declared.

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Multimedia Appendix 1
Ecological momentary assessment items.
[DOCX File , 17 KB - resprot_v12i1e47320_app1.docx]

Multimedia Appendix 2
Peer-review reports from Behavioral Medicine, Interventions and Outcomes (BMIO) Study Section Risk, Prevention and Health Behavior Integrated Review Group - Center for Scientific Review (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 157 KB - resprot_v12i1e47320_app2.pdf]

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Abbreviations

EMA: ecological momentary assessment
PA: physical activity
SB: sedentary behavior
SMART: Studying Maintenance and Adoption in Real Time

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Protocol

Adapting Effective mHealth Interventions to Improve Uptake and Adherence to HIV Pre-Exposure Prophylaxis Among Thai Young Men Who Have Sex With Men: Protocol for a Randomized Controlled Trial

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Abstract

Background: Young men who have sex with men (YMSM) are the fastest-growing HIV-positive population worldwide. Thailand has the highest adult HIV seroprevalence in Asia; over 25% of men having sex with men in Bangkok are HIV positive. Pre-exposure prophylaxis (PrEP) is an efficacious HIV prevention strategy recommended for all at-risk individuals. PrEP is highly effective when taken as prescribed, but PrEP utilization rate has been low, and adherence is often inadequate.

Objective: We propose to develop and pilot a multicomponent, technology-based intervention to promote motivation to begin PrEP ("uptake") and sustained adherence to PrEP among HIV-negative Thai YMSM. We will adapt an existing 2-session technology-delivered, motivational interviewing–based intervention to focus on PrEP use in YMSM in Thailand. The resulting intervention is called the Motivational Enhancement System for PrEP Uptake and Adherence (MES-PrEP). We will also develop motivational text messaging (MTM) to send two-way motivational messages to promote PrEP use.

Methods: The proposed study includes 3 phases. Phase 1 includes in-depth interviews with HIV-negative Thai YMSM and providers to explore barriers and facilitators of PrEP initiation and adherence, aiming to inform intervention content. Phase 2 consists of adapting and beta-testing MES-PrEP and MTM for functionality and feasibility using a youth advisory board of Thai YMSM. In Phase 3, we will conduct a pilot randomized controlled trial to evaluate the feasibility, acceptability, and preliminary efficacy of MES-PrEP and MTM to increase PrEP uptake and adherence among Thai YMSM. A total of 60 HIV-negative Thai YMSM who have not started PrEP and 60 YMSM who are on PrEP but not adherent to it will be randomized 2:1 to receive MES-PrEP and MTM (n=40) or standard PrEP counseling (n=20). The feasibility and acceptability of the intervention will be assessed through usage patterns and the System Usability Scale. The preliminary impact will be assessed by evaluating the proportion of PrEP initiation and level of adherence to PrEP. Participants will complete the assessments at baseline and at 1-, 3-, and 6-month postintervention. Biomarkers of adherence to PrEP and biomarkers of HIV and sexually transmitted infections will be collected.

Results: Recruitment for this study began in January 2022 for phase 1. Qualitative interviews were completed with 30 YMSM and 5 clinical providers in May 2022. Phase 3, the pilot feasibility and acceptability trial, began in July 2023. Upon project completion, we shall have developed a highly innovative mobile health intervention to support YMSM using PrEP, which will be ready for testing in a larger efficacy trial.

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Conclusions: This study addresses a critical problem (ie, high HIV incidence and low PrEP use) among Thai YMSM. We are developing 2 potentially synergistic technology-based, theory-driven interventions aimed at maximizing PrEP use. The proposed project has the potential to make significant contributions to advancing HIV prevention research and implementation science.

Trial Registration: ClinicalTrials.gov NCT05243030; https://clinicaltrials.gov/ct2/show/NCT05243030

International Registered Report Identifier (IRRID): DERR1-10.2196/46435

(JMIR Res Protoc 2023;12:e46435) doi:10.2196/46435

KEYWORDS

young men who have sex with men; pre-exposure prophylaxis; PrEP; HIV prevention; mHealth; motivational interviewing; motivational text messaging; Thailand

Introduction

Overview

Men who have sex with men (MSM) are 19 times more likely to be HIV positive than the general population worldwide, with an HIV prevalence of 20%-30% in many countries [1-4]. New infection rates are particularly high in young MSM (YMSM), whose developmental period is associated with increased risk-taking [5]. Thailand has the highest adult HIV seroprevalence in Asia (1.1% in 2017) [6]. The rate of new HIV infections among MSM dramatically increased in the past 20 years [7], with an HIV prevalence rate reaching 30% and an incidence rate of 12 per 100 person-years among those aged 15-21 years [4]. Effective interventions for this high-risk population are critical to the success of the UNAIDS' Fast Track Strategy—ending the AIDS epidemic by 2030 [8].

Pre-exposure prophylaxis (PrEP) is an efficacious HIV prevention strategy. The Centers for Disease Control and Prevention recommends PrEP for all individuals at substantial risk for HIV infection, including HIV-negative MSM [9]. Despite high levels of efficacy when taken as prescribed, PrEP uptake and adherence have been low [10], with high discontinuation rates reported among YMSM [11,12]. The existing literature suggests that YMSM generally lack awareness of PrEP and their uptake motivation and adherence are often inadequate [13-15]. In Thailand, only 9.3% of MSM who were offered PrEP agreed to take it [16]. Commonly cited barriers to initiating or staying on PrEP have included low self-perceived risk, concerns about medication side effects, concerns about maintaining daily oral PrEP regimen, drug use, and HIV stigma [17-19]. Given this evidence of low uptake and high discontinuance rates of PrEP, effective behavior-change interventions are needed to motivate the uptake of and sustain adherence to PrEP among HIV-negative YMSM in Thailand.

Mobile health (mHealth) interventions for high-risk YMSM have the potential to reduce HIV risk behaviors and increase HIV testing rates [20]. These interventions may be particularly well suited for youth because they tend to use computers, cell phones, and texting very frequently [21,22]. Motivational interviewing (MI) is the only evidence-based behavioral intervention that has demonstrated success across the youth HIV prevention and care cascades [23-25]. MI has been linked with improved medication adherence, decreased depression, and decreased risky sexual behaviors in people living with HIV [26]. Interactive text messaging provides ongoing support to maintain motivation for behavior change. Text messaging has a beneficial impact on antiretroviral therapy adherence and provides ongoing behavioral reinforcement for HIV-positive MSM, and the effect is stronger when combined with other interventions [27,28]. Despite the rapid growth of technology in behavioral health, there have been very few technology-based interventions that have specifically targeted HIV-negative YMSM for PrEP uptake and adherence.

Study Aims

We propose to develop and pilot a multicomponent, technology-based intervention to promote both motivation to begin PrEP ("uptake") and sustained adherence to PrEP. Intervention development and testing will be guided by the framework of the ADAPT-ITT model [29]. First, we will adapt an existing 2-session technology-delivered, MI-based intervention to focus on PrEP uptake and adherence in HIV-negative YMSM through a systematic, multistep process [30]. The resulting brief technology-based intervention will be called the Motivational Enhancement System for PrEP Uptake and Adherence (MES-PrEP). We shall develop and pilot-test motivational text messaging (MTM) to promote PrEP uptake and adherence. These intervention components will be integrated to enhance the impact of MES-PrEP through MTM. Second, we will conduct a pilot randomized controlled trial (RCT) to evaluate the feasibility, acceptability, and preliminary efficacy of an intervention combining MES-PrEP and MTM to increase PrEP uptake and adherence in Thai YMSM. This study will pave the way for the successful scale-up of PrEP implementation among MSM in Thailand.

Theoretical Frameworks of Behavior Change

The Information-Motivation-Behavioral Skills (IMB) model and the Socioecological Model will serve as the conceptual frameworks for developing our PrEP mobile intervention. Both theoretical models have been applied to a variety of health promotion topics, including HIV health behaviors [31-33] and PrEP uptake and adherence [34,35]. Although the IMB model includes only individual-level factors, the Socioecological Model captures individual-, structural-, and social-level factors around PrEP use. The proposed intervention is primarily focused on behavior change at the level of the individual and also addresses structural- and social-level factors, such as HIV stigma and depression as well as access to PrEP. According to the IMB model, behavior change results from the joint function of 3 critical elements: accurate information about risk behaviors (eg, risks of not taking PrEP while engaging in unprotected sex),

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the motivation to change behavior, and the perceived behavioral skills necessary to perform the behavior (eg, self-efficacy). For this study, we will develop intervention content to address each core element of the IMB model to facilitate PrEP adoption and adherence among Thai YMSM.

Intervention Components

MES-PrEP Intervention

MES-PrEP is a 2-session computer-delivered intervention. At the start of each session, the participant chooses a preferred character (avatar) who will deliver the intervention in a way that has high fidelity to the most recent edition of MI (MI-3) [36]. The avatar evokes both importance and confidence (key components of readiness or motivation) with MI strategies, such as identifying the pros of behavior change, providing affirmations to reinforce change talk and boost confidence, as well as identifying strengths and resources. MI strategies used within the motivational enhancement system to promote autonomy, boost self-efficacy, and identify social supports are also designed to address HIV stigma and coping. The intervention manages counterchange talk by having the avatar reflect without judgment and providing statements to emphasize autonomy. Importantly, the interactions between the avatar and the participant are synchronous and not reliant on feedback at the completion of the session. Small amounts of education about PrEP are integrated with motivational elements. The intervention is adjusted based on participants' ratings of the perceived importance of and confidence in taking PrEP by routing each participant to different content based on these assessments. For example, participants who perceive initiation of PrEP to be of low importance are branched to decisional balance exercises, while participants who perceive this to be very important receive reinforcement for this perception. Youth, regardless of the level of importance and confidence, are also directed to content designed to explore HIV stigma, including exploration of autonomy, self-efficacy, and social support. Youth are given feedback on their PrEP knowledge assessment followed by information about the protective effect that can result from improved PrEP adherence. Each participant will be asked to set a goal (obtain PrEP prescription, maintain optimal adherence, practice steps, or think about it more), identify possible barriers (eg, concerns around stigma, forgetting, and side effects), and form plans for overcoming these barriers. In the second session (1 month later), participants are assigned to new branches based on whether they felt that they met their goal (reinforcement and plan for continued success), partially met the goal (identifying plans for overcoming barriers), or did not meet the goal. Youth may choose to plan for a new goal or continue the same goal.

MTM Intervention

Text messages are motivational statements promoting the uptake of and adherence to PrEP. We will use LINE for automated but bidirectional MTM to send and receive text messages to promote PrEP initiation and adherence. The program features automatic prompts and response data capturing, requires no internet, and works in the Thai language. The interface program will allow flexibility in the timing and frequency of MTM; message selections from the message libraries; and automatic recording of the message sent, the message received, and whether the message fails. All MTM activities will be performed by an information technologist at the Institute of HIV Research and Innovation. MTM will be sent daily for 1 month, followed by weekly for an additional 5 months (months 2-6) at a time chosen by the participant to promote autonomy. The message content is individualized based on participant responses to the baseline survey. Those participants who indicate that they are "ready" to initiate PrEP and set the goal to take their medications as prescribed will receive MTM to remind them to take PrEP. Those who indicate that they are less ready to take PrEP can choose from alternatives, including taking on-demand PrEP or just thinking about taking PrEP. MTM content for those who are not ready to take PrEP will be individualized based on the participant's choice, that is, a daily message encouraging them to work toward their chosen goal. Participants who are not prescribed PrEP receive daily text messages regarding PrEP effectiveness, HIV risk, and getting prescribed PrEP.

Standard PrEP Counseling (Control Condition)

All study participants will receive one-on-one, face-to-face counseling focused on sexual and behavioral risk assessment for HIV and sexually transmitted infections as well as risk reduction. For those who are at high risk but not yet ready to start PrEP, the focus will be on risk assessment skills or risk perception, awareness of PrEP or postexposure prophylaxis, as well as facilitators and barriers to accessing PrEP. For those already on PrEP, the focus will be on adherence. Counseling is a standard practice within our partner clinics and will last about 15-20 minutes.

Methods

Study Setting

YMSM will be recruited from 2 large clinics in Bangkok, Thailand, to ensure diversity in the respondent population. Thai Red Cross Anonymous Clinic has a large YMSM client population. Over 3500 YMSM (aged 16-25 years) attended this clinic in 2020 [37]. Rainbow Sky Association of Thailand (RSAT) clinic is among the first community-based organizations working to serve key populations in Thailand. RSAT has implemented the Key Population-Led Health Services model since 2015 in a highly populated area in Bangkok to provide HIV-related health services for key populations, including MSM. Annually, approximately 1500 YMSM (aged 16-25 years) have attended the RSAT clinic.

Study Design

There are 3 phases in the study: phase 1 (formative research), phase 2 (intervention adaptation), and phase 3 (pilot RCT).

Phase 1: Formative Research

In-Depth Interviews

We will conduct interviews with 30 HIV-negative Thai YMSM (15 PrEP-naïve YMSM and 15 YMSM on PrEP, including 5 with good adherence) to explore factors related to PrEP uptake and adherence. An interview guide will be created by the investigator team that will provide a general structure for the interview. Based on the IMB model, we will explore their "information" (ie, their knowledge of PrEP and HIV

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transmission risk and their perceived advantages and disadvantages of PrEP), "motivation" (ie, attitudes toward PrEP, perceptions of HIV risk, willingness and interest to use PrEP, reasons for accepting or declining PrEP), and "behavioral skills" (ie, specific behavioral skills relevant to PrEP initiation and adherence, facilitators and barriers to PrEP initiation and adherence, reasons for keeping scheduled appointments or filling PrEP prescription, and reasons for discontinuing or restarting PrEP). We will also explore sources of social support and past successes. Responses will be used to broadly inform intervention content (eg, which modules to include in the intervention framework). The responses will also be used for more specific purposes (eg, response options for barriers and identifying sources of social support). We will also prompt the participants for feedback on intervention content (eg, what they would like to know about PrEP) and delivery (eg, how often they would like to receive text messages to help them take PrEP). Interviews will be audiotaped, transcribed, and translated into English by an independent translator. Interviews will last about 30 minutes.

Youth Advisory Board

A youth advisory board (YAB) of 8-10 eligible Thai YMSM will be identified and assembled by Thailand investigators who have strong relationships with medical providers serving YMSM in Bangkok. YAB members will be high-risk YMSM and selected to ensure diversity in age and socioeconomic status. Members will meet quarterly (with additional meetings as needed). The primary role of the YAB will be providing iterative feedback on study materials, recruitment and retention strategies, intervention approach and content, and disseminating study findings. The operational guidelines will follow the best processes for community-participatory research (eg, establishing the YAB's function and promoting empowerment) [38]. Any inconsistencies in feedback will be resolved during the meeting, or if necessary, via discussions with the Thai-US study team. Detailed notes will be taken during meetings. Study materials will be revised based on YAB feedback.

Phase 2: Adapting and Refining MES-PrEP and MTM

Adapting Motivational Enhancement System for Adherence to Focus on PrEP Uptake and Adherence (Development of "MES-PrEP")

We will build upon existing infrastructure to adapt the 2 components of the intervention (MES-PrEP and MTM) based on responses to interviews. We will use interviews in Phase 1 to adapt the 2-session intervention to promote PrEP. The adaptation process of the Motivational Enhancement System for Adherence will involve two steps: (1) initial programming of sessions of PrEP uptake and adherence intervention in collaboration with the YAB and (2) evaluation of cultural acceptability and intervention content via the YAB and beta-testing. The YMSM will complete 2 MES-PrEP sessions over 1 month.

Developing and Programming MTM

We will use automated, bidirectional ("two-way") MTM via LINE as a tool to support PrEP initiation and adherence [39]. MTM will be developed using information from interviews in Phase 1. Motivational statements promoting PrEP use will be generated from each theme and grouped into one of the 2 MTM libraries—PrEP initiation or PrEP adherence library. Participants will respond to MTM using multiple-choice or open-ended responses, alternated to avoid fatigue. MTM will be sent daily for 1 month, followed by weekly for an additional 5 months (months 2-6) at a time chosen by the participant to promote autonomy.

Beta-Testing of MES-PrEP and MTM

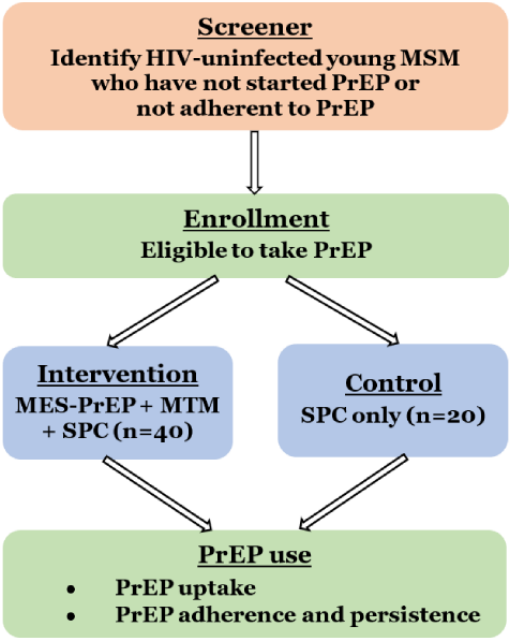
The MES-PrEP system will be beta-tested among 10 HIV-negative Thai YMSM. The youth will complete 2 MES-PrEP sessions over 1 month. Each session will be videotaped. We will also assess the MTM system functionality with the same 10 participants who will receive daily MTM between MES-PrEP sessions, using the 2 message libraries. YMSM on PrEP will receive messages from the PrEP adherence library; PrEP-naïve YMSM will receive messages from the PrEP initiation library. Participants will be asked to respond to the prompt(s). After 24 hours of sending the first text message, the staff will call the participant to check if they have encountered any issues with MTM. A brief face-to-face interview will be conducted to (1) identify and correct any technical or other issues encountered in delivering MTM and MES-PrEP and (2) solicit input on how to refine MTM and MES-PrEP delivery and content.

Phase 3: Pilot RCT Trial

We will launch a pilot RCT (registered with ClinicalTrials.gov registry: NCT05243030) to evaluate the feasibility, acceptability, and preliminary efficacy of MES-PrEP and MTM to increase PrEP uptake and adherence among Thai YMSM. The design is shown in Figure 1. We will enroll 120 YMSM (60 YMSM on PrEP and 60 PrEP-naïve YMSM) from the 2 HIV clinics. The 60 PrEP-naïve YMSM are those who are at high risk and eligible for PrEP but have not decided to start PrEP. We anticipate enrollment of 20 participants per month (for 6 months). Participants will be randomized to receive MES-PrEP and MTM (intervention) versus standard PrEP counseling (control) in a 2:1 ratio, stratified by current use of PrEP (PrEP naive vs PrEP users). The 2:1 allocation was chosen to maximize the collection of feasibility and acceptability data among intervention participants. Separate randomization for YMSM who are currently on PrEP and YMSM who are not starting PrEP will be computer-generated using Qualtrics. The primary outcome will be acceptability, feasibility, as well as PrEP uptake and adherence assessed through Computer-Assisted Self-Interview and Dried Blood Spot testing.

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Figure 1. Pilot randomized controlled trial schema. MES-PrEP: Motivational Enhancement System for Pre-Exposure Prophylaxis; MSM: men who have sex with men; MTM: motivational text messaging; PrEP: pre-exposure prophylaxis; SPC: standard PrEP counseling.



Study Sample

YMSM will be eligible based on inclusion criteria consistent with the Centers for Disease Control and Prevention and Thailand National HIV/AIDS Treatment and Prevention Guidelines [40,41], as follows: (1) age between 16 and 25 years; (2) men who report sex with men in the past 12 months; (3) laboratory-confirmed HIV-negative status; (4) self-reported evidence of being at risk for HIV acquisition, including one of the following in the past 6 months: having sex with an HIV-positive partner, having anal sex without using a condom, being diagnosed with a sexually transmitted infection, or having any illicit drug use (eg, amphetamine-type stimulants); (5) able to understand, read, and speak Thai; and (6) either have not started PrEP (group 1: PrEP naive) or currently on PrEP but not adherent to PrEP (taking ≤3 pills/week) in the past month (group 2: PrEP users). Exclusion criteria are as follows: (1) in a mutually monogamous relationship of >6 months with a partner who recently tested negative for HIV, (2) a serious cognitive or psychiatric problem that would compromise the ability to provide informed consent, and (3) currently enrolled in another HIV intervention study.

Sample Size of Trial

We use PrEP adherence as a calculating variable, as it is a primary outcome. Using the G*power 3.2 program (2-tailed *t* test: “difference between 2 independent means” procedure), a set effect size of 0.80 (large), α=.05, power=0.80, and an allocation ratio of 2:1, the calculated sample size is 58, with 39 participants in the intervention and 19 in the control group. To detect a medium effect size in PrEP adherence (set effect size 0.50), a sample of 144 is required (96 participants in the intervention and 48 in the control group). Our proposed pilot RCT is not an efficacy study, and thus, it is not able to achieve full statistical power (to detect a small-medium effect size).

Recruitment and Enrollment Procedures

Young male clients presenting at the 2 study clinics will be prescreened by the clinic service staff based on the study’s eligibility criteria. Potential participants will be referred to trained research staff for more information and the informed consent process. After providing verbal informed consent, the research staff will determine if the youth meets the inclusion criteria. Those who have an HIV-negative status and meet the other inclusion criteria will be invited to join the study. Clinic staff will facilitate the PrEP evaluation, including anti-HIV testing. Those found to have a confirmed HIV-positive status will undergo an evaluation for antiretroviral therapy by clinic staff (standard of care will be provided for HIV-infected youth). The screening visit, enrollment, and baseline assessment should take place on the same day, or failing that, within 1 week. After signed consent is obtained, participants will be asked to provide a phone number or email address and contact information for a family member or friend who can be called in case the participant cannot be reached by phone, email, or text.

Ethics Approval

This protocol was reviewed and approved by the institutional review boards at the University of Massachusetts Chan Medical School in the United States (H00023523) and Chulalongkorn University in Thailand (Med Chula IRB 919/2564).

Results

Recruitment for this study began in January 2022 for phase 1. Qualitative interviews were completed with 30 YMSM and 5 clinical providers in May 2022. Qualitative data analysis has been completed, and the results were used to inform intervention adaptation and refinement. In phase 2, our team developed 2 motivational text message libraries, which contain nearly 100 motivational text messages; these messages were reviewed by the YAB and the investigator team for improvement and

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refinement. Our team also developed a 2-session intervention (MES-PrEP) to promote PrEP uptake and adherence using the Computerized Intervention Authorizing Software (CIAS 3.0; Steven Ondersma). Individual YAB members completed one-on-one beta-testing of the intervention components and provided additional feedback to guide refinement. Phase 3, the pilot feasibility and acceptability trial, began in July 2023. The findings will be disseminated to stakeholders and communities of interest using peer-reviewed journals, academic conferences, and other communication channels.

Discussion

Expected Outcomes

We anticipate developing 2 integrated mobile interventions to improve PrEP uptake and adherence among YMSM in Thailand. YMSM are among the most at-risk groups for HIV transmission, yet PrEP use has been low, and adherence is often inadequate. Combining MES-PrEP and MTM may help increase the uptake of and sustained adherence to PrEP among HIV-negative Thai YMSM. We will evaluate the feasibility, acceptability, and preliminary efficacy of an mHealth intervention combining MES-PrEP and MTM. Based on our theoretical models of behavior change, we anticipate that the mHealth intervention will be found to be effective, but this is yet to be determined. Our study addresses major challenges related to PrEP use. If successful, this study will be among the first to identify an mHealth intervention for YMSM in Thailand toward improving PrEP use. Our research is integrated within Thailand's national HIV prevention effort. The commitment and ongoing involvement of the Institute of HIV Research and Innovation at a national level will allow this research to serve as a global model for HIV prevention among at-risk groups, especially for low- and middle-income countries.

Planned Next Steps

The project will be conducted to develop an integrated technology-based intervention for HIV-negative Thai YMSM and prepare for a future large-scale RCT. For a fully powered project, we would propose a multisite study to test the efficacy of MES-PrEP and MTM. We will adopt a type-2 effectiveness-implementation design with dual testing of the intervention's effectiveness in achieving the desired outcomes across the PrEP cascade. Additionally, we will gather information on the implementation of technology-based interventions, including cost analysis to assess the relative cost of implementing the intervention.

Conclusions

This study addresses a critical problem (high HIV incidence and low PrEP use) among an at-risk population (YMSM) in Thailand. We are developing 2 potentially synergistic technology-based, theory-driven interventions aimed at maximizing PrEP uptake and sustained PrEP adherence. Even though Thailand was involved in the world's first PrEP clinical trial (iPrEP) and several PrEP demonstration projects, PrEP uptake and adherence remain low in Thailand. Our study addresses major challenges related to PrEP use. It is responsive to the US Preventive Services Task Force's recommendations that call for research on methods to increase PrEP uptake and adherence [30]. If successful, this study will pave the way for the successful scale-up of PrEP implementation among MSM in Thailand.

Acknowledgments

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Data Availability

The data generated during this study are available from the corresponding author upon reasonable request.

Authors' Contributions

BW, NP, and KM wrote the manuscript and designed the study protocol. BW, NP, KM, RJ, CR, ES, and SN are designing the intervention content. RJ led stakeholder engagement and focus groups. All authors provided input for the protocol design and reviewed the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review reports from the HIV/AIDS Intra- and Inter-personal Determinants and Behavioral Interventions Study Section (HIBI) - Risk, Prevention and Health Behavior Integrated Review Group - Center for Scientific Review (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 145 KB - resprot_v12i1e46435_app1.pdf]

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Abbreviations

IMB: Information-Motivation-Behavioral Skills Model
MES-PrEP: Motivational Enhancement System for Pre-Exposure Prophylaxis

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mHealth: mobile health
MI: motivational interviewing
MSM: men who have sex with men
MTM: motivational text messaging
PrEP: pre-exposure prophylaxis
RCT: randomized controlled trial
RSAT: Rainbow Sky Association of Thailand
YAB: youth advisory board
YMSM: young men who have sex with men

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Protocol

Addressing the Chronic Pain–Early Cognitive Decline Comorbidity Among Older Adults: Protocol for the Active Brains Remote Efficacy Trial

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Abstract

Background: Chronic pain and early cognitive decline, which are costly to treat and highly prevalent among older adults, commonly co-occur, exacerbate one another over time, and can accelerate the development and progression of Alzheimer disease and related dementias. We developed the first mind-body activity program (Active Brains [AB]) tailored to the needs of older adults with chronic pain and early cognitive decline. Results from our previous study strongly supported the feasibility of conducting AB remotely and provided evidence for improvements in outcomes.

Objective: We are conducting a single-blinded, National Institutes of Health stage-2, randomized clinical trial to establish the efficacy of AB versus a time-matched and dose-matched education control (Health Enhancement Program [HEP]) in improving self-reported and objective outcomes of physical, cognitive, and emotional functions in 260 participants. The methodology described in this paper was informed by the *lessons learned* from the first year of the trial.

Methods: Participants are identified and recruited through multidisciplinary clinician–referred individuals (eg, pain psychologists and geriatricians), the Rally Research platform, social media, and community partnerships. Interested participants complete eligibility screening and electronic informed consent. Baseline assessments include self-report, performance-based measures (eg, 6-min walk test) and objective measures (eg, Repeatable Battery for the Assessment of Neuropsychological Status). Participants are mailed a wrist-worn ActiGraph device (ActiGraph LLC) to passively monitor objective function (eg, steps) during the week between the baseline assessment and the beginning of the programs, which they continue to wear throughout the programs. After baseline assessments, participants are randomized to either AB or HEP and complete 8 weekly, remote, group sessions with a Massachusetts General Hospital psychologist. The AB group receives a Fitbit (Fitbit Inc) to help reinforce increased activity. Assessments are repeated after the intervention and at the 6-month follow-up. Coprimary outcomes include multimodal physical function (self-report, performance based, and objective). Secondary outcomes are cognitive function (self-report and objective), emotional function, and pain.

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Results: We began recruitment in July 2022 and recruited 37 participants across 4 cohorts. Of them, all (n=37, 100%) have completed the baseline assessment, 26 (70%) have completed the posttest assessment, and 9 (24%) are actively enrolled in the intervention (total dropout: n=2, 5%). In the three cohorts (26/37, 70%) that have completed the AB or HEP, 26 (100%) participants completed all 8 group sessions (including minimal makeups), and watch adherence (1937/2072, 93.48%, average across ActiGraph and Fitbit devices) has been excellent. The fourth cohort is ongoing (9/37, 24%), and we plan to complete enrollment by March 2026.

Conclusions: We aim to establish the efficacy of the AB program over a time-matched and dose-matched control in a live video-based trial and test the mechanisms through theoretically driven mediators and moderators. Findings will inform the development of a future multisite effectiveness-implementation trial.

Trial Registration: ClinicalTrials.gov NCT05373745; https://classic.clinicaltrials.gov/ct2/show/NCT05373745

International Registered Report Identifier (IRRID): DERR1-10.2196/47319

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KEYWORDS

chronic pain; cognitive decline; physical activity; mind-body therapies; aged; telemedicine; randomized clinical trial; mobile phone

Introduction

Background

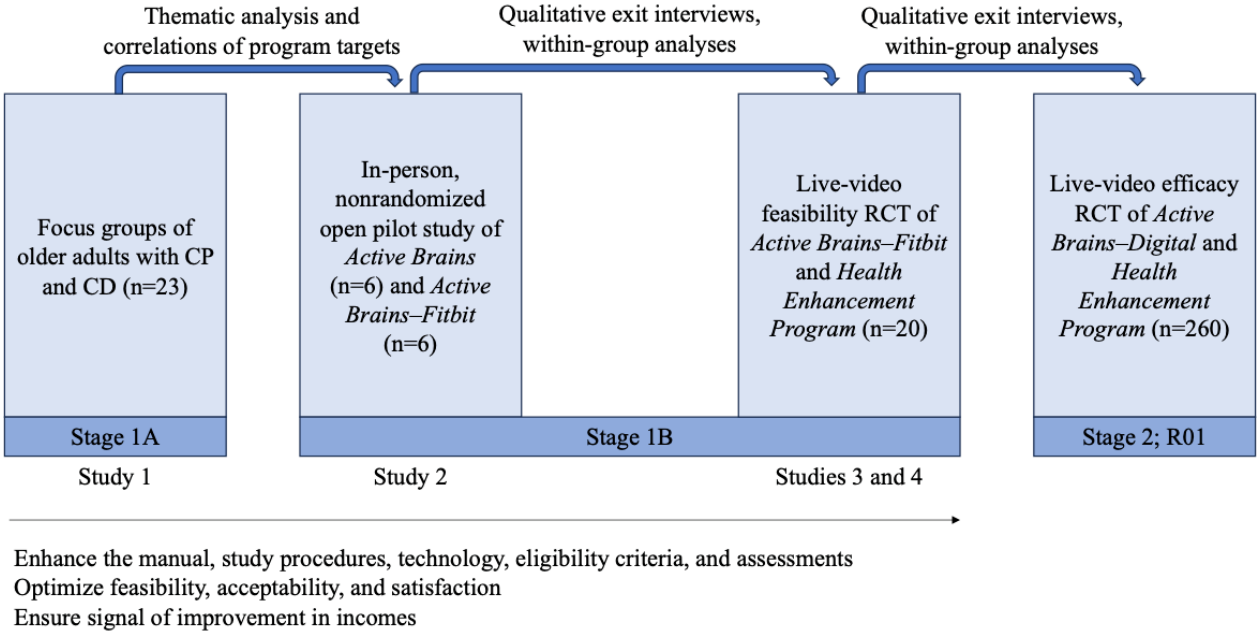
Chronic pain (CP; ie, pain lasting ≥3 mo) and early cognitive decline (ECD; ie, subjective cognitive decline [1] or mild cognitive impairment [2]) commonly co-occur among older adults. An estimated 60% to 75% of people aged >65 years report at least some persistent pain [3]. Older adults with CP are twice as likely to also report ECD [4,5]. The presence of both CP and ECD has an even greater negative impact on older adults' physical and emotional functioning than either of these conditions separately [6]. Pain impairs cognitive function, accelerates ECD, and is a modifiable risk factor for developing Alzheimer disease and related dementias [5,7]. In contrast, ECD alters pain perception, reduces treatment compliance, and increases the risk for subsequent disability [8]. Consequently, older adults with CP along with ECD (CP-ECD) can become caught in a *disability spiral* whereby cognitive, physical, emotional, and social functioning are interrelated and progressively worsen over time [9,10]. Addressing this comorbidity in the ECD stage is an unexplored opportunity to stop the disability spiral and potentially slow the transition toward dementia.

The current model of treating the CP-ECD comorbidity is incomplete [11]. Medications have limited efficacy [11-15], increase the risk of adverse events such as falls [16], and have harmful side effects that can impair cognition [17]. Walking interventions provide a safe, nonpharmacological alternative for older adults [18,19], with benefits for both CP and ECD [20-22]. However, older adults with CP-ECD face numerous barriers to walking, including pain misconceptions (eg, *hurt equals harm*), maladaptive thoughts (eg, fear avoidance and pain catastrophizing), and rigid regimens (eg, interferes with life and very difficult to implement) [23-26]. Mind-body interventions can directly address these barriers to sustained walking by teaching evidence-based skills (eg, diaphragmatic breathing and mindfulness exercises) to manage CP-ECD and engage in values-based activities. Older adults have increasingly embraced technologies for health care (known as *digital health*), in part owing to the COVID-19 pandemic [27]. Digital health technologies can enhance the delivery, accessibility (eg, live video), and reinforcement of mind-body interventions (eg, Fitbit [Fitbit Inc] reinforcement of walking goals) to address the CP-ECD comorbidity.

Our interdisciplinary team has iteratively developed the first web-based, mind-body activity program (Active Brains [AB]) aided by a Fitbit to address the CP-ECD comorbidity among older adults [28]. We followed the National Institutes of Health (NIH) Stage Model [29] and used mixed methods to develop and iteratively optimize the program (Figure 1). We conducted and published the following: (1) qualitative focus groups to understand the needs of older patients with CP-ECD and develop AB [28] (NIH stage 1A); (2) a nonrandomized open pilot study with exit interviews to test the feasibility, satisfaction, and preliminary improvements of AB delivered in-person [30] (NIH stage 1A); (3) adaptation of study procedures for fully remote delivery of AB in response to patient preferences and COVID-19 [31] (NIH stage 1A); and (4) a single-blind feasibility randomized clinical trial (RCT) of AB versus an attention-matched education control (Health Enhancement Program [HEP]), both delivered via live video (NIH stage 1B). Results supported the feasibility, acceptability, credibility, satisfaction, and adherence regarding the web-based AB program and study procedures. Signals of improvement were stronger for AB than for the control in multimodal physical function (step count and self-report) and cognitive function (objective cognitive test and self-reported ECD), emotional function (anxiety), pain intensity, and hypothesized mechanistic targets (mindfulness, coping, catastrophic thoughts about pain, and self-efficacy).

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Figure 1. Iterative stages of Active Brains intervention development. The study described in this paper was informed by studies 1 to 4 shown in the figure. CD: cognitive decline; CP: chronic pain; R01: 1R01AG075899-01; RCT: randomized clinical trial.



Objectives

Building on our promising feasibility RCT, we are conducting a web-based RCT of AB versus an attention-matched education control (HEP) in a fully powered study of older adults with CP-ECD (N=260). Randomization is stratified according to ECD type (subjective vs mild cognitive impairment). Our RCT aims to determine the following: (1) efficacy of AB versus HEP on multimodal physical function (coprimary outcomes), cognitive function, emotional function, and pain intensity (secondary outcomes); (2) sustainability of improvements through 6-month follow-up; and (3) mediators (nonadaptive coping, adaptive coping, social factors, and compensatory strategies) and moderators (ECD type, demographics, and clinical variables) of improvement in coprimary and secondary outcomes. To address the lack of diversity in our pilot studies (100% of participants were White) [28,30], our goal is to recruit >38% ethnoracially diverse older adults to align our sample with the US distribution [32]. In this protocol paper, we have described the enhanced methodology, manualized treatments, outcome assessments, current recruitment, and *lessons learned* from the ongoing RCT so far. AB has the potential to be the first evidence-based program for older adults with CP-ECD, with important implications for the prevention of dementia in this high-risk population.

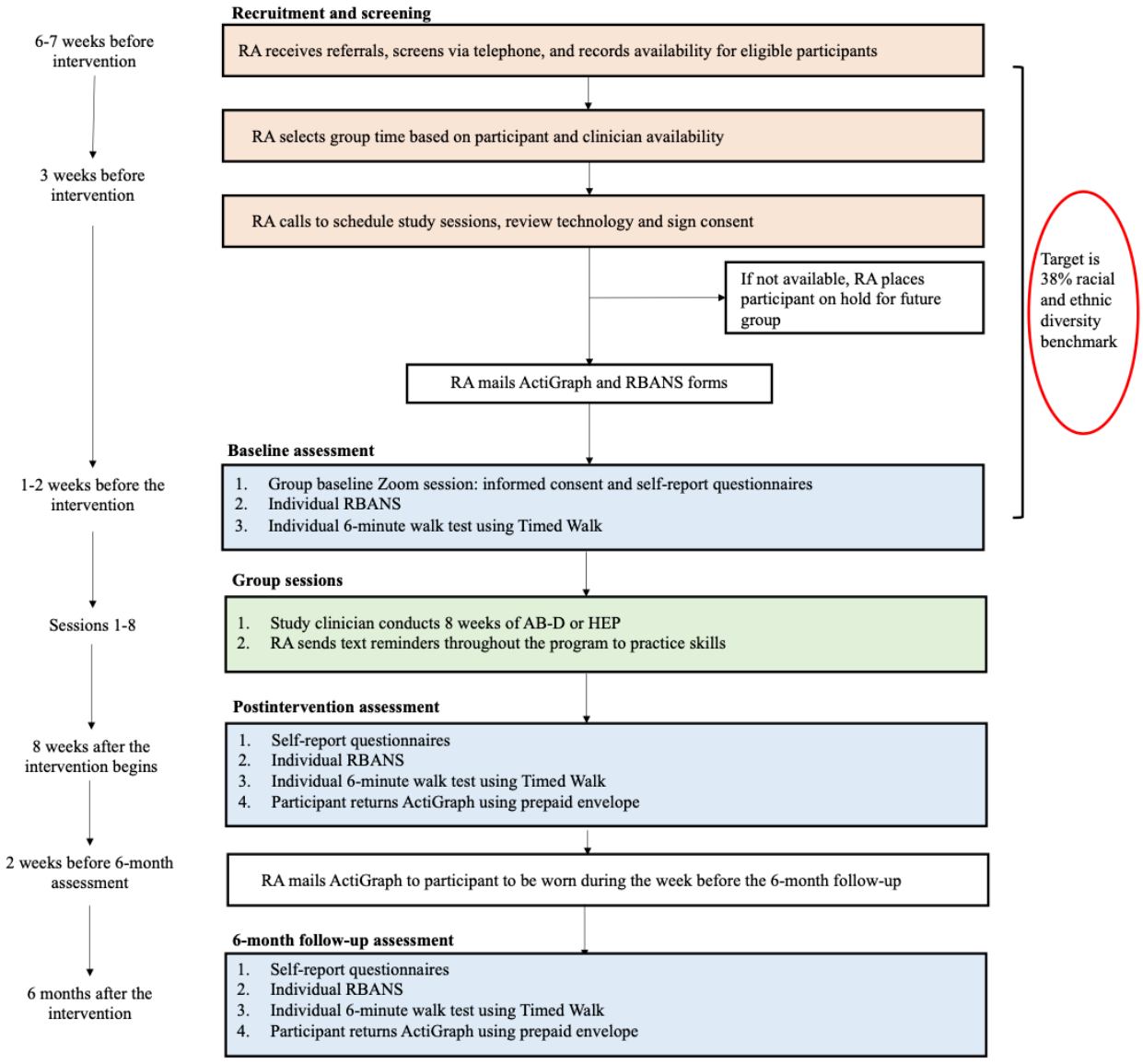
Methods

Overview

We are conducting this single-blind, NIH stage-2, fully powered, parallel-group efficacy RCT of the AB intervention versus the HEP control at the Massachusetts General Hospital (MGH). Figure 2 depicts the study flow and procedural timeline. We followed live video and technology guidelines for older adults with CP and ECD from our previous protocol [31].

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Figure 2. Study design and timeline. AB-D: Active Brains–digital; HEP: Health Enhancement Program; RA: research assistant; RBANS: Repeatable Battery for the Assessment of Neuropsychological Status.



Ethical Considerations

The Mass General Brigham institutional review board (IRB) approved all the study procedures (2021P002811).

Participants

Participants are older adults (aged ≥59 y) with self-reported, nonmalignant, musculoskeletal CP (≥3 mo) and ECD (subjective or mild cognitive impairment). Textbox 1 reports full details about the inclusion and exclusion criteria. These eligibility criteria were informed by similar mind-body trials for CP [33,34] and were refined through our previous AB studies [28,30,31,35]. We included older adults with both ECD types (subjective and mild cognitive impairment) because (1) both types increase the risk for dementia among people with CP [7]; (2) our pilot studies included both ECD types, and we did not observe differences in outcomes or skills use [30,35]; (3) it increases generalizability; and (4) it can help to test moderation by ECD type in this fully powered trial.

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Textbox 1. Study eligibility criteria and rationale.

Inclusion criteria and rationale

- Aged ≥59 y—population under study
- Have self-identified nonmalignant chronic pain for >3 mo—International Association for the Study of Pain criteria [36]
- Early cognitive decline (subjective or mild cognitive impairment)—both are comorbid with chronic pain and are precursors to dementia
- Telephone Interview for Cognitive Status [37] to confirm the absence of severe cognitive decline that would preclude them from meaningfully engaging with the study
- Functional Activities Questionnaire [38] score <9—to ensure that participants are able to meaningfully engage with the program
- Able to perform a 6-min walk test at an accelerated pace—the Active Brains intervention will involve increasing the number of steps for the coprimary physical function outcome measure
- English fluency and literacy—all measures are validated for use in English
- Ability and willingness to participate and use an ActiGraph watch and smartphone app—the study involves use of multiple technologies, and all participants will receive technological support, but the study requires willingness to learn
- Free of concurrent psychotropic or pain medication for at least 2 wk before initiation of treatment or stable on current psychotropic or pain medication for a minimum of 6 wk and willing to maintain a stable dose—changing pain or psychotropic medication introduces an additional intervention that may act as a third variable

Exclusion criteria and rationale

- Diagnosed with dementia or another neurodegenerative disease—these individuals would require a different intervention
- Diagnosed with a medical illness expected to worsen in the next 6 mo (eg, malignancy)—a serious medical illness may act as a third variable
- Active, untreated serious mental illness or substance use disorder—participant safety
- Current, active suicidal ideation—participant safety
- Started a regular mindfulness practice of ≥45 min/wk in the past 6 wk—treatment involves mind-body techniques, and recent initiation of practice would introduce confounds
- Started a course of cognitive behavioral therapy in the last 3 mo—treatment involves cognitive behavioral skills, and recent initiation of treatment would introduce confounds
- Regular use of a digital monitoring device to monitor step count—treatment confound
- Engage in regular exercise for >30 min/d—treatment confound
- Not at risk for falls assessed by the Stopping Elderly Accidents, Deaths, and Injuries Three Key Questions [39,40] or self-reported clearance by a physician for engaging in light physical activity—to ensure the safety of participants

Recruitment and Screening

We began recruiting participants in July 2022. Older adults with self-reported ECD and CP are recruited from MGH clinics (Pain Clinic, Memory Unit, Multicultural Alzheimer Prevention Program, and Geriatric Medicine Unit) through multidisciplinary clinician–referred individuals (ie, pain psychologists and geriatricians), by distributing our IRB-approved study flyer through hospital-wide emails via the Rally Research web-based platform, and via social media. Our entirely web-based trial enables us to recruit from the local community and nationally (eg, memory cafes and organizations for older adults). Research assistants log all incoming referred individuals in a REDCap (Research Electronic Data Capture; Vanderbilt University) database (for storing protected health information) and a recruitment log (for tracking the flow of referred individuals and contact attempts). Research assistants conduct individual phone screening to provide study details and determine eligibility. We embedded an R code in the recruitment flyer that allows referred individuals to complete the initial eligibility screening on their own via a simple REDCap checklist. Research assistants answer questions about the study and collect information about availability with all eligible referred individuals. Self-reported CP and ECD are confirmed by referring clinicians and a review of the patient's medical records when available. Referred individuals that do not meet the study criteria are offered a resource sheet for CP and ECD developed for older patients. The principal investigator confirms all the screening before enrollment and consults with the interdisciplinary team of psychologists, neuropsychologists, and geriatricians as needed.

Inclusion of Ethnoracially Diverse Older Adults

Our team developed strategies to increase the recruitment and retention of ethnoracially diverse older adults. We included recruitment sites within our institution that serve ethnoracially diverse older patients, including the Multicultural Alzheimer Prevention Program and Senior Health. We have consulted with the MGH Community Access, Recruitment, and Engagement Center about a variety of outreach strategies, which include community talks and presentations, tabling, health fairs, individual meetings, and events. We are prioritizing the recruitment of ethnoracially diverse older adults by using recommendations from the literature. These include, but are not

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limited to, the following: (1) developing culturally sensitive and inclusive study materials, (2) exercising flexibility in scheduling and emphasizing study resources to reduce barriers to participation, (3) asking trusted clinicians (ie, physicians, nurses, social workers, psychologists, and medical assistants) and community members to introduce the study to patients, (4) training the staff on culturally sensitive communication and recruitment strategies that focus on building trust and rapport, (5) prioritizing approaching all ethnoracially diverse older patients who present to recruitment sources as feasible, (6) inviting family into the decision-making process and to support participation (eg, reinforce attendance and troubleshoot technology), (7) addressing the stigma associated with CP and ECD, (8) providing tablets and smartphones with data plans to older adults who do not have them, (9) providing one-on-one training to learn technology, and (10) increasing the diversity of study staff [41-45]. If needed, we will expand recruitment to satellite clinics (MGH Dimmock, Chelsea, Revere, and Waltham) and the Boston Medical Center Pain Clinic.

Assessments and Enrollment

Informed Consent and Mailing of Study Materials

After recruiting at least 8 eligible participants (ie, the minimum threshold to start forming a round of groups), research assistants contact each participant to coordinate the informed consent process and mailing of study procedures. A total of 3 weeks before the first AB or HEP session, research assistants conduct 30-minute Zoom (Zoom Video Communications) meetings with participants to: (1) review and sign the electronic consent form, (2) test Zoom and eliminate barriers to web-based participation, (3) download the Timed Walk app [46] (to self-administer the 6-min walk test), (4) schedule the baseline assessments, (5) assess delivery preferences (timing, email, or SMS text) for receiving daily study reminders, (6) collect an address to mail the study materials, and (7) identify a friend or family member to troubleshoot technology if needed. After consent, a research assistant mails the following to each participant: (1) a study welcome letter, (2) a complementary pen and magnet with the study logo and contact information, (3) Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) Update [47] cognitive assessment forms, and (4) a wrist-worn ActiGraph wGT3X-BT (ActiGraph LLC) [48,49] watch and materials (user-friendly instructions and charger) for blinded step count assessment. We provide tablets (to sync watches, respond to surveys, and attend the AB or HEP sessions) to promote equitable participation of older adults who do not own these devices. These participants receive an additional tutorial with a research assistant to set up their tablet. Participants are instructed to leave the study package unopened until the group, baseline assessment Zoom session. So far, all participants have provided informed consent, and all study procedures have been conducted in accordance with our IRB-approved protocol.

Assessments

We selected measures based on the Initiative of Methods, Measurement, and Pain Assessment in Clinical Trials [50] and International Classification of Functioning [51] guidelines for CP clinical trials, our conceptual model [10,52-55], and previous AB studies [28,30]. All outcome measures are assessed at baseline, after the intervention, and at 6-month follow-up. Table 1 reports details about the measures, organized according to construct.

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Table 1. Study measures and constructs.

Categories and subcategories	Time points
Demographic factors	
Date of birth, gender, weight, height, handedness, race or ethnicity, marital status, education level, employment status, income, and concurrent medical therapies	Baseline
Clinical factors	
Type of ECD[a] (subjective or objective), pain diagnoses, pain location, length of chronic pain, comorbid medical conditions, current and history of mental health conditions, current pain medication, current memory medication, and current treatments (eg, physiotherapy and occupational therapy)	Baseline
Coprimary outcomes	
Accelerometer (wrist-worn ActiGraph wGT3X-BT)—measures 7-d average step count [48,49]	Baseline, after the intervention, and 6-mo follow-up
6-min walk test using the Timed Walk app—measures the distance walked in meters at a fast pace for 6 min using smartphone GPS [46]	Baseline, after the intervention, and 6-mo follow-up
PROMIS[b] (version 1.2.8b)—measures the level of difficulty with daily function [56,57]	Baseline, after the intervention, and 6-mo follow-up
Secondary outcomes	
Repeatable Battery for the Assessment of Neuropsychological Status—measures 5 cognitive domains (immediate memory, visuospatial and constructional, language, attention, and delayed memory) and global cognition [47]	Baseline, after the intervention, and 6-mo follow-up
Everyday Cognition Scale—measures self-reported cognitive functioning by comparing current performance on cognitive tasks with that a decade ago [58]	Baseline, after the intervention, and 6-mo follow-up
PROMIS Depression (version 1.0.8b)—measures negative mood, views of self, engagement in daily living, and social components [59]	Baseline, after the intervention, and 6-mo follow-up
PROMIS Anxiety (version 1.08a)—measures fear, worry, hyperarousal, and somatic symptoms [59]	Baseline, after the intervention, and 6-mo follow-up
Numerical Rating Scale—measures pain intensity at rest and during activity during the past week [60]	Baseline, after the intervention, and 6-mo follow-up
PROMIS Pain Interference (version 1.0.8a)—measures the consequences of pain on relevant aspects of life, including social, cognitive, emotional, physical, and recreational activities [56,61]	Baseline, after the intervention, and 6-mo follow-up
The Pain, Enjoyment of Life, and General Activity Scale [62]—measures pain intensity and pain interference in the past week	Baseline, after the intervention, and 6-mo follow-up
Mechanisms	
Quota-based pacing—measures the perceived use of quota-based activity pacing using a 4-item scale adapted from the Activity Pacing Questionnaire [63]	Baseline, after the intervention, and 6-mo follow-up
Memory Compensation Questionnaire—measures the use of cognitive compensatory strategies for actual or perceived memory loss [64,65]	Baseline, after the intervention, and 6-mo follow-up
Pain Catastrophizing Scale—measures hopelessness, helplessness, and rumination about pain [66]	Baseline, after the intervention, and 6-mo follow-up
Tampa Kinesiophobia Scale—measures the fear of activity owing to pain or injury [67]	Baseline, after the intervention, and 6-mo follow-up
Pain Self-Efficacy Questionnaire—measures self-efficacy for performing activities of daily living despite pain [68]	Baseline, after the intervention, and 6-mo follow-up
Self-Compassion Scale—measures self-compassion in the face of stressors or challenges [69]	Baseline, after the intervention, and 6-mo follow-up
Measures of Current Status—measures the ability to engage in a series of general coping skills (eg, relaxation, being aware of tension, expressing needs, confidence in coping, and assertiveness) [70]	Baseline, after the intervention, and 6-mo follow-up
Gratitude Questionnaire—measures the ability to experience gratitude daily [71]	Baseline, after the intervention, and 6-mo follow-up
Toronto Mindfulness Scale—measures self-reported state-level mindfulness [72]	Baseline, after the intervention, and 6-mo follow-up
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Categories and subcategories	Time points
Global Cognitive and Social Engagement—measures the perceived engagement in mentally stimulating social and cognitive activities (involving meaning, learning, challenge, and creativity) and passive activities (eg, watching television)	Baseline, after the intervention, and 6-mo follow-up
NIH[c] Toolbox Loneliness Fixed Form Age 18+ (version 2.0)—measures the perception that one is alone, lonely, or socially isolated from others [73]	Baseline, after the intervention, and 6-mo follow-up
PROMIS Satisfaction with Social Roles and Activities (version 2.0.8a)—measures satisfaction with social roles and responsibilities [74]	Baseline, after the intervention, and 6-mo follow-up
OQ[d] Therapeutic Alliance—assesses participant perceptions about therapeutic alliance [75]	After the intervention

[a]ECD: early cognitive decline.

[b]PROMIS: Patient-Reported Outcomes Measurement Information System.

[c]NIH: National Institutes of Health.

[d]OQ: Outcome Questionnaire.

Self-Report Measures

Participants complete the self-report measures via the web-based REDCap platform during a 60-minute group assessment via Zoom. In our previous AB studies, we learned that group assessments allow our research assistants to efficiently provide technical support with Zoom (eg, connectivity issues) and REDCap (eg, accessing or responding to survey questions) for multiple participants simultaneously. To encourage focus and privacy during the self-reports, the Zoom host mutes all participants and asks them to use the chat or *raise hand* function for help. After completing the surveys, participants have the option of remaining on the call to receive additional technological support from the research assistants. Research assistants review all self-reports for missing data and errors that were not prevented by the REDCap response validation features.

ActiGraph wGT3X-BT

During the group baseline (1-2 wk before the first session), participants open their study package and place the ActiGraph watch on their nondominant wrist to measure step count. Participants are instructed to wear the ActiGraph watch daily (except when bathing) until 1 week after the intervention. Participants sync (using the CentrePoint smartphone app) the watch daily and charge weekly. The research assistants review tips to care for their ActiGraph watch, address common misconceptions (eg, no GPS tracking or on or off switch), and encourage them to contact the study staff for technical support. ActiGraph wGT3X-BT is widely used [49] to measure step count and has demonstrated validity in older adults [76]. Participants receive and wear the ActiGraph watch for 1 more week at the 6-month follow-up and return it in a prepaid envelope.

We estimate an average 7-day step count for each participant, measured by ActiGraph wGT3X-BT at baseline, after the intervention, and at 6-month follow-up using an established protocol [30,34,35]. First, we exclude nonwear (no data) or invalid wear days, which is defined as less than 7 hours of wear time during waking hours [77,78]. Next, we exclude the highest and lowest step-total days to prevent very active or inactive days from skewing average step counts. Finally, we average the remaining valid days (minimum days to calculate average count=3).

RBANS Assessment

After the group assessment, participants complete an individual 30-minute RBANS cognitive assessment with trained clinicians via Zoom. The clinician confirms that participants have received the testing materials (RBANS figure copy and coding sheets) and have secured an ideal testing environment. This includes (1) stable connectivity, (2) full-screen Zoom on a tablet or laptop (no smartphone), (3) clear audio, (4) no environmental (phone is silenced and no background activity) distractions, (5) proper lighting, (6) flat surface to write, (7) screen-sharing capability, and (8) privacy for the duration of the test. Following the established telepractice guidelines [79], the clinician shares their screen to show the stimulus book, takes screenshots for scoring, and instructs participants to mail written items (figure drawing and coding) in a prepaid envelope.

The 6-Minute Walk Test

After completing RBANS, the clinician instructs the participant to complete the 6-minute walk test outside, on flat terrain using Timed Walk. Timed Walk is a GPS-enabled smartphone app, which enables users to measure walking distance within a fixed time frame. The 6-minute walk test performed using Timed Walk is a valid performance-based measure of physical function and presents a reliable alternative to traditional laboratory assessments [46]. The assessment period is complete once the participants call the research assistant with their 6-minute walk test score.

Randomization

A week before the first AB or HEP session, research assistants randomize and enroll participants via phone. Participants are randomly assigned in a 1:1 ratio to AB intervention or HEP control to ensure comparability between groups. The unblinded study biostatistician created the randomization schedule with permuted blocks of random sizes and implemented it in REDCap. Randomization is stratified according to ECD type (subjective vs mild cognitive impairment). To maintain single-arm blinding, study staff and materials refer to AB and HEP as AB1 and AB2, respectfully. Without unblinding, research assistants notify each participant about their group assignment, schedule weekly session times, and provide links to the AB or HEP websites. Research assistants review expectations for attending the group sessions, including the

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following: (1) timeliness, (2) quiet location, (3) respectfulness of others, (4) no multitasking, (5) wearing the watch, (6) having a pen and the manual ready, and (7) responding to daily smartphone surveys to complete home practice. The research assistant mails a printed copy of the program manual to be received by participants before the first group session. Participants in the AB arm receive a Fitbit to wear, starting after session 1 to ensure that step count assessment remains blind in both groups. Participants are considered to be enrolled after completing session 1 of the AB or HEP arms.

Treatment Arms

Overview

We iteratively developed AB and HEP for the specific needs of older adults with CP-ECD through our previous studies [28,30,31,35]. The control (education only; no skills) is dose-matched and time-matched to the intervention. Both treatment arms are group-based and the intervention is delivered by trained clinicians over 8 weeks (90-min sessions) in addition to patients' usual care. Participants receive both a paper copy of the structured treatment manual and access to a digital copy through the program website. Both manuals refer to ECD as *memory-related problems* because it was preferred by patients who participated in our qualitative focus groups to develop AB. Participants are encouraged to take notes in the treatment manuals during the sessions and for home practice to promote comprehension and retention. Treatment completers are those who complete a minimum of 6 out of 8 sessions. If participants are unable to attend a session, they are offered a 15-minute makeup with the clinician via Zoom to review missed content and address adherence barriers as needed.

AB Intervention

Overview

The AB intervention is a multimodal walking program informed by the fear-avoidance model [10]. It integrates relaxation response [52], mindfulness [53], pain-specific cognitive behavioral [54], and operant and physical restoration elements [55]. AB teaches skills to break the *disability spiral* of worsening cognitive, physical, emotional, and social functioning in response to comorbid CP and ECD [9,10]. AB skills include the following: (1) *walking skills* to gradually increase step count through individualized quota-based pacing and goal setting reinforced by a digital monitoring device (Fitbit) linked to valued activities; (2) *mind-body skills* to reduce reactivity to pain or cognitive symptoms through diaphragmatic breathing, body scanning, and mindfulness exercises; (3) *pain-cognition-behavior* awareness skills to educate on myths about CP and ECD and understand the disability spiral; (4) *cognitive functioning skills* to develop cognitive compensatory strategies and increase intellectual stimulation; and (5) *social-emotional functioning skills* to cope with stress or setbacks and increase social factors (obtaining social support and decreasing isolation) through self-compassion, gratitude, and acceptance (Table 2). The goal is to provide patients with coping skills to manage pain and develop compensatory strategies to improve their physical, cognitive, and emotional function.

Table 2. Session outline for the Active Brains (AB) intervention and Health Enhancement Program (HEP) for older adults with chronic pain (CP) and early cognitive decline.

Session	AB topic	AB skills and session content	HEP topic	HEP session content
1	Taking charge of pain and MRP[a]	Deep breathing	Program overview and CP and MRP	Program goals, understanding CP and MRP, how CP and MRP are connected, and the impact of stress
2	Pace yourself	Mindful breathing and quota-based pacing	The connection among CP, MRP, and physical wellness	The connection between CP and MRP
3	Walk all over pain and MRP	Body scan, mindful walking, and gratitude	Sleep and wellness	Healthy sleeping strategies and cognitive and physical health
4	Mindfulness of pain and MRP	Self-compassion and mindful STOP[b]	Exercise and wellness	Physical exercise, maintaining healthy weight, and tips for becoming active
5	Building brain reserve	Mindful focus	Nutrition 1: the basics	Basic nutrition, portion size and calories, and understanding food labels
6	Staying in the upward spiral	Skill review	Nutrition 2: healthy weight and weight loss	Eating healthy meals and snacks, eating out healthy, and weight loss and BMI
7	Feeling connected with others	Love and kindness mindfulness	Managing your health care for CP and MRP	Communicating with physicians, health diary, medical emergencies, and medication adherence
8	Staying on track and maintaining your progress	Mountain mindfulness	Review of AB	Overview of program content

[a]MRP: memory-related problem.

[b]Stop, Take a breath, Observe with curiosity, Proceed mindfully.

In each session of AB, the clinician and participants review previous session material, discuss home practice, solve barriers, learn educational material, practice program skills and apply them to participants' daily lives, and create an individualized walking plan (eg, "I will walk to the park once per day while calling family then do housework until I hit my daily goal of

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1,200 steps.") to achieve their step goal. For home practice, participants execute their walking plan, practice skills for at least 5 minutes per day, and log their adherence via daily SMS text messages sent from Twilio [80]. Participants are encouraged to regularly visit the program website to watch videos that explain core concepts (eg, disability spiral and myths about pain) and listen to clinician-guided recordings of mindfulness skills.

Fitbit and Quota-Based Pacing

Participants randomized to the AB group receive a Fitbit Inspire [81] to wear from the first session through the 6-month follow-up. Fitbit is a user-friendly and commercially available activity watch that enables participants to monitor (updated step count data on the wrist and Fitbit app) and reinforce (motivating reminders to walk and notifications when step goals are achieved) their daily walking. The AB treatment manual contains written instructions and a tutorial video about wearing, charging, and syncing Fitbit daily. Informed by our internal testing, we instruct participants to wear Fitbit on the nondominant wrist below ActiGraph wGT3X-BT and remove Fitbit during activities with repetitive arm movement (eg, gardening and washing dishes) to prevent step count overinflation. To justify wearing 2 activity watches, we explain that ActiGraph is for the research-grade assessment of step count and Fitbit is to reinforce their quota-based pacing plan.

AB participants are taught to increase their daily step count gradually and safely by following evidence-based guidelines for quota-based pacing [55,82]. The research assistant sets each participant's initial goal by calculating a truncated average (removing the highest and lowest observation) step count for valid days (≥7 h/d) measured by Fitbit Inspire during the week after session 1. Each subsequent week, the research assistant updates AB participants' step goal by calculating a weekly truncated average using Fitbit Inspire data synced via the Fitabase web-based platform [83]. AB participants (1) increase their goal by 10% if they achieve their goal, (2) reattempt their goal if they did not achieve their goal for 1 week, or (3) decrease their goal by 10% to 20% if they did not achieve their goal for 2 weeks. Clinicians guide participants in applying AB skills to make the patient's walking plan noncontingent on CP and ECD symptoms or other barriers to achieving their step goal (eg, weather and time). Research assistants routinely monitor ActiGraph and Fitbit adherence using CentrePoint [84] and Fitabase [83] web-based dashboards, respectively. Participants with 24 hours of nonadherence are contacted for reminders and troubleshooting as needed.

Improvements to AB for This Trial

We refined AB based on the results of our pilot feasibility RCT and feedback from participants during exit interviews [35]. First, we streamlined the content in our treatment manual to focus more directly on walking and mindfulness skills. In the updated manual, walking is emphasized as the primary target of AB, and mindfulness is described as a tool to improve coping and support increased activity. Second, we replaced Specific, Measurable, Attainable, Realistic, and Timed (SMART) goals with a simplified walking plan based on feedback from participants stating that the acronym overcomplicated weekly walking goals. Third, we restructured the intervention sessions to incorporate more guided mindfulness practices to support learning before home practice. Similarly, we added structured check-ins at the beginning and summaries at the end of each session to consolidate learning, solve challenges with participants, and encourage skills practice. Fourth, we added information about ActiGraph (for research) and Fitbit (for tracking the daily step goal) to help participants understand the differences between the 2 devices. Fifth, we selected a large font and used a white background with black and dark blue text to maximize contrast, to make the manual more readable for older adults [85]. Sixth, we removed scientific jargon, explained key terms (eg, mindfulness, CP, and ECD) with patient-friendly language, and added figures (eg, to validate that CP-ECD can feel similar to *climbing a mountain* but that gaining AB skills along the way can help). We revised both patient and clinician manuals to ensure that the AB skills are taught to encourage understanding of language in the study outcome measures. Finally, we created animated videos to support the learning of program skills and linked these via a program website throughout the manual.

HEP Education Control

Our previous study provides full details about HEP [31]. Briefly, this time-matched and dose-matched attention control accounts for the effects of time spent, feedback, and support from the study clinician and other group members. It consists of lifestyle education consistent with public health recommendations and standards for health promotion (eg, physical activity, sleep, nutrition, healthy weight, and medical appointments). Our team has successfully used HEP as an active control in multiple previous studies [86-88]. We adapted HEP to include population-specific information about CP and ECD symptoms. Consistent with a similar efficacy trial [89], the HEP participants are instructed to journal for 5-10 minutes per day to match the dose of mind-body skill practice in the AB intervention.

Population-Specific Technology Considerations

Overview

Our web-based trial implements several technological solutions to improve the experience of older participants in our study. The treatment arms are delivered via Zoom, which overcomes cost, transportation, and scheduling as important barriers to care in this population. The ActiGraph watch continuously and passively collects step count, which reduces the burden of assessments. Walking goals are reinforced in real time via Fitbit, which addresses difficulty in planning and initiating behavior change with CP and ECD. To bypass ECD symptoms (ie, forgetfulness, distractibility, and difficulty in planning), participants receive SMS text messages to attend sessions, practice program skills, record home practice, and self-monitor pain interference with daily activities. During enrollment, research assistants help AB participants install a shortcut to our program website on their smartphones to easily access clinician-guided recordings of all mindfulness skills. Our pilot study showed that older adults with CP and ECD benefited from and could use these technologies with high feasibility, acceptability, and satisfaction [35].

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Our previous study [31] describes our protocol for teaching older adults about technologies based on the National Council on Aging guidelines [90]. During enrollment, research assistants assess participants' familiarity with technology (eg, experience with Zoom and devices owned), identify individual preferences for remote communication (eg, SMS text, email, or phone), and develop individualized support plans (eg, specific family members who can help). During training sessions, research assistants clarify the value and rationale of each technology, allow time for experimentation, and avoid common pitfalls for communicating with older adults (eg, speaking very loudly or slowly). Our qualitative study has revealed that scheduled, individualized learning sessions; frequent encouragement; and on-call technical support help older participants overcome any initial lack of technological readiness [35].

Informed by *lessons learned* from our pilot RCT, we refined our procedures to further improve participants' experience with technology. First, we streamlined the written materials in the manual and before-treatment packet on wearing, syncing, and charging the watches. Second, we created a demonstration video about wearing and caring for the watches that participants could easily access on the program website. Third, we increased the involvement of family members and friends to help participants troubleshoot challenges with Zoom, email, and responding to SMS text message surveys. Fourth, participants can receive in-person device setup and training with a research assistant during the baseline period (US $10 is provided for travel). Fifth, participants are encouraged to contact the research assistant with technology-related questions and are offered one-on-one appointments when more extensive troubleshooting or training is required.

Treatment Fidelity

We follow the NIH Science of Behavioral Change guidelines to support treatment fidelity [91]. We have developed structured manuals and standard operating procedures that we revised based on the lessons learned after our feasibility pilot study of AB [35] and similar efficacy trials [86]. All study staff meet weekly to discuss participant progress through the study, including session attendance, watch use, home practice adherence, and any deviations from the treatment protocol. All study clinicians are Doctor of Philosophy level clinical psychologists and doctoral-level trainees. The clinicians are directly supervised by the project manager who has extensive training in geriatrics, CP, and mind-body treatments. Following a standardized training protocol, clinicians read selected papers about treating CP and ECD in older adults, listen to audio recordings of the sessions, rehearse the clinician manuals, and colead with a senior clinician before running their first group. Clinicians receive training about adherence to the treatment manual, completion of study forms, assessing participant comprehension, and monitoring the use of skills. During weekly in-person supervision, the clinicians receive feedback about protocol adherence, specific participant or group concerns, and session preparation. All sessions are audio recorded. Clinicians record participant attendance and complete checklists of the content delivered. We will randomly select up to 20% (approximately 40) of these checklists to review. Independent coders will assess each session against a coding scheme to evaluate protocol fidelity, with attention to coder discrepancies. Home practice (eg, step count and skills used) is tracked automatically and reviewed during weekly supervision.

Data Analytic Plan

Power Analysis

Our blinded statistician used SAS (version 9.4; SAS Institute) [92] for the power analysis. Our primary outcome requires clinically important improvements in both functional measures (step count and 6-min walk test) and patient-reported outcome (Patient-Reported Outcomes Measurement Information System Physical Function). Allowing for 20% dropouts, 260 participants recruited (130/group; 104/group completing the study) would provide 92.3% power (Cronbach α=.05; 2 sided) to detect the minimum clinically important difference in step count (1000 steps) [93,94] between the AB and HEP groups in the change from baseline to postintervention assessment. This assumes an SD of 2120, which is the upper 80% confidence limit for the SD observed in our pilot study, as recommended [95]. We also assume 50% correlation between preintervention and postintervention measures. This sample size provides 81.8% power for a difference of 54 meters (the minimum clinically important difference) [96] in the 6-minute walk test (SD 135 based on our pilot data) and >99.9% power for a difference of 5.48 points (minimum clinically important difference) [97] for the Patient-Reported Outcomes Measurement Information System Physical Function score (SD 7.61 based on our pilot data). Assuming a correlation of 0.5 between significant results of step count and 6-minute walk test, the power of the study would be 80.7% (based on simulations) of having a statistically significant result for all 3 coprimary end points.

Data Analyses

Overview

Our blinded statistician will conduct all data analyses using SAS (version 9.4) [92]. We will estimate treatment-dependent changes in primary (objective, performance-based, and patient-reported physical function) and secondary outcomes (patient-reported and objective cognitive function and emotional function). We will follow the intention-to-treat principle and include all randomized participants in our primary efficacy analyses. Data will be analyzed using a shared-baseline, linear mixed model with fully unstructured covariance among repeated measures. The shared-baseline assumption reflects the true state of the population before randomization and has the benefit of adjusting for chance differences at baseline. Linear mixed models with maximum likelihood estimation are unbiased when data are missing at random, conditional on the observed data. If loss to follow-up is strongly treatment-dependent (relative risk >2), we will use perturbed multiple imputation to assess the robustness of estimates from the primary model if data were missing in not-at-random manner.

Aim 1: Efficacy of AB (Baseline to Posttest Period)

We have already established the feasibility benchmarks of the intervention and control [28,30]; therefore, emphasis of this study is on establishing the efficacy of AB. Accordingly, the primary analysis will compare the changes in primary and

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secondary outcomes (continuous measures) from baseline to posttest period between the randomized conditions. For each outcome, we will compare the effect of AB versus control on changes from baseline to the posttest period using linear contrasts. With 3 coprimary outcomes, no adjustment for multiple comparisons is needed; therefore, we will use 2-sided tests at $P<.05$ to declare the superiority of AB, maintaining an overall 5% type-1 error at our primary postintervention time point. The success of the trial will be declared if participation in AB is associated with statistically significant and clinically important improvement from baseline to posttest period over participation in control based on the 3 physical function outcomes.

We will conduct several sensitivity analyses to ensure that a conclusion about efficacy is robust to possible deviations from the assumptions of the primary model. Baseline parameters will be included to account for chance differences owing to randomization and to explain the sources of variation in response that are independent of treatment group. We will also use a Wilcoxon rank sum test comparing the change in scores between the 2 groups to avoid any parametric assumptions about the data. All secondary outcome measures will be analyzed using the same shared-baseline, linear mixed model and the same secondary sensitivity analyses. Step-down, Bonferroni-adjusted *P* values will be used to control for multiple comparisons regarding the secondary outcomes.

Aim 2: Sustainability of AB (Posttest Period to Follow-Up)

The same shared-baseline analyses will be used to determine durability (eg, changes between *after the intervention* and *6-month follow-up*) on the coprimary and secondary outcomes. Specifically, the persistence of a benefit from AB at 6-month follow-up will be estimated from linear contrasts of the postintervention period to 6 months least-square means and analyzed as a noninferiority test of durability. Noninferiority of AB in maintaining benefits relative to control will be declared if the lower 1-sided 95% confidence bound for a given coprimary outcome is less negative than each outcome's minimum clinically important difference in favor of control.

Aim 3: Mediation and Moderation

We will explore the extent to which treatment-dependent effects are associated with a priori–defined mediators and moderators. Mediation analyses of postintervention change scores will be conducted following a causal model [98] that extends traditional models for mediation [99,100]. The magnitude of the mediated effect will be estimated as the natural indirect effect, which includes effects mediated by an interaction between the treatment and the mediator [101,102]. This extends the traditional Baron and Kenny method and is equivalent to the analysis of Kraemer et al [103] for the linear models. Tests of significance for natural indirect effect estimates will use 2-tailed *t* tests based on SEs estimated using the delta method. Mediation tests will be conducted separately for changes in outcomes of physical, emotional, and cognitive function and pain intensity. The possible effect of moderators of a beneficial effect of AB will be investigated by adding moderator (eg, gender and subjective vs objective cognitive decline), moderator × treatment, and moderator × treatment × visit interaction terms to the repeated-measures analysis of variance described for aim 1.

Results

The study was funded by the National Institute on Aging in December 2021. The study was approved by the IRB on December 8, 2021. We began recruitment in July 2022. As of March 2023, a total of 201 individuals have been referred and all have been contacted. Of these 201 individuals, we screened 141 (70.1%) and enrolled 37 (18.4%) participants (n=18, 49% in AB and n=19, 51% in HEP) across 4 group cohorts (largest group: n=10, 27%). All (37/37, 100%) participants completed the baseline assessment. Of the 37 participants, 1 (3%) dropped after the first AB session owing to an unrelated psychiatric hospitalization and 1 (3%) dropped after the second HEP session owing to extreme orofacial pain. In the three cohorts (26/37, 70%) that have completed the AB or HEP, 26 (100%) participants completed all 8 of the group sessions (including minimal makeups) and the posttest assessment. Adherence has been high for the Fitbit and ActiGraph watches, with 93.48% (1937/2072) valid days of wear compliance for both devices across the 2 group cohorts. The fourth group cohort is ongoing (9/37, 24%). We plan to complete enrollment by March 2026 and data analyses by February 2027.

Discussion

Significance

Our single-blinded, NIH stage-2 RCT (N=260) is designed to test the efficacy, sustainability, and mechanisms of the AB program in improving self-reported and objective outcomes of physical, cognitive, and emotional function. We anticipate that the results will inform nonpharmacological interventions targeting CP and ECD in older adults. Although most nonpharmacological CP interventions address a discrete pain condition (eg, back pain), we developed our mind-body activity program to address issues that are common across all nonmalignant CP conditions. This is important because most older adults have ≥1 type of pain condition [104]. We are targeting people with both subjective and objective ECD because both are precursors of dementia [1], have similar symptom presentations, and require similar tailoring of skills [105,106]. Our web-based mind-body activity program is grounded in strong theoretical and empirical frameworks [10,52-54], combines mind-body skills with quota-based pacing and engagement in activities of daily living, is delivered in a group format to foster social support, and uses a pacing plan that is tailored to each individual. AB has been iteratively refined using the NIH Stage Model [29] guidelines; follows the Initiative of Methods, Measurement, and Pain Assessment [50] and International Classification of Functioning [51] criteria for CP clinical trials; and has demonstrated excellent feasibility markers and proof of concept [28,30]. The groups conducted so far, although preliminary, show high initial participant retention and adherence to both treatment arms and the study technologies.

This study addresses three key limitations of our pilot studies: (1) recruitment of ethnoracially diverse older adults (38% is the

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benchmark [32]), (2) assessment of longitudinal follow-up (6 mo), and (3) enhanced methodology for blinded assessment (ActiGraph) and reinforcement (Fitbit) of our step count coprimary outcome. Testing AB versus the education control will yield critical information about the efficacy and durability of improving multimodal physical function in older adults with CP-ECD. We plan to assess the mechanisms for improving the coprimary physical function and secondary outcomes (cognitive function, emotional function, and pain intensity). We will test mediation through theoretically informed constructs (nonadaptive coping, adaptive coping, social factors, and compensatory strategies). We will also test moderation by type of ECD (subjective and objective) and relevant demographic and clinical variables. The results will inform future trials of AB and targets in psychosocial treatments for CP and ECD to optimize physical, emotional, and cognitive outcomes.

Limitations

Despite our emphasis on refining our RCT methodology, we anticipate several limitations. First, it is challenging to include ethnoracially diverse older adults in clinical trials at our academic medical center. We developed specific strategies to recruit and retain a diverse sample. However, this is our first attempt at implementing these strategies and building trust with new communities of potential participants. Despite plans for future translation studies, the programs are only available in English, which limits diverse groups from participating. Next, we have designed a more *digitally inclusive* trial by providing free tablets, watches, and smartphones with data plans and offering hands-on training to participants who do not have access to or are unfamiliar with these technologies. Some older adults may not be able to meaningfully participate in the web-based group program owing to significant visual, speech, or hearing impairment. In addition, wearing 2 watches may be a burden for some participants. We selected ActiGraph and Fitbit because there were no research-grade accelerometry watches that could remotely toggle between blinded assessment and real-time reinforcement of participants' step count. Our internal testing and the literature [107-109] show that Fitbit tends to overestimate step count relative to ActiGraph, which has made it challenging to set valid and meaningful quota-based step goals during the intervention. Finally, we risk unblinding participants who find our study on ClinicalTrials.gov [110] database or web-based publications.

Conclusions

We aim to establish the efficacy of the AB program over a time-matched and dose-matched control in a web-based trial. Our findings from this trial will be used to inform the development of a future multisite, hybrid, effectiveness-implementation trial. We hope to implement AB in routine care for older adults across medical settings and train different disciplines (eg, nurses, social workers, and peer coaches) to deliver it. We plan to culturally adapt the program, through collaborations with community partners, to increase the generalizability of the program and disseminate it to diverse older adults living in the community. AB has the potential to be an effective, low-cost, and sustainable treatment for older adults with CP-ECD, with important implications for the prevention of dementia in this high-risk population.

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Data Availability

Once the trial is complete, data will be made available upon request.

Conflicts of Interest

YTQ serves as a consultant for Biogen.

Multimedia Appendix 1
Peer-reviewer report from the Biobehavioral Medicine and Health Outcomes (BMHO) Study Section - Risk, Prevention and Health Behavior Integrated Review Group - Center for Scientific Review (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 143 KB - resprot_v12i1e47319_app1.pdf]

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Abbreviations

AB: Active Brains
CP: chronic pain

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CP-ECD: chronic pain along with early cognitive decline
ECD: early cognitive decline
HEP: Health Enhancement Program
IRB: institutional review board
MGH: Massachusetts General Hospital
NIH: National Institutes of Health
RBANS: Repeatable Battery for the Assessment of Neuropsychological Status
RCT: randomized clinical trial
REDCap: Research Electronic Data Capture
SMART: Specific, Measurable, Attainable, Realistic, and Timed

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Protocol

Teleworking to Support Accommodation, Inclusion, and Health of Aging Workers: Protocol for a Study to Design, Validate, and Test a Reflective Application Guide

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Abstract

Background: Aging workers constitute a growing population in many countries and form an indispensable and qualified resource, especially in the context of the labor shortage. Despite work's many benefits for individuals, organizations, and societies, it also presents several risks and challenges that may lead to occupational injuries. Thus, rehabilitation professionals and managers working with this emerging and unique clientele during their return to work after an absence often lack the tools and skills to support them, especially in the changing world of work that includes the rise of telework. Indeed, as an increasingly present work arrangement, telework has the potential to be used as an accommodation modality that can facilitate inclusion and healthy participation in the workplace. However, the implications of this topic for aging workers require study.

Objective: This paper presents the protocol of a study that aims to develop a reflective telework application guide to support the accommodation, inclusion, and health of aging workers after an absence from work. Specifically, this study will (1) explore the experience of aging workers, managers, and rehabilitation professionals regarding telework and its impact on accommodation, inclusion, and health; (2) use a validated logic model to design a reflective application guide; and (3) test and evaluate the guide.

Methods: Following a 3-phase developmental research design, individual interviews with aging teleworkers, managers, and rehabilitation professionals will enable the collection of qualitative data to be used in generating a logic model of levers and good practices, leading to the creation of a reflective application guide. Validation of this guide by workers and managers to measure its acceptability and applicability in daily life will precede its implementation.

Results: Data collection began in spring 2023 and initial results are expected in fall 2023. This study aims to generate a concrete tool—namely, the reflective telework application guide—that rehabilitation professionals could use to support managers and aging workers during their return to work through the healthy use of telework. All phases of the study include conducting dissemination activities to share the results of the project and increase its sustainability potential (ie, publication through social networks, podcasts, conferences, and scientific publications).

Conclusions: As the first of its kind, this project aims to produce innovative impacts at several levels, including practical, scientific, and societal impacts. In addition, the results will provide healthy solutions to the labor shortage in a changing world of work, where digital and teleworking are becoming increasingly important.

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KEYWORDS

aging workers; health; intervention; qualitative research; telecommute; telework

Introduction

The number of aging workers (ie, aged 55 years or over [1]) is growing worldwide and forming an indispensable population contributing to economic life, especially in the context of a critical labor shortage. In Canada, this workforce represents more than one-third of the working-age population, almost 40% of whom are active in the labor market [2]. These are the highest proportions that the statistical account of work in Canada has noted. In the United States, the only group of workers on the rise since the mid-1990s are workers over the age of 55 years [3]. Moreover, they represent the group of workers that will grow the most by 2030 [4]. The European Union is also experiencing a similar situation, with a 17% increase in workers aged 55 to 64 years since 2009 [5].

This increase raises awareness of the importance of this group of workers who have specific characteristics differentiating them from other active generations at work. Indeed, this older generation of workers has distinctive values regarding work. For instance, older workers seem less likely than other generations to value the extrinsic advantages of work less than such intrinsic advantages as social contacts, challenges, and opportunities for responsibility [6]. In addition, some authors report that the baby boomer generation (ie, people born between 1946 and 1964 [7]) tends to show the greatest employer loyalty and a lower propensity than younger workers to leave their jobs [8]. These workers are also subject to particular representations by their younger colleagues. The results of a study on stereotypes of older workers show that others generally perceive them as more faithful but less likely to be fast adapters to technology [9].

Although work leads to many benefits for aging workers, such as developing a sense of belonging or ensuring financial security, it also carries risks [10]. Aging workers face higher probabilities of experiencing one or more periods of disability, either due to an occupational injury or a personal medical reason [10]. Moreover, the severity of the injury and the duration of disabling conditions escalate with age [11,12]. Indeed, workers aged 55 years and over are twice as likely as their younger colleagues to have a work-related accident and 6 times more likely than those colleagues to develop a musculoskeletal disorder [11]. Some authors report that gaps between workers' abilities and job demands [13] as well as the decline of certain senses (eg, vision and audition [14]) partly explain these differences. Moreover, a major difference of nearly 100 days exists between the average duration of the disability period following an occupational injury for workers at least 55 years of age and that of younger workers aged 15 to 24 years [15]. Factors related to injury severity, presence of comorbidities, and tissue repair speed may mean longer periods of disability for aging workers [12,16], contributing to a marked increase in their use of rehabilitation services [17].

The increasing rehabilitation needs of aging workers create changes in the profile of the rehabilitation-service clientele [18]. Rehabilitation professionals now work with this emerging population and its distinctive characteristics. Professionals are generally aware of the growing presence of aging workers among the clients receiving their services. Nonetheless, they often do not know how to respond to this singular population in a changing world of work, and most clinical settings have not yet added specific services to meet those needs [18]. In addition, managers need resources to support aging workers in their return to work after an absence. Indeed, a recent scoping review revealed a gap between the needs of aging workers returning to work and the responses from managers [19]. Therefore, developing resources to help rehabilitation professionals support and guide managers and aging workers is essential, considering their singular characteristics.

The situation is even more complex because the COVID-19 pandemic fundamentally changed the way many people do their work, forcing a shift to digital work and telework [20,21]. As we emerge from this period of crisis, telework is clearly a work arrangement that will remain [22], with its advantages and challenges. Indeed, the research on telework during the pandemic has exploded, revealing some health benefits for individuals (eg, schedule flexibility [23]) but also challenges (eg, disconnection difficulties [24]) that may specifically impact aging workers' mental health [25]. Other authors report the added value of telework in promoting inclusion and health for all worker populations [26,27], especially such marginalized populations as aging workers. While telework had been an exceptional accommodation for some workers (eg, workers with physical disabilities) from the 1990s until the late 2010s [28,29], workplace stakeholders more widely accept and recognize it now, resulting in less marginalization of workers who benefit from it.

Studies have highlighted the potential of telework as an accommodation for people living with specific health conditions as they feel more able to perform their work while managing their fatigue or pain levels [27,30-32]. Thus, using telework to accommodate individuals who may have challenges performing work in a conventional manner after a period of absence may be of interest. Indeed, this form of work provides "invisibility," ensuring greater equality [26,27] as well as protection against prejudice and discrimination [31,33]. Some exploratory work suggests ways to use telework as a modality to facilitate accommodation, inclusion, and health for unique worker populations, such as people with physical disabilities [20,21] or neurodivergent workers [22]. Nonetheless, to our knowledge, there are not yet guidelines for ensuring a healthy application of telework for aging people. Recent research results have suggested that telework is particularly challenging for aging workers [34]. How can we ensure that this work arrangement promotes the accommodation, inclusion, and health of this workforce?

To optimize the contribution of all available people and reduce the labor shortage while promoting the principles of equity, diversity, and inclusion in the workplace, addressing this

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contemporary issue is important. Developing innovative tools to guide the healthy use of telework among aging people who have experienced an absence and improving knowledge about the use of telework as an accommodation modality for aging workers could help equip the rehabilitation professionals who support managers and workers in the trajectory of rehabilitation, return, and stay at work.

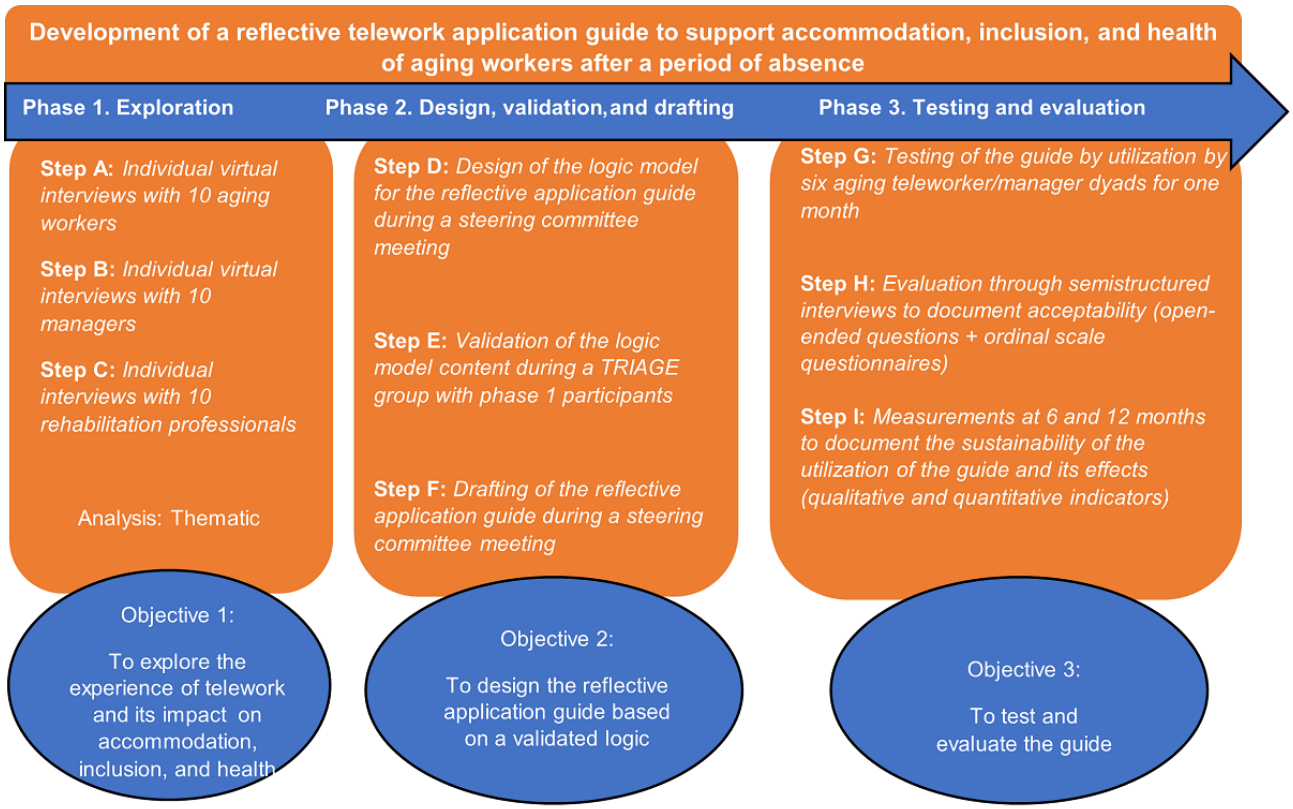
This study aims to develop a reflective telework application guide to support the accommodation, inclusion, and health of aging workers after an absence. Specifically, this study (1) explores the telework experience of aging workers, managers, and rehabilitation professionals; (2) designs the reflective application guide on the basis of a validated logic model; and (3) tests and evaluates the guide.

Methods

Design

This project will proceed according to a developmental research design [35] that includes a steering committee comprising 8 stakeholders (researchers, workers, managers, and rehabilitation professionals). Such a design engages researchers and participants in a reflective process as, together, they seek solutions to an issue. It enables the production of useful and accurate knowledge that corresponds to stakeholders' realities [36]. Therefore, this study will focus on aging workers who have returned to work after an absence during the past 2 years and experienced telework as an accommodation modality. Managers and rehabilitation professionals will also participate in the study to provide other perspectives. The research involves the following three phases: (1) exploration; (2) design, validation, and drafting; and (3) testing and evaluation. Figure 1 shows the phases of the research leading to the development of the reflective guide.

Figure 1. Phases, steps, and objectives of the research project. TRIAGE: technique for research of information by animation of a group of experts.



Procedure, Participants, and Analysis

Phase 1

This phase will address objective 1 in 3 steps.

Overview

Recruiting all participants in this study will occur through social media announcements and contacts with clinical settings and organizations within the research team member networks. We will use a purposive sampling method to recruit participants and a maximum variation sampling strategy to select them [37]. Recruiters will ensure diversity in terms of gender, age, and employment sector.

Step A

A 60-minute individual web-based interview with 10 aging workers, respectively, will address various themes (eg, work practices, life role balance, feeling inclusion and satisfaction at work, and perceived health status) using a pretested interview guide. Eligibility to participate will depend on candidates being at least 55 years of age and having experienced telework as an

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accommodation modality upon returning to work after an absence during the previous 2 years.

Step B

A 60-minute individual web-based interview will occur with each of the 10 managers working with aging workers, addressing themes similar to those in step A with an emphasis on management practices and using an equivalent pretested interview guide. Managers will have accommodated at least one aging worker with telework after an absence during the previous 2 years.

Step C

A 60-minute individual web-based interview will occur with 10 rehabilitation professionals, respectively. Recruits will be working in occupational rehabilitation (ie, occupational therapists, physiotherapists, and psychologists). Each interview will address themes similar to those in step A, emphasizing rehabilitation practices and using an equivalent pretested interview guide. Eligible rehabilitation professionals will have accompanied at least one aging worker returning to work through telework after an absence during the past 2 years.

A member of the research team will conduct all interviews, digitally audio-recording each. Based on the available literature [38,39], a total of 30 participants should enable reaching content saturation. A questionnaire will collect sociodemographic data (eg, age, gender, marital status, employment experience, and health status) for each participant.

Analysis

Following the transcription of interviews, 2 research team members will analyze the data using an inductive posture and a 5-step thematic-analysis strategy [40]: (1) repeated readings of the data corpus to enable researchers to develop a sense of immersion; (2) initial coding with descriptive codes assigned to the units of significance found in the corpus; (3) units of meaning transformed into meaningful expressions of participants' perspectives; (4) synthesis of expressions allowing the organization of the data in a general structure; (5) back and forth between the raw data and the general structure, allowing clarification and interpretation of the data while respecting participants' perspectives. The 2 coders will first analyze each transcript individually, then compare their structure of codes and generate a new, improved version. This process prevents the analysis from reflecting a single person's perspective and ensures interjudge agreement. The research team may produce several versions of the structure until the team agrees on a structure that most accurately reflects the data. QDA Miner software will support the analysis process.

The researchers expect that the results obtained in this phase will enable generating various elements, such as questions to ask, factors to consider, levers, good practices, and obstacles to avoid, to promote the accommodation, inclusion, and health of aging workers returning to work after an absence.

Phase 2

This phase will address objective 2 in 3 steps.

Step D

Identified Phase 1 elements will support designing the logic model of a reflective telework application guide for aging workers and their managers. The logic model will present the goals, supporting theories, components, sections, and expected outcomes of its use [41]. Some authors have suggested the added value of creating a logic model in the process of developing a new tool, especially because this preliminary step facilitates communication between the actors involved and promotes their common understanding of the tool to be developed [41,42]. The steering committee will develop this logic model using a co-construction approach during a working day.

Step E

Validation of the logic model will involve a 120-minute web-based group using the "technique for research of information by animation of a group of experts (TRIAGE)" [43,44], namely, a group of 8 participants in Phase 1. The TRIAGE technique allows structuring discussions between participants to obtain a consensus on specific ideas while encouraging the emergence of new ones [44]. Two research team members will facilitate the group. Various indicators of validity related to logic models (ie, relevance and clarity) will be documented [41] with a pretested guide. Data analysis related to the validation of the logic model will occur during the session (in situ), consistent with the TRIAGE technique [44].

Step F

Based on this validation of the logic model, the steering committee will create the first version of the complete guide during a second working day.

Phase 3

This phase will address objective 3 in 3 steps.

Step G

This phase aims to test and evaluate the guide with respect to the accommodation, inclusion, and health of aging workers. It will determine whether users of the guide consider it appropriate, particularly in terms of acceptability [45] and satisfaction. We will invite 6 teleworker-manager dyads to familiarize themselves with the guide and use it in their daily work for a month.

Step H

Following this trial period, the perceptions of the dyads will be collected in a semistructured interview to document various indicators of acceptability (eg, affective attitude, perceived effectiveness, and opportunity costs [45]), and satisfaction regarding accommodation, inclusion, and health. Qualitative open-ended questions will support this purpose ("Which barriers to the use of the guide have been faced?" "How much has the guide facilitated a sense of inclusion at work?") along with quantitative closed-ended ordinal scale questions ("What is your level of satisfaction regarding the use of the guide?"). A thematic analysis strategy [40] will support analyzing qualitative data, and descriptive statistical analysis (eg, frequency, means, and SDs) will enable quantitative data analysis [46].

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Step I

Finally, applying the same measures to the same participants in step G will occur at 6 and 12 months to document the sustainability of the guide's use and its effects on the accommodation, inclusion, and healthy work participation of aging workers.

Ethics Approval

This study obtained ethical approval from the Ethics Committee of the Centre intégré universitaire en santé et services sociaux de la Capitale-Nationale (project 2023-2805) and the Human Research Ethics Committee of the Université du Québec à Trois-Rivières (project CER-23-298-10.01)

Results

Data collection began in spring 2023 and initial results are expected in fall 2023. This study aims to produce a concrete tool, namely, a reflective telework application guide for short-term use by rehabilitation professionals, managers, and aging workers, to improve the implementation of telework as an accommodation modality to support the inclusion and health of aging people in their return to work after an absence. The guide will also serve to influence policy makers regarding telework. Since rehabilitation professionals and managers are often poorly equipped to respond to such a unique population, the results should propose guidelines for using telework to return to work.

To share the results of the project and increase its sustainability potential, the steering committee will organize several dissemination activities, either during the project or at its end. The researchers will frequently post the study's progress on social media and in a newsletter. We will record a podcast with a researcher, a worker, a manager, and a rehabilitation professional to publicize the guide and its potential utilization. We will invite various stakeholders in the world of work (ie, unions, insurers, and employer and worker associations) to listen to this podcast. Also, we will submit the results for publication in scientific journals and presentation at international scientific conferences. To ensure rigor in the dissemination of results, we will follow the Standards for Reporting Qualitative Research (SRQR) [47]. Finally, we will promote the use of the guide to government authorities.

Discussion

Overview

This study will create a reflective telework application guide through a rigorous, multistep research process involving various work-related stakeholders. This study constitutes a first of its kind and is highly relevant, especially in the context of the labor shortage and the recent major changes in the world of work. To our knowledge, there are no tools, guidelines, or "best practices" for rehabilitation professionals, managers, or workers to use to ensure a healthy application of telework, specifically for the aging population. This project is particularly innovative on several levels. On a *practical level*, the guide represents a concrete tool that rehabilitation professionals, managers, and aging workers can use upon returning to work after an absence. This study's *research* contribution is to pave the way for other projects aimed at developing innovative and effective solutions in promoting the accommodation, inclusion, and health of aging workers after an absence. Finally, on a *societal level*, the study results will help to explain the influence of telework on the health and inclusion of aging workers and encourage people to use the guide to promote healthy participation in telework.

Conclusion

This paper presents a research protocol to develop a reflective telework application guide with its basis in scientific and experiential knowledge. The results of this study will lead to implications at practical, scientific, and societal levels. Moreover, the results of this study should pave the way for further studies and interventions to ensure aging workers' healthy work participation.

Acknowledgments

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Data Availability

The data sets generated and analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

AL, QNH, JM, and CV reflected on this study protocol. AL and RBM drafted this manuscript. QNH, JM, CV, NB, and M-ML carefully read the manuscript and made changes to improve it. The manuscript was submitted when all authors were satisfied.

Conflicts of Interest

None declared.

Multimedia Appendix 1

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Peer-reviewer report from Réseau Québécois de Recherche sur le Vieillissement (Quebec Network for Research on Aging, Quebec, Canada).
[XLSX File (Microsoft Excel File), 14 KB - resprot_v12i1e46114_app1.xlsx]

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Abbreviation

TRIAGE: technique for research of information by animation of a group of experts

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Protocol

Development of a Preventive Health Screening Procedure Enabling Supportive Service Planning for Home-Dwelling Older Adults (PORI75): Protocol for an Action Research Study

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Abstract

Background: In Finland, at least 1 in 4 residents will be >75 years of age in 2030. The national aging policy has emphasized the need to improve supportive services to enable older people to live in their own homes for as long as possible.

Objective: This study aimed to develop a preventive health screening procedure for home-dwelling older adults aged 75 years to enable the use of clinical patient data for purposes of strategic planning of supportive services in primary care.

Methods: The action research method was applied to develop the health screening procedure with selected validated health measures in cooperation with the local practicing interprofessional health care teams from 10 primary care centers in the Social Security Center of Pori, Western Finland (99,485 residents, n=11,938, 12% of them >75 years). The selection of evidence-based validated health measures was based on the national guide to screen factors increasing fall risk and the national functioning measures database. The cut-off points of the selected health measures and laboratory tests were determined in consecutive consensus meetings with the local primary care physicians, with decisions based on internationally validated measures, national current care guidelines, and local policies in clinical practice.

Results: The health screening procedure for 75-year-old residents comprised 30 measures divided into three categories: (1) validated self-assessments (9 measures), (2) nurse-conducted screenings (14 measures), and (3) laboratory tests (7 measures). The procedure development process comprised the following steps: (1) inventory and selection of the validated health measures and laboratory tests, (2) training of practical nurses to perform screenings for the segment of 75-year-old residents and to guide them to possible further medical actions, (3) creation of research data from clinical patient data for secondary use purposes, (4) secondary data analysis, and (5) consensus meeting after the pilot test of the health screening procedure for 75-year-old residents procedure in 2019 based on the experiences of health care professionals and collected research data.

Conclusions: The developed preventive health screening procedure for 75-year-old residents enables the use of clinical patient data for purposes of strategic planning of supportive services in primary care if the potential bias by a low participation rate is controlled.

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KEYWORDS

health screening; older adults; community health care; secondary use; Finland; screening; supportive service; clinical patient data; community; develop; primary care; self-assessment; pilot test; testing; planning; data collection

Introduction

Between the years 2015 and 2050, the number of people aged >60 years will increase globally from 900 million to 2 billion [1]. In Finland, at least 1 in 4 residents will be >75 years of age in 2030 [2]. Health care systems should be realigned to meet the needs of growing older populations and be capable of providing person-centered integrated care that meets the needs of this population segment. Most health systems globally are ill-prepared to address the service needs of older people who often have multiple chronic conditions or geriatric syndromes.

Finland has one of the fastest-aging populations in the world [2]. Finnish aging policy and health and social policy have emphasized the need to enhance support services to enable older people to live in their own homes for as long as possible, even when daily home care support is regularly needed [2-4]. To enhance support for living at home, new effective preventive actions are needed to maintain the functional ability of older adults [2]. Early detection of diseases and efforts to prevent or attenuate the complications of chronic diseases may provide a cost-effective strategy for maintaining the health and functional ability of older adults, although conclusive evidence is still lacking [5-7]. Screening for the subclinical state of a disease has benefitted many asymptomatic patients [8] but applying preventive health screening to old people may be problematic for several reasons such as geriatric disorders with multiple risk factors, having less physiological reserve than younger adults, and having higher comorbidity rate often leading to polypharmacy. In general, older adults are often excluded from clinical trials influencing outcomes measured and reported for evidence synthesis and thus interpreted for medical interventions [8,9]. The abovementioned issues have contributed to the lack of comprehensive health screening procedures suitable for home-dwelling older adults and suitable to be used in clinical practice to guide preventive actions.

Our extensive literature searches did not find any studies reporting preventive comprehensive health screening tools or procedures specifically designed and validated for home-dwelling older adults. Existing age-specific health screening tools are disease or symptom specific (eg, cancer [10], mental disorders [11], frailty [12], cognitive impairment [13], falls [14], and nutritional status [15]) [10-21] and they primarily focus on community settings [17,22-26]. As health systems are becoming increasingly digitalized, screening tools should be suitable for structured and cumulative data recording in electronic patient databases, enabling data-driven management practices and the secondary use of social and health data in the future. The aim of this study was to develop a preventive health screening procedure for home-dwelling older adults aged 75 years to enable the use of clinical patient data for the strategic planning of supportive services in primary care.

Methods

Context of the Study

The Finnish health care and social services system is currently undergoing a major reform [27]. Since the beginning of 2023, these services have been organized by 22 well-being service counties [28,29]. According to the new Act on Organizing Social Welfare and Healthcare [30], the planning and implementation of publicly funded health care and social services in the well-being service counties should be guided by patient data aggregated in care processes. The Act on the Secondary Use of Health and Social Data [31] was enacted in 2019 and states how patient data can be used by service providers for organizing services, planning their equal availability, and optimizing cost-effectiveness [30].

This study was conducted in the Social Security Center of Pori, which was transferred to the well-being service county of Satakunta at the beginning of 2023 (1 of the 22 regional providers of social and health services in Finland) [28,29]. In the Satakunta Wellbeing Service County, institutional care for older residents has been significantly more common than in the rest of Finland. Therefore, the county made a strategic decision in 2019 to find new ways to remarkably reduce the proportion of older residents aged >75 years requiring expensive institutional care (reduction from 9% to 4.5% by 2024) [32]. The goal was for older residents to favor living at home for as long as possible by providing them with new community housing solutions, extending home care into round-the-clock services, and resourcing client-specific home care to support residents in poorer health. This study was started to support the strategic goal of the well-being service county by developing a preventive health screening procedure to identify home-dwelling older adults at risk of impaired health and functional ability.

According to the Finnish legislation, it is mandatory for the well-being service counties to use the Resident Assessment Instrument (RAI) assessment tools [33,34] in assessing the functional capacity of an older person if the person needs regularly provided social services to ensure sufficient care and support [35]. RAI is a comprehensive assessment tool specifically designed for the evaluation of the care needs of vulnerable populations [33,34]. The RAI assessment system consists of several assessment instruments designed for varied care contexts such as nursing home [36], home care [37] rehabilitation [38], palliative care [39], or acute care [40]. In contrast, a preventive health screening assesses home-dwelling older adults' overall potential health risks and can be used for individuals regardless of their service needs.

This study included 10 public health care centers from 3 municipalities within the Satakunta Wellbeing County—Pori, Ulvila, and Merikarvia—located in Western Finland, with

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99,485 inhabitants, of whom 12% (n=11,938) were ≥75 years in 2020 [41]. Pori Home Care Unit is divided into 3 service areas: North, West, and East. Each service area has 3-4 local public health centers. Every health center has a practical nurse (PN) who is trained in health screening. Health screenings are a publicly funded part of primary care services in Finland [42]. Since the beginning of 2023, well-being service counties have been funded mainly by the government and partly by collecting service fees from service users [28].

Study Design and Method

This study applied the action research method to develop a preventive health screening procedure for home-dwelling older adults aged 75 years [43,44]. The action research method is suitable for identifying problems in clinical practice and developing potential solutions to improve the practice [43]. It involves researchers working with and for people rather than undertaking research on them [43]. The study design was developed in cooperation between the Satakunta University of Applied Sciences, the Social Security Center of Pori, and the University of Helsinki, Finland. Advanced-level nursing students from the Satakunta University of Applied Sciences were also involved in training PNs to conduct health screenings.

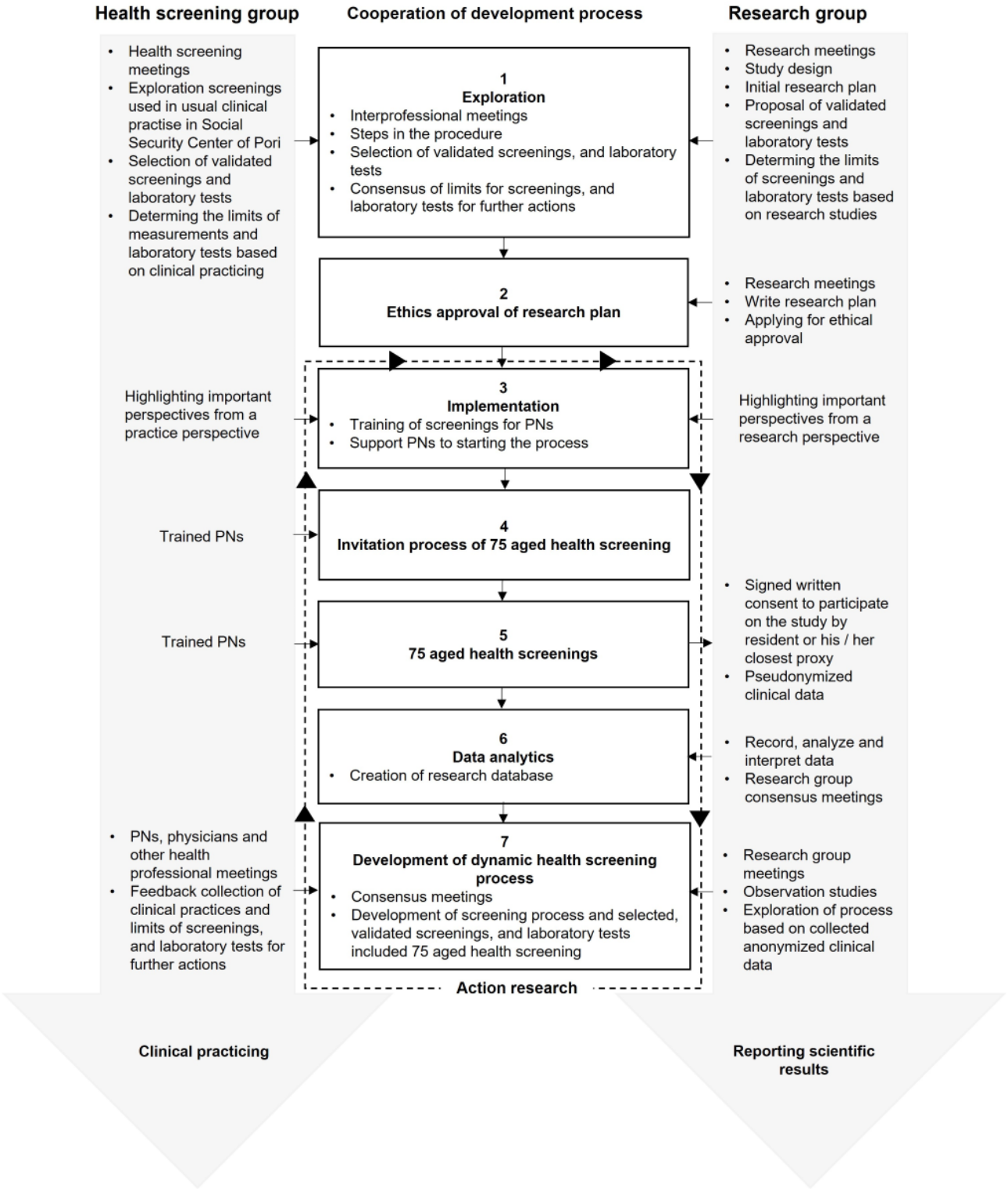
Development Process of the Health Screening Procedure

The following were the starting points for the development of the health screening procedure: (1) the screening could be performed every year for a new segment of 75-year-old residents; (2) the health measures included should provide sufficient information about the health status of the home-dwelling residents in this age segment to plan for required health services and be suitable for structured and cumulative data recording enabling data-driven management practices; and (3) the health screening procedure should be dynamic, allowing changes in measures while maintaining comparability between annual cohorts to observe the possible changes in the health status of 75-year-old residents and their service needs over time.

The health screening procedure was developed in 7 steps and close cooperation between the health screening group—comprising the care team personnel from the Social Security Center of Pori—and the research group, comprising the researchers (Figure 1). The health screening group comprised all PNs, their managers (nurses), physicians, and other health care professionals involved in the 10 care centers of the 3 municipalities involved in the study. The research group comprised 3 clinically trained researchers: a physician, a pharmacist, and a clinical physicist.

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Figure 1. The development process of the preventive health screening procedure for home-dwelling older adults aged 75 years (PORI75) using the action research method [43,44]. PN: practical nurse.



Ethical Considerations

This study was approved by the Ethics Committee of the Hospital District of Southwest Finland (ETMK 58/2019). The research permit was approved by the Social Security Center of Pori, Finland to conduct research at the health center. Informed consent was obtained from each client and their closest proxy before any study procedure was performed. This study was conducted in accordance with the principles of the Declaration of Helsinki.

Inventory of Potential Health Measures to be Included in the Procedure (Step 1)

Meetings between the health screening group, which was familiar with health screenings in practice, and the research group conducting research played a crucial role in developing the health screening procedure (Figure 1). The first step was to

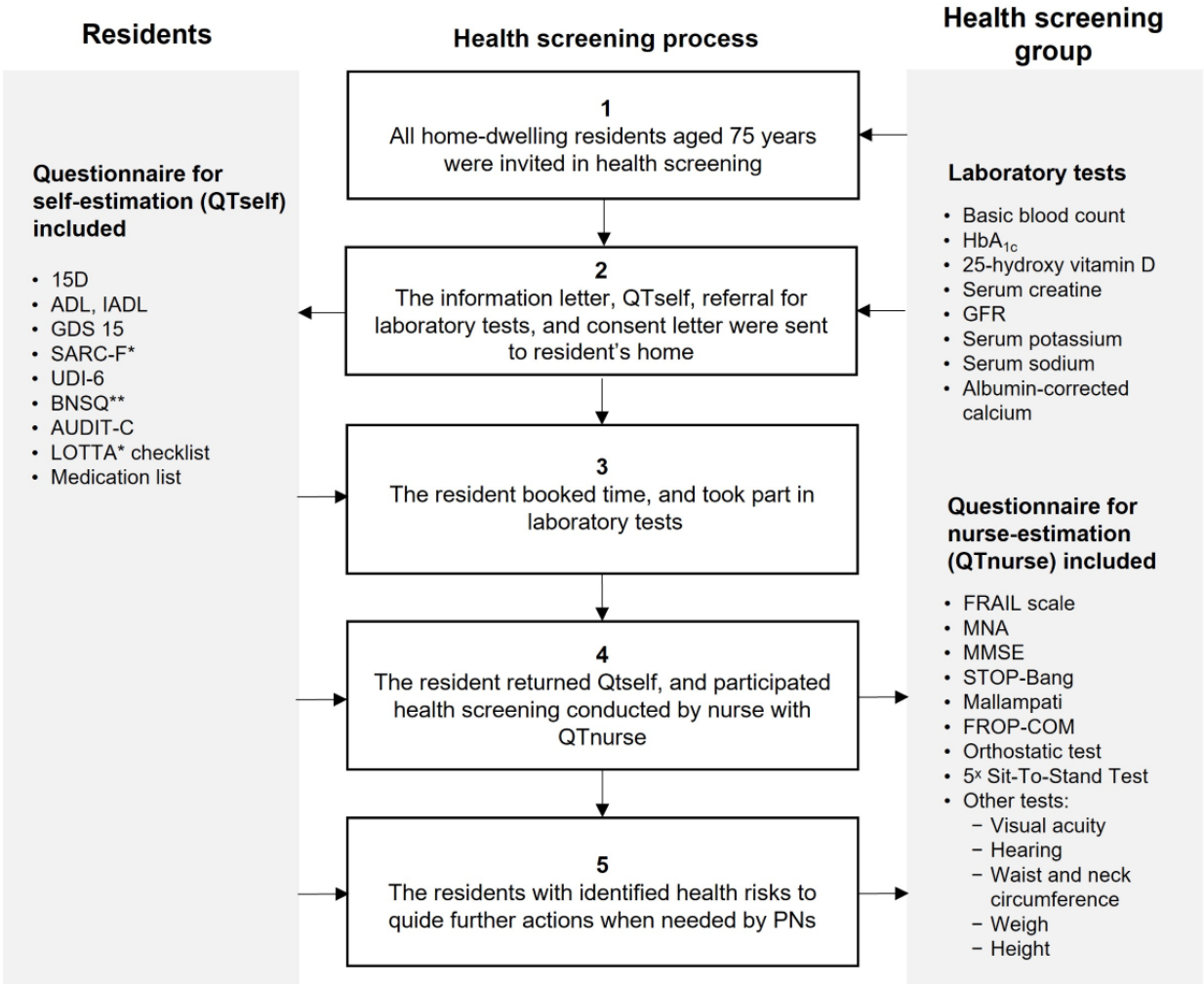
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make an inventory of potential health measures to be included in the procedure (research group). The inventory and selection of measures were based on evidence-based, validated, client-oriented measures covering the typical symptoms and conditions in older adults who may influence their functional ability to live at home. Our inventory found the national guide on preventing falls in older adults by the Finnish Institute for Health and Welfare as a useful evidence-based source of measures to be used in our study [45]. The guide presented a holistic approach to factors that have been associated with an increased risk of falls and that are recommended to be screened in older adults. Thus, we drew all the recommended health measures from the guide to form a preliminary set of measures for our health screening procedure.

In cases where a validated health measure recommended by the fall prevention guide [45] was not available in the guide, it was drawn from the National TOIMIA Functioning Measures Database, which is also maintained by the Finnish Institute for Health and Welfare [46]. The TOIMIA Functioning Measures Database is an open-access and free-of-charge database designed for experts and professionals to measure functioning in clinical practice and research. The database contains the basic descriptions of functioning measures, assessments of psychometric properties, and the feasibility of these measurement instruments for different purposes and guidelines and recommendations by experts concerning the measure of functioning in different situations and contexts. The guidelines and measures published in the database have been systematically evaluated by the TOIMIA network of experts with regard to their validity, reliability, and usability for different purposes.

When possible, the health measures used in routine clinical practice at the Social Security Center of Pori were selected for the health screening procedure to minimize additional work for PNs and inconvenience for residents (Figure 2). Laboratory tests were selected to screen for diseases and conditions prevalent in older adults according to the fall prevention guide [45] and to optimize drug treatment.

Figure 2. Description of the developed health screening procedure for 75-year-old residents (PORI75). * LOTTA checklist and SARC-F test were included in 2020. ADL: activities of daily living; AUDIT-C: Alcohol Use Disorders Identification Test—Consumption; BNSQ: Basic Nordic Sleep Questionnaire; FROP-Com: Falls Risk for Older People in the Community; GDS 15: Geriatric Depression Scale; GFR: glomerular filtration rate; HbA1c: hemoglobin A1c; IADL: Instrumental Activities of Daily Living; PN: practical nurse; QTnurse: questionnaire included screenings performed by a health care professional; QTself: questionnaire included screenings suitable for self-assessment; UDI-6: Urinary Distress Inventory; LOTTA: Checklist for Successful Medication Therapy (translated in English). ** The BNSQ questionnaire was included only in 2019, not in 2020.



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The cutoff points of the selected health measures and laboratory tests for possible further medical examination to treat the identified health problems were agreed upon in a consensus meeting with the local physicians (Multimedia Appendix 1 shows this in more detail). The criteria for the cut-off points were based on the categorization of internationally validated tests, national current care guidelines [47], and local policies. Consensus was reached when all the local physicians agreed on the cutoff points of the measures and tests in the meeting.

Implementation of the Health Screening Procedure (Steps 2-7)

After consensus was reached between the research group and health screening group on the health measures and laboratory tests included in the procedure, named health screening procedure for 75-year-old residents (PORI75), a study protocol was developed to implement the procedure (Figure 1). The study protocol was evaluated by the Ethics Committee of the Hospital District of Southwest Finland (step 2).

For the implementation of the procedure in steps 3-7, all 75-year-old residents living at home were selected from 10 public health care centers in 3 municipalities within Satakunta Wellbeing Service County and were invited by a postal letter to participate in the health screening by a trained PN (Figure 1). The recruitment process was conducted between June 2019 and December 2020 and invited only those residents who turned 75 years old that year. All residents were given oral and written information about the study protocol prior to consenting. Written informed consent was obtained from all voluntary participants in person or with the help of their caregiver or closest proxy.

PNs were prepared to perform the health screenings for the consented residents of 75 years of age (Figure 1; step 3). During this preparatory phase, PNs were encouraged to comment on the health screening process to the research group to make it fit the usual clinical practice. PNs were trained to identify residents with elevated health risks in the health screening phase and to guide them to refer a health care professional or provider or visit a clinic for further medical examination to manage the problems when needed (Multimedia Appendix 1).

Step 5 was designed for implementing the health screenings using the health measures and tests included in the procedure in step 1 (Figure 1). The aim was to assess the current health status of home-dwelling 75-year-old residents by identifying potential ageing-specific issues for diseases prevalent in older adults as well as their medication-related risks.

In the data analysis step (step 6), the research group created a retrospective pseudonymized research database for the secondary use of the collected patient data (Figure 1). They analyzed the data and interpreted the obtained results to produce information on the health status of the residents and to identify the needs for health service use.

After the first segment of 75-year-old residents screened in 2019, the health screening group and research group conducted regular meetings to further develop the health screening process including the measures and tests used, and shared the preliminary results of the screening (step 7). The research group closely worked with PNs and physicians in consensus meetings to facilitate integration between the steps (steps 3-7) and the tasks of the health care professionals involved. The development of the dynamic health screening process as well as the appropriateness of the selected and validated screening measures is planned to be annually assessed in these consensus meetings (step 7). In addition, the health screening group will share the results of the screening with the steering committee to assess the quality and adequacy of available health services compared to the care and support needs of the home-dwelling older residents. This study was limited to describing the development process of the procedure, and the results of the screenings will be published in several different publications.

Results

Description of the Health Screening Procedure for 75-year-Old Home-Dwelling Residents

The health screening procedure for 75-year-old home-dwelling residents comprised 30 measures and tests divided into three categories: (1) validated self-assessments (9 measures), (2) nurse-conducted screenings (14 measures), and (3) laboratory tests (7 measures; Figure 2). Figure 2 presents the 5-stage process of conducting the measures and tests in practice.

The screenings are divided into 3 blocks, 2 of which are presented in 2 separate questionnaires (Figure 2). In the first block, the questionnaire is named as QTself (questionnaire included screenings suitable for self-assessment at home such as quality of life, functional capability, mood and depressive symptoms, the probability of sleep disorders, alcohol use, inability to urinate, and possible problems and risks in medication use; Table 1). In the second block, the questionnaire is named QTnurse (questionnaire included screenings performed by a health care professional) comprises screenings to be performed by a health care professional, that is, a trained PN. These screenings include frailty, nutritional status, cognition (memory and reasoning), sleep apnea, fall risk, lower body strength, orthostatism (difficulty in achieving stable blood pressure), and other tests such as those for identifying impaired vision and hearing (Table 2). The third block, the laboratory tests, includes the following tests such as basic blood count, long-term blood glucose, vitamin D, serum creatine, glomerulus filtration rate, serum sodium and potassium, and albumin-corrected calcium (Table 3).

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Table 1. Health screening procedure for 75-year-old residents: the measures included in the self-assessment instrument (QTself questionnaire) are designed to be used by 75-year-old home-dwelling residents by themselves or with the help of their caregiver or closest proxy.

Test and health measure	Definition and description
ADL, IADL [a,b,c,d]	• ADL [48] is the scale of assessment of daily activities, where the amount of help needed in basic daily activities is scored, and the total of the points describes the amount of help needed by others. • IADL [49] describes the need for assistance in instrumental daily activities.
AUDIT-C [a,b,e]	• Alcohol Use Disorder Identification Test (AUDIT) [50] is a screening instrument for hazardous and harmful alcohol consumption. • (AUDIT-C) [51] questions have been previously validated as a 3-item screening tool for alcohol misuse.
GDS 15 [a,b,f]	• GDS 15 [52] is a validated self-rating depression screening scale for older adults.
BNSQ[g,h,i]	• BNSQ [53] has been used widely in a variety of studies and has proven to be a valid tool for measuring subjective sleep complaints.
15D[i,j]	• 15D [54] is a generic, comprehensive, 15-dimensional, standardized, and self-administered measure of health-related quality of life that can be used both as a profile and single index score measure.
SARC-F[i,k,l]	• The SARC-F [55] questionnaire is a rapid diagnostic test for sarcopenia and covers the following components: Strength, Assistance with walking, Rise from a chair, Climb stairs and Falls.
UDI-6[i,m]	• UDI-6 [56,57] is for assessing the life impact and symptom distress of urinary incontinence and related conditions for both men and women.
LOTTA checklist[i,l,n]	• The LOTTA checklist is a validated self-assessment tool [58] for older adults aged >65 years to identify medication-related risks. The checklist aims to (1) ensure that the medication is being taken as directed, (2) encourage older adults to maintain an up-to-date medication list, and (3) monitor the therapeutic effects of their medication.
Medication list[i]	• A medication list comprises the medicines currently in use and is filled by the older adult themselves or by the closest proxy at home.

[a]A measure included in the fall prevention guide [45].

[b]Measures given in italics are already in use at the Social Security Center of Pori before the PORI75 procedure was established.

[c]ADL: activities of daily living.

[d]IADL: Instrumental Activities of Daily Living.

[e]AUDIT-C: Alcohol Use Disorders Identification Test—Consumption.

[f]GDS 15: Geriatric Depression Scale.

[g]BNSQ: Basic Nordic Sleep Questionnaire.

[h]BNSQ was included only in 2019 and was excluded based on the experiences of its use in 2019.

[i]A measure recommended to be screened in older adults by the fall prevention guide [45] but the measure was retrieved from the National TOIMIA Functioning Measures Database [46].

[j]15D: comprehensive health-related quality of life instrument

[k]SARC-F: Strength, Assistance with walking, Rise from a chair, Climb stairs, and Falls.

[l]The LOTTA checklist and SARC-F test were included as new measures in 2020.

[m]UDI-6: Urinary Distress Inventory.

[n]LOTTA: Checklist for Successful Medication Therapy (translated in English).

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Table 2. The health measures planned to be screened at the nurse's appointment by trained PNs as part of the health screening procedure for 75-year-old residents (QTnurse questionnaire).

Test and health measure	Definition and description
FROP-COM [a,b,c]	• FROP-Com [59] are tools used in the community for the assessment or screening of falls risk.
MMSE [a,d]	• MMSE [60] is a test of cognitive function among older adults.
MNA [a,e]	• MNA [61] is a simple tool useful in clinical practice to measure nutritional status in older persons.
Orthostatic test [a]	• The orthostatic test [62] is used to determine how the position of the body affects the heart rate and blood pressure. Orthostatic hypotension is defined as a decrease in systolic blood pressure of at least 20 mm Hg or in diastolic blood pressure of 10 mm Hg when assuming an upright position.
5×sit-to-stand test[a] (Chair stand, 5 times)	• The 5 times sit to stand test (5×sit-to-stand test) [63,64] is used to assess the functional lower extremity strength, transitional movements, balance, and fall risk in older adults.
FRAIL scale[f,g]	• The FRAIL scale [65] is a screening tool for clinicians to identify frail persons at risk of developing disability as well as experiencing a decline in health functioning and mortality.
STOP-Bang, Mallampati[f,h,i]	• The STOP-Bang [66,67] questionnaire is used to screen patients for obstructive sleep apnea. • The Mallampati [68] score is used to identify patients at risk for difficult tracheal intubation and evaluate obstructive sleep apnea.
Other tests[b] • Visual acuity[a] (random E test) • Hearing[a] (tympanometry) • Weight[a] • Height[a] • Waist circumference[f] • Neck circumference[f]	• Clients are also examined, and the values for disease identification and those necessary for the study are measured.

[a]A measure included in the fall prevention guide [45].

[b]Measures given in italics are already used at the Social Security Center of Pori.

[c]FROP-Com: Falls Risk for Older People in the Community.

[d]MMSE: Mini-Mental State Examination.

[e]MNA: Mini Nutritional Assessment.

[f]A measure recommended to be screened in older adults by the fall prevention guide [45] but the measure retrieved from the National TOIMIA Functioning Measures Database [46].

[g]FRAIL: simple frailty questionnaire; fatigue, resistance, aerobic capacity, illnesses and loss of weight.

[h]The measure is not specific and sensitive for older adults.

[i]STOP-Bang: Score for obstructive sleep apnea, Snoring, Tired, Observed, Pressure, Body Mass Index.

All chosen measures are specific and sensitive for older adults, except the quality of life measure (Comprehensive Health-Related Quality of Life Instrument [15D]) [54] and 2 measures for sleeping disorders (Score for obstructive sleep apnea, Snoring, Tired, Observed, Pressure, Body Mass Index [STOP-Bang] [66,67] and Mallampati [68]). The 15D is a comprehensive health-related quality of life instrument for adults but is not specifically designed for older adults [54]. In the same way, STOP-BANG [66,67] and Mallampati [68] are used to evaluate obstructive sleep apnea in adults but not particularly in older adults.

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Table 3. Laboratory tests are included in the PORI75 health screening procedure for 75-year-old home-dwelling residents to screen for diseases prevalent in older adults.

Laboratory tests	Definition and description
25-hydroxy vitamin D[a]	The measurement of serum vitamin level is generally recognized as the clinical standard for the evaluation of vitamin D status.
Albumin-corrected calcium[b]	Total plasma calcium is bound to protein, with albumin being the most abundant binding protein. Albumin-corrected calcium is used as a measure of calcium balance.
Basic blood count[b]	The basic blood count is an important basic laboratory examination that indicates various ways to analyze the condition of the body.
Hemoglobin A_{1c}[b]	Glycated hemoglobin levels are a measure of average sugar levels in the blood and are commonly used in relation to diabetes.
Serum creatinine glomerular filtration rate[c]	A blood creatinine examination is a part of a routine health examination for recognizing kidney damage or the risk of developing kidney disease. Glomerular filtration rate is the measurement used to determine kidney function.
Serum potassium[c]	Serum potassium is a measure of average potassium levels in the blood.
Serum sodium[c]	Serum sodium is a measure of average sodium levels in the blood.

[a]A measure included in the fall prevention guide [45].

[b]A measure recommended to be screened in older adults by the fall prevention guide [45].

[c]A measure recommended to optimize drug treatment.

Performing the Pilot PORI75 Health Screenings in 2019

All residents (n=1104) who turned 75 years old in 2019 and lived at home were sent an invitation letter to participate in the PORI75 health screening (Figure 2, stage 1). Of the invited residents, the participation rate for health screening was 37% (n=415). Among these 415 participants, 407 (98%) gave written consent to be included in the study.

The invitation letter contained a reserved time for the PN's appointment, a request to fill in the QTself questionnaire before the appointment, instructions to book a slot for laboratory tests (Table 3), and an informed consent letter for the study participation (Figure 2, stage 2). The residents were recommended to book an appointment for the laboratory tests no later than 5 days before the PN's appointment (Figure 2, stage 3). They were also asked to return the filled QTself form at the PN's appointment when the PN conducted the health screenings according to the QTnurse form and reconciled the medication list (Figure 2, stage 4). Residents signed the written informed consent during the PN's appointment if they were willing to participate in the study. An appointment took about 2 hours including screening, reconciling the medication list, and recording results in the electronic patient information system. If a PN identified potential health risks based on the predetermined health risk cut-off points (Multimedia Appendix 1), they advised the resident to contact a health care provider for further medical examination to manage the observed health risks (Figure 2, stage 5).

Experiences From the First Pilot-Year Screenings in 2019

The consensus meeting after the pilot screenings in 2019 considered the content of the PORI75 procedure to be appropriate and applicable to a new segment of 75-year-old residents in 2020. The only changes made to the measures were the removal of the Basic Nordic Sleep Questionnaire [53] for measuring sleep disorders from the procedure. This is because the Basic Nordic Sleep Questionnaire [53] lacked an easily applicable and validated scoring method, thus making it difficult for PNs to identify residents at risk. In addition, the following 2 new measures were added to the health screening: a tool (Strength, Assistance with walking, Rise from a chair, Climb stairs, and Falls) for identifying sarcopenia in older adults [55] and a checklist (LOTTA) for assessing medication-related risks and problems [58]. Strength, Assistance with walking, Rise from a chair, Climb stairs, and Falls measure [55] was chosen because sarcopenia may impede daily activities and increase the rate of complications in older persons [69]. The validated LOTTA checklist was nationally launched in Finland in 2020 by the Finnish Medicines Agency [58]. This self-assessment tool for adults aged >65 years aims to identify the potentially harmful risks and problems in their medication use.

Discussion

Principal Findings

The PORI75 preventive health screening procedure was successfully developed and piloted with 75-year-old home-dwelling residents. The procedure includes a coordinated set of health measures covering the most common age-related diseases and other conditions that may affect older adults' functionality and survival at home. The established questionnaires of health measures and laboratory tests enable systematic and structured patient data recording and management, with potential for secondary use in planning preventive services for older adults according to their needs. This aligns with the ongoing social and health care reform goals in Finland [70]. The developed health screening procedure is dynamic and can be expanded and annually supplemented with new health screening data from 75-year-old residents. At the moment, the database includes data from the years 2019-2022. If the number of measures is wanted to be increased, modern pervasive computing technology with sensors could provide

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new additions enabling continuous monitoring of selected health functions in home-dwelling older adults [16,17,71].

The final health screening procedure consists of quite a high number of validated measures (n=30 measures), some of which are extensive and time-consuming to apply (eg, quality of life [54] and functional ability [63,64] measures). This increases the workload of the Social Security Center personnel, especially the PNs who perform the measures. However, the majority of the measures (22/30, 73%) were already in use at the Social Security Center before the PORI75 procedure was established. Although these health measures were used in different health care wards and contexts, systematic preventive screening was missing. Of the existing measures, 10 measures were included in the QTnurse questionnaire and 7 in laboratory tests of the PORI75 procedure.

Delegating the task of self-assessment for some measures to the older residents themselves proved to be a feasible practice (9 measures, of which 5 were already applied at the Social Security Center before PORI75). Based on the pilot experiences, 75-year-old home-dwelling residents were able to actively participate in health screening by answering the QTself questionnaire for the chosen measures. As all the residents were interviewed by a PN during their health screening appointment, PNs were able to confirm whether all measures of QTself questionnaire had been completed and what problems the residents may have experienced in filling in their personal information. Thus, we can assume that all residents who consented to fill the QTself questionnaire did so. Unfortunately, the PNs did not keep records of the difficulties the residents may have experienced in completing the QTself questionnaire, so we cannot report these findings. Difficulty in self-completing the questionnaires could have been one of the reasons for not participating in the health screening. These findings suggest the need for making a more detailed analysis of health screening participants and nonparticipants in the future.

The participation rate in the health screening was not very high (n=415, 37%), even though the health screening was provided free of charge for all 75-year-old home-dwelling residents. If the health screening for 75-year-old residents will become a routine practice, it is important to find new strategies to increase the participation rate. Otherwise, the procedure will not reach its primary goal of helping older residents to live at home for as long as possible and lowering the proportion of older residents living in assisted living facilities and nursing homes.

Another consequence of the low participation rate can be biased on estimates for planning social and health services needed for geriatric care. The bias in the allocation of resources can be aggravated by the assumption that many nonparticipants may have had a poorer health status and functional ability than the participants. This will lead to underestimating the resources needed for geriatric care. Therefore, it is important in future studies to investigate the characteristics of health screening participants and nonparticipants to estimate the bias caused by the participation rate. Based on this analysis, a suitable correction should be used in data analysis to consider this potential source of bias that can reflect on health services planning and allocation of resources in the well-being services county. It is also important to understand other complications encountered in the process and to focus on them in future studies. A potential option for increasing the participation rate could be to conduct health screening in connection with emergency department visits. It is important to note that in any case, the health screening is entirely voluntary, and it is everyone's right to choose whether they want to participate.

In Finland, 75-year-old residents or any other segment of older adults do not routinely have PN’s appointments and the related opportunities for preventive health counseling such as those presented here. Systematic health checks are routine in most countries [72] but are more typically focused on specific diseases or symptoms [10-21] or medication management [73]. The PORI75 is a unique and comprehensive health screening procedure for home-dwelling older adults where the effectiveness and cost-effectiveness should be evaluated in future studies when we have gathered sufficient data for statistical analyses. In forthcoming studies, we will evaluate the effectiveness of the health screening by comparing emergency department visits before and after the health screening for both participants and nonparticipants. If the outcomes are positive, the procedure has the potential to be implemented in other well-being services counties, or even nationally in Finland and beyond. As the measures and tests were chosen by the local health screening group based on proposals from the interprofessional research group, consensus meetings with an extended representation should be carried out to confirm the consensus findings.

The PORI75 health screening procedure is still under development. The procedure has been pilot-tested and used in clinical practice at the Social Security Center of Pori as presented in this study. The development continues towards a digital data lake and a template facilitating the use of the data in data-driven management in the regional well-being services county.

Conclusions

The developed preventive PORI75 enables the use of clinical patient data for purposes of strategic planning of supportive services in primary care if the potential bias by a low participation rate is controlled.

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Data Availability

The data that support the findings of this study are available from the Social Security Center of Pori but restrictions apply to the availability of these data, which were used under license for the current study and are therefore not publicly available. Data are, however, available from the patient document archive of Pori Town (arkisto.ter@porinperusturva.fi) based on the Act on the Secondary Use of Health and Social Data upon reasonable request.

Authors' Contributions

JCK, AH, SK, and JP contributed to the study concept and design. JCK, AH, JB, and JP acquired and analyzed the data. JCK, AH, MA, and JP drafted the manuscript. JCK, AH, MA, and JP critically revised the manuscript for important intellectual content. JCK, AH, SK, PH, ALK, JB, MA, and JP read and approved the final manuscript. JCK, AH, and JP contributed equally to this work.

Conflicts of Interest

None declared.

Multimedia Appendix 1
The cut-off points of screenings and laboratory tests for further actions.
[DOCX File , 58 KB - resprot_v12i1e48753_app1.docx]

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Abbreviations

15D: Comprehensive Health-Related Quality of Life Instrument
PN: practical nurse
PORI75: health screening procedure for 75-year-old residents
QTself: questionnaire included screenings suitable for self-assessment
QTnurse: questionnaire included screenings performed by a healthcare professional
RAI: Resident Assessment Instrument
STOP-Bang: Score for obstructive sleep apnea, Snoring, Tired, Observed, Pressure, Body Mass Index

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